Carbon-carbon bond formation via rhodium-catalysed C-S activation processes

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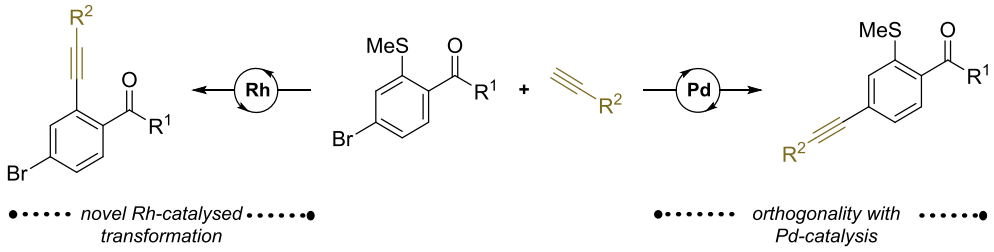
Abstract

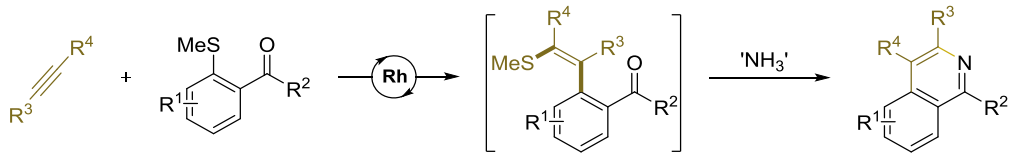
In the following thesis, new methodologies towards harnessing C-S activation processes are documented. These methods utilise rhodium catalysis and are focused on the activation of aryl methyl sulfides.

Chapter **1** provides an overview of the development of metal-catalysed C-S activation chemistry, with a focus on the catalytic systems, reagents and starting materials used to facilitate various C-C bond forming transformations.

Chapter **2** describes a novel rhodium-catalysed cross-coupling reaction of aryl and alkyl terminal alkynes with simple aryl sulfides. This resulted in a Sonogashira-type transformation which exhibited orthogonality with traditional palladium catalysed Sonogashira chemistry.



Chapter **3** documents a new catalytic system which allowed for the practical and efficient alkyne carbothiolation reactions of ketone-baring methyl sulfides. The carbothiolation products can be conveniently utilised in a one-pot three-component reaction to form highly substituted isoquinolines.



Chapter **4** discusses the potential for future work.

Chapter **5** presents the experimental data.

Acknowledgments

Firstly I would like to thank Professor Michael Willis for giving me the opportunity to undertake this project. He has been instrumental in the success of this thesis, his energy and enthusiasm has been of continuous motivation throughout my time at Oxford. Without his ongoing support, input and guidance, the completion of this project would not have been possible. Thank you.

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Finally, I would like to say thank you to my grandmother, whose strength and energy for life, even during the darkest of times has been such an inspiration to myself and my family.

List of Abbreviations

acac	– acetylacetone
AG	– activating group
Ac	– acyl
Ar	– aryl
BAr^F_4	– 3,5-$(CF_3)C_6H_3$
9-BBN	– 9-borabicyclo[3.3.1]nonyl
bda	– dibenzylideneacetone
Bn	– benzyl
Boc	– *tert*-butyloxycarbonyl
BODIPY	– boron-dipyrromethene
cat	– catalyst or catalytic
Cbz	– carboxybenzyl
COSY	– correlation spectroscopy
CuTc	– copper(I)thiophene-2-carboxylate
Cy	– cyclohexyl
d	– doublet or deuterated
DCE	– 1,2-dichloroethane
DCM	– dichloromethane
dcpb	– 1,1-bis(dicyclohexylphosphino)butane
dcpe	– 1,1-bis(dicyclohexylphosphino)ethane
dcpm	– 1,1-bis(dicyclohexylphosphino)methane
de	– diastereomeric excess
°C	– degrees centigrade
DMA	– N,N-dimethylacetamide
DMF	– N,N-dimethylformamide
DMP	– Dess-Martin periodinane
DPEphos	– bis(2-diphenylphosphionophenyl)ether
DPhil	– Doctor of Philosophy
dppe	– 1,1-bis(diphenylphosphino)ethane
n	– normal
dppf	– 1,1-bis(diphenylphosphino)ferrocene
dppm	– 1,1-bis(diphenylphosphino)methane
ee	– enantiomeric excess
eq	– equivalents
ESI	– electrospray ionisation
Et	– ethyl
fac	– facial
FI	– field ionisation
g	– gram
h	– hours
Het	– heterocycle
HOMO	– Highest Occupied Molecular Orbital
HPLC	– High Performance Liquid Chromatography
HRMS	– High Resolution Mass Spectrometry
Hz	– hertz
^{i}Pr	– isopropyl
J	– coupling constant
kcal	– kilocalories
L	– litre
LUMO	– Lowest Unoccupied Molecular Orbital
M	– metal
m	– milli (10^{-3}) or multiplet
m/z	– mass to charge ratio
mer	– meridinal
min	– minutes
mol	– mole
Mp.	– melting point
MS	– mass spectrometry
µW	– microwave
Sal	– salicylate

nbd	– norbornadiene
Bu	– butyl
NMR	– Nuclear Magnetic Resonance
nOe	– nuclear Overhauser effect
o	– *ortho*
OTf	– $[CF_3SO_3]^-$
p	– *para*
P	– monophosphine ligand
PCC	– pyridinium chorochromate
Ph	– phenyl
PMB	– *para*-methoxybenzyl ether
q	– quartet
quin	– quintet
R	– generic group/substituent
r.t	– room temperature
Rf	– retention factor
SME	– 2-(trimethylsilyl)ethoxy methyl acetal
S_nAr	– nucleophilic aromatic substitution
S-Phos	– 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	– tertiary
t	– triplet
TBAB	– tetrabutylammonium bromide
TBAF	– tetra-n-butylammonium fluoride
TBS	– *tert*-butyl dimethylsilyl
temp	– temperature
TES	– triethylsilane
THF	– tetrahydrofuran
TLC	– thin layer chromatography
UV	– ultra violet
X	– (pseudo)halide (unless stated otherwise)
Xantphos	– 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Content

Chapter 1: Introduction

1.1 Project Origins

Within the Willis group, the majority of work has revolved around the development of the hydroacylation reaction. Through years of investigations the process has been well-established and found to be most effective on benzaldehydes which bear *ortho*-SMe directing groups (Figure 1.1).

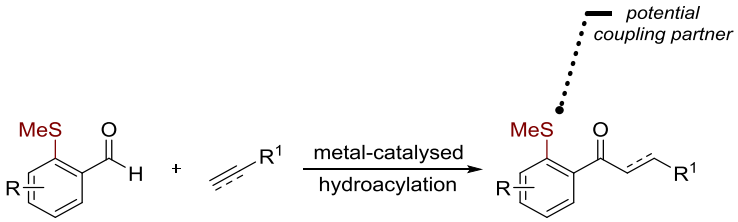


Figure 1.1 Aryl methyl sulfide's in hydroacylation chemistry

The consequence of this efficient transformation is that the products are limited by the retention of the sulfide moiety. As a solution, recent work in the group has been orientated around utilisation of this functional group in a bid to access more applicable and significant structures. The aim of this project was to make use of β-sulfide-ketones as effective coupling partners in facile rhodium catalysed processes.

1.2 Metal-catalysed C-C Bond Formation

Transition metal-catalysed C-C bond formation has been well studied over the last four decades.[1] Since its discovery it has become a powerful tool for organic chemists with the literature replete with elegant methodology describing an array of useful transformations. The emergence of multiple catalytic processes for selective activation and subsequent functionalisation of specific bonds have proven to be an indispensable tool for target or parallel synthesis of important motifs. From chemical biology and material science to supramolecular chemistry and key intermediates in natural product synthesis, transition metal-catalysis has been employed in essential C-C bond forming steps.[2,3,4] Its importance is demonstrated by the

pioneering work by Suzuki, Heck and Negishi among others who were recently awarded with the Nobel Prize.[5]

In traditional cross-coupling reactions, a sub-stoichiometric amount of metal-catalyst is employed to mediate the coupling of an electrophilic and nucleophilic component. The mechanisms of various metal-catalysed C-C bond-forming reactions commonly involve a combination of three stages: oxidative addition, transmetallation and reductive elimination. Generally for C-C bond-forming reactions there exists two main classes; reactions which employ a nucleophilic organometallic reagent or reactions which use alkenes or alkynes as one component. Both classes usually react with an electrophilic partner, commonly an aryl/alkenyl/heteroaryl halide or pseudohalide. Despite containing traditional leaving groups, these substrates are generally unable to undergo typical nucleophilic substitution because the (pseudo)hailde is attached to a sp^2 hybridised carbon. The ability to functionalise at these traditionally unreactive sites provides an invaluable tool for molecule construction.

The nucleophilic species in these reactions can range from organometallics such as Grignard reagents,[6] organolithiums,[7] organozinc reagents,[8] organotin reagents[9] and boronic acids and esters[10], to hydride equivalents[11] and heteroatomic nucleophiles including enolates,[12] alkenes[13] and alkynes.[14]

The nature of the catalyst itself also plays an integral role in these reactions. The application of d-block metals has increased significantly with transition metals proving to be useful catalysts for both highly specific organic “fine chemical” reactions and commodity scale industrial processes. Low-valence transition metal complexes of palladium, nickel, platinum, rhodium and iridium are all applicable in catalytic C-C bond formation, this is due to their ability to coordinate and activate organic molecules through donating and accepting electrons. Owing to their low oxidation states, the transition metal’s valence orbitals are usually filled by coordination of ligands. In most cases 16 and 18 valence electrons lead to the most stable

complexes. Owing to the versatility of palladium in this field, much effort has been devoted to the development of new reactions with novel transformations still being reported. However, over the past two decades rhodium catalysis has been investigated extensively within the context of C-C bond formation. Rhodium shows significant activity for C-H and C-O bond activation and has high resistance to catalyst poisoning, with the ability to conduct catalysis in water.[15] Rhodium catalysis allows access to valuable organic frameworks by elegant C-C bond construction and is pertinent to this thesis.

1.3 Rhodium and Phosphines

First discovered in 1803 by William Hyde Wollaston, rhodium is one of the rarest metals in the earth's crust; usually occurring in ores mixed with other metals such as palladium, silver, platinum and gold.[16] Used as a catalytic converter in automobile exhausts to reduce nitrogen oxides to nitrogen and oxygen, rhodium is a metal in high demand.[17] With over 80% of solid rhodium extracted being used in this way, its widespread use and high demand justifies the costly and complex method used to extract rhodium from its ore.[18] It is also involved in many laboratory and industrial scale processes such as the production of butanal from propene (hydroformylation), olefin hydrogenation, olefin isomeristion and the Monsanto acetic acid process.[19,20] Rhodium is a d-block transition metal with the electronic configuration [Kr]$4d^8 5s^1$. Although oxidation states of 0 to +VI are observed, the most common oxidation states for rhodium are +I and +III. By shuttling between these oxidation states rhodium can be used as an effective catalyst as it can facilitate both oxidative (addition) and reductive (elimination) transformations. Rhodium +I has 8d electrons and generally adopts a square planar configuration which is rationalised by its high energy field splitting and large size (Figure 1.2). The d-orbitals are split into four sets where the highest occupied molecular orbital (HOMO) is $2a_{1g}$ (d_z^2) and the lowest unoccupied molecular orbital (LUMO) is the highest energy orbital $2b_{1g}$ (d_x^2-d_y^2). Rhodium +III has 6d electrons and adopts an octahedral configuration, where

the d-orbitals are split into a LUMO triply degenerate t_{2g} set and HOMO doubly degenerate e_g set (figure **1.2**).

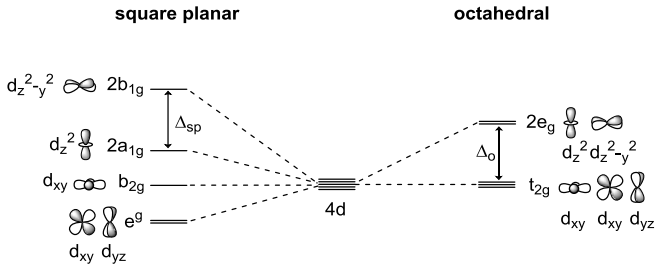


Figure 1.2 Molecular orbital diagram for octahedral and square planar complexes involving only the metal d orbitals

Elemental rhodium is rarely used in homogenous catalysis but when complexed to ligands such as phosphines, the properties of the complex is changed making it ideal for homogenous catalysis. The shuttling between low oxidation states +I and +III requires catalyst stability, which can only be achieved if ligands are coordinated to rhodium species.

The nature of the phosphine ligand that is bound to the metal plays an essential role in altering the properties of the resulting transition metal complexes.[21] Through variation of the phosphine's electronic and steric properties, it is possible to tune the reactivity of the complex. A large variety of phosphines are available and due to their ability to stabilise a broad range of oxidation states, they are considered very useful in catalytic reactions.

Phosphines with organic moieties are most commonly used as ligands in metal catalysis. Organo-phosphines (PR_3) are neutral 'soft' donor ligands. They primarily function as Lewis bases, interacting with metals as dative σ-donor ligands which simultaneously increases the electron density and steric crowding at the metal centre (figure **1.3i**). Additionally, they are able to accept electron density from metal p- or d-orbitals due to the presence of low energy LUMO's. Initially, it was thought that the back donation from the metal occurred into the empty, low energy P-R d-orbitals, forming an M-P π-bond. Recent work has found this not to be the case and has suggested that back bonding in fact populates the P-R σ*-antibonding

orbitals, owing to their lower energy and π-symmetry.[18] The strength of this π-acidity is highly dependent on the R-substituents on the PR_3.[22]

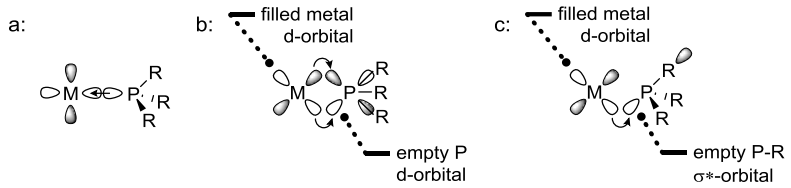


Figure 1.3 i) lone-pair donation to an empty metal d orbital ii) back-bonding between metal and the phosphine ligand d-orbitals iii) back-bonding between metal and the phosphine ligand σ*-orbitals

The steric demands of phosphine ligands also play a large role in affecting the reactivity and stability of the catalyst.[23] For example, if dissociation of one of the phosphine ligands leads to the formation of the active catalyst, the bulk can determine the position of this equilibrium. The bulky nature of the phosphine could result in dissociation of one of the ligands, leading to a vacant site and formation of an active catalyst. Conversely, the bulky phosphine may inhibit the approach of the substrate, shutting down the reaction. It is therefore important to consider the bulk of the phosphines for different catalytic reactions. Other factors like the number of phosphorus chelates and the hemilability of the ligand can also have an impact on the nature of the metal complex.[24]

Mechanistically, rhodium presents a more flexible catalyst when looking at generalised catalytic cycles compared to more commonly used catalysts like nickel, palladium and platinum. When looking at a typical C-C bond forming process, group 10 metals such as nickel, palladium and platinum typically operate within catalytic cycles shuttling between 0 and +II oxidation states. As a result, transmetalation can only occur with the M(+II) species. In contrast, group 9 metals such as rhodium, shuttle between the +I and +III oxidation states. As a consequence transmetalation can theoretically occur at two points in the catalytic cycle depending on the nature of the rhodium catalyst (anionic or cationic). This reaction pathway is illustrated in Figure 1.4 below.

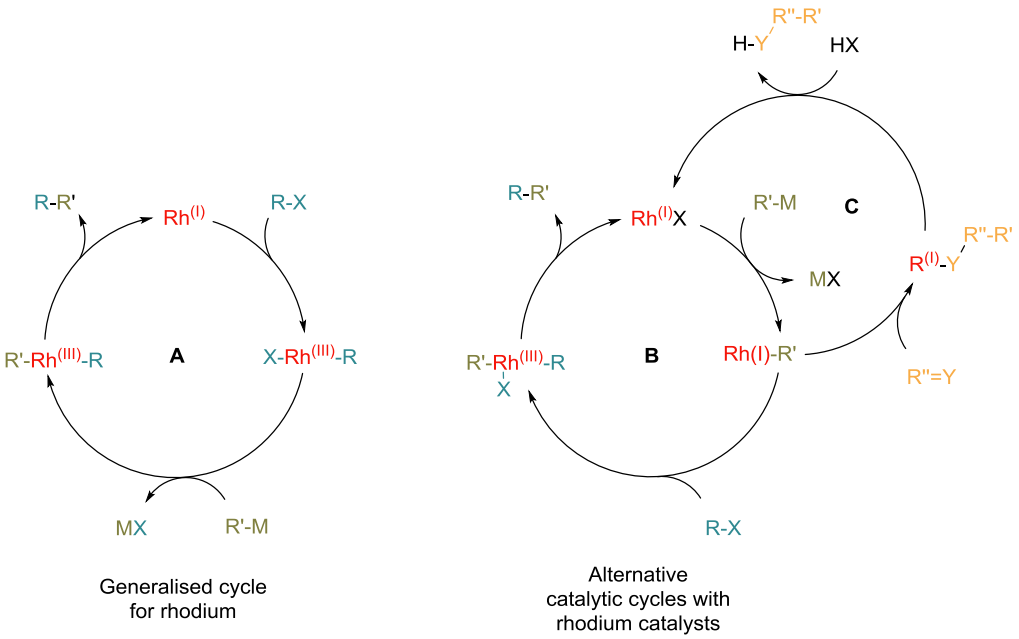


Figure 1.4 Possible catalytic cycles with rhodium catalysis

Both cationic and anionic rhodium catalysts can partake in coupling through the general catalytic cycle **A**. A suitable electrophilic component such as an aryl halide can oxidatively add to the complex, generating a Rh(III) metal centre. This then undergoes transmetalation with an organometallic component and subsequently reductively couples with the electrophile to produce the final product and regenerate the Rh(I) species. It is also possible that transmetalation can occur in the early stages of the catalytic cycle as illustrated by cycle **B**. A halide on the metal complex can be substituted with an organic group which then forms a stable organorhodium(I) complex. Since oxidative addition is still possible, addition of a suitable electrophile will allow the cycle to continue and result in the product and regeneration of Rh(I). Alternatively, the transmetalated product can be coupled with unsaturated organic compounds resulting in the addition of H and R across the unsaturated unit, as demonstrated in cycle **C**.

1.4 C-S Bond Activation

As mentioned previously, cross-coupling reactions utilising (pseudo)halides remain the most studied electrophilic partner in this field. Great advances have also been made in the activation of C-H, C-C and C-N bonds, with a wide range of new catalysts and ligands contributing to the success in this area.[1,25] The increased understanding of mechanistic aspects has encouraged chemists to develop and explore the scope of these reactions, which can be demonstrated by the plethora of literature available.

Despite the abundance of literature relating to cross-coupling reactions, relatively little work has been undertaken in employing thioorganic compounds as electrophiles in C-Heteroatom bond activation. C-S bonds are widely present in natural products and potential drug targets. Their activation, cleavage and transformation *via* transition metal catalysis is becoming increasingly important in organic chemistry.[26,27] The C-S bond is somewhat easier to activate than C-H, C-N or C-O bonds due to its lower bond strength when comparing bond dissociation enthalpies (H_3C-S 307.8 $kcalmol^{-1}$, H_3C-H 438.6 $kcalmol^{-1}$, H_3C-N 356.0 $kcalmol^{-1}$, H_3C-O 385.7 $kcalmol^{-1}$); while oxidative addition to the C-halide bond is notably easier compared to the C-S bond.[28] However, the lack of examples exhibiting metal-catalysed C-S activation could be in part due to the formation of strong metal-sulfur bonds which can prevent catalyst turn-over.[29] Hence, the key in promoting catalysis with thioorganic compounds is to activate stable M-S bonds between the soft sulfur atom and the relatively soft transition metal centre.

A number of C-S activation reactions under stoichiometric conditions using a range of transition metals have been reported, but only a limited number of catalytic examples are known. In this context, most couplings have been undertaken using sulfur compounds such as sulfonyl chlorides, sulfoxides and sulfones, whilst relatively little work has been reported utilising thioorganics of low sulfur oxidation, such as thiol ethers, thiol esters and other related thiol-derived functional groups.

1.5 Overview of Metal-catalysed C-C bond formation *via* C-S Bond Activation

1.5.1 Thiol esters

In the sole presence of a palladium catalyst, simple thiol esters and boronic acids do not participate directly in cross-coupling reactions. In 2000, Liebeskind and co-workers demonstrated an efficient palladium-catalysed thiol ester-boronic acid cross-coupling, utilising an alkylating agent **1** that is appended to the thiolate residue (Figure **1.5**).[30] A system using 5 mol% palladium catalyst produced ketones ranging from average to excellent yields (51-100%). No reaction occoured in the absence of the alkyalting agent. The authors inferred that alkylative conversion of the very stable palladium–thiolate bond to a labile palladium–thiol ether bond is crucial to the catalysis. Notably, the role of the NaI is also imperative in this transformation. The generation of the alkyl iodide from the bromide could lead to the formation of the highly reactive acyl sulfonium salt **2** which could go on to react with the boronic acid to afford the ketone product. Additionally, the iodide could potentially ligate to the palladium and generate an anionic acyl-palladate, which increases electron density for the alkylative step.

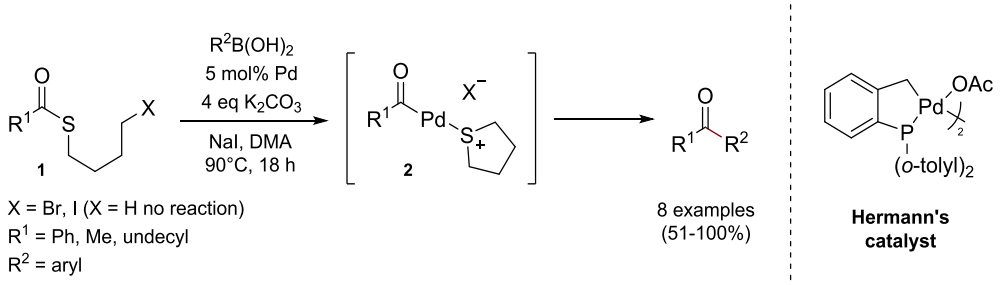


Figure 1.5 Thiol ester cross-coupling using alkylative activation

Following the discovery of the alkylative activation protocol, a new synthetic method was developed that takes place at neutral pH without the requirement for thiolate alkylation. Liebeskind and Srogl reported the first examples of palladium-catalysed, copper mediated cross-coupling between thiol esters and boronic acids under neutral conditions (Figure **1.6**).[31]

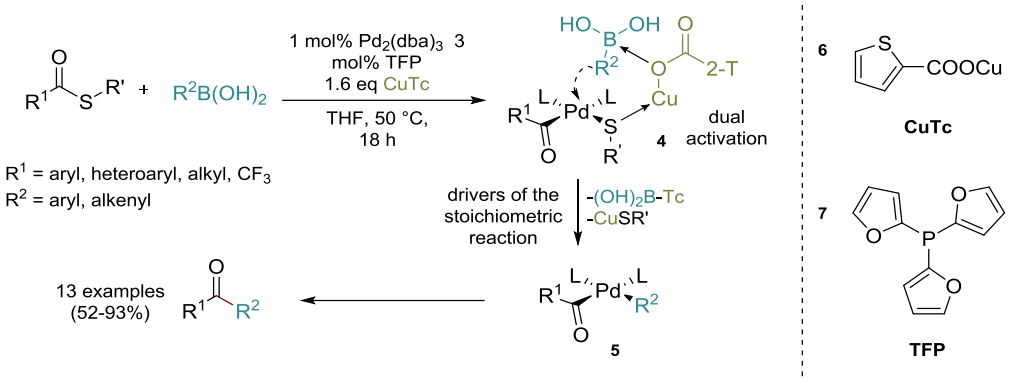


Figure 1.6 'First generation' of the Liebeskind-Srogl copper-mediated thiol ester-boronic acid cross-coupling

A variety of alkyl and (hetero)aryl thiol esters were investigated, including examples of electron-rich and electron-deficient aromatic thiol esters as well as α-substituted and hindered aliphatic thiol esters. To this they coupled a number of aryl and alkenyl boronic acid reagents, producing ketones in 52-93% yields. Interestingly a stoichiometric amount of CuTc **6** is needed to mediate the catalytic reaction along with 1 mol% palladium and 3 mol% TFP **7**. The desulfitative cross-coupling can be rationalised in terms of a joint thiophilic/borophilic effect. The copper(I) coordinates to the sulfur, activating the palladium-thiolate bond and simultaneously activating the boron compound through coordination of the carboxylate to the trivalent boron centre **4**. Thus, the polarisable copper(I) is consumed, 'scavenging' the thiolate from the reaction cycle by forming a thermodynamically strong Cu-SR bond. When the copper(I) carboxylate was replaced with copper(I) halide no coupling product was observed, highlighting the importance of the carboxylate. In addition, a change of metal to zinc afforded no product even though it is known as an effective thiophile. This reaction is known as the first generation of the Liebeskind-Srogl cross-coupling reaction.

The scope of boron reagents compatible with the Liebeskind-Srogl reaction was soon broadened to aliphatic boron nucleophiles (Figure **1.7**).[32]

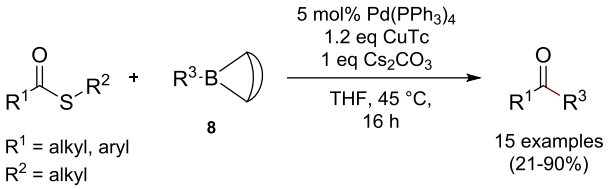


Figure 1.7 Coupling of thiol esters with aliphatic organoboron BBN reagents

Analogous to traditional Suzuki cross-coupling, alkyl-boranes suffer from low reactivity issues in cross-coupling reactions. Initially, bulky B-alkyl-9-BBN (**8**) reagents performed poorly in the Liebeskind-Srogl coupling under neutral conditions, presumably due to their bulky nature preventing dual activation by the CuTc of the C-S bond and the boronate. Therefore, it was rationalised that a base was required to activate the boron reagent. Under these modified Liebeskind-Srogl conditions employing $Pd(PPh_3)$ as a catalyst, a variety of aryl-alkyl and dialkyl ketones were synthesised in poor to excellent yields (21-90%).

The mildness and versatility of the Liebeskind-Srogl reaction was demonstrated by its compatibility in peptide chemistry. Liebeskind and co-workers described a successful example of cross-coupling of *N*-protected mono-, di- and tri-peptides with aryl, heteroaryl or alkenylboronic acids (Figure **1.8**).[33]

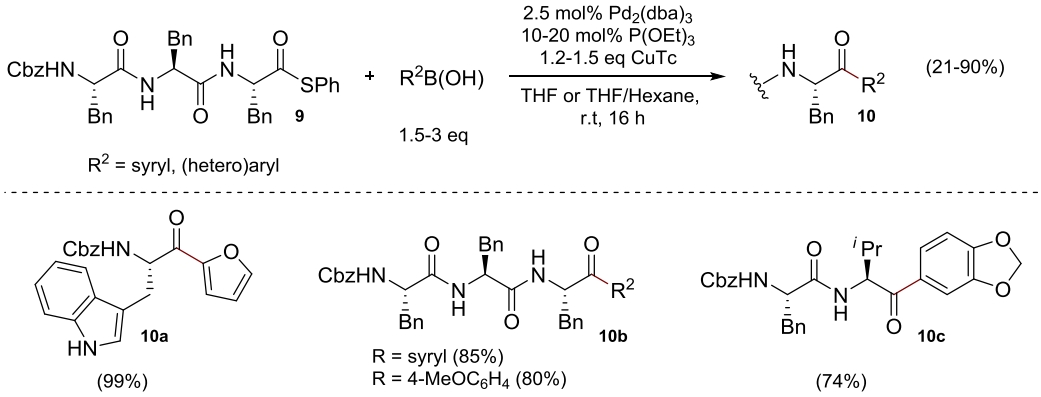


Figure 1.8 Mono, di, tripeptide thiol ester-boronic acid coupling

In the presence of stoichiometric CuTc and catalyst $Pd_2(dba)_3/P(OEt)_3$ the corresponding pH-sensitive, *N*-protected peptidyl ketones were produced in high yield and high enantiopurity. The small and weakly donating $P(OEt)_3$ ligand was found to be essential in eliminating the decarbonylative-β-hydride elimination side reaction. They presumed that this poorly basic and ligand would fill coordination sites at Pd but not attenuate electrophilicity and thus not suppress transmetalation. The peptidyl ketone synthesis proceeded at ambient temperature while completely preserving the configuration of stereogenic centres and demonstrated a high tolerance for unprotected sensitive polar functionalities.

Its application was also demonstrated by Yang, in an elaborate six-step total synthesis of highly enantiomerically pure (-)*D*-erythro-sphingosine (Figure **1.9**).[34] Treatment of *N*-Boc- and *O*-TBS-protected serine thiophenyl ester **11** with (*E*)-1-pentadecenylboronic acid **12** in the presence of a palladium catalyst and copper(I) carboxylate delivered **13** in high yield (94%) and high enantiomeric purity (> 99% ee).

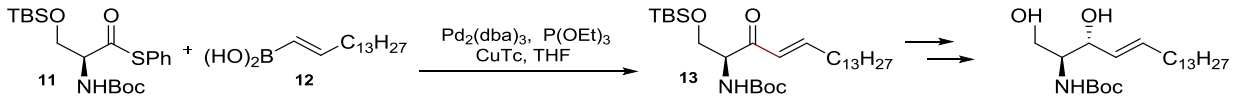


Figure 1.9 The use of Liebeskind-Srogl reaction in a practical and scalable route to (-)-D-*erythro* sphingosine

The use of organostannanes as effective coupling partners with thiol esters was first introduced by Liebeskind. This represented an extension of the thiophilic activation methodology described previously using boronic acids and relies on the same palladium, copper(I), base-free protocol (Figure **1.10**).[35]

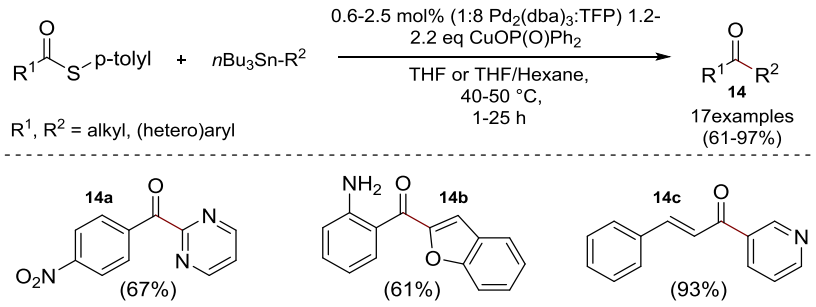


Figure 1.10 Cross-coupling of thiol esters with organostannanes

Treatment of thioesters and *tert*-butylorganostannanes with commercially available $Pd_2(dba)_3$/TFP and stoichiometric CuDPP provided the desired ketones in 61-97% yield. It is not clear if the copper(I) diphenylphosphinate is associated with the activation of the stannane but it does play a key part in S-Pd bond activation and aids in the removal of tin in the work up. This variant broadens the scope of nucleophiles due to the fact that some stannanes are more accessible than boronic acids. Furthermore, various α-heteroatom heteroarylboronic acids are very sluggish in cross-coupling.

Its advantages are also demonstrated by Liebeskind's report on the efficient synthesis of highly enantiopure *N*-protected α-amino ketones **16** (Figure **1.11**).[36]

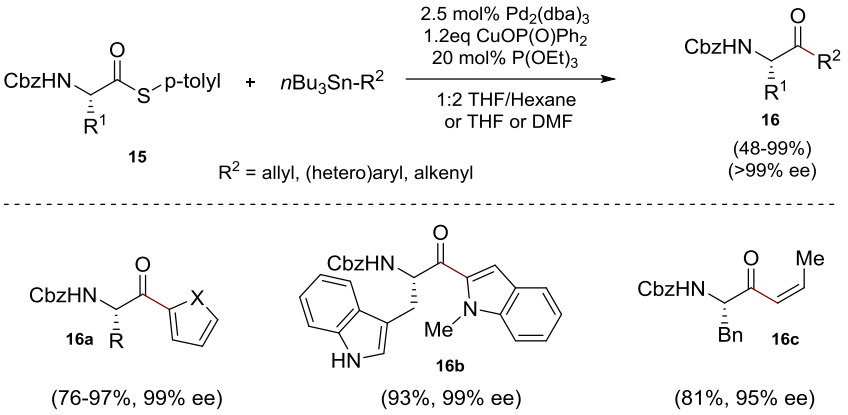


Figure 1.11 Peptidic thiol ester-$RSnBu_3$ cross-coupling

This work is analogous to previous examples using boronic acids but provides the advantage of using only 1.1 eq of the stannane coupling partner, and significantly, π-deficient heteroaromatic peptidyl ketones can be prepared which are important in drug design. Subsequently, this methodology was successfully applied in the synthesis of a family of mono and 1,1'-*bis*-substituted ferrocenyl-aryl ketones.[37]

The Liebeskind-Srogl reaction can also be applied in a natural product synthesis protocols. An elegant six-step enantioselective total synthesis of the (1*R*,5*S*) stereoisomer of litseaverticillol B was described by Kawahara and co-workers (Figure **1.12**).[38] The crucial intramolecular C-C bond

forming step in **17** proceeds smoothly under microwave irradiation for 1 h to form the cyclic product **18.**

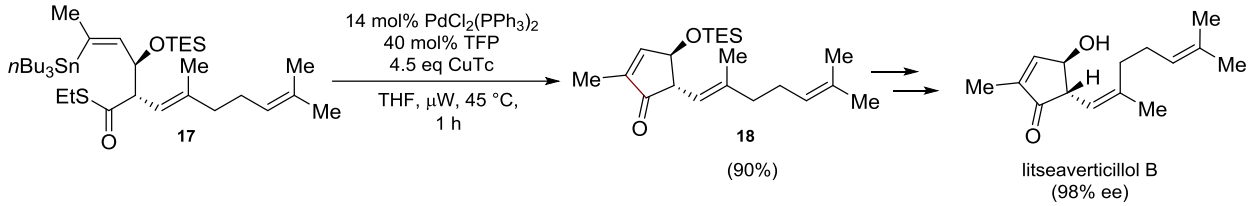


Figure 1.12 Total synthesis of litseaverticillol B. Pd/Cu-mediated intramolecular coupling of the stannylated thiol ester **17**

As mentioned previously, the key obstacle to catalytic turnover in C-S activation is the high stability of the M-S bond following the oxidative insertion of the metal. If the organometallic coupling partner is thiophilic enough, then the weakening of the M-S bond could feasibly drive the catalysis without the aid of a copper(I) activator. Using this rationale along with Pearson's Hard-Soft Principle led Liebeskind and co-workers to consider the use of triorganoindium reagents (Figure **1.13**).[39]

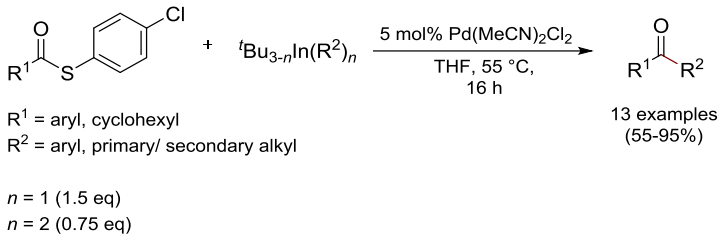


Figure 1.13 Palladium-catalysed coupling of thiol esters with organoindium reagents

In the presence of sub-stoichiometric $Pd(MeCN)_2Cl_2$ the reaction of thiol esters with aryl, primary and secondary alkyl organoindium reagents produced ketones in good to excellent yields (55-95%). Due to their low reactivity, alkylindium reagents provide a high degree of chemo-, regio-and stereoselectivity as well as good functional group compatibility. This method has two main advantages over the coupling of thiol esters with organoboronates or organostannanes; (a) no added copper reagent is required to mediate the reaction, and (b) in the case of alkyl transfer, no added base is required to activate organoindium reagents for cross-coupling, in contrast to alkyl boron reagents which require a base to initiate the reaction. The variety of nucleophilic reagents compatible with the cross-coupling of thiol esters is not limited to the cases mentioned above.

Seminal work by Fukuyama uses organozinc reagents effectively in a novel synthesis of ketones.[40] Since then, Stambuli and co-workers have ameliorated the reaction by developing a phosphine-free reaction of a diverse range of thiol esters and readily available organozinc reagents, using $Pd(dba)_2$ as a catalyst at room temperature, affording the corresponding diaryl ketones in yields of 61-93% (Figure **1.14**).[41]

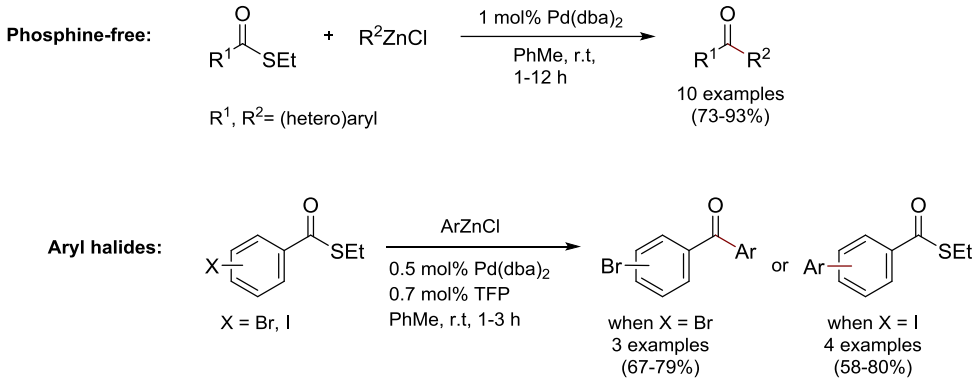


Figure 1.14 Phosphine-free Fukuyama-type cross-coupling of thiol esters.

Under the phosphine free conditions, a complex mixture of products was observed when attempting the coupling in the presence of aryl halides. Upon addition of TFP, bromine substituents are well tolerated and only the C-S activated cross-coupling products are obtained. In the case of iodine substitution only the corresponding Negishi products were formed albeit in good yields.

Recently, Reisman and co-workers have published examples of the cross-coupling of secondary organozinc reagents with thiol esters (Figure **1.15**).[42] Unsymmetrical ketones were formed using a $Pd_2(dba)_3$, PCy_3, $ZnCl_2$ system that furnishes ketone products in a convergent fashion.

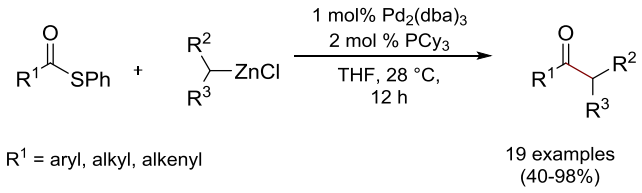


Figure 1.15 Palladium-catalysed Fukuyama cross-coupling of secondary organozinc reagents for the direct synthesis of unsymmetrical ketones

Interestingly, Seki and co-workers revealed the first Fukuyama reaction to be catalysed by a nickel complex (Figure 1.16).[43]

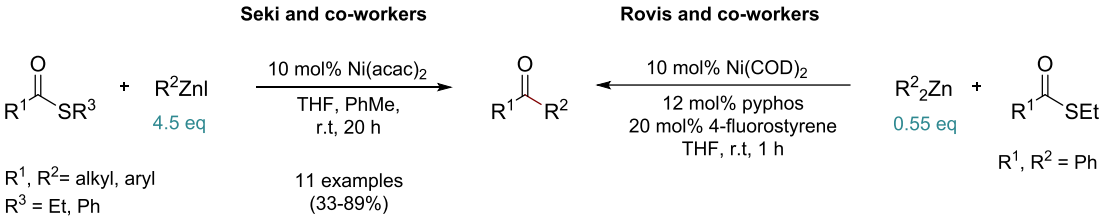


Figure 1.16 Nickel-catalysed organozinc-thiol ester cross-coupling

They coupled a range of thiol esters but required the use of 4 eq of organozinc reagent to produce the ketone products. Two years later, Rovis and co-workers elaborated on this system by coupling an impressive range of acid derivatives, which include thiol esters, using an air stable $Ni(acac)_2$ catalyst and only half an equivalent of diorganozinc starting material.[44]

In 2008, Van der Eycken and co-workers described the first desulfitative Hiyama-type cross-coupling protocol (Figure 1.17).[45]

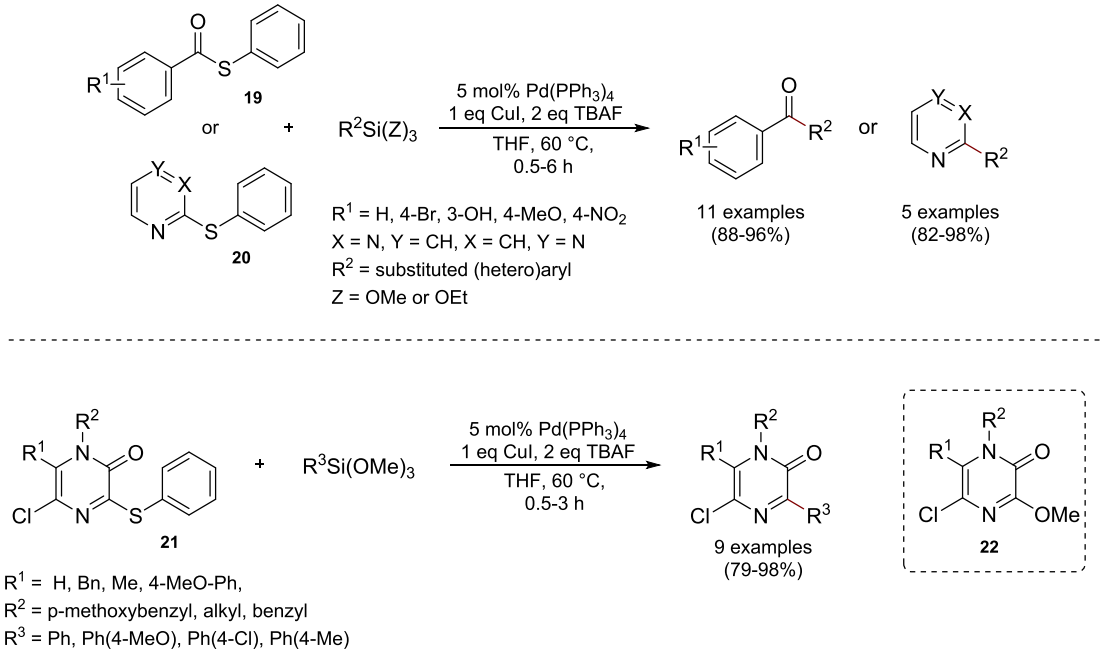


Figure 1.17 Palladium-catalysed desulfitative Hiyama-type cross-coupling

The authors coupled various arylsiloxanes with both thiol esters 19 and thiol ethers 20 which was exemplified by the arylation of substituted arylpyrazinones 21. In establishing this methodology, they unexpectedly found that when applying standard Hiyama conditions with selected pyrazinones and trimethoxyphenylsilane, the reaction produced the methoxylated compound 22 as the major product. They discovered that by adding CuI, they could effectively suppress the formation of 22 and selectively form the arylated products. Using TBAF to activate the siloxane, 5 mol% of $Pd(PPh_3)_4$ as a catalyst and CuI as the cofactor, the corresponding arylated pyrazines were produced in excellent yields. The methodology was successfully applied to benzophenones and heteroaryls. Notably, the use of methyl and vinylsiloxanes proved to be incompatible under these conditions. The advantages of using silanes over previously mentioned coupling partners (tin and boron complexes) is that they are environmentally benign and safe to prepare and handle.

1.5.2 Thiol Ethers and Related Substrates

Prior to Van der Eycken's work using heteroaryl sulfides in palladium-catalysed cross-coupling, other groups had demonstrated their applications in metal-catalysed C-S activation reactions.

Taking inspiration from their first generation catalytic system, Liebeskind and co-workers showed that a variety of thioorganic starting materials could allow for successful desulfitative C-C bond formation. These additional substrates include thioalkynes, methyl thiopseudourea derivatives, benzyl thiocyanates and (hetero)arylthiol ethers.

Alkynes are important building blocks in organic synthesis, materials science and polymer chemistry.[46] In 2001, Liebeskind and co-workers described the coupling of functionalised thioalkynes with boronic acids by again exploiting the use of a palladium catalyst and copper additive (Figure 1.18).[47]

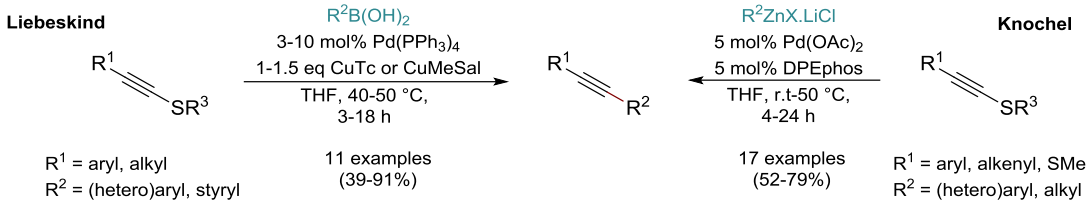


Figure 1.18 Examples of palladium-catalysed alkynylation

The reaction produced symmetrical and unsymmetrical alkynes, providing an alternative to the traditional Sonogashira reaction. Oxidative addition of the C-S bond of the thioalkyne to the palladium(0) centre was confirmed by the isolation of the alkynyl palladium thiolate. At the start of this decade, Knochel and co-workers reported a palladium-catalysed cross-coupling reaction of substituted organozinc compounds with thiomethylated alkynes (Figure **1.18**).[48] Using palladium and DPEPhos, a wide range of functional groups were tolerated and various classes of zinc reagents (alkyl, aryl, and heteroaryl) were utilised.

Liebeskind's coupling methodology was again expanded by the use SEM-protected methyl thiopseudoureas **23** (Figure **1.19**).[49]

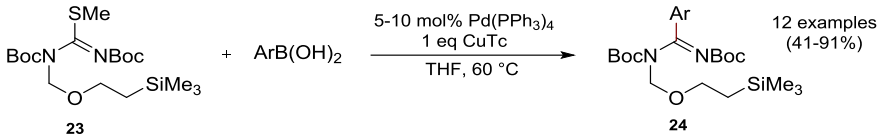


Figure 1.19 Synthesis of fully protected benzamidines

After SEM-protection of a commercially available precursor, it was then treated with palladium and a boronic acid in the presence of CuTc to afford the fully protected benzamidines **24** in good to excellent yield (41-91%).

Metal-catalysed cyanations are useful and important transformations in synthesis. Aryl nitriles are a significant class of compounds that are not only functional constituents of dyes and herbicides, but also useful components of many natural products and pharmaceuticals. They still prove to be challenging to prepare due to the tendency of the excess cyanide anion to poison the metal catalyst. In 2006, as a further examination of the scope of thioorganic cross-couplings, the reaction

of benzyl thiocyanates with boronic acids (aryl, heteroaryl and alkenyl) was explored (Figure **1.20**).[50] This non-basic cyanation reaction proved general and high yielding for all but the most electron-deficient boronic acids using benzyl thiocyanates.

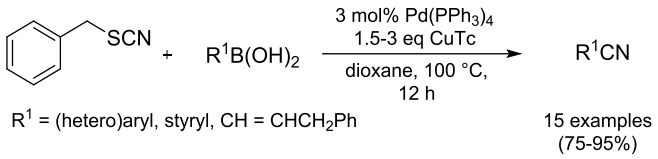


Figure 1.20 A cyanide-free cyanation of boronic acids

Tang and co-workers demonstrated a means of introducing benzyl groups to various substituted aryls (Figure **1.21**).[51] In the presence of $FeBr_3$ without any solvent, the authors showcased alternative reactivity of the thiocyanates by apparent activation of the sp^3C-S bond in a catalytic dethiocyanation reaction. This reaction is based on Friedel–Crafts-type reactions.

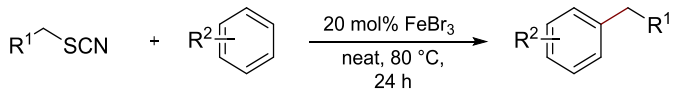


Figure 1.21 Synthesis of diarylmethanes by Fe-catalysed Friedel–Crafts-type reaction

One of the main applications of the desulfitative cross-coupling reactions has been the decoration of heteroaromatic rings. The enhanced reactivity of heterocyclic thiol ethers can be rationalised in terms of the π-deficient aromatic core. The ring must always have an electronegative atom in the *α*-position to the sulfide leaving group, increasing its activity towards metal catalysts. Heterocyclic structures have long been important to the pharmaceutical industry[52]. In recent years, heterocycles have been successfully applied as scaffold systems for lead discovery and research for biological activity *via* the combinatorial and parallel medicinal chemistry formats.[53]

Originally, Grignard reagents were the first organometallic partners to be coupled across thiosulfide-substituted heteroaryl C-S bonds in a catalytic fashion by a nickel complex.[54] Later,

inspired by metalloenzyme-induced biotransformations, Liebeskind and co-workers reported the activation of (hetero)aryl benzyl sulfonium salts using both Pd and Ni catalysts (Figure **1.22**).[55,56]

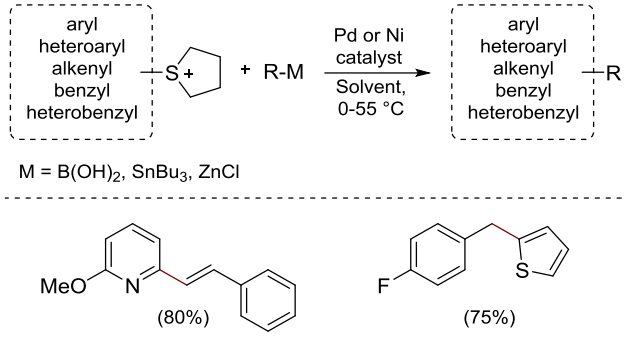


Figure 1.22 Sulfonium salts as coupling partners with a variety of nucleophilic reagents

Their work showed that various electrophiles could undergo smooth cross-coupling reactions with organostannanes (Stille-type reactions), (hetero)aryl boronic acids (Suzuki-Miyaura-type reactions) and (2-thienyl)zinc chloride (Negishi-type reactions) showcasing an impressive range of more modern, functionally tolerant nucleophiles which proved to be effective in aryl-C-S bond activation processes.

Casalnuovo and co-workers were the first group to successfully report cross-coupling of simple methylthio-substituted heterocycles without using Grignard reagents (Figure **1.23**).[57]

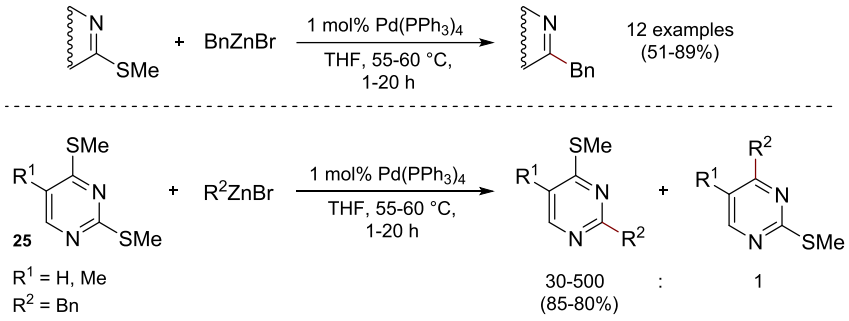


Figure 1.23 The first examples of heteroaryl methylsulfide cross-coupling

The reactions were typically carried out using $Pd(PPh_3)_4$ and either benzylzinc bromide or 3-(trifluoromethyl)benzylzinc bromide to afford a variety of heterocyclic products in moderate to good yields. Unlike the nickel-catalysed Grignard cross-coupling reactions, their experiments

suggest that the methylthio group must occupy a position activated towards nucleophilic substitution in order for cross-coupling to occur. 2-(Methylthio)pyrimidines were particularly reactive substrates in this reaction. As a result, the regioselectivity of 2,4-bis(methylthio)pyrimidines **25** was found to be opposite to that of their 2,4-dichloropyrimidine analogues. This offers the possibility to prepare important heterocyclic compounds.

Leading on from their seminal work using thiol esters, Liebeskind and Srogl reported an extension of their cross-coupling reaction to heteroaryl thiol ethers with boronic acids (Figure **1.24**).[58]

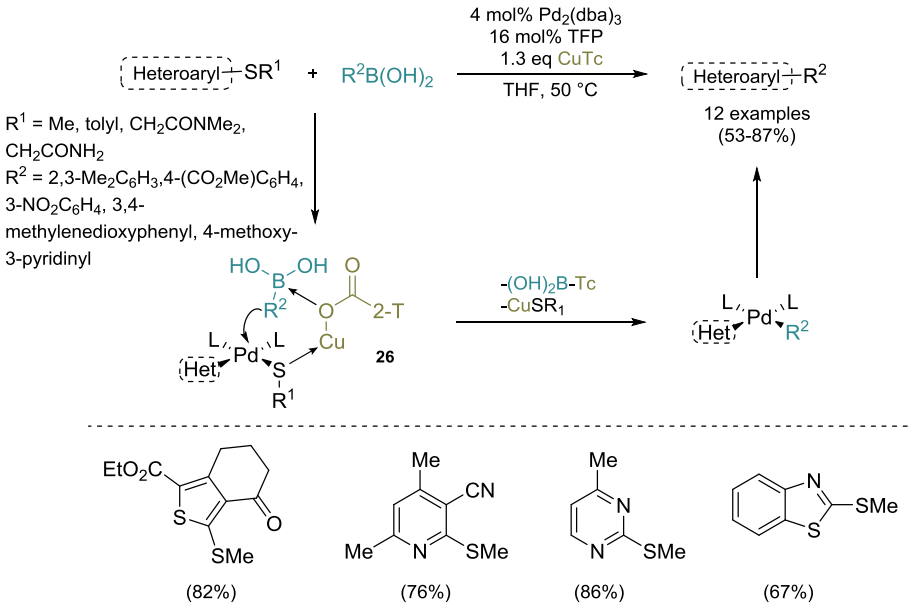


Figure 1.24 Liebeskind-Srogl cross-coupling of heteroaryls and boronic acids

The best results were obtained when they used a Pd_2dba_3/TFP catalytic system and allowed for the effective synthesis of important medicinally relevant compounds. The scope of methylsulfide-substituted heteroaryls ranged from pyridines to pyrizines, benzoxazoles and benzothiazoles. The proposed mechanism of this Suzuki-Miyaura-type cross-coupling reaction is shown in Figure **1.24**. It implies the formation of the intermediate **26** resulting from the oxidative addition of the Csp^3-S bond to the palladium. Coordination with the CuTc and the boronic acid provides the activation for the next step, analogous to the thiol ester reactivity. In the specific case of coupling 2-(methylthio)benzothiazole with 3-pyridylboronic acid, the addition of $Zn(OAc)_2$ significantly

improved the reaction. They presumed that the $Zn(OAc)_2$ may aid the reaction by tying up basic nitrogen atoms that could potentially interfere with the reaction system.

A year later, an extension to this methodology was reported with the use of organostannanes as versatile reaction partners in cross-coupling reactions of heteroaryl thiol ethers.[59] Although this system somewhat overlaps with the analogous boronic acid-heteroaryl coupling system published earlier, the tin variant finds use in cases where stannanes are more accessible. In their investigation they discovered that a switch from heteroaryl-SMe ethers to heteroaryl-SAr ethers improved reactivity. They attributed this to the sluggish copper-mediated transmetalation from tin to the heteroaryl-PdL_2-SMe (**26**) intermediate. In both systems a variety of heteroaryl sulfides and organostannanes were cross-coupled when CuMeSal was present as an activator.

Van der Eycken and co-workers reported a previously unprecedented microwave-assisted C-S activation Sonogashira-type protocol for the alkynylation at the C-3 position of phenylsulfanylated pyrazinones **27** (Figure **1.25**).[60]

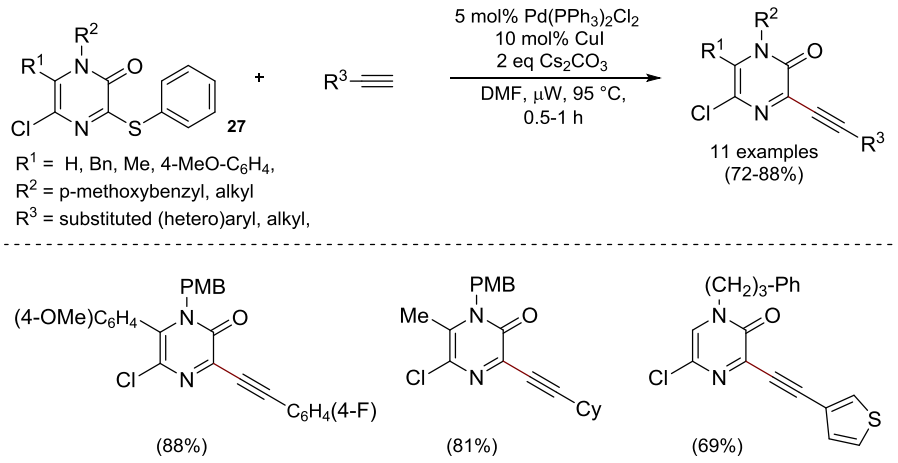


Figure 1.25 Sonogashira-type desulfitative C3-alkynylation of 2(1H)-pyrazinones

Using various acetylenes in combination with a sub-stoichiometric amount of palladium catalyst and CuI, the corresponding products were obtained in excellent yields. These optimized conditions were also extended to solid-supported pyrazinone affording the alkynylated compounds in good

yields.[61] This was the first example of cleavage from the resin without prior oxidation of the sulfur linker, employing a Sonogashira-type alkynylation.

Shook and co-workers reported an extension of the concept of desulfitative Sonogashira-type coupling on five and six-membered heterocycles (Figure **1.26**).[62] Using microwave irradiation, terminal alkynes were coupled affording alkynylated heterocycles in moderate to good yields.

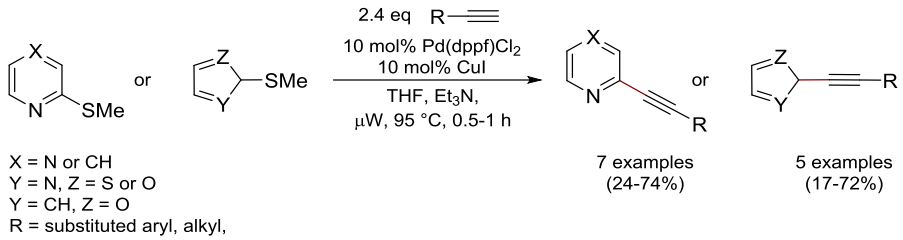


Figure 1.26 Sonogashira-type desulfitative alkynylation of heteroarylthio ethers

Finally, Hintermen and co-workers have demonstrated an elegant synthesis of aldehydes which are known to undergo autocatalytic amplification of chirality (Figure **1.27**).[63]

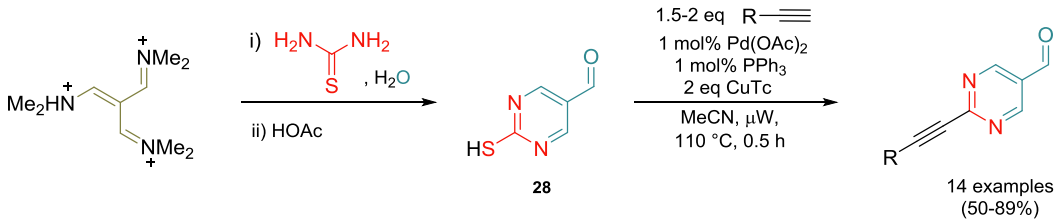


Figure 1.27 Synthesis of Soai aldehydes for asymmetric autocatalysis by desulfitative cross-coupling

The authors used palladium catalysed dehydrosulfurative Liebeskind–Srogl coupling of terminal alkynes with aldehyde **28** under base-free conditions providing alkynyl-substituted aldehydes. This Sonogashira-like coupling illustrates the elegance of dehydrosulfurative Liebeskind–Srogl-type couplings, which start from thio-heterocyclic building blocks as electrophiles, rather than introducing leaving groups in extra synthetic steps.

Using the standard Liebeskind-Srogl conditions: a sub-stoichiometric amount of palladium source ($Pd(PPh_3)_4$ or Pd_2dba_3) with a stoichiometric amount of copper(I) additive (CuTc or CuMeSal) has allowed for a variety of other heteroaromatic ring systems to be furnished.

Guillaumet and co-workers published a series of papers investigating the desulfitative C-C couplings of (tetra)triazines boronic acids and organostannanes (Figure 1.28, 29).[64,65,66]

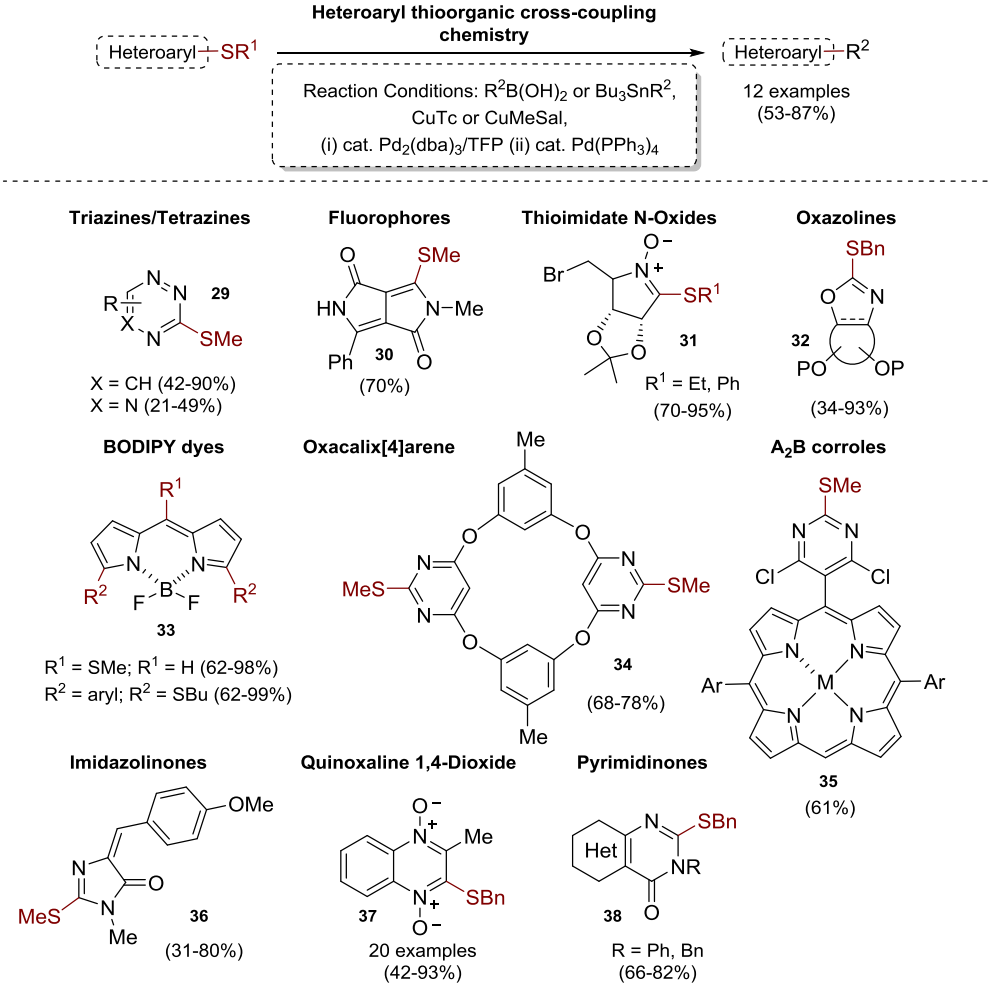


Figure 1.28 Thiol-substituted heteroaryl partners that participate in C-S activated cross-coupling

Additionally, Dehaen and co-workers displayed the generation of fluorophores 30, as well as corroles 35 which were furnished using the same reaction conditions.[67,68] The same group also showed the synthesis of diversely functionalised oxacalix[2]arene[2]pyrimidines 34 by two efficient postmacrocyclisation pathways.[69] Furthermore, a method has been developed to

prepare aryl and vinyl-substituted cyclic ketonitrones **31**, from *d*-ribose derived cyclic nonaromatic thiomidates *N*-oxides.[70] This has recently been extended to quinoxaline derivatives **37**, again by using conditions initially developed by Liebeskind and Srogl for the cross-couplings of (hetero)aromatic thiol ethers.[71] Chemoselective cross-coupling reactions were demonstrated in BODIPY dyes **33**, with several of the BODIPY derivatives displaying emission in the near-infrared region.[72,73,74] As well as oxazolines **32**, sulfide substituted imidazolinones **36** and pyrimidinones **38** have all been subjected to Liebeskind-Srogl cross-coupling conditions with both boronic acids and organostannane reagents producing broad scope products.[75,76,77]

Analogous to the work by Casalnuovo, organozinc reagents have been used in the functionalisation of heteroaryl compounds. Knochel and co-workers utilised different catalytic systems based on $Pd(OAc)_2$ or $Ni(acac)_2$ in combination with Buchwald ligands that were developed for C-heteroatom bond formation, *S*-Phos or DPE-Phos, to give best results (Figure **1.29**).[78] Heterocyclic thiol ethers **39** based on a pyridine, pyrimidine, pyrazine, pyridazine, triazine, benzothiazole, benzoxazole, pyrrole, and quinazoline rings were all coupled with organozinc reagents with sensitive functionalities, such as ester, nitrile, or ketone groups. At the same time, Stambuli and co-workers reported the coupling to oxazoles **40** using similar nickel- and margnesium-catalysed conditions.[79]

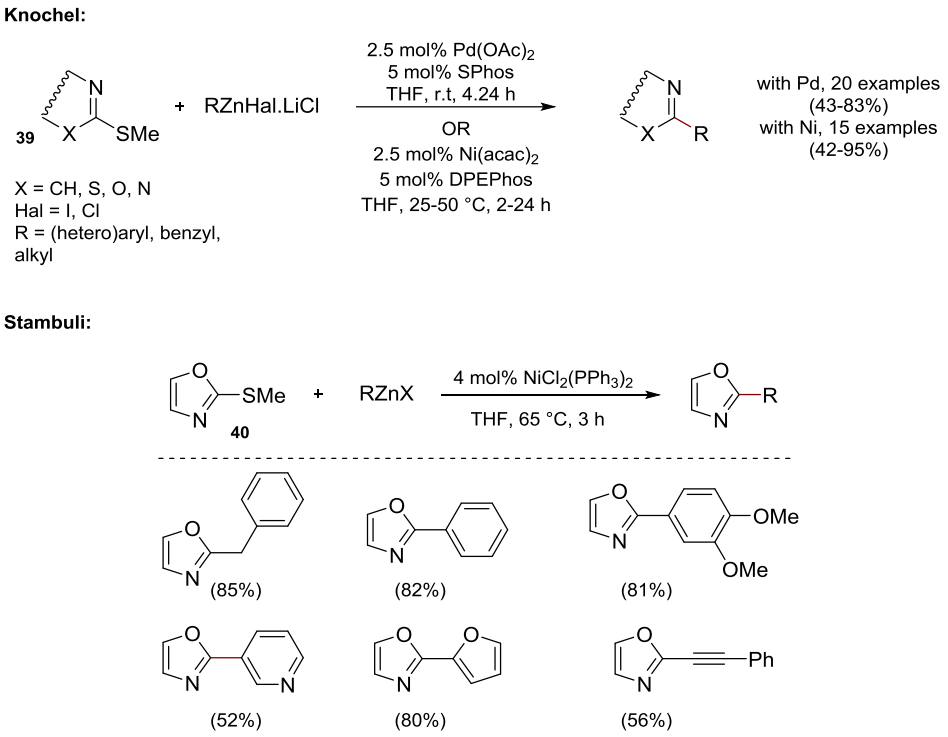


Figure 1.29 Functionalisation of heteroaromatic thiol ethers using organozinc coupling partners

1.5.3 Orthogonal Chemistry

The ability to discriminate between reactive sites is an essential tool in organic chemistry. When substrates possess multiple functionalities this task becomes increasingly difficult. Within the field of metal-catalysed C-S cleavage, the orthogonal activation of C-S bonds has been boosted by the discovery of the role of a copper(I) additive. The strong thiophilic nature of the copper(I) reagents make them essential for the selective reactivity of thioorganic compounds under Liebeskind-Srogl conditions. Due to this highly selective nature, orthogonal reactivity may be observed with appropriate nucleophiles and partners with multiple electrophilic centres (usually halides). To this end, the synthesis of substituted pyrimidinones **41** and **42** and cyclobutenedione **43** illustrates the chemoselectivity of the reaction by targeting a sulfide or a halide bond with the use of CuTc or a base, respectively (Figure **1.30**).[80,81]

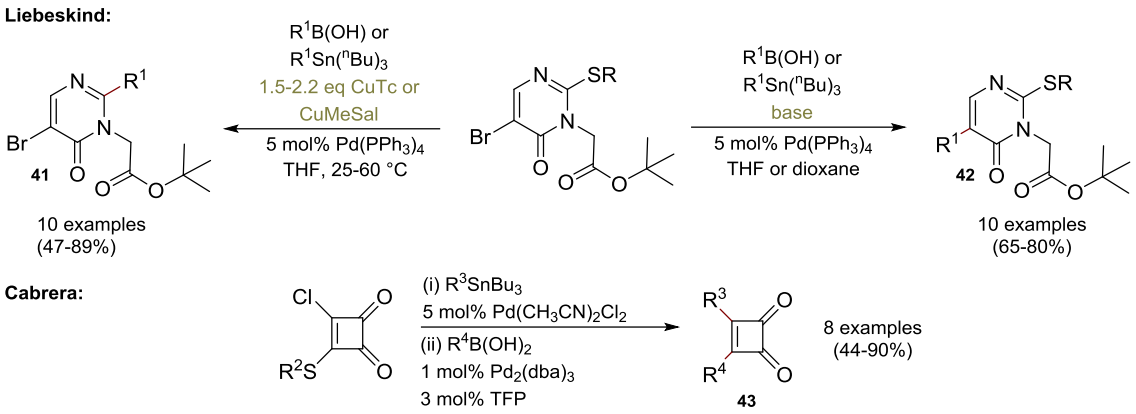


Figure 1.30 Tuneable catalysis: Liebeskind's synthesis of functionalised pyrimidinones. Cabrera's sequential Stille-Liebeskind/Srogl reaction of 3-chloro-4-arylthiocyclobutene-1,2-diones

Orthogonality has also been demonstrated in the construction of asymmetrical pyrimidines (Figure 1.31).[82] Initially the compounds were subjected to Suzuki conditions promoting coupling across the C-Cl bond. This was followed by a Liebeskind-Srogl cross-coupling at the C-S bond.

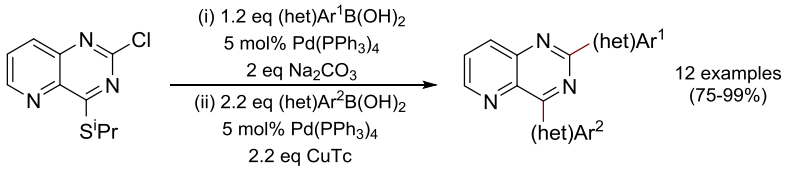


Figure 1.31 Tuneable catalysis: assymmetric 2,4-di(het)aryl-pyrido[3,2,d]pyrimidines *via* regioselective cross-coupling reactions

Another orthogonal procedure was developed for the generation of tetra-substituted pyrazines (Figure 1.32).[83] The 5-chloro-substituent **44** is suitable for derivatisation *via* Suzuki and Sonogashira coupling reactions, while the thiol ether moiety can be subjected to Liebeskind-Srogl coupling to yield asymmetrically substituted pyrazines.

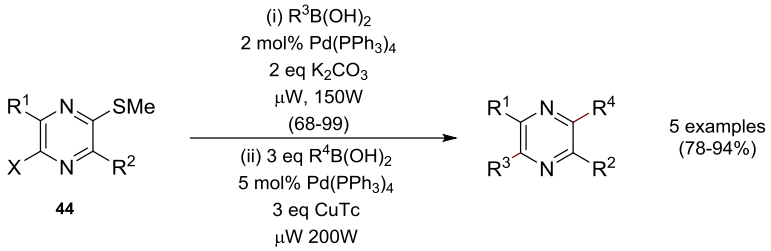


Figure 1.32 Tuneable catalysis: formation of asymmetrically substituted pyrazines

Selective *bis*-functionalisation of pyrimidines at their 2- and 4-positions was also achieved by Knochel and co-workers (Figure **1.33**).[84] They showed that both bromo- and iodo-functionalised pyrimidines could be coupled with organozinc reagents preferentially using a $Pd(dba)_2$/TFP system and could be proceeded by activation and cross-coupling of the sulfide by a $Pd(OAc)_2$/SPhos system, in one-pot.

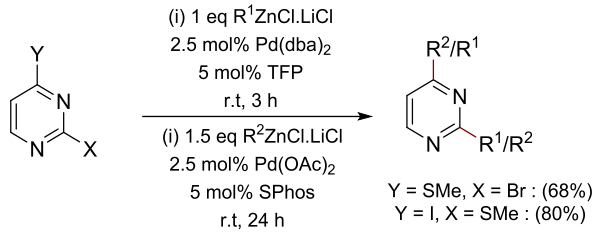


Figure 1.33 Selective one-pot cross-coupling reactions of 2-bromo-4-(methylthio)pyrimidine or 4-iodo-2-(methylthio)pyrimidine

1.5.4 Copper-Catalysed C-S Activation

A drawback of the 'first generation' of the Liebeskind-Srogl reaction is the requirement of a stoichiometric amount of copper(I) additive in combination with a catalytic amount of precious metal catalyst. These reactions are undertaken in an inert atmosphere to prevent oxidation of the expensive metal catalyst and of the cofactor to a copper(II) species. The requirement for a equivalent of copper(I) is fully understood and its role has been explained in previous sections: the copper(I) ion ligates to the thiolate through thermodynamically strong Cu-SR bonds, whereas a full equivalent of the borophilic carboxylate counterion activates the $-B(OH)_2$ moiety.[85]

Using this rationale, Liebeskind and co-workers presented a mechanistically unprecedented ketone synthesis involving the coupling of thiol esters and boronic acids under non-basic conditions (Figure **1.34**).[86,87]

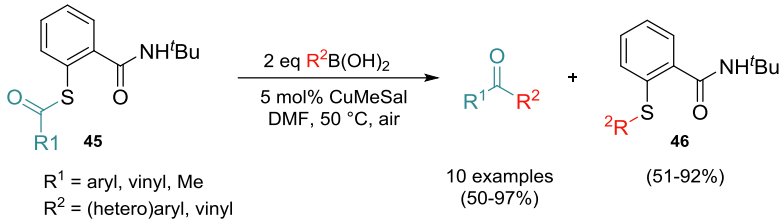


Figure1.34 'Second generation' Liebeskind/Srogl Pd-free Cu-catalysed aerobic cross-coupling

This 'second generation' desulfitative cross-coupling was developed using only a catalytic amount of copper(I) to mediate the reaction, with no other metal catalysts involved. They reasoned that to allow copper turnover, the strong Cu-SR bond must be cleaved in a way that removes both the thiolate from the reaction cycle and simultaneously regenerates the active copper species. Following this logic, the authors demonstrated that by coupling under aerobic conditions and using a second sacrificial equivalent of boronic acid they achieved this goal. Two equivalents of boronic acid are needed because the C-S bond of the thiol ester is cleaved and both the C- and S-residues are each arylated by an equivalent of the boronic acid which in turn returns an active copper species into the catalytic system. It is important to note that reactions only took place with thiol **45**, constructed with pendent amide tethers which are able to coordinate to the copper. Bulky -NH^{i}Pr and -NH^{t}Bu thiosalicylamides proved to be most effective and must be positioned *ortho* to the thioester. The arylation of this thiosalicylamide pendent formed product **46** in a 1:1 ratio with the desired product. The investigation showed that a variety of thiol esters and boronic acids could be coupled under aerobic conditions with 5 mol% CuMeSal and its novel synthetic utility was highlighted by the synthesis of peptides.

Further work by Liebeskind demonstrated a complementary anaerobic, copper(I) catalysed coupling of thiol esters and boronic acids (Figure **1.35**).[88] The anaerobic system was designed to only require one equivalent of the boronic acid rather than the two equivalents for the aerobic system previously discussed.

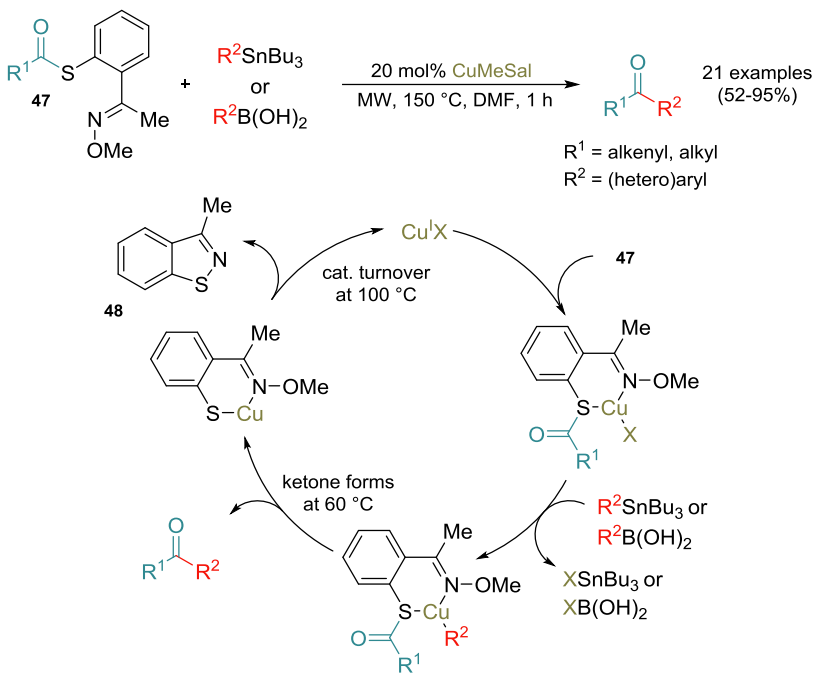


Figure 1.35 'Third generation' Liebeskind-Srogl anaerobic Cu-catalysed desulfitative chemistry: the assumed catalytic cycle

This 'third generation' cross-coupling takes inspiration from biological metallothionein systems. This system constitutes the exposure of a metal-bound thiolate ligand to a disulfide, which converts the strongly binding thiolate to a weakly binding disulfide ligand, liberating the metal from the protein through an *S*-centered oxidation. To mimic this, a thiol ester was designed bearing an *S*-tethered oxime **47**. Through the thiol ester-oxime N-O bond, an internal trap is present to mildly oxidise the copper(I) thiolate, resulting in the conversion of the strongly bonding thiolate to a weakly bound benzoisothiazole **48**. Crucially, this mild oxidative trapping mechanism releases the catalytically active copper species which can resume catalysing the C-C bond-forming reaction. The internal oxime group is not only involved in scavenging the sulfur but also lowers the barrier to reaction through pre-association of reactants. The system involved treatment of thiol esters with an equivalent of boronic acid or organostannane reagent in the presence of 20 mol% of CuMeSal under microwave irradiation. A range of boronic acids and organostannanes were explored and were coupled to aromatic, heteroaromatic, and aliphatic thiol esters. In some cases loadings of less than 20 mol% CuMeSal were tolerated.

1.5.5 Summary

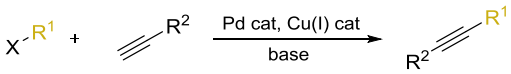
Since the start of the millennium, the majority of the work on C-C bond formation *via* C-S activation has revolved around the Liebeskind-Srogl reaction. Initially described for the synthesis of ketones from thiol esters and boronic acids, the method has been extended to a variety of thioorganics. This methodology has led to a number of interesting applications in heterocyclic and medicinal chemistry, peptide and solid-phase synthesis and the total synthesis of natural products. Previously existing methods for catalytic C-C bond construction from thioorganics required highly nucleophilic Grignard and organolithium reagents which are unsuitable for the synthesis of more complex multifunctional substrates, which require a higher degree of chemoselectivity. Groups have shown that by utilising Fukuyama-type chemistry, C-C bond construction from thiol esters and ethers can be achieved without a stoichiometric amount of copper cofactor but is limited to organozinc coupling partners. Moreover, Liebeskind and co-workers have demonstrated a 'third generation' catalytic system harnessing the chelating abilities of nitrogen tethers to couple both organoboron and organostannanes using catalytic copper. All of the investigations so far, with the exception examples utilising Grignards have been conducted using 'activated' C-S bonds. Utilising the methodologies described in this chapter to design novel processes that can be conducted on 'non-activated' thioorganics, would not only enhance the potential of C-S activation, but also strengthen its importance as a synthetic tool for general C-C bond construction. It is this principle that will form the basis of this thesis.

Chapter 2: Rhodium-catalysed carbon-carbon bond construction using terminal alkynes and aryl methyl sulfides: An example of catalyst orthogonality

2.1 Introduction

2.1.1 The Sonogashira Reaction

Cross-coupling reactions of terminal alkynes with aryl or alkenyl halides in the presence of a metal catalyst, copper iodide and a base, are extensively used in organic chemistry and materials science for the preparation of alkynyl arenes and enynes. The process involves the formation of C-C bonds between sp and sp^2 centres and is known as the Sonogashira reaction (Figure 2.0). [89,90]



R^1 = aryl, heteroaryl, vinyl
R^2 = aryl , heteroaryl, alkenyl, alkyl, SiR^3
X = I, Br, Cl, OTf

Figure 2.0 The Sonogashira cross-coupling reaction

The Sonogashira reaction is used in numerous syntheses of natural products, such as enediyne antibiotics. It has also found use in the preparation of liquid crystals, conducting polymers and other engineering materials.[91,92] The reported coupling of aryl halides with alkynyl copper(I) species in 1963 by Stephens and Castro was the first example of a metal-mediated synthesis of arylacetylenes.[93] This investigation, along with seminal work by Kumada and Tamao, inspired the discovery of a palladium-catalysed method that did not require stoichiometric copper by Sonogashira and co-workers.[94,94] Since then the reaction has been used extensively and is viewed as one of the most important C-C bond forming reactions. Other metals have been employed as catalysts and have proven to be effective in this cross-coupling process, including nickel and gold.[94,95,96]

The Sonogashira reaction has been applied to vinyl halides, aryl iodides and bromides and more recently, aryl chlorides.[97,98] In the case of aryl iodides, the cross-coupling can sometimes be carried

out under mild conditions, such as at room temperature, but in general, the reaction times are relatively long. For aryl bromides, the reaction usually requires high temperatures. Subsequently, independent works by Buchwald and Fu harnessed the use of a bulky, electron rich phosphine ligand, $Pd(P^tBu)_3$ which resulted in a more active palladium catalyst system which could couple relatively inactive aryl bromides at room temperature.[99] Aryl chlorides, which show a much lower reactivity than bromo and iodo analogues, have been used only more recently. This low reactivity has been ascribed to their significantly lower tendency to undergo oxidative addition to Pd(0) in the catalytic cycle.

Although there has been an abundance of examples showcasing metal-catalysed cross-coupling reactions using the halide reactants mentioned above, relatively few have displayed site selectivity when molecules bear multiple electrophilic activating groups. The ability to effectively achieve monofunctionalisation through metal-catalysed cross-coupling can be a powerful synthetic tool, allowing rapid generation of molecular complexity. Currently, the "site-selective" Sonogashira reactions can only make use of highly functionalised substrates, which are not truly orthogonal. Investigations by Hu and co-workers into nickel-catalysed Sonogashira coupling using non-activated alkyl halides exploit the difference in reactivity of alkyl-X (X = I, Br, Cl) bonds, allowing them to develop coupling protocols selective for specific C-X bonds, leaning towards orthogonal functionalisation of alkyl halides.[101] The ability to perform Sonogashira reactions preferentially on less activated coupling partners could potentially make orthogonal reactions possible as shown in the figure below (Figure 2.1).

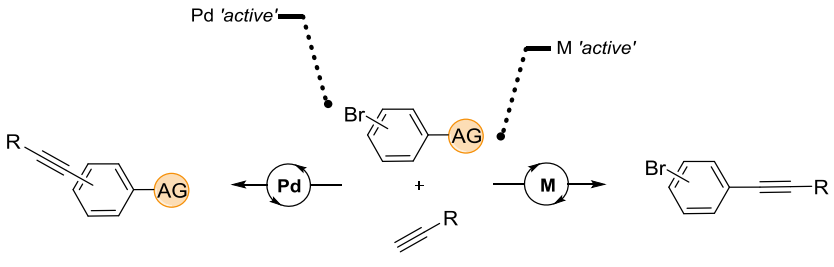


Figure 2.1 Potential orthogonal reactivity of the Sonogashira reaction

2.1.2 Previous Rhodium-Catalysed C-S Activation Protocols

As discussed in chapter **1.5**, the use of sulfides as activating groups in metal-catalysed cross-coupling has proved successful and can be achieved in a selective fashion in the presence of other electrophilic activating groups (chapter **1.5.3**). The use of thiophilic reagents aids the orthogonal activation of the C-S bond, but all known examples are limited to highly active hetero-aromatic substrates. In order to address this, previous members of the Willis group developed a Suzuki-coupling of aryl and alkenyl boronic acids with simple aryl and alkenyl methyl sulfides (Figure **2.2**).[100]

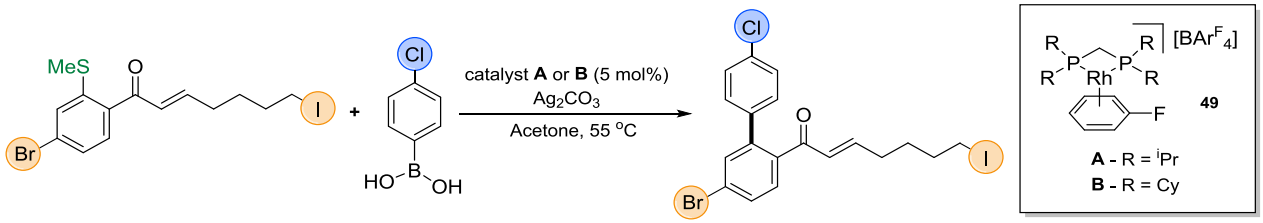


Figure 2.2 Rhodium(I)-catalysed Suzuki coupling of aryl and alkenyl boronic acids with simple aryl and alkenyl methyl sulfides (24 examples 56-95%)

It was discovered that the strong aryl-S bond possesses only limited reactivity towards standard palladium-Suzuki-/Miyaura cross-coupling conditions and alternatively the cleavage could be achieved using a rhodium-catalyst. The process employs the rhodium(I) pre-catalyst **49** incorporating a small bite-angle chelating phosphine ligand ($R_2PCH_2PR_2$, R = ^{i}Pr, Cy) and proceeds under mild conditions allowing for good functional group tolerance. Significantly, the aryl sulfide must have an *ortho*-directing group for the reaction to proceed. Additionally, as in previous C-S activation processes, the use of a thiophilic additive (Ag_2CO_3) is necessary for promoting the catalytic turnover. Impressively, multiple halide substituents could be incorporated on the aryl sulfide and the aryl boronic acid with no evidence of cross-coupling at these sites. Due to its high selectivity, the orthogonality of the developed reaction was demonstrated with Pd-catalysed coupling reactions of aryl halides. For example, aryl sulfide bromide **50** was coupled with phenyl boronic acid utilising both traditional and the developed Suzuki reaction conditions (Figure **2.3**). Initially, the use of a palladium catalyst resulted in cross-coupling at the C-Br bond to produce the

biaryl sulfide **51**. This compound would then be subjected to cross-coupling conditions using rhodium catalyst **49-A** to give the triaryl product **52**. Using compound **50**, the coupling process was repeated in reverse order to demonstrate the orthogonal flexibility of the new rhodium-catalysed Suzuki coupling.

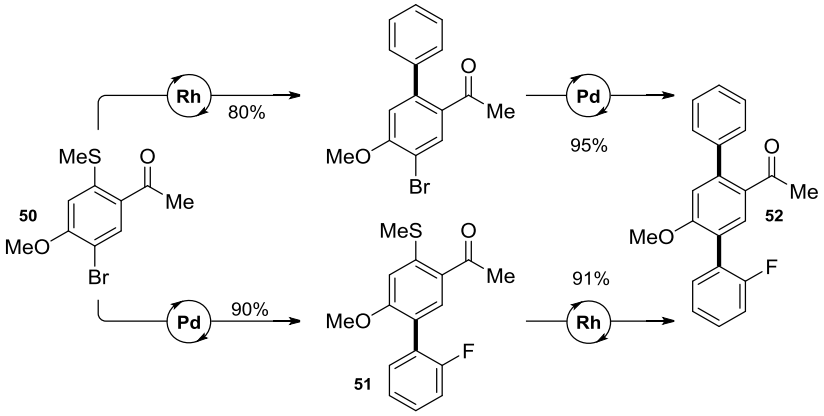


Figure 2.3 Orthogonal reactivity in rhodium- and palladium-catalysed Suzuki-type coupling reactions

2.1.3 Project Aims

Inspired by the work showcased above by previous Willis group members, the initial aim of this project was to develop an efficient rhodium-catalysed Sonogashira-type reaction using simple aryl sulfides and terminal alkynes (Figure **2.4**).

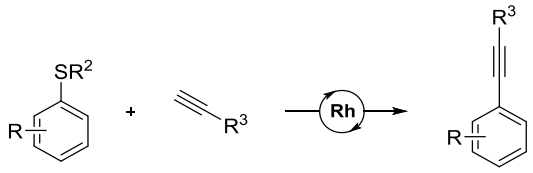


Figure 2.4 A Sonogashira-type cross-coupling reaction utilising simple aryl sulfides

Our ultimate goal was to design a catalytic system that would specifically target the sulfide moiety in the presence of other active electrophilic groups. The aim was to display orthogonal reactivity in palladium-and rhodium-catalysed Sonogashira cross-couplings with terminal alkynes (Figure **2.5**).

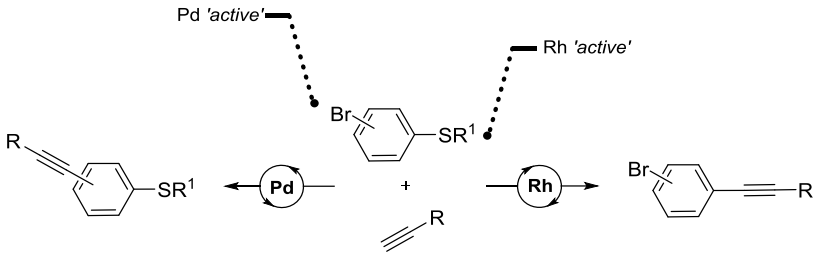


Figure 2.5 Potential orthogonal reactivity in rhodium- and palladium-catalysed cross coupling with simple aryl sulfide bromides

2.2 Results and Discussion

In order to address these objectives, we began by investigating the metal-catalysed Sonogashira cross-coupling of phenylacetylene and aryl methyl sulfide **53.** Compound **53** contains an *ortho*-directing acyl group which is essential for rhodium activation of the C-S bond (Figure **2.6**). This tether helps direct the C-S activation and once the rhodium oxidatively adds in the C-S bond, it forms part of a stable 5-membered rhodacycle **55**.

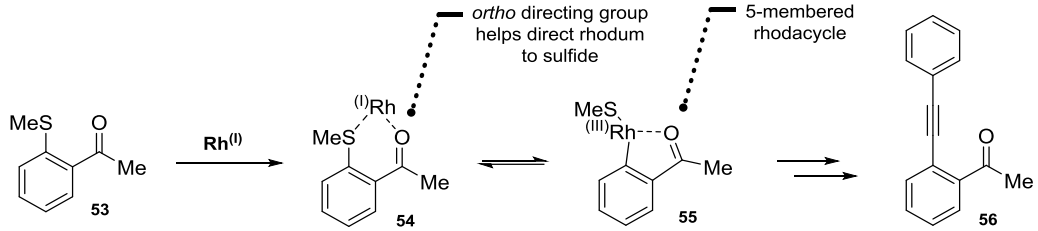
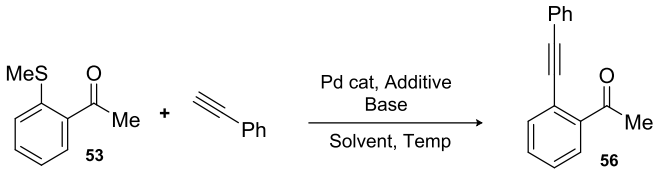


Figure 2.6 Emphasising the importance of the *ortho* directing group

Starting material **53** can easily be synthesised *via* a smooth S_NAr reaction from the corresponding fluoro-ketone and sodiumthiolate salt in quantitative yield. Initially, the two potential coupling partners were subjected to traditional palladium-catalysed Sonogashira conditions (Table **2.0**, entries **1**-**4**). A number of bases were tested which resulted in no product formation. Increasing the amount of CuI in an attempt to activate the C-S bond again resulted in starting material recovery. Next, Liebeskind-Srogl conditions optimized for Sonogashira-type reactions on highly activated heteroaryl sulfides were applied (Table **2.0**, entries **5**-**6**). These conditions were unreactive, presumably owing to the stability of the aryl-C-S bond in **53** when compared to heteroaryl sulfides.

Table 2.0 Initial attempts at C-S activation *via* precedented Sonogashira conditions

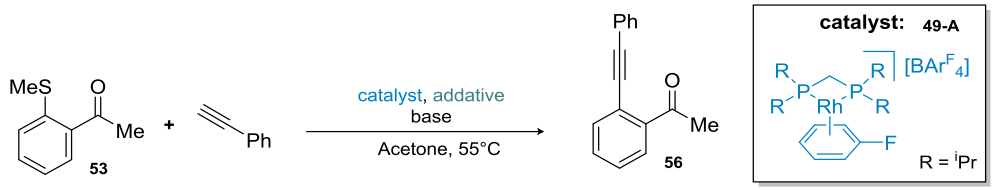


Entry	Catalyst	Additive	Base	Solvent	Temperature(°C)	Conversion to **56**
1	$Pd(PPh_3)_4$	CuI (10 mol%)	Net_3	THF	µW 100	0%
2	$Pd(PPh_3)_4$	CuI (10 mol%)	Cs_2CO_3	THF	µW 100	0%
3	$Pd(PPh_3)_4$	CuI (10 mol%)	-	THF	µW 100	0%
4	$Pd(PPh_3)_4$	CuI (2 eq)	NEt_3	THF	µW 100	0%
5	$Pd(PPh_3)_2Cl_2$	CuI (1.5 eq)	Cs_2CO_3	DMF	µW 95	0%
6	$Pd(PPh_3)_2Cl_2$	CuI (1.5 eq)	Cs_2CO_3	DCM	50	0%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), cat (0.10 mmol), additive, base (0.15 mmol), solvent (2 mL), 1 h. Conversions calculated using ^1H NMR spectroscopy.

Attention was soon shifted to the use of a rhodium catalyst. Following the success of our group's previous work on the Suzuki-type cross-coupling, the same catalytic conditions were applied during testing with alkynes. Rhodium(I) pre-catalysts **49-A** and a number of thiophilic additives were tested. Unfortunately, using either Ag_2CO_3 or Cu(OAc) resulted in starting material recovery and the more traditional Sonogashira additive CuI only offered a complex mixture of unidentifiable compounds.

Table 2.1 Attempts at a rhodium-catalysed Sonogashira-type reaction using catalyst **49-A**



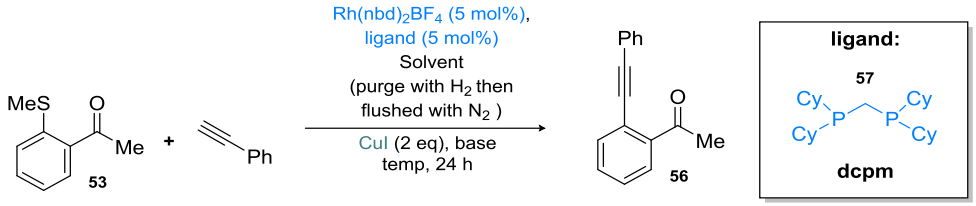
Entry	Additive	Base	Conversion to **56**
1	Ag_2CO_3	-	0%
2	Ag_2CO_3	Cs_2CO_3	0%
3	Cu(OAc)	-	0%
4	Cu(OAc)	Cs_2CO_3	0%
5	CuI	-	complex mixture
6	CuI	Cs_2CO_3	complex mixture

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), cat (0.10 mmol), additive (0.30 mmol), base (0.15 mmol), ACetone (2 mL), 24 h. Conversions calculated using ^{1}H NMR spectroscopy.

2.2.1 Reaction Optimisation

With no sign of the desired reactivity using the precedented conditions, a thorough and more extensive screen of conditions was undertaken exploring temperature, reaction time, solvents, additives, bases and reagent stoichiometry. A variety of *bis*-phosphine ligands were also tested and were combined with the rhodium precursor $Rh(nbd)_2BF_4$ to form the active catalyst *in situ* for each reaction. The mixture was purged with hydrogen in a solution to produce the active catalyst and then flushed with nitrogen to remove any residual hydrogen gas. Initially, to determine the optimal cross-coupling conditions a $Rh(nbd)_2BF_4$/dcpm catalyst system was used along with CuI as the additive while the remaining variables were evaluated (Table **2.2**). The *bis*-phosphine dcpm (**57**) serves as a less hindered and electron rich phosphine ligand compared to the (^{i}Pr)$_2$PCP (**49-A**) used in the Suzuki chemistry. CuI is known to activate the terminal alkyne in the Sonogashira reaction and its thiophilicity could help in C-S activation.

Table 2.2 Optimisation of reaction conditions using dcpm as phosphine ligand



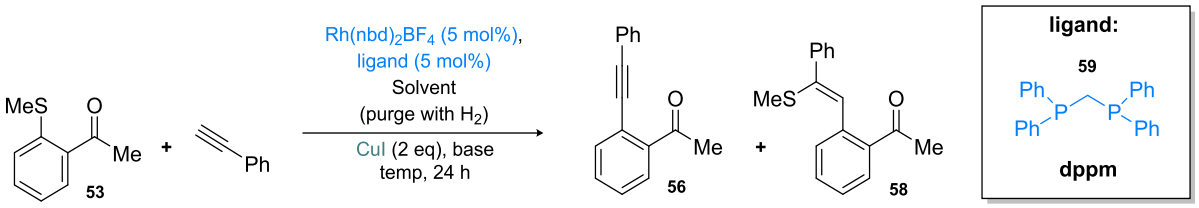
Entry	Solvent	Base	Temperature(°C)	Conversion to **56**
1	THF	-	60	10%
2	Acetone	-	55	10%
3	DCE	-	80	15%
4	Polycarbonate	-	100	13%
5	THF	NEt_3	60	6%
6	Acetone	NEt_3	55	4%
7	DCE	NEt_3	80	7%
8	Polycarbonate	NEt_3	100	0%
9	THF	Cs_2CO_3	60	trace
10	Acetone	Cs_2CO_3	55	6%
11	DCE	Cs_2CO_3	80	6%
12	Polycarbonate	Cs_2CO_3	100	0%
13	THF	K_2CO_3	60	9%
14	Acetone	K_2CO_3	55	5%
15	DCE	K_2CO_3	80	30%
16	Polycarbonate	K_2CO_3	100	16%
17	THF	KO^{t}Bu	60	trace
18	Acetone	KO^{t}Bu	55	trace
19	DCE	KO^{t}Bu	80	7%
20	Polycarbonate	KO^{t}Bu	100	6%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpm (0.05 mmol), CuI (0.15 mmol), base (0.30 mmol), solvent (2 mL), 24 h. Conversions calculated using ^{1}H NMR spectroscopy.

The desired Sonogashira product was successfully accessed using a range of solvent systems. Although the conversions were low, the fact that any cross-coupling was observed at all was a promising start. Interestingly, the exclusion of base produced the most consistent results across the various solvents, with 10-15% conversion to the phenylethynyl product observed (Table **2.2**, entries **1-4**). Employing either inorganic or organic bases seemed to impede the turnover of the catalyst with the exception of entry **15**, which showed an improved conversion of 30% when using K_2CO_3 with DCE as solvent.

Having demonstrated that it is possible to obtain the product using a rhodium/dcpm catalyst system, we then explored the effect of using dppm (**59**); a less sterically hindered and more electron-poor bisphosphine linked by a methylene. (Table **2.3**).

Table 2.3 Optimisation of reaction conditions using dppm as phosphine ligand



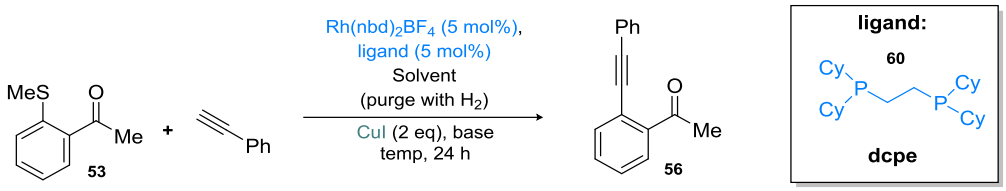
Entry	Solvent	Base	Temperature(°C)	Conversion to **56**	Conversion to **58**
1	Acetone	-	55	trace	trace
2	DCE	-	80	8%	15%
3	Polycarbonate	-	100	trace	trace
4	DCE	NEt_3	80	0%	0%
5	DCE	Cs_2CO_3	80	5%	0%
6	DCE	K_2CO_3	80	19%	5%
7	DCE	Na_2CO_3	80	12%	11%
8	DCE	NaOH	80	0%	0%
9	DCE	KO^{t}Bu	80	0%	0%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dppm (0.05 mmol), CuI (0.15 mmol), base (0.30 mmol), solvent (2 mL), 24 h. Conversions calculated using ^1H NMR spectroscopy.

Once again, DCE proved to be the most effective solvent system and the addition of K_2CO_3 improved the conversion to **56** (entries **2** and **6**). Overall, the rhodium/dppm catalyst was shown to be less active compared to the dcpm system. Additionally, upon further analysis of the crude reaction mixtures, a by-product was observed. This was characterised as **58**, stemming from addition of sulfide **53** across the phenylacetylene to form a vinyl sulfide product. This addition process is known as the carbothiolation reaction (see chapter **3** later). Without any base, this addition product seemed to be more favourable than the intended cross-coupling Sonogashira reaction (entry **2**). Interestingly, introducing an equivalent of base partially suppressed the addition reaction while simultaneously promoting the formation of the desired acetylene **56** (entries **5-7**).

Due to the unexpected results when using the phenyl-substituted PCP phosphine, we reverted back to a cyclohexene-substituted phosphine and began testing the effect of the carbon backbone length. Variation of this property of the ligand can affect its physical properties by increasing the bite-angle and flexibility when bound to the rhodium centre. Using dcpe (**60**), which contains a two carbon spacer between the phosphine atoms, a number of screening experiments were conducted (Table **2.4**).

Table 2.4 Optimisation of reaction conditions using dcpe as phosphine ligand

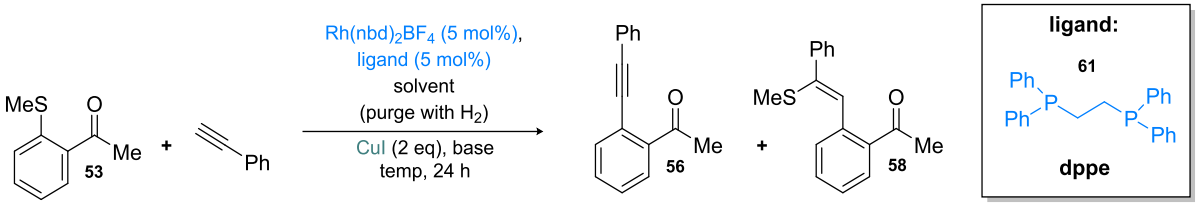


Entry	Solvent	Base	Temperature(°C)	Conversion to **56**
1	Acetone	-	55	38%
2	DCE	-	80	39%
3	Polycarbonate	-	100	37%
4	DCE	NEt_3	80	0%
5	DCE	K_2CO_3	80	44%
6	DCE	Na_2CO_3	80	12%
7	DCE	Cs_2CO_3	80	24%
8	DCE	NaOH	80	0%
9	DCE	KO^{t}Bu	80	0%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI (0.15 mmol), base (0.30 mmol), solvent (2 mL), 24 h. Conversions calculated using ^{1}H NMR spectroscopy.

The results were very encouraging, showing an overall improvement in yields signifying a more active catalytic system. Attempts with and without base proved to be successful, with the addition of K_2CO_3 giving the best conversion of 44% (entry **5**). Pleasingly, no addition product was detected, suggesting that alkyl-substituted electron-rich phosphine favours the Sonogashira reaction pathway, while the aromatic-substituted phosphines favour the addition of the sulfide across the alkyne. This hypothesis was tested by repeating the screen using the analogous phenyl-substituted phosphine ligand, dppe (**61**) (Table **2.5**).

Table 2.5 Optimisation of reaction conditions using dppe as phosphine ligand



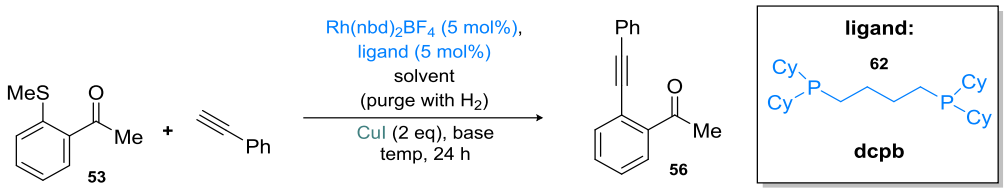
Entry	Solvent	Base	Temperature(°C)	Conversion to **56**	Conversion to **58**
1	Acetone	-	55	trace	trace
2	DCE	-	80	6%	14%
3	Polycarbonate	-	100	6%	13%
4	DCE	K_2CO_3	80	41%	11%
5	DCE	Na_2CO_3	80	39%	13%
6	DCE	NaOH	80	0%	0%
7	DCE	KO^{t}Bu	80	0%	0%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dppe (0.05 mmol), CuI (0.15 mmol), base (0.30 mmol), solvent (2 mL), 24 h. Conversions calculated using ^{1}H NMR spectroscopy.

As predicted, the conditions were non-selective as both **56** and **58** were identified in the crude reaction mixtures. In the absence of base, the carbothiolation dominates as the major product (entries **1-3**). Employing K_2CO_3 or Na_2CO_3 resulted in good conversion to **56**, comparable to the results seen with dcpe. Unfortunately, these conditions do not suppress the formation of **58**, with ~10% conversion observed (entries **4-5**). Overall, these results reaffirm that having cyclohexene-substituted phosphines offers greater selectivity for the Sonogashira-type reaction. They also indicate that the longer two-carbon backbone offers a more active catalyst, as better conversions were seen for dcpe and dppe compared with dcpm and dppm.

Leading on from the results above, the *bis*-phosphine ligand dcpb (**62**) was investigated in the hope that the longer 4-carbon backbone might produce a noticeably more active catalyst when combined with the $Rh(nbd)_2BF_4$ (Table **2.6**). In contrast, the system proved to be less active but was however selective for **56** formation as anticipated.

Table 2.6 Optimisation of reaction conditions using dcpb as phosphine ligand



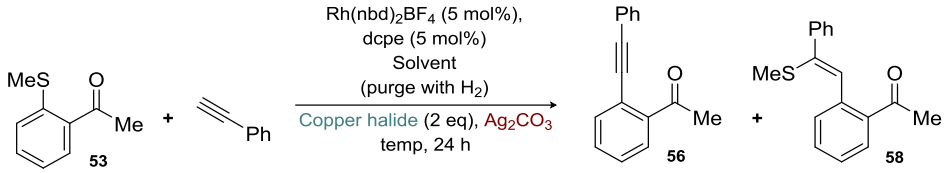
Entry	Solvent	Base	Temperature(°C)	Conversion to **56**
1	Acetone	-	55	19%
2	DCE	-	80	19%
3	DCE	K_2CO_3	80	28%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpb (0.05 mmol), CuI (0.15 mmol), base (0.30 mmol), solvent (2 mL), 24 h. Conversions calculated using ^1H NMR spectroscopy.

2.2.2 Additive Screening

Following this partially successful screen of *bis*-phosphine ligands, the identity of the basic additive was investigated in more detail. In traditional and C-S activated Sonogashira cross-couplings, a base, commonly Et_3N or Cs_2CO_3, is required for the deprotonation of the alkyne component which is activated by the copper halide species, in this case CuI. During the ligand screen a number of organic and inorganic bases were tested with an optimum of 44% selective conversion of **53** with the application of an equivalent of K_2CO_3 (Table **2.4**, entry **5**). From the literature and the work showcased by the Willis group, it has been shown that in most cases an appropriate auxiliary thiophilic reagent is needed when attempting a coupling reaction across a C-S bond. To this end, CuI was used specifically for its thiophilic properties and also its key role in alkyne activation. Taking this into account, we envisaged that by replacing K_2CO_3 with a reagent with similar basic properties and one which simultaneously offers an affinity to sulfur, may help drive the catalytic reaction to completion. Thus, Ag_2CO_3 was chosen due to its high thiophilicity and previous success in C-S activated Suzuki-type chemistry, and applied in a brief screen of conditions (Table **2.7**).

Table 2.7 Investigation into the use of Ag_2CO_3 as additive in the developed rhodium-catalysed Sonogashira-type chemistry

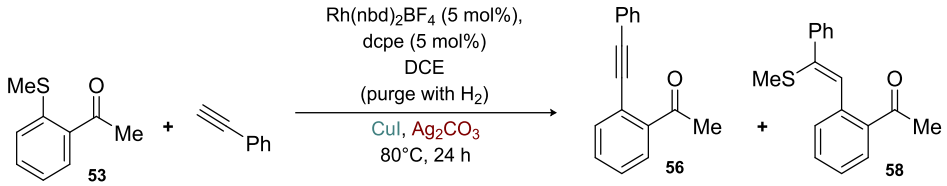


Entry	Ligand	Solvent	Copper halide	Temperature(°C)	Conversion to **56**	Conversion to **58**
1	dcpe	Acetone	CuI	55	9%	trace
2	dcpe	DCE	CuI	80	61%	12%
3	dcpe	DCE	-	80	22%	9%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI (0.15 mmol), Ag_2CO_3 (0.15 mmol), solvent (2 mL), 24 h. Conversions calculated using ^1H NMR spectroscopy.

This successfully increased the conversion of **56** by 17% to 61% when compared to previously optimum conditions (entry **1-2**). The presence of CuI remained integral to the success of the reaction as in its absence the conversion was greatly reduced (entry **3**). However, the addition of Ag_2CO_3 also seemed to facilitate the addition reaction pathway as **58** was produced as a minor product in the reactions (entries **1-3**). This might be attributed to the high thiophilic properties of silver which could rapidly activate the C-S bond, allowing for the addition pathway to commence. Next, a screen of reagent equivalences was undertaken to see the effect on conversions of both major and minor products (Table **2.8**).

Table 2.8 Identification of optimum reagent equivalence for optimum Sonogashira-type reaction



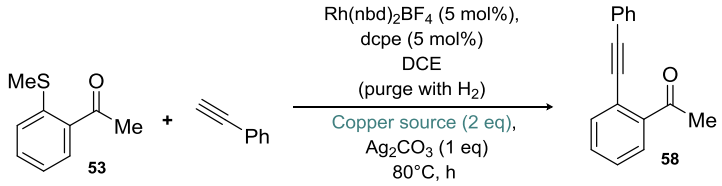
Entry	CuI (eq)	Ag_2CO_3 (eq)	Conversion to **56**	Conversion to **58**
1	1	1	61%	15%
2	0.5	1	55%	23%
3	0.1	1	30%	18%
4	1	3	79%	15%
5	1.5	1	83%	6%
6	2	1	93%	3%
7	2	0.5	93%	5%
8	2	1.5	92%	4%
9	3	3	89%	6%
10	3	1	82%	7%
11	3	1.5	93%	4%
12	5	0	50%	0%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI, Ag_2CO_3, solvent (2 mL), 24 h. Conversions calculated using ^1H NMR spectroscopy.

It was found that by simply increasing the amount of copper iodide to two equivalents an excellent conversion to the Sonogashira cross-coupling product could be achieved. These optimised conditions also helped to suppress **58** formation to only 3% (entry **6**).

After this success, a final evaluation of several copper sources was conducted using the optimised conditions above (Table **2.9**). All the copper sources tested were of the +1 oxidation state, which has a larger affinity to sulfur than copper(II) species and all have successfully been used in C-S activation couplings as seen in previous literature examples.

Table 2.9 *Screen of various copper(I) sources*



Entry	Copper source	Base	Time (h)	Conversion to **56**
1	Cu(OAc)	Ag_2CO_3	24	0%
2	$Cu(OTf)_2$	Ag_2CO_3	24	0%
3	CuTc	Ag_2CO_3	24	0%
4	Cu 3-methylsalicylate	Ag_2CO_3	24	0%
5	CuCl	Ag_2CO_3	24	0%
6	CuBr	Ag_2CO_3	16	100%
7	CuBr	K_2CO_3	48	95%

Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI (0.30 mmol), Ag_2CO_3 (0.15 mmol), DCE (2 mL), 24 h. Conversions calculated using ^1H NMR spectroscopy.

We found that the all but one of the copper sources tested had a detrimental impact on the reaction as only starting material was recovered (entries **1-5**). Replacing the copper iodide with copper bromide resulted in quantitative conversion to **53** with no sign of any addition side product (entry **6**). Using copper bromide even allowed for the use of K_2CO_3, omitting the use of silver, although this requires a longer reaction time (entry **7**).

2.2.3 Reaction Mechanism

As aforementioned, the tentative assumption was that the mechanistic pathway begins with a C-S activation step to generate a rhodium(III)-intermediate which forms part of a 5-membered rhodacycle, which can go on to take part in the catalytic cycle (Figure **2.7**). Taking into consideration the findings from the reaction optimisation, the suggested pathway was questioned.

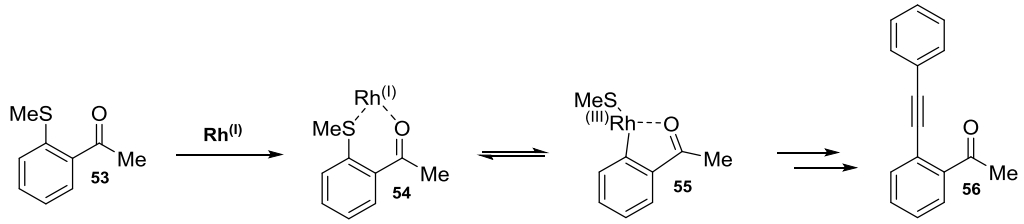


Figure 2.7 Suggested reaction pathway via direct C-S activation

In light of the fact that the optimal conditions require two equivalents of either CuI or CuBr suggests a more prominent involvement than first anticipated. The inability to employ CuI/Br in sub-stoichiometric amounts and the fact that all other copper(I) sources proved ineffective suggests that the halide might be involved in an initial substitution of the methyl sulfide (Figure 2.8).

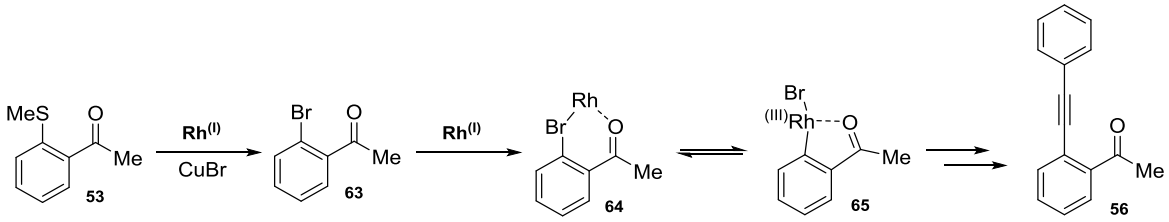
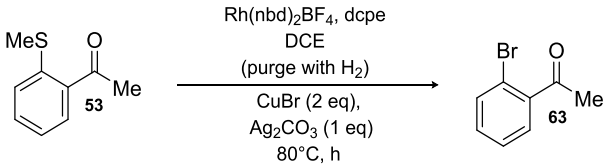


Figure 2.8 Alternative pathway suggested due to findings from reaction optimisation

Test reactions were run in an attempt to isolate the corresponding aryl-bromide 63 (Table 2.10). Attempting the reaction with and without a rhodium catalyst proved unsuccessful (entries 1-3) and monitoring these reaction mixtures *via* mass spectrometry and ^{1}H NMR spectroscopy showed no sign of the aryl bromide compound.

Table 2.10 Attempts to provide evidence of alternative bromide formation

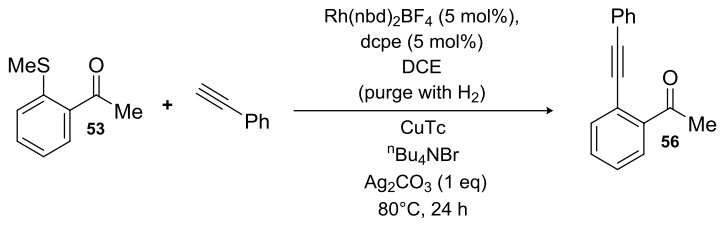


Entry	$Rh(nbd)_2BF_4$/dcpe	Time (h)	Conversion to 63
1	10 mol%	24	0%
2	1.1 eq	24	0%
3	-	24	0%

Reaction Conditions: 53 (0.15 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuBr (0.30 mmol), Ag_2CO_3 (0.15 mmol), DCE (2 mL), 24 h. Conversions calculated *via* ^{1}H NMR spectroscopy.

Having failed to isolate or identify bromide **63**, the hypothesis was tested through a different approach. Reactions were conducted using CuTc and tetrabutylamonium bromide as substitutes for CuBr (Table **2.11**). Having previously unsuccessfully tested CuTc as a copper source in the development of reaction, we proposed that the addition of a bromide source might initiate the reaction which would suggest an integral involvement of the halide in the reaction mechanism.

Table 2.11 Attempts to repeat the developed reaction using an alternative bromide source



Entry	CuTc (eq)	$^{n}Bu_4NBr$ (eq)	Conversion to **56**
1	1	1	0%
2	0.1	1	0%
3	1	0.1	0%

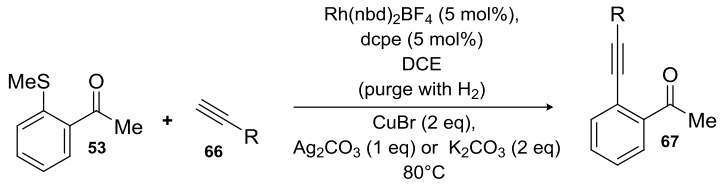
Reaction Conditions: **53** (0.15 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), $^{n}Bu_4NBr$, CuTc, Ag_2CO_3 (0.15 mmol), DCE (2 mL), 24 h. Conversions calculated *via* ^1H NMR spectroscopy.

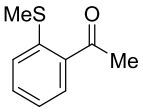
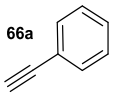
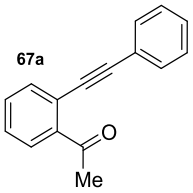
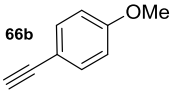
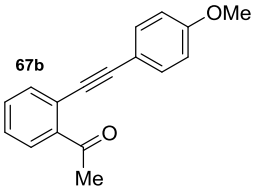
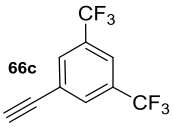
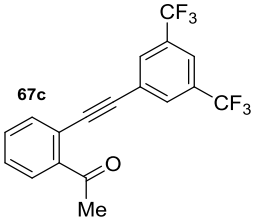
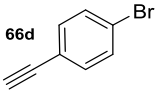
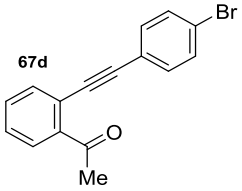
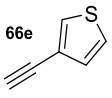
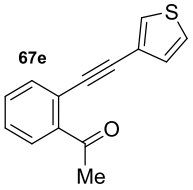
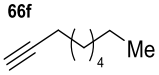
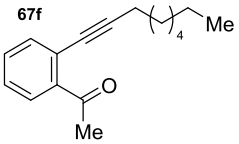
These conditions resulted in no conversion to **56** with no trace of the product when monitoring with mass spectrometry and ^1H NMR spectroscopy. Even though the reactions seemed to fail, the feasibility of this mechanistic alternative has to be taken into account.

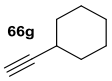
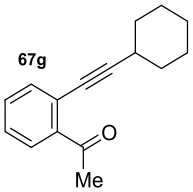
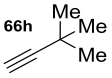
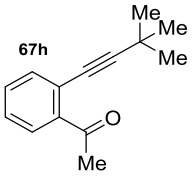
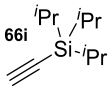
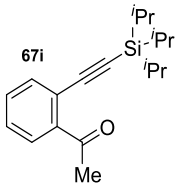
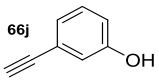
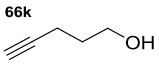
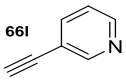
2.2.4 Reaction Scope

With an optimal set of cross-coupling reaction conditions established, it was necessary to determine the scope of the process. Initially, the generality of the terminal alkyne was examined. The reaction generally produced acceptable yields (45 - 96%) and tolerated a wide range of functionality (Table **2.12**).

Table 2.12 Scope of alkynes compatible in the rhodium-catalysed Sonogashira-type reaction with simple aryl methyl sulfides



Entry	Ketone SM	Alkyne	Product	Reaction Time (h)	Base	Isolated Yield
1				4 48	Ag_2CO_3 K_2CO_3	95%, (96%)* 79%
2	**53**			3	Ag_2CO_3	92%
3	**53**			8	Ag_2CO_3	96%
4	**53**			16 24	Ag_2CO_3 K_2CO_3	89% 75%
5	**53**			16 24	Ag_2CO_3 K_2CO_3	69% 70%
6	**53**			16	K_2CO_3	45%

7	**53**	**66g** 	**67g** 	24	Ag_2CO_3	35%
				24	K_2CO_3	50%
8	**53**	**66h** 	**67h** 	24	Ag_2CO_3	73%
9	**53**	**66i** 	**67i** 	24	Ag_2CO_3	96%
10	**53**	**66j** 	-	24	Ag_2CO_3	0%
					K_2CO_3	0%
11	**53**	**66k** 	-	24	Ag_2CO_3	0%
					K_2CO_3	0%
12	**53**	**66l** 	-	24	Ag_2CO_3	0%
					K_2CO_3	0%

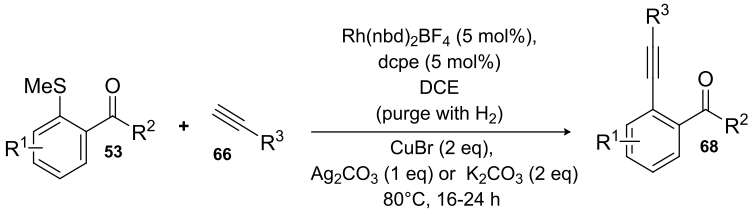
Reaction Conditions: **53** (0.15 mmol), acetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI (0.30 mmol), Ag_2CO_3 (0.15 mmol), DCE (2 mL).

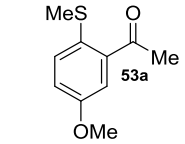
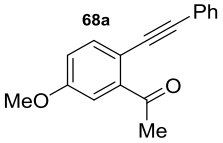
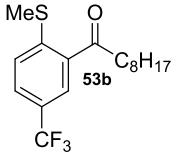
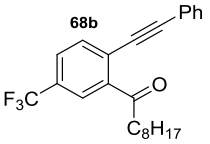
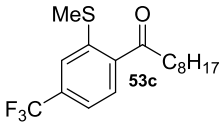
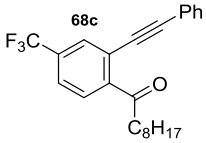
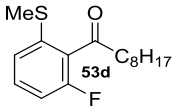
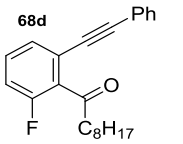
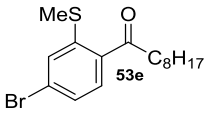
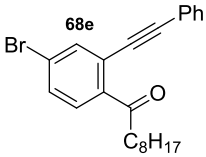
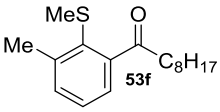
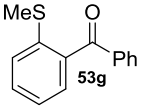
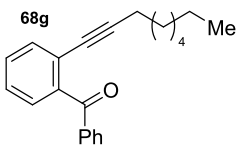
Both electron-rich and electron-poor aryl alkynes were compatible allowing for the formation of the respected products in high yields (entries **1-3**). The potential orthogonality of the reaction is demonstrated by the use of alkyne **66d** (entry **4**). The reaction was highly selective with no evidence of reactivity at the bromo-substituent. Heterocyclic alkyne **66e** showed good reactivity, generating compound **67e** in a good yield (entry **5**). Alkyl alkynes could also be used in this reaction to deliver products in moderate to excellent yields (entries **6-8**). Silyl acetylene **66i** also displayed good activity, delivering the coupled product **66i** in excellent yields (entry **9**). The reaction could also be performed with a reduced catalyst loading with no decrease in the yield; employing phenylacetylene as the alkyne component, the reaction was performed on 30.0 mmol scale using 2.5 mol % Rh, to deliver the coupled product in 96% yield (entry **1***). Oxygen and nitrogen

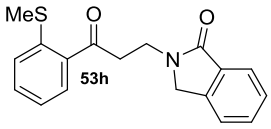
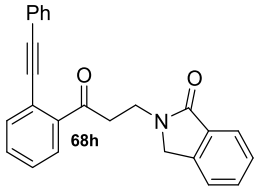
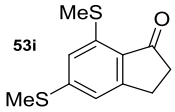
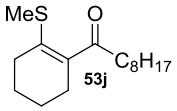
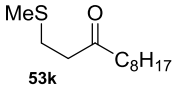
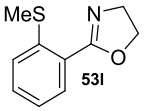
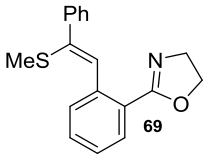
containing alkynes were not tolerated as they did not deliver the Sonogashira cross-coupling product (entries 10-12).

The arene portion of the aryl methyl sulfide component of this reaction could easily be varied, and very good functional group tolerance was observed (Table 2.13).

Table 2.13 Scope of methyl sulfides compatible in the rhodium-catalysed Sonogashira-type reaction with phenylacetylene



Entry	Ketone SM	Alkyne	Product	Base	Isolated Yield
1		66a		Ag_2CO_3	76%
				K_2CO_3	77%
2		66a		Ag_2CO_3	89%
				K_2CO_3	76%
3		66a		Ag_2CO_3	91%
4		66a		Ag_2CO_3	88%
				K_2CO_3	91%
5		66a		K_2CO_3	97%
6		66a	-	Ag_2CO_3	0%
				K_2CO_3	0%
7		66f		Ag_2CO_3	56%
				K_2CO_3	90%

8	 53h	66a	 68h	K_2CO_3	89%
9	 53i	66a	-	Ag_2CO_3	0%
				K_2CO_3	0%
10	 53j	66a	-	Ag_2CO_3	0%
				K_2CO_3	0%
11	 53k	66a	-	Ag_2CO_3	0%
				K_2CO_3	0%
12	 53l	66a	 69	K_2CO_3	90%

Reaction Conditions: methyl sulfide (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI (0.30 mmol), Ag_2CO_3 (0.15 mmol), DCE (2 mL).

The reaction is compatible with both electron-withdrawing and -donating groups on the aryl sulfide (entries **1-3**). Pleasingly, aryl halides were also tolerated, allowing for the possibility of further functionalisation of the products and orthogonal compatibility (entries **4-5**). Three of the four substitution patterns on the arene ring were possible, as substituents positioned *ortho* to the methylsulfide proved challenging with no reaction seen (entry **6**). A possible explanation for this result could be attributed to *ortho* substituents hindering the attack of incoming alkynes, therefore impeding the reaction. Switching from a methyl ketone to aromatic ketone **53g** was possible as the reaction with alkyl alkyne **66f** produced the corresponding Sonogashira product in excellent yield (entry **7**). The integration of a pendent heterocycle was also accomplished, exhibiting an excellent yield (entry **8**). On the other hand, employing sulfide **53i** which contains a fused cyclopentanone ring resulted in no cross-coupling with phenylacetylene (entry **9**). This could be due to the cyclic ketones inflexibility, contributing to its inability to form the 5-membered rhodacycle intermediate (Figure **2.7, 55**). Moving away from the aromatic sulfide proved detrimental as both the aliphatic sulfide **53j** and β-enal **53k** were unreactive under these

conditions (entries 10-11). Interestingly, changing the directing group from a ketone to an oxazoline completely shut down the Sonogashira reaction pathway and only produced the addition product in a quantitative yield (entry 12).

2.2.5 Demonstration of Orthogonality

An important goal in exploring this C-S activation chemistry was to demonstrate the orthogonality of the developed rhodium-catalysed Sonogashira-type reactions with palladium-catalysed coupling reactions of aryl halides (Figure 2.9).

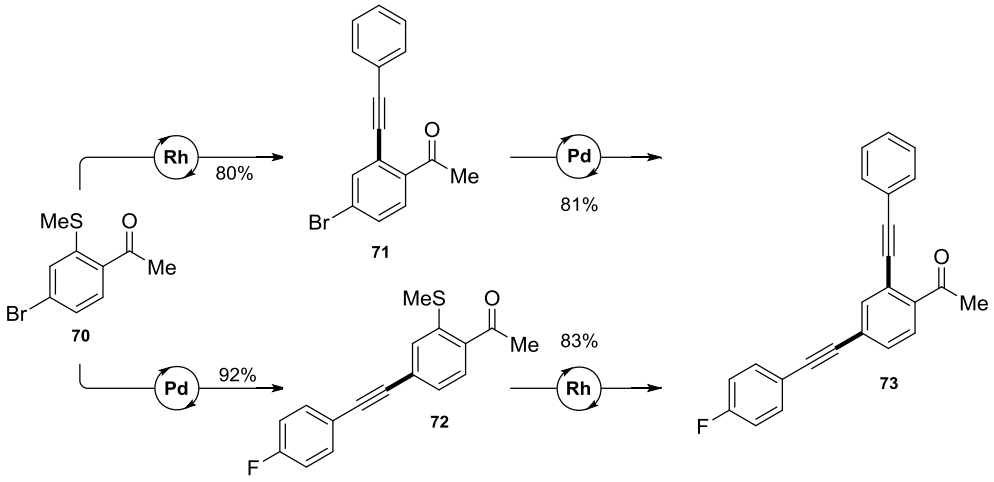


Figure 2.9 Orthogonal reactivity in rhodium- and palladium-catalysed Sonogashira-type coupling reactions. Reaction Conditions: Rh: Methyl sulfide (0.15 mmol), acetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), CuI (0.30 mmol), Ag_2CO_3 (0.15 mmol), DCE (2 mL). Pd: methyl sulfide (0.15 mmol), phenylacetylene (0.30), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.04 mmol), CuI (0.04 mmol), DIEA (2 mL).

As seen before, employing substrate 70, bearing both methyl sulfide and aryl bromide substituents can undergo a selective C-S activation and subsequent Sonogashira-type cross-coupling to generate bromo-substituted 1-(2-alkynyl-phenyl)ketone 71 in a good yield. Alternatively, classic Sonogashira coupling of substrate 70 using a palladium-catalyst, delivers methyl sulfide-substituted 1-(2-alkynyl-phenyl) ketone 72 in an excellent yield. Both alkynyl ketone products (71 and 72) can then be converted into dialknyl spiecies 73 using the complementary catalyst system. This particular feature of the developed chemistry demonstrates a marked improvement on the existing orthogonal C-S activation procedures, allowing complementary use of either palladium or

rhodium catalysts without the use of highly activated sulfide coupling partners.

2.2.6 Development of Hydroacylation-Sonogashira Cascade Reaction

Rhodium-catalysis in conjunction with tethered directing groups has been utilised extensively by the Willis group. Previous work revolving around rhodium-catalysed hydroacylation transformations makes use of directing groups much in the same way as seen in this project. Hydroacylation is formally the addition of an acyl unit and a hydride across a C-C unsaturated system; typically an alkene or alkyne (Figure 2.10).

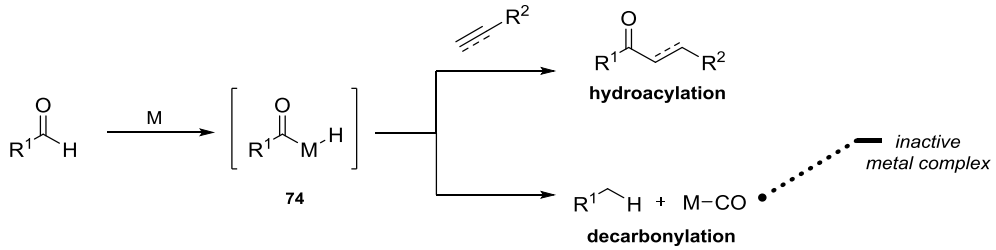


Table 2.10 General outline of hydroacylation and decarbonylation processes

Following the oxidative insertion of the metal, typically rhodium, to form the metal hydride 74, an alternative pathway is also possible which forms a metal carbonyl species and decarbonylated product. This decarbonylative process is the main competitive pathway and obstacle in the development of hydroacylation chemistry. By employing β-sulfur-containing aldehydes, the Willis group has shown that this deactivating pathway can be suppressed, while simultaneously directing the oxidative addition of the rhodium catalyst (Figure 2.11).

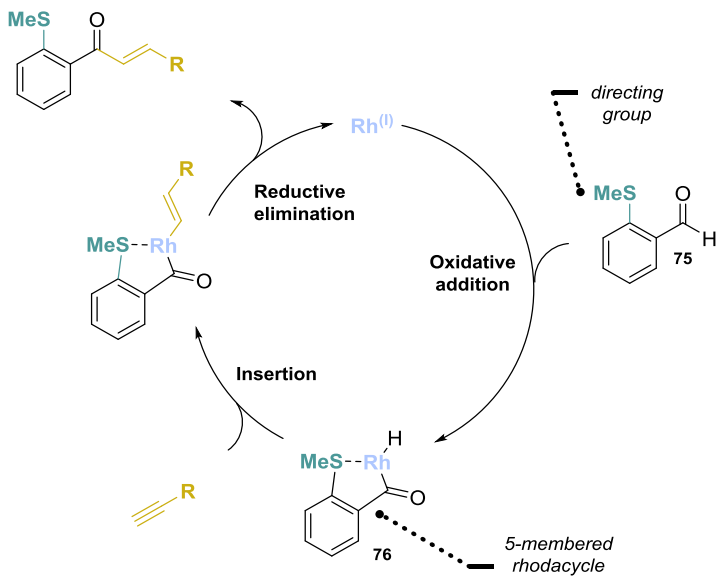


Table 2.11 General mechanism of the hydroacylation reaction using β-sulfur-containing aldehydes

Once the β-sulfide has directed the oxidative addition of the rhodium, a 5-membered rhodacycle **76** is formed which stabilises the rhodium-hydride species, therefore preventing the reductive decarbonylative pathway. The position of the sulfide directing group was crucial, as γ- and δ-substituted aldehydes resulted in only the decarbonylation product.

Since this discovery, a variety of rhodium-catalysed systems are now used within the group to promote the hydroacylation reaction. One such system employs the *bis*-phosphine ligand dcpe which can produce highly linear selective enones (**77**) from a variety of aldehydes and electron-poor alkynes (Figure **2.12**).

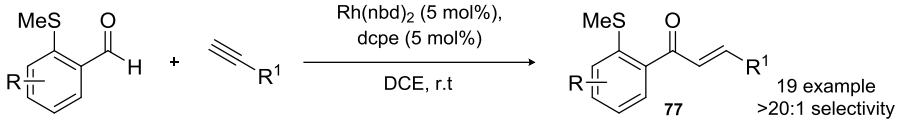


Table 2.12 The use of dcpe as an effective ligand in the hydroacylation of terminal acetylenes with β-sulfur-containing aldehydes

Given that this transformation utilised the same *bis*-phosphine ligand used in the developed rhodium-catalysed Sonogashira-type chemistry, a one-pot cascade reaction was targeted (Figure **2.13**). The aldehyde **75** can participate in the hydroacylation reaction where the rhodium catalyst is directed and stabilised by the β-substituted-sulfide. This then forms an enone (**77**) with an ideal

molecular framework for the subsequent C-S activation. Adding CuBr and Ag_2CO_3 should promote the Sonogashira-type cross-coupling where the rhodium-catalyst is directed, in this case by the newly formed enone **78**.

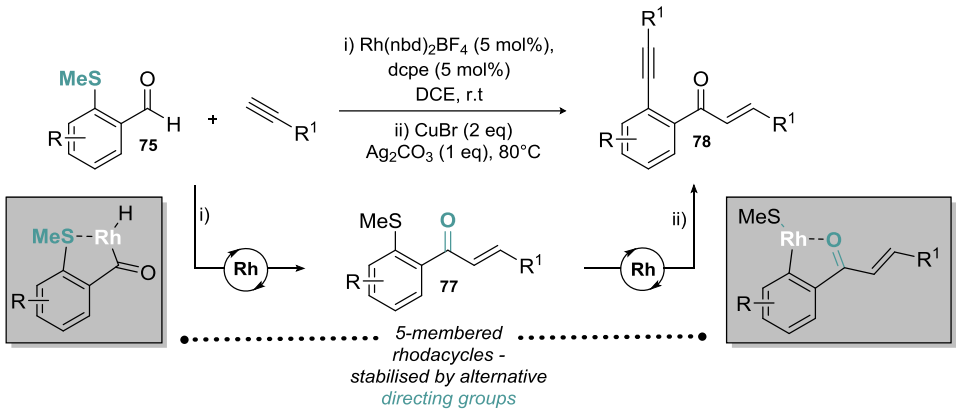
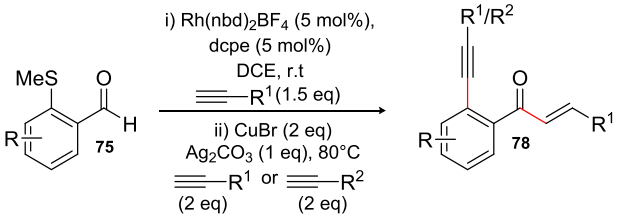
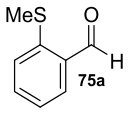
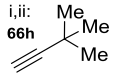
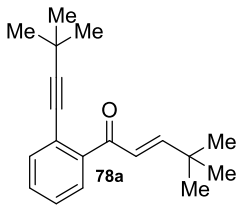


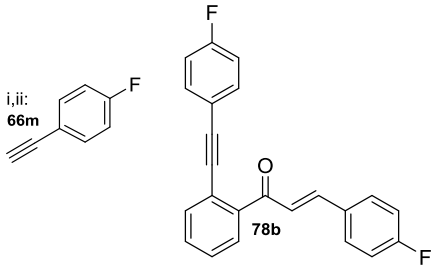
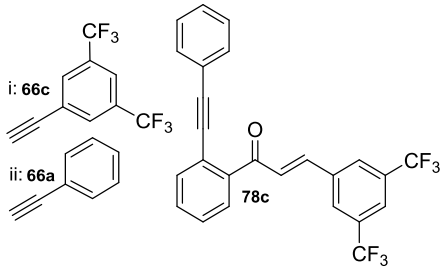
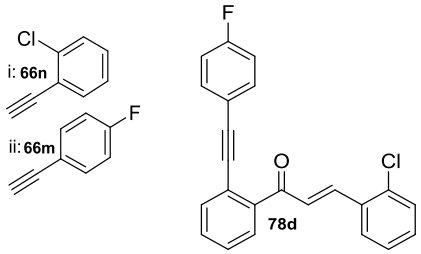
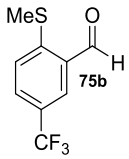
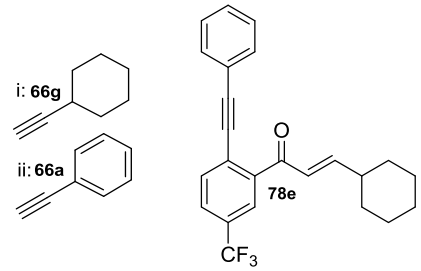
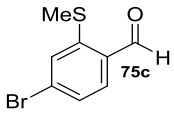
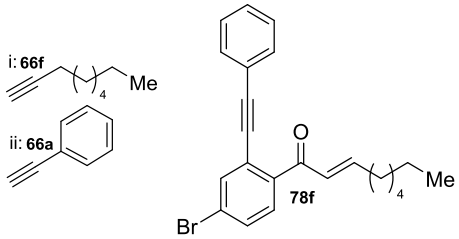
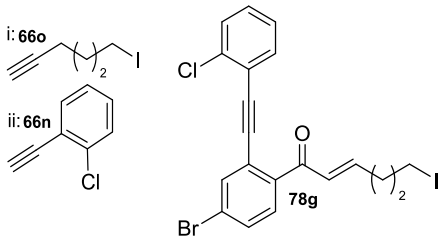
Table 2.13 Outlining the utilisation of one rhodium catalyst to achieve successive hydroacylation and Sonogashira –type reactions through a one-pot cascade reaction

Such an approach would allow a three-component combination of an aldehyde and two identical or distinctive alkynes resulting in the formation of two new C–C bonds. This convenient one-pot cascade reaction was evaluated using a number of aldehydes and alkynes (Table **2.14**).

Table 2.14 Scope of the one-pot reaction towards alkenyl enones



Entry	Ketone SM	Alkyne	Product	Hydroacylation Time (h)	Sonogashira Time (h)	Isolated Yield
1				4	24	64%

2	**75a**		0.5	6	76%
3	**75a**		1	24	73%
4	**75a**		0.5	6	88%
5			0.15	6	87%
6			0.5	24	55%
7	**75c**		1	24	62%

Reaction Conditions: methyl sulfide (0.15 mmol), acetylene (0.15 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), dcpe (0.05 mmol), DCE (2 mL), once complete CuI (0.30 mmol), Ag_2CO_3 (0.15 mmol), acetylene (0.15).

Using the same alkyne component for both the hydroacylation and Sonogashira reaction worked well with both bulky *tert*-butyl- and 4-fluorobenzene-substituted alkynes (entries **1-2**). Using alternative alkynes for each stage of the cascade also proved successful, producing good to excellent yields (entries **3-7**). The reaction could tolerate electron-poor aldehyde substrates with the initial hydroacylations, all going to completion within an hour at room temperature (entries **5-7**). High tolerance of halide-substituents on the aldehyde and alkyne components was seen for both hydroacylation and Sonogashira reactions (entries **2,4,6-7**). Importantly, no side products were detected that suggest any reactivity at the halide-substituent of the arene. In order to demonstrate the full compatibility of this methodology with halide functionality, enone **78g** was prepared from components featuring aryl chloride, aryl bromide and alkyl iodide substituents, giving access to trihalo-products that are inaccessible using Pd- or Ni-catalysed methods. Notably, we had to revert back to employing CuI due to the facile nature of the *in-situ* Finkelstein reaction, which occurred at the iodide when using CuBr. All enones produced showed excellent *trans*-selectivity as seen by ^{1}H NMR spectroscopy.

2.2.7 Rapid formation of 1-2-dihydronaphthalenes

Having designed an efficient mono-catalytic cascade reaction that forms an interesting range of *o*-(alkynyl)phenylenones, we decided to investigate their applications. Both *o*-(alkynyl)benzaldehyde and *o*-(alkynyl)phenylenones are found to be convenient precursors to highly functionalised 1-2-dihydronaphthalenes (**81**) (Figure **2.14**).

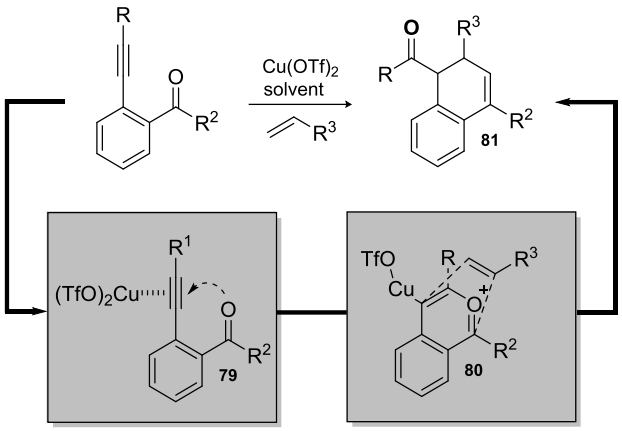


Figure 2.14 Yamamoto's synthesis of 1,2-dihydronaphthalenes *via* alkyne activation

The reaction requires an alkene and a metal-catalyst, commonly gold or copper based.[101] The metal can coordinate to the triple bond enhancing the electrophilicity of the alkyne and allowing for nucleophilic attack of the carbonyl oxygen atom, which forms the oxomium complex **80**. This then undergoes a Diels-Alder reaction with the alkene, followed by a C-O bond cleavage and subsequent proton elimination to produce the 1-2-dihydronaphthalene bearing a ketone function at the 1-position.

Initially, we envisaged the possibility of this process being incorporated into the existing one-pot cascade reaction (Figure **2.15**). It was hoped that once the Sonogashira reaction was complete the existing rhodium catalyst could bind to the alkyne in the product, activating the triple bond **82**. Following this, the simple addition of an alkene could produce the 1-2-dihydronaphthalene in a one-pot scenario. This process could offer the ability to rapidly generate molecular complexity through a four-component reaction, starting from simple sulfide-substituted benzaldehydes through to the 1-2-dihydronaphthalene in one-pot.

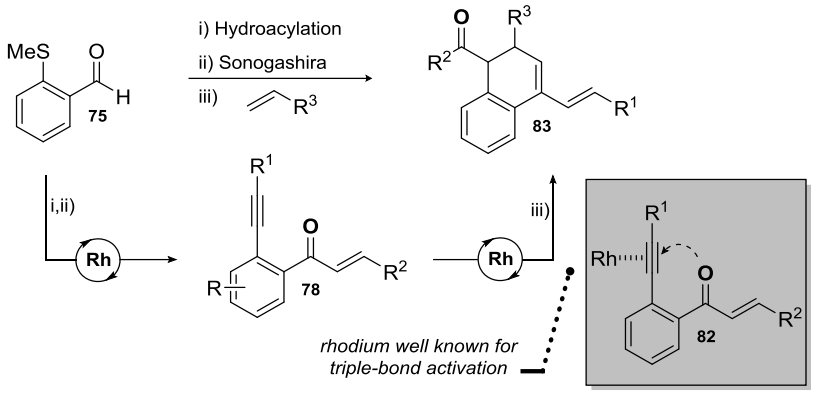


Figure 2.15 Proposed integration of alkynes activation chemistry to generate a one-pot casecad reaction towards the synthesis of 1,2-dihydronaphthalenes

At the outset, test reactions were conducted using **67a** and it was found that rhodium serves as an excellent catalyst for the reaction, producing **85** in a quantitative yield (Figure **2.16**).

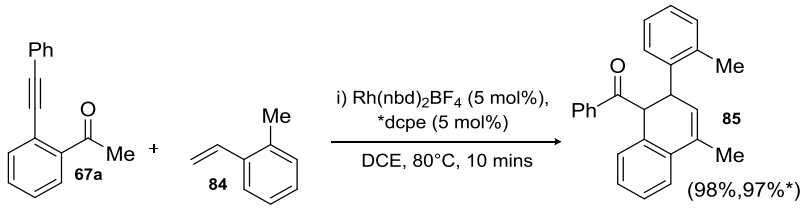


Figure 2.16 Successful use of rhodium as alkyne activation catalyst to promote the synthesis of 1,2 dihydronaphthalene **85**. *result when using dcpm.

Unfortunately, when applied in the one-pot reaction it was clear that the residual reagents carried through from previous reactions were effecting the sought-after transformation (Figure **2.17**). Though conversion to the 1-2-dihydronaphthalene **86** was observed, a host of other unidentifiable compounds were formed. Even the addition of $Cu(OTf)_2$ in the third step also produced mixture of compounds.

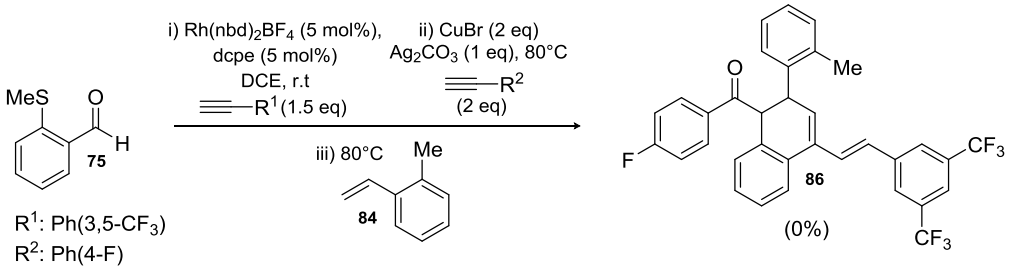


Figure 2.17 Failed attempt to synthesise 1,2-dihydronaphthalenes **86** *via* one-pot reaction

In light of these results, an alternative protocol was considered. Following the hydroacylation and Sonogashira reactions, filtration through a plug of silica would remove the unwanted reagents, allowing for a cleaner reaction. As a consequence, the rhodium catalyst would also be filtered, so a catalytic amount of $Cu(OTf)_2$ would be needed to catalyse the formation of **86.** This procedure worked effectively and resulted in the isolation of the 1-2-dihydronaphthalene **86** in a good yield (Figure **2.18**).

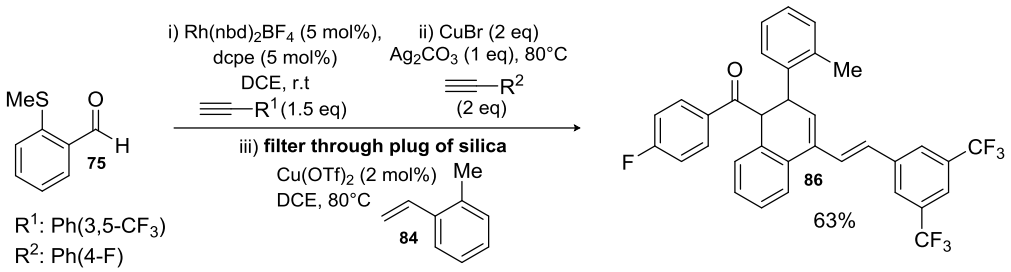


Figure 2.18 The successful synthesis of 1,2 dihydronaphthalene **86**

2.2.8 Summary

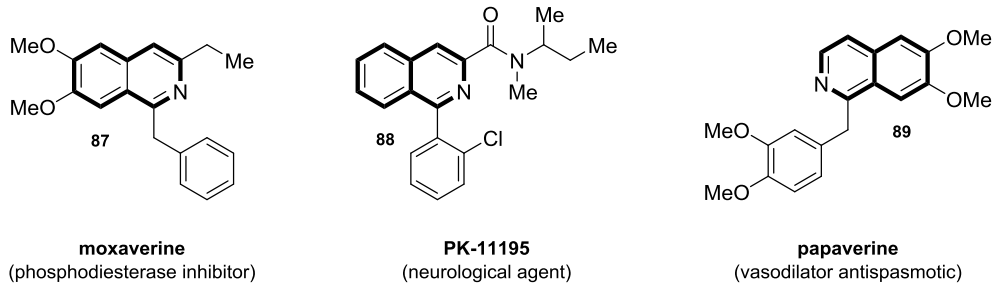
We have successfully developed a novel Rh(I)-catalysed cross-coupling reaction of aryl and alkyl terminal alkynes with simple aryl sulfides. Copper bromide along with silver carbonate or potassium carbonate are essential to the reaction. We demonstrated a broad range of functional group tolerance on both the sulfide and the alkyne coupling partners, as well as incorporating the developed reaction into a three-component hydroacylation/Sonogashira process using a single catalyst. This was then expanded to show a rapid synthesis of 1,2-dihydronaphthylenes. The expansion of the Sonogashira-type reaction is highly tolerant of halide functional groups and displays orthogonal reactivity to traditional palladium-catalysed Sonogashira chemistry.

Chapter 3: Rhodium-catalysed carbothiolation: A route to substituted isoquinolines

3.1 Introduction

3.1.1 Isoquinolines

Aromatic heterocycles represent the dominant structural motif in medicinal chemistry. Amongst the varied range of architectures found within this group, isoquinolines play an important role.[102] The isoquinoline skeleton is found abundantly in the plant world and is widely incorporated into medicinally important compounds (Figure 3.1). For example, the drug PK-11195 (88) based on the 1,3-substituted isoquinoline structure is one of the most widely used peripheral benzodiazepine receptor binding ligands.[103]



moxaverine
(phosphodiesterase inhibitor)

PK-11195
(neurological agent)

papaverine
(vasodilator antispasmotic)

Figure 3.1 Important pharmaceutical drugs containing the isoquinoline moiety

While there exists a range of methodologies for transforming relatively complex starting materials into substituted isoquinolines, the majority of "classic" routes to isoquinolines – the Pictet-Spengler, Bischler-Napieralski, and Pomeranz-Fritsch syntheses – involve key bond-forming steps which are largely centred on an electrophilic substitution process.[104] The reliance on electrophilic aromatic substitutions in these protocols imposes significant constraints on the substitution pattern that that can be applied on the starting arene and on the substitution patterns that can be accessed, due to the inherent electronic bias of this class of transformation. As such, methods which allow for the synthesis of substituted isoquinolines (or their precursors) with high efficiency and substrate tolerance are of significant value.

3.1.2 Carbothiolation

The synthesis of aromatic heterocycles has been transformed by the use of transition metal catalysis. The application of such metal catalysts has allowed access to non-traditional disconnections that complement the many classic approaches to these molecules.[105] Notably, the application of cross-coupling processes have permitted the use of new classes of building blocks for heterocycles synthesis. As mentioned previously, the majority of these methods rely on activation groups (such as the C-S moiety) to secure reactivity and to control regioselectivity; an intrinsic feature of these reactions is that on completion of the transformation, the activating group is usually discarded as waste (figure **3.2a**). This generation of waste is increasingly at odds with the demands of sustainable synthesis in which waste-free, atom-economic transformations are the ideal.[106] Coupling reactions that rely on addition processes, as opposed to substitution reactions, allow the activating group to be reincorporated into the product; the activating group is effectively recycled (figure **3.2b**). Reincorporation of the original activating group into the newly formed product, efficiently primes the product for subsequent synthetic transformations and begins to address the demands to produce more sustainable synthetic routes.[107]

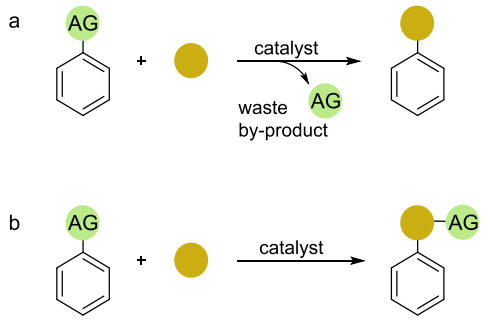


Figure 3.2 Activating group (AG) recycling. **a**, the traditional use of an activating group resulting in the desired bond construction but also in the formation of by-product waste. **b**, activating group recycling in which the original activating group is re-incorporated into the product with no waste generated.

One such process which meets these prerequisites is the carbothiolation reaction. The carbothiolation reaction is a metal-catalysed C-S activation process which involves the simultaneous introduction of carbon and sulfur functional groups to a C–C triple bond (figure **3.3**).

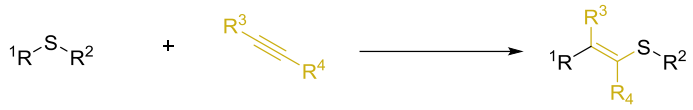


Figure 3.3 The carbothiolation reaction; an example of activating group reincorporation

The literature exhibits a handful of examples of carbothiolation reactions, requiring either high pressure systems or the use of activated sulfide starting materials, such as thiol esters, vinylsulfides or thiol cyanates.[108,109] In a complementary approach, Willis and co-workers have recently developed the first rhodium-catalysed carbothiolation reaction of alkynes using simple aryl sulfides (Figure **3.4**).[110] This carbothiolation approach allows for a wide range of substrates with different electronic and steric properties to be used. While unstrained aryl–alkyl sulfides have been employed in some early examples of Ni-catalysed cross-coupling reactions with Grignard reagents, no cases of simple aryl–alkyl sulfides taking part in addition-type processes were known prior to this this example.[111]

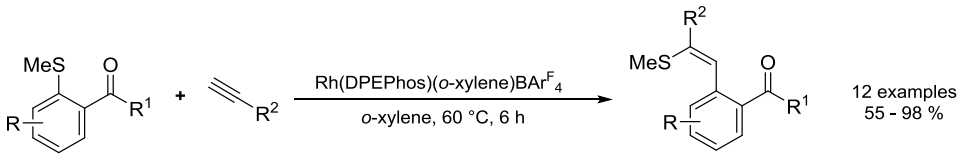


Figure 3.4 An efficient carbothiolation of alkynes using β-activating group-containing aryl sulfides developed by Willis and co-workers

Analysis of minor by-products from our related studies employing aryl–alkyl sulfide-substituted aldehydes in rhodium-catalysed hydroacylation reactions, inspired previous group members to develop this analogous carbothiolation approach using cationic rhodium(I)-chelating-*bis*-phosphine complexes. Akin to hydroacylation, a directing group must be positioned *ortho* to the activating group. The significance of the *ortho*-directing group is evident when looking closer at the mechanism suggested by Willis, Weller and co-workers (figure **3.5**).

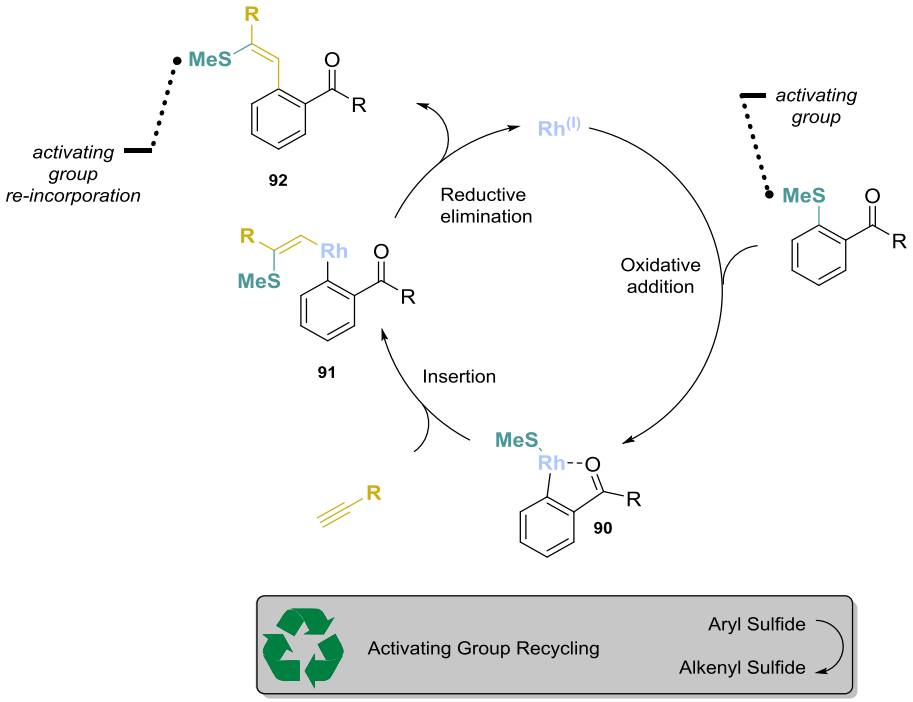


Figure 3.5 A mechanistic overview of the carbothiolation reaction using a rhodium(I)-catalyst

Initially, the cationic rhodium(I) catalyst oxidatively adds across the C-S bond to produce a rhodium(III) metal complex **90**. This C-S activation process can only occur in the presence of an acetyl group which must be positioned *ortho* to the sulfide. This moiety can not only direct the metal catalyst to initiate C-S activation but also presumably polarises the Rh-S bond to allow for subsequent insertion of the alkyne (**91**). This is followed by reductive elimination to afford the carbothiolation product with the reincorporation of the sulfide activating group (**92**) and regeneration of the rhodium(I) catalyst.

3.1.3 Project Aims

As previously discussed, our group has demonstrated the chelation-assisted carbothiolation of alkynes, as a way to showcase activating group recycling in action. The aim of this project was to illustrate that the recycled activating group still maintains synthetic value by developing a one-pot approach to the synthesis of highly substituted isoquinolines. Crucially, the alkenyl sulfide functionality incorporated in the carbothiolation product represents a masked carbonyl unit, and

as such provides a powerful handle for further functionalisation. The key transformation involves the Rh-catalysed carbothiolation of alkynes with carbonyl-containing aryl methyl sulfides, leading to the formation of a masked benzo-fused 1,5-dicarbonyl; treatment of dicarbonyl **94** with an ammonia source would allow access to isoquinolines (Figure **3.6**).

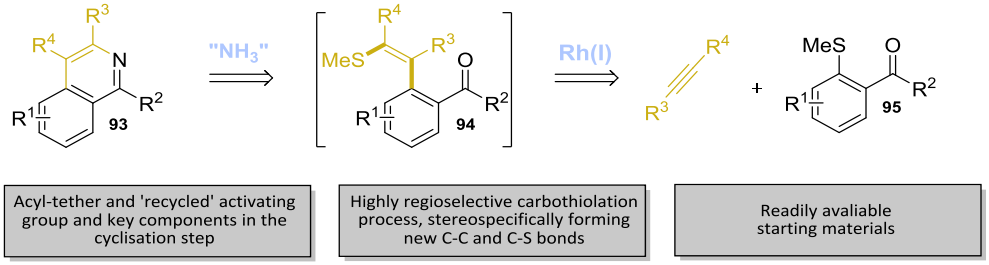


Figure 3.6 A retrosynthesis of the targeted isoquinoline moiety

3.2 Results and Discussion

3.2.1 Initial Screening

Initial studies focused on seeking to establish a new catalytic system for the preliminary carbothiolation transformation. The Willis groups initial report on the rhodium-catalysed alkyne carbothiolation reaction employed the Rh(DPEphos)(o-xylene)BAr^F_4 complex as a pre catalyst, in *o*-xylene.[110] Although this complex represents an efficient catalyst system, significantly the catalyst is not commercially available and is also difficult to prepare without the use of a glove box. Additionally, the use of the BAr^F_4 counter-ion makes this catalyst relatively expensive, with the $NaBAr^F_4$ precursor costing 25 times as much as the $RhCl_3$ precursor.[112] In order to deliver a practical solution, we therefore sought to identify a new catalyst system which retained the activity of complex the Rh(DPEphos)(o-xylene)BAr^F_4, was easily prepared, used commercially available components and avoided the use of the BAr^F_4 anion.

We began by employing the precursor $Rh(nbd)_2BF_4$ (**96**) which is commercially available and can be routinely employed without recourse to a glove box. The rhodium precursor can be combined

with an appropriate phosphine ligand and subsequently hydrogenated to generate the active catalyst *in situ* (97) (Figure 3.7).

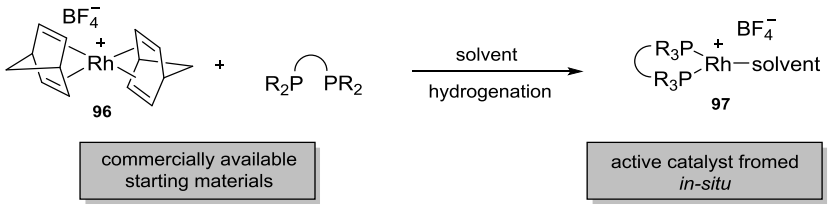
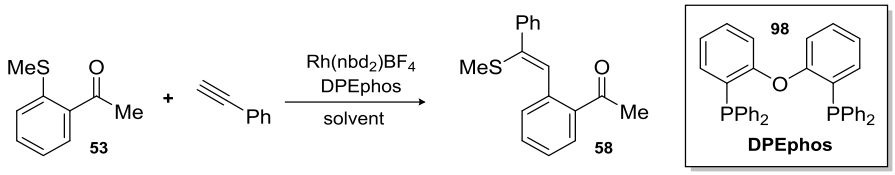


Figure 3.7 Illustration of the *in situ* formation of the active catalyst 97 from rhodium and phosphine precursors

We initially employed the *bis*-phosphine ligand DPEphos (98) due to its key role in the targeted transformation as shown by our group's earlier investigation. Akin to this previous work around carbothiolation, we set about testing our proposed catalyst system by exploring the coupling of aryl methyl sulfide 53 and phenylacetylene. Starting material 53 can easily be synthesised *via* a smooth S_NAr substitution reaction from the corresponding fluoro-ketone and sodium thiolate salt in quantitative yield (Chapter 5, 53).

Due to the significant decrease in catalyst solubility when moving from the $BAr^F{}_4$ to the BF_4 counter-ion, a new solvent system was established (Table 3.0). Moving away from *o*-xylene, we evaluated a variety of solvents and temperatures and found that heteroatom containing solvents such as 1,2-DCE and chlorobenzene displayed the best results, generating alkyl sulfide 58 in good yield.

Table 3.0 Solvent screen

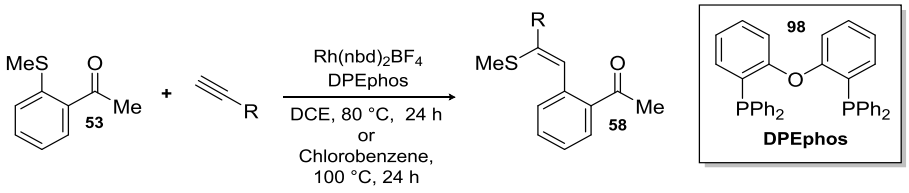


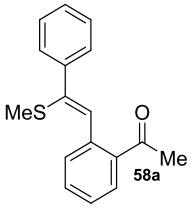
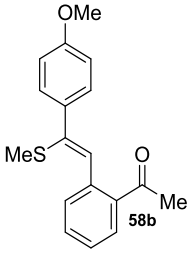
Entry	Solvent	Temperature (°C)	Isolated yield of 58
1	DMF	125	-
2	Dioxane	-	-
3	Acetone	55	44%
4	THF	55	48%
5	THF (10% water)	55	46%
6	DCE	80	75%
7	Chlorobenzene	100	73%

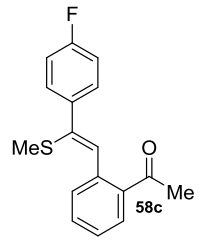
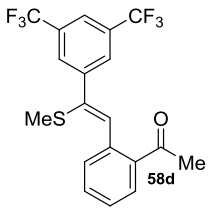
Reaction Conditions: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), DPEphos (0.05 mmol), solvent (2 mL), 24 h.

At this point testing was carried out on selection of terminal alkynes to examine the new catalytic system while varying the electronics of the alkyne component (Table **3.1**).

Table 3.1 Investigation into the performance of an *in situ* catalytic system in both DCE and ClPh



Entry	Product	Yield (DCE)	Yield (C_6H_5Cl)	Yield (*o*-xylene with ($Rh(DPEphos)(nbd)BAr^F_4$)
1		75%	73%	98%
2		77%	73%	85%

3		83%	70%	97%
4		33%	24%	82%

Reaction Conditions: Aryl methyl sulfide (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), DPEphos (0.05 mmol), solvent (2 mL), 24 h.

Both electron-rich (entry **2**) and in particular electron-poor (entries **3-4**) acetylene derivatives showed a marked decrease in catalytic activity when using the *in situ* catalyst compared directly with the complex (Rh(DPEphos)(nbd)$BAr^F{}_4$ in *o*-xylene. It was evident that moving from a $BAr^F{}_4$ counter-anion to BF_4 anion limited turnover. A possible explanation for this is that the $BAr^F{}_4$ anion has bulky, non-polar, weakly coordinating properties which can lead to a more active metal-centered catalyst. Traditional counter-ions such as BF_4^- are far stronger coordinating and more likely to form tighter ion-pairs with a metal centre. This could obstruct or slow down the addition of substrates to the metal centre, decreasing the rate or deactivating the catalyst altogether.

3.2.2 Ligand Investigation

In an attempt to design a faster catalyst we next focused on the design of the ligand. Due to its structure and presence of a hemilabile oxygen, DPEphos is known to be a relatively flexible ligand displaying a wide natural bite angle of 102°. Previous members of the Willis group have probed the mechanism of the carbothiolation reaction and discovered that once DPEphos is bound to the metal centre it can adopt a number of conformational modes (figure **3.8**).[110]

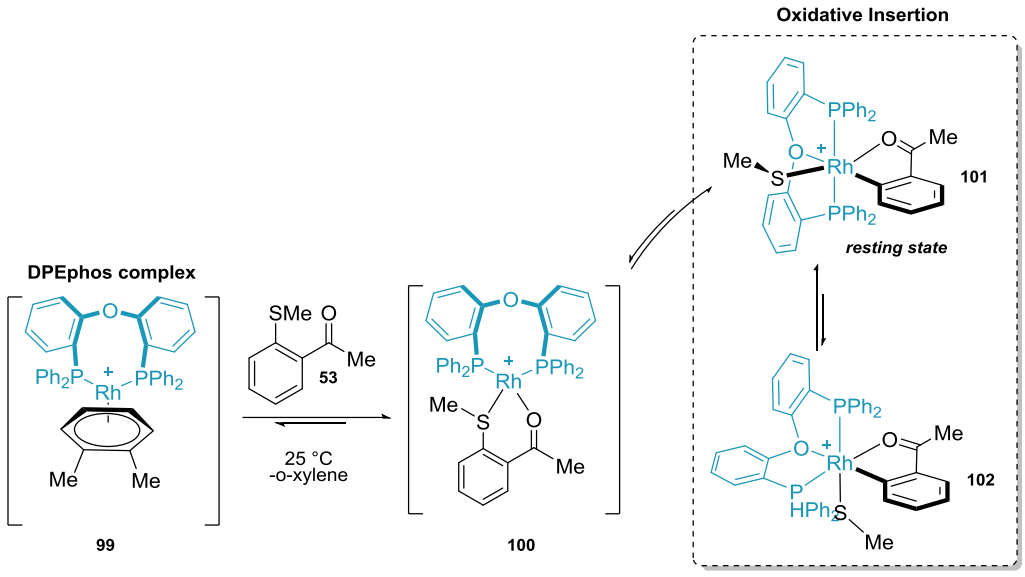
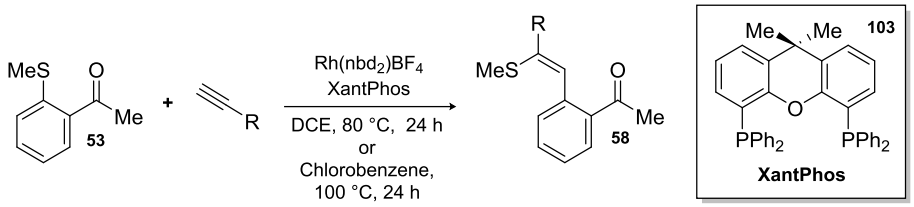


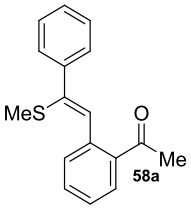
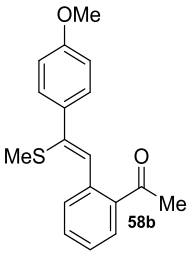
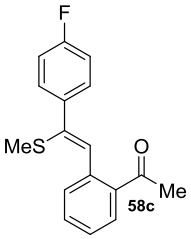
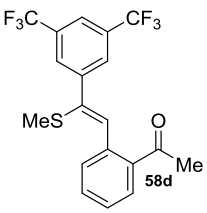
Figure 3.8 Proposed mechanism for the initial C-S activation of 53 with catalyst 99

Using Rh(DPEphos)(*o*-xylene)BAr^F_4 (99) as the active catalyst in *o*-xylene, they had observed that the reaction of 99 with ketone 53 produces an equilibrium mixture of the isomeric complexes [Rh(***fac***-κ^3–P,O,P–DPEphos)(SMe)σ,κ^1-$C_6H_4C(O)Me$)][BAr^F_4] 102 and [Rh(***mer***-κ^3–P,O,P–DPEphos)(SMe)(σ,κ^1-$C_6H_4C(O)Me$)][BAr^F_4] 101 alongside free xylene (298 K, 99 : 102 : 101 0.1 : 0.1 : 1.0). Characterisation of 102 and 101 was completed by (^{1}H, ^{13}C, ^{31}P) NMR spectroscopy (CD_2Cl_2) and ESI–MS. It was also shown that the interconversion between the major and minor conformers occurs *via O*–decoordination of the DPEphos ligand to access a conformationally flexible 5-coordinate intermediate.

On the basis of these observations we speculated that by locking the ligand into a single, active conformation, the efficiency of the reaction might be improved. To impede this flexibility around the P-O-P bonds present in DPEphos, we explored the use of a rigid DPEphos analogue, Xantphos (103). Pleasingly, when evaluated in the carbothiolation of phenylacetylene, the reaction employing Xantphos reached completion in 2 h compared to 75% in 24 h when using DPEphos (Table 3.2, entry 1). The carbothiolation of both electron-rich and electron-poor alkynes was performed with quantitative conversion to the carbothiolated product providing a marked improvement from the previous catalytic system (entries 2-4).

Table 3.2 Use of Xantphos as ligand in the carbothiolation reaction



Entry	Product	Yield (DCE)	Yield (C_6H_5Cl)	Yield (with DPEphos in DCE or C_6H_5Cl)	Yield (*o*-xylene with (Rh(DPEphos)(nbd)BAr^F_4)
1		99%	95%	75%, 73%	98%
2		95%	98%	77%, 73%	85%
3		89%	98%	83%, 70%	97%
4		75%	77%	33%, 24%	82%

Reaction Conditions: Aryl methyl sulfide (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), solvent (2 mL), 24 h.

Due to restricted flexibility of the Xantphos ligand, we speculated that once the catalyst oxidatively inserts into the C-S bond, the Xantphos preferentially adopts a meridinal conformation. The improved activity of this specific isomer also suggests that the analogous *mer*-isomer of the

DPEphos complex (**101**) is the active species in the carbothiolation. To understand the activity of these systems in more detail, pre-formed and *in situ* prepared Xantphos- and DPEphos containing catalysts were compared by monitoring the reactions by HPLC (Figure **3.9**).

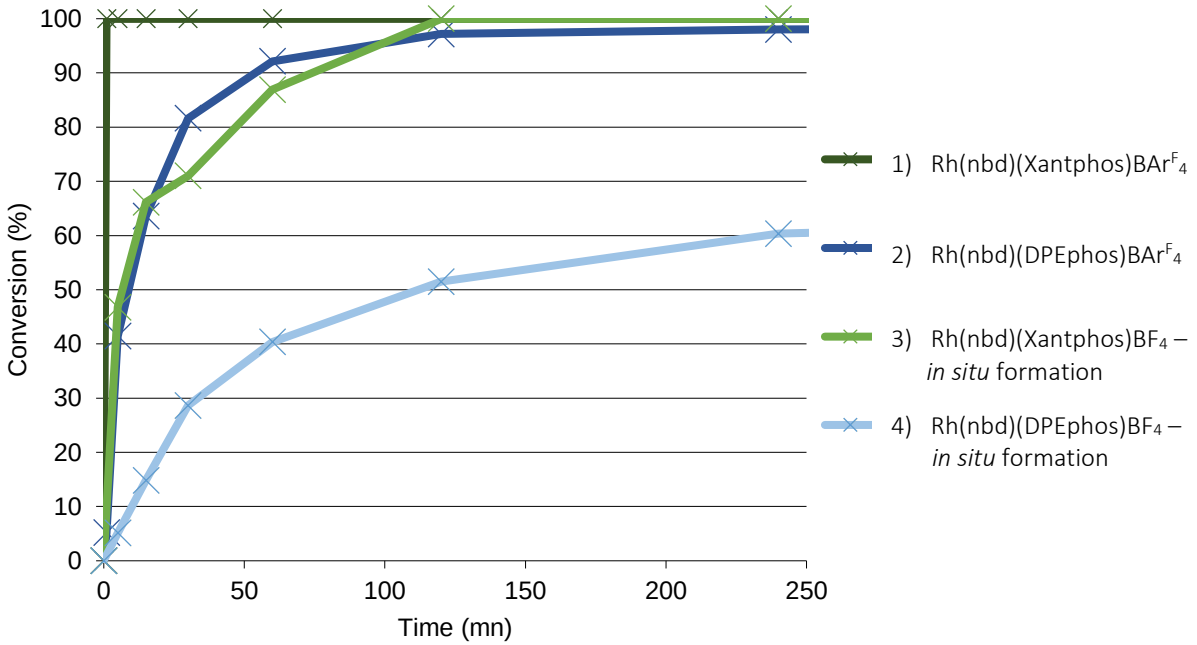


Figure 3.9 Investigation into the performance of DPEphos and Xantphos ligands

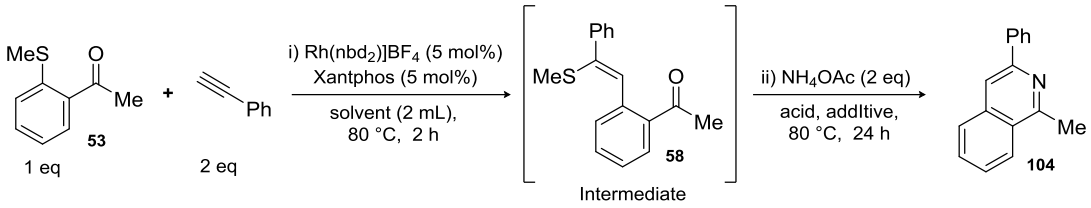
Preformed catalysts containing the BAr$^F_4$ counter-anion showed higher rates of conversion relative to the BF$_4$ catalysts (**1,2** vs **3,4**). Additionally, when moving from DPEphos to Xantphos there was a dramatic increase in the rate of turnover in both preformed and *in situ* prepared catalysts (**1,3** vs **2,4**). Catalyst **1** comprising of the Xantphos ligand and BAr$^F_4$ counter-anion, displayed exceptional activity with full conversion to the product in minutes. Nevertheless, the Rh(Xantphos)(nbd)BF$_4$ complex, formed *in situ*, showed very good activity with comparable performance to that of the preformed catalyst **2**.

3.2.3 Cyclisation Optimisation

Having established an efficient and easily accessible catalytic system for the carbothiolation step, the next task was to address the subsequent cyclisation of our one-pot synthesis. The

carbothiolation adducts featuring the recycled methyl sulfide activating group are convenient precursors to highly substituted isoquinolines. We hypothesised that a reaction of intermediate **58** with a nitrogen source under acidic conditions would induce the necessary cyclisation (Table **3.3**). Pleasingly, we found that adding ammonium acetate (2 eq) and acetic acid (2 mL) directly into the crude mixture of the initial carbothiolation reaction, followed by heating (80 °C) for 24 h resulted in the desired 1,3-substituted isoquinoline (**104**) in 51% yield (Table **3.3**, entry **1**).

Table 3.3 initial screening of cyclisation condition



Entry	Solvent	Acid	Additive	Conversion **104**
1	DCE	Acid (2 mL)	-	51%
2	DCE	Acid (2 mL)	Copper(I) acetate (1 eq)	48%
3	DCE	Acid (2 mL)	Copper(II) triflate (1 eq)	52%
4	DCE	Acid (2 mL)	Copper(I) acetate (3 eq)	54%
5	DCE	Acid (2 mL)	Copper(II) triflate (3 eq)	49%
6	DCE	Formic Acid (2 mL)	-	0%
7	DCE	Formic Acid (2.5 eq)	-	0%
8	DCE	TFA (2 mL)	-	0%
9	DCE	TFA (2.5 eq)	-	0%
10	DCE	TFA (1 drop)	-	0%

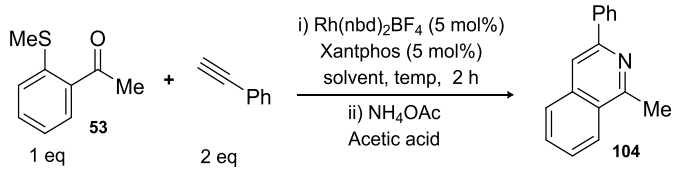
Reaction Conditions: Carbothiolation: **53** (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), solvent (2 mL), 2 h. Cyclisation: Acetic acid (2 mL), NH_4OAc (0.30 mmol), 80 °C, 24 h. Conversions calculated using ^1H NMR spectroscopy.

During the purification of this reaction, it was noticed a strong odour was produced by the reaction. We reasoned that this could be attributed to methanethiol gas, which was presumed to be a by-product of the desulfitative cyclisation and a driving force of the reaction. In an attempt to improve conversion to the isoquinoline from the alkenyl sulfide intermediate, we hypothesized that the addition of a thiophilic additive could help promote cyclisation by binding to the methyl sulfide moiety and subsequently activating the C-S bond. A small selection of copper sources were

tested in various quantities but resulted in no effect on the overall conversion (entries 2-5). Interestingly, upon workup no unpleasant odours were detected suggesting complexation of the copper to the thiol by-product, either prior to or after cyclisation. Next, we selected a variety of acids to screen in an effort to push the reaction to completion. Unfortunately we found that by replacing AcOH with more acidic reagents proved unsuccessful and resulted in decomposition of the dicarbonyl intermediate (entries 6-11).

Satisfyingly, switching from conventional heating to microwave heating at an increased temperature of 95 °C for the cyclisation step, improved conversion to the isoquinoline 104 to 65% (Table 3.4, entry 1).

Table 3.4 Investigation into reagent equivalences and reaction time



Entry	i) Solvent (mL)	i) Temp (°C)	AcOH (mL)	NH_4.OAc (eq)	ii)Temp (°C)	ii)Time (h)	Conversion to 104
1	DCE (2 mL)	80	2	2	μW 95	2	65%
2	PhCl (2 mL)	100	2	2	110	24	74%
3	PhCl (2 mL)	100	2	5	110	24	83%
4	PhCl (2 mL)	100	4	5	110	24	89%
5	PhCl (4 mL)	100	2	5	110	24	45%
6	PhCl (4 mL)	100	2	10	110	24	58%
7	PhCl (1 mL)	100	4	5	110	24	96%
8	PhCl (0.5 mL)	100	4	5	110	16	100%

Reaction Conditions: Carbothiolation: 53 (0.15 mmol), phenylacetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), solvent, 2 h. Cyclisation: Acetic acid, NH_4OAc. Conversions calculated using ^1H NMR spectroscopy.

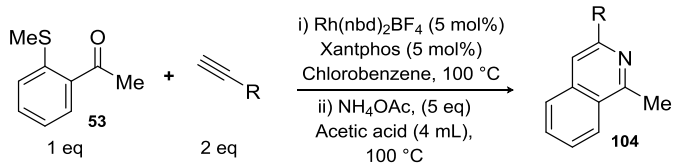
This suggested that higher reaction temperatures might contribute to an increase in conversion. As the initial carbothiolation step was performed in 1,2-dichloroethane which has a boiling point of 85 °C, temperatures for the cyclisation step are also limited to this value. We were pleased to discover a change to chlorobenzene in the initial step offered the ability to increase reaction temperature of the cyclisation step, which improved conversion (entry 2). Interestingly, increasing

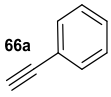
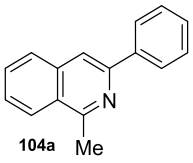
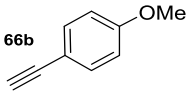
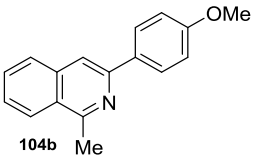
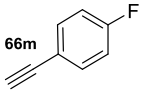
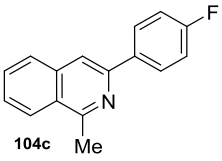
the amount of AcOH and NH_4.OAc increased conversion, whilst increasing the initial volume of chlorobenzene suppressed the amount of product formed (entry 3-6). As a result, it was found that reducing the amount of organic solvent, hence increasing the concentration of AcOH and increasing the equivalents of ammonium acetate, resulted in a 100% conversion to the isoquinoline (entry 8).

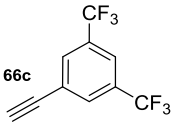
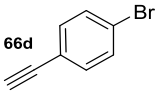
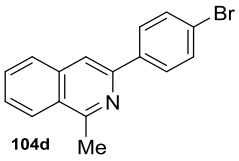
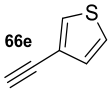
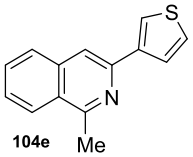
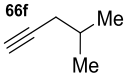
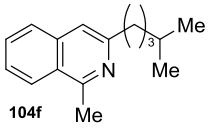
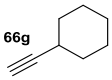
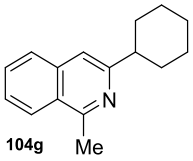
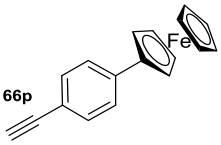
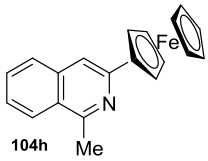
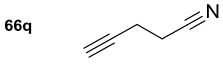
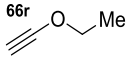
3.2.4 Reaction Scope

These conditions were applied then to the synthesis of a variety of 1,3-substituted isoquinolines employing 53 as the standard sulfide and a range of alkynes (Table 3.5). All alkynes used were commercially available and were purified before use. Notably, all products could be purified *via* dry loading directly onto silica column, without the need for an aqueous work up.

Table 3.5 Scope of terminal alkynes compatible in the one-pot rhodium-catalysed alkyne carbothiolation-based isoquinoline synthesis



Entry	Ketone SM	Alkyne	Product	Carbothiolation Time (h)	Cyclisation Time (h)	Isolated Yield
1	**53**	 **66a**	 **104a**	2	16	90% (93%)*
2	**53**	 **66b**	 **104b**	3	16	85%
3	**53**	 **66m**	 **104c**	2	16	85%

4	**53**		-	2	-	0%
5	**53**			2	16	80%
6	**53**			4	16	76%
7	**53**			4	16	84%
8	**53**			2	16	82%
9	**53**			3	16	90%
10	**53**		-	-	-	0%
11	**53**		-	-	-	0%

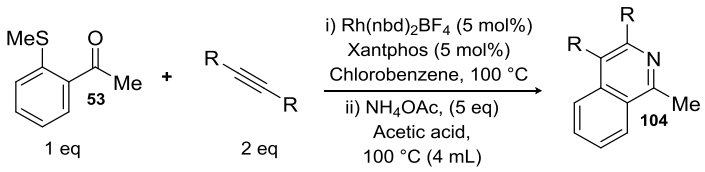
Reaction Conditions: Carbothiolation: **53** (0.15 mmol), acetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), ClPh (2 mL), 100 °C, 2 h. Cyclisation: Acetic acid (4 mL), NH_4OAc (0.75 mmol), 100 °C, 16 h.

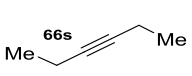
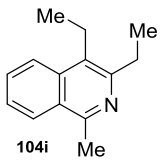
We were pleased to observe that a variety of alkynes were compatible in this isoquinoline forming reaction. This allowed access to a range of alternative substituents in the 3-position including electron-donating (**104b**) and electron- withdrawing groups (**104c**). The *bis*-CF_3 substituted aryl alkyne **66c** showed good activity in the rhodium-catalysed carbothiolation step to produce the dicarbonyl intermediate, however this subsequently decomposed once subjected to cyclisation conditions (entry **4**). Entries **3** and **5** show that it was possible to incorporate halide substituents into the isoquinoline product as they remain intact throughout the one-pot process. This enables

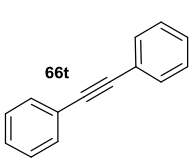
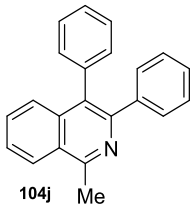
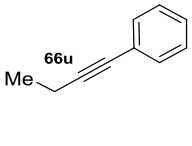
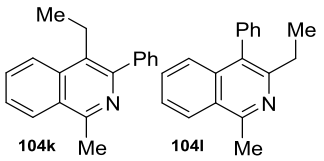
the potential for further functionalisation through metal-catalysed cross-coupling or simple S_NAr processes. Heterocyclic substituents, such as thiophene, could be carried through both reactions to generate the biheteroaryl product **104e** in good yield. Aliphatic alkynes were also excellent substrates for this reaction, with linear (**104f**) and cyclic (**104g**) aliphatic groups efficiently incorporated into the product. Additionally, a ferrocene unit could be installed without incident (**104h**). Unfortunately, it was not possible to utilise alkynes containing heteroatoms as this shut down the initial carbothiolation reaction (entries **10-11**). This could be attributed to the ligating nature of these atoms, as they can bind to the rhodium and impede the reaction. The reaction could also be performed with a reduced catalyst loading with no decrease in the yield; employing phenylacetylene as the alkyne component, the reaction was performed on a 1.2 mmol scale using 1 mol% rhodium, to deliver the isoquinoline product **104a** in 93% yield.

Unlike the previous system which uses DPEphos, this new catalytic system was not limited to the use of terminal alkynes. For example, employing 3-hexyne allowed isoquinoline **104i** to be isolated in 45% yield, while diphenylacetylene allowed the formation of **104j** (Table **3.6**).

Table 3.6 Scope of internal alkynes compatible in the one-pot rhodium-catalysed alkyne carbothiolation-based isoquinoline synthesis



Entry	Ketone SM	Alkyne	Product	Carbothiolation Time (h)	Cyclisation Time (h)	Isolated Yield
1	**53**	 **66s**	 **104i**	2	16	45%

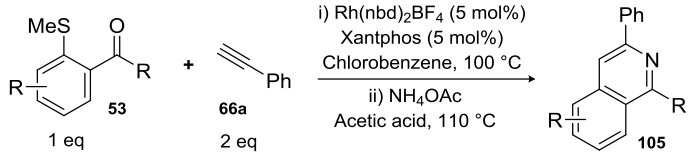
1	**53**			2	72	39%
3	**53**			5	72	61% (104k:104l) (3:1)

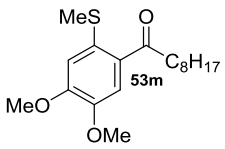
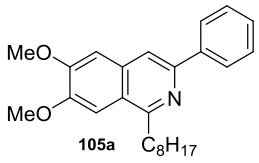
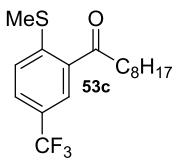
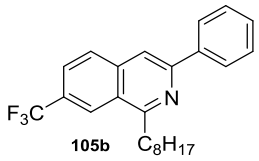
Reaction Conditions: Carbothiolation: **53** (0.15 mmol), acetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), ClPh (2 mL), 100 °C, 2 h. Cyclisation: Acetic acid (4 mL), NH_4OAc (0.75 mmol), 100 °C, 16 h.

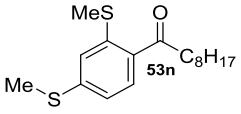
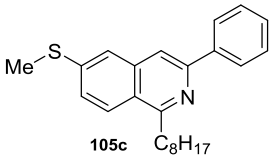
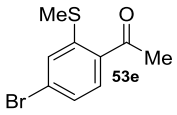
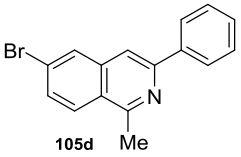
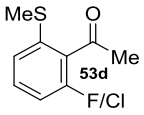
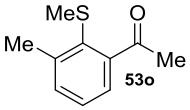
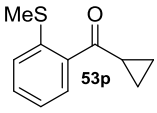
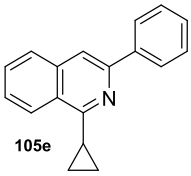
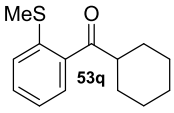
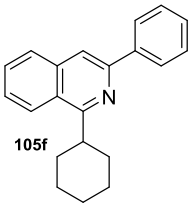
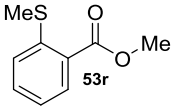
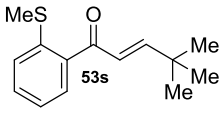
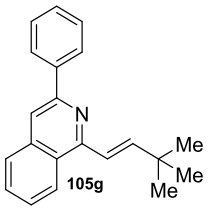
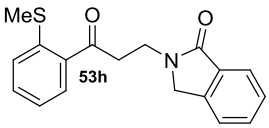
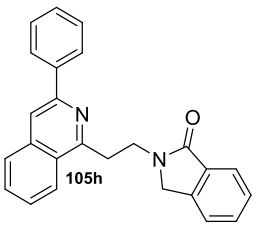
This allows rapid access to 1,3,4-substituted isoquinolines. Although the use of an unsymmetrical internal alkyne was successful, a mixture of regioisomers was obtained (entry 3, **104k**, **104l**). The regioisomers were assigned using a combination of nOe and COSY experiments.

We next examined the scope of the substitution possible on the sulfide fragment and began by exploring variation on the carbocyclic ring employing phenylacetylene as the common alkyne (Table **3.7**).

Table 3.7 Scope of aryl methyl sulfides compatible in the one-pot rhodium-catalysed alkyne carbothiolation-based isoquinoline synthesis



Entry	Ketone SM	Product	Carbothiolation Time (h)	Cyclisation Time (h)	Yield
1			2	16	79%
2			2	16	50%

3			2	16	88%
4			2	16	76%
5		-	-	-	0%
6		-	-	-	0%
8			2	16	47%
9			4	16	60%
7		-	-	-	0%
10			4	16	55%
11			4	16	71%

Reaction Conditions: Carbothiolation: **53** (0.15 mmol), acetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), ClPh (2 mL), 100 °C, 2 h. Cyclisation: Acetic acid (4 mL), NH_4OAc (0.75 mmol), 100 °C, 16 h.

Electron-donating and withdrawing groups delivered the substituted isoquinolines in average to excellent yields (entries 1-4). Isoquinoline 105c containing an -SMe group positioned *para* to the acyl tether remained untouched during the one pot synthesis, demonstrating the high levels of regiocontrol possible. Again, an aryl bromide, this time positioned *para* to the ketone, remained intact throughout the reaction (entry 4). Unfortunately, substituents positioned *ortho* to the ketone did not undergo the initial rhodium catalysed carbothiolation. This could be explained by the steric effect of the *ortho* substituent, particularly its effect on the formation of the 5-membered rhodacycle intermediate. Similarly, substituents *ortho* to the sulfide were not tolerated. Having a substituent here could potentially sterically hinder the oxidative insertion of the rhodium metal into the C-S bond or the approach of the alkyne. Variation in the substitution of the carbonyl group was also possible, including longer aliphatic ketones (105a-c), cyclopropyl (105e) and cyclohexyl ketones (105f), and an α,β-unsaturated ketone (105g). Good functional group tolerance was also displayed by the incorporation of a pendant oxindole (105h). Finally, changing from a ketone to a methyl ester shut down the first carbothiolation and no intermediate product was detected (entry 7).

3.2.5 Synthesis of 3-Pr-moxaverine

To demonstrate the value of the newly developed 3-compoment-one-pot methodology, the reaction was applied to the preparation of a simple derivative of the phosphodiester inhibitor moxaverine (106). A disconnection back to the methylsulfide ketone and but-1-yne was envisaged, but due to the volatility of this alkyne a heavier, more practical analogue was used. The phenylethan-ketone 107 substrate could be readily prepared *via* thiolation of 6-fluoroveratraldehyde 110 followed by a Grignard addition and oxidation of the subsequent alcohol 108 (Figure 3.10).

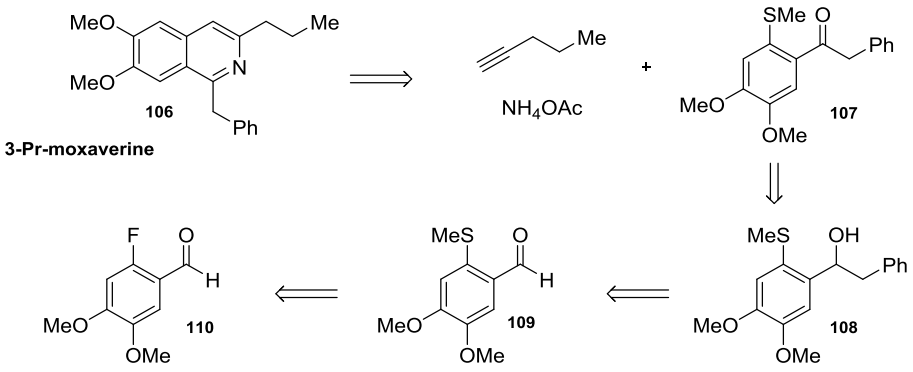


Figure 3.10 Retrosynthesis of 3-Pr-moxaverin

In the forward direction, we began by simply thiolating the 6-fluoroveratraldehyde *via* an S_NAr reaction using NaSMe salt to produce sulfide **109** in a 97% yield (Figure **3.11**). The Grignard addition proved challenging; after testing a number of conditions with both commercially available benzylmagnesium and traditionally synthesised Grignard using magnesium turnings and benzylbromide in THF, only a 45% yield was obtained of the alcohol **108**.

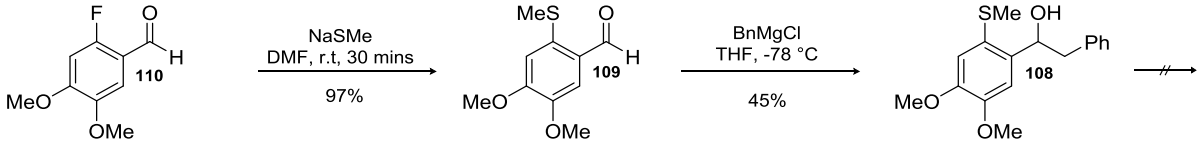


Figure 3.11 Initial failed synthesis of 3-Pr-moxaverine

At this point it was decided to change the order of reaction and start with the Grignard addition directly to the *o*-fluoro-aldehyde **110**, which proved more successful, giving a 70% yield of the alcohol (Figure **3.12**)

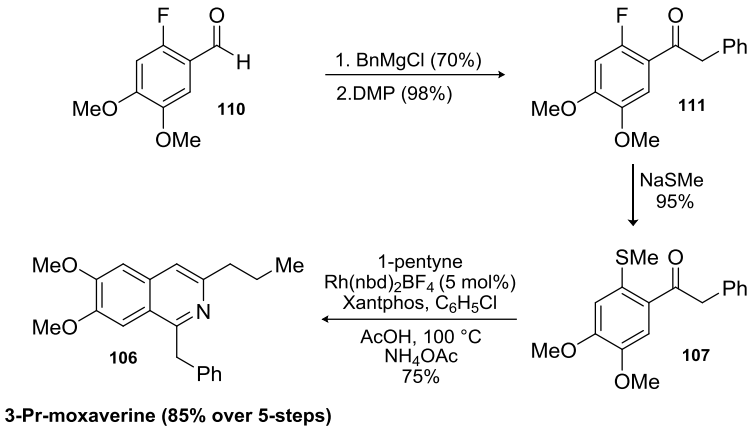


Figure 3.12 Formation of 3-Pr-moxaverine via 3-steps synthesis starting from 110

Multiple oxidative conditions were explored to reach 111, including MnO_2, PCC, Parikh Doering and Oppenauer oxidations but all returned starting material or gave undesired side products. Eventually it was found that oxidising with DMP produced 111 in an excellent yield. This was then followed by the S_NAr substitution reaction to give sulfide 107 in near quantitative yield. Finally, combination of sulfide 107 with 1-pentyne, employing the optimized carbothiolation/cyclization conditions, delivered 3-propyl moxaverine in good overall yield. The intermediacy of sulfide 107 serves as a useful diversity generating branch point, as simply exchanging 1-pentyne for alternative alkynes would allow the rapid preparation of further derivatives.

3.2.6 Employing Alternative *N*-Nucleophiles

Having used our new methodology to develop an array of substituted isoquinolines, we wished to explore its utility by investigating the use of alternative *N*-nucleophiles in the cyclisation process. Whilst the majority of other isoquinoline syntheses can only give access to the isoquinoline manifold in one oxidation level, a strength of this method is that by variation of one of the reaction components, isoquinolines of a higher oxidation level could be readily accessed. For example, after using 53 and phenylacetylene in the carbothiolation reaction, we substituted the ammonium acetate with hydroxylamine hydrochloride to access the isoquinoline *N*-oxide 112 (Figure 3.13).

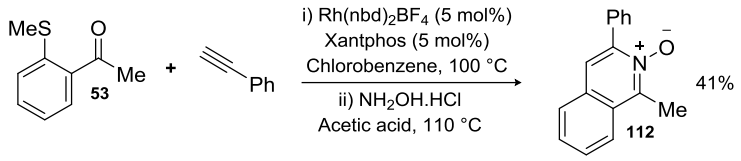


Figure 3.13 Example of successful isoquinoline *N*-oxide synthesis

We felt that this powerful and direct approach to their synthesis would prove extremely useful as alternative procedures involving direct oxidations of isoquinolines to their *N*-oxides can have limited functional group tolerance and use a stoichiometric equivalent of an oxidising agent in the process.

Next, we sought to utilise the developed carbothiolation/cyclisation sequence to display its practicality in the formation of isoquinolinium salts. By replacing ammonium acetate with a primary amine, we envisaged this would allow access to a variety of *N*-substituted isoquinolinium acetates (Figure 3.14).

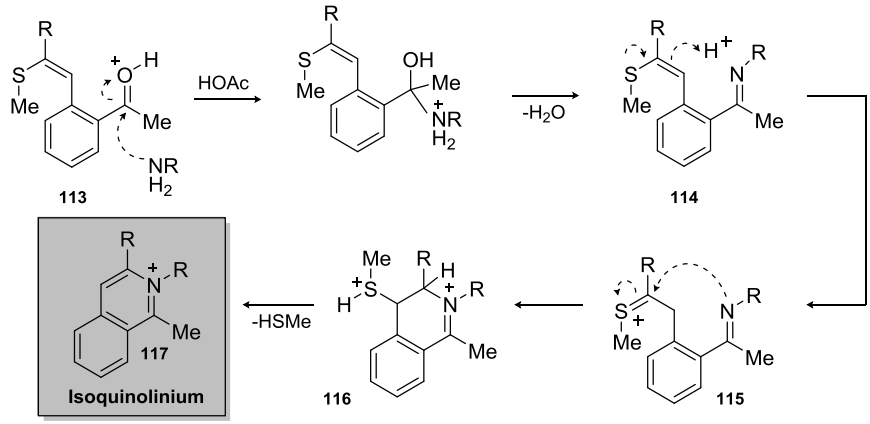


Figure 3.14 Proposed mechanism for the cyclisation of reaction intermediate 113

To investigate this, once the carbothiolation of 53 and phenylacetylene was complete, *p*-anisidine was employed as the nucleophilic nitrogen source in the cyclisation step (Figure 3.15). After leaving the cyclisation reaction for 24 h, the carbothiolation intermediate had been completely consumed, producing two new compounds as seen by TLC. Both compounds were highly florescent under UV and had respective R_f values of 0 and 0.45 (7.5% ether/petrol). Once an aqueous work-up was completed, we noticed the compound on the baseline had been transferred to the aqueous extracts. This finding suggested it may have been be the isoquinolinium salt, which

was confirmed by mass spectrometry. Unfortunately, repeated attempts to isolate the salt by concentration of the aqueous solution only resulted in the decomposition of the isoquinolinium. The less polar side product was isolated by column chromatography and was found to be amino-naphthalene **119**.

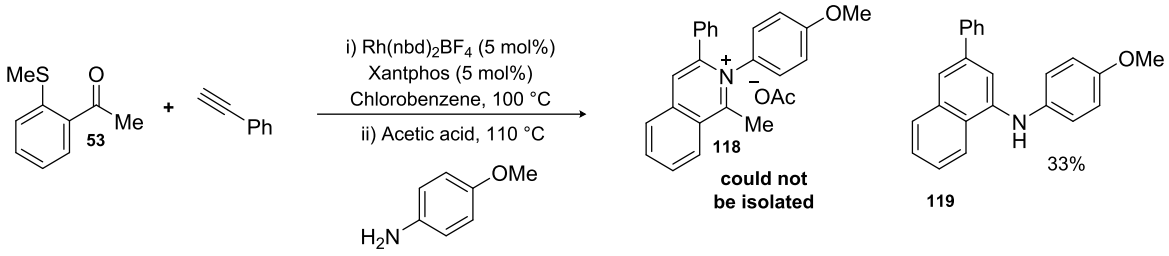


Figure 3.15 Investigation into the use of p*-anisidine as an alternative nitrogen-source*

It was considered that the formation of the amino-naphthalene **119** could be attributed to the formation of an emanine intermediate (Figure **3.16**, **120**). Mechanistically, the enamine could go on to attack the electrophilic carbon and cyclise to eventually form the amino-naphthalene **121** (Figure **3.16**).

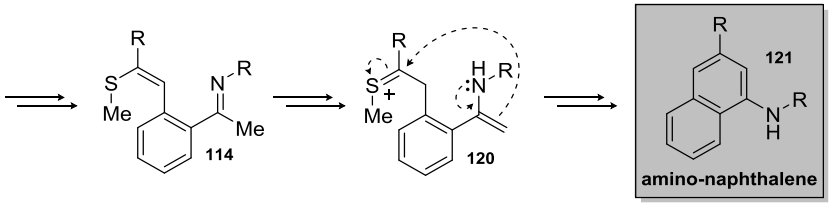


Figure 3.16 Proposed mechanism for the formation of amino-naphthalene product

Due to the difficulties in purification of the ionic complex **118**, we proposed that an *in situ* reduction of the salt would form the less polar, non-ionic dihydroisoquinoline compound, which would hopefully be easier to purify and isolate. Treating the crude cyclisation mixture with $NaBH_4$/MeOH would presumably selectively reduce the iminium in **118** and also be non-reactive towards the amino-naphthalene side product. This proved successful, producing dihydroisoquinoline **122** in a yield of 58% along with the amino-naphthalene **119** in 30% (Figure **3.17**)

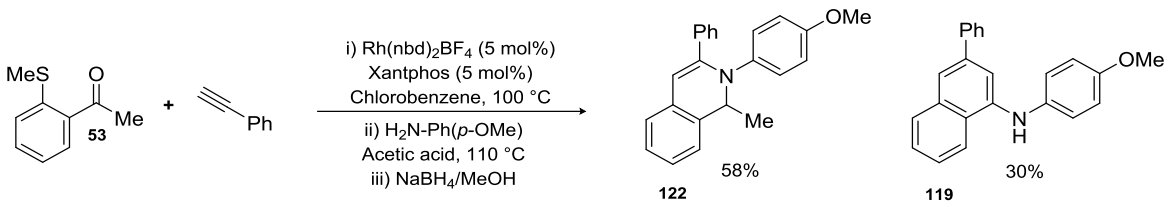
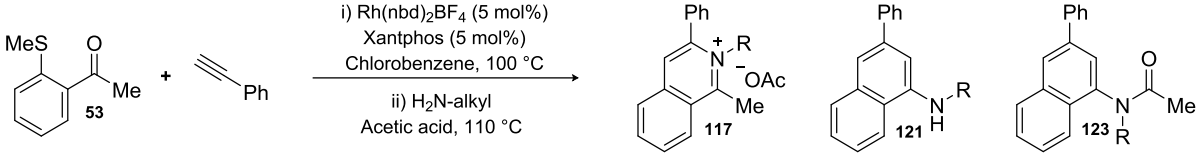


Figure 3.17 Isolation of dihydroisoquinoline 122 via reduction of isoquinolinium salt

Next, we decided to investigate the use of alkyl amines as possible *N*-nucleophiles in the cyclisation step. We began by using liner aliphatic amines and immediately noticed a difference in reactivity when compared to previous results using *p*-anisidine (Table 3.8).

Table 3.8 Investigation into the use of alkyl-amines in the cyclisation step



Entry	Alkyl amine	Yield 117	Yield 121	Yield 123
1	ethyl amine	-	32%	47%
2	pentyl amine	-	23%	30%
3	octyl amine	-	45%	50%

Reaction Conditions: Carbothiolation: 53 (0.15 mmol), acetylene (0.30), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), ClPh (2 mL), 100 °C, 2 h. Cyclisation: Acetic acid (4 mL), alkyl amine (0.75 mmol), 100 °C, 16 h.

Once the carbothiolation intermediates had been consumed in the cyclisation step, we saw that three new products had been formed. Each reaction showed a highly fluorescent compound on the base line of the TLC and two others compounds with good separation. The highly polar compounds on the base line were confirmed by mass spectrometry to be the isoquinolinium salts. Isolation of the salts again proved elusive and even attempts to reduce them to the dihydroisoquinoline failed, giving only trace amounts of product. The remaining two compounds were isolated *via* column chromatography and were characterised as the corresponding amino-naphthalene 121 and acetamide-naphthalene 123. Mechanistically, the formation of acetamide-naphthalene 123 could occur via a reaction between acetic acid and the corresponding amino-naphthalene. Alternatively the alkyl amine could potentially react with acetic acid, either prior to or after condensation of the ketone (Figure 3.18).

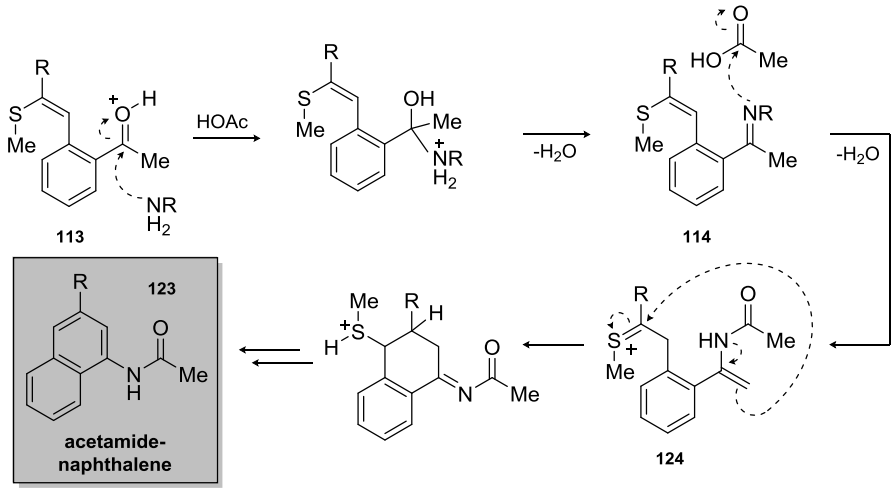
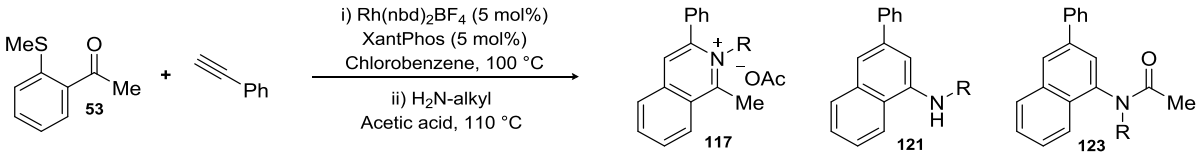


Figure 3.18 Proposed mechanism for the formation of acetamide-naphthalene

From these initial results using linear alkyl amines, it was evident that the isoquinolinium salts were not isolable and were in fact minor by-products of the reaction. In an attempt to design a more selective reaction, attention turned to promoting the cyclisation of the amino-naphthalene-type carbocycles. It was hypothesised that the use of a more bulky alkyl amine could hinder the attack of the imine on the acetic acid and prevent the formation of the acyl-substituted enamine, hence suppressing formation of **123**. Pleasingly, after testing with isopropyl- and cyclohexylamines, exclusive formation of the amino-naphthalene **121** was achieved in excellent yields (Table **3.9**).

Table 3.9 Investigation into the use of branched alkyl-amines in the cyclisation step



Entry	Alkyl amine	Yield **117**	Yield **121**	Yield **123**
1	isopropyl amine	-	77%	-
2	cyclohexyl amine	-	82%	-

Reaction Conditions: Carbothiolation: **53** (0.15 mmol), acetylene (0.30 mmol), $Rh(nbd)_2BF_4$ (0.05 mmol), Xantphos (0.05 mmol), ClPh (2 mL), 100 °C, 2 h. Cyclisation: Acetic acid (4 mL), alkyl amine (0.75 mmol), 100 °C, 16 h.

3.2.7 Summary

In conclusion, we have demonstrated the application of rhodium-catalysed intermolecular carbothiolation to the synthesis of highly substituted isoquinolines in a fashion which proceeds through a 100% atom-economic multiple (carbon-carbon and carbon-sulfur) bond forming step followed by a simple acid catalysed cyclisation. We have also demonstrated that the carbothiolation transformation is an example of 'activating group recycling', in that the initial methyl sulfide activating group is embedded in the alkenyl sulfide product, providing an active group for the isoquinoline transformation. Importantly, we have developed a second-generation catalyst system for this alkyne carbothiolation. This new catalyst offers reduced reaction times and low catalyst loadings, allowing an 'activating group recycling' approach to arene functionalisation to be achieved in a practical manner. Notably, the catalyst is generated *in situ* from commercial components. We have utilised this approach to arene functionalisation in a one-pot, three-component synthesis of isoquinolines and have delivered a convergent and efficient synthetic sequence that allows for the preparation of a diverse family of isoquinolines. We have also demonstrated that this process has further applications in the synthesis of drug derivative, 3-Pr-moxaverin and also the construction of amino-naphthalene carbocycles.

Chapter 4: Conclusion and Future work

Due to the highly valuable structures that can be accessed through cross-coupling reactions, research groups have focused on finding new ways to expand the capacity of compounds applicable for such reactions. As discussed in the Introduction Chapter, sulfides have been found to be effective partners in metal-catalysed C-S activation protocols, however they are limited to highly activated substrates, such as thiol ester and heteroaromatic sulfides. Over the last few years, the Willis and Weller groups have managed to use aryl methyl sulfides to exhibit a range of rhodium-catalysed C-S activation protocols. This thesis has demonstrated an extension of this work by developing the first rhodium-catalysed C-S activation Sonogashira-type coupling-reaction of terminal alkynes and simple aryl methyl sulfides.

Although many cross-coupling methodologies are effective at rapid molecular construction, these protocols are not atom economic and are inherently waste producing. Previous members within the group have successfully developed a 100% atom efficient rhodium-catalysed C-S activation addition-type reaction, known as the carbothiolation reaction. This thesis illustrates further advances made in this field by developing a highly active, bench-friendly catalytic system and demonstrating its practicality in a one-pot synthesis of a variety of highly substituted isoquinolines.

As a relatively young area of work, future investigation into application of rhodium-catalysed C-S activation protocols in organic chemistry has the potential to be very fruitful. Further exploration could be carried out to fully understand the key mechanistic pathway of the developed Sonogashira-type chemistry. More generally, it would be very interesting to continue the exploration of catalyst design, with the ultimate aim of developing C-S activation reactions that do not require tethered directing groups. Additionally, extending the scope of methodologies compatible with such substrates would broaden the use of C-S activation catalysis. For example,

other C-C bond forming transformations such as trifluoromethylation or even C-N bond construction *via* amination-type reactions.

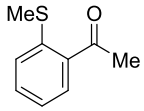
Chapter 5: Experimental

Reactions were performed under an inert atmosphere of nitrogen, using anhydrous solvent unless otherwise stated. All glassware was oven dried at >80 °C, and allowed to cool to room temperature under a positive nitrogen pressure. Reactions were monitored by TLC until deemed complete using aluminum backed silica plates. Plates were visualized under ultraviolet light and or by staining with $KMnO_4$. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Lancaster Synthesis Ltd, or Strem Chemicals Inc. and were used as supplied unless otherwise stated. *Ortho*-xylene (<0.003% H_2O) was purchased from Sigma-Aldrich Chemical Co. Ltd. Anhydrous acetonitrile, diethylether, dichloromethane, toluene and tetrahydrofuran were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Acetone was distilled from Drierite®. Petrol refers to the fractions obtained between 60 °C and 80 °C. Ether refers to diethyl ether. Flash chromatography was carried out using matrix 60 silica.

^{1}H NMR spectra were obtained on a Bruker DQX-400 (400 MHz) spectrometer using the residual solvent as an internal standard. ^{13}C NMR spectra were obtained on a Bruker DQX-400 (101 MHz) spectrometer using the residual solvent as an internal standard. Chemical shifts were reported in parts per million (ppm) with the multiplicities of the spectra reported as following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Low-resolution ESI mass spectra were recorded on a Fisons Platform spectrometer. High-resolution ESI mass spectrometry measurements were recorded on a Brucker Daltronics microTO (ESI) spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

5.1 Starting material synthesis

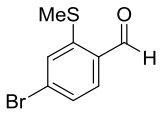
1-(2-(Methylthio)phenyl)ethanone (53)



To a stirred suspension of sodium methanethiolate (5.0 g, 71 mmol) in DMF (100 mL) was added 2-(chloroacetophenone) (9.25 mL, 71 mmol) dropwise over 30 minutes. After the addition was complete the solution was stirred at room temperature for a further 30 minutes. The solvent was decanted off and the resulting yellow solid was recrystallized (CH_3Cl_2/petrol) producing the sulfide as fine colourless needles (7.5 g, 63%); m.p 45-47 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.80 (d, *J* = 8.5 Hz, 1H), 7.45 (td, *J* = 8.5, 1.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.17 (td, *J* = 8.5, 1.0 Hz, 1H), 2.65 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.1, 142.7, 132.5, 131.3, 130.7, 124.8, 123.3, 28.0, 15.5; ν_{max} (film)/cm^{-1} 1718, 1656, 1501, 1327, 749.

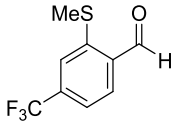
Data consistent with the literature.[113]

4-Bromo-2-(methylthio)benzaldehyde (75c)



To a stirred suspension of sodium thiomethoxide (345.2 g, 4.9 mmol) in DMF (25 mL) was added 4-bromo-2-fluorobenzaldehyde (1.0 g, 4.9 mmol) over 30 mins at −45 °C. After the addition was complete, the solution was stirred for a further 3 h at −45 °C, then stirred at room temperature overnight. The reaction was then quenched with water and the precipitate was filtered off to yield the sulfide product as white needles (747 mg, 66%); m.p: 78 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.13 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.38-7.35 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 190.3, 145.5, 134.6, 131.3, 129.7, 127.8, 127.5, 15.4; ν_{max} (film)/cm^{-1} 2920, 2825, 2776, 2733, 1682; HRMS (FI$^+$) 229.9398 ((M)$^+$, $C_8H_7O^{79}BrS$ requires 229.9401).

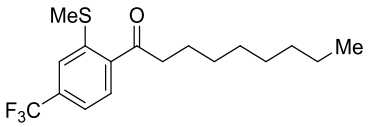
2-(Methylthio)-4-(trifluoromethyl)benzaldehyde



The title aldehyde was prepared from 2-fluoro-4-(trifluoromethyl)benzaldehyde, according to the procedure of Willis *et al*.[106] and isolated as a white solid. m.p. 90-92 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.21 (s, 1H), 7.95 (d, J = 1.0 Hz, 1H), 7.71 (dd, J = 8.5, 1.0 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): 189.5, 148.5, 135.1 (q, *J* = 32.5 Hz), 134.6, 133.5, 122.4 (q, *J* = 273.5 Hz), 121.9 (q, *J* = 4.0 Hz), 120.9 (q, *J* = 4.0 Hz), 15.3; ν_{max} (film)/cm^{-1} 1689, 1608, 699; *m/z* (rel intensity) 243 [90, (M+Na)$^{+}$].

Data consistent with the literature.[106]

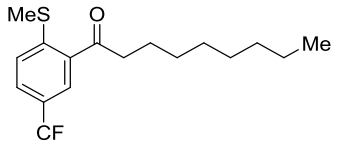
1-(2-(Methylthio)-4-(trifluoromethyl)phenyl)nonan-1-one (53c)



The title aldehyde was prepared from 2-(methylthio)-4-(trifluoromethyl)benzaldehyde, according to the procedure of Willis *et al*.[106] and isolated as a colourless oil. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.98 (d, J = 1.5 Hz, 1H), 7.62 (dd, J = 8.5, 1.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 2.94 (t, J = 7 Hz, 2H), 2.42 (s, 3H), 1.72 (pent, J = 7 Hz, 2H), 1.37-1.24 (m, 10H), 0.85 (t, J = 7 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): 190.5, 147.5, 134.1 (q, *J* = 35.0 Hz), 132.6, 131.5, 121.4 (q, *J* = 271.5 Hz), 119.4 (q, *J* = 3.5 Hz), 118.6 (q, *J* = 3.5 Hz), 39.1, 31.9, 29.2, 29.1, 28.9, 24.4, 22.7, 15.1, 14.4; ν_{max} (film)/cm^{-1} 1675, 161; *m/z* (rel intensity) 355 [40, (M+Na)$^{+}$].

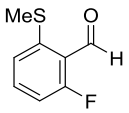
Data consistent with the literature.[106]

1-(2-(Methylthio)-5-(trifluoromethyl)phenyl)nonan-1-one (53b)



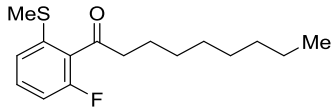
To a solution of 2-(methylthio)-5-(trifluoromethyl)benzaldehyde (45 mg, 0.35 mmol) $Rh(^{i}Pr_2PCH_2P^{i}Pr_2)(C_6H_5F)BAr^{F}_4$ (2.7 mg, 0.002) in acetone (0.25 mL) was added 1-octene (47 µL, 0.30 mmol). This was stirred at 55 °C for 4 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the ketone as a yellow oil (116 mg, 97%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.93 (d, *J* = 1.0 Hz, 1H), 7.57 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.66 (quintet, *J* = 7.5 Hz, 2H), 1.66 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.5, 147.5, 134.3, 128.1 (q, *J* = 3.5 Hz), 126.6 (q, *J* = 3.5 Hz), 126.5 (q, *J* = 33.0 Hz), 125.1, 123.8 (q, *J* = 271.5 Hz), 39.9, 31.8, 29.4, 29.2, 29.1, 24.2, 22.7, 15.9, 14.1; ν_{max} (film)/cm^{-1} 1674, 1116.

2-Fluoro-6-(methylthio)benzaldehyde



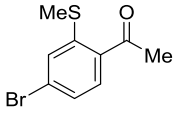
To a stirred suspension of sodium thiomethoxide (494 mg, 7.0 mmol) in DMF (25 mL) was added 2,6-difluorobenzaldehyde (1.0 g, 7.0 mmol) over 30 mins at −45 °C. After the addition was complete, the solution was stirred for a further 3 h at −45 °C. The reaction was then quenched with water and the precipitate was filtered off to yield the sulfide product as pale yellow needles (786 mg, 66%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.48 (d, *J* = 5.2 Hz, 1H), 7.52-7.45 (m, 1H), 6.91-6.86 (m, 1H), 2.46-2.45 (sd, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 187.2 (d, *J* = 11.0 Hz), 166.6 (d, *J* = 259.0 Hz), 146.1, 135.1 (d, *J* = 11.0 Hz), 120.6 (d, *J* = 8.0 Hz), 119.8 (d, *J* = 3.5 Hz), 110.9 (d, *J* = 22.0 Hz), 15.4; ν_{max} (film)/cm^{-1} 1672, 773; *m/z* (rel intensity) 193 [100, $(M+Na)^+$], HRMS (ESI^+) 171.02744 ($(M+H)^+$, C_8H_8OFS requires 171.02744).

1-(2-Fluoro-6-(methylthio)phenyl)nonan-1-one (53d)



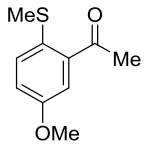
To a solution of 2-fluoro-6-(methylthio)benzaldehyde (85 mg, 0.50 mmol) and [Rh(Bn-(*p*-F))(dtmp)].BAr$^{f}_{4}$ (70 mg, 0.025 mmol) in acetone (0.25 mL) was added 1-octene (118 µL, 0.75 mmol). This was stirred at 55 °C for 4 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the ketone as a colourless oil (64 mg, 46%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31 (td, *J* = 8.0, 6.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.88 (ddd, *J* = 8.0, 6.0, 1.0 Hz, 1H), 2.84 (td, *J* = 7.5, 2.0 Hz, 2H), 2.43 (s, 3H), 1.70 (quintet, *J* = 7.5 Hz, 2H), 1.36-1.25 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 202.3, 156.8 (d, *J* = 249.0 Hz), 139.7 (d, *J* = 4.0 Hz), 131.2 (d, *J* = 9.0 Hz), 128.2 (d, *J* = 18.0 Hz), 122.4 (d, *J* = 3.0 Hz), 112.4 (d, *J* = 22.0 Hz), 44.6, 44.5, 31.9, 29.4, 29.2, 23.8, 22.7, 16.9, 14.1; ν_{max} (film)/cm^{-1} 1687, 1447, 894, 777.

1-(4-Bromo-2-(methylthio)phenyl)ethanone (70)



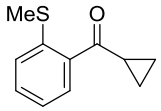
To a stirred suspension of sodium thiomethoxide (323 mg, 4.6 mmol) in DMF (25 mL) was added 1-(4-bromo-2-fluorophenyl)ethanone (1.0 g, 4.6 mmol) over 30 mins at −45 °C. After the addition was complete, the solution was stirred for a further 3 h at −45 °C. The reaction was then quenched with water and the precipitate was filtered off to yield the sulfide product as a white solid (913 mg, 81%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.70 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.3, 1.9 Hz, 1H), 2.59 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 197.9, 145.4, 132.5, 132.4, 127.8, 127.5, 126.4, 28.1, 16.0 ν_{max} (film)/cm^{-1} 1739, 1663, 788; *m/z* (rel intensity) 267 [50, $(M+Na)^+$]; HRMS (ESI^+) 244.96303 ($(M+H)^+$, $C_9H_{10}O^{79}BrS$ requires 244.96303).

1-(5-Methoxy-2-(methylthio)phenyl)ethanone (53a)



To a stirred suspension of sodium thiomethoxide (282 mg, 4.0 mmol) in DMF (25 mL) was added 1-(2-bromo-5-methoxyphenyl)ethanone (1.0 g, 3.36 mmol) over 30 mins at 0 °C. After the addition was complete, the solution was stirred for a further 3 h at r.t. The reaction was then quenched with water and the precipitate was filtered off to yield the sulfide product as pale yellow needles (481 mg, 73%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.07 (dd, *J* = 8.7, 2.5 Hz, 1H), 2.68 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 199.5, 156.6, 137.1, 131.8, 127.7, 118.0, 116.0, 55.6, 28.7, 16.9; ν_{max} (film)/cm^{-1} 1659; *m/z* (rel intensity) 219 [100, $(M+Na)^+$], HRMS (ESI^+) 197.0636 ($(M+H)^+$, $C_{10}H_{13}O_2S$ requires 197.0639).

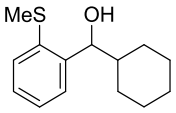
Cyclopropyl(2-(methylthio)phenyl)methanone (53p)



To a stirred solution of 2-bromothioanisole (200 mg, 0.98 mmol) in anhydrous THF (2 mL) at −78 °C was added nBuLi (1.6 M, 0.675 mL, 1.08 mmol) dropwise over 10 mins under nitrogen. After stirring for 20 mins, a solution of cyclopropanecarboxaldehyde (81 µL, 1.1 mol) in anhydrous THF (1 mL) was added dropwise over 20 mins at −78 °C. The mixture was stirred for a further 1 h at −78 °C before being allowed to warm to room temperature. The reaction was quenched with sat. NH_4Cl solution (10 mL) and the organic product extracted with diethyl ether (3x10 mL). The ethereal extract was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to leave the crude alcohol. This was dissolved in DCM (7 mL), once cooled to 0 °C, TEA (550 µL, 3.90 mmol) was added and the mixture stirred for further 10 mins. To this was added a solution of SO_3.pyridine (467 mg, 2.94 mmol) in DMSO (3 mL) dropwise. The resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with sat. $NaHCO_3$ (20 mL) and the organic product extracted with diethyl ether (3x10 mL). The ethereal extract was dried ($MgSO_4$), filtered, solvent removed *in vacuo* and purified

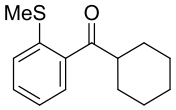
by flash chromatography (5% ether/petrol) to yield the ketone as a colorless oil (112 mg, 60%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.92 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.45 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.23-7.19 (m, 1H), 2.55 (tt, *J* = 8.0, 4.5 Hz, 1H), 2.43 (s, 3H), 1.29-1.25 (m, 2H), 1.05-1.00 (m, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 201.9, 141.1, 136.4, 131.8, 130.0, 125.4, 123.8, 19.3, 16.2, 12.0; ν_{max} (film)/cm^{-1} 3007, 2920, 2362, 2342, 1658; MS (ESI$^+$) *m/z* (rel intensity) 215 [100, $(M+Na)^+$]; HRMS (ESI$^+$) 215.0500 ($(M+Na)^+$, $C_{11}H_{12}NaOS$ requires 215.0501).

Cyclohexyl(2-(methylthio)phenyl)methanol



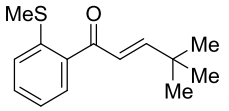
To a stirred solution of 2-bromothioanisole (200 mg, 0.98 mmol) in THF (2 mL) was added ^{n}BuLi (0.675 mL, 1.08 mmol, 1.60M) dropwise at −78 °C. After stirring for 20 mins a solution of cyclohexyl carboxaldehyde (131 µL, 1.08 mmol) in THF (1 mL) was added dropwise at −78 °C. This was brought back to room temperature and stirred for a futher 1 h. The reaction was quenched with sat. NH_4Cl solution (10 mL) and the organic product extracted with diethyl ether (3x10 mL). The ethereal extract was then dried ($MgSO_4$), filtered, solvent removed *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the alcohol as colourless oil. (151 mg, 65%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.24-7.17 (m, 3H), 4.87 (d, *J* = 6.5 Hz, 1H), 2.46 (s, 3H), 2.30 (s, 1H), 1.92 (d, *J* = 11.0 Hz, 1H), 1.75-1.65 (m, 3H), 1.41 (d, *J* = 10.0 Hz, 1H), 1.21-1.11 (m, 5H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 142.2, 136.0, 127.6, 126.9, 126.3, 125.2, 75.2, 44.1, 29.6, 28.0, 26.4, 26.3, 26.1, 16.7; ν_{max} (film)/cm^{-1} 3414, 2921, 2850, 1588; MS (ESI$^+$) *m/z* (rel intensity) 219 [70], 259 [100, $(M+Na)^+$]; HRMS (ESI$^+$) 259.1119 ($(M+Na)^+$, $C_{14}H_{20}NaOS$ requires 259.1127).

Cyclohexyl(2-(methylthio)phenyl)methanone (53q)



To a stirred solution of cyclohexyl(2-(methylthio)phenyl)methanol (105 mg, 0.45 mmol) in DCM (4.5 mL) was added DMP (382 mg, 0.90 mmol) in one portion. The mixture was stirred for 30 mins at room temperature. The reaction was washed with sat. $Na_2S_2O_3$ and the organic product extracted with DCM (3x10 mL). The DCM extract was washed once more with $NaHCO_3$ and the aqueous extracts were further washed with DCM. The combined organic layers were dried ($MgSO_4$), filtered, solvent removed *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the ketone as a colourless oil. (103 mg, 99%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.70 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.46-7.42 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.21-7.17 (m, 1H), 3.18 (tt, *J* = 11.5, 3.5 Hz, 1H), 2.43 (s, 3H), 1.90-1.71 (m, 5H), 1.56-1.50 (m, 2H), 1.35-1.26 (m, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 205.7, 141.3, 135.5, 131.5, 129.2, 125.8, 123.7, 47.5, 29.2, 25.94, 25.84, 16.3; ν_{max} (film)/cm^{-1} 2929, 2854, 1666; MS (ESI$^+$) *m/z* (rel intensity) 235 [50, (M+H)$^+$], 257 [100, (M+Na)$^+$]; HRMS (ESI$^+$) 257.0971 ((M+Na)$^+$, $C_{14}H_{18}NaOS$ requires 257.0971).

(*E*)-4,4-Dimethyl-1-(2-(methylthio)phenyl)pent-2-en-1-one (53s)



$Rh(nbd)_2BF_4$ (12 mg, 0.033 mmol) and bis(dicyclohexylphosphino)methane (13 mg, 0.033 mmol) were dissolved in acetone (0.25 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. To this solution was added 2-(methylthio)benzaldehyde (46 mg, 0.30 mmol) and 3,3-dimethylbut-1-yne (55 µL, 0.45 mmol). The reaction mixture was heated to 55 °C for 4 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the enone product (52 mg, 74%) as a yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.58 (dd, *J* =

8.0, 1.5 Hz, 1H), 7.45-7.41 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22-7.18 (m, 1H), 6.87 (d, *J* = 16.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 2.44 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 194.1, 160.5, 140.4, 137.4, 131.4, 129.5, 126.3, 124.1, 123.9, 34.3, 28.8, 16.6; ν_{max} (film)/cm^{-1} 3002, 2969, 2959, 2573, 1738, 1614, 1366, 1217; MS (ESI$^+$) *m/z* (rel intensity) 257 [100, $(M+Na)^+$]. HRMS (ESI$^+$) 257.0968 ($(M+Na)^+$, $C_{14}H_{18}NaOS$ requires 257.0971).

5.2 Formation of ethynyl compounds via rhodium-catalysis

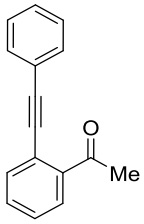
General procedure A

$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and dcpe (3.2 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This was transferred via cannula to a mixture of aryl sulfide (0.15 mmol), alkyne (0.30 mmol), copper bromide (42 mg, 0.3 mmol) and silver carbonate (41 mg, 0.15 mmol). The reaction mixture was heated to 80 °C for 2-16 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography to yield the product.

General procedure B

$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and dcpe (3.2 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This was transferred via cannula to a mixture of aryl sulfide (0.15 mmol), alkyne (0.30 mmol), copper bromide (84 mg, 0.60 mmol) and potassium carbonate (40 mg, 0.30 mmol). The reaction mixture was heated to 80 °C for 2-16 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography to yield the internal alkyne product.

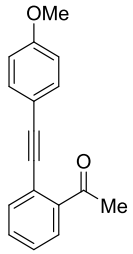
1-(2-(Phenylethynyl)phenyl)ethanone (67a)



Prepared following general procedure **A** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and Phenylacetylene (33 µL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether/petrol), to yield the product **67a** as a dark yellow oil (31 mg, 95%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.60-7.57 (m, 2H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.44-7.39 (m, 4H), 2.83 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.4, 140.8, 133.9, 131.6, 131.4, 128.8, 128.7, 128.5, 128.3, 122.9, 121.7, 95.1, 88.6, 30.0; ν_{max} (film)/cm^{-1} 1681, 755.

Data consistent with the literature.[114]

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)ethanone (67b)

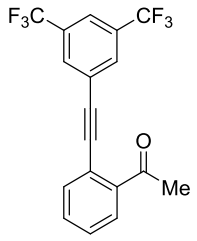


Prepared following general procedure **A** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 4-Ethynylanisole (39 µL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether/petrol), to yield the product **67b** as a bright yellow oil (34 mg, 92%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.43-7.37 (m, 3H), 7.30 (td, *J* = 7.5, 1.3 Hz, 1H), 6.84-6.81 (m, 2H), 3.76 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.6,

160.1, 140.6, 133.7, 133.1, 131.3, 128.7, 127.9, 122.1, 115.0, 114.2, 95.3, 87.4, 55.4, 30.1; ν_{max} (film)/cm^{-1} 2212, 1979, 1510, 1247; MS (ESI$^+$) *m/z* (rel intensity) 273 [100, (M+Na)$^+$].

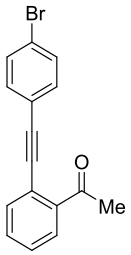
Data consistent with the literature.[115]

1-(2-((3,5-Bis(trifluoromethyl)phenyl)ethynyl)phenyl)ethanone (67c)



Prepared following general procedure **A** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and (3-5-trifuloro)-1-Ethynyl-benzene (53 µL, 0.30 mmol). After 8 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether/petrol), to yield the product **67c** as a white solid, (50 mg, 96%); m.p: 72 °C; ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.91 (s, 2H), 7.76 (s, 1H), 7.74 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.61 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 199.1, 140.5, 134.5, 132.1 (q, *J* = 33.5 Hz), 131.6, 131.4 (q, *J* = 3.5 Hz), 129.2, 129.1, 125.4, 122.9 (q, *J* = 272.0 Hz), 122.0 (hep, *J* = 3.5 Hz), 20.4, 91.8, 90.9, 29.3; ν_{max} (film)/cm^{-1} 1691,1377, 1131; HRMS (FI$^+$) 358.0630 ((M)$^+$, $C_{18}H_{10}OF_6$ requires 358.063).

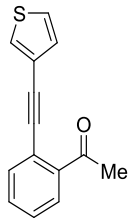
1-(2-((4-Bromophenyl)ethynyl)phenyl)ethanone (67d)



Prepared following general procedure **A** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-Bromo-ethynyl-benzene (54 mg, 0.30 mmol). After 16 h the mixture was allowed to

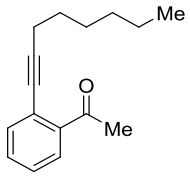
cool to room temperature and the crude product was purified by column chromatography (70% petrol/toluene), to yield the product **67d** as a yellow oil, (39 mg, 89%); preparation following general procedure **B** gave yellow oil, (33 mg, 75%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.69 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.56-7.54 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.44-7.39 (m, 3H), 7.36-7.32 (m, 3H), 2.69 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.0, 140.6, 134.0, 133.0, 131.8, 131.4, 128.9, 128.5, 123.1, 121.9, 121.4, 93.7, 89.6, 29.8; ν_{max} (film)/cm^{-1} 2360, 1686, 1491, 823, 761; MS (ESI$^+$) *m/z* (rel intensity) 321 [100, (M+Na)$^+$], 323 [97, (M+Na)$^+$], 299 [40, (M+H)$^+$]; HRMS (ESI$^+$) 299.0070 ((M+H)$^+$, $C_{16}H_{12}OBr^{79}$ requires 299.0065).

1-(2-(Thiophen-3-ylethynyl)phenyl)ethanone 67e



Prepared following general procedure **B** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 3-ethynylthiophene (30 µL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% petrol/toluene), to yield the product **67e** as a dark yellow oil, (23 mg, 70%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.50 (dd, *J* = 3.0, 1.0 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (td, *J* = 7.5, 1.0 Hz, 1H), 7.26 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 1.0 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.3, 140.7, 133.8, 131.3, 129.6, 129.2, 128.8, 128.2, 125.7, 122.0, 121.7, 90.3, 88.1, 30.0; ν_{max} (film)/cm^{-1} 1672, 1283, 700; MS (ESI$^+$) *m/z* (rel intensity) 249 [100, (M+Na)$^+$]; HRMS (ESI$^+$) 226.0460 ((M+H)$^+$, $C_{14}H_{10}OS$ requires 226.0452).

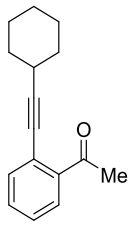
1-(2-(Dec-1-yn-1-yl)phenyl)ethanone (67f)



Prepared following general procedure **A** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-octyne (44 µL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% petrol/toluene), to yield the product **67f** as a pale yellow oil, (17 mg, 45%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.59 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.33 (td, *J* = 7.5, 1.0 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 2.65 (s, 3H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.55 (dt, *J* = 15.0, 7.5 Hz, 3H), 1.42-1.35 (m, 3H), 1.26-1.23 (m, 4H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 201.2, 141.1, 134.0, 131.1, 128.3, 127.6, 122.5, 97.0, 79.7, 31.4, 28.7, 28.5, 22.6, 19.8, 14.1; ν_{max} (film)/cm^{-1} 2926, 1711, 756; MS (ESI^{+}) *m/z* (rel intensity) 229 [70, (M+Na)$^{+}$].

Data consistent with the literature.[116]

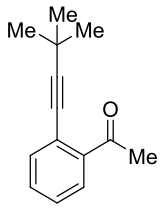
1-(2-(Cyclohexylethynyl)phenyl)ethanone (67g)



Prepared following general procedure **B** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and cyclohexylacetylene (30 µL, 0.30 mmol). After 16 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% petrol/toluene), to yield the product **67g** as a dark yellow oil, (16 mg, 50%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.59 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H), 7.25 (td, *J* = 7.5, 1.5 Hz, 1H), 2.64 (s, 3H), 2.60-2.53 (m, 1H), 1.85-1.82 (m, 2H), 1.72-1.65 (m, 2H),

1.54-1.44 (m, 4H), 1.29-1.26 (m, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 201.3, 141.1, 134.0, 131.1, 128.3, 127.5, 122.5, 100.9, 79.7, 32.4, 30.3, 30.0, 25.9, 25.0; ν_{max} (film)/cm^{-1} 2927, 2362, 1703, 1647, 1448, 756; *m/z* (rel intensity) 267 [100, $(M+H)^+$].

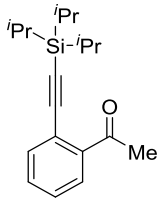
1-(2-(3,3-Dimethylbut-1-yn-1-yl)phenyl)ethanone (67h)



Prepared following general procedure **A** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 3,3-dimethyl-1-butyne (25 mg, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (50% petrol/toluene), to yield the product **67h** as a pale yellow oil, (22 mg, 75%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H), 7.31 (td, *J* = 7.5, 1.5 Hz, 1H), 2.74 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 201.3, 141.1, 133.8, 131.1, 128.3, 127.6, 122.4, 104.7, 78.5, 30.7, 30.3, 28.3; ν_{max} (film)/cm^{-1} 2967, 1684, 1278, 759; MS (ESI$^+$) *m/z* (rel intensity) 223 [90, $(M+Na)^+$].

Data consistent with the literature.[117]

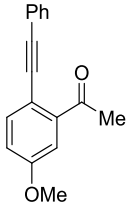
1-(2-((Triisopropylsilyl)ethynyl)phenyl)ethanone (67i)



Prepared following general procedure **B** using 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and (triisopropylsilyl)-acetylene (67 µL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5%

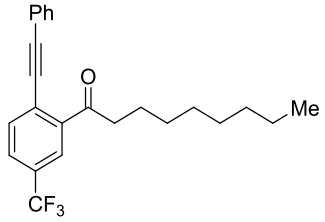
ether/petrol), to yield the product **67i** as a pale yellow oil, (43 mg, 96%); using procedure **A** also gave colourless oil, (42 mg, 94%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.68 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37 (td, *J* = 7.5, 1.5 Hz, 1H), 2.78 (s, 3H), 1.12-1.15 (m, 21H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.8, 141.4, 134.8, 131.0, 128.4, 128.3, 121.8, 105.6, 98.2, 30.3, 18.7, 11.4; ν_{max} (film)/cm^{-1} 2942, 2864, 2153, 1685; MS (ESI$^+$) *m/z* (rel intensity) 323 [100, (M+Na)$^+$], 301 [45, (M+H)$^+$]; HRMS (ESI$^+$) 323.1799 ((M+Na)$^+$, $C_{19}H_{28}NaOSi$ requires 323.1802).

1-(5-Methoxy-2-(phenylethynyl)phenyl)ethanone (68a)



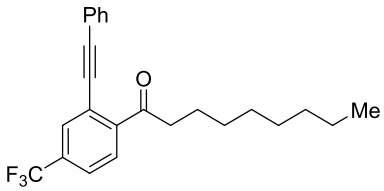
Prepared following general procedure **B** using 1-(5-methoxy-2-(methylthio)phenyl)ethanone (29 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (0.5% ether/toluene), to yield the product **68a** as a yellow oil, (27 mg, 77%), using general procedure **A** also gave desired product (57 mg, 76%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.48 (d, *J* = 8.5 Hz, 1H), 7.46-7.43 (m, 2H), 7.27-7.20 (m, 3H), 7.20 (d, *J* = 3.0 Hz, 1H), 6.94 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.79 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.4, 159.5, 142.3, 135.4, 131.3, 128.5, 124.6, 123.2, 118.0, 114.0, 113.1, 93.8, 88.5, 55.6, 30.3; ν_{max} (film)/cm^{-1} 1679, 1223, 822, 756; *m/z* (rel intensity) 273 [100, (M+Na)$^+$]; HRMS (ESI$^+$) 251.1065 ((M+H)$^+$, $C_{17}H_{15}O_2$ requires 251.1067).

1-(2-(Phenylethynyl)-5-(trifluoromethyl)phenyl)nonan-1-one (68b)



Prepared following general procedure **A** using $Rh(nbd)_2BF_4$ (2.1 mg, 0.0055 mmol), dcpe (2.3 mg, 0.0055 mmol), 1-(2-(methylthio)-5-(trifluoromethyl)phenyl)nonan-1-one (35 mg, 0.11 mmol) and phenylacetylene (25 µL, 0.22 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% DCM/petrol), to yield the product **68b** as a yellow oil, (37 mg, 89%), using general procedure **B** also gave desired product (32 mg, 76%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.83 (s, 1H), 7.66-7.60 (m, 2H), 7.49-7.46 (m, 2H), 7.34-7.30 (m, 3H), 3.09 (t, *J* = 7.5 Hz, 2H), 1.68 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.32-1.15 (m, 10H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 202.4, 141.8, 134.2, 131.7, 130.2 (q, *J* = 33 Hz), 129.3, 128.6, 127.2 (q, *J* = 3.5 Hz), 125.2 (q, *J* = 3.5 Hz), 124.8, 122.2, 120.8 (q, *J* = 273 Hz), 97.1, 87.1, 42.3, 31.8, 29.42, 29.34, 29.17, 24.3, 22.7, 14.1; ν_{max} (film)/cm^{-1} 2926, 1688, 1127; *m/z* (rel intensity) 409 [100, $(M+Na)^+$], 387 [50, $(M+H)^+$]; HRMS (ESI$^+$) 387.1928 ($(M+H)^+$, $C_{24}H_{26}O_2F_3$ requires 387.1930).

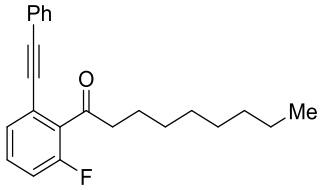
1-(2-(Phenylethynyl)-4-(trifluoromethyl)phenyl)nonan-1-one (68c)



Prepared following general procedure **A** using $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol), dcpe (6.4 mg, 0.015 mmol), 1-(2-(methylthio)-4-(trifluoromethyl)phenyl)nonan-1-one (40 mg, 0.12 mmol) and phenylacetylene (30 µL, 0.24 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5-30% DCM/petrol),

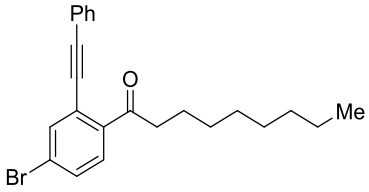
to yield the product **68c** as a yellow oil, (46 mg, 91%); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.79 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.33-7.29 (m, 3H), 3.07 (t, *J* = 7.5 Hz, 2H), 1.67 (quintet, *J* = 7.5 Hz, 2H), 1.30-1.12 (m, 10H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 203.2, 144.5, 132.7 (q, *J* = 33 Hz), 131.7, 130.4 (q, *J* = 3.5 Hz), 129.3, 128.6, 128.5, 124.8 (q, *J* = 3.5 Hz), 123.3 (q, *J* = 273 Hz), 122.2, 121.9, 96.0, 86.7, 42.4, 31.8, 29.42, 29.34, 29.17, 24.3, 22.7, 14.1; ν_{max} (film)/cm^{-1} 2926, 1689, 1336, 1130, 755; *m/z* (rel intensity) 409 [100, $(M+Na)^+$], 387 [40, $(M+H)^+$]; HRMS (ESI$^+$) 387.1926 ($(M+H)^+$, $C_{24}H_{26}O_2F_3$ requires 387.1930).

1-(2-Fluoro-6-(phenylethynyl)phenyl)nonan-1-one (68d)



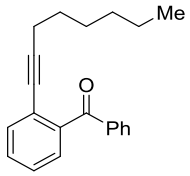
Prepared following general procedure **B** using 1-(2-fluoro-6-(methylthio)phenyl)nonan-1-one (42 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (45% ether/petrol), to yield the product **68d** as a yellow oil, (45 mg, 91%); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.42-7.40 (m, 2H), 7.29-7.26 (m, 5H), 7.00 (ddd, *J* = 9.5, 7.5, 2.0 Hz, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 1.66 (quintet, *J* = 7.5 Hz, 2H), 1.32-1.27 (m, 2H), 1.22-1.13 (m, 8H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 202.2, 158.7 (d, *J* = 273.0 Hz), 131.89 (d, *J* = 20.0 Hz), 131.71, 130.7 (d, *J* = 8.5 Hz), 128.9, 128.5 (d, *J* = 3.0 Hz), 128.43, 122.4, 122.1 (d, *J* = 6.0 Hz), 116.0 (d, *J* = 22.0 Hz), 94.2, 85.86 (d, *J* = 3.0 Hz), 44.49, 31.8, 29.43, 29.23, 29.16, 23.8, 22.7, 14.1; ν_{max} (film)/cm^{-1} 2925, 1705, 755; *m/z* (rel intensity) 359 [100, $(M+Na)^+$], 337 [75, $(M+H)^+$]; HRMS (ESI$^+$) 337.1958 ($(M+H)^+$, $C_{23}H_{26}OF$ requires 337.1962).

1-(4-Bromo-2-(phenylethynyl)phenyl)nonan-1-one (68e)



Prepared following general procedure **B** using $Rh(nbd)_2BF_4$ (1.9 mg, 0.005 mmol), dcpe (2.1 mg, 0.005 mmol), 1-(4-bromo-2-(methylthio)phenyl)nonan-1-one (35 mg, 0.10 mmol) and phenylacetylene (22 µL, 0.20 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (20% toluene/petrol), to yield the product **68e** as a yellow oil, (38 mg, 97%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.77 (d, *J* = 1.5 Hz, 1H), 7.54-7.52 (m, 4H), 7.39-7.36 (m, 3H), 3.12 (t, *J* = 7.5 Hz, 2H), 1.73 (app. pent, *J* = 7.5 Hz, 2H), 1.34-1.22 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 202.6, 139.9, 136.2, 131.6, 131.5, 129.8, 129.1, 128.5, 125.3, 123.2, 122.4, 95.8, 87.0, 42.2, 31.8, 29.44, 29.37, 29.19, 24.5, 22.7, 14.1; ν_{max} (film)/cm^{-1} 2924, 1685, 755, 689; HRMS (ESI$^+$) 397.1160 ((M+H)$^+$, $C_{23}H_{26}O^{79}Br$ requires 397.1161).

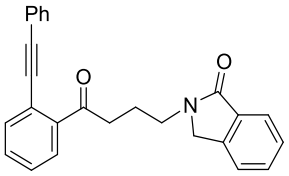
(2-(Oct-1-yn-1-yl)phenyl)(phenyl)methanone (68g)



Prepared following general procedure **B** using (2-(methylthio)phenyl)(phenyl)methanone (44 mg, 0.15 mmol) and 1-octyne (44 µL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (1% EtOAc/petrol), to yield the product **68g** as a yellow oil, (39 mg, 90%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.74 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.48 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.41-7.27 (m, 6H), 2.02 (t, *J* = 6.5 Hz, 2H), 1.18-1.05 (m, 8H), 0.78 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 197.4, 141.8, 137.4, 133.0, 132.6, 130.2, 130.1, 128.3, 128.1, 127.4, 122.5, 96.7, 78.6, 31.3, 28.4, 28.2, 22.5, 19.3, 14.1; ν_{max}

(film)/cm^{-1} 2929, 1666, 1287, 755, 703; MS (ESI^+) *m/z* (rel intensity) 313 [100, $(M+Na)^+$], 291 [65, $(M+H)^+$]; HRMS (ESI^+) 291.1743 ($(M+H)^+$, $C_{21}H_{22}O$ requires 291.1743).

2-(4-Oxo-4-(2-(phenylethynyl)phenyl)butyl)isoindolin-1-one (68h)



Prepared following general procedure **B** using 2-(4-(2-(methylthio)phenyl)-4-oxobutyl)isoindolin-1-one (49 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol). After 24 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (45% ether/petrol), to yield the product **68h** as a yellow oil, (50 mg, 89%). ^1H NMR (400 MHz; $CDCl_3$): δ 7.60 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.45-7.43 (m, 2H), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H), 7.32 (td, *J* = 7.5, 1.5 Hz, 1H), 7.29-7.26 (m, 3H), 7.18-7.12 (m, 2H), 6.95-6.90 (m, 2H), 3.73 (t, *J* = 7.5 Hz, 2H), 3.39 (s, 2H), 3.19 (t, *J* = 7.0 Hz, 2H), 2.07 (pentet, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 202.1, 175.1, 144.5, 140.8, 133.9, 131.6, 131.2, 128.8, 128.6, 128.4, 128.3, 128.0, 124.6, 124.4, 122.8, 122.2, 121.3, 108.6, 94.7, 88.2, 39.3, 38.9, 35.8, 22.1; ν_{max} (film)/cm^{-1} 1708, 1614, 753; *m/z* (rel intensity) 402 [100, $(M+Na)^+$], 380 [80, $(M+H)^+$]; HRMS (ESI^+) 380.1644 ($(M+H)^+$, $C_{26}H_{22}O_2N$ requires 380.1645).

5.3 Hdroacylation-Sonogashira cascade

General procedure C – Tandem reactions

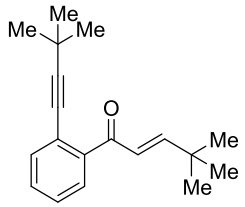
$Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This was transferred via cannula to a mixture of aldehyde (0.30 mmol), alkyne (0.45 mmol) and stirred at room temperature until starting material was consumed. This was then transferred to a mixture containing copper bromide (86 mg, 0.60 mmol), silver carbonate (83 mg, 0.30 mmol) and the appropriate alkyne (0.60 mmol). The reaction mixture was stirred and

heated to 80 °C until completion, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography to yield the product.

General procedure D – Tandem reactions

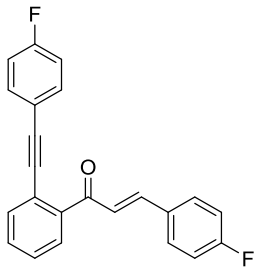
$Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This was transferred via cannula to a mixture of aldehyde (0.30 mmol), alkyne (0.45 mmol) and stirred at room temperature until starting material was consumed. This was then transferred to a mixture containing copper bromide (172 mg, 1.2 mmol), potassium carbonate (80 mg, 0.60 mmol) and the appropriate alkyne (0.60 mmol). The reaction mixture was stirred and heated to 80 °C for 0.5-24 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography to yield the enone product.

(*E*)-1-(2-(3,3-Dimethylbut-1-yn-1-yl)phenyl)-4,4-dimethylpent-2-en-1-one (78a)



Prepared following general procedure **C** using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 3,3-dimethylbut-1-yne (55 µL, 0.45 mmol) for 4h. Followed by 3,3-dimethylbut-1-yne (74 µL, 0.60 mmol) for 24 . The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (45% ether/petrol), to yield the enone product as a yellow oil, (55 mg, 64%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.42 (d, *J* = 0.5 Hz, 1H), 7.40-7.28 (m, *J* = 1.5 Hz, 3H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 1.27 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 196.3, 159.7, 142.6, 133.0, 129.9, 127.7, 127.4, 125.1, 121.8, 104.0, 77.5, 34.1, 30.8, 28.7, 28.2; ν_{max} (film)/cm^{-1} 2963, 1658, 1615, 1300, 753; *m/z* (rel intensity) 269 [100, $(M+H)^+$]; HRMS (ESI$^+$) 269.1899 ($(M+H)^+$, $C_{19}H_{25}O$ requires 269.1899).

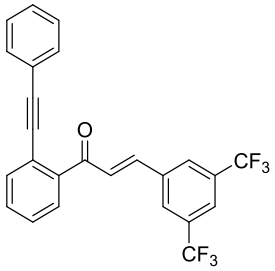
(*E*)-3-(4-Fluorophenyl)-1-(2-((4-fluorophenyl)ethynyl)phenyl)prop-2-en-1-one (78b)



Prepared following general procedure **C** using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-ethynyl-4-fluorobenzene (52 µL, 0.45 mmol) for 30 mins. Followed by 1-ethynyl-4-fluorobenzene (69 µL, 0.60 mmol) for 6 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (5% ether/petrol), to yield the enone product as a pale yellow solid, (78 mg, 76%); m.p: 102 °C; ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.70-7.62 (m, 3H), 7.59-7.56 (m, 2H), 7.50 (td, *J* = 7.5, 1.5 Hz, 1H), 7.47-7.43 (m, 2H), 7.35-7.31 (m, 2H), 7.07-7.03 (m, 2H), 6.94-6.89 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 193.4, 164.1 (d, *J* = 250.0 Hz), 162.7 (d, *J* = 250.0 Hz), 143.0, 141.8, 133.4 (d, *J* = 8.5 Hz), 133.1, 131.1, 130.9, 130.4 (d, *J* = 8.5 Hz), 128.8, 128.5, 125.5 (d, *J* = 3.0 Hz), 121.4, 118.8 (d, *J* = 3.0 Hz), 116.1 (d, *J* = 22.0 Hz), 115.7 (d, *J* = 22.0 Hz), 94.3, 87.7; ν_{max} (film)/cm^{-1} 1665, 1597, 1507, 1231, 832; *m/z* (rel intensity) 345 [100, $(M+H)^+$]; HRMS (ESI^+) 345.1085 ($(M+H)^+$, $C_{23}H_{15}OF_2$ requires 345.1085).

Data consistent with the literature.[118]

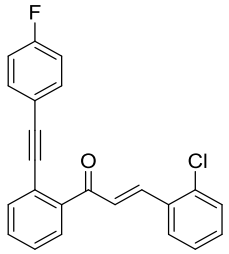
(*E*)-3-(3,5-Bis(trifluoromethyl)phenyl)-1-(2-(phenylethynyl)phenyl)prop-2-en-1-one (78c)



Prepared following general procedure **D** using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) for 10 mins. Followed by

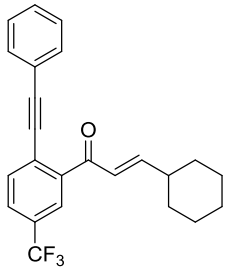
phenylacetylene (66 µL, 0.60 mmol) for 6 h. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography 20% DCM/petrol), to yield the enone product as a pale yellow solid, (97 mg, 73%); m.p: 85 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.88 (s, 2H), 7.74 (s, 1H), 7.70-7.65 (m, 3H), 7.61-7.57 (m, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.40-7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28-7.25 (m, 2H), 7.21-7.17 (m, 1H), 7.14-7.10 (m, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 192.4, 141.1, 139.6, 137.2, 133.4, 132.4 (q, *J* = 33.0 Hz), 131.6, 131.3, 129.1, 129.0, 128.9, 128.6, 128.4, 127.8 (br), 123.3 (quintet, *J* = 3.5 Hz), 123.0 (q, *J* = 273 Hz), 122.2, 121.8, 96.3, 87.9; ν_{max} (film)/cm^{-1} 1665, 1129; HRMS (FI^{+}) 444.095 ((M)$^{+}$, $C_{25}H_{14}F_6O$ requires 444.094).

(*E*)-3-(2-Chlorophenyl)-1-(2-((4-fluorophenyl)ethynyl)phenyl)prop-2-en-1-one (78d)



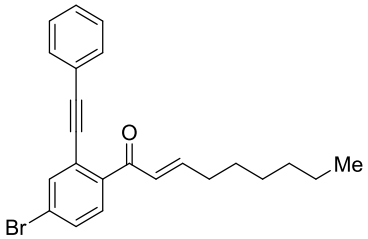
Prepared following general procedure **D** using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-chloro-2-ethynylbenzene (55 µL, 0.45 mmol) for 30 mins. Followed by 1-ethynyl-4-fluorobenzene (69 µL, 0.60 mmol) for 6 h . The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography 5% ether/petrol), to yield the enone product as a yellow oil, (95 mg, 88%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.02 (d, *J* = 16.0 Hz, 1H), 7.64-7.53 (m, 3H), 7.46-7.31 (m, 4H), 7.31-7.23 (m, 2H), 7.21 (td, *J* = 7.5, 1.5 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.88-6.81 (m, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 193.3, 162.7 (d, *J* = 250.0 Hz), 141.6, 140.0, 135.5, 133.50 (d, *J* = 8.5 Hz), 133.19, 133.15, 131.2, 131.0, 130.3, 128.9, 128.5, 128.2, 127.8, 127.1, 121.5, 118.83 (d, *J* = 3.0 Hz), 115.6 (d, *J* = 22.0 Hz), 94.5, 87.8; ν_{max} (film)/cm^{-1} 1662, 1597, 1506, 754; *m/z* (rel intensity) 383 [100, (M+Na)$^{+}$]; HRMS (ESI^{+}) 361.0791 ((M+H)$^{+}$, $C_{23}H_{15}O^{35}ClF$ requires 361.0790).

(*E*)-3-Cyclohexyl-1-(2-(phenylethynyl)-5-(trifluoromethyl)phenyl)prop-2-en-1-one (78e)



Prepared following general procedure **D** using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde (66 mg, 0.30 mmol) and ethynylcyclohexane (59 µL, 0.45 mmol) for 1h. Followed by phenylacetylene (66 µL, 0.60 mmol) for 24. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (20% tol/petrol), to yield the enone product as a yellow oil, (92 mg, 87%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.64-7.61 (m, 2H), 7.43-7.39 (m, 2H), 7.32-7.26 (m, 3H), 6.80 (dd, *J* = 16.0, 6.5 Hz, 1H), 6.65 (dd, *J* = 16.0, 1.5 Hz, 1H), 2.16-2.08 (m, 1H), 1.70-1.57 (m, 5H), 1.21-1.04 (m, 5H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 193.5, 156.6, 142.5, 133.4, 131.7, 130.1 (q, *J* = 33.0 Hz), 129.2, 128.4, 126.8 (q, *J* = 3.0 Hz), 126.7, 125.5 (q, *J* = 3 Hz), 125.0, 123.6 (q, *J* = 272.0 Hz), 122.3, 97.3, 86.7, 41.0, 31.6, 25.9, 25.7; ν_{max} (film)/cm^{-1} 2926, 1663, 1617,1334, 1126; HRMS (FI^{+}) 382.1553 ((M)$^{+}$, $C_{24}H_{21}OF_3$ requires 382.1544).

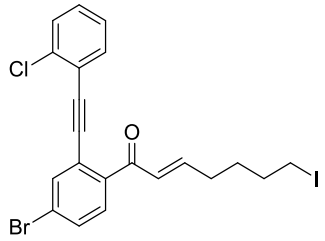
(*E*)-1-(4-Bromo-2-(phenylethynyl)phenyl)non-2-en-1-one (78f)



Prepared following general procedure **D** using 4-bromo-2-(methylthio)benzaldehyde (69 mg, 0.30 mmol) and 1-octyne (66 µL, 0.45 mmol) for 30 mins. Followed by phenylacetylene (66 µL, 0.60 mmol) for 24. The mixture was allowed to cool to room temperature and the crude product was

purified by column chromatography (30% tol/petrol), to yield the enone product as a yellow oil, (65 mg, 55%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.75 (d, *J* = 12.0 Hz, 1H), 7.52 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.48-7.41 (m, 3H), 7.37-7.33 (m, 3H), 6.91 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.75 (dt, *J* = 15.5, 1.5 Hz, 1H), 2.29-2.24 (m, 2H), 1.43 (quintet, *J* = 7.0 Hz, 2H), 1.31-1.18 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 193.5, 151.4, 140.6, 135.5, 131.6, 131.4, 130.0, 129.3, 129.0, 128.4, 124.7, 123.4, 122.5, 96.1, 86.5, 32.9, 31.6, 29.0, 28.0, 22.5, 14.1; ν_{max} (film)/cm^{-1} 2926, 16662, 1616; HRMS (FI^{+}) 394.0928 ((M)$^{+}$, $C_{23}H_{23}{}^{79}BrO$ requires 394.0932).

(*E*)-1-(4-Bromo-2-((2-chlorophenyl)ethynyl)phenyl)-7-iodohept-2-en-1-one (78g)

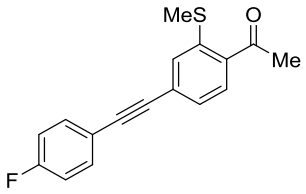


$Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol) and dcpe (6.3 mg, 0.015 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This was transferred via cannula to a mixture of 4-bromo-2-(methylthio)benzaldehyde (69 mg, 0.30 mmol), 6-iodohex-1-yne (52 µL, 0.45 mmol) and stirred at room temperature for 1 h. This was then transferred to a mixture containing copper iodide (86 mg, 0.60 mmol), silver carbonate (83 mg, 0.30 mmol) and 1-chloro-2-ethynylbenzene (73 µL, 0.60 mmol). The reaction mixture was stirred and heated to 80 °C for 24 h, and then allowed to cool to room temperature and the crude product was purified by column chromatography (50% tol/petrol), to yield the enone product as a colourless oil, (97 mg, 63%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.72 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.43 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.37-7.34 (m, 2H), 7.25-7.16 (m, 2H), 6.79 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.70 (d, *J* = 15.5 Hz, 1H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.22 (q, *J* = 7.0 Hz, 2H), 1.71 (quintet, *J* = 7.5 Hz, 2H), 1.48 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 193.1, 150.2, 140.4, 136.0, 135.8, 133.4, 131.9, 130.0, 129.94, 129.86, 129.5,

126.6, 124.8, 122.9, 122.4, 92.7, 91.2, 32.8, 31.7, 28.9, 6.1; ν_{max} (film)/cm^{-1} 1659, 1616, 1577, 755; HRMS (FI$^+$) 527.9152 ((M)$^+$, $C_{21}H_{17}{}^{127}I^{79}Br^{35}O$ requires 527.9175).

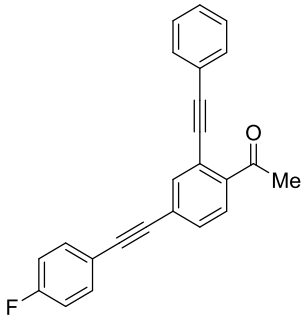
5.4 Formation of ethynyl compounds *via* rhodium- and palladium-catalysis

1-(4-((4-Fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone (72)



Diisopropylamine (4 mL) was added to a mixture of 1-(4-bromo-2-(methylthio)phenyl)ethanone (100 mg, 0.41 mmol), 1-ethynyl-4-fluorobenzene (57 µL, 0.50 mmol), palladium acetate (1.9 mg, 0.0082 mmol), triphenylphosphine (4.3 mg, 0.0164 mmol) and copper iodide (3.2 mg, 0.0164 mmol) in an inert atmosphere. This was heated to 75 °C and stirred for 2 h. The mixture was allowed to cool to room temperature, dried under *vacuo* and the crude product was purified by column chromatography (1% ethyl acetate/petrol), to yield product **72** as white needles (34 mg, 92%); m.p: 125 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.57-7.52 (m, 2H), 7.41 (d, *J* = 1.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.10-7.04 (m, 2H), 2.62 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 198.2, 162.9 (d, *J* = 250.0 Hz), 143.3, 133.8 (d, *J* = 8.0 Hz), 133.2, 131.1, 127.5, 127.4, 126.3, 118.6 (d, *J* = 3.0 Hz), 115.9 (d, *J* = 22.0 Hz), 91.4, 88.2, 28.1, 15.9; ν_{max} (film)/cm^{-1} 1668, 1584, 835; *m/z* (rel intensity) 307 [100, (M+Na)$^+$], 285 [30, (M+H)$^+$]; HRMS (ESI$^+$) 307.0560 ((M+Na)$^+$, $C_{17}H_{13}O^{23}Na^{32}S$ requires 307.0563).

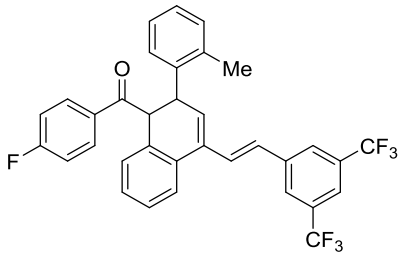
1-(4-((4-Fluorophenyl)ethynyl)-2-(phenylethynyl)phenyl)ethanone (73)



Prepared following general procedure **B** using 1-(4-((4-fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone (30 mg, 0.11 mmol) and phenylacetylene (24 µL, 0.22 mmol). After 4 h the mixture was allowed to cool to room temperature and the crude product was purified by column chromatography (40% DCM/petrol), to yield the product as a white solid, (31 mg, 83%); Diisopropylamine (4 mL) was added to a mixture of 1-(4-((4-fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone (50 mg, 0.17 mmol), 1-ethynyl-4-fluorobenzene (24 µL, 0.204 mmol), palladium acetate (1.0 mg, 0.0034 mmol), triphenylphosphine (1.7 mg, 0.0068 mmol) and copper iodide (1.7 mg, 0.0068 mmol) in an inert atmosphere. This was heated to 75 °C and stirred for 2 h. The mixture was allowed to cool to room temperature, dried under *vacuo* and the crude product was purified by column chromatography (1% ethyl acetate/petrol), to yield the diethynyl product as white solid (47 mg, 81%); m.p: 65 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.79 (d, *J* = 1.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.58-7.50 (m, 5H), 7.40-7.37 (m, *J* = 2.0 Hz, 3H), 7.10-7.05 (m, 2H), 2.81 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 199.4, 162.6 (d, *J* = 250.0 Hz), 139.5, 136.8, 133.8 (d, *J* = 8.0 Hz), 131.6, 131.0, 129.1, 129.0, 128.6, 126.7, 122.7, 122.3, 118.7 (d, *J* = 3.0 Hz), 115.8 (d, *J* = 22.0 Hz), 95.7, 91.6, 87.9, 87.5, 30.0; ν_{max} (film)/cm^{-1} 1680, 753; HRMS (FI^{+}) 338.1112 ((M)$^{+}$, $C_{24}H_{15}OF$ requires 338.1107).

5.5 Formation of 1,2 dihydronaphthylene

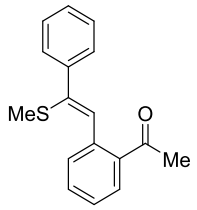
(*E*)-(4-(3,5-Bis(trifluoromethyl)styryl)-2-(*o*-tolyl)-1,2-dihydronaphthalen-1-yl)(4-fluorophenyl)methanone (86)



Prepared following general procedure **D** using 2-(methylthio)benzaldehyde (38 mg, 0.30 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (80 µL, 0.45 mmol) for 10 mins. This was followed by the addition of phenylacetylene (66 µL, 0.60 mmol) stirred for a further 6 h. The mixture was allowed to cool to room temperature and the crude product was filtered through a plug of silica then dried under *vacuo*. To this was added $Cu(OSO_2CF_3)_2$ (12 mg, 0.030 mmol), 1-methyl-2-vinylbenzene (58 µL, 0.45 mmol), DCE (2 mL) and stirred under nitrogen at 80 °C for 5 mins. The mixture was allowed to cool to room temperature and the crude product was purified by column chromatography 20% (toluene/petrol), to yield product **86** as a pale yellow solid, (66 mg, 61%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.90-7.88 (m, 4H), 7.75 (s, 1H), 7.57-7.51 (m, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.21-6.98 (m, 7H), 6.28 (d, *J* = 3.8 Hz, 1H), 5.18 (d, *J* = 9.5 Hz, 1H), 4.58 (dd, *J* = 9.5, 3.9 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 201.4, 140.3, 139.5, 137.6, 135.8, 134.8, 134.0, 133.3, 133.2, 132.1 (q, *J* = 33.0 Hz), 131.6, 130.9, 130.5, 128.8, 128.4, 128.3, 128.1, 127.8, 127.6, 127.4, 126.9, 126.3, 126.2(q, *J* = 3.5 Hz), 124.5, 123.3 (d, *J* = 275.0 Hz) 120.8 (q, *J* = 3.5 Hz), 52.1, 39.5, 19.9; ν_{max} (film)/cm^{-1} 1681, 1277, 1130, 751; ν_{max} (film)/cm^{-1} 1668, 1587, 1516, 854; HRMS (FI$^+$) 580.1637 ((M)$^+$, $C_{34}H_{23}F_7O$ requires 580.1639).

5.6 Formation of alkenyl sulfides

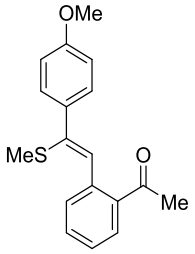
(*Z*)-1-(2-(2-(Methylthio)-2-phenylvinyl)phenyl)ethanone (58)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. To this solution was added 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol). The reaction mixture was heated to 80 °C for 24 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the vinyl sulfide product (39 mg, 99%) as a yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.70-7.68 (m, 2H), 7.55-7.45 (m, 2H), 7.43-7.41 (m, 4H), 7.18 (s, 1H), 2.65 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.1, 139.5, 138.6, 137.2, 136.9, 131.5, 131.2, 131.0, 129.1, 128.46 (2C), 128.40, 127.8, 29.0, 16.1; ν_{max} (film)/cm^{-1} 1726, 1656, 1420, 1361, 1245, 780, 700; MS (ESI$^+$) *m/z* (rel intensity) 291 [100, $(M+Na)^+$].

Data consistent with the literature.[106]

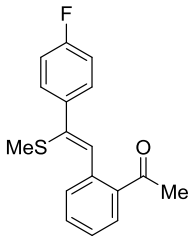
(*Z*)-1-(2-(2-(4-Methoxyphenyl)-2-(methylthio)vinyl)phenyl)ethanone (58b)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. To this solution was added 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-ethynyl-4-methoxybenzene (39 µL, 0.30 mmol). The reaction mixture was heated to 80 °C for 24 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the vinyl sulfide product (43 mg, 96%) as a yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.65-7.58 (m, 2H), 7.55-7.50 (m, 2H), 7.39 (ddd, *J* = 9.0, 6.5, 2.0 Hz, 2H), 7.2 (s, 1H), 6.98 (ddd, *J* = 9.5, 5.0, 3.0 Hz, 1H), 3.90 (s, 3H), 2.60 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 201.0, 158.9, 139.7, 137.6, 137.2, 132.4, 131.5, 131.2, 131.0, 129.4, 129.0, 127.4, 113.8, 55.3, 29.5, 16.9; ν_{max} (film)/cm^{-1} 1725, 1613; MS (ESI$^+$) *m/z* (rel intensity) 321 [100, (M+Na)$^+$].

Data consistent with the literature.[106]

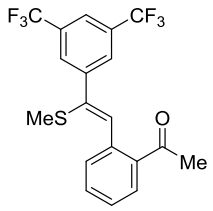
(*Z*)-1-(2-(2-(4-Fluorophenyl)-2-(methylthio)vinyl)phenyl)ethanone (58c)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was

purged with N_2 gas for a further 30 seconds. To this solution was added 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-ethynyl-4-fluorobenzene (59 µL, 0.30 mmol). The reaction mixture was heated to 80 °C for 24 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the vinyl sulfide product (41 mg, 99%) as a yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.65 (m, 2H), 7.54 (d, *J* = 5.0 Hz, 2H), 7.42-7.37 (m, 1H), 7.15 (s, 1H), 7.10 (tt, *J* = 9.0 Hz, 2H), 2.61 (s, 3H,), 1.88 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 200.9, 162.7(d, *J* = 247.5 Hz, CF), 137.4, 137.1, 136.1, 131.6, 131.5, 131.4, 130.2, 130.1, 129.4, 127.4, 115.5 (d, *J* = 21 Hz), 29.3, 16.4; ν_{max} (film)/cm^{-1} 2923, 1763, 1681; MS (ESI$^+$) *m/z* (rel intensity) 309 [100, (M+Na)$^+$]; HRMS (ESI$^+$) 309.0725 ((M+Na)$^+$, $C_{17}H_{15}FOSNa$ requires 309.0720).

(*Z*)-1-(2-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-(methylthio)vinyl)phenyl)ethanone (58d)



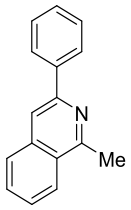
$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xanpthos (4.3 mg, 0.0075 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. To this solution was added 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and 1-ethynyl-3,5-bis(trifluoromethyl)benzene (35 µL, 0.30 mmol). The reaction mixture was heated to 80 °C for 24 h, and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and purified by flash chromatography (5% ether/petrol) to yield the vinyl sulfide product (48 mg, 80%) as a yellow oil; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.15 (s, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.65-7.55 (m, 2H), 7.48-7.44 (m, 1H), 7.40 (m, 1H), 2.67 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): 200.1, 142.7, 136.8, 135.5, 135.0, 134.5, 133.2 (q, *J* = 35.5 Hz),

131.7, 128.9, 128.2, 125.1 (q, J = 269.0 Hz, CF_3), 122.9 (q, J = 4.0 Hz), 28.9, 16.4; ν_{max} (film)/cm^{-1} 1691; MS (ESI^+) *m/z* (rel intensity) 427 [70, $(M+Na)^+$], 684 [100].

Data consistent with the literature.[106]

5.7 Formation of isoquinolines

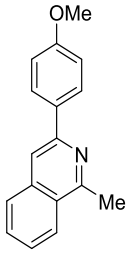
General Procedure E exemplified by the preparation of 1-Methyl-3-phenylisoquinoline (104a)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and ammonium acetate (115 mg, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed *in vacuo* and the crude product purified by column chromatography (5% ether/petrol), to yield the isoquinoline product as a pale yellow oil (30 mg, 90%); ^1H NMR (400 MHz; $CDCl_3$): δ 8.15-8.12 (m, 3H), 7.93 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.67 (ap. td, J = 8.0, 1.0 Hz, 1H), 7.57 (ap. td, J = 8.5, 1.0 Hz, 1H), 7.51 (ap. t, J = 8.0, Hz, 2H), 7.40 (ap. t, J = 8.0, Hz, 1H), 3.05 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.8, 150.3, 140.1, 137.0, 130.3, 129.0, 128.6, 127.9, 127.2, 127.0, 126.8, 125.9, 115.5, 23.0; ν_{max} (film)/cm^{-1} 2950, 2370, 2351, 1738; MS (ESI^+) *m/z* (rel intensity) 242 [100, $(M+H)^+$].

Data consistent with the literature.[119]

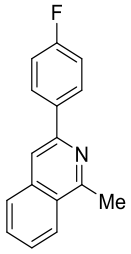
3-(4-Methoxyphenyl)-1-methylisoquinoline (104b)



Prepared following general procedure **E** using 1-ethynyl-4-methoxybenzene (39 µL, 0.30 mmol). The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104b** as a pale yellow solid (32 mg, 85%); m.p: 41-43 °C; ^{1}H NMR (200 MHz; $CDCl_3$): δ 8.15-8.06 (m, 3H), 7.87-7.78 (m, 2H), 7.65 (ap.ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.53 (app. ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.10-6.99 (m, 2H), 3.88 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 160.1, 158.5, 149.9, 137.0, 132.6, 130.1, 128.3, 127.6, 126.5, 126.4, 125.8, 114.2 (2C), 55.5, 22.8; ν_{max} (film)/cm^{-1} 2970, 2360, 2341, 1739, 1670, 1568; MS (ESI$^+$) *m/z* (rel intensity) 250 [100, $(M+H)^+$], 251 [40]; HRMS (ESI$^+$) 250.1226 ($(M+H)^+$, $C_{17}H_{15}NO$ requires 250.1226).

Data consistent with the literature.[120]

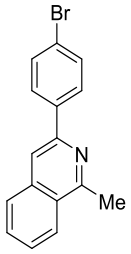
3-(4-Fluorophenyl)-1-methylisoquinoline (104c)



Prepared following general procedure **E** using 1-ethynyl-4-fluorobenzene (59 µL, 0.30 mmol). The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104c** as a pale pink solid (35 mg, 88%); m.p: 60-63 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.18-8.08 (m, 3H), 7.88-7.81 (m, 2H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 7.18 (t, *J* = 9.0 Hz), 3.03 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 163.3 (d, *J* = 247.5 Hz) 158.8, 149.1, 136.8, 130.3, 128.84,

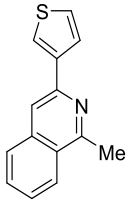
128.76, 127.7, 127.0, 126.6, 125.8, 115.7 (d, J = 22.5 Hz), 115.0, 22.8; ν_{max} (film)/cm^{-1} 3016, 2970, 1739, 1569, 1510, 1443; MS (ESI$^+$) *m/z* (rel intensity) 238 [100, (M+H)$^+$]; HRMS (ESI$^+$) 238.2031 ((M+H)$^+$, $C_{16}H_{13}NF$ requires 238.1027).

3-(4-Bromophenyl)-1-methylisoquinoline (104d)



Prepared following general procedure **E** using 1-bromo-4-ethynylbenzene (54 mg, 0.30 mmol). The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104d** as a red solid (35 mg, 80%); m.p: 46-48 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.12 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.59 (m, 3H), 3.03 (s, 1H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.9, 148.8, 138.8, 136.8, 131.9, 130.3, 128.6, 127.8, 127.2, 126.8, 125.8, 122.8, 115.2, 22.8; ν_{max} (film)/cm^{-1} 2361, 1621, 1592, 1568, 1498, 1444; HRMS (FI$^+$) 297.0146 ((M)$^+$, $C_{16}H_{12}NBr^{79}$ requires 297.0153).

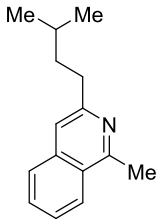
1-Methyl-3-(thiophen-3-yl)isoquinoline (104e)



Prepared following general procedure **E** using 3-ethynylthiophene (53 µL, 0.30 mmol). The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104e** as a yellow oil (25 mg, 76%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.11 (dd, J = 8.5, 0.5 Hz, 1H), 8.08 (dd, J = 3.0, 1.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.73 (dd, J = 5.0, 1.0 Hz, 1H), 7.66 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.55 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.42 (dd, J = 5.0, 3.0 Hz, 1H), 3.03 (s, 3H);

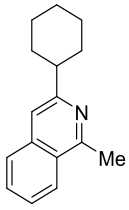
^{13}C NMR (101 MHz; $CDCl_3$): δ 158.4, 145.7, 141.8, 136.5, 130.0, 127.1, 126.4, 126.1, 125.9, 125.8, 125.4, 123.0, 114.4, 22.1; ν_{max} (film)/cm^{-1} 3016, 2360, 1760, 1716, 1368, 1229, 1216; MS (ESI$^+$) *m/z* (rel intensity) 144 [50], 226 [100, (M+H)$^+$], HRMS (ESI$^+$) 226.0687 ((M+H)$^+$, $C_{14}H_{12}NS$ requires 226.0685).

3-Isopentyl-1-methylisoquinoline (104f)



Prepared following general procedure **E** using 5-methylhex-1-yne (37 µL, 0.30 mmol). The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104f** as a colorless oil (39 mg, 84%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.08 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.33 (s, 1H), 2.96 (s, 3H), 2.91 (t, *J* = 8.0 Hz, 2H), 1.74-1.65 (m, 3H), 0.98 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.1, 155.0, 136.8, 129.9, 126.9, 126.1, 125.9, 125.7, 116.4, 39.2, 36.3, 28.1, 22.8, 22.6; ν_{max} (film)/cm^{-1} 3067, 2953, 2869, 2360, 2341, 1626, 1591, 1497, 1467, 1446, 1366, 1333, 747; MS (ESI$^+$) *m/z* (rel intensity) 214 [100, (M+H)$^+$]; HRMS (ESI$^+$) 214.1593 ((M+H)$^+$, $C_{15}H_{20}N$ requires 214.1590).

3-Cyclohexyl-1-methylisoquinoline (104g)

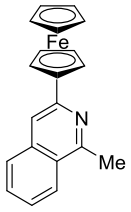


Prepared following general procedure **E** using ethynylcyclohexane (39 µL, 0.30 mmol). The crude product was purified by column chromatography (30% ether/petrol), to yield the product **104g** as an orange oil (28 mg, 82%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0

Hz, 1H), 7.61 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.49 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.32 (s, 1H), 2.95 (s, 3H), 2.82 (tt, *J* = 12.0, 4.0 Hz, 1H), 2.10 (d, *J* = 12.0 Hz, 2H), 1.89 (d, *J* = 12.0 Hz, 2H), 1.81-1.76 (m, 1H), 1.60-1.43 (m, 4H), 1.37-1.26 (m, 1H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 159.4, 158.0, 137.1, 129.9, 127.3, 126.4, 126.3, 125.8, 114.7, 46.4, 33.6, 27.1, 26.6, 22.7; ν_{max} (film)/cm^{-1} 2924, 2853, 2360, 2341, 1733, 1624, 1571, 1277, 748; MS (ESI$^+$) *m/z* (rel intensity) 226 [100, (M+H)$^+$]; HRMS (ESI$^+$) 226.1595 ((M+H)$^+$, $C_{16}H_{20}N$ requires 226.1590).

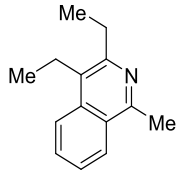
Data consistent with the literature.[121]

3-Ferrocenyl-1-methylisoquinoline (104h)



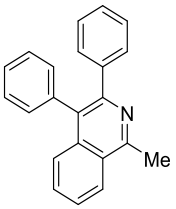
Prepared following general procedure **E** using ethynylferrocene (63 mg, 0.30 mmol). The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104h** as a red solid (45 mg, 91%); m.p: 158-160 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.64-7.61 (m, 2H), 7.51 (t, *J* = 8.5 Hz, 1H), 5.05 (s, 2H), 4.41 (s, 2H), 4.06 (s, 5H), 3.00 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 157.9, 136.6, 129.8, 126.9, 126.0, 125.8, 113.7, 69.6, 69.5, 67.3, 65.9, 22.7, 15.3; ν_{max} (film)/cm^{-1} 2970, 1744, 1567, 1367, 1229, 1216, 818; MS (ESI$^+$) *m/z* (rel intensity) 144 [40], 328 [100, (M+H)$^+$]; HRMS (ESI$^+$) 328.0775 ((M+H)$^+$, $C_{20}H_{18}FeN$ requires 328.0783).

3,4-Diethyl-1-methylisoquinoline (104i)



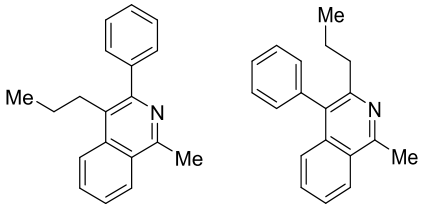
Prepared following general procedure **E** using $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol), Xantphos (8.6 mg, 0.015 mmol) and hex-3-yne (34 µL, 0.30 mmol). The crude product was purified by column chromatography (15% ether/DCM), to yield the product **104i** as yellow oil (14 mg, 47%); ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.09 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.67 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 3.05 (q, *J* = 7.5 Hz, 2H), 2.97 (q, *J* = 7.5 Hz, 2H), 2.92 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 3H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 155.8, 152.5, 135.2, 129.5, 127.2, 126.2, 126.1, 125.3, 123.4, 28.5, 22.3, 20.7, 15.2, 14.9; ν_{max} (film)/cm^{-1} 2950, 1739, 1558, 1366, 1216, 770; HRMS (FI$^+$) 199.1358 ((M)$^+$, $C_{14}H_{17}N$ requires 199.1361).

1-Methyl-3,4-diphenylisoquinoline (104j)



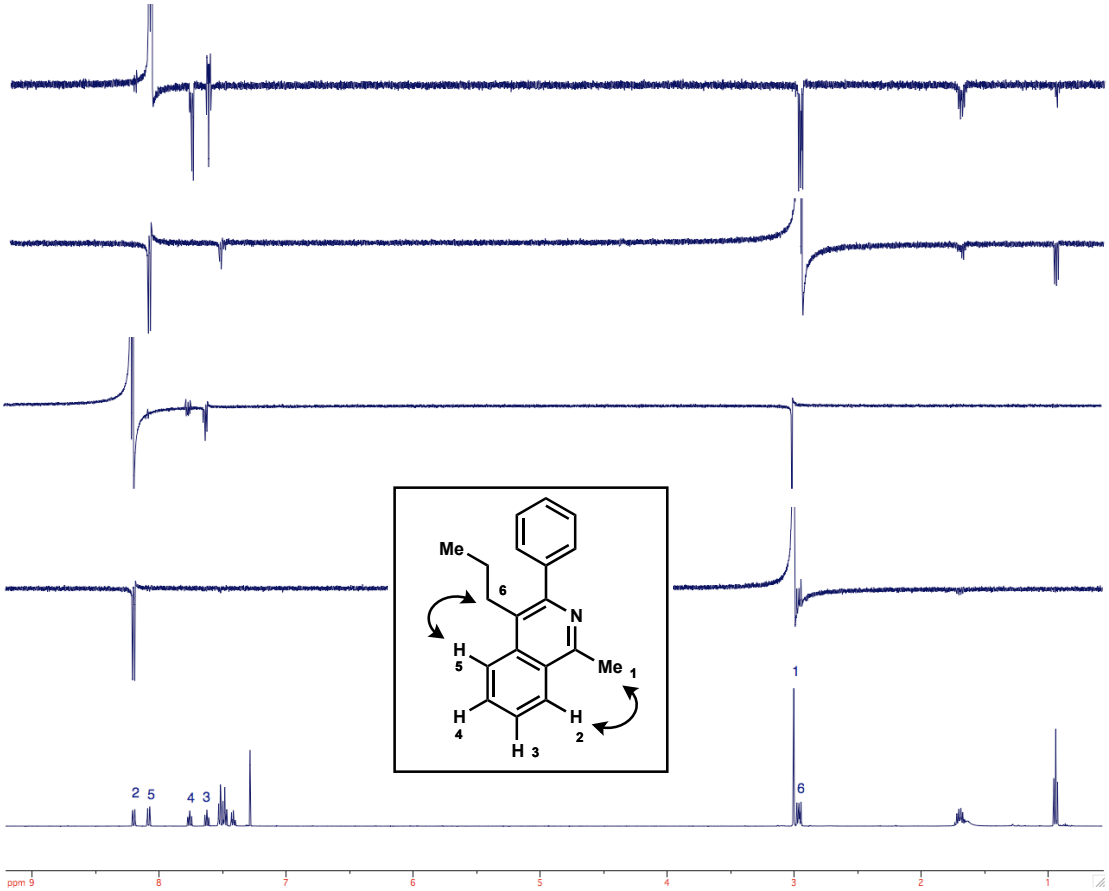
Prepared following general procedure **E** using $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol), Xantphos (8.6 mg, 0.015 mmol) and 1,2-diphenylethyne (53 mg, 0.30 mmol). The cyclisation was stirred for 72 h. The crude product was purified by column chromatography (5% ether/petrol), to yield the product **104j** as yellow oil (19 mg, 43%); ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.24-8.20 (m, 1H), 7.69-7.66 (m, 1H), 7.62-7.59 (m, 2H), 7.39-7.33 (m, 5H), 7.25-7.17 (m, 5H), 3.10 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 157.7, 149.4, 140.9, 137.6, 136.0, 131.4, 130.3, 129.9, 129.2, 128.2, 127.6, 127.1, 126.9, 126.5, 126.2, 126.1, 125.5, 22.7; ν_{max} (film)/cm^{-1} 2971, 2362, 1739, 1366, 1216, 779; HRMS (FI$^+$) 295.1364 ((M)$^+$, $C_{22}H_{17}N$ requires 295.1361).

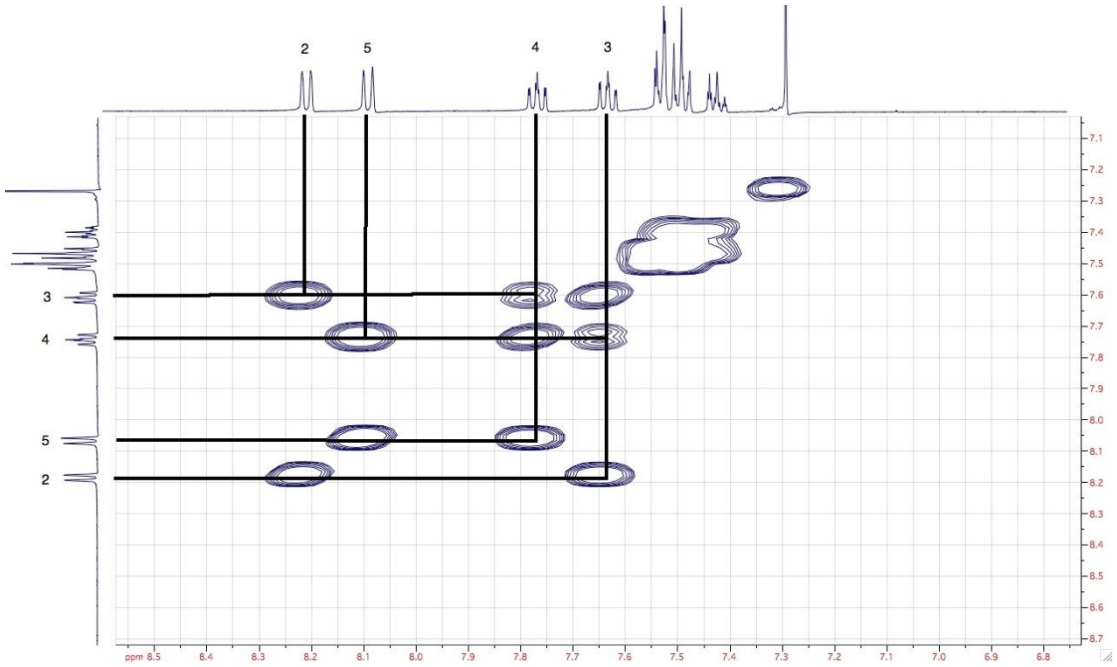
1-Methyl-3-phenyl-4-propylisoquinoline and 1-Methyl-4-phenyl-3-propylisoquinoline (104k & 104l)



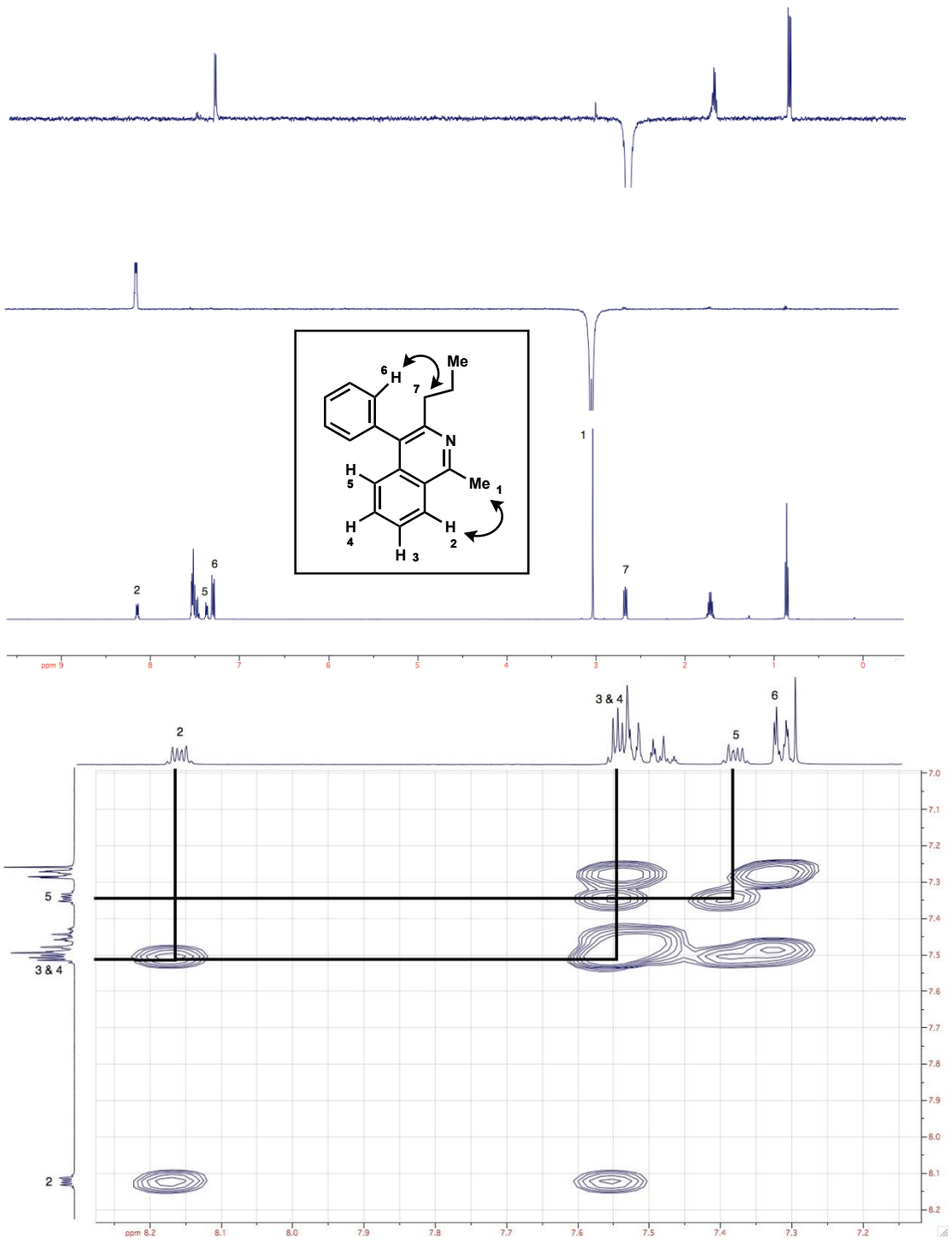
Prepared following general procedure **E** using 1-(2-(methylthio)phenyl)ethanone (50 mg, 0.30 mmol) $Rh(nbd)_2BF_4$ (11.2 mg, 0.030 mmol), Xantphos (17.2 mg, 0.030 mmol) and 1-Phenyl-1-pentyne (96 µL, 0.60 mmol). The cyclisation prepared using ammonium acetate (220 mg, 3.0 mmol) and acetic acid (4 mL), which was stirred for 72 h. The crude product was purified by column chromatography (1% acetone/petrol), to yield the product as a mixture of regioisomers (**104k**:**104l**, 2.9:1, 47 mg, 61%); **104k**: m.p: 102-105 °C; ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.18 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.74 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.52-7.45 (m, 4H), 7.42-7.39 (m, 1H), 2.99 (s, 3H), 2.95 (t, *J* = 8.0 Hz, 2H), 1.72-1.64 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl^3$): δ 155.8, 150.9, 141.8, 135.4, 129.8, 129.3, 128.1, 127.4, 127.3, 126.6, 126.3, 126.2, 124.3, 30.7, 24.6, 22.5, 14.4. ν_{max} (film)/cm^{-1} 2961, 2160, 2013, 1561, 775, 699. HRMS (ESI$^+$) 262.1600 ((M+H)$^+$, $C_{19}H_{19}N$ requires 262.1590). **104l**: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.14-8.12 (m, 1H), 7.53-7.47 (m, 4H), 7.47-7.44 (m, 1H), 7.37-7.33 (m, 1H), 7.30-7.28 (m, 2H), 3.02 (s, 3H), 2.65 (t, *J* = 8.0 Hz, 2H), 1.74-1.66 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 157.4, 151.4, 137.9, 136.1, 130.5, 129.6, 129.1, 128.3, 127.3, 125.9, 125.7, 125.4, 125.4, 37.6, 23.7, 22.5, 14.2. ν_{max} (film)/cm^{-1} 2959, 1562, 758, 701. HRMS (ESI$^+$) 262.1593 ((M+H)$^+$, $C_{19}H_{19}N$ requires 262.1587).

nOe and COSY of 104k

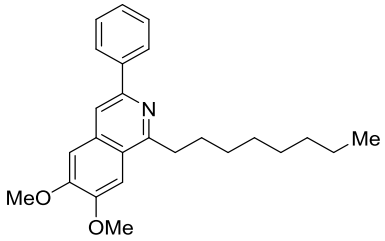




nOe and COSY of 104l

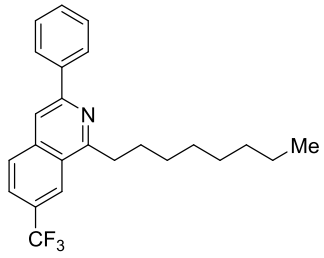


6,7-Dimethoxy-1-octyl-3-phenylisoquinoline (105a)



Prepared following general procedure **E** using 1-(4,5-dimethoxy-2-(methylthio)phenyl)nonan-1-one (48 mg, 0.15 mmol). The crude product was purified by column chromatography (20-30% DCM/petrol), to yield the product **105a** as a pale yellow solid (37 mg, 66%); m.p: 67-70 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.14-8.11 (m, 2H), 7.79 (s, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.37 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.35 (s, 1H), 7.11 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.27 (t, *J* = 8.0 Hz, 2H), 1.97 (ap. quin, *J* = 7.5, 2H) 1.54-1.48 (m, 2H), 1.47-1.39 (m, 2H), 1.38-1.26 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 159.6, 152.5, 149.8, 149.1, 140.4, 133.9, 128.7, 128.1, 126.9, 121.8, 114.2, 105.9, 103.8, 56.1, 56.1, 35.5, 32.1, 30.0, 29.7, 29.5, 29.1, 22.8, 14.3; ν_{max} (film)/cm^{-1} 3004, 2953, 2926, 2853, 1738, 1728, 1573, 1507, 1467, 1425, 1368, 1245, 1217, 1162; MS (ESI$^+$) *m/z* (rel intensity) 378 [55, $(M+H)^+$], 817 [100]; HRMS (ESI$^+$) 378.2418 ($(M+H)^+$, $C_{25}H_{32}NO_2$ requires 378.2428).

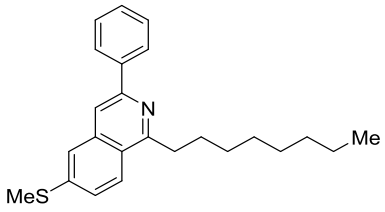
1-Octyl-3-phenyl-7-(trifluoromethyl)isoquinoline (105b)



Prepared following general procedure **E** using 1-(2-(methylthio)-5-(trifluoromethyl)phenyl)nonan-1-one[1] (50 mg, 0.15 mmol). The crude product was purified by column chromatography (20-30% DCM/petrol), to yield the product **105b** as a pale yellow oil (29 mg, 50%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.45 (s, 1H), 8.20-8.18 (m, 2H), 8.00-7.90 (m, 2H), 7.84-7.82 (m, 1H), 7.52 (t, *J* = 7.5 Hz,

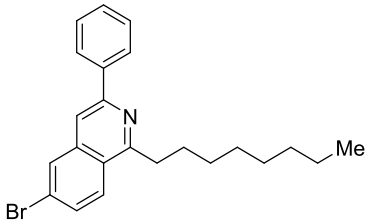
2H), 7.50-7.40 (m, 1H), 3.42 (t, *J* = 7.4 Hz, 2H), 1.98 (ap. quin, *J* = 7.5 Hz, 2H), 1.55-1.51 (m, 2H), 1.44-1.30 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 163.1, 151.8, 139.2, 138.6, 129.0, 128.9, 128.8, 128.3 (q, *J* = 32.4), 127.1, 126,0 (q, *J* = 222.1), 125.4 (q, *J* = 2.9), 123.3 (q, *J* = 4.5), 114.4, 35.2, 31.9, 29.7, 29.5, 29.3, 29.2, 22.7 14.1; ν_{max} (film)/cm^{-1} 2926, 2855, 1633, 1573, *m/z* (rel intensity) 386 [55, $(M+H)^+$]; HRMS (ESI^+) 386.2082 ($(M+H)^+$, $C_{24}H_{27}F_3N$ requires 386.2090).

6-(Methylthio)-1-octyl-3-phenylisoquinoline (105c)



Prepared following general procedure **E** using 1-(2,4-bis(methylthio)phenyl)nonan-1-one[5] (57 mg, 0.18 mmol). The crude product was purified by column chromatography (20-30% DCM/petrol), to yield the product **105c** as a yellow oil (57 mg, 88%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.17-8.15 (m, 2H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 7.52-7.49 (m, 3H), 7.43-7.38 (m, 2H), 3.31 (t, *J* = 8.0 Hz, 2H), 2.61 (s, 3H), 1.95 (ap. quin, *J* = 8.0 Hz, 2H) 1.54-1.47 (m, 2H), 1.44-1.25 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 162.0, 150.7, 141.7, 140.0, 137.8, 128.8, 128.4, 127.1, 125.8, 125.6, 123.8, 114.0, 35.5, 32.0, 30.0, 29.7, 29.6, 29.5, 22.8, 15.1, 14.3; ν_{max} (film)/cm^{-1} 3016, 1739, 1367; HRMS (FI^+) 363.2021 ($(M)^+$, $C_{24}H_{29}SN$ requires 363.2018).

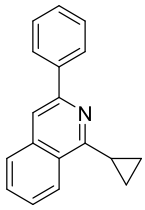
6-Bromo-1-octyl-3-phenylisoquinoline (105d)



Prepared following general procedure **E** using 1-(4-bromo-2-(methylthio)phenyl)nonan-1-one (50 mg, 0.15 mmol). The crude product was purified by column chromatography (20% DCM/petrol),

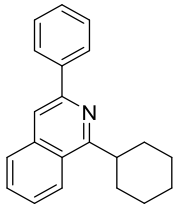
to yield the product **105d** as a pale yellow solid (45 mg, 76%); m.p: 39-40 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.16-8.13 (m, 2H), 8.02-7.99 (m, 2H), 7.80 (s, 1H), 7.61 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.42 (tt, *J* = 7.5, 1.5 Hz, 1H), 3.32 (t, *J* = 8.0 Hz, 2H), 1.93 (ap. quin, *J* = 8.0 Hz, 2H), 1.53-1.26 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 162.4, 151.0, 139.6, 138.5, 130.2, 129.9, 128.9, 128.8, 127.2, 127.2, 124.6, 113.9, 35.5, 32.1, 29.9, 29.7, 29.5, 29.5, 22.8, 14.3; ν_{max} (film)/cm^{-1} 3063, 2924, 2853, 1610, 1563, 1452, 1402, 1380, 1261, 1071, 1029, 887, 821, 803, 766, 691, 678; MS (ESI$^+$) *m/z* (rel intensity) 144 [90], 237 [100] 396 [55, (M+H)$^+$]; HRMS (ESI$^+$) 396.1308 ((M+H)$^+$, $C_{23}H_{27}{}^{79}BrN$ requires 396.1321).

1-Cyclopropyl-3-phenylisoquinoline (105e)



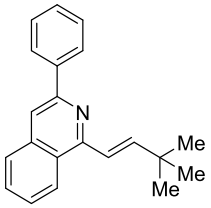
Prepared following general procedure **E** using cyclopropyl(2-(methylthio)phenyl)methanone (26 mg, 0.14 mmol). The crude product was purified by column chromatography (2.5% DCM/petrol), to yield the product **105e** as a pale yellow solid (16 mg, 47%); m.p: 35-37 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.41 (d, *J* = 8.5 Hz, 1H), 8.18-8.16 (m, 2H), 7.89 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.66 (td, *J* = 7.5, 1.0 Hz, 1H), 7.58 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H), 7.51-7.47 (m, 2H), 7.41-7.37 (m, 1H), 2.85-2.77 (m, 1H), 1.43 (ap. dq, *J* = 3.0, 4.5, 2H), 1.14 (ap. dq, *J* = 8.0, 3.0, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 153.5, 149.3, 139.9, 137.1, 129.9, 128.7, 128.4, 127.9, 126.9, 126.8, 126.7, 125.1, 114.0, 13.6, 10.0; ν_{max} (film)/cm^{-1} 3058, 3005, 2924, 2852, 1620, 1565, 1499, 1412; HRMS (FI$^+$) 245.1199 ((M)$^+$, $C_{18}H_{15}N$ requires 245.1205).

1-Cyclohexyl-3-phenylisoquinoline (105f)



Prepared following general procedure **E** using cyclohexyl(2-(methylthio)phenyl)methanone (20 mg, 0.09 mmol). The crude product was purified by column chromatography (2.5% DCM/petrol), to yield the product **105f** as a pale yellow oil (16 mg, 60%); ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.25-8.20 (m, 3H), 7.92 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.63 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.52-7.48 (m, 2H), 7.39 (tt, *J* = 7.5, 1.5 Hz, 1H), 3.62-3.56 (m, 1H), 2.07-1.93 (m, 6H), 1.59-1.41 (m, 4H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 165.2, 149.3, 140.0, 137.3, 129.5, 128.6, 128.2, 128.0, 126.8, 126.5, 125.3, 124.7, 114.3, 41.9, 32.6, 26.9, 26.3; ν_{max} (film)/cm^{-1} 3057, 2928, 2851, 2360, 1620, 1567, 1450, 770; HRMS (FI^{+}) 287.1675 ((M+H)$^{+}$, $C_{21}H_{21}N$ requires 287.1674).

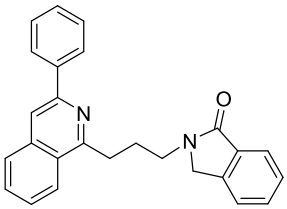
(*E*)-1-(3,3-Dimethylbut-1-en-1-yl)-3-phenylisoquinoline (105g)



Prepared following general procedure **E** using *E*)-4,4-dimethyl-1-(2-(methylthio)phenyl)pent-2-en-1-one (52 mg, 0.22 mmol). The crude product was purified by column chromatography (5% DCM/petrol), to yield the product **105g** as a pale yellow solid (35 mg, 55%); m.p: 84-86 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 2H), 7.97 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.68-7.64 (m, 1H), 7.60-7.50 (m, 3H), 7.45-7.41 (m, 1H), 7.36 (d, *J* = 15.5 Hz, 1H), 7.28 (d, *J* = 15.5 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 155.1, 150.1, 150.0, 140.0, 137.8, 130.0, 128.8, 128.5, 127.8, 127.2, 126.8, 125.6, 124.9, 120.1, 115.4, 34.2, 29.7; ν_{max} (film)/cm^{-1} 2958,

2360, 1640, 1558, 1359, 1260, 972, 787, 692; HRMS (FI$^+$) 287.1674 ((M)$^+$, $C_{21}H_{21}N$ requires 287.1663).

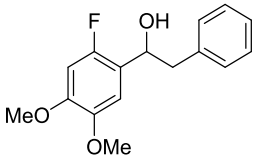
2-(3-(3-Phenylisoquinolin-1-yl)propyl)isoindolin-1-one (105h)



Prepared following general procedure **E** using 2-(4-(2-(methylthio)phenyl)-4-oxobutyl)isoindolin-1-one (48 mg, 0.15 mmol). The crude product was purified by column chromatography (2.5-5% ether/DCM), to yield the product **105h** as white needles (40 mg, 71%); m.p: 116- 119 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.19-8.16 (m, 2H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.94 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.58-7.49 (m, 3H), 7.45-7.40 (m, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.99 (td, *J* = 7.5, 1.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 3.95 (t, *J* = 7.5 Hz, 2H), 3.51-3.45 (m, 4H), 2.49 (quin, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 175.3, 160.0, 149.7, 144.8, 139.7, 137.1, 130.2, 128.8, 128.6, 128.0, 127.2, 127.1, 126.3, 125.0, 124.6, 124.4, 122.2, 115.5, 108.9, 40.1, 36.0, 31.7, 25.6; ν_{max} (film)/cm^{-1} 3057, 1706, 1615, 1490, 1357, 749, 696; MS (ESI$^+$) *m/z* (rel intensity) 379 [100, (M+H)$^+$], HRMS (ESI$^+$) 379.1794 ((M+H)$^+$, $C_{26}H_{23}N_2O$ requires 379.1805).

5.8 3-Pr-moxaverine synthesis

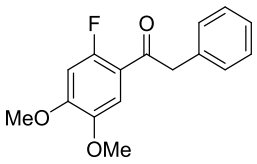
1-(2-Fluoro-4,5-dimethoxyphenyl)-2-phenylethanol



To a stirred solution of 6-Fluoroveratraldehyde (200 mg, 1.09 mmol) in THF (2 mL) was added benzyl magnesium chloride (1.2 mL, 2.1 mmol, 1.83M) dropwise at −78 °C. The mixture was stirred for 6 h and was allowed to warm room temperature. The reaction was quenched with sat. NH_4Cl

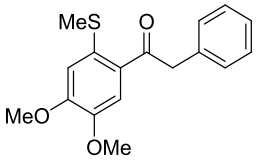
solution (7 mL) and the organic product was extracted with ether (3x10 mL). The ethereal extract was dried ($MgSO_4$), filtered, solvent removed in *vacuo* and purified by flash chromatography (15% ether/petrol) to yield the alcohol as a pale yellow solid (210 mg, 70%); m.p: 98-100 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.35-7.23 (m, 5H), 6.94 (d, *J* = 7.0 Hz, 1H), 6.62 (d, *J* = 11.5 Hz, 1H), 5.21 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.10 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.96 (dd, *J* = 13.5, 8.5 Hz, 1H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 153.5 (d, J = 239.0 Hz), 148.9 (d, *J* = 10.0 Hz), 145.4, 137.8, 129.59, 128.52, 126.7, 121.3 (d, *J* = 15.0 Hz), 109.2 (d, *J* = 6.0 Hz), 99.8 (d, *J* = 28.5 Hz), 68.7, 56.4, 56.2, 45.0; ν_{max} (film)/cm^{-1} 3503, 2937; MS (ESI$^+$) *m/z* (rel intensity) 259 [100], 299 [100, (M+Na)$^+$]; HRMS (ESI$^+$) 299.1062 ((M+Na)$^+$, $C_{16}H_{17}FNaO_3$ requires 299.1054).

1-(2-Fluoro-4,5-dimethoxyphenyl)-2-phenylethanone (111)



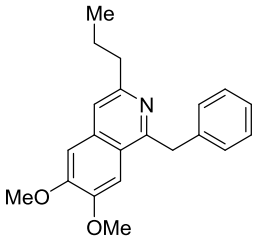
To a stirred solution of 1-(2-fluoro-4,5-dimethoxyphenyl)-2-phenylethanol (200 mg, 0.72 mmol) in DCM (10 mL) was added DMP (610 mg, 1.44 mmol) in one portion. The mixture was stirred for 25 mins at room temperature. The reaction was washed with sat. $Na_2S_2O_3$ and the organic product was extracted with DCM (3x10 mL). The DCM extract was washed once more with $NaHCO_3$ and the aqueous extracts were further washed with DCM. The combined organic layers were dried ($MgSO_4$), filtered, solvent removed *in vacuo* and purified by flash chromatography (25% ether/petrol) to yield the ketone as a white solid (193 mg, 98%); m.p: 109-111 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (d, *J* = 7.0 Hz, 1H), 7.37-7.33 (m, 2H), 7.29-7.28 (m, 3H), 6.64 (d, *J* = 12.5 Hz, 1H), 4.29 (d, *J* = 3.0 Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 194.5, 157.8 (d, J = 250.0 Hz), 154.3 (d, *J* = 10.0 Hz), 145.6, 134.5, 129.6, 128.5, 126.8, 116.4 (d, *J* = 14.4 Hz), 111.1 (d, *J* = 3.7 Hz), 100.0 (d, *J* = 30.0 Hz), 56.47, 56.28, 49.6; ν_{max} (film)/cm^{-1} 1702, 1669, 1609, 1519, 1325, 1133, 1024, 843, 711; MS (ESI$^+$) *m/z* (rel intensity) 275 (M+H)$^+$ [100], 297 [50, (M+Na)$^+$]; HRMS (ESI$^+$) 297.0899 ((M+Na)$^+$, $C_{16}H_{15}FNaO_3$ requires 297.0897).

1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-phenylethanone (107)



To a stirred suspension of sodium thiomethoxide (48 g, 0.69 mmol) in DMF (5 mL) was added 1-(2-fluoro-4,5-dimethoxyphenyl)-2-phenylethanone (184 mg, 64 mmol) over 5 mins at –45 °C. After the addition was complete, the solution was stirred for a further 3 h at room temperature. The reaction was then quenched with water and the organic product was extracted with DCM (3x10 mL). The combined organic layers were dried ($MgSO_4$), filtered, solvent removed *in vacuo* and purified by flash chromatography (45% ether/petrol) to yield the sulfide as a thick yellow oil (180 mg, 95%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.26-7.12 (m, 6H), 6.69 (s, 1H), 4.16 (s, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 197.1, 152.4, 145.3, 136.7, 135.2, 129.3, 128.7, 127.1, 126.8, 114.0, 108.5, 56.2, 56.0, 47.4, 16.6; ν_{max} (film)/cm^{-1} 1739, 1655, 1552, 1501, 1340, 1257, 1205, 1166; MS (ESI$^+$) *m/z* (rel intensity) 303 $(M+H)^+$ [100], 225 [30, $(M+Na)^+$]; HRMS (ESI$^+$) 325.0866 ($(M+Na)^+$, $C_{17}H_{18}NaO_3S$ requires 325.0869).

1-Benzyl-6,7-dimethoxy-3-propylisoquinoline – Moxaverine derivative (106)

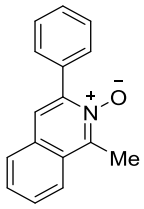


Prepared following general procedure **E** using 1-(4,5-dimethoxy-2-(methylthio)phenyl)-2-phenylethanone (50 mg, 0.165 mmol) and 1-pentyne (162 µL, 1.65 mmol) at 80 °C. The crude product was purified by column chromatography (20-30% ether/petrol) to give the product **106** as a yellow oil (40 mg, 75%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.77 (s, 1H), 7.21-7.14 (m, 5H), 7.09-7.06 (m, 1H), 6.90 (s, 1H), 4.55 (s, 2H), 3.90 (s, 3H), 3.75 (s, 3H), 2.85 (t, *J* = 8.0 Hz, 2H), 1.76 (qt, *J*

= 7.5, 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 175.6, 156.9, 152.8, 152.7, 149.4, 139.6, 134.5, 128.5, 126.2, 121.2, 116.9, 104.9, 104.4, 56.0, 55.8, 41.8, 39.3, 23.4, 13.9; ν_{max} (film)/cm^{-1} 2958, 2359, 1598, 1251, 1160; MS (ESI$^+$) *m/z* (rel intensity) 322 $(M+H)^+$ [100]; HRMS (ESI$^+$) 322.1804 ($(M+H)^+$, $C_{21}H_{24}NO_2$ requires 322.1802).

5.9 Formation of *N*-oxide-isoquinoline and amino- and acetamide-naphthylenes

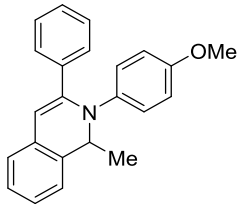
1-Methyl-3-phenylisoquinoline 2-oxide (112)



To a solution of (*Z*)-1-(2-(2-(methylthio)-2-phenylvinyl)phenyl)ethanone (29 mg, 0.26 mmol) in AcOH (2 mL) was added hydroxylamine hydrochloride (118 mg, 1.7 mmol). The resulting mixture was heated to 110 °C for 16 h and allowed to cool to room temperature. The solvent was removed *in vacuo* and the crude product purified by column chromatography (5-30% ether/petrol) - (20-80% ethyl acetate/petrol), to yield the product as a pale colourless solid (23 mg, 58%); m.p: 142-145 °C, ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.79-7.76 (m, 3H), 7.69 (s, 1H), 7.63 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.50-7.44 (m, 3H), 2.96 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 146.9, 146.5, 133.8, 130.0, 129.2, 129.0, 128.8, 128.5, 128.4, 128.2, 127.5, 124.1, 122.8, 13.8; ν_{max} (film)/cm^{-1} 3382, 3057, 2925, 2360, 2341, 1500, 1353, 1333, 1290, 1203, 1153, 1153, 1137, 770, 696; MS (ESI$^+$) *m/z* (rel intensity) 236 [100, $(M+H)^+$], 258 [35], 274 [10]; HRMS (ESI$^+$) 236.1065 ($(M+H)^+$, $C_{16}H_{14}NO$ requires 236.1070).

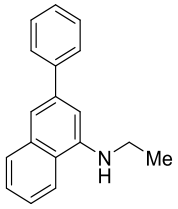
Data consistent with the literature.[122]

2-(4-Methoxyphenyl)-1-methyl-3-phenyl-1,2-dihydroisoquinoline (122)



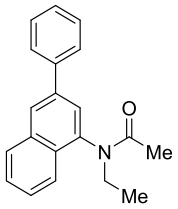
$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 mins, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture acetic acid (4 mL) and *p*-anisidine (185 µL, 1.5 mmol) were added. This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed *in vacuo* and the reaction mixture was then re-dissolved in MeOH (5 mL). To this sodium borohydride (85 mg, 2.25 mmol) was added in portions at 0 °C while stirring vigorously. The solution was allowed to warm to room temperature and then stirred for a further 24 h. The reaction was quenched with water (20 mL) and the organic product extracted with ether (3 x 10 mL). This was then dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by column chromatography (5-30% DCM/petrol), to yield the product as a yellow oil (21 mg, 43%); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.54-7.52 (m, 2H), 7.27-7.20 (m, 5H), 7.16-7.12 (m, 1H), 7.00 (d, *J* = 7.0 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.64 (d, *J* = 9.0 Hz, 2H), 6.46 (s, 1H), 5.00 (q, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 1.52 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 138.4, 135.8, 134.1, 131.7, 129.6, 128.3, 127.8, 127.7, 127.1, 126.3, 125.1, 124.2, 123.5, 114.0, 111.2, 110.0, 61.2, 55.5, 22.0; ν_{max} (film)/cm^{-1} 3016, 2970, 1739, 1601, 1508, 1442; HRMS (FI$^+$) 327.1623 ((M)$^+$, $C_{23}H_{21}NO$ requires 327.1623).

N-Ethyl-3-phenylnaphthalen-1-amine (121, R: Et)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 minutes, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and ethyl amine in THF (2M, 0.75 mL, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed in *vacuo* and the crude product purified by column chromatography (7-20% DCM/petrol) to yield the amine product as a colourless oil (12 mg, 33 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86-7.82 (m, 2H), 7.74-7.72 (m, 2H), 7.49-7.42 (m, 5H), 7.37 (tt, *J* = 7.4, 1.5 Hz, 1H), 6.88 (s, 1H), 3.41 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz); ^{13}C NMR (101 MHz; $CDCl_3$): 143.7, 142.1, 139.4, 134.5, 129.0, 128.7, 127.4, 127.2, 126.1, 124.7, 122.6, 119.7, 115.7, 104.2, 38.9, 29.3; ν_{max} (film)/cm^{-1} 3429, 3060, 2969, 2927, 2853, 2360; HRMS (FI$^+$) 247.1354 ((M)$^+$, $C_{18}H_{17}N$ requires 247.1361).

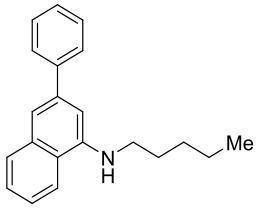
N-Ethyl-*N*-(3-phenylnaphthalen-1-yl)acetamide (123, R: Et)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 minutes, and the solution

was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and ethyl amine in THF (2M, 0.75 mL, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed in *vacuo* and the crude product purified by column chromatography (5-100% EtOAc/petrol) to yield the amide product as a yellow oil (20 mg, 47%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.09 (s, 1H), 8.00-7.95 (m, 1H), 7.86-7.83 (m, 1H), 7.73-7.70 (m, 2H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.60-7.55 (m, 2H), 7.53-7.50 (m), 7.42 (tt, *J* = 7.3, 1.2 Hz, 1H), 4.29 (dq, *J* = 13.7, 6.9 Hz, 1H), 3.51 (dq, *J* = 13.7, 6.9 Hz, 1H), 1.81 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 171.1, 140.0, 139.7, 138.8, 135.1, 129.7, 129.2, 129.0, 128.1, 127.5, 127.4, 127.2, 126.4, 126.1, 122.6, 44.0, 22.6, 13.7; ν_{max} (film)/cm^{-1} 2970, 2928, 2853, 2361; HRMS (FI$^+$) 289.1464 ((M)$^+$, $C_{20}H_{19}NO$ requires 289.1467).

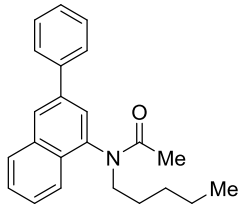
N-Pentyl-3-phenylnaphthalen-1-amine (121, R: pentyl)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 minutes, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and pentyl amine (137 µL, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed in *vacuo* and the crude product purified by

column chromatography (10-30% DCM/petrol) to yield the amine product as a colourless oil (10 mg, 23 %).^{1}H NMR (400 MHz; $CDCl_3$): δ 7.88-7.84 (m, 2H), 7.74-7.70 (m, 2H), 7.50-7.44 (m, 6H), 7.37 (tt, *J* = 7.4, 1.5 Hz, 1H), 6.97 (s, 1H), 3.37 (t, *J* = 7.3 Hz, 2H), 1.84 (dt, *J* = 14.8, 7.4 Hz, 2H), 1.51-1.37 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): 143.0, 141.9, 139.3, 134.6, 129.0, 128.7, 127.5, 127.2, 126.2, 125.0, 124.9. 122.9, 119.9, 116.3, 45.0, 29.1, 28.8, 22.5, 14.0; ν_{max} (film)/cm^{-1} 3442, 3029, 2955, 2928, 2857, 2361; HRMS (FI^{+}) 289.1838 ((M)$^{+}$, $C_{21}H_{23}N$ requires 289.1830).

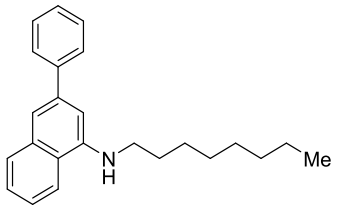
N-Pentyl-*N*-(3-phenylnaphthalen-1-yl)acetamide (123, R: Pentyl)



$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 minutes, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and pentyl amine (137 µL, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed in *vacuo* and the crude product purified by column chromatography (10-30% DCM/petrol)-(30-100% EtOAc/prtrol), to yield the amide product as a yellow oil (15 mg, 30%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.09 (s, 1H), 7.99-7.98 (m, 1H), 7.85-7.83 (m, 1H), 7.73-7.72 (m, 1H), 7.72-7.71 (m, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.59-7.57 (m, 2H), 7.55-7.51 (m, 2H), 7.43 (tt, *J* = 7.4, 1.5 Hz, 1H), 4.29-4.20 (m, 1H), 3.41-3.25 (m, 1H), 1.80 (s, 3H), 1.71-1.56 (m, 3H), 1.33-1.28 (m, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 171.1, 140.1, 140.0, 138.8, 135.2, 129.7, 129.2, 129.1, 128.1, 127.5, 127.4, 127.3, 126.3, 126.1, 122.6,

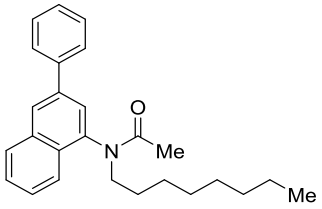
49.3, 29.3, 28.1, 22.7, 22.6, 14.2; ν_{max} (film)/cm^{-1} 2956, 2930, 2860, 2361, 1738, 1660; HRMS (FI$^+$) 331.1937 ((M)$^+$, $C_{23}H_{25}NO$ requires 331.1936).

N-Octyl-3-phenylnaphthalen-1-amine (121, R: octyl)



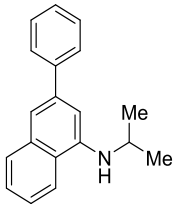
$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 minutes, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and octyl amine (194 µL, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed in *vacuo* and the crude product purified by column chromatography (10-30% DCM/petrol), to yield the amine product as a colourless oil (22 mg, 45 %). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.77-7.75 (m, 2H), 7.51-7.44 (m, 5H), 7.39 (t, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 3.37 (t, *J* = 7.2 Hz, 2H), 1.84 (quintet, *J* = 7.4 Hz, 2H), 1.51-1.45 (m, 2H), 1.45-1.27 (m, 8H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 143.6, 142.2, 139.5, 134.7, 129.1, 128.8, 127.6, 127.3, 126.3, 124.9, 122.9, 119.9, 116.0, 104.9, 44.9, 32.0, 29.8, 29.58, 29.42, 27.5, 22.8, 14.3; ν_{max} (film)/cm^{-1} 3060, 2925, 2854, 2310, 1625, 1582, 1526; HRMS (FI$^+$) 331.2275 ((M)$^+$, $C_{24}H_{29}N$ requires 331.2300).

N-Octyl-*N*-(3-phenylnaphthalen-1-yl)acetamide (123, R: octyl)



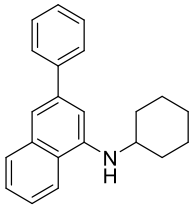
$Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol) and Xantphos (4.3 mg, 0.0075 mmol) were dissolved in chlorobenzene (0.5 mL). H_2 gas was bubbled through the solution for 2 minutes, and the solution was purged with N_2 gas for a further 30 seconds. This solution was then transferred to mixture of 1-(2-(methylthio)phenyl)ethanone (25 mg, 0.15 mmol) and phenylacetylene (33 µL, 0.30 mmol) under a nitrogen atmosphere. The reaction mixture was heated to 100 °C, stirred for 1.5 h and then allowed to cool to room temperature. To the reaction mixture was added acetic acid (4 mL) and octyl amine (194 µL, 1.5 mmol). This was heated to 110 °C, stirred for 16 h and allowed to cool to room temperature. The solvent was removed in *vacuo* and the crude product purified by column chromatography (10-30% DCM/petrol), to yield the amide product as a yellow oil (25 mg, 50 %).^{1}H NMR (400 MHz; $CDCl_3$): δ 8.09 (s, 1H), 8.00-7.96 (m, 1H), 7.85-7.81 (m, 1H), 7.73-7.71 (m, 2H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.59-7.57 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 4.29-4.20 (m 1H), 3.40-3.32 (m, 1H), 1.80 (s, 3H), 1.71-1.54 (m, 3H), 1.29-1.18 (m, 9H), 0.84 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$): δ 171.1, 140.0, 138.7, 135.2, 129.7, 129.22, 129.06, 128.0, 127.52, 127.42, 127.25, 126.3, 126.1, 122.6, 49.3, 31.9, 29.49, 29.39, 28.5, 27.1, 22.74, 22.68, 14.2; ν_{max} (film)/cm^{-1} 3056, 2926, 2854, 2361, 2342, 1662, 1449, 1408, 1301, 888, 785, 697; HRMS (FI$^+$) 373.2401 ((M)$^+$, $C_{26}H_{31}NO$ requires 373.2406).

N-Isopropyl-3-phenylnaphthalen-1-amine (121, R: ^{i}Pr)



Prepared following general procedure **E** using isopropyl amine (128 µL, 1.5 mmol). The crude product was purified by column chromatography (10% DCM/petrol), to yield the amine product as a green solid (30 mg, 77%); m.p: 71-73 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.76-7.74 (m, 2H), 7.52-7.37 (m, 6H), 6.90 (s, 1H), 3.95 (hep, *J* = 6.5 Hz, 1H), 1.40 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (101 MHz; $CDCl_3$): 142.0, 139.3, 134.7, 132.9, 129.0, 128.7, 127.4, 127.2, 126.2, 125.3, 124.9, 124.5, 123.0, 120.0, 115.8, 105.1, 44.7, 22.6; ν_{max} (film)/cm^{-1} 3434, 2970, 1739, 1592, 1525, 1416, 1366, 1228, 761, 698; HRMS (FI^{+}) 261.1520 ((M)$^{+}$, $C_{19}H_{19}N$ requires 261.1518).

N-Cyclohexyl-3-phenylnaphthalen-1-amine (121, R: Cy)



Prepared following general procedure **E** using cyclohexyl amine (172 µL, 1.5 mmol). The crude product was purified by column chromatography (10-30% DCM/petrol), to yield the amine product as a white solid (40 mg, 89%); m.p: 92 °C; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.84-7.82 (m, 2H), 7.72-7.70 (m, 2H), 7.50-7.40 (m, *J* = 7.5 Hz, 5H), 7.38 (tt, *J* = 7.5, 1.5 Hz, 1H), 6.92 (bs, 1H), 3.59-3.55 (m, 1H), 2.23-2.21 (m, 2H), 1.84-1.81 (m, 2H), 1.61-1.29 (m, 6H); ^{13}C NMR (101 MHz; $CDCl_3$): 142.6, 142.3, 139.4, 134.8, 129.0, 128.7, 127.5, 127.1, 126.1, 124.7, 122.8, 119.9, 115.3, 104.3, 51.8, 33.1, 25.9, 25.0; ν_{max} (film)/cm^{-1} 2928, 2853, 1581, 1525, 1414, 761; HRMS (FI^{+}) 301.1837 ((M)$^{+}$, $C_{22}H_{33}N$ requires 301.1830).

Chapter 6: References

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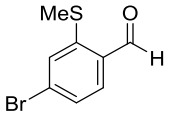
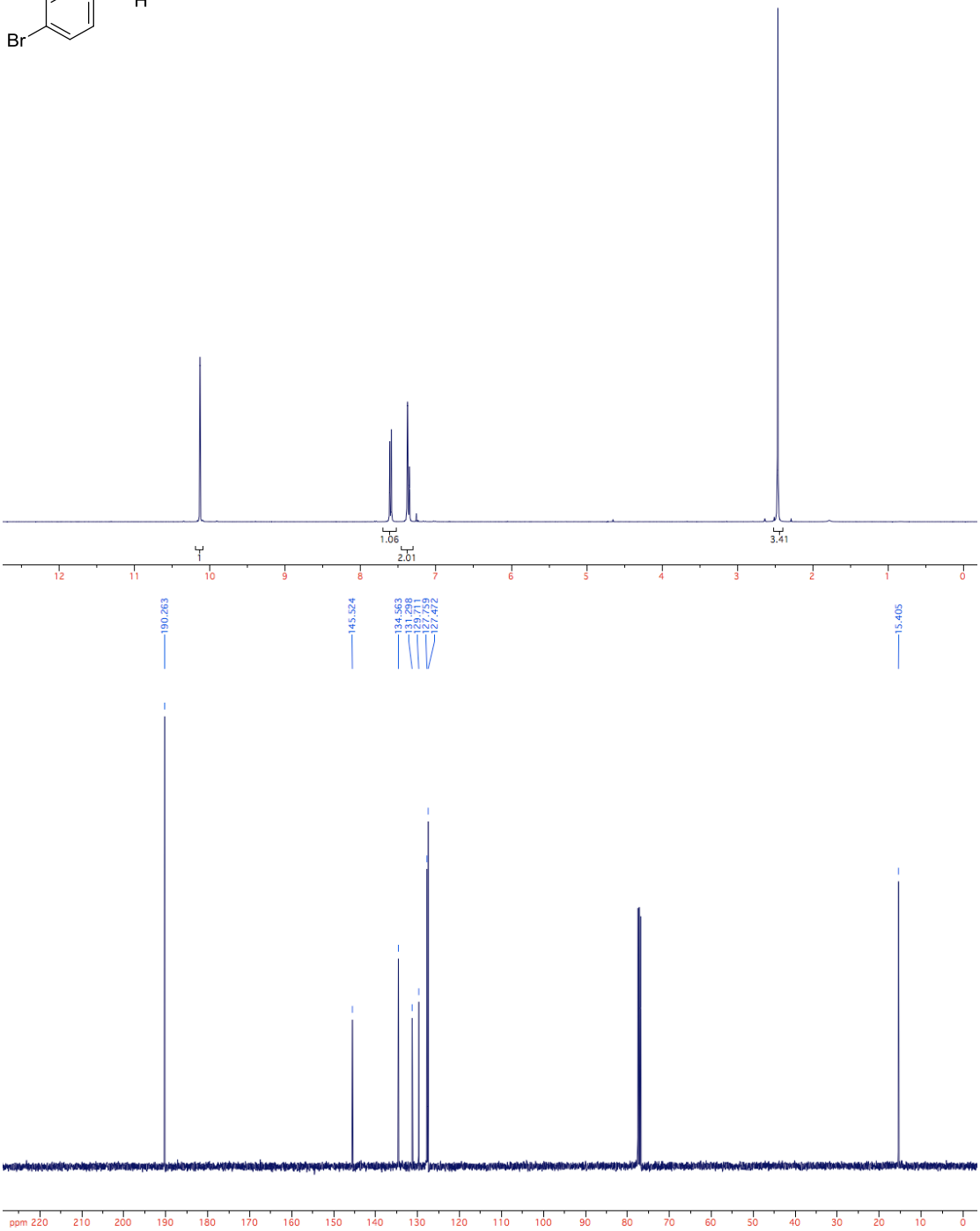
Chapter 7: Appendix

Novel Starting Materials:

4-Bromo-2-(methylthio)benzaldehyde (75c)



NMR Spectra: The following shows ^{1}H NMR and ^{13}C NMR Spectroscopy spectra of all novel starting material and all the compounds reported in Chapter 2 and 3. NMR Spectra were recorded either on Bruker DPX200 (200 MHz), DQX400 (400 MHz), AVC400 (400 MHz), DRX500 (500 MHz), AVC500 (500 MHz) spectrometers.



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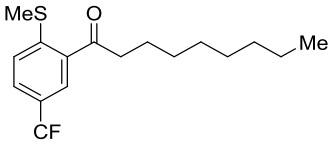
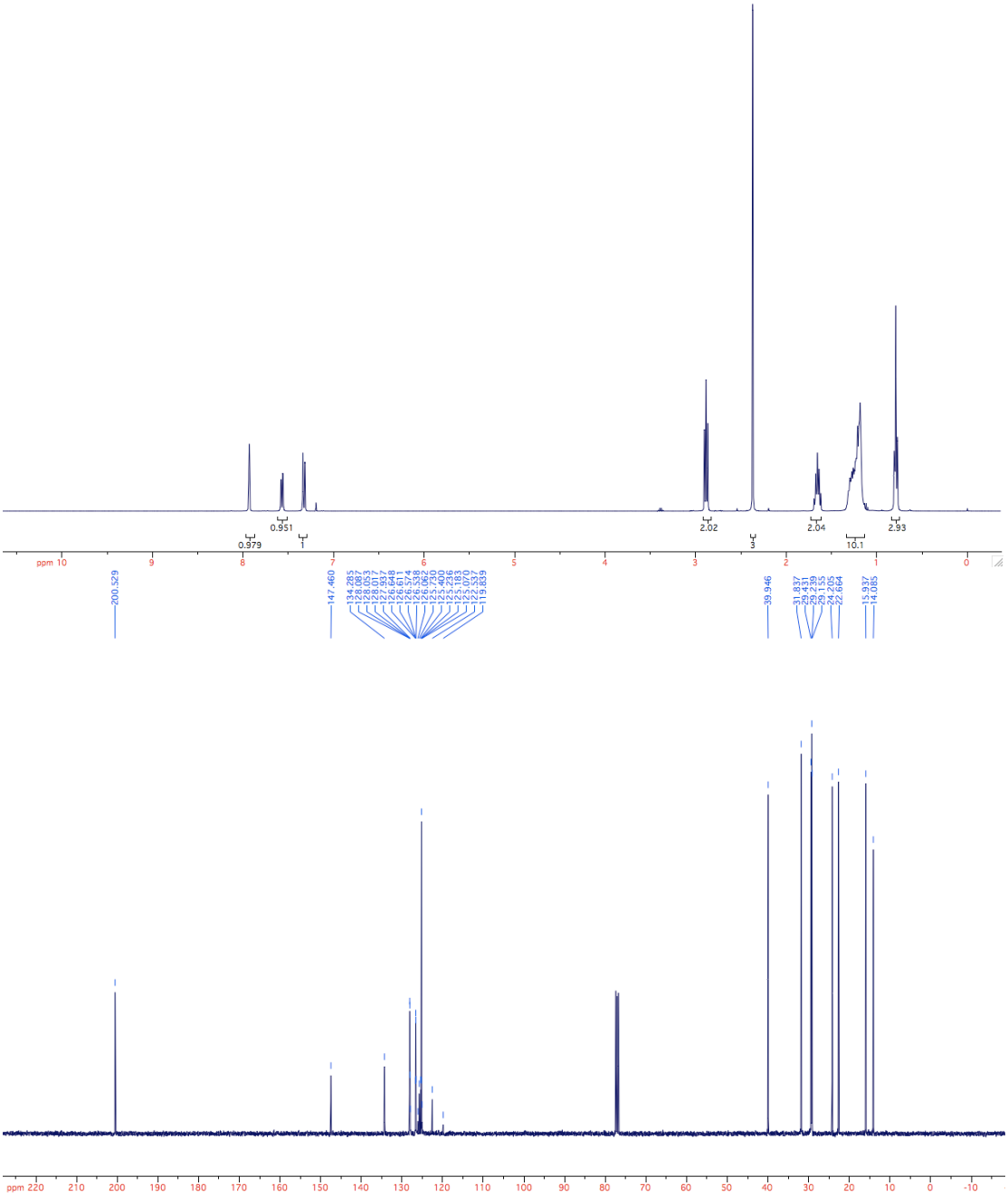
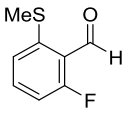
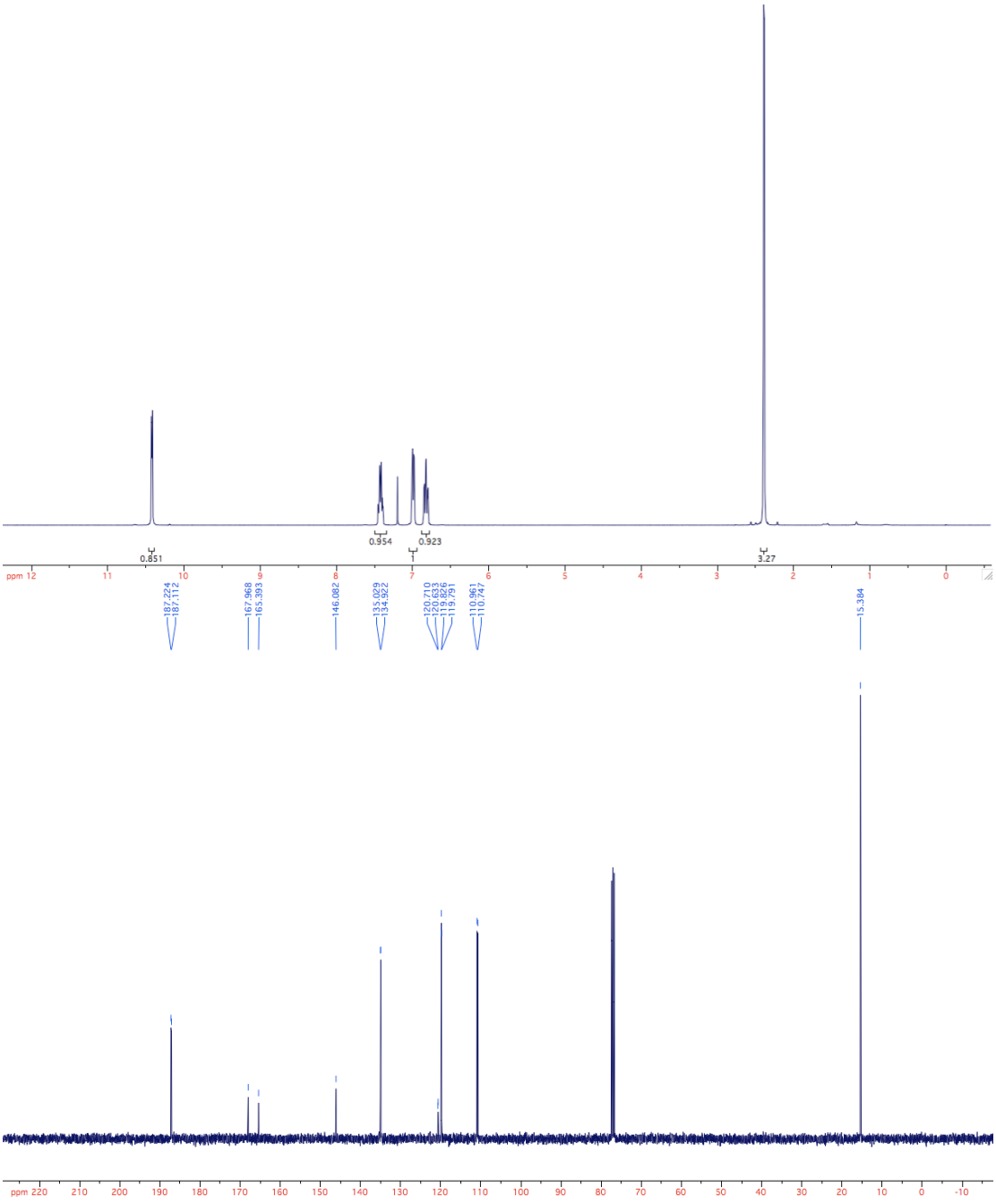




2-fluoro-6-(methylthio)benzaldehyde





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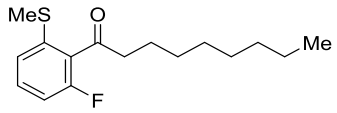
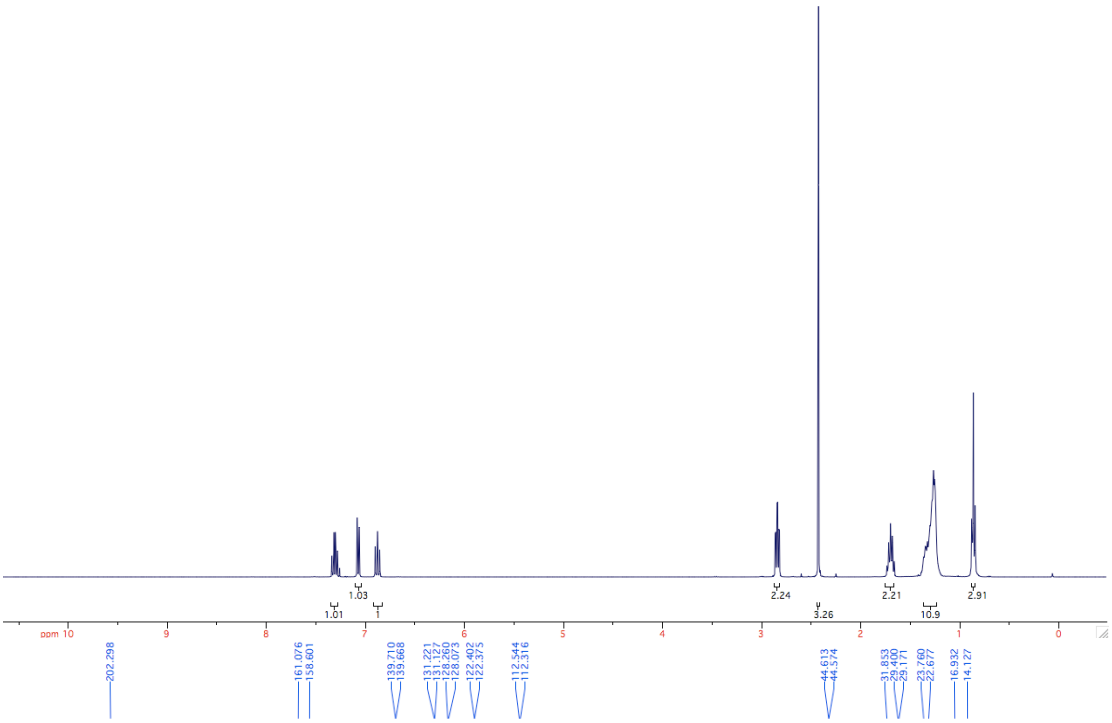
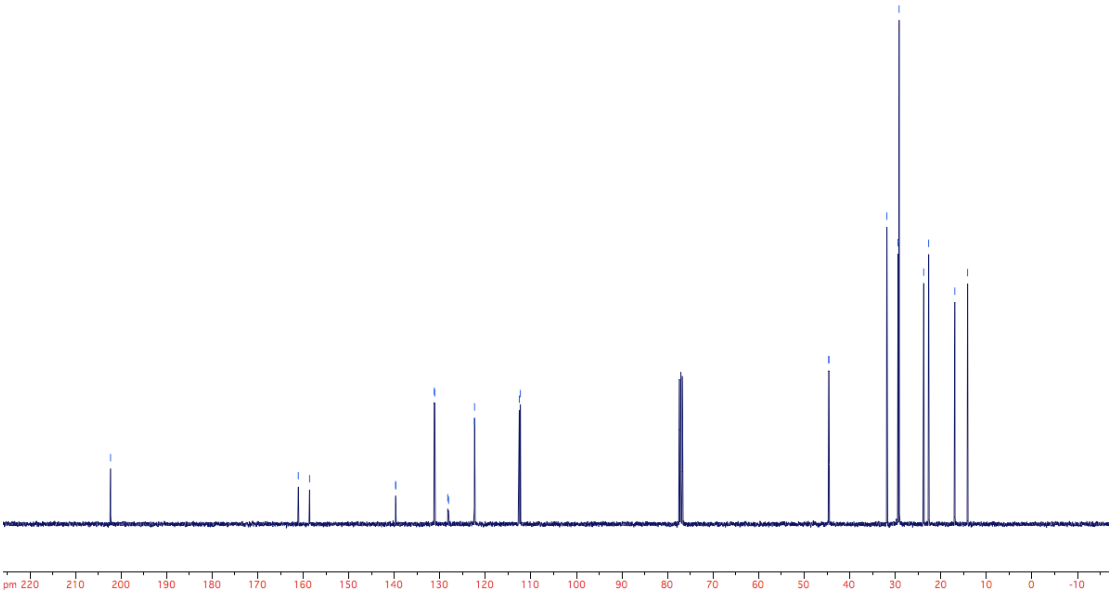
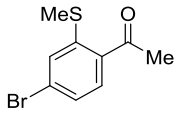
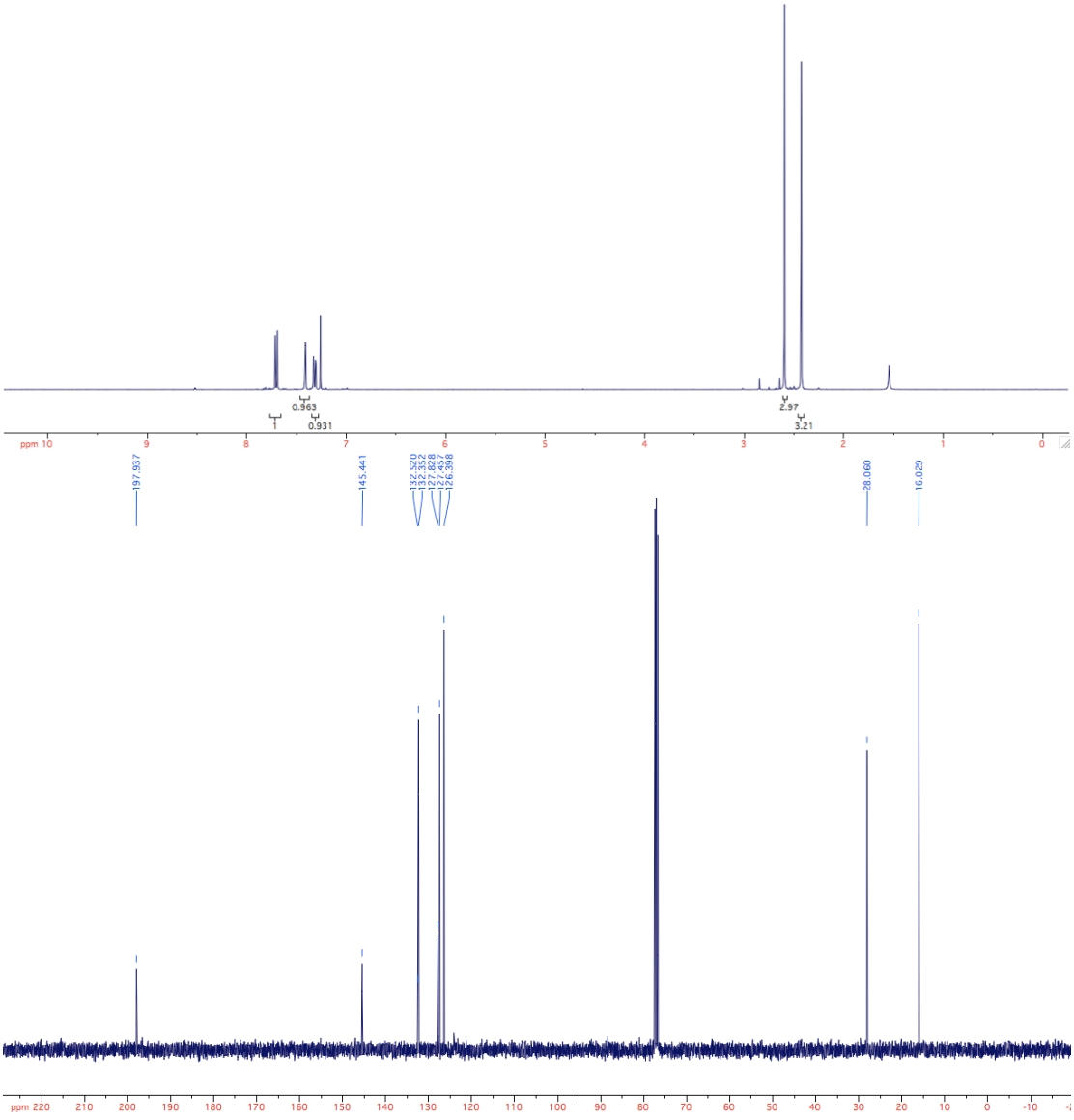






1-(4-bromo-2-(methylthio)phenyl)ethanone (70)





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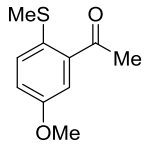

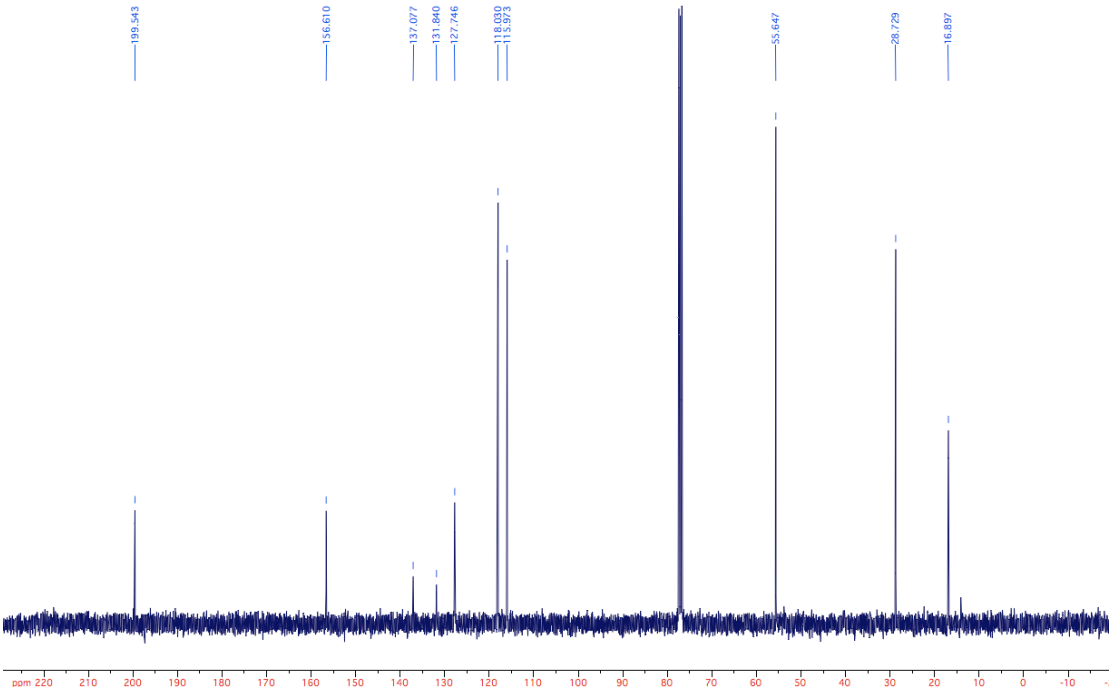

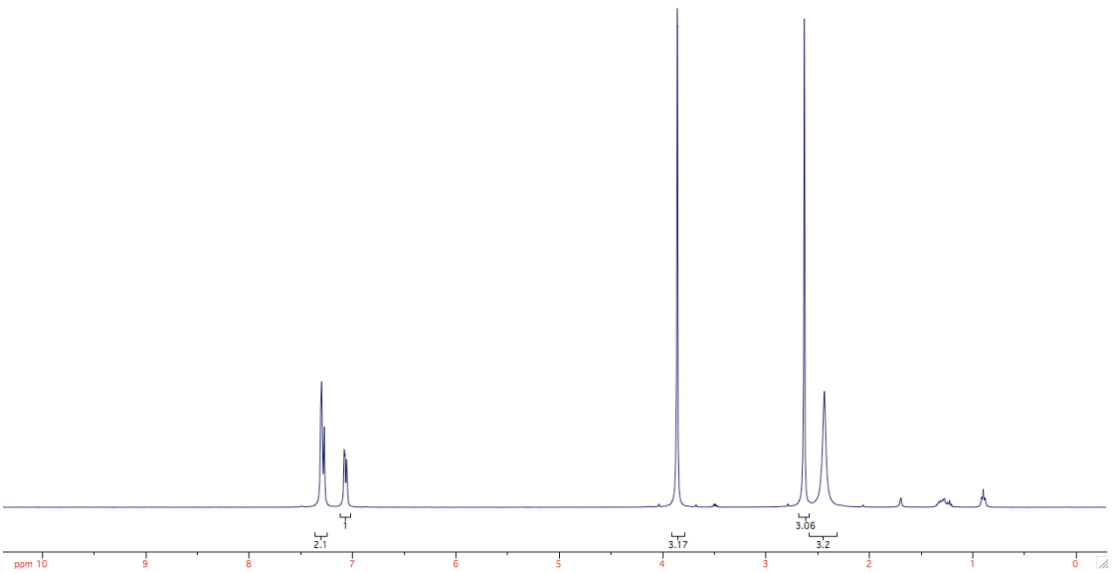

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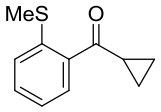

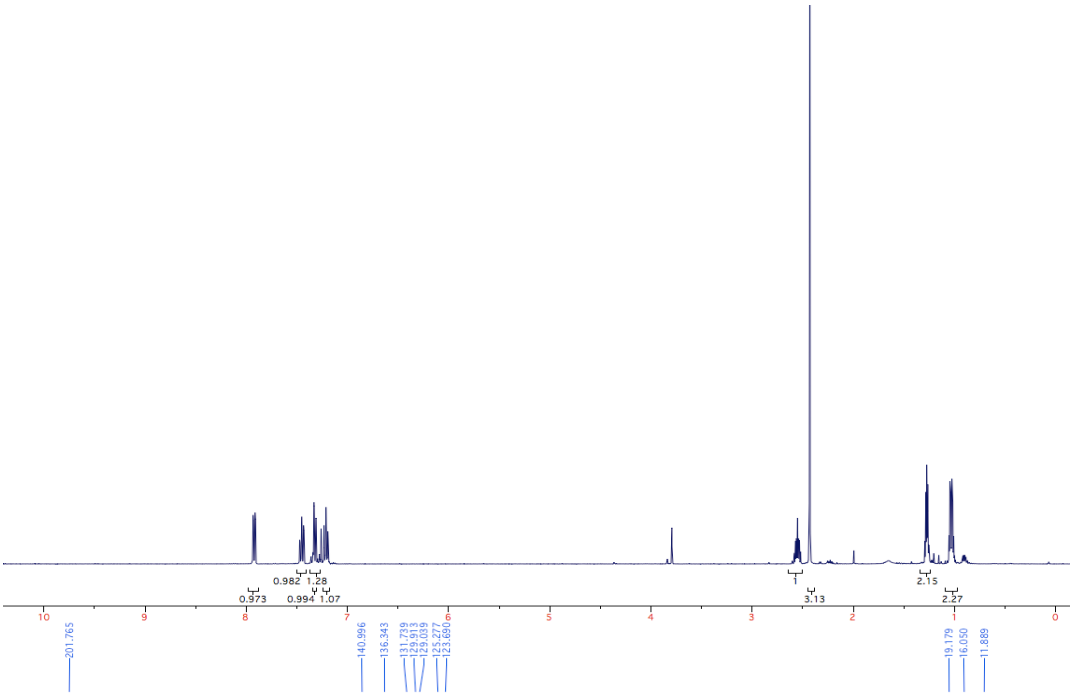

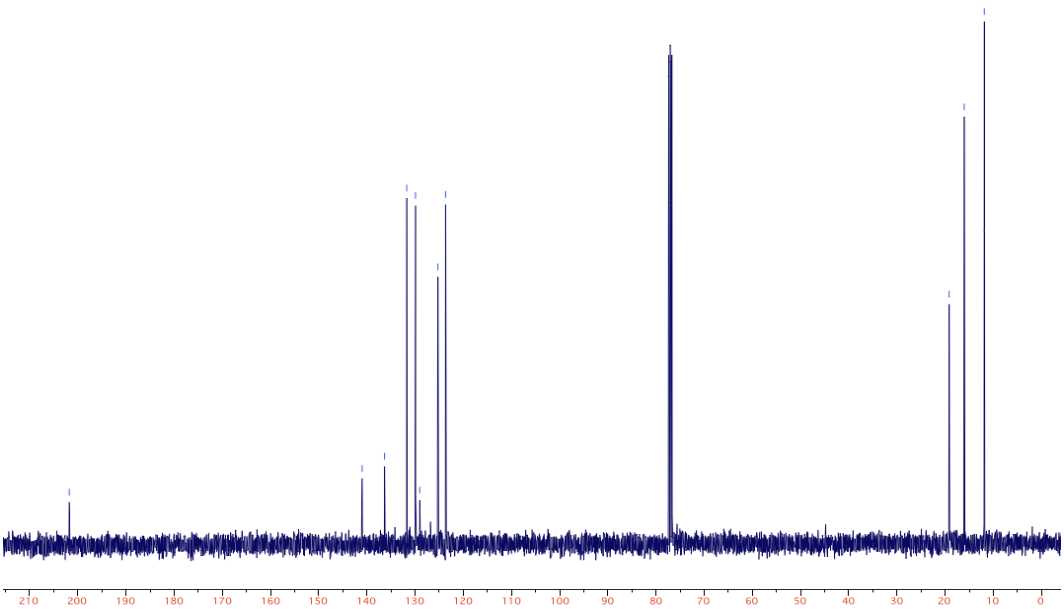

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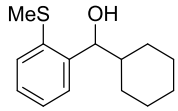
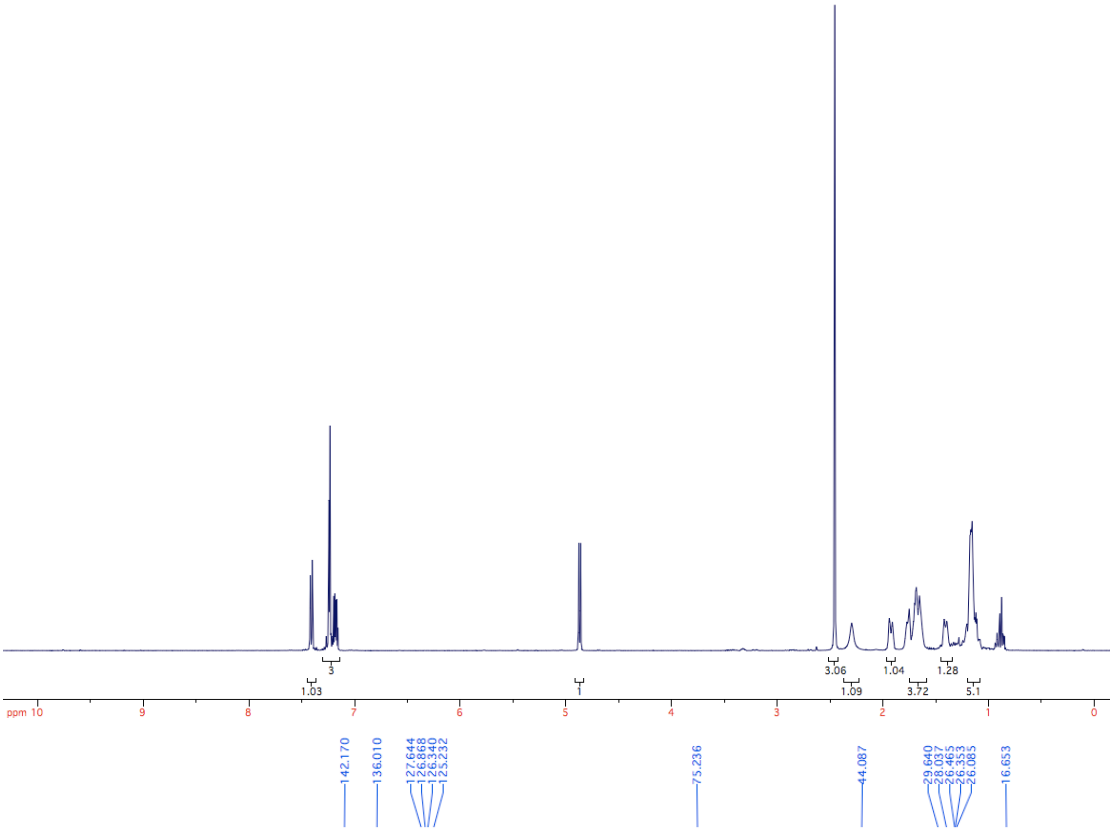
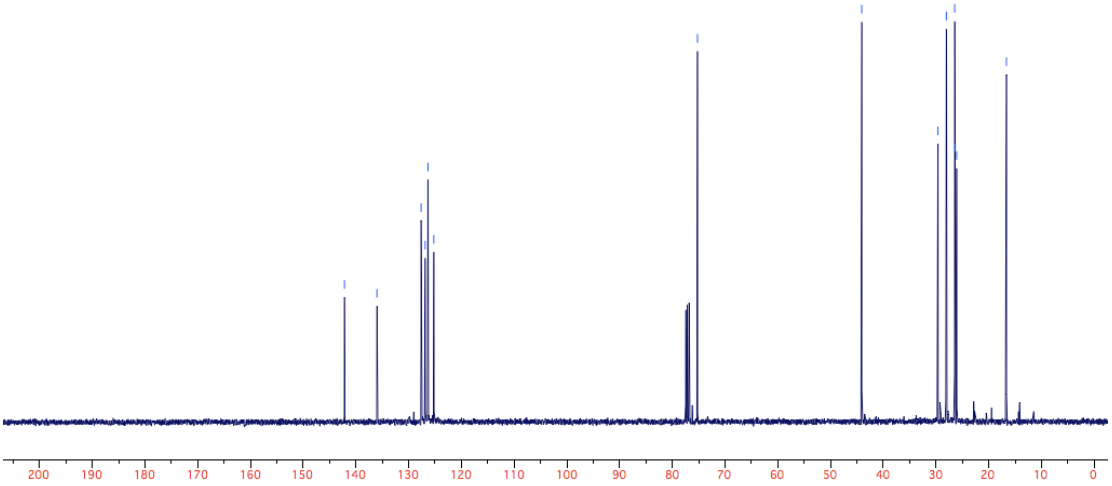
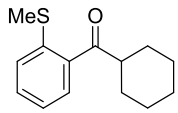
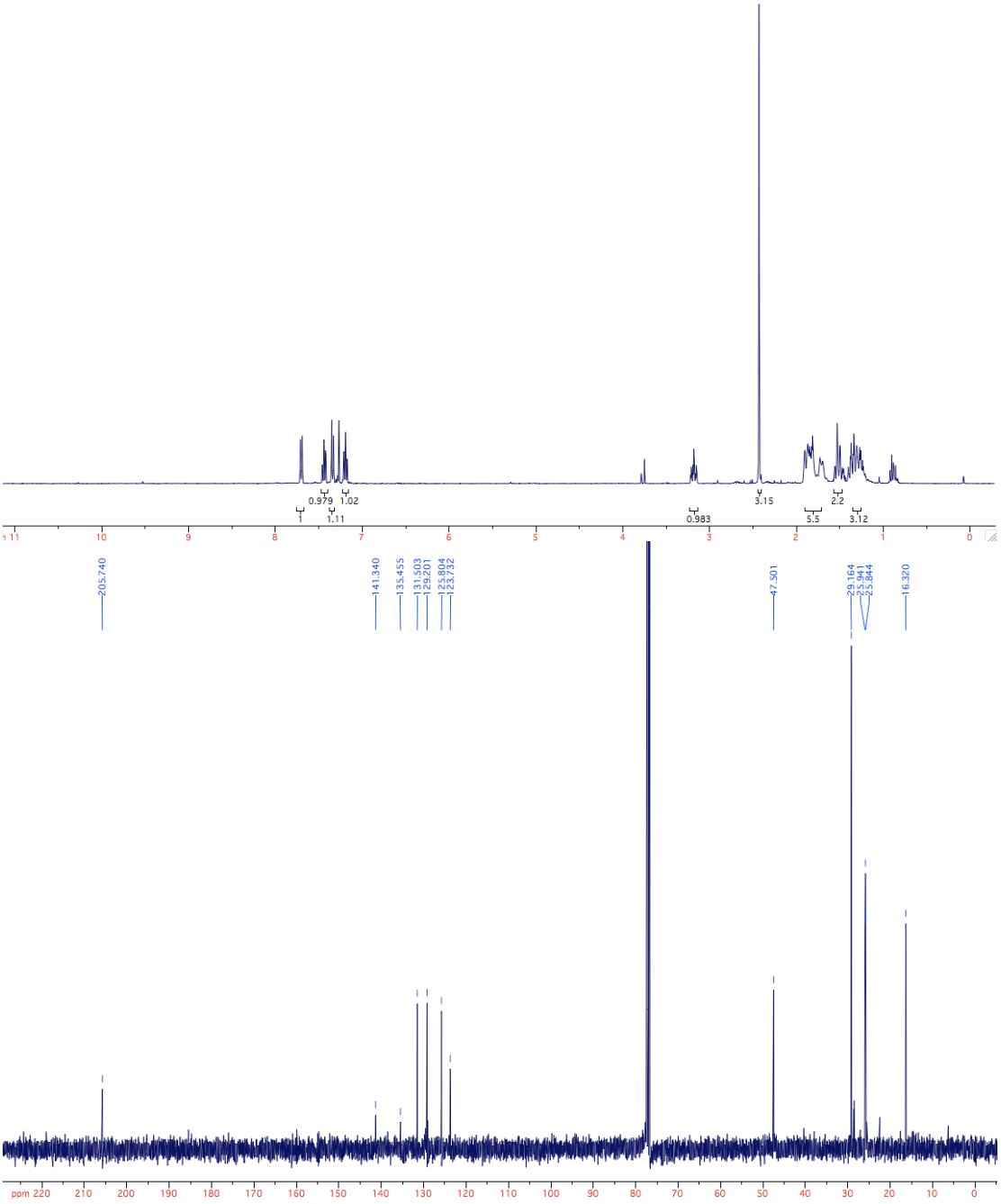




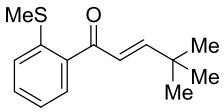


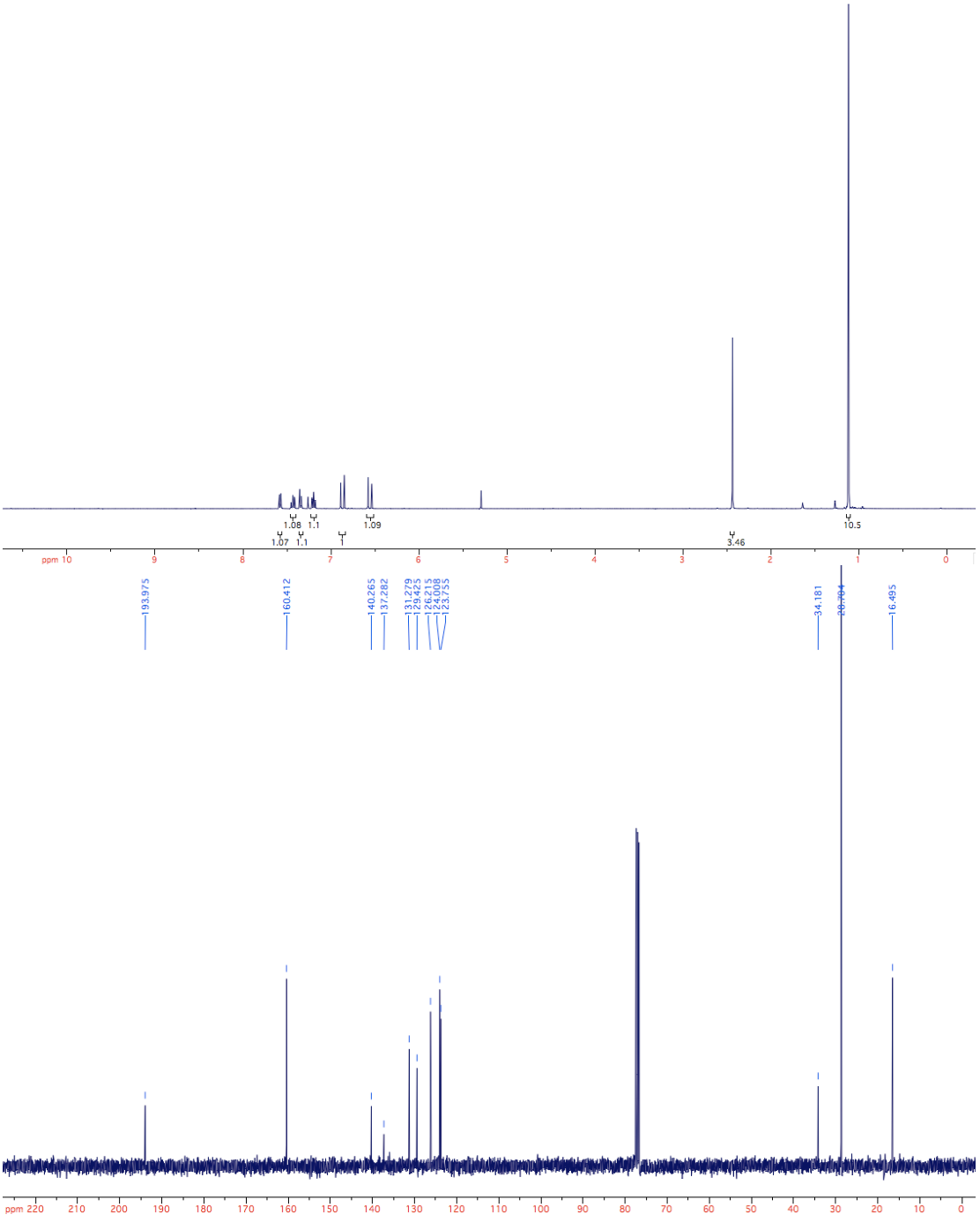
Cyclohexyl(2-(methylthio)phenyl)methanone (53q)





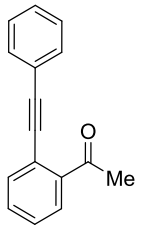
(*E*)-4,4-Dimethyl-1-(2-(methylthio)phenyl)pent-2-en-1-one (53s)

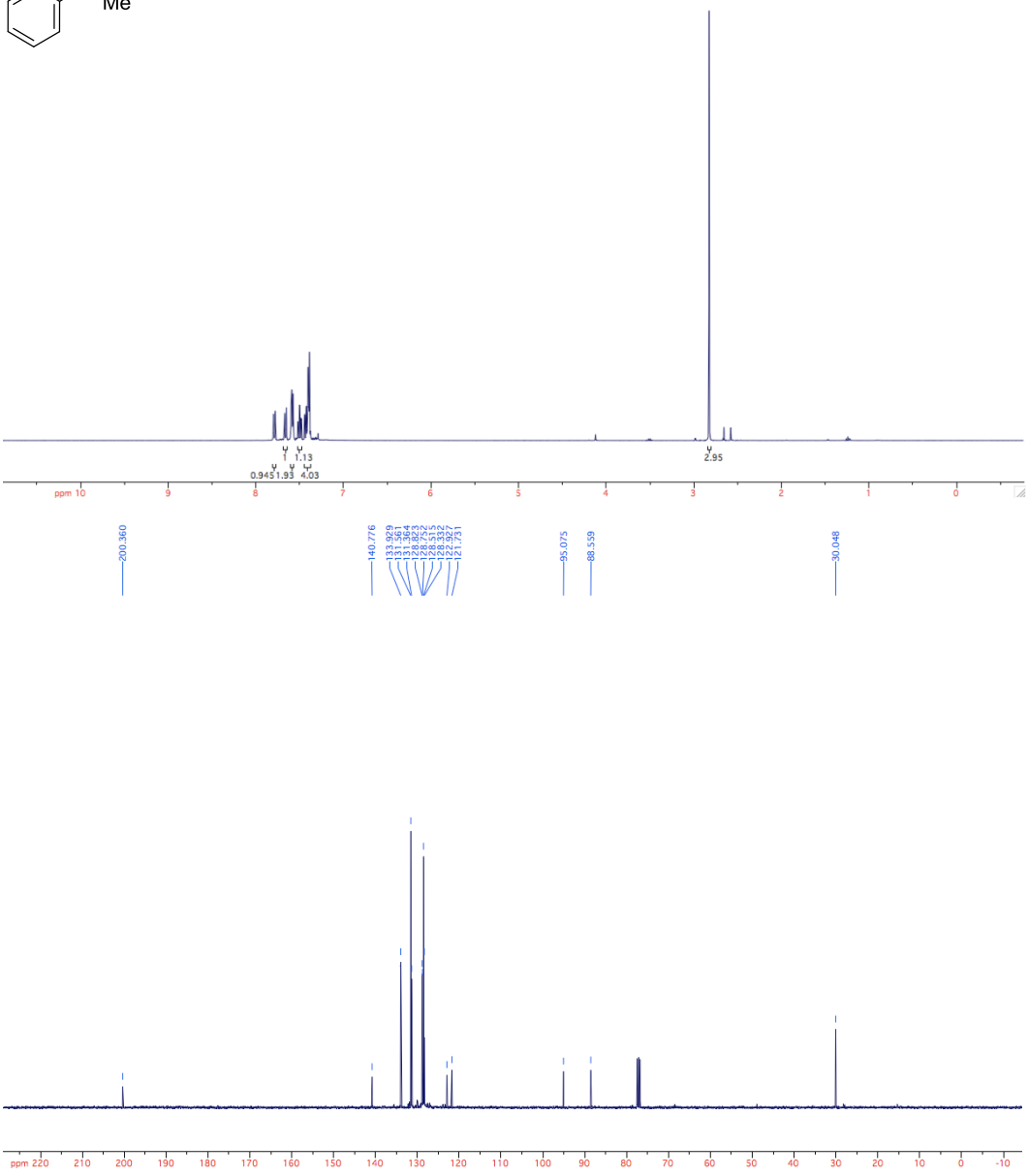




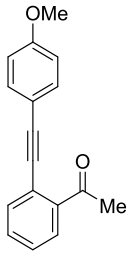
Compounds from Chapter 2:

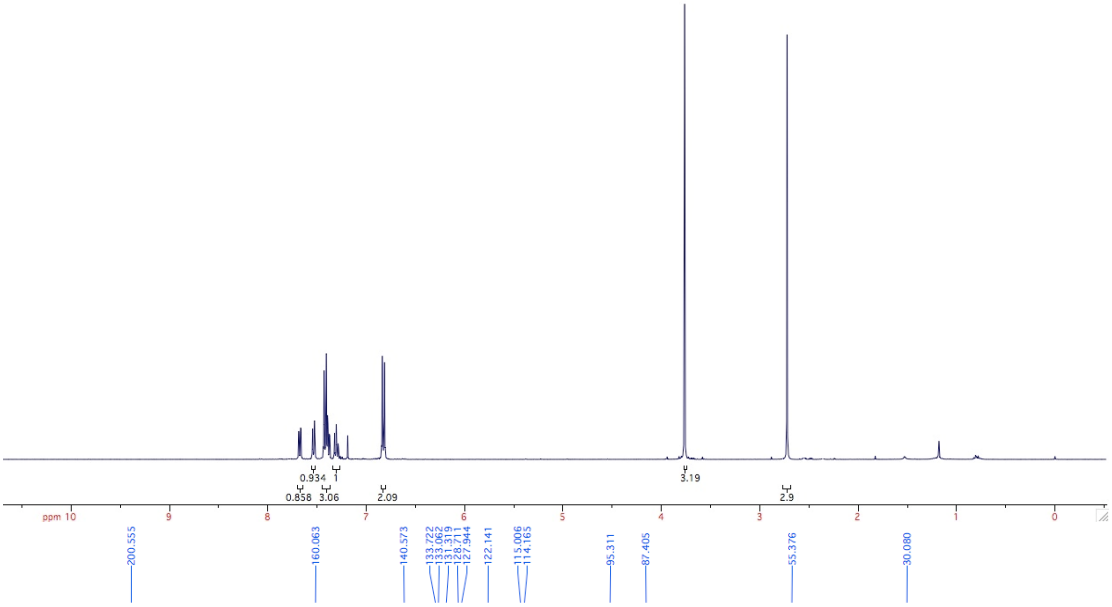
1-(2-(phenylethynyl)phenyl)ethanone (67a)

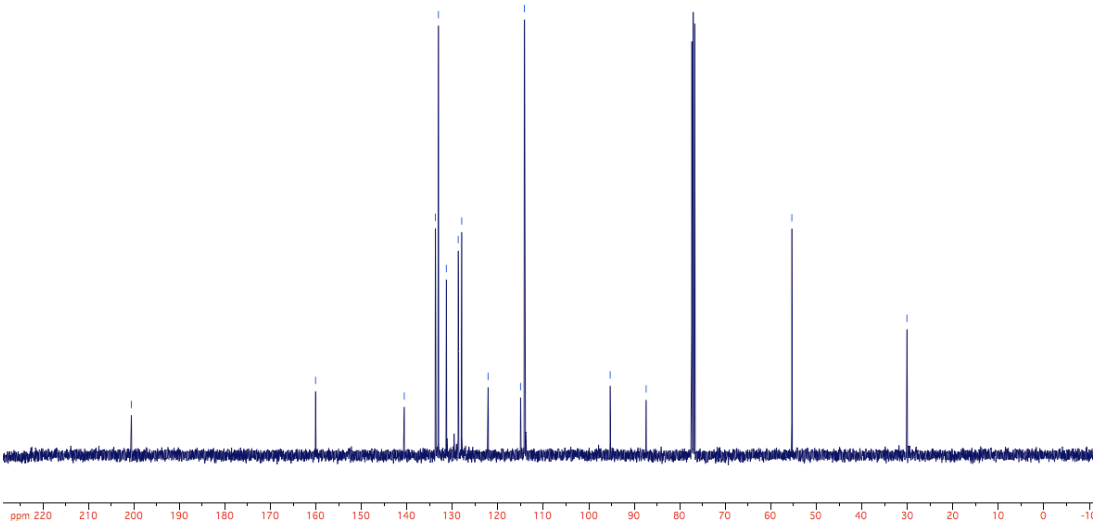




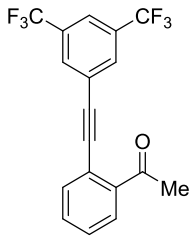
1-(2-((4-methoxyphenyl)ethynyl)phenyl)ethanone (67b)

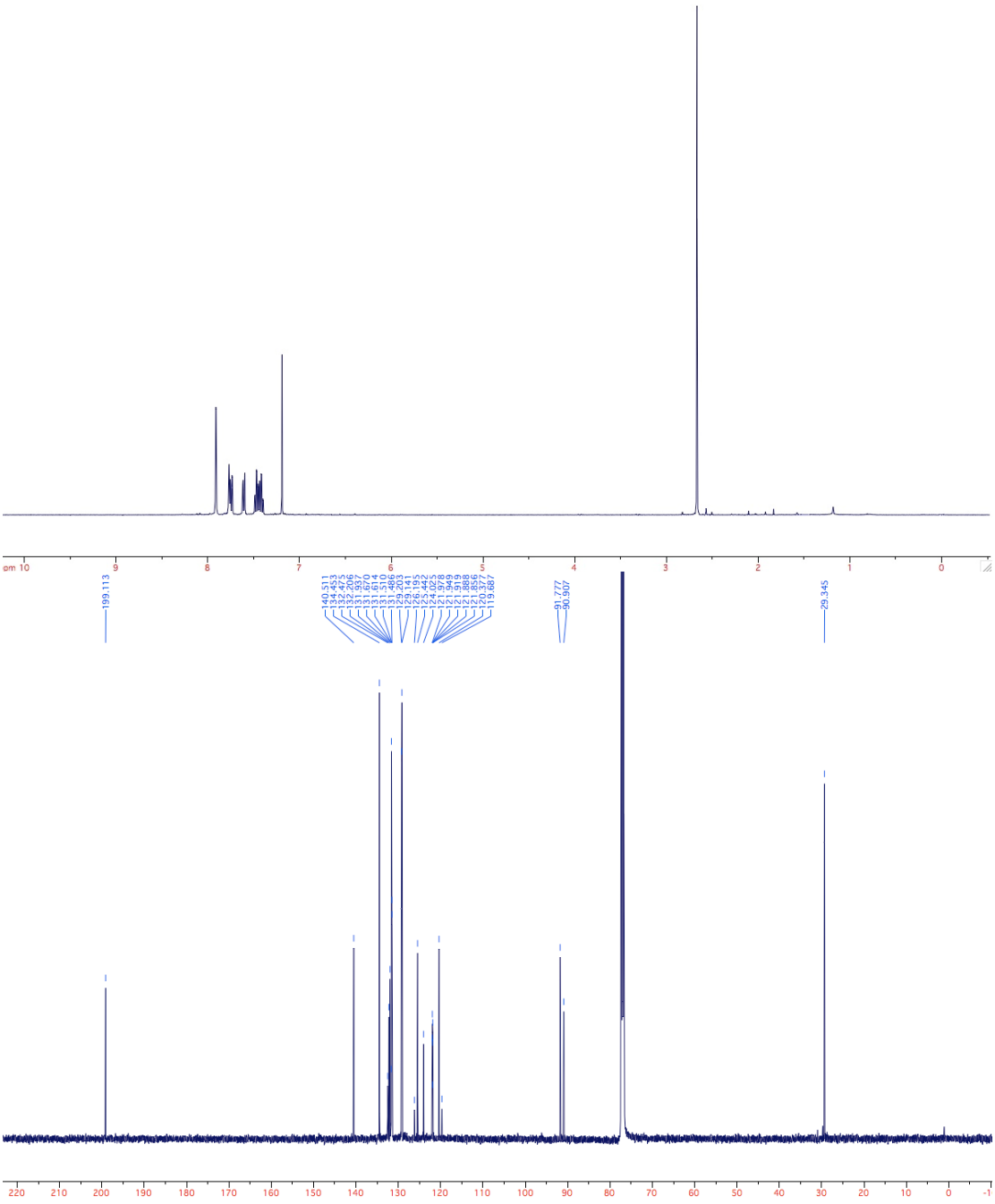




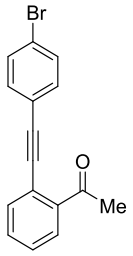


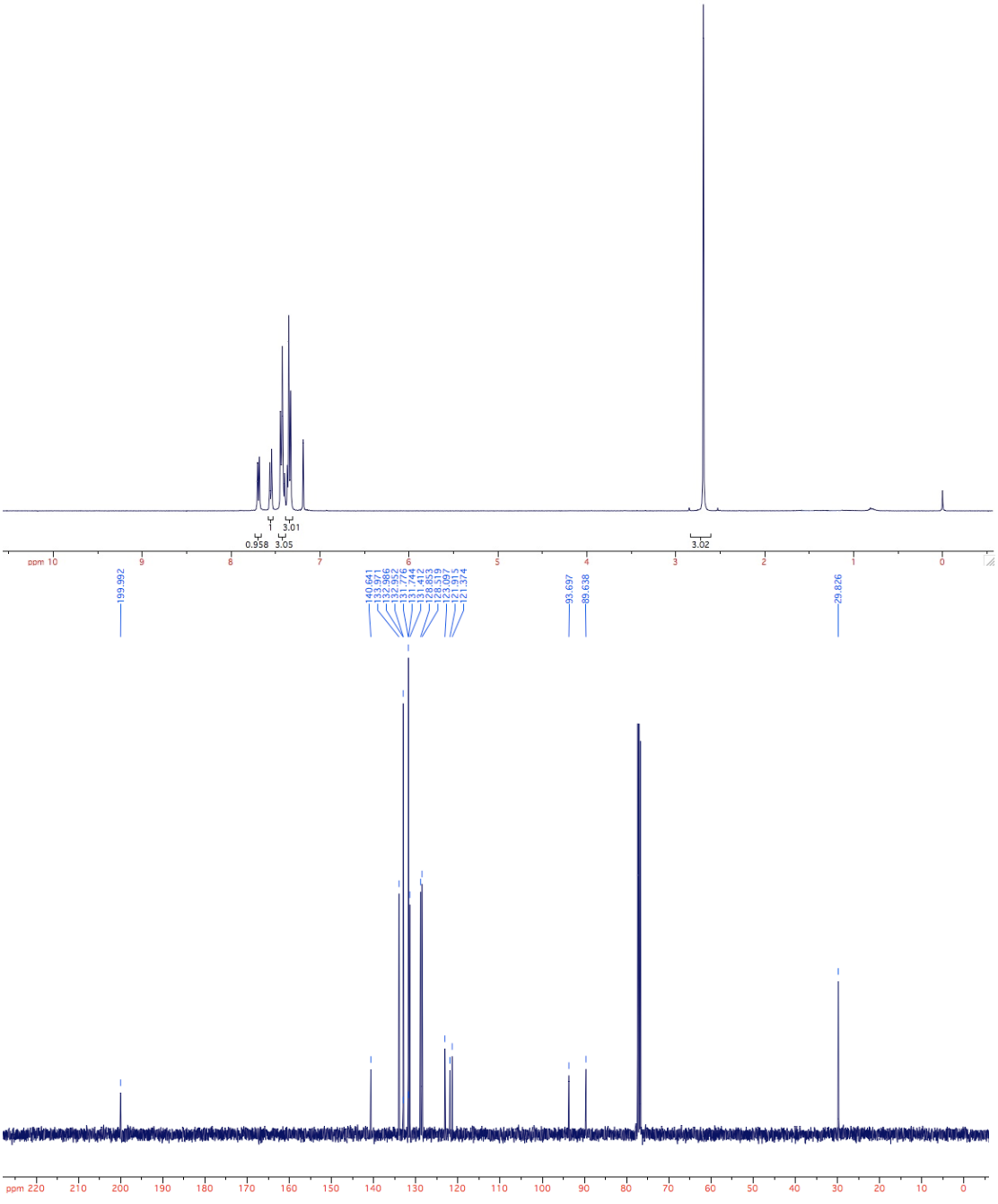
1-(2-((3,5-bis(trifluoromethyl)phenyl)ethynyl)phenyl)ethanone (67c)



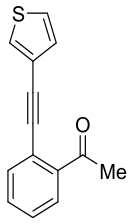


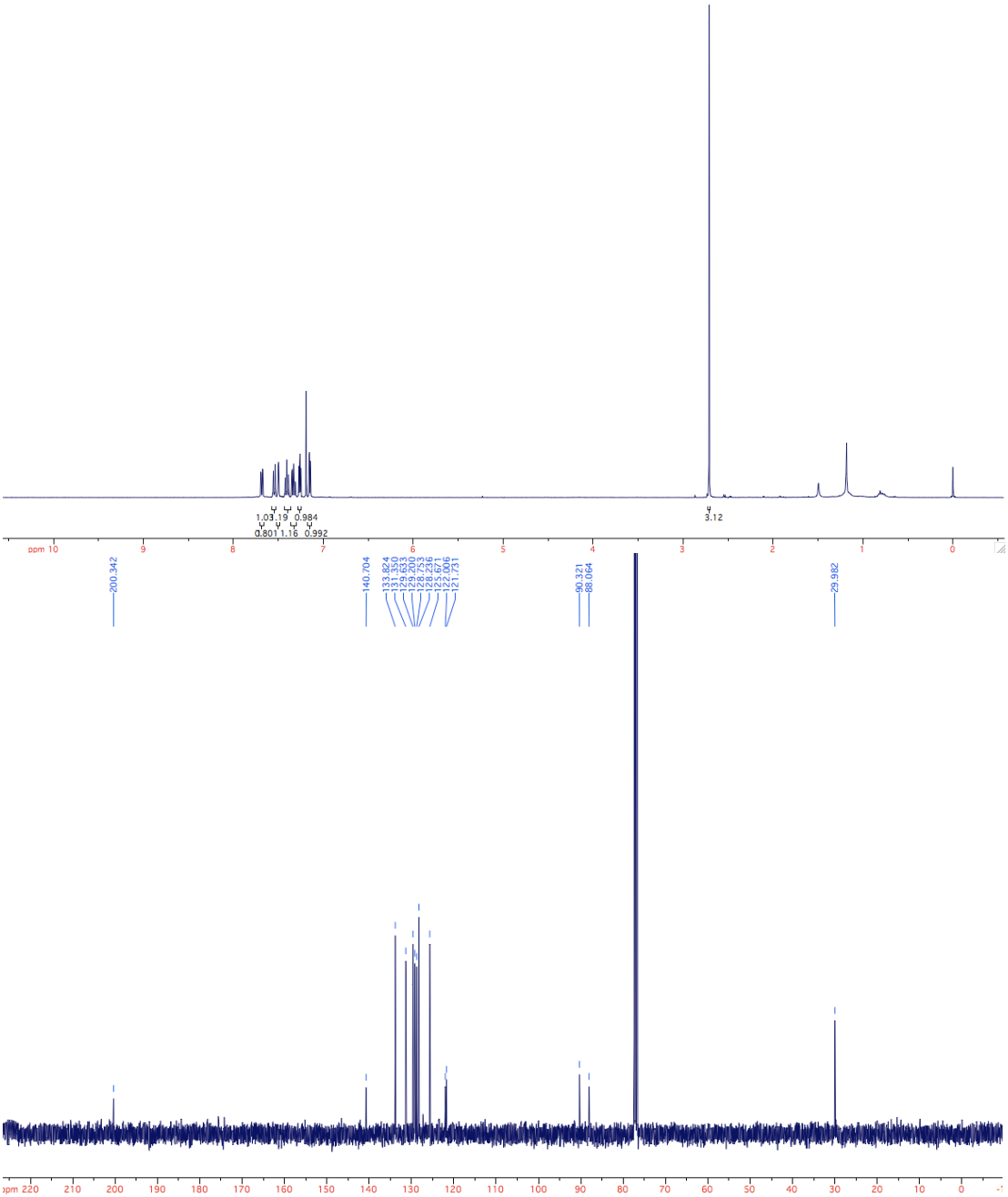
1-(2-((4-bromophenyl)ethynyl)phenyl)ethanone (67d)



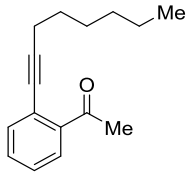


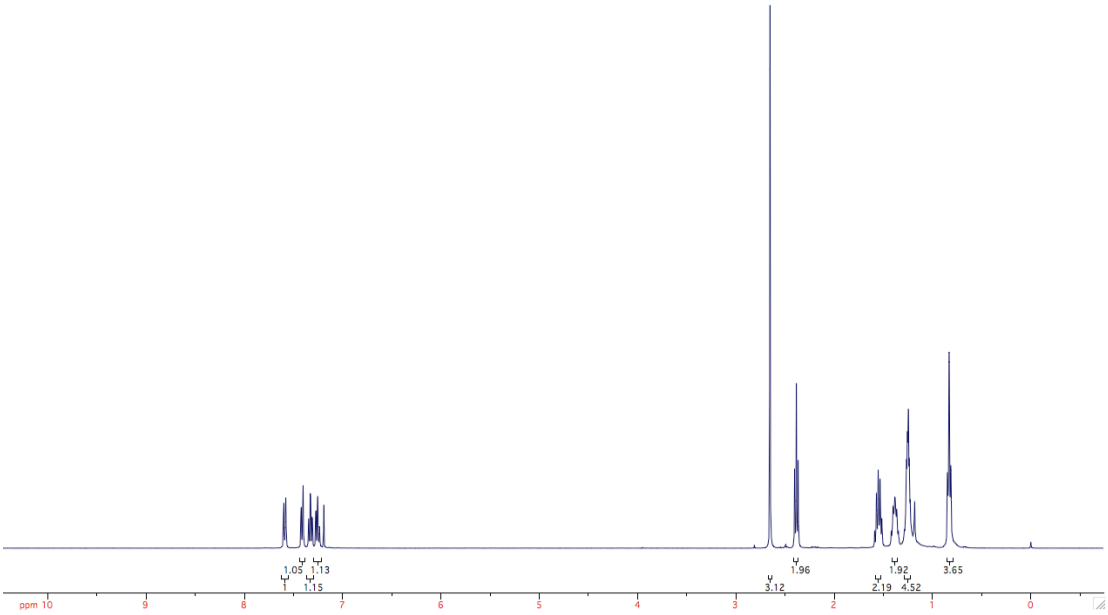
1-(2-(thiophen-3-ylethynyl)phenyl)ethanone (67e)

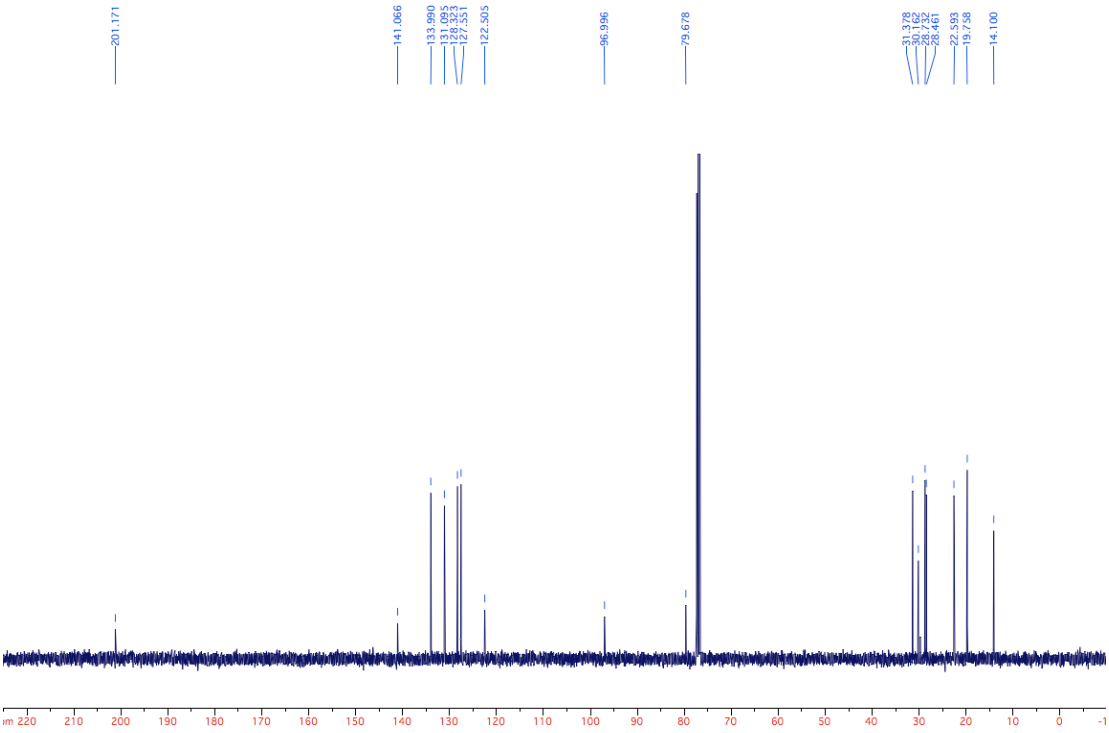




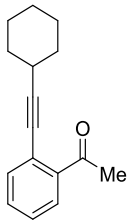
1-(2-(dec-1-yn-1-yl)phenyl)ethanone (67f)

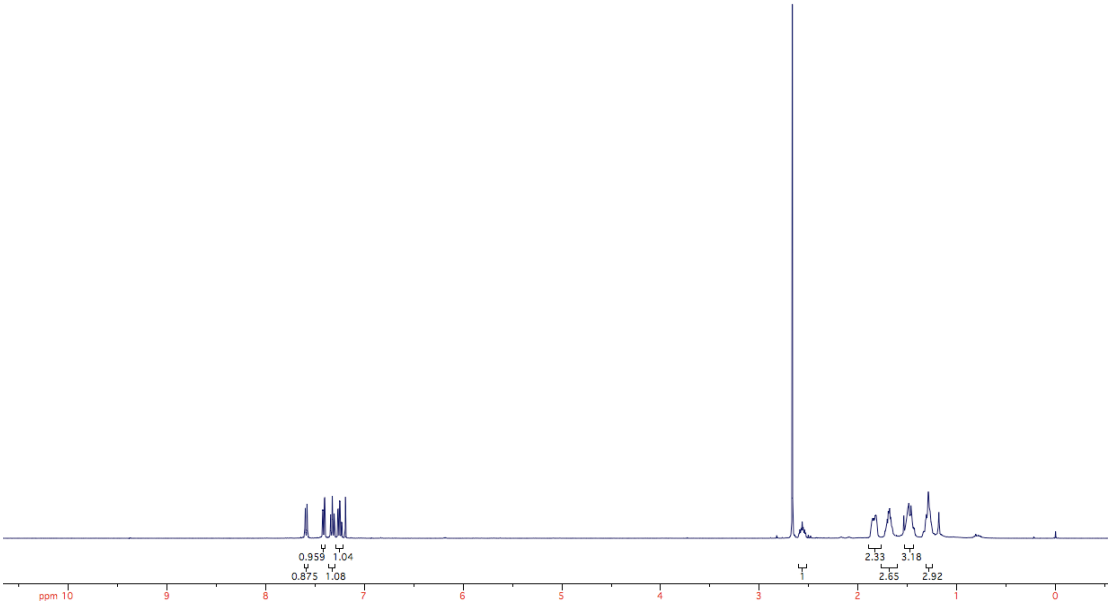


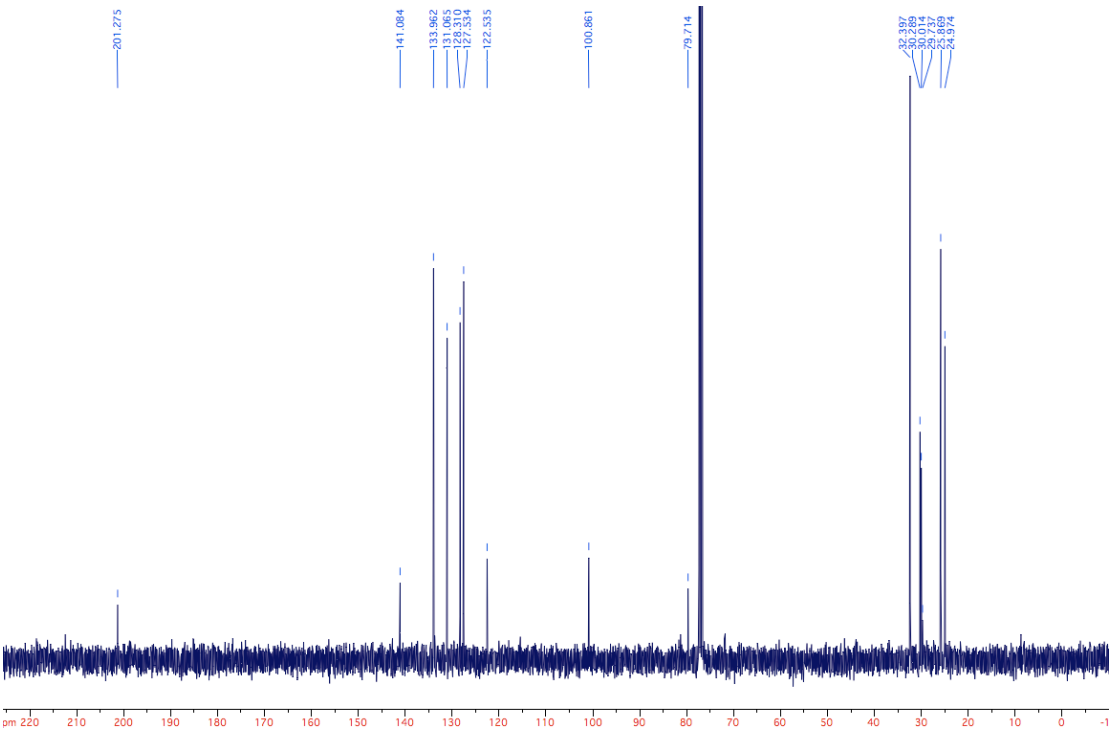




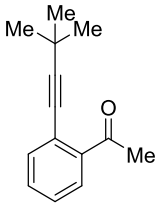
1-(2-(cyclohexylethynyl)phenyl)ethanone (67g)

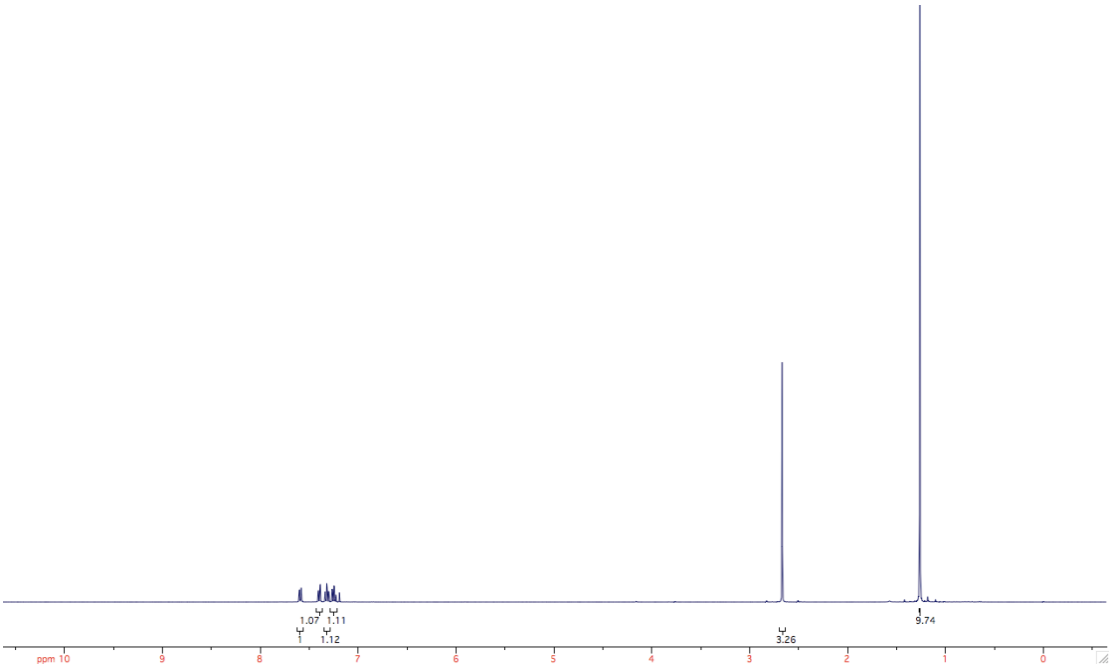


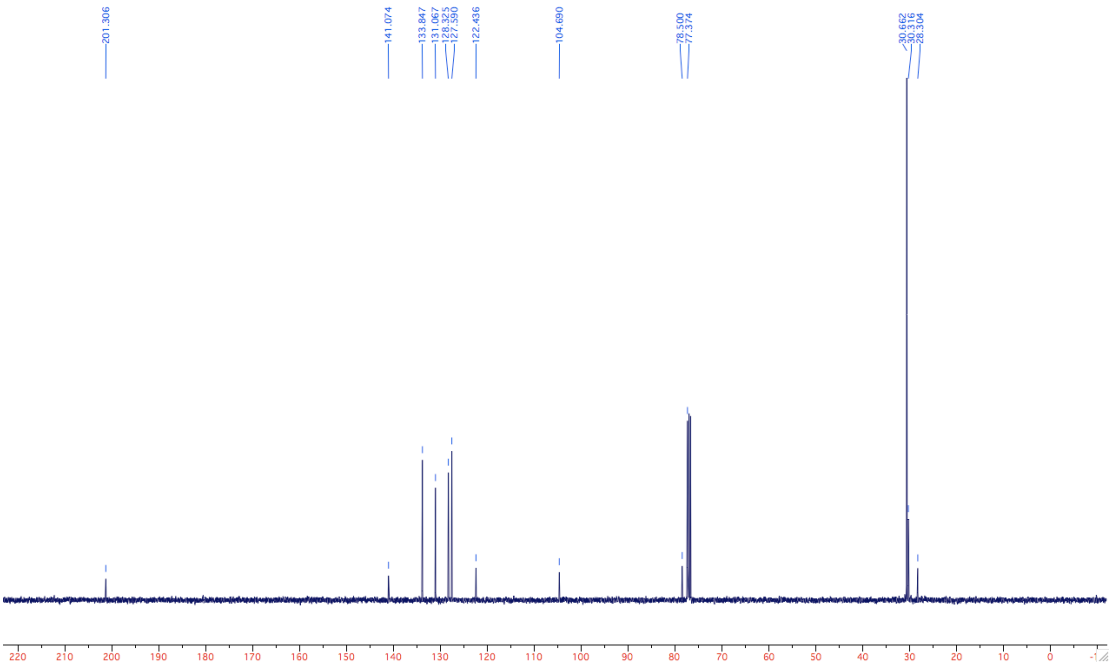




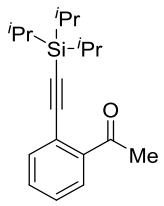
1-(2-(3,3-dime thylbut-1-yn-1-yl)phenyl)ethanone (67h)

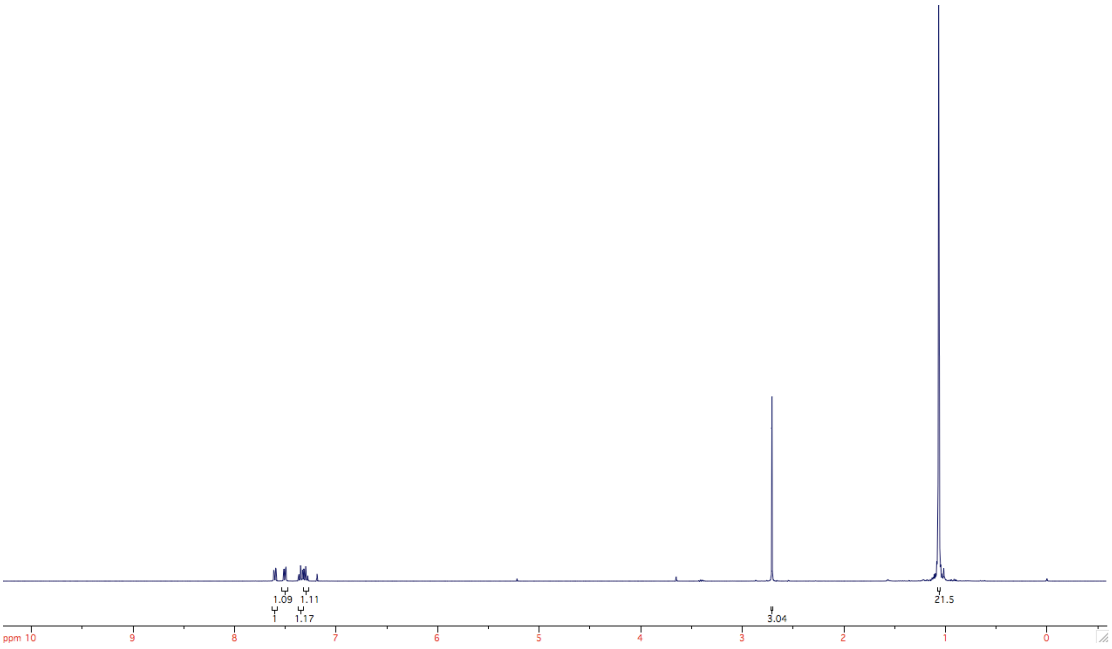


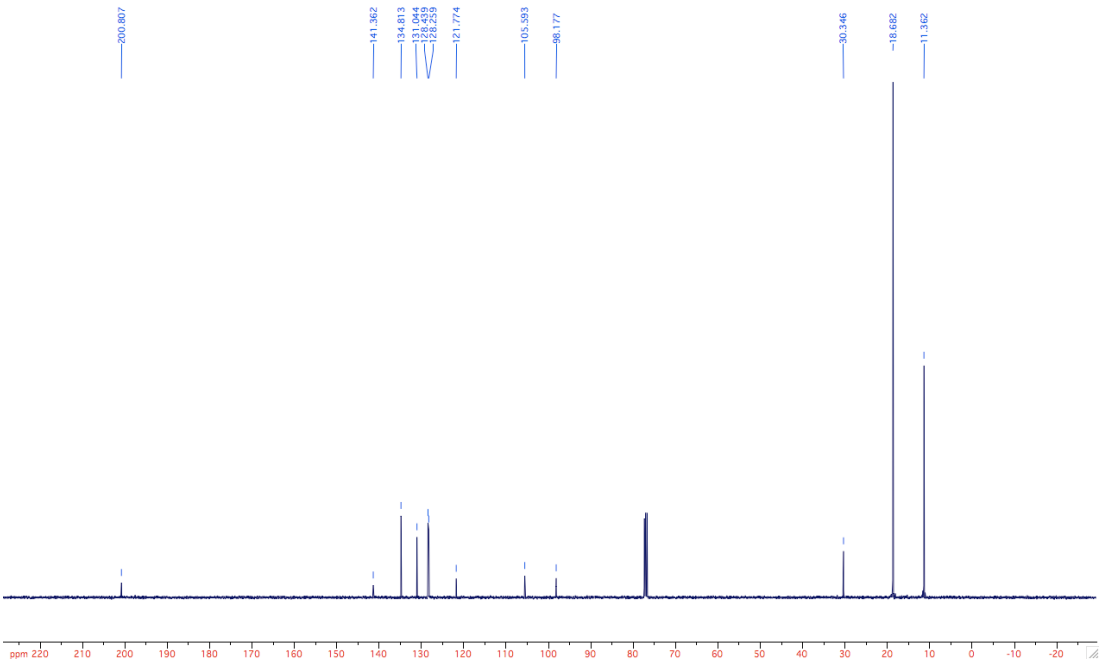




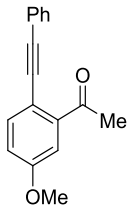
1-(2-((triisopropylsilyl)ethynyl)phenyl)ethanone (67i)

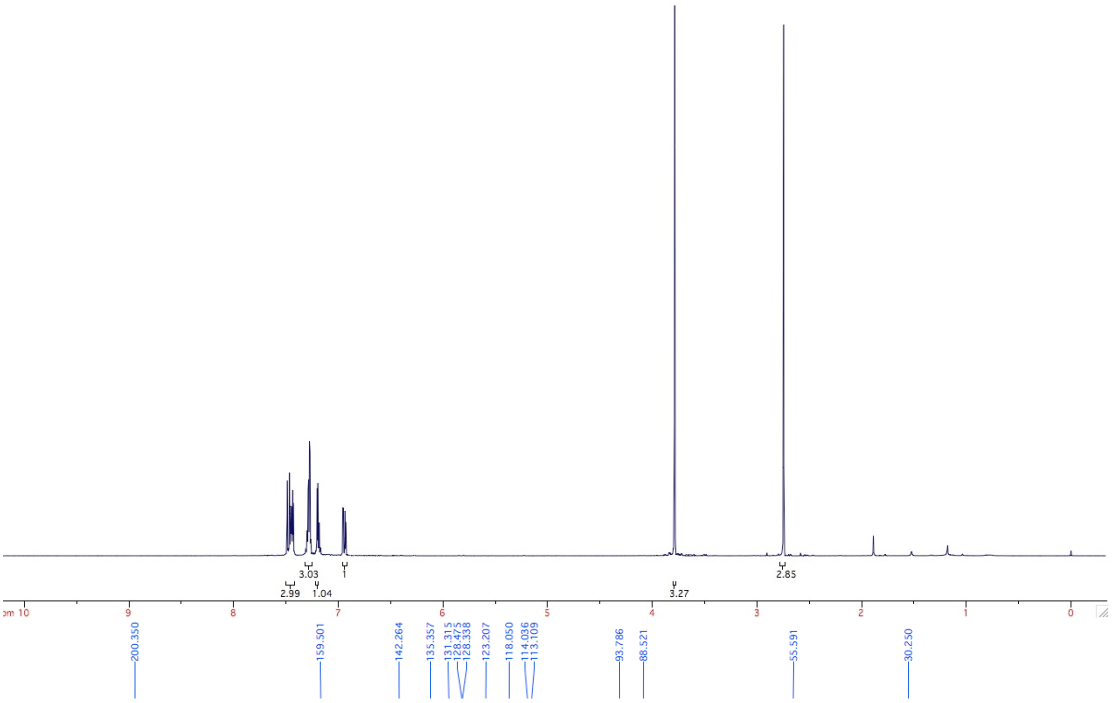


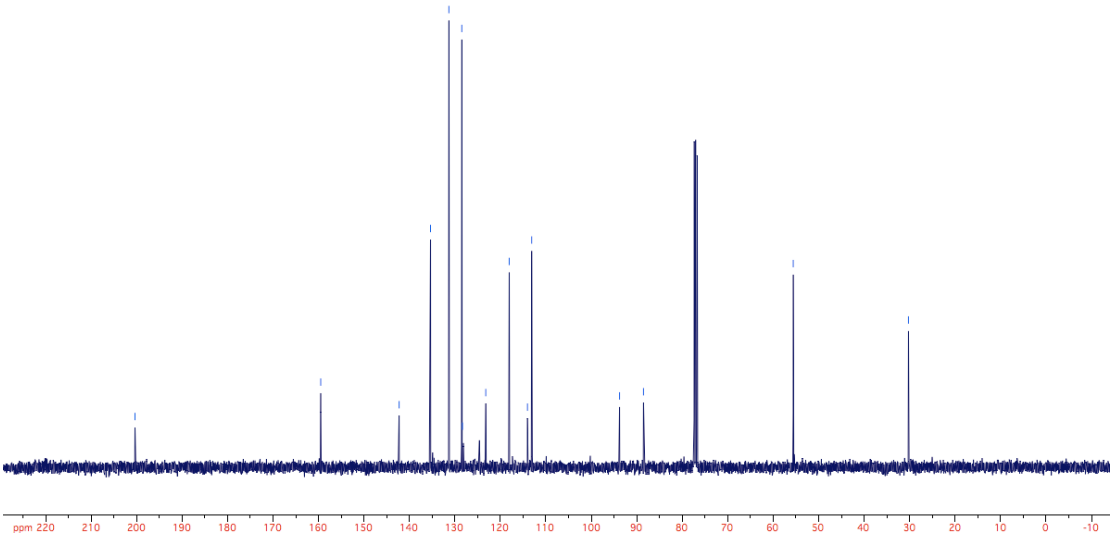




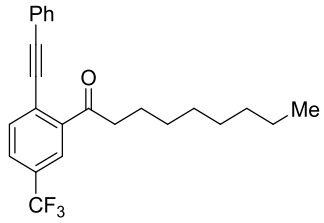
1-(5-methoxy-2-(phenylethynyl)phenyl)ethanone (68a)

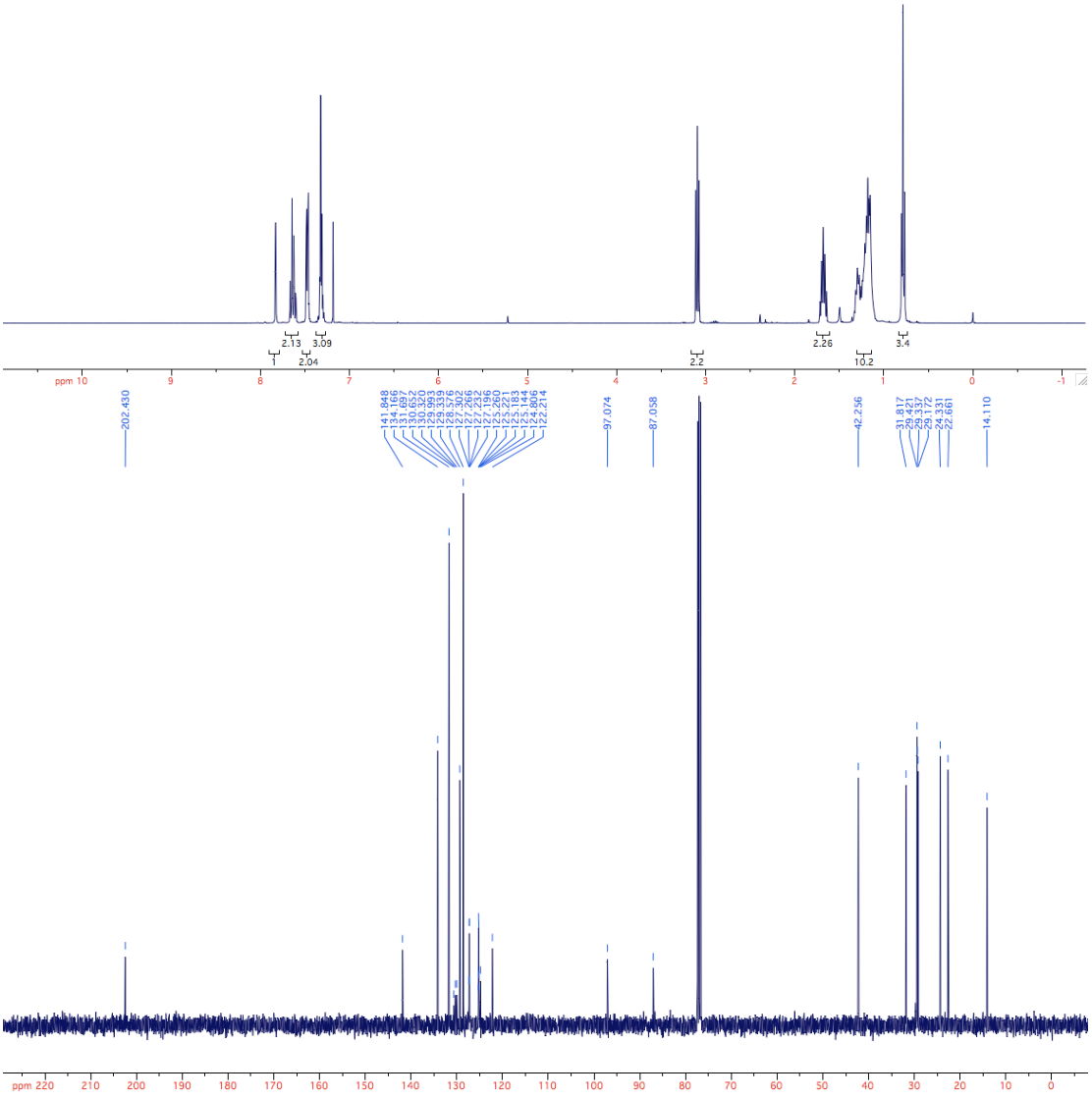




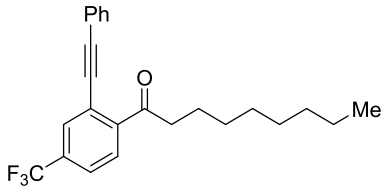


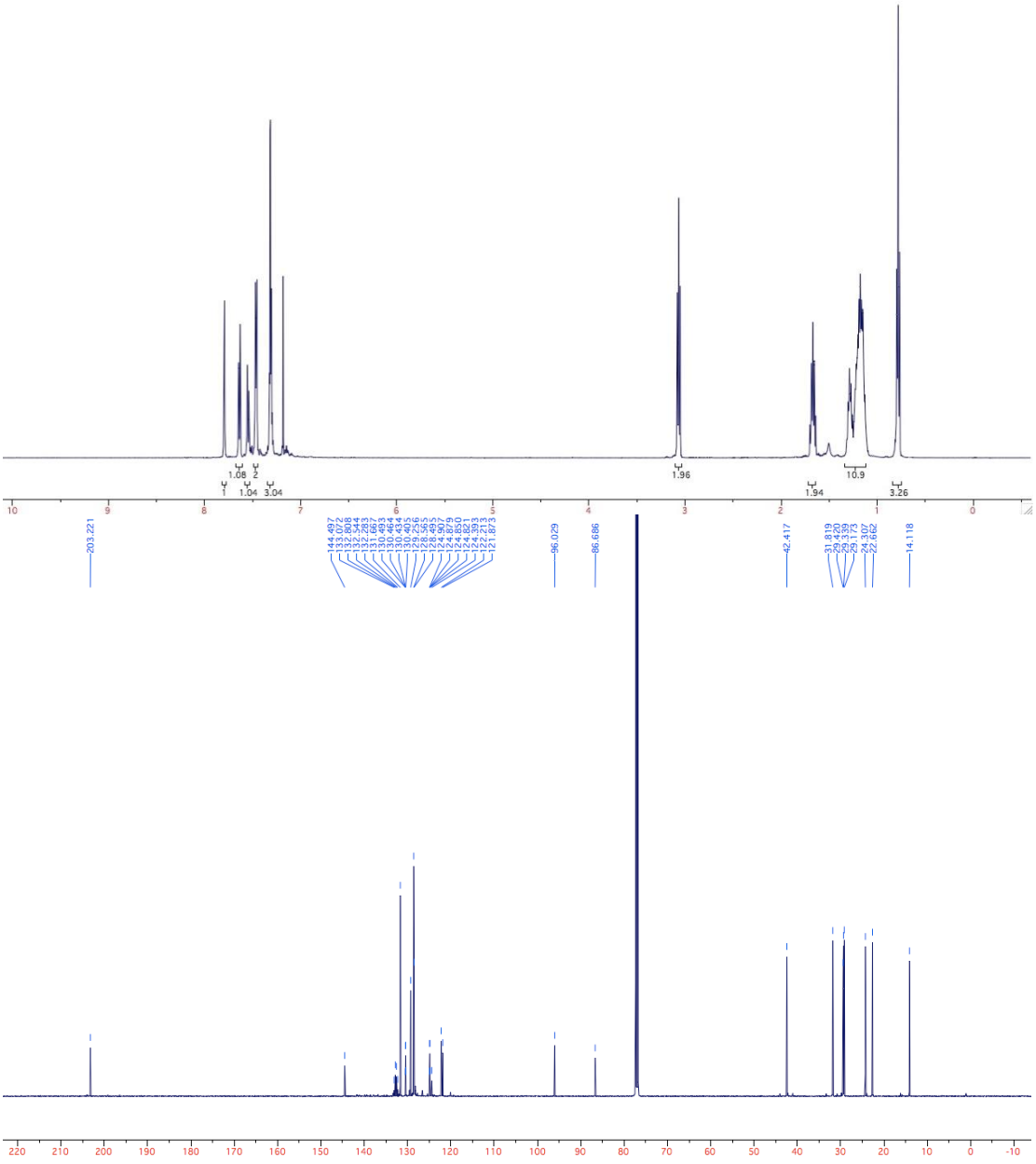
1-(2-(phenylethynyl)-5-(trifluoromethyl)phenyl)nonan-1-one (68b)



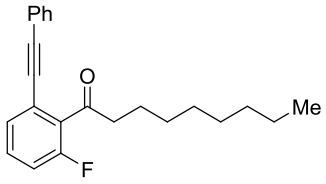


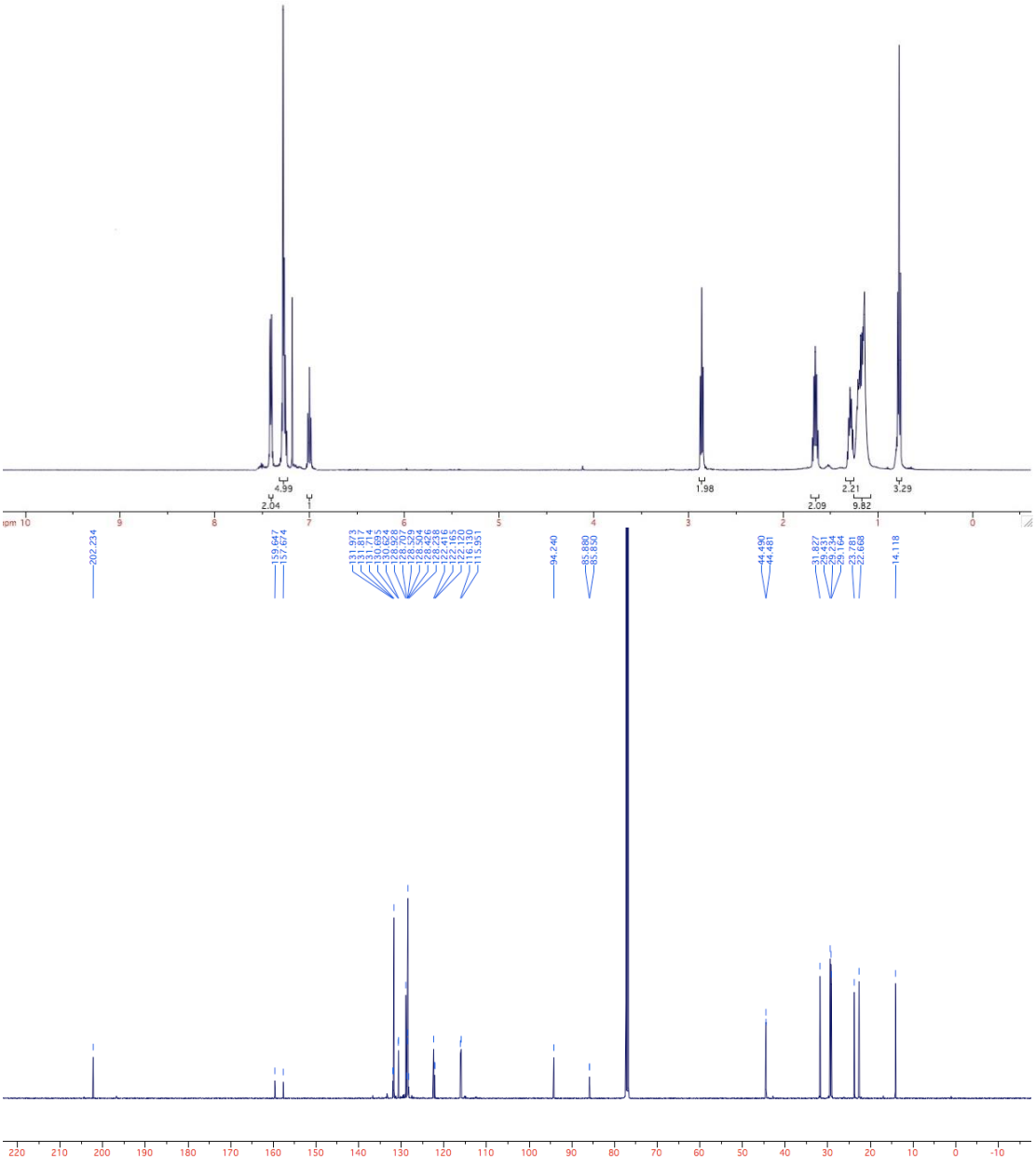
1-(2-(phenylethynyl)-4-(trifluoromethyl)phenyl)nonan-1-one (68c)



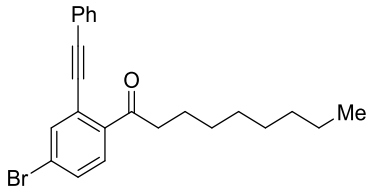


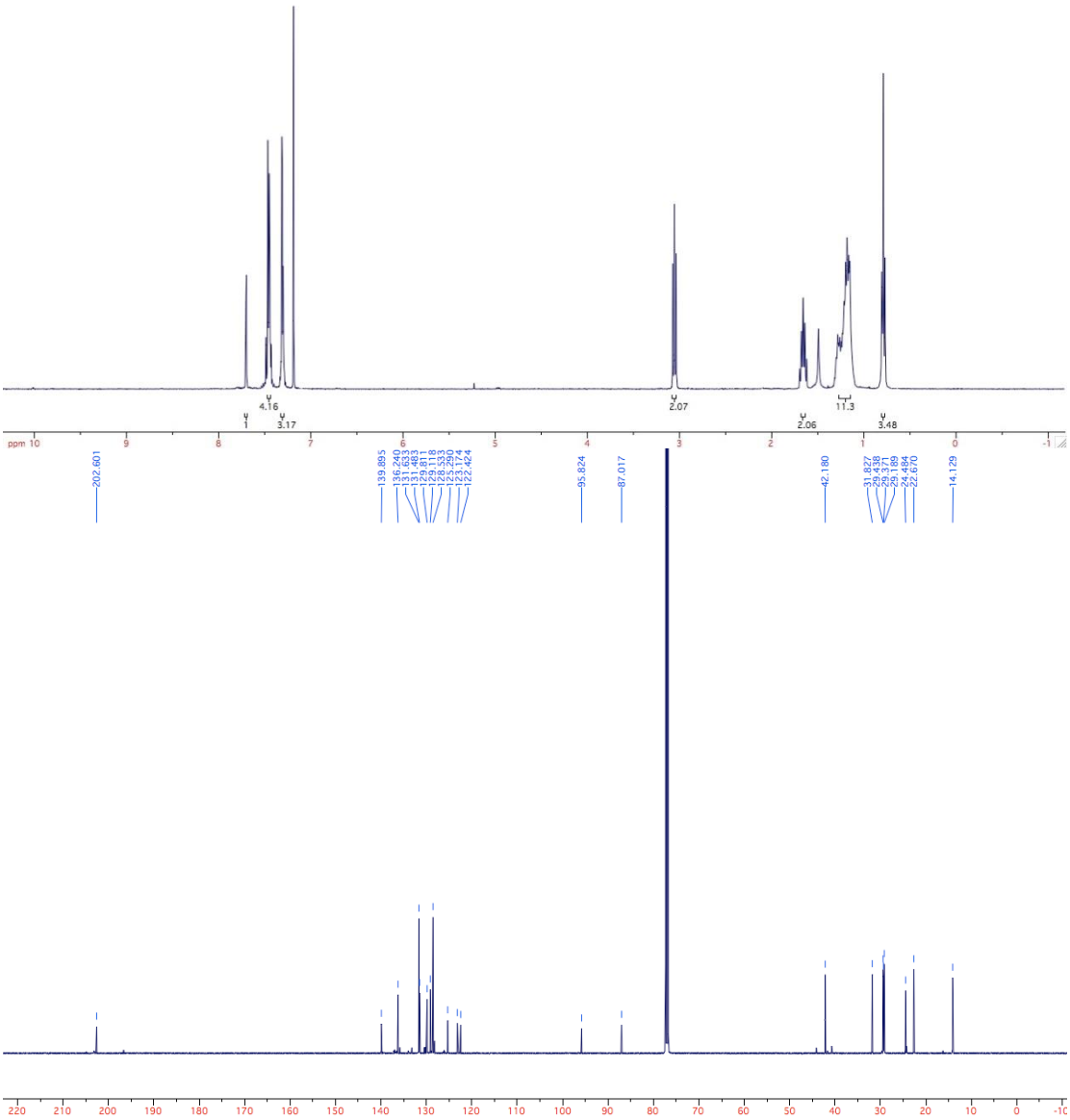
1-(2-fluoro-6-(phenylethynyl)phenyl)nonan-1-one (68d)



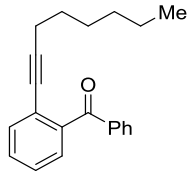


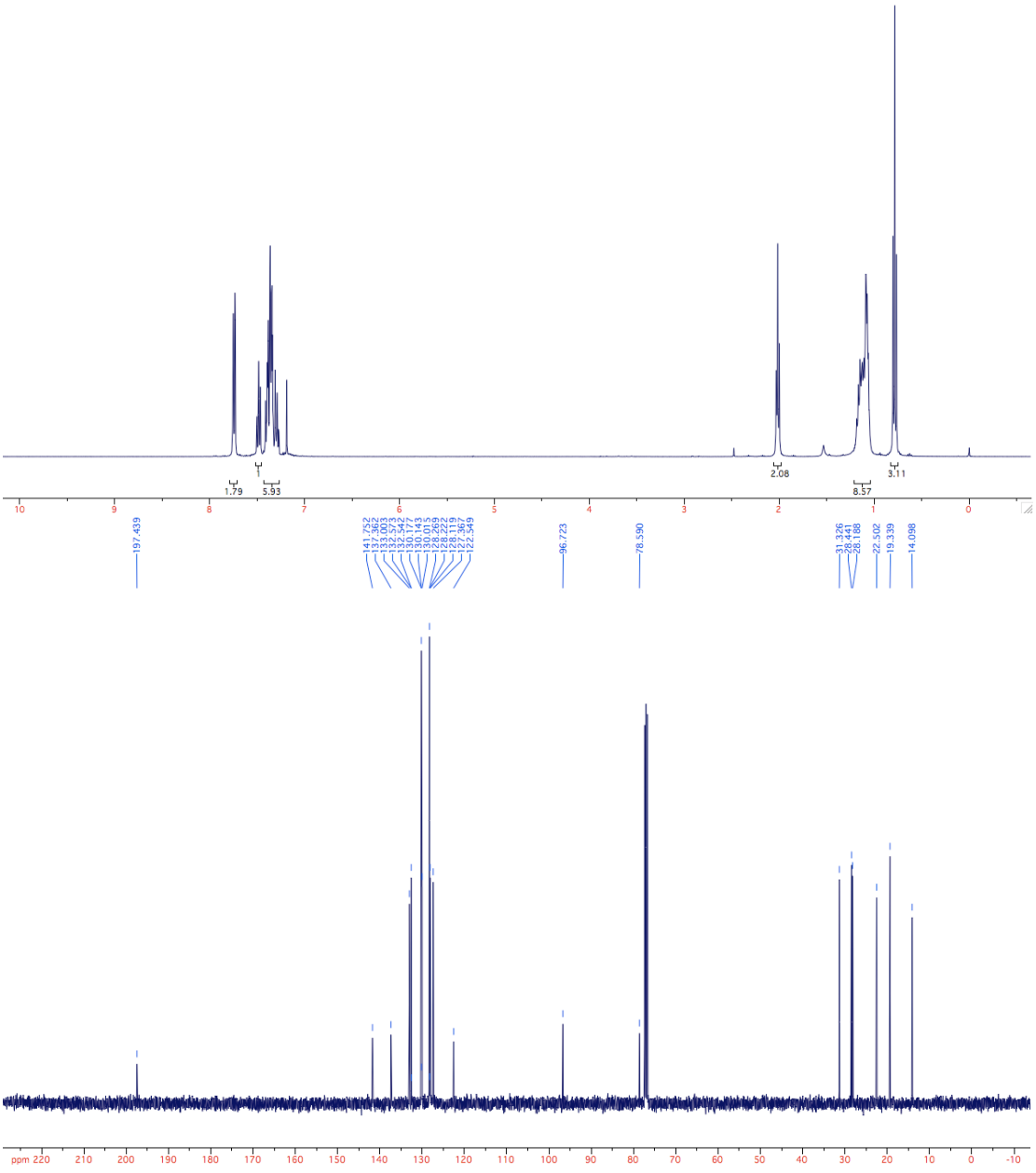
1-(4-bromo-2-(phenylethynyl)phenyl)nonan-1-one (68e)



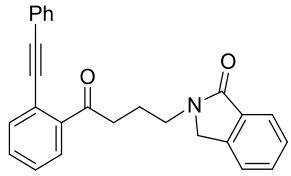


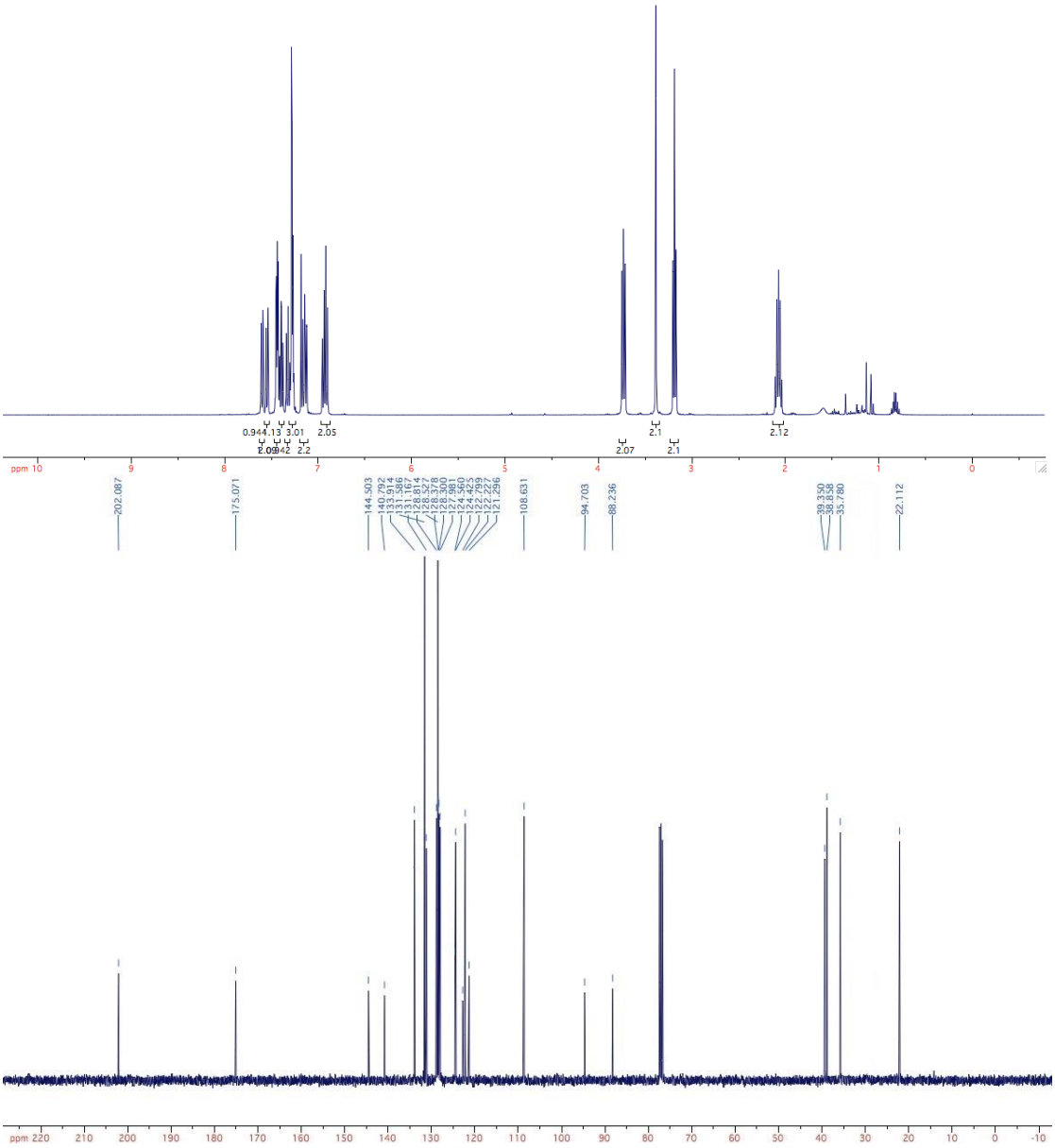
(2-(oct-1-yn-1-yl)phenyl)(phenyl)methanone (68g)



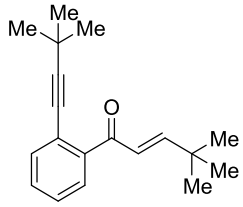


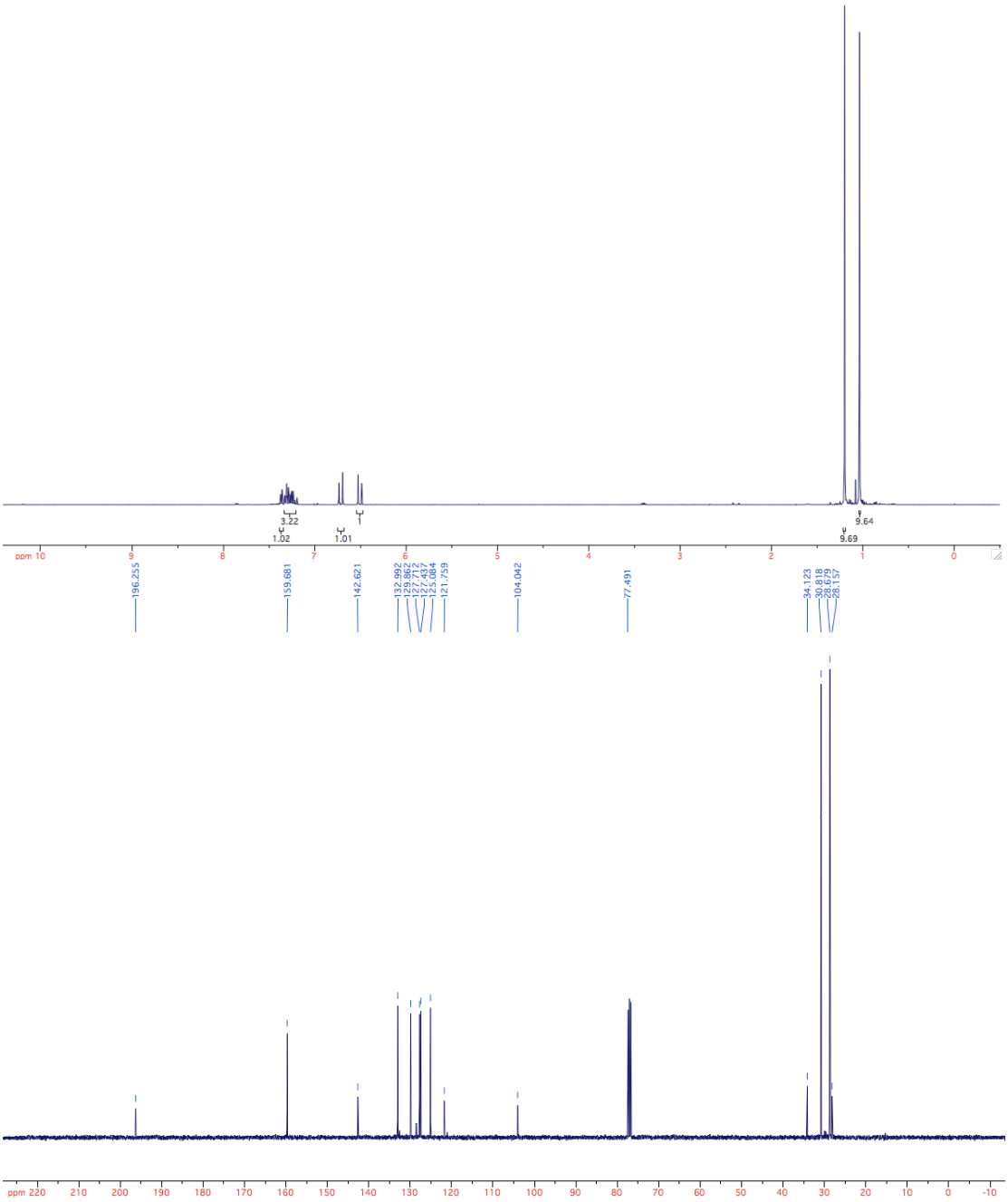
2-(4-oxo-4-(2-(phenylethynyl)phenyl)butyl)isoindolin-1-one (68h)



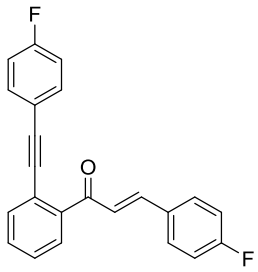


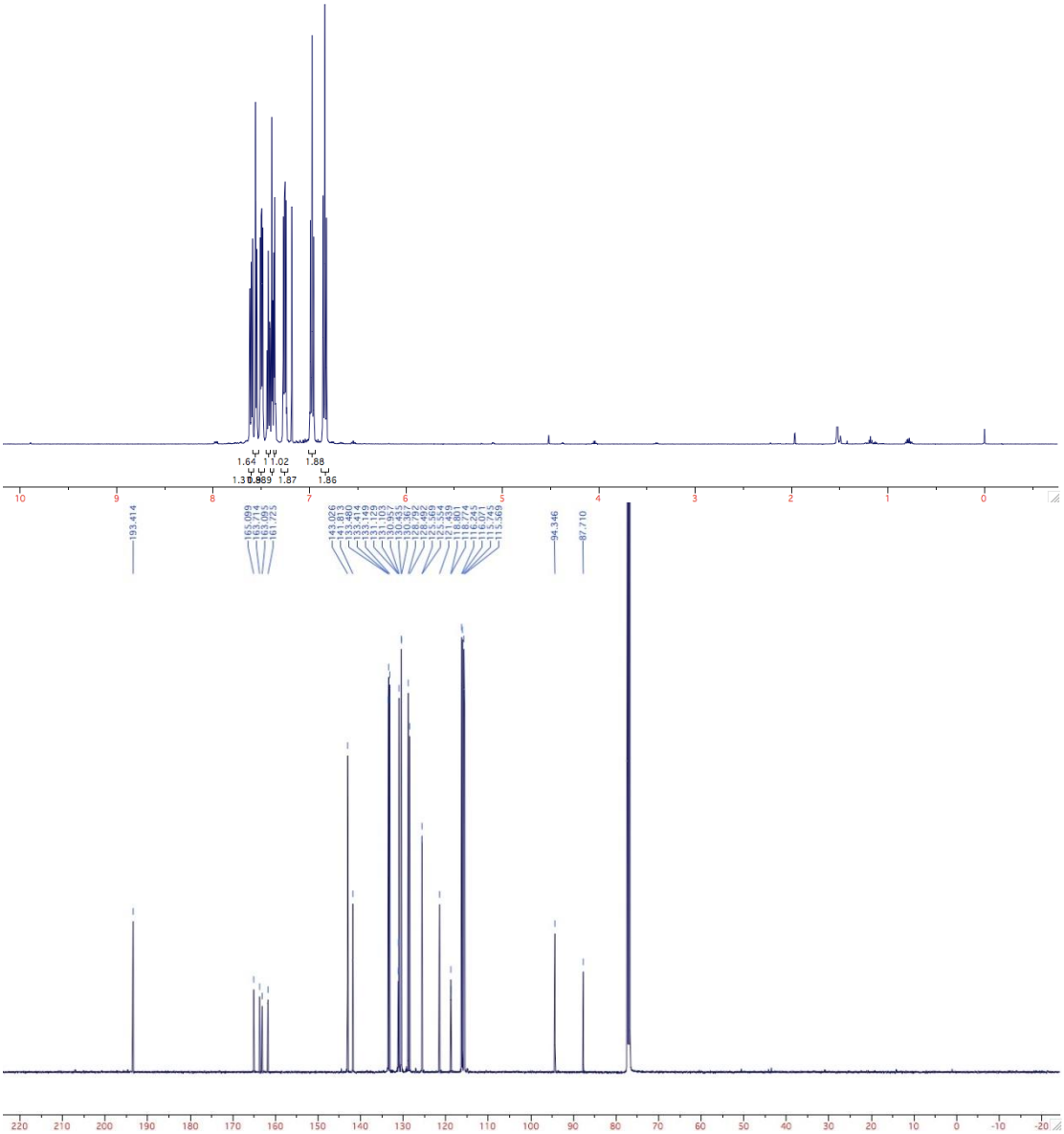
(*E*)-1-(2-(3,3-dimethylbut-1-yn-1-yl)phenyl)-4,4-dimethylpent-2-en-1-one (78a)



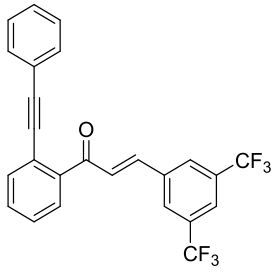


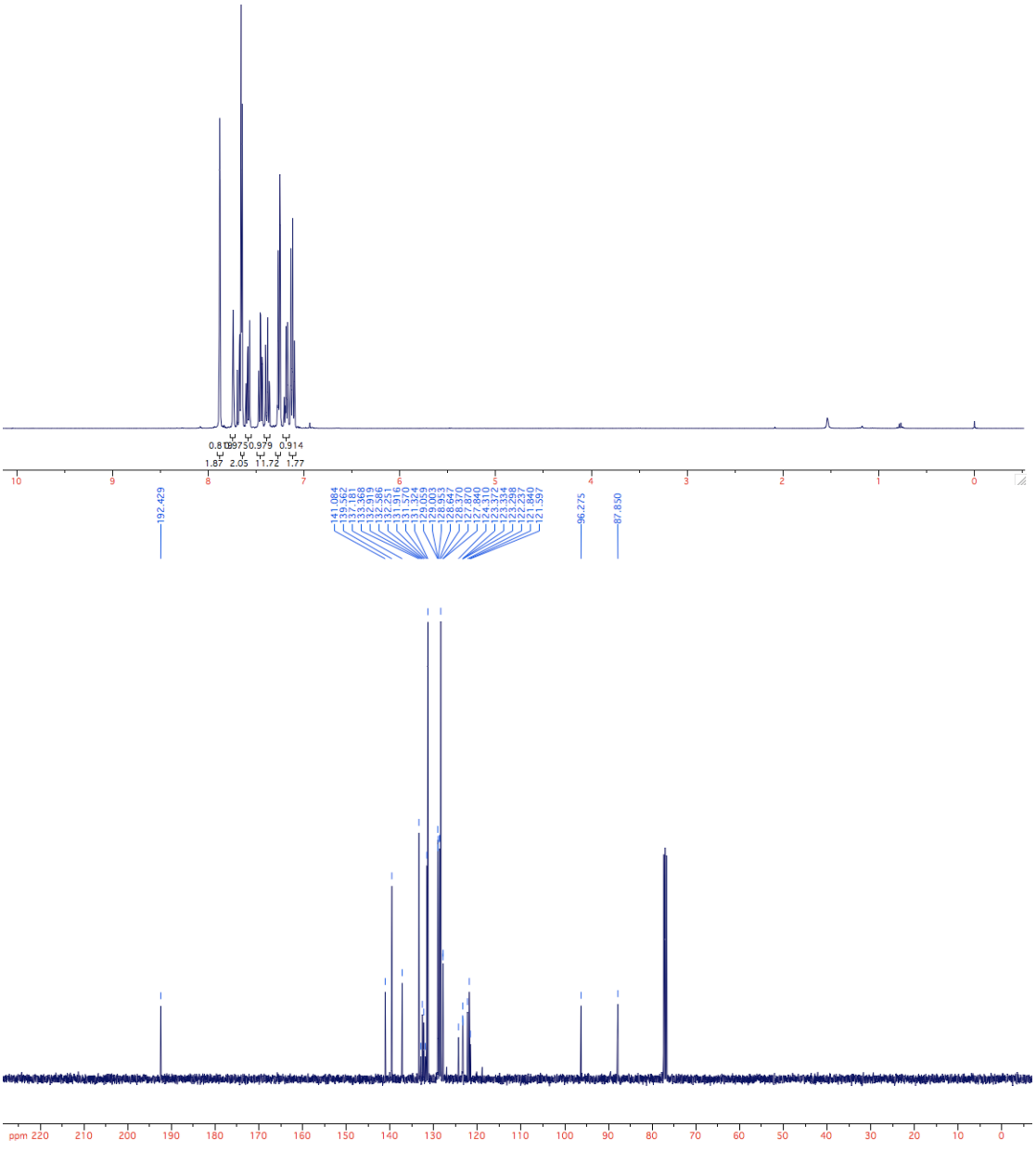
(*E*)-3-(4-fluorophenyl)-1-(2-((4-fluorophenyl)ethynyl)phenyl)prop-2-en-1-one (78b)



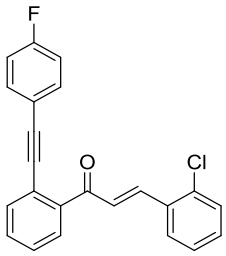


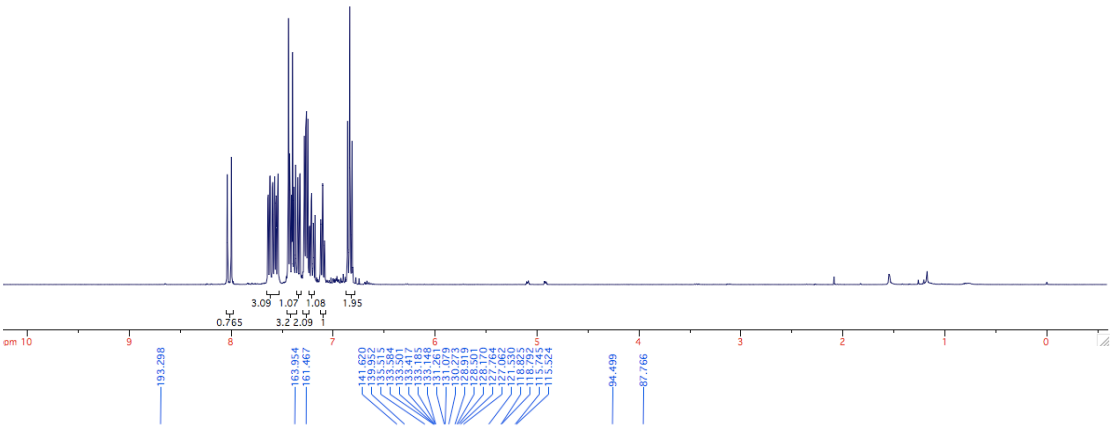
(*E*)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(2-(phenylethynyl)phenyl)prop-2-en-1-one (78c)

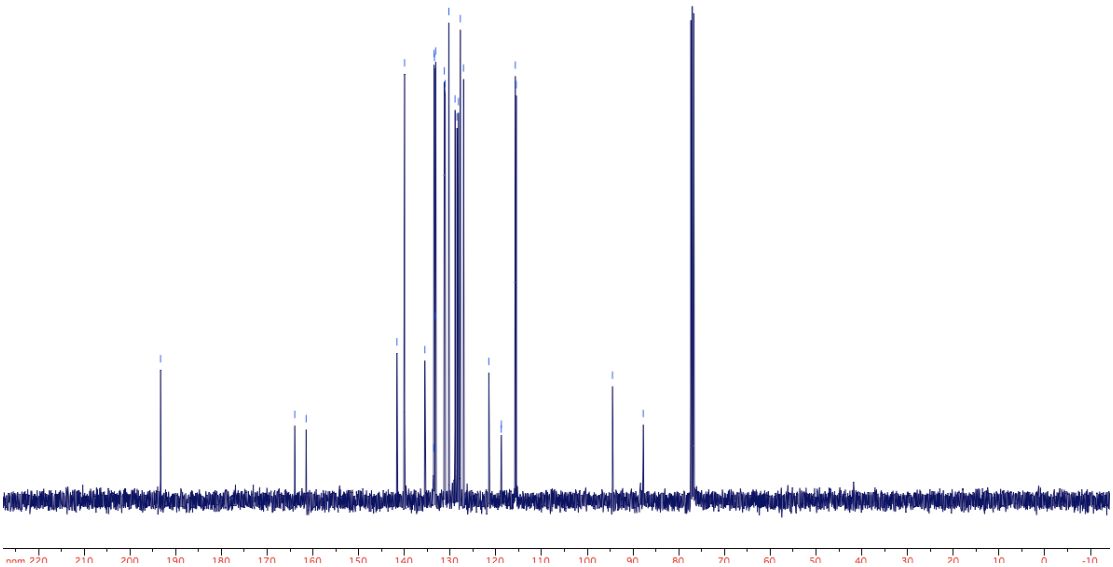




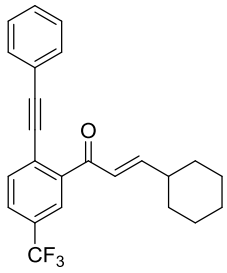
(*E*)-3-(2-chlorophenyl)-1-(2-((4-fluorophenyl)ethynyl)phenyl)prop-2-en-1-one (78d)

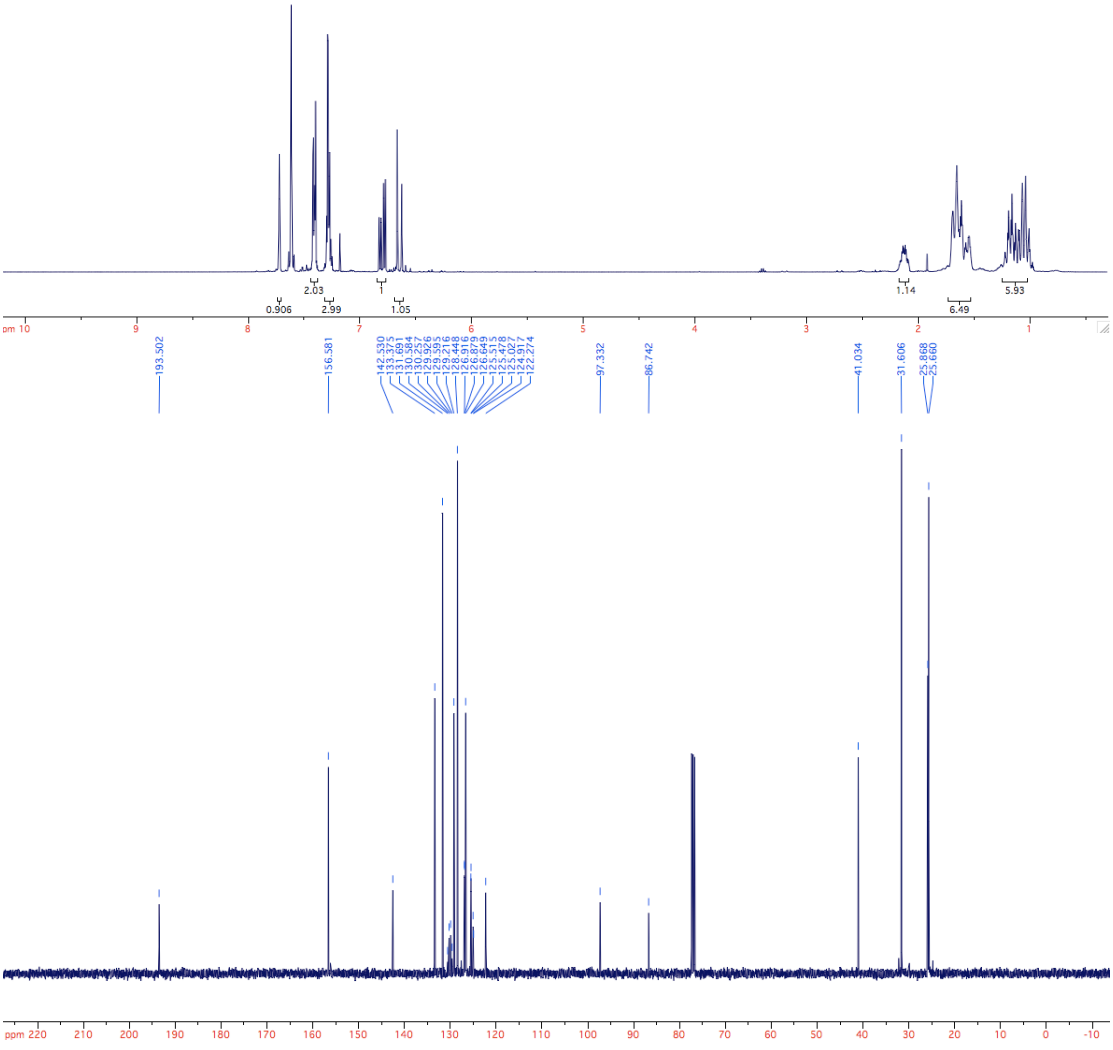




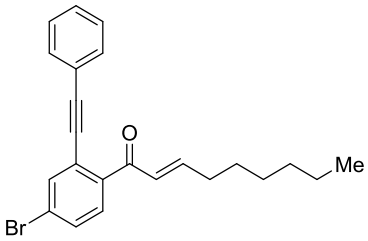


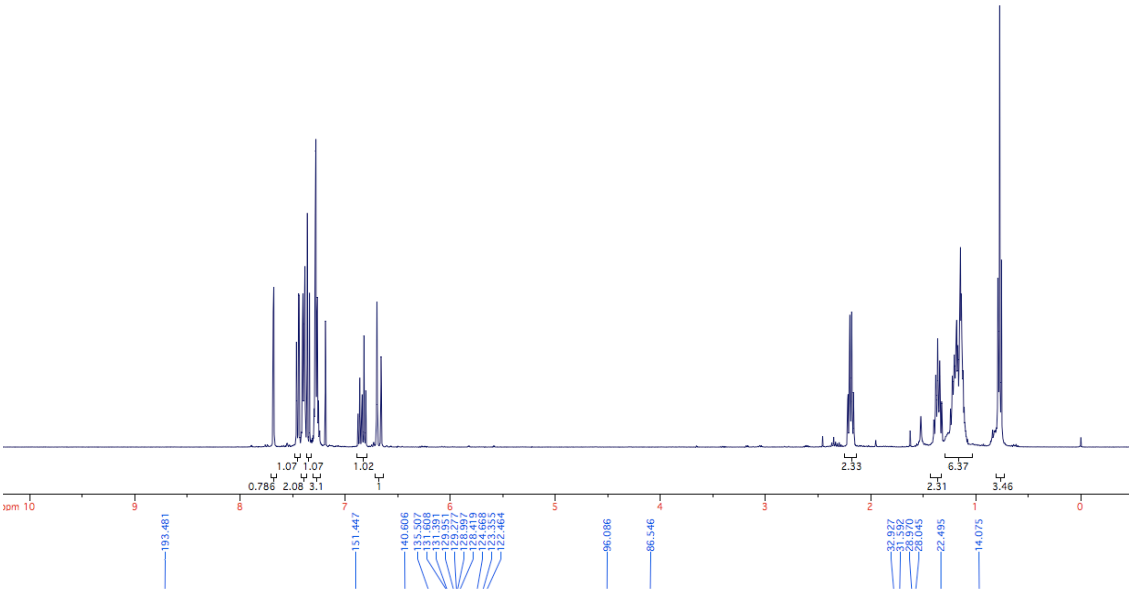
(*E*)-3-cyclohexyl-1-(2-(phenylethynyl)-5-(trifluoromethyl)phenyl)prop-2-en-1-one (78e)

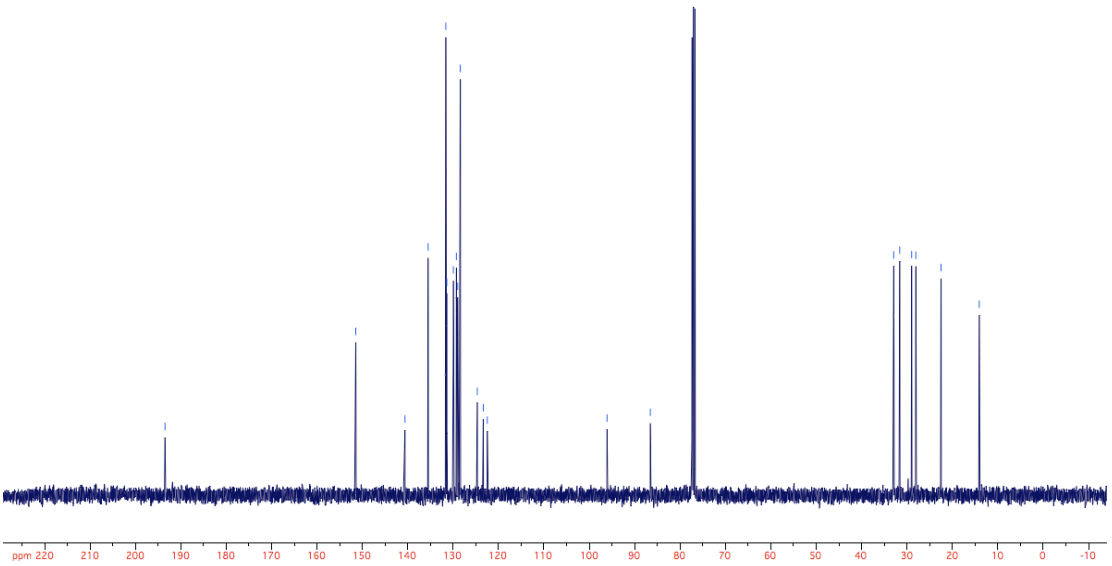




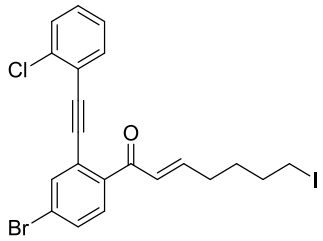
(*E*)-1-(4-bromo-2-(phenylethynyl)phenyl)non-2-en-1-one (78f)

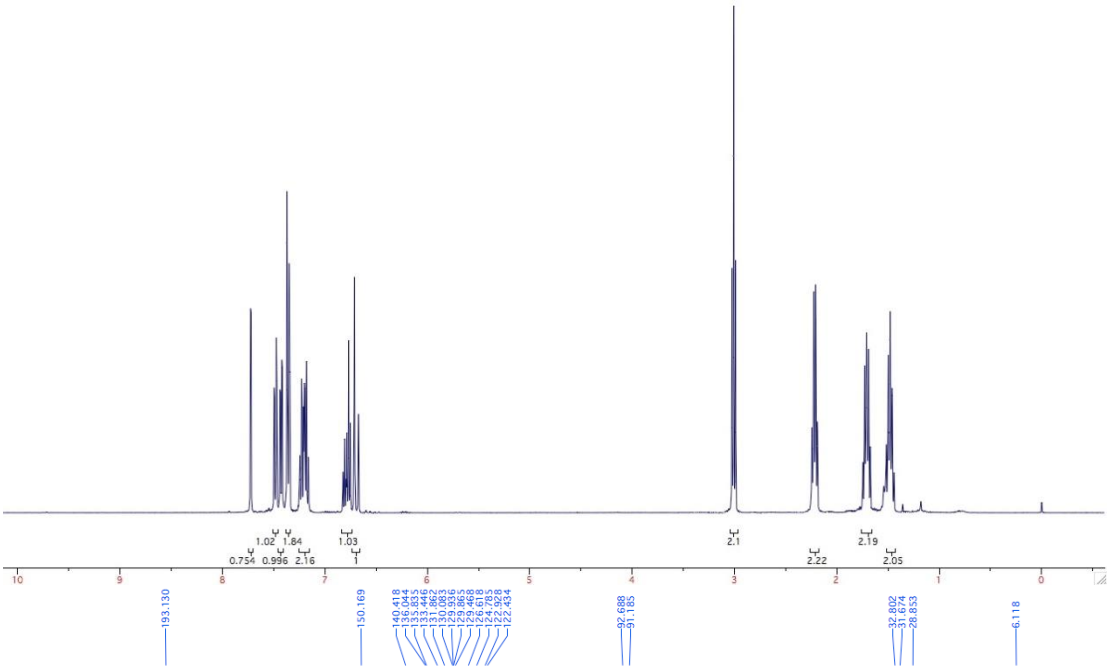


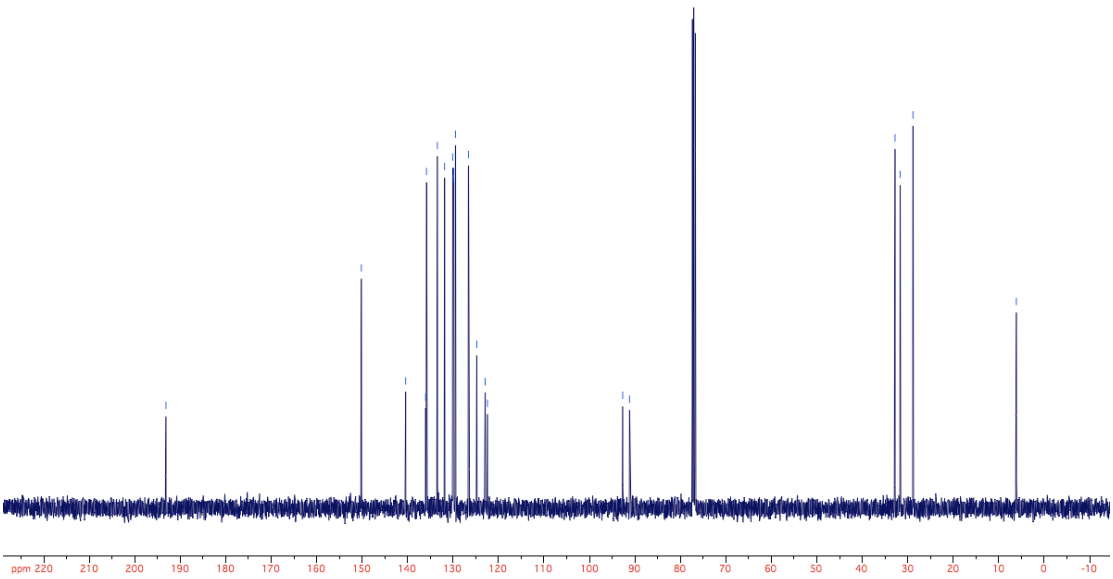




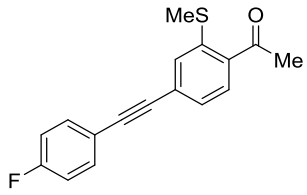
(*E*)-1-(4-bromo-2-((2-chlorophenyl)ethynyl)phenyl)-7-iodohept-2-en-1-one (78g)

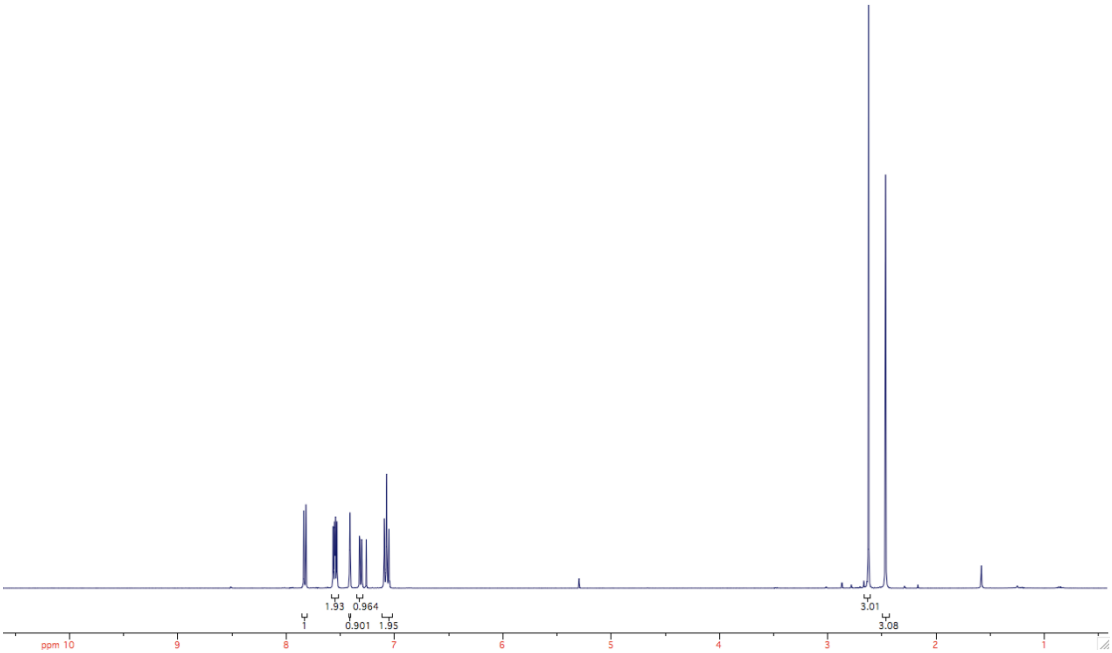


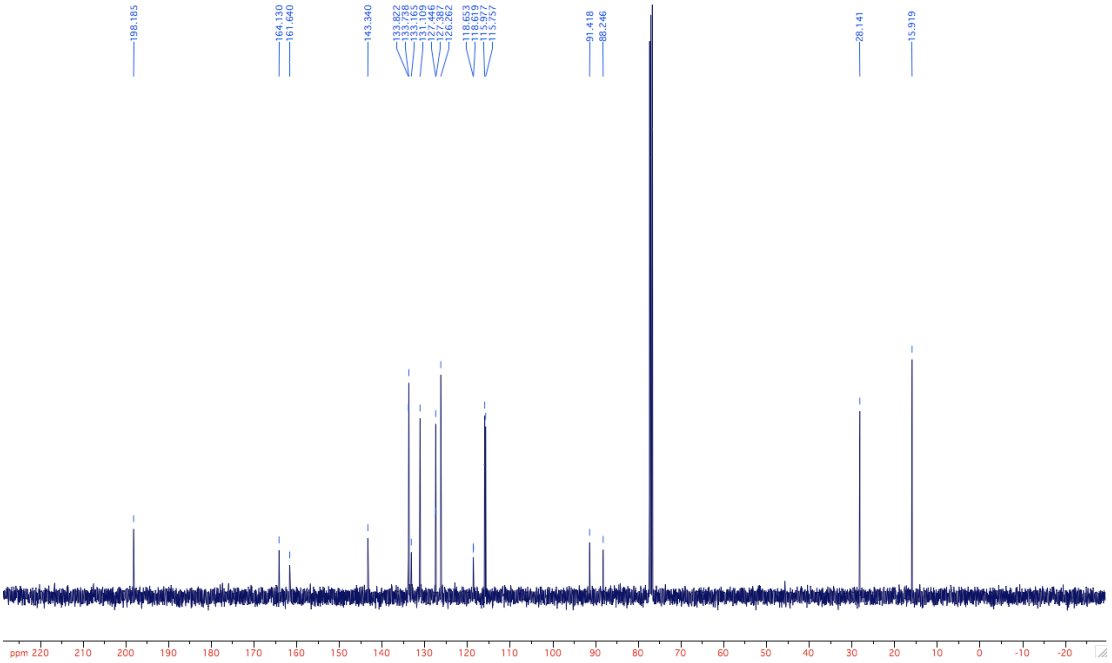




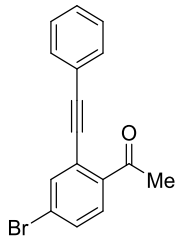
1-(4-((4-fluorophenyl)ethynyl)-2-(methylthio)phenyl)ethanone (72)

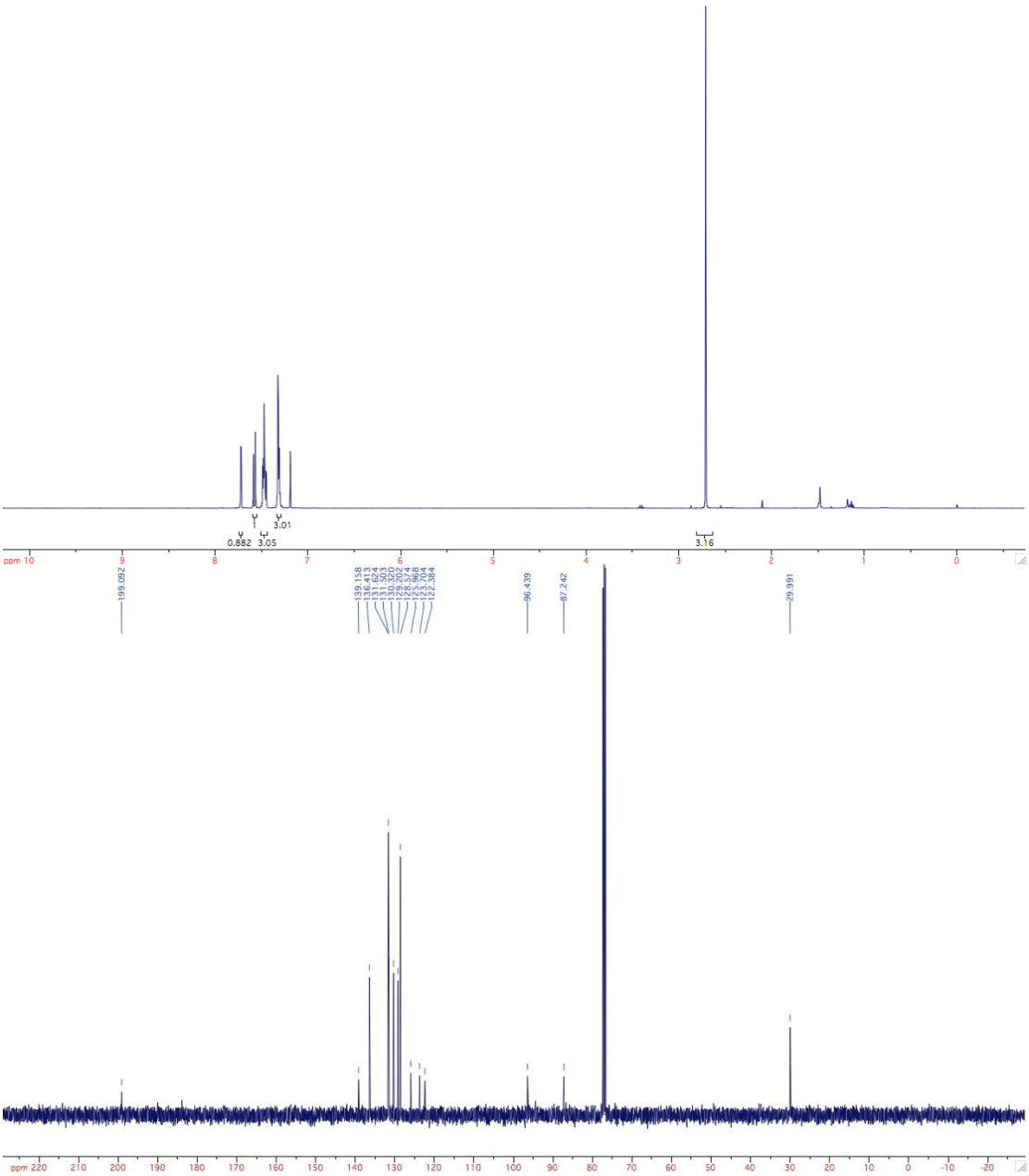




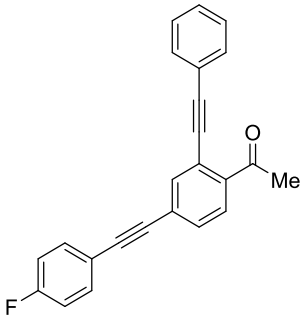


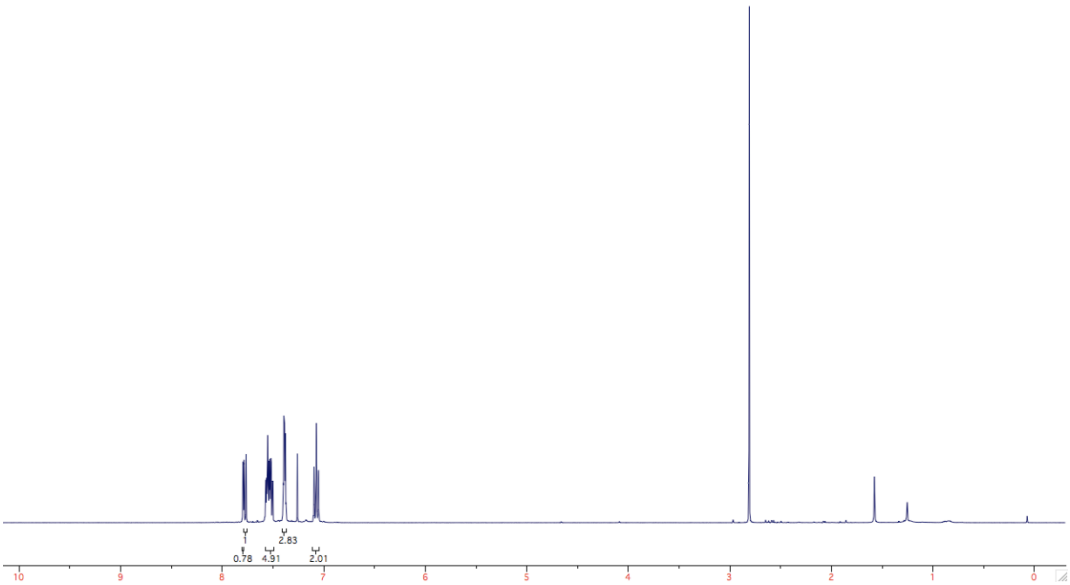
1-(4-bromo-2-(phenylethynyl)phenyl)ethan-1-one (71)

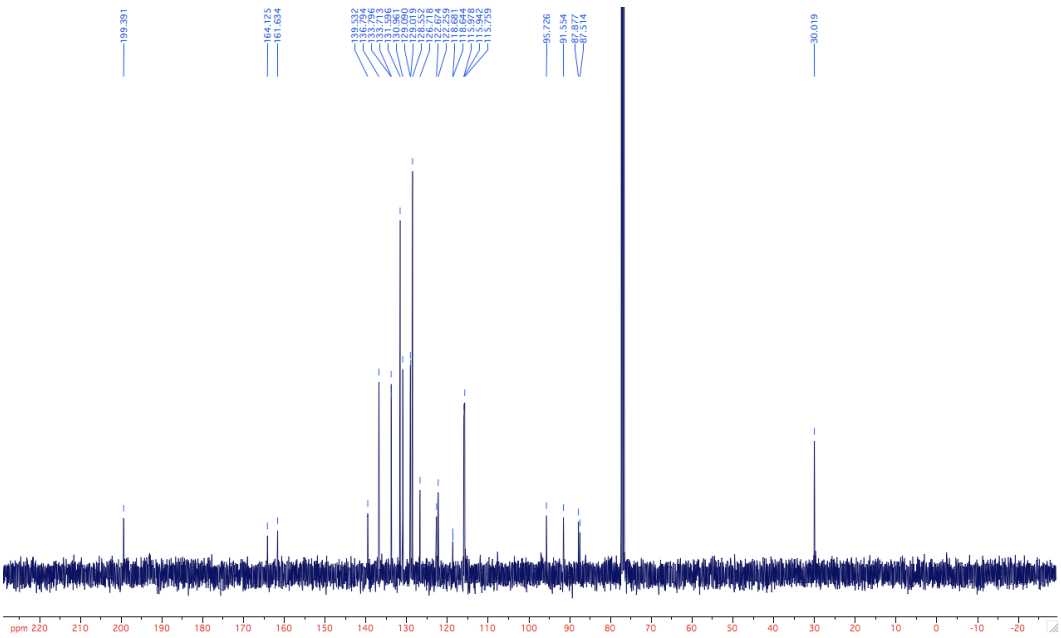




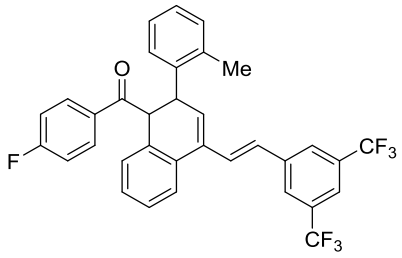
1-(4-((4-fluorophenyl)ethynyl)-2-(phenylethynyl)phenyl)ethanone (73)

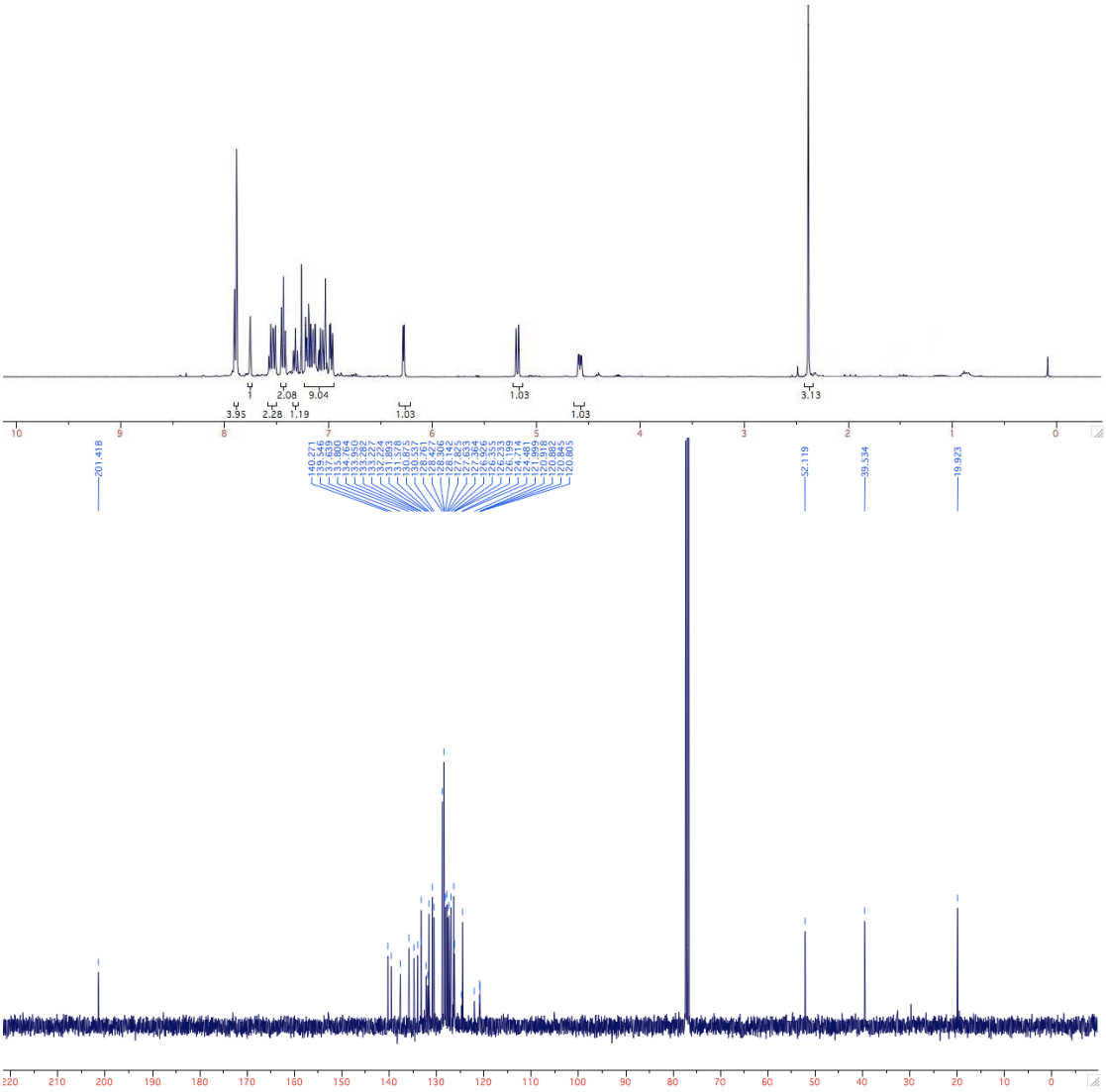






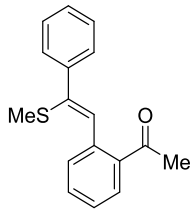
(*E*)-(4-(3,5-bis(trifluoromethyl)styryl)-2-(*o*-tolyl)-1,2-dihydronaphthalen-1-yl)(4-fluorophenyl)methanone (83)

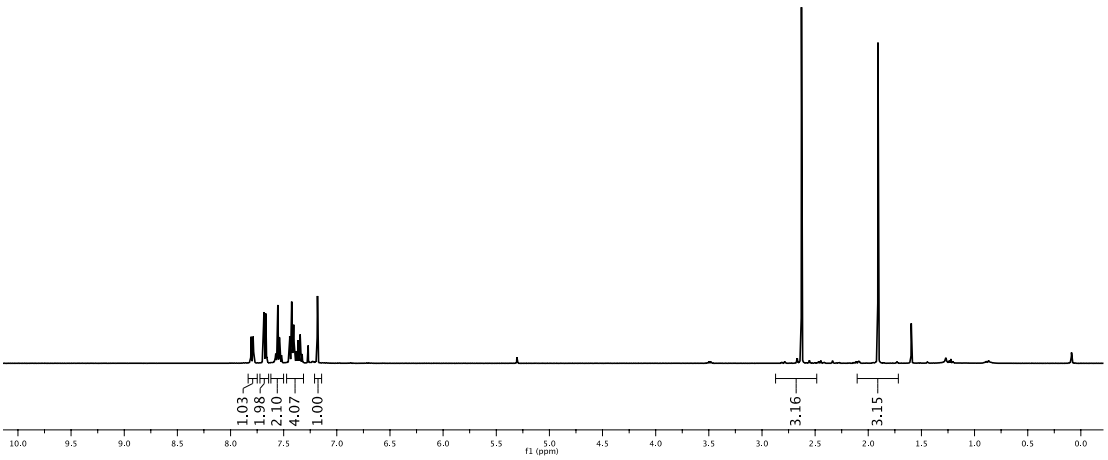


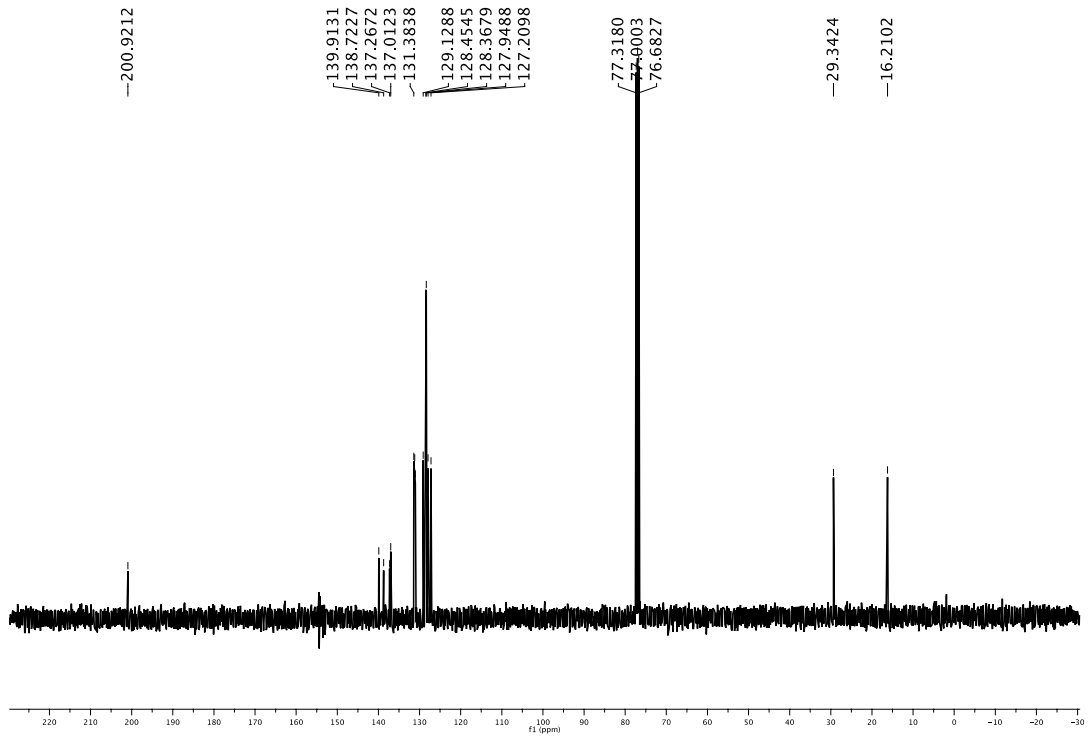


Compounds from Chapter 3:

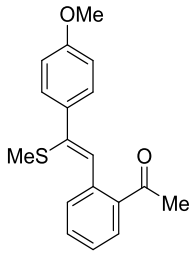
(*Z*)-1-(2-(2-(Methylthio)-2-phenylvinyl)phenyl)ethanone (58)

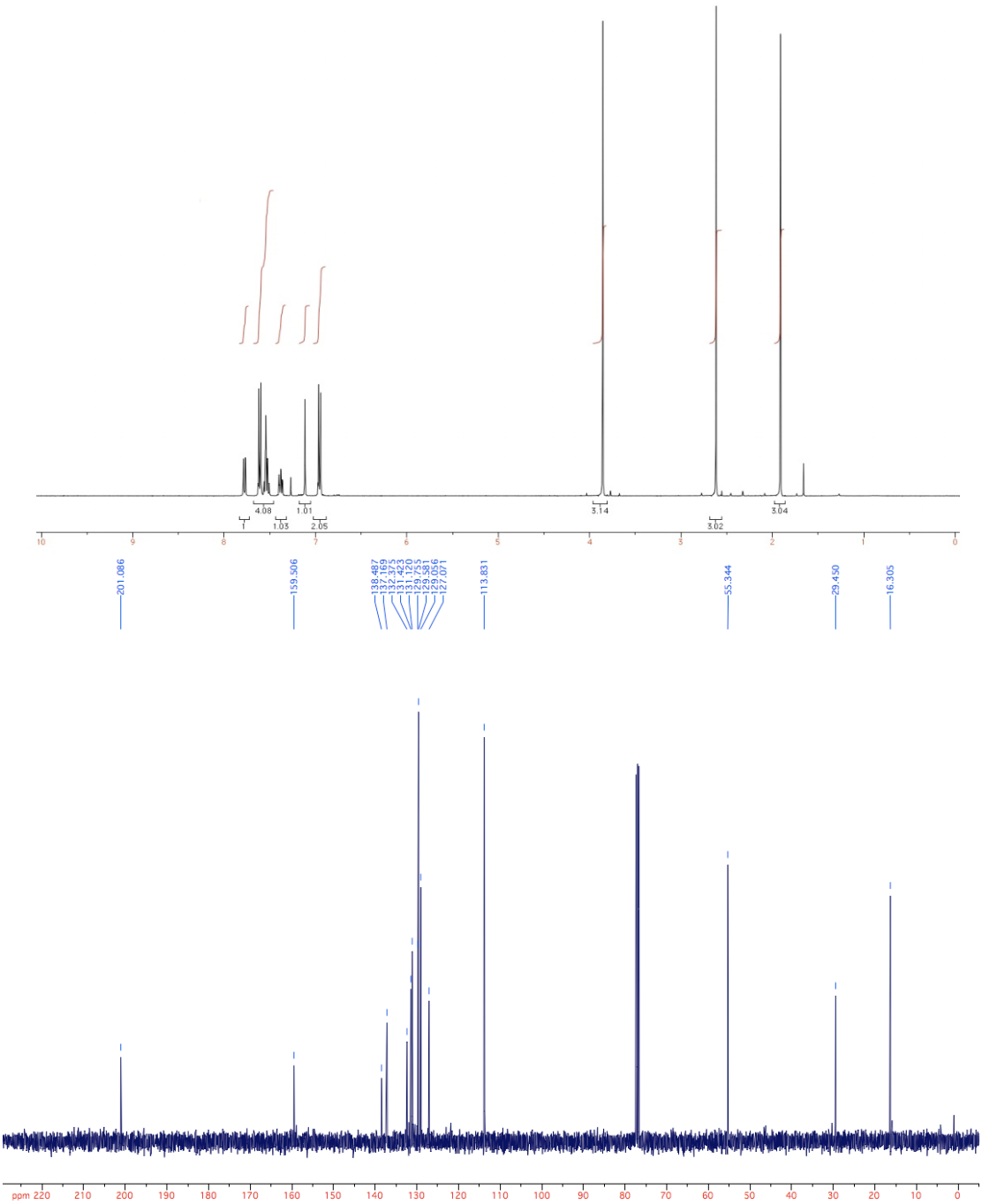




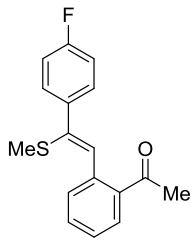


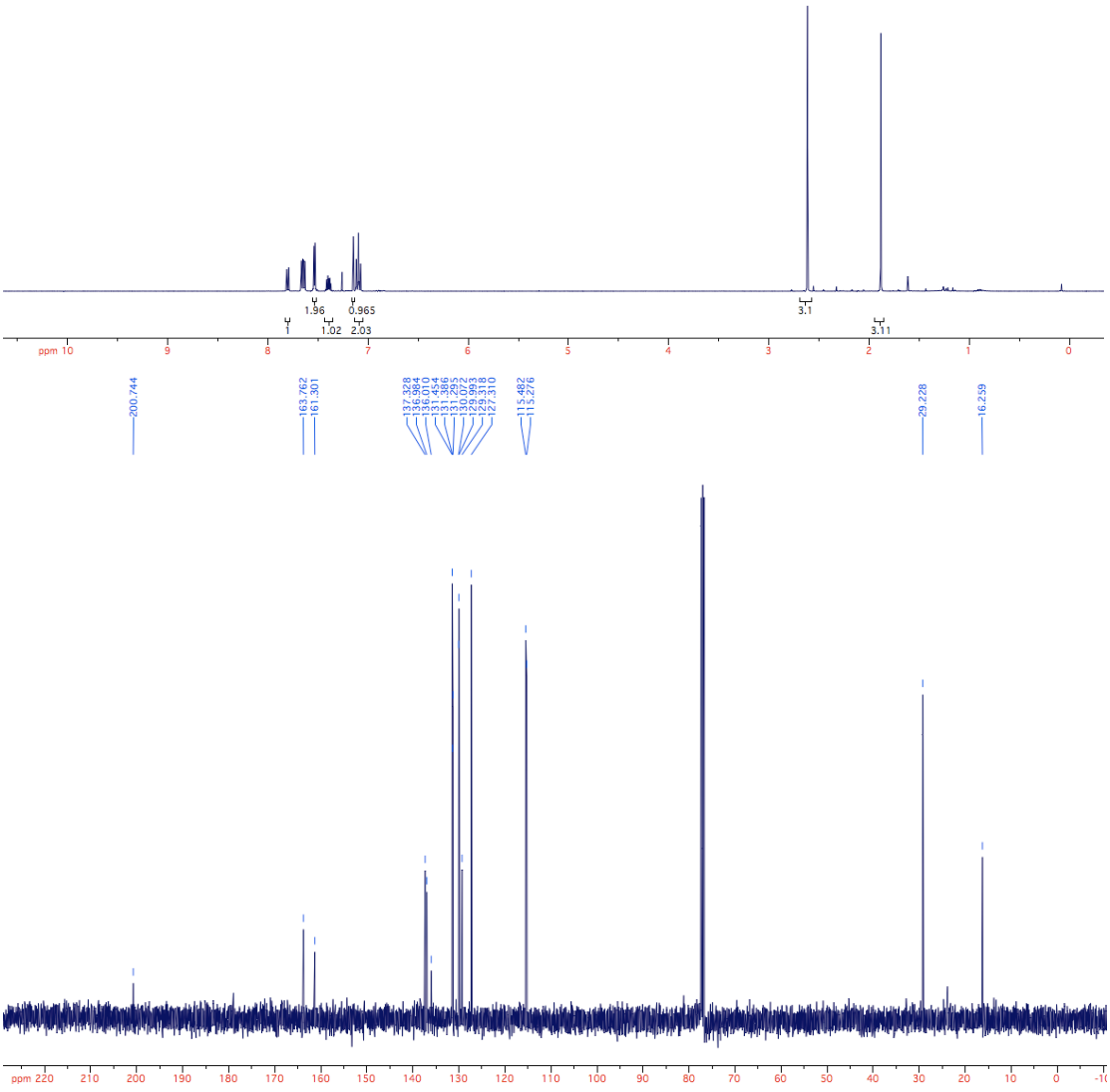
(*Z*)-1-(2-(2-(4-Methoxyphenyl)-2-(methylthio)vinyl)phenyl)ethanone (58b)



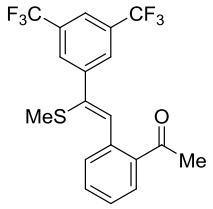


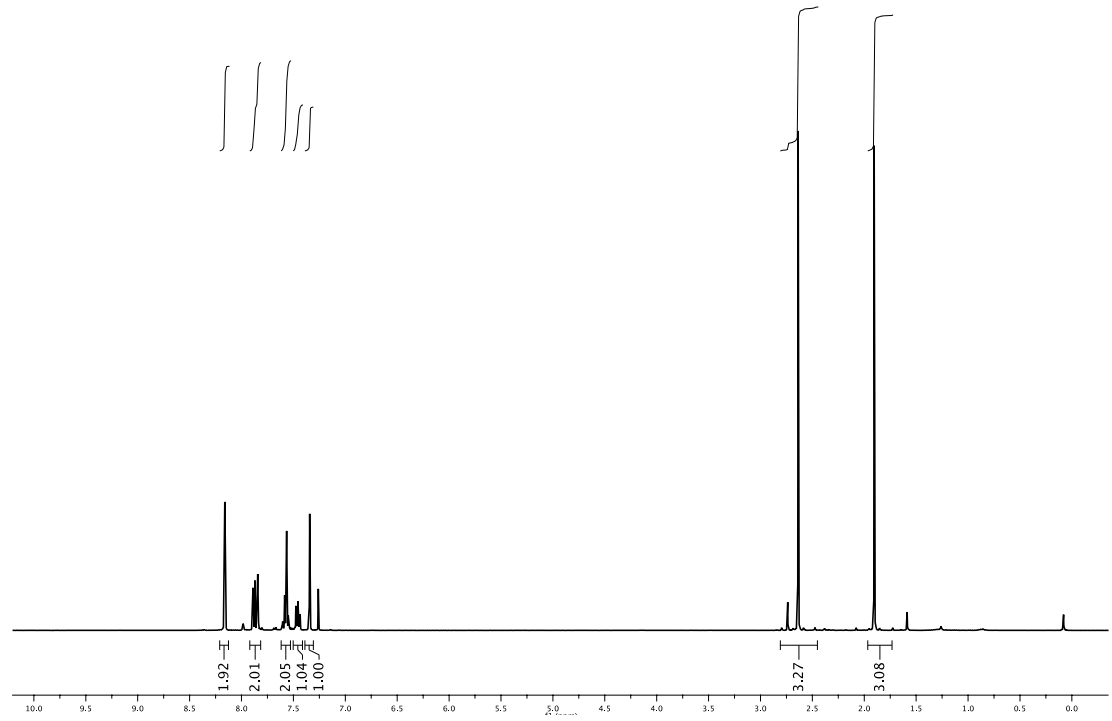
(*Z*)-1-(2-(2-(4-Fluorophenyl)-2-(methylthio)vinyl)phenyl)ethanone (58c)

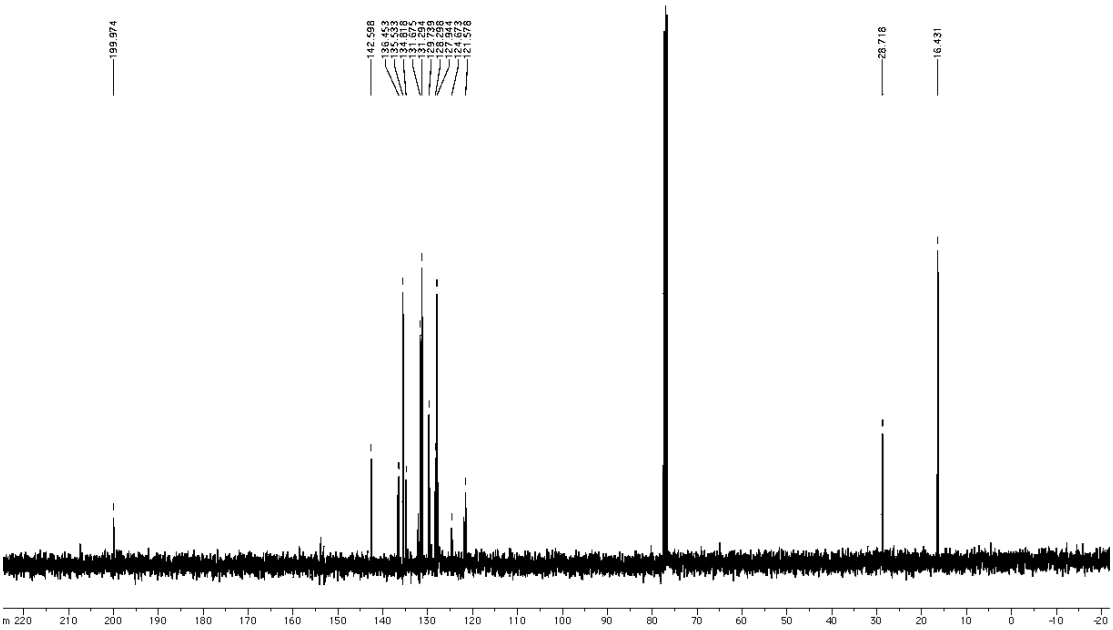




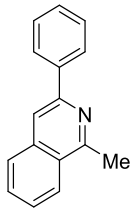
(*Z*)-1-(2-(2-(3,5-Bis(trifluoromethyl)phenyl)-2-(methylthio)vinyl)phenyl)ethanone (58d)



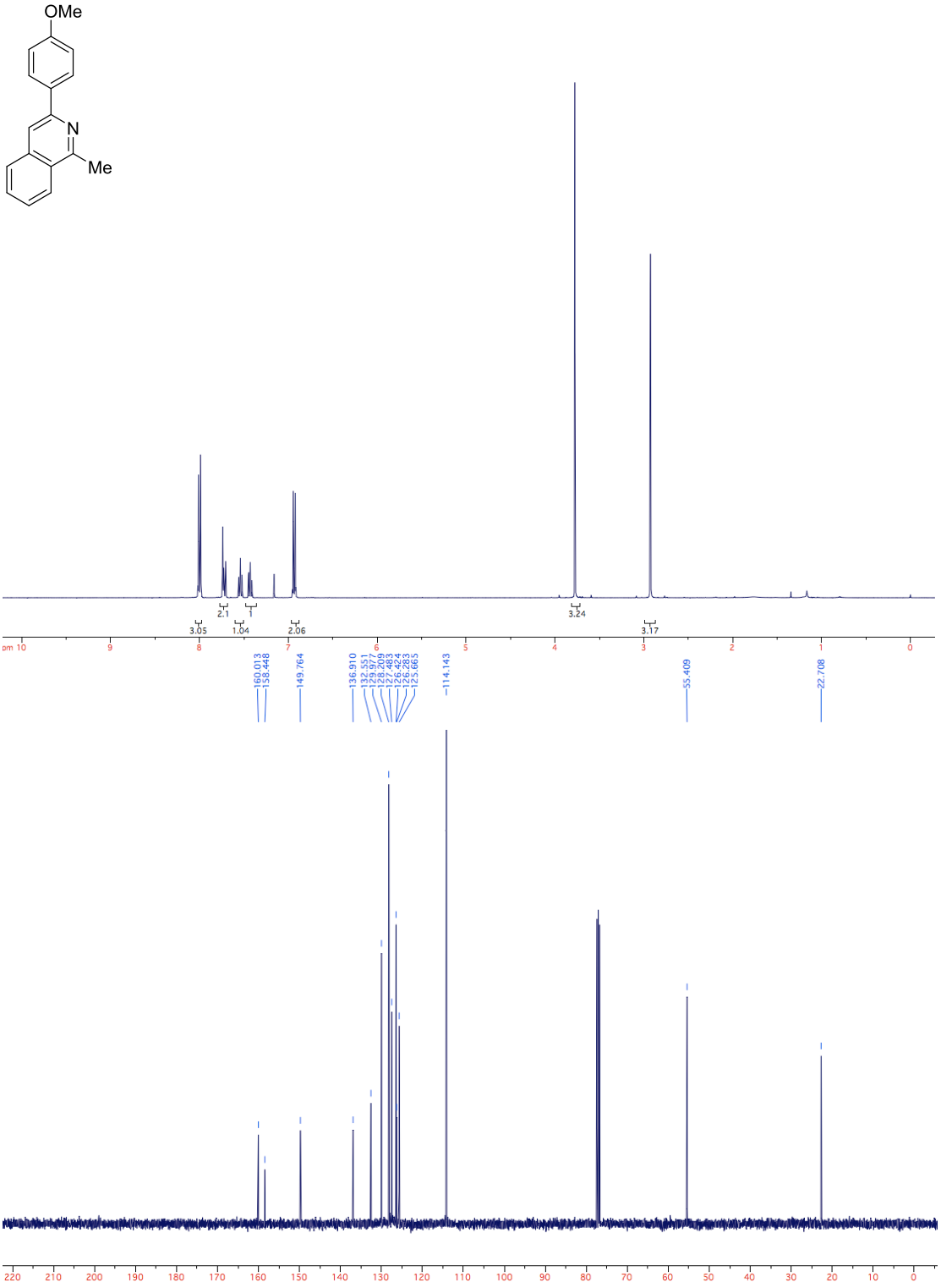




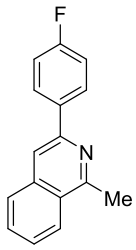
1-Methyl-3-phenylisoquinoline (104a)



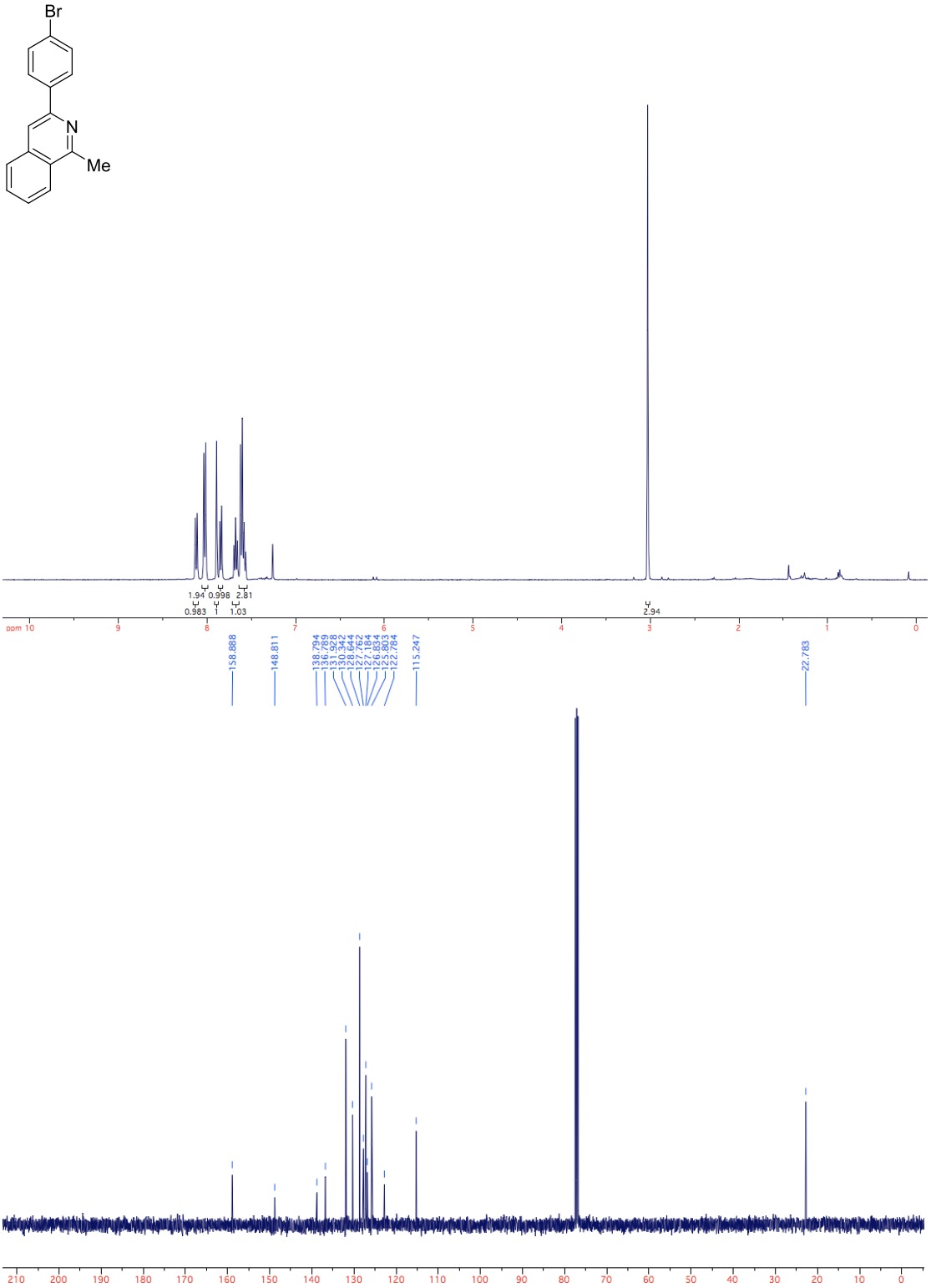
3-(4-Methoxyphenyl)-1-methylisoquinoline (104b)



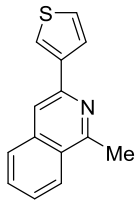
3-(4-Fluorophenyl)-1-methylisoquinoline (104c)

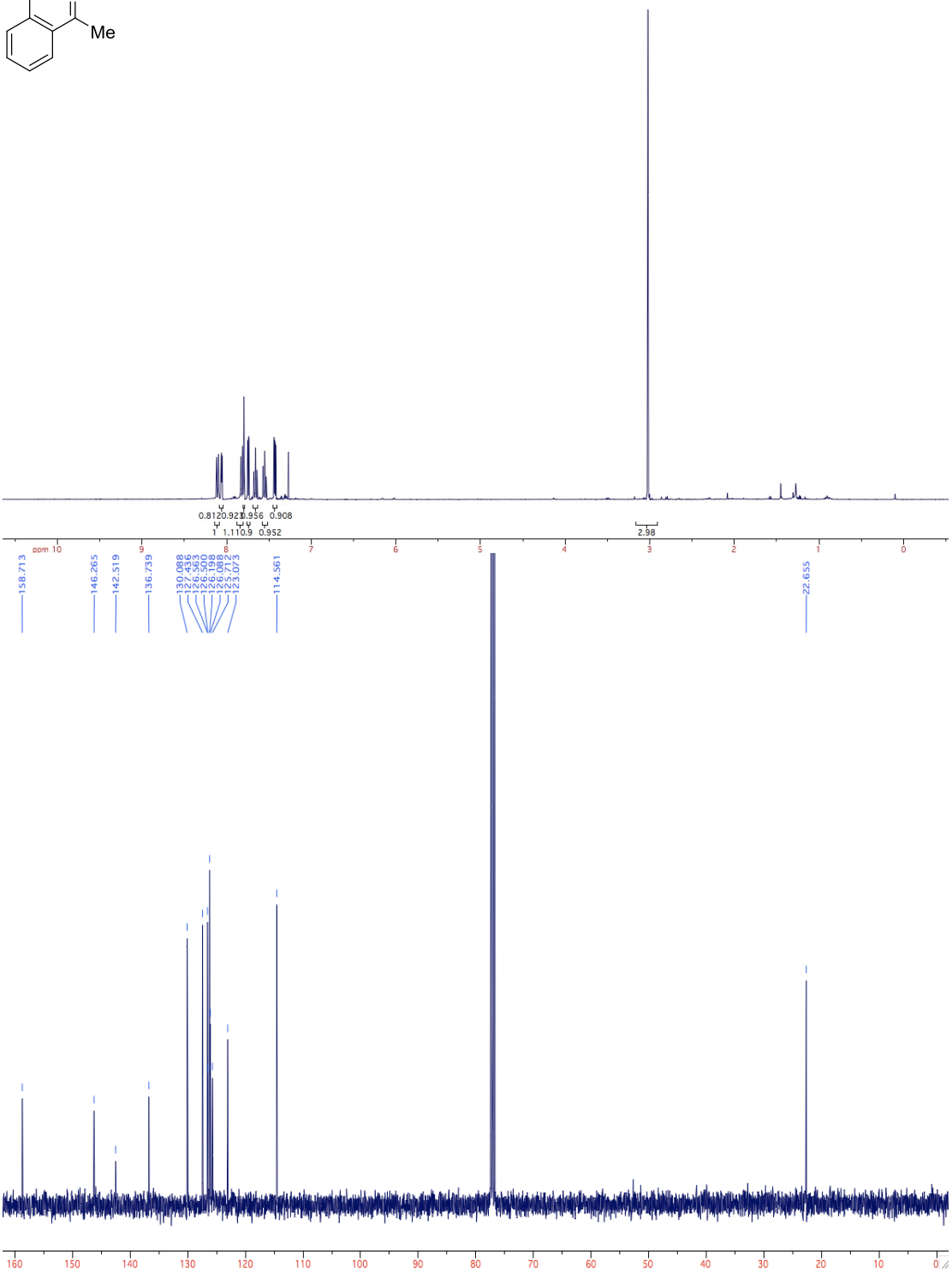


3-(4-Bromophenyl)-1-methylisoquinoline (104d)

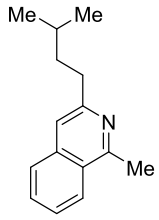


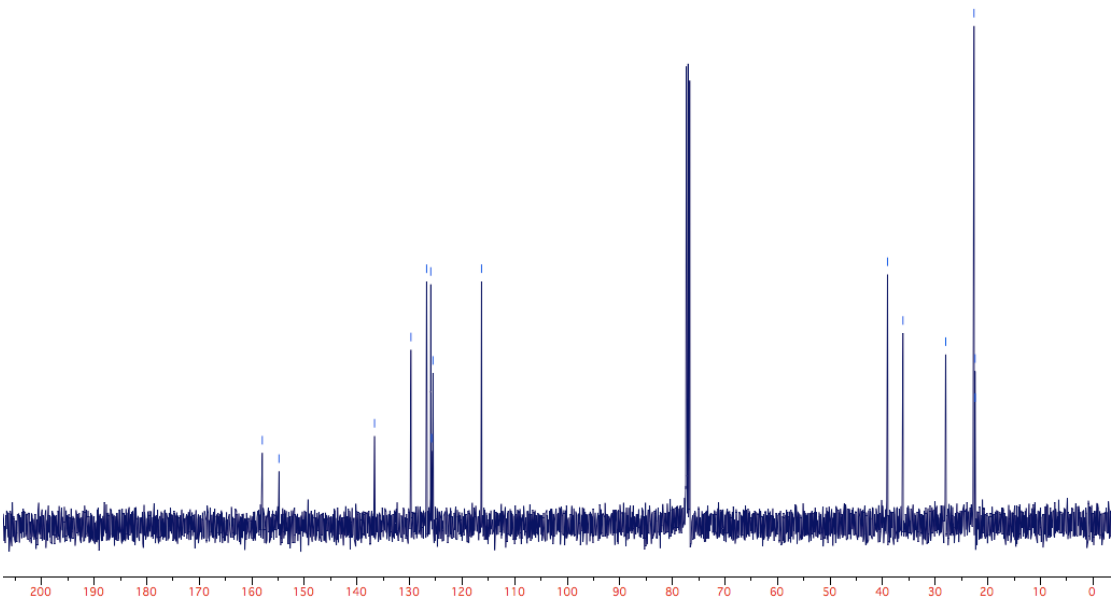
1-Methyl-3-(thiophen-3-yl)isoquinoline (104e)



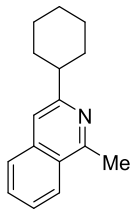


3-Isopentyl-1-methylisoquinoline (104f)

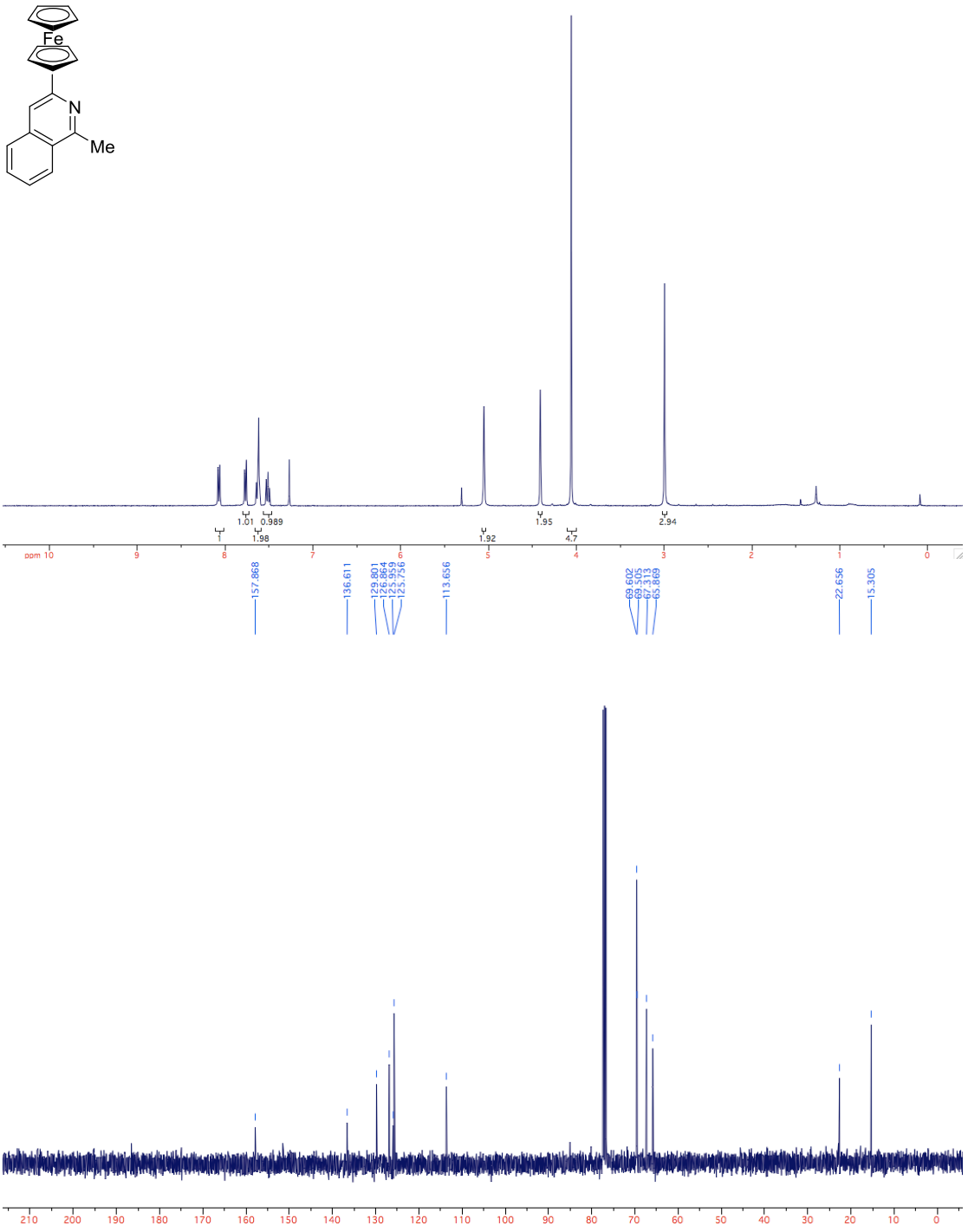




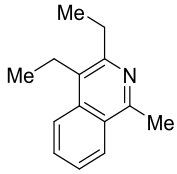
3-Cyclohexyl-1-methylisoquinoline (104g)

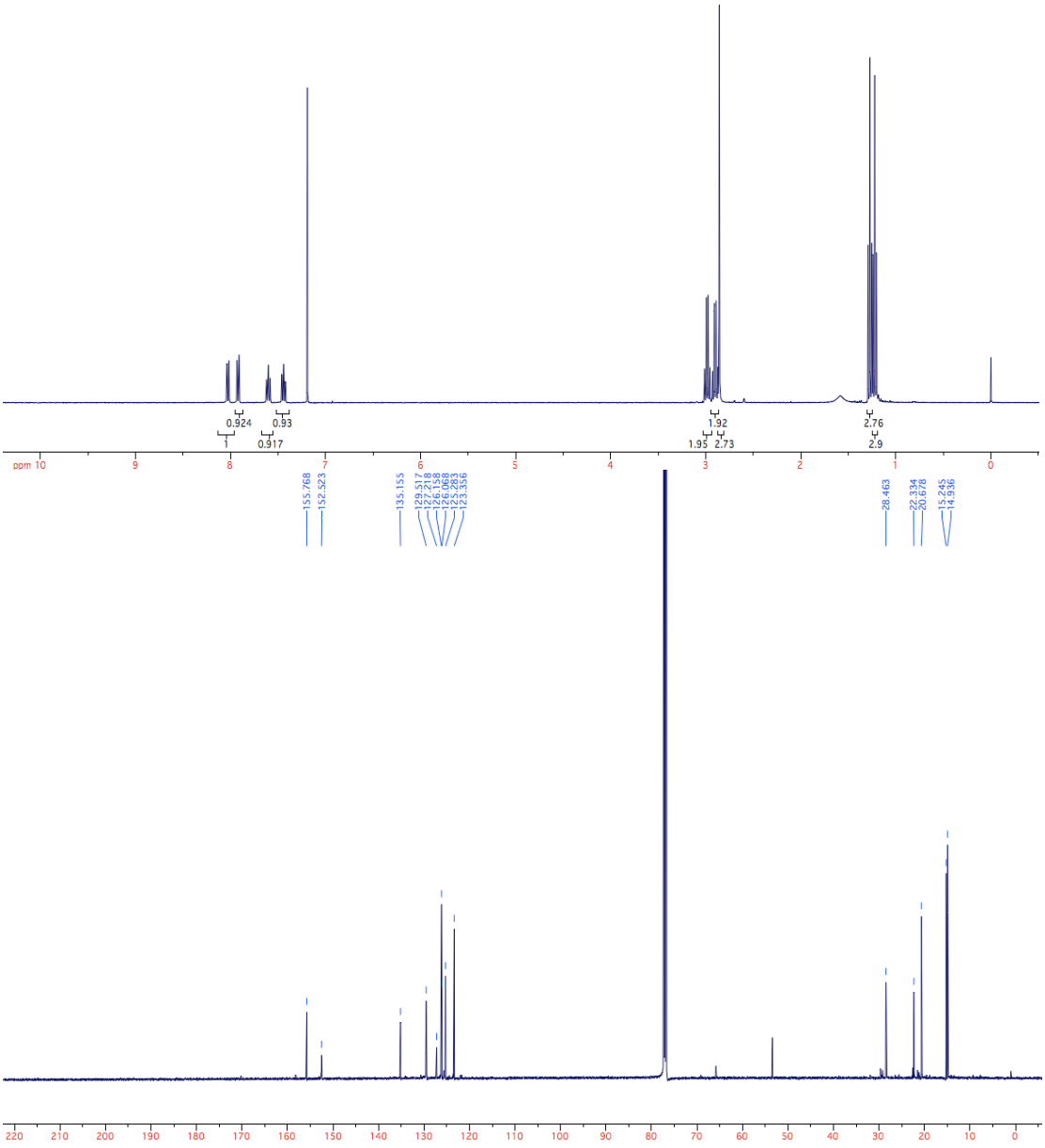


3-Ferrocenyl-1-methylisoquinoline (104h)

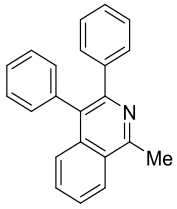


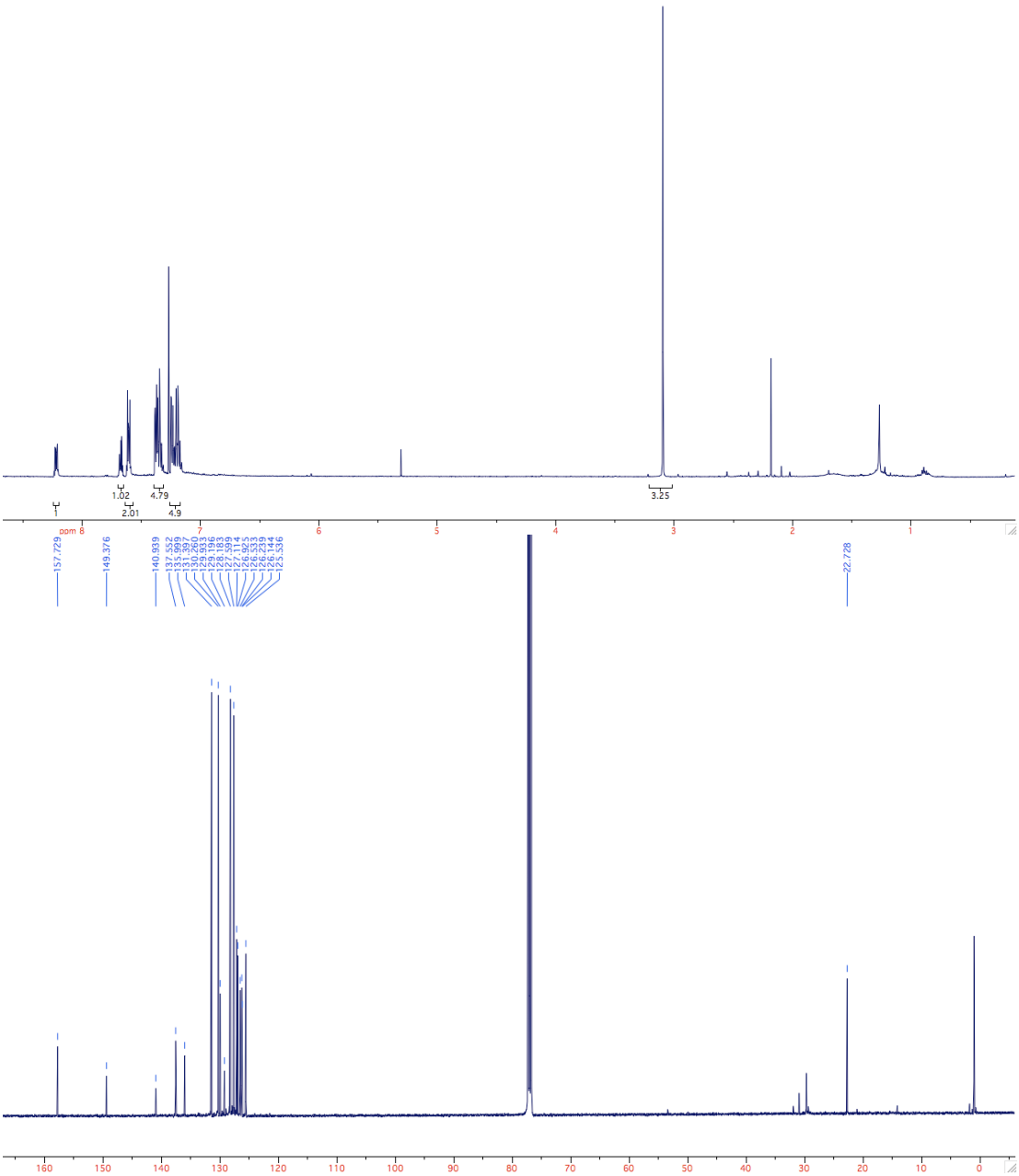
3,4-Diethyl-1-methylisoquinoline (104i)



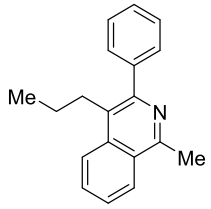


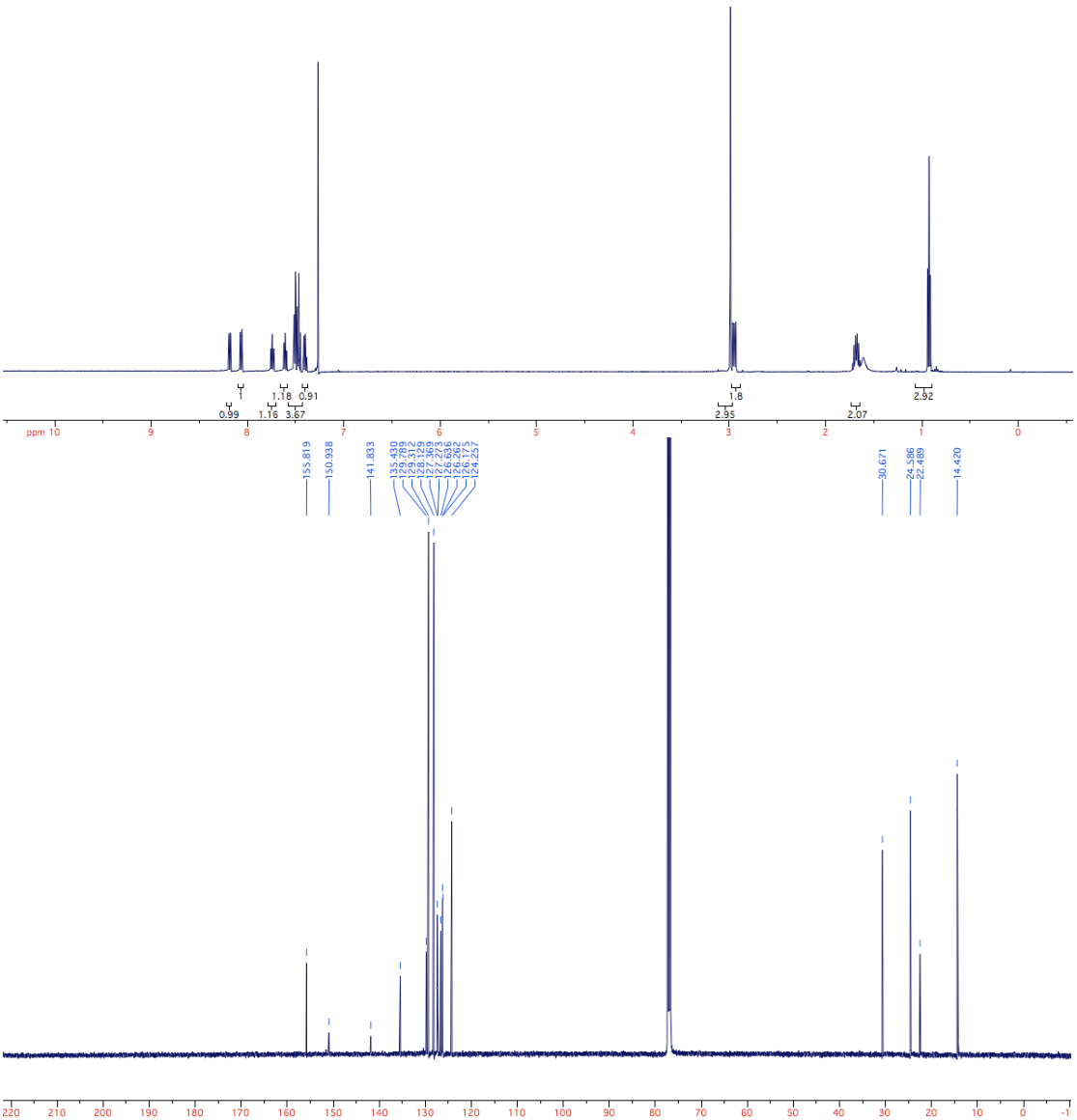
1-Methyl-3,4-diphenylisoquinoline (104j)



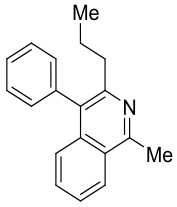


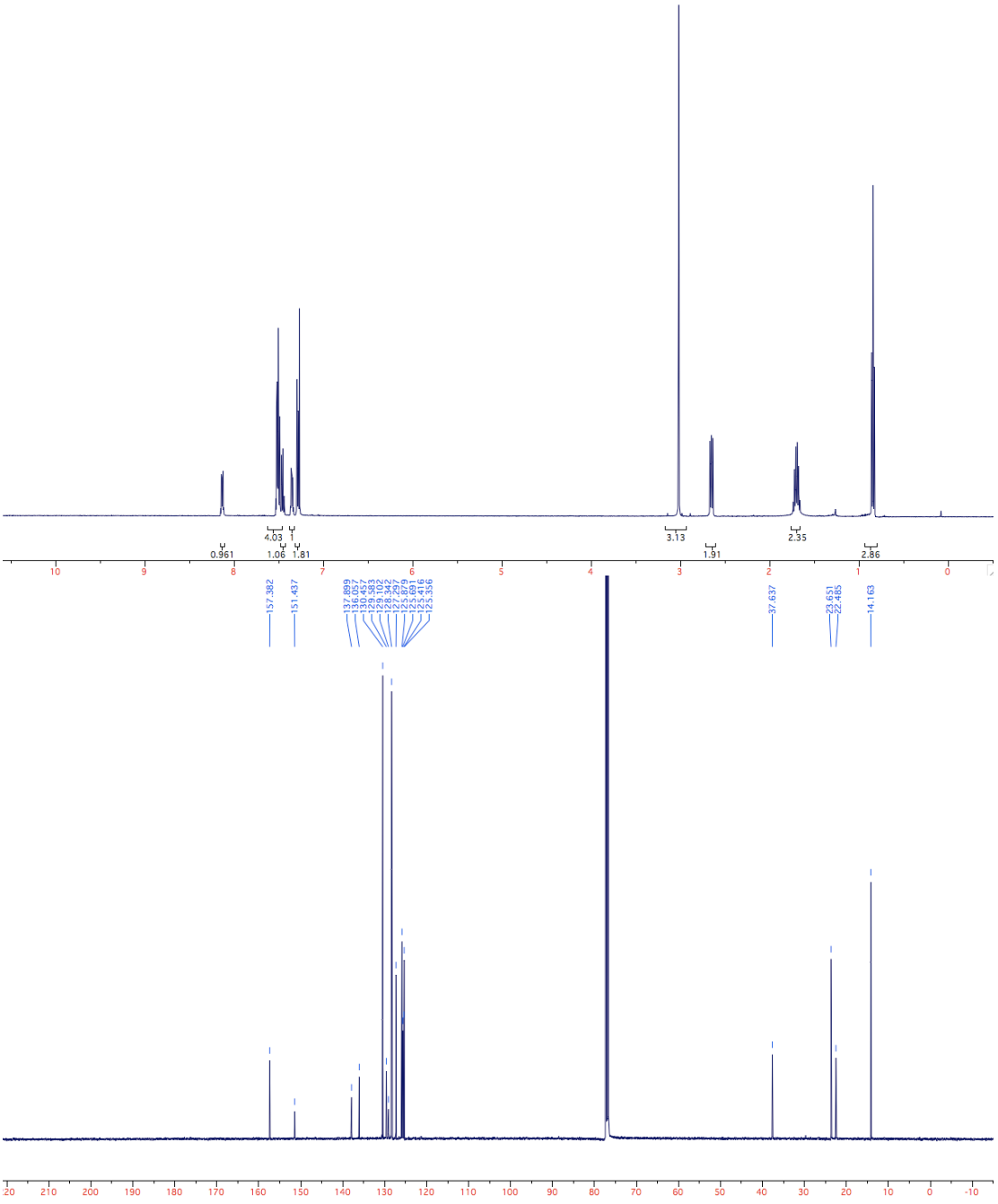
1-Methyl-3-phenyl-4-propylisoquinoline (104k)



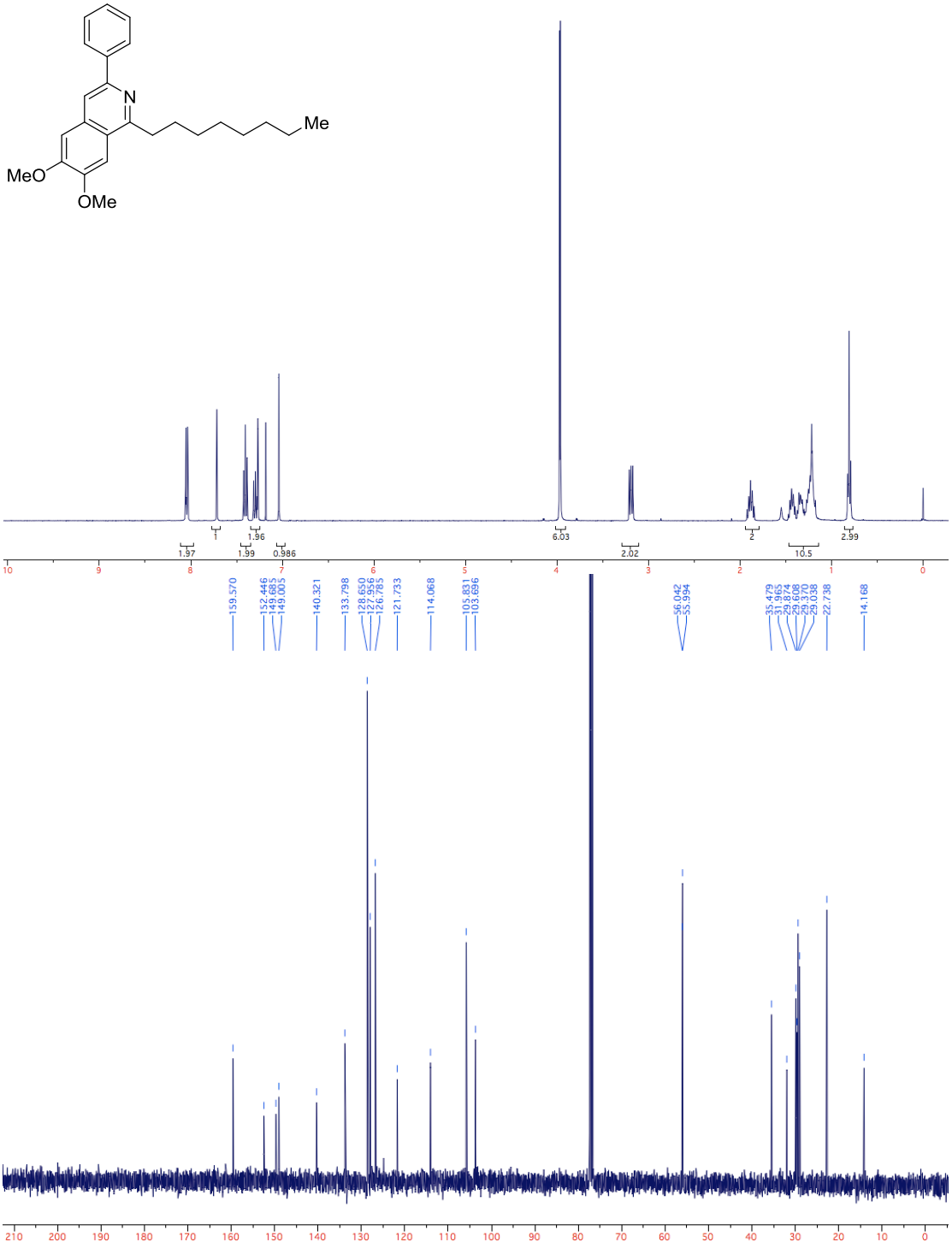


1-Methyl-4-phenyl-3-propylisoquinoline (104l)

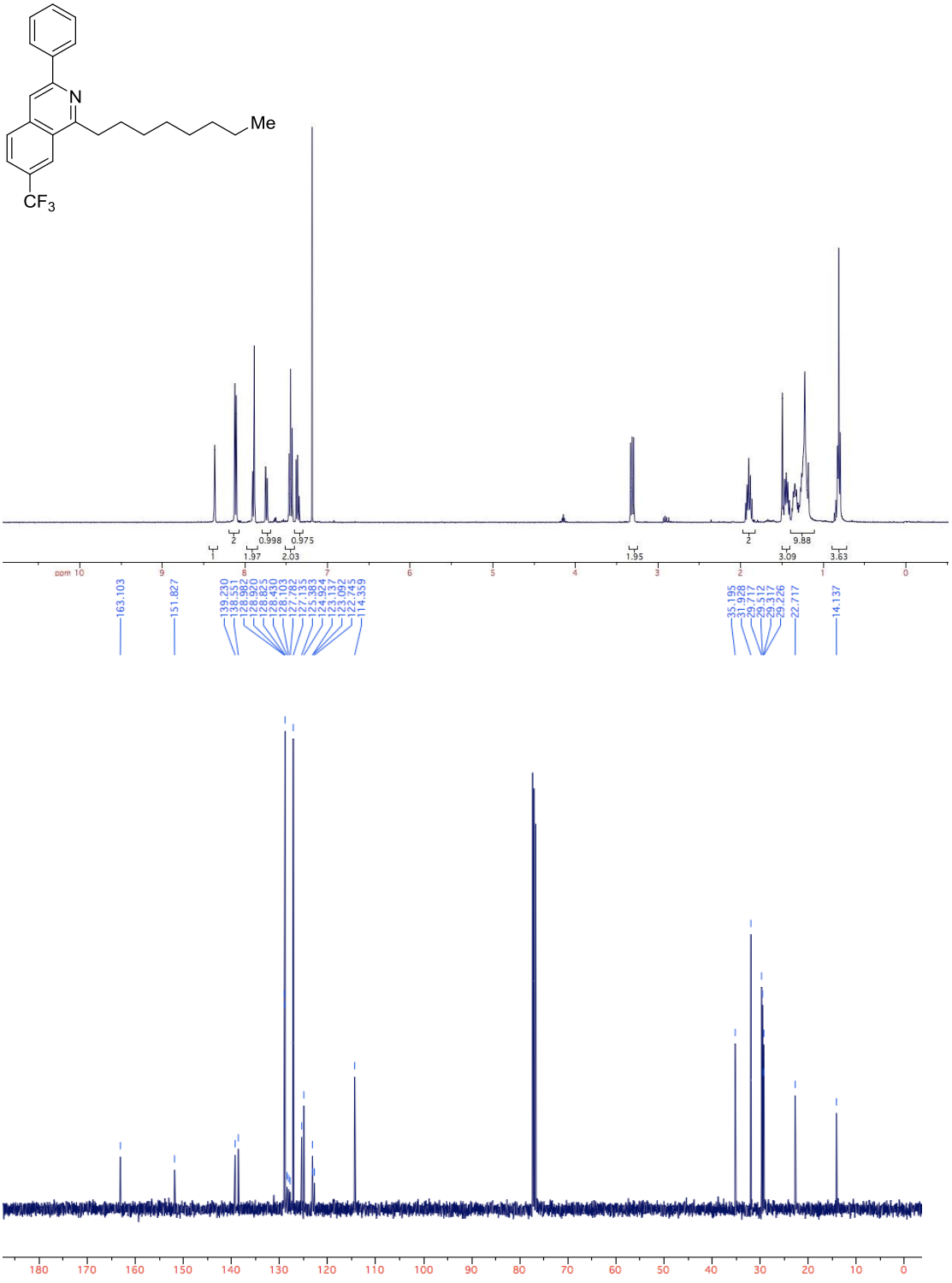




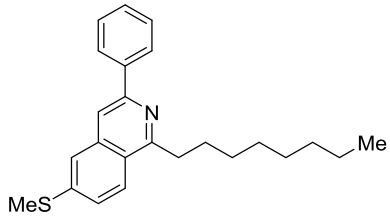
6,7-Dimethoxy-1-octyl-3-phenylisoquinoline (105a)

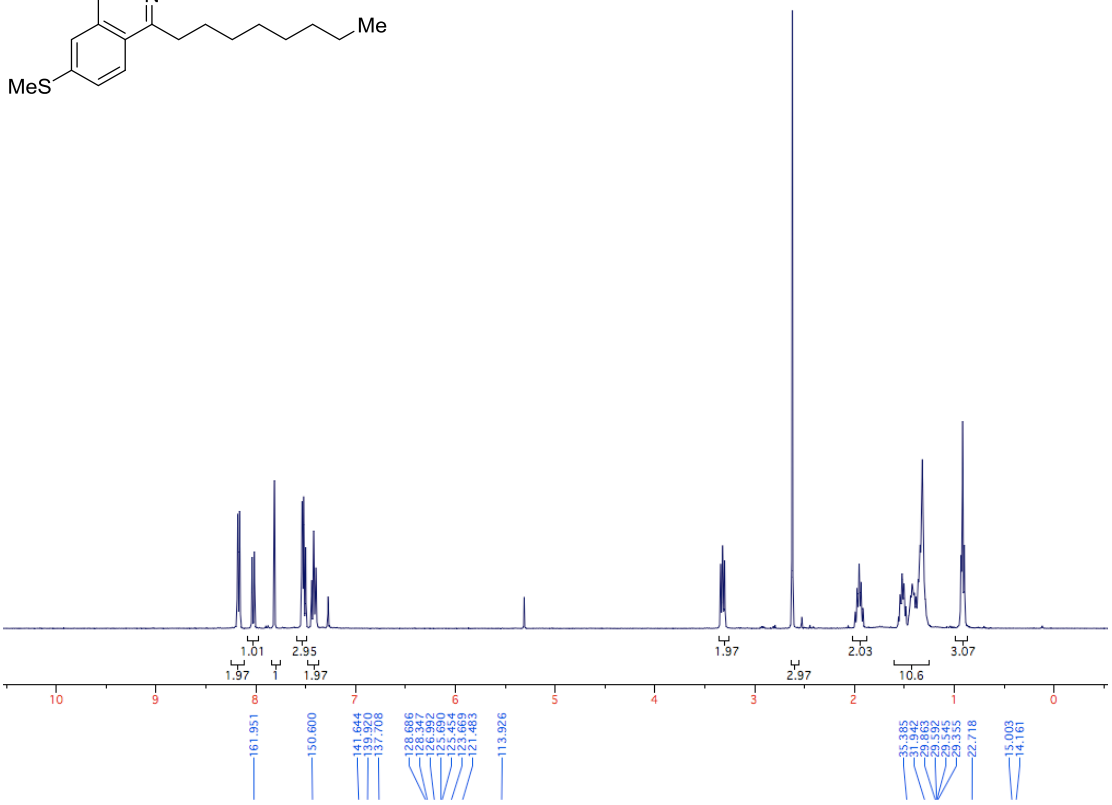


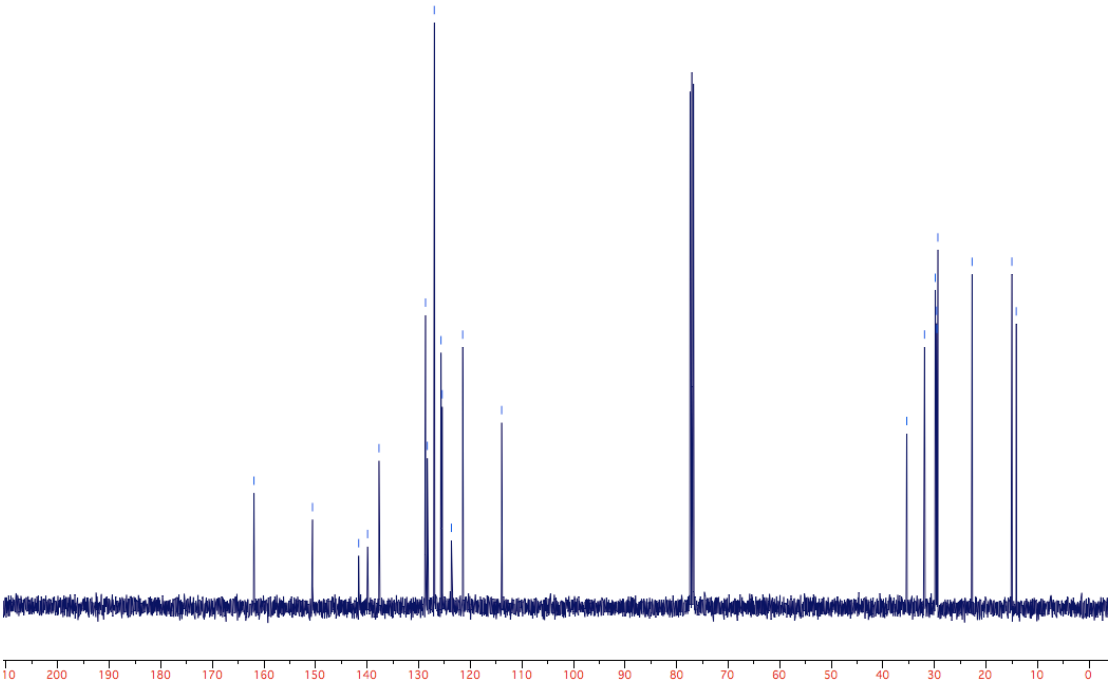
1-Octyl-3-phenyl-7-(trifluoromethyl)isoquinoline (105b)



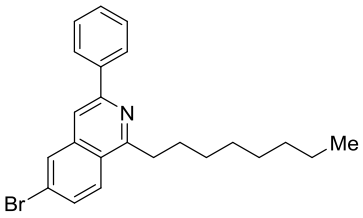
6-(Methylthio)-1-octyl-3-phenylisoquinoline (105c)

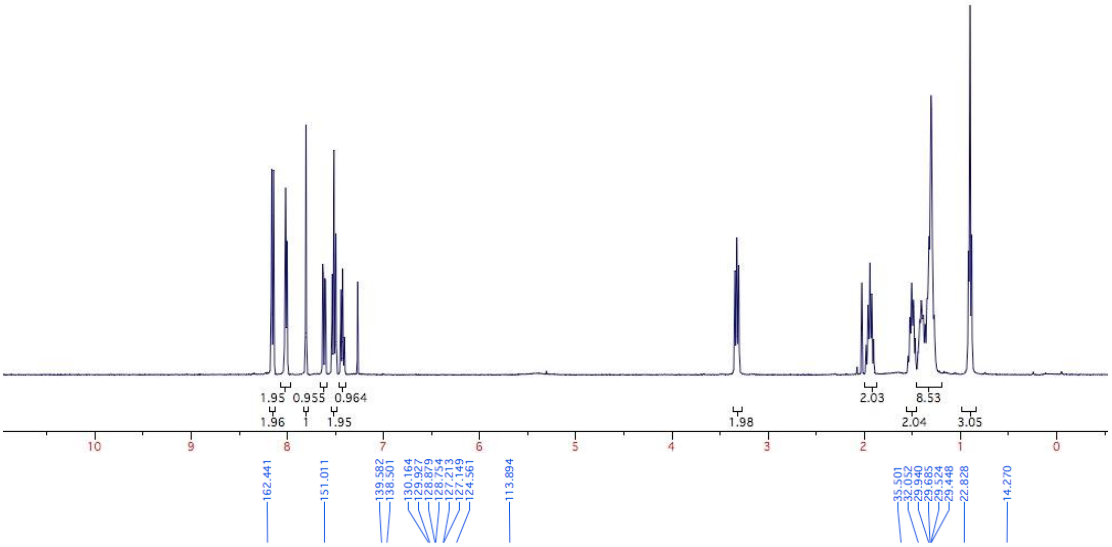


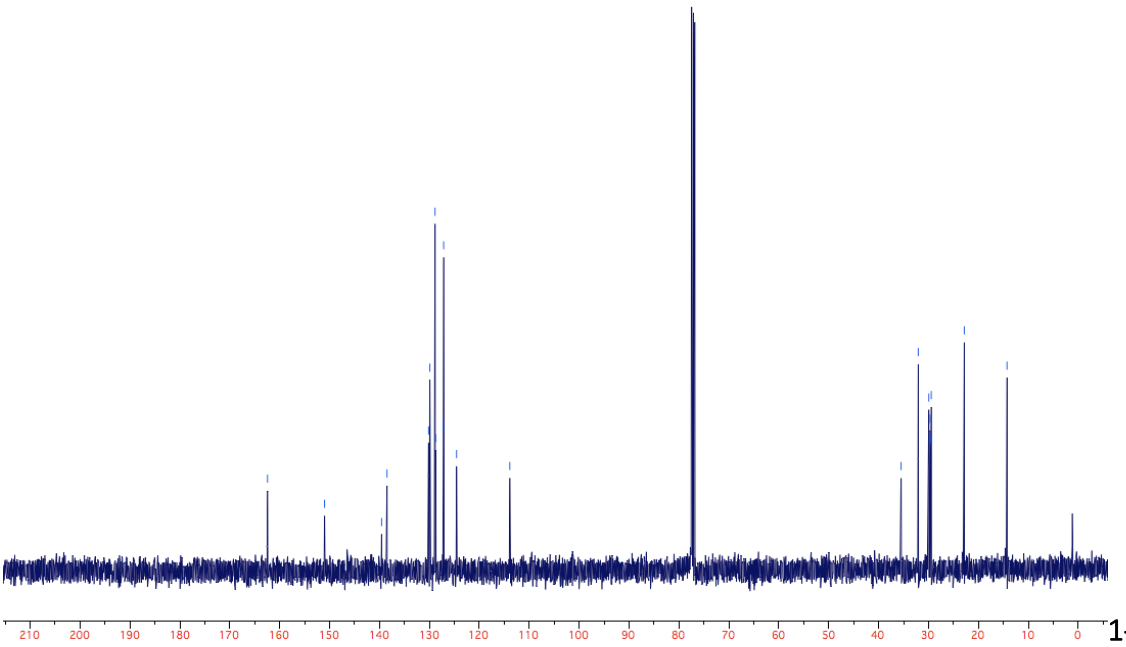




6-Bromo-1-octyl-3-phenylisoquinoline (105d)

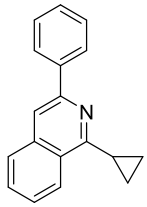


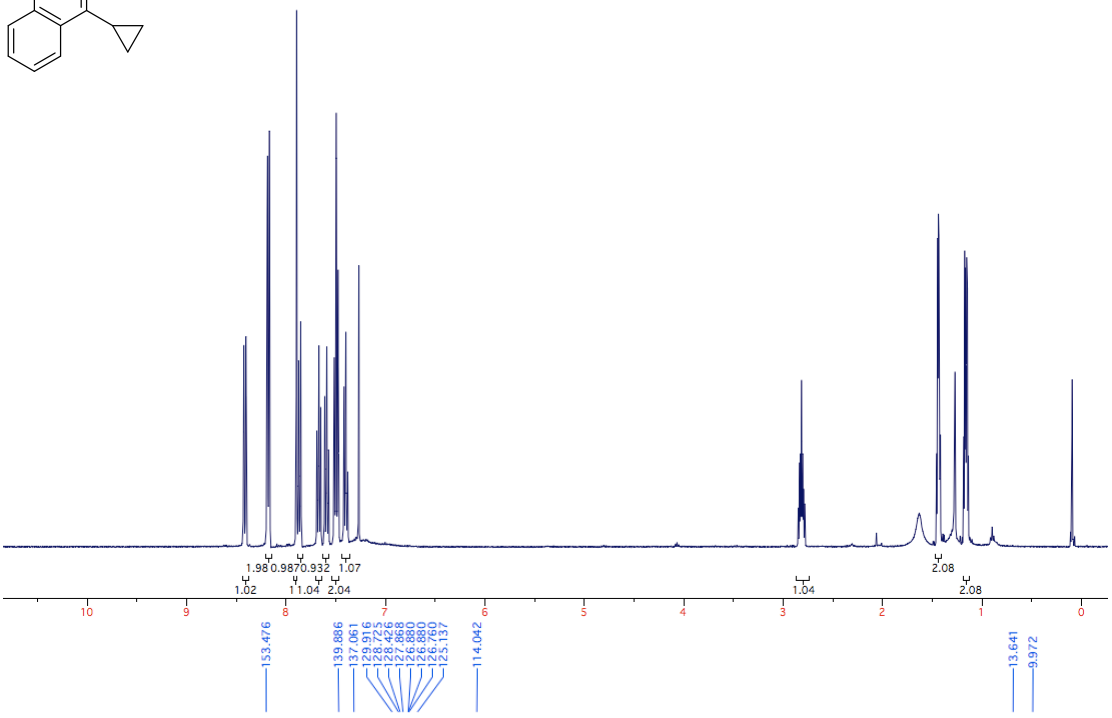


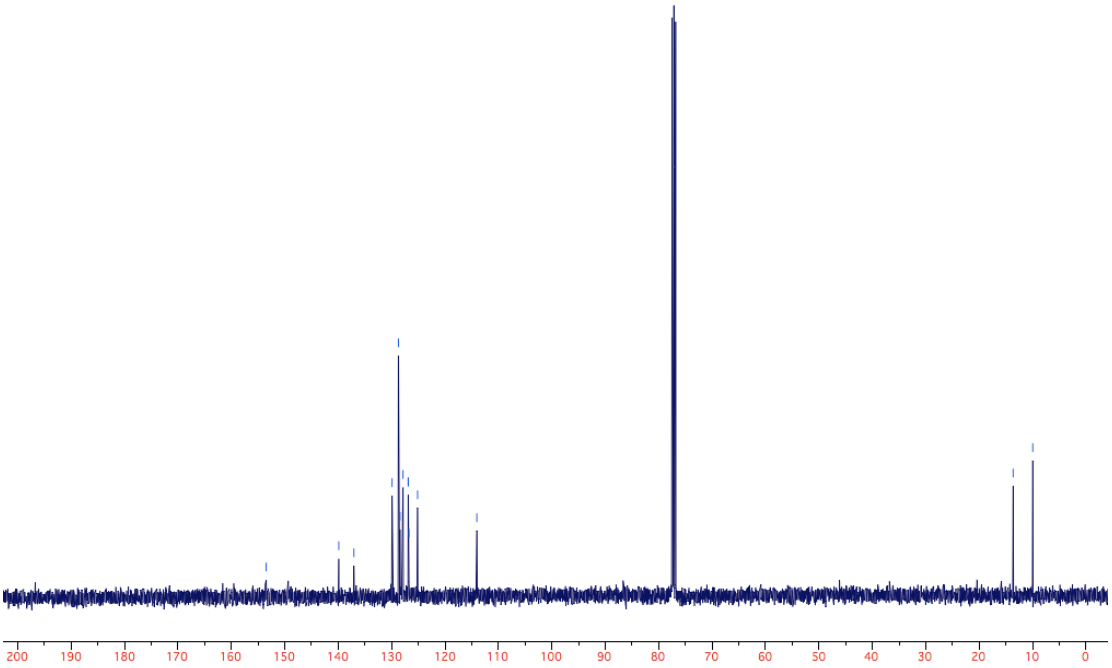


1-

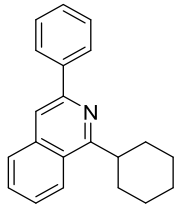
Cyclopropyl-3-phenylisoquinoline (105e)

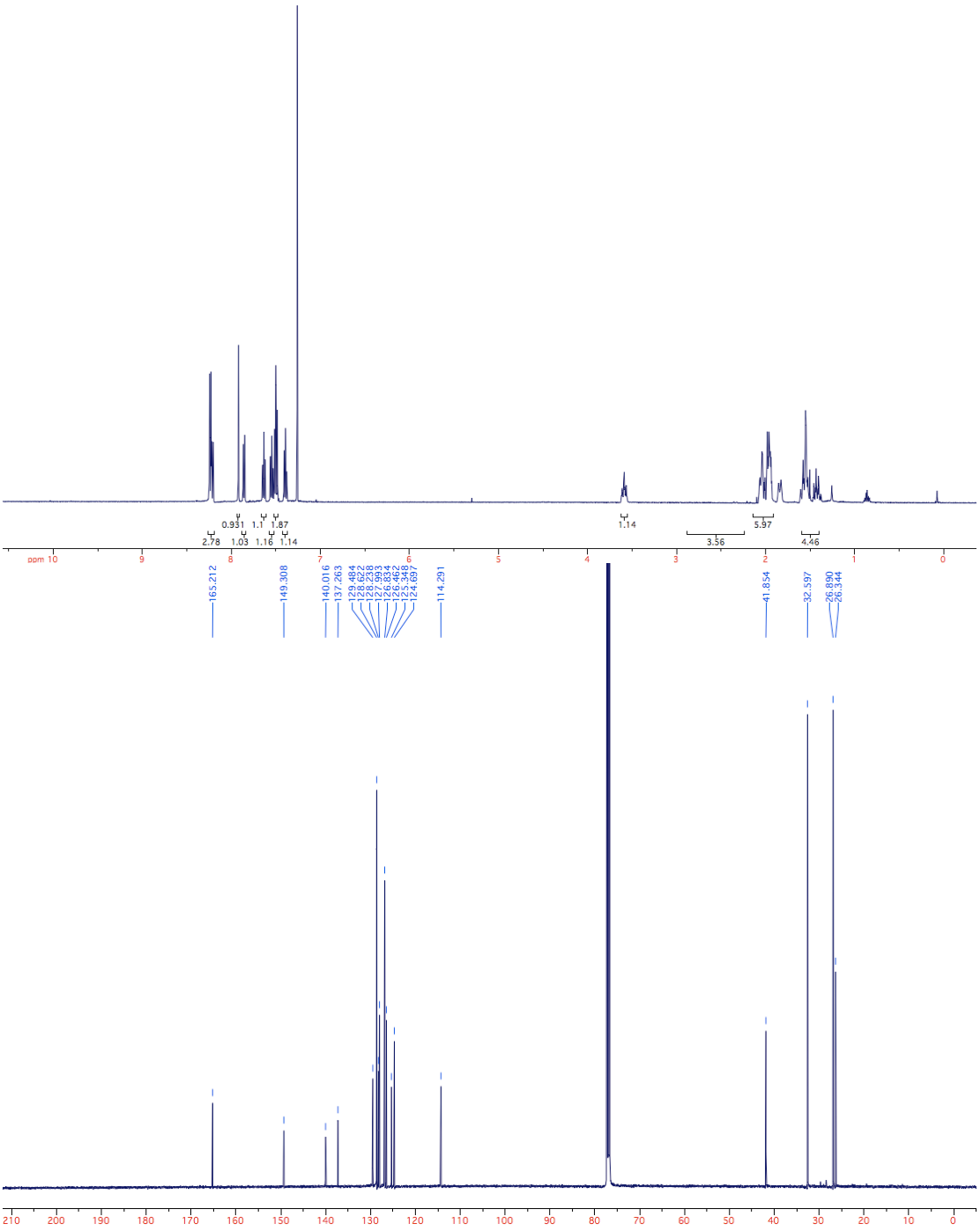




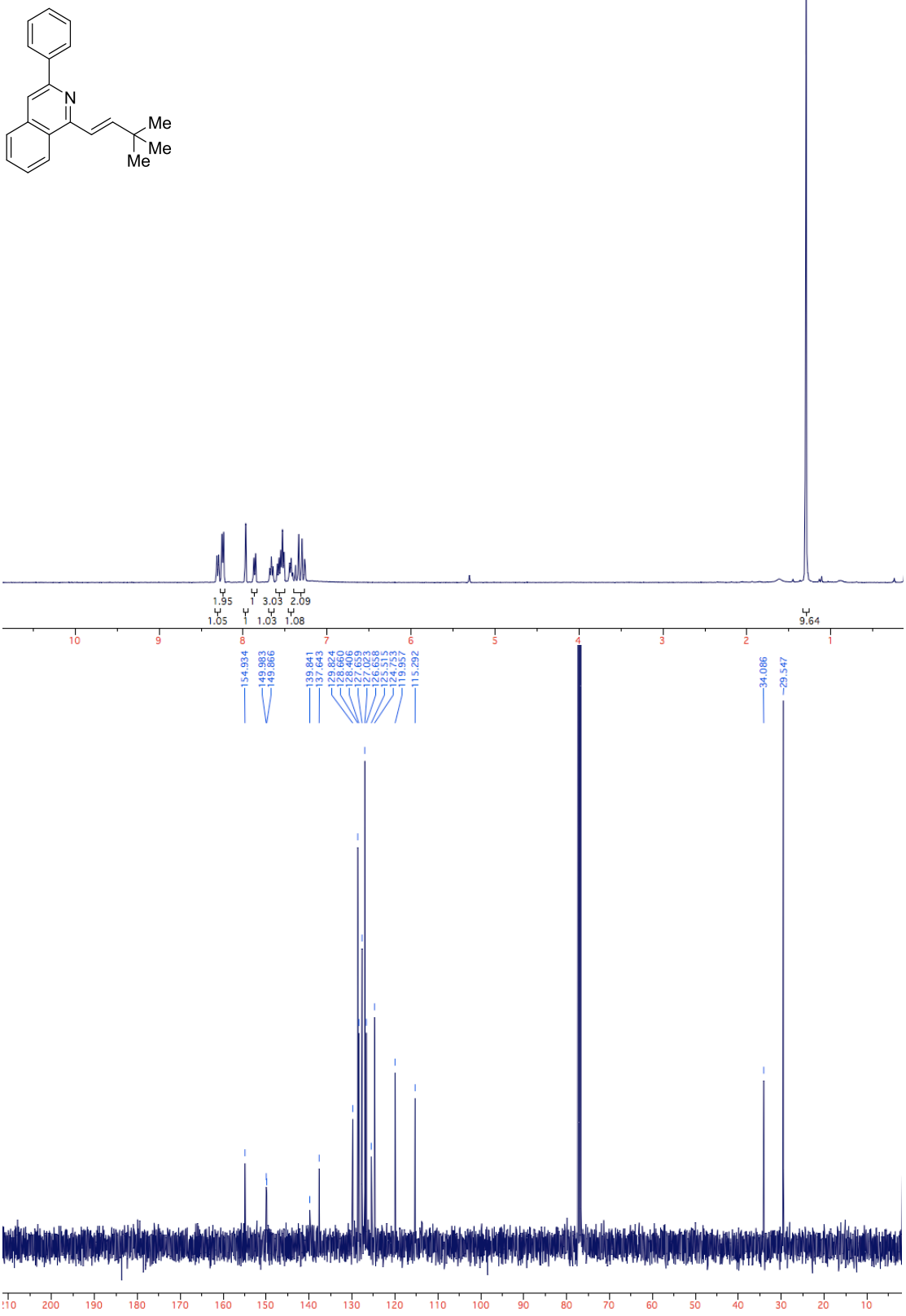


1-Cyclohexyl-3-phenylisoquinoline (105f)

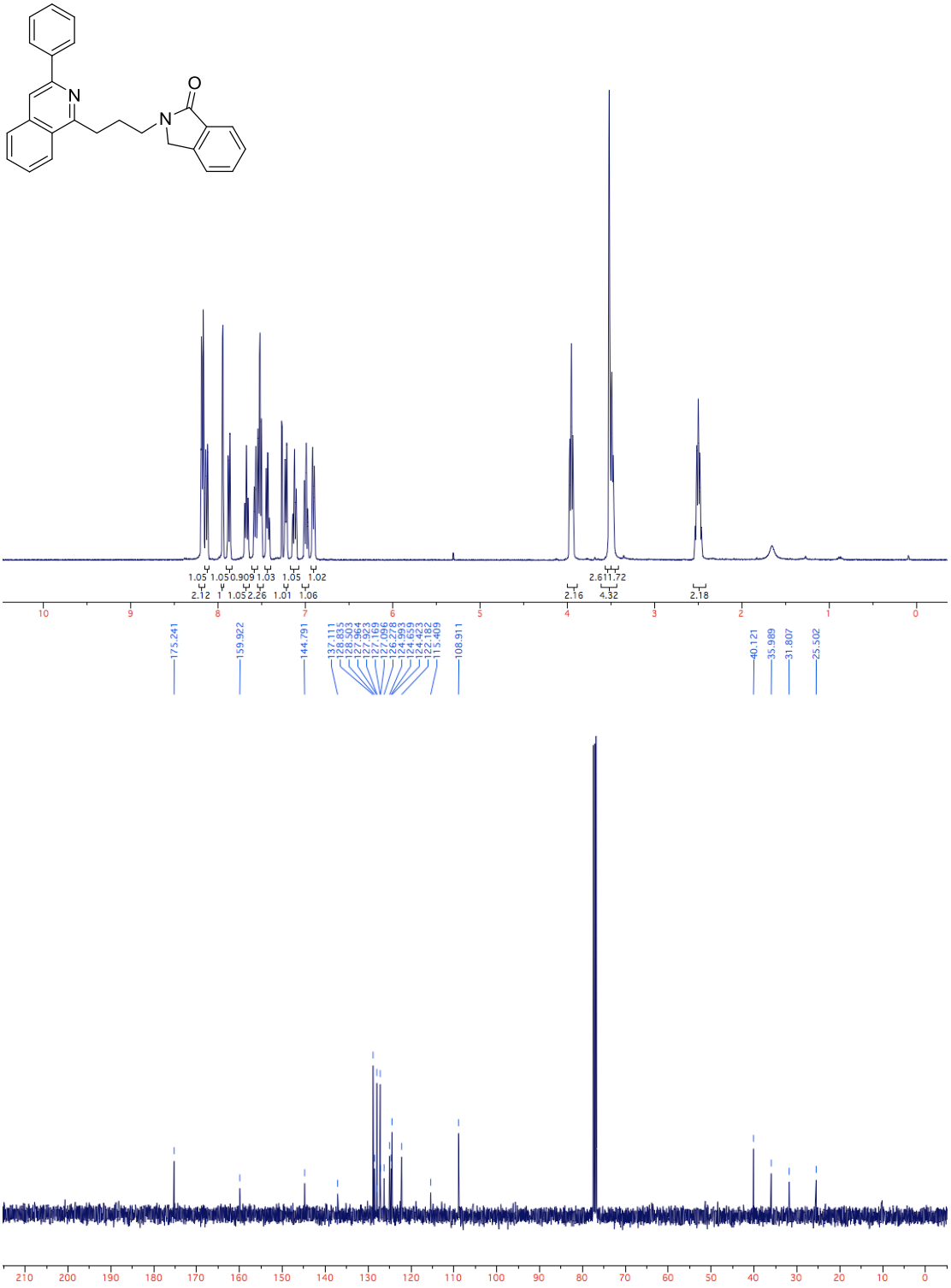




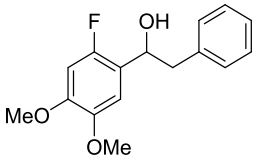
(*E*)-1-(3,3-Dimethylbut-1-en-1-yl)-3-phenylisoquinoline (105g)

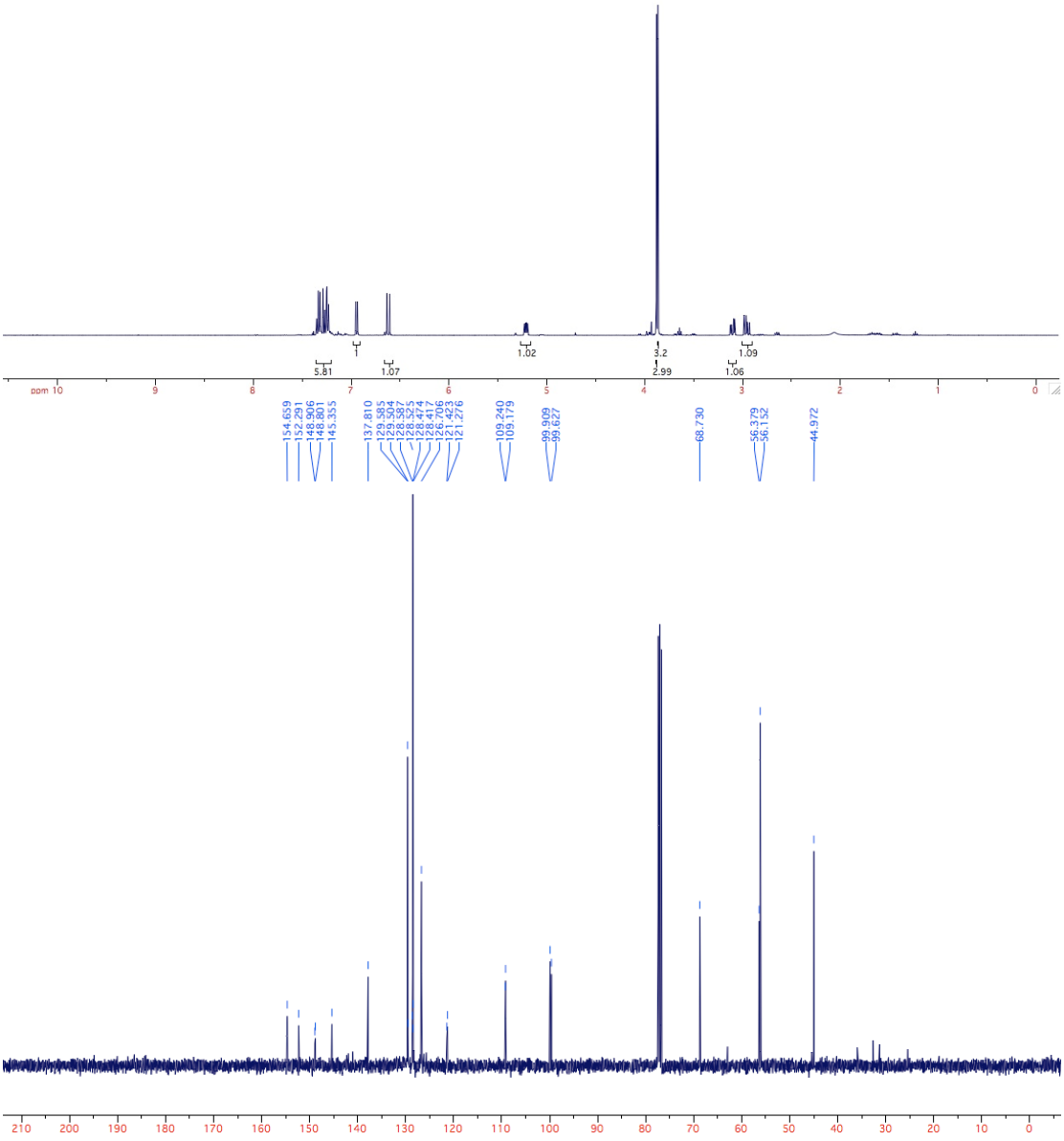


2-(3-(3-Phenylisoquinolin-1-yl)propyl)isoindolin-1-one (105h)

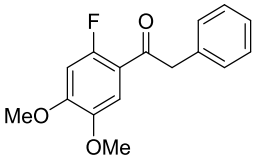


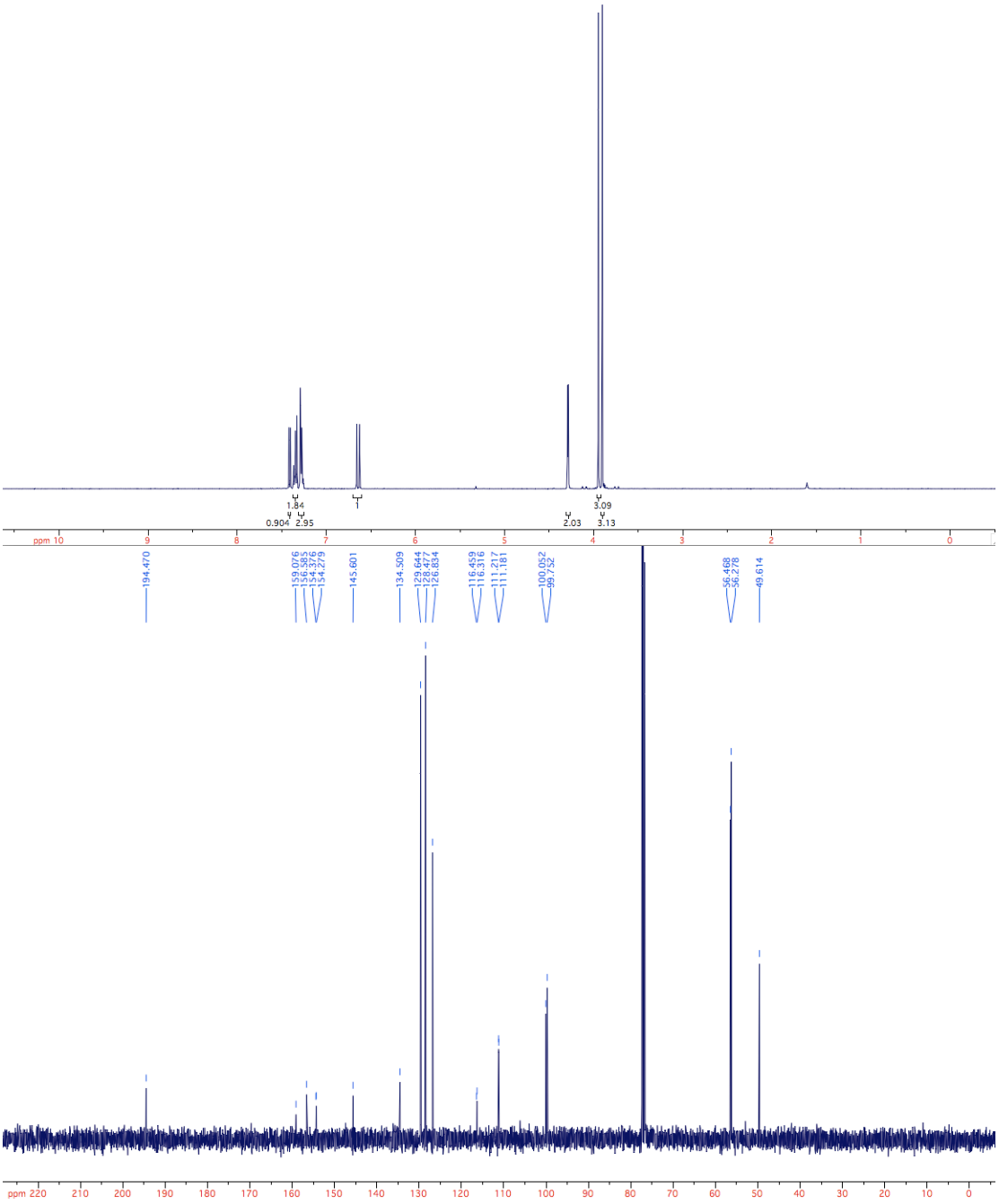
1-(2-Fluoro-4,5-dimethoxyphenyl)-2-phenylethanol



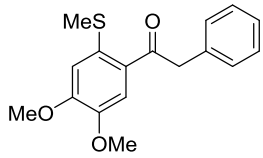


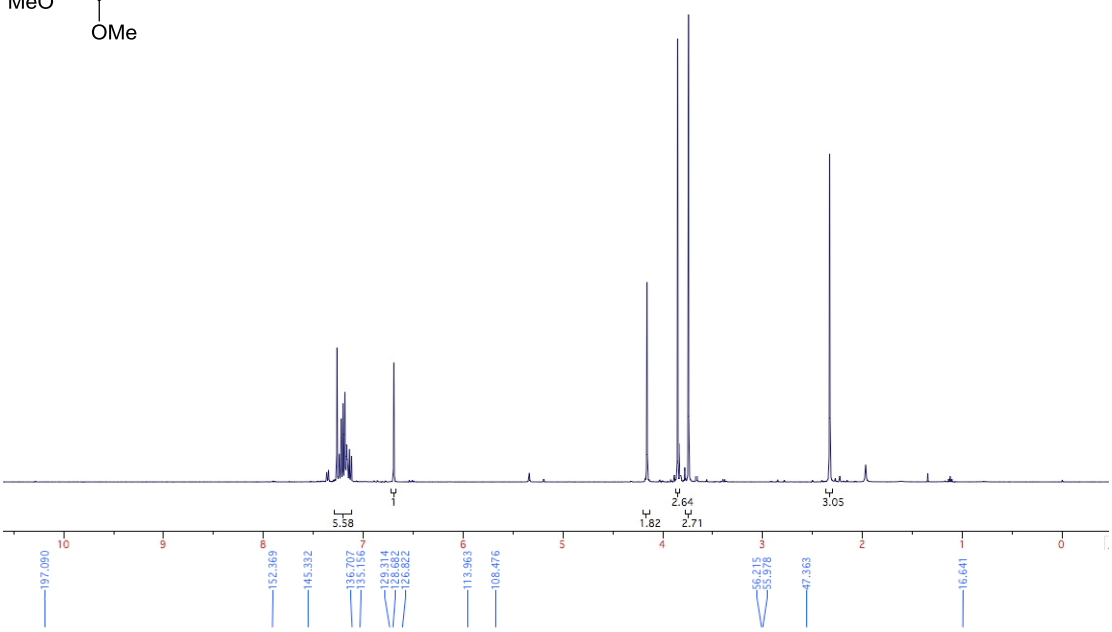
1-(2-Fluoro-4,5-dimethoxyphenyl)-2-phenylethanone (111)

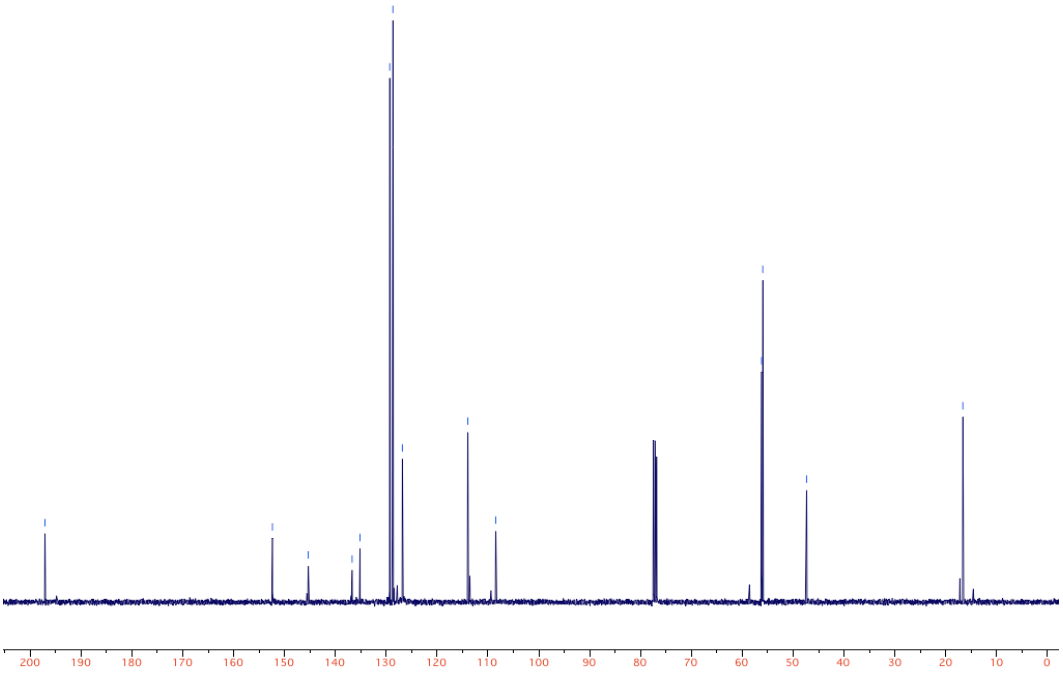




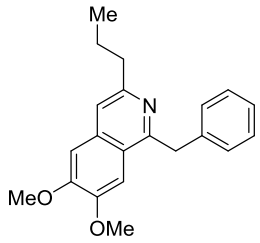
1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-phenylethanone (107

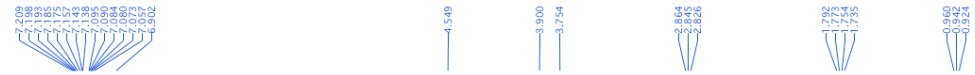


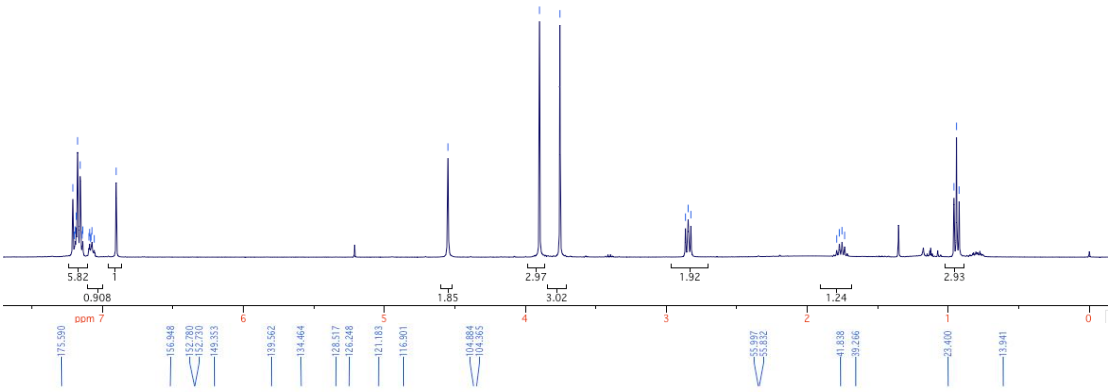


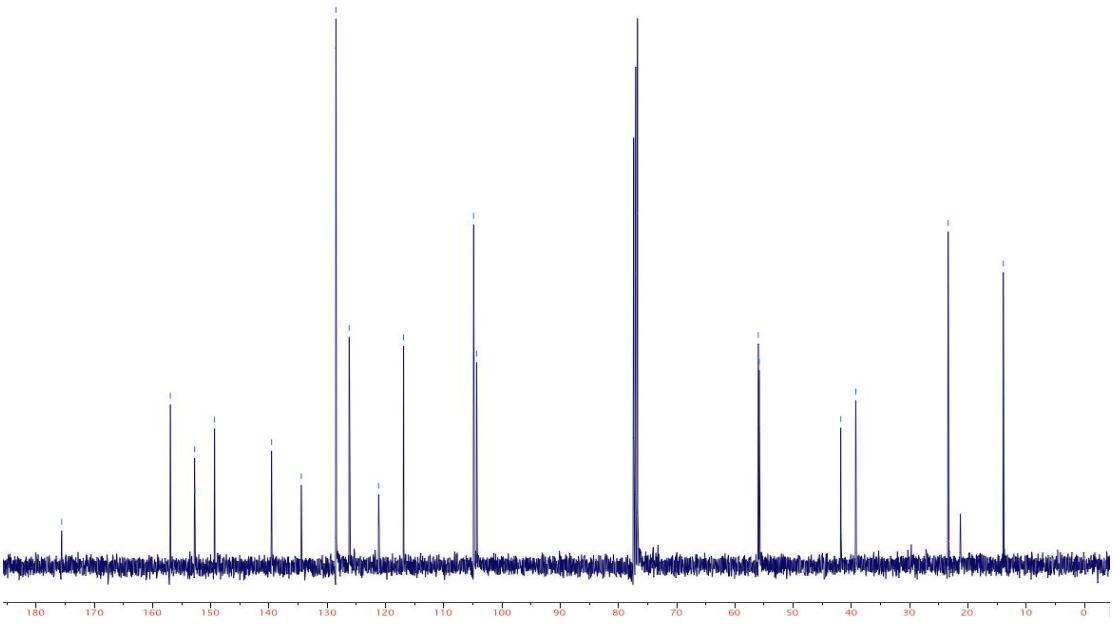


1-Benzyl-6,7-dimethoxy-3-propylisoquinoline – Moxaverine derivative (106)

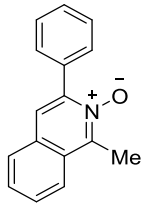


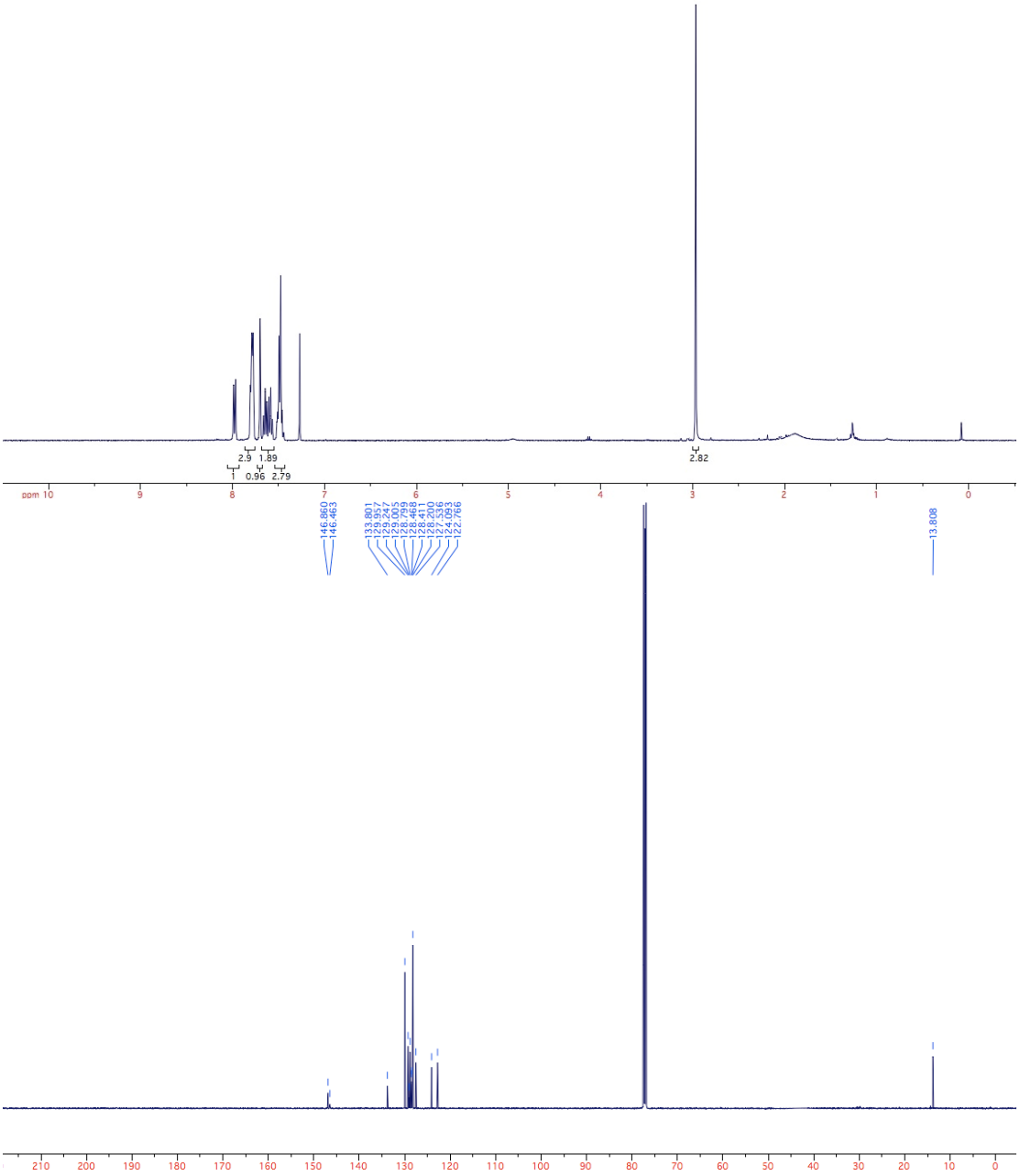




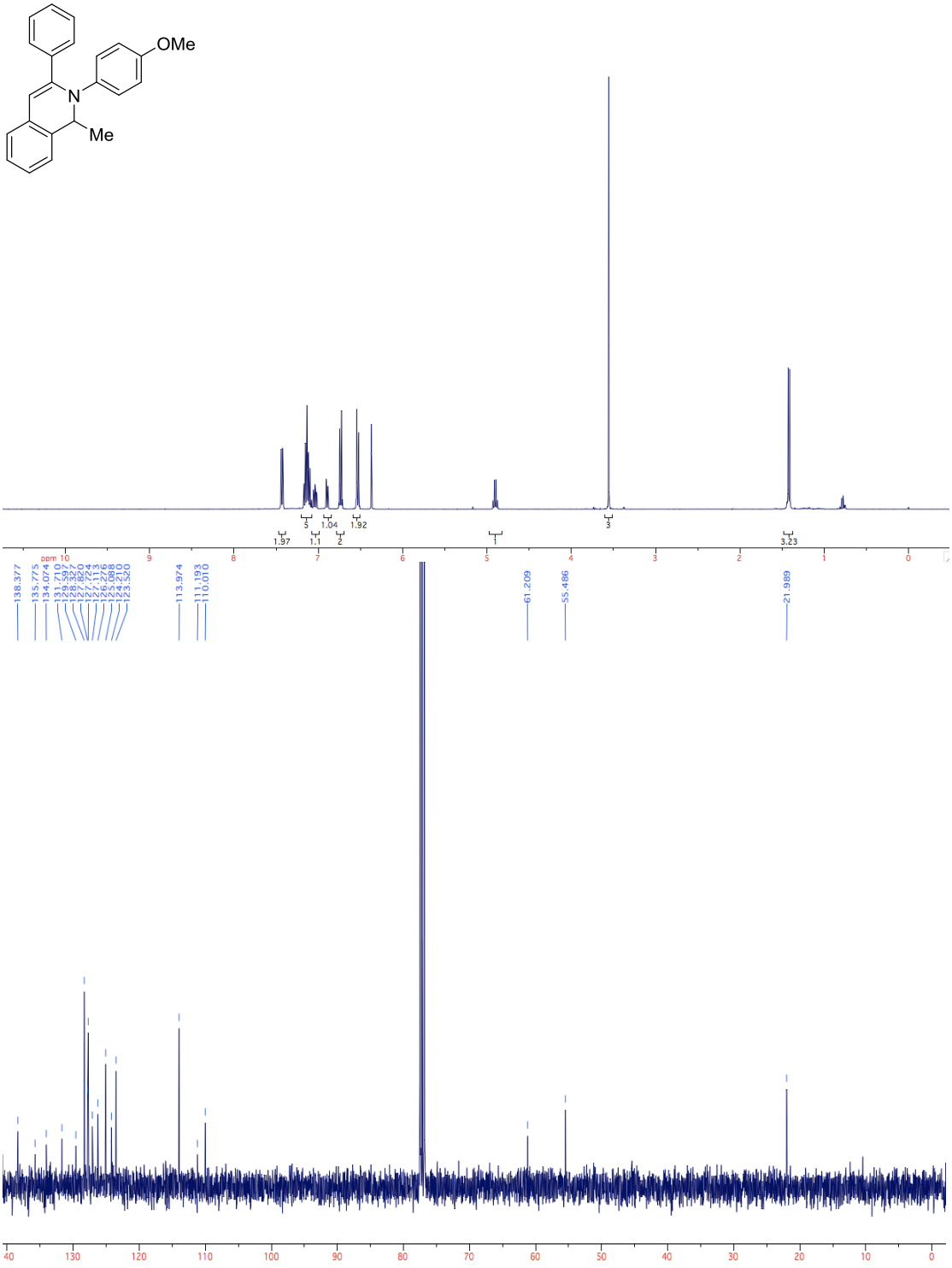


1-Methyl-3-phenylisoquinoline 2-oxide (112)

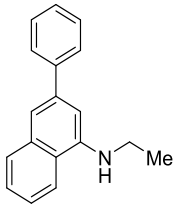


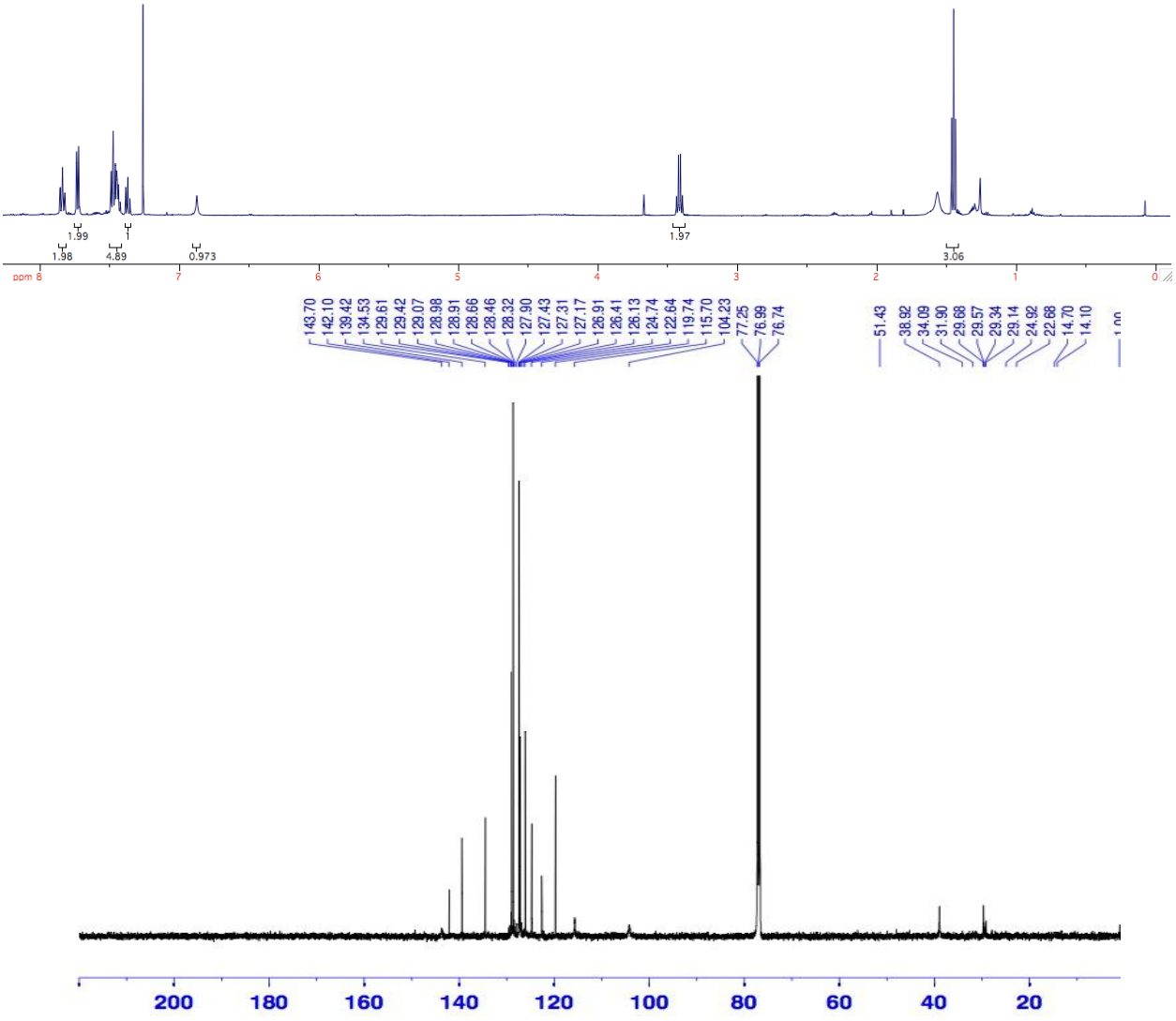


2-(4-Methoxyphenyl)-1-methyl-3-phenyl-1,2-dihydroisoquinoline (122)

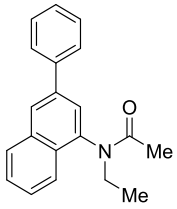


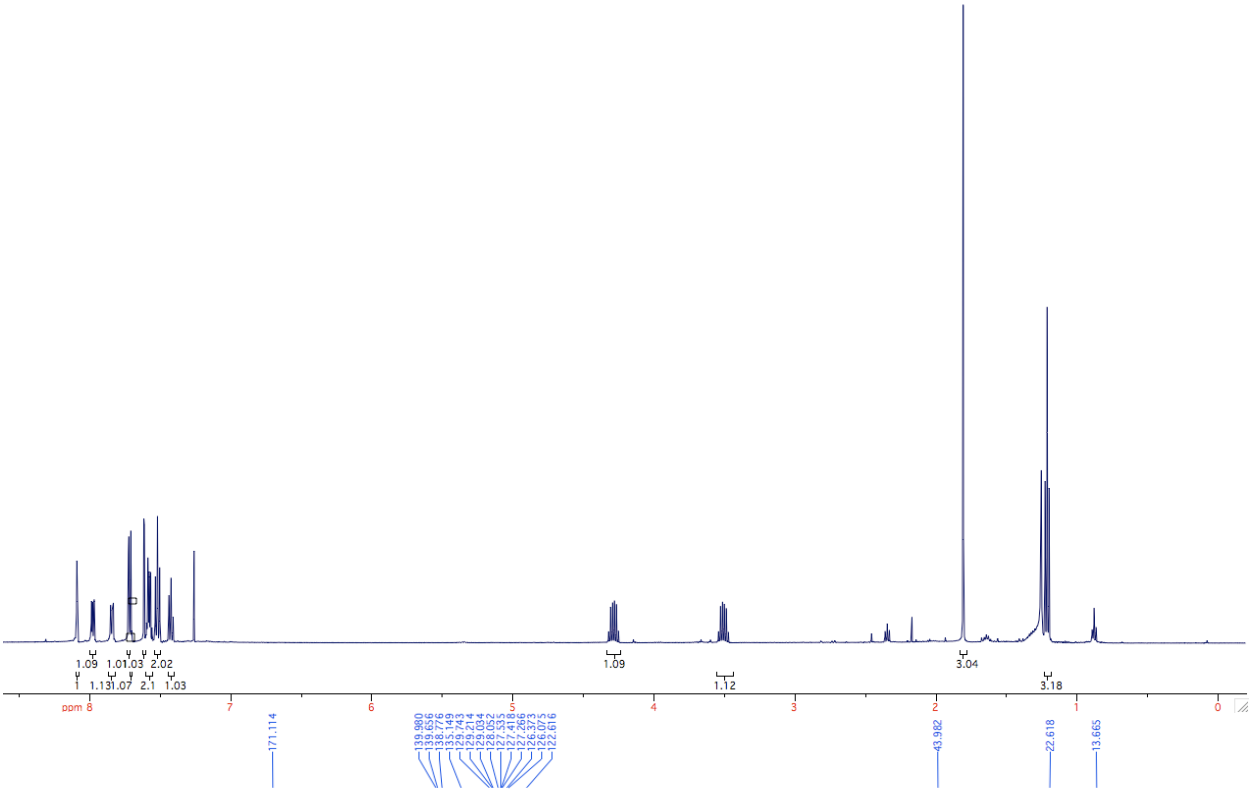
N-ethyl-3-phenylnaphthalen-1-amine (121, R: Et)

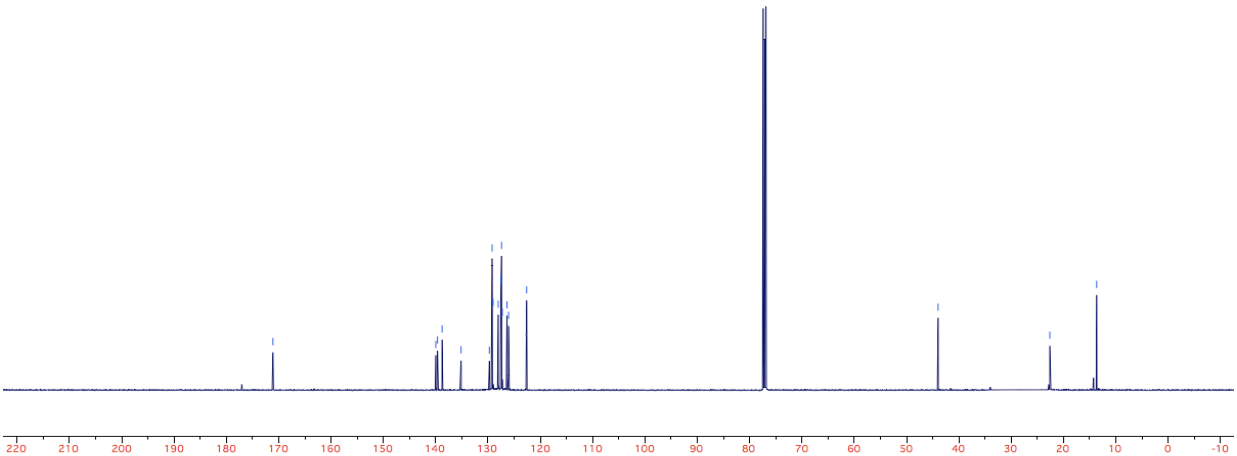




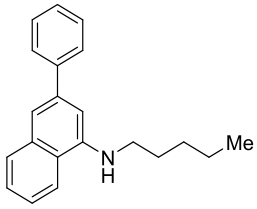
N-ethyl-*N*-(3-phenylnaphthalen-1-yl)acetamide (123, R: Et)

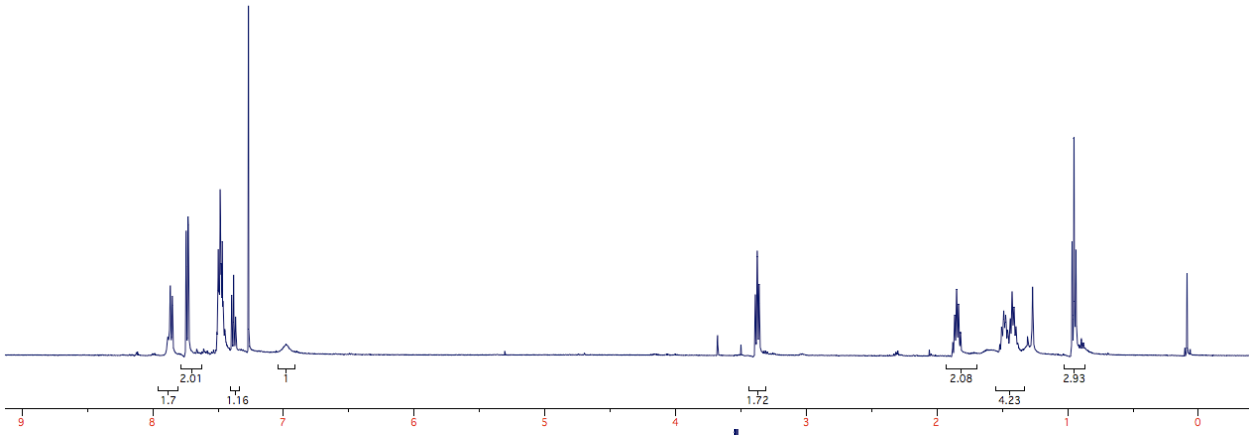


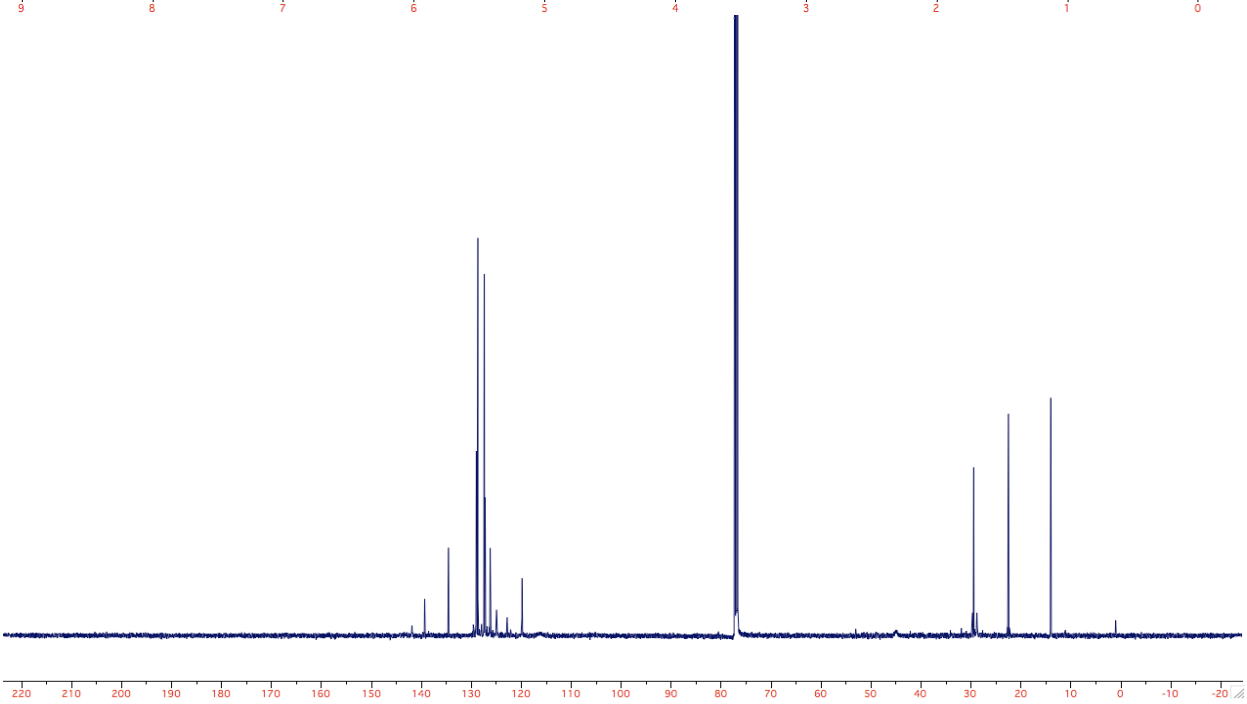




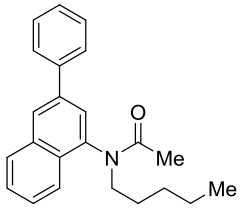
N-pentyl-3-phenylnaphthalen-1-amine (121, R: Pentyl)

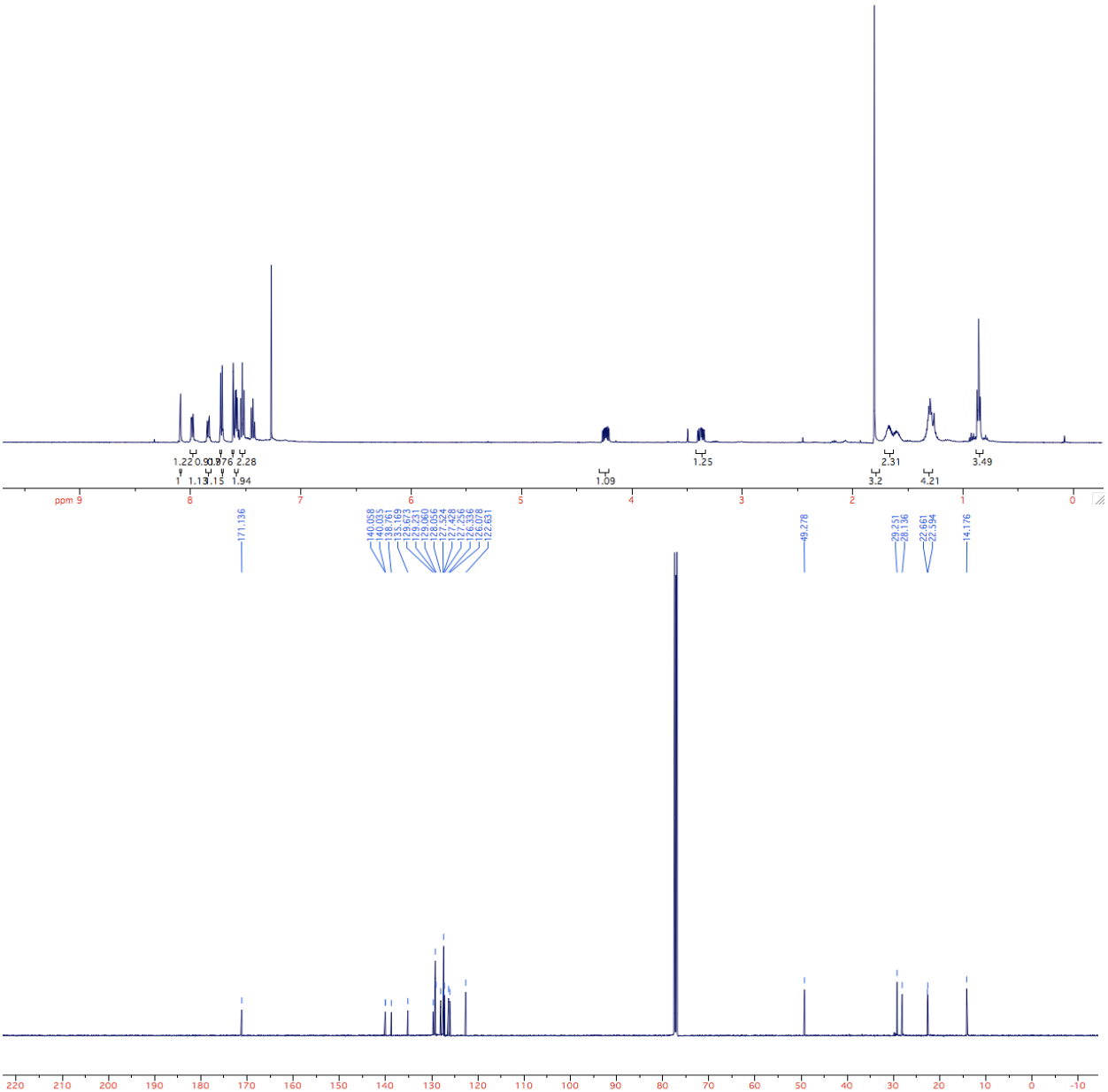




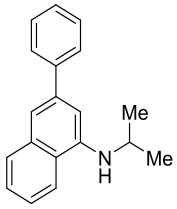


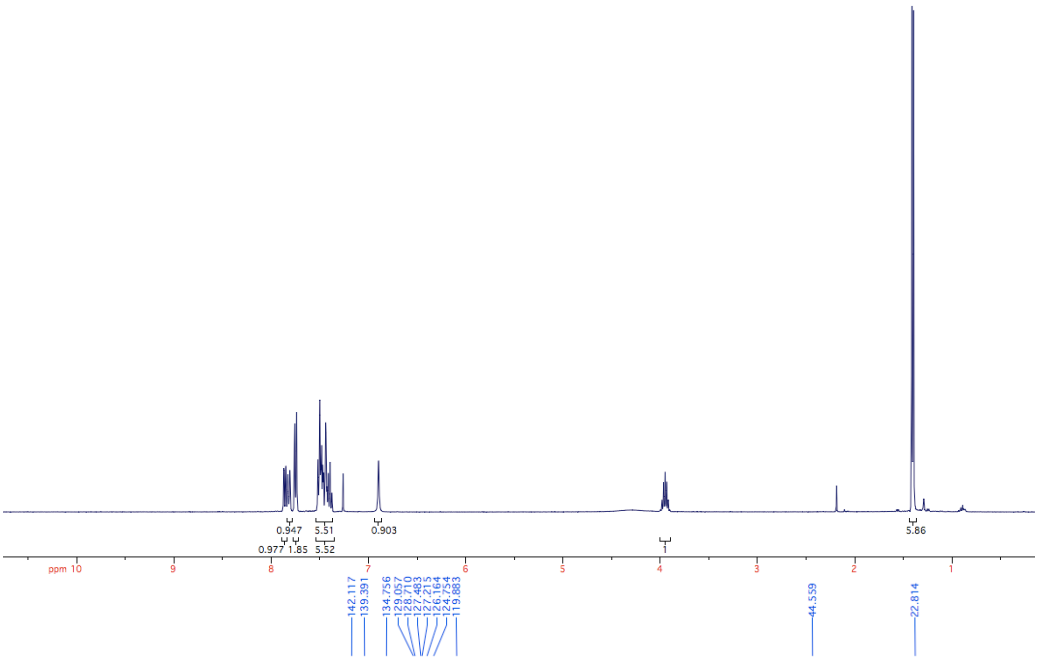
N-pentyl-*N*-(3-phenylnaphthalen-1-yl)acetamide (123, R: Pentyl)

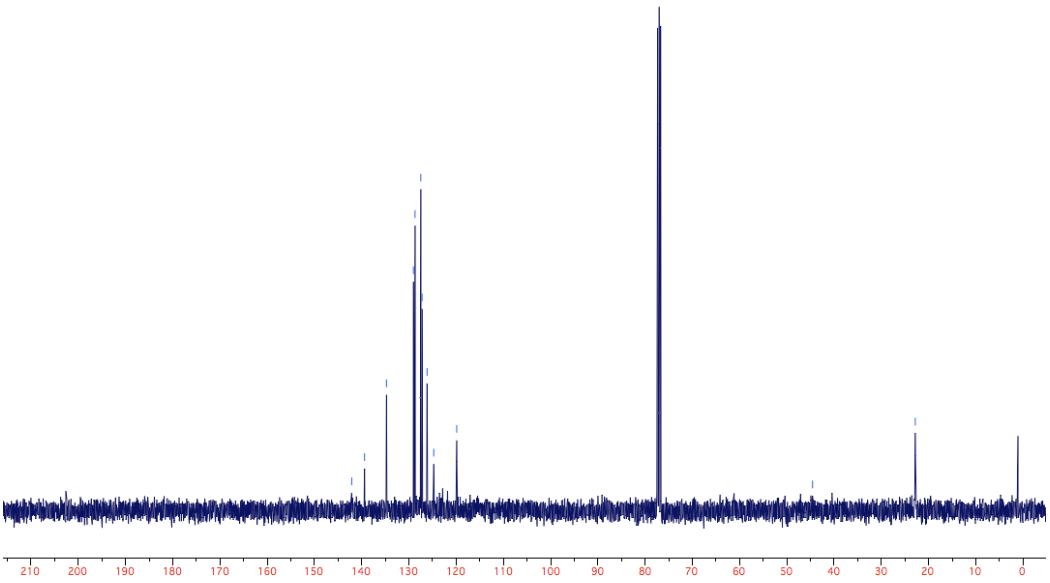




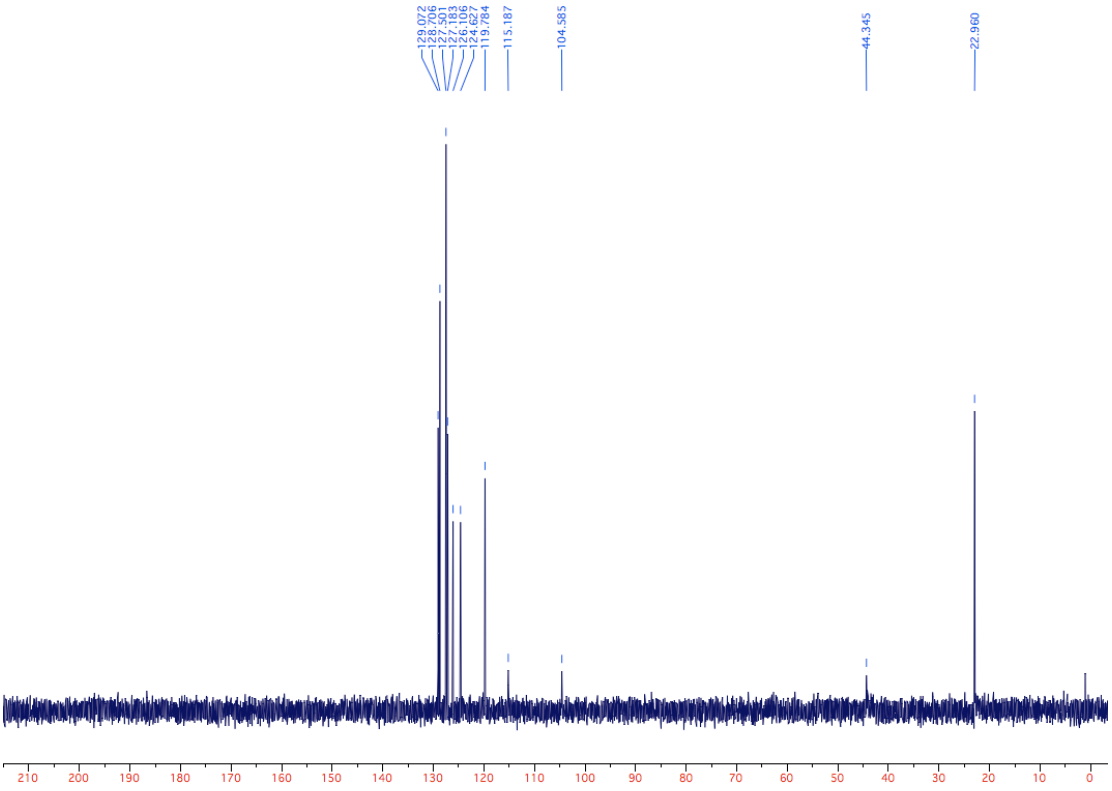
N-Isopropyl-3-phenylnaphthalen-1-amine (121, R: ^{i}Pr)







13C DEPT: **(121, R: Et)**



N-Cyclohexyl-3-phenylnaphthalen-1-amine (121, R: Cy)