Synthesis of Heterocycles

via Palladium-Catalysed Direct Arylation

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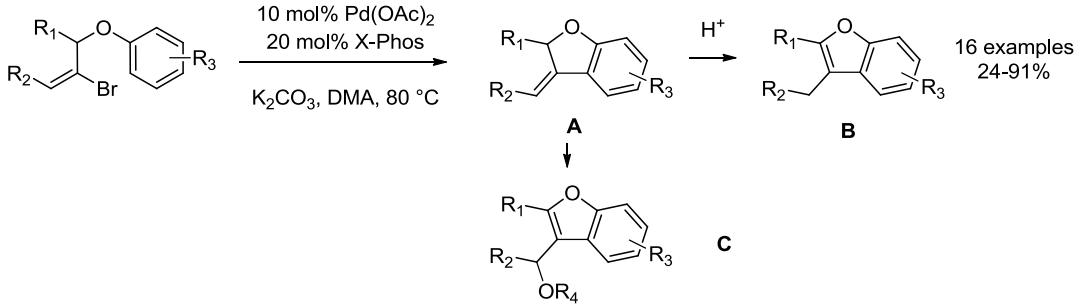
Abstract

Chapter 1 is a brief review on some of the recents developments in palladium-catalysed C-H functionalisation chemistry. The synthesis and functionalisation of heterocycles using these methodologies was particularly emphasised.

Chapter 2 presents our efforts to identify a new catalytic system to promote the intramolecular coupling of vinyl bromides with unfunctionalised aryl C-H bonds for the formation of benzofurans. Dihydrobenzofurans **A** were obtained efficiently under mild conditions in the presence of $Pd(OAc)_2$, X-Phos and K_2CO_3 in DMA at 80 °C and a subsequent one-pot isomerisation under acidic conditions afforded the desired benzofurans **B** (**Scheme 1**). A new strategy has also provided access to more complex benzofurans **C** by functionalisation of the *exo*cyclic alkene isomer in both a chiral and achiral manner.

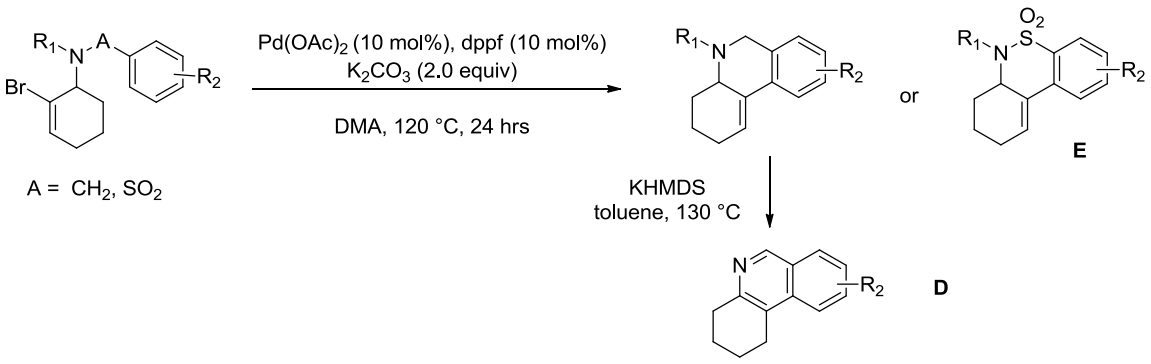


Scheme 1: Palladium-catalysed intramolecular arylation of alkenyl bromides

In **Chapter 3**, mechanistic studies were performed on the benzofuran formation reaction. The analysis of substituent effects on the aromatic ring is in accordance with an electrophilic aromatic substitution mechanism (S_EAr); however, the existence of both intra and intermolecular kinetic isotope effects suggest a S_E3 type pathway rather than a pure S_EAr.

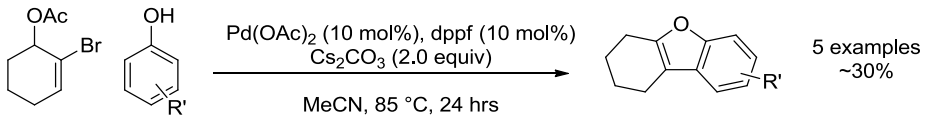
In **Chapter 4**, the intramolecular coupling of vinyl bromides with unfunctionalised aryl C-H bonds was further extended to the synthesis of six-membered heterocycles by direct arylation of alkenyl bromide

derivatives in the presence of $Pd(OAc)_2$, dppf and K_2CO_3 in DMA at 120 °C. The synthetic utility of this methodology was exemplified by the synthesis of substituted isoquinolines **D** in six steps. Moreover, we have applied our methodology to the direct arylation of sulfonamides, leading to an interesting synthesis of widely used sultams **E** (**Scheme 2**). Both these new routes are currently being investigated and should provide access to a variety of differently substituted cyclic sulfonamides and isoquinolines.



Scheme 2: Extension of the scope of heterocycles accessible by modification of our methodology

Finally, **Chapter 5** presents a new strategy for the synthesis of benzo[*b*]furan was briefly investigated. It consists in consecutive Tsuji-Trost and C-H functionalisation reactions. This methodology requires simpler and more versatile substrates, allowing access to various heteroaromatics in a single step (**Scheme 3**). We successfully proved the viability of this reaction through the synthesis of a range of benzofurans in modest yields. To our knowledge, this is the first example of a single palladium catalyst performing these different reactions in tandem in a simple procedure.



Scheme 3: Synthesis of benzofurans by a tandem Tsuji-Trost reaction/C-H functionalisation reaction

Contents

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Thanks to Chien and Alessandro for having been such good friends and shared multi-disciplinary DPhil angst. I also want to thank my flatmates, especially Souad, Adam, Mikey and Phil to have been such great fun.

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Merci à toute mes parents et à Sam pour avoir cru en moi quand je doutais.

Abbreviations and Acronyms

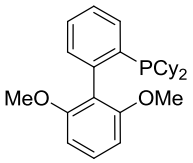
Ac	Acetyl
acac	Acetylacetone
AD	Asymmetric dihydroxylation
Ad	Adamantyl
Ar	Aryl
Atm	Atmosphere
BQ	Benzoquinone
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Cy	Cyclohexyl
dba	(*E*,*E*)-Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	Dichlorodicyanoquinone
DEAD	Diethyl azodicarboxylate
DMDO	Dimethyldioxirane
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
dmpe	Dimethylphosphine ethane
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
equiv	Equivalents
Et	Ethyl

HMDS	Hexamethyldisilazane
HPLC	High Pressure Liquid Chromatography
*i*Pr	*iso*-Propyl
LA	Lewis acid
LC/MS	Liquid chromatography/mass spectroscopy
LDA	Lithium diisopropylamide
M	Molar
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mp	Melting point
MS	Molecular sieves
Ms	Methanesulfonyl
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect SpectroscopY
Nu	Nucleophile
o	*ortho*
Oxone^{TM}	Potassium peroxymonosulfate
Ph	Phenyl
Phen	Phenanthridine
Piv	Pivalic
PPA	Polyphosphoric acid
*p*TSA	*para*-Toluenesulfonic acid
Py	Pyridine
rt	Room temperature
SEM	[β-(trimethylsilyl)ethoxy]methyl
SM	Starting material
TBAB	Tetrabutylammonium bromide
t	*tert*

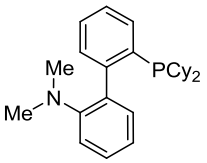
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	4-Toluenesulfonic
Δ	Heat
µW	Microwave radiation

Ligands

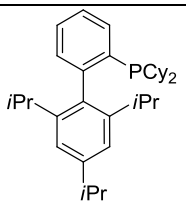
Monophosphine ligands



L_1: S-Phos



L_2: Dave-Phos



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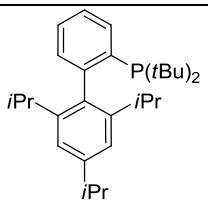
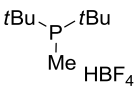
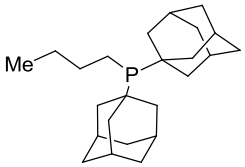


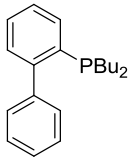
L_4: *t*Bu-X-Phos



L_5

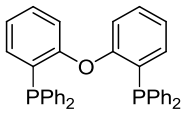


L_6: CatCXium A



L_7

Bidentate phosphine ligands



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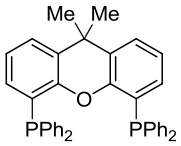

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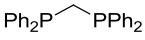
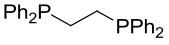
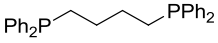


L_{10}: Dppm

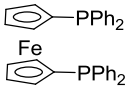


L_{11}: Dppe

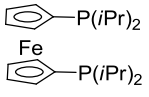
L_{12}: Dppp



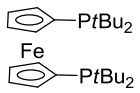
L_{13}: Dppb



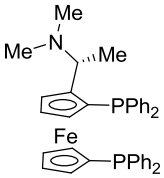
L_{14}: Dppf



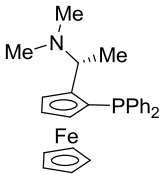
L_{15}: Di-*i*Pr dppf



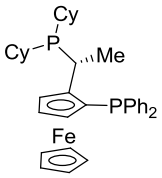
L_{16}: Di-*t*Bu dppf



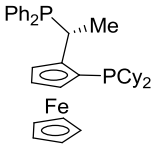
L_{17}: (*R*)-(*S*)-BPPFA



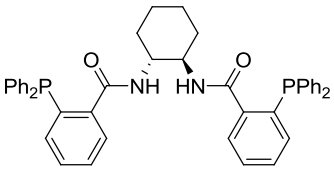
L_{18}: (*R*)-(*S*)-PPFA



L_{19}: Josiphos 001

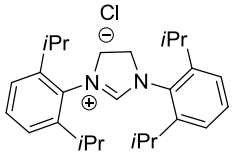


L_{20}: Josiphos 004

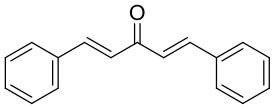


L_{21}: (*R*,*R*)-Dach phenyl Trost ligand

Other type of ligands



L_{21}: *N*-heterocyclic ligand



L_{22}: dba

Chapter 1. Introduction

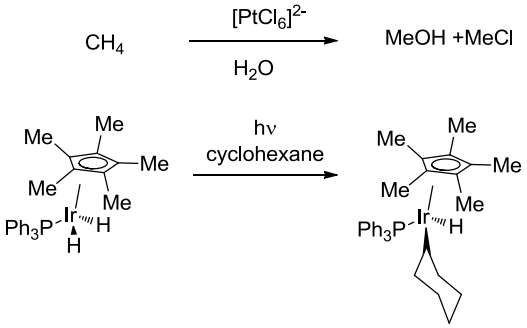
1.1 C-H functionalisation

1.1.1 The concept of C-H activation

One of the main goals in modern organic chemistry is to increase efficiency and minimise chemical waste. The term atom economy has been coined to describe such a goal.[1] One of the most atom economic processes is the transformation of a non-activated C-H bond into a C-C or C-heteroatom bond. However, these transformations are limited due to the low reactivity of C-H bond as well as the lack of methodologies available, and, when available, their poor selectivity. Over the past thirty years, a new area of organometallic chemistry has emerged which is now largely known as “C-H activation” or direct functionalisation chemistry.[2] This term of C-H activation has been employed over the past three decades to describe several different phenomena.[3-5] Overall it refers to the direct transformation of a C-H bond, introducing a new functionality or creating a C-C bond. While this expression could easily refer to a deprotonation, the formation of a radical intermediate, an electrophilic substitution or even an activation of the bond by a Lewis acid, it has been used in organometallic chemistry to describe a metal-mediated process ultimately leading to the breaking of a C-H bond. In this context, the term C-H activation has also been employed as a description of the mechanism of the metal-catalysed proton abstraction. It has however been discovered that these types of reactions can proceed *via* several different mechanisms, although they have not all been investigated thoroughly. In the following discussion, we will use the term “C-H activation” as a generic one when the exact mechanism of the C-H bond breaking is not known. For the reactions involving the formation of an aryl-C or aryl-heteroatom bond, we will also use the equivalent terms direct arylation and direct hetero-arylation.

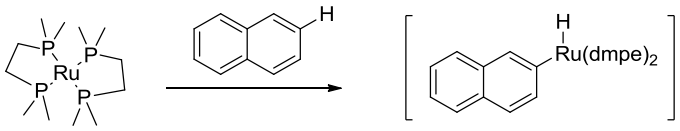
1.1.2 Early examples

Historically, focus has been drawn to the developing field of C-H activation by the formal deprotonation of simple alkanes and their incorporation into metallic complexes by metal-catalysts. As early as 1969, Shilov and co-workers described the oxidation of methane by a platinum chloride complex generating methanol and methyl chloride, a process still in use in industry for the production of alcohols (**Scheme 4**).[5] In 1982, the addition of a cyclohexane C-H bond to an iridium complex was reported by Bergman and co-workers.[6]



Scheme 4: Early examples of alkane "activation" by platinum and iridium complexes

C-H activation reactions are not limited to saturated alkanes and unsaturated hydrocarbons have become the favoured substrates for these types of reactions. As early as 1965, Chatt and Davidson postulated that alkyl phosphines could stabilise zerovalent metals. They illustrated this theory by inserting the [Ru(dmpe)$_2$] complex into a naphthalene C-H bond (**Scheme 5**).[7]

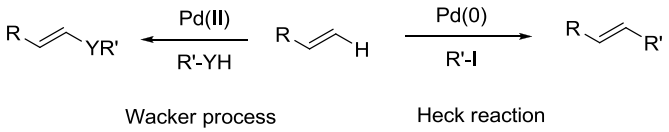


Scheme 5: Arene "activation" by an alkyl phosphine-ruthenium complex developed by Chatt and Davidson

1.1.3 Types of C-H bonds affected

1.1.3.1 sp^2 carbon atoms

sp^2 C-H bonds are the main substrates for C-H activation reactions. Functionalisation of alkene C-H bonds has attracted much attention and highly synthetically useful methods have been developed. The Mizoroki-Heck reaction and the Wacker process are probably the most celebrated examples of the utility of alkene C-H bond activation, allowing the formation of C-C or C-heteroatom bonds (**Scheme 6**).[8] They also highlight the diversity of mechanisms involved in metal catalysed and more particularly, palladium-catalysed reactions.



Scheme 6: Variety of palladium-catalysed alkene C-H activation processes

1.1.3.2 sp carbon atoms

Acetylenes have been used as substrates for C-H functionalisation chemistry. The relatively acidic proton (pKa ≈ 25) and strong s character of terminal alkynes have been utilised in many methods, including the palladium-catalysed Sonogashira reaction[9] or the hydroacylation of alkynes with aldehydes.[10]

1.1.3.3 sp^3 carbon atoms

C-H activation of sp^3 carbon centers is far more challenging compared to sp and sp^2 C-H activation as sp^3 centers comprise less s character. This type of transition metal catalysis usually involves harsh

conditions and high temperatures which have a negative effect on selectivity.[6] Alternatively, adjacent heteroatoms have been used to facilitate the reaction and improve its selectivity.[11]

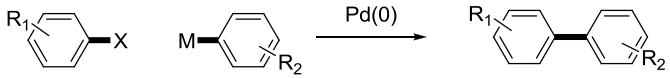
1.2 The building of C-C bonds by palladium-catalysed processes

Given the extreme significance C-H activation chemistry has taken on over the past decades, it is no wonder that such a tremendous number of books and reviews have been dedicated to the topic.[3,5,12-21] Many metals can successfully catalyse C-H activation processes. The activation of alkanes with iridium complexes is amongst the first C-H activation described[6] and since then many other metals - Ru, Rh, Pt, Fe, Ni, Pd- were used in C-H functionalisation reactions.[3] Our particular interest lies in palladium chemistry, mainly for the mildness of its reaction conditions and its tolerance towards a large variety of functional groups.

In this review, we will not attempt to present an extensive review of C-H activation but instead report a brief overview of palladium-catalysed construction of C-C bonds *via* C-H functionalisation. We will focus more precisely on the advances made for the functionalisation and the synthesis of heterocycles. Selected examples will be given and the reader may refer to more general books and reviews for more details. Mechanistic aspects of the C-H functionalisation will be tackled separately in Chapter 3, focusing on the particular case of direct arylation.

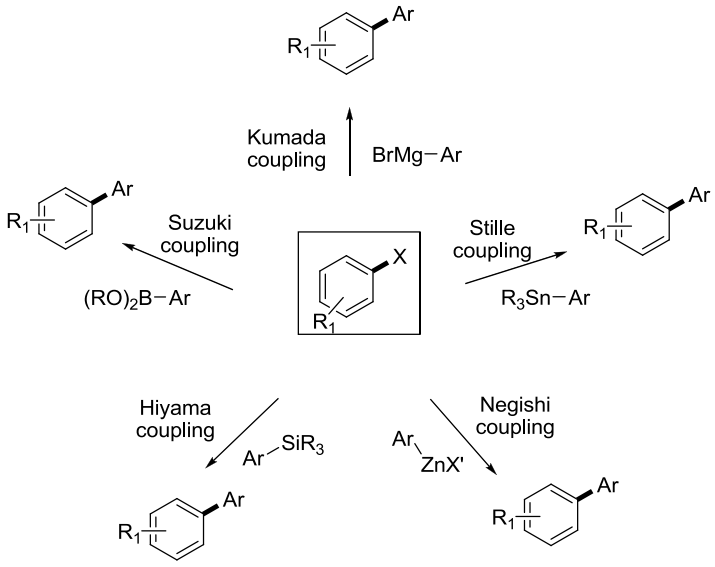
1.2.1 Cross-coupling reactions

Since the pioneering work of Ullmann on Cu-promoted formation of biaryls,[22] revolutionary discoveries have been made in the field of metal-promoted C-C bond formation. Among them, palladium-catalysed cross-coupling reactions are probably the most convenient and versatile methods, allowing the coupling of aryl, alkenyl or even alkyl halides with a stoichiometric organometallic compound (**Scheme 7**).[8,23,24]



Scheme 7: Strategy for palladium-catalysed cross-coupling reaction in the case of biaryl formation

Suzuki,[25,26] Stille,[27] Negishi,[8] Kumada[8] and Hiyama[28] coupling reactions are the most widely used (**Scheme 8**).

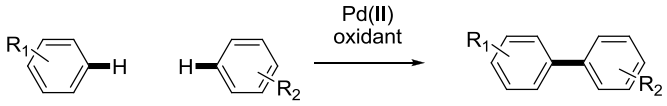


Scheme 8: Examples of cross-coupling reactions for the synthesis of biaryls

Despite their high efficiency and selectivity, these coupling reactions suffer some drawbacks, including the need for the pre-functionalisation of one coupling partner with an organometallic species and the generation of toxic by-products such as stannates for the Stille reaction.

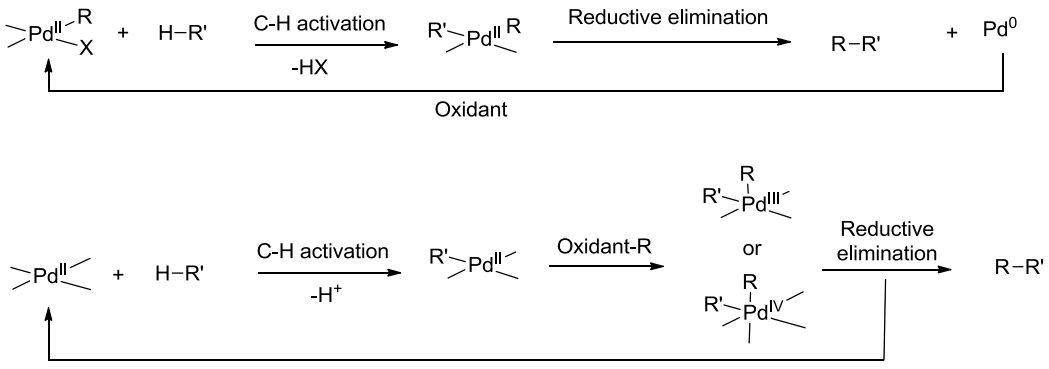
1.2.2 Oxidative direct functionalisation

Oxidative direct functionalisation is based on the use of a metal catalyst in a high oxidation state.[12,18] In the case of palladium, the active palladium(II) species requires a terminal oxidant in order to be regenerated as the active catalyst after the reductive elimination. This methodology has been used to create many different C-heteroatom bonds[18] but we will focus on C-C bonds and more precisely on aryl-aryl bond formation as a comparison with our own methodology (**Scheme 9**). This short review will not cover decarboxylative oxidative arylation, however, as this process is comparable to the one described below.[29]



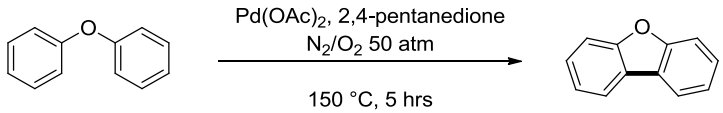
Scheme 9: Strategy for palladium-catalysed oxidative aryl-aryl bond formation

Two main pathways have been proposed for oxidative direct arylation. In most cases a palladium(II)/palladium(0) mechanism is proposed where the functionalisation occurs during the reductive process to release the product. The resulting palladium(0) complex is then oxidised to regenerate the active palladium(II) catalyst. The second pathway involves the formation of a highly oxidised intermediate, palladium(IV) or palladium(III), by means of a terminal oxidant. The active palladium(II) is then regenerated during the reductive process, along with the desired product (**Scheme 10**).[18]



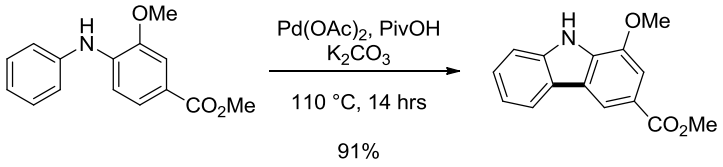
Scheme 10: Main pathways proposed for the oxidative direct arylation

The small difference in energy between different C-H bonds usually means that these reactions are poorly regioselective. Early examples of such an oxidative coupling were intramolecular and were usually performed at high pressure and temperature (**Scheme 11**).[30]



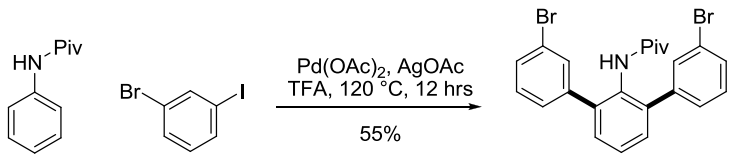
Scheme 11: Early example of dehydrogenative arylation to form dibenzofurans

More recently, the scope of heterocycles accessible by this type of chemistry has been increased and heterocyclic natural products can be synthesised by similar processes under milder conditions. For example Fagnou and co-workers synthesised naturally occurring mukonine using a dehydrogenative coupling under phosphine free conditions (**Scheme 12**).[31]



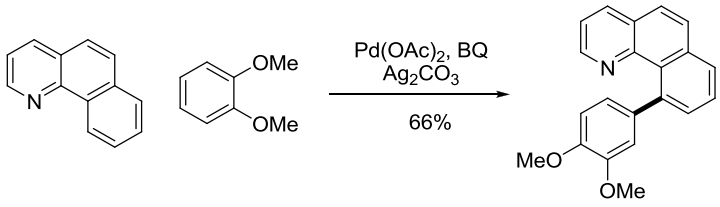
Scheme 12: Synthesis of mukonine by intramolecular dehydrogenative coupling

Advances in intermolecular aryl-aryl bond formation have been made with the use of directing groups either as a cleavable functionality or as part of the molecule itself. Consequently, the functionalisation of heteroaromatics has become progressively more represented over the past few years. **Scheme 13** depicts an example of regio and chemoselective arylation directed by a cleavable pivalic group on the aniline which allows the arylation of the substrate in a moderate yield.[32]



Scheme 13: Palladium-catalysed regio and chemoselective oxidative arylation

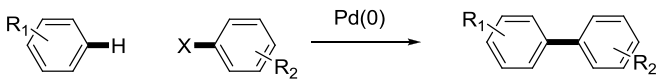
In **Scheme 14**, the benzoquinoline's coordinating nitrogen allows a highly selective aryl-aryl bond formation.



Scheme 14: Palladium-catalysed cross-arylation of benzo[*h*]quinoline

Although highly atom-economic in itself, oxidative direct functionalisation suffers several drawbacks. Achieving regio and chemoselectivity in these reactions is a significant challenge and the need for a stoichiometric terminal oxidant generates chemical waste. Although these reactions rarely require a stoichiometric transition-metal oxidant anymore, sacrificial oxidants are often present in large excess and the use of the atom economic oxidant O_2 is rarely possible. These obstacles are considerably reduced in direct arylation using halide moieties as electrophiles.

1.2.3 Reaction with halide and pseudo-halide moieties as electrophiles

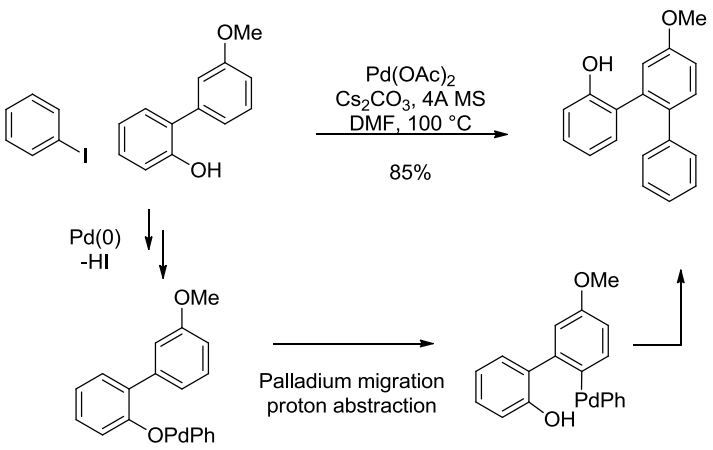


Scheme 15: Strategy for palladium-catalysed direct arylation using halides moieties as electrophiles

One of the main advantages of the direct arylation strategy is the avoidance of pre-functionalisation of substrates with organometallic groups. These are often relatively expensive and not commercially available, requiring several steps to be installed. However, the advantage offered by the absence of pre-functionalisation is also the origin of the main challenge encountered with this methodology which is the regioselectivity of the reaction.

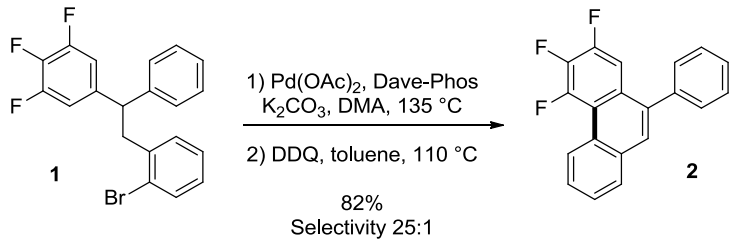
While some approaches have used the electronic properties of the arene to direct proton abstraction, the small differences in energy between C-H bonds often lead to poor regioselectivity. An alternative strategy consists in using appropriately functionalised aromatic substrates such as phenols or carbonyl compounds, which are used as directing groups for the formation of the palladated species.[3]

Miura and co-workers have studied the regioselective arylation of phenols with aryl halides.[33] To explain the selectivity of the reaction they propose that the palladium complex formed after the oxidative addition of palladium(0) to phenyl iodide is coordinated to the phenolic oxygen allowing the palladation at the spatially close 2'-position (**Scheme 16**). Similarly, simple phenols, aryl ketones or benzanilides among others, were arylated with excellent regioselectivity using this methodology.[3]



Scheme 16: Palladium-catalysed regioselective arylation of 2-phenylphenols

Several examples demonstrate that high regioselectivity can be obtained by using the electronic properties of arenes. Echavarren and co-workers showed that in substrate **1** the less nucleophilic but more acidic fluorinated ring was preferentially functionalised, selectively forming compound **2** (**Scheme 17**).[34,35]



Scheme 17: Intramolecular competitive direct arylation

1.3 Heterocyclic chemistry

The importance of heterocycles in both biological and medicinal compounds does not need to be demonstrated.[36,37] Their unique properties of stability, hydrogen "shuffling" and hydrogen bonding explain their presence in virtually every type of biological molecule, from DNA bases to enzymes, as well as vitamins and alkaloids.[36] Logically, medicinal sciences have also used these advantages, mimicking natural molecules. In 2008, 63% of the top 200 best selling drugs contained heterocyclic molecules. Among the immense family of heterocycles, heteroaromatic compounds play an important role.

Molecules containing heteroaromatic moieties range from the simplest to some of the most complex compounds, with a wide range of substitution patterns. As opposed to benzenoid compounds,

commonly originating from benzene derivatives, the preparation of heteroaromatic compounds often involves ring synthesis. Moreover, each type of heteroaromatic molecule has its own properties, making it difficult to find general methodologies for their synthesis. Therefore there is a constant need for improved ring synthesis and functionalisation reactions.[38]

Heterocycle synthesis *via* palladium-catalysed direct arylation has been extensively studied. Several books[3,8] and many reviews[12,13,17,18,21,39] have been dedicated to this topic. In the following section, we will therefore only provide representative examples of palladium-catalysed direct arylation applied to the functionalisation and the synthesis of heterocycles.

1.3.1 Functionalisation of heterocycles

Functionalisation of heteroaromatic compounds has been the subject of intensive research over the last decade. In particular, formation of sp^2-sp^2 C-C bonds by direct arylation or vinylation has gained a considerable interest in the scientific community.[3]

1.3.1.1 Formation of aryl-aryl bonds

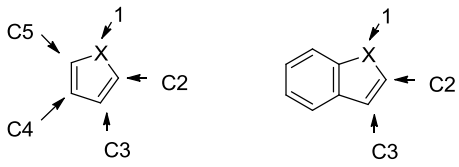


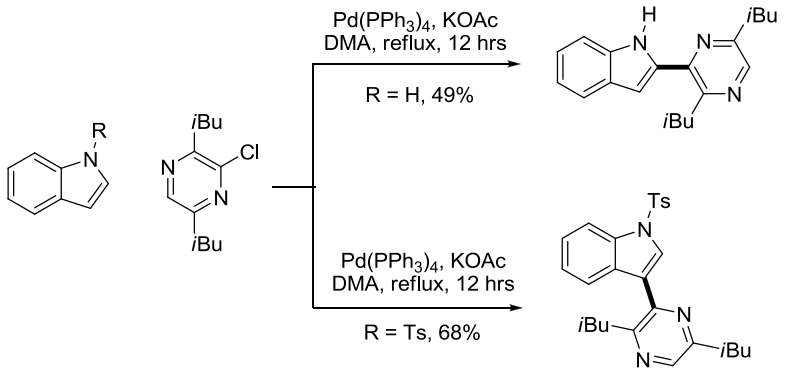
Figure 1: Numbering of five-membered heterocycles such as pyrrole, furan, thiophene and derivatives

Indoles are arguably the most abundant heteroaromatic molecules in biologically active compounds as well as natural products.[36] It is therefore not surprising that many efforts have been made into the development of regioselective functionalisation of indoles by direct arylation. The C2-position is the

most reactive towards palladium-catalysed transformations and many methodologies have taken advantage of this fact.[12,13]

For example, Sames and co-workers reported a ligand free palladium-catalysed C2-arylation of indole using aryl iodides. The reaction scope allowed for a variety of alkyl substituents at the N1-position but also at various other locations on the indole ring.[40] Mechanistic studies later suggested a C3-metalation of the indole followed by the migration of the palladium moiety to the C2-position.[41]

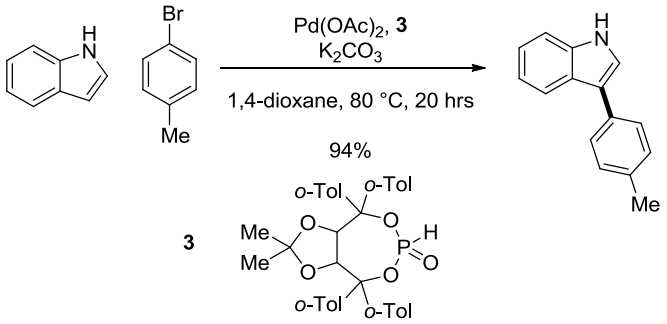
Substitution at the C3-position of indole is however possible and early examples of heteroarene functionalisation by Ohta and co-workers have shown that the nitrogen substitution can greatly influence the reactivity of the indole motif. The introduction of an electron-withdrawing tosyl group switched the reactivity of the indole with the substitution now occurring selectively in the C3-position (**Scheme 18**).[42] They subsequently demonstrated that other electron-rich five-membered heteroarenes such as pyrroles, furans, thiophenes, benzofurans and benzothiophenes can also be arylated using palladium catalysis.[43]



Scheme 18: Palladium-catalysed intermolecular direct arylation of indoles

More recently, generally applicable methods have been elaborated for the selective substitution of the C3-position of heteroarenes. Zhang, He *et al.* have reported a highly selective functionalisation of indoles with an unprotected nitrogen using a palladium catalyst with a phosphinous acid complex.[44] Ackermann and co-workers developed their own method to decorate similar unprotected indoles and

used an *in situ* generated catalyst derived from $Pd(OAc)_2$ and preligand **3**; an air-stable heteroatom-substituted secondary phosphine oxide (**Scheme 19**).[45]



Scheme 19: Method developed by Ackermann *et al.* for the selective C3-substitution of N-H indoles

Although the functionalisation of simple heteroaromatics described previously has received the most interest, other classes of heterocycles have also been studied.

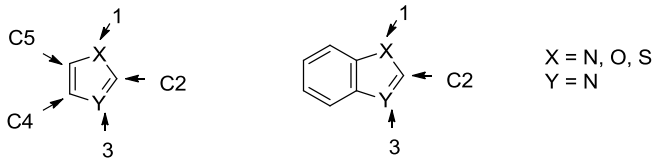
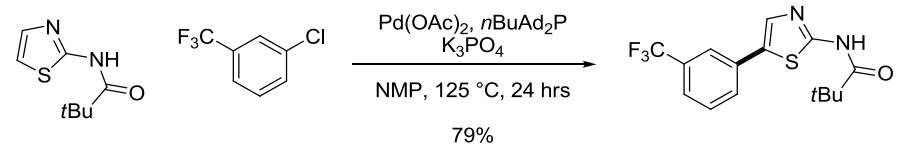


Figure 2: Numbering of five-membered heterocycles such as imidazole, oxazole, thioxazole and derivatives

The order of reactivity in 1,3-diheteroatom heterocycles for electrophilic reactions is known to be C5 > C4 > C2. Arylation at the most electron-rich position, C5, can therefore be regarded as similar to the reactivity in pyrroles or other five-membered heteroarenes. Reaction at the C2-position proceed by a different mechanism, probably involving a base-assisted deprotonation of the heteroaromatic compound followed by its palladation with a palladium(II) complex.

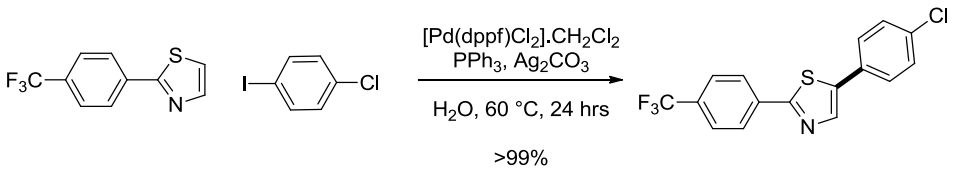
Daugulis and co-workers have developed a new method for the palladium-catalysed coupling of heteroarenes with aryl chlorides as electrophiles, which is a challenge due to the lower reactivity of aryl chlorides compared to aryl iodides or bromides. Their method is applicable to a large range of

heteroarenes and uses a palladium catalyst derived from the electron-rich phosphine nBuAd$_2$P (CatCXium A), enabling the regioselective functionalisation of C-H bonds (**Scheme 20**).[46]



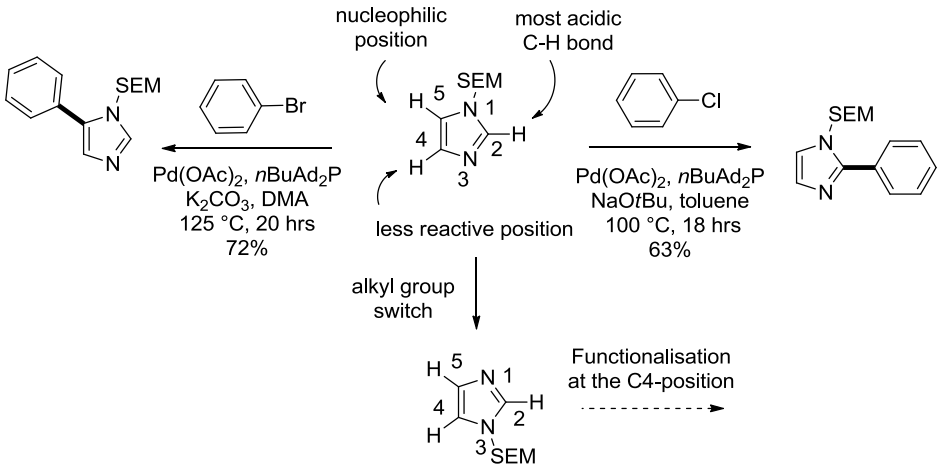
Scheme 20: Palladium-catalysed direct arylation of thiazole

Greaney and co-workers developed a highly efficient direct arylation of thiazoles with aryl iodides. They found that the reaction proceeded significantly faster "on water" than it did in organic solvents, which was explained as a concentration effect (**Scheme 21**).[47] The scope of this transformation was later extended to indazoles[48] and oxazoles.[49,50]



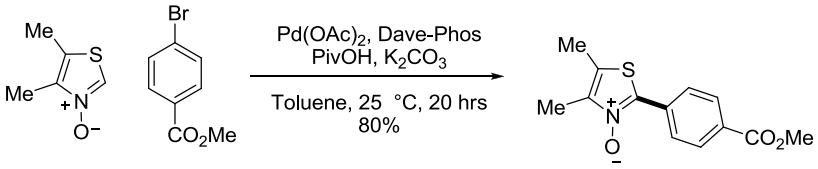
Scheme 21: "On water" direct arylation of thioxazole developed by Greaney and co-workers

The substitution of various SEM-protected heteroarenes in the presence of a bulky NHC-palladium catalyst was reported by Sames and co-workers.[51-53] The introduction of this *N*-protecting group first allowed the C2-selective arylation of indoles[41] and was later applied to pyrroles,[51] pyrazoles[52] and imidazoles.[53] Taking advantage of the difference in reactivity between the C-H bonds and of the possibility to transpose the SEM-protecting group, they proposed a method allowing the sequential arylation of the three C-H positions (**Scheme 22**).



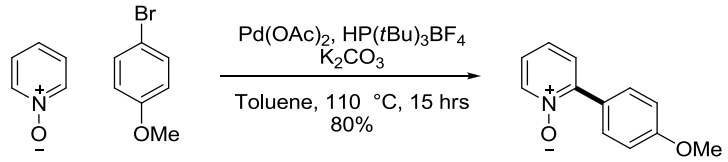
Scheme 22: Sames and co-workers approach to regioselective arylation of imidazoles

Fagnou and co-workers found that *N*-oxides of electron-rich heteroarenes were highly reactive towards direct arylation. The catalytic efficiency was improved by the presence of the co-catalyst PivOH.[54] Later studies suggested that the role of the pivalate anion in this type of reaction is to act as a proton shuttle, allowing the chelation of both the catalyst and the arene and therefore playing a key role in the concerted metalation/deprotonation mechanism (**Scheme 23**).[55]



Scheme 23: Palladium-catalysed direct arylation of thiaoxazole *N*-oxide developed by Fagnou *et al.*

Subsequently, Fagnou and co-workers also observed that more challenging electron-poor arenes such as pyridine *N*-oxide could be selectively functionalised at the C2 position *via* a similar process (**Scheme 24**).[56] This method was then applied to a wider range of substrates and enabled the synthesis of aporphine derivatives in high yields.[57-59]

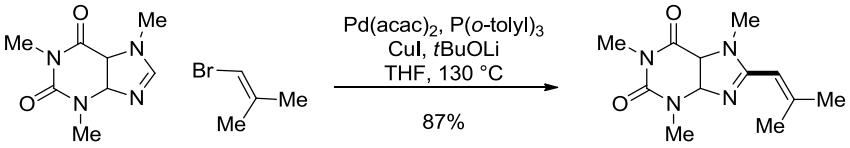


Scheme 24: Palladium-catalysed direct arylation of pyridine *N*-oxide developed by Fagnou *et al.*

1.3.1.2 Formation of aryl-alkene bonds

Although the arylation of heteroaromatic compounds has been the most explored area of study, interesting examples of direct alkenylation using vinyl halides have been reported. These new routes are complementary to traditional methods like Friedel-Crafts alkylation and acetylation which, despite their undeniable synthetic use, are poorly efficient with electron-poor arenes. The use of strong Lewis acids also minimises functional group tolerance.

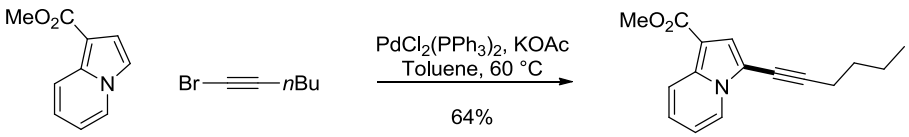
Alami and co-workers have, for example, presented the direct alkenylation of caffeine and other heteroaromatic molecules not only with styrene but also using simple vinyl halides (**Scheme 25**).[60]



Scheme 25: Direct alkenylation of caffeine with a vinylbromide

1.3.1.3 Formation of aryl-alkyne bonds

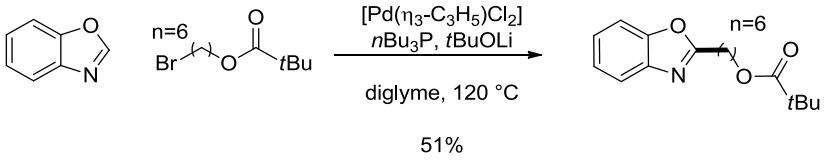
The creation of sp^2-sp C-C bond has attracted less interest than direct vinylation or arylation; however, the direct alkynylation of heterocycles with alkynylhalides has also been reported. An early example was reported by Gevorgyan and co-workers for the palladium-catalysed direct alkynylation of *N*-fused heteroaromatic molecules with a range of alkynylbromides using mild conditions (**Scheme 26**).[61]



Scheme 26: Palladium-catalysed direct alkynylation of *N*-fused heterocycles

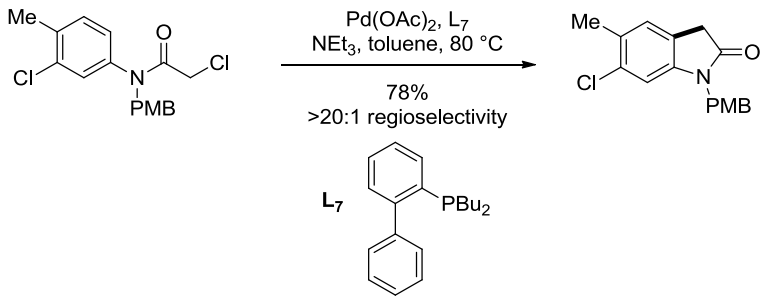
1.3.1.4 Formation of aryl-alkane bonds

Compared to direct arylation or alkenylation, alkylation with alkyl halides has also received comparatively less attention, largely due to the difficulty of controlling undesired *β*-hydrogen elimination. Miura and co-workers reported an interesting alkylation of benzoxazoles with alkyl chlorides and bromides. Their methodology tolerated a wide range of functional groups and long lipophillic chains (**Scheme 27**).[62] The strong basic *t*BuOLi was necessary for the deprotonation of the relatively acidic C2 proton. The lithiated species can then undergo a transmetalation with the alkylpalladium(II) complex. Although this reaction was also successful with 5-aryl oxazoles, it was not applicable to other related compounds such as benzothiazoles, demonstrating once again the specificities and limitations running across families of heterocycles and the need for general syntheses.



Scheme 27: Alkylation of benzoxazoles reported by Miura and co-workers

Buchwald and co-workers developed a simple synthesis of oxindoles *via* direct arylation of preformed α-chloro-acetanilidines in high yields with high regioselectivity. This reaction occurs using mild conditions and tolerates a variety of functional groups usually incompatible with Friedel-Crafts reaction conditions (**Scheme 28**).[11]

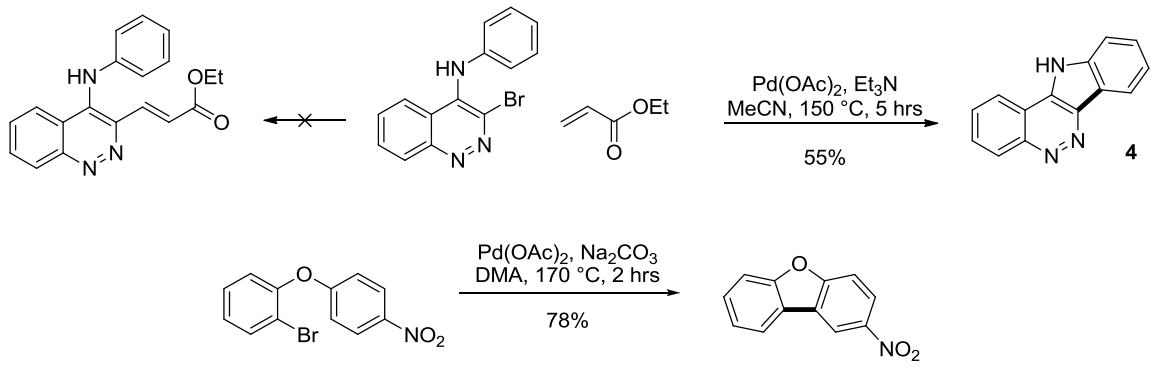


Scheme 28: Synthesis of oxindoles by palladium-catalysed direct alkylation

1.3.2 Synthesis of heterocycles

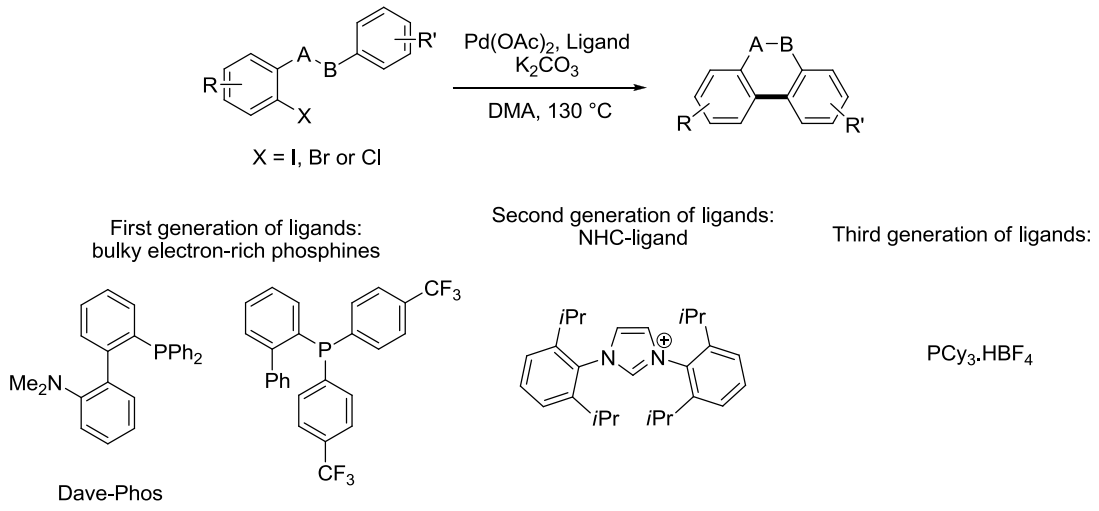
1.3.2.1 Intramolecular direct arylation

Regioselectivity in intramolecular direct arylation relies on a tethered approach which limits the degree of freedom in the system. Early examples of palladium-catalysed intramolecular direct arylation were reported by Ames and Bull.[63,64] While investigating intermolecular Heck reactions on bromocinnolines with ethyl acrylate, they obtained carbazole **4**, a product of the intramolecular direct arylation. Further studies proved the presence of the alkene was not required for the direct arylation to occur and they could extend the scope of the reaction to other heteroarenes such as dibenzofurans (**Scheme 29**).



Scheme 29: Early examples of palladium-catalysed intramolecular direct arylation for the synthesis of substituted carbazoles and benzofurans by Ames and co-workers

Fagnou and co-workers designed several related syntheses of heteroaromatics. The group reported the synthesis of various five, six and even seven-membered heterocycles using $Pd(OAc)_2$ and K_2CO_3 in DMA at 130 °C (**Figure 3**). They subsequently increased the range of available substrates by developing three generations of catalysts (**Scheme 30**).[65] They first used electron-rich Buchwald-type ligands to synthesise a wide range of heterocycles. Although extremely efficient for the arylation of aryl bromides, this methodology was low yielding for both aryl chlorides and aryl iodides. A second generation of the methodology which relies on *N*-heterocyclic carbenes (NHC) allowed the use of aryl chlorides, but good reactivity with aryl iodides was only obtained when using HBF_4 salts of PCy_3 and $P(t\text{Bu})_2\text{Me}$, along with Ag_2CO_3 as an additive, minimising the accumulation of iodide ions in the reaction.[66,67]



Scheme 30: Investigations for a general palladium catalysed heterocyclic synthesis by Fagnou and co-workers

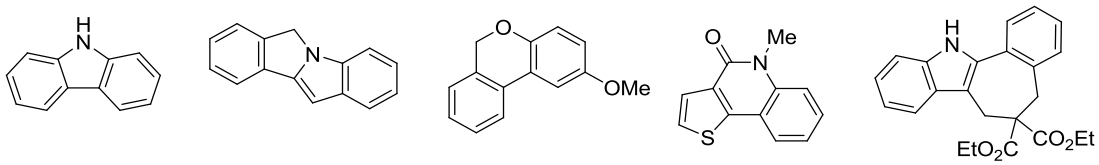
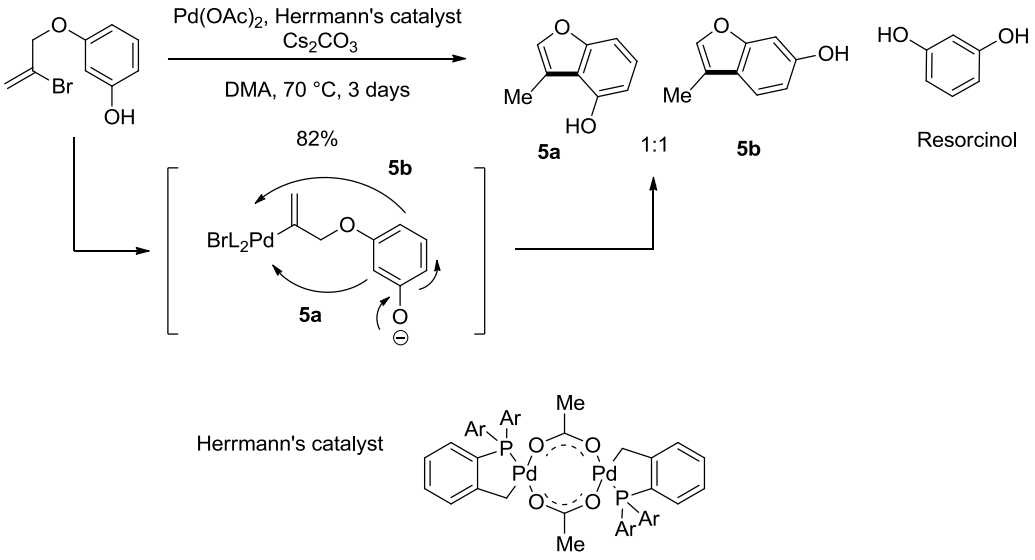


Figure 3: Selected examples of heteroarenes accessible by these methodologies

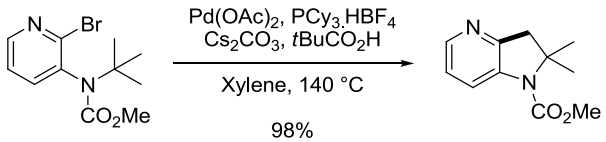
Although intramolecular aryl-aryl bond formation for the synthesis of fused heterocycles has been intensively studied, less is known about intramolecular direct alkenylation. This complementary reactivity would considerably extend the scope of accessible heterocyclic compounds. In 1997, Rawal and co-workers reported an anion-accelerated synthesis of benzofurans **5** by palladium-catalysed direct arylation (**Scheme 31**).[68,69] They speculated that after the initial oxidative addition to the vinyl bromide, the cyclisation occurs *via* a S_EAr type mechanism and after reductive elimination isomerisation of the *exo*-alkene affords the final product. The acceleration of the reaction in the presence of base supported their hypothesis of a S_EAr type addition of the phenol onto the palladium complex. This can be explained by the increased nucleophilicity of the phenolate anion formed compared to phenol itself. Although different palladium catalysts were found to facilitate the reaction, they also promoted the formation of significant quantities of resorcinol, probably the product of the

reaction of palladium(0) with allyl phenyl ethers to afford a π-allyl palladium species and a phenolate anion. Finally, Hermann's catalyst was found to be the best for this transformation and was later used in the synthesis of a range of benzofurans, indoles and benzopyrans.



Scheme 31: Synthesis of benzofuran *via* direct arylation using vinyl bromide by Rawal and co-workers

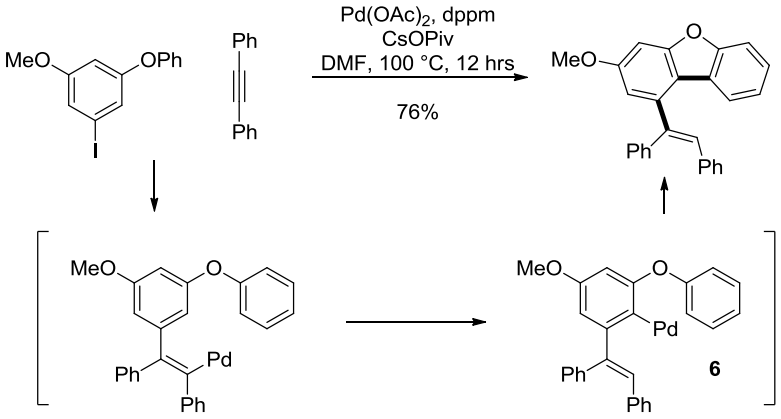
Recently, Ohno and co-workers reported a novel palladium-catalysed synthesis of indolines from *N*-alkyl 2-bromoanilines by activation of a sp^3 C-H bond (**Scheme 32**).[70] It is one of the first examples of functionalisation of a simple alkyl group.



Scheme 32: Synthesis of indolines by direct alkylation of arenes

1.3.2.2 Tandem processes

The search for short, efficient and divergent synthesis of heterocycles has prompted the development of many palladium-catalysed tandem reactions. Most of them use the ambivalence of the catalyst to associate direct arylation with well-known palladium-catalysed reactions but others associate it with another metallic catalyst or even with non-catalysed processes. An elegant sequence using biaryl ethers and alkynes to synthesised substituted dibenzofurans was developed by Larock and co-workers (**Scheme 33**).[71] The initial Heck reaction of a non-terminal alkyne and an aryl iodide was followed by a 1,4-migration of the palladium species. Once the key arylpalladium intermediate **6** was generated it proceeded to form a C-C bond *via* intramolecular direct arylation. The mechanism for the proposed vinyl to aryl palladium migration were provided by isotopically labelled substrates.[72] More recently, this strategy has been extended to the synthesis of carbazoles, indoles and other heterocycles.[71,73]

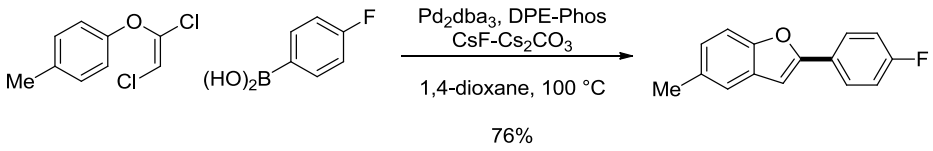


Scheme 33: Dibenzofuran synthesis developed by Larock *et al.* involving Pd migration

A similar reaction was studied in the Fagnou group using their optimised direct arylation conditions. They also performed this sequence in tandem with an *in situ* hydrogenation of the final alkene product.[74] A similar methodology involving an intramolecular Heck reaction followed by an intermolecular direct heteroarylation allowed them to access sp^2-sp^3 C-C bonds.[75]

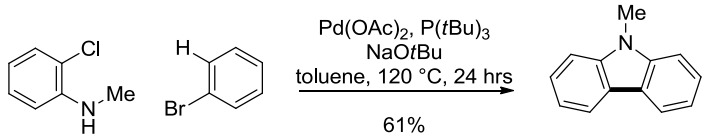
Hultin and co-workers described a tandem Suzuki coupling/direct arylation, allowing access to 2-aryl or styryl-substituted benzofurans.[76] They submitted various vinylic ethers to the reaction conditions in

presence of different boronic acids and observed that the Suzuki cross-coupling took place selectively at the C2 position, allowing the subsequent intramolecular direct arylation to proceed. Interestingly, the completion of the cross-coupling reaction seems necessary for the cyclisation to happen as reactions without added boronic acid gave no reaction, highlighting the difference of reactivity between styryl and vinylic halides in direct arylation reactions (**Scheme 34**).



Scheme 34: Tandem Suzuki coupling/direct arylation described by Hultin and co-workers

Bedford and co-workers developed an interesting methodology involving successive intermolecular Buchwald-Hartwig type amination and an intramolecular direct arylation.[77-80] Using the difference of reactivity between aryl bromides and chlorides, the amination occurred prior to the direct arylation, allowing the facile synthesis of a range of carbazoles (**Scheme 35**).

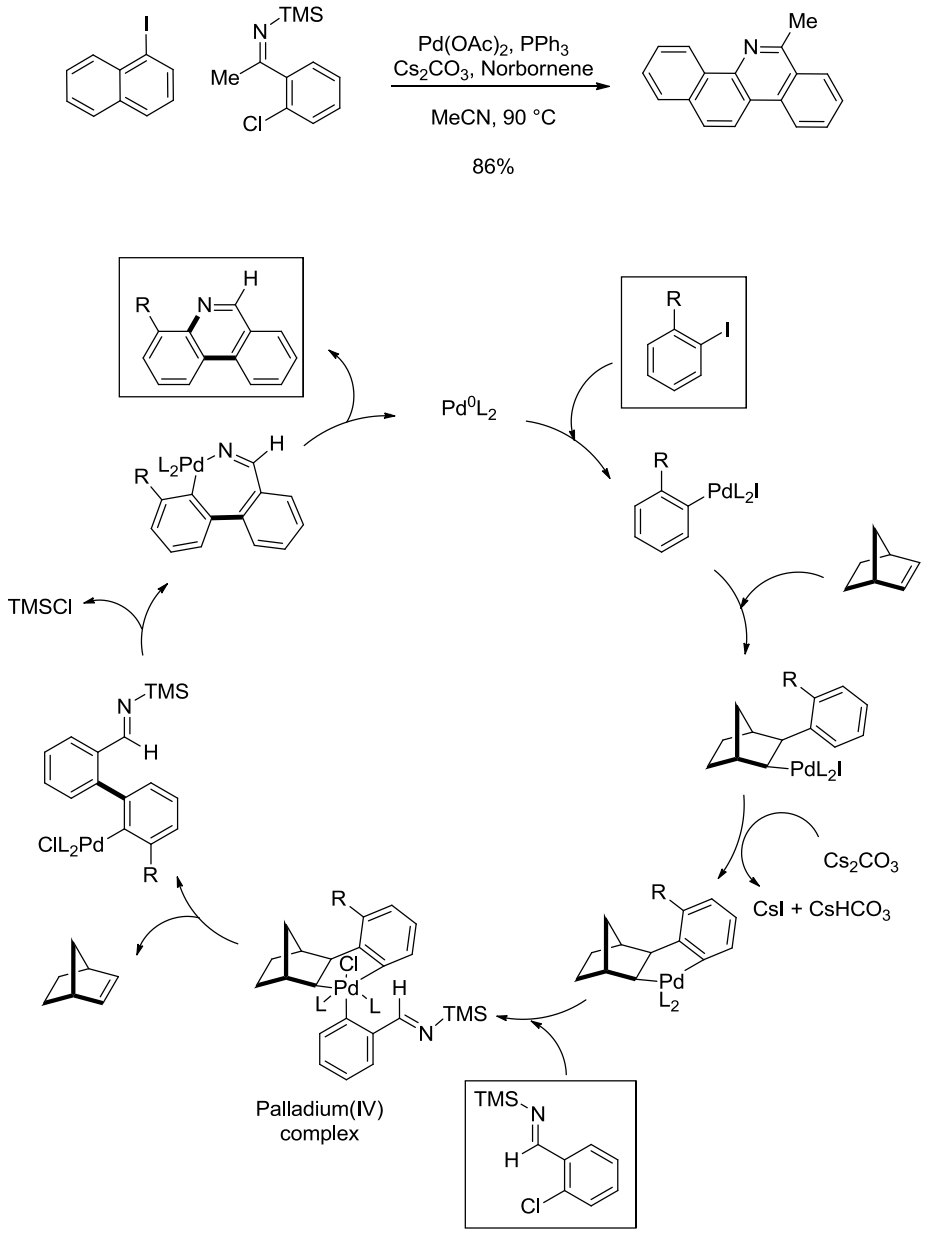


Scheme 35: Palladium-catalysed sequential synthesis of a carbazole developed by Bedford *et al.*

This approach has been more recently applied by other groups to a wider scope of substrates, including phenanthridines, unprotected carbazoles and derived natural products such as murrayafoline A. [12,81,82] One of the major improvements brought by these new methodologies is the use of anilines and di-haloarenes, including di-chloro aryl substrates.

Lautens and co-workers developed a palladium-catalysed, norbornene-mediated domino reaction[83-89] based on the work of Catellani *et al.*[90-92] to allow novel syntheses of functionalised carbocycles and

heterocycles. A complex catalytic cycle allows multiple functionalisation of arenes using norbornene for the assembly of the product scaffold but without itself being incorporated into the final compound. Relying on the generation of palladium(II) and palladium(IV) complexes, this methodology allows multiple *ortho*-C-H functionalisation of arenes as well as C-heteroatom bond formations to occur within a single catalytic cycle, thus leading to a highly general and versatile approach to functionalised carbocycles, heterocycles, and fused compounds. The example of the synthesis of phenanthridines using this methodology is described below (**Scheme 36**).[93]



Scheme 36: Proposed palladacycle for the domino palladium-catalysed synthesis of phenanthridine

This methodology has been applied to a large range of heterocyclic compounds[84,85,87-89,94] and the formal syntheses of anti-HIV and anti-cancer drugs Nitidine and NK109 later demonstrated the validity of the method (**Figure 4**).[95]

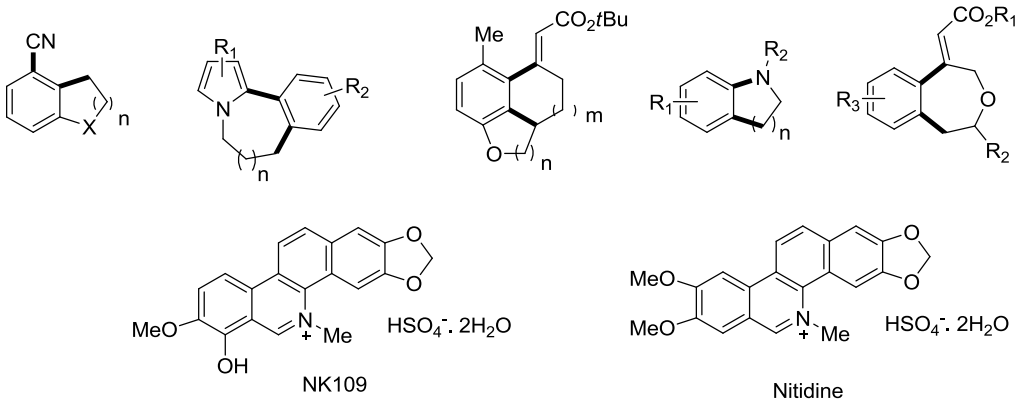
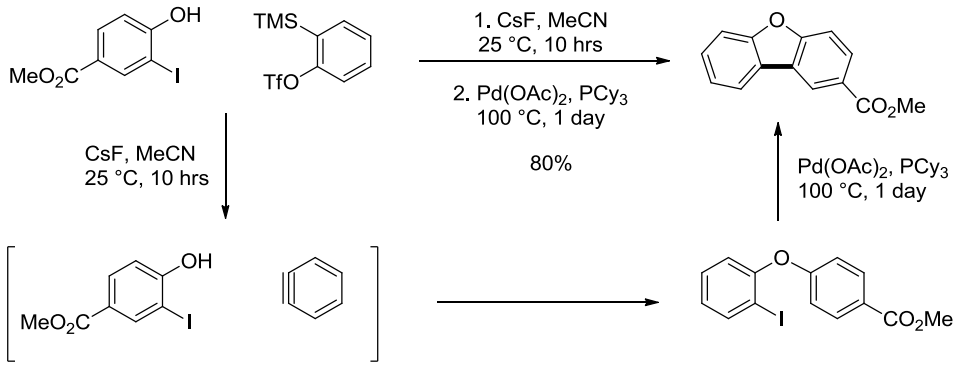


Figure 4: Selected examples of accessible substrates *via* Lautens and co-workers methodology

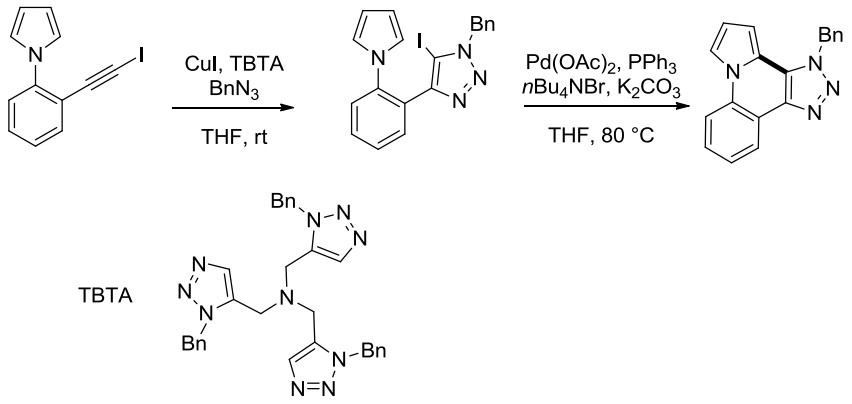
Larock and co-workers also developed an efficient “one-pot” synthesis of carbazole and dibenzofurans through the cross coupling of *o*-iodoanilines or *o*-iodophenol with silylaryl triflates, an *in situ* source of aryne, followed by palladium-catalysed intramolecular cyclisation (**Scheme 37**).[96,97] In this reaction, only the second step was palladium-catalysed. This synthesis is a good example of the versatility of metal catalysis as it can be combined with a wide range of other preparative methods.



Scheme 37: Tandem synthesis of dibenzofuran developed by Larock and co-workers

One-pot palladium/copper catalysis has also contributed to the development of heterocycle synthesis. Lautens and co-workers combined the high efficiency of the copper(I)-catalysed azide-alkyne

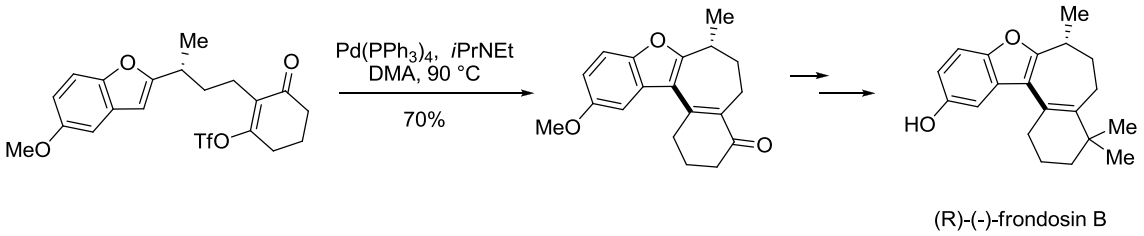
cycloaddition with palladium-catalysed C-H functionalisation to build complex fused triazoles (**Scheme 38**).[98]



Scheme 38: One-pot copper/palladium-catalysed synthesis of fused triazoles

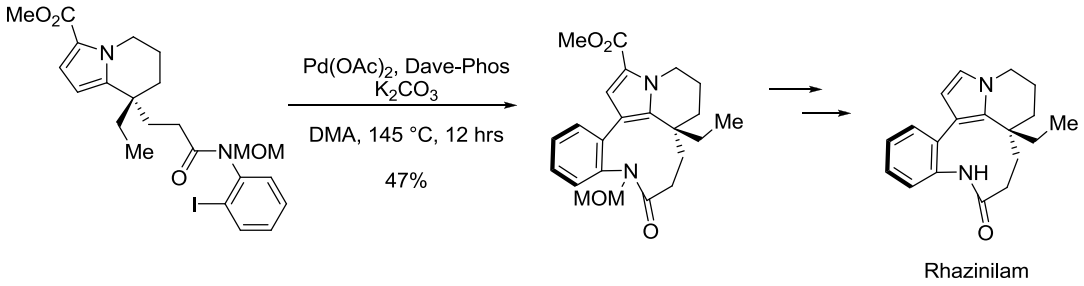
1.3.3 Natural product synthesis

Trauner and co-workers reported a novel total synthesis of (*R*)-(-)-frondosin B, the enantiomer of natural product (*S*)-(+)-frondosin B which is a member of the frondosins, a family of marine terpenoids isolated in the sponge *Dysidea frondosa*. This synthesis relies on the key formation of the seven-membered ring by intramolecular direct arylation between a vinylic triflate and the C3-position of a benzofuran (**Scheme 39**).[99,100]



Scheme 39: Synthesis of (*R*)-(-)-frondosin B by Trauner *et al.*

They later demonstrated the use of Fagnou and co-workers' methodology building the highly strained nine-membered ring of rhazinilam (**Scheme 40**).[101]

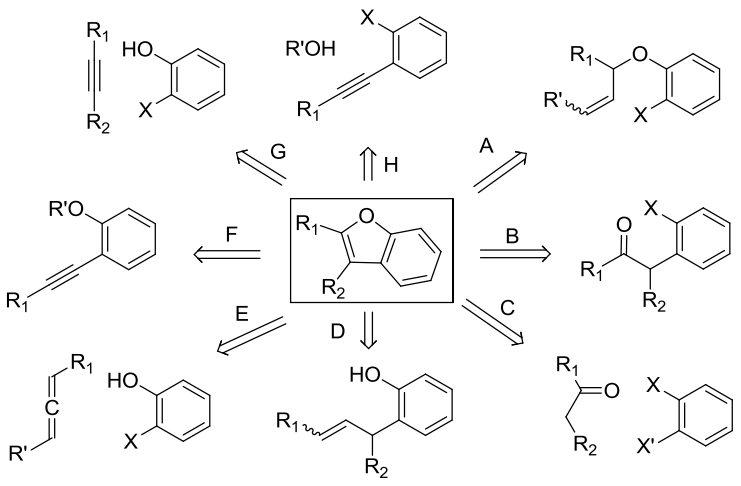


Scheme 40: Synthesis of rhazinilam by Trauner *et al.*

Chapter 2. Synthesis of Benzo[*b*]furans: Intramolecular Palladium-Catalysed Direct Arylation of Alkenyl Bromides

2.1 Introduction

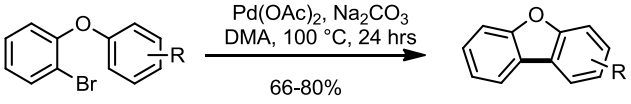
The importance of the benzofuran motif in pharmaceutical, agrochemical and other bio-active molecules has prompted the development of many synthetic methods to access them. While many metal-catalysed benzofuran syntheses have been published over the years, palladium chemistry has played an important role in the development of mild methods which tolerate a wide variety of functional groups, therefore avoiding protection/deprotection chemistry and usually allowing good stereo- and regio-control during the synthesis.[102] Although most of the newly developed palladium-catalysed methods describe attempts to decorate already formed benzofuran motifs, much has also been done to develop new routes for the formation of the aromatic ring itself. **Scheme 41** depicts a retrosynthetic analysis of the main routes used.[39,103]



Scheme 41: Retrosynthetic representation of selected examples of palladium-catalysed benzofuran synthesis

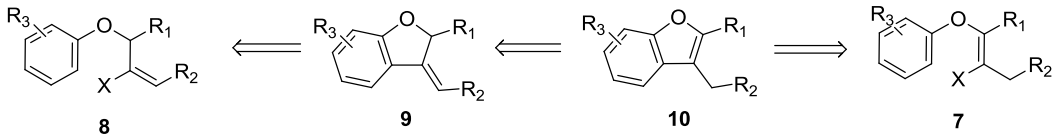
One of the best established methods, A, generates benzofurans *via* an intramolecular Heck-cyclisation.[104-106] Methods B and C rely on the *in situ* formation of an enolate followed by a Buchwald-Hartwig type C-O bond formation.[107-109] Methods D and E are based on π-olefin chemistry,[110-112] combined in the case of E with a Heck coupling.[113,114] Finally, methods F to H employ π-alkyne chemistry,[115-118] with an internal nucleophile for methods F and G,[119] and an external one in the case of method H.[120]

Among palladium-catalysed methods, we were particularly interested in intramolecular direct arylation as it offers new opportunities for the design of atom economical and efficient synthetic routes. The first example of the synthesis of dibenzofurans by this methodology was described by Ames *et al.* who obtained moderate to very good yields by heating 2-bromophenyl phenyl ethers in DMA in the presence of $Pd(OAc)_2$ and Na_2CO_3 (**Scheme 42**).[63,64] Since then other related methods have been described, extending the scope of accessible dibenzofurans.[66,121,122] Many of these methods have previously been discussed in **Chapter 1**.



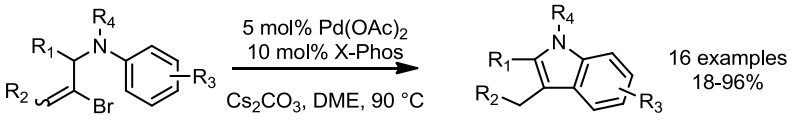
Scheme 42: Construction of dibenzofuran by direct arylation by Ames *et al.*

This interesting approach to the formation of heterocycles by direct arylation was nevertheless mostly limited to the construction of aryl-aryl bonds and therefore dibenzofurans. Extending the scope of this methodology to substituted benzofurans would require the use of phenyl vinyl ether **7** as the substrate for the direct arylation (**Scheme 43**). This class of compounds is however not easily accessed and fairly unstable, so we envisioned a different approach relying on easily accessible phenyl allyl ether **8**. The direct arylation of ether **8** would afford *exo*-alkene **9**, which can in turn be isomerised into the desired benzofuran **10**. We were confident that the isomerisation of the double bond was possible as it had been previously reported by different groups for substituted benzofurans.[68,69,123]



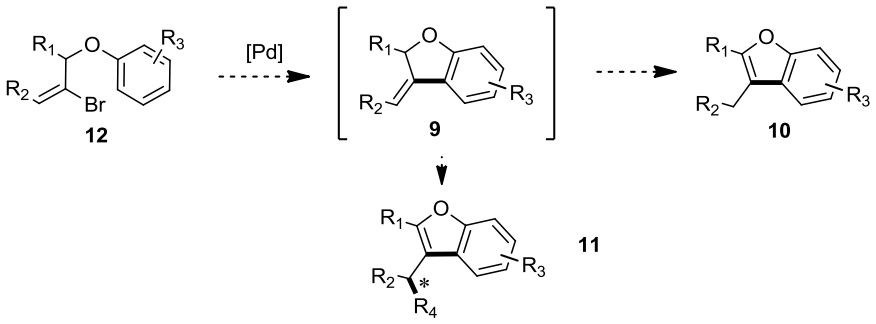
Scheme 43: Retrosynthetic analysis for the construction of benzofurans

Previously in the group, a similar synthesis of indoles using $Pd(OAc)_2$ and the electron-rich phosphine ligand X-Phos had been successfully developed (**Scheme 44**).[124] This route confirmed not only the possibility to form the aryl-vinyl bond but also to isomerise the *exo*-alkenic double bond to form the more thermodynamically stable indole.



Scheme 44: Palladium-catalysed synthesis of indoles *via* C-C bond formation

The initial success of this methodology prompted us to explore the analogous synthesis of benzofurans **10** using versatile and readily available starting materials (**Scheme 45**). In this new synthesis, the *exo*-alkene product **9** of the key direct arylation could be isomerised *in situ* to the more thermodynamically stable benzofuran **10** or alternatively isolated and further functionalised, allowing us to access a new family of substituted benzofurans **11**.

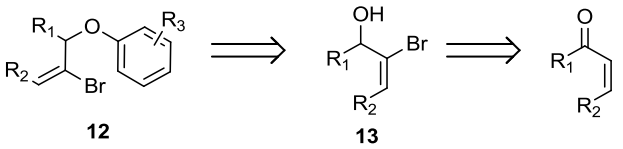


Scheme 45: Proposed novel route to the synthesis of benzo[*b*]furans *via* palladium-catalysed direct arylation of alkenyl bromides

2.2 Intramolecular palladium-catalysed direct arylation of alkenyl bromides: synthesis of benzo[*b*]furans

2.2.1 Synthesis of the direct arylation substrates

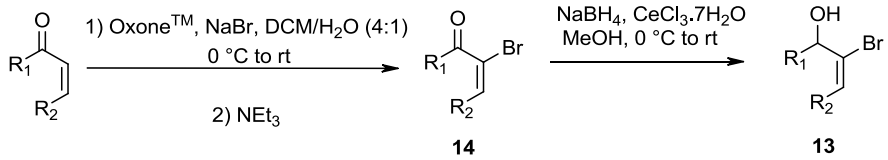
Our desire to design a synthesis of benzofurans directed our attention to α-bromo alcohol **13** which could be a versatile precursor to our starting substrate **12**, allowing the modification of the aromatic region of the benzofuran in the last stage of the synthesis. This α-bromo alcohol can be readily obtained in two steps from commercially available enones (**Scheme 46**).[125-127]



Scheme 46: Retrosynthetic analysis of the construction of allyl aryl ethers, substrates of the direct arylation

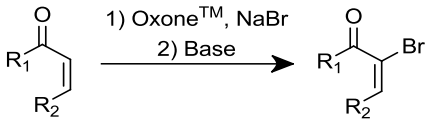
The synthesis of α-bromo enones is usually achieved by the addition of bromine (Br_2) across the double bond of the corresponding α,β-enone followed by the elimination of the most acidic proton (α to the ketone) using NEt_3. However, the necessity to handle this hazardous compound on a large scale in the first step of our synthesis prompted us to use an alternative route. The generation of

bromine *in situ* with an aqueous mixture of Oxone™ and sodium bromide allows efficient and safe bromination of the enone followed by the subsequent elimination of HBr with NEt_3 to afford unsaturated α-bromo enone **14**.[125,126,128] Using this approach, a series of cyclic and acyclic enones were brominated to give the corresponding α-bromo enones in moderate to excellent yields (**Scheme 47**, **Table 1**).

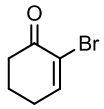
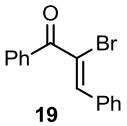
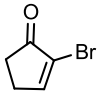
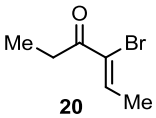
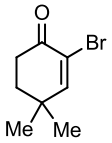
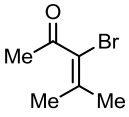
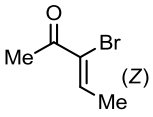


Scheme 47: Synthesis of versatile α-bromo alcohol **13**

Table 1: α-Bromination of enones [a]



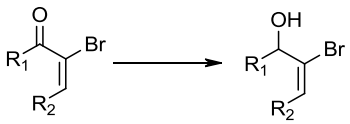
14

Entry	Product	Yield	Entry	Product	Yield
1	 **15**	88%	**5**	 **19**	99% [b,e]
2	 **16**	77%	**6**	 **20**	75% [c,e]
3	 **17**	92%	**7**	 **21**	30% [d]
4	 **18**	51%			

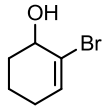
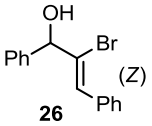
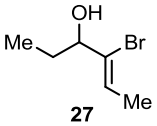
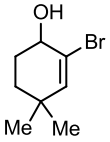
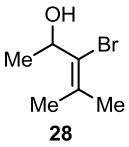
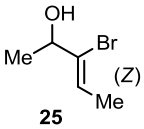
a. 1) Oxone™ (2.0 equiv), NaBr (2.0 equiv), DCM/H_2O, 0 °C to rt, 3 hrs; 2) NEt_3 (3.0 equiv), DCM/H_2O, 0 °C to rt, 5 hrs; b. (*E*):(*Z*) = 1:1.2; c. 1) Oxone™ (2.0 equiv), NaBr (2.0 equiv), CH_3Cl/H_2O, 0 °C to rt, 7 hrs; 2) NEt_3 (3.0 equiv), $CHCl_3$/H_2O, 0 °C to 75 °C, 30 hrs; d. 2) KOH (1.0 equiv), MeOH, rt, 4 days; e. A single diastereoisomer of unknown geometry was obtained.

A Luche reduction of the α-bromo enones allowed the selective 1,2-reduction of the enones and a range of cyclic and acyclic α-bromo alcohols were obtained in excellent yields (**Table 2**). [127]

Table 2: Luche reduction [a]



14 **13**

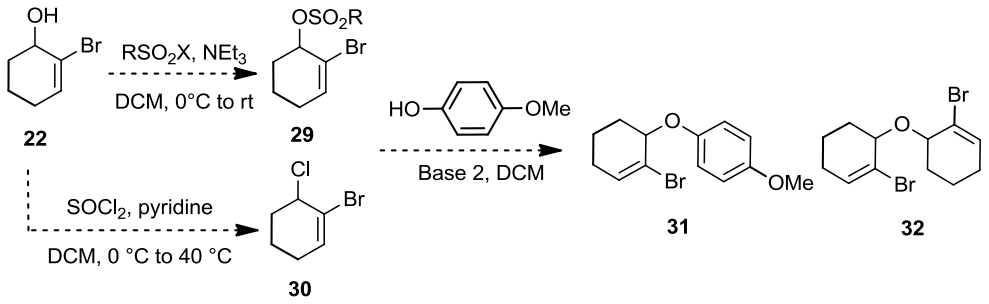
Entry	Product	Yield	Entry	Product	Yield
1	 **22**	97%	**5**	 **26**	99%
2	 **23**	86%	**6**	 **27**	89% [b]
3	 **24**	74%	**7**	 **28**	59%
4	 **25**	69%			

a. $NaBH_4$ (1.2 equiv), $CeCl_3.7H_2O$ (1.1 equiv), MeOH, 0 °C to rt, 1 hr; b. A single diastereoisomer of unknown geometry was obtained.

2.2.2 Synthesis of arene erthers

The synthesis of the phenyl ether itself was carried out using different methods depending on the electronic and steric properties of the desired product.

We first selected a model substrate to test the direct arylation conditions. The mixed ether 1-(2-bromocyclohex-2-enyloxy)-4-methoxybenzene **31** was selected and we undertook to design an efficient and practical method to prepare our key substrate. The initial activation of the hydroxyl group of α-bromo alcohol **22** would be followed by its *in situ* nucleophilic substitution by 4-methoxyphenol. This reaction would ideally afford the desired ether **31** but homo-allylic ether **32** could also be obtained by the reaction of unreacted α-bromo alcohol **22** with its activated counterpart **29** or **30** (**Scheme 48**).

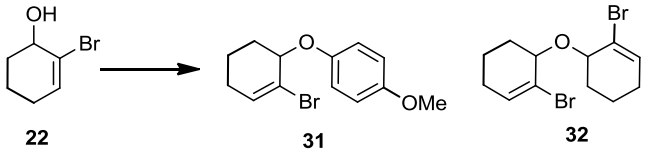


Scheme 48: Design of our substrate synthesis

After an initial unsuccessful attempt at reacting the pre-formed 1-bromo-6-chlorocyclohex-1-ene **30** with the corresponding phenol (**Table 3**, **Entry 1**), we turned to the functionalisation of the hydroxyl group with a sulfonyl moiety, followed by an *in situ* nucleophilic substitution by a commercially available phenolic derivative. As we started to investigate this method, we were surprised to observe the presence of homocoupling product **32** as the main by-product of the reaction. Considering that it probably originated from the nucleophilic attack of the unprotected alcohol **22** onto the formed sulfonyl derivative **29**, we focused on the identification of an appropriate sulfonyl group which would allow the first step of the reaction to proceed to completion while being less reactive towards alcohol **22**. After evaluation, we found that trifluoromethanesulfonic anhydride was producing a very reactive intermediate which led to the undesired homocoupled ether **32** in high yield (**Entry 2**). On the contrary, toluenesulfonic anhydride was barely reactive towards the α-bromo alcohol, only forming

traces of the intermediate sulfonyl derivative **29** (**Entry 3**). We therefore focused our study on the moderately reactive methanesulfonyl derivative. Disappointingly, methanesulfonyl chloride, used either in small or large excess (**Entries 4 to 7**), delivered low yields of the desired ether. Switching to the alternative methanesulfonyl anhydride, however, we obtained a good 67% yield of compound **31** (**Entry 8**). Increasing the temperature during the second step of the reaction (**Entry 9**) further improved the yield (88%) of the desired ether, noticeably without producing any homocoupled by-product **32**. In order to avoid hydrolysis and degradation of intermediate **29**, it was never isolated and the two steps of the reaction were carried out in one-pot. It was also noted that the presence of homocoupling product **32** was highly dependent on the purity of the phenol used.

Table 3: Evaluation of the feasibility of alkenyl bromide moiety **31** synthesis [a]



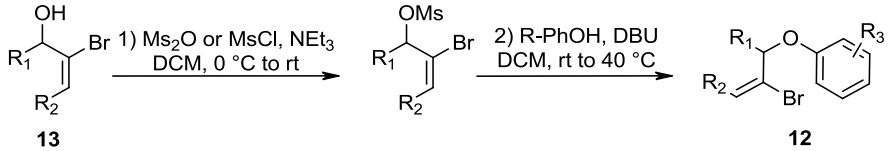
22 31 32

Entry	RSO_2X (equiv)	Base (equiv)	Temperature Step 2	Base 2	31	32
1	$SOCl_2$	Pyridine (1.5)	0 °C to 40 °C	DBU	0%	0%
2	Tf_2O (1.0)	NEt_3 (1.1)	0 °C to rt	DBU	0%	83%
3	TsCl (1.2)	NEt_3 (1.2)	0 °C to rt	DBU	0%	0%
4	MsCl (1.1)	NEt_3 (1.1)	0 °C to rt	/	26%	60%
5	MsCl (1.2)	NEt_3 (1.2)	0 °C to rt	/	0%	80%
6	MsCl (2.0)	NEt_3 (2.5)	0 °C to rt	/	23%	60%
7	MsCl (2.0)	NEt_3 (2.5)	0 °C to rt	DBU	30%	60%
8	Ms_2O (1.2)	NEt_3 (1.2)	0 °C to rt	DBU	67%	trace
9	Ms_2O (1.2)	NEt_3 (1.2)	rt to 40 °C	DBU	88%	0%

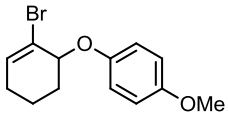
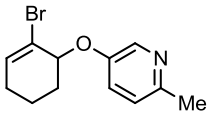
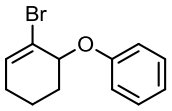
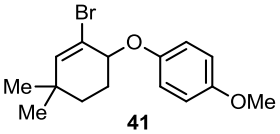
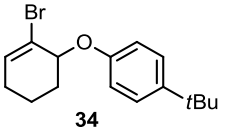
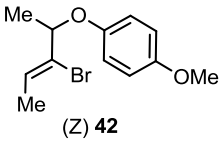
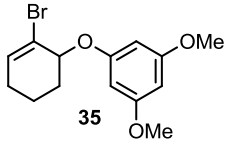
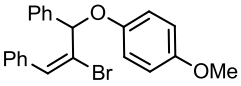
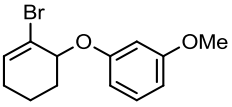
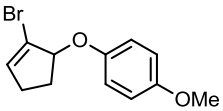
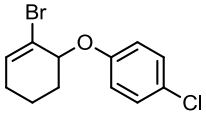
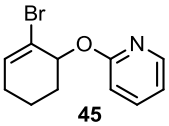
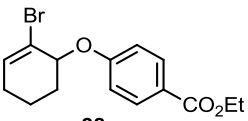
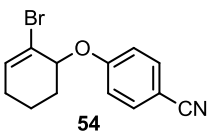
a i) α-bromo alcohol (1.0 equiv), RSO_2X and base in dry DCM (0.2 $mol.L^{-1}$), 0 °C to rt, 1 hr; ii) 4-methoxyphenol (3.0 equiv), base 2 (3.0 equiv) in dry DCM (0.2 $mol.L^{-1}$)

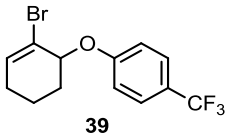
This practical and efficient strategy enabled us to access a wide variety of substrates. The reaction conditions were optimised in the particular case of compound **31** (**Table 4**, **Entry 1**) with purified reagents and solvent. During the synthesis of our range of alkenyl bromide moieties however, reagents and solvents were used directly as purchased and no further optimisation was made. We were therefore pleased to observe the formation of the following compounds in moderate to good yields.

Table 4: Preparation of alkenyl bromide moieties [a]



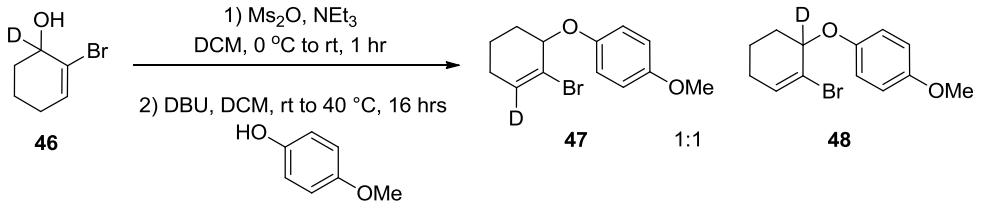
13 **12**

Entry	Product	Yield	Entry	Product	Yield
1	 **31**	88%	**9**	 **40**	54%
2	 **33**	43%	**10**	 **41**	17%
3	 **34**	66%	**11**	 (Z) **42**	37% [b]
4	 **35**	51%	**12**	 **43**	51% [b, c]
5	 **36**	63%	**13**	 **44**	53%
6	 **37**	57%	**14**	 **45**	23%
7	 **38**	76%	**15**	 **54**	55%

8	 **39**	51%

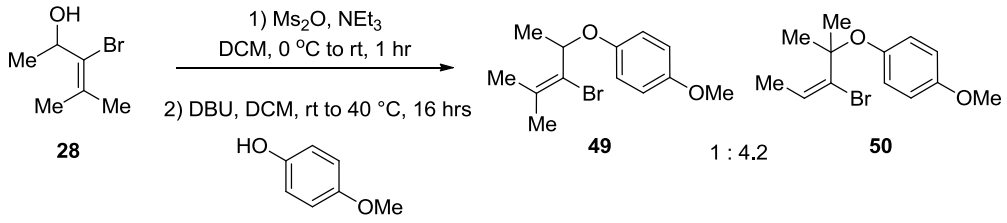
a. Reaction conditions: 1) α-Bromo alcohol (1.0 equiv), Ms_2O (1.5 equiv), NEt_3 (1.5 equiv), DCM, 0 °C to rt, 1 hr; 2) R-PhOH (3 equiv), DBU (3 equiv), DCM, rt to 40 °C, 16 hrs; b. Only one diastereoisomer detected by ^1H NMR spectroscopy; c. A single diastereoisomer of unknown geometry was obtained.

In order to clarify the mechanism of this nucleophilic substitution in the case of cyclic compounds, deuterated α-bromo alcohol **46** was synthesised and submitted to the reaction conditions. It afforded a mixture of isomers **47** and **48** (1:1) and it is therefore very likely that the nucleophilic substitution proceeds *via* both S_N and S_N' mechanisms (**Scheme 49**).



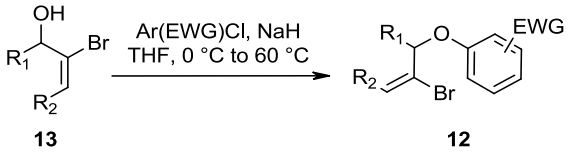
Scheme 49: Investigation on the mechanism of the substitution

We envisioned that the substitution pattern of the substrate would influence the ratio between S_N and S_N' mechanisms, disallowing the substitution near a sterically hindered carbon center. In order to facilitate the S_N pathway, we chose 3-bromo-4-methylpent-3-en-2-ol **28** as the substrate but, disappointingly, we observed a mixture of alkenyl bromide derivatives (**Scheme 50**), the major one being the ether **50**.



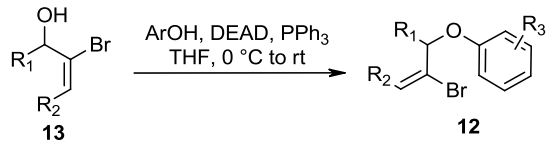
Scheme 50: Further investigation on the mechanism of the substitution

We investigated alternative synthetic methods to access a wider range of substrates without being constrained by the competition between S_N and S_N' mechanisms. As electron-poor phenols usually gave low yields in our substitution reaction, we used an alternative aromatic nucleophilic substitution route (**Scheme 51**) with moderate to good results (**Table 5**, **Entries 3-6**).



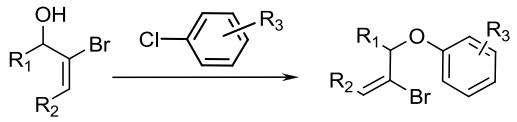
Scheme 51: Synthesis of the substrate by aromatic nucleophilic substitution

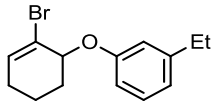
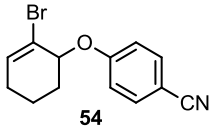
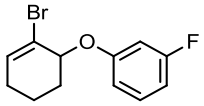
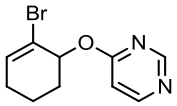
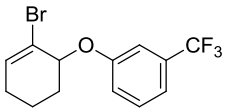
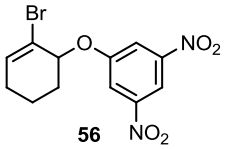
For more electron-rich substrates, the competition between the different pathways was suppressed using a Mitsunobu coupling reaction (**Scheme 52**). This method could also be applied in low to moderate yields to the synthesis of phenols bearing either electron-donating or electron-withdrawing substituents (**Table 5**, **Entries 1** and **2**).



Scheme 52: Synthesis of the substrate by a Mitsunobu coupling reaction

Table 5: Preparation of additional alkenyl bromide moieties



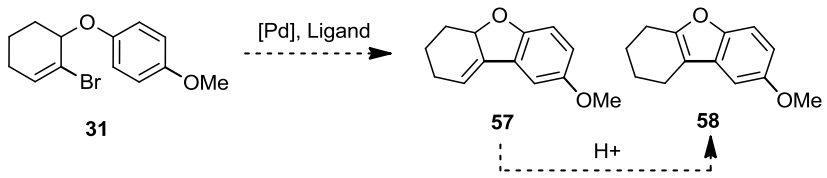
Entry	Product	Yield	Entry	Product	Yield
1	 **51**	60% [a]	**4**	 **54**	75% [b, c]
2	 **52**	78% [a]	**5**	 **55**	49% [b]
3	 **53**	10% [b, c]	**6**	 **56**	57% [b, c]

a. Reaction conditions: α-Bromo alcohol **22** (1.0 equiv), ArOH (1.2 equiv), PPh_3 (1.2 equiv), DEAD (1.2 equiv), DCM, 0 ^{o}C to rt, 17 hrs; b. Reaction conditions: α-bromo alcohol **22** (1.0 equiv), Ar-Cl (1.2 equiv), NaH (60% dispersion in mineral oil, 3.0 equiv), DMF, 0 ^{o}C to 90 ^{o}C, 17 hrs; c. Ar-F used instead of Ar-Cl.

2.2.3 Palladium-catalysed direct arylation

To evaluate the feasibility of the palladium-catalysed direct arylation, we studied the conversion of substrate **31** into benzofuran **58** (**Scheme 53**). Based on literature precedent,[12,13] we focused on the use of palladium acetate and the bulky electron-rich phosphine ligands developed by Buchwald. As expected, the reaction delivered a mixture of the desired benzofuran **58** and its *exo*-alkene isomer **57**,

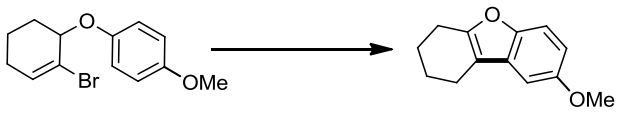
the latter often in excellent yields. In order to obtain the benzofuran, the isomerisation of the crude mixture was then carried out with excellent conversion under acidic conditions.[68,69,123]



Scheme 53: Evaluation of the feasibility of our benzo[b]furan synthesis

An initial ligand screen showed that the transformation could be accomplished in moderate to good yields with a large variety of electron-rich phosphine ligands, both mono and bidentate (**Table 6**). As a general rule, the starting material **31** was entirely consumed in every reaction and the main by-product observed was the corresponding 4-methoxyphenol. An exception was found in the case of bulky ligand *t*BuX-Phos where low conversion was observed (**Entry 5**). Our efforts then concentrated on the reduction of the side reaction responsible for the formation of this undesired compound. Finally, the most efficient ligand screened was found to be monophosphine ligand X-Phos (**Entry 11**).

Table 6: First condition screen for the palladium-catalysed C-C bond formation [a]



31 **58**

Entry	Ligand	Yield [b]
1	XantPhos	48%
2	DPE Phos	35%
3	S-Phos	60%
4	Dppe	42%
5	*t*BuX-Phos	<20%[c]
6	Dppm	49%
7	Dppp	45%
8	Dppb	35%
9	DavePhos	70%
10	$t\text{Bu}_2\text{MeP,HBF}_4$	44%
11	X-Phos	79%

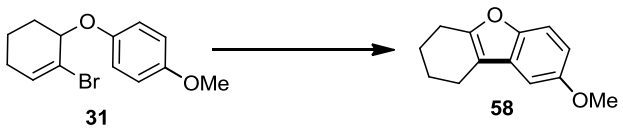
a. Alkenyl bromide **31** (1.0 equiv), $Pd(OAc)_2$ (10 mol%), Ligand (20 mol%), Cs_2CO_3 (2 equiv) in DME (0.2 M), 90 °C, 17 hrs; b. 20 mol% monophosphine ligand or 10 mol% of di-phosphine ligand; b Isolated yield after isomerisation with 10 mol% *p*TSA in DCM (0.2 M); c. Presence of starting material.

Having chosen X-Phos as the best ligand for this transformation, we evaluated the role of the other reaction components. A brief solvent screen was carried out (**Table 7**, **Entries 1-6**) showing that the polar solvent *N,N*-dimethylacetamide (DMA) was superior to all other solvents tested, including

similarly polar DMF or NMP, delivering the expected benzofuran **58** in 85% yield. Slight modifications of the temperature and solvent concentration (**Entries 1, 13-15**) led us to our final reaction conditions, delivering benzofuran **58** in 87% yield.

The use of organic bases such as NEt_3 and NBu_3, which had previously been reported as efficient when using Buchwald-type ligands, did not succeed in our system (**Entries 7-8**). Lowering the catalyst loading decreased the yield of the reaction (**Entries 10-13**) although using 5 mol% of catalyst (**Entry 10**) still allowed us to access the desired benzofuran in good yield. Interestingly, we also observed the formation of benzofuran **58** in average yield when the reaction was performed without ligand (**Entry 19**). This effect had been previously observed for palladium-catalysed reactions performed in DMA.[12,13] Therefore we believe that this reaction is still catalysed by a palladium(0) species and that the coordinating solvent DMA plays the role of the ligand in this case. Finally, attempting to replace our palladium source by $Pd_2(dba)_3$ was unsuccessful, leading to a complex mixture of products (**Entry 20**).

Table 7: Second condition screen for the palladium-catalysed C-C bond formation [a]



Entry	Pd	Base	Solvent	Temperature	Yield [b]
1	$Pd(OAc)_2$ %	K_2CO_3	DMA (0.2 M)	90°C	85%
2	10%	Cs_2CO_3	CH_3CN (0.2 M)	90°C	68%
3	10%	Cs_2CO_3	1,4-dioxane (0.2 M)	90°C	71%
4	10%	K_2CO_3	DMF (0.2 M)	90°C	80%
5	10%	K_2CO_3	Toluene (0.2 M)	90°C	73%
6	10%	K_2CO_3	NMP (0.2 M)	90°C	66%

7	10%	NEt_3	DMA (0.18 M)	80°C	30%
8	10%	NBu_3	DMA (0.18 M)	80°C	20% [c]
9	10%	Cs_2CO_3	DMA (0.18 M)	80°C	65%
10	5%	K_2CO_3	DMA (0.18 M)	80°C	76%
11	2,5%	K_2CO_3	DMA (0.18 M)	80°C	54%[c]
12	4%	K_2CO_3	DMA (0.18 M)	80°C	56%[c]
13	10%	K_2CO_3	DMA (0.4 M)	80°C	72%
14	10%	K_2CO_3	DMA (0.18 M)	80°C	87%
15	10%	K_2CO_3	DMA (0.1 M)	80°C	66%
16	10%	K_2CO_3	DMA (0.18 M)	80°C [e]	80%
17	/	K_2CO_3	DMA (0.18 M)	80°C	0%[b]
18	10%	/	DMA (0.18 M)	80°C	Trace
19	10%	K_2CO_3	DMA (0.18 M)	80°C	58% [c, d]
20	10% $Pd_2(dba)_3$	K_2CO_3	DMA (0.18 M)	80°C	0%[d]

a. Alkenyl bromide **31** (1.0 equiv), Pd-2 X-Phos, base (2.0 equiv) in solvent, 17 hrs; b. Isolated yield after isomerisation with 10 mol% *p*TSA in DCM (0.2 M); c. Presence of starting material; d. Reaction performed without ligand; e. Reaction performed in the microwave.

2.2.4 Reaction scope: Benzo[*b*]furan synthesis *via* palladium-catalysed direct arylation of alkenyl bromides

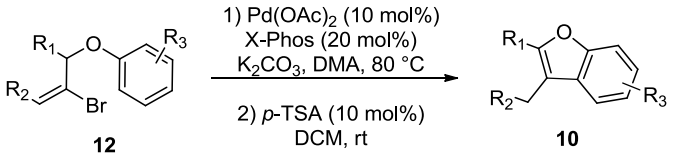
With efficient conditions in hand for the conversion of alkenyl bromide **31** into benzofuran **58**, we explored the scope of the reaction (**Table 8**). A variety of electron-donating substituents could be readily incorporated, delivering the expected benzofurans in excellent yields (**Entries 2-6**). Employing phenol itself delivered benzofuran **59** in 79% yield (**Entry 1**). The incorporation of electron-withdrawing groups was less straightforward; although the Cl-, F- and ester-substituted benzofurans **67** and **68** (**Entries 8-9**) were obtained in good yields, the more electron-poor trifluoromethyl- and nitrile-derivatives **70**, **72** and **73** (**Entries 10-12**) were isolated in only 44%, 29% and 36% yields respectively. The reason for the lower yields was not the efficiency of the direct arylation steps, which were achieved in very good yields, but the difficulty in achieving efficient isomerisation of the resultant electron-poor *exo*-alkene ether.

To demonstrate the use of a simple heterocyclic derivative, we synthesised the *exo*-alkene intermediate of 6-azabenzofuran **74** but it could not be isomerised to the corresponding benzofuran under our standard conditions. However, performing a similar reaction in the absence of the ligand X-Phos surprisingly allowed direct access to 6-azabenzofuran **74** in 66% yield without the need for a separate isomerisation step (**Entry 13**).

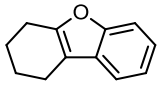
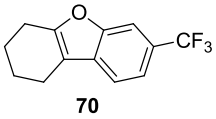
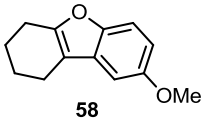
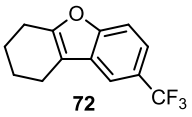
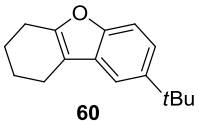
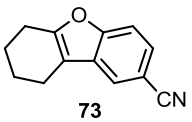
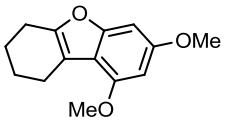
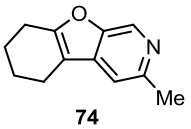
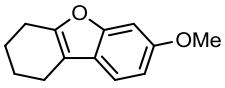
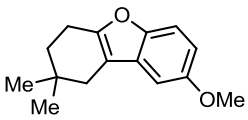
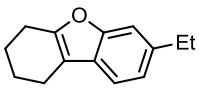
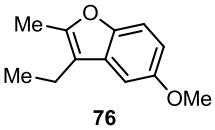
Variation of the α-bromo-enone components allowed dimethyl-derivative **75** (**Entry 14**), as well as acyclic variants **76** and **77** (**Entries 15-16**) to be prepared in reasonable yields. The strained, cyclopentane-derived, benzofuran **78** was obtained in poor yield, although the C-C bond forming process was moderately efficient, affording the *exo*-alkene in 50% yield (**Entry 17**).

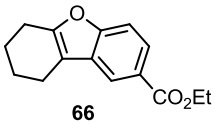
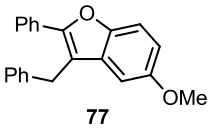
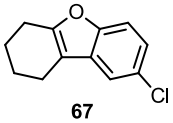
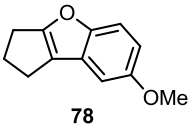
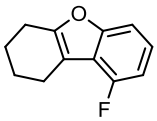
The benzofuran-forming reactions also displayed some interesting regio-control; benzofurans **62**, **64** and **70**, incorporating *m*-methoxy-, *m*-ethyl and *m*-trifluoromethane phenol respectively, result from arylation para to the substituent, presumably due to steric influences (**Entries 5, 6 and 10**). However, benzofuran **68**, derived from *m*-F-phenol, was formed from preferential arylation next to the F-substituent (**Entry 9**). This reaction therefore seems to be little affected by the electronic properties of the arene but to be more sensitive to steric hindrance. Similar regio-selectivity had previously been observed by Fagnou and co-workers.[66]

Table 8: Benzofuran formation by palladium-catalysed C-C bond formation [a]



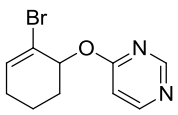
12 **10**

Entry	Product	Yield / Time	Entry	Product	Yield / Time
1	 **59**	79% 90 min	**10**	 **70** >20:1 with regioisomer **71**	44% 90 min
2	 **58**	86% 75 min	**11**	 **72**	29%[c] 90 min
3	 **60**	89% 90 min	**12**	 **73**	36%[b,d] 60 min
4	 **61**	91% 60 min	**13**	 **74**	66%[e] 24 hrs
5	 **62** 4.5:1 with regioisomer **63**	87% 90 min	**14**	 **75**	73% 8 hrs
6	 **64** >20:1 with regioisomer **65**	89% 90 min	**15**	 **76**	68% 5 hrs

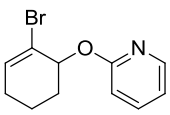
7	 **66**	70%[b] 90 min	**16**	 **77**	45% 17 hrs
8	 **67**	75% 120 min	**17**	 **78**	7%[f] 60 min
9	 **68**	80% 90 min			
	4:1 with regioisomer **69**				

a. Reaction conditions: 1) bromoalkene (1.0 equiv), $Pd(OAc)_2$ (10 mol%), X-Phos (20 mol%), K_2CO_3 (2.0 equiv), DMA, 80 °C, 1.5-24 hrs; 2) *p*TSA (0.1 equiv.), DCM, rt, 3-15 hrs. Isolated yields; b. K_2CO_3 (1.1 equiv.) employed; c. 79% for C-C formation; d. 74% for the C-C bond formation; e. No ligand employed; f. 50% for the C-C bond formation.

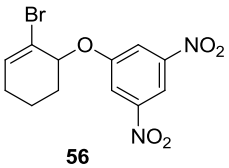
In some cases however, the direct arylation reaction delivered no product (**Figure 5**). Substrates **45** and **55** were recovered unreacted, possibly due to the coordination of the nitrogen of the pyridine or the pyrimidine to the catalyst. In the case of extremely electron-deficient substrate **56**, the reaction led only to a complex mixture of degradation products.



55



45



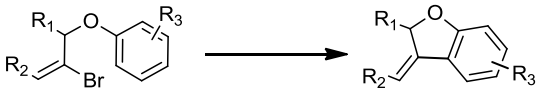
56

Figure 5: Unsuccessful substrates for direct arylation

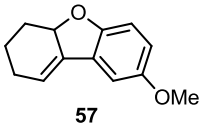
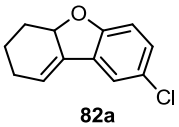
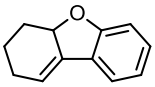
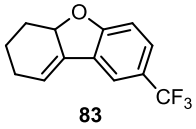
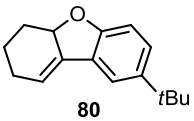
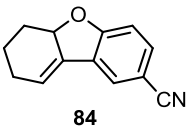
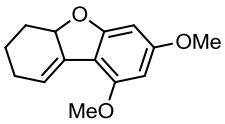
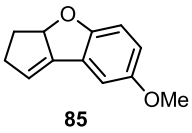
2.2.5 Reaction scope: Dihydrobenzofuran synthesis *via* palladium-catalysed direct arylation of alkenyl bromides

In most cases, we were able to isolate the *exo*-alkene intermediate formed during the direct arylation. When carefully monitored, the electron-rich substrates delivered the expected *exo*-alkenic benzofuran in excellent yields (**Table 9**, **Entries 1-4**). However, they were shown to be prone to isomerise to the more stable aromatic benzofuran, either under the palladium-catalysed reaction conditions or at room temperature. On the contrary, more electron-deficient substrates which gave lower yields of benzofuran afforded the *exo*-alkenic benzofuran in very good to excellent yields (**Entries 5 to 7**). Although these compounds degraded slowly under the reaction conditions after completion of the transformation, when carefully monitored, they showed that our C-C bond formation is efficient for a large range of substrates. To our delight, we were also able to isolate a synthetically useful amount (50% yield) of the strained compound **85** (**Entry 8**).

Table 9: Dihydrobenzofuran formation by palladium-catalysed C-C bond formation [a]



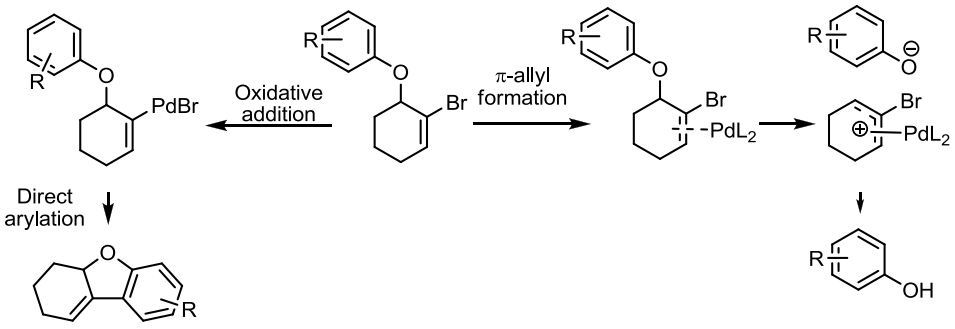
12 **9**

Entry	Product	Yield / Time	Entry	Product	Yield / Time
1	 **57**	89% / 75 min	**5**	 **82a**	88% / 75 min
2	 **79**	80% / 90 min	**6**	 **83**	79% / 90 min
3	 **80**	92% / 90 min	**7**	 **84**	74%[b] / 90 min
4	 **81**	93% / 75 min	**8**	 **85**	50% / 75 min

a. Reaction conditions: Alkenyl bromide (1.0 equiv), $Pd(OAc)_2$ (10 mol%), ligand X-Phos (20 mol%), K_2CO_3 (2.0 equiv), DMA, 80 °C. Isolated yields; b. K_2CO_3 (1.1 equiv.) employed.

2.2.6 Rationalisation of the formation of the by-product

The study of the direct arylation reaction showed complete conversion of the alkenyl bromide starting material for every transformation tested. The difference between the yields is mainly accounted for by the decomposition of the substrate into the corresponding phenol (**Scheme 54**). Moreover, the lower yields observed for the transformation of more electron-poor substrates suggest the formation of a π-allyl palladium complex leading to the decomposition of the substrate. Literature precedent has demonstrated that aryl ethers are suitable leaving groups for this kind of transformation.[8,129]



Scheme 54: Proposed mechanism for the formation of phenolic by-product

2.3 Functionalisation of the *exo*cyclic alkene-benzofuran isomers

The relative stability of the *exo*-alkene compounds obtained during the direct arylation reaction offered the possibility to further extend the scope of the benzofurans and 2,3-dihydrobenzofurans obtained *via* alkene functionalisation. Several natural products possess a dihydrobenzofuran structure as well as a chiral center at the C2 and C3-positions and could be accessible *via* such a methodology (**Figure 6**).

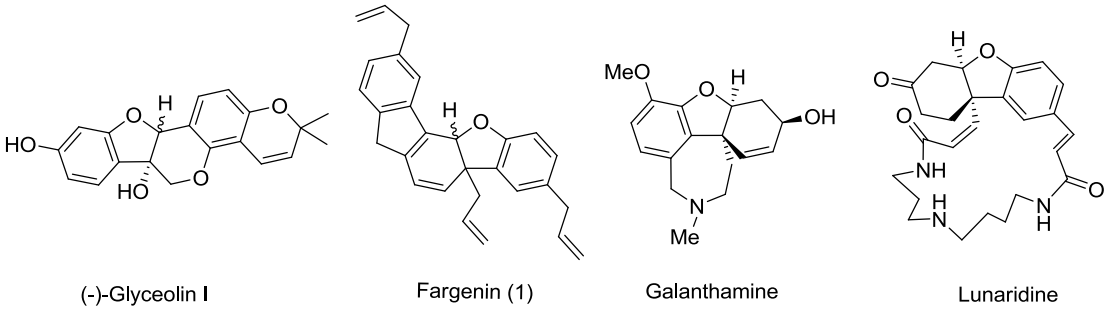
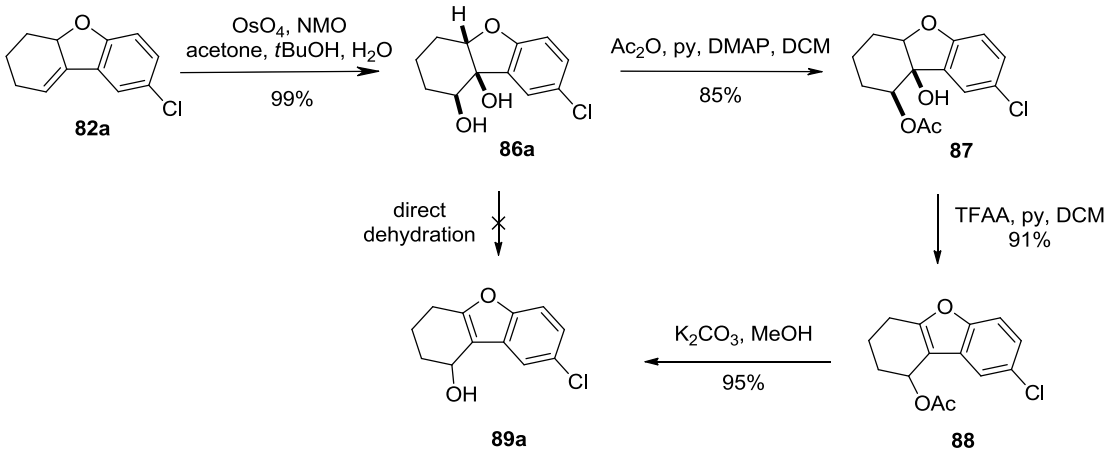


Figure 6: Selected natural compounds presenting a dihydrobenzofuran structure with chiral centres

2.3.1 Racemic functionalisation

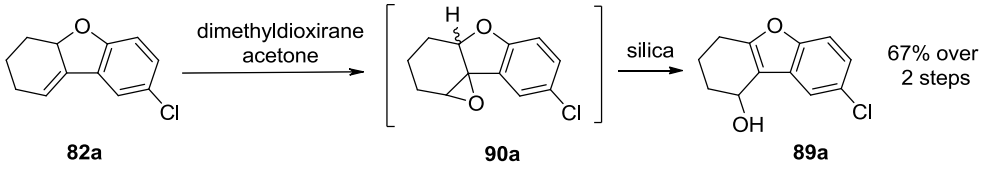
We first intended to explore the scope of possible functionalisation reactions applicable to our substrates. *Exo*-alkene **82a** had previously been obtained in good yield (88%) by the direct arylation and its stability towards isomerisation made it the model substrate of choice for our study.

Exo-alkene **82a** was first submitted to the Upjohn reaction[130] and afforded the desired dihydroxy compound **86a** in almost quantitative yield (**Scheme 55**). NMR spectroscopy studies showed the exclusive *cis* configuration of the molecule (**Appendix 3**). The subsequent direct formation of the corresponding hydroxyl substituted benzofuran **89a** by direct dehydration proved difficult, but protection of the secondary alcohol *via* acetate formation followed by treatment with trifluoroacetic anhydride afforded acetate **88** in a good overall yield. Deprotection of the acetate yielded the desired alcohol **89a** in an excellent 73% yield over four steps.



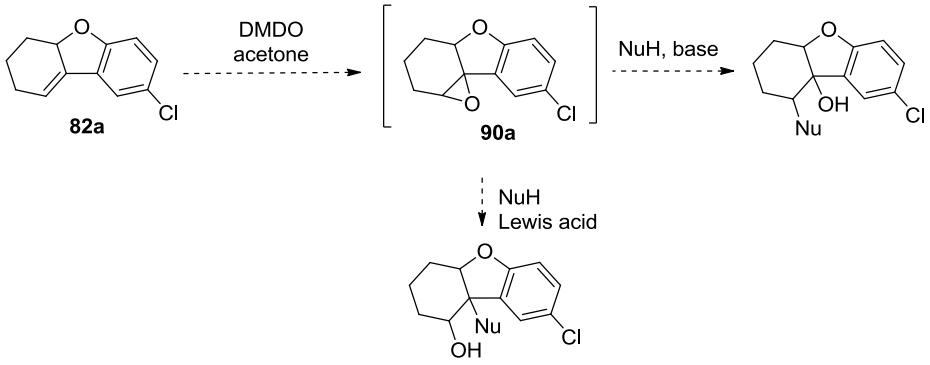
Scheme 55: Synthesis of hydroxybenzofuran **89a** *via* dihydroxylation

Alternatively, epoxidation of *exo*-alkene **82a** with dimethyldioxirane (DMDO) generated epoxide **90a**, which, when treated with silica gel, delivered the corresponding hydroxyl substituted benzofuran **89a** in good yield over 2 steps (67%, **Scheme 56**). Addition of molecular sieves during the first step of the reaction allowed us to isolate the epoxide **90a** in high purity after removal of the solvent. In the absence of molecular sieves, the epoxide contained about 10% of final alcohol **89a**. It is noteworthy that treatment of substrate **82a** with *m*CPBA left the alkene untouched.



Scheme 56: One-pot synthesis of hydroxyl substituted benzofuran **89a** *via* epoxidation

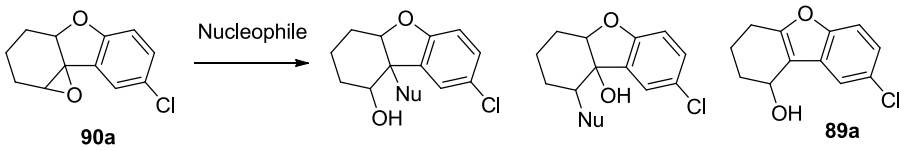
The facile opening of epoxide **90a** to yield alcohol **89a** prompted us to study its opening with different nucleophiles (**Scheme 57**). The epoxide can be opened at either carbon and we envisaged taking advantage of this fact. The secondary alcohol could be obtained under acidic conditions, as the nucleophile attacks the carbon that will form the most stable carbocation, whereas the tertiary alcohol could be formed under basic conditions as the nucleophile attacks the least substituted carbon, *via* a S_N2 mechanism.

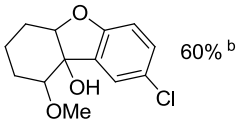


Scheme 57: Opening of epoxide **90a** with nucleophiles under different conditions

In every case the epoxidation was carried out as previously reported, i. e, in acetone and in the presence of molecular sieves. After completion of the reaction, acetone was removed *in vacuo* and the formation of the epoxide was confirmed by ^{1}H NMR spectroscopy. The crude reaction mixture was then submitted to the reaction conditions described below (**Table 10**).

Table 10: Study of the opening of epoxide **91a** using a variety of nucleophiles

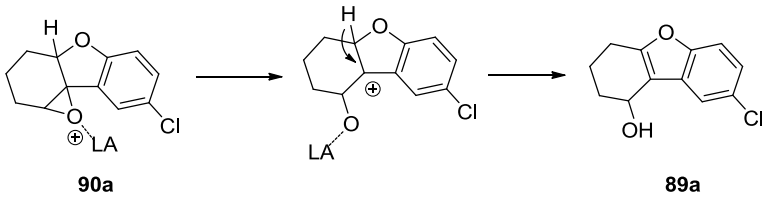


Entry	Nucleophile	Conditions [a]	Result
1	MeONa (2.0 equiv)	60 °C, MeOH, 20 hrs	 60% [b] **91**
2	MeMgBr (3.0 equiv)	DCM, 40 °C, 17 hrs	0% [c]
3	MeMgBr (3.0 equiv)	CuI (10 mol%), DCM, 40 °C, 17 hrs	Alcohol **89a** [d]
4	MeMgBr (3.0 equiv)	BF_3.THF (10 mol%), DCM, 40 °C, 17 hrs	Alcohol **89a** [d]

5	Allylmagnesium bromide (5.0 equiv)	0 °C to 50 °C, THF, 17 hrs	0% [c]
6	Allylmagnesium bromide (5.0 equiv)	$FeCl_2.4H_2O$ (1 equiv), THF, -78 °C to rt, 17 hrs	Alcohol **89a** [d]
7	Morpholine (5.0 equiv)	Cs_2CO_3 (5 equiv), THF, rt to 70 °C	0% [c]
8	4-Methoxythiophenol (3.0 equiv)	DCM, rt to 40 °C	0% [c]
9	Indole (3.0 equiv)	$InBr_3$ (10 mol%), DCM, rt, 24 hrs	Alcohol **89a** [d]
10	KCN (3.0 equiv)	THF, 0 °C to 70 °C, 17 hrs	0% [c]
11	KCN (3.0 equiv)	$LiClO_4$ (1 equiv), THF, 0 °C to 70 °C, 17 hrs	Alcohol **89a** [d]
12	TMSCN (3.0 equiv)	$LiClO_4$ (1 equiv), THF, 0 °C to 70 °C, 17 hrs	0% [e]
13	Water (solvent)	$KHCO_3$, rt, 15 min	0% [c]

a. Molecular sieves present in the reaction; b. Isolated yield; c. Recovered starting material; d. Detected by crude ^{1}H NMR spectroscopy analysis; e. Complex mixture.

Except in the case of where the reaction was performed with a large excess of nucleophile (**Table 10**, **Entry 1**), we were unable to react epoxide **90a** with any type of nucleophile, whether carbon, nitrogen, oxygen or sulfur-based (**Entries 2-11**). The epoxide was unreactive towards S_N2 reaction conditions (**Entries 7-10 and 12**) but under acidic conditions it is likely that the elimination of the tertiary proton was fast and led exclusively to alcohol **89a** (**Scheme 58**).

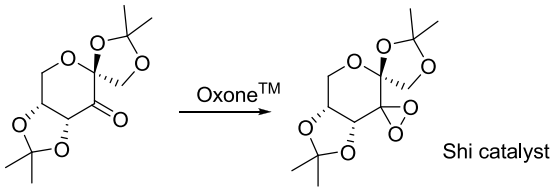


Scheme 58: Possible mechanism for the formation of alcohol **89a**

2.3.2 Enantioselective functionalisation of the racemic substrate

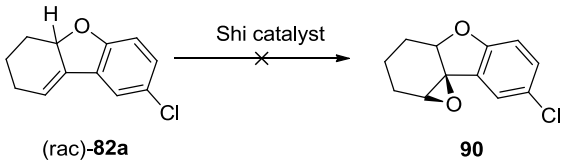
2.3.2.1 Enantioselective epoxidation

As the epoxidation of *exo*cyclic intermediate **82a** using a solution of DMDO in acetone had previously been successful, asymmetric versions of this reaction were considered. Due to the use of the racemic *exo*-alkene **82a**, we expected a kinetic resolution to take place, favouring the reaction of one enantiomer of the alkene over the other. A single enantiomer of epoxide **90** should therefore be obtained with a maximum yield of 50%. The Shi epoxidation first attracted our attention for its similarity to our previous method. The oxidising agent, a chiral dioxirane derivated from fructose, is formed *in situ* by the oxidation of the Shi catalyst with Oxone™ (**Scheme 59**).[131]



Scheme 59: *In situ* generation of the Shi catalyst

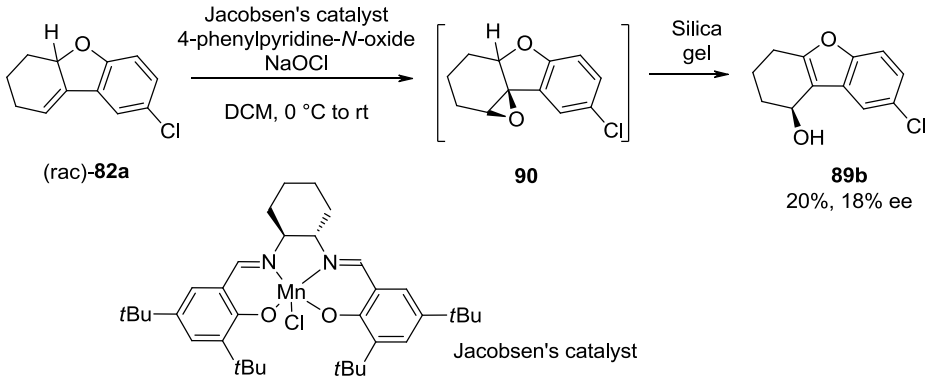
This methodology, which had been reported to proceed very efficiently in the case of trisubstituted alkenes,[132] was unsuccessful in our case. The starting material **82a** was recovered untouched even after 12 hrs at 0 °C and 24 hrs at room temperature (**Scheme 60**).



(rac)-**82a** **90**

Scheme 60: Attempts of resolution of *exo*-alkene **82a** with an asymmetric Shi epoxidation

An alternative method to the Shi epoxidation is the Jacobsen epoxidation; probably the most used asymmetric epoxidation. As for the Shi epoxidation, it was also reported as working efficiently on trisubstituted alkenes.[133] At 0 °C, traces of both the expected epoxide **90** and its by-product, alcohol **89**, were observed, although in small quantities. Allowing the reaction to warm up to room temperature overnight slightly enhanced the conversion to 20% but remained far from the expected 50% yield. Unreacted starting material was recovered from the reaction mixture (**Scheme 61**). The measured enantiomeric excess (ee) of alcohol **89b** was low (18%), probably due to the higher temperature required to perform this reaction compared to the literature.[133]

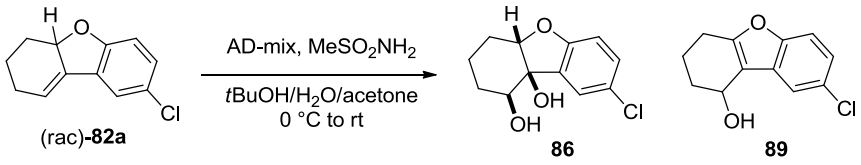


(rac)-**82a** **90** **89b**
20%, 18% ee

Scheme 61: Attempted resolution of *exo*-alkene **82a** with an asymmetric Jacobsen epoxidation

2.3.2.2 Enantioselective dihydroxylation

Asymmetric dihydroxylation of substrate **82a** was also investigated (**Scheme 62**). The widely used Sharpless dihydroxylation was chosen as both a reliable and practical method to perform this oxidation.[134] The availability of AD-mix α and AD-mix β allows an easy set-up of the reaction. Alternatively, a dihydroxylation mixture could be prepared *in situ*. As with the attempted asymmetric epoxidation, we expected a kinetic resolution to take place, favouring the reaction of one enantiomer of the alkene over the other. A single enantiomer of diol **86** should therefore be obtained with a maximum yield of 50%.

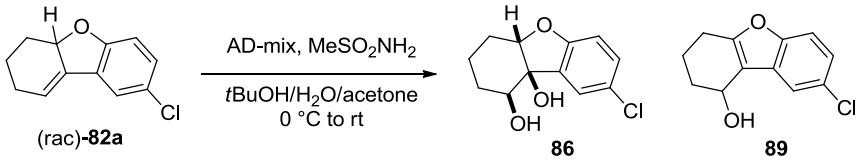


Scheme 62: Resolution of *exo*-alkene **82a** with an asymmetric Sharpless dihydroxylation

In contrast to the racemic dihydroxylation where only traces of alcohol **89** were observed, both diol **86** and alcohol **89** were formed during the Sharpless dihydroxylation. Monitoring these reactions by LC/MS analysis showed that their relative proportions were almost constant during the entire reaction. Although it is probable that the alcohol results from the dehydration of the diol **86**, other formation pathways remain possible. Similarly to our racemic dihydroxylation, only one diastereoisomer of the diol was observed and NMR spectroscopy studies confirmed its *cis* relative configuration (**Appendix 3**).

As the dihydroxylation reactions proceeded poorly at 0 °C, the reaction temperature was raised to room temperature, resulting in poor enantioselectivity for both the diol **86** and the alcohol **89** (**Table 11**).

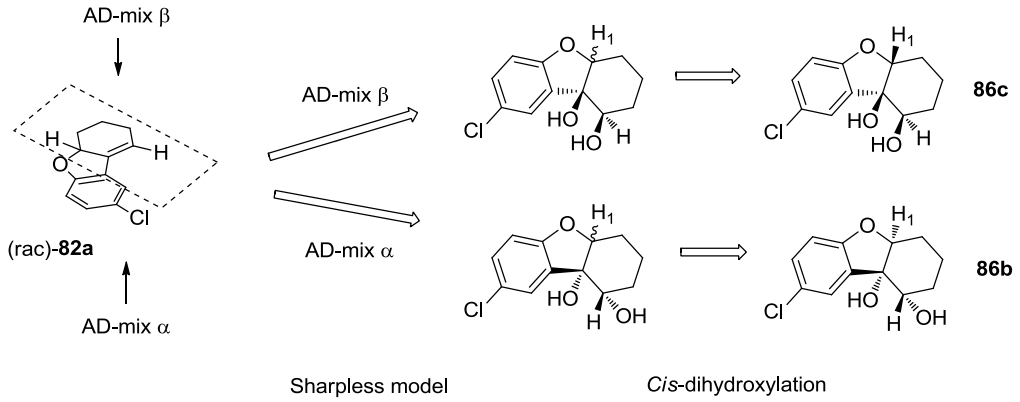
Table 11: Attempted enantioselective dihydroxylation of racemic alkene **82a** [a]



Entry	Reaction conditions	Diol 86 (yield, ee)	Alcohol 89 (yield, ee)
1	AD-mix α	21%, -31% ee	35%, -17% ee
2	AD-mix β	29%, +26% ee	7%, +7% ee
3	In situ AD-mix α	43%, -12% ee	7%, -21% ee

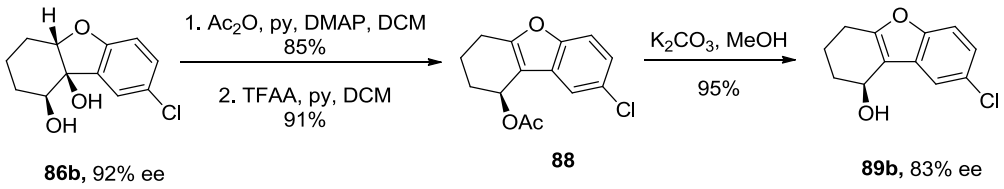
a. Reaction conditions: Alkene **82a** (1.0 equiv), methanesulfonamide (1.0 equiv), AD-mix in *t*BuOH and water at 0 ºC for 8 hrs and at rt for 17 hrs.

The dihydroxylation of *exo*-alkene **82a** afforded the same major enantiomer of both diol **86** and alcohol **89**. We also noted that opposite enantiomers were obtained when using AD-mix α or AD-mix β, revealing a certain level of catalyst control of the reaction. **Scheme 63** shows the predicted enantiomers obtained according to Sharpless model and taking into account the observed *cis*-dihydroxylation relative to proton H_1. In the absence of X-ray crystallography data for these compounds, however, it was not possible at that stage to confirm the validity of this model.



Scheme 63: Prediction of the product of the dihydroxylation taking into account both the Sharpless model and our observations of a *cis*-dihydroxylation

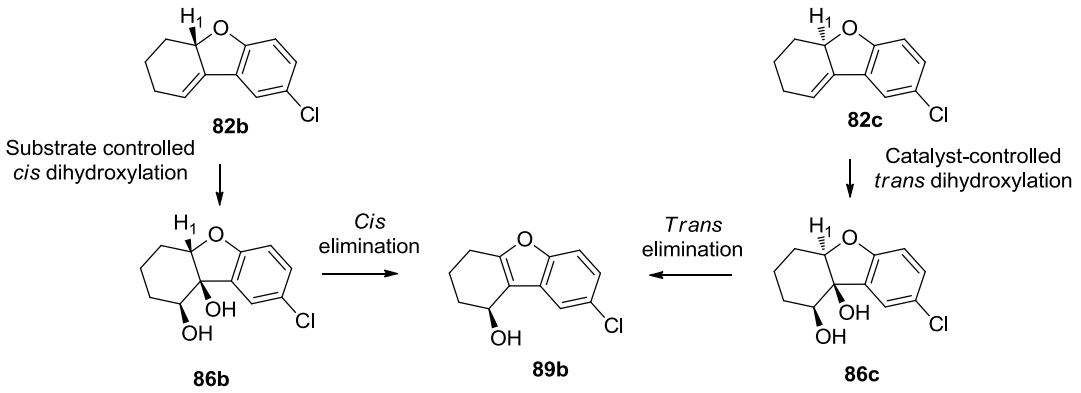
We then proceeded to identify the origin of undesired alcohol **89**. As we were not able to obtain direct data about the configuration of the diol by X-ray crystallography, we determined the relation existing between diol **86b** and alcohol **89b**. Enantiopure diol **86b** (see **2.3.3.2**) was converted into alcohol **89b** in three steps (**Scheme 64**). Acetylation of the secondary alcohol was followed by a *cis*-elimination of the tertiary alcohol in trifluoroacetic acid and pyridine. The alcohol was recovered after deprotection of the ester and we were able to confirm by chiral HPLC analysis that the alcohol formed during the dihydroxylation reaction and the one proceeding from the transformation of the diol were indeed the same enantiomer.



Scheme 64: Synthesis of alcohol **89b** from diol **86b**

Alcohol **89b** can therefore originate either from a *cis*-elimination of diol **86b** or from a *trans*-elimination of diol **86c**, the product of the catalyst-controlled dihydroxylation occurring on the opposite face to

proton H_1 (**Scheme 65**). Submitting diol **86b** to the dihydroxylation conditions did not result in degradation of the diol or in any loss of enantioselectivity, reducing the possibility of the formation of alcohol **89b** by *cis*-elimination.



Scheme 65: Proposed mechanisms for the formation of alcohol **89b**

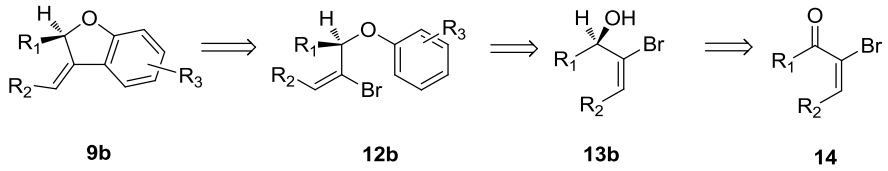
2.3.3 Functionalisation of chiral substrates

The poor results obtained for the asymmetric functionalisation of racemic substrates prompted us to study in more detail the functionalisation of the chiral material, in particular by performing matched and mismatched experiments to understand the levels of catalyst and substrate control for this reaction. The synthesis of the chiral diol **86b** originating from known chiral substrates would also allow us to confirm the validity of Sharpless model for the dihydroxylation of trisubstituted alkenes in the case of substrate **82a** (**Scheme 63**).

2.3.3.1 Asymmetric synthesis of *exo*-alkene 9b

In order to access enantiopure dihydrobenzofurans **9b** using our methodology, we first needed to obtain the corresponding alkenyl bromide **12b** in enantiopure form. The retrosynthetic analysis (**Scheme 66**) relies on the preservation of the chiral centre in the *exo*-alkene **9b** during the palladium-catalysed C-C bond formation step. The substrate **12b**, the product of the coupling between an

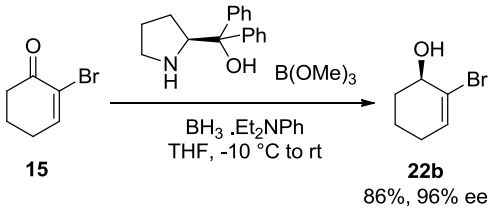
aromatic compound and chiral alcohol **13b**, could be obtained with high enantioselectivity by a variety of methods, including electrophilic aromatic substitution and Mitsunobu coupling. The alcohol itself originated from a CBS reduction of the corresponding α-bromo enone **14**.[135]



Scheme 66: Retrosynthesis of enantiopure dihydrobenzofuran **9b** from easily accessible chiral alcohol **13b**

2.3.3.1.1 Synthesis of chiral α-bromo alcohol 22b

Chiral α-bromo alcohol **22b** was obtained with an excellent yield and enantioselectivity *via* CBS reduction of the corresponding α-bromo enone **15** using a modified CBS catalyst prepared *in situ* (**Scheme 67**) and obtained in excellent yield and ee (**Appendix 4**).[135]



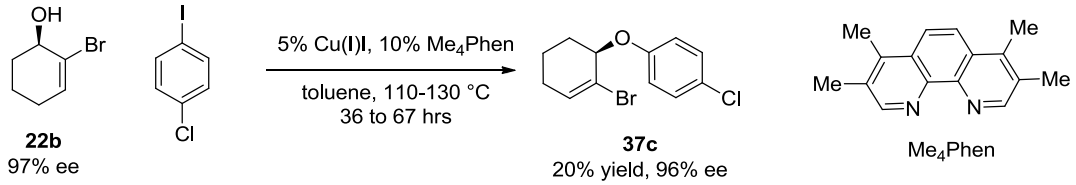
Scheme 67: CBS reduction of α-bromo enone **15**

2.3.3.1.2 Synthesis of chiral ether 37b

We have previously demonstrated that in our general reaction conditions (**1.2.2**), the formation of the mesylate of the alcohol **22** followed by its displacement by the desired phenolic compound does not

proceed *via* a pure S_N2 mechanism but rather by a mixture of different mechanisms (S_N, S_N'). In order to preserve the initial enantiopurity of our alcohol, different methods were tested.

We first attempted to prepare chiral ether **37c** using copper-catalysed couplings described by Buchwald *et al* using a Cu(I)I source and electron-rich tetramethylphenanthroline as the ligand (**Scheme 68**).[136]



Scheme 68: Buchwald copper-catalysed C-O bond formation

Different temperatures and reaction times were tested (**Table 12**) and we obtained the desired product without any loss of enantiopurity but in insufficient yields.

Table 12: Attempts of Buchwald copper-catalysed C-O bond formation [a]

Entry	Temperature (°C)	Time (hrs)	Yield [b]
1	110	36	20%, 96% ee
2	130 [c]	8	Product present among unidentified degradation products
3	130	67	

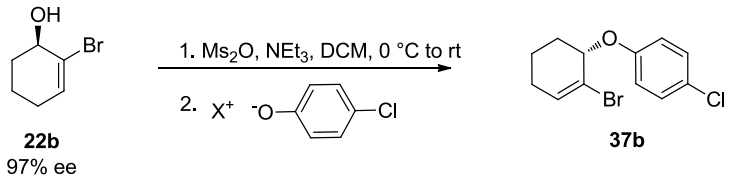
a. Reaction conditions: 4-Chloroiodobenzene (1.0 equiv), alcohol **22b** (97% ee, 1.5 equiv), Cu(I)I (5 mol%), Me_4-phenanthroline (10 mol%), toluene; b. Isolated yield; c. Microwave.

Our second attempt to obtain the alkenyl bromide with good enantioselectivity consisted of repeating our previously developed reaction; synthesising the mesylate of alcohol **22b** before displacing it with

deprotonated 4-chlorophenol In order to preserve the high enantiopurity of our material we had to avoid S_N1 and S_N1' type mechanisms and favour S_N2 reaction conditions.

Several reaction conditions were tested (**Table 13**), mainly varying the nucleophilicity of the phenol and the polarity of the solvent. We decided not to use polar solvents which could stabilise carbocation intermediates formed by a S_N1 mechanism. By varying the counter cation of the phenoxide, we modulated the softness of the oxygen nucleophile to favour S_N substitution over S_N'. Using DCM as an apolar solvent and the nucleophilic sodium alkoxide, we were able to reduce the loss of enantiopurity but we could not obtain the desired product **37b** with a synthetically useful enantiopurity under the tested conditions. We therefore investigated alternative syntheses which, although less atom economical, would afford the desired ether **37** with higher enantioselectivity.

Table 13: S_N2 conditions tested for the preservation of the high ee [a]



22b
97% ee

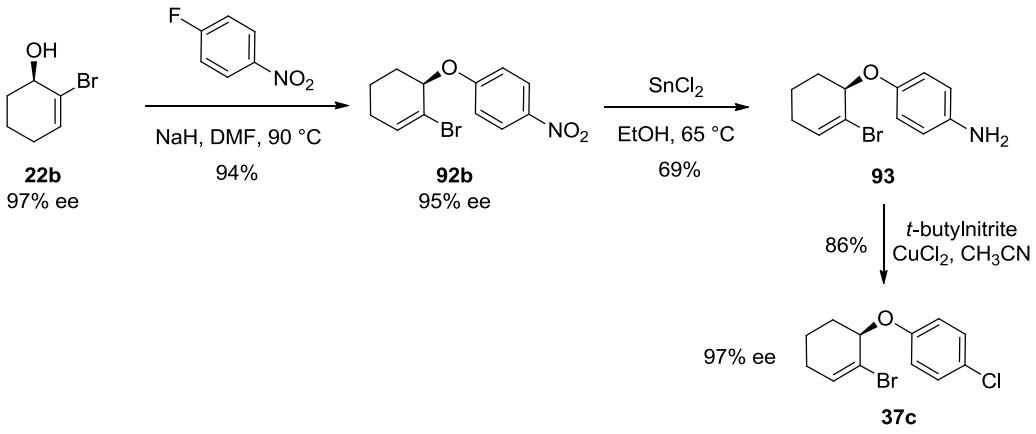
37b

Entry	Base	Solvent	Yield [b]	Retention of ee [c]
1	NaH	DCM	43%	81%
2	KH	DCM	43%	49%
3	*n*BuLi	DCE	0% [d]	/
4	KO*t*Bu	DCE	/	51%
5	LiHMDS	toluene	/	22%
6	NaHMDS	toluene	/	46%
7	KHMDS	toluene	45%	73%

a. Reaction conditions: 1) Ms_2O (1.2 equiv), α-bromo alcohol **22b** (1.0 equiv) and NEt_3 (1.2 equiv) in dry solvent (0.2 $mol.L^{-1}$), 0 °C to rt, 1hr; 2) 4-chlorophenol (3.0 equiv), base 2 (3.0 equiv) in dry DCM

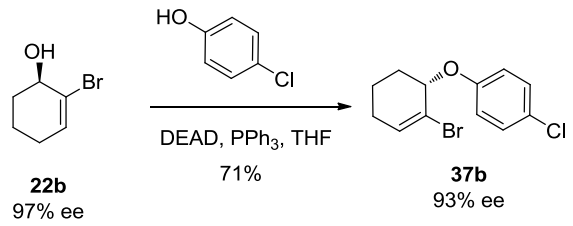
(0.2 mol.L^{-1}), 0 °C to rt, 17 hrs; b. Isolated yield; c. Retention of ee = ee of product/ee of substrate; d. Decomposition.

A reliable method to synthesise our model substrate was to use the chiral alcohol as a nucleophile on an electron poor arene such as 4-fluoro-nitrobenzene, which would then be converted to the desired chloride *via* a Sandmeyer reaction. Alkenyl bromide **37c** was synthesised following literature procedures. Displacement of electron poor *p*-fluoronitrobenzene by our chiral alcohol **22b** was followed by a reduction of the nitro group to the aniline **92**.[137] The chloride was finally installed with a modified Sandmeyer reaction.[138] The final compound **37c** was obtained with a good overall yield and excellent enantioselectivity (**Scheme 69**). Although high yielding and extremely selective, this sequence of reactions was too long and involved the presence of metallic species which are not desired in the development of an atom economical process. We therefore continued our search for a more efficient transformation.



Scheme 69: Alternative synthesis of alkenyl bromide **37c**

The other enantiomer of alkenyl bromide **37**, alkenyl bromide **37b** was then synthesised by a Mitsunobu reaction in a good yield and with little loss of ee (**Scheme 70**, **Appendix 5**). Performing the reaction at lower temperatures did not improve its selectivity. The Mitsunobu reaction requires the use of PPh_3 and DEAD, which is not ideal from the perspective of atom economy. However, the desired transformation could be achieved in a single step with good efficiency and was therefore used for the synthesis of ether **37b**.



22b
97% ee

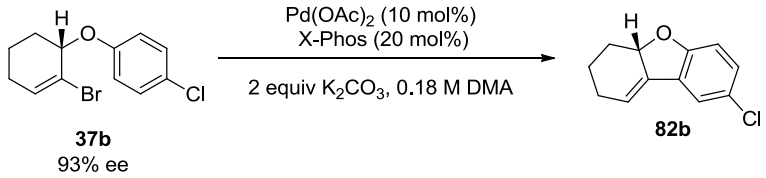
37b
93% ee

Scheme 70: Synthesis of alkenyl bromide **37b** *via* Mitsunobu reaction

2.3.3.1.3 C-C bond formation

The final step of the synthesis of *exo*-alkene **82b** was the key palladium-catalysed C-C bond formation (**Table 14**). When performed at 80 °C, a slight loss of ee was observed (**Entry 1**) but carrying out the reaction at a lower temperature allowed us to obtain the desired alkene **82b** with excellent enantioselectivity (**Entries 2-3**). At 40 °C however, the transformation did not proceed to completion (**Entry 4**). The reaction was therefore performed at 50 °C on half a gram scale without loss of yield or selectivity (**Appendix 6**), demonstrating the validity of our methodology for the synthesis of asymmetric dihydrobenzofurans.

Table 14: Effect of the temperature on the racemisation of the chiral center during the C-C bond formation [a]



37b
93% ee

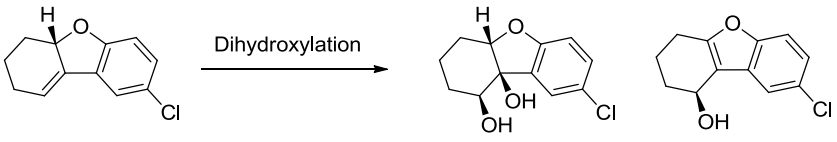
82b

Entry	Temperature (°C)	Yield	ee
1	80	88%	89%
2	70	88%	89%
3	50	88%	92%
4	40	20%	/

a. Reaction conditions: Alkenyl bromide **37b** (93% ee, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), ligand X-Phos (20 mol%), K_2CO_3 (2.0 equiv), DMA, 80 °C, 1.5 hr.

2.3.3.2 Functionalisation of chiral *exo*-alkene 82b

With chiral alkene **82b** in our hands, we were able to study its dihydroxylation and more specifically to observe a possible match and mismatch effect of the catalyst (**Scheme 71**).



82b **86b** **89b**

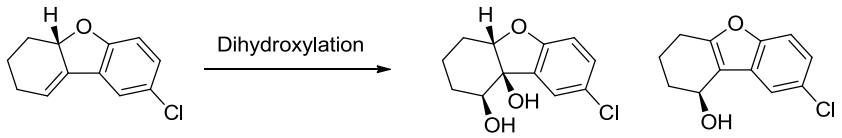
Scheme 71: Dihydroxylation of chiral *exo*-alkene **82b**

Pleasingly, when performing the Upjohn dihydroxylation, we obtained the desired diol **86b** in high yield and high ee (**Table 15**, **Entry 1**).

When the reaction was performed with an enantiomerically pure catalyst however, we observed a slight match/mismatch effect. Using matching catalyst AD-mix α gave the product **86b** in extremely high enantioselectivity (**Entry 2**, **Appendix 7**) while the use of mismatching AD-mix β resulted in a small decrease of the ee from 92 to 90% (**Entry 3**). In both cases however the same diastereoisomer of the diol **86** was obtained in moderate yield and alcohol **89b** was isolated from the reaction, albeit in poor yield and with a considerable loss of ee (**Appendix 8**).

In order to understand if the presence of the ligand was responsible for the formation of undesired alcohol **89b**, we preformed a racemic analog of the dihydroxylation catalyst called RD-mix where quinuclidine was used as a racemic ligand. Literature precedent has shown the utility of this method compared to Upjohn dihydroxylation.[139] The catalyst was prepared with Os(VI) instead of Os(VIII) in order to reduce the toxicity of this reagent. It has also been shown that the presence of the ligand in excess to the metal catalyst accelerates of the reaction. In our case, this method would give us an indication about the role of the ligand in the formation of alcohol **86**, although quinuclidine is a smaller molecule than the $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$, the most common ligands used for asymmetric dihydroxylation. Performing this reaction, we indeed observed the formation of diol **86b** in modest yield compared to the Upjohn dihydroxylation, although the ees were comparable (**Entry 4**). Alcohol **89b** was also detected in poor yield and with a dramatic loss of ee.

Table 15: Dihydroxylation of chiral alkene **37b**



82b **86b** **89b**

Entry	Reaction conditions	Diol 86b (yield, ee) [a]	Alcohol 89b (yield, ee) [a]
1	Upjohn dihydroxylation	95%, -92% ee	trace
2	AD-mix α	39%, >-99% ee	13%, -56% ee
3	AD-mix β	42%, -90% ee	10%, -74% ee
5	RD-mix	50%, -93% ee	4%, -64% ee

a. Isolated yields.

These results therefore confirm the possibility that the ligand has a determinant role in preventing the dihydroxylation from occurring. More generally, it seems that *exo*-alkene **37b** reacts well with small reagents, ie, OsO_4, but that its size limits its reactivity with more sterically demanding reagents such as AD-mix α and β. We also validated the Sharpless prediction model for the dihydroxylation of tri-substituted alkenes in the case of our substrate and confirmed the catalyst control of the dihydroxylation of our racemic alkene **86a** (**1.3.2.2**).

2.4 Conclusion

In summary, we have developed a new method for the synthesis of benzofurans *via an* atom efficient palladium-catalysed direct arylation. This reaction is performed under mild conditions and short reaction times. A one-pot isomerisation process delivers a wide range of benzofurans bearing electronically different aromatic substituents as well as cyclic and acyclic backbones. Moreover, the reaction has shown interesting regiocontrol.

This process also allows the use of simple and readily available starting materials which can be synthesised in an asymmetric fashion. Our new methodology can therefore deliver chiral dihydrobenzofurans.

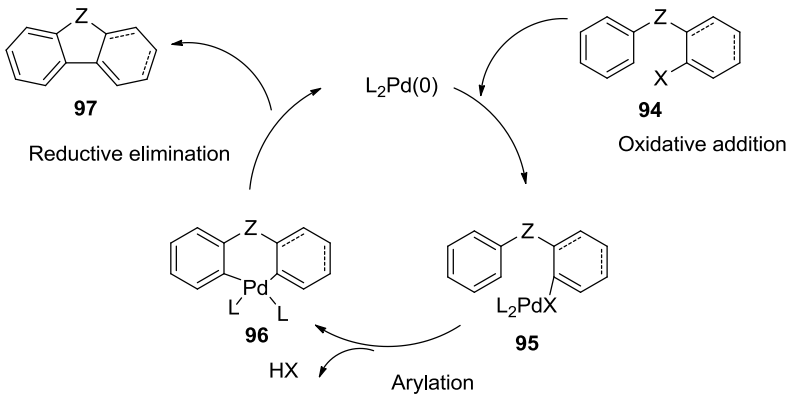
A new strategy has provided access to more complex benzofurans by functionalisation of the *exo*cyclic alkene isomer in both a chiral and achiral manner. Overall, this strategy can lead to new efficient routes to the synthesis of complex structures and natural products.

Chapter 3. Mechanistic and Kinetic Studies of the Formation of Benzo[*b*]furans

3.1 Introduction

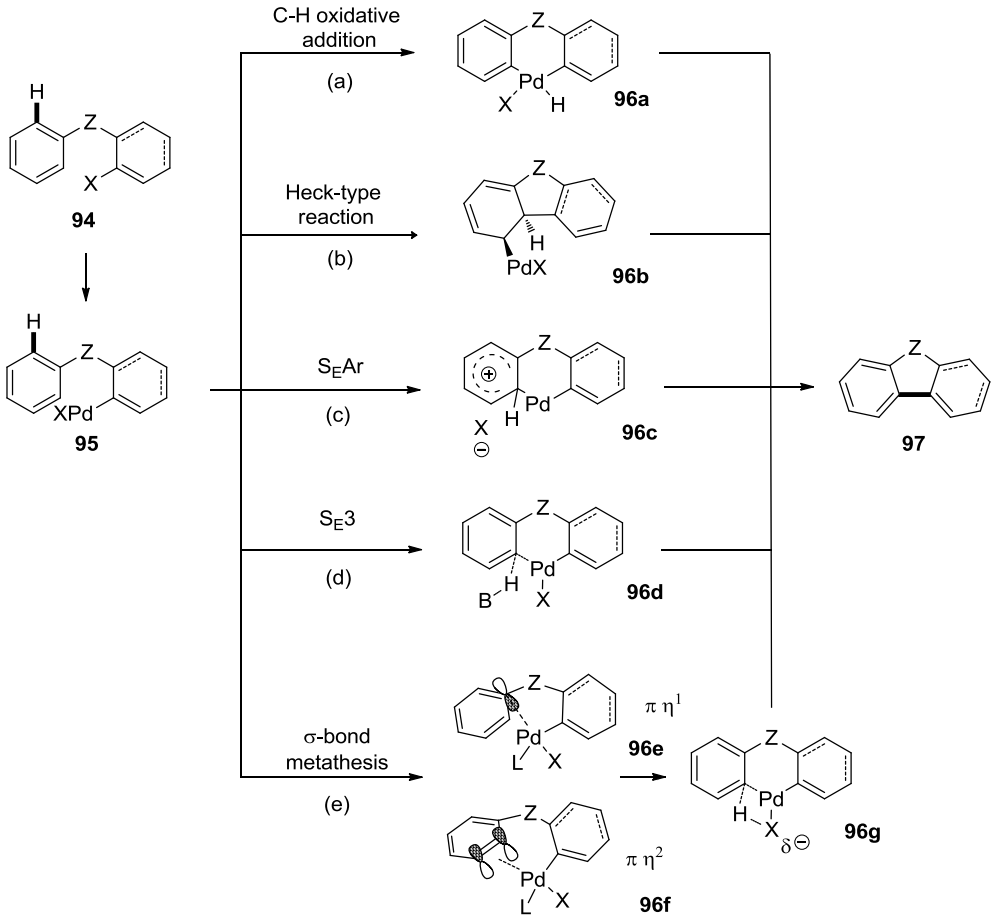
Having studied the synthesis and reactivity of benzofurans by direct arylation, we were interested in understanding the mechanistic aspects of the reaction, more especially the palladium-catalysed proton abstraction which leads to the formation of the C-C bond. While palladium-catalysed cross coupling reactions have been widely studied (**Chapter 1**), little is known about the C-H activation process. A brief overview of the most important results achieved in this area for the intramolecular formation of C-C bonds will provide interesting insights on our previously developed methodology.

It is widely accepted that the intramolecular arylation is initiated by an oxidative addition of the palladium(0) complex into the substrate **94** to form palladium(II) complex **95**. Direct arylation follows and the product **97** is finally released during the reductive elimination step (**Scheme 72**).



Scheme 72: General mechanism for direct arylation reactions

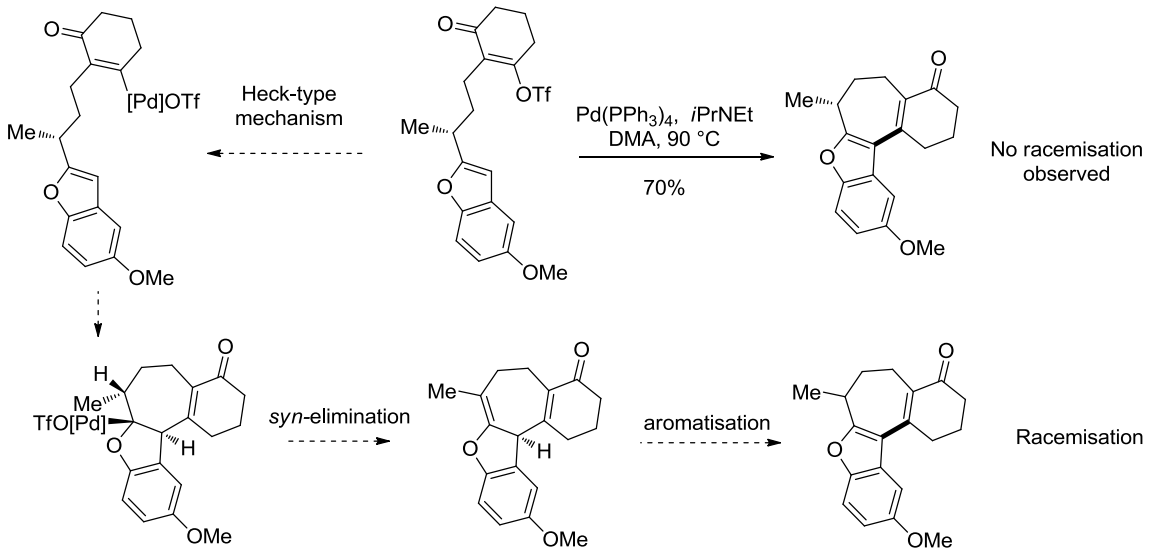
Reaction pathways are highly dependent on the substrate and the reaction conditions. It has even been suggested that different pathways could participate in a single transformation. However, five major mechanisms have been proposed to explain the proton abstraction that occurs during the direct arylation step (**Scheme 73**).[12,35,140]



Scheme 73: Proposed mechanisms for the aromatic proton abstraction process

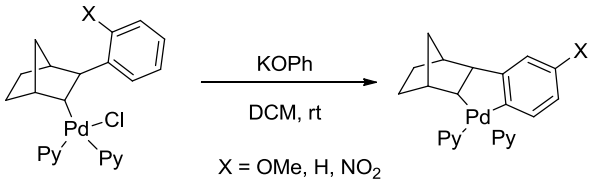
(a) Oxidative C-H insertion to palladium(II) complex **95** leading to a palladium(IV) complex **96a** has been proposed.[90,91,141] Catellani *et al.* have isolated alkyl and benzyl palladium(IV) complexes[90,91,142] but computational studies indicate that in many cases, the C-H insertion is higher in energy and therefore less favourable than alternative pathways.[143,144]

(b) A carbopalladation or Heck-type process which would regenerate the aromatic ring by syn β-hydride elimination has been proposed. Trauner *et al.* have observed that, when the substrate contained a stereocenter neighbouring the C-palladium(II) bond in intermediate **96b**, no racemisation occurred (**Scheme 74**).[99] A Heck-type process was therefore considered unlikely.



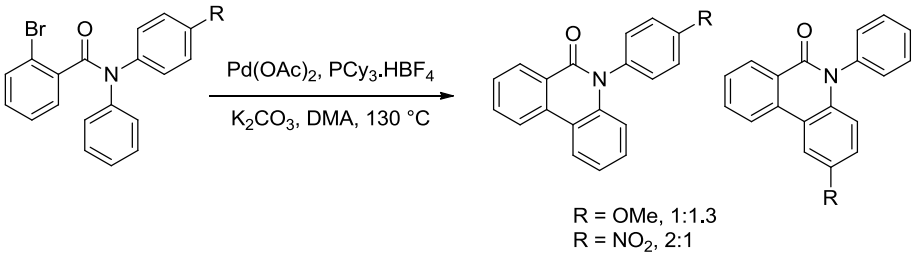
Scheme 74: The key cyclization in the synthesis of (*R*)-(-)-frondosin B is unlikely to proceed by a carbopalladation

(c) S_EAr is the most frequently proposed mechanism to rationalise direct arylation.[13,17] In support for this theory, Catellani *et al* have studied the substituent effects for the formation of palladacycles **96c**. After isolating the complexes **96c** with pyridine ligands, they showed that the rate of the reaction followed the expected rate MeO > H > NO_2 (**Scheme 75**).[90,145]



Scheme 75: Formation of stabilised palladacycles by Catellani and co-workers

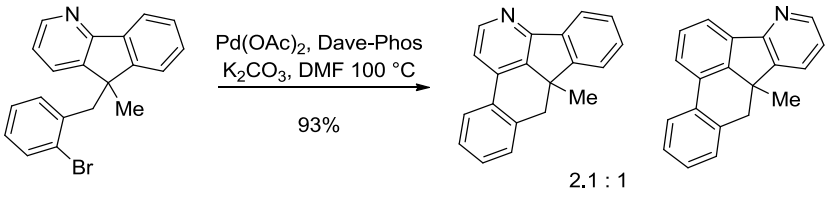
Additionally, competition studies have highlighted a significant electronic bias for the more electron-rich arenes (**Scheme 76**).[65] Moreover, in some cases, no isotope effect was observed which is consistent with S_EAr as the proton abstraction is not rate determining for the formation of the arenium complex.



Scheme 76: Competition study on intramolecular direct arylation performed by Fagnou *et al*

(d) Interestingly, an isotope effect has been detected for reactions where the substituent effects previously indicated a S_EAr mechanism.[11] These results were rationalised either by a C-H activation step *via* a S_E3 process where the base or another compound assists the reaction; or by an alternative σ-bond metathesis pathway. The term concerted metalation/deprotonation (CMD) is also used to describe such processes. The proposition of a S_E3 mechanism is supported by computational evidence suggesting that the participation of a carbonate or an acetate molecule could significantly lower the energy of the transition state.[143]

(e) However different studies have shown a reactivity that is clearly inconsistent with the hypothesis of an electrophilic substitution. For example, in the competition study performed by Echavarren *et al*., the palladium-catalysed reaction is facilitated by electron-withdrawing substituents on the aromatic ring (**Scheme 77**).[34,35] In addition, important isotopic effects (k_H/k_D = 6.7 at 100 °C) were found. These results tend to indicate a mechanism where palladium facilitates the abstraction of an acidic proton by a base as the key step and therefore do not point towards a S_EAr pathway. In these cases a σ-bond metathesis pathway has been proposed involving an initial agostic interaction forming either a π-η^1 complex **96e** or a π-η^2 complex **96f**.[65,146,147]

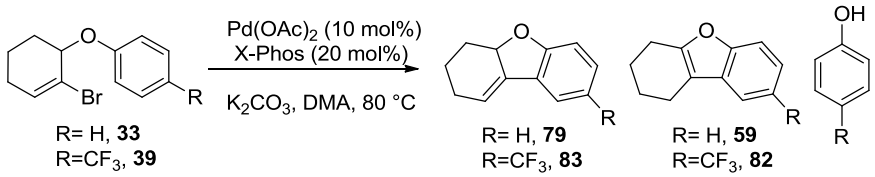


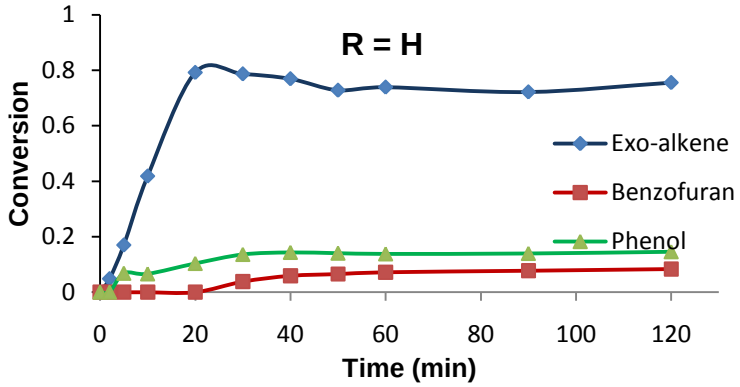
Scheme 77: Competition studies on direct arylation realised by Echavarren *et al*

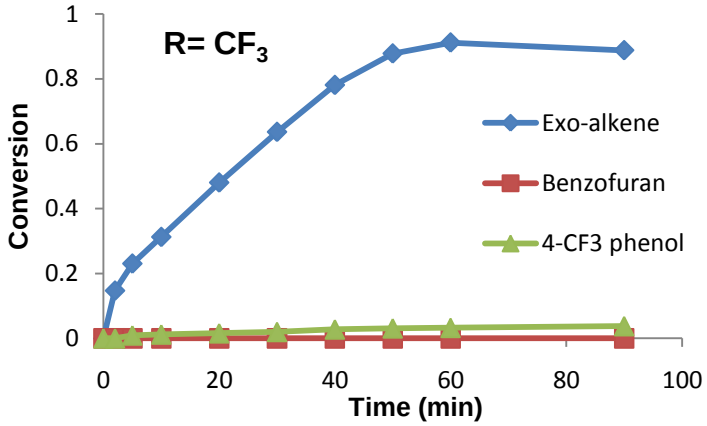
3.2 Results and discussion

3.2.1 Kinetic studies for the formation of benzofurans

During our study of the synthesis of benzo[*b*]furans by direct arylation, we monitored the reaction by HPLC analysis (**Scheme 78**). We observed not only the formation of expected *exo*-alkene followed by its palladium-catalysed isomerisation but also the appearance of the corresponding phenol as a side product at the beginning of the reaction and during the isomerisation step. The initial degradation of the alkenyl bromide can be explained by the formation of a η^3-palladium-complex releasing the phenol as a leaving group.[8,129] This reaction would then be reversible. Independently, we noticed that the isomerisation reaction is favoured for electron-rich substrates.

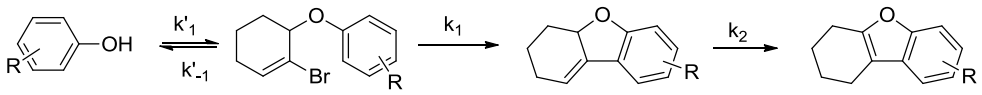






Scheme 78: HPLC monitoring of the arylation of alkenyl bromides **33** and **39**

According to these observations, we propose the following mechanism, summarised in **Scheme 79**.



Scheme 79: Proposition for the overall reaction mechanism

During the first stage of the reaction (t≈0) the direct arylation is predominant while the formation of the η^3 palladium-complex is negligible.

$k \approx k_1$; k'_1 and $k'_{-1} \approx 0$; $k_2 = 0$

During the second step of the reaction, the direct arylation is still the main reaction to take place but the formation of the η^3 palladium-complex is no longer negligible.

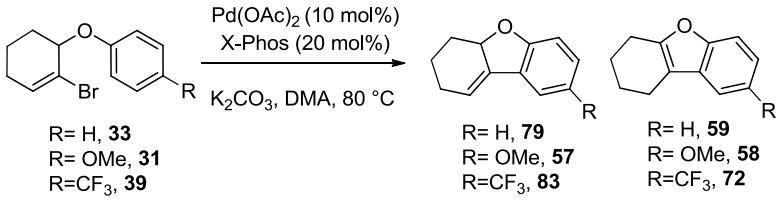
The last step occurs when the direct arylation is complete. The isomerisation of the *exo*-alkenic compound is then the main reaction to take place.

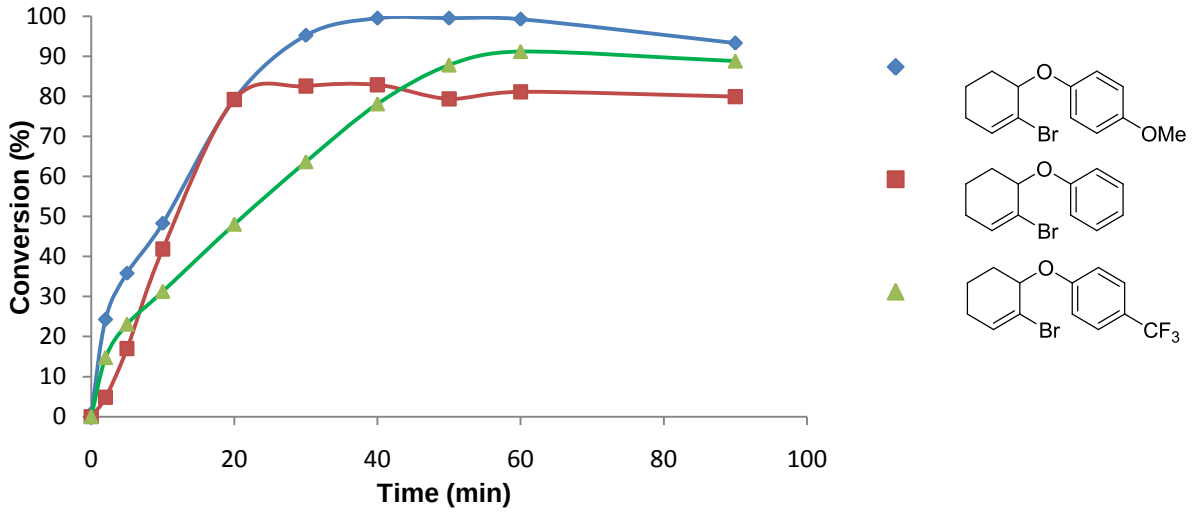
$k_1 = k'_1 = k'_{-1} = 0$

3.2.2 Investigations into the proton abstraction mechanism

3.2.2.1 Kinetic study

We next compared the rate of arylation of arenes with different electronic properties using HPLC analysis (**Scheme 80**). It was clear in the case of electron-rich substrates that the reaction happens faster and with better conversion. However, the rates of degradation and isomerisation of alkenyl bromide **31** also increased leading to similar final yields for all substrates.



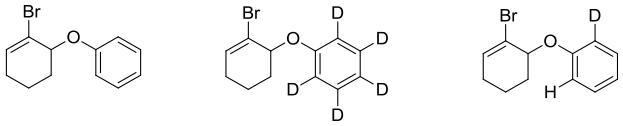


Scheme 80: Kinetic study for the direct arylation of alkenyl bromides

3.2.2.2 Isotope effect for the direct arylation of alkenyl bromide to generate benzofurans

The kinetic isotope effect (KIE) is a comparison between the reaction rates of two isotopic molecules. In our case, we first compared the reaction rates of *exo*-alkene ether **33** containing exclusively protons and *exo*-alkene **98** possessing a fully deuterated aromatic ring (**Figure 7**). In a second time, we synthesised ether **100** containing both an ortho C-H and a C-D bond in order to calculate the intramolecular kinetic isotope effect for this reaction.

Alkenyl bromide **98** was synthesised in one step by a Mitsunobu reaction between α-bromo alcohol **22a** and commercially available d6-phenol.



33 98 100

Figure 7: Subtrates for the comparison of the reaction rate of deuterated or protonated aryl ethers

$$KIE = \frac{k_H}{k_D}$$

Since four species are involved in the depicted route, it should theoretically be a fourth order reaction.

$$r = k\,[Palladium][Ligand][Base][sm]$$

Both the palladium and the ligand species are present as catalysts. Although their concentration may vary, in order to simplify the previous equation we will assume that it is constant during the active phase of the reaction. Similarly, as we are using an excess of base, we will assume its concentration remains constant during the reaction despite the low solubility of K_2CO_3 in DMA. We will therefore assume as a first rough approximation that the system is behaving as a pseudo-first order reaction. We can define a new reaction constant k', proportional to the actual constant k.

$$[Palladium] = R \text{ and } [Ligand] = R'$$

$$[Base] \gg [sm]$$

$$k' = k\,[Palladium][Ligand][Base]$$

$$r = k'[sm] = -\frac{d\,[sm]}{dt}$$

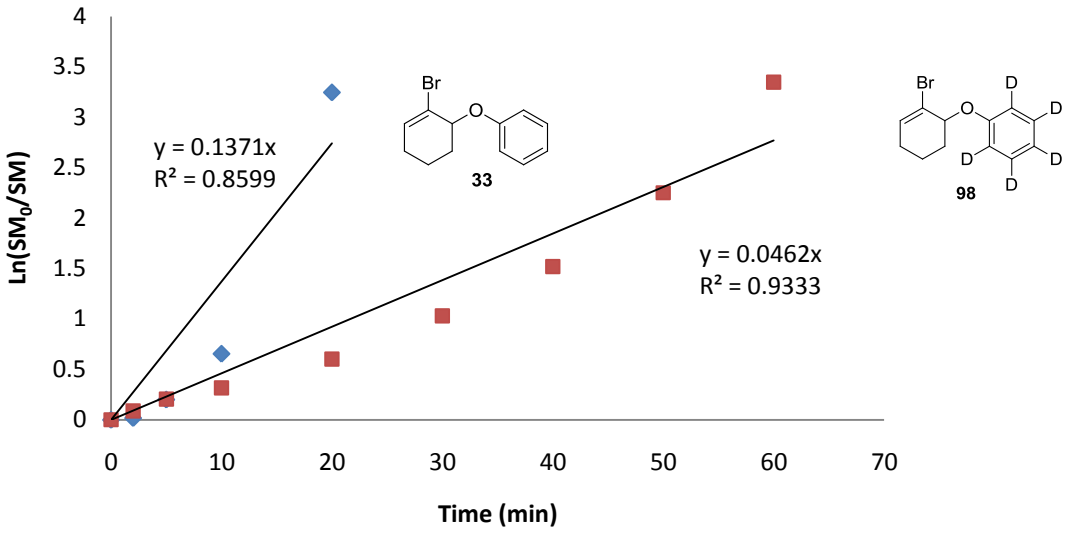
By integrating this equation, we obtain

$$Ln\left(\frac{[sm_0]}{[sm]}\right) = -k't \quad \textbf{Equation (1)}$$

As we have shown previously (**3.2.1**), this equation is true when only the direct arylation reaction takes place for t≈0.

Competition study between ether 33 and deuterated ether 98

We performed the reaction at 80 °C. Compound **33** was entirely consumed by the reaction after 30 min while deuterated ether **98** was consumed after 90 min. At this temperature, the reaction takes place quickly with side reactions occuring after 10 min. As noted before, the complexity of the transformation means that it cannot be considered as a true pseudo-first order reaction. This is confirmed by the mediocre correlation coefficients obtained. However, **Equation (1)** was verified for the first 70 mins of the reaction (**Scheme 81**) and an isotope effect k_H/k_D = 3.0 was calculated. This value is slightly smaller than expected for a truly primary isotope effect but still indicates that the dissociation of the C-H bond is part of the rate determining step.

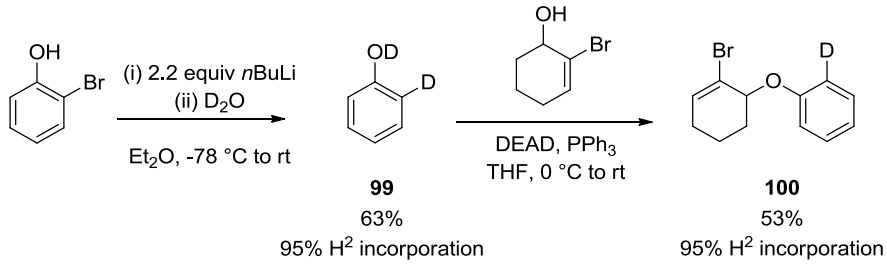


Scheme 81: Determination of the isotope effect by comparing the reaction rates of ethers **33** and **98**

Intramolecular isotope effect

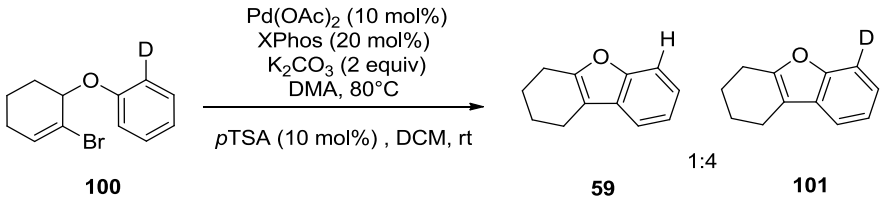
To determine the intramolecular isotope effect alkenyl bromide **100** was synthesised (**Scheme 82**). 2-Deuteriophenol **99** was obtained from 2-bromophenol by halogen-lithium exchange and subsequent quenching with D_2O. This transformation occurred in 63% yield with a satisfactory 95% deuterium incorporation determined by quantitative ^{13}C NMR spectroscopy (**Appendix 8**). Alkenyl bromide **100**

was then obtained by a Mitsunobu coupling reaction in 53% yield and the previously observed deuterium incorporation was retained (**Appendix 9**).



Scheme 82: Synthesis of the substrate for the intramolecular isotope effect study

Alkenyl bromide **100** was submitted to the optimised reaction conditions: $Pd(OAc)_2$ (10 mol%), X-Phos (20 mol%), K_2CO_3 (2.0 equiv), DMA (0.18 M), 80 °C (**Scheme 83**). After the cyclisation reaction the ratio of deuterated product **101** and non deuterated product **59** was 0.8:0.2 (determined by ^1H NMR spectroscopy, **Appendix 11**). Taking into account the 95% deuterium incorporation on the starting material, we obtain a intramolecular isotope effect k_H/k_D at 80 °C of 4.20, which indicates that the dissociation of the C-H bond is part of the rate determining step.



Scheme 83: Determination of the intramolecular isotope effect

3.3 Conclusion

Thanks to the kinetic studies performed on the benzofuran system, we have gained a better understanding of the direct arylation reaction we have developed. After highlighting the complexity of this transformation which involves not only a direct arylation step, but also isomerisation and degradation of both product and starting material, we have investigated the mechanism involved in the proton abstraction leading to the direct arylation. The analysis of substituent effects on the aromatic ring is in accordance with an electrophilic aromatic substitution mechanism (S_EAr); however, the presence of both intra and intermolecular kinetic isotope effects, while not disproving this hypothesis, suggest a S_E3 type pathway, for which the breaking of the C-H bond is part of the rate determining step, rather than a pure S_EAr.

Chapter 4. Synthesis of Isoquinolines: Intramolecular Palladium-Catalysed Direct Arylation of Alkenyl Bromides

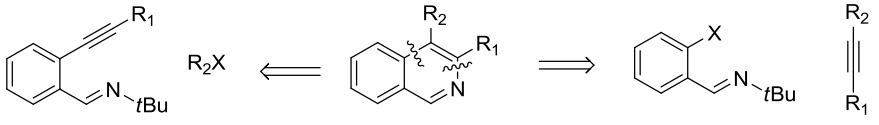
4.1 Introduction

Heterocycles have a prominent place in biologically active molecules and constitute the bulk of available drugs. During our investigation of the synthesis of heterocyclic motifs using a palladium-catalysed direct arylation, we became particularly interested in isoquinolines and cyclic sulfonamides.

4.1.1 Isoquinolines

Isoquinoline ring systems are found in numerous natural alkaloids that display a wide range of biological activities. Traditional approaches to assemble these rings depend heavily on Bischler-Napieralsky, Pictet-Spengler and Pomeranz-Fritsch reactions which all revolve around the condensation of various primary amines with carbonyl compounds.[36] They normally require harsh conditions which prevent the elaboration of more sensitive motifs.

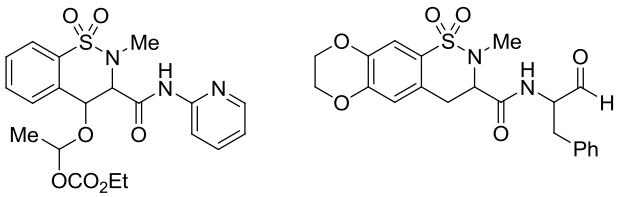
Alternative metal-catalysed methods have been developed over the years involving intra or intermolecular Heck reactions or annulations of alkynes. Larock and co-workers have developed several related palladium(0)-catalysed methodologies for the synthesis of 3,4-disubstituted isoquinolines by the annulations of external or internal alkynes using *t*Bu-imines (**Scheme 84**).[148,149]



Scheme 84: Routes for the synthesis of isoquinolines developed by Larock and co-workers

4.1.2 Sultams

Cyclic sulfonamides or sultams display important and diverse pharmacological activities such as antiviral, anticancer, antimicrobial, anti-inflammatory and antimalarial. Selected examples of such sulfonamides are presented in **Figure 8**.



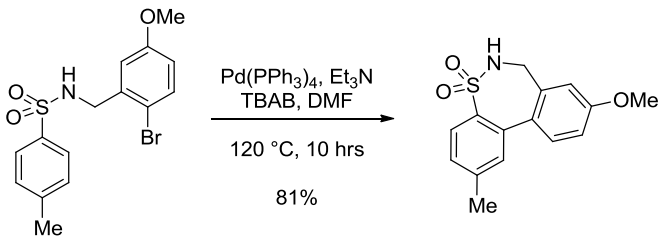
Anti inflammatory drug
Ampiroxicam

Calpain **I** inhibitor

Figure 8: Selected examples of sultams used in pharmaceutical industry

They have consequently been synthesised in a large variety of ways but only recently have palladium catalysis approaches been investigated including, intramolecular Heck cyclisations, intramolecular hydro-amination and direct arylation.[150] An interesting tandem benzyne/C-H activation was reported by Larock and co-workers where the sultam was formed through the cross coupling of *o*-iodoanilines or *o*-iodophenol with silylaryl triflates, an *in situ* source of aryne, followed by palladium-catalysed intramolecular cyclisation (**Chapter 1, Scheme 37**) .[97]

Although synthesis of sultams by direct arylation is known, it usually involves functionalisation of an arene or heteroarene.[151] Activation of the sulfonamide arene ring has only been reported recently by Majumdar and co-workers, leading to the formation of various sultam rings during arene-arene bond formation (**Scheme 85**).[152]



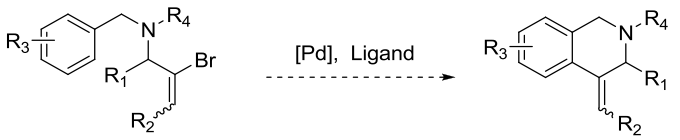
Scheme 85: Synthesis of sultams by direct arylation reported by Majumdar and co-workers

Encouraged by these results, we proposed to apply our novel direct arylation methodology towards the synthesis of isoquinolines and sultams.

4.2 Results and discussion

4.2.1 Preliminary results: synthesis of tetrahydroisoquinolines

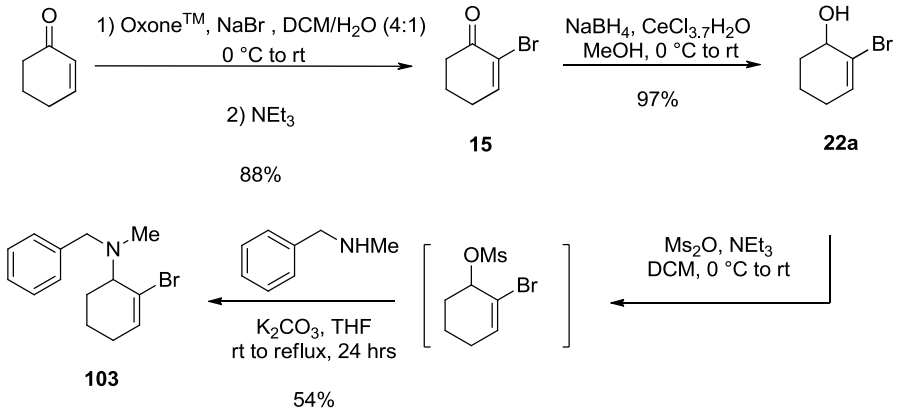
We first attempted to synthesise tetrahydroisoquinolines, a simpler substrate than isoquinoline, to demonstrate the possibility of forming a six-membered ring using our palladium-catalysed C-H activation methodology (**Scheme 86**).



Scheme 86: Planned synthesis of substituted piperidines *via* palladium-catalysed C-C bond formation

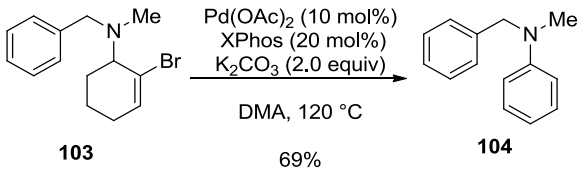
Alkenyl bromide **103** was chosen as a suitable substrate and prepared in a similar fashion to benzo[*b*]furans (**Chapter 2**). α-Bromo alcohol **22a** was synthesised in two steps from the commercially available corresponding enone. Bromination of the double bond followed by a base-induced elimination afforded the α-bromoenone **15** which was then converted to the α-bromo alcohol **22a** *via* a Luche reduction. Versatile α-bromo alcohol **22a** was then transformed using

methanesulfonic anhydride in presence of triethylamine; *N*-methylbenzylamine was then added directly without isolating the intermediate and amine **103** obtained in 54% yield (**Scheme 87**).



Scheme 87: Preparation of substrate **103**

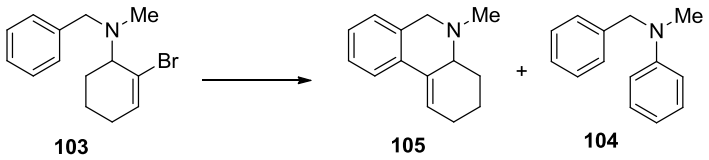
To our surprise, submitting amine **103** to the reaction conditions developed during the synthesis of benzo[*b*]furans did not allow the formation of the desired piperidine but lead exclusively to the formation of *N*-benzyl-*N*-methylaniline **104** in good yield (**Scheme 88**).



Scheme 88: Unsuccessful attempt of piperidine synthesis

We decided to screen different reaction conditions, varying the solvent and the base employed (**Table 16**). Unfortunately, we were not able to form the expected six-membered ring **105** but always obtained *N*-benzyl-*N*-methylaniline **104** along with unreacted starting material **103**.

Table 16: Conditions screening for the piperidine synthesis [a]



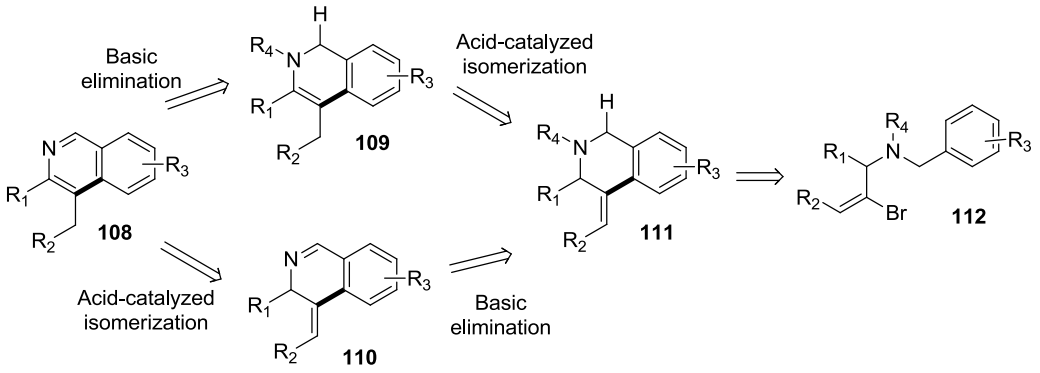
103 105 104

Entry	Conditions	*N*-benzyl-*N*-methylaniline 104
1	DMA / K_2CO_3	69% [b]
2	DME / K_2CO_3	0% [c]
3	Toluene / K_2CO_3	10% [d]
4	Acetonitrile / K_2CO_3	65% [d]
5	1,2-Dioxane / K_2CO_3	0% [c]
6	DME / CsOAc	0% [c]
7	DME / NaO*t*Bu	38% [d]

a. Conditions: Alkenyl bromide **103** (1.0 equiv), $Pd(OAc)_2$ (10 mol%), X-Phos (20 mol%), base (2.0 equiv), 0.2 M in selected solvent, 120 °C, 24 hrs; b. Isolated yield; c. Unreacted starting material **103**; d. ^{1}H NMR spectroscopy conversion.

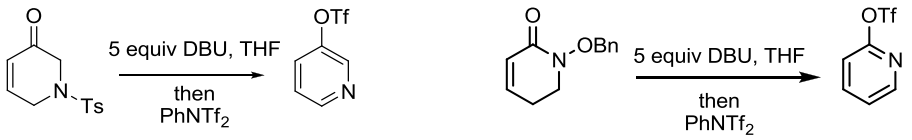
4.2.2 Strategy for the synthesis of isoquinolines

After our initial lack of success with the piperidine system, we decided to attempt the isoquinoline synthesis, hoping that varying the amine substituent R_4 and therefore the electronic properties of the substrate would modify its reactivity towards the catalyst. A retrosynthetic analysis (**Scheme 89)** showed that the desired isoquinoline **108** could derive from *exo*-alkene **111** after consecutive isomerisation of the *exo*-cyclic double bond and elimination of the benzylic proton. The *exo*-alkene **111** itself is synthesised by direct arylation of alkenyl bromide **112**. The interchange of the isomerisation and elimination steps allows a degree of flexibility in the synthesis.



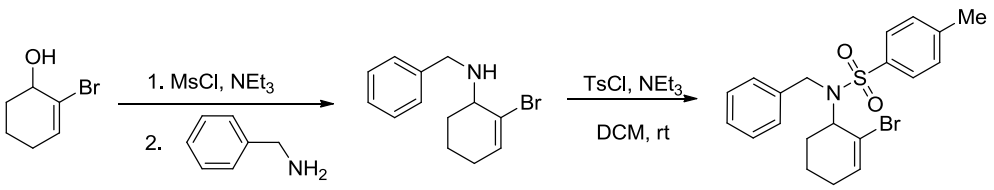
Scheme 89: Retrosynthetic analysis of the construction of an isoquinoline using this methodology

The elimination of the benzylic proton is key to this synthesis and relies on a careful choice of the R_4 group substituting the nitrogen. Pyridine motifs have been formed *via* elimination under basic condition[153,154] (**Scheme 90**) which lead us towards the synthesis of hydroxylamine and sulfonamide based starting materials. The ability to eliminate the benzylic proton under the basic conditions of the palladium-catalysed step and therefore generate the isoquinoline *in situ* was particularly attractive to us. As shown previously within the group in the case of the indole system, the isomerisation of the *exo*-cyclic double bond can occur during the palladium-catalysed step but our success with the acid-catalysed isomerisation (**Chapter 2**) offers the possibility to perform this reaction separately.



Scheme 90: Base-induced eliminations

Sulfonamide **114** was chosen as our model substrate due to the good availability of 4-toluenesulfonamides and the precedent of elimination of protons *ortho* to this motif (**Scheme 90**).[153,154] It was synthesised in two steps from α-bromo alcohol **22a**. Firstly, alcohol **22a** was transformed into secondary amine **113** by *in situ* mesylation followed by a displacement by benzylamine. The secondary amine **113** was then tosylated to afford the desired sulfonamide **114** in very good yield (**Scheme 91**). We then submitted this substrate to our reaction conditions.



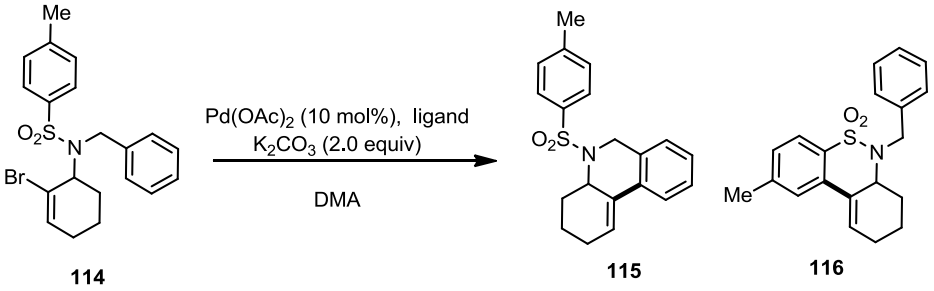
22a **113** 52% **114** 78%

Scheme 91: Synthesis of sulfonamide substrate **114**

4.2.3 Optimisation of the reaction

To our delight, the initial screening (**Table 17**) delivered the expected amine **115**, demonstrating that the formation of a non aromatic six-membered ring using our direct arylation methodology was indeed possible. Amine **115** was obtained as a mixture with unknown compound **116**, the structure of which was determined by X-ray crystallography analysis (**Appendix 12**). It was shown to be the cyclic sulfonamide **116** (sultam) resulting from the direct arylation of the tosyl aromatic ring. No other compound was isolated from the reaction. Although the use of Fu salt (**Entry 6**) led mainly to unreacted starting material **114**, every other condition examined afforded a mixture of these two sulfonamides in different ratios, but with no trace of tri-aromatic compound **104** being observed, as it was the case in the piperidine synthesis (**Entries 1-5** and **7-9**).

Table 17: Initial screening of conditions for the synthesis of cylic sulfonamides [a]



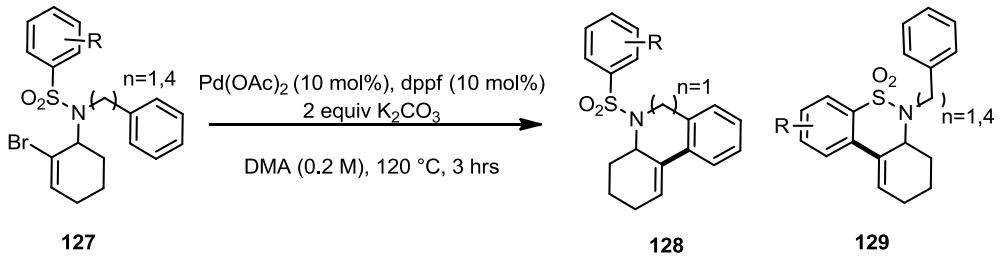
114 **115** **116**

Entry	Conditions	Starting material 114 ratio [b]	Compound 115 ratio [b]	Compound 116 ratio [b]
1	X-Phos	0.4	1.7	1.0
2	XantPhos	3.2	2.7	1.0
3	DavePhos	0.4	1.5	1.0
4	Dppf	/	2.5	1.0
5	Dppp	traces	1.9	1.0
6	$PMe(tBu)_2$-HBF_4	main	traces	traces
7	Dppf, 3 hrs	/	1.0 (57% [c])	1.0 (33% [c])
8	No ligand, 5 hrs	/	(46% [c])	(30% [c])
9	Dppf, 80 °C, 27 hrs	/	1.0	1.0

a Reaction conditions: Sulfonamide **114** (1.0 equiv), $Pd(OAc)_2$ (10 mol%), monophosphine ligand (20 mol%) or di-phosphine (10 mol%) ligand, K_2CO_3 (2.0 equiv), DMA (0.20 M), 24 hrs at 120 °C; b. Determined by ^1H NMR spectroscopy; c. Isolated yields.

4.2.4 Scope of the reaction

Following on from these promising initial results, different substrates were synthesised in order to evaluate the formation of both acyclic sulfonamide **128** and sultam **129** (**Scheme 92**)

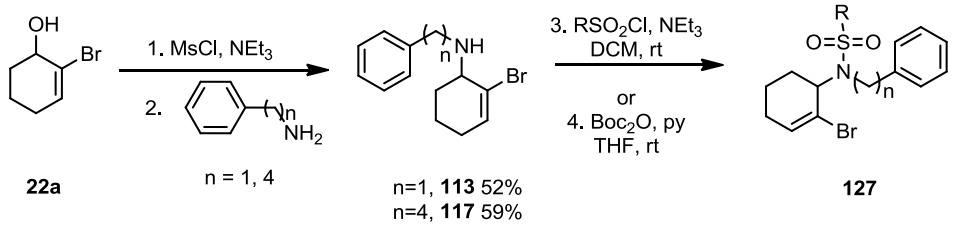


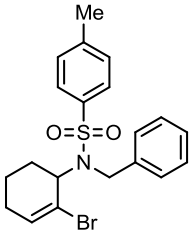
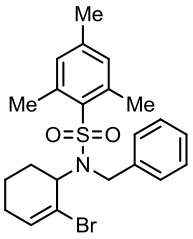
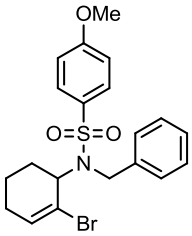
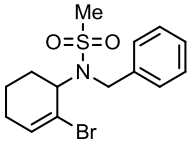
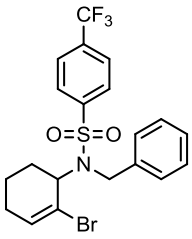
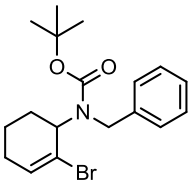
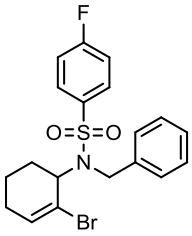
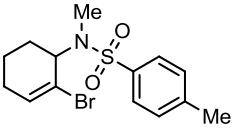
127 **128** **129**

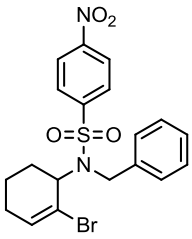
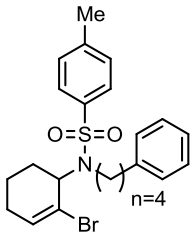
Scheme 92: Evaluation of the formation of acyclic sulfonamide **128** and sultam **129**

Firstly, we investigated the influence of the electronic properties of the sulfonamide on the relative ratio of acyclic and cyclic sulfonamides. We therefore prepared a family of differently substituted substrates (**Table 18**, **Entries 1-5**). Secondly, we synthesised a range of substrates that would allow a selective direct arylation either on the benzylic ring, therefore forming amine **128** (**Entries 6-8**), or on the aryl of the sulfonamide, producing this time sultam **129** (**Entries 9-10**). This selective arylation could be achieved by different means such as introducing a substituent on the sulfonamide arylation site (**Entry 6**), protecting the amine with non-aromatic groups (**Entries 7-9**) or finally disfavouring the formation of a nine-membered ring amine as opposed to a six-membered ring sultam (**Entry 10**).

Table 18: Synthesis of substrates for the scope investigation [a]



Entry	Product	Yield step 2	Entry	Product	Yield step 2
1	 **114**	78%	**6**	 **122**	96%
2	 **118**	46%	**7**	 **123**	39%
3	 **119**	>99%	**8**	 **124**	51% [b]
4	 **120**	99%	**9**	 **125**	16%

5	 **121**	59%	**10**	 **126**	75%

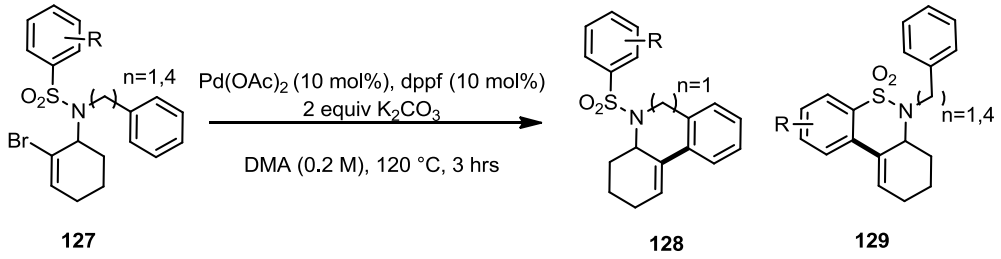
a. Conditions: 1. α-Bromo alcohol **22a** (1.0 equiv), MsCl (1.1 equiv), NEt_3 (1.2 equiv), DCM, 0 ^oC to rt, 1 hr; 2. H_2N-$(CH_2)_n$-Ph (3 equiv), DCM, rt, 20 hrs; 3. Amine (1.0 equiv), R-SO_2Cl (1.1 equiv), NEt_3 (2.0 equiv), DCM, 0 °C to rt, 20 hrs; b. 4. Amine (1.0 equiv), Boc_2O (3.0 equiv), pyridine (3.0 equiv), DMAP (10 mol%), THF, rt, 20 hrs;

With these substrates in hand, we evaluated the scope of the reaction (**Table 19**). To our surprise, we soon noticed that the substitution of the sulfonamide arene did not dramatically influence the ratio of cyclic amine and cyclic sulfonamide (**Entries 1-4**), except in the case of the nitro-substituted compound **121** which resulting sultam may not be stable under the reaction conditions (**Entry 5**). In every case the cyclic sufonamide **129** was obtained as the minor product in about (1:2) ratio to the cyclic amine **128**. The overall transformation, however, seems favoured by more electron-rich compounds.

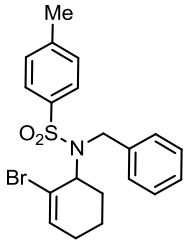
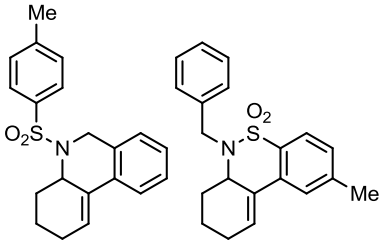
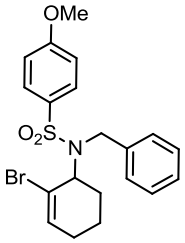
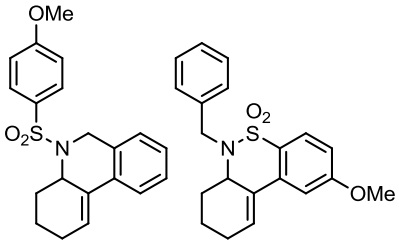
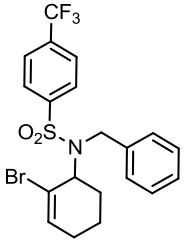
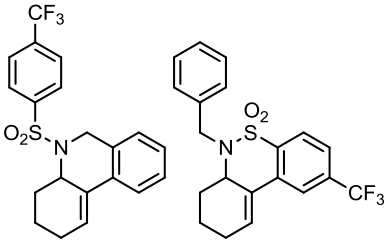
Prohibiting the formation of the cyclic sulfonamide with the use of an *ortho*-substituted mesitylene, we obtained the desired cyclic amine **137** in 76% yield (**Entry 6**). Employing the more commonly used methylsulfonamide, cyclic amine **138** was synthesised in 50% (**Entry 7**), probably due to its degradation under the reaction conditions. Attempting the selective formation of cyclic sulfonamide **139** however, we isolated it in a disappointing 5% yield along with unidentified compounds (**Entry 8).**

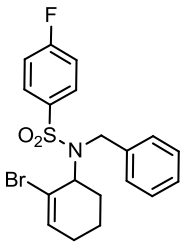
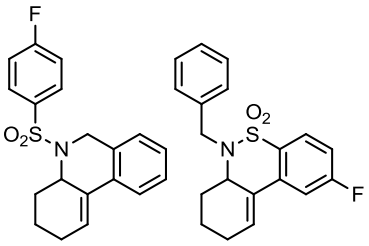
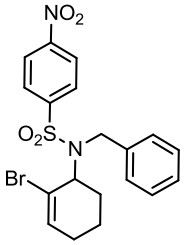
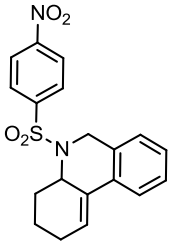
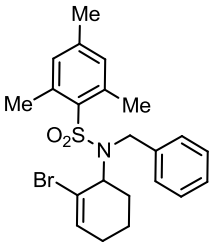
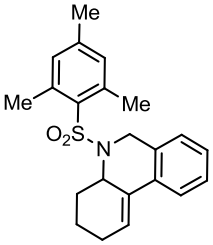
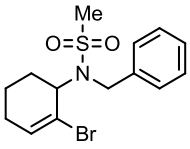
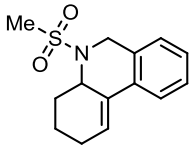
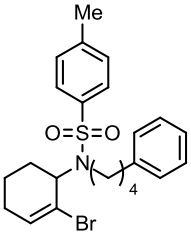
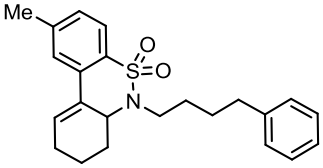
It is also noteworthy that no isoquinoline was detected in any of the tested reaction conditions. Instead of the intended one-pot formation of the final isoquinoline we decided to develop a step-wise synthesis of the isoquinoline.

Table 19: Scope of the reaction



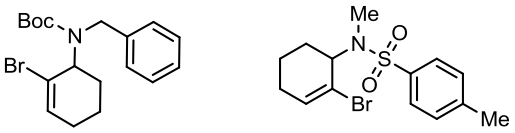
127 128 129

Entry	Substrate	Products	Isolated yield
1	 114	 115 116	90% (1.7 : 1)
2	 118	 130 131	61% (2 : 1)
3	 119	 132 133	42% (1.7 : 1)

4	 **120**	 **134** **135**	59% (2 : 1)
5	 **121**	 **136**	25%
6	 **122**	 **137**	76%
7	 **125**	 **138**	50%
8	 **126**	 **139**	5%

a. Reaction conditions: Sulfonamide **127** (1.0 equiv), $Pd(OAc)_2$ (10 mol%), dppf ligand (10 mol%), K_2CO_3 (2.0 equiv), DMA (0.20 M), 120 °C, 3 hrs.

We were disappointed to observe that some promising substrates gave no result under C-H activation conditions. Submitting the Boc-protected amine **124** to the reaction conditions led to partial degradation and although some potential product was observed by mass spectroscopy, no product could be isolated. Submitting sulfonamide **125** to the reaction conditions led exclusively to *N*,4-dimethylbenzenesulfonamid, the result of the ionisation of the substrate to form a π-allyl palladium(II) complex (**Figure 9**).

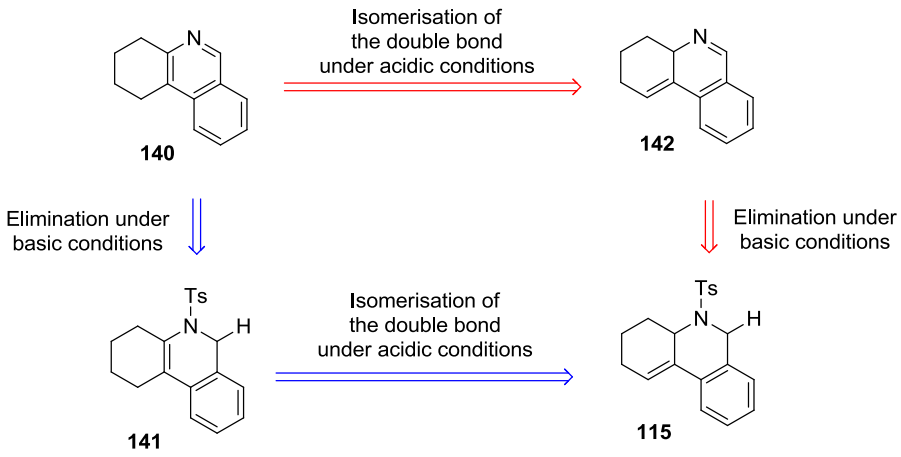


124 **125**

Figure 9: Unsuccessful substrates for the direct arylation

4.2.5 Isoquinoline synthesis

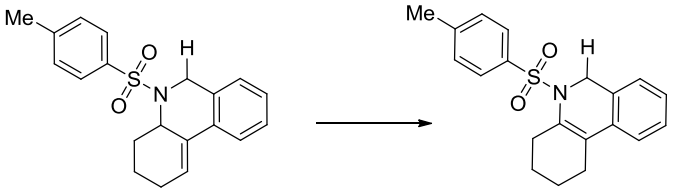
Two converging strategies were envisioned to obtain the desired isoquinoline **140** (**Scheme 93**). They both involve sequential isomerisation of the *exo*-alkenic double bond and a base-induced elimination of the sulfinate to afford the isoquinoline **140**. Each route relies on a facile final step driven by the aromatisation of the pyridinic cycle. We therefore went on to compare the feasibility of the first step under different reaction conditions.



Scheme 93: Retrosynthetic analysis of isoquinoline **140** formation from cyclic sulfonamide **115**

The first strategy, namely the isomerisation of the *exo*cyclic alkene **115** under acidic conditions was unsuccessful and led only to untouched starting material or degradation product (**Table 20**). It is therefore probable that for the isomerisation to occur, it needs to lead to the thermodynamically favourable aromatisation of the substrate.

Table 20: Screening of condition for the isomerisation of *exo*cyclic compound **115**

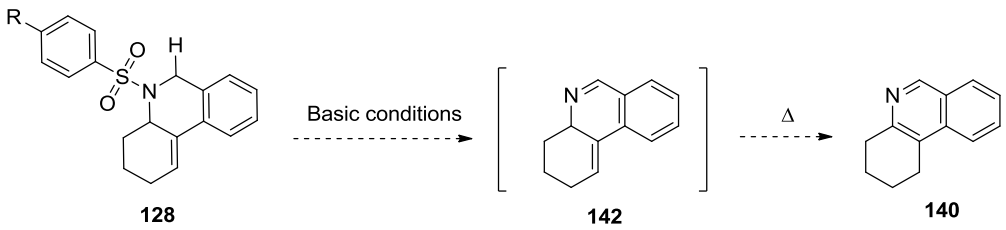


115 **141**

Entry	Reaction conditions	Sulfonamide 141
1	1.1 equiv *p*TSA, DCM, rt	0% [a]
2	1.1 equiv *p*TSA, DCM, reflux	0% [b]
3	1.1 equiv TFA, DCM, rt	0% [a]
4	Excess PPA, DCM, rt	0% [a]
5	1.1 equiv triflic acid, DCM, rt	0% [c]
6	1.1 equiv triflic acid, DCM, 0 °C	0% [b]
7	1.1 equiv H_2SO_4, DCM, rt	0% [b]

a. Starting material **115** recovered; b. Starting material **115** recovered along with degradation products; c. Complex mixture.

We then tested our second strategy, submitting our substrates to different basic reaction conditions, hoping to obtained either intermediate **142** or isoquinoline **140** (**Scheme 94**).

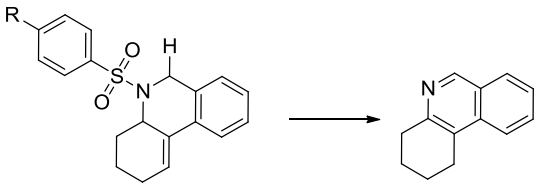


Scheme 94: Second strategy for the isoquinoline synthesis

Our initial attempts to access the isoquinoline **140** from the tosyl substituted cyclic amine **115** using this strategy were unsuccessful (**Table 21**). The basic elimination did not happen with DBU at room temperature (**Entry 1**) and led only to degradation products at higher temperature (**Entry 2**). The use of stronger base, KHMDS, at room temperature was equally inefficient (**Entry 3**) but to our delight, refluxing the reaction for 3 days afforded isoquinoline **140** in 55% yield along with untouched starting material (**Entry 4**). It is probable that although the base was responsible for the elimination of the sulfinate, the aromatisation itself was thermally induced. Attempts to replace toluene by DMA in order to perform a one-pot synthesis of the isoquinoline **140** were unsuccessful (**Entry 5**). The use of an even stronger base did not improve the conversion in the reaction but did lead to the degradation of the substrate (**Entries 6-7**). Finally, attempting to obtain isoquinoline **140** with a more traditional oxidation method (**Entry 8**) was ineffective.[155]

To our delight, switching from the tosyl protected amine **115** to more electron-withdrawing amines **119** and **120**, the same reaction conditions afforded quantitative yields of the desired isoquinoline **140** (**Entries 9** and **10**).

Table 21: Screening of condition for the synthesis of isoquinoline **140** in basic conditions



128 **140**

Entry	R	Reagent	Solvent	Temperature Time	Yield [a]
1	Me	DBU	THF	rt, 1 day	0% [b]
2	Me	DBU	THF	75 °C, 3 days	0% [d]
3	Me	KHMDS	Toluene	rt, 1 day	0% [b]
4	Me	KHMDS	Toluene	110 °C, 3 days	55% [c]
5	Me	KHMDS	DMA	120 °C, 4 hrs	0% [d]
6	Me	LDA	Toluene	-78 °C to rt, 15 hrs	0% [d]
7	Me	*n*BuLi	Toluene	-78 °C to rt, 1 day	0% [d]
8	Me	DDQ	THF	rt to 50 °C, 1 day	0% [b]
9	F	KHMDS	Toluene	110 °C, 1 day	>99%
10	CF_3	KHMDS	Toluene	110 °C, 1 day	>99%

a. Isolated yield; b. Starting material recovered; c. 45% of starting material recovered; d. Complex mixture

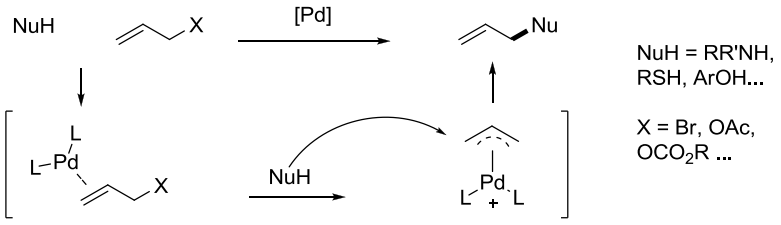
4.3 Conclusion and future work

These initial studies have demonstrated that we can successfully form six-membered ring heterocycles by direct arylation of alkenyl bromide derivatives. The synthetic utility of this methodology was exemplified by the synthesis of substituted isoquinolines in six steps. In the future, these initial results should lead to an extension of the scope of isoquinolines accessible *via* direct arylation. Moreover, we have applied our methodology to the direct arylation of sulfonamides, leading to an interesting synthesis of widely used sultams. This novel route is currently being investigated within the group and should provide a new route to a variety of differently substituted cyclic sulfonamides.

Chapter 5. Synthesis of Benzo[*b*]furans: Tandem Tsuji-Trost/ Direct Arylation Palladium-Catalysed Couplings

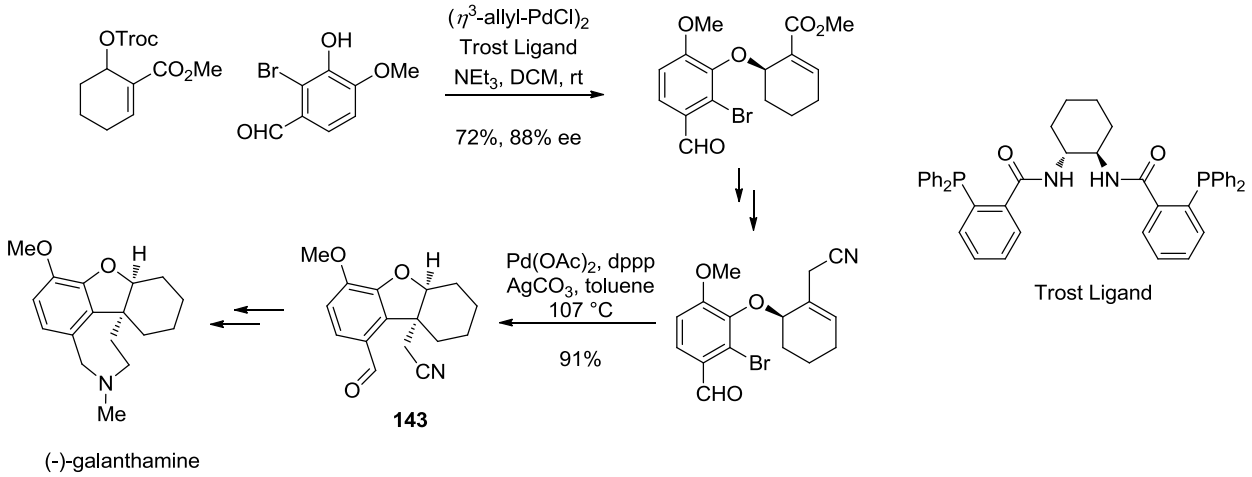
5.1 Introduction

The Tsuji-Trost allylation is one of the most synthetically useful palladium-catalysed reactions.[8,156] Since its discovery it has mainly been used to install new chiral centres with a variety of nucleophiles (**Scheme 95**).



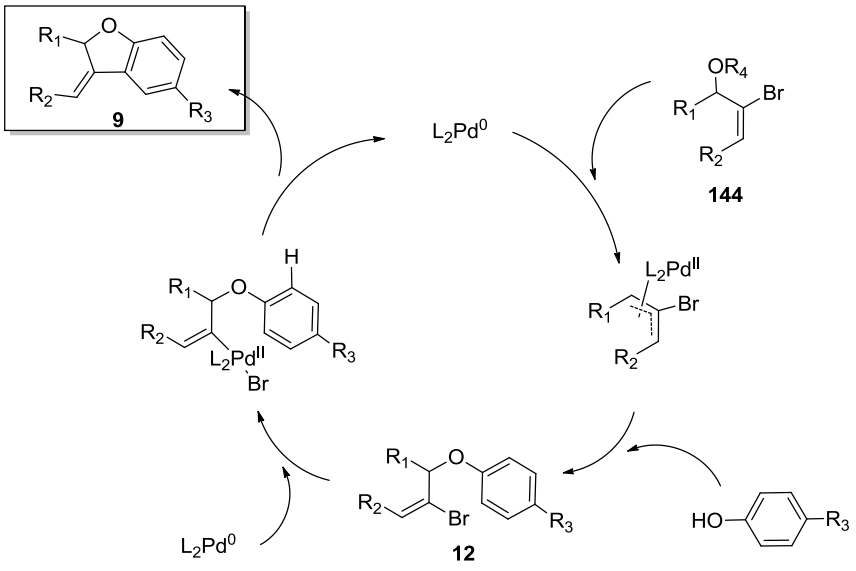
Scheme 95: Tsuji-Trost allylation

During our study of the direct arylation of alkenyl bromides to form benzofurans, we discovered a side reaction delivering the corresponding phenol (**Chapter 2**). Indeed, the use of aryl ethers as leaving groups for the formation of π-allylpalladium complexes was reported very early on in the study of the Tsuji-Trost allylation.[8,129] However, this reaction is reversible and phenol derivatives are also commonly used as nucleophiles in this allylation. Trost and co-workers' total synthesis of (-)-galanthamine is a striking example of palladium-catalysed substitution of a hindered allyl substrate by a highly decorated phenol and subsequent Heck coupling to furnish asymmetric dihydrobenzofuran **143** (**Scheme 96**).[157]



Scheme 96: Total synthesis of (-)-galanthamine by Trost and co-workers

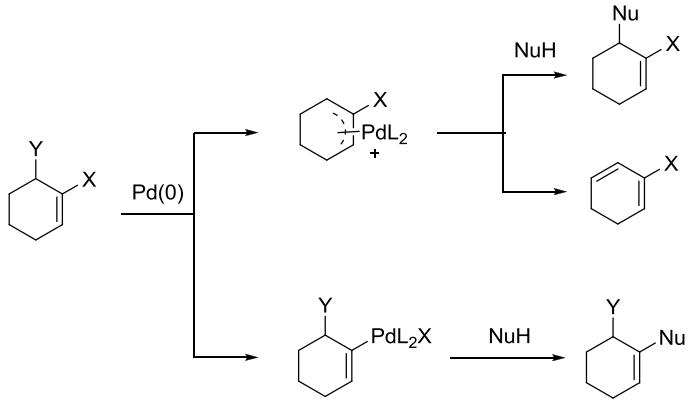
We postulated that to further simplify our initial synthesis of benzo[*b*]furans we could develop a sequential Tsuji-Trost allylation/direct arylation process (**Scheme 97**).



Scheme 97: Synthesis of tetrahydrobenzofuran **9** by tandem palladium-catalysed coupling

This methodology would allow a more divergent approach to heterocycles due to an extremely versatile starting material **144** and a unique catalytic system which would then grant access to benzofurans.

The main difficulties arising from this route are, on one hand, the identification of a catalytic system allowing both the formation of a η^3-allylpalladium complex and oxidative addition to a vinyl C-X bond and, on the other hand, the possibility of a competition between the two processes. In our system, the allylic ionisation must take place before the oxidative addition. Moreover, an elimination occurring after the formation of the π-allylpalladium complex would lead to the formation of a diene and would also be detrimental to the tandem process (**Scheme 98**).



Scheme 98: Competition between allylic ionisation and oxidative addition into vinyl C-X bond

Studies of the control of the chemoselectivity in vinylic and allylic C-X bond activation in palladium catalysis have been carried out, mainly by Nwokogu[158,159] and Organ and co-workers,[160-165] and four major factors were identified:

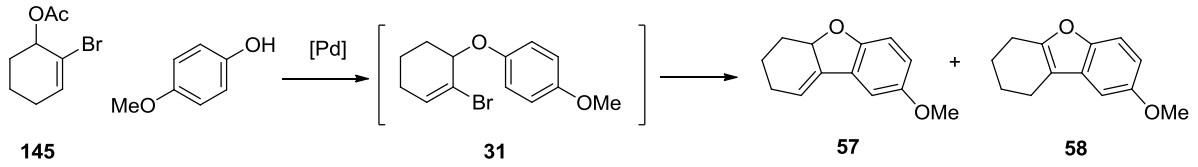
- The ionisaton step commonly occurs at low temperature while the oxidative addition usually requires thermal activation.
- Depending on the leaving group, the formation of the η^3-allylpalladium complex can be slowed down which in turn favours the oxidative addition step.
- The choice of the reaction solvent affects mainly the reversibility of the ionisation. If a coordinating solvent like THF is chosen, few free ions originating from the leaving group will be available as nucleophiles and the attack of the desired nucleophile onto the π-allylcomplex will be favoured.
- Finally, the nucleophile used in the reaction is extremely important as it was proven that the nature of the nucleophile influences the ionisation step through a pre-coordination to the

catalyst. The relative softness/hardness of the nucleophile is also of prime importance to the chemoslectivity of the reaction as hard nucleophiles tend to undergo oxidative additions whilst soft ones prefer allylic substitution. Careful choice of base and therefore of counter-cation for the deprotonated nucleophile are essential.

5.2 Results and discussion

5.2.1 Initial studies and evaluation of the feasibility of the reaction

In order to begin our investigation, we chose the model system depicted in **Scheme 99**. Allylic acetate **145** was selected as the most common substrate for Tsuji-Trost coupling while the choice of 4-methoxyphenol as the second partner of the reaction was based on our previous study (**Chapter 2**) of the transformation of intermediate **31** to *exo*-alkene **57** and benzofuran **58**.

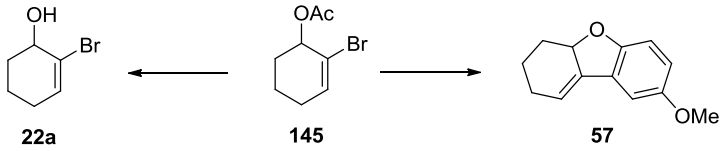


Scheme 99: Selected model system for the tandem allylation/arylation synthesis of benzofurans

Based on literature precedent,[158,159,162] we selected palladium tetrakis triphenyl phosphine as an ambivalent catalyst able to promote the formation of both π-allyl and σ-vinylpalladium complexes. It would also allow us to avoid using an additional ligand, therefore decreasing the variables to be initially screened. For our first screening (**Table 22**) we limited ourselves to a small range of bases and solvents, two variables which may be critical for the Tsuji-Trost allylation, if not for the C-C bond formation, to take place. TLC and non-calibrated routine LC/MS analyses provided fast but non-quantitative results. First results were encouraging as they showed formation of the desired *exo*cyclic alkene **57**, alkenyl bromide intermediate **31** and deprotected alcohol **22a** as the only products of the reaction. No product of the direct oxidative addition followed by C-O bond formation was detected.

The starting material was left mainly untouched which indicated that temperature and reaction times should be increased. In every solvent, the use of NBu_3 (**Entries 10-12**) as a base afforded mainly deprotected alcohol **22a**. Associated with other bases, DME and DMF showed encouraging traces of the desired compound by LC/MS analysis (**Entries 1-3, 5-7**). Finally, acetonitrile was identified as the best solvent so far (**Entries 9-11**) affording about 20% of the desired compound **57** by ^1H NMR spectroscopy when combined with Cs_2CO_3 as a base (**Entry 9**).

Table 22: Initial base and solvent screening [a]



22a **145** **57**

Entry	Base	Solvent	Results (HPLC [b])
1	Cs_2CO_3	DME	SM and traces of product **57** (4%)
2	KO*t*Bu	DME	SM and traces of product **57** (1%)
3	KOH	DME	SM and traces of product **57** (2%)
4	NBu_3	DME	SM and alcohol **22a**
5	Cs_2CO_3	DMF	SM and traces of product **57** (1%)
6	KO*t*Bu	DMF	SM and traces of product **57** (2%)
7	KOH	DMF	SM and traces of product **57** (1%)
8	NBu_3	DMF	SM and alcohol **22a**
9	Cs_2CO_3	CH_3CN	SM and product **57** (34%) 20% of product **57** [c]
10	KO*t*Bu	CH_3CN	SM and traces of product **57** (3%)
11	KOH	CH_3CN	SM and product **57** (15%)
12	NBu_3	CH_3CN	SM and alcohol **22a**

a. Reaction conditions: Acetate **145** (1.0 equiv), 4-methoxyphenol (1.0 equiv), palladium tetrakis triphenyl phosphine (10 mol% equiv), base (2.0 equiv), 20 min at 50 °C then 20 min at 80 °C in the microwave; b Peak area in percentage of the total peak area detected by non-calibrated LC/MS analysis; c. Determined by ^{1}H NMR spectroscopy.

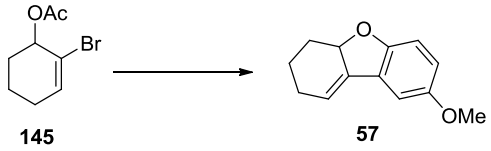
5.2.2 Optimisation of the process: catalyst and reaction conditions screen

After identifying Cs_2CO_3 and acetonitrile as the best combination of base and solvent for the reaction, we proceeded with a catalyst screen. 1.2 equivalents of 4-methoxyphenol was used instead of the previous 1.0 equivalent and for practical reasons the reaction was heated *via* an oil bath instead of using the microwave. We were first able to confirm the presence of the desired benzofuran isomer **57** by repeating our previously found best reaction conditions (**Table 23**, **Entry 1**). *Exo*alkene **57** was isolated in a very promising 27% yield.

Other palladium sources were tested according to literature precedent but neither Pd_2dba_3 nor $PdCl_2$ alone or associated with *N*-heterocyclic ligands gave any encouraging result (**Entries 2-4**). We then turned our attention towards cheaper and easier to handle $Pd(OAc)_2$ and associated it with a range of mono and bidentate ligands. Whilst X-Phos, DavePhos and dppp led to a complex mixture of unidentified compounds (**Entries 5-7**), we were pleased to obtain an encouraging 30% yield using ferrocene ligand dppf (**Entry 8**). Surprisingly, the use of the preformed catalyst $Pd(dppf)Cl_2$.DCM resulted in unreacted starting material (**Entry 9**). Bulkier versions of dppf, namely di-*i*Prphosphino ferrocene (**Entry 10**) and di-*t*Buphosphino ferrocene (**Entry 11**) were tested but only complex mixtures were recovered. These results corroborate the observation made during our study of the synthesis of benzofuran by C-H activation that very bulky ligands were not beneficial to the reaction. Several other ferrocene-type ligands were tested without much success. Ligands containing phosphines on the same cyclopentadienyl cycle (**Entries 12-14**) were totally inefficient whilst (*R*)-(*S*)-BPPFA which, like dppf, possesses its two phosphines on different cyclopentadienyl rings afforded traces of the desired product albeit in negligible quantities (**Entry 15**). Furthermore, the small amount of product **57** isolated was analysed by chiral HPLC and found to be completely racemic.

Finally, in an attempt to favour the first step of the reaction, (*R*,*R*)-Dach phenyl Trost ligand, which is known to be extremely effective for the catalysis of Tsuji-Trost allylation reactions, was tested (**Entry 16**). Surprisingly, only a mixture of starting material and deprotected starting material **22a** was recovered. This result can be compared to those obtained during our first screening where NEt_3 was used as a base. As it has been previously described, we can surmise that the presence of amines leads to the deprotection of the acetate.[158,159]

Table 23: Catalyst screening [a]



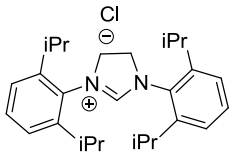
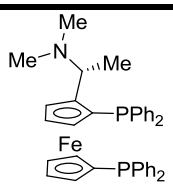
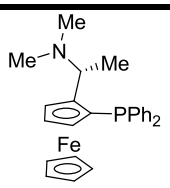
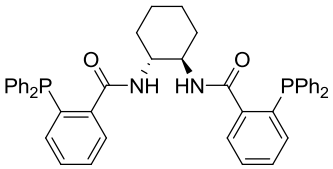
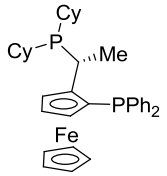
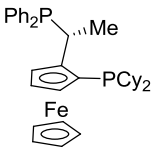
145 57

Entry	Palladium source	Ligand	Result [b]
1	$Pd(PPh_3)_4$	/	27%
2	Pd_2dba_3	/	0% [c]
3	Pd_2dba_3	NHC L	0% [d]
4	$PdCl_2$	NHC L	SM
5	$Pd(OAc)_2$	X-Phos	0% [d]
6	$Pd(OAc)_2$	Dave-Phos	0% [d]
7	$Pd(OAc)_2$	Dppp	0% [c,d]
8	$Pd(OAc)_2$	Dppf	30%
9	$Pd(dppf)Cl_2$.DCM	/	0% [c]
10	$Pd(OAc)_2$	Di-*i*Prphosphino ferrocene	0% [d]
11	$Pd(OAc)_2$	Di-*t*Buphosphino ferrocene	0% [d]
12	$Pd(OAc)_2$	Josiphos 004	0% [c,d]
13	$Pd(OAc)_2$	Josiphos 001	0% [c]
14	$Pd(OAc)_2$	(*R*)-(*S*)-PPFA	0% [c]
15	$Pd(OAc)_2$	(*R*)-(*S*)-BPPFA	Mixture of intermediate and

			desired compound
16	$Pd(OAc)_2$	(*R*,*R*)-Dach phenyl Trost ligand	0% [e]

a. Reaction conditions: Acetate **145** (1.0 equiv), 4-methoxyphenol (1.2 equiv), palladium source (10 mol%), ligand (20 mol% monodentate or 10 mol% bidentate), Cs_2CO_3 (2.0 equiv), MeCN (0.23 M), 24 hrs at 80 °C; b Isolated yields; c. starting material recovered; d. Complex mixture; e. Mixture of starting material **145** and deprotected alcohol **22a**.

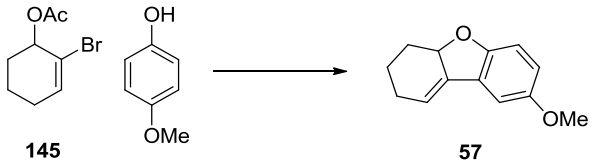
Table 24: Ligands used in Table 23

		
***N*-heterocyclic ligand (NHC L)**	**(*R*)-(*S*)-BPPFA**	**(*R*)-(*S*)-PPFA**
		
(*R*,*R*)-Dach phenyl Trost ligand	**Josiphos 001**	**Josiphos 004**

We next evaluated the importance of the ratio between the acetate **145** and the nucleophile, the amount of catalyst and the temperature of the reaction (**Table 25**). Heating the reaction mixture slightly above the boiling point of acetonitrile led to a positive effect on the reaction (**Entry 2**) and 85 °C was therefore adopted as the new reaction temperature. Performing the reaction at 50 °C, which had been shown previously (**Chapter 2**) to be the lowest temperature for the C-C bond coupling to happen, also improved its yield; however, the 3 days reaction time discouraged from using these

conditions for extensive screening (**Entry 3**). Variations of the ratio between the acetate **145** and the nucleophile and the amount of catalyst used afforded disappointing results (**Entries 4-6**).

Table 25: Ratio of 4-methoxyphenol, catalyst and temperature [a]



145 **57**

Entry	4-Methoxyphenol	Catalyst [b]	Temperature	Yield [c] (^{1}H NMR spectroscopy conversion)
1	1.2 equiv	10 mol%	80 °C	27%
2	1.2 equiv	10 mol%	85 °C	30% (90%)
3	1.2 equiv	10 mol%	50 °C	34% [d]
4	1.2 equiv	5 mol%	85 °C	traces
5	0.9 equiv	10 mol%	85 °C	(65%)
6	2.0 equiv	10 mol%	85 °C	26% (65%)

a. Reaction conditions: Acetate **145** (1.0 equiv), 4-methoxyphenol, catalyst, Cs_2CO_3 (2.0 equiv), MeCN (0.23 M), 24 hrs at 85 °C; b. Catalyst: $Pd(OAc)_2$ (1.0 equiv), dppf (1.0 equiv); c. Isolated yield; d. 3 days.

We suspected the nature of the base was an important determinant of the reaction success, especially as deprotonation of the nucleophile, either before or after the palladium-catalysed allylation, may greatly influence the rate of the reaction. During our first screening (**Table 22**) we noticed that NEt_3 was completely ineffective in the reaction and mainly lead to the deprotection of the acetate **145** and that other bases (KOH, KO*t*Bu and Cs_2CO_3) were unequally effective. After choosing Cs_2CO_3 as a base during the catalyst screening, we wanted to compare it with other weak inorganic bases

(**Table 26**). CsOAc, maybe due to its high hydrophilicity was difficulty to handle in anhydrous conditions and did not deliver any desired product **57** or intermediate **31** (**Entry 1**). The stronger base K_3PO_4 afforded some product **57** (**Entry 2**) but in lower conversion than Cs_2CO_3 (**Entry 4**). Using only a small excess of Cs_2CO_3 in the reaction proved detrimental (**Entry 3**) whilst 3 equivalents of base hardly improved the reaction (**Entry 5**). Surprisingly, the harder carbonate K_2CO_3 was totally ineffective, highlighting the importance of the counter-ion of the phenolate for the allylation step (**Entry 6**); however, conserving the cesium whilst using an extremely weak fluoride base (**Entry 7**) was similarly disappointing.

Table 26: Base screen [a]

Entry	Base (equiv)	Yield (^{1}H NMR spectroscopy conversion)
1	CsOAc (2.0)	0% [b]
2	K_3PO_4 (2.0)	(15%)
3	Cs_2CO_3 (1.1)	(15%)
4	Cs_2CO_3 (2.0)	30% (70%)
5	Cs_2CO_3 (3.0)	32% (90%)
6	K_2CO_3 (2.0)	0% [c]
7	CsF (2.0)	0% [c]

a. Reaction conditions: Acetate **145** (1.0 equiv), 4-methoxyphenol (1.2 equiv), $Pd(OAc)_2$ (10 mol%), dppf ligand (10 mol%), MeCN (0.23 M), 24 hrs at 85 °C; b. Complex mixture; c. Starting material **145** recovered.

Having not observed any notable improvement after our base screen, we decided to conserve our initial two equivalents of base and to proceed to an evaluation of the reaction solvent (**Table 27**).

During our first screening (**Table 22**) we had discarded both DME and DMF as less effective than acetonitrile. This study allowed us to confirm than less polar solvents (**Entries 5-7**) do not favour the reaction, presumably due to the destabilisation of the ionic palladium η^3-complex of the Tsuji-Trost reaction. More polar solvents (**Entries 1-4**) gave comparable results whilst distilled acetonitrile (**Entry 2**) remained the solvent of choice for this transformation.

Table 27: Solvent screen [a]

Entry	Solvent	Yield [b]
1	Acetonitrile	30%
2	Acetonitrile (distilled)	39%
3	THF	33%
4	DMA	28%
5	DCE	22%
6	1,4-Dioxane	24%
7	Toluene	15%

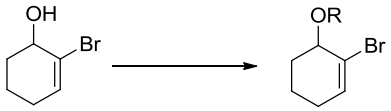
a. Reaction conditions: Acetate **145** (1.0 equiv), 4-methoxyphenol (1.2 equiv), $Pd(OAc)_2$ (10 mol%), dppf ligand (10 mol%), Cs_2CO_3 (2.0 equiv), solvent (0.23 M), 24 hrs at 85 °C; b Isolated yield.

5.2.3 Alternative allylic substrates

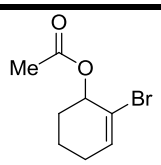
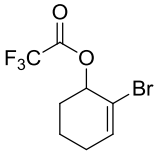
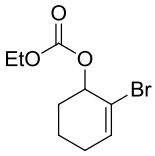
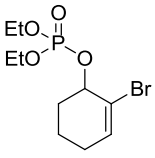
Many allylic compounds have been described as highly efficient substrates for the Tsuji-Trost allylation.[8] While the acetate is the more commonly used, the electronic properties of the leaving group can be modulated to promote faster or slower ionisation of the substrate. In order to perform our tandem process, we synthesised four different substrates using described procedures in good to

excellent yields from the corresponding α-bromo alcohol **22a**, which was synthesised in two steps from a commercially available enone as described in **Chapter 1** (**Table 28**).

Table 28: Synthesis of allylic substrates



22a

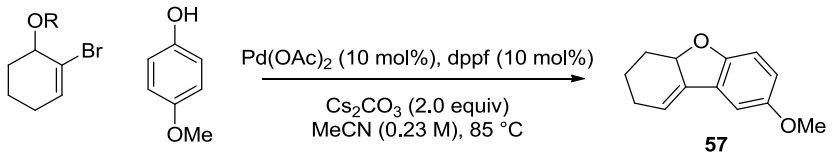
Entry	Product	Reaction conditions[a]	Result [b]
1	 145	Acetic anhydride (1.5 equiv), DMAP (0.1 equiv) and pyridine (30.0 equiv), DCM, rt, 15 hrs	96%
2	 **146**	Trifluoroacetic anhydride (2.0 equiv) and pyridine (6.0 equiv), DCM at 0 °C, 1 hr	48%
3	 **147**	Ethyl chloroformate (2.0 equiv) and pyridine (2.0 equiv), DCM, rt, 5 days	80%
4	 **148**	$(EtO)_2P(O)Cl$ (1.2 equiv), DMAP (0.1 equiv) and pyridine (13 equiv), DCM, rt, 1day	88%

a. 2-bromo-2-cyclohexen-1-ol **22a** (1.0 equiv), rt; b. Isolated yield.

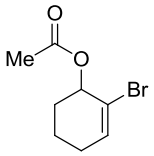
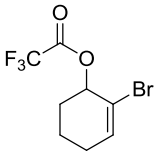
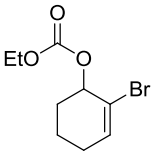
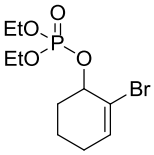
However, the comparison between several known allylic substrates for the palladium-catalysed allylation did not afford the expected results. While the most electron deficient trifluoroacetate **146**

gave a poor 7% yield of the expected *exo*-alkenic product **57** (**Entry 2**), carbonate **147** (**Entry 3**) and phosphate **148** (**Entry 4**) behaved similarly to acetate **145** (**Entry 1**), despite the reaction of phosphate **148** with 4-methoxyphenol not proceeding to completion after 2 days (**Table 29**).

Table 29: Alternative leaving groups [a]



57

Entry	Starting material	Result
1	 **145**	30%
2	 **146**	7%
3	 **147**	28%
4	 **148**	23% [b]

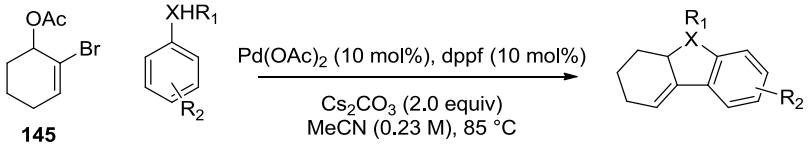
a. Reaction conditions: Starting material (1.0 equiv), 4-methoxyphenol (1.2 equiv), $Pd(OAc)_2$ (10 mol%), dppf (10 mol%), Cs_2CO_3 (2.0 equiv), MeCN (0.23 M), 24 hrs at 85 °C; b. 30% of starting material recovered.

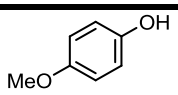
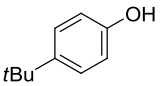
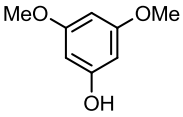
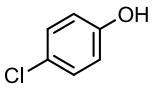
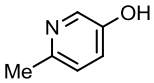
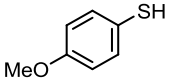
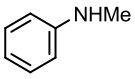
5.2.4 Reaction scope

Although only a moderate yield was attained after our initial screening, a restricted scope of the reaction was studied in order to evaluate the viability of the transformation (**Table 30**). As expected, electron-rich phenols 4-*t*Bu-phenol and 3,5-dimethoxyphenol afforded the corresponding *exo*-alkenic compound **80** and **81** sometimes in addition to the aromatised benzofuran (**Entries 2-3**). Pleasingly, the more electron-deficient phenols 4-chlorophenol or 2-methyl,5-hydroxypyridine afforded the corresponding products in similar yields although the reaction was not complete after 2 days (**Entries 4-5**).

Attempts to synthesise other types of heterocycles such as benzothiophenes and indoles using this methodology were unsuccessful. It is likely that 4-methoxythiophenol bound to the metal catalyst leaving the starting material untouched (**Entry 6**). It is more difficult to understand why *N*-methylaniline was equally unreactive (**Entry 7**) as the palladium-catalysed allylation has been described for similar systems.[8]

Table 30: Reaction scope [a]



Entry	Nucleophile	Isolated yield
1		30%
2		28%
3		23% [b]
4		26% [c]
5		(55%) [d]
6		0% [c]
7		0% [c]

a Reaction conditions: Acetate **145** (1.0 equiv), nucleophile (1.2 equiv), $Pd(OAc)_2$ (10 mol%), dppf (10 mol%), Cs_2CO_3 (2.0 equiv), MeCN (0.23 M), 24 hrs at 85 °C; b. Composed of *exo*-alkene and benzofuran **74** (1 :1); c. (1.1 : 1) mixture of product and starting material; d. ^1H NMR conversion; e. Recovered starting material.

5.3 Conclusion

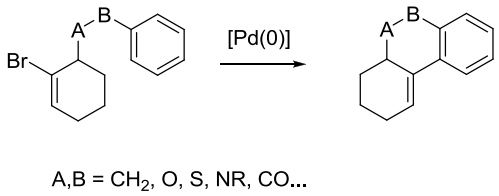
In conclusion, we have initiated the development of a novel methodology to synthesise benzo[*b*]furans *via* a palladium-catalysed tandem process combining the well-known Tsuji-Trost allylation and our own C-C bond formation methodology. The preliminary results shown here demonstrate that this tandem process can be performed under mild conditions and that it is a general reaction, tolerant of a variety of substituents. The highly versatile substrate for this reaction can be easily accessed in an excellent yield and allows the formation of a wide range of heterocycles thanks to a single starting material. Although we were unable to perform this reaction in a truly synthetically useful yield, we believe that conditions can be found allowing both steps to be accomplished in excellent yields. Moreover, an asymmetric version of this reaction is yet to be investigated. Importantly, the early results described here are positive and strongly encourage further research.

Chapter 6. Conclusion and Future Work

A new method for the coupling of unfunctionalised aryl C-H bonds with a vinyl halide was developed and applied to the synthesis of benzofurans (**Chapter 2)**,[124] isoquinolines and sultams (**Chapter 4).** With this strategy new C-C bonds were formed under mild conditions from readily available starting materials. The reaction also proved to be compatible with a wide range of functional groups. A new strategy has also provided access to more complex benzofurans in both a chiral and achiral manner by functionalisation of the *exo*cyclic alkene intermediate. A mechanistic insight was given by kinetic and substituent studies for the benzofuran formation reaction. Analysis of the effects of the substituents on the aromatic ring suggests that the reaction proceeds *via* an electrophilic aromatic substitution mechanism (S_EAr); however the existence of both intra and intermolecular kinetic isotope effects suggest a S_E3 type pathway rather than a simple S_EAr (**Chapter 3**).

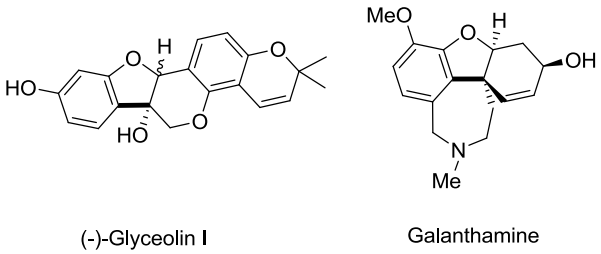
Finally, a new strategy based on consecutive Tsuji-Trost reaction and C-H functionalisation for the synthesis of benzo[*b*]furan was also briefly investigated. This methodology requires simpler and more versatile substrates, allowing access to variously decorated aromatics in a single step. To our knowledge, this is the first example of a single palladium catalyst performing these two reactions in tandem (**Chapter 5**). We hope this methodology will be further developed and applied to the synthesis of chiral molecules using an asymmetric Tsuji-Trost allylation.

The results obtained during this project are encouraging and further developments are currently ongoing within the group. The synthesis of both sultams and isoquinolines is particularly important as these compounds frequently show biological properties and are used in the pharmaceutical industry. Access to many more heterocycles could be unlocked using this methodology (**Scheme 100**).



Scheme 100: Heterocycles accessible *via* palladium-catalysed direct arylation of alkenyl bromides

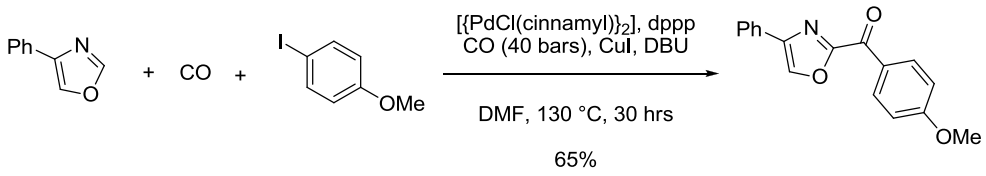
This methodology could also be an attractive tool for the efficient preparation of complex natural products. The ability to form chiral quaternary centres using a simple procedure is particularly interesting and molecules such as (-)-glyceolin I[166] and (-)-galanthamine[157] could be synthesised using a key C-H functionalisation step (**Figure 10**).



(-)-Glyceolin **I** Galanthamine

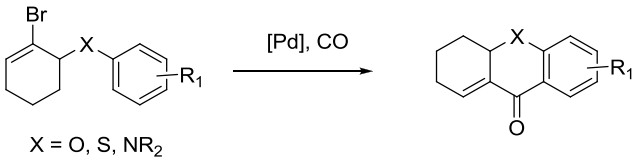
Figure 10: Examples of natural products which could potentially be synthesised using our direct arylation methodology

While tandem reactions involving direct arylations have attracted much interest over the past few years, the related carbonylative coupling reactions of arenes using C-H functionalisation have been scarcely studied. Most of the studied systems use a ruthenium catalyst[167] or proceed *via* a palladium(II)-catalysed oxidative direct arylation.[168,169] Only recently have Beller and co-workers developed a palladium-catalysed tandem carbonylation/direct arylation reaction (**Scheme 101**).[170]



Scheme 101: Palladium-catalysed carbonylative direct arylation of heteroarenes

Developing a new carbonylative direct arylation based on our previously described methodology would allow us to access new classes of heterocycles such as chromones, thiochromones and pyridones (**Scheme 102**).



Scheme 102: Possible synthesis of 4-chromones, 4-thiochromones and 4-pyridones

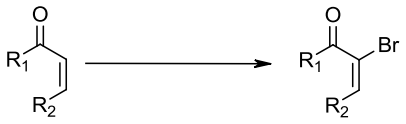
Chapter 7. Experimental

General information:

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker 200, 400 or 500 MHz spectrometer. ^{1}H NMR chemical shifts have an internal referenced tetramethylsilane (δH 0.00 ppm) or residual $CHCl_3$ (δH 7.27 ppm) and ^{13}C NMR uses $CDCl_3$ (δC 77.0 ppm) as an internal reference. Chemical shifts (δ) were reported in ppm and coupling constants (J) are in Hertz (Hz). The multiplicities of the spectra are reported as follows: singlet (s), broad singlet (br. s.), doublet (d), triplet (t), quartet (q) and unresolved multiplicity (m). Infrared (IR) spectra were collected on a Perkin-Elmer 1600 series FTIR spectrometer and Bruker Tensor 27 FT-IR with internal calibration in the range 4000-500 cm^{-1}. Samples for IR were prepared as a thin film on NaCl plate either directly for liquid samples or by dissolving the solid compound in dichloromethane and then evaporating the solvent. Optical rotations were measured on an Perkin-Elmer 241 polarimeter at 25 °C. Mass spectrometry was carried out on a Bruker MicroTOF and Micromass SYNAPT ion. Melting points were determined using a Büchi 535 melting point apparatus. Analytical thin layer chromatography was carried out using pre-coated aluminium backed silica plates (Merck Kieselgel 60F254) and pre-coated plastic backed silica plates (Polygram® Sil G/UV254). Plates were visualized under ultraviolet light (254 nm) and by staining with $KMnO_4$. Flash flash chromatography was carried out using Merck Kieselgel 60H silica. Chiral HPLC analyses were carried out on a Dionex HPLC system utilising Daicel chiral columns.

Dry and purified tetrahydrofuran (THF) and dichloromethane (DCM) were obtained from a MBraun SPS solvent purification system. Dry *N,N*-dimethylacetamide (DMA) and methanol (MeOH) were purchased from Aldrich in a Sure-Seal bottle. 1,2-Dimethoxyethane (DME) was distilled from sodium, using benzophenol ketal as an indicator. Triethylamine (NEt_3) was distilled from calcium hydride (CaH_2) under nitrogen (N_2) and dry 1,2-dichloroethane (DCE) was also distilled from CaH_2 under N_2. Petroleum ether refers to light petroleum ether, bp 40-60 °C. All chemicals were purchased from Acros, Aldrich or Alfa Aesar and used without further purification. All reagents were weighed and handled in air and refilled with an inert atmosphere of N_2 or argon (Ar) at room temperature.

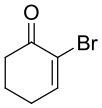
General procedure A: the preparation of α bromo enones 14



14

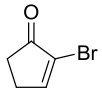
α-Bromo enone **14** was prepared using literature procedure.[125,128] Sodium bromide (2.0 equiv) was added portion-wise over 15 min to a stirred solution of Oxone^{TM} (2.0 equiv) in DCM (3 L.mol^{-1}) and water (0.7 L.mol^{-1}) at 0 °C and was stirred for 40 min. The enone (1.0 equiv) was then added drop-wise over 15 min, stirred for 16 hrs allowing to warm to room temperature and then stirred at 40 °C for 4 hrs. The reaction was then cooled to 0 °C and NEt_3 (3.0 equiv) added drop-wise over 20 min and stirred for 4 hrs. The mixture was diluted with water (0.7 L.mol^{-1}), the phases separated, the aqueous phase extracted with DCM (3 × 0.7 L.mol^{-1}), the organic phases combined, washed with water (1 L.mol^{-1}) and brine (1 L.mol^{-1}), dried ($MgSO_4$) and evaporated under reduced pressure. The dark resulting oil was then crystallised (5% MeOH in petroleum ether) to yield the desired α-bromo enone **14**.

2-Bromocyclohex-2-enone, 15



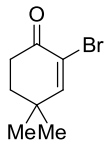
α-Bromo enone **15** was prepared using general procedure **A**. Starting with cyclohexen-2-one (5.0 mL, 52.0 mmol) the desired α-bromo enone **15** was obtained as a white crystalline solid (8.0 g, 88%); mp 72-73°C (*lit*. 72-75°C). ν_{max} (DCM)/cm^{-1} 1684, 1599, 1318, 914, 731; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44 (t, *J* = 4.4 Hz, 1H, C*H*=CBr), 2.68-2.61 (m, 2H, OCC*H*$_2$CH$_2$CH$_2$), 2.51-2.43 (m, 2H, OCCH$_2$CH$_2$C*H*$_2$), 2.15-2.02 (m, 2H, OCH$_2$C*H*$_2$CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 151.7, 124.4, 38.8, 28.8, 23.2. Data in accordance with literature.[171]

2-Bromocyclopenten-2-one, 16



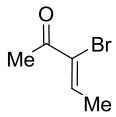
α-Bromo enone **16** was prepared using general procedure **A**. Starting with cyclopenten-2-one (5.00 g, 60.9 mmol), the desired α-bromo enone **16** was obtained (7.57g, 77%) as yellow solid, mp 31-32 °C (*lit.* 34-35°C), after purification by flash chromatography (20% Et_2O in petroleum ether). ν_{max} (liquid film)/cm^{-1} 1717, 1590, 1290, 935; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.79 (t, *J* = 2.8 Hz, 1H, C*H*=CBr); 2.73-2.70 (td, *J* = 4.4, 2.8 Hz, 2H, OCCH_2CH$_2$), 2.54 (t, *J* = 4.4 Hz, 2H, OCCH$_2$CH_2), ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 161.8, 126.3, 32.4, 28.0. Data in accordance with literature.[128,171]

2-Bromo-4,4-dimethylcyclohex-2-enone, 17



α-Bromo enone **17** was prepared using general procedure **A**. Starting with 4,4-dimethylcyclohex-2-enone (2.00 g, 16.0 mmol), the desired α-bromo enone **17** was obtained as light yellow solid (3.0 g, 92%), mp 25-26°C (*lit.* 29°C), after purification by flash chromatography (10% Et_2O in petroleum ether). ν_{max} (liquid film)/cm^{-1} 2962, 1697, 1597, 1323, 1146; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13 (s, 1H, C*H*=CBr), 2.66 (t, *J* = 6.8 Hz, 2H, OCCH_2CH$_2$), 1.92 (t, *J* = 6.8 Hz, 2H, OCCH$_2$CH_2), 1.22 (s, 6H, 2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 159.9, 121.8, 36.7, 35.8, 34.6, 27.5. Data in accordance with literature.[128,171]

(*Z*)-3-Bbromopent-3-en-2-one, 18



Sodium bromide (7.33 g, 71 mmol) was added portion-wise over 15 min to a stirred solution of Oxone^{TM} (43.85 g, 71 mmol) in $CHCl_3$ (120 mL) and water (30 mL) at 0 °C and was stirred for 40 min. 3-Penten-2-one (3.48 mL, 36 mmol) was then added drop-wise over 15 min, stirred for 16 hrs allowing to warm to room temperature and then stirred at 40 °C for 4 hrs. The reaction mixture was then cooled to 0 °C and NEt_3 (25 mL, 178 mmol) added drop-wise over 20 min and stirred for 15 h. The mixture was diluted with water (50 mL), the phases separated, the aqueous phase extracted with DCM (3 x 50 mL), the organic phases combined, washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The dark resulting oil was purified by flash chromatography (5% Et_2O in petroleum ether) to yield the desired α-bromo-enone **18** (2.90 g, 51%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (q, *J* = 6.8 Hz, 1H, C*H*=CBr), 2.47 (s, 3H, CH_3CO), 2.04 (d, *J* = 6.8 Hz, 3H, CH_3CH=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 141.1, 129.0, 26.4, 18.4. Data in accordance with literature.[172]

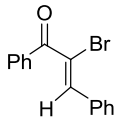
(*Z*)-2-bromo-1,3-diphenylprop-2-en-1-one, 19a

(E)-2-bromo-1,3-diphenylprop-2-en-1-one, 19b

Sodium bromide (1.98 g, 19 mmol) was added portion-wise over 15 min to a stirred solution of Oxone^{TM} (11.81 g, 19 mmol) in DCM (60 mL) and water (15 mL) at 0 °C and was stirred for 40 min. Trans-chalcone (2.00 g, 10 mmol) was then added drop-wise over 15 min, stirred for 90 min allowing to warm to room temperature. The reaction was then cooled to 0 °C and NEt_3 (2.7 mL, 29 mmol) added *drop-wise* over 20 min and stirred for 4 days. The mixture was diluted with water (15 mL), the phases separated, the aqueous phase extracted with DCM (3 x 15 mL), the organic phases combined, washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting oil was purified by flash chromatography (5% Et_2O in petroleum

ether) to yield the desired α-bromo enone **19** as a mixture of diastereoisomers (2.77 g, quantitative, (*Z*):(*E*), 1.2:1).

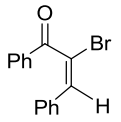
(*Z*)-2-bromo-1,3-diphenylprop-2-en-1-one, 19a



(Z)

ν_{max} (liquid film)/cm^{-1} 1669, 1448, 1226, 689; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.88-7.85 (m, 2H, Ar-*H*), 7.84-7.80 (m, 2H, Ar-*H*), 7.71 (d, *J* = 0.51 Hz, 1H, C=C*H*Ar), 7.64-7.58 (m, 2H, Ar-*H*), 7.54-7.48 (m, 2H, Ar-*H*), 7.48-7.43 (m, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 136.0, 134.3, 134.2, 133.5, 130.0, 128.9, 128.7, 128.6, 128.2, 116.7. Data in accordance with literature.[173]

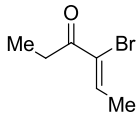
(*E*)-2-bromo-1,3-diphenylprop-2-en-1-one, 19b



(E)

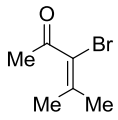
ν_{max} (liquid film)/cm^{-1} 1664, 1596, 1447, 1247, 1066, 691; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.99 (dd, *J* = 8.5, 1.4 Hz, 2H, Ar-*H*), 7.59-7.53 (m, 1H, Ar-*H*), 7.40-7.47 (m, 2H, Ar-*H*), 7.39 (s, 1H, C=C*H*Ar), 7.22-7.14 (m, 5H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 142.8, 136.5, 133.6, 132.7, 130.4, 130.3, 129.7, 128.6, 128.5, 122.6. Data in accordance with literature.[173]

4-Bromohex-4-en-3-one, 20



Sodium bromide (3.10 g, 31 mmol) was added portion-wise over 15 min to a stirred solution of Oxone^{TM} (18.80 g, 31.0 mmol) in $CHCl_3$ (100 mL) and water (25 mL) at 0 °C and was stirred for 40 min. 4-hexen-3-one (1.8 mL, 15 mmol) was then added drop-wise over 15 min, stirred for 7 hrs allowing to warm to room temperature. The reaction was then cooled to 0 °C and NEt_3 (13.0 mL, 92 mmol) added drop-wise over 20 min, stirred at 0 °C for 4 hrs and at 75 °C for 30 hrs. The mixture was diluted with water (75 mL), the phases separated, the aqueous phase extracted with DCM (3 x 30 mL), the organic phases combined, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The brown resulting oil was purified by flash chromatography (10% Et_2O in petroleum ether) to yield the desired α-bromo enone **20** as a thick yellow oil (2.0 g, 75%). A single diastereoisomer was observed but its geometry is unknown. ν_{max} (liquid film)/cm^{-1} 2937, 2850, 1643, 1460, 1325, 1162, 1113, 823; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24 (q, *J* = 6.8 Hz, 1H, BrC=C*H*), 2.80 (q, *J* = 7.2 Hz, 2H, COCH_2), 2.00 (d, *J* = 6.8 Hz, 3H, BrC=CHCH_3), 1.13 (t, *J* = 7.2 Hz, 3H, $COCH_2CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.7, 139,5, 128.5, 32.0, 18.2, 8.6. Data in accordance with literature.[128]

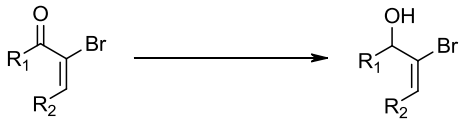
3-Bromo-4-methylpent-3-en-2-one, 21



α-Bromo enone **21** was prepared using literature procedure.[128,174] Sodium bromide (2.52 g, 24.5 mmol) was added portion-wise over 15 min to a stirred solution of Oxone^{TM} (15.05 g, 24.5 mmol) in DCM (50 mL) and water (15 mL) at 0 °C and was stirred for 40 min. 4-methylpent-3-en-2-one (1.4 mL, 12 mmol) was then added drop-wise over 15 min, stirred for 1 hr allowing to warm to room temperature. The mixture was diluted with water (15 mL), the phases separated, the aqueous phase

extracted with DCM (3 x 15 mL), the organic phases combined, washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting brown solid, was then dissolved in MeOH (40 mL) without further purification, KOH (0.65 g, 12 mmol) was added portion-wise over 20 min and stirred for 4 days. Water (75 mL) and Et_2O (75 mL) were added, the phases separated, the aqueous phase extracted with Et_2O (3 x 30 mL), the organic phases combined, washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The brown resulting oil was first purified by flash chromatography (5 % Et_2O in petroleum ether) to yield the desired α-bromo enone **21** as a thick yellow oil (0.70 g, 30%). ν_{max} (liquid film)/cm^{-1} 2937, 2858, 1643, 1472, 1325, 1162, 823; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C=CCH_3CH$_3$), 2.02 (s, 3H, C=CCH$_3$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 145.5, 118.1, 30.4, 27.3, 23.4. Data in accordance with literature.[128,172]

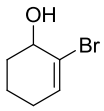
General procedure B: the Luche reduction of α-bromo-enones 13



14 **13**

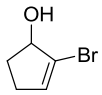
α-Bromo alcohol **13** was prepared using literature procedure.[127] $NaBH_4$ (1.2 equiv) was added portion-wise to a stirred solution of the α-bromo-enone **14** (1.0 equiv) and $CeCl_3.7H_2O$ (1.1 equiv) in MeOH (2 $L.mol^{-1}$) at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and was stirred for a further 1 hr. The reaction mixture was then partitioned between water (2 $L.mol^{-1}$) and Et_2O (2 $L.mol^{-1}$). The aqueous phase was extracted with Et_2O (4 x 1 $L.mol^{-1}$), the organic layers were combined, washed with water (1 $L.mol^{-1}$) and brine (1 $L.mol^{-1}$) then dried ($MgSO_4$) and reduced *in vacuo* to afford the desired α-bromo-alcohol **13**, sometimes without any further purification.

2-Bromocyclohexen-2-ol, 22



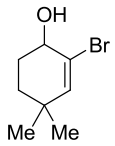
α-Bromo alcohol **22** was prepared using general procedure **B**. Starting with 2-bromocyclohexen-2-one **15** (7.30 g, 42.0 mmol) the desired α-bromo alcohol **22** was obtained (7.20 g, 97%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 3363, 2941, 1640, 1436, 1330, 1162, 1080, 1054, 980, 807, 748; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.22 (t, *J* = 4.2 Hz, 1H, C*H*=CBr), 4.26-4.18 (m, 1H, C*H*OH), 2.20-2.04 (m, 2H, $OCH_2CH_2CH_2$),1.99-1.88 (m, 2H, $OCH_2CH_2CH_2$), 1.78-1.59 (m, 2H, $OCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6, 125.8, 69.9, 31.9, 27.8, 17.6. Data in accordance with literature.[175,160]

2-Bromocyclopenten-2-ol, 23



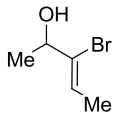
α-Bromo alcohol **23** was prepared using general procedure **B**. Starting with 2-bromocyclopenten-2-one **16** (7.00 g, 44 mmol) the desired α-bromo alcohol **23** was obtained (6.13 g, 86%) as white solid, mp 25-26 °C (*lit.* 26-27°C), after purification by flash chromatography (20% Et_2O in petroleum ether). ν_{max} (liquid film)/cm^{-1} 3363, 2938, 2853, 1619, 1330, 1198, 1156, 1071, 1049, 902, 819; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.06 (t, *J* = 2.4 Hz, 1H, C*H*=CBr); 4.71 (m, 1H, C*H*OH), 2.51-2.43 (m, 1H), 2.41-2.35 (m,1H), 2.32-2.24 (m, 1H), 2.16 (d, *J* = 5.6 Hz, 1H, O*H*), 1.91-1.84 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 124.9, 79.3, 31.9, 30.3. Data in accordance with literature.[176]

2-Bromo-4,4-dimethylcyclohex-2-enol, 24



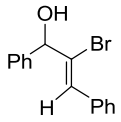
α-Bromo alcohol **24** was prepared using general procedure **B**. Starting with 4,4-dimethyl-2-bromocyclohexen-2-one **17** (1.10 g, 5 mmol) the desired α-bromo alcohol **24** was obtained (0.82 g, 74%) as a white solid, mp 42-44 °C (lit. 49-50 °C), after purification by flash chromatography (10% Et_2O in petroleum ether). ν_{max} (DCM)/cm^{-1} 3384, 2957, 2865, 1462, 1045, 989, 736; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.95 (s, 1H, C*H*=CBr), 4.17 (m, 1H, C*H*OH), 2.13 (d, *J* = 3.2 Hz, 1H, O*H*), 2.09-2.01 (m, 1H), 1.92-1.85 (m, 1H), 1.66-1.59 (m, 1H), 1.50-1.43 (m, 1H), 1.07 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 124.5, 69.7, 36.0, 32.2, 29.0, 28.9, 27.9; HRMS (FI+) Found $(M^{\cdot})^+$ 204.0151, $C_8H_{13}O^{79}Br$ requires 204.0150.

(*Z*)-3-Bromopent-3-en-2-ol, 25



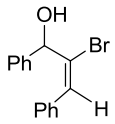
α-Bromo alcohol **25** was prepared using general procedure **B**. Starting with α-bromo enone **20** (1.40 g, 9.0 mmol) the desired α-bromo alcohol **25** was obtained (0.98 g, 69%) as an oil. ν_{max} (liquid film)/cm^{-1} 3356, 2981, 1657, 1371, 1073, 925, 866, 813; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.07 (q, *J* = 6.6 Hz, 1H, C*H*=CBr), 4.32 (m, 1H, C*H*OH), 2.02 (d, *J* = 4.5 Hz, 1H, CHO*H*), 1.77 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CH=C), 1.37 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.32, 22.34, 72.52, 123.69, 133.73; LRMS (CI+) found $(M+H)^+$ 164.0086, $C_5H_9O^{79}Br$ requires 163.9837. Data in accordance with literature.[177,178]

(*Z*)-2-Bromo-1,3-diphenylprop-2-en-1-ol, 26a



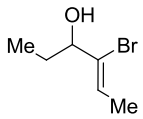
α-Bromo alcohol **26a** was prepared using general procedure **B**. Starting with α-bromo enone **19a** (1.61 g, 6 mmol) the desired α-bromo alcohol **26a** was obtained (1.65 g, quantitative) as a thick oil after purification by flash chromatography (20% Et_2O in petroleum ether). ν_{max} (liquid film)/cm^{-1} 3775, 1493, 1448, 751, 696; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.70-7.63 (m, 2H, Ar-*H*), 7.53-7.47 (m, 2H, Ar-*H*), 7.45-7.31 (m, 6H, Ar-*H*), 7.29 (s, 1H, C=C*H*), 5.48 (d, *J* = 5.6 Hz, 1H, C*H*OH), 2.52 (d, *J* = 5.6 Hz, 1H, CHO*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.0, 129.2, 128.7, 128.6, 128.31, 128.29, 128.2, 126.7, 79.2, Data in accordance with literature.[179]

(*E*)-2-Bromo-1,3-diphenylprop-2-en-1-ol, 26b



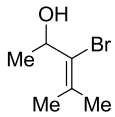
α-Bromo alcohol **26b** was prepared using general procedure **B**. Starting with α-bromo enone **19b** (1.30 g, 5 mmol) the desired α-bromo alcohol **26b** was obtained (0.35 g, 27%) as white needles, mp 81-82 °C (*lit* 78-80 °C) after purification by flash chromatography (20% Et_2O in petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.44 (m, 2H, Ar-*H*), 7.44-7.28 (m, 9H, Ar-*H*, C=C*H*), 5.83 (d, *J* = 8.8 Hz, 1H, C*H*OH), 2.51 (d, *J* = 8.59 Hz, 1H, CHO*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 135.4, 135.1, 131.7, 128.8, 128.5, 128.2, 128.1, 127.9, 126.0, 71.3. Data in accordance with literature.[179]

4-Bromohex-4-en-3-ol, 27



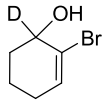
α-Bromo alcohol **27** was prepared using general procedure **B**. Starting with 4-bromohex-4-en-3-ol **20** (1.95 g, 11 mmol) the desired α-bromo alcohol **27** was obtained (1.75 g, 89%) as a yellow oil without further purification. Only one diastereoisomer was obtained but its geometry is unknown. ν_{max} (liquid film)/cm^{-1} 3357, 2966, 2935, 2877, 1656, 1460, 1032, 813; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.06 (q, *J* = 6.6 Hz, 1H, CH=CBr), 3.99 (m, 1H, C*H*OH), 1.87 (m, 1H, O*H*), 1.79 (d, *J* = 6.8 Hz, 3H, BrC=CHCH_3), 1.67 (m, 2H, CH_2CH$_3$), 0.88 (t, *J* = 7.6 Hz, 3H, CH$_2$CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 125.2, 78.1, 28.6, 16.3, 9.8; HRMS (FI+) found $(M^{\cdot})^+$ 177.9989, $C_6H_{11}{}^{79}BrO$ requires 177.9993.

3-Bromo-4-methylpent-3-en-2-ol, 28



α-Bromo alcohol **28** was prepared using general procedure **B**. Starting with 3-bromo-4-methylpent-3-en-2-one **21** (0.65 g, 4 mmol) the desired α-bromo alcohol **28** was obtained (0.39 g, 59%).as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, *J* = 6.3 Hz, 1H, C*H*OH), 1.91 (s, 3H, H_3CC=C), 1.87 (s, 3H, H_3CC=C), 1.32 (d, J = 6.3 Hz, 3H, H_3CCOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 128.1, 67.1, 26.0, 23.3, 21.1; LRMS (FI+) found $(M^{\cdot})^{+}$ 178.02, $C_6H_{11}BrO$ requires 178.00. Data in accordance with literature.[180]

(1-D)-2-Bromocyclohex-2-enol, 46

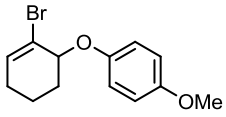


$NaBD_4$ (0.29 g, 7 mmol) was added portion-wise to a stirred solution of 2-bromocyclohexen-2-one **15** (1.00 g, 6 mmol) and $CeCl_3.7H_2O$ (2.34 g, 6 mmol) in dry MeOH (15 mL) at 0 °C. After stirring 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and was stirred for a further 1 hr. The reaction mixture was then partitioned between water (20 mL) and Et_2O (20 mL). The aqueous phase was extracted with Et_2O (4 x 10 mL), the organic layers combined, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and reduced *in vacuo* to afford the desired α-bromo alcohol **46** (1.00 g, 99%, 90% deuterium incorporation) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3362, 2941, 1638, 1174, 1095, 1008, 987, 945; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.22 (t, *J* = 4.2 Hz, 1H, C*H*=CBr), 2.04-1.80 (m, 2H), 1.99-1.88 (m, 2H), 1.78-1.59 (m, 2H, $OCH_2CH_2CH_2$); ^{2}H NMR (77 MHz, $CDCl_3$) δ 4.20 (s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6, 125.7, 69,4 (t, J_{CD}=22.9 Hz), 31.8, 27.8, 17.6; LRMS (CI+) found $(M+H)^{+}$ 177.0075, $C_6H_9DO^{79}Br$ requires 177.9972. Deuterium incorporation was determined by quantitative ^{13}C NMR spectroscopy (**Appendix 2**)

General procedure C: the preparation of vinyl aryl ethers

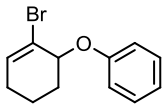
A solution of Ms_2O (1.5 equiv) in dry DCE (0.7 $L.mol^{-1}$) was added drop-wise to a stirred solution of α-bromo alcohol (1.0 equiv) and NEt_3 (1.5 equiv) in dry DCE (0.7 $L.mol^{-1}$) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature over 1 hr. A solution of corresponding phenol (3.0 equiv) and DBU (3.0 equiv) in dry DCE (0.7 $L.mol^{-1}$) was then added drop-wise to the reaction mixture. After stirring for 2 hrs at room temperature and 5 additional hrs at 80 °C, the reaction mixture was washed with water (3 × 1 $L.mol^{-1}$), the aqueous phase extracted with DCM (2 $L.mol^{-1}$), the organic extracts were washed with water (1 $L.mol^{-1}$) and brine (1 $L.mol^{-1}$), dried ($MgSO_4$) and reduced *in vacuo*. The resulting oil was purified by flash chromatography (10% Et_2O in petroleum ether) to afford the expected vinyl aryl ether.

1-(2-Bromocyclohex-2-enyloxy)-4-methoxybenzene, 31



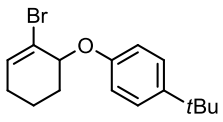
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (1.50 g, 8.5 mmol) was submitted to the reaction conditions and the desired compound **31** was obtained (2.40 g, 88%) a colourless oil. ν_{max} (liquid film)/cm^{-1} 2945, 2833, 1645, 1505, 1395, 1224, 1038, 951, 823, 757; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.00-6.95 (m, 2H, Ar-*H*), 6.88-6.82 (m, 2H, Ar-*H*), 6.38 (dd, *J* = 4.8, 3.0 Hz, 1H, C*H*=CBr), 4.60 (t, *J* = 3.0 Hz, 1H, C-C*H*O), 3.79 (s, 3H, Ar-OCH_3), 2.22-2.09 (m, 3H, CH_2), 1.88-1.62 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 152.1, 134.6, 121.4, 118.6, 114.7, 77.9, 55.7, 29.1, 27.8, 16.6; HRMS (FI+) found $(M^{\cdot})^+$ 282.0250, $C_{13}H_{15}O_2{}^{79}Br$ requires 282.0255.

(2-Bromocyclohex-2-enyloxy)benzene, 33



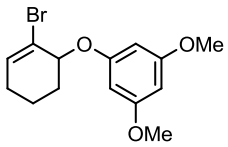
Following general procedure **C**, replacing Ms_2O by MsCl, 2-bromocyclohex-2-enol **22** (1.0 g, 5.65 mmol) was submitted to the reaction conditions and the desired compound **33** was obtained (0.62 g, 43%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 3038, 2944, 1492, 1368, 1229, 1169, 1077, 1058, 975, 753, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H, Ar-*H*), 7.02-6.98 (m, 3H, Ar-*H*), 6.40 (dd, *J* = 5.2, 3.2 Hz, 1H, C*H*=CBr), 4.79 (t, *J* = 2.8 Hz, 1H, C-C*H*O), 2.29-2.06 (m, 3H, CH_2), 1.86-1.82 (m, 2H, CH_2), 1.68-1.63 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 134.8, 129.6, 121.5, 121.0, 116.6, 76.3, 29.0, 27.7, 16.6; HRMS (FI+) found $(M^{\cdot})^+$ 252.0146, $C_{12}H_{13}O^{79}Br$ requires 252.0150. Data in accordance with literature.[161]

1-(2-Bromocyclohex-2-enyloxy)-4-*tert*-butylbenzene, 34



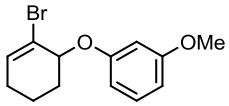
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (1.00 g, 5.65 mmol) was submitted to the reaction conditions and the desired compound **34** was obtained (1.16 g, 66%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 3038, 2958, 1607, 1511, 1364, 1291, 1237, 1190, 1057, 979, 829, 746; ^{1}H NMR 400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.43 (dd, *J* = 5.6, 3.2 Hz, 1H, C*H*=CBr), 4.75 (m, 1H, C-C*H*O), 2.22-2.08 (m, 3H, CH_2), 1.85-1.81 (m, 2H, CH_2), 1.66-1.64 (m, 1H, CH_2), 1.31 (s, 9H, C-(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 144.1, 134.7, 126.3, 121.2, 115.9, 76.2, 34.1, 31.5, 29.0, 27.7, 16.6; HRMS (FI+) found $(M^{\cdot})^+$ 308.0770, $C_{16}H_{21}O^{79}Br$ requires 308.0776.

1-(2-Bromocyclohex-2-enyloxy)-3,5-dimethoxybenzene, 35



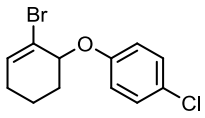
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (1.00 g, 5.65 mmol) was submitted to the reaction conditions and the desired compound **35** was obtained (0.91 g, 51%) as a dense yellowish oil. ν_{max} (liquid film)/cm^{-1} 3000, 2940, 2838, 1593, 1455, 1203, 1150, 1065, 818; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.40 (dd, *J* 3.0, 4.8 Hz, 1H, C*H*=CBr), 6.18 (d, *J* = 2.0 Hz, 2H, Ar-*H*), 6.12 (t, *J* = 2.2 Hz, 1H, Ar-*H*), 4.74 (m, 1H, C-C*H*O), 3.78 (s, 6H, 2 × Ar-OCH_3), 2.21-2.08 (m, 3H, CH_2), 1.87-1.65 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 160.2, 135.3, 121.2, 95.5, 94.0, 76.5, 55.8, 29.4, 28.1, 17.1; HRMS (FI+) found $(M^{\cdot})^{+}$ 312.0366, $C_{14}H_{17}O_3{}^{79}Br$ requires 312.0361.

1-(2-Bromocyclohex-2-enyloxy)-3-methoxybenzene, 36



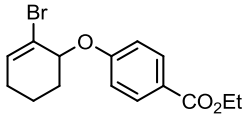
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (1.00 g, 5.65 mmol) was submitted to the reaction conditions and the desired compound **36** was obtained (0.90 g, 63%) as a light yellow oil. ν_{max} (liquid film)/cm^{-1} 2941, 1590, 1592, 1490, 1198, 1147, 1057; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dt, *J* = 8.0, 4.0 Hz, 1H, Ar-*H*), 6.62-6.54 (m, 3H, Ar-*H*), 6.40 (dd, *J* = 4.8, 3.2 Hz, 1H, C*H*=CBr), 4.76 (m, 1H, C-C*H*O), 3.80 (s, 3H, Ar-OCH_3), 2.23-2.08 (m, 3H, CH_2), 1.87-1.65 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.1, 134.8, 129.9, 120.9, 108.3, 107.0, 102.9, 76.7, 55.3, 29.0, 27.7, 16.6; HRMS (FI+) found $(M^{\cdot})^{+}$ 282.0255, $C_{13}H_{15}O_2{}^{79}Br$ requires 282.0255.

1-(2-Bromocyclohex-2-enyloxy)-4-chlorobenzene, 37a



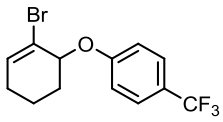
Following general procedure **C**, replacing Ms_2O by MsCl, 2-bromocyclohex-2-enol **22** (0.70 g, 4.0 mmol) was submitted to the reaction conditions and the desired compound **37a** was obtained (0.65 g, 57%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 2945, 2866, 1645, 1488, 1234, 1056, 999, 974, 952, 821; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H, Ar-*H*), 6.96-6.92 (m, 2H, Ar-*H*), 6.40 (dd, *J* = 4.8, 3.2 Hz, 1H, C*H*=CBr), 4.71 (m, 1H, C-C*H*O), 2.28-2.21 (m, 1H, CH_2), 2.15-2.06 (m, 2H, CH_2), 1.88-1.63 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 135.0, 129.4, 126.4, 120.6, 118.0, 76.7, 28.9, 27.7, 16.5; HRMS (FI+) found $(M^{\cdot})^+$ 285.9752, $C_{12}H_{12}O^{79}BrCl$ requires 282.9760.

Ethyl 4-(2-bromocyclohex-2-enyloxy)benzoate, 38



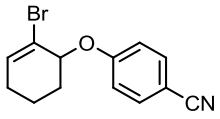
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (0.50 g, 2.8 mmol) was submitted to the reaction conditions and the desired compound **38** was obtained (0.70g, 76%) as a white crystalline solid mp 74-75 °C. ν_{max} (DCM)/cm^{-1} 2935, 2846, 1612, 1474, 1266, 1211, 1188, 1122, 1033, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.00 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 6.43 (dd, *J* = 5.2, 3.2 Hz, 1H, C*H*=CBr), 4.88 (m, 1H, C-C*H*O), 4.35 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 2.31-2.23 (m, 1H, CH_2), 2.16-2.08 (m, 2H, CH_2), 1.94-1.81 (m, 2H, CH_2), 1.72-1.65 (m, 1H, CH_2), 1.39 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.6, 135.2, 131.61, 123.4, 120.6, 115.5, 75.9, 60.6, 29.0, 27.6, 16.6, 14.3; HRMS (FI+) found $(M+H)^+$ 324.0358 $C_{15}H_{17}O_3{}^{79}Br$ requires 324.0361.

1-(2-Bromocyclohex-2-enyloxy)-4-(trifluoromethyl)benzene, 39



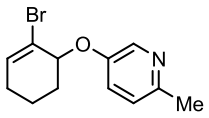
Following general procedure **C**, but using MsCl instead of Ms_2O, 2-bromocyclohex-2-enol **22** (1.00 g, 5.65 mmol) was submitted to the reaction conditions and the desired compound **39** was obtained (0.93 g, 51%) as colorless oil. ν_{max} (liquid film)/cm^{-1} 2948, 1612, 1516, 1328, 1247, 1161, 1111, 1068, 1053, 975, 836; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.6, 2H, Ar-*H*), 7.06 (d, *J* = 8.6, 2H, Ar-*H*), 6.43 (dd, *J* = 5.2, 3.4 Hz, 1H, C*H*=CBr), 4.85 (m, 1H, C-C*H*O), 2.29-2.06 (m, 3H, CH_2), 1.95-1.68 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 135.7, 127.42, 127.39, 126.0, 120.5, 116.4, 76.6, 28.3, 28.0, 17.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ 61.5; HRMS (FI+) found $(M^{\cdot})^{+}$ 320.0033, $C_{13}H_{12}O^{79}BrF_3$ requires 320.0024.

1-(2-Bromocyclohex-2-enyloxy)-4-cyanobenzene, 54



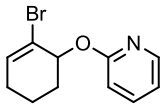
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (0.50 g, 2.8 mmol) was submitted to the reaction conditions and the desired compound **54** was obtained (0.43 g, 55%) as a white crystalline solid mp 84-86 °C. ν_{max} (DCM)/cm^{-1} 2946, 2225, 1644, 1505, 1296, 1250, 1171, 973, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.03 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.44 (dd, *J* = 5.2, 2.8 Hz, 1H, C*H*=CBr), 4.86 (m, 1H, C-C*H*O), 2.31-2.23 (m, 1H, CH_2), 2.16-2.08 (m, 2H, CH_2), 1.99-1.91 (m, 1H, CH_2), 1.84-1.65 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 135.6, 134.1, 119.6, 119.1, 116.5, 104.4, 76.1, 28.9, 27.6, 16.5; HRMS (FI+) found $(M^{\cdot})^{+}$ 277.0108, $C_{13}H_{12}NO^{79}Br$ requires 277.0102.

2-(2-Bromocyclohex-2-enyloxy)pyridine, 40



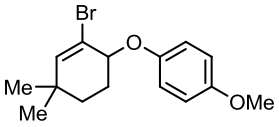
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (0.50 g, 2.8 mmol) was submitted to the reaction conditions and the desired compound **40** was obtained (0.41 g, 54 %) yield as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2942, 1594, 1469, 1431, 1268, 973, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.9 Hz, 1H, Ar-*H*), 7.23 (dd, *J* = 8.6, 2.9 Hz, 1H, Ar-*H*), 7.08 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 6.40 (dd, *J* = 5.2, 3.0 Hz, 1H, C*H*=CBr), 4.70 (t, *J* = 3.4 Hz, 1H, C-C*H*O), 2.50 (s, 3H, CH_2), 2.29-2.19 (m, 1H, CH_2), 2.19-2.04 (m, 2H, CH_2), 1.92-1.60 (m, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 151.5, 139.2, 135.2, 124.6, 123.5, 120.5, 77.6, 29.1, 27.7, 23.5, 16.6, HRMS (FI+) found $(M+H)^+$ 268.0332, $C_{12}H_{15}ON^{79}Br$ requires 268.0332.

2-(2-Bromocyclohex-2-enyloxy)pyridine, 45



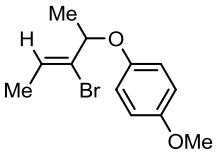
Following general procedure **C**, 2-bromocyclohex-2-enol **22** (1.00 g, 5.7 mmol) was submitted to the reaction conditions and the desired compound **45** was obtained (0.33 g, 23%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2942, 1594, 1469, 1431, 1268, 973, 778; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 8.15 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H, Ar-*H*), 7.77-7.42 (m, 1H, Ar-*H*), 6.94-6.84 (m, 1H, Ar-*H*), 6.81 (td, *J* = 8.4, 0.9 Hz, 1H, Ar-*H*), 6.40 (dd, *J* = 4.9, 3.2 Hz, 1H, C*H*=CBr), 5.79 (t, *J* = 3.9 Hz, 1H, C*H*O), 2.38-1.85 (m, 4 H, CH_2), 1.85-1.60 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.14, 27.81, 29.72, 72.06, 111.82, 116.95, 121.33, 134.84, 138.82, 146.63, 163.00; HRMS (FI+) found $(M+H)^+$ 253.0106, $C_{11}H_{13}ON^{79}Br$ requires 253.0102.

1-(2-Bromo-4,4-dimethylcyclohex-2-enyloxy)-4-methoxybenzene, 41



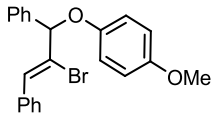
Following general procedure **C**, 2-bromo-4,4-dimethylcyclohex-2-enol **22** (0.80 g, 3.90 mmol) was submitted to the reaction conditions and the desired compound **41** was obtained (0.21 g, 17%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 2957, 2864, 1505, 1464, 1361, 1226, 1038, 986, 824; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.00 6.-95 (m, 2H, Ar-*H*), 6.88-6.82 (m, 2H, Ar-*H*), 6.11 (br. s, 1H, C*H*=CBr), 4.55 (t, *J* = 3.8 Hz, 1H, C-C*H*O), 3.79 (s, 3H, Ar-OCH_3), 2.11-1.62 (m, 3H, CH_2), 1.48-1.38 (m, 1H, CH_2), 1.11 (s, 3H, CCH_3CH$_3$), 1.03 (s, 3H, CCH$_3$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 152.6, 144.4, 120.4, 119.0, 115.0, 77.8, 56.1, 36.4, 31.6, 30.0, 27.3, 26.6; HRMS (FI+) found $(M^{\cdot})^{+}$ 310.0569, $C_{15}H_{19}{}^{79}BrO_3$ requires 310.0568.

(*Z*)-1-(3-Bromopent-3-en-2-yloxy)-4-methoxybenzene, 42



Following general procedure **C**, 3-bromopent-3-en-2-ol **25** (0.80 g, 4.9 mmol) was submitted to the reaction conditions and the desired compound **42** was obtained (0.50 g, 37%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2986, 2934, 1506, 1225, 1039, 891, 823, 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89-6.78 (m, 4H, Ar-*H*), 6.04 (dq, *J* = 6.8, 1.0 Hz, 1H, C*H*=CBr), 4.65 (q, *J* = 6.0 Hz, 1H, C-C*H*O), 3.77 (s, 3H, Ar-OCH_3), 1.73 (d, *J* = 6.5 Hz, 3H, $_3$*H*CC=CBr), 1.54 (d, *J* = 6.2 Hz, 3H, $_3$*H*CC-CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 151.3, 129.5, 125.0, 117.8, 114.4, 79.2, 55.6, 21.0, 16.3; HRMS (CI+) found $(M+NH_4)^{+}$ 288.0594, $C_{12}H_{19}O_2{}^{79}BrN$ requires 288.0599. The (*Z*) geometry of the alkene was confirmed by NOESY experiment (**Appendix 1**).

2-Bromo-3-(4-methoxyphenoxy)prop-1-ene-1,3-diyl)dibenzene, 43



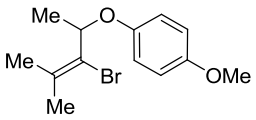
Following general procedure **C**, (*Z*)-2-bromo-1,3-diphenylprop-2-en-1-ol **26a** (0.70 g, 2.4 mmol) was submitted to the reaction conditions and the desired compound **43** was obtained (0.49 g, 51%) as a thick colourless oil. Only one diastereoisomer was obtained but its geometry is unknown. ν_{max} (liquid film)/cm^{-1} 3028, 2833, 1505, 1448, 1221, 1037, 824, 751, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.0 Hz, 2H, Ar-*H*), 7.61-7.55 (m, 2H, Ar-*H*), 7.48-7.31 (m, 6H, Ar-*H*), 7.27 (s, 1H, Ar-*H*), 7.04-6.96 (m, 2H, Ar-*H*), 6.88-6.81 (m, 2H, Ar-*H* and C*H*=CBr), 5.74 (s, 1H, C-C*H*O), 3.78 (s, 3H, Ar-OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 151.5, 138.2, 134.8, 129.5, 129.1, 128.5, 128.4, 128.3, 128.1, 127.4, 125.1, 117.8, 114.5, 86.0, 55.6; HRMS (ESI+) found $(M+Na)^+$ 417.0460, $C_{22}H_{19}O_2{}^{79}BrNa$ requires 417.0461.

1-(3-Bromo-4-methylpent-3-en-2-yloxy)-4-methoxybenzene, 49

1-(3-Bromo-2-methylpent-3-en-2-yloxy)-4-methoxybenzene, 50

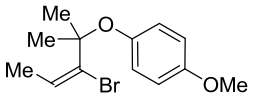
Following general procedure **C**, 3-bromo-4-methylpent-3-en-2-ol **28** (0.30 g, 1.7 mmol) was submitted to the reaction conditions and an inseparable mixture of ether **49** and ether **50** (1:4.2) was obtained (0.25 g, 52%) as a thick colourless oil.

1-(3-Bromo-4-methylpent-3-en-2-yloxy)-4-methoxybenzene, 49



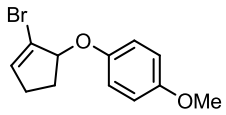
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.88-6.74 (m, 4H, Ar-*H*), 5.03 (q, *J* = 6.1 Hz, 1H, C-C*H*O), 3.77 (s, 3H, Ar-OCH_3), 1.93 (s, 3H, CH_3CH$_3$C=), 1.89 (s, 3H, CH$_3$CH_3C=C), 1.51 (t, *J* = 5.6 Hz, 3H, CH_3CHO); HRMS (FI+) found $(M^{\cdot})^{+}$ 284.0405, $C_{13}H_{17}O_2{}^{79}Br$ requires 284.0412.

1-(3-Bromo-2-methylpent-3-en-2-yloxy)-4-methoxybenzene, 50



Ether **50** was obtained as a single diastereoisomer but its geometry is unknown. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95 (app. d., *J* = 9.2 Hz, 2H, Ar-*H*), 6.77 (app. d., *J* = 9.2 Hz, 2H, Ar-*H*), 5.98 (q, *J* = 6.5 Hz, 1H, C*H*=CBr), 3.77 (s, 3H, Ar-OCH_3), 1.82 (d, *J* = 6.4 Hz, 3H, CH_3CH=CBr), 1.53 (s, 6H, 2CH_3-CO); HRMS (FI+) found $(M^{\cdot})^{+}$ 284.0409, $C_{13}H_{17}O_2{}^{79}Br$ requires 284.0412.

1-(2-Bromocyclopent-2-enyloxy)-4-methoxybenzene, 44



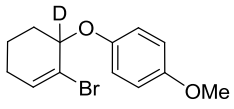
Following general procedure **C**, 2-bromocyclopent-2-enol **23** (0.50 g, 3.08 mmol) was submitted to the reaction conditions and the desired compound **44** was obtained (0.44 g, 53%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 2935, 2833, 1506, 1464, 1354, 1226, 1044, 908, 824; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (m, 2H, Ar-*H*); 6.85 (m, 2H, Ar-*H*), 6.22 (m, 1H, C*H*=CBr), 5.09-5.06 (m, 1H, C-C*H*O), 3.79 (s, 3H, Ar-OCH_3), 2.58-2.53 (m, 1H, CH_2), 2.42-2.31 (m, 2H, CH_2), 2.12-2.06 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 152.1, 136.5, 121.1, 117.3, 114.6, 86.2, 55.7, 30.7, 29.9; HRMS (FI+) found $(M^{\cdot})^{+}$ 268.0098, $C_{12}H_{13}O_2{}^{79}Br$ requires 268.0099.

1-(2-Bromo-(1-D)-cyclohex-2-enyloxy)-4-methoxybenzene, 48

1-(2-Bromo-(3-D)-cyclohex-2-enyloxy)-4-methoxybenzene, 47

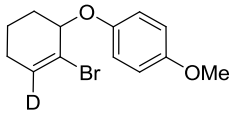
Following general procedure **C**, α-bromo alcohol **46** (1.00 g, 5.6 mmol) was submitted to the reaction conditions an inseparable mixture (1:1) of ethers **47** and **48** (0.97 g, 61%) was obtained as a colourless oil.

1-(2-Bromo-(1-D)-cyclohex-2-enyloxy)-4-methoxybenzene, 48



^{1}H NMR (200 MHz, $CDCl_3$) δ 7.03-6.92 (m, 2H, Ar-*H*), 6.92-6.79 (m, 2H, Ar-*H*), 6.38 (dd, *J* = 4.9, 3.2 Hz, 1H, C*H*=CBr), 3.79 (s, 3H, CH_3O), 2.35-2.03 (m, 3H, CH_2), 1.90-1.60 (m, 3H, CH_2); ^{2}H NMR δ (77 MHz, $CDCl_3$) 4.59 (s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 152.1, 134.6, 121.3, 118.6, 114.6, 77.5 (t, J_{CD} = 22.9 Hz), 55.7, 29.0, 27.8, 16.6, HRMS (CI+) found $(M+H)^{+}$ 283.0312, $C_{13}H_{14}DO_2{}^{79}Br$ requires 283.0317.

1-(2-Bromo-(3-D)-cyclohex-2-enyloxy)-4-methoxybenzene, 47

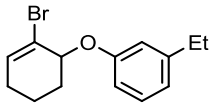


^{1}H NMR (200 MHz, $CDCl_3$) δ 7.03-6.92 (m, 2H, Ar-*H*), 6.92-6.79 (m, 2H, Ar-*H*), 4.60 (t, *J* = 2.9 Hz, 1H, C*H*O), 3.79 (s, 3H, CH_3O), 2.35-2.03 (m, 3H, CH_2), 1.90-1.60 (m, 3H, CH_2); ^{2}H NMR δ (77 MHz, $CDCl_3$) 6.41 (s, 1D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 152.1, 134.3 (t, J_{CD} = 24.8 Hz), 121.3, 118.6, 114.6, 77.9, 55.79, 29.1, 27.7, 16.6; HRMS (CI+) found $(M+H)^+$ 283.0312, $C_{13}H_{14}DO_2{}^{79}Br$ requires 283.0317.

General procedure D: the preparation of vinyl aryl ethers by a Mitsunobu reaction

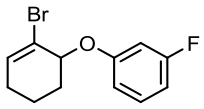
The vinyl aryl ether was prepared using literature procedure.[181] DEAD (1.2 equiv) was added drop-wise to a stirred mixture of α-bromo alcohol (1.0 equiv), corresponding phenol (1.2 equiv) and PPh_3 (1.2 equiv) in dry THF (1 $L.mol^{-1}$) at 0°C over 5 min. It was then stirred at 0°C for 40 min and then allowed to warm up at room temperature and stirred for 15 hrs. The reaction mixture was then concentrated *in vacuo* and directly purified by flash chromatography (5% Et_2O in petroleum ether) to afford the expected vinyl aryl ether.

1-(2-Bromocyclohex-2-enyloxy)-3-ethylbenzene, 51



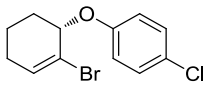
Following general procedure **D**, 2-bromocyclohex-2-enol **22** (0.50 g, 2.8 mmol) was submitted to the reaction conditions and the desired compound **51** was obtained (0.53 g, 60%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 2932, 1582, 1486, 1448, 1256, 1152, 1058, 1003, 971, 695; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26-7.16 (m, 1H, Ar-*H*), 6.90-6.77 (m, 3H, Ar-*H*), 6.40 (dd, *J* = 4.9, 3.2 Hz, 1H, C*H*=CBr), 4.77 (br s, 1H, C-C*H*O), 2.64 (q, *J* = 8.7 Hz, 2H, Ar-C$H_2$$CH_3$), 2.23-2.10 (m, 3H, C$H_2$), 1.86-1.66 (m, 3H, C$H_2$), 1.25 (t, *J* = 7.8 Hz, 3H, Ar-CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 146.0, 134.7, 129.3, 121.1, 121.1, 116.4, 113.4, 76.1, 29.0, 28.8, 27.7, 16.6, 15.4; HRMS (CI+) found $(M+H)^+$ 280.0468, $C_{14}H_{18}O^{79}Br$ requires 280.0463.

1-(2-Bromocyclohex-2-enyloxy)-3-fluorobenzene, 52



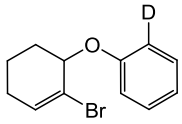
Following general procedure **D**, 2-bromocyclohex-2-enol **22** (1.00 g, 5.7 mmol) was submitted to the reaction conditions and the desired compound **52** was obtained (1.19 g, 78%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 2946, 1607, 1592, 1487, 1277, 1164, 1132, 984; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.27-7.22 (m, 1H, Ar-*H*), 6.79 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar-*H*), 6.74-6.67 (m, 2H, Ar-*H*), 6.41 (dd, *J* = 4.8, 2.8 Hz, 1H, C*H*=CBr), 4.75 (br s, 1H, C-C*H*O), 2.29-2.23 (m, 1H, CH_2), 2.14-2.09 (m, 2H, CH_2), 1.87-1.78 (m, 2H, CH_2), 1.69-1.66 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, $^{1}J_{CF}$ = 244 Hz), 159.3 (d, $^{3}J_{CF}$ = 11 Hz), 130.3, 135.1, 120.4, 112.1 (d, $^{4}J_{CF}$ = 3 Hz), 108.2 (d, $^{2}J_{CF}$ = 21 Hz), 104.1 (d, $^{2}J_{CF}$ = 24 Hz), 76.5, 28.9, 27.6, 16.6; ^{19}F NMR (377MHz , $CDCl_3$) δ -111.7; HRMS (CI+) found $(M+NH_4)^+$ 288.0401, $C_{12}H_{16}ON^{79}BrF$ requires 288.0399.

(*S*)-1-((2-bromocyclohex-2-en-1-yl)oxy)-4-chlorobenzene, 37b



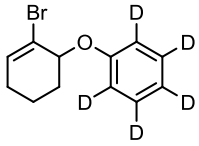
Following general procedure **D**, (1*R*)-2-bromo-2-cyclohexen-1-ol **22b** (1.44 g, 8.1 mmol) was submitted to the reaction conditions and the desired compound **37b** was obtained (1.65 g, 71%, 93% ee) as a colorless oil. The enantiomeric excess was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 2% IPA in *n*-hexane, 1 mL/min, T_{R1}=7.3 min (major), T_{R2}=8.1 min, **Appendix 5**); data as recorded previously for compound **37a**.

(2-Bromocyclohex-2-enyloxy)-(2-D)-benzene, 100



Following general procedure **D**, 2-bromocyclohex-2-enol **22a** (1.11 g, 6.3 mmol) and 2-deuteriophenol[182] (500 mg, 5.26 g) were submitted to the reaction conditions and the desired compound **100** was obtained (710 mg, 53%) as a colorless oil. 95% ^{2}H incorporation determined by quantitative ^{13}C NMR (**Appendix 9**). ν_{max} (liquid film)/cm^{-1} 3038, 2944, 1492, 1368, 1229, 1169, 1077, 1058, 975, 753, 692; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H, Ar-*H*), 7.02-6.98 (m, 2H, Ar-*H*), 6.40 (dd, *J* = 3.2, 5.2 Hz, 1H, C*H*=CBr), 4.79 (t, *J* = 2.8 Hz, 1H, OC*H*), 2.29-2.06 (m, 3H, CH_2), 1.86-1.82 (m, 2H, CH_2), 1.68-1.63 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 134.8, 129.6, 129.4, 121.5, 121.1, 116.7, 116.4 (t, *J* = 16.15 Hz), 76.3, 29.0, 27.8, 16.6; HRMS (CI+) found $(M+H)^+$ 254.0271, $C_{12}H_{13}DO^{79}Br$ requires 254.0290.

(2-Bromocyclohex-2-enyloxy)(D-5)benzene, 98

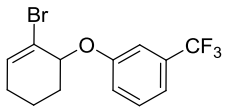


Following general procedure **D**, 2-bromocyclohex-2-enol **22a** (1.06 g, 6.0 mmol) and d_6-phenol (0.50 g, 5.0 mmol) were submitted to the reaction conditions and the desired compound **98** was obtained (0.67 g, 43%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 2932, 1557, 1385, 1178, 974; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (dd, *J* = 5.2, 3.0 Hz, 1H, C*H*=CBr) 4.81-4.74 (m, 1H, OC*H*), 2.32-2.20 (m, 1H, CH_2), 2.20-2.02 (m, 2H, CH_2), 1.92-1.62 (m, 3H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 157.94, 134.78, 129.05(t, J_{CD} = 96 Hz), 121.08, 120.99 (t, J_{CD} = 96 Hz), 116.28 (t, J_{CD} = 96 Hz), 76.34, 29.03, 27.74, 16.64; HRMS (CI+) found $(M+1)^+$ 258.0543, $C_{12}H_9O^{79}BrD_5$ requires 258.0537.

General procedure E: the preparation of vinyl aryl ethers by nucleophilic aromatic substitution

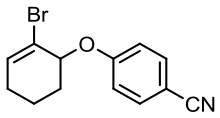
Sodium hydride (60% dispersion in mineral oil, 3 equiv) was added portion-wise to a stirred solution of α-bromo alcohol (1.0 equiv) and halo-benzene derivative (1.2 equiv) in DMF (10 $L.mol^{-1}$) at 0 ºC and allowed to warm up to room temperature and then refluxed for 1 day. Water (1 $L.mol^{-1}$) and Et_2O (1 $L.mol^{-1}$) were then added to the reaction mixture, the phases were separated, the aqueous phase extracted with Et_2O added (1 $L.mol^{-1}$) and the organic phase was washed with water (2 × 1 $L.mol^{-1}$), brine (1 $L.mol^{-1}$), dried ($MgSO_4$) and reduced *in vacuo*. The crude mixture was then purified by flash chromatography (10 to 25% AcOEt in *n*-hexane) to yield the expected vinyl aryl ether.

1-(2-Bromocyclohex-2-enyloxy)-3-(trifluoromethyl)benzene, 53



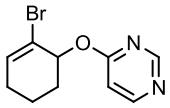
Following general procedure **E**, 2-bromocyclohex-2-enol **22** (0.50 g, 2.8 mmol) and 1-fluoro-4-(trifluoromethyl)benzene (0.56 g, 3.4 mmol) were submitted to the reaction conditions and the desired compound **53** was obtained (0.09 g, 10%) as a colorless oil. ν_{max} (liquid film)/cm^{-1} 2947, 1591, 1450, 1328, 1167, 1127; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.27-7.22 (m, 2H, Ar-*H*), 7.18 (dd, *J* = 8.3, 2.3 Hz, 1H, Ar-*H*), 6.43 (dd, *J* = 5.1, 3.0 Hz, 1H, C*H*=CBr), 4.81 (t, *J* = 3.4 Hz, 1H, OC*H*), 2.34-2.21 (m, 1H, CH_2), 2.20-2.06 (m, 2H, CH_2), 1.95-1.85 (m, 1H, CH_2), 1.85-1.74 (m, 1H, CH_2), 1.74-1.64 (m, 1H, CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ 62.65; ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 135.2, 132.0 (q, J_{CF}=64.8 Hz), 130.1, 123.9 (q, J_{CF}=272.8 Hz), 120.3, 119.8, 118.1 (q, J_{CF}=7.0 Hz), 113.4 (q, J_{CF}=6.8 Hz), 76.6, 29.0, 27.7, 16.6; HRMS (FI+) found $(M^{\cdot})^+$ 320.0031, $C_{13}H_{12}O^{79}BrF_3$ requires 320.0024.

1-(2-Bromocyclohex-2-enyloxy)-4-cyanobenzene, 54



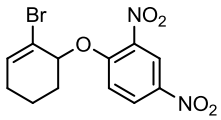
Following general procedure **E**, 2-bromocyclohex-2-enol **22** (0.50 g, 2.8 mmol) and 4-fluorobenzonitrile (0.41 g, 3.4 mmol) were submitted to the reaction conditions and the desired compound **54** was obtained (0.59 g, 75%) as a white crystalline solid mp 84-86 °C. Data as recorded previously for compound **54**.

4-[(2-Bromo-2-cyclohexen-1-yl)oxy]pyrimidine, 55



Following general procedure **E**, 2-bromocyclohex-2-enol **22** (0.27 mg, 1.5 mmol) and 4-chloropyrimidine (0.21 g, 1.8 mmol) were submitted to the reaction conditions and the desired compound **55** was obtained (0.15 g, 49%) as a thick colorless oil. ν_{max} (liquid film)/cm^{-1} 2951, 1602, 1469, 1430, 1265, 778; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H, Ar-*H*), 8.45 (d, *J* = 5.9 Hz, 1H, Ar-*H*), 6.79 (dd, *J* = 5.7, 1.1 Hz, 1H, Ar-*H*), 6.43 (dd, *J* = 4.9, 3.2 Hz, 1H, C*H*=CBr), 5.88 (t, *J* = 3.9 Hz, 1H, OC*H*), 2.32-2.19 (m, 1H, CH_2), 2.19-2.05 (m, 2H, CH_2), 2.06-1.94 (m, 1H, CH_2), 1.82-1.64 (m, 2H, CH_2), ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 158.2, 157.5, 135.7, 119.9, 109.3, 73.0, 29.6, 27.7, 17.1; HRMS (ESI+) found $(M^{+}H)^{+}$ 255.0133, $C_{10}H_{12}{}^{79}BrN_2O$ requires 255.0128.

1-[(2-Bromo-2-cyclohexen-1-yl)oxy]-2,4-dinitrobenzene, 56

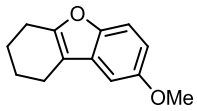


Following general procedure **E**, 2-bromocyclohex-2-enol **22** (0.50 mg, 2.8 mmol) and 1-fluoro-3,5-dinitrobenzene (0.63 g, 3.4 mmol) were submitted to the reaction conditions and the desired compound **56** was obtained (0.55 g, 57%) as a thick colorless oil. ν_{max} (DCM)/cm^{-1} 2951, 1610, 1514, 1336, 1261, 1033, 741; ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.71 (d, *J* = 2.9 Hz, 1H, Ar-*H*), 8.42 (dd, *J* = 9.3, 2.7 Hz, 1H, Ar-*H*), 7.37 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 6.48 (dd, *J* = 5.3, 2.3 Hz, 1H, C*H*=CBr), 5.08 (t, *J* = 3.4, 1H, OC*H*), 2.38-2.25 (m, 1H, CH_2), 2.24-2.08 (m, 2H, CH_2), 2.04-1.94 (m, 1H, CH_2), 1.94-1.80 (m, 1H, CH_2), 1.80-1.67 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 140.4, 140.3, 137.1, 128.6, 121.8, 117.6, 116.0, 79.4, 29.6, 27.6, 16.5; HRMS (FI+) found $(M+H^{\cdot})^{+}$ 341.9868, $C_{12}H_{11}O_5{}^{79}BrN_2$ requires 341.9851.

General procedure F: the preparation of benzo[*b*]furan derivatives 10

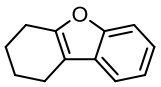
An oven dried flask flushed with N_2 was charged with alkenyl bromide **12** (1.0 equiv), palladium acetate (10 mol %), X-Phos (20 mol%), K_2CO_3 (2.0 equiv), DMA (0.18 mol.L^{-1}) and heated at 80 °C. The reaction mixture was cooled to room temperature, diluted in Et_2O (5 mL) and washed with brine (3 × 5 mL). The solvent was dried ($MgSO_4$) and removed *in vacuo*. The resultant crude product was dissolved in DCM (10 mL) and a catalytic amount of *p*TSA (10 mol %) was added. The reaction mixture was stirred at room temperature for 2 hrs, washed with water (5 mL) and brine (5 mL), the solvent was removed *in vacuo* and the crude purified by flash chromatography (1% Et_2O in petroleum ether) to yield the desired benzo[*b*]furan **10**.

8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 58



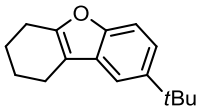
Following general procedure **F**, alkenyl bromide **31** (100 mg, 0.35 mmol) was submitted to the reaction conditions and the desired benzofuran **58** was obtained (62 mg, 86%) as a colorless oil after 75 min. ν_{max} (liquid film)/cm^{-1} 2935, 2846, 1613, 1471, 1266, 1211, 1188, 1122, 1033, 907, 822, 799; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.8, 0.8 Hz, 1H, Ar-*H*), 6.88 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.80 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 3.86 (s, 3H, Ar-OCH_3), 2.76-2.69 (m, 2H, CH_2), 2.64-2.57 (m, 2H, CH_2), 1.99-1.79 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.9, 149.1, 129.3, 112.9, 111.0, 110.9, 101.5, 55.9, 23.5, 22.9, 22.6, 20.4; HRMS (FI+) found $(M^{\cdot})^+$ 202.0997, $C_{13}H_{14}O_2$ requires 202.0994. Data in accordance with literature.[183]

1,2,3,4-Tetrahydrodibenzo[*b,d*]furan, 59



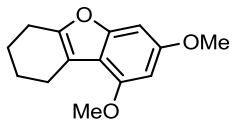
Following general procedure **F**, alkenyl bromide **33** (114 mg, 0.45 mmol) was submitted to the reaction conditions and the desired benzofuran **59** was obtained (61 mg, 79%) as a yellow oil after 90 min. ν_{max} (liquid film)/cm^{-1} 2934, 2846, 1640, 1453, 1190, 1122, 743; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H, Ar-*H*), 7.23-7.19 (m, 2H, Ar-*H*), 2.79-2.75 (m, 2H, C*H*$_2$), 2.67-2.63 (m, 2H, C*H*$_2$), 1.99-1.94 (m, 2H, C*H*$_2$), 1.95-1.90 (m, 2H, C*H*$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.2, 154.0, 128.8, 122.9, 122.0, 118.3, 112.8, 110.7, 23.4, 22.9, 22.6, 20.45; HRMS (CI+) found $(M^{\cdot})^{+}$ 172.0885, $C_{12}H_{12}O_2$ requires 172.0888. Data in accordance with literature.[184]

8-*tert*-Butyl-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 60



Following general procedure **F**, alkenyl bromide **34** (114 mg, 0.37 mmol) was submitted to the reaction conditions and the desired benzofuran **60** was obtained (75 mg, 89%) as a thick colorless oil after 90 min. ν_{max} (liquid film)/cm^{-1} 2954, 1463, 1262, 1194, 1124; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.34 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar-*H*), 7.27 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar-*H*), 2.76-2.74 (m, 2H, C*H*$_2$), 2.65-2.58 (m, 2H, C*H*$_2$), 1.96-1.94 (m, 2H, C*H*$_2$), 1.88-1.86 (m, 2H, C*H*$_2$), 1.40 (s, 9H, Ar-C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 152.8, 145.5, 128.8, 121.0, 114.9, 113.2, 110.4, 35.1, 32.3, 23.8, 23.4, 23.1, 20.9; HRMS (FI+) found $(M^{\cdot})^{+}$ 228.1512, $C_{16}H_{20}O$ requires 228.1514. Data in accordance with literature.[185]

7,9-Dimethoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 61



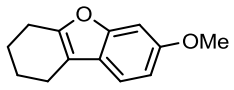
Following general procedure **F**, alkenyl bromide **35** (110 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **61** was obtained (74 mg, 91%) after 1 hr as a light yellow solid, mp 44-45 °C. ν_{max} (DCM)/cm^{-1} 2935, 2849, 1601, 1504, 1454, 1314, 1287, 1210, 1145, 1106, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 6.27 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 3.85 (s, 3H, Ar-OC*H*$_3$), 3.83 (s, 3H, Ar-OC*H*$_3$), 2.81-2.76 (m, 2H, C*H*$_2$), 2.69-2.64 (m, 2H, C*H*$_2$), 1.95-1.74 (m, 4H, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 155.8, 154.0, 150.9, 112.2, 112.0, 93.5, 88.3, 55.7, 55.3, 23.3, 22.9, 22.8, 22.1; HRMS (FI+) found $(M^{\cdot})^{+}$ 232.1099, $C_{14}H_{16}O_3$ requires 232.1099.

7-Methoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 62

9-Methoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 63

Following general procedure **F**, alkenyl bromide **36** (100 mg, 0.35 mmol) was submitted to the reaction conditions and an inseparable mixture of regioisomers **62** and **63** (5.6:1) was obtained (62 mg, 87%) as an oil after 90 min.

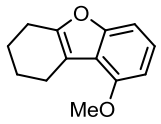
7-Methoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 62



ν_{max} (liquid film)/cm^{-1} 2935, 2845, 1624, 1590, 1494, 1439, 1360, 1331, 1299, 1213, 1192, 1143, 1033, 936, 872, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.98 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 6.83 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar-*H*), 3.85 (s, 3H, Ar-OC*H*$_3$), 2.73-2.71 (m, 2H, C*H*$_2$), 2.90-2.58 (m, 2H, C*H*$_2$), 1.96-1.90 (m, 2H, C*H*$_2$), 1.87-1.82 (m, 2H, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0,

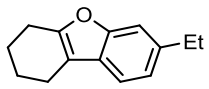
155.1, 152.9, 122.3, 118.3, 112.5, 110.3, 96.1, 55.7, 23.3, 22.9, 22.6, 20.4; HRMS (FI+) found $(M^{\cdot})^{+}$ 202.1006, $C_{13}H_{14}O_2$ requires 202.0994. Data in accordance with literature.[186]

9-Methoxy-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 63



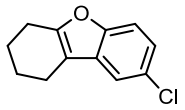
ν_{max} (liquid film)/cm^{-1} 2935, 2845, 1624, 1590, 1494, 1439, 1360, 1331, 1299, 1213, 1192, 1143, 1033, 936, 872, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 16.0, 8.0 Hz, 1H, Ar-*H*), 7.03 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.61 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 3.89 (s, 3H, Ar-OCH_3), 2.84-2.81 (m, 2H, CH_2), 2.73-2.71 (m, 2H, CH_2), 1.96-1.90 (m, 2H, CH_2), 1.87-1.82 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.47, 154.1, 152.1, 123.4, 118.3, 112.4, 104.2, 103.0, 55.4, 23.3, 22.9, 22.7, 22.2; HRMS (FI+) found (M.)+ 202.0923, $C_{13}H_{14}O_2$ requires 202.0994. Data in accordance with literature.[187]

7-Ethyl-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 64



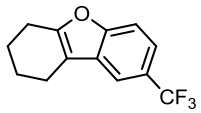
Following general procedure **F**, alkenyl bromide **51** (101 mg, 0.36 mmol) was submitted to the reaction conditions and the desired compound **64** was obtained (64 mg, 89%) in mixture with a trace amount of isomer 7-ethyl-1,2,3,4-tetrahydrodibenzo[*b,d*]furan **65** as a colorless oil after 90 min. ν_{max} (liquid film)/cm^{-1} 2962, 1769, 1489, 1457, 1261, 1117; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.27-7.24 (m, 1H, Ar-*H*), 7.06 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar-*H*), 2.77 (q, *J* = 7.7 Hz, 2H, CCH_2CH$_3$), 2.76-2.72 (m, 2H, CH_2), 2.65-2.61 (tt, *J* = 4.5, 2.0 Hz, 2H, CH_2), 1.99-1.90 (m, 2H, CH_2), 1.90-1.80 (m, 2H, CH_2), 1.29 (t, *J* = 7.6 Hz, 3H, CCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 153.4, 139.7, 126.5, 122.2, 117.9, 112.6, 109.8, 29.1, 23.4, 22.9, 22.7, 20.5, 16.2, HRMS (CI+) found $(M+H)^{+}$ 201.1275, $C_{14}H_{17}O$ requires 201.1279.

8-chloro-2,3,4,4a-Tetrahydrodibenzo[*b,d*]furan, 67



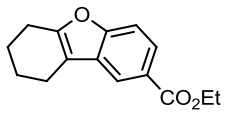
Following general procedure **F**, alkenyl bromide **37a** (102 mg, 0.35 mmol was submitted to the reaction conditions and the desired compound **67** was obtained (54 mg, 75%) after 2 hrs as a white solid, mp 64-66 °C. ν_{max} (NaBr)/cm^{-1} 2938, 1439, 1190, 1122, 857, 800; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.31 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 7.14 (dd, *J* = 8.4, 2.2Hz, 1H, Ar-*H*), 2.76-2.73 (m, 2H, C*H*$_2$), 2.617-2.57 (m, 2H, C*H*$_2$), 1.97-1.92 (m, 2H, C*H*$_2$), 1.87-1.84 (m, 2H, C*H*$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.7, 152.6, 130.2, 127.6, 122.9, 118.1, 112.7, 111.6, 23.4, 22.7, 22.5, 20.3; HRMS (FI+) found (M.)$^+$ 206.0491, $C_{12}H_{11}ClO$ requires 206.0498. Data in accordance with literature.[185]

8-(Trifluoromethyl)-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 72



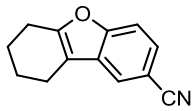
Following general procedure **F**, alkenyl bromide **39** (114 mg, 0.35 mmol) was submitted to the reaction conditions and heated at 80 °C for 90 min. The isomerisation step was carried out at 40 ˚C overnight and the desired compound **72** was obtained (24 mg, 29%) as a white solid mp 48-50 °C. ν_{max} (DCM)/cm^{-1} 2982, 2941, 1721, 1694, 1618, 1379, 1190; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H, Ar-*H*), 7.47 (s, 1H, Ar-*H*), 7.46 (s, 1H, Ar-*H*), 2.79-2.76 (m, 2H, C*H*$_2$), 2.67-2.63 (m, 2H, C*H*$_2$), 1.99-1.94 (m, 2H, C*H*$_2$), 1.90-1.85 (m, 2H, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.7, 128.9, 120.1, 120.0, 115.99, 115.95, 113.1, 110.9, 23.3, 22.7, 22.4, 20.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -60.6; HRMS (FI+) found (M$^{\cdot}$)$^+$ 240.0769, $C_{13}H_{11}F_3O$ requires 240.0762.

Ethyl 6,7,8,9-tetrahydrodibenzo[*b,d*]furan-2-carboxylate, 66



Following general procedure **F**, alkenyl bromide **38** (57 mg, 0.18 mmol), palladium acetate (5 mol %), X-Phos-**x** (10 mol %), K_2CO_3 (1.1 equiv), were submitted to the reaction conditions and the desired compound **66** was obtained (28 mg, 70%) as a dense yellow oil after 90 min. ν_{max} (liquid film)/cm^{-1} 2936, 1715, 1456, 1301, 1264, 1238, 1189, 1088, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 1.0 Hz, 1H, Ar-*H*), 7.95 (dd, *J* = 4.2, 1.0 Hz, 1H, Ar-*H*), 7.41 (d, *J* = 4.2 Hz, 1H, Ar-*H*), 4.41 (q, *J* = 3.2 Hz, 2H, $CO_2CH_2CH_3$), 2.77-2.73 (m, 2H, CH_2), 2.68-2.64 (m, 2H, CH_2), 1.99-1.93 (m, 2H, CH_2), 1.88-1.84 (m, 2H, CH_2), 1.43 (t, *J* = 3.2 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 157.0, 155.5, 128.8, 124.8, 124.7, 120.7, 113.4, 110.4, 60.8, 23.88, 22.80, 22.4, 20.3, 14.4; HRMS (CI+) found $(M+H)^+$ 245.1192, $C_{15}H_{17}O_3$ requires 245.1178.

6,7,8,9-Tetrahydrodibenzo[*b,d*]furan-2-carbonitrile, 73



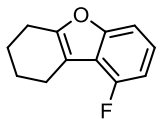
Following general procedure **F**, alkenyl bromide **54** (97 mg, 0.35 mmol), palladium acetate (5 mol %), X-Phos (10 mol %), K_2CO_3 (1.1 equiv), were submitted to the reaction conditions and heated at 80 °C for 1 hr. The isomerisation step was carried out at 40 ˚C overnight and the desired compound **73** was obtained (25 mg, 36%) as a white solid, mp 95-96 °C. ν_{max} (DCM)/cm^{-1} 2933, 2847, 2349, 2338, 2215, 1638, 1461, 1443, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (m, 1H, Ar-*H*), 7.53-7.43 (m, 2H, Ar-*H*), 2.80-2.74 (m, 2H, CH_2), 2.67-2.60 (m, 2H, CH_2), 2.02-1.94 (m, 2H, CH_2), 1.89-1.83 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 156.1, 129.5, 126.8, 123.2, 119.8, 112.9, 111.7, 105.8, 23.3, 22.6, 22.3, 20.1; HRMS (FI+) found $(M^{\cdot})^+$ 197.0844, $C_{13}H_{11}NO$ requires 197.0841.

9-Fluoro-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 68

7-Fluoro-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 69

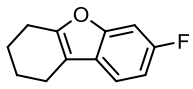
Following general procedure **F**, alkenyl bromide **52** (95 mg, 0.38 mmol) was submitted to the reaction conditions and an inseparable mixture of regioisomers **68** and **69** (4:1) was obtained (50 mg, 75%) as a slightly yellow oil after 90 min.

9-Fluoro-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 68



ν_{max} (liquid film)/cm^{-1} 2937, 1592, 1494, 1437, 1268, 1247, 1208, 1123, 1028, 776, 731;^{1}H NMR (400 MHz , $CDCl_3$) δ 7.19 (dd, *J* = 8.0, 0.8 Hz, 1H, Ar-*H*), 7.10 (td, *J* = 8.0, 5.3 Hz, 1H, Ar-*H*), 6.85 (ddd, *J* = 9.9, 8.1, 0.8 Hz, 1H, Ar-*H*), 2.80 (tt, *J* = 6.0, 2.0 Hz, 2H, CH_2), 2.73 (tt, *J* = 6.1, 2.0 Hz, 2H, CH_2), 1.99-1.90 (m, 2H, CH_2), 1.89-1.81 (m, 2H, CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ -124.2; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.23 (J_{CF} = 11.5 Hz), 156.21 (J_{CF} = 247.3 Hz), 153.7, 123.1 (J_{CF} = 7.7 Hz), 117.5 (J_{CF} = 21.0 Hz), 111.0, 108.0 (J_{CF} = 19.2 Hz), 107.0 (J_{CF} = 4.8 Hz), 23.3, 22.7, 22.6, 21.5; HRMS (FI+) found (M)+˙190.0799, $C_{12}H_{12}OF$ requires 190.0794.

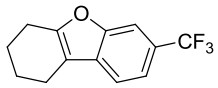
7-Fluoro-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 69



ν_{max} (liquid film)/cm^{-1} 2937, 1592, 1494, 1437, 1268, 1247, 1208, 1123, 1028, 776, 731; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.30 (dd, *J* = 8.6, 5.6 Hz, 1H, Ar-*H*), 7.13 (dd, *J* = 9.2, 2.0 Hz, 1H, Ar-*H*), 6.95 (ddd, *J* = 9.7, 8.4, 2.4 Hz, 1H, Ar-*H*), 2.80 (tt, *J* = 6.0, 2.0 Hz, 2H, CH_2), 2.73 (tt, *J* = 6.1, 2.0 Hz, 2H, CH_2), 1.99-1.90 (m, 2H, CH_2), 1.89-1.81 (m, 2H, CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ -119.6; ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1(J_{CF} = 239.8 Hz), 154.6 (J_{CF} = 3.8 Hz), 154.1 (J_{CF} = 13.4 Hz), 125.1, 118.2(J_{CF} =

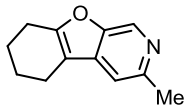
9.5 Hz), 112.6, 109.9 (J_{CF} = 23.9 Hz), 98.7 (J_{CF} = 26.8 Hz), 23.3, 22.8, 22.5, 20.3; HRMS (FI+) found (M) 190.0799, $C_{12}H_{12}OF$ requires 190.0794. Data in accordance with literature.[184]

7-(Trifluoromethyl)-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 70



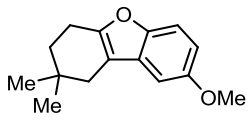
Following general procedure **F**, alkenyl bromide **53** (100 mg, 0.31 mmol) was submitted to the reaction conditions and benzofuran **70** was obtained (21 mg, 44%) as a slightly yellow oil after 1 hr. ν_{max} (liquid film)/cm^{-1} 2940, 1328, 1159, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H, Ar-*H*) 7.51-7.42 (m, 2H, Ar-*H*) 2.84-2.73 (m, 2H, C*H*$_2$) 2.69- 2.58 (m, 2H, C*H*$_2$) 2.02-1.93 (m, 2H, C*H*$_2$) 1.92-1.83 (m, 2H, C*H*$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ -60.70; ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 153.4, 131.9, 125.1 (J_{CF} = 32.4 Hz), 124.8 (J_{CF} = 272.2 Hz), 119.16 (J = 3.8 Hz), 118.6, 113.0, 108.1 (J_{CF} = 4.8 Hz), 23.5, 22.7, 22.5, 20.3; HRMS (FI+) found (M) 240.0748, $C_{13}H_{11}OF_3$ requires 240.0762.

3-Methyl-5,6,7,8-tetrahydrobenzofuro[2,3-c]pyridine, 74



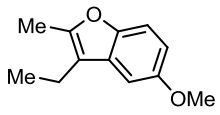
Following general procedure **F**, alkenyl bromide **40** (110 mg, 0.41 mmol) was submitted to the reaction conditions in absence of ligand X-Phos and the desired benzofuran **74** was obtained (50 mg, 66%) as a colorless oil after 24 hrs. ν_{max} (liquid film)/cm^{-1} 3385, 2931, 1606, 1462, 1179; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H, Ar-*H*), 7.18 (s, 1H, Ar-*H*), 2.76 (t, J = 6.3 Hz, 2H, C*H*$_2$), 2.62 (s, 3H, Ar-C*H*$_3$), 2.58 (t, J = 6.1 Hz, 2H, C*H*$_2$), 1.95 (m, 2H, C*H*$_2$), 1.85 (m, 2H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 150.3, 150.2, 136.1, 131.3, 112.4, 112.2, 24.0, 23.5, 22.5, 22.3, 20.2; HRMS (CI+) found $(M+1)^+$ 188.1073, $C_{12}H_{14}ON$ requires 188.1075.

8-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 75



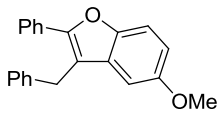
Following general procedure **F**, alkenyl bromide **41** (109 mg, 0.35 mmol) was submitted to the reaction conditions and the desired benzofuran **75** was obtained (58 mg, 73%) as a light yellow oil after 8 hrs. ν_{max} (liquid film)/cm^{-1} 2952, 1615, 1475, 1458, 1217, 1201, 1164, 1034, 804; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 1H, Ar-*H*), δ 6.88 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.80 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar-*H*), 3.85 (s, 3H, Ar-OCH_3), 2.75-2.72 (m, 2H, CH_2), 2.41 (t, *J* = 2.0 Hz, 2H, CH_2), 1.70 (t, *J* = 6.4 Hz, 2H, CH_2), 1.07 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 153.8, 149.6, 129.6, 112.3, 111.0, 110.9, 101.4, 55.9, 35.8, 34.3, 30.1, 27.9, 21.0; HRMS (FI+) found $(M^{\cdot})^{+}$ 130.1308, $C_{15}H_{18}O_2$ requires 130.1307.

3-Ethyl-5-methoxy-2-methylbenzofuran, 76



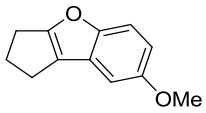
Following general procedure **F**, alkenyl bromide **42** (105 mg, 0.39 mmol) was submitted to the reaction conditions and the desired compound **76** was obtained (50 mg, 68%) as a light yellow oil after 5 hrs. ν_{max} (liquid film)/cm^{-1} 2964, 2931, 1612, 1476, 1213, 1177, 1082, 802; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 6.93 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.80 (dd, *J* = 8.7, 2.6 Hz, 1H, Ar-*H*), 3.86 (s, 3H, Ar-OCH_3), 2.61 (q, *J* = 7.6 Hz, 2H, CCH_2CH_3), 2.38 (s, 3H, OCCH_3), 1.24 (t, *J* = 7.5 Hz, 3H, CCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 150.9, 148.8, 130.1, 116.1, 110.8 (2 C), 101.9, 55.9, 16.9, 14.3, 11.9; HRMS (CI+) found $(M+H)^{+}$ 191.1078, $C_{12}H_{15}O_2$ requires 191.1072.

3-Benzyl-5-methoxy-2-phenylbenzofuran, 77



Following general procedure **F**, alkenyl bromide **43** (138 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **77** was obtained (50 mg, 45%) after 17 hrs as a light yellow solid mp 71-73 °C. ν_{max} (DCM)/cm^{-1} 2933, 2832, 1602, 1476, 1211, 1028, 766, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.70 (m, 2H, Ar-*H*), 7.48-7.40 (m, 3H, Ar-*H*), 7.40-7.36 (m, 1H, Ar-*H*), 7.30-7.20 (m, 5H, Ar-*H*), 6.91 (dd, *J* = 8.8, 2.5 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 4.30 (s, 2H, CC*H*$_2$-Ar), 3.77 (s, 3H, OCC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 152.9, 149.0, 139.2, 131.0, 130.9, 128.7, 128.6, 128.3, 128.1, 126.8, 126.3, 113.8, 112.9, 111.5, 102.4, 55.8, 30.1; HRMS (FI+) found (M.)$^+$ 314.1306, $C_{22}H_{18}O_2$ requires 314.1307.

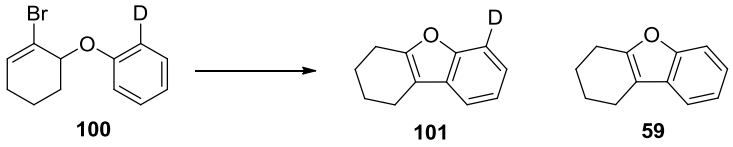
7-Methoxy-2,3-dihydro-1H-benzo[b]cyclopenta[d]furan, 78



Following general procedure **F**, alkenyl bromide **44** (94 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **78** was obtained as an inseparable mixture with its *exo*-alkene isomer (6 mg, 7%, calculated by ^{1}H NMR) after 1 hr as a white solid; ν_{max} (DCM)/cm^{-1} 2967, 2815, 1605, 1473, 1183, 795; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 6.89 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 6.78 (dd, *J* = 8.8, 2.5 Hz, 1H, Ar-*H*), 3.85 (s, 3H, OCC*H*$_3$), 2.89-2.82 (m, 2H, C*H*$_2$), 2.77-2.71 (m, 2H, C*H*$_2$), 2.56 (m, 2H, C*H*$_2$); HRMS (CI+) found (M+H)$^+$ 189.0913, $C_{12}H_{13}O_2$ requires 189.0916. Data in accordance with literature[187].

6-D-1,2,3,4-Tetrahydrodibenzo[*b,d*]furan, 101

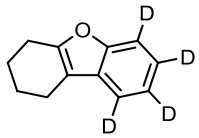
1,2,3,4-Tetrahydrodibenzo[*b,d*]furan, 59



100 **101** **59**

Following general procedure **F**, alkenyl bromide **100** (102 mg, 0.40 mmol) was submitted to the reaction conditions and a mixture of compounds **101** and **59** (4:1) was obtained (52 mg, 76%) after 3 hrs as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2934, 2846, 1640, 1453, 1190, 1122, 743; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.40 (m, 1.2H, Ar-*H*), 7.23-7.19 (m, 2H, Ar-*H*), 2.79-2.75 (m, 2H, C*H*$_2$), 2.67-2.63 (m, 2H, C*H*$_2$), 1.99-1.94 (m, 2H, C*H*$_2$), 1.90-1.95 (m, 2H, C*H*$_2$); data as reported previously for benzofuran **59.**

(6,7,8,9-D$_4$)-1,2,3,4-tetrahydrodibenzo[*b,d*]furan, 102

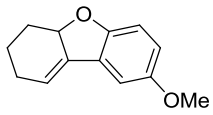


Following general procedure **F**, alkenyl bromide **98** (90 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **102** was obtained (46 mg, 75%) as a colourless oil after 90 min. ν_{max} (liquid film)/cm^{-1} 2934, 2850, 1646, 1453, 1190, 1122, 743; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.79-2.75 (m, 2H, C*H*$_2$), 2.67-2.63 (m, 2H, C*H*$_2$), 1.99-1.94 (m, 2H, C*H*$_2$), 1.90-1.95 (m, 2H, C*H*$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.2, 154.0, 128.8, 122.9, 122.0, 118.3, 112.8, 110.7, 23.4, 22.9, 22.6, 20.45; HRMS (CI+) found $(M^{\cdot})^{+}$ 176.0885, $C_{12}H_8D_4O_2$ requires 176.1139.

General procedure G: preparation of dihydrodibenzo[*b*,*d*]furan derivatives

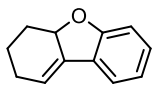
An oven dried flask flushed with N_2 was charged with alkenyl bromide (1 equiv), palladium acetate (10 mol %), X-Phos (20 mol%), K_2CO_3 (2 equiv), DMA (0.18 mol.L^{-1}) and heated at 80 °C. The reaction mixture was cooled to room temperature, diluted in Et_2O (5 mL) and washed brine (3 × 5 mL). The solvent was dried ($MgSO_4$) and removed *in vacuo* and the crude purified by flash chromatography (1% Et_2O in petroleum ether) to yield the desired tetrahydrodibenzo[*b,d*]furan.

8-Methoxy-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 57



Following general procedure **G**, alkenyl bromide **31** (100 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **57** was obtained (63 mg, 89%) after 75 min. ν_{max} (liquid film)/cm^{-1} 3450, 2941, 1710, 1480, 1031; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.91-6.82 (m, 1H, Ar-*H*), 6.79-6.64 (m, 2H, Ar-*H*), 5.82 (q, *J* = 3.5 Hz, 1H, C*H*=C-Ar), 5.08-4.90 (m, 1H, C-C*H*O), 3.78 (s, 3H, OCH_3), 2.50-2.21 (m, 2H, CH_2), 2.10-1.89 (m, 1H, CH_2), 1.84-1.48 (m, 2H, CH_2), 1.44-1.03 (m, 1H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.8, 154.4, 139.0, 127.0, 116.8, 115.2, 110.3, 105.7, 83.2, 56.0, 27.6, 24.6, 19.5; HRMS (FI+) found $(M^{\cdot})^+$ 202.0995, $C_{13}H_{14}O_2$ requires 202.0994.

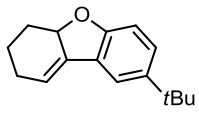
2,3,4,4a-Tetrahydrodibenzo[*b,d*]furan, 79



Following general procedure **G**, alkenyl bromide **33** (89 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **79** was obtained (48 mg, 80%) after 90 min as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2945, 1608, 1461, 1223, 1204, 1019, 702; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.5, 0.9 Hz, 1H, Ar-*H*), 7.16 (td, *J* = 7.8, 1.3 Hz, 1H, Ar-*H*), 6.90 (td, *J* = 7.5, 0.8 Hz, 1H, Ar-*H*),

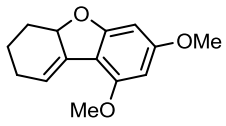
6.86 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 5.84 (q, *J* = 3.4 Hz, 1H, C*H*=C-Ar), 5.16-4.91 (m, 1H, C-C*H*O), 2.46-2.37 (m, 1H, CH_2), 2.35-2.27 (m, 2H, CH_2), 2.06-1.97 (m, 1H, CH_2), 1.81-1.64 (m, 2H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.5, 138.6, 129.3, 126.5, 120.8, 120.4, 116.7, 110.3, 82.9, 27.6, 24.6, 19.5; HRMS (CI+) found $(M+H)^+$ 173.0974, $C_{12}H_{13}O$ requires 173.0966.

8-tert-butyl-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 80



Following general procedure **G**, alkenyl bromide **34** (108 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **80** was obtained (74 mg, 92%) after 90 min as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2954, 1482, 1210, 1014, 817; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.1 Hz, 1H, Ar-*H*), 7.20 (dd, *J* = 8.4, 2.2 Hz, 1H, Ar-*H*), 6.78 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 5.84 (q, *J* = 3.4 Hz, 1H, C*H*=C-Ar), 5.02 (br. s, 1H, C-C*H*O), 2.45-2.36 (m, 1H, CH_2), 2.31 (td, *J* = 7.4, 3.6 Hz, 2H, CH_2), 1.98 (br. s, 1H, CH_2), 1.74-1.60 (m, 2H, CH_2), 1.32 (s, 9H, Ar-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 143.8, 138.9, 126.5, 125.9, 117.1, 116.1, 109.5, 83.1, 34.3, 31.7, 27.6, 24.6, 19.6; HRMS (FI+) found $(M^{\cdot})^+$ 228.1513, $C_{16}H_{20}O$ requires 228.1514.

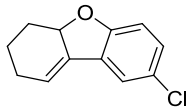
7,9-dimethoxy-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 81



Following general procedure **G**, alkenyl bromide **35** (110 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **81** was obtained (76 mg, 93%) as a thick oil after 1 hr. ν_{max} (liquid film)/cm^{-1} 2938, 1619, 1213, 1147, 1103; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 1.8, 1.9 Hz, 2H, Ar-*H*), 5.93-5.83 (m, 1H, C*H*=C-Ar), 5.12-4.87 (m, 1H, C-C*H*O), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.35-2.17 (m, 3H, CH_2), 2.01-1.90 (m, 1H, CH_2), 1.62 (s, 2H, CH_2); ^{13}C NMR (125

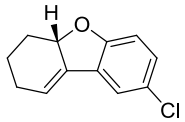
MHz, $CDCl_3$) δ 163.8, 162.3, 156.4, 136.5, 115.2, 107.4, 91.6, 88.7, 84.0, 55.6, 55.3, 27.7, 24.6, 19.5; HRMS (ESI+) found $(M+H)^+$ 233.1172, $C_{14}H_{17}O_3$ requires 233.1172.

8-Chloro-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 82a



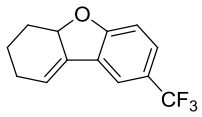
Following general procedure **G**, alkenyl bromide **37a** (100 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **82a** was obtained (63 mg, 88%) after 75 min as a white crystalline solid mp 61-62 °C. ν_{max} (liquid film)/cm^{-1} 2947, 2866, 1608, 1459, 1187, 1152, 1117, 1011, 812, 686.; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.08 (dd, *J* = 8.6, 2.4 Hz, 1H, Ar-*H*), 6.74 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 5.84 (dd, *J* = 7.4, 3.8 Hz, 1H, C*H*=C-Ar), 5.08-4.94 (m, 1H, C-C*H*O), 2.43-2.39 (m, 1H, CH_2), 2.34-2.25 (m, 2H, CH_2), 2.03-1.94 (m, 1H, CH_2), 1.71-1.61 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 130.0, 128.8, 128.1, 125.6, 120.4, 118.3, 111.1, 83.6, 27.5, 24.6, 19.3; HRMS (CI+) found $(M+H)^+$ 206.0495, $C_{12}H_{11}O$ requires 206.0498.

(*S*)-8-chloro-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 82b



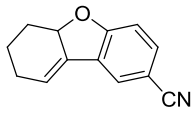
Following general procedure **G**, alkenyl bromide **37b** (100 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **82b** was obtained (63 mg, 88%, 92% ee) after 24 hrs at 50 °C as a white crystalline solid mp 61-62 °C. The enantiomeric excess was determined by chiral HPLC analysis (ee measured on an AS-H HPLC column, 0.5% IPA in *n*-hexane, 1.5 mL/min, T_{R1}=4.1 min, T_{R2}=4.8 min (major), **Appendix 6**); Data as described above for compound **82a**.

8-(Trifluoromethyl)-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 83



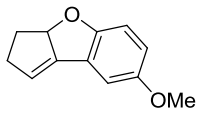
Following general procedure **G**, alkenyl bromide **39** (112 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **83** was obtained (66 mg, 79%) after 90 min as a white crystalline solid mp 51-53°C. ν_{max} (liquid film)/cm^{-1} 1327, 1316, 1262, 113, 1009, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H, Ar-*H*), 7.41 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 6.87 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 5.93 (q, *J* = 3.5 Hz, 1H, C*H*=C-Ar), 5.12-5.02 (m, 1H, C-C*H*O), 2.46-2.39 (m, 1H, CH_2), 2.36-2.30 (m, 2H, CH_2), 2.07-1.98 (m, 1H, CH_2), 1.76-1.64 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 137.0, 127.1, 126.7 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 271.8 Hz), 123.2 (q, *J* = 32.4 Hz),118.9, 117.8 (q, *J* = 3.8 Hz), 110.2, 84.0, 27.4, 24.6, 19.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.25; HRMS (FI) found (M.) 240.0763, $C_{13}H_{11}O_3F$ requires 240.0762.

5a,6,7,8-Tetrahydrodibenzo[*b,d*]furan-2-carbonitrile, 84



Following general procedure **G**, alkenyl bromide **54** (97 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **84** was obtained (51 mg, 74%) after 90 min as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3463, 2941, 1714, 1245; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.47 (dd, *J* = 8.3, 1.8 Hz, 1H, Ar-*H*), 6.89 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 5.98 (q, *J* = 3.5 Hz, 1H, C*H*=C-Ar), 5.10 (d, *J* = 4.2 Hz, 1H, C-C*H*O), 2.49-2.41 (m, 1H, CH_2), 2.40-2.30 (m, 2H, CH_2), 2.12-1.99 (m, 1H, CH_2), 1.81-1.62 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.5, 134.5, 128.3, 124.8, 120.6, 119.9, 111.6, 104.4, 84.7, 27.7, 25.0, 19.6; HRMS (FI+) found $(M^{\cdot})^{+}$ 197.0836, $C_{13}H_{11}NO$ requires 197.0841.

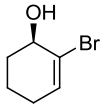
7-Methoxy-3,3a-dihydro-2H-benzo[*d*]cyclopenta[*b*]furan, 85



Following general procedure **G**, alkenyl bromide **44** (94 mg, 0.35 mmol) was submitted to the reaction conditions and the desired compound **85** was obtained (33 mg, 50%) after 75 min as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3427, 2935, 1710, 1468, 1028; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05-6.84 (m, 3H, Ar-*H*), 6.29 (m, 1H, C*H*=C-Ar), 5.21-5.05 (m, 1H, C-C*H*O), 3.85 (s, 3H, CH_2), 2.71-2.36 (m, 3H, CH_2), 2.25-2.04 (m, 1H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.8, 152.7, 142.5, 125.5, 123.9, 113.2, 112.3, 105.7, 90.2, 56.0, 31.9, 28.0; HRMS (FI+) found $(M^{\cdot})^{+}$ 188.0845, $C_{12}H_{12}O_2$ requires 188.0837.

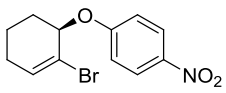
The functionalisation of the alkenyl bromide intermediate

(1*R*)-2-bromo-2-cyclohexen-1-ol, 22b



Alcohol **22b** was prepared using literature procedure.[135] Under an Ar atmosphere, (*S*)-(-)-α,α-diphenylprolinol (0.145 g, 0.57 mmol) and trimethyl borate (0.08 mL, 0.69 mmol) were dissolved in dry THF (10 mL). The mixture was stirred for 1 hr at room temperature before borane-diethylaniline complex (1.02 mL, 5.71 mmol) was added and the resulting solution cooled to -10 ºC. A solution of enone **15** (1.00 g, 5.71 mmol) in dry THF (10 mL) was added over 45 min. After complete conversion of the ketone, quenching was carried out by addition of 1 M aqueous HCl solution (10 mL) and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and reduced *in vacuo*. The crude was then purified by flash chromatography (10 to 30% AcOEt in *n*-hexane) to yield alcohol **22b** (869 mg, 86% yield, 97% ee) as a colourless oil. The enantiomeric excess was determined both by optical rotation and chiral HPLC analysis (ee measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1 mL/min, T_{R1}=8.8 min (major), T_{R2}=10.0 min, **Appendix 4**); optical rotation: $[\alpha]_D$ (methanol, 1 mgl/mL)= 96.0. Data in accordance with literature.[188]

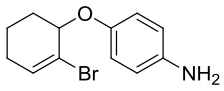
(*R*)-1-(2-Bromocyclohex-2-enyloxy)-4-nitrobenzene, 92b



NaH (60% dispersion in mineral oil, 339 mg, 8.47 mmol) was added portion-wise to a solution of alcohol **22b** (0.500 g, 2.82 mmol, 97% ee) and 4-fluoro-1-nitrobenzene (0.45 mL, 4.24 mmol) in dry DMF (12 mL) at room temperature under N_2 atmosphere. The mixture was stirred at room temperature for 1 hr and refluxed overnight. Water (10 mL) was then added to the mixture, the resulting solution extracted with Et_2O (3 × 7 mL) and the organic phase was washed with brine (3 × 5 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography (5% Et_2O in

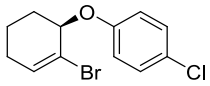
petroleum ether) yielded the desired ether **92b** (790 mg, 94%, 97% ee) as a thick yellow oil. The enantiomeric excess was determined by chiral HPLC analysis (measured on an AS-H HPLC column, 4% IPA in *n*-hexane, 1 mL/min, T_{R1}=14.3 min, T_{R2}=17.1 min (major)); ν_{max} (liquid film)/cm^{-1} 3362, 2929, 1622, 1508, 1224, 729; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.22 (m, 2H, Ar-*H*), 7.04 (m, 2H, Ar-*H*), 6.46 (dd, *J* = 3.2, 5.0 Hz, 1H, C*H*=CBr), 4.91 (t, *J* = 3.8 Hz, 1H, OC*H*), 2.29-2.03 (m, 3H, CH_2), 2.03-1.87 (m, 1H, CH_2), 1.87-1.62 (m, 2H, CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.1; 141.7, 135.8, 126.0, 119.4, 115.7, 29.7, 29.0, 27.6, 16.6; HRMS (CI+) found $(M+1)^+$ 298.0067, $C_{14}H_{15}N$ requires 298.0079.

4-(2-Bromocyclohex-2-enyloxy)aniline, 93



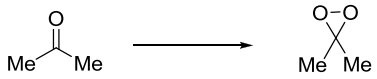
Aniline **93** was prepared using literature procedure.[137] (*R*)-1-(2-Bromocyclohex-2-enyloxy)-4-nitrobenzene **92b** (200 mg, 0.67 mmol) and anhydrous $SnCl_2$ (636 mg, 3.35 mmol) were stirred in EtOH at 70 °C overnight under N_2 atmosphere. The reaction mixture was then allowed to cool down to room temperature and poured onto 20 mL of ice. After the addition of a saturated solution of $NaHCO_3$ to attain a basic pH, the solution was extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography (50% Et_2O in petroleum ether) yielded the desired aniline **93** (124 mg, 69%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2928, 1622, 1508, 1224,824; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.65 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.39-6.31 (m, 1H, C*H*=CBr), 4.54 (br. s, 1H, OC*H*), 3.48 (br. s, 2H, NH_2), 2.29-2.17 (m, 1H, CH_2), 2.17 (m, 2H, CH_2), 1.86-1.70 (m, 2H, CH_2), 1.70-1.57 (m, 1H, CH_2); HR*MS* (ESI) found $(M+1)^+$ 268.0332, $C_{12}H_{15}NOBr$ requires 268.0332.

(*R*)-1-(2-Bromocyclohex-2-enyloxy)-4-chlorobenzene, 37c



The chlorobenzene derivative **37c** was prepared using literature procedure.[138] A solution of $CuCl_2$ (121 mg, 0.90 mmol) and *t*-butylnitrite (0.13 mL, 1.12 mmol) in dry acetonitrile (10 mL) was warmed to 65 °C. A solution of aniline **93b** (200 mg, 0.75 mmol) in dry acetonitrile (5 mL) was added to the solution over 5 min and the resulting mixture was then stirred at 65 °C for 4 hrs. The cooled reaction mixture was poured into a solution of HCl (120 mL, 3N) and extracted with Et_2O (3 × 50 mL). The organic phase was washed with a 1 N aqueous HCl solution (50 mL), dried ($MgSO_4$) and reduced *in vacuo*. Purification by flash chromatography (5% Et_2O in petroleum ether) yielded the desired chlorobenzene derivative **37c** (186 mg, 86%, 97% ee). The enantiomeric excess was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 2% IPA in *n*-hexane, 1 mL/min, T_{R1}=7.3 min, T_{R2}=8.1 min (major)); data as recorded previously for compound **37a**.

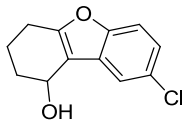
Dimethyldioxirane



Dimethyldioxirane was prepared using literature procedure.[189] A one-liter three-necked flask was equipped with a mechanical stirrer and an addition flask connected *via* a rubber tube to a two-necked receiving flask. The two-necked flask was cooled at -78 °C using a dry ice and ethanol bath. The reaction flask was charged with water (65 mL), acetone (50 mL) and $NaHCO_3$ (14.5 g) and cooled at 5-10 °C using an ice and water bath. While vigorously stirring, Oxone^{TM} was added in 5 portions, allowing the reaction to stir for three minutes between every portion. Three minutes after the last addition, a moderate vacuum (80-100 Torrs) was applied, the ice bath removed and the solution of DMDO in acetone distilled in the cooled (-78 °C) receiving flask. This solution was dried with K_2CO_3, filtered and stored at -20 °C over 4 Å molecular sieves. The solution was later titrated three times as follow.

Methyl-*p*-tolylsulfide (20 µL, 0.14 mmol) was dissolved in acetone (1 mL) and the solution of DMDO in acetone (1 mL) added slowly at room temperature. After 1 hr, the reaction mixture was removed in vacuo and the presence of methyl-*p*-tolylsulfinyl in mixture with methyl-*p*-tolylsulfide (1:1.8) confirmed by ^{1}H NMR spectroscopy. The process was repeated three times to obtain the concentration of DMDO in acetone (0.06 M).

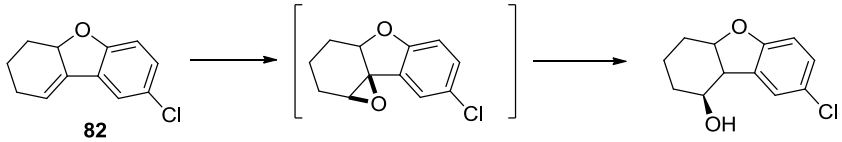
8-Chloro-1,2,3,4-tetrahydrodibenzo[*b,d*]furan-1-ol 89



Dimethyldioxirane (2.2 mL of a 0.06M solution in acetone[189]) was added to a solution of *exo*-alkene **82** (25 mg, 0.12 mmol) in acetone (0.5 mL) at room temperature. After 1 hr, the acetone was removed *in vacuo* and the residue was purified by flash chromatography (25% Et_2O in petroleum ether) to afford the desired alcohol **89** (18 mg, 67%) as white needles; mp 143-144 °C. ν_{max} (DCM)/cm^{-1} 3314, 2940, 1058, 937, 874, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.33 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 7.19 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar-*H*), 5.02 (br. s, 1H, C*H*OH), 2.86-2.64 (m, 2H, CH_2), 2.15-1.99 (m, 2H, CH_2), 1.97-1.89 (m, 2H, CH_2), 1.69 (br. s, 1H, CHO*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.9, 128.6, 128.2, 123.5, 118.9, 115.4, 111.9, 63.3, 32.5, 23.3, 18.7; HRMS (ESI+) found $(M+Na)^+$ 245.0336, $C_{12}H_{11}O_2ClNa$ requires 245.0340.

Jacobsen epoxidation:

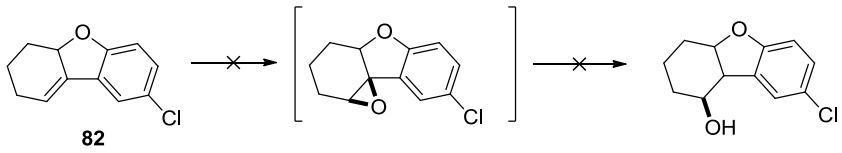
(1*S*)-8-chloro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1-ol, 89b



Alcohol **89b** was prepared using literature procedure.[133] A solution of *exo*-alkene **82** (100 mg, 0.48 mmol), (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III)

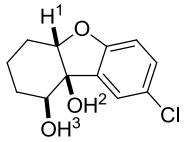
chloride, Jacobsen's catalyst (9 mg, 0.02 mmol) and 4-phenylpyridine *N*-oxide (17 mg, 0.10 mmol) in DCM (1 mL) was cooled to 0 ºC. A buffered aqueous solution of sodium hypochlorite (1.30 mL, 0.73 mmol) (pH = 11.3) was pre-cooled to 0 ºC and added to the solution before the reaction was stirred at 0 ºC for 20 hrs. The 2 phases were then separated, the aqueous phase extracted with DCM (3 × 5 mL) and the combined organic phase were washed with water (3 × 2 mL), brine (2 mL), dried over $MgSO_4$ and reduced *in vacuo*. Purification by flash chromatography (0 to 40% AcOEt in *n*-hexane) yielded alcohol **89b** (21 mg, 20%, 18.3% ee). The enantiomeric excess was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1.5 mL/min, T_{R1}=14.7 min T_{R2}=18.5 min, (major)); data as recorded previously for compound **89**.

Shi epoxidation



Preparation of alcohol **89b** was attempted using literature procedure.[131] To a solution of *exo*-alkene **82** (50 mg, 0.24 mmol) and Shi diketal catalyst (9 mg, 0.04 mmol) in DME (4.5 mL) were added buffer (0.2M K_2CO_3-AcOH in $4x10^{-4}$ M aqueous EDTA, 4.50 mL) and tetrabutylammonium hydrogen sulfate (3 mg, 10 µmol) with stirring. The mixture was cooled to -10 ºC, oxone (268 mg, 0.44 mmol) in EDTA (2.5 mL, 1 µmol) and K_2CO_3 (134 mg, 0.97 mmol) in EDTA (2.5 mL, 1 µmol) were added drop-wise separately and simultaneously *via* syringe pump over a period of 2 hrs and then stirred for 2 hrs, allowing the reaction to warm up to room temperature. The mixture was extracted with DCM (3 × 5 mL), the combined organic phase was washed with brine (5 mL), dried ($MgSO_4$) and reduced *in vacuo*. Unreacted *exo*-alkene **82** was recovered.

8-Chloro-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan-1,9b(1H)-diol, 86

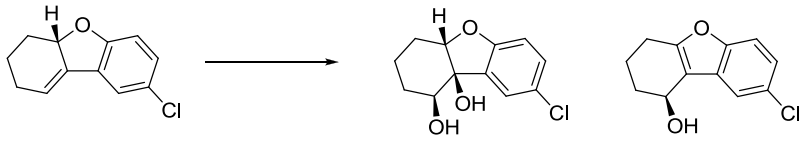


Diol **86** was prepared using literature procedure.[130] Osmium tetroxide (6 µL, 0.02 mmol) in a solution of acetone (3 mL) was added to a solution of *exo*-cyclic alkene **82** (100 mg, 0.48 mmol) and NMO (60. mg, 0.51 mmol) in *t*-butanol (0.15 mL) and water (0.15 mL) at room temperature and stirred for 15 hrs. The reaction mixture was washed with a saturated aqueous solution of sodium thiosulfate (6 mL) and the aqueous phase extracted with DCM (3 × 2 mL). The organic phase was dried ($MgSO_4$), the solvent removed *in vacuo* and the reaction crude mixture purified by flash chromatography (30 to 50% AcOEt in *n*-hexane) to yield diol **86** (106 mg, 91 % yield) as white needles mp 94-95 °C. ν_{max} (DCM)/cm^{-1} 3431, 3353, 2944, 1464, 1062, 823, 681; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 7.20 (dd, *J* = 8.5, 2.3 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 5.47 (s, 1H, Ar-CO*H*), 4.85 (d, *J* = 5.6 Hz, 1H, C*H*OH), 4.46 (t, *J* = 4.9 Hz, 1H, *H*CO-Ar), 3.53 (ddd, *J* = 9.1, 5.6, 3.4 Hz, 1H, CHO*H*), 1.90-1.79 (m, 1H, CH_2), 1.67 (dq, *J* = 14.6, 4.9 Hz, 1H, CH_2), 1.64-1.56 (m, 1H, CH_2), 1.57-1.49 (m, 1H, CH_2), 1.44-1.38 (m, 1H, CH_2), 1.42-1.33 (m, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.3, 136.0, 128.5, 124.1, 123.7, 111.5, 88.7, 78.3, 70.8, 27.8, 25.5, 17.6; HRMS (FI+) found $(M.)^+$ 240.0561, $C_{12}H_{13}O_3Cl$ requires 240.0553. The *cis* geometry of the three protons H_1, H_2 and H_3 of diol **86** was determined by nOe spectroscopy (**Appendix 3**).

Sharpless dihydroxylation with commercial AD-mix α:

(1*S*,4a*S*,9b*S*)-8-chloro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1,9b-diol, 86b

(1*S*)-8-chloro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1-ol, 89b

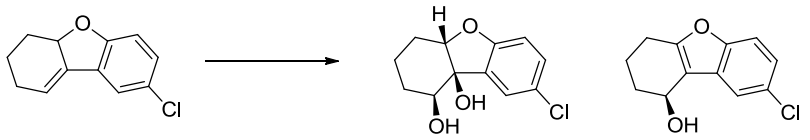


Diol **86b** was prepared using literature procedure.[190] Methanesulfonamide (23 mg, 0.24 mmol) was added to a heterogeneous solution of AD-mix-α (678 mg) in *t*-butanol (1.2 mL) and water (1.2 mL). The mixture was cooled to 0 ºC and *exo*-alkene **82b** (50 mg, 0.24 mmol, 93% ee) added at once. The mixture was vigorously stirred at 0 ºC for 8 hrs and then at room temperature for 72 hrs. An aqueous solution of sodium thiosulfate was added to the mixture, stirred for 30 min and then extracted with DCM (3 × 2 mL). The combined organic phases were washed with brine (3 mL), dried over $MgSO_4$ and reduced *in vacuo*. The crude reaction was purified by flash chromatography (15 to 35% AcOEt in *n*-hexane) to yield diol **86b** (23 mg, 39%, 99% ee) as white needles and alcohol **89b** (7 mg, 13%, 56% ee) as white needles. Diol **86b**, $[\alpha]_D$ (MeOH, 1 mgl/mL) = 40 °; the enantiomeric excess was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1.5 mL/min, T_{R1}=16.6 min (major), T_{R2}=18.8 min, **Appendix 7**). The enantiomeric excess of hydroxybenzofuran **89b** was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1.5 mL/min, T_{R1}=16.4 min, T_{R2}=20.3 min (major)); data as recorded previously for diol **86b** and alcohol **89b**.

Sharpless dihydroxylation with *in situ* preparation of the AD-mix α:

(1*S*,4a*S*,9b*S*)-8-chloro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1,9b-diol, 86b

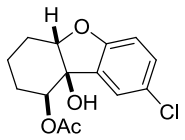
(1*S*)-8-chloro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1-ol, 89b



(rac)-**82** **86b** **89b**

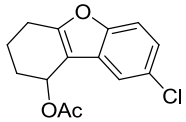
Diol **86b** was prepared using literature procedure.[190] Potassium osmate dihydrate (1.0 mg, 3 μmol), $(DHQ)_2PHAL$ (7.5 mg, 10 μmol), potassium hexacyanoferrate(III) (478 mg, 1.45 mmol) and potassium carbonate (201 mg, 1.45 mmol) were stirred in *t*-butanol (1.2 mL) and water (1.2 mL) at 0 ºC for 30 min. Methanesulfonamide (23 mg, 0.24 mmol) was added, the mixture was cooled to 0 ºC and *exo*-alkene **82** (50 mg, 0.24 mmol) was added at once. The mixture was vigorously stirred at 0 ºC for 8 hrs and then at room temperature for 72 hrs. An aqueous solution of sodium thiosulfate was added the mixture, stirred for 30 min and then extracted with DCM (3 × 2 mL). The combined organic phases were washed with brine (3 mL), dried over $MgSO_4$ and reduced *in vacuo*. The crude reaction was purified by flash chromatography (15 to 35% AcOEt in *n*-hexane) to yield diol **86b** (25 mg, 43%, 12% ee) as white needles and alcohol **89b** (4 mg, 7%, 21% ee) as white needles. The enantiomeric excess of diol **86b** was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1.5 mL/min, T_{R1}=16.8 min (major), T_{R2}=19.1 min); the enantiomeric excess of hydroxybenzofuran **89b** was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1.5 mL/min, T_{R1}=16.4 min, T_{R2}=20.3 min (major)); data as recorded previously for diol **86b** and alcohol **89b**.

8-Chloro-9b-hydroxy-1,2,3,4,4a,9b-hexahydrodibenzo[*b,d*]furan-1-yl acetate, 87



Acetate **87** was prepared using literature procedure.[191] To a solution of diol **82a** (50 mg, 0.21 mmol) in DCM (1.0 mL) were added acetic anhydride (0.03 mL, 0.36 mmol), pyridine (0.50 mL, 6.18 mmol) and DMAP (3 mg, 0.02 mmol) at room temperature and the reaction was stirred overnight. A saturated aqueous solution of $KHCO_3$ (3 mL) was added and the phases separated. The aqueous phase was extracted with DCM (3 × 1 mL), the organic fractions were combined, washed with brine (3 mL), dried ($MgSO_4$) and reduced *in vacuo*. The brown residue was then purified by flash chromatography (30 to 50% AcOEt in *n*-hexane) to yield the expected acetate **87** (50 mg, 85%) as a thick oil. ν_{max} (liquid film)/cm^{-1} 3423, 2989, 2870, 1718, 1464, 1233, 1187, 1025; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.19 (m, 2H, Ar-*H*), 6.78 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 5.10 (dd, *J* = 7.7, 3.5 Hz, 1H, *H*COAc), 4.62 (t, *J* = 5.4 Hz, 1H, *H*CO-Ar), 2.89 (s, 1H, Ar-CO*H*), 2.15 (s, 3H, OC(O)CH_3), 1.97-2.11 (m, 1H, CH_2), 1.74 (m, 2H, CH_2), 1.66 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 157.7, 132.5, 130.2, 125.9, 123.1, 112.4, 88.4, 78.7, 74.4, 26.3, 25.3, 21.2, 16.9; HRMS (FI+) found $(M.)^+$ 282.0672, $C_{14}H_{15}O_4Cl$ requires 282.0659.

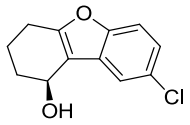
8-Chloro-1,2,3,4-tetrahydrodibenzo[*b,d*]furan-1-yl acetate, 88



Acetate **88** was prepared using literature procedure.[192] Trifluoroacetic anhydride (0.04 mL, 0.29 mmol) and pyridine (0.07 mL, 0.87 mmol) were added to a stirred solution of acetate **87** (41 mg, 0.15 mmol) in DCM (1.0 mL) at 0 ºC and stirred for 2 hrs at that temperature. The mixture was then hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (2 mL) and extracted with DCM (3 × 2 mL). The combined organic phases were washed with brine (2 mL), dried over $MgSO_4$ and reduced *in vacuo* to yield acetate **88** (35 mg, 91%) as an oil. ν_{max} (liquid film)/cm^{-1} 1719, 1464, 1223, 975; ^{1}H NMR (400

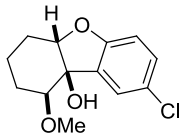
MHz , $CDCl_3$) δ 7.51 (d, *J* = 2.2 Hz, 1H, Ar-*H*), 7.32 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 7.18 (dd, *J* = 8.6, 2.2 Hz,1H, Ar-*H*), 6.13 (t, *J* = 3.3 Hz, 1H, C*H*OAc), 2.89-2.78 (m, 1H, CH_2), 2.66-2.77 (m, 1H, CH_2), 2.18-2.10 (m, 1H, CH_2), 2.10 (s, 3H, OC(O)CH_3), 2.09-1.91 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 159.1, 152.9, 128.5, 128.2, 123.8, 119.3, 112.3, 111.9, 64.6, 29.0, 23.3, 21.3, 18.6; HRMS (FI+) found $(M.)^+$ 264.0560, $C_{14}H_{13}O_3Cl$ requires 264.0553.

(1*S*)-8-chloro-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1-ol, 89b



Acetate **88b** (20 mg, 0.08 mmol) and K_2CO_3 (33 mg, 0.24 mmol) were stirred in MeOH (1 mL) at room temperature for 3 hrs. A saturated aqueous solution of $KHCO_3$ (2 mL) was added and the solution was extracted with Et_2O (3 × 1 mL), the organic fractions were combined, washed with brine (1 mL), dried ($MgSO_4$) and reduced *in vacuo*. Alcohol **89b** was obtained (16 mg, 95%, 88% ee) without further purification. $[\alpha]_D$ (MeOH, 1 mgl/mL) = 66 °, the enantiomeric excess was determined by chiral HPLC analysis (measured on an OJ-H HPLC column, 4% IPA in *n*-hexane, 1 mL/min, T_{R1}=16.1 min, T_{R2}=19.6 min (major), **Appendix 8**). Data as recorded previously for alcohol **89a**.

2-Chloro-9-methoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-9a-ol, 91

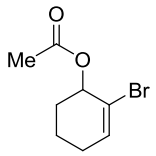


Dimethyldioxirane (3.0 mL of a 0.06M solution in acetone[189]) was added to a solution of alkene **82a** (21 mg, 0.10 mmol) in acetone (0.5 mL) in the presence of 4 Å molecular sieves at room temperature. After 1 hr, the acetone was removed *in vacuo* and the crude material was dissolved in MeOH (1 mL) and MeONa (20 mg, 0.37 mmol) was added at room temperature. The mixture was stirred at room temperature for 1 hr then at 60 °C for 16 hrs. The solvent was removed *in vacuo* and the crude

reaction purified by flash chromatography (10 to 30% Et_2O in petroleum ether) to afford benzofuran **91** (15 mg, 60%) as a colourless oil and alcohol **89a** (3 mg, 11%) as white needles. ν_{max} (liquid film)/cm^{-1} 3541, 2942, 1470, 1098; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar-*H*), 7.20 (d, *J* = 2.3 Hz, 1H, Ar-*H*), 6.82 (d, *J* = 8.6 Hz, 1H, Ar-*H*), 4.79 (t, *J* = 6.5 Hz, 1H, C*H*-O-Ar), 4.25 (t, *J* = 3.5 Hz, 1H, C*H*-OCH_3), 3.11 (s, 3H, CH-OC*H*$_3$), 3.02 (br. s, 1H, C-O*H*), 2.22-2.18 (m, 1H, C*H*$_2$), 1.93-1.84 (m, 1H, C*H*$_2$), 1.74-1.68 (m, 1H, C*H*$_2$), 1.48-1.38 (m, 3H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 130.9, 127.1, 125.4, 124.9, 112.1, 85.2, 84.7, 68.8, 50.7, 28.0, 27.2, 15.0; HRMS (FI+) found $(M.)^+$ 254.0705, $C_{13}H_{15}O_3Cl$ requires 254.0710.

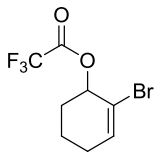
The preparation of Tsuji-Trost substrates 144

2-Bromocyclohex-2-enyl acetate, 145



Acetate **145** was prepared using literature procedure.[191] To a solution of 2-bromo-2-cyclohexen-1-ol **22a** (2.700 g, 15.3 mmol) in DCM (40 mL) were added pyridine (37.0 mL), DMAP (0.186 g, 1.5 mmol) and acetic anhydride (2.16 mL, 22.9 mmol) at room temperature. The mixture was stirred overnight at room temperature then quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL). The 2 layers were separated and the combined organic phases were washed with a 10 % aqueous solution of copper sulphate (3 × 15 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$ and reduced *in vacuo*. The crude was then filtrated through silica (25% AcOEt in *n*-hexane), reduced *in vacuo* to afford 2-bromo-2-cyclohexen-1-yl acetate **145** (3.224 g, 96 %) as a colourless oil. ^{1}H NMR δ (400 MHz, $CDCl_3$) 6.36 (dd, *J* = 4.8, 3.3 Hz, 1H, C*H*=CBr), 5.42 (t, *J* = 4.3 Hz, 1H, C-C*H*O), 2.25-2.14 (m, 1H, C=CH-CH_1H_2), 2.12 (s, 3H, C(O)CH_3), 2.11-2.02 (m, 1H, =CCH_2H_1), 1.97-1.89 (m, 2H, CH_2), 1.68 (m, 2H, CH_2); ^{13}C NMR δ (100 MHz , $CDCl_3$) 170.3, 135.4, 119.9, 71.3, 30.0, 27.6, 21.2, 17.3; LRMS (ESI+) found $(M+Na)^+$ 240.99, $C_8H_{11}{}^{79}BrO_2Na$ requires 240.98. Data in accordance with literature.[159]

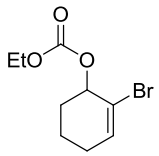
2-Bromocyclohex-2-enyl 2,2,2-trifluoroacetate, 146



Trifluoroacetate **146** was prepared using literature procedure.[192] Trifluoroacetic anhydride (0.8 mL, 5.7 mmol) and pyridine (1.4 mL, 16.9 mmol) were added to a stirred solution of alcohol **22a** (500 mg, 2.8 mmol) in DCM (10 mL) at 0 ºC and stirred for 1 hr at that temperature. The mixture was then

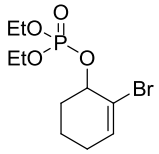
hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, reduced *in vacuo* and purified by flash chromatography (5% Et_2O in petroleum ether) to yield trifluoroacetate **146** (360 mg, 48%) as a colourless liquid. ν_{max} (liquid film)/cm^{-1} 2955, 1784, 1223, 1148; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 5.1, 3.3 Hz, 1H, C*H*=CBr), 5.59 (t, *J* = 4.2 Hz, 1H, C-C*H*O), 2.32-2.20 (m, 1H, CH_2), 2.19-2.08 (m, 1H, CH_2) 2.06-1.99 (m, 2H, CH_2), 1.78-1.70 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (J_{CF}=42.7 Hz), 137.4, 116.9, 114.5 (J_{CF}=287.1 Hz), 75.7, 29.5, 27.3, 16.7; ^{19}F NMR (377 MHz, $CDCl_3$) δ -75.1; HRMS (FI+) found $(M)^+$ 271.9664, $C_8H_8O_2{}^{79}BrF_3$ requires 271.9660.

2-Bromocyclohex-2-enyl ethyl carbonate, 147



Carbonate **147** was prepared using literature procedure.[193] To a solution of 2-bromo-2-cyclohexen-1-ol **22a** (500 mg, 2.8 mmol) and pyridine (0.5 mL, 5.7mmol) in DCM (5 mL) was added ethyl chloroformate (0.5 mL, 5.7 mmol) drop-wise. The mixture was stirred at room temperature for 5 days then quenched with water (10 mL) and extracted with AcOEt (3 × 5 mL), dried over MgSO4 and reduced *in vacuo*. The crude was then filtrated through a pad of silica (25% AcOEt in *n*-hexane), reduced *in vacuo* to afford 2-bromocyclohex-2-enyl ethyl carbonate **147** (560 mg, 80%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 4.8, 3.4 Hz, 1H, C*H*=CBr), 5.26 (t, *J* = 3.9 Hz, 1H, C-C*H*O), 4.24 (q, *J* = 7.2 Hz, 2H, $CO_3CH_2CH_3$), 2.22-2.10 (m, 1H, C=CH-CH_1H_2), 2.09-1.95 (m, 2H, CH_2), 1.95-1.83 (m, 1H, =CCH_2H_1), 1.79-1.52 (m, 2H, CH_2), 1.37-1.21 (t, *J* = 7.0 Hz, 3H, $CO_3CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 135.7, 119.0, 74.9, 64.1, 29.9, 27.5, 16.9, 14.2; LRMS (ESI+) found $(M+Na)^+$ 271.01, $C_9H_{13}O_3{}^{79}BrNa$ requires 270.99. Data in accordance with literature.[159]

2-Bromocyclohex-2-enyl diethyl phosphate, 148

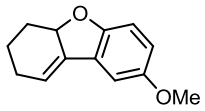


Phosphate **148** was prepared using literature procedure.[194] To a solution of 2-bromo-2-cyclohexen-1-ol **22a** (500 mg, 2.8 mmol) in DCM (10 mL), DMAP (34 mg, 0.3 mmol), pyridine (3 mL, 37.2 mmol), and $(EtO)_2P(O)Cl$ (0.5 mL, 3.4 mmol) were sequentially added at room temperature[195]. The mixture was stirred at room temperature for 1 day then filtrated through celite and reduced *in vacuo*. The crude was then filtrated through a pad of silica (25% AcOEt in *n*-hexane) and reduced *in vacuo* to afford 2-bromo-2-cyclohexen-1-yl acetate **148** (776 mg, 88%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 5.1, 3.3 Hz, 1H, C*H*=CBr), 4.93-4.82 (m, 1H, C-C*H*O), 4.24-4.07 (m, 4H, $PO_3CH_2CH_3$), 2.23-2.12 (m, 2H, CH_2), 2.12-2.04 (m, 1H, CH_2), 1.96-1.85 (m, 1H, CH_2), 1.80-1.59 (m, 2H, CH_2), 1.37-1.30 (qd, *J* = 6.8, 0.8 Hz, 6H, $PO_3CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 120.0 (d, J_{CP}=8.0 Hz), 76.0 (d, J_{CP}=3.2 Hz), 63.6 (dd, J_{CP}=6.4, 28.8 Hz), 31.2, 27 6, 16.4, 16.1 (d, J_{CP}=6.4 Hz); LRMS (ESI+) found $(M+Na)^+$ 335.03, $C_{10}H_{18}O_4{}^{79}BrPNa$ requires 335.00. Data in accordance with literature.[159]

General procedure H: the preparation of tetrahydrodibenzo[*b*,*d*]furan derivatives 9 by tandem palladium-catalysed coupling

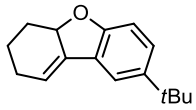
An oven dried flask flushed with N_2 was charged with acetate **145** (1.0 equiv), substituted phenol (1.5 equiv), palladium acetate (10 mol %), dppf (20 mol%), Cs_2CO_3 (2.0 equiv) in acetonitrile (0.20 mol.L^{-1}) and heated at 80 °C. The reaction mixture was then cooled to room temperature, diluted with Et_2O (5 mL) and washed with brine (3 × 5 mL). The solvent was dried ($MgSO_4$) and removed *in vacuo* and the crude purified by flash chromatography (1% Et_2O in petroleum ether) to yield the desired tetrahydrodibenzo[*b,d*]furan **9**.

8-Methoxy-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 57



Following general procedure **H**, acetate **145** (50 mg, 0.23 mmol) and 4-methoxyphenol (35 mg, 0.28 mmol) were submitted to the reaction conditions and the desired compound **57** was obtained (17 mg, 30%) after 20 hrs. Data as recorded previously for *exo*-alkene **57**.

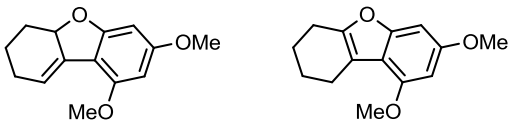
8-*tert*-butyl-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 80



Following general procedure **H**, acetate **145** (50 mg, 0.23 mmol) and 4-*t*butylphenol (51 mg, 0.35 mmol) were submitted to the reaction conditions and the desired compound **80** was obtained (15 mg, 28%) after 20 hrs as a colourless oil. Data as recorded previously for *exo*-alkene **80**.

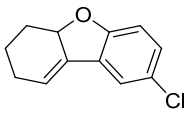
7,9-dimethoxy-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 81

7,9-dimethoxy-2,3,4,4a-tetrahydrodibenzo[b,d]furan, 61



Following general procedure **H**, acetate **145** (50 mg, 0.23 mmol) and 3,5-dimethoxyphenol (53 mg, 0.35 mmol) were submitted to the reaction condition and a mixture of benzofuran **61** (9 mg, 11%) and tetrahydrobenzofuran **81** (10 mg, 12%) was obtained after 21 hrs. Data as recorded previously for *exo*-alkene **81** and benzofuran **61**.

8-Chloro-2,3,4,4a-tetrahydrodibenzo[*b,d*]furan, 82a

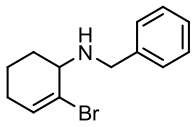


Following general procedure **H**, acetate **145** (50 mg, 0.23 mmol) was submitted to the reaction conditions and the desired compound **82a** was obtained (13 mg, 28%) after 75 min as a white crystalline solid. Data as recorded previously for *exo*-alkene **82a**.

General procedure I: the preparation of secondary amines

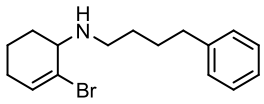
Mesyl chloride (1.05 equiv) was added drop-wise to a solution of 2-bromocyclohexen-2-enol **22a** (1.0 equiv) and NEt_3 (1.1 equiv) in DCM (0.5 $L.mol^{-1}$) at 0 °C. This solution was stirred for 30 min at 0 °C and a further 1 hr at room temperature after which the appropriate amine (3.0 equiv) was added drop-wise. After stirring for 20 hrs at room temperature, the reaction mixture was washed with water and extracted with DCM (2 $L.mol^{-1}$). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude material was purified by flash chromatography (10% Et_2O in petroleum ether) to yield the desired amine.

***N*-Benzyl-2-bromocyclohex-2-amine, 113**



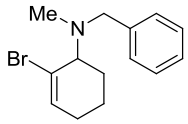
Amine **113** was prepared using general procedure **I**. Starting with 2-bromocyclohexen-2-enol **22a** (2.50 g, 14.12 mmol) and benzylamine, **113** was obtained (1.95 g, 52%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2937, 1453, 1108, 735, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.7 Hz, 2H, Ar-*H*), 7.34 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.30-7.23 (m, 1H, Ar-*H*), 6.22 (t, *J* = 4.0 Hz, 1H, BrC=C*H*C), 3.90-3.84 (d, *J* = 13.2 Hz, 1H, NH-CH*H*-Ar), 3.78 (d, *J* = 13.2 Hz, 1H, NH-C*H*H-Ar), 3.37 (br. s, 1H, C*H*-N), 2.26-1.70 (m, 6H, N*H* and CH_2), 1.70-1.51 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 132.5, 128.4, 128.3, 126.9, 126.4, 58.1, 50.7, 29.2, 27.9, 18.3; HRMS (ESI+) found $(M+H)^+$ 266.0539, $C_{13}H_{17}{}^{79}BrN$ requires 266.0539.

2-Bromo-*N*-(4-phenylbutyl)cyclohex-2-amine, 117



Amine **117** was prepared using general procedure **I**. Starting with 2-bromocyclohexen-2-enol **22a** (1.00 g, 5.65 mmol) and 4-phenylbutylamine, **117** was obtained (1.03 g, 59%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2934, 2858, 1721, 1454, 747, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 2H, Ar-*H*), 7.24-7.16 (m, 3H, Ar-*H*), 6.19 (td, *J* = 4.0, 0.8 Hz, 1H, BrC=C*H*C), 3.34-3.26 (m, 1H, C*H*-N), 2.75-2.63 (m, 3H, NH-CH_2-CH$_2$ and Ar-CH*H*-CH$_2$), 2.63-2.55 (m, 1H, Ar-C*H*H-CH$_2$), 2.17-1.97 (m, 3H, N*H*-CH$_2$-CH$_2$ and C=CH-CH_2), 1.87-1.81 (m, 2H, C=CH-CH$_2$-CH_2), 1.77-1.68 (m, 3H, N-CH-CH_2 and Ar-CH$_2$-C*H*H), 1.63-1.53 (m, 3H, Ar-CH$_2$-CH*H* and NH-CH$_2$-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 132.2, 128.5, 128.3, 126.8, 125.7, 58.7, 46.6, 35.9, 30.0, 29.4, 29.3, 28.0, 18.5; HRMS (ESI+) found $(M+H)^+$ 308.1006, $C_{16}H_{23}{}^{79}BrN$ requires 308.1008.

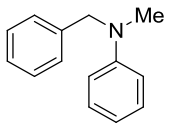
***N*-Benzyl-2-bromo-*N*-methylcyclohex-2-amine, 103**



Methanesulfonic anhydride (0.739 g, 4.24 mmol) was added portion-wise to a solution of 2-bromo-2-cyclohexen-1-ol **22a** (0.500 g, 2.82 mmol) and triethylamine (0.6 ml, 4.24 mmol) in THF (22.0 ml) at 0 ºC, and allowed to warm to room temperature after 30 min. After an additional 30 min at room temperature, a stirred solution of *N*-methylbenzylamine (0.514 g, 4.24 mmol) and K_2CO_3 (1.612 g, 8.48 mmol) in THF (12.0 ml) was added drop-wise, stirred at room temperature for 2 then refluxed for 16 hrs. Water (40 mL) was then added to the reaction mixture, the phases separated, the organic phase washed with water (3 x 40 mL), brine (40 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude mixture was purified by flash chromatography (10% Et_2O in petroleum ether) to afford the desired amine **103** (425 mg, 54 % yield) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2936, 2791, 1452, 736, 698; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.47 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.33 (t, *J* = 7.3 Hz, 2H, Ar-*H*), 7.25 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.39-6.32 (m, 1H, C*H*=CBr), 3.82 (d, *J* = 13.4 Hz, 1H, N-

C*H*H-Ph), 3.50 (d, *J* = 13.4 Hz, 1H, N-CH*H*-Ph), 3.48 (br. s, 1H, BrC-C*H*-N), 2.26 (s, 3H, CH_3N), 2.17-2.03 (m, 2H, CH_2), 1.93-1.84 (m, 2H, CH_2), 1.84-1.73 (m, 1H, CH_2), 1.69-1.55 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0; 133.9, 128.7, 128.2, 127.3, 126.8, 63.2, 57.2, 37.2, 27.8, 23.4, 20.9, HRMS (CI+) found $(M+H)^+$ 280.0706, $C_{14}H_{19}N^{79}Br$ requires 280.0701. Data in accordance with literature.[196]

_N_-Benzyl-_N_-methylaniline, 104

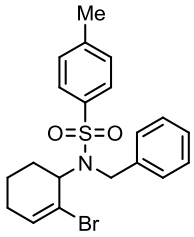


An oven dried flask flushed with nitrogen was charged with compound **103** (98 mg, 0.35 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol, 10 mol%), X-Phos (33 mg, 0.07 mmol), K_2CO_3 (97 mg, 0.70 mmol), DMA (2.0 mL) and heated at 80 °C for 4 hrs then at 120 °C for 3 hrs. The reaction mixture was cooled to room temperature, diluted with Et_2O (5 mL) and washed with brine (3 × 5 mL). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* and the crude purified by flash chromatography (5% Et_2O in petroleum ether) to yield unexpected compound **104** (35 mg, 69%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2936, 1493, 801, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (m, 2H, Ar-*H*), 7.29-7.21 (m, 5H, Ar-*H*), 6.79 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 6.74 (t, *J* = 7.1 Hz, 1H, Ar-*H*), 4.56 (s, 2H, CH_2NCH$_3$) 3.04 (s, 3H, CH$_2$NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 139.1, 129.2, 128.6, 126.9, 126.8, 116.5, 112.4, 56.7 38.6; LRMS (CI+) found $(M+H)^+$ 197.24, $C_{14}H_{16}N$ requires 197.12. Data in accordance with literature.[197]

General procedure J: the preparation of sulfonamides

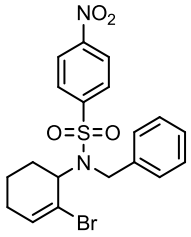
Sulfonyl chloride (1.10 equiv) was added portion-wise to a solution of amine (1.00 equiv) and NEt_3 (2.00 equiv) in DCM (0.3 $mol.L^{-1}$) at 0 °C. This solution was stirred for 30 min at 0 °C and overnight at room temperature. Diethyl ether (0.2 $mol.L^{-1}$) and water (0.2 $mol.L^{-1}$) were added, the organic layer was washed successively with 2 N HCl solution (0.3 $mol.L^{-1}$), 5% $NaHCO_3$ aqueous solution (0.3 $mol.L^{-1}$) and finally with brine (0.3 $mol.L^{-1}$). The organic extract was dried over $MgSO_4$, filtered and reduced *in vacuo.* The crude material was purified by flash chromatography (20% Et_2O in petroleum ethereum ether) to yield the appropriate sulfonamide.

_N_-Benzyl-_N_-(2-bromocyclohex-2-enyl)-4-methylbenzenesulfonamide, 114



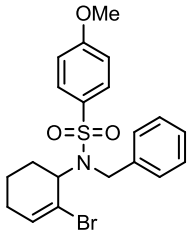
Sulfonamide **114** was prepared using general procedure **J**. Starting with amine **113** (1.20 g, 4.50 mmol) and 4-toluenesulfonyl chloride, sulfonamide **114** was obtained (1.47g, 78%) as a white crystalline solid, mp 107-108 °C. ν_{max} (liquid film)/cm^{-1} 2924, 1339, 1159, 661; ^{1}H NMR (400 MHz, CDCl) δ 7.69 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.40 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.34-7.16 (m, 5H, Ar-*H*), 6.34 (br. s, 1H, BrC=C*H*C), 4.78 (d, *J* = 16.2 Hz, 1H, N-C*H*H-Ar), 4.61 (br. s, 1H, C*H*-N), 4.10 (d, *J* = 16.2 Hz, 1H, N-CH*H*-Ar), 2.41 (s, 3H, Ar-CH_3), 1.96-2.10 (m, 1H, CH_2), 1.84-1.96 (m, 2H, CH_2), 1.85-1.68 (m, 1H, CH_2), 1.51-1.37 (m, 1H, CH_2), 1.29 (dd, *J* = 8.0, 4.7 Hz, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 138.5, 137.7, 137.3, 129.2, 128.5, 128.2, 127.6, 127.3, 120.8, 60.1, 48.8, 32.3, 27.3, 21.5, 19.8; HRMS (ESI+) found $(M+Na)^+$ 442.0440, $C_{20}H_{22}O_2{}^{79}BrNNaS$ requires 470.0447.

***N*-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-nitrobenzenesulfonamide, 121**



Sulfonamide **121** was prepared using general procedure **J**. Starting with amine **113** (400 mg, 1.5 mmol) and 4-nitrobenzenesulfonyl chloride, sulfonamide **121** was obtained (0.46 g, 59%) as a yellow crystalline solid, mp 107-109 °C. ν_{max} (DCM)/cm^{-1} 2939, 1530, 1349, 1165, 740, 618; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.87 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 7.41-7.32 (m, 2H, Ar-*H*), 7.27-7.21 (m, 3H, Ar-*H*), 6.42 (t, *J* = 3.4 Hz, 1H, BrC=C*H*C), 4.74 (d, *J* = 15.7 Hz, 1H, N-C*H*H-Ar), 4.68 (br. s, 1H, C*H*-N), 4.15 (d, *J* = 15.7 Hz, 1H, N-CH*H*-Ar), 2.08 (ddt, *J* = 13.6, 6.7, 3.4 Hz, 1H, CH_2), 2.01-1.91 (m, 2H, CH_2), 1.87-1.72 (m, 1H, CH_2), 1.59-1.46 (m, 1H, CH_2), 1.46-1.33 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 146.4, 138.1, 136.9, 128.9, 128.6, 128.4, 127.7, 123.8, 120.3, 60.8, 49.0, 32.3, 27.3, 19.9; HRMS (ESI+) found $(M+Na)^+$ 473.0134, $C_{19}H_{19}O_4{}^{79}BrN_2NaS$ requires 473.0141.

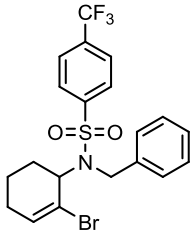
***N*-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-methoxybenzenesulfonamide, 118**



Sulfonamide **118** was prepared using general procedure **J**. Starting with amine **113** (500 mg, 1.9 mmol) and 4-methoxybenzenesulfonyl chloride, sulfonamide **118** was obtained (350 mg, 46%) as a white solid, mp 76-77 °C. ν_{max} (DCM)/cm^{-1} 2941, 1597, 1498, 1337, 1259, 1153, 1096, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.40 (d, *J* = 7.3 Hz, 2H, Ar-*H*), 7.19-7.31 (m, 3H, Ar-*H*), 6.91 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.37-6.30 (m, 1H, BrC=C*H*C), 4.76 (d, *J* = 16.2 Hz, 1H, N-C*H*H-

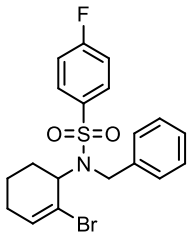
Ar), 4.60 (br. s, 1H, C*H*-N), 4.10 (d, *J* = 16.2 Hz, 1H, N-CH*H*-Ar), 3.85 (s, 3H, Ar-OCH_3), 2.07-1.96 (m, 1H, CH_2), 1.94-1.85 (m, 2H, CH_2), 1.79 (dd, *J* = 6.7, 3.2 Hz, 1H, CH_2), 1.44 (dd, *J* = 6.2, 3.7 Hz, 1H, CH_2), 1.35-1.22 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 138.4, 137.3, 132.6, 129.7, 128.5, 128.2, 127.3, 120.9, 113.8, 60.0, 55.6, 48.8, 32.3, 27.3, 19.8; HRMS (ESI+) found $(M+Na)^+$ 458.0385, $C_{20}H_{22}O_3{}^{79}BrNNaS$ requires 458.0396.

_N_-Benzyl-_N_-(2-bromocyclohex-2-enyl)-4-(trifluoromethyl)benzenesulfonamide, 119



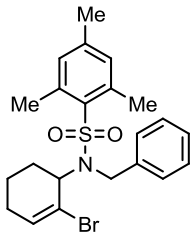
Sulfonamide **119** was prepared using general procedure **J**. Starting with amine **113** (500 mg, 1.9 mmol) and 4-(trifluoromethyl)benzenesulfonyl chloride, sulfonamide **119** was obtained (890 mg, quantitative) as a white solid, mp 83-85 °C. ν_{max} (liquid film)/cm^{-1} 2940, 1324, 1167, 1132, 1063; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.67 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.42-7.31 (m, 2H, Ar-*H*), 7.30-7.17 (m, 3H, Ar-*H*), 6.46-6.34 (m, 1H, BrC=C*H*C), 4.74 (d, *J* = 15.7 Hz, 1H, N-C*H*H-Ar), 4.68 (br. s, 1H, C*H*-N), 4.14 (d, *J* = 15.7 Hz, 1H, N-CH*H*-Ar), 2.07 (dd, *J* = 7.0, 3.2 Hz, 1H, CH_2), 1.95 (dd, *J* = 8.1, 3.3 Hz, 2H, CH_2), 1.83 (d, *J* = 3.0 Hz, 1H, CH_2), 1.56-1.45 (m, 1H, CH_2), 1.40 (d, *J* = 4.6 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 137.8, 137.2, 134.0, 128.8, 128.3, 127.9, 127.6, 125.7 (q, J_{CF} = 6.4 Hz), 124.7 (q, J_{CF} = 296.8 Hz), 120.5 (q, J_{CF} = 32.1 Hz), 60.6, 48.9, 32.3, 27.3, 19. 9; ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.03; HRMS (ESI+) found $(M+H)^+$ 496.0166, $C_{20}H_{19}{}^{79}BrF_3NNaO_2S$ requires 496.0164.

_N_-Benzyl-_N_-(2-bromocyclohex-2-enyl)-4-fluorobenzenesulfonamide, 120



Sulfonamide **120** was prepared using general procedure **J**. Starting with amine **113** (500 mg, 1.9 mmol) and 4-fluorobenzenesulfonyl chloride, sulfonamide **120** was obtained (790 mg, 99%) as a white solid, mp 84-86 °C. ν_{max} (liquid film)/cm^{-1} 2939, 1592, 1494, 1342, 1153, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 8.8, 5.1 Hz, 2H, Ar-*H*), 7.38 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 7.32-7.21 (m, 3H, Ar-*H*), 7.10 (t, *J* = 8.6 Hz, 2H, Ar-*H*), 6.38 (td, *J* = 4.2, 1.6 Hz, 1H, BrC=C*H*C), 4.75 (d, *J* = 15.9 Hz, 1H, N-C*H*H-Ar), 4.62 (br. s, 1H, C*H*-N), 4.11 (d, J = 15.9 Hz, 1H, N-CH*H*-Ar), 2.11-1.99 (m, 1H, CH_2), 1.99-1.85 (m, 2H, CH_2), 1.80 (ddd, J = 13.3, 6.3, 3.7 Hz, 1H, CH_2), 1.54-1.41 (m, 1H, CH_2), 1.40-1.26 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3 (d, J_{CF}=254.9 Hz), 137.8, 137.6, 136.9, 130.1 (d, J_{CF}=8.1 Hz), 128.6, 128.3, 127.5, 120.6, 115.8 (d, J_{CF}=22.3 Hz), 60.3, 48.9, 32.3, 27.3, 19.8;^{19}F NMR (377 MHz, $CDCl_3$) δ -113.35; HRMS (ESI+) found $(M+H)^+$ 446.0197, $C_{19}H_{19}{}^{79}BrFNNaO_2S$ requires 446.0196.

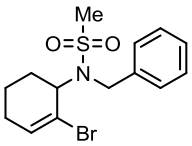
_N_-Benzyl-_N_-(2-bromocyclohex-2-enyl)-2,4,6-trimethylbenzenesulfonamide, 122



Sulfonamide **122** was prepared using general procedure **J**. Starting with amine **113** (1.00 g, 3.75 mmol) and 2-mesitylene chloride, sulfonamide **122** was obtained (1.62 g, 96%) as a white crystalline solid, mp 111-112 °C. ν_{max} (DCM)/cm^{-1} 2938, 1327, 1153, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.24-7.13 (m, 3H, Ar-*H*), 6.87 (s, 2H, Ar-*H*), 6.40 (br. s, 1H, BrC=C*H*C), 4.99 (d, *J* = 16.2 Hz, 1H, N-C*H*H-Ar), 4.47-4.37 (m, 1H, C*H*-N), 4.20 (d, *J* = 16.4 Hz, 1H, N-CH*H*-Ar), 2.63

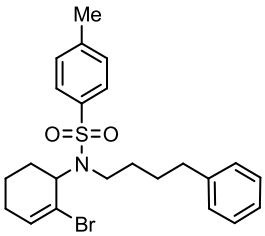
(s, 6H, 2 × Ar-CH_3), 2.27 (s, 3H, Ar-CH_3), 2.20-2.05 (m, 1H, CH_2), 1.93 (d, J = 2.8 Hz, 2H, CH_2), 1.88-1.76 (m, 1H, CH_2), 1.51-1.33 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 140.1, 138.5, 137.7, 133.8, 131.9, 128.1 (4 ×C), 127.0, 121.3, 59.1, 48.9, 31.0, 27.4, 23.8, 20.9, 20.3; HRMS (ESI+) found $(M+Na)^+$ 470.0758, $C_{22}H_{26}O_2{}^{79}BrNNaS$ requires 470.0760.

_N_-Benzyl-_N_-(2-bromocyclohex-2-enyl)methanesulfonamide, 123



Sulfonamide **123** was prepared using general procedure **J**. Starting with amine **113** (300 mg, 1.1 mmol) and methanesulfonyl chloride, sulfonamide **123** was obtained (0.15, 39%) as a white crystalline solid, mp 81-82 °C. v_{max} (DCM)/cm^{-1} 2935, 1332, 1146, 1028, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.3 Hz, 2H, Ar-H), 7.37-7.31 (m, 2H, Ar-H), 7.31-7.25 (m, 1H, Ar-H), 6.48 (t, J = 3.4 Hz, 1H, BrC=CHC), 4.66 (d, J = 15.7 Hz, 1H, N-CHH-Ar), 4.62 (br. s, 1H, CH-N), 4.17 (d, J = 15.9 Hz, 1H, N-CHH-Ar), 2.94 (s, 3H, SO_2-CH_3), 2.06-1.92 (m, 3H, CH_2), 1.81-1.68 (m, 1H, CH_2), 1.55-1.43 (m, 1H, CH_2), 1.43-1.31 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.6, 128.7, 128.4, 127.6, 121.4, 60.6, 48.6, 40.8, 32.4, 27.4, 20.1; HRMS (ESI+) found $(M+Na)^+$ 366.0136, $C_{14}H_{18}{}^{79}BrNNa\ O_2S$ requires 366.0134.

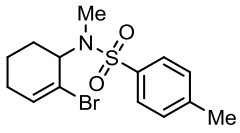
_N_-(2-Bromocyclohex-2-enyl)-4-methyl-_N_-(4-phenylbutyl)benzenesulfonamide, 126



Sulfonamide **126** was prepared using general procedure **J**. Starting with amine **117** (0.80 g, 2.60 mmol) and 4-toluenesulfonyl chloride, sulfonamide **126** was obtained (1.20 g, 75%) as a colourless

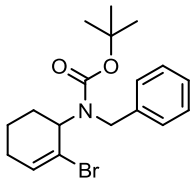
oil. v_{max} (liquid film)/cm^{-1} 2937, 1454, 1339, 1155, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.32-7.23 (m, 4H, Ar-*H*), 7.22-7.12 (m, 3H, Ar-*H*), 6.32 (td, *J* = 4.2, 1.8 Hz, 1H, BrC=C*H*C), 4.56 (br. s, 1H, C*H*-N), 3.30-3.16 (m, 1H), 3.02 (d, *J* = 4.8 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H, Ar-CH_3), 2.11-1.99 (m, 3H, CH_2), 1.96-1.76 (m, 2H, CH_2), 1.74-1.63 (m, 2H, CH_2), 1.63-1.53 (m, 3H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 142.1, 138.1, 136.2, 129.3, 128.4, 128.3, 127.5, 125.8, 122.4, 59.8, 45.2, 35.4, 31.5, 30.5, 29.1, 27.3, 21.5, 20.5; HRMS (ESI+) found $(M+Na)^+$ 484.0915, $C_{23}H_{28}O_2{}^{79}BrNNaS$ requires 484.0916.

***N*-(2-Bromocyclohex-2-enyl)-*N*,4-dimethylbenzenesulfonamide, 125**



MsCl (0.46 mL, 6.0 mL) was added drop-wise to a stirred solution of α-bromo alcohol **22a** (1.00 g, 5.7 mmol) and NEt_3 (0.88 mL, 6.1 mmol) in dry DCM (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature over 1 hr. A slurry of *N*,4-dimethylbenzenesulfonamide (3.14 g, 17.0 mmol) and NaH (60% dispersion in mineral oil, 0.68 g, 17.0 mmol) in dry DCM (20 mL) was then added slowly to the reaction mixture. After stirring for 24 hrs at room temperature the reaction mixture was quenched slowly with water (20 mL), the aqueous phase extracted with DCM (3 × 10 mL), the organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and reduced i*n vacuo*. The resulting solid was recrystallized (5% AcOEt in hexane) to afford sulfonamide **125** (320 mg, 16%) as a white cubic crystal, mp 181-185 °C. v_{max} (DCM)/cm^{-1} 2941, 1338, 1156, 1038, 664, 603; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 7.29 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 6.36 (td, *J* = 4.1, 1.6 Hz, 1H, BrC=C*H*C), 4.77-4.52 (m, 1H, C*H*-N), 2.74 (s, 3H, N-CH_3), 2.42 (s, 3H, Ar-CH_3), 2.03 (m, 2H, CH_2), 1.96 (m, 1H, CH_2), 1.89-1.77 (m, 1H, CH_2), 1.75-1.62 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 136.9, 136.2, 129.4, 127.5, 121.8, 58.7, 29.6, 29.4, 27.3, 21.5, 20.2; HRMS (ESI+) found $(M+H)^+$ 366.0131, $C_{14}H_{18}{}^{79}BrNNaO_2S$ requires 366.0134.

***tert*-Butyl benzyl(2-bromocyclohex-2-enyl)carbamate, 124**



To a solution of amine **113** (500 mg, 1.9 mmol) in THF (25 mL) were added di-*tert*-butyl dicarbonate (1.230 g, 5.6 mmol), NEt_3 (0.79 mL, 5.6 mmol) and DMAP (23 mg, 0.2 mmol) at room temperature and the reaction stirred overnight. The reaction mixture was concentrated *in vacuo* and the brown residue purified by flash chromatography (10% Et_2O in petroleum ether) to yield the expected carbamate **124** (350 mg, 51 % yield) as a white solid, mp 71-72 °C. ν_{max} (liquid film)/cm^{-1} 2933, 1696, 1403, 1167; ^{1}H NMR (500 MHz, 363 K,d_8-toluene) δ 7.23 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.15 (t, *J* = 7.7 Hz, 2H, Ar-*H*), 7.08-7.03 (m, 1H, Ar-*H*), 6.04 (br. s, 1H, BrC=C*H*C), 4.63 (d, *J* = 16.1 Hz, 2H, N-CH_2-Ar), 4.33-4.03 (m, 1H, C*H*-N), 1.75-1.64 (m, 3H, CH_2), 1.63-1.53 (m, 1H, CH_2), 1.42 (s, 9H, $CO_2C(CH_3)_3$), 1.35-1.27 (m 1H, CH_2), 1.27-1.17 (m, 1H, CH_2); ^{13}C NMR (125 MHz, 363 K,d_8-toluene) δ 155.6, 140.7, 133.4, 128.3, 127.4, 126.8, 125.4, 79.7, 58.8, 49.2, 30.5, 28.4, 27.4, 21.2; HRMS (ESI+) found $(M+Na)^+$ 388.0871, $C_{18}H_{24}{}^{79}BrNNaO_2S$ requires 388.0883.

General procedure K: the preparation of piperidine derivatives 128 and 129

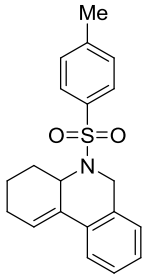
An oven dried flask flushed with N_2 was charged with alkenyl bromide **127** (1.0 equiv), palladium acetate (10 mol %), dppf (20 mol%), K_2CO_3 (2 equiv), DMA (0.20 mol.L^{-1}) and heated at 120 °C for 3 hrs. The reaction mixture was cooled to room temperature, diluted in Et_2O (0.10 mol.L^{-1}) and washed with brine (3 × 0.10 mol.L^{-1}). The organic layer was dried ($MgSO_4$), the solvent removed *in vacuo* and the crude reaction mixture purified by flash chromatography (5% AcOEt in hexane) to yield the desired heterocycle.

5-Tosyl-2,3,4,4a,5,6-hexahydrophenanthridine, 115

***N*-Benzyl-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 116**

Sulfonamides **115** and **116** were prepared using general procedure **K**. Starting with sulfonamide **114** (100 mg, 0.24 mmol), sulfonamide **115** was obtained (46 mg, 57%) as a mixture with sultam **116** (27 mg, 33%), both as white crystalline solids.

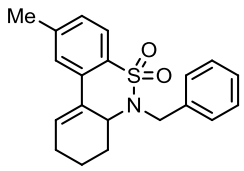
5-Tosyl-2,3,4,4a,5,6-hexahydrophenanthridine, 115



mp 109-111 °C. ν_{max} (DCM)/cm^{-1} 2926, 1345, 1161, 739, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.1 Hz, 2H, Ar-*H*), 7.11-7.04 (m, 1H, Ar-*H*), 7.04-6.97 (m, 2H, Ar-*H*), 6.93 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 7.1 Hz, 1H, Ar-*H*), 5.82 (br. s, 1H, C=C*H*C), 4.60 (d, *J* = 16.2 Hz, 1H, N-C*H*H-Ar), 4.36 (br. s, 1H, C*H*-N), 4.12 (d, *J* = 15.9 Hz, 1H, N-CH*H*-Ar), 2.38-2.27 (m, 3H, CH_2), 2.24 (s, 3H, Ar-CH_3), 2.02-1.71 (m, 3H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 136.9, 136.3, 134.0, 133.8, 129.0,

127.7, 127.2, 127.1, 126.5, 125.1, 124.3, 55.5, 45.8, 30.2, 25.4, 21.3, 21.2; HRMS (ESI+) found $(M+Na)^+$ 362.1184, $C_{20}H_{21}O_2NNaS$ requires 362.1185.

_N_-Benzyl-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[_c_,_e_][1,2]thiazine 5,5-dioxide, 116



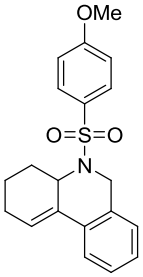
mp 160-161 °C. v_{max} (DCM)/cm^{-1} 2939, 1330, 1166, 735, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H, Ar-*H*), 7.42 (s, 1H, Ar-*H*), 7.39-7.34 (m, 2H, Ar-*H*), 7.31 (t, *J* = 7.3 Hz, 2H, Ar-*H*), 7.27-7.18 (m, 2H, Ar-*H*), 6.56 (br. s, 1H, C=C*H*C), 4.65 (dd, *J* = 5.7, 2.7 Hz, 1H, C*H*-N) 4.18 (d, *J* = 2.5 Hz, 2H, N-CH_2-Ar) 2.43 (s, 3H, Ar-CH_3) 2.29 (m, 2H, CH_2) 1.94-1.88 (m, 1H, CH_2), 1.85-1.68 (m, 1H, CH_2), 1.75 (m, 1H, CH_2), 1.56 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 137.8, 134.8, 132.3, 130.4, 128.5, 128.44, 128.40, 127.7, 127.3, 125.0, 124.6, 59.3, 50.9, 29.4, 26.0, 21.8, 21.2; HRMS (ESI+) found $(M+Na)^+$ 362.1184, $C_{20}H_{21}O_2NNaS$ requires 362.1185.

5-((4-Methoxyphenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 130

_N_-Benzyl-2-methoxy-6a,7,8,9-tetrahydro-6H-dibenzo[_c_,_e_][1,2]thiazine 5,5-dioxide, 131

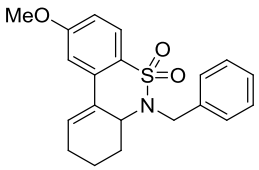
Sulfonamides **130** and **131** were prepared using general procedure **K**. Starting with sulfonamide **118** (100 mg, 0.27 mmol), an inseparable mixture of sulfonamide **130** and sultam **131** (2:1) was obtained (58 mg, 61%)

5-((4-Methoxyphenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 130



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 7.10-7.06 (m, 1H, Ar-H) 7.03-6.98 (m, 2H, Ar-H), 6.87 (d, *J* = 6.9 Hz, 1H, Ar-H), 6.60 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 5.82 (q, *J* = 3.1 Hz, 1H, C=C*H*C), 4.59 (d, *J* = 16.0 Hz, 1H, N-C*H*H-Ar), 4.33 (dd, *J* = 6.1, 3.1 Hz, 1H, C*H*-N), 4.11 (d, *J* = 16.0 Hz, 1H, N-C*H*H-Ar), 3.73 (s, 6H, Ar-OCH_3), 2.36-2.20 (m, 2H, CH_2), 1.98-1.67 (m, 4H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 136.9, 134.0, 133.8, 131.0, 129.2, 127.8, 127.1, 126.6, 125.0, 124.3, 113.5, 55.5, 55.4, 45.8, 30.2, 25.4, 21.2; HRMS (ESI+) found $(M+Na)^+$ 378.1123, $C_{20}H_{21}O_3NNaS$ requires 378.1134.

_N_-Benzyl-2-methoxy-6a,7,8,9-tetrahydro-6H-dibenzo[_c_,_e_][1,2]thiazine 5,5-dioxide, 131



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.38-7.33 (m, 2H, Ar-H), 7.27-7.22 (m, 1H, Ar-H), 7.06 (d, *J* = 0.6 Hz, 1H, Ar-H), 6.92 (dd, *J* = 8.5, 2.4 Hz, 1H, Ar-H), 6.87 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 6.57-6.50 (m, 1H, C=C*H*C), 4.64 (td, *J* = 5.5, 2.7 Hz, 1H, C*H*-N), 4.16 (s, 2H, N-CH_2-Ar), 3.87

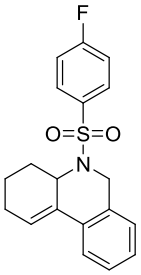
(s, 3H, Ar-OC*H*$_3$), 2.36-2.20 (m, 4H, C*H*$_2$), 1.98-1.67 (m, 2H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 137.8, 136.8, 130.7, 128.6, 128.4, 127.7, 127.5, 127.3, 126.6, 113.3, 109.7, 59.4, 55.6, 51.1, 29.5, 26.0, 21.2; HRMS (ESI+) found $(M+Na)^+$ 378.1123, $C_{20}H_{21}O_3NNaS$ requires 378.1134.

5-((4-Fluorophenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 134

***N*-Benzyl-2-fluoro-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 135**

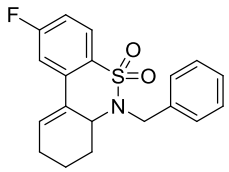
Sulfonamides **134** and **135** were prepared using general procedure **K**. Starting with sulfonamide **120** (85 mg, 0.20 mmol), a partially separable mixture of sulfonamide **134** and sultam **135** (2:1) was obtained (41 mg, 59%) as a thick colourless oil.

5-((4-Fluorophenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 134



mp 122-125 °C. ν_{max} (liquid film)/cm^{-1} 2931, 1592, 1493, 1337, 1166, 1090, 671; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.41 (m, 2H, Ar-H), 7.17-6.95 (m, 3H, Ar-H), 6.93-6.70 (m, 3H, Ar-H), 5.83 (q, *J* = 3.1 Hz, 1H, C=C*H*C), 4.60 (d, *J* = 16.0 Hz, 1H, N-C*H*H-Ar), 4.34 (br. s, 1H, C*H*-N), 4.14 (d, *J* = 16.0 Hz, 1H, N-CH*H*-Ar), 2.45-2.20 (m, 3H, C*H*$_2$), 2.05-1.71 (m, 3H, C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7 (d, J_{CF}=254.1 Hz), 136.8, 135.4, 133.7, 133.5, 129.8 (d, J_{CF}=9.5 Hz), 128.0, 127.4, 126.7, 125.0, 124.4, 115.5 (d, J_{CF}=22.4 Hz), 55.7, 45.9, 30.1, 25.4, 21.2; HRMS (ESI+) found $(M+Na)^+$ 366.0921, $C_{19}H_{18}O_2NNaFS$ requires 366.0934.

***N*-Benzyl-2-fluoro-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 135**



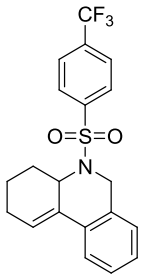
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.5, 5.5 Hz, 1H, Ar-H), 7.42-7.22 (m, 6H, Ar-H), 7.02-6.95 (m, 1H, Ar-H), 6.63-6.47 (m, 1H, C=C*H*C), 4.69 (m, 1H, C*H*-N), 4.18 (s, 2H, N-CH_2-Ar), 2.28-2.19 (m, 2H, CH_2) 2.03-1.77 (m, 3H, CH_2), 1.74-1.61 (m, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8 (d, J_{CF}=252.0 Hz), 137.7 (d, J_{CF} = 8.6 Hz), 137.4, 131.9, 131.3 (d, J_{CF} = 3.8 Hz), 128.5, 127.7, 127.5, 127.3 (d, J_{CF} = 9.5 Hz), 114.5 (d, J_{CF} = 65.5 Hz), 111.4 (d, J_{CF} = 83.2 Hz), 59.2, 50.9, 29.2, 26.0, 21.1; HRMS (ESI+) found $(M+Na)^+$ 366.0921, $C_{19}H_{18}O_2NNaFS$ requires 366.0934.

5-((4-(Trifluoromethyl)phenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 132

***N*-Benzyl-2-(trifluoromethyl)-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 133**

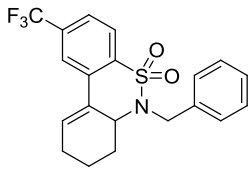
Sulfonamides **132** and **133** were prepared using general procedure **K**. Starting with sulfonamide **119** (95 mg, 0.20 mmol), a partially separable mixture of sulfonamide **132** and sultam **133** (1.7:1) was obtained (31 mg, 42%).

5-((4-(trifluoromethyl)phenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 132



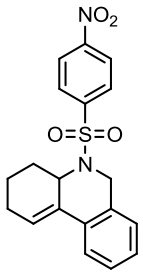
mp = 128-130 °C. v_{max} (DCM)/cm^{-1} 2924, 1324, 1167, 1132; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.10-7.02 (app. t., *J* = 7.0 Hz, Ar-H), 7.02-6.94 (app. t., *J* = 7.0 Hz, 2H, Ar-H), 6.82 (d, *J* = 7.6 Hz, 1H, Ar-H), 5.83 (q, *J* = 3.0 Hz, 1H, C=C*H*C), 4.59 (d, *J* = 15.9 Hz, 1H, N-C*H*H-Ar), 4.38 (d, *J* = 9.4 Hz, 1H, C*H*-N), 4.16 (d, *J* = 15.4 Hz, 1H, N-CH*H*-Ar), 2.39-2.16 (m, 3H, CH_2), 2.02-1.80 (m, 3H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7 (q, J_{CF}=2.5 Hz), 136.7, 133.6 (q, J_{CF}= 64.4 Hz), 133.29, 133.27 128.1, 127.63, 127.57, 126.7, 125.44 (q, J_{CF}=7.6 Hz), 125.1, 124.5, 123.1 (q, J_{CF}= 296.1 Hz), 56.0, 45.9, 30.0, 25.3, 21.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.3; HRMS (ESI+) found $(M+Na)^+$ 416.0893, $C_{20}H_{18}O_2NNaF_3S$ requires 416.0903.

***N*-Benzyl-2-(trifluoromethyl)-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 133**



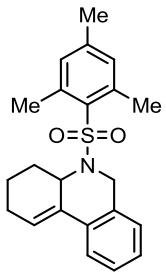
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.65 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.35-7.29 (m, 4H, Ar-H), 7.30-7.26 (m, 1H, Ar-H), 6.60 (br. s, 1H, C=C*H*C), 4.63 (br. s, 1H, C*H*-N), 4.24 (s, 2H, N-CH_2-Ar), 2.44-2.24 (m, 2H, CH_2), 2.01-1.91 (m, 2H, CH_2), 1.91-1.71 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 138.3 (q, J_{CF}=2.5 Hz), 137.0, 136.0, 134.2 (q, J_{CF}=65.6 Hz), 132.4, 128.5, 128.0, 127.8, 125.1, 124.3 (q, J_{CF}=7.4 Hz), 123.3 (q, J_{CF}=273.5 Hz), 122.0 (q, J_{CF}=7.7 Hz), 59.3, 51.3, 30.0, 26.1, 21.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.2; HRMS (ESI+) found $(M+Na)^+$ 416.0897, $C_{20}H_{18}O_2NNaF_3S$ requires 416.0903.

5-(4-Nitrophenylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 136



Sulfonamide **136** was prepared using general procedure **K**. Starting with sulfonamide **121** (100 mg, 0.22 mmol), sulfonamide **136** was obtained (21 mg, 25%) as a white crystalline solid, mp 65-70 °C. ν_{max} (DCM)/cm^{-1} 2927, 2257, 1530, 1349, 1164, 910, 738; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.67 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 7.06 (t, *J* = 7.3, 1H, Ar-*H*), 7.01 (td, *J* = 7.4, 1.3 Hz, 1H, Ar-*H*), 6.98 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.88 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.84 (q, *J* = 3.5 Hz, 1H, C=C*H*C), 4.63 (d, *J* = 16.0 Hz, 1H, N-C*H*H-Ar), 4.44-4.27 (m, 1H, C*H*-N), 4.18 (d, *J* = 16.0 Hz, 1H, N-CH*H*-Ar), 2.39-2.21 (m, 3H, CH_2), 2.07-1.75 (m, 3H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 145.0, 136.7, 133.3, 133.0, 128.4, 128.3, 127.9, 126.7, 125.1, 124.6, 123.5, 56.0, 46.0, 29.9, 25.3, 21.1; HRMS (ESI+) found $(M+Na)^+$ 393.0878, $C_{19}H_{18}O_4N_2NaS$ requires 393.0879.

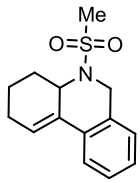
5-(Mesitylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 137



Sulfonamide **137** was prepared using general procedure **K**. Starting with sulfonamide **122** (108 mg, 0.24 mmol), sulfonamide **137** was obtained (67 mg, 76%) as a viscous oil. ν_{max} (liquid film)/cm^{-1} 2938, 1603, 1318, 1154, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.24 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.12 (td, *J* = 7.6, 1.3 Hz, 1H, Ar-*H*), 6.91 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.89 (s, 2H, Ar-*H*), 5.96 (app. q, *J* = 3.2 Hz, 1H, C=C*H*C), 4.61-4.47 (m, 1H, C*H*-N), 4.31 (d, *J* = 15.4 Hz, 1H, N-C*H*H-Ar), 4.02 (d, *J* = 15.4 Hz, 1H, N-CH*H*-Ar), 2.54 (s, 6H, 2 × Ar-CH_3), 2.29 (s, 3H, Ar-CH_3), 2.28 (m, 2H, CH_2), 2.00-1.90 (m, 1H, CH_2), 1.90-1.80 (m, 1H, CH_2), 1.73 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$)

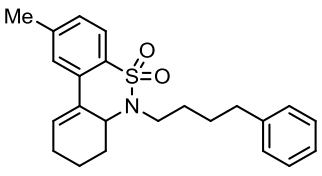
δ 142.3, 140.2, 137.0, 134.9, 134.4, 133.5, 131.9, 127.9, 126.84, 126.80, 125.5, 124.4, 54.7, 44.5, 28.4, 25.4, 22.9, 21.1, 20.9; HRMS (ESI+) found $(M+Na)^+$ 390.1497, $C_{22}H_{25}O_2NNaS$ requires 390.1498.

5-(Methylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 138



Sulfonamide **138** was prepared using general procedure **K**. Starting with sulfonamide **123** (50 mg, 0.15 mmol), sulfonamide **138** was obtained (20 mg, 50%) as a white crystalline solid, mp 168-170 °C. v_{max} (DCM)/cm^{-1} 2921, 1328, 1151, 964; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.6, 4.2 Hz, 1H, Ar-*H*), 7.34 (dd, *J* = 7.6, 0.5 Hz, 2H, Ar-*H*), 7.24 (td, *J* = 7.0, 1.6 Hz, 1H, Ar-*H*), 7.16 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.99 (app. d, *J* = 3.2 Hz, 1H, C=C*H*C), 4.54 (d, *J* = 15.9 Hz, 1H, N-C*H*H-Ar), 4.30-4.19 (m, 1H, C*H*-N), 4.12 (d, *J* = 16.1 Hz, 1H, N-CH*H*-Ar), 2.40-2.31 (m, 1H, CH_2), 2.30 (s, 3H, SO_2-CH_3), 2.28-2.22 (m, 1H, CH_2), 1.99-1.90 (m, 1H, CH_2), 1.85 (s, 1H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 134.4, 133.5, 128.5, 127.8, 127.4, 125.0, 124.9, 55.7, 45.7, 37.4, 30.1, 25.5, 21.2; HRMS (ESI+) found $(M+Na)^+$ 286.0873, $C_{14}H_{17}O_2NNaS$ requires 286.0872.

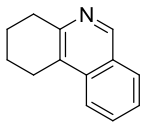
***N*-Phenylbutyl-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 139**



Sultam **139** was prepared using general procedure **K**. Starting with sulfonamide **126** (100 mg, 0.22 mmol), sultam **139** was obtained (4 mg, 5%) as a colourless oil. v_{max} (liquid film)/cm^{-1} 2925, 1332, 1165, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H, Ar-*H*), 7.39 (s, 1H, Ar-*H*), 7.29-7.24 (m, 2H, Ar-*H*), 7.20-7.16 (m, 2H, Ar-*H*), 7.14 (d, *J* = 6.9 Hz, 2H, Ar-*H*), 6.57-6.49 (m, 1H, C=C*H*C),

4.63-4.55 (m, 1H, C*H*-N), 2.95 (t, *J* = 6.6 Hz, 2H, CH_2), 2.60 (t, *J* = 7.1 Hz, 2H, CH_2), 2.40 (s, 3H, Ar-CH_3), 2.38-2.23 (m, 2H, CH_2), 2.21-2.11 (m, 1H, CH_2), 2.01-1.89 (m, 1H, CH_2), 1.89-1.76 (m, 1H, CH_2), 1.70-1.59 (m, 5H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 142.1, 134.5, 132.2, 129.5, 128.6, 128.5, 128.4, 128.3, 125.7, 124.7, 124.6, 59.2, 47.3, 35.4, 30.0, 29.4, 28.4, 26.1, 21.8, 21.4; HRMS (ESI+) found $(M+Na)^+$ 404.1644, $C_{23}H_{27}O_2NNaS$ requires 404.1655.

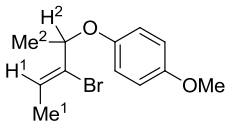
1,2,3,4-Tetrahydrophenanthridine, 140

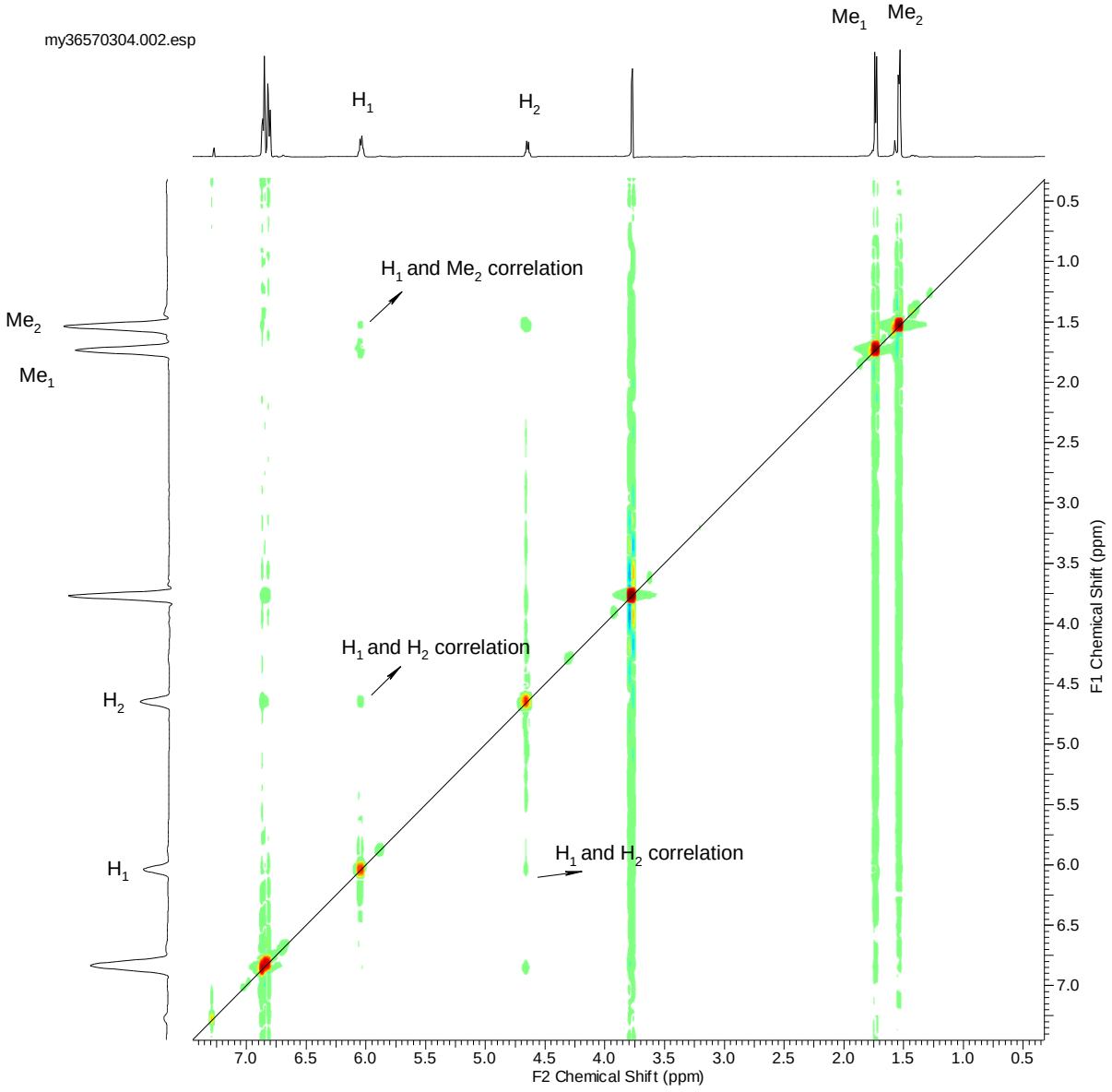


KHMDS (3 mL, 0.5 M in toluene) was added drop-wise at room temperature to a solution of sulfonamide **115** (40 mg, 0.12 mmol) in toluene (3 mL) and the solution was refluxed for 3 days. The reaction mixture was washed with water (3 × 1 mL) and brine (2 mL), the solvent was removed *in vacuo* and the crude product purified by flash chromatography (0 to 50% Et_2O in petroleum ether) to yield desired isoquinoline **140** (12 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H, N=C*H*-Ar), 7.92 (dd, *J* = 8.3, 4.3 Hz, 2H, Ar-*H*), 7.70 (ddd, *J* = 8.5, 7.0, 1.3 Hz, 1H, Ar-*H*), 7.54 (app. t., *J* = 7.2 Hz, 1H, Ar-*H*), 3.10 (m., 4H, CH_2), 2.04-1.91 (m, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 135.0, 130.1, 128.1, 127.0, 125.8, 124.5, 121.9, 32.8, 24.8, 23.0, 22.7; LRMS (ESI+) found $(M+H)^+$ 184.10, $C_{13}H_{14}N$ requires 184.11. Data in accordance with literature.[198]

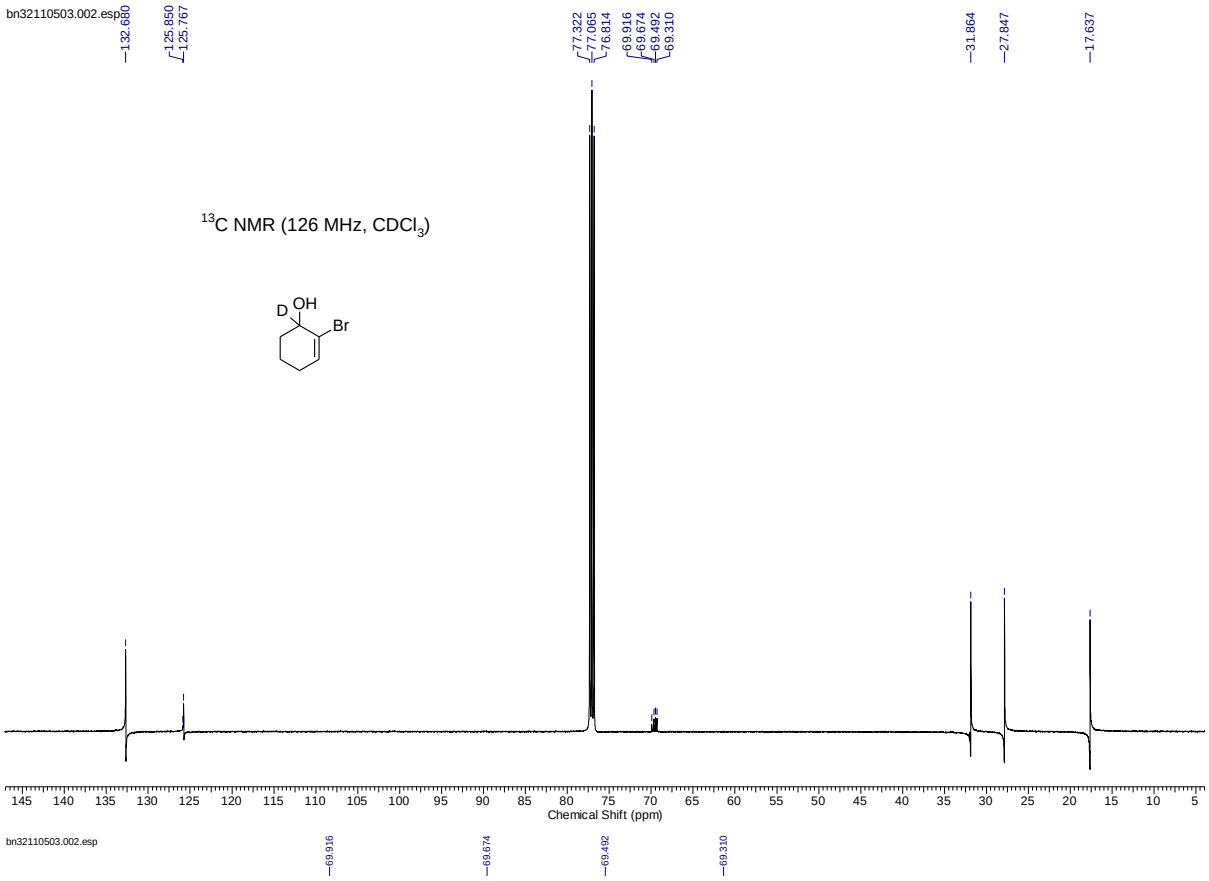
Appendix

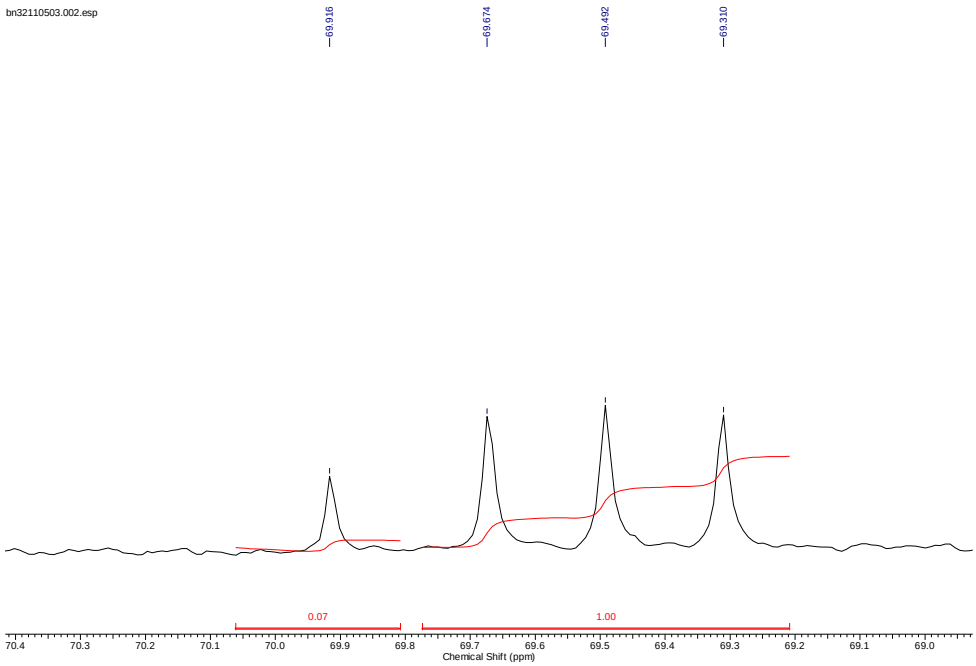
Appendix 1: NOESY determination of the geometry of (*Z*)-1-(3-Bromopent-3-en-2-yloxy)-4-methoxybenzene, 42



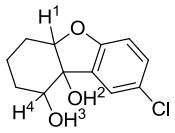


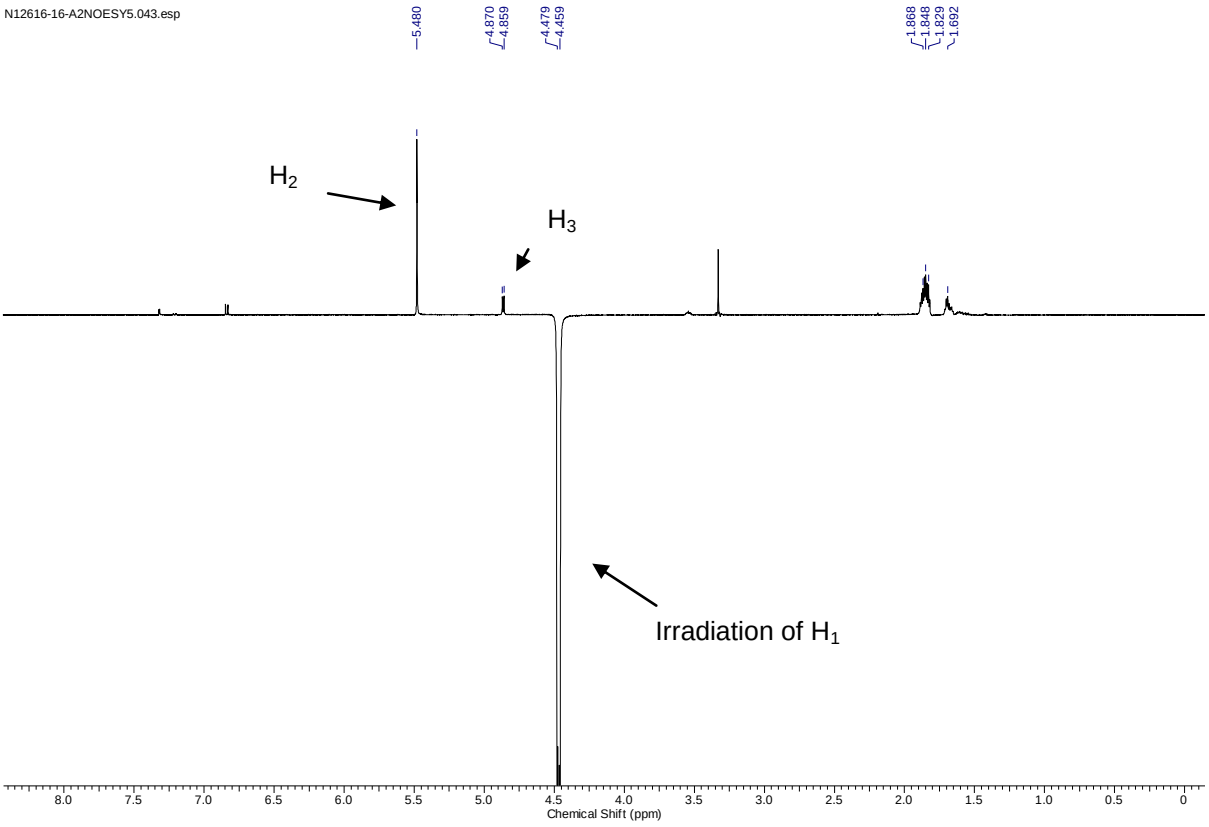
Appendix 2: Determination of ^{2}H incorporation in alcohol 46 by quantitative ^{13}C NMR spectroscopy



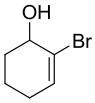


Appendix 3: Determination of diol 86 configuration by nOe spectroscopy

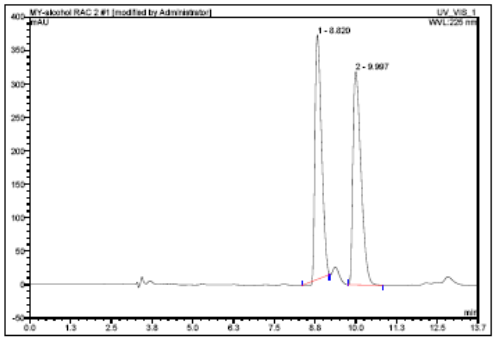




Appendix 4: Chiral HPLC analysis of alcohol 22

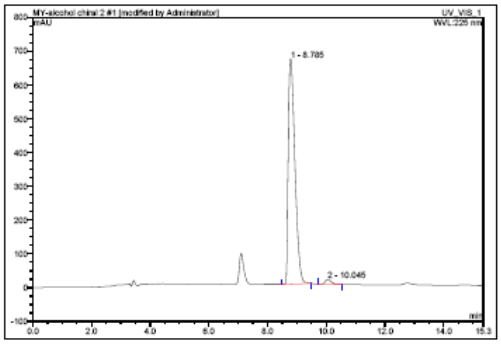


Sample Name:	MY-alcohol RAC 2	Injection Volume:	10.0
Vial Number:	BA4	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	4 % col B	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recording Time:	6/11/2009 17:01	Sample Weight:	1.0000
Run Time (min):	13.75	Sample Amount:	1.0000



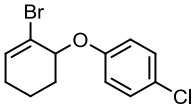
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.82	n.a.	365.232	84.702	48.02	n.a.	BMB*
2	10.00	n.a.	318.582	91.676	51.98	n.a.	BMB*
Total:			683.814	176.378	100.00	0.000	

Sample Name:	MY-alcohol chiral 2	Injection Volume:	10.0
Vial Number:	BA6	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	4 % col B	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recording Time:	9/11/2009 13:56	Sample Weight:	1.0000
Run Time (min):	15.35	Sample Amount:	1.0000

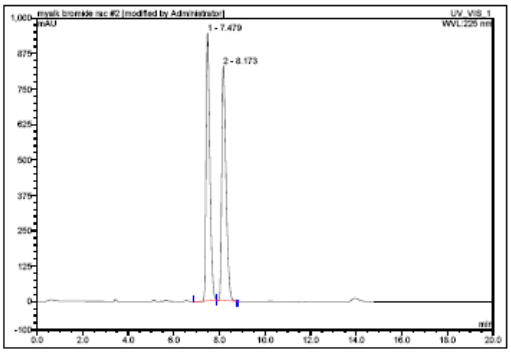


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.78	n.a.	666.318	174.603	98.05	n.a.	BMB*
2	10.04	n.a.	14.066	3.465	1.95	n.a.	BMB*
Total:			680.384	178.069	100.00	0.000	

Appendix 5: Chiral HPLC analysis of alkene 37

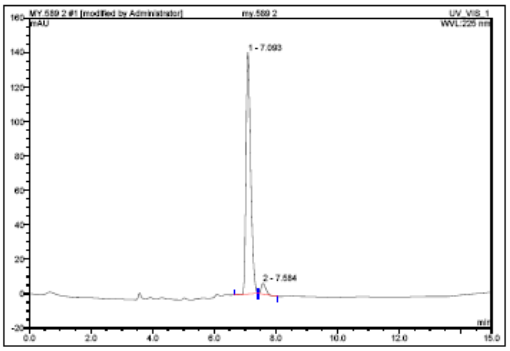


Sample Name:	myalk bromide rac1	Injection Volume:	5.0
Vial Number:	BA7	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	2% colB	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recording Time:	17/11/2009 11:06	Sample Weight:	1.0000
Run Time (min):	20.00	Sample Amount:	1.0000



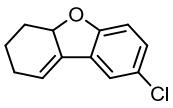
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.48	n.a.	945.036	179.063	50.01	n.a.	BMb*
2	8.17	n.a.	827.626	178.991	49.99	n.a.	bMB*
Total:			1772.661	358.054	100.00	0.000	

Sample Name:	my.589 2	Injection Volume:	2.0
Vial Number:	BA8	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	2% colB	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recording Time:	15/9/2010 9:48	Sample Weight:	1.0000
Run Time (min):	15.00	Sample Amount:	1.0000

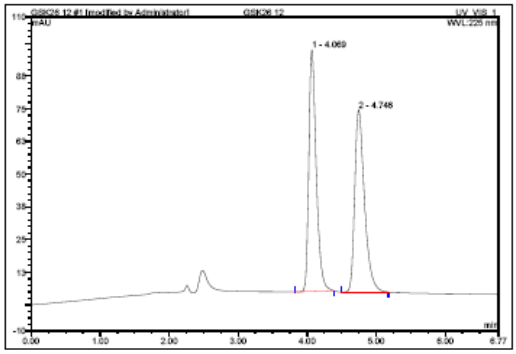


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.09	n.a.	140.249	24.457	95.96	n.a.	BMb*
2	7.58	n.a.	6.222	1.030	4.04	n.a.	bMB*
Total:			146.470	25.487	100.00	0.000	

Appendix 6: Chiral HPLC analysis of *exo*-alkene 82

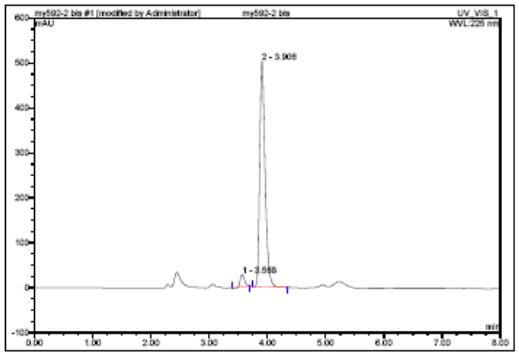


Sample Name:	GSK26 12	Injection Volume:	1.0
Vial Number:	BB7	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	0,5% colA	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recorded Time:	29/1/2010 15:50	Sample Weight:	1.0000
Run Time (min):	6.77	Sample Amount:	1.0000



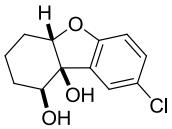
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.07	n.a.	92.458	11.513	50.24	n.a.	BMB*
2	4.75	n.a.	69.677	11.403	49.76	n.a.	BMB*
Total:			162.136	22.916	100.00	0.000	

Sample Name:	my592-2 bis	Injection Volume:	5.0
Vial Number:	BA12	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	0,5% colA	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recorded Time:	8/10/2010 12:05	Sample Weight:	1.0000
Run Time (min):	8.00	Sample Amount:	1.0000

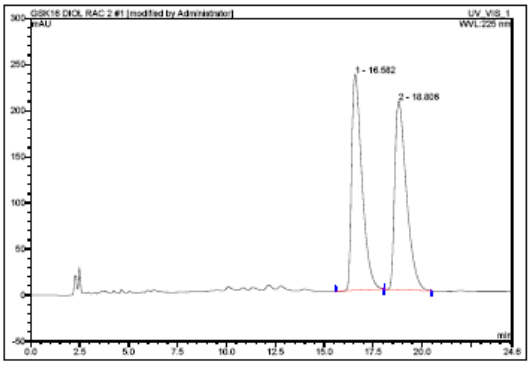


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.57	n.a.	27.163	2.183	3.92	n.a.	BMB*
2	3.91	n.a.	501.457	53.562	96.08	n.a.	BMB*
Total:			528.620	55.745	100.00	0.000	

Appendix 7: Chiral HPLC analysis of diol 86

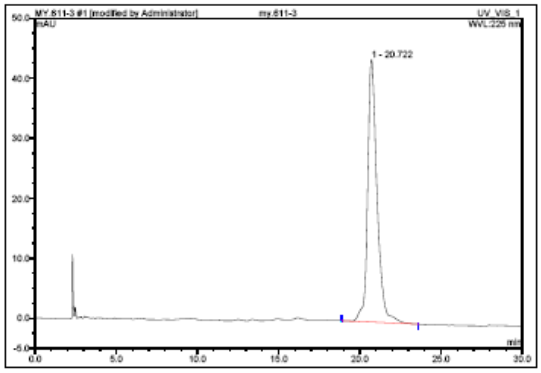


Sample Name:	GSK16 diol rac 2	Injection Volume:	10.0
Vial Number:	BB9	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	4% colB 30min	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recorded Time:	3/2/2010 10:17	Sample Weight:	1.0000
Run Time (min):	24.60	Sample Amount:	1.0000



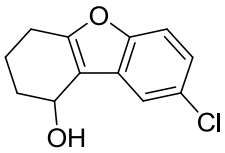
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.58	n.a.	233.942	142.699	50.19	n.a.	BMB*
2	18.81	n.a.	204.183	141.591	49.81	n.a.	BMB*
Total:			438.125	284.290	100.00	0.000	

Sample Name:	my.611-3	Injection Volume:	10.0
Vial Number:	BB2	Channel:	UV_VIS_1
Sample Type:	unknown	Wavelength:	225
Control Program:	4 % 1,5 mL col B	Bandwidth:	1
Quantif. Method:	Ph-pent	Dilution Factor:	1.0000
Recorded Time:	15/10/2010 15:13	Sample Weight:	1.0000
Run Time (min):	30.00	Sample Amount:	1.0000

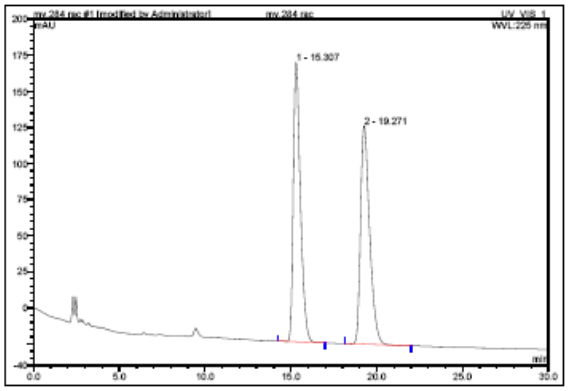


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.72	n.a.	43.714	29.380	100.00	n.a.	BMB*
Total:			43.714	29.380	100.00	0.000	

Appendix 8: Chiral HPLC analysis of hydroxy benzofuran 89

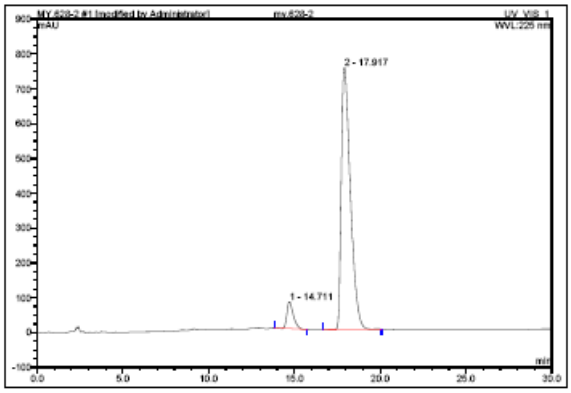


Sample Name:	**my.284 rac**	*Injection Volume:*	**10.0**
Vial Number:	**BA10**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**4 % 1,5 mL col B**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**25/10/2010 10:01**	*Sample Weight:*	**1.0000**
Run Time (min):	**30.00**	*Sample Amount:*	**1.0000**



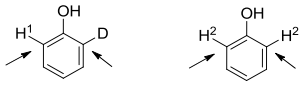
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.31	n.a.	193.847	92.591	49.92	n.a.	BMB*
2	19.27	n.a.	151.501	92.890	50.08	n.a.	BMB*
Total:			345.348	185.481	100.00	0.000	

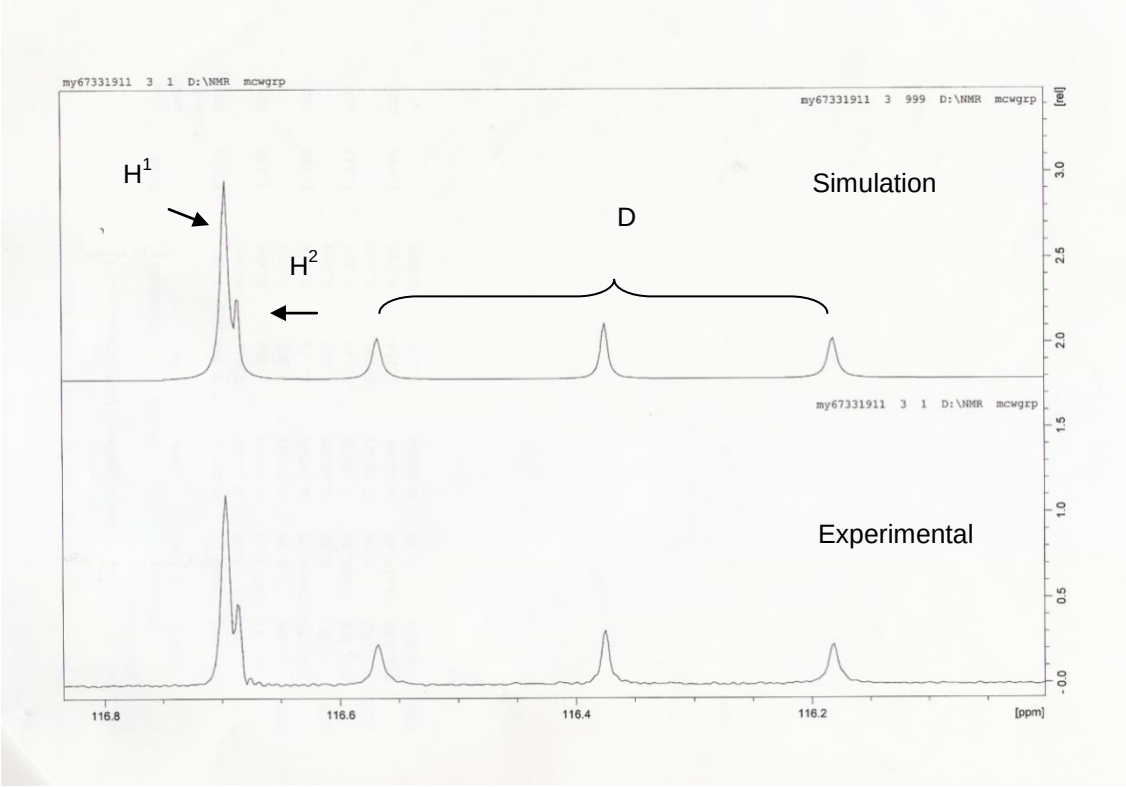
Sample Name:	**my.628-2**	*Injection Volume:*	**10.0**
Vial Number:	**BA10**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**4 % 1,5 mL col B**	*Bandwidth:*	**1**
Quantif. Method:	**Ph-pent**	*Dilution Factor:*	**1.0000**
Recording Time:	**29/10/2010 13:38**	*Sample Weight:*	**1.0000**
Run Time (min):	**30.00**	*Sample Amount:*	**1.0000**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.71	n.a.	77.065	32.639	6.60	n.a.	BMB*
2	17.92	n.a.	752.284	461.883	93.40	n.a.	BMB*
Total:			829.349	494.522	100.00	0.000	

Appendix 8: Deuterium incorporation in phenol 99 by quantitative ^{13}C NMR spectroscopy





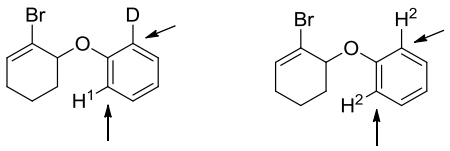
Fri Nov 20 15:23:52 GMT 2009

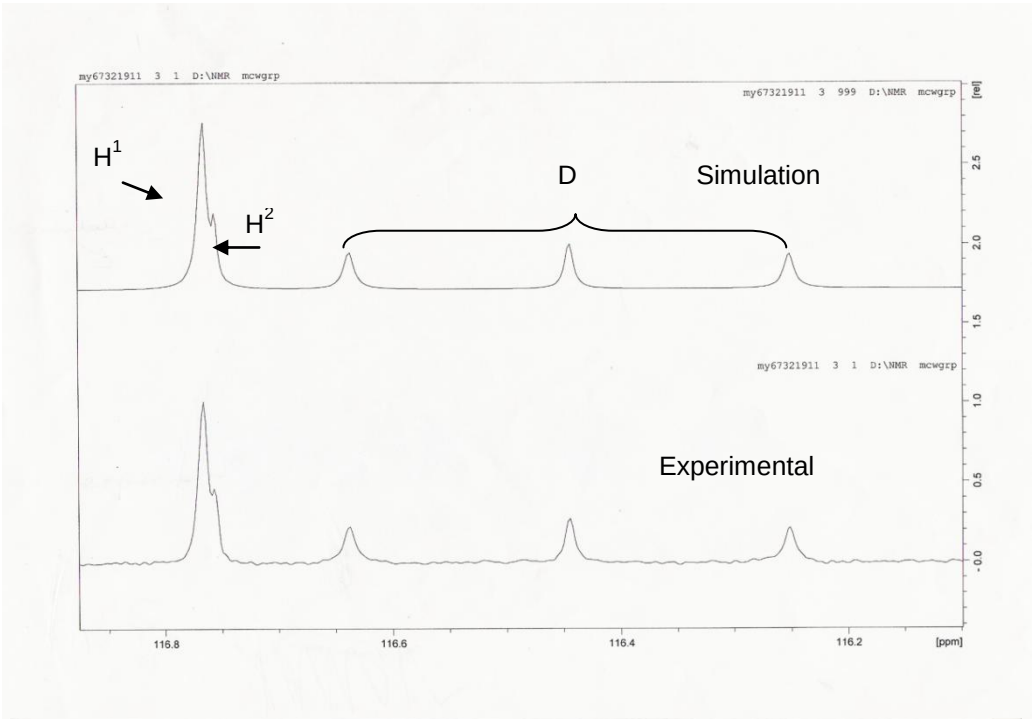
Data set: D:/NMR/data/mcwgrp/nmr/my67331911/3/pdata/1/
Fit type: Lorentzian

Fit	Frequency		Width		Intensity	Area	%Lor
	ppm	Hz	ppm	Hz			chis
1							2.2e+01
	116.697	14680.60	0.00715	0.899	1.157	6.855	100.
STD:	0.000	0.00	0.00010	0.012	0.010		
	116.687	14679.27	0.00290	0.364	0.494	1.185	100.
STD:	0.000	0.00	0.00024	0.031	0.029		
	116.569	14664.41	0.00886	1.114	0.244	1.789	100.
STD:	0.000	0.02	0.00045	0.057	0.009		
	116.376	14640.11	0.00671	0.845	0.331	1.842	100.
STD:	0.000	0.01	0.00029	0.036	0.010		
	116.182	14615.81	0.00886	1.115	0.240	1.766	100.
STD:	0.000	0.02	0.00046	0.058	0.009		

8.8%

Appendix 9: Deuterium incorporation in alkenyl bromide 100 by quantitative ^{13}C NMR spectroscopy





Thu Nov 19 16:02:14 GMT 2009

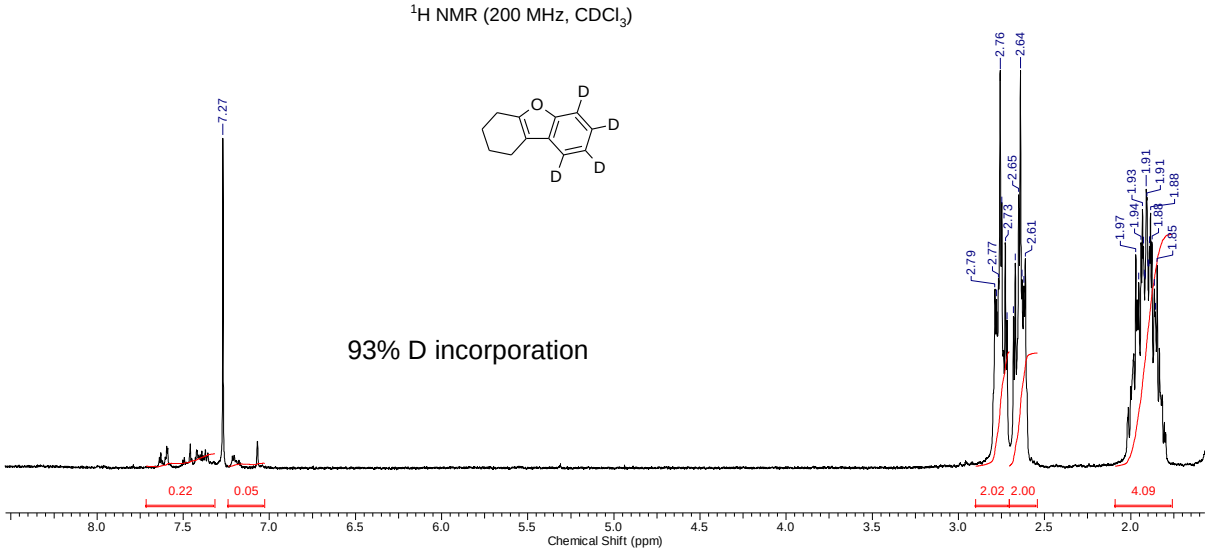
Data set: D:\NMR/data/mcwgrp/nmr/my67321811/4/pdata/1/
Fit type: Lorentzian

Fit	Frequency		Width		Intensity	Area	%Lor
	ppm	Hz	ppm	Hz			chis
1							8.2e+01
	116.698	14680.67	0.00696	0.876	1.410	8.133	100.
STD:	0.000	0.00	0.00011	0.013	0.013		
	116.687	14679.30	0.00315	0.396	0.589	1.535	100.
STD:	0.000	0.01	0.00025	0.031	0.031		
	116.569	14664.48	0.00869	1.093	0.291	2.094	100.
STD:	0.000	0.02	0.00049	0.062	0.012		
	116.376	14640.16	0.00655	0.824	0.406	2.202	100.
STD:	0.000	0.01	0.00031	0.039	0.014		
	116.183	14615.85	0.00913	1.148	0.284	2.152	100.
STD:	0.000	0.02	0.00052	0.065	0.011		

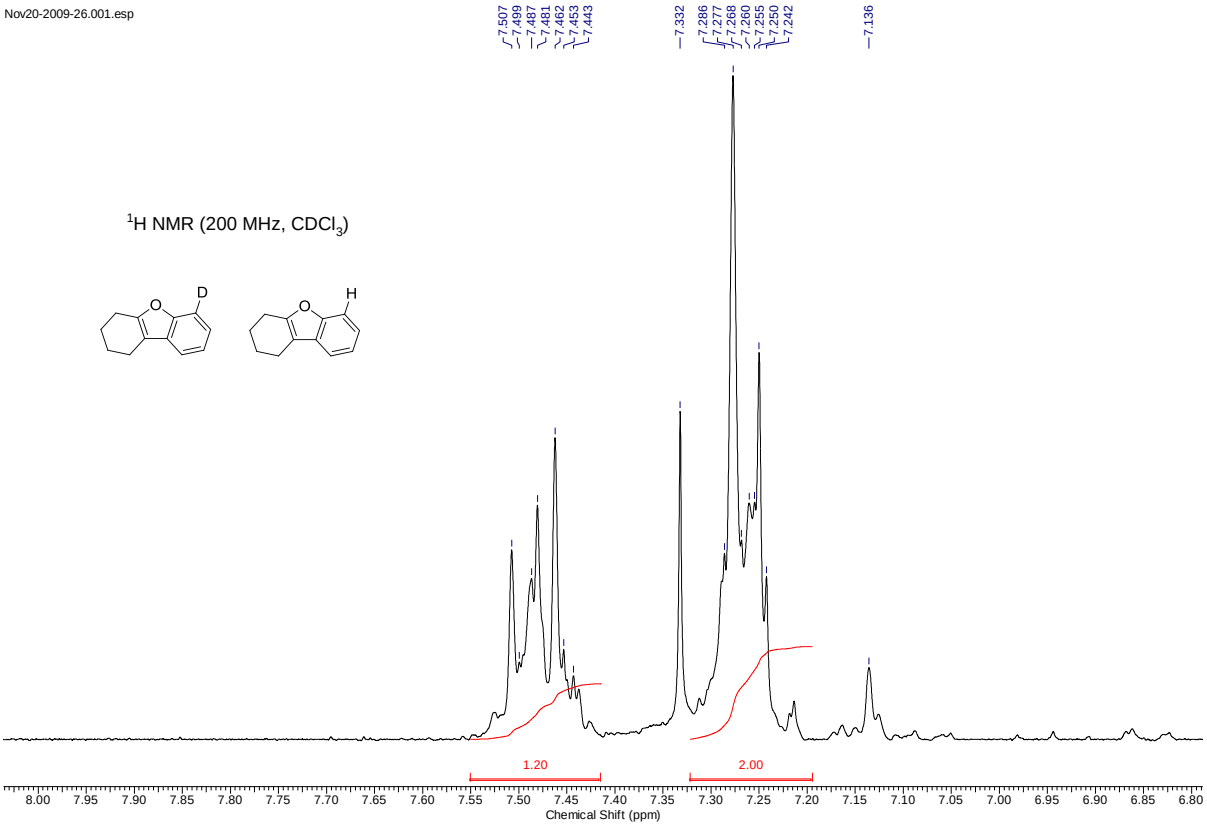
9.6%

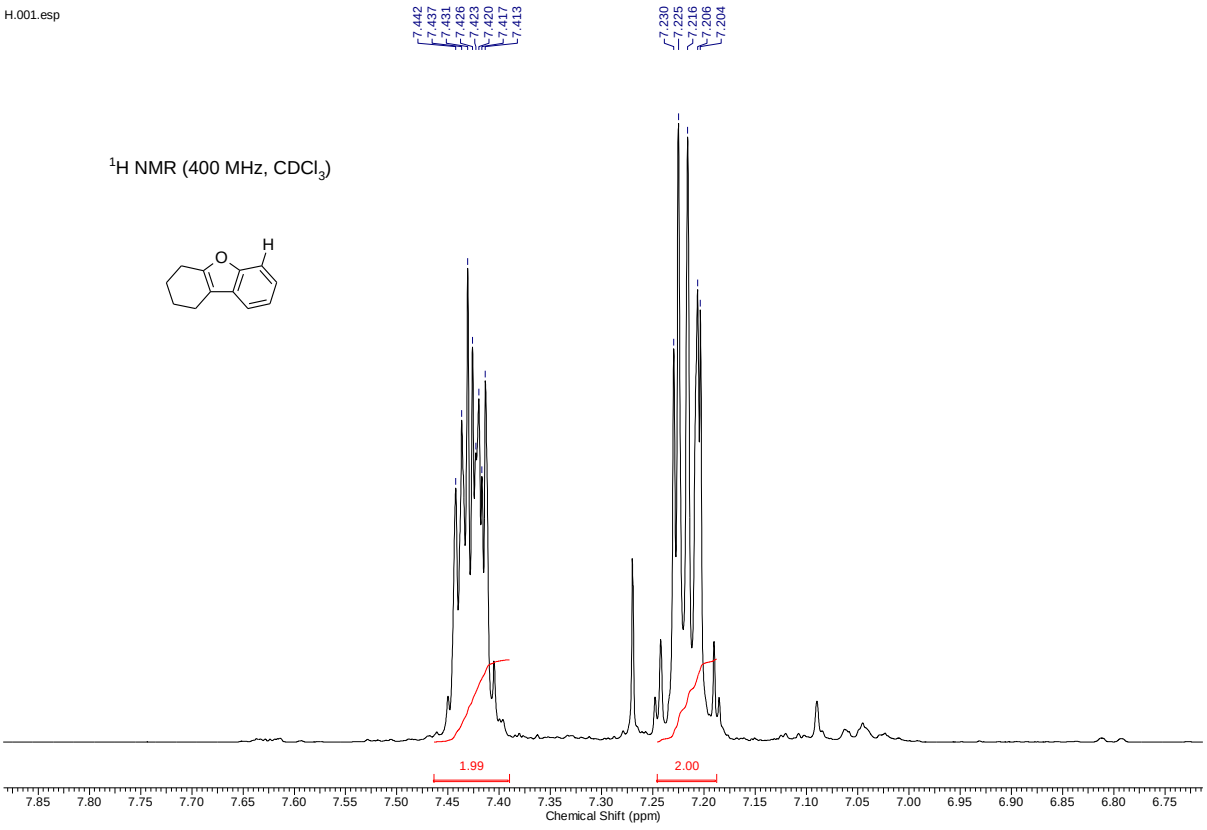
Appendix 10: Deuterium incorporation in benzofuran 102 determined by ^{1}H NMR spectroscopy

Sep16-2010-1_001000fid

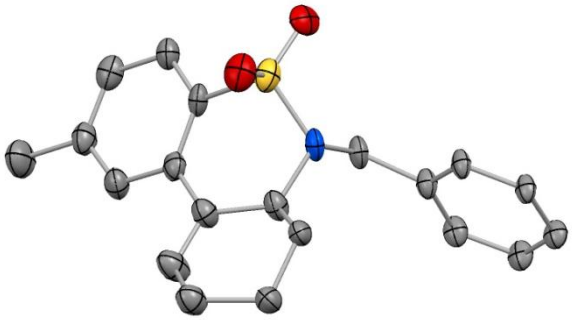


Appendix 11: Intramolecular kinetic isotope effect determined by ^{1}H NMR spectroscopy of benzofurans 101 and 59





Appendix 12: X-ray crystollagraphy of sultam 116



Crystal Structure Data

Spacegroup Symbol:	(not used)
Origin Offset:	(none)
Lattice Type:	P

General Equivalent Positions

+x +y +z	-x -y -z	1/2+x 1/2-y 1/2+z
1/2-x 1/2+y 1/2-z		

Unit Cell Parameters

a [Å]	b [Å]	c [Å]	alpha [°]	beta [°]	gamma [°]
10.6800	10.6510	15.1190	90.000	96.619	90.000

Fractional Coordinates of Atoms in the Asymmetric Unit

Site Label	Element	x	y	z
C2	C	0.8564	0.5889	0.3634

C3	C	0.9373	0.6248	0.4379
C4	C	0.8868	0.6763	0.5115
C5	C	0.7550	0.6931	0.5083
C6	C	0.6993	0.7462	0.5893
C7	C	0.6778	0.6583	0.4324
C8	C	0.7245	0.6045	0.3572
C9	C	0.6395	0.5570	0.2793
C11	C	0.6889	0.5561	0.1938
C12	C	0.6253	0.4663	0.1260
C13	C	0.4830	0.4607	0.1241
C14	C	0.4396	0.4404	0.2164
C15	C	0.5202	0.5394	0.2831
C16	C	0.8661	0.6979	0.1555
C17	C	0.8449	0.7124	0.0542
C18	C	0.8726	0.6128	0.9993
C19	C	0.8623	0.6292	0.9068
C20	C	0.8220	0.7446	0.8693
C21	C	0.7910	0.8430	0.9241
C22	C	0.7995	0.8258	0.0164
C31	C	0.6955	0.4776	0.1931
C32	C	0.5996	0.4899	0.1122
C33	C	0.4832	0.4262	0.1392
C34	C	0.4276	0.4926	0.2082
C35	C	0.5331	0.5026	0.2882
C36	C	0.8135	0.6748	0.1560
C37	C	0.8155	0.6867	0.0544
C38	C	0.8608	0.5876	0.0064
C39	C	0.8657	0.5997	0.9145
C40	C	0.8243	0.7105	0.8708
C41	C	0.7815	0.8107	0.9192
C42	C	0.7763	0.7985	0.0109
H31	H	0.0249	0.6154	0.4388
H41	H	0.9396	0.6998	0.5617
H61	H	0.7045	0.8361	0.5890
H62	H	0.6130	0.7208	0.5880
H63	H	0.7457	0.7152	0.6425
H71	H	0.5910	0.6706	0.4302
H111	H	0.6552	0.6343	0.1690
H121	H	0.6476	0.4875	0.0674
H122	H	0.6570	0.3837	0.1422
H131	H	0.4509	0.3927	0.0848
H132	H	0.4479	0.5397	0.1022
H141	H	0.3510	0.4612	0.2145
H142	H	0.4536	0.3537	0.2362
H151	H	0.4794	0.5840	0.3250
H161	H	0.8192	0.7631	0.1824
H162	H	0.9549	0.7082	0.1747
H181	H	0.8979	0.5356	0.0240

H191	H	0.8812	0.5637	0.8696
H201	H	0.8168	0.7563	0.8077
H211	H	0.7640	0.9207	0.8999
H221	H	0.7748	0.8902	0.0527
H311	H	0.7099	0.3889	0.2087
H321	H	0.5830	0.5777	0.0979
H322	H	0.6294	0.4476	0.0616
H331	H	0.5068	0.3421	0.1599
H332	H	0.4210	0.4203	0.0872
H341	H	0.4012	0.5747	0.1873
H342	H	0.3558	0.4474	0.2258
H351	H	0.5194	0.4698	0.3429
H361	H	0.8854	0.7197	0.1862
H362	H	0.7355	0.7118	0.1711
H381	H	0.8873	0.5132	0.0353
H391	H	0.8967	0.5342	0.8824
H401	H	0.8245	0.7177	0.8094
H411	H	0.7567	0.8855	0.8908
H421	H	0.7467	0.8649	0.0429
N10	N	0.8263	0.5740	0.1860
N30	N	0.8181	0.5417	0.1872
O23	O	0.8751	0.3848	0.2786
O24	O	0.0466	0.5437	0.2667
O43	O	0.9225	0.3788	0.2795
O44	O	0.0335	0.5890	0.2678
S1	S	0.9172	0.5149	0.2730

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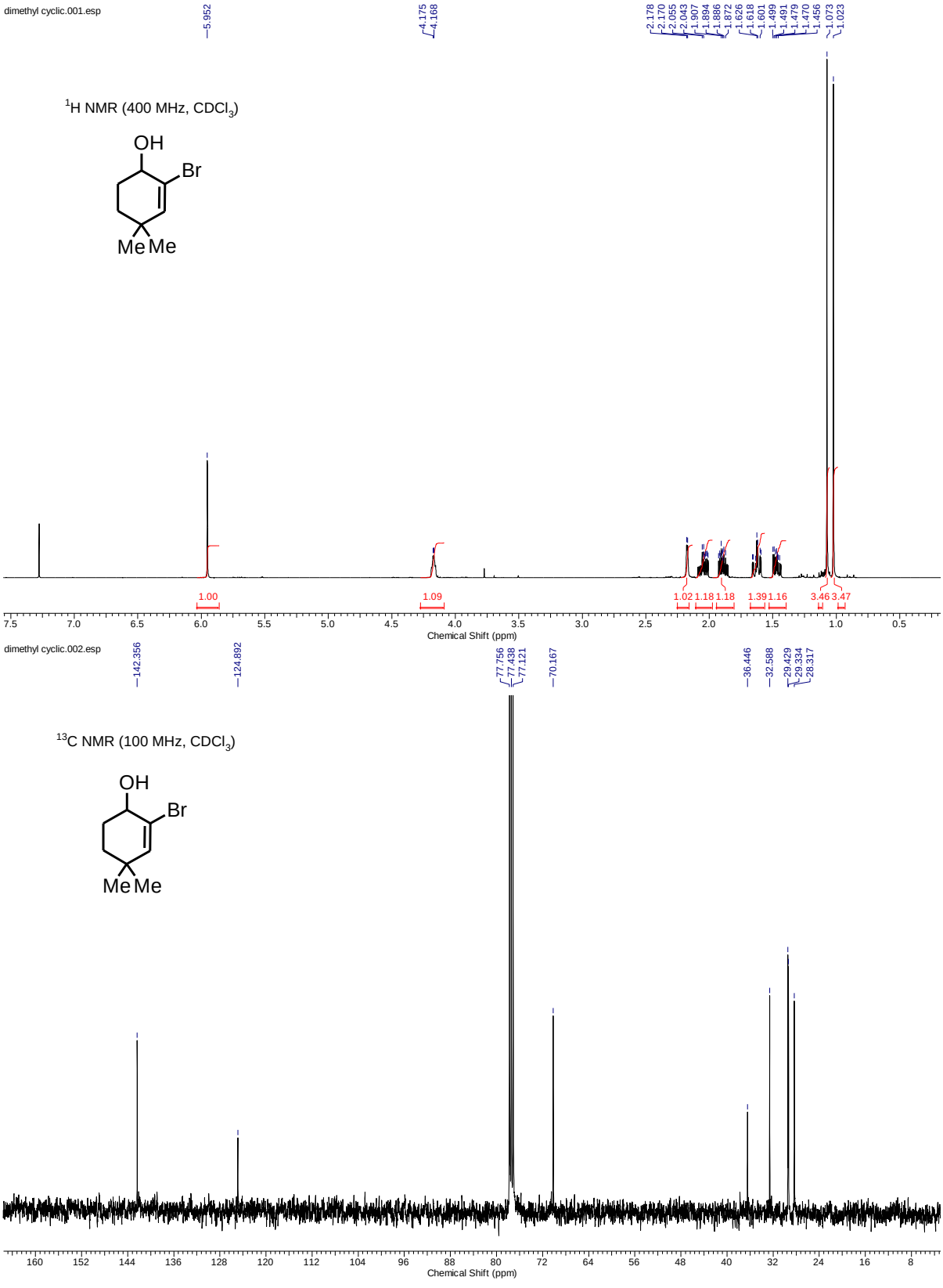
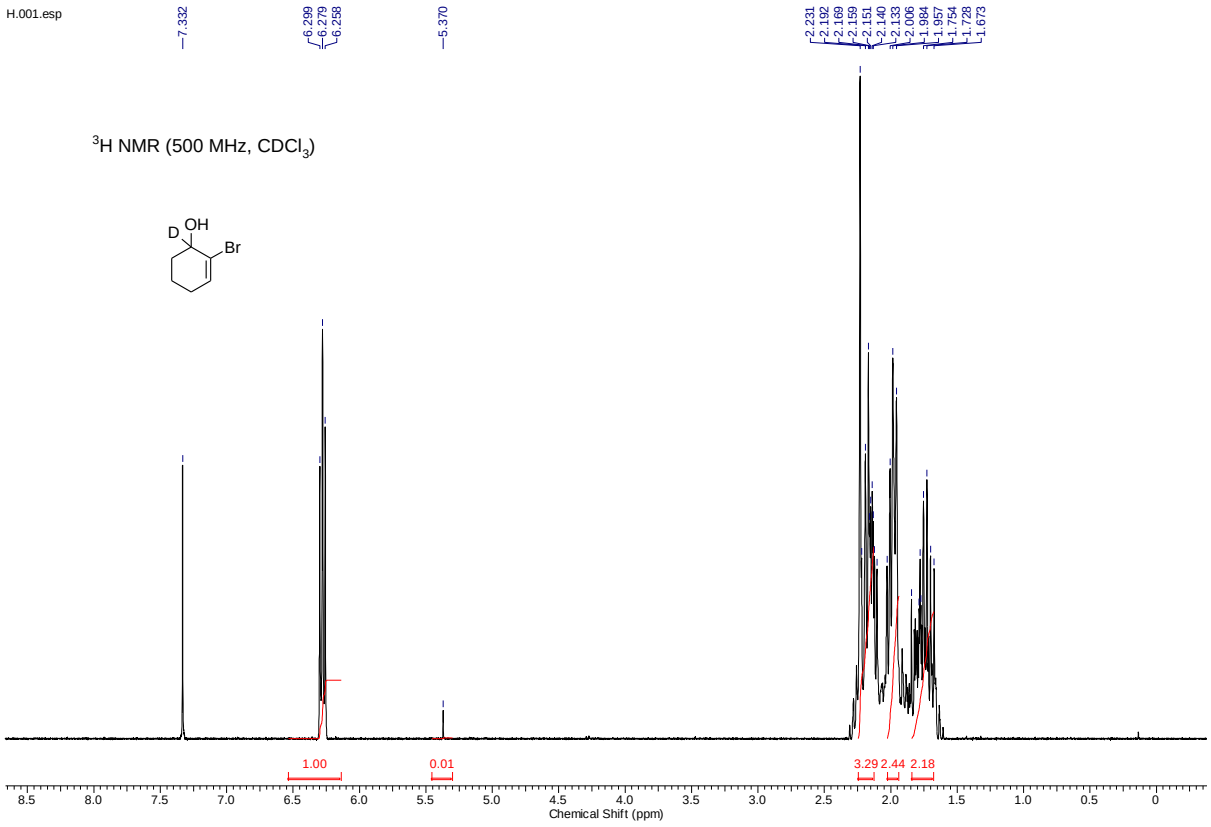
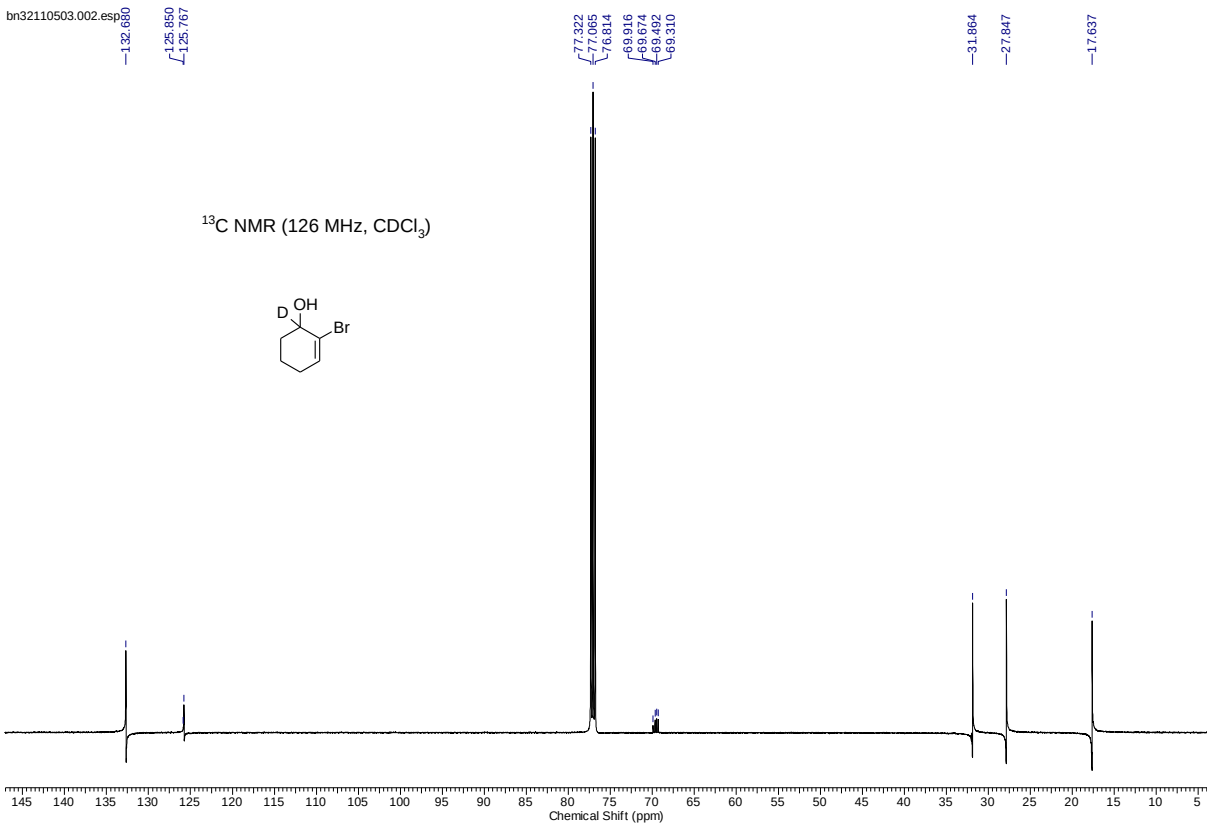
Spectral data for novel compounds

2-Bromo-4,4-dimethylcyclohex-2-enol, 24

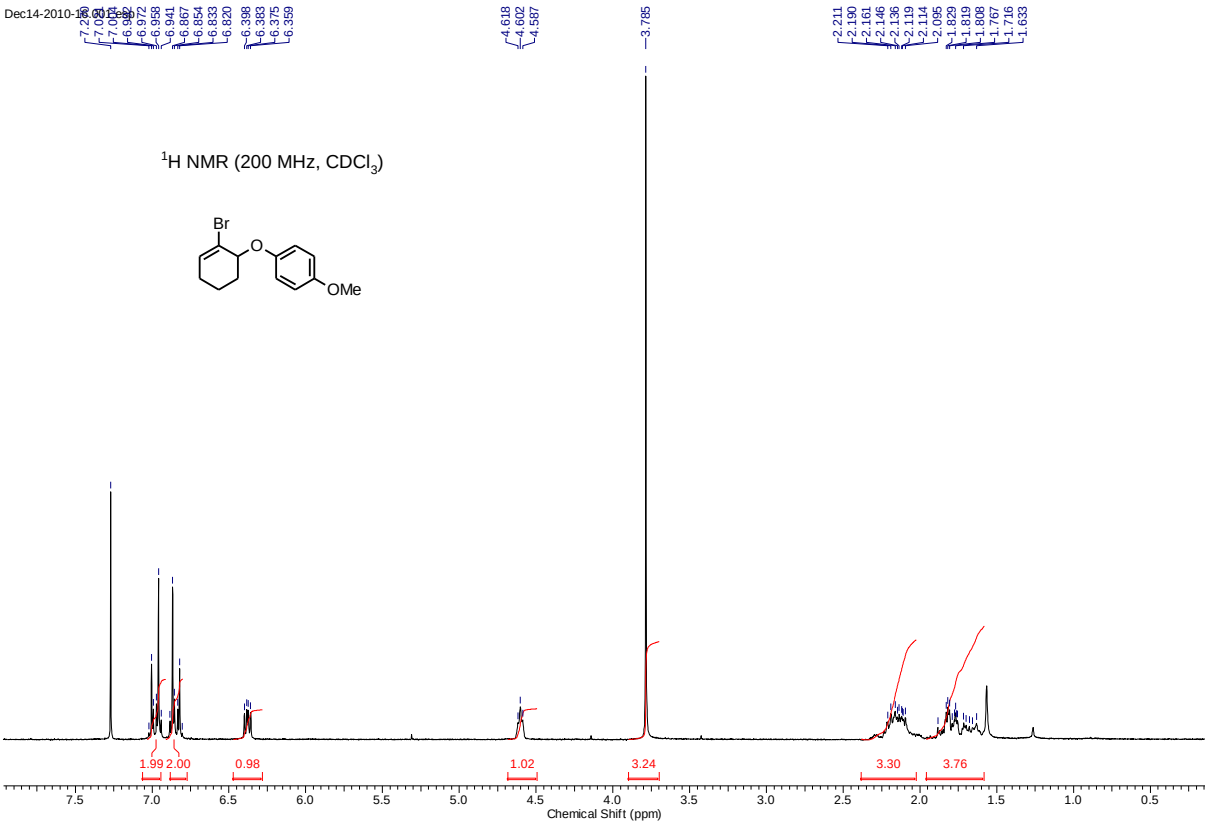


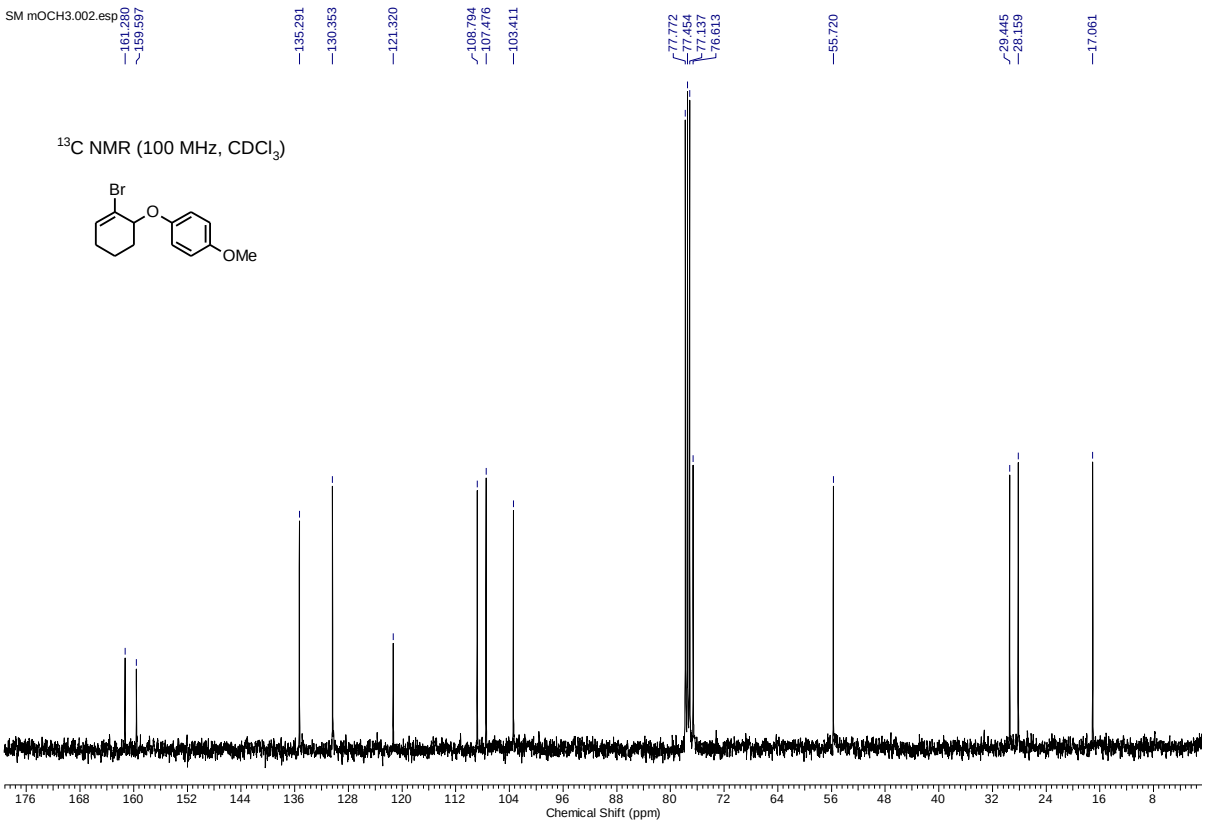
(1-D-)2-Bromocyclohex-2-enol, 46



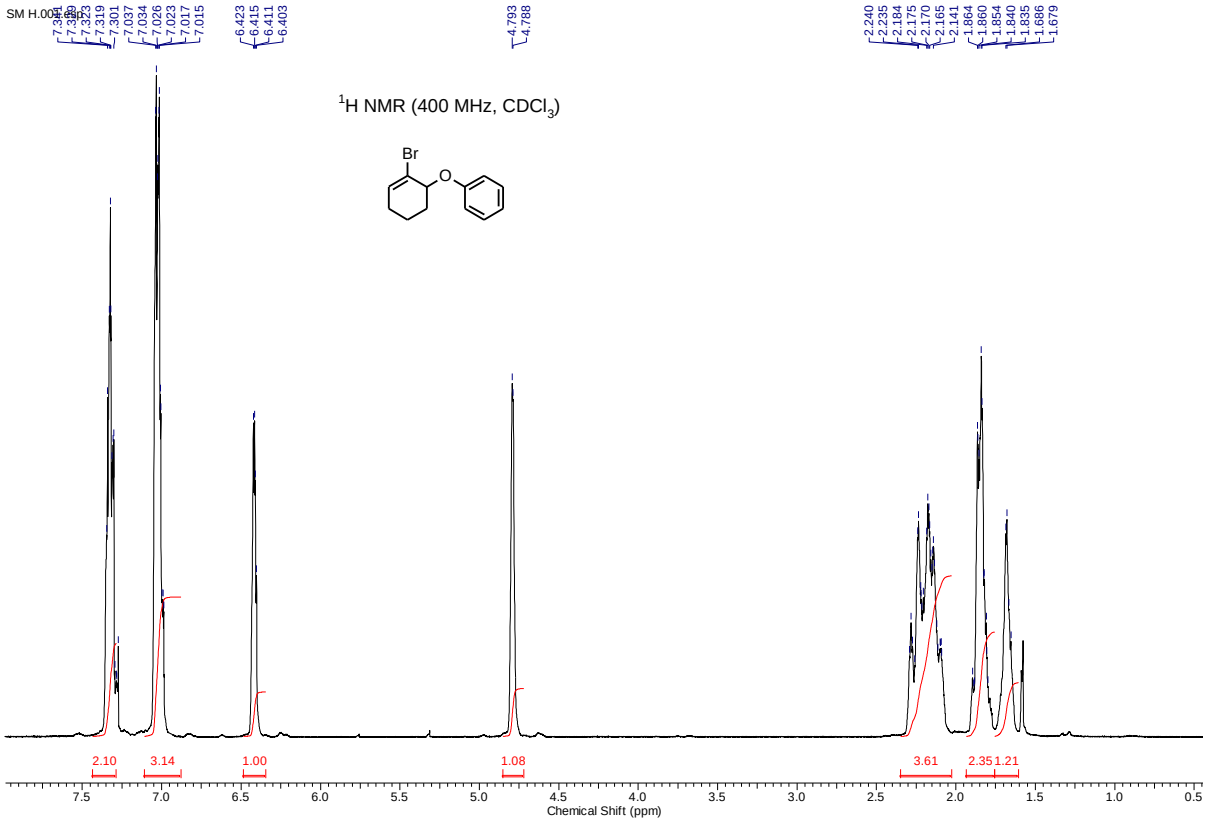


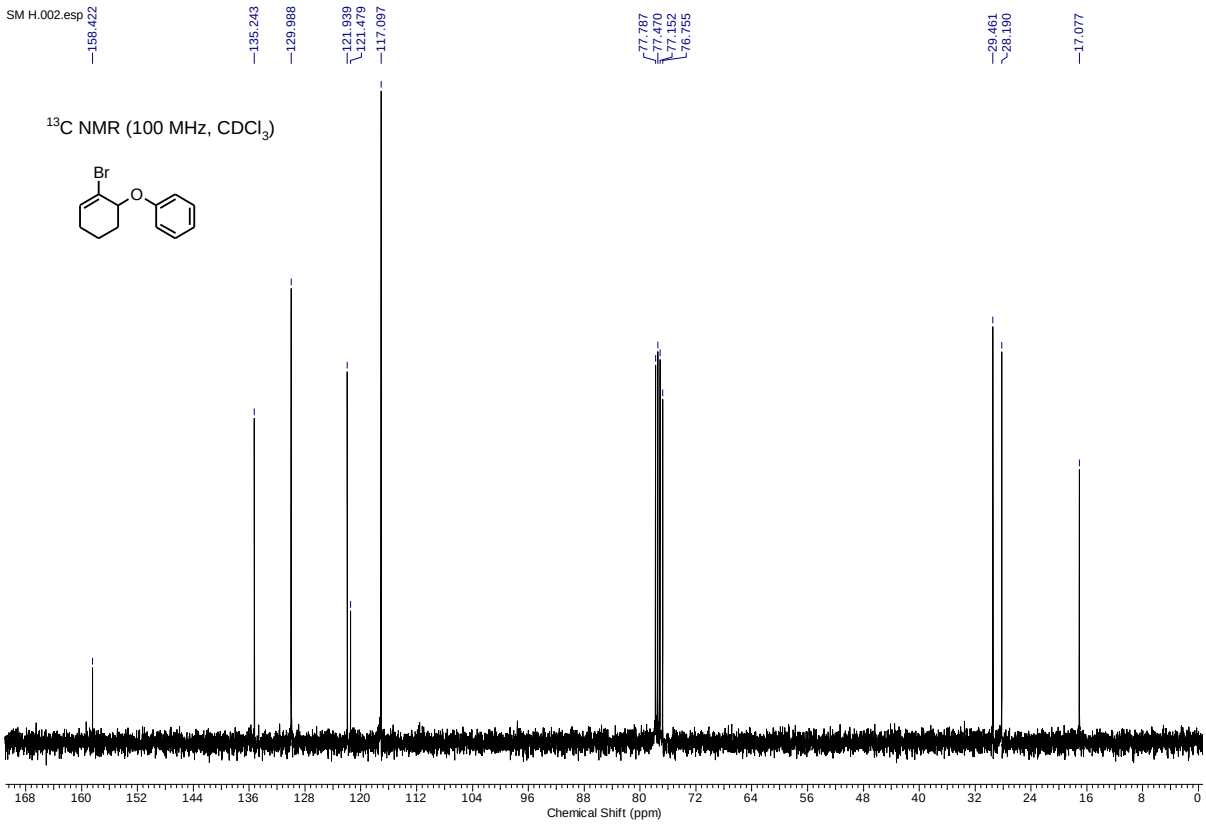
1-(2-Bromocyclohex-2-enyloxy)-3-methoxybenzene, 31





(2-Bromocyclohex-2-enyloxy)benzene, 33





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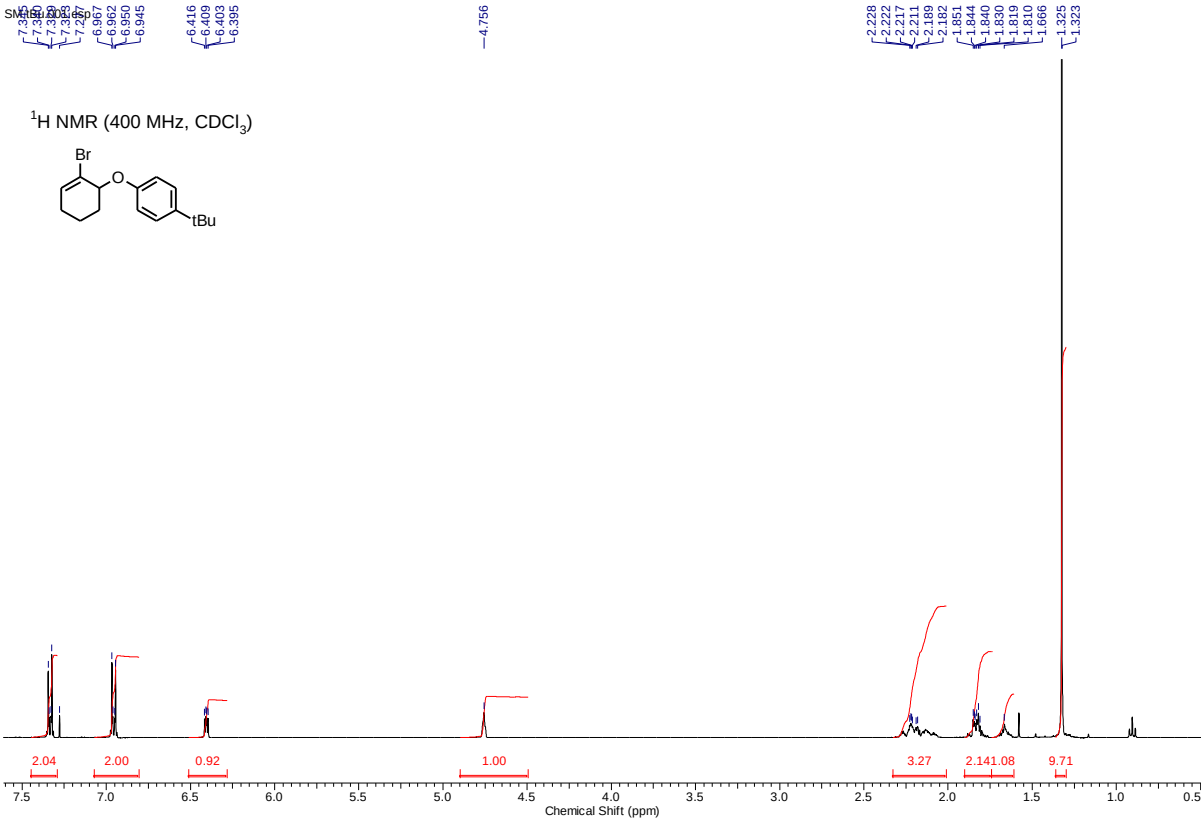

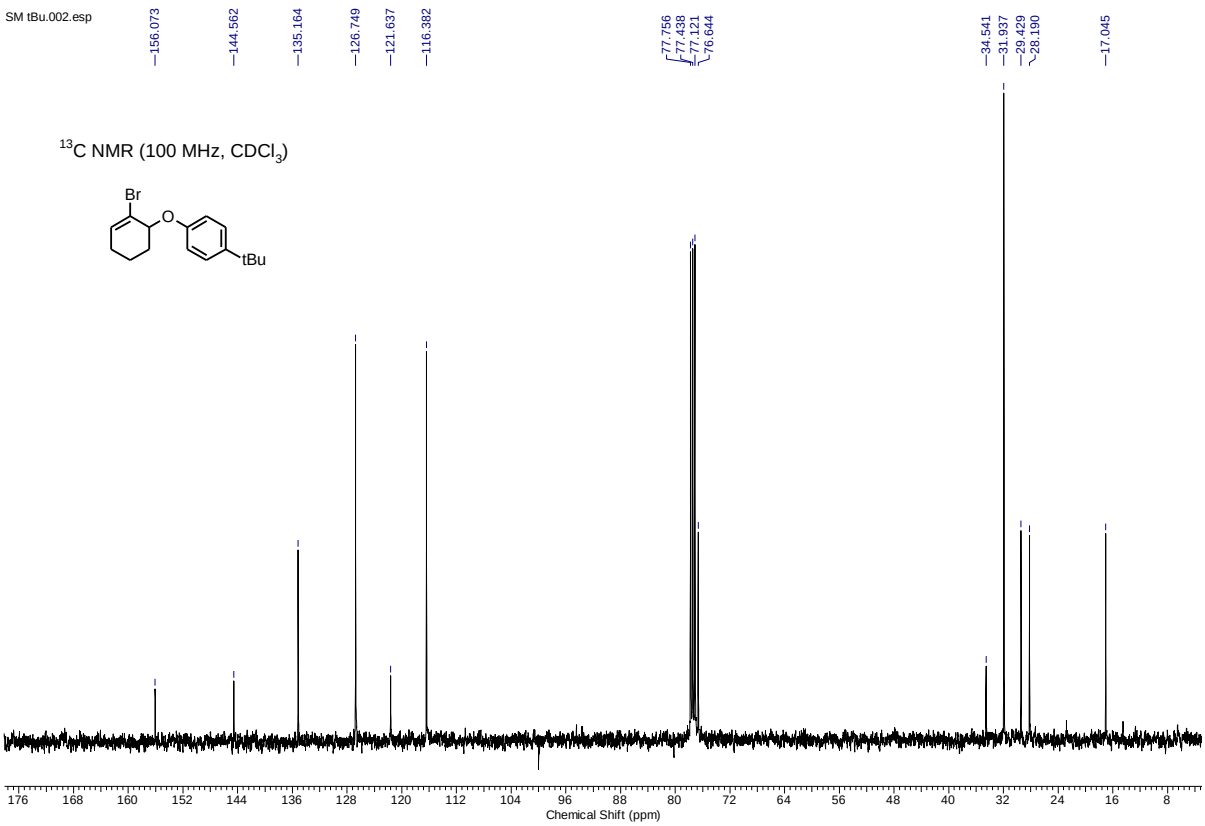

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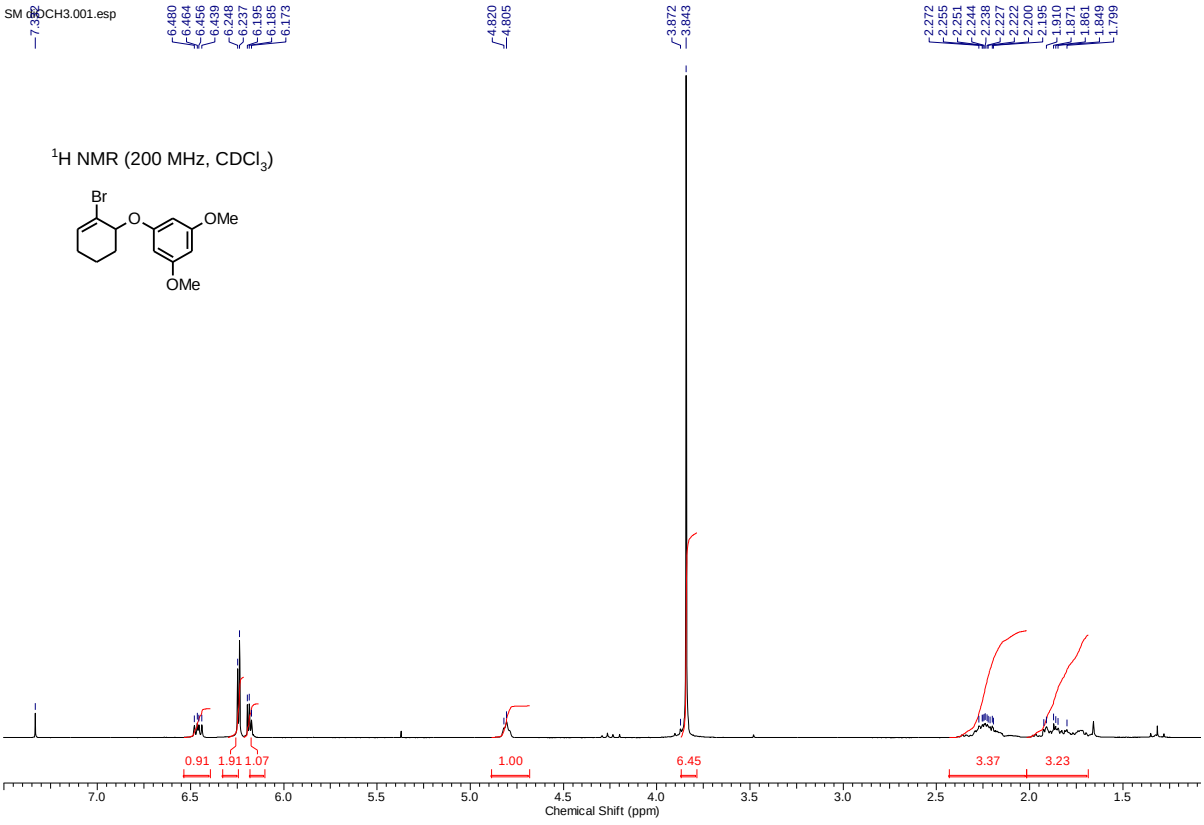

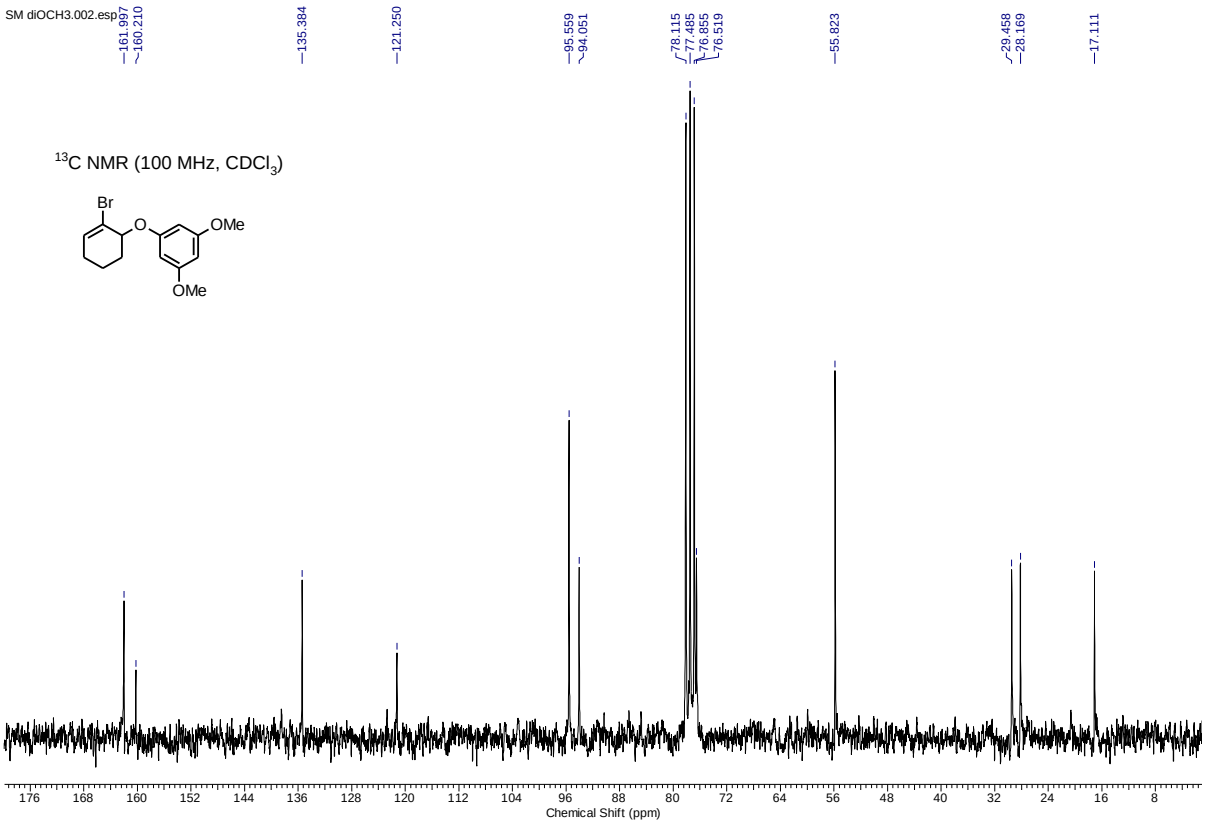

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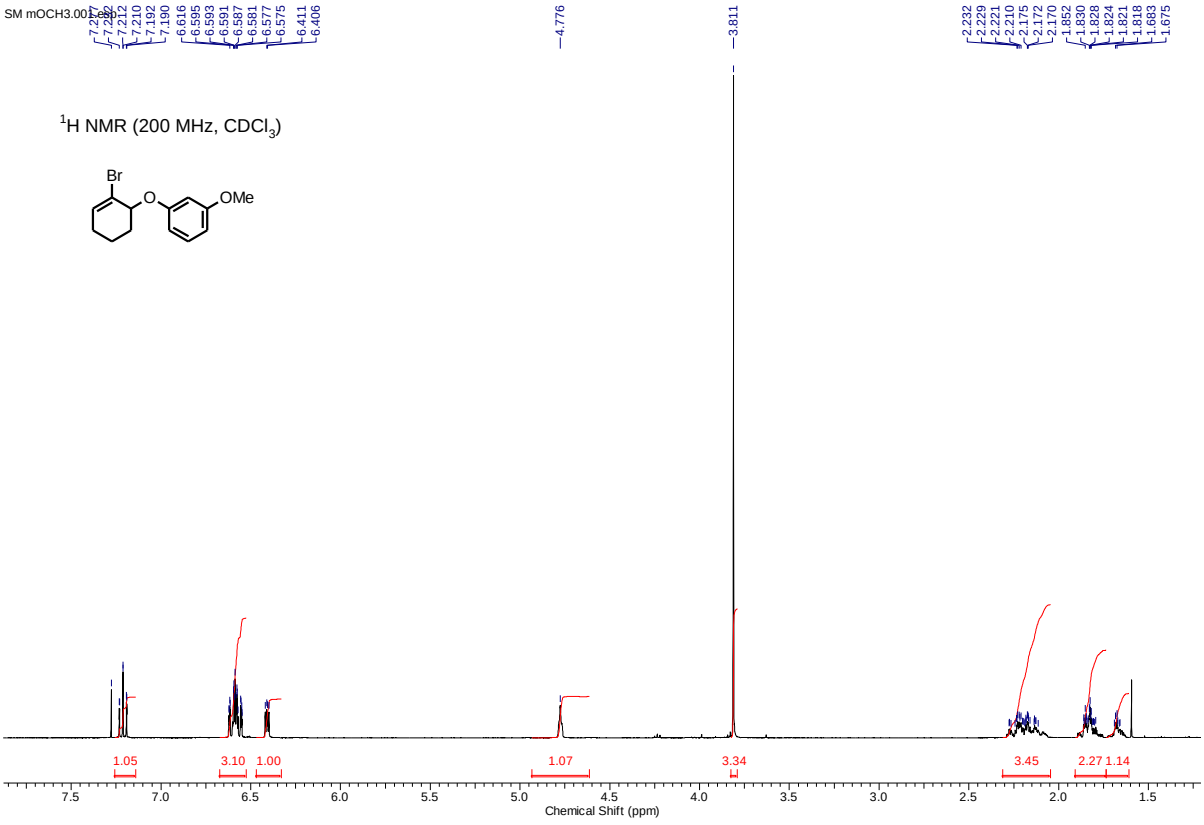
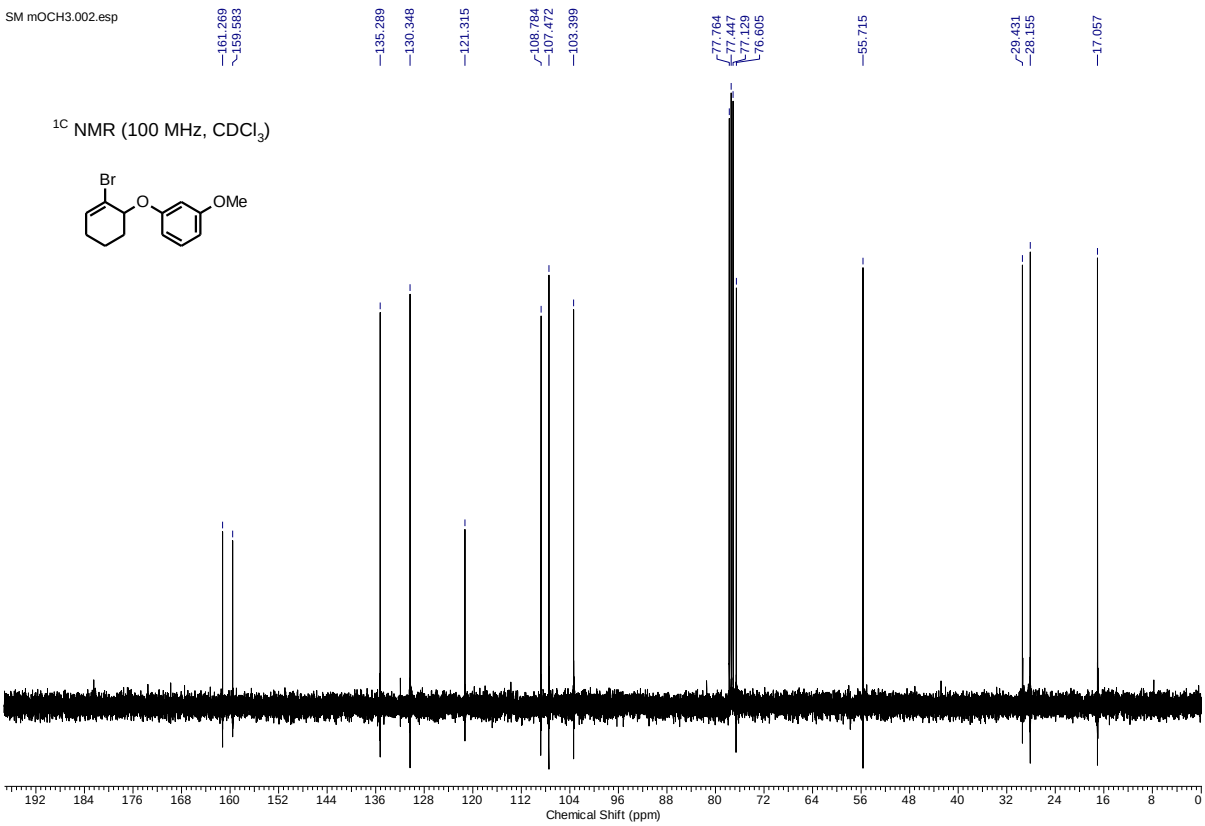
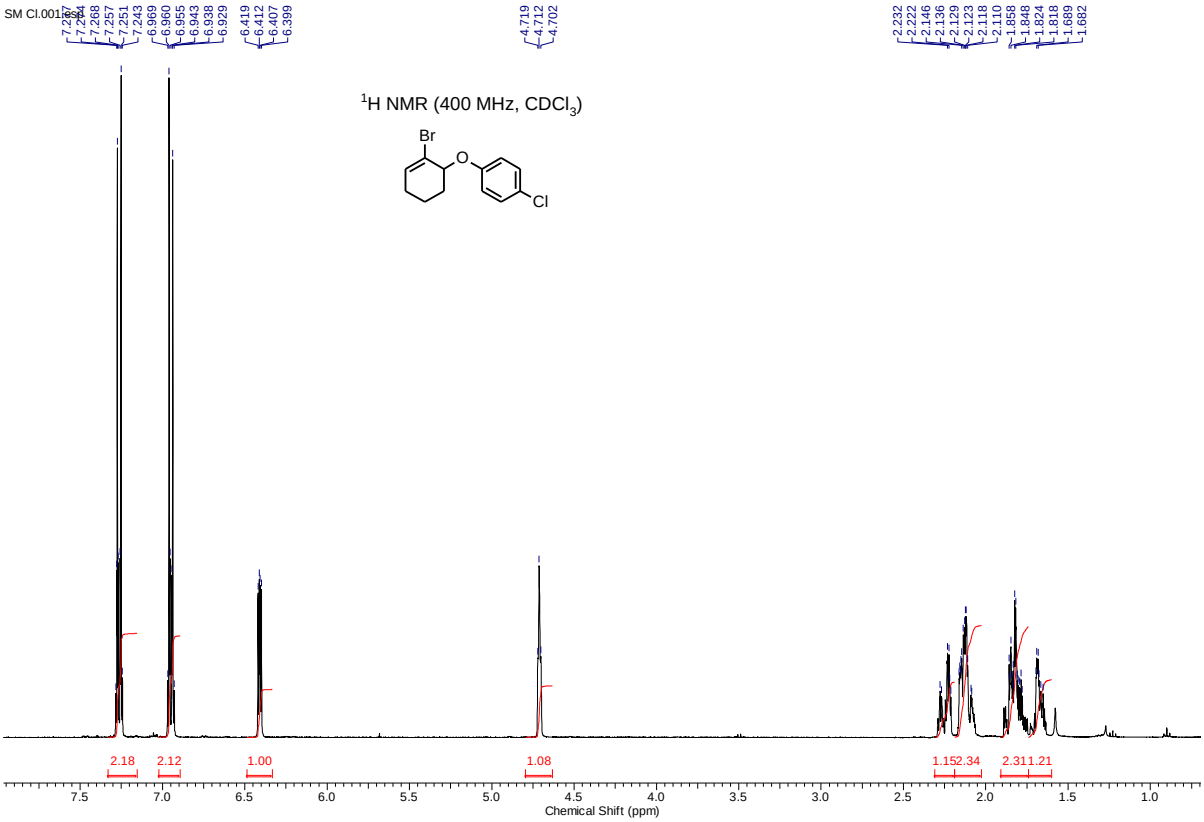
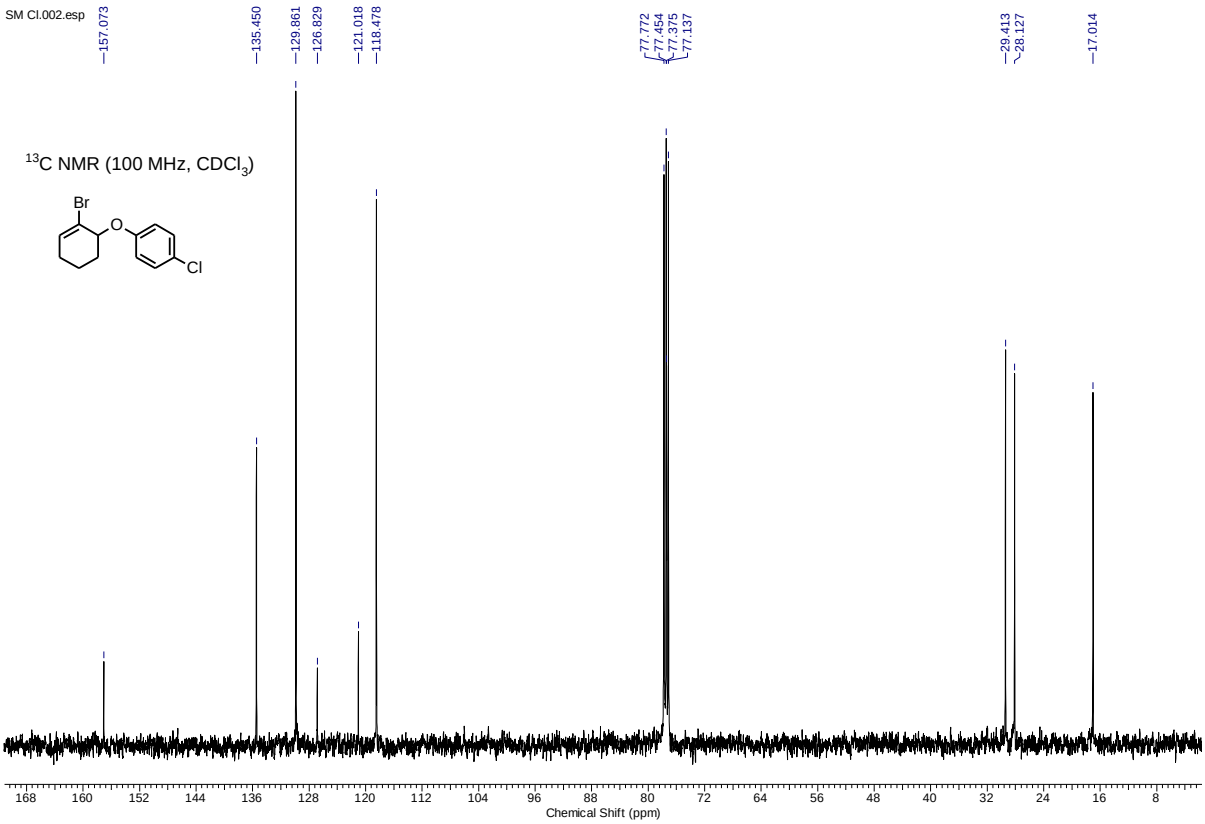




1-(2-Bromocyclohex-2-enyloxy)-4-chlorobenzene, 37





Ethyl 4-(2-bromocyclohex-2-enyloxy)benzoate, 38

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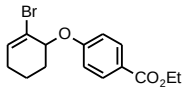
^{1}H NMR (400 MHz, $CDCl_3$)



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132.020
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120.621
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76.390
61.102
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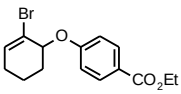
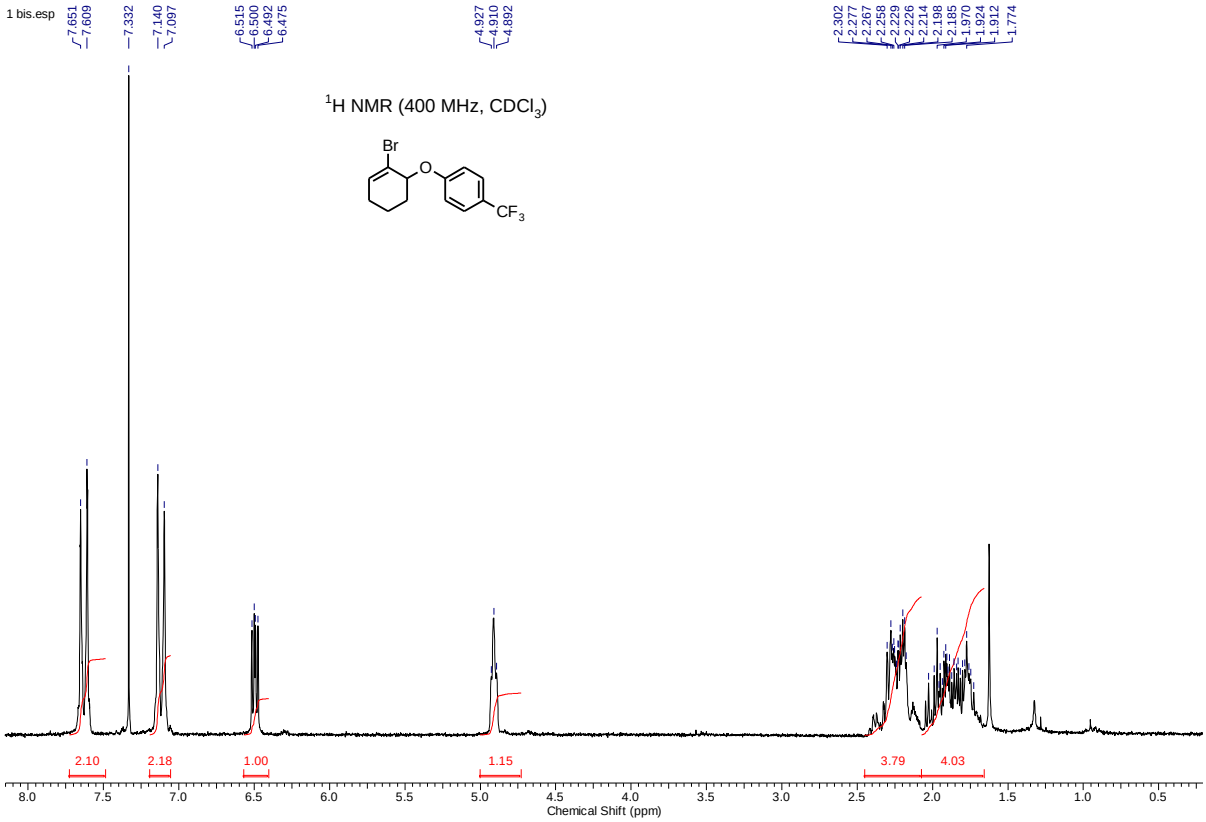
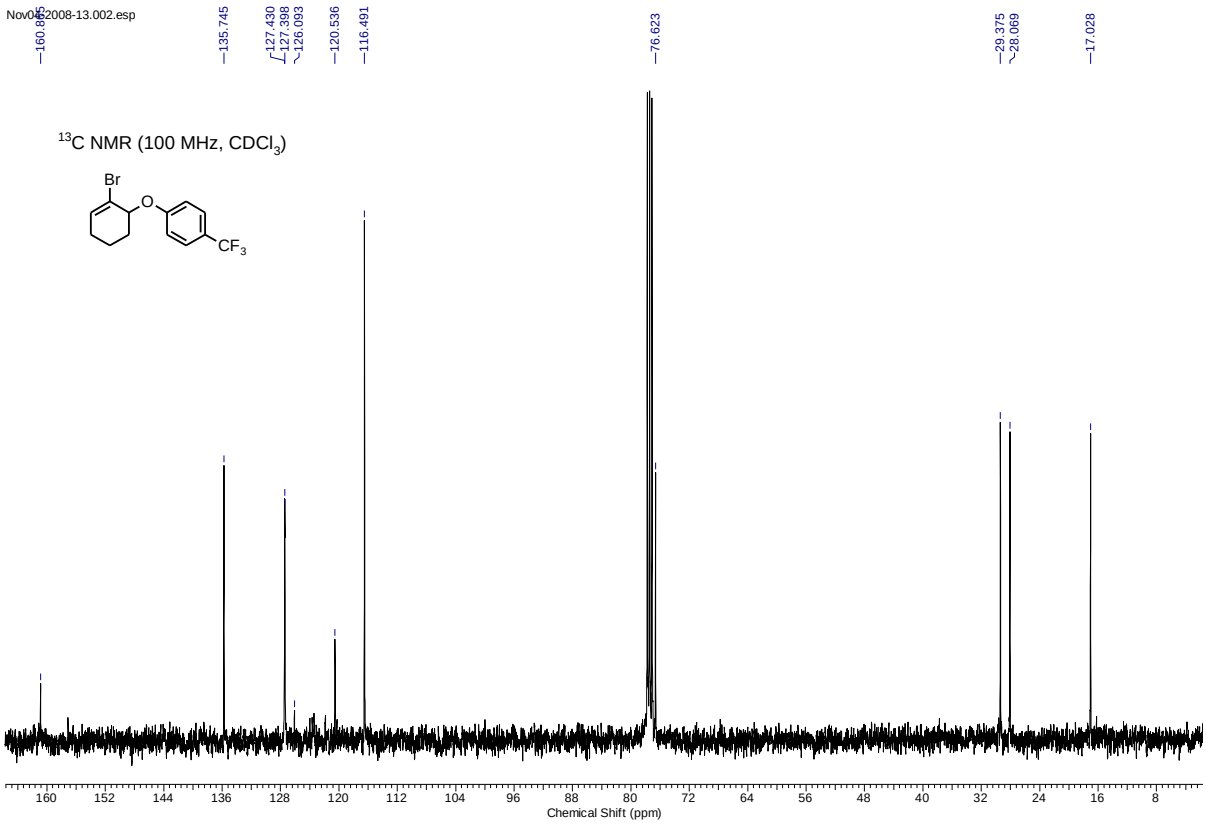
17.061
14.807

^{13}C NMR (100 MHz, $CDCl_3$)

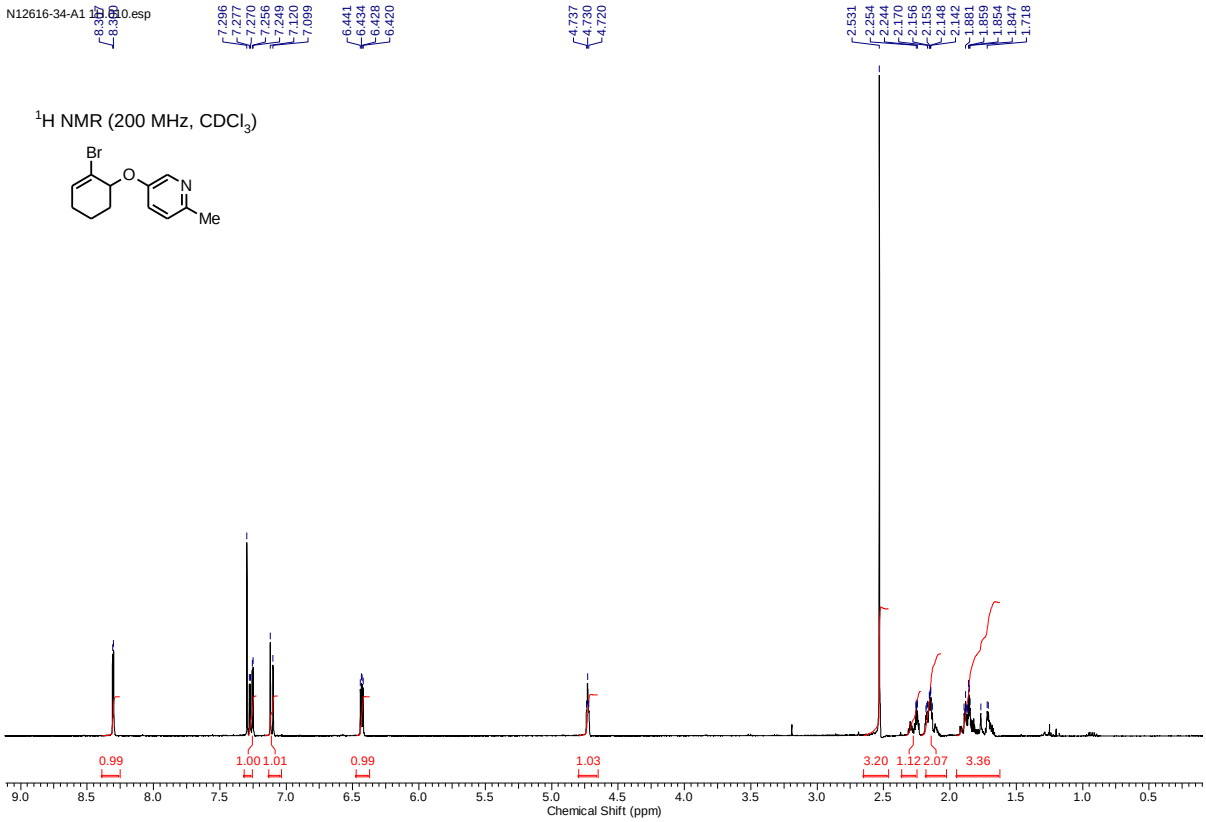


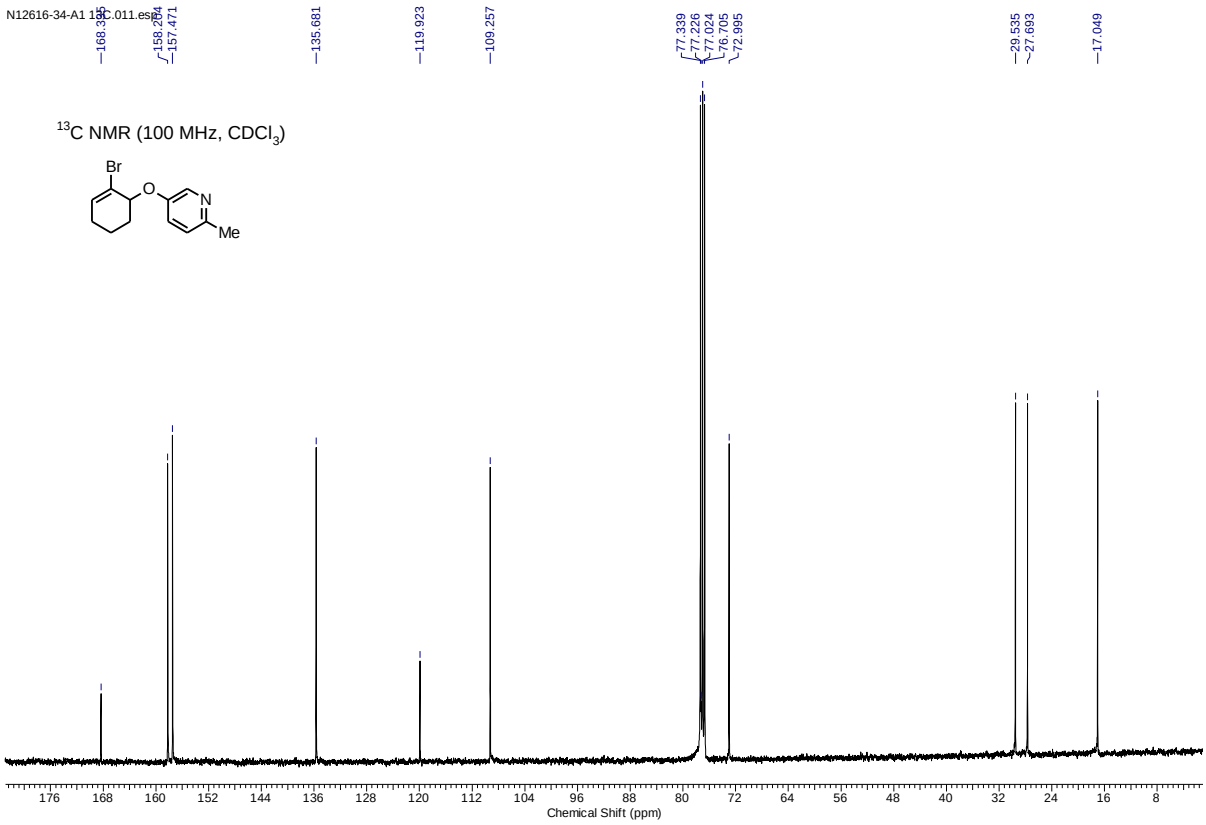
1-(2-Bromocyclohex-2-enyloxy)-4-(trifluoromethyl)benzene, 39



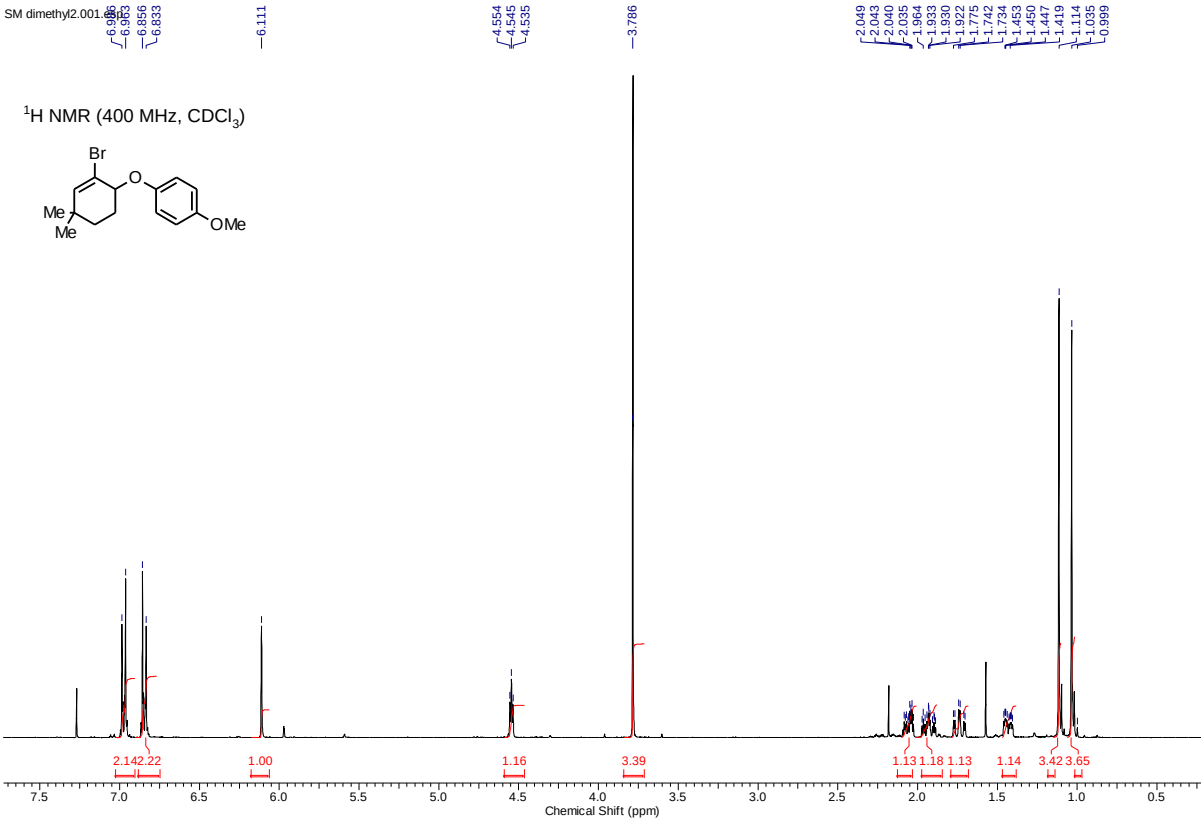


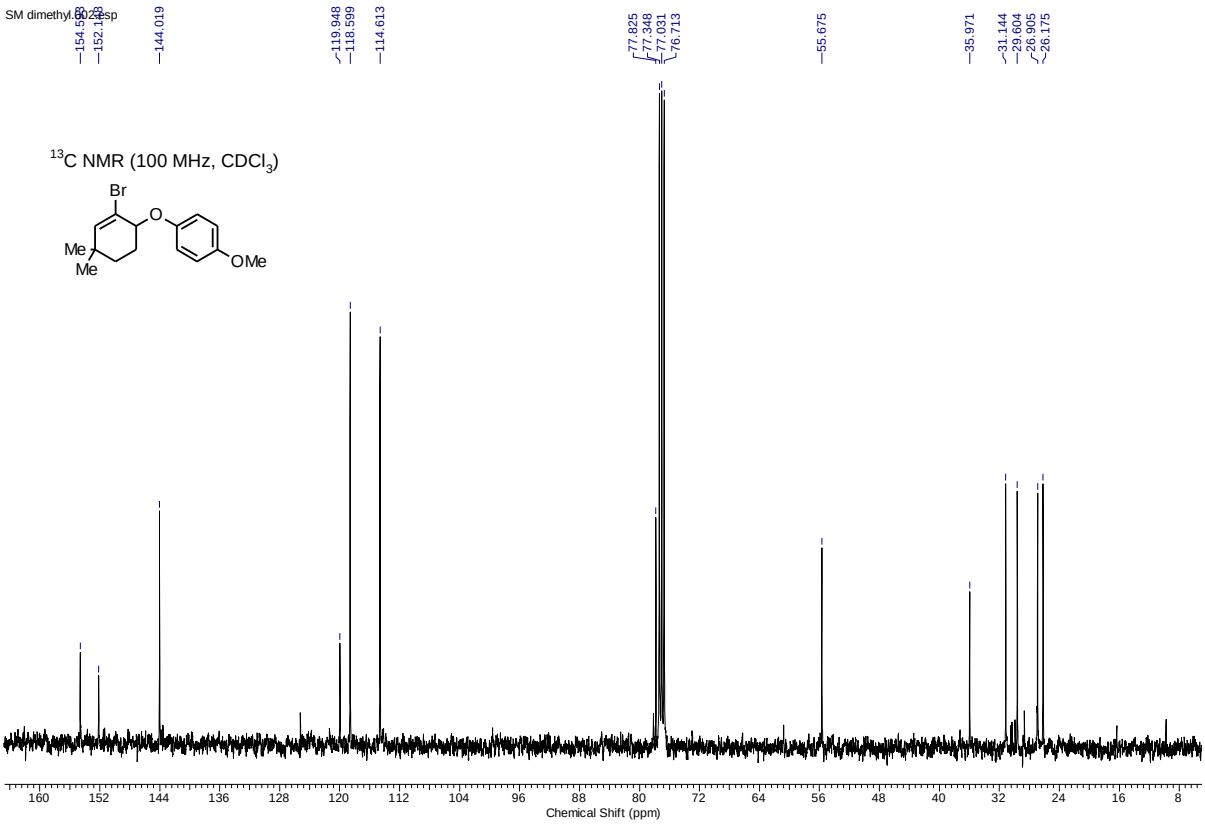
5-(2-Bromocyclohex-2-enyloxy)-2-methylpyridine, 40



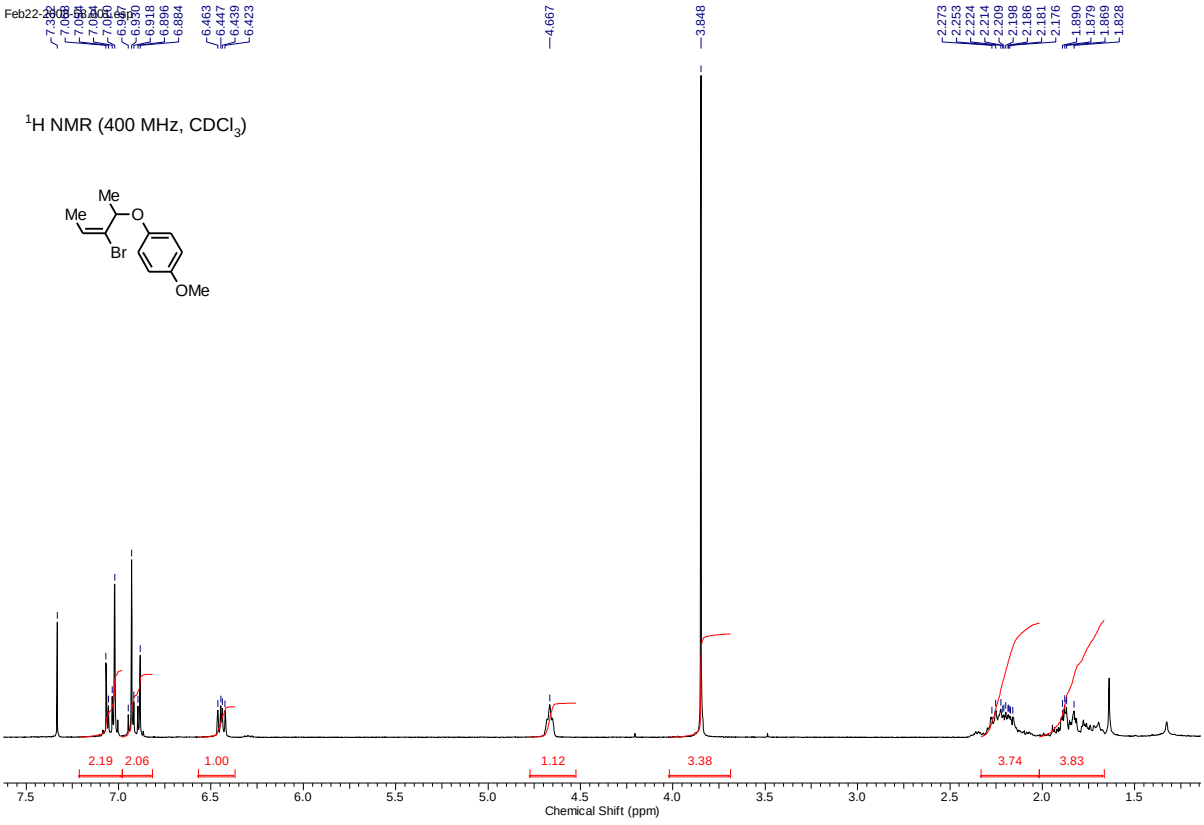


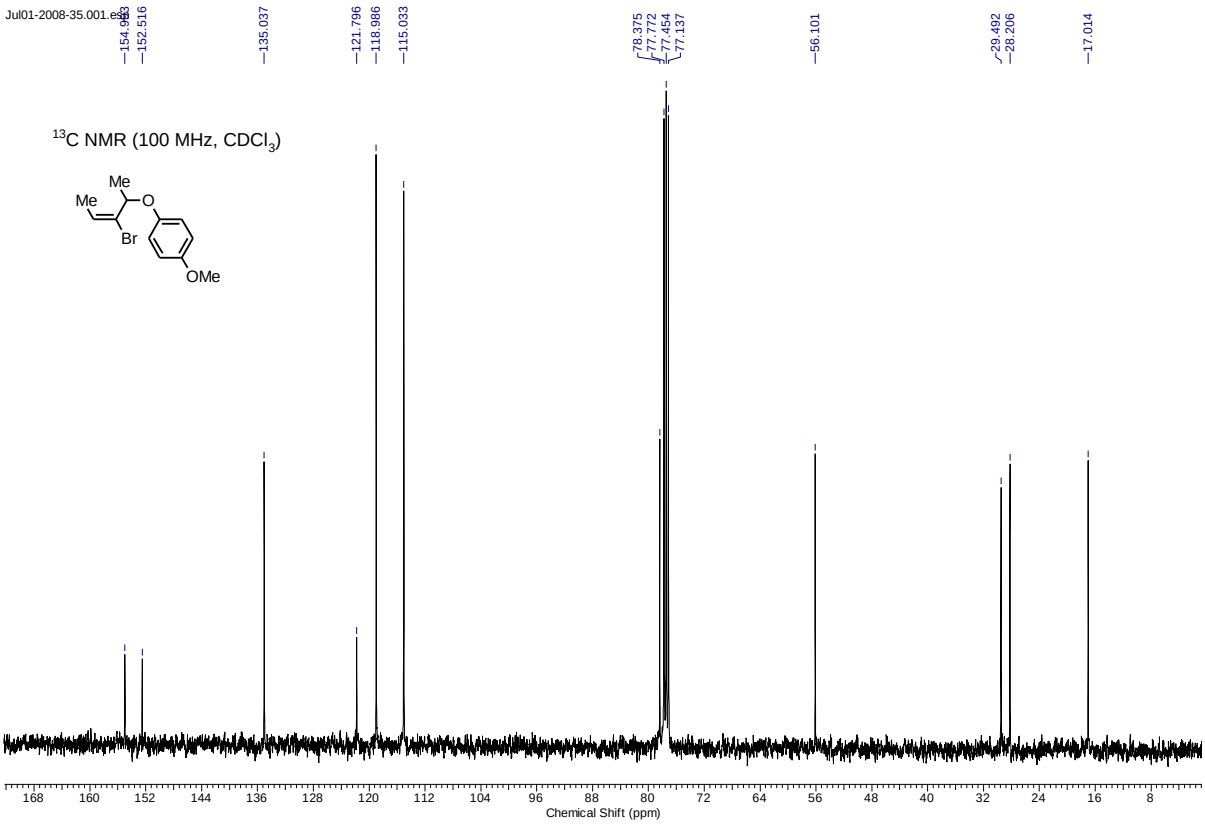
1-(2-Bromo-4,4-dimethylcyclohex-2-enyloxy)-4-methoxybenzene, 41



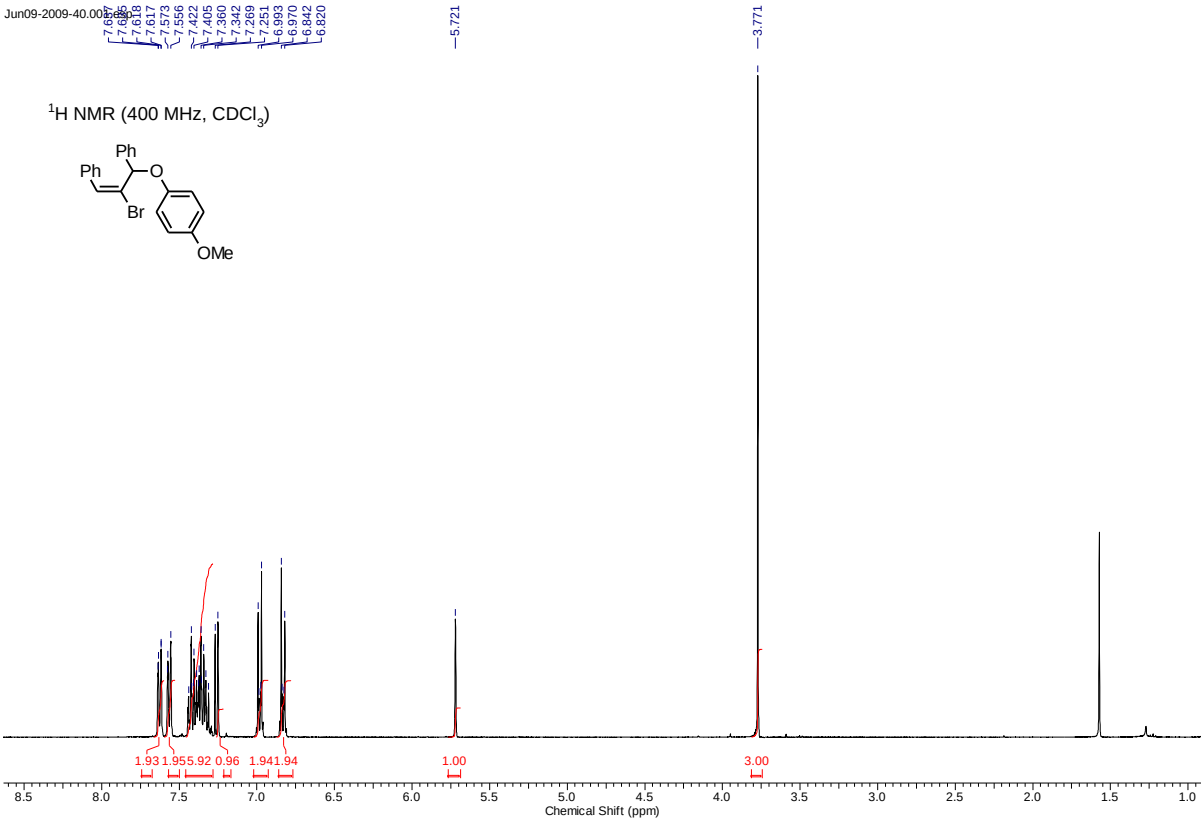


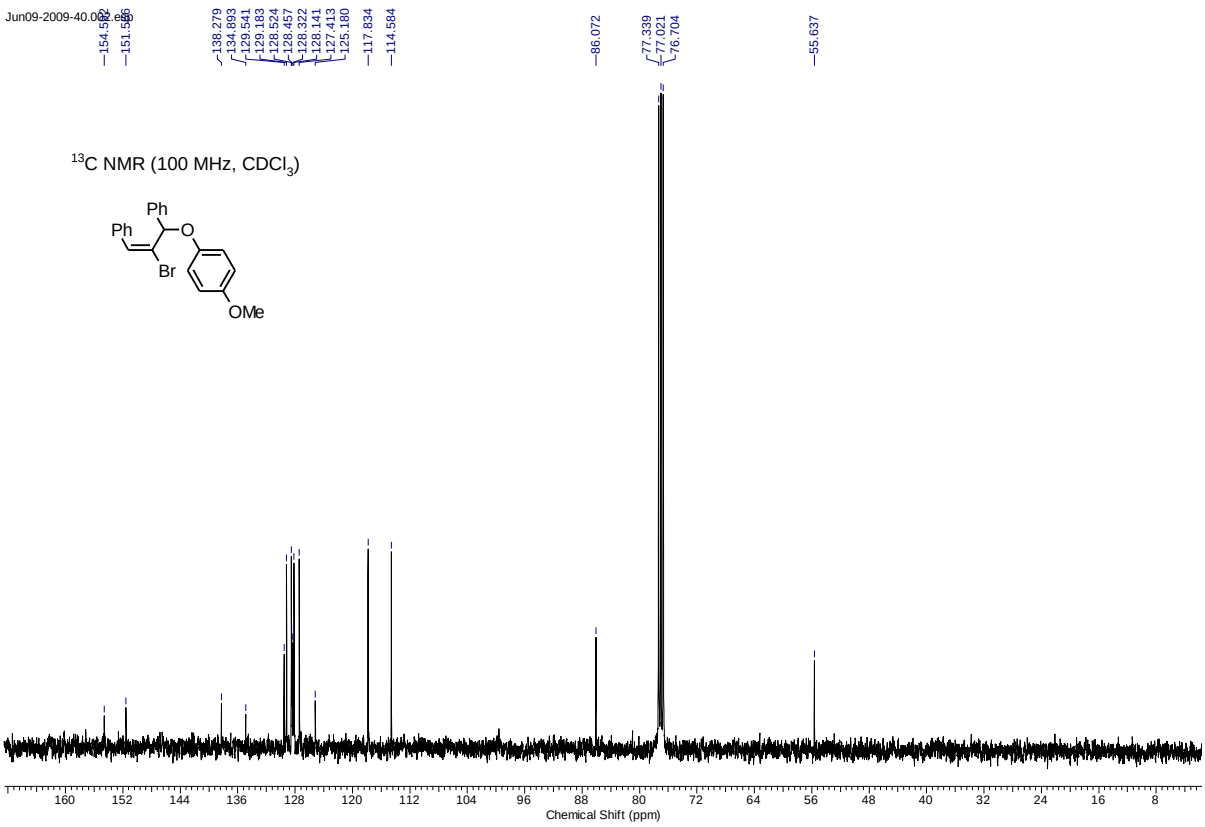
1-(3-Bromopent-3-en-2-yloxy)-4-methoxybenzene, 42



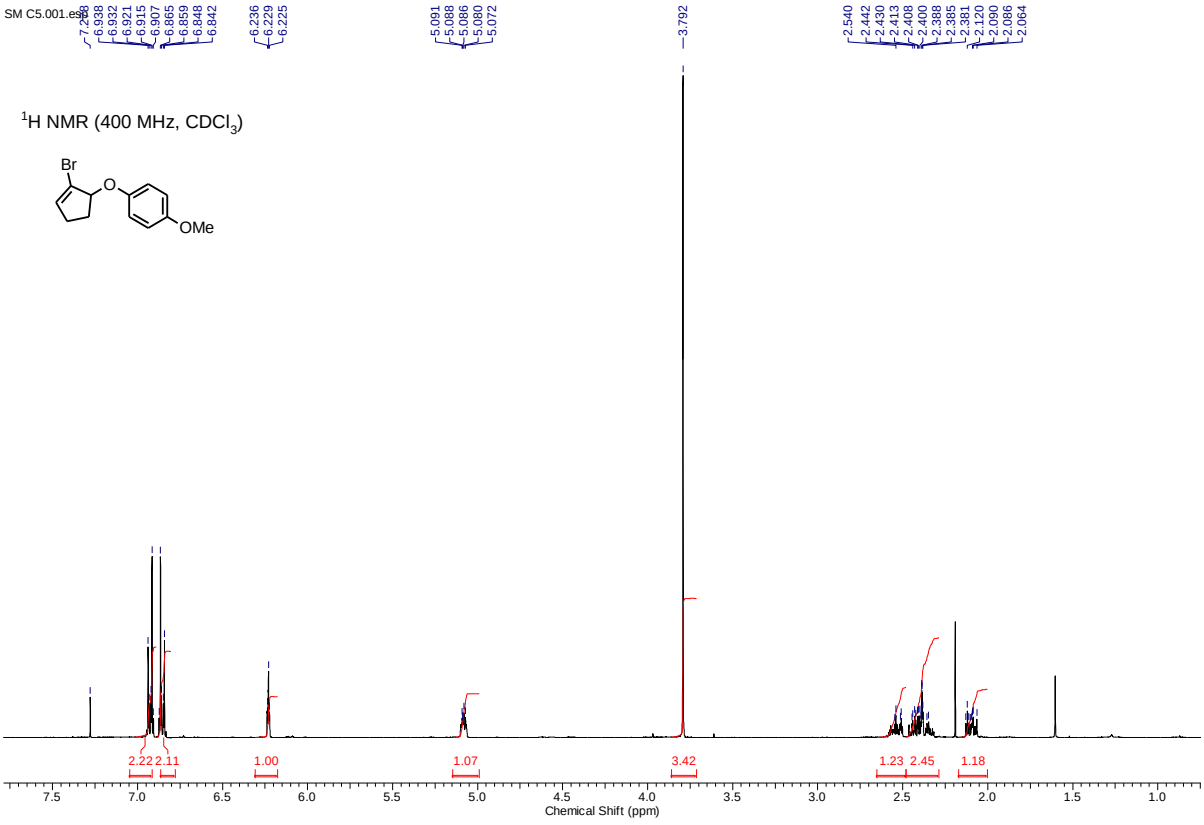


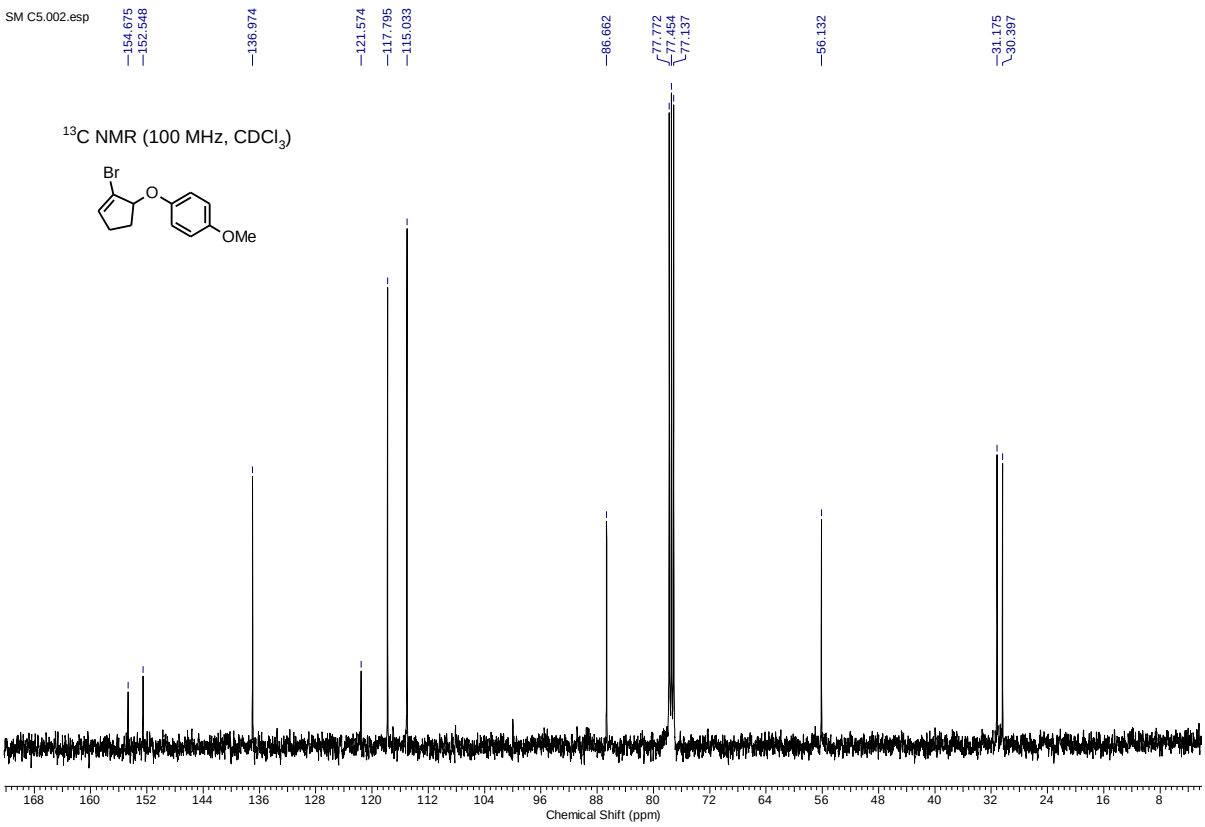
(2-Bromo-3-(4-methoxyphenoxy)prop-1-ene-1,3-diyl)dibenzene, 43



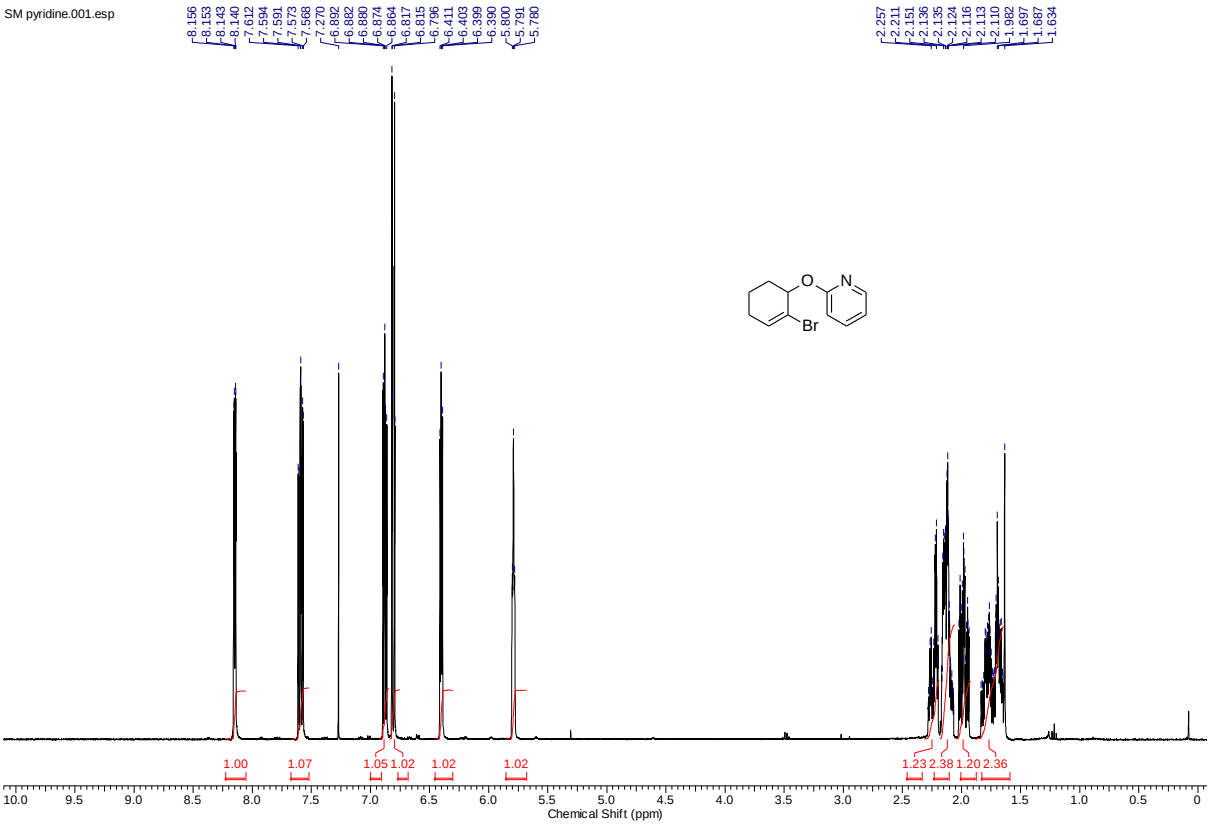


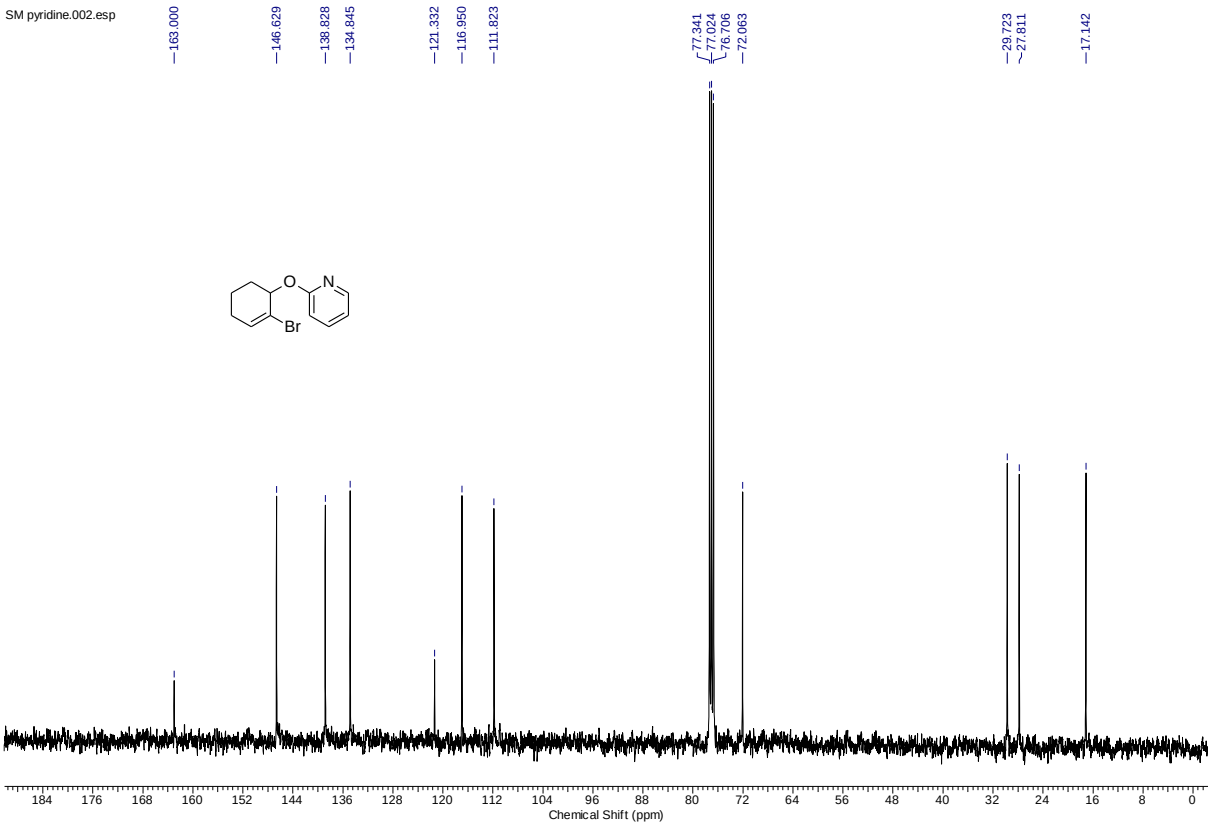
1-(2-Bromocyclopent-2-enyloxy)-4-methoxybenzene, 44



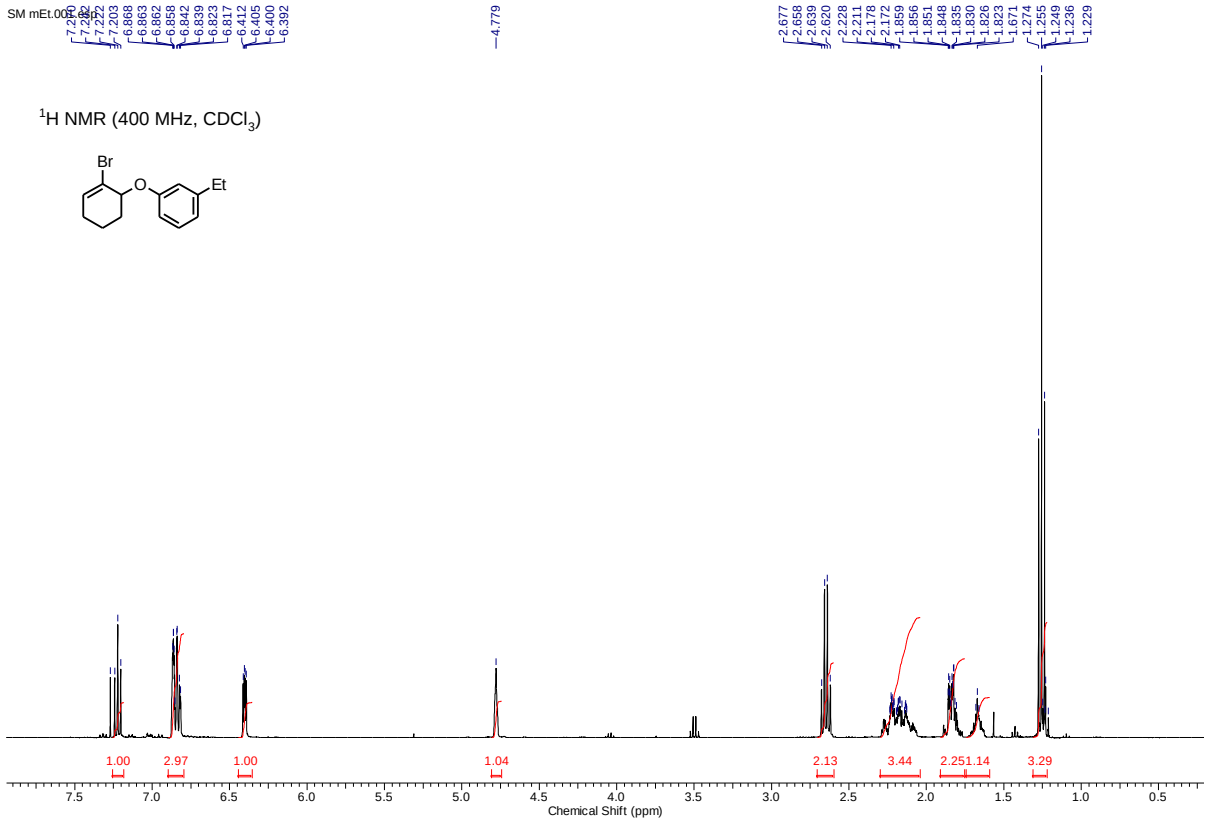


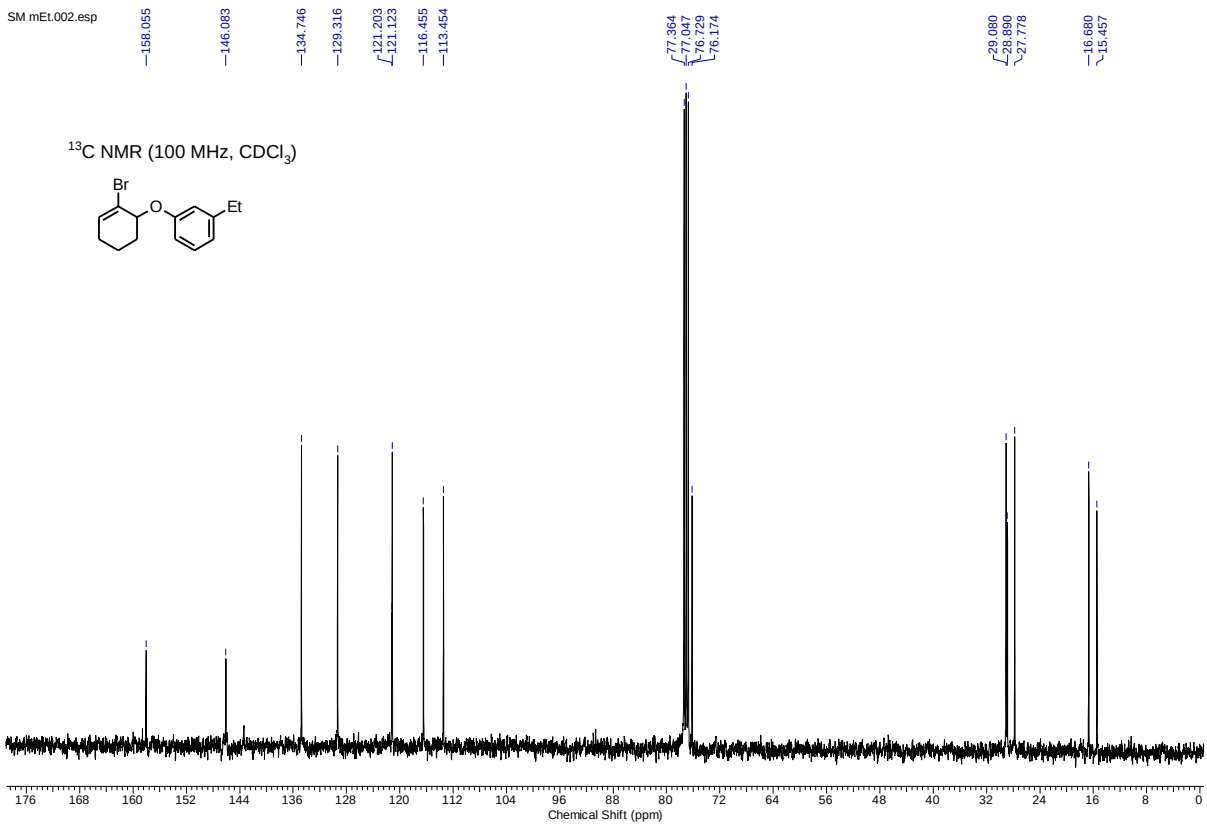
2-(2-Bromocyclohex-2-enyloxy)pyridine, 45



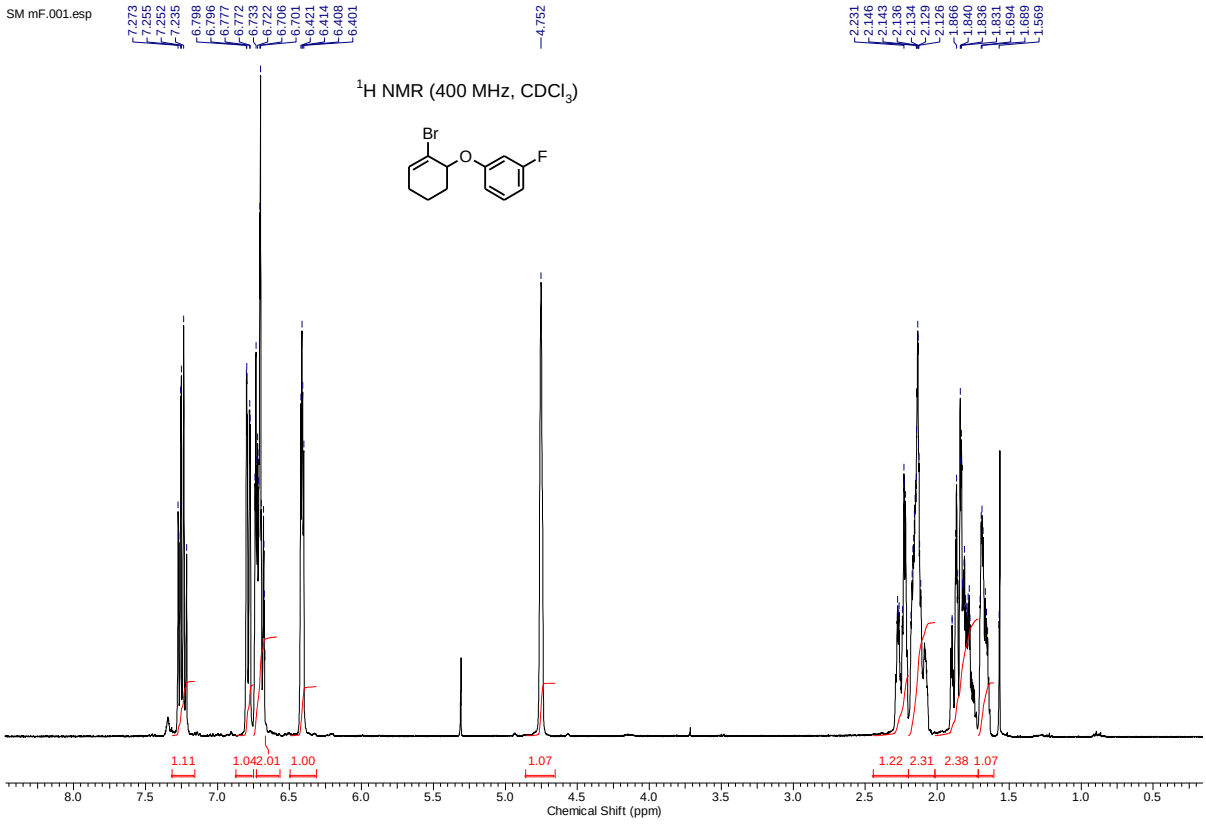


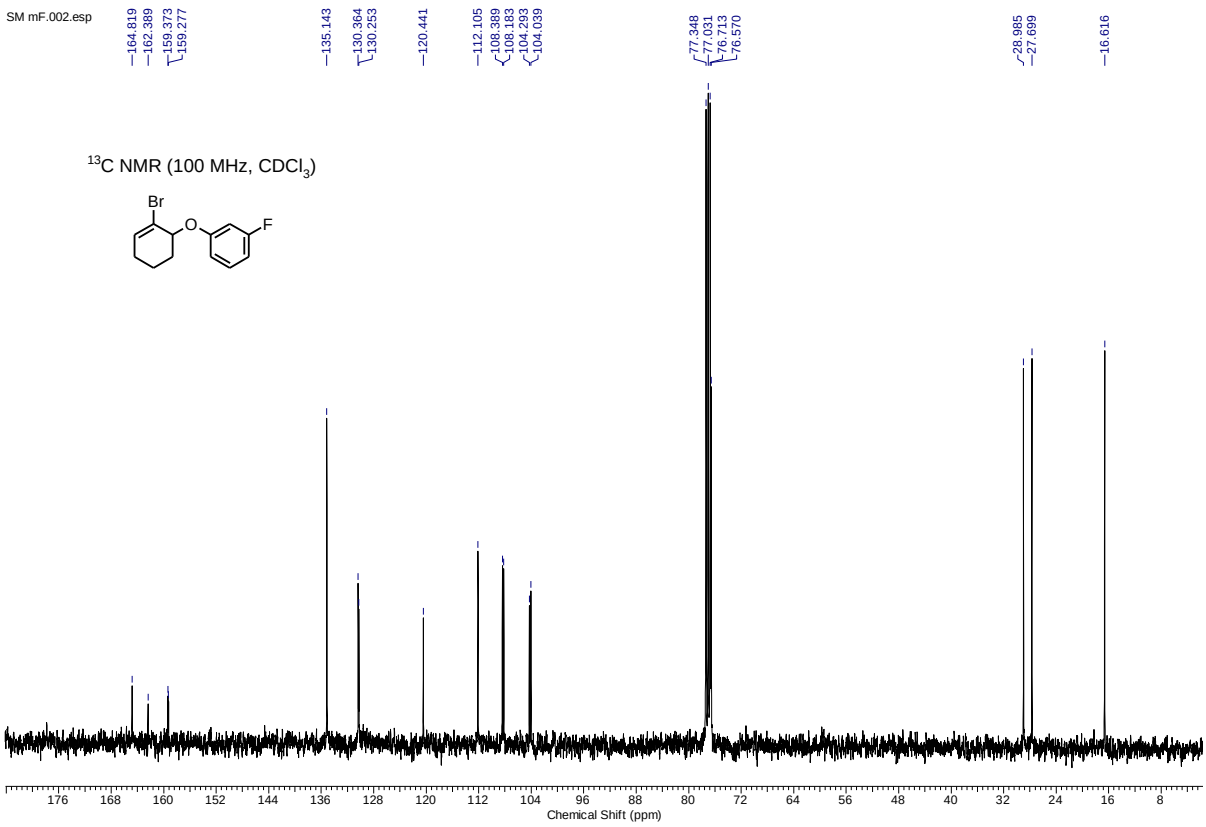
1-(2-Bromocyclohex-2-enyloxy)-3-ethylbenzene, 51



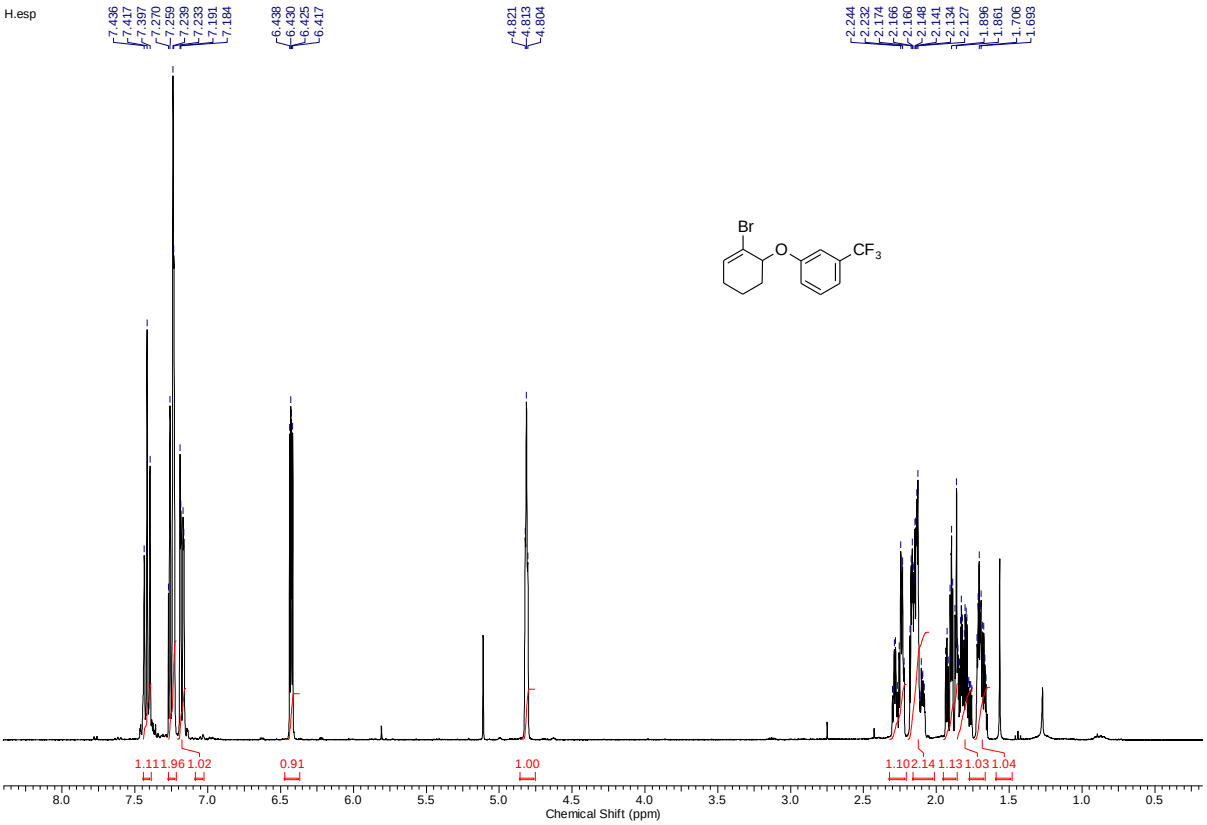


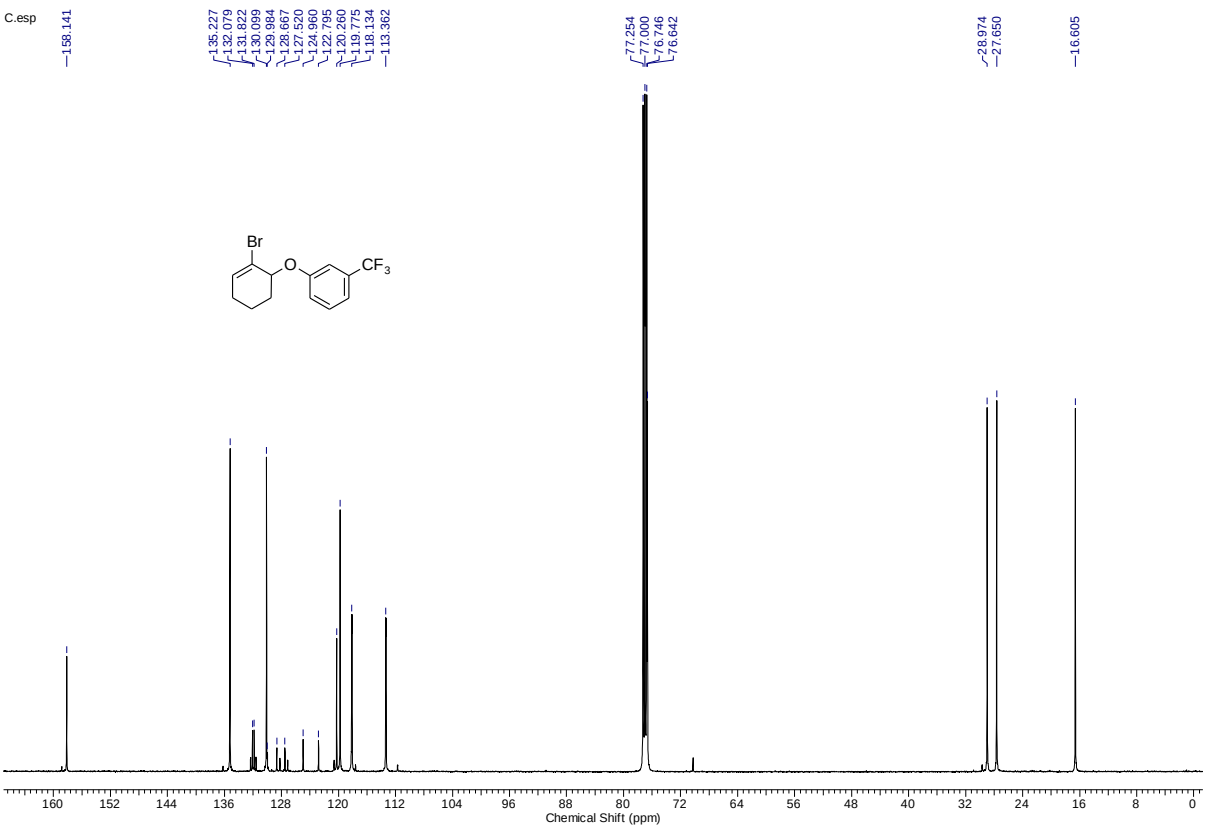
1-(2-Bromocyclohex-2-enyloxy)-3-fluorobenzene, 52



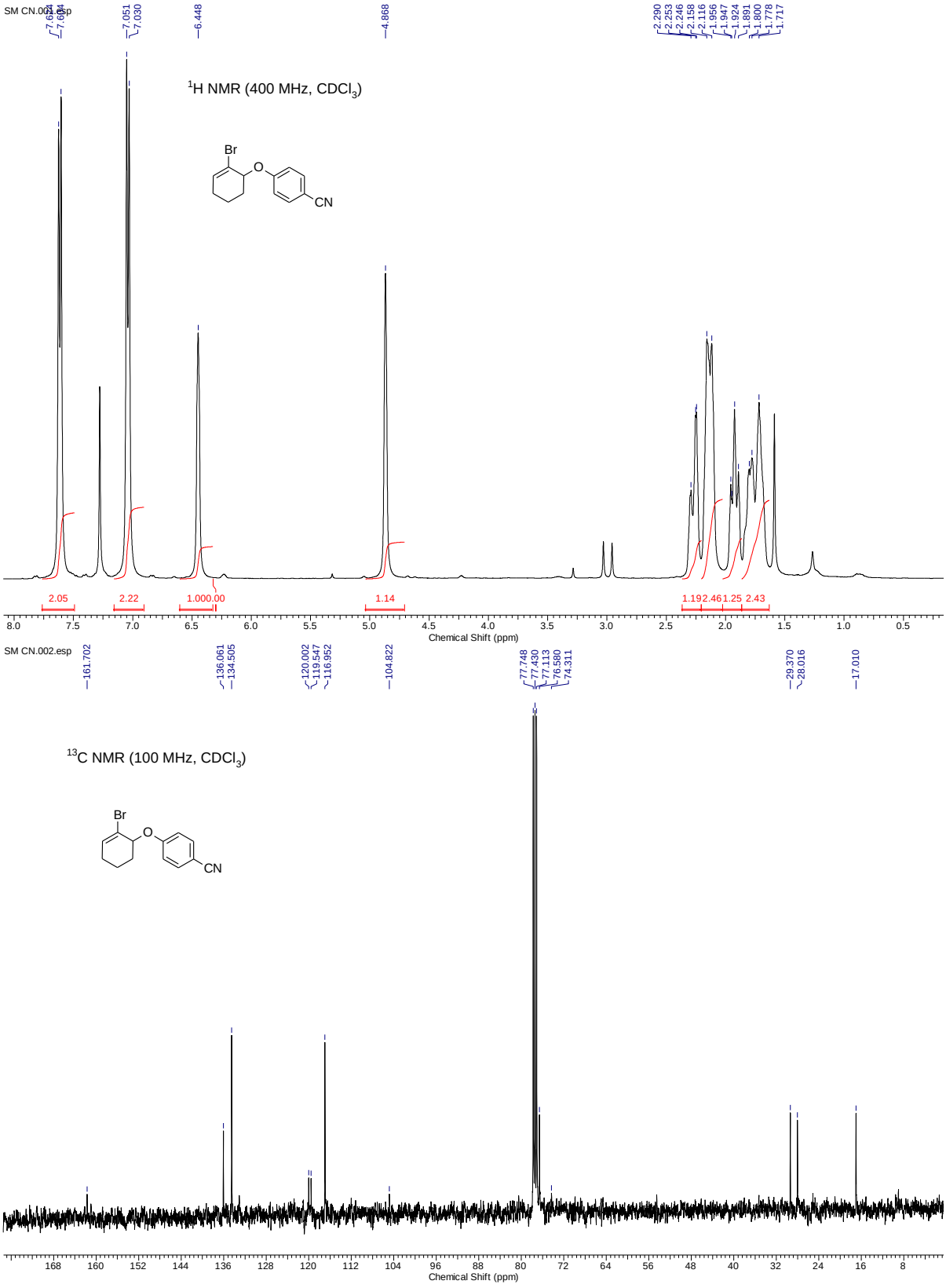


1-(2-Bromocyclohex-2-enyloxy)-3-(trifluoromethyl)benzene, 53

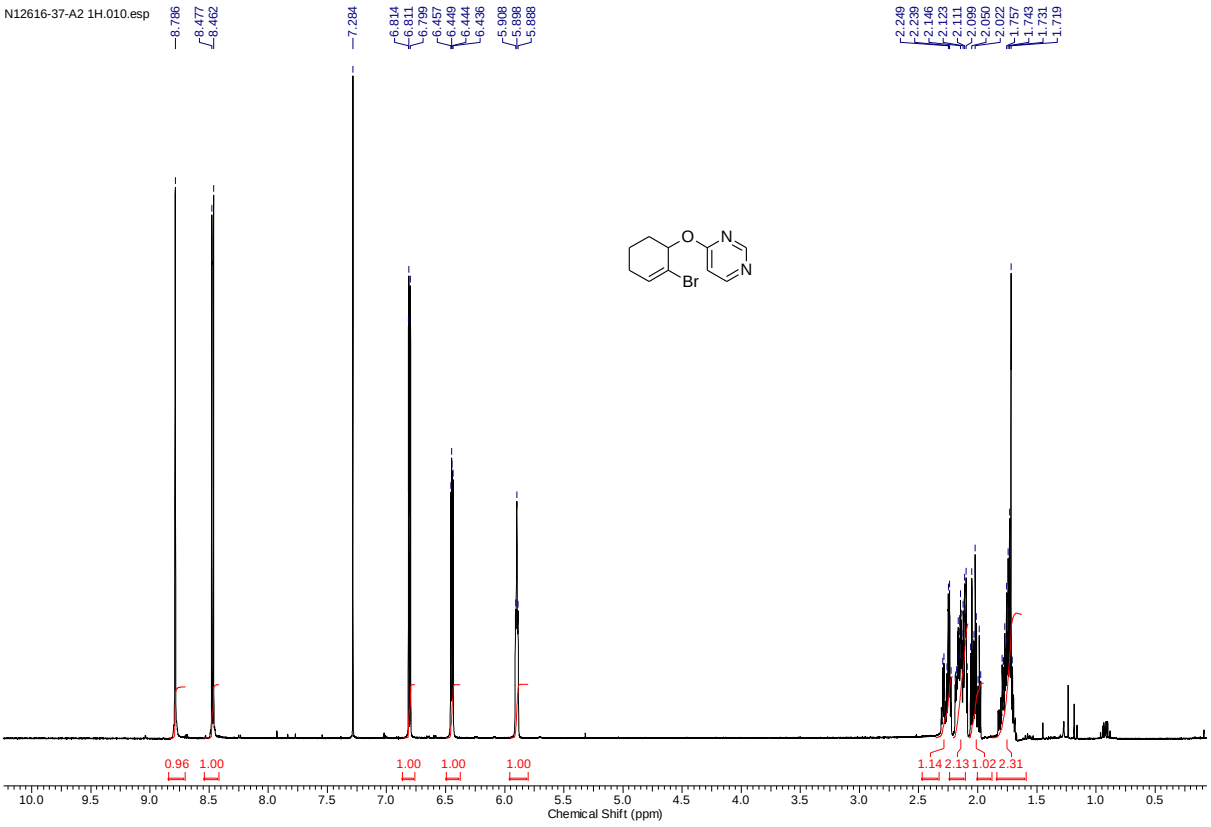


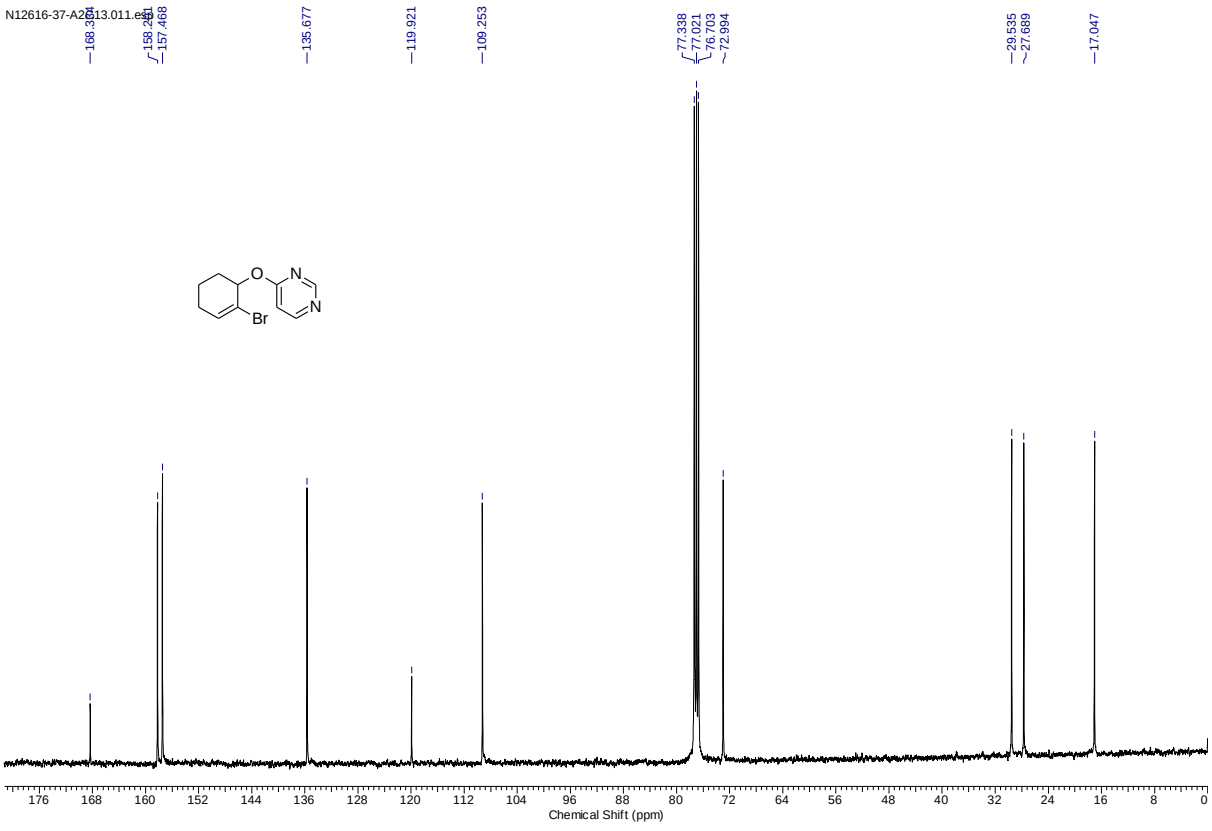


4-(2-Bromocyclohex-2-enyloxy)benzonitrile, 54

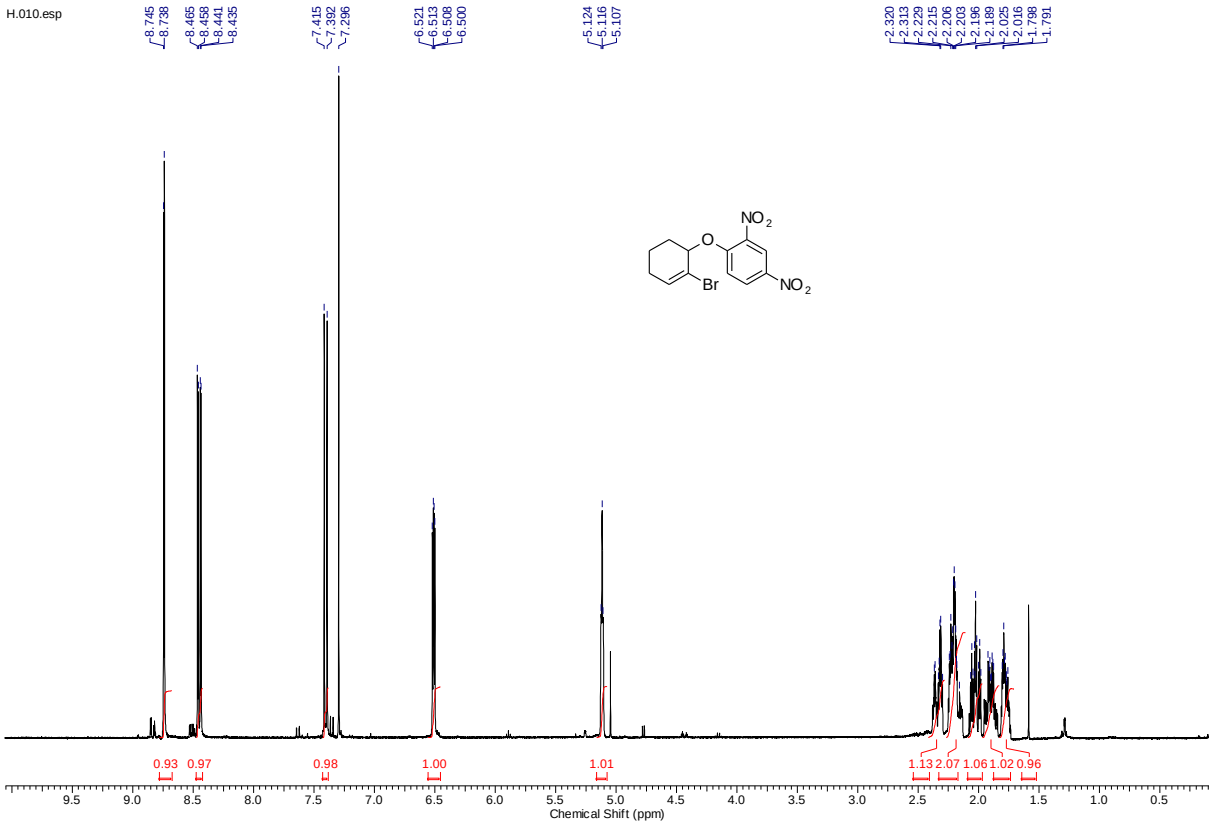


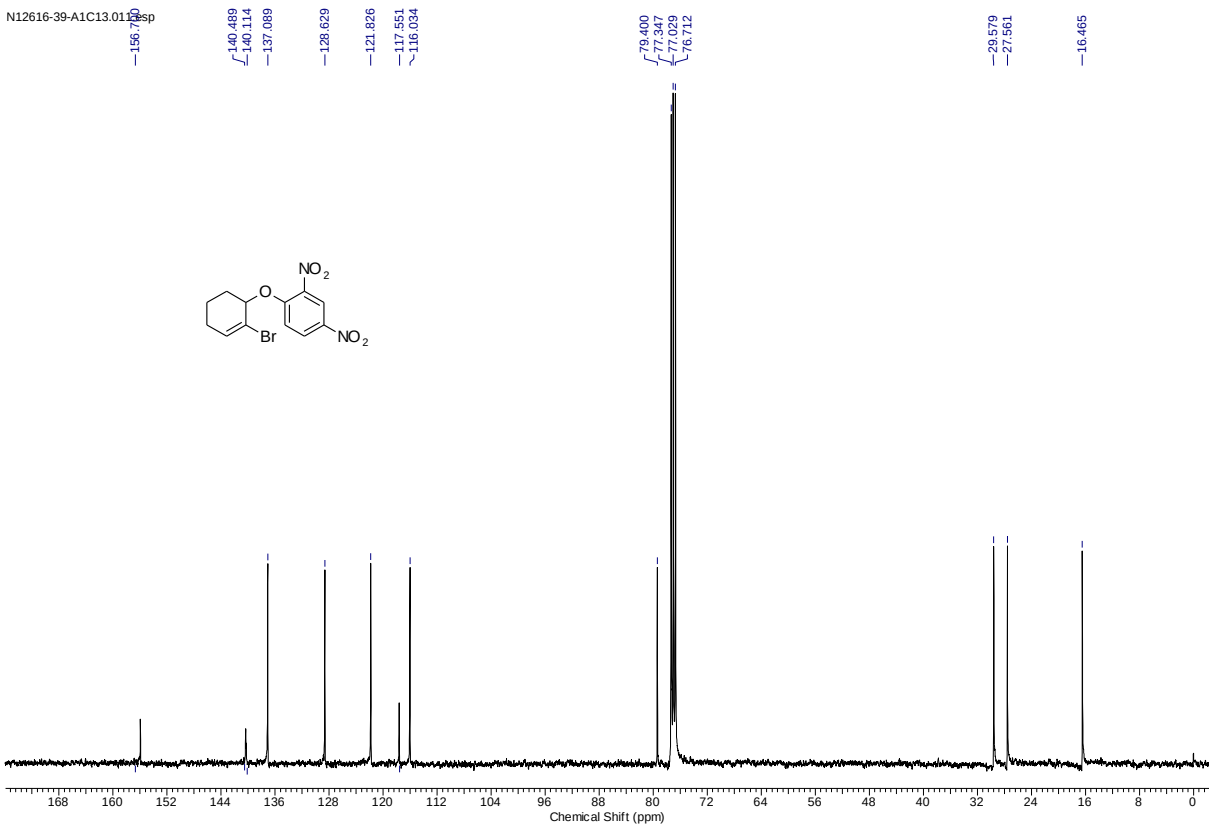
4-(2-Bromocyclohex-2-enyloxy)pyrimidine, 55



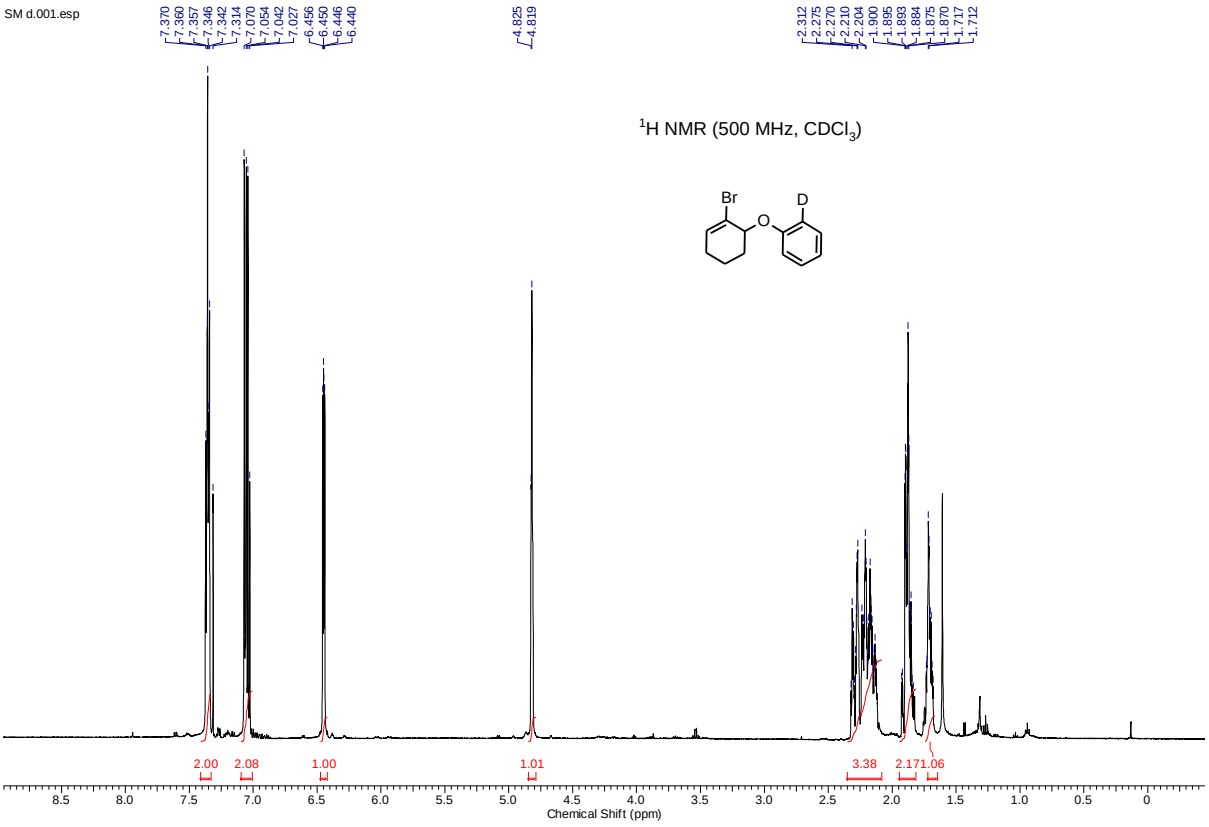


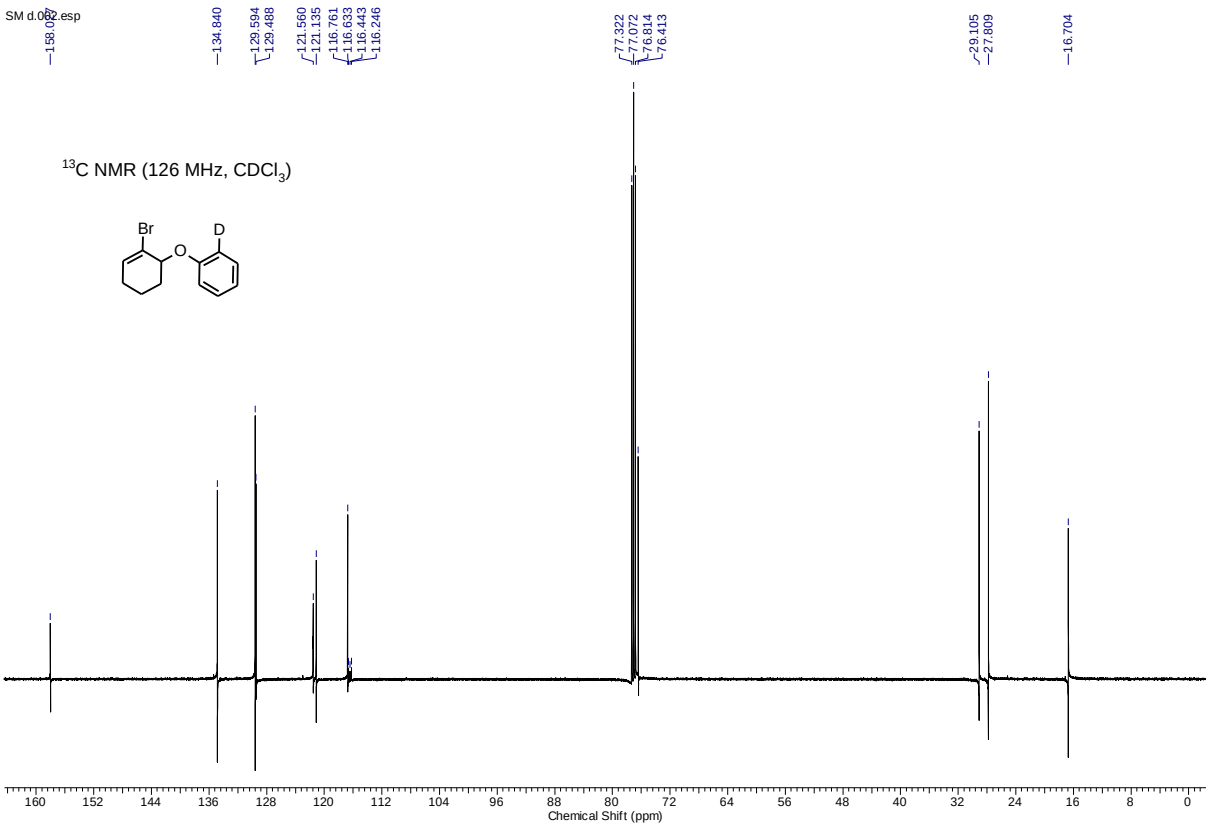
1-(2-Bromocyclohex-2-enyloxy)-2,4-dinitrobenzene, 56



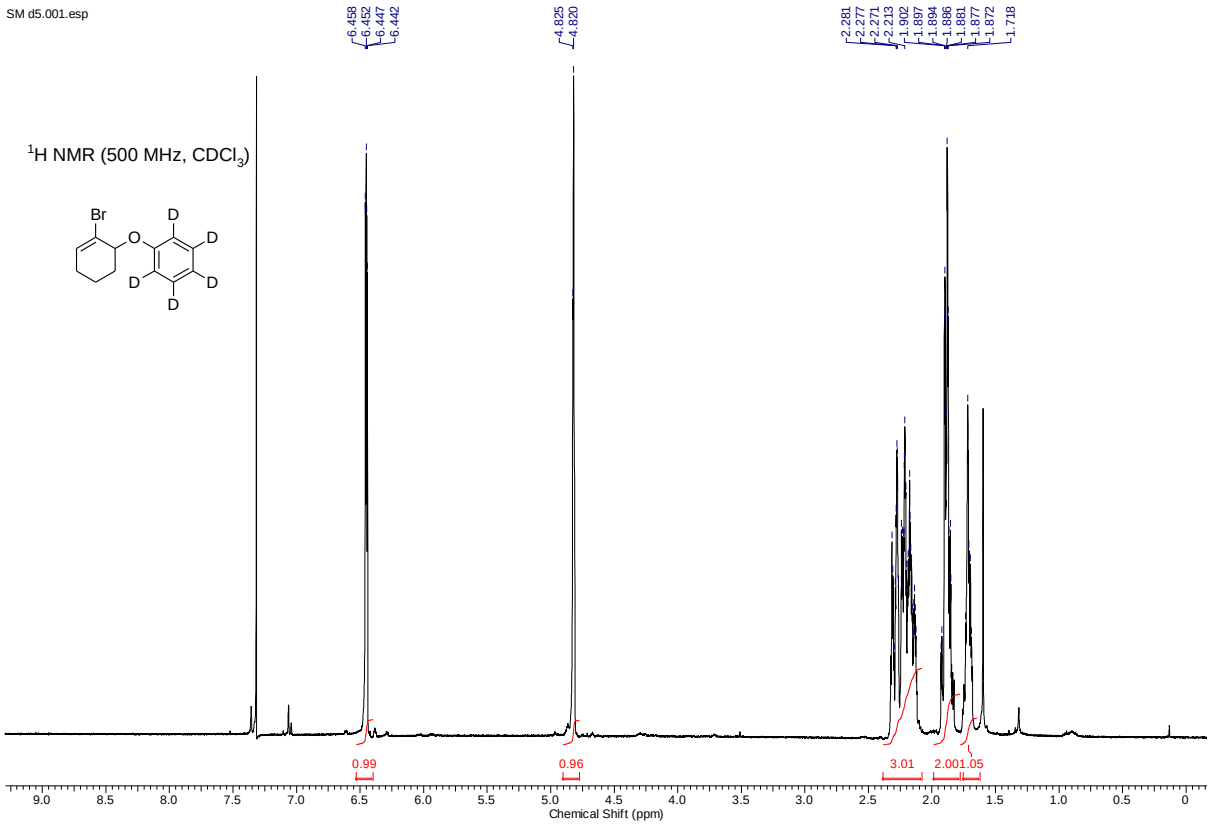


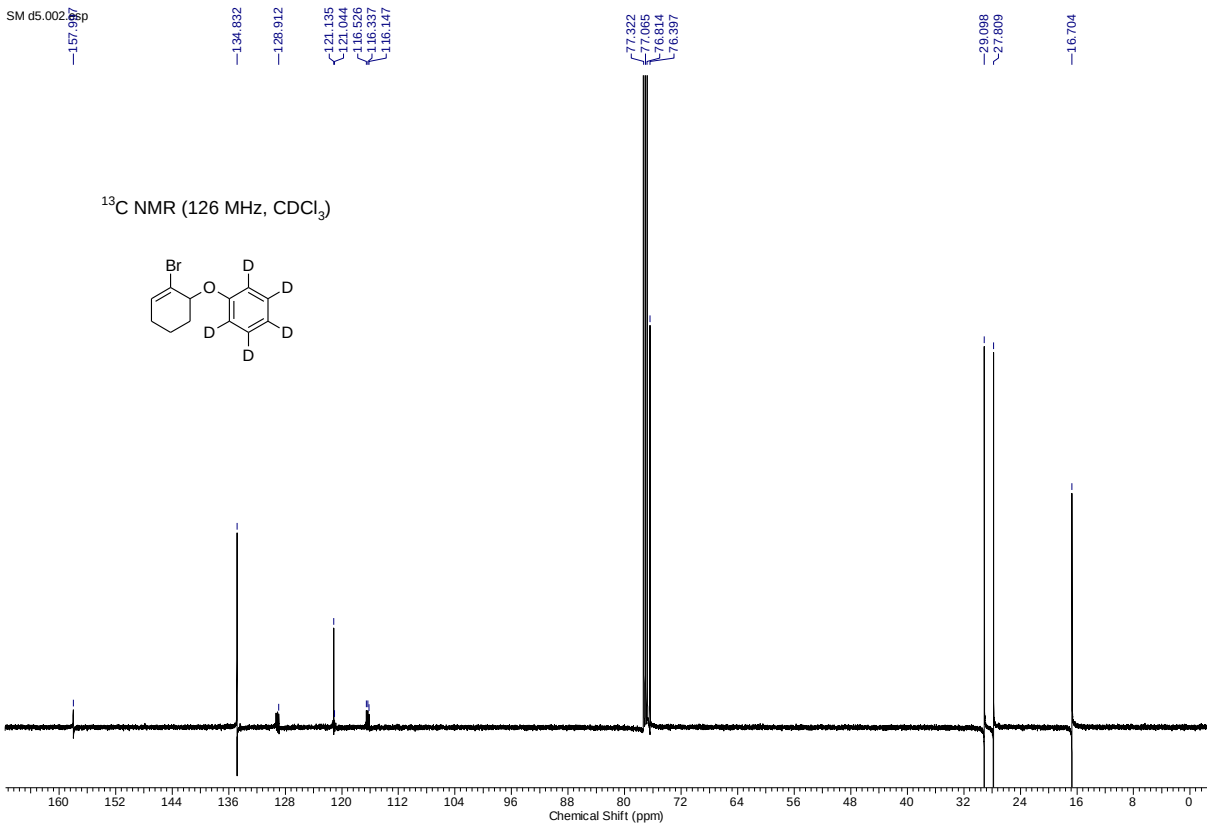
(2-Bromocyclohex-2-enyloxy)-(2-D)-benzene, 100



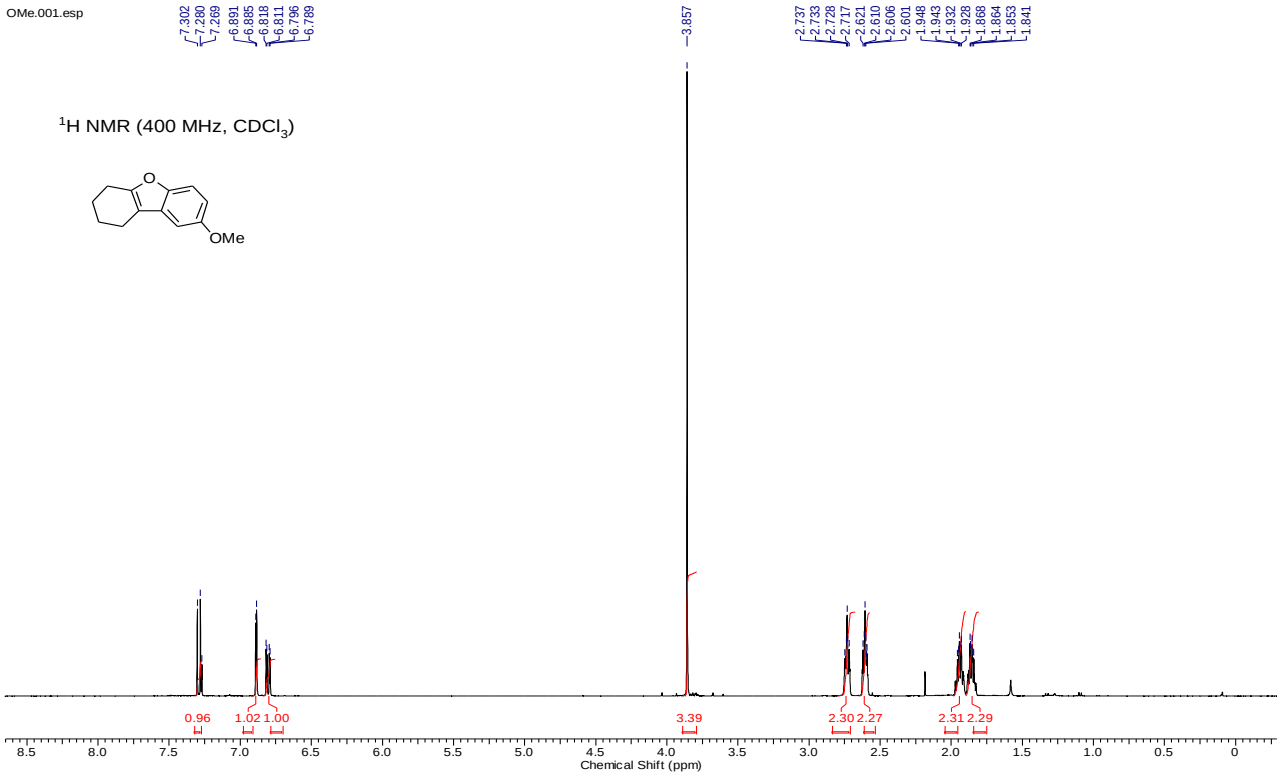


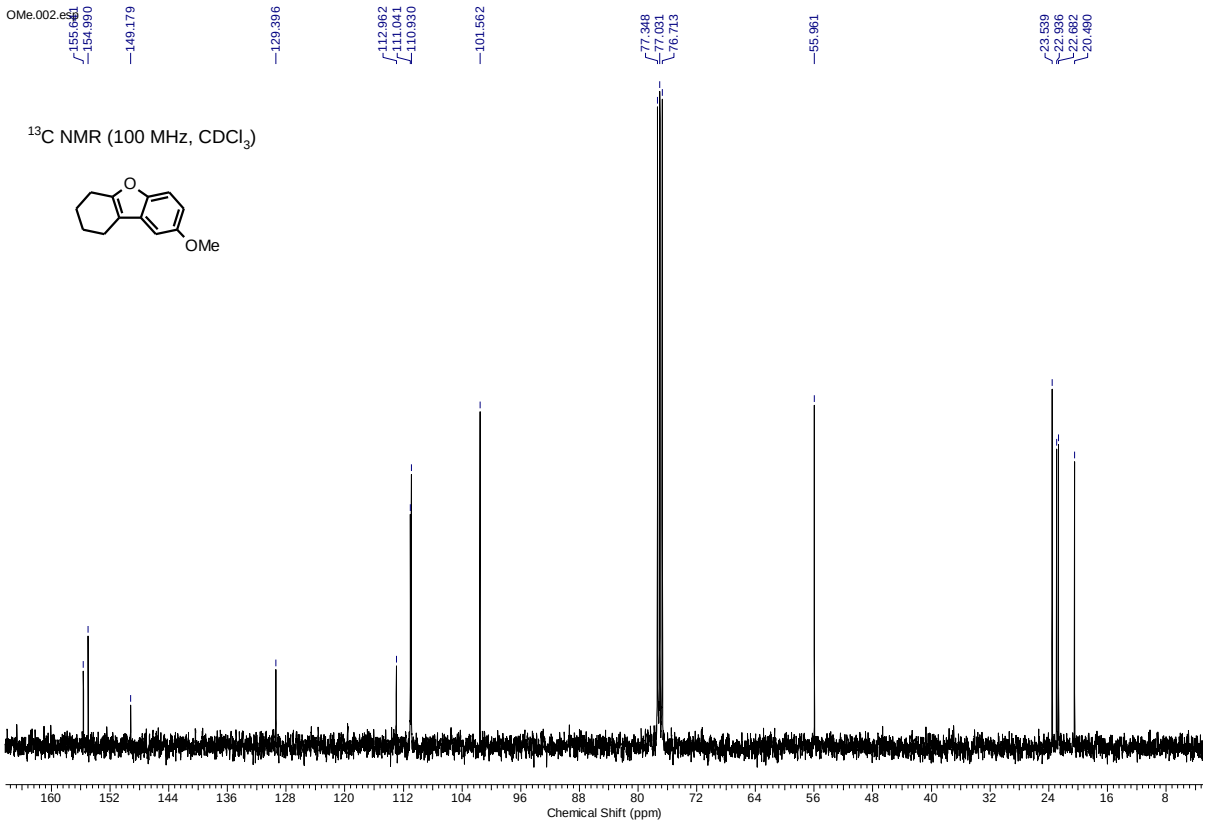
(2-Bromocyclohex-2-enyloxy)-2,3,4,5,6-(D_5)-benzene, 98



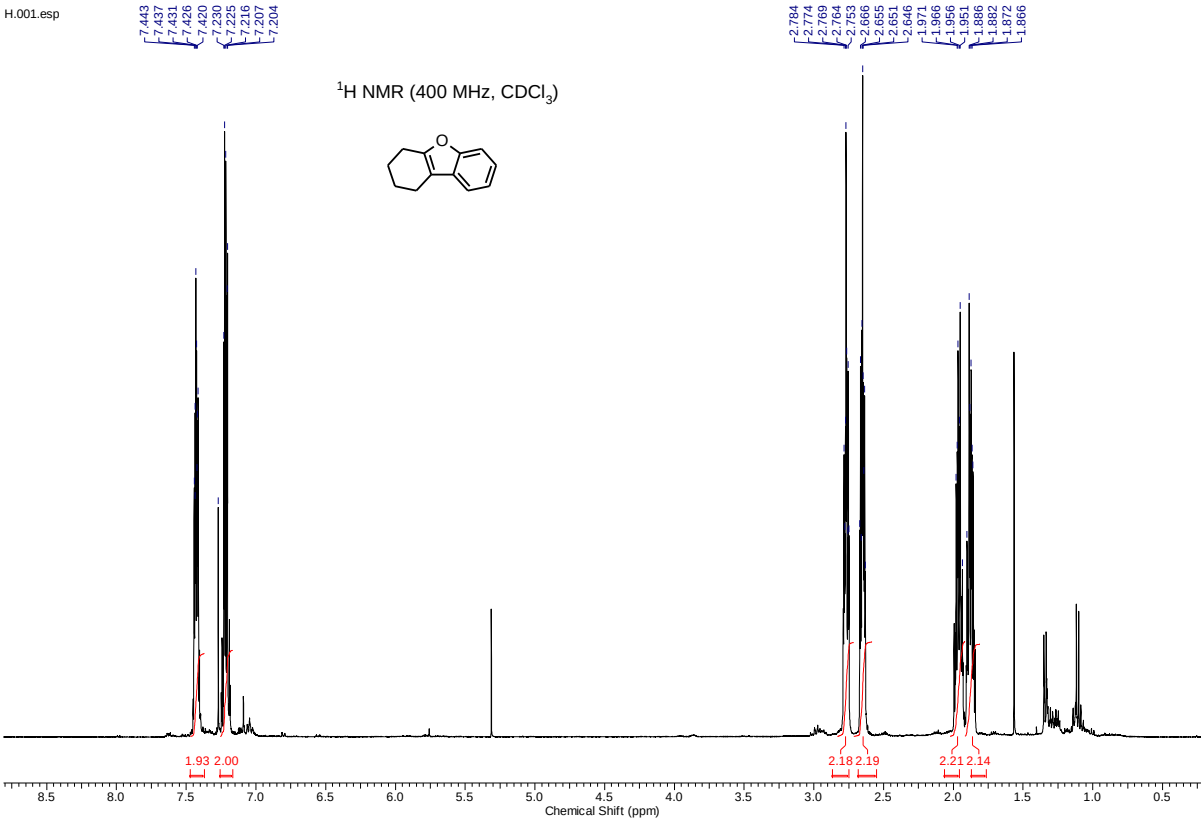


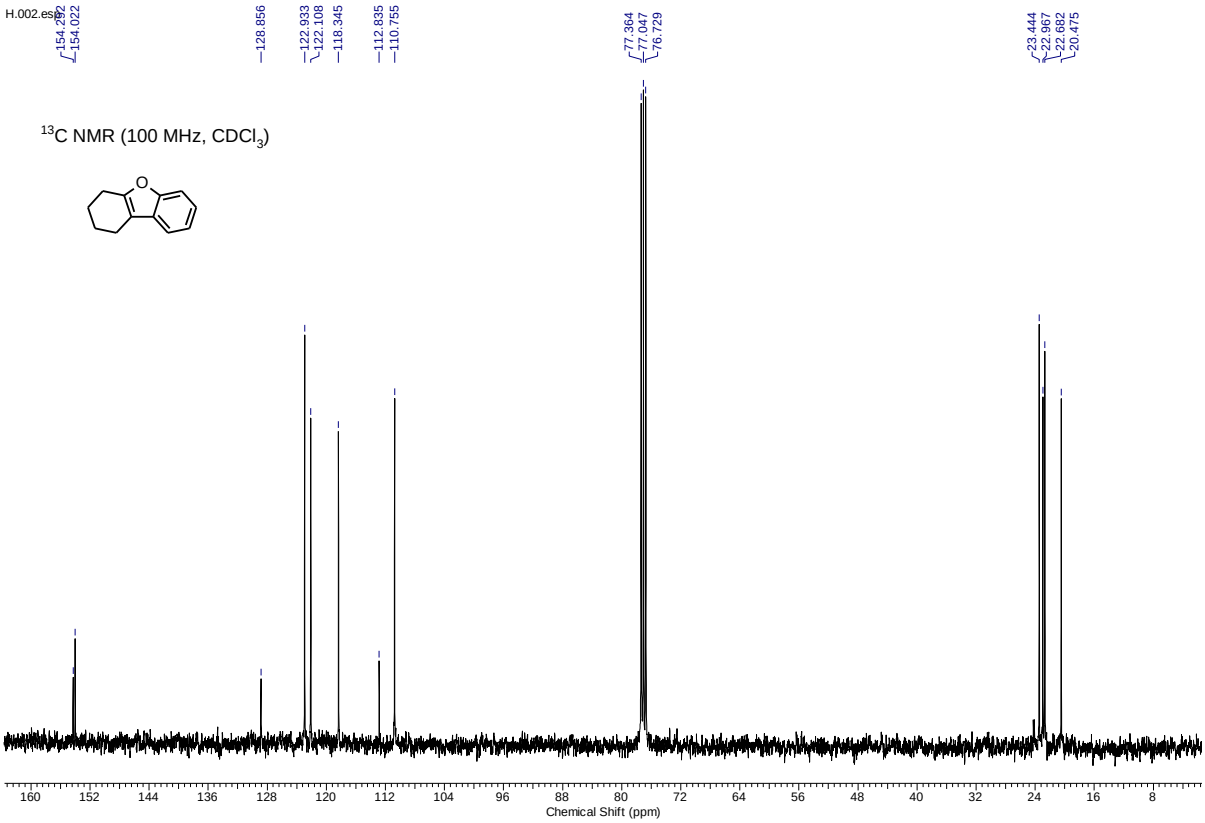
8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 58



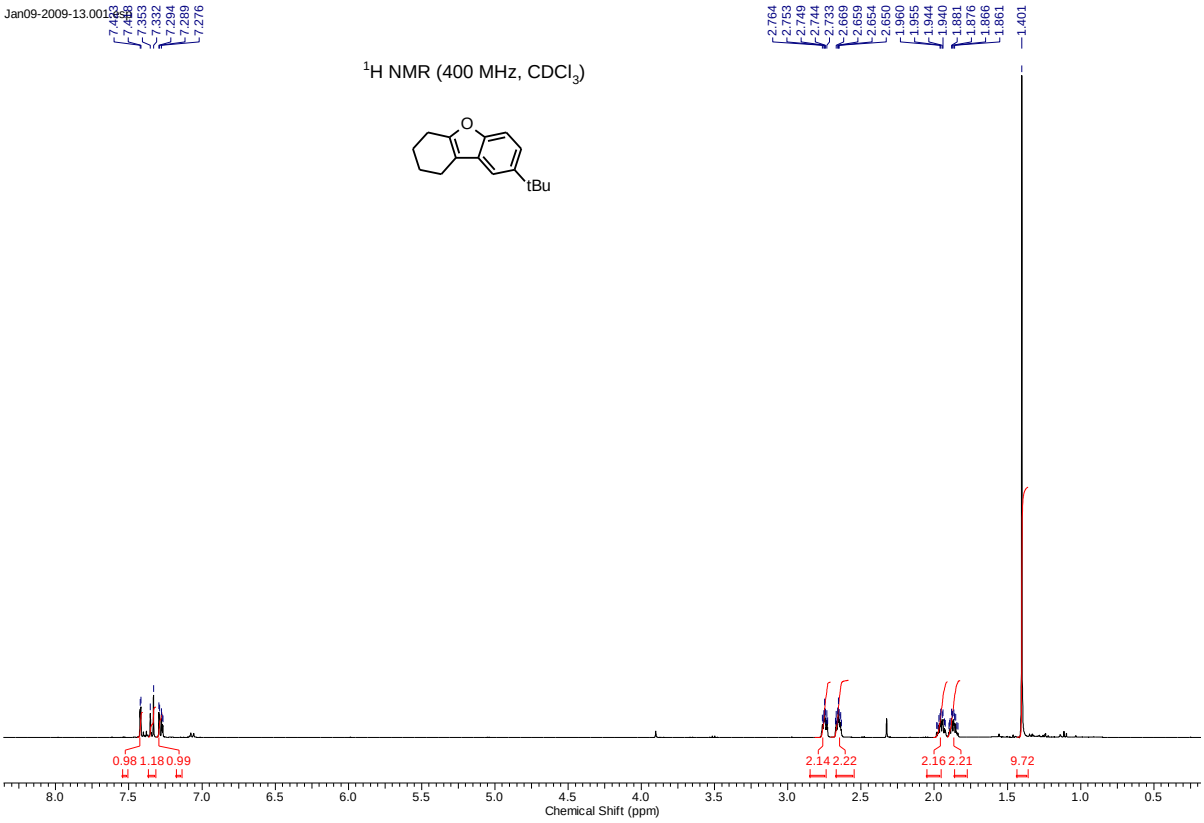


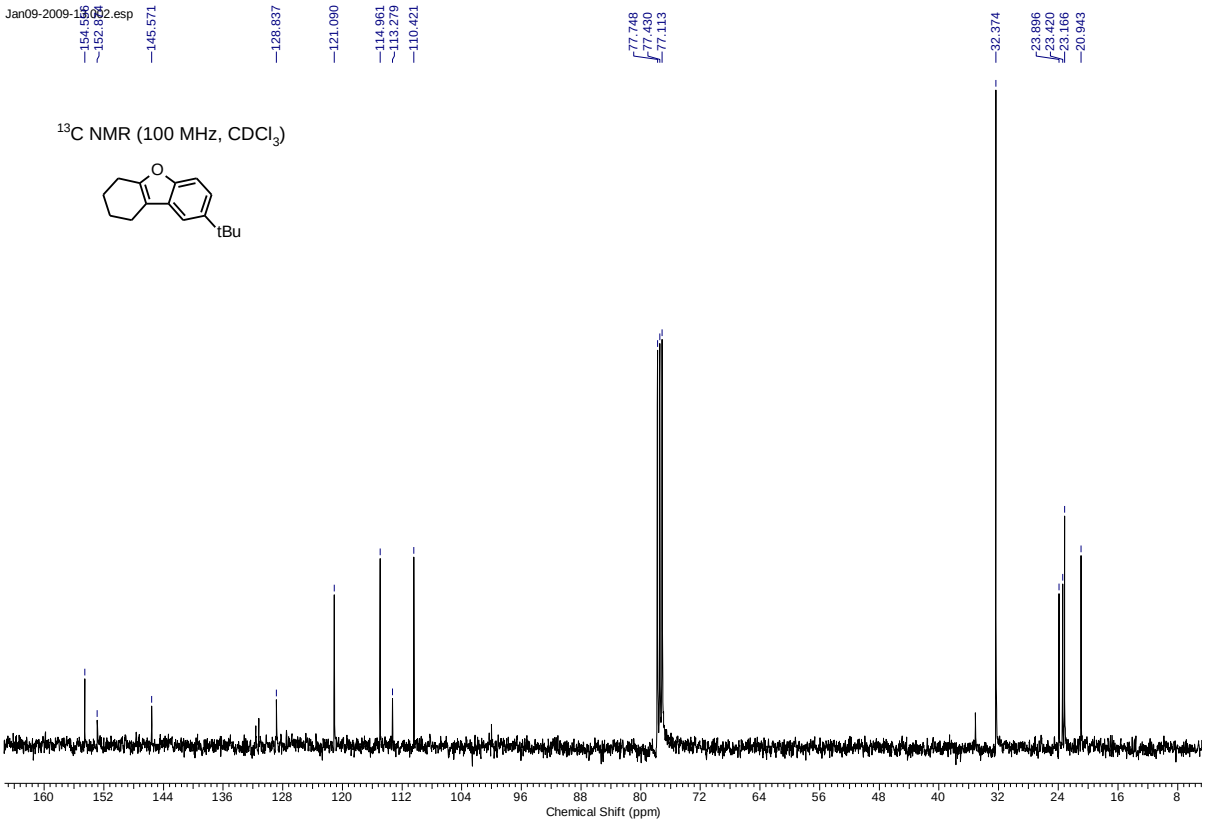
1,2,3,4-Tetrahydrodibenzo[*b*,*d*]furan, 59



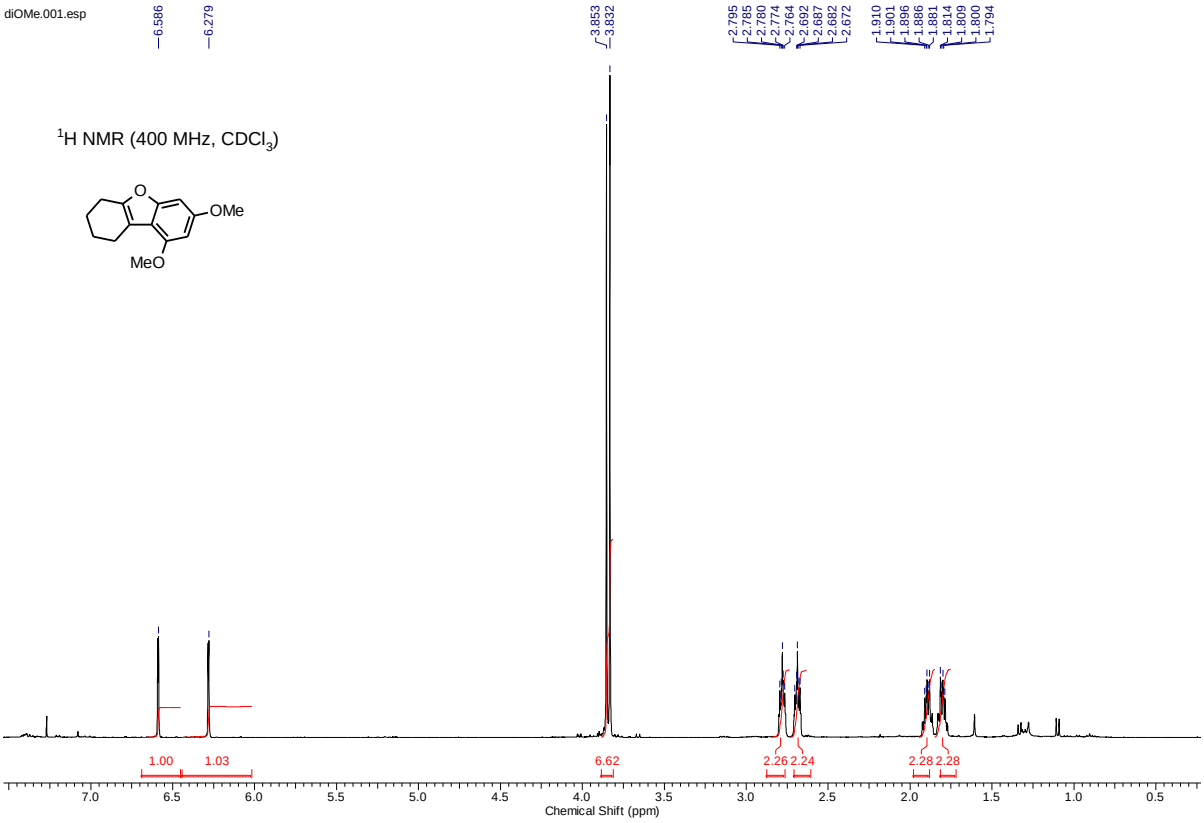


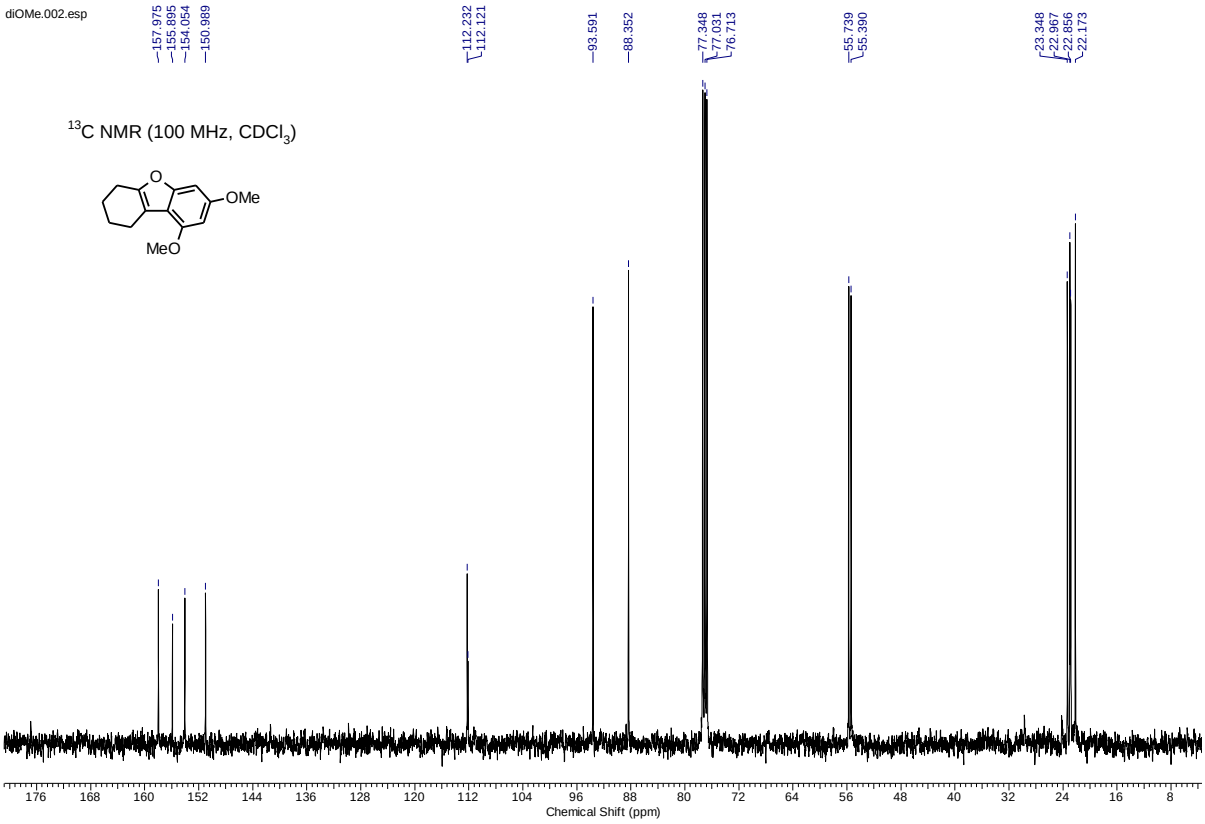
8-*tert*-Butyl-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 60



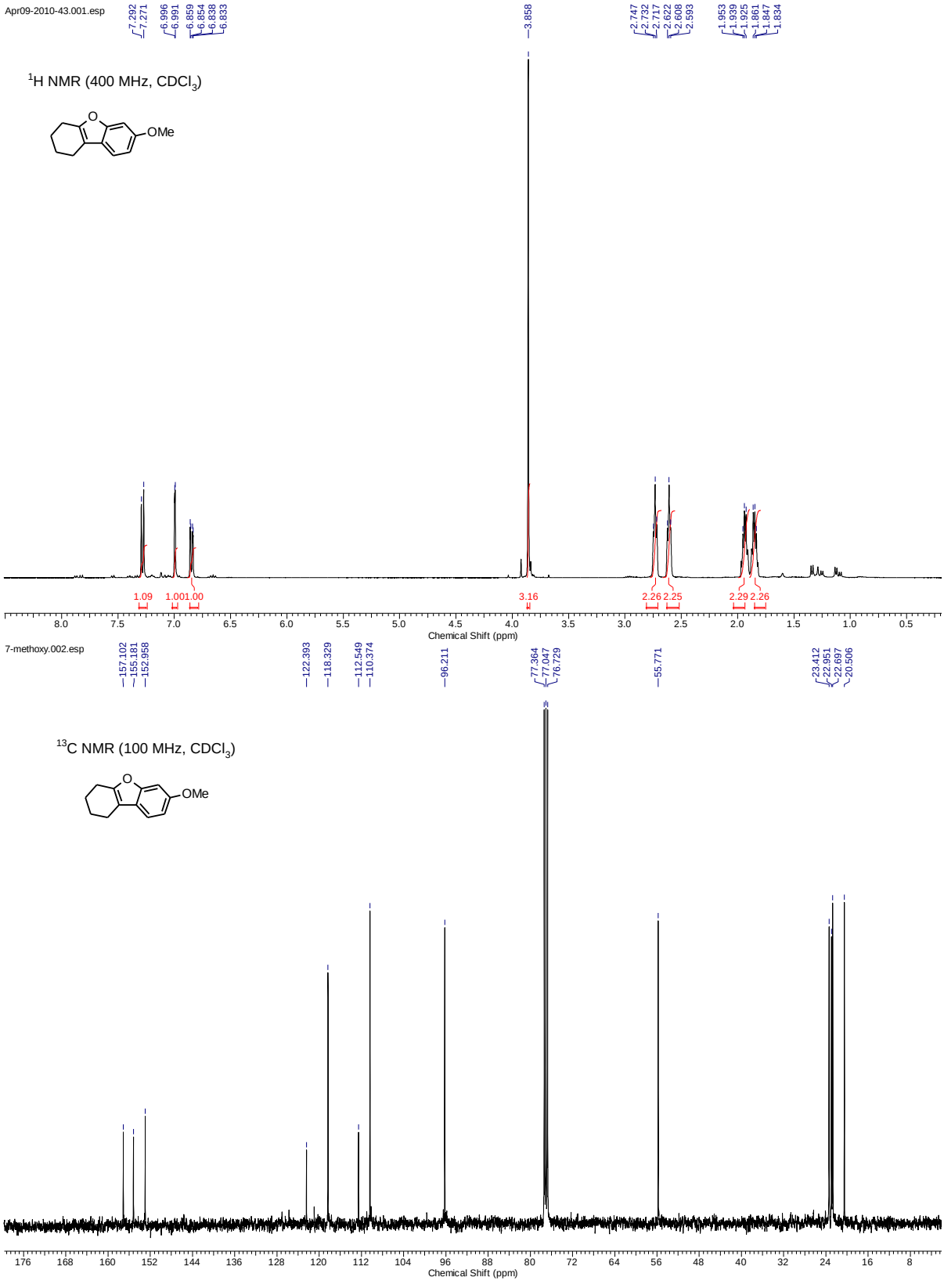


7,9-Dimethoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 61

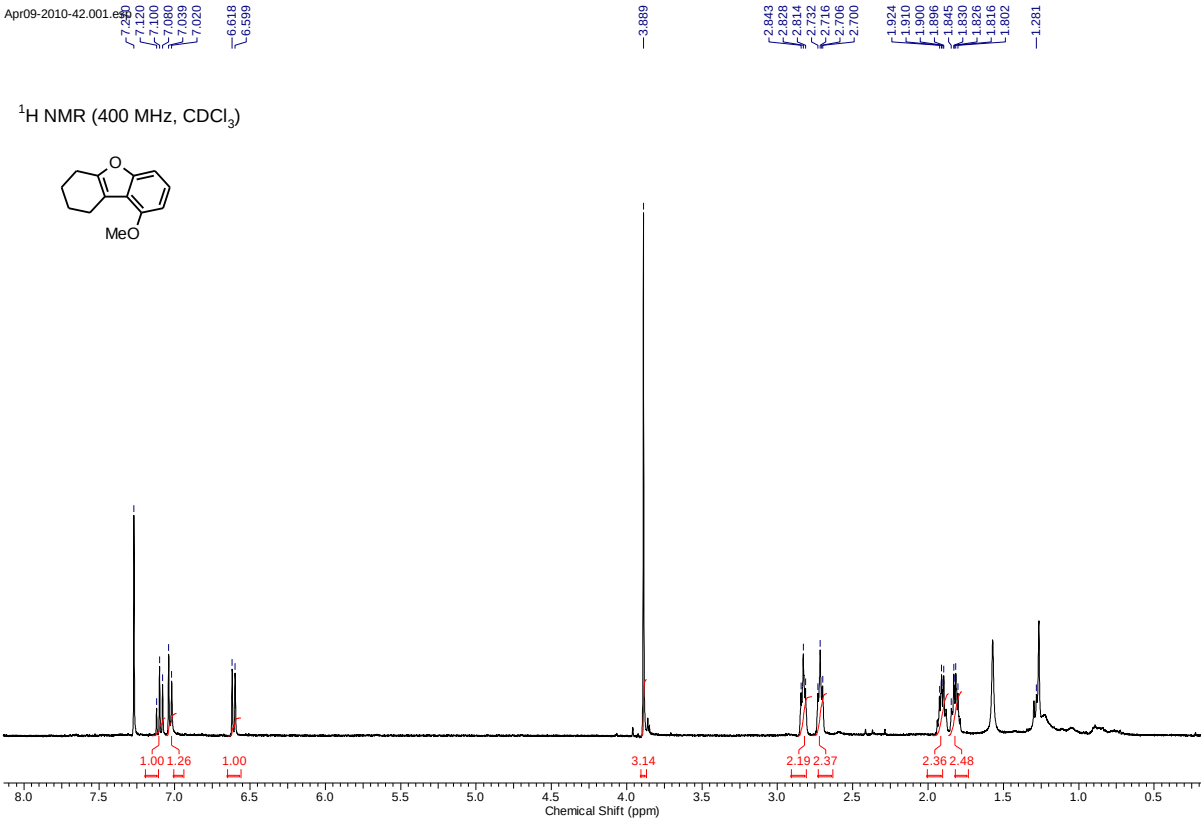


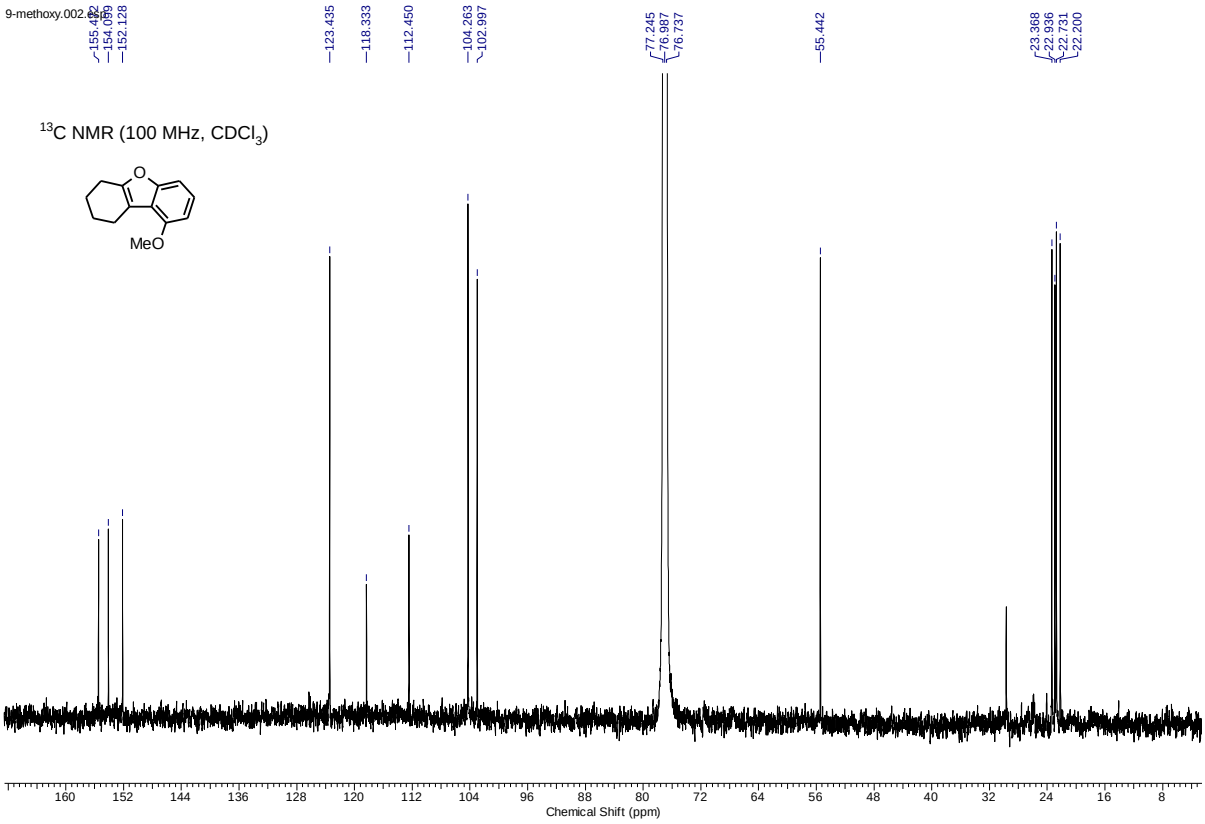


7-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 62

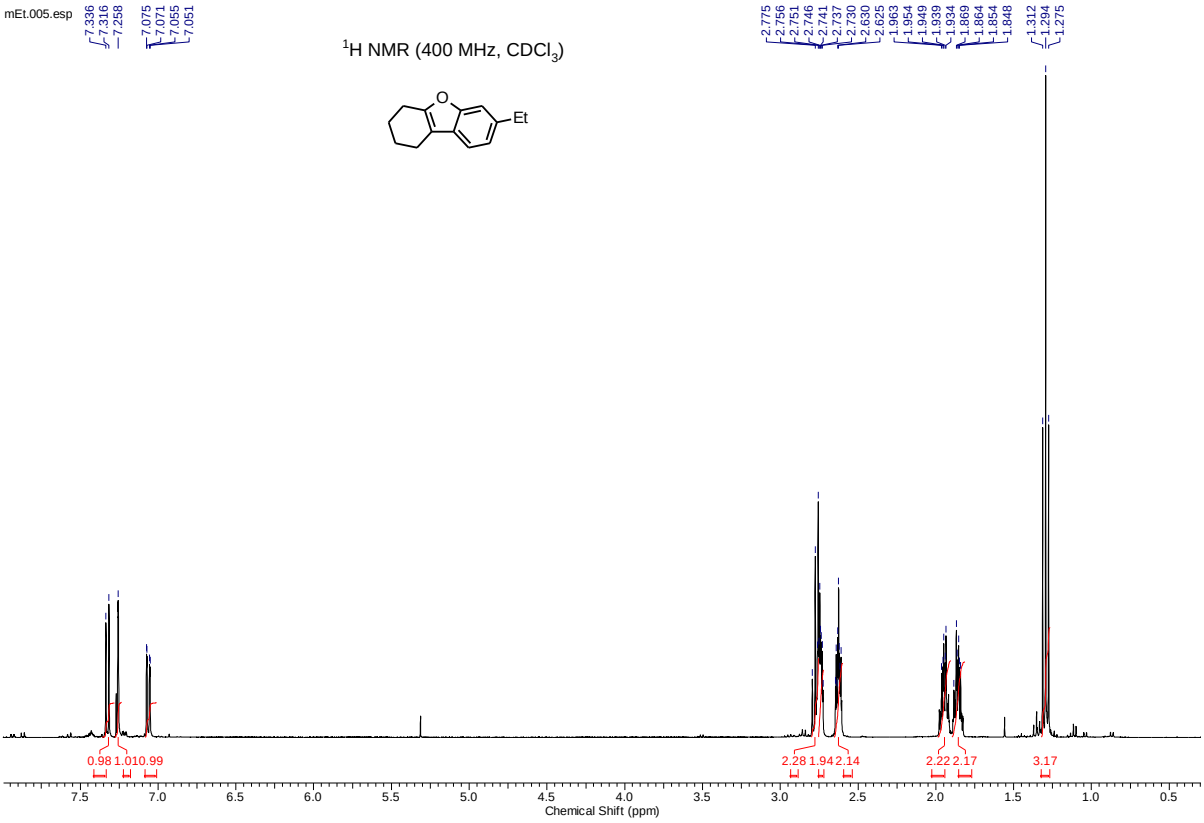


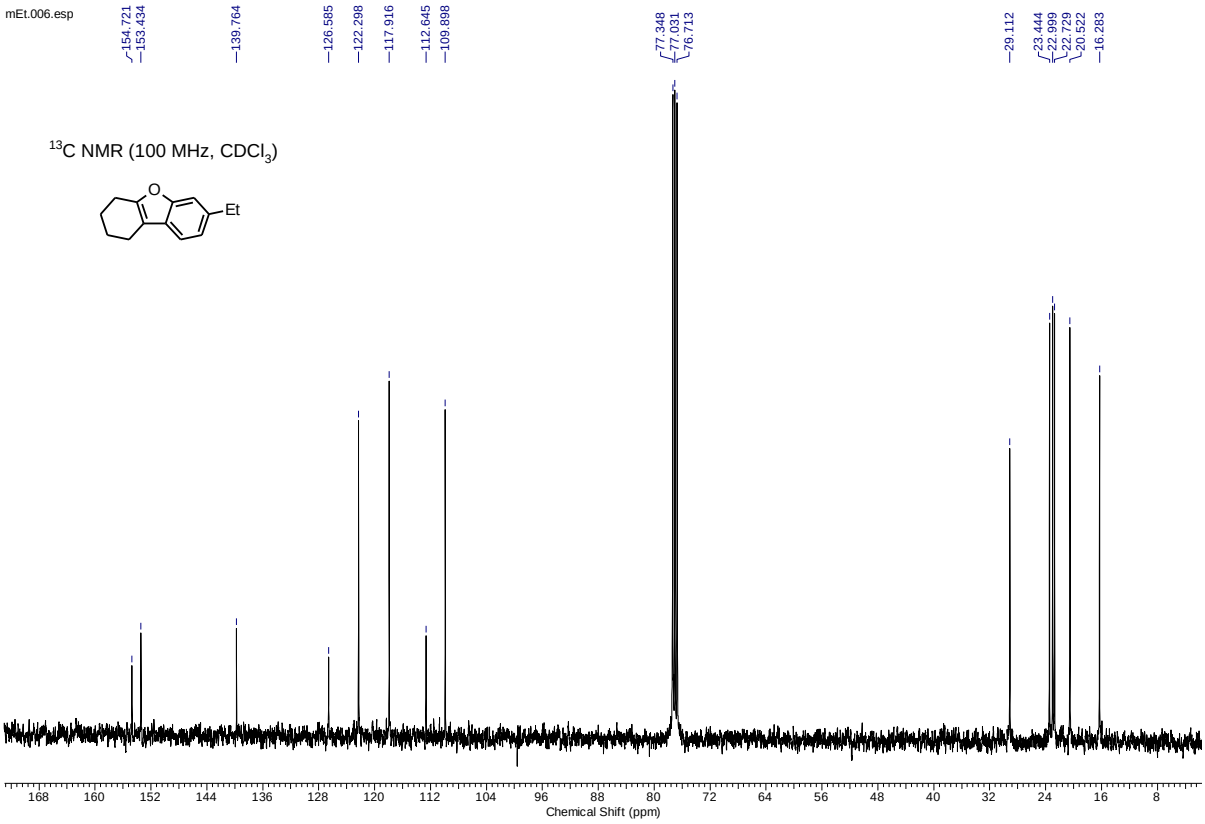
9-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 63



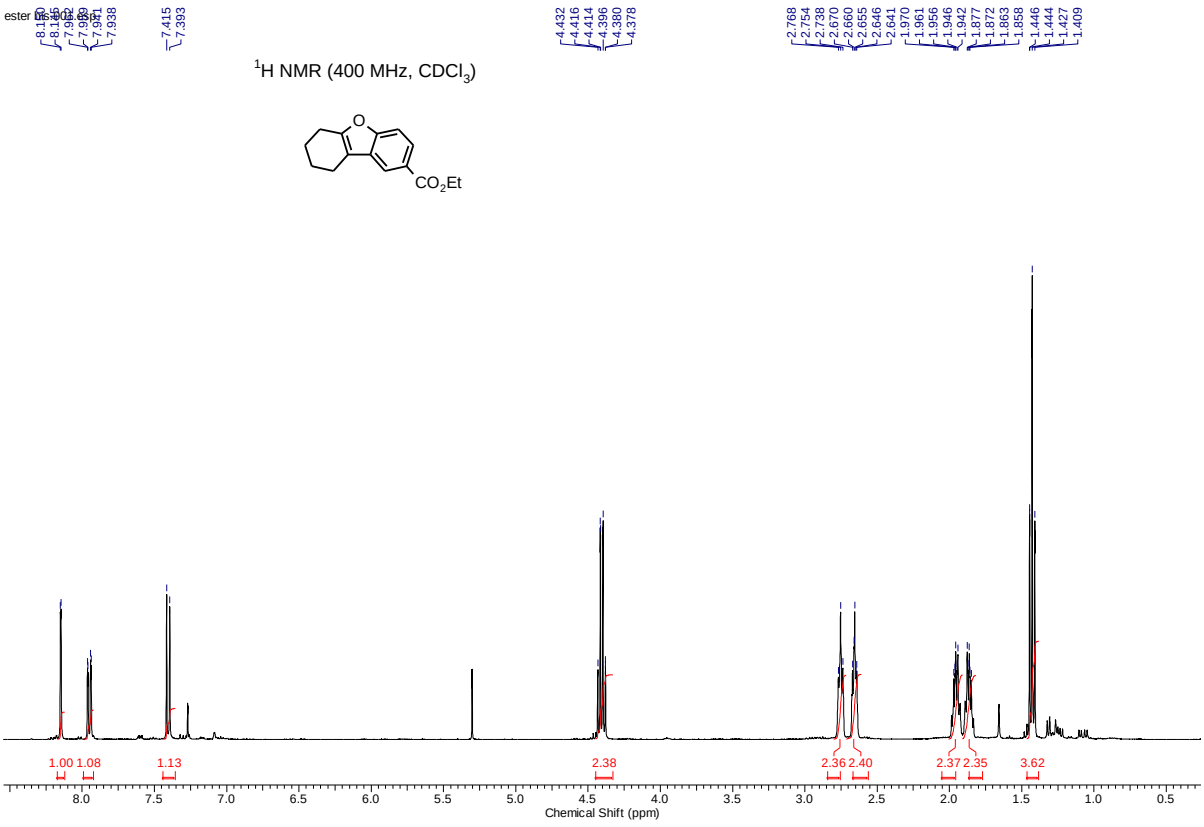


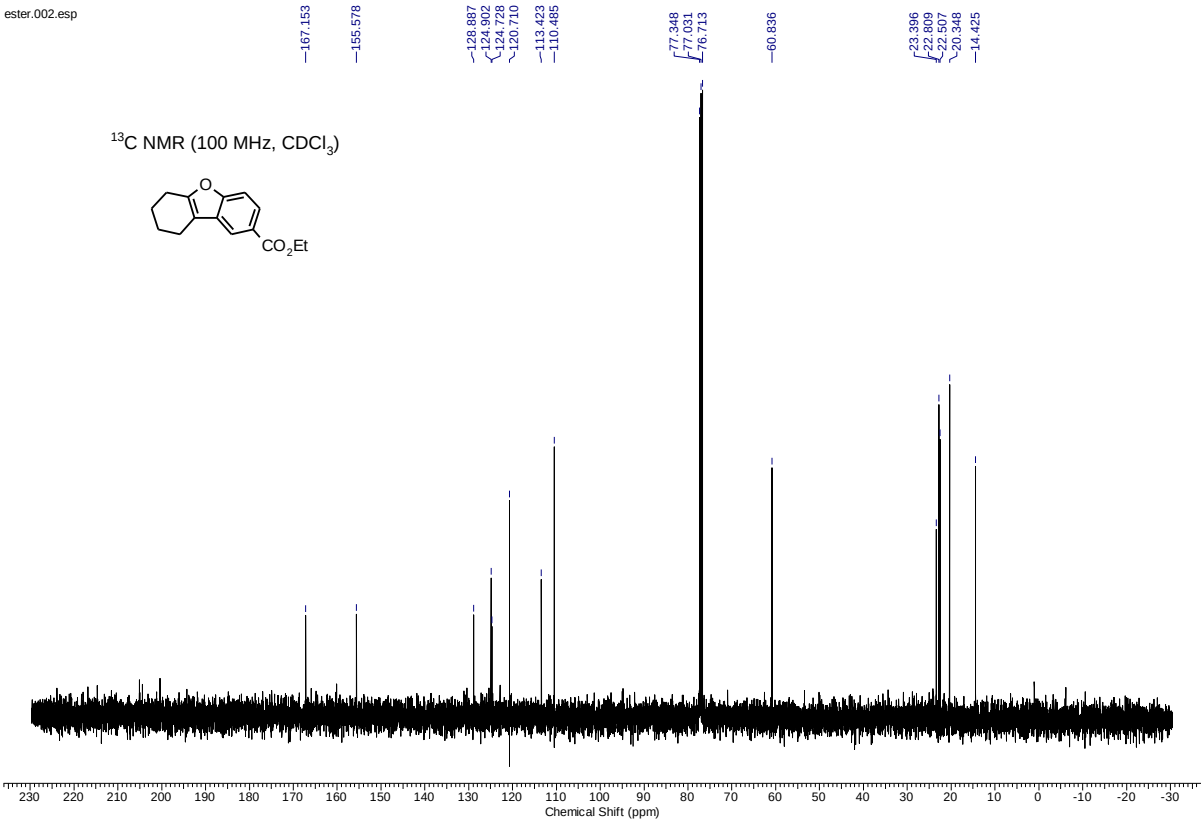
7-Ethyl-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 64



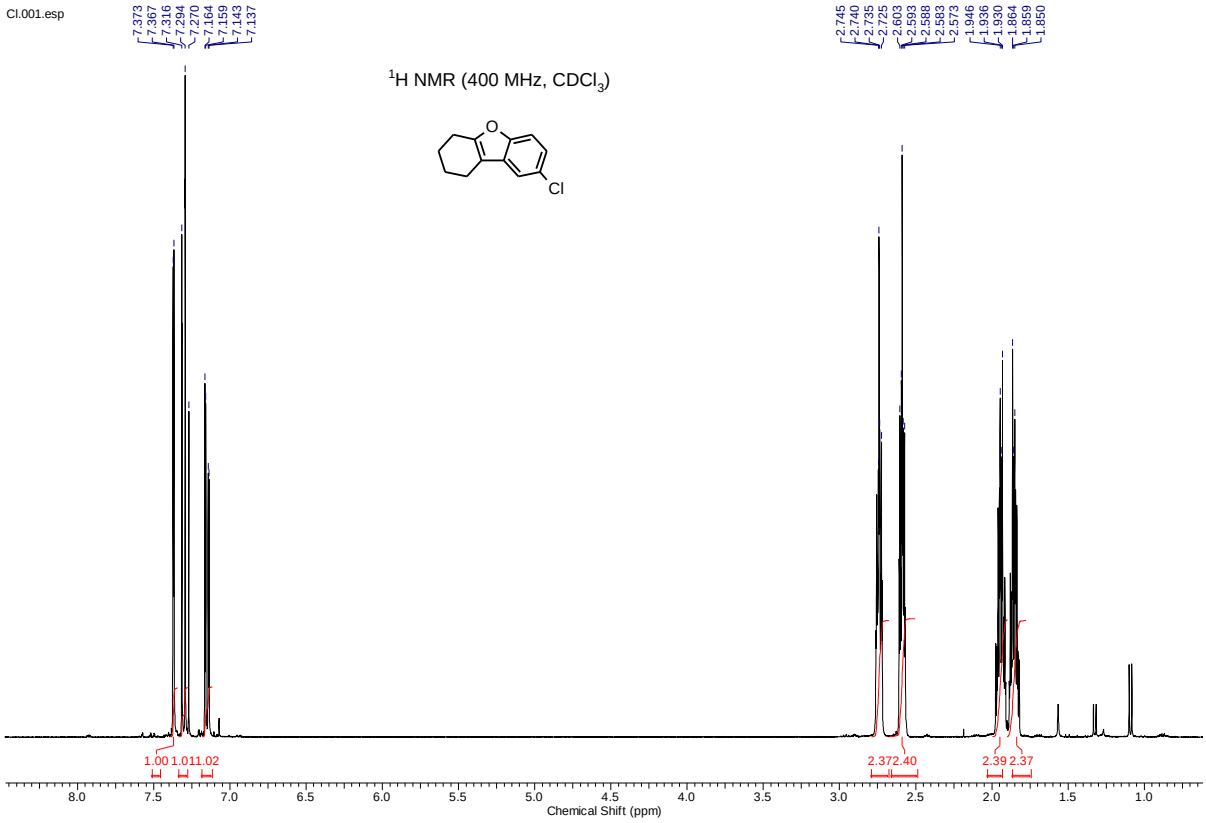


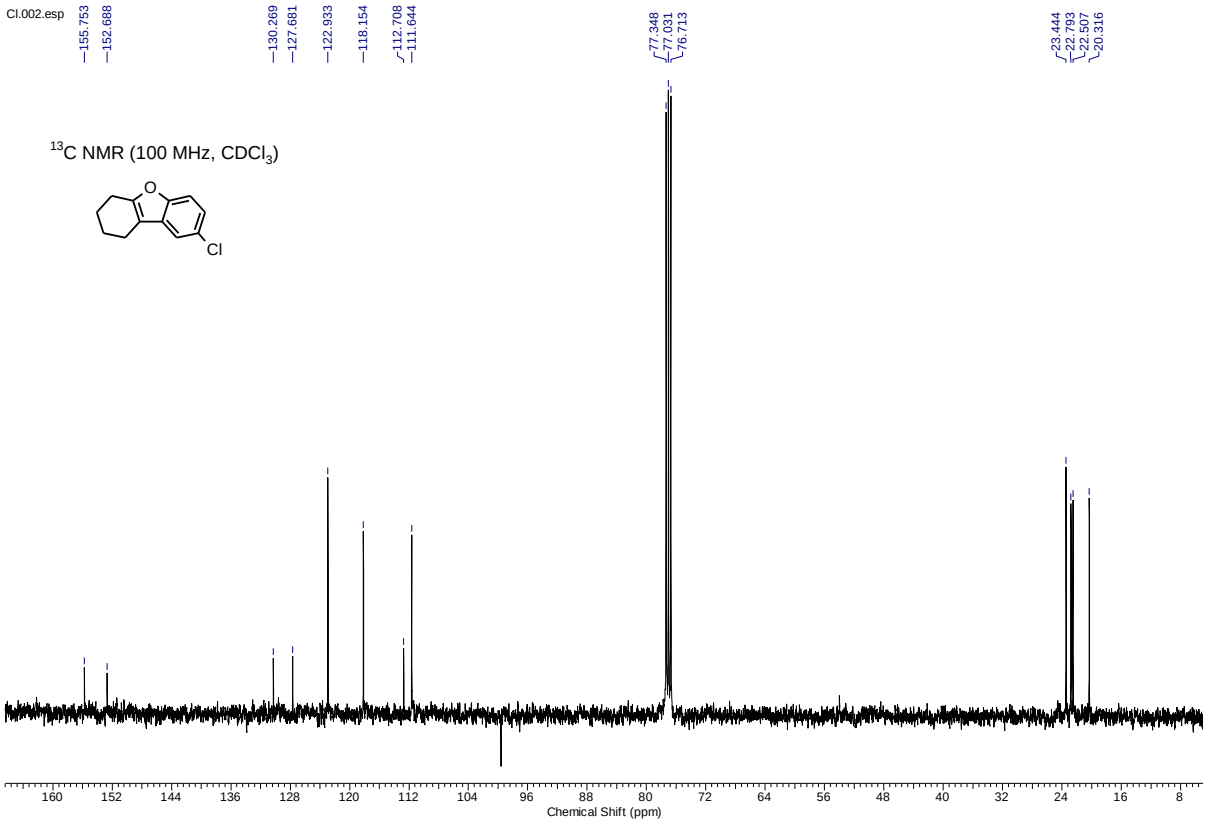
Ethyl 6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-carboxylate, 66



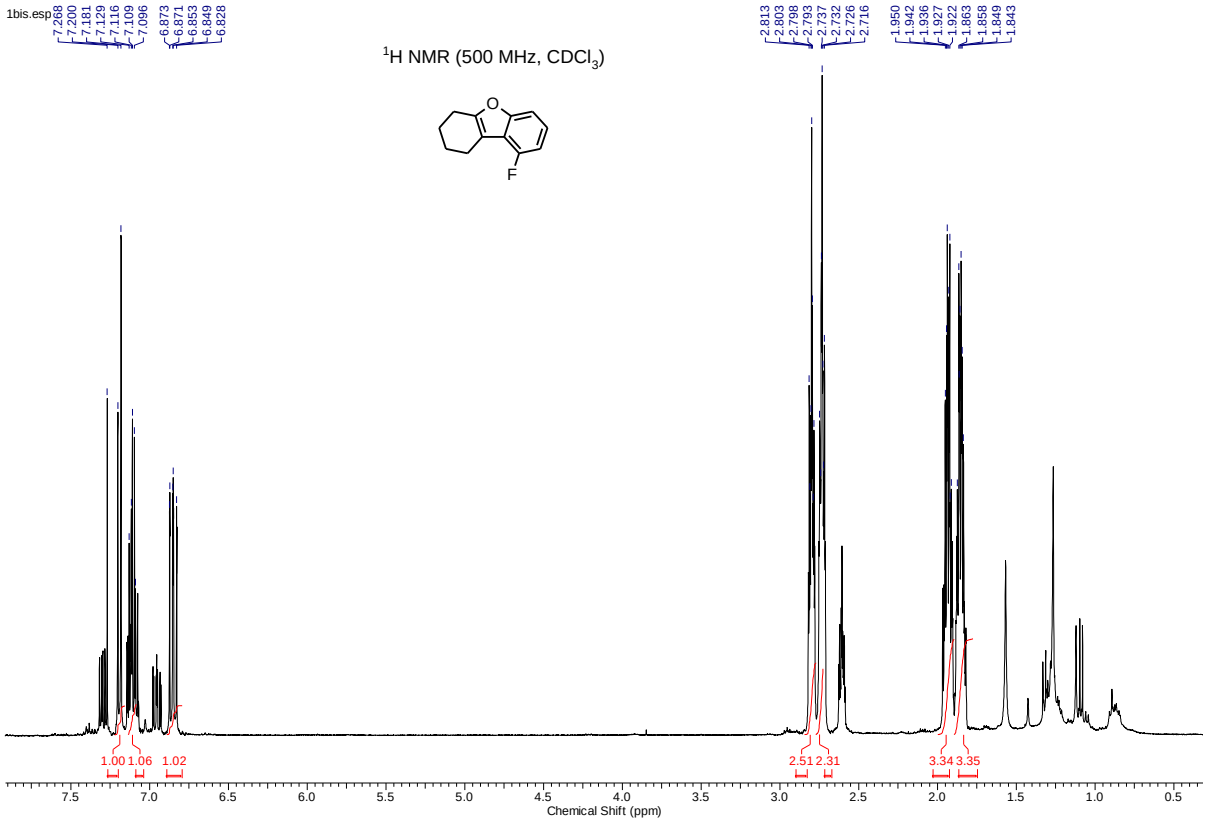


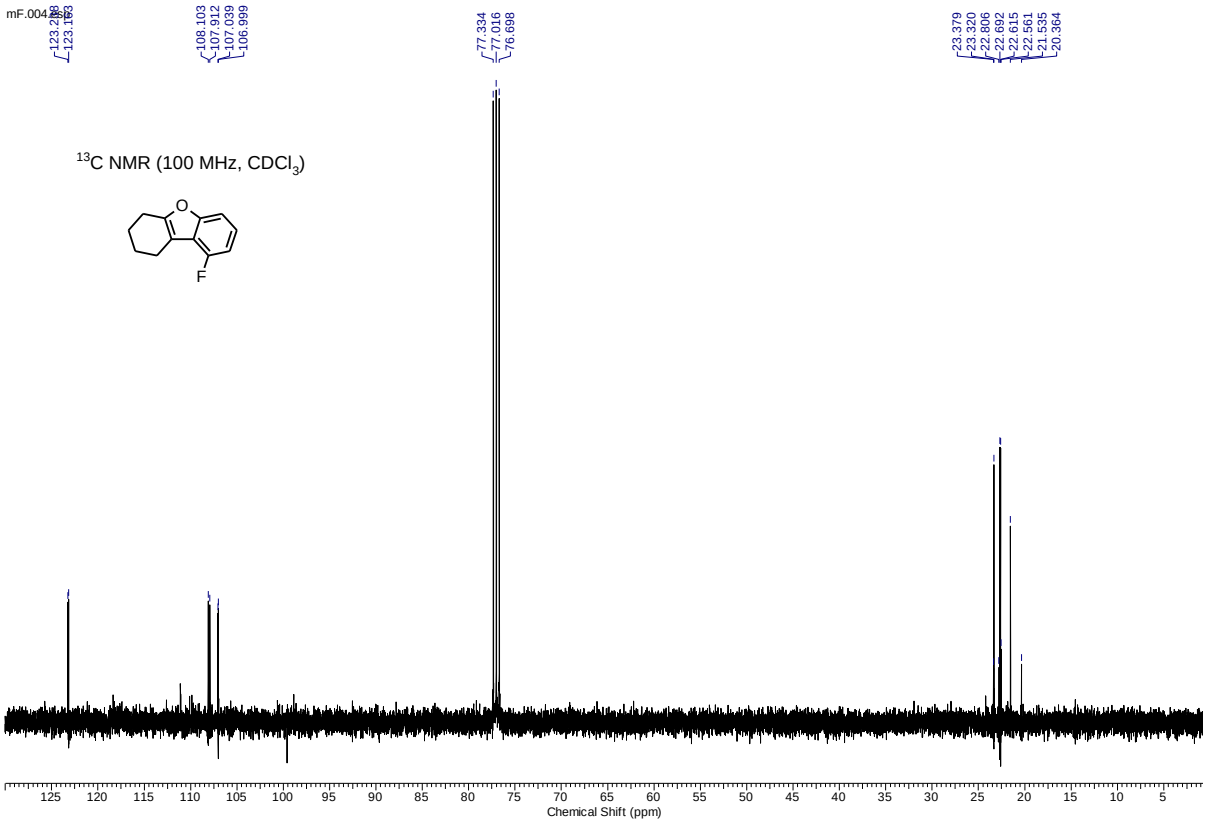
8-Chloro-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 67



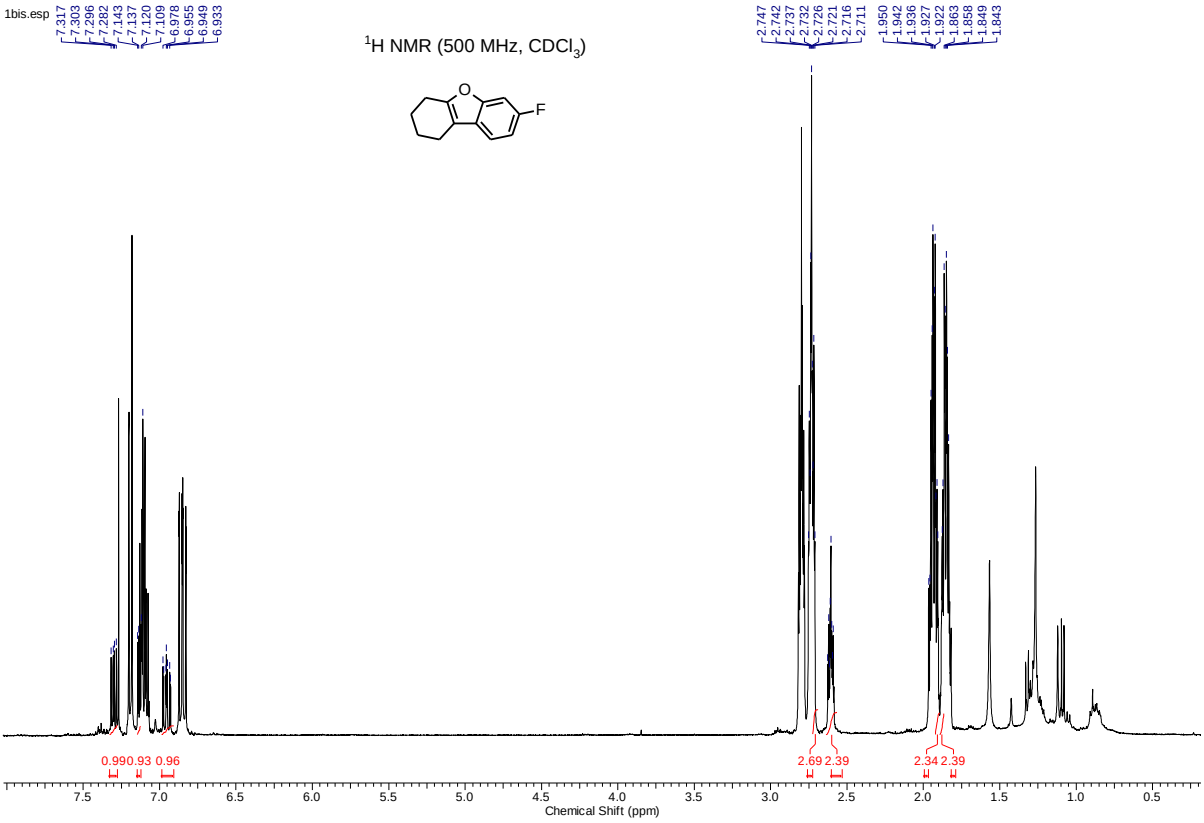


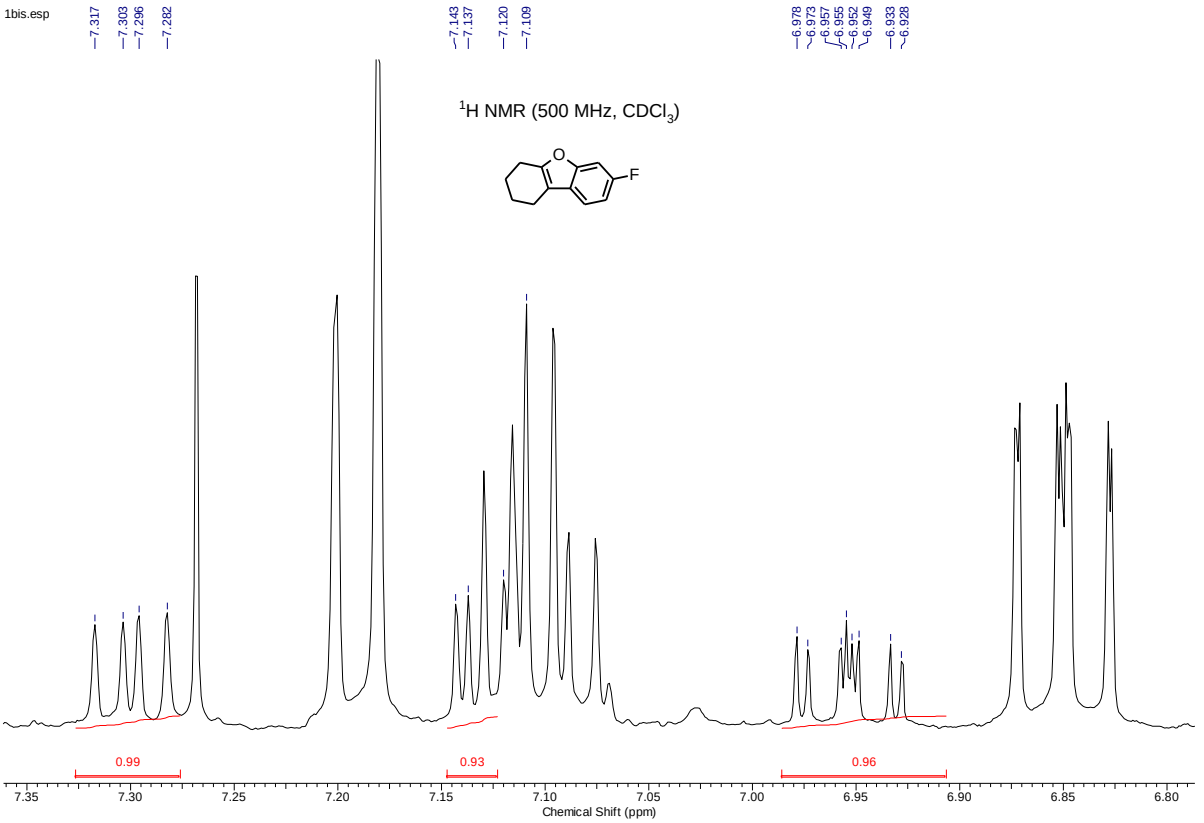
9-Fluoro-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 68



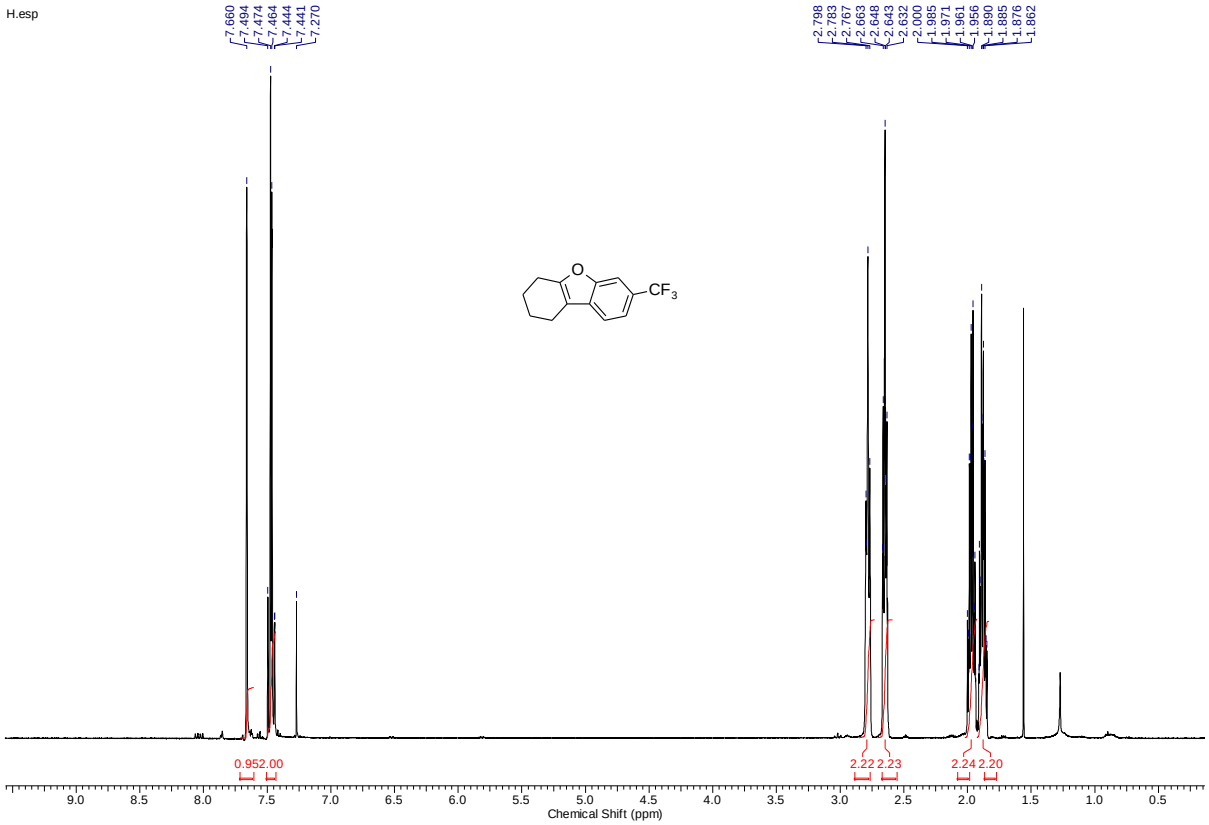


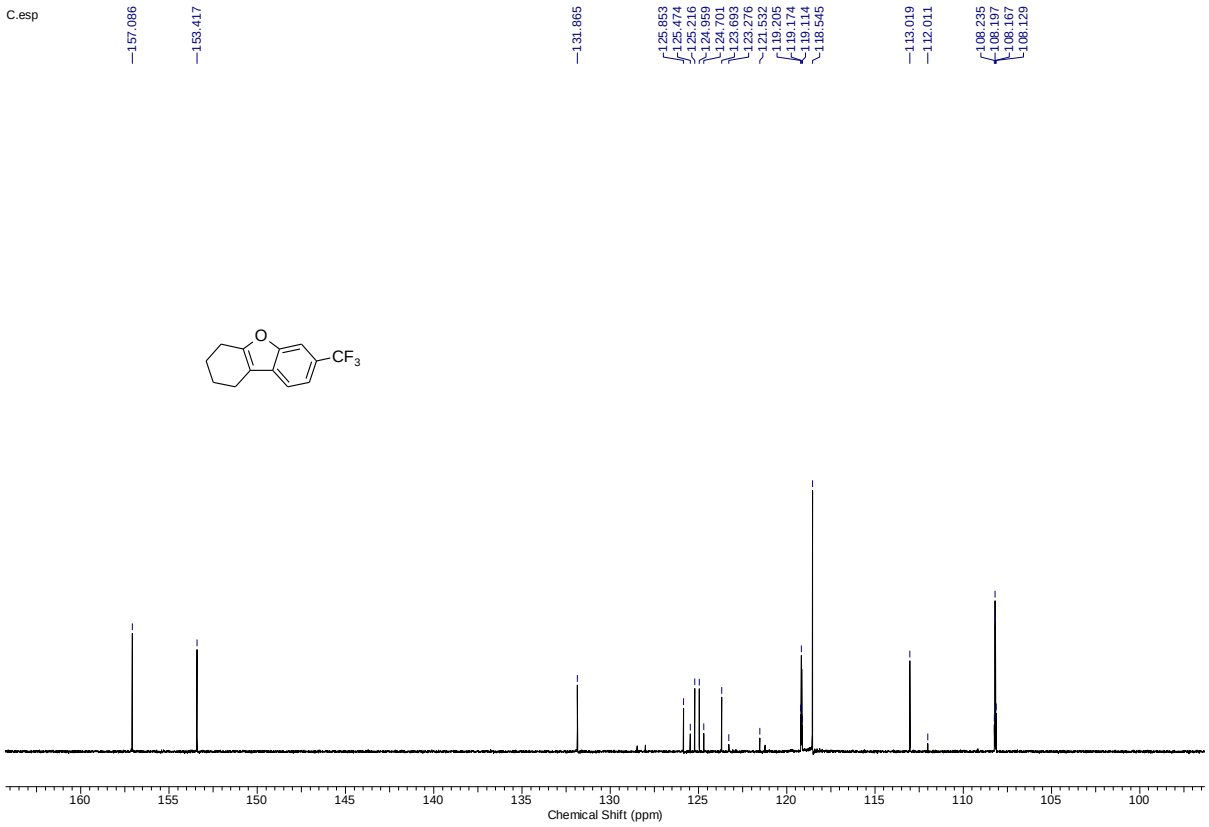
7-Fluoro-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 69



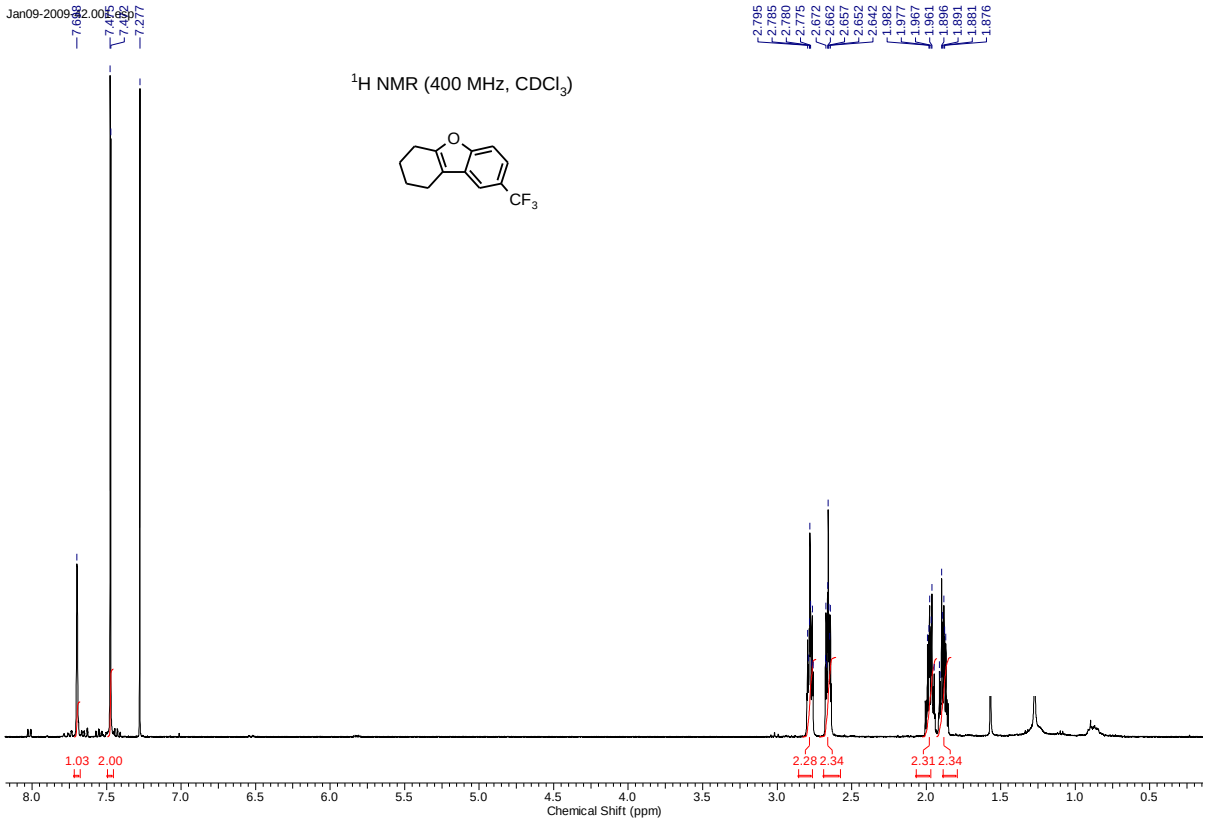


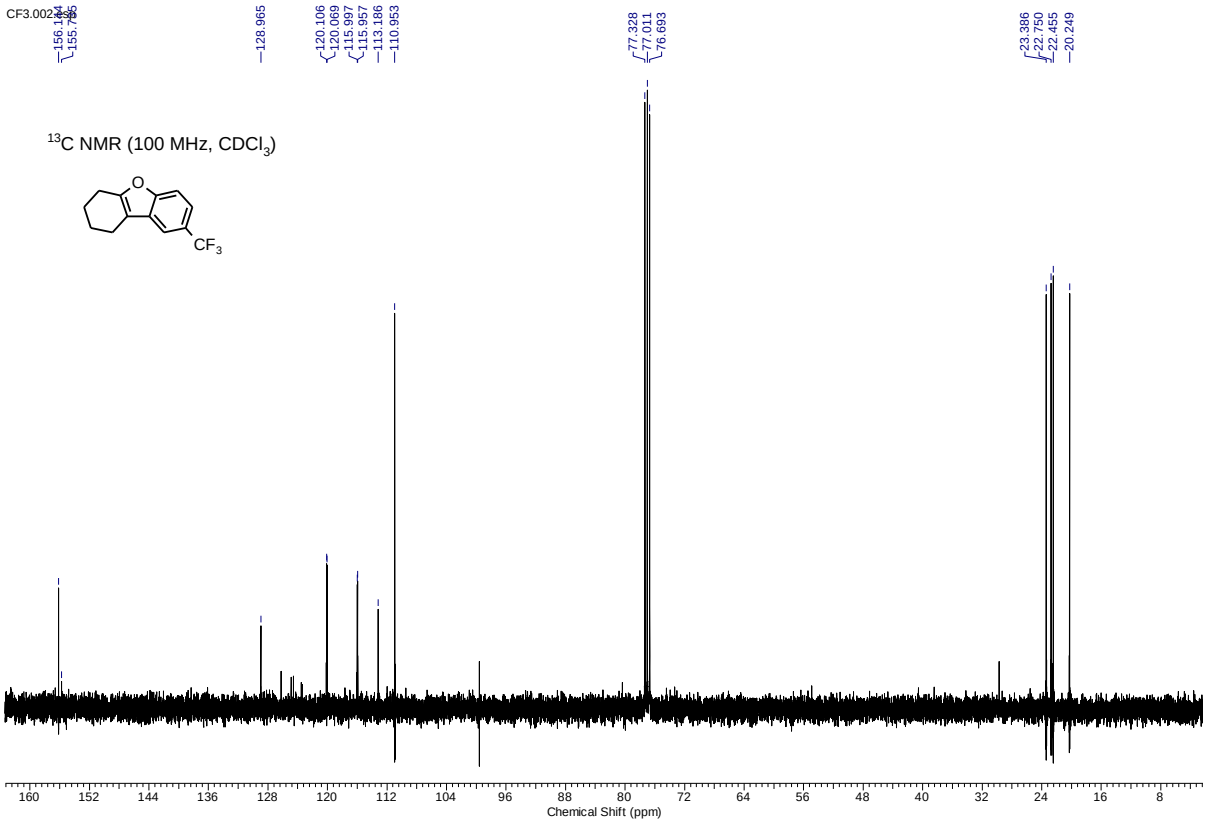
7-(Trifluoromethyl)-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 70



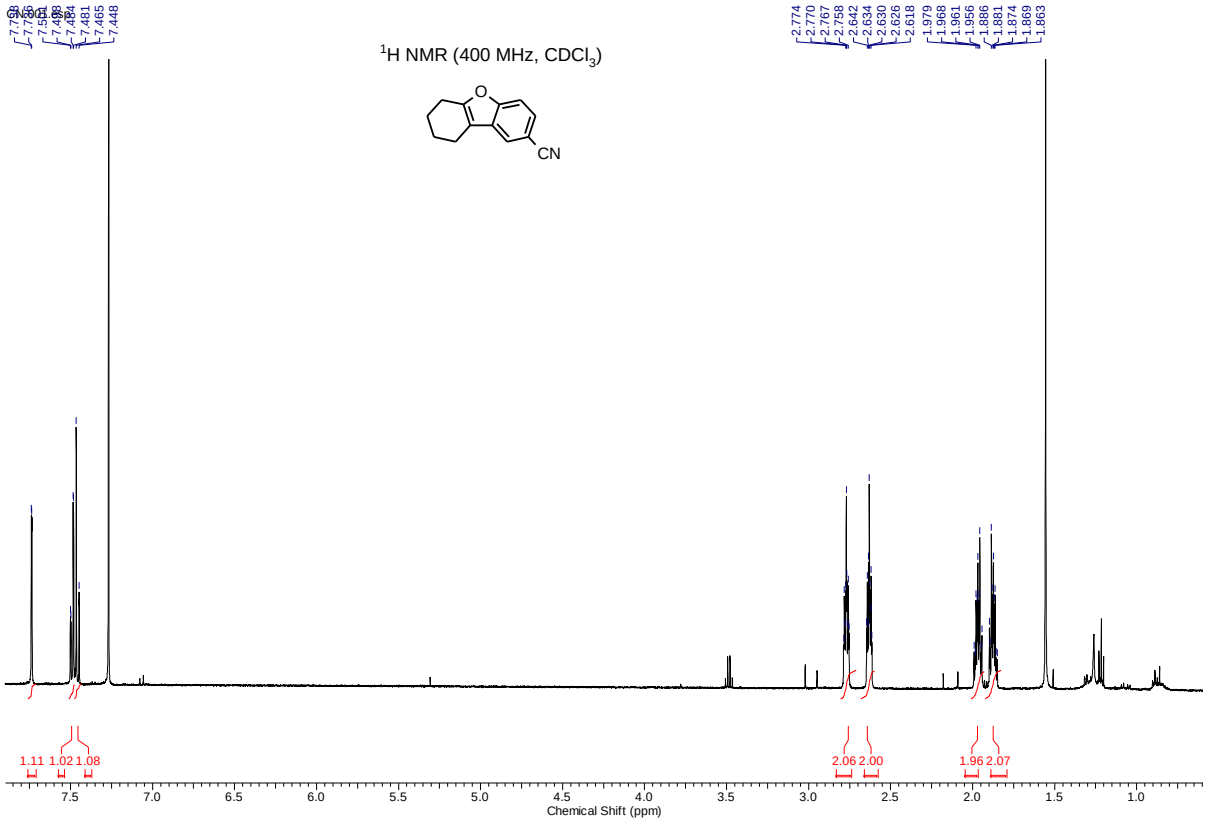


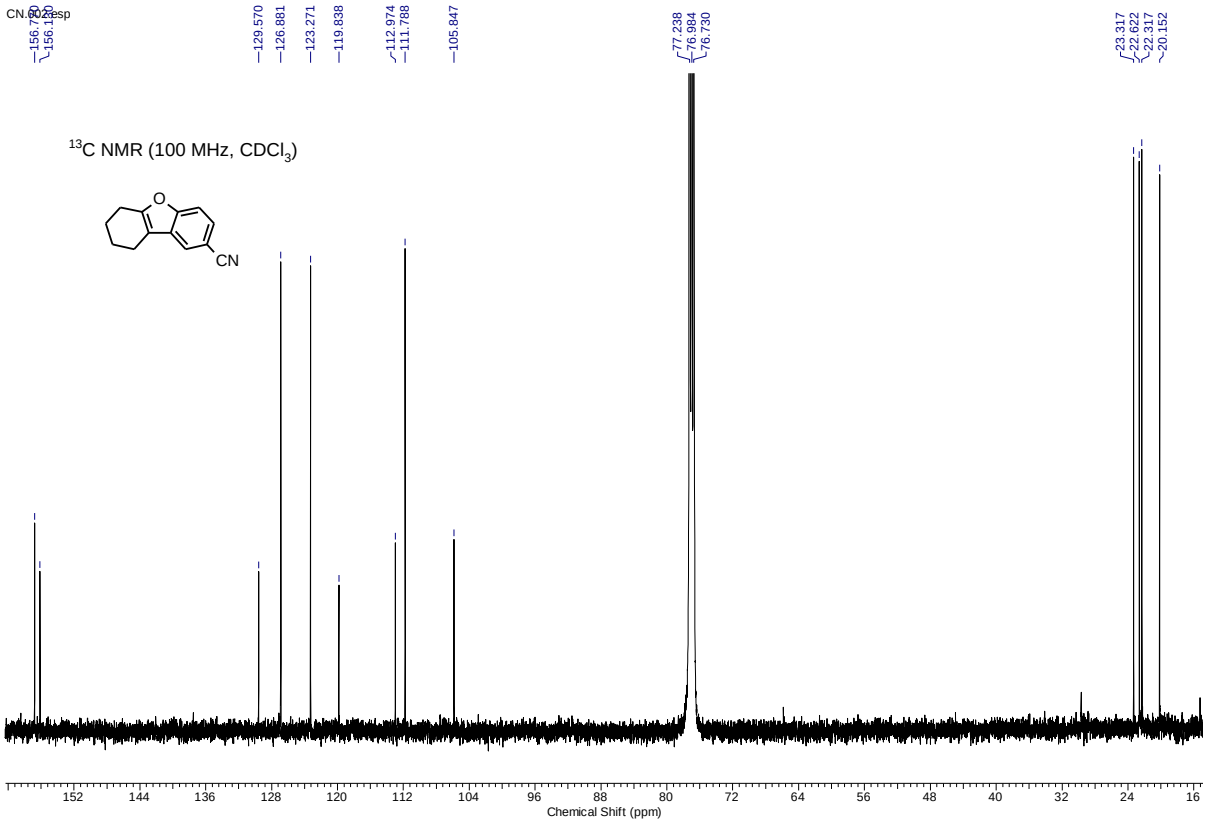
8-(Trifluoromethyl)-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 72



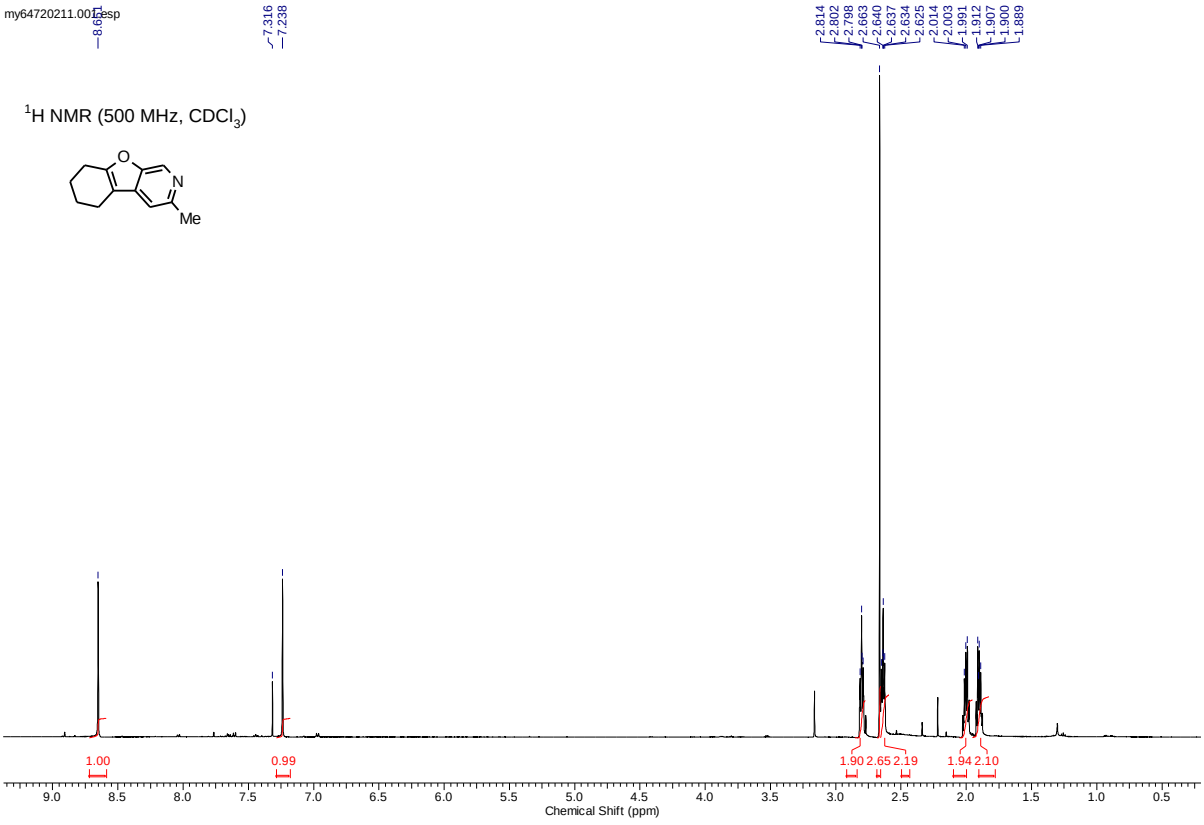


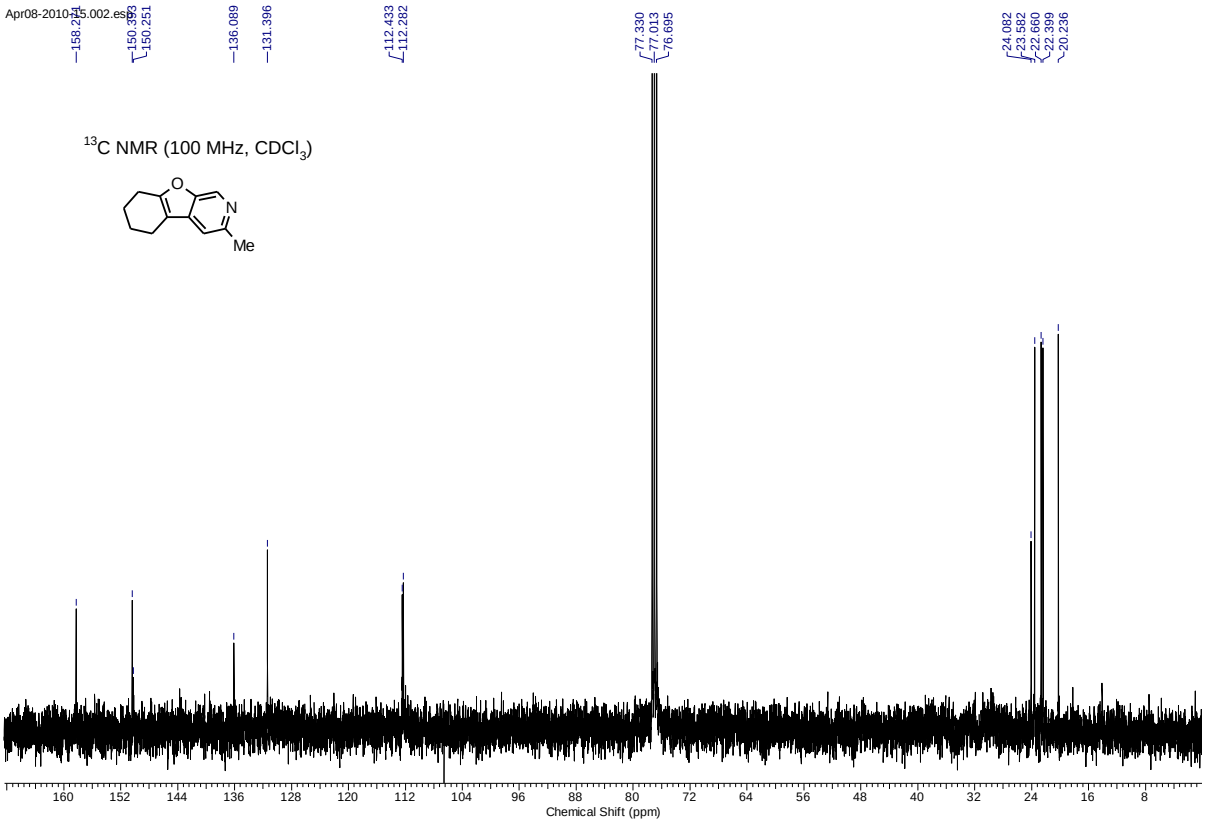
6,7,8,9-Tetrahydrodibenzo[*b*,*d*]furan-2-carbonitrile, 73



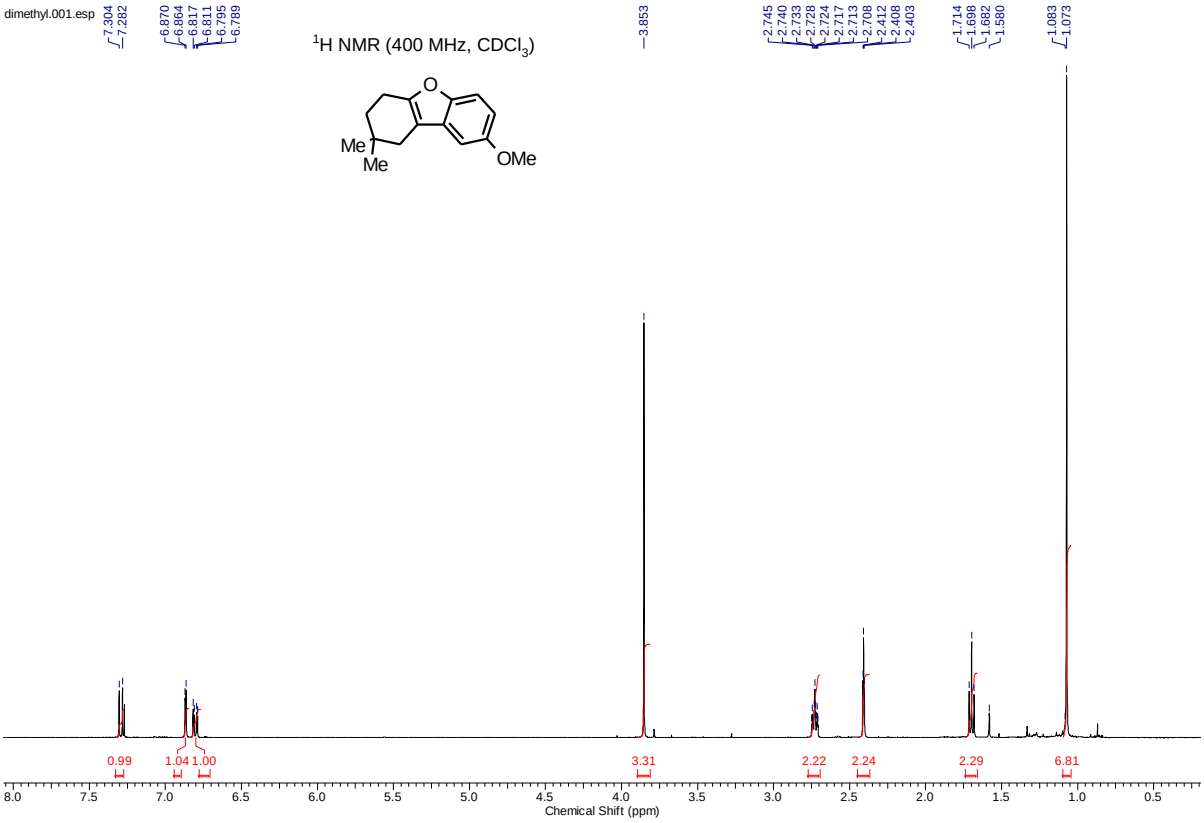


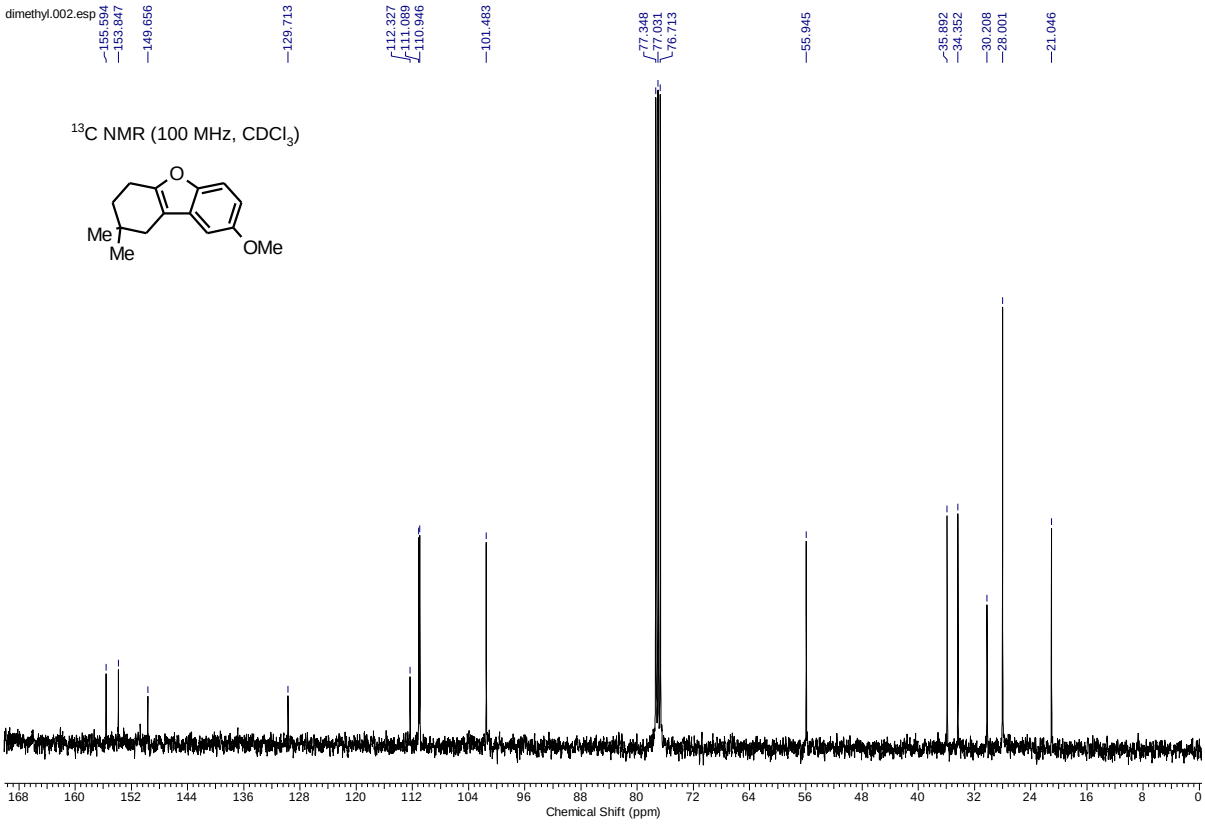
3-Methyl-5,6,7,8-tetrahydrobenzofuro[2,3-*c*]pyridine, 74



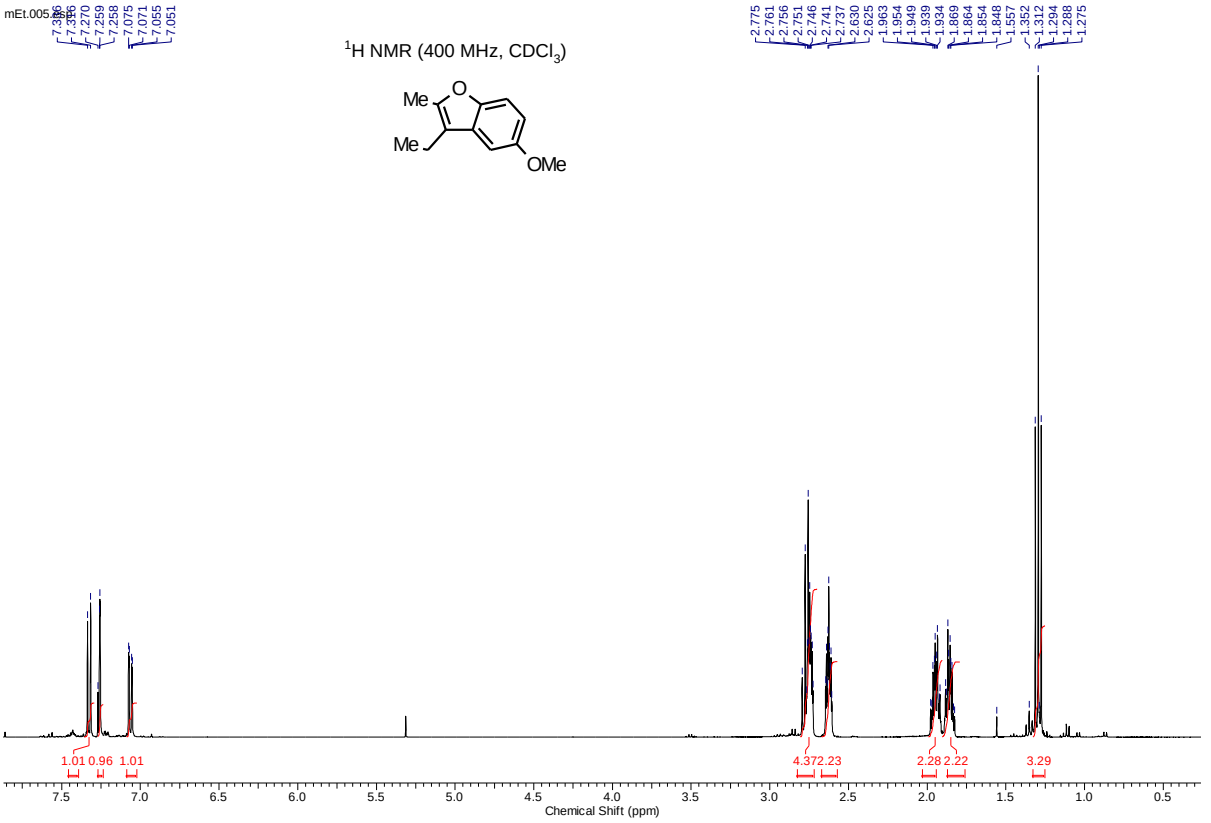


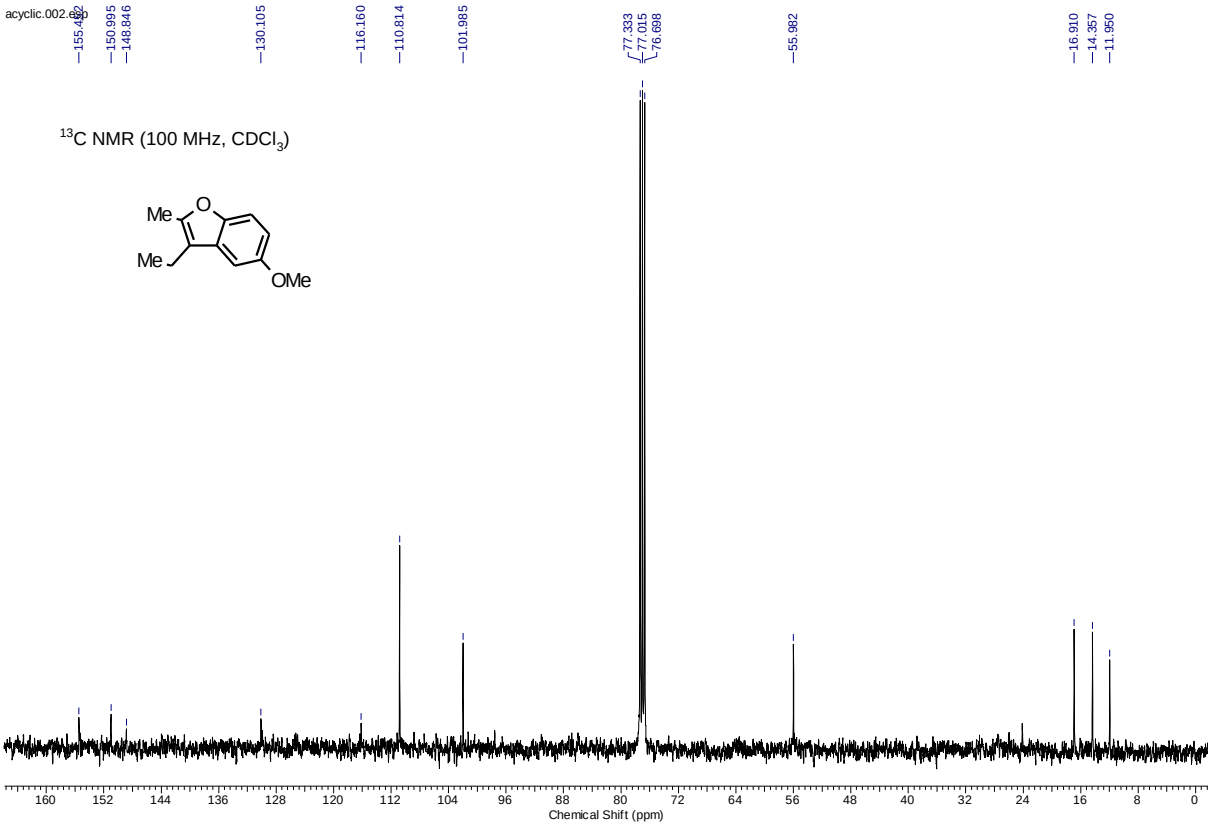
8-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 75



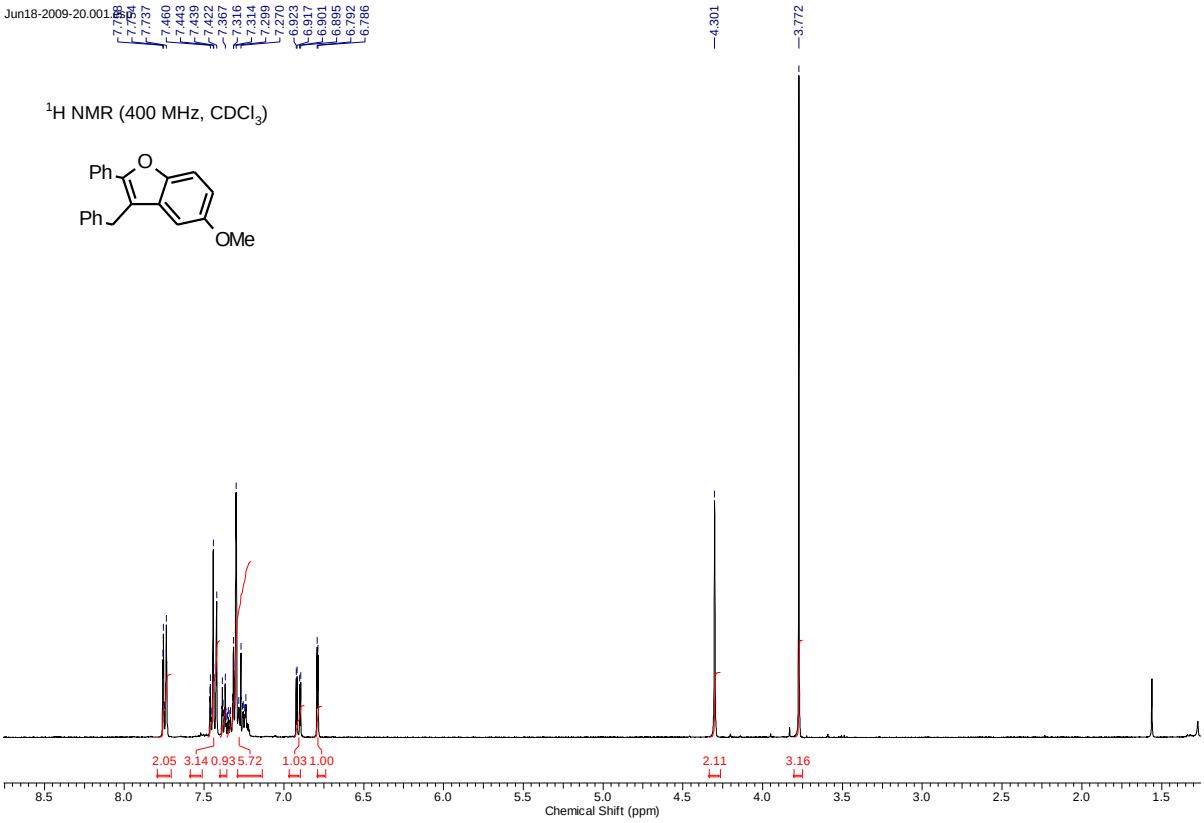


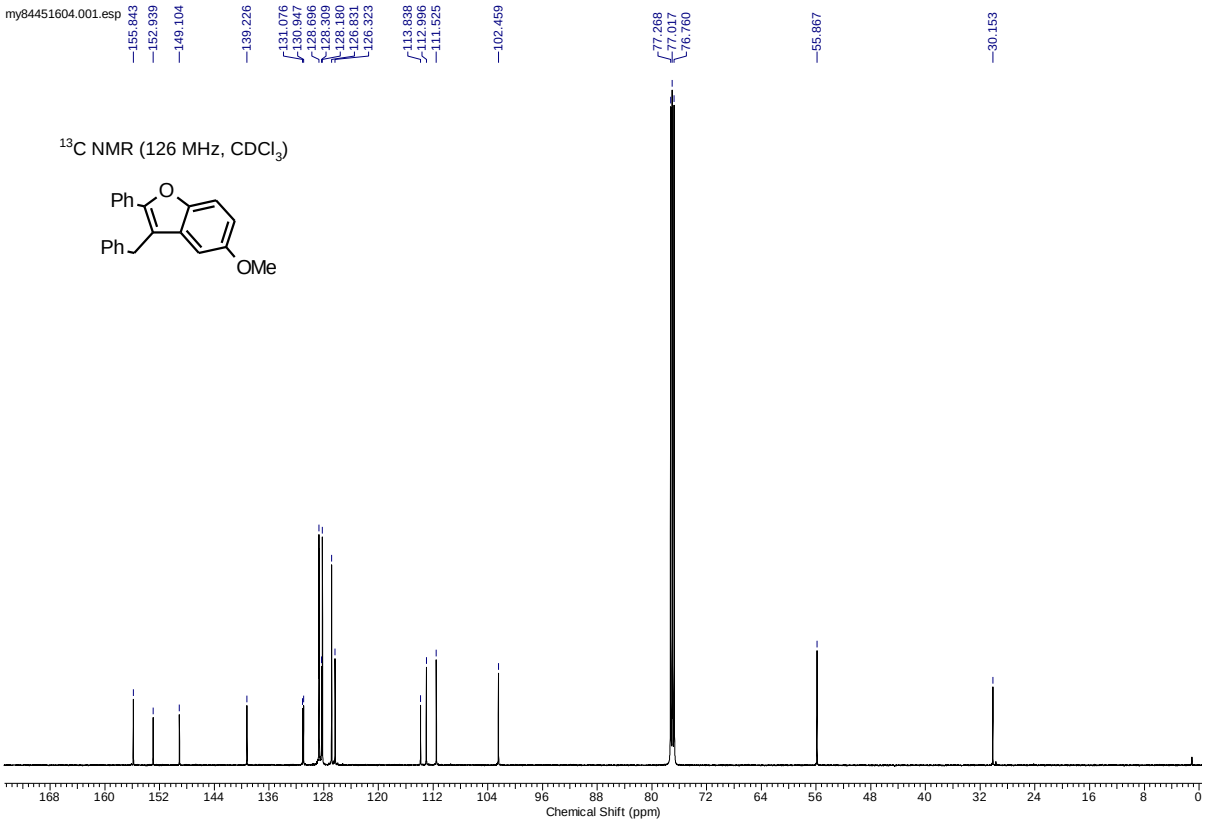
3-Ethyl-5-methoxy-2-methylbenzofuran, 76



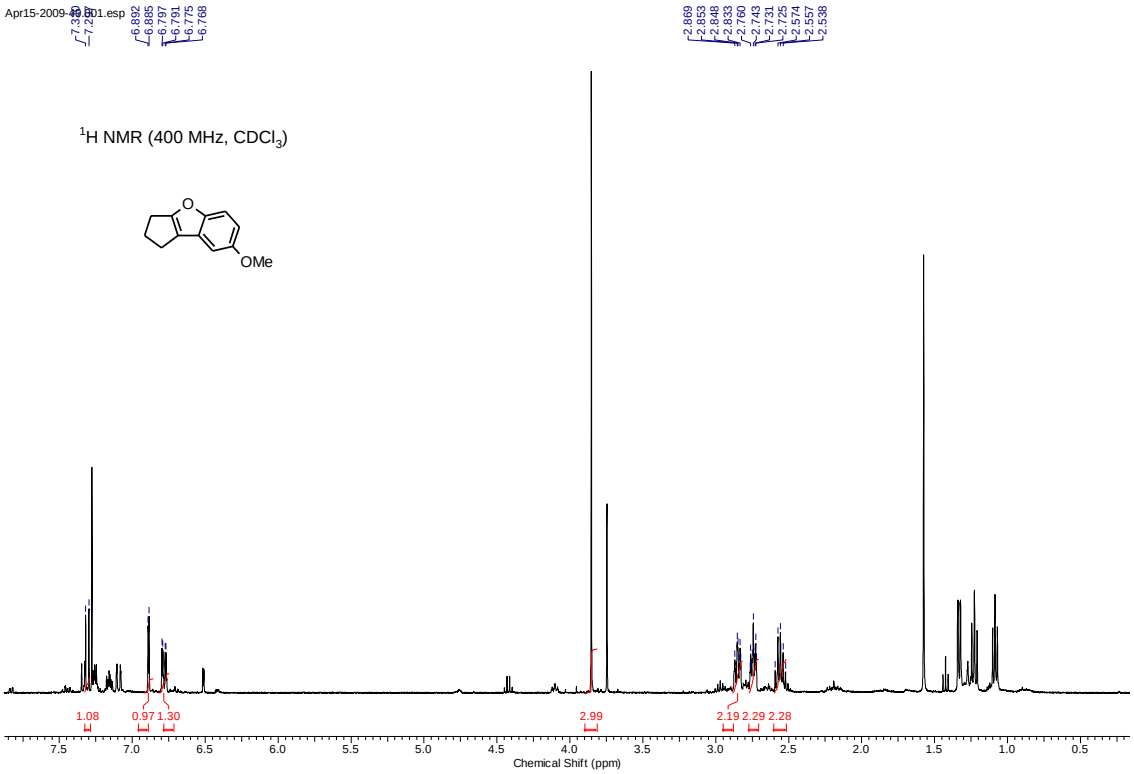


3-Benzyl-5-methoxy-2-phenylbenzofuran, 77

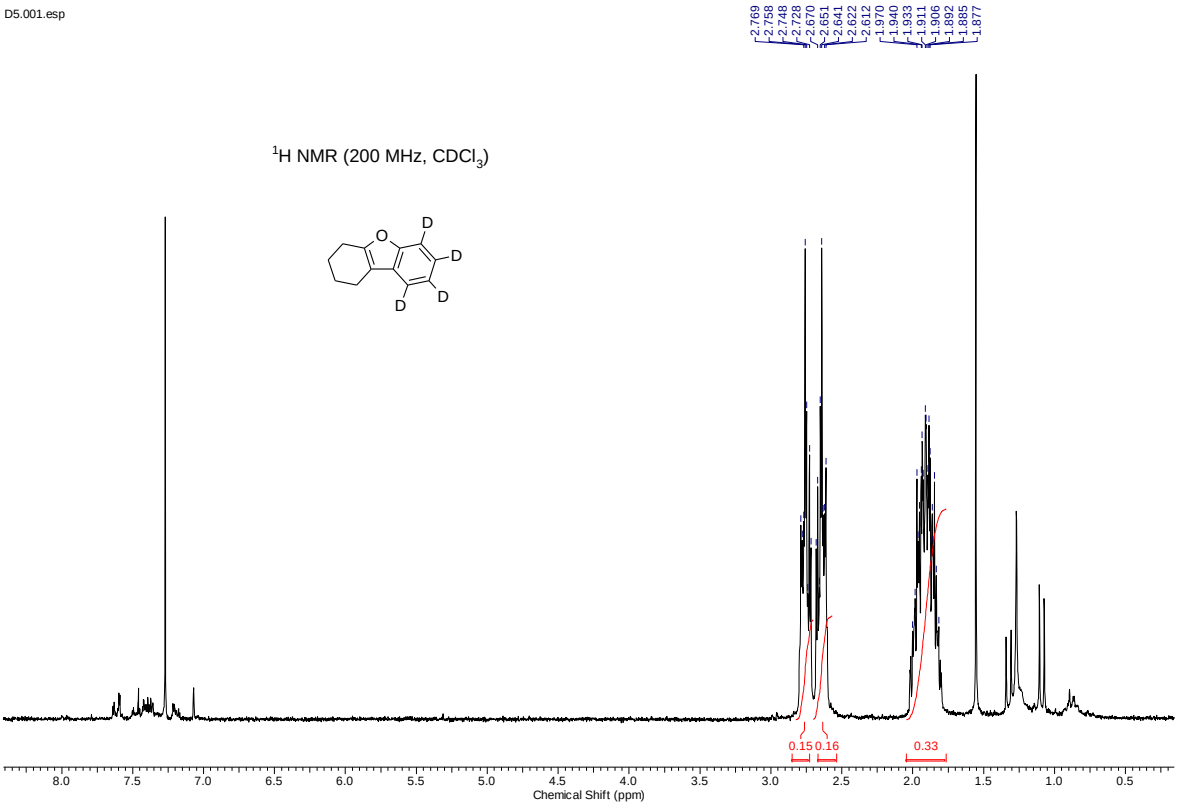




7-Methoxy-2,3-dihydro-1H-benzo[b]cyclopenta[d]furan, 78

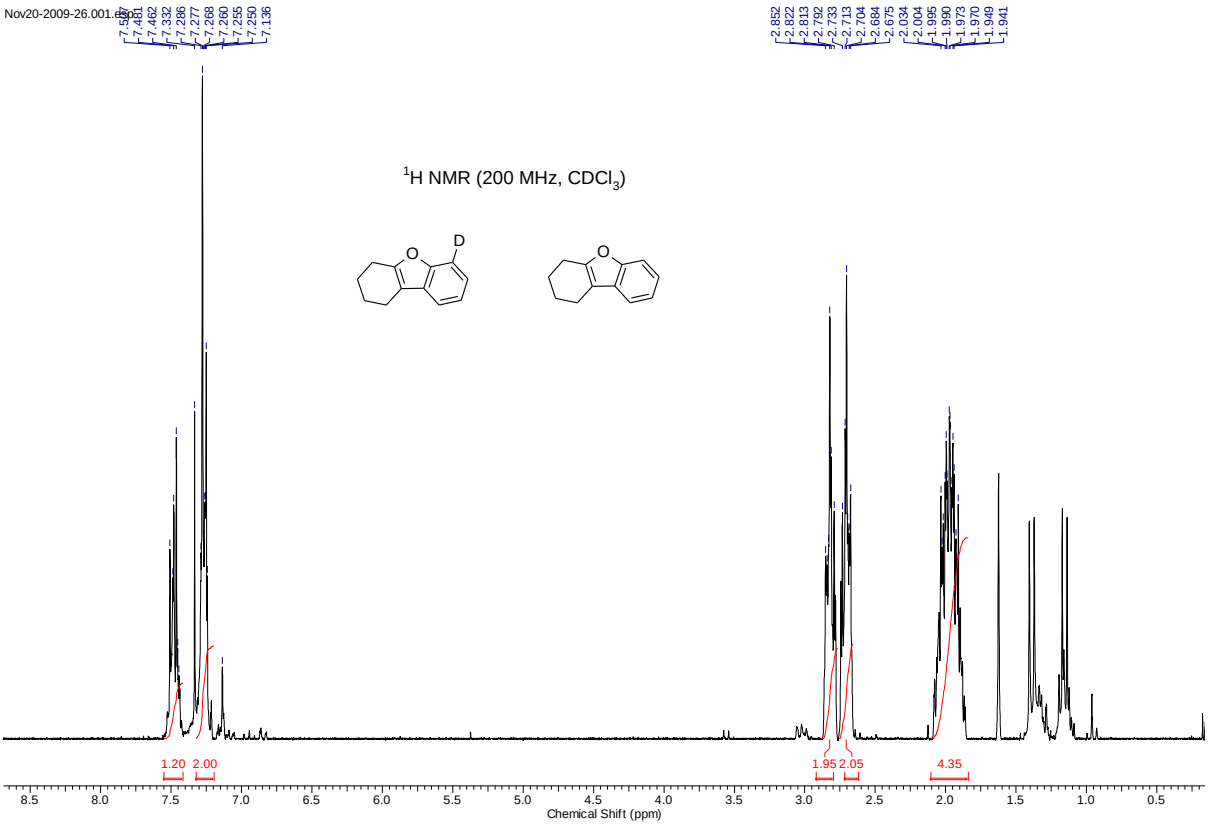


1,2,3,4-(D_4)-dibenzo[*b*,*d*]furan, 102

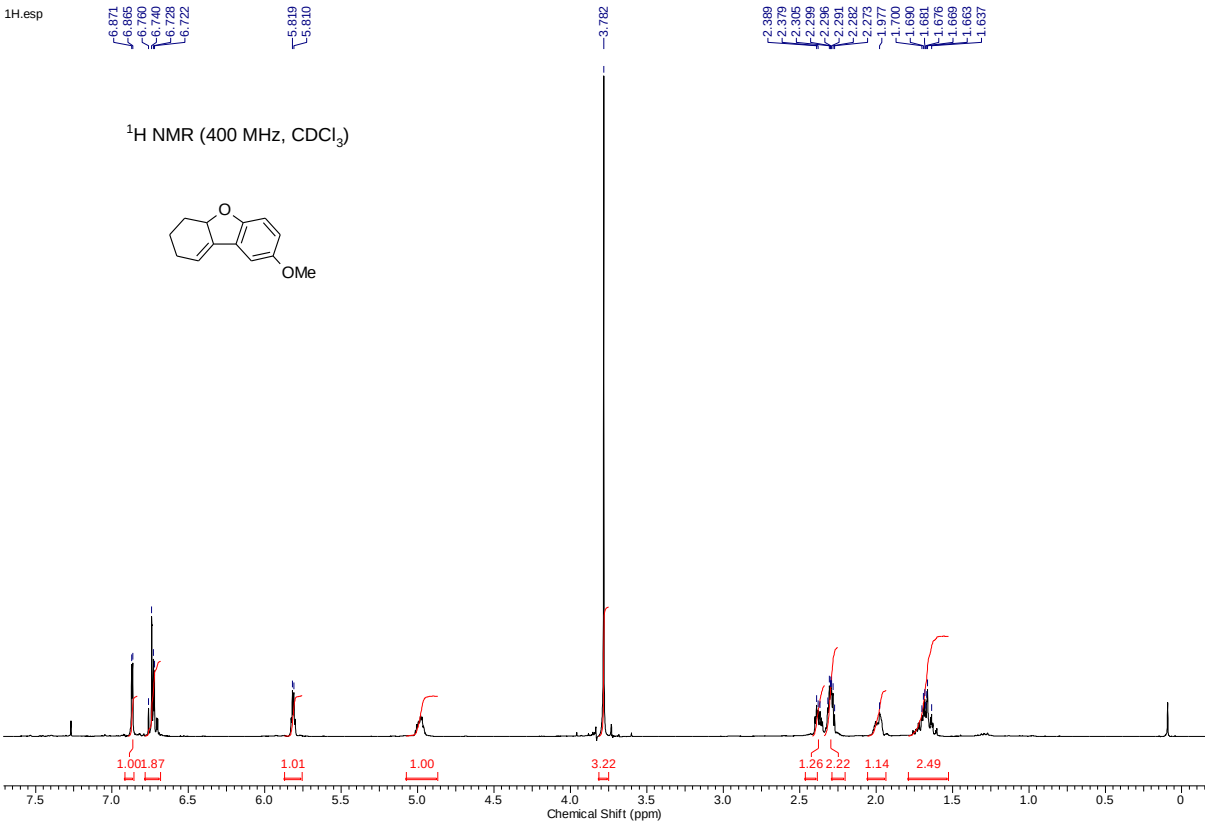


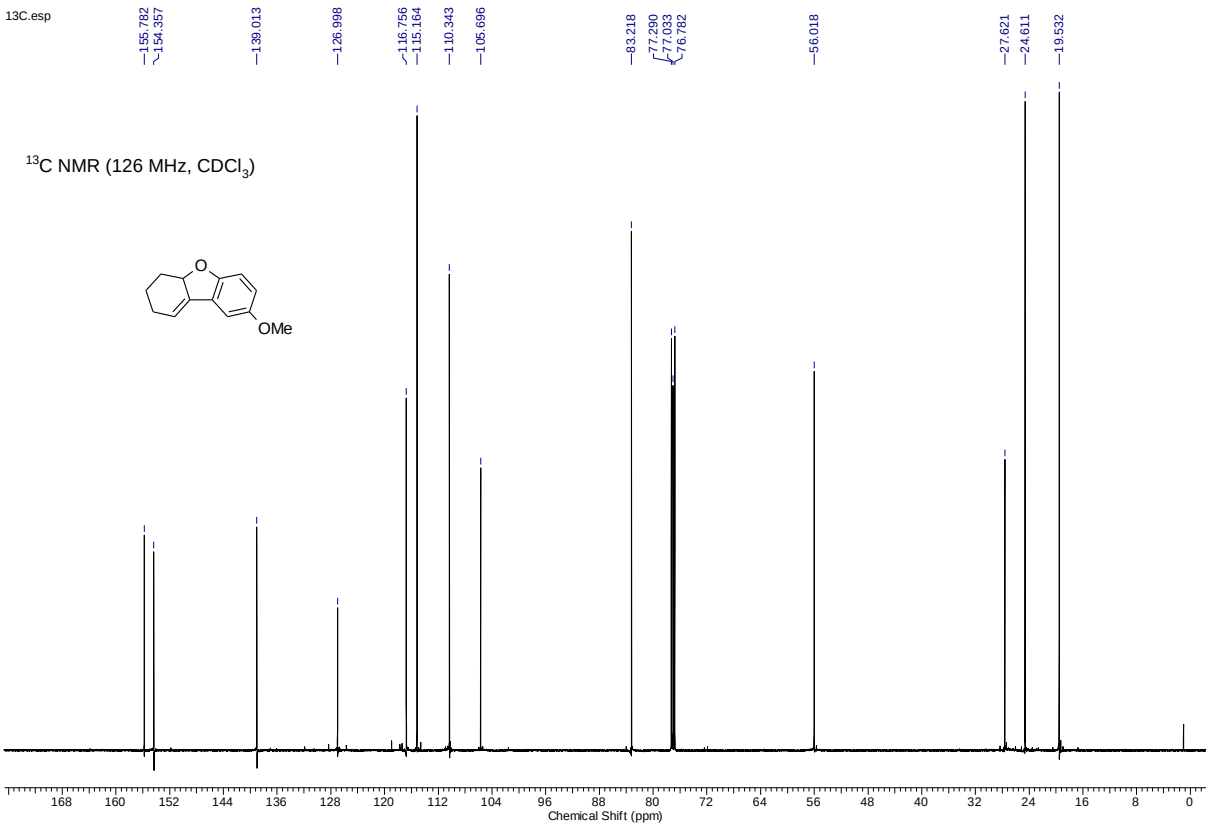
6-D-1,2,3,4-Tetrahydrodibenzo[*b*,*d*]furan, 101

1,2,3,4-Tetrahydrodibenzo[*b*,*d*]furan, 59

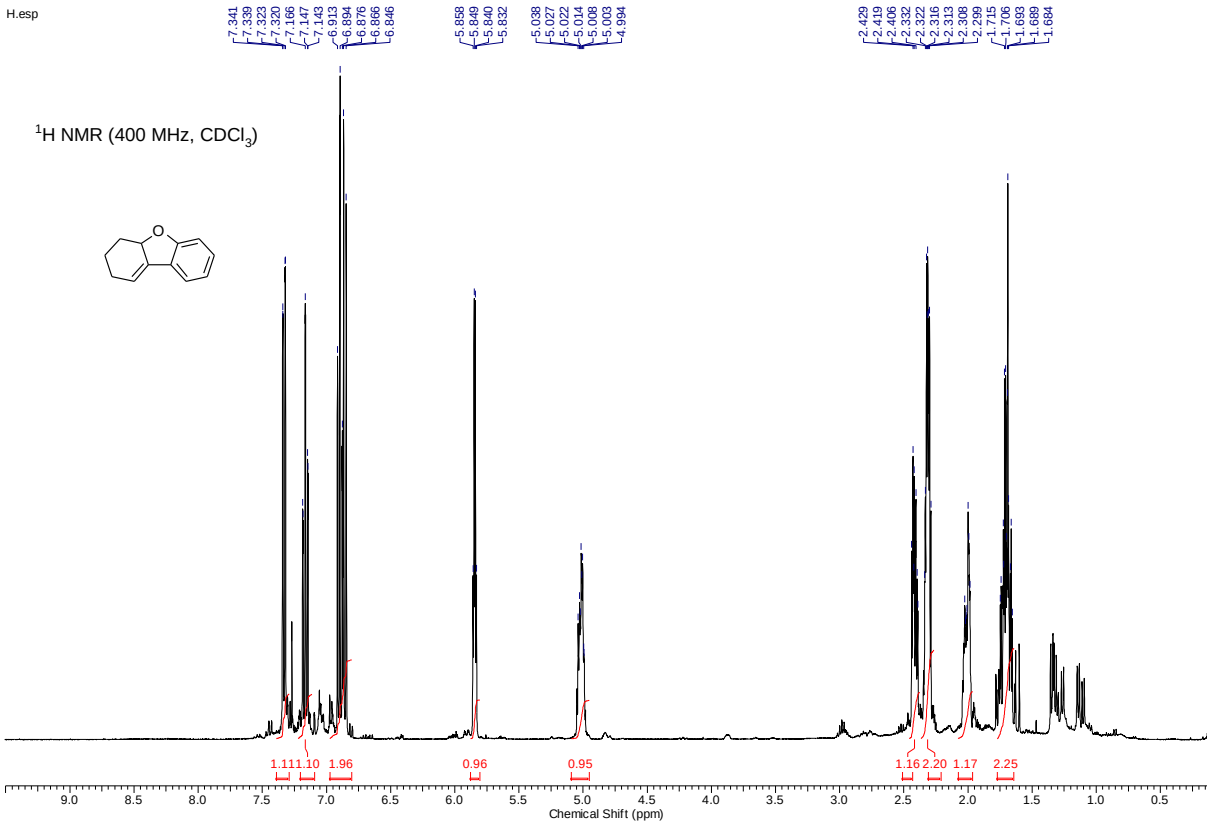


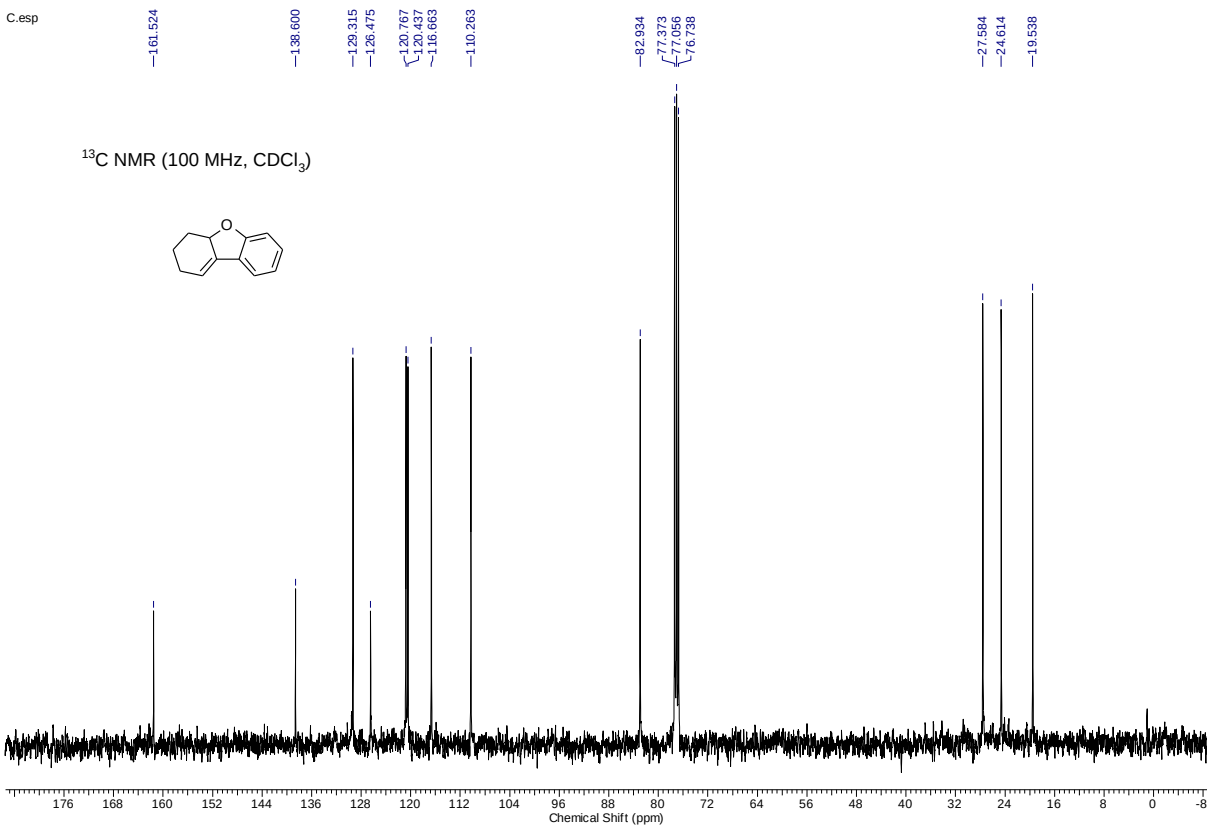
8-Methoxy-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 57



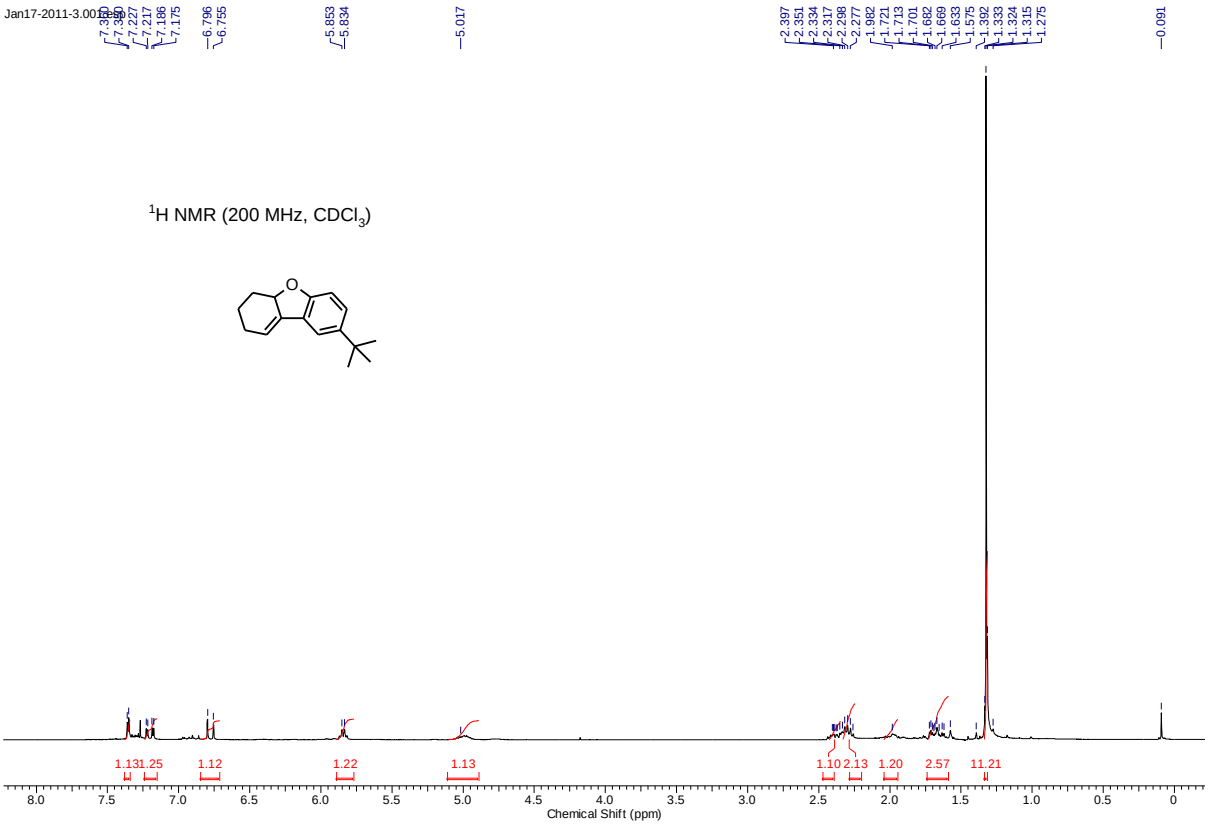


2,3,4,4a-Tetrahydrodibenzo[*b*,*d*]furan, 79

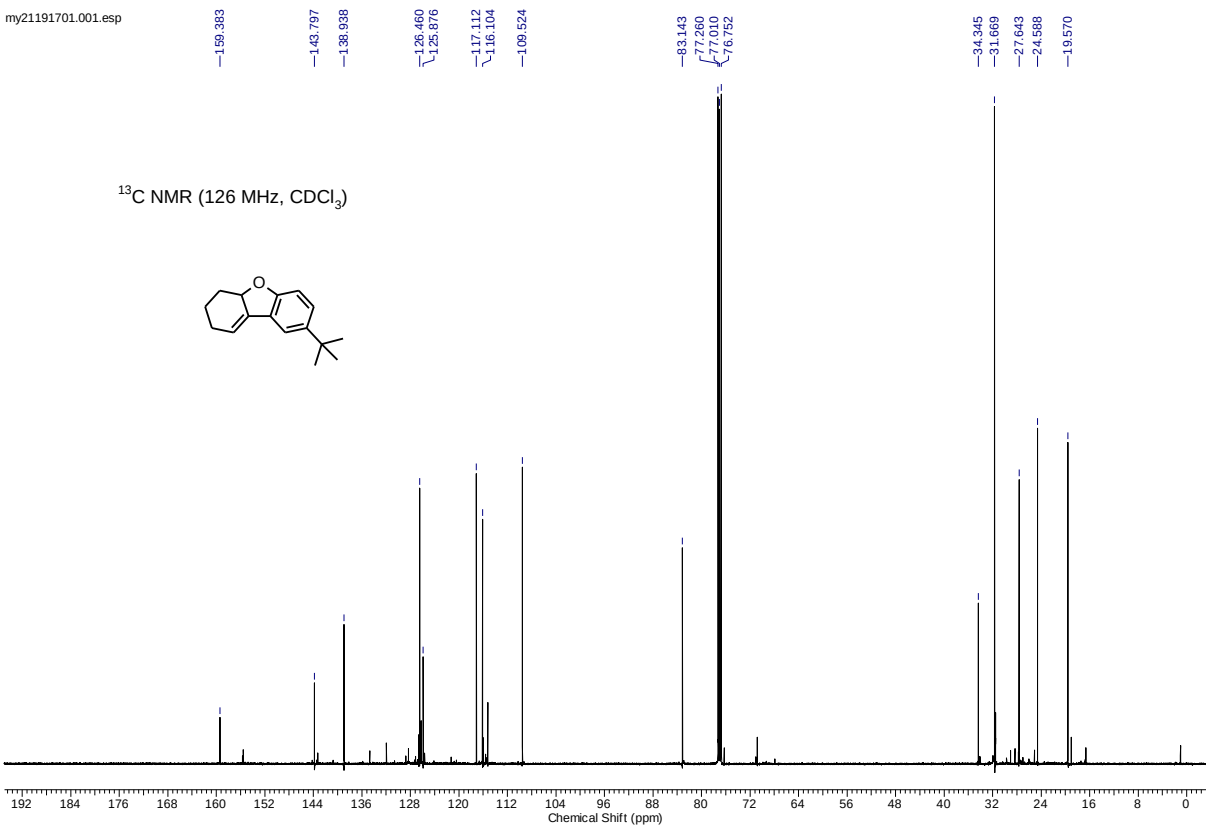




8-*tert*-Butyl-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 80

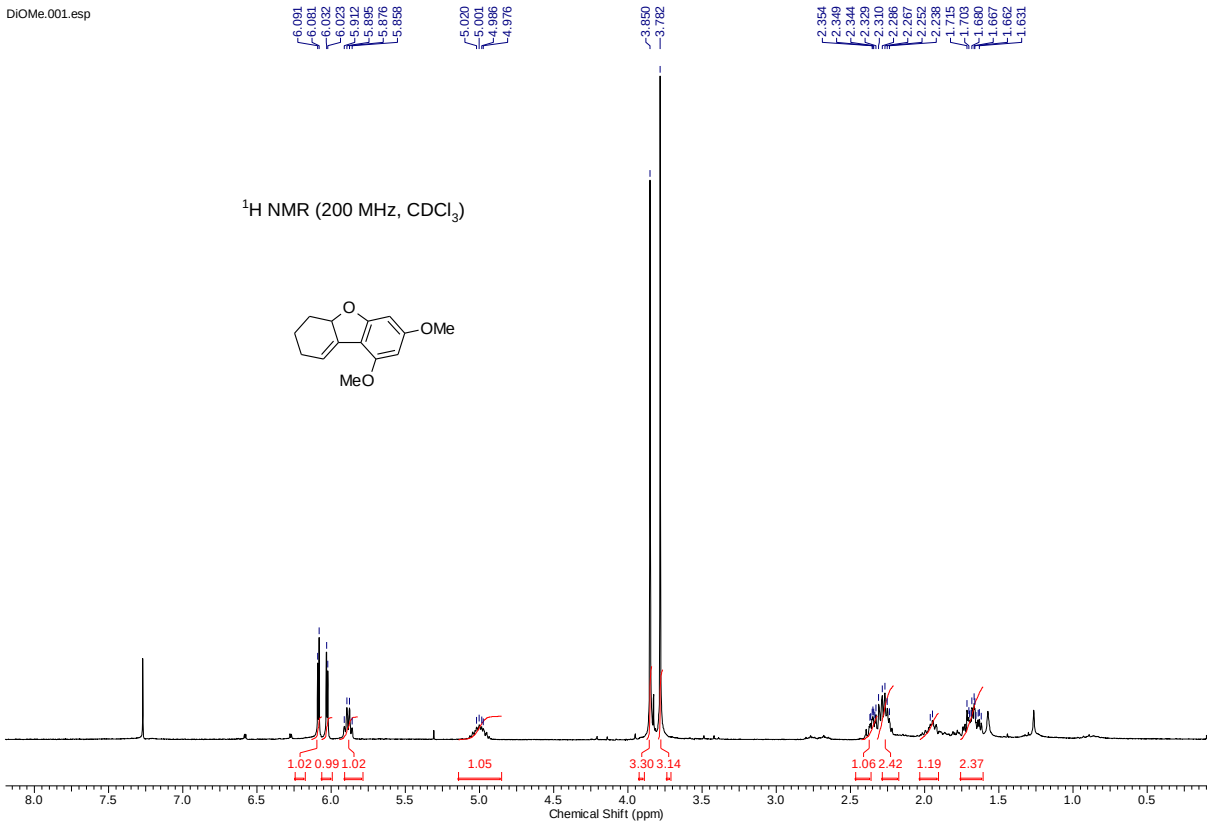


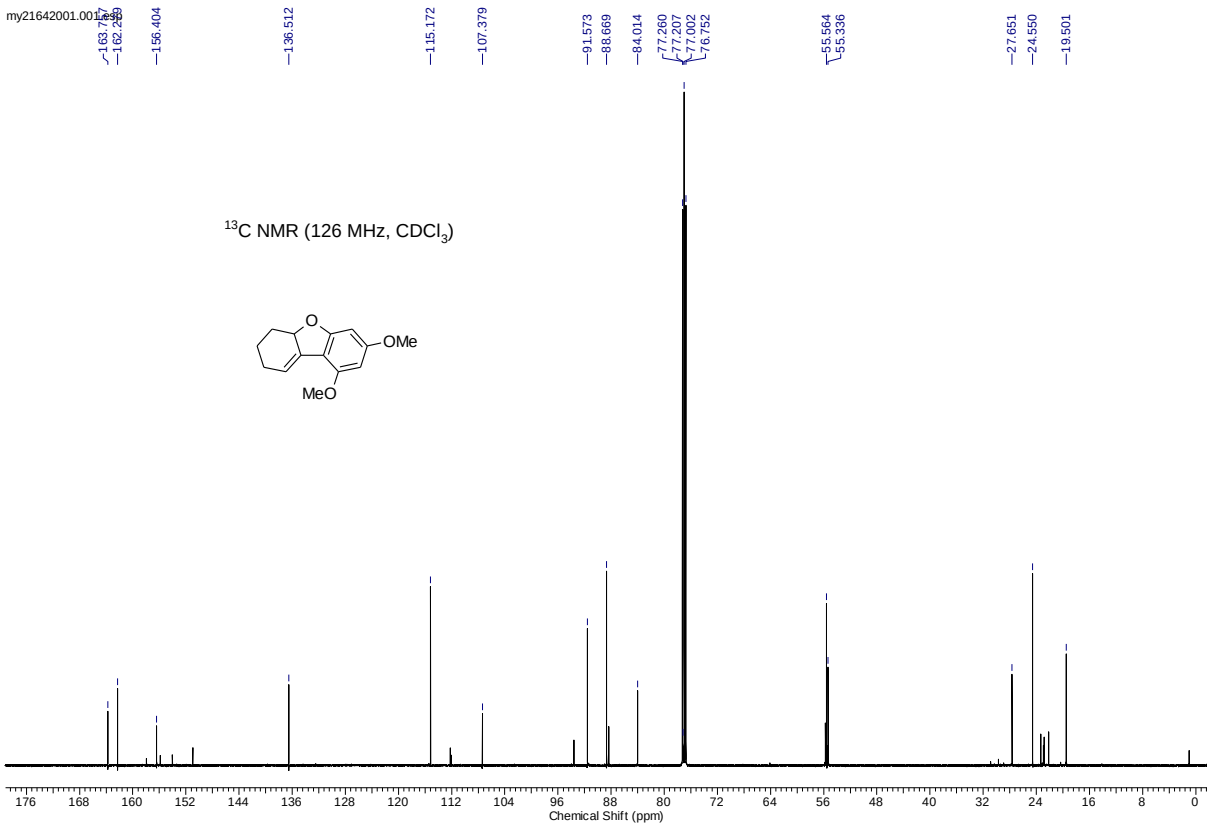
^{1}H NMR (200 MHz, $CDCl_3$)



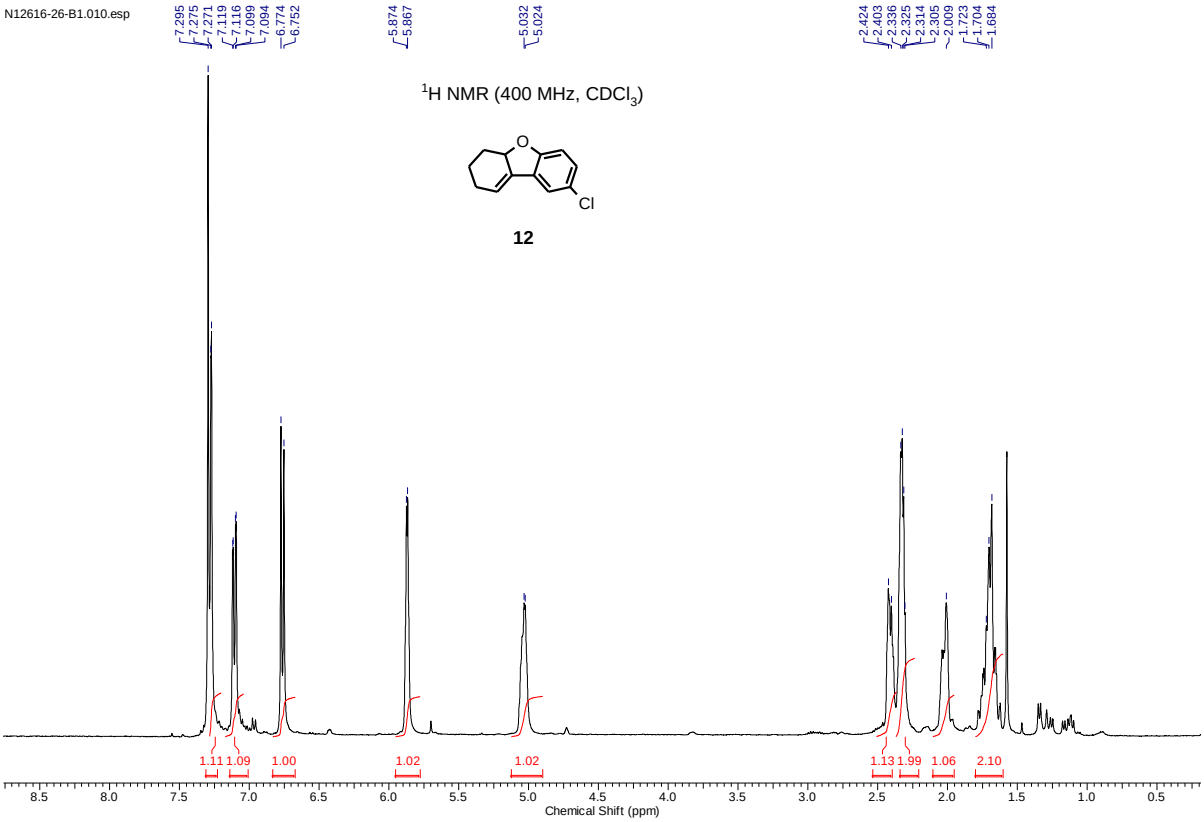
^{13}C NMR (126 MHz, $CDCl_3$)

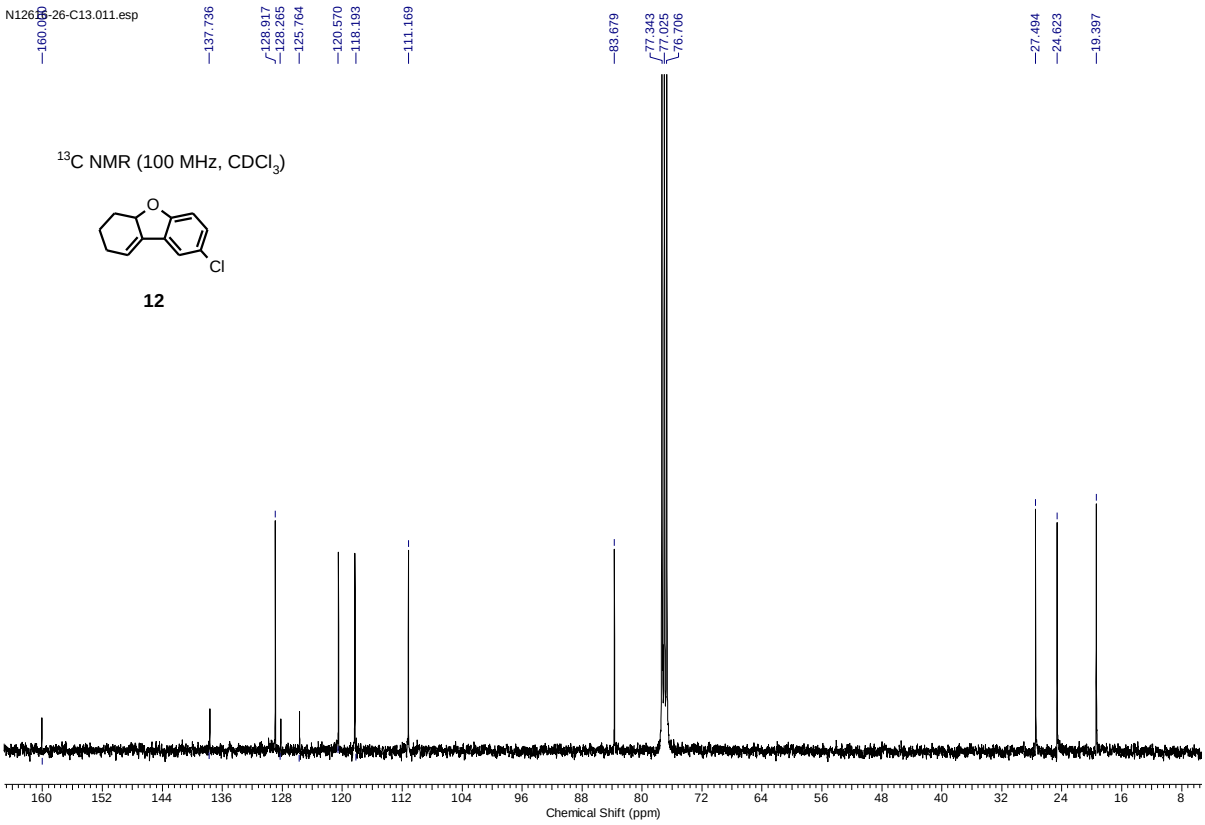
7,9-Dimethoxy-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 81



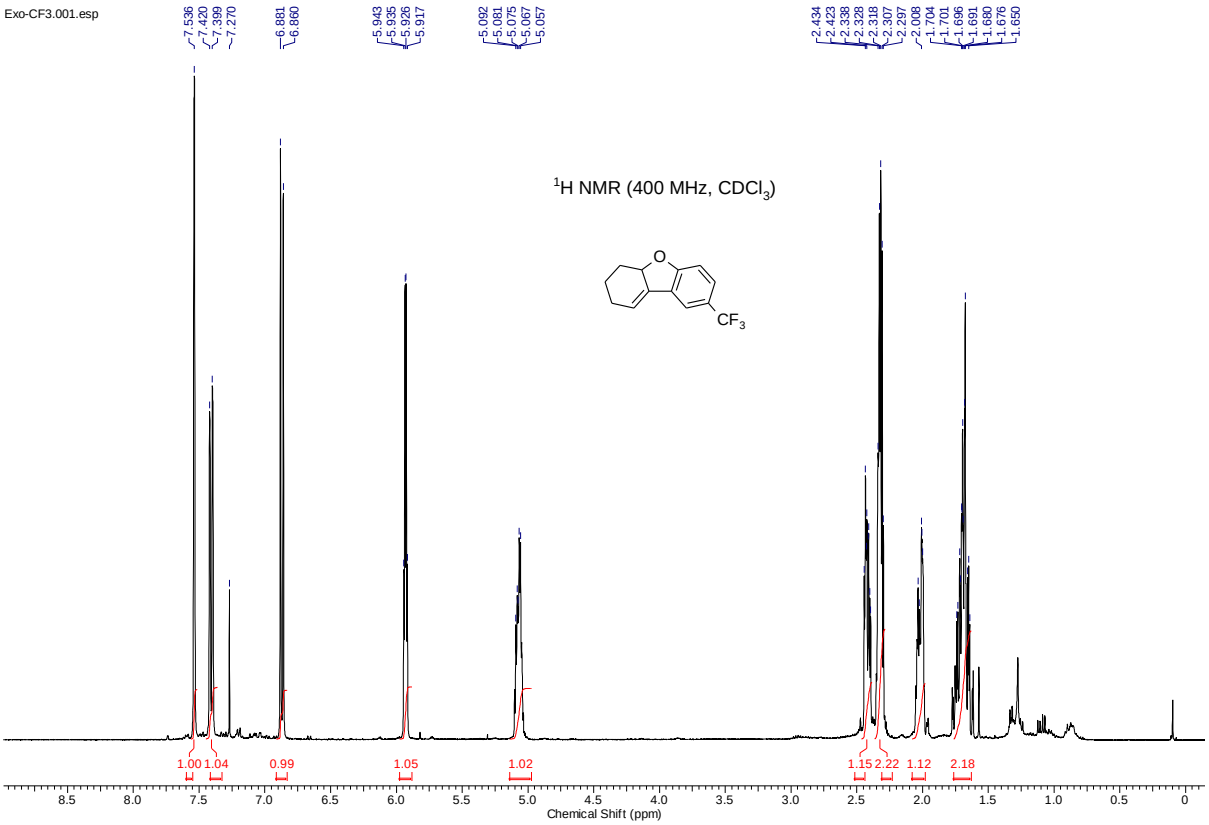


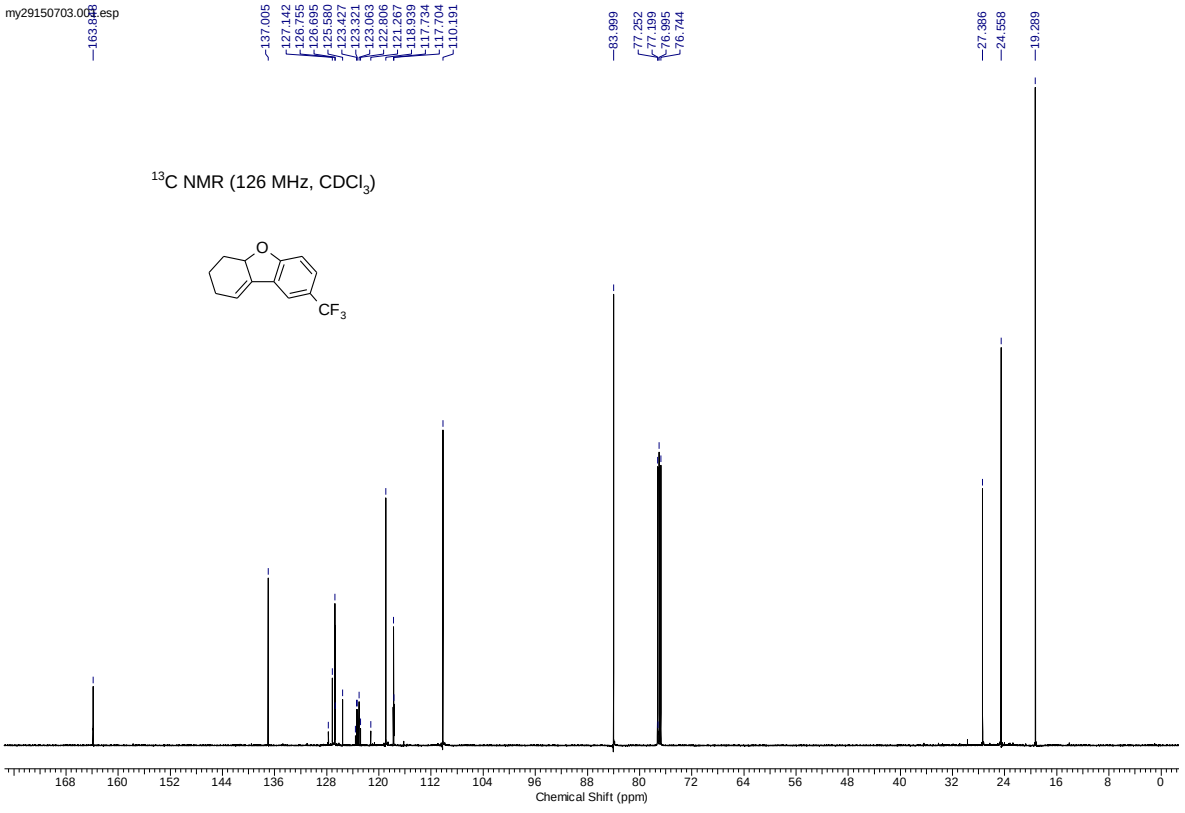
8-Chloro-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 82



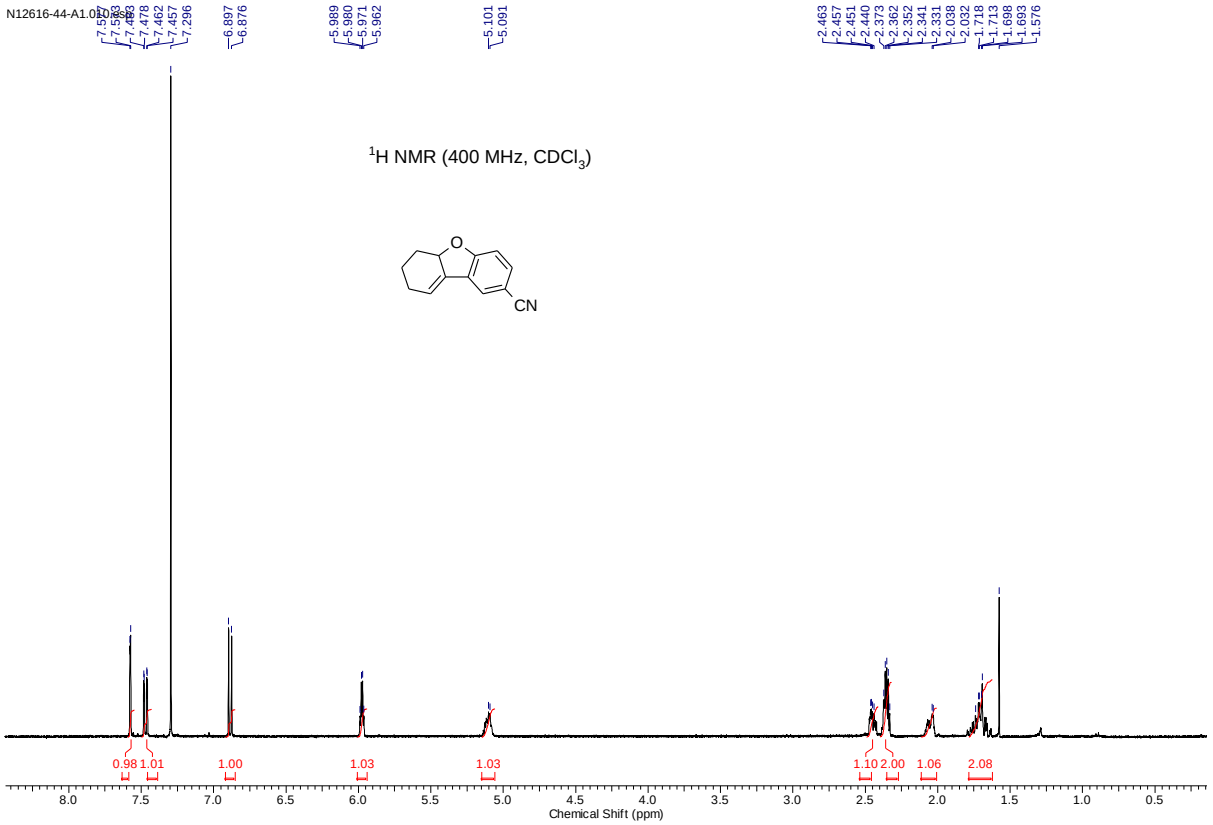


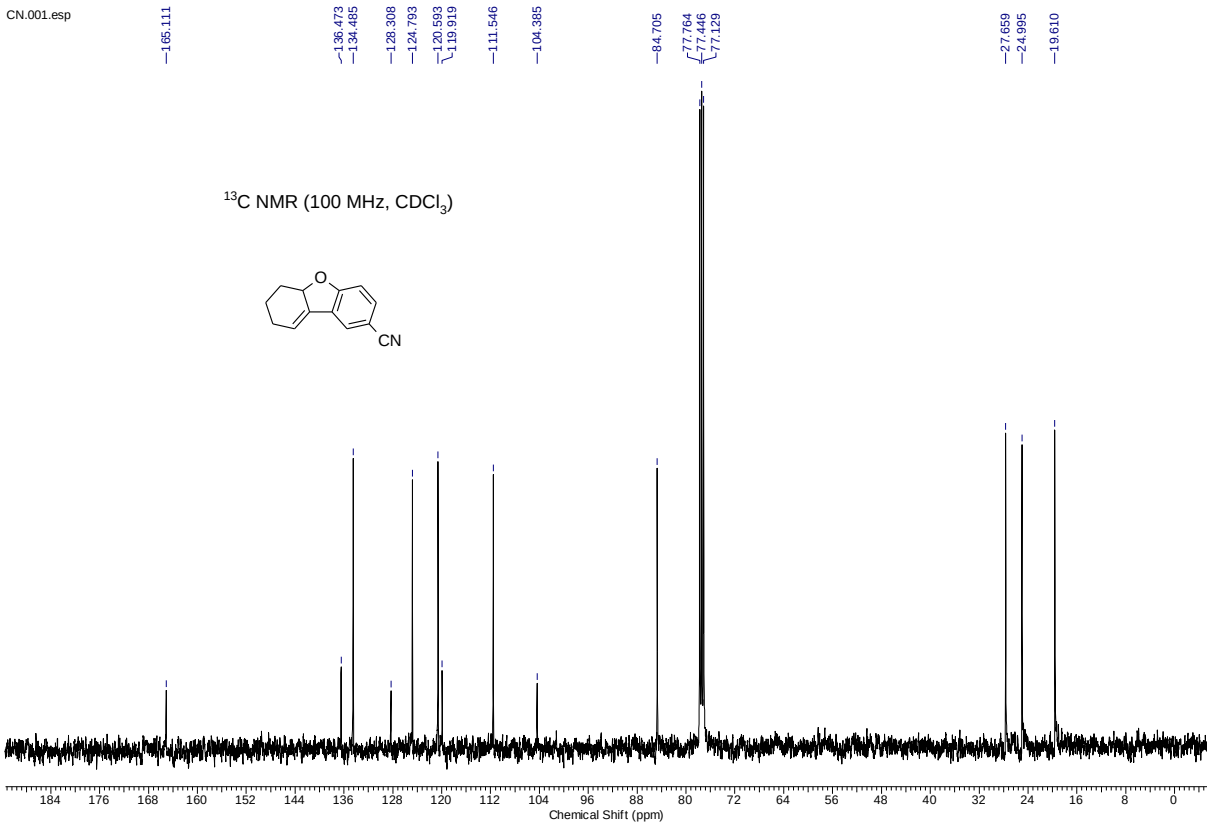
8-(Trifluoromethyl)-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan, 83



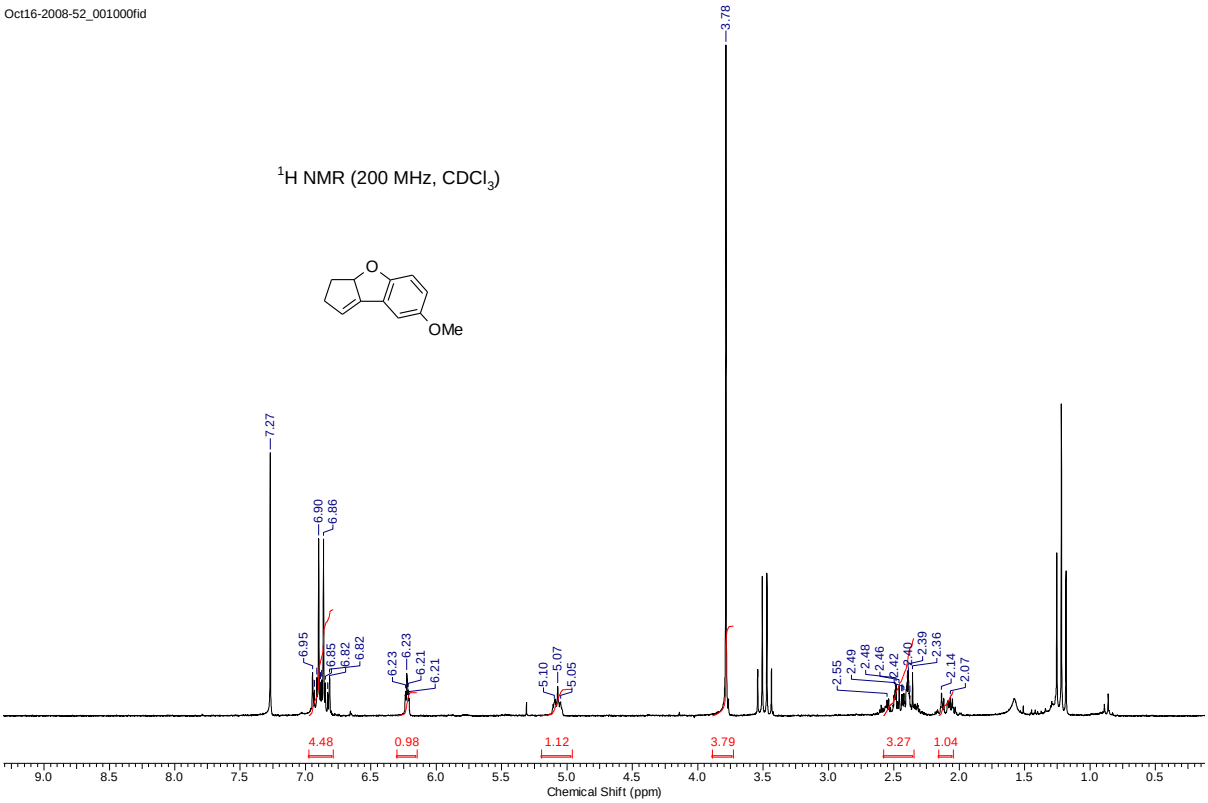


5a,6,7,8-Tetrahydrodibenzo[*b*,*d*]furan-2-carbonitrile, 84

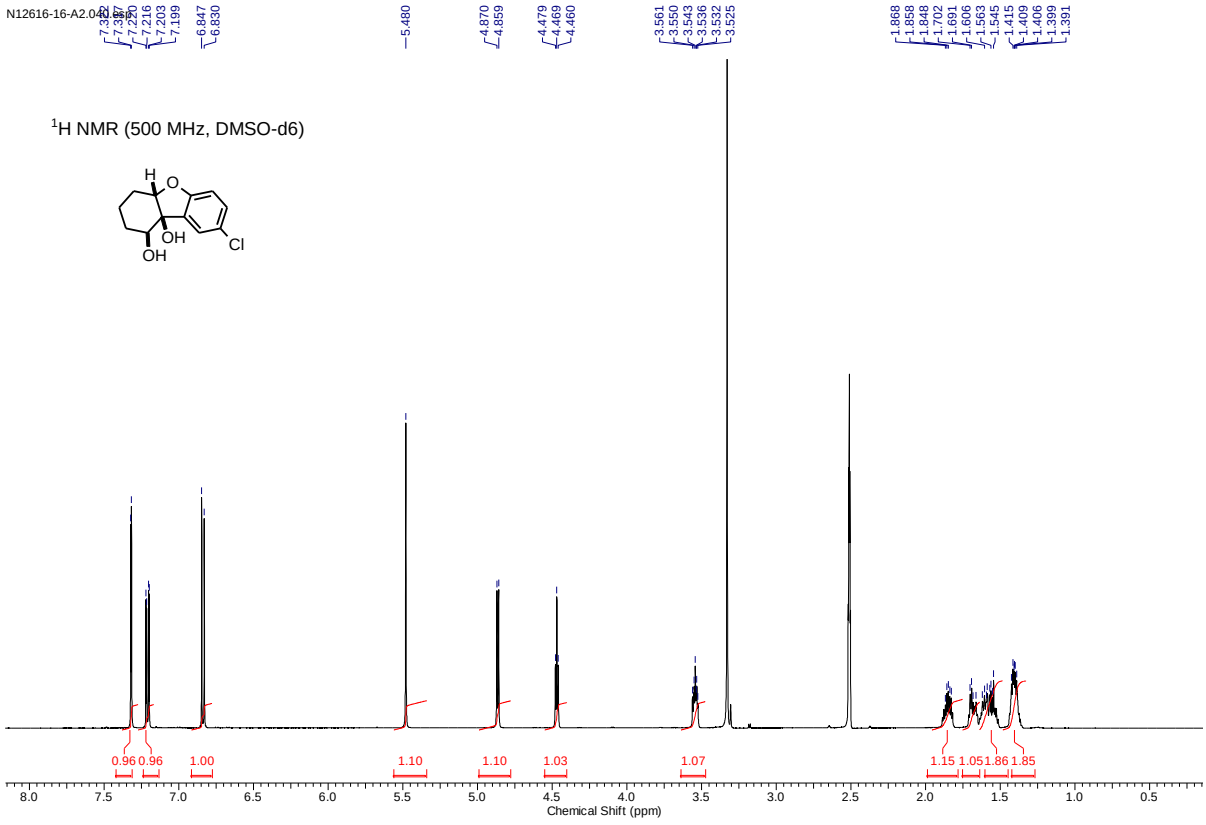


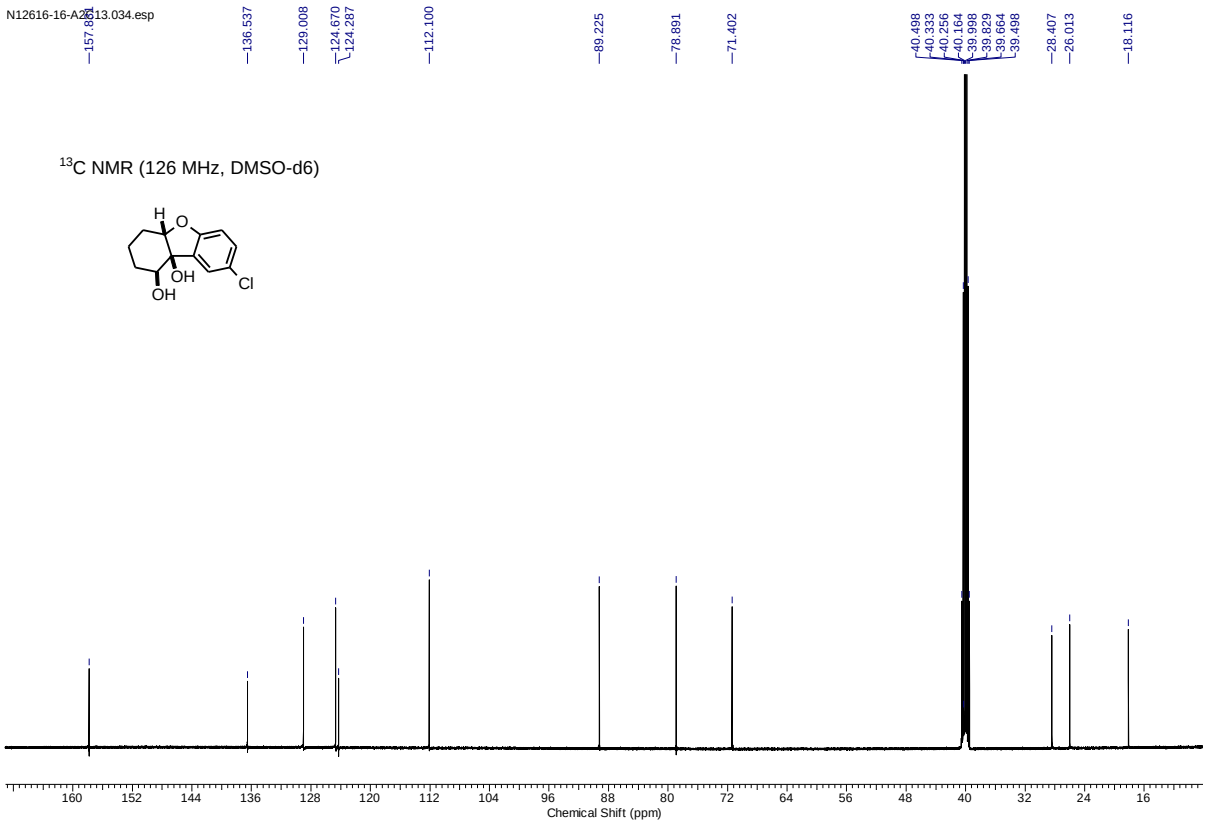


7-Methoxy-3,3a-dihydro-2H-cyclopenta[*b*]benzofuran, 85

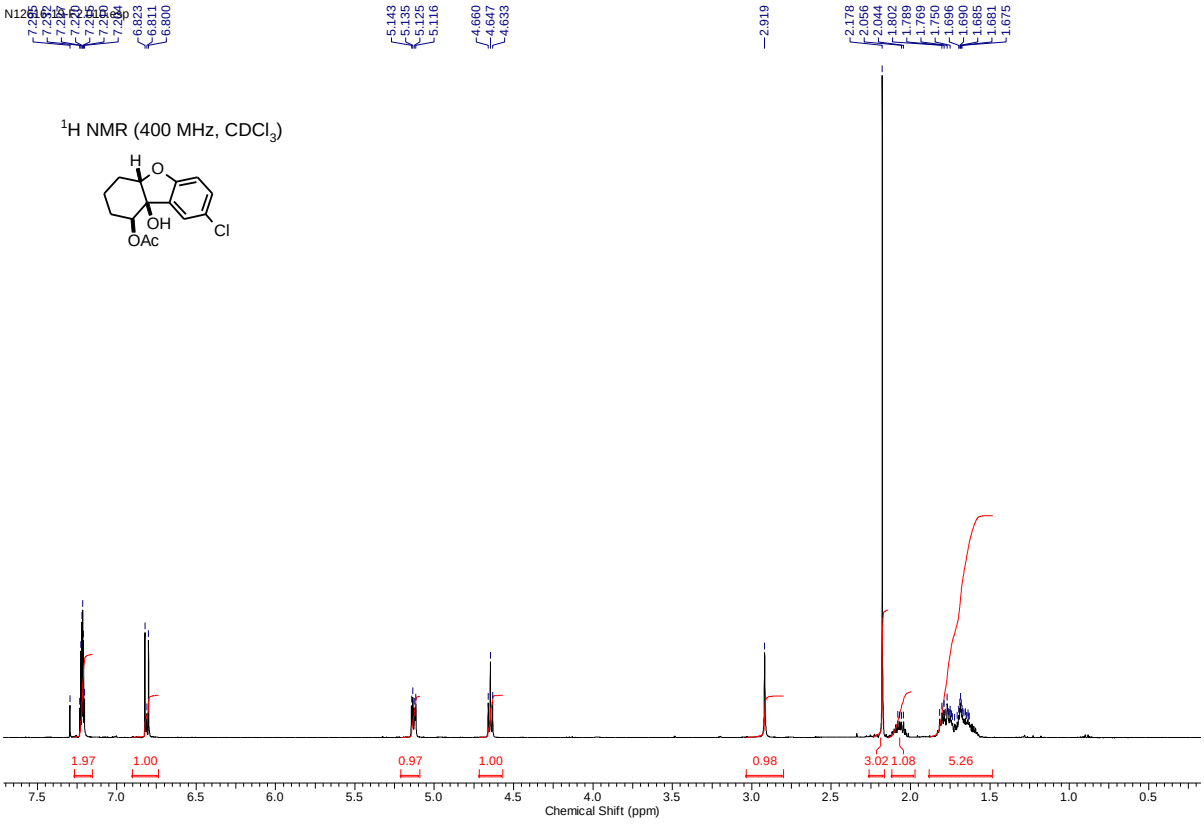

Oct16-2008-52_001000fid
^{1}H NMR (200 MHz, $CDCl_3$)
OMe
7.27
6.90
6.86
6.95
6.85
6.82
6.82
6.23
6.23
6.21
6.21
5.10
5.07
5.05
3.78
2.55
2.49
2.48
2.46
2.42
2.40
2.39
2.36
2.14
2.07
4.48
0.98
1.12
3.79
3.27
1.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

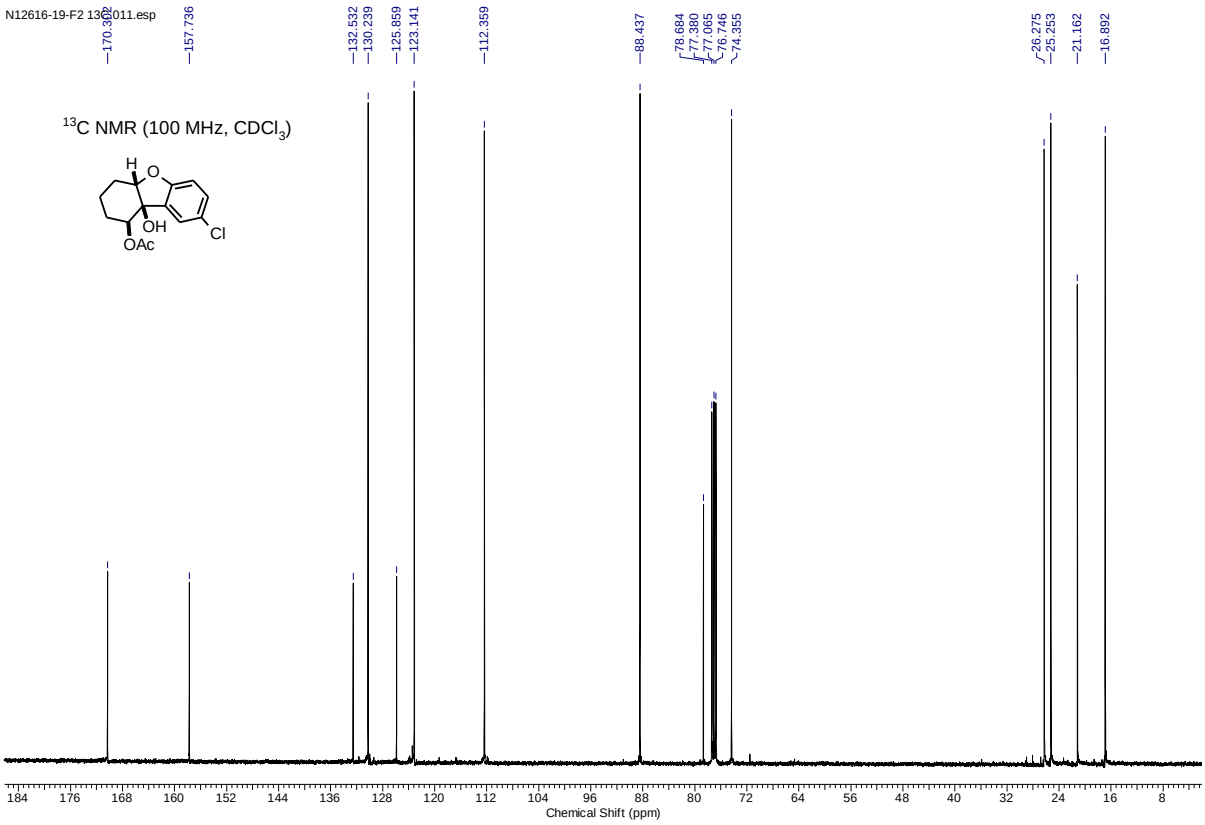
8-Chloro-2,3,4,4a-tetrahydrodibenzo[*b*,*d*]furan-1,9b(1H)-diol, 86



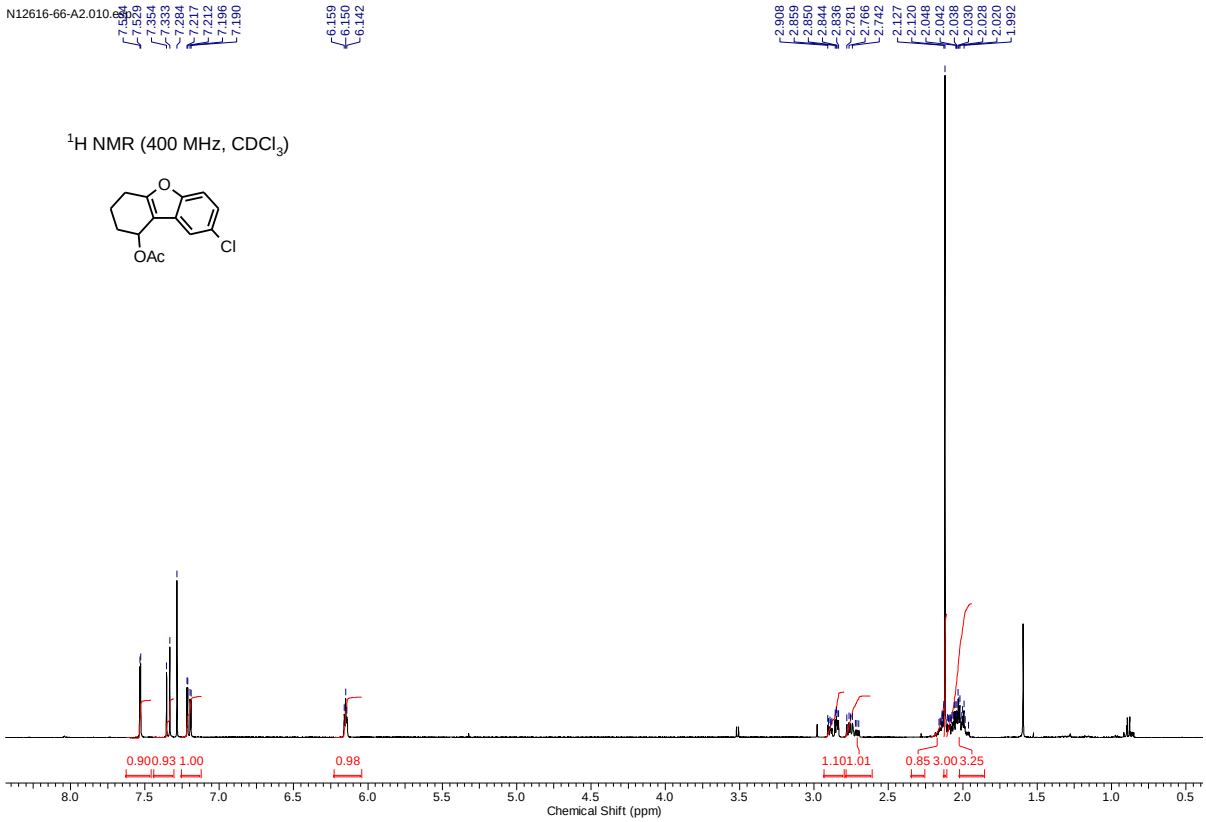


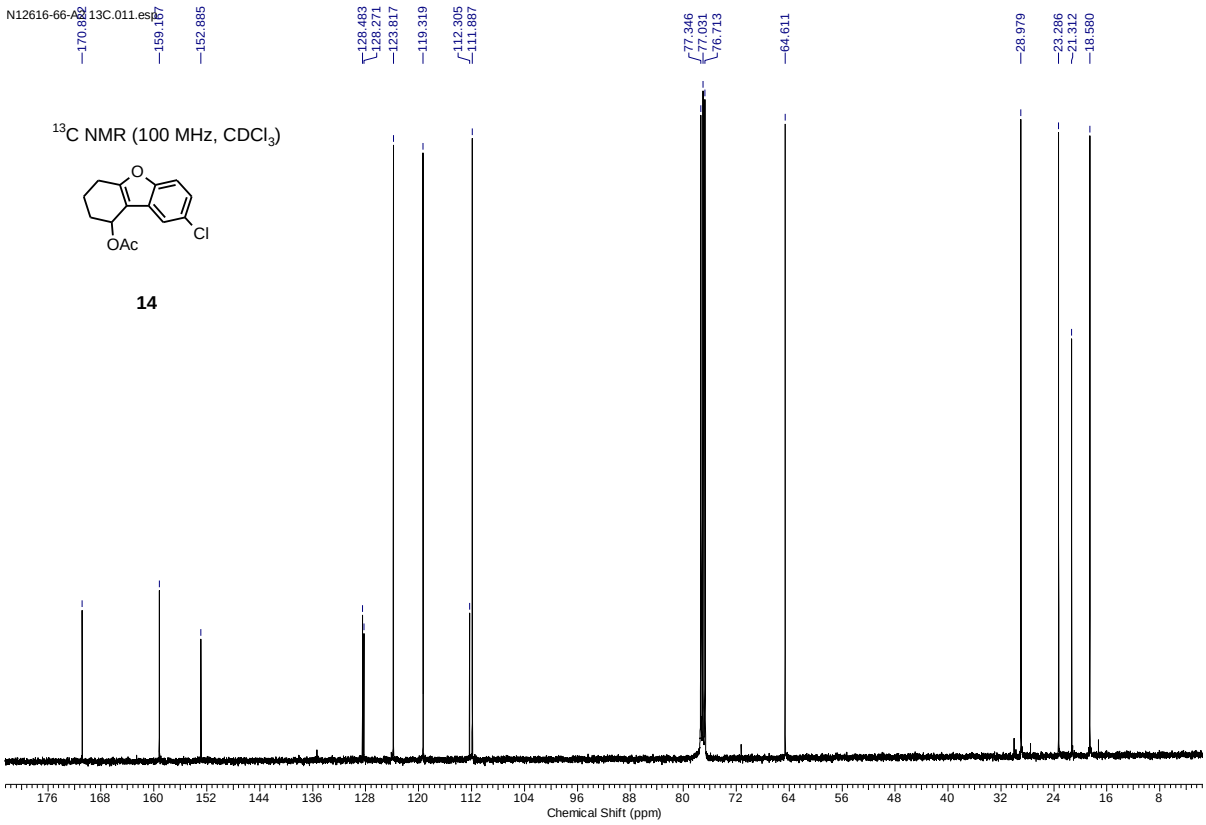
8-Chloro-9b-hydroxy-1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-1-yl acetate, 87





8-Chloro-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl acetate, 88





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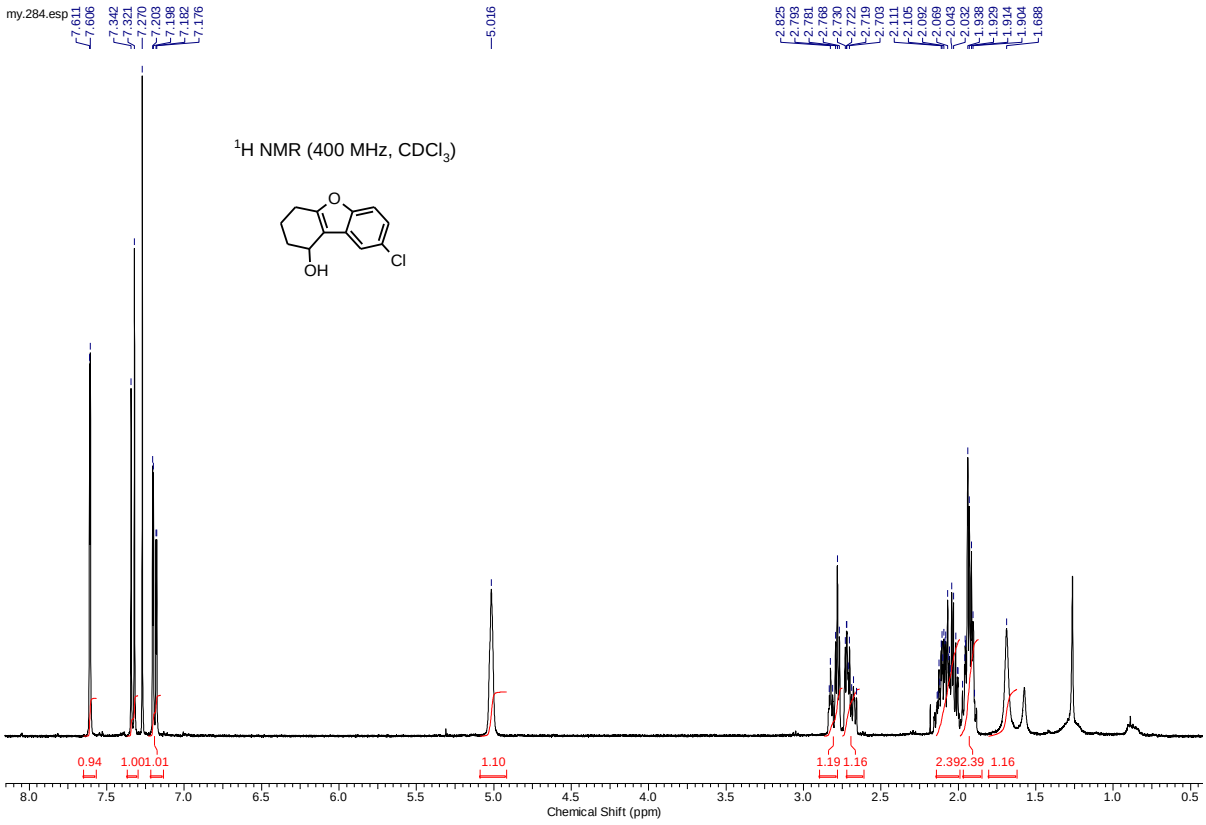
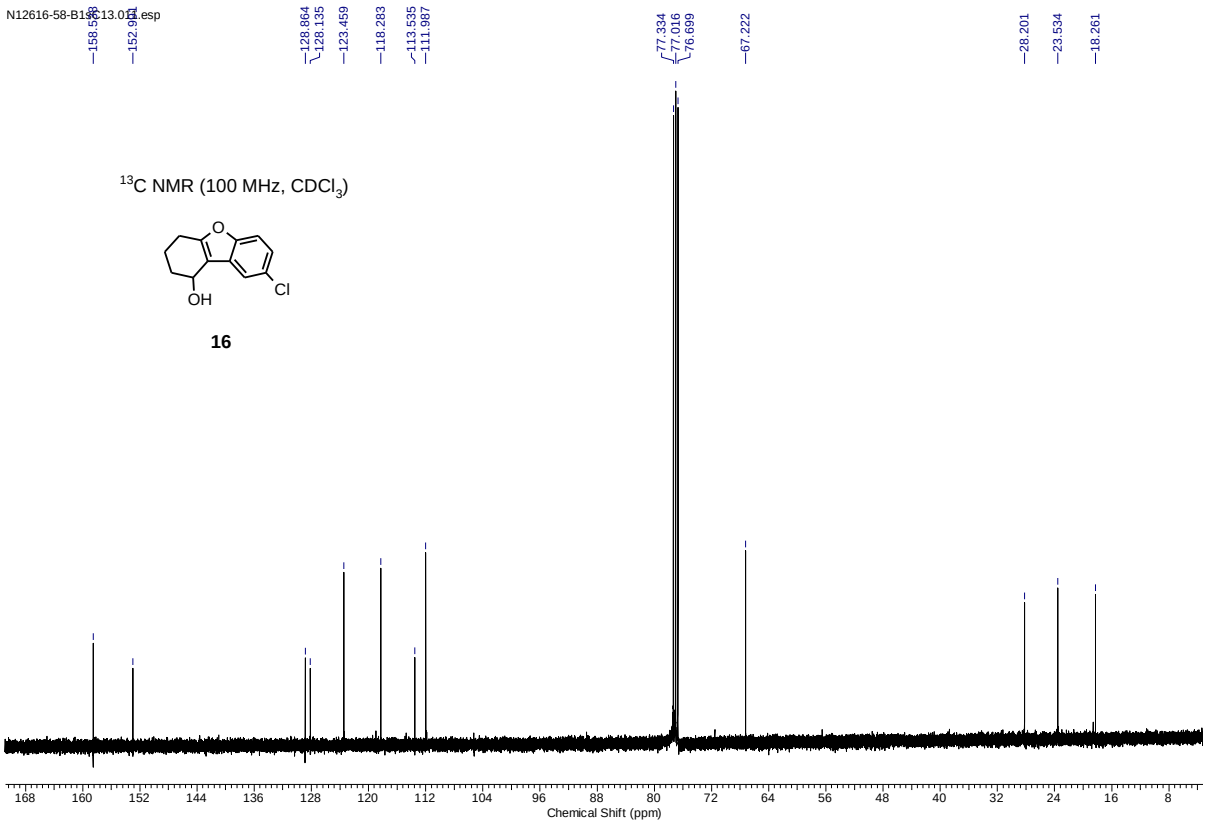
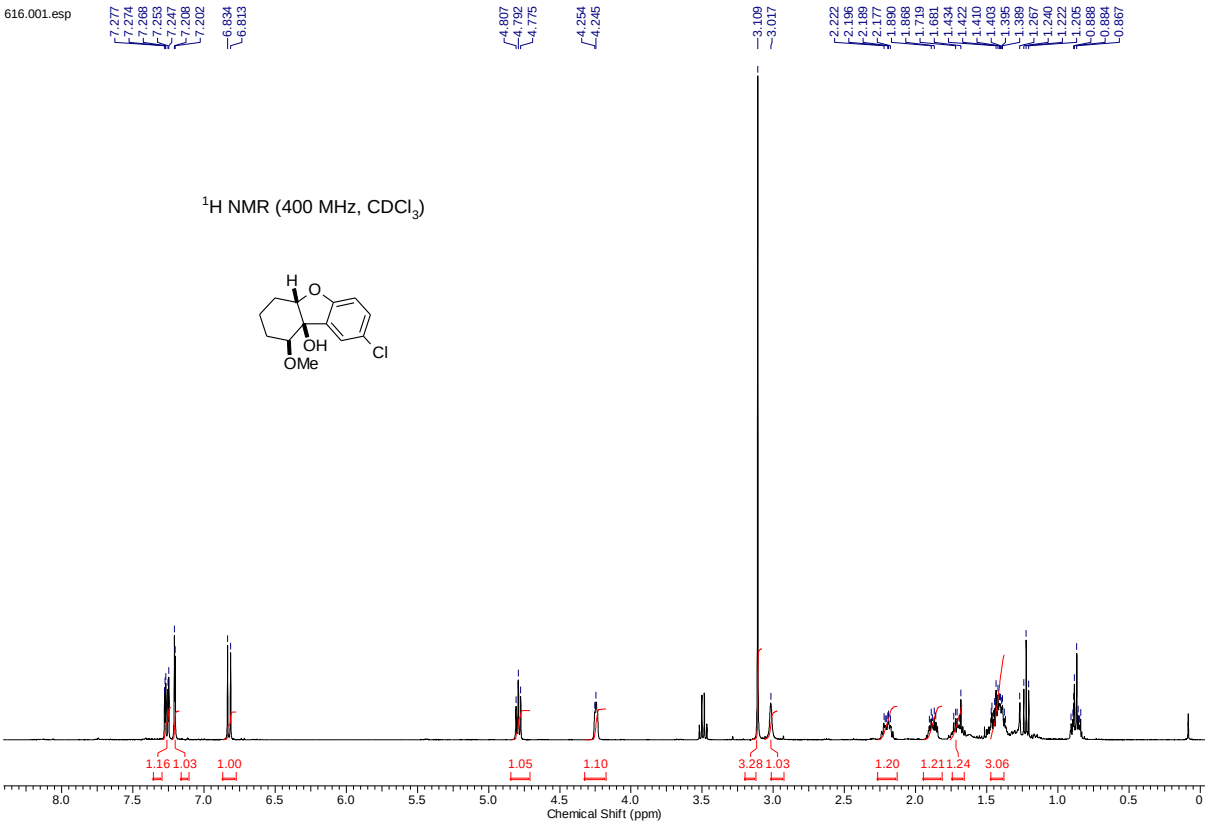
8-Chloro-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-ol, 89

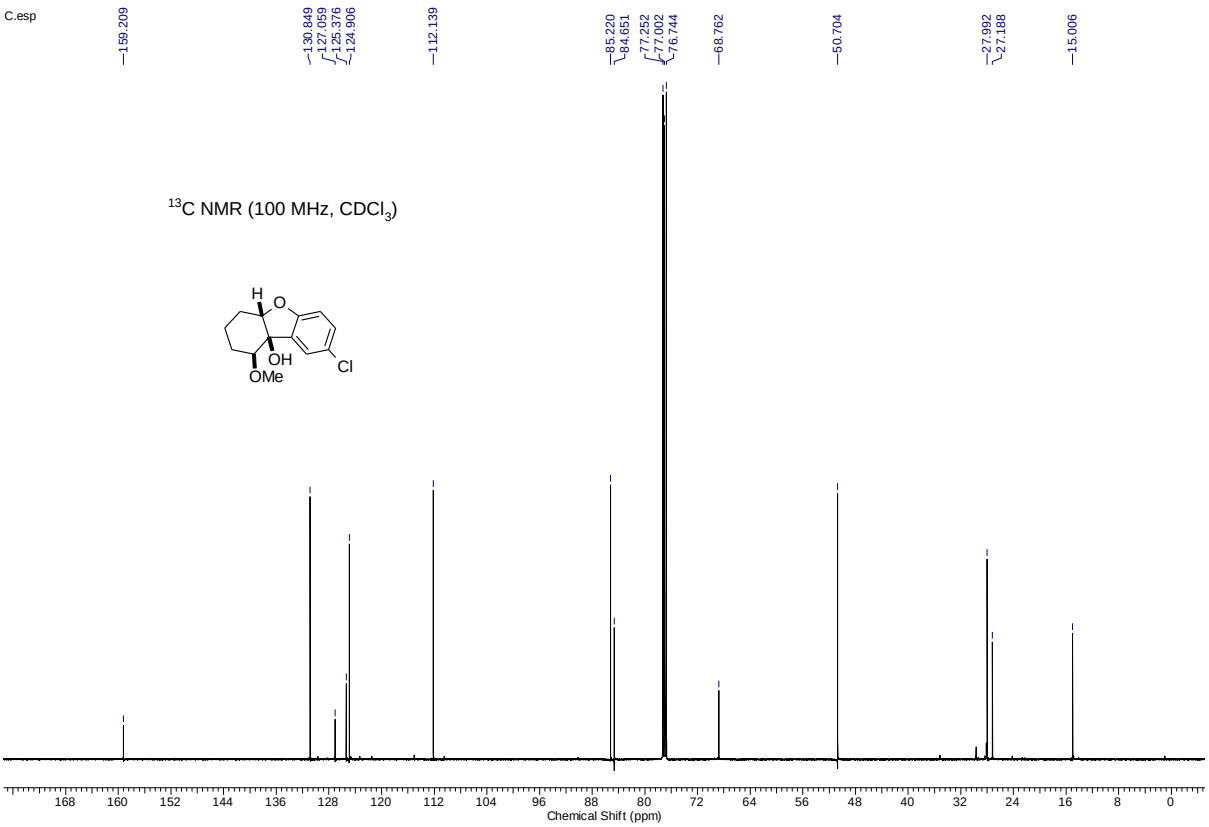




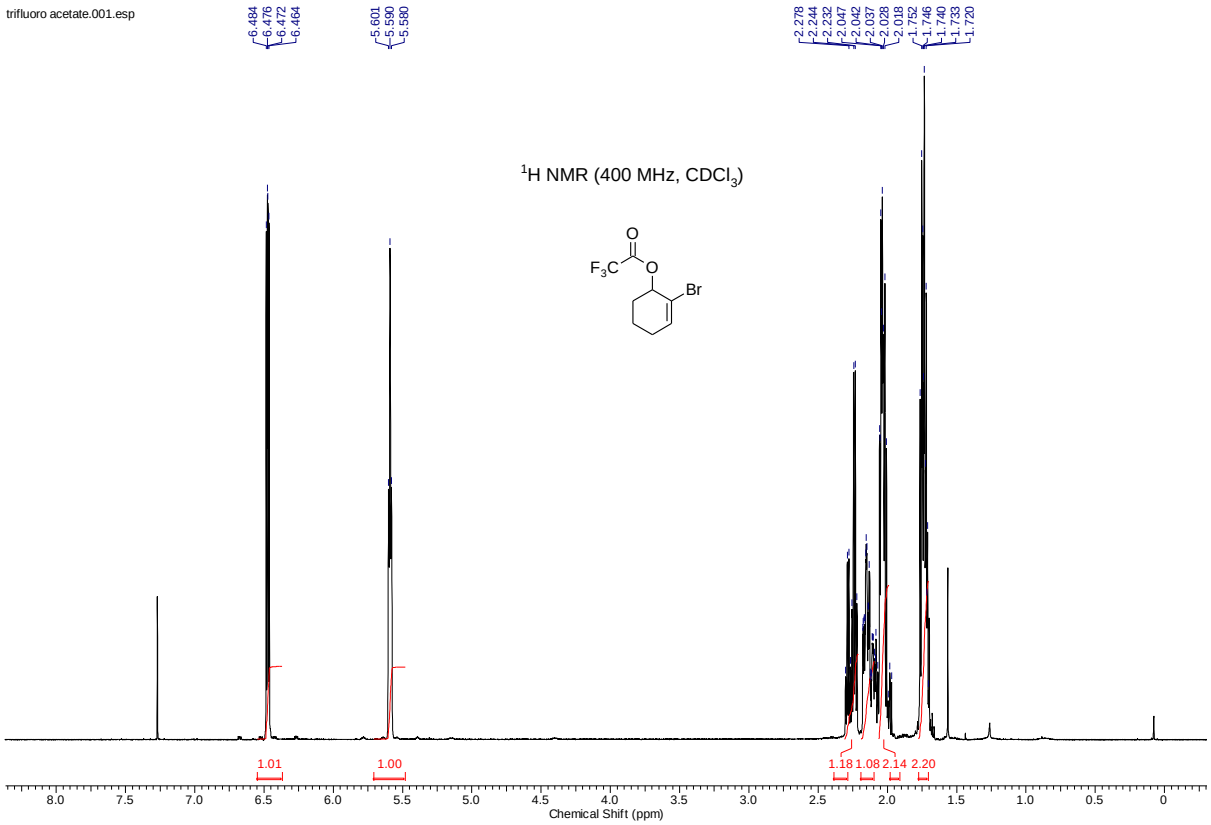
16

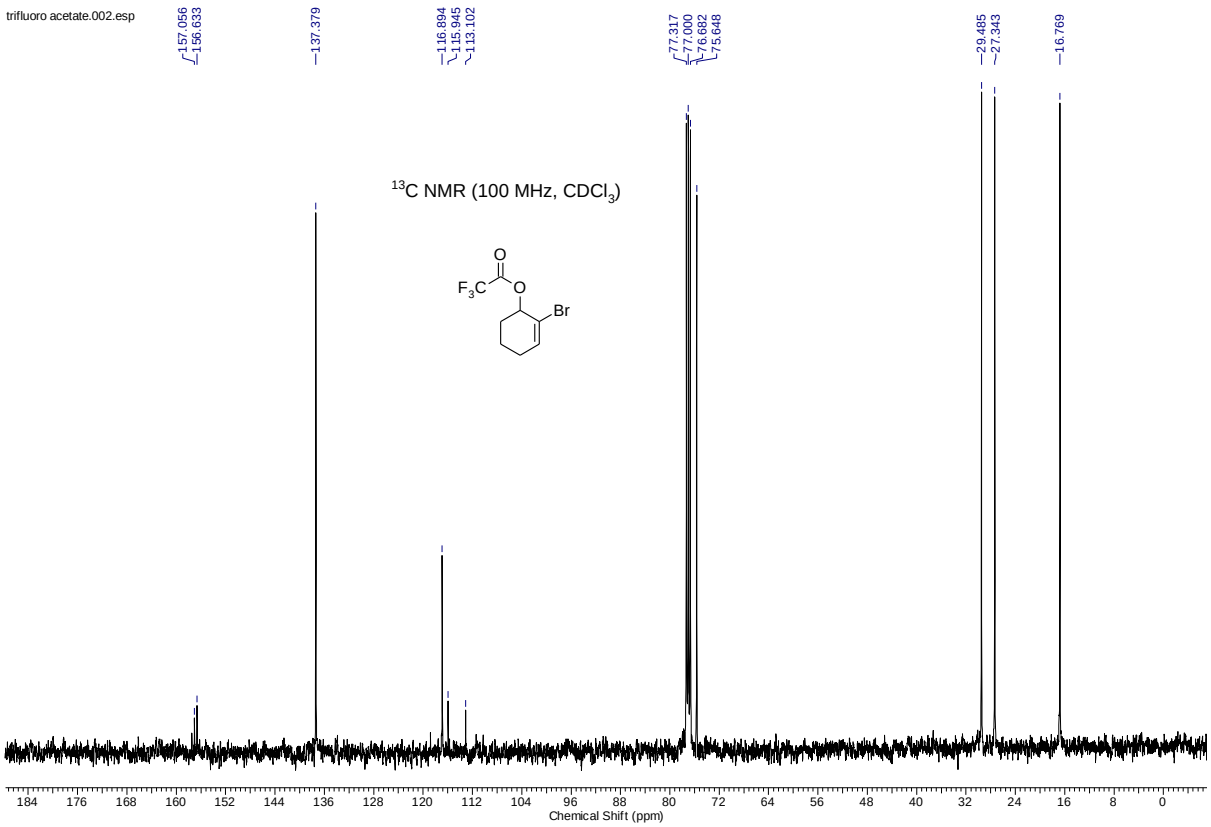
2-Chloro-9-methoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-9a-ol, 91



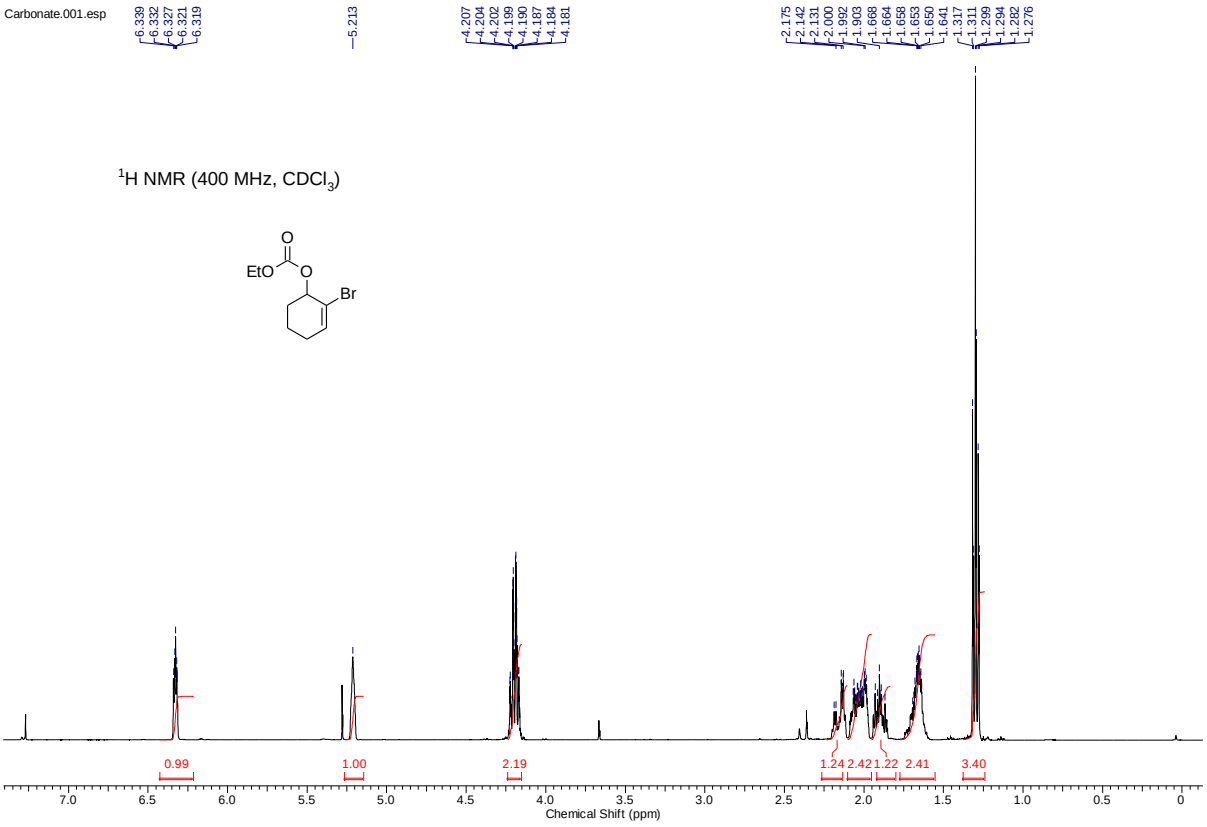


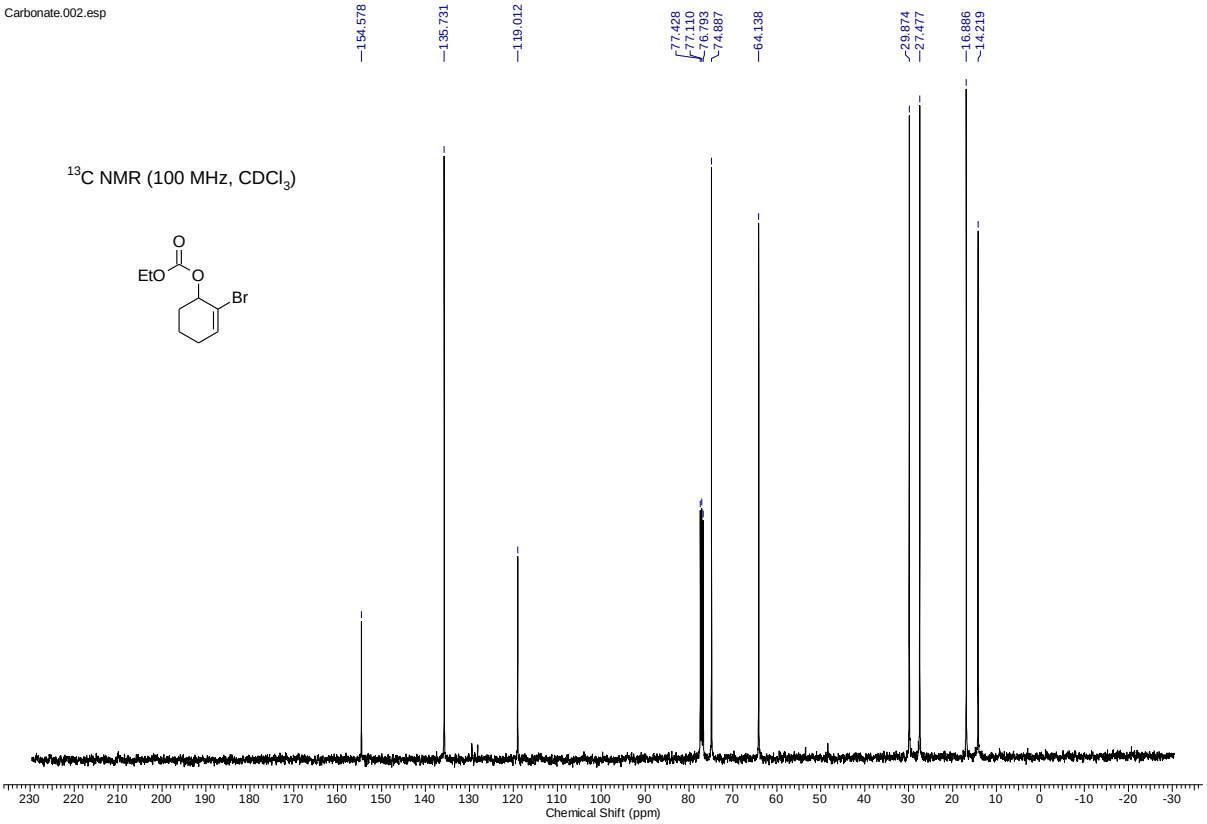
2-Bromocyclohex-2-enyl 2,2,2-trifluoroacetate, 146



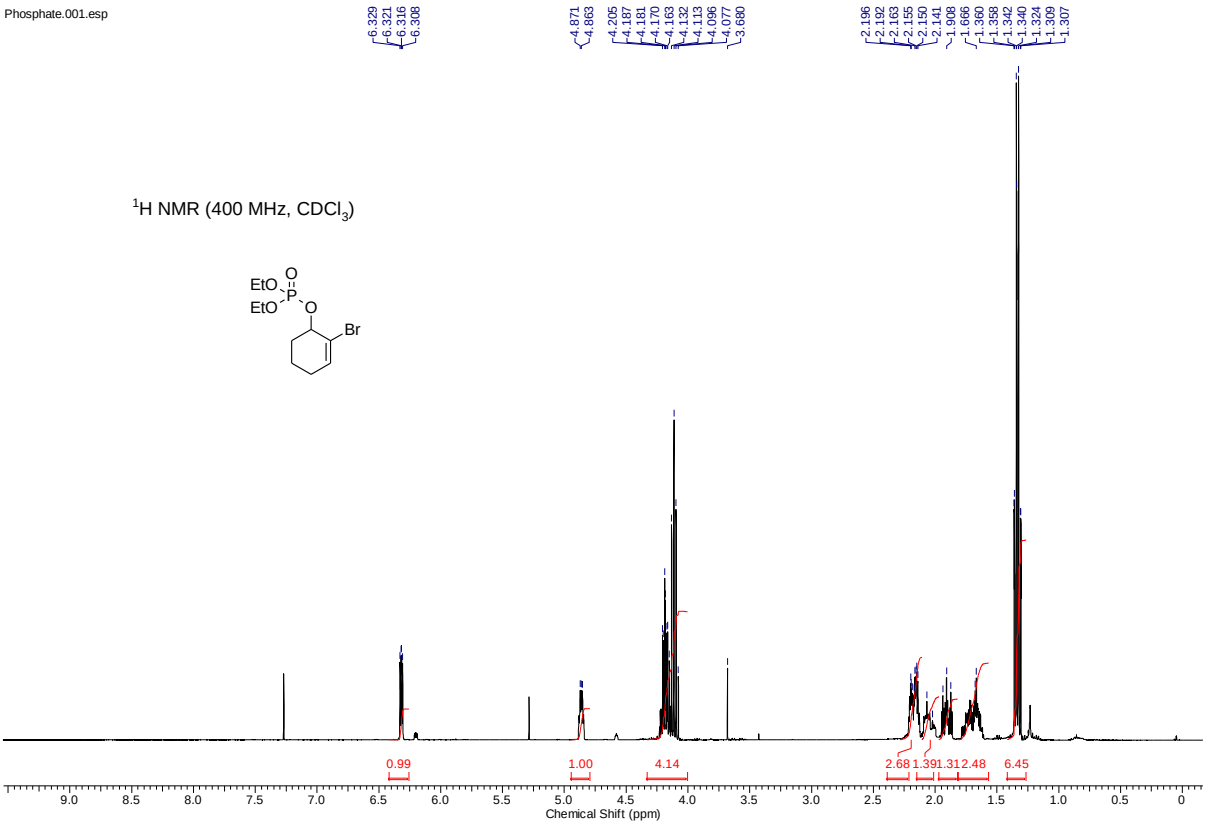


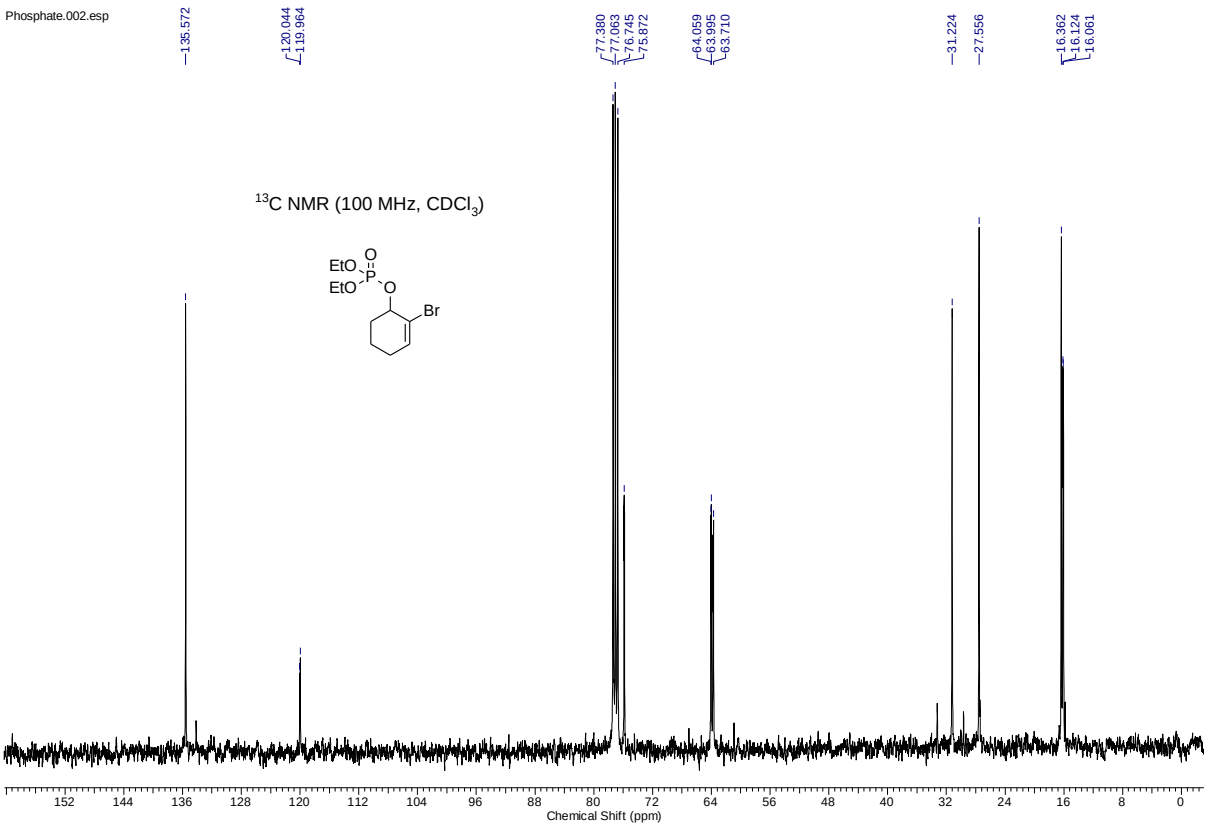
2-Bromocyclohex-2-enyl ethyl carbonate, 147



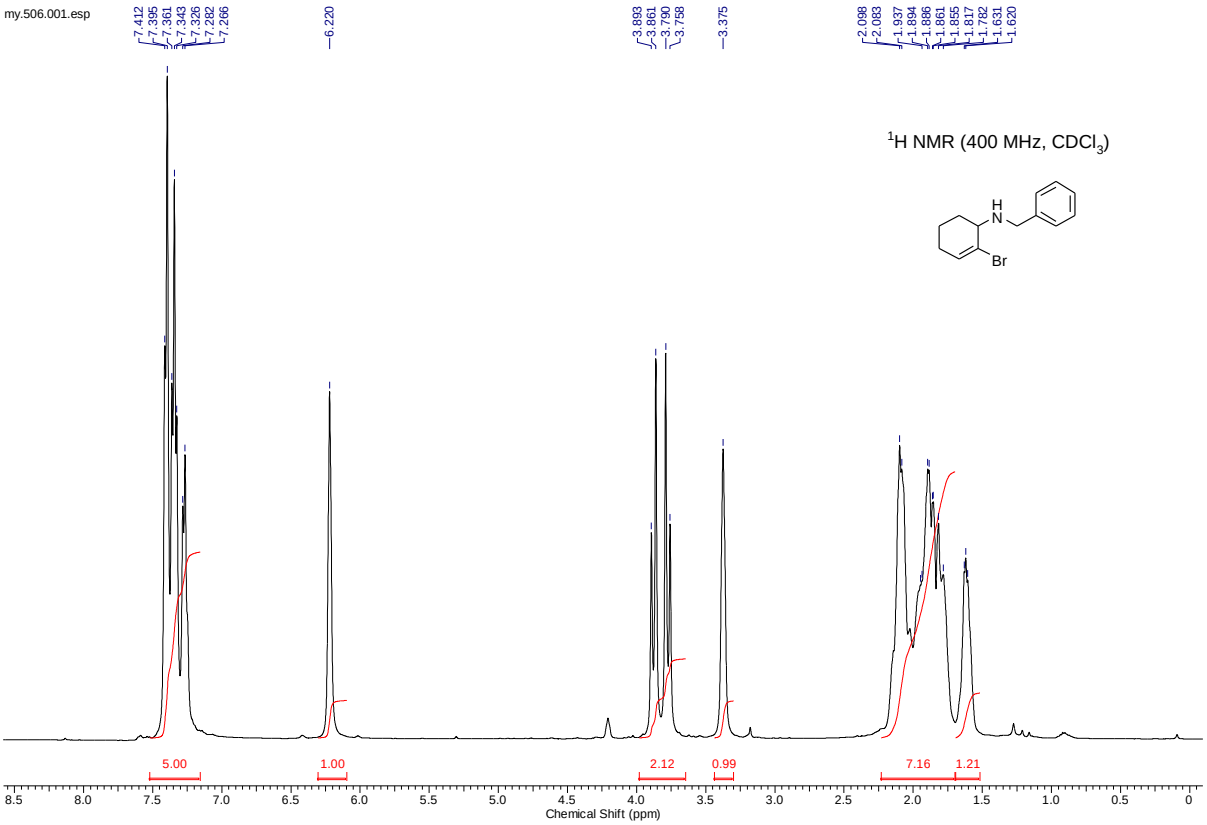


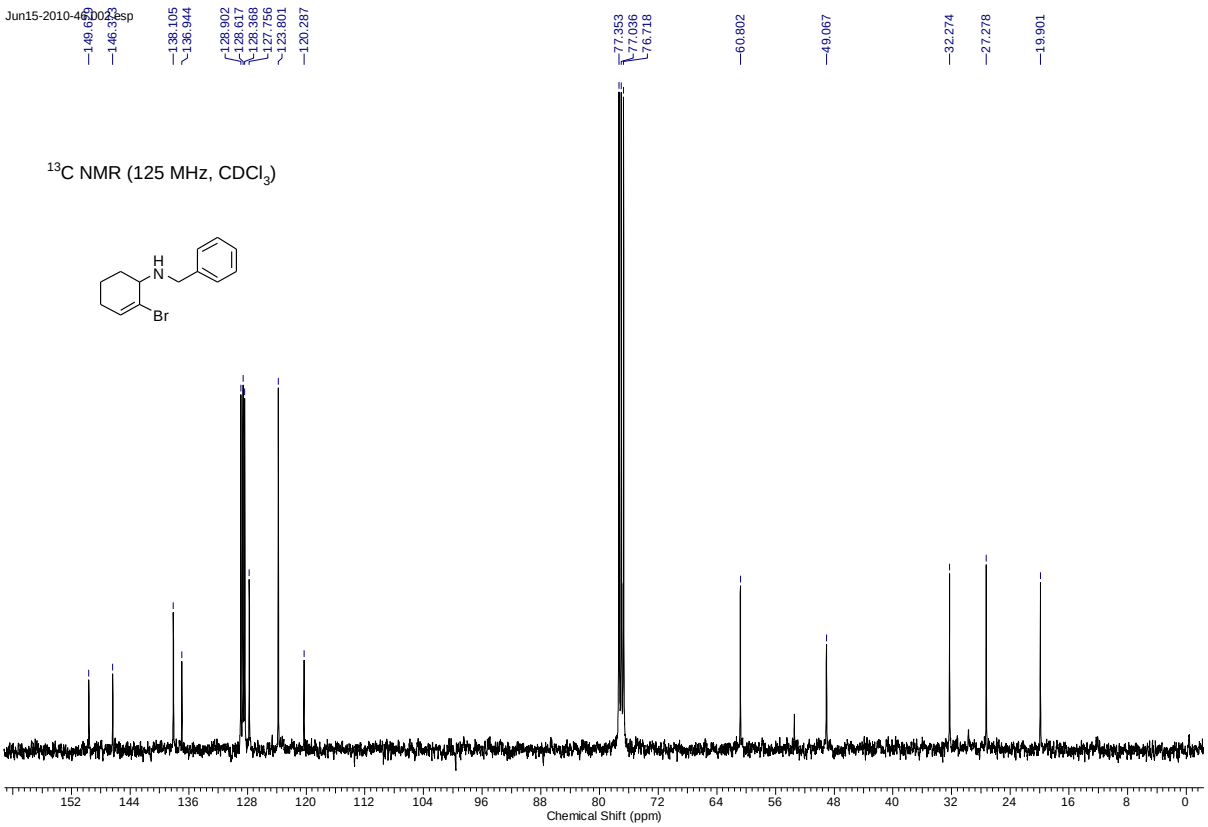
2-Bromocyclohex-2-enyl diethyl phosphate, 148



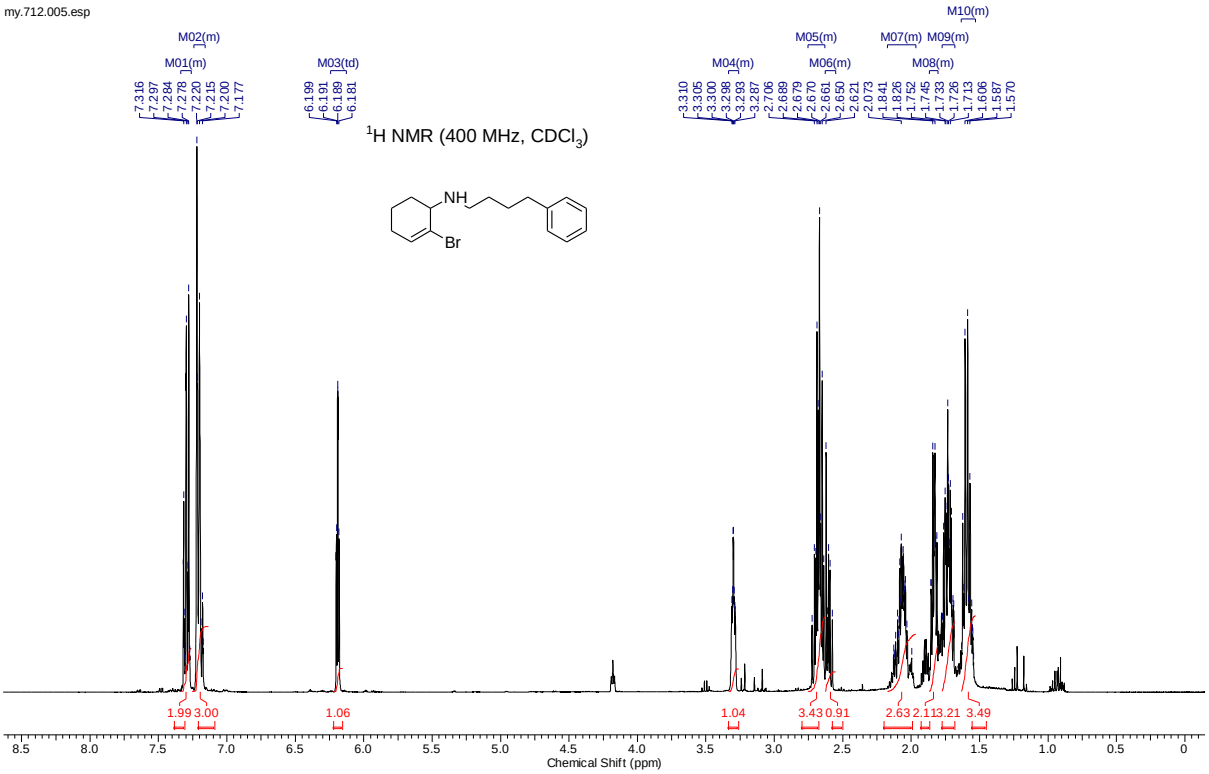


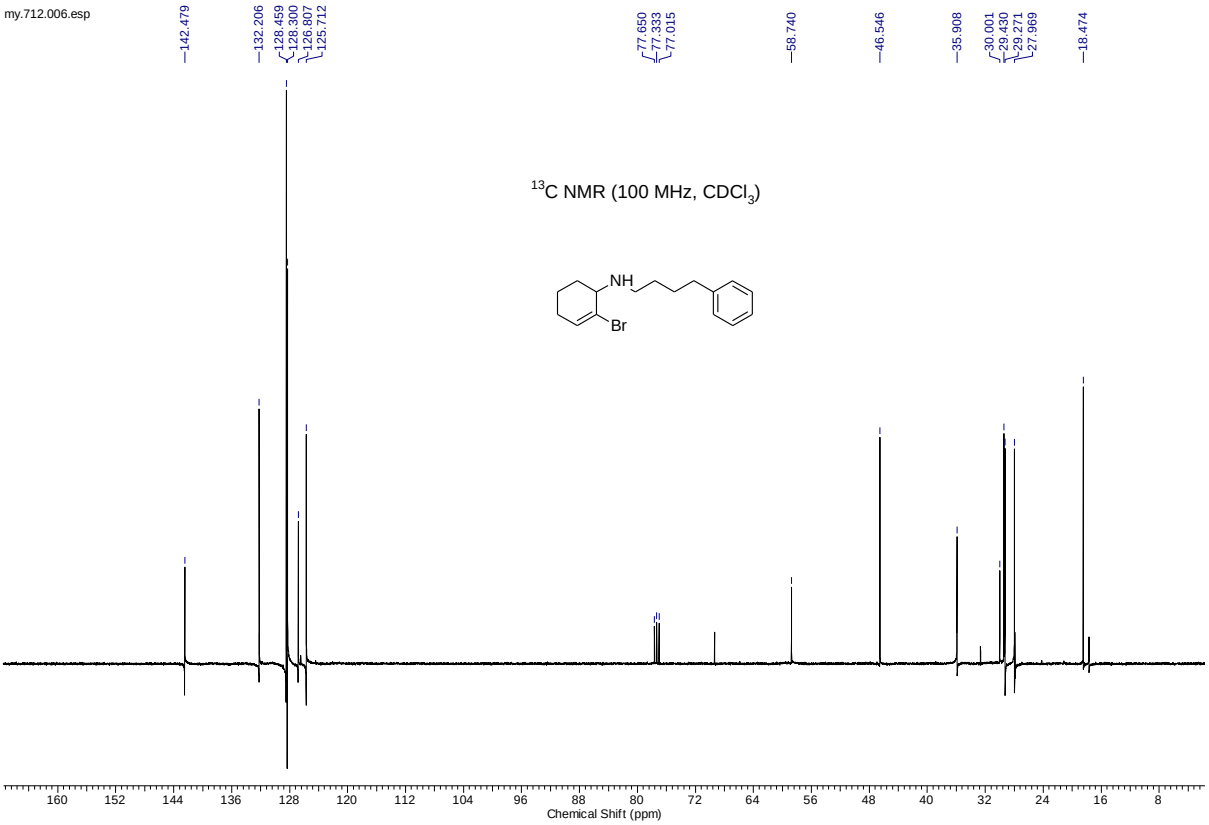
N-Benzyl-2-bromocyclohex-2-enamine, 113



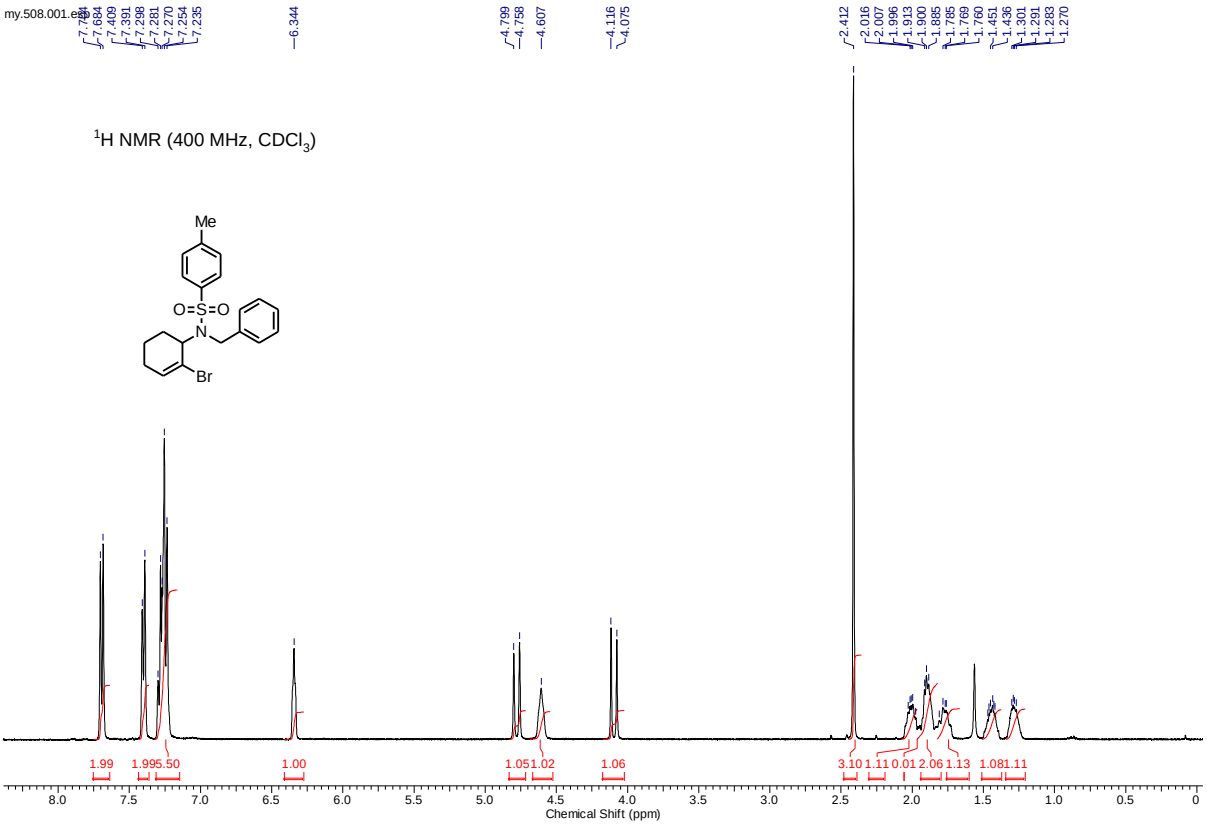


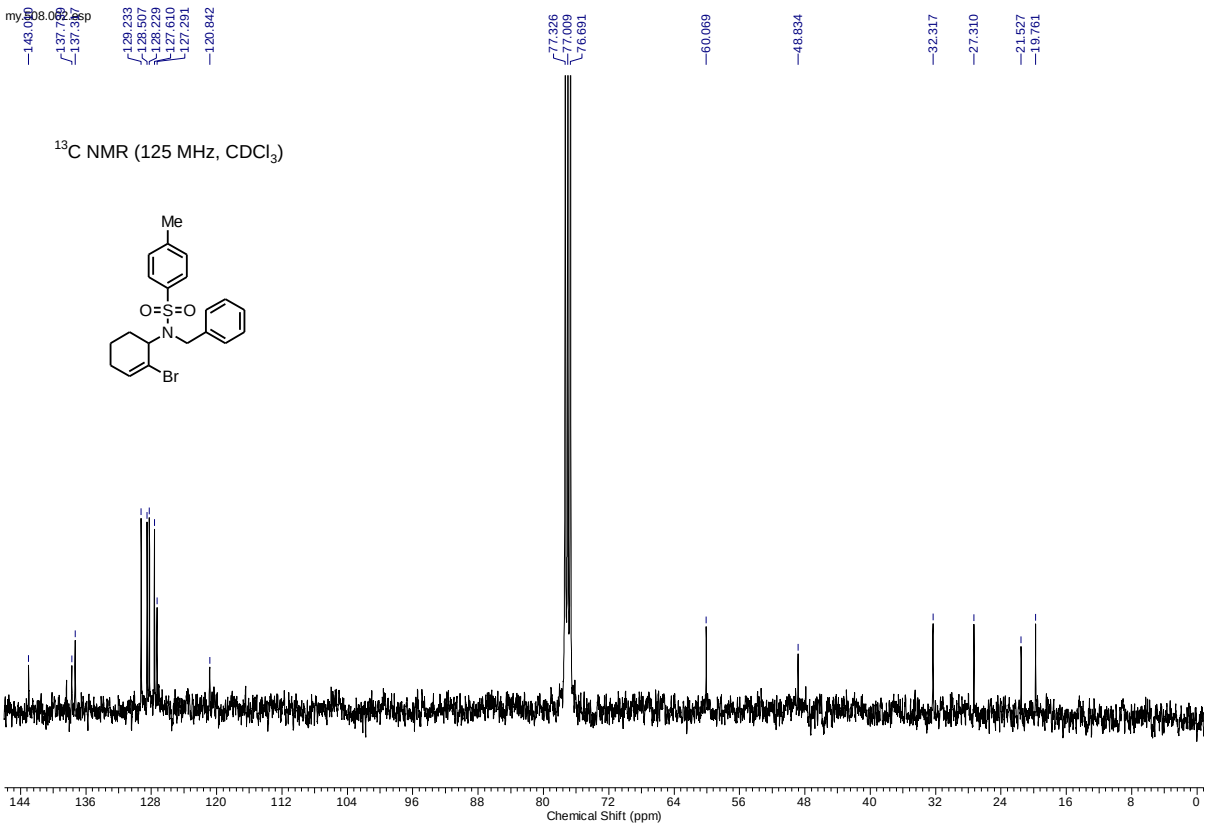
2-Bromo-*N*-(4-phenylbutyl)cyclohex-2-enamine, 117



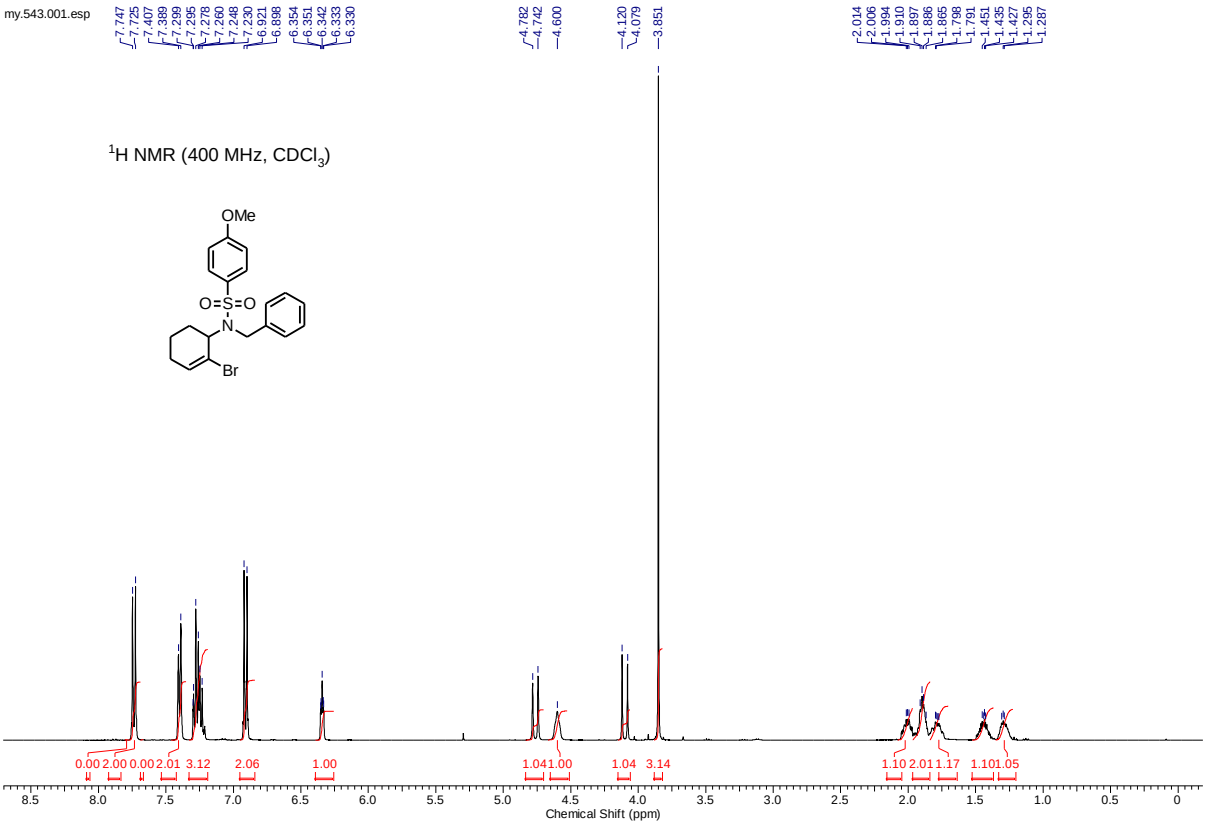


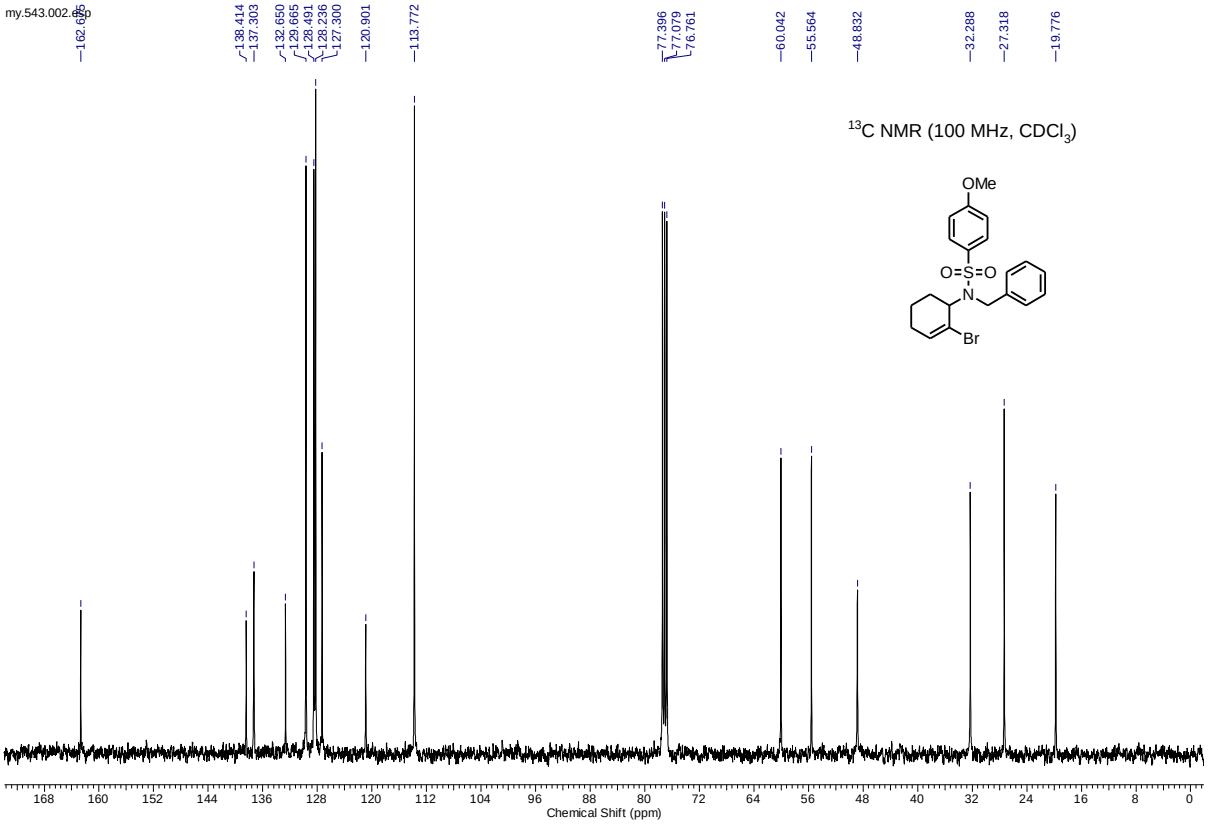
N-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-methylbenzenesulfonamide, 114



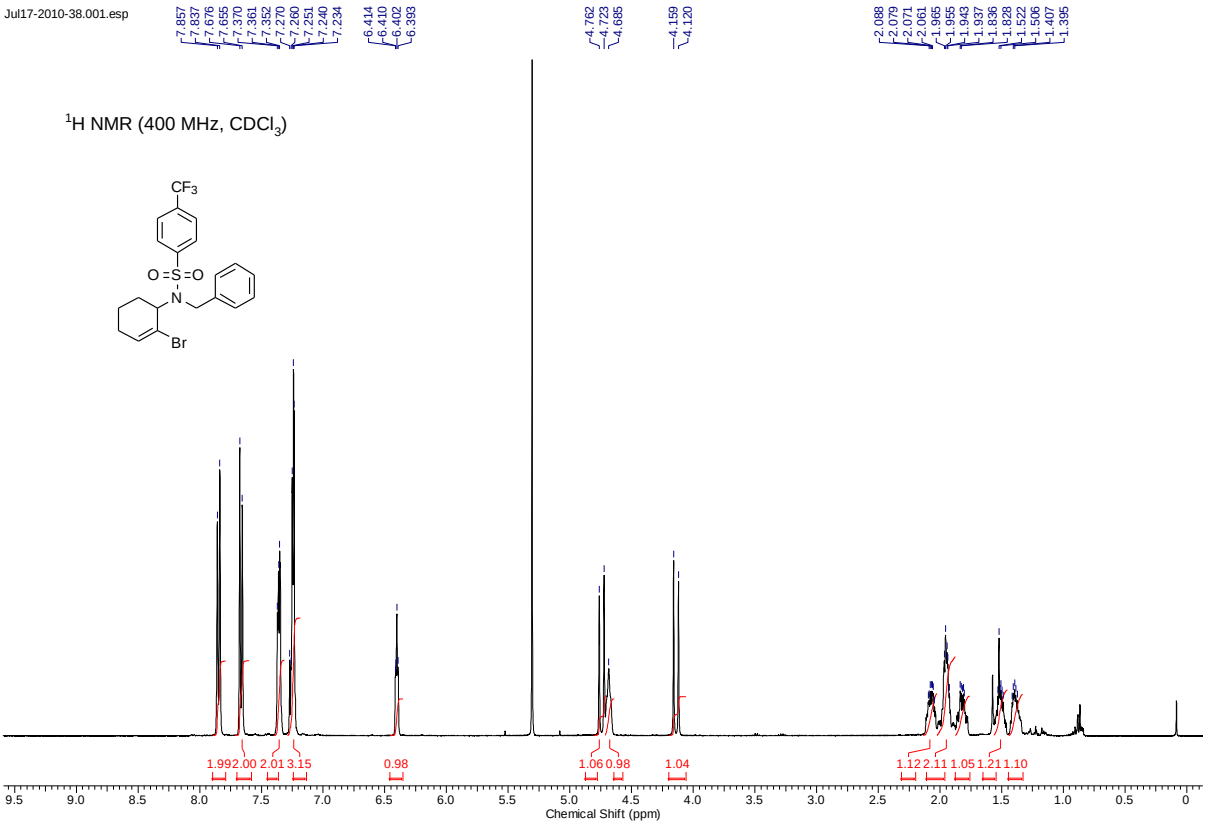


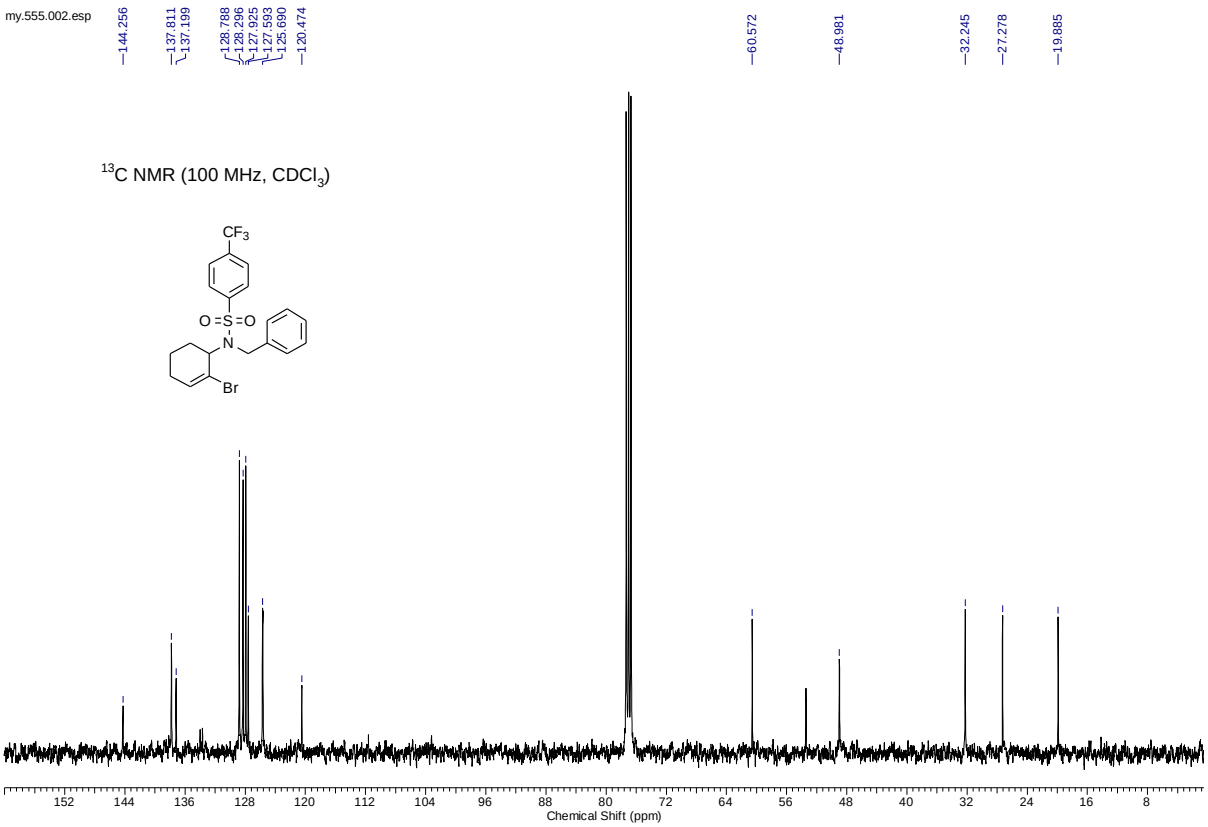
N-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-methoxybenzenesulfonamide, 118



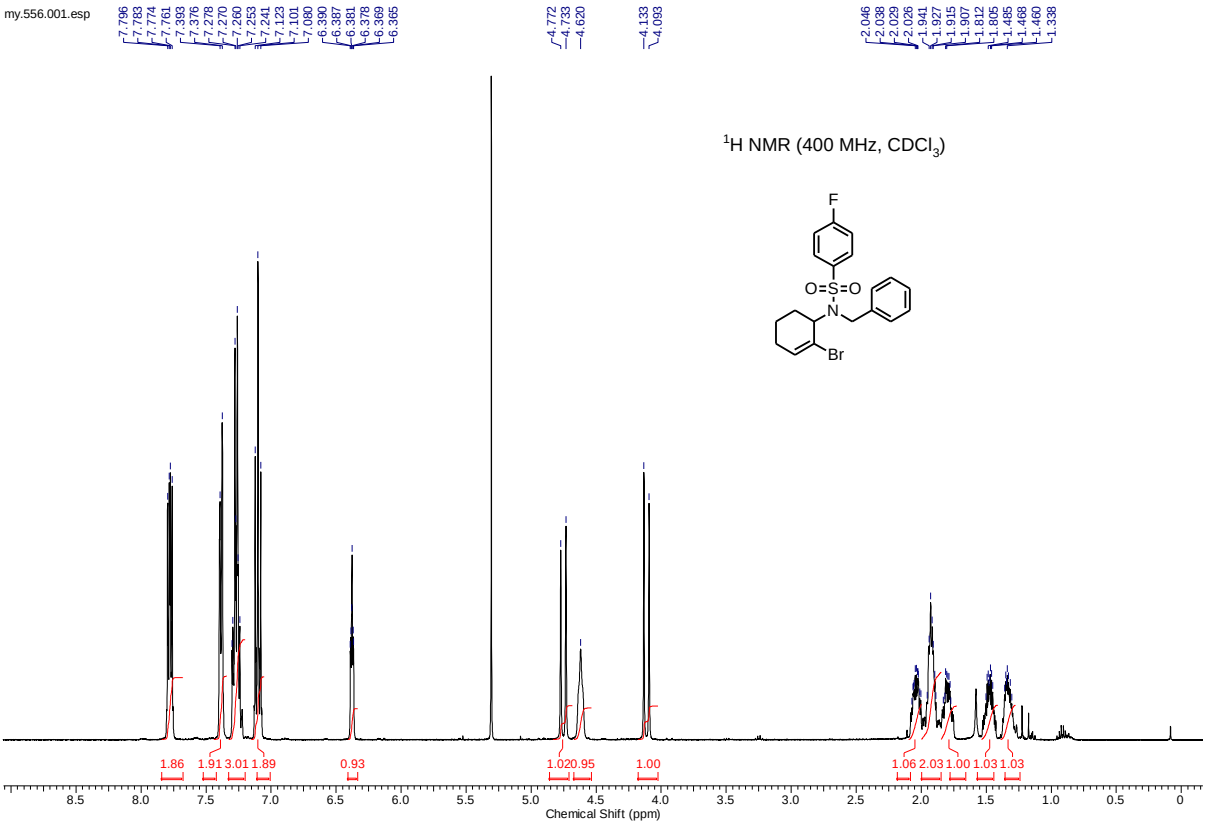


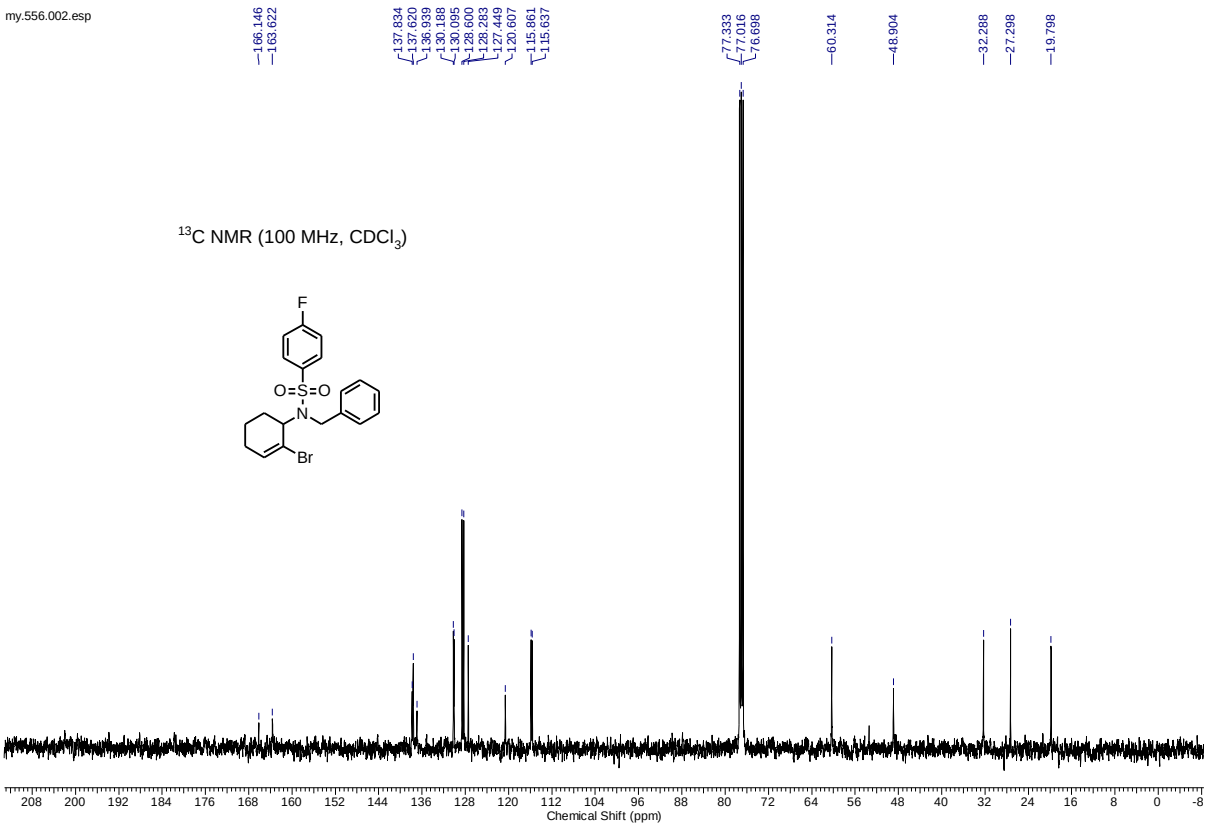
N-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-(trifluoromethyl)benzenesulfonamide, 119



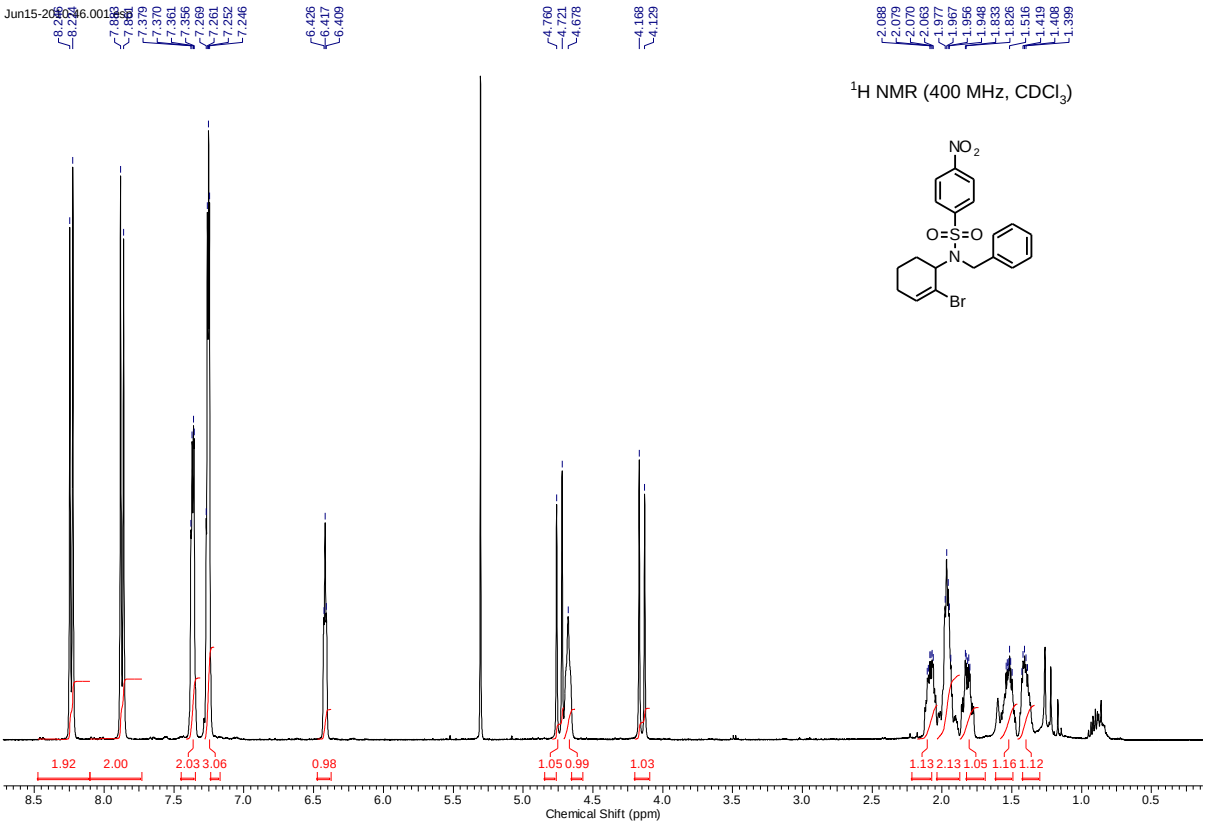


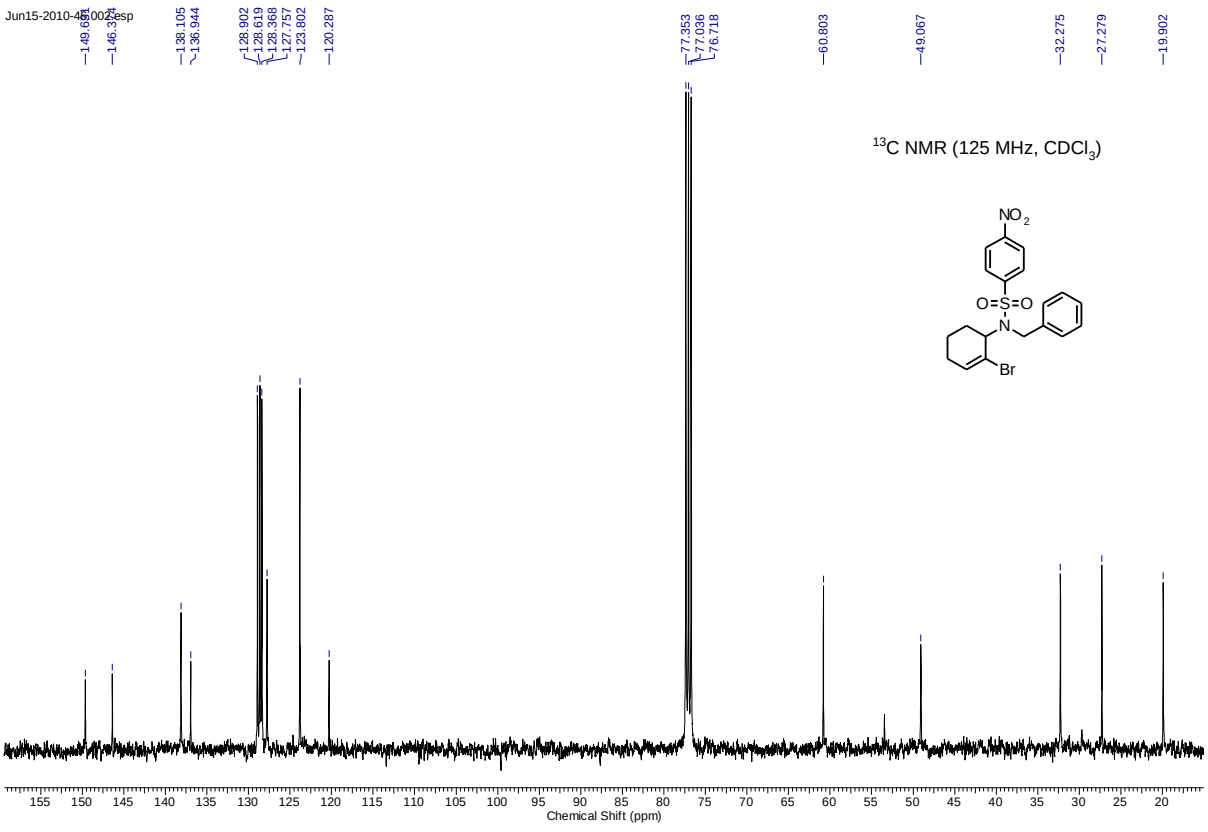
N-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-fluorobenzenesulfonamide, 120



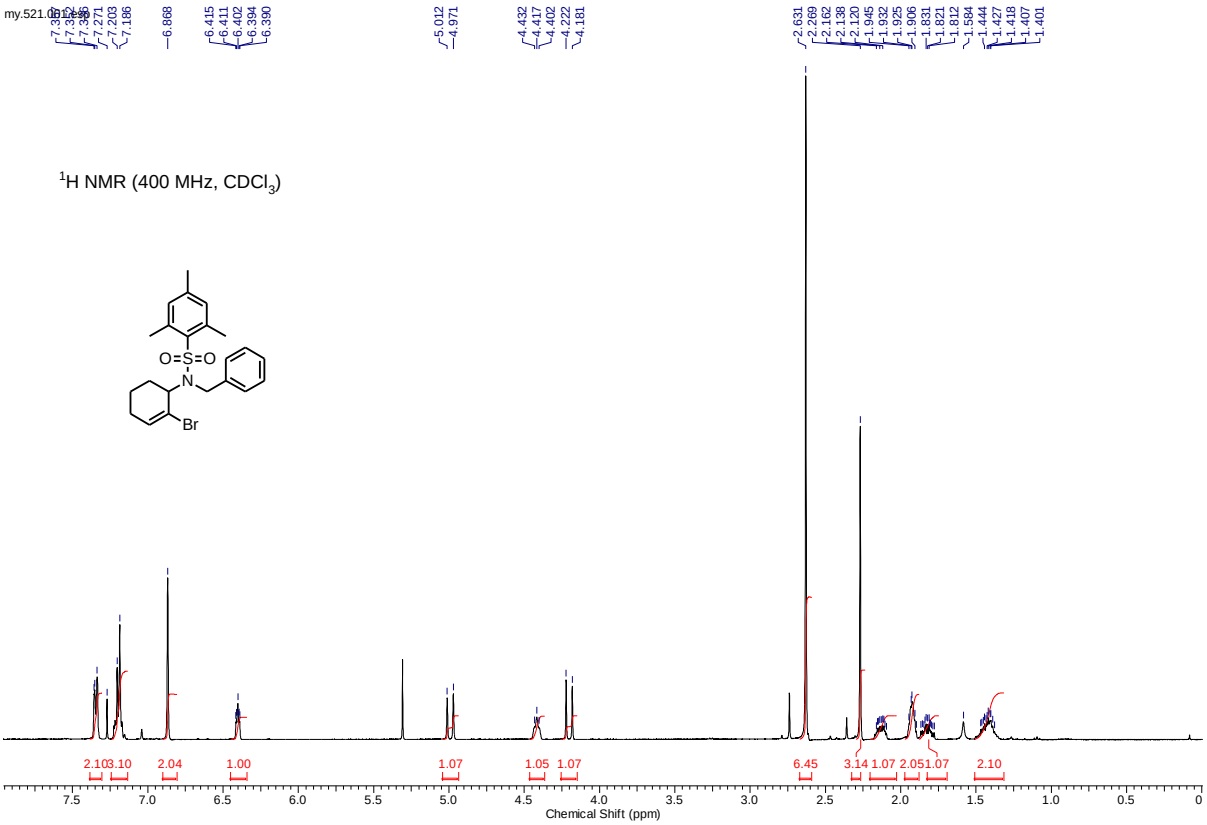


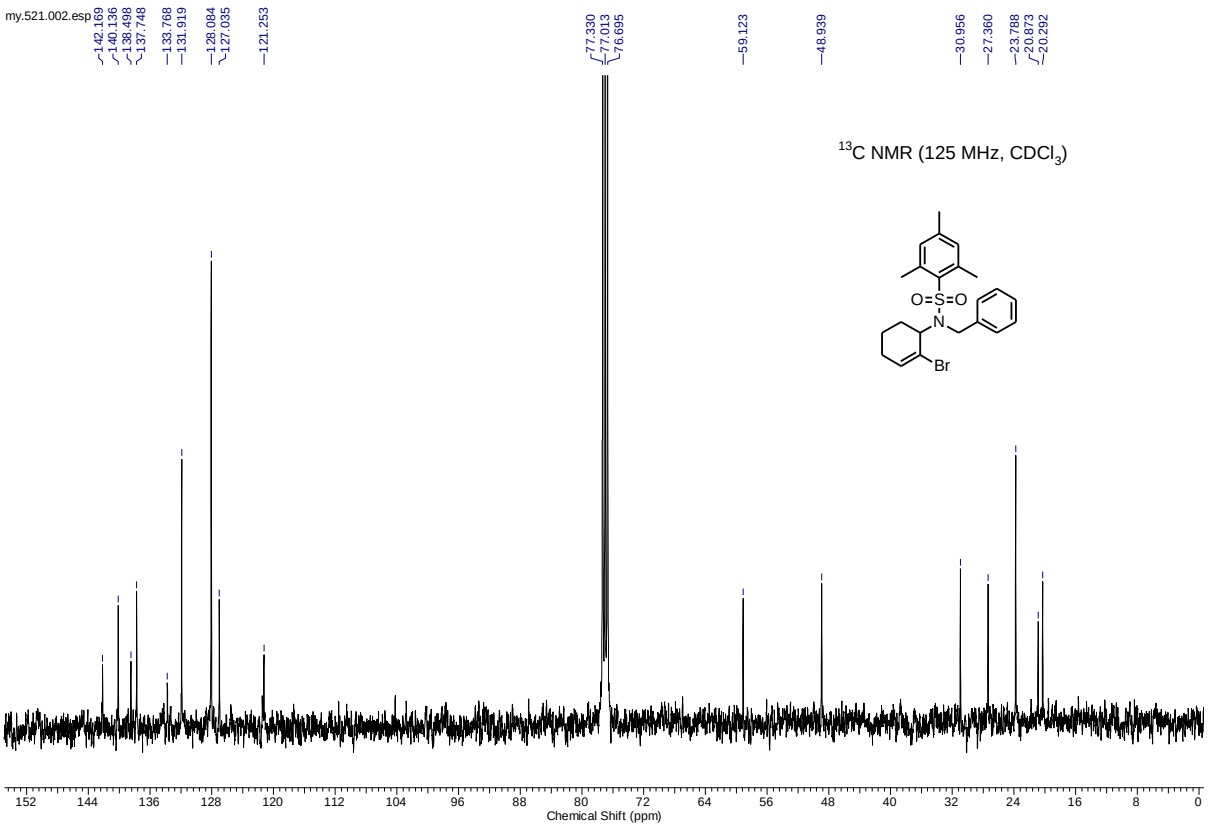
N-Benzyl-*N*-(2-bromocyclohex-2-enyl)-4-nitrobenzenesulfonamide, 121



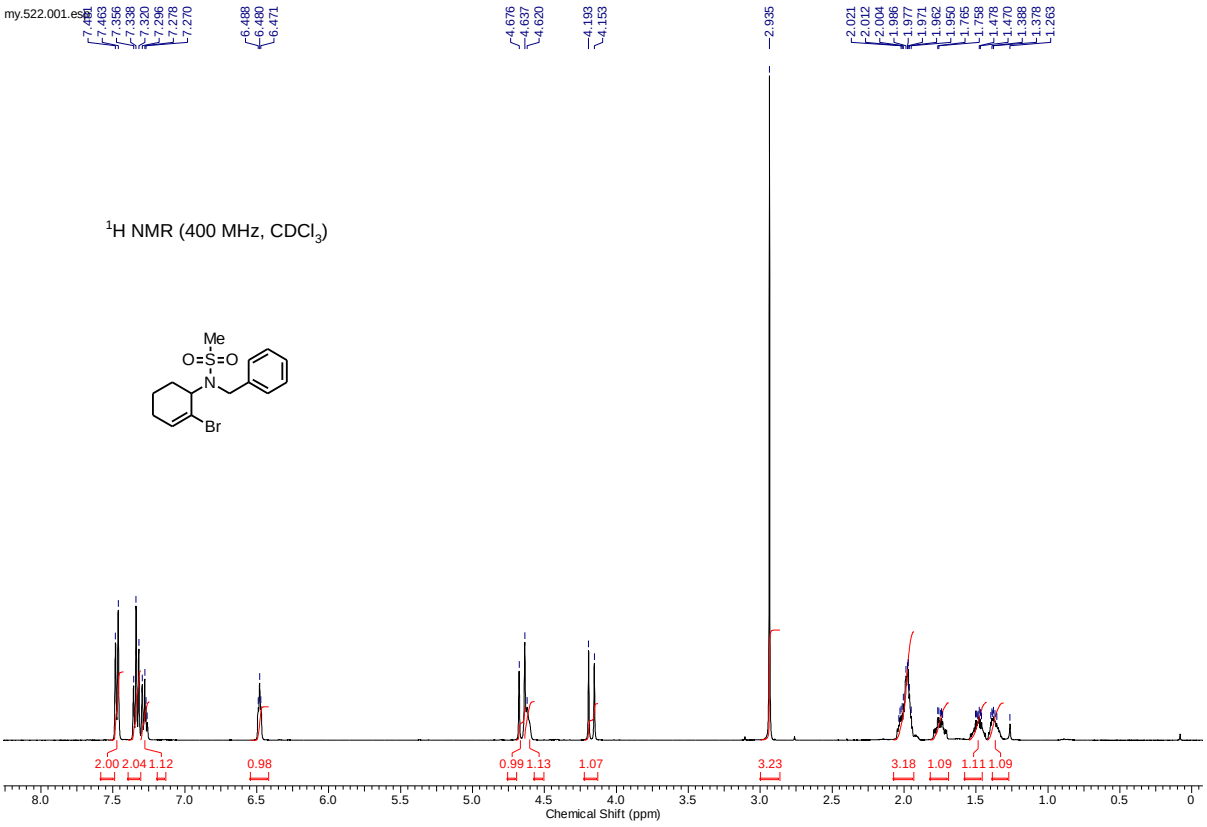


N-Benzyl-*N*-(2-bromocyclohex-2-enyl)-2,4,6-trimethylbenzenesulfonamide, 122

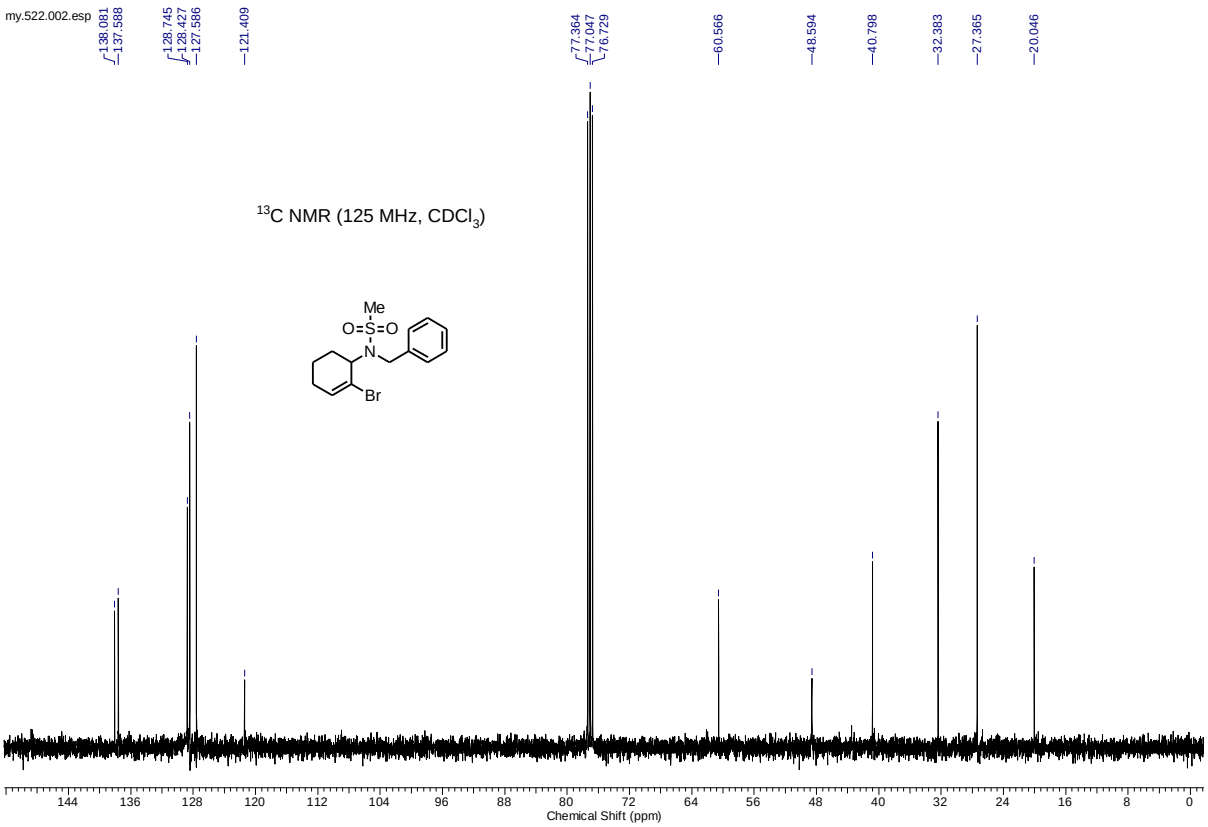




N-Benzyl-*N*-(2-bromocyclohex-2-enyl)methanesulfonamide, 123

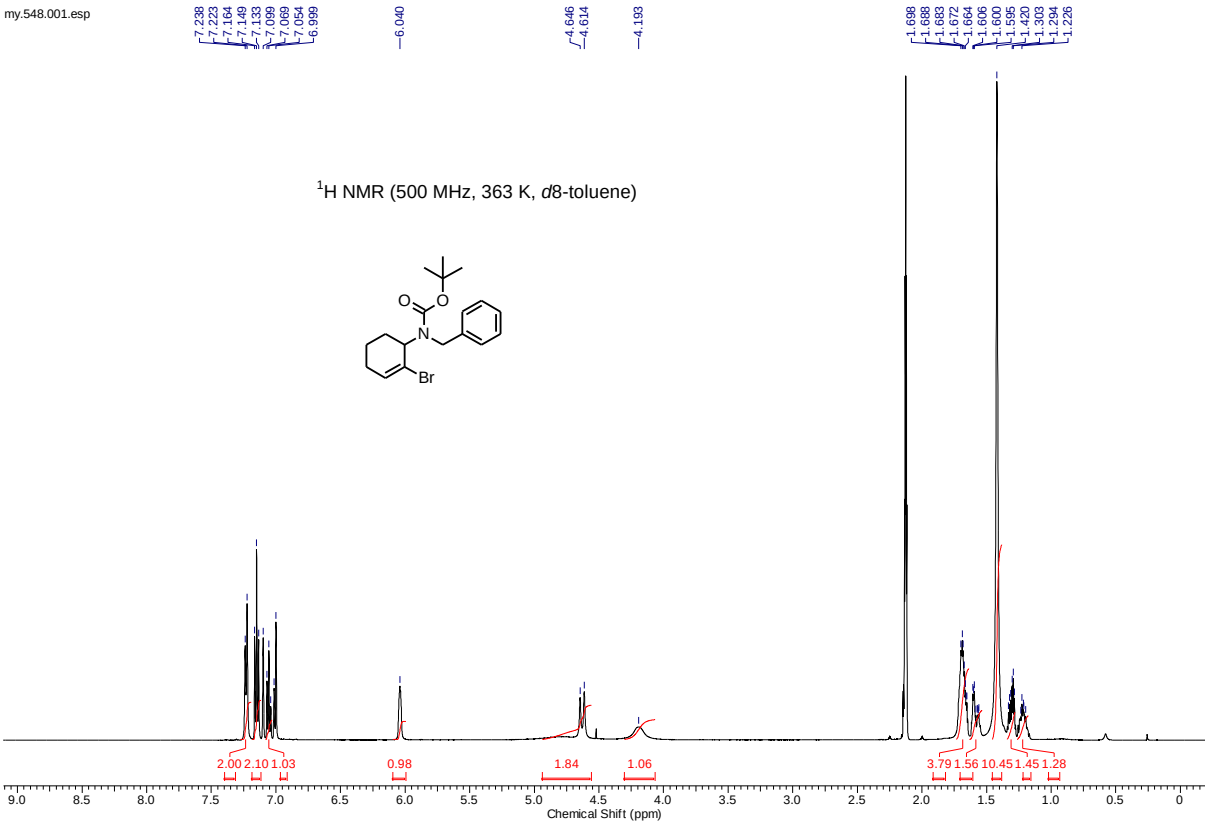


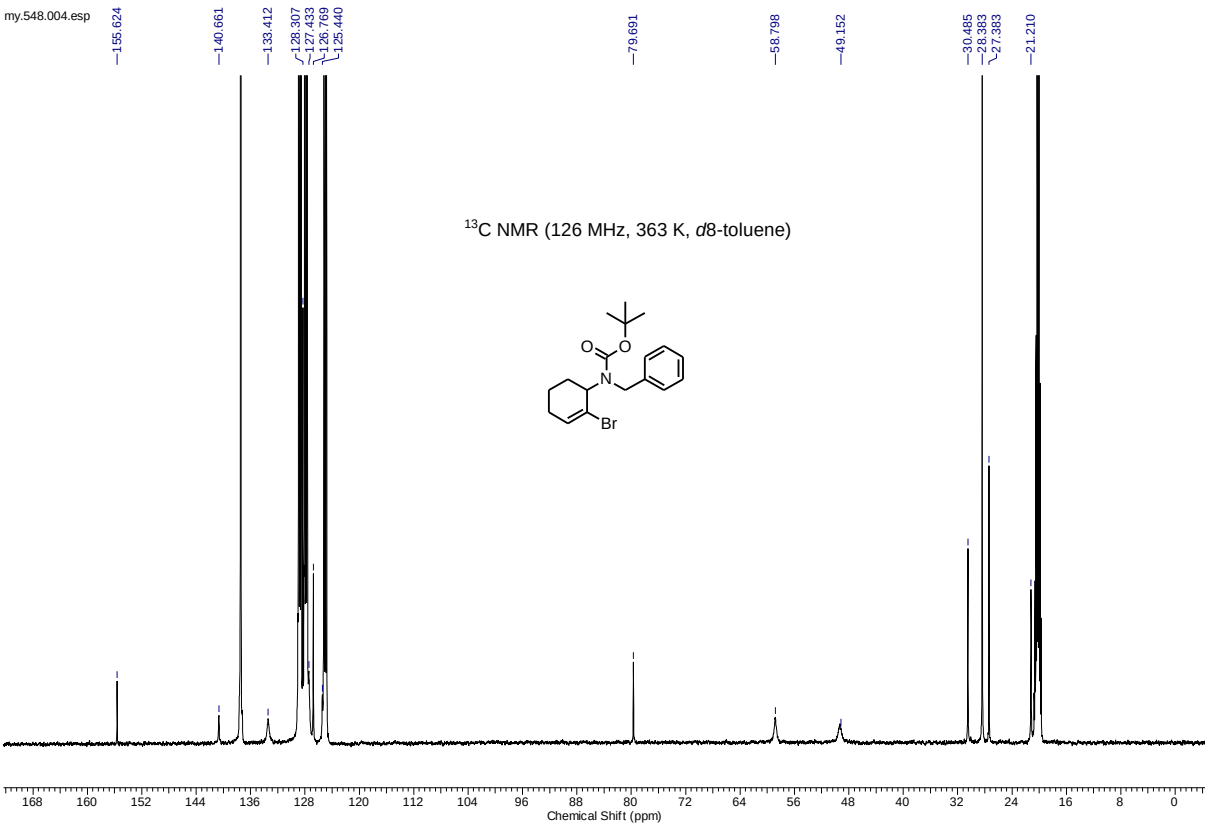
^{1}H NMR (400 MHz, $CDCl_3$)



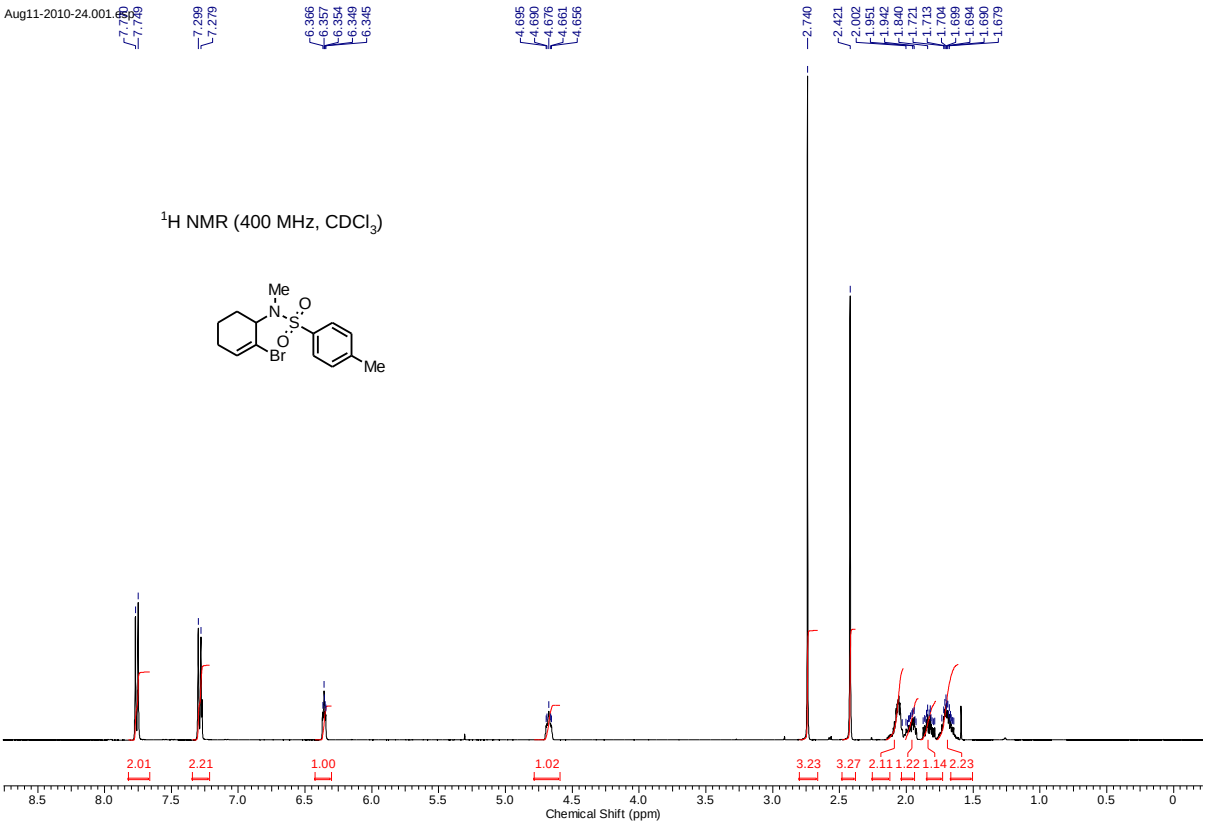
^{13}C NMR (125 MHz, $CDCl_3$)

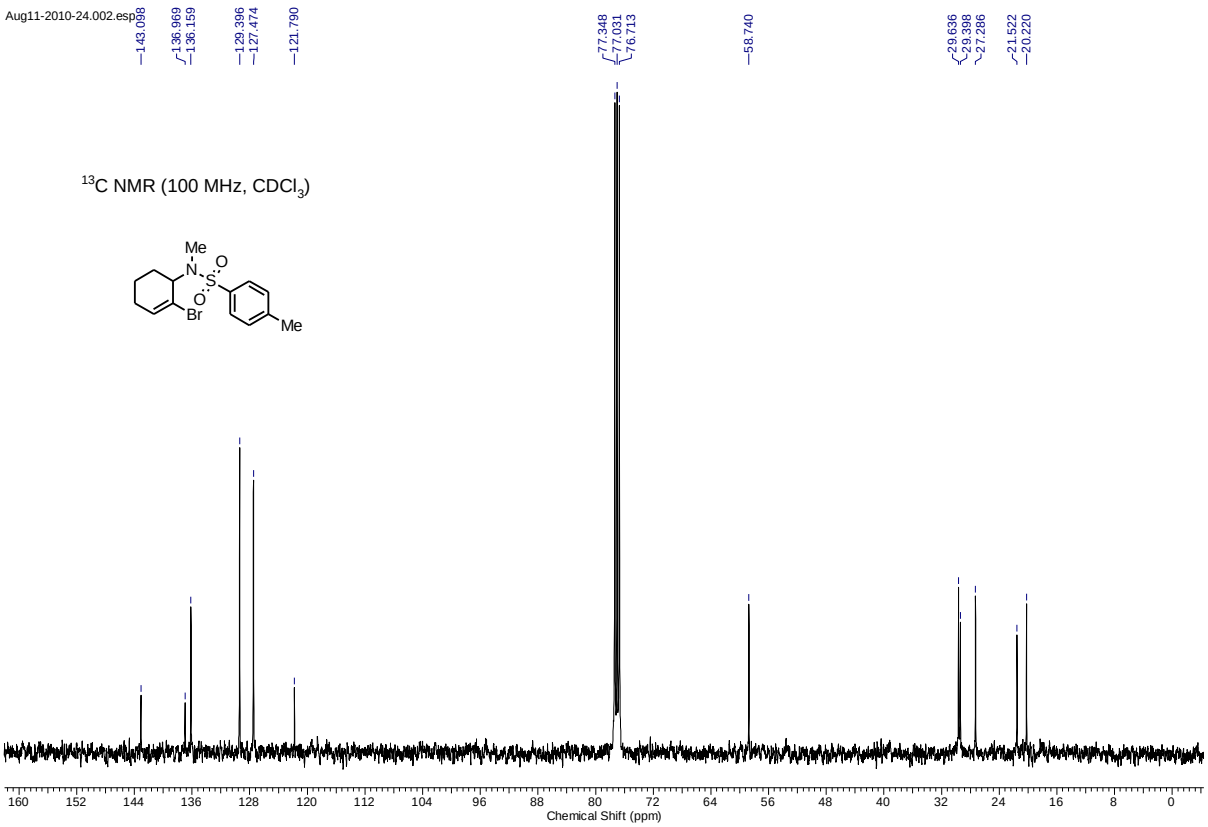
tert-Butyl benzyl(2-bromocyclohex-2-enyl)carbamate, 124



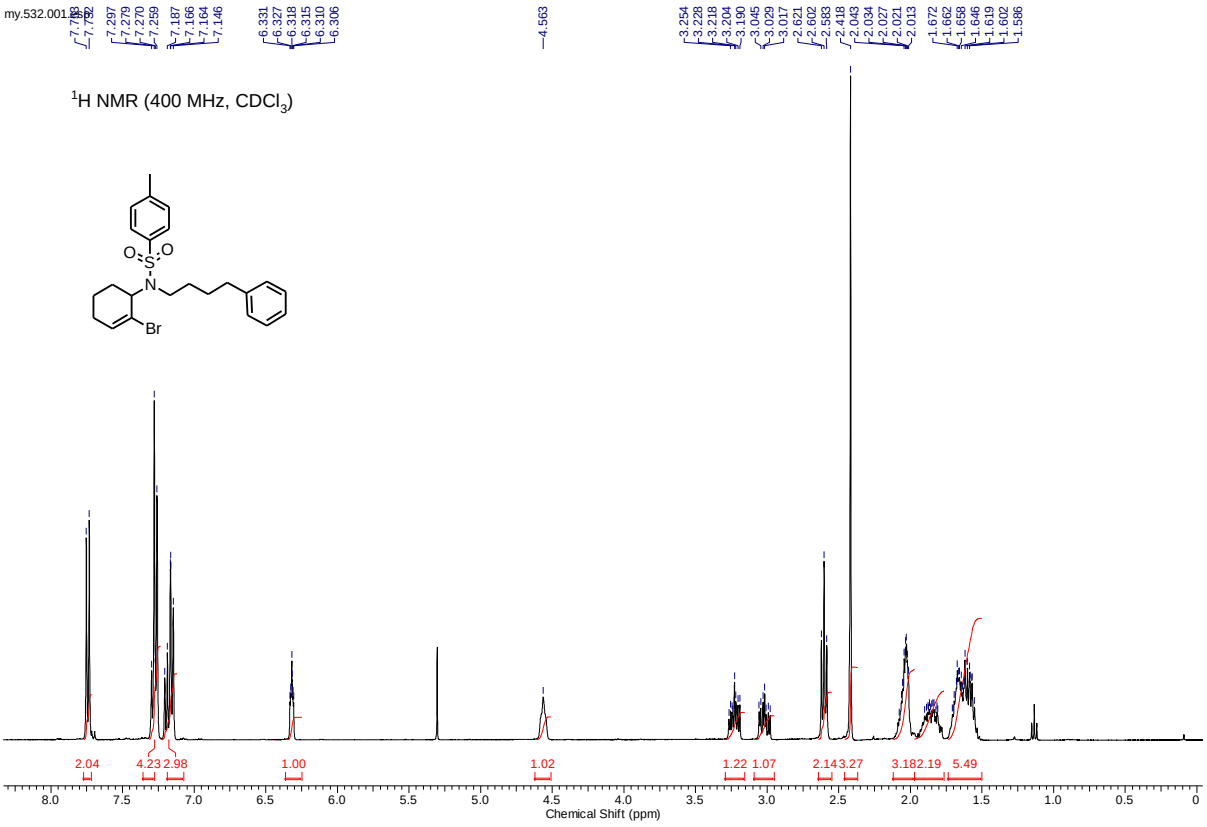


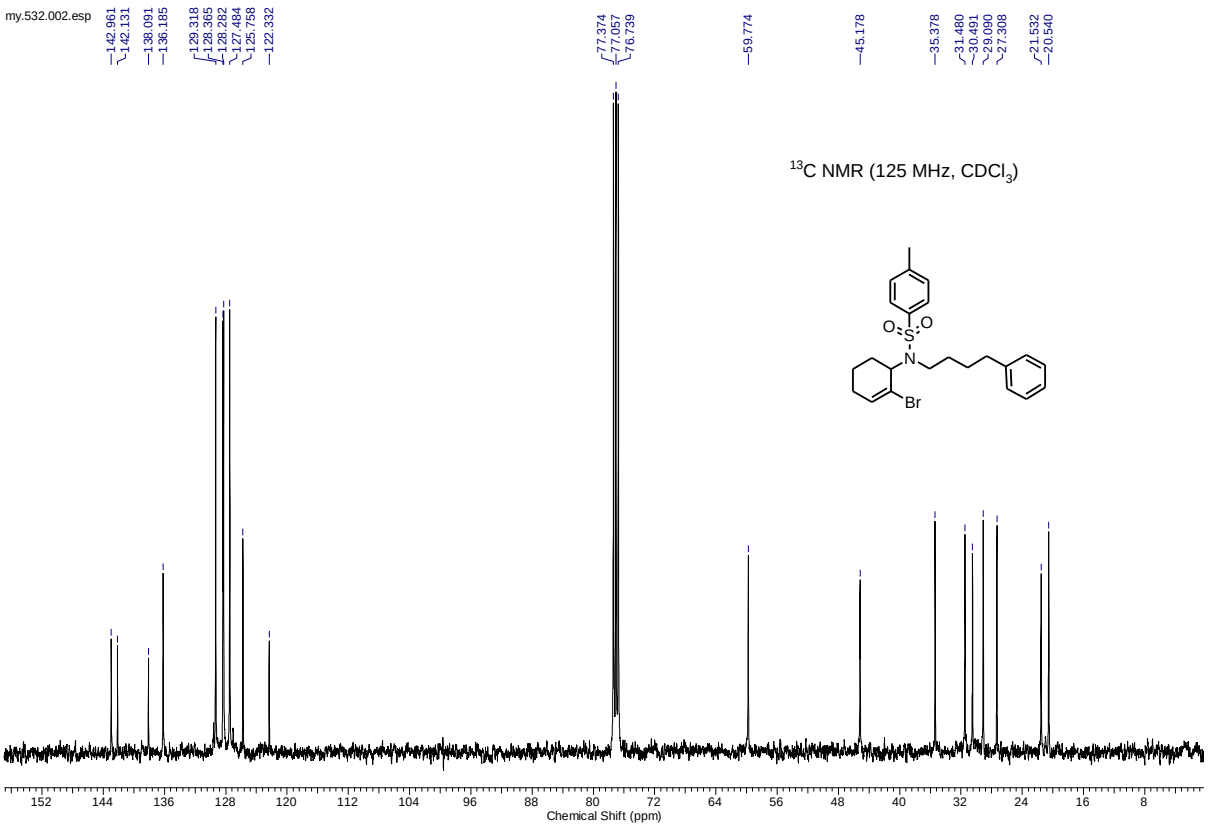
N-(2-Bromocyclohex-2-enyl)-*N*,4-dimethylbenzenesulfonamide, 125



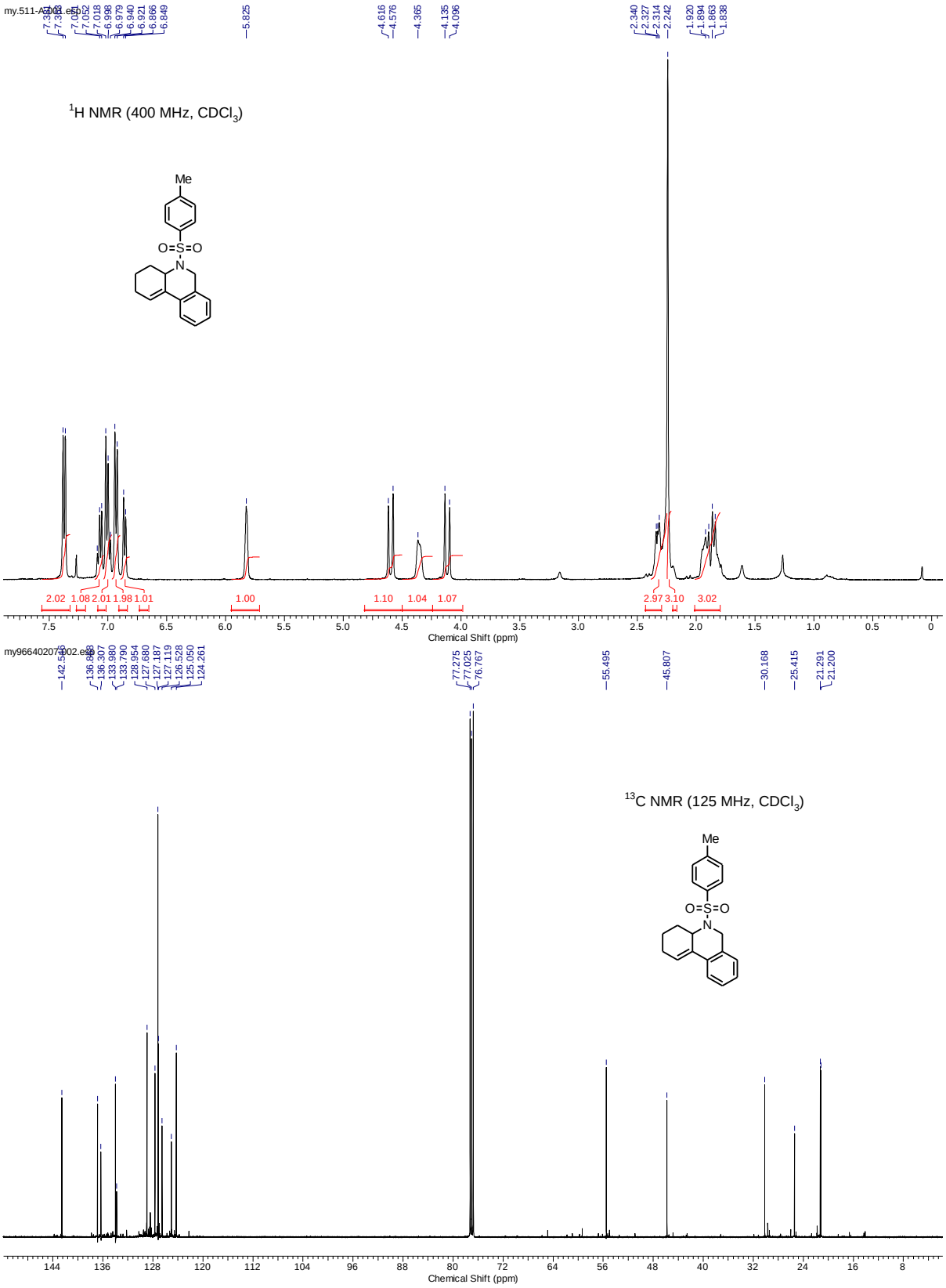


N-(2-Bromocyclohex-2-enyl)-4-methyl-*N*-(4-phenylbutyl)benzenesulfonamide, 126

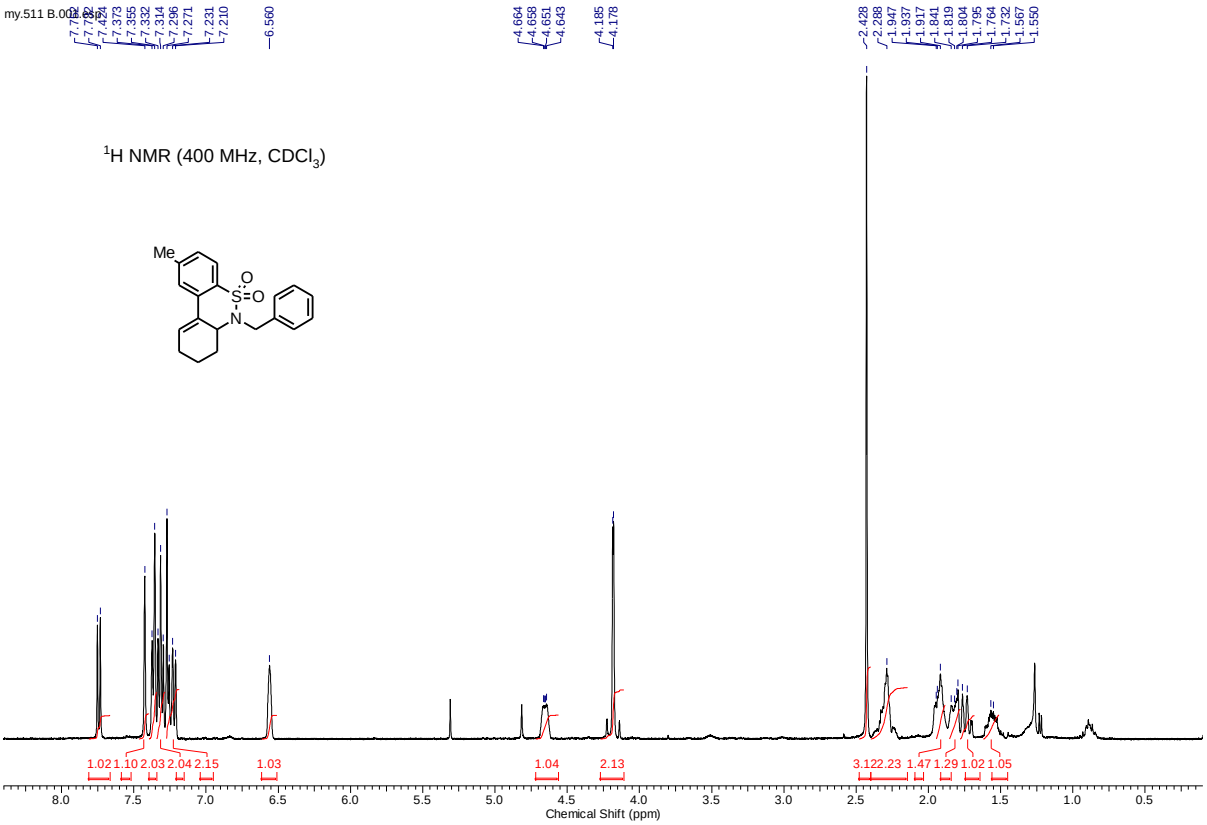


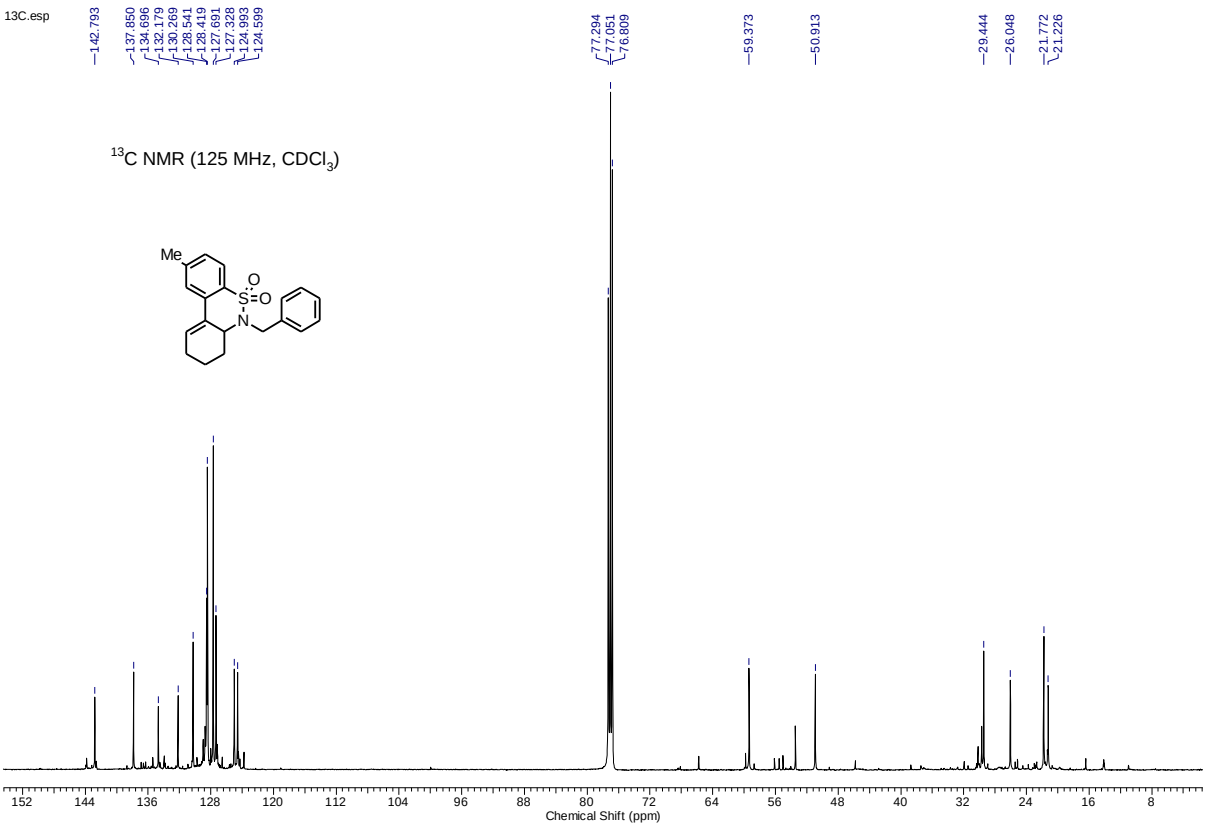


5-Tosyl-2,3,4,4a,5,6-hexahydrophenanthridine, 115



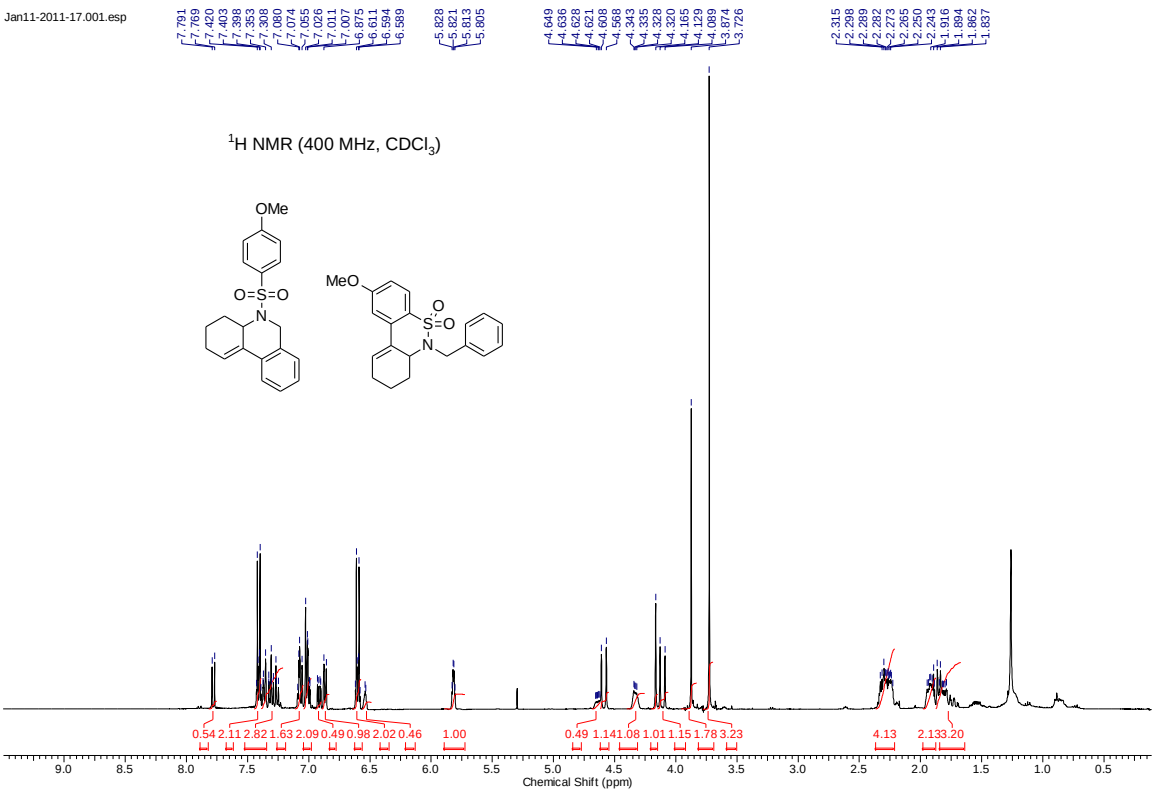
N-Benzyl-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 116

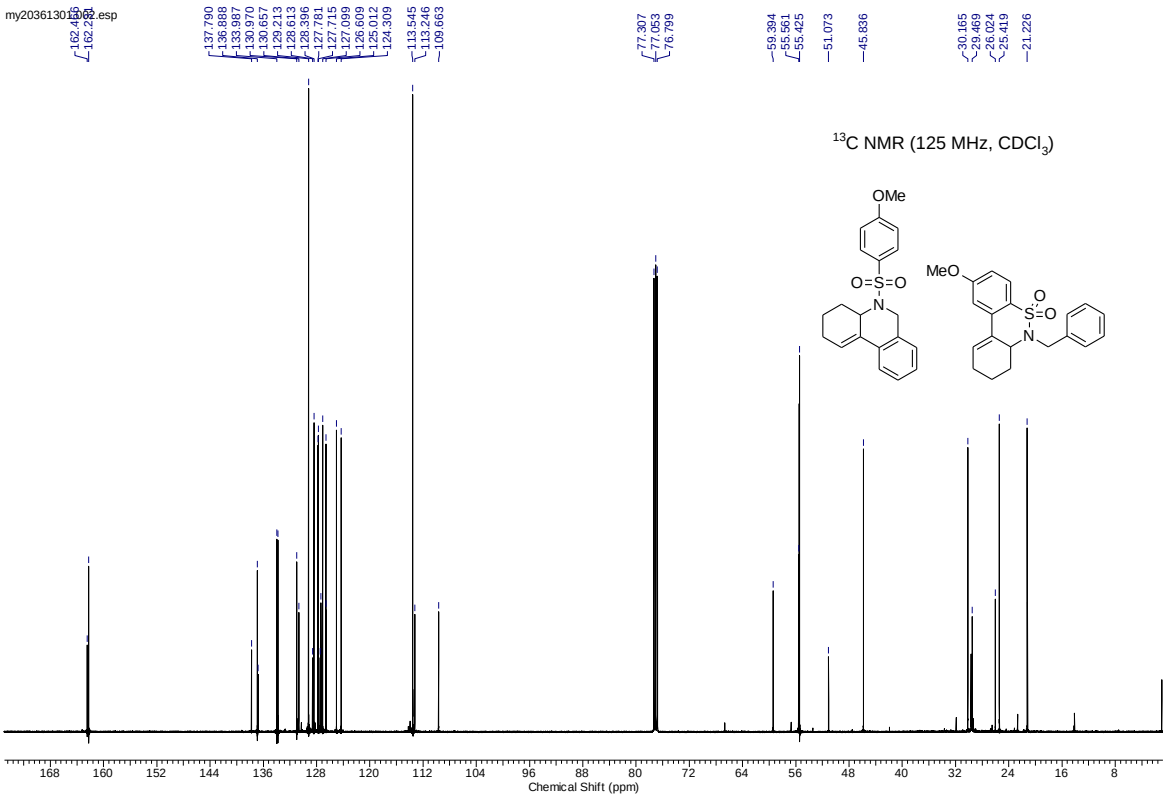




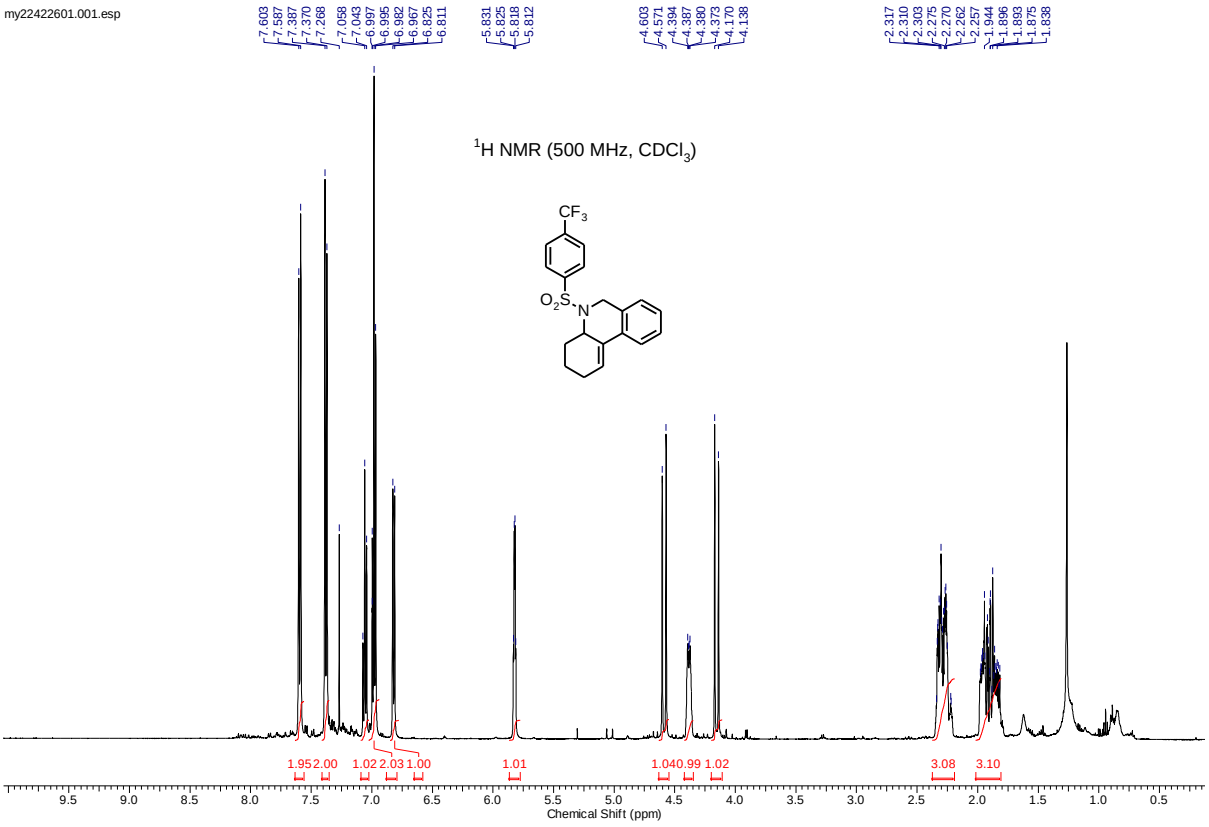
5-((4-Methoxyphenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 130

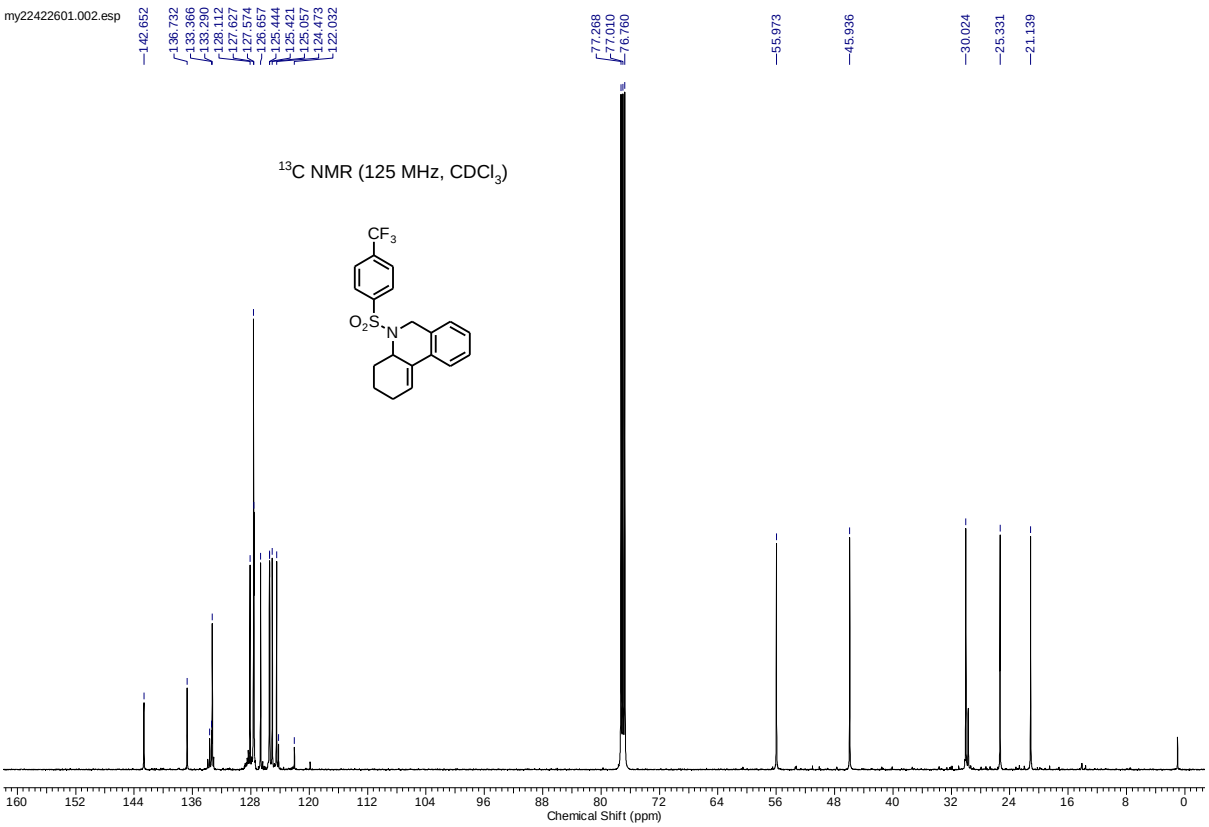
_N_-Benzyl-2-methoxy-6a,7,8,9-tetrahydro-6H-dibenzo[_c_,_e_][1,2]thiazine 5,5-dioxide, 131





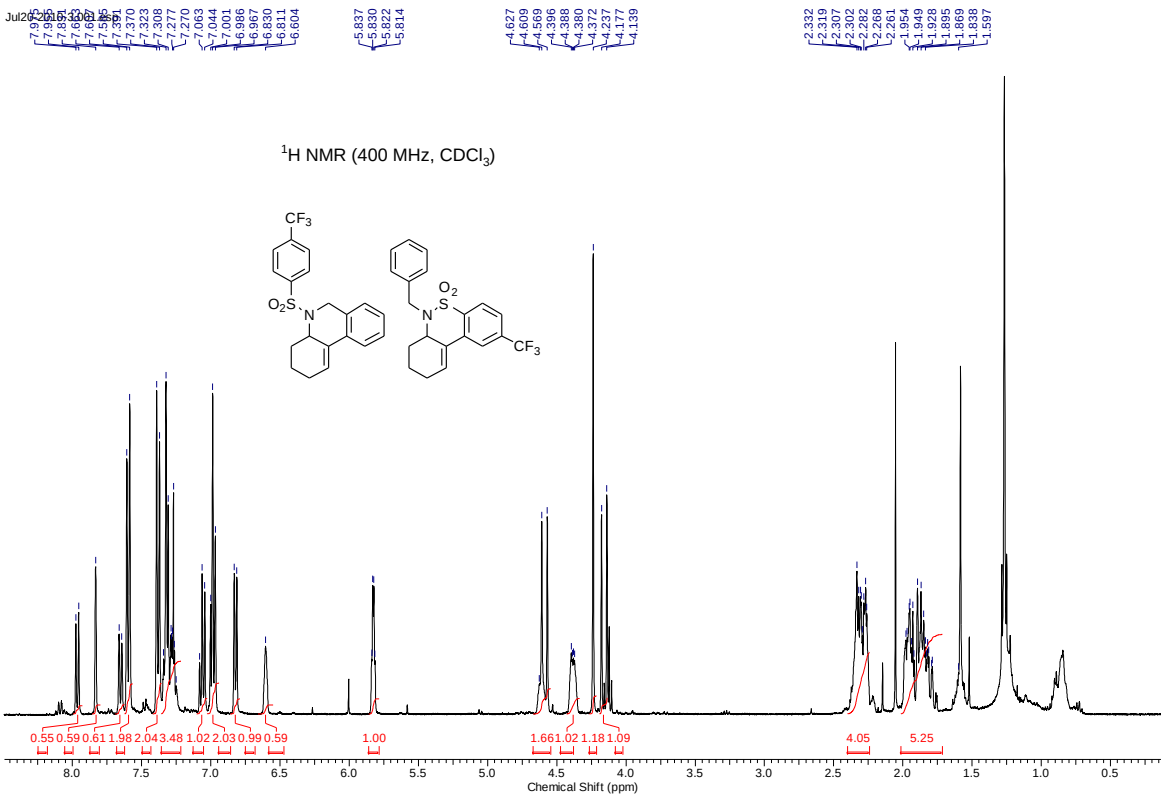
5-((4-(Trifluoromethyl)phenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 132

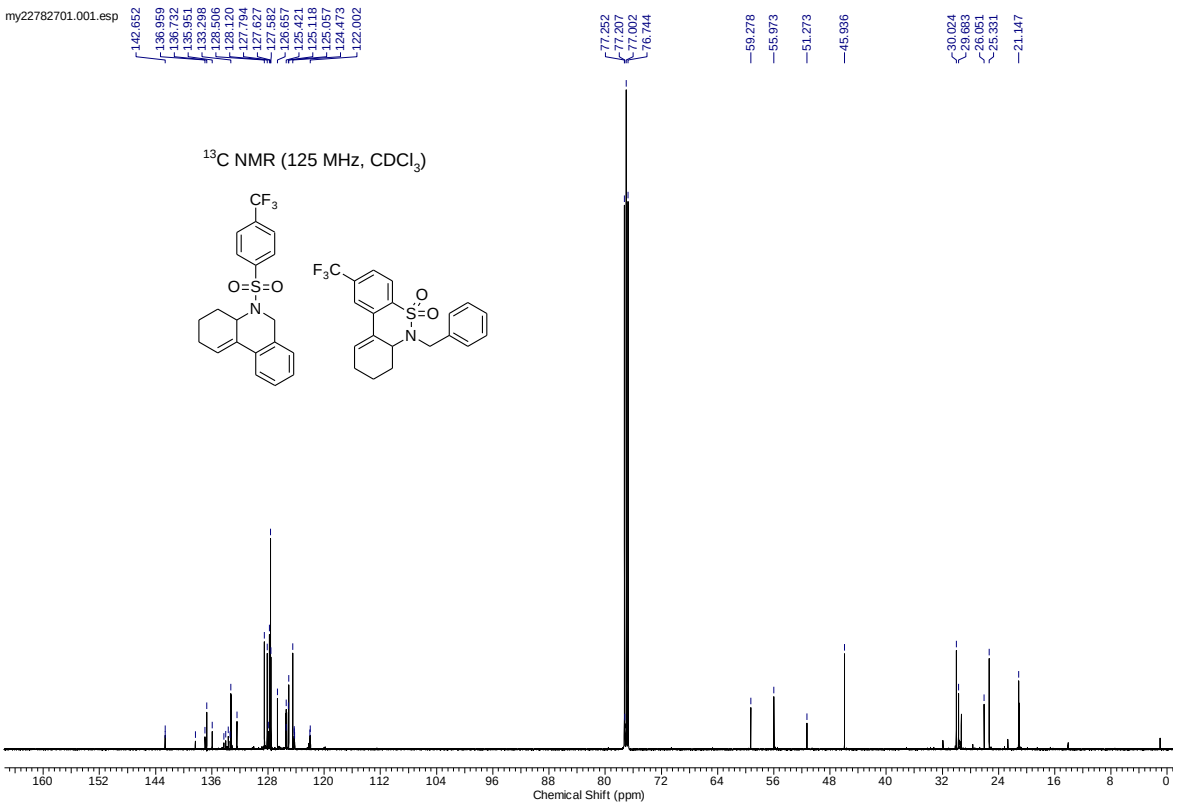




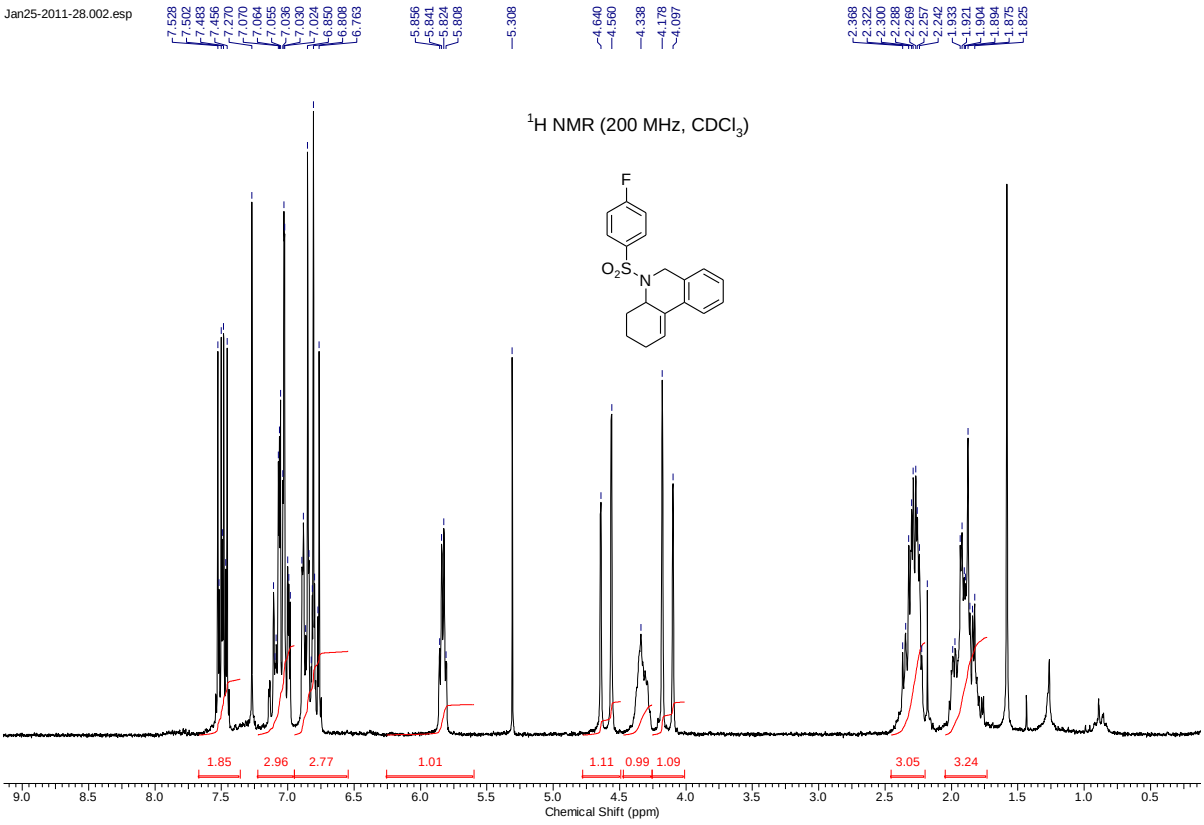
5-((4-(Trifluoromethyl)phenyl)sulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 132

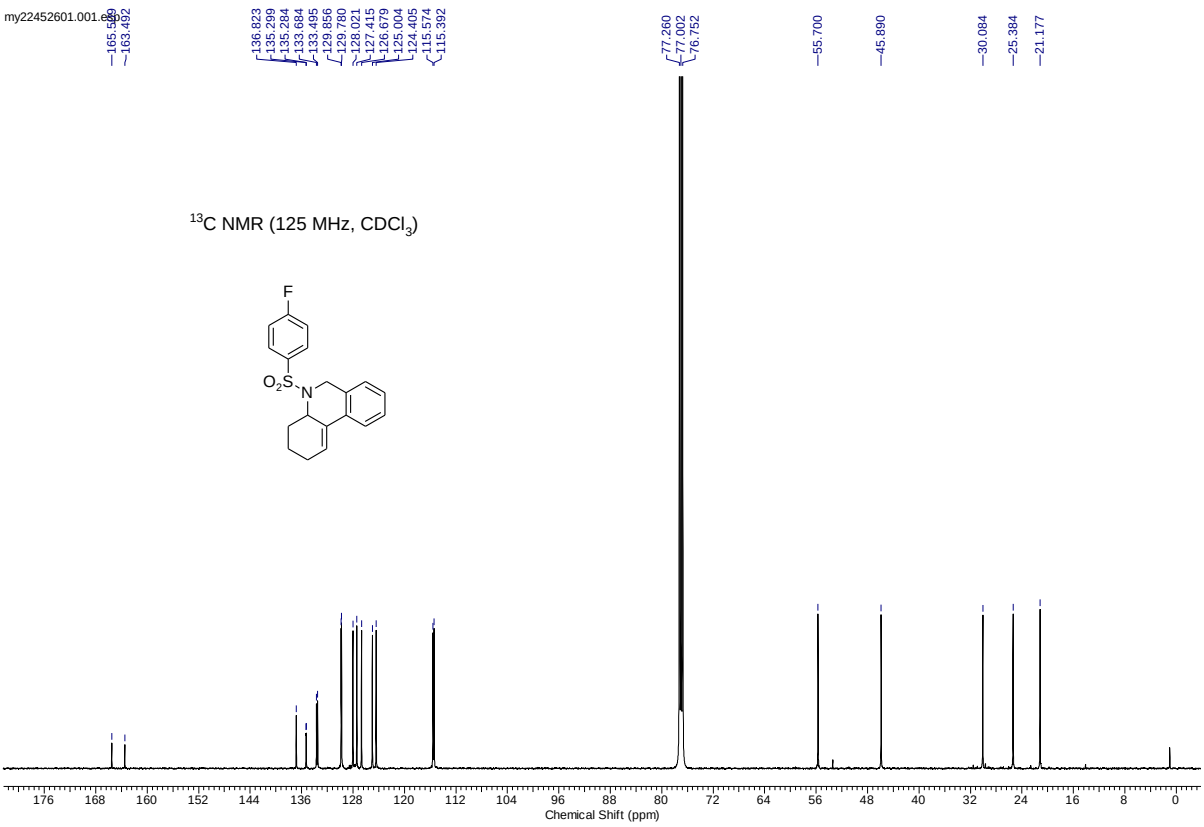
***N*-Benzyl-2-(trifluoromethyl)-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 133**





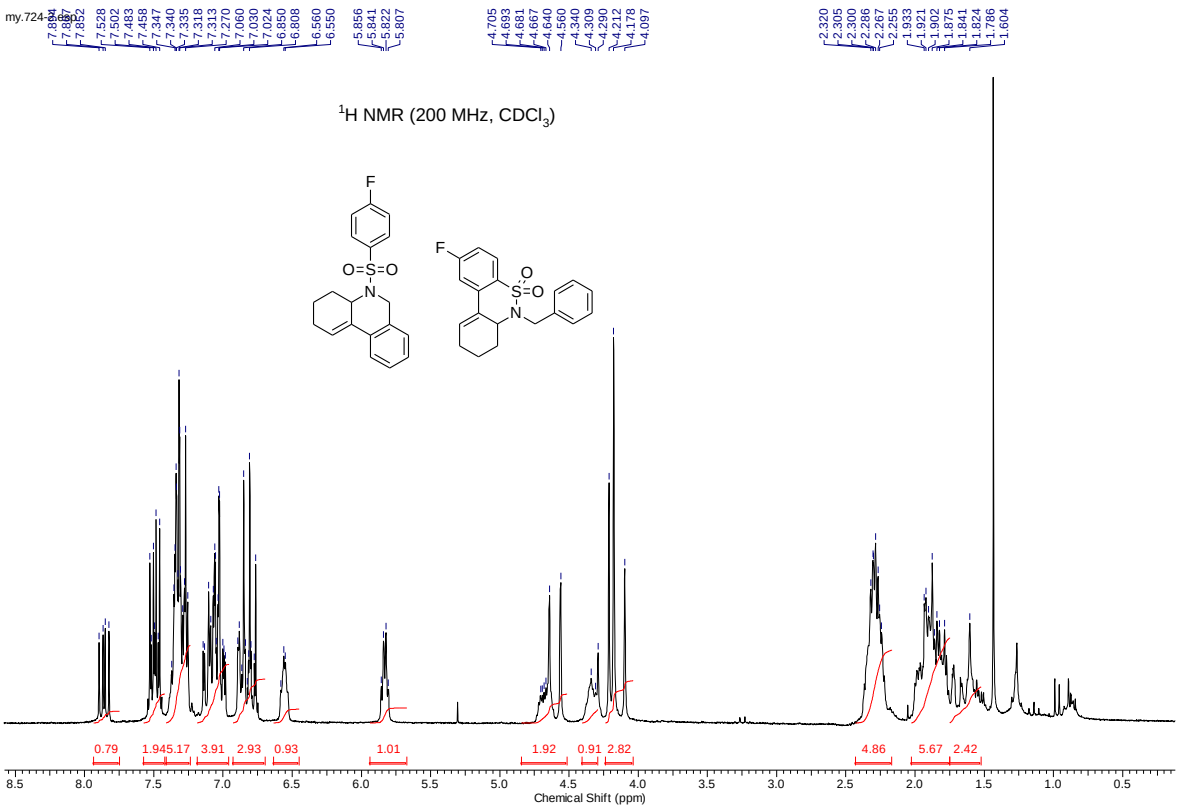
5-(4-Fluorophenylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 134

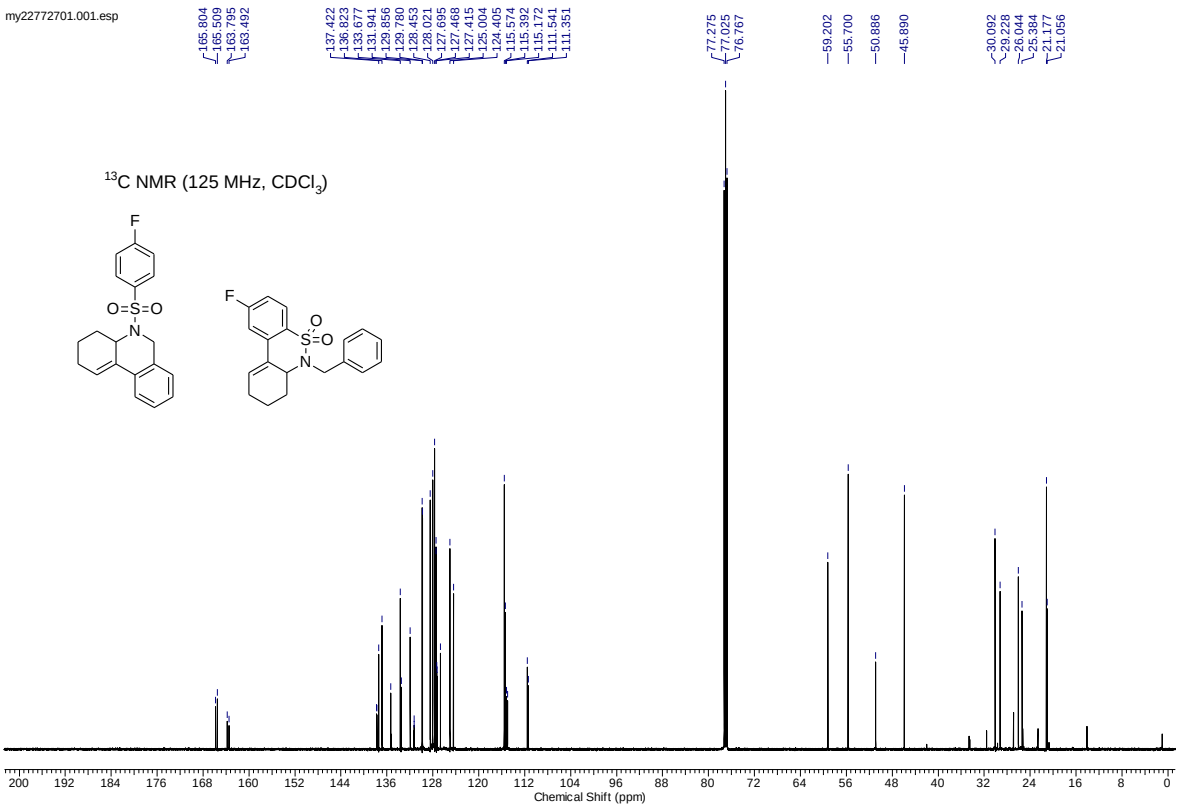




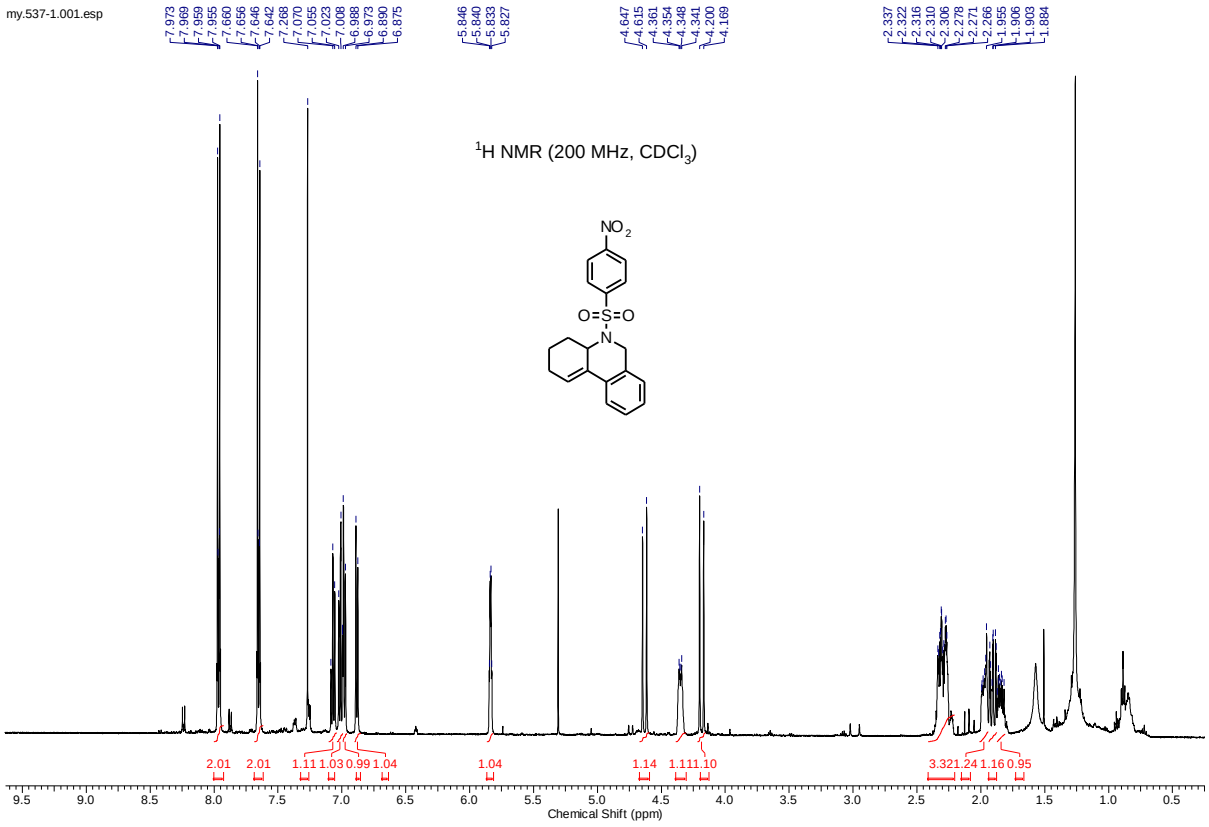
5-(4-Fluorophenylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 134

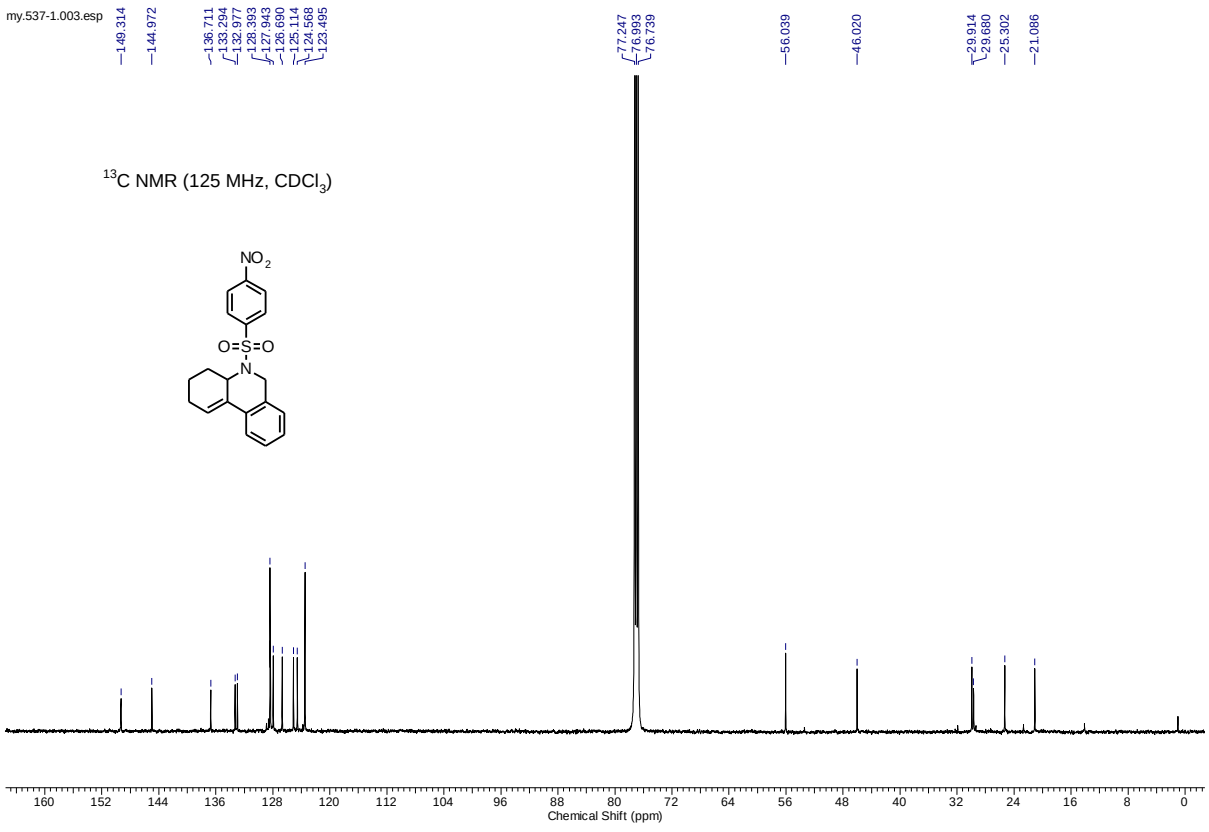
_N_-Benzyl-2-fluoro-6a,7,8,9-tetrahydro-6H-dibenzo[_c_,_e_][1,2]thiazine 5,5-dioxide, 135



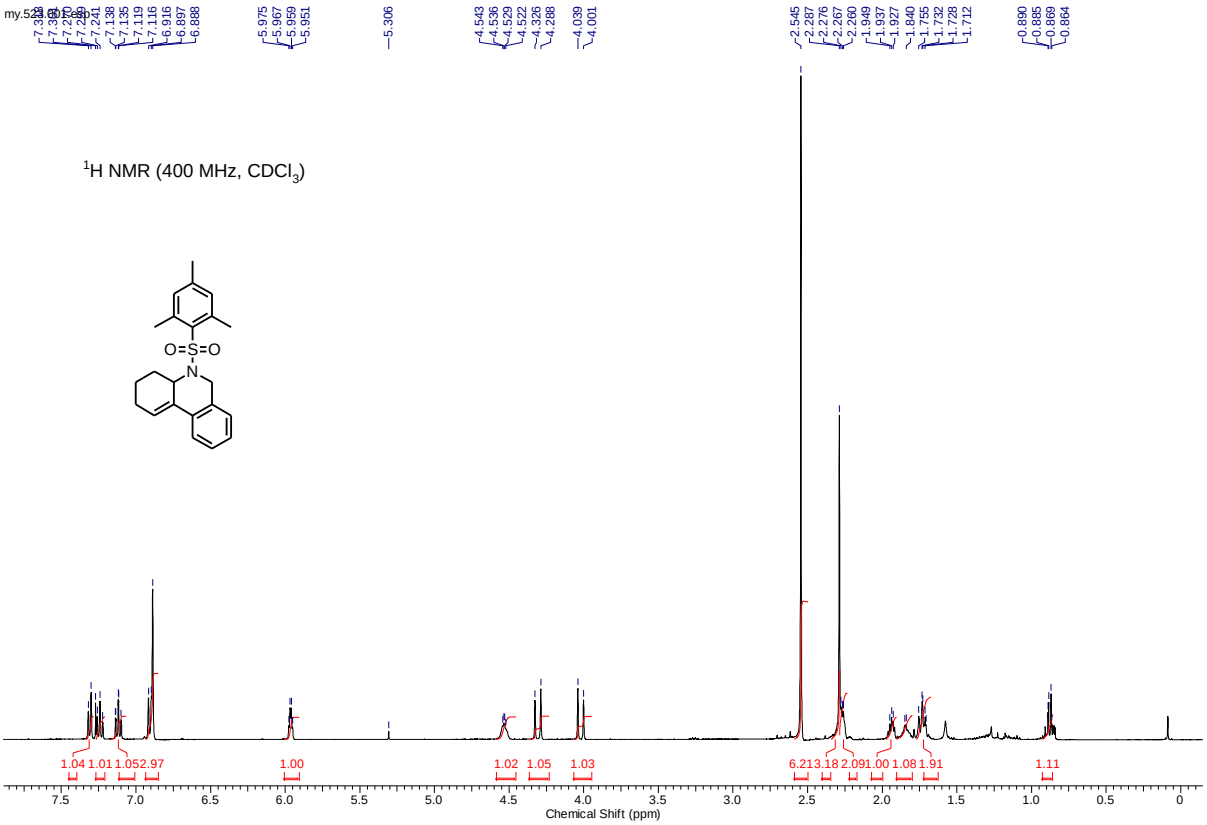


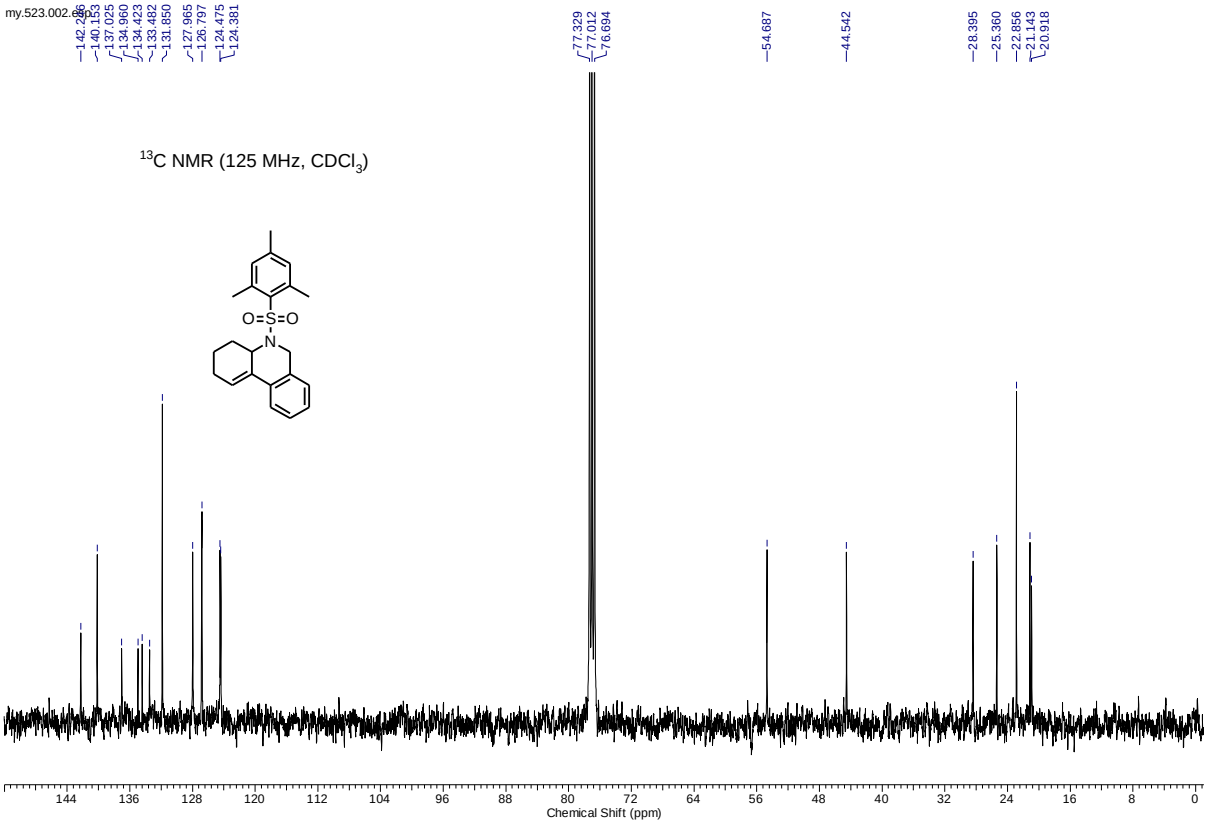
5-(4-Nitrophenylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 136



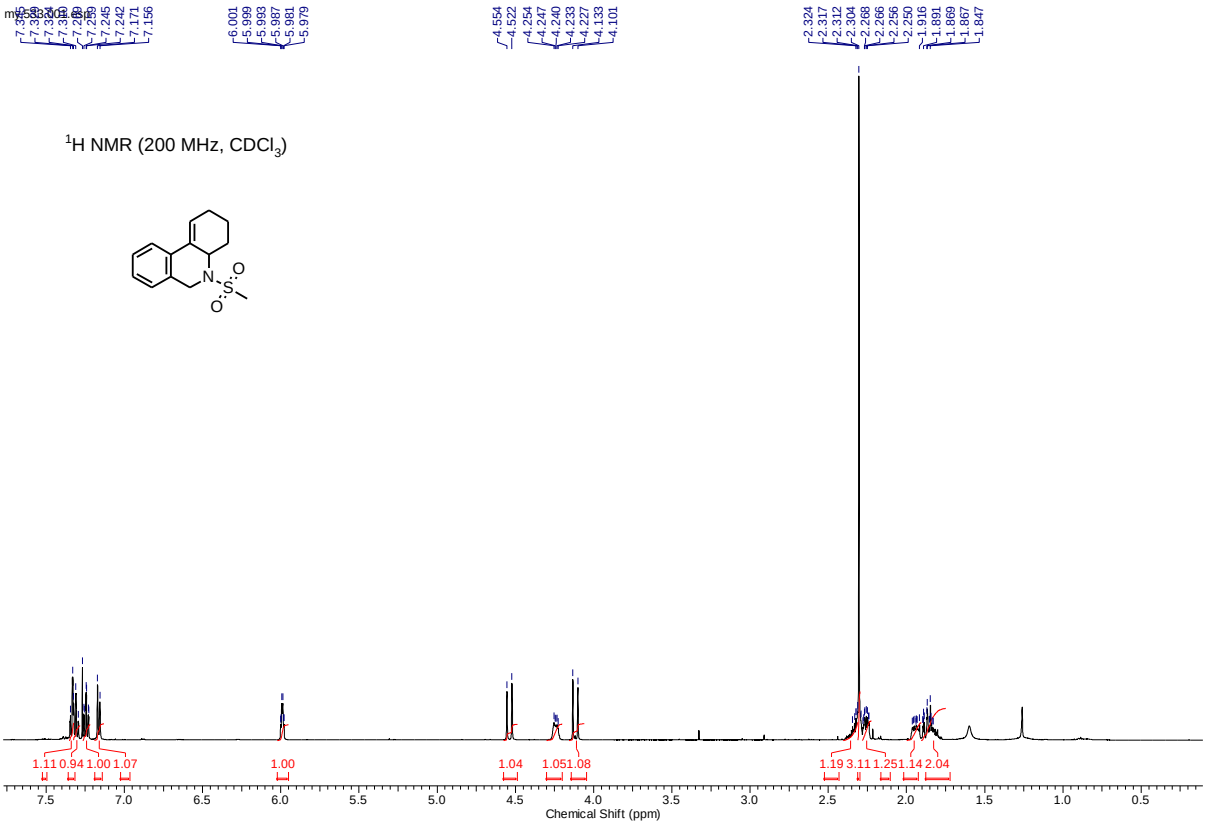


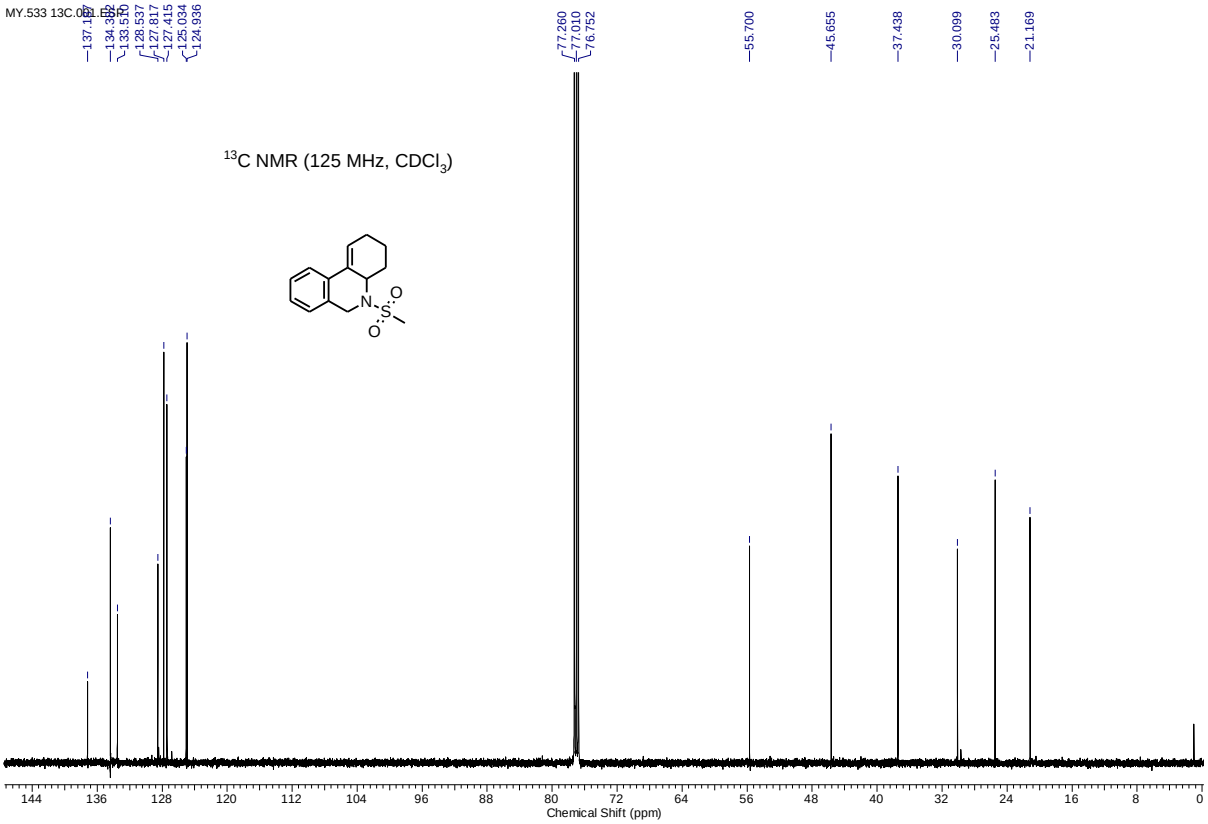
5-(Mesitylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 137





5-(Methylsulfonyl)-2,3,4,4a,5,6-hexahydrophenanthridine, 138





N-Phenylbutyl-2-methyl-6a,7,8,9-tetrahydro-6H-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide, 139