

Synthesis and Elaboration of Heterocycles
***via* Palladium-Catalyzed C-H Functionalization**

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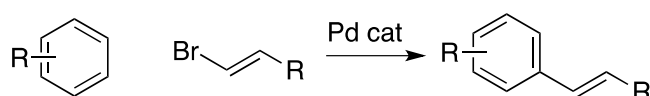
University of Oxford

2012

Abstract

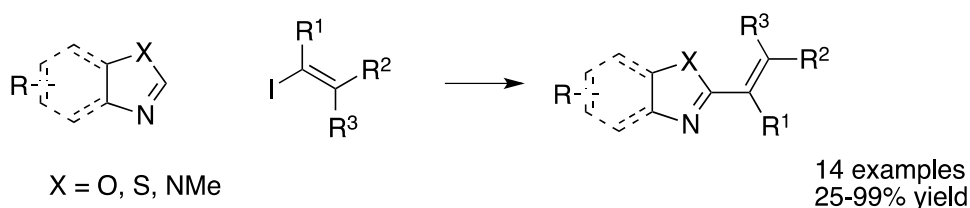
Chapter 1 is a brief literature review of the most recent progress in the area of C-H functionalization *via* palladium catalysis. This covers the functionalization of electron deficient arenes and heterocycles with alkenyl and alkyl halides both using inter- and intra-molecular reactions. The chapter also contains an overview of recent work from the Willis group.

Chapter 2 presents the functionalization of electron deficient arenes and alkenyl bromides using palladium catalysis (Scheme 1), as well as the use of statistical analysis software for optimizing the cross-coupling reaction.



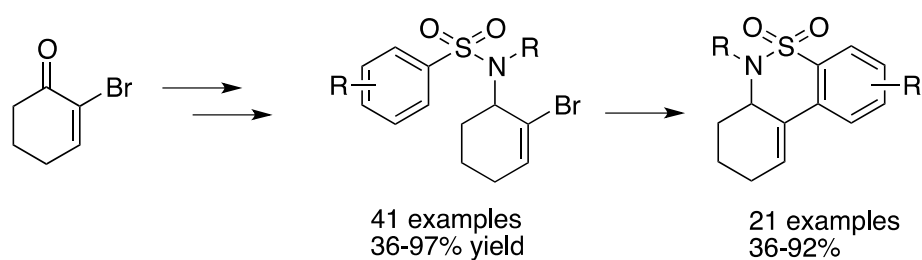
Scheme 1: Functionalization of electron deficient arenes using palladium catalysis

Chapter 3 describes the cross-coupling of substituted benzoxazoles, benzothiazole and benzimidazole with a range of alkenyl iodides using palladium catalysis (Scheme 2). The reaction can tolerate both (*E*) and (*Z*) disubstituted alkenes and tri-substituted alkenyl iodides, with retention of the double bond geometry.



Scheme 2: Cross-coupling using benzoxazoles, benzothiazole and benzimidazole with alkenyl iodides

Chapter 4 details the synthesis of sultams *via* an intramolecular C-H functionalization using palladium catalysis. The chapter covers the optimization of the starting material synthesis as well as the cross-coupling reaction. We can access the sulfonamides from cyclohexenone and were able to incorporate a large range of substitution patterns (Scheme 3).



Scheme 3: Synthesis of sultams from cyclohexenone

Finally, Chapter 5 contains all the experimental details, general considerations and compound data. All the NMR spectra of novel compounds can be found in the appendix.

Acknowledgements

I would like thank Dr. Michael Willis for his help, supervision, patiences and guidance during my DPhil, especially during my 2nd year when I went through some hard times.

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Contents

Abstract.....	0
Acknowledgements	3
Contents	5
Abbreviations.....	7
Ligands	12
Chapter 1 Introduction.....	14
1.1 Traditional Metal-Catalyzed Cross-Coupling.....	14
1.2 C-H functionalization	16
1.2.1 Mechanism.....	17
1.2.2 Early Examples	19
1.3 Intramolecular Aryl-Aryl Cross-Coupling.....	20
1.4 Intermolecular Aryl-Aryl Cross-Coupling	23
1.4.1 Direct Arylation Employing Directing Groups	24
1.4.2 Direct Arylation of Electron Deficient Arenes	27
1.4.3 Direct Arylation of Heterocycles.....	31
1.5 Alkenyl-Aryl Cross-Coupling.....	34
1.6 Alkyl-Aryl Cross-Coupling	39
1.8 Previous Work in the Willis Group	40
Chapter 2 Palladium Catalysed Cross-Coupling of Electron Deficient Arenes and Alkenyl Bromide	42
2.1 Introduction.....	42
2.2 Synthesis of Alkenyl Bromide.....	44
2.3 Optimization of the Cross-Coupling Reaction	46

2.4	Design of Experiment.....	55
2.4.1	Fractional Factorial Design.....	57
2.4.2	Design parameters.....	59
2.4.3	Results of Amber Design.....	60
2.5	Conclusion.....	65
Chapter 3	Palladium-Catalyzed Direct Functionalization of Heteroarenes with Alkenyl Iodides	67
3.1	Introduction.....	67
3.2	Alkenyl Halide Synthesis	68
3.3	Initial Screen and Optimization	71
3.4	Reaction Scope	73
3.5	Conclusion and Future Work	77
Chapter 4	Synthesis of Sultams: Palladium-Catalyzed Intramolecular Cross-Coupling.....	79
4.1	Introduction.....	79
4.2	Original Strategy: Synthesis of Sultam Precursors.....	83
4.3	Revised Strategy: Synthesis of Sultam Precursors.....	89
4.4	Optimization: Palladium-Catalyzed Intramolecular Cross-Coupling.....	104
4.5	Synthesis of sultams <i>via</i> intramolecular palladium cross-coupling.....	112
4.6	Functionalization	120
4.7	Conclusion and Future Work	125
Chapter 5	Experimental Procedures	128
Appendix.....		240
References.....		357

Abbreviations

Ac	Acetyl
α	Alpha
Ar	Arene
ANOVA	Analysis of Variance
β	Beta
BINAP	1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine
br. s	broad singlet
Bu	Butyl
CataCXium A	Di(1-adamantyl)- <i>n</i> -butylphosphine
CataCXium C	<i>trans</i> -Di(μ -acetato)bis[o-(di- <i>o</i> -tolylphosphino)benzyl] dipalladium(II)
CBS	Corey-Bakshi-Shibata
Cbz	Carboxybenzyl
CMPhos	2-[2-(Dicyclohexylphosphino)phenyl]-1-methyl-1H-indole
Cp	Cyclopentyl
Cy	Cyclohexyl
d	Doublet
DABSO	1,4-Diazabicyclo[2.2.2]octane-bis(sulfur dioxide)
DavePhos	2-(Dicyclohexylphosphino)-2'-(N,N-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
°C	Degrees Celsius

DIBAL	Diisobutylaluminum hydride
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	Dimethyl sulfoxide
DPPA	Diphenyl phosphoryl azide
dppb	1,4-Bis(diphenylphosphino)butane
dppe	Ethylenebis(diphenylphosphine)
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
<i>E</i>	Entgegen
ESI	Electrospray ionization
Et	Ethyl
Eq	Equivalence
FI	Field Ionization
h	Hour(s)
HMDS	Bis(trimethylsilyl)amide
HPLC	High-Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
<i>i</i> Pr	<i>iso</i> -Propyl
IR	Infrared
<i>J</i>	Coupling constant measured in Hz

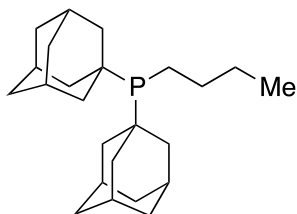
L	Liter
LG	Leaving Group
LDA	Lithium diisopropylamide
m	Milli
M	Molar (g/dm ³)
m	Multiplet
μw	microwave
M.p.	Melting Point
<i>m</i> CPBA	3-Chloroperbenzoic acid
Me	Methyl
MePhos	2-Dicyclohexylphosphino-2'-methylbiphenyl
Ms	Mesylate
MS	Molecular Sieves
nbd	Norbornadiene
NBS	<i>N</i> -Bromosuccinimide
NHC	<i>N</i> -Heterocyclic Carbene
nm	Nanometer
NMR	Nuclear Magnetic Resonance
NIS	<i>N</i> -Iodosuccinimide
NMP	1-Methyl-2-pyrrolidinone
OFAT	One-Factor-at-a-Time
<i>o</i>	Ortho
o/n	Overnight
Oxone [®]	Potassium peroxymonosulfate
PCC	Pyridinium chlorochromate

PDC	Pyridinium dichromate
PEPPSI	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Ph	Phenyl
Piv	Pivalic
PMA	Phosphomolybdic acid
PPA	Polyphosphoric acid
PS	Polymer Support
<i>p</i> TSA	<i>para</i> -Toluenesulfonic acid monohydrate
rt	Room temperature
q	Quartet
qin	Quintet
s	Singlet
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium
SIPr	1,3-Bis(2,6-di- <i>i</i> -propylphenyl)-4,5-dihydroimidazolium
S _N Ar	Nucleophilic Aromatic Substitution
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAB	Tetrabutylammonium bromide
t	Triplet
^t Bu	<i>tert</i> -Butyl
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl

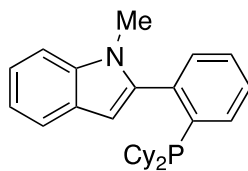
Ts	Tosyl
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Z	Zusammen

Ligands

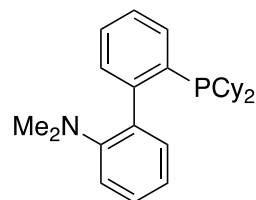
Monophosphine Ligands



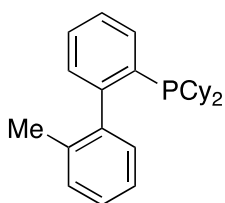
CataCXium A



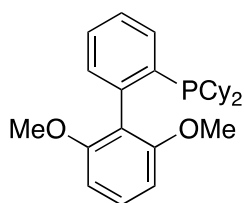
CMPhos



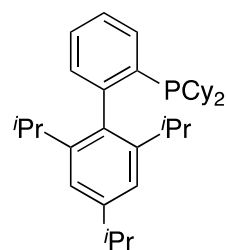
DavePhos



MePhos

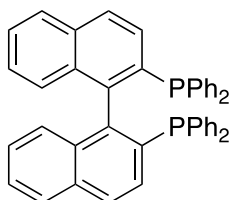


SPhos

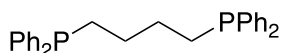


XPhos

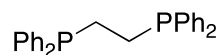
Biphosphine Ligands



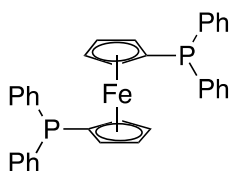
BINAP



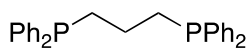
dppb



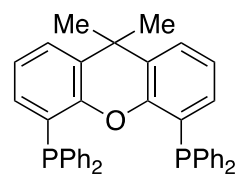
dppe



dppf

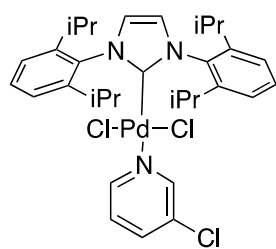


dppp

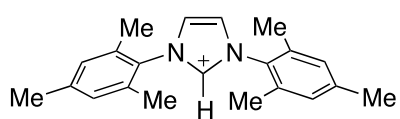


XantPhos

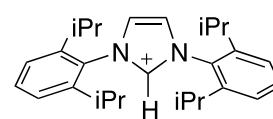
N-Heterocyclic Carbenes



PEPPSI-IPr

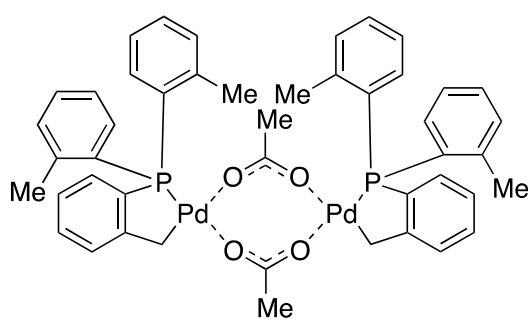


BF_4^-
SIMes-HBF₄

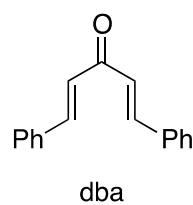


BF_4^-
SIPr-HBF₄

Others



CataCXium C
Herrmann's Catalyst

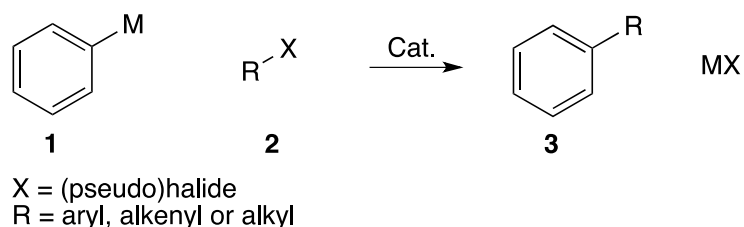


dba

Chapter 1 Introduction

1.1 Traditional Metal-Catalyzed Cross-Coupling

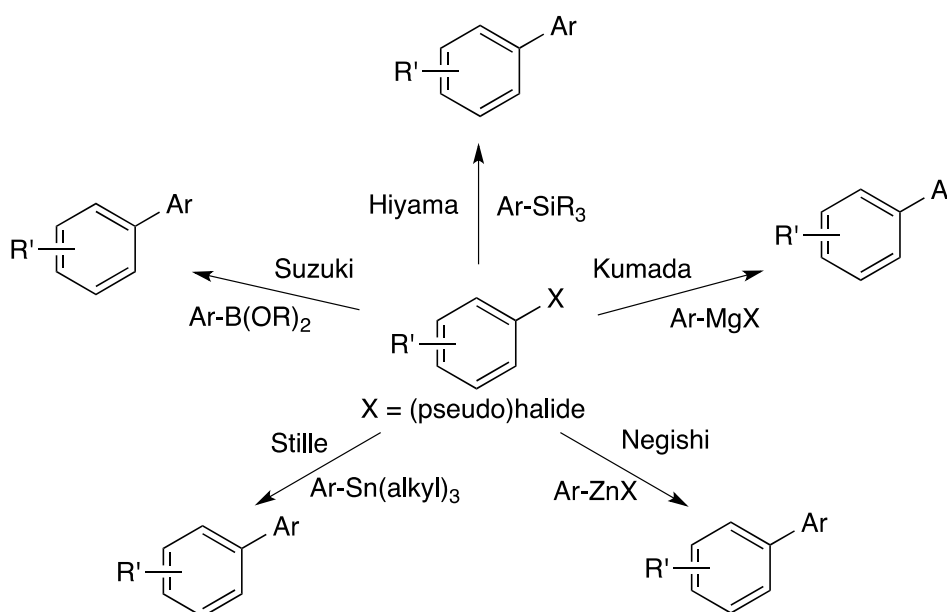
For over 100 years transition metal catalysis has been used in organic chemistry. It has enabled chemists to synthesize molecules that would otherwise be impossible or very time-consuming to make using conventional chemistry. Traditional transition metal cross-coupling reactions involve the reactions between an organometallic species **1** and a (pseudo)halide **2** to yield the coupled product **3** and stoichiometric by-product (Scheme 4).



Scheme 4: Traditional metal-catalyzed cross-coupling

Some of the most well known examples of transition metal-catalyzed cross-couplings are: Hiyama, Kumada, Negishi, Stille and Suzuki reactions (Scheme 5). The Hiyama coupling is the palladium-catalyzed C-C bond formation between aryl, alkenyl or alkyl halides or pseudohalides and organosilanes.¹ This reaction is comparable to the Suzuki coupling and also requires an activating agent such as the fluoride ion or a base.² The Kumada cross-coupling is between aryl and alkenyl halides and Grignard reagents.³ The Negishi reaction is between organozincs and aryl, alkenyl or alkynyl halides or

pseudohalides.⁴ The Stille coupling is the palladium-catalyzed cross-coupling between an organostannane and aryl halides or pseudohalides to form a new C-C sigma bond.⁵ Lastly, the Suzuki reaction is a cross-coupling between organoboron and organic halides or triflates.⁶ The disadvantage of all these palladium cross-coupling reactions is the need for the pre-existing activation of both coupling partners. This leads to further problems such as the disposal of stoichiometric by-products, as well as time consuming and complicated starting material syntheses since many are not commercially available. Another major problem is the toxicity and sensitivity of the organometallic species. Even with the disadvantages presented these reactions are still widely used today due to their reliability and the importance of the products.



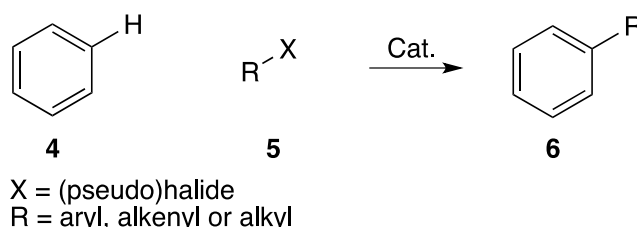
Scheme 5: Well known transition metal-catalyzed coupling reactions

The cross-coupling reactions mentioned thus far have been developed to incorporate alkyl and alkenyl species. However, the Heck and Sonogashira reactions were discovered for the purpose of coupling alkenes and alkynes. Heck reactions progressed the transition metal catalyzed cross-coupling reaction. The Heck reaction allows

nucleophilic attack on an unfunctionalized alkene in the presence of a palladium catalyst.⁷ It does not however tolerate the presence of β -hydrogens on the alkyl halide and generally electron poor alkenes are better substrates for the reaction. The Sonogashira cross-coupling involves the reaction between terminal alkynes and aryl or alkenyl halides or pseudohalides, giving enynes.⁸

1.2 C-H functionalization

To overcome the drawbacks of traditional transition metal-catalyzed cross-coupling, chemists have been investigating C–H functionalization as a plausible alternative. There are many types of C–H functionalization, one version is *via* palladium catalysis describes the reaction between a species containing an unactivated C–H bond **4** and (pseudo)halide **5** to give the desired product **6** (Scheme 6).



Scheme 6: Metal catalyzed C–H functionalization

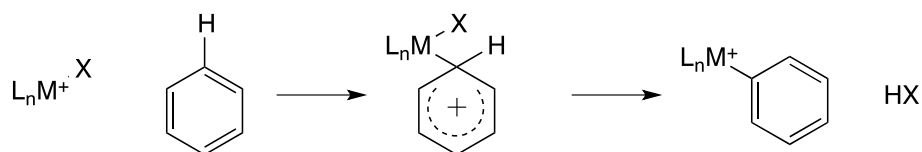
The concept of C–H functionalization is a more environmentally friendly approach as it eliminates the need for the stoichiometric metallic activating group. This also avoids complicated starting material syntheses and in turn makes the overall process more atom efficient.⁹ The process of C–H functionalization does come with some drawbacks, namely the inert nature of the C–H bond, which leads to harsh conditions, and the need

to control the site of reactivity as C-H bonds are so prevalent. Many transition metals have been reported as possible catalysts including ruthenium,¹⁰ rhodium,¹¹ copper¹², iron^{13,14} and gold.¹⁵ In this brief review, only the use of palladium and the recent advances that have been made in this field, will be described, due to the vast amount of literature on this subject.¹⁶⁻¹⁹

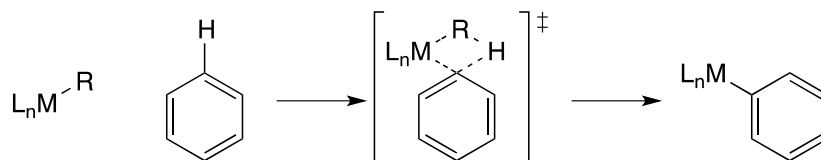
1.2.1 Mechanism

The majority of proposed mechanisms for palladium-catalyzed C-H functionalization start with the oxidative addition of palladium into the aryl halide bond followed by one of five possible C-C bond forming steps;²⁰ electrophilic aromatic substitution, which results in a cationic transition state thus requiring a nucleophilic arene;²⁰ σ -bond metathesis, is a concerted mechanism by which two σ bonds are broken and two new σ -bonds are formed, without change of the metal oxidation state;²¹ carbometalation which proceeds *via* a formal *anti*- β -hydride elimination or isomerization followed by a *syn*- β -hydride elimination to give the desired product;^{22,23} a C-H bond oxidative addition mechanism which involves the simultaneous breaking of the C-H bond and the formation of the C-M and M-H bond in the transition state; this increases the oxidation state of the palladium by 2;²⁴ base-assisted concerted metalation-deprotonation (CMD) describes a process by which C-H bond cleavage happens *via* simultaneous metalation and intramolecular deprotonation.²⁵ The base plays a crucial role in the mechanism, especially carboxylate-type bases. CMD has also been referred to as internal electrophilic substitution (IES)²⁶ and ambiphilic metal-ligand activation (AMLA) (Scheme 7).²⁷

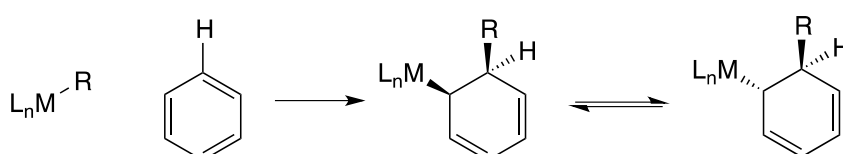
Electrophilic Aromatic Substitution



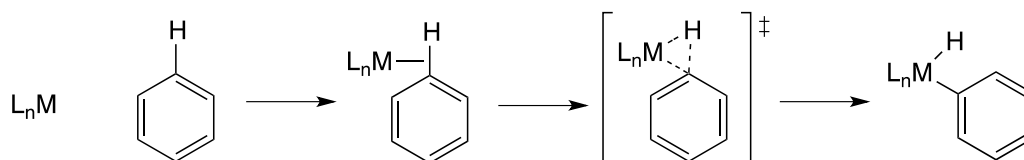
σ -Bond Metathesis



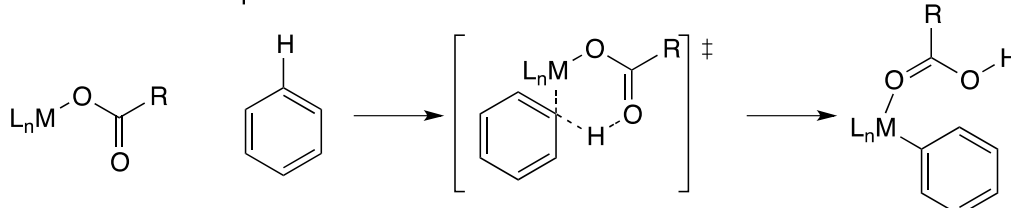
Carbometalation



C-H Oxidative Addition



Concerted Metalation-deprotonation

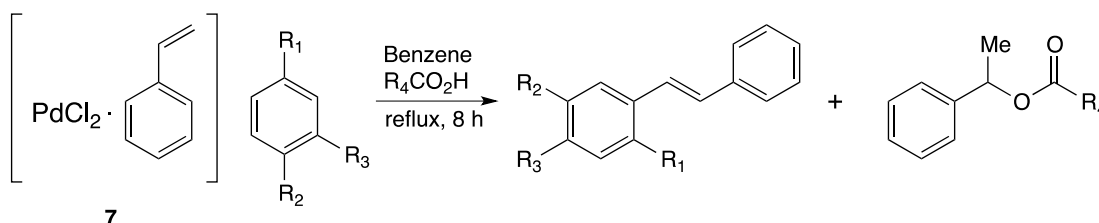


Scheme 7: Mechanisms for C-H functionalization

The mechanism of an individual reaction depends strongly on the substrate, solvent, base and catalyst used. Electrophilic aromatic substitution and concerted metalation-deprotonation have been studied the most.²⁸

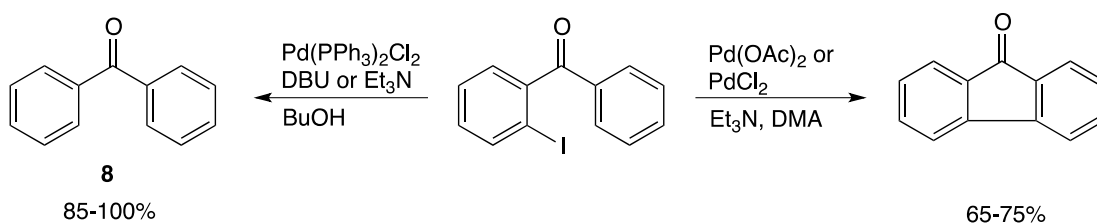
1.2.2 Early Examples

Fujiwara and Moritani reported one of the first examples of C-H activation in 1967. They showed that the reaction between an aromatic compound and a double bond by means of alkene-palladium complex **7** was possible, albeit in only 56% yield (Scheme 8).²⁹ Despite the use of a stoichiometric amount of palladium this represents an important discovery.



Scheme 8: One of the first examples of C-H activation

Some of the earliest examples of catalysis were performed by the groups of Tajima³⁰ and Ames^{31,32} in the early 1980s. Ames *et al.* reported on the discovery and development of catalytic C-H activation in direct intramolecular arylation reactions. They found they could synthesize both five- and six- membered rings using a catalyst loading of just 10 mol%, although employing forcing conditions of 150-170 °C. They found they could suppress the competing pathway of dehalogenation to give the undesired product **8**, by subtly changing the reaction conditions (Scheme 9).³³

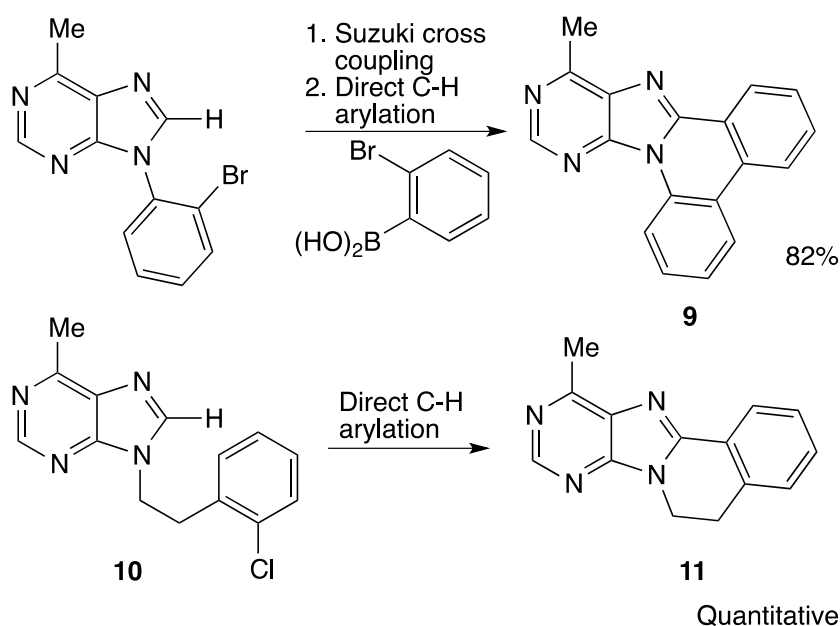


Scheme 9: Ames' example of catalytic C-H functionalization

1.3 Intramolecular Aryl-Aryl Cross-Coupling

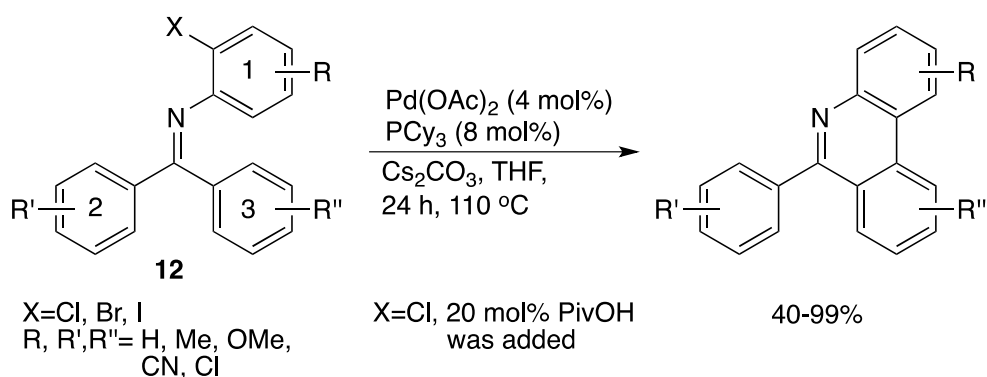
Many examples have been published of intramolecular aryl-aryl cross-coupling by C-H activation.³⁴ Some of the most recent examples that employ a palladium catalyst in direct arylation, which result in heterocycle synthesis, are discussed below.

Hoeck and co-workers have reported on several ways to access novel purines, all of which involve direct arylation as the key step. In their first approach, they combined a traditional Suzuki cross-coupling with direct C-H arylation. The direct arylation reaction which was performed with palladium(II) acetate, tricyclohexylphosphine tetrafluoroborate, potassium carbonate in DMF at 150 °C for 17 hours with an overall yield of **9** over two steps of 82% (Scheme 10). The first step of the second approach was alkylation of the purine using 2-chlorophenethyl bromide giving **10**, followed by direct arylation under the same conditions as for their first approach to yield the product **11**.³⁵ When the methyl group was substituted for an amino group they observed a significant drop in yield, which was the only other substituent investigated. The drawbacks include the direct arylation requiring both elevated temperatures and extended reaction times, as well as only demonstrating a very limited substrate scope.



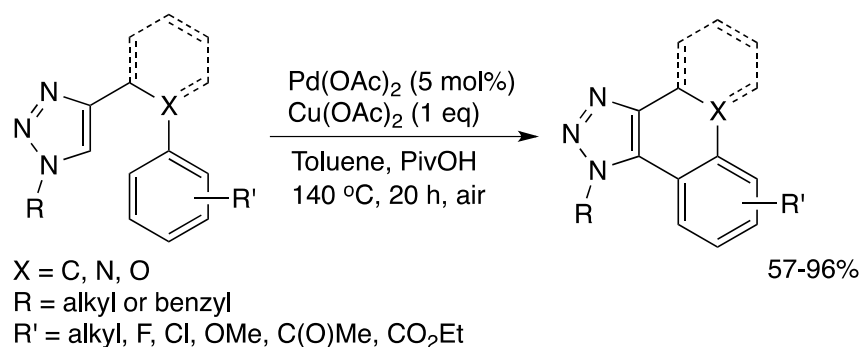
Scheme 10: Synthesis of purines via C-H functionalization

Li and his group have focused on improving the synthesis of phenanthridines and specifically moving away from harsh conditions that have often limited substrate scope. They reported on a C-H direct arylation using *N*-(2-haloaryl)-imines **12** as the cross-coupling precursor.³⁶ The reaction could tolerate both electron-withdrawing and -donating substituents on all three rings. The reaction could tolerate a chlorine substituent when X was bromine or iodine. The cyano group was only tolerated on ring 1 when X was iodine. When X was chlorine the reaction required the addition of 20 mol% of pivalic acid as an additive (Scheme 11). The Li group observed a mixture of products but reactions involving the most electron-poor ring were favored. They have proposed that the reaction mechanism goes through a concerted metalation-deprotonation transition state.



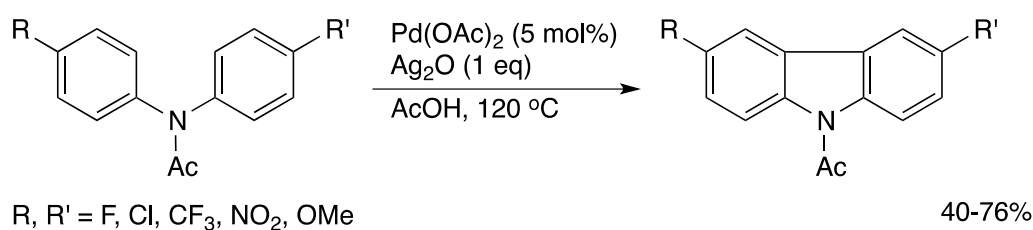
Scheme 11: Synthesis of phenanthridines *via* intramolecular cyclization

Ackermann and co-workers further improved C-H activation by reporting on transition metal-catalyzed dehydrogenative biaryl synthesis, using a direct arylation of 1,2,3-triazoles to form phenanthrenes (Scheme 12).³⁷ They found it necessary to add a stoichiometric amount of copper(II) acetate. However, for the final optimized conditions they found that adding the base was not necessary. Even though the reaction required an elevated temperature and extended reaction times they showed the reaction could be performed without any pre-activation from a halogen and the reaction was even successful in the presence of air. Even with the harsh conditions the reaction could tolerate a range of substitution patterns giving phenanthrenes in moderate to excellent yields.



Scheme 12: Synthesis of phenanthrenes *via* dehydrogenative direct arylation

Another class of heterocycles that has been synthesized *via* dehydrogenative arylation is carbazoles. One of the most recent papers was published by Pan *et al.* where they reported on the synthesis of carbazoles from biaryl amines.³⁸ They found they could access the biaryl amines from acetanilides and iodobenzenes *via* an Ullmann reaction. They were inspired by the work of Fagnou where pivalic acid was used as solvent, which will be discussed later,³⁹ however they wanted to investigate if they could find a cheaper alternative. They discovered that they could use acetic acid as a solvent together with palladium(II) acetate and silver(I) oxide (Scheme 13). They proposed a mechanism with two tandem C-H activations both assisted by the acetate anion.



Scheme 13: Synthesis of carbazoles *via* dehydrogenative direct arylation

1.4 Intermolecular Aryl-Aryl Cross-Coupling

Aryl-aryl cross-couplings have been known for more than 100 years. The Ullmann reaction was one of the first examples with the use of stoichiometric copper to facilitate the homocoupling of iodobenzene.⁴⁰ The importance of biaryl molecules has later discovered as they are found in a range of pharmaceuticals, agrochemicals, liquid crystal displays and they have even been included in molecular switches.⁴¹

1.4.1 Direct Arylation Employing Directing Groups

One of the main problems when using C-H functionalization as an approach for C-C bond formation is the potential selectivity issues that can arise. One way to overcome this problem is the use of a directing group such as acetyl, amide, pyridyl, nitro, hydroxy and imino groups to direct the metal to a specific site. General mechanistic studies have shown that the C-H functionalization proceeds *via* a 5 membered palladacycle which includes co-ordinating to the directing group (Figure 1).^{35,41-45}

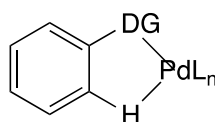
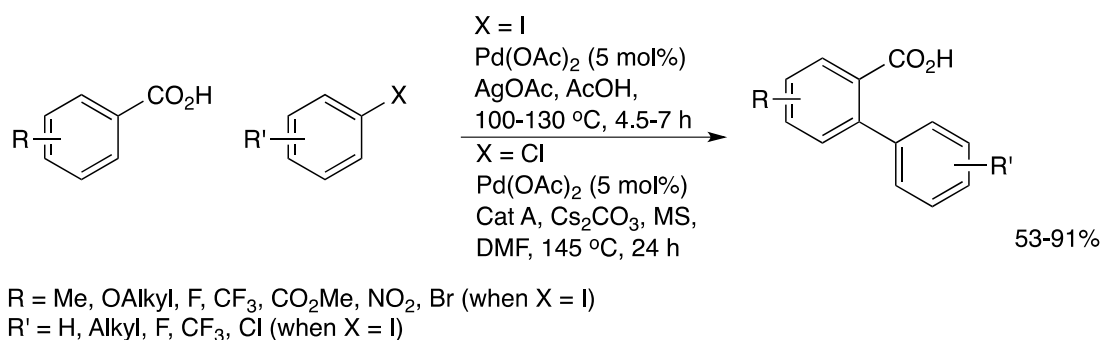


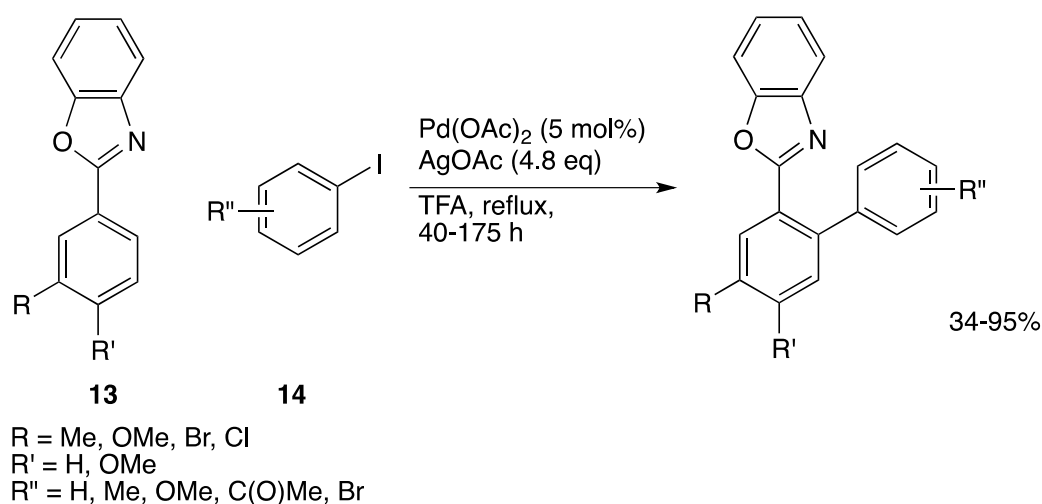
Figure 1: 5-membered palladacycle

Recently Daugulis and co-workers developed the first example of benzoic acids being used as a direct group in a cross-coupling reaction, where unprotected carboxylic acids act to direct *ortho* arylation.⁴⁶ They do not observe decarbonylation during cross-coupling, although the carboxylic acid moiety can easily be removed after, if so required. This is significant as it results in a regioselective arylation using a traceless directing group. They reported two methods according to the identity of activating group X and the reaction can tolerate electron-rich as well as moderately electron-poor coupling partners. The coupled products are formed in good to excellent yields (Scheme 14). They showed that they could use both aryl iodides and aryl chlorides as coupling partners; however, when the less reactive aryl chlorides are used the reaction requires both elevated temperatures and extended reaction times.



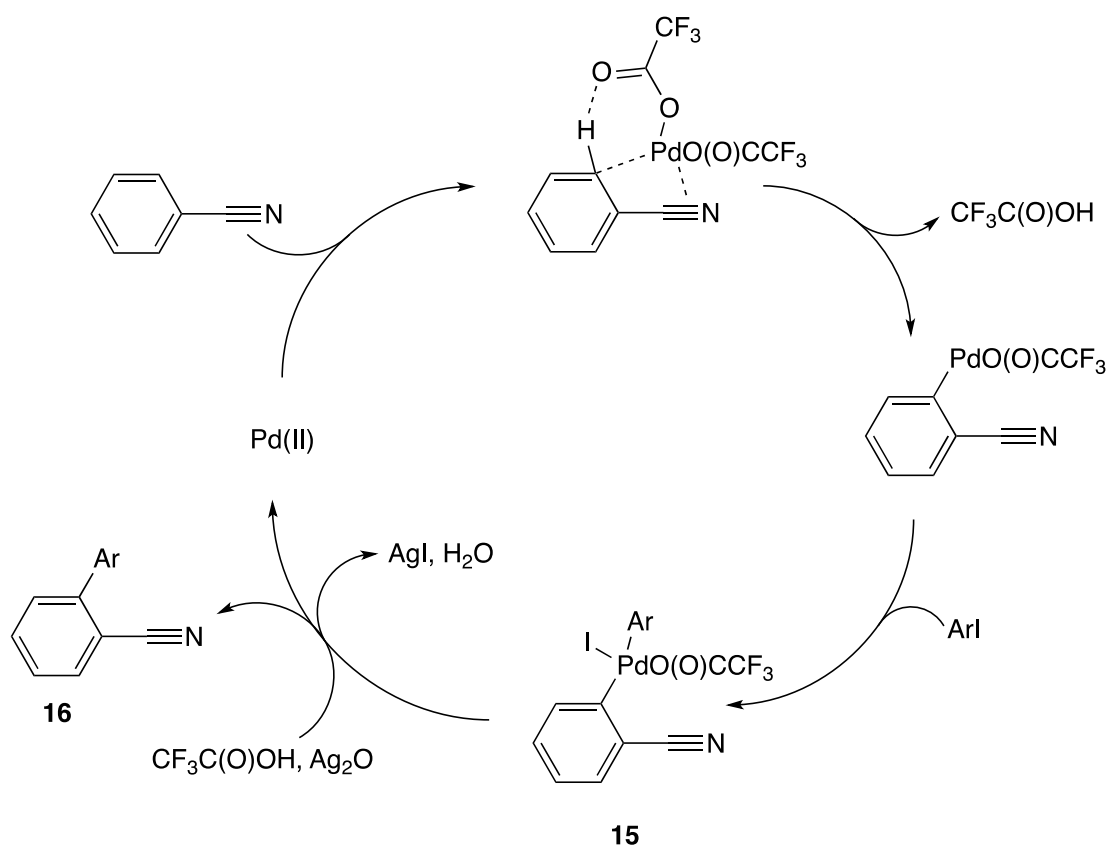
Scheme 14: Direct *ortho* arylation using a carboxylic acid directing group

Wu *et al.* were the first to report the use of benzoxazoles as a directing group for *ortho*-C-H functionalization using aryl iodides.⁴⁷ Although they needed a large excess of silver acetate, by using TFA as a solvent the reaction could proceed in the presence of air. They did, however, require a *meta* substituent on the 2-arylbenzoxazoles **13** to prevent diarylation. They found that the electronics of the aryl ring were important. The reaction rate increased if either the 2-arylbenzoxazole **13** or aryl iodide **14** carried electron-donating substituents. The reaction could tolerate various substituents including halogens on 2-arylbenzoxazoles and as well as on the aryl iodides (Scheme 15). The disadvantage of this reaction is the extremely extended reaction times required.



Scheme 15: Direct *ortho* arylation using benzoxazole as a directing group

Finally, Sun and co-workers have recently reported the first use of a nitrile group as a directing group for *ortho* C-H functionalization.⁴⁸ They wanted to explore the use of nitriles as directing groups since this would provide a good handle for subsequent functionalization. They developed a system, which again required palladium(II) acetate and a silver salt in acidic media. During their study they found their coupling conditions favored aryl iodides containing electron-withdrawing substituents. Based on their results they propose a mechanism that does not proceed *via* the standard five membered palladacycle. They propose that due to the linear nature of the nitrile group, the reaction proceeds *via* a CMD mechanism but the coordination of the palladium to the nitrile group still determines the selectivity. The oxidation state of the palladium changes from palladium(II) to palladium(IV) when the aryl iodides adds in **15**, which is followed by reductive elimination to give the desired product **16** (Scheme 16).



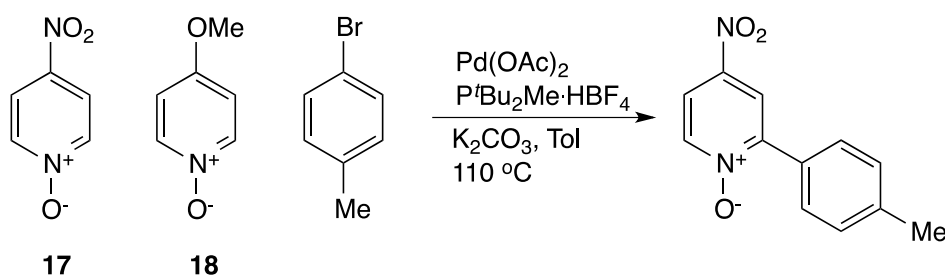
Scheme 16: The proposed catalytic cycle for direct *ortho* arylation using a nitrile directing group

1.4.2 Direct Arylation of Electron Deficient Arenes

Fagnou and his group pioneered the direct arylation of electron deficient arenes. When they started their investigations, the most accepted mechanism was electrophilic aromatic substitution, which requires an electron-rich aromatic ring and an electrophilic transition metal catalyst. This unfortunately excluded the use of electron deficient arenes as substrates unless they carried a directing group, which installs the palladium next to the site of reactivity.

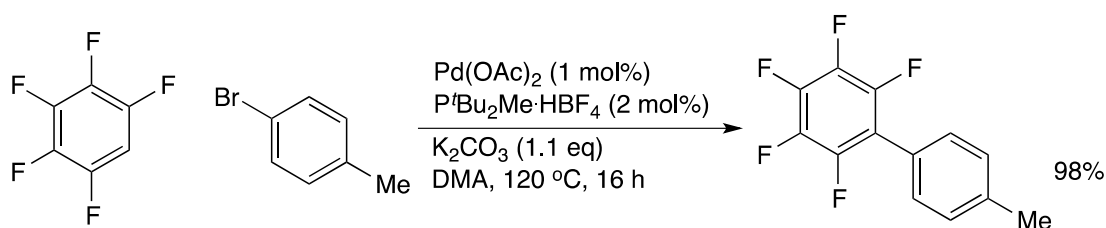
Fagnou *et al.* wanted to investigate the direct arylation of the challenging pyridine substrate by reporting on the coupling of pyridine-*N*-oxides with aryl bromides. The

direct arylation occurred in excellent yields and could tolerate both electron-withdrawing and -donating groups on both coupling partners. To investigate the mechanism they performed a competition experiment between 4-nitropyridine-*N*-oxide **17**, and 4-methoxypyridine-*N*-oxide **18**, with 4-bromotoluene under their standard reaction conditions. They only observed the reaction between the electron deficient pyridine-*N*-oxide **17** and bromotoluene, which was not consistent with the electrophilic aromatic substitution mechanism (Scheme 17).⁴⁹



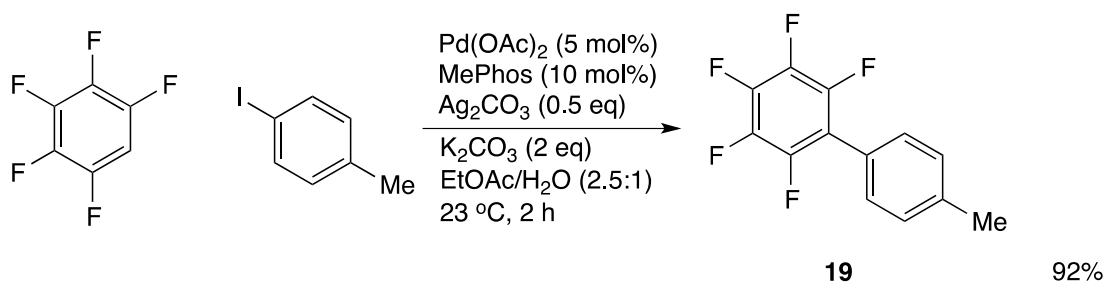
Scheme 17: Competition experiment between electron rich and electron poor pyridine-*N*-oxides

The following year, Fagnou's group proposed a CMD mechanism, which involved concerted arene metalation and proton abstraction as the key step. This mechanism shows opposite reactivity compared to the electrophilic aromatic substitution and was dependent on the acidity of the C-H bond. They could couple a range of fluorinated arenes with bromoarenes in good to excellent yields. The reaction time was increased when the palladium loading was dropped from 5 to 1 mol% (Scheme 18).⁵⁰



Scheme 18: Direct arylation of pentafluorobenzene with 4-bromotoluene

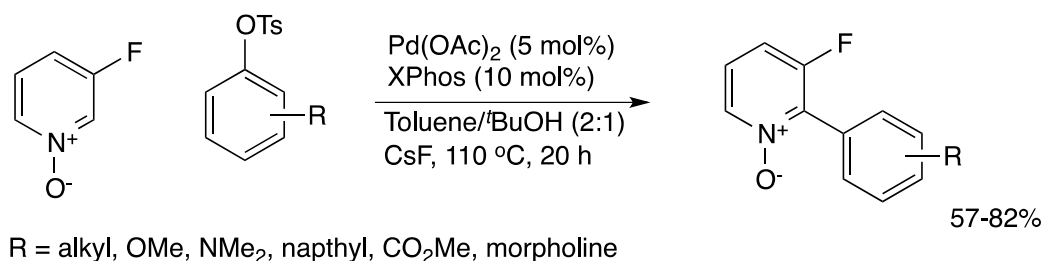
Even though Fagnou is recently deceased, his group continues to work and publish their research in this field. In one of the most recent papers they report the use of a biphasic solvent mixture in the direct arylation of polyfluorinated arenes. This enabled them to lower the temperature to room temperature compared to temperatures in excess of 100 °C for conventional solvents. They were the first to report on the direct arylation of electron deficient arenes under mild conditions and in aqueous media that allowed them to incorporate a range of substitution patterns on both coupling partners. The most remarkable example is the coupling of iodotoluene with pentafluorobenzene to yield the biaryl **19** in 92% in just 2 hours (Scheme 19). The requirement of an equivalent of silver was suggested to be that the silver(I) salt assists in the abstraction of the iodine ligand from the palladium(II) complex to yield the palladium intermediate.⁵¹



Scheme 19: Direct arylation of pentafluorobenzene with 4-iodotoluene at room temperature

As has been showed by this brief review, aryl halides are most commonly used as electrophilic coupling partners in direct arylations reactions. Aryl tosylates are generally not chosen, even though they are moisture-stable and easily accessible from phenols, due to their inherent stability. Ackermann and his group have developed a catalytic system for the direct arylation of electron deficient (hetero)arenes with aryl

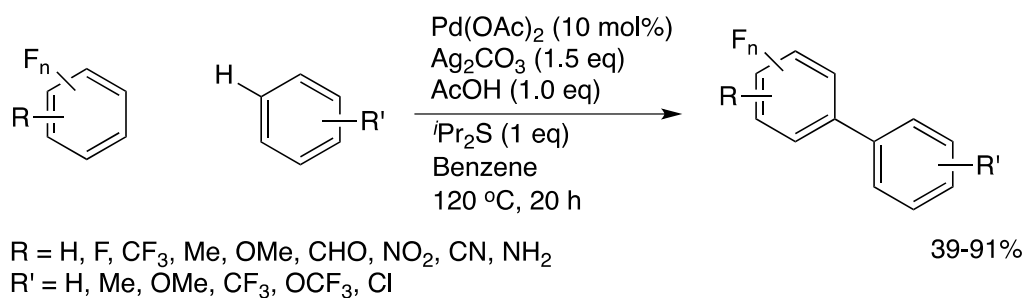
tosylates (Scheme 20). Ackermann's optimized system also proved compatible with the more atom economic aryl mesylates and showed that they could include alkenyl tosylates as coupling partners.⁵²



Scheme 20: Direct arylation of electron deficient pyridine-*N*-oxides with aryl tosylates

By changing the solvent system to a mixture of DMF and *tert*-butanol, and exchanging cesium fluoride for potassium carbonate they further broadened the scope of the reaction to include other heterocycles such as benzoxazoles, substituted oxazoles and triazoles.⁵³

Finally Shi and co-workers have reported on the palladium-catalyzed cross-coupling of polyfluorinated arenes and unactivated arenes, which builds on Fagnou's previous work.⁵⁴ They investigated additives, which would complement the oxidant. They started by adding stoichiometric amounts of DMSO and the desired product was observed in 39% yield. They chose DMSO as an additive since it has been reported to act as ligand to activate the palladium and prevent the formation of palladium black.⁵⁵ After further optimization they found that using diisopropyl sulfide led to complete conversion to the desired product (Scheme 21). They also performed experiments to elaborate on the mechanism, which was consistent with the concerted metalation-deprotonation mechanism previously reported by Fagnou.⁵⁶



Scheme 21: Direct arylation of pentafluorobenzene with unfunctionalized arenes

1.4.3 Direct Arylation of Heterocycles

An extensive volume of literature has been published in the area of C-H activation of heterocycles using indoles, pyrroles and pyridines.^{57,58} However, given the subject of this thesis, we are going to focus on the examples using other five membered heterocycles and other fused ring systems.

Unlike the intermolecular direct arylation of arenes, the inherent electronic bias of the heterocycle itself is often sufficient to control the regioselectivity of the direct arylation, rendering the need for directing groups unnecessary (Figure 2).²⁰

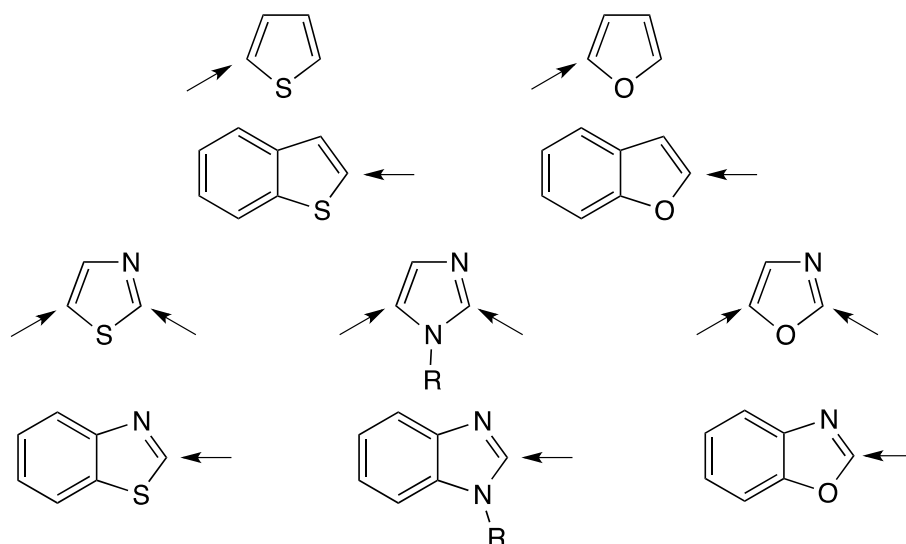
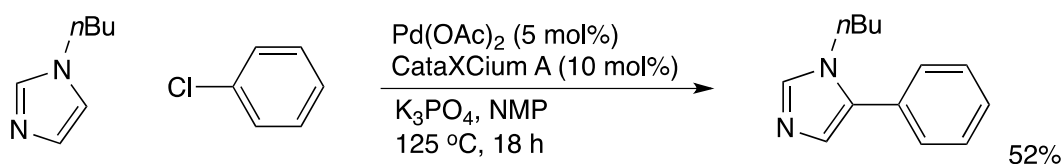


Figure 2: Favored sites for direct arylation of some common heterocycles.

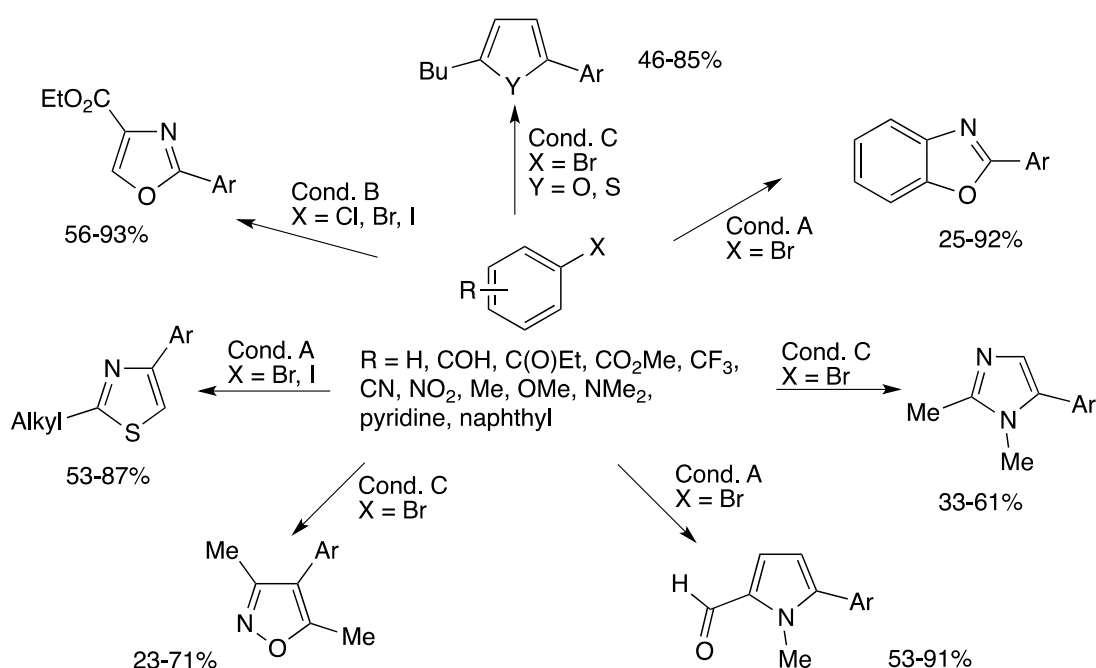
Daugulis' group has shown that they can couple a range of aryl chlorides with heterocycles including thiophenes, benzothiophenes, isoxazoles, benzofurans, benzoxazoles, benzothiazoles, thiazoles and imidazoles. They performed a preliminary mechanistic investigation, which suggested that coupling proceeds *via* an aromatic electrophilic substitution. This result is further supported by the regioselectivity of the *N*-butylimidazole arylation (Scheme 22).⁵⁹



Scheme 22: Direct arylation of *N*-butylimidazole with chlorobenzene

Doucet and co-workers demonstrated that it was possible to use green solvents such as diethyl carbonates in the direct arylation of heterocycles. For the direct arylation of substituted benzoxazole, oxazoles and thiazoles using aryl bromides as coupling partners, low catalyst loadings of 1 mol% were possible but it did require elevated

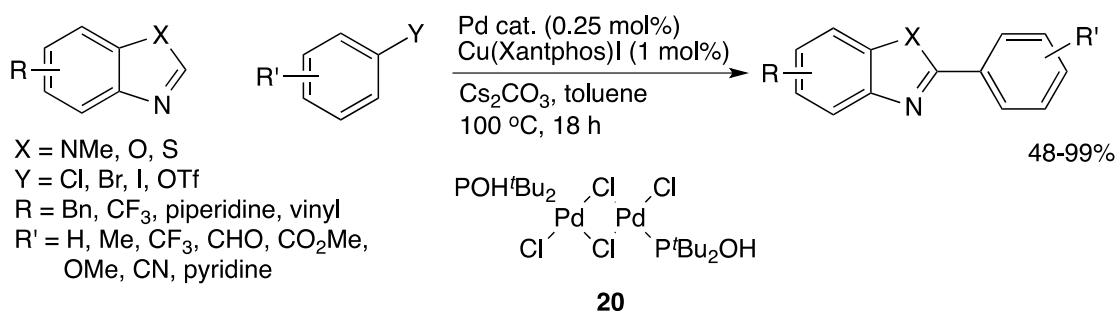
temperatures (Scheme 23). They had to further increase the temperature when they coupled furans, thiophenes, pyrroles, imidazoles and isoxazoles. The coupled heterocycles were all formed in good to excellent yields and a wide range of functional groups were tolerated. Most reactions occurred in the space of 18 hours, although some examples did require extended reaction times.⁶⁰



Scheme 23: Direct arylation of heterocycles using low catalyst loadings and green solvents according to Doucet.

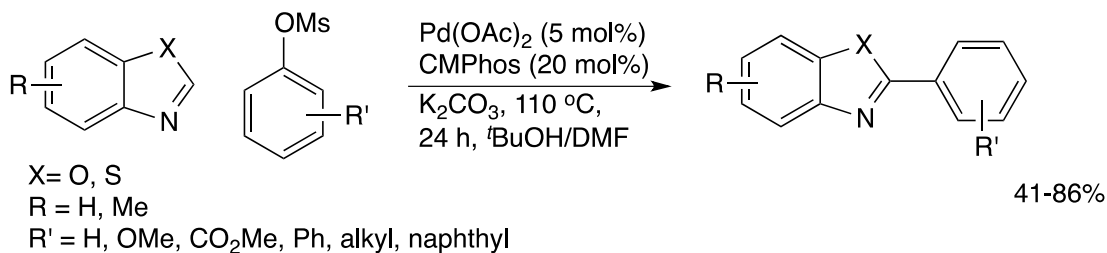
The Huang group have also contributed to the direct arylation of heterocycles, focusing specifically on low catalyst loadings. They can couple a large range of benzothiazoles as well as benzoxazoles and benzimidazoles with aryl halides or pseudohalides. The cross-coupling reaction could tolerate aryl chlorides, bromides,

iodides and triflates as the coupling partner. They also showed that bromopyridines can react under these conditions. The reaction required a co-catalytic system of palladacycle **20** and a copper Xantphos complex (Scheme 24).⁶¹



Scheme 24: Direct arylation of heterocycles using extremely low catalyst loadings

Lastly, Kwong's group showed it that is possible to directly arylate a range of heterocycles including benzoxazoles and benzothiazoles, as well as caffeine using aryl mesylates without the need for supplementary acids or copper salts (Scheme 25).⁶²

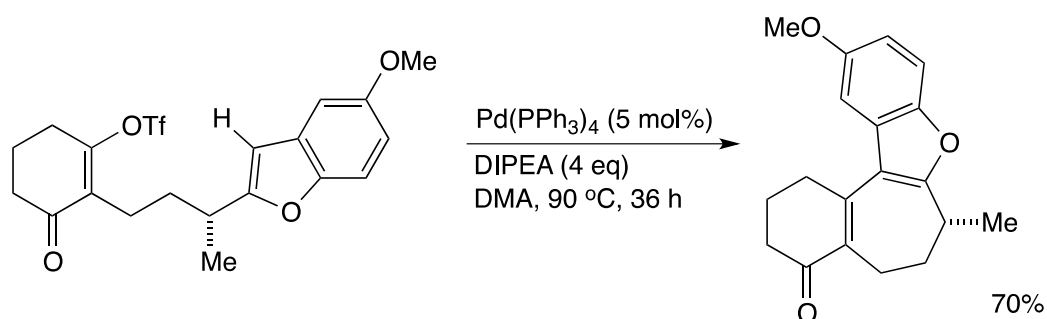


Scheme 25: Direct arylation of heterocycles with aryl mesylates

1.5 Alkenyl–Aryl Cross-Coupling

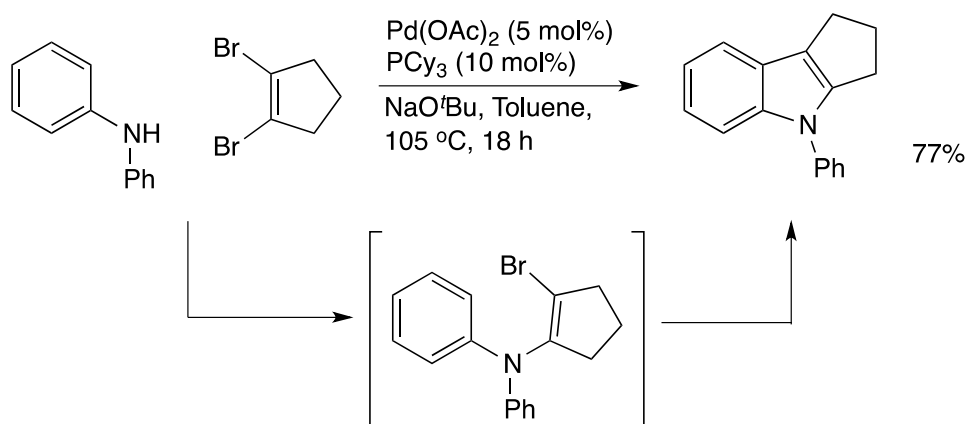
As demonstrated, much work has gone in to the development of aryl-aryl cross-coupling *via* C-H activation. The use of alkenyl halides or pseudohalides although not as common, is becoming more prevalent.

Trauner and co-workers used an intramolecular palladium-catalyzed direct alkenylation reaction as the key cyclisation step for the total synthesis of (–)-frondosin B. This novel approach allowed them to perform the key cyclization step in 70% yield with complete retention of stereochemistry (Scheme 26). They tried raising the temperature to shorten the reaction time, however when the temperature was increased, the *ee* of the product dropped to 86%.⁶³



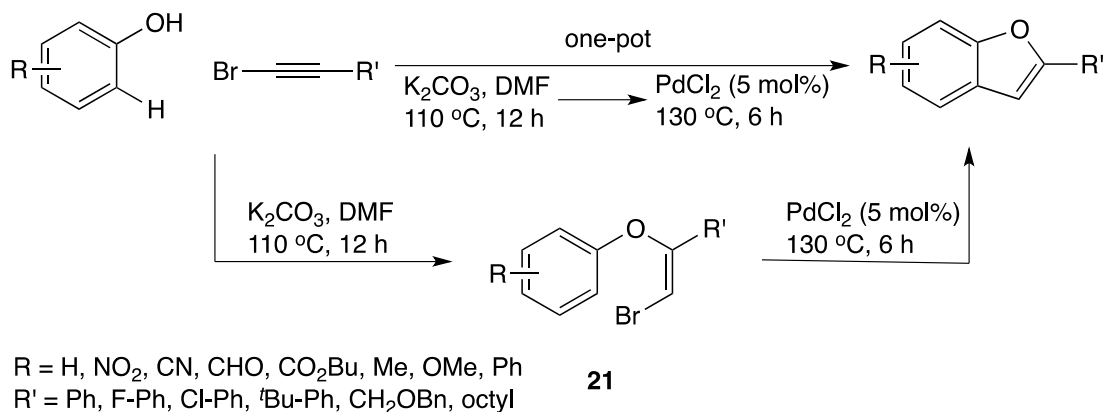
Scheme 26: Direct arylation as the key cyclization step in the synthesis of (–)-Frondosin B

Ackermann's group extended their synthesis of *N*-heterocycles using palladium-catalyzed direct arylation with aryl halides, to include one example of an alkenyl halide. They used a domino synthesis to access a range of substituted carbazoles and one indole. The first step is an intermolecular amination followed by an intramolecular direct arylation (Scheme 27).⁶⁴



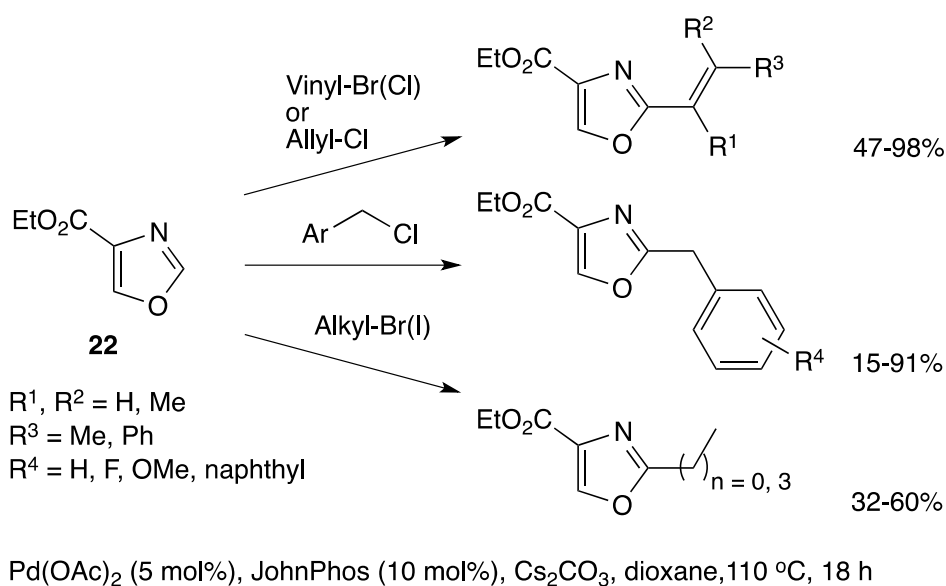
Scheme 27: Domino synthesis of indoles

Wang and co-workers reported the novel synthesis of benzofurans with a palladium-catalyzed C-H functionalization as the key ring forming step.⁶⁵ They found they could react simple phenols with bromoalkynes to generate (*Z*)-2-bromovinyl phenyl ethers **21** under metal free conditions. The (*Z*)-2-bromovinyl phenyl ethers were synthesized with excellent control of regio- and stereochemistry and in very good to excellent yields. During the optimization of the reaction they found that potassium carbonate can promote the addition of the alkyne as well as being the preferred base for the cross-coupling, so they investigated the possibility of a one-pot procedure. They found the reaction became more efficient when performed in a one-pot set up. For the synthesis of 5-nitro-2-phenylbenzofuran the overall yield for the two-step reaction was 86% whereas the one-pot reaction gave a 91% yield (Scheme 28). They proposed that the reaction proceeds *via* electrophilic aromatic substitution.



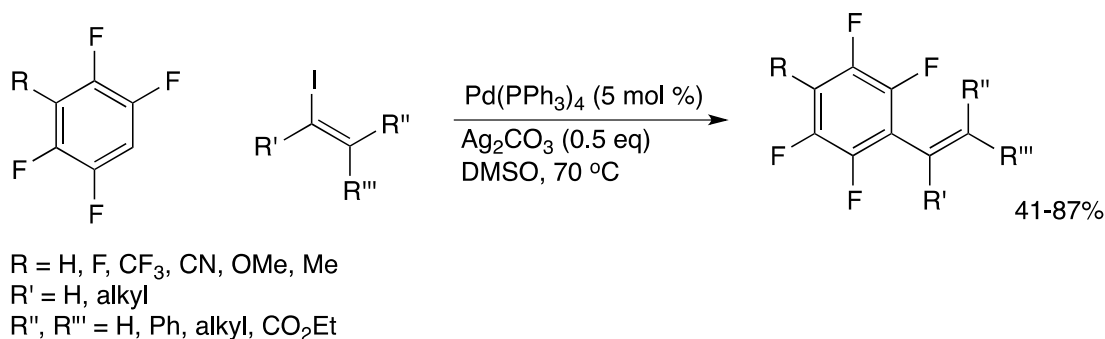
Scheme 28: Tandem and one-pot synthesis of substituted benzofurans

Hoarau *et al.* reported one of the first examples of intermolecular palladium-catalyzed direct C-H benzylation and alkylation of heteroaromatics. They described a regioselective coupling of ethyl oxazole-4-carboxylate **22** with alkenyl-, benzyl- and alkyl halides. Along with investigating the scope of the reaction they performed a small mechanistic study and concluded the reaction did not proceed *via* the anionic cross-coupling mechanism which would include a formal deprotonation of the C-2 position of the oxazole **22**. They proposed to undertake a further mechanistic study to determine which palladium-catalyzed pathway applied to their reactions (Scheme 29).⁶⁶



Scheme 29: Direct alkenylation of substituted oxazoles

Zhang and co-workers showed that it is possible to perform direct alkenylation of electron deficient polyfluoroarenes with alkenyl iodides using relatively mild conditions. The alkenylation was performed in good to excellent yields with both high yields and stereoselectivity (Scheme 30). The reaction can tolerate the change of one substituent on the aromatic ring including electron-donating and -withdrawing groups. The reaction also proceeded when tetrafluoropyridine was used as the coupling partner.⁶⁷

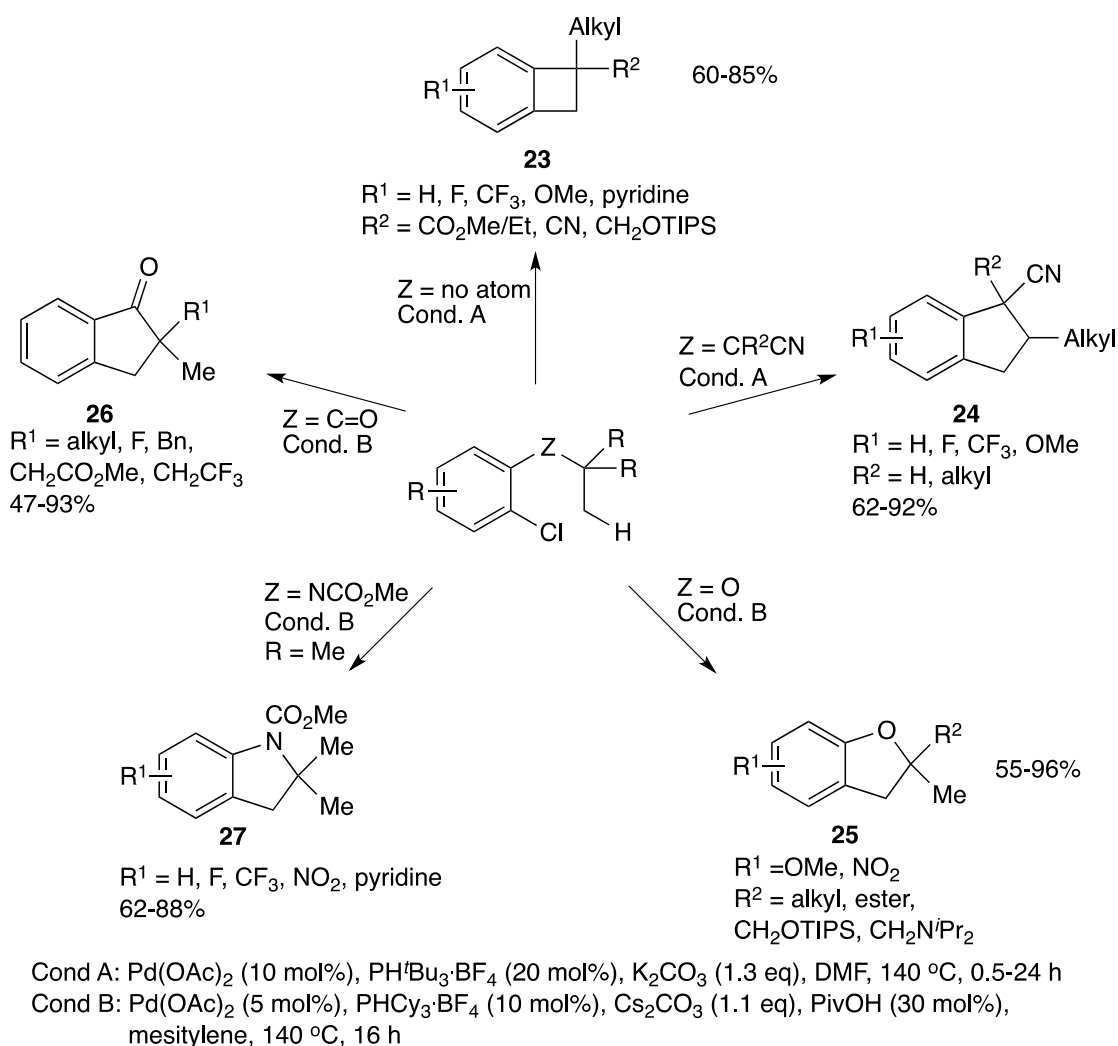


Scheme 30: Direct alkenylation of polyfluorobenzene

1.6 Alkyl-Aryl Cross-Coupling

Relatively little work has been reported in the area of aryl-alkyl bond formation *via* C-H functionalization compared to that of aryl-aryl and aryl-alkenyl. The main problem facing the use of alkyl species in palladium cross-coupling is the potential for an undesirable β -hydride elimination. These new approaches are more efficient and have better tolerance for functional groups compared to the traditional approach using Friedel-Crafts alkylation. The direct arylation does not require strong Lewis acids and works well for electron deficient arenes.

A collaboration between the groups of Clot, Fagnou and Baudoin to investigate and improve the scope of C(sp³)-H arylation was undertaken.⁶⁸ They wanted to investigate (hetero)aryl chlorides as only aryl bromides and iodides had been previously used. They also suggested that this would improve C-H arylation due to the reduction in steric hindrance. It was possible to access, using this methodology, a wide range of polycyclic molecules including cyclobutarenes, indanes, indolines, dihydrobenzofurans, and indanones (Scheme 31). During their research, they found that they could access different classes of molecules by altering the base and solvent. Cyclobutarenes **23** and indanes **24** required potassium carbonate in DMF. Dihydrobenzofurans **25**, indanones **26** and (aza)indolines **27** used cesium carbonate and pivalic acid in mesitylene. The mechanistic studies performed showed that all proceed *via* a base-assisted concerted metalation-deprotonation processes.

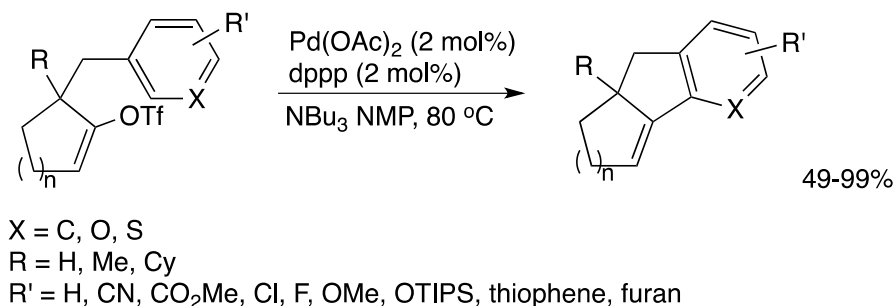


Scheme 31: Direct alkylation in the synthesis of polycyclic molecules

1.8 Previous Work in the Willis Group

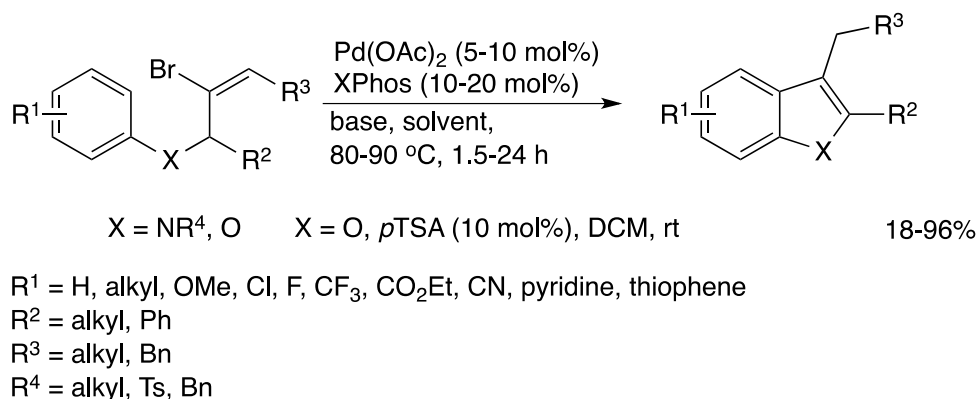
In the Willis group we have explored the intramolecular cross-coupling of alkenyl halides or pseudohalides *via* C-H functionalization and have shown that they can access a range of fused ring systems. Alkene-containing carbocycles can be formed by the direct arylation of alkenyl triflates.⁶⁹ The reaction could tolerate a range of substituents on the aromatic ring, including simple heterocycles (Scheme 32). The

initial mechanistic studies suggest that the reaction proceeds *via* either a σ -bond metathesis or concerted metalation-deprotonation mechanism.



Scheme 32: Synthesis of carbocycles *via* intramolecular C-H functionalization.

This work was extended to the synthesis substituted indoles and benzofurans.⁷⁰ The key step is a palladium-catalyzed intramolecular direct arylation followed by an isomerization to give the final aromatic compounds. The isomerization to form indoles occurred during the palladium coupling, but for the formation of benzofurans, the addition of *p*TSA was required. Both cross-coupling precursors could be synthesized from readily available starting materials and the palladium-catalyzed reaction could tolerate a wide range of substitution patterns (Scheme 33).

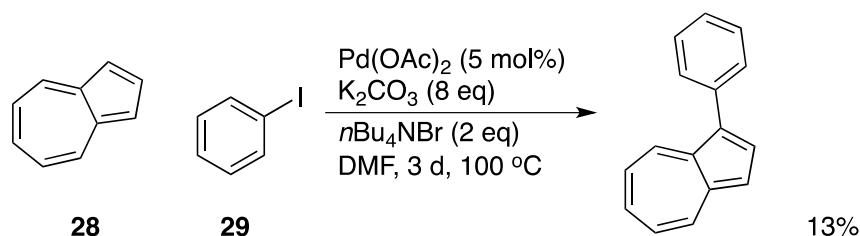


Scheme 33: Synthesis of indoles and benzofurans *via* intramolecular direct arylation

Chapter 2 Palladium Catalysed Cross-Coupling of Electron Deficient Arenes and Alkenyl Bromide

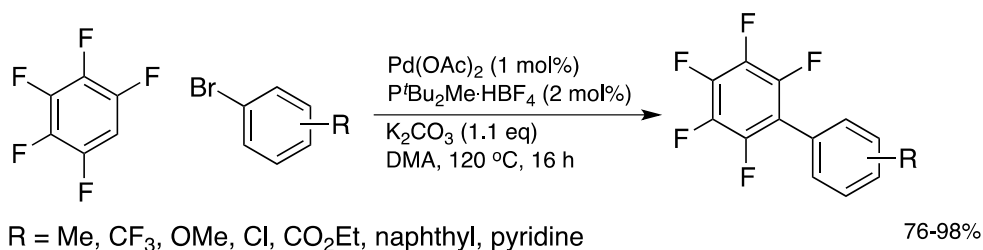
2.1 Introduction

Palladium catalysed cross-coupling reactions are very important in organic chemistry but they generally employ a metallic or pseudo metallic functional group like a boronic acid, as discussed in more detail in Chapter 1. Dyker *et al.* was one of the first to report a cross-coupling that did not use such an activating group (Scheme 34).⁷¹ The best yield, 13%, for the cross-coupling of azulene **28** and iodobenzene **29** was obtained under rather harsh conditions; 3 days at 100 °C, and with a vast excess of the iodobenzene. The result was still a breakthrough in the field but at the same time shows the difficulty of intermolecular coupling of unfunctionalized arenes.



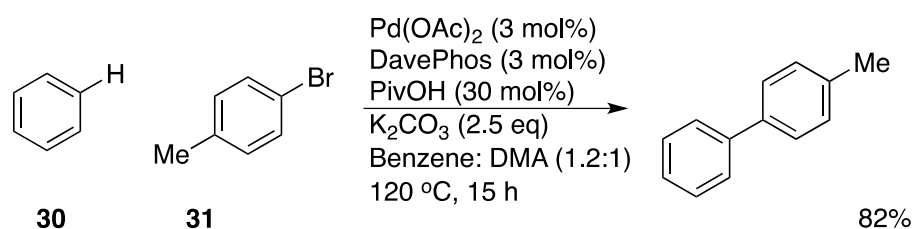
Scheme 34: Intermolecular cross-coupling by Dyker

Fagnou expanded the work of Dyker by achieving intermolecular direct arylation of pentafluorobenzene (Scheme 35). Mechanistic studies indicated that the catalytic cycle did not involve fluorine-catalyst interactions, suggesting that it was possible to use any electron deficient arene as coupling partner, as discussed in Chapter 1.⁵⁰



Scheme 35: Intermolecular direct arylation of pentafluorobenzene by Fagnou

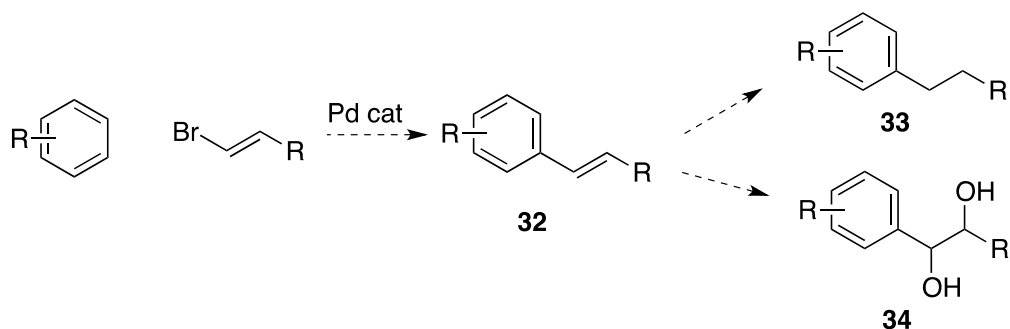
Fagnou's group managed to go one step further when they showed it was possible to couple benzene **30** with *para*-bromotoluene **31** (Scheme 36). Several modifications were made to the reaction conditions; the ligand was changed to DavePhos instead of P'Bu₂Me-HBF₄, but most importantly pivalic acid was used as an additive. The group tried a range of different carboxylic acid additives but none gave that same result. Mechanistic studies showed the importance of the pivalate anion as a proton shuttle from benzene to the base.⁵⁴ Even with an excess of benzene, 30 eq, and the high temperature, 120 °C, this progress was very promising for further investigation.



Scheme 36 Palladium-catalyzed benzene arylation by Fagnou

The goals for this project developed from the results above. The general aim for the project was to investigate the possibility of performing an intermolecular coupling of electron deficient arenes with alkenyl bromides. The coupled product **32** would then be reduced from the alkene to the alkane to give the Friedel-Crafts alkylation-type product **33** or oxidized to give the diol **34** (Scheme 37). Earlier work in the Willis

group has established that an intramolecular version of this process was viable.⁶⁹ In order to draw a direct correlation to Fagnou's work, we wanted to investigate the cross-coupling using alkenyl bromides.

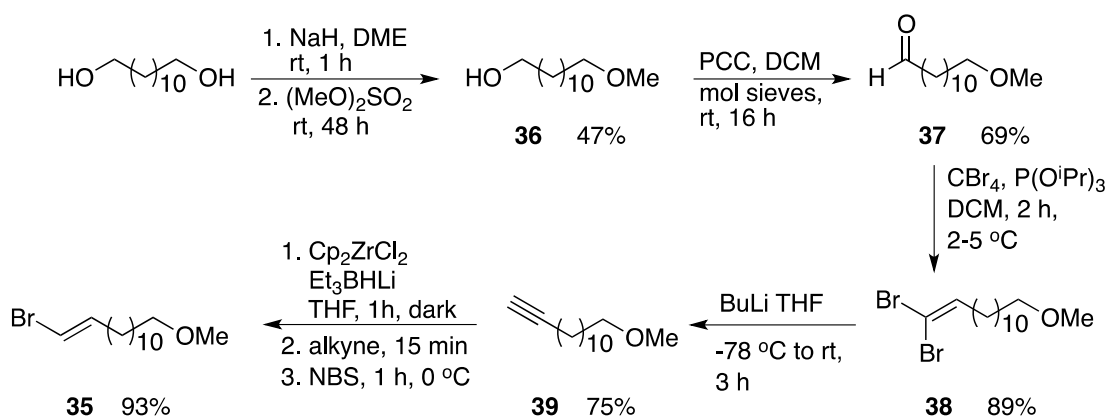


Scheme 37 General project aims

2.2 Synthesis of Alkenyl Bromide

The investigation started by synthesizing the unfunctionalized alkenyl bromide **35**. We chose this alkenyl bromide as it was non-volatile and contained a distinctive ¹H NMR indicator. This method was required because it was scalable and used relatively few steps. Importantly, it allowed the alkenyl bromide to be obtained as a single geometric isomer (Scheme 38). The synthesis of alkenyl bromide **35** started with 1,12-dodecanediol, which was mono-protected to give a 47% yield of 12-methoxydodecanol **36** as a white solid, using sodium hydride and dimethyl sulphate. The alcohol **36** was next oxidised to the aldehyde using PDC in DCM, producing the aldehyde as a white solid in 69% yield. Various other oxidation conditions were tried to improve the yield including TEMPO⁷², Parikh-Doering⁷³ and PCC.⁷⁴ We found that PCC gave the best yield on a small scale (86%) which was also reproducible on a multiple gram scale (76%). The aldehyde **37** was originally transformed to the *gem*-

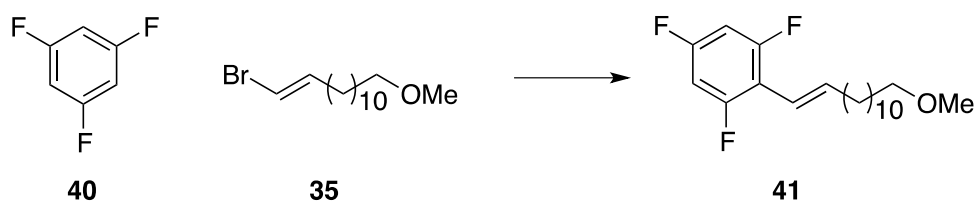
dibromide **38** using standard Corey-Fuchs conditions.⁷⁵ However, the reaction was modified employing Lautens conditions of triisopropyl phosphite, which avoided the formation of triphenylphosphine oxide, and thus work up and purification became quicker and easier.⁷⁶ The *gem*-dibromide **38** was subsequently converted to the alkyne **39** in a 75% yield. Originally, the alkenyl bromide **35** was prepared with an *in situ* formed Schwartz reagent using DIBAL, to transform the alkyne, which was achieved in a 66% yield of the *E* isomer.^{77,78} However, when the reaction was attempted on a larger scale (3 g) a significant amount of the terminal alkene was observed. Lipshutz's group found that using Superhydride[®] to form the Schwartz reagent gave the most consistent results.⁷⁹ They also found that the zirconium complex that is formed *in situ* is very light sensitive, so the reaction had to be performed in the dark. Finally, if the mixture was cooled 0 °C before the NBS was added the terminal alkene was not formed at all and the yield was increased to 93% of the single (*E*)-isomer.



Scheme 38: Synthesis of alkenyl bromide

2.3 Optimization of the Cross-Coupling Reaction

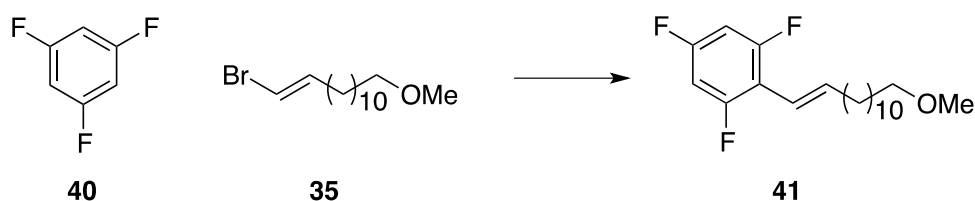
With the alkenyl bromide **35** in hand, we began to explore the cross-coupling reaction between polyfluorinated benzenes and alkenyl bromide and chose 1,3,5-trifluorobenzene **4** as the initial coupling partner. The reaction conditions used were identical to the ones reported by Fagnou, which were 5 mol% of palladium(II) acetate, 10 mol% of DavePhos, 30 mol% of pivalic acid, 2 equivalents of potassium carbonate in DMA at 120 °C for 16 h.⁵⁰ The first aspect of the reaction we wanted to investigate was the ligand. The ligands were chosen because they had previously been reported as performing well in C-H activation reactions.^{80,81} The use of simple phosphonium salts gave the desired product in 16% and 18% yield (Table 1, Entries 1-2). As for the more complex phosphine ligands, the use of SPhos resulted in a slightly higher yield of 26% (Entry 3), whereas when XPhos was used none of the coupled product was formed (Entry 4). However, when DavePhos was used as the ligand the coupled product was isolated in 34% yield (Entry 5). When the bidentate dppe ligand was used none of the desired product was observed (Entry 6). The initial reaction using PEPPSI showed a 35% conversion to the desired product (Entry 7). Therefore we continued to work with DavePhos and PEPPSI as they gave very similar results.

Table 1: Ligand screen

Entry	Ligand	Yield ^a	Entry	Ligand	Yield ^a
1	P ^t Bu ₂ Me·HBF ₄	16%	5	DavePhos	34%
2	P ^t Bu ₃ ·HBF ₄	18%	6	dppe	NR
3	SPhos	26%	7	PEPPSI	35%
4	XPhos	NR			

Alkenyl bromide (1 eq), arene (47 eq), Pd(OAc)₂ (5 mol%), ligand (10 mol%), PivOH (30 mol%), K₂CO₃ (2 eq), DMA (0.2 M), 120 °C, 16 h. ^aIsolated yields.

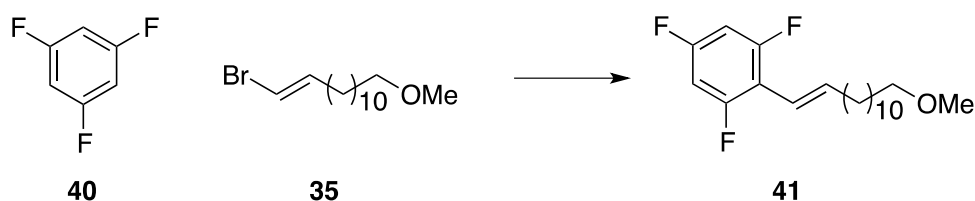
Based on this result we decided to perform an additive screen. Also, to make the reaction more efficient it would be essential to reduce the number of equivalents of arene used. In parallel with the additive screen we looked at reducing the amount of arene. The additive was changed from pivalic acid to cesium pivalate (Table 2), as cesium salts are known to have good solubility in organic solvents. Reducing the number of equivalents of arene (from 47 to 5) decreased the yields to 16% for the DavePhos and 11% for the PEPPSI reaction (Entries 1 and 2). However, when cesium pivalate was used with the reduced amount of arene no reaction was observed (Entry 3 and 4). As no reaction was observed when cesium pivalate was used, further reactions were carried out using pivalic acid.

Table 2: Additive screen

Entry	Ligand	Additive	Yield ^a	Entry	Ligand	Additive	Yield ^a
1	DavePhos	Pivalic acid	16%	3	DavePhos	Cesium Pivalate	NR ^b
2	PEPPSI	Pivalic acid	11%	4	PEPPSI	Cesium Pivalate	NR ^b

Alkenyl bromide (1 eq), arene (5 eq), Pd(OAc)₂ (5 mol%), ligand (10 mol%), additive (30 mol%), K₂CO₃ (2 eq), DMA (0.2 M), 120 °C, 16 h. ^aIsolated yields. ^bNo reaction

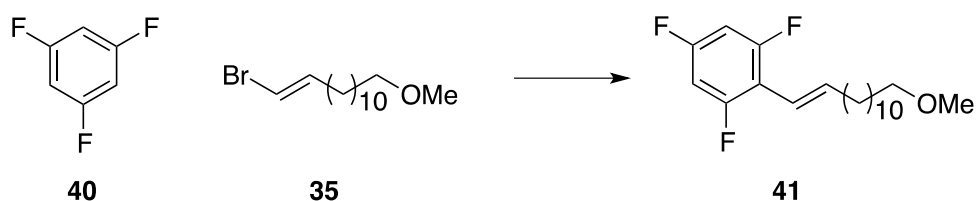
In an attempt to increase the yield, the reaction concentration was increased from 0.2 M to 2.0 M (Table 3). The ten-fold increase was chosen to ensure if any change was observed it would be due to the concentration. The reaction was performed again with both 47 and 5 equivalents of arene to get a full comparison of the effect of increasing concentration. When the reaction was performed with 47 equivalents of 1,3,5-trifluorobenzene a yield of around 13% for both DavePhos and PEPPSI was obtained (Entry 1 and 2). Similar to previous results, a drop in yield was observed when the amount of arene was reduced. Based on these results it was decided to carry out the remainder of the screening at 0.2 M.

Table 3: Concentration screen

Entry	Ligand	Eq of arene	Yield ^a	Entry	Ligand	Eq of arene	Yield ^a
1	DavePhos	47	14%	3	DavePhos	5	6%
2	PEPPSI	47	13%	4	PEPPSI	5	NR ^b

Alkenyl bromide (1 eq), arene, Pd(OAc)₂ (5 mol%), ligand (10 mol%), PivOH (30 mol%), K₂CO₃ (2 eq), DMA (2.0 M), 120 °C, 16 h. ^aIsolated yields. ^bNo reaction

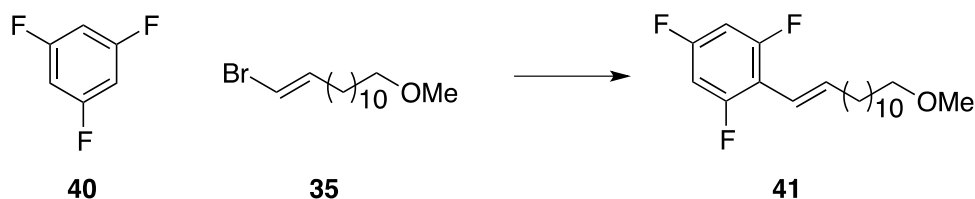
Due to the long reaction time and high temperature required, this reaction was an ideal candidate for using a microwave reactor. The reaction was tried at 10 min, 30 min and 1 hour at 120 °C using both DavePhos and PEPPSI ligands to find the optimum time for the reaction (Table 4). The best yield of 15% for the DavePhos reaction was observed after 30 min, which was only a small improvement on the 10 min reaction, but interestingly more than when it was heated for 1 hour (Entries 1-3). The same trend was seen for the reaction with PEPPSI. The best yield was 17% when the reaction was left for 30 min (Entries 4-6). Based on the above results it was decided to continue using the PEPPSI catalyst and carry out the reaction in a microwave, as both performed similarly to DavePhos.

Table 4: Reaction time screen

Entry	Ligand	Time in min	Yield ^a	Entry	Ligand	Time in min	Yield ^a
1	DavePhos	10	13%	4	PEPPSI	10	16%
2	DavePhos	30	15%	5	PEPPSI	30	17%
3	DavePhos	60	9%	6	PEPPSI	60	11%

Alkenyl bromide (1 eq), arene (5 eq), $\text{Pd}(\text{OAc})_2$ (5 mol%), ligand (10 mol%), PivOH (30 mol%), K_2CO_3 (2 eq), DMA (0.2 M), 120 °C. ^aIsolated yields.

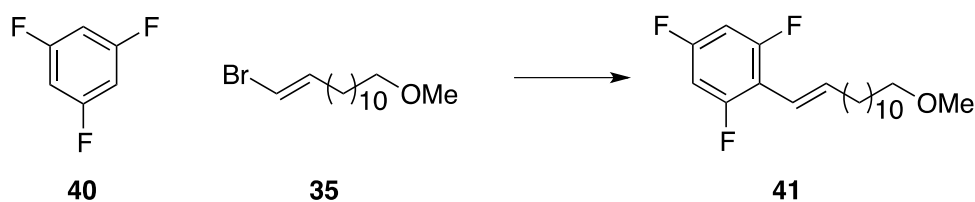
A variety of solvents have been reported in C-H functionalization reactions but the most common are DMF, dioxane and toluene.^{82,83} When the PEPPSI reaction was tried with DMF only a trace amount of product was observed (Table 5, Entry 1). When dioxane was used the coupled product was isolated in 7% yield (Entry 2). However, no reaction was observed when toluene was used as a solvent (Entry 3). Therefore, further reactions were carried out in DMA.

Table 5: Solvent screen

Entry	Solvent	Yield ^a	Entry	Solvent	Yield ^a
1	DMF	Trace Product ^b	3	Toluene	NR ^c
2	Dioxane	7%			

Alkenyl bromide (1 eq), arene (5 eq), Pd(OAc)₂ (5 mol%), PEPPSI (10 mol%), PivOH (30 mol%), K₂CO₃ (2 eq), solvent (0.2 M), 120 °C, 30 min, μ w. ^aIsolated yields. ^bLess than 5%. ^cNo reaction

During the initial ligand screen only one *N*-heterocyclic carbene ligand (NHC) was tested, PEPPSI, which gave one of the best results, so we wanted to test a few more commercial NHC ligands (Table 6). The experiments showed a small increase when SIPr ligand was used compared to PEPPSI (Entry 1). However, more surprisingly the other NHC ligand, SIMes, only gave a yield of 9% (Entry 2).

Table 6: Ligand screen

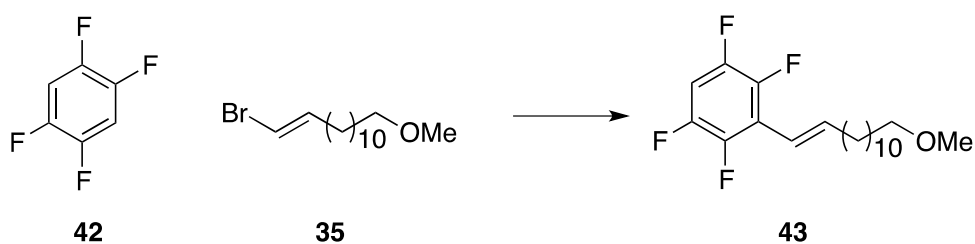
Entry	Ligand	Yield	Entry	Ligand	Yield
1	SIPr HBF ₄	19%	2	SIMes HBF ₄	9%

Alkenyl bromide (1 eq), arene (5 eq), Pd(OAc)₂ (5 mol%), ligand (10 mol%), PivOH (30 mol%), K₂CO₃ (2 eq), DMA (0.2 M), 120 °C, 30 min, μ w ^aIsolated yields.

The reaction was next performed with 1,2,4,5-tetrafluorobenzene to see if the low yield was due to the 1,3,5-trifluorobenzene being a poor coupling partner. Interestingly, the yield increased to 29%. Taking in to account this result, further investigation of the reaction was performed with 1,2,4,5-tetrafluorobenzene instead of 1,3,5-trifluorobenzene.

Since the optimization had not led to any great improvement of the yield it was decided to perform a series of control experiments and to investigate the effect of the individual components within the reaction. The reaction was first tried without any base, and only alkenyl bromide was recovered. The same was the case when the reaction was tried without palladium and ligand. However, a very interesting result was found when the reaction was performed with palladium but no ligand. The reaction gave the coupled product in a 26% yield compared to 29% yield when ligand was used. In light of the result it was decided to investigate if altering the palladium source would have a positive effect on the yield of the reaction.

For this screen a selection of palladium(II) sources were tried as well as one palladium(0) source (Table 7). Bis(acetonitrile)dichloropalladium(II) and palladium(II) dichloride both gave yields similar to that of palladium(II) acetate (Entries 1-2). However, using bis(dibenzylideneacetone)palladium(0) decreased the yield to 17% (Entry 3). The best result from the palladium screen was observed when (2-methylallyl)palladium(II) chloride dimer was used. The yield increased by 10%, to give the best yield observed throughout the optimisation process (Entry 4).

Table 7: Palladium source screen

Entry	Palladium Source	Yield ^a	Entry	Palladium Source	Yield ^a
1	Pd(MeCN) ₂ Cl ₂	21%	3	Pd(dba) ₂	17%
2	PdCl ₂	24%	4	[Pd(C ₃ H ₅)Cl] ₂	39%

Alkenyl bromide (1 eq), arene (5 eq), Pd source (5 mol%), PivOH (30 mol%), K₂CO₃ (2 eq), DMA (0.2

M), 120 °C, 30 min, μ w. ^aIsolated yields.

With the positive result from the palladium screen it was decided to investigate other arenes as coupling partners (Table 8). From the arene screen it can be seen that the more acidic the proton on the arene, the better the yield is for the coupling reaction. The best yields of 39% and 32% were seen with tetrafluorobenzene and pentafluorobenzene, respectively (Entries 1-2), followed by the trifluorinated benzenes with yields around 18% (Entries 3-4). When the difluorinated arenes were used only a trace of coupled product was observed (Entries 5-7). When the reaction was tried with the electron-rich 1,4-dimethoxybenzene none of the coupled product was observed (Entry 8).

Table 8: Arene screen

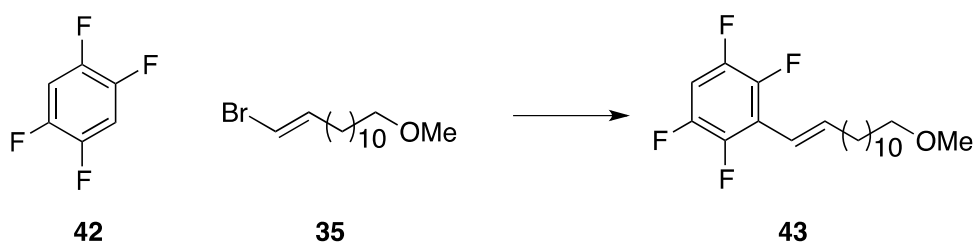
Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 44	32%	5		Trace product ^b
2	 43	39%	6		Trace product ^b
3	 41	18%	7		Trace product ^b
4	 45	16%	8		NR ^c

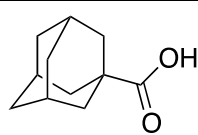
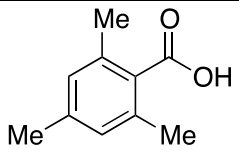
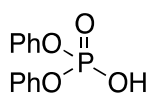
Alkenyl bromide (1 eq), arene (5 eq), [Pd(C₃H₅)Cl]₂ (2.5 mol%), PivOH (30 mol%), K₂CO₃ (2 eq), DMA (0.2 M), 120 °C, 30 min, μ w. ^aIsolated yields. ^bLess than 5%. ^cNo reaction.

In the hope of further increasing the yield of the reaction, it was decided to do a further additive screen, but this time looking at other bulky carboxylic acids. Ackermann's group showed, in their work with ruthenium catalyzed direct alkylation of arenes with unactivated alkyl halides through C–H bond cleavage, that even without the use of

ligands the desired product could still be formed.⁸⁴ Instead of using a ligand, they employed a co-catalytic system similar to the one we have used. They found that the best results were seen when bulky acids like 1-adamantanecarboxylic acid, 2-mesitylenecarboxylic acid and diphenyl phosphate were used. Unfortunately, changing the additive did not improve our reaction compared to the use of pivalic acid (Table 9). When 1-adamantanecarboxylic acid, 2-mesitylenecarboxylic acid were used the yield of the coupled product was around 20% and when diphenyl phosphate was used only starting material was recovered.

Table 9: Additive screen



Entry	Additive	Yield ^a	Entry	Additive	Yield ^a	Entry	Additive	Yield ^a
1		20%	2		17%	3		NR ^b

Alkenyl bromide (1 eq), arene (5 eq), [Pd(C₃H₅)Cl]₂ (2.5 mol%), additive (30 mol%), K₂CO₃ (2 eq), DMA (0.2 M), 120 °C, 30 min, μ w. ^aIsolated yields. ^bNo reaction.

2.4 Design of Experiment

Since we had not been able to increase the yield of the coupled product to a satisfactory level using conventional optimization methods we decided to investigate the using of a statistical approach. This approach is called statistical factorial design,

which makes it possible to investigate the interaction between several variables (e.g. time or temperature) simultaneously. These variables are generally referred to as factors. The factorial design has many advantages over the standard ‘one-factor-at-a-time’ (OFAT) approach. The statistical analysis allows for the creation of a multidimensional design space rather than a two-dimensional space created from the information obtained from the ‘OFAT’ approach (Figure 3). The statistical approach creates a reaction space, which is represented by the cube, and it can predict the reaction outcome for any point in that reaction space. Although, for the OFAT approach the reaction space cannot be extrapolated and results can only be found on the arrows drawn. The factorial design is more efficient as fewer experiments are required to obtain the same information. Finally, factorial design can extrapolate the interaction between the different factors, which can be key to the understanding of complex processes. Factorial design generally consists of factors which can be associated with a high or low level, which is known as a two-level factorial design, for example changing the temperature from 90 °C to 150 °C.⁸⁵

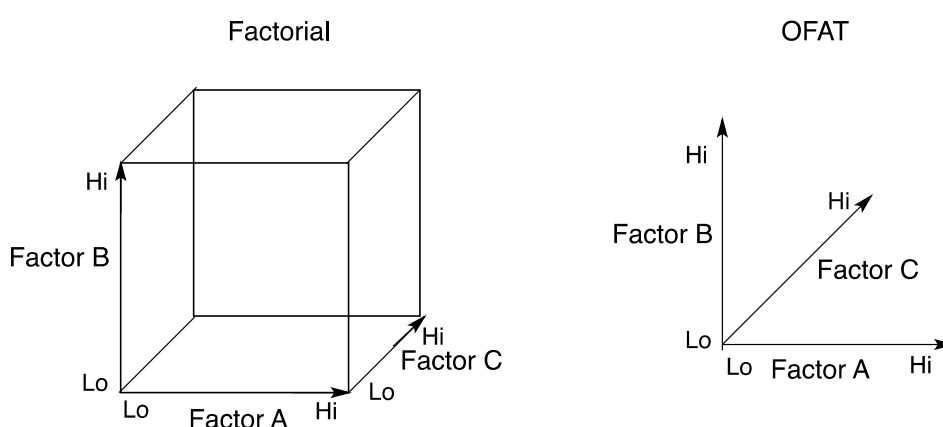


Figure 3: Factorial design vs ‘OFAT’

A full factorial design, where all the combinations of factors are investigated, would allow for the estimate of all main interactions as well as two and three way interactions. A two-way interaction describes the relationship between two factors and how that can affect the outcome of the reaction, for example increasing the temperature might reduce the reaction time required. However, the number of experiments would increase exponentially with the number of factors (n) according to 2^n .

2.4.1 Fractional Factorial Design

A fractional factorial design is an experimental design which only includes a subset of all possible combinations of factor levels. Rather than using a full factorial design, we used a fractional factorial design, which significantly reduced the number of experiments required, as we wanted to investigate six separate factors. The fractional factorial design assumes the main factors (e.g. A: time, B: temperature, C: base eq) and the two-way interactions (e.g. AB: time-temperature, AC: time-base eq, BC: temperature-base eq) are of greatest importance and three way interactions (e.g. ABC: time-temperature-base eq) are eliminated. The loss of resolutions leads to the combination of factors, which are known as sum of effects (e.g. $[A] = A + ABC$). As we used a design involving six factors, higher interactions are possible but they are deemed statistically insignificant. Fractional factorial design is therefore generally used for screening, with the possibility of further investigation.

There are three levels of fractional factorial design, which are used to describe the level of interactions resolved and the number of experiments required increase with each design. These definitions are specific for our software.

Red design (8 experiments for investigating 6 factors)

Main factors are combined with two factor interactions.

$$[A] = A + AB$$

Amber design (16 experiments for investigating 6 factors)

Main factors are combined with three-way interaction. Some two-way interactions are combined with other two-factor interaction.

$$[A] = A + ABC \quad [AB] = AB + CD$$

Green design (32 experiments for investigating 6 factors)

All main and two-way interactions are separately expressed. Some three-way interactions are combined with two-way interactions.

$$[A] = A \quad [AB] = AB \quad [ABC] = ABC + DE$$

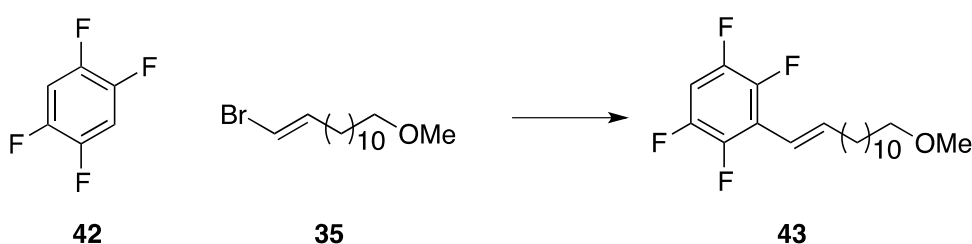
Full design (64 experiments for investigating 6 factors)

All factors and multi-way interactions are separately expressed.

The red design is generally not used as two-way interactions are often important in complex systems and significant interaction can easily be overlooked. The amber design is very useful as two-way interactions are separated from the main factors but it has to be kept in mind that the two-way interactions can represent several interactions. The green design is the most detailed as both main and two-way interactions are separated.

2.4.2 Design parameters

For the design we investigated the coupling between alkenyl bromide **35** and 1,2,4,5-tetrafluorobenzene **42** (Scheme 39). We decided to use an amber design as we hoped it would provide enough information to improve our understanding of the coupling reaction and it was the best compromise between experiments needed and information gained.



Scheme 39: Cross-coupling reaction investigated using DoE

We decided to investigate 6 factors and by using the amber design, we reduced the number of experiments to 16 compared to 64 for a full factorial design. The parameters for the design can be found in Table 10. All the experimental details and results can be found in the appendix. The range for the factors were chosen so to investigate the reaction space around which all OFAT optimization had been done.

Table 10: Parameters for first design

Entry	Factor	Minimum	Maximum
A	Time (min)	15	45
B	Temperature (°C)	90	150
C	Base equivalence	1.5	3.5
D	Arene equivalence	3	5
E	Pivalic acid equivalence	0.1	0.5
F	Volume (mL)	0.96	4.8

Alkenyl bromide (1 eq), arene, $[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2]$ (2.5 mol%), PivOH, K_2CO_3 , DMA (0.2 M), μw .

2.4.3 Results of Amber Design

The data was analysed using State-Ease DX7.⁸⁶ The software enabled us to process the data according to two parameters: yield and residual alkenyl bromide, which is labelled impurity. This would also give us information about the potential decomposition of the alkenyl bromide. The values were interpreted from HPLC analysis. The first step in analysing the data was done using a half-normal plot. The half-normal plot displays which factors are statistically significant. The factors that fall on the straight line represent normal scattering and are used to estimate error for the analysis of variance (ANOVA). The factors, which are significant, do not fall on the straight line drawn. The main factors which influence the yield are the temperature, base and equivalents of pivalic acid as well as some two-way interactions. Fewer factors affect the amount of alkenyl bromide present at the end of the reaction, mainly temperature and equivalents of base (Figure 4). The further the factors fall from the straight line, the greater the effect is on the outcome of the reaction.

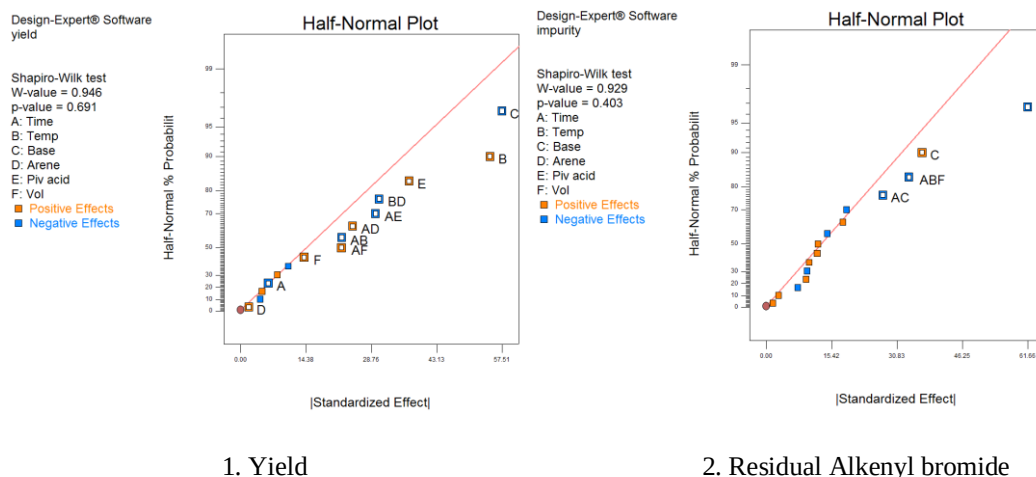


Figure 4: Half-normal plot for the design

For further analysis of the results, we specified the parameters to maximize the yield and minimize the amount of alkenyl bromide at the end of the reaction. The statistical result suggested that the previous reaction conditions were not optimal and it would be possible to improve the outcome of the reaction (Figure 5). The graphs are colour coded; red indicates highest yield and blue is for the lowest yield.

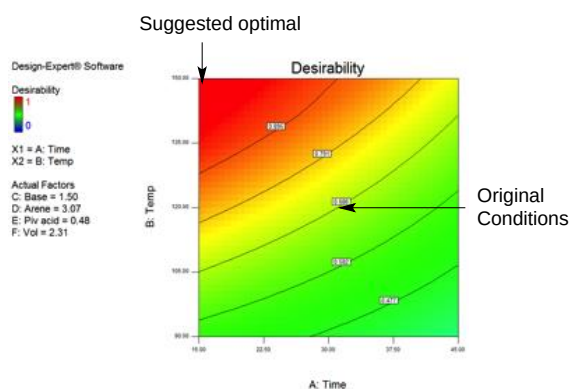
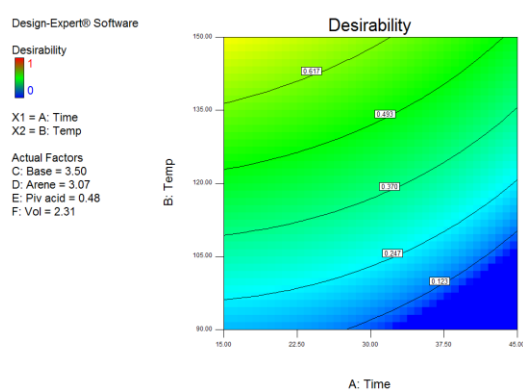
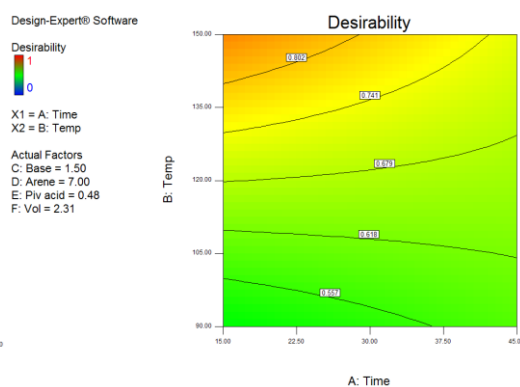


Figure 5: Optimal statistical conditions

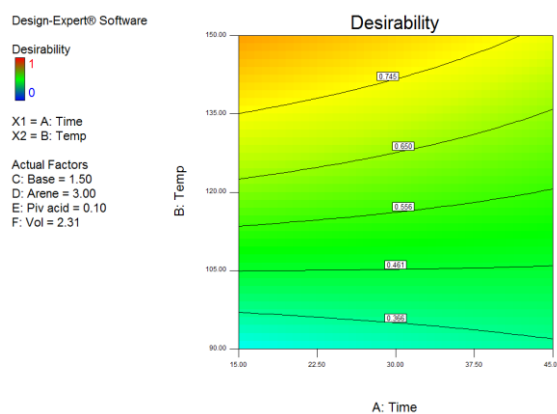
As predicted by the half-normal plot the amount of base should have the biggest impact on the outcome of the reaction. When the equivalents of base were increased to 3.5 from the optimized 1.5 equivalents, the yield drops dramatically over the temperature range (Figure 6.1). On the other hand, increasing the amount of arene and decreasing the pivalic acid from the optimized conditions reduced the yield of the reaction over the temperature range (Figure 6.2 and 6.3).



6.1 Base



6.2 Arene

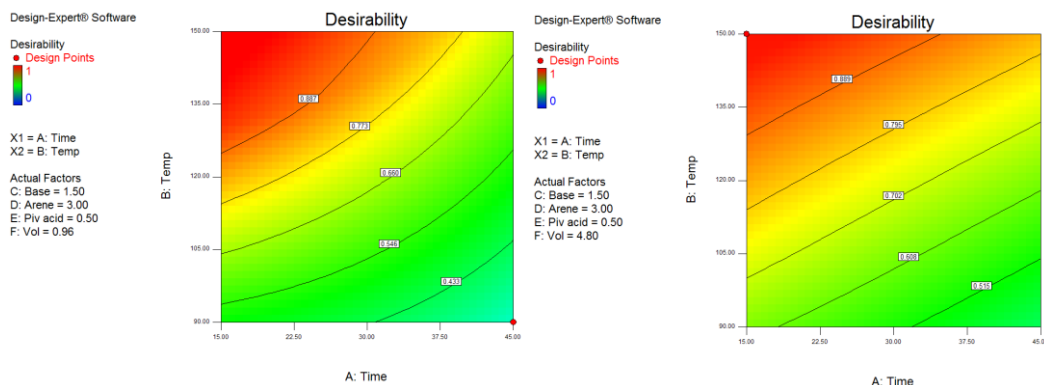


6.3 Pivalic acid

Figure 6: Effects of altering various factors

We were surprised that the concentration had little to no effect on the outcome of the reaction as that normally plays an important role in catalysis. The graphs show little to

no change when concentration is changed from maximum to minimum (Figure 7.1 and 7.2).



7.1 Maximum concentration

7.2 Minimum concentration

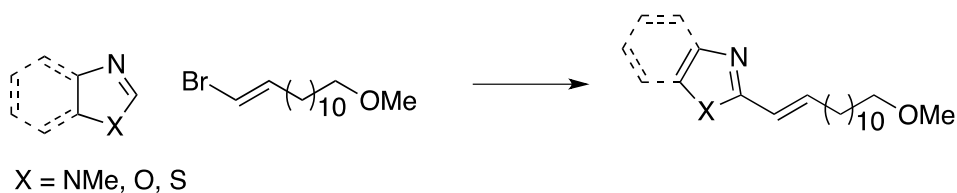
Figure 7: Effect of concentration

The cross-coupling reaction was tried again with the new conditions identified by the DoE results as optimal conditions (Table 11). We wanted to investigate if it would be possible to further increase the yield by 30% as was indicated by Figure 3. Unfortunately, when the cross-coupling reaction was tried under the new conditions, no improvement in yield was observed and the coupled product was still only isolated in 40% yield. We cannot account for the big discrepancy from the HPLC conversion to the isolated yield. Purification issues and potential lack of stability of the final compound could explain the lack of improvement.

Table 11: Conditions for coupling reaction

Entry	Factor	Improved conditions
A	Time (min)	15
B	Temperature (°C)	150
C	Base equiv.	1.5
D	Arene equiv.	3
E	Pivalic acid equiv.	0.5
F	Volume (mL)	2.4

We decided to investigate alternative coupling partners for the reaction, since the yield, when coupling with perfluorinated benzene rings, had not yet proved satisfactory. The reaction was tried with a range of heterocycles but unfortunately all of the reactions were unsuccessful (Table 12). The heterocycles were selected based on having similar pKa values to tetrafluorobenzene. The pKa values were predicted by Guo's group as a result of computational studies.⁸⁷

Table 12: Cross-coupling with alkenyl bromide **35** and heterocycles

Entry	Product	Yield	Entry	Product	Yield
1		NR ^a	5		NR ^a
2		NR ^a	6		NR ^a
4		NR ^a	7		NR ^a

Alkenyl bromide (1 eq), arene (3 eq), [Pd(C₃H₅)Cl]₂ (2.5 mol%), PivOH (50 mol%), K₂CO₃ (1.5 eq), DMA (0.2 M), 150 °C, 15 min, μ w. ^aNo reaction

2.5 Conclusion

During the investigation of the cross-coupling of electron deficient arene and alkenyl bromides we tried to optimize the reaction looking at individual components such as time, temperature, palladium source, additive and solvents. We also used Design of Experiment in an attempt to achieve a better understanding of the reaction. Unfortunately, we never managed to synthesize the cross-coupled product in greater than 40% yield. We also investigated a small range of heterocycles as coupling partners for the alkenyl bromide, and again they all proved unsuccessful. The one

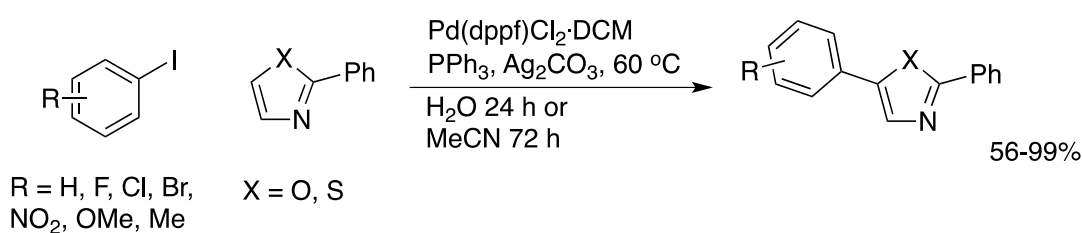
interesting discovery was that the cross-coupling reaction did not require any phosphine ligand to proceed. This could be explained by the presence of pivalic acid which can act as a ligand.

Chapter 3 Palladium-Catalyzed Direct Functionalization of Heteroarenes with Alkenyl Iodides

3.1 Introduction

C-H functionalization using alkenyl or alkyl halides has emerged over the last few years as a prominent area of research, as discussed in Chapter 1. We were particularly interested in the functionalization of heteroarenes.

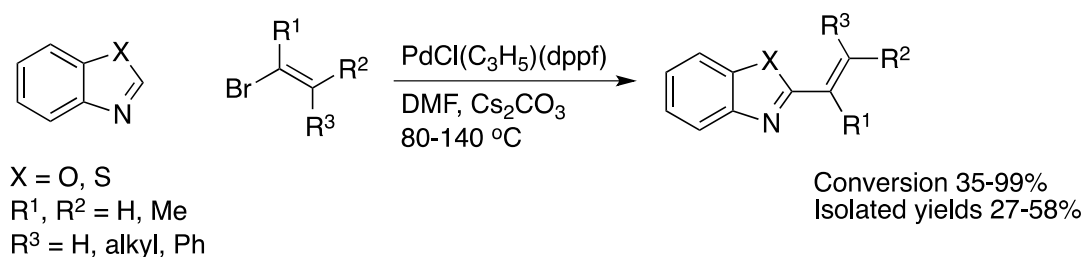
Greaney's 'on water' approach to the synthesis of substituted oxazoles represented a significant advance, as it showed that direct arylation of heterocycles is possible under mild conditions. This methodology tolerates a broad range of heterocycles and uses a commercially available catalyst. The only drawback with this system is that reaction times varied from 24 – 72 hours depending on the solvent used (Scheme 40).^{88,89}



Scheme 40: Direct arylation of heteroarenes

Also of interest was a paper by the Doucet group where they successfully coupled alkenyl bromides with benzoxazoles and benzothiazoles *via* palladium-catalyzed C-H functionalization; this was one of the first examples of alkylation of heterocycles. Even at high temperatures their catalyst system required extended reaction times. They also

reported problems with the isolation of their final product, which led to a large discrepancy between conversions and isolated yields (Scheme 41).⁹⁰

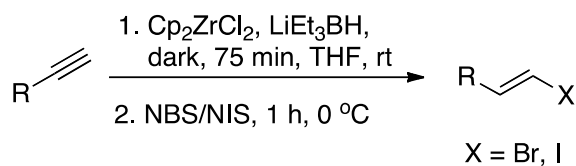


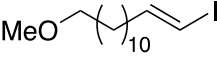
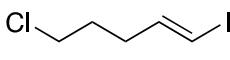
Scheme 41: Direct alkenylation of heteroarenes

We wanted to investigate the possibility of developing a catalytic system for the functionalization of heteroarenes with alkenyl halides that would be reactive enough to minimize reaction times. We also wanted a catalytic system that could tolerate a range of functional groups for the cross-coupling of heteroarenes with alkenyl halides.

3.2 Alkenyl Halide Synthesis

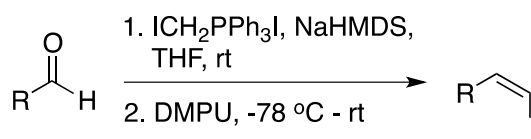
Given that we wanted to study the cross-coupling between alkenyl halides and various heteroarenes, we needed ready access to a range of alkenyl halide substrates. We wanted both (*E*) and (*Z*) disubstituted alkenes and cyclic examples. We found that the (*E*)-alkenyl halides could be accessed from commercially available or easily accessible alkynes. The alkynes were treated with *in situ* generated Schwartz reagent.⁷⁹ The zirconylated species were trapped with either NBS or NIS to yield alkenyl bromides or iodides, respectively. All of the alkenyl halides were synthesized in good to excellent yields (Table 13). We only observed the (*E*)-isomer of the synthesized alkenes according to ¹H NMR spectroscopy.

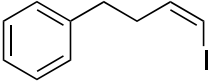
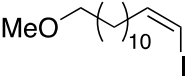
Table 13: Synthesis of (*E*)-alkenyl halides

Entry	Arene	Yield ^a	Entry	Arene	Yield ^a
1	 46	79%	3	 48	90%
2	 47	86%	4	 49	73%

Alkyne (1 eq), *bis*(cyclopentadienyl)zirconium(IV) dichloride (1.5 eq), Superhydride (1.5 eq), NBS or NIS (1.5 eq). ^aIsolated yields.

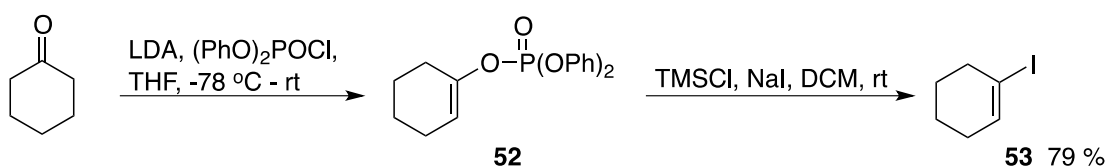
The corresponding (*Z*)-alkenyl iodides were synthesized from the corresponding aldehydes *via* a Wittig reaction.⁹¹ (Iodomethyl)trimethylphosphonium iodide was used to generate the corresponding phosphonium ylide, which reacted with the aldehyde to generate the (*Z*)-alkenyl iodides in good to excellent yields, with the generation of phosphine oxide by-product (Table 14). Only the (*Z*)-isomer was isolated of the alkenyl iodides synthesized and only the (*Z*)-isomer could be detected by proton NMR spectroscopy.

Table 14: Synthesis of (*Z*)-alkenyl iodides

Entry	Arene	Yield ^a	Entry	Arene	Yield ^a
1	 50	98%	2	 51	80%

Aldehyde (1 eq), (iodomethyl)trimethylphosphonium iodide (1.5 eq), NaHMDS (1.4 eq), DMPU (7.5 eq). ^aIsolated yield.

A different approach was used for the synthesis of 1-iodocyclohexene **53** (Scheme 42). Cyclohexanone was treated with LDA and diphenyl phosphorochloridate to form the enol phosphate **52**. This compound was subsequently treated with TMSI, generated *in situ* from TMSCl and sodium iodide.^{92,93} 1-Iodocyclohexene **53** was synthesized in 79% yield over the two steps.

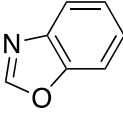
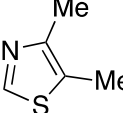
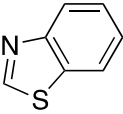
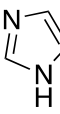
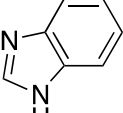
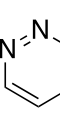
**Scheme 42:** Synthesis of 1-iodocyclohexene

With a range of alkenyl halides in hand, we investigated the coupling of these compounds with a range of heterocycles.

3.3 Initial Screen and Optimization

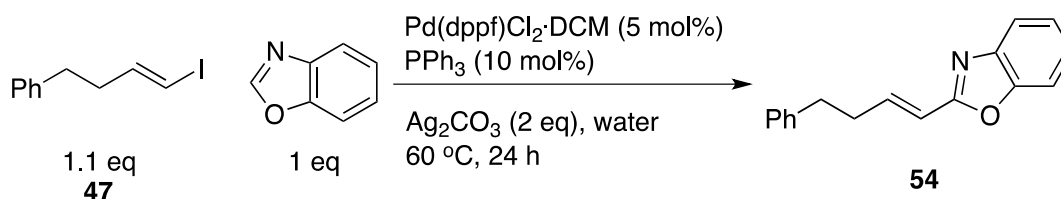
We started our screening by replicating the conditions, which Greaney successfully used for the coupling of substituted thiazoles and aryl iodides. The initial screen showed that benzoxazole was the best coupling partner, leading to 35% yield of the coupled product (Table 15, Entry 1). When benzothiazole was used as a coupling partner only a trace amount of product was observed (Entry 2). Unfortunately, none of the other heterocycles employed for the initial screen yielded any of the desired products (Entry 3-8).

Table 15: Coupling of alkenyl iodide with heteroarenes

$ \begin{array}{ccc} \text{Ph}-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-\text{I} & \text{X}-\text{C}_6\text{H}_4-\text{R} & \xrightarrow[\text{Ag}_2\text{CO}_3 (2 \text{ eq}), \text{ water}]{\text{Pd(dppf)Cl}_2\cdot\text{DCM} (5 \text{ mol}\%), \text{ PPh}_3 (10 \text{ mol}\%), 60^\circ\text{C}, 24 \text{ h}} \\ 1.1 \text{ eq} & 1 \text{ eq} & \text{Ph}-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-\text{C}_6\text{H}_3(\text{X})-\text{R} \end{array} $					
Entry	Heterocycle	Yield ^a	Entry	Heterocycle	Yield ^a
1		35%	5		NR ^c
2		Trace ^b	6		NR ^c
3		NR ^c	7		NR ^c
4		NR ^c	8		NR ^c

Arene (0.5 mmol), alkenyl iodide 0.6 (mmol), Pd(dppf)Cl₂·DCM (0.025 mmol), PPh₃ (0.05 mmol), Ag₂CO₃ (1.00 mmol), water (3.5 mL), 60 °C, 24h. ^aIsolated yield. ^bLess than 5%. ^cNo reaction.

For further optimization of the cross-coupling reaction, benzoxazole and (*E*)-(4-iodobut-3-en-1-yl)benzene **47** was used. Initially the temperature was raised from 60 °C to 100 °C, which resulted in a reduction in yield (Table 16, Entry 2). The reaction was then performed in a microwave reactor at 100 °C for 1 hour, which gave an increased yield of 58% (Entry 3). However, when the temperature was further increased to 120 °C the product was only formed in 49% yield (Entry 4). The reaction was attempted with the addition of re-oxidant benzoquinone, to aid the re-oxidation of the catalyst, but the yield significantly decreased (Entry 5). The same was the case when silver carbonate was substituted with silver oxide (Entry 6). The reaction was also tried without the triphenylphosphine ligand and with extra dppf ligand added instead, but in both cases only a mixture of the product and benzoxazole was obtained in low yields (Entry 6 and 7). Finally, the reaction was performed with 1 eq. of alkenyl iodide to 2 eq. of benzoxazole, where previously the alkenyl iodide had been used in excess. The yield increased to 70%, the best yield obtained for the reaction thus far (Entry 8). The coupling reaction was also performed in acetonitrile instead of water. However, again only a mixture of coupled product and benzoxazole was obtained in low yields, even when reaction time and temperature were increased (Entry 9 and 10). When the cross-coupling reaction was performed under the new conditions in the microwave and using conventional heat, no difference in yield was observed.

Table 16: Optimization conditions

Entry	Variations from original conditions	Yield ^a
1	Original conditions	35%
2	100 °C, 24 h	17%
3	MW, 100 °C, 1 h	58%
4	MW, 120 °C, 1 h	49%
5	Add benzoquinone	23%
6	No PPh ₃ added	Mixture
7	Dppf instead of PPh ₃	Mixture
8	1 eq of 47 , 2 eq of benzoxazole, sealed tube, 100 °C, 1 h	70%
9	MW, 100 °C, 1 h, acetonitrile	Mixture
10	MW, 120 °C, 1 h, acetonitrile	Mixture

^aIsolated yield

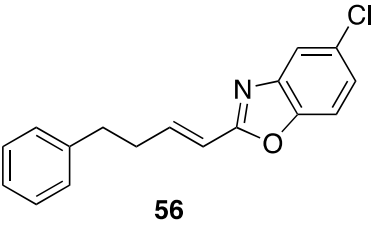
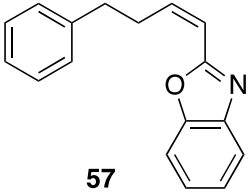
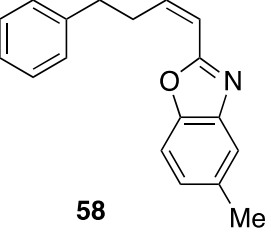
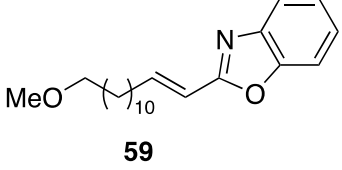
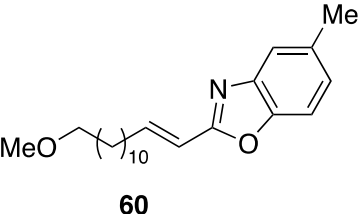
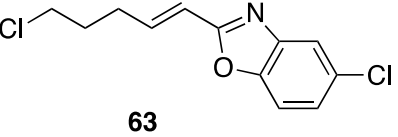
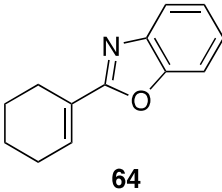
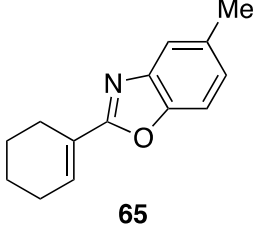
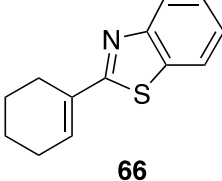
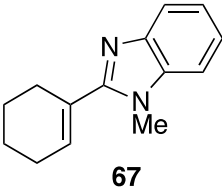
3.4 Reaction Scope

With the improved reaction conditions for this palladium-catalyzed cross-coupling reaction, we wanted to investigate the scope by using a range of alkenyl iodides and substituted benzoxazoles (Table 17). The reaction conditions could tolerate both *E* and *Z* isomers of the alkenyl iodides with complete retention of the double bond geometry

in the coupled products (Entry 1, 2, 4 and 5). The reaction conditions could also tolerate small variation on the benzoxazole, such as methyl and chloro substituents (Entry 2 and 3, for example). Overall, variation of the alkenyl iodides was well tolerated including a methyl ether (Table 5, Entry 6 and 7), chloroalkanes (Entry 8-10) and trisubstituted alkenyl iodides (Entry 11-14). All of the coupled products containing benzoxazoles were formed in good to excellent yields. A range of substituted benzothiazoles were tried as coupling partners. However, only when 1-iodocyclohexene **53** was coupled with benzothiazole was the desired product observed (Entry 13). Since 1-iodocyclohexene has proven to be the most versatile of the of the alkenyl iodides, it was also used in the coupling with *N*-methylbenzimidazole and formed the product in 73% (Entry 14). These results have now been published.⁹⁴

Table 17: Coupling reactions between a selection of alkenyl iodides and benzoxazoles

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1		70%	8		62%
2		83%	9		88%

3		40%
4		99%
5		59%
6		49%
7		78%
10		45%
11		61%
12		42%
13		25%
14		73%

Arene (1.0 mmol), alkenyl iodide (0.5 mmol), Pd(dppf)Cl₂·DCM (0.025 mmol), PPh₃ (0.05 mmol), Ag₂CO₃ (1.00 mmol), water (3.5 mL), 100 °C, 1 h, sealed tube. ^aIsolated yield.

The reaction was attempted between benzoxazole and (*E*)-(4-bromobut-3-en-1-yl)benzene **46** rather than the iodo counterpart **47** but none of the desired product was observed (Table 18, Entry 1). The same was the case when Doucet's conditions, which are 5 mol% PdCl(C₃H₅)(dppb), 5 mol% PPh₃ (0.05 mmol) and Cs₂CO₃ in DMF at 100 °C for 20 h, were tried both for benzoxazole and (*E*)-(4-iodobut-3-en-1-yl)benzene **47**

or (*E*)-(4-bromobut-3-en-1-yl)benzene **46** (Entry 2 and 3). The cross-coupling was also tried with other heterocycles such as 2-phenyloxazole and 2-phenylthiazole, which previously worked very well for Greaney using aryl halides but only produced a trace amount of product under our conditions (Entry 4 and 5).^{88,89} The reduced versatility of the alkenyl iodides compared their aryl counterpart could be a result of the lower stability of alkenyl versus aryl metal intermediates, which leads to decomposition and in return reduced reactivity.⁹⁵

Table 18: Unsuccessful coupling reaction between alkenyl halides and heterocycles

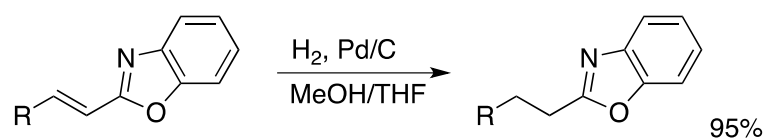
Entry	Alkenyl Halide	Heterocycle	Product	Yield ^a
1				NR ^{a,c}
2				NR ^{b,c}
3				NR ^{b,c}
4				Trace Product ^{a,d}
5				Trace Product ^{a,d}

^aArene (1.0 mmol), alkenyl iodide (0.5 mmol), Pd(dppf)Cl₂·DCM (0.025 mmol), PPh₃ (0.05 mmol), Ag₂CO₃ (1.00 mmol), water (3.5 mL), 100 °C, 1h, sealed tube. ^bArene (2.0 mmol), alkenyl iodide (1.0 mmol), PdCl(C₃H₅)(dppb) (0.05 mmol), PPh₃ (0.05 mmol), Cs₂CO₃ (2.00 mmol), DMF (10 mL), 100 °C, 20 h. ^cNo reaction. ^dLess than 5%.

3.5 Conclusion and Future Work

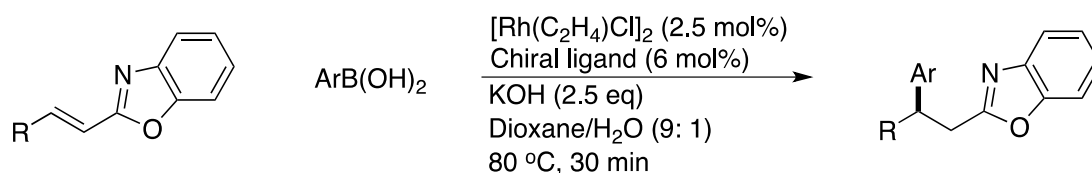
In conclusion we have developed a method for the direct functionalization of benzoxazoles with alkenyl iodides using palladium catalysis. Our system employs water as a solvent and mild reaction conditions which has allowed us to access a variety of 2-substituted benzoxazoles in moderate to excellent yields, as well as maintaining the double bond geometry.

The first aspect we want to focus on would be to improve the cross-coupling reaction to expand the scope to include a wider range of heterocycles. There is a range of possibilities for further functionalizing the 2-alkenylated benzoxazoles. The alkene double bond could be reduced to yield the 2-alkylated benzoxazoles. Saari *et al.* showed it was possible to selectively reduce the alkenyl double bond in the presence of heterocycles using palladium on carbon (Scheme 43).⁹⁶



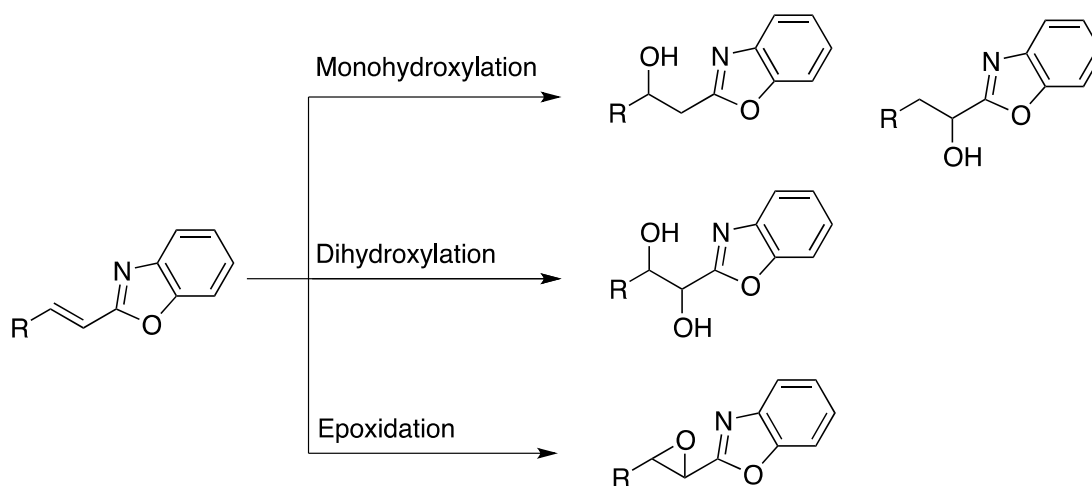
Scheme 43: Reduction of the double bond.

The 2-alkenylated benzoxazoles could also be further functionalized using the conditions recently reported by the Lam group.⁹⁷ Lam's group have showed that boronic acids can be enantioselectively added across the double bond using rhodium catalysis (Scheme 44).



Scheme 44: Enantioselective addition to the double bond

There is also potential for oxidation of the double bond. There are several opportunities including monohydroxylation, dihydroxylation and epoxidation (Scheme 45). There is also the possibility of performing these reactions stereospecifically. These reactions would lead to a diverse range of products from an efficient palladium coupling reaction.



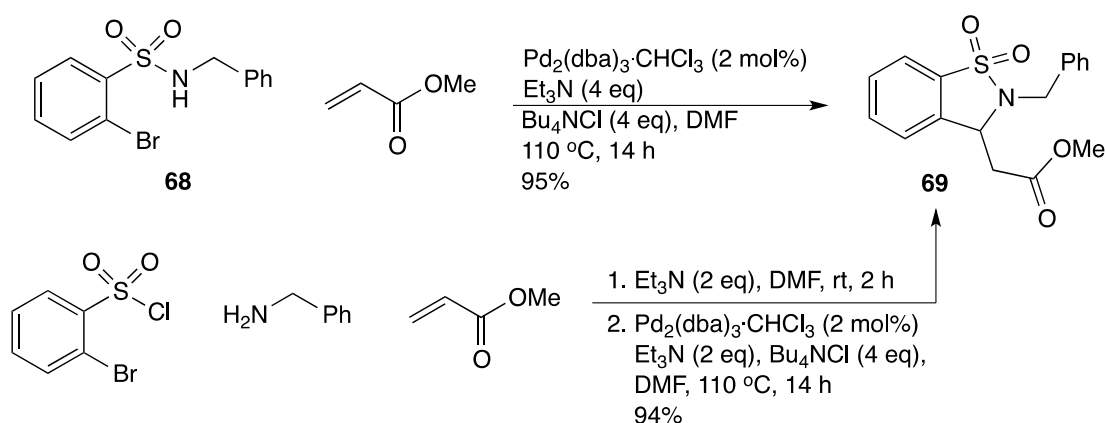
Scheme 45: Oxidation of 2-alkenylated benzoxazoles

Chapter 4 Synthesis of Sultams: Palladium-Catalyzed Intramolecular Cross-Coupling

4.1 Introduction

Sultams have emerged over the last decade as an interesting structural motif due to their biological activity and medicinal use. Fused sultams have shown the ability to inhibit a range of enzymes.^{98,99} Many synthetic strategies have been reported for the synthesis of sultams. A few examples include using a Pictet-Spengler reaction¹⁰⁰ and cyclization of aminosulfonyl chlorides.¹⁰¹ In this brief review we will focus on the synthesis of sultams using palladium catalysis.

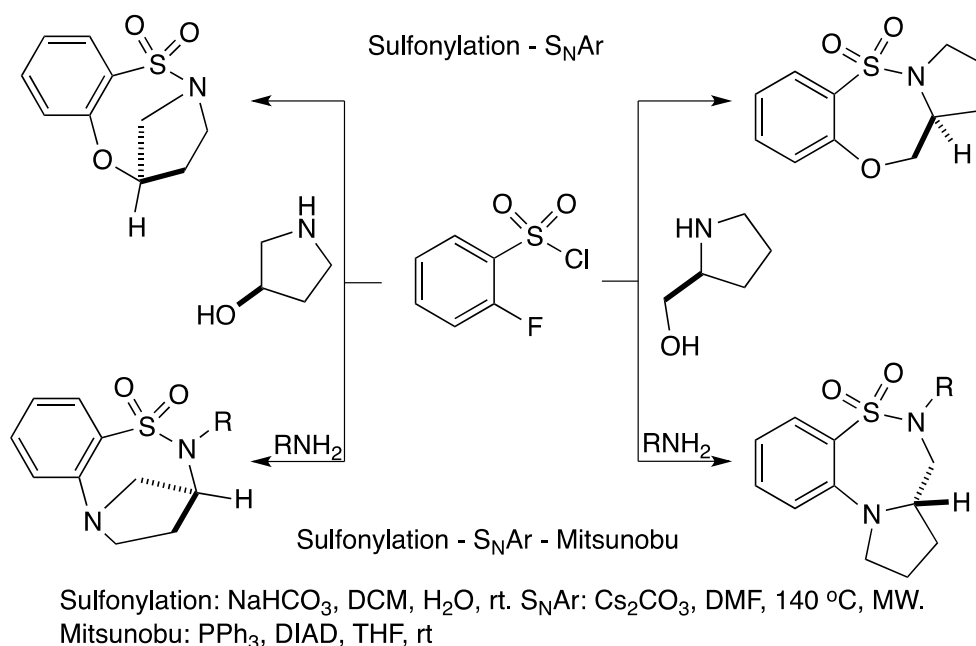
When Hanson and co-workers reported on the synthesis of bicyclic sultams they wanted to explore the use of palladium catalysis. They envisaged the use of a domino Heck-*aza*-Michael reaction as no such example had been reported before for the synthesis of sultams. They reported on the synthesis of 1,1-dioxido-1,2-benzisothiazoline-3-acetic acid **69** by the use of their domino strategy, which ultimately led to a three component, one-pot system from commercially available starting materials.¹⁰² Having shown the Heck-*aza*-Michael reaction was a viable synthetic route for sultams they wanted to further improve the process, by forming the sulfonamide **68** *in situ* and thereby creating a three component, one-pot reaction. The yield of the one pot reaction was comparable to the original Heck-*aza*-Michael reactions (Scheme 46). This process could also be used for the synthesis of oxindoles and isoindolines as well.



Scheme 46: Synthesis of sultams using a domino Heck-*aza*-Michael reaction

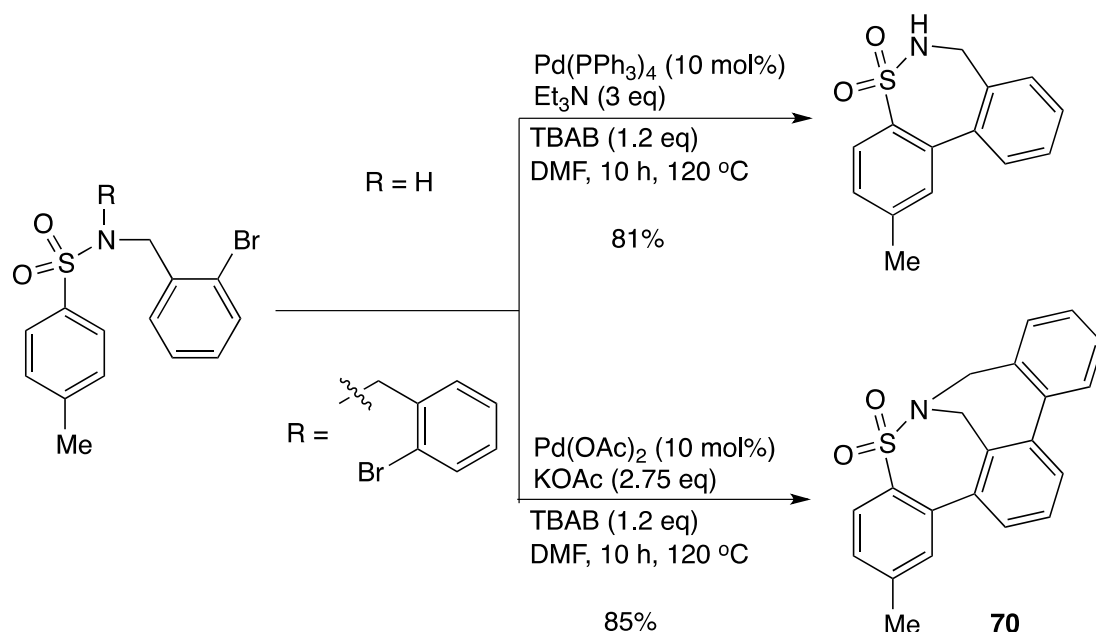
They extended their synthesis to include the formation of six and seven membered sulfonamides using different pathways such as Heck and Sonogashira reactions. All the different routes gave good to excellent yields of the sultams.¹⁰³

The Hanson group further elaborated their chemistry by using a diversity oriented synthesis concept in their most recent report on the synthesis of fused and bridged sultams. They showed that by starting from the same α -halosulfonyl chloride building block, they could easily access a range of complex multifunctional sultams.¹⁰⁴ They used a combination of three reactions: sulfonylation, nucleophilic aromatic substitution and the Mitsunobu reaction. Simply by changing the combination of reactions, they accessed four different types of sultams with great stereochemical and functional diversity (Scheme 47).



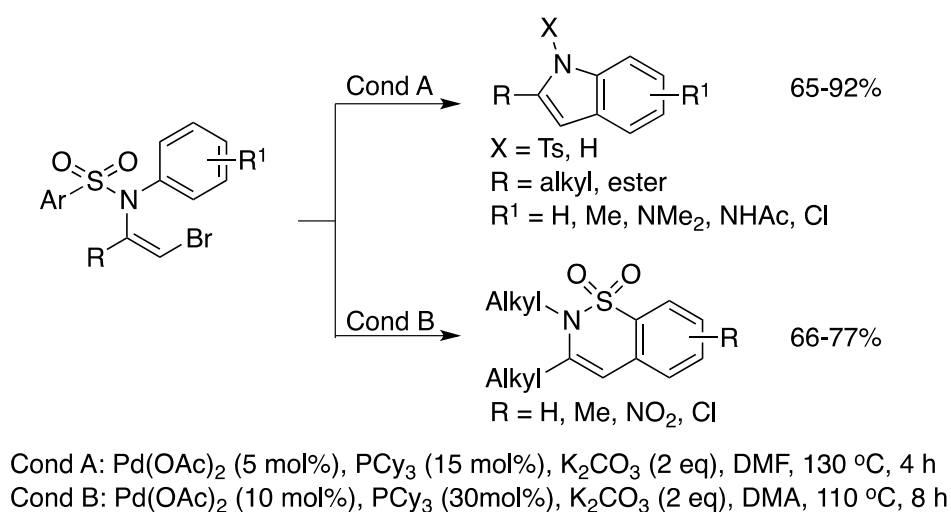
Scheme 47: Synthesis of sultams from 2-fluorobenzenesulfonyl chloride

Majumdar and co-workers have shown interest in developing and synthesizing biologically active heterocycles *via* palladium catalysis. They have now developed a palladium-catalyzed, ligand free intramolecular direct arylation for the synthesis of sultams.¹⁰⁵ They focused mainly on the synthesis of 7 membered sultams with a range of substitution patterns and the palladium cross-coupling could proceed in the presence of an unprotected nitrogen. When they designed a substrate where a tandem C-H functionalization process was possible they could obtain the product **70** by simply changing the palladium source and base (Scheme 48).



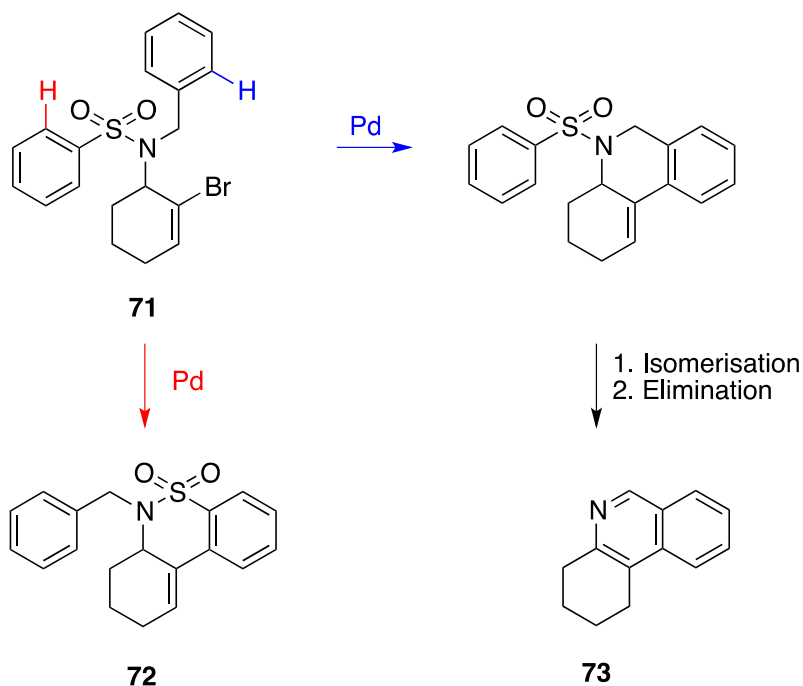
Scheme 48: Synthesis of sultams using C-H functionalization

The Urabe group reported the most recent example. They were investigating the synthesis of indoles from alkenyl bromides *via* a palladium catalysed cyclization. They found with only a slight modification of the cyclization conditions, they formed the sultam in good to excellent yields (Scheme 49).¹⁰⁶



Scheme 49: Synthesis of indoles and sultams

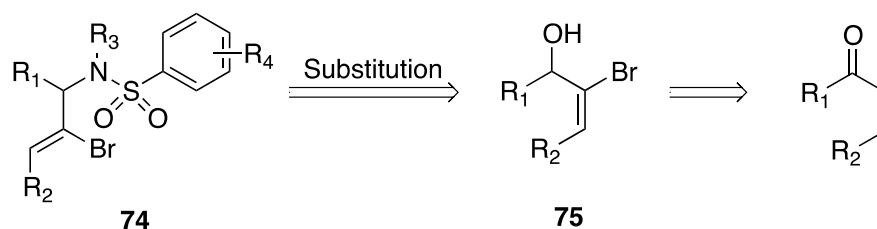
Some initial work within the group has shown it is possible to form substituted isoquinolines **73** and sultams **72** from the same precursor **71** (Scheme 50). We wanted to see if it's possible to selectively form one motif using either sterics or ligand control.



Scheme 50: Project aims

4.2 Original Strategy: Synthesis of Sultam Precursors

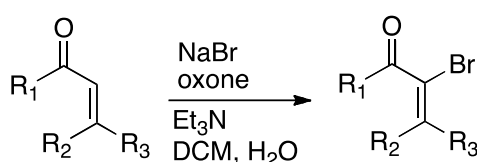
Our retrosynthetic analysis for the sultam precursor is shown in Scheme 51. We envisaged that the sultam precursors could be accessed relatively easily from commercially available α,β -unsaturated ketones, allowing good variation of both the aliphatic and aromatic elements. The α -bromo alcohol **75** could be formed from a bromination followed by a reduction. The alcohol could subsequently be activated *in situ* and the aromatic sulfonamide could react to form the cross-coupling precursor **74** *via* nucleophilic substitution (Scheme 51).



Scheme 51: Original retrosynthetic strategy

Bromination of α,β -unsaturated carbonyls is normally performed with bromine (Br_2), which adds across the double bond to give the dibromide. The product is then treated with triethylamine to eliminate hydrogen bromide (HBr).¹⁰⁷⁻¹⁰⁹ Due to the toxicity of Br_2 and the large scale of the reactions we wished to perform, it was decided to use sodium bromide and Oxone which would form Br_2 *in situ*.¹¹⁰ A small selection of α -bromoketones were synthesized using this procedure, in good to excellent yields (Table 19). Only the (*Z*)-isomer was isolated of 2-bromo-1,3-diphenylprop-2-en-1-one **78**.

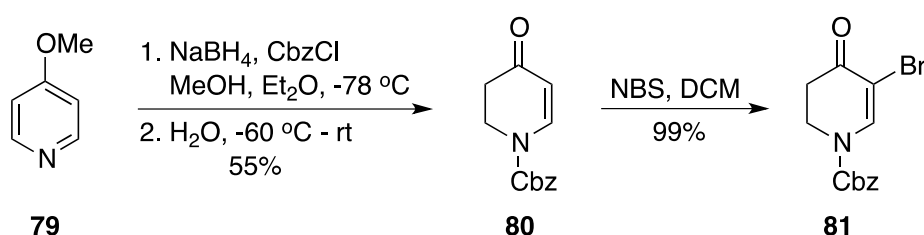
Table 19: Bromination of α,β -unsaturated ketones



Entry	Product	Yield ^a	Entry	Product	Yield ^a	Entry	Product	Yield ^a
1		90%	2		77%	3		77%
	76			77			78	

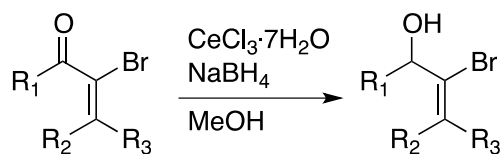
Ketone (1 eq), NaBr (2 eq), oxone (2 eq), Et_3N (3 eq), DCM, water, 0 °C - rt, 4 h – 3 days. ^a Isolated yield

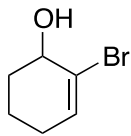
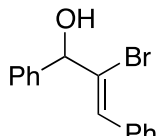
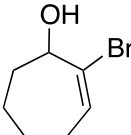
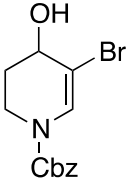
A slightly different approach was taken to synthesize the brominated dihydropiperidinone **81**. Rather than starting from the α,β -unsaturated ketone, we started with 4-methoxypyridine **79** which was reduced and protected to give the dihydropiperidinone in 55% yield. The dihydropiperidinone **80** was then treated with NBS in DCM to form the α -bromoketone **81** in 99% yield, (Scheme 2).¹¹¹



Scheme 52: Synthesis of α -bromoketone from 4-methoxypyridine.

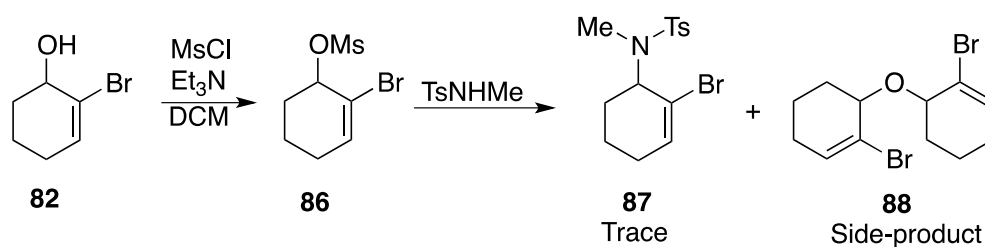
In the second step, the ketone was reduced *via* a Luche reduction using sodium borohydride and cerium trichloride. The Luche reduction allowed a selective 1,2-reduction of the enones.¹¹² The four α -bromo alcohols were all formed in good to excellent yields (Table 20).

Table 20: Luche Reduction

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 82	79%	3	 84	92%
2	 83	76%	4	 85	99%

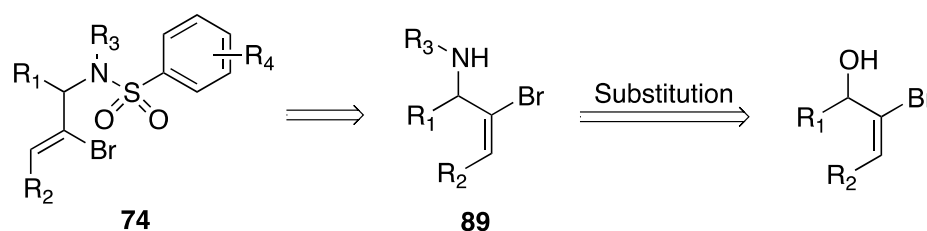
Ketone (1 eq), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.1 eq), NaBH_4 (1.1 eq), MeOH, 0 °C for 30 minrt 2-4 h. ^a Isolated yield

Following our original strategy we tried to promote a nucleophilic substitution reaction between the activated alcohol and tosylated methylamine to produce the cyclisation precursor. The alcohol **82** was reacted with mesyl chloride to form the mesylate **86** *in situ*, and then tosylated methylamine was added in the hope that it would react to yield the sultam precursor **87**. Unfortunately the desired product was not formed, and only the homo coupled by-product **88** and the starting materials were recovered. The same was the case when the unprotected *p*-toluenesulfonamide was used (Scheme 53). We tried to optimise this by altering the order and rate of addition as well as the temperature but unfortunately all attempts proved unsuccessful.



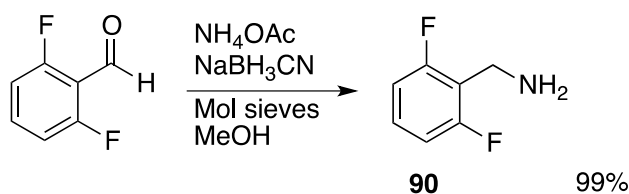
Scheme 53: Direct formation of cyclisation precursor

With direct formation of the sultam precursor unsuccessful we decided to alter our approach. We would again use nucleophilic substitution but this time to form a secondary amine **89**, which could then react with a sulfonyl chloride to yield the desired precursor (Scheme 54).



Scheme 54: Alternative strategy for synthesis of sultam precursor

In order to provide a simple substrate for the palladium cross-coupling reaction, we elected to use 2,6-difluorobenzylamine **90** as the nucleophilic amine, as this would allow the 2- and 6-positions to be blocked from reacting in the palladium catalysed step. We hoped the fluorine groups would not interfere with the cross-coupling reaction either electronically or due to steric bulk. The amine was formed from the aldehyde *via* a reductive amination; the reaction yielded the desired benzylamine in a quantitative yield (Scheme 55).

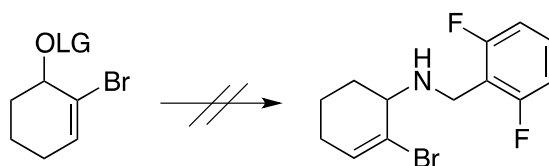


Scheme 55: Reductive amination to yield 2,6-fluorobenzylamine

Arene **90** was then reacted with the *in situ* generated mesylate **86**. Unfortunately, as before, only starting materials and the previously identified homo-coupled side-product **88** was recovered.

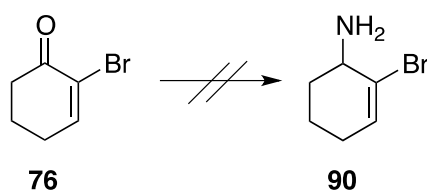
We also considered the use of a Tsuji-Trost reaction as a method to access the coupled benzylamine **89**, which is known for the palladium mediated reaction of allylic esters and carbonates with soft nitrogen nucleophiles.¹¹³ The acetate and the carbonate were formed from the alcohol. Several conditions were tried; unfortunately none were successful, and only starting materials were recovered from the reactions (Table 21).¹¹⁴

Table 21: Tsuji-Trost conditions



Entry	LG	Pd source	Ligand	Solvent	Time	Temp
1	Acetate	Pd/ C	PPh ₃	water /DME	4 h	70 °C
2	Acetate	Pd(dba) ₂	PPh ₃	DCM	16 h	reflux
3	Acetate	Pd(PPh ₃) ₄	PPh ₃	MeCN	16 h	reflux
4	Methyl carbonate	Pd(PPh ₃) ₄	PPh ₃	MeCN	16 h	reflux

We thought that another method to access the starting material would be to start from the cyclohexenyl amine **90** rather than the alcohol. This would then allow alternative groups to be attached to the nitrogen. Several reductive amination conditions of the ketone were tried but all attempts were unfortunately unsuccessful (Scheme 56).

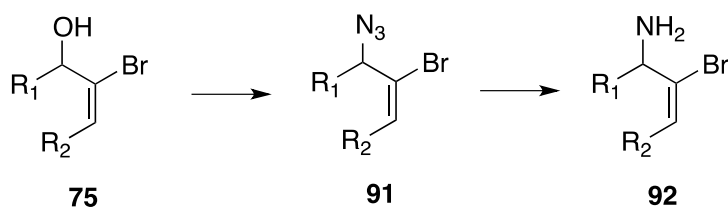


Scheme 56: Reductive amination of the ketone

It was decided to rethink the original strategy, as this approach had been unsuccessful thus far.

4.3 Revised Strategy: Synthesis of Sultam Precursors

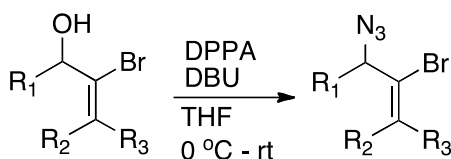
Since all our attempts to synthesise the sultam precursor were unsuccessful we decided to investigate a slightly longer approach to the synthesis of the primary amine building block. We envisaged the azide **91** could be simply reduced to the desired amine **92**. In turn, the azide should be available by substitution of the activated allylic alcohol (Scheme 57).



Scheme 57: Synthesis of primary amine building block

Azides can be formed using anionic azide, *via* the Mitsunobu reaction or from the reaction of the alcohol with DPPA and DBU.¹¹⁵⁻¹¹⁷ All three reactions have drawbacks; however, we found the use of DPPA most agreeable, as DPPA is the most stable and potentially least explosive azide delivery system. Using this process the four azides were formed in moderate to good yields (Table 22).

Table 22: Azide formation



Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	93	71%	3	95	45%
2	94	72%	4	96	66%

Alcohol (1eq), DPPA (1.5 eq), DBU (1.2 eq), THF, 0 °C for 30 min, rt for 2 h. ^a Isolated yield

The azides were then reduced to the corresponding amines using a Staudinger reduction (Table 23). The triphenylphosphine reacts with the azide to form a phosphoazide, which is then converted to an amine in the presence of water.¹¹⁸

Table 23: Staudinger Reduction

$$\text{R}_1\text{-CH(N}_3\text{)-C(Br)=CH-R}_2\text{-R}_3 \xrightarrow[\text{reflux, 2 h}]{\text{PPh}_3, \text{H}_2\text{O, Toluene}} \text{R}_1\text{-CH(NH}_2\text{)-C(Br)=CH-R}_2\text{-R}_3$$

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1		78%	3		79%
	90			98	
2		32%	4		80%
	97			99	

Azide (1 eq), PPh₃ (2 eq) (1 eq), toluene, water, reflux, 2 h. ^a Isolated yield

The conversion of the azides to the amines was a very clean process according to crude ¹H NMR spectroscopy, however, isolation of the amine proved difficult due to the separation from triphenylphosphine oxide. This was responsible for the low yield of the seven-membered amine (Table 23, Entry 2). Due to those difficulties we investigated alternative azide reductions.

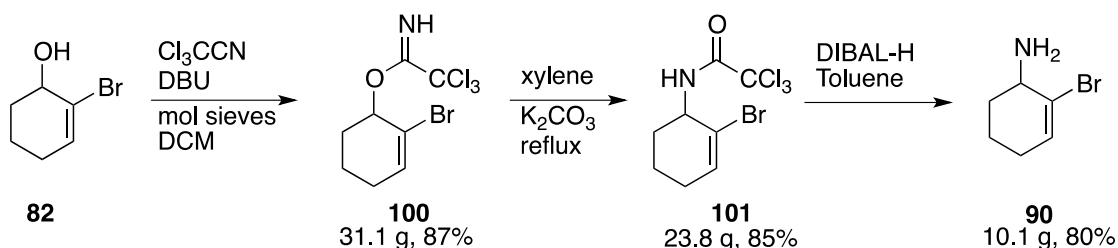
Lu *et al.* used tributylphosphine instead of triphenylphosphine as the corresponding phosphine oxide is water-soluble and can be removed by aqueous work-up. They mainly reduced aromatic azides.¹¹⁹ However, when used in our system the reaction returned only starting material (Table 24, Entry 1). The lack of reactivity was attributed to the quality of the tributylphosphine. Kamal *et al.* showed in their paper that by using chlorotrimethylsilane and sodium iodide they could reduce a range of aromatic and aliphatic azides in high yields under very mild conditions.¹²⁰ They also showed that they could selectively reduce aromatic azides to the amines in the presence of carboxylic acid, ester and halide substituents, using boron trifluoride diethyl etherate and sodium iodide.¹²¹ Again, their reaction conditions did not work for our azide (Entry 2 and 3). A Luche reduction and a reduction with Lindlar's catalyst was also tried but unfortunately all the reactions proved unsuccessful and only the starting azide was recovered (Entry 4 and 5).

Table 24: Reduction conditions

	Conditions	Yield
1	PBu ₃ , 1 M NaOH, THF, H ₂ O, 0 °C - rt	SM ^a
2	Me ₃ SiCl, NaI, MeCN, rt	SM ^a
3	BF ₃ .OEt ₂ , NaI, MeCN, rt	SM ^a
4	CeCl ₃ .7H ₂ O, NaBH ₄ , MeOH, 0 °C - rt	SM ^a
5	Lindlar cat., H ₂ , MeOH, rt	SM ^a

^aStarting material

Despite the purification difficulties, the current triphenylphosphine based reduction gave us access to the amines on a multiple gram scale. However, when we wanted to scale-up the synthesis of 2-bromocyclohex-2-enamine we could not use the established route due to the potentially explosive nature of the azide. The scale-up was performed at Syngenta. Instead of converting from the alcohol to the azide, we formed an acetimidate **100** from the reaction of trichloroacetonitrile in the presence of DBU in an 87% yield. This was then converted to the corresponding acetamide **101** using an Overman rearrangement under thermal conditions. This is one of the few examples of the Overman rearrangement taking place in the presence of a halogenated alkene.¹²² The acetamide was reduced to the amine **90** using DIBAL-H in an 80% yield. The overall process could be preformed on a 10 g scale (Scheme 8).

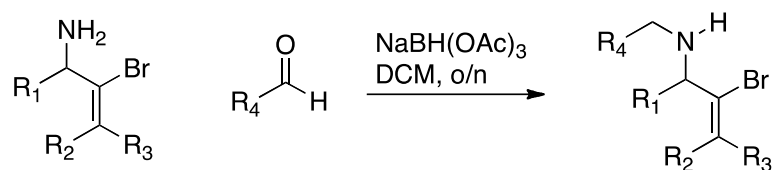


Scheme 58: Large scale synthesis of the primary amine building block

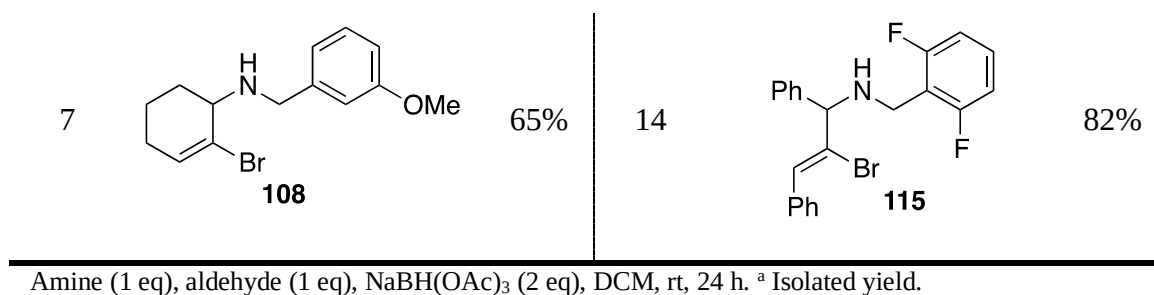
With the four primary amine building blocks in hand we used the strategy previously outlined of converting the primary amine into a secondary amine *via* a reductive amination with a selection of aldehydes (Table 25). Originally the reactions were performed using sodium cyanoborohydride as the reducing agent and methanol as the solvent. However, we did not achieve satisfactory yields so we changed to sodium tris(acetoxy)borohydride in DCM, which both improved the yields and simplified the quenching of the reaction.¹²³

We synthesized three secondary amines, where the 2 and 6 positions on the aryl ring were blocked either with a methyl group or a halogen, all in excellent yields (Entries 1-3). The 2-fluoropyridine derivative was also synthesized in excellent yield (Entry 4), however the pyrazole based aldehyde did not react, which can be explained due to the electronics of the pyrazole ring which makes the carbonyl less reactive towards attack of the amine (Entry 5). The pyridine and pyrazole derivatives were selected as we wanted to investigate if the cross-coupling reaction would tolerate the presence of heteroatoms. The amines containing benzyl groups with trifluoromethyl and the methoxy groups in the 3 position were both synthesized in moderate yields (Entry 6 and 7). These substrates were selected because we hoped to observe a difference in selectivity during the C-H functionalization, which would indicate if either the more electron-rich or electron-poor ring was preferred. We also wanted to investigate if the intramolecular palladium-catalyzed cyclization reaction would be affected by having an aliphatic protecting group, so a small range of secondary amines were synthesized in moderate to excellent yields (Entry 8-11). Finally, we used three different primary amines, which all delivered the 2,6-fluorobenzyl derivatives in moderate to excellent yields (Entry 12-14).

Table 25: Reductive Amination

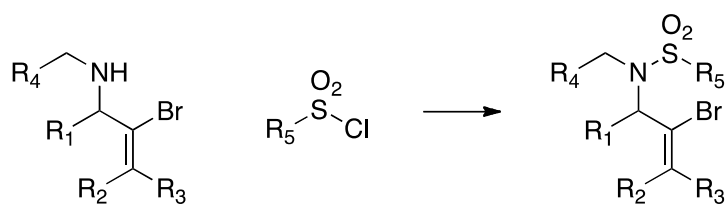


Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 102	81%	8	 109	68%
2	 103	83%	9	 110	55%
3	 104	90%	10	 111	97%
4	 105	89%	11	 112	85%
5	 106	0%	12	 113	54%
6	 107	68%	13	 114	99%

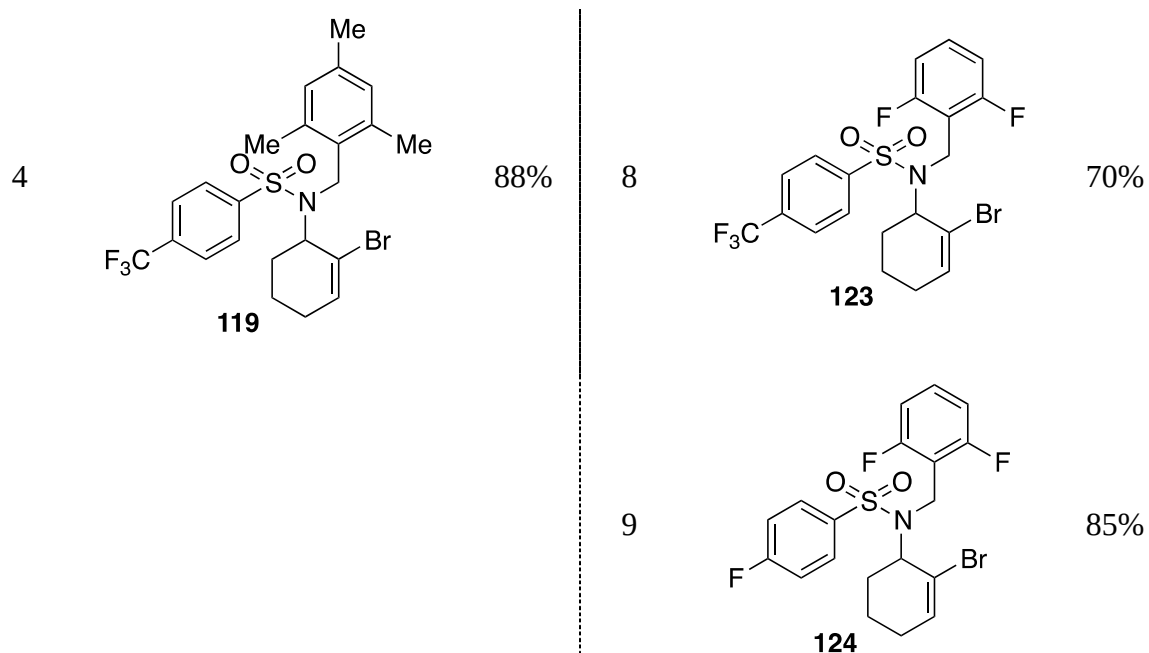


With the 13 secondary amines in hand we were only one step away from the sultam precursors. The next step was to introduce the sulfonamide group, and this was achieved by reacting the amines with a series of sulfonyl chlorides. This was originally performed in DCM with triethylamine at room temperature overnight, which yielded the sulfonamide **116** in 21% yield with 68% recovered starting amine. The reaction temperature was raised to reflux but the sulfonamide was still only formed in 36% with 61% recovered starting material. However, changing the reaction conditions to include catalytic DMAP and pyridine at 50 °C for 24 h increased the yield to 81% (Table 26, Entry 1).^{124,125} We selected a small range of sulfonyl chlorides to investigate if electron-donating and -withdrawing groups would have an effect on the cross-coupling reactions. When the amine with the 2,4,6-trimethylbenzyl protecting group **102** was used the sulfonamides were synthesised in good yields (Entry 1,2 and 4). The same was the case when the 2,6-difluoro secondary amine **103** was used (Entry 5-6 and 8-9). However, in both cases when the 4-acetylbenzenesulfonyl chloride was used a small drop in yield was observed (Entry 3 and 7).

Table 26: Sulfonamide formation with 2 and 6 position blocked for C–H activation



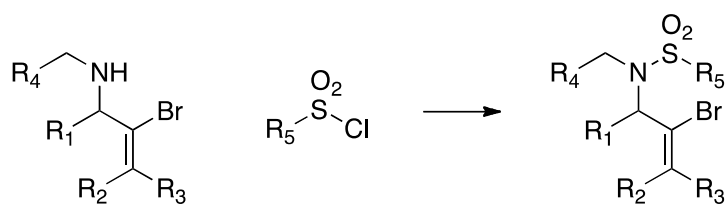
Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 116	81%	5	 120	84%
2	 117	85%	6	 121	82%
3	 118	56%	7	 122	65%



Amine (1 eq), sulfonyl chloride (2 eq), DMAP (0.1 eq), pyridine, 50 °C, 24 h. ^a Isolated yield.

When the amine with the 2,6-dichlorobenzene protecting group **104** was used for the formation of sulfonamides the yields for the four samples containing electron-donating and -withdrawing groups were all moderate (Table 27, Entry 1-4). However the yield varied from moderate to good when the 2-fluoropyridine protected amine **105** was used (Entry 5-8).

Table 27: Sulfonamide formation



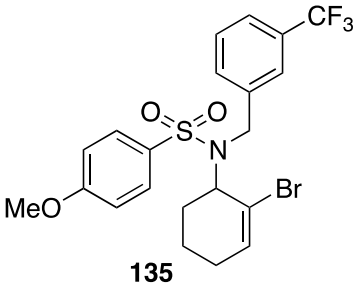
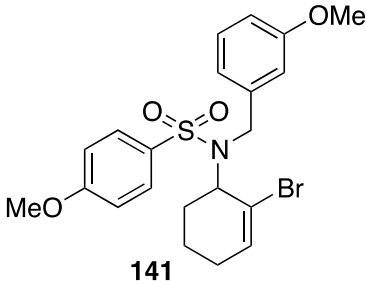
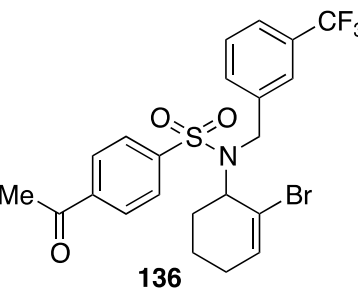
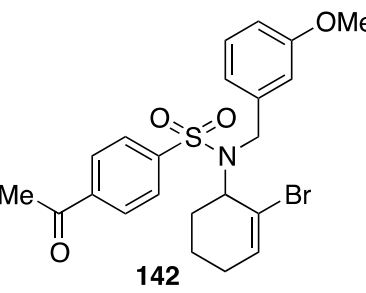
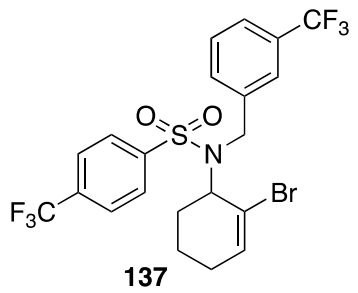
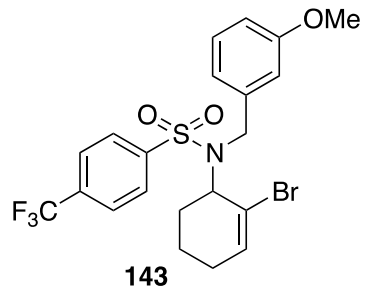
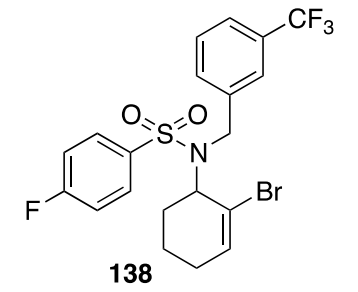
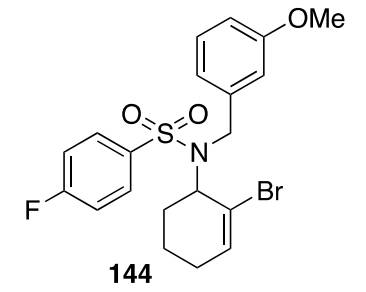
Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 125	68%	5	 129	78%
2	 126	66%	6	 130	58%
3	 127	54%	7	 131	62%
4	 128	64%	8	 132	83%

Amine (1 eq), sulfonyl chloride (2 eq), DMAP (0.1 eq), pyridine, 50 °C, 24 h. ^a Isolated yield.

When the amine protecting groups contained either the trifluoromethyl or methoxy group in the 3 position all the sulfonamides were formed in good to excellent yield (Table 28). However, it would be interesting to see if there is any selectivity observed based on the electronics since the 2 and 6 positions are not blocked. This would allow the possible formation of sultam or isoquinoline and hopefully we would observe a preference for C-H activation on either the electron-rich or electron-poor aromatic ring. It would be particularly interesting to see the result of the coupling reaction when the groups are electronically reinforcing (Entry 5 and 9) or in opposing cases (Entry 3 and 11).

Table 28: Sulfonamide formation with possibility of selectivity due to electronics

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 133	97%	7	 139	90%
2	 134	90%	8	 140	87%

3	 135	97%	9	 141	88%
4	 136	79%	10	 142	87%
5	 137	85%	11	 143	84%
6	 138	85%	12	 144	80%

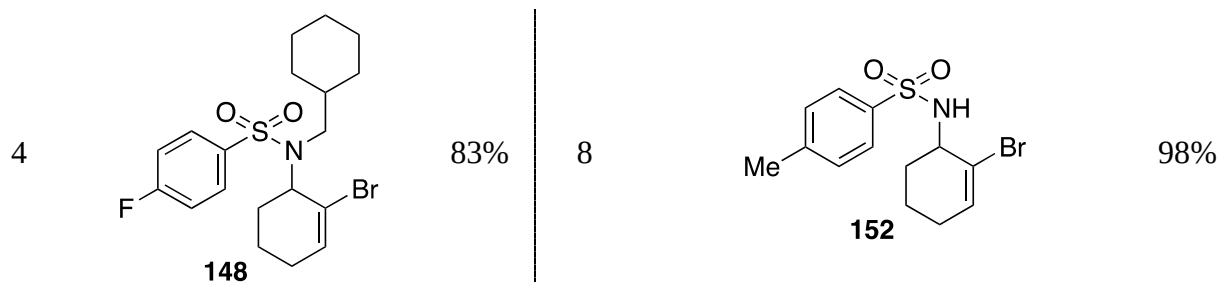
Amine (1 eq), sulfonyl chloride (2 eq), DMAP (0.1 eq), pyridine, 50 °C, 24 h. ^a Isolated yield.

We also wanted to investigate the effect of using non-aromatic protecting groups in the cross-coupling reaction. We synthesised four sulfonamides containing the cyclohexyl protecting group **112** in moderate to excellent yields (Table 29, Entry 1-4). We also synthesized one example each containing the *neopentyl* **111**, *isobutyl* **110** and heptyl **109** protecting group in average to excellent yield (Entry 5-7). Finally we also

synthesised the unprotected sulfonamide in excellent yield to investigate if the cross-coupling reaction would tolerate the presence of an unprotected N-H bond (Entry 8).

Table 29: Sulfonamide formation with alkyl groups

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 145	89%	5	 149	42%
2	 146	58%	6	 150	66%
3	 147	62%	7	 151	97%



Amine (1 eq), sulfonyl chloride (2 eq), DMAP (0.1 eq), pyridine, 50 °C, 24 h. ^a Isolated yield.

The last four sulfonamides **153-156** we synthesised were from different primary amine building blocks (Table 30). The sulfonamide containing the 7-membered ring was synthesised in good yield (Entry 1). The open chain derivative was formed in excellent yield (Entry 2). The two examples containing the protected nitrogen in the unsaturated ring were formed in poor to moderate yields (Entry 3 and 4)

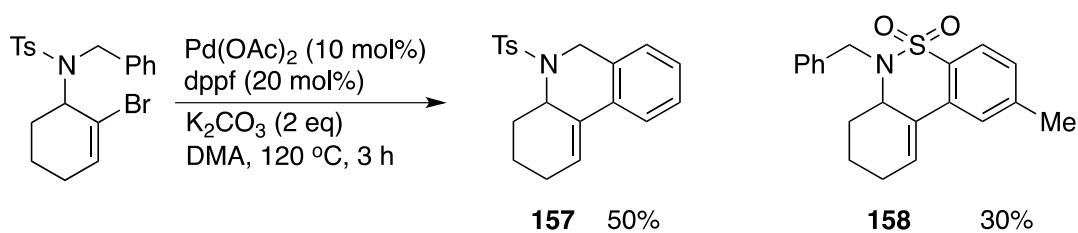
Table 30: Sulfonamide formation from alternate secondary amines

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 153	75%	3	 155	36%
2	 154	94%	4	 156	53%

Amine (1 eq), sulfonyl chloride (2 eq), DMAP (0.1 eq), pyridine, 50 °C, 24 h. ^a Isolated yield.

4.4 Optimization: Palladium-Catalyzed Intramolecular Cross-Coupling

With a large range of sulfonamides in hand we started to investigate the palladium catalysed intramolecular cross-coupling. We based our initial screen on work previously done in the group synthesizing dihydroisoquinoline **157**, during which some sultam **158** formation was first seen in Myriam Yaguobi's unpublished work (Scheme 59).¹²⁶



Scheme 59: Intramolecular palladium-catalyzed cross-coupling to form dihydroisoquinoline and sultam

To prevent the formation of dihydroisoquinolines our initial screen contained sulfonamides with aliphatic protecting groups or the 2,6-fluorobenzyl group. To investigate the coupling reaction to form substituted sultams the conditions used were 10 mol% palladium acetate, 20 mol% dppf, 2 equivalents of potassium carbonate in DMA, and the reaction was heated for 3 h at 120 °C (Table 3). None of the desired sultam was observed in any of the reactions. Interestingly the allylic substitution product **159** was observed when the amine had a heptyl-protecting group (Entry 1).

Table 32: Ligand screen using heptyl and neopentyl protecting groups

	R group	Ligand	Results
1		XPhos	Trace product ^a
2		XantPhos	Trace product ^a
3		DavePhos	Trace product ^a
4		XPhos	Complex mixture
5		XantPhos	Trace product ^a
6		DavePhos	Trace product ^a
7		Fu's Salt	Complex mixture
8		CataCXium C	Decomposed SM

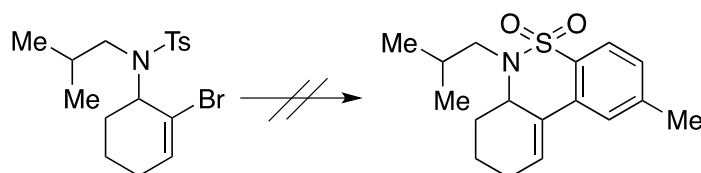
Sultam precursor (0.195 mmol), Pd(OAc)₂ (10 mol%), ligand (20 mol%), DMA (1 mL), 3 h, 120 °C.

^aLess than 5%.

With the lack of improvement we decided to investigate some very different conditions for the coupling reaction (Table 33) using the *isobutyl* protected sulfonamide **150**, to see if we could assist sultam formation. Buchwald reported a phosphine free catalytic system for direct alkenylation of substitution of alkenes, which was a completely different approach to what we had previously tried. Unfortunately, the reaction only returned starting material when tried with our system (Entry 1).¹²⁷ Fu described very mild conditions for Heck reactions coupling a range of aryl chlorides and bromides with substituted alkenes. These conditions were

ineffective when used for our sultam synthesis and only trace product was observed (Entry 2).¹²⁸ Finally, we wanted to see if eliminating the ligand would have an effect on the reaction. We tried with three different palladium sources; palladium-tetrakis(triphenylphosphine), palladium acetate and tris(dibenzylideneacetone)dipalladium(0), but unfortunately none of the changes improved the reaction (Entry 3-5).

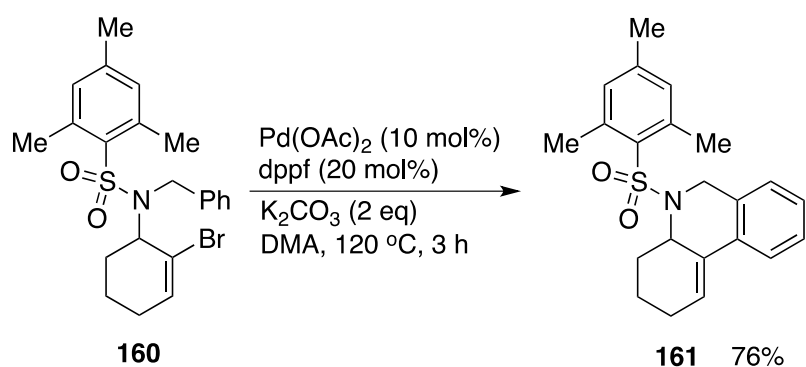
Table 33: Coupling conditions



	Pd source	Ligand	Base	Solvent	Time	Temp	Result
1	Pd(OAc) ₂	Et ₄ NCl	Cy ₂ NMe	DMA	24 h	100 °C	SM ^a
2	Pd ₂ (dba) ₃	Fu's salt	Cy ₂ NMe	DMA	24 h	rt	Trace product ^b
3	Pd(PPh ₃) ₄		K ₂ CO ₃	DMA	3 h	100 °C	SM ^a
4	Pd(OAc) ₂		K ₂ CO ₃	DMA	3 h	100 °C	SM ^a
5	Pd ₂ (dba) ₃		K ₂ CO ₃	DMA	3 h	100 °C	Trace product ^b

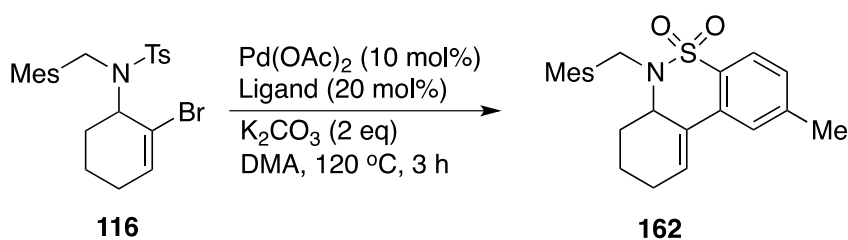
^a Starting material. ^b Less than 5%.

Having not observed any of the desired sultam being formed in all the coupling reactions tried thus far, we decided to return to the use of a benzyl protecting group for the sulfonamide. Unpublished work carried out by Myriam, performed in parallel, on the formation of the dihydroisoquinoline precursor **160** showed that blocking the 2, 4 and 6 positions on the benzene ring exclusively gave the desired product **161** in very good yield (Scheme 60).¹²⁶



Scheme 60: Cross coupling to form the isoquinoline precursor

We decided to apply this strategy to our sultam synthesis. With the new 2,4,6-trimethylbenzyl protecting group the reaction was tried with the original reaction conditions and the sultam was obtained in a 44% yield (Table 34, Entry 1). We decided to investigate a small range of ligands from different classes to see if we could improve the yield. Two other complex phosphine ligands were tried (XPhos and XantPhos), which gave similar yields to dppf (Entry 2 and 3). The yields were again around 40% when bulky monodentate phosphines such as Fu's salt and CataCXium A were used. However, 28% of starting material was also recovered from the reaction with CataCXium A (Entry 4 and 5). When palladacycle CataCXium C was used, the yield the decreased to only 19% (Entry 6). Finally the use of an *N*-heterocyclic, PEPPSI, yielded only returned starting material (Entry 7).

Table 34: Ligand screen

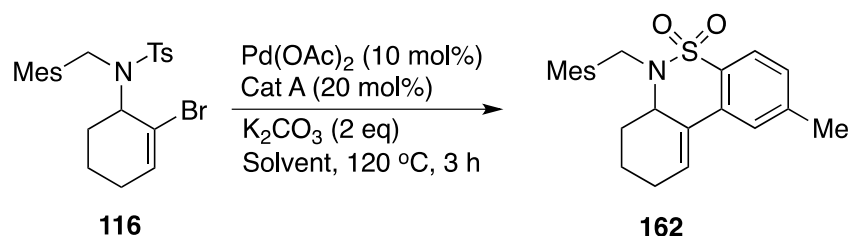
Entry	Ligand	Yield ^a
1	dppf	44%
2	XPhos	40%
3	XantPhos	37%
4	Fu's Salt	42%
5	CataCXium A	42% (28% SM ^b)
6	CataCXium C	19% (49% SM ^b)
7	PEPPSI	SM ^b

Sultam precursor (0.195 mmol), Pd(OAc)₂ (10 mol%), ligand (20 mol%), K₂CO₃ (2 eq), DMA (1 mL), 3 h, 120 °C. ^aIsolated yields, ^b starting material.

Next the reaction solvent was varied in the hope that we could further increase the yield of the reaction. We selected a range of solvents with boiling points above 120 °C as we did not want pressure to be a factor in the reaction (Table 35). CataXCium A was chosen as the best ligand. When ethylene glycol was used a 1:1 mixture of starting material and sultam was recovered in 40% yield (Entry 1). The yield remained around 40% when NMP was used (Entry 2). However, when *o*-xylene was used the yield increased to 59% but the product did contain 10% starting material (Entry 3). The yield further increased to 66% when the solvent was changed to DMSO, but dropped to 59% when the ligand was changed to dppf (Entry 4). When DMSO was used as a

solvent we did have some solubility problems but a 1:4 mixture of *o*-xylene: DMSO, pleasingly improved solubility and increased the yield to 73% (Entry 5).

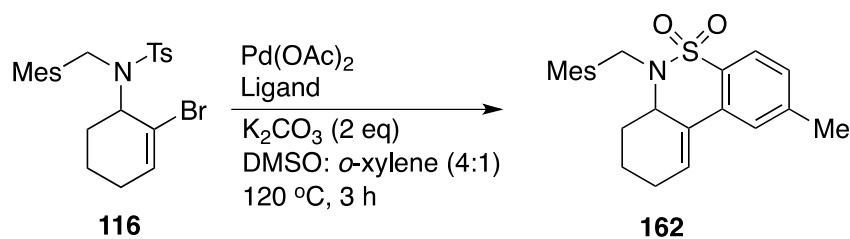
Table 35: Solvent screen



Entry	Solvent	Yields ^a
1	Ethylene glycol	40% 1:1 SM ^b :product
2	NMP	42%
3	<i>o</i> -xylene	59% with 10% SM impurity
4	DMSO	66% (59% with dppf)
5	DMSO: <i>o</i> -xylene (4:1)	73%

Sultam precursor (0.195 mmol), Pd(OAc)₂ (10 mol%) CataXCium A (20 mol%), K₂CO₃ (2 eq), solvent (1 mL), 3 h, 120 °C. ^a Isolated yields. ^b Starting material

The final aspect of the reaction that we wanted to optimize was the catalyst and ligand loading, as all the optimization thus far had been carried out with a high loading of 10 mol% palladium and 20 mol% ligand. The new solvent mixture was tried with both dppf and CataXCium A yielding 66% and 73% of the sultam respectively (Table 36, Entry 1 and 3). When the catalyst and ligand loading was dropped to 5 and 10 mol%, the yield respectively of the reaction dropped to 56% with dppf, (Entry 2), but with CataXCium A the yield of the reaction remained at 73% (Entry 4).

Table 36: Catalyst loading

Entry	Ligand	Pd mol%	Ligand mol%	Yield ^a
1	dppf	10	20	66%
2	dppf	5	10	56%
3	CataCXium A	10	20	73%
4	CataCXium A	5	10	73%

Sultam precursor (0.195 mmol), Pd(OAc)₂, ligand, K₂CO₃ (2 eq), DMSO: *o*-xylene (4:1, 1 mL), 3 h, 120 °C. ^a Isolated yields.

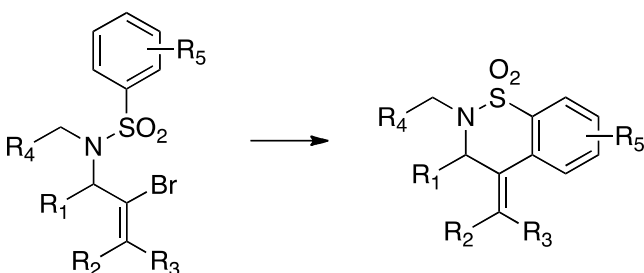
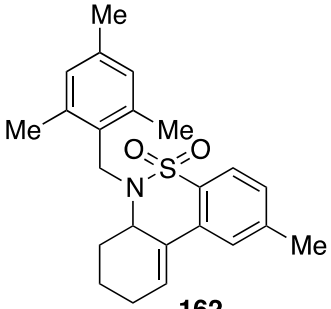
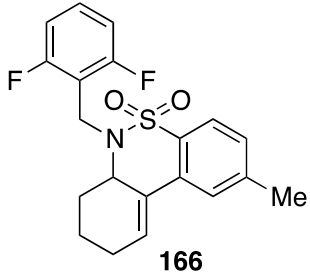
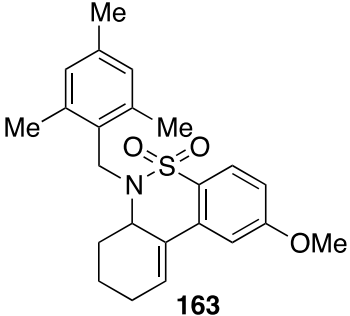
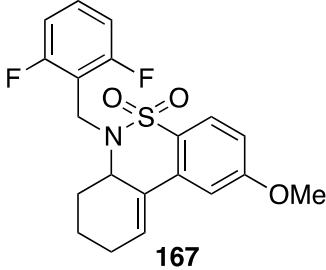
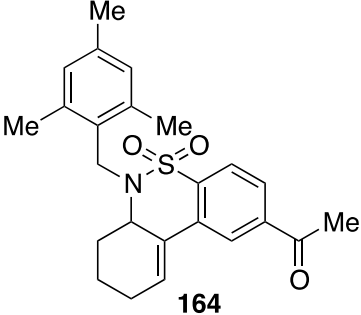
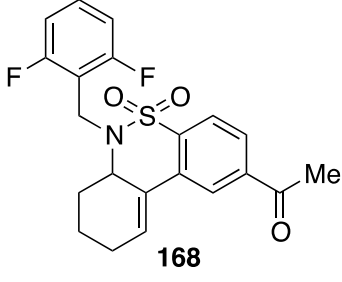
With these now optimized conditions of 5 mol% palladium acetate, 10 mol% CataCXium A, 2 equivalents of potassium carbonate, DMSO: *o*-xylene (4:1), 0.19 M, 3 h at 120 °C, the scope of the reaction was explored.

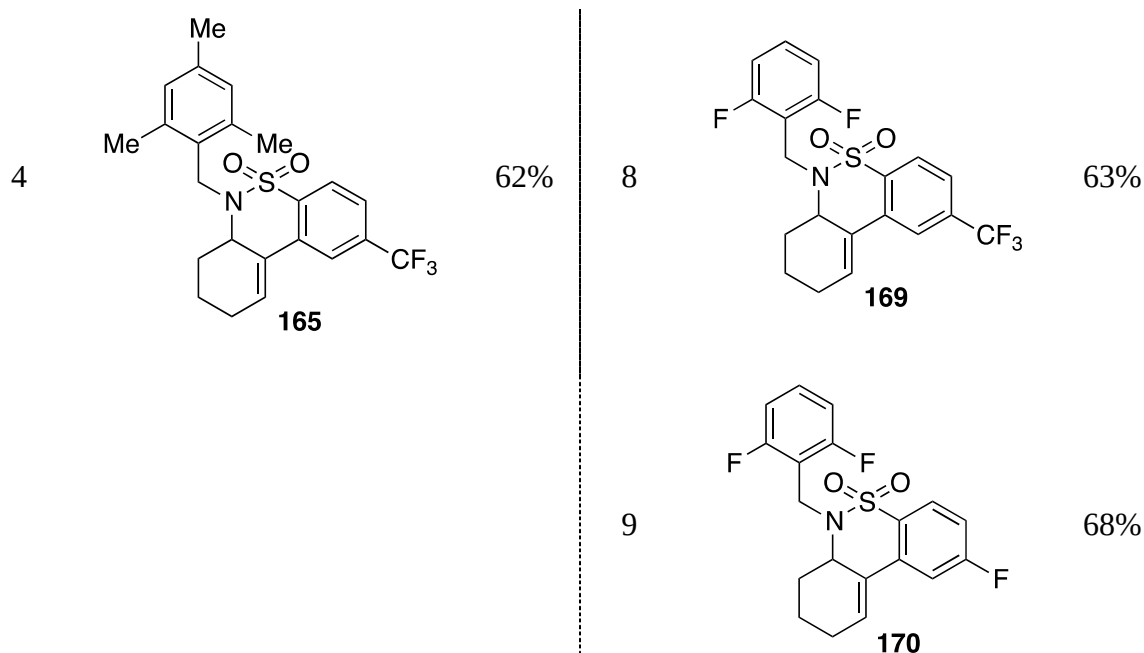
4.5 Synthesis of sultams *via* intramolecular palladium cross-coupling

More than 40 sultam precursors were synthesised, which were designed to fully explore the scope of the cross-coupling reaction. We started by investigating the cross-coupling reaction using the sultam precursors which contained groups to block the 2 and 6 positions. Firstly, we looked at the precursors containing the 2,4,6-trimethylbenzyl protecting group; 4 sultams were successfully synthesized in average to good yields (Table 37, Entry 1-4). We also wanted to establish that the cross-

coupling reaction could tolerate the presence of halogens in the protecting group, when the nitrogen was protected using the 2,6-difluorobenzyl group, and five sultams with this protecting group were synthesized in average to good yields (Entry 5-9).

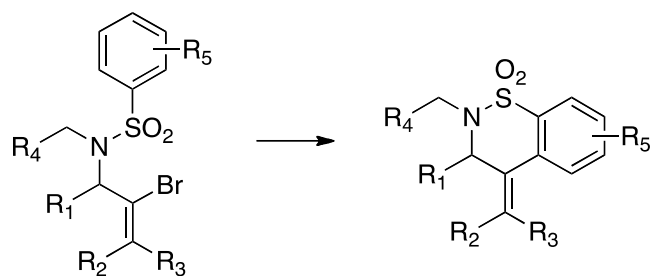
Table 37: Sultam formation with 2 and 6 positions blocked to C–H activation

					
Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 162	73%	5	 166	75%
2	 163	43%	6	 167	62%
3	 164	59%	7	 168	48%



Sultam precursor (0.195 mmol), Pd(OAc)₂ (5 mol%), CataXCium A (10 mol%), K₂CO₃ (2 eq), DMSO: *o*-xylene (4:1, 1 mL), 3 h, 120 °C. ^a Isolated yields

Since we found that fluorine groups could be tolerated in the cross-coupling reaction, the analogous and more synthetically versatile chloro substrates were investigated (Table 38). The sultams containing electron-donating groups were both formed in average yield (Entry 1 and 2). However, when the electron-withdrawing ketone and fluorine groups were present only a trace amount of product was observed (Entry 3 and 4). The lower yield observed with these chloro substrates could be due to competing oxidative addition of the palladium in the C-Cl bond. Indeed, there are several cases reported of a system containing palladium and CataCXium A catalytic system functionalizing aryl chlorides.¹²⁹⁻¹³¹ We also wanted to examine if the cross-coupling reaction would tolerate the presence of a pyridine ring; unfortunately none of the four sultam precursors yielded any product, only complex mixtures being observed (Entry 5-8).

Table 38: Sulfonamide formation

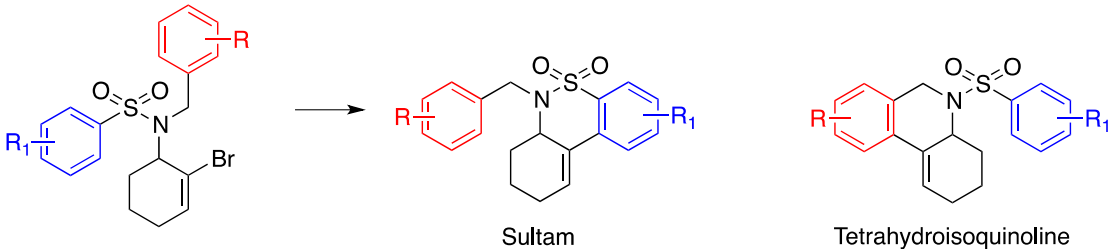
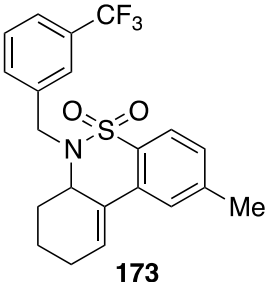
Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 171	59%	5		Complex mixture
2	 172	59%	6		Complex mixture
3		Trace product ^b	7		Complex mixture
4		Trace product ^b	8		Complex mixture

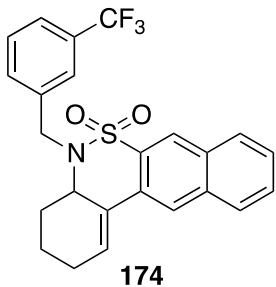
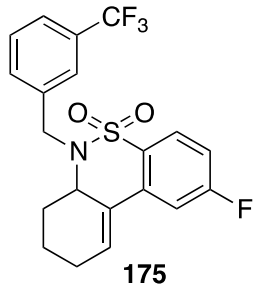
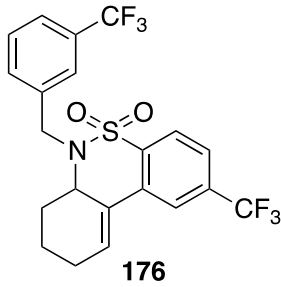
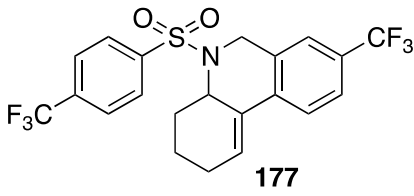
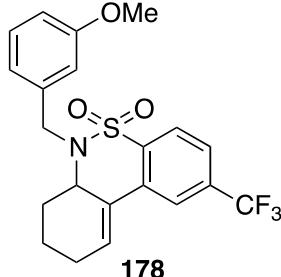
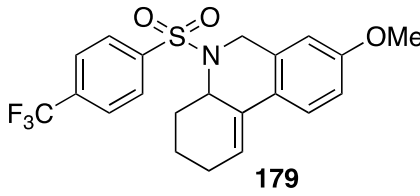
Sultam precursor (0.195 mmol), Pd(OAc)₂ (5 mol%), CataXCium A (10 mol%), K₂CO₃ (2 eq), DMSO:

o-xylene (4:1, 1 mL), 3 h, 120 °C. ^a Isolated yields. ^b Less than 5%.

Having investigated sultam formation by blocking possible sites for side reactivity to form isoquinolines, we wanted to investigate if selectivity could be controlled by the electronics of the protecting group. In three cases where the sultam precursor contained a trifluoromethyl group on the protecting benzyl ring, we observed the sultam in poor to average yields with only a trace of the isoquinoline side product (Table 39, Entry 1-3). We observed as a mixture of the sultam and isoquinoline in a 2.5:1 ratio favouring the sultam (Entry 4). When the trifluoromethyl group was substituted for a methoxy group, a mixture of sultam and isoquinoline was observed in a similar ratio of 2:1, again favouring the sultam (Entry 5). The remainder of examples tried with either the trifluoromethyl or methoxy group on the benzyl protecting ring led to a complex mixture of products where only a trace of sultam and isoquinoline were observed.

Table 39: Sultam and isoquinoline formation

 Sultam Tetrahydroisoquinoline				
Entry	Sultam	Isoquinoline	Ratio ^a	Yield ^b
1	 173	Trace product ^c		46%

2	 174	Trace product	30%	
3	 175	Trace product ^c	51%	
4	 176	 177	2.5:1	56%
5	 178	 179	2:1	36%

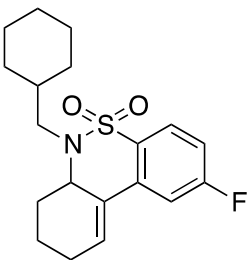
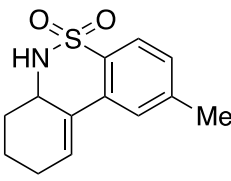
Sultam precursor (0.195 mmol), Pd(OAc)₂ (5 mol%), CataXCium A (10 mol%), K₂CO₃ (2 eq), DMSO: *o*-xylene (4:1, 1 mL), 3 h, 120 °C. ^a Ratios calculated from ¹H NMR spectra. ^b Isolated yields. ^c Less than 5%.

All the sultams that we had synthesised thus far contained an aromatic protecting group. We were pleased to find that when the protecting group was changed, to cyclohexyl the desired sultams was still successful formed. Four examples gave mixed

results in the cross-coupling reactions. The sultam was formed in good to excellent yield when the benzyl sulfonamide contained the methoxy and acetyl group (Table 40, Entry 2 and 4). However, when the methyl and fluorine group were present only a trace amount of sultam was observed (Entry 1 and 3). We also synthesized sultam **182** containing an isobutyl protecting group in excellent yield (Entry 5). Finally, when the unprotected sultam was subjected to the conditions a complex mixture containing none of the desired product was observed (Entry 6).

Table 40: Sultam formation with alkyl protecting groups

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1		Trace product ^b	4		62%
2		81%	5		90%

3		Trace product ^b	6		Complex mixture
Sultam precursor (0.195 mmol), Pd(OAc)₂ (5 mol%) CataXCium A (10 mol%), K₂CO₃ (2 eq), DMSO: o-xylene (4:1, 1 mL), 3 h, 120 °C. ^a Isolated yields. ^b Less than 5%					

The final aspect we wanted to investigate was the alteration of the primary amine that the sultam precursor was synthesised from. We successfully formed the sultam with a 7-membered unsaturated ring in moderate yield (Table 41, Entry 1). However, when the cross-coupling was attempted with the open chain equivalent only a trace about of product was observed. When a protected nitrogen in the bottom ring was incorporated, we observed some mixed results. For example, when the sulfonamide ring contained an electron-withdrawing fluorine, the sultam **184**, was synthesized in a 45% yield (Entry 3). However, when the fluorine group was changed to the electron-donating methoxy group only a trace amount of the sultam was observed (Entry 4).

Table 41: Sultam formation from alternative secondary amines

Entry	Product	Yield ^a	Entry	Product	Yield ^a
1	 183	53%	3	 184	45%
2		Trace product ^b	4		Trace product ^b

Sultam precursor (0.195 mmol), Pd(OAc)₂ (5 mol%) CataXCium A (10 mol%), K₂CO₃ (2 eq), DMSO: *o*-xylene (4:1, 1 mL), 3 h, 120 °C. ^a Isolated yields. ^b Less than 5%

4.6 Functionalization

Finally, we wanted to investigate if the *exo*-alkene product **162** could be isomerized into the sultam ring. Maddaluno showed it was possible to isomerize *exo*-alkenes into lactam rings using both acidic and basic conditions.¹³² A range of acids were selected to preform this transformation (Table 42). Only starting material was observed when *p*-toluenesulfonic, trifluoroacetic and polyphosphoric acids were used (Entry 1-3). In

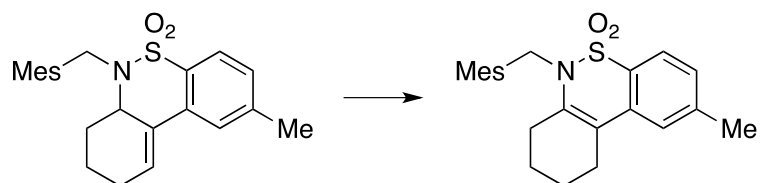
addition, only the debenzylated product **185** was seen, by ^1H NMR spectroscopy, when triflic acid was employed (Entry 4). When sulfuric acid was used 80% of the same debenzylated by-product was observed (Entry 5).

Table 42: Isomerization under acidic conditions

Entry	Acidic conditions	Yields	By-product
1	pTSA, DCM, rt, o/n	SM ^a	
2	TFA, DCM, rt, o/n	SM ^a	
3	PPA, rt, o/n	SM ^a	
4	Triflic acid, DCM, 0 °C, 3 h	100% ^b	 185
5	H ₂ SO ₄ , DCM, rt, 3 h	80% ^b	

^a Starting material, ^b conversion by ^1H NMR spectroscopy.

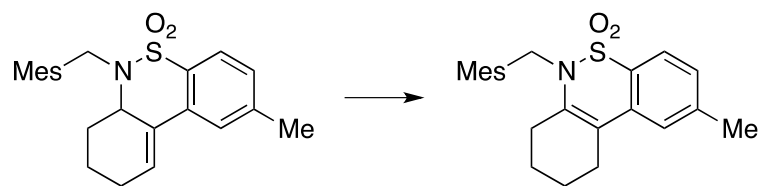
Since isomerization had not been achieved under acidic conditions, a small selection of bases were investigated (Table 43). Unfortunately, none of the basic conditions we tried led to the isomerized product, even when the temperature was elevated (Entry 1-3) or when strong base was used (Entry 4).

Table 43: Isomerization under basic conditions

Entry	Basic conditions	Results
1	DBU, THF, 2 h rt, 50 °C o/n	SM ^a
2	KHMDS, toluene, rt, o/n	SM ^a
3	KHMDS, toluene, reflux, o/n	SM ^a
4	<i>n</i> BuLi, toluene, 3 h, -78 °C, rt, o/n	SM ^a + complex mixture

^a Starting material

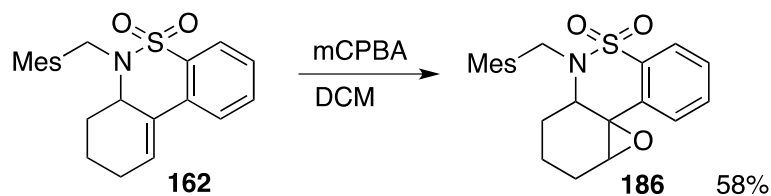
Having not been able to isomerize the *exo*-alkene under either acidic or basic conditions we investigated a range of other isomerization possibilities (Table 44). Firstly we tried the reaction with catalytic iodine (Entry 1), which was unsuccessful. It has been shown that rhodium catalysis can be used to isomerize double bonds, one of the first examples of which was reported by Noyori.¹³³ In addition, Yudin showed it was possible to isomerize allyl amines and aziridines to the corresponding enamines using cationic rhodium.¹³⁴ Unfortunately his conditions, with or without BINAP, only yielded recovered starting material (Entry 2 and 3). Sulphur dioxide is also known to assist the isomerization of *exo*-alkenes, the first being example demonstrated by Rogic in 1977.¹³⁵ We tried both sulphur dioxide gas and DABSO, a solid equivalent of sulphur dioxide, which has been developed in the Willis group.¹³⁶ Again, both reactions only returned starting material (Entry 4 and 5).

Table 44: Alternative isomerization conditions

Entry	Alternative conditions	Results
1	Cat. I ₂ , toluene, 3 h, rt, reflux o/n	SM ^a
2	Rh(nbd) ₂ BF ₄ , THF, 60 °C, o/n	SM ^a
3	Rh(nbd) ₂ BF ₄ , BINAP, THF, 60 °C, o/n	SM ^a
4	SO ₂ gas, dioxane, 3 h, rt, 60 °C, o/n	SM ^a
5	DABSO, dioxane, 3 h, rt, 60 °C, o/n	SM ^a

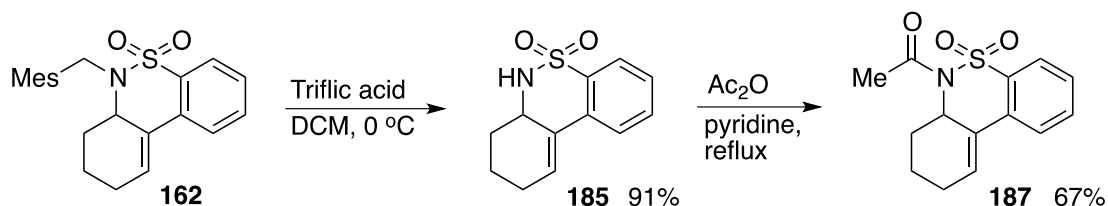
^a Starting material

Since we had been unsuccessful in isomerizing the double bond we decided to examine other ways of functionalizing the substituted sultams. The sultam was treated with *meta*-chloroperoxybenzoic acid in DCM to successfully form the epoxide **186** in 58% yield (Scheme 61).¹³⁷ Only one diastereoisomer was observed but which has not been identified.

**Scheme 61:** Synthesis of epoxide

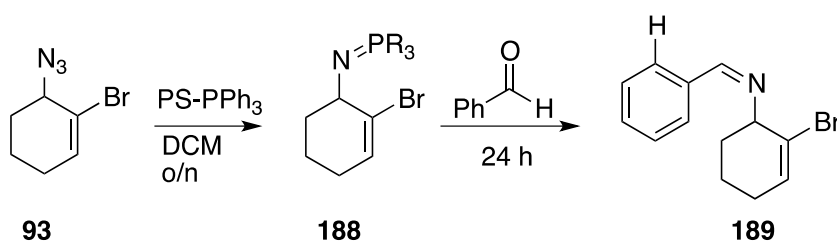
Due to constraints in the method used to synthesize the sultam precursor, it was not possible to incorporate any functionality adjacent to the nitrogen. Building on the

result of debenzylation, seen when the sultam was treated with triflic acid, we wanted to deprotect the sultam and subsequently acylate. The deprotected sultam **185** was isolated in 91% yield. Sultam **185** was then treated with acetic anhydride in refluxing pyridine to yield the acylated sultam **187** in 67% yield (Scheme 62).¹³⁸



Scheme 62: Deprotection and acylation of the sultam

As well as preparing sultams we were also interested in the synthesis of isoquinolines and with access to the azide **93** it might be possible to form the imine **188** directly (Scheme 63), which we hoped would form the isoquinoline after being submitted to our cross-coupling conditions. The idea was based on a similar principal used by Crich in his related sugar chemistry.¹³⁹



Scheme 63: Imine formation.

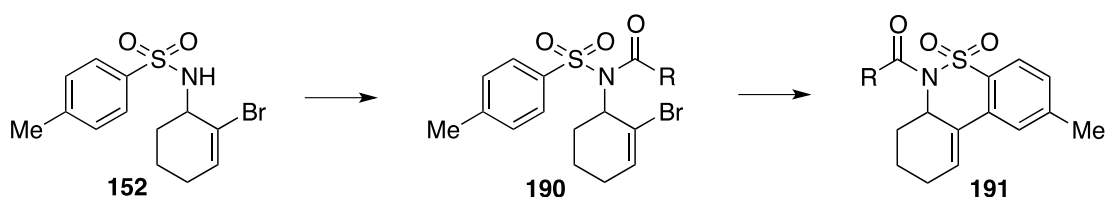
The reaction was originally tried using triphenylphosphine and the resulting imine was seen in the crude ¹H NMR spectrum but unfortunately it was impossible to isolate. The reaction was then tried with polymer supported triphenylphosphine, as it was hoped the phosphine residue could simply be filtered off after the reaction, therefore

eliminating the need for further purification. Unfortunately that was not the case and none of the desired imine was observed from the reaction.

4.7 Conclusion and Future Work

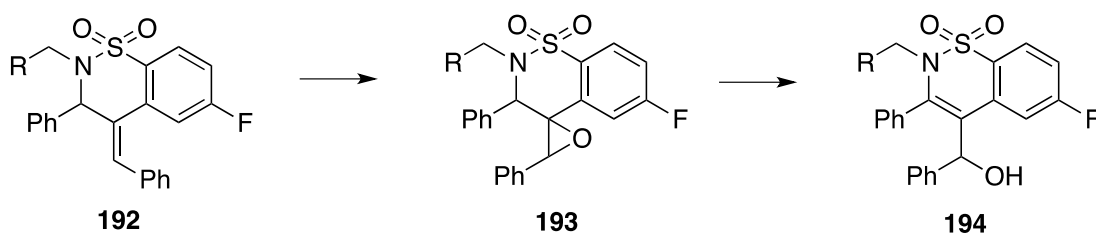
In summary, we have successfully achieved the synthesis of a range of sultams with complex substitution patterns from simple and commercially available starting materials. We have shown that the sultams could be accessed *via* a palladium catalysed intramolecular cross-coupling C-H functionalization reaction of an alkenyl bromine and an aryl ring. We have also demonstrated that it is possible to further functionalize the sultams either *via* epoxidation or debenzylation, which widens the scope of the accessible sultams. All of the sulfonamides and sultams have been tested by Syngenta for early leads in their screening assays for crop protection programs; unfortunately none returned any positive hits.

Our initial attempts to functionalize the sultam have led to ideas for future work. It would also be interesting to see if we could use an acyl derivative as a protecting group for nitrogen during the cross-coupling as that would expand the scope of further functionalizing the sultam. The synthesis of the sultam precursor would however have to be altered slightly. The synthesis would start from sulfonamide **152**, which we have already shown can be formed in excellent yield. This would be followed by an acylation forming the precursor for the cross-coupling chemistry (Scheme 64).



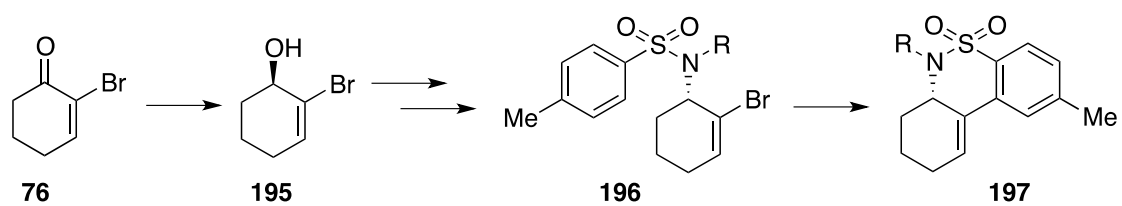
Scheme 64: Alternative amine protecting group

It would also be interesting to reoptimize the palladium cross-coupling for the open chain sultam precursor **153**. Hopefully it would prove possible to synthesize the sultam from the open chain motif followed by an epoxidation of the *exo*alkene and opening of the epoxide, as this would lead to a new and interesting substitution pattern of the sultams (Scheme 65).



Scheme 65: Functionalization of sultam **192**

The final aspect we would like to investigate would be the asymmetric synthesis of sultams and their further functionalization. Instead of using a Luche reduction to form the alcohol, we could use a CBS reduction as Knochel has shown.¹⁴⁰ The rest of our developed sulfonamide synthesis as well as the cross-coupling would hopefully not interfere with the established stereocentre (Scheme 66). As regard to the asymmetric functionalization we could use either a Jacobsen or Shi epoxidation.^{141,142}



Scheme 66: Asymmetric synthesis of the sultam

Chapter 5 Experimental Procedures

General consideration

All reactions were performed under an inert atmosphere of nitrogen or argon, in oven dried glassware, using dry solvents and under anhydrous conditions, unless otherwise stated.

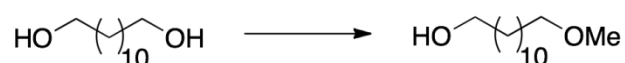
Analytical thin layer chromatography was carried out using pre-coated aluminium backed silica plates (Merck Kieselgel 60F254). Plates were visualised under ultraviolet light (254 nm) and/or by staining with KMnO₄ or PMA. Flash column chromatography was carried out using Merck Kieselgel 60H silica. Pressure was applied at the column head *via* hand bellows. When working at Syngenta the automated columnning was performed using a Combiflash Rf by Teledyne.

Infrared measurements were carried out as liquid films on NaCl discs or neat using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-500 cm⁻¹. Mass spectrometry was carried out on a Bruker microTOF and Micromass SYNAPT ion. Melting points were determined using a Buchi 535 melting point apparatus. ¹H and ¹³C nuclear magnetic resonance experiments were carried out using a Bruker 400 or 500 UltraShield™ spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane for ¹H and ¹³C experiments. The residual solvent peak was used as an internal reference. ¹H-NMR chemical shifts have residual CHCl₃ (δ_H 7.26 ppm), DMSO (δ_H 2.50 ppm) and ¹³C-NMR CDCl₃ (δ_C 77.1 ppm), DMSO (δ_C 39.5ppm). All coupling constants (*J*) are given in Hertz (Hz). The multiplets reported in the spectra are: single (s), broad singlet (br. s), doublet (d), triplet (t), quartet (q), quintet (quin) and unresolved multiplet (m).

Dry and purified tetrahydrofuran, dichloromethane, methanol and toluene, were used

from a MBraun SPS solvent purification system. Dry *N,N*-dimethylformamide 99.8%, dimethyl sulfoxide $\geq 99.9\%$ ($\leq 0.01\%$ water) and *o*-xylene was purchased from Aldrich in a Sure-Seal bottle. 1,2-Dimethoxyethane and triethylamine were distilled from calcium hydride. Pyridine was dried over molecular sieves, distilled and stored over potassium hydroxide. All other solvents were used as purchased from Rathburn or Fischer at HPLC grade. Petrol refers to light petroleum ether, bp 40-60 °C. All other chemicals were purchased from Acros, Aldrich, Alfa Aesar or Strem chemical companies and used without further purification.

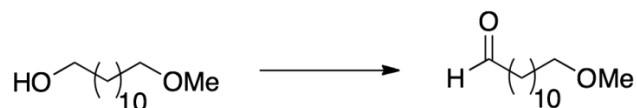
12-Methoxydodecan-1-ol, 36



Sodium hydride (60% dispersion in mineral oil, 2.17 g, 54.4 mmol, 1.1 eq) was added to a solution of 1,12-dodecanediol (10.0 g, 49.4 mmol, 1 eq) in DME (35 mL) cooled to 0 °C. The solution was allowed to warm to ambient temperature and stirred for 1 h. Dimethyl sulfate (4.65 mL, 49.4 mmol, 1 eq) was added and the reaction was stirred for 48 h. The reaction was quenched with a saturated ammonium chloride solution (35 mL). The quenched mixture was extracted with ethyl acetate (4 × 35 mL). The organic layers were combined and washed with brine (35 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (10 - 40% ethyl acetate/petrol) to yield the title compound as a white solid (5.06 g, 47%). ν_{max} (liquid film)/cm⁻¹ 3371, 2993, 2921, 2850, 1739, 1461, 1122, 1035, 755. δ_{H} (400 MHz, CDCl₃) 3.59 (2H, t, *J*=8.0, CH₂OH), 3.34 (2H, t, *J*=8.0, CH₂OMe), 3.31 (3H, s, CH₂OCH₃), 1.97 (1H, s, CH₂OH), 1.56-1.51 (4H, m, 2 × OCH₂CH₂), 1.34-1.22 (16H, m, 8 × CH₂). δ_{C} (100 MHz, CDCl₃) 72.9, 62.6, 58.5, 32.7, 29.6, 29.5 (5C), 29.4, 26.1, 25.7. HRMS (FI⁺) calculated for C₁₃H₂₈O₂ [M+H]⁺

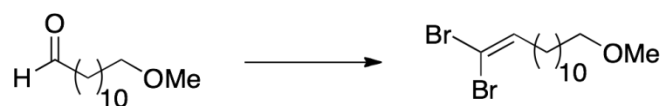
216.2089, found 216.2089. M.p. (diethyl ether/chloroform) = 31-33 °C. Data in accordance with literature.¹⁴³

12-Methoxydodecanal, 37



A mixture of 12-methoxy-dodecan-1-ol (38.3 g, 177 mmol, 1 eq), PCC (38.2 g, 177 mmol, 1 eq) and 4 Å molecular sieves (30 g) was stirred in DCM (325 mL) at ambient temperature for 16 h. The reaction was passed through a Celite pad and washed with diethyl ether (325 mL). The filtrate was filtered through a basic silica plug and eluted with 40% ethyl acetate/ petrol/ 0.5% triethylamine and concentrated *in vacuo* to yield the title compound as a colourless oil (29.0 g, 76%). $\nu_{\max}$ (liquid film)/cm⁻¹ 2924, 2852, 1708, 1463, 1119, 944. δ_{H} (400 MHz, CDCl₃) 9.71 (1H, t, $J=4.0$, C(O)H), 3.31 (2H, t, $J=7.0$, CH₂OMe), 3.27 (3H, s, CH₂OCH₃), 2.36 (2H, td, $J=7.0$, $J=2.0$, CH₂C(O)H), 1.61-1.47 (4H, m, 2 × OCH₂CH₂), 1.34-1.22 (14H, m, 7 × CH₂). δ_{C} (100 MHz, CDCl₃) 179.3, 72.9, 58.4, 34.4, 29.6 (2C), 29.5 (2C), 29.4, 29.1, 28.6, 26.1, 22.0. HRMS (FI⁺) calculated for C₁₃H₂₆O₂ [M+H]⁺ 214.1933, found 214.1937.

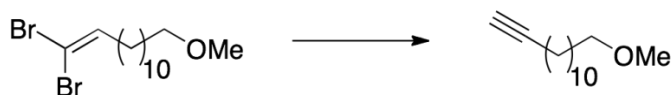
1,1-Dibromo-13-methoxytridec-1-ene, 38



A solution of 12-methoxydodeca-1-nal (7.72 g, 36.0 mmol, 1 eq) and carbon tetrabromide (17.9 g, 54.0 mmol, 1.5 eq) in DCM (150 mL) was cooled to 2-3 °C (internal temperature). A solution of triisopropyl phosphite (19.6 mL, 79.2 mmol, 2.2 eq) in DCM (30 mL) was added over 1 h maintaining internal temperature. The

reaction was stirred for a further 1 h. The mixture was quenched with saturated solution of sodium bicarbonate (100 mL) slowly, to avoid an exotherm. The aqueous layer was extracted with DCM (3×100 mL). The organic layers were combined and dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (10% diethyl ether/petrol) to yield the title compound as colourless oil (11.8 g, 89%). ν_{max} (liquid film)/ cm^{-1} 2925, 2853, 1734, 1437, 1119, 720, 694. δ_{H} (400 MHz, CDCl_3) 6.39-6.34 (1H, m, $\text{CH}=\text{Br}_2$), 3.31 (2H, t, $J=7.0$, CH_2OMe), 3.27 (3H, s, CH_2OCH_3), 2.10-2.04 (2H, m, CH_2CHBr_2), 1.57-1.51 (2H, m, CH_2), 1.44-1.36 (2H, m, CH_2), 1.34-1.22 (14H, m, $7 \times \text{CH}_2$). δ_{C} (100 MHz, CDCl_3) 138.9, 88.5, 72.9, 58.5, 33.0, 29.7, 29.5 (3C), 29.4 (2C), 29.0, 27.8, 26.1. HRMS (FI^+) calculated for $\text{C}_{14}\text{H}_{26}^{77}\text{Br}_2\text{O}$ $[\text{M}]^+$ 368.0350, found 368.0356.

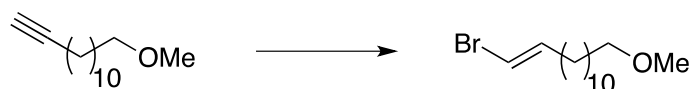
13-Methoxytridec-1-yne, 39



A solution of $n\text{BuLi}$ (2.30 M in hexane, 19.9 mL, 45.9 mmol, 2 eq) was added dropwise to a solution of the 1,1-dibromo-13-methoxytridec-1-ene (8.50 g, 22.9 mmol, 1 eq) in THF (125 mL) at -78°C . After 1 h the reaction was allowed to warm to ambient temperature and stirred for a further 2 h. The reaction was cooled to 0°C and quenched with water (125 mL) and extracted with diethyl ether (3×125 mL). The organic layer was washed with 1 M aqueous solution of hydrogen chloride (125 mL), brine (125 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (10% diethyl ether/pentane) to yield the title compound as colourless oil (3.89 g, 81%). ν_{max} (liquid film)/ cm^{-1} 3312, 2926, 2854, 2150, 1462, 1120. δ_{H} (400 MHz, CDCl_3) 3.31 (2H, t, $J=7.0$, CH_2OMe),

3.27 (3H, s, CH₂OCH₃), 2.16 (2H, td, *J*=7.0, *J*=2.5, CH₂C≡CH), 1.91 (1H, t, *J*=4.0, C≡CH), 1.56-1.46 (4H, m, 2×CH₂), 1.34-1.22 (14H, m, 7 × CH₂). δ_C (100 MHz, CDCl₃) 84.7, 72.9, 68.0, 58.5, 29.7, 29.5 (6C), 28.8, 26.2, 18.4. HRMS (FI⁺) calculated for C₁₄H₂₆ONa⁺ [M+Na]⁺ 233.1881, found 233.1885.

(*E*)-1-Bromo-13-methoxytridec-1-ene, 35



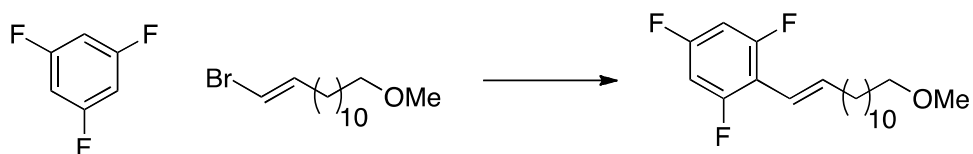
A round bottom flask charged with *bis*(cyclopentadienyl)zirconium(IV) dichloride (2.71 g, 9.27 mmol, 1.5 eq) was purged with argon. THF (30 mL) was added followed by dropwise addition of a solution of Superhydride (1.0 M in THF, 9.27 mL, 9.27 mmol, 1.5 eq). The reaction mixture was stirred in the dark for 1 h before a solution of 13-methoxytridec-1-yne (1.30 g, 6.18 mmol, 1 eq) in THF (30 mL) was added. The reaction was stirred for 15 min before NBS (1.65 g, 9.27 mmol, 1.5 eq) was added. When the reaction mixture turned cloudy, it was poured into a saturated solution of sodium bicarbonate (30 mL). The reaction was extracted with diethyl ether (3 × 30 mL), and the combined organic layers were washed with a saturated solution of sodium bicarbonate (30 mL), brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (5% diethyl ether/petrol) to yield the title compound as colourless oil (1.36 g, 76%). ν_{max} (liquid film)/cm⁻¹ 2926, 2845, 1621, 1462, 1386, 1196, 1120, 732, 685. δ_H (400 MHz, CDCl₃) 6.22-6.17 (1H, m, CH=HBr), 6.05 (1H, dt, *J*=12.0, *J*=2.0, CHBr), 3.31 (2H, t, *J*=7.0, CH₂OMe), 3.27 (3H, s, CH₂OCH₃), 2.04 (2H, m, CH₂CH=CHBr), 1.57-1.51 (2H, m, CH₂), 1.34-1.22 (16H, m, 8 × CH₂). δ_C (100 MHz,

CDCl₃) 138.9, 104.2, 72.9, 58.5, 33.0, 29.7, 29.5 (4C), 29.4, 29.0, 27.8, 26.1. HRMS (FI⁺) calculated for C₁₄H₂₇⁷⁹BrO [M]⁺ 290.1245, found 290.1255

General Procedure A: Direct arylation of polyfluorobenzenes

A microwave tube containing base (2.5 eq) was purged with argon. A solution of the alkenyl bromide (1 eq) in arene (5 eq) was added followed by a solution of Pd source (5 mol%) and pivalic acid (0.3 eq) in DMA. The reaction mixture was heated in the microwave to 120 °C for 30 min. The reaction was cooled, diluted with diethyl ether and washed with water. The organic layer was washed with brine and dried over MgSO₄, filtered and dried *in vacuo*. The crude product was purified using flash column chromatography (5% diethyl ether/petrol) to yield the coupled product.

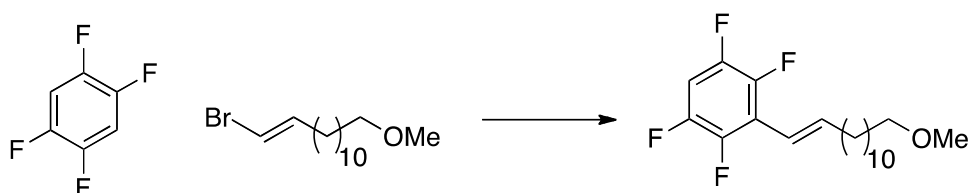
(*E*)-1,3,5-Trifluoro-2-(12-methoxydodec-1-enyl)benzene, 41



Synthesized using General Procedure A. Potassium carbonate (167 mg, 1.21 mmol, 2.5 eq), (*E*)-1-Bromo-13-methoxytridec-1-ene (140 mg, 0.49 mmol, 1 eq), 1,3,5-trifluorobenzene (250 μ L, 2.42 mmol, 5 eq) allyl palladium chloride dimer (4.8 mg, 0.01 mmol, 0.025 eq), pivalic acid (15 mg, 0.15 mmol, 0.3 eq) and DMA (2.4 mL). The title compound was isolated as a colourless oil (35 mg, 34%). ν_{max} (liquid film)/cm⁻¹ 2926, 2854, 1619, 1464, 1120. δ_{H} (400 MHz, CDCl₃) 6.64 (2H, t, $J_{\text{F}}=8.0$, 2 $\times$ ArH), 6.47-6.43 (1H, m, ArCH=CH), 6.30-6.26 (1H, m, ArCH=CH), 3.37 (2H, t, $J=7.0$, CH₂OCH₃), 3.32 (3H, s, CH₂OCH₃), 2.23 (2H, q, $J=7.0$, CH₂CH=CHAr), 1.59-1.54 (2H, m, CH₂), 1.51-1.44 (2H, m, CH₂), 1.37-1.24 (14H, m, 7 $\times$ CH₂). δ_{C} (100

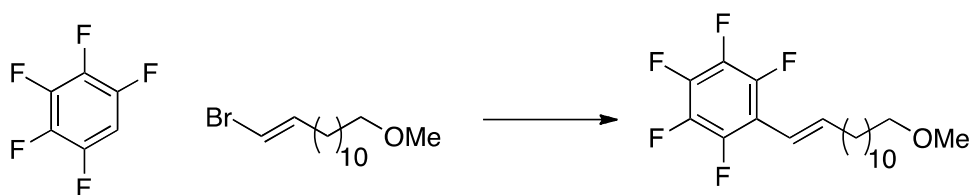
MHz, CDCl₃) 138.4, 115.2, 100.2, 99.9, 73.0, 58.6, 38.1, 34.3, 31.2, 29.7, 29.5, 29.2, 29.1, 26.2. ¹³C NMR not strong enough to see aromatic carbons due to multiple splitting from the fluorines. HRMS (FI⁺) calculated for C₂₀H₂₉F₃O [M]⁺ 342.2171, found 342.2169.

(E)-1,2,4,5-Tetrafluoro-3-(12-methoxydodec-1-enyl)benzene, 43



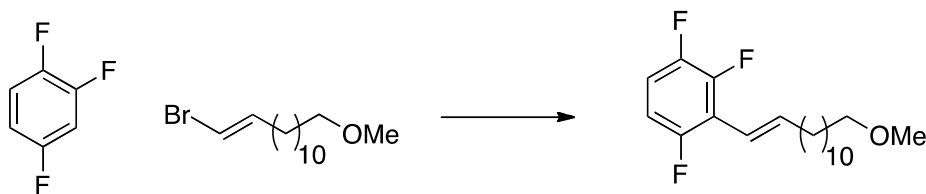
Synthesized using General Procedure A. Potassium carbonate (167 mg, 1.21 mmol, 2.5 eq), (E)-1-bromo-13-methoxytridec-1-ene (140 mg, 0.49 mmol, 1 eq), 1,3,4,5-trifluorobenzene (250 μ L, 2.42 mmol, 5 eq), allyl palladium chloride dimer (4.8 mg, 0.01 mmol, 0.025 eq), pivalic acid (15 mg, 0.15 mmol, 0.3 eq) and DMA (2.4 mL). The title compound was isolated as a colourless oil (50 mg, 29%). ν_{max} (liquid film)/cm⁻¹ 2927, 2855, 1743, 1641, 1453, 1387, 1280, 1251, 1171, 1144, 1120. δ_{H} (400 MHz, CDCl₃) 6.92-6.83 (1H, m, ArH), 6.62 (1H, dt, $J=16.0$, $J=7.0$, ArCH=CH), 6.35 (1H, d, $J=16.0$, ArCH=CH), 3.37 (2H, t $J=7.0$, CH₂OCH₃), 3.33 (3H, s, CH₂OCH₃), 2.27 (2H, q, $J=7.0$, CH₂CH=CHAr), 1.60-1.53 (2H, m, CH₂), 1.51-1.45 (2H, m, CH₂), 1.37-1.24 (12H, m, 6 $\times$ CH₂). δ_{C} (100 MHz, CDCl₃) 141.6, 115.2, 100.2, 99.9, 73.0, 58.5, 34.3, 29.6, 29.5, 29.4, 29.2, 28.9, 26.1. ¹³C NMR not strong enough to see aromatic carbons due to multiple splitting from the fluorines. HRMS (FI⁺) calculated for C₂₀H₂₈F₄O [M]⁺ 360.2076, found 360.2080.

(E)-Pentafluoro-(12-methoxydodec-1-enyl)benzene, 44



Synthesized using General Procedure A. Potassium carbonate (167 mg, 1.21 mmol, 2.5 eq), (E)-1-bromo-13-methoxytridec-1-ene (140 mg, 0.49 mmol, 1 eq), pentafluorobenzene (270 μ L, 2.42 mmol, 5 eq) allyl palladium chloride dimer (4.8 mg, 0.01 mmol, 0.03 eq), pivalic acid (15 mg, 0.15 mmol, 0.3 eq) and DMA (2.4 mL). The title compound was isolated as a colourless oil (61 mg, 33%). $\nu_{\max}$ (liquid film)/ cm^{-1} 2928, 2856, 1521, 1492, 1465, 1120. δ_{H} (400 MHz, CDCl_3) 6.55 (1H, dt, $J=16.5$, $J=7.0$, ArCH=CH), 6.25 (1H, d, $J=16.5$, ArCH=CH), 3.36 (2H, t, $J=7.0$, CH_2OCH_3), 3.32 (3H, s, CH_2OCH_3), 2.24 (2H, q, $J=7.0$, $\text{CH}_2\text{CH=CHAr}$), 1.59-1.53 (2H, m, CH_2), 1.50-1.45 (2H, m, CH_2), 1.37-1.24 (14H, m, $7 \times \text{CH}_2$). δ_{C} (100 MHz, CDCl_3) 141.3, 113.9, 72.9, 58.5, 34.3, 29.5 (2C), 29.4 (2C), 29.1, 28.8 26.1. ^{13}C NMR not strong enough to see aromatic carbons due to multiple splitting from the fluorines. HRMS (FI^+) calculated for $\text{C}_{20}\text{H}_{27}\text{F}_5\text{O}$ $[\text{M}]^+$ 378.1981, found 378.1980.

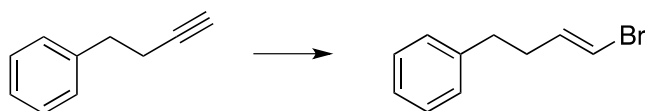
(E)-1,2,4-Trifluoro-3-(12-methoxydodec-1-enyl)benzene, 45



Synthesized using General Procedure A. Potassium carbonate (167 mg, 1.21 mmol, 2.5 eq), (E)-1-bromo-13-methoxytridec-1-ene (140 mg, 0.49 mmol, 1 eq), 1,2,4-trifluorobenzene (250 μ L, 2.42 mmol, 5 eq), allyl palladium chloride dimer (4.8 mg, 0.01 mmol, 0.025 eq), pivalic acid (15 mg, 0.15 mmol, 0.3 eq) and DMA (2.4 mL).

The title compound was isolated as a colourless oil (26 mg, 16%). $\nu_{\max}$ (liquid film)/ cm^{-1} 2927, 2855, 1743, 1509, 1492, 1143, 1121. δ_{H} (400 MHz, CDCl_3) 6.75-6.64 (2H, m, $2 \times \text{ArH}$), 6.48-6.41 (1H, m, ArCH=CH), 6.32-6.26 (1H, m, ArCH=CH), 3.36 (2H, t $J=7.0$, CH_2OCH_3), 3.33 (3H, s, CH_2OCH_3), 2.25-2.19 (2H, m, $\text{CH}_2\text{CH=CHAr}$), 1.60-1.54 (2H, m, CH_2), 1.49-1.27 (2H, m, CH_2), 1.37-1.27 (14H, m, $7 \times \text{CH}_2$). δ_{C} (100 MHz, CDCl_3) 138.4, 115.3, 100.2, 99.9, 73.0, 58.7, 38.1, 34.4, 31.4, 29.7, 29.4, 29.2, 29.1, 26.2. ^{13}C NMR not strong enough to see aromatic carbons due to multiple splitting from the fluorines. HRMS (FI^+) calculated for $\text{C}_{20}\text{H}_{29}\text{F}_3\text{O}$ $[\text{M}]^+$ 342.2171, found 342.2170.

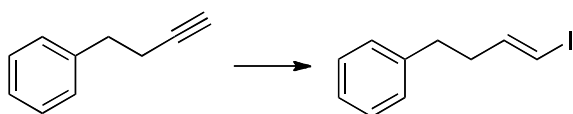
(E)-(4-Bromobut-3-en-1-yl)benzene, 46



A round bottom flask charged with *bis*(cyclopentadienyl)zirconium(IV) dichloride (4.50 g, 15.4 mmol, 2 eq) was purged with argon. THF (35 mL) was added followed by dropwise addition of Superhydride (1.0 M in THF, 15.4 mL, 15.4 mmol, 2 eq). The reaction mixture was stirred in the dark for 1 h before a solution of the but-3-yn-1-ylbenzene (1.00 g, 7.68 mmol, 1 eq) in THF (35 mL) was added. The reaction was stirred for 15 min and cooled to 0 °C before the NBS (2.74 g, 15.4 mmol, 2 eq) was added. The reaction mixture was stirred for 1 h whereafter it was poured into saturated solution of sodium bicarbonate (50 mL). The reaction was extracted with diethyl ether (3×50 mL), and the combined organic layers were washed with brine (50 mL) and dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (100% petrol) to yield the title compound as a colourless oil (1.27 g, 79%). $\nu_{\max}$ (neat)/ cm^{-1} 3020, 2928, 2853, 1603, 1496, 1453,

1206, 1029, 941, 751, 698, 667. δ_{H} (400 MHz, CDCl_3) 7.31-7.24 (2H, m, $2 \times \text{ArH}$), 7.20-7.13 (3H, m, $3 \times \text{ArH}$), 6.15 (1H, dt, $J=15.0$, $J=8.0$, $\text{CH}=\text{CHBr}$), 6.09-6.05 (1H, m, $\text{CH}=\text{CHBr}$), 2.73 (2H, t, $J=8.0$, ArCH_2), 2.36 (2H, q, $J=8.0$, CHCH_2CH_2). δ_{C} (100 MHz, CDCl_3) 144.9, 128.4, 128.4, 126.0, 125.5, 123.4, 116.5, 84.1, 41.2, 37.8, 34.7. HRMS (FI^+) calculated for $\text{C}_{10}\text{H}_{11}^{79}\text{Br}$ $[\text{M}]^+$ 210.0044, found 210.0051.

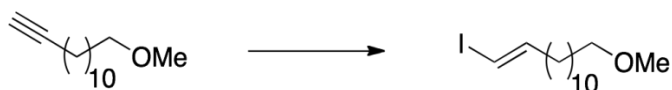
(E)-(4-Iodobut-3-en-1-yl)benzene, 47



A round bottom flask charged with *bis*(cyclopentadienyl)zirconium(IV) dichloride (4.49 g, 15.4 mmol, 2 eq) was purged with argon. THF (35 mL) was added followed by dropwise addition of Superhydride (1.0 M in THF, 15.4 mL, 15.4 mmol, 2 eq). The reaction mixture was stirred in the dark for 1 h before a solution of the but-3-yn-1-ylbenzene (1.00 g, 7.68 mmol, 1 eq) in THF (35 mL) was added. The reaction was stirred for 15 min and cooled to 0 °C before the NIS (3.45 g, 15.4 mmol, 2 eq) was added. The reaction mixture was stirred for 1 h whereafter it was poured into saturated solution of sodium bicarbonate (50 mL). The reaction was extracted with diethyl ether (3×50 mL), and the combined organic layers were washed with brine (50 mL) and dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified using Combiflash Rf (0 – 20% ethyl acetate/*iso*-hexane) to yield the title compound as a colourless oil (1.70 g, 86%). ν_{max} (neat)/ cm^{-1} 3026, 2922, 2854, 1603, 1496, 1453, 1205, 1029, 940, 751, 692, 667. δ_{H} (400 MHz, CDCl_3) 7.30-7.25 (2H, m, $2 \times \text{ArH}$), 7.20-7.12 (3H, m, $3 \times \text{ArH}$), 6.55 (1H, dt, $J=16.0$, $J=7.0$, $\text{CH}=\text{CHI}$), 6.03 (1H, dt, $J=16.0$, $J=1.5$, $\text{CH}=\text{CHI}$), 2.70 (2H, t, $J=8.0$, ArCH_2), 2.35 (2H, q, $J=8.0$, CHCH_2CH_2). δ_{C} (100 MHz, CDCl_3) 145.5, 140.8, 128.4, 128.1, 126.0, 125.5, 84.1, 41.2, 37.7, 34.7.

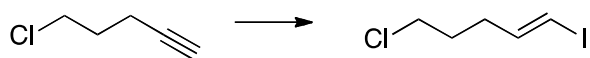
HRMS (FI⁺) calculated for C₁₀H₁₁I [M]⁺ 257.9906, found 257.9907. Data in accordance with literature.¹⁴⁴

(E)-1-Iodo-13-methoxytridec-1-ene, 48



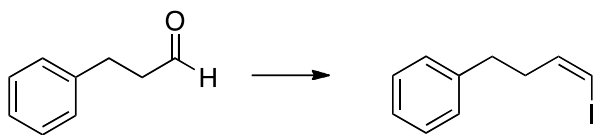
A round bottom flask charged with *bis*(cyclopentadienyl)zirconium(IV) dichloride (2.71 g, 9.27 mmol, 1.5 eq) was purged with argon. THF (30 mL) was added followed by dropwise addition of Superhydride (1.0 M in THF, 9.27 mL, 9.27 mmol, 1.5 eq). The reaction mixture was stirred in the dark for 1 h before a solution of 13-methoxytridec-1-yne (1.30 g, 6.18 mmol, 1 eq) in THF (30 mL) was added. The reaction was stirred for 15 min before NIS (1.65 g, 9.27 mmol, 1.5 eq) was added. When the reaction mixture turned cloudy, it was poured into saturated solution of sodium bicarbonate (30 mL). The reaction was extracted with diethyl ether (3 × 30 mL), and the combined organic layers were washed with saturated solution of sodium thiosulfate (30 mL), brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (5% diethyl ether/petrol) to yield the title compound as a colourless oil (1.88 g, 90%). $\nu_{\max}$ (neat)/cm⁻¹ 2920, 2846, 1621, 1463, 1388, 1196, 1126. δ_{H} (400 MHz, CDCl₃) 6.55-6.50 (1H, m, CH=CHI), 6.15 (1H, dt, *J*=12.0, *J*=2.5, CHI), 3.32 (2H, t, *J*=7.0, CH₂OMe), 3.28 (3H, s, CH₂OCH₃), 2.03 (2H, m, CH₂CH=CHI), 1.57-1.51 (2H, m, CH₂), 1.34-1.21 (16H, m, 8 × CH₂). δ_{C} (100 MHz, CDCl₃) 141.0, 82.1, 72.8, 59.3, 33.8, 29.8, 29.5 (4C), 29.3, 29.0, 27.8, 26.1. HRMS (FI⁺) calculated for C₁₄H₂₇OI [M]⁺ 338.1107, found 338.1107.

(E)-5-Chloro-1-iodopent-1-ene, 49



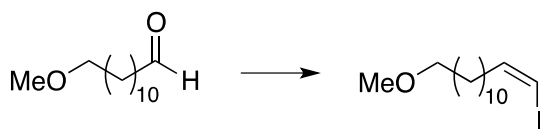
A round bottom flask charged with *bis*(cyclopentadienyl)zirconium(IV) dichloride (8.30 g, 28.38 mmol, 1.5 eq) was purged with argon. THF (90 mL) was added followed by dropwise addition of Superhydride (1 M in THF, 28.4 mL, 28.4 mmol, 1.5 eq). The reaction mixture was stirred in the dark for 1 h before a solution of 5-chloro-1-pentyne (2.00 mL, 18.9 mmol, 1 eq) in THF (90 mL) was added. The reaction was stirred for 15 min and cooled to 0 °C before NIS (6.38 g, 28.4 mmol, 1.5 eq) was added. The reaction mixture was stirred for 1h where after it was poured into a saturated solution of sodium bicarbonate (100 mL). The reaction was extracted with diethyl ether (3 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography (5% ethyl acetate/petrol) to yield the title compound as a colourless oil (2.88 g, 73%). ν_{max} (neat)/cm⁻¹ 2955, 1606, 1441, 1270, 1217, 943, 860, 780, 728, 650. δ_{H} (400 MHz, CDCl₃) 6.48 (1H, dt, $J=14.0$, $J=7.0$, CHCH₂), 6.10 (1H, d, $J=14.0$, ICH=CH), 3.53 (2H, t, $J=6.0$, ClCH₂), 2.23 (2H, q, $J=7.0$, CHCH₂), 1.86 (2H, quin, $J=7.0$, CH₂). δ_{C} (100 MHz, CDCl₃) 144.4, 76.1, 43.8, 33.0, 30.9. HRMS (FI⁺) calculated for C₅H₈³⁵ClI [M]⁺ 229.9359, found 229.9369.

(Z)-(4-Iodobut-3-en-1-yl)benzene, 50



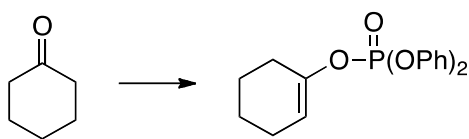
A suspension of (iodomethyl)trimethylphosphonium iodide (5.00 g, 9.40 mmol, 1.5 eq) in THF (40 mL) was treated with NaHMDS (4.40 mL, 8.78 mmol, 1.4 eq) at room temperature. When the mixture turned orange, the reaction was cooled to -78 °C and DMPU (5.69 mL, 47.0 mmol, 7.5 eq) was added. After 10 min a solution of hydrocinnamaldehyde (825 μ L, 6.27 mmol, 1 eq) in THF (16 mL) was added *via* cannula and round bottom flask was washed with THF (6 mL). The reaction was stirred for a further 30 min at -78 °C and 30 min at rt. The reaction was poured into vigorously stirring hexane (200 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* and redissolved in diethyl ether. The organic layer was washed with saturated ammonium chloride (50 mL), water (2 $\times$ 50 mL), brine (50 mL) and dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography (5% diethyl ether/petrol) to yield the the title compound as a pale yellow oil (1.59 g, 98%). ν_{max} (neat)/cm⁻¹ 3028, 2915, 2853, 1603, 1495, 1449, 1211, 1029, 941 761, 693, 665. δ_{H} (400 MHz, CDCl₃) 7.38-7.33 (2H, m, 2 $\times$ ArH), 7.29-7.23 (3H, m, 3 $\times$ ArH), 7.03 (1H, t, J =7.0, CH=CHI), 6.29-6.24 (1H, m, CH=CHI), 2.79 (2H, t, J =8.0, ArCH₂), 2.32-2.28 (2H, m, CHCH₂CH₂). δ_{C} (100 MHz, CDCl₃) 151.9, 140.5, 140.3, 128.5, 128.2, 126.3, 83.3, 41.3, 36.4, 34.1. HRMS (FI⁺) calculated for C₁₀H₁₁I [M]⁺ 257.9906, found 257.9907. Data in accordance with literature.¹⁴⁴

(Z)-1-Iodo-13-methoxytridec-1-ene, 51



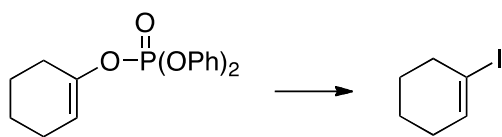
A suspension of (iodomethyl)trimethylphosphonium iodide (5.00 g, 9.40 mmol, 1.5 eq) in THF (40 mL) was treated with NaHMDS (4.40 mL, 8.78 mmol, 1.4 eq) at room temperature. When the mixture turned orange, the reaction was cooled to -78 °C and DMPU (5.69 mL, 47.0 mmol, 7.5 eq) was added. After 10 min a solution of 12-methoxydodec-1-al (1.34 g, 6.27 mmol, 1 eq) in THF (16 mL) was added *via* cannula and round bottom flask was washed with THF (6 mL). The reaction was stirred for a further 30 min at -78 °C and 30 min at rt. The reaction was poured into vigorously stirring hexane (200 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* and redissolved in diethyl ether. The organic layer was washed with saturated ammonium chloride (50 mL), water (2 × 50 mL), brine (50 mL) and dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography (5% diethyl ether/petrol) to yield the title compound as a pale yellow oil (1.69 g, 80%). ν_{max} (neat)/cm⁻¹ 2925, 2845, 1624, 1463, 1386, 1196, 1129, 958. δ_{H} (400 MHz, CDCl₃) 6.60-6.57 (1H, m, CH=CHI), 6.16-14 (1H, m, CHI), 3.31 (2H, t, *J*=7.0, CH₂OMe), 3.27 (3H, s, CH₂OCH₃), 2.04 (2H, m, CH₂CH=CHI), 1.57-1.51 (2H, m, CH₂), 1.34-1.22 (16H, m, 8 × CH₂). δ_{C} (100 MHz, CDCl₃) 143.3, 102.5, 72.9, 58.5, 33.0, 29.7, 29.5 (4C), 29.4, 29.0, 27.8, 26.1. HRMS (FI⁺) calculated for C₁₄H₂₇OI [M]⁺ 338.1107, found 338.1107.

Phosphoric acid cyclohex-1-enyl ester diphenyl ester, 52



LDA (1.8 M in THF, 6.22 mL, 11.21 mmol, 1.1 eq) was added to a solution of cyclohexanone (1.06 mL, 10.2 mmol, 1 eq) in THF (10 mL) at -78 °C. The reaction mixture was stirred for 30 min before a solution of diphenyl phosphate (3.17 mL, 15.3 mmol, 1.5 eq) in THF (10 mL). The reaction was stirred for a further 30 min at the same temperature before warming up to rt and stirring for 1 h. The reaction was quenched with a saturated solution of ammonium chloride (10 mL). The reaction mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using Combiflash Rf (0 – 20% ethyl acetate/*iso*-hexane) to yield the title compound as a colourless oil (2.83 g, 88%). ν_{max} (neat)/cm⁻¹ 3072, 2932, 2843, 1683, 1589, 1488, 1297, 1187, 1161, 1111, 1008, 956, 754, 688. δ_{H} (400 MHz, CDCl₃) 7.37-7.32 (4H, m, 4 × ArH), 7.26-7.22 (4H, m, 4 × ArH), 7.20-7.18 (2H, m, 2 × ArH), 5.57 (1H, m, CHCH₂), 2.22-2.17 (2H, m, CHCH₂), 2.11-2.05 (2H, m, CH₂), 1.75-1.65 (2H, m, CH₂), 1.59-1.50 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 129.7 (6C), 125.3, 120.4 (4C), 120.3, 120.1, 120.0, 27.5, 23.5, 22.6, 21.4. δ_{P} (400 MHz, CDCl₃) -17.4. HRMS (ESI⁺) calculated for C₁₈H₁₉O₄P [M]⁺ 353.0913, found 353.0907.

1-Iodocyclohexene, 53



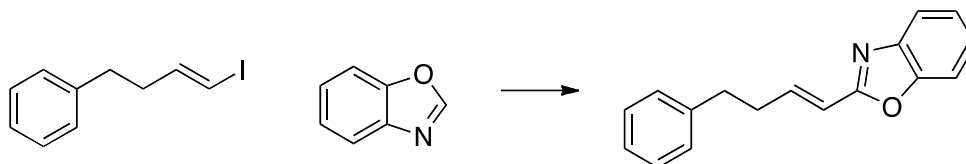
TMSI (3.80 mL, 26.7 mmol, 3 eq) was added dropwise to a solution of phosphoric acid cyclohex-1-enyl ester diphenyl ester (2.80 g, 8.91 mmol, 1 eq) in DCM (20 mL) maintaining the internal temperature below 25 °C. The reaction was stirred for 30 min where after it was quenched with a saturated solution of ammonium chloride (5 mL). The reaction was extracted with DCM (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using a Combiflash Rf (0 – 20% ethyl acetate/*iso*-hexane) to yield the title compound as pale pink oil (1.27 g, 69%). ν_{max} (neat)/cm⁻¹ 2957, 2855, 1443, 1327, 1242, 1113, 990. 727, 674. δ_{H} (400 MHz, CDCl₃) 6.46 (1H, sept, *J*=2.0, CHCH₂), 2.51-2.43 (2H, m, CHCH₂), 2.11-2.05 (2H, m, CH₂), 1.75-1.60 (4H, m, 2 × CH₂). δ_{C} (100 MHz, CDCl₃) 137.4, 54.7, 39.3, 28.9, 25.3, 20.8. HRMS (FI⁺) calculated for C₆H₉I [M]⁺ 207.9749, found 207.9749. Data in accordance with literature.¹⁴⁵

General Procedure B: Direct arylation of heterocycles

A 10 mL boiling tube was charged with silver carbonate (2 eq), ligand (10 mol%), palladium salt (5 mol%). The solids were mixed thoroughly before the arene (2 eq) and alkenyl iodide (1 eq) were added, follow by water (3.5 mL). The reaction mixture was heated to 100 °C for 60 min in a sealed tube. The reaction was cooled, filtered through a Celite pad and washed with acetone and DCM. The solvent was concentrated and redissolved in DCM and washed with water. The organic layer was washed with brine

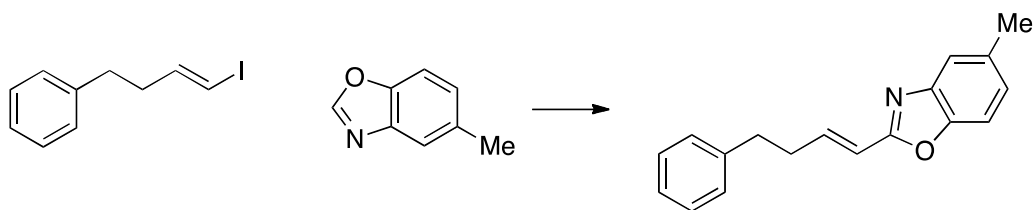
and dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified using a Combiflash Rf (0 – 20% ethyl acetate/ *iso*-hexane) or by flash chromatography (10% ethyl acetate/ petrol).

2-((*E*)-4-Phenyl-but-1-enyl)-benzoxazole, 54



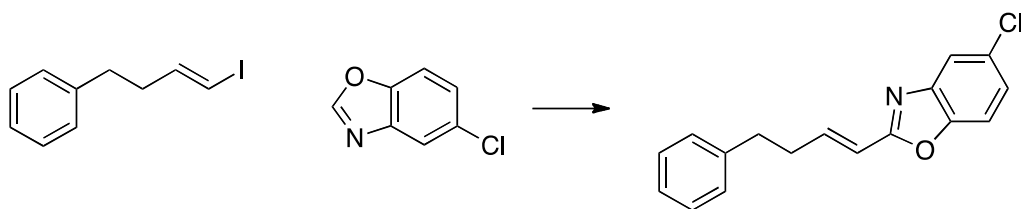
Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), $\text{Pd(dppf)Cl}_2 \cdot \text{DCM}$ (20 mg, 0.03 mmol, 5 mol%), benzoxazole (119 mg, 1.00 mmol, 2 eq) and (*E*)-(4-iodobut-3-en-1-yl)benzene (129 mg, 0.50 mmol, 1 eq). The title compound was isolated as a pale brown waxy solid (85 mg, 70%). ν_{max} (neat)/ cm^{-1} 3026, 2926, 1659, 1538, 1453, 1243, 1176, 966, 759, 699. δ_{H} (400 MHz, CDCl_3) 7.70-7.65 (1H, m, ArH), 7.50-7.45 (1H, m, ArH), 7.31-7.26 (4H, m, 4 $\times$ ArH), 7.23-7.18 (3H, m, 3 $\times$ ArH), 7.05 (1H, dt, $J=16.0$, $J=7.0$, CH=CHAr), 6.45 (1H, dt, $J=16.0$, $J=2.0$, CH=CHAr), 2.85 (2H, t, $J=8.0$, ArCH₂), 2.65 (2H, q, $J=7.0$, CHCH₂CH₂). δ_{C} (100 MHz, CDCl_3) 1150.2, 42.8, 140.7, 128.5 (2C), 128.4 (2C), 126.1, 124.9, 124.3, 119.7, 117.4, 110.2, 34.7, 34.6. HRMS (ESI^+) calculated for $\text{C}_{17}\text{H}_{16}\text{NO}^+$ [$\text{M}+\text{H}$] $^+$ 250.1226, found 250.1223.

(E)-5-Methyl-2-(4-phenylbut-1-en-1-yl)benzoxazole, 55



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), 5-methylbenzoxazole (133 mg, 1.00 mmol, 2 eq) and (E)-(4-iodobut-3-en-1-yl)benzene (129 mg, 0.50 mmol, 1 eq). The title compound was isolated as a brown solid (109 mg, 83%). ν_{max} (neat)/cm⁻¹ 3027, 2919, 1654, 1535, 1259, 963, 802, 799. δ_{H} (400 MHz, CDCl₃) 7.48 (1H, s, ArH), 7.37-7.31 (3H, m, 3 × ArH), 7.25-7.21 (3H, m, 3 × Ar), 7.13-7.11 (1H, m, Ar), 7.05 (1H, dt, $J=16.0$, $J=7.0$, CH=CHAr), 6.46 (1H, dt, $J=16.0$, $J=2.0$, CH=CHAr), 2.87 (2H, t, $J=8.0$, ArCH₂), 2.63-2.69 (2H, m, CHCH₂CH₂), 2.47 (3H, s, CH₃). δ_{C} (100 MHz, CDCl₃) 148.5, 142.5, 142.0, 148.0, 134.1, 128.5 (3C), 128.2 (2C), 126.1, 126.0, 119.7, 117.5, 109.6, 34.7, 34.6, 21.4. HRMS (ESI⁺) calculated for C₁₈H₁₈NO⁺ [M+H]⁺ 264.1383, found 264.1378. M.p. (diethyl ether/chloroform) = 53-54 °C.

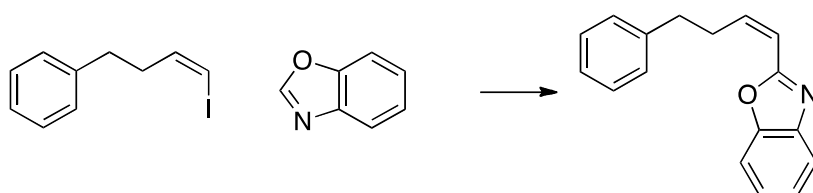
(E)-5-Chloro-2-(4-phenylbut-1-en-1-yl)benzoxazole, 56



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), 5-chlorobenzoxazole (154 mg, 1.00 mmol, 2 eq) and (E)-(4-iodobut-

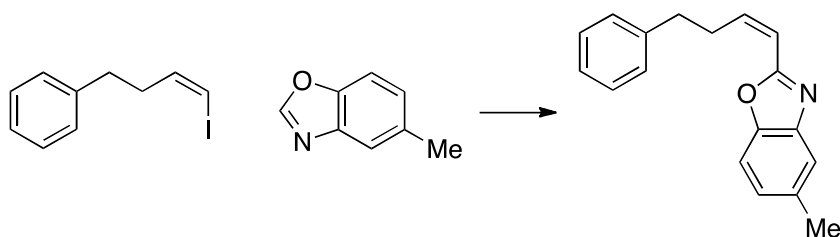
3-en-1-yl)benzene (129 mg, 0.50 mmol, 1 eq). The title compound was isolated as a pale brown solid (57 mg, 40%). $\nu_{\max}$ (neat)/ cm^{-1} 3027, 2927, 2858, 1703, 1470, 1333, 1129, 920, 857. δ_{H} (400 MHz, CDCl_3) 7.65 (1H, s, ArH), 7.39 (2H, d, $J=8.5$, $2 \times \text{ArH}$), 7.36-7.30 (2H, m, $2 \times \text{Ar}$), 7.29-7.26 (1H, m, ArH), 7.24-7.22 (2H, m, $2 \times \text{ArH}$), 7.08 (1H, dt, $J=16.0$, $J=7.0$, $\text{CH}=\text{CHAr}$), 6.44 (1H, d, $J=16.0$, $\text{CH}=\text{CHAr}$), 2.87 (2H, t, $J=8.0$, ArCH_2), 2.67 (2H, q, $J=7.0$, CHCH_2CH_2). δ_{C} (100 MHz, CDCl_3) 163.3, 148.8, 143.8, 143.0, 140.6, 129.7 (2C), 128.5 (2C), 126.2 (2C), 125.1, 119.7, 117.1, 110.9, 34.6 (2C). HRMS (ESI^+) calculated for $\text{C}_{17}\text{H}_{15}\text{ClNO}^+$ $[\text{M}+\text{H}]^+$ 284.0837, found 284.0832. M.p. (diethyl ether/chloroform) = 43-45 °C.

(Z)-2-(4-Phenylbut-1-en-1-yl)benzoxazole, 57



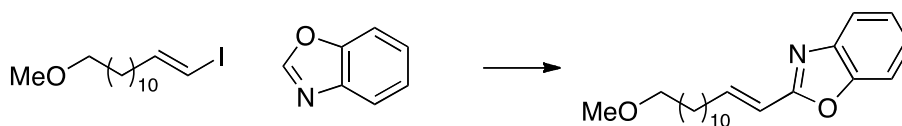
Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), $\text{Pd(dppf)Cl}_2 \cdot \text{DCM}$ (20 mg, 0.03 mmol, 5 mol%), benzoxazole (119 mg, 1.00 mmol, 2 eq) and (Z)-4-iodobut-3-en-1-yl)benzene (129 mg, 0.50 mmol, 1 eq). The title compound was isolated as a dark yellow oil (137 mg, 99%). $\nu_{\max}$ (neat)/ cm^{-1} 3026, 2923, 2857, 1603, 1475, 1285, 1141, 821, 742. δ_{H} (400 MHz, CDCl_3) 7.77-7.75 (1H, m, Ar), 7.55-7.51 (1H, m, ArH), 7.38-7.30 (6H, m, $6 \times \text{ArH}$), 7.28-7.24 (1H, m, ArH), 6.45 (1H, dt, $J=12.0$, $J=1.5$, $\text{CH}=\text{CHAr}$), 6.30 (1H, dt, $J=12.0$, $J=4.5$, $\text{CH}=\text{CHAr}$), 3.26-3.20 (2H, m, ArCH_2), 2.91 (2H, t, $J=7.5$, CHCH_2CH_2). δ_{C} (100 MHz, CDCl_3) 162.2, 149.9, 143.7, 141.7, 141.2, 128.5 (2C), 128.4 (2C), 126.1, 125.0, 124.4, 120.0, 115.7, 110.4, 35.2, 31.3. HRMS (ESI^+) calculated for $\text{C}_{17}\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 250.1226, found 250.1224.

(Z)-5-Methyl-2-(4-phenylbut-1-en-1-yl)benzoxazole, 58



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), 5-methylbenzoxazole (133 mg, 1.00 mmol, 2 eq) and (Z)-(4-iodobut-3-en-1-yl)benzene (129 mg, 0.50 mmol, 1 eq). The title compound was isolated as a dark yellow solid (77 mg, 59%). ν_{max} (neat)/cm⁻¹ 3027, 2919, 2860, 1655, 1536, 1453, 1299, 1181, 963, 831. δ_{H} (400 MHz, CDCl₃) 7.47 (1H, s, ArH), 7.30-7.37 (3H, m, 3 × ArH), 7.25-7.21 (3H, m, 3 × ArH), 7.13-7.11 (1H, m, ArH), 7.09-7.01 (1H, m, CH=CHAr), 6.46 (1H, dt, *J*=16.0, *J*=1.5, CH=CHAr), 2.89-2.85 (2H, m, ArCH₂), 2.70-2.64 (2H, m, CHCH₂CH₂), 2.46 (3H, s, CH₃). δ_{C} (100 MHz, CDCl₃) 162.4, 142.5, 140.8, 134.1, 128.5, 128.4, 128.3, 128.2, 126.1, 126.0, 119.6, 117.4, 109.6, 34.7, 34.6, 21.4. HRMS (ESI⁺) calculated for C₁₈H₁₈NO⁺ [M+H]⁺ 264.1383, found 264.1382. M.p. (diethyl ether/chloroform) = 58-59 °C.

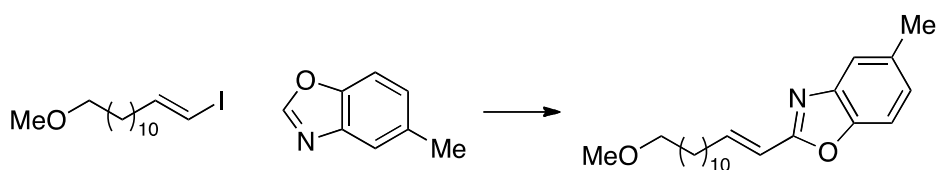
(E)-2-(13-Methoxytridec-1-en-1-yl)benzoxazole, 59



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), benzoxazole (119 mg, 1.00 mmol, 2 eq) and (E)-1-iodo-13-

methoxytridec-1-ene (169 mg, 0.50 mmol, 1 eq). The title compound was isolated as a waxy orange solid (80 mg, 49%). $\nu_{\max}$ (neat)/ cm^{-1} 2918, 2848, 1662, 1539, 1454, 1243, 1117, 845, 741. δ_{H} (400 MHz, CDCl_3) 7.69-7.65 (1H, m, ArH), 7.48-7.44 (1H, m, ArH), 7.30-7.26 (2H, m, 2 $\times$ ArH), 7.03 (1H, dt, $J=16.0$, $J=7.0$, CH=CHAr), 6.42 (1H, dt, $J=16.0$, $J=2.0$, CH=CHAr), 3.35 (2H, t, $J=6.5$, MeOCH_2), 3.32 (3H, s, OCH_3), 2.35-2.29 (2H, m, CH_2), 1.57-1.48 (4H, m, 2 $\times$ CH_2), 1.34-1.28 (14H, m, 7 $\times$ CH_2). δ_{C} (100 MHz, CDCl_3) 162.5, 150.2, 144.3, 141.9, 128.5, 128.4, 124.8, 124.2, 119.6, 116.7, 110.1, 72.9, 58.5, 33.0, 29.6, 29.5, 29.4 (2C), 29.2, 28.4, 26.1. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{32}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 330.2428, found 330.2421.

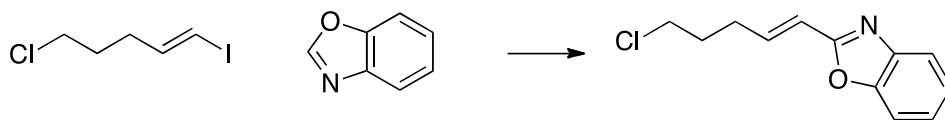
(E)-2-(13-methoxytridec-1-en-1-yl)-5-methylbenzoxazole, 60



Synthesized using general procedure A. Ag_2CO_3 (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 0.10 eq), $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{DCM}$ (20 mg, 0.025 mmol, 0.05 eq), 5-methylbenzoxazole (133 mg, 1.00 mmol, 2 eq) and vinyl iodide (169 mg, 0.50 mmol, 1 eq). The title product was isolated as a light brown waxy solid (133 mg, 78%). $\nu_{\max}$ (liquid film)/ cm^{-1} 2919, 2848, 1538, 1459, 1259, 1118, 963, 801. δ_{H} (400 MHz, CDCl_3) 7.44-7.42 (1H, m, Ar), 7.34-7.31 (1H, m, Ar), 7.10-7.01 (1H, m, Ar), 6.99 (1H, dt, $J=16.0$, $J=7.0$, CH=CHAr), 6.40 (1H, dt, $J=16.0$, $J=1.5$, CH=CHAr), 3.35 (2H, t, $J=6.5$, MeOCH_2), 3.31 (3H, s, CH_3), 2.47-2.43 (2H, m, CH_2), 1.59-1.48 (4H, m, 2 $\times$ CH_2), 1.36-1.26 (14H, m, 7 $\times$ CH_2). δ_{C} (100 MHz, CDCl_3) 162.3, 150.2, 143.8, 134.0, 128.6, 128.5, 124.8, 124.7, 119.6, 116.8, 109.5, 72.9, 58.5, 29.6, 29.5,

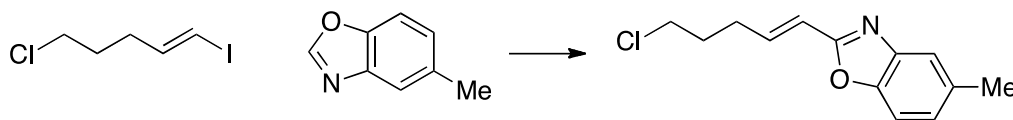
29.2 (2C), 29.1, 28.4, 26.1 (2C), 21.4. HRMS (ESI) calculated for $C_{22}H_{33}NO_2$ $[M^+]$ 344.2584, found 344.2576.

(E)-2-(5-Chloropent-1-en-1-yl)benzoxazole, 61



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 0.10 mol%), $Pd(dppf)Cl_2 \cdot DCM$ (20 mg, 0.03 mmol, 5 mol%), benzoxazole (119 mg, 1.00 mmol, 2 eq) and (E)-5-chloro-1-iodopent-1-ene (115 mg, 0.50 mmol, 1 eq). The title compound was isolated as a brown oil (68 mg, 62%). ν_{max} (neat)/ cm^{-1} 3165, 3071, 2960, 1678, 1485, 1115, 903, 807. δ_H (400 MHz, $CDCl_3$) 7.70-7.63 (1H, m, ArH), 7.55-7.49 (1H, m, ArH), 7.29-7.21 (2H, m, 2 $\times$ ArH), 6.94 (1H, dt, $J=16.0$, $J=7.0$, $CH=CHAr$), 6.46 (1H, dt, $J=16.0$, $J=1.5$, $CH=CHAr$), 3.55 (2H, t, $J=6.5$, CH_2), 2.51-2.46 (2H, m, CH_2), 2.02-1.97 (2H, m, CH_2). δ_C (100 MHz, $CDCl_3$) 163.3, 155.2, 143.0, 142.7, 129.8, 125.2, 119.7, 117.7, 111.0, 43.9, 31.0, 30.0. HRMS (ESI $^+$) calculated for $C_{12}H_{13}^{35}ClNO^+$ $[M+H]^+$ 222.0680, found 222.0684.

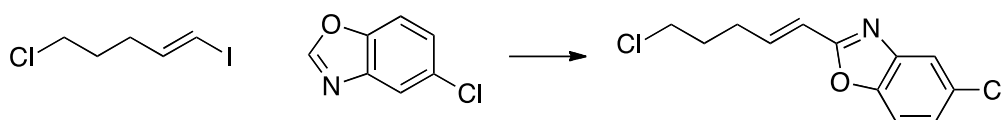
(E)-2-(5-Chloropent-1-en-1-yl)-5-methylbenzoxazole, 62



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 0.10 mol%), $Pd(dppf)Cl_2 \cdot DCM$ (20 mg, 0.03 mmol, 5 mol%), 5-methylbenzoxazole (133 mg, 1.00 mmol, 2 eq) and (E)-5-chloro-1-iodopent-1-ene (115 mg, 0.50 mmol, 1 eq). The title compound was isolated as a dark

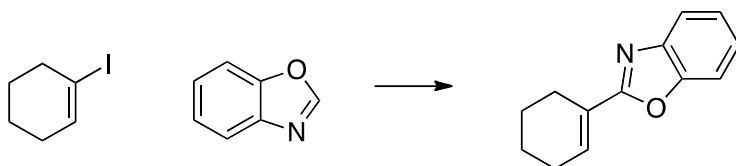
brown oil (103 mg, 88%). $\nu_{\max}$ (neat)/ cm^{-1} 3050, 2955, 2867, 1660, 1536, 1296, 1182, 968. δ_{H} (400 MHz, CDCl_3) 7.44 (1H, s, ArH), 7.33 (1H, d, $J=8.0$, ArH), 7.09 (1H, d, $J=8.0$, ArH), 6.94 (1H, dt, $J=16.0$, $J=7.0$, CH=CHAr), 6.46 (1H, dt, $J=16.0$, $J=1.5$, CH=CHAr), 3.58 (2H, t, $J=7.0$, CH_2), 2.45-2.51 (2H, m, CH_2), 2.43 (3H, s, CH_3), 2.02-1.96 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 162.0, 148.4, 142.0, 141.2, 134.1, 126.1, 119.7, 118.1, 109.6, 43.9, 31.1, 29.9, 21.4. HRMS (ESI^+) calculated for $\text{C}_{13}\text{H}_{15}^{35}\text{ClNO}^+$ $[\text{M}+\text{H}]^+$ 236.0837, found 236.0832.

(E)-5-Chloro-2-(5-chloropent-1-en-1-yl)benzoxazole, 63



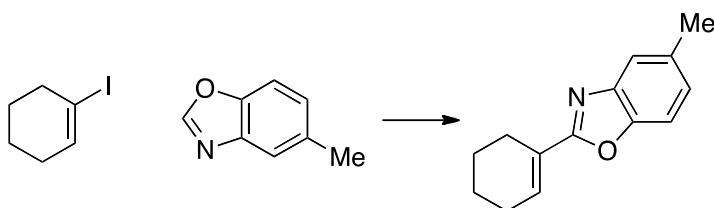
Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ (20 mg, 0.03 mmol, 5 mol%), 5-chlorobenzoxazole (154 mg, 1.00 mmol, 2 eq) and (E)-5-chloro-1-iodopent-1-ene (115 mg, 0.50 mmol, 1 eq). The title compound was isolated as a waxy brown solid (58 mg, 45%). $\nu_{\max}$ (neat)/ cm^{-1} 3165, 3070, 2958, 1678, 1485, 1110, 901, 803. δ_{H} (400 MHz, CDCl_3) 7.66-7.64 (1H, m, ArH), 7.28 (2H, dd, $J=8.5$, $J=2.0$, ArH), 7.02 (1H, dt, $J=16.0$, $J=7.0$, CH=CHAr), 6.48 (1H, dt, $J=16.0$, $J=1.5$, CH=CHAr), 3.61 (2H, t, $J=7.0$, CH_2), 2.56-2.50 (2H, m, CH_2), 2.02 (2H, quin, $J=6.6$, CH_2). δ_{C} (100 MHz, CDCl_3) 163.3, 153.6, 142.9, 129.8, 125.2, 120.6, 119.7, 117.7, 110.9, 43.9, 31.0, 30.1. HRMS (ESI^+) calculated for $\text{C}_{12}\text{H}_{12}^{35}\text{Cl}_2\text{NO}^+$ $[\text{M}+\text{H}]^+$ 255.0218, found 255.0220.

2-Cyclohex-1-enyl-benzoxazole, 64



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), benzoxazole (119 mg, 1.00 mmol, 2 eq) and 1-iodocyclohexene (104 mg, 0.50 mmol, 1 eq). The title compound was isolated as a light brown solid (61 mg, 61%). $\nu_{\max}$ (neat)/cm⁻¹ 3055, 2933, 2299, 1648, 1537, 1453, 1240, 1017, 749, 705. δ_{H} (400 MHz, CDCl₃) 7.71-7.68 (1H, m, ArH), 7.50-7.43 (1H, m, ArH), 7.30-7.25 (2H, m, 2 × ArH) 7.10-7.08 (1H, m, CHCH₂), 2.65-2.58 (2H, m, CHCH₂), 2.35-2.29 (2H, m, CH₂), 1.81-1.69 (4H, m, 2 × CH₂). δ_{C} (100 MHz, CDCl₃) 164.1, 150.2, 141.9, 135.4, 126.2, 124.6, 124.0, 119.7, 110.1, 25.8, 24.7, 22.0, 21.6. HRMS (ESI⁺) calculated for C₁₃H₁₄NO⁺ [M+H]⁺ 200.1070, found 200.1066. M.p. (diethyl ether/chloroform) = 52-53 °C.

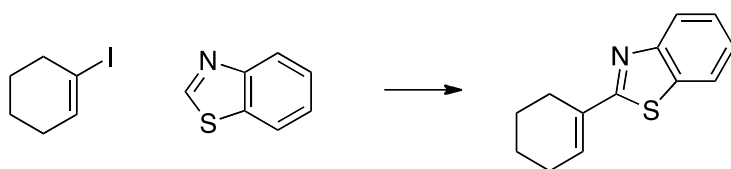
2-(Cyclohex-1-en-1-yl)-5-methylbenzoxazole, 65



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 0.10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), 5-methylbenzoxazole (133 mg, 1.00 mmol, 2 eq) and 1-iodocyclohexene (104 mg, 0.50 mmol, 1 eq). The title compound was isolated as a pale yellow solid (44 mg, 41%). $\nu_{\max}$ (neat)/cm⁻¹ 3045, 2922, 2852, 1645, 1535, 1489,

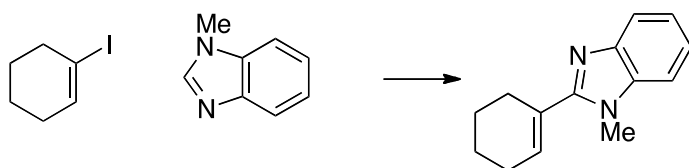
1262, 1189, 919, 810. δ_{H} (400 MHz, CDCl_3) 7.47 (1H, s, ArH), 7.33 (1H, d, $J=8.5$, ArH), 7.10-7.04 (2H, m, ArH + ArC=CH), 2.63-2.58 (2H, m, CHCH₂), 2.45 (3H, s, CH₃), 2.33-2.28 (2H, m, CH₂), 1.82-1.76 (2H, m, CH₂), 1.74-1.67 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 164.2, 148.4, 142.1, 135.0, 133.8, 126.3, 125.7, 119.6, 109.4, 25.8, 24.7, 22.0, 21.7, 21.5. HRMS (ESI⁺) calculated for $\text{C}_{14}\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 214.1226, found 214.1226. M.p. (diethyl ether/chloroform) = 58-60 °C.

2-(Cyclohex-1-en-1-yl)benzo[d]thiazole, 66



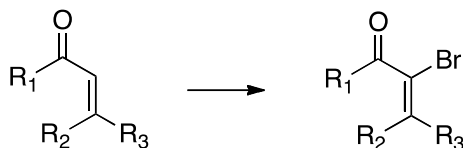
Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 0.10 eq), $\text{Pd}(\text{dppf})\text{Cl}_2\cdot\text{DCM}$ (20 mg, 0.03 mmol, 0.05 eq), benzothiazole (109 μL , 1.00 mmol, 2 eq) and 1-iodocyclohexene (104 mg, 0.50 mmol, 1 eq). The title compound was isolated as a yellow waxy solid (27 mg, 25%). ν_{max} (neat)/ cm^{-1} 3050, 2925, 2855, 1655, 1489, 1350, 1266, 963, 849. δ_{H} (400 MHz, CDCl_3) 7.97 (1H, dq, $J=8.5$, $J=0.5$, ArH), 7.82 (1H, dq, $J=8.5$, $J=0.5$, ArH), 7.43 (1H, dt, $J=8.5$, $J=1.0$, ArH), 7.33 (1H, dt, $J=8.5$, $J=1.0$, ArH), 6.81 (1H, sept, $J=1.5$, CHCH₂), 2.71-2.66 (2H, m, CHCH₂), 2.33-2.28 (2H, m, CH₂), 1.85-1.78 (2H, m, CH₂), 1.76-1.70 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 170.5, 153.7, 134.1, 134.0, 133.4, 125.8, 124.0, 122.8, 121.3, 26.4, 26.0, 22.3, 21.9. HRMS (ESI⁺) calculated for $\text{C}_{13}\text{H}_{14}\text{NS}^+$ $[\text{M}+\text{H}]^+$ 216.10841, found 216.0845.

2-(Cyclohex-1-en-1-yl)-1-methyl-1H-benzimidazole, 67



Synthesized using General Procedure B. Silver carbonate (274 mg, 1.00 mmol, 2 eq), triphenylphosphine (13 mg, 0.05 mmol, 10 mol%), Pd(dppf)Cl₂.DCM (20 mg, 0.03 mmol, 5 mol%), *N*-methylbenzimidazole (132 mg, 1.00 mmol, 2 eq) and 1-iodocyclohexene (104 mg, 0.50 mmol, 1 eq). The title compound was isolated as a pale yellow solid (88 mg, 73%). ν_{max} (neat)/cm⁻¹ 3051, 2930, 2857, 1665, 1489, 1398, 1267, 963, 849, 739. δ_{H} (400 MHz, CDCl₃) 7.76-7.74 (1H, m, ArH), 7.33-7.31 (1H, m, ArH), 7.28-7.24 (2H, m, 2 × ArH), 6.19 (1H, quin, *J*=1.5, CHCH₂), 3.79 (3H, s, CH₃), 2.60-2.56 (2H, m, CHCH₂), 2.33-2.28 (2H, m, CH₂), 1.87-1.80 (2H, m, CH₂), 1.78-1.72 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 155.3, 142.5, 136.1, 133.2, 128.8, 122.3, 122.0, 119.4, 109.3, 31.5, 27.9, 25.6, 22.4, 21.7. HRMS (ESI⁺) calculated for C₁₄H₁₇N₂⁺ [M+H]⁺ 213.1386, found 213.1388. M.p. (diethyl ether/chloroform) = 45-46 °C.

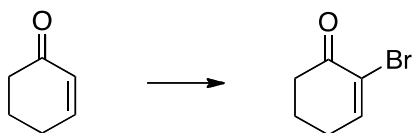
General Procedure C: Bromination



A suspension of Oxone[®] (2 eq) in DCM and water was cooled to 0 °C and sodium bromide (2 eq) was added in small portions. The reaction was stirred for 15 min at 0 °C and 30 min at rt. The reaction was cooled to 0 °C and the ketone (1 eq) was added slowly. The reaction was stirred for 30 min at 0 °C and then 30 min at rt until the ketone was consumed (1-2 h). The reaction was cooled to 0 °C and triethylamine (3

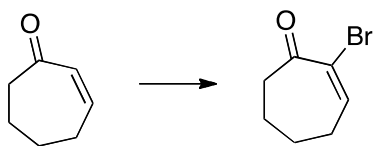
eq) was added drop-wise. The reaction was allowed to warm to rt and stirred until complete (2 h – 4 days). The reaction was diluted with water (the same volume as used for reaction). The water was extracted with DCM. The organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude mixture was purified *via* a low temperature crystallization from methanol and petrol or using flash column chromatography.

2-Bromocyclohex-2-enone, 76



Synthesized using General Procedure C. 2-Cyclohexen-1-one (15.0 mL, 156 mmol, 1 eq), sodium bromide (32.1 g, 312 mmol, 2 eq), Oxone[®] (192 g, 312 mmol, 2 eq), triethylamine (66.0 mL, 468 mmol, 3 eq), DCM (900 mL) and water (225 mL). Purified by crystallization to yield the title compound as white crystals (24.7 g, 90%). ν_{max} (neat)/ cm^{-1} 3411, 2943, 1681, 1598, 1424, 1317, 1125, 993, 971, 915, 819, 732, 704, 643. δ_{H} (400 MHz, CDCl_3) 7.43 (1H, t, $J=7.5$, $\text{CH}=\text{CBr}$), 2.65-2.62 (2H, m, CH_2), 2.48-2.43 (2H, m, CH_2), 2.08 (2H, quint, $J=2.0$ CH_2). δ_{C} (100 MHz, CDCl_3) 192.0, 151.1, 123.8, 38.6, 28.3, 22.7. Data in accordance with literature.¹⁰⁹

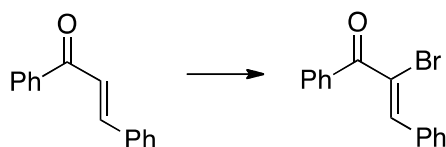
2-Bromocyclohept-2-enone, 77



Synthesized using General Procedure C: 2-Cyclohepten-1-one (1.20 mL, 10.7 mmol, 1

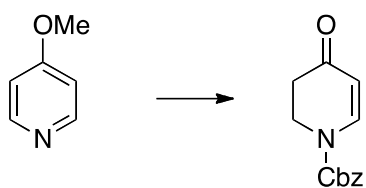
eq), sodium bromide (2.21 g, 21.5 mmol, 2 eq), Oxone[®] (13.3 g, 21.5 mmol, 2 eq), triethylamine (4.50 mL, 32.1 mmol, 3 eq), DCM (65 mL) and water (16 mL). Purified by crystallization to yield the title compound as pale orange crystals (1.55 g, 77%). $\nu_{\max}$ (neat)/cm⁻¹ 3059, 3027, 2937, 2867, 1678, 1595, 1580, 1496, 1448, 1380, 1272, 1148, 1098, 1074, 934, 917, 886, 720, 696. δ_{H} (400 MHz, CDCl₃) 7.32 (1H, t, $J=6.5$, CH=CBr), 2.71 (2H, t, $J=6.5$, CH₂), 2.44-2.41 (2H, m, CH₂), 1.86-1.76 (4H, m, 2 × CH₂). δ_{C} (100 MHz, CDCl₃) 196.2, 147.9, 126.8, 41.3, 29.3, 24.7, 21.1. Data in accordance with literature.¹⁴⁶

(Z)-2-Bromo-1,3-diphenylprop-2-en-1-one, 78



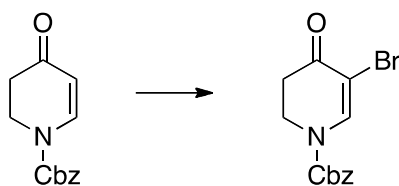
Synthesized using General Procedure C. (2*E*)-1,3-Diphenyl-2-propen-1-one (2.00 g, 9.60 mmol, 1 eq), sodium bromide (1.98 g, 19.0 mmol, 2 eq), Oxone[®] (11.8 g, 19.2 mmol, 2 eq), triethylamine (4.02 mL, 28.8 mmol, 3 eq), DCM (60 mL) and water (15 mL). Purified by flash column chromatography to yield the title compound as a colourless oil (5% diethyl ether/petrol) (11.3 g, 77%). $\nu_{\max}$ (neat)/cm⁻¹ 3058, 3025, 2360, 2341, 1719, 1660, 1595, 1573, 1490, 1316, 1204, 1177, 1065, 926, 886, 710. δ_{H} (400 MHz, CDCl₃) 7.87-7.85 (2H, m, 2 × ArH), 7.83-7.81 (2H, m, 2 × ArH), 7.70 (1H, br. s, CH=CBr), 7.61 (1H, tt, $J=7.5$, $J=1.5$, ArH), 7.52-7.48 (2H, m, 2 × ArH), 7.46-7.44 (3H, m, 3 × ArH). δ_{C} (100 MHz, CDCl₃) 191.5, 142.7, 133.6, 132.6, 130.3 (2C), 130.2, 129.7, 128.5 (5C), 122.5, 53.4. Data in accordance with literature.¹⁴⁷

Benzyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate, 80



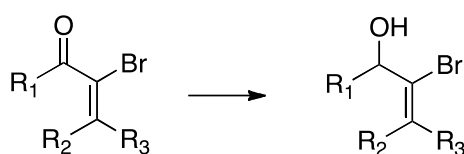
A solution of *para*-methoxypyridine (2.50 mL, 24.6 mmol, 1 eq) in methanol (50 mL) was cooled to -78 °C, sodium borohydride (1.55 g, 27.1 mmol, 1.1 eq) was added in small portions. The reaction was stirred for 15 min. A solution of benzyl chloroformate (4.20 mL, 29.4 mmol, 1.2 eq) in diethyl ether (5 mL) was added over 30 min. The reaction was stirred for 1h at -78 °C. The reaction was quenched with water (40 mL) at -60 °C and allowed to warm to rt. The mixture was extracted with ethyl acetate (3 × 60 mL) and the organic layer was washed with water (2 × 60 mL) and brine (30 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a colourless oil (2.78 g, 49%). ν_{max} (neat)/cm⁻¹ 3436, 3033, 2897, 1722, 1665, 1599, 1497, 1455, 1422, 1323, 1297, 1251, 1206, 1104, 1044, 997, 872, 810, 738. δ_{H} (400 MHz, CDCl₃) 7.84 (1H, br. s, NCH=CH), 7.43-7.33 (5H, m, 5 × ArH), 5.33 (1H, br. s, C(O)CH=CH), 5.26 (2H, C(O)CH₂Ar), 4.04 (2H, t, *J*=7.5, NCH₂), 2.55 (2H, t, *J*=7.5, C(O)CH₂). δ_{C} (100 MHz, CDCl₃) 193.3, 134.8, 128.8 (2C), 128.7 (2C), 128.5, 127.5, 126.9, 69.1, 65.2, 42.6, 35.6. Data in accordance with literature.¹¹¹

Benzyl 5-bromo-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate, 81



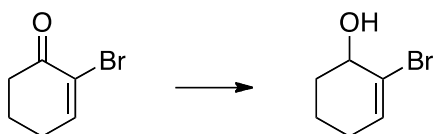
Benzyl 4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (2.00 g, 6.83 mmol, 1 eq) and NBS (1.69 g, 9.49 mmol, 1.1 eq) was stirred in DCM (40 mL) at rt for 5 h. The reaction was concentrated *in vacuo*. The crude product was purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a colourless oil (2.64 g, 99%). $\nu_{\max}$ (neat)/cm⁻¹ 3067, 2961, 1724, 1681, 1586, 1497, 1456, 1359, 1335, 1286, 1229, 1201, 1113, 1046, 996, 879, 837, 743. δ_{H} (400 MHz, CDCl₃) 7.25 (1H, br. s, NCH=CH), 7.40 (5H, br. s, 5 × ArH), 5.26 (2H, C(O)CH₂Ar), 4.09 (2H, t, *J*=7.5, NCH₂), 2.74 (2H, t, *J*=7.5, C(O)CH₂). δ_{C} (100 MHz, CDCl₃) 185.9, 138.5, 129.0, 128.8 (5C), 128.6, 101.5, 69.6, 42.7, 35.4. Data in accordance with literature.¹¹¹

General Procedure D: Luche Reduction



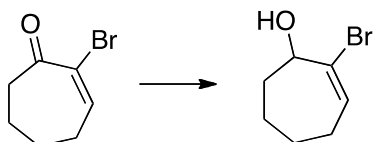
A solution of the ketone (1 eq), cerium chloride heptahydrate (1.1 eq) in methanol was cooled to 0 °C. Sodium borohydride (1.1 eq) was added in small portions. The reaction was stirred at 0 °C for 30 min, allowed to warm to rt and stirred until complete (1-2 h). The reaction was diluted with water (same as reaction volume) and extracted with diethyl ether (3 × reaction vol.). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. If further purification was required it was performed using flash column chromatography.

2-Bromocyclohex-2-enol, 82



Synthesized using General Procedure D. 2-Bromocyclohex-2-enone (24.7 g, 141 mmol, 1 eq), cerium chloride heptahydrate (57.9 g, 155 mmol, 1.1 eq), sodium borohydride (8.98 g, 155 mmol, 1.1 eq), methanol (750 mL). No further purification required to yield a thick pale brown oil (19.8 g, 79%). ν_{max} (neat)/ cm^{-1} 3354, 2940, 2360, 1640, 1435, 1329, 1162, 1080, 1054, 979, 936, 908, 832, 807, 748, 701. δ_{H} (400 MHz, CDCl_3) 6.21 (1H, t, $J=4.0$, $\text{CH}=\text{CBr}$), 4.26-4.18 (1H, br. s, OH) 4.21 (1H, t, $J=5.0$, OHCH), 2.23-2.06 (2H, m, CH_2), 1.96-1.89 (2H, m, CH_2), 1.79-1.59 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 132.6, 125.7, 69.9, 31.9, 27.7, 17.6. Data in accordance with literature.¹⁴⁸

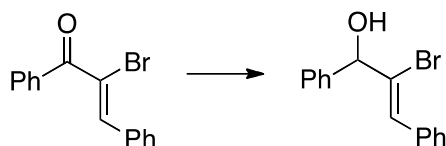
2-Bromocyclohept-2-enol, 83



Synthesized using General Procedure D. 2-Bromocyclohept-2-enone (1.48 g, 7.75 mmol, 1 eq), cerium chloride heptahydrate (3.18 g, 8.53 mmol, 1.1 eq), sodium borohydride (493 mg, 8.53 mmol, 1.1 eq), methanol (40 mL). No further purification required to yield the title compound as a bright yellow oil (1.12 g, 76%). ν_{max} (neat)/ cm^{-1} 3372, 2926, 2857, 1636, 1445, 1262, 1082, 1038, 996, 931, 891, 867, 816, 768, 733. δ_{H} (400 MHz, CDCl_3) 6.32 (1H, t, $J=6.5$, $\text{CH}=\text{CBr}$), 4.44 (1H, d, $J=7.5$, OH), 4.25-4.16 (1H, m, OHCH), 2.12-2.03 (2H, m, CH_2), 1.95-1.58 (6H, m, $3\times\text{CH}_2$). δ_{C}

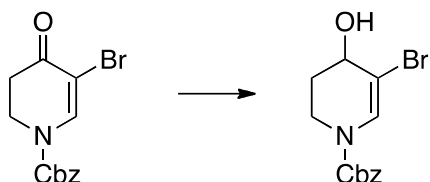
(100 MHz, CDCl₃) 134.4, 129.8, 75.4, 32.3, 27.9, 25.8, 23.1. HRMS (ESI⁺) calculated for C₇H₁₁⁷⁹BrNONa⁺ [M+Na]⁺ 212.9885, found 212.9878.

(Z)-2-Bromo-1,3-diphenylprop-2-en-1-ol, 84



Synthesized using General procedure D. (Z)-2-Bromo-1,3-diphenylprop-2-en-1-one (2.11 g, 7.78 mmol, 1 eq), cerium chloride heptahydrate (3.02 g, 8.12 mmol, 1.1 eq), sodium borohydride (469 mg, 8.12 mmol, 1.1 eq) and methanol (37 mL). The crude product was purified using flash column chromatography (5% diethyl ether/ petrol) to yield the title compound as a colourless oil (1.86 g, 92%). $\nu_{\max}$ (neat)/cm⁻¹ 3355, 3058, 3027, 1951, 1640, 1600, 1492, 1447, 1385, 1259, 1188, 1062, 1005, 918, 859, 813, 748, 626. δ_{H} (400 MHz, CDCl₃) 7.68-7.65 (2H, m, 2 × ArH), 7.51-7.49 (2H, m, 2 × ArH), 7.43-7.32 (6H, m, 6 × ArH), 7.29 (1H, br. s, PhCH=CBr), 5.47 (1H, br. s, OHCH), 2.55 (1H, br. s, OH). δ_{C} (100 MHz, CDCl₃) 140.4, 139.9, 129.1, 128.7 (4C), 128.5 (4C), 128.3, 128.3, 126.7, 79.1. Data in accordance with literature.¹⁴⁹

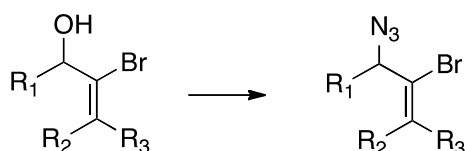
Benzyl 5-bromo-4-hydroxy-3,4-dihydropyridine-1(2H)-carboxylate, 85



Synthesized using General Procedure D. Benzyl 5-bromo-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (2.10 g, 6.76 mmol, 1 eq), cerium chloride heptahydrate (2.79 g, 7.47 mmol, 1.1 eq), sodium borohydride (431 mg, 7.47 mmol, 1.1 eq), methanol (35 mL). No further purification was required to yield the title compound as a colourless

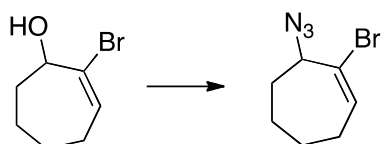
oil (2.10 g, 99%). $\nu_{\max}$ (neat)/ cm^{-1} 3434, 3091, 3033, 2934, 2886, 1706, 1640, 1586, 1455, 1397, 1301, 1194, 1027, 809, 696. δ_{H} (400 MHz, CDCl_3) 7.39-7.34 (5H, m, $5 \times \text{ArH}$), 7.23 (1H, br. s, $\text{NCH}=\text{CBr}$), 5.21 (2H, $\text{C}(\text{O})\text{CH}_2$), 4.27-4.24 (1H, m, OH), 4.07-3.95 (1H, m, OHCH), 3.40-3.28 (2H, m, NCH_2), 2.10-2.04 (1H, m, OHCHCH_a), 1.98-1.90 (1H, m, OHCHCH_b). δ_{C} (100 MHz, CDCl_3) 135.3, 128.7 (2C), 128.5, 128.4, 128.3, 128.2, 127.8, 68.2, 66.6, 37.1, 39.6, 30.3. HRMS (ESI⁺) calculated for $\text{C}_{13}\text{H}_{14}^{79}\text{BrNO}_3\text{Na}^+ [\text{M}+\text{Na}]^+$ 334.0049, found 334.0049.

General Procedure E: Azide formation



DPPA (1.5 eq) was added to a solution of the alcohol (1 eq) in THF. The reaction was cooled to 0 °C and DBU (1.2 eq) was added slowly. The reaction was stirred for 30 min at 0 °C and 2 h at rt. The mixture was concentrated and redissolved in DCM. The organic layer was washed with saturated solution of ammonium chloride (2 $\times$ reaction vol), a saturated solution of sodium bicarbonate (1 $\times$ reaction vol.) and brine (1 $\times$ reaction vol), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

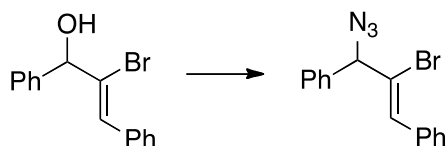
7-Azido-1-bromocyclohept-1-ene, 94



Synthesized using General Procedure E. DPPA (1.79 mL, 8.29 mmol, 1.5 eq), 2-bromocyclohept-2-en-1-ol (1.05 g, 5.52 mmol, 1 eq), DBU (0.99 mL, 6.62 mmol, 1.2 eq)

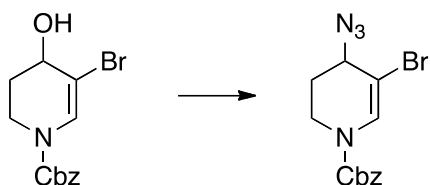
and THF (8 mL). Purified by flash column chromatography (100% DCM) to yield the title compound as a yellow oil (859 mg, 72%). $\nu_{\max}$ (neat)/cm⁻¹ 2930, 2092, 1448, 1244, 1041, 967, 866, 776, 645. δ_{H} (400 MHz, CDCl₃) 6.48 (1H, t, $J=6.5$, BrC=CH), 4.43-4.41 (1H, m, N₃CH), 2.22-2.12 (2H, m, CH₂), 1.93-1.85 (2H, m, CH₂), 1.78-1.70 (2H, m, CH₂), 1.59-1.51 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 138.0, 122.2, 69.0, 30.9, 28.4, 26.0, 23.7. HRMS (FI⁺) calculated for C₇H₁₀⁷⁹BrN₃ [M]⁺ 215.0058, found 215.0051.

(Z)-(3-Azido-2-bromoprop-1-ene-1,3-diyl)dibenzene, 95



Synthesized using General Procedure E. DPPA (14.6 mL, 67.7 mmol, 1.5 eq), (Z)-2-bromo-1,3-diphenylprop-2-en-1-ol (13.0 g, 45.1 mmol, 1 eq), DBU (8.09 mL, 54.1 mmol, 1.2 eq) and THF (80 mL). The crude product was purified by flash column chromatography (100% DCM) to yield a yellow oil (6.40 g, 45%). $\nu_{\max}$ (neat)/cm⁻¹ 3060, 3028, 2885, 2361, 2341, 2098, 1952, 1600, 1492, 1398, 1248, 1157, 1077, 1029, 919, 817, 749. δ_{H} (400 MHz, CDCl₃) 7.68-7.66 (2H, m, 2 × ArH), 7.44-7.34 (8H, m, 8 × ArH), 7.27 (1H, br. s, PhCH=CBr), 5.45 (1H, br. s, N₃CH). δ_{C} (100 MHz, CDCl₃) 136.4, 134.6, 130.6, 129.2, 128.7 (4C), 128.5 (3C), 128.2, 127.5, 123.6, 72.2. HRMS (FI⁺) calculated for C₁₅H₁₂⁷⁹BrN₃ [M]⁺ 313.0215, found 313.0221.

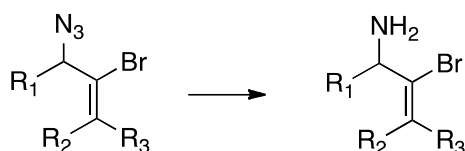
Benzyl 4-azido-5-bromo-3,4-dihydropyridine-1(2H)-carboxylate, 96



Synthesized using General procedure E. DPPA (2.18 mL, 10.1 mmol, 1.5 eq), alcohol

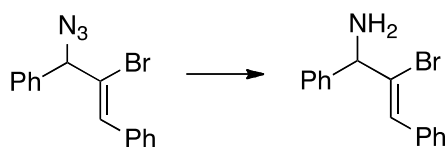
(2.10 g, 6.75 mmol, 1 eq), DBU (1.21 mL, 8.10 mmol, 1.2 eq) and THF (12 mL). The crude product was purified by flash column chromatography (100% DCM) to yield a dark orange oil (1.49 g, 66%). $\nu_{\max}$ (neat)/ cm^{-1} . δ_{H} (400 MHz, CDCl_3) 7.42-7.35 (6H, m, $6 \times \text{ArH} + \text{NCH}=\text{CBr}$), 5.22 (2H, s, $\text{C}(\text{O})\text{CH}_2$), 4.13-4.01 (2H, m, $\text{N}_3\text{CH} + \text{N}_3\text{CHCH}_a$), 3.29-3.22 (1H, m, N_3CHCH_b), 2.13-1.96 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 135.9, 129.6, 129.1, 128.7, 128.6, 128.4, 128.3, 68.4, 58.7, 58.6, 37.3, 37.0, 28.8. HRMS (ESI^+) calculated for $\text{C}_{13}\text{H}_{13}^{79}\text{BrN}_4\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 359.0114, found 359.0112.

General Procedure F: Staudinger Reduction



Water and triphenylphosphine (2 eq) was added to a solution of azide (1 eq) in toluene and the reaction was stirred for 2 h at reflux. The reaction mixture was diluted with ethanol and concentrated. The crude product was purified by flash column chromatography.

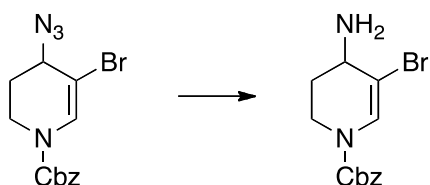
(Z)-2-Bromo-1,3-diphenylprop-2-en-1-amine, 98



Synthesized using General Procedure F. Water (50 mL), triphenylphosphine (10.5 g, 40.2 mmol, 2 eq), (Z)-(3-azido-2-bromoprop-1-ene-1,3-diyl)dibenzene (6.30 g, 20.1 mmol, 1 eq) and toluene (235 mL). The crude product was purified by flash column chromatography (1% ethyl acetate/methanol) to yield the title compound as a dark

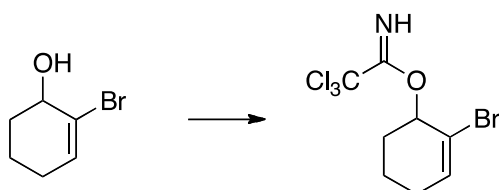
yellow oil (4.59 g, 79%). ν_{max} (neat)/ cm^{-1} 3370, 2360, 2341, 1711, 1491, 1446, 1360, 1220, 748, 697, 613. ^1H NMR (δ_{H} (400 MHz, CDCl_3) 7.66-7.64 (2H, m, $2 \times \text{ArH}$), 7.50-7.48 (2H, m, $2 \times \text{ArH}$), 7.41-7.30 (6H, m, $6 \times \text{ArH}$), 7.22 (1H, br. s, $\text{PhCH}=\text{CBr}$), 4.86 (1H, br. s, NH_2CH), 1.88 (2H, br. s, NH_2). δ_{C} (100 MHz, CDCl_3) 141.5, 135.4, 132.5, 129.1, 128.4 (4C), 128.1 (2C), 128.0, 127.7, 127.6, 126.9, 64.0. HRMS (ESI^+) calculated for $\text{C}_{15}\text{H}_{14}^{79}\text{BrNNa}^+ [\text{M}+\text{Na}]^+$ 310.0202, found 310.0205.

Benzyl 4-amino-5-bromo-3,4-dihydropyridine-1(2H)-carboxylate, 99



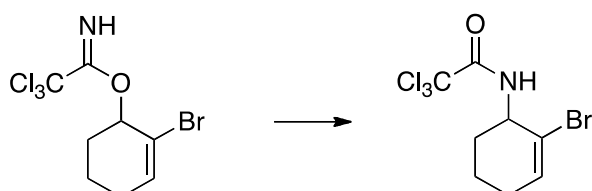
Synthesized using General Procedure F. Water (10 mL), PPh_3 (2.11 g, 8.04 mmol, 2 eq), benzyl 4-azido-5-bromo-3,4-dihydropyridine-1(2H)-carboxylate (1.35 g, 4.02 mmol, 1 eq) and toluene (47 mL). The crude product was purified by flash column chromatography (5% ethyl acetate/methanol) to yield the title compound as a dark orange oil (1.00 g, 80%). ν_{max} (neat)/ cm^{-1} 3369, 3033, 2931, 2879, 1703, 1642, 1497, 1455, 1398, 1339, 1299, 1211, 1173, 1112, 1028, 989, 868, 820, 755. δ_{H} (400 MHz, CDCl_3) 7.68-7.63 (1H, m, $\text{NCH}=\text{CBr}$), 7.37-7.33 (5H, m, $5 \times \text{ArH}$), 5.19 (2H, $\text{C}(\text{O})\text{CH}_2$), 6.65-6.48 (1H, m, NH_2CH), 3.93-3.79 (1H, m, NCH_a), 3.50-3.48 (1H, m, NCH_b), 1.94-1.87 (4H, m, $\text{NH}_2 + \text{NH}_2\text{CHCH}_2$). δ_{C} (100 MHz, CDCl_3) 135.6, 132.1, 131.8, 128.7, 128.5, 128.3, 128.2, 68.1, 53.4, 49.4, 38.1, 37.9, 31.0. HRMS (ESI^+) calculated for $\text{C}_{13}\text{H}_{15}^{79}\text{BrN}_2\text{O}_2\text{Na}^+ [\text{M}+\text{Na}]^+$ 333.0209, found 333.0208.

2-Bromocyclohex-2-en-1-yl 2,2,2-trichloroacetimidate, 100



A suspension of 2-bromocyclohex-2-enol (19.8 g, 112 mmol, 1 eq) and molecular sieves (15.0 g) in DCM (625 mL) was cooled to 0 °C. DBU (25.1 mL, 168 mmol, 1.5 eq) was added slowly followed by 2,2,2-trichloroacetonitrile (20.2 mL, 202 mmol, 1.8 eq). The reaction was allowed to warm to rt over 30 min and stirred for a further 1.5 h. The reaction was quenched with a saturated solution of ammonium chloride (625 mL) and extracted with DCM (3 × 625 mL). The organic layers were washed with brine (625 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (100% DCM) to yield the title compound as a waxy brown solid (31.3 g, 87%). ν_{max} (neat)/cm⁻¹ 2954, 1446, 1379, 1333, 1307, 1153, 1095, 958, 894, 869, 810, 786, 662. δ_{H} (400 MHz, CDCl₃) 8.39 (1H, br. s, NH), 6.44-6.42 (1H, m, CH=CBr), 5.55-5.53 (1H, m, COCH), 2.28-2.07 (2H, m, CH₂), 1.97-1.89 (2H, m, CH₂), 1.81-1.67 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 161.9, 136.0, 118.9, 91.5, 28.6, 27.6, 16.9. HRMS (ESI⁺) calculated for C₈H₉⁷⁹Br³⁵Cl₃NONa⁺ [M+Na]⁺ 341.8825, found 341.8828.

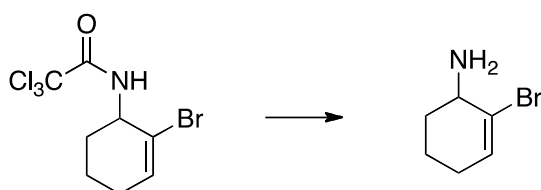
N-(2-Bromocyclohex-2-en-1-yl)-2,2,2-trichloroacetamide, 101



A solution of the 2-bromocyclohex-2-en-1-yl 2,2,2-trichloroacetimidate (28.1 g, 87.5 mmol, 1 eq) and potassium carbonate (3.02 g, 21.9 mmol, 0.25 eq) in *o*-xylene was

stirred at reflux for 24 h. The reaction mixture was cooled, concentrated *in vacuo* and purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a beige solid (23.8 g, 85%). $\nu_{\max}$ (neat)/ cm^{-1} 3281, 2950, 1691, 1531, 1311, 1252, 1172, 1088, 1065, 988, 918, 882, 850, 833, 819, 753, 720, 647. δ_{H} (400 MHz, CDCl_3) 6.74 (1H, br. s, NH), 6.37 (1H, td, $J=4.5$, $J=1.0$, $\text{CH}=\text{CBr}$), 4.59-4.57 (1H, m, NCH), 2.23-2.13 (2H, m, CH_2), 2.10-2.01 (1H, m, NHCHCH_a), 1.97-1.89 (1H, m, NHCHCH_b), 1.81-1.72 (1H, m, $\text{CBr}=\text{CHCH}_a$), 1.66-1.57 (1H, m, $\text{CBr}=\text{CHCH}_b$). δ_{C} (100 MHz, CDCl_3) 161.2, 135.2, 120.1, 52.9, 30.1, 27.4 (2C), 17.9. HRMS (ESI⁺) calculated for $\text{C}_8\text{H}_9^{79}\text{Br}^{35}\text{Cl}_3\text{NONa}^+ [\text{M}+\text{Na}]^+$ 341.8825, found 341.8822. M.p. (diethyl ether/chloroform) = 128-130 °C.

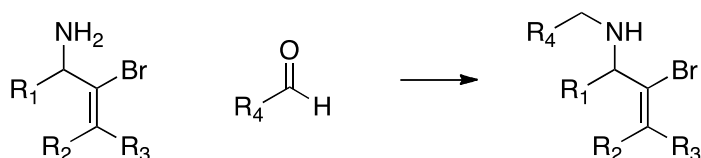
2-Bromocyclohex-2-enamine, 92



DIBAL-H (1.48M in toluene, 242 mL, 358 mmol, 5 eq) was added dropwise to a solution of *N*-(2-bromocyclohex-2-en-1-yl)-2,2,2-trichloroacetamide (23.0 g, 71.6 mmol, 1 eq) in toluene (250 mL) at -78 °C. The reaction was stirred for 30 min and treated with ice cold acetone (100 mL) and allowed to warm to rt. A sat. solution of Rochelle salt (50 mL) was added and the reaction mixture was allowed to stir for 2 h. The mixture was filtered through Celite and extracted with DCM. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (1% methanol/ethyl acetate) to yield the title compound as a brown oil (10.1 g, 80%). $\nu_{\max}$ (neat)/ cm^{-1} 3369, 2928, 1637, 1437, 1316, 1194, 1118, 977, 803, 720, 694, 616. δ_{H} (400 MHz, CDCl_3) 6.04-5.97 (1H, m, $\text{BrC}=\text{CH}$), 3.31 (1H, br. s, NCH), 2.06-1.89 (2H,

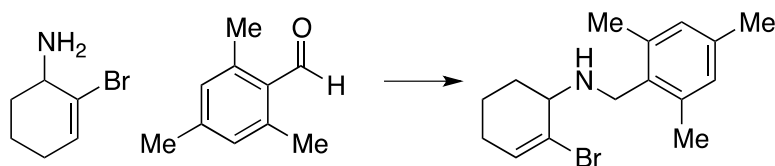
m, CH₂), 1.67-1.47 (4H, m, 2 × CH₂). δ_C (100 MHz, CDCl₃) 130.1, 129.7, 52.7, 32.8, 27.7, 18.6. HRMS (ESI⁺) calculated for C₆H₁₁⁷⁹BrN⁺ [M+H]⁺ 176.0075, found 176.0075.

General procedure G: Reductive amination



Aldehyde (1 eq) was added to the amine (1 eq) in a DCM. Sodium triacetoxyborohydride (2 eq) was added once the aldehyde was consumed (1-6 h). The reaction was stirred overnight. The reaction mixture was concentrated *in vacuo* and redissolved in diethyl ether and quenched with a saturated solution of sodium bicarbonate. The organic layer was washed with a saturated solution of sodium bicarbonate, brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

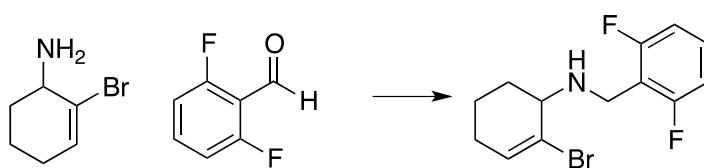
2-Bromo-N-(2,4,6-trimethylbenzyl)cyclohex-2-enamine, 102



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (900 mg, 5.11 mmol, 1 eq), mesitaldehyde (0.75 ml, 5.11 mmol, 1 eq), sodium triacetoxyborohydride (2.17 g, 10.2 mmol, 2 eq), DCM (40 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (1.27g, 81%).
 ν_{max} (neat)/cm⁻¹ 3359, 2945, 1582, 1434, 1263, 1271, 1089, 1031, 975, 938, 838, 742.
 δ_H (400 MHz, CDCl₃) 6.85 (2H, s, 2 × ArH) 6.17-6.15 (1H, m, CH=CBr), 3.81 (1H, d,

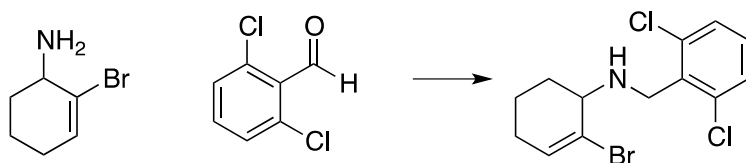
$J=11.0$, ArCH_a), 3.68 (1H, d, $J=11.0$, ArCH_b), 3.37-3.35 (1H, m, NHCH), 2.41 (6H, s, 2 × Me), 2.26 (3H, s, Me), 2.11-1.99 (3H, m, CH₂), 1.89-1.79 (2H, m, CH₂), 1.66-1.60 (1H, m, CH₂). δ_C (100 MHz, CDCl₃) 137.0, 136.4, 133.4, 132.0, 128.9 (2C), 125.9 (2C), 59.5, 45.5, 29.2, 27.9, 20.9, 19.4, 17.7 (2C). HRMS (ESI⁺) calculated for C₁₆H₂₂⁷⁹BrN⁺ [M+H]⁺ 308.1008, found 308.1010.

2-Bromo-*N*-(2,6-difluorobenzyl)cyclohex-2-enamine, 103



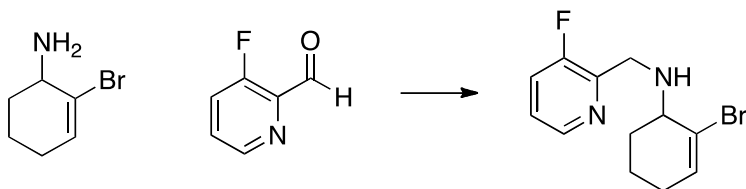
Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (500 mg, 2.84 mmol, 1 eq), 2,6-difluorobenzaldehyde (300 μ l, 2.84 mmol, 1 eq), sodium triacetoxyborohydride (1.20 g, 5.68 mmol, 2 eq), DCM (23 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (461 mg, 54%). $\nu_{\max}$ (neat)/cm⁻¹ 3357, 2939, 1624, 1591, 1468, 1264, 1226, 1099, 1029, 972, 918, 828, 781, 741. δ_H (400 MHz, CDCl₃) 7.24-7.18 (1H, m, ArH), 6.87 (2H, t, $J=8.0$, 2 × ArH), 6.17 (1H, td, $J=4.5$, $J=1.0$, CH=CBr), 3.95 (1H, d, $J=13.5$, ArCH_a), 3.87 (1H, d, $J=13.5$, ArCH_b), 3.24-3.22 (1H, m, NHCH), 2.09-2.04 (2H, m, CH₂), 1.96-1.91 (1H, m, CH_a), 1.83-1.75 (2H, m, CH₂), 1.62-1.56 (1H, m, CH_b). δ_C (100 MHz, CDCl₃) 161.9 (d, $J_{CF}=256$, 2C), 132.5, 128.8, 128.7, 125.4, 111.2 (d, $J_{CF}=26$, 2C), 57.5, 37.9, 28.9, 27.9, 17.7. HRMS (ESI⁺) calculated for C₁₃H₁₄⁷⁹BrF₂N⁺ [M+H]⁺ 302.0350, found 302.0344.

2-Bromo-N-(2,6-dichlorobenzyl)cyclohex-2-enamine, 104



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (750 mg, 4.26 mmol, 1 eq), 2,6-dichlorobenzaldehyde (749 mg, 4.26 mmol, 1 eq), sodium triacetoxyborohydride (1.80 g, 8.52 mmol, 2 eq), DCM (35 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a orange oil (1.28 g, 90%). $\nu_{\max}$ (neat)/ cm^{-1} 3358, 2938, 1580, 1561, 1434, 1331, 1193, 1099, 955, 902, 863, 806, 765. δ_{H} (400 MHz, CDCl_3) 7.30 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 7.13 (1H, dd, $J=8.0$, $J=7.0$, $2 \times \text{ArH}$), 6.17-6.15 (1H, m, $\text{CH}=\text{CBr}$), 4.11 (1H, d, $J=13.0$, ArCH_a), 4.06 (1H, d, $J=13.0$, ArCH_b), 3.28-3.26 (1H, m, NHCH), 2.20-2.15 (1H, m, NH), 2.10-2.02 (3H, m, CH_2), 1.85-1.77 (2H, m, CH_2), 1.64-1.58 (1H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 136.0, 135.6, 132.5 (2C), 128.9, 128.3 (2C), 125.2, 57.9, 46.0, 29.1, 27.9, 17.5. HRMS (ESI^+) calculated for $\text{C}_{13}\text{H}_{15}^{79}\text{Br}^{35}\text{Cl}_2\text{NNa}^+$ $[\text{M}+\text{Na}]^+$ 333.9759, found 333.9763.

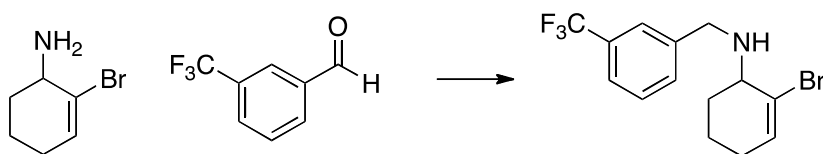
2-Bromo-N-((3-fluoropyridin-2-yl)methyl)cyclohex-2-enamine, 105



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (750 mg, 4.26 mmol, 1 eq), 3-pyridinecarboxaldehyde (0.51 ml, 4.26 mmol, 1 eq), sodium triacetoxyborohydride (1.80 g, 8.52 mmol, 2 eq), DCM (23 mL). Purified by flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a

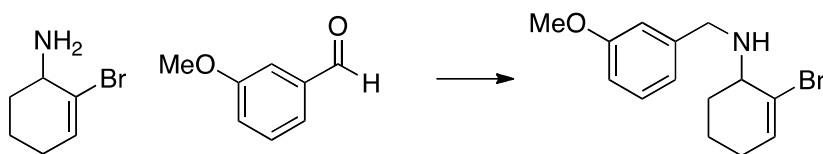
brown oil (1.08 g, 89%). $\nu_{\max}$ (neat)/ cm^{-1} 3359, 2936, 2360, 1602, 1444, 1246, 1166, 1105, 982, 801, 720. δ_{H} (400 MHz, CDCl_3) 8.38 (1H, dt, $J=8.5$, $J=1.5$, ArH), 7.34 (1H, dt, $J=8.5$, $J=1.5$, ArH), 7.21-7.17 (1H, m, ArH), 6.19 (1H, dt, $J=4.0$, $J=1.0$, CH=CBr), 4.05 (1H, dd, $J=14.0$, $J=2.0$, ArCH_a) 3.97 (1H, dd, $J=14.0$, $J=2.0$, ArCH_b), 3.40-3.37 (1H, m, NHCH), 2.66 (1H, br. s, NH), 2.03-2.12 (2H, m, CH₂), 1.93-1.86 (2H, m, CH₂), 1.82-1.56 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 157.4 (d, $J_{\text{CF}}=267$), 147.6 (d, $J_{\text{CF}}=31$), 144.9, 132.6, 125.8, 123.3, 122.4 (d, $J_{\text{CF}}=31$), 58.1, 45.6, 29.3, 27.8, 18.2. HRMS (ESI⁺) calculated for $\text{C}_{12}\text{H}_{15}^{79}\text{BrFN}_2^+$ [M+H]⁺ 285.0397, found 285.0400.

2-Bromo-N-(3-(trifluoromethyl)benzyl)cyclohex-2-enamine, 107



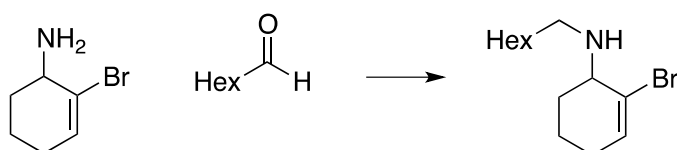
Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (500 mg, 2.84 mmol, 1 eq), 3-trifluoromethylbenzaldehyde (380 μL , 2.84 mmol, 1 eq), sodium triacetoxyborohydride (1.20 g, 5.68 mmol, 2 eq), DCM (23 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (525 mg, 55%). $\nu_{\max}$ (neat)/ cm^{-1} 3360, 2938, 1448, 1326, 1160, 1119, 1071, 988, 905, 797, 743, 701, 657. δ_{H} (400 MHz, CDCl_3) 7.68 (1H, s, ArH), 7.58 (1H, d, $J=7.5$, ArH), 7.50 (1H, d, $J=7.5$, ArH), 7.44 (1H, t, $J=7.5$, ArH), 6.23 (1H, td, $J=4.0$, $J=1.0$, CH=CBr), 3.92 (1H, d, $J=13.5$, ArCH_a), 3.84 (1H, d, $J=13.5$, ArCH_b), 3.36-3.34 (1H, m, NHCH), 2.11-2.06 (1H, m, CH₂), 1.88-1.83 (2H, m, CH₂), 1.80-1.74 (2H, m, CH₂), 1.64-1.61 (1H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 141.4, 132.7, 131.5, 128.7 (q, $J_{\text{CF}}=32$), 127.6, 126.0, 124.9 (q, $J_{\text{CF}}=270$), 123.7, 122.8, 58.8, 50.2, 29.2, 27.8, 18.2. HRMS (ESI⁺) calculated for $\text{C}_{14}\text{H}_{16}^{79}\text{BrF}_3\text{N}^+$ [M+H]⁺ 334.0413, found 334.0398.

2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-enamine, 108



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (500 mg, 2.84 mmol, 1 eq), 3-methoxybenzaldehyde (380 μ l, 2.84 mmol, 1 eq), sodium triacetoxyborohydride (1.20 g, 5.68 mmol, 2 eq), DCM (23 mL). Purified by flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a yellow oil (398 mg, 47%). ν_{max} (neat)/ cm^{-1} 3358, 2936, 1598, 1488, 1454, 1313, 1261, 1152, 1121, 1044, 987, 906, 875, 779, 742, 692. δ_{H} (400 MHz, CDCl_3) 7.25 (1H, t, $J=7.5$, ArH), 6.98-6.95 (2H, m, $2 \times$ ArH), 6.82-6.79 (1H, m, ArH), 6.21 (1H, td, $J=4.0$, $J=1.0$, CH=CBr), 3.85 (1H, d, $J=13.0$, ArCH_a), 3.82 (3H, s, Me), 3.75 (1H, d, $J=13.0$, ArCH_b), 3.34-3.37 (1H, m, NHCH), 2.10-2.05 (1H, m, CH₂) 1.90-1.73 (4H, m, $2 \times$ CH₂), 1.62-1.57 (1H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 159.7, 141.9, 132.5, 129.4, 123.3, 120.2, 113.5, 112.6, 58.0, 55.2, 50.6, 29.1, 27.9, 18.3. HRMS (ESI⁺) calculated for $\text{C}_{14}\text{H}_{19}^{79}\text{BrNO}^+$ $[\text{M}+\text{H}]^+$ 296.0645, found 296.0642.

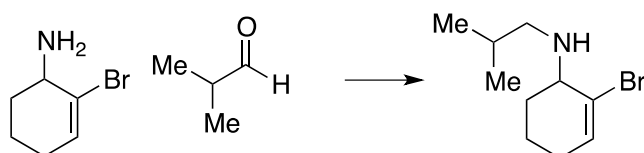
2-Bromo-*N*-heptylcyclohex-2-enamine, 109



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (150 mg, 0.837 mmol, 1 eq), heptanal (110 μ l, 0.837 mmol, 1 eq), sodium triacetoxyborohydride (354 mg, 1.67 mmol, 2 eq), DCM (8 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a orange oil (156 mg, 68%). ν_{max} (neat)/ cm^{-1} 3357, 2924, 2854, 2361, 2340, 1736, 1644, 1464, 1376, 1350, 1331, 1314,

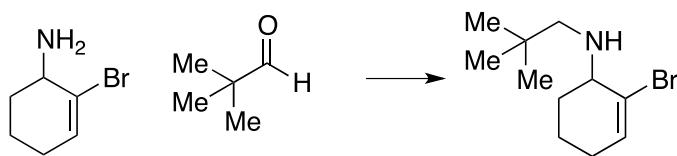
1111, 1070, 946, 873, 806, 723. δ_{H} (400 MHz, CDCl_3) 6.18-6.16 (1H, m, $\text{CH}=\text{CBr}$), 3.28-3.24 (1H, m, NHCH), 2.66-2.59 (1H, m, NHCH_a), 2.56-2.50 (1H, m, NHCH_b), 2.09-2.02 (3H, m, $\text{NH} + \text{CH}_2$), 1.84-1.79 (2H, m, CH_2), 1.75-1.48 (4H, m, $2 \times \text{CH}_2$), 1.35-1.25 (8H, m, $4 \times \text{CH}_2$), 0.89-0.86 (3H, m, Me). δ_{C} (100 MHz, CDCl_3) 132.0, 126.8, 58.7, 46.7, 31.8, 30.3, 29.3, 29.2, 27.9, 27.3, 22.6, 18.4, 14.0. HRMS (ESI^+) calculated for $\text{C}_{13}\text{H}_{24}^{79}\text{BrN}$ $[\text{M}+\text{H}]^+$ 274.1165, found 274.1159.

2-Bromo-*N*-isobutylcyclohex-2-enamine, 110



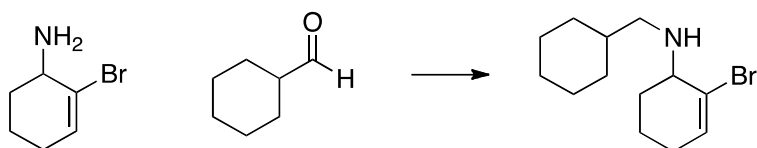
Synthesized using General procedure G. 2-Bromocyclohex-2-enamine (200 mg, 1.13 mmol, 1 eq), *iso*-butyraldehyde (103 μL , 1.13 mmol, 1 eq), sodium triacetoxyborohydride (478 mg, 2.26 mmol, 2 eq), DCM (10 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (145 mg, 55%). ν_{max} (neat)/ cm^{-1} 3357, 2951, 2870, 2359, 1643, 1469, 1386, 1365, 1332, 1107, 1069, 1023, 979, 806, 744. δ_{H} (400 MHz, CDCl_3) 6.17 (1H, td, $J=3.0$, $J=1.0$, $\text{CH}=\text{CBr}$), 3.28-3.26 (1H, m, NHCH), 2.45-2.36 (2H, m, NHCH_2), 2.07-2.03 (2H, m, CH_2), 1.83-1.77 (3H, m, $\text{NH} + \text{CH}_2$), 1.75-1.68 (2H, m, CH_2), 1.62-1.54 (1H, m, NHCH_2CH), 0.95-0.93 (6H, m, 2Me). δ_{C} (100 MHz, CDCl_3) 132.2, 126.7, 58.6, 54.6, 29.5, 29.2, 27.9, 20.8, 20.7, 18.4. HRMS (ESI^+) calculated for $\text{C}_{10}\text{H}_{18}^{79}\text{BrN}^+$ $[\text{M}+\text{H}]^+$ 232.0695, found 232.0697.

2-Bromo-N-neopentylcyclohex-2-enamine, 111



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (150 mg, 0.837 mmol, 1 eq), pivalaldehyde (90 μ l, 0.837 mmol, 1 eq), sodium triacetoxyborohydride (354 mg, 1.67 mmol, 2 eq), DCM (8 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (198 mg, 97%). ν_{max} (neat)/ cm^{-1} 3358, 2947, 2863, 2833, 2360, 2341, 1738, 1643, 1471, 1446, 1363, 1312, 1286, 1228, 1216, 1173, 1109, 1045, 996, 978, 872, 834, 741. δ_{H} (400 MHz, CDCl_3) 6.18-6.16 (1H, m, $\text{CH}=\text{CBr}$), 3.27-3.21 (1H, m, NHCH), 2.33 (2H, qd, $J=10.5$, $J=1.5$, NHCH_2), 2.12-1.99 (3H, m, $\text{NH} + \text{CH}_2$), 1.82-1.69 (2H, m, CH_2), 1.61-1.51 (2H, m, CH_2), 0.94 (9H, m, $3 \times \text{Me}$). δ_{C} (100 MHz, CDCl_3) 132.1, 59.2, 58.8, 31.4, 29.3 (2C), 27.9, 27.7, 18.3. HRMS (ESI^+) calculated for $\text{C}_{11}\text{H}_{21}^{79}\text{BrN}^+$ $[\text{M}+\text{H}]^+$ 246.0852, found 246.0847.

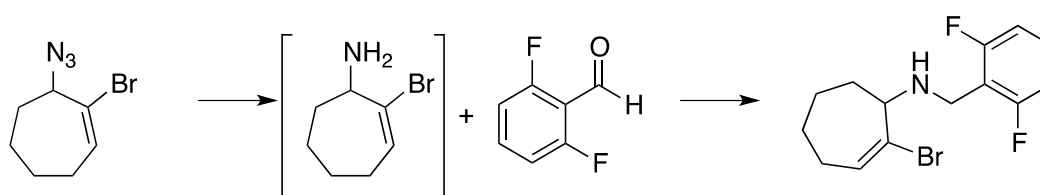
2-Bromo-N-(cyclohexylmethyl)cyclohex-2-enamine, 112



Synthesized using General Procedure G. 2-Bromocyclohex-2-enamine (750 mg, 4.26 mmol, 1 eq), cyclohexanecarboxaldehyde (0.520 mL, 4.26 mmol, 1 eq), sodium triacetoxyborohydride (1.80 g, 8.52 mmol, 2 eq), DCM (23 mL). Purified by flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as an orange oil (982 mg, 85%). ν_{max} (neat)/ cm^{-1} 3360, 2919, 2849, 1642, 1447, 1331, 1117, 1065, 980, 908, 874, 805, 743. δ_{H} (400 MHz, CDCl_3) 6.16 (1H, td, $J=4.0$, $J=1.0$,

CH=CBr), 3.26-3.23 (1H, m, NHCH), 2.41 (2H, qd, $J=12.5$, $J=6.5$, CyCH₂), 2.08-2.01 (3H, m, NH + CH₂), 1.82-1.77 (4H, m, 2 × CH₂), 1.75-1.53 (4H, m, 4 × CH₂), 1.47-1.39 (1H, m, CH₂), 1.29-1.01 (4H, m, 2 × CH₂), 0.98-0.89 (2H, m, CH₂). δ_C (100 MHz, CDCl₃) 132.1, 126.8, 58.7, 53.4, 38.1, 31.6, 31.5, 29.1, 27.9 (2C), 26.7, 26.0, 18.4. HRMS (ESI⁺) calculated for C₁₃H₂₃⁷⁹BrN⁺ [M+H]⁺ 272.1008, found 272.1011.

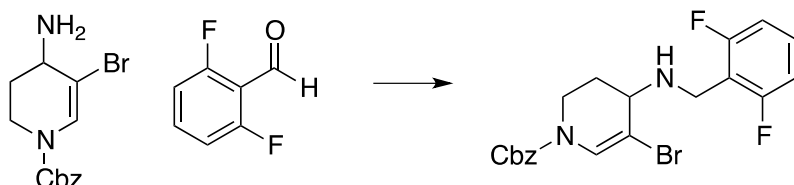
2-Bromo-*N*-(2,6-difluorobenzyl)cyclohept-2-enamine, 113



Synthesized using General Procedure F. Water (10 mL), triphenylphosphine (2.03 g, 7.72 mmol, 2 eq), 7-azido-1-bromocyclohept-1-ene (830 mg, 3.86 mmol, 1 eq) and toluene (45 mL). The crude product was filtered through Celite eluting with (1% ethyl acetate/ methanol). 2-Bromocyclohept-2-enamine with a trace of triphenylphosphine impurity was used without any further purification. Synthesized using General Procedure G. 2-Bromocyclohept-2-enamine (200 mg, 1.05 mmol, 1 eq), 2,6-fluorobenzaldehyde (110 μ l, 1.05 mmol, 1 eq), sodium triacetoxyborohydride (445 mg, 2.01 mmol, 2 eq), DCM (10 mL). Purified by flash column chromatography (5% ethyl acetate/petrol) to yield the title compound as a pale yellow oil (178 mg, 54%). $\nu_{\max}$ (neat)/cm⁻¹ 3361, 2927, 1624, 1591, 1468, 1265, 1227, 1100, 1030, 989, 918, 781, 704. δ_H (400 MHz, CDCl₃) 7.25-7.17 (1H, m, ArH), 6.88 (2H, t, $J=8.0$, 2 × ArH), 6.31 (1H, t, $J=6.5$, CH=CBr), 3.92 (2H, s, ArCH₂), 3.58 (1H, dd, $J=7.0$, $J=3.0$, NHCH), 2.26-2.17 (2H, m, NH + NHCHCH_a), 2.12-2.01 (1H, m, NHCHCH_b), 1.93-1.78 (4H, m, 2 × CH₂), 1.72-1.63 (2H, m, CH₂). δ_C (100 MHz, CDCl₃) 161.8 (2C, d, $J_{CF}=256$), 153.9,

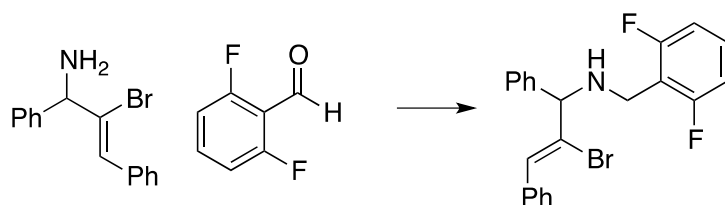
134.7, 128.8, 115.1 (d, $J_{\text{CF}}=26$), 111.1 (2C, d, $J_{\text{CF}}=26$), 64.8, 38.6, 29.5, 27.9, 26.0, 24.0. HRMS (ESI⁺) calculated for C₁₄H₁₇⁷⁹BrF₂N⁺ [M+H]⁺ 316.0507, found 316.0509.

Benzyl 5-bromo-4-((2,6-difluorobenzyl)amino)-3,4-dihydropyridine-1-(2H)-carboxylate, 114



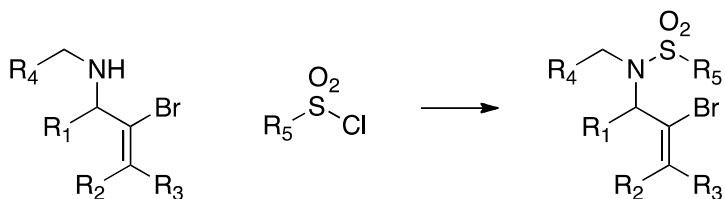
Synthesized using General Procedure G. Benzyl 4-amino-5-bromo-3,4-dihydropyridine-1(2H)-carboxylate (1.00 g, 3.22 mmol, 1 eq), 2,6-fluorobenzaldehyde (350 μ l, 3.22 mmol, 1 eq), sodium triacetoxymethylborohydride (1.36 g, 6.44 mmol, 2 eq), DCM (30 mL). Purified by flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a pale yellow oil (1.40 g, 99%). ν_{max} (neat)/cm⁻¹ 3359, 2959, 2360, 2341, 1708, 1646, 1624, 1591, 1497, 1342, 1301, 1214, 1195, 909, 874, 758, 729, 696. δ_{H} (400 MHz, CDCl₃) 7.39-7.31 (5H, m, 5 $\times$ ArH), 7.28-7.18 (2H, m, ArH + CH=CBR), 6.92-6.87 (2H, m, 2 $\times$ ArH), 5.15 (2H, s, C(O)OCH₂), 4.01-3.87 (2H, m, ArCH_a + NHCH), 3.46-3.37 (1H, m, ArCH_b), 3.24 (1H, br. s, NH), 2.04-2.11 (1H, m, C(O)NCH_a), 1.93-1.82 (1H, m, C(O)NCH_b), 1.84-1.77 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 162.3 (2C, d, $J_{\text{CF}}=274$), 152.0, 135.7, 129.0, 128.6, 128.3, 128.0, 127.5, 115.2, 111.3 (3C, d, $J_{\text{CF}}=27$), 104.1, 103.7, 68.0, 67.9, 54.5, 37.9, 37.2, 27.2. HRMS (ESI⁺) calculated for C₂₀H₂₀⁷⁹BrF₂N₂O₂⁺ [M+H]⁺ 437.0671, found 437.0672.

(Z)-2-Bromo-N-(2,6-difluorobenzyl)-1,3-diphenylprop-2-en-1-amine, 115



Synthesized using General Procedure G. (Z)-2-Bromo-1,3-diphenylprop-2-en-1-amine (1.50 g, 5.22 mmol, 1 eq), 2,6-fluorobenzaldehyde (560 μ l, 5.22 mmol, 1 eq), sodium triacetoxyborohydride (2.21g, 10.4 mmol, 2 eq), DCM (50 mL). Purified by flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a pale yellow oil (1.76 g, 82%). ν_{max} (neat)/ cm^{-1} 3359, 2360, 1625, 1592, 1491, 1462, 1265, 1078, 1029, 908, 783, 730, 693. δ_{H} (400 MHz, CDCl_3) 7.74-7.71 (2H, m, $2 \times \text{ArH}$), 7.51-7.54 (2H, m, $2 \times \text{ArH}$), 7.44-7.32 (7H, m, $6 \times \text{ArH} + \text{CH}=\text{CBr}$), 7.30-7.22 (1H, m, Ar), 6.94 (2H, t, $J=8.0$, $2 \times \text{ArH}$), 4.64 (1H, s, NHCH), 4.09 (1H, d, $J=13.0$, ArCH_a), 4.01 (1H, d, $J=13.0$, ArCH_b), 2.21 (1H, br. s, NH). δ_{C} (100 MHz, CDCl_3) 161.8 (2C, d, $J_{\text{CF}}=248$), 140.4, 135.5, 129.4, 129.3, 129.2, 129.1 (4C), 129.0 (2C), 128.4, 128.0, 127.8, 127.5, 115.7 (d, $J_{\text{CF}}=25$), 111.3, (2C, d, $J_{\text{CF}}=25$) 70.6, 38.8. HRMS (ESI^+) calculated for $\text{C}_{22}\text{H}_{18}^{79}\text{BrF}_2\text{NNa}^+$ $[\text{M}+\text{Na}]^+$ 436.0483, found 436.0464.

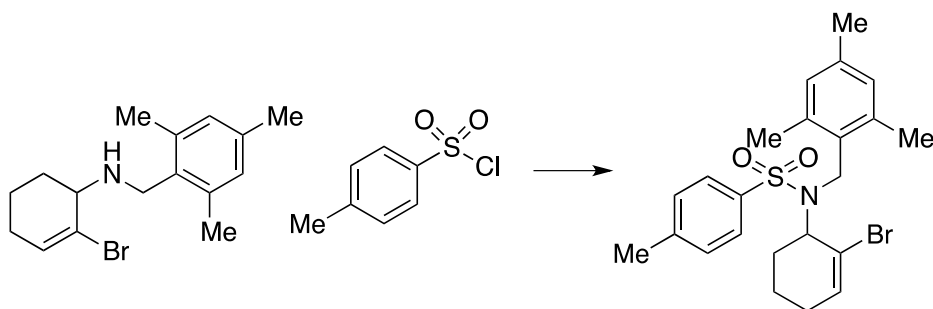
General Procedure H: Sulfonamide formation



Sulfonyl chloride (2 eq) and DMAP (0.1 eq) was added to a solution of amine (1 eq) in pyridine. The reaction was heated to 50 $^{\circ}\text{C}$ and stirred overnight. The reaction was diluted with DCM (5 vol.) and washed with 1M $\text{HCl}_{(\text{aq})}$ (3×5 vol.), a saturated solution of sodium bicarbonate (1 vol.) and brine (1 vol.). The organic layer was dried

over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

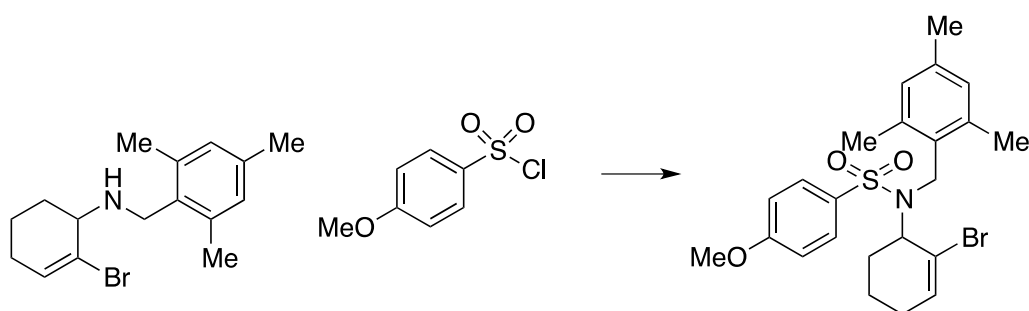
***N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-(2,4,6-trimethylbenzyl) benzenesulfonamide, 116**



Synthesized using General Procedure H. 2-Bromo-*N*-(2,4,6-trimethylbenzyl) cyclohex-2-enamine (2.68 g, 8.73 mmol, 1 eq), tosyl chloride (3.33 g, 17.5 mmol, 2 eq), DMAP (106 mg, 0.87 mmol, 0.1 eq), pyridine (70 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (3.26 g, 81%). ν_{max} (neat)/ cm^{-1} 2954, 1446, 1379, 1333, 1209, 1153, 1010, 958, 854, 810, 717, 699. δ_{H} (500 MHz, DMSO-d_6 , VT, 363 K) 7.66-7.62 (2H, m, $2 \times \text{ArH}$), 7.31 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 6.74 (2H, br. s, $2 \times \text{ArH}$), 6.24-6.21 (1H, m, $\text{CH}=\text{CBr}$), 4.57 (1H, d, $J=13.5$, ArCH_a), 4.31 (1H, d, $J=13.5$, ArCH_b), 4.28-4.13 (1H, m, NCH), 2.40 (3H, s, Me), 2.21-2.17 (9H, m, $3 \times \text{Me}$) 2.09-1.91 (4H, m, $2 \times \text{CH}_2$), 1.62-1.39 (2H, m, CH_2). δ_{C} (125 MHz, DMSO-d_6 , VT, 363 K) 142.3, 138.0 (2C), 137.3, 136.4, 128.5, 128.4 (3C), 127.9, 127.0, 58.7, 29.4, 26.4, 20.3, 20.0, 19.8, 19.2. HRMS (ESI^+) calculated for $\text{C}_{23}\text{H}_{28}^{79}\text{BrNO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 484.0916, found 484.0915. M.p. (diethyl ether/chloroform) = 137-138 °C.

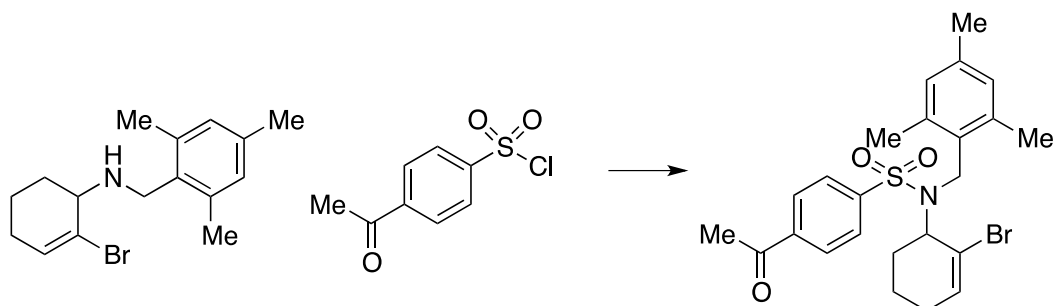
***N*-(2-Bromocyclohex-2-en-1-yl)-4-methoxy-*N*-(2,4,6-trimethylbenzyl)**

benzenesulfonamide, 117



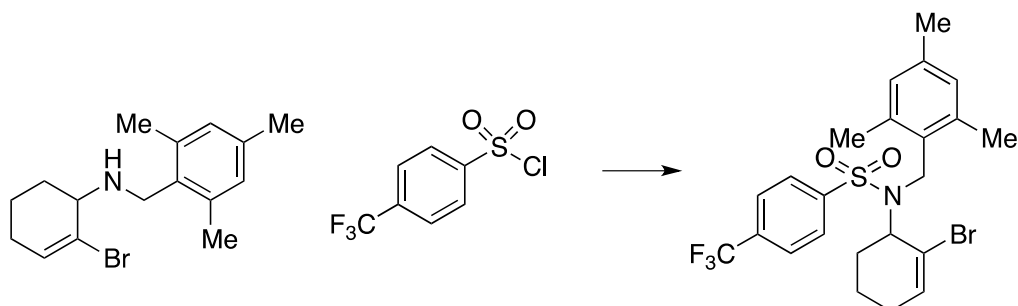
Synthesized using General Procedure H. 2-Bromo-*N*-(2,4,6-trimethylbenzyl) cyclohex-2-enamine (200 mg, 0.65 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (268 mg, 1.30 mmol, 2 eq), DMAP (8 mg, 0.07 mmol, 0.1 eq), pyridine (5 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as an opaque white solid (266 mg, 85%). ν_{max} (neat)/ cm^{-1} 2944, 2917, 2847, 1634, 1592, 1577, 1496, 1461, 1440, 1373, 1330, 1303, 1258, 1188, 1091, 1042, 965, 923, 752, 639. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.71-7.63 (2H, m, $2 \times \text{ArH}$), 7.02 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 6.74 (2H, br. s, $2 \times \text{ArH}$), 6.24-6.21 (1H, m, $\text{CH}=\text{CBr}$), 4.55 (1H, d, $J=13.5$, ArCH_a), 4.29 (1H, d, $J=13.5$, ArCH_b), 4.27-2.20 (1H, m, NCH), 3.86 (3H, s, Me), 2.21-2.17 (9H, m, $3 \times \text{Me}$) 2.09-1.91 (4H, m, $2 \times \text{CH}_2$), 1.62-1.41 (2H, m, CH_2). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 163.4, 139.4, 137.7 (4C), 133.3, 130.5, 129.8 (2C), 129.3 (2C), 114.8 (2C), 60.0, 56.6 (2C), 30.8, 27.8, 21.4, 21.2, 20.6 (2C). HRMS (ESI $^{+}$) calculated for $\text{C}_{23}\text{H}_{28}^{79}\text{BrNO}_3\text{SNa}^{+}$ $[\text{M}+\text{Na}]^{+}$ 500.0865, found 500.0863. M.p. (diethyl ether/chloroform) = 79-80 $^{\circ}\text{C}$.

4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(2,4,6-trimethylbenzyl)benzenesulfonamide, 118



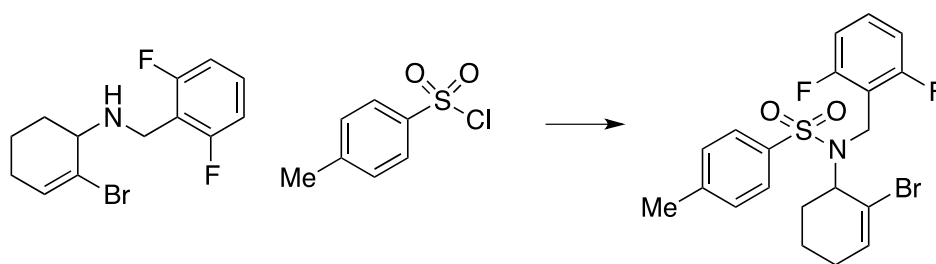
Synthesized using General procedure G. 2-Bromo-*N*-(2,4,6-trimethylbenzyl) cyclohex-2-enamine (200 g, 0.65 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (284 mg, 1.30 mmol, 2 eq), DMAP (8 mg, 0.07 mmol, 0.1 eq), pyridine (5 ml). Purified using flash column chromatography (10% EtOAc/ petrol) to yield the title compound as a white solid (179 mg, 56%). $\nu_{\max}$ (neat)/ cm^{-1} 3074, 2925, 1680, 1596, 1571, 1489, 1461, 1361, 1294, 1261, 1159, 1090, 1036, 1012, 985, 843, 798, 767, 634. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.98-7.96 (2H, m, $2 \times \text{ArH}$), 6.78-6.75 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 6.74 (2H, br. s, $2 \times \text{ArH}$), 6.28-6.24 (1H, m, $\text{CH}=\text{CBr}$), 4.57 (1H, d, $J=13.5$, ArCH_a), 4.28 (1H, d, $J=13.5$, ArCH_b), 4.26-2.21 (1H, m, NCH), 2.65 (3H, s, Me), 2.21-2.17 (9H, m, $3 \times \text{Me}$), 2.09-1.95 (4H, m, $2 \times \text{CH}_2$), 1.62-1.45 (2H, m, CH_2). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 195.9, 142.3, 139.4, 138.1, (2C) 137.8 (2C), 143.3, 130.5 (2C), 129.9, 129.7, 129.4, 126.4, 114.8, 60.0, 56.6, 56.4, 30.8, 27.7, 21.4, 21.2, 20.6 (2C). HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{28}^{79}\text{BrNO}_3\text{SNa}^+ [\text{M} + \text{Na}^+]$ 512.0865, found 512.0870. M.p. (diethyl ether/chloroform) = 144-145 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-(trifluoromethyl)-*N*-(2,4,6-trimethylbenzyl) benzenesulfonamide, 119**



Synthesized using General Procedure H. 2-Bromo-*N*-(2,4,6-trimethylbenzyl) cyclohex-2-enamine (200 mg, 0.65 mmol, 1 eq), 4-(trifluoromethyl)benzenesulfonyl chloride (318 mg, 1.30 mmol, 2 eq), DMAP (8 mg, 0.07 mmol, 0.1 eq), pyridine (5 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a colourless solid (297 mg, 88%). ν_{max} (neat)/ cm^{-1} 2925, 1686, 1609, 1450, 1348, 1322, 1164, 1117, 1094, 1059, 982, 848, 738, 709. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.82-7.75 (4H, m, 4 $\times$ ArH), 6.68 (2H, br. s, 2 $\times$ ArH), 6.36-6.33 (1H, m, CH=CBBr), 4.62 (1H, d, J =13.5, ArCH_a), 4.57-4.43 (1H, m, NCH), 4.35 (1H, d, J =13.5, ArCH_b), 2.22 (6H, s, 2 $\times$ Me), 2.18 (3H, m, Me) 2.09-2.00 (2H, m, CH₂), 1.98-1.95 (2H, m, CH₂), 1.62-1.48 (2H, m, CH₂). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 145.2, 139.4, 138.0 (2C), 133.1 (q, J_{CF} =35) 129.7 (2C), 128.9, 129.7, 126.6, 126.5, 126.4, 126.3, 125.4, 124.3 (q, J_{CF} =275), 60.8, 59.7, 31.0, 27.7, 21.3, 21.1, 20.6 (2C). HRMS (ESI⁺) calculated for C₂₃H₂₅⁷⁹BrF₃NO₂SNNa⁺ [M+Na]⁺ 538.0634, found 538.0639. M.p. (diethyl ether/chloroform) = 111-113 °C.

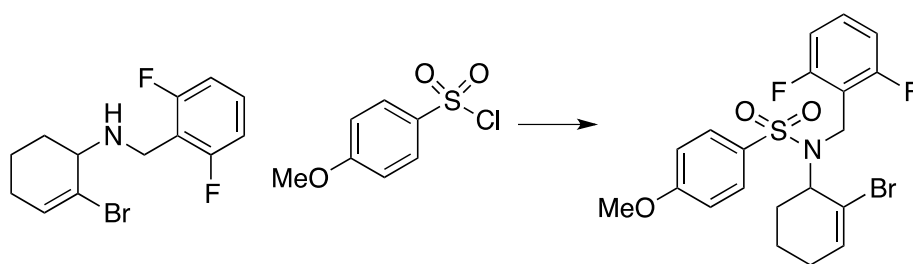
***N*-(2-Bromocyclohex-2-en-1-yl)-(2,6-difluorobenzyl)-4-methyl
benzenesulfonamide, 120**



Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-difluorobenzyl)cyclohex-2-enamine (440 mg, 1.45 mmol, 1 eq), tosyl chloride (554 mg, 2.91 mmol, 2 eq), DMAP (18 mg, 0.15 mmol, 0.1 eq), pyridine (10 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound a white solid (553 mg, 84%). $\nu_{\max}$ (neat)/cm⁻¹ 2955, 2936, 1625, 1591, 1497, 1469, 1455, 1441, 1385, 1359, 1202, 1030, 877, 770, 618. δ_{H} (400 MHz, CDCl₃) 7.70 (2H, br. d, $J=8.0$, 2 $\times$ ArH), 7.23-7.16 (3H, m, 3 $\times$ ArH), 6.57 (2H, t, $J=8.0$, 2 $\times$ ArH), 6.23-6.20 (1H, m, CH=CBr), 4.70-4.57 (2H, m, NHCH + ArCH_a), 4.49 (1H, d, $J=15.0$, ArCH_b), 2.40 (3H, s, Me), 2.10-1.96 (4H, m, 2 $\times$ CH₂), 1.69-1.56 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 161.7 (2C, d, $J_{\text{CF}}=252$), 143.0, 137.5, 130.2, 129.9, 129.8, 129.1 (3C), 127.6, 111.2 (d, $J_{\text{CF}}=26$), 111.1 (2C, d, $J_{\text{CF}}=26$), 59.9, 59.8, 29.6, 27.2, 21.5, 20.9. HRMS (ESI⁺) calculated for C₂₀H₂₀⁷⁹BrF₂NO₂SN⁺ [M+Na]⁺ 478.0255, found 478.0255. M.p. (diethyl ether/chloroform) = 128-130 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-methoxybenzene**

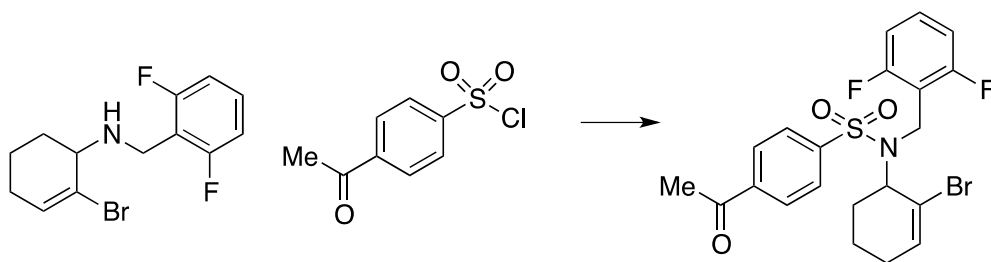
sulfonamide, 121



Synthesized using General procedure H. 2-Bromo-*N*-(2,6-difluorobenzyl)cyclohex-2-enamine (150 mg, 0.49 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (205 mg, 0.99 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a yellow oil (192 mg, 82%). ν_{max} (neat)/cm⁻¹ 2954, 2839, 1625, 1597, 1579, 1498, 1470, 1441, 1385, 1257, 1147, 1073, 901, 825, 791, 683. δ_{H} (400 MHz, CDCl₃) 7.77 (2H, d, $J=8.5$, 2 $\times$ ArH), 7.20 (2H, dt, $J=15.0$, $J=2.0$, 2 $\times$ ArH), 6.92-6.88 (1H, m, ArH), 6.73-6.80 (2H, m, 2 $\times$ ArH), 6.23-6.20 (1H, m, CH=CBr), 4.69-4.60 (2H, m, NHCH + ArCH_a), 4.48 (1H, d, $J=15.0$, ArCH_b), 3.85 (3H, s, Me), 2.16-2.03 (2H, m, CH₂), 2.01-1.92 (2H, m, CH₂), 1.73-1.53 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 163.3, 162.1 (2C, d, $J_{\text{CF}}=251$), 132.2, 129.9 (3C), 129.7 (2C), 113.7 (2C), 111.1 (3C, d, $J_{\text{CF}}=25$), 55.5 (2C), 29.6, 27.2 (2C), 20.9. HRMS (ESI⁺) calculated for C₂₀H₂₀⁷⁹BrF₂NO₃Na⁺ [M+Na]⁺ 494.0208, found 494.0210.

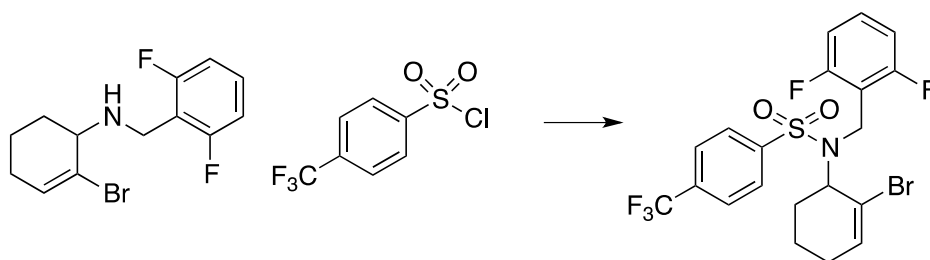
4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)benzenesulfonamide, 122

benzenesulfonamide, 122



Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-difluorobenzyl)cyclohex-2-enamine (150 mg, 0.49 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (217 mg, 0.99 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a white solid (155 mg, 65%). ν_{max} (neat)/ cm^{-1} 2954, 2937, 1688, 1626, 1592, 1470, 1455, 1431, 1397, 1361, 1341, 1293, 1179, 1164, 1073, 960, 877, 791, 710. δ_{H} (400 MHz, CDCl_3) 7.99-7.97 (2H, m, $2 \times \text{ArH}$), 7.87 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 7.20 (1H, dt, $J=14.5$, $J=2.0$, Ar), 6.76-6.72 (2H, m, $2 \times \text{ArH}$), 6.28-6.25 (1H, m, $\text{CH}=\text{CBr}$), 4.76-4.67 (2H, m, $\text{NHCH} + \text{ArCH}_a$), 4.50 (1H, d, $J=15.0$, ArCH_b), 2.64 (3H, s, Me), 2.12-2.08 (2H, m, CH_2), 2.01-1.96 (2H, m, CH_2), 1.73-1.59 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 196.9, 161.5 (2C, d, $J_{\text{CF}}=250$), 144.3, 139.5, 130.1, 128.4 (4C), 127.7 (2C) 111.2 (3C, d, $J_{\text{CF}}=25$), 60.3, 30.0, 27.2, 26.8 (2C), 20.8. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{20}^{79}\text{BrF}_2\text{NO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 506.0208, found 506.0203. M.p. (diethyl ether/chloroform) = 143-144 °C.

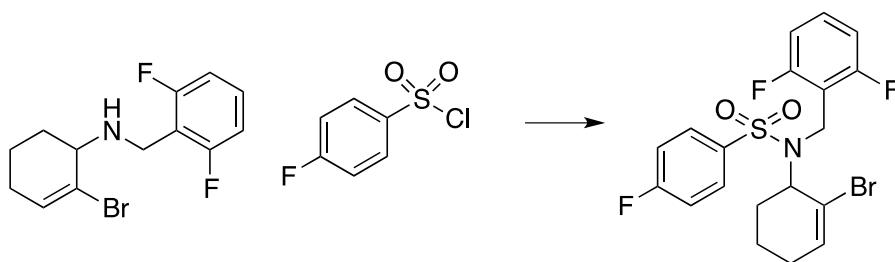
***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-(trifluoromethyl)benzenesulfonamide, 123**



Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-difluorobenzyl)cyclohex-2-enamine (150 mg, 0.49 mmol, 1 eq), 4-(trifluoromethyl)benzenesulfonyl chloride (243 mg, 0.99 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (176 mg, 70%). $\nu_{\max}$ (neat)/cm⁻¹ 3077, 2954, 1626, 1592, 1567, 1473, 1455, 1441, 1386, 1264, 1162, 1061, 1028, 928, 852, 807, 793. δ_{H} (400 MHz, CDCl₃) 7.85 (2H, d, J =8.0, 2 $\times$ ArH), 7.66 (2H, d, J =8.5, 2 $\times$ ArH), 7.19 (1H, dt, J =15.0, J =2.0, ArH), 6.75-6.69 (2H, m, 2 $\times$ ArH), 6.31-6.29 (1H, m, CH=CBr), 4.83-4.67 (2H, m, NHCH + ArCH_a), 4.46 (1H, d, J =15.0, ArCH_b), 2.17-2.11 (2H, m, CH₂), 2.05-1.96 (2H, m, CH₂), 1.67-1.58 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 162.0 (2C, d, J_{CF} =251), 144.1, 136.7, 133.8 (2C, q, J_{CF} =33), 130.2, 127.8, 125.6, 123.8 (q, J_{CF} =272), 121.0, 112.0, 111.1 (3C, d, J_{CF} =25), 60.5, 55.3, 30.0, 27.2, 20.8. HRMS (ESI⁺) calculated for C₂₀H₁₇⁷⁹BrF₅NO₂SNa⁺ [M+Na]⁺ 531.9976, found 531.9978. M.p. (diethyl ether/chloroform) = 122-124 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-fluorobenzene**

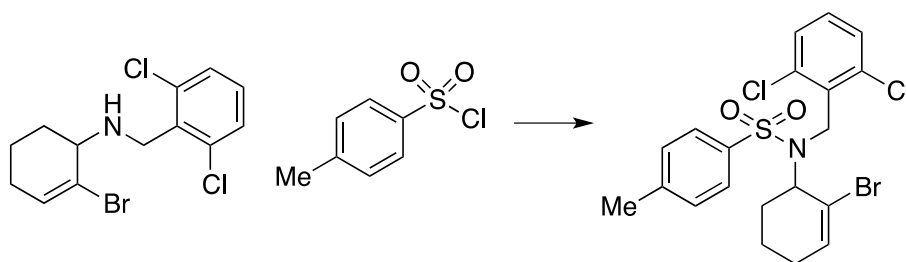
sulfonamide, 124



Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-difluorobenzyl)cyclohex-2-enamine (150 mg, 0.49 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (193 mg, 0.99 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as colourless crystals (168 mg, 74%). ν_{max} (neat)/ cm^{-1} 3074, 2955, 2937, 1625, 1592, 1494, 1470, 1455, 1441, 1316, 1233, 1125, 1012, 982, 832, 707. δ_{H} (400 MHz, CDCl_3) 7.81-7.78 (2H, m, $2 \times \text{ArH}$), 7.20 (1H, dt, $J=15.0$ $J=2.0$, ArH), 7.10-7.06 (2H, m, $2 \times \text{ArH}$), 6.78-6.73 (2H, m, $2 \times \text{ArH}$), 6.27-6.23 (1H, m, $\text{CH}=\text{CBr}$), 4.71-4.63 (2H, m, $\text{NHCH} + \text{ArCH}_a$), 4.48 (1H, d, $J=15.0$, ArCH_b), 2.12-2.06 (2H, m, CH_2), 1.99-1.96 (2H, m, CH_2), 1.72-1.57 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 164.2 (d, $J_{\text{CF}}=250$), 161.5 (2C, d, $J_{\text{CF}}=251$), 136.7, 130.2, 130.1, 121.2, 115.7 (2C, d, $J_{\text{CF}}=29$), 112.3, 111.1 (3C, d, $J_{\text{CF}}=26$), 60.2, 60.1, 29.9, 27.2 (2C), 20.8. HRMS (ESI^+) calculated for $\text{C}_{19}\text{H}_{17}^{79}\text{BrF}_3\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 482.0008, found 482.0012. M.p. (diethyl ether/chloroform) = 109-110 °C.

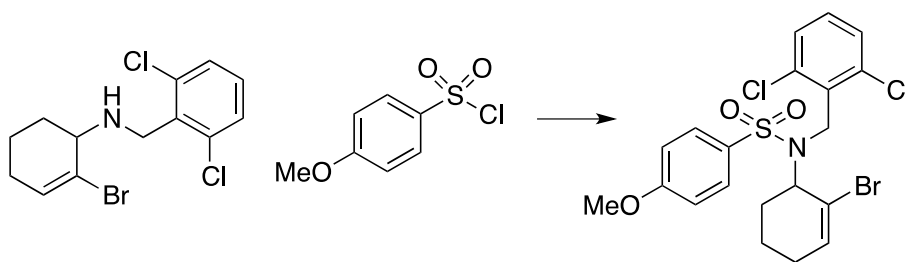
***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-dichlorobenzyl)-4-methylbenzene**

sulfonamide, 125



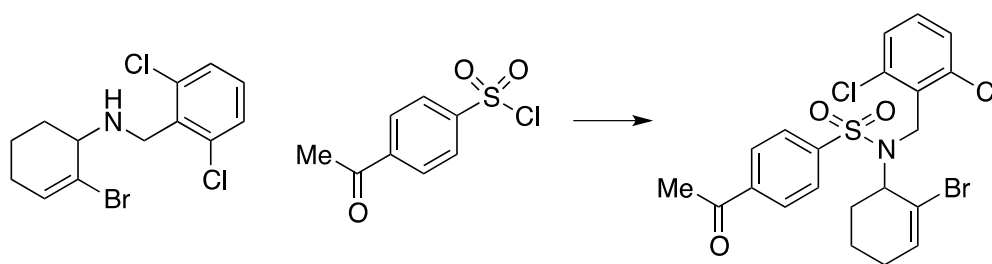
Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-dichlorobenzyl)cyclohex-2-enamine (166 mg, 0.50 mmol, 1 eq), tosyl chloride (191 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (166 mg, 68%). ν_{max} (neat)/ cm^{-1} 3083, 2926, 1636, 1598, 1581, 1561, 1493, 1452, 1452, 1433, 1369, 1329, 1184, 1160, 1018, 984, 959, 944, 828, 806, 793, 770, 756, 633. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.68 (2H, d, $J=8.0$, $2 \times \text{ArH}$) 7.36-7.27 (5H, m, $5 \times \text{ArH}$), 6.25-6.22 (1H, m, $\text{CH}=\text{CBr}$), 4.81 (1H, d, $J=14.0$, ArCH_a), 4.67 (1H, d, $J=14.0$, ArCH_b), 4.33 (1H, br. s, NCH), 2.40 (3H, s, Me), 2.18-2.04 (2H, m, CH_2), 1.98-1.94 (2H, m, CH_2), 1.67-1.47 (2H, m, CH_2). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 143.9, 138.5, 137.8, 131.7 (2C), 131.4, 130.0 (4C), 129.6 (2C), 128.5 (2C), 60.8 (2C), 30.1, 27.7, 21.7, 21.4. HRMS (ESI $^{+}$) calculated for $\text{C}_{20}\text{H}_{20}^{79}\text{Br}^{35}\text{Cl}_2\text{NO}_2\text{SNa}^{+}$ $[\text{M}+\text{Na}]^{+}$ 509.9667, found 509.9666. M.p. (diethyl ether/chloroform) = 153-154 $^{\circ}\text{C}$.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-dichlorobenzyl)-4-methoxybenzene sulfonamide, 126**



Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-dichlorobenzyl)cyclohex-2-enamine (166 mg, 0.50 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (207 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a beige solid (167 mg, 66%). ν_{max} (neat)/ cm^{-1} 3074, 3011, 2924, 2840, 1637, 1595, 1579, 1561, 1498, 1434, 1265, 1157, 1142, 1060, 1017, 984, 959, 807, 792. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.73 (2H, d, $J=8.5$, $2 \times \text{ArH}$), 7.37-7.29 (3H, m, $3 \times \text{ArH}$), 7.06-7.02 (2H, m, $2 \times \text{ArH}$), 6.28-6.25 (1H, m, $\text{CH}=\text{CBr}$), 4.76 (1H, d, $J=14.0$, ArCH_a), 4.67 (1H, d, $J=14.0$, ArCH_b), 4.33-4.27 (1H, m, NCH), 3.86 (3H, s, Me), 2.20-2.00 (2H, m, CH_2), 1.95-1.92 (2H, m, CH_2), 1.67-1.45 (2H, m, CH_2). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 163.5, 137.7 (2C), 137.6, 133.1, 131.8, 131.5 (2C), 131.4, 130.7 (2C), 129.6, 114.9 (2C), 60.7, 56.6 (2C), 30.1, 27.7, 21.4. HRMS (ESI^+) calculated for $\text{C}_{20}\text{H}_{20}^{79}\text{Br}^{35}\text{Cl}_2\text{NO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 525.9617, found 525.9613. M.p. (diethyl ether/chloroform) = 101-103 °C.

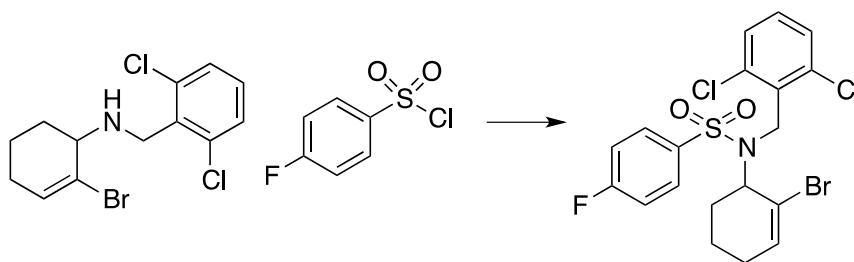
4-Acetyl-N-(2-bromocyclohex-2-en-1-yl)-N-(2,6-dichlorobenzyl)benzene sulfonamide, 127



Synthesized using General Procedure H. 2-Bromo-N-(2,6-dichlorobenzyl)cyclohex-2-enamine (166 mg, 0.50 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (219 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a mother of pearl coloured solid (139 mg, 54%). $\nu_{\max}$ (neat)/ cm^{-1} 3090, 2940, 1690, 1596, 1579, 1561, 1435, 1398, 1198, 1164, 1012, 865, 838, 700, 641. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 8.03 (2H, d, $J=8.5$, $2 \times \text{ArH}$), 7.87 (2H, d, $J=8.5$, $2 \times \text{ArH}$), 7.36-7.30 (3H, m, $3 \times \text{ArH}$), 6.30-6.28 (1H, m, $\text{CH}=\text{CBr}$), 4.87 (1H, d, $J=14.0$, ArCH_a), 4.69 (1H, d, $J=14.0$, ArCH_b), 4.47 (1H, app. br. s, NCH), 3.68 (3H, s, Me), 2.15-2.03 (2H, m, CH_2), 1.96-1.92 (2H, m, CH_2), 1.63-1.50 (2H, m, CH_2). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 198.0, 144.8, 140.8, 137.8, 136.8 (2C), 131.6, 131.5 (2C), 129.6, 129.2 (2C), 128.6 (2C), 122.1, 61.1, 46.6, 30.4, 27.7, 27.6, 21.3. HRMS (ESI $^{+}$) calculated for $\text{C}_{21}\text{H}_{20}^{79}\text{Br}^{35}\text{Cl}_2\text{NO}_3\text{SNa}^{+}$ $[\text{M}+\text{Na}]^{+}$ 537.9617, found 537.9601. M.p. (diethyl ether/chloroform) = 106-107 $^{\circ}\text{C}$.

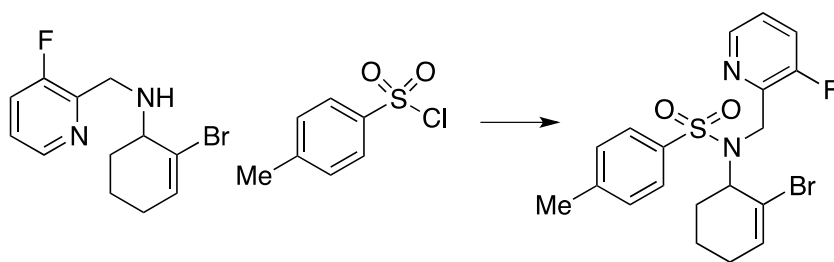
***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-dichlorobenzyl)-4-fluorobenzene**

sulfonamide, 128



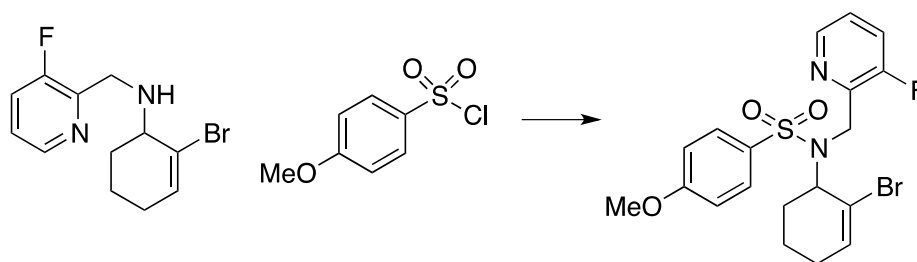
Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-dichlorobenzyl)cyclohex-2-enamine (166 mg, 0.50 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (194 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (158 mg, 64%). ν_{max} (neat)/ cm^{-1} 3106, 2930, 2865, 1636, 1590, 1562, 1489, 1435, 1286, 1198, 1163, 984, 961, 819, 730. δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.83 (2H, dd, $J=8.5$ $J=5.0$, $2 \times \text{ArH}$), 7.37-7.30 (5H, m, $5 \times \text{ArH}$), 6.28-6.25 (1H, m, $\text{CH}=\text{CBr}$), 4.83 (1H, d, $J=14.0$, ArCH_a), 4.67 (1H, d, $J=14.0$, ArCH_b), 4.40 (1H, br. s, NCH), 2.18-2.02 (2H, m, CH_2), 1.97-1.95 (2H, m, CH_2), 1.67-1.49 (2H, m, CH_2). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 165.4 (d, $J_{\text{CF}}=261$) 137.8, 137.7 (2C), 131.6 (2C), 131.5, 131.4 (2C), 131.3 (2C), 129.6, 116.6 (2C, d, $J_{\text{CF}}=26$) 61.0, 46.6, 30.4, 27.7, 21.3. HRMS (ESI $^{+}$) calculated for $\text{C}_{19}\text{H}_{17}^{79}\text{Br}^{35}\text{Cl}_2\text{FNO}_2\text{SNa}^{+}$ $[\text{M}+\text{Na}]^{+}$ 513.9417, found 513.9409. M.p. (diethyl ether/chloroform) = 134-135 $^{\circ}\text{C}$.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-((3-fluoropyridin-2-yl)methyl)-4-methylbenzenesulfonamide, 129**



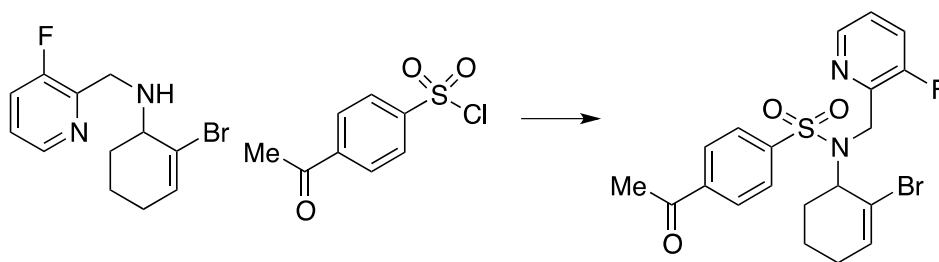
Synthesized using General Procedure H. 2-Bromo-*N*-((3-fluoropyridin-2-yl)methyl)cyclohex-2-enamine (143 mg, 0.50 mmol, 1 eq), tosyl chloride (191 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as off white crystals (171 mg, 78%). $\nu_{\max}$ (neat)/cm⁻¹ 2922, 1443, 1420, 1363, 1336, 1216, 1155, 1091, 1037, 951, 876, 841, 731. δ_{H} (400 MHz, CDCl₃) 8.30-8.28 (1H, m, ArH), 7.70 (2H, d, J =8.0, 2 $\times$ ArH), 7.32-7.27 (1H, m, ArH), 7.23 (2H, d, J =8.0, 2 $\times$ ArH), 7.19-7.15 (1H, m, ArH) 6.29-6.27 (1H, m, CH=CBr), 4.86 (1H, dd, J =16.5, J =1.5, ArCH_a), 4.62-4.66 (1H, m, NCH), 4.34 (1H, dd, J =16.5, J =1.5, ArCH_b), 2.39 (3H, s, Me), 2.26-1.94 (4H, m, 2 $\times$ CH₂), 1.66-1.53 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 157.6 (d, J_{CF} =258), 145.6, 145.0 (d, J_{CF} =33), 144.6, 142.9, 137.5, 136.8, 129.1, 127.7, 123.8, 121.9 (d, J_{CF} =33), 59.9 (2C), 44.0, 31.4, 27.3, 21.5, 20.1. HRMS (ESI⁺) calculated for C₁₉H₂₀⁷⁹BrFN₂O₂SNa⁺ [M+Na]⁺ 461.0305, found 461.0306. M.p. (diethyl ether/chloroform) = 115-116 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-((3-fluoropyridin-2-yl)methyl)-4-methoxybenzenesulfonamide, 130**



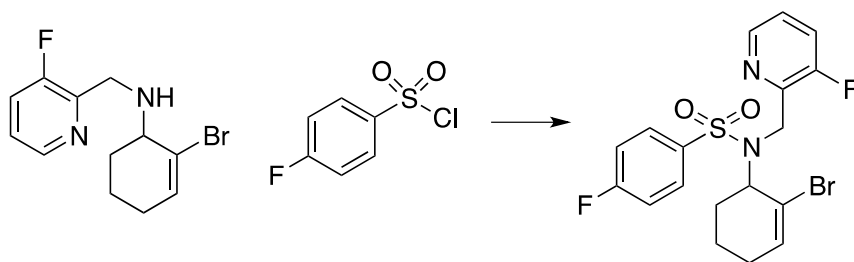
Synthesized using General Procedure H. 2-Bromo-*N*-((3-fluoropyridin-2-yl)methyl)cyclohex-2-enamine (143 mg, 0.50 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (207 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as nude coloured crystals (201 mg, 88%). $\nu_{\max}$ (neat)/cm⁻¹ 3063, 3013, 2954, 2919, 1640, 1595, 1444, 1366, 1303, 1224, 1150, 1089, 1036, 945, 874, 842, 811, 732, 709, 626. Δ_H (400 MHz, CDCl₃) 8.32-8.30 (1H, m, ArH), 7.79-7.76 (2H, m, 2 × ArH), 7.32-7.26 (2H, m, 2 × ArH), 7.17 (1H, app. Quint, *J*=4.0, ArH), 6.92-6.88 (1H, m, ArH), 6.29-6.27 (1H, m, CH=CBr), 4.84 (1H, dd, *J*=16.5, *J*=1.5, ArCH₂), 4.64-4.60 (1H, m, NCH), 4.34 (1H, dd, *J*=16.5, *J*=1.5, ArCH₂), 3.84 (3H, s, Me), 2.26-1.94 (4H, m, 2 × CH₂), 1.67-1.52 (2H, m, CH₂). Δ_C (100 MHz, CDCl₃) 162.6, 157.6 (d, *J*_{CF}=263), 144.7 (d, *J*=33), 144.6, 136.8, 132.3, 129.8 (2C), 123.7, 122.5 (d, *J*=33), 121.5, 113.6, 59.8 (2C), 44.0, 31.4, 27.4, 27.3, 20.1. HRMS (ESI⁺) calculated for C₁₉H₂₀⁷⁹BrFN₂O₃Na⁺ [M+Na]⁺ 477.0257, found 477.0257. M.p. (diethyl ether/chloroform) = 100-101 °C.

4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-((3-fluoropyridin-2-yl)methyl)benzenesulfonamide, 131



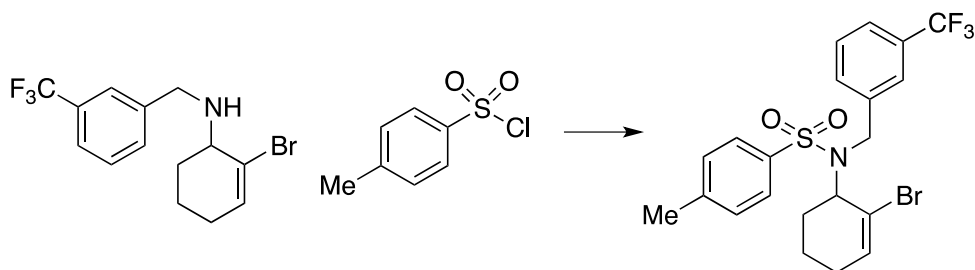
Synthesized using General Procedure H. 2-Bromo-*N*-((3-fluoropyridin-2-yl)methyl)cyclohex-2-enamine (143 mg, 0.50 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (219 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.050 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as pale orange crystals (194 mg, 83%). ν_{max} (neat)/cm⁻¹ 3074, 2925, 1682, 1596, 1571, 1447, 1429, 1351, 1294, 1261, 1159, 1135, 1090, 1036, 1012, 985, 878, 843, 798, 767, 634. δ_{H} (400 MHz, CDCl₃) 8.26-8.24 (1H, m, ArH), 8.01-7.98 (2H, m, 2 × ArH), 7.91-7.89 (2H, m, 2 × ArH), 7.31 (2H, dt, $J=9.5$, $J=1.0$, 2 × ArH), 7.18 (1H, app. quint, $J=4.0$, ArH), 6.33-6.30 (1H, m, CH=CBr), 4.90 (1H, dd, $J=16.5$, $J=1.5$, ArCH_a), 4.68-4.64 (1H, m, NCH), 4.34 (1H, dd, $J=16.5$, $J=1.5$, ArCH_b), 2.63 (3H, s, Me), 2.21-1.97 (4H, m, 2 × CH₂), 1.64-1.55 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 197.0, 157.5 (d, $J_{\text{CF}}=262$), 145.2, 144.7 (d, $J_{\text{CF}}=34$), 144.3, 139.5, 137.3, 128.4 (2C), 127.9, 124.0, 123.9, 122.9 (d, $J_{\text{CF}}=34$), 121.0, 60.3, 43.4, 31.4, 27.3, 26.9, 20.0. HRMS (ESI⁺) calculated for C₂₀H₂₀⁷⁹BrFN₂O₃SN⁺ [M+Na]⁺ 489.0254, found 489.0253. M.p. (diethyl ether/chloroform) = 154-155°C.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-fluoro-*N*-((3-fluoropyridin-2-yl)methyl)benzenesulfonamide, 132**



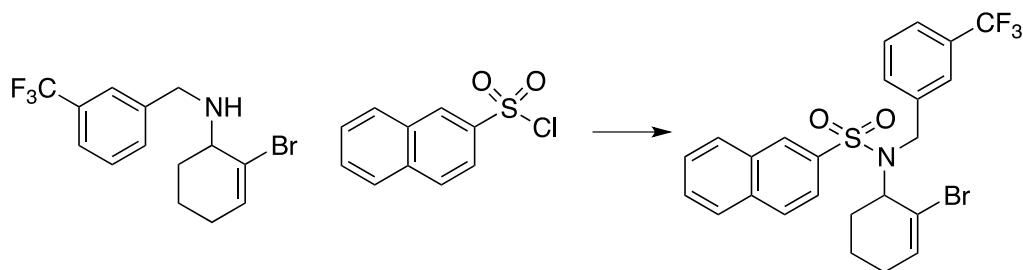
Synthesized using General Procedure H. 2-Bromo-*N*-((3-fluoropyridin-2-yl)methyl)cyclohex-2-enamine (143 mg, 0.500 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (195 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as beige crystals (200 mg, 90%). ν_{max} (neat)/cm⁻¹ 3069, 2922, 2854, 1591, 1493, 1445, 1345, 1334, 1229, 1160, 1090, 1013, 985, 947, 907, 879, 711, 662. δ_{H} (400 MHz, CDCl₃) 8.29-8.27 (1H, m, ArH), 7.87-7.83 (2H, m, 2 × ArH), 7.33-7.28 (1H, m, ArH) 7.20-7.16 (2H, m, 2 × ArH) 7.12-7.08 (1H, m, ArH) 6.33-6.30 (1H, m, CH=CBr), 4.86 (1H, dd, $J=16.5$, $J=1.5$, ArCH_a), 4.65-4.61 (1H, m, NCH), 4.34 (1H, dd, $J=16.5$, $J=1.5$, ArCH_b), 2.25-1.96 (4H, m, 2 × CH₂), 1.66-1.53 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 164.9 (d, $J_{\text{CF}}=262$), 157.6 (d, $J=259$), 145.4 (d, $J=34$), 144.7, 137.6, 130.4, 123.9, 123.8, 122.5 (d, $J=34$), 121.6, 115.6 (2C, d, $J_{\text{CF}}=26$), 60.1, 43.9, 31.4, 29.6, 27.3, 20.0. HRMS (ESI⁺) calculated for C₁₈H₁₇⁷⁹BrF₂N₂O₂SN⁺ [M+Na]⁺ 465.0054, found 465.0053. M.p. (diethyl ether/chloroform) = 113-114 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-(3-(trifluoromethyl)benzyl)benzenesulfonamide, 133**



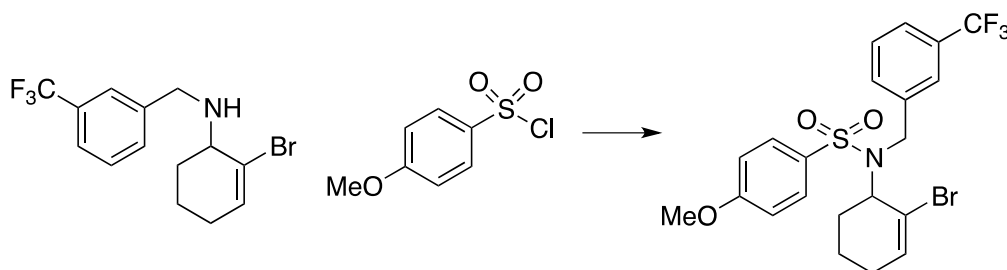
Synthesized using General Procedure H. 2-Bromo-*N*-(3-(trifluoromethyl)benzyl)cyclohex-2-en-1-amine (460 mg, 1.37 mmol, 1 eq), tosyl chloride (525 mg, 2.75 mmol, 2 eq), DMAP (17 mg, 0.14 mmol, 0.1 eq), pyridine (10 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (652 mg, 97%). $\nu_{\max}$ (neat)/cm⁻¹ 2940, 1598, 1451, 1327, 1157, 1120, 1072, 1032, 955, 903, 836, 729, 701. δ_{H} (400 MHz, CDCl₃) 7.66 (1H, d, $J=7.6$, Ar), 7.64 (2H, d, $J=8.0$, Ar), 7.50-7.47 (2H, m, 2 $\times$ ArH), 7.40 (1H, d, $J=7.5$, ArH), 7.21 (2H, d, $J=8.5$, 2 $\times$ ArH), 6.39-6.36 (1H, m, CH=CBr), 4.73 (1H, d, $J=16.0$, ArCH_a), 4.70-4.67 (1H, m, NCH), 4.19 (1H, d, $J=16.0$, ArCH_b), 2.39 (3H, s, Me), 2.13-1.74 (4H, m, 2 $\times$ CH₂), 1.54-1.32 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 143.3, 139.1, 137.6, 137.5, 132.1 (q, $J_{\text{CF}}=33$), 129.2 (3C), 128.7, 127.4 (2C), 125.2, 124.2 (q, $J_{\text{CF}}=251$), 124.1, 120.7, 60.1, 48.3, 32.1, 27.2, 21.4, 19.8. HRMS (ESI⁺) calculated for C₂₁H₂₁⁷⁹BrF₃NO₂SN⁺ [M+Na]⁺ 510.0321, found 510.0328. M.p. (diethyl ether/chloroform) = 64-65 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(3-(trifluoromethyl)benzyl)naphthalene-2-sulfonamide, 134**



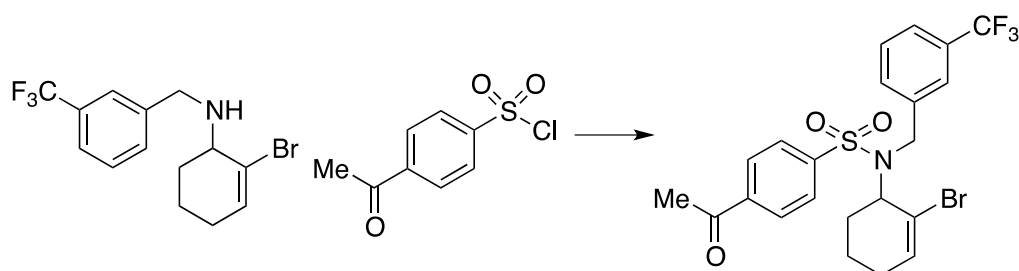
Synthesized using General Procedure H. 2-Bromo-*N*-(3-(trifluoromethyl)benzyl)cyclohex-2-enamine (150 mg, 0.45 mmol, 1 eq), 2-naphthalenesulfonyl chloride (204 mg, 0.90 mmol, 2 eq), DMAP (5 mg, 0.05 mmol, 0.1 eq), pyridine (3.5 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a pale yellow oil (212 mg, 90%). $\nu_{\max}$ (neat)/cm⁻¹ 3058, 2940, 1592, 1504, 1452, 1326, 1269, 1120, 953, 859, 700. δ_{H} (400 MHz, CDCl₃) 8.23 (1H, bs, *ArH*), 7.91-7.85 (3H, m, 3 × *ArH*), 7.79 (1H, dd, *J*=8.5, *J*=2.0, *ArH*), 7.70-7.54 (4H, m, 4 × *ArH*), 7.41-7.31 (2H, m, 2 × *ArH*), 6.38-6.36 (1H, m, *CH*=CBr), 4.83-4.79 (2H, m, NCH + *ArCH*_a), 4.24 (1H, d, *J*=16.0, *ArCH*_b), 2.16-2.08 (1H, m, *CH*₂), 1.98-1.90 (2H, m, *CH*₂), 1.86-1.78 (1H, m, *CH*₂), 1.59-1.32 (2H, m, *CH*₂). δ_{C} (100 MHz, CDCl₃) 138.8, 137.6, 137.3, 134.7, 132.2, 131.9, 130.4 (q, *J*_{CF}=32), 129.2, 129.0 (2C), 128.7, 128.6, 127.8, 127.3 (2C), 125.3, 124.3, 124.2 (q, *J*_{CF}=244), 122.5, 60.3, 48.4, 32.1, 27.7, 19.8. HRMS (ESI⁺) calculated for C₂₄H₂₁⁷⁹BrF₃NO₂SNa⁺ [*M*+Na]⁺ 546.0321, found 546.0333.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-methoxy-*N*-(3-(trifluoromethyl)benzyl)benzenesulfonamide, 135**



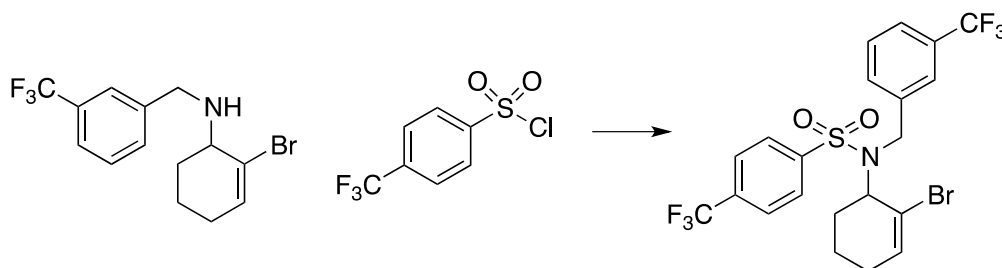
Synthesized using General procedure H. 2-Bromo-*N*-(3-(trifluoromethyl)benzyl)cyclohex-2-enamine (150 mg, 0.45 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (186 mg, 0.90 mmol, 2 eq), DMAP (5 mg, 0.05 mmol, 0.1 eq), pyridine (3.5 mL). Purified using flash column chromatography (15% ethyl acetate/petrol) to yield the title compound as a yellow oil (230 mg, 97%). $\nu_{\max}$ (neat)/cm⁻¹ 2944, 2842, 2360, 2341, 1593, 1578, 1496, 1456, 1442, 1373, 1260, 1151, 1121, 1091, 986, 955, 874, 860, 802, 661. δ_{H} (400 MHz, CDCl₃) 7.70-7.66 (3H, m, 3 × ArH), 7.52 (1H, br. s, ArH), 7.47 (1H, d, *J*=8.0, ArH), 7.71 (1H, t, *J*=7.5, ArH), 6.87 (2H, app. d, *J*=9.0, 2 × ArH), 6.39-6.36 (1H, m, CH=CBr), 4.72 (1H, d, *J*=16.0, ArCH_a), 4.70-4.67 (1H, m, NCH), 4.16 (1H, d, *J*=16.0, ArCH_b), 3.84 (3H, s, Me), 2.10-1.74 (4H, m, 2 × CH₂), 1.57-1.30 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 164.9, 162.7, 139.1, 137.5, 136.0, 132.2 (q, *J*_{CF}=33), 129.5, 128.7, 125.2, 124.1, 123.7 (q, *J*_{CF}=268), 122.6, 120.7, 114.7, 113.8, 60.1, 55.5, 48.3, 32.1, 27.2, 19.7. HRMS (ESI⁺) calculated for C₂₁H₂₁⁷⁹BrF₃NO₃SNa⁺ [M+Na]⁺ 526.0270, found 526.0265.

4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(3-(trifluoromethyl)benzyl)benzenesulfonamide, 136



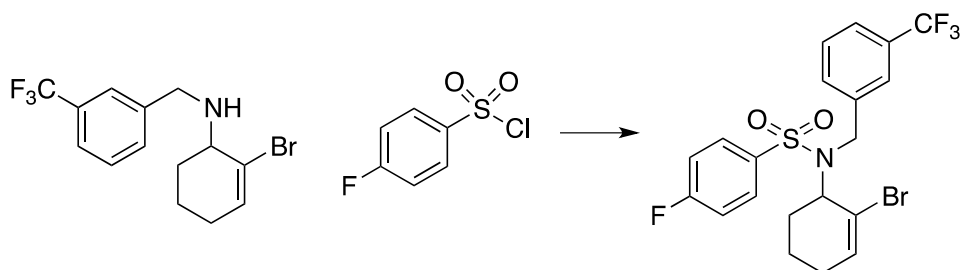
Synthesized using General Procedure H. 2-Bromo-*N*-(3-(trifluoromethyl)benzyl)cyclohex-2-en-1-amine (150 mg, 0.45 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (196 mg, 0.90 mmol, 2 eq), DMAP (5 mg, 0.05 mmol, 0.1 eq), pyridine (3.5 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a colourless oil (184 mg, 79%). ν_{max} (neat)/ cm^{-1} 2941, 2359, 1572, 1456, 1196, 1160, 1030, 957, 803, 729, 605. δ_{H} (400 MHz, CDCl_3) 7.99-7.94 (2H, m, $2 \times \text{ArH}$), 7.81-7.77 (2H, m, $2 \times \text{ArH}$), 7.66 (1H, d, $J=7.5$, ArH), 7.51-7.47 (2H, m, $2 \times \text{ArH}$), 7.43-7.39 (1H, m, ArH) 6.342-6.39 (1H, m, $\text{CH}=\text{CBr}$), 4.76-4.70 (2H, m, $\text{NCH} + \text{ArCH}_a$), 4.20 (1H, d, $J=16.0$, ArCH_b), 2.62 (3H, s, Me), 2.13-1.73 (4H, m, $2 \times \text{CH}_2$), 1.58-1.35 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 196.8, 144.2, 139.6, 138.4, 138.2, 132.3, 130.6 (q, $J_{\text{CF}}=34$), 128.9, 128.5 (2C), 127.6, 126.4, 124.3 (q, $J_{\text{CF}}=244$), 120.3, 60.6, 48.8, 32.2, 27.2, 26.7, 26.6, 19.8. HRMS (ESI⁺) calculated for $\text{C}_{22}\text{H}_{21}^{79}\text{BrF}_3\text{NO}_3\text{SNa}^+ [\text{M}+\text{Na}]^+$ 538.0270, found 538.0272.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-(trifluoromethyl)-*N*-(3-(trifluoromethyl)benzyl)benzenesulfonamide, 137**



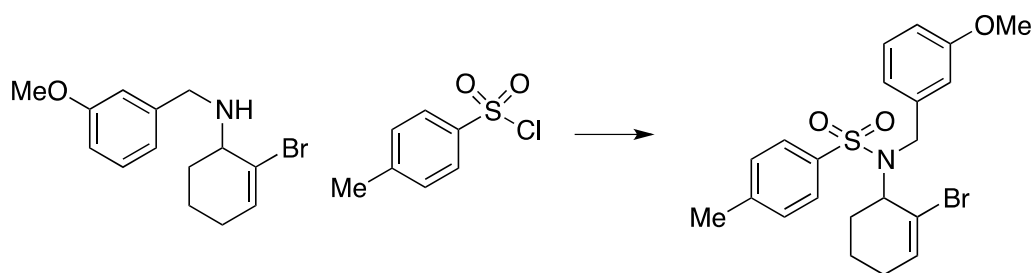
Synthesized using General Procedure H. 2-Bromo-*N*-(3-(trifluoromethyl)benzyl)cyclohex-2-enamine (150 mg, 0.45 mmol, 1 eq), 4-(trifluoromethyl)benzenesulfonyl chloride (220 mg, 0.90 mmol, 2 eq), DMAP (5 mg, 0.05 mmol, 0.1 eq), pyridine (3.5 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (207 mg, 85%). $\nu_{\max}$ (neat)/ cm^{-1} 2943, 2360, 1609, 1453, 1322, 1107, 1073, 986, 876, 842, 804, 737, 620. δ_{H} (400 MHz, CDCl_3) 7.82 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 7.66-7.62 (3H, m, $3 \times \text{ArH}$), 7.52-7.47 (2H, m, $2 \times \text{ArH}$), 7.39 (1H, t, $J=7.5$, Ar), 6.44-6.41 (1H, m, $\text{CH}=\text{CBr}$), 4.74-4.70 (2H, m, $\text{NCH} + \text{ArCH}_a$), 4.22 (1H, d, $J=16.0$, ArCH_b), 2.13-1.76 (4H, m, $2 \times \text{CH}_2$), 1.60-1.39 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 144.0, 139.5, 138.1, 134.1 (q, $J_{\text{CF}}=32$), 132.3, 130.6 (q, $J_{\text{CF}}=32$), 128.8, 127.8, 125.8, 125.7, 126.0 (q, $J_{\text{CF}}=280$), 125.5, 124.6, 124.4 (q, $J_{\text{CF}}=243$), 120.2, 60.7, 56.7, 48.4, 32.1, 27.4, 19.8. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{18}^{79}\text{BrF}_6\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 564.0038, found 564.0024. M.p. (diethyl ether/chloroform) = 64-66 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-fluoro-*N*-(3-(trifluoromethyl)benzyl)benzenesulfonamide, 138**



Synthesized using General Procedure H. 2-Bromo-*N*-(3-(trifluoromethyl)benzyl)cyclohex-2-enamine (150 mg, 0.45 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (175 mg, 0.90 mmol, 2 eq), DMAP (5 mg, 0.05 mmol, 0.1 eq), pyridine (3.5 mL). Purified using flash column chromatography (15% ethyl acetate/petrol) to yield the title compound as a white solid (187 mg, 85%). $\nu_{\max}$ (neat)/cm⁻¹ 2942, 2360, 2341, 1592, 1494, 1405, 1237, 1197, 1164, 1124, 1091, 1073, 1012, 986, 838, 666. δ_{H} (400 MHz, CDCl₃) 7.72-7.76 (2H, m, 2 × *ArH*), 7.67 (1H, d, *J*=7.5, *ArH*), 7.54 (1H, br. s, *ArH*), 7.50 (1H, d, *J*=8.0, *ArH*), 7.41 (1H, t, *J*=7.5, *ArH*), 7.10-7.06 (2H, m, 2 × *ArH*), 6.41-6.39 (1H, m, *CH*=CBr), 4.72 (1H, d, *J*=16.0, *ArCH_a*), 4.68-4.65 (1H, m, *NCH*), 4.21 (1H, d, *J*=16.0, *ArCH_b*), 2.12-1.74 (4H, m, 2 × *CH₂*), 1.58-1.32 (2H, m, *CH₂*). δ_{C} (100 MHz, CDCl₃) 166.2 (d, *J*_{CF}=260), 138.7, 137.9, 136.6, 132.2, 130.4 (q, *J*_{CF}=33), 130.0, 128.8, 125.2, 124.3 (q, *J*_{CF}=267), 120.3, 115.8 (2C, d, *J*_{CF}=25), 60.4, 48.4, 32.1, 27.5, 27.2, 19.7, 17.9. HRMS (ESI⁺) calculated for C₂₀H₁₈⁷⁹BrF₄NO₂SNa⁺ [*M*+Na]⁺ 514.0070, found 514.0069. M.p. (diethyl ether/chloroform) = 90-91 °C.

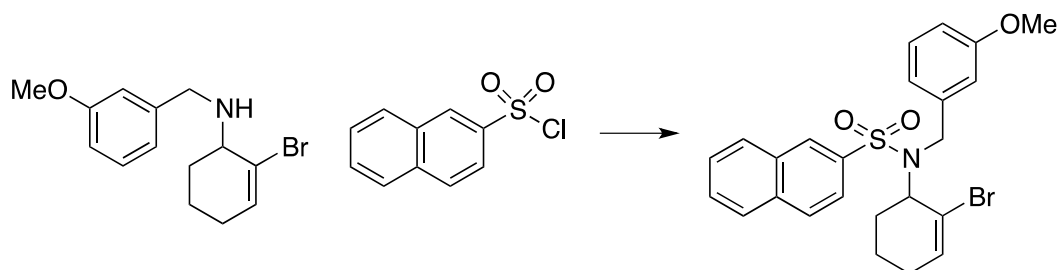
***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(3-methoxybenzyl)-4-methylbenzenesulfonamide, 139**



Synthesized using General Procedure H. 2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-enamine (380 mg, 1.41 mmol, 1 eq), tosyl chloride (538 mg, 2.82 mmol, 2 eq), DMAP (17 mg, 0.14 mmol, 0.1 eq), pyridine (10 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a white solid (573 mg, 90%). $\nu_{\max}$ (neat)/ cm^{-1} 2938, 2360, 1600, 1489, 1455, 1333, 1154, 1130, 1075, 985, 814, 726, 691, 616. δ_{H} (400 MHz, CDCl_3) 7.67-7.69 (2H, m, $2 \times \text{ArH}$), 7.24 (1H, t, $J=8.0$, ArH) 7.18 (1H, t, $J=8.0$, ArH) 6.96-6.94 (2H, m, $2 \times \text{ArH}$) 6.76-6.70 (1H, m, ArH) 6.36-6.33 (1H, m, $\text{CH}=\text{CBr}$), 4.72 (1H, d, $J=16.0$, ArCH_a) 4.63-4.61 (1H, m, NCH), 4.07 (1H, d, $J=16.0$, ArCH_b) 3.75 (3H, s, Me) 2.41 (3H, s, Me) 2.06-1.76 (4H, m, $2 \times \text{CH}_2$), 1.51-1.32 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 159.5, 143.0, 139.8, 137.8 (2C), 137.3, 129.2 (2C), 129.1, 127.6, 127.4, 120.9, 120.8, 113.6, 113.2, 60.1, 55.1, 32.2, 27.3, 21.5, 19.8. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{24}^{79}\text{BrNO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 472.0552, found 472.0550. M.p. (diethyl ether/chloroform) = 64-65 °C.

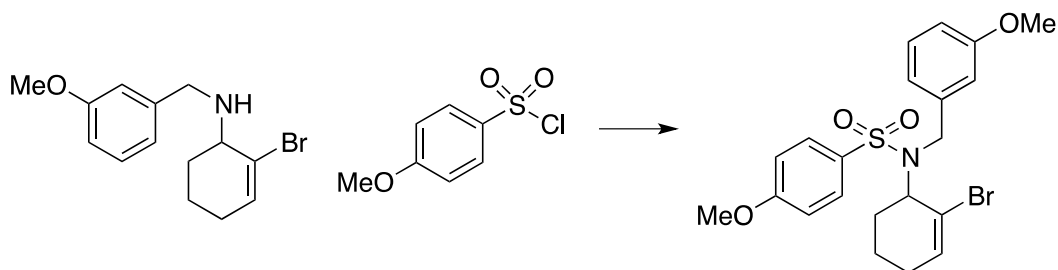
***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(3-methoxybenzyl)naphthalene-2-sulfonamide,**

140



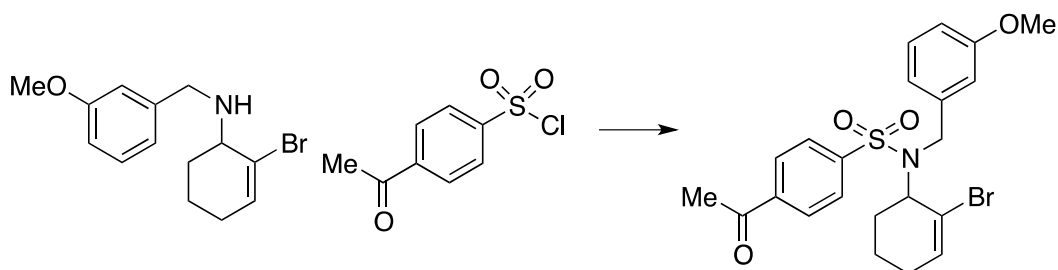
Synthesized using General Procedure H. 2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-enamine (150 mg, 0.51 mmol, 1 eq), 2-naphthalenesulfonyl chloride (230 mg, 1.01 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a clear yellow oil (215 mg, 87%). ν_{max} (neat)/cm⁻¹ 2938, 2360, 1600, 1489, 1455, 1333, 1261, 1154, 1130, 1075, 985, 906, 814, 785, 726. δ_{H} (400 MHz, CDCl₃) 8.26 (1H, br. s, *ArH*), 7.85-7.90 (3H, m, 3 × *ArH*), 7.81 (1H, dd, *J*=8.5, *J*=2.0, *ArH*), 7.62-7.53 (2H, m, 2 × *ArH*) 7.13 (1H, t, *J*=8.0, *ArH*), 6.97-6.91 (2H, m, 2 × *ArH*), 6.69 (1H, dd, *J*=8.0, *J*=2.0, *ArH*), 6.34-6.32 (1H, m, *CH*=CBr), 4.80-4.75 (2H, m, *NCH* + *ArCH_a*), 4.15 (1H, d, *J*=16.0, *ArCH_b*), 3.64 (3H, s, Me), 2.12-1.81 (4H, m, 2×*CH₂*), 1.54-1.36 (2H, m, *CH₂*). δ_{C} (100 MHz, CDCl₃) 159.4, 139.3, 137.7, 137.4, 134.6, 131.9, 129.2, 129.1, 128.8, 128.6, 128.5, 127.7, 127.1, 123.1, 121.0, 120.9, 113.9, 113.2, 60.3, 55.0, 48.9, 32.2, 27.3, 19.9. HRMS (ESI⁺) calculated for C₂₄H₂₄⁷⁹BrNO₃SNa⁺ [*M*+Na]⁺ 508.0552, found 508.0559.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-methoxy-*N*-(3-methoxybenzyl)benzene sulfonamide, 141**



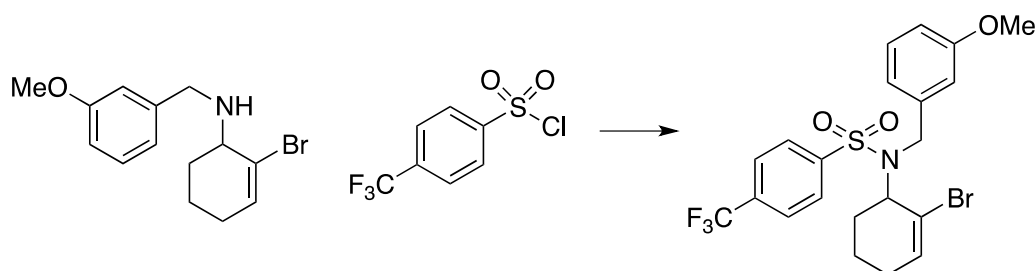
Synthesized using General Procedure H. 2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-en-1-amine (150 mg, 0.50 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (209 mg, 1.01 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as an opaque yellow oil (208 mg, 88%). ν_{max} (neat)/ cm^{-1} 2940, 1596, 1496, 1457, 1333, 1256, 1149, 1093, 1026, 986, 907, 803, 728. δ_{H} (400 MHz, CDCl_3) 7.41-7.30 (2H, m, $2 \times \text{ArH}$), 7.19-7.15 (1H, m, ArH), 6.96-6.94 (2H, m, $2 \times \text{ArH}$), 6.91-6.86 (2H, m, $2 \times \text{ArH}$), 6.78-6.75 (1H, m, ArH), 6.35-6.33 (1H, m, $\text{CH}=\text{CBr}$), 4.72 (1H, d, $J=16.0$, ArCH_a), 4.61-4.56 (1H, m, NCH), 4.08 (1H, d, $J=16.0$, ArCH_b), 3.85 (3H, s, Me), 3.75 (3H, s, Me), 2.05-1.76 (4H, m, $2 \times \text{CH}_2$), 1.49-1.30 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 162.6, 159.5, 139.9, 137.3 (2C), 132.6 (2C), 129.6 (2C), 129.1, 120.9, 120.8, 113.6, 113.1, 60.7, 55.5, 55.1, 48.8, 32.2, 22.3, 19.8. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{24}^{79}\text{BrNO}_4\text{SNa}^+$ [$\text{M}+\text{Na}$] $^+$ 488.0502, found 488.0496.

4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(3-methoxybenzyl)benzene sulfonamide, 142



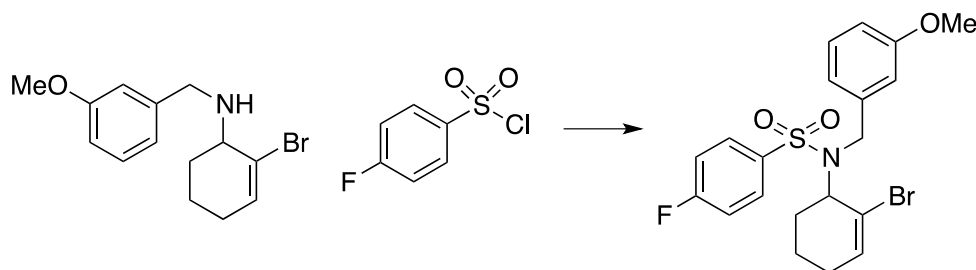
Synthesized using General Procedure H. 2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-en-1-amine (150 mg, 0.50 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (221 mg, 1.01 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (211 mg, 87%). ν_{max} (neat)/ cm^{-1} 2939, 1687, 1597, 1489, 1455, 1397, 1340, 1159, 1032, 986, 957, 832, 790, 636. δ_{H} (400 MHz, CDCl_3) 7.98-7.94 (2H, m, $2 \times \text{ArH}$), 7.82-7.80 (2H, m, $2 \times \text{ArH}$), 7.16 (1H, t, $J=8.0$, ArH), 6.93-6.86 (2H, m, $2 \times \text{ArH}$), 6.76 (1H, dd, $J=8.0$, $J=2.5$, ArH), 6.37-6.35 (1H, m, $\text{CH}=\text{CBr}$), 4.72-4.64 (2H, m, $\text{NCH} + \text{ArCH}_a$), 4.07 (1H, d, $J=16.0$, ArCH_b), 3.72 (3H, s, Me), 2.62 (3H, s, Me), 2.08-1.76 (4H, m, $2 \times \text{CH}_2$), 1.53-1.34 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 196.9, 159.5, 144.5, 139.5, 139.0, 137.7, 129.2 (2C), 128.4 (2C), 127.8, 127.7, 121.0, 120.5, 113.9, 111.2, 60.5, 55.1, 32.2, 27.3, 26.8, 19.8. HRMS (ESI^+) calculated for $\text{C}_{22}\text{H}_{24}^{79}\text{BrNO}_4\text{SNa}^+$ [$\text{M}+\text{Na}$] $^+$ 500.0502, found 500.0497.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(3-methoxybenzyl)-4-(trifluoromethyl)benzene sulfonamide, 143**



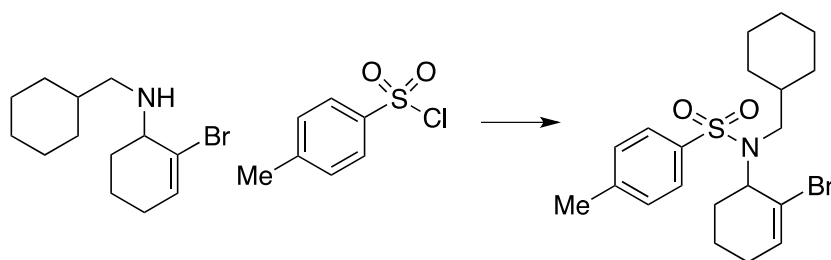
Synthesized using General Procedure H. 2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-enamine (150 mg, 0.50 mmol, 1 eq), 4-(trifluoromethyl)benzenesulfonyl chloride (248 mg, 1.01 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow oil (214 mg, 84%). ν_{max} (neat)/cm⁻¹ 2941, 1601, 1490, 1456, 1403, 1320, 1262, 1163, 1129, 1061, 986, 840, 792, 736. δ_{H} (400 MHz, CDCl₃) 7.81 (2H, d, $J=8.0$, 2 $\times$ ArH), 7.66 (1H, d, $J=8.0$, ArH), 7.16 (1H, t, $J=8.0$, ArH), 6.93 (1H, d, $J=7.5$, ArH), 6.87 (1H, br. s, ArH), 6.76 (1H, dd, $J=8.0$, $J=2.5$, ArH), 6.41-6.36 (1H, m, CH=CBr), 4.70-4.64 (2H, m, NCH + ArCH_a), 4.11 (1H, d, $J=15.5$, ArCH_b), 3.72 (3H, s, Me), 2.12-1.80 (4H, m, 2 $\times$ CH₂), 1.58-1.31 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 159.5, 144.3, 138.6, 137.8, 133.9, 133.4 (q, $J_{\text{CF}}=34$), 133.2, 129.2, 127.9, 125.6, 125.5, 124.6 (q, $J_{\text{CF}}=265$), 120.5, 114.1, 113.3, 60.6, 55.1, 48.9, 32.1, 27.3, 19.9. HRMS (ESI⁺) calculated for C₂₁H₂₁⁷⁹BrF₃NO₃SNa⁺ [M+Na]⁺ 526.0270, found 525.0269.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-fluoro-*N*-(3-methoxybenzyl)benzene sulfonamide, 144**



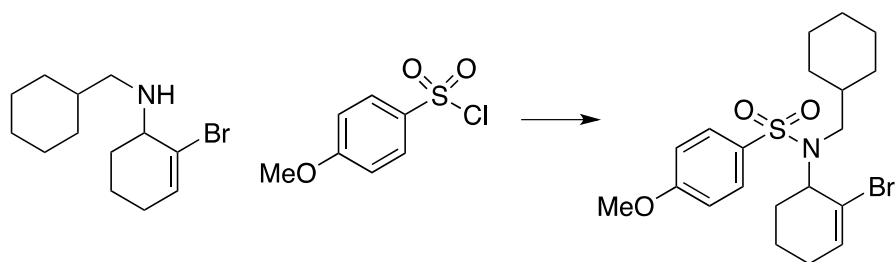
Synthesized using General Procedure H. 2-Bromo-*N*-(3-methoxybenzyl)cyclohex-2-enamine (150 mg, 0.50 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (197 mg, 1.01 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a colourless oil (185 mg, 80%). ν_{max} (neat)/ cm^{-1} 2940, 2360, 1591, 1492, 1455, 1338, 1261, 1234, 1151, 1091, 1032, 986, 906, 836, 786, 728. δ_{H} (400 MHz, CDCl_3) 7.79-7.74 (2H, m, $2 \times \text{ArH}$), 7.20-7.16 (1H, m, ArH), 7.12-7.06 (2H, m, $2 \times \text{ArH}$), 6.95-6.93 (2H, m, $2 \times \text{ArH}$), 6.79-6.76 (1H, m, ArH), 6.78-6.67 (1H, m, ArH), 6.38-6.36 (1H, m, $\text{CH}=\text{CBr}$), 4.69 (1H, d, $J=15.5$, ArCH_a), 4.66-4.62 (1H, m, NCH), 4.08 (1H, d, $J=15.5$, ArCH_b), 3.76 (3H, s, Me), 2.07-1.77 (4H, m, $2 \times \text{CH}_2$), 1.53-1.33 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 164.9 (d, $J_{\text{CF}}=251$), 159.6, 139.3, 137.6, 136.9, 130.1, 129.2 (2C), 120.9, 120.6, 115.7 (2C, d, $J_{\text{CF}}=24$), 113.9, 113.1, 60.3, 55.1, 48.8, 32.2, 27.3, 19.8. HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{21}^{79}\text{BrFNO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 476.0302, found 476.0301.

***N*-(2-bromocyclohex-2-en-1-yl)-*N*-(cyclohexylmethyl)-4-methylbenzene
sulfonamide, 145**



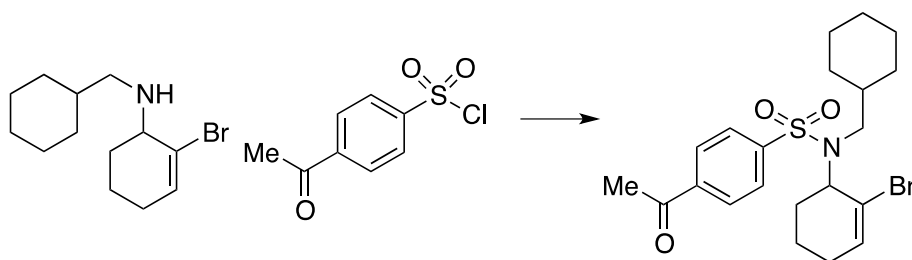
Synthesized using General Procedure H. 2-Bromo-*N*-(cyclohexylmethyl)cyclohex-2-enamine (136 mg, 0.50 mmol, 1 eq), tosyl chloride (191 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a pale yellow solid (190 mg, 89%). ν_{max} (neat)/cm⁻¹ 2925, 2850, 1595, 1442, 1374, 1331, 1305, 1160, 1147, 1088, 911, 888, 831, 811, 768, 704. δ_{H} (400 MHz, CDCl₃) 7.72 (2H, d, $J=8.2$, 2 $\times$ ArH), 7.26 (2H, d, $J=8.0$, 2 $\times$ ArH), 6.36-6.30 (1H, m, CH=CBr), 4.59 (1H, br. s, NCH), 3.12 (1H, dd, $J=14.5$, $J=7.0$, CyCH_a), 2.87 (1H, dd, $J=14.5$, $J=7.0$, CyCH_b) 2.41 (3H, s, Me), 2.12-1.80 (4H, m, 2 $\times$ CH₂), 1.75-1.60 (8H, m, 4 $\times$ CH₂), 1.17-1.08 (3H, m, NCH₂CH + CH₂), 0.88-0.74 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 142.8 (2C), 138.1, 129.2 (2C), 127.4 (2C), 122.3, 59.7, 37.2, 31.6, 31.2, 27.3, 26.4, 26.0 (2C), 25.9, 21.5, 20.7. HRMS (ESI⁺) calculated for C₂₀H₂₈⁷⁹BrNO₂SNa⁺ [M+Na]⁺ 448.0916, found 488.0915. M.p. (diethyl ether/chloroform) = 95-97 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(cyclohexylmethyl)-4-methoxybenzene
sulfonamide, 146**



Synthesized using General Procedure H. 2-Bromo-*N*-(cyclohexylmethyl)cyclohex-2-enamine (136 mg, 0.50 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (207 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a white solid (128 mg, 58%). ν_{max} (neat)/ cm^{-1} 2919, 2845, 1595, 1496, 1334, 1255, 1150, 1034, 1012, 977, 889, 810, 778, 730. δ_{H} (400 MHz, CDCl_3) 7.80-7.76 (2H, m, 2 $\times$ ArH), 6.96-6.92 (2H, m, 2 $\times$ ArH), 6.33-6.30 (1H, m, CH=CBr), 4.63-4.51 (1H, m, NCH), 3.86 (1H, s, Me) 3.13 (1H, dd, $J=14.5$, $J=7.0$, CyCH_a) 2.88 (1H, dd, $J=14.5$, $J=7.0$, CyCH_b) 2.12-1.84 (4H, m, 2 $\times$ CH₂), 1.76-1.62 (8H, m, 4 $\times$ CH₂), 1.17-1.00 (3H, m, NCH₂CH + CH₂), 0.87-0.74 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 162.5, 132.9, 129.5 (2C), 133.7, 113.7 (2C), 101.0, 55.5 (2C), 37.2, 31.6, 31.3, 31.2, 27.3, 26.4 (2C), 26.0, 25.9, 20.7. HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{28}^{79}\text{BrNO}_3\text{SNa}^+$ [M+Na]⁺ 464.0865, found 464.0861. M.p. (diethyl ether/chloroform) = 77-79 °C.

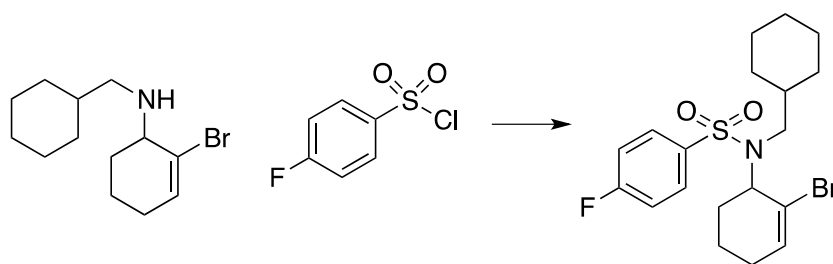
**4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(cyclohexylmethyl)benzene
sulfonamide, 147**



Synthesized using General Procedure H. 2-Bromo-*N*-(cyclohexylmethyl)cyclohex-2-enamine (136 mg, 0.50 mmol, 1 eq), 4-acetylbenzenesulfonyl chloride (219 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield a beige solid (142 mg, 62%). $\nu_{\max}$ (neat)/ cm^{-1} 2924, 2851, 1686, 1449, 1397, 1332, 1260, 1152, 1091, 1008, 960, 910, 891, 836, 787, 730. δ_{H} (400 MHz, CDCl_3) 8.06-8.03 (2H, m, $2 \times \text{ArH}$), 7.95-7.92 (2H, m, $2 \times \text{ArH}$), 6.34-6.31 (1H, m, $\text{CH}=\text{CBr}$), 4.65-4.54 (1H, m, NCH), 3.16 (1H, dd, $J=14.5$, $J=7.0$, CyCH_a), 2.88 (1H, dd, $J=14.5$, $J=7.0$, CyCH_b), 2.64 (3H, s, Me) 2.14-1.83 (4H, m, $2 \times \text{CH}_2$), 1.77-1.62 (8H, m, $4 \times \text{CH}_2$), 1.16-1.07 (3H, m, $\text{NCH}_2\text{CH} + \text{CH}_2$), 0.90-0.76 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 196.9, 144.7, 139.5, 136.4, 129.4 (2C), 128.6, 127.7, 127.3, 121.5, 38.8, 37.3 (2C), 31.6, 31.1, 27.3, 26.8 (2C), 26.3, 25.9, 20.7. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{28}^{79}\text{BrNO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 476.0865, found 476.0873. M.p. (diethyl ether/chloroform) = 87-88 °C.

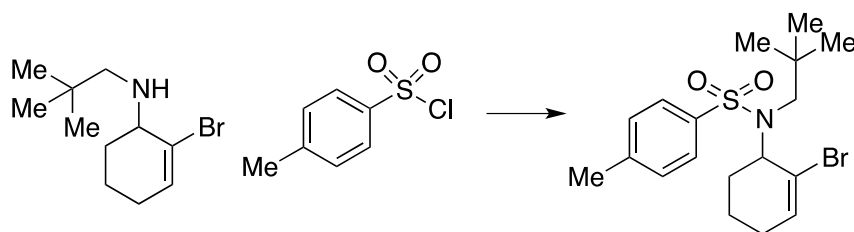
***N*-(2-bromocyclohex-2-en-1-yl)-*N*-(cyclohexylmethyl)-4-fluorobenzene**

sulfonamide, 148



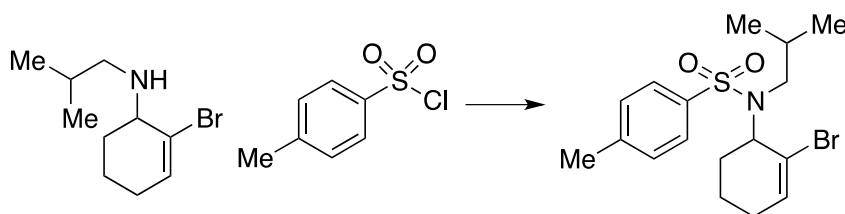
Synthesized using General Procedure H. 2-Bromo-*N*-(cyclohexylmethyl)cyclohex-2-enamine (136 mg, 0.50 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (195 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield clear yellow crystals (179 mg, 83%). $\nu_{\max}$ (neat)/cm⁻¹ 2919, 2845, 1595, 1496, 1459, 1334, 1308, 1255, 1112, 1094, 1034, 1012, 977, 889, 840, 810, 778, 730. δ_{H} (400 MHz, CDCl₃) 7.88-7.84 (2H, m, 2 × ArH), 7.17-7.13 (2H, m, 2 × ArH), 6.38-6.31 (1H, m, CH=CBr), 4.60-4.55 (1H, m, NCH), 3.13 (1H, dd, $J=14.5$, $J=7.0$, CyCH_a), 2.86 (1H, dd, $J=14.5$, $J=7.0$, CyCH_b), 2.12-1.84 (4H, m, 2 × CH₂), 1.78-1.60 (8H, m, 4 × CH₂), 1.16-1.08 (3H, m, NCH₂CH + CH₂), 0.87-0.77 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 164.8 (d, $J_{\text{CF}}=255$), 137.0, 136.3, 130.1, 121.7, 115.8 (2C, d, $J_{\text{CF}}=24$), 59.9, 37.3, 31.6 (2C), 31.1, 27.3, 26.3 (4C), 25.9, 20.7. HRMS (ESI⁺) calculated for C₁₉H₂₅⁷⁹BrFNO₂SNa⁺ [M+Na]⁺ 452.0666, found 452.0661. M.p. (diethyl ether/chloroform) = 99-100 °C.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-neopentylbenzenesulfonamide, 149**



Synthesized using General Procedure H. 2-Bromo-*N*-neopentylcyclohex-2-enamine (123 mg, 0.50 mmol, 1 eq), tosyl chloride (198 mg, 1.00 mmol, 2 eq), DMAP (6 mg, 0.05 mmol, 0.1 eq), pyridine (4 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a colourless oil (85 mg, 42%). ν_{max} (neat)/ cm^{-1} 2930, 2856, 2363, 1596, 1490, 1455, 1337, 1158, 1091, 984, 812, 667, 608 δ_{H} (500 MHz, DMSO- d_6 , VT, 363 K) 7.76 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 7.39 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 6.28-6.25 (1H, m, $\text{CH}=\text{CBr}$), 4.39-4.29 (1H, m, NCH), 3.08 (2H, d, $J=14.0$, ArCH_2), 2.40 (3H, s, Me), 2.13-1.95 (4H, m, $2 \times \text{CH}_2$), 1.95-1.92 (2H, m, CH_2), 1.80-1.58 (2H, m, CH_2) 0.93 (9H, s, $3 \times \text{Me}$). δ_{C} (125 MHz, DMSO- d_6 , VT, 363 K) 142.5, 137.4, 128.8 (2C), 127.2 (2C), 123.1, 31.6, 28.8 (4C), 28.0, 26.4 (3C), 20.4, 20.3. HRMS (ESI $^{+}$) calculated for $\text{C}_{18}\text{H}_{26}^{79}\text{BrNO}_2\text{SNa}^{+}$ $[\text{M}+\text{Na}]^{+}$ 422.0760, found 422.0758.

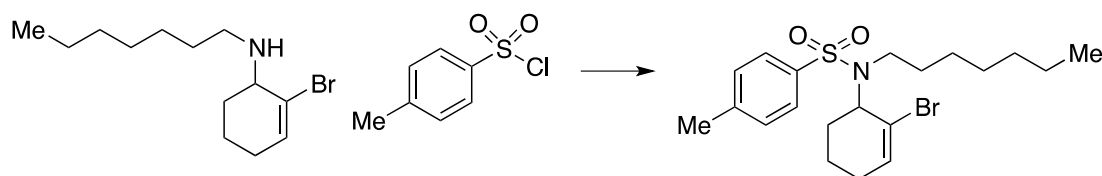
***N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-isobutylbenzenesulfonamide, 150**



Synthesized using General Procedure H. 2-Bromo-*N*-isobutylcyclohex-2-enamine (175 mg, 0.75 mmol, 1 eq), tosyl chloride (290 mg, 1.50 mmol, 2 eq), DMAP (9 mg, 0.08 mmol, 0.1 eq), pyridine (6 mL). Purified using flash column chromatography (10%

ethyl acetate/petrol) to yield the title compound as a colourless oil (200 mg, 69%). $\nu_{\max}$ (neat)/ cm^{-1} 2955, 2360, 1466, 1335, 1152, 1089, 1005, 916, 812, 769, 728, 659. δ_{H} (400 MHz, CDCl_3) 7.73 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 7.27 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 6.32-6.28 (1H, m, $\text{CH}=\text{CBr}$), 4.63-4.58 (1H, m, NCH), 3.1 (1H, dd, $J=14.5$, $J=7.0$, NCH_a), 2.87 (1H, dd, $J=14.5$, $J=7.0$, NCH_b), 2.41 (3H, s, Me), 2.09-1.89 (4H, m, $2 \times \text{CH}_2$), 1.92-1.86 (1H, m, NCH_2CH), 1.73-1.62 (2H, m, CH_2) 0.88 (6H, app t, $J=7.0$, $2 \times \text{Me}$) δ_{C} (100 MHz, CDCl_3) 142.9, 137.6, 135.9, 129.3 (2C), 127.4, 122.1, 59.6 (2C), 31.2, 27.8, 27.3, 21.5, 20.7, 20.6 (2C), 20.5. HRMS (ESI^+) calculated for $\text{C}_{17}\text{H}_{24}^{79}\text{BrNO}_2\text{SNa}^+ [\text{M}+\text{Na}]^+$ 408.0603, found 408.0591.

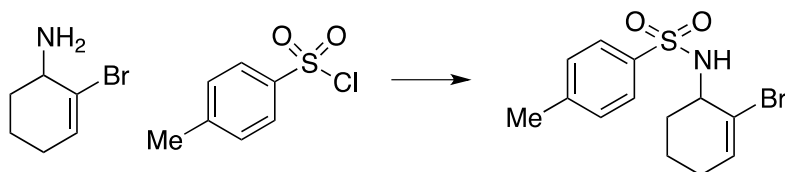
***N*-(2-Bromocyclohex-2-en-1-yl)-*N*-heptyl-4-methylbenzenesulfonamide, 151**



Synthesized using General Procedure H. 2-Bromo-*N*-heptylcyclohex-2-enamine (96 mg, 0.35 mmol, 1 eq), tosyl chloride (133 mg, 0.70 mmol, 2 eq), DMAP (6 mg, 0.035 mmol, 0.1 eq), pyridine (3 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a very thick beige opaque solid (145 mg, 97%). $\nu_{\max}$ (neat)/ cm^{-1} 2925, 2856, 2362, 1598, 1494, 1456, 1337, 1152, 1090, 982, 905, 812, 660, 608. δ_{H} (400 MHz, CDCl_3) 7.76 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 7.26 (2H, d, $J=8.3$, $2 \times \text{ArH}$), 6.34-6.31 (1H, m, $\text{CH}=\text{CBr}$), 4.57-4.51 (1H, m, NCH), 3.18 (1H, td, $J=11.5$, $J=5.0$, NCH_a), 2.96 (1H, td, $J=11.5$, $J=5.0$, NCH_b), 2.41 (1H, s, Me), 2.09-2.03 (2H, m, CH_2), 1.91-1.81 (2H, m, CH_2), 1.75-1.57 (2H, m, CH_2), 1.28-1.19 (8H, m, $4 \times \text{CH}_2$), 0.87 (3H, app br. s, CH_3). δ_{C} (100 MHz, CDCl_3) 142.8, 138.1, 136.0, 129.2 (2C), 127.5, 122.4, 59.8, 45.3, 31.7 (2C), 31.5 (2C), 31.0, 28.8, 27.3, 22.5, 21.5, 20.5,

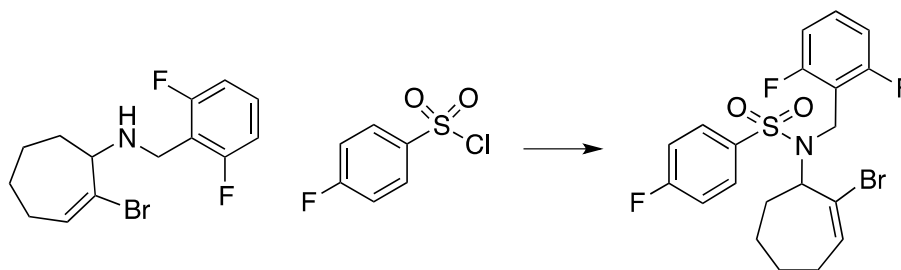
14.0. HRMS (ESI⁺) calculated for C₂₀H₃₀⁷⁹BrNO₂SNa⁺ [M+Na]⁺ 450.1073, found 450.1059.

***N*-(2-Bromocyclohex-2-en-1-yl)-4-methylbenzenesulfonamide, 152**



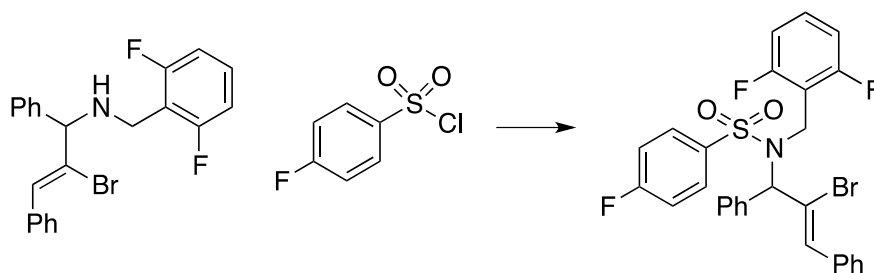
Synthesized using General Procedure H. 2-Bromocyclohex-2-enamine (150 mg, 0.84 mmol, 1 eq), tosyl chloride (319 mg, 1.67 mmol, 2 eq), DMAP (10 mg, 0.08 mmol, 0.1 eq), pyridine (7 mL). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a pale yellow solid (270 mg, 98%). $\nu_{\max}$ (neat)/cm⁻¹ 3273, 2942, 2360, 2341, 1642, 1598, 1496, 1445, 1351, 1328, 1154, 1086, 1006, 949, 910, 868, 842, 812, 730, 705, 663. δ_{H} (400 MHz, CDCl₃) 7.78 (2H, d, $J=8.0$, 2 $\times$ ArH), 7.27 (2H, d, $J=8.0$, 2 $\times$ ArH), 6.16 (1H, t, $J=4.0$, CH=CBr), 5.15 (1H, d, $J=7.0$, NH), 3.85-3.78 (1H, m, NCH), 2.40 (3H, s, Me), 2.07-1.73 (4H, m, 2 $\times$ CH₂), 1.61-1.57 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 143.4, 137.2, 135.1, 129.5 (2C), 127.4 (2C), 120.2, 55.0, 31.5, 27.4, 21.5, 16.5. HRMS (ESI⁺) calculated for C₁₃H₁₆⁷⁹BrNO₂SNa⁺ [M+Na]⁺ 351.9977, found 351.9972. M.p. (diethyl ether/chloroform) = 79-81 °C.

***N*-(2-Bromocyclohept-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-fluorobenzene
sulfonamide, 153**



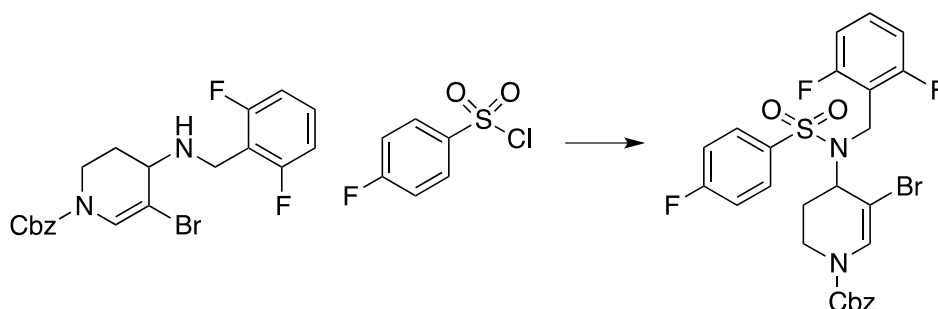
Synthesized using General Procedure H. 2-Bromo-*N*-(2,6-difluorobenzyl)cyclohept-2-enamine (126 mg, 0.40 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (155 mg, 0.80 mmol, 2 eq), DMAP (5 mg, 0.04 mmol, 0.1 eq), pyridine (3 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound a colourless thick oil (194 mg, 83%). ν_{max} (neat)/ cm^{-1} 3074, 2946, 2867, 1626, 1590, 1495, 1471, 1376, 1349, 1271, 1162, 1151, 1039, 898, 808, 709, 616. δ_{H} (400 MHz, CDCl_3) 7.86-7.83 (2H, m, $2 \times \text{ArH}$), 7.25-7.18 (1H, m, ArH), 7.09 (2H, t, $J=8.5$, $2 \times \text{ArH}$) 6.78 (1H, t, $J=8.0$, ArH), 6.29-6.25 (1H, m, $\text{CH}=\text{CBr}$), 4.91 (1H, d, $J=14.5$, ArCH_a) 4.50-4.36 (2H, m, $\text{NCH} + \text{ArCH}_b$), 2.26-1.99 (2H, m, CH_2), 1.92-1.78 (2H, m, CH_2), 1.64-1.58 (2H, m, CH_2), 1.43-1.34 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 164.8 (d, $J_{\text{CF}}=254$), 161.9 (2C, d, $J_{\text{CF}}=251$), 136.5, 136.4, 130.5, 130.4, 130.1, 130.0, 123.2, 115.6 (2C, d, $J_{\text{CF}}=23$), 112.4 (d, $J_{\text{CF}}=25$), 111.3 (2C, d, $J_{\text{CF}}=25$), 68.3, 28.6, 24.1, 23.6, 20.5. HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{19}^{79}\text{BrF}_3\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 496.0164, found 496.0161.

(Z)-N-(2-Bromo-1,3-diphenylallyl)-N-(2,6-difluorobenzyl)-4-fluorobenzenesulfonamide, 154



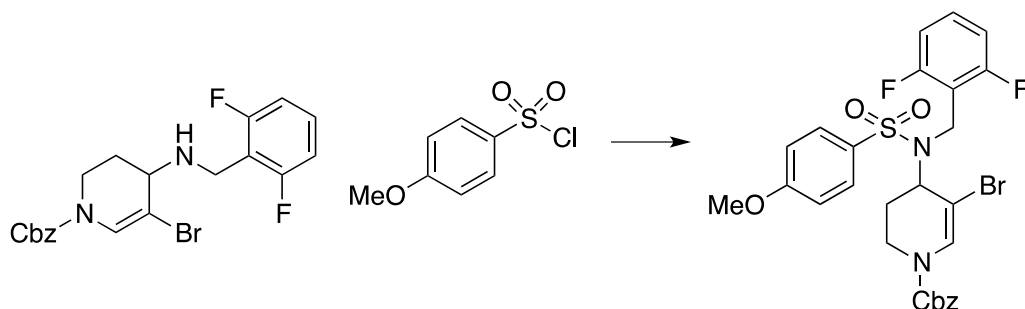
Synthesized using General Procedure H. (Z)-2-Bromo-N-(2,6-difluorobenzyl)-1,3-diphenylprop-2-en-1-amine (615 mg, 1.49 mmol, 1 eq), tosyl chloride (580 mg, 2.98 mmol, 2 eq), DMAP (18 mg, 0.15 mmol, 0.1 eq), pyridine (13 mL). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a pale yellow oil (802 mg, 94%). ν_{max} (neat)/ cm^{-1} 3104, 3064, 3028, 2857, 2339, 1906, 1625, 1491, 1379, 1241, 1179, 1098, 908, 749, 730. δ_{H} (400 MHz, CDCl_3) 8.10 (2H, dd, $J=9.0$, $J=5.0$, $2 \times \text{ArH}$), 7.70-7.67 (2H, m, $2 \times \text{ArH}$), 7.53-7.50 (2H, m, $2 \times \text{ArH}$), 7.41-7.23 (10H, m, $9 \times \text{Ar} + \text{CH}=\text{CBr}$), 6.91 (2H, t, $J=7.5$, Ar), 4.65 (1H, s, NCH), 4.04 (2H, d, $J=13.0$, ArCH_2). δ_{C} (100 MHz, CDCl_3) 166.4 (d, $J_{\text{CF}}=259$), 161.8 (2C, d, $J_{\text{CF}}=257$), 140.2, 135.3, 130.2, 130.1, 129.4, 129.3 (4C), 129.2 (2C), 128.4 (2C), 128.1, 127.9 (2C), 127.5, 117.1 (d, $J_{\text{CF}}=25$), 111.3 (3C, d, $J_{\text{CF}}=26$), 70.4, 38.8, 38.7. HRMS (ESI⁺) calculated for $\text{C}_{28}\text{H}_{21}^{79}\text{BrF}_3\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 495.0321, found 495.0322.

Benzyl 5-bromo-4-(*N*-(2,6-difluorobenzyl)-4-fluorophenylsulfonamido)-3,4-dihydropyridine-1(2*H*)-carboxylate, 155



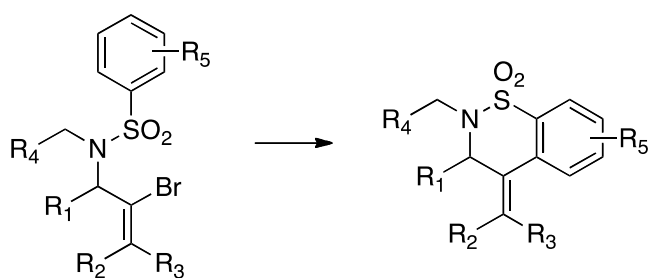
Synthesized using General Procedure H. Benzyl 5-bromo-4-((2,6-difluorobenzyl)amino)-3,4-dihydropyridine-1(2*H*)-carboxylate (650 mg, 1.49 mmol, 1 eq), 4-fluorobenzenesulfonyl chloride (580 mg, 2.98 mmol, 2 eq), DMAP (18 mg, 0.15 mmol, 0.1 eq), pyridine (13 mL). Purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as a colourless oil (320 mg, 36%). ν_{max} (neat)/ cm^{-1} 3104, 2958, 2360, 1711, 1643, 1625, 1591, 1494, 1317, 1290, 1166, 1154, 968, 908, 727, 698. δ_{H} (400 MHz, CDCl_3) 7.86-7.82 (2H, m, $2 \times \text{ArH}$), 7.41-7.36 (5H, m, $5 \times \text{ArH}$), 7.25 (1H, br. s, $\text{CH}=\text{CBr}$), 7.15-7.11 (3H, m, $3 \times \text{ArH}$), 6.75-6.66 (2H, m, $2 \times \text{ArH}$), 5.20-5.11 (2H, m, $\text{C}(\text{O})\text{OCH}_2$), 4.71 (1H, d, $J=15.0$, ArCH_a), 4.61-4.75 (1H, m, NCH), 4.58 (1H, d, $J=15.0$, ArCH_b), 3.67-3.61 (1H, m, $\text{C}(\text{O})\text{NCH}_a$), 3.36-3.27 (1H, m, $\text{C}(\text{O})\text{NCH}_b$), 2.20-2.17 (1H, m, NCHCH_a), 2.17-2.12 (1H, m, NCHCH_b). δ_{C} (100 MHz, CDCl_3) 165.9 (d, $J_{\text{CF}}=263$), 161.5 (2C, d, $J_{\text{CF}}=265$), 135.0, 130.2, 130.1, 128.7, 128.6, 128.5, 128.4 (2C), 128.3, 128.2, 116.2 (2C, d, $J_{\text{CF}}=32$), 111.2 (3C, d, $J_{\text{CF}}=30$), 68.3, 68.2, 68.1, 56.6, 39.2, 37.6, 29.4. HRMS (ESI^+) calculated for $\text{C}_{26}\text{H}_{22}^{79}\text{BrF}_3\text{N}_2\text{O}_4\text{SNa}^+ [\text{M}+\text{Na}]^+$ 617.0328, found 617.0316.

Benzyl 5-bromo-4-(*N*-(2,6-difluorobenzyl)-4-methoxyphenylsulfonamido)-3,4-dihydropyridine-1(2H)-carboxylate, 156



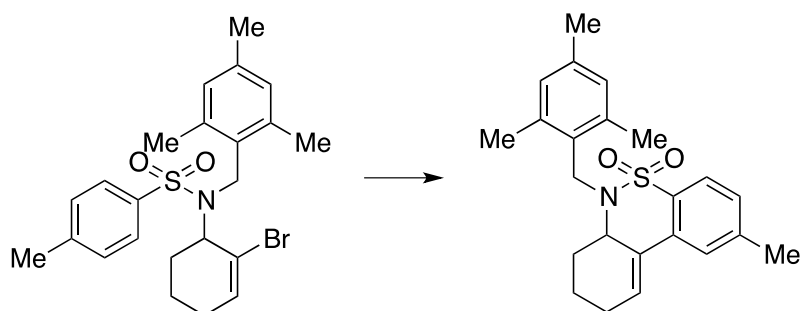
Synthesized using General Procedure H. Benzyl 5-bromo-4-((2,6-difluorobenzyl)amino)-3,4-dihydropyridine-1(2H)-carboxylate (650 mg, 1.49 mmol, 1 eq), 4-methoxybenzenesulfonyl chloride (615 mg, 2.98 mmol, 2 eq), DMAP (18 mg, 0.15 mmol, 0.1 eq), pyridine (13 mL). Purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as a colourless oil (476 mg, 53%). ν_{max} (neat)/ cm^{-1} 2949, 2360, 2341, 1711, 1644, 1625, 1594, 1398, 1233, 1011, 832, 805, 698, 684. δ_{H} (400 MHz, CDCl_3) 7.72-7.70 (2H, m, $2 \times \text{ArH}$), 7.43-7.30 (6H, m, $5 \times \text{ArH} + \text{CH}=\text{CBr}$), 7.18-7.07 (1H, m, ArH), 6.93 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 6.75-6.66 (2H, m, $2 \times \text{ArH}$), 5.22-5.10 (2H, m, C(O)OCH_2), 4.70 (1H, d, $J=15.0$, ArCH_a), 4.57-4.54 (1H, m, NCH), 4.38 (1H, d, $J=15.0$, ArCH_b), 3.86 (3H, s, Me), 3.65-3.60 (1H, m, C(O)NCH_a), 3.32-3.11 (1H, m, C(O)NCH_b), 2.39-2.36 (1H, m, NCHCH_b), 2.17-2.08 (1H, m, NCHCH_b). δ_{C} (100 MHz, CDCl_3) 163.1, 161.3 (2C, d, $J_{\text{CF}}=251$), 135.5, 131.7, 131.4, 131.1, 130.0, 129.9, 129.8, 129.7, 128.6, 128.4, 128.3, 113.9, 111.2 (3C, d, $J_{\text{CF}}=26$), 68.2, 68.1, 56.3, 55.6, 39.2, 39.1, 37.5, 29.7, 29.3. HRMS (ESI^+) calculated for $\text{C}_{27}\text{H}_{25}^{79}\text{BrF}_2\text{N}_2\text{O}_5\text{SNa}^+ [\text{M}+\text{Na}]^+$ 629.0528, found 629.0520.

General procedure I: Palladium cross-coupling



Alkenyl bromide (1 eq), palladium(II) acetate (5 mol%), CataCXium A (10 mol%), potassium carbonate (2 eq), DMSO (0.8 mL) and *o*-xylene (0.2 mL) were mixed and heated to 120 °C for 3 h. The reaction was diluted with diethyl ether (10 mL) and washed with brine (3 × 20 mL). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography.

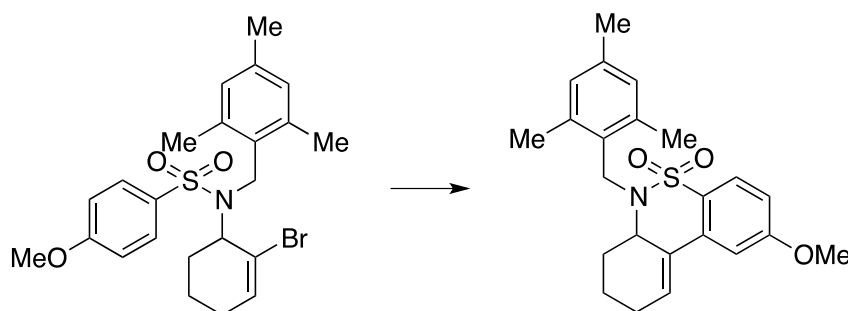
2-Methyl-6-(2,4,6-trimethylbenzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide, 162



Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-(2,4,6-trimethylbenzyl) benzenesulfonamide (90 mg, 0.19 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a white solid (52 mg, 70%). ν_{max} (neat)/cm⁻¹ 2940, 1597, 1461, 1378, 1336, 1241, 1182, 1165, 1143,

1011, 967, 853, 814, 719. δ_{H} (400 MHz, CDCl_3) 7.71 (1H, d, $J=8.0$, ArH), 7.28 (1H, s, ArH), 7.24 (1H, d, $J=7.8$, ArH), 6.84 (2H, s, $2 \times \text{ArH}$), 6.12-6.10 (1H, m, CH=C), 4.53 (1H, d, $J=13.0$, ArCH_a), 3.83-3.80 (2H, m, ArCH_b + NCH), 2.48 (3H, s, OMe), 2.30 (6H, s, $2 \times \text{Me}$), 2.73 (3H, s, Me), 2.21-1.80 (2H, m, CH₂), 1.72-1.64 (2H, m, CH₂), 1.45-1.34 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 143.2 (2C), 138.0 (2C), 137.5 (3C), 129.5 (2C), 129.4 (2C), 128.2, 128.1, 126.1, 123.8, 58.8, 48.3, 30.8, 25.8, 21.7, 20.9, 20.2 (2C). HRMS (ESI^+) calculated for $\text{C}_{23}\text{H}_{27}\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 404.1655, found 404.1657. M.p. (diethyl ether/chloroform) = 167-168 °C.

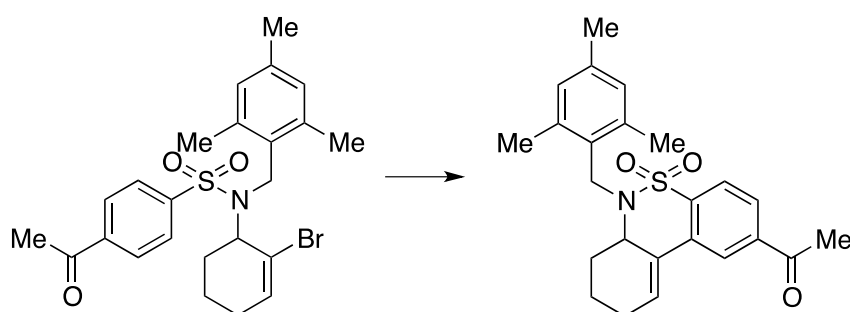
2-Methoxy-6-(2,4,6-trimethylbenzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 163



Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-methoxy-*N*-(2,4,6-trimethylbenzyl) benzenesulfonamide (93 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a beige solid (53 mg, 43%). ν_{max} (neat)/ cm^{-1} 3001, 2952, 1645, 1610, 1590, 1572, 1438, 1334, 1314, 1199, 1165, 1127. 1029, 914, 834, 773, 623. δ_{H} (400 MHz, CDCl_3) 7.77 (1H, d, $J=8.5$, ArH), 6.96-6.91 (2H, m, $2 \times \text{ArH}$), 6.84 (2H, s, $2 \times \text{ArH}$), 6.12-6.10 (1H, m, CH=C), 4.52 (1H, d, $J=13.0$, ArCH_a), 3.90 (3H, s, OMe), 3.79 (1H, d, $J=13.0$, ArCH_b),

3.37-3.32 (1H, m, NCH), 2.30 (6H, s, 2Me), 2.27 (3H, s, Me), 2.22-1.86 (2H, m, CH₂), 1.72-1.66 (2H, m, CH₂), 1.46-1.34 (2H, m, CH₂). δ_c (100 MHz, CDCl₃) 138.1, 137.5 (3C), 130.7 (2C), 129.9 (2C), 129.4, 128.1, 127.6, 125.9, 112.4, 111.0, 58.7, 55.5, 48.4, 30.9, 25.8, 21.8, 20.9, 20.2 (2C). HRMS (ESI⁺) calculated for C₂₃H₂₇NO₃SNa⁺ [M+Na]⁺ 420.1604, found 420.1599. M.p. (diethyl ether/chloroform) = 122-124 °C.

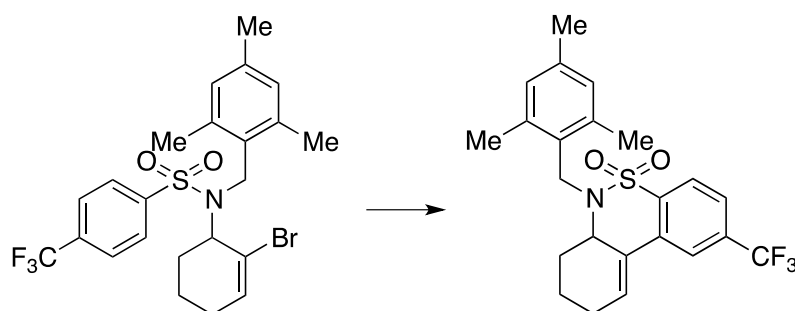
1-(5,5-Dioxido-6-(2,4,6-Trimethylbenzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazin-2-yl)ethanone, 164



Synthesized using General procedure I. 4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(2,4,6-trimethylbenzyl) benzenesulfonamide (96 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/ petrol) to yield the title compound as a eggshell coloured solid (47 mg, 59%). $\nu_{\max}$ (neat)/cm⁻¹ 2931, 1686, 1644, 1566, 1378, 1337, 1250, 1201, 1133, 1079, 962, 901, 851, 819, 771, 720, 640. δ_H (400 MHz, CDCl₃) 8.05 (1H, d, *J* = 1.5, *ArH*) 7.98 (1H, dd, *J*=8.0, *J*=1.5, *ArH*), 7.92 (1H, d, *J*=8.0, *ArH*), 6.85 (2H, s, 2 × *ArH*), 6.22-6.20 (1H, m, CH=C), 4.56 (1H, d, *J*=13.5, *ArCH_a*), 3.87-3.78 (2H, m, *ArCH_b* + NCH), 2.68 (3H, s, Me), 2.28 (6H, s, 2×Me) 2.27 (3H, s, Me), 2.28-2.18 (2H, m, CH₂), 1.90-1.69 (2H, m, CH₂), 1.47-1.35 (2H, m, CH₂). δ_c (100 MHz, CDCl₃) 196.9, 140.3, 139.7, 138.0 (2C), 137.8 (3C), 131.3 (2C), 130.1, 129.5, 127.7,

127.2, 125.5, 124.1, 58.8, 48.2, 30.7, 26.8, 25.8, 21.0, 20.1 (2C). HRMS (ESI⁺) calculated for C₂₄H₂₇NO₃SNa⁺ [M+Na]⁺ 432.1604, found 432.1594. M.p. (diethyl ether/chloroform) = 165-167 °C.

2-(Trifluoromethyl)-6-(2,4,6-trimethylbenzyl)-6a,7,8,9-tetrahydro-6H-dibenzo [c,e][1,2]thiazine 5,5-dioxide, 165

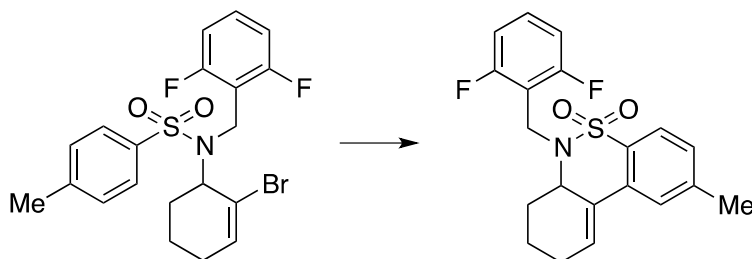


Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-(trifluoromethyl)-*N*-(2,4,6-trimethylbenzyl) benzenesulfonamide (101 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a yellow solid (53 mg, 62%). ν_{max} (neat)/cm⁻¹ 2944, 1643, 1613, 1575, 1484, 1451, 1420, 1259, 1203, 1118, 1052, 964, 876, 866, 835, 822, 727, 661. δ_{H} (400 MHz, CDCl₃) 7.95 (1H, d, *J*=8.0, Ar*H*), 7.73 (1H, s, Ar*H*), 7.71 (1H, d, *J*=8.0, Ar*H*), 6.85 (2H, s, 2 × Ar*H*), 6.22-6.20 (1H, m, CH=C), 4.58 (1H, d, *J*=13.5, ArCH_a), 3.89-3.83 (2H, m, ArCH_b + NCH), 2.39-2.31 (1H, m, CH₂), 2.29 (6H, s, 2Me), 2.28 (3H, s, Me), 2.24-2.18 (1H, m, CH₂), 1.90-1.75 (2H, m, CH₂), 1.47-1.37 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 138.6, 138.0, 137.8 (3C), 131.9 (d, *J*_{CF}=33), 129.7 (2C), 129.5, 128.6, 127.6, 124.9, 124.4, 124.2, 122.8 (d, *J*_{CF}=272), 58.8, 48.2, 30.6, 25.8, 21.6, 20.9, 20.1 (2C).

HRMS (ESI⁺) calculated for C₂₄H₂₄F₃NO₂SNa⁺ [M+Na]⁺ 458.1372, found 458.1358.

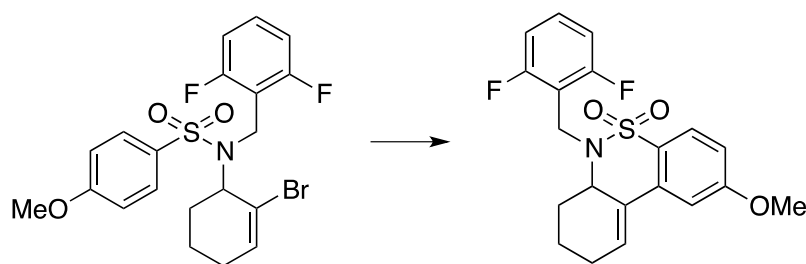
M.p. (diethyl ether/chloroform) = 159-160 °C.

6-(2,6-Difluorobenzyl)-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 166



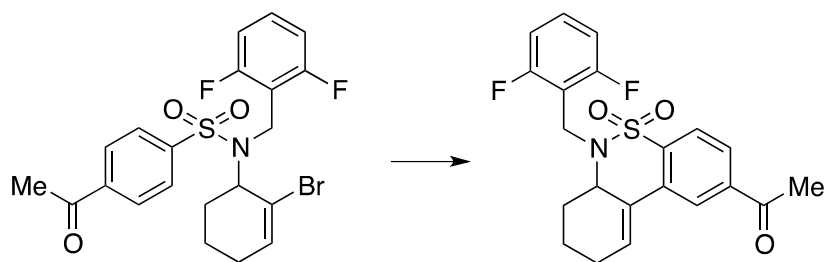
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-(2,6-difluorobenzyl)-4-methyl benzenesulfonamide (89 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a beige solid (55 mg, 75%). ν_{max} (neat)/cm⁻¹ 2953, 2872, 1627, 1592, 1560, 1469, 1330, 1233, 1182, 1168, 1090, 1065, 965, 910, 831, 819, 733, 714, 639. δ_{H} (400 MHz, CDCl₃) 7.70 (1H, d, *J*=8.0, Ar*H*), 7.31 (1H, br. s, Ar*H*), 7.29-7.19 (2H, m, 2 × Ar*H*), 6.89-6.83 (2H, m, 2 × Ar*H*), 6.32-6.30 (1H, m, CH=C), 4.46 (1H, d, *J*=14.5, ArCH_a), 4.35-4.33 (1H, m, NCH) 4.12 (1H, d, *J*=14.5, ArCH_b), 2.43 (3H, s, Me) 2.37-2.21 (2H, m, CH₂), 1.97-1.83 (2H, m, CH₂), 1.64-1.55 (2H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 161.2 (2C, d, *J*_{CF}=250), 160.3, 142.9, 132.6, 130.0, 129.4, 128.2, 125.6, 123.9, 113.0, 111.3 (3C, d, *J*_{CF}=25), 60.2, 40.6, 29.9, 15.9, 21.7, 21.5. HRMS (ESI⁺) calculated for C₂₀H₁₉F₂NO₂SNa⁺ [M+Na]⁺ 398.0997, found 42398.0998. M.p. (diethyl ether/chloroform) = 144-146 °C.

6-(2,6-Difluorobenzyl)-2-methoxy-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 167



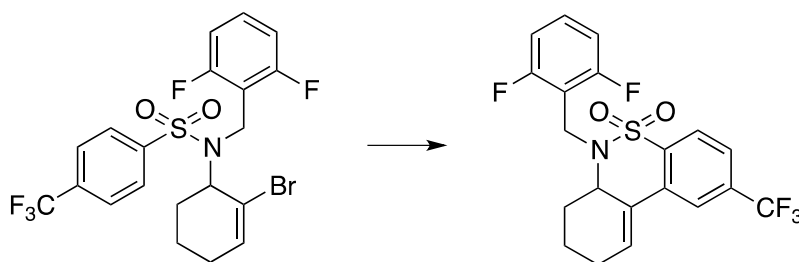
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-methoxybenzene sulfonamide (92 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a colourless crystals (57 mg, 62%). ν_{max} (neat)/ cm^{-1} 3002, 2946, 2837, 1628, 1593, 1429, 1375, 1264, 1165, 1078, 909, 889, 813, 733, 608. δ_{H} (400 MHz, CDCl_3) 7.74 (1H, d, $J=8.5$, ArH), 7.26-7.21 (1H, m, ArH), 6.98 (1H, d, $J=2.5$, ArH), 6.84 (3H, s, $3 \times$ ArH), 6.32-6.30 (1H, m, CH=C), 4.55 (1H, d, $J=14.5$, ArCH_a), 4.34-4.29 (1H, m, NCH), 4.10 (1H, d, $J=14.5$, ArCH_b), 3.87 (3H, s, OMe), 2.21-2.40 (2H, m, CH₂), 1.98-1.54 (4H, m, $2 \times$ CH₂). δ_{C} (100 MHz, CDCl_3) 161.7 (2C, d, $J_{\text{CF}}=251$), 154.1, 137.8, 130.2, 130.0, 129.9, 127.8, 125.9, 112.8, 111.4 (3C, d, $J_{\text{CF}}=25$), 110.4, 60.2, 55.5, 40.8, 29.9, 25.9, 21.5. HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{19}\text{F}_2\text{NO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 414.0946, found 414.0944. M.p. (diethyl ether/chloroform) = 149-151 °C.

1-(6-(2,6-Difluorobenzyl)-5,5-dioxido-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazin-2-yl)ethanone, 168



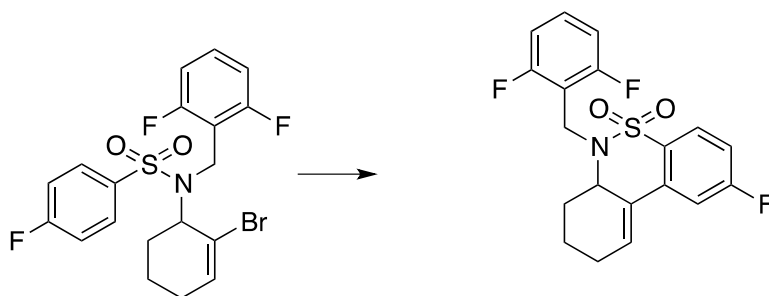
Synthesized using General procedure I. 4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl) benzenesulfonamide (94 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a pale yellow solid (38 mg, 48%). ν_{max} (neat)/ cm^{-1} 2944, 1688, 1626, 1592, 1558, 1471, 1332, 1265, 1200, 1171, 1039, 1018, 960, 908, 827, 768, 690, 633. δ_{H} (400 MHz, CDCl_3) 8.05 (1H, bs, *ArH*), 7.94-7.87 (2H, m, $2 \times \text{ArH}$), 7.29-7.21 (1H, m, *ArH*), 6.88-6.81 (2H, m, $2 \times \text{ArH}$), 6.40-6.35 (1H, m, $\text{CH}=\text{C}$), 4.49 (1H, $J=14.5$, ArCH_a) 4.31-4.23 (2H, m, $\text{NCH} + \text{ArCH}_b$) 2.65 (3H, s, Me), 2.30-1.87 (4H, m, $2 \times \text{CH}_2$), 1.68-1.58 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 196.9, 161.3 (2C, d, $J_{\text{CF}}=251$), 139.9, 139.5, 136.5, 131.5, 130.2, 129.1, 127.1, 125.2, 112.4, 111.4 (3C, d, $J_{\text{CF}}=25$), 59.9, 50.3. 29.7, 26.8, 25.9, 21.4. HRMS (ESI^+) calculated for $\text{C}_{21}\text{H}_{19}\text{F}_2\text{NO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 426.0946, found 426.0942. M.p. (diethyl ether/chloroform) = 112-113 °C.

**6-(2,6-Difluorobenzyl)-2-(trifluoromethyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e]
[1,2]thiazine 5,5-dioxide, 169**



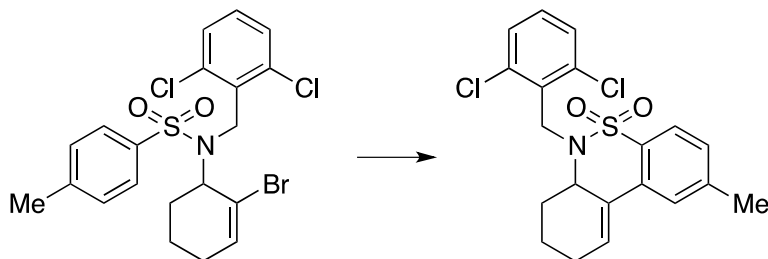
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-(trifluoromethyl) benzenesulfonamide (100 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound a very thick yellow oil (53 mg, 63%). ν_{max} (neat)/ cm^{-1} 2938, 2874, 1629, 1592, 1564, 1454, 1427, 1288, 1270, 1199, 1062, 1001, 931, 878, 863, 801, 788, 715, 682. δ_{H} (400 MHz, CDCl_3) 7.90 (1H, d, $J=8.0$, ArH), 7.71 (1H, br. s, ArH), 7.60 (1H, d, $J=8.0$, ArH), 7.25 (1H, dt, $J=13.5$, $J=2.0$, ArH), 6.88-6.82 (2H, m, $2 \times$ ArH), 6.38-6.35 (1H, m, CH=C), 4.50 (1H, d, $J=14.5$, ArCH_a), 4.39-4.27 (2H, m, NHCH + ArCH_b), 2.45-2.36 (2H, m, CH₂), 2.01-1.60 (4H, m, $2 \times$ CH₂). δ_{C} (100 MHz, CDCl_3) 161.4 (2C, d, $J_{\text{CF}}=249$), 139.9, 134.3 (q, $J_{\text{CF}}=32$), 130.3, 130.2, 128.9 (2C), 124.1, 123.3 (q, $J_{\text{CF}}=273$), 122.5, 111.4 (3C, d, $J_{\text{CF}}=25$), 59.9, 40.5, 29.7, 25.9, 21.4 (2C). HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{16}\text{F}_5\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 452.0714, found 452.0715.

6-(2,6-Difluorobenzyl)-2-fluoro-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 170



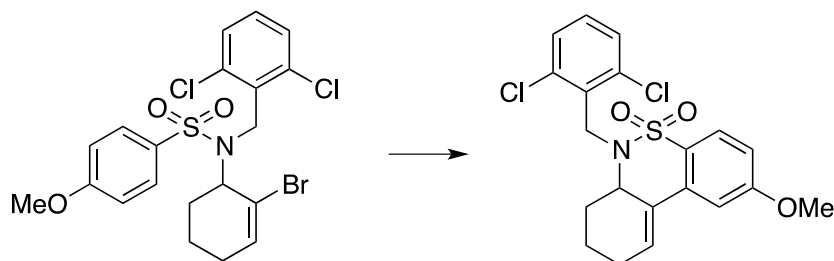
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-fluorobenzenesulfonamide (90 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a pale yellow solid (50 mg, 68%). $\nu_{\max}$ (neat)/cm⁻¹ 3085, 2956, 2929, 2869, 1628, 1604, 1570, 1472, 1330, 1234, 1127, 1015, 940, 886, 817, 702, 645. δ_{H} (400 MHz, CDCl₃) 7.81 (1H, dd, $J=8.5$, $J=5.5$, ArH), 7.27-7.21 (1H, m, ArH), 7.18 (1H, dd, $J=9.5$, $J=2.5$, Ar), 7.07 (1H, dt, $J=8.5$, $J=2.5$, ArH), 6.89-6.83 (2H, m, 2 $\times$ ArH), 6.34-6.32 (1H, m, CH=C), 4.44 (1H, d, $J=14.5$, ArCH_a), 4.37-4.33 (1H, m, NCH), 4.21 (1H, d, $J=14.5$, ArCH_b), 2.43-2.23 (2H, m, CH₂), 1.99-1.59 (4H, m, 2 $\times$ CH₂). δ_{C} (100 MHz, CDCl₃) 164.8 (d, $J_{\text{CF}}=252$), 161.5 (2C, d, $J_{\text{CF}}=249$), 138.6, 131.8, 130.0, 128.9, 126.4, 114.6, 112.2 (2C, d, $J_{\text{CF}}=24$), 111.4 (3C, d, $J_{\text{CF}}=26$), 59.9, 40.4, 29.6, 25.6, 21.4. HRMS (ESI⁺) calculated for C₁₉H₁₆F₃NO₂SN⁺ [M+Na]⁺ 402.0746, found 402.0743. M.p. (diethyl ether/chloroform) = 141-142 °C.

6-(2,6-Dichlorobenzyl)-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide, 171



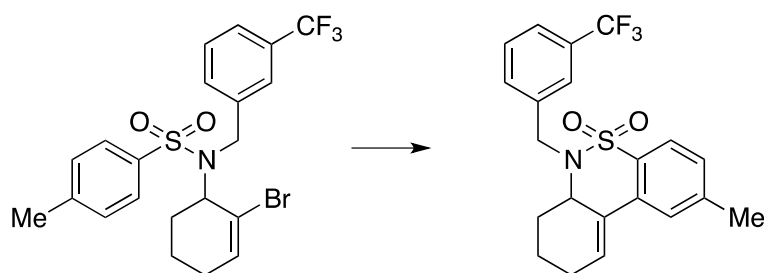
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-dichlorobenzyl)-4-methylbenzene sulfonamide (95 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a opaque thick oil (47 mg, 59%). ν_{max} (neat)/ cm^{-1} 2939, 1562, 1436, 1338, 1182, 1164, 1095, 910, 809, 762, 726, 684. δ_{H} (400 MHz, CDCl_3) 7.70 (1H, d, $J=8.0$, ArH), 7.33 (2H, d, $J=8.0$, 2 $\times$ ArH), 7.28 (1H, br. s, ArH), 7.22 (2H, d, $J=8.0$, 2 $\times$ ArH), 6.17-6.12 (1H, m, CH=C), 4.79 (1H, d, $J=13.5$, ArCH_a), 4.25 (1H, d, $J=13.5$, ArCH_b), 4.10-4.06 (1H, m, NCH), 2.43 (3H, s, Me) 2.37-2.17 (2H, m, CH₂), 1.91-1.73 (2H, m, CH₂), 1.53-1.44 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 143.1 (2C), 137.0, 136.6, 132.9 (2C), 131.4, 130.2, 129.9, 129.6, 128.7, 128.0, 126.2, 123.5, 59.7 (2C), 48.8, 30.8, 25.8, 21.7. HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{19}^{35}\text{Cl}_2\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 430.0411, found 4030.0408.

6-(2,6-Dichlorobenzyl)-2-methoxy-6a,7,8,9-tetrahydro-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide, 172



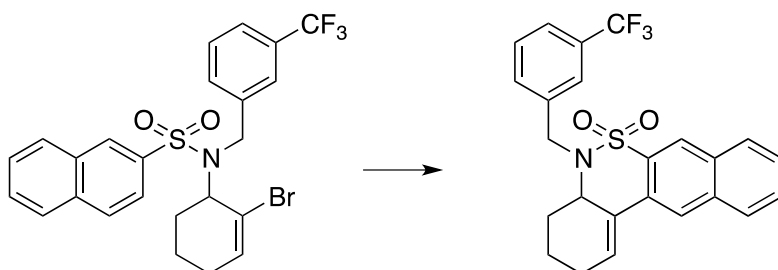
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(2,6-dichlorobenzyl)-4-methoxybenzenesulfonamide (98 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a opaque thick oil (49 mg, 59%). ν_{max} (neat)/ cm^{-1} 2939, 1594, 1564, 1470, 1437, 1337, 1293, 1242, 1224, 1168, 1095, 1027, 970, 913, 809, 729, 686, 633. δ_{H} (400 MHz, CDCl_3) 7.75 (1H, d, $J=8.5$, ArH), 7.33 (2H, d, $J=8.0$, $2 \times$ ArH), 7.21 (2H, d, $J=8.0$, $2 \times$ ArH), 6.96-6.90 (2H, m, $2 \times$ ArH), 6.17-6.12 (1H, m, CH=C), 4.79 (1H, d, $J=13.5$, ArCH_a), 4.22 (1H, d, $J=13.5$, ArCH_b), 4.08-4.04 (1H, m, NCH), 3.98 (3H, s, Me) 2.37-2.17 (2H, m, CH₂), 1.95-1.73 (2H, m, CH₂), 1.52-1.43 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 162.8, 138.7 (2C), 137.0, 131.4 (2C), 130.4, 130.0, 129.9, 128.7, 128.1, 125.6, 112.4, 111.1, 59.7, 55.5, 49.0, 30.8, 25.8, 21.7. HRMS (ESI⁺) calculated for $\text{C}_{20}\text{H}_{20}^{35}\text{Cl}_2\text{NO}_3\text{SNa}^+$ [M+Na]⁺ 446.0360, found 446.0365.

2-Methyl-6-(3-(trifluoromethyl)benzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide, 173



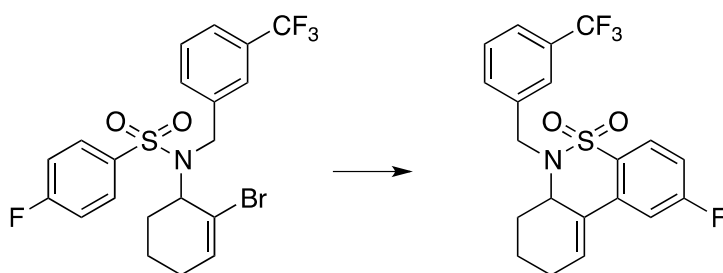
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-(3-(trifluoromethyl)benzyl) benzenesulfonamide (95 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/ petrol) to yield the title compound as a nude coloured solid (36 mg, 46%). Only one product isolated. ν_{max} (neat)/ cm^{-1} 3061, 2930, 2867, 1646, 1616, 1599, 1495, 1428, 1325, 1188, 1161, 1116, 1079, 1060, 997, 950, 907, 753, 705, 678. δ_{H} (400 MHz, CDCl_3) 7.37-7.35 (2H, m, ArH), 7.28 (1H, d, $J=8.5$, ArH), 7.10 (1H, d, $J=8.0$, ArH), 6.99 (1H, br. s, ArH), 6.91 (2H, d, $J=8.0$, $2 \times$ ArH), 5.93-5.90 (1H, m, CH=C), 4.56 (1H, d, $J=16.0$, ArCH_a), 4.48-4.42 (1H, m, NCH), 4.09 (1H, d, $J=16.0$, ArCH_b), 2.37-2.28 (3H, m, CH₂), 2.21 (3H, s, Me), 1.99-1.91 (1H, m, CH₂), 1.90-1.82 (2H, m, CH₂). δ_{C} (100 MHz, CDCl_3) 143.2, 140.5, 136.0, 134.4, 133.1 (q, $J_{\text{CF}}=34$), 129.2 (2C), 128.8, 128.1, 127.0, 126.8, 124.4 (q, $J_{\text{CF}}=250$), 122.1, 51.6, 55.5, 45.3, 30.8, 25.4, 21.1 (2C). HRMS (ESI⁺) calculated for $\text{C}_{21}\text{H}_{20}\text{F}_3\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 430.1059, found 430.1055. M.p. (diethyl ether/chloroform) = 125-127°C.

5-(3-(Trifluoromethyl)-3,4,4a,5-tetrahydro-2H-benzo[c]naphtho[2,3,*e*][1,2]thiazine-6,6-dioide, 174



Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(3-(trifluoromethyl)benzyl)naphthalene-2-sulfonamide (102 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as an off white coloured solid (27 mg, 30%). Only one product isolated. ν_{max} (neat)/ cm^{-1} 2938, 1429, 1327, 1160, 1121, 1074, 1025, 948, 906, 887, 838, 753, 730, 674, 656, 645, 612. δ_{H} (400 MHz, CDCl_3) 8.10 (1H, br. s, *ArH*), 7.76 (1H, d, $J=7.5$, *ArH*), 7.71 (1H, d, $J=7.5$, *ArH*), 7.55-7.51 (3H, m, $3 \times \text{ArH}$), 7.41 (1H, dd, $J=8.5$, $J=1.5$ *ArH*), 7.07 (1H, d, $J=8.0$, *ArH*), 7.03 (1H, br. s, *ArH*), 6.97 (2H, d, $J=8.0$, $2 \times \text{ArH}$), 5.93-5.85 (1H, m, $\text{CH}=\text{C}$), 4.71 (1H, d, $J=16.0$, ArCH_a), 4.53-4.46 (1H, m, *NCH*), 4.14 (1H, d, $J=16.0$, ArCH_b), 2.40-2.36 (1H, m, CH_2), 2.32-2.25 (2H, m, CH_2), 1.99-1.86 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 135.8, 134.4, 134.3, 132.9 (2C), 131.7 (q, $J_{\text{CF}}=33$), 129.4, 128.8, 128.7, 128.5, 127.5, 127.2, 124.7, 124.6, 124.5, 124.4 (q, $J_{\text{CF}}=251$), 122.2, 121.8, 55.5, 45.5, 38.8, 30.1, 25.5, 21.1. HRMS (ESI^+) calculated for $\text{C}_{24}\text{H}_{20}\text{F}_3\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 466.1059, found 466.1043. M.p. (diethyl ether/chloroform) = 194-195 °C.

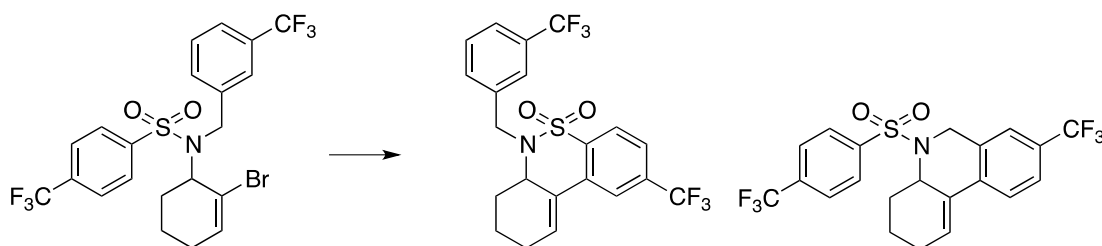
2-Fluoro-6-(3-(trifluoromethyl)benzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 175



Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-fluoro-*N*-(3-(trifluoromethyl)benzyl) benzenesulfonamide (96 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a beige coloured solid (44 mg, 51%). Only one product isolated. ν_{max} (neat)/ cm^{-1} 2936, 2360, 1594, 1494, 1327, 1240, 1166, 1154, 1119, 1089, 1024, 958, 909, 886, 836, 754, 731, 680, 657, 627. δ_{H} (400 MHz, CDCl_3) 7.51-47 (2H, m, $2 \times \text{ArH}$), 7.33 (1H, d, $J=8.0$, ArH), 7.11 (1H, d, $J=8.0$, ArH), 7.07 (1H, br. s, ArH), 6.81 (2H, t, $J=8.5$, $2 \times \text{ArH}$), 5.93-5.90 (1H, m, $\text{CH}=\text{C}$), 4.62 (1H, d, $J=16.0$, ArCH_a), 4.41-4.37 (1H, m, NCH), 4.12 (1H, d, $J=16.0$, ArCH_b), 2.34-2.24 (3H, m, CH_2), 1.98-1.94 (1H, m, CH_2), 1.92-1.82 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 163.3 (d, $J_{\text{CF}}=251$), 140.4, 135.0, 134.2, 132.7, 129.8 (q, $J_{\text{CF}}=32$), 129.7, 129.6, 128.4, 125.1, 124.9 (q, $J_{\text{CF}}=272$), 122.1, 122.0, 115.8 (2C, d, $J_{\text{CF}}=25$), 55.6, 45.5, 30.0, 25.4, 21.0. HRMS (ESI^+) calculated for $\text{C}_{20}\text{H}_{17}\text{F}_4\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 434.0808, found 343.0798. M.p. (diethyl ether/chloroform) = 144-146 °C.

2-Trifluoromethyl-6-(3-(trifluoromethyl)benzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2] thiazine 5,5-dioxide, 176

8-(Trifluoromethyl)-5-((4-(trifluoro)phenyl)sulphonyl)-2,3,4,4a,5,6,hexahydrophenathridine, 177



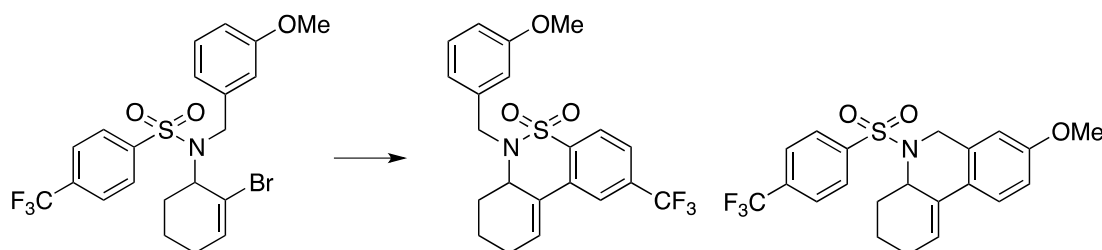
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-(trifluoromethyl)-*N*-(3-(trifluoromethyl)benzyl) benzenesulfonamide (106 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield an inseparable mixture of the title compounds as an off white coloured solid (1:0.4, sultam:isoquinoline, 53 mg, 56%). * denotes protons associated with the isoquinoline.

$\nu_{\max}$ (neat)/cm⁻¹ 2945, 1404, 1323, 1164, 1120, 1091, 1074, 1062, 1027, 950, 912, 838, 730, 711, 665, 639. δ_{H} (400 MHz, CDCl₃) 7.96 (1H*, d, *J*=8.0, Ar*H*), 7.86 (1H*, br. s, Ar*H*), 7.65 (1H*, d, *J*=8.0, Ar*H*), 7.61 (2H, d, *J*=8.0, 2 × Ar*H*), 7.57-7.51 (1H*, 1H, m, 2 × Ar*H*), 7.45 (1H*, d, *J*=8.0, Ar*H*), 7.40 (2H, d, *J*=8.0, 2 × Ar*H*), 7.29 (1H, d, *J*=8.0, Ar*H*), 7.10-7.05 (2H*, 1H, m, 3 × Ar*H*), 6.71-6.67 (1H*, m, CH=C), 5.93-5.90 (1H, m, CH=C), 4.74-4.68 (1H*, m, NCH), 4.64 (1H, d, *J*=16.0, ArCH_a), 4.46-4.41 (1H, m, NCH), 4.35 (1H*, d, *J*=16.0, ArCH_a), 4.22 (1H*, d, *J*=16.0, ArCH_b), 4.15 (1H, d, *J*=16.0, ArCH_b), 2.37-2.24 (4H*, 2H, m, 3 × CH₂), 2.04-1.58 (2H*, 4H, m, 3 × CH₂). δ_{C} (100 MHz, CDCl₃) 142.4 (2C), 140.3, 138.2 (2C), 137.9 (2C), 134.0 (q, *J*_{CF}=27),

133.8 (q, $J_{CF}=30$), 133.7, 132.8, 132.4 (2C), 131.0 (q, $J_{CF}=28$), 129.8 (q, $J_{CF}=30$), 129.7, 127.5, 127.3, 125.7 (2C, q, $J_{CF}=275$) 125.6, 125.5, 125.3, 125.0, 124.9 (2C, q, $J_{CF}=279$), 124.7, 124.5, 124.3, 124.2, 122.4, 122.3, 122.1, 121.8, 59.2, 55.8, 29.9, 29.1, 26.0, 25.4, 21.0, 20.4. HRMS (ESI⁺) calculated for C₂₁H₁₇F₆NO₂SNa⁺ [M+Na]⁺ 484.0776, found 484.0765. M.p. (diethyl ether/chloroform) = 144-146 °C.

**2-Trifluoromethyl-6-(3-(methoxy)benzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[*c,e*]
[1,2] thiazine 5,5-dioxide, 178**

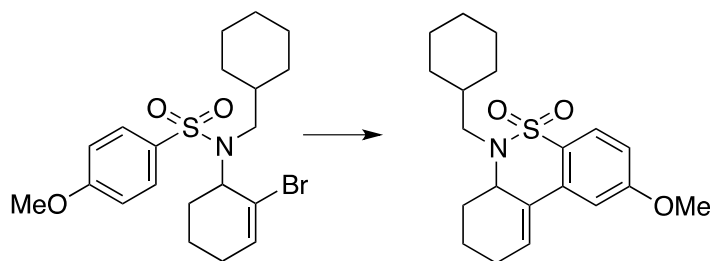
**8-Methoxy-5-((4-(trifluoro)phenyl)sulphonyl)-2,3,4,4a,5,6,
hexahydrophenathridine, 179**



Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(3-methoxybenzyl)-4-(trifluoromethyl)benzene sulfonamide (96 mg, 0.195 mmol, 1 eq), palladium(II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield an inseparable mixture of the title compounds as a very thick dark yellow oil (1:0.5, sultam:isoquinoline, 30 mg, 36%). * denotes protons associated with the isoquinoline. $\nu_{\max}$ (neat)/cm⁻¹ 2940, 2360, 1583, 1478, 1403, 1321, 1262, 1164, 1130, 1107, 1088, 1061, 1027, 962, 888, 842, 736, 710, 643, 616. δ_H (400 MHz, CDCl₃) 7.83 (2H*, d, $J=8.0$, 2 × ArH), 7.65 (2H*, d, $J=8.0$, 2 × ArH), 7.57 (2H, d, $J=8.0$, ArH), 7.36 (2H, d, $J=8.0$, 2 × ArH), 7.16 (1H*, t, $J=8.0$,

ArH), 6.92 (1H, d, $J=7.5$, ArH), 6.68 (1H*, br. s, ArH), 6.78-6.74 (1H*, m, ArH), 6.61 (1H, d, $J=8.0$, ArH), 6.54 (1H, d, $J=8.0$, ArH), 6.42-6.39 (1H*, m, CH=C), 6.09-6.06 (1H, m, CH=C), 4.74-4.64 (2H*, m, NCH + ArCH_a), 4.56 (1H, d, $J=16.0$, ArCH_a), 4.39-4.30 (1H, m, NCH), 4.13-4.06 (1H*, m, 2 × ArCH_b), 3.72 (3H*, s, Me), 3.62 (3H, s, Me), 2.38-3.17 (2H*, 2H, m, 2 × CH₂), 2.09-1.82 (4H*, 2H, m, 3 × CH₂), 1.63-1.40 (2H, m, CH₂). δ_c (100 MHz, CDCl₃) 159.5 (2C), 155.5, 138.6, 137.8 (2C), 135.6 (2C, q, $J_{CF}=28$), 133.7, 133.6 (2C), 130.4, 129.2 (2C), 127.9, 127.6, 127.2, 127.0, 125.5, 125.4, 125.3, 125.2, 124.2 (2C, q, $J_{CF}=267$), 121.1, 120.5, 118.3, 114.1, 113.2, 110.0, 60.6 (2C), 55.9 (2C), 55.3, 46.1, 32.1, 30.0, 27.3, 25.4, 21.0, 19.9. HRMS (ESI⁺) calculated for C₂₁H₂₀F₃NO₃SNa⁺ [M+Na]⁺ 446.1008, found 446.0999.

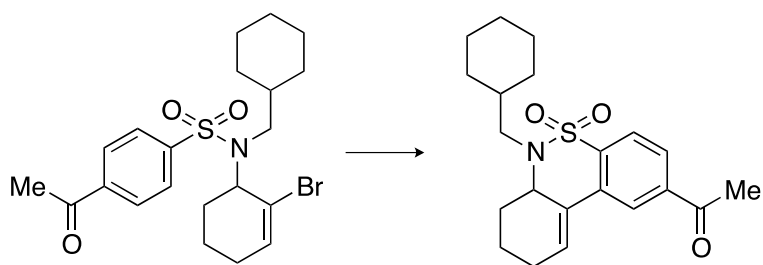
6-(Cyclohexylmethyl)-2-methoxy-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 180



Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-*N*-(cyclohexylmethyl)-4-methoxybenzenesulfonamide (86 mg, 0.195 mmol, 1 eq), palladium (II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a yellow oil (57 mg, 81%). $\nu_{\max}$ (neat)/cm⁻¹ 2924, 2851, 1594, 1564, 1448, 1323, 1292, 1241, 1165, 1079, 1028, 888, 830, 733, 703. δ_H (400 MHz, CDCl₃) 7.72 (1H, d, $J=8.5$, ArH), 7.06 (1H, d, $J=2.5$, ArH), 6.80 (1H, dd, $J=8.5$, $J=2.5$, ArH) 6.57-6.51 (1H, m, CH=C), 4.65-

4.58 (1H, m, NCH), 3.84 (3H, s, OMe), 2.67 (2H, dd, $J=20.0$, $J=6.5$, CyCH₂), 2.35-2.16 (3H, m, NCH₂CH + CH₂), 1.97-1.63 (8H, m, 4×CH₂), 1.60-1.09 (4H, m, 2×CH₂), 0.90-0.80 (2H, m, CH₂). δ_c (100 MHz, CDCl₃) 162.2, 136.4, 136.0, 128.5, 127.0, 126.9, 113.2, 109.2, 59.7, 55.5, 53.7, 38.4, 30.9, 30.8, 29.5 (2C), 26.1, 25.8 (2C), 21.2. HRMS (ESI⁺) calculated for C₂₀H₂₇NO₃SNa⁺ [M+Na]⁺ 384.1604 found 384.1600.

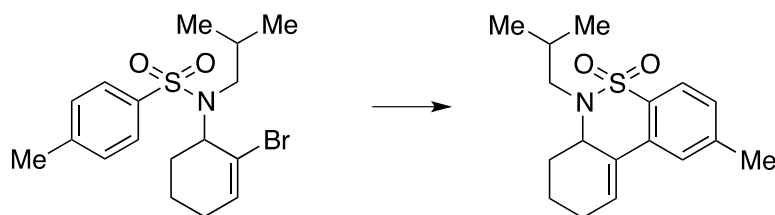
1-(6-(Cyclohexylmethyl)-5,5-dioxido-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazin-2-yl)ethanone, 181



Synthesized using General Procedure I. 4-Acetyl-*N*-(2-bromocyclohex-2-en-1-yl)-*N*-(cyclohexylmethyl)benzene sulfonamide (87 mg, 0.195 mmol, 1 eq), palladium (II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as a dark orange oil (45 mg, 62%). $\nu_{\max}$ (neat)/cm⁻¹ 2923, 2852, 2360, 1690, 1558, 1449, 1415, 1335, 1230, 1172, 1094, 991, 960, 885, 823, 774, 736. δ_H (400 MHz, CDCl₃) 8.18 (1H, s, ArH), 7.91-7.86 (2H, m, 2 × ArH), 6.76-6.70 (1H, m, CH=C), 4.66-4.57 (1H, m, NCH), 2.75 (2H, dd, $J=14.0$, $J=8.0$, CyCH₂) 2.68-2.62 (4H, m, Me + NCH₂CH) 2.39-2.34 (2H, m, CH₂), 2.23-2.96 (2H, m, CH₂), 1.91-1.82 (2H, m, CH₂), 1.75-1.64 (4H, m, 2 × CH₂), 1.28-1.10 (4H, m, 2 × CH₂), 0.90-0.80 (2H, m, CH₂). δ_c (100 MHz, CDCl₃) 196.9, 139.5, 138.2, 135.2, 131.4, 128.4, 127.1, 125.2, 124.2, 60.3, 53.7, 38.2, 30.8,

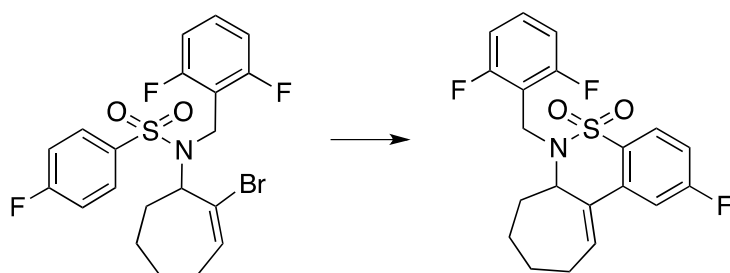
30.7, 29.6, 29.4, 26.8, 26.4, 25.8, 21.2, 14.1. HRMS (ESI⁺) calculated for C₂₁H₂₇NO₃SNa⁺ [M+Na]⁺ 396.1604 found 396.1602.

2-Methyl-6-isobutyl-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 182



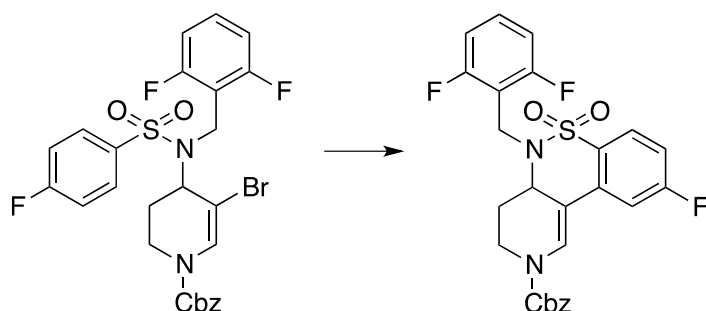
Synthesized using General Procedure I. *N*-(2-Bromocyclohex-2-en-1-yl)-4-methyl-*N*-isobutylbenzenesulfonamide (75 mg, 0.195 mmol, 1 eq), palladium (II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (5% ethyl acetate/petrol) to yield the title compound as a colourless oil (54 mg, 90%). ν_{max} (neat)/cm⁻¹ 2957, 2871, 2362, 1738, 1602, 1572, 1466, 1334, 1271, 1164, 1108, 1091, 912, 865, 777, 731, 613. δ_{H} (400 MHz, CDCl₃) 7.67 (1H, d, *J*=8.0, Ar*H*), 7.40 (1H, br. s, Ar*H*), 7.17 (1H, d, *J*=8.0, Ar*H*) 6.58-6.52 (1H, m, CH=C), 4.64-4.60 (1H, m, NCH), 2.69 (1H, dd, *J*=14.0, *J*=8.0, ArCH_a), 2.61 (1H, d, *J*=14.0, *J*=8.0, ArCH_b), 2.39 (3H, s, Me), 2.37-2.31 (3H, m, NCH₂CH + CH₂), 1.97-1.65 (4H, m, 2 × CH₂), 0.94 (3H, d, *J*=15.0, Me), 0.90 (3H, d, *J*=15.0, Me). δ_{C} (100 MHz, CDCl₃) 142.4, 134.4, 131.7, 129.6, 128.5, 128.4, 124.8, 124.6, 59.7, 54.8, 29.6, 29.0, 26.0, 21.7, 21.3, 20.2, 19.9. HRMS (ESI⁺) calculated for C₁₇H₂₃NO₂SNa⁺ [M+Na]⁺ 328.1342 found 328.1338.

**6-(2,6-Difluorobenzyl)-2-fluoro-6,6a,7,8,9,10-hexahydrobenzo[e]cyclohepta[c]
[1,2]thiazine 5,5-dioxide, 183**



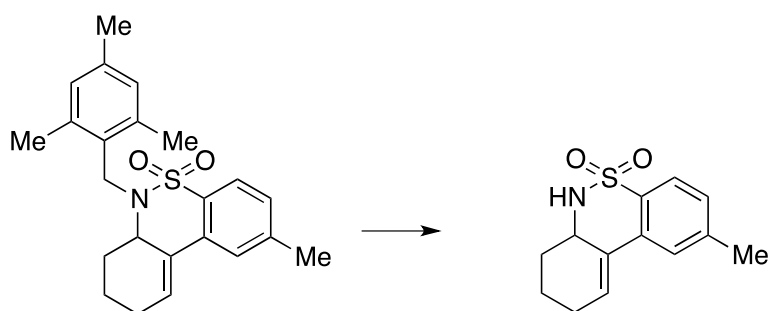
Synthesized using General Procedure I. *N*-(2-Bromocyclohept-2-en-1-yl)-*N*-(2,6-difluorobenzyl)-4-fluorobenzene sulfonamide (92 mg, 0.195 mmol, 1 eq), palladium (II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a pale yellow oil (41 mg, 53%). $\nu_{\max}$ (neat)/cm⁻¹ 2927, 2365, 1626, 1591, 1493, 1348, 1268, 1234, 1152, 1092, 909, 785, 729. δ_{H} (500 MHz, CDCl₃) 7.90-7.87 (2H, m, 2 × ArH), 7.19 (2H, t, *J*=8.5, ArH) 6.85 (2H, t, *J*=8.0, 2 × ArH) 5.85-5.81 (1H, m, C=CH), 5.48-5.43 (1H, m, NCH), 4.62 (2H, br. s, ArCH₂), 2.35 (2H, t, *J*=5.0), 2.24-2.21 (2H, m, CH₂), 1.66-1.61 (2H, m, CH₂). δ_{C} (125 MHz, CDCl₃) 163.0 (d, *J*_{CF}=265), 161.3 (2C, d, *J*_{CF}=250), 140.8, 136.6, 134.8, 130.5, 127.3, 121.7, 115.9 (2C, d, *J*_{CF}=31), 111.2 (3C, d, *J*_{CF}=33), 53.4, 41.0, 36.0, 31.7, 29.6, 23.9. HRMS (ESI⁺) calculated for C₂₀H₁₈NF₃O₂SNa⁺ [M+Na]⁺ 416.0902 found 416.0892.

**Benzyl 5-(2,6-difluorobenzyl)-9-fluoro-3,4,4a,5-tetrahydro-2H-benzo[e]pyrido
[4,3-c][1,2]thiazine-2-carboxylate 6,6-dioxide, 184**



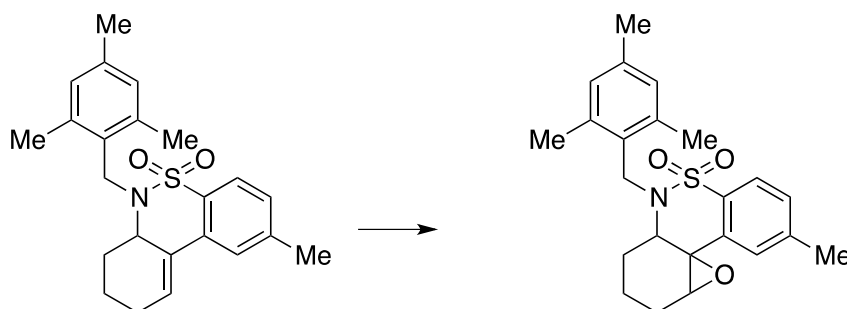
Synthesized using General Procedure I. Benzyl 5-bromo-4-(*N*-(2,6-difluorobenzyl)-4-fluorophenylsulfonamido)-3,4-dihydropyridine-1(2H)-carboxylate (116 mg, 0.195 mmol, 1 eq), palladium (II) acetate (2 mg, 0.01 mmol, 5 mol%), CataCXium A (11 mg, 0.02 mmol, 10 mol%), potassium carbonate (54 mg, 0.39 mmol, 2 eq). Purified using flash column chromatography (20% ethyl acetate/petrol) to yield the title compound as an yellow oil (45 mg, 45%). ν_{max} (neat)/ cm^{-1} 2935, 2360, 1713, 1626, 1601, 1573, 1470, 1396, 1325, 1230, 1170, 1134, 998, 781, 730. δ_{H} (400 MHz, CDCl_3) 7.83-7.80 (1H, m, ArH), 7.55 (5H, br. s, $5 \times \text{ArH}$) 7.28-7.18 (2H, m, $\text{ArH} + \text{C}=\text{CH}$) 7.09-7.00 (2H, m, $2 \times \text{ArH}$), 6.86 (2H, t, $J=8.0$, $2 \times \text{ArH}$) 5.24 (2H, br s, $\text{C}(\text{O})\text{CH}_2$), 4.48-4.31 (2H, d, $\text{C}(\text{O})\text{NCH}_a + \text{ArCH}_a$), 4.21-4.10 (2H, m, $\text{C}(\text{O})\text{NCH}_b + \text{ArCH}_b$), 3.35-3.27 (1H, m, NCH), 2.28-1.96 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 164.0 (q, $J_{\text{CF}}=34$), 161.4 (2C, d, $J_{\text{CF}}=245$), 148.0, 135.4, 130.3, 128.7, 128.6, 128.4 (2C), 128.3, 127.2 (2C), 126.8, 126.4, 113.9 (2C, d, $J_{\text{CF}}=28$), 111.5 (3C, d, $J_{\text{CF}}=31$) 68.5, 58.6, 56.9, 42.1, 27.7, 27.6. HRMS (ESI^+) calculated for $\text{C}_{26}\text{H}_{21}\text{N}_2\text{F}_3\text{O}_4\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 537.1066 found 537.1072.

2-Methyl-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide, 185



Triflic acid (25 μ l, 0.28, 1.1eq) was added to a solution of the 2-methyl-6-(2,4,6-trimethylbenzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide (100 mg, 0.26 mmol, 1 eq) in DCM (4 mL) cooled to 0 $^{\circ}$ C. The reaction was stirred for 3 h before being quenched with a saturated solution of sodium bicarbonate (4 mL). The organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (30% ethyl acetate/petrol) to yield a colourless oil (59 mg, 91%). ν_{max} (neat)/ cm^{-1} 3234, 2925, 2856, 2360, 2255, 1635, 1561, 1476, 1449, 1317, 1279, 1146, 1072, 968, 909, 811, 638. δ_{H} (400 MHz, CDCl_3) 7.70 (1H, d, $J=8.0$, ArH), 7.73 (1H, br. s, ArH), 7.20 (1H, d, $J=8.0$, ArH), 6.60 (1H, t, $J=4.0$, CH=C), 4.47-4.43 (1H, m, NH), 4.25 (1H, d, $J=12.0$, NHCH), 2.40 (3H, s, Me), 2.35-2.87 (4H, m, $2 \times \text{CH}_2$), 1.62-1.45 (2H, m, CH_2). δ_{C} (100 MHz, CDCl_3) 142.4, 133.2, 129.6, 128.9 (2C), 128.6, 124.6, 124.2, 52.7, 30.3, 26.1, 21.7, 20.4. HRMS (ESI^+) calculated for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 272.0716, found 272.0710.

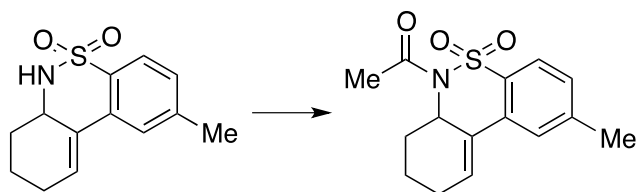
**8-Methyl-4-(2,4,6-trimethylbenzyl)-1,2,3,3a,4,10a-hexahydrobenzo[e]oxireno
[2',3':2,3]benzo[1,2-c][1,2]thiazine 5,5-dioxide, 186**



mCPBA (97 mg, 70% wet, 0.93 mmol, 2 eq) was added to a solution of 2-methyl-6-(2,4,6-trimethylbenzyl)-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazine 5,5-dioxide (75 mg, 0.196 mmol, 1 eq) in DCM (2.50 mL). The reaction was stirred overnight at rt. The reaction was washed with a saturated solution of sodium sulphite (3 mL) and sodium hydroxide (3 mL). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (10% ethyl acetate/petrol) to yield the title compound as a colourless oil (45 mg, 58%). Only one diastereoisomer isolated. ν_{max} (neat)/cm⁻¹ 3734, 3628, 2935, 2360, 2341, 1602, 1576, 1456, 1340, 1326, 1243, 1188, 1143, 1077, 1041, 911, 820, 767, 669. δ_{H} (400 MHz, CDCl₃) 7.74 (1H, d, $J=7.5$, ArH), 7.29-7.26 (2H, m, 2 $\times$ ArH), 6.85 (2H, br. s, 2 $\times$ ArH), 4.54 (1H, d, $J=13.0$, ArCH_a), 3.57 (1H, d, $J=13.0$, ArCH_b), 3.21 (1H, dd, $J=11.5$, $J=6.0$, NCH), 3.08 (1H, s, OCH), 2.45 (3H, s, Me), 2.29 (6H, s, 2 $\times$ Me), 2.27 (3H, s, Me), 1.97-1.85 (2H, m, CH₂), 1.36-1.14 (4H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 143.8, 138.4, 137.9, 136.7, 133.1, 129.4 (2C), 128.4, 127.1, 124.4, 124.3, 66.0, 57.1, 55.0, 49.1, 30.2, 25.1, 21.8, 20.9, 20.0 (3C), 16.6. HRMS (ESI⁺) calculated for C₂₃H₂₇NO₃SN⁺ [M+Na]⁺ 420.1604, found 420.1596.

1-(2-Methyl-5,5-dioxido-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazin-6-yl)

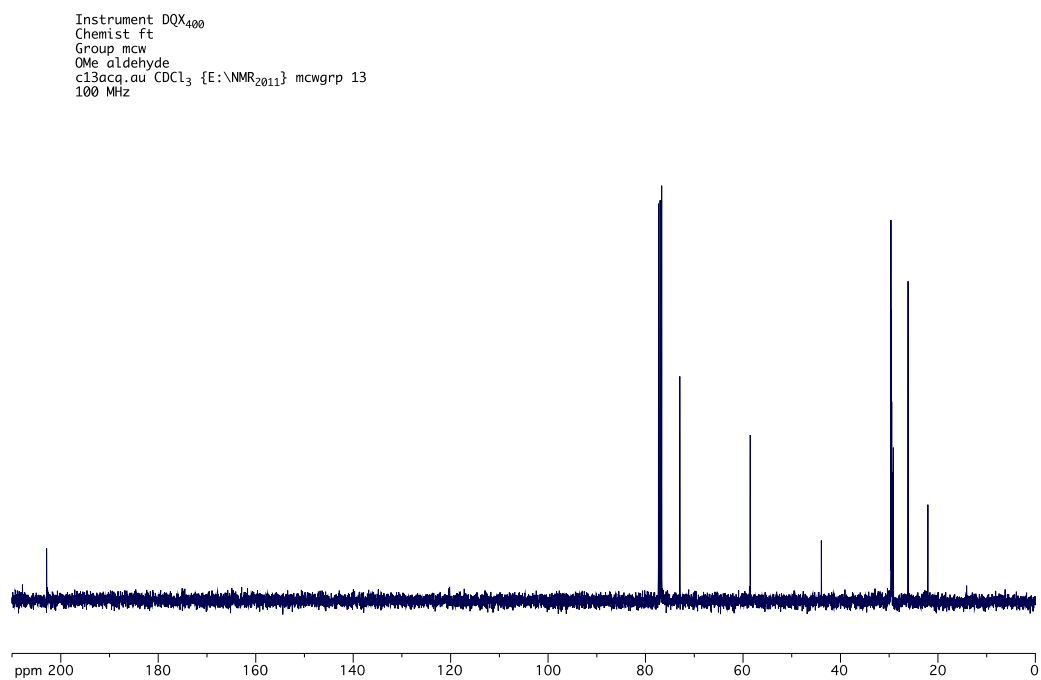
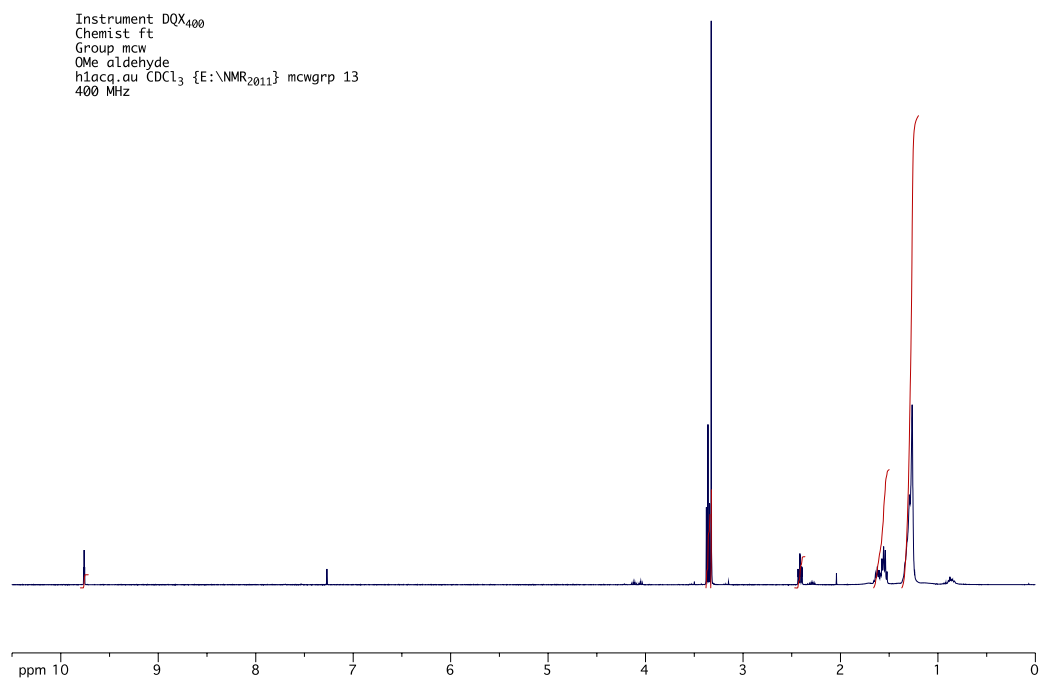
ethanone, 187



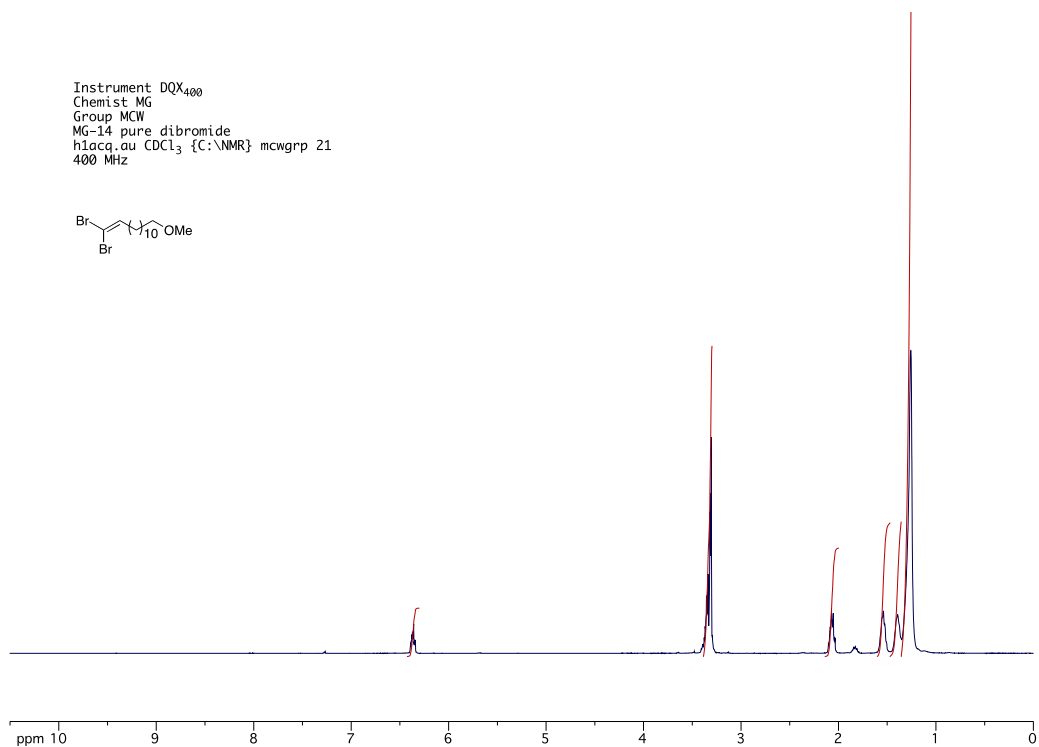
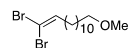
Acetic anhydride (210 μ l, 2.20 mmol, 10 eq) was added to a solution of 1-(2-methyl-5,5-dioxido-6a,7,8,9-tetrahydro-6H-dibenzo[c,e][1,2]thiazin-6-yl) ethanone (55 mg, 0.22 mmol, 1 eq) in pyridine (1 mL). The reaction was stirred at reflux for 2 h. The reaction mixture was allowed to cool to rt and poured onto water (5 mL) and extracted with ethyl acetate (3 $\times$ 5 mL). The organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (30% ethyl acetate/petrol) to yield the title compound as a colourless oil (43 mg, 67%). ν_{max} (neat)/cm⁻¹ 2941, 2359, 2341, 1690, 1597, 1573, 1448, 1347, 1320, 1215, 1186, 1101, 1038, 981, 880, 754, 682. δ_{H} (400 MHz, CDCl₃) 7.68 (1H, d, J =8.0, ArH), 7.23 (1H, br. s, ArH), 7.19 (1H, d, J =8.0, ArH), 6.14-6.10 (1H, m, CH=C), 5.32-5.25 (1H, m, NCH), 2.50 (3H, s, Me), 2.42-2.38 (4H, m, Me + CH₂), 2.34-2.22 (2H, m, CH₂), 1.98-1.90 (2H, m, CH₂), 1.88-1.80 (1H, m, CH₂). δ_{C} (100 MHz, CDCl₃) 168.8, 144.7, 137.3, 134.3, 130.5, 130.4, 127.9, 136.9, 122.2, 56.7, 28.8, 26.0, 25.7, 21.7, 21.4. HRMS (ESI⁺) calculated for C₁₅H₁₇NO₃SN⁺ [M+Na]⁺ 314.0821 found 314.0809.

Appendix

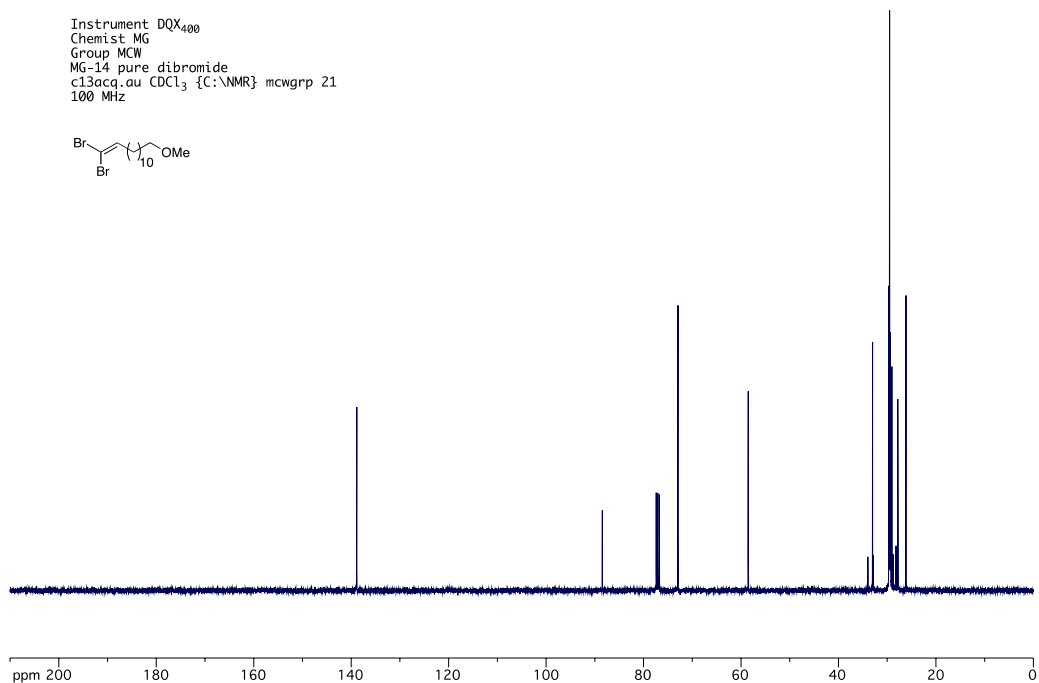
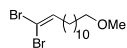
Copies of ^1H and ^{13}C Spectra



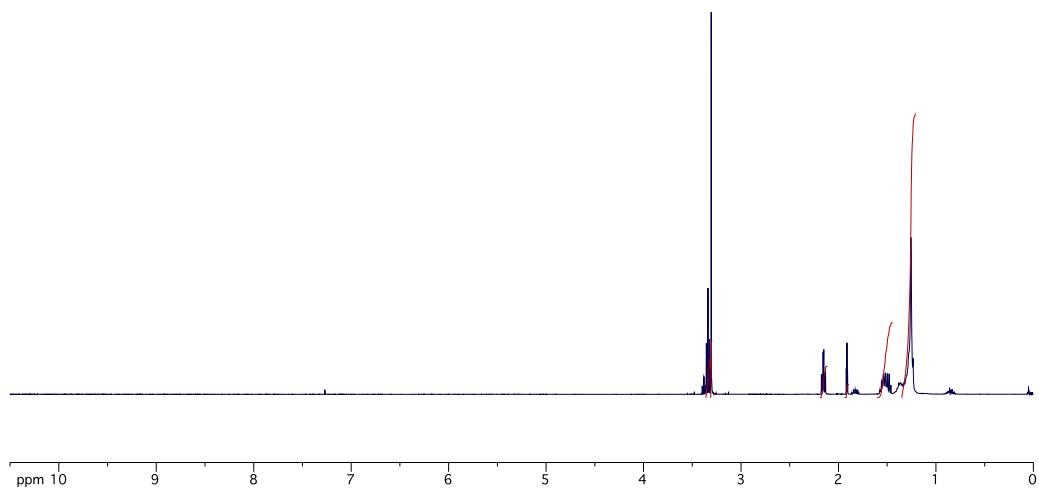
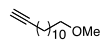
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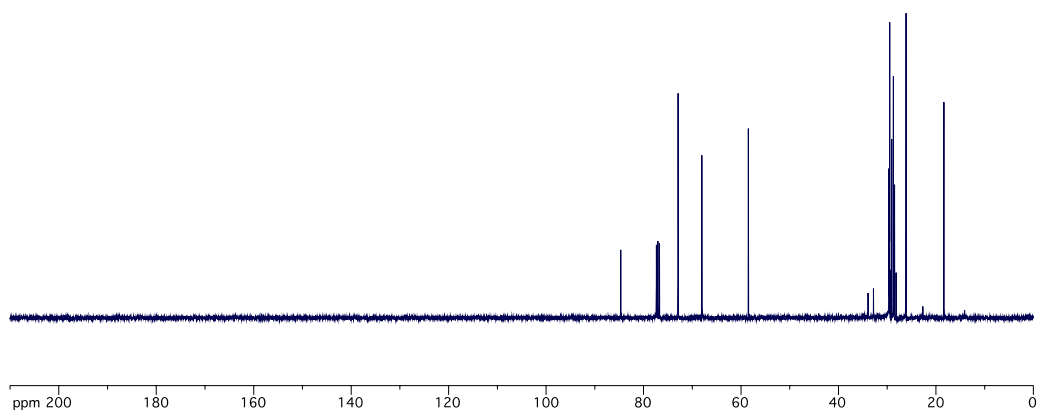
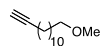
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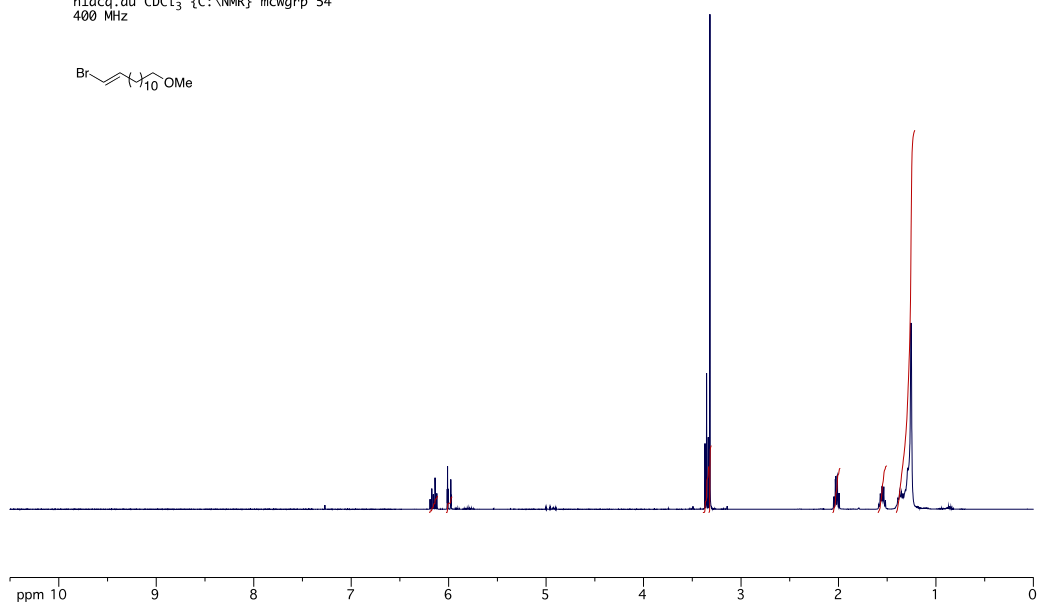
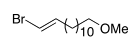
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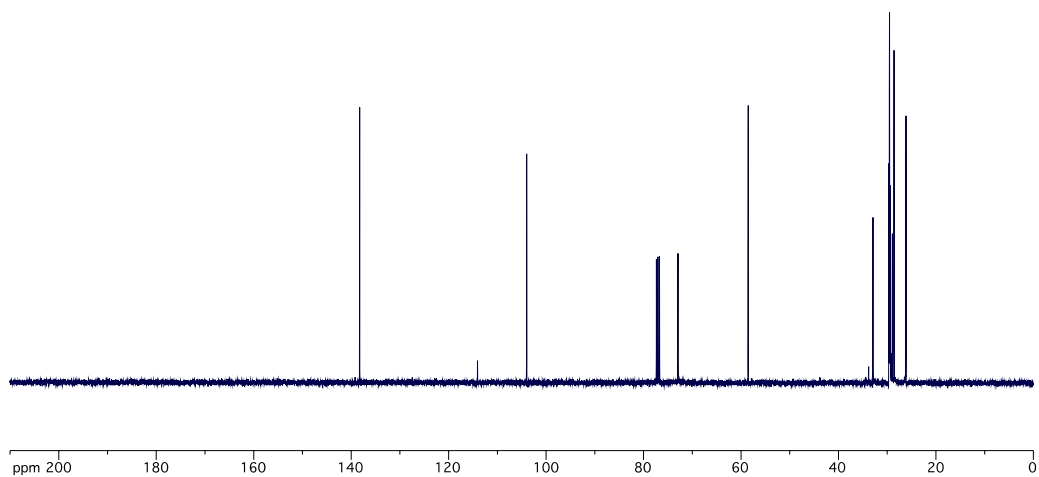
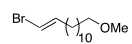
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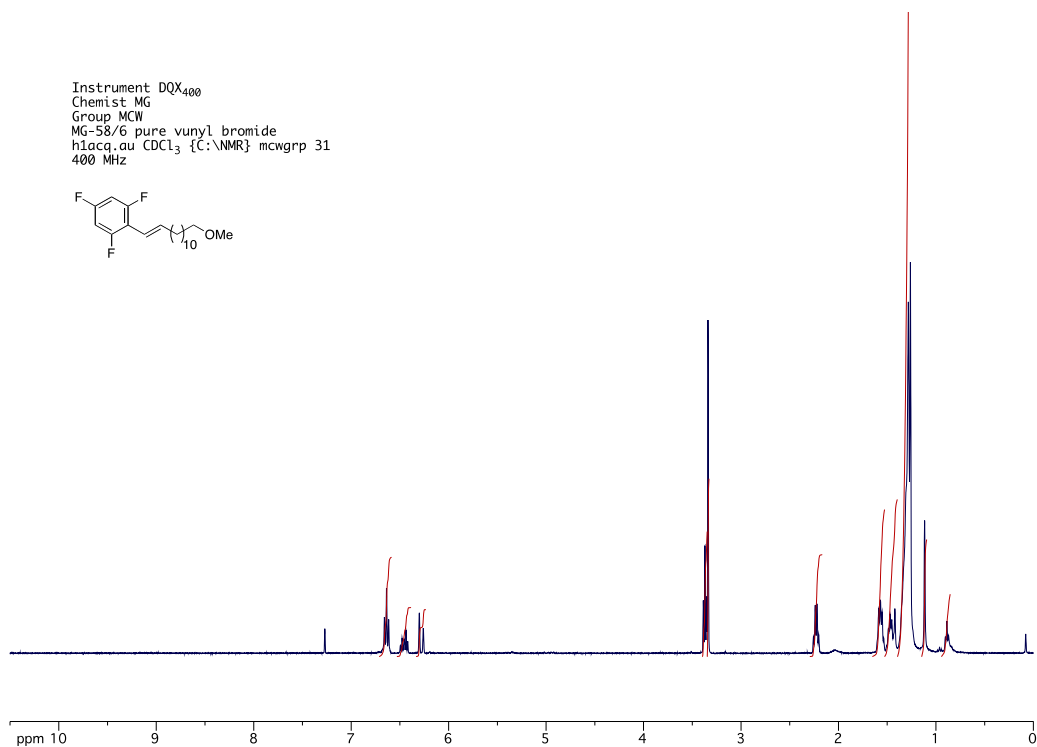
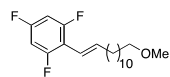
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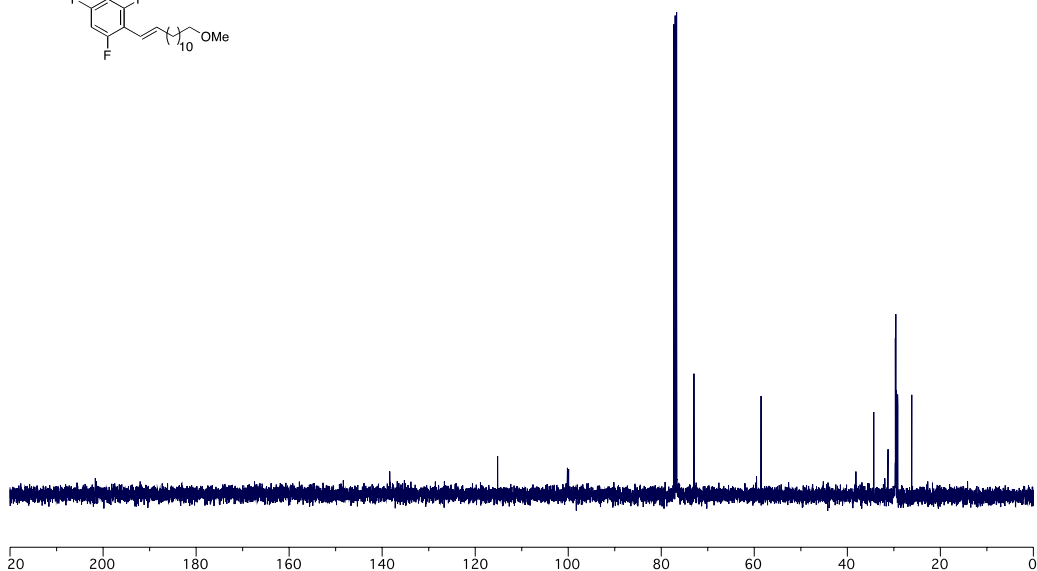
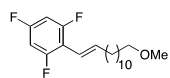
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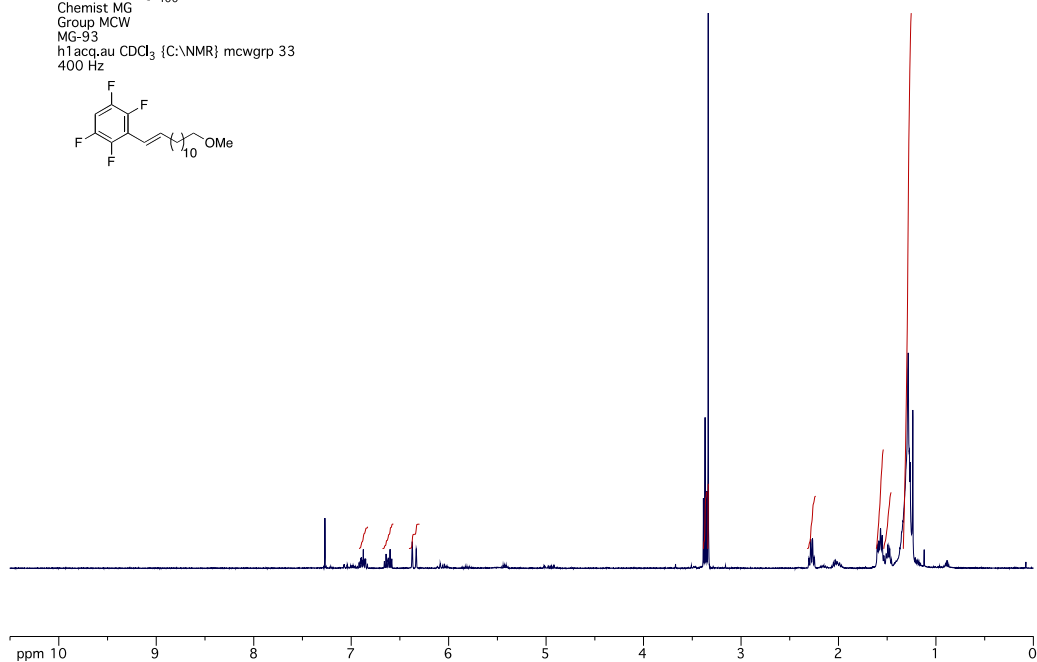
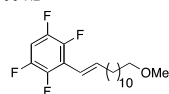
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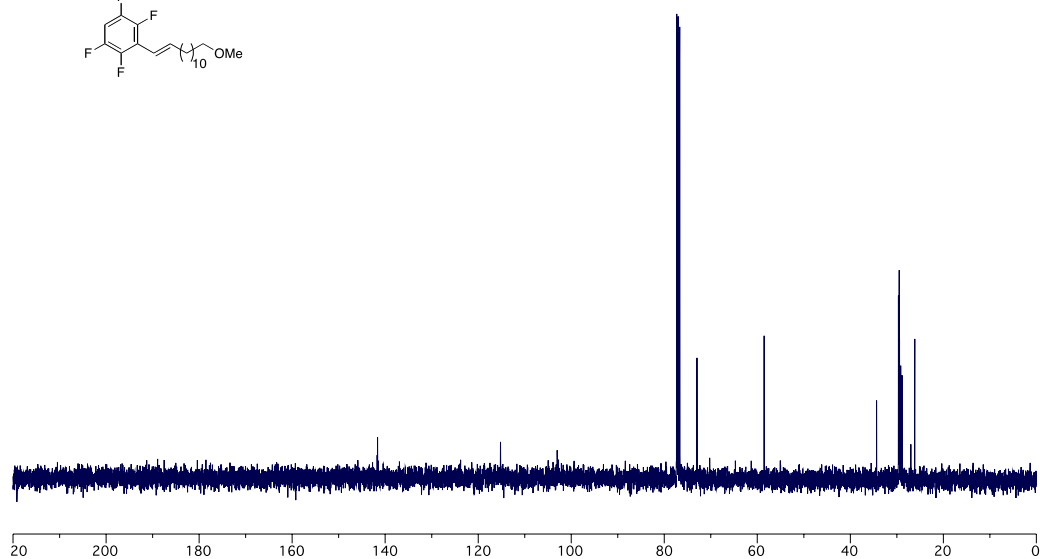
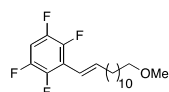
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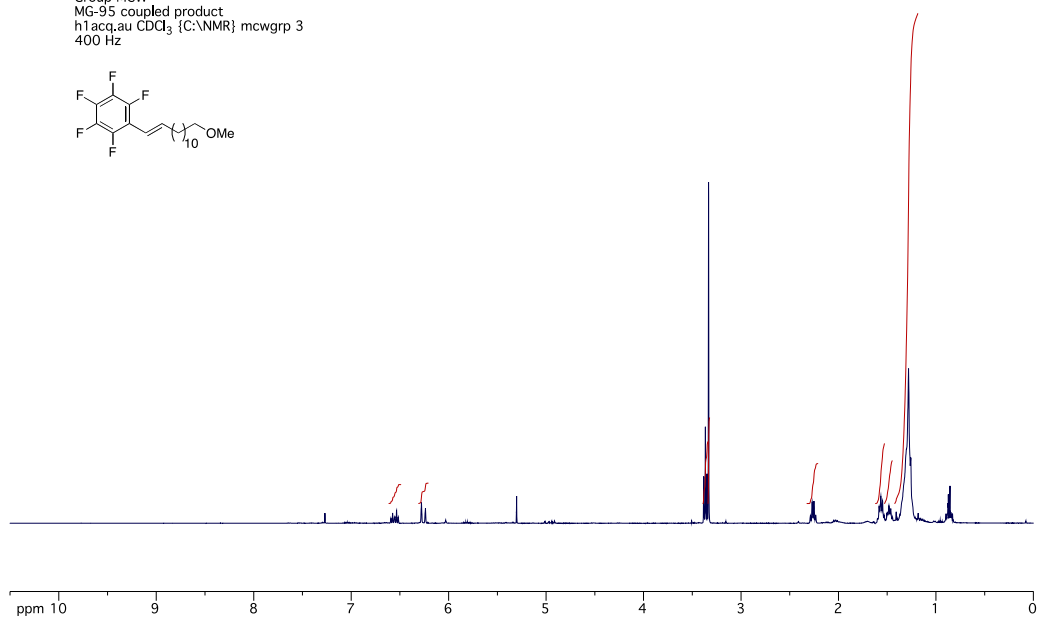
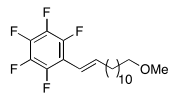
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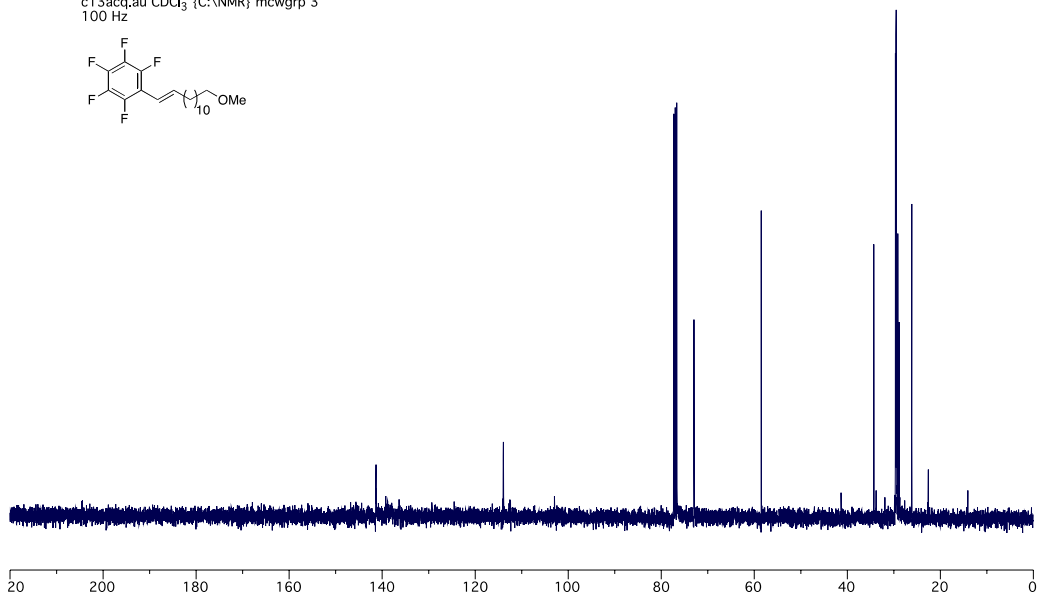
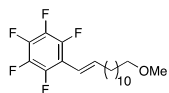
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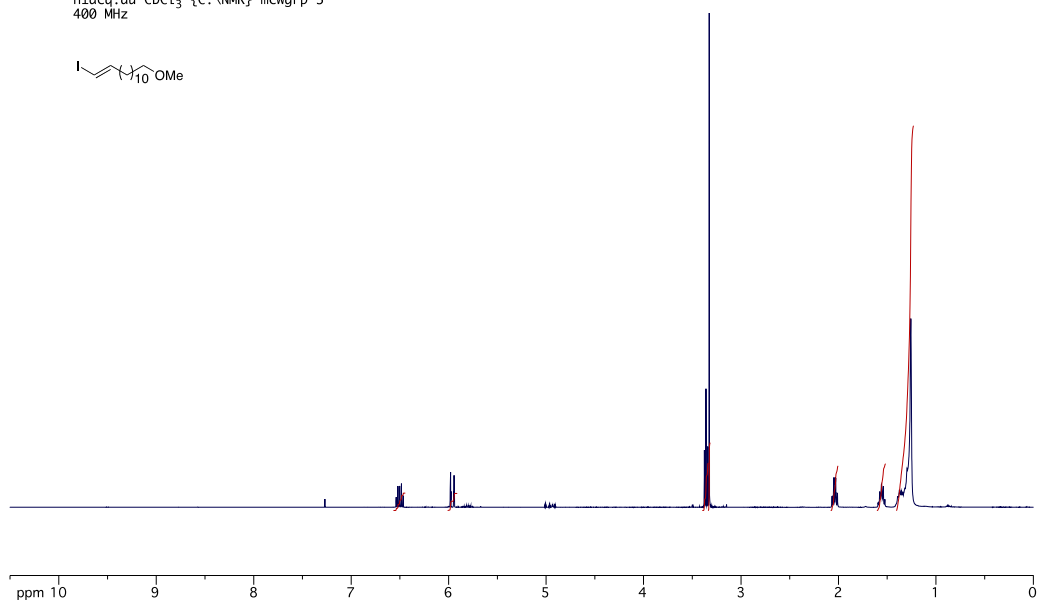
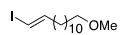
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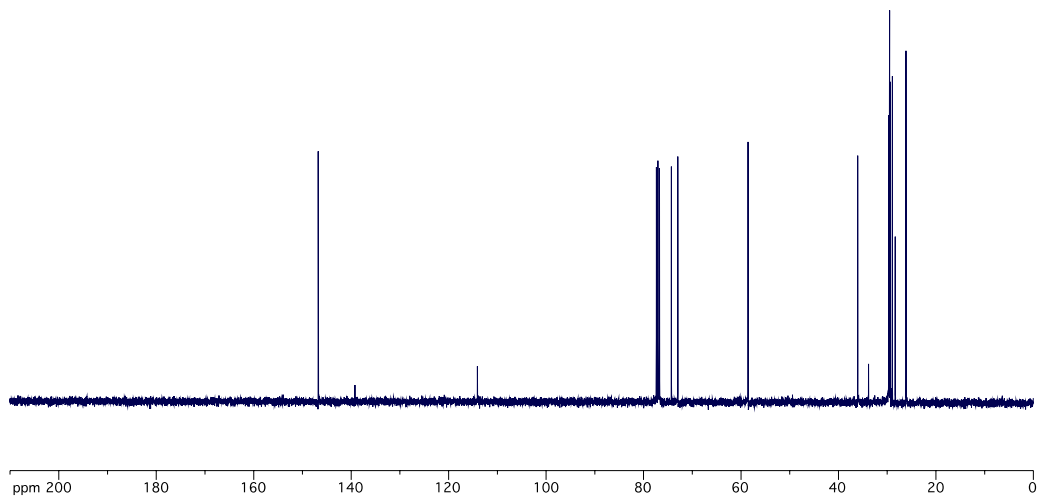
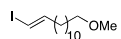
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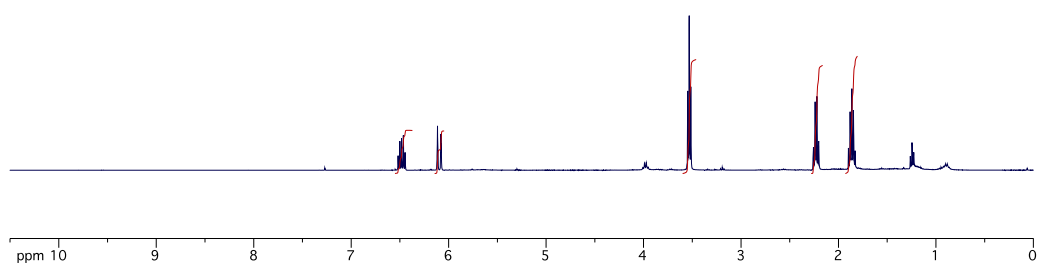
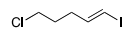
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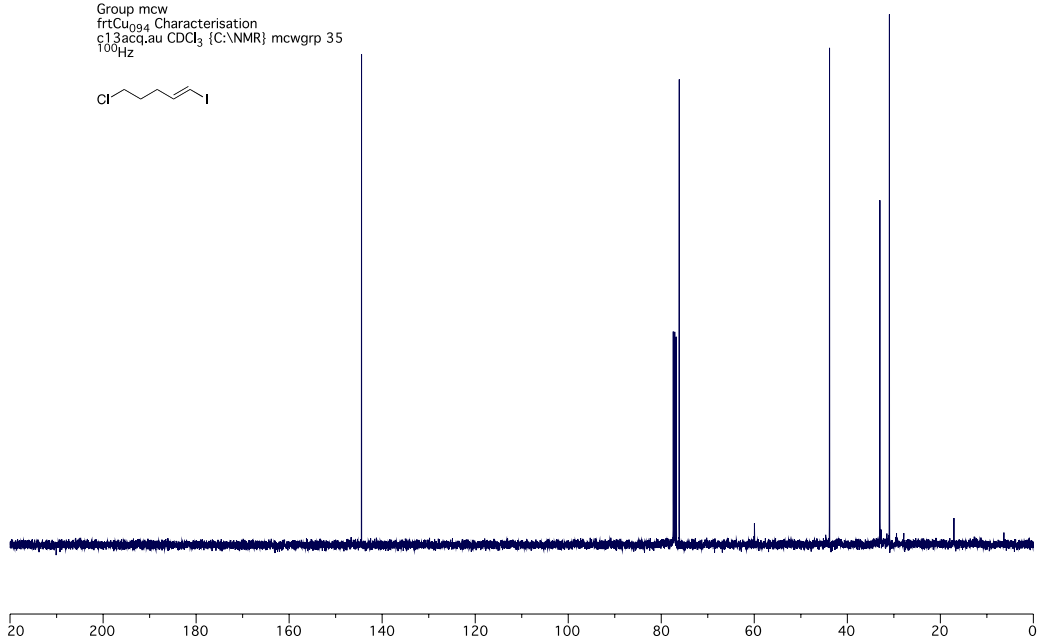
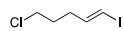
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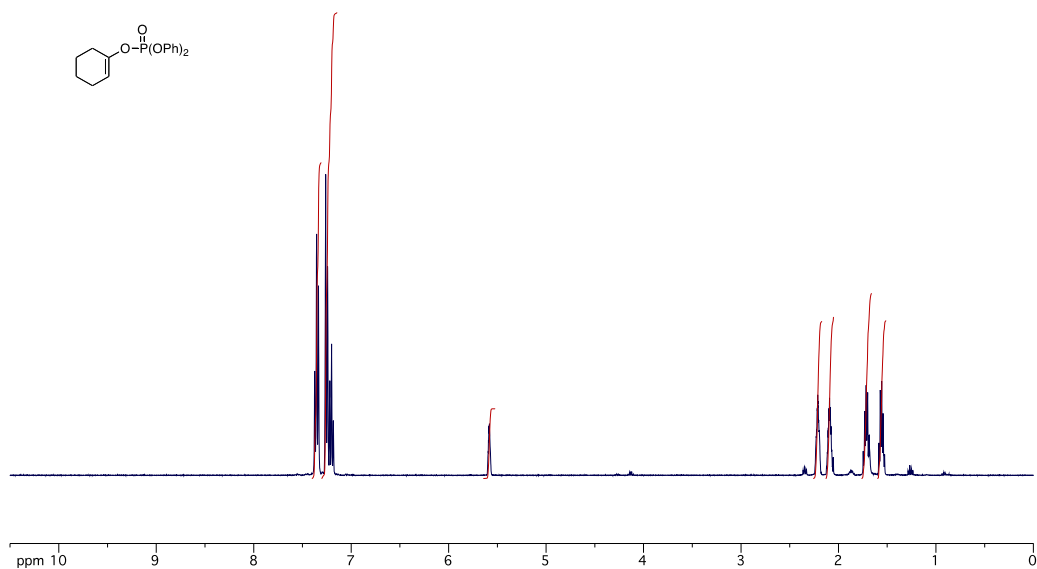
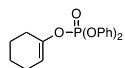
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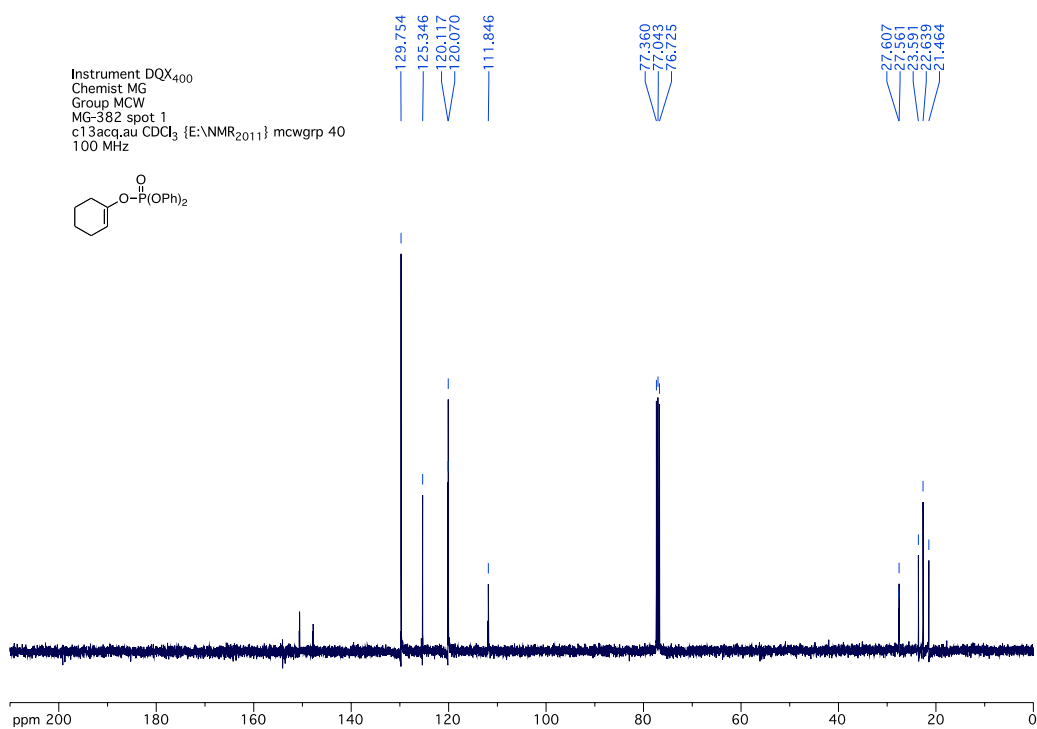
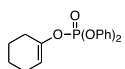
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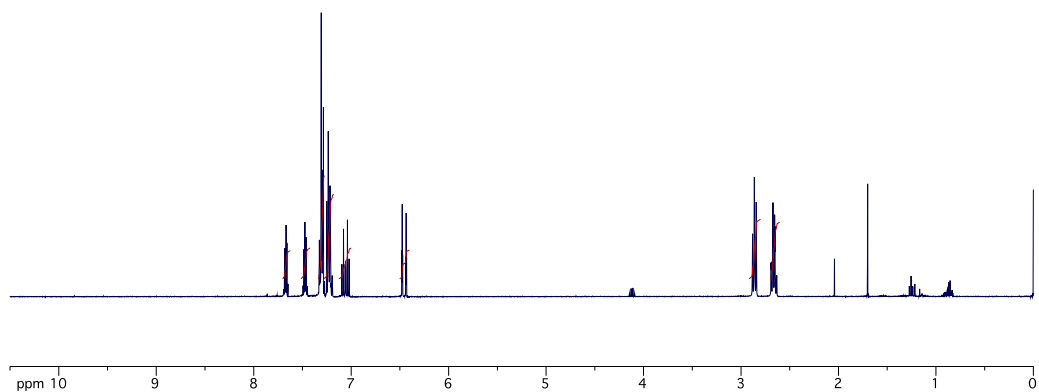
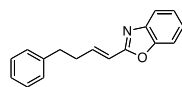
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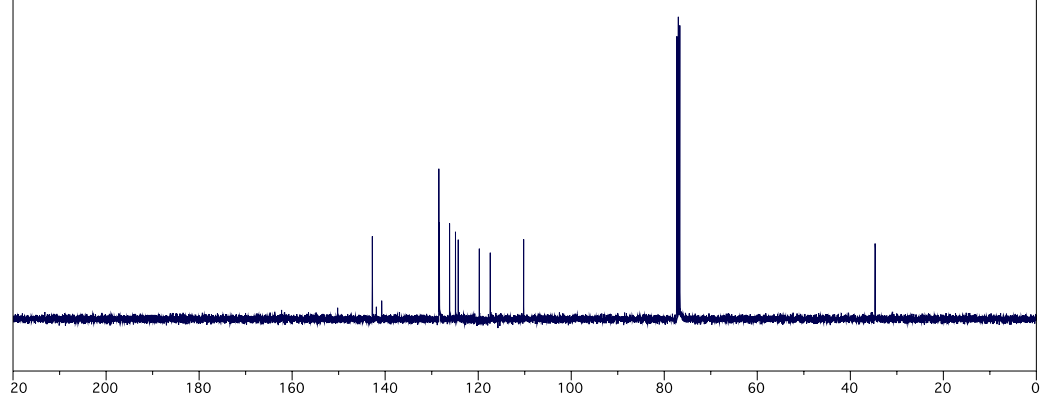
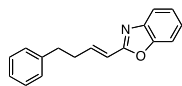
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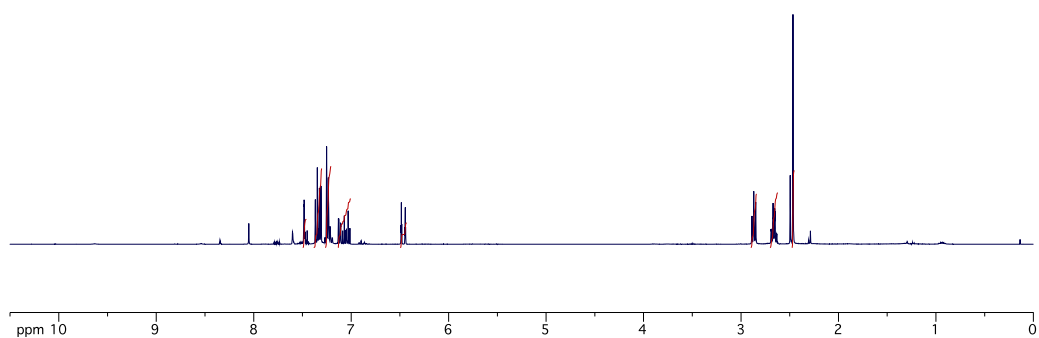
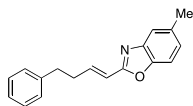
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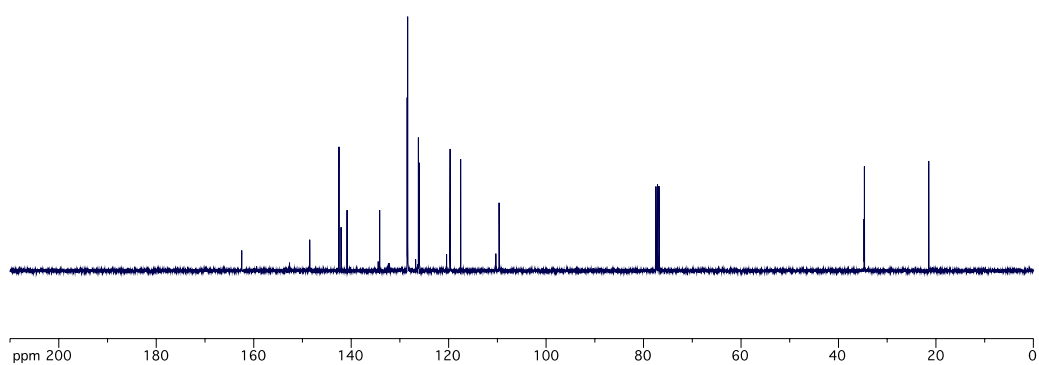
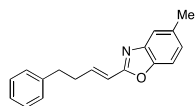
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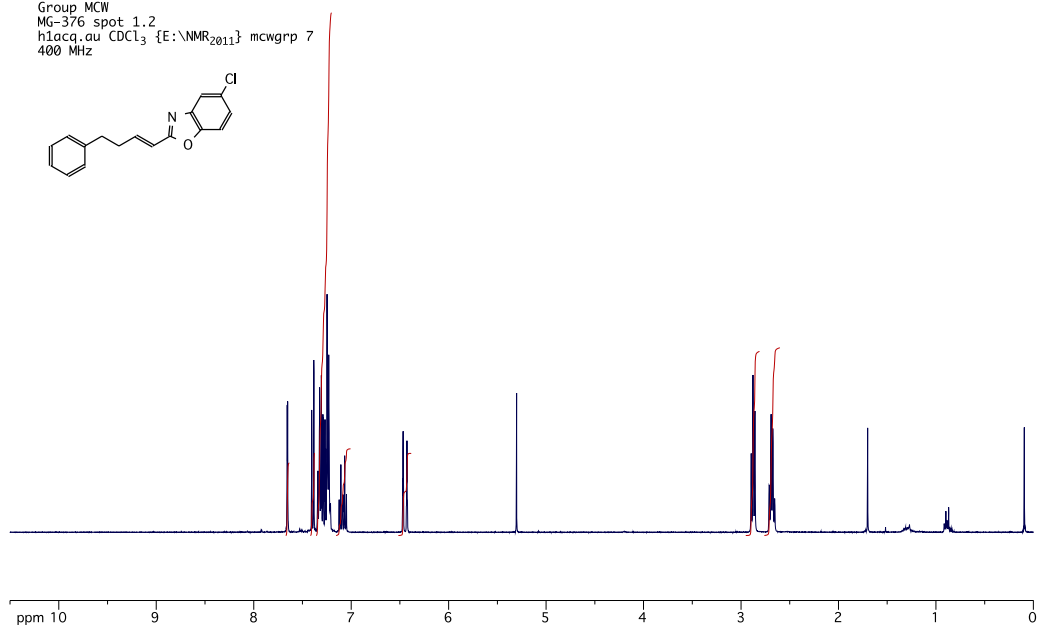
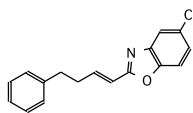
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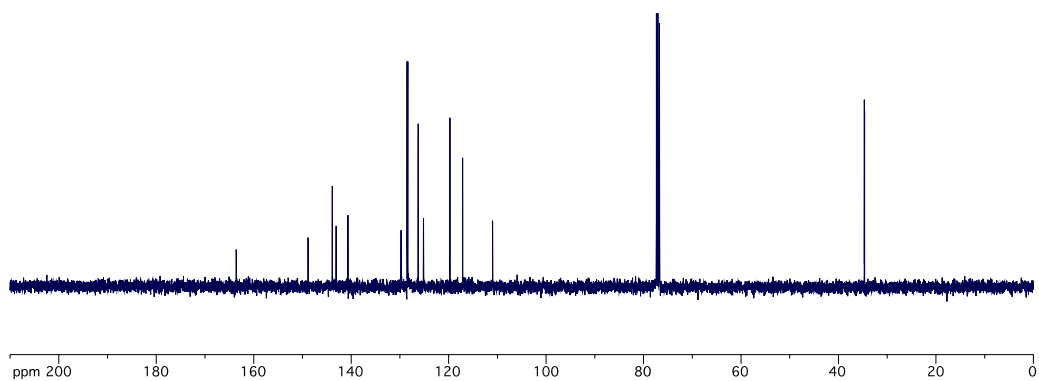
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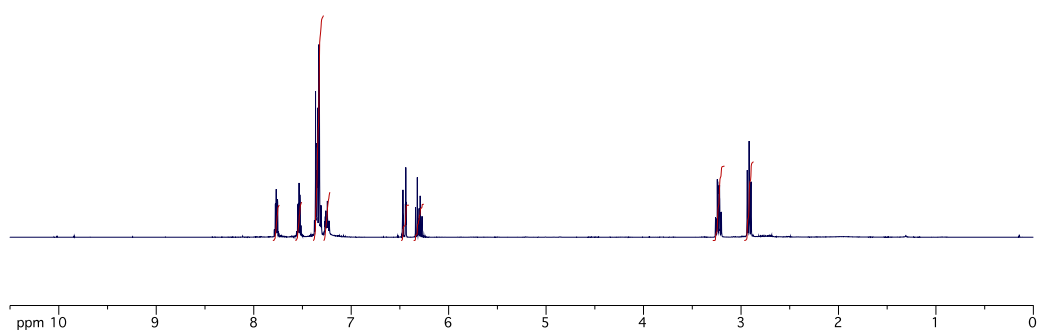
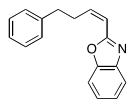
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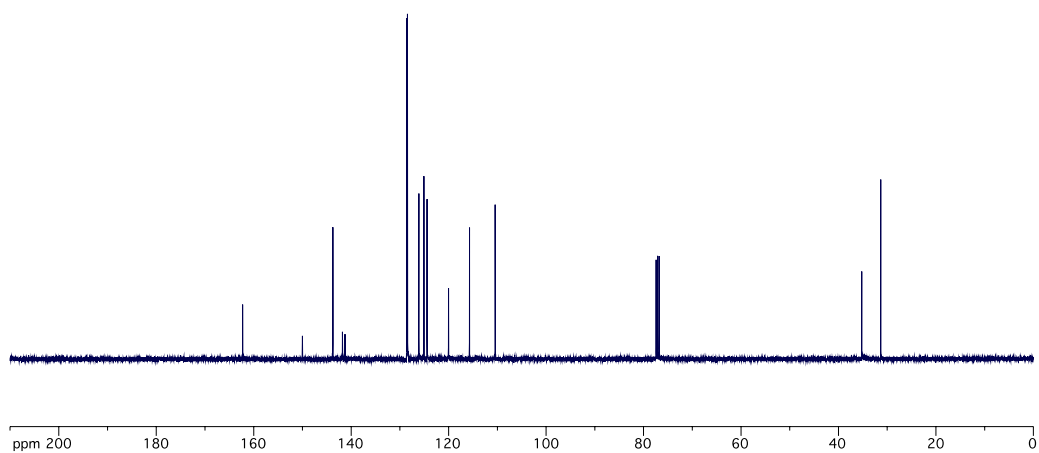
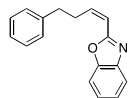
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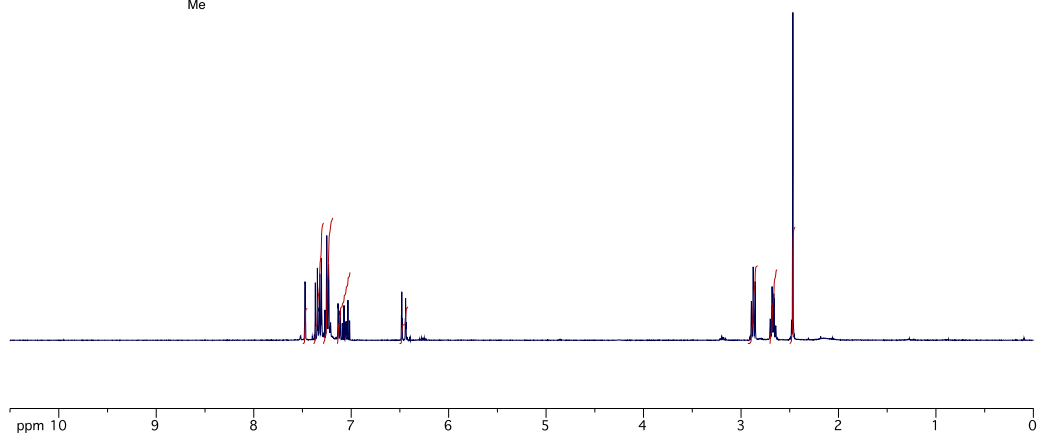
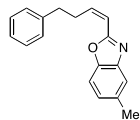
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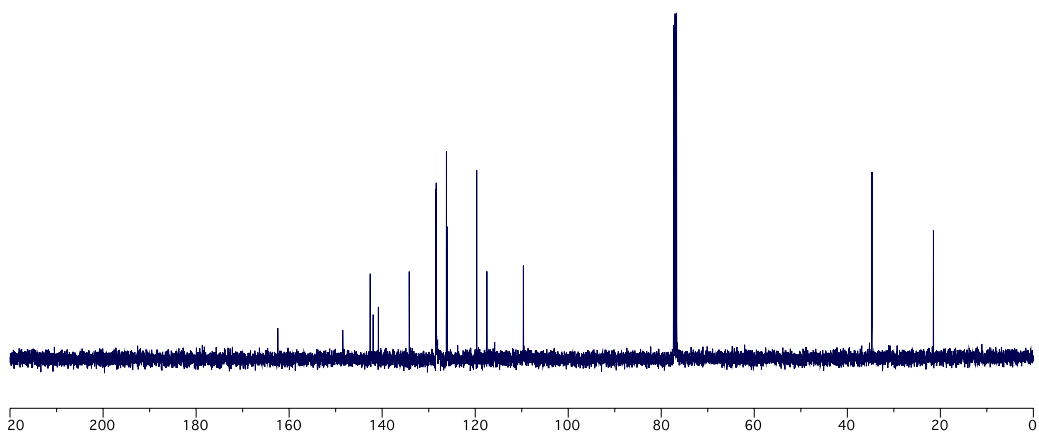
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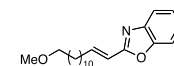


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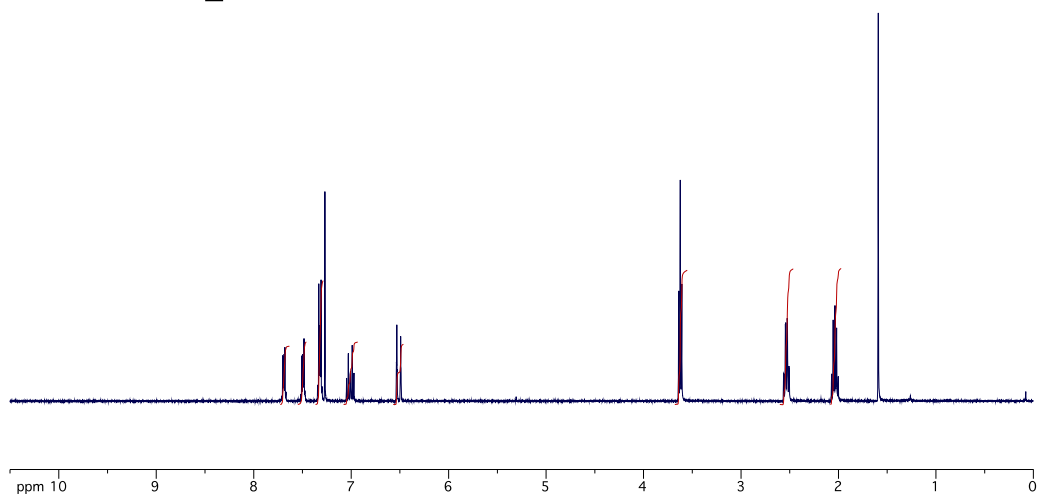
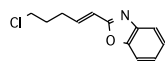


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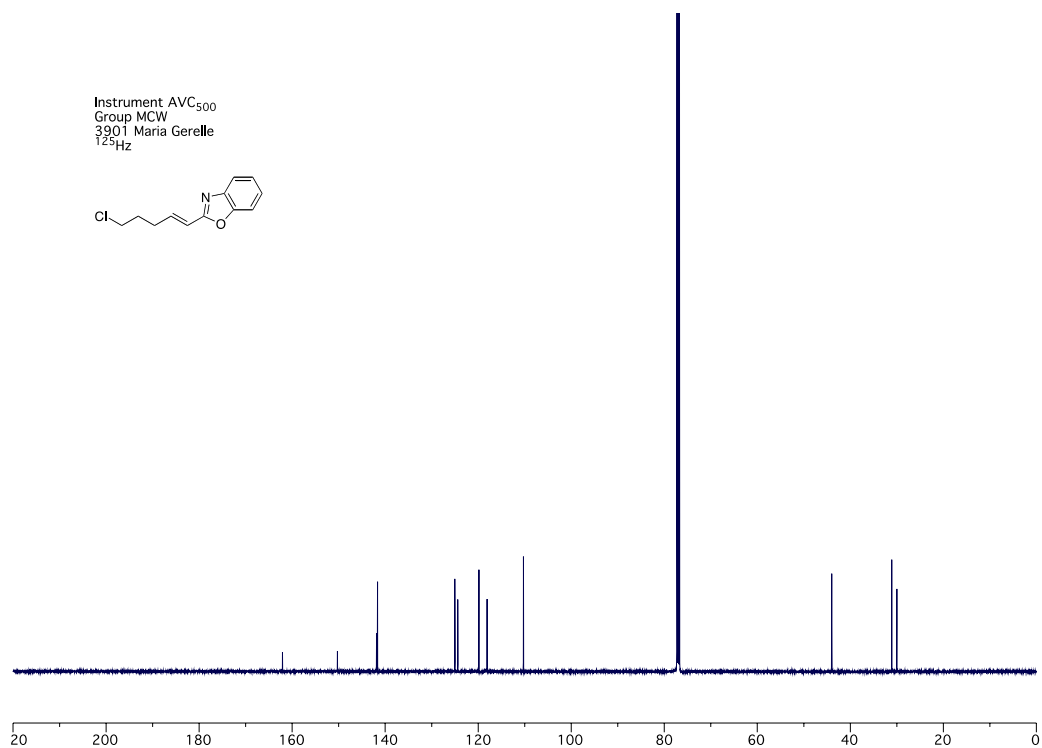
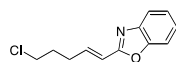


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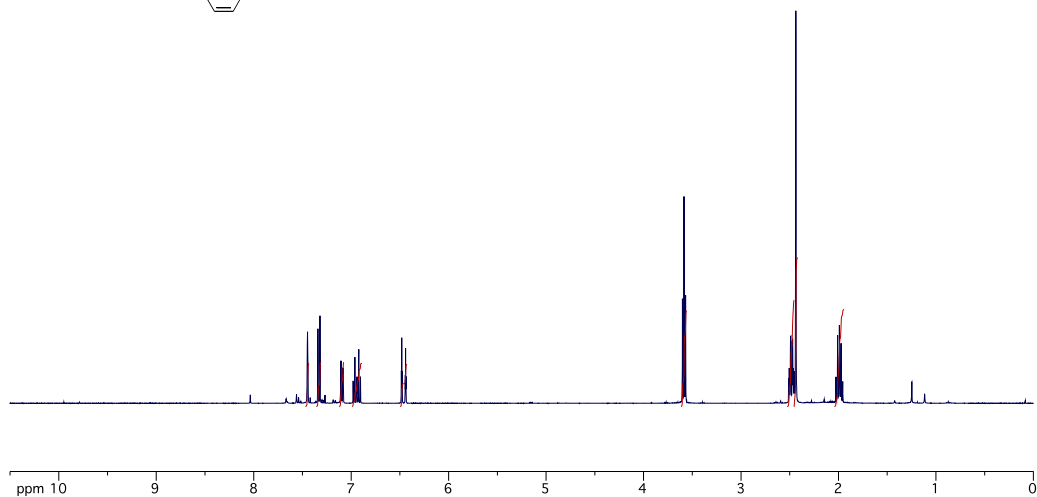
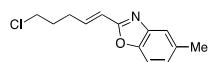
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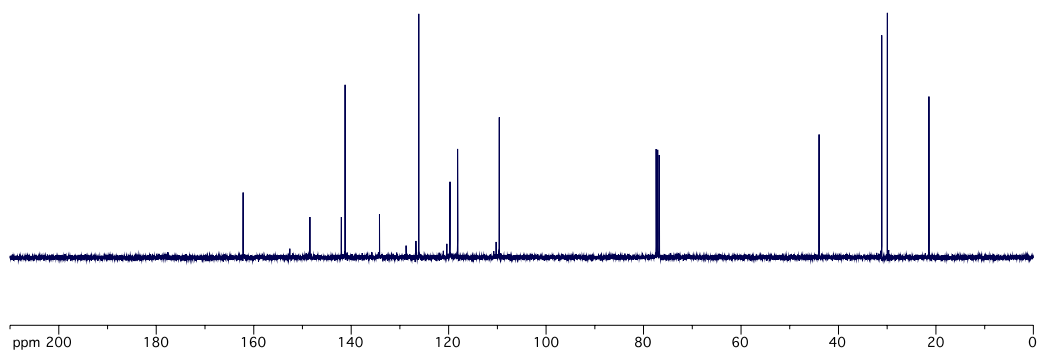
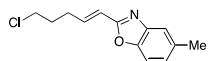
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 3901 Maria Gerelle
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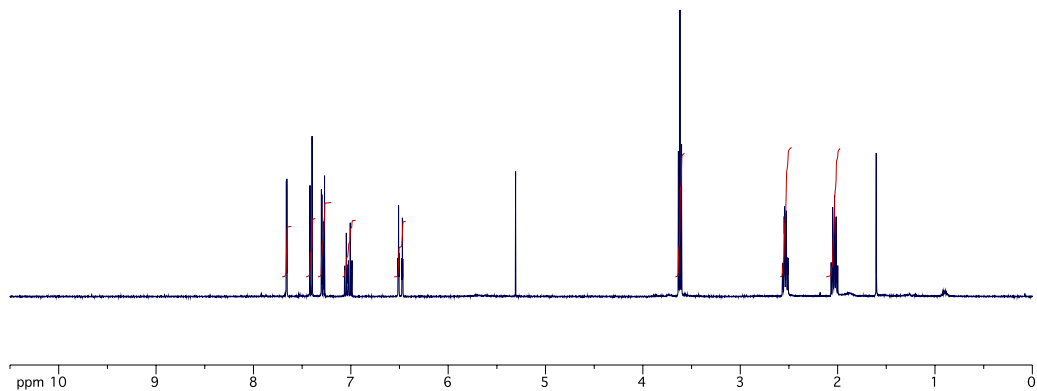
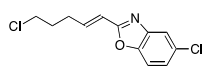
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 Group MCW
 MG-246/3 spot 1
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 400 MHz



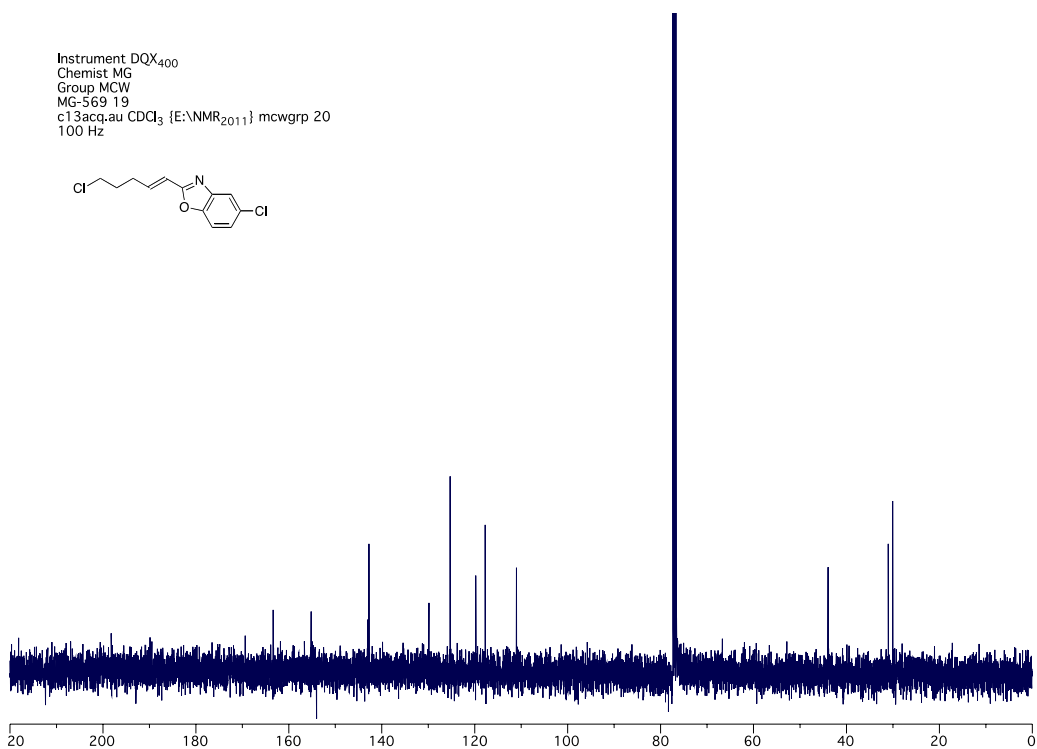
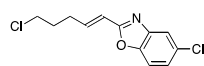
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 Group MCW
 MG-246/3 spot 1
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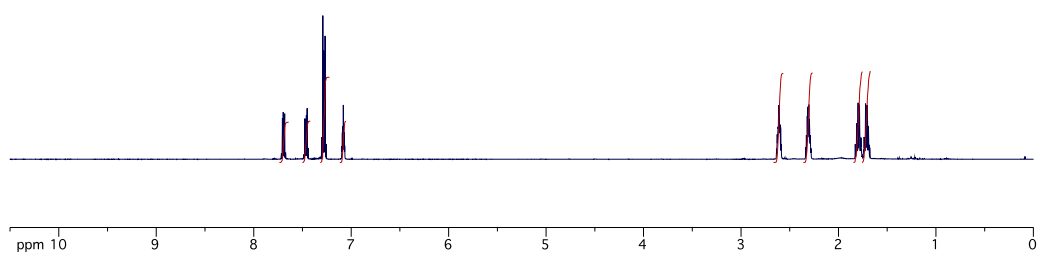
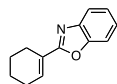
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 MG-569 19
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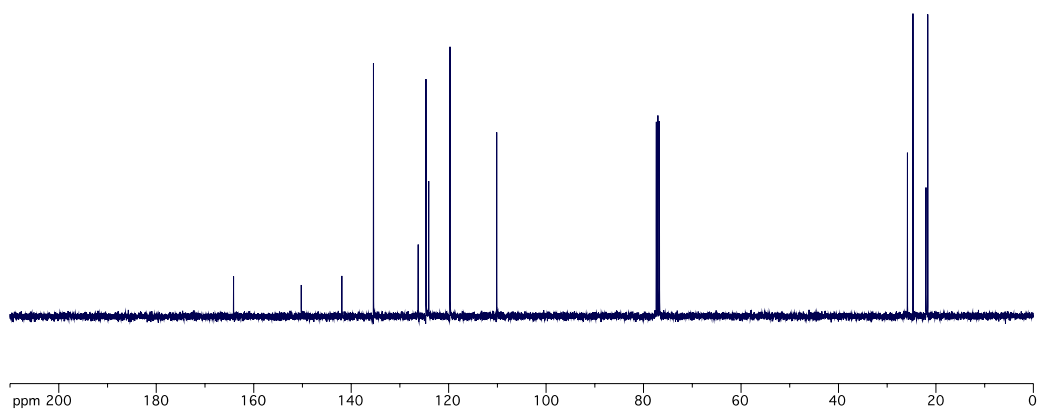
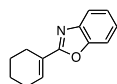
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 Group MCW
 MG-569 19
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Instrument DQX400
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 Group MCW
 MG-254/1 spot 1
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 400 MHz

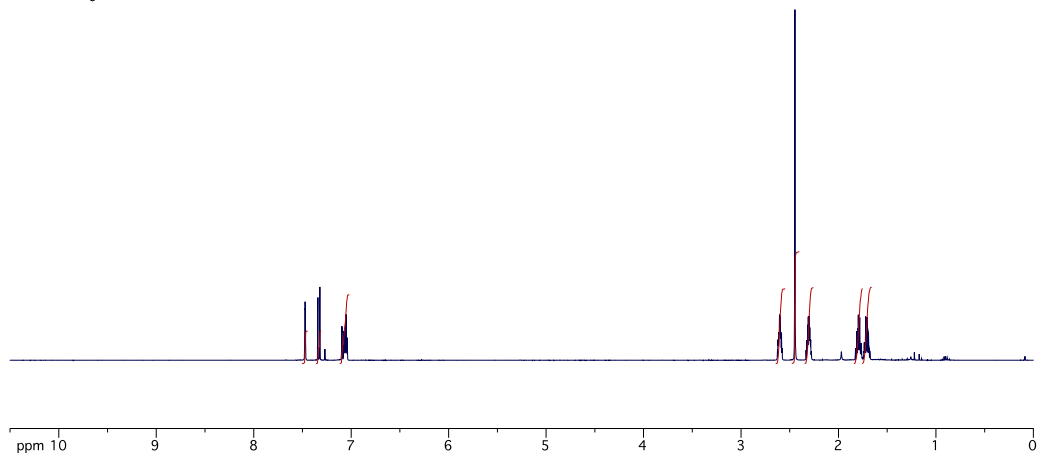
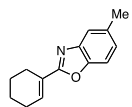


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 Group MCW
 MG-254/1 spot 1
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 100 MHz



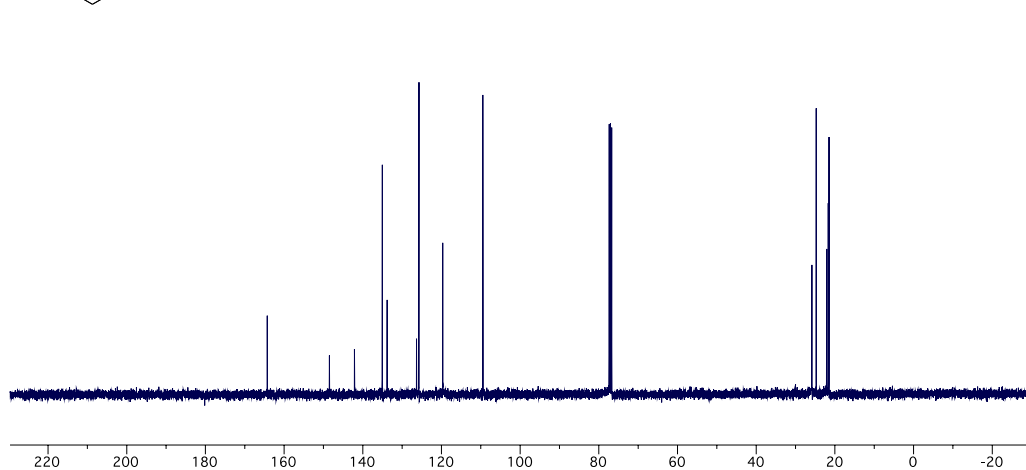
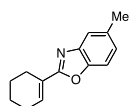
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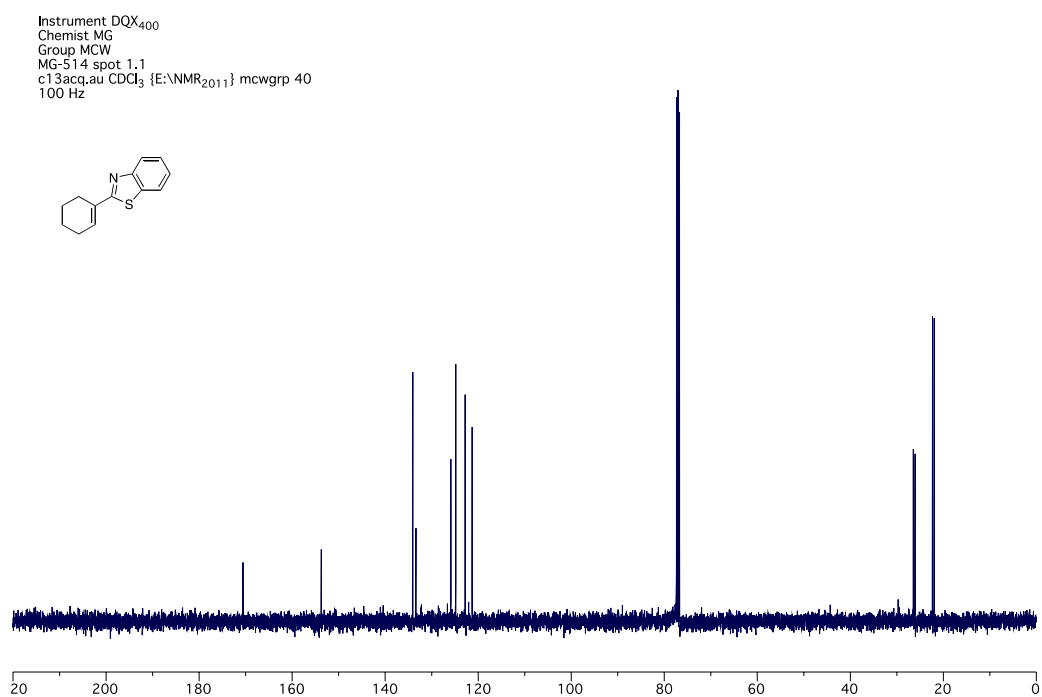
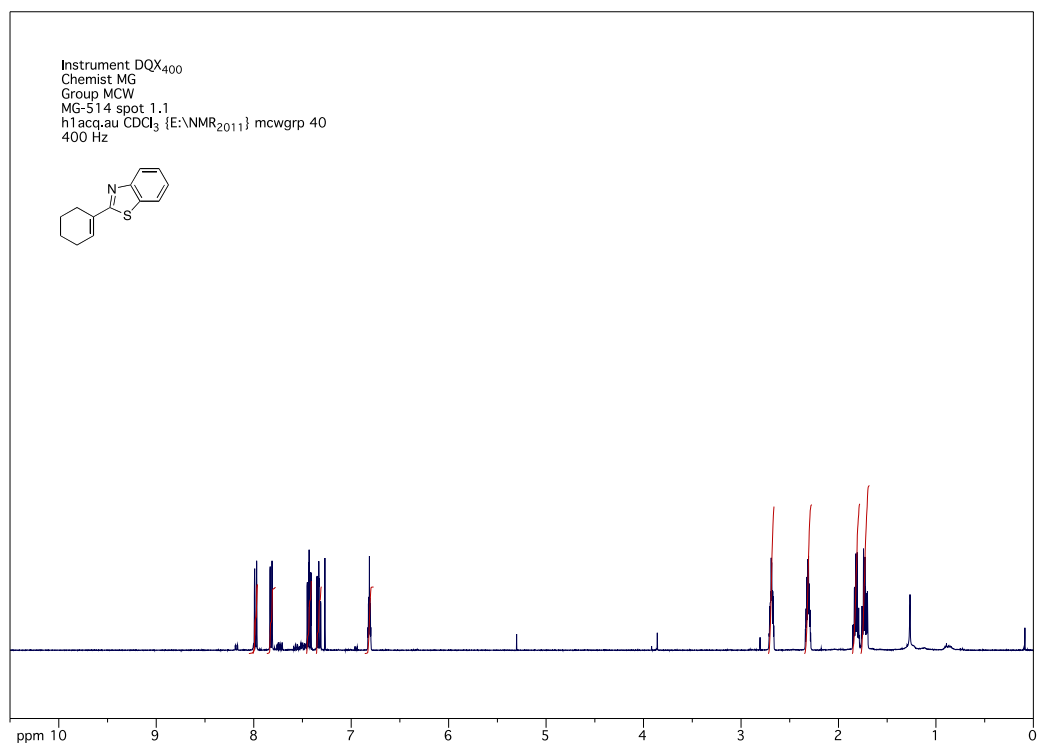
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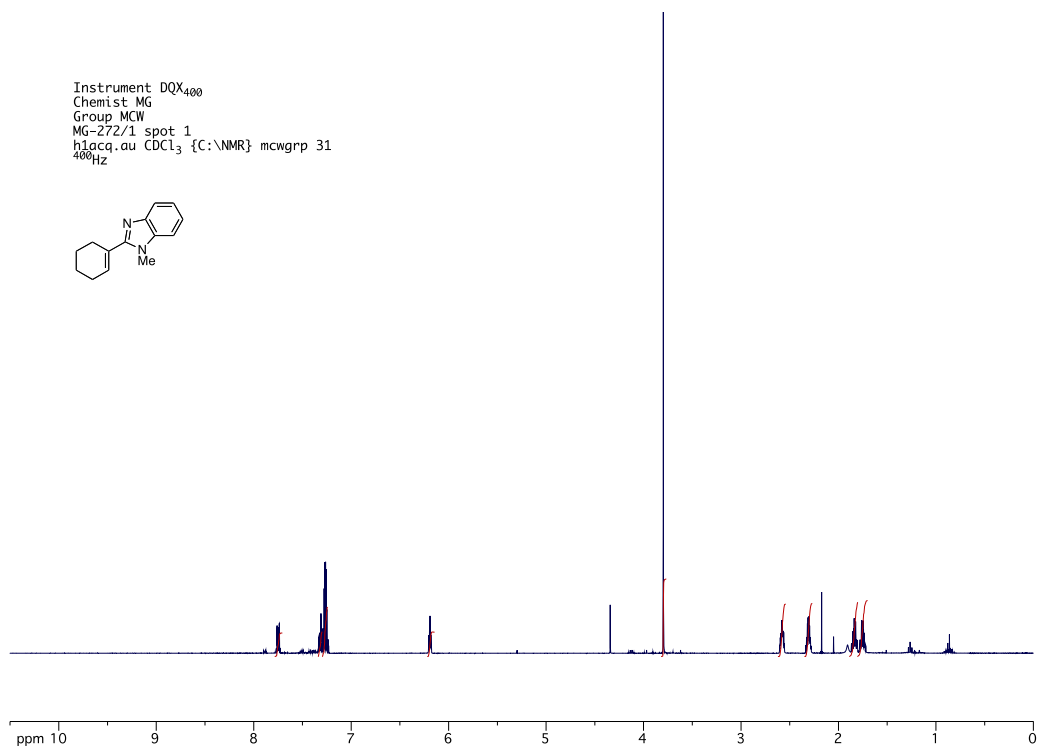
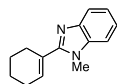
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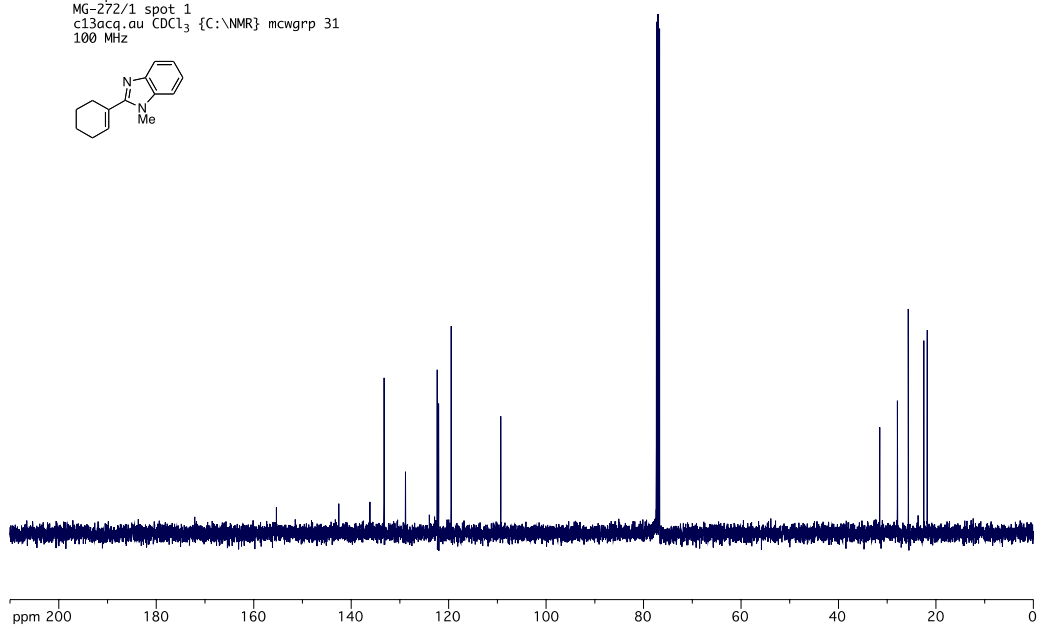
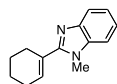




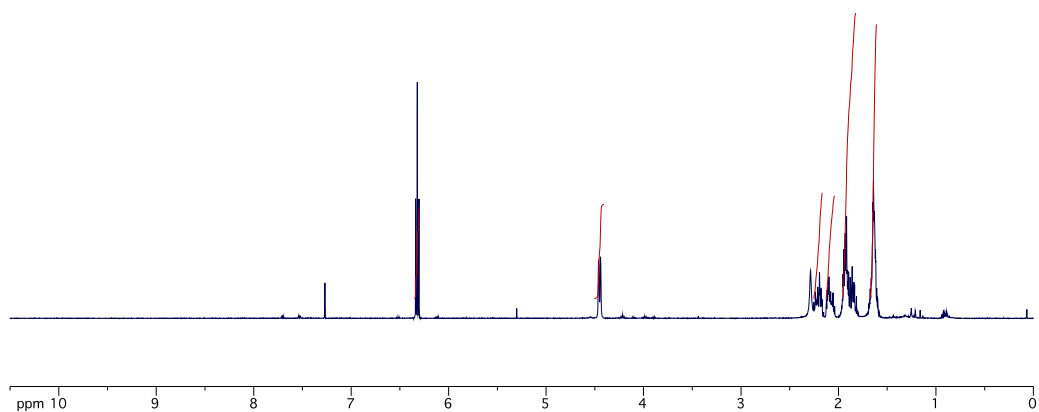
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 Group MCW
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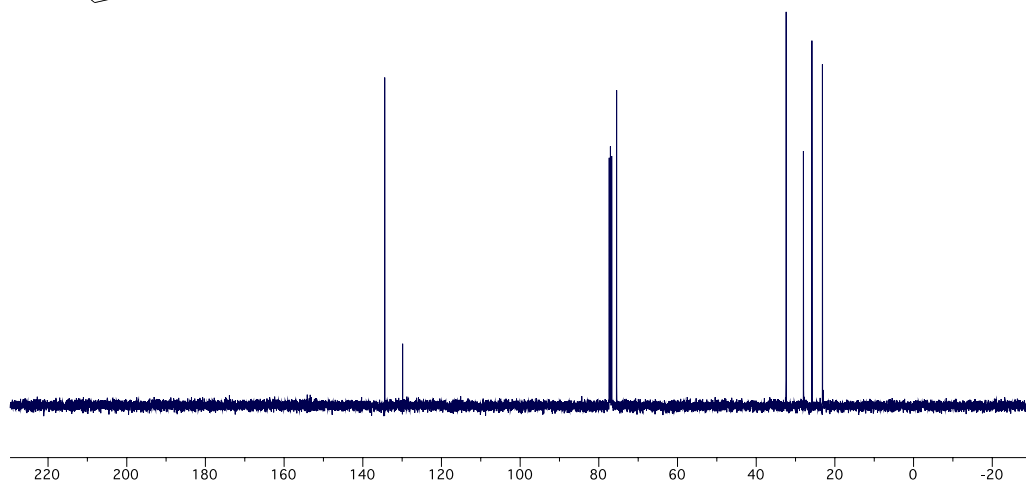
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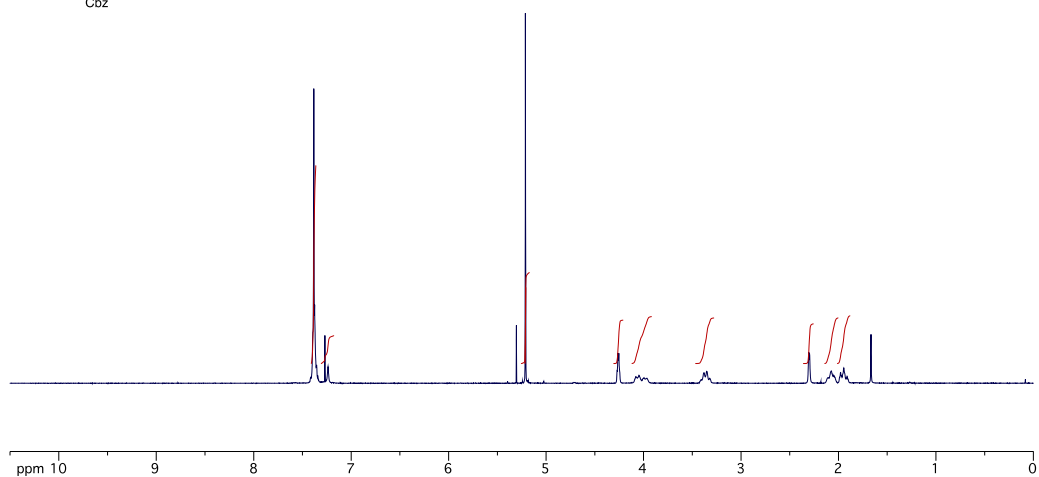
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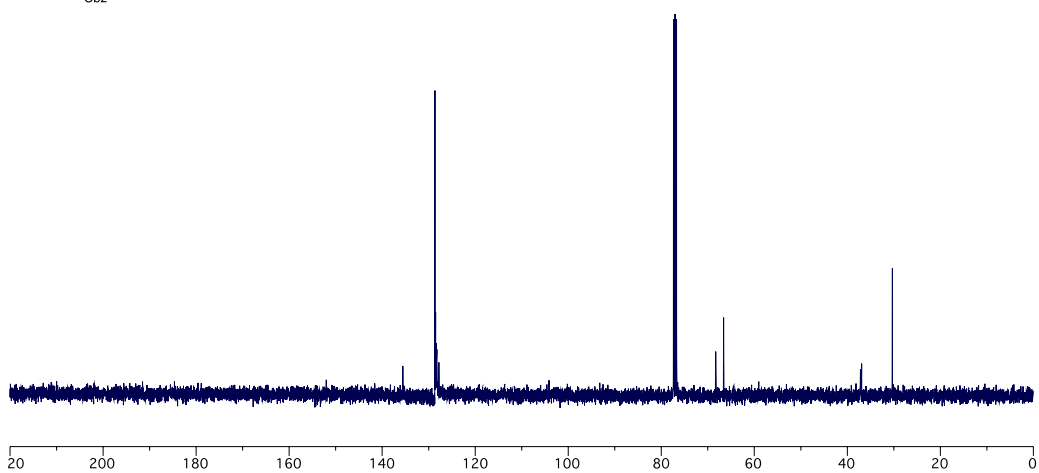
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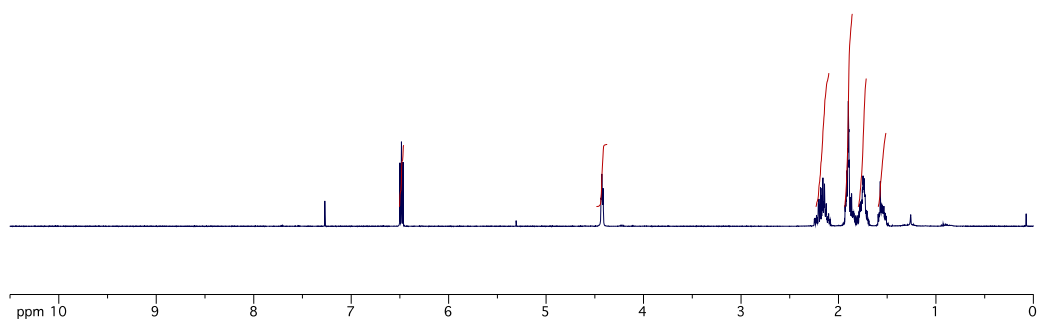
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 Group MCW
 MG-548
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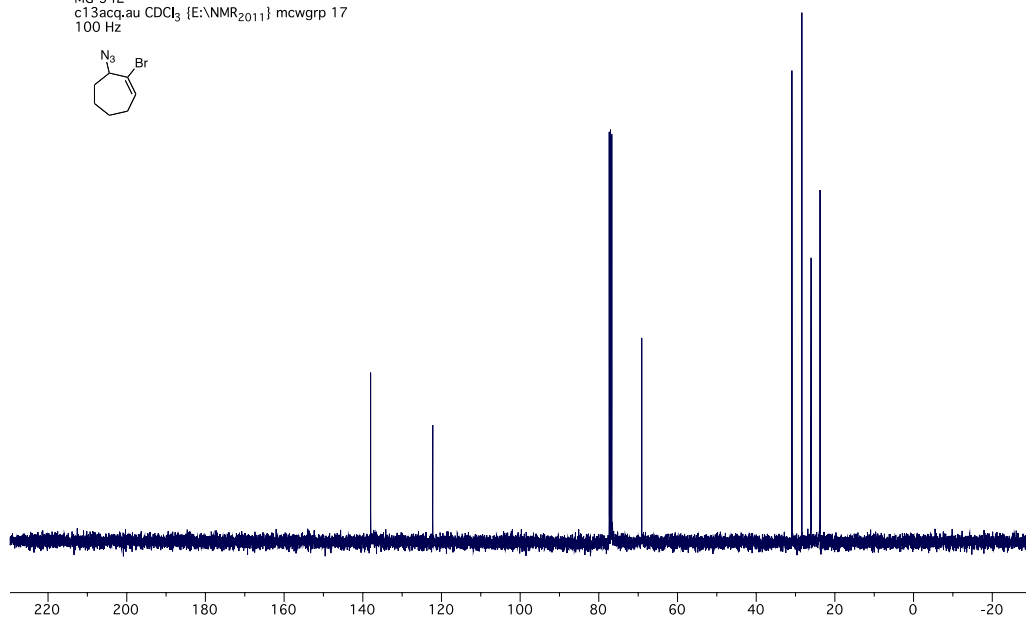
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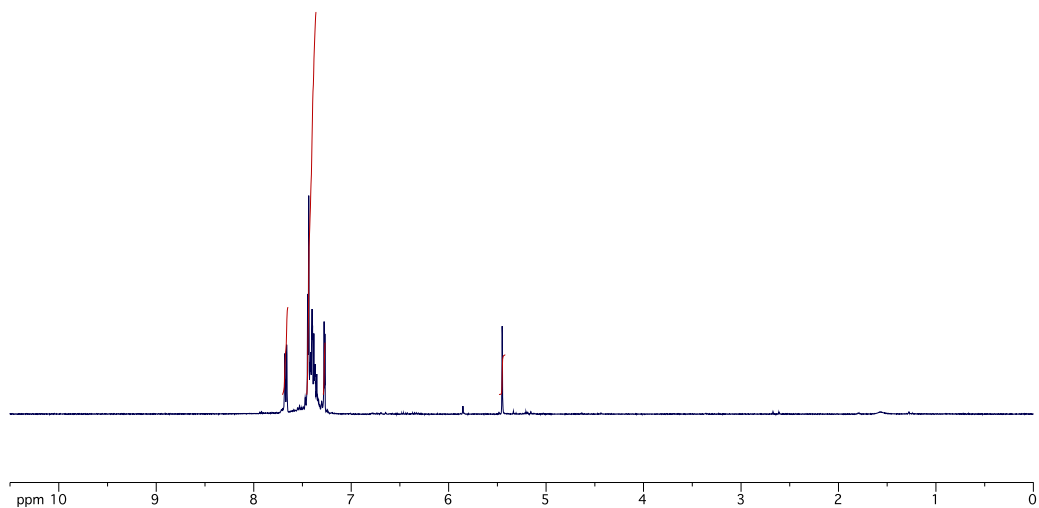
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 Group MCW
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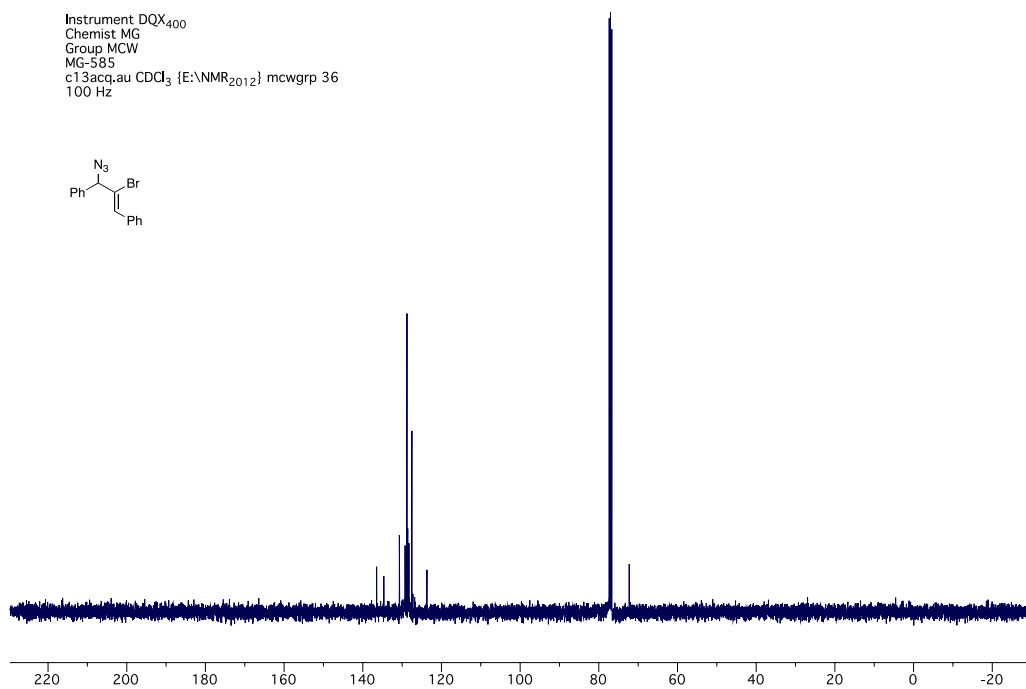
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 Group MCW
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 100 Hz



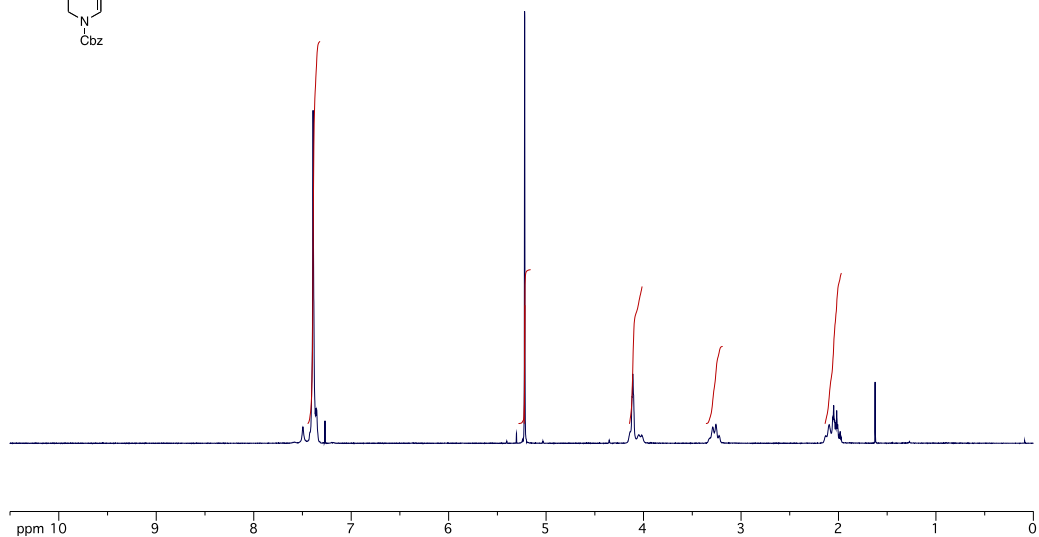
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 Chemist MG
 Group MCW
 MG-585
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 400 Hz



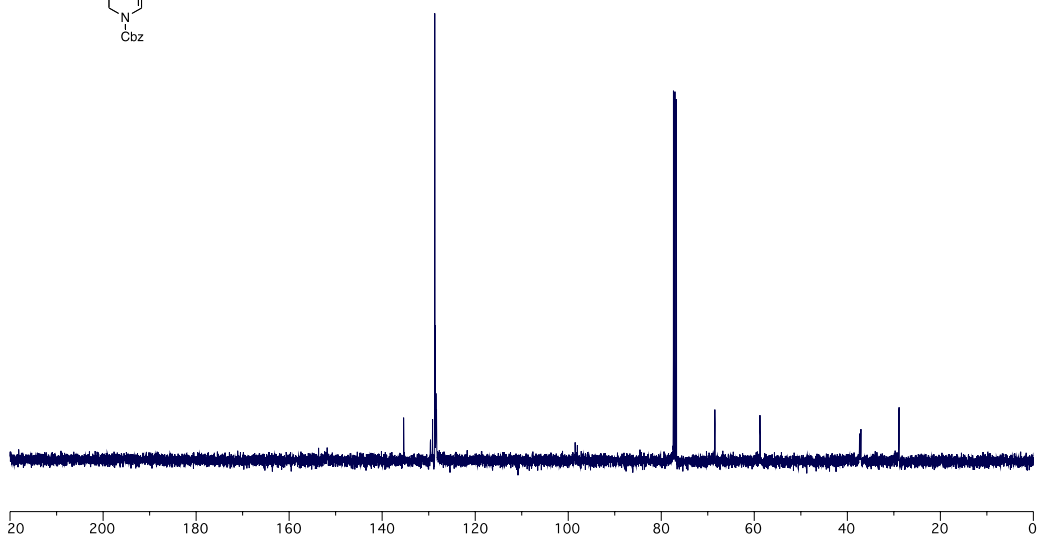
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 Group MCW
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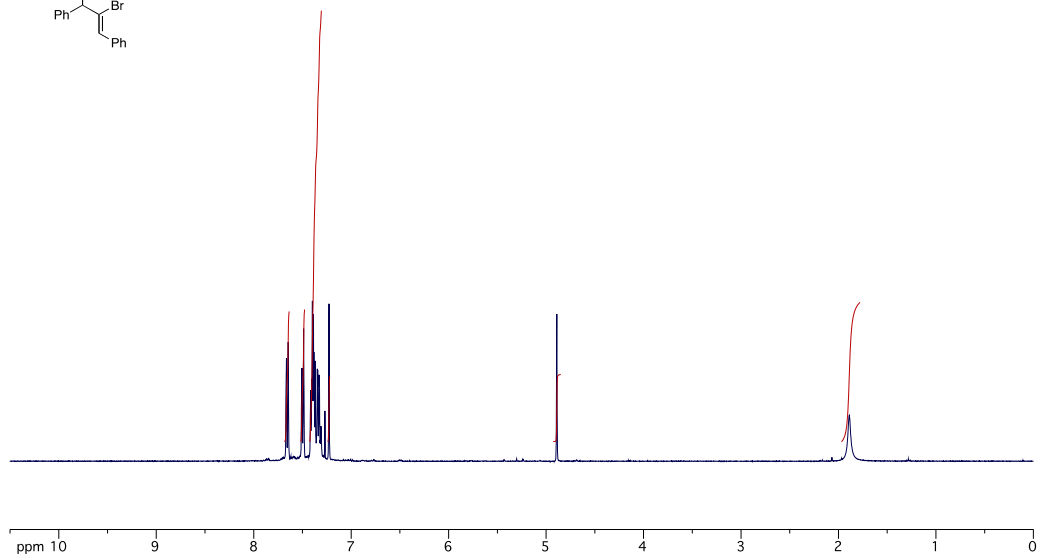
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 Chemist MG
 Group MCW
 MG-550
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 400 Hz



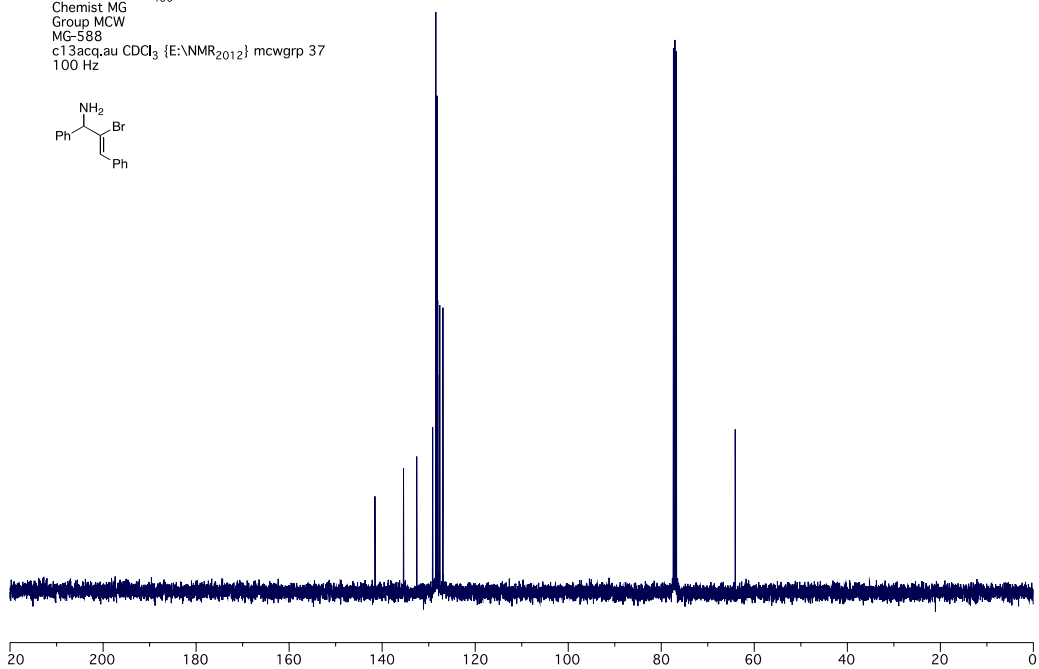
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 Group MCW
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 100 Hz



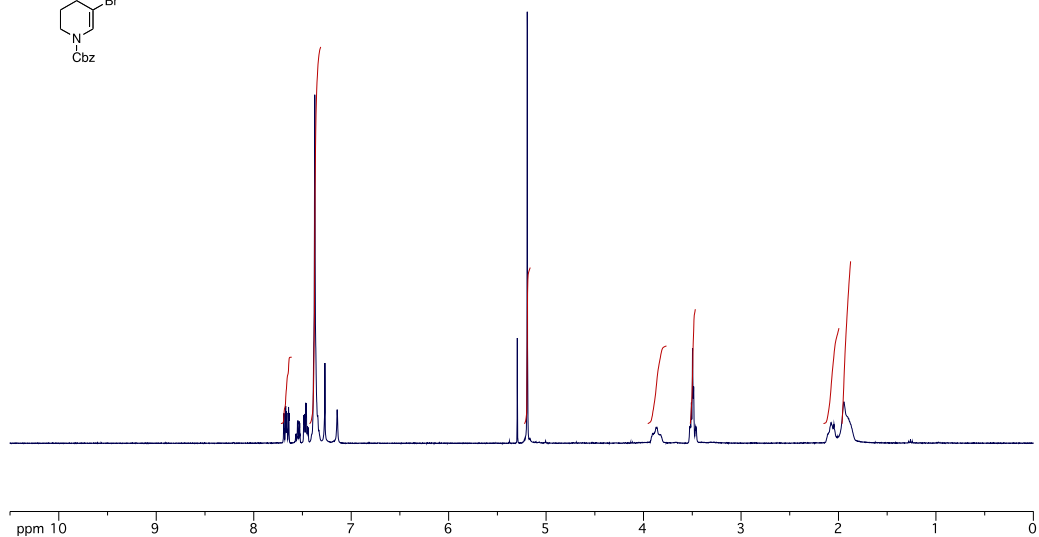
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 Group MCW
 MG-588
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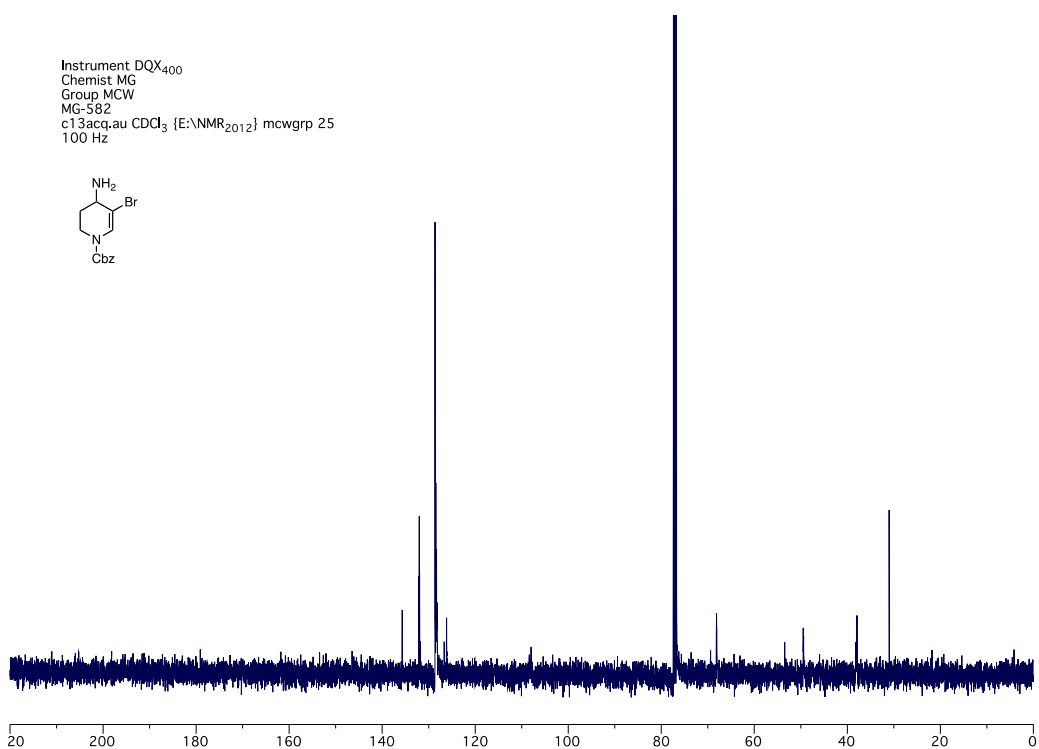
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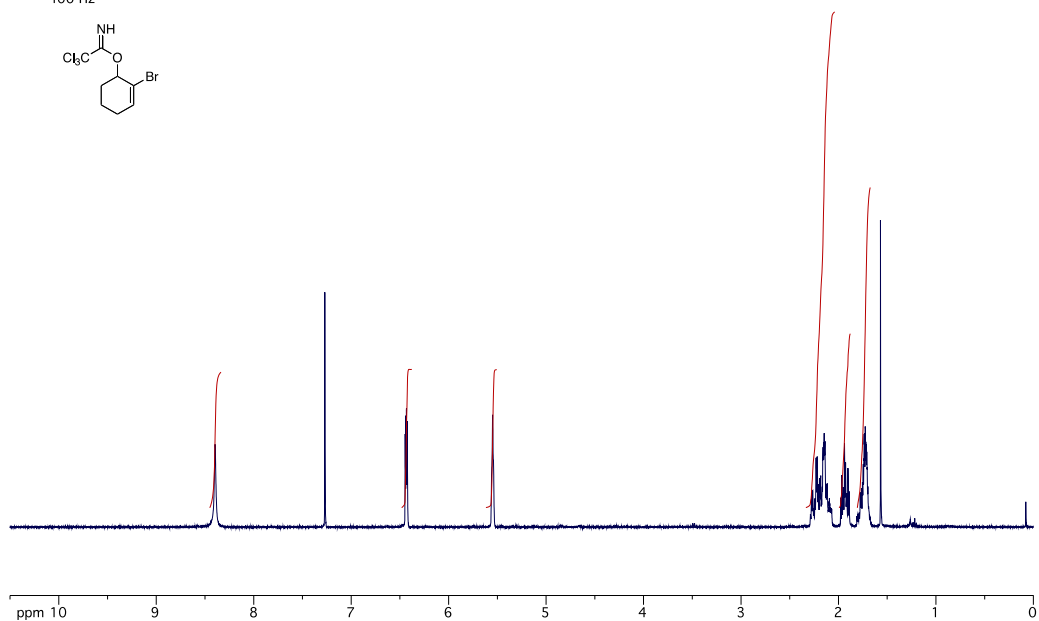
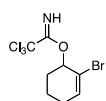
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 Group MCW
 MG-582
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 400 Hz



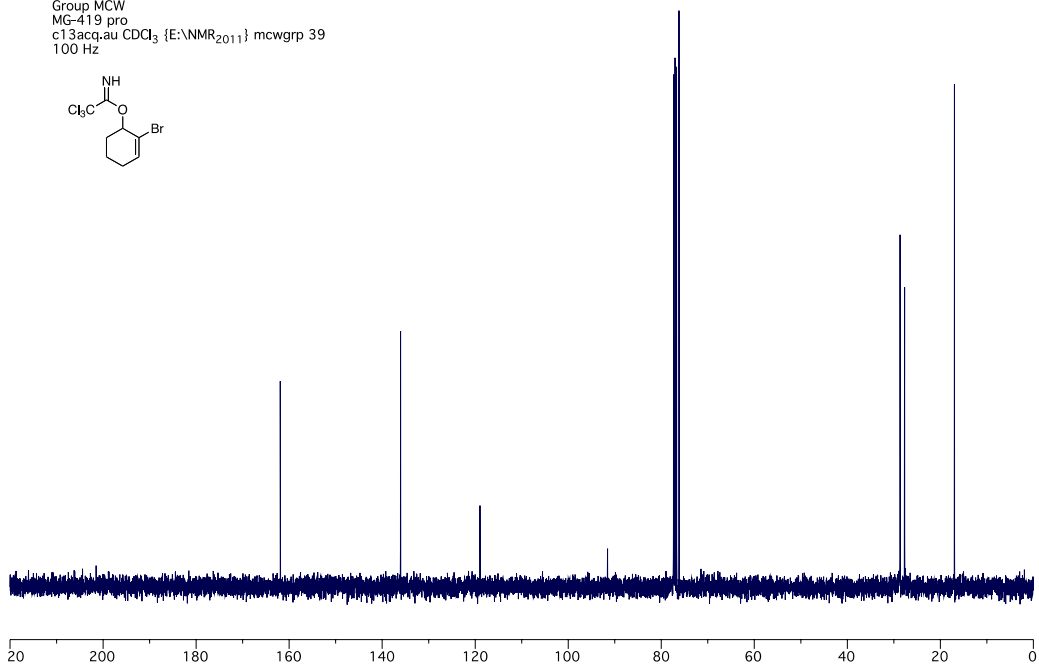
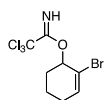
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 Group MCW
 MG-582
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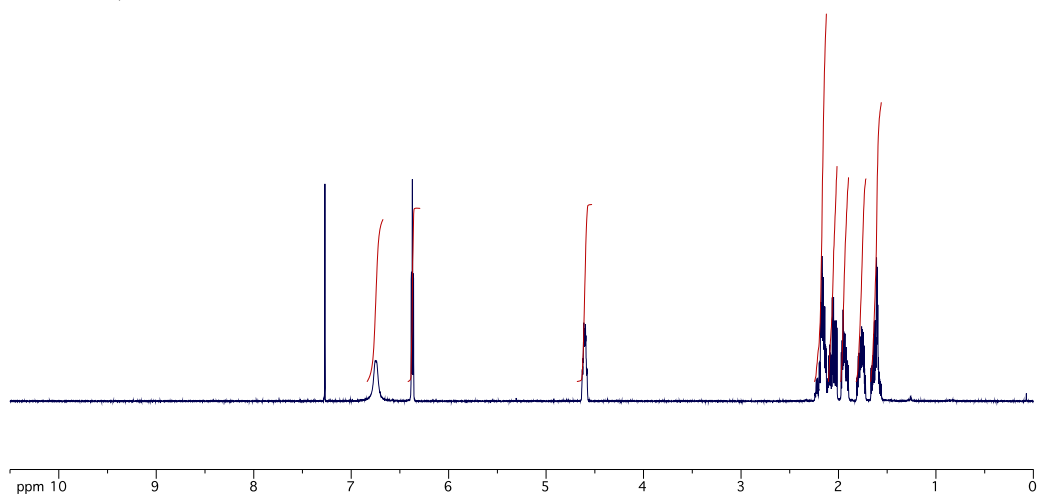
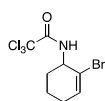
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 Group MCW
 MG-416 spot 1
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 400 Hz



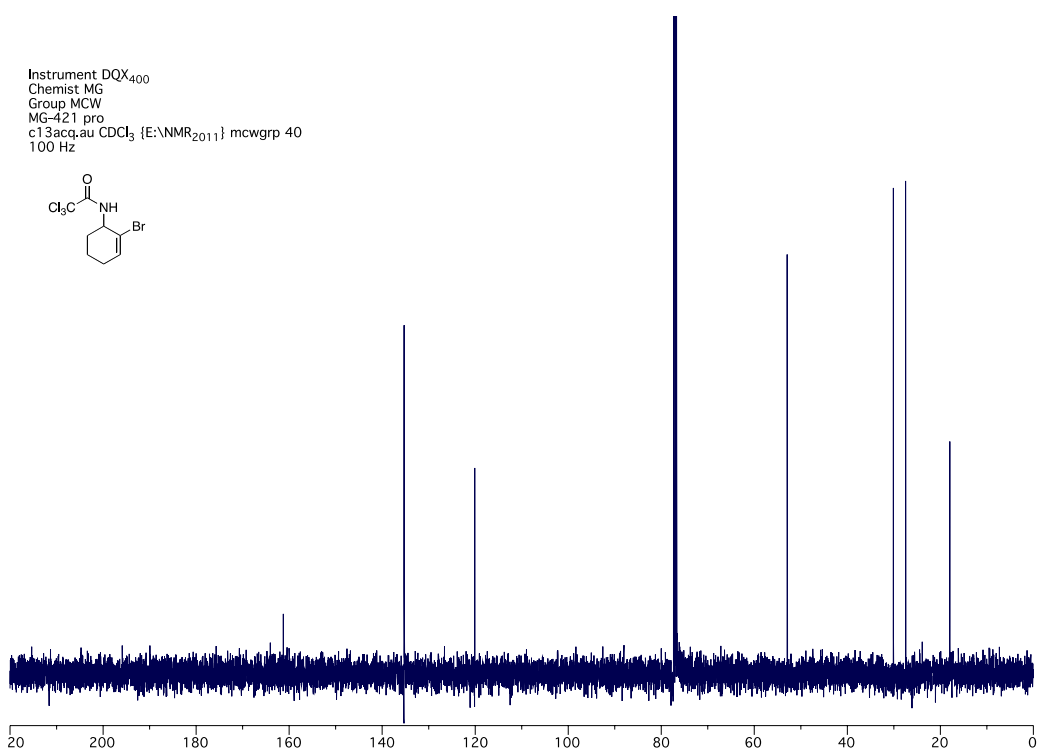
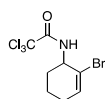
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 Group MCW
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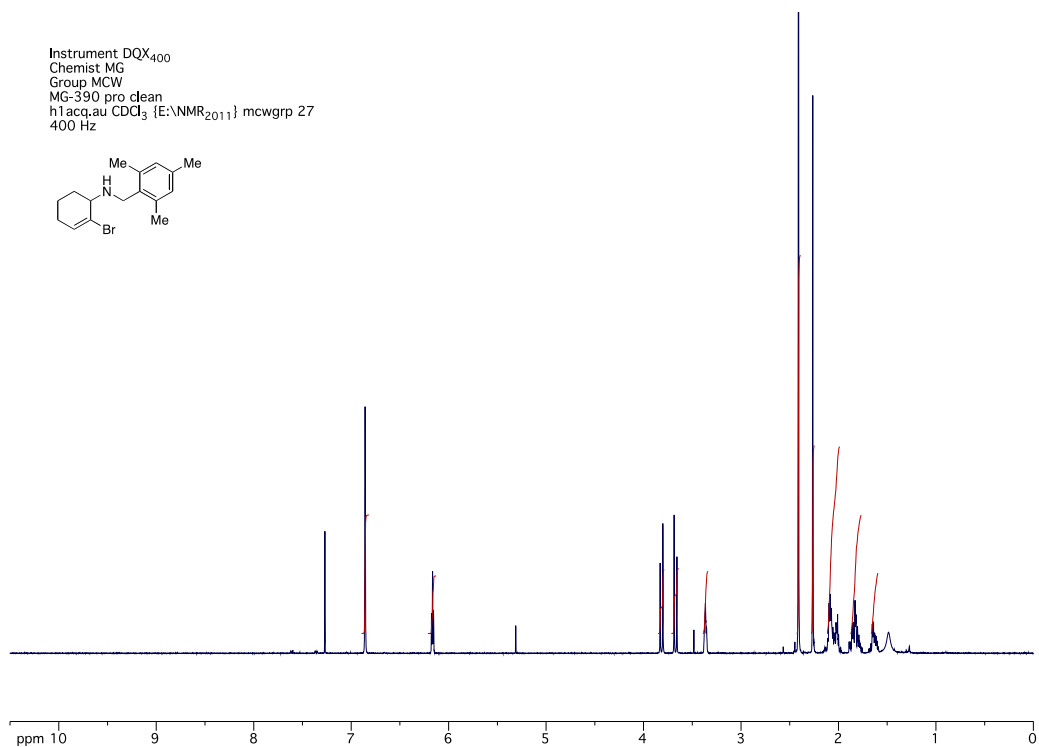
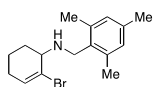
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 Group MCW
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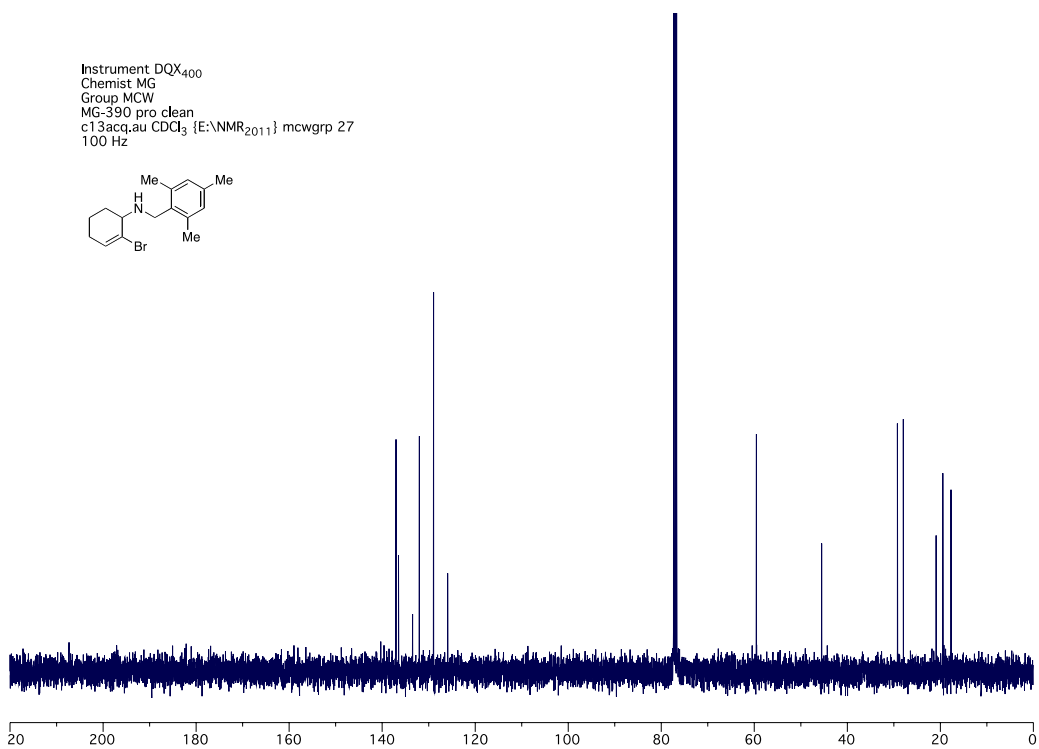
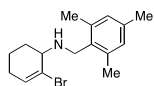
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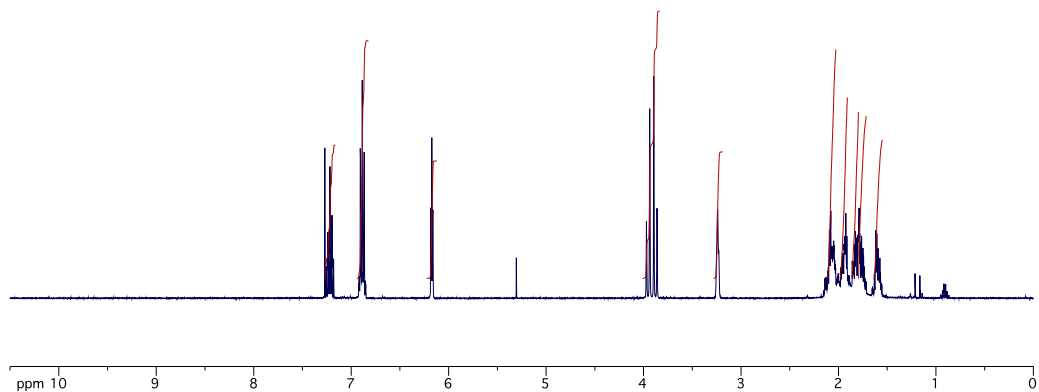
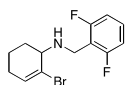
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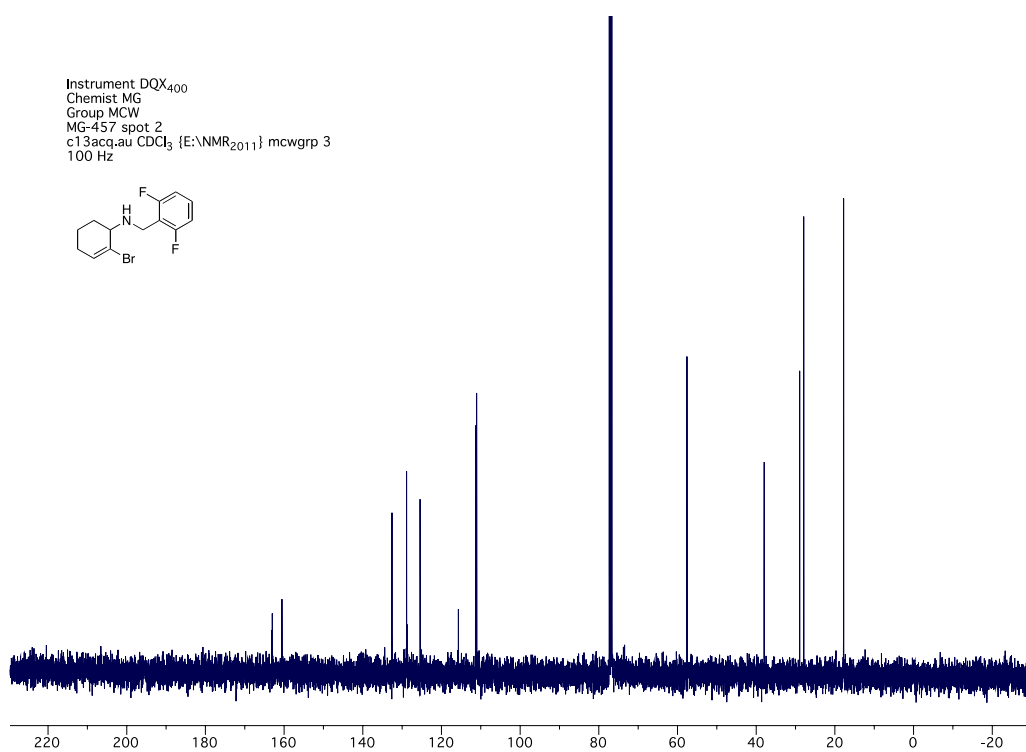
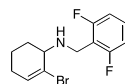
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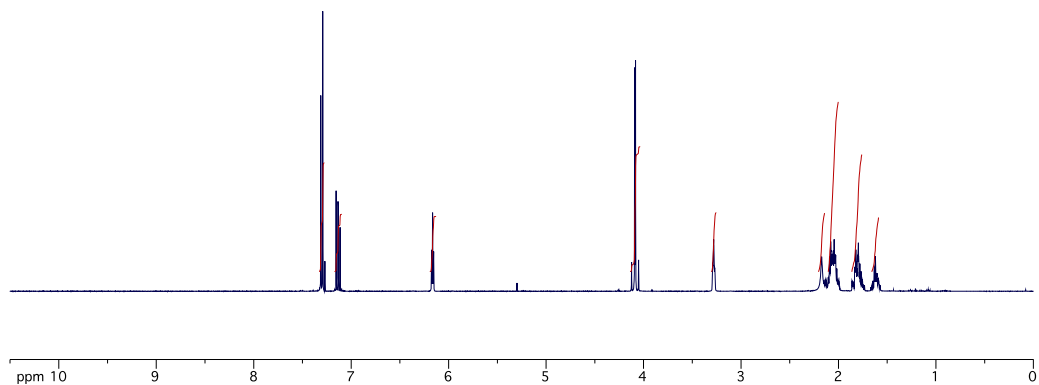
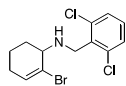
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 Group MCW
 MG-457 spot 2
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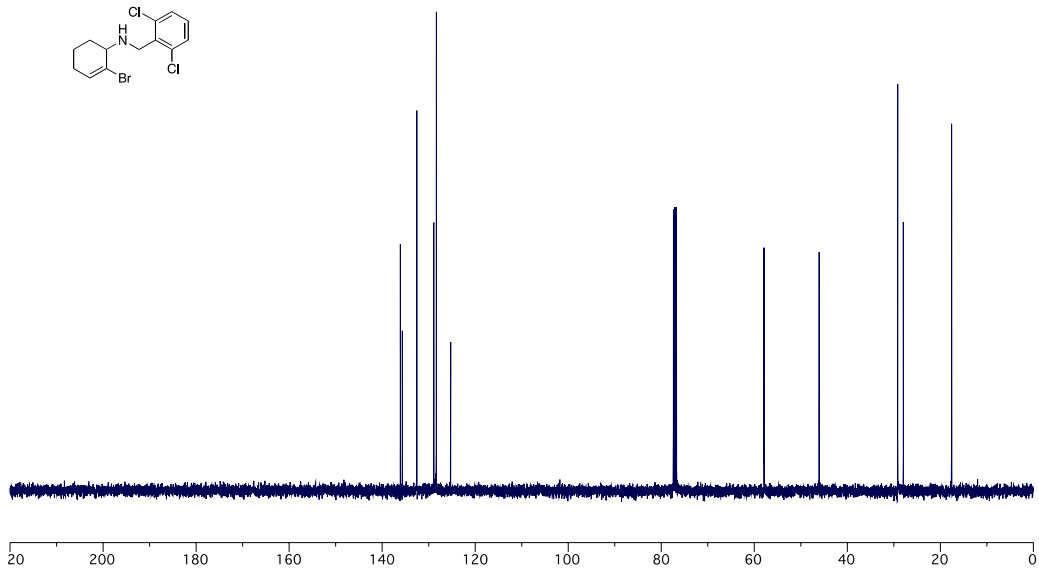
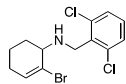
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 MG-457 spot 2
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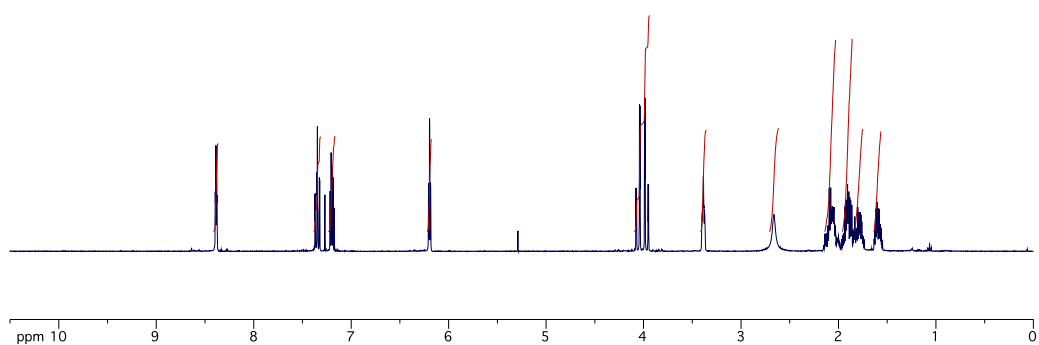
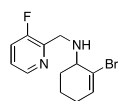
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 MG-508
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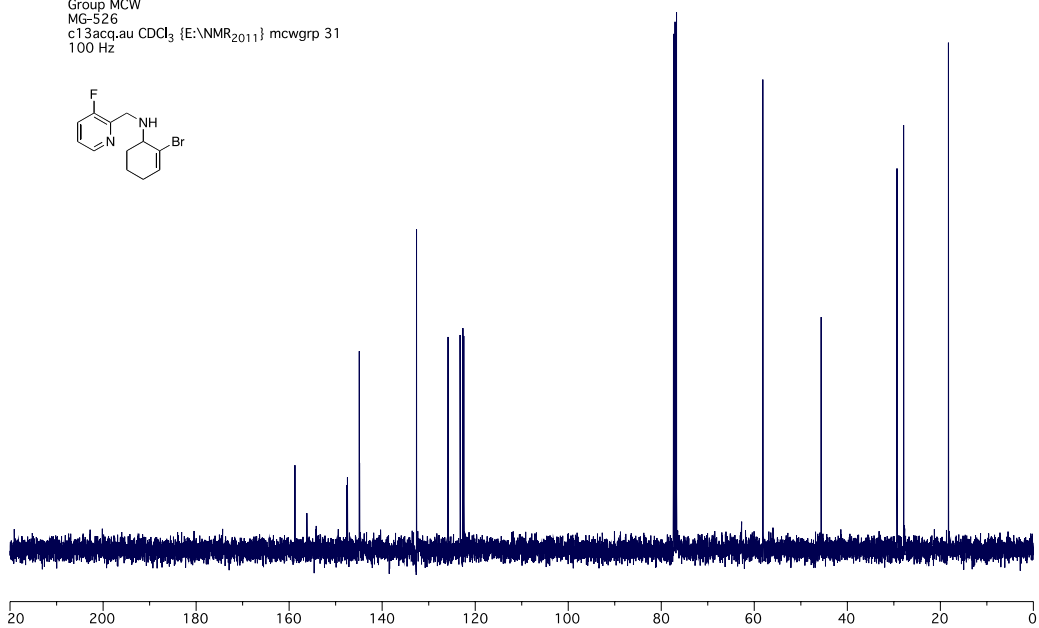
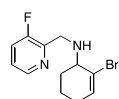
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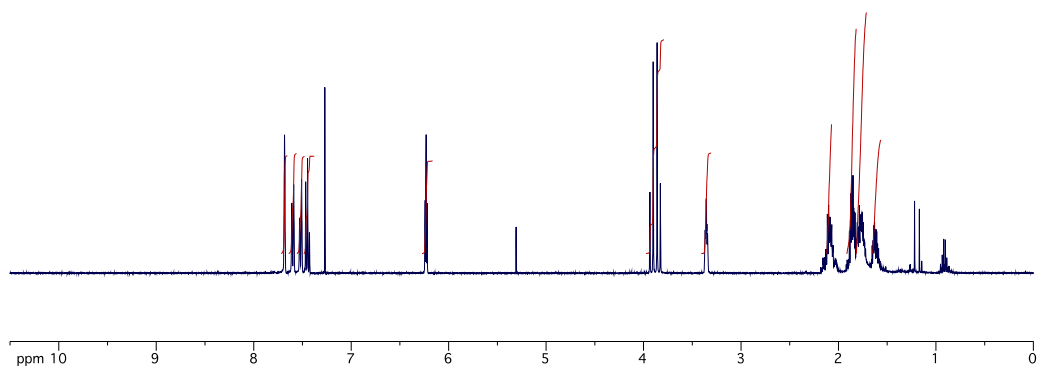
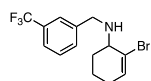
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 Group MCW
 MG-526
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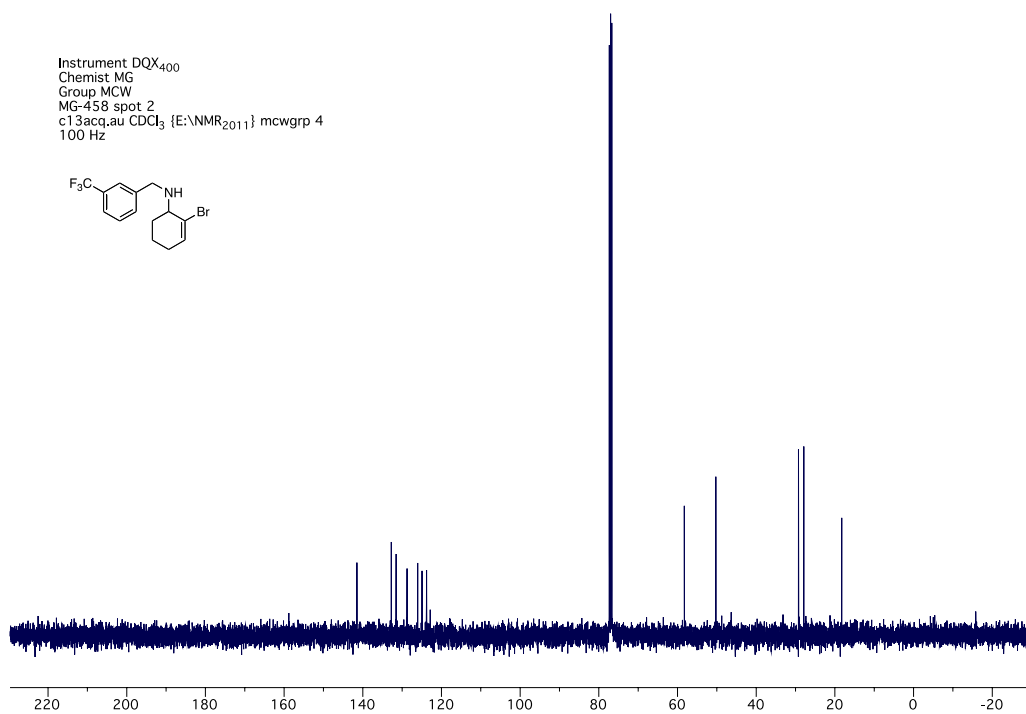
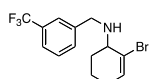
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 Group MCW
 MG-526
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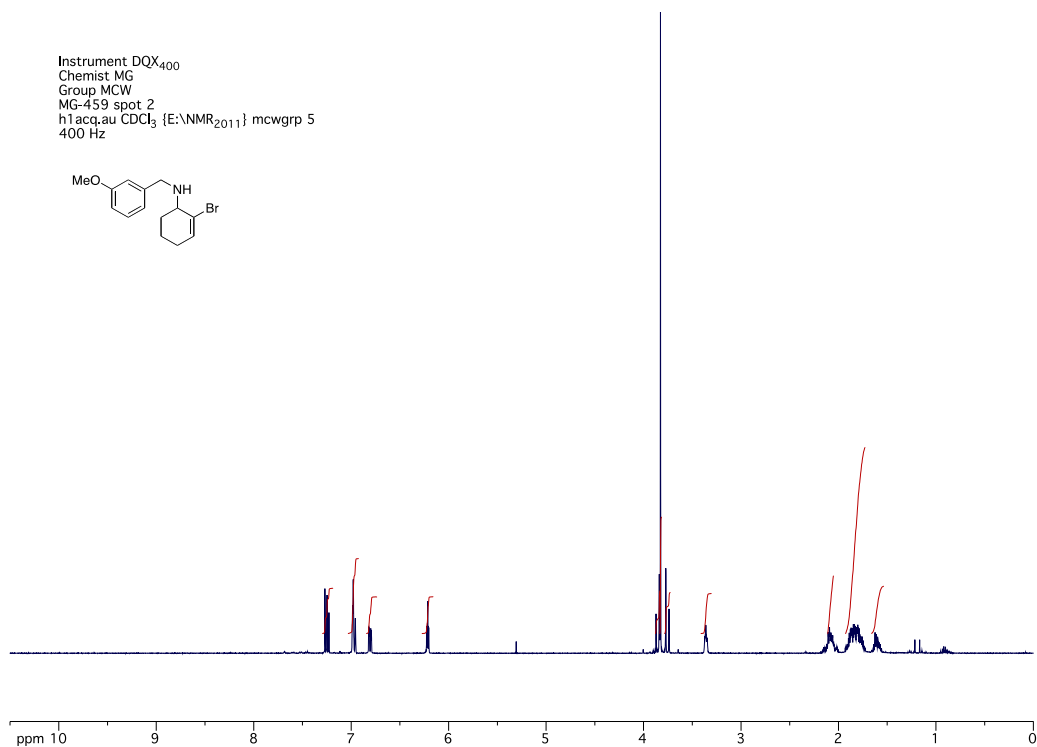
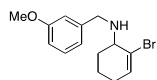
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 Group MCW
 MG-458 spot 2
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 400 Hz



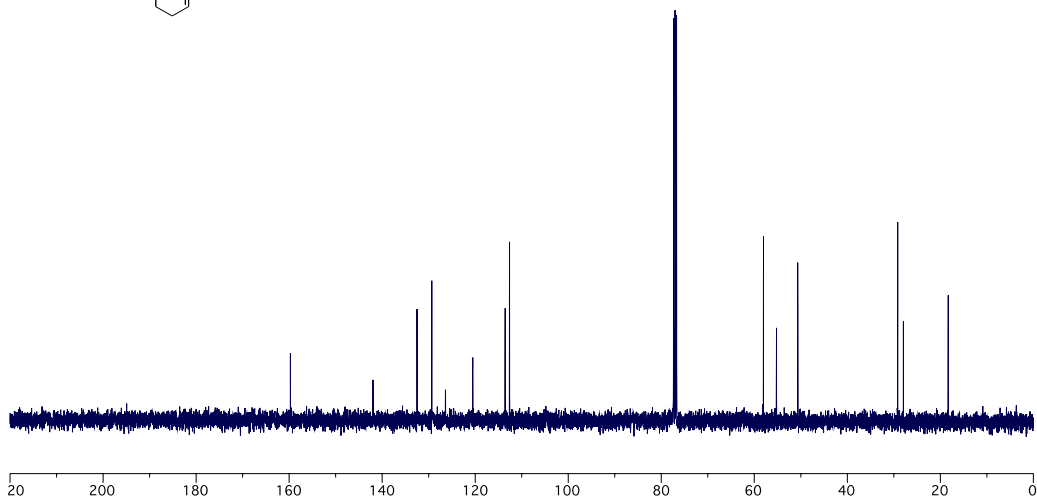
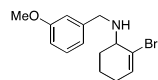
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 Group MCW
 MG-458 spot 2
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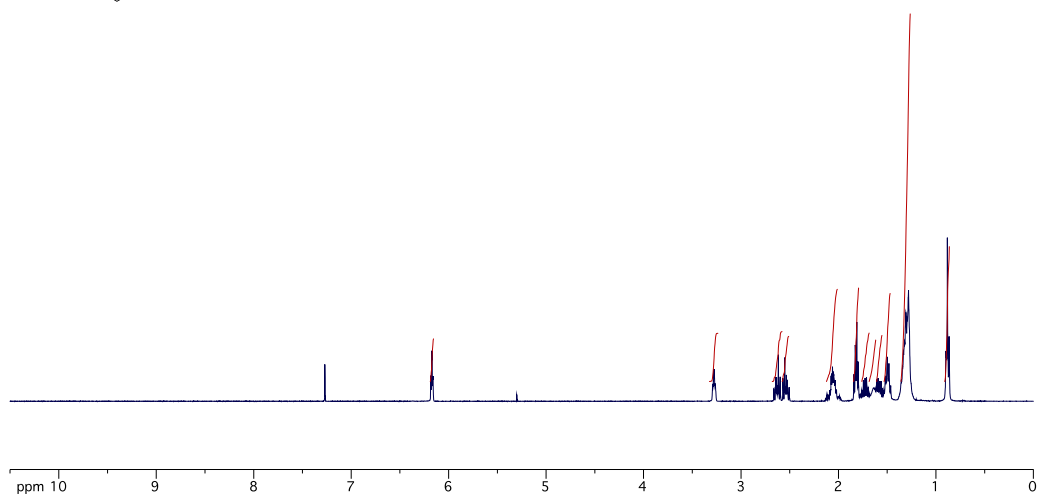
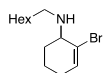
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 Group MCW
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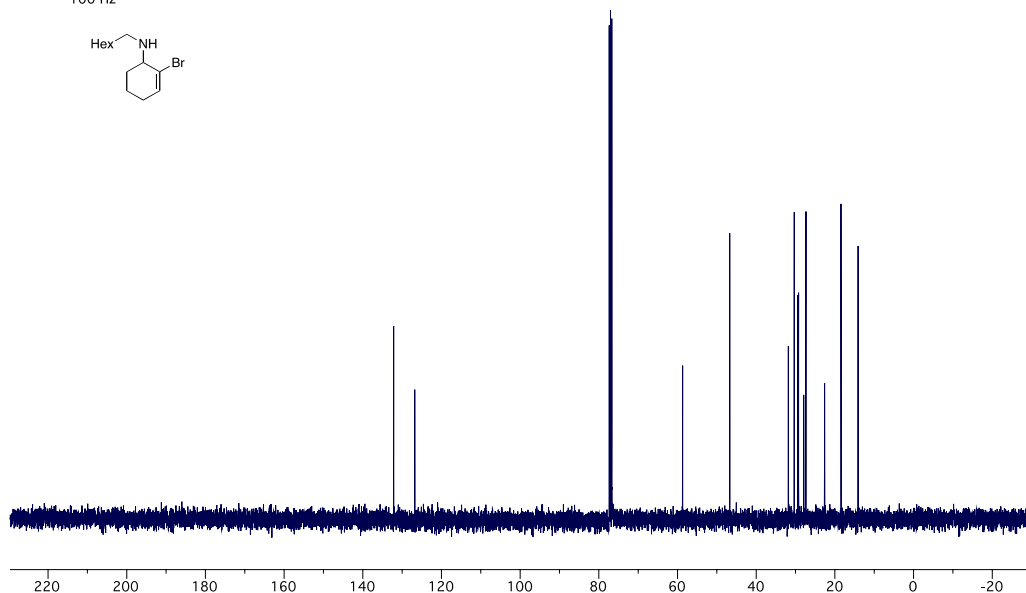
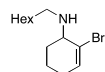
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 MG-459 spot 2
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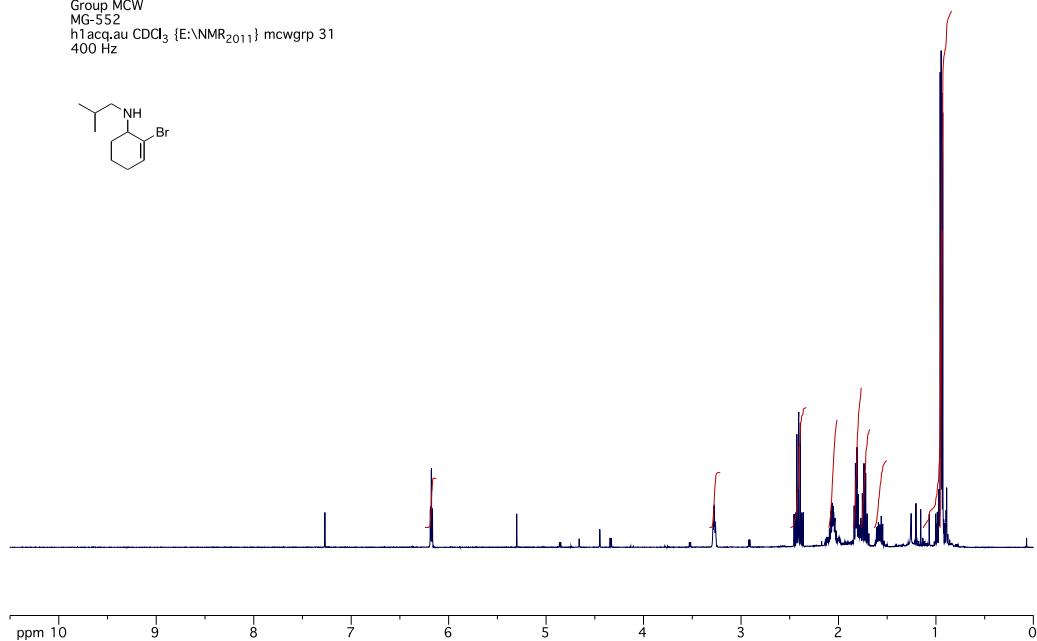
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 Group MCW
 MG-611
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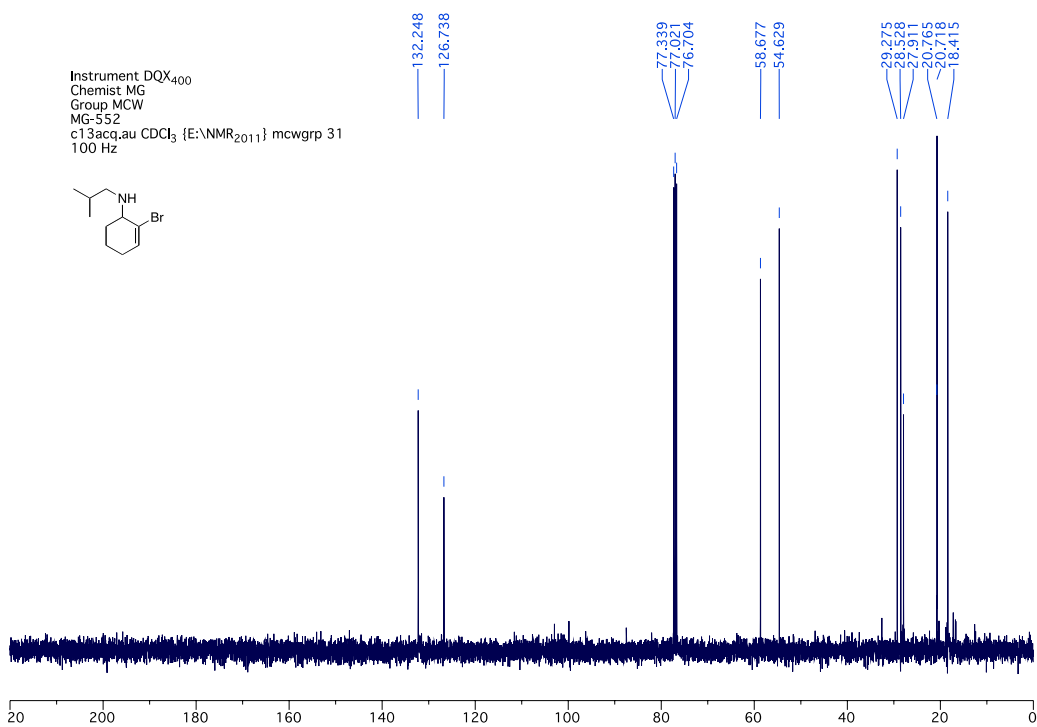
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 MG-611
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 100 Hz



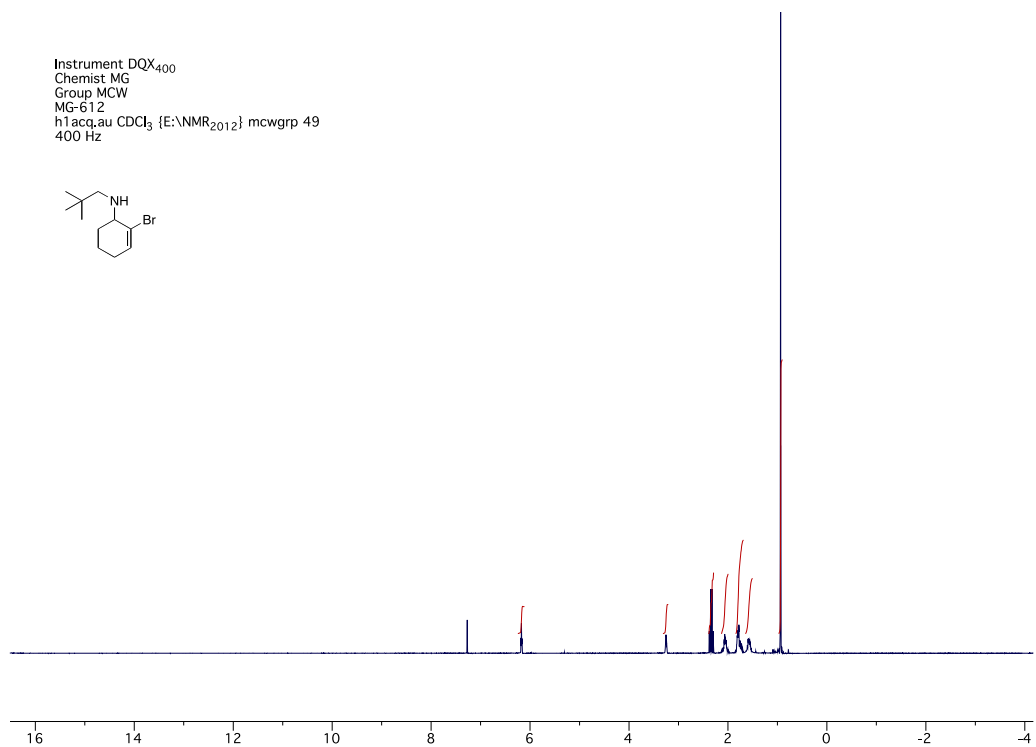
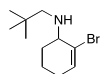
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 Group MCW
 MG-552
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 400 Hz



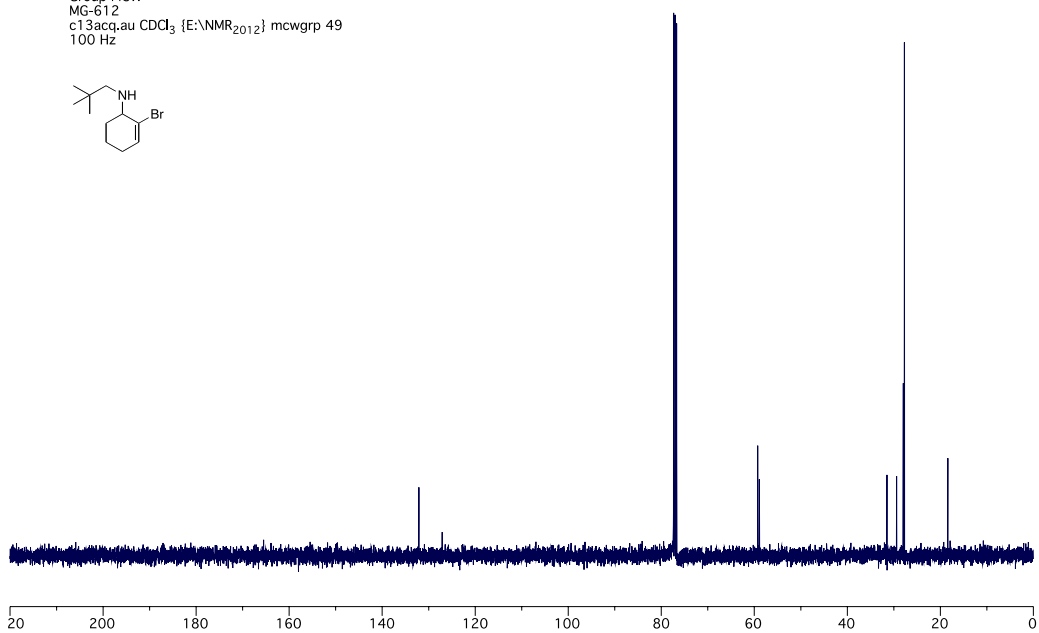
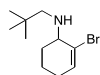
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 Group MCW
 MG-552
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 100 Hz



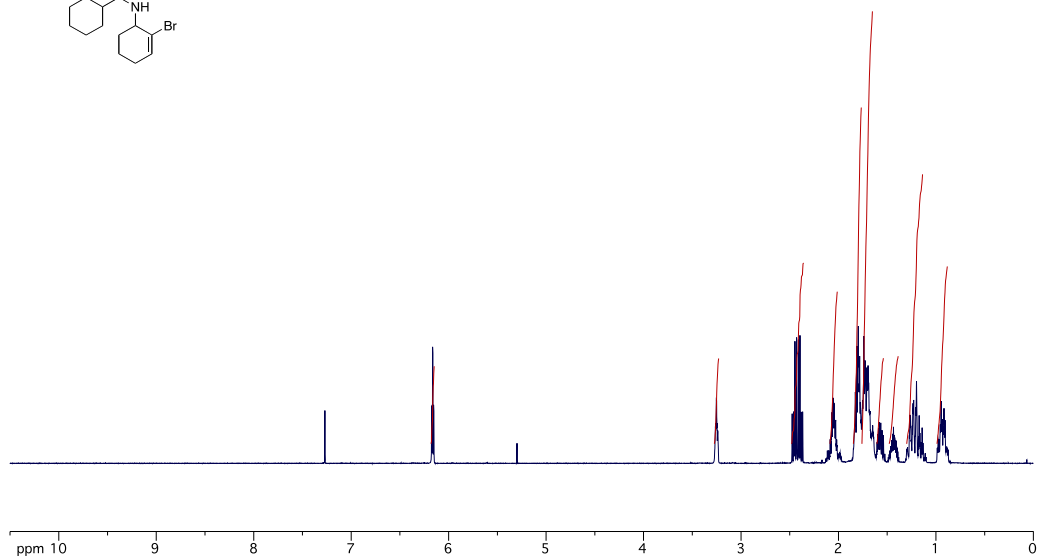
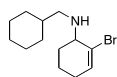
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 Chemist MG
 Group MCW
 MG-612
 h1acq.au CDCl₃ {E:\NMR₂₀₁₂} mcwgrp 49
 400 Hz



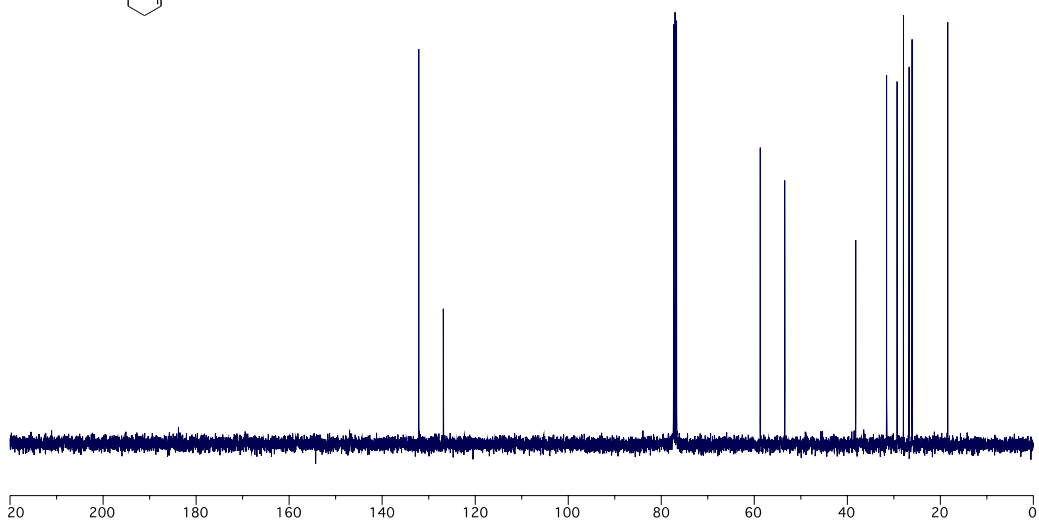
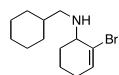
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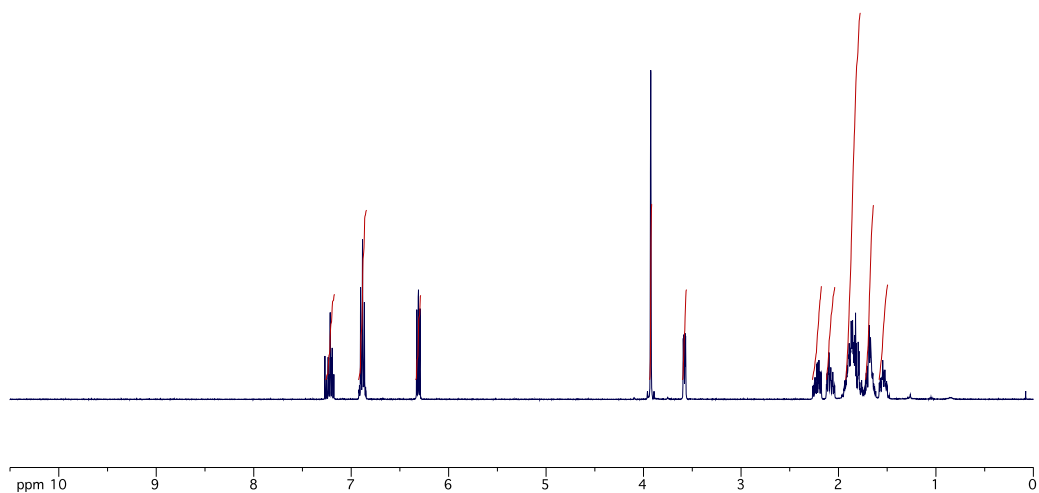
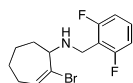
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 Chemist MG
 Group MCW
 MG-509
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 400 Hz



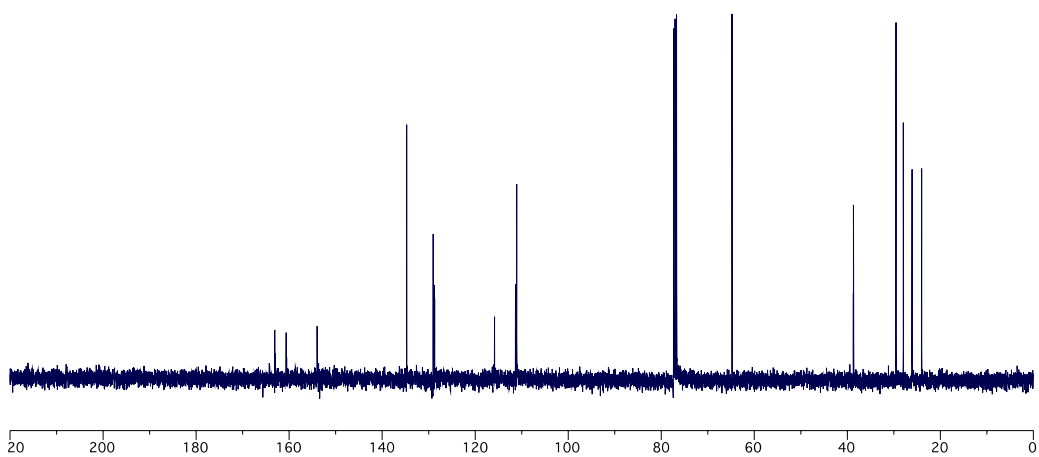
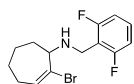
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 Group MCW
 MG-509
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 100 Hz

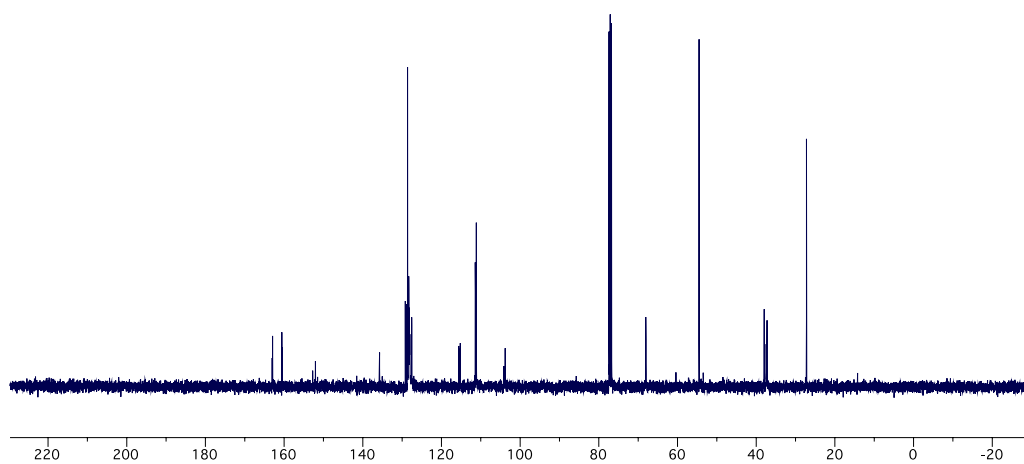
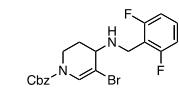


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 Group MCW
 MG-553
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 400 Hz

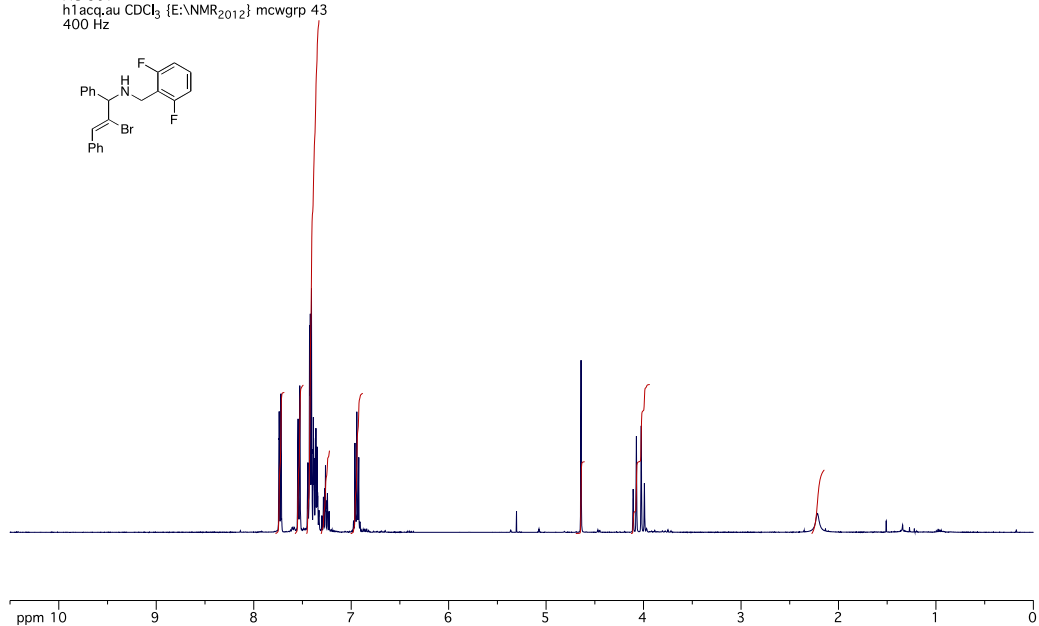
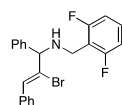


Instrument DQX400
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 Group MCW
 MG-553
 c13acq.au CDCl₃ {E:\NMR₂₀₁₁} mcwgrp 20
 100 Hz

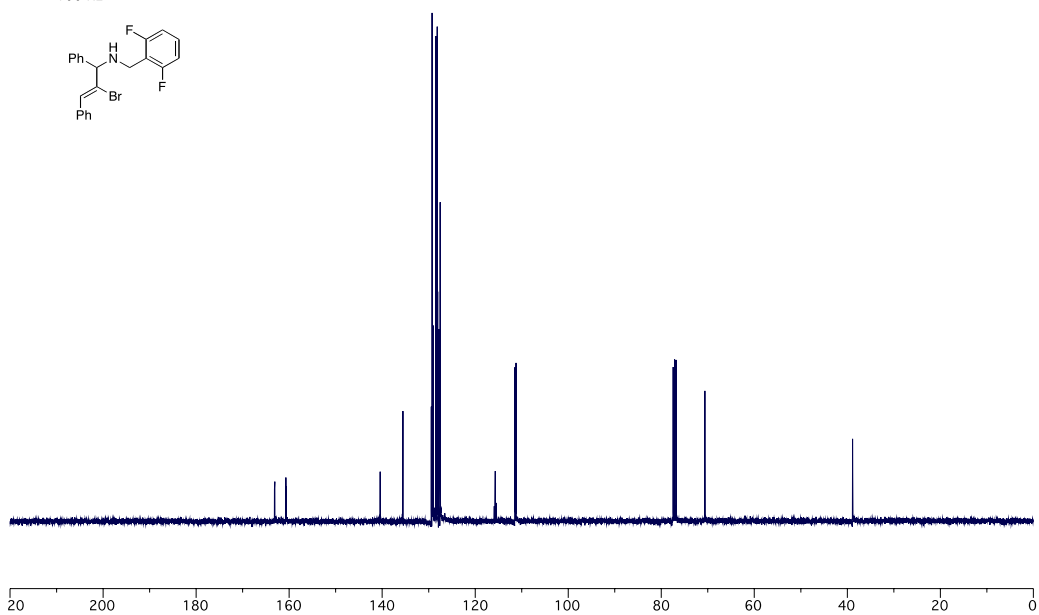
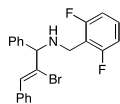


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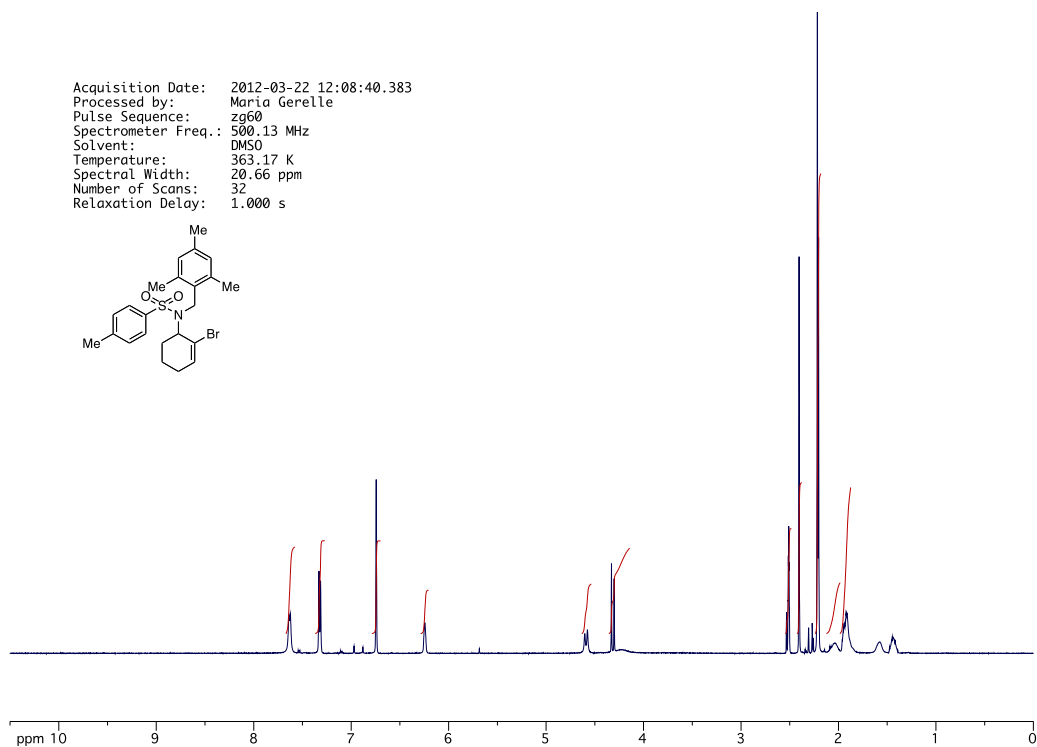
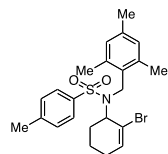
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 Chemist MG
 Group MCW
 MG-561
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 400 Hz



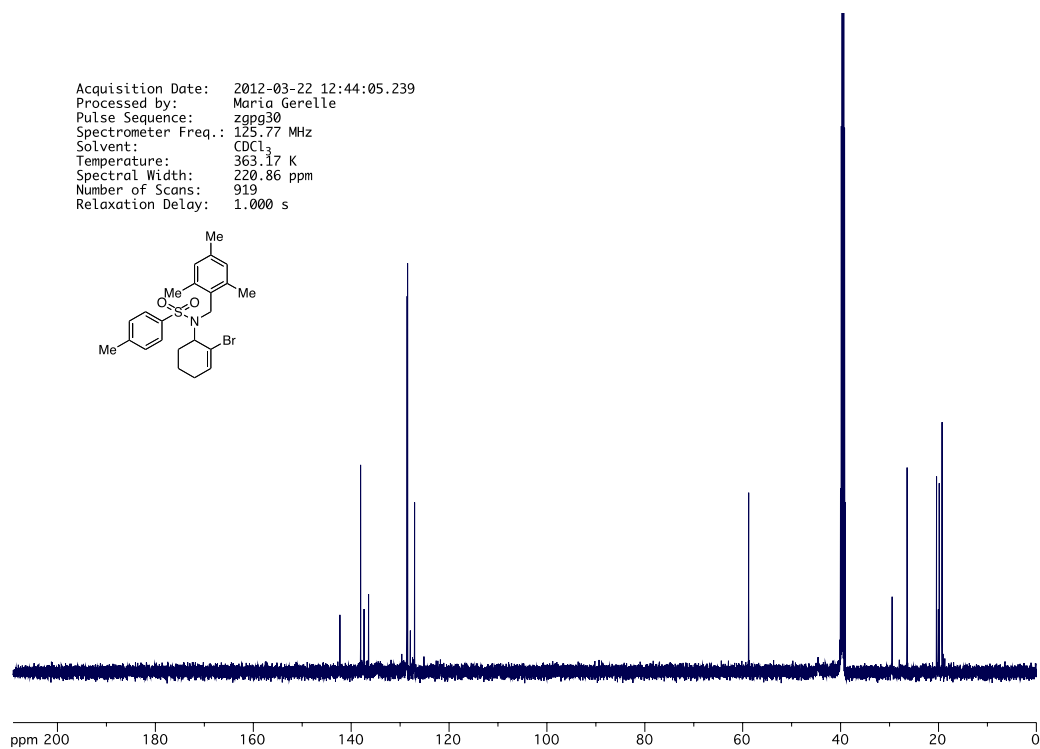
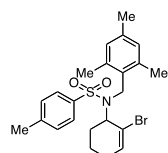
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 Group MCW
 MG-561
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 100 Hz



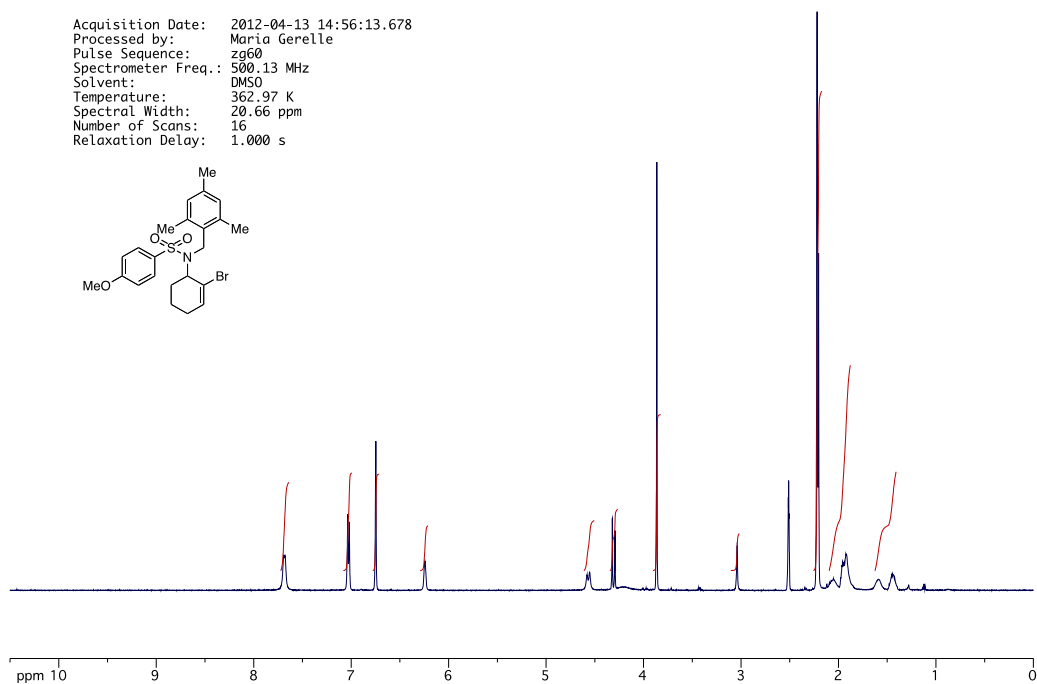
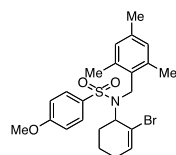
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 Solvent: DMSO
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 Spectral Width: 20.66 ppm
 Number of Scans: 32
 Relaxation Delay: 1.000 s



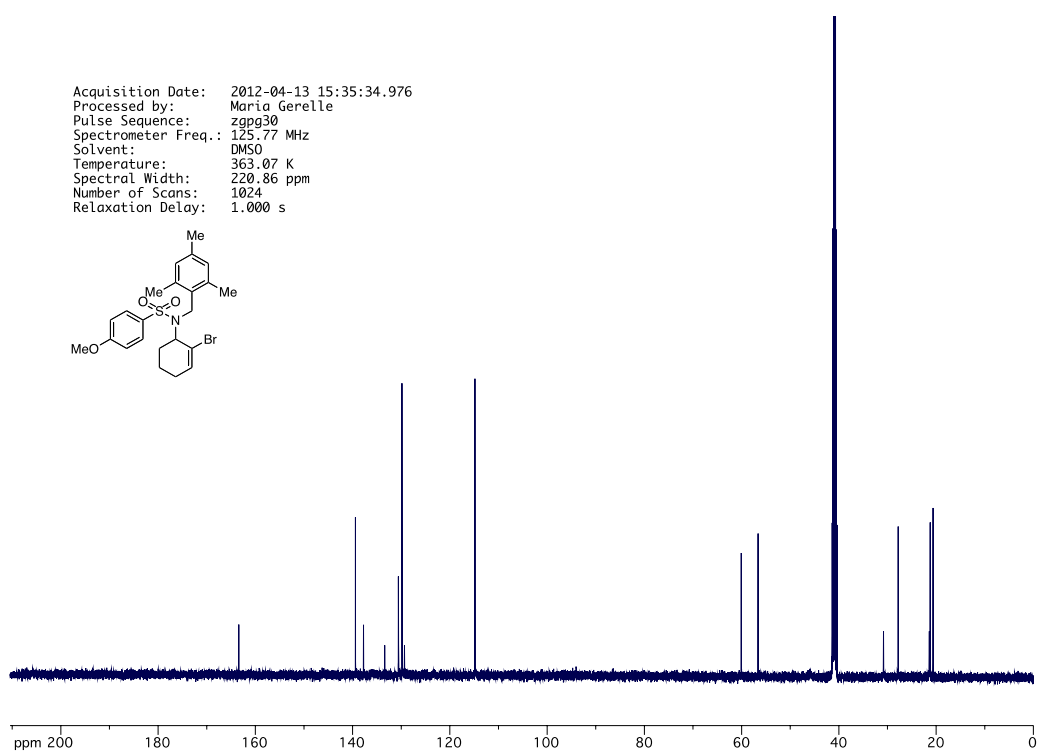
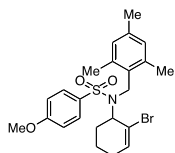
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 Pulse Sequence: zgpg30
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 Spectral Width: 220.86 ppm
 Number of Scans: 919
 Relaxation Delay: 1.000 s



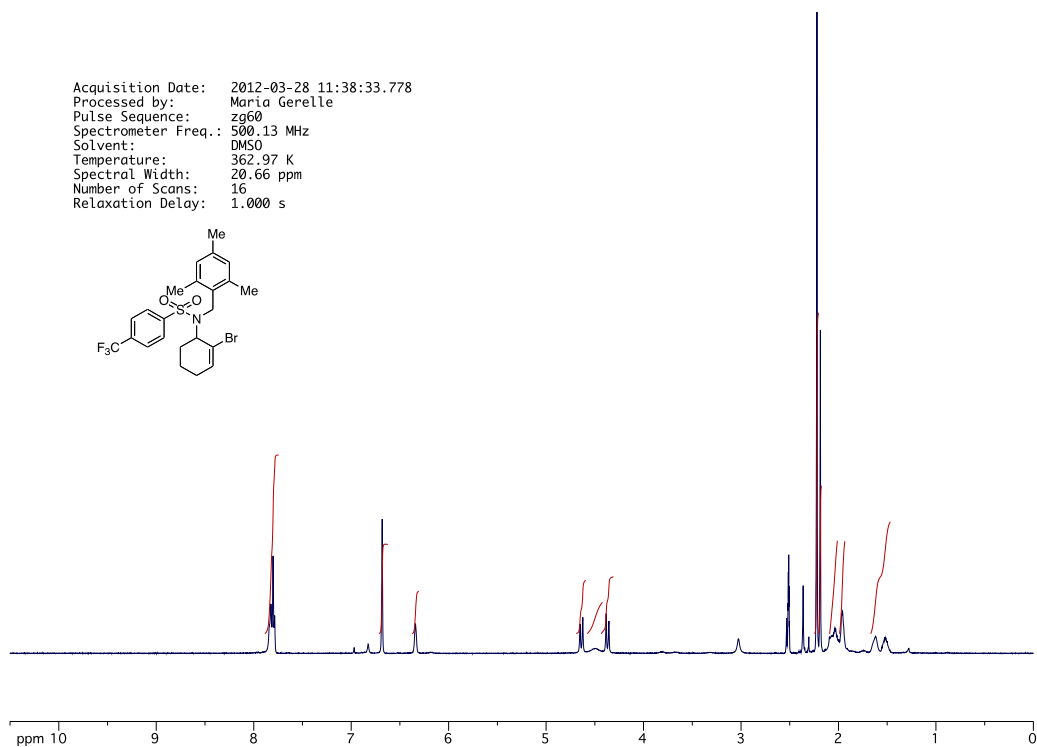
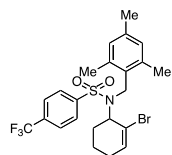
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 Number of Scans: 16
 Relaxation Delay: 1.000 s



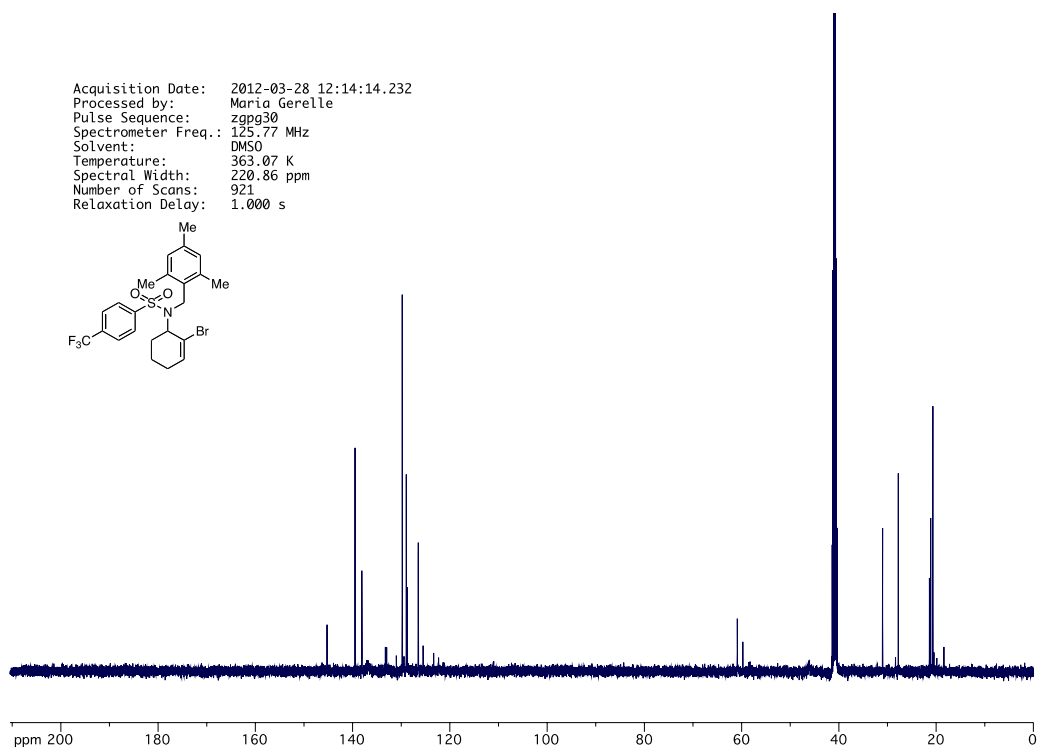
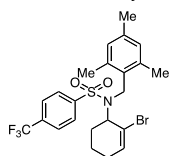
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 Pulse Sequence: zgpg30
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 Solvent: DMSO
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 Spectral Width: 220.86 ppm
 Number of Scans: 1024
 Relaxation Delay: 1.000 s



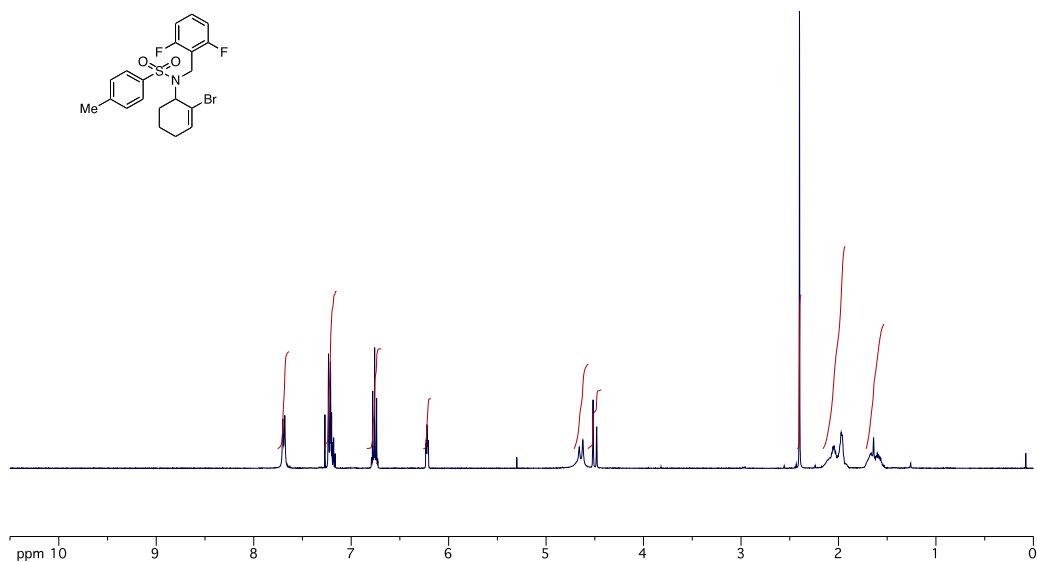
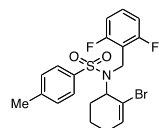
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 Spectrometer Freq.: 500.13 MHz
 Solvent: DMSO
 Temperature: 362.97 K
 Spectral Width: 20.66 ppm
 Number of Scans: 16
 Relaxation Delay: 1.000 s



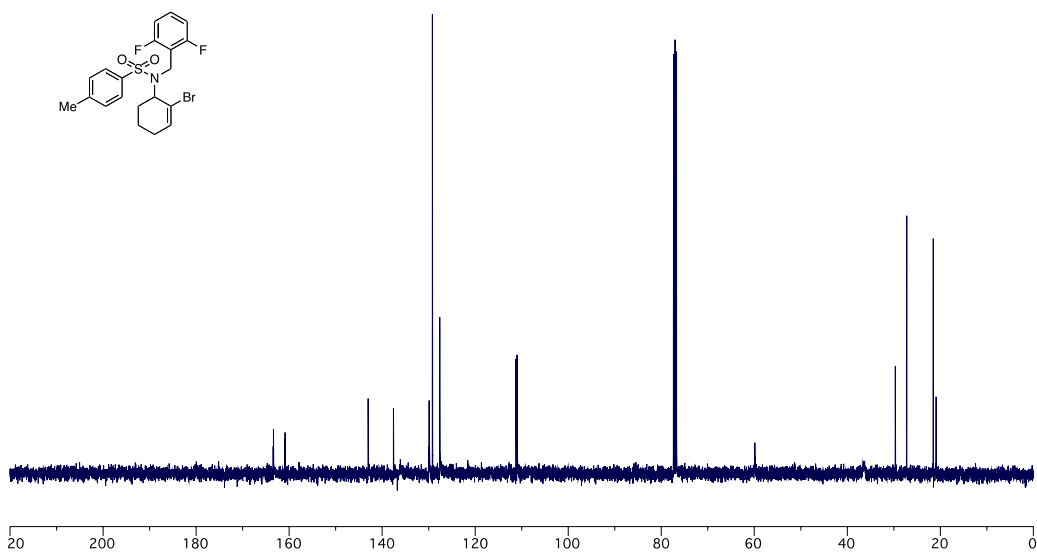
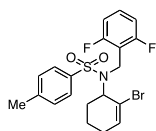
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 Pulse Sequence: zgpg30
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 Solvent: DMSO
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 Spectral Width: 220.86 ppm
 Number of Scans: 921
 Relaxation Delay: 1.000 s



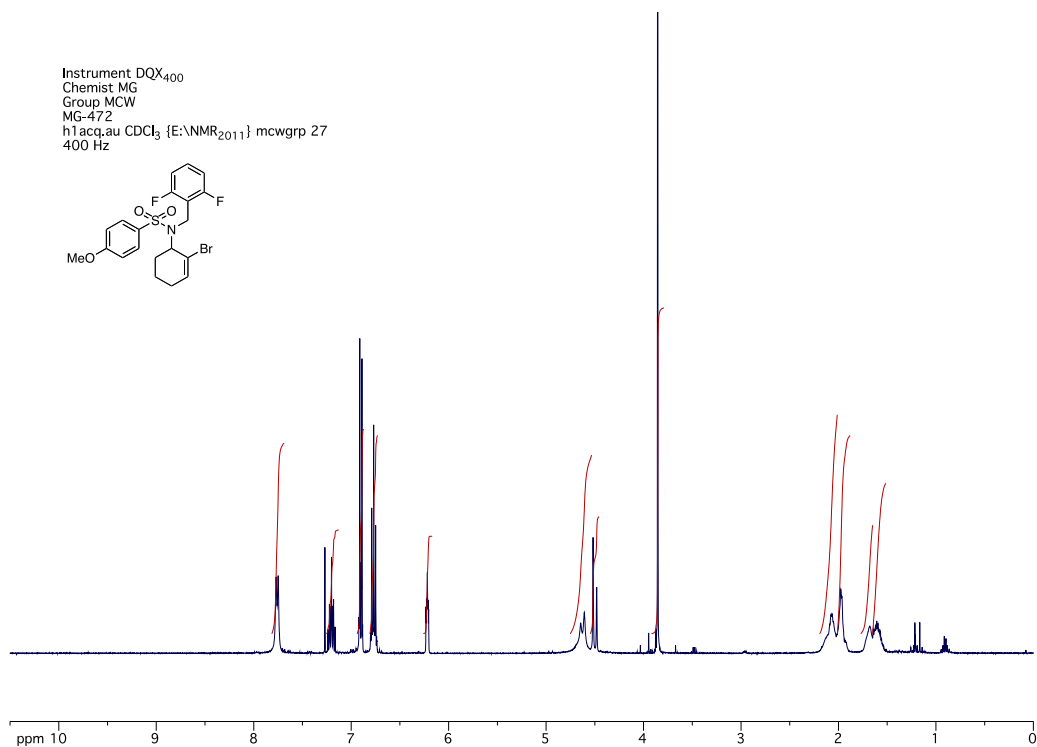
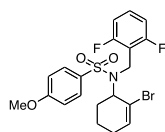
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 Chemist MG
 Group MCW
 MG-460
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 400 Hz



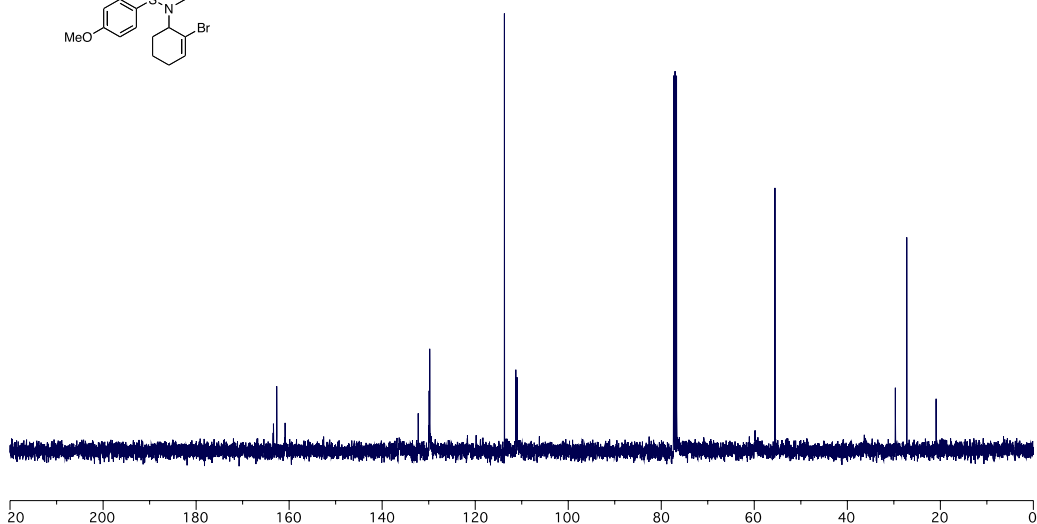
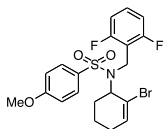
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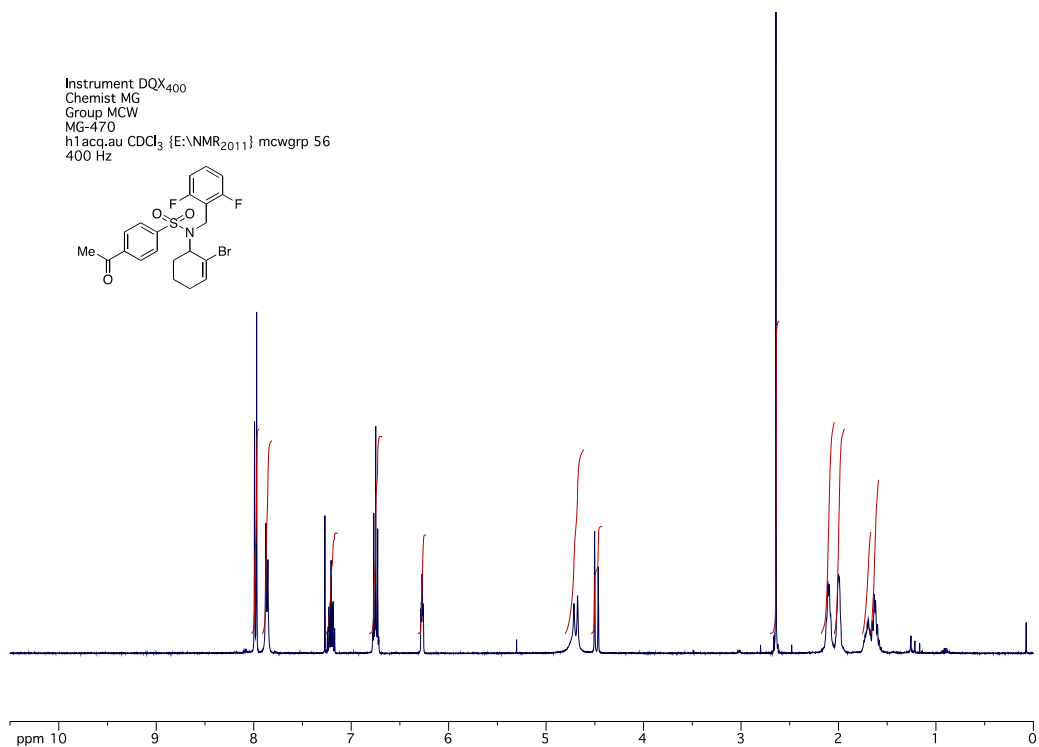
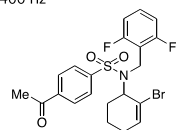
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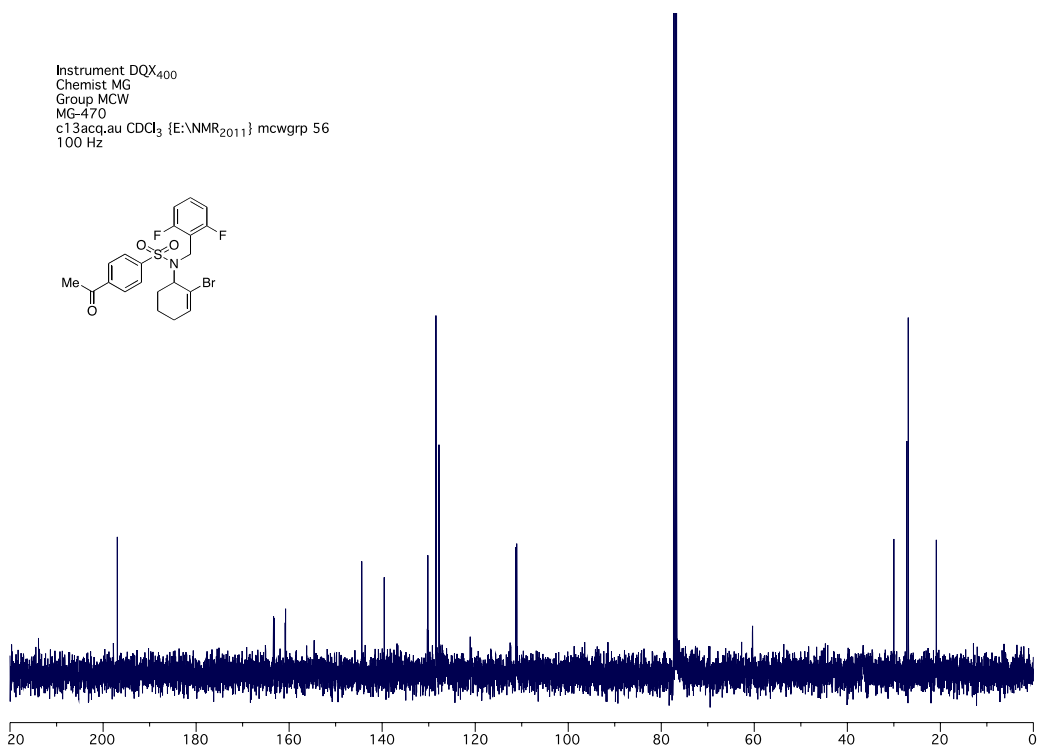
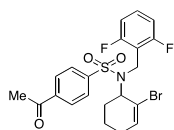
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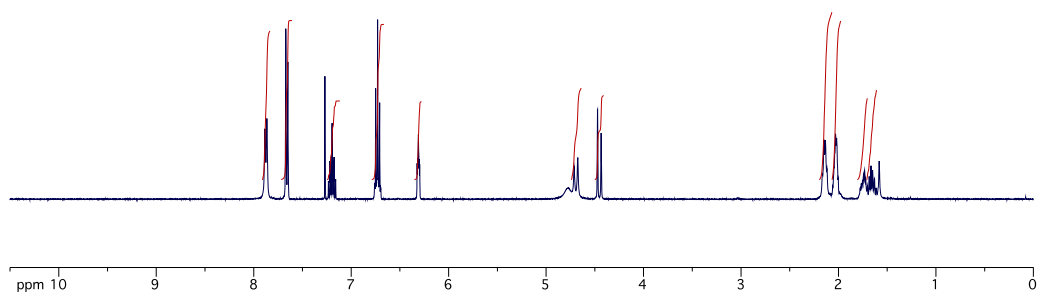
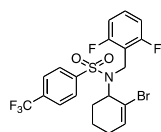
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 Group MCW
 MG-470
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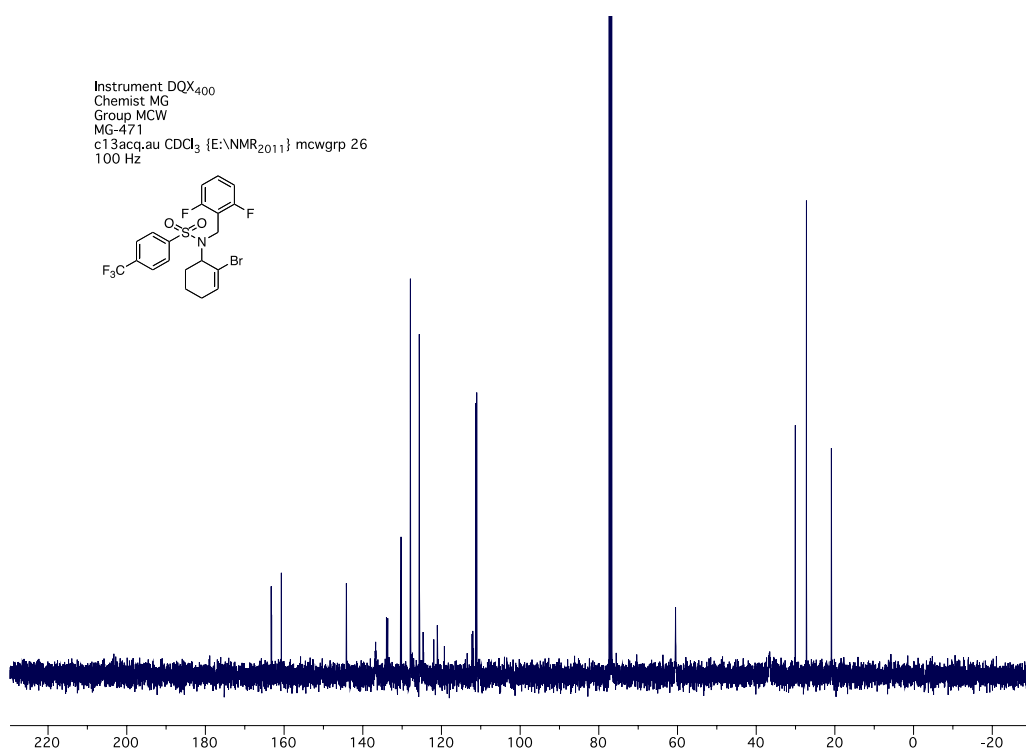
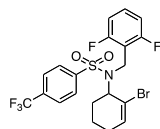
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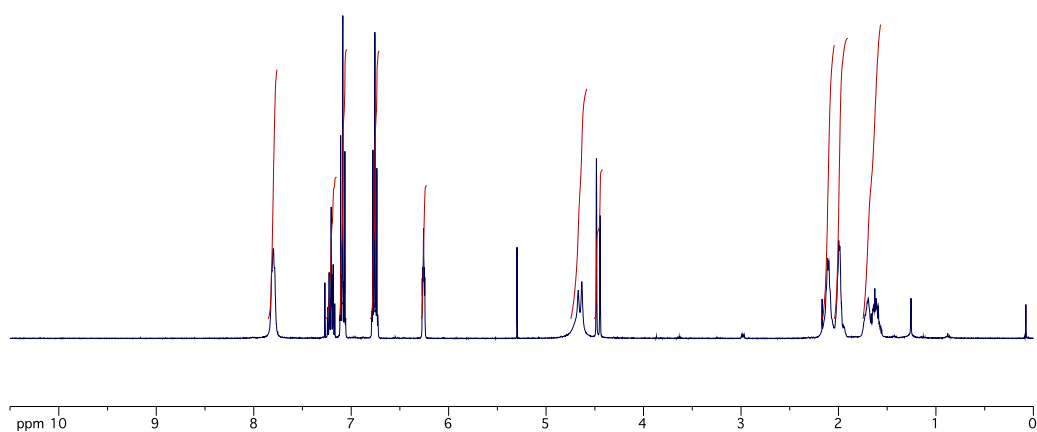
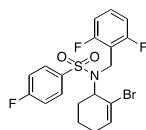
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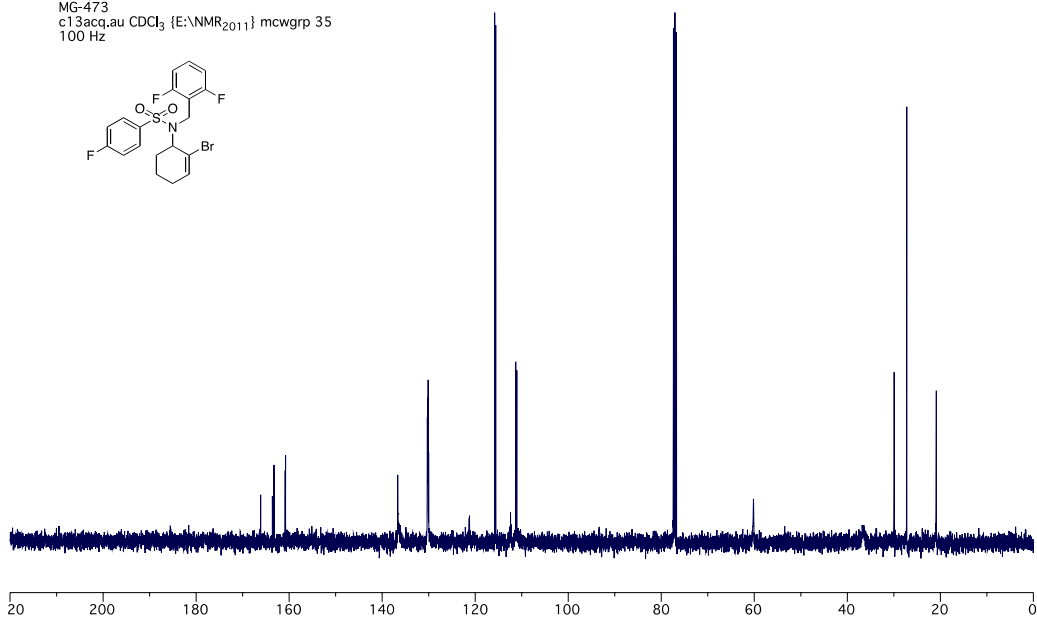
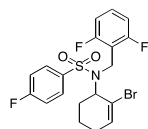
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 Group MCW
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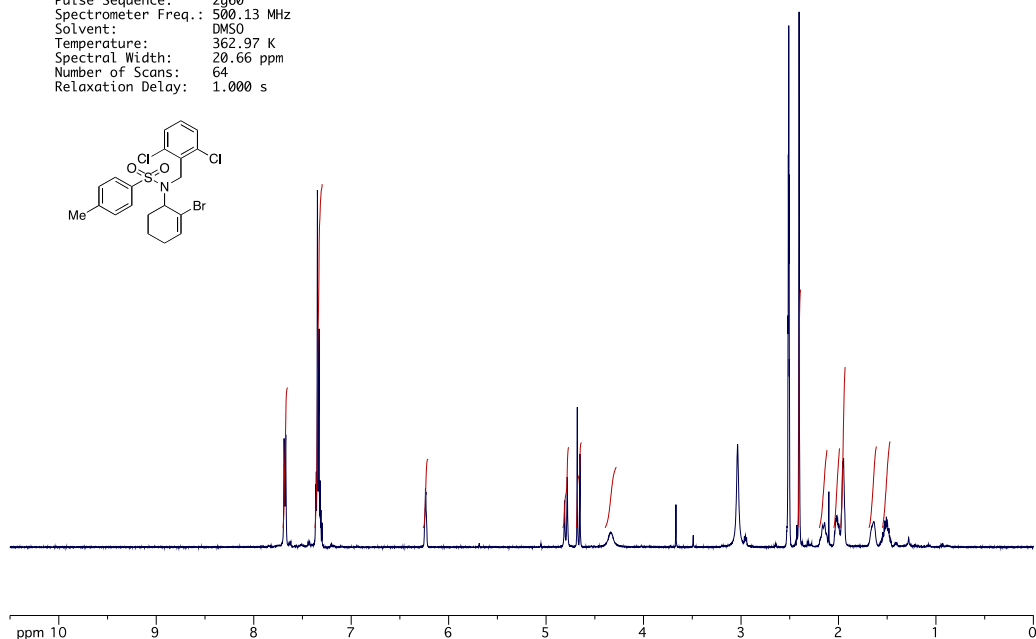
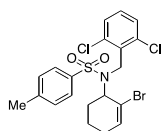
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 Group MCW
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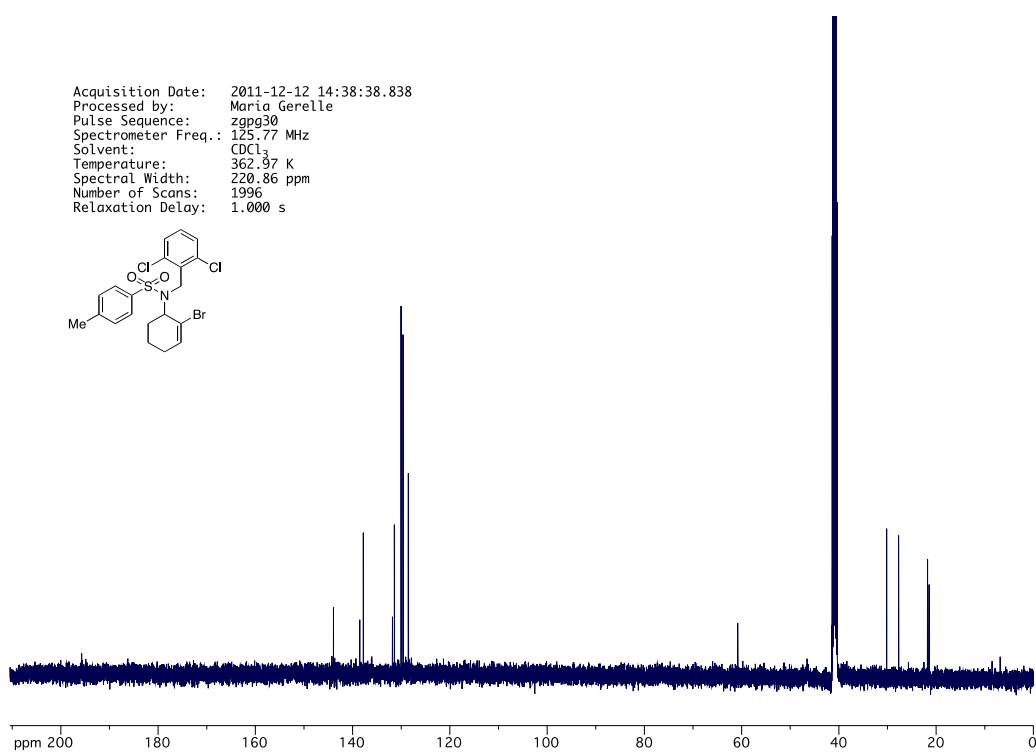
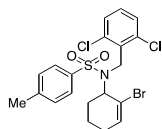
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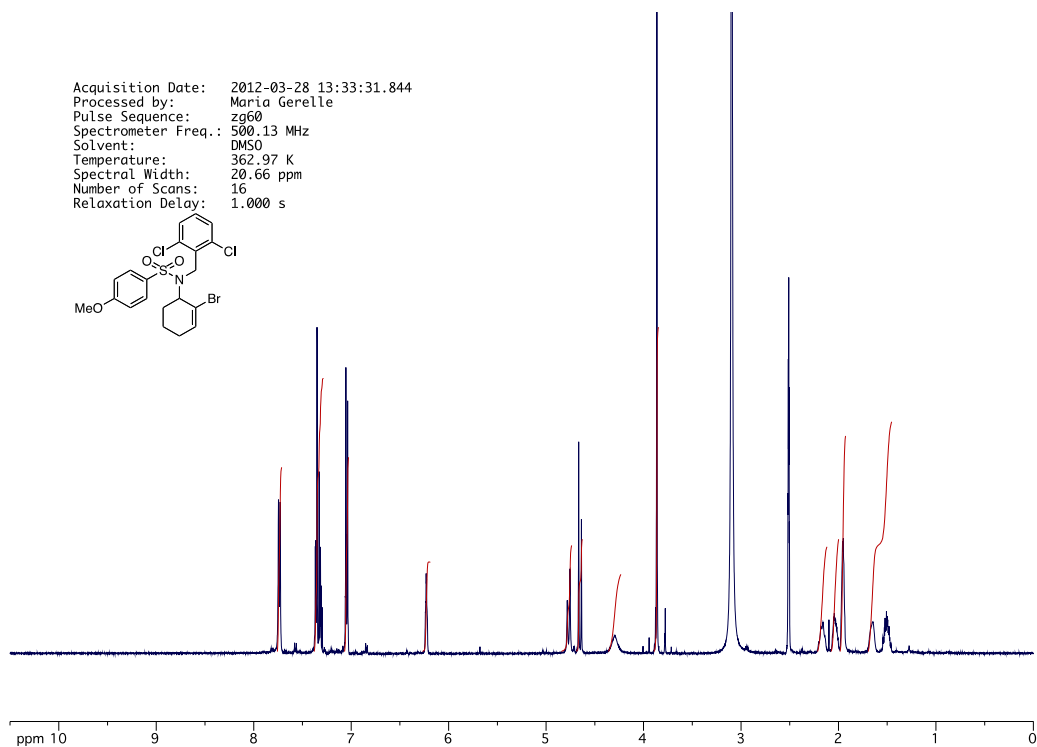
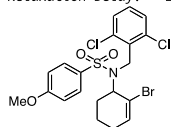
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 Temperature: 362.97 K
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 Number of Scans: 64
 Relaxation Delay: 1.000 s



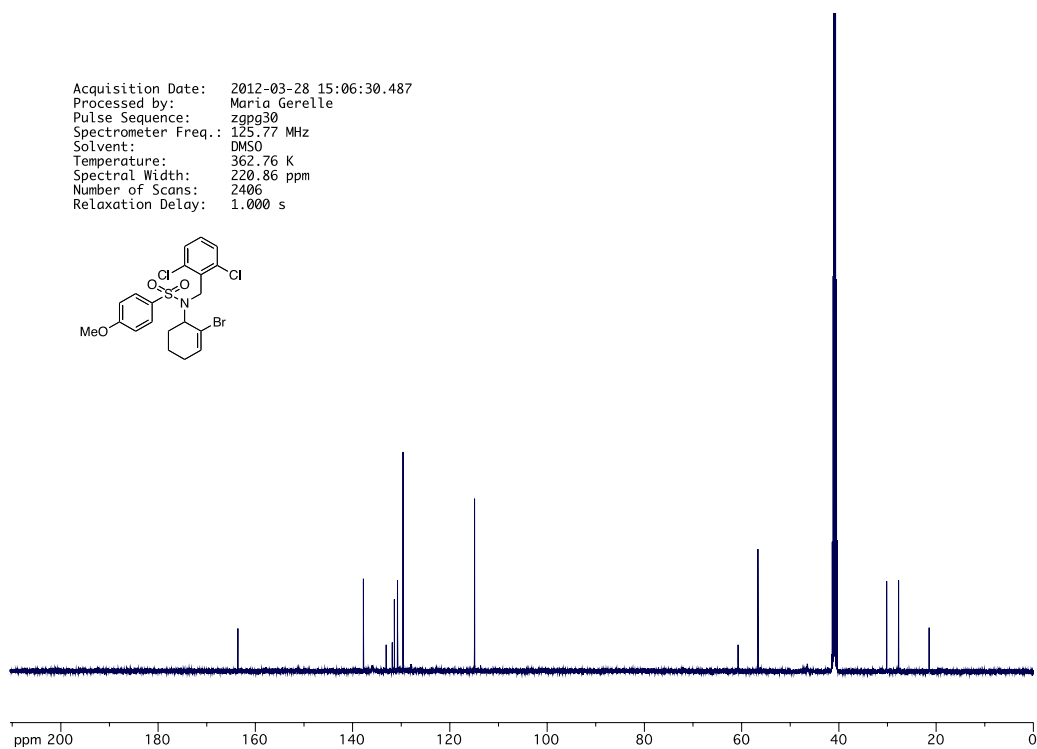
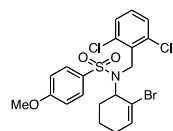
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 Pulse Sequence: zgpg30
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 Spectral Width: 220.86 ppm
 Number of Scans: 1996
 Relaxation Delay: 1.000 s



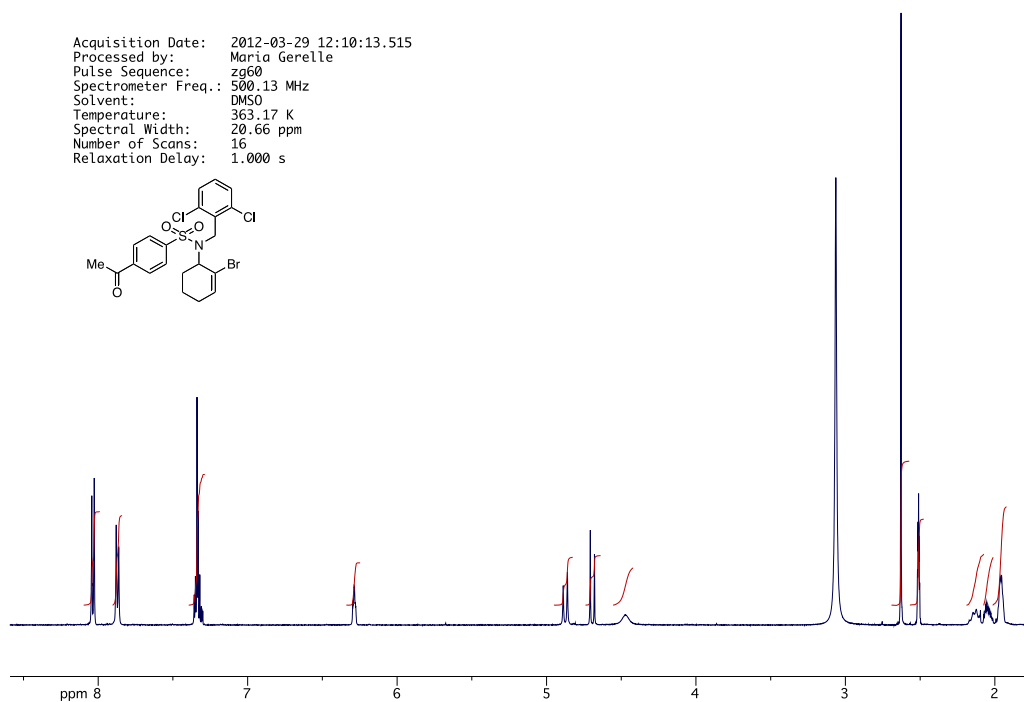
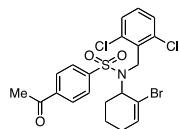
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 Pulse Sequence: zg60
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 Solvent: DMSO
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 Number of Scans: 16
 Relaxation Delay: 1.000 s



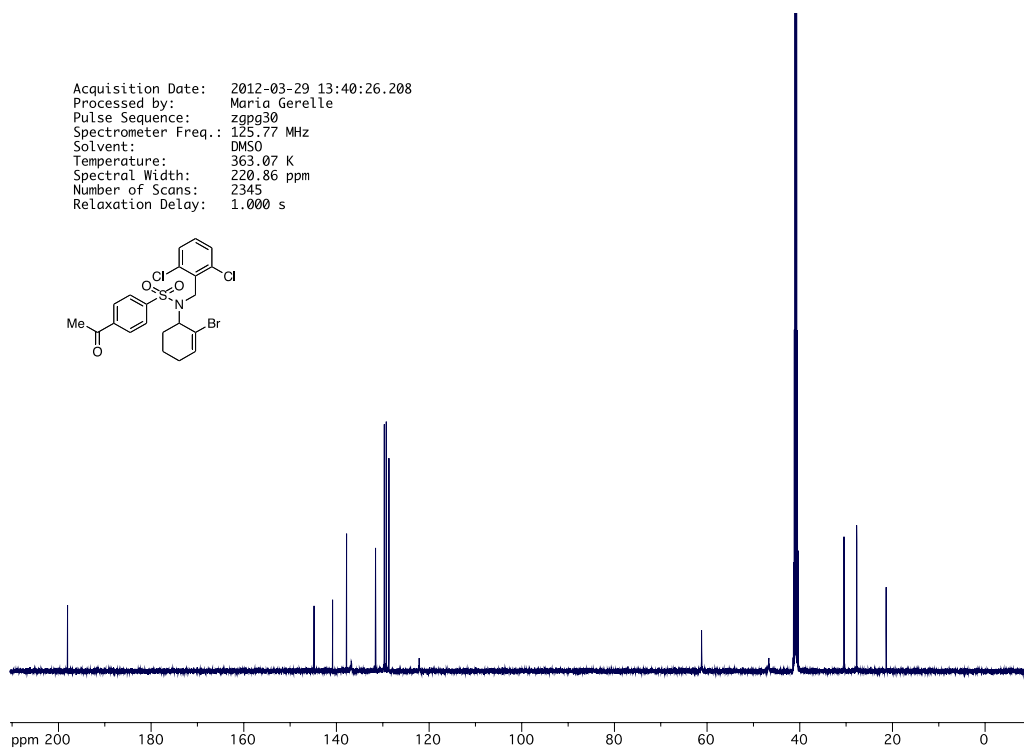
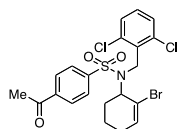
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 Relaxation Delay: 1.000 s



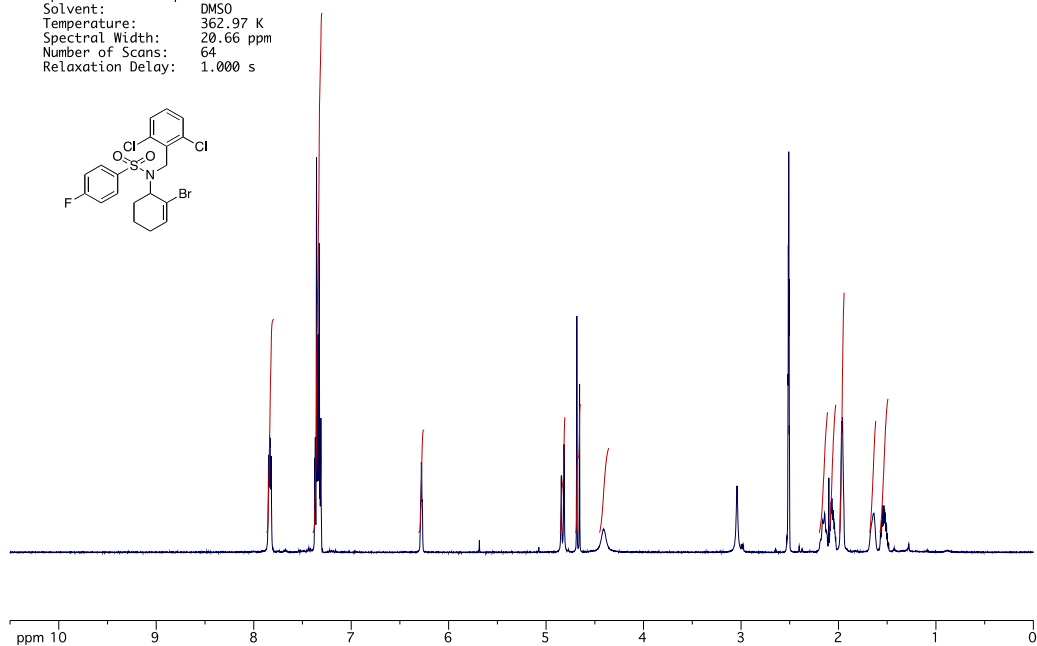
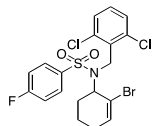
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 Solvent: DMSO
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 Number of Scans: 16
 Relaxation Delay: 1.000 s



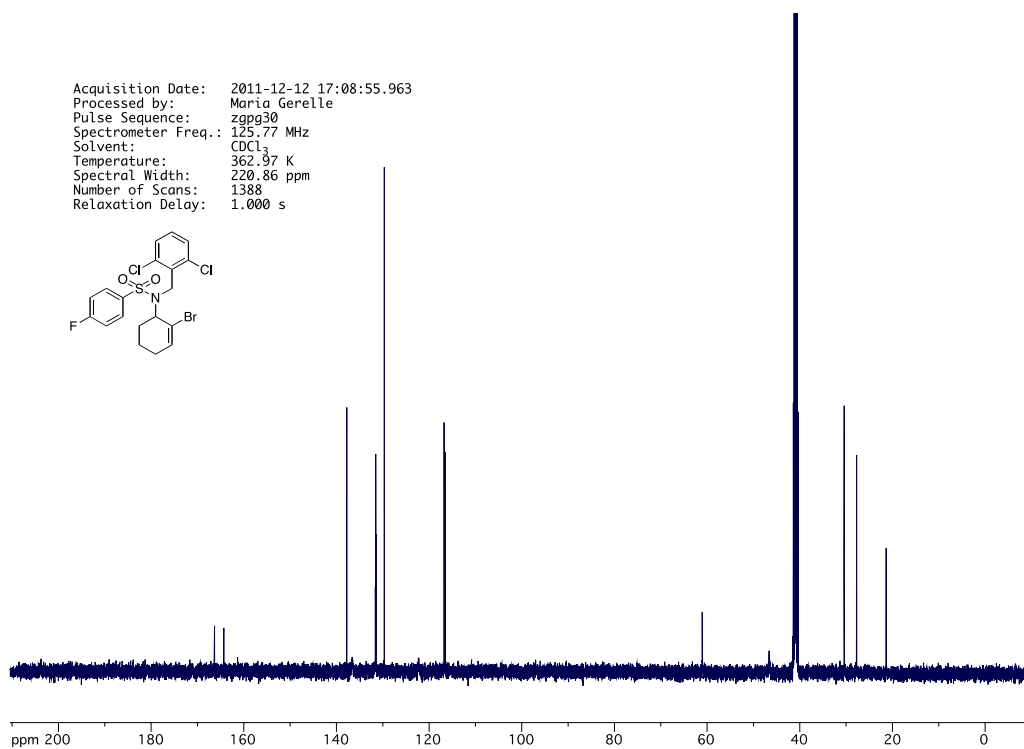
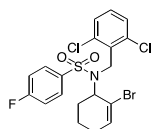
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 Pulse Sequence: zgpg30
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 Solvent: DMSO
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 Spectral Width: 220.86 ppm
 Number of Scans: 2345
 Relaxation Delay: 1.000 s



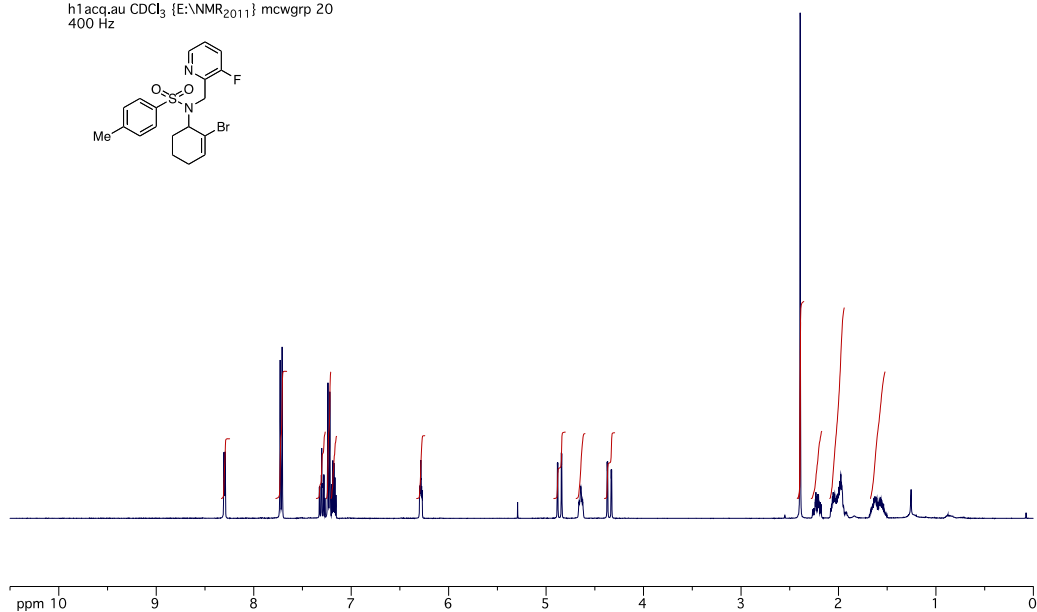
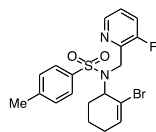
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 Pulse Sequence: zg60
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 Number of Scans: 64
 Relaxation Delay: 1.000 s



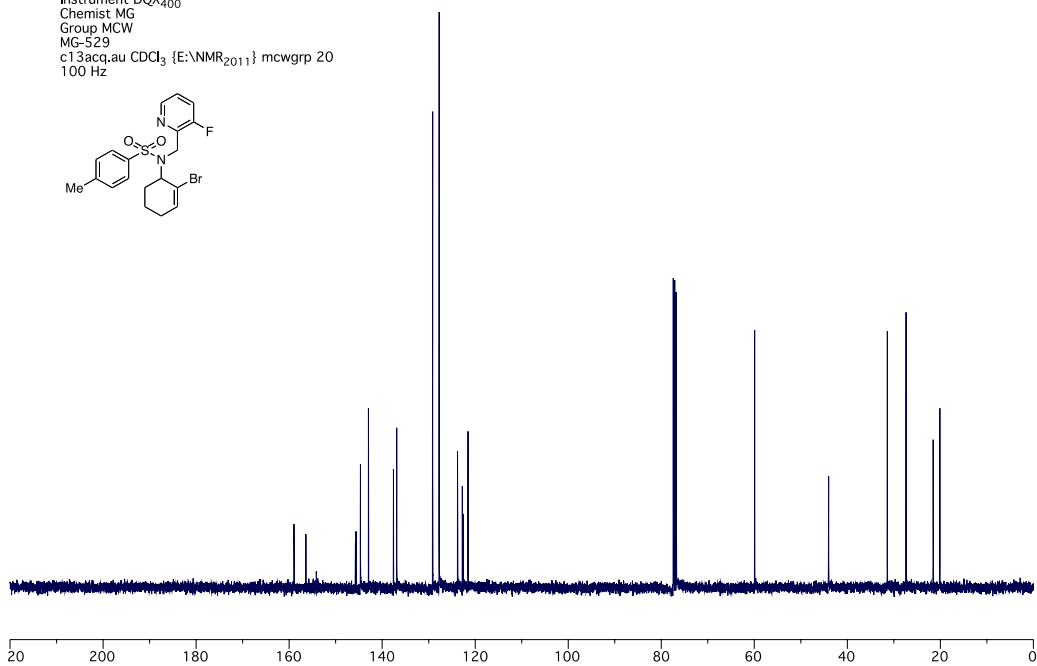
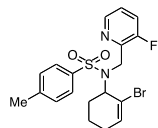
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 Relaxation Delay: 1.000 s



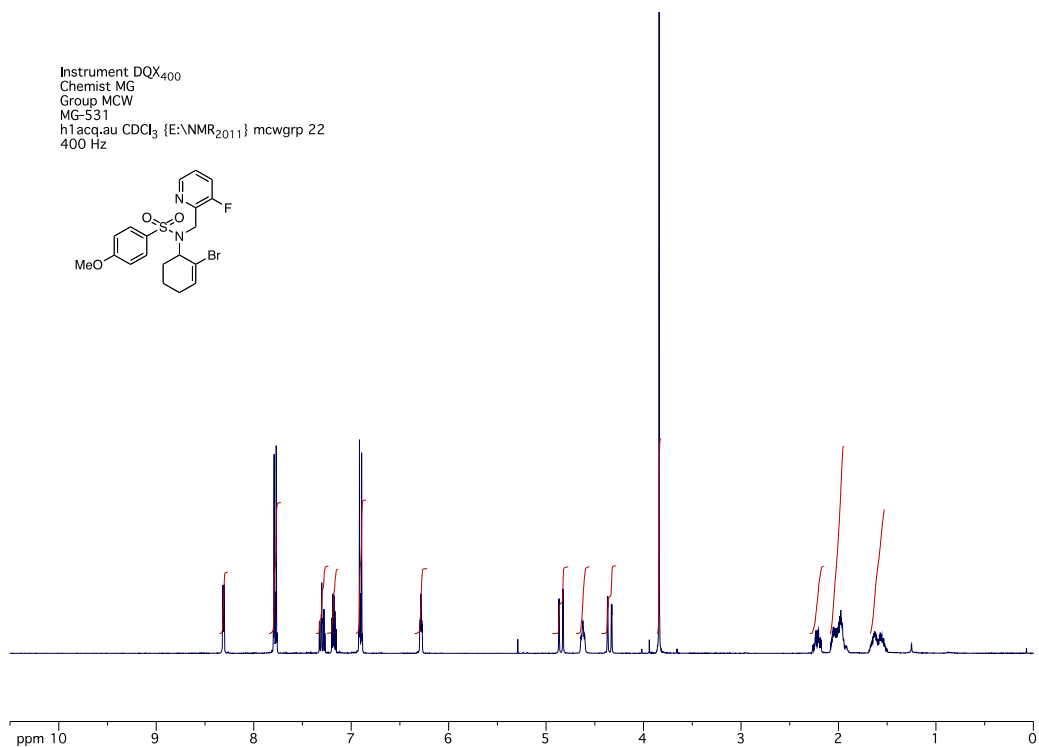
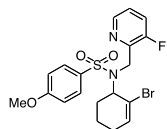
Instrument DQX400
 Chemist MG
 Group MCW
 MG-529
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 400 Hz



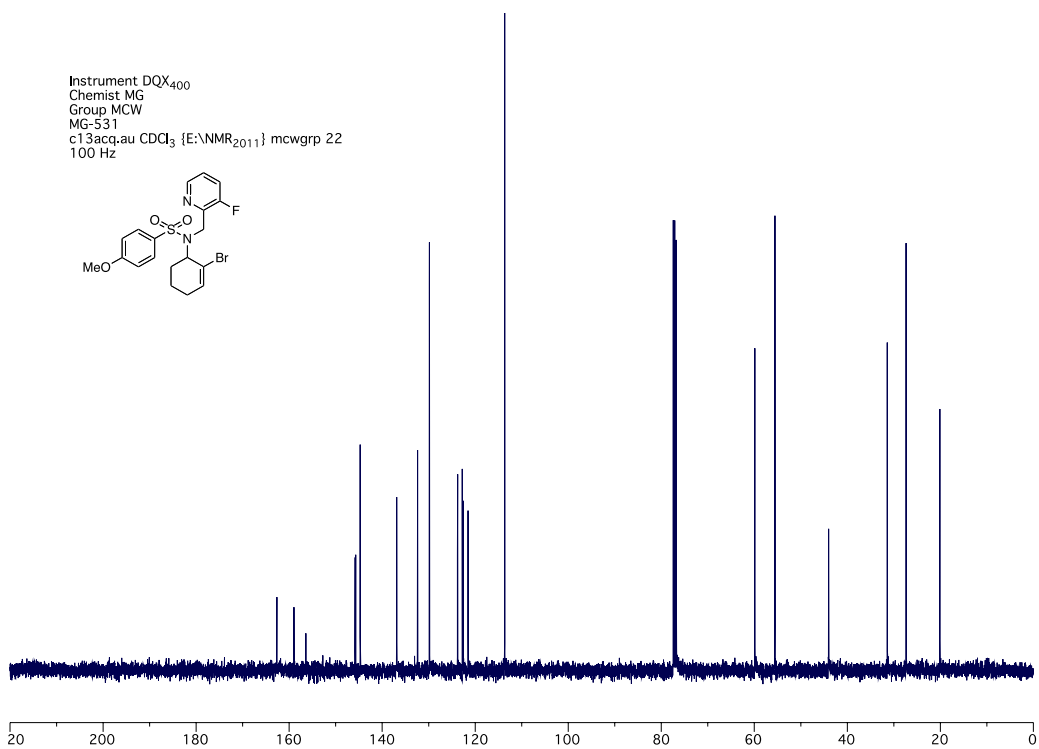
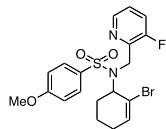
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 Group MCW
 MG-529
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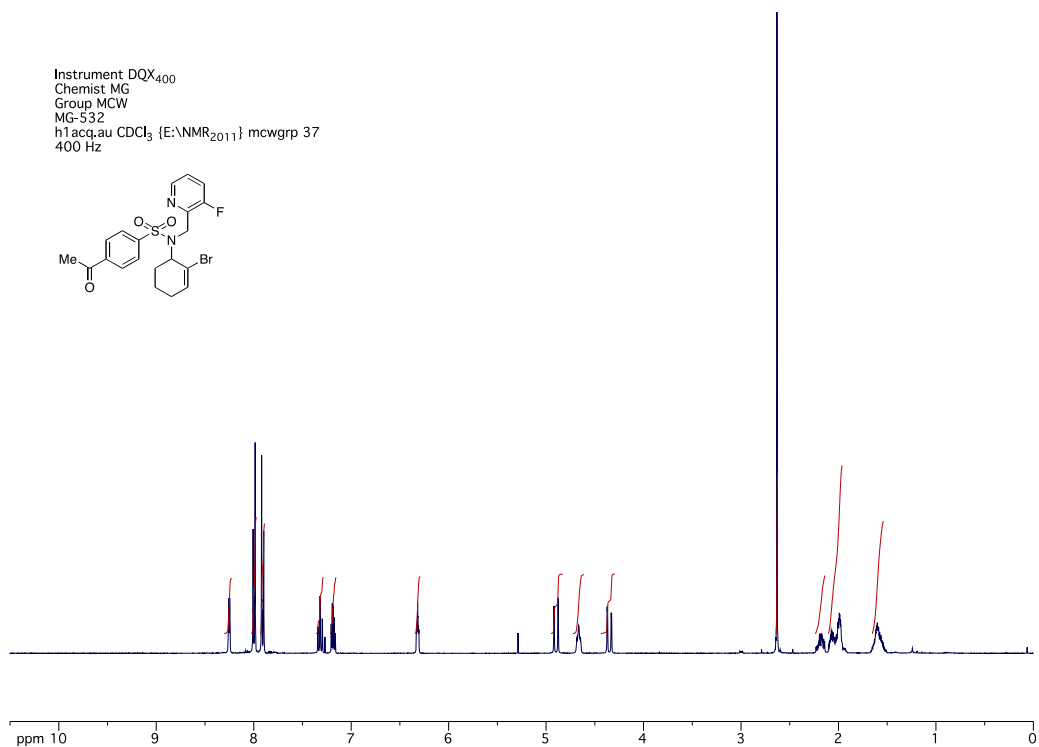
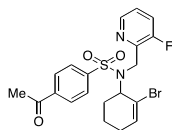
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 Chemist MG
 Group MCW
 MG-531
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 400 Hz



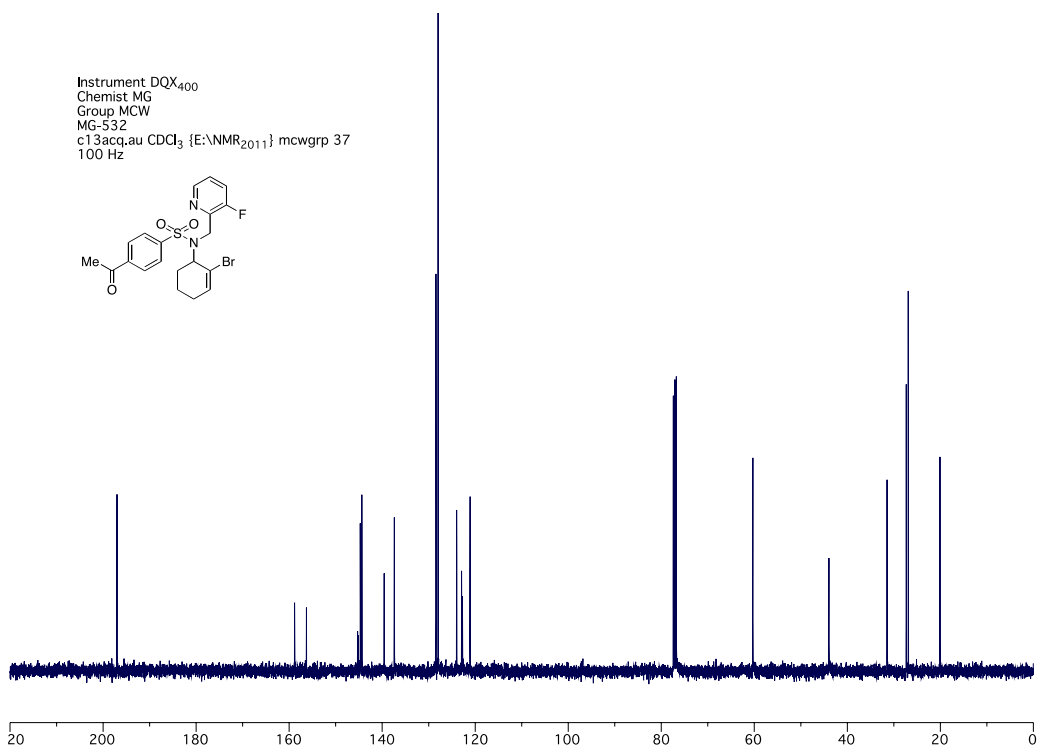
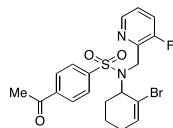
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 Group MCW
 MG-531
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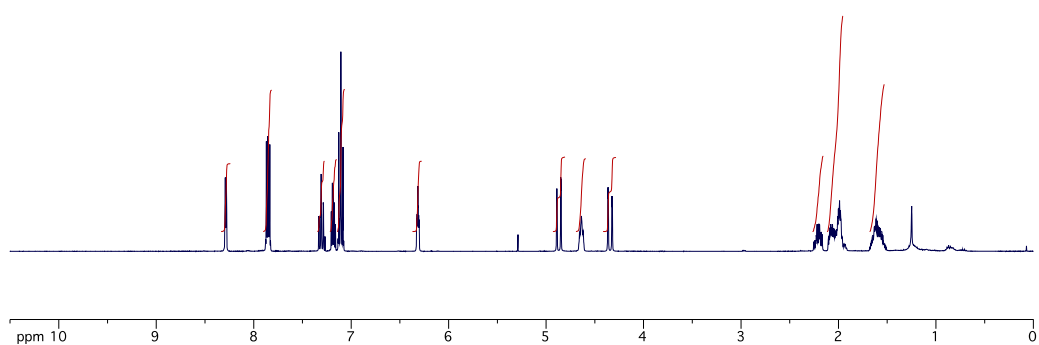
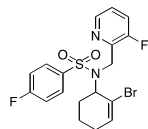
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 Group MCW
 MG-532
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 400 Hz



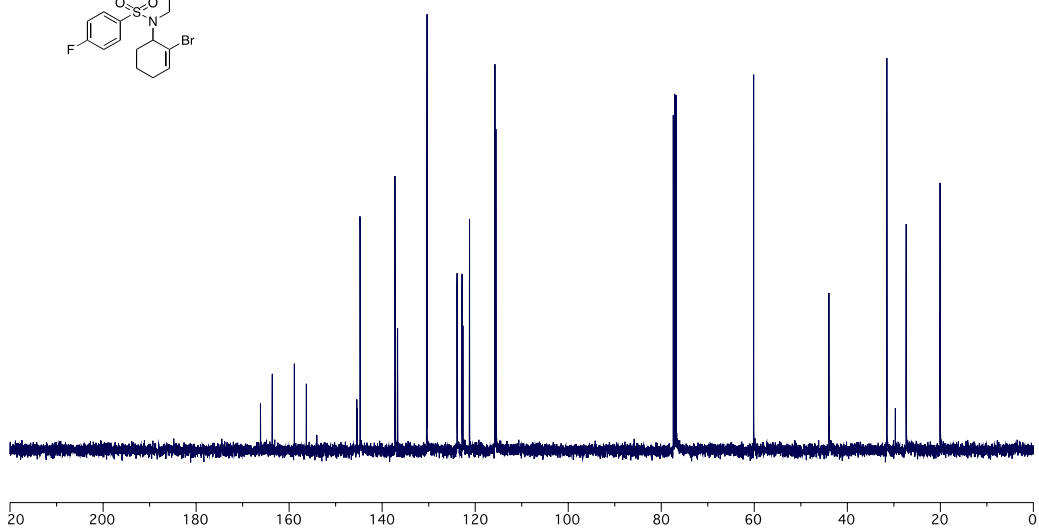
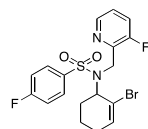
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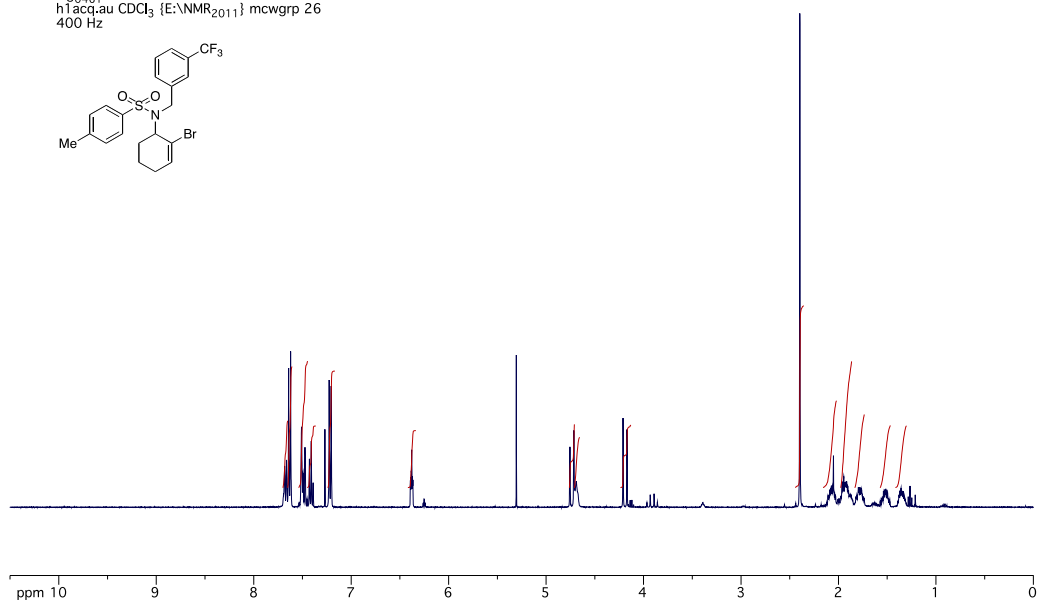
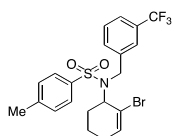
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 Chemist MG
 Group MCW
 MG-530
 h1 acq.au CDCl₃ {E:\NMR2011} mcwgrp 21
 400 Hz



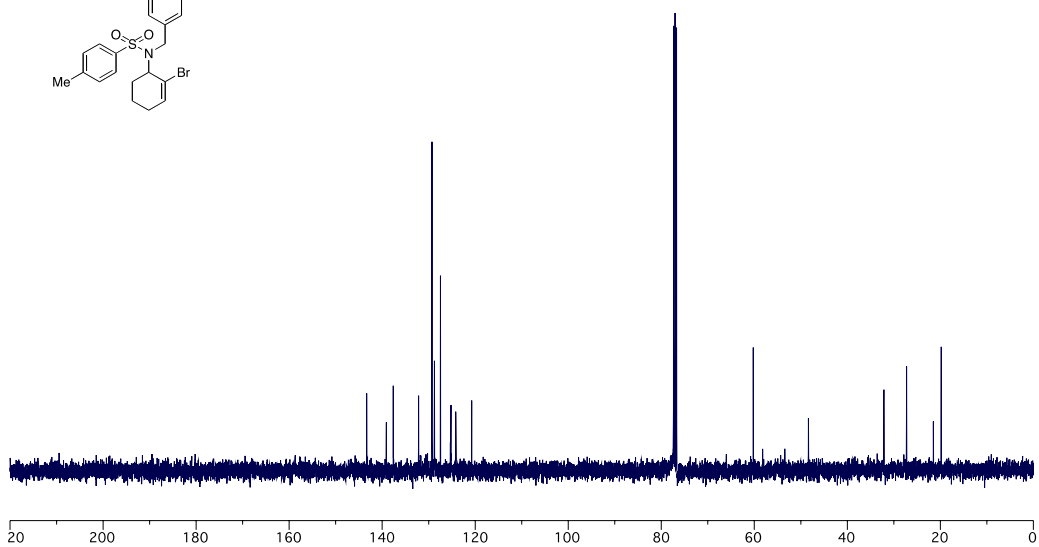
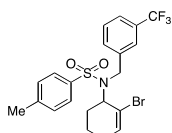
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 MG-530
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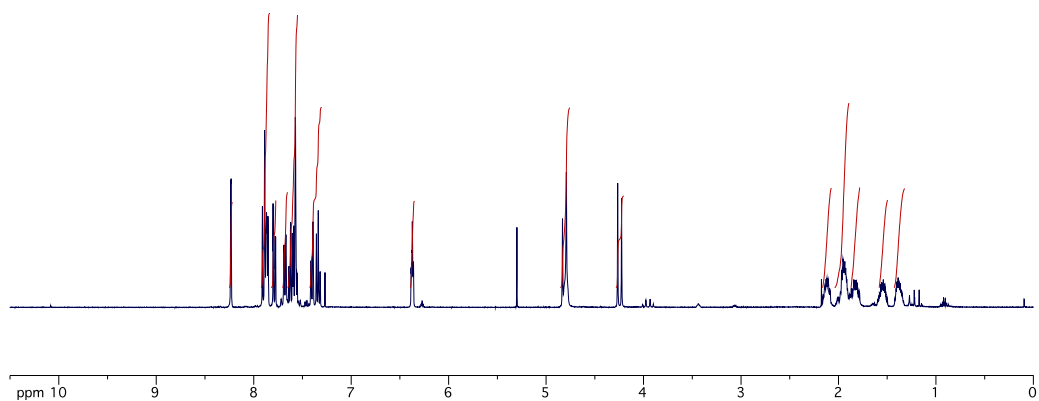
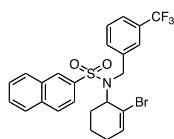
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 Group MCW
 M90461
 h1acq.au CDCl₃ {E:\NMR2011} mcwgrp 26
 400 Hz



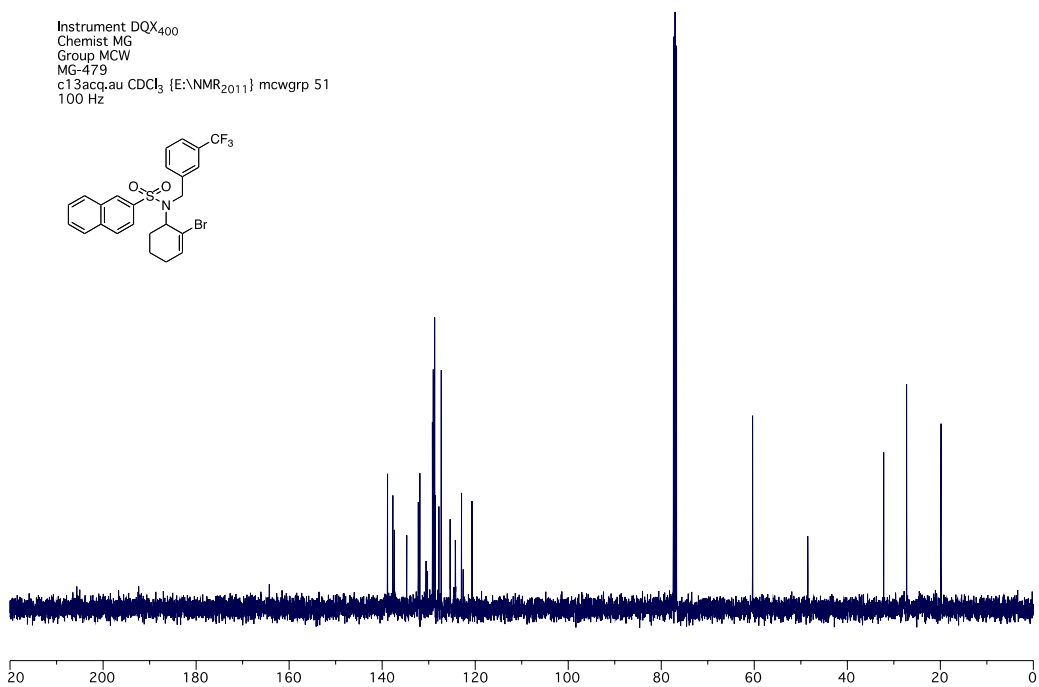
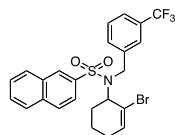
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 Group MCW
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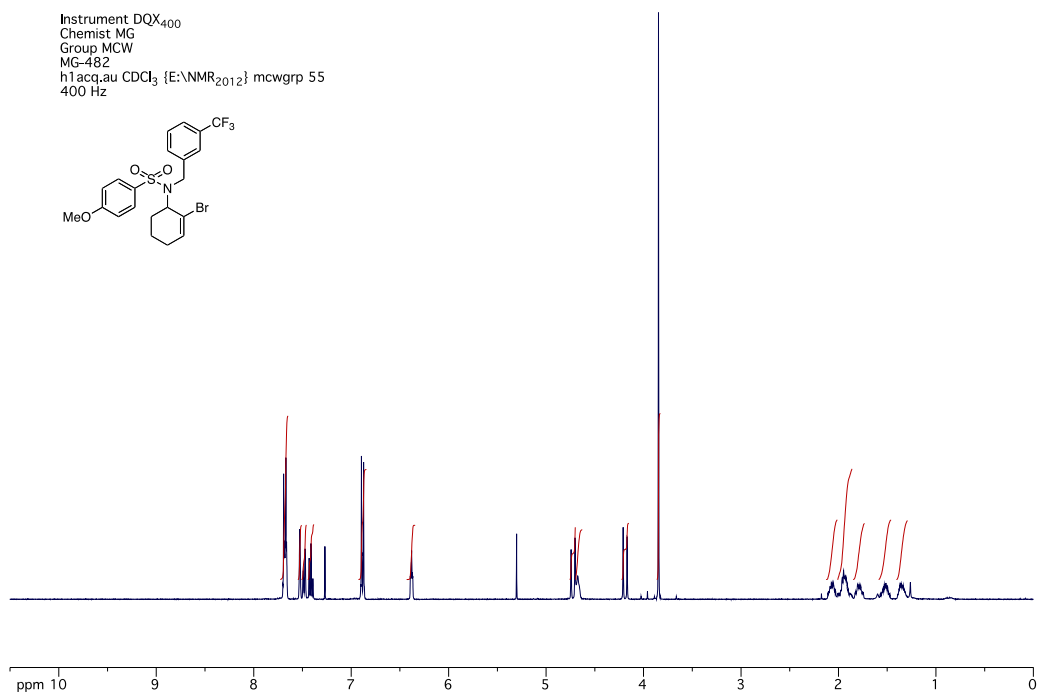
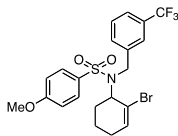
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-479
 h1acq,au CDCl₃ {E:\NMR2011} mcwgrp 51
 400 Hz



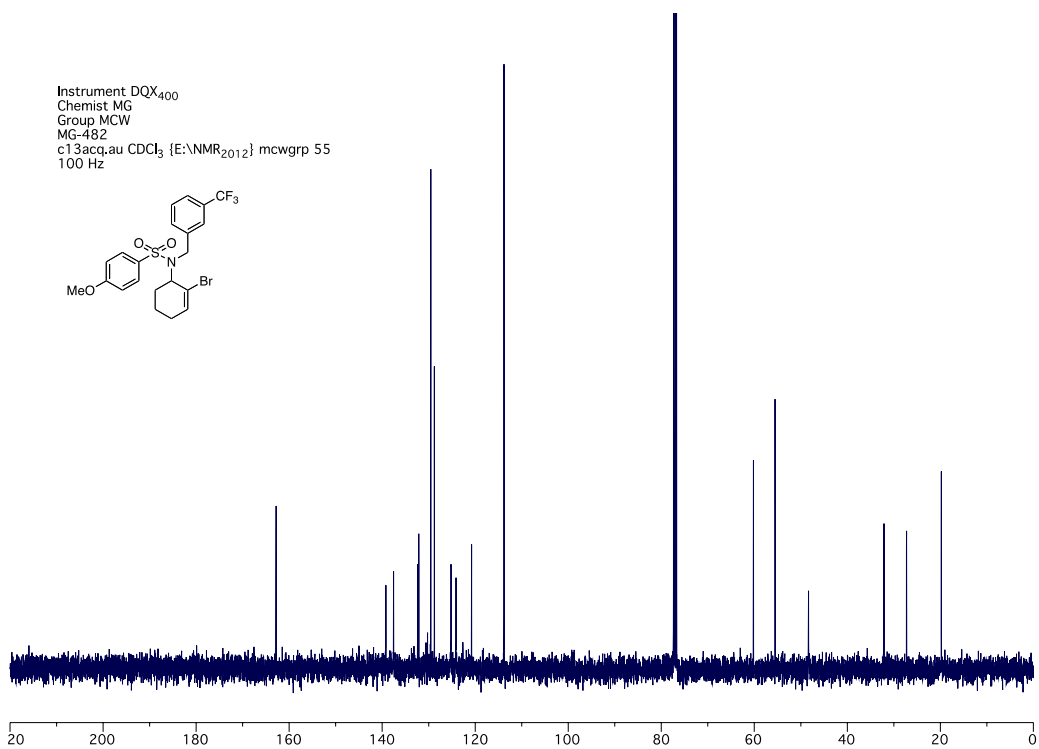
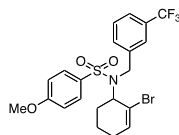
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 Chemist MG
 Group MCW
 MG-479
 c13acq,au CDCl₃ {E:\NMR2011} mcwgrp 51
 100 Hz



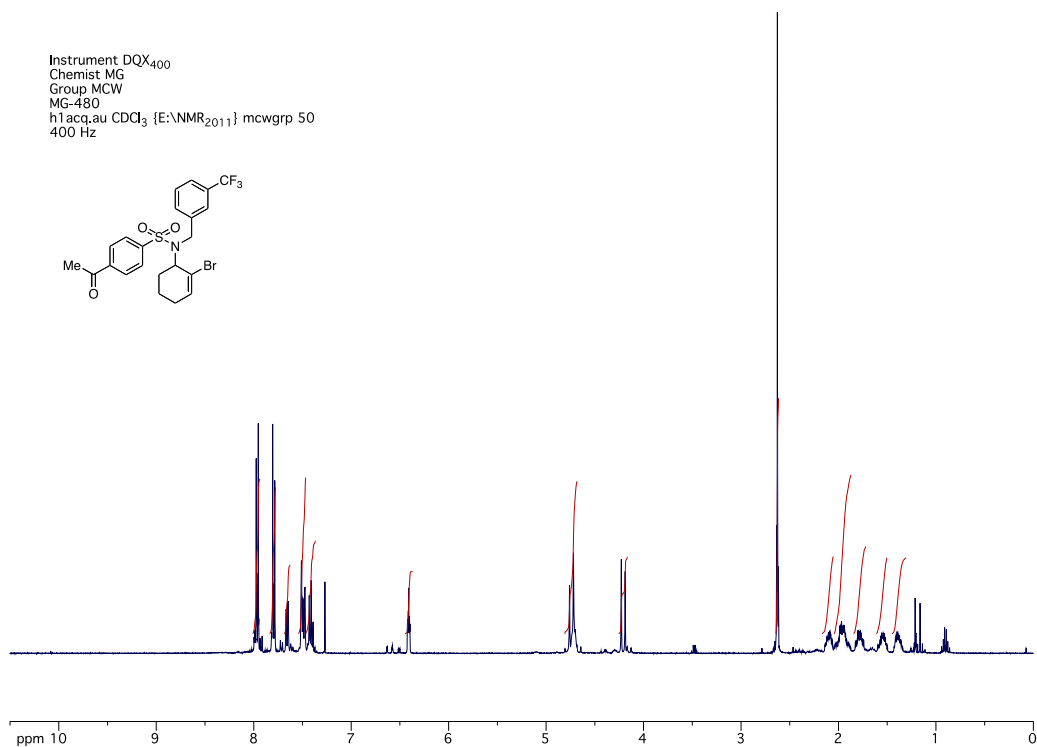
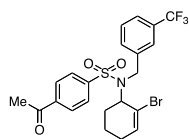
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-482
 h1acq,au CDCl₃ {E:\NMR₂₀₁₂} mcwgrp 55
 400 Hz



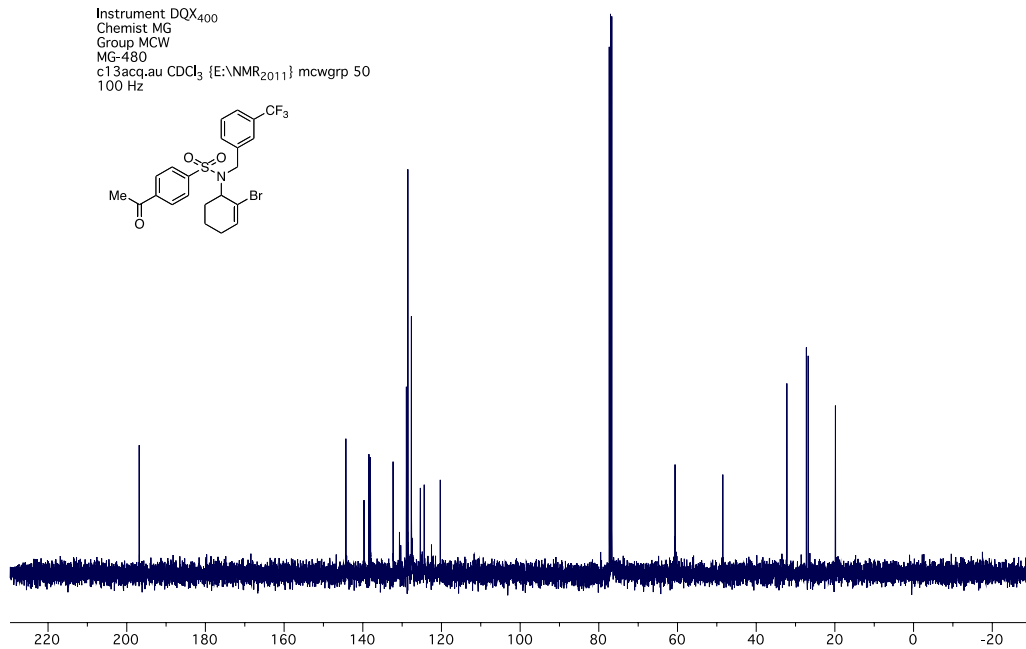
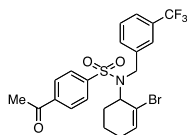
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 Chemist MG
 Group MCW
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 100 Hz



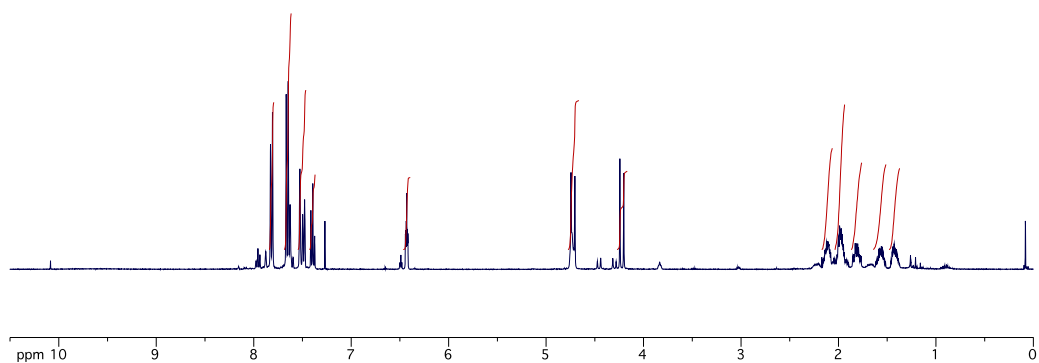
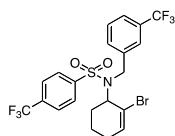
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 Chemist MG
 Group MCW
 MG-480
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 400 Hz



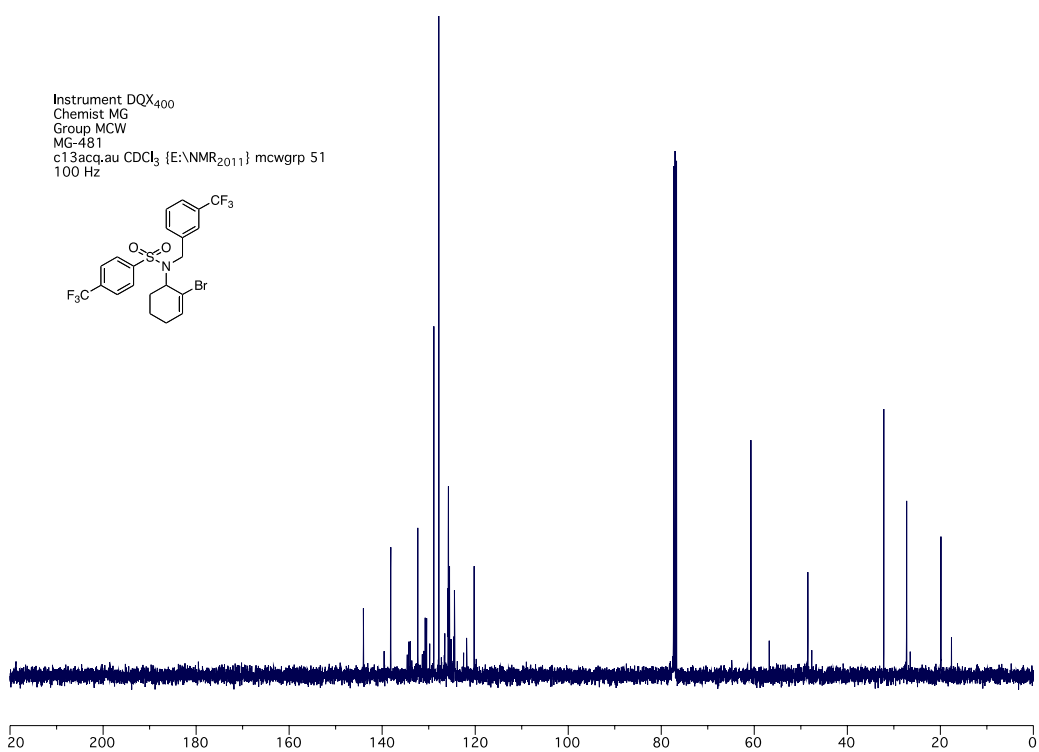
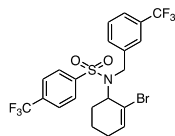
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 Group MCW
 MG-480
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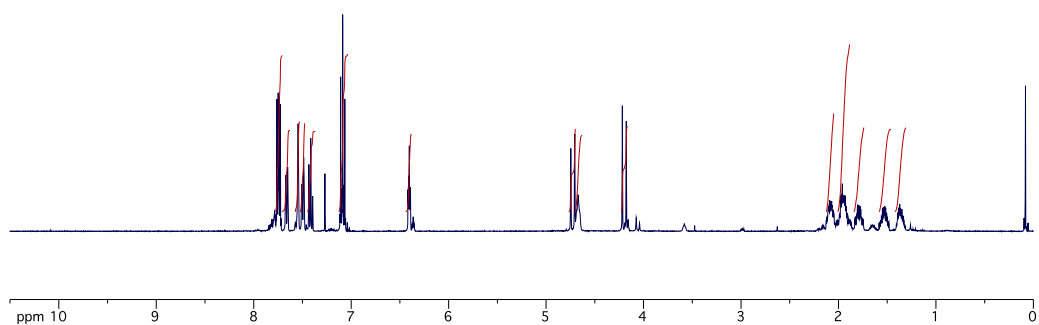
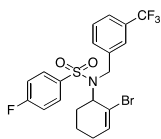
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-431
 h1acq,au CDCl₃ {E:\NMR₂₀₁₁} mcwgrp 51
 400 Hz



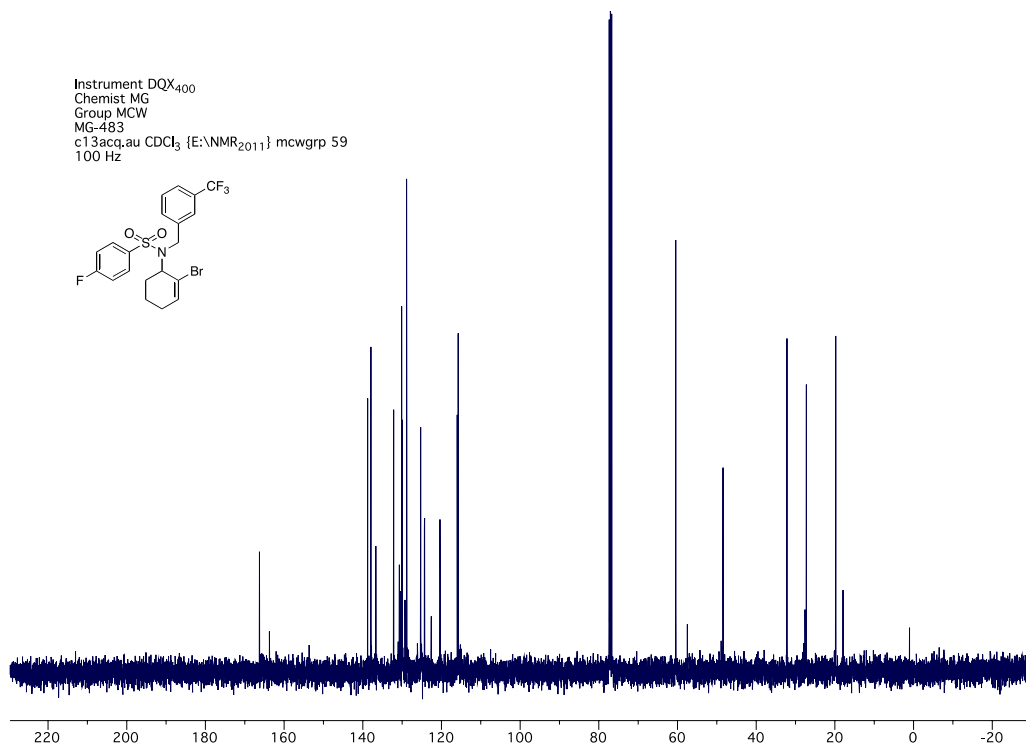
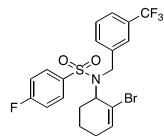
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 Chemist MG
 Group MCW
 MG-431
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 100 Hz



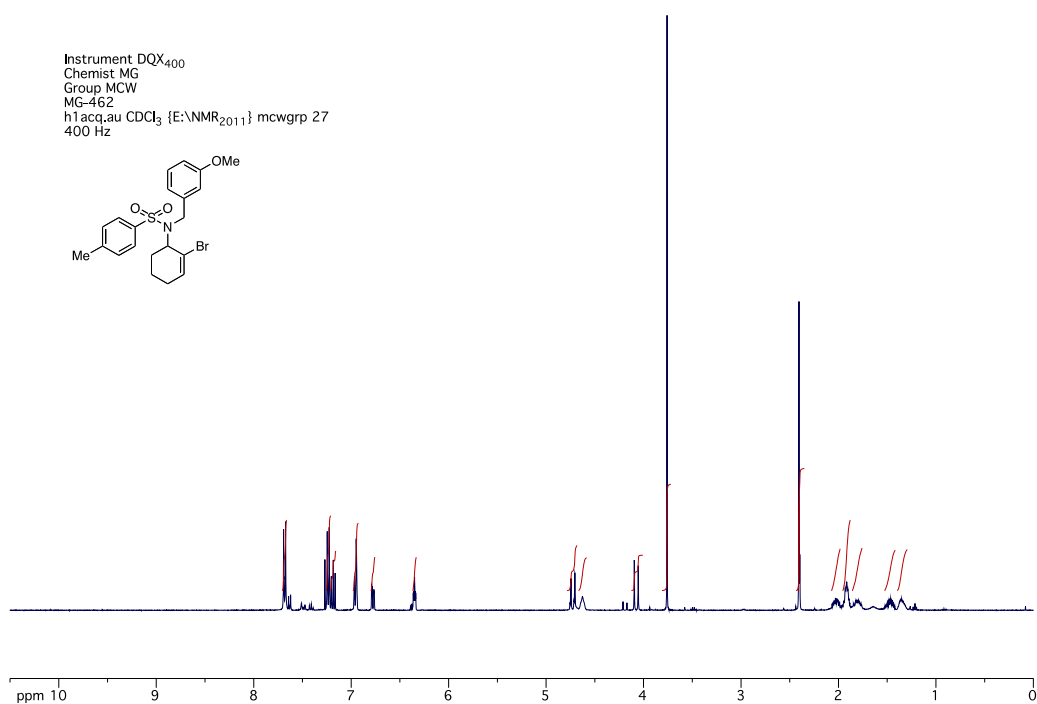
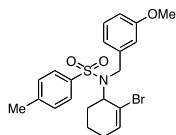
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-483
 h1acq.au CDCl₃ {E:\NMR₂₀₁₁} mcwgrp 59
 400 Hz



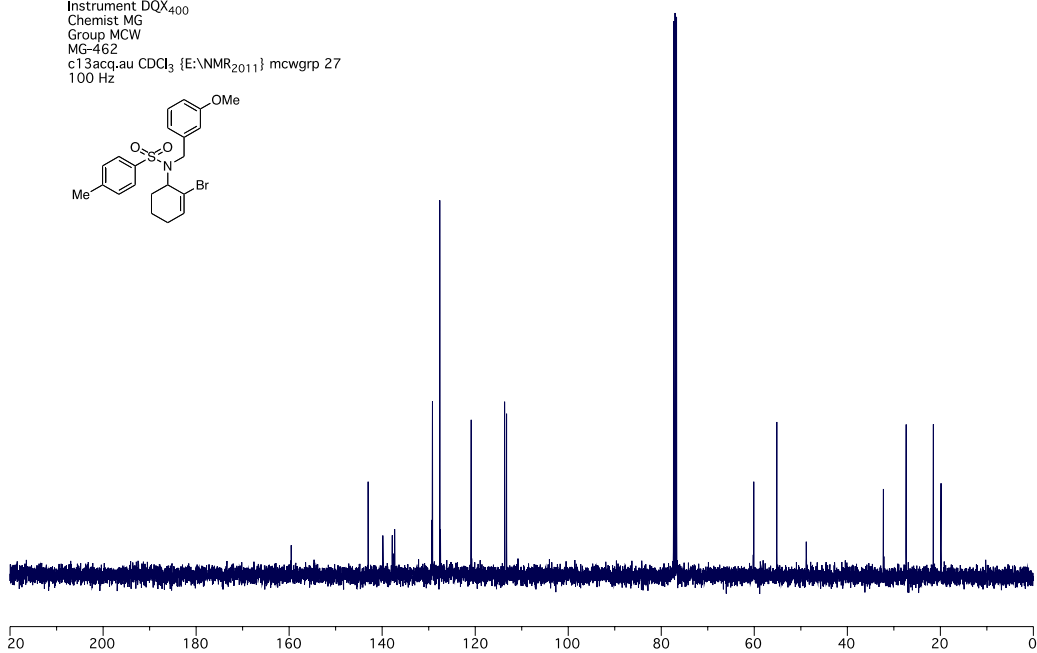
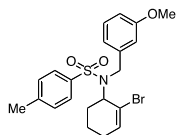
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 Chemist MG
 Group MCW
 MG-483
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 100 Hz



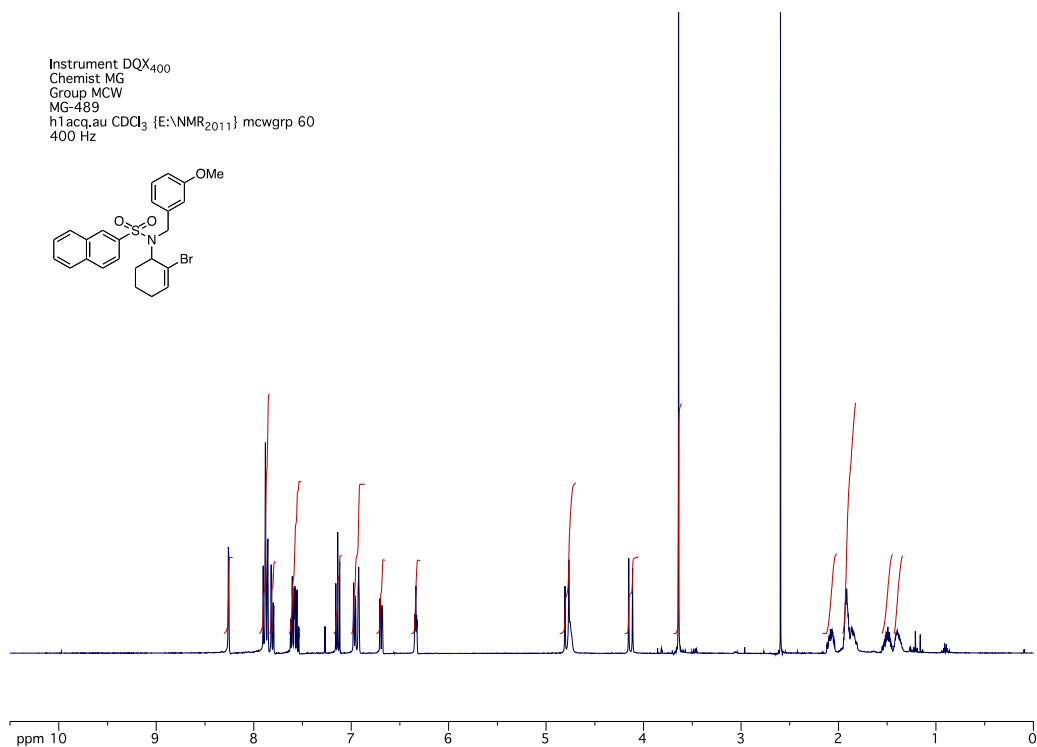
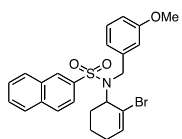
Instrument DQX400
 Chemist MG
 Group MCW
 MG-462
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 400 Hz



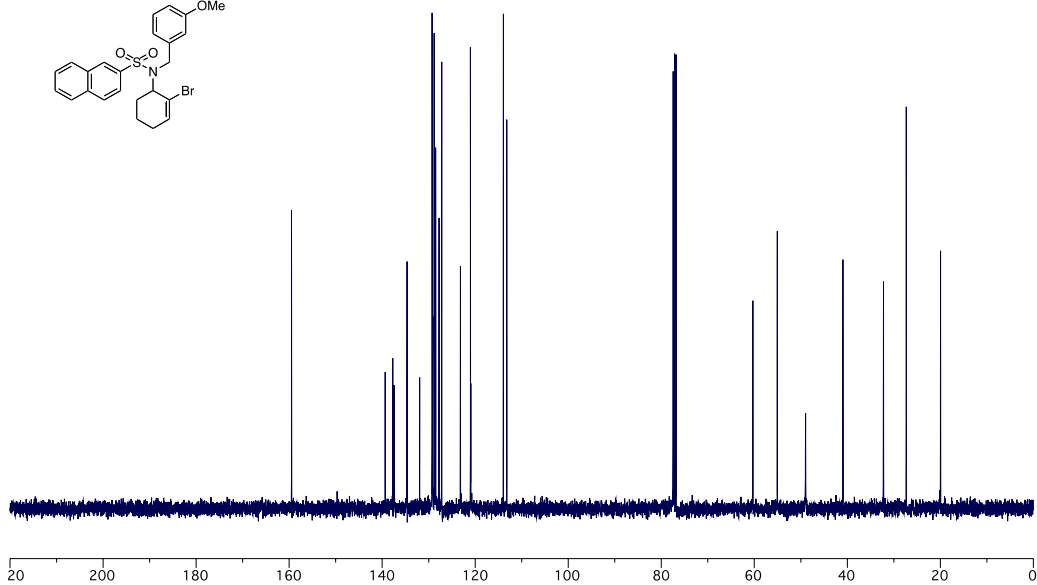
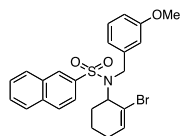
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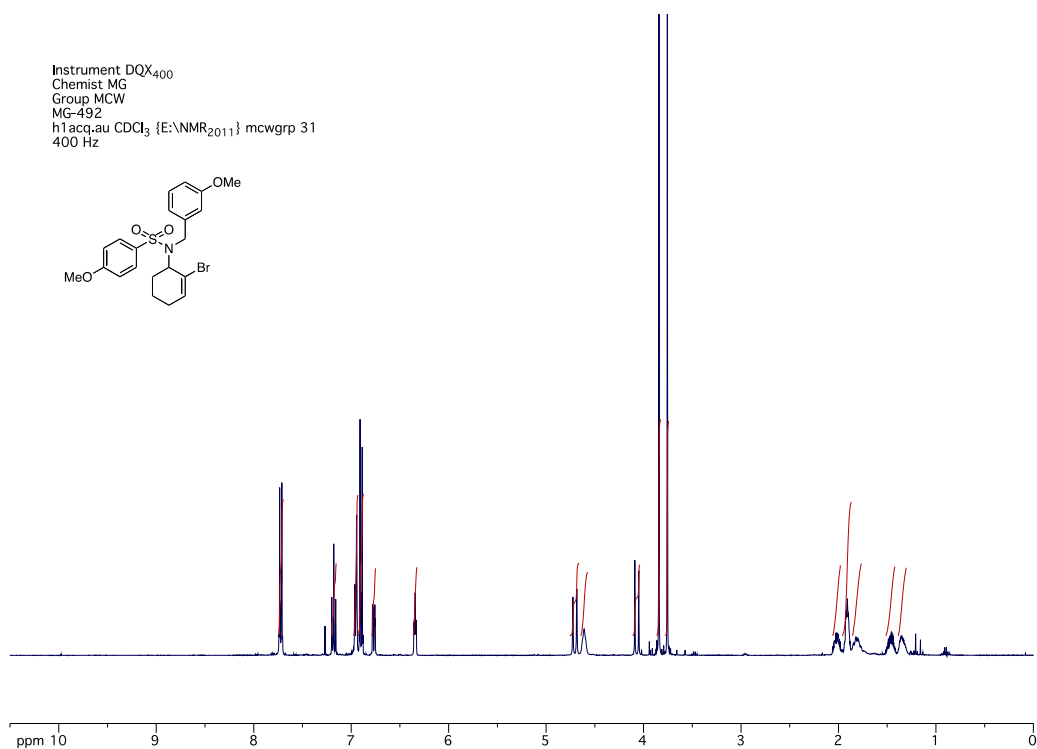
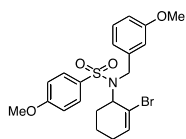
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 Group MCW
 MG-489
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 400 Hz



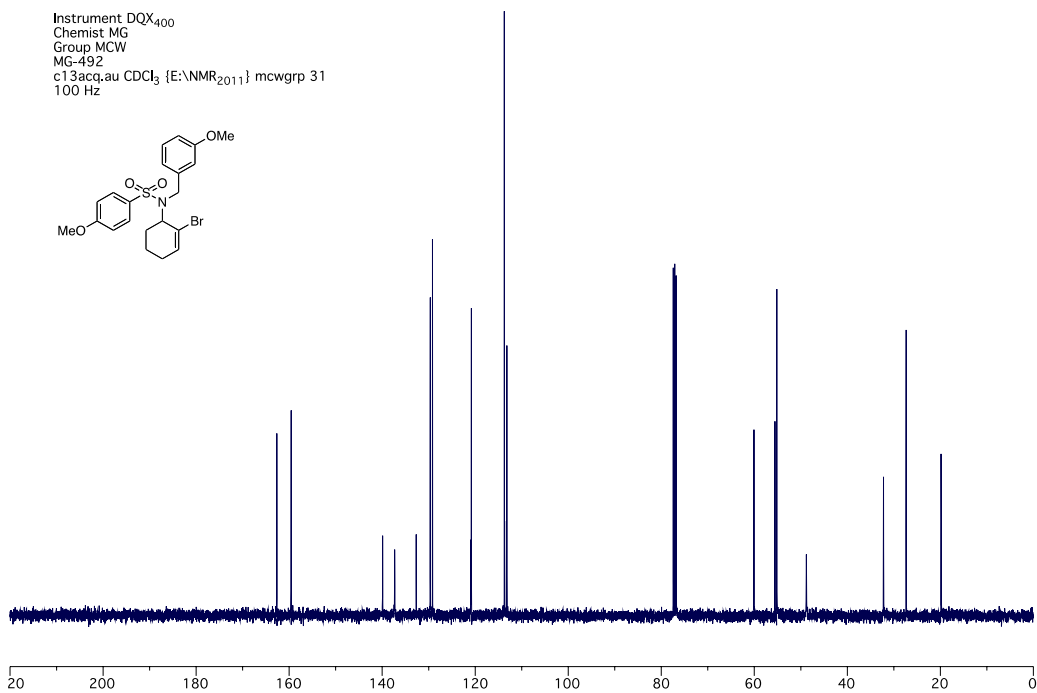
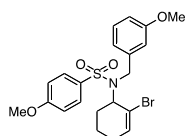
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 Chemist MG
 Group MCW
 MG-489
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 100 Hz



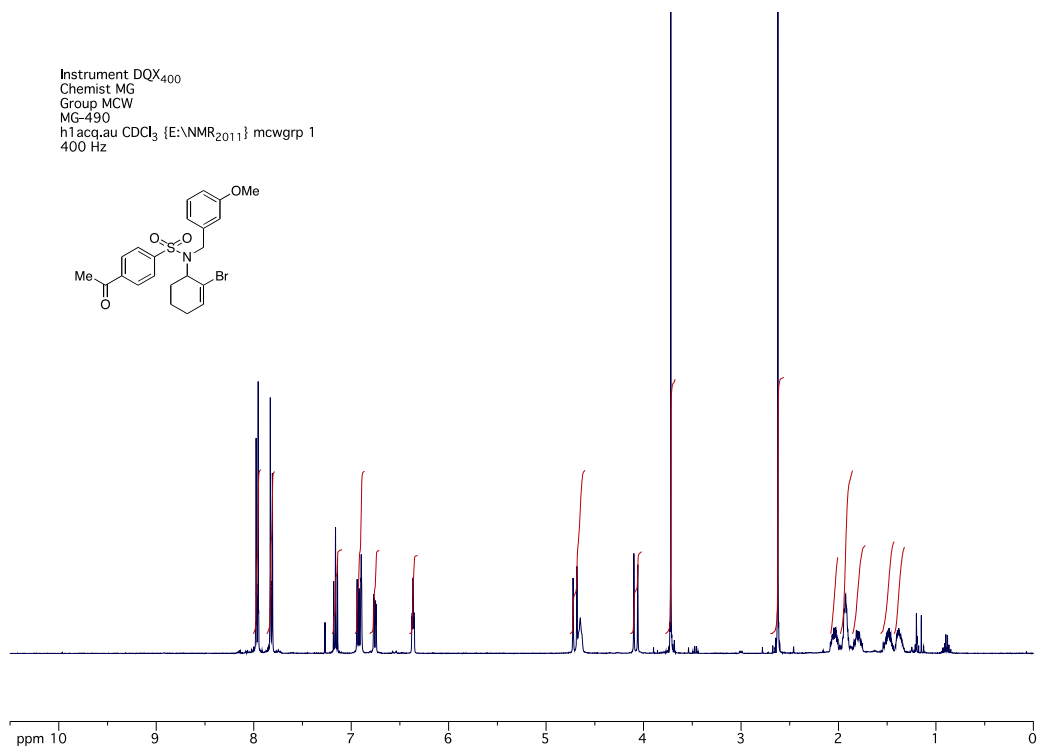
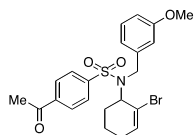
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-492
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 400 Hz



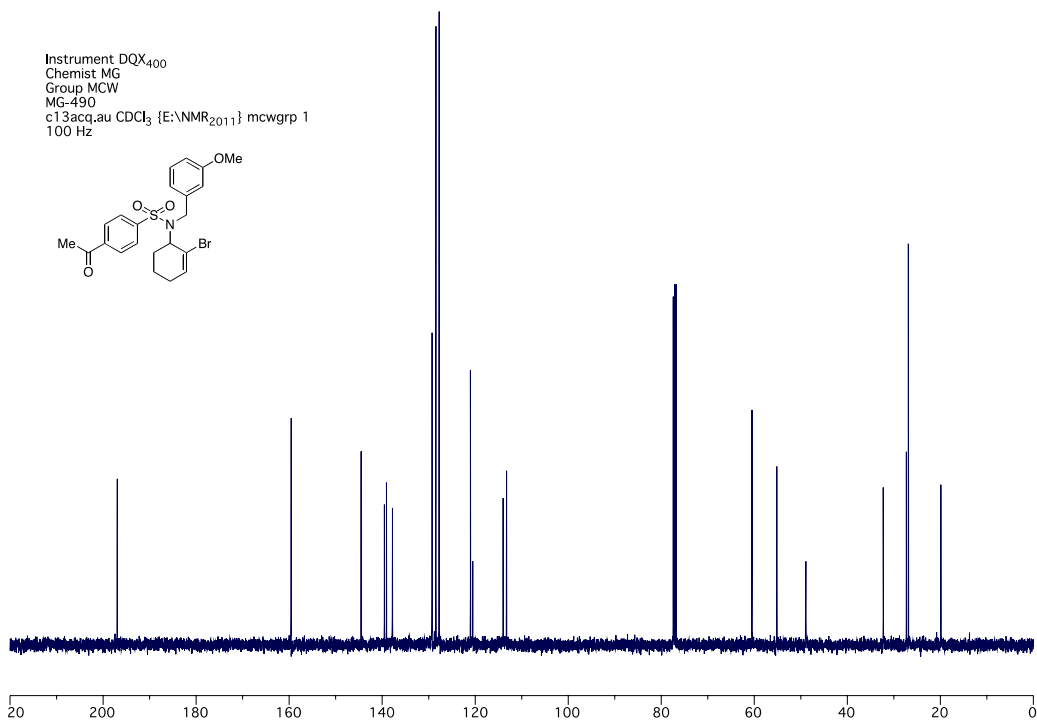
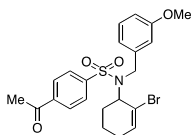
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 Group MCW
 MG-492
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 100 Hz



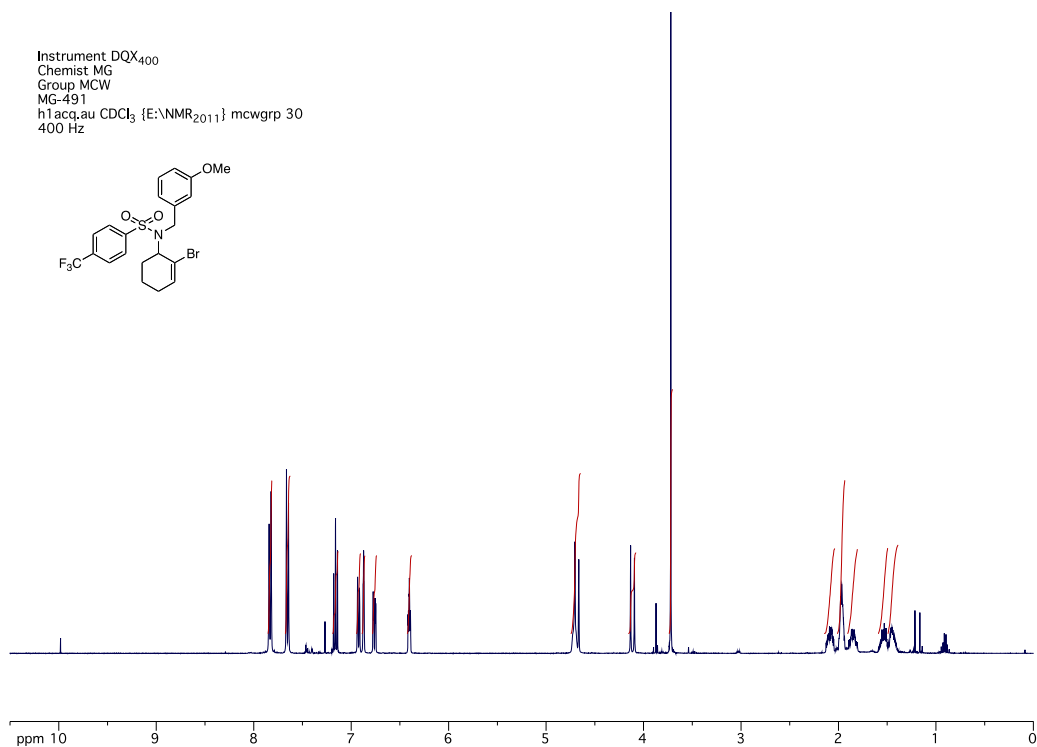
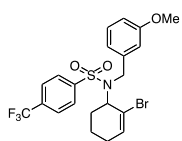
Instrument DQX400
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 Group MCW
 MG-490
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 400 Hz



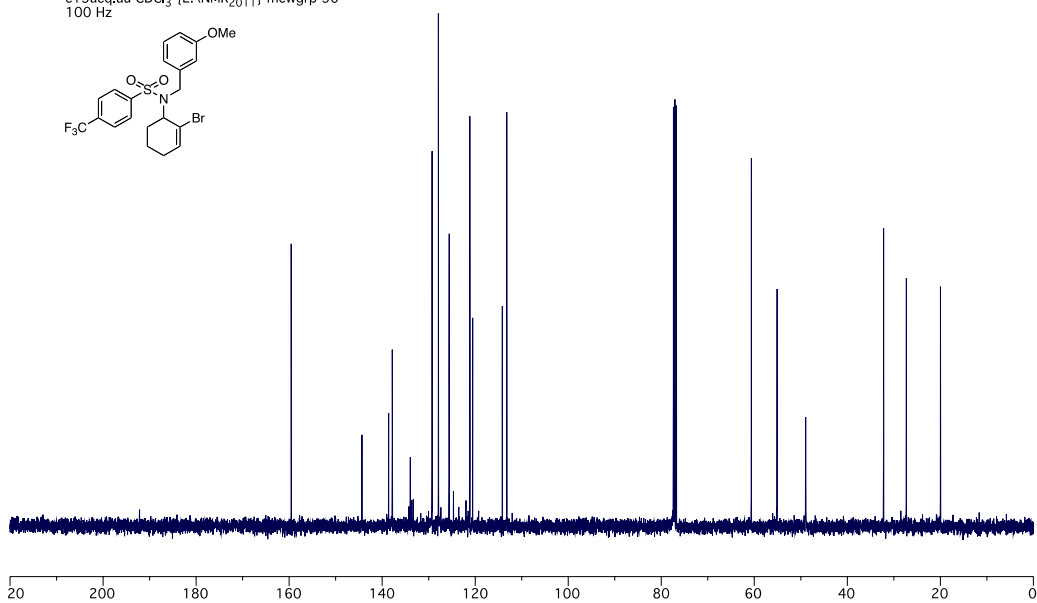
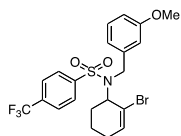
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 MG-490
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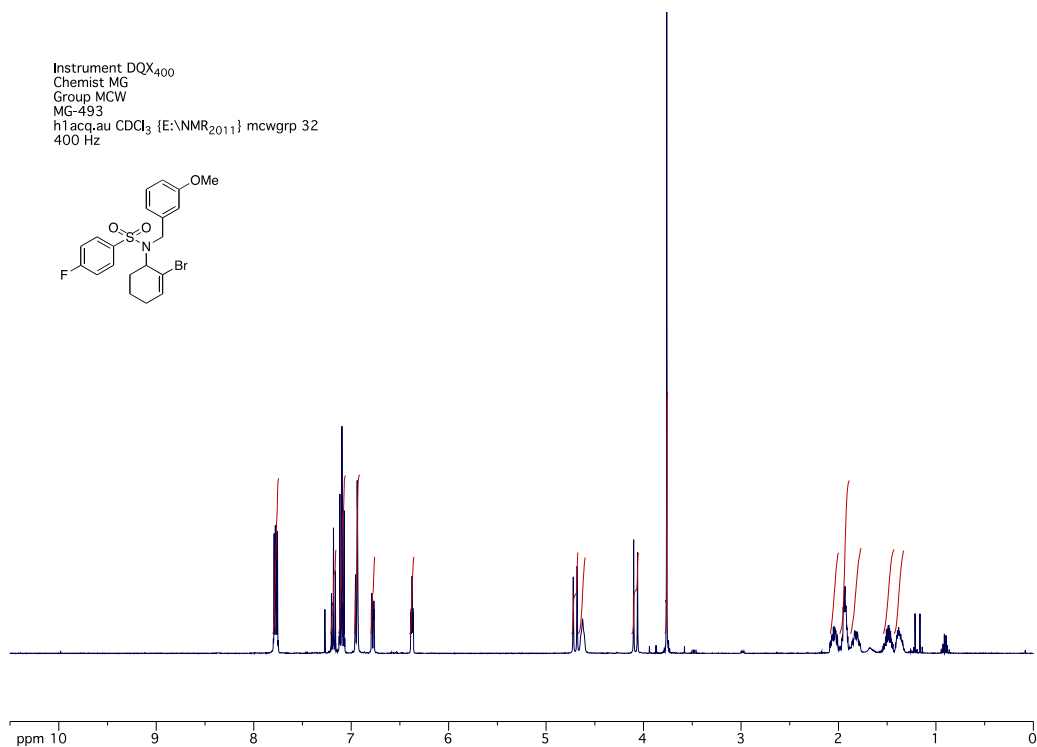
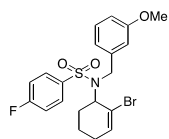
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 Chemist MG
 Group MCW
 MG-491
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 400 Hz



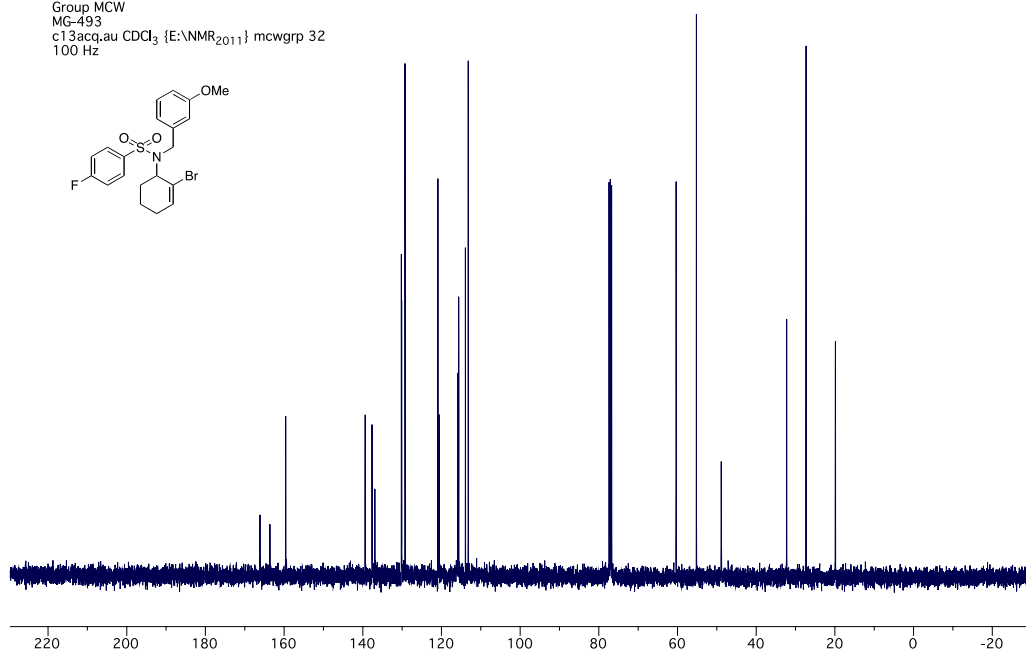
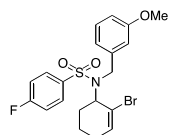
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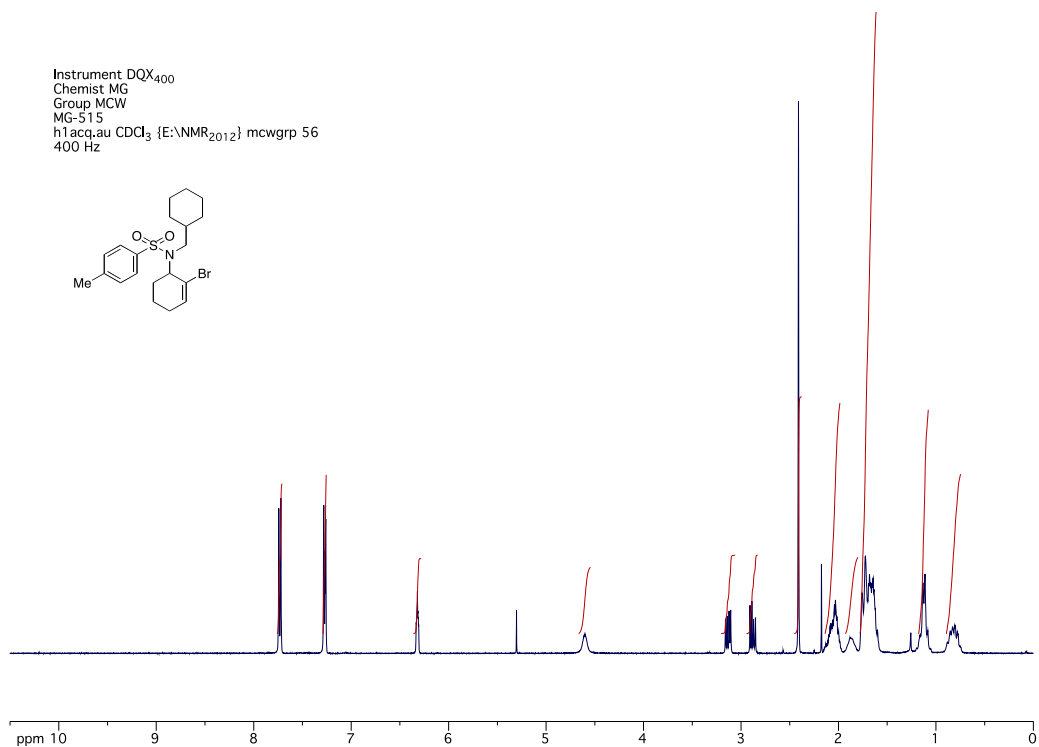
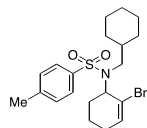
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-493
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 400 Hz



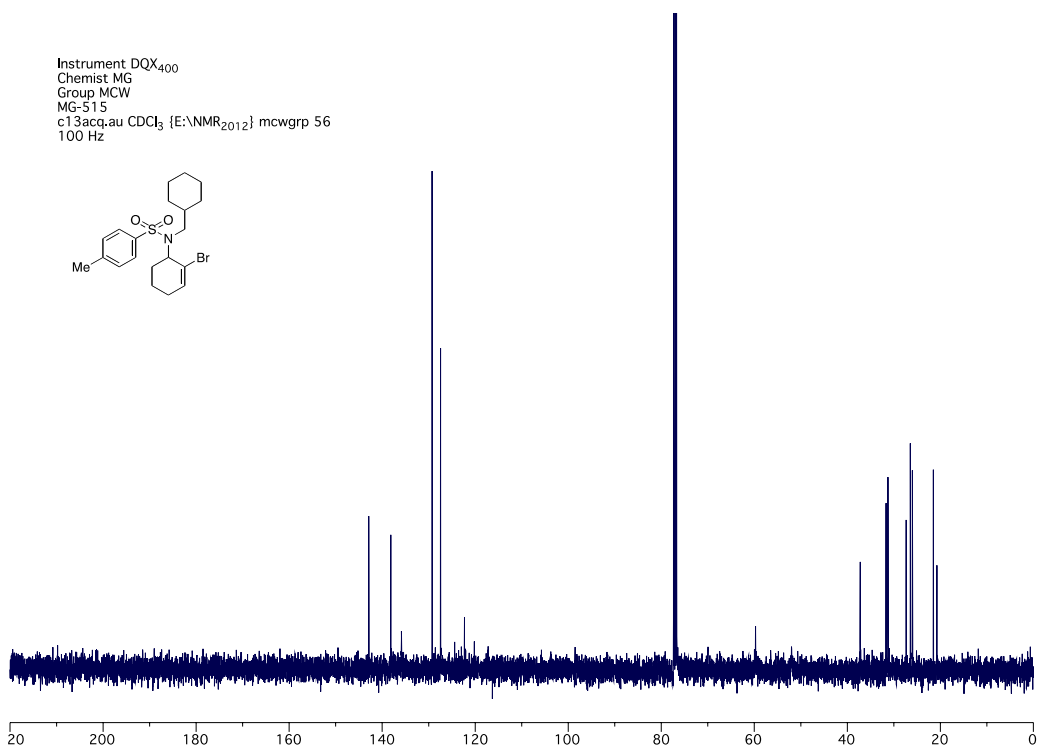
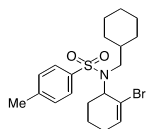
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 Group MCW
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 100 Hz



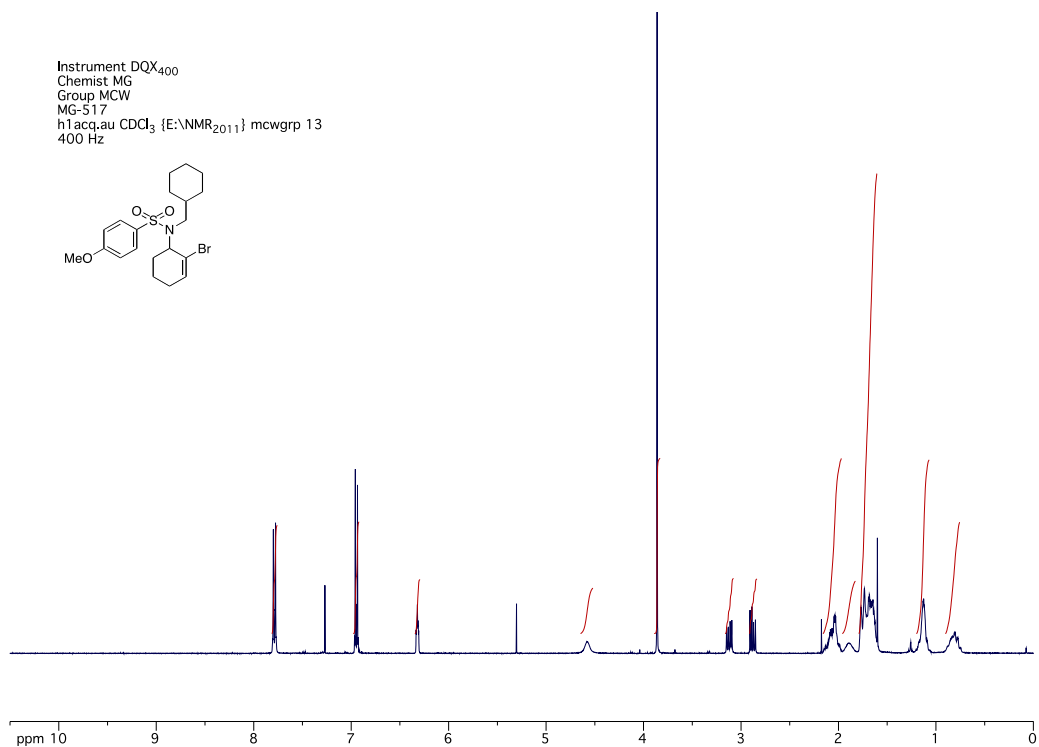
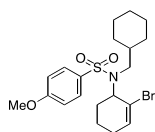
Instrument DQX400
 Chemist MG
 Group MCW
 MG-515
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 400 Hz



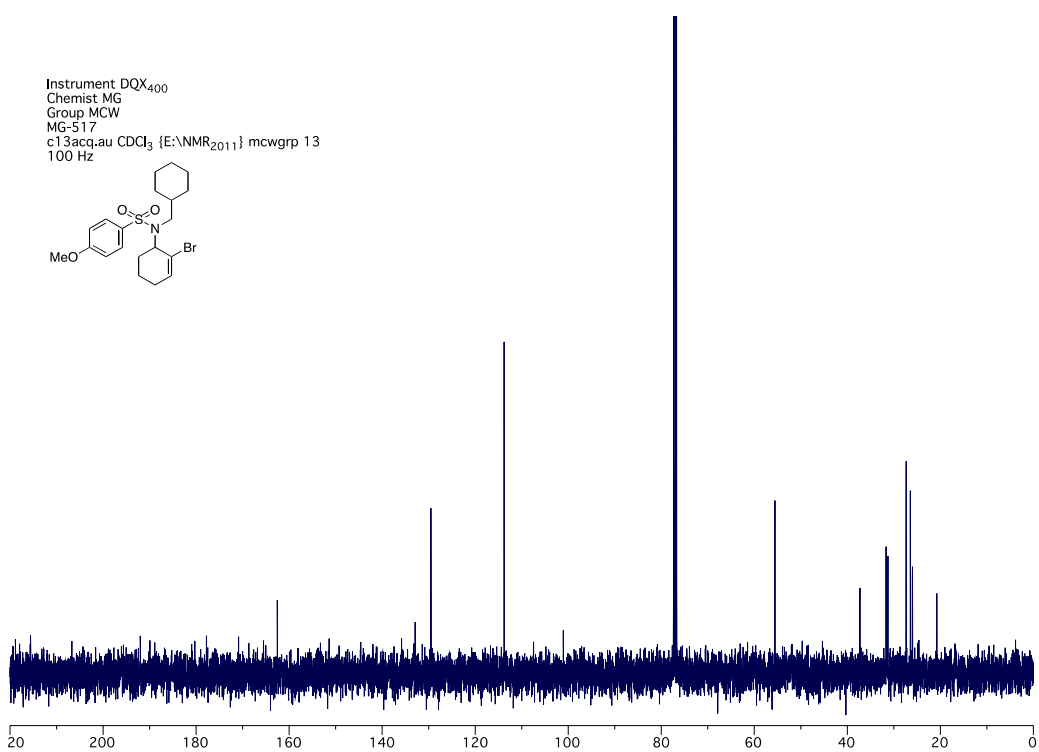
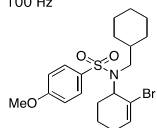
Instrument DQX400
 Chemist MG
 Group MCW
 MG-515
 c13acq,au CDCl₃ {E:\NMR2012} mcwgrp 56
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Instrument DQX400
 Chemist MG
 Group MCW
 MG-517
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 400 Hz

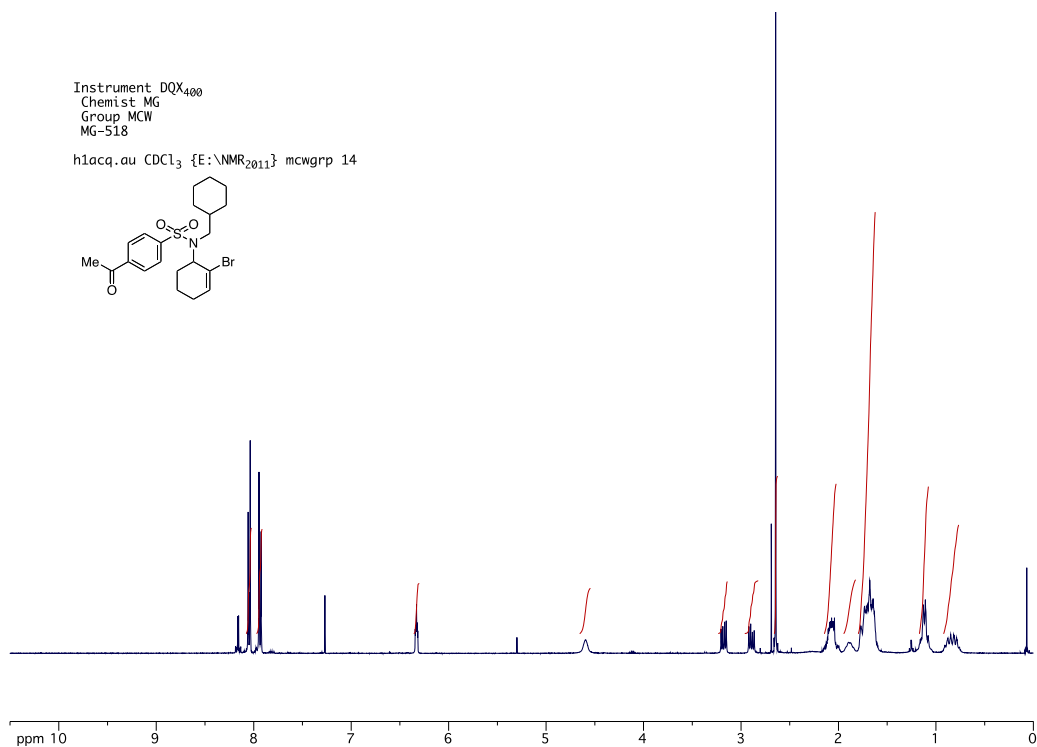
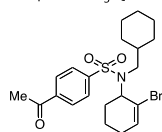


Instrument DQX400
 Chemist MG
 Group MCW
 MG-517
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 100 Hz

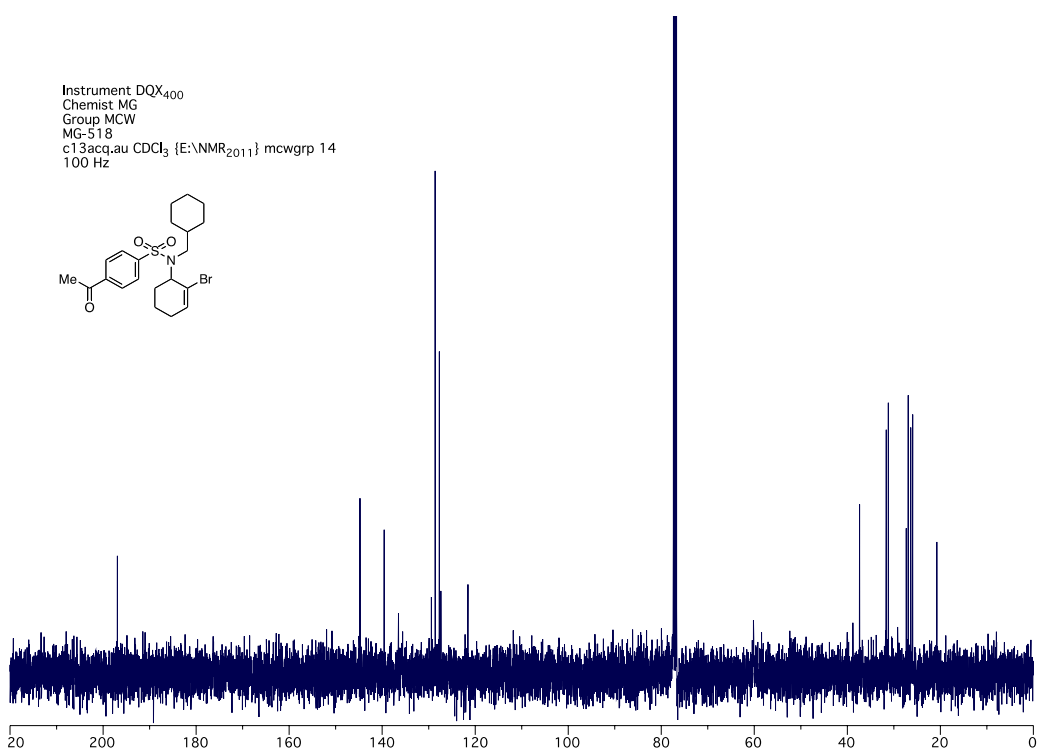
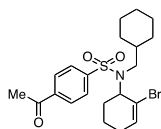


Instrument DQX400
 Chemist MG
 Group MCW
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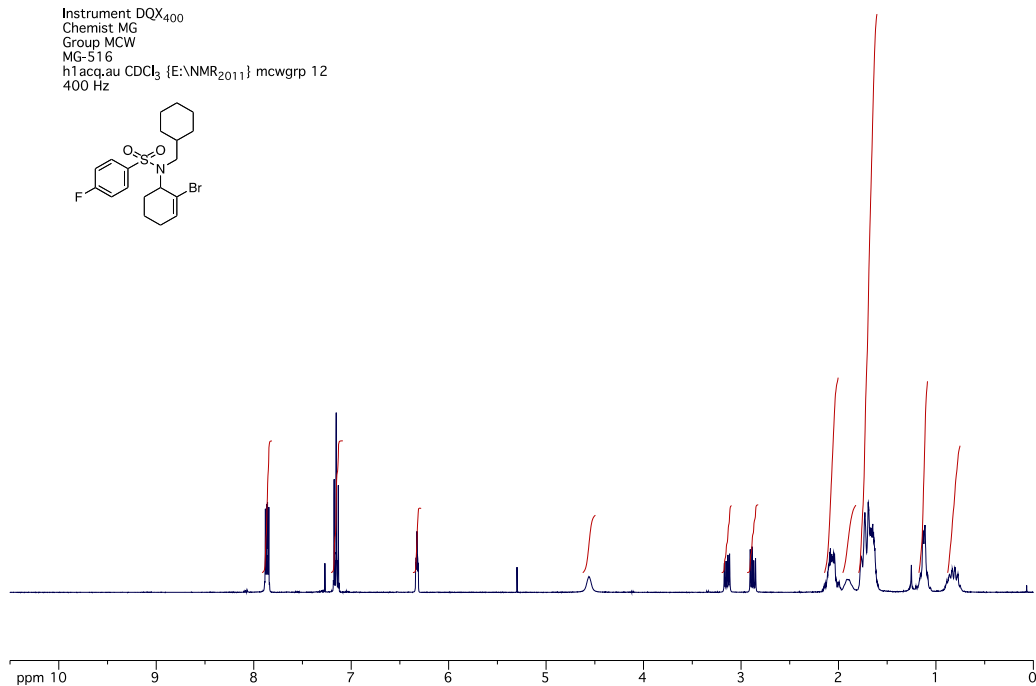
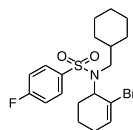
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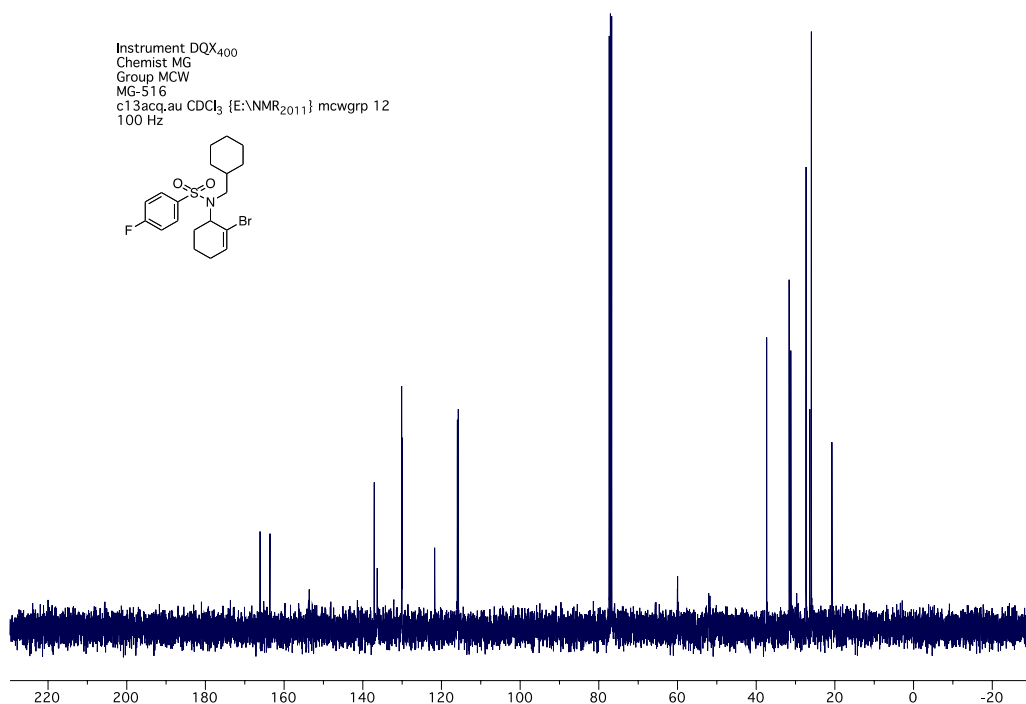
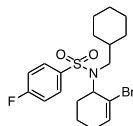
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 Chemist MG
 Group MCW
 MG-518
 c13acq.au CDCl₃ {E:\NMR2011} mcwgrp 14
 100 Hz



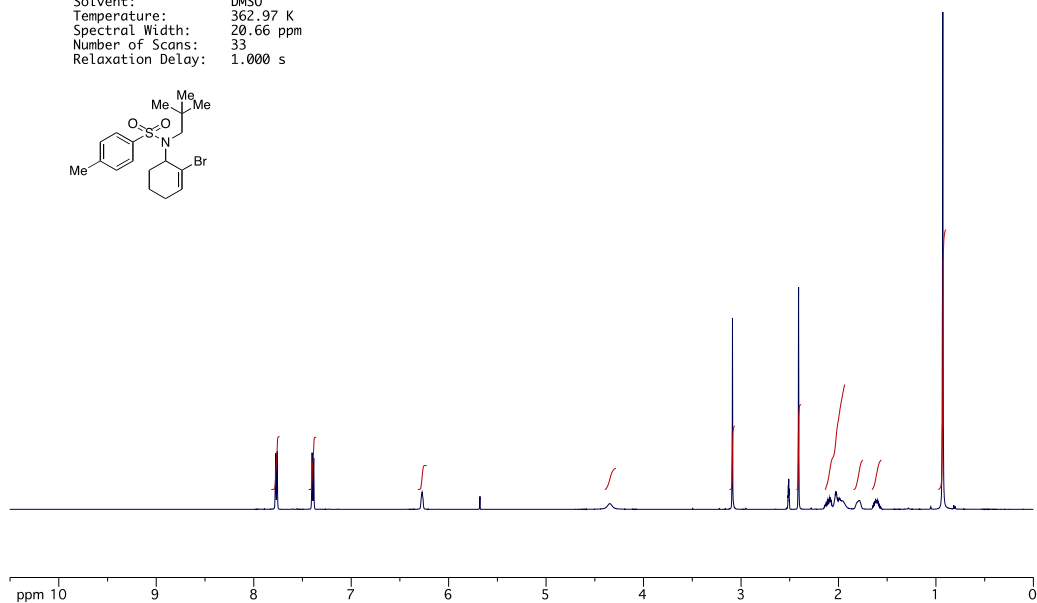
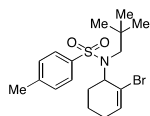
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 Chemist MG
 Group MCW
 MG-516
 h1acq.au CDCl₃ {E:\NMR₂₀₁₁} mcwgrp 12
 400 Hz



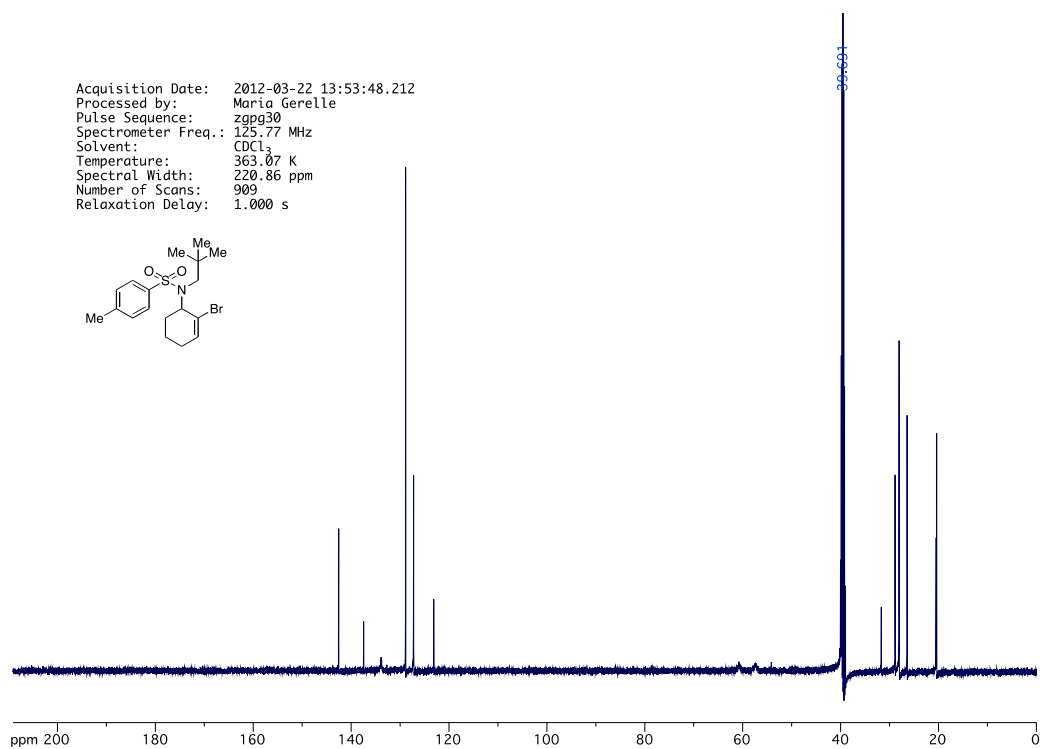
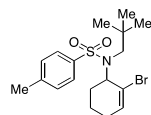
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 Chemist MG
 Group MCW
 MG-516
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 100 Hz



Acquisition Date: 2012-03-22 13:17:06.432
 Processed by: Maria Gerelle
 Pulse Sequence: zg60
 Spectrometer Freq.: 500.13 MHz
 Solvent: DMSO
 Temperature: 362.97 K
 Spectral Width: 20.66 ppm
 Number of Scans: 33
 Relaxation Delay: 1.000 s

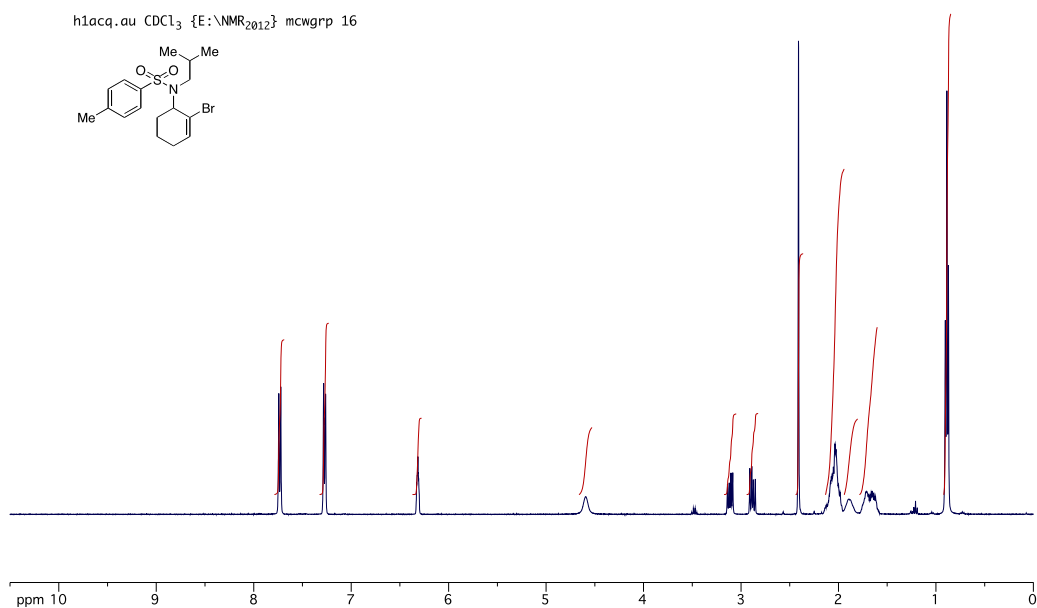
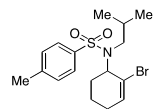


Acquisition Date: 2012-03-22 13:53:48.212
 Processed by: Maria Gerelle
 Pulse Sequence: zgpg30
 Spectrometer Freq.: 125.77 MHz
 Solvent: CDCl₃
 Temperature: 363.07 K
 Spectral Width: 220.86 ppm
 Number of Scans: 909
 Relaxation Delay: 1.000 s



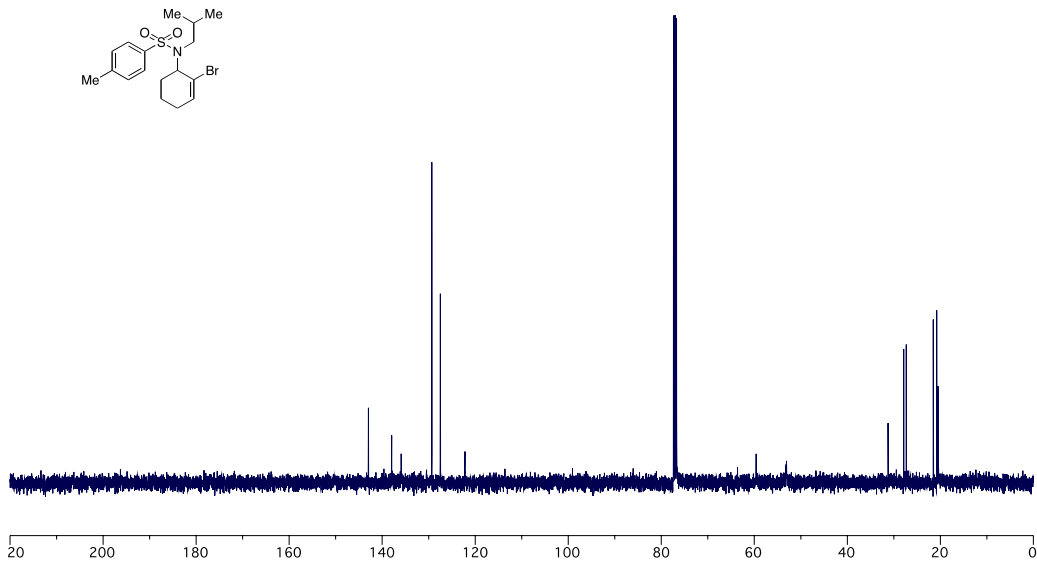
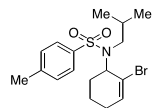
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 Chemist MG
 Group MCW
 MG-634

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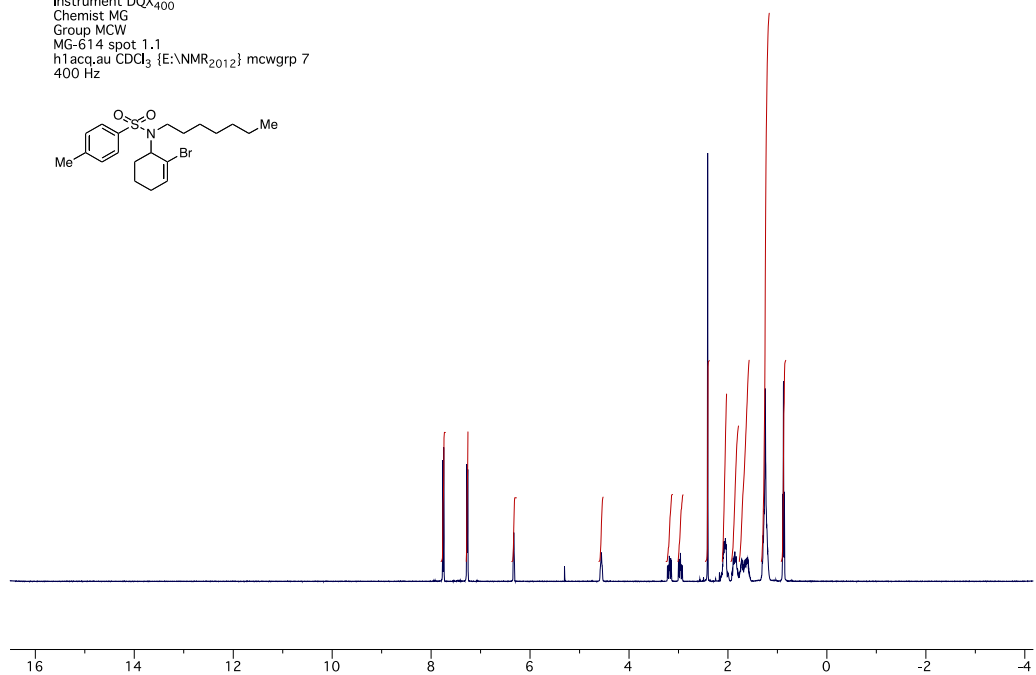
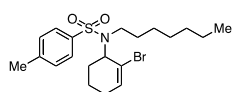


Instrument DQX400
 Chemist MG
 Group MCW
 MG-634

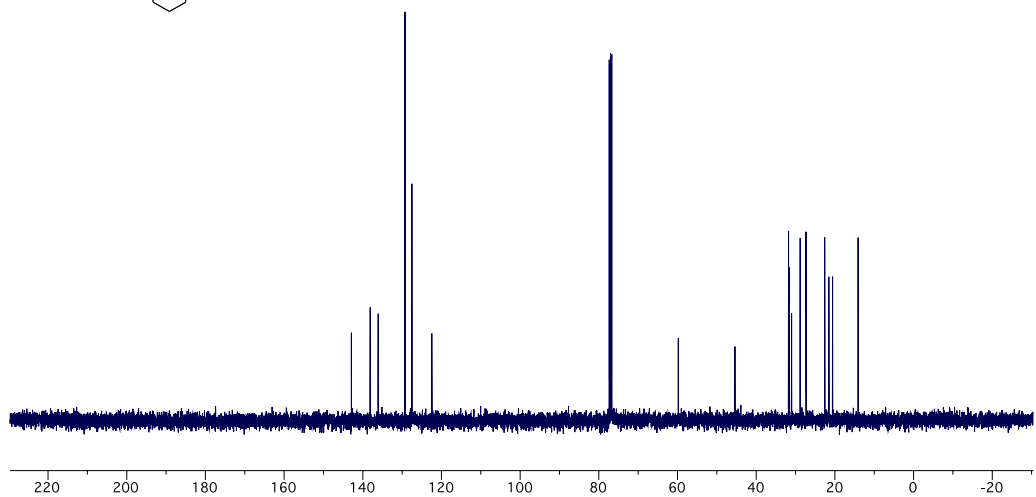
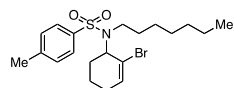
c13acq.au CDCl₃ {E:\NMR2012} mcwgrp 16



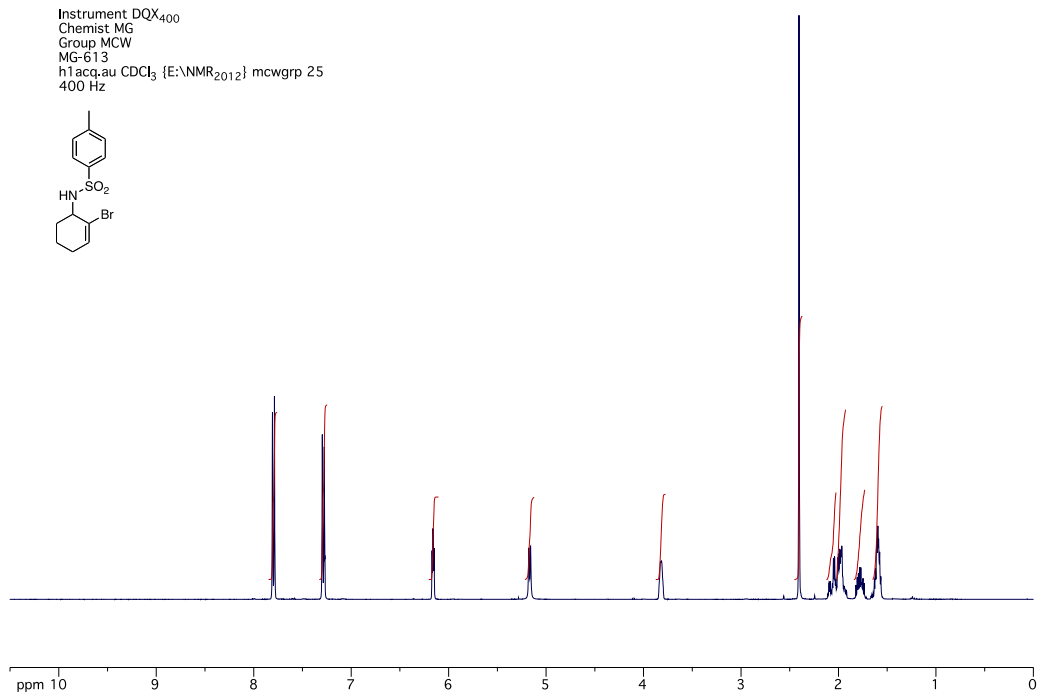
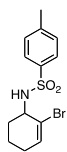
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 Chemist MG
 Group MCW
 MG-614 spot 1.1
 h1acq.au CDCl₃ {E:\NMR₂₀₁₂} mcwgrp 7
 400 Hz



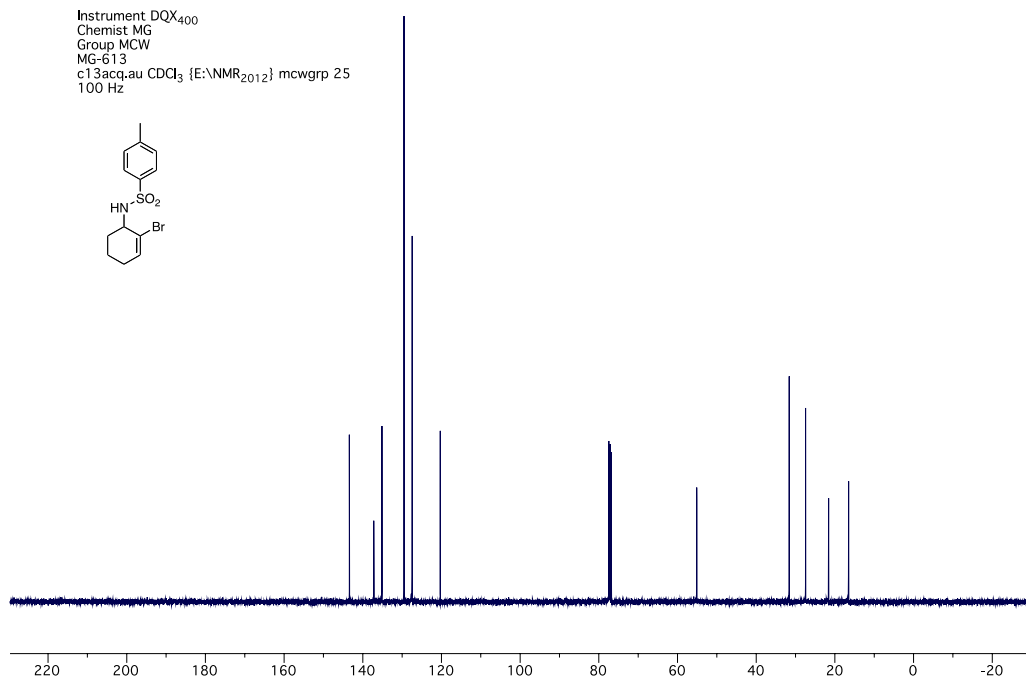
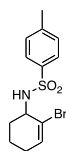
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 Chemist MG
 Group MCW
 MG-614 spot 1.1
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 100 Hz



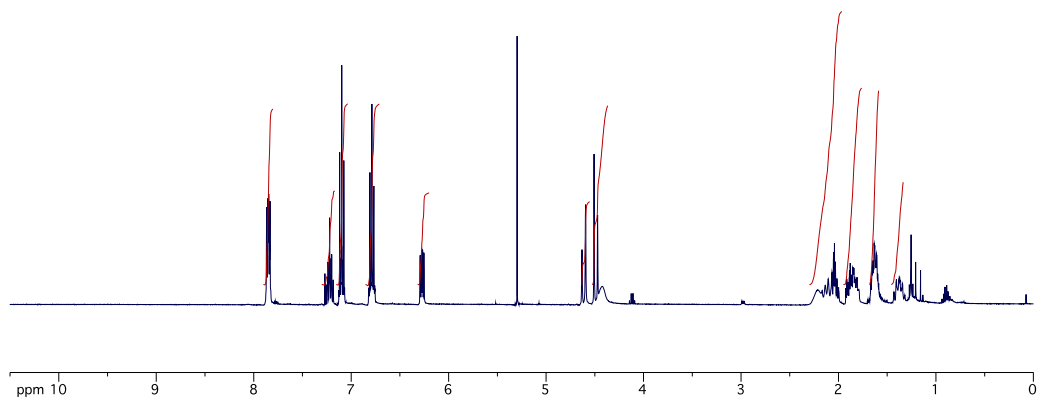
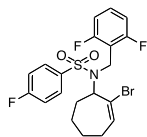
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-613
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 400 Hz



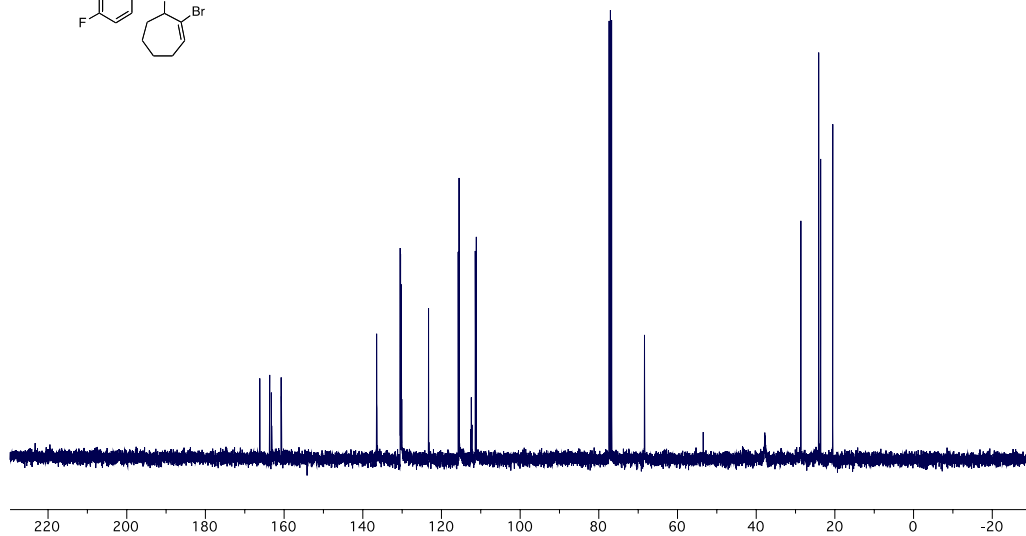
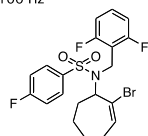
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-613
 c13acq.au CDCl₃ {E:\NMR₂₀₁₂} mcwgrp 25
 100 Hz



Instrument DQX400
 Chemist MG
 Group MCW
 MG-555
 h1acq.au CDCl₃ {E:\NMR2011} mcwgrp 32
 400 Hz

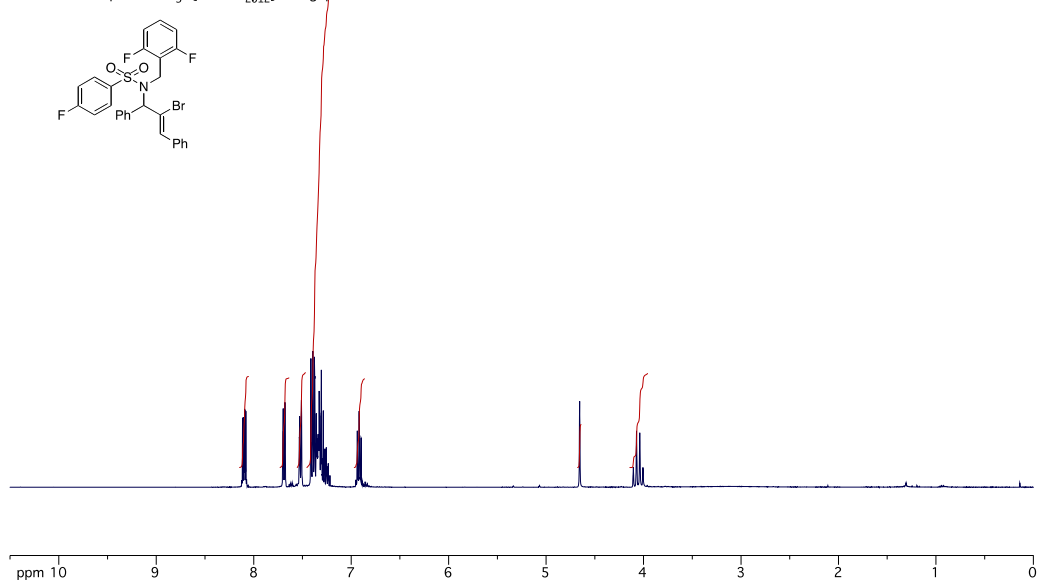
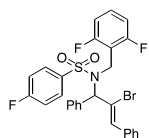


Instrument DQX400
 Chemist MG
 Group MCW
 MG-555
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 100 Hz

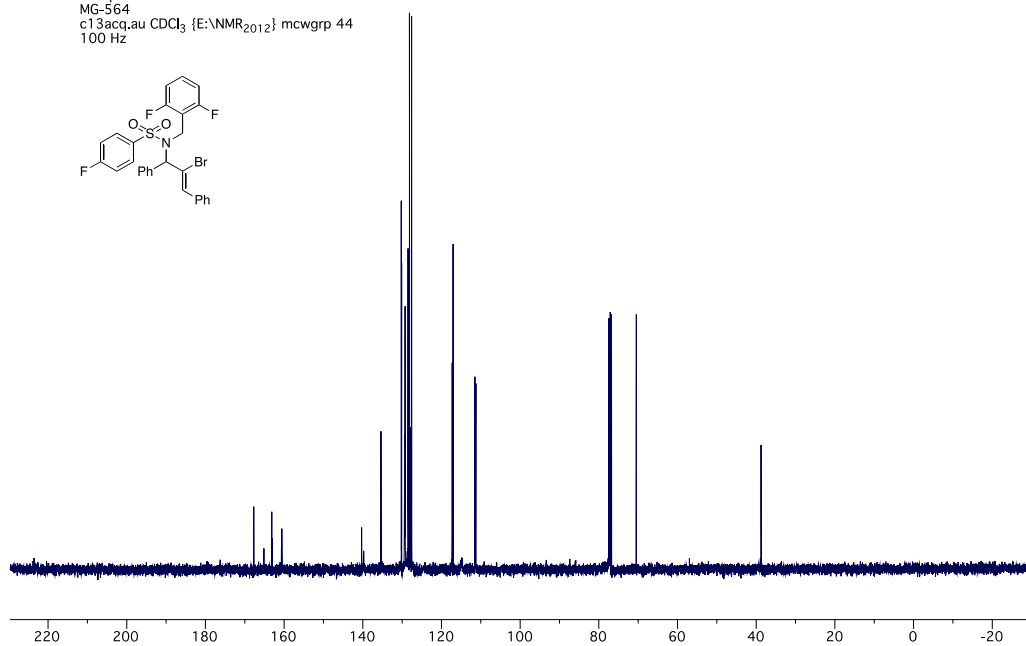
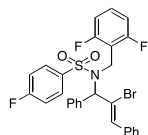


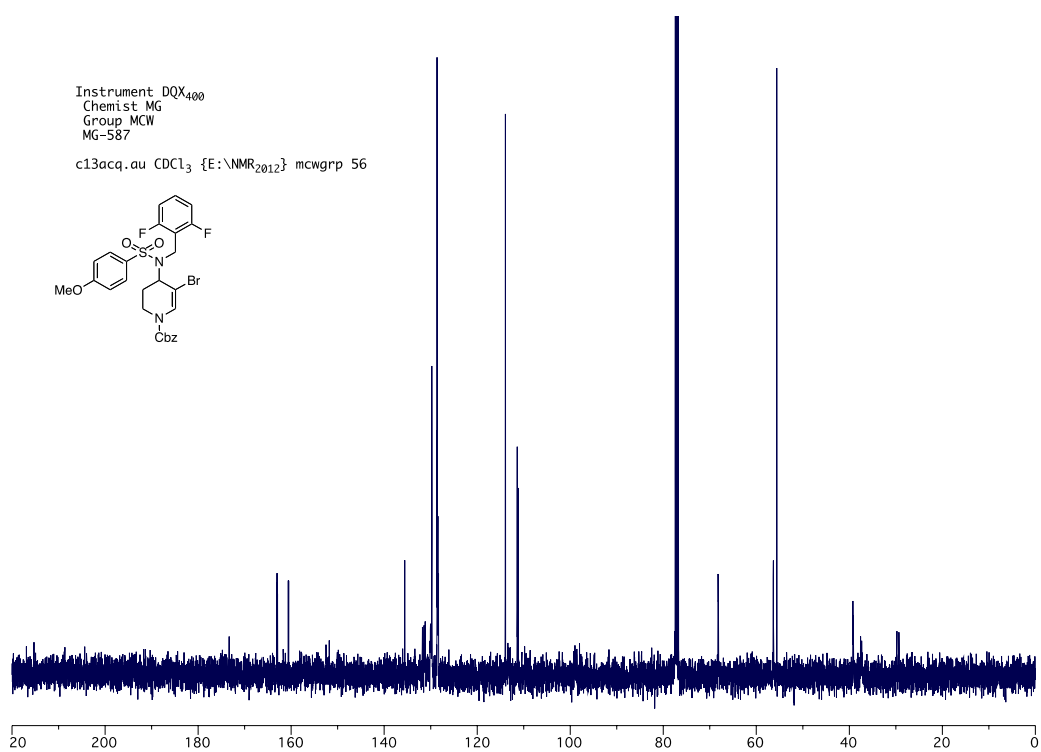
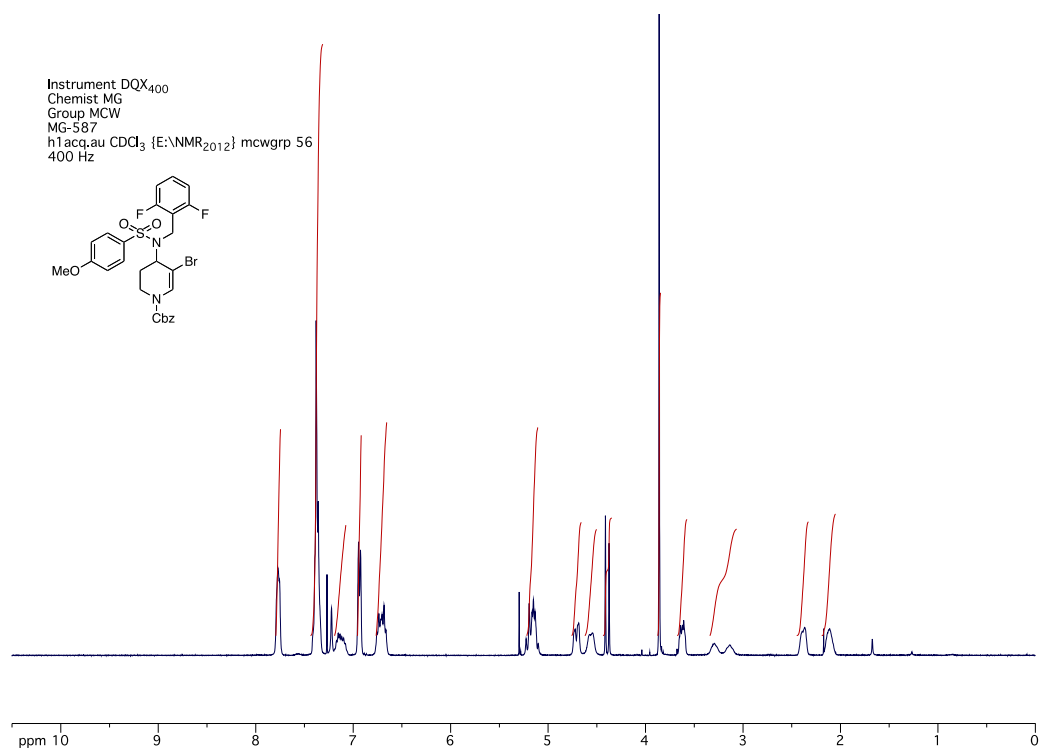
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 Group MCW
 MG-564

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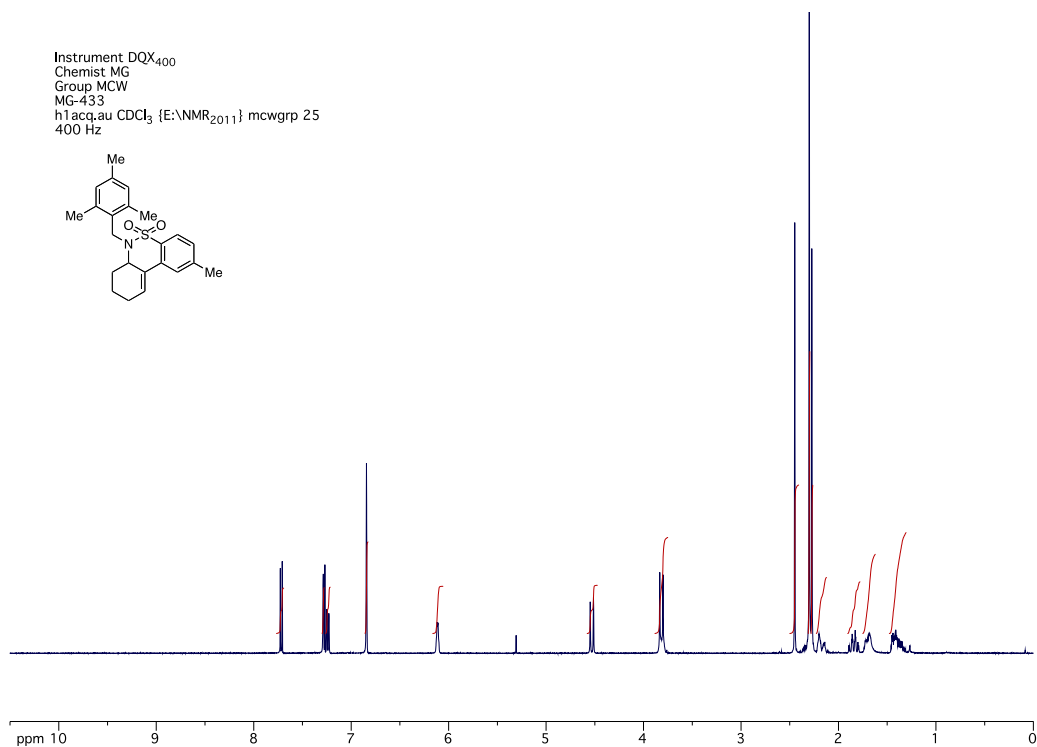
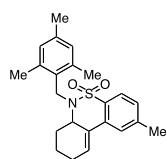


Instrument DQX400
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 Group MCW
 MG-564
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 100 Hz

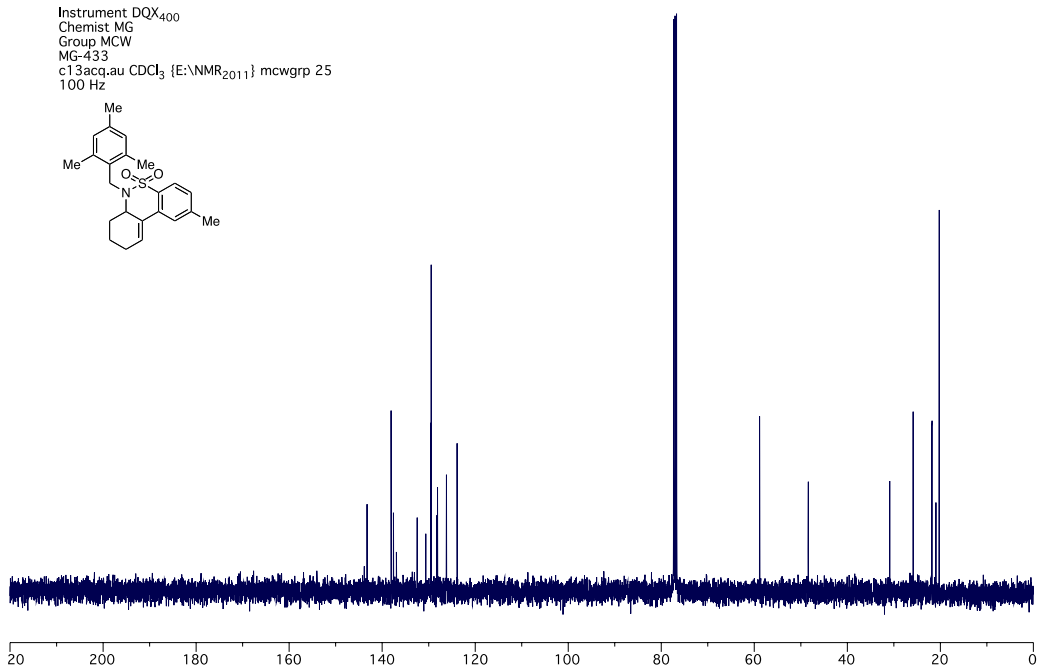
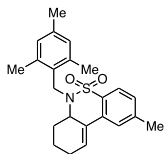




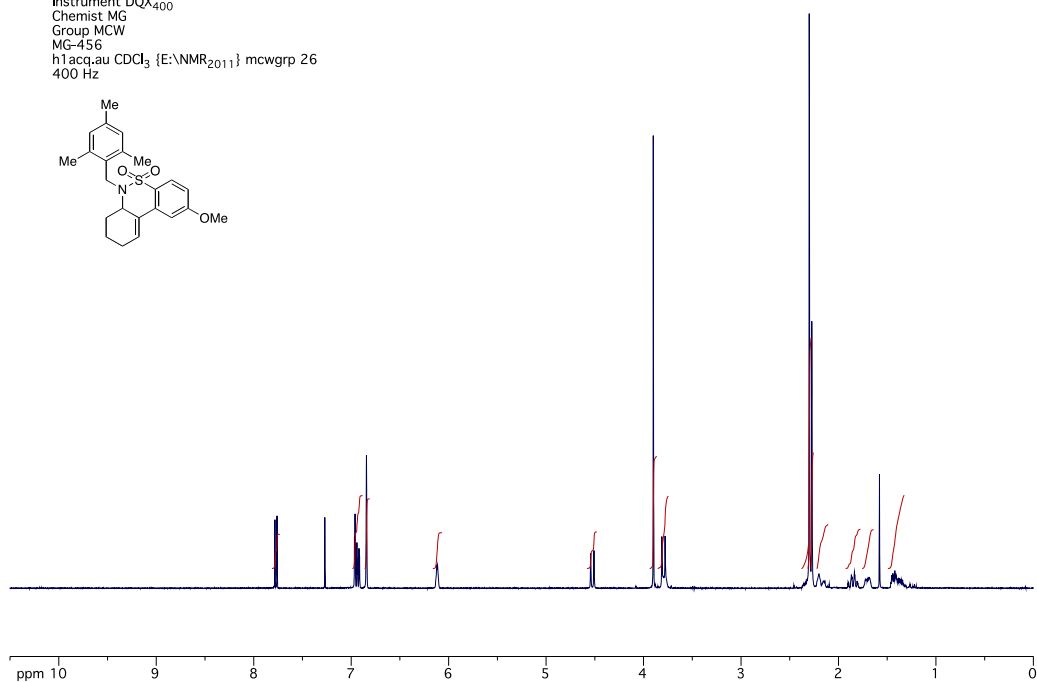
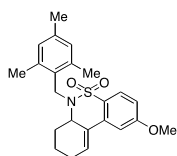
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 Chemist MG
 Group MCW
 MG-433
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 400 Hz



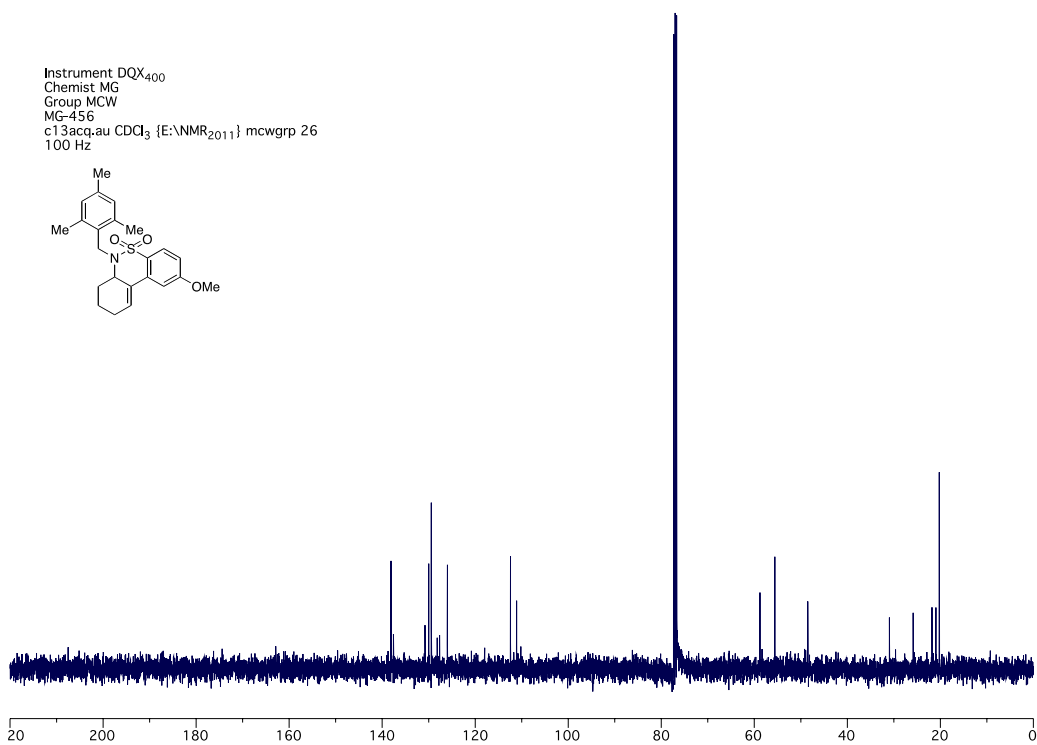
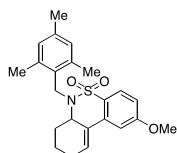
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 Group MCW
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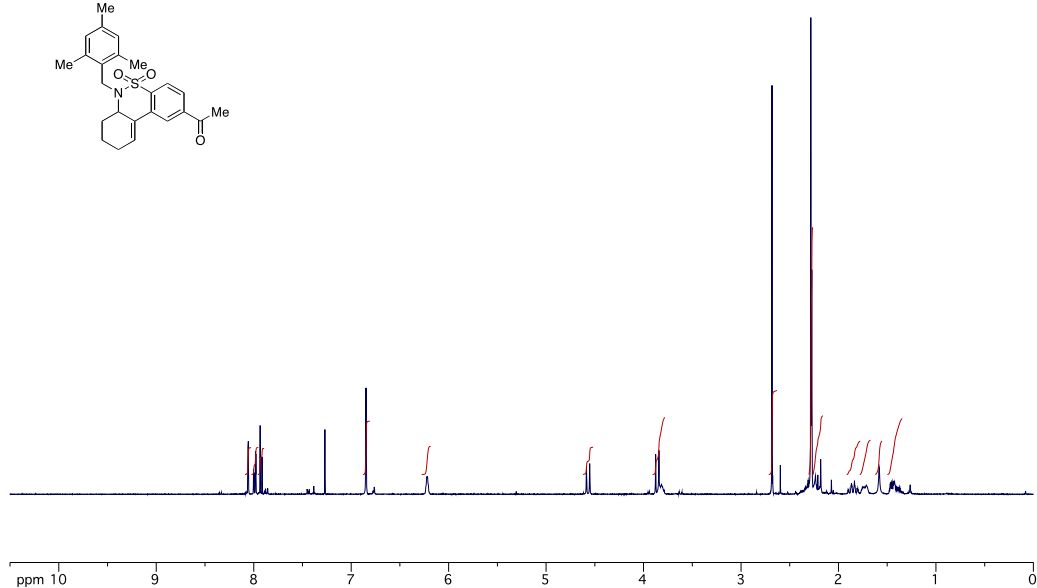
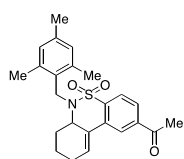
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 Chemist MG
 Group MCW
 MG-456
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 400 Hz



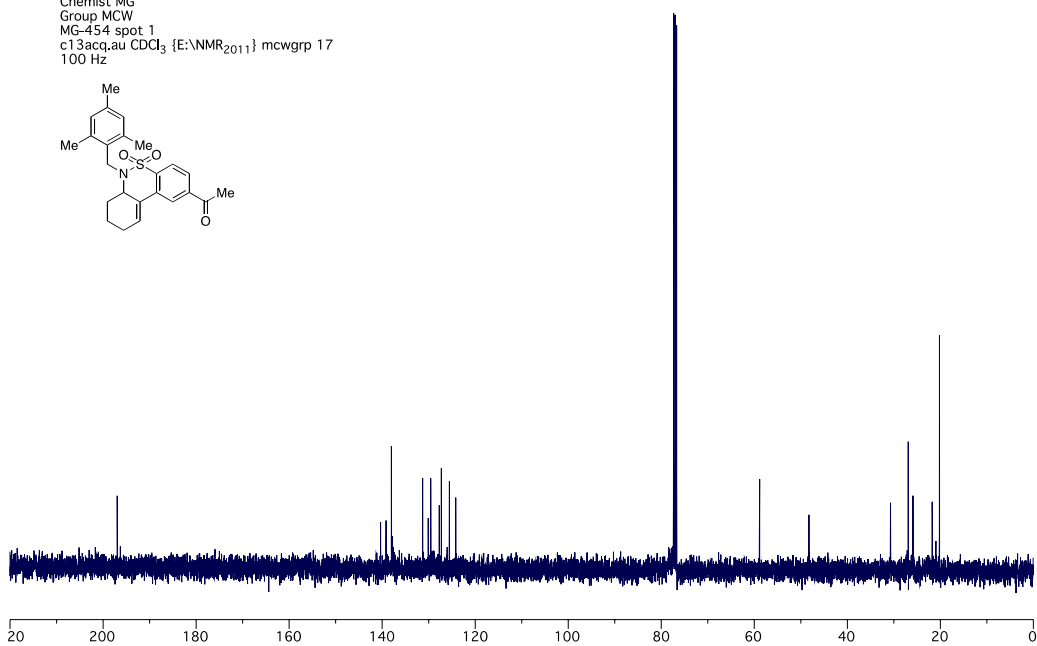
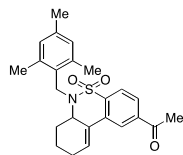
Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-456
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 100 Hz

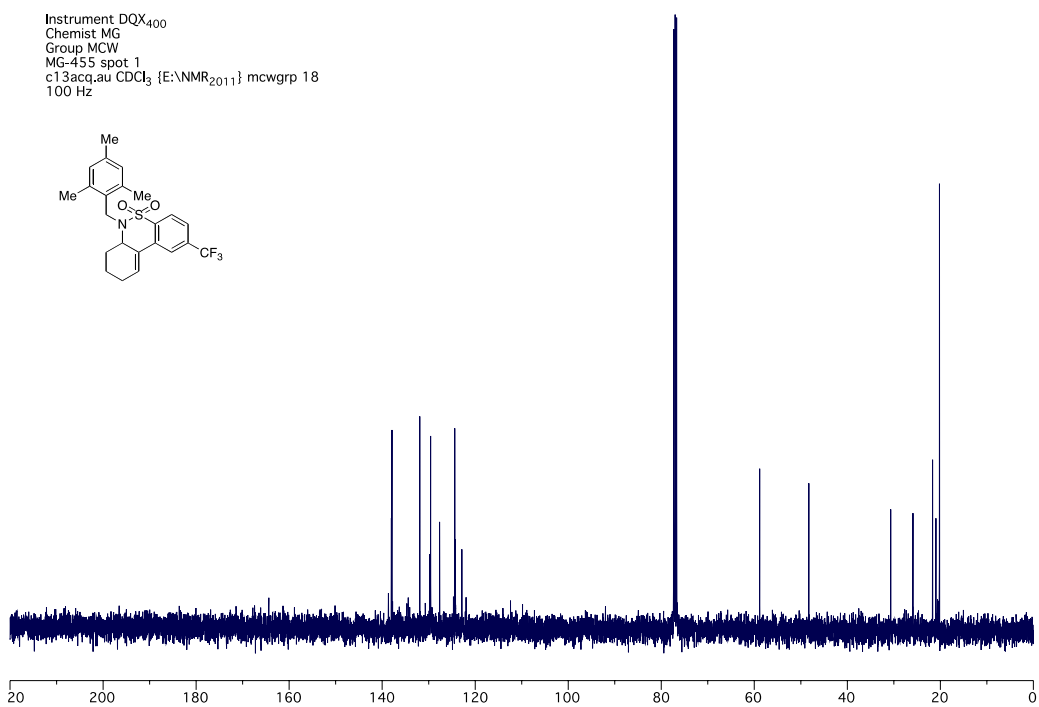
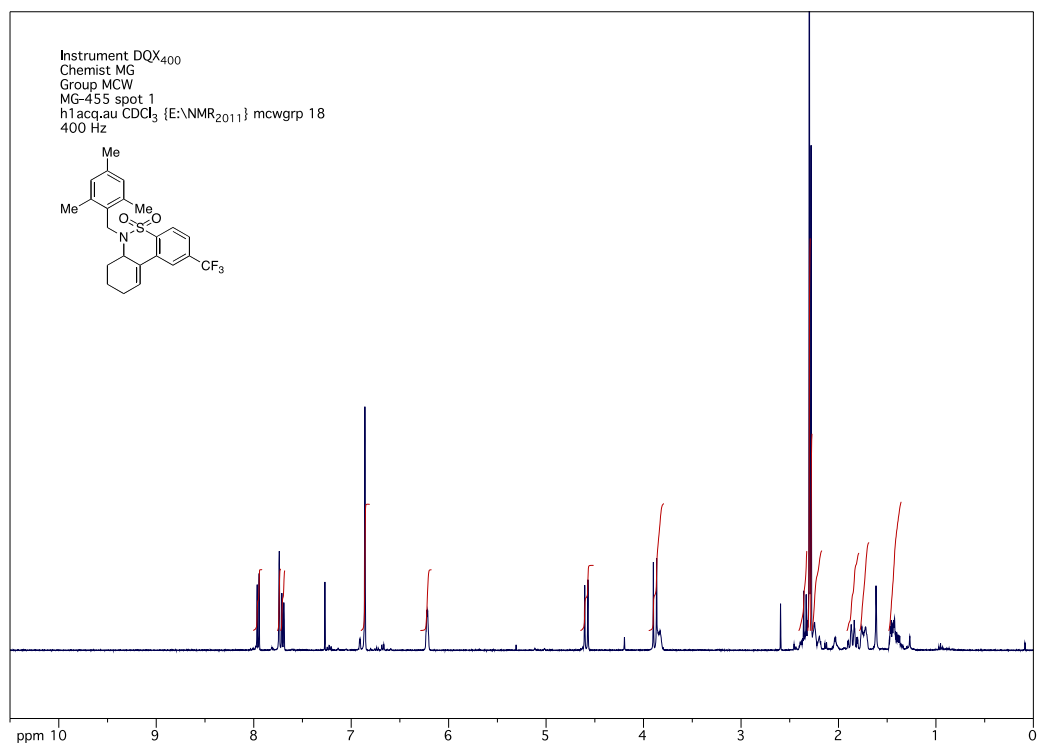


Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-454 spot 1
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 400 Hz

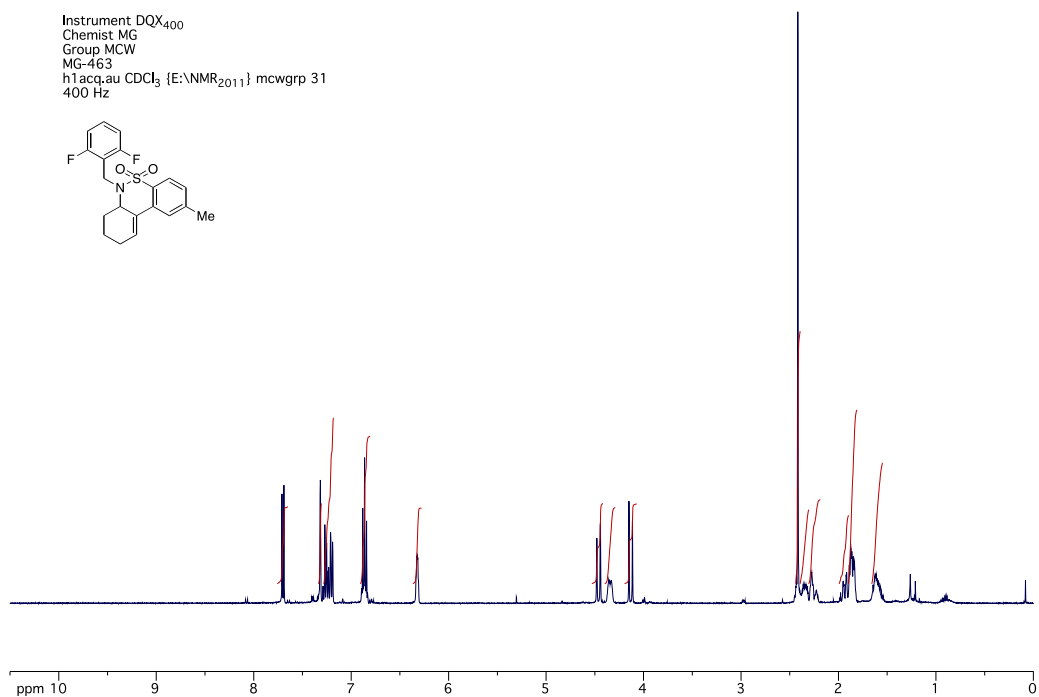
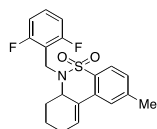


Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-454 spot 1
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 100 Hz

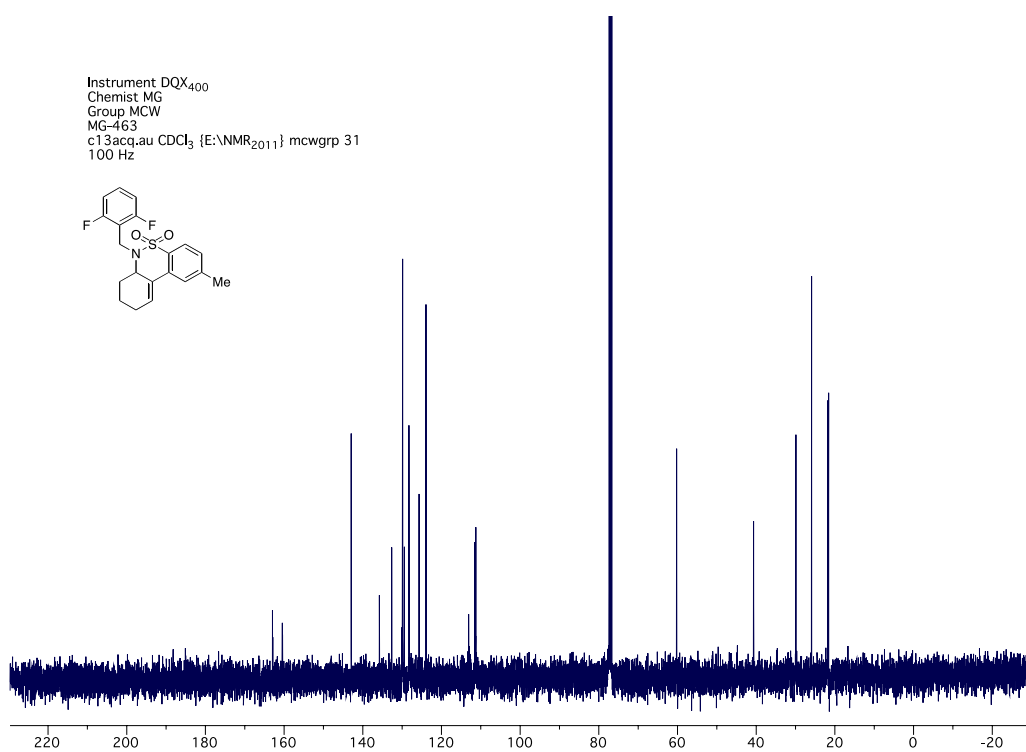
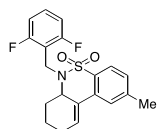




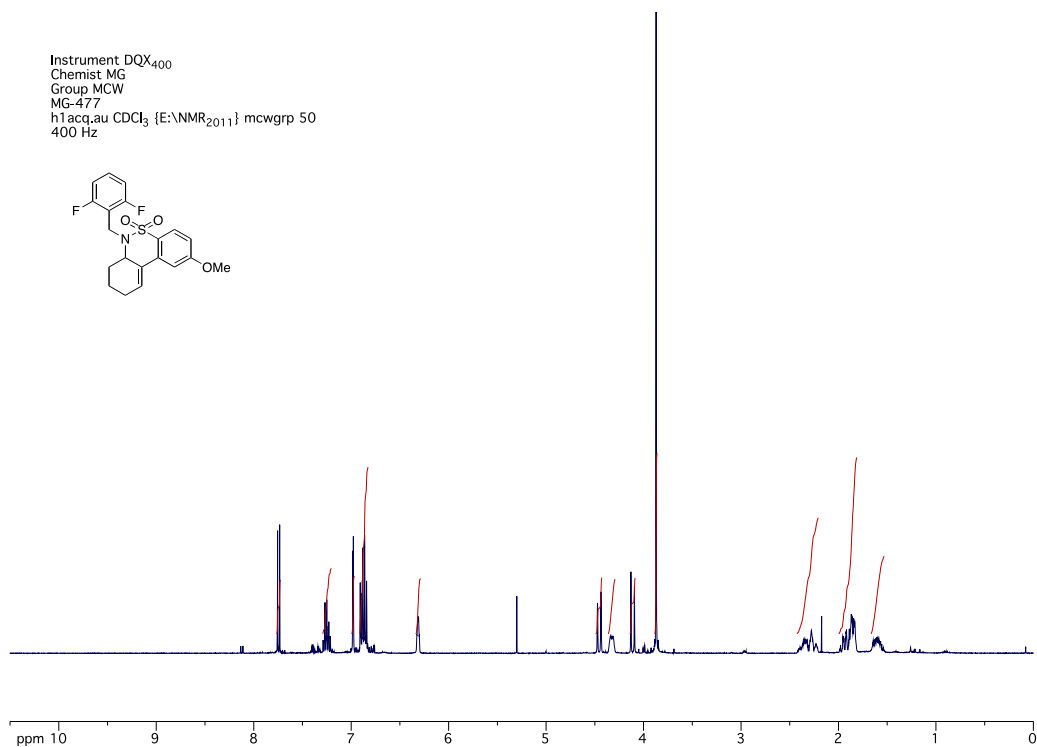
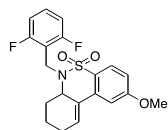
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 Group MCW
 MG-463
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 400 Hz



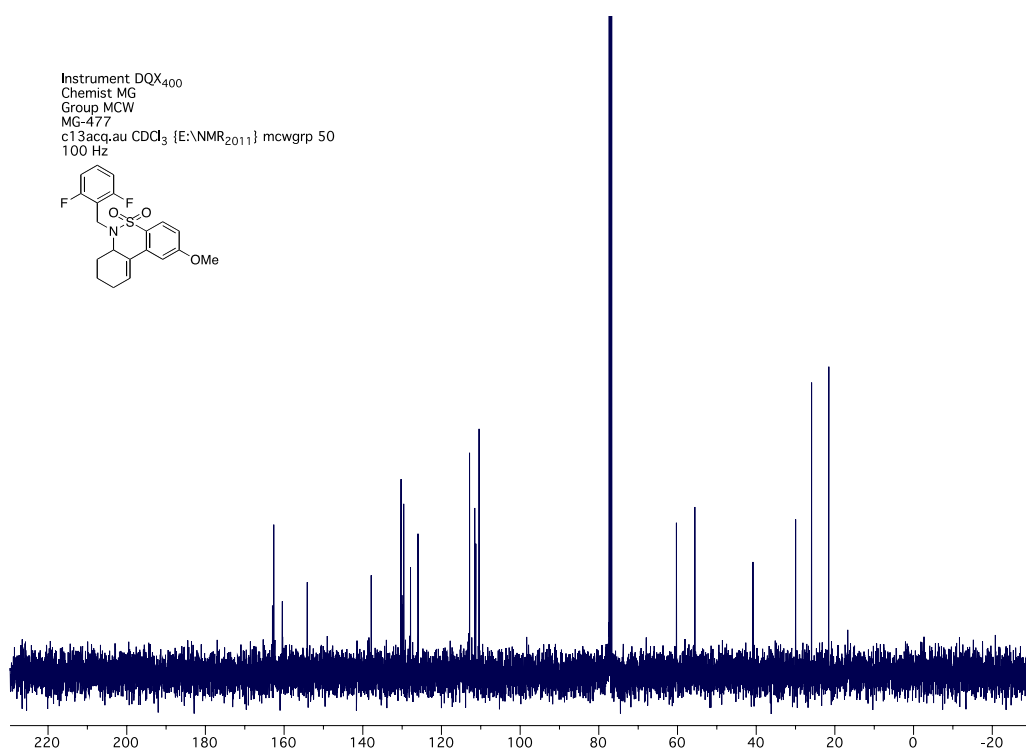
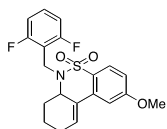
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 Group MCW
 MG-463
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 100 Hz



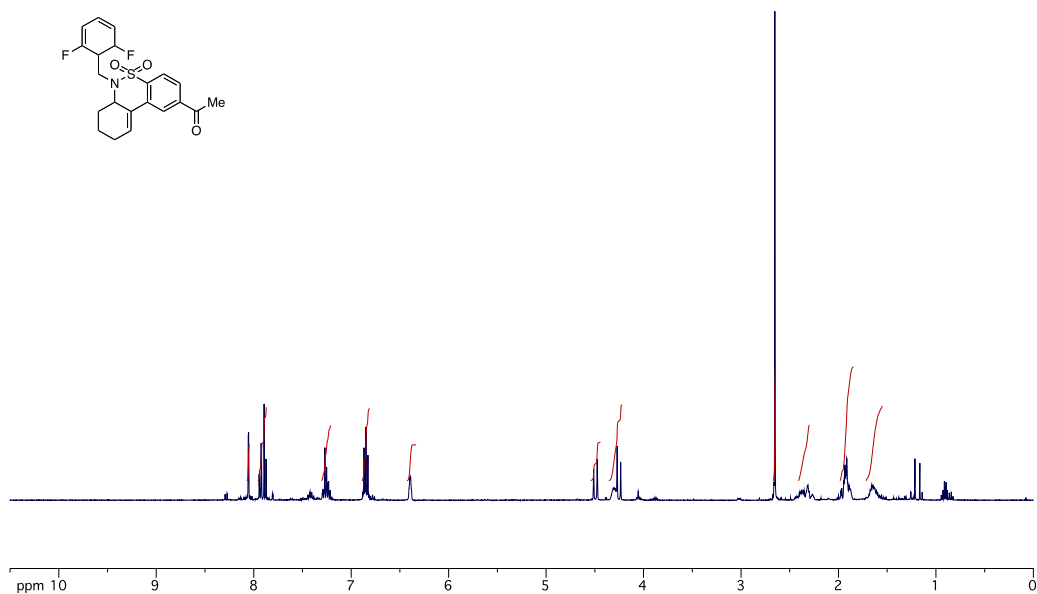
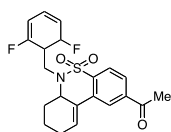
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 Group MCW
 MG-477
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 400 Hz



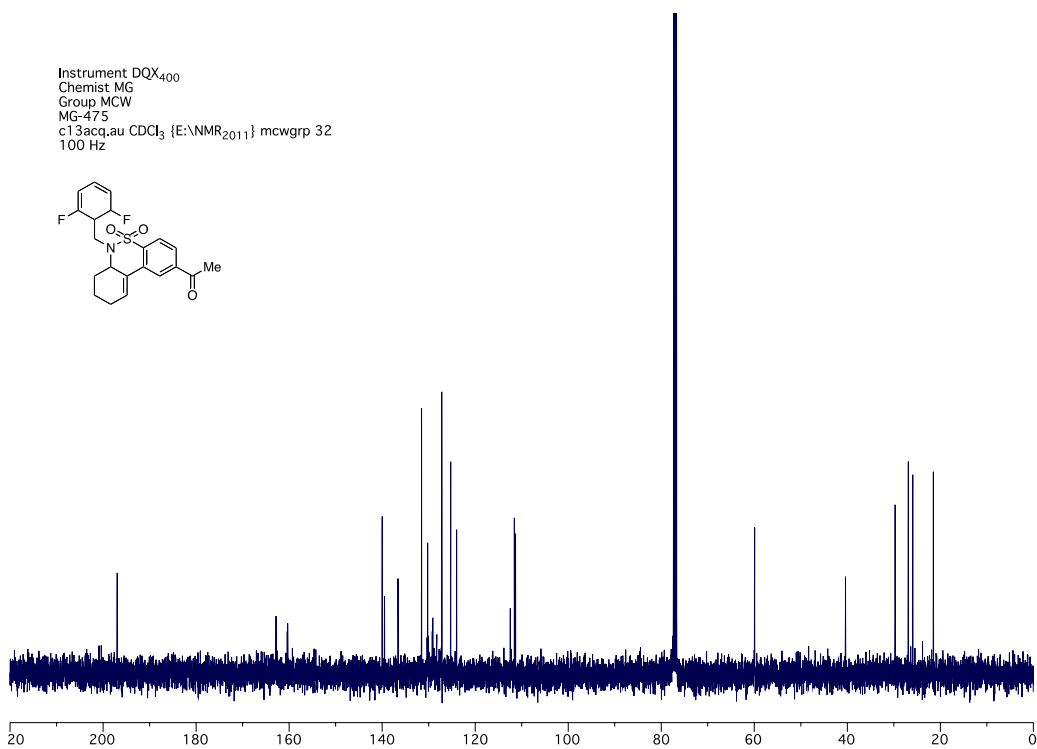
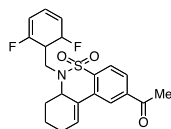
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 Group MCW
 MG-477
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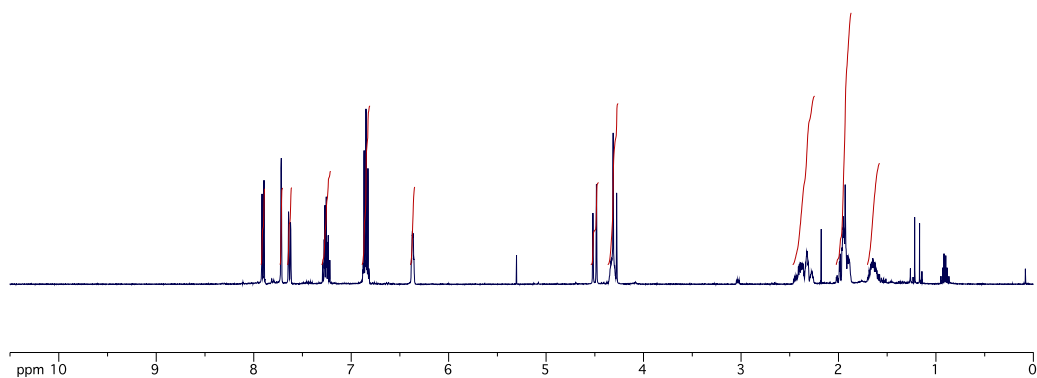
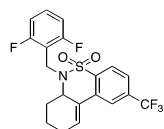
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 Chemist MG
 Group MCW
 MG-475
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 400 Hz



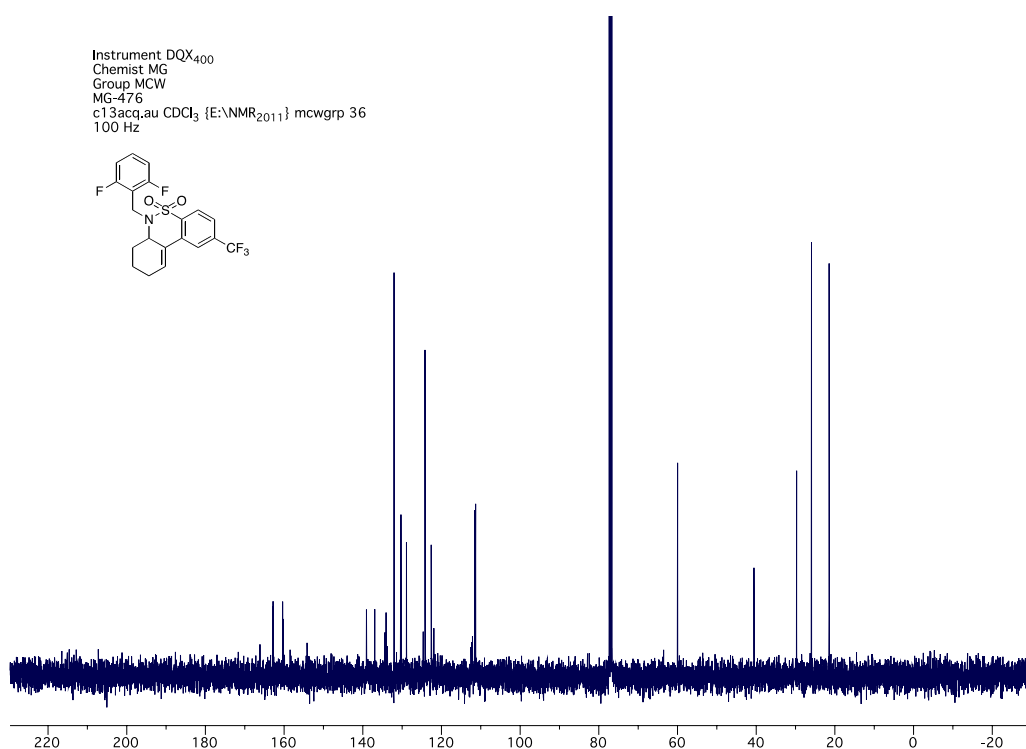
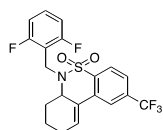
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 Chemist MG
 Group MCW
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 100 Hz



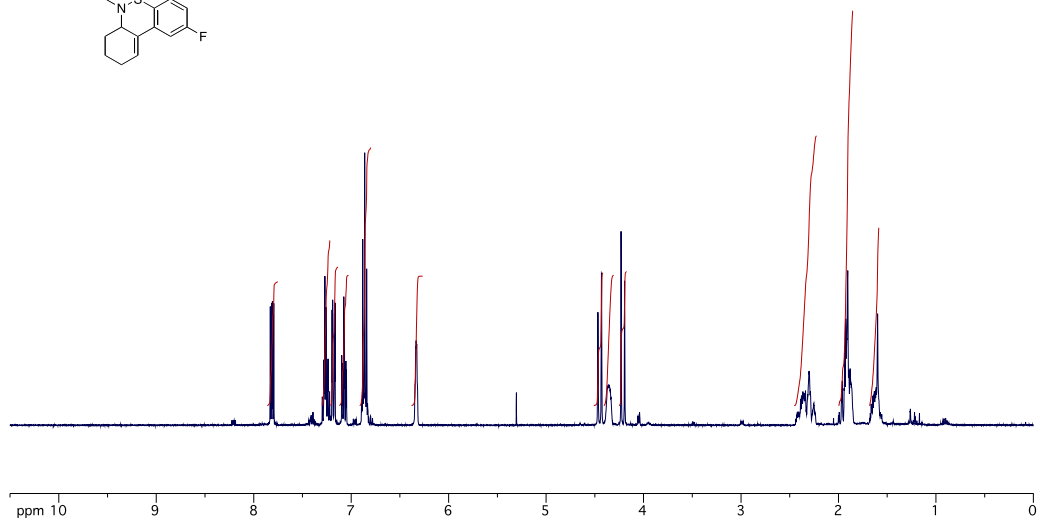
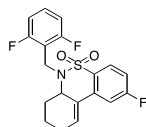
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 Group MCW
 MG-476
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 400 Hz



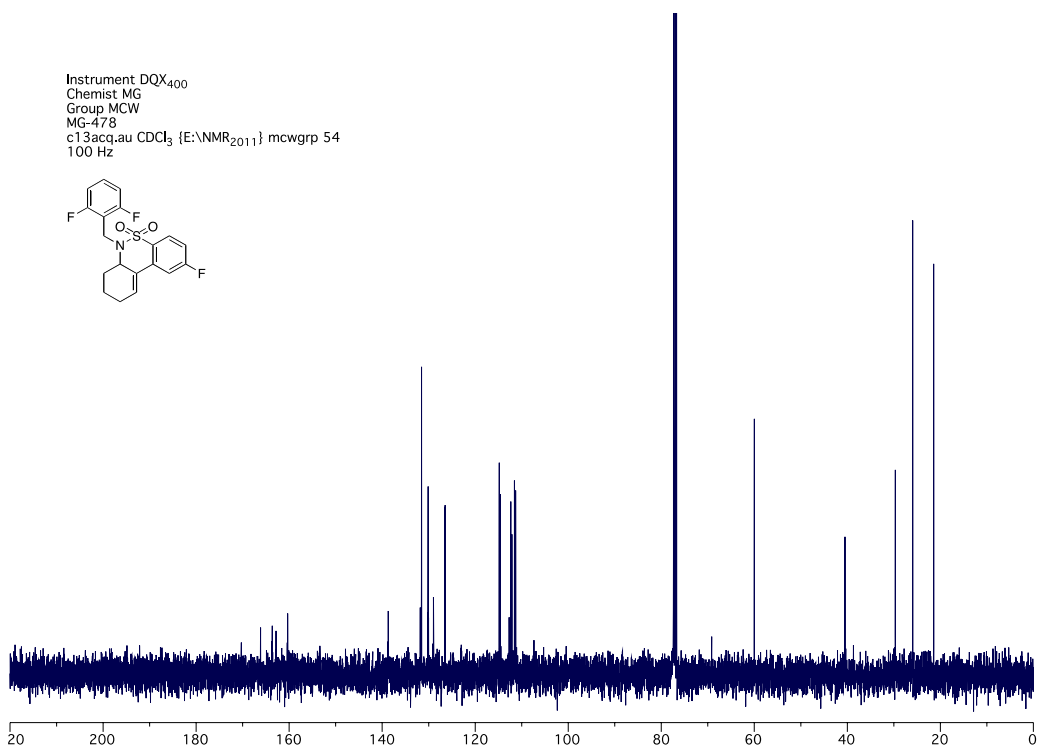
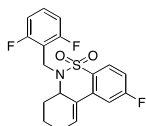
Instrument DQX400
 Chemist MG
 Group MCW
 MG-476
 c13acq.au CDCl₃ {E:\NMR2011} mcwgrp 36
 100 Hz



Instrument DQX400
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 Group MCW
 MG-478
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 400 Hz

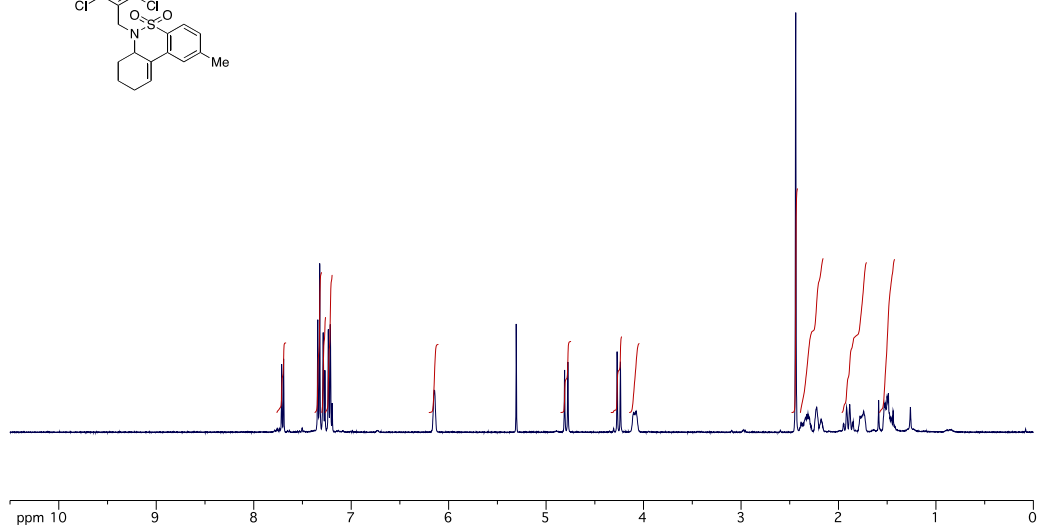
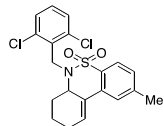


Instrument DQX400
 Chemist MG
 Group MCW
 MG-478
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 100 Hz



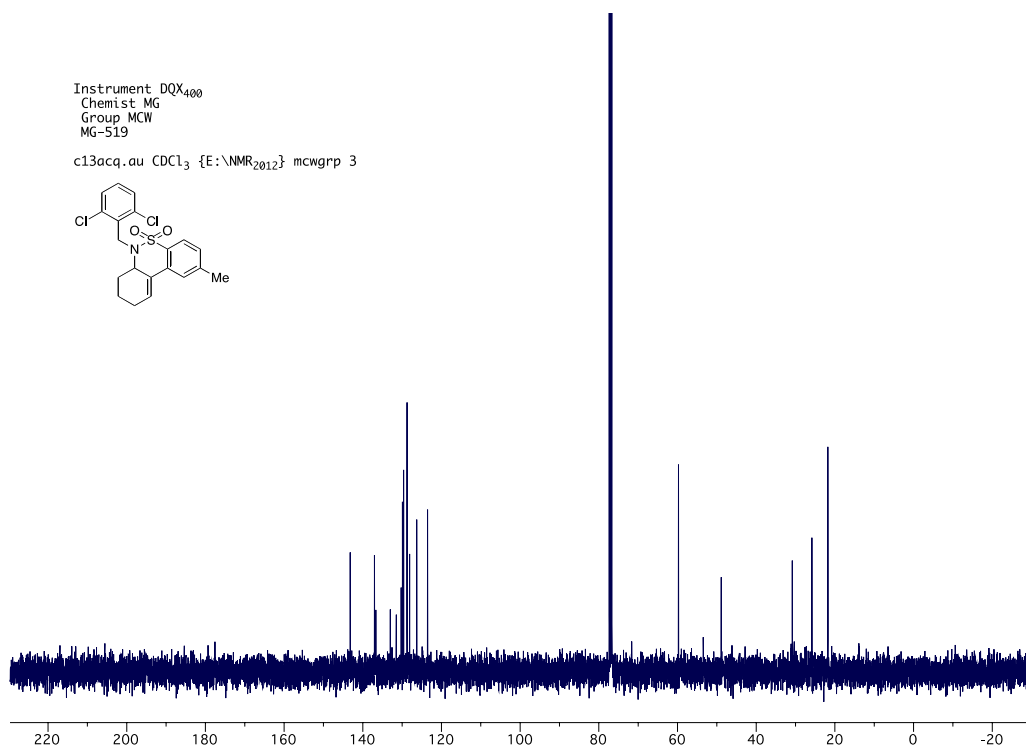
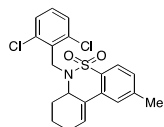
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 Chemist MG
 Group MCW
 MG-519

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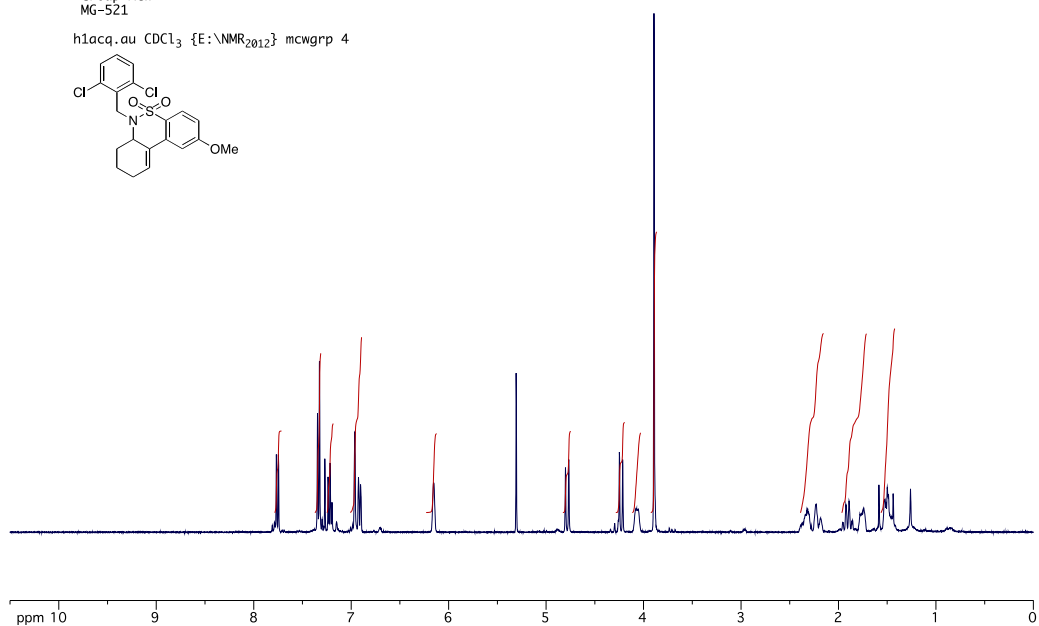
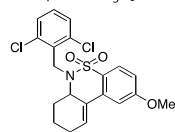
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 Group MCW
 MG-519

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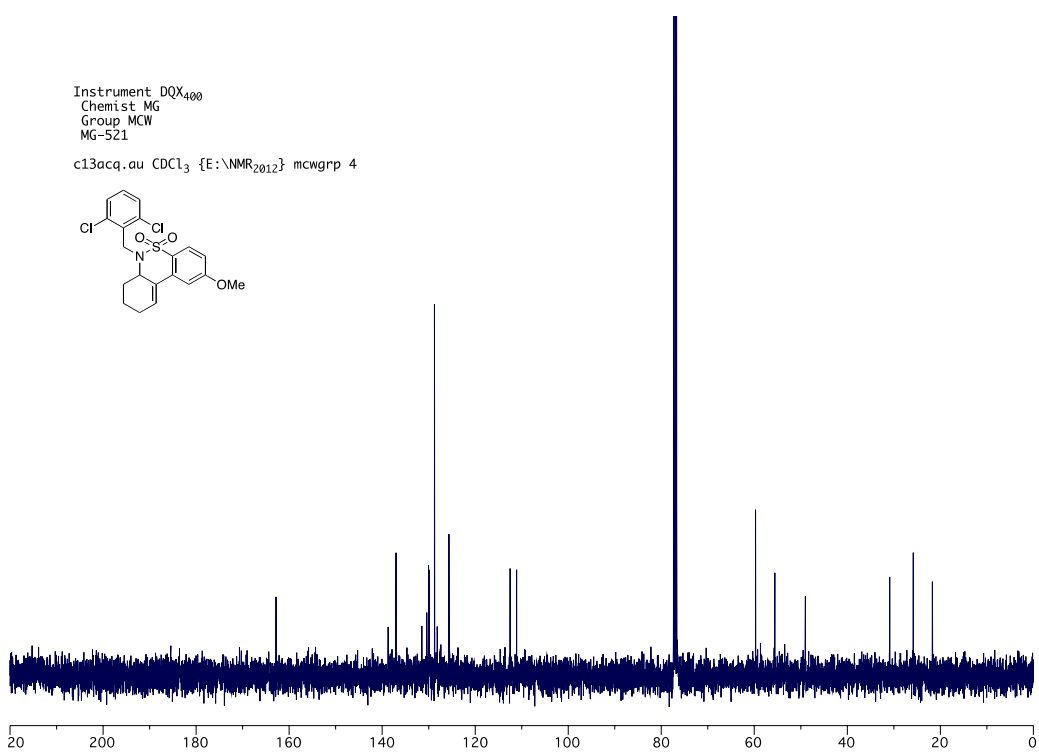
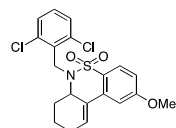
Instrument DQX400
 Chemist MG
 Group MCW
 MG-521

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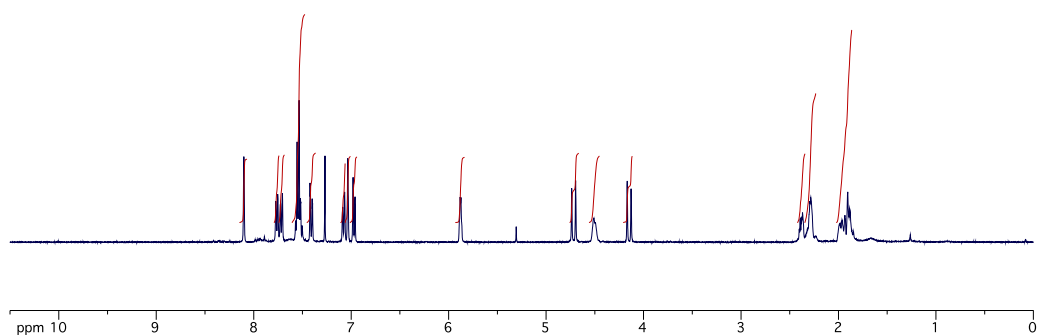
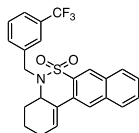
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 Chemist MG
 Group MCW
 MG-521

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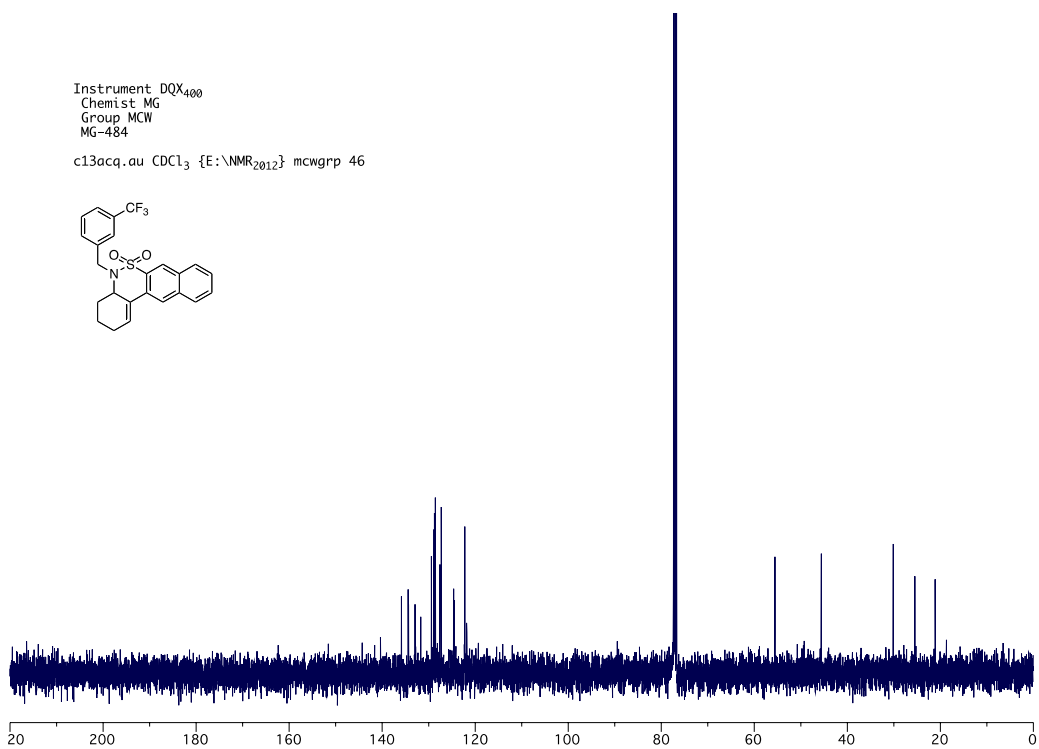
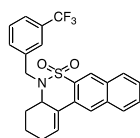
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 Chemist MG
 Group MCW
 MG-484

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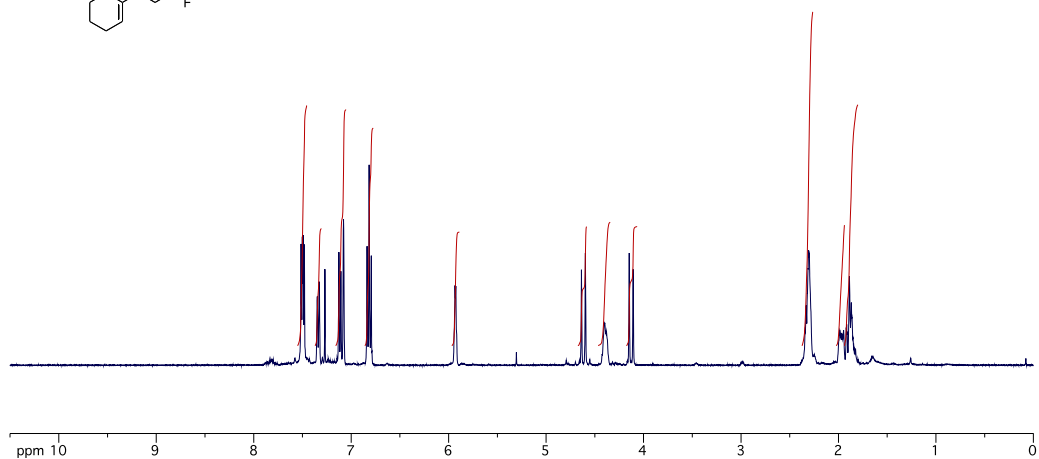
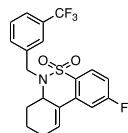
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 Chemist MG
 Group MCW
 MG-484

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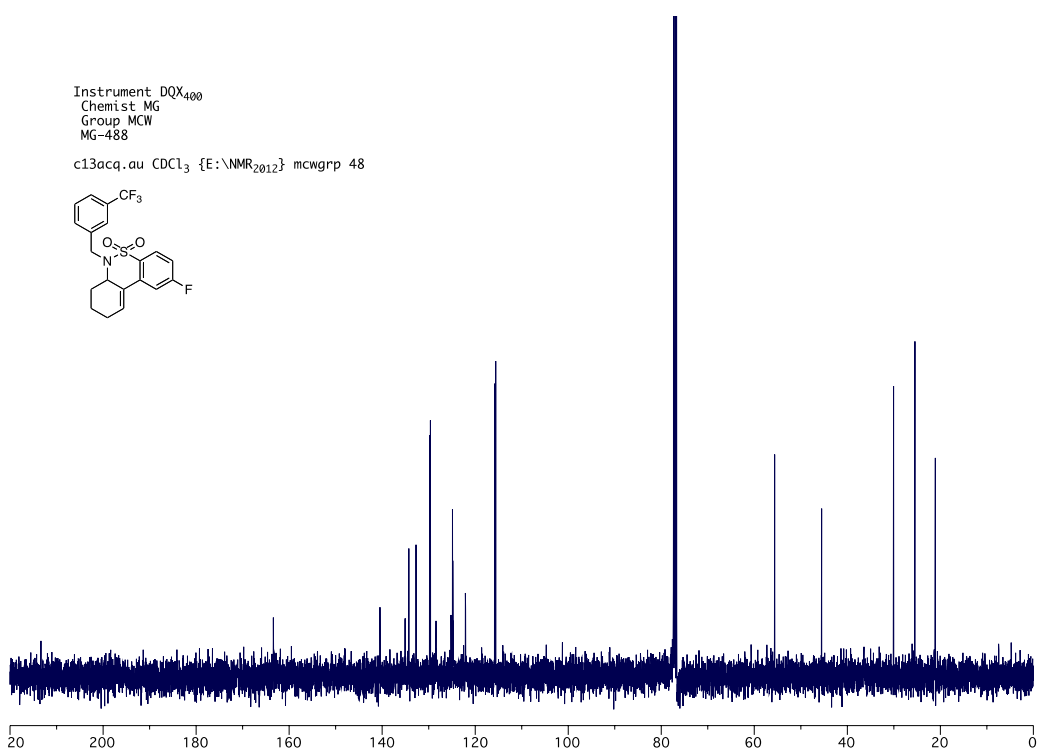
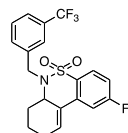
Instrument DQX400
Chemist MG
Group MCW
MG-488

h1acq.au CDCl₃ {E:\NMR2012} mcwgrp 48



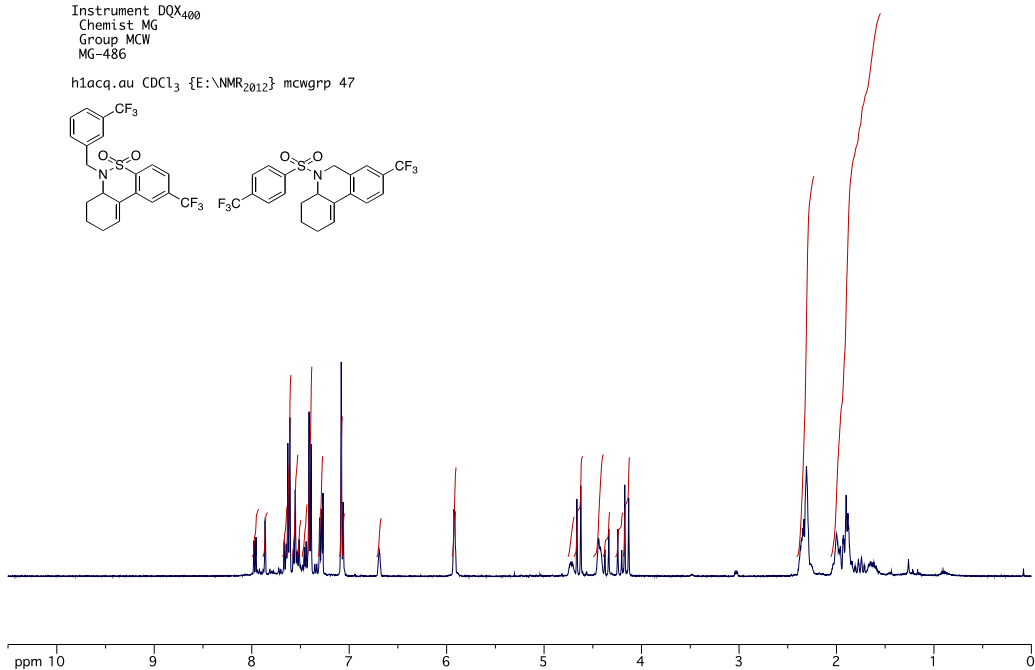
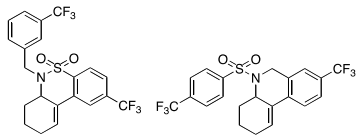
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Chemist MG
Group MCW
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c13acq.au CDCl₃ {E:\NMR2012} mcwgrp 48



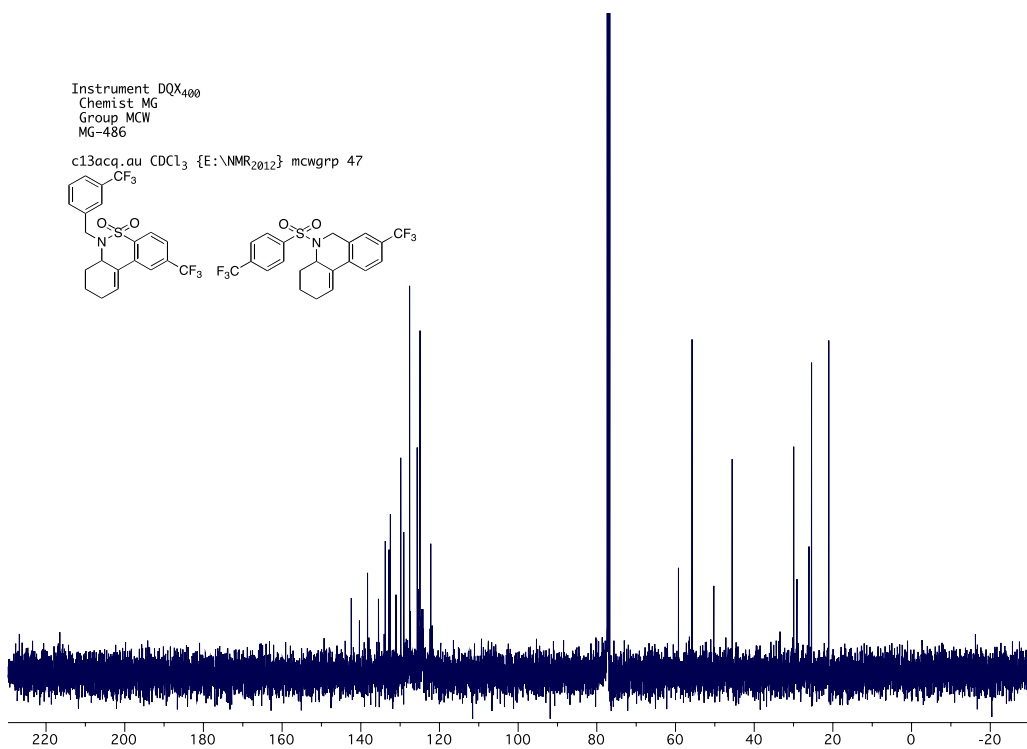
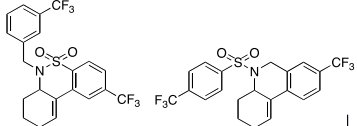
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Chemist MG
Group MCW
MG-486

h1acq.au CDCl₃ {E:\NMR2012} mcwgrp 47

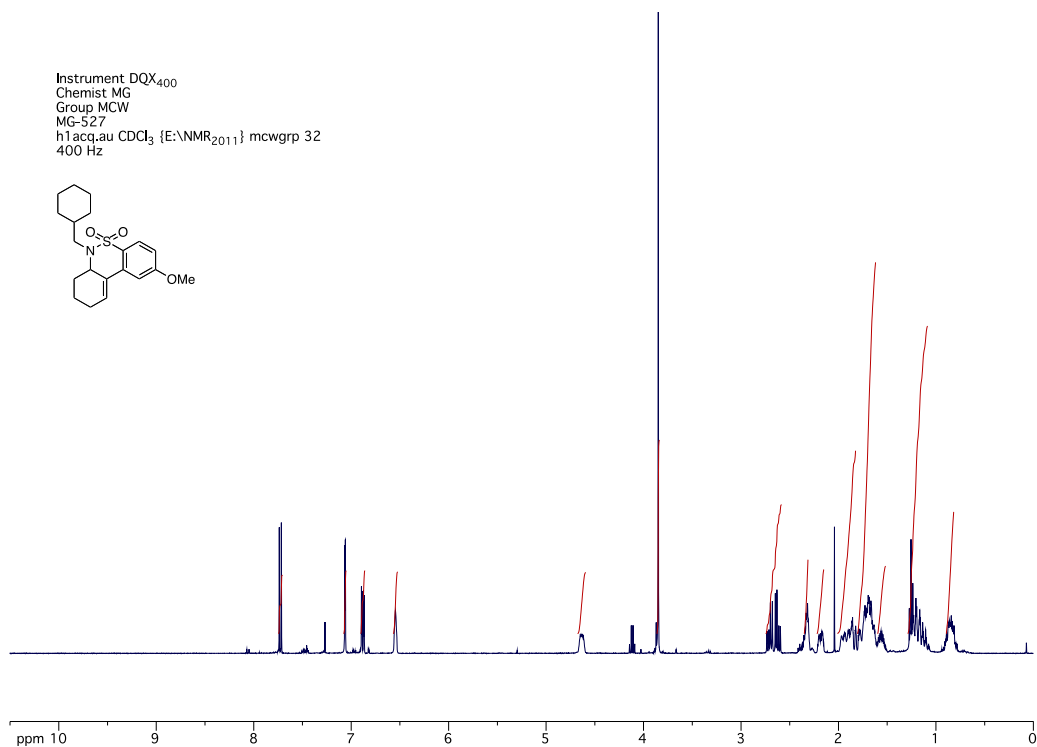
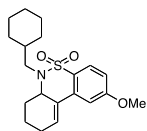


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Chemist MG
Group MCW
MG-486

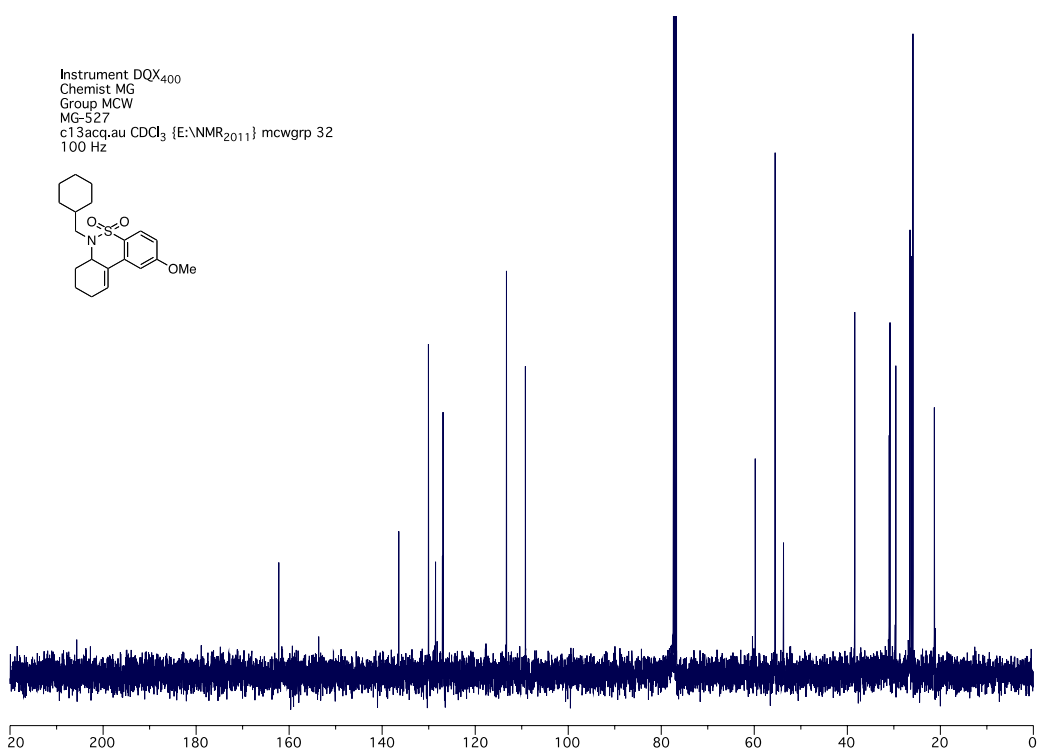
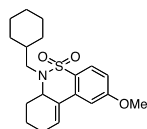
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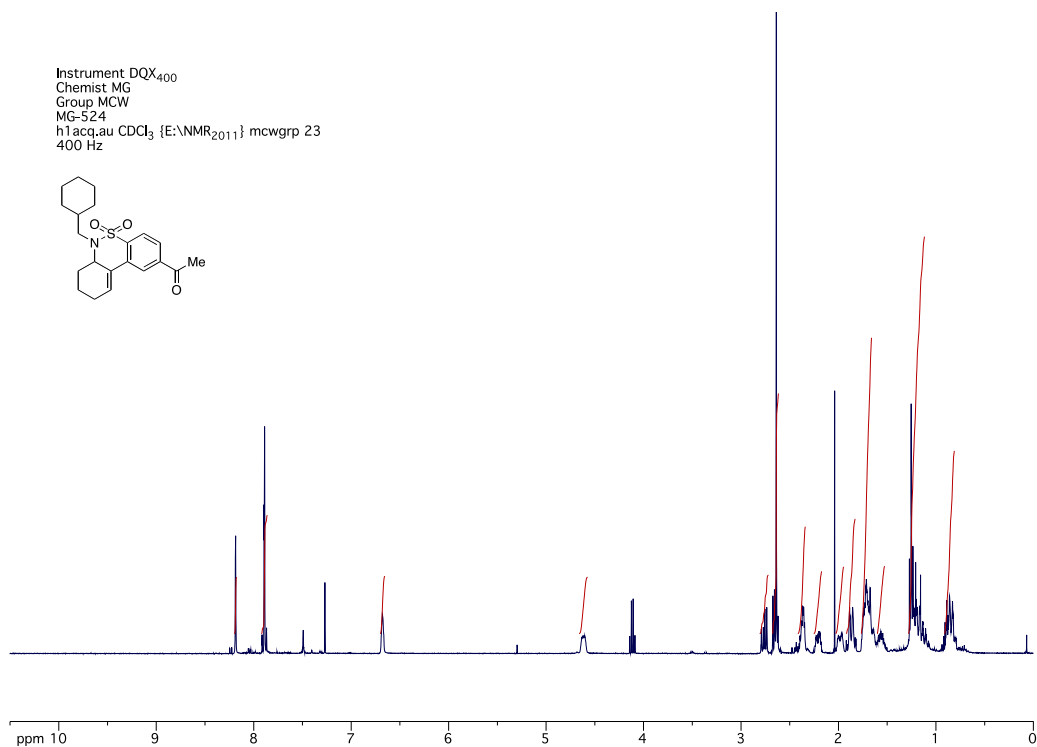
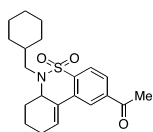
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 Chemist MG
 Group MCW
 MG-527
 h1acq.au CDCl₃ {E:\NMR2011} mcwgrp 32
 400 Hz



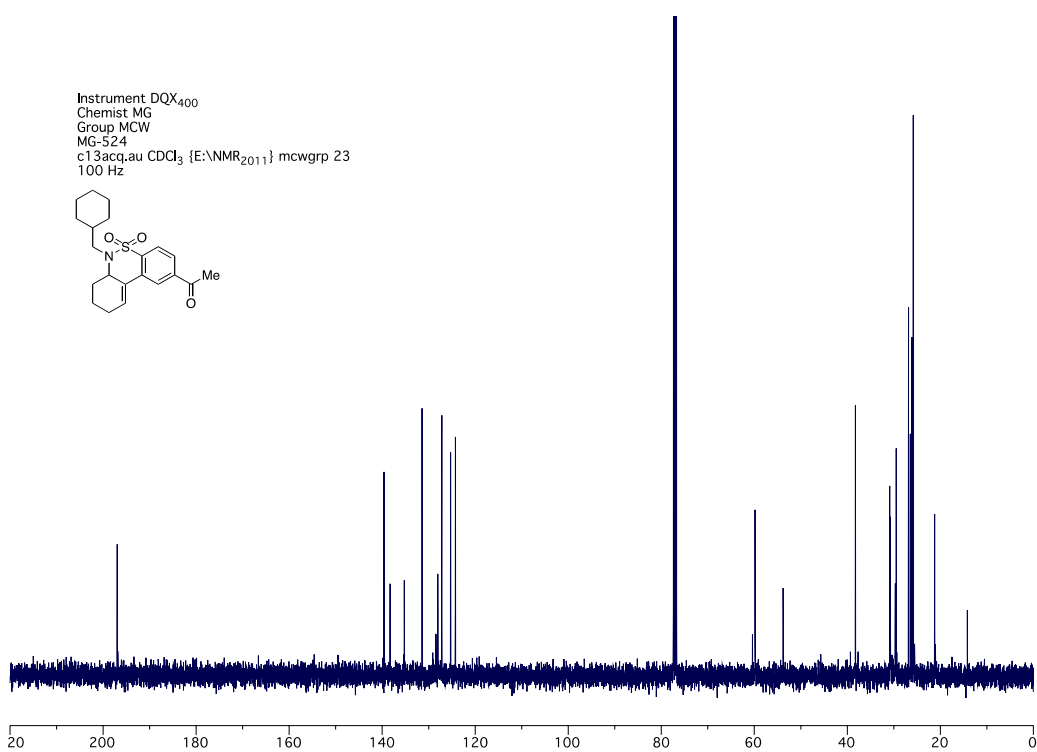
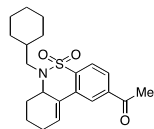
Instrument DQX400
 Chemist MG
 Group MCW
 MG-527
 c13acq.au CDCl₃ {E:\NMR2011} mcwgrp 32
 100 Hz



Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-524
 h1acq.au CDCl₃ {E:\NMR2011} mcwgrp 23
 400 Hz

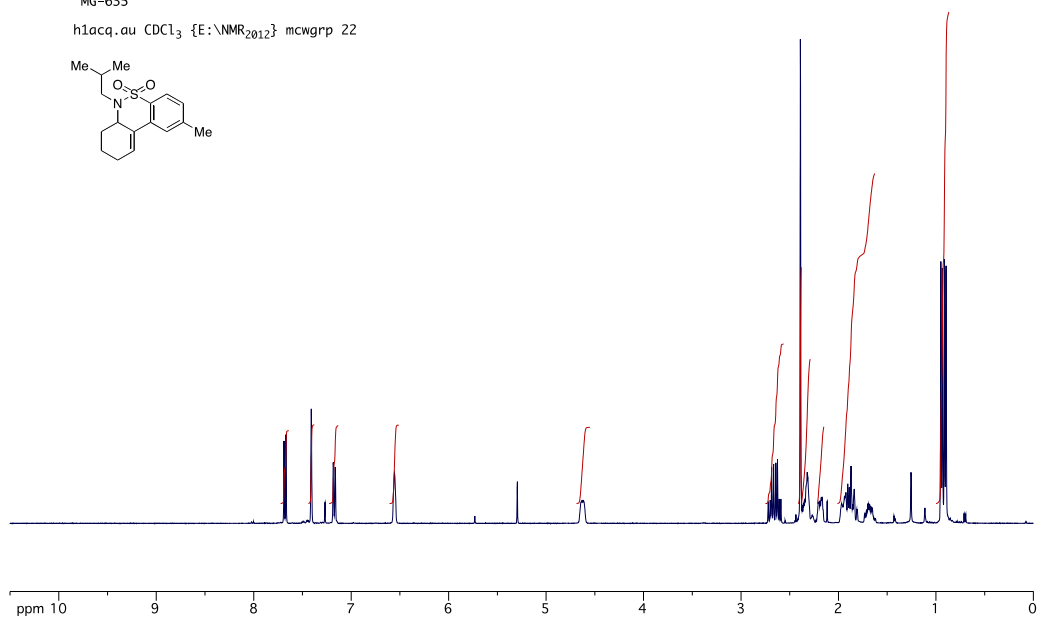
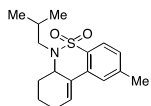


Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-524
 c13acq.au CDCl₃ {E:\NMR2011} mcwgrp 23
 100 Hz



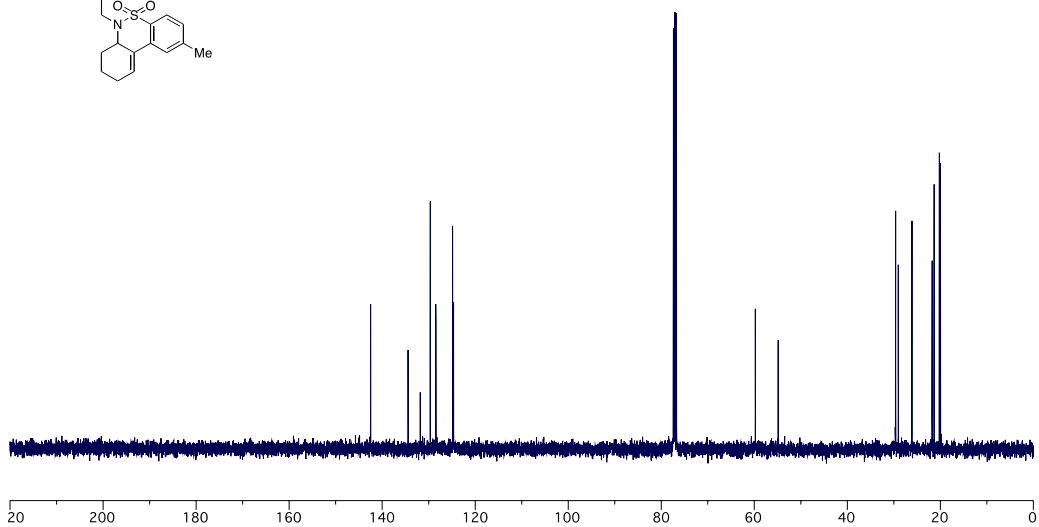
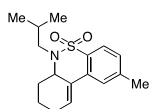
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Chemist MG
Group MCW
MG-635

h1acq.au CDCl₃ {E:\NMR2012} mcwgrp 22

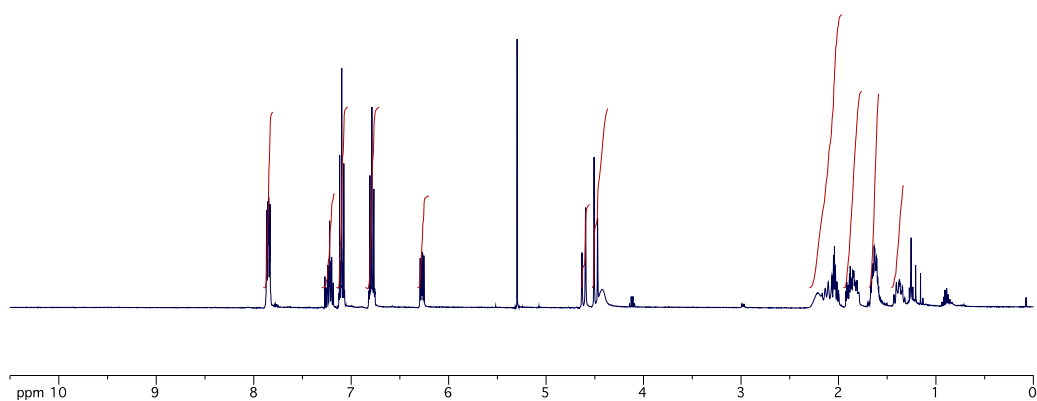
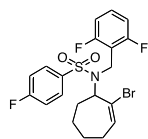


Instrument DQX400
Chemist MG
Group MCW
MG-635

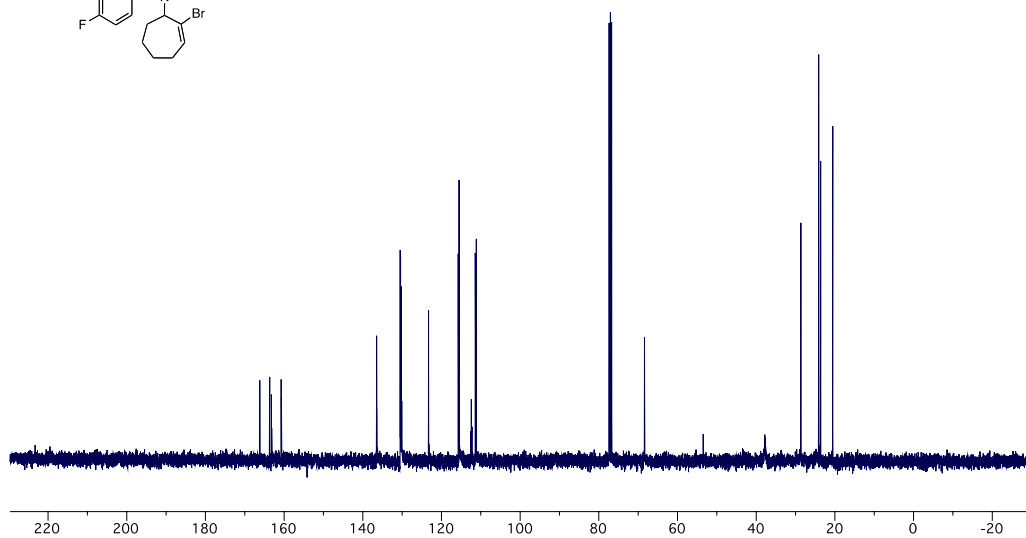
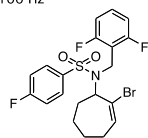
c13acq.au CDCl₃ {E:\NMR2012} mcwgrp 22



Instrument DQX400
 Chemist MG
 Group MCW
 MG-555
 h1acq.au CDCl₃ {E:\NMR2011} mcwgrp 32
 400 Hz

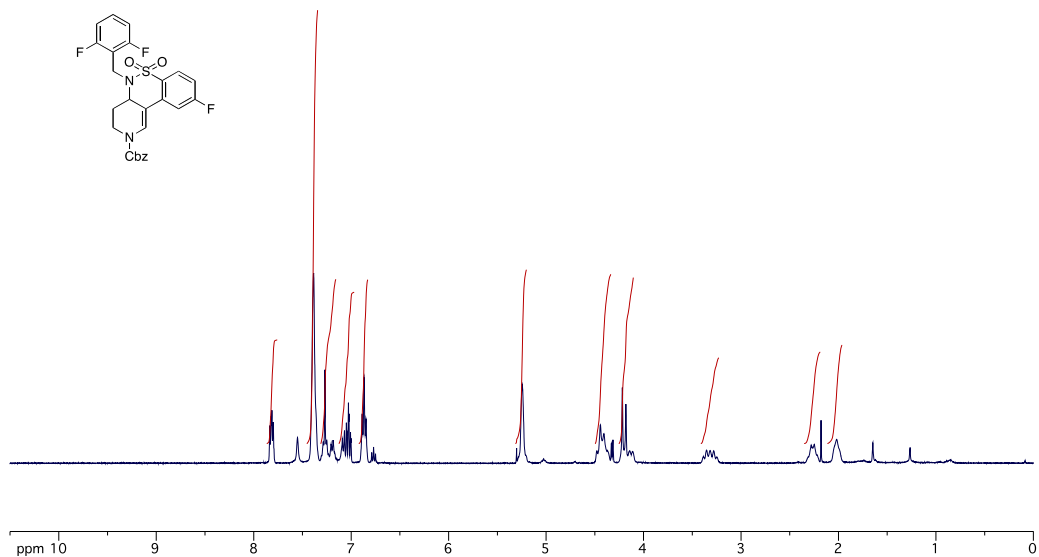
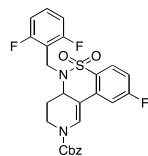


Instrument DQX400
 Chemist MG
 Group MCW
 MG-555
 c13acq.au CDCl₃ {E:\NMR2011} mcwgrp 32
 100 Hz



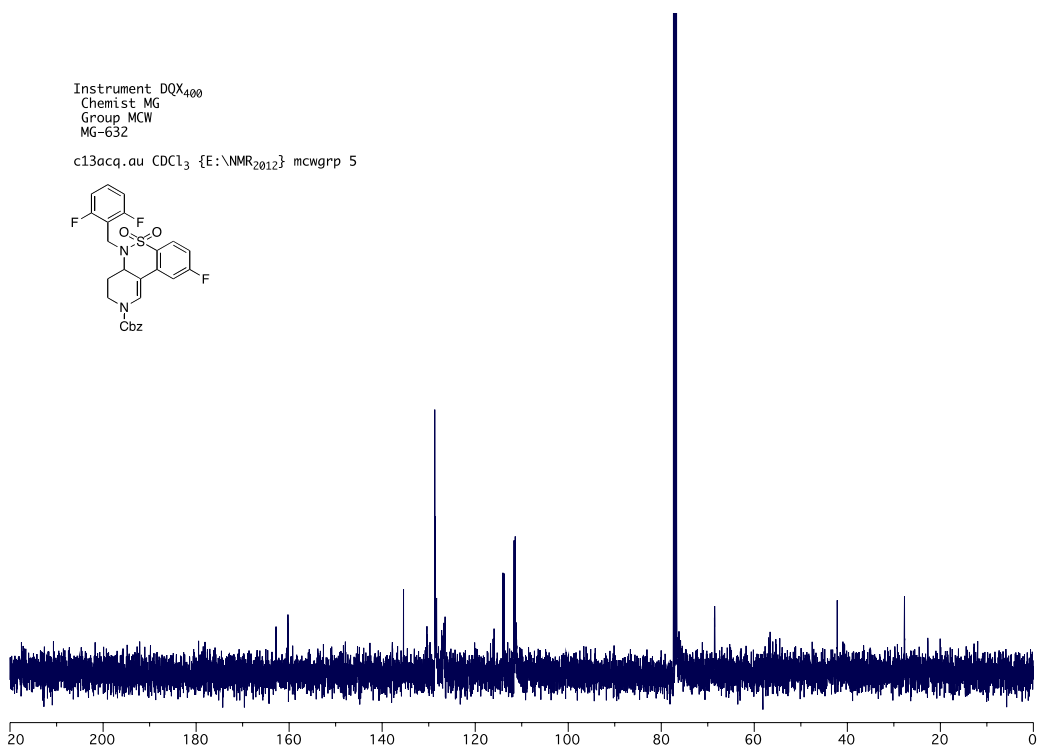
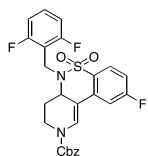
Instrument DQX400
 Chemist MG
 Group MCW
 MG-632

h1acq.au CDCl₃ {E:\NMR2012} mcwgrp 5



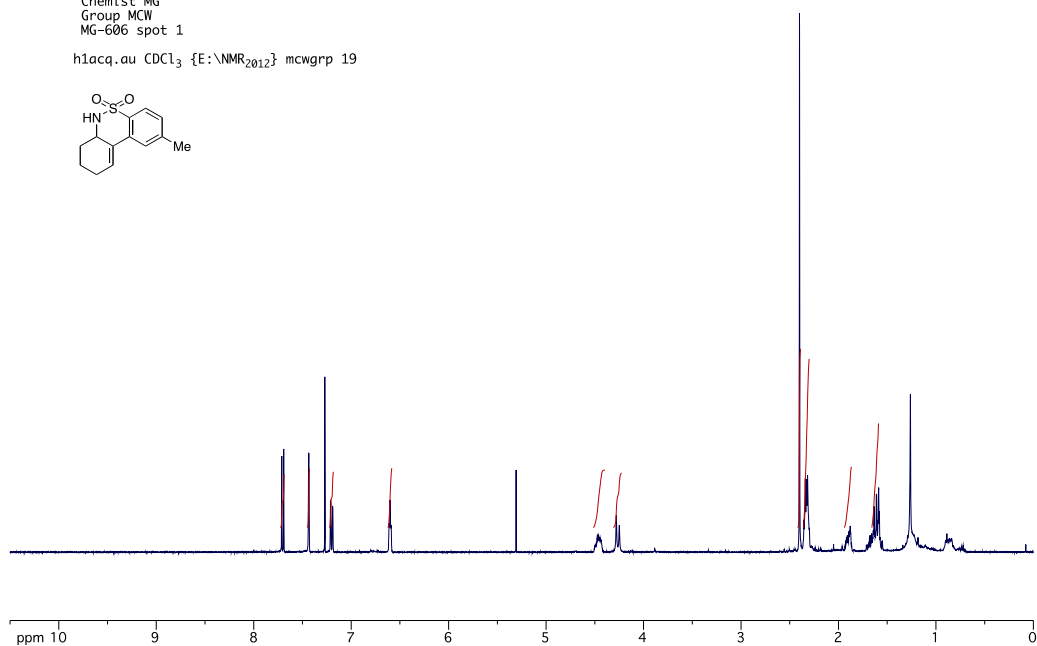
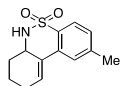
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 Chemist MG
 Group MCW
 MG-632

c13acq.au CDCl₃ {E:\NMR2012} mcwgrp 5



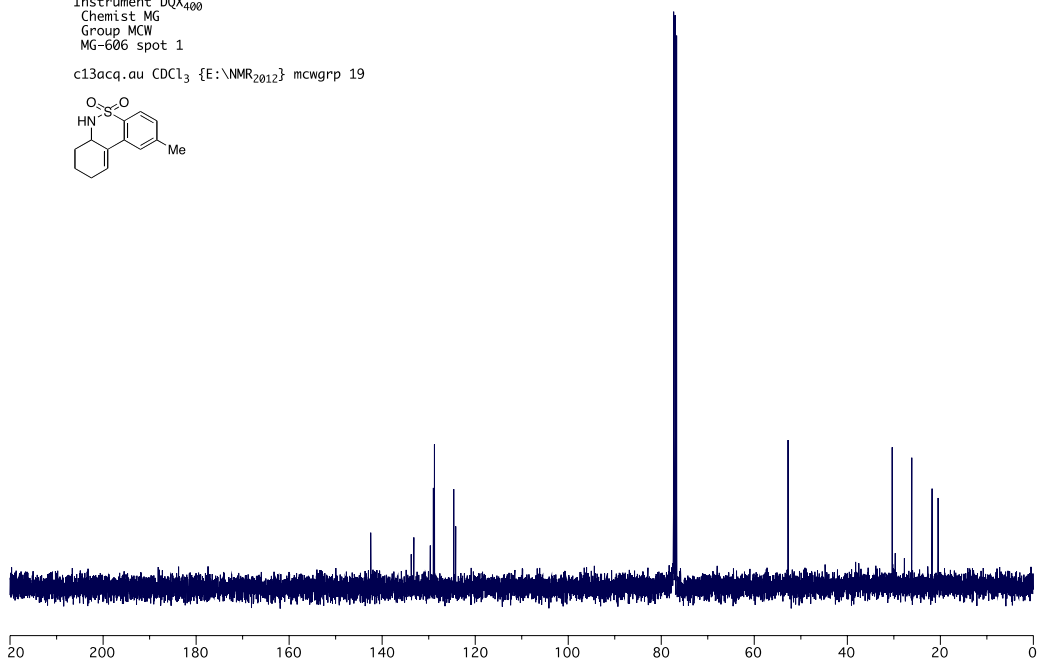
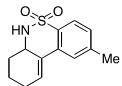
Instrument DQX400
 Chemist MG
 Group MCW
 MG-606 spot 1

h1acq.au CDCl₃ {E:\NMR2012} mcwgrp 19

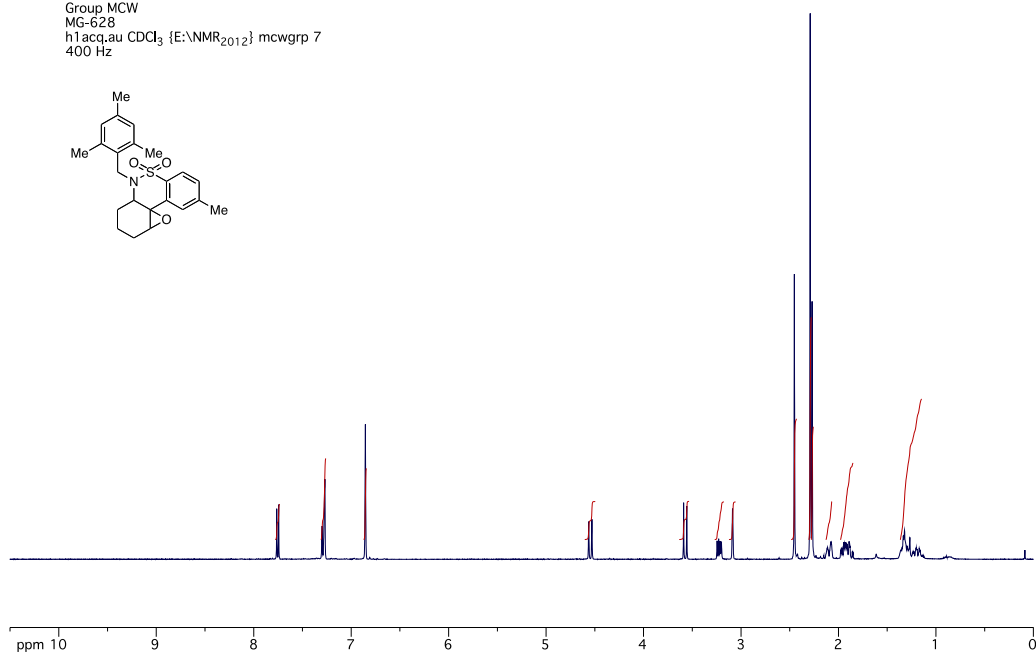
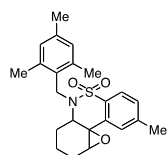


Instrument DQX400
 Chemist MG
 Group MCW
 MG-606 spot 1

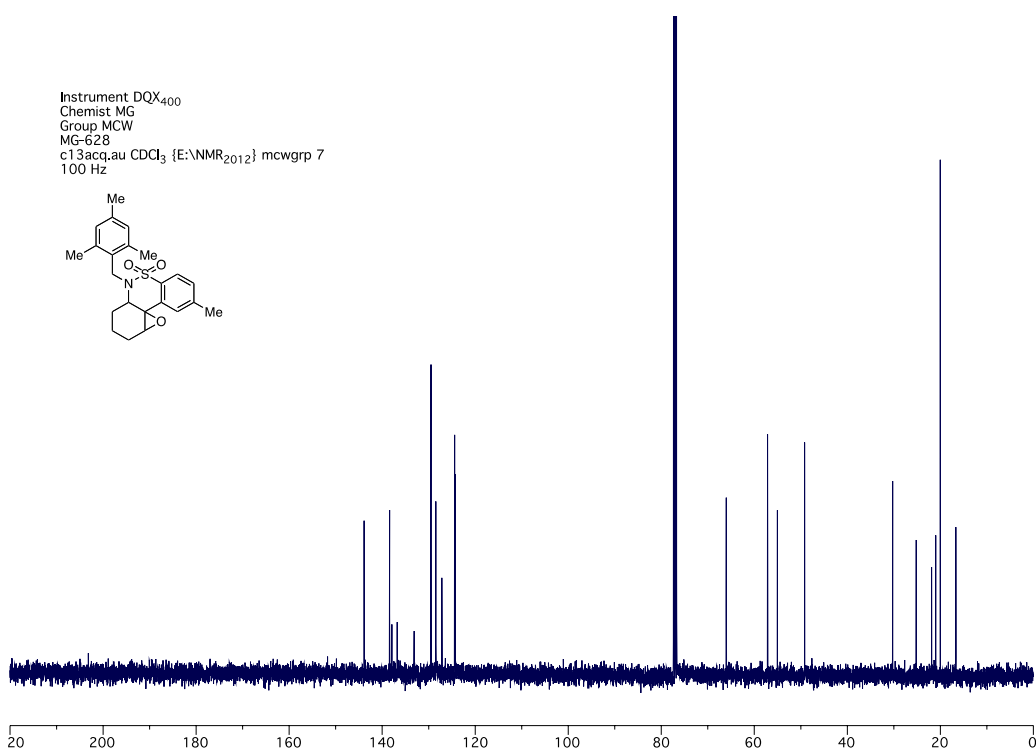
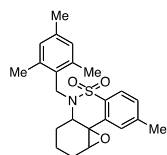
c13acq.au CDCl₃ {E:\NMR2012} mcwgrp 19



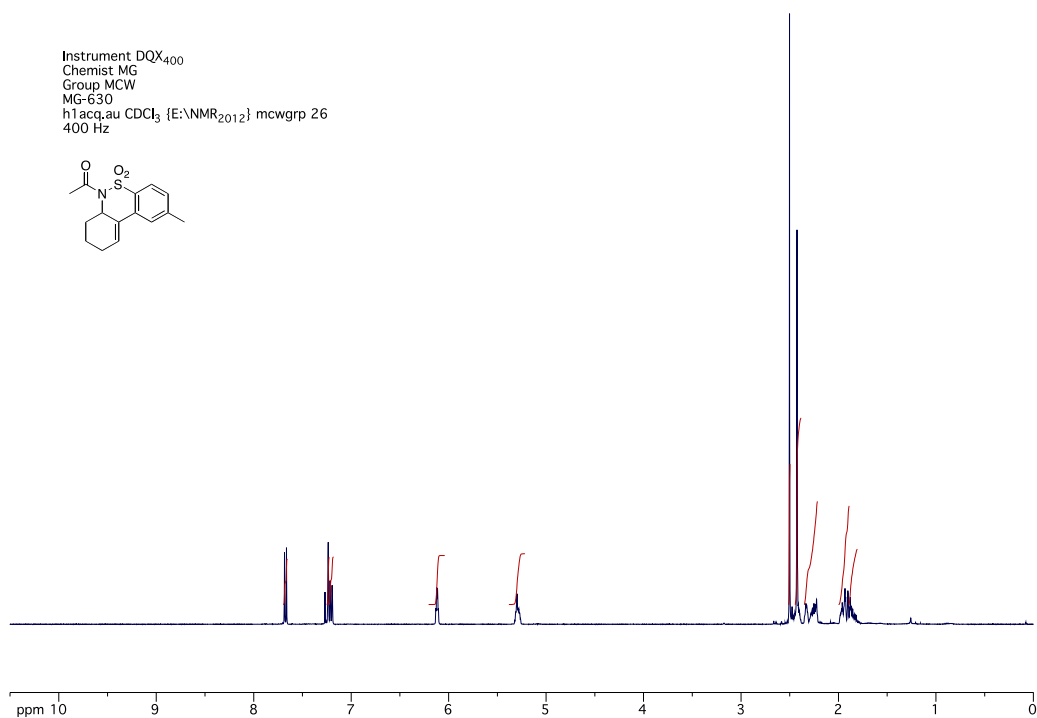
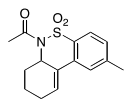
Instrument DQX400
 Chemist MG
 Group MCW
 MG-628
 h1acq.au CDCl₃ {E:\NMR2012} mcwgrp 7
 400 Hz



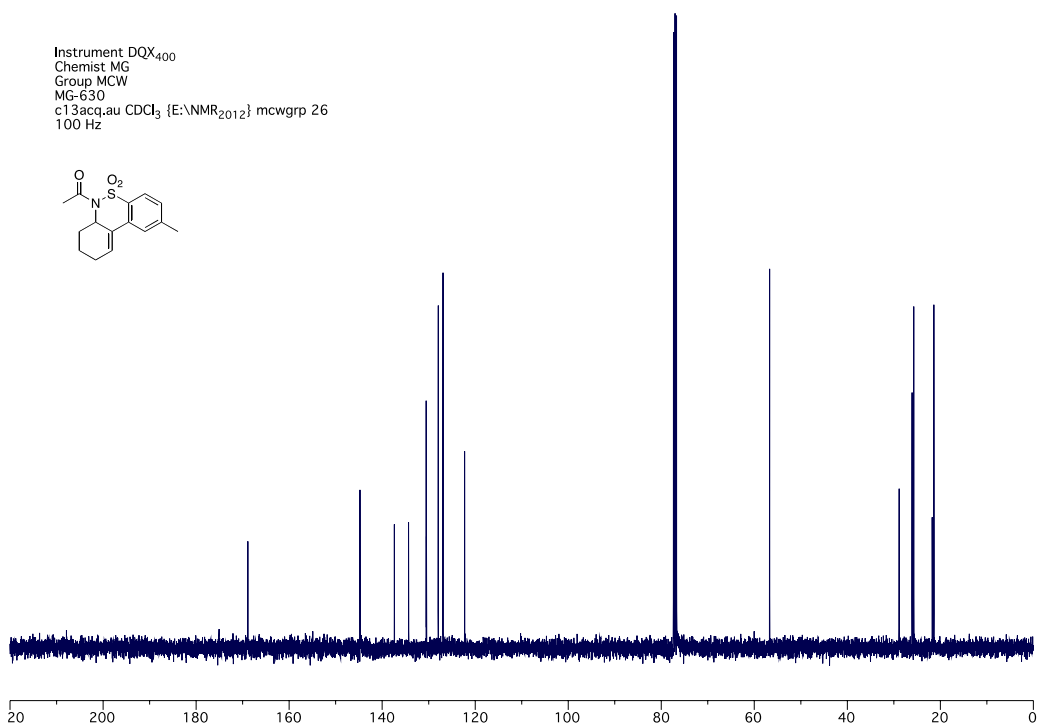
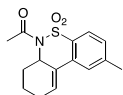
Instrument DQX400
 Chemist MG
 Group MCW
 MG-628
 c13acq.au CDCl₃ {E:\NMR2012} mcwgrp 7
 100 Hz



Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-630
 h1acq.au CDCl₃ {E:\NMR₂₀₁₂} mcwgrp 26
 400 Hz



Instrument DQX₄₀₀
 Chemist MG
 Group MCW
 MG-630
 c13acq.au CDCl₃ {E:\NMR₂₀₁₂} mcwgrp 26
 100 Hz



Design of Experiment Data

Select	Std	Run	Factor 1 A:Time	Factor 2 B:Temp	Factor 3 C:Base	Factor 4 D:Arene	Factor 5 E:Piv acid	Factor 6 F:Vol	Response 1 yield	Response 2 impurity
5		1	15.00	90.00	3.50	3.00	0.50	4.80	31.2	96.2
	8	2	45.00	150.00	3.50	3.00	0.50	0.96	29.6	17.7
	7	3	15.00	150.00	3.50	3.00	0.10	0.96	84.9	1.5
	1	4	15.00	90.00	1.50	3.00	0.10	0.96	7.2	72.7
	12	5	45.00	150.00	1.50	7.00	0.10	0.96	84.8	1.4
	3	6	15.00	150.00	1.50	3.00	0.50	4.80	178.1	0
	10	7	45.00	90.00	1.50	7.00	0.50	4.80	121.5	76.8
	14	8	45.00	90.00	3.50	7.00	0.10	0.96	13.8	54.1
	9	9	15.00	90.00	1.50	7.00	0.10	4.80	30	20
	11	10	15.00	150.00	1.50	7.00	0.50	0.96	146.8	2.6
	16	11	45.00	150.00	3.50	7.00	0.50	4.80	64.2	11.4
	13	12	15.00	90.00	3.50	7.00	0.50	0.96	33.2	164.1
	4	13	45.00	150.00	1.50	3.00	0.10	4.80	117.9	0
	2	14	45.00	90.00	1.50	3.00	0.50	0.96	30.7	51.3
	15	15	15.00	150.00	3.50	7.00	0.10	4.80	0	90.6
	6	16	45.00	90.00	3.50	3.00	0.10	4.80	0	83.3

6 Factors: A, B, C, D, E, F

Design Matrix Evaluation for Factorial Reduced 3FI Model

Factorial Effects Aliases

[Est. Terms] Aliased Terms

[Intercept] = Intercept

[A] = A + BCE + DEF

[B] = B + ACE + CDF

[C] = C + ABE + BDF

[D] = D + AEF + BCF

[E] = E + ABC + ADF

[F] = F + ADE + BCD

$$[AB] = AB + CE$$

$$[AC] = AC + BE$$

$$[AD] = AD + EF$$

$$[AE] = AE + BC + DF$$

$$[AF] = AF + DE$$

$$[BD] = BD + CF$$

$$[BF] = BF + CD$$

$$[ABD] = ABD + ACF + BEF + CDE$$

$$[ABF] = ABF + ACD + BDE + CEF$$

Design Matrix Evaluation Performed Omitting Aliased Terms

Aliases are calculated based on your response selection,
taking into account missing datapoints, if necessary.
Watch for aliases among terms you need to estimate.

Factorial Effects Defining Contrast

$$I = ABCE = ADEF = BCDF$$

Defining Contrast Word Lengths

1	2	3	4	5	6
0	0	0	3	0	0

Degrees of Freedom for Evaluation

Model	15
Residuals	0
<i>Lack Of Fit</i>	0
<i>Pure Error</i>	0
Corr Total	15

A recommendation is a minimum of 3 lack of fit df and 4 df for pure error.
This ensures a valid lack of fit test.
Fewer df will lead to a test that may not detect lack of fit.

Power at 5 % alpha level to detect signal/noise ratios of

Term	StdErr** 1 Std. Dev.	2 Std. Dev.	VIF	Ri-Squared	0.5 Std. Dev.
A	0.25	1.00	1.00	0.0000	Not Defined when the Residual Degrees of Freedom is 0.
B	0.25	1.00	1.00	0.0000	
C	0.25	1.00	1.00	0.0000	
D	0.25	1.00	1.00	0.0000	
E	0.25	1.00	1.00	0.0000	
F	0.25	1.00	1.00	0.0000	
AB	0.25	1.00	1.00	0.0000	
AC	0.25	1.00	1.00	0.0000	
AD	0.25	1.00	1.00	0.0000	
AE	0.25	1.00	1.00	0.0000	
AF	0.25	1.00	1.00	0.0000	
BD	0.25	1.00	1.00	0.0000	
BF	0.25	1.00	1.00	0.0000	
ABD	0.25	1.00	1.00	0.0000	
ABF	0.25	1.00	1.00	0.0000	

****Basis Std. Dev. = 1.0**

Standard errors should be similar within type of coefficient. Smaller is better.

Ideal VIF is 1.0. VIF's above 10 are cause for alarm,
indicating coefficients are poorly estimated due to multicollinearity.

Ideal Ri-squared is 0.0. High Ri-squared means terms are correlated with each other,
possibly leading to poor models.

Power should be approximately 80% for the effect you want to detect.

Be sure to set the Model (on previous screen) to be an estimate of the terms you
expect to be significant.

Measures Derived From the $(X'X)^{-1}$ Matrix

Std	Leverage	Point Type
1	1.0000	Fact
2	1.0000	Fact
3	1.0000	Fact
4	1.0000	Fact
5	1.0000	Fact
6	1.0000	Fact
7	1.0000	Fact
8	1.0000	Fact
9	1.0000	Fact
10	1.0000	Fact
11	1.0000	Fact
12	1.0000	Fact
13	1.0000	Fact
14	1.0000	Fact
15	1.0000	Fact
16	1.0000	Fact
Average =	1.0000	

Watch for leverages close to 1.0. Consider replicating these points or make sure they are run very carefully.

Use your mouse to right click on individual cells for definitions.

Response 1 yield

ANOVA for selected factorial model

Analysis of variance table [Partial sum of squares - Type III]

Sum of Mean Fp-value

Source	Squares	df	Square	Value	Prob > F	
Model	45342.84	11	4122.08	19.02	0.0059	significant
<i>A-Time</i>	149.45	1	149.45	0.69	0.4530	
<i>B-Temp</i>	12028.61	1	12028.61	55.50	0.0017	
<i>C-Base</i>	13230.75	1	13230.75	61.05	0.0014	
<i>D-Arene</i>	13.51	1	13.51	0.062	0.8152	
<i>E-Piv acid</i>	5501.93	1	5501.93	25.39	0.0073	
<i>F-Vol</i>	782.60	1	782.60	3.61	0.1302	
<i>AB1973.58</i>		1	1973.58	9.11	0.0393	
<i>AD2437.89</i>		1	2437.89	11.25	0.0285	
<i>AE3531.33</i>		1	3531.33	16.29	0.0156	
<i>AF1969.14</i>		1	1969.14	9.09	0.0394	
<i>BD3724.05</i>		1	3724.05	17.18	0.0143	
Residual		866.90	4	216.72		
Cor Total		46209.73	15			

The Model F-value of 19.02 implies the model is significant. There is only a 0.59% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
 In this case B, C, E, AB, AD, AE, AF, BD are significant model terms.
 Values greater than 0.1000 indicate the model terms are not significant.
 If there are many insignificant model terms (not counting those required to support hierarchy),
 model reduction may improve your model.

Std. Dev.	14.72	R-Squared	0.9812
Mean	60.87	Adj R-Squared	0.9296
C.V. %	24.19	Pred R-Squared	0.6998
PRESS	13870.36	Adeq Precision	14.790

The "Pred R-Squared" of 0.6998 is not as close to the "Adj R-Squared" of 0.9296 as one might normally expect. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 14.790 indicates an adequate signal. This model can be used to navigate the design space.

Coefficient Standard		95% CI		95% CI		
Factor	Estimate	df	Error	Low	High	VIF
Intercept	60.87	1	3.68	50.65	71.09	
A-Time	-3.06	1	3.68	-13.27	7.16	1.00
B-Temp	27.42	1	3.68	17.20	37.64	1.00
C-Base	-28.76	1	3.68	-38.97	-18.54	1.00
D-Arene	0.92	1	3.68	-9.30	11.14	1.00
E-Piv acid	18.54	1	3.68	8.33	28.76	1.00
F-Vol	6.99	1	3.68	-3.22	17.21	1.00
AB-11.11		1	3.68	-21.32	-0.89	1.00
AD12.34		1	3.68	2.13	22.56	1.00
AE-14.86		1	3.68	-25.07	-4.64	1.00
AF11.09		1	3.68	0.88	21.31	1.00
BD-15.26		1	3.68	-25.47	-5.04	1.00

Final Equation in Terms of Coded Factors:

$$\begin{aligned} \text{yield} = & +60.87 \\ & -3.06 \quad * A \\ & +27.42 \quad * B \\ & -28.76 \quad * C \\ & +0.92 \quad * D \\ & +18.54 \quad * E \\ & +6.99 \quad * F \\ & -11.11 \quad * A * B \\ & +12.34 \quad * A * D \\ & -14.86 \quad * A * E \\ & +11.09 \quad * A * F \\ & -15.26 \quad * B * D \end{aligned}$$

Final Equation in Terms of Actual Factors:

$$\begin{aligned} \text{yield} = & -202.38750 \\ & +1.07687 \quad * \text{Time} \\ & +2.92573 \quad * \text{Temp} \\ & -28.75625 \quad * \text{Base} \\ & +18.62812 \quad * \text{Arene} \\ & +241.28125 \quad * \text{Piv acid} \\ & -7.91341 \quad * \text{Vol} \\ & -0.024681 \quad * \text{Time} * \text{Temp} \\ & +0.41146 \quad * \text{Time} * \text{Arene} \\ & -4.95208 \quad * \text{Time} * \text{Piv acid} \\ & +0.38520 \quad * \text{Time} * \text{Vol} \\ & -0.25427 \quad * \text{Temp} * \text{Arene} \end{aligned}$$

The Diagnostics Case Statistics Report has been moved to the Diagnostics Node.

In the Diagnostics Node, Select Case Statistics from the View Menu.

Proceed to Diagnostic Plots (the next icon in progression). Be sure to look at the:

- 1) Normal probability plot of the studentized residuals to check for normality of residuals.
- 2) Studentized residuals versus predicted values to check for constant error.
- 3) Externally Studentized Residuals to look for outliers, i.e., influential values.
- 4) Box-Cox plot for power transformations.

If all the model statistics and diagnostic plots are OK, finish up with the Model Graphs icon.

Response 2 impurity
ANOVA for selected factorial model
Analysis of variance table [Partial sum of squares - Type III]
Sum of Mean F p-value

Source	Squares	df	Square	Value	Prob > F
Model	33404.18	12	2783.68	8.75	0.0500 not significant
<i>A-Time</i>	<i>1438.31</i>	<i>1</i>	<i>1438.31</i>	<i>4.52</i>	<i>0.1235</i>
<i>B-Temp</i>	<i>15209.06</i>	<i>1</i>	<i>15209.06</i>	<i>47.80</i>	<i>0.0062</i>
<i>C-Base</i>	<i>5405.93</i>	<i>1</i>	<i>5405.93</i>	<i>16.99</i>	<i>0.0259</i>
<i>D-Arene</i>	<i>603.93</i>	<i>1</i>	<i>603.93</i>	<i>1.90</i>	<i>0.2621</i>
<i>E-Piv acid</i>	<i>582.02</i>	<i>1</i>	<i>582.02</i>	<i>1.83</i>	<i>0.2691</i>
<i>F-Vol</i>	<i>10.40</i>	<i>1</i>	<i>10.40</i>	<i>0.033</i>	<i>0.8680</i>
<i>AB</i>	<i>33.93</i>	<i>1</i>	<i>33.93</i>	<i>0.11</i>	<i>0.7655</i>
<i>AC</i>	<i>3027.75</i>	<i>1</i>	<i>3027.75</i>	<i>9.52</i>	<i>0.0539</i>
<i>AD</i>	<i>833.77</i>	<i>1</i>	<i>833.77</i>	<i>2.62</i>	<i>0.2039</i>
<i>AF</i>	<i>411.08</i>	<i>1</i>	<i>411.08</i>	<i>1.29</i>	<i>0.3382</i>
<i>BF</i>	<i>1308.63</i>	<i>1</i>	<i>1308.63</i>	<i>4.11</i>	<i>0.1356</i>
<i>ABF</i>	<i>4539.39</i>	<i>1</i>	<i>4539.39</i>	<i>14.27</i>	<i>0.0325</i>
Residual	954.47	3	318.16		
Cor Total	34358.64	15			

The Model F-value of 8.75 implies the model is significant. There is only a 5.00% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case B, C, ABF are significant model terms.

Values greater than 0.1000 indicate the model terms are not significant.

If there are many insignificant model terms (not counting those required to support hierarchy),

model reduction may improve your model.

Std. Dev.	17.84	R-Squared	0.9722
Mean	46.48	Adj R-Squared	0.8611
C.V. %	38.37	Pred R-Squared	0.2098
PRESS	27149.28	Adeq Precision	11.234

The "Pred R-Squared" of 0.2098 is not as close to the "Adj R-Squared" of 0.8611 as one might

normally expect. This may indicate a large block effect or a possible problem with your model

and/or data. Things to consider are model reduction, response transformation, outliers, etc.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your

ratio of 11.234 indicates an adequate signal. This model can be used to navigate the

design space.

Coefficient	Standard	95% CI	95% CI			
Factor	Estimate	df	Error	Low	High	VIF
Intercept	46.48	1	4.46	32.29	60.67	
A-Time	-9.48	1	4.46	-23.67	4.71	1.00
B-Temp	-30.83	1	4.46	-45.02	-16.64	1.00
C-Base	18.38	1	4.46	4.19	32.57	1.00
D-Arene	6.14	1	4.46	-8.05	20.34	1.00
E-Piv acid	6.03	1	4.46	-8.16	20.22	1.00
F-Vol	0.81	1	4.46	-13.39	15.00	1.00
AB	1.46	1	4.46	-12.74	15.65	1.00
AC	-13.76	1	4.46	-27.95	0.44	1.00
AD	-7.22	1	4.46	-21.41	6.97	1.00
AF	5.07	1	4.46	-9.12	19.26	1.00
BF	9.04	1	4.46	-5.15	23.24	1.00
ABF	-16.84	1	4.46	-31.04	-2.65	1.00

Final Equation in Terms of Coded Factors:

impurity = +46.48
 -9.48 * A
 -30.83 * B
 +18.38 * C
 +6.14 * D
 +6.03 * E
 +0.81 * F
 +1.46 * A * B
 -13.76 * A * C
 -7.22 * A * D
 +5.07 * A * F
 +9.04 * B * F
 -16.84 * A * B * F

Final Equation in Terms of Actual Factors:

impurity = +295.56875
 -4.76896 * Time
 -3.26135 * Temp
 +45.89375 * Base
 +10.29063 * Arene
 +30.15625 * Piv acid
 -93.88346 * Vol

+0.059382	* Time * Temp
-0.91708	* Time * Base
-0.24063	* Time * Arene
+2.51541	* Time * Vol
+0.74186	* Temp * Vol
-0.019495	* Time * Temp * Vol

The Diagnostics Case Statistics Report has been moved to the Diagnostics Node.
In the Diagnostics Node, Select Case Statistics from the View Menu.

Proceed to Diagnostic Plots (the next icon in progression). Be sure to look at the:

- 1) Normal probability plot of the studentized residuals to check for normality of residuals.
- 2) Studentized residuals versus predicted values to check for constant error.
- 3) Externally Studentized Residuals to look for outliers, i.e., influential values.
- 4) Box-Cox plot for power transformations.

If all the model statistics and diagnostic plots are OK, finish up with the Model Graphs icon.

Constraints

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
Time	is in range		15	45	1	3
Temp	is in range		90	150	1	3
Base	is in range		1.5	3.5	1	3
Arene	is in range		3	7	1	3
Piv acid	is in range		0.1	0.5	1	3
Vol	is in range		0.96	4.8	1	3
yield	maximize		0	178.1	1	3
impurity	minimize		0	164.1	1	3

Solutions

	Time	Temp	Base	Arene	Piv acid	Vol	yield	imp	Desirability
1	15.06	144.57	1.51	3.07	0.48	2.31	178.366	-14.729	1.000
2	15.43	149.53	1.50	3.02	0.50	4.15	185.631	-0.9714	1.000
3	15.49	147.50	1.55	3.03	0.49	1.38	185.501	-26.245	1.000
4	15.22	149.55	1.72	3.35	0.48	1.45	178.257	-22.089	1.000
5	15.97	149.74	1.63	3.19	0.47	2.11	178.111	-18.531	1.000
6	15.52	147.52	1.54	3.33	0.50	2.89	179.812	-9.2122	1.000
7	15.01	149.82	1.51	3.03	0.43	2.70	179.431	-18.973	1.000
8	17.24	149.17	1.57	3.07	0.49	2.71	178.83	-12.456	1.000

9	15.22	149.92	1.58	3.09	0.45	1.88	180.527	-24.981	1.000
10	16.48	148.22	1.56	3.14	0.47	1.13	179.466	-28.076	1.000
11	15.00	150.00	1.50	4.46	0.50	1.63	174.358	-20.136	0.989
12	15.00	149.95	1.71	3.96	0.48	0.96	173.787	-24.59	0.988
13	15.02	150.00	1.50	3.00	0.45	4.79	177.933	4.1598	0.987
14	15.00	147.46	2.10	3.06	0.50	0.96	172.733	-12.729	0.985
15	15.00	150.00	1.50	4.67	0.50	1.82	171.321	-16.579	0.981
16	15.00	145.69	1.50	3.89	0.50	3.44	171.083	-0.078	0.980
17	15.38	150.00	1.50	4.11	0.50	3.88	173.649	2.9255	0.979
18	15.00	149.94	1.52	4.00	0.43	0.96	170.144	-32.129	0.977
19	15.00	150.00	1.55	4.66	0.50	2.73	168.102	-4.8432	0.972
20	20.31	150.00	1.51	3.72	0.50	2.18	167.865	-13.432	0.971
21	15.00	150.00	1.50	4.76	0.50	2.93	167.761	-3.5266	0.971
22	15.16	150.00	1.50	4.56	0.50	3.64	168.322	3.2203	0.963
23	16.15	149.79	1.50	3.63	0.47	4.80	172.023	9.1425	0.955
24	15.00	149.98	1.57	3.58	0.40	4.06	162.174	0.5969	0.953
25	15.00	150.00	1.50	4.40	0.38	0.98	157.326	-31.312	0.940
26	15.00	137.90	1.50	3.11	0.40	0.96	156.219	-16.173	0.937
27	15.00	150.00	1.50	5.82	0.43	1.00	146.375	-20.162	0.907
28	23.46	149.88	1.50	3.00	0.30	4.80	144.662	0.5988	0.900
29	19.82	150.00	1.73	5.94	0.50	1.06	138.548	-5.9347	0.882
30	30.79	150.00	1.53	3.13	0.50	0.96	138.305	-10.422	0.881
31	26.73	150.00	1.50	4.98	0.50	4.31	145.453	11.222	0.872
32	44.18	150.00	1.50	3.00	0.12	4.78	119.556	-3.3548	0.819
33	40.49	150.00	1.55	6.26	0.50	4.79	124.8	10.054	0.811
34	44.82	150.00	1.50	6.85	0.50	4.67	121.623	6.2607	0.810
35	44.20	149.98	1.57	6.67	0.42	4.80	119.736	4.8471	0.808
36	44.98	147.20	1.51	6.95	0.10	4.80	114.773	-2.4521	0.803
37	15.00	150.00	1.69	3.08	0.10	4.76	113.978	-0.0302	0.800
38	43.64	146.23	1.50	6.88	0.11	4.80	113.152	0.0004	0.797
39	36.58	150.00	1.50	6.97	0.37	4.80	118.201	9.5722	0.791
40	37.49	150.00	1.55	5.56	0.17	4.80	111.512	1.5764	0.787
41	15.02	148.99	2.04	3.00	0.10	1.41	110.263	-25.272	0.787
42	15.45	121.92	1.50	5.02	0.50	4.80	124.062	25.605	0.767
43	15.00	113.60	1.50	3.93	0.50	4.80	118.116	19.814	0.764
44	33.21	150.00	1.50	6.41	0.26	2.74	102.032	0.0053	0.757
45	15.01	112.10	1.50	3.29	0.50	0.96	126.348	38.026	0.738
46	45.00	146.38	1.55	6.85	0.10	2.36	90.8579	-0.0031	0.714

46 Solutions found

Number of Starting Points: 46

Time	Temp	BaseArene	Piv acidVol
15.00	150.00	3.50	7.00
45.00	90.00	3.50	3.00
45.00	150.00	1.50	3.00
45.00	90.00	3.50	7.00
15.00	150.00	1.50	3.00

45.00	150.00	1.50	7.00	0.10	0.96
15.00	150.00	1.50	7.00	0.50	0.96
15.00	90.00	1.50	3.00	0.10	0.96
45.00	90.00	1.50	3.00	0.50	0.96
45.00	150.00	3.50	7.00	0.50	4.80
15.00	150.00	3.50	3.00	0.10	0.96
45.00	90.00	1.50	7.00	0.50	4.80
15.00	90.00	3.50	3.00	0.50	4.80
15.00	90.00	1.50	7.00	0.10	4.80
45.00	150.00	3.50	3.00	0.50	0.96
15.00	90.00	3.50	7.00	0.50	0.96
28.41	94.08	3.46	3.26	0.25	1.36
22.83	107.77	3.08	5.52	0.21	1.18
35.39	92.47	1.58	6.98	0.18	1.32
20.50	103.40	3.12	5.19	0.32	2.26
39.69	126.31	2.53	5.53	0.27	1.19
21.92	129.04	2.71	5.19	0.27	3.83
18.79	139.65	2.00	6.22	0.49	2.77
37.52	135.74	2.40	6.59	0.29	1.41
20.74	98.24	3.03	3.21	0.30	1.85
20.12	111.32	1.92	5.80	0.39	3.88
21.68	146.45	2.05	6.61	0.23	0.98
42.04	120.32	1.98	5.59	0.22	0.98
25.67	91.06	2.28	3.83	0.26	4.71
42.58	101.34	2.28	4.46	0.25	1.18
41.88	100.46	1.53	6.04	0.22	1.05
18.85	124.78	3.47	6.33	0.33	2.73
39.67	96.74	2.77	6.44	0.26	3.90
17.63	104.13	1.78	6.29	0.41	4.28
26.74	149.42	2.47	3.49	0.23	2.73
21.10	144.01	1.98	6.37	0.47	2.05
20.66	128.49	3.10	3.79	0.35	1.78
44.34	97.84	3.34	5.27	0.41	3.32
29.20	145.23	2.74	5.46	0.19	2.75
27.24	118.72	2.32	3.72	0.38	3.31
19.62	98.59	2.22	5.11	0.48	1.87
18.81	116.02	2.61	5.61	0.37	0.97
22.44	95.66	2.85	4.96	0.16	1.34
26.63	141.47	2.34	4.51	0.24	1.14
19.71	123.89	2.89	3.33	0.35	2.20
29.19	97.33	2.96	3.63	0.44	1.59

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