Applications of Rhodium-Catalysed Hydroacylation in Heterocycle Synthesis

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Trinity Term 2016

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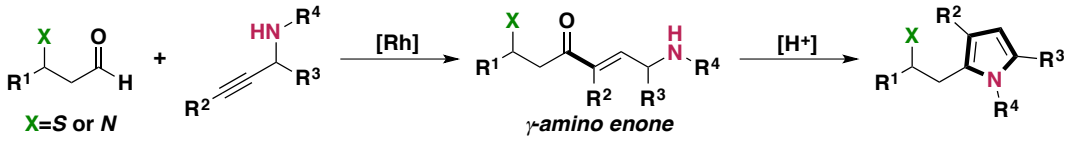
A thesis submitted for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

The work compiled in this thesis documents the development of new methodologies towards the synthesis of a range of *N*-containing heterocycles. These methods utilise intermolecular Rh(I)-catalysed hydroacylation of chelating aldehydes with alkynes and alkenes to install carbonyl groups, which are exploited in subsequent heterocycle forming cascades.

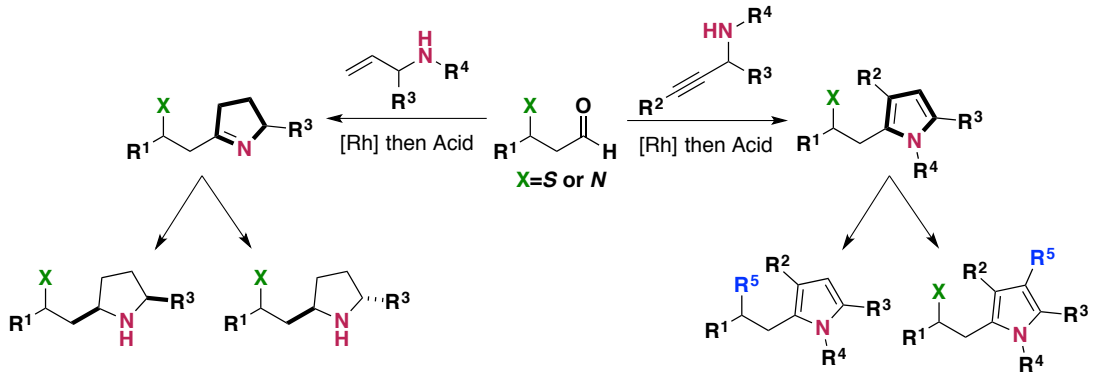
Chapter 1 presents a literature review of the development of both intramolecular and intermolecular rhodium-catalysed hydroacylation, with the focus of different methods to suppress decarbonylation and promote constructive catalysis. A brief description of some precedented examples of hydroacylation in heterocycle synthesis is also included.

Chapter 2 describes the optimisation studies for the hydroacylation of *S*-/*N*-chelating aldehydes with terminal and internal propargylic amines. The studies are largely focussed on achieving high regioselectivity for the linear *γ*-amino enone product. The cyclisation of these *γ*-amino enone adducts to form pyrrole rings is also described.

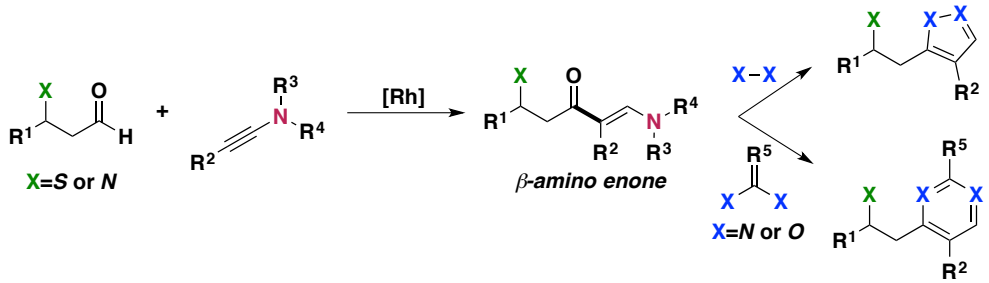


Chapter 3 presents the *de novo* one-pot cascade synthesis of mono-, di- and tri-substituted pyrroles *via* a highly regioselective hydroacylation pathway. The pyrroles are exploited in further modifications to access fully substituted heteroaromatic systems or

in a three-component coupling of aldehydes, propargylic amines and boronic acids or alkynes to access 'traceless' pyrrole rings. The one-pot cascade methodology is extended to the synthesis of dihydropyrroles, through the hydroacylation of allylic amines, which grants access to pyrrolidine rings *via* diastereoselective reductions.



Chapter 4 details the initial investigations towards the development of rhodium-catalysed hydroacylation of ynamides with chelating aldehydes. This provides access to *β*-amino enones in a regioselective manner. These hydroacylation products, which are known to be versatile building blocks, are subsequently exploited in the synthesis of five- and six-membered heterocycles *via bi*-nucleophilic additions.



Chapter 5 discusses the conclusions of the research and the potential for further work.

Chapter 6 compiles the experimental procedures and data.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Manjeet K. Majhail

Trinity term 2016

Acknowledgements

Firstly, I would like to thank Prof. Michael Willis for giving me the opportunity of staying in his group and completing the DPhil. I have gained so much from this experience and for that I am truly grateful. For the support, advice and input over the past four years, thank you.

I must thank all the members of the Willis group, past and present, for the best of times in and out of the lab. Thanks to Joel, Indrek, Milan and James for helping me get started when I moved into F4. In particular, a huge thank you to Maitane, Anaïs and Sarah for your support, friendship, guidance and our girls' nights, which we will continue in more exotic places than the Duke of Cambridge! Sang, thank you for enlightening me about many things, including good hair and skin techniques, but especially for all your help and advice when it was needed. Thanks also to Ming for being a great neighbour in the lab, the Thai food and the gossip. A special thank you to Nate and Tom, who have joined me from the very beginning through this entire journey. The past four years would have been considerably less enjoyable without you both. Nate, thank you for always putting a smile on my face and Tom, thank you for being my constant go-to guy and a great friend. A final thank you to Mike, Maitane, Sang, Tom, Anaïs, Rob, Jimmy, Ming, Alyn, Yiding, Tim and Thomas for the proof reading, and to team Rh for the advice and suggestions throughout this project.

I would also like to acknowledge my friends from Wolfson for making my time in Oxford so enjoyable, and my friends from home for constantly including me even though I was further away; -you guys are the best support system. Gurdip, thank you for always being

there for me no matter what, your support and encouragement is eternally appreciated. As for my parents, I cannot express how grateful I am for their patience, sacrifices and love (and of course their food). This journey would not have been possible without them.

Finally, I would like to dedicate this thesis to my grandad, who came to this country almost 50 years ago, with hopes of providing a better future and education for his children and grandchildren. He is a constant source of love for our family and has always been a huge advocate for me pursuing chemistry. He will be so proud to see me finish this.

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Abbreviations

Ac	acetate
app	apparent
aq.	aqueous
Ar	aryl
b	branched
BAr^F_4	tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate
binap	2,2'-bis(diphenylphophino)-1,1'-binapthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
Bus	*tert*-butylsulfonyl
Bz	benzoate
ºC	degrees Celsius
cat.	catalyst or catalytic
Cbz	carboxybenzyl
cm^{-1}	wavenumber
CM	complex mixture
cod	1,5-cyclooctadiene
coe	*cis*-cyclooctene
conc.	concentration
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl
CyPr	cyclopropyl
d	doublet
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCEPhos	bis(2-dicyclohexylphosphino)phenyl ether
dcpe	1,2-bis(dicyclohexylphosphino)ethane
dcpm	1,1-bis(dicyclohexylphosphino)methane
DEPT	distortionless enhancement by polarisation transfer
dioxane	1,4-dioxane

DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMB	dimethoxylbenzyl
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPEPhos	bis(2-diphenylphosphino)phenyl ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppe(o^iPr)	1,2-bis(diphenyl-*ortho*-isopropylphosphino)ethane
dppf	1,1'-bis(diphosphino)ferrocene
dppm	1,1-bis(diphenylphosphino)methane
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FI	field ionisation
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
G-H-II	Grubbs-Hoveyda II
h	hour(s)
hr	hour(s)
h^{-1}	per hour
$[H^+]$	acid
Het	heterocycle
Hex	hexyl
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
IR	infrared
J	coupling constant

l	linear
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet or meter
m	*meta*
M	molar
[M]	metal
Me	methyl
mg	milligram(s)
min	minute(s)
mol	moles
mol. sieves	molecular sieves
mp	melting point
Ms	mesylate
MTM	methyl thiomethyl
μW	microwave
n	normal (unless otherwise stated)
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nuc	nucleophile
o	*ortho*
p	*para*
P	phosphine ligand
P*	enantiomerically pure phosphine ligand
PCP(^{i}Pr)	1,1-bis(diisopropylphosphino)methane
P(^{t}Bu)CP(Cy)	di-*tert*-butyl[(dicyclohexylphosphanyl)methyl]phosphane
PCP(^{t}Bu)	1,1-bis(di-*tert*-butylphosphino)methane
Pent	pentyl
PG	protecting group
Ph	phenyl
PNP(Cy)	1,1-dicyclohexyl-*N*-(dicyclohexylphosphanyl)-*N*-methylphosphanamine
PNP(^{i}Pr)	*N*-(diisopropylphosphanyl)-1,1-diisopropyl-*N*-methylphosphanamine

ppm	parts per million
Pr	propyl
p-TSA	*para*-toluenesulfonic acid
q	quartet
quant.	quantitative
R	generic group/substituent
rt	room temperature
s	singlet
sat.	saturated
sec	second(s)
sec	secondary
SM	starting material
S_N	nucleophilic substitution
t	triplet
t	tertiary
TBS	*tert*-butyldimethylsilyl
TCE	trichloroethane
temp.	temperature
tert	tertiary
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet
X	heteroatom (unless otherwise stated)
δ	chemical shift
η	hapticity
μ	micro
ν_{max}	frequency
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

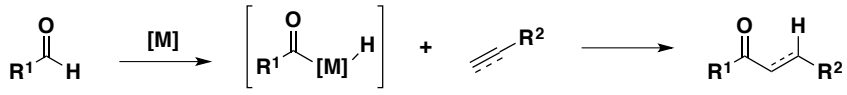
Chapter 1

Introduction

1.1 Hydroacylation: General Overview

Given the abundance of C-H bonds in organic compounds, it is unsurprising that synthetic chemists have been interested in functionalising a variety of C-H bonds for some time now.[1-3] The appeal of C-H functionalisation is particularly significant within organometallic chemistry, as the formation of new C-C bonds *via* C-H activation can be facilitated by low catalyst loadings and mild reaction conditions.[4-17]

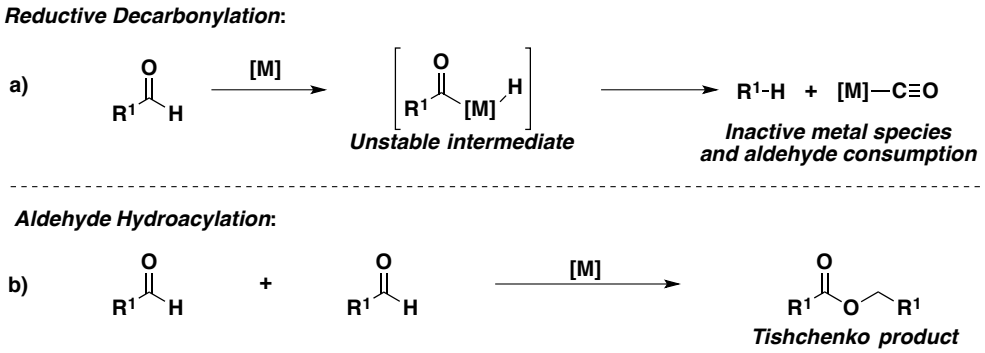
One such type of C-H functionalisation, which has emerged as a useful synthetic tool for the formation of ketones and enones over the past four decades, is hydroacylation.[18-22] This reaction typically involves the transition metal-catalysed addition of the C-H bond of an aldehyde across an unsaturated C-C bond, usually an alkene or an alkyne, in an inherently atom-economical manner (Scheme 1.1).[23]



Scheme 1.1: General outline of a typical hydroacylation reaction.

The potential of hydroacylation is illustrated by the number of possible combinations (almost 1 million) of commercially available aldehydes, alkenes and alkynes to form versitile carbonyl containing compounds.[24] However, this is currently not attainable due

to either deactivation of the catalyst or consumption of starting material *via* deleterious side-reactions (Scheme 1.2). The most prominent of these is reductive decarbonylation; the result of an unstable acylmetal hydride intermediate (Scheme 1.2 a).[18-20] Additional side-reactions can involve coupling of the aldehyde substrate with itself in a Tishchenko reaction (Scheme 1.2 b) or the polymerisation of the alkene or alkyne substrates resulting in a variety of oligomeric by-products.[19,25,26]



Scheme 1.2: Reductive decarbonylation and aldehyde hydroacylation pathways.

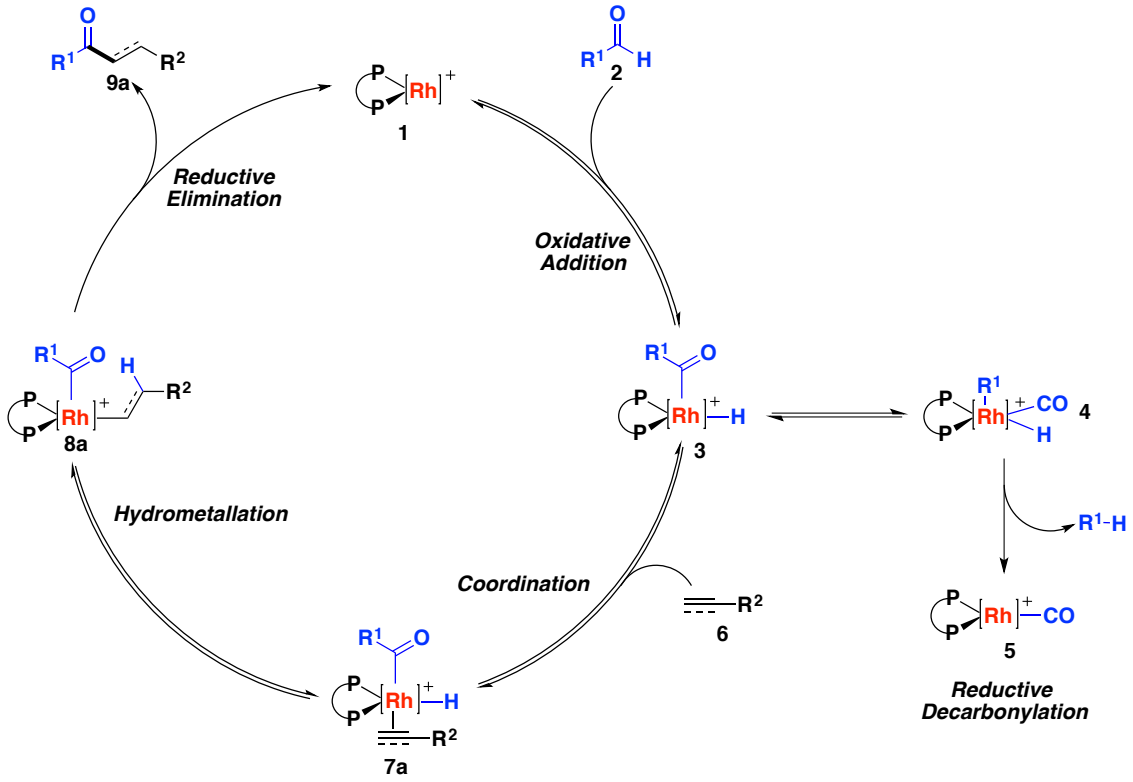
Avoiding the largest challenge facing hydroacylation *i.e.* reductive decarbonylation, has attracted a great deal of attention. Despite recent advances in the field including non-transition metal-catalysed hydroacylation, such as the use of *N*-heterocyclic carbene (NHC) catalysts [27-31] and photocatalysts,[32-34] the majority of investigations have involved the use of transition metals, such as ruthenium,[35-39] cobalt,[40-43] nickel,[44-47] iridium,[48,49] and gold.[50] However, rhodium is by far the most studied and the most relevant to this work, hence only rhodium-based systems will be discussed in this chapter.

1.2 The Mechanism of Rhodium-Catalysed Hydroacylation

Extensive mechanistic studies have been carried out on a variety of different rhodium-catalysed hydroacylation reactions. Early deuterium-labelling experiments on intramolecular alkene hydroacylation were conducted by Miller,[51,52] which were

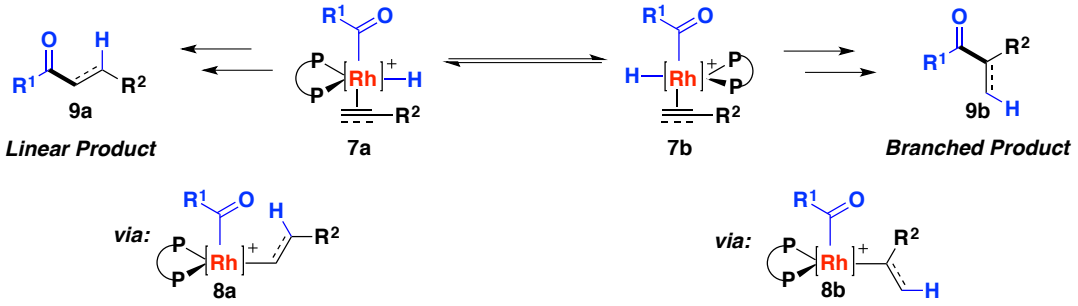
followed up by comprehensive NMR spectroscopy studies by Bosnich.[53] These studies proposed the presence of a key acylrhodium hydride intermediate during the Rh(I)/Rh(III) catalytic cycle. Computational studies, primarily conducted by Morehead and Sargent,[54] have also aided this proposal by calculating the mechanism, as well as the impact of coordinating solvents on the pathway of hydroacylation *versus* decarbonylation. Numerous others also followed up with supportive computational evidence for the intermolecular hydroacylation of alkenes and alkynes.[55,56] Further mechanistic insights into Rh(I) catalysis were supplied by Brookhart, who confirmed that the rate limiting step was reductive elimination, with kinetic and spectroscopic verification for a particular intermolecular alkene hydroacylation.[57] This was supported by more recent studies from Weller and Willis centred around *S*-chelation controlled hydroacylation.[58-61] This latter work involved isolating key intermediates on or close to the generally accepted catalytic cycle for hydroacylation. Taking all the studies into account a general catalytic cycle has been established (Scheme 1.3).

Firstly, the oxidative addition of metal catalyst **1** into the C-H bond of aldehyde **2** occurs, resulting in formation of the key acylmetal hydride intermediate **3**. Due to the presence of a *cis*-vacant site at the metal centre, carbonyl extrusion can occur to generate species **4**, which can either return to the hydroacylation cycle or undergo irreversible reductive elimination to form the inactive metal carbonyl complex **5** *via* the decarbonylation pathway. However, if acylmetal hydride **3** undergoes complexation with unsaturated coupling partner **6**, it can produce species **7a**. Hydrometallation followed by reductive elimination of intermediate **8a** furnishes the desired carbonyl containing product **9a**. Mechanistic studies have shown that this final reductive elimination step is irreversible, while all other steps in the catalytic cycle can be reversible.



Scheme 1.3: A generally accepted mechanism for rhodium-catalysed hydroacylation.

Hydride insertion during hydrometallation is pivotal in controlling regioselectivity of the reaction, as both 'linear' **9a** and 'branched' **9b** enones or ketones can be observed (Scheme 1.4). Recent deuterium-labelling studies, employing *O*-chelation controlled alkene hydroacylation by the Dong group, proposed that hydride insertion for the linear product was a largely irreversible process, whereas hydrometallation in favour of the branched product was fully reversible.[62] Moreover, the Willis and Weller groups have confirmed that the hydrometallation process for *S*-chelation controlled alkene and alkyne hydroacylation is more inclined to yield the linear product. The formation of the branched isomer is typically unfavourable due to an increased energy barrier for the construction of this adduct and a slower rate of reductive elimination.[61]



Scheme 1.4: Regioselectivity during hydrometallation.

The general mechanism presented in Scheme 1.3 highlights the instability of the key intermediate in the catalytic cycle – complex **3**. While the vacant site on the acylmetal hydride intermediate is essential for product formation, it also facilitates deactivation of the catalyst. Therefore, much of the research within hydroacylation chemistry describes efforts to tune the availability of this vacant site.

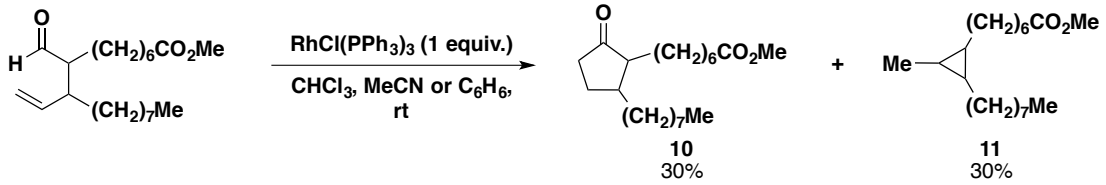
1.3 Intramolecular Hydroacylation

It is understood that one way to stabilise an acylmetal hydride complex, which is required to perform a successful hydroacylation reaction, is to proceed *via* a metallacyclic intermediate.[18] In addition to forming a stable metallacycle, intramolecular hydroacylation also forces proximity of the aldehyde C-H bond to the metal-centre due to the chelating olefin, essentially directing C-H activation. Therefore, it is of no surprise that seminal reports of hydroacylation described an intramolecular reaction in the synthesis of five-membered ring systems.

1.3.1 Early Hydroacylation: Cyclopentanone Synthesis

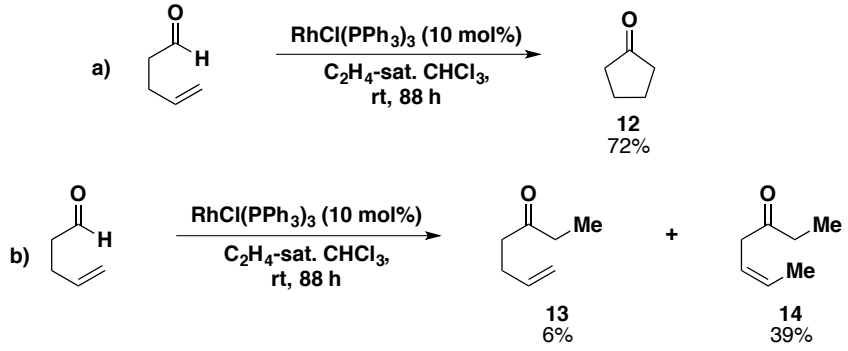
The first reported example of hydroacylation by Sakai in 1972 was performed using stoichiometric amounts of Wilkinson's complex[63] to catalyse the intramolecular

cyclisation of 4-enals (Scheme 1.5).[64] These conditions delivered equal amounts of both cyclopentanone **10**, *i.e.* the hydroacylation product, and cyclopropane **11**; a side-product derived from the decarbonylation pathway and known to be facilitated by rhodium.[65-67] This initial result displayed how challenging overcoming reductive decarbonylation would be. Thus, the majority of early investigations into hydroacylation were focused on this type of cyclopentanone synthesis.



Scheme 1.5: The first reported example of rhodium-catalysed intramolecular hydroacylation.

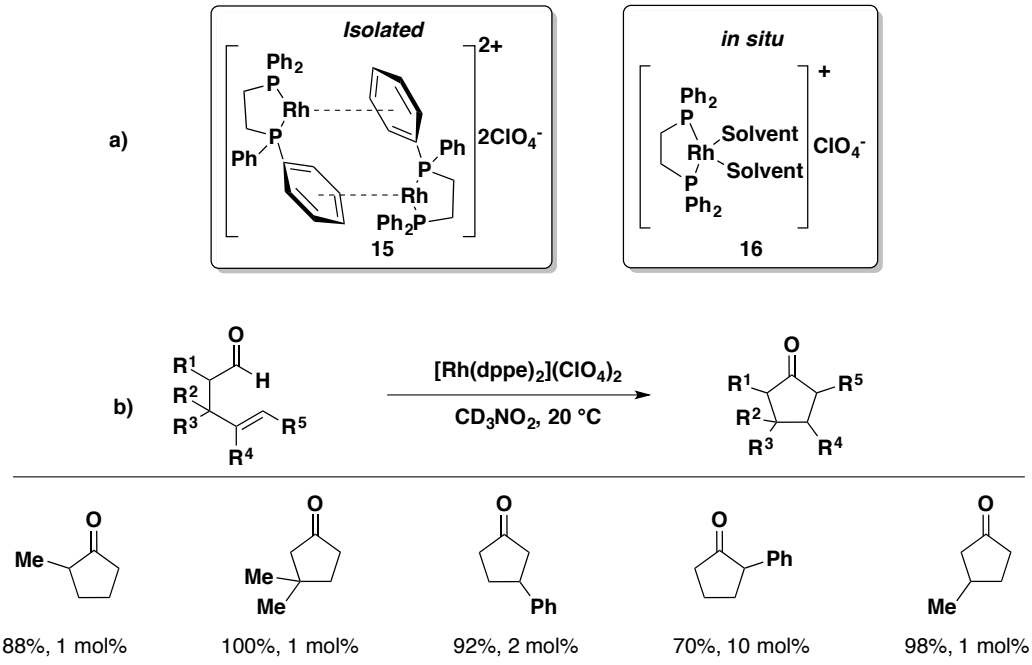
Soon after, the first report employing a sub-stoichiometric amount of rhodium was described by Miller and co-workers, who suppressed decarbonylation by saturating the metal centre with an ethylene based solvent (Scheme 1.6 a).[68] This technique achieved a 72% yield of desired cyclopentanone **12** by using only 10 mol% of Wilkinson's catalyst. This report also highlighted the first signs of intermolecular hydroacylation as compound **13** (Scheme 1.6 b), the hydroacylation product of ethylene and pentenal, and product **14**, which is the isomerised hydroacylation product, were isolated in low yields. [51]



Scheme 1.6: Miller's work with sub-stoichiometric Wilkinson's catalyst.

Extensive optimisation of Wilkinson-type complexes by Larock in 1980 delivered a wider scope of cyclopentanones by using a variety of different mono-phosphine ligands.

However, the requisite catalyst loadings were high (50 mol%) and the use of ethylene saturated solvents remained fundamental.[69] The real turning-point for this cyclisation came eight years later with the development of cationic rhodium complexes, pioneered by Bosnich.[53] Investigations were centred around exploiting *bi*-dentate phosphine ligands with a cationic rhodium metal-centre. [Rh(dppe)]ClO_4 was identified as the optimal catalyst for this intramolecular cyclisation (Scheme 1.7 b). The complex could be used as the isolated dimer **15** or *in situ* as the solvated complex **16** (Scheme 1.7 a). The use of these new rhodium(I) complexes allowed Bosnich to describe an effective intramolecular hydroacylation, which furnished 2-, 3-, 4- and 5-substituted cyclopentanones in good yields, with dependably low catalyst loadings (usually 1 mol%) and no significant observations of decarbonylation (Scheme 1.7 b).



Scheme 1.7: a) Catalytically relevant species of [Rh(dppe)]ClO_4. b) Bosnich's intramolecular hydroacylation.

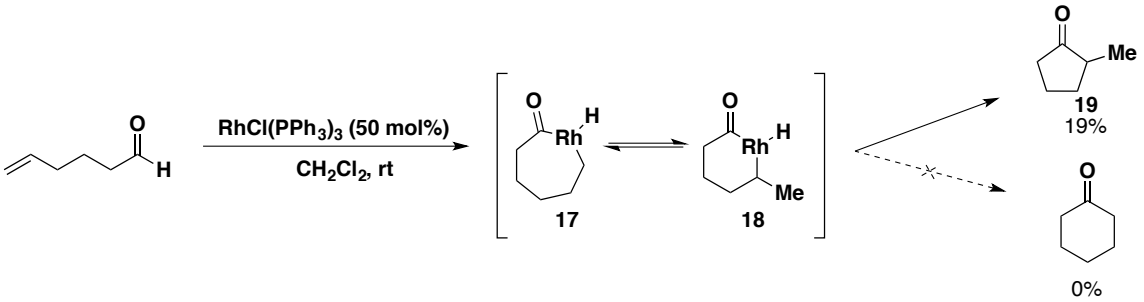
Cationic rhodium complexes were undoubtedly the most active and popular catalysts for intramolecular hydroacylation. Many examples of their use in analogous hydroacylation reactions have been described, as well as examples by Fu and Tanaka expanding the

substrate scope from alkene-containing aldehydes to alkyne-containing starting materials (4- and 5-alkynals).[70,71]

1.3.2 Larger Ring Synthesis

The synthesis of five-membered rings *via* hydroacylation has been very well investigated. More recently, the formation of larger ring systems has received a lot of interest within synthetic chemistry and accordingly, accessing larger rings by hydroacylation was pursued.

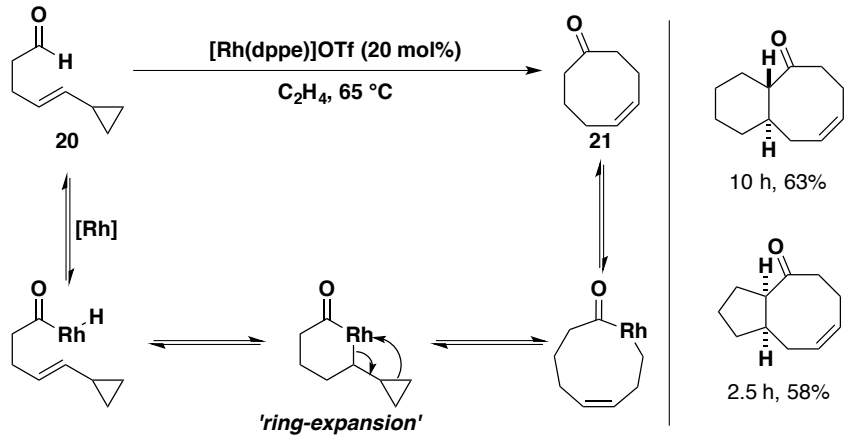
Using hydroacylation to form ring systems larger than cyclopentanone has not been a straightforward task and this was proven by Miller and co-workers.[68] Their investigations revealed that larger ring acylrhodium hydride intermediates, such as **17** (Scheme 1.8), would isomerise to a more favourable ring size, such as a six-membered rhodacycle **18**, to deliver cyclopentanone **19** as the major product. This can be attributed to the potential rapid isomerisation of **17** to a more stable complex, **18**, which outcompetes the slower reductive elimination of metallacycle **17**.



Scheme 1.8: Preferential formation of five-membered rings.

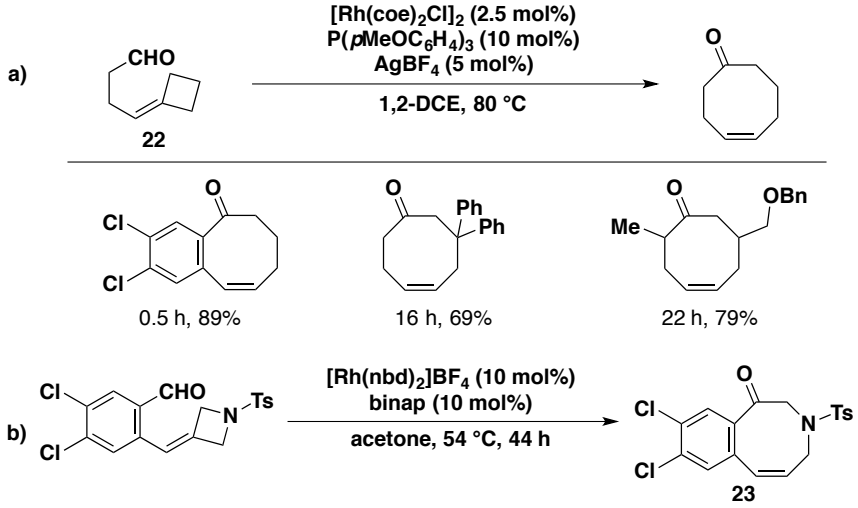
The strategies used to avoid the formation of cyclopentanones involved additional functionality on the enal starting material. Twelve years after the dissemination of Bosnich's catalyst, the Shair group published the synthesis of eight-membered rings by incorporating a cyclopropane into the enal substrate **20** (Scheme 1.9). This strained ring system was used to promote ring expansion of the rhodium acyl intermediate during

hydroacylation to enable the formation of cyclooctenones, such as **21**.[72] It was noted that the use of a cationic rhodium species in this type of cyclisation was superior to Wilkinson's catalyst however, decarbonylation was still attenuated through the use of ethylene saturated solvents.



Scheme 1.9: Intramolecular hydroacylation of vinyl cyclopropanes.

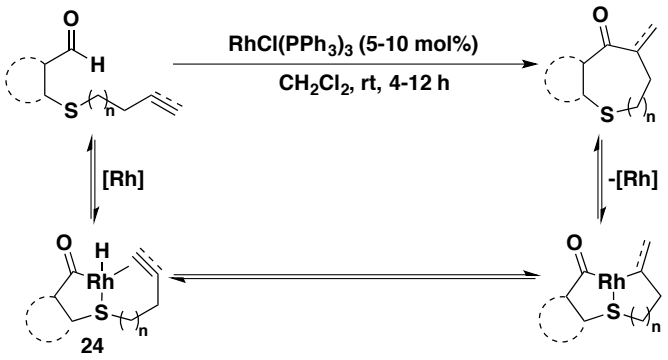
More recently, Aïssa and co-workers used a similar technique with cationic rhodium complexes (Scheme 1.10 a), but this time with cyclobutane based starting materials **22**. This protocol also alleviated the need for ethylene saturated solvent and achieved excellent yields of the desired eight-membered rings.[73]



Scheme 1.10: Intramolecular hydroacylation of cyclobutane containing aldehydes.

In addition, it was also possible to introduce a heteroatom into cyclooctenone **23** (Scheme 1.10 b). While this method was efficient, the substrate scope was limited as the synthesis of starting materials was not straightforward.

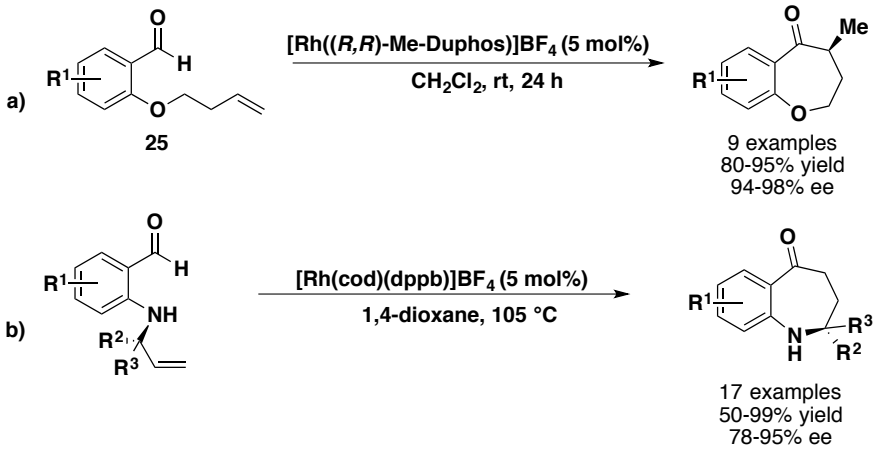
Since then, an alternative strategy has been employed to access larger ring systems; heteroatom chelation. Bendorf incorporated sulfur into a long chain enal (Scheme 1.11), inhibiting reductive decarbonylation by stabalising large ring intermediate **24** through chelation. Good yields were achieved in the synthesis of seven- and eight-membered rings with this methodology, employing Wilkinson's catalyst (5-10 mol%) with both alkenes and alkynes.[74]



Scheme 1.11: Mechanism of Bendorf's *S*-chelated intramolecular hydroacylation.

An extension to this reaction was later developed by Dong (Scheme 1.12 a). The group managed to render this cyclisation asymmetric by using ether-linked alkenes **25** and switching to cationic rhodium with a chiral *bis*-phosphine ligand.[75] While all the substrates studied displayed excellent yields and enantioselectivity, the scope was limited to modification of the aryl ring only.

Following this report, Nguyen and co-workers described *N*-chelation in the synthesis of seven-membered cyclic aza-ketones using a cationic rhodium species (Scheme 1.12b). Substrate scope, in this case, was vastly improved and achieved a variety of substitution patterns in excellent yields, without loss of enantiopurity.[76]



Scheme 1.12: a) Dong's *O*-chelating intramolecular hydroacylation. b) Nguyen's *N*-chelating cyclisation.

1.4 Intermolecular Hydroacylation

Intramolecular hydroacylation finds its major limitations in substrate scope and design of suitable starting materials. Nevertheless, extending hydroacylation chemistry to intermolecular systems has proved highly challenging. This is largely down to the decarbonylation pathway presenting itself as a greater hindrance in these types of systems. Hence intermolecular hydroacylation appeared five years after the intramolecular variant. The majority of approaches to overcome the predisposition of aldehydes to undergo decarbonylation invoke some form of substrate chelation.

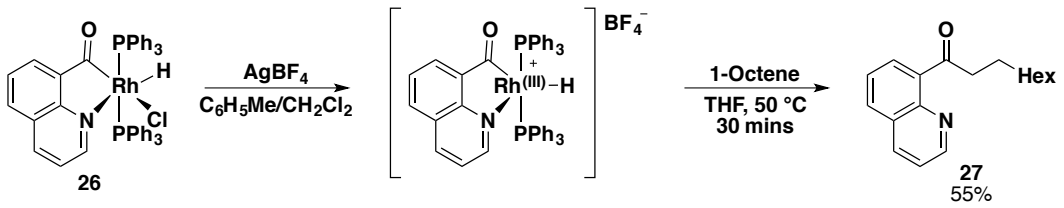
1.4.1 Chelation-Controlled Hydroacylation

Early approaches were analogous to those methods used for intramolecular hydroacylation; saturating the unstable acylmetal intermediate with ethylene. This not only delivered modest yields, but it required the use of high pressure gas or less readily available solvents, which limited the utility of the reaction. Subsequently, the use of heteroatom chelation emerged as an incredibly successful strategy, which has radically improved the field. Chelation tactics have primarily been centred around the inclusion of

heteroatom coordinating motifs on the aldehyde substrate, with a few reports of chelation control arising from the unsaturated coupling partner.

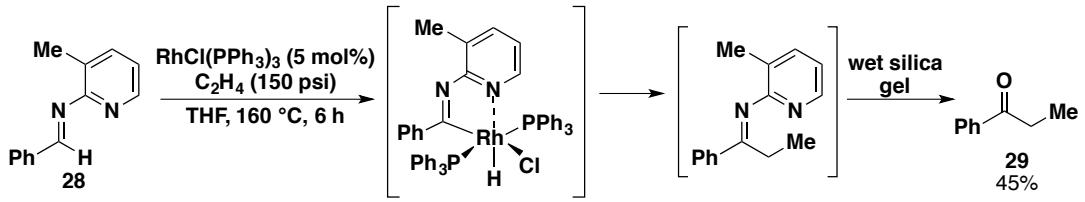
1.4.2 Nitrogen Based Chelation Control

The power of heteroatom chelation was demonstrated by the pioneering work of Suggs and co-workers in 1978, who were able to isolate stabilised acylrhodium complex **26** (Scheme 1.13) by treating 8-quinoline carboxaldehyde with stoichiometric Wilkinson's catalyst.[77,78] Subsequent treatment of complex **26** with silver tetrafluoroborate and 1-octene delivered hydroacylation product **27**. However, attempts to convert this into a catalytic protocol led to reduced yields.



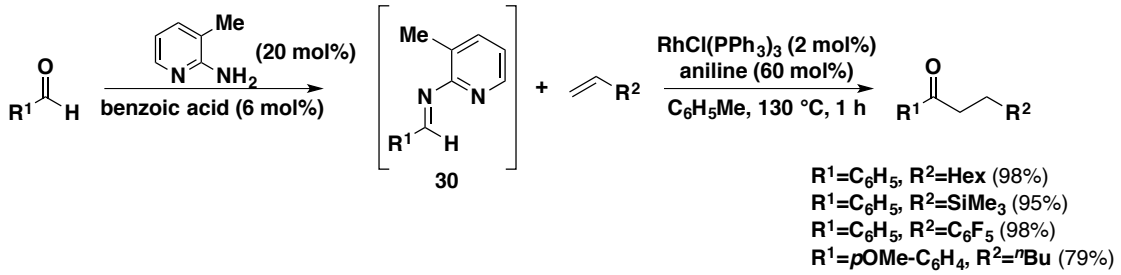
Scheme 1.13: The first example of *N*-chelation controlled hydroacylation by Suggs.

In an attempt to perform catalytic hydroacylation, the Suggs group turned their attention to picolyl imines **28** (Scheme 1.14);[79] a smaller, as well as removable, chelating unit. Unfortunately, this reaction required high pressures of ethylene gas and elevated reaction temperatures. Nevertheless, it could be performed with 5 mol% of catalyst to deliver 'tether-free' or 'traceless' hydroacylation product **29** in a 45% yield.



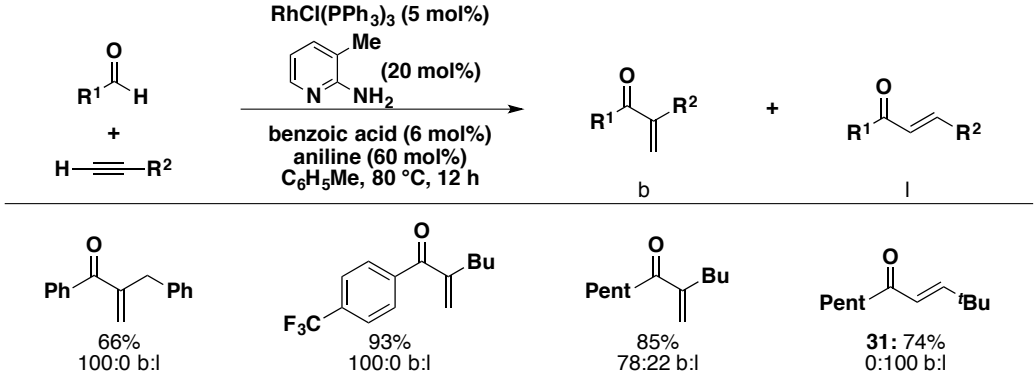
Scheme 1.14: Picolyl imines in chelation controlled intermolecular hydroacylation.

This imine-based methodology was considerably improved in the late 1990s by the Jun group, who described an elegant way to form and remove the chelating imine group *in situ* by combining additives with benzaldehydes and Wilkinson's catalyst (Scheme 1.15).[80] Jun proposed that small amounts of benzoic acid would catalyse the formation of imine intermediate **30**, while the introduction of an aniline would catalyse its hydrolysis. The use of these two additives allowed for a general method with low catalyst loadings and removed the requirement of high ethylene pressures.



Scheme 1.15: Jun's 'tether-free' intermolecular hydroacylation.

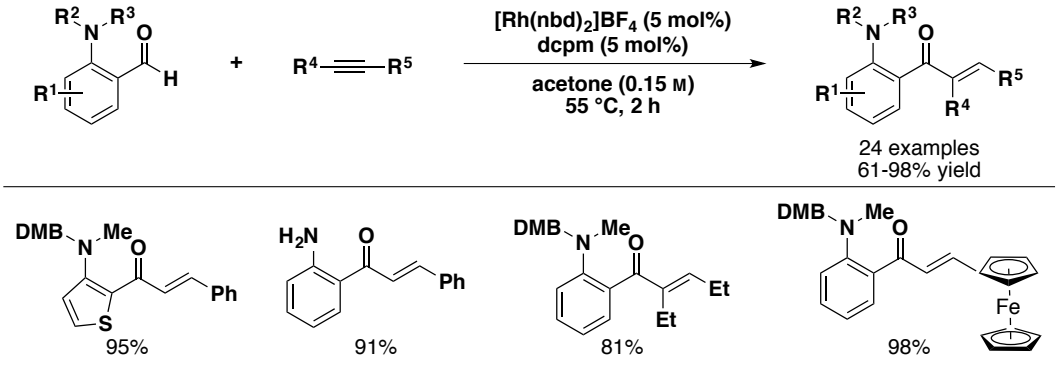
Further developments by this group continued into the early 2000s. The reaction was developed to include the use of alkynes as coupling partners. An extended scope was obtained using relatively low catalyst loadings, which afforded excellent yields (Scheme 1.16).[81-85] Interestingly, the branched regioisomers were the favoured products in the majority of examples studied. Formation of the linear enone was only achievable when using an alkyl aldehyde in combination with an alkyne bearing a sterically demanding substituent **31**.[86]



Scheme 1.16: Alkyne hydroacylation *via* picolyl imine intermediates.

This observation, with regards to regioselectivity, was unique within the literature for *N*-tethered intermolecular hydroacylation, which resulted in further studies by Castillón.[87] The observed regioselectivity was attributed to the relatively small size of PPh_3 in Wilkinson's catalyst. The linear regioisomers could be obtained by using more sterically demanding phosphine ligands. In addition, the requirement of Wilkinson's complex over the generally more reactive $[Rh(phosphine)]^+$ was also peculiar, hence it was investigated by Bo and Castillón. Theoretical studies found that the formation of an acylrhodium intermediate with a neutral rhodium chloride catalyst, through the oxidative addition of an imine C-H bond, is thermodynamically favoured. In comparison, the rhodium acyl intermediate formed from a cationic rhodium complex is unstable, thus preventing the use of such catalysts.[88] Therefore, it was assumed that the success of an *N*-chelating group with a cationic rhodium complex compelled moving away from imine hydroacylation. The first reported example was by Stremmler and Bolm, ten years after the use of imine chelation. The authors presented a single example of a hydroacylation coupling, using a cationic rhodium complex, of a simple aniline aldehyde with the strained and highly-reactive norbornene.[89]

However, more recently, the Willis group have reported the use of *ortho*-amino aldehydes as excellent coupling partners for unactivated alkynes in hydroacylation (Scheme 1.17), using a commercially available *bis*-phosphine ligand in low catalyst loadings.[90]

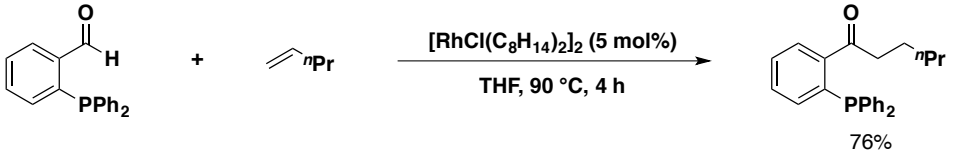


Scheme 1.17: *Ortho*-amino benzaldehyde hydroacylation by Willis and co-workers.

The reaction displayed high regiocontrol and good-to-excellent yields for a range of aldehydes and alkynes, including unprotected amines as the directing group, heteroatom substituents and internal alkynes. Interestingly, the authors also noted that catalyst loadings could be decreased to 2 mol% with the use of an acetonitrile additive (10 mol%).

1.4.3 Phosphorous in Chelation Control

Jun briefly investigated nitrogen's pentavalent congener, phosphorous, as a potential chelating group.[91] A system using diphenyl phosphine as the coordinating unit was developed (Scheme 1.18).

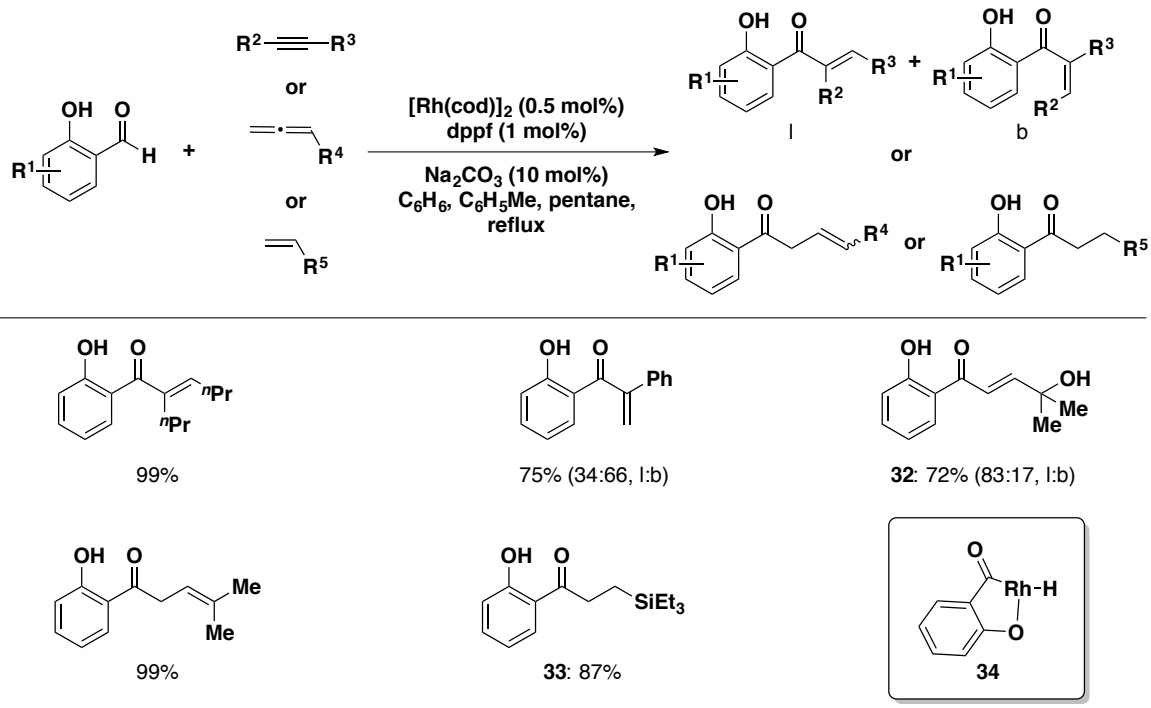


Scheme 1.18: Phosphorous chelation control in intermolecular hydroacylation.

However, since products containing a phosphine group have not been the subject of significant synthetic demand, the interest of this procedure was limited.

1.4.4 Oxygen Based Directing Groups

Phenolic derivatives are valuable precursors in synthetic chemistry, therefore the incorporation of an oxygen group as a coordinating motif would be beneficial. In this sense, salicylaldehydes present themselves as archetypal substrates for hydroacylation as they are readily available with the potential chelating group pre-installed. Despite this, oxygen based chelation has not been as widely used as expected due to a series of initial reports describing a lack of regiocontrol. The first report was described by the Miura group, who demonstrated the coupling of salicylaldehydes with alkynes, allenes and alkenes (Scheme 1.19).[92,93]

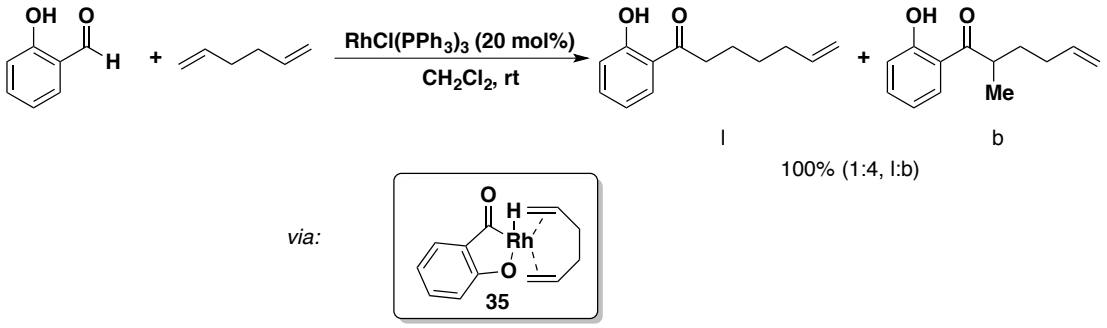


Scheme 1.19: Miura's work with salicylaldehydes.

Miura employed low loadings of a neutral rhodium catalyst, with a ferrocene based *bis*-phosphine ligand, in the presence of sub-stoichiometric base, which the authors believed deprotonated the alcohol to promote its chelating ability **34**. Alkynes proved to be reactive coupling partners, yet regioselectivity proved difficult to control. The use of terminal alkynes delivered the branched enones with moderate regiocontrol, and in order to access the linear enones propargylic alcohols had to be employed **32**. Salicylaldehydes could be readily coupled with allene substrates although this was not the case for alkenes, as they were largely unreactive. Norbornene only yielded 6% of the product and the one successful example was with a triethylsilane substituted alkene **33**. Overall the catalyst system was active in hydroacylation and salicylaldehdyes were able to circumvent any decarbonylation, with the major difficulty being the lack of control.

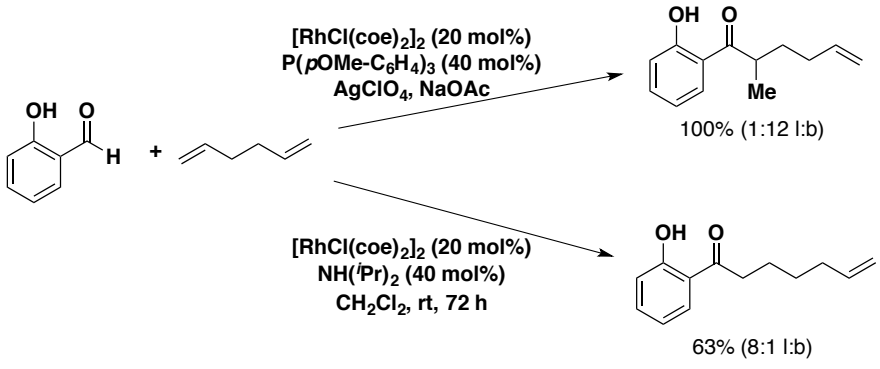
Soon after, further work with these aldehydes was undertaken by the Suemune group. They described the coupling of salicylaldehdyes with 1,4- and 1,5-dienes under ambient reaction conditions (Scheme 1.20), which was achievable through the use of Wilkinson's

catalyst.[94,95] In this report, the first use of chelating unsaturated coupling partners, in combination with chelating aldehydes, was proposed. This approach involved the chelation of both the heteroatom present in the aldehyde substrate, as well as an extra chelating group present on the alkene coupling partner, such as in complex **35**. This technique was initially employed with Wilkinson's catalyst.



Scheme 1.20: Hydroacylation of salicylaldehydes and dienes.

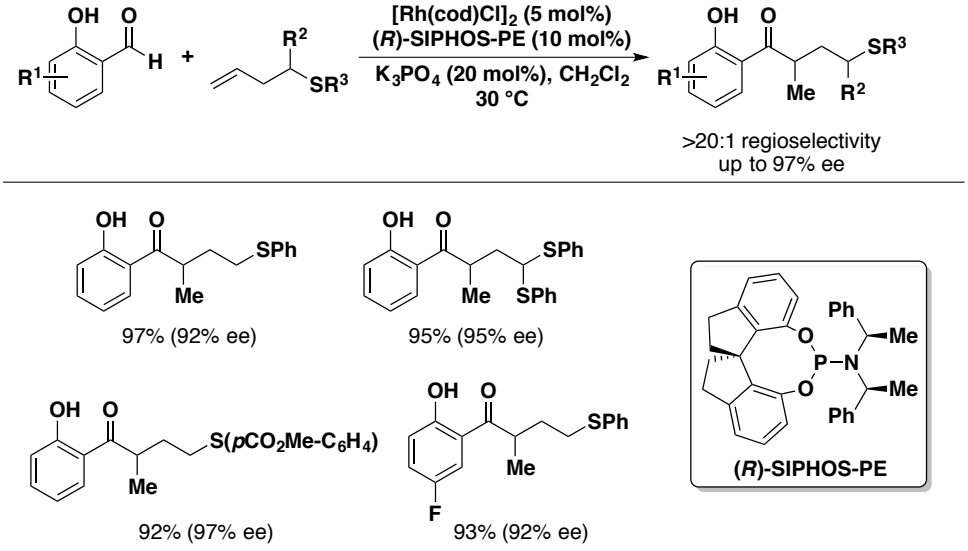
Sadly, regiocontrol remained an issue with the majority of diene substrates investigated and required improvement. In this regard, Suemune carried out a screen of catalytic systems to enable the formation of either regioisomer selectively (Scheme 1.21). The group found that the use of a different rhodium source, together with additives, was able to provide a good handle on regiocontrol, particularly for the branched isomer.[95]



Scheme 1.21: Suemune's regiocontrolled hydroacylation using *O*-chelation.

Dong has since developed this idea of chelation control arising from both starting materials. The authors still employed salicylaldehydes, but replaced the second double

bond on the olefin coupling partner, used for chelation by Suemune, with a heteroatom, namely sulfur or oxygen. In the case of homoallylic sulfides as hydroacylation coupling partners, the Dong group proposed that the strongly coordinating heteroatom on the alkene would be able to direct regioselectivity more efficiently than a secondary π-bond (Scheme 1.22).[96]

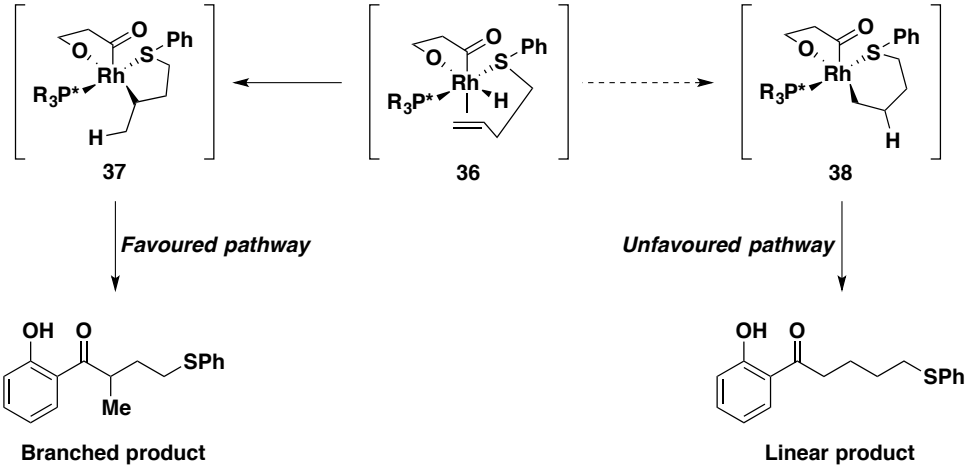


Scheme 1.22: Intermolecular enantioselective hydroacylation of homoallylic sulfides.

The study showed that sulfur aided in delivering a branched-selective intermolecular hydroacylation, and in doing so created a stereogenic centre. With the use of a suitable monodentate phosphoramidite ligand, and a neutral rhodium source, the reaction exhibited good enantiocontrol, albeit with limited scope at the α-branched position.

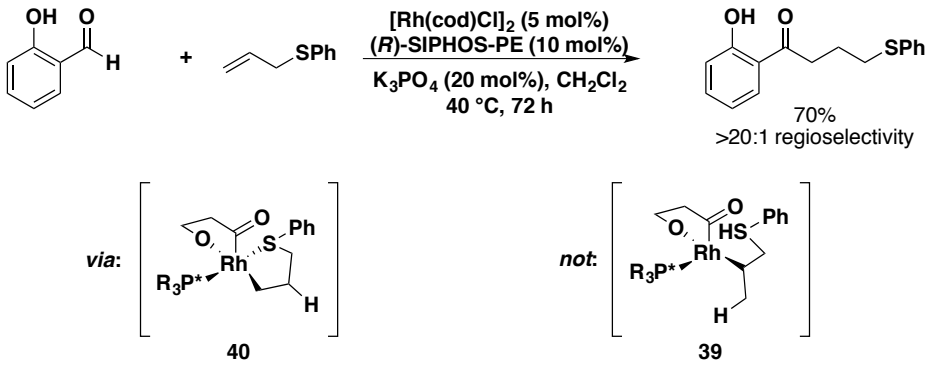
This report also provided mechanistic insight into the use of both chelating aldehydes and chelating alkenes on regioselectivity (Scheme 1.23). The authors proposed that coordination sites on the Rh(III) hydride can be occupied by two chelating substrates to form **36**. The monodentate ligands used in this study were accredited to promoting the formation of **36** as they presumably aided in accommodating the high degree of coordination required at the metal centre. Complex **36** was postulated go on to form a five- (species **37**) or six-membered (species **38**) chelate after hydrometallation. As hydride intermediates preferentially undergo hydroacylation *via* five-membered

rhodacycles, over four- or six-membered rings, the formation of the branched product would be favoured in this case.



Scheme 1.23: Proposed rationale for regioselectivity when employing chelating aldehydes and alkenes.

This theory was also proven by switching substrate to allylic sulfides (Scheme 1.24), which would require a four-membered metallacycle to produce the branched product **39** and a five-membered metallacycle to form the linear **40**; allylic sulfides selectively formed the linear ketone as expected. Using this information, the Dong group subsequently advanced this methodology to encompass allylic alcohols as coupling partners.[97]

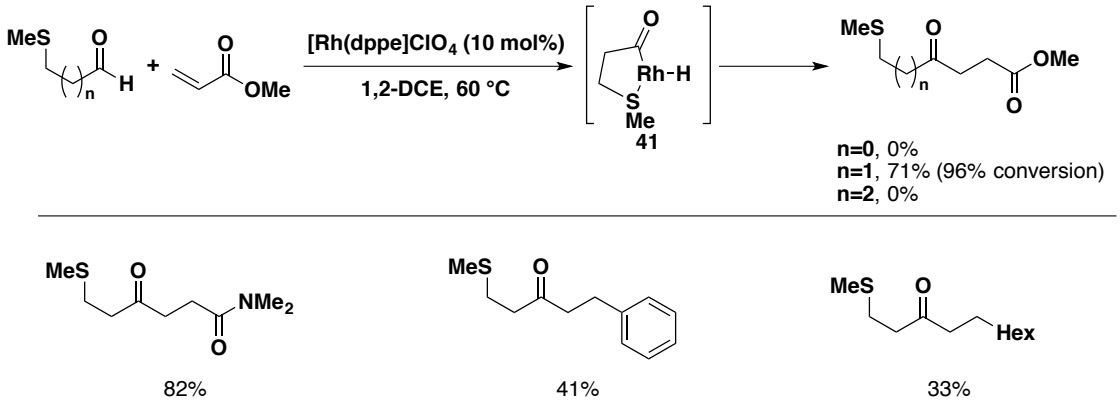


Scheme 1.24: Allylic sulfides in linear-selective hydroacylation.

1.4.5 Sulfur Based Chelation Control

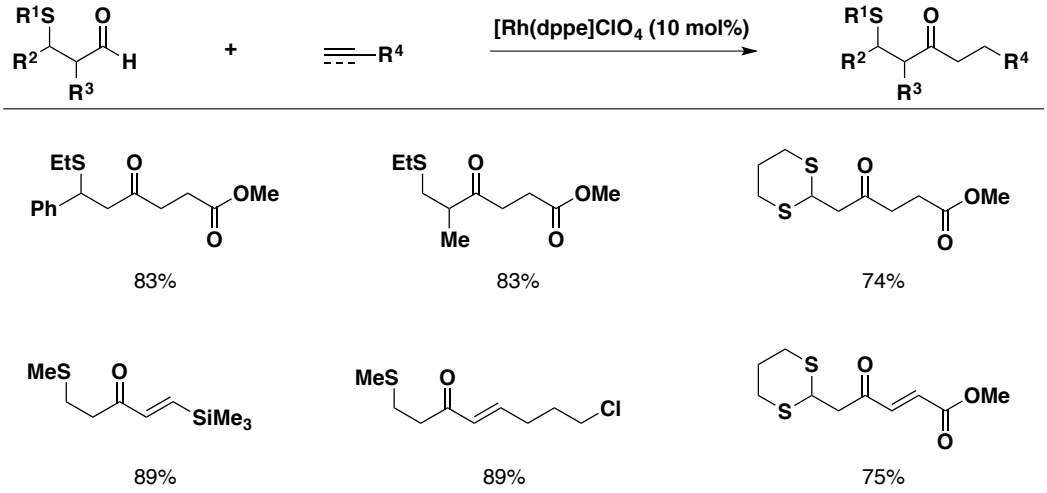
As was mentioned previously, sulfur was described as an effective chelating heteroatom within intramolecular hydroacylation (Scheme 1.11). Since, the Willis group has pioneered the use of sulfur chelation within the field of intermolecular hydroacylation chemistry and considerably driven the reaction forward by continually developing catalysts, in collaboration with the Weller group. Willis has made extensive use of Bosnich-type, cationic rhodium *bis*-phosphine complexes with a range of sulfur coordinating motifs and a variety of aldehydes, alkenes, alkynes and allenes.

In the initial report in 2004, Willis and co-workers employed [Rh(dppe)]ClO_4 and determined that the position of sulfur β-to the aldehyde was imperative (Scheme 1.25). Provided that a β-sulfur aldehyde was used, a range of electron deficient alkenes could successfully undergo hydroacylation.[98] The authors attributed this reactivity to five-membered *S*-containing chelate **41**, which gave rise to a stable hydride intermediate. However, the use of unactivated alkenes, such as 1-octene, delivered diminished yields.



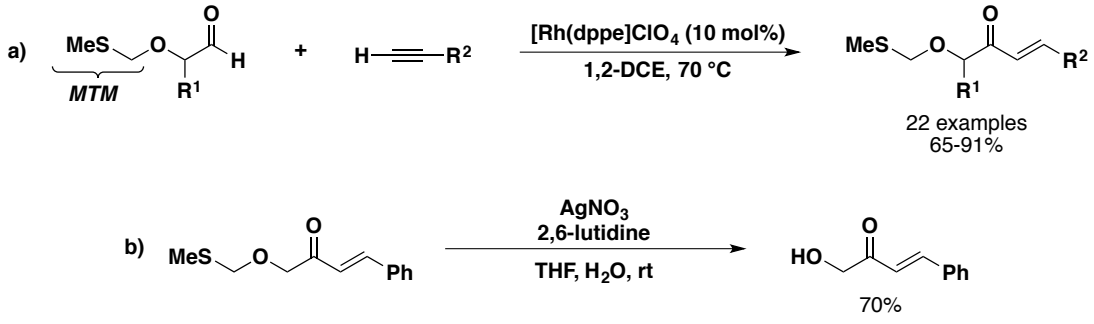
Scheme 1.25: Willis' sulfur tethered hydroacylation of alkenes.

Using the same catalytic system, the methodology could be expanded to a range of substrates, such as α- and β-branched aldehydes,[99] in addition to terminal alkynes, in the presence of hydroxyl, silyl and halogen groups (Scheme 1.26).[100]



Scheme 1.26: Substrate scope of Bosnich's catalyst in sulfur chelated intermolecular hydroacylation.

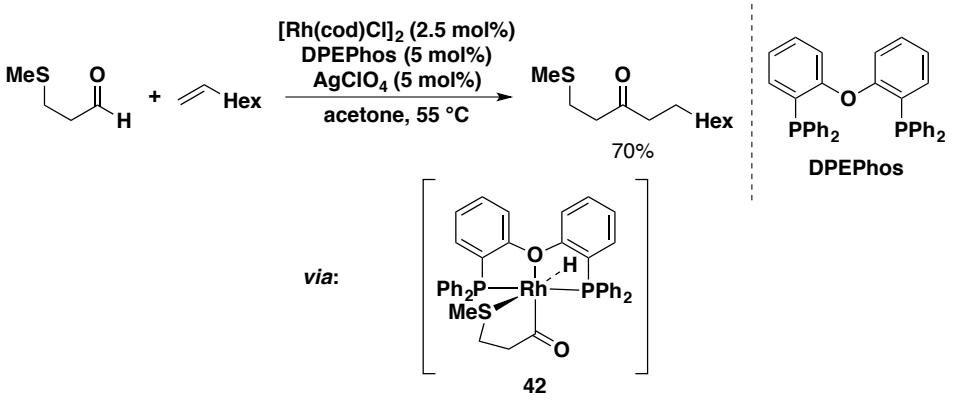
Willis and co-workers have additionally utilised the methylthiomethyl (MTM) group as a chelating unit (Scheme 1.27). The authors described MTM ethers performing as successful chelating groups in the combination of aldehydes and terminal alkynes in excellent yields, with branching at the α-position to the carbonyl also compatible (Scheme 1.27 a).[101] It is an easily removable group that would increase synthetic utility of hydroacylation reactions (Scheme 1.27 b). However, the tether did display lower reactivity in comparison to the β-sulfur aldehydes with a few substrates, such as alkenes and internal alkynes.



Scheme 1.27: The use of MTM ethers in hydroacylation.

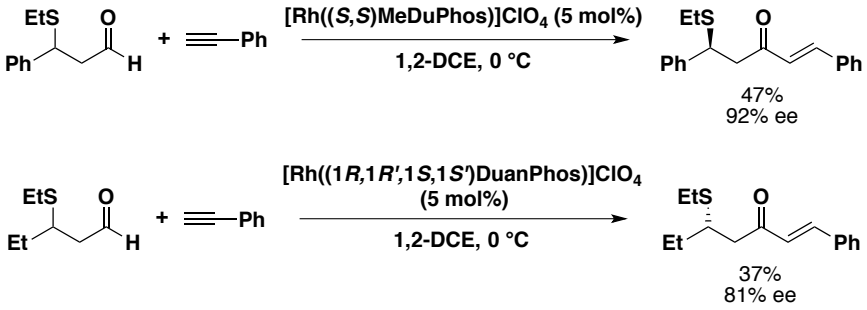
Soon after, Weller and Willis reported an improved catalytic system; the so-called 'second-generation', utilising a DPEPhos ligand (Scheme 1.28). This system afforded

higher reactivity with lower catalyst loadings and reaction temperatures. The DPEPhos ligand contained a hemi-labile oxygen chelating atom in the phosphorous backbone as an additional stabilisation aid to the crucial acylrhodium hydride intermediate. This proposed stabilising effect of DPEPhos was confirmed by ^{1}H and ^{31}P NMR spectroscopy, mass spectrometry and X-ray crystallography (complex **42**).[58] The new catalytic system permitted the coupling of *S*-containing aldehydes with unactivated alkenes *e.g.* hydroacylation of 1-octene now yielded 70% of product in comparison to 33% with the first generation catalyst system. In addition, this catalyst can be formed *in situ* from commercially available starting materials and no longer required glove-box techniques for synthesis.[59]



Scheme 1.28: 'Second-generation' catalytic system reported by Weller and Willis.

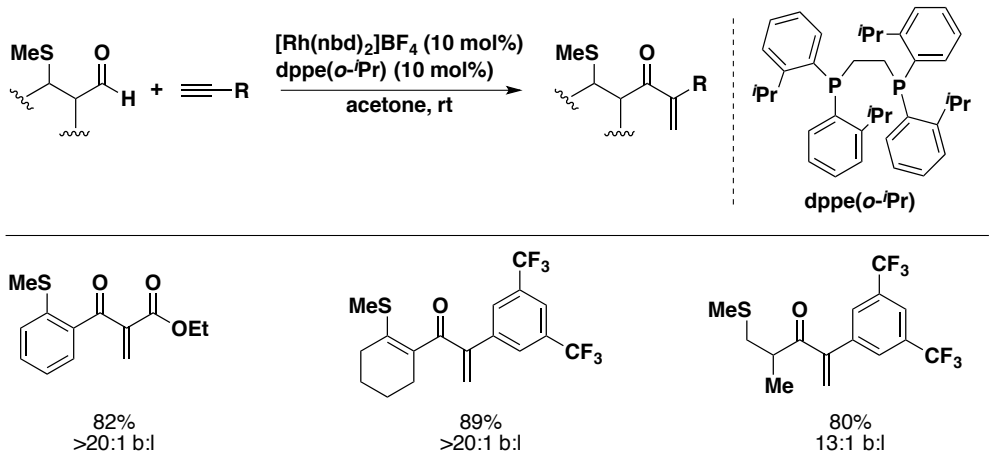
Furthermore, Willis and co-workers have reported the first asymmetric versions of intermolecular hydroacylation using sulfide chelation, for the synthesis of chiral α- and β-substituted enones *via* kinetic resolution of racemic aldehydes (Scheme 1.29).[102,103] While [Rh(MeDuPhos)]ClO_4 was the most selective catalyst for the majority of substrates, DuanPhos outperformed MeDuPhos as a ligand when using β-alkyl aldehydes.



Scheme 1.29: Asymmetric intermolecular hydroacylation using sulfur chelation.

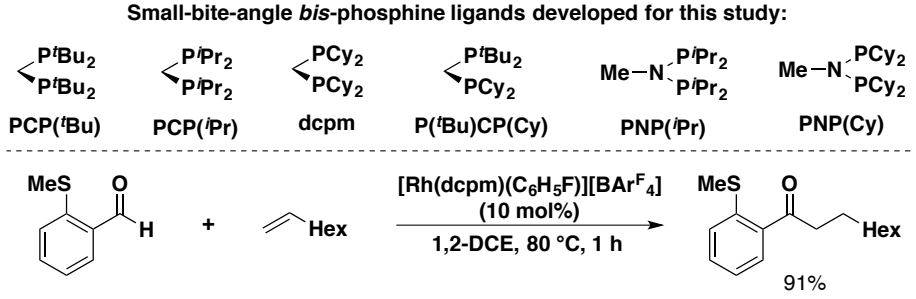
Further development in the Weller and Willis labs has led to a 'third-generation' of catalyst, incorporating small bite-angle *bis*-phosphine ligands, with the general structure $[Rh(R_2PCH_2PR_2)(\eta^6\text{-}C_6H_5F)][BAr^F{}_4]$. Since 2012, these catalysts have substantially improved reactivity for *β*-sulfur and *β*-oxygen aldehyde based intermolecular hydroacylation.

The small bite-angle ligands were initially investigated as highly linear-selective reactions were required. The authors believed that another way to improve the constructive catalysis pathway of hydroacylation would be to outcompete decarbonylation by accelerating the rate limiting step. Thus, increasing the rate of reductive elimination of the enone or ketone was pursued. Traditionally, wide bite-angles ($Ph_2P(CH_2)_nPPh_2$, n=2-5) as well as steric bulk on the ligand is known to encourage reductive elimination. However, within the context of olefin hydroacylation, it was observed that increased bite-angles reduced the regioselectivity.[104] Recent results proved this effect, as branched-selective catalysis was actually favoured when bulky, larger bite-angle *bis*-phosphine ligands were employed in alkyne hydroacylation (Scheme 1.30).[105]



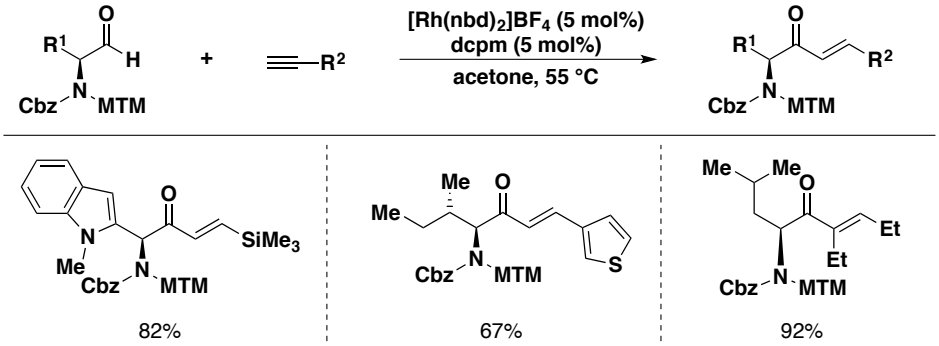
Scheme 1.30: Branched-selective alkyne hydroacylation by Willis.

Following these results, Weller and Willis turned to small bite-angle ligands. It had been proven that a small P-M-P angle promotes *cis*-geometry and favours Rh(I) complexes,[106-108] as well as Werner's studies demonstrating that small bite-angles promoted reductive elimination due to chelating ring strain.[109] This information led the authors to prepare such complexes, which indeed displayed the desired effect in catalysis with only 0.1 mol% of catalyst. Additionally, these small bite-angle catalysts achieved 300 h^{-1} turnover frequencies.[61] Upon comparison of the second- and third-generation catalysts in the hydroacylation of 1-octene, the second generation catalyst achieved a 70% yield in the coupling reaction, whereas the third generation catalyst outperformed this and achieved a 91% yield of the hydroacylation product, with extremely high linear-selectivity (Scheme 1.31).[110]



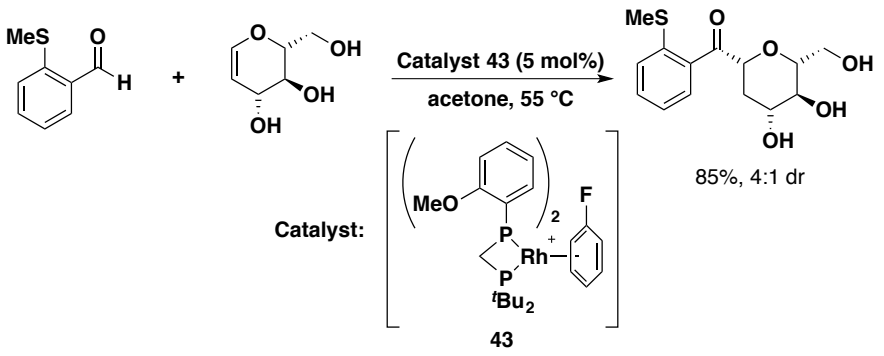
Scheme 1.31: Use of small bite-angle ligands in hydroacylation by Weller and Willis.

This catalyst design enabled sulfur tethered intermolecular hydroacylation to become one of the most robust hydroacylations available, and has since been used with some of the more challenging substrates. This system has vastly improved the use of MTM as a chelating group (Scheme 1.32).[111] MTM protected α-amino aldehydes were used to deliver the corresponding hydroacylation products in high yields, with retention of stereochemistry. This protocol is a vast improvement on the previous report employing second generation catalysis with MTM chelation (Scheme 1.27), as even internal alkynes can now be coupled. The prevalence of this type of substrate allowed for this methodology to be applied to the total synthesis of sphingosine.



Scheme 1.32: Hydroacylation of α-amino aldehydes.

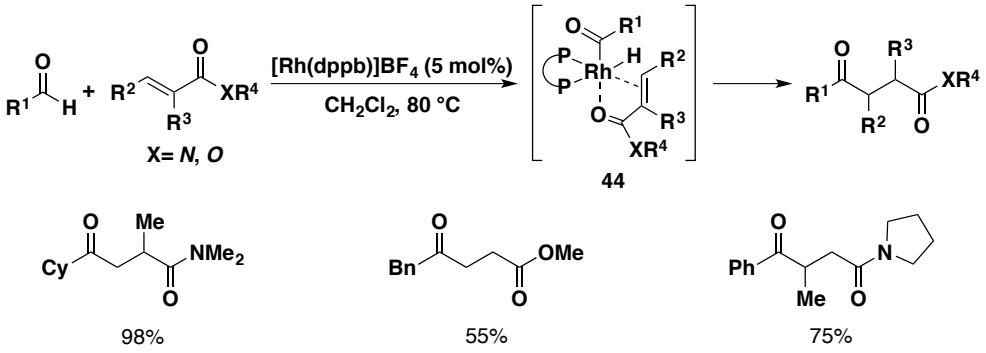
Another beneficial factor about these small bite-angle based catalysts is that the electronic and steric properties can be tuned, as they are very simple to synthesise, therefore they can be adjusted for numerous reactions in a straightforward manner. In this sense, slight adjustment from the usual small bite-angle ligands enabled the formation of catalyst **43**, which contains a potentially chelating *o*-methoxy group on one phosphine (Scheme 1.33). This catalyst has recently been used to successfully perform hydroacylation on a notoriously difficult coupling partner – internal alkenes (Scheme 1.33).[112]



Scheme 1.33: Willis and Weller's optimised hydroacylation of internal alkenes.

1.4.6 Non-Chelating Aldehydes in Intermolecular Hydroacylation

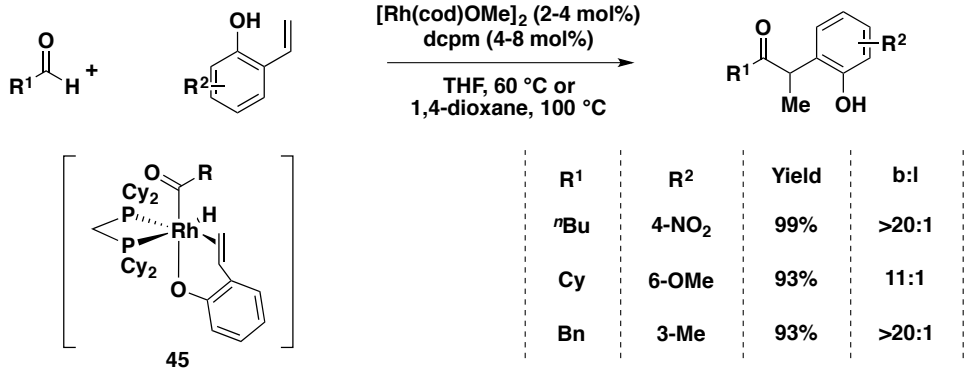
Cationic rhodium species $[Rh(dppb)]BF_4$ was described as the catalyst for the combination of non-chelating aldehydes and acrylamides by Tanaka and co-workers (Scheme 1.34). In this system the authors presumed that the acylrhodium hydride intermediate was stabilised by the alkoxy and olefin moieties solely in acrylamide (complex **44**).[113] Another example using acrylate esters was also described, and the use of methyl acrylamides allowed for the development of an asymmetric version.[114]



Scheme 1.34: Hydroacylation of non-chelating aldehydes with acrylates.

This type of chelation occurring solely from the non-aldehyde component, was further developed by Dong and co-workers, who employed vinyl phenols in hydroacylation. The oxygen heteroatom on the olefin offered substantial stabilisation **45**, to allow for a productive reaction (Scheme 1.35). The combination of *ortho*-vinyl phenols with a

variety of aliphatic, aromatic and alkenyl aldehydes was described with excellent selectivity for the branched regioisomer.[115]



R^1	R^2	Yield	b:l
^{n}Bu	4-NO_2	99%	>20:1
Cy	6-OMe	93%	11:1
Bn	3-Me	93%	>20:1

Scheme 1.35: Dong's branched-selective hydroacylation with non-chelating aldehydes.

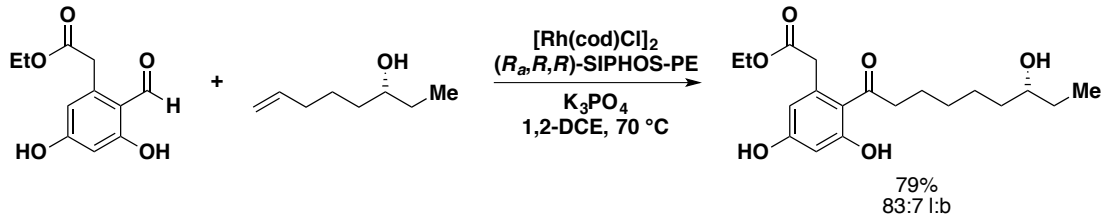
The authors proposed that the use of small bite-angle ligands allowed the formation of an electron-rich neutral rhodium complex. These types of complexes have a lower barrier for the turnover limiting, non-directed oxidative addition of rhodium into the C-H bond of an aldehyde.[116]

1.5 Applications of Intermolecular Hydroacylation

The majority of reports regarding intermolecular hydroacylation discussed during this chapter have focussed on either reaction or catalyst development. Given the success of a number of these systems, the logical next step was to apply these methods to access synthetically more useful and biologically relevant compounds. Intermolecular hydroacylation provides the option of an unconventional disconnection in regards to target synthesis. The substrate compatibility, use of low rhodium catalytic loadings, and mild reaction conditions have promoted the use of this reaction in the synthesis of natural products, as well as accessing synthetically useful precursors to target compounds.

1.5.1 Natural Product Synthesis

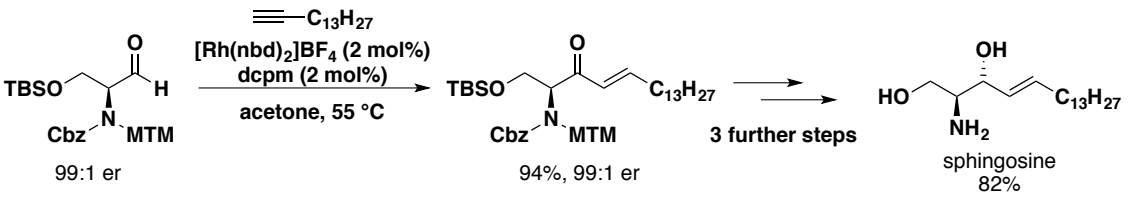
The Dong group was first to apply intermolecular hydroacylation to the synthesis of natural products (Scheme 1.36), exploiting the previously described hydroacylation of salicylaldehydes in the synthesis of eight biologically active compounds, derived from the dothiorelone, cystosporone and phomopsin families, five of which were prepared for the first time.[62] These type of natural products have shown anti-cancer properties, however, it has not been straightforward to synthesise analogues.[117,118] The hydroacylative pathway described provided a novel disconnection and a mild, step- and



atom-economic route through the use of an oxygen chelating heteroatom that is widely present in nature.

Scheme 1.36: The key hydroacylation step in the synthesis of dothiorelone A.

Another example was described by the Willis group; an efficient and economical route to sphingosine by employing MTM protected aldehydes in hydroacylation for the crucial C-C bond forming step (Scheme 1.37). The mild reaction conditions also allowed the straightforward preparation of derivatives.[111]

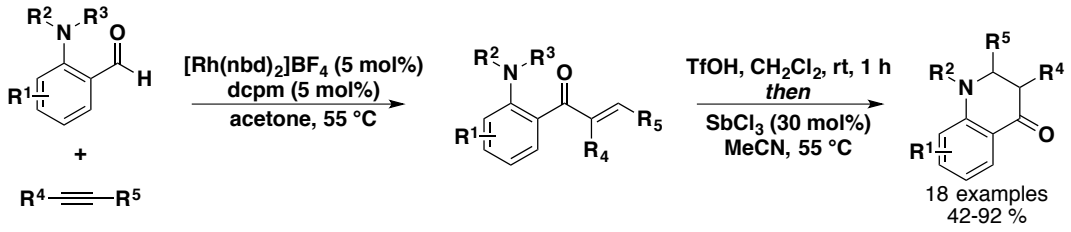


Scheme 1.37: The synthesis of sphingosine by the Willis group.

1.5.2 Synthesis of Heterocycles

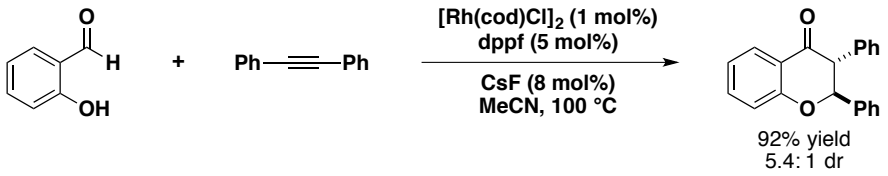
Incorporating heteroatoms into compounds is a valuable field within organic chemistry, especially when heteroatoms are in a ring system, as these structures are prevalent as central scaffolds in natural products and drug compounds.[119] Products of chelation-controlled hydroacylation usually possess a pre-installed heteroatom, consequently they are the ideal substrates to be used in heterocycle synthesis. Therefore, over the past few years there has been a surge of reports within this area of hydroacylation.

Willis and co-workers reported the synthesis of dihydro-4-quinolones (Scheme 1.38); compounds that display anti-bacterial properties, in an entirely atom-economical fashion. The reaction begins with an *N*-chelation-controlled hydroacylation reaction, followed by an intramolecular aza-Michael addition in a sequential manner.[90]



Scheme 1.38: Willis and co-workers' synthesis of dihydroquinolones.

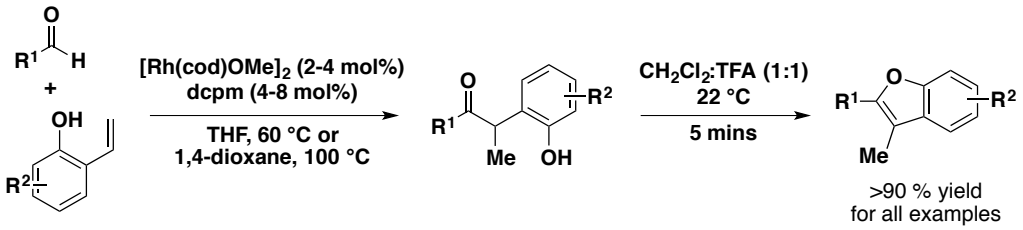
More recently, the Stanley group described a similar protocol employing salicylaldehydes in the cascade synthesis of chroman-4-ones, achieving excellent yields and a good diastereomeric ratio on a wide scope of substrates (Scheme 1.39).[120]



Scheme 1.39: Chroman-4-one synthesis *via* a tandem hydroacylation/Michael addition.

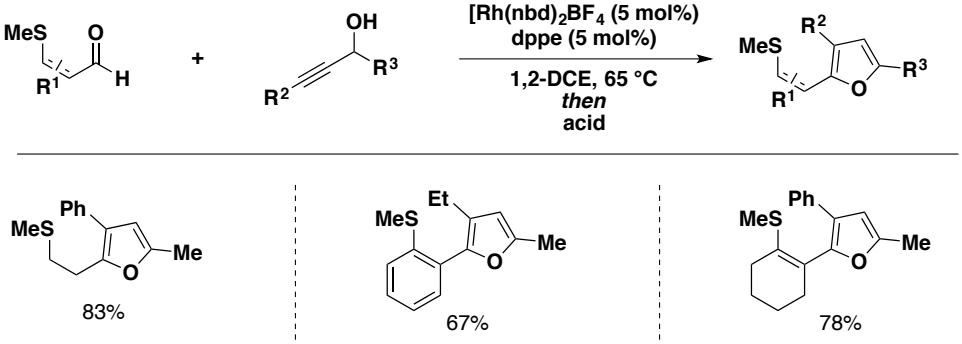
Moving away from alkyne hydroacylation, the Dong group described the efficient synthesis of benzofuran rings following the hydroacylation of vinyl phenols with non-

chelating aldehydes (Scheme 1.40). They employed this methodology in the synthesis of valuable targets in three steps *i.e*. eupomatenoids, which have a range of biological properties from insecticidal to antioxidant.[115]



Scheme 1.40: Dong's benzofuran synthesis using non-chelating aldehydes.

Regardless of whether the tether from hydroacylation is incorporated or not, the formation of heterocycles is a valuable field and new methods to synthesise them are extensively pursued. Therefore, the Willis group has also demonstrated the use of the carbonyl unit installed after hydroacylation (Scheme 1.41). *S*-Chelating aldehydes have been coupled with propargylic alcohols, which sets up the hydroacylation product to undergo an *in situ* intramolecular dehydrative cyclisation, furnishing a range of furan rings in a synthetically convenient method.[121]



Scheme 1.41: An alkyne hydroacylation route to substituted furans.

1.6 Summary

The majority of research undertaken within rhodium-catalysed hydroacylation has been focused around preventing the undesired decarbonylation pathway. For intramolecular

hydroacylation this methodology is relatively mature. However, for intermolecular reactions, there has been a vast amount of development over recent years due to the potential power of the specified coupling reaction. Decarbonylation can now be successfully attenuated *via* some form of chelation control, whether it is from the aldehyde, unsaturated coupling partner, ligand or a combination. Nevertheless, there are still limitations with regards to the complexity of coupling partners employed, understanding of regiocontrol, as well as moving away from the use of chelation control altogether.

Although the methodology is becoming more general due to beneficial advances in catalyst design, its application remains limited. There has been a recent interest in the use of hydroacylation in heterocycle synthesis and initial reports look promising however, the need for more selective, general and user-friendly methods persist.

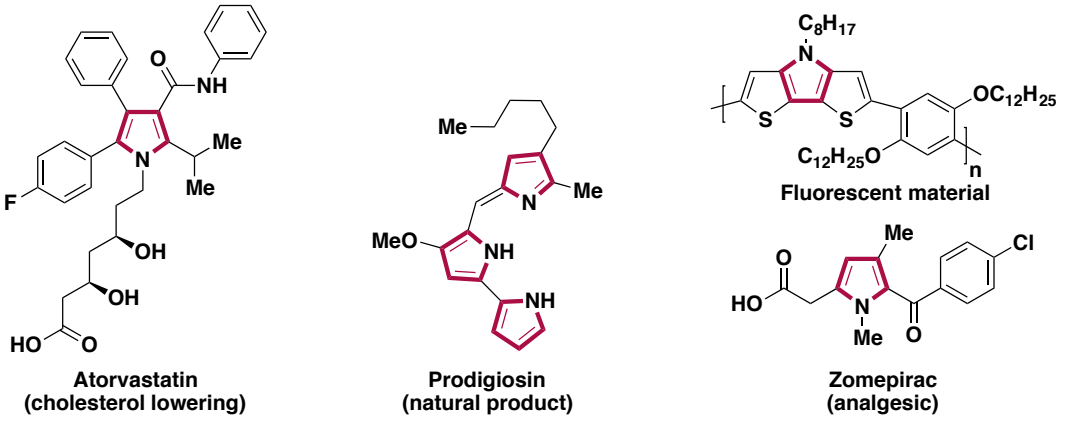
It is the aim of this thesis to explore advances in the coupling partners employed in rhodium-catalysed intermolecular hydroacylation and apply these reactions to the synthesis of highly sought after heterocycles.

Chapter 2

Pyrrole Synthesis *via* Highly Regioselective Hydroacylation

2.1 Introduction

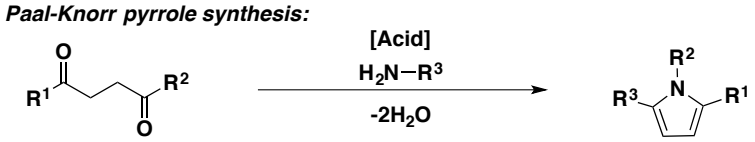
The synthesis of aza-heterocycles has been the subject of much investigation over recent years due to their abundance in nature and their wide application. Of particular significance is the pyrrole motif, as it is integral to many bioactive natural products, successful pharmaceuticals, and has a growing presence in materials science (Scheme 2.1).[122-126]



Scheme 2.1: Selected examples of pyrroles in bioactive molecules and materials.

The traditional methods for the preparation of pyrroles employ 1,4-dicarbonyl compounds, with initial reports originating from Paal and Knorr independently in 1884,

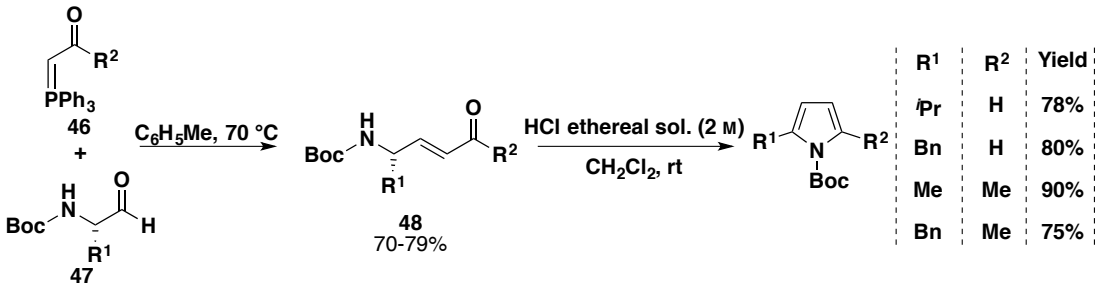
now known as the Paal-Knorr synthesis (Scheme 2.2).[127,128] The 1,4-diketone undergoes amine addition promoted by the use of a protic or Lewis acid, followed by dehydration.



Scheme 2.2: Classical Paal-Knorr pyrrole synthesis.

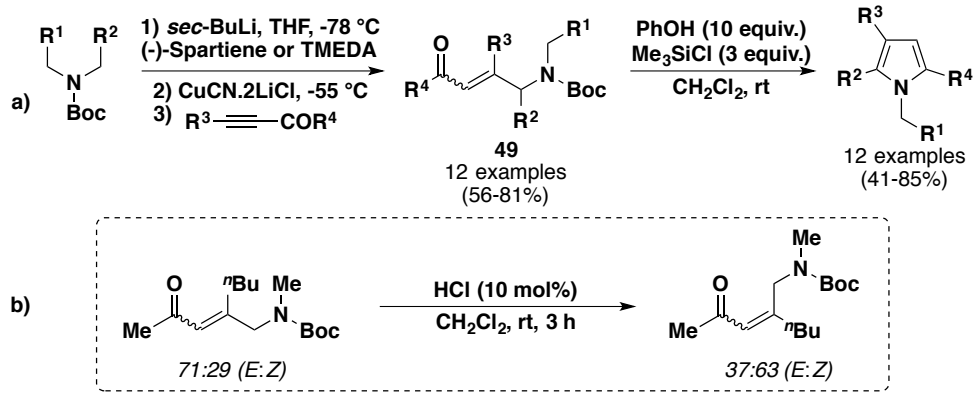
Although this method is popular due to its simplicity, there are a number of shortcomings. Firstly, the substrate scope is limited by the lack of availability of 1,4-diketones, especially when structural complexity in the product is required, which has led to the use of masked 1,4-diketones.[129-132] Secondly, the reaction is usually subject to harsh conditions, such as prolonged heating in acid, which can lead to degradation of the functionality being incorporated or polymerisation and decomposition of the pyrrole ring itself.[133] Hence, there has been a recent surge in reported catalytic protocols that utilise non-traditional starting materials to access carbonyl containing compounds;[134-140] these can be exploited to deliver this ubiquitous heterocycle. In particular, the γ–amino enone moiety has been heavily investigated as a cyclisation precursor for regiodefined and highly functionalised pyrrole rings.[141]

In 2002, Alcaraz and co-workers described a route whereby a Wittig condensation of (triphenyl phosphoranylidene) ketones **46** with *N*-Boc α-aminoaldehydes **47** afforded (*E*)-γ-amino enones **48**, which were the incorrect stereoisomers for cyclisation (Scheme 2.3). However, the authors demonstrated that (*E*)- to (*Z*)-isomerisation of these enones was permitted upon treatment with acid, resulting in dehydrative cyclisation. Consequently, a range of *N*-Boc protected 2,5-substituted pyrroles were obtained in good yields over two-steps.[142]



Scheme 2.3: Pyrrole formation *via* a Wittig condensation.

Prior to the Alcaraz report, the Dieter group had investigated acid-catalysed isomerisation of *N*,*N*-disubstituted-*γ*–amino enones **49** (Scheme 2.4 a)[143] The methodology consisted of a conjugate addition reaction of *α*-amino-alkylcuprates to alkynyl ketones. They obtained mixtures of (*E*)- and (*Z*)-amino enones, in which the selectivity varied from 71:29 (*E*:*Z*) to 24:76 (*E*:*Z*). Even so, the corresponding cyclised pyrrole products could be accessed in similarly good yields from the mixture of enone stereoisomers *via* a Boc-deprotection. The deprotection employed phenol and trimethylsilyl (TMS) chloride in CH_2Cl_2, with hydrochloric acid (HCl) produced as a by-product.

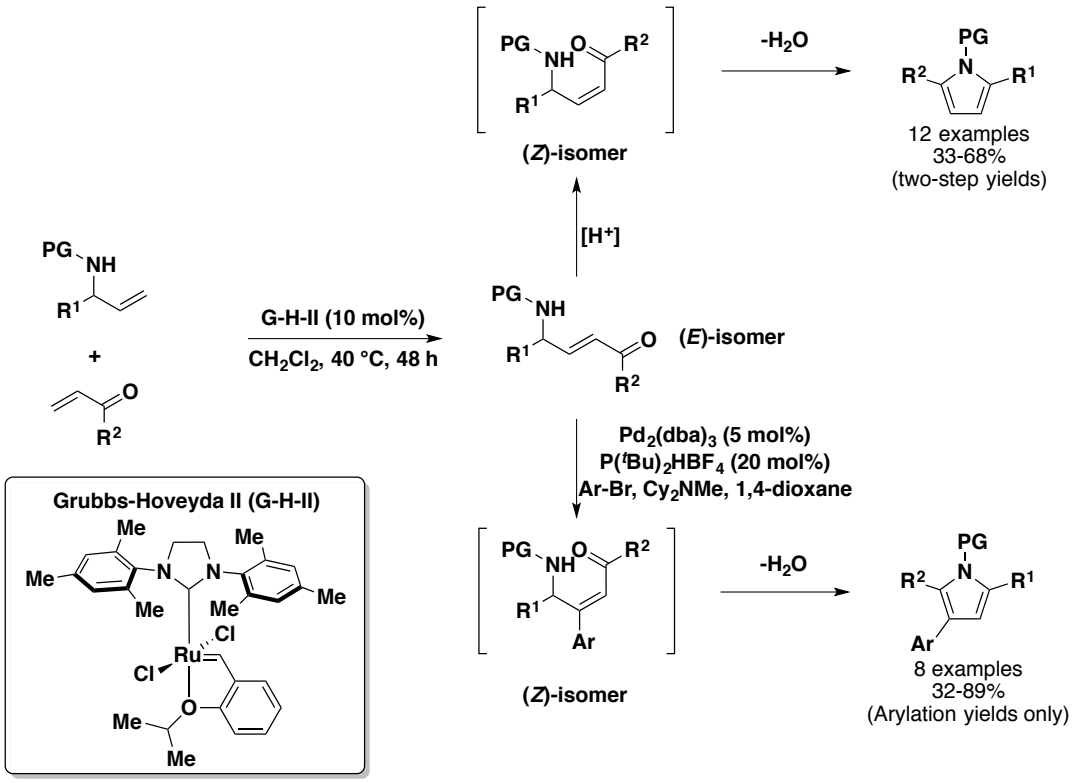


Scheme 2.4: Pyrrole formation from *γ*–amino enone intermediates reported by Dieter.

The Boc-deprotection and (*E*)- to (*Z*)-isomerisation occurred readily, and it was thought that 1,4-conjugate addition of the phenol to the enone intermediate was responsible for the isomerisation. However, upon treatment of the enones with only anhydrous HCl (10 mol%), the (*E*)- to (*Z*)-ratio of the amino enone changed from 71:29 (*E*:*Z*) to 37:63 (*E*:*Z*) (Scheme 2.4 b), which was only visible as Boc-deprotection was not

observed under these conditions. Therefore, it was concluded that trace amounts of HCl, generated during the successful Boc-deprotection, was responsible for the isomerisation and subsequent pyrrole synthesis.

The Donohoe group has also recently exploited γ–amino enones in pyrrole formation (Scheme 2.5).[144] The group described accessing (*E*)-γ–amino enones *via* the cross-metathesis of readily-available allylic amines and enones. This step was followed by the key manipulation of the (*E*)-isomer to (*Z*)-γ–amino enone, by the use of an acid co-catalyst or by a separate Heck arylation step. This protocol facilitated the production of mono-, di- or tri-substituted pyrrole rings. Although the methodology achieved a high level of functionalisation, it was unsuitable for a one-pot procedure without a substantial decline in yield.



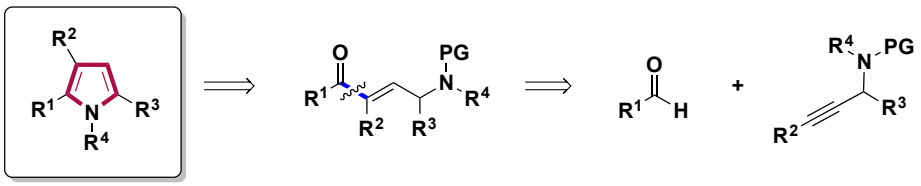
Scheme 2.5: Donohoe's cross-metathesis method for pyrrole synthesis.

It became evident that γ–amino enone compounds are archetypal intermediates for pyrrole synthesis. Therefore, catalytic reactions that deliver this moiety, preferably from

alternative feedstocks, are ideal reactions to be employed in this venture; one such method could be hydroacylation. This atom-economic coupling could address many of the shortfalls associated with classical heterocycle syntheses, and therefore enable efficient access to valuable ring systems in a user-friendly manner.

2.2 Project Aims and Previous Work

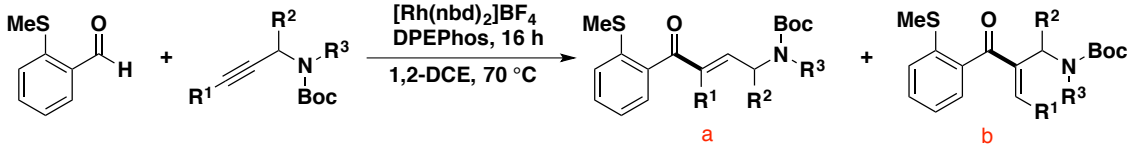
Considering the potential substitution patterns achievable on carbonyl-containing compounds *via* alkyne hydroacylation, this reaction was envisaged as a mechanistically distinct route to the *γ*–amino enone pyrrole precursors, as the proposed retrosynthesis displays (Scheme 2.6). This approach would involve the novel hydroacylative union of aldehydes and propargylic amines to effect the umpolung connection and deliver the (*E*)-*γ*–amino enone intermediate. Successive deprotection of an acid-labile protecting group, isomerisation and dehydration would furnish the pyrrole ring.



Scheme 2.6: Proposed alkyne hydroacylation route to pyrrole synthesis.

Preliminary investigations were carried out by a previous member of the Willis group, and the results acknowledged that the use of a cationic rhodium(I) complex was successful in the combination of *S*-chelating aldehyde **50** with various propargylic amines (Scheme 2.7).[145] This previous work included an extensive catalyst screening of the common diphosphine ligands available at the time. The 'second generation', hemi-labile DPEPhos ligand, along with the rhodium pre-catalyst $[Rh(nbd)_2]BF_4$, was selected as the optimal system. The propargylic amines employed in these reactions utilised the benefits

of a Boc protected nitrogen, which would potentially be ideal for the essential acid-promoted deprotection and cyclisation steps. Additionally, the requirement of a second protecting group on the nitrogen was deemed necessary for reactivity.



50	**51**: R^1=H, R^2=H, R^3=Bn	**55**: R^1=H, R^2=H, R^3=Bn (94%, 1.7:1 (a:b))
	52: R^1=H, R^2=H, R^3=Me	**56**: R^1=H, R^2=H, R^3=Me (80%, 1.8:1 (a:b))
	53: R^1=H, R^2=H, R^3=Ph	**57**: R^1=H, R^2=H, R^3= Ph (86%, 1.1:1 (a:b))
	54: R^1=Et, R^2=Me, R^3=Ph	**58:** R^1=Et, R^2=Me, R^3=Ph (82%, 5:1 (a:b))

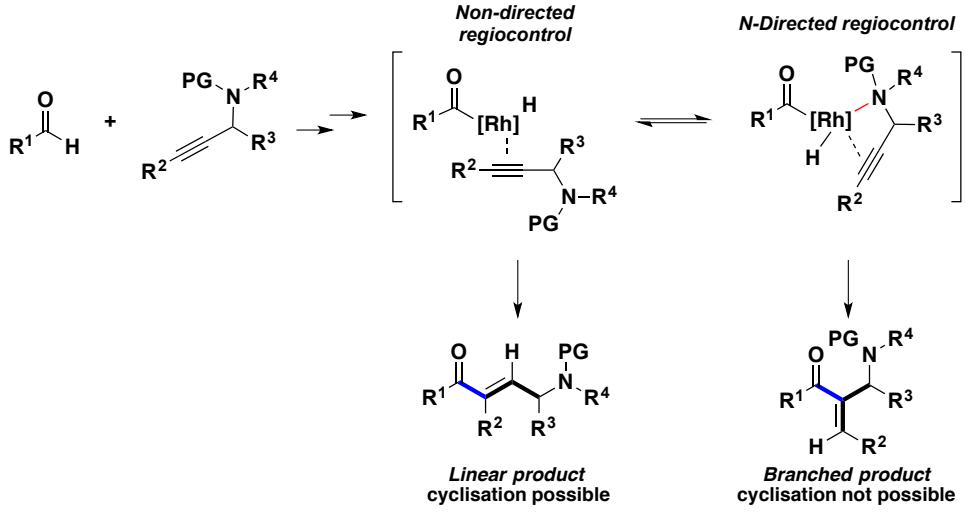
Scheme 2.7: Previously optimised chelation controlled hydroacylation of propargylic amines.[145]

The aforementioned results set the foundations for this particular project. However, there were severe limitations and the most prominent was the lack of regiocontrol (typically 1.5:1 linear:branched), which had previously been unobserved for other alkynes within the Willis group chemistry. Poor regiocontrol would have significant consequences for our designed pyrrole synthesis, as only the linear hydroacylation adducts are capable of undergoing a pyrrole-forming cyclisation. Additionally, the optimised method required elevated catalyst loadings (10 mol%) and temperatures (70 °C) as well as low-yielding access to the target heterocycle.

The principal aim of this project was to demonstrate that valuable pyrrole rings could be accessed, in a high yielding fashion, through a novel hydroacylation reaction. Furthermore, this chapter focuses on fully investigating the effect of propargylic amines in hydroacylation, paying particular attention to regioselectivity.

2.3 Hydroacylation of Fully Protected *N*-Propargylic Amines

Although there are a number of successful non-chelation intermolecular hydroacylation methods,[20] the most general and selective processes invariably rely on chelation control.[19] Accordingly, *S*-chelating aldehydes were selected as our preferred substrates. The presence of coordinating functionality on the alkene or alkyne coupling partner had also been shown to have a significant impact on the course of several hydroacylation reactions, and had been employed to facilitate selectivity. For example, both Suemune and Dong employed alkenes bearing coordinating functionality to achieve branched-selective reactions (Chapter 1, section 1.4.4).[94,95,97] We were therefore conscious that our designed alkyne substrates, propargylic amines, may well be involved in coordination to the metal catalyst to effect poor regioselectivity of the proposed reactions. (Scheme 2.8).



Scheme 2.8: Proposed linear- *versus* branched-selectivity in propargylic amine hydroacylation.

With this information in hand, we turned our attention to the *de novo* third generation of small bite-angle ligands to begin addressing these concerns (Figure 2.1).[61] It was believed that these ligands would be advantageous, as the Willis group had recently reported that small bite-angle, methylene-bridged diphosphines generated efficient and selective catalysts for a variety of hydroacylation reactions.[110] Another positive aspect of these

ligands was that the majority were available without pre-complexing to rhodium, which obviates the requirement of a glove-box.

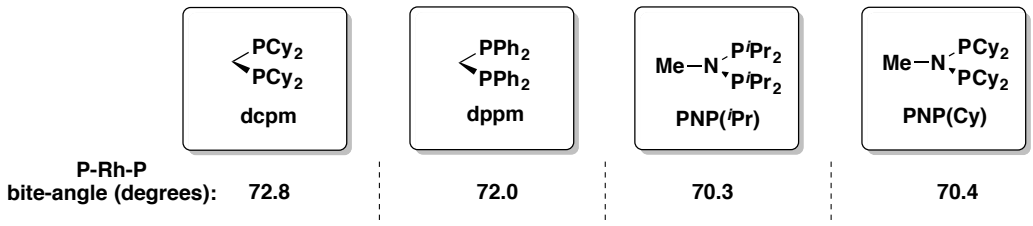
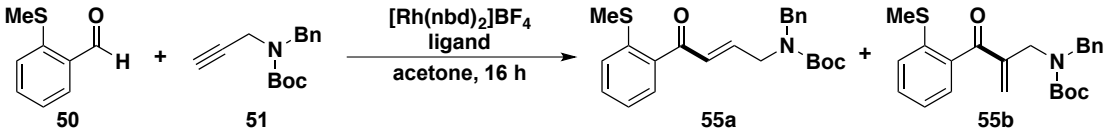


Figure 2.1: Small bite-angle *bis*-phosphine ligands used in this study.[61,110,146]

We began our investigation by studying the coupling of *o*-SMe-benzaldehyde **50** and the previously optimised, doubly protected propargylic amine **51** (Table 2.1). These ligands were tested under similar conditions to those seen in Scheme 2.7. The previous observations with the use of first or second generation catalyst systems were confirmed, as the hydroacylation adducts were delivered as a 3:1 or 2:1 mixture of linear and branched enones, respectively (entry 1-2). Unfortunately, in the present study, both commercially available small bite-angle dcpm and dppm ligands offered only modest improvement on the regioselectivity (entries 3-4). It was the electronic parameters of the PNP ligand systems, specifically PNP(Cy), that offered a significant increase in the level of regiocontrol (entry 5-6). However, disappointingly, the PNP-based small bite-angle ligands did not permit complete consumption of the starting material. The poor catalytic activity observed with the most regioselective ligand–PNP(Cy)–was improved through a judicious choice of solvent, temperature and substrate/catalyst concentration.

Table 2.1: Ligand screening on fully protected *N*-propargylic amines.

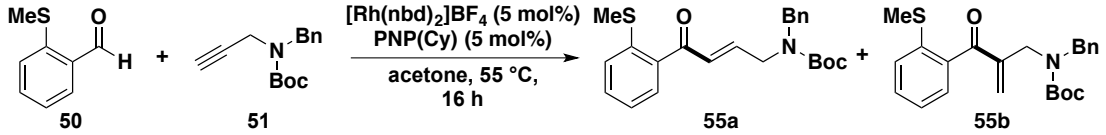


Entry	Ligand	Catalyst loading (mol%)	Temperature (°C)	Conversion[a] (%)	a:b ratio[a]
1[b]	dppe	10	70	100 (63)	3:1
2	DPEPhos	10	55	100 (63)	2:1
3	dcpm	5	55	100 (60)	6:1
4	dppm	5	55	76	7:1
5	PNP(^{i}Pr)[c]	5	55	20	13:1
6	PNP(Cy)	5	55	53	18:1

Conditions: **50** (0.15 mmol, 1 equiv.), **51** (1.5 equiv.), $[Rh(nbd)_2]BF_4$, solvent (0.3 M total volume with respect to the aldehyde, minus the volume of starting materials), 16 h. Value in parenthesis is the isolated yield of combined linear and branched products. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Performed in 1,2-dichloroethane. [c] PNP(^{i}Pr) was used as the pre-formed $[Rh(PNP(^iPr))(\eta^6C_6H_5F)][BAr^F{}_4]$ complex.

Firstly, we investigated the effect of reaction concentration. It was understood that decarbonylation is independent of substrate concentration, whereas this is unlikely for the constructive catalysis. Therefore, increasing the concentration should kinetically favour the desired intermolecular reaction with little effect on the intramolecular decarbonylation pathway.[61] The resultant investigations verified this hypothesis (Table 2.2) and established that a concentration of 1 M with respect to the aldehyde permitted quantitative conversions (entry 3), mitigating the issue of catalytic activity. In this regard, increasing the concentration further should have displayed beneficial results, however complete solubility of the catalyst was not achieved hence the poor reactivity (entry 4).

Table 2.2: The effect of substrate concentration on propargylic amine hydroacylation.



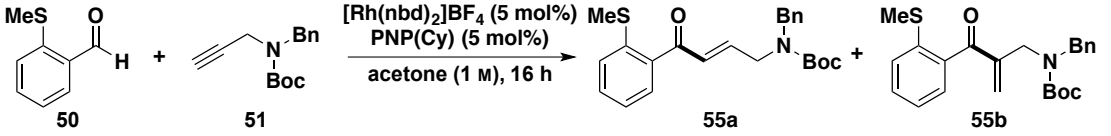
Entry	Concentration (M)	Conversion[a] (%)	a:b ratio[a]
1	0.1	26	-
2	0.3	53	18:1
3	1.0	100	17:1
4	2.0	3	-

Conditions: **50** (0.15 mmol, 1 equiv.), **51** (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone, 55 °C, 16 h. [a] Determined by ^1H NMR spectroscopy of crude reaction mixtures.

In order to further optimise this reaction, we studied the effect of the temperature and solvent. Recent reports from the Weller group had proved that accessing the branched hydroacylation product required a higher energy, therefore we postulated that increasing the temperature may have a detrimental effect on selectivity.[61,110] When assessing the impact of the temperature (Table 2.3), the general trend indicated that lower temperatures achieved greater linear-selectivity, although if temperatures below room temperature were employed, catalytic turnover decreased significantly, with no improvement in linear-selectivity (entry 4). As a result, it was evident that performing these reactions at room temperature was necessary (entry 3).

Moreover, we decided to perform this hydroacylation in acetone, as it is not only less toxic than 1,2-dichloroethane (1,2-DCE) but it is known to assist in preventing reductive decarbonylation through weak coordination to the metal-centre. [98]

Table 2.3: The effect of temperature on propargylic amine hydroacylation.



50 51 55a 55b

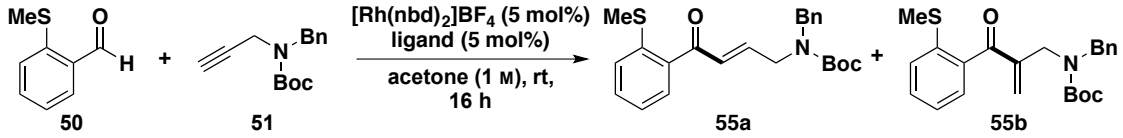
Entry	Temperature (°C)	Conversion[a] (%)	a:b ratio[a]
1[b]	70	100	10:1
2	55	100	16:1
3	rt	100	22:1
4	0	54	21:1

Conditions: **50** (0.15 mmol, 1 equiv.), **51** (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), solvent (1 M total volume with respect to the aldehyde, minus the volume of starting materials), 16 h. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Performed in 1,2-DCE.

Encouragingly, following these optimisations, the catalyst was active at 5 mol%, with a reaction time of 16 hours, however, a lower catalyst loading than this was not tolerated. Hydroacylation reactions attempted with 2 mol% catalyst loading resulted in only a 7% conversion to both linear and branched hydroacylation products (Table 2.4, entry 5). After a final ligand screening with the optimised external conditions, in which all reactions employing 5 mol% catalytic loading reached 100% conversation by ^{1}H NMR spectroscopy (Table 2.4), it was apparent that the small bite-angle ligands were indeed higher yielding and more linear-selective than the ligands used in the prior work. The nitrogen containing phosphine ligands displayed greater regiocontrol than the PCP alternatives, now achieving selectivities of over 20:1 (linear:branched).

Based on these observations, we decided to advance with the PNP-based catalysts. However, as PNP(^{i}Pr) is not stable in ligand form and requires pre-complexation to rhodium, it was decided to progress with PNP(Cy) for experimental convenience.[110]

Table 2.4: Ligand screening using optimised external conditions.



Entry	Ligand	Catalyst loading (mol%)	Yield (%)	a:b ratio[a]
1	dcpm	5	62	9:1
2	dppm	5	80	3:1
3	PNP(^{i}Pr)[b]	5	98	21:1
4	PNP(Cy)	5	96	22:1
5	PNP(Cy)	2	7	-

Conditions: **50** (0.15 mmol, 1 equiv.), **51** (1.5 equiv.), $[Rh(nbd)_2]BF_4$, PNP(Cy), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt, 16 h. Yield is the isolated yield of combined linear and branched products. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] PNP(^{i}Pr) was used as the pre-formed $[Rh(PNP(^iPr))(\eta^6C_6H_5F)][BAr^F_4]$ complex.

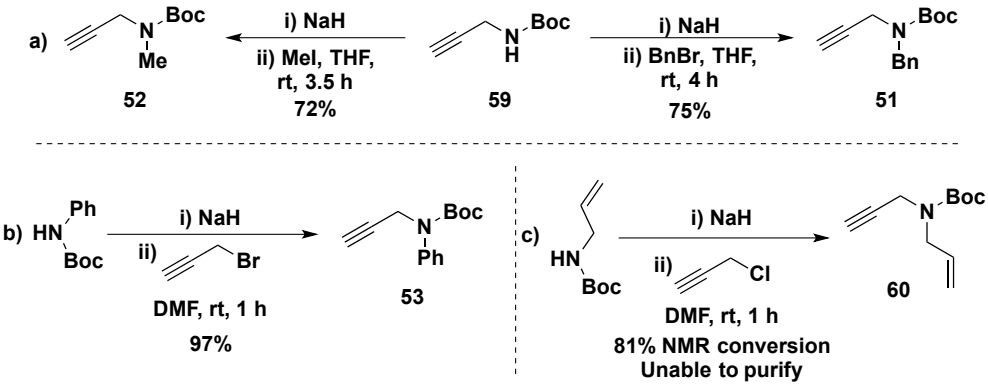
2.4 Substrate Scope of Fully Protected *N*-Propargylic Amines in Hydroacylation

With the optimised conditions in hand for the synthesis of *γ*–amino enones *via* hydroacylation, we intended to understand the complexity of doubly-protected propargylic amines that could be used in hydroacylation and began by synthesising a variety of substrates.

2.4.1 Synthesis of Doubly *N*-Protected Propargylic Amines

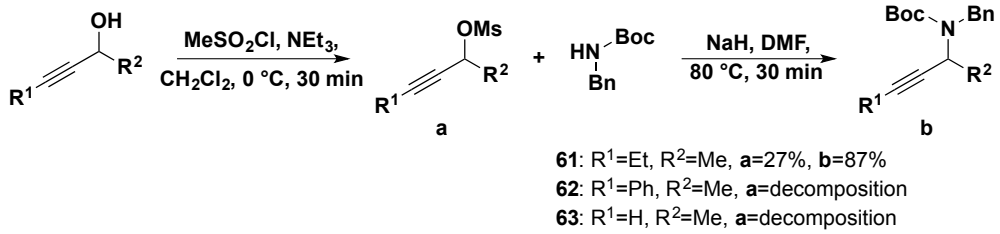
The electronic nature and steric parameters of the nitrogen heteroatom on the propargylic amine is fundamental to the initial hydroacylation step. This is because the affinity of the nitrogen atom to the rhodium metal-centre is impacted by this specific substitution pattern. Therefore, it was decided to synthesise propargylic amines with different groups present on the *N*-Boc-protected nitrogen. The formation of such terminal propargylic

amines was relatively straightforward (Scheme 2.9). Compounds **51** and **52** were prepared by the alkylation of commercially available *N*-Boc propargyl amine **59** (Scheme 2.9 a). Alkylation of *N*-Boc aniline with propargyl bromide allowed access to alkyne **53** in a quantitative fashion (Scheme 2.9 b). Although, the analogous reaction using *N*-Boc allylamine also gave a good conversion (Scheme 2.9 c), the purification by column chromatography led to an inseparable mixture of decomposition products and therefore this alkyne **60** could not be examined in hydroacylation.



Scheme 2.9: Synthesis of fully protected terminal propargylic amines.

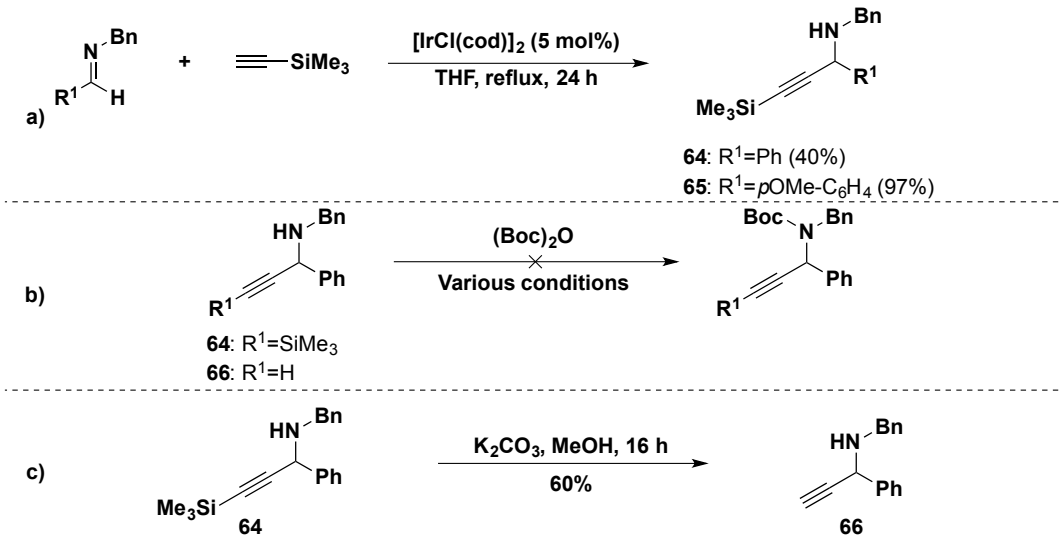
As use of internal alkyne substrates would be more desirable, as they could grant access to the most possible substitution available on a pyrrole ring *via* our proposed route. One method used to access α-alkyl internal propargylic amines was the alkylation of *N*-Boc benzylamine with a secondary mesylate (Scheme 2.10).[147] This approach afforded propagylic amine **61b** *via* mesylate **61a** in an overall yield of 23%, although this yield was not ideal it was a sufficient start to begin examining these internal propargylic alkynes in hydroacylation. Unfortunately, subsequent attempts to synthesise variations of the mesylate substrate resulted in extreme exotherms, degrading the intermediate in addition to becoming experimentally hazardous; we decided to pursue an alternative methodology.



Scheme 2.10: Attempted internal propargylic amine synthesis *via* mesylate compounds.

It soon became evident that gaining access to doubly *N*-Boc and benzyl protected propargylic amines was not a trivial task. Hence, we decided to synthesise *N*-benzyl propargylic amines, followed by a Boc-protection of the nitrogen to form our proposed substrate.

Application of Carriera's iridium-catalysed addition of TMS-acetylene into a variety of imines enabled access to alkynes **64** and **65** (Scheme 2.11a).[148] The succeeding step consisted of a classical Boc-protection to access the substrates required to form cyclisable enones (Scheme 2.11 b). Regrettably all endeavors to perform Boc-protection on these *N*-benzyl propargylic amines were futile. This included the use of forceful reaction conditions, employing a large excess of Boc-anhydride, strong bases, prolonged refluxing, the use of Boc-ON as well as a nucleophilic catalyst (4-dimethylaminopyridine, DMAP). Compound **64** underwent a desilylation in good yield to form alkyne **66** (Scheme 2.11 c). Propargylic amine **66** was also subjected to all the protection conditions described above, however to no avail.



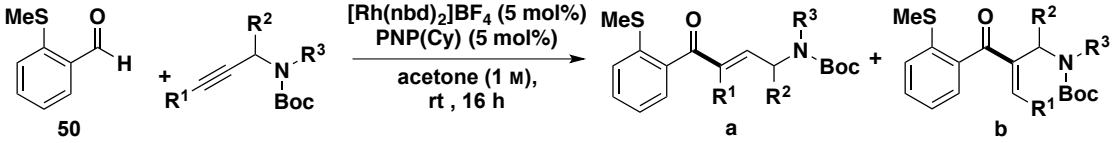
Scheme 2.11: a) Synthesis of *N*-benzyl propargylic amines. b) Attempted Boc protection of *N*-benzyl propargylic amines. c) Desilylation of *N*-benzyl propargylic amine.

2.4.2 Scope of Doubly *N*-Protected Propargylic Amines

Although a wide range of fully protected propargylic amines could not be synthesised, we had obtained a few propargylic amines that would enable a direct comparison of our newly optimised hydroacylation conditions (Table 2.5) to that in previous work (Scheme 2.7). It was evident that this new catalyst system considerably enhanced linear-selectivity for terminal alkynes (Table 2.5, entry1-3). Good yields were achieved using half the catalyst loading employed in previous work, as well as mild reaction conditions. The combination of the *N*-Boc and benzyl groups on the nitrogen effected an incredibly selective reaction, appearing to deliver the linear hydroacylation adduct in a 22:1 excess (entry 1). The *N*-Boc/benzyl substitution pattern was consequently selected as the optimal unit for doubly protected propargylic amines. It was however disappointing that employing internal alkynes under the described conditions resulted in poor regiocontrol, in addition to lower reactivity; achieving only 60% conversion (entry 4). Previous work (Scheme 2.7) had displayed better regiocontrol with internal alkynes when using the older

generation catalyst system. This observation indicated the use of internal propargylic amines would require re-optimisation.

Table 2.5: Substrate scope of propargylic amines with optimised reaction conditions.



Entry	Alkyne	R^1	R^2	R^3	Conversion (%)[a]	a:b[a]	Product
1	**51**	H	H	Bn	100 (78)	22:1	**55**
2	**52**	H	H	Me	100 (76)	8:1	**56**
3	**53**	H	H	Ph	100 (59)	5:1	**57**
4	**61b**	Et	Me	Bn	60	2:1	**67**

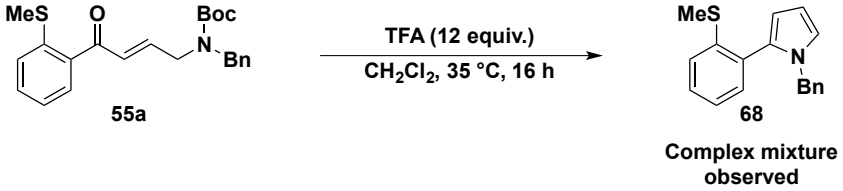
Conditions: **50** (0.15 mmol, 1 equiv.), propargylic amine (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt, 16 h. Value in parenthesis is the isolated yield of linear hydroacylation product **a**. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures.

2.5 Deprotection-Cyclisation Cascade of γ–Amino Enones

At this point, we were experiencing difficulty in obtaining the correct substitution pattern on the starting propargylic amines. The attention of the project turned towards examining the behaviour of doubly protected propargylic amines in the entire pyrrole-forming sequence.

As discussed in section 2.1, many acid-catalysed cyclisation methods of γ-amino enones exist. With our Boc-protected substrates, we hoped that both Boc-deprotection and subsequent cyclisation could be achieved under mildly acidic conditions. Initially we attempted deprotection/cyclisation of enone **55a** using the traditional conditions of trifluoroacetic acid (TFA) in CH_2Cl_2, which resulted in a complex mixture with trace amounts of isolable product (Scheme 2.12).[149] If less equivalents of TFA were employed, only starting material was returned. This suggested that although *N*-benzyl pyrrole may

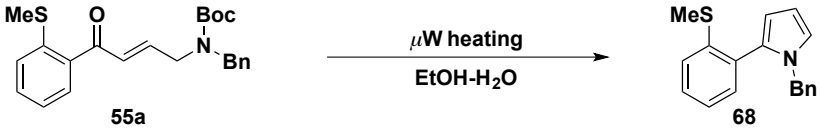
be materialising, it is unstable to the strong acidic conditions used. Given the sensitivity of the *N*-benzyl pyrroles, we looked at neutral conditions for Boc-deprotection.



Scheme 2.12: Attempted acid promoted Boc-deprotection.

Precedent for the cleavage of a Boc-group occurring at extremely high temperatures (>150 °C) existed.[150,151] Additionally there had been reports of dehydrative enone cyclisation occurring under microwave conditions.[152] This information assisted a previous member of the Willis group to establish a cyclisation of *γ*-amino enones *via* a thermal Boc-deprotection.[145] Consequently similar conditions were explored (Table 2.6).

Table 2.6: Investigating thermal Boc-deprotection and pyrrole formation.



Entry	Solvent (volume)	Temperature	Time (min)	Yield (%)
1	EtOH:H_2O (1 mL:1 mL)	170 °C	60	52[a]
2[b]	EtOH:H_2O (1 mL:1 mL)	170 °C	60	14
3	EtOH:H_2O (1.5 mL:1.5 mL)	170 °C	60	23
4	EtOH:H_2O (1 mL:1 mL)	150 °C	60	0
5	EtOH:H_2O (1 mL:1 mL)	170 °C	45	27

Conditions: **55** (0.06-0.25 mmol, 1 equiv.), base-washed silica-gel column. Isolated yields of the pure *N*-benzyl pyrrole. [a] Previous member of the Willis group achieved 79% yield under the described conditions.[145] [b] Purification *via* an aqueous work up.

As the established thermal cyclisation conditions had already been fine-tuned to a very specific procedure, it was challenging to improve on or even achieve the conditions described in the previous work (entry 1).[145] The purification of the pyrrole was just as

vital as the cyclisation procedure, and required instantaneous column chromatography using base-washed silica-gel. Attempts to observe the crude reaction mixtures *via* an aqueous work-up had a detrimental effect on the yield (entry 2). It was thought that decomposition accounted for the majority of the loss in yield, therefore we investigated lower temperatures (entry 4) and shorter reaction times (entry 5). However, upon examination it was apparent that a temperature of 170 °C was vital for reactivity and 60 minutes were required to achieve full conversion. Attempts to use base-activated alumina in place of silica gel was also unsuccessful. In addition, benzyl-protected pyrrole **68** was unstable upon isolation and decomposed over a short time at room temperature or in solution.

2.6 Exploring Singly Protected Terminal Propargylic Amines

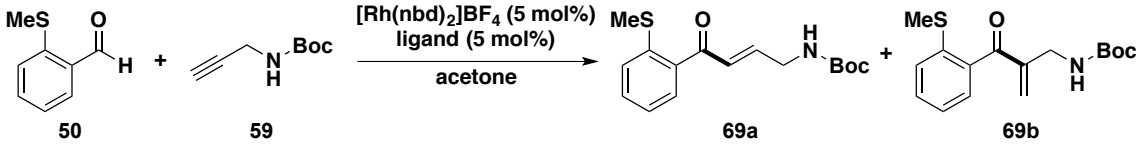
2.6.1 Optimisation of Singly Protected Terminal Propargylic Amines in Hydroacylation

In response to the limitations of substrate synthesis, as well as to the low yields and poor stability of the pyrrole products, an alternative class of propargylic amine for hydroacylation was sought. The ideal substrates would arise from a simple synthesis and allow equally as high linear-selectivity, yet afford stable pyrroles. We initially focused our attention on the more selective terminal alkynes and proposed that electron-withdrawing groups, as well as steric bulk on the nitrogen, would aid in blocking any undesired nitrogen-rhodium coordination. Moreover, an electron-withdrawing group on the nitrogen would stabilise the final cyclised product. For these reasons, in addition to the convenient cyclisation methods already described,[142,144] we decided to investigate the

behaviour of singly protected nitrogen in these hydroacylations; beginning investigations with commercially available *N*-Boc propargyl amine **59**.

Although we assumed that the previously optimised catalyst system would be the most efficient, we appreciated that singly protected propargylic amines had previously been poorly reactive. Therefore, we investigated a range of ligands under a variety of conditions (Table 2.7).

Table 2.7: Optimising the hydroacylation of *N*-Boc propargyl amine.



50 **59** **69a** **69b**

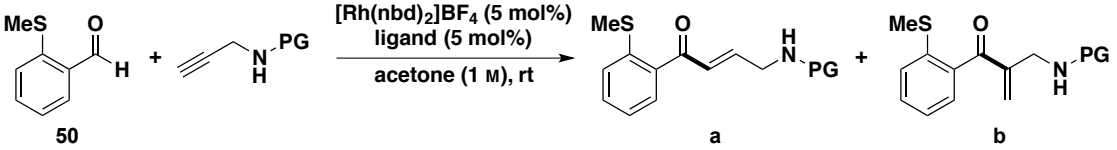
Entry	Ligand	Time (h)	Temp. (°C)	Conc. (M)	Conv. (%)[a]	a:b[a]
1	DPEphos	16	55	0.3	41 (32)	2:1
2	dppm	16	55	0.3	76 (69)	5:1
3	dcpm	16	55	0.3	85	3:1
4	dcpm	1	55	1	100 (87)	5:1
5	PNP(Cy)	16	55	0.3	78	9:1
6	PNP(Cy)	10 min	55	1	100	10:1
7[b]	PNP(Cy)	10 min	80	1	100	7:1
8[c]	PNP(Cy)	30 min	rt	1	100 (90)[d]	17:1
9	PNP(Cy)	2	0	1	100 (94)	20:1
10	dppe (*o*-^{i}Pr)	16	55	0.5	100 (85)[e]	>1:25

Conditions: **50** (0.15 mmol, 1 equiv.), **59** (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone. Value in parenthesis is the isolated yield of combined linear and branched products. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Performed in 1,2-DCE. [c] $[Rh(nbd)_2]BF_4$ (2 mol%), PNP(Cy) (2mol%), **59** (1.3 equiv.). [d] 86% isolated yield of linear isomer **69a**. [e] Value in parenthesis is the isolated yield for branched hydroacylation product **69b**.

The hemi-labile DPEPhos ligand was not only poorly selective, it was also a very inefficient catalytic system for this reaction (entry 1). As anticipated, the methylene bridged small bite-angle diphosphine ligands delivered poor regiocontrol (entry 2-4), in

keeping with the previous optimisations. It was soon evident that the PNP(Cy) ligand would again be the most efficient in this particular coupling to access the linear product (entry 5-9). This catalyst system behaved in a similar fashion to external deviations as previously described (section 2.3), leading to the optimised conditions invariably employing a 1 M concentration at room temperature to achieve a 17:1 ratio (entry 8). Although this selectivity was similar to the doubly protected terminal alkynes examined previously, the reactivity of this catalyst with the presented substrate was vastly superior. This system now only required a small excess of alkyne coupling partner (1.3 equivalents from 1.5-2.0 equivalents) and enabled the reaction to reach completion in 30 minutes when using only 2 mol% catalyst loading. It should be noted that this reaction was a lot faster when employing 5 mol% catalyst loading (5-10 minutes) achieving consistent yields and regioselectivity. The rate of the reaction could be slowed down in order to observe slightly better regiocontrol (entry 9), however for pragmatic reasons performing reactions at 0 °C was avoided and substrate scope was conducted with 5 mol% catalytic loading. Finally, we observed that the opposite type of catalyst system could achieve a branched-selective reaction; when employing a wide bite angle, sterically bulky ligand while heating, the branched product could be obtained as the sole regioisomer (entry 10). Pleasingly, we now had access to highly linear-selective conditions to be employed with readily-available aldehyde and alkyne substrates. Therefore, we advanced with singly protected propargylic amines as the desired coupling partner for this project. Consequently, we examined different protecting groups for linear-selectivity (Table 2.8).

Table 2.8: Protecting group optimisation of propargylic amines.



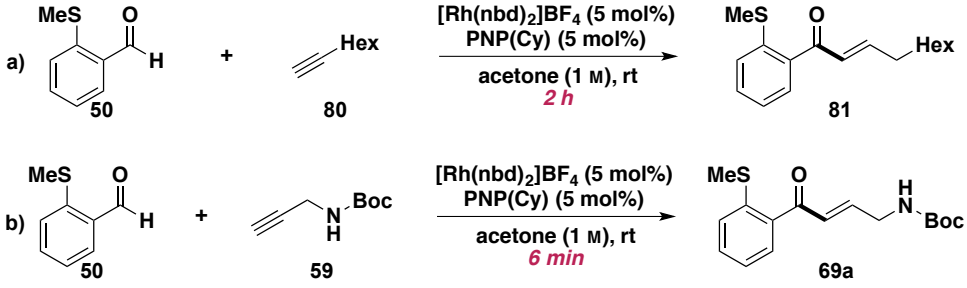
Entry	PG	Ligand	Time (h)	Conv. (%)[a]	Compound	a:b[a]
1	H (**70**)	PNP(Cy)	16	0	**75**	-
2	Cbz (**71**)	PNP(Cy)	30 min	100 (82)	**76**	12:1
3	Cbz (**71**)	dcpm	16	100 (79)	**76**	4:1
4	Fmoc (**72**)	PNP(Cy)	16	100 (69)[b]	**77**	16:1
5	Ts (**73**)	PNP(Cy)	10 min	100 (43)	**78**	4:1
6	Ts (**73**)	dcpm	16	100 (84)	**78**	1:1
7	Bus (**74**)	PNP(Cy)	16	84 (53)[b]	**79**	7:1

Conditions: **50** (0.15 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials). Bus = *tert*-butyl sulfonyl. Value in parenthesis is the isolated yield of combined linear and branched products. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Value in parenthesis is the isolated yield of the linear product only **a**.

The unprotected propargylic amine was not tolerated (entry 1), potentially due to strong coordination of the substrate to rhodium. Carbamates (entry 2-4 and for Boc group see Table 2.7 entry 3 and 8) significantly outperformed sulfonyl containing groups (entry 5-7) in regards to linear-selectivity. Although both Boc- and Fmoc- were highly regioselective with the PNP(Cy) ligand, the Boc-group appeared to be more reactive in general as well as more readily available, hence we were certain that the *N*-Boc propargylic amines would be the ideal substrates for this hydroacylation. Investigating both the PNP(Cy) and dcpm ligands with selected protecting groups ensured that the protecting group trends observed were not specific to the PNP(Cy) catalyst.

2.6.2 Kinetics of Propargylic Amines in Hydroacylation

With the optimum propargylic amines for hydroacylation identified, an experiment was designed to evaluate whether the nitrogen atom on the alkyne substrate was actually directing unsaturated C-C bond coordination. It was postulated that if the nitrogen on the alkyne directs the unsaturated triple-bond to the rhodium metal centre, then it should also promote the coordination. This aided coordination of the unsaturated bond could potentially cause a difference in the rate of hydroacylation in comparison to alkynes that do not possess directing ability. A simple kinetic study was conducted, in which both 1-octyne **80** (Scheme 2.13 a) and *N*-Boc propargyl amine **59** (Scheme 2.13 b) were subjected to identical hydroacylation conditions simultaneously.



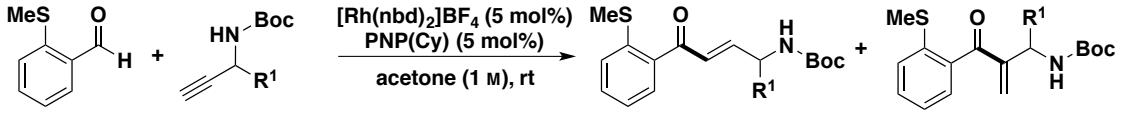
Scheme 2.13: Reaction times accurately observed for a non-chelating alkyne (a) and potentially chelating alkyne (b).

The competition study displayed that formation of the hydroacylation product **69a** was 20 times faster than the synthesis of **81**, which employed non-directing alkyne **80**, which could be suggestive of a directing ability of propargylic amines, similar to that discussed previously (Scheme 2.8). However, this study is not conclusive as only one catalytic system was studied.

2.6.3 Scope of Terminal Propargylic Amines in Hydroacylation

In a bid to further understand the reactivity of *N*-Boc propargylic amines, a brief scope was conducted and confirmed that the linear-selectivity was enhanced with substitution

at the propargylic position (Scheme 2.14). When α-substitution incorporated groups larger than a methyl group (**86**, **87**) linear-selectivity was enhanced to >25:1, which meant that the branched regioisomer could no longer be detected by ^{1}H NMR spectroscopy. This demonstrated that further improvements in regiocontrol could be achieved by substrate design. Additionally, both alkyl and aromatic groups (**82**-**84**) at this position could be accommodated, with little effect on the yield.



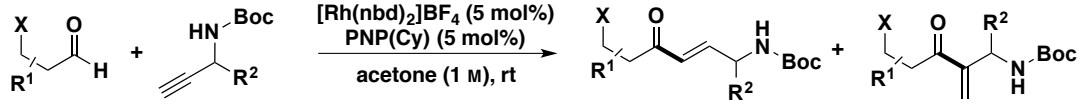
Compound	R^1	Product	R^1	Yield (a only)	a:b
82	Me	85	Me	89%	25:1
83	Ph	86	Ph	88%	>25:1
84	^{t}Bu	87	^{t}Bu	91%	>25:1

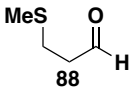
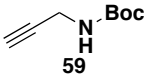
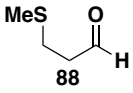
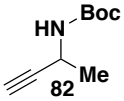
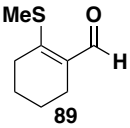
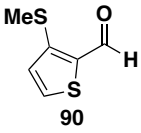
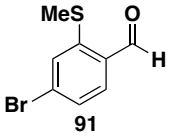
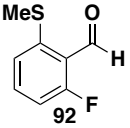
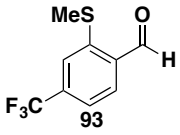
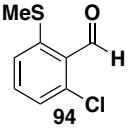
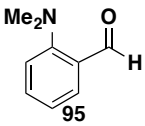
Scheme 2.14: Scope of *N*-Boc propargylic amines.

2.7 Reactivity of β-Heteroatom Chelating Aldehydes

Thus far only the reactivity of 2-(methylthio)benzaldehyde **50** had been tested during the optimisation studies, as this substrate is a generally reliable and efficient aldehyde for rhodium-catalysed hydroacylation. With the optimised conditions in place, we wished to expand the substrate scope by investigating how different aldehydes would fair in the synthesis of γ-amino enones (Table 2.9). Pleasingly, a range of aldehydes, including alkyl (entry 1-2), alkenyl (entry 3) and substituted aryl and heteroaryl (entry 4-7) were introduced without incident. Curiously, alkenyl aldehyde **89** displayed less pronounced linear-selectivity, however performing the reaction at reduced temperatures overcame this issue (entry 3). Although functionalisation at the *ortho*-position of aromatic aldehydes could be tolerated, this was limited to a fluorine atom. This specific substitution pattern also displayed a notable increase in reactivity (entry 6).

Table 2.9: Chelating aldehyde scope in γ-amino enone synthesis.

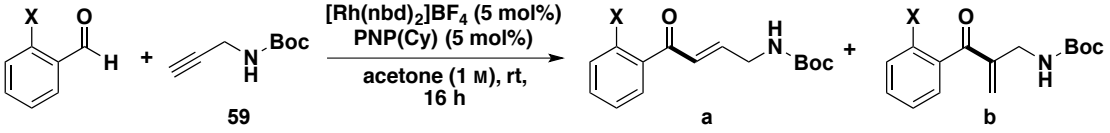


Entry	Aldehyde	Alkyne	Product	Time	Yield	a:b[a]
1	 88	 59	**96**	3 h	64%	25:1
2	 88	 82	**97**	16 h	71%	>25:1
3[b]	 89	**59**	**98**	15 min	71%	12:1
4	 90	**59**	**99**	16 h	77%	6:1
5	 91	**59**	**100**	1 h	80%	18:1
6	 92	**59**	**101**	5 min	70%	11:1
7	 93	**59**	**102**	3 h	84%	11:1
8	 94	**59**	**103**	16 h	0%	-
9	 95	**59**	**104**	6 h	99%	>25:1

Conditions: aldehyde (0.15 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt. Yield is isolated yield of linear hydroacylation product **a**. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Performed at 0 °C.

It was believed that the possible steric constraints enforced around the metal centre by the fluorine atom promoted reductive elimination, however increasing the size of this group hinders the C-H activation process and results in lack of reactivity (entry 8). This methodology also tolerated a change in chelating atom on the aldehyde; the use of a nitrogen chelating motif (entry 9) achieved quantitative yield and produced only the linear regioisomer detectable by ^{1}H NMR spectroscopy. Upon observing the excellent regioselectivity of the NMe_2 chelating group in comparison to SMe, we postulated that this could be a result of a more sterically demanding directing group. It was assumed that larger steric occupation around the rhodium metal-centre would preclude heteroatom chelation from the alkyne component. Consequently, the size of the directing group was examined (Table 2.10).

Table 2.10: Steric impact of the chelating heteroatom on aldehydes.



Entry	Aldehyde	X group	Conversion (%)[a]	Product	a:b[a]
1[b]	**50**	SMe	100 (86)	**69**	17:1
2	**105**	S^{i}Pr	100 (80)	**108**	>25:1
3	**106**	S^{t}Bu	94 (70)	**109**	4:1
4[c]	**95**	NMe_2	100 (99)	**104**	>25:1
5	**107**	NH_2	100 (58)[d]	**110**	1:3

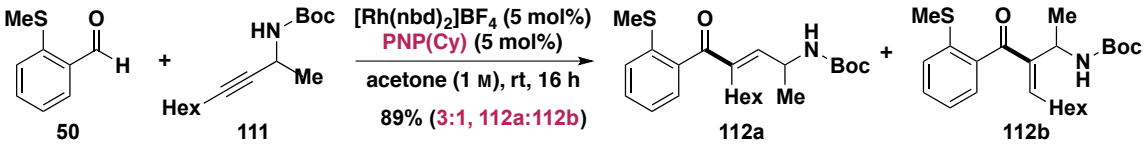
Conditions: aldehyde (0.15 mmol, 1 equiv.), **59** (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt, 16 h. Value in parenthesis is the isolated yield of linear hydroacylation product **a**. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Reaction time of 10 mins. [c] Reaction time of 6 h. [d] Value in parenthesis is the isolated yield of branched hydroacylation product **b**.

Increasing the size of the directing group to an extent, from SMe **50** to S^{i}Pr **105** (entry 1-2), had the desired effect and regioselectivity was enhanced, resulting in no observation

of the branched isomer. However, when increasing the directing group size further, to S^{t}Bu **106** (entry 3), regioselectivity plummeted down to 4:1 for the linear product. Although a curious observation, it could be explained by lack of availability of the sulfur to behave as a directing group due to hindrance from the *tert*-butyl. This is proven by the decrease in reactivity observed with this aldehyde, as even after 16 hours the reaction did not reach completion. Decreasing the tether size of the nitrogen heteroatom to NH_2 **107** had the anticipated effect and regioselectivity was actually inverted in comparison to the linear-selective NMe_2 tether **95** (entry 4-5).

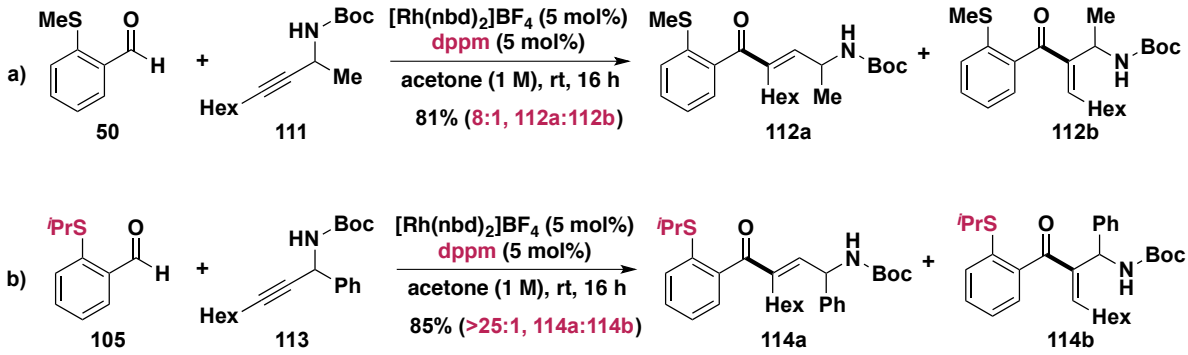
2.8 Reactivity of Internal Propargylic Amines

Preliminary attempts to substitute internal alkynes for terminal propargylic amines under the optimised conditions were unsuccessful with regards to regiocontrol (Scheme 2.15). Although hydroacylation did occur, the linear-selectivity declined to 3:1 when employing internal propargylic amine **111**. Subsequent ligand alterations, either using DPEPhos or dcpm displayed poor levels of catalytic turnover.



Scheme 2.15: Reactivity of internal alkynes with PNP(Cy)-based catalyst.

Pleasingly, the use of PCP ligand dppm enabled complete consumption of the starting materials to form the linear hydroacylation product **112a** with adequate levels of regiocontrol (Scheme 2.16 a). Moreover, increasing the size of the sulfur directing group **105** in combination with aryl substitution at the α-position of the propargylic amine **113** delivered excellent linear selectivity of **114** (Scheme 2.16 b).

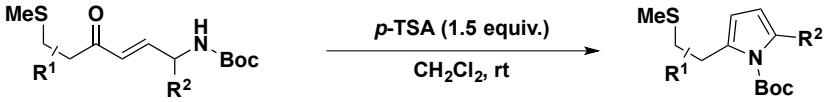


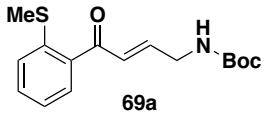
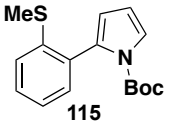
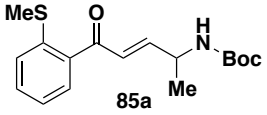
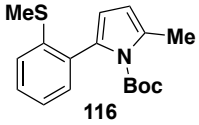
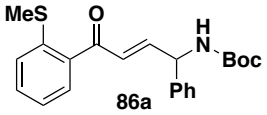
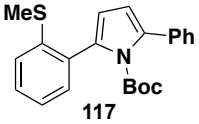
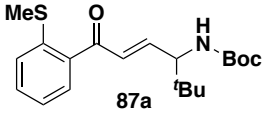
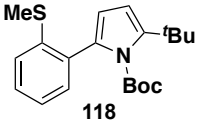
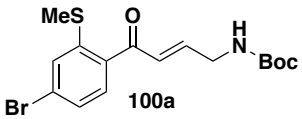
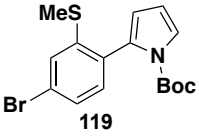
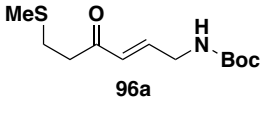
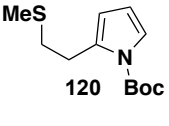
Scheme 2.16: Optimised hydroacylation of internal propargylic amines.

2.9 Pyrrole Formation through γ-Amino Enone Dehydration

Precedent for the acid promoted cyclisation of singly protected γ-amino enones was discussed in section 2.1. The described dehydrations involved the use of either 2.0 M HCl in ether, or *para*-toluenesulfonic acid (*p*-TSA) to initiate isomerisation and cyclisation. It was hoped that this methodology could be applied to the *N*-Boc γ-amino enones obtained from the previous hydroacylation step. Gratifyingly, the cyclisation of the hydroacylation adducts proceeded smoothly when exposed to relatively mild acidic conditions, such as *p*-TSA. Synthetically stable 2,5-substituted *N*-Boc pyrroles were obtained in excellent yields (Table 2.11). All the cyclisations attempted resulted in clean formation of the *N*-Boc pyrroles, with no deprotection or side-reactions observed. The only exception to the high yields was when employing alkyl amino enone **96a** (entry 6) and this was attributed to volatility of both starting material and pyrrole product. It should also be noted that these reactions were performed under air and an inert atmosphere had no effect on yield.

Table 2.11: Synthesis of *N*-Boc pyrroles *via* isolated hydroacylation adducts.



Entry	γ-Amino enone	Time (h)	Pyrrole	Isolated yield (%)	Two-step yield (%)
1	 69a	4	 115	97	83
2	 85a	2	 116	83	74
3	 86a	4	 117	93	82
4	 87a	16	 118	90	82
5	 100a	2	 119	93	74
6	 96a	4	 120	62	40

Conditions: γ-amino enone (1 equiv.), *p*-TSA (1.5 equiv.), CH_2Cl_2, rt. Two-step yield=combined yield over both hydroacylation and cyclisation steps.

2.10 Summary

To conclude, a novel synthetic route to γ-amino enones has been developed through the hydroacylation coupling of aldehydes and propargylic amines. This reaction exploits an electron-rich rhodium(I) catalyst for hydroacylation, employing a relatively new *bis*-phosphine PNP ligand. The amalgamation of this catalytic system and substrate design has enabled full control over the reactivity and regioselectivity in this hydroacylation. In addition, access to both linear and branched γ-amino enones has been described through

the use of a ligand switch. The development of a highly linear-selective hydroacylation has led to a better understanding of the effect of chelating groups on the alkyne coupling partners.

Finally, the formation of desirable pyrrole rings has been reported in very good yields over two steps. This chapter proves that the synthesis of a variety of substituted pyrrole heterocycles is possible *via* rhodium-catalysed intermolecular hydroacylation. Efforts to improve this pyrrole synthesis, as well as expand the field of hydroacylative disconnections in five-membered aza-heterocycle synthesis, will be discussed in Chapter 3.

Chapter 3

One-Pot Cascade Synthesis of Five-Membered Aza-Heterocycles

3.1 Introduction

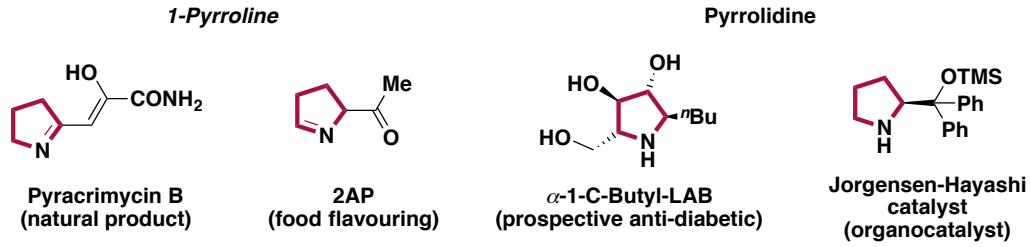
3.1.1 One-Pot Synthesis

In recent years, efficiency and environmental sustainability have been central issues for synthetic chemists, particularly within the industrial sector. One method that is widely considered to be an efficient approach in contemporary organic chemistry is so-called 'one-pot synthesis'.[153] This approach permits several synthetic transformations to occur in one-reaction vessel, avoiding intermediate purification processes. Such methods save time and simplify practical procedures, whilst also being considered 'green' as they minimise chemical wastage.[154]

The applications of one-pot synthesis have been prevalent within industry and natural product synthesis for nearly 100 years now.[155] However, applying this type of reaction to organometallic chemistry has been more challenging, as highly active metal species can be detrimental when present during a secondary bond-forming step. Therefore, one-pot synthesis within organometallic chemistry would vastly increase the appeal of the methodology.

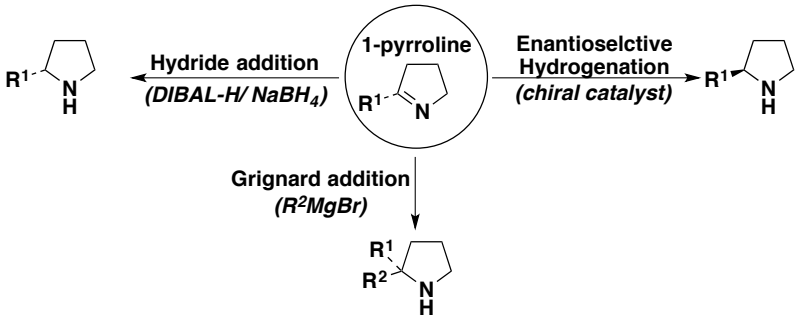
3.1.2 Synthesis of Aza-Heterocycles

As previously discussed in Chapter 2, section 2.1, the importance of efficient techniques to access pyrrole rings has been firmly established. However, the presence of saturated or partially-saturated five-membered heterocycles is also widespread within nature, pharmaceutical compounds and organocatalysts (Scheme 3.1).[156-158]



Scheme 3.1: Presence of saturated and partially-saturated aza-heterocycles in useful compounds.

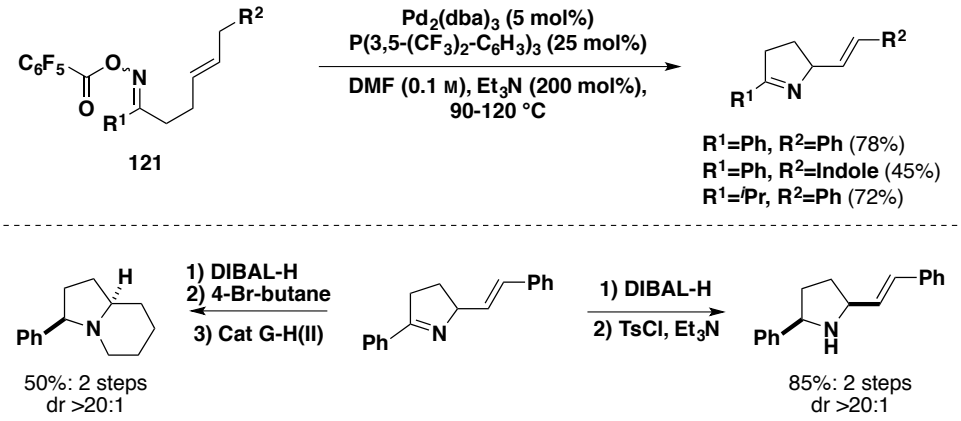
Partially-saturated ring systems are inherently versatile building blocks, as they can grant access to so-called 'privileged structures', such as pyrrolidines. Obtaining highly sought after pyrrolidine rings *via* their partially-saturated analogues has proven to be a relatively straightforward and popular route (Scheme 3.2). This can be achieved either with traditional reducing agents,[159,160] organometallic additions,[161] or by hydrogenation reactions, which can also proceed enantioselectively when exploiting the appropriate catalytic systems.[162-164]



Scheme 3.2: Pyrrolidine synthesis *via* cyclic imine reduction.

It is for this reason that targeting the synthesis of cyclic imine moieties would be attractive. Currently, methodology for the synthesis of 1-pyrrolines *via* transition metal-

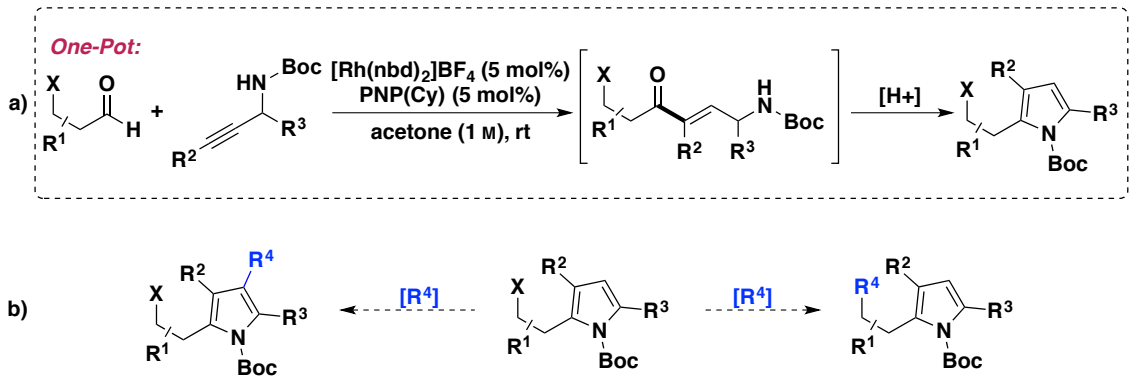
catalysis is extremely limited, and usually employs very specific connectivity.[161,165-167] Additionally, the use of intermolecular rhodium(I)-catalysis is non-existent within the field of 1-pyrroline synthesis. Despite this, one elegant method, recently described by the Bower group, involved the intramolecular palladium-catalysed cyclisation of oxime esters with alkenes (Scheme 3.3).[161] Readily assembled compounds, such as **121**, delivered good yields and selectivity in the described transformation to 1-pyrrolines. The dihydropyrroles were subsequently derivatised to a variety of pyrrolidines and a single example of a fused ring system.



Scheme 3.3: Synthesis of cyclic imines reported by Bower and co-workers.

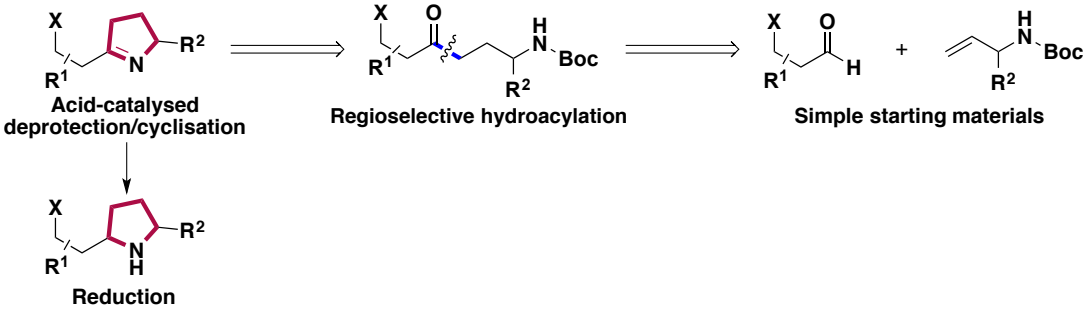
3.2 Project Aims and Previous Work

With an appreciation for the requirement of environmentally-friendly and synthetically appealing transformations, we first aimed to revisit the pyrrole formation optimised in Chapter 2. We proposed that the hydroacylation and cyclisation steps could occur in one-pot, without isolation of the *γ*-amino enone intermediate (Scheme 3.4 a). Moreover, we aimed to prove the robustness and utility of this one-pot heterocycle formation, by providing an extended substrate scope and further functionalisation to obtain highly-substituted pyrrole ring manifolds (Scheme 3.4 b).



Scheme 3.4: a) Proposed one-pot synthesis of pyrrole rings. b) Further manipulations of pyrrole substrates.

We also designed a related methodology to synthesise partially-saturated five-membered heterocycles, due to a lack of succinct and effective methods available to access this type of heterocycle (Scheme 3.5). Replacing propargylic amines in hydroacylation with an alkene coupling partner was envisaged. The coupling of readily-accessible *N*-Boc allylic amines with chelating aldehydes would afford cyclisable adducts, which could yield 1-pyrrolines through an *in situ* Boc-deprotection/dehydrative cyclisation. We also aimed to access fully-saturated heterocycles through subsequent reductions.



Scheme 3.5: Retrosynthetic pathway to dihydropyrroles and access to pyrrolidines.

3.3 Synthesis of Pyrroles *via* a One-Pot Cascade Reaction

As concluded from the investigations conducted in Chapter 2, it was evident that *N*-Boc propargylic amines were the optimal coupling partners for a linear-selective

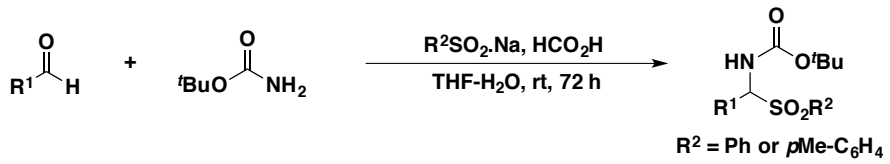
hydroacylation, and a high yielding two-pot pyrrole synthesis. In order to afford the correct regioisomer of the γ-amino enone intermediate, the reaction required a PNP(Cy)-based rhodium(I) catalyst for terminal alkynes (Chapter 2, Scheme 2.14) and a dppm-based catalyst for internal alkynes (Chapter 2, Scheme 2.16). Thus far, a wide aldehyde scope has been established for the hydroacylation step (Chapter 2, Table 2.9). However, the alkyne scope remained to be suitably investigated.

3.3.1 Synthesis of Alkyne Starting Materials

One critical factor in affirming that *N*-Boc propargylic amines were ideal alkynes for hydroacylation was their convenient and high-yielding synthesis. Petrini reported a propargylic and allylic amine synthesis, whereby organometallic reagents are added into the synthetic equivalents of *N*-acyl imines; α-amido sulfones.[168] This method has since been used by numerous groups as a reliable route to access a huge array of substituted propargylic and allylic amines.[169-171] Initially, we applied this methodology to the synthesis of a variety of *N*-Boc α-amido sulfones (Table 3.1). Achieving aryl and heteroaryl substitution was very dependable (entry 4-16), although a slight decrease in yield was observed when the requisite aldehydes were not distilled. However, the formation of alkyl substituted α-amido sulfones was more challenging; **122** and **124** required the use of a tolyl sulfonyl stabilising group (entry 1 and 3).

Following addition of organometallic reagents to α-amido sulfones, a range of terminal *N*-Boc propargylic amines was synthesised in moderate to good yields (Scheme 3.6). Almost all of the sulfones employed afforded some addition product that we believed would facilitate interesting substitution patterns on the final pyrrole ring.

Table 3.1: Range of α-amido sulfones synthesised.

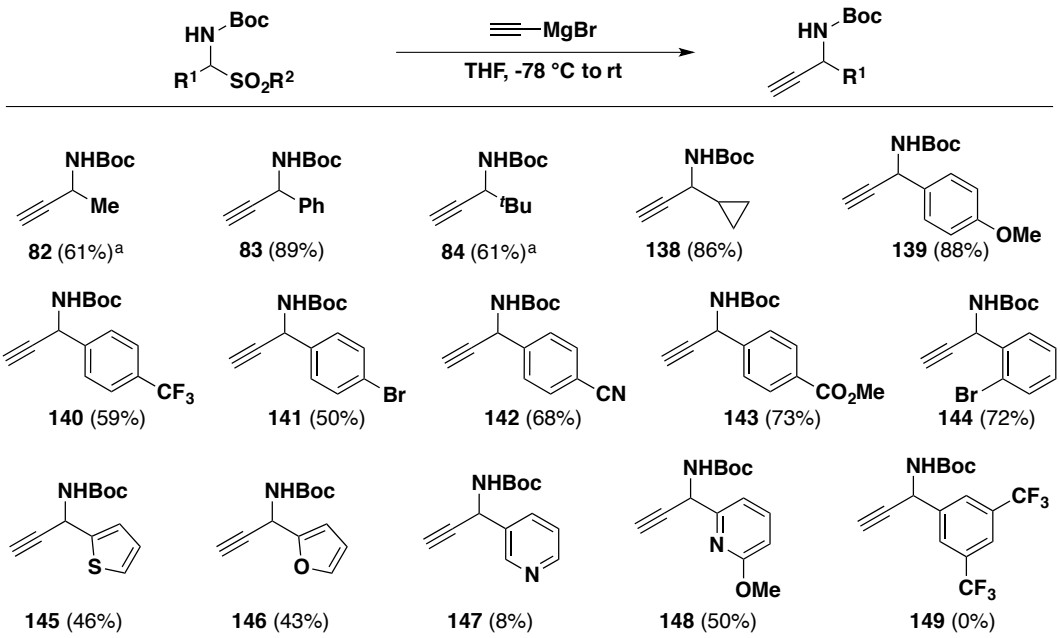


Entry	R^1	α-Amido sulfone	Isolated yield
1[a]	Me	**122**	61%
2	^{t}Bu	**123**	74%
3[a]	CyPr	**124**	35%
4	Ph	**125**	86%
5	*p*OMe-C_6H_4	**126**	49%
6	*p*CF_3-C_6H_4	**127**	55%
7	*p*Br-C_6H_4	**128**	26%
8	*p*CN-C_6H_4	**129**	88%
9	*p*CO_2Me-C_6H_4	**130**	30%
10	3,5-$(CF_3)_2$-C_6H_3	**131**	45%
11	*o*Br-C_6H_4	**132**	55%
12	2-thienyl	**133**	25%
13	3-thienyl	**134**	41%
14	2-furyl	**135**	50%
15	3-pyridyl	**136**	44%
16	3-OMe-2-pyridyl	**137**	74%

Conditions: *tert*-butyl-carbamate (1 equiv.), aldehyde (2 equiv.), sodiumbenzene sulfinate salt (2 equiv.), formic acid (0.02-6.5 equiv.), THF:H_2O (0.3-0.7 M, 1:2), rt, 72 h. [a] R^2=*p*Me-C_6H_4, through the use of sodiumtoluene sulfinate salt (2 equiv.).

The synthesis of alkynes containing electron-deficient aromatic rings (**140**, **141**), was considerably lower yielding, and in the case of *bis*-CF_3-substitution (**149**), no reactivity was observed. Pleasingly, five-membered heteroaromatic rings could be introduced to afford terminal alkynes **145** and **146** with ease. In contrast, obtaining alkyne **147**, with an unsubstituted six-membered heterocyclic pyridine as a substituent, resulted in an extremely poor yield, as the reaction mixture contained many non-isolatable by-products.

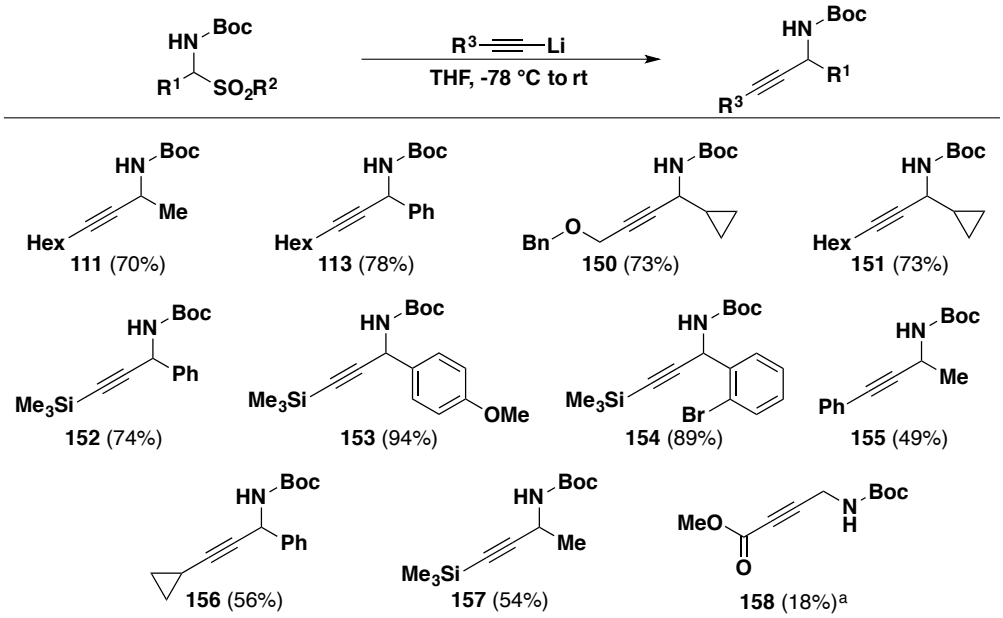
However, substitution *ortho*- to the nitrogen in the pyridine ring bypassed this issue for the successful formation of **148**. These heterocyclic substrates are valuable starting materials as they could potentially grant access to linked heterocyclic systems after the designed one-pot reaction.



Conditions: α-amido sulfone (1 equiv.), ethynylmagnesium bromide (2.2 equiv.) THF, addition at -78 °C then warmed to rt. [a] Organometallic reagent=lithiated TMS-acetylene, isolated yield displayed is after TMS deprotection.

Scheme 3.6: Synthesis of terminal *N*-Boc propargylic amines.

We continued to use this methodology to afford internal propargylic amines in good yields (Scheme 3.7). Bearing in mind the significant impact of the alkyne terminus on reactivity and regioselectivity in hydroacylation, we synthesised a variety of substitution patterns at the terminal position. Alkyl and aromatic groups (**111**, **113**, **151** and **155**), sterically demanding substituents (**152-154**, **156**), heteroatom-based functionalisation (**150**) and an sp^2 centre (**158**) (which was synthesised *via* an alternative methodology[136]) were all deemed as potentially active functionalities for hydroacylation.



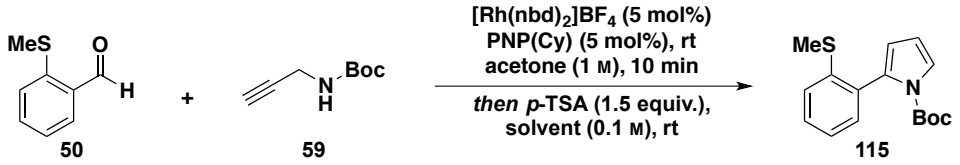
Conditions: α-amido sulfone (1 equiv.), terminal alkyne (2.2 equiv.), organometallic reagent (2.2 equiv.) THF, addition at -78 °C then warmed to rt. [a] Alkyne synthesised by an alternative method described by Trost *et. al.*[136]

Scheme 3.7: Range of internal alkynes synthesised.

3.3.2 Optimisation of a Cascade One-Pot Pyrrole Synthesis

Investigations began with the previously employed model substrates for the two-pot optimisation. The hydroacylation of *o*-SMe-benzaldehyde **50** with *N*-Boc propargyl amine **59** was performed, and once the reaction had reached completion, as detected by TLC analysis, it was opened to air and subjected to the optimised cyclisation conditions of 1.5 equivalents of *p*-TSA in CH_2Cl_2 at room temperature (Chapter 2, Table 2.11). Unfortunately, in comparison to the two-step procedure, which achieved an 83% overall yield (Table 2.11, entry 1), the initial attempts to combine the two protocols displayed a diminished yield (Table 3.2, entry 1). Although the majority of the linear hydroacylation adduct was consumed under the pyrrole-forming conditions, the reaction was sluggish (16 h) and formed many other polar byproducts, however any branched enone formed through hydroacylation was left intact.

Table 3.2: Optimisation of cyclisation conditions for a one-pot reaction.



Entry	Solvent	Time (h)	Isolated yield
1	CH_2Cl_2	16	74%
2[a]	CH_2Cl_2	16	66%
3	CH_2Cl_2 (0.5 M)	16	59%
4[b]	CH_2Cl_2	6	61%
5[c]	CH_2Cl_2	5	47%
6[d]	CH_2Cl_2	6	68%
7[e]	CH_2Cl_2	6	81%
8	CH_2Cl_2/H_2O	16	0%
9	CH_2Cl_2/Silica	16	62%
10	Acetone	6	42%
11	EtOH	16	63%
12[a]	EtOH	16	65%
13	Et_2O	16	45%
14	THF	48	51%
15	PhMe	16	46%
16	MeCN	4	81%
17	MeCN	2	57%

Conditions: **50** (0.15 mmol, 1 equiv.), **59** (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt, 10 min *then* add *p*-TSA (1.5 equiv.) under the conditions stated. [a] Entire sequence performed under a N_2 atmosphere. [b] Cyclisation performed at 55 °C. [c] 3 equiv. of *p*-TSA. [d] Evaporated all acetone before dissolving residue in CH_2Cl_2 for cyclisation. [e] Filtered through silica plug (acetone) and solvent evaporated before dissolving in CH_2Cl_2.

In an attempt to improve the yield displayed in entry 1, it was thought that maintaining an inert atmosphere throughout both steps would be beneficial (entry 2), however this had little effect on yield, therefore we continued to open the reaction vessel to air before

cyclisation. Increasing the concentration (entry 3) or the temperature (entry 4) slightly decreased the yield, presumably promoting the adverse side-reactions observed. In order to counteract the sluggish pace of the reaction, more acid was employed (entry 5), unfortunately this resulted in increased decomposition. It was thought that the small amount of acetone present from the initial hydroacylation reaction was having a detrimental effect on the cyclisation, however removing the acetone had no impact on the pyrrole formation (entry 6). Finally, it became apparent that the presence of rhodium in the reaction mixture was hindering the pyrrole-forming cyclisation, because a similar yield to the two-step reaction was obtained when filtering the rhodium before cyclisation (entry 7), however this entailed that the procedure was no longer truly one-pot.

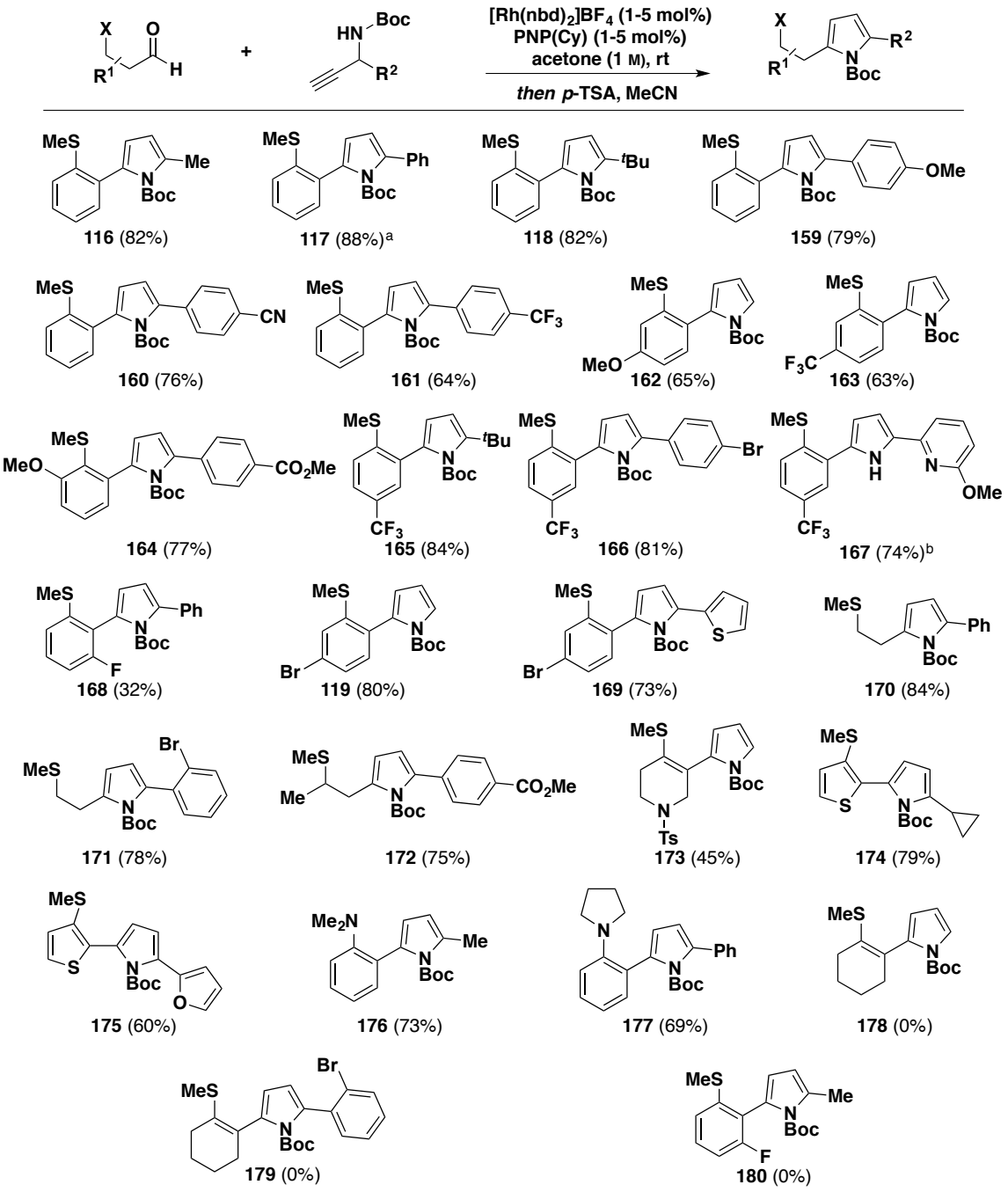
With this result in hand, we aimed to deactivate any rhodium before adding the acid for cyclisation. Initially, we investigated whether the rhodium could be taken up by the aqueous layer in a biphasic reaction solvent (entry 8), which lead to complete failure to consume any starting material. Placing silica gel into the reaction mixture, essentially to allow rhodium adsorption, did not have the desired effect on the yield (entry 9). Therefore, we then turned our attention to deactivating the rhodium through the use of solvents, either by insolubility (entry 13 and 15) or over-coordination (entry 14, 16-17). We found that addition of acetonitrile, at a 0.1 M concentration, was sufficient to enable a clean pyrrole-forming cyclisation, in an adequate time-frame (Entry 16). We postulated that the yield may be improved further upon using more functionalised propargylic amines, which would provide additional stabilisation to the pyrrole ring system. The conditions described in Table 3.2, entry 16 were selected as the optimal for this one-pot cascade pyrrole synthesis and the substrate scope was examined.

3.3.3 One-Pot Synthesis of Mono- and Di-Substituted Pyrrole Rings

Pleasingly, the addition of *p*-TSA and a small quantity of acetonitrile directly to the reaction mixtures, upon completion of the hydroacylation process, allowed rapid and clean conversions to a range of 2,5-*N*-Boc functionalised pyrroles (Scheme 3.8). Varied substitutions arising from the propargylic amine could be readily incorporated, including alkyl (**116**, **118**), functionalised aryl and heteroaryl groups (**159**, **160** and **169**). Moreover, the aryl substituents could possess steric bulk at the hindered *ortho*-position (**171**). Useful functionalities from the propargylic amines were also compatible in this sequence, such as halides (**166**), esters (**164**, **172**) and nitrile (**160**).

Variation of the aldehyde component was similarly key in accessing differently functionalised pyrroles. Substitution on every position of the aromatic ring of aryl aldehydes was achieved in good-to-excellent yields, including the presence of a fluorine atom at the hindered *ortho*-aldehyde position (**168**), albeit in a decreased yield. Alkyl aldehydes generally displayed good reactivity (**170**-**172**) and we were also successful in exchanging the chelating atom to nitrogen in very good yields (**176**, **177**). Interestingly, it was noted that when employing an aldehyde possessing a *para*-CF_3 substituent to the sulfur (**165**-**167**), extremely effective hydroacylation couplings were observed, *e.g.* the hydroacylation coupling to synthesise pyrrole **165** required only 2 minutes and was significantly faster than the hydroacylation step for the synthesis of **118** (30 minutes). Unfortunately, not all aldehydes were compatible in this cascade protocol; alkenyl aldehydes were limited to a single *N*-containing example (**173)**. The carbocyclic alkenyl aldehydes were found to not only be poorly linear-selective in hydroacylation, but less stable under the acidic cyclisation conditions (**178**, **179**). Despite this, functional group tolerance at the 2- and 5-position of the pyrrole ring was excellent and we were able to synthesise several interesting linked heterocycles in a concise and direct manner, which

would otherwise require a stepwise synthesis (**169**, **175**).[172,173] Formation of the pyrrole ring bearing a pyridine heterocycle required a higher catalyst loading of 7 mol% and resulted in instantaneous Boc-deprotection during cyclisation (**167**).



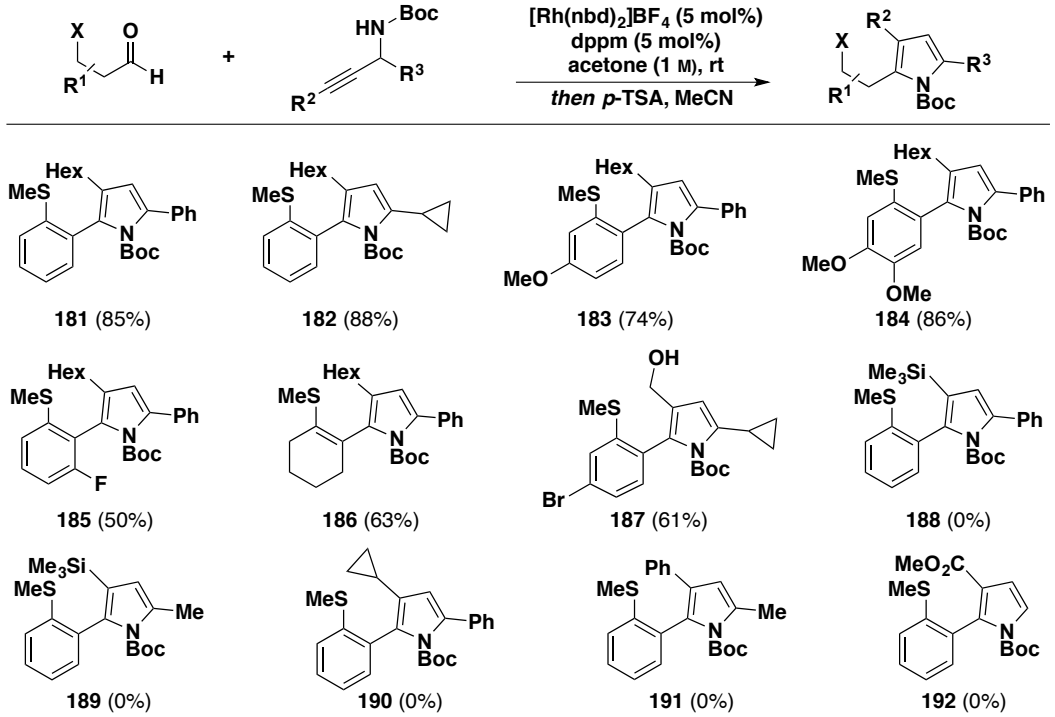
Conditions: aldehyde (0.15 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt, *then* *p*-TSA (1.5 equiv.), MeCN (0.1 M), rt. [a] Performed at 3.2 mmol scale, 1 mol% catalyst loading and obtained 1.04 g of product. [b] Performed at 7 mol% catalyst loading.

Scheme 3.8: Scope of terminal propargylic amines in a one-pot pyrrole formation.

Finally, a larger scale preparation of pyrrole **117** was achieved in an 88% yield, employing very low catalyst loadings (1 mol%). This reaction afforded over 1 g of product and along with the rest of the substrate scope displays the robustness and potential utility of this pyrrole formation.

3.3.4 One-Pot Synthesis of Tri-Substituted Pyrrole Rings

Pleasingly, we were able to apply the optimised one-pot conditions to internal propargylic amines, in conjunction with a dppm derived catalyst for the hydroacylation step (Scheme 3.9). A range of tri-substituted *N*-Boc pyrroles were accessed; alkyl chains (**181**-**186**) as well as a hydroxymethyl group (**187**) were successfully installed at the 3-position of the ring. Unfortunately, the scope of internal propargylic amines was heavily limited at the terminal position of the alkyne, due to lack of reactivity in the hydroacylation coupling. When both sides of the C-C triple bond were occupied by sterically demanding groups, including an aryl ring or an sp^2 centre, no coupling was observed (**188**-**192**). We did however manage to place steric bulk one carbon atom away from the terminus to synthesise pyrrole **187**, which involved the successful coupling of a benzyl protected internal propargylic amine (Scheme 3.7, **150**), followed by benzyl-deprotection during the cyclisation step. Throughout these investigations, it became evident that the formation of tri-substituted pyrroles was faster than the assembly of mono- or di-substituted rings, and also resulted in more stable products, hence previously unstable aldehydes could be coupled with internal substrates to access pyrroles **185** and **186**. Owing to the difficulty of internal alkyne hydroacylation, catalyst loadings lower than 5 mol% for the primary step could not be employed. Despite this, a good range of highly-substituted heterocycles could be assembled in a direct and synthetically appealing manner.



Conditions: aldehyde (0.15 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), dppm (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), rt, *then* *p*-TSA (1.5 equiv.), MeCN (0.1 M), rt.

Scheme 3.9: Scope of internal propargylic amines in one-pot pyrrole synthesis.

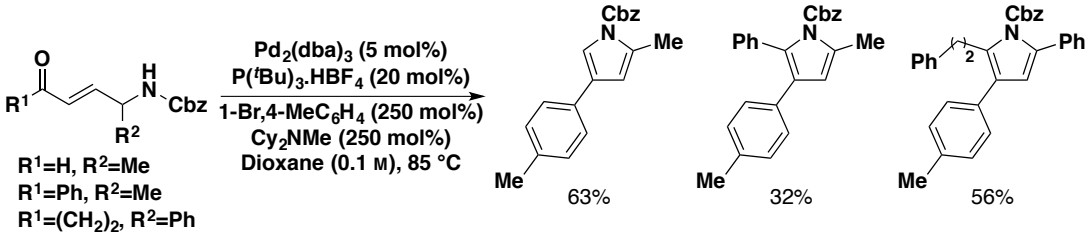
3.4 Functionalising the Final Position on the Pyrrole Ring

A limitation of the presented pyrrole synthesis is the use of an alkyne as one of the reaction components, as this necessarily means that one C-3 position of the pyrrole product is invariably unsubstituted. Accordingly, we chose to demonstrate the preparation of tetra-substituted pyrroles, by using a variety of activating methodologies of both the hydroacylation intermediates and the pyrrole products themselves.

3.4.1 Heck Reactions on Hydroacylation Adducts

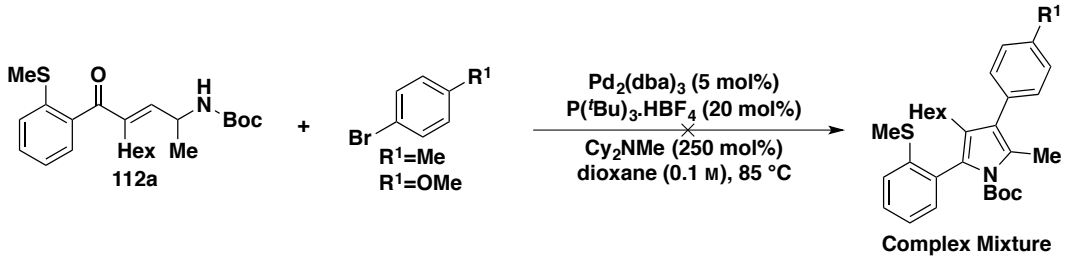
Initially, the possibility of applying a Heck arylation to the γ-amino enone intermediates was explored, using methodology disclosed by the Donohoe group for the synthesis of tri-substituted pyrroles (Scheme 3.10).[144] The authors subjected singly substituted enones to Heck arylation conditions that were previously reported by Fu.[174] This resulted in the

isolation of pyrroles in good yields, without the requirement of acid to cyclise; they proposed that isomerisation of the arylated intermediate occurred during the course of the reaction.



Scheme 3.10: The Donohoe group's approach to tri-substituted pyrroles.

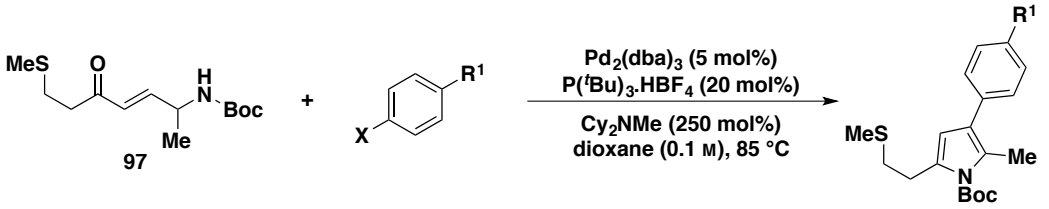
It was hoped that the application of this chemistry to a more substituted amino enone, such as **112a**, would permit the synthesis of fully-substituted pyrrole rings (Scheme 3.11).

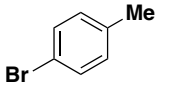
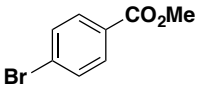
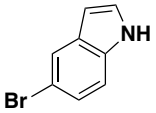
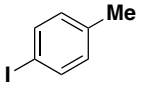
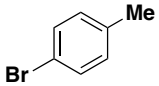


Scheme 3.11: Attempted Heck arylation of substituted γ-amino enones.

Although some of enone **112a** was consumed, multiple products were detected, none of which were the tetra-substituted pyrrole or arylated enone and the only identifiable compound obtained was the homo-coupled aryl halide. It appeared that the Heck conditions reported by the Donohoe group did not prove to be applicable to the synthesis of a tetrasubstituted example. Hence, control experiments were conducted on less substituted enones, similar to the substrates employed in the Donohoe chemistry. The Heck arylation of enone **97** was attempted with a range of aryl bromides (Table 3.3, entry 1-3) and under a selection of conditions (entry 4 and 5), including coupling with a traditionally more reactive aryl iodide (entry 4). No pre- or post-cyclisation product was observed, only varying degrees of homo-coupling of the aryl halide. Hence we pursued accessing tetra-substituted pyrroles by directly functionalising the existing heterocycle.

Table 3.3: Heck arylation screening using a less sterically demanding enone.

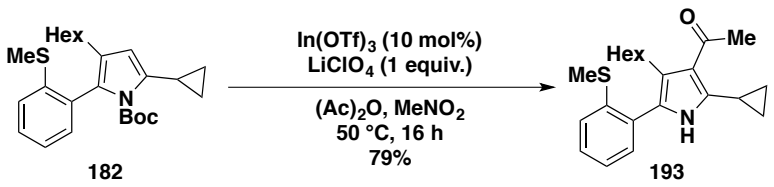


Entry	Aryl halide	Reaction conditions	Isolated Yield
1[a]		$Pd_2(dba)_3$ (5 mol%), $P(^tBu)_3.HBF_4$, Cy_2NMe	0%
2[a]		$Pd_2(dba)_3$ (5 mol%), $P(^tBu)_3.HBF_4$, Cy_2NMe	0%
3[a]		$Pd_2(dba)_3$ (5 mol%), $P(^tBu)_3.HBF_4$, Cy_2NMe	0%
4[b]		$Pd(OAc)_2$ (10 mol%), $AgCO_3$	0%
5[c]		$Pd(OAc)_2$ (5 mol%), Et_4NCl, Cy_2NMe	0%

Conditions: as stated in table. [a] Performed for 16 h. [b] Performed in DMF at 120 °C for 24 h. [c] Performed in DMA at 100 °C for 16 h.

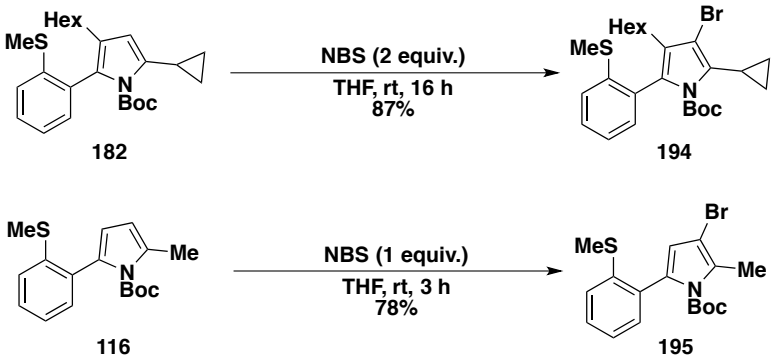
3.4.2 Functionalising Existing Pyrrole Rings

Although numerous methods to functionalise existing pyrrole rings have been reported,[175-177] we wished to solely achieve substitution at the C-3 position, which is much less explored.[178-179] Indium(III) reagents have increasingly been used as Lewis acid catalysts,[180] particularly in Friedel Crafts acylations of heterocyclic systems.[181] One efficient example was reported by Frost,[182] in which catalytic $In(OTf)_3$ and stoichiometric $LiClO_4$ are used for the acylation of a variety of aryl units, including one example that afforded 2-acetylfuran from the free furan ring in a 99% yield. We hoped that we could apply the unmodified conditions to a tri-substituted pyrrole ring, in order to achieve acylation at the only remaining unsubstituted position (Scheme 3.12). Pleasingly, acylation was observed in good yields, considering the steric hindrance. The Boc-group was also labile under the disclosed conditions.



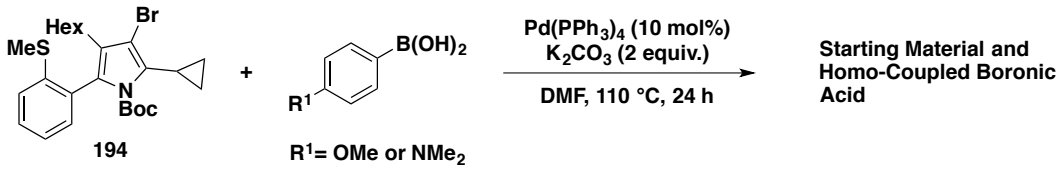
Scheme 3.12: Application of the Frost group's acylation chemistry to a tri-substituted pyrrole.

Another useful functional group incorporation would be a bromine atom, as a brominated pyrrole could undergo further functionalisation, either by electrophilic trapping during a lithium-halogen exchange, or be used in a palladium-catalysed cross-coupling reaction. We found that exposing pyrrole rings to brominating agent *N*-bromosuccinimide (NBS) resulted in a clean and high yielding addition of a bromine unit (Scheme 3.13). The reaction afforded tetra-substituted pyrrole **194** in excellent yield. A single C-3 bromination was also achieved regioselectivly, which was confirmed by NOE experiments, when using a di-substituted starting material.



Scheme 3.13: NBS brominations of pyrrole units.

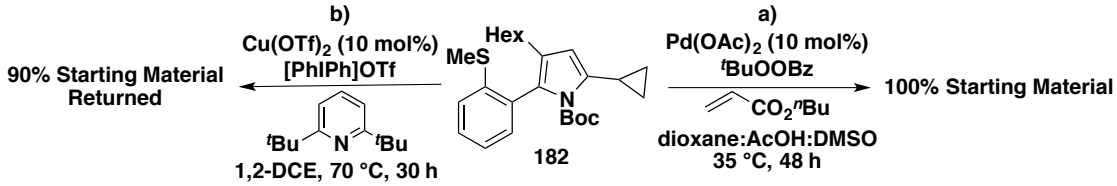
Unfortunately, brief attempts to perform palladium-catalysed Suzuki couplings on pyrrole **194** (Scheme 3.14), using conditions described by the Kerr group for the coupling of trisubstituted bromopyrroles with arylboronic acids,[183] only returned starting material and homocoupled boronic acid, presumably due to the steric constraints imposed by the cyclopropane group.



Scheme 3.14: Attempted Suzuki-couplings on a brominated pyrrole.

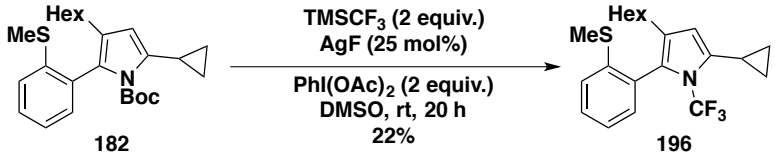
Given the failure of the cross-coupling of brominated pyrroles, direct C-H substitution at the C-3 position was attempted, as the C-H activation of heteroaromatic systems has been extensively explored.[184-187] Initial attempts to perform pyrrole alkenylation were motivated by reports from the Gaunt group, which demonstrated the selective activation of the C-3 C-H bond of a pyrrole unit, with catalytic $Pd(OAc)_2$. C-3 selectivity, in the reported case, was sterically controlled thorough 'blocking' availability of the more reactive C-2 position with a bulky *N*-protecting group.[188] The protocol required catalytic quantities of palladium, with an external oxidant and butyl acrylates as the primary alkenylation agents. Unfortunately, when these conditions were applied to our tri-substituted pyrrole (Scheme 3.15 a), no trace of coupled product was observed. When examining the substrate scope of the reported work, it was evident that less substituted pyrrole rings were usually employed. Additionally, alkenylation *ortho*-to a substituted C-2 position on the pyrrole ring had not been reported.

Subsequently, we attempted arylation work, also reported by Gaunt, describing the 2- and 3-arylation of indoles,[189] proceeding *via* a highly electrophilic aryl-Cu(III) species (Scheme 3.15 b). The optimised conditions described by the authors again delivered no sign of C-H activation of our substituted pyrrole unit.



Scheme 3.15: Attempted C-H activation processes described by the Gaunt group.
a) Alkenylation. b) Arylation.

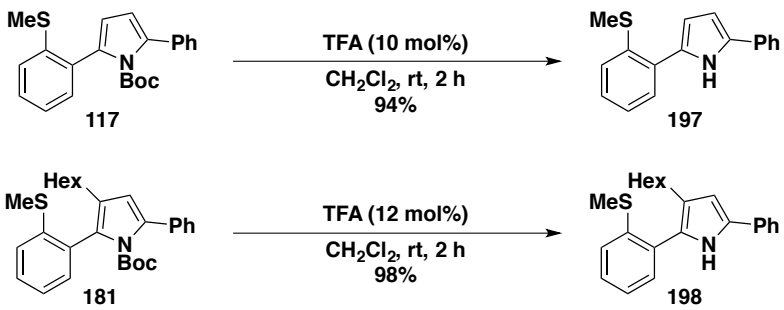
We advanced by investigating a trifluoromethylation procedure reported by Greaney and co-workers.[190] This methodology incorporated CF_3 units to arenes using $TMSCF_3$, with a $PhI(OAc)_2$ oxidant and a silver(I) fluoride base, in DMSO at room temperature. Under the mild reaction conditions C-2 trifluoromethylation of an unsubstituted pyrrole was reported in a 93% NMR yield. We employed the reported reaction conditions with pyrrole **182**, in the hope of forcing substitution onto the only unoccupied position on the pyrrole ring (Scheme 3.16). A variety of products were detected upon consumption of the starting material, with only one major product isolated; the *N*-trifluoromethylated pyrrole, arising through a Boc-deprotection under the conditions displayed. A maximum yield of only 22% was achieved.



Scheme 3.16: Trifluoromethylation of a tri-substituted pyrrole.

After attempting many palladium-catalysed C-H functionalisations,[191-193] it was evident that an arylation or alkenylation reaction would not be applicable to pyrrole **182**, either because activation at the C-3 position was unfavoured or substitution at this position was too restricted.

Finally, we established that *N*-deprotection to the parent NH-pyrrole was straightforward, and achieved excellent yields with TFA treatment of pyrroles **117** and **181** (Scheme 3.17).



Scheme 3.17: Deprotection of *N*-Boc pyrroles.

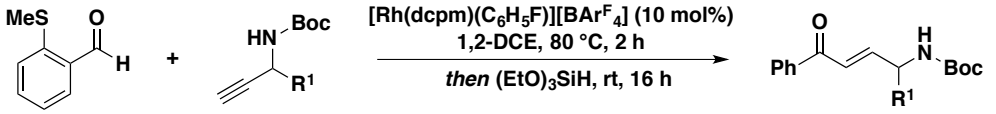
3.5 Functionalising the Sulfur Chelating Motif

As the examples in Scheme 3.8 and 3.9 demonstrate, the use of chelating aldehydes as substrates allowed the preparation of a broad range of pyrroles in good-to-excellent yields, under ambient reaction conditions. However, the caveat to employing chelating aldehydes as substrates is that the pyrrole products also feature the chelating substituent. In the majority of examples, this chelating substituent is an SMe group. Not only is this unit very effective in hydroacylation,[19,98] but it can also provide a handle for further manipulation, be it removal or additional funtionalisation. Reports from the Willis group have recently shown that the methyl sulfide group can undergo a variety of processes in conjunction with hydroacylation to obtain 'traceless' products.[194-196] For many of these protocols, the addition of a final pyrrole-forming step would afford 'traceless' and/or highly functionalised pyrrole rings.

3.5.1 Removal of the Sulfur Chelating Group

The Willis group have described a method whereby rhodium-catalysed triethoxysilane reduction of the methyl sulfide group was performed upon completion of the hydroacylation coupling; both steps were facilitated by the same rhodium species in a tandem process.[194] The initial hydroacylation step occurred under elevated temperatures with a dcpm-based rhodium catalyst. We were aware that the described conditions would result in decreased linear-selectivity for our nitrogen-containing alkyne substrates and endeavored to explore the reactivity of propargylic amines in this one-pot procedure, before attempting *in situ* pyrrole formation (Table 3.4).

Table 3.4: Attempted cascade hydroacylation/reduction sequence.



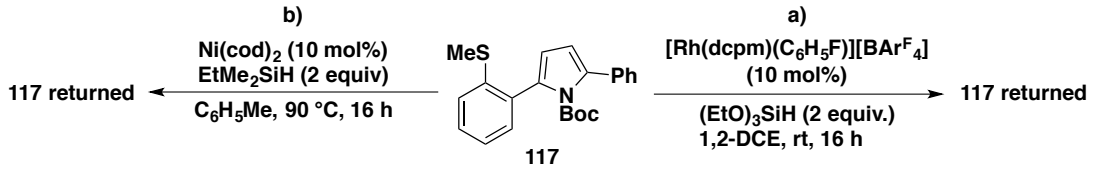
Entry	R^1 (alkyne)	Equivalents of $(EtO)_3SiH$	Isolated yield of *S*-HA intermediate	Isolated yield
1	^{t}Bu (**84**)	2	25% (**87**)	0%
2	Ph (**83**)	2	8% (**86**)	0%
3	*p*OMe-C_6H_4 (**139**)	2	13% (**199**)	0%
4	Ph (**83**)	1	33% (**86**)	0%
5	Ph (**83**)	4	0% (**86**)	0%

Conditions: **50** (0.15 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(dcpm)(C_6H_5F)][BAr^F{}_4]$ (10 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), 80 °C, 2h, *then* $(EtO)_3SiH$ as stated, rt, 16 h. *S*-HA= *S*-containing hydroacylation.

We began by using terminal alkynes with α-substitution to aid linear-selectivity of the first step. When applying the unmodified conditions for the hydroacylation/reduction cascade (Table 3.4, entry 1), we pleasingly observed a relatively linear-selective hydroacylation reaction. However, upon silane addition, although the majority of hydroacylation adduct was consumed, none of the methyl sulfide reduced product was detected; only trace amounts of the seemingly C-C and C-O reduction products were observed, along with decomposed intermediates. Unfortunately, varying the propargylic amine coupling partner had little impact on the outcome of the attempted reduction (entry 2-3). Lowering the equivalents of reductant (entry 4) in order to prevent the adverse side-reactions, reduced reactivity of the silane in general and thus larger quantities of the *S*-containing hydroacylation adduct could be isolated. Increasing the equivalents of silane in order to drive the reduction (entry 5), resulted in complete consumption of the *S*-containing enone intermediate, however a mixture of products was continually observed and each one in very small quantities.

Henceforth, we attempted the direct reduction of the methyl sulfide group from the

pyrrole product (Scheme 3.18). Alongside the above-described chemistry, the Willis group also stated that the rhodium-catalysed silane reduction could be used in heteroatom-directed aryl methyl sulfide reduction.[194] To observe whether the nitrogen in the pyrrole ring could direct this reduction process, we applied the unmodified reported conditions. Unfortunately, only clean starting material was observed (Scheme 3.18 a), presumably because heterocycle **117** lacked adequate directing ability. We then attempted methodology reported by the Martin group using a nickel catalyst, for the reduction of methyl sulfides on unactivated arene rings.[197] Regrettably, this methodology was also not applicable to our substrates (Scheme 3.18 b).

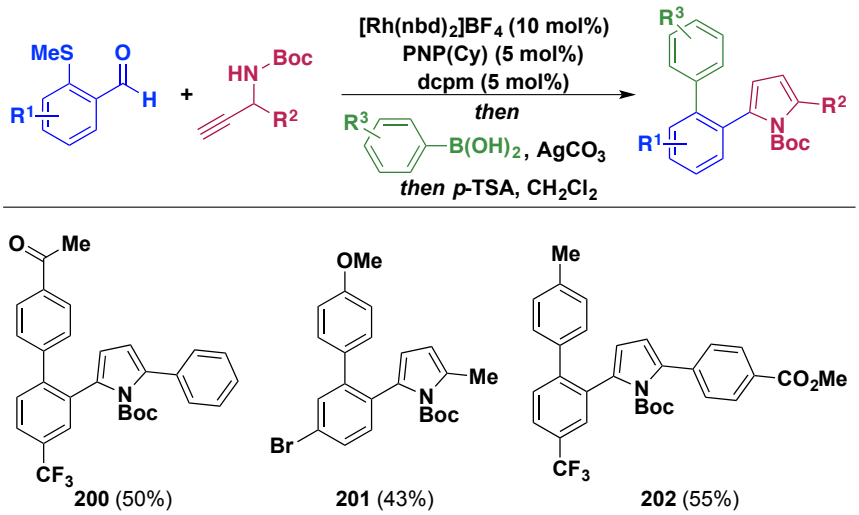


Scheme 3.18: Reduction of aryl methyl sulfides on pyrrole rings.

3.5.2 Functionalisation of the Sulfur Chelating Group

Due to lack of success in removing the *S*-chelating unit, we hoped to utilise the chelating motif as an activating group for a further rhodium-catalysed process. Willis and co-workers recently reported a tandem C-H/C-S activation method.[195] The authors invoked the use of one rhodium species to assist both hydroacylation and a formal Suzuki coupling, in which the carbonyl moiety from the enone directed C-S insertion of the catalyst, and enabled the methyl sulfide group to act as a pseudo-halide, in a coupling with boronic acids. This reaction employed the PCP(^{i}Pr) or dcpm ligand at 7.5 mol% catalytic loading. Additionally, a thiophilic agent was required to aid C-S activation (Ag_2CO_3). When translated to the present study (Scheme 3.19), it became clear that the propargylic amines reacted less linear-selectively with the dcpm catalyst than desirable. Moreover, the Suzuki-type couplings were inefficient with the optimal ligand for

propargylic amines–the PNP(Cy) ligand. Therefore, it was necessary to employ a mixed ligand system to achieve an efficient overall three-component coupling. The ligand system used both PNP(Cy) and dcpm, present from the start of the reaction, in combination with a common Rh(I) salt. We were pleased to show that this enabled access to 'traceless' pyrrole products by combining key linear-selective hydroacylation reactions with SMe-Suzuki-type couplings using aryl boronic acids. Pleasingly the displayed formation of two C-C and one C-N bonds occurred in a telescoped manner, with only one purification step at the end.

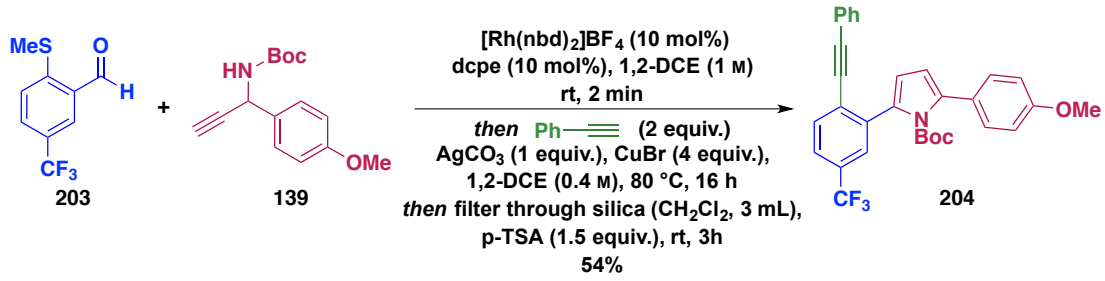


Conditions: aldehyde (0.15 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (10 mol%), PNP(Cy) (5 mol%), dcpm (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), 55 °C, 5 mins. *Then* $AgCO_3$ (1 equiv.), $ArB(OH)_2$ (1.5 equiv.) in acetone (0.3 M total volume with respect to the aldehyde, minus the volume of starting materials), 55 °C, 5 h. *Then*, filter through a small pad of silica (CH_2Cl_2, 5 mL) and add *p*-TSA (2 equiv.), rt, 3-6 h.

Scheme 3.19: Three-component coupling to access formal Suzuki coupled pyrroles.

Although this approach allowed the preparation of pyrroles **200**-**202**, the reaction was very substrate specific and required the hydroacylation reaction to reach completion in a swift manner or a reactive aryl boronic acid. This C-H/C-S activation cascade has recently been further developed by the Willis group to a hydroacylation/formal Sonogashira coupling process.[198] This methodology functions in a similar manner, however replaces the boronic acid coupling with the coupling of an aryl alkynyl unit. Pleasingly, the methodology was directly applicable to our substrates and enabled a three

component coupling to afford pyrrole **204** in a telescoped fashion (Scheme 3.20).

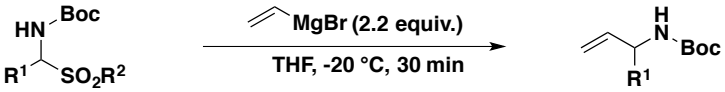


Scheme 3.20: Three component coupling to access a formal Sonogashira coupled pyrrole.

3.6 Synthesis of Dihydropyrroles

As described in Scheme 3.5, we intended to extend the general process of pyrrole synthesis to the formation of dihydropyrroles, more specifically 1-pyrrolines. This would require the hydroacylative coupling of chelating aldehydes with *N*-Boc allylic amines, which were readily accessible through an analogous procedure to the one used to form propargylic amines, affording a similar variety of functionality (Table 3.5).

Table 3.5: Synthesised *N*-Boc allylic amines.

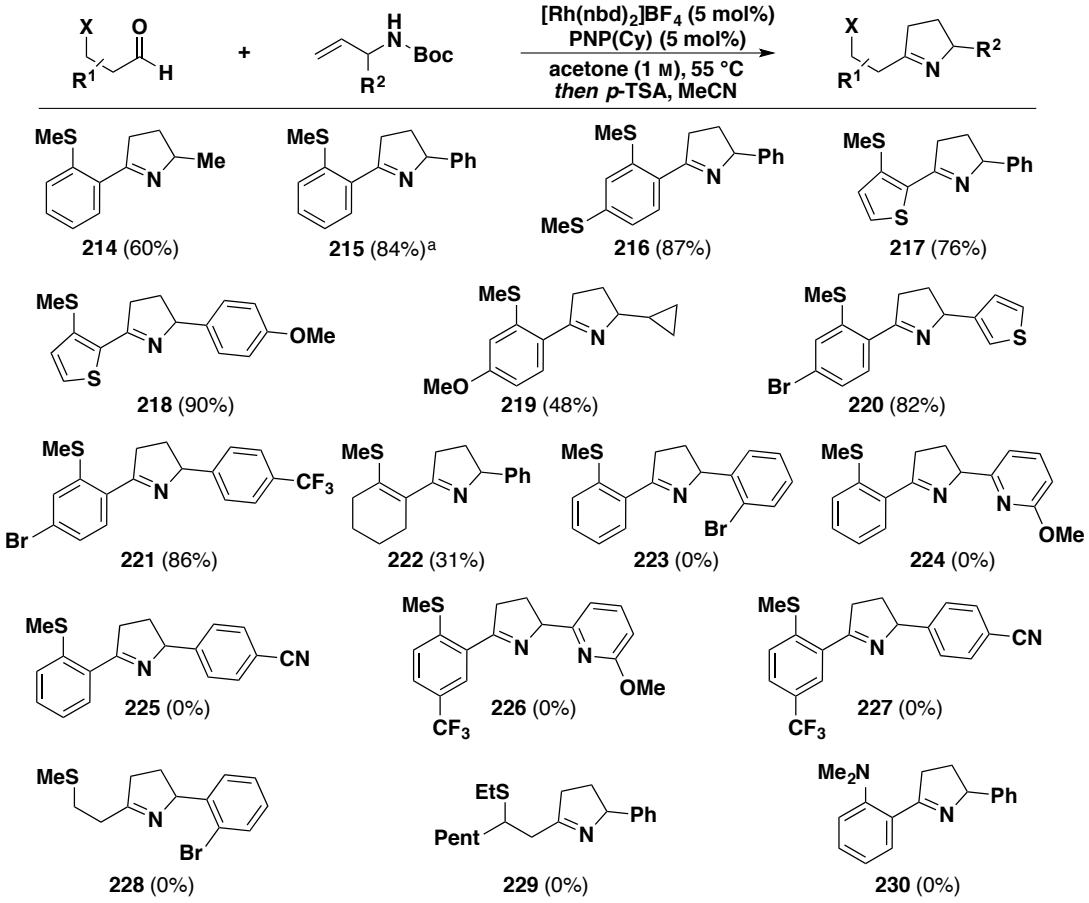


Entry	R^1	α-Amido sulfone	Allylic amine	Isolated yield
1	Me	**122**	**205**	17%
2	CyPr	**124**	**206**	51%
3	Ph	**125**	**207**	84%
4	*p*OMe-C_6H_4	**126**	**208**	80%
5	*p*CF_3-C_6H_4	**127**	**209**	90%
6	*p*CN-C_6H_4	**129**	**210**	94%
7	*o*Br-C_6H_4	**132**	**211**	34%
8	3-thienyl	**134**	**212**	65%
9	3-OMe-2-pyridyl	**137**	**213**	71%

Conditions: α-amido sulfone (1 equiv.), vinylmagnesium bromide (2.2 equiv.), THF, -20 °C, 30 min.

While the hydroacylation of terminal alkenes has been reported within our group, they were noticeably less reactive substrates than alkynes, which are more usually employed with *S*-chelating aldehydes. Therefore, we were very pleased when the PNP(Cy)-derived catalyst allowed the efficient reaction of terminal *N*-Boc allylic amines with *S*-chelating aldehydes (Scheme 3.21). In contrast to the *N*-containing alkyne system, slightly elevated temperatures (55 °C) and longer reaction times (16 h) for the hydroacylation step were required. Even so, the hydroacylation coupling occurred in a completely linear-selective manner, with no detection of the branched isomer in either the ^{1}H NMR spectra or by TLC analysis for any allylic amines employed. As with the pyrrole synthesis, we aimed to access these heterocycles in one-pot. Therefore, upon consumption of the staring aldehyde, the hydroacylation adducts were not isolated but treated directly with *p*-TSA to induce cyclisation (Scheme 3.21). Pleasingly, this cyclisation event proceeded smoothly, and the acid also prompted cleavage of the Boc-group *in situ*, resulting in the formation of 2,5-substituted 1-pyrrolines.

A variety of alkyl (**214**, **219**), aryl (**215**, **218**, **221**) and heteroaryl (**220**) substituents were permissible at the allylic position of the alkenes. Substituted aryl (**216**, **219**-**221**), as well as heteroaryl (**217**, **218**) aldehydes could also be employed without incident. Unfortunately, attempts with 2 mol% catalytic loading resulted in an incomplete hydroacylation coupling (**215**).

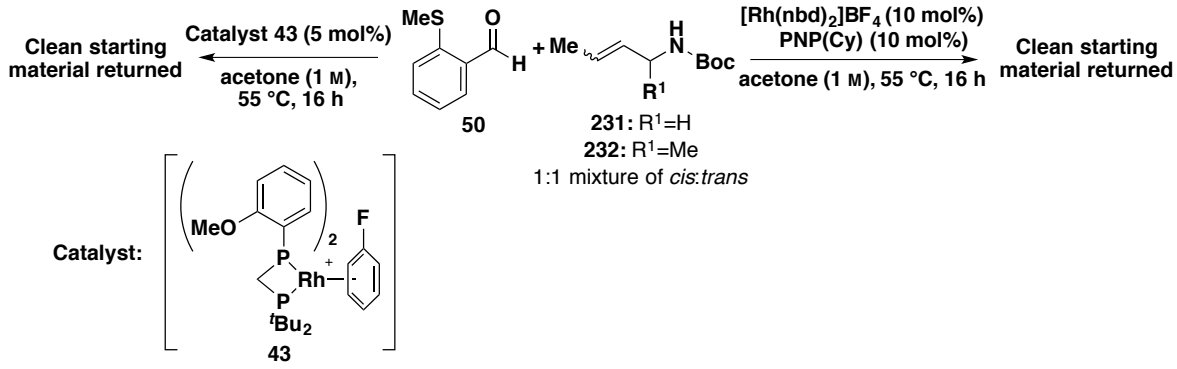


Conditions: aldehyde (0.2 mmol, 1 equiv.), alkyne (1.3 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), PNP(Cy) (5 mol%), acetone (1 M total volume with respect to the aldehyde, minus the volume of starting materials), 55 °C, 16 h, *then* p-TSA (1 equiv.), MeCN (0.1 M), rt, 3-6 h. [a] Reaction attempted using 2 mol% catalyst loading and obtained 0% hydroacylation coupling.

Scheme 3.21: Scope of one-pot dihydropyrrole synthesis *via* a hydroacylation/cyclisation cascade of allylic amines.

Due to the increased level of difficulty for this alkene hydroacylation, more challenging allylic substituents were not tolerated, such as a nitrile functionality (**225**), a sterically demanding aryl ring (**223**) and a pyridine substituent (**224**), even upon attempts with more reactive aldehydes (**226**, **227**) or with less sterically demanding aldehydes (**228**). Although the hydroacylation with an alkenyl aldehyde reached 100% conversion to the hydroacylation intermediate, the acidic cyclisation conditions proved too harsh for this substrate, resulting in a poor overall yield (**222**). Additionally, aldehydes featuring a coordinating amino-substituent (**230**) or alkyl based aldehydes (**229**) proved to be unreactive in this system.

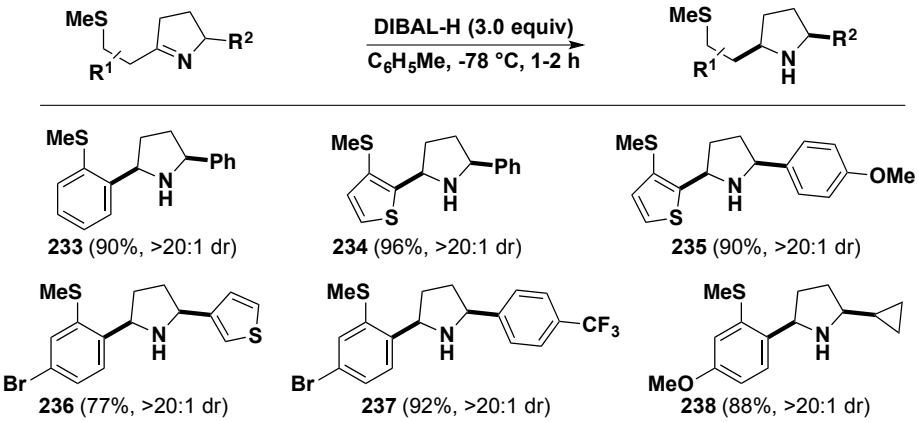
Internal alkenes are notoriously difficult coupling partners for chelation-controlled intermolecular hydroacylation,[112] hence both our group and the Weller group have conducted investigations into catalytic systems specifically for internal alkenes. The recent development of catalyst **43** has considerably improved their reactivity.[112] However, this rhodium complex could not facilitate the coupling of aldehyde **50** with internal *N*-Boc allylic amines **231** and **232**, which prevented the synthesis of tri-substituted dihydropyrroles (Scheme 3.22).



Scheme 3.22: Attempted optimisation of internal allylic amine hydroacylation.

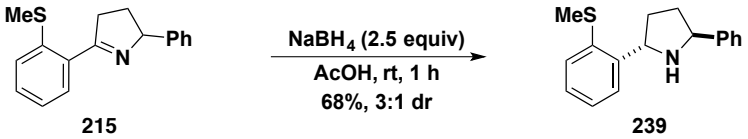
3.7 Synthesis of Pyrrolidines

We intended to use the dihydropyrroles, obtained from the one-pot hydroacylative route, as intermediates for the formation of desirable pyrrolidine structures. 1-Pyrrolines established themselves as effective adducts to access the corresponding saturated heterocycles. For example, reduction of dihydropyrroles, through the *syn*-addition of hydride was achieved by the use of diisobutylaluminium hydride (DIBAL-H) (Scheme 3.23).[199] Employing this bulky reducing agent, in a very experimentally convenient method, allowed the formation of a range of *cis*-pyrrolidines, as established by NOE experiments, as the only observed diastereoisomer by crude ^{1}H NMR spectroscopy. All the 1-pyrrolines subjected to these reduction conditions proceeded cleanly and efficiently.



Scheme 3.23: DIBAL-H reduction of 1-pyrrolines.

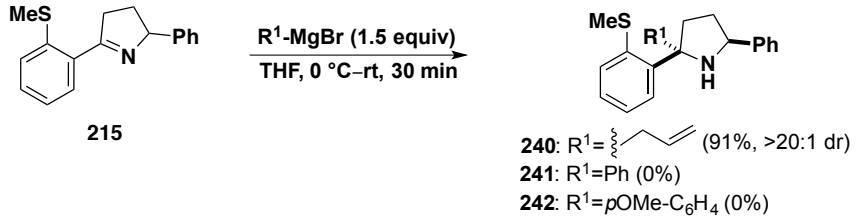
However, formation of the *trans*-pyrrolidine was not as straightforward. The use of a smaller reducing agent, sodium borohydride, resulted in a mixture of diastereoisomers, slightly in favour of the *trans*-isomer (Scheme 3.24).[200] For example, pure *trans*-pyrrolidine **239** was obtained in a 68% yield from a crude 3:1 mixture of diastereomers.



Scheme 3.24: $NaBH_4$ reduction of a 1-pyrroline to access the *trans*-pyrrolidine.

We proposed that protecting the cyclic imine to form the *N*-protected enamine would induce conformational constraints and enable a selective formation of the *trans*-isomer, however the attempted Cbz, Boc and Ts protections were not successful.

Finally, an allyl Grignard reagent could also be employed through a nucleophilic addition (Scheme 3.25),[161] delivering pyrrolidine **240**, featuring a quaternary centre, in excellent yield and diastereoselectivity. However, the addition of aryl Grignards was unfortunately not possible (**241**, **242**).



Scheme 3.25: Grignard additions to a 1-pyrroline.

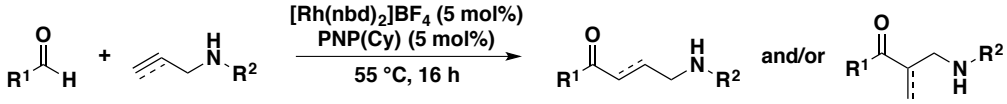
3.8 Hydroacylation of Non-Chelating Aldehydes

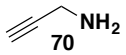
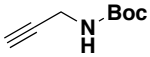
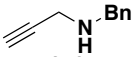
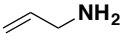
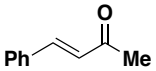
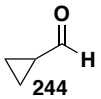
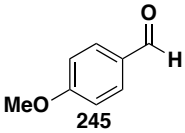
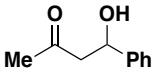
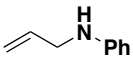
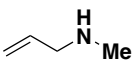
One strategy to avoid the use of chelating aldehydes in rhodium-catalysed hydroacylation is to employ chelating olefins instead.[113,115] This method was recently explored by the Dong group in the synthesis of benzofuran rings and briefly mentioned in Chapter 1, Scheme 1.40.[115] The authors reported that the strong binding of a vinylphenolate to rhodium was key in promoting hydroacylation over competitive decarbonylation (Chapter 1, Scheme 1.35 **45**).[115] Employing these chelating alkenes resulted in selective formation of the branched-regioisomer using $[Rh(cod)OMe]_2$ (2 mol%) and dcpm (4 mol%) as the catalyst, in THF at 60 °C for 1 to 2 days. The authors postulated that the phenolic group on the alkene promoted the branched-selectivity by proceeding *via* a favoured five-membered rhodacycle intermediate over the linear-product yielding six-membered metallacycle.[116] The use of non-chelating aldehydes enabled one of the largest scope of aldehydes for a branched-selective hydroacylation to be reported.

Bearing this in mind, we hypothesised that if our *N*-containing hydroacylation coupling partners do indeed coordinate to rhodium in some manner, then these hydroacylation reactions could potentially occur with non-chelating aldehydes, considerably broadening the substrate scope of this hydroacylation. Preliminary investigations conducted invoked the use of terminal propargylic amines possessing an unprotected nitrogen, which should enable more chelation than protected variants (Table 3.6, entry 1). Propargylic amines were employed with benzaldehyde **243** under the previously discerned cationic, linear-

selective hydroacylation conditions. Unfortunately, after 16 hours only the starting material was returned cleanly or in a complex mixture (CM) (entry 1-3).

Table 3.6: Attempted hydroacylation of non-chelating aldehydes.



Entry	Aldehyde	Alkyne or alkene	Solvent	Additive	Product	Isolated yield
1	 243	 70	acetone	-	SM	-
2	**243**	 59	acetone	-	SM	-
3	**243**	 246	acetone	-	SM and CM	-
4	**243**	 247	acetone	-	 250	Trace
5	**243**	**247**	1,2-DCE	-	SM	-
6	 244	**247**	acetone	-	SM and CM	-
7	 245	**247**	acetone	-	SM and CM	-
8	**243**	**247**	acetone	K_2CO_3	 251	51%
9	**243**	**247**	1,2-DCE	K_2CO_3	SM	-
10	**243**	 248	acetone	K_2CO_3	SM and CM	-
11	**243**	 249	acetone	K_2CO_3	SM and CM	-

Conditions: alkyne (0.15 mmol, 1 equiv.), aldehyde (1.3 equiv), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), K_2CO_3 (10 mol%), solvent (1 M total volume with respect to the aldehyde, minus the volume of starting materials), 55 °C, 16 h. SM=staring material, CM=complex mixture. Yields are of the isolated product after column chromatography on silica gel.

Modifying the substrate to allylic amine **247** instead delivered condensed aldol product **250** derived from the aldehyde substrate and the solvent (acetone), this compound was only observed in trace amounts along with recovered starting material (entry 4). In an attempt to suppress this aldol reactivity, 1,2-DCE was employed as the solvent (entry 5), but only the clean starting materials **243** and **247** were returned. Use of more reactive aldehydes for C-H activation had no effect either (entry 6 and 7). In an attempt to deprotonate the allylic amine, potassium carbonate (K_2CO_3) (10 mol%) was added alongside the catalyst system and 51% yield of the aldol product was isolated, with no hydroacylation coupling evident (entry 8). Employing different ligands only resulted in varying degrees of the aldol coupling. Use of potentially more coordinating alkyne coupling partners was also futile (entry 10 and 11). Due to time constraints this reaction was not further investigated. It is perhaps unsurprising that no hydroacylation products were observed under the catalytic system employed; the use of a neutral rhodium species would better permit C-H activation of non-chelating aldehydes,[201-203] and investigating such catalyst systems would be recommended to promote reactivity. If any reactivity could be achieved with allylic or propargylic amines in a linear-fashion, this could provide valuable access to 'tether free' heterocyclic systems.

3.9 Summary

In conclusion, we have demonstrated the applicability of regioselective hydroacylation in the direct synthesis of mono-, di- and tri-substituted pyrroles, with the ability to install a variety of functional groups in a one-pot cascade using low catalyst loadings (as low as 1 mol%). We have shown that access to fully substituted pyrroles can be obtained by classical brominations and acylations. Furthermore, we have demonstrated that the methyl sulfide group, utilised as a chelating motif for the hydroacylation reaction, can act

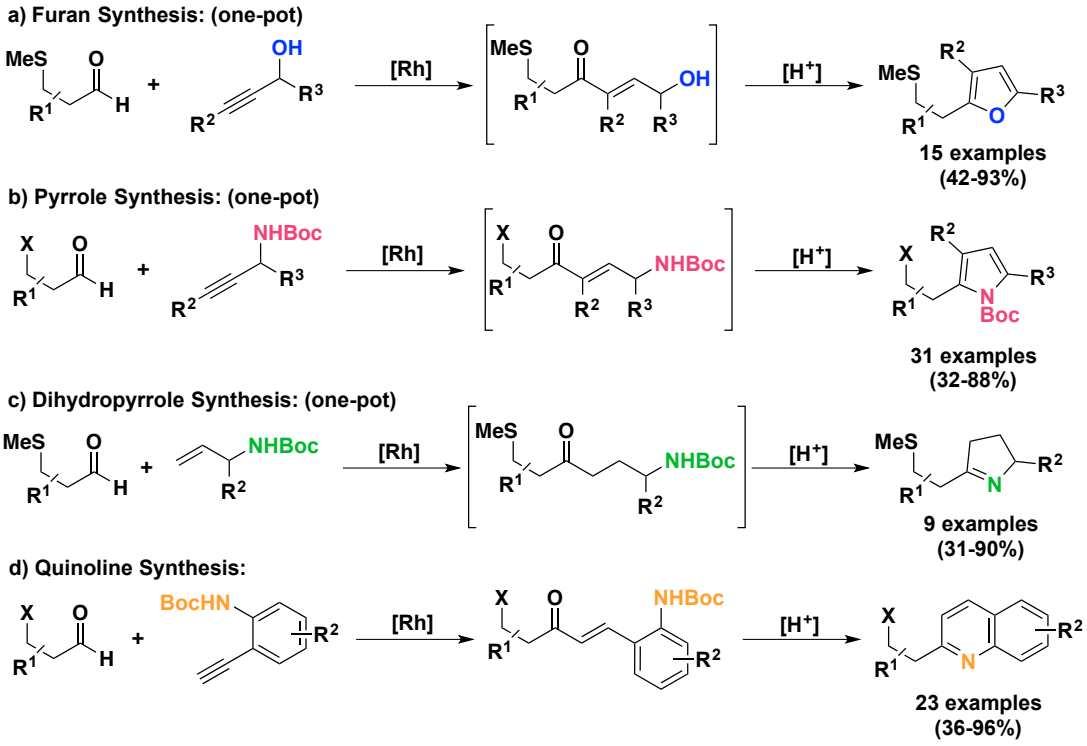
as a pseudo-halide and be exploited in telescoped three-component couplings. These telescoped Suzuki/Sonogashira-type reactions allowed access to considerable structural diversity from simple starting materials by an experimentally straightforward method. In addition, we have demonstrated that the methodology developed for the coupling of alkynes and aldehydes is equally applicable to alkenes, allowing extension of the procedure to the synthesis of dihydropyrroles in one-pot, and following diastereoselective derivatisations, to pyrrolidines. Finally, we have displayed that the proposed chelating effect of *N*-containing unsaturated coupling partners is either not strong enough to prevent decarbonylation of acylrhodium intermediates, or that cationic rhodium(I) catalysts do not facilitate any level of C-H activation of non-chelating aldehydes.

Chapter 4

Ynamide Hydroacylation in the Synthesis of Heterocycles

4.1 Introduction

Employing hydroacylation products-enones or ketones-in the synthesis of heterocycles has been well established (Scheme 4.1). These heterocycle formations have occurred *via* a rhodium(I)-catalysed C-C bond formation, using a coupling partner that contains the desired heteroatom for the target heterocycle. The carbonyl unit installed by hydroacylation then undergoes an intramolecular 1,2-nucleophilic addition, incorporating the heteroatom into a ring system, usually in an acid-catalysed and dehydrative manner. This type of hydroacylation/intramolecular cyclisation chemistry has been used within our group to synthesise furans (Scheme 4.1 a),[121] pyrroles (Scheme 4.1 b),[204] dihydropyrroles (Scheme 4.1 c),[204] and quinolines (Scheme 4.1 d).[205] For each of these protocols, separate starting material syntheses and separate optimisation studies took place. Although the reported methodologies provided wide substrate scopes and good-to-excellent yields; only one, specific-type of ring system could be accessed from each optimisation study.

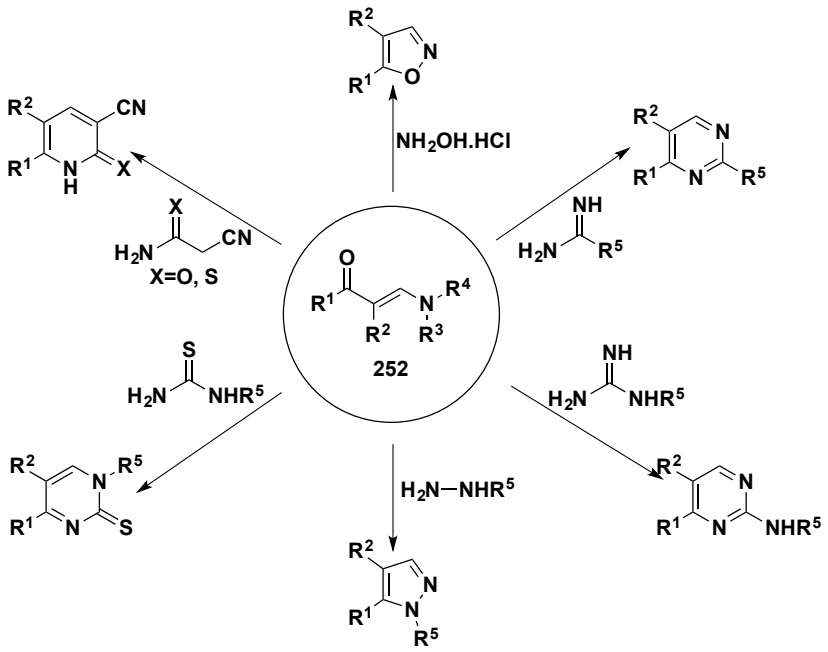


Scheme 4.1: Previous examples of hydroacylation adducts exploited in heterocycle synthesis.

Our group has previously reported a limited set of hydroacylation reactions, employing propargylic alcohols, to access to 1,4-diketones, which subsequently afforded a range of heterocycles under a variety of conditions.[121] We hoped to extend this hydroacylative protocol to a more general method that would enable access to numerous valuable heterocycles, from a single optimised reaction; obviating the need to employ specific starting materials to access the corresponding heterocycles. We believed that this type of methodology would considerably improve the synthetic utility of hydroacylation in heterocycle synthesis, as this field remains of great interest to various industries.[206]

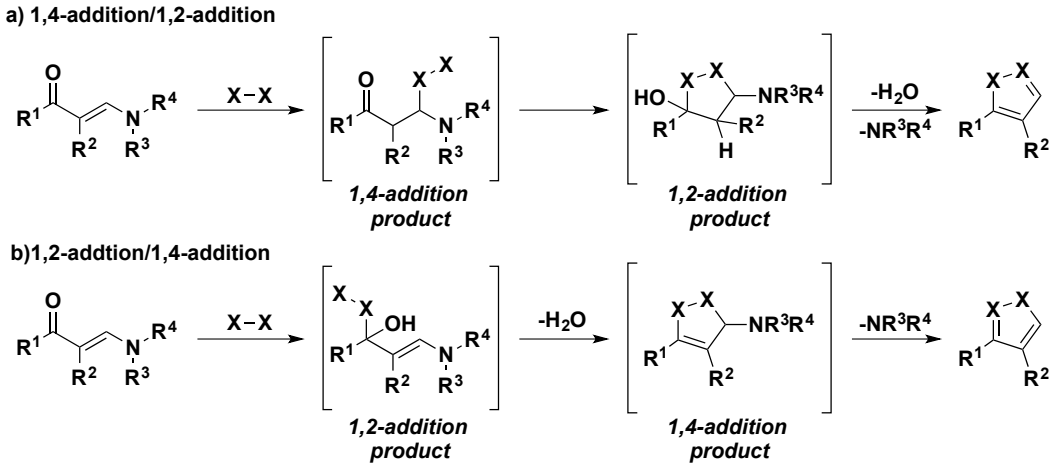
Achieving this aim would require the design of a single intermediate that could be obtained through hydroacylation, and subsequently be exploited in the synthesis of a range of heterocycles. A popular and effective precursor to copious nucleophilic addition/heterocycle forming cascades is a *β*-amino enone or enaminone, such as compound **252** (Scheme 4.2), as they have displayed themselves to be excellent

intermediates for further syntheses.[207-209]



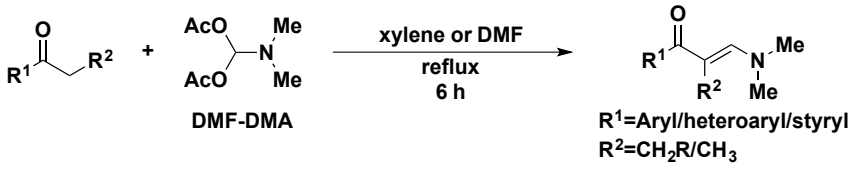
Scheme 4.2: Enaminones in heterocycle synthesis.

Enaminones are known to be reactive towards *bi*-nucleophilic addition in one of two ways (Scheme 4.3). Firstly, an intermolecular 1,4-nucleophilic addition to the enaminone can occur, followed by an intramolecular 1,2-addition, which promotes aromatisation by the loss of the nitrogen unit on the enaminone, as well as dehydration (Scheme 4.3 a). Alternatively, an initial intermolecular 1,2-addition occurs, followed by a subsequent intramolecular 1,4-addition, which also enables heteroaromatic ring formation by loss of an amine unit (Scheme 4.3 b). The enaminone is a very versatile intermediate as it can facilitate the synthesis of both five- and six-membered heterocyclic ring systems, with the possibility of accessing different regioisomers depending on the favoured mechanistic pathway. Moreover, this type of *bi*-nucleophilic addition process is well precedented to occur in a tandem fashion, without isolation of intermediates.[210]



Scheme 4.3: Synthesis of five-membered heterocycles from enaminone substrates.

Due to the utility of *β*-amino enones, methods to access them, especially with various substitution patterns, has been extensively explored.[211-213] The traditional, and by-far most popular protocol used within the pharmaceutical industry, is the reaction of active methylene compounds, such as activated ketones, with the formylating agent *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) (Scheme 4.4).[213,214]



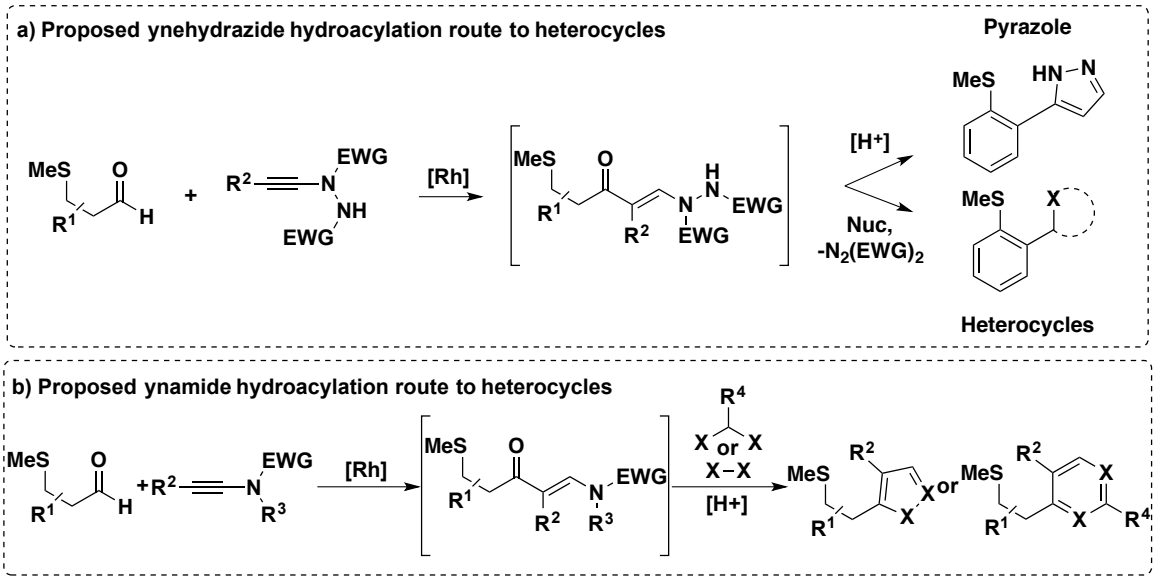
Scheme 4.4: Traditional synthesis of *β*-amino enone using DMF-DMA.

Although this described reaction has been successful in transforming readily available ketones to adaptable building blocks,[215] there are various drawbacks associated with this protocol. Presently, this method requires the use of excess (1.5-4 equivalents) DMF-DMA, which is an expensive and harmful reagent.[216,217] High-boiling solvents are generally employed (DMF and xylene),[218,219] making purification arduous, and high temperatures are often essential (110-180 °C).[220,221] Additionally, the substrate scope is heavily limited, as only *N*-dimethyl can be incorporated and the R^1 group is limited to activated aryl substituents. Several accounts employing novel methodology for these

interesting scaffolds have appeared,[222-224] however reports are still scarce.

4.2 Project Aims

With the aim of accessing a variety of heterocycles from one hydroacylation intermediate, as well as our experience with *N*-containing alkynes in hydroacylation, and the requirement of novel methodology to access important enaminone precursors; we proposed two routes to access heterocycles. Firstly, employing the hydroacylation of chelating aldehydes with internal ynehydrazides to access interesting *β,γ*-amino enones, which could be used in a more tradition intramolecular manner to afford pyrazole rings, or the '*N*-*N*' unit could act as a leaving group upon addition of heteroatom containing nucleophiles, which would grant access an array of heterocycles (Scheme 4.5 a).



Scheme 4.5: Proposed ynehydrazide (a)/ynamide (b) hydroacylation route to a variety of heterocycles.

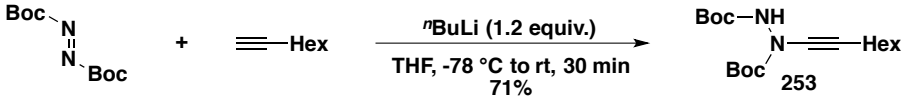
Secondly, we hoped to synthesise *β*-amino enones, that are known to be used in many heterocycle syntheses, through the hydroacylation of internal ynamides (Scheme 4.5 b). We envisaged that accessing these highly useful building blocks by employing more versatile starting materials and mild reaction conditions, would enable the possibility of

a wider variety of functionalisation on the ring systems. We subsequently aimed to perform these hydroacylation/nucleophilic addition cascades in a one-pot manner.

Ynehydrazides and ynamides may seem like an unusual choice of substrate in terms of availability however, there have been recent breakthroughs for their convenient preparation[225] and a few substrates are now commercially available.[24] This is because ynamides (electron deficient ynamines) have gained popularity in synthetic chemistry over recent years,[225,226] due to the presence of a strongly polarised and reactive triple-bond. This is particularly true within heterocycle synthesis,[227] although, usually the methodology consists of intramolecular cyclisations which, unlike the reaction we have proposed, incorporates the nitrogen on the ynamide into the ring system.[227] Therefore, this pathway would be a rare example of ynamide use in intermolecular heterocycle formation, as well as the first report of ynamide/ynehydrazide hydroacylation.

4.3 Ynehydrazide Hydroacylation

Firstly, we hoped to examine ynehydrazides in hydroacylation, as the product would provide two modes of heterocycle synthesis. Therefore, following the procedure described by the Batey group, reporting an effective reaction that proceeds through the addition of lithium acetylides to commercially available di-*tert*-butylazodicarboxylate (DBAD),[228] ynehydrazide **253** was synthesised in an experimentally convenient manner and high yield (Scheme 4.6).

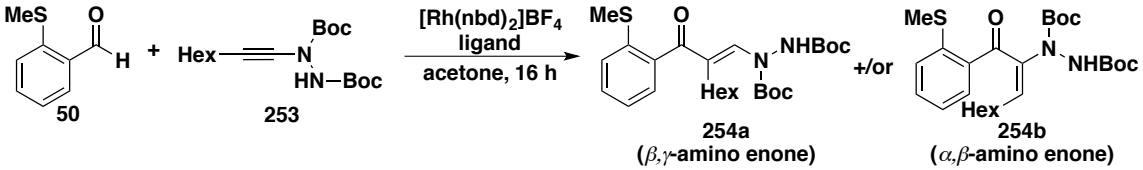


Scheme 4.6: Ynehydrazide synthesised following a protocol reported by Batey.

Investigations into ynehydrazide hydroacylation began with attempts to couple *S*-chelating aldehyde **50** with ynehydrazide **253**. We examined the reactivity of

ynehydrazides under a variety of hydroacylation conditions, fully aware that regioselectivity could well be an issue, as it is notoriously difficult to control the manner of hydrometallation when using internal alkyne substrates (Table 4.1).[229]

Table 4.1: Optimisation of ynehydrazides in hydroacylation with *S*-chelating aldehydes.



Entry	Ligand	Catalyst loading	Conc. (M)	Temp. (°C)	Conversion[a]
1	dcpm	10 mol%	0.3	rt	41%
2	dcpm	10 mol%	1.0	rt	36%
3	dcpm	10 mol%	1.0	55	53%
4	dcpm	5 mol%	1.0	55	25%
5[b]	dcpm	5 mol%	0.3	80	35%[c]
6	dppm	5 mol%	0.8	55	59%
7	DPEPhos	5 mol%	0.8	55	0%
8	PNP(Cy)	5 mol%	0.8	rt	63%
9	PNP(Cy)	5 mol%	0.3	55	60%
10	PNP(Cy)	5 mol%	0.8	55	62%
11[b]	PNP(Cy)	5 mol%	0.8	80	42%[c]
12	PNP(Cy)	7 mol%	0.3	55	67%
13	PNP(Cy)	10 mol%	0.3	55	100% (82%)

Conditions: **50** (0.15 mmol, 1 equiv.), **253** (1.3 equiv.), $[Rh(nbd)_2]BF_4$, ligand, under stated conditions for 16 h. Value in parenthesis is the isolated yield of hydroacylation product **254a**. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Performed in 1,2-DCE. [c] Small amounts of α,β-amino enone visible in crude ^{1}H NMR spectrum.

While the use of rhodium pre-catalyst remained consistent, we started with an initial 10 mol% catalytic loading. Pleasingly, upon employing commercially available small bite-angle dcpm, it was evident that the formation of the desired β,γ-amino enone regioisomer **254a** was heavily favoured, as the α,β-amino enone isomer **254b** was not

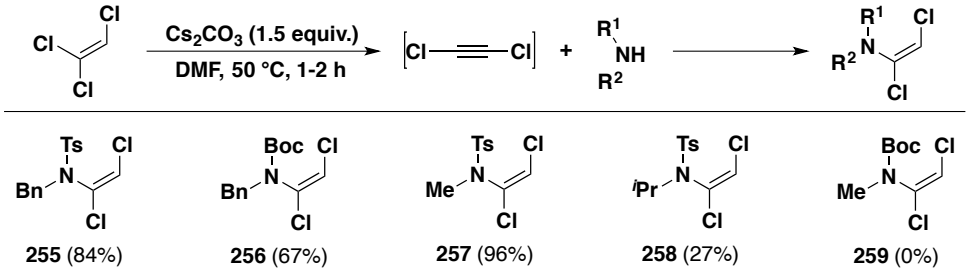
detected in the crude ^{1}H NMR spectrum, however only a 41% conversion was achieved at room temperature (entry 1). It had previously been observed that an increasing the reaction concentration resulted in a corresponding increased rate of hydroacylation,[61] unfortunately in this case the increased concentration seemed to bear little effect on the overall conversion (entry 2), which was also evident with an alternative ligand system (entry 9 and 10). On the other hand, increasing the temperature to 55 °C had a positive effect on the conversion (entry 3), although a further increase to 80 °C in 1,2-DCE had an undesirable effect with regards to both conversion and regioselectivity (entry 5 and 11). Although the coupling reaction was not yet effective, we were aware that the synthetic utility of this reaction would be limited with a 10 mol% catalytic loading, and therefore attempted the coupling with a 5 mol% rhodium loading, however the conversion dropped considerably (entry 4). When investigating other ligands at 55 °C and 5 mol% of the catalyst, it became evident that PNP(Cy) was the optimal ligand, enabling the highest conversion thus far of 60-62% (entry 9 and 10). We then found that increasing the catalytic loading of the PNP(Cy) based catalyst to 7 mol% only enabled a modest improvement (entry 12), and 10 mol% was required to achieve full conversion to the product (entry 13), with an isolated yield of 82%. This indicated that the level of difficulty of this coupling reaction was elevated and therefore this would not bode well for a potential substrate scope. Hence a 10 mol% catalytic loading was deemed unacceptably high and we decided to abandon ynehydrazides as hydroacylation coupling partners.

4.4 Hydroacylation of Internal Ynamides

4.4.1 Synthesis of Internal Ynamides

As we moved on to investigating the activity of ynamides in hydroacylation, we were conscious of designing the ideal substrates for both a reactive rhodium-catalysed hydroacylation and *bi*-nucleophilic addition. Furthermore, it has been demonstrated within this thesis, that the use of sterically demanding internal propargylic amines resulted in inactivity during hydroacylation (Chapter 3, Scheme 3.9), therefore we aimed to initially incorporate less intrusive functionality on the terminus of the ynamide, such as alkyl chains. We were also aware that the regioselectivity of internal alkyne hydroacylation was heavily influenced by both the steric and electronic properties on either side of the triple-bond;[229] we intended to use an ynamide synthesis that would allow as much variation on both the nitrogen and alkynyl position as possible.

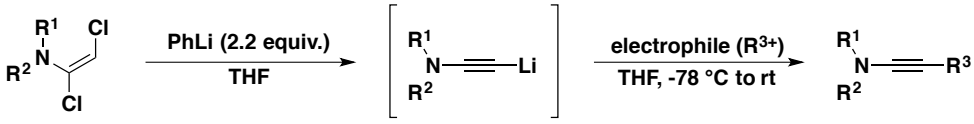
Therefore, we initially investigated a modular approach reported by Anderson and co-workers.[230] This procedure involved the use of dichloroacetylene, which is formed *in situ* from trichloroethene (TCE) and a mild base. The dichloroacetylene undergoes amide addition to synthesise dichloroenamides, which are bench stable. These intermediates are subsequently subjected to electrophilic addition to enable functionalisation of the alkynyl position of the ynamide. Application of this protocol afforded a range of nitrogen groups on the dichloroenamide intermediates (Scheme 4.7). We could access both *N*-Boc- (**256**) and *N*-tosyl(Ts)-benzylated products (**255**) in comparable yields. Although accessing *N*-Ts dichloroenamides was relatively straightforward (**257**, **258**), *N*-Boc variants were more challenging (**259**).

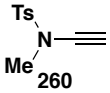
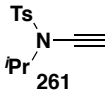


Scheme 4.7: Synthesised dichloroenamide intermediates *via* Anderson's protocol.

Unfortunately, attempts to convert these precursors into internal ynamides were ineffective (Table 4.2). Synthesis of *N*-Boc ynamides proved difficult, as the formation of propyl or methyl containing *N*-Boc ynamides led to decomposition of starting material (entry 1 and 2).

Table 4.2: Attempted ynamide synthesis from dichloroenamides.

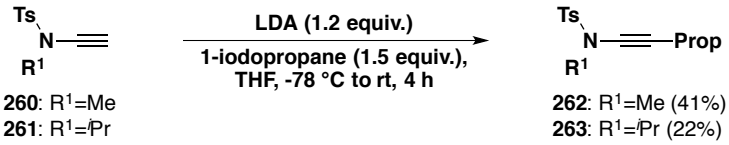


Entry	R^1, R^2 (Dichloroenamide)	Electrophile (R^{3+})	Product	Isolated yield
1	Boc, Bn (**256**)	1-Iodopropane	complex mix	-
2	Boc, Bn (**256**)	Methyliodide	complex mix	-
3	Ts, Bn (**255**)	1-Iodohexane	SM	-
4	Ts, Me (**257**)	1-Iodohexane	 **260**	19%
5	Ts, ^{i}Pr (**258**)	1-Iodohexane	 **261**	38%
6	Ts, ^{i}Pr (**258**)	1-Iodopropane	**261**	37%

Conditions: Dichloroenamide (1 equiv.), PhLi (2 M, 2.2 equiv.) at -78 °C for 1 h, then add electrophile (1.2 equiv.) and warm to rt over 1-2 h.

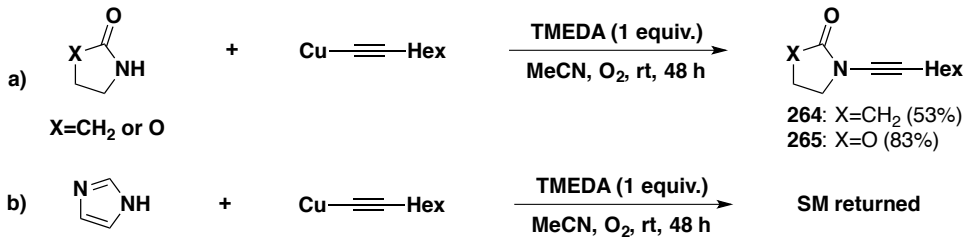
Electrophilic addition to the *N*-Ts dichloroenamides either resulted in inactivity (entry 3), or the starting material was consumed on addition of the lithium reagent, however electrophilic addition did not occur and the terminal ynamides were isolated upon aqueous work-up (entry 4-6). This was problematic as our designed heterocycle synthesis

required the use of internal ynamides only, as this would be the sole functionality arising from the alkyne coupling partner incorporated into the final heterocyclic product. Nevertheless, we were successful in formally deprotonating the terminal ynamides, using LDA, to afford the electrophilic addition products **262** and **263** in moderate yields (Scheme 4.8).



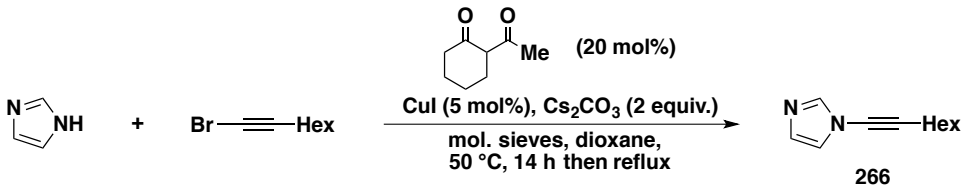
Scheme 4.8: Synthesis of internal ynamides from corresponding terminal ynamides.

We then turned our attention to ynamides possessing cyclic nitrogen units, because these substrates would better the atom-economy of our designed heterocycle formation. The Evano group have described a variety of copper-catalysed protocols for the synthesis of ynamides from lactam derivatives,[231,232] however as we had access to pre-formed, bench stable alkyl copper-acetylides, we employed the reported oxidative cross-coupling of these alkynylcopper reagents and heteronucleophiles (Scheme 4.9 a).[233] Pleasingly, the mild reaction conditions aided in the synthesis of ynamides **264** and **265** in good yields. Additionally, we attempted to apply the unmodified Evano coupling conditions in the synthesis of an ynimidizole (Scheme 4.9 b). Although no product formation was observed, the copper acetylide was consumed, presumably in a homocoupling reaction.



Scheme 4.9: Ynamides synthesised using Evano's methodology.

The synthesis of *N*-heteroaromatic ynamides do not have much precedent, we postulated that this was due to a lack of reactivity or a lack of electron-withdrawing nature of the amine unit to stabilise the ynamide-type product. However, there is a single report in the literature by Kerwin,[234] detailing the synthesis of ynimidizole **266** (Scheme 4.10). We believed that these substrates would provide interesting coupling partners for hydroacylation, unfortunately all efforts to reproduce these results were futile.

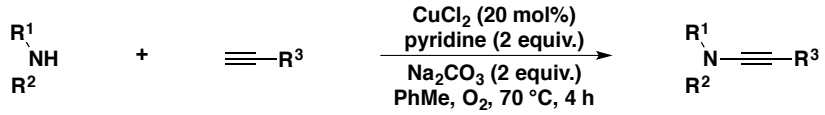


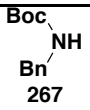
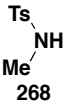
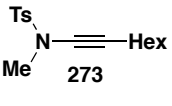
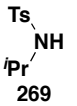
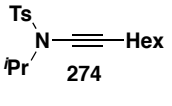
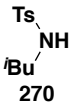
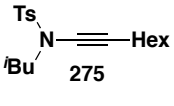
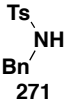
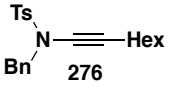
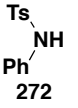
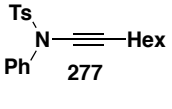
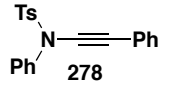
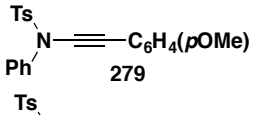
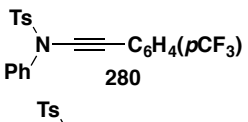
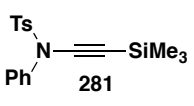
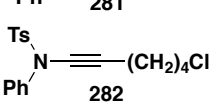
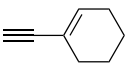
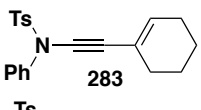
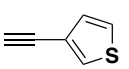
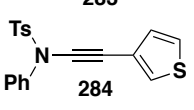
Scheme 4.10: Kerwin's synthesis of ynimidizoles.

Besides the Anderson and Evano methodology, there are two other prevalent and efficient routes to ynamides; the Hsung and Stahl protocols, respectively. The Hsung method relies on the catalytic copper cross-coupling of amides with alkynyl bromides,[235] whereas the Stahl synthesis omits the need for alkynyl bromides and can use commercially available terminal alkynes.[236] As both methods delivered a wide substrate scope and excellent yields, the Stahl protocol was selected for experimental convenience (Table 4.3).

A good range of ynamides, which would enable us to examine the steric parameters of the nitrogen unit, were furnished (entry 2-6). We had also accessed an excellent variety of functionalisation on the alkynyl position, from aryl rings (entry 7-9), to an sp^2 centre (entry 12), and a thiophene ring (entry 13). Unfortunately, desirable oxygen containing groups (entry 14-16) and *N*-Boc units (entry1) were not tolerated under the Cu(II)-catalysed coupling conditions.

Table 4.3: Internal ynamides accessed through methodology reported by Stahl.



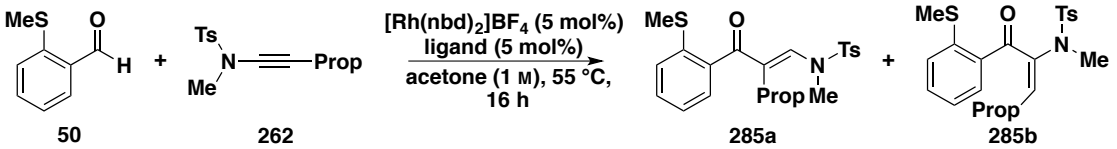
Entry	Nitrogen nucleophile	Alkyne	Product	Isolated Yield
1	 267		-	-
2	 268		 273	94%
3	 269		 274	14%
4	 270		 275	11%
5	 271		 276	11%
6	 272		 277	79%
7	**272**		 278	76%
8	**272**		 279	71%
9	**272**		 280	38%
10	**272**		 281	70%
11	**272**		 282	89%
12	**272**		 283	67%
13	**272**		 284	51%
14	**272**		-	-
15	**272**		-	-
16	**272**		-	-

Conditions: Amide (5 equiv.), Na_2CO_3 (2 equiv.), $CuCl_2$ (20 mol%), pyridine (2 equiv.), PhMe (0.1 M), O_2 (1 atm), 70 °C, add alkyne (1 equiv.) over 4 h, stir for further 4 h.

4.4.2 Ynamide Hydroacylation

Firstly, we decided to study the coupling of ynamide **262** in sulfur-chelation controlled hydroacylation (Table 4.4). We believed that this ynamide would be the most promising for constructive catalysis, as both sides of the alkyne were the least sterically demanding. Our investigation was primarily centered around catalyst optimisation. Employing 5 mol% of small bite-angle ligands dcpm and dppm resulted in extremely poor reactivity and little regiocontrol (entry 1 and 2). This was particularly disappointing as the ynehydrazide substrate had displayed very good regioselectivity for the requisite amino enone for heterocycle formation. In this case, achieving excellent selectivity for the β-amino enone would be paramount for the subsequent nucleophilic addition/heterocycle formation. Therefore, we moved on to a previously selective ligand-PNP(Cy) (entry 3 and 4). These results highlighted the requirement of a 1 M reaction concentration to achieve quantitative conversions; surprisingly the reaction was more selective for the undesired and uncyclisable α-amino enone **285b** in a 2.5:1 selectivity. Following this disappointing observation, we investigated whether traditionally 'branched-selective' ligands would more strongly favour the formation of the α-amino enone (entry 5 and 6). Unfortunately, dppe derived ligands did not permit any coupling. Interestingly, on application of hemi-labile DPEPhos ligand, not only was 100% conversion to hydroacylation product observed, but the reaction was very selective for the required regioisomer **285a** (entry 7). Based on this positive result, we investigated the similar ligand systems DCEPhos and XantPhos (entry 8 and 9), yet both were unreactive. Hence, we decided to advance with a DPEPhos-based catalyst system (5 mol%), under the conditions described in entry 7 of Table 4.4, as our optimum conditions for the regioselective hydroacylation of ynamides.

Table 4.4: Ligand screening in ynamide hydroacylation.

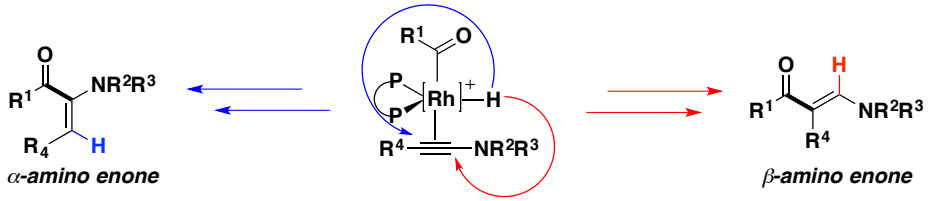


50 262 285a 285b

Entry	Ligand	Conversion (%)[a]	a:b[a]
1	dcpm	24%	1.5:1
2	dppm	16%	3:1
3[b]	PNP(Cy)	86%	1:2.5
4	PNP(Cy)	100% (65%)[c]	1:2.5
5	dppe	0%	-
6	dppe(o^iPr)	0%)	-
7	DPEPhos	100% (71%)[d]	9:1
8	DCEPhos	0%	-
9	XantPhos	3%	-

Conditions: **50** (0.15 mmol, 1 equiv.), **262** (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1 M with respect to aldehyde), 55 °C, 16 h. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Performed at 0.3 M concentration (with respect to aldehyde). [c] Value in parenthesis is the isolated yield of hydroacylation product **285b**. [d] Value in parenthesis is the isolated yield of hydroacylation product **285a**.

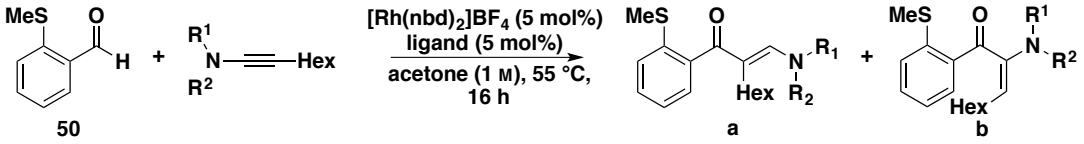
With the optimised hydroacylation conditions in hand, we hoped to mitigate the issue of poor regioselectivity, by variation of the prominent nitrogen group on the ynamide substrate. We postulated that a careful balance of steric availability and electronic parameters of the nitrogen group would be fundamental in promoting hydride insertion closest to the nitrogen unit during hydrometallation, essentially opposite to traditional ynamide reactivity (Scheme 4.11).

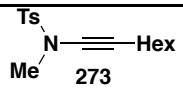
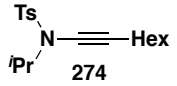
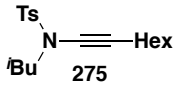
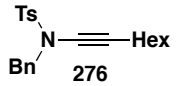
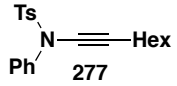
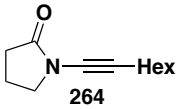
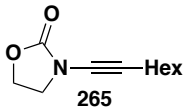


Scheme 4.11: Proposed origins of regioselectivity in ynamide hydroacylation.

We had synthesised a range of *N*-Ts ynamides (*N*-Boc ynamides could not be accessed) possessing the same alkyl chain on the alkynyl position, but with differing levels of steric hindrance on the nitrogen group. We subjected these substrates to hydroacylation couplings employing our most regioselective ligand for the desired *β*-amino enone (DPEPhos), and the most selective system for the *α*-amino enone (PNP(Cy)), to see whether we could obtain high levels of selectivity for both regioisomers (Table 4.5). Variation of the nitrogen group seemed to have a dramatic effect on the regioselectivity of the reaction. Employing a more sterically demanding group (^{i}Pr) on the *N*-Ts position displayed enhanced selectivity for the undesired *α*-amino enone, even when using the *β*-amino enone-selective catalytic system (entry 3). Surprisingly, moving the steric bulk one carbon atom away from the nitrogen, such as in compound **275**, completely switched regioselectivity to favour *β*-amino enone synthesis by 22:1 (entry 4). However, both the synthesis and reactivity in hydroacylation of ynamides **274** and **275** was poor. Pleasingly, employing a phenyl ring on the nitrogen, as in **277**, delivered complete consumption of starting materials under the DPEPhos conditions and excellent regioselectivity for the desired amino enone (entry 7). Additionally, this substrate facilitated catalyst-based regiocontrol, as the *α*-amino enone could be accessed selectively under the PNP(Cy) conditions (entry 8). Using the *N*-Ts, *N*-benzyl motif was also successful in terms of selectivity (entry 5 and 6), although the reactivity was diminished in comparison to ynamide **277**. Additionally, lack of reactivity was displayed when employing the lactam-based groups on the ynamide (entry 9-12). Therefore, we selected the *N*-Ts, *N*-phenyl ynamide **277** as our preferred nitrogen unit for further investigation.

Table 4.5: Regioselectivity of *N*-Ts ynamides in hydroacylation.



Entry	Ynamide	Ligand	Conversion[a]	Product	a:b[a]
1	 273	DPEPhos	96% (71%)	**286a**	9:1
2	**273**	PNP(Cy)	85% (55%)	**286b**	1:2.5
3	 274	DPEPhos	22% (18%)	**287b**	1:15
4	 275	DPEphos	77% (56%)	**288a**	22:1
5	 276	DPEPhos	80% (74%)	**289a**	>25:1
6	**276**	PNP(Cy)	69% (15%)	**289b**	1:4
7	 277	DPEPhos	100% (61%)	**290a**	>25:1
8	**277**	PNP(Cy)	70% (48%)	**290b**	1:8
9	 264	DPEPhos	0%	-	-
10	**264**	PNP(Cy)	0%	-	-
11	 265	DPEPhos	0%	-	-
12	**265**	PNP(Cy)	0%	-	-

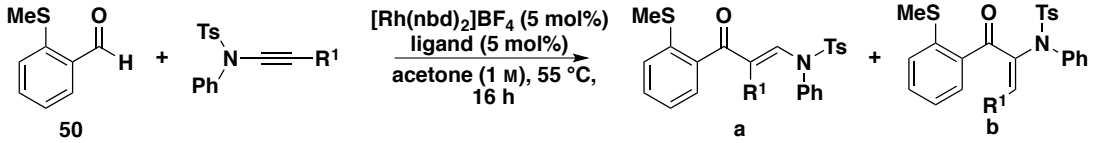
Conditions: **50** (0.15 mmol, 1 equiv.), ynamide (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1 M with respect to aldehyde), 55 °C, 16 h. Value in parenthesis is the isolated yield of product. [a] Determined by ^1H NMR spectroscopy of crude reaction mixtures.

4.4.3 Scope of Ynamides in Hydroacylation

Within previous work, modifying functionality on the alkynyl position from an alkyl chain has resulted in diminished hydroacylation coupling, hence we explored the scope of what could be incorporated on the alkynyl position (Table 4.6). Pleasingly, aromatic systems could be installed in good yields (entry 1) although, selectivity was decreased

presumably due to the slightly electron withdrawn nature of aromatic rings, which could favour hydride insertion closer to the aryl group and thus promote α-amino enone (**b**) formation. However, as the electronic parameters around the C-C triple bond are not the sole aspect influencing regioselectivity, employing an α-amino enone selective system did not promote the formation of the α-amino enone substrate as expected (entry 2). We also observed that a more electron rich aryl ring at the alkynyl position, such as **279**, resulted in slightly higher selectivity for the desired β-amino enone than an electron poor ring (entry 3 and 4). Additionally, it became apparent that substantial steric bulk at the alkynyl position, such a TMS group, caused the rhodium-catalysed coupling to fail (entry 5).

Table 4.6: Investigating regioselectivity of internal ynamides.

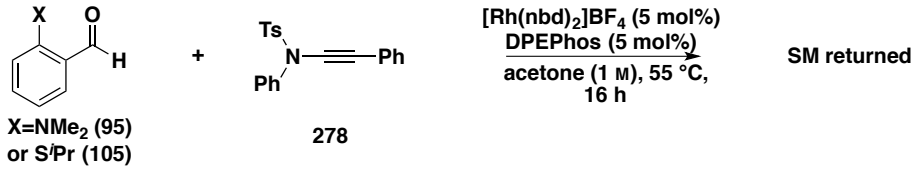


Entry	R^1 (ynamide)	Ligand	Product	Conversion[a]	a:b[a]
1	Ph (**278**)	DPEPhos	**291a**	100% (79%)	6:1
2	Ph (**278**)	PNP(Cy)	**291b**	100% (40%)	1.3:1
3	*p*OMe-C_6H_4 (**279**)	DPEPhos	**292**	100% (82%)[b]	6.3:1
4	*p*CF_3-C_6H_4 (**280**)	DPEPhos	**293**	100% (75%)[b]	5:1
5	$SiMe_3$ (**281**)	DPEPhos	-	-	-

Conditions: **50** (0.15 mmol, 1 equiv.), ynamide (1.5 equiv.), $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), acetone (1 M with respect to aldehyde), 55 °C, 16 h. Value in parenthesis is the isolated yield of product. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [b] Value in parenthesis is the isolated yield of β-amino product only (**a**).

Further to these observations, we tried to improve the regioselectivity of ynamide **278** by attempting to couple it with aldehydes that had exhibited high regioselectivity in the past, such as *N*-chelating aldehyde **95**, and aldehyde **105**, which possesses a sterically demanding chelating motif (Scheme 4.12). However, neither of these aldehydes were

responsive with the DPEPhos-based catalytic system.



Scheme 4.12: Attempted hydroacylation coupling of selective aldehydes and ynamides.

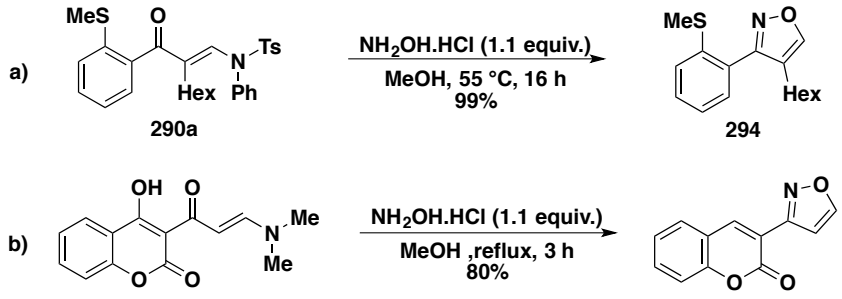
4.5 Heterocycle Formation

With an effective hydroacylative synthesis of *β*-amino enones in place, we moved forward with the assembly of a variety of heterocycles from these hydroacylation adducts, initially investigating the addition of *bi*-nucleophilic compounds. In such reactions, the leaving group is usually a dimethylamine unit however, we postulated that *N*-Ts aniline would also stable enough to be a reliable leaving group.

4.5.1 Synthesis of Isoxazole Ring Systems

Firstly, we investigated the addition/cyclisation protocol for the formation of isoxazoles. Employing hydroxylamine in methanol, while heating, was known to commonly promote double nucleophilic addition in a tandem and efficient manner.[237] Pleasingly, these conditions could be applied to our hydroacylation substrate and delivered hexyl substituted isoxazole ring **294** in a quantitative yield (Scheme 4.13 a). The regioisomer observed from this addition reaction seemed to arise from an initial 1,2-carbonyl addition of the nitrogen in hydroxylamine, following the oxygen closing the isoxazole ring by the loss of aniline. Although the more common pathway for this addition is through a primary 1,4-addition,[238] which delivers the opposite regioisomer, precedent for the reactivity we observed does exist under similar reaction conditions to the ones employed (Scheme 4.13 b).[239] Even though we observed an excellent yield for the heterocycle forming step, the

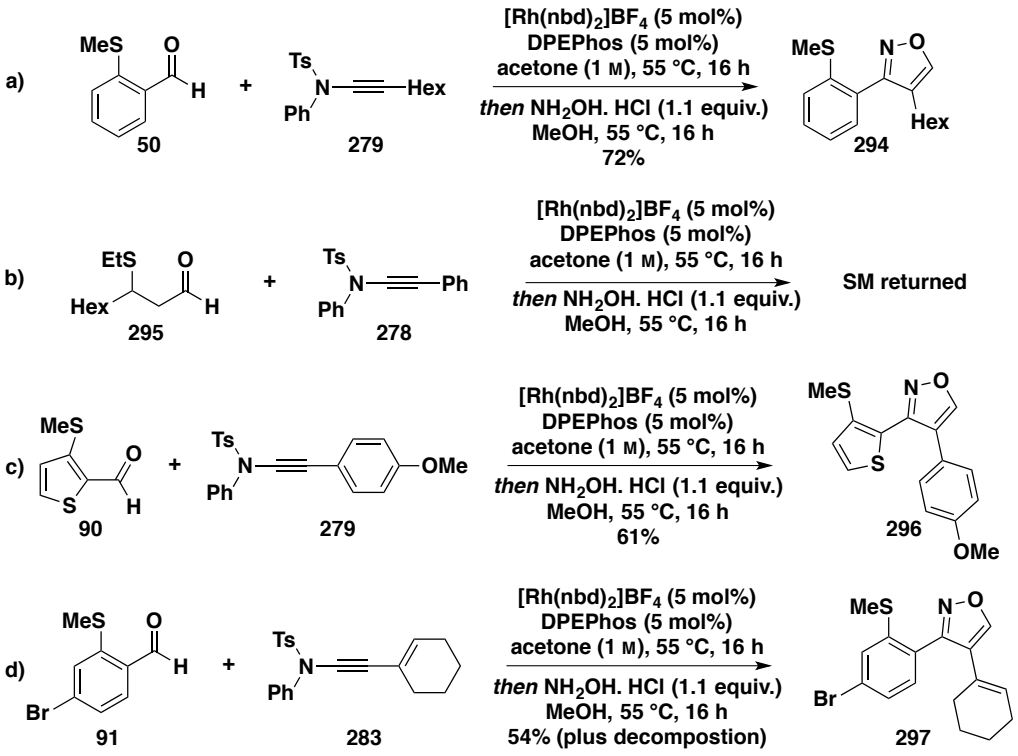
isolated yield of the hydroacylation product was lowered by the instability of the amino enone, therefore the overall two-pot yield was a moderate 60% for the entire sequence.



Scheme 4.13: 1,2-Addition promoted isoxazole formation from enaminones.

We hoped to circumvent instability issues of the isolated hydroacylation adduct by performing the reaction in one-pot (Scheme 4.14 a). Once the hydroacylation step had been performed, the reaction vessel was opened to air and exposed to the cyclisation conditions displayed above in Scheme 4.13 a, which furnished isoxazole **294**. The one-pot reaction delivered the isoxazole in a good 72% yield; improved on the two-pot method. This reaction proved that the three bond forming steps occurring were transferable to an efficient one-pot protocol. Pleased with this result, we attempted to expand the substitution pattern present on the isoxazole ring (Scheme 4.14).

It became evident that alkyl aldehydes were not compatible with ynamide coupling partners in this hydroacylation reaction (Scheme 4.14 b) and both the aldehyde and ynamide were returned. The coupling of ynamide **279** with a heteroaromatic aldehyde **90** was successful, although not to a quantitative conversion, however isoxazole **296** was still obtained in an adequate 61% yield (Scheme 4.14 c). On the other hand, although the hydroacylation coupling of aryl aldehyde **91** with alkenyl ynamide **283** was effective, the cyclisation step proved troublesome, as only a 54% yield was achieved due to the many by-products present during this heterocycle formation (Scheme 4.14 d).



Scheme 4.14: Substrate scope of one-pot isoxazole synthesis *via* hydroacylation.

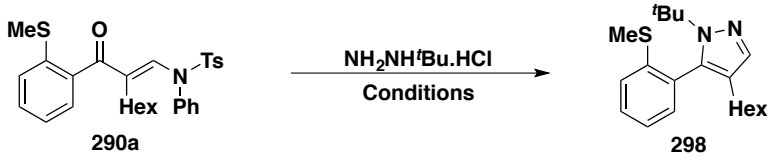
4.5.2 Synthesis of Pyrazole Ring Systems

Application of this methodology to pyrazole synthesis was attempted in a two-pot manner, employing hydrazines with *β*-amino enone **290a** as the model substrate. The addition of hydrazine hydrate to enone **290a** resulted in a complex mixture, therefore we decided to use a substituted hydrazine hydrochloride instead. We attempted the addition of *tert*-butyl hydrazine hydrochloride into the enaminone, as this group enables easy detection of the product and similar reactions have been described in the literature under basic, neutral and microwave conditions several times.[240-242] Hence, we subjected our substrate to a selected range of described conditions (Table 4.7).

It was evident that the same regioisomer of the pyrazole was formed in every case (**298**), which was confirmed by the ^{1}H NMR spectrum in combination with NOE experiments. The formation of this regioisomer indicated that the addition of the free NH_2 on the hydrazine was occurring in a 1,4-fashion, as this would be more sterically favoured,

followed by a dehydrative cyclisation, which is the more common pathway in the literature.[243]

Table 4.7: Optimisation of pyrazole formation from β-amino enones.



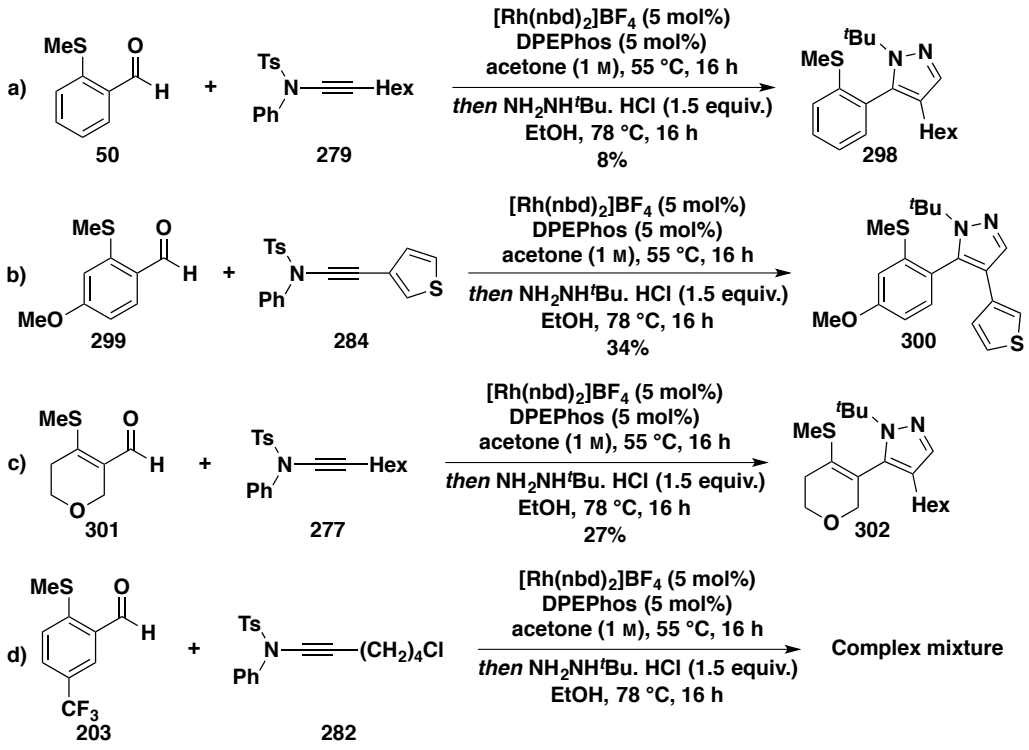
290a 298

Entry	$NH_2NH^tBu.HCl$ (equiv.)	Conditions	Conversion[a]
1	1.5	EtOH, 60 °C, 16 h	80%
2	1.5	EtOH, 78 °C, 16 h	98% (82%)
3	5.0	EtOH, μW, 100 °C, 1 h	100% (47%)
4	1.2	EtOH, NEt_3 (2 equiv.), μW, 125 °C, 2 h	14%
5	1.2	EtOH, NaOCOMe (1.3 equiv.), 78 °C, 16 h	16%

Conditions: **290a** (0.1 mmol, 1 equiv.), conditions as stated. Value in parenthesis is the isolated yield of product **298**. [a] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures.

Addition of the *tert*-butyl hydrazine hydrochloride in EtOH under basic conditions resulted in very poor conversion to the product (Table 4.7, entry 4 and 5). Therefore, we decided to omit base and perform the reaction at either 78 °C for 16 hours, or 100 °C under microwave conditions for 1 hour to obtain complete or almost complete consumption of starting material (entry 2 and 3). We found that employing the microwave irradiation to heat the reaction resulted in significant decomposition, hence the low 47% isolated yield (entry 3). However, when lower temperatures were employed for a longer period of time; a clean conversation to the heteroaromatic product was obtained in an excellent 82% isolated yield (entry 2). We proceeded with these as the optimum conditions for pyrazole formation from isolated β-amino enones. Consequently, we attempted to perform this reaction sequence, starting from the aldehyde and ynamide hydroacylation, in one-pot. We endeavored to combine the optimised features for hydroacylation and cyclisation for the model substrate and concurrently attempted the

sequence on a range of aldehydes and ynamides (Scheme 4.15).

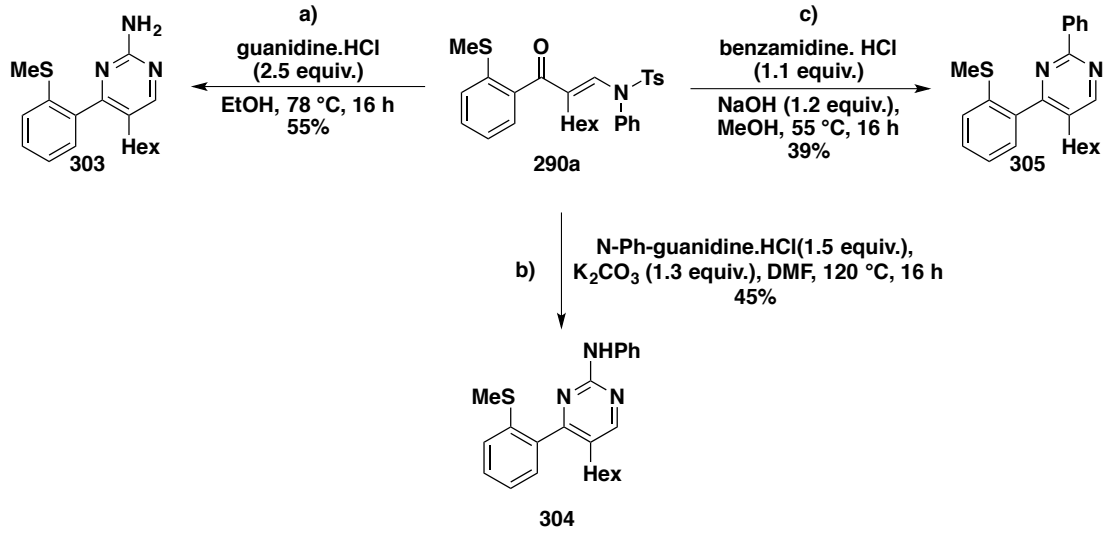


Scheme 4.15: Attempted one-pot hydroacylation/addition/cyclisation sequences.

Pleasingly, all the hydroacylation couplings attempted in Scheme 4.15 resulted in complete consumption of the aldehyde and formed the enaminone cleanly. It should be noted that hydroacylation 4.15 b, employing heteroaromatic ynamide **284**, was less regioselective and formed some of the α-amino enone. Upon completion of hydroacylation, the hydrazine was added under the optimised conditions. Unfortunately, all the heterocycle forming reactions resulted in extremely impure complex mixtures. The combination of modest conversions to the desired pyrazoles, and difficulty in isolation, resulted in overall poor-yields for this one-pot reaction. The 8% isolated yield of model pyrazole **298** (Scheme 4.15 a) is extremely diminished in comparison to the two-pot procedure, which achieved an overall yield of 50%. Slightly higher yields could be obtained for pyrazoles **300** and **302** (Scheme 4.15 b and c), however the yields are still not acceptable to constitute this as an efficient synthesis of heterocycles and this method would require further optimisation.

4.5.3 Synthesis of Six-Membered Heterocycles

The synthesis of pyrimidines is widely investigated due to their significance in biologically active compounds.[244] Numerous reaction conditions for transforming *β*-amino enones into pyrimidines exist,[245-247] however the use of *N*-Ts aniline as a leaving group has never been investigated. Thus, we subjected hydroacylation product **290a** to acidic and basic conditions with a few different *bi*-nucleophiles to determine whether six-membered heterocycles could be accessed through our designed hydroacylative route (Scheme 4.16).



Scheme 4.16: Attempted synthesis of pyrimidines *via* cyclisation of hydroacylation adducts.

The addition of free guanidine hydrochloride, without the addition of base, resulted in a 55% isolated yield of pyrimidine **303** (Scheme 4.16 a), however the reaction did not deliver complete consumption of the enone starting material. We then attempted the addition of a protected guanidine under basic conditions, although this reaction also displayed low reactivity of the starting material, delivering a yield of 45% of pyrimidine **304** (Scheme 4.16 b). We postulated that the presence of an amine substituent on the pyrimidine ring could be problematic and hence attempted the addition of an amidine instead, again under the more prevalent basic conditions (Scheme 4.16 c). Pyrimidine formation was observed, nevertheless the reaction suffered from low conversions and low

isolated yield of pyrimidine **305**. Despite the moderate yields observed, we were pleased that, for the first time in this thesis, the hydroacylation coupling of nitrogen containing alkynes could grant access to valuable six-membered heterocycles. We presumed that a larger variety of reaction conditions would need to be examined, in addition to another leaving group for the nucleophilic substitution, as aniline may not be a favourable unit for this reaction. However, due to time constraints these issues were not examined further and the project is currently ongoing within the group.

4.6 Summary

To conclude, we have described the first application of ynamides, and to a lesser extent ynehydrazides, in an efficient and regioselective rhodium(I)-catalysed hydroacylation. Regioselectivity could be controlled through a judicious choice of catalyst (DPEPhos-based) and nitrogen substitution patterns on the ynamide substrate. We have also varied both the aldehyde and ynamide components within hydroacylation. Additionally, we have applied this new reactivity of ynamides in the synthesis of five- and six-membered aza-heterocycles. This includes both the one- and two-pot syntheses of isoxazoles, as well as the two-pot synthesis of pyrazoles and pyrimidines. Unfortunately, the transfer of the pyrazole and pyrimidine syntheses to a one-pot protocol was not possible under the limited conditions attempted.

Chapter 5

Conclusions and Future Work

The work presented herein has demonstrated that propargylic amines, allylic amines and ynamides are efficient and versatile reagents to be employed in Rh(I)-catalysed hydroacylation reactions with chelating aldehydes. These reactions have been targeted to further improve the synthetic utility of hydroacylation couplings by developing novel routes to various biologically relevant heterocycles. From the developed methodologies we could conclude the following:

a) Propargylic and allylic amines as substrates for hydroacylation

The efficient and robust hydroacylation coupling of terminal propargylic amines has been developed, circumventing the regioselectivity issues through the use of a small bite-angle ligand PNP(Cy).[61] Furthermore, we have overcome the difficulties of using traditionally challenging coupling partners for hydroacylation reactions, such as internal propargylic amines and alkenes (allylic amines). Thus, this work has significantly expanded the substrate compatibility of chelation-controlled hydroacylation.

b) One-pot synthesis of pyrroles, dihydropyrroles and access to pyrrolidines

The development of these regioselective hydroacylation couplings has facilitated the formation of five-membered aza-heterocycles in one-pot cascade reactions. A wide

variety of novel pyrroles and dihydropyrroles have been accessed in excellent yields, with low catalytic loadings, on large scales, and allowing for the use of different chelating motifs on the aldehyde. Furthermore, subsequent one-step manipulations of the heterocycles granted access to fully-substituted pyrrole rings, 'traceless' pyrroles, as well as fully-saturated pyrrolidine heterocycles in a diastereoselective manner.

c) Ynamides as substrates for hydroacylation

This thesis has also presented the successful use of internal ynamide substrates in Rh(I)-catalysed hydroacylation with *S*-chelating aldehydes. A thorough optimisation has provided a regioselective and effective reaction to access *β*-amino enones, which are extremely versatile building blocks. Moreover, these hydroacylation adducts have been converted into a variety of five- and six-membered heterocycles *i.e*. isoxazoles, pyrazoles and pyrimidine rings. Further investigations are being carried out in the group to optimise these processes into one-pot protocols, and to use these adducts in a more diverse manner.

Overall, this thesis widely exemplifies the importance of regioselective hydroacylation as an effective route to varied heterocycles, as well as enabling access to interesting substitution patterns through novel disconnections. There are however still some challenges that could be investigated in the future, such as better understanding regioselectivity when employing potentially chelating alkynes and further improving the protocol for accessing heterocycles from the hydroacylation of ynamides. A more substantial future aim would be to develop the use of non-chelating aldehydes in hydroacylation reactions with chelating alkynes or alkenes (Scheme 5.1), which would have the ability to provide a direct route to 'tether free' hydroacylation products and potentially heterocyclic systems.



Scheme 5.1: Potential hydroacylation of non-directing aldehydes and propargylic/allylic amines.

Although initial investigations employing cationic rhodium(I) catalysts in Chapter 3, table 3.6 were unsuccessful, it is known that the C-H activation of aldehydes is more readily achieved with neutral rhodium species and this could be attempted in the future. Once the C-H activation of these aldehydes is achieved, the design of the directing unsaturated coupling partner could be modified to best prevent decarbonylation and facilitate constructive catalysis.

Chapter 6

Experimental Data and Procedures

6.1 General Considerations

Reactions were conducted with continuous magnetic stirring under an inert atmosphere of nitrogen and using dry solvents unless otherwise stated. Nitrogen gas was passed through a Drierite® and silica filled drying tube before use. Glassware was oven-dried (>200 °C), and allowed to cool to room temperature under vacuum once assembled. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Alfa Aesar, Strem Chemicals Inc., or Fluorochem Ltd., and used as supplied. PNP(Cy) was synthesised according to a reported procedure[110] and was weighed out in air and stored in a Schlenk tube under nitrogen. Solvents were collected fresh from an in-house solvent purification system, which involves passing the solvent through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. 'Petrol' to the fraction of light petroleum ether, boiling in the range of 40-60 ºC. Acetone, for use in rhodium reactions, was purchased from Sigma-Aldrich (HPLC grade), distilled over Drierite® and degassed prior to use.

Reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium backed silica plates (Merck Kieselgel 60 F254). Plates were visualised under

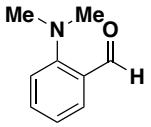
ultraviolet light (254 nm) followed by staining with potassium permanganate, vanillin or Seebach's stain (Magic).[248] Flash column chromatography was carried out using matrix 60 silica gel.

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were obtained on a Bruker AVIIIHD 400 NanoBay (400 MHz) or AVII 500 with He cryoprobe (500 MHz) spectrometers, using the residual solvent as an internal standard, and at an ambient temperature unless otherwise stated. Chemical shifts (δ) are reported in parts per million (ppm) with the multiplicities of the spectra reported as following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. Coupling constants (*J*) are given in Hertz (Hz) and reported to the nearest 0.5 Hz. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, DEPT, NOE data and comparison with spectra of related compounds.

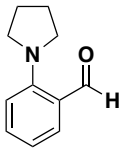
Low-resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High-resolution ESI mass spectrometry measurements were recorded on a Bruker Daltronics microTOF (ESI^{+}) spectrometer or Micromass LCT under the conditions of field ionisation (FI) by the internal service at the Department of Chemistry, University of Oxford. Values quoted are a ratio of mass to charge in Daltons and relative intensities of peaks observed are quoted as a percentage. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer with internal calibration in the range 4000-600 cm^{-1}. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

The following reagents were obtained from members of the Willis group and prepared according to literature procedures:

2-(Dimethylamino)benzaldehyde, 95 and 2-(pyrrolidin-1-yl)benzaldehyde



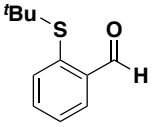
95



2-(pyrrolidin-1-yl)benzaldehyde

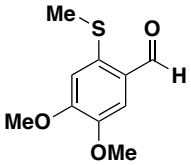
Obtained from Maitane Fernández-Chento; prepared according to a procedure reported by Willis *et. al.*[90]

2-(*tert*-Butylthio)benzaldehyde, 106



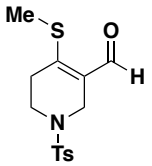
Obtained from Jack Glancy; prepared according to a procedure reported by Lee *et. al.*[249]

4,5-Dimethoxy-2-(methylthio)benzaldehyde

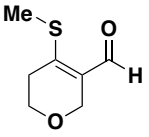


Obtained from Sarah-Jane Poingdestre; prepared according to a procedure reported by Willis *et. al.*[250]

4-(Methylthio)-1-tosyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde and 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde, 301



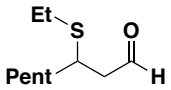
4-(methylthio)-1-tosyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde



301

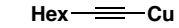
Obtained from Jingze Niu; prepared according to a procedure reported by Willis *et. al.*[196]

3-(Ethylthio)octanal, 295



Obtained from Ming Gao/Anaïs Bouisseau; prepared according to a procedure reported by Willis *et. al.*[102]

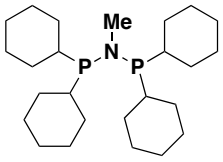
Oct-1-yn-1-ylcopper



Obtained from Vincent Vedovato; prepared according to a procedure reported by Evano *et. al.*[233]

6.2 Chapter 2 Experimental

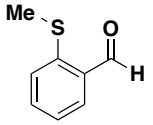
1,1-Dicyclohexyl-*N*-(dicyclohexylphosphino)-*N*-methylphosphinamine (PNP(Cy))



Dicylohexylchlorophosphine (0.37 mL, 1.67 mmol, 2.3 equiv.) was added dropwise to a solution of methylamine hydrochloride (50.0 g, 0.74 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) and Et_3N (0.33 mL, 2.37 mmol, 3.2 equiv.). The resulting solution was stirred at room temperature for 16 hrs. The suspension was filtered through a short alumina column (CH_2Cl_2) under an inert atmosphere. The solution was concentrated under reduced pressure to obtain ligand **PNP(Cy)** as a white solid (80.0 mg, 26%)

^{1}H NMR (400 MHz, $CDCl_3$): 2.69 (3H, t, $^3J_{PH}$ 3.0, NC*H*$_3$), 2.13-2.09 (4H, m, 4 × PC*H*), 1.94-1.84 (16H, m, PCy-*H*), 1.75-1.73 (4H, m, PCy-*H*), 1.57-1.47 (8H, m, PCy-*H*), 1.41-1.27 (12H, m, PCy-*H*); ^{13}C NMR (101 MHz, C_6D_6): 37.1 (app t, $^2J_{PH}$ 7.0), 30.6 (app t, $^2J_{PH}$ 7.0), 29.7 (app t, $^1J_{PH}$ 10.0), 27.6 (app t, $^4J_{PH}$ 6.0), 27.3 (app t, $^3J_{PH}$ 5.0); ^{31}P NMR (162 MHz, C_6D_6): 85.0 (s). This data is consistent with literature.[110]

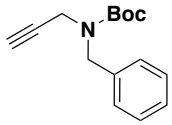
General procedure A for the synthesis of *ß*-sulfur tethered aldehydes, exemplified by the preparation of 2-(methylthio)benzaldehyde, 50



Methanethiol sodium salt solution (17.7 mL, 3.0 M in water, 53.1 mmol, 1.1 equiv.) was added dropwise to 2-fluorobenzaldehyde (5.10 mL, 48.3 mmol, 1.0 equiv.) in DMF (60 mL) at 0 °C. The stirring solution was warmed to room temperature over 16 hrs, after which it was diluted with water (40 mL). The aqueous mixture was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with sat. $LiCl_{(aq.)}$ (3 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification *via* flash column chromatography (20% EtOAc in petrol) afforded the title *ß*-sulfur tethered aldehyde **50** as a yellow oil (5.76 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (1H, s, C*H*O), 7.83 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.56 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.36 (1H, dd, *J* 8.0, 0.5, Ar-*H*), 7.31 (1H, app td, *J* 7.5, 0.5, Ar-*H*), 2.52 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.4, 143.4, 133.9, 133.4, 132.8, 125.4, 124.3, 15.5; LRMS (ESI$^+$): *m/z* 153 ([M+H]$^+$, 100%), 175 ([M+Na]$^+$, 80%). This data is consistent with literature.[251]

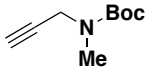
tert-Butyl benzyl(prop-2-yn-1-yl)carbamate, 51



A solution of *N*-Boc propargyl amine **59** (3.00 g, 19.2 mmol, 1.0 equiv.) in THF (6.3 mL) was added to a suspension of sodium hydride (92 mg, 60% in mineral oil, 23 mmol, 1.2 equiv.) in THF (45 mL) and stirred at room temperature for 1 hr. Subsequently, benzyl bromide (3.40 mL, 28.8 mmol, 1.5 equiv.) was added to the mixture dropwise and stirred at room temperature for a further 3 hrs, after which the reaction was cooled to 0 °C and quenched with sat. $NH_4Cl_{(aq.)}$ (15 mL). The product was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0-15% EtOAc in petrol) to obtain propargylic amine **51** as a pale yellow oil (3.51 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.35 (5H, m, Ar-*H*), 4.62 (2H, s, CHCC*H*$_2$), 4.05 (2H, br s, NC*H*$_2$Ar), 2.28 (1H, t, *J* 2.5, C*H*CCH$_2$), 1.56 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 155.1, 128.5, 128.1, 127.7, 127.4, 80.6, 80.2, 79.3, 71.7, 65.9, 28.4; LRMS (ESI$^+$): *m/z* 268 ([M+Na]$^+$, 100%), 513 ([2M+Na]$^+$, 25%). This data is consistent with literature.[252]

tert-Butyl methyl(prop-2-yn-1-yl)carbamate, 52

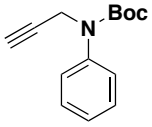


A solution of *N*-Boc propargyl amine **59** (2.00 g, 12.9 mmol, 1.0 equiv.) in THF (3.2 mL) was added to a suspension of sodium hydride (1.03 g, 60% in mineral oil, 25.8 mmol, 2.0 equiv.) in THF (4.4 mL) at 0 °C. After the mixture was stirred at 0 °C for 1 hr, methyl

iodide (0.96 mL, 15.4 mmol, 1.2 equiv.) was added dropwise. The solution was allowed to warm to room temperature over 2.5 hrs. The reaction mixture was cooled to 0 °C and quenched with sat. $NH_4Cl_{(aq.)}$ (10 mL). The product was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0-10% Et_2O in petrol) to obtain propargylic amine **52** as a yellow oil (1.57 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.06 (2H, br s, CHCC*H*$_2$), 2.94 (3H, s, NC*H*$_3$), 2.24 (1H, t, *J* 2.5, C*H*CCH$_2$), 1.49 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.5, 129.7, 126.1, 124.0, 34.5, 28.4, 16.4; LRMS (ESI$^+$): *m/z* 192 ([M+Na]$^+$, 100%). This data is consistent with literature.[253]

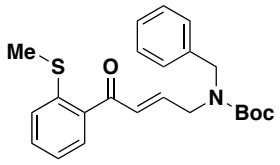
***tert*-Butyl phenyl(prop-2-yn-1-yl)carbamate, 53**



A suspension of sodium hydride (47.6 mg, 60% in mineral oil, 12.4 mmol, 1.2 equiv.) in DMF (20 mL) was stirred at 0 °C for 10 mins, after which a solution of *N*-Boc aniline (2.00 g, 10.3 mmol, 1.0 equiv.) in DMF (10 mL) was added dropwise over 10 mins and the mixture stirred at 0 °C for 1 hr. Propargyl bromide (1.00 mL, 11.3 mmol, 1.1 equiv.) was then added dropwise and the reaction mixture was warmed to room temperature over 1 hr. Upon completion, the reaction was cooled to 0 °C and quenched with sat. $NH_4Cl_{(aq.)}$ (10 mL). The product was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (0-20% EtOAc in petrol) to obtain propargylic amine **53** as a pale yellow oil (2.31 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.36 (4H, m, Ar-*H*) 7.27-7.23 (1H, m, Ar-*H*), 4.39 (2H, d, *J* 2.5, CHCC*H*$_2$), 2.27 (1H, t, *J* 2.5, C*H*CCH$_2$), 1.49 (9H, s, $CO_2C(CH_3)_3$; ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.1, 142.1, 128.7, 126.3, 123.0, 81.0, 80.0, 71.7, 39.8, 28.3; LRMS (ESI$^+$): *m/z* 254 ([M+Na]$^+$, 100%). This data is consistent with literature.[254]

General procedure B for the synthesis of linear *γ*-amino enones *via* rhodium-catalysed hydroacylation of terminal propargylic amines, as exemplified by the synthesis of *tert*-butyl (*E*)-benzyl{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 55a

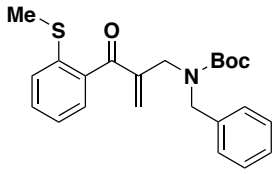


An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%), once under an inert atmosphere, they were dissolved in acetone (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalytic species (colour change from red to pale yellow). The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (75 μL, 1.0 M with respect to aldehyde minus the volume or mass of both aldehyde and alkyne) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and propargylic amine (*tert*-butyl benzyl(prop-2-yn-1-yl)carbamate **51**) (56.3 mg, 0.225 mmol, 1.5 equiv.). The reaction mixture, once homogenous (on occasion, sonication was required), was then stirred at room temperature. The reaction was monitored by TLC until complete. After 16 hrs, the reaction mixture was filtered through a plug of silica (acetone, 10 mL) and the solvent removed *in vacuo* to obtain the crude product. The crude product was analysed by ^{1}H NMR spectroscopy to measure the ratio of the linear to branched products (22:1, linear: branched). The regioisomers were then separated by flash column chromatography (5-20% EtOAc in petrol) to afford title linear *γ-amino enone* **55a** as a yellow oil (46.4 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* 8.0, Ar-*H*), 7.48 (1H, app t, *J* 7.5, Ar-*H*), 7.37-7.33 (4H, m, Ar-*H*), 7.27-7.19 (3H, m, Ar-*H*), 6.76 (1H, dt, *J* 15.5, 5.5, COCHC*H*), 6.68 (1H, d, *J* 15.5, COC*H*), 4.49 (2H, d, *J* 5.5, NCH_2CHCH), 4.04 (2H, app d, *J* 40.0, NCH_2Ar), 2.47 (3H, s, SCH_3), 1.51 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.3, 144.6, 137.8, 132.3, 131.7, 131.0, 129.7, 128.7, 128.6, 128.1, 127.5, 126.2, 124.0, 123.6, 80.5, 47.3, 43.2, 28.4, 16.4; IR: ν_{max} (neat)/cm^{-1} 2977, 1692, 1621, 1586, 1454, 1433, 1408, 1366, 1246,

1163, 1122; LRMS (ESI^+): *m/z* 420 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 420.1621 $[M+Na]^+$, $C_{23}H_{27}NO_3SNa^+$ requires 420.1604.

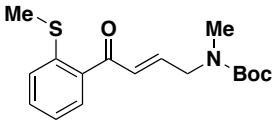
General procedure C for the synthesis of branched *β*-amino enones *via* rhodium-catalysed hydroacylation of terminal propargylic amines, as exemplified by the synthesis of *tert*-butyl benzyl{2-[2-(methylthio)benzoyl]allyl}carbamate, 55b



Prepared following a procedure adapted from Willis *et. al*.,[105] an oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (5.6 mg, 10 mol%) and dppe(*o*-iPr) (8.5 mg, 10 mol%), once under an inert atmosphere, they were dissolved in acetone (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (0.5 mL) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 *μ*L, 0.15 mmol, 1.0 equiv.) and propargylic amine (*tert*-butyl benzyl(prop-2-yn-1-yl)carbamate **51**) (56.3 mg, 0.225 mmol, 1.5 equiv.). The reaction was monitored by TLC until complete. After 6 hrs the vial was opened to air and filtered through a plug of silica (acetone, 15 mL) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford title branched *amino enone* **55b** as a yellow oil (35.0 mg, 59%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, app t, *J* 7.5, Ar-*H*), 7.39-7.29 (7H, m, Ar-*H*), 7.21 (1H, app t, *J* 7.0, Ar-*H*), 5.92 (1H, d, *J* 30.0, $NCH_2CCH_aH_b$), 5.68 (1H, app br s, $NCH_2CCH_aH_b$), 4.53 (2H, app d, *J* 13.5, NCH_2Ar), 4.24 (2H, d, *J* 30.0, $NCH_2CCH_aH_b$), 2.45 (3H, s, SCH_3), 1.51 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9, 155.7, 144.8, 138.4, 138.0, 131.0, 129.7, 129.2, 128.5, 128.2, 128.0, 127.5, 127.3, 124.6, 80.1, 50.3, 46.5, 28.4, 17.0; IR: ν_{max} (neat)/cm^{-1} 2979, 1691, 1366, 1245, 1164, 1121, 908, 730; LRMS (ESI^+): *m/z* 398 ($[M+H]^+$, 100%), 420 ($[M+Na]^+$, 25%); HRMS (ESI^+) found 420.1611 $[M+Na]^+$, $C_{23}H_{27}NO_3SNa^+$ requires 420.1604.

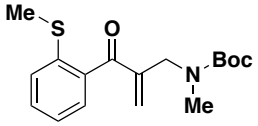
tert-Butyl (*E*)-methyl{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 56a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl methyl(prop-2-yn-1-yl)carbamate **52**) (38.1 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (93 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (8:1, linear: branched). The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield linear *γ-amino enone* **56a** as a yellow oil (36.7 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* 8.0, Ar-*H*), 7.48 (1H, app t, *J* 7.5, Ar-*H*), 7.38 (1H, d, *J* 8.0, Ar-*H*), 7.23 (1H, app t, *J* 7.5, Ar-*H*), 6.80-6.70 (2H, m, COC*H*C*H*), 4.09 (2H, d, *J* 13.0, NCH_2), 2.92 (3H, app d, *J* 10.0, NCH_3), 2.47 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 155.5, 144.5, 136.3, 131.8, 129.7, 128.7, 127.8, 126.2, 124.0, 80.1, 34.5, 31.0, 28.4, 16.4; IR: ν_{max} (neat)/cm^{-1} 2976, 1692, 1621, 1586, 1434, 1391, 1365, 1289, 1248, 1146, 1048; LRMS (ESI$^+$): *m/z* 344 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 344.1294 [M+Na]$^+$, $C_{17}H_{23}NO_3SNa^+$ requires 344.1291.

tert-Butyl methyl{2-[2-(methylthio)benzoyl]allyl}carbamate, 56b

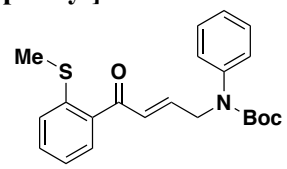


Prepared according to general procedure **C** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl methyl(prop-2-yn-1-yl)carbamate **52**) (58 mg, 0.30 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (5.6 mg, 10 mol%) and dppe(*o*-iPr) (8.5 mg, 10 mol%) in acetone (0.5 mL) for 16 hrs at room temperature. The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield branched *amino enone* **56b** as a yellow oil (35.1 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.37 (3H, m, Ar-*H*), 7.21 (1H, app t, *J* 6.5, Ar-*H*), 5.86 (1H, d, *J* 19.0, $NCH_2CCH_aH_b$), 5.67 (1H, app s, $NCH_2CCH_aH_b$), 4.25 (2H, br s, NCH_2), 2.95

(3H, s, NC*H*$_3$), 2.44 (3H, s, SC*H*$_3$), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9, 155.9, 144.7, 138.0, 131.0, 129.5, 129.1, 127.5, 126.9, 124.6, 79.7, 49.2, 34.9, 28.4, 17.0; IR: ν_{max} (neat)/cm^{-1} 2977, 1691, 1585, 1434, 1391, 1366, 1307, 1247, 1147; LRMS (ESI$^+$): *m/z* 344 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 344.1292 [M+Na]$^+$, $C_{17}H_{23}NO_3SNa^+$ requires 344.1291.

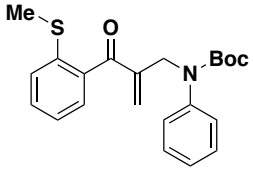
***tert*-Butyl (*E*)-{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}(phenyl)carbamate, 57a**



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl phenyl(prop-2-yn-1-yl)carbamate **53**) (53.1 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (78 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (5:1, linear: branched). The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield linear *γ-amino enone* **57a** as a yellow oil (34 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (1H, dd, *J* 6.5, 1.5, Ar-*H*), 7.49-7.45 (1H, m, Ar-*H*), 7.38-7.33 (2H, m, Ar-*H*), 7.29-7.18 (5H, m, Ar-*H*), 6.93 (1H, dt, *J* 15.5, 5.0, COCHC*H*), 6.83 (1H, d, *J* 15.5, COC*H*), 4.50 (2H, dd, *J* 5.0, 1.5, NC*H*$_2$), 2.46 (3H, s, SC*H*$_3$), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.3, 154.3, 144.8, 142.5, 141.1, 136.2, 134.3, 131.7, 129.8, 129.7, 128.9, 128.6, 126.1, 123.9, 81.0, 51.7, 28.3, 16.4; IR: ν_{max} (neat)/cm^{-1} 2977, 1697, 1621, 1597, 1496, 1434, 1367, 1281, 1155, 1045; LRMS (ESI$^+$): *m/z* 406 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 406.1446 [M+Na]$^+$, $C_{22}H_{25}NO_3SNa^+$ requires 406.1447.

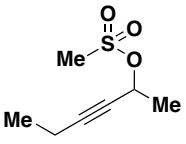
tert-Butyl {2-[2-(methylthio)benzoyl]allyl}(phenyl)carbamate, 57b



Prepared according to general procedure **C** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl phenyl(prop-2-yn-1-yl)carbamate **53**) (69.4 mg, 0.30 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (5.6 mg, 10 mol%) and dppe(*o*-iPr) (8.5 mg, 10 mol%) in acetone (0.5 mL) for 16 hrs at room temperature. The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield branched *amino enone* **57b** as a yellow oil (38.0 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.38 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.34-7.29 (5H, m, Ar-*H*), 7.21-7.17 (2H, m, Ar-*H*), 6.05 (1H, app t, *J* 1.5, $NCH_2CCH_aH_b$), 5.74 (1H, app t, *J* 1.5, $NCH_2CCH_aH_b$), 4.73 (2H, s, NCH_2), 2.43 (3H, s, SCH_3), 1.49 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.4, 154.5, 145.0, 142.7, 138.6, 137.8, 131.0, 129.4, 128.6, 127.6, 127.4, 125.8, 125.6, 124.5, 80.8, 50.5, 28.3, 17.0; IR: ν_{max} (neat)/cm^{-1} 2976, 2925, 1697, 1657, 1495, 1382, 1307, 1153, 1020, 755; LRMS (ESI^+): *m/z* 384 ($[M+H]^+$, 100%); HRMS (ESI^+) found 384.16265 $[M+H]^+$, $C_{22}H_{26}NO_3S^+$ requires 384.16279.

Hex-3-yn-2-yl methanesulfonate, 61a

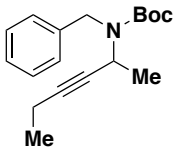


Et_3N (1.42 mL, 10.2 mmol, 1.0 equiv.) was added to a solution of 3-hexyn-2-ol (1.10 mL, 10.2 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at 0 °C and stirred for 30 mins. Subsequently, mesyl chloride (0.80 mL, 10.2 mmol, 1.0 equiv.) was added to the solution, after which it was allowed to warm to room temperature for 30 mins. The reaction mixture was again cooled to 0 °C followed by the addition of water (20 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with $HCl_{(aq.)}$ (10 mL, 0.5 M) and brine (10 mL) and then dried over $MgSO_4$, filtered and concentrated under

reduced pressure to afford the desired methanesulfonate **61a** (0.45 g, 27%) as a light brown oil. The crude product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30 (1H, qt, *J* 6.5, 2.0, OC*H*), 3.13 (3H, s, SO_2CH_3), 2.28 (2H, qd, *J* 7.5, 2.0, CH_3CH_2), 1.64 (3H, d, *J* 6.5, OCHC*H*$_3$), 1.18 (3H, t, *J* 7.5, CH_3CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 90.6, 76.2, 69.0, 39.1, 23.0, 13.4, 12.3; IR: ν_{max} (neat)/cm^{-1} 2982, 1357, 1178, 1049, 889; LRMS (ESI$^+$): *m/z* 177 ([M+H]$^+$, 100%). This data is consistent with literature.[255]

***tert*-Butyl benzyl(hex-3-yn-2-yl)carbamate, 61b**

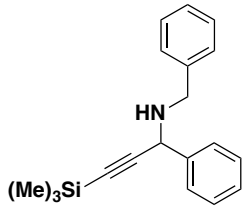


A suspension of sodium hydride (140 mg, 60% in mineral oil, 3.41 mmol, 1.5 equiv.) was stirred in DMF (6 mL) at 0 °C for 10 mins, followed by the dropwise addition of *N*-Boc benzylamine (470 mg, 2.27 mmol, 1.0 equiv.) in DMF (0.5 mL). After stirring for 30 mins at 0 °C, a solution of methanesulfonate (hex-3-yn-2-yl methanesulfonate **61a**) (400 mg, 2.27 mmol, 1.0 equiv.) in DMF (1.0 mL) was added dropwise and the reaction was stirred at room temperature for 16 hrs. The reaction was heated to 80 °C for 30 mins and then cooled to 15 °C. Sat. $NH_4Cl_{(aq.)}$ (5 mL) was added followed by water (10 mL). The aqueous mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc in petrol) to obtain a mixture of the desired product and *N*-Boc benzylamine. Trituration (hexane) and concentration *in vacuo* afforded the desired *propargylic amine* **61b** as a pale yellow oil (0.57 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.29 (4H, m, Ar-*H*), 7.25-7.22 (1H, m, Ar-*H*), 5.23 (1H, app br s, NC*H*(CH_3)), 4.61-4.42 (2H, app m, NCH_2Ar), 2.14 (2H, qd, *J* 7.5, 2.0, CH_3CH_2), 1.36-1.27 (12H, m, $CO_2C(CH_3)_3$ and NCH(C*H*$_3$)), 1.06 (3H, t, *J* 7.5, CH_3CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.1, 128.0, 127.4, 127.0, 126.4, 80.0, 78.9, 58.8, 55.9, 47.1, 28.3, 21.7, 13.8, 12.3; IR: ν_{max} (neat)/cm^{-1} 2977, 2930, 1693, 1453, 1401, 1366, 1321, 1253, 1167,

1119, 1042; LRMS (ESI^+): *m/z* 310 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 310.1779 $[M+Na]^+$, $C_{18}H_{25}NO_2Na^+$ requires 310.1778.

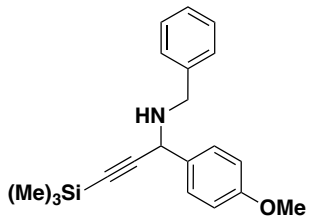
_N_-Benzyl-1-phenyl-3-(trimethylsilyl)prop-2-yn-1-amine, 64



Benzylamine (3.20 mL, 30.0 mmol, 1.0 equiv.) was added to a solution of benzaldehyde (3.06 mL, 30.0 mmol, 1.0 equiv.) in Et_2O (30 mL). After the addition of $MgSO_4$ (50 mg) the reaction mixture was left to stir at room temperature for 24 hrs. The reaction mixture was dried with additional $MgSO_4$, filtered and concentrated in *vacuo* to afford an imine intermediate as a colourless oil (5.82 g, 99%), which was used directly without further purification. $[IrCl(cod)]_2$ (0.27 g, 5 mol%) was placed under an inert atmosphere and was dissolved in a solution of the imine intermediate (1.56 g, 8.00 mmol, 1.0 equiv.) in THF (40 mL), followed by the quick addition of TMS-acetylene (1.71 mL, 12.0 mmol, 1.5 equiv.). The reaction mixture was refluxed for 24 hrs after which it was quenched by the addition of water (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc in hexane) to obtain the desired propargylic amine **64** as a pale yellow oil (0.93 g, 40%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (2H, m, Ar-*H*), 7.43-7.37 (6H, m, Ar-*H*), 7.35-7.30 (2H, m, Ar-*H*), 4.62 (1H, s, NHC*H*), 3.99-3.92 (3H, m, N*H*C*H*$_2$Ar), 0.26 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.7, 139.5, 128.5, 128.44, 128.41, 127.8, 127.7, 127.1, 75.8, 68.0, 63.7, 50.9, 0.1; LRMS (ESI^+): *m/z* 294 ($[M+H]^+$, 100%). This data is consistent with literature.[148]

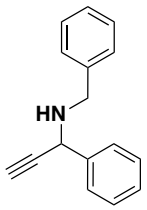
_N_-Benzyl-1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-amine, 65



4-Methoxylbenzaldehyde (1.1 mL, 10 mmol, 1.0 equiv.) was added to a solution of benzylamine (1.2 mL, 10 mmol, 1.0 equiv.) in Et_2O (10 mL). After the addition of $MgSO_4$ (50 mg) the reaction mixture was left to stir at room temperature for 24 hrs. The reaction mixture was dried with additional $MgSO_4$, filtered and concentrated in *vacuo* to afford the imine intermediate as a colourless oil (2.20 g, 98%) and this was used directly without further purification. $[IrCl(cod)]_2$ (29.8 mg, 5 mol%) was placed under an inert atmosphere and was dissolved in a solution of the imine intermediate (500 mg, 2.22 mmol, 1.0 equiv.) in THF (12 mL), followed by the quick addition of TMS-acetylene (0.5 mL, 3.33 mmol, 1.5 equiv.). The reaction mixture was refluxed for 24 hrs after which it was quenched by the addition of water (10 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc in hexane) to obtain the desired propargylic amine **65** as a pale yellow oil (0.695 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (2H, m, Ar-*H*), 7.42-7.40 (2H, m, Ar-*H*), 7.38-7.34 (3H, m, Ar-*H*), 6.92-6.90 (2H, m, Ar-*H*), 4.58 (1H, s, NHC*H*), 3.95-3.90 (3H, m, N*H*C*H*$_2$Ar), 3.83 (3H, s, OC*H*$_3$), 0.25 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.0, 139.5, 131.5, 129.4, 128.4, 127.2, 121.6, 100.0, 76.5, 68.0, 53.1, 50.9, 25.6, 0.1; LRMS (ESI^+): *m/z* 324 ($[M+H]^+$, 100%). This data is consistent with literature.[148]

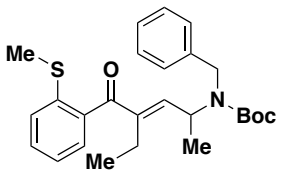
_N_-Benzyl-1-phenylprop-2-yn-1-amine, 66



Propargylic amine (*N*-benzyl-1-phenyl-3-(TMS)prop-2-yn-1-amine **64**) (0.77 g, 2.62 mmol, 1.0 equiv.) was dissolved in MeOH (16 mL) and potassium carbonate (0.36 g, 2.62 mmol, 1.0 equiv.) was added, the reaction was stirred for 16 hrs at room temperature. Water (15 mL) was added to the reaction mixture and the product was extracted with Et_2O (3 × 10 mL) and washed with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (5-10% EtOAc in petrol) to give the title propargylic amine **66** as a pale yellow oil (0.35 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (2H, d, *J* 7.5, Ar-*H*), 7.43-7.34 (8H, m, Ar-*H*), 4.62 (1H, d, *J* 2.0, NHC*H*), 4.00-3.92 (3H, m, N*HCH*$_2$Ar), 2.57 (1H, d, *J* 2.0, C*H*CCHNH); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.9, 139.7, 128.5, 128.4, 128.3, 127.8, 127.5, 127.1, 77.2, 73.5, 52.9, 51.0; LRMS (ESI$^+$): *m/z* 222 ([M+H]$^+$, 100%). This data is consistent with literature.[256]

***tert*-Butyl (*E*)-benzyl{4-[2-(methylthio)benzoyl]hex-3-en-2-yl}carbamate, 67a**

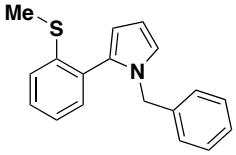


Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl benzyl(hex-3-yn-2-yl)carbamate **61b**) (64.7 mg, 0.225 mmol, 1.5 equiv.), [Rh(nbd)$_2$]BF_4 (2.5 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (66 μL, 1.0 M). After stirring for 16 hrs at 80 °C the reaction gave a crude mixture of regioisomers (2:1, linear: branched) and a NMR conversion of 60%. The compounds were separated by flash column chromatography (5-20% EtOAc in petrol) to yield linear *γ-amino enone* **67a** as a pale yellow oil (18.6 mg, 28%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.34 (2H, m, Ar-*H*), 7.31-7.21 (4H, m, Ar-*H*), 7.21-7.12 (3H, m, Ar-*H*), 7.08 (1H, d, *J* 7.5, COCC*H*), 6.14 (1H, app br s, NC*H*), 4.39 (2H, app br s,

NC*H*$_2$), 2.47 (2H, q, *J* 6.5, CH$_3$C*H*$_2$), 2.42 (3H, s, SC*H*$_3$), 1.39 (9H, s, CO$_2$C(C*H*$_3$)$_3$), 1.24 (3H, d, *J* 7.0, NCHC*H*$_3$), 1.07 (3H, t, *J* 6.5, C*H*$_3$CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.0, 155.3, 130.2, 128.5, 128.4, 128.3, 128.2, 128.1, 127.4, 127.1, 127.0, 126.8, 126.1, 124.7, 80.2, 29.7, 28.3, 22.7, 19.5, 17.0, 14.2, 13.6; IR: ν_{max} (neat)/cm^{-1} 2909, 2854, 1706, 1666, 1632, 1543, 1246; LRMS (ESI$^+$): *m/z* 440 ([M+H]$^+$, 100%), 462 ([M+Na]$^+$, 60%); HRMS (ESI$^+$) found 440.22487 [M+H]$^+$, $C_{26}H_{34}NO_3S^+$ requires 440.22539.

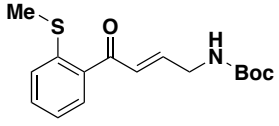
1-Benzyl-2-[2-(methylthio)phenyl]-1*H*-pyrrole, 68



γ-Amino enone **55a** (40.1 mg, 0.10 mmol, 1.0 equiv.) was dissolved in EtOH/H_2O (2 mL, 1:1, v/v) in a microwave vial. This mixture was heated in a dynamic microwave (up to 300 W, maximum pressure 250 psi) at 170 °C for 1 hr. The mixture was directly loaded onto a column of base washed silica and purified by column chromatography (0.5% NEt_3 in petrol) to obtain the *pyrrole* **68** as a colourless oil (14.6 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.33 (1H, m, Ar-*H*), 7.27-7.22 (4H, m, Ar-*H*), 7.16 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.10 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.99-6.97 (2H, m, Ar-*H*), 6.77 (1H, dd, *J* 2.5, 1.5, NC*H*), 6.31 (1H, dd, *J* 3.5, 2.5, NCHC*H*), 6.23 (1H, dd, *J* 3.5, 1.5, NCC*H*), 4.93 (2H, s, NC*H*$_2$Ar), 2.39 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 138.5, 131.8, 131.5, 128.7, 128.4, 127.2, 127.1, 124.11, 124.05, 121.6, 109.6, 108.3, 108.0, 50.9, 15.3; IR: ν_{max} (neat)/cm^{-1} 3060, 2980, 2920, 1662, 1395, 1311, 1256, 1074, 1039; HRMS (FI$^+$) found 279.1136 [M$^+$], $C_{18}H_{17}NS^+$ requires 279.1140.

***tert*-Butyl (*E*)-[4-(2-(methylthio)phenyl)-4-oxobut-2-en-1-yl]carbamate, 69a**

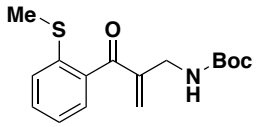


Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (30.2 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd)$_2$]BF$_4$ (1.1 mg, 2 mol%) and PNP(Cy) (1.3 mg, 2 mol%) in acetone (100 μL, 1.0 M).

After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (17:1, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **69a** as a pale yellow oil (39.7 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* 7.5, Ar-*H*), 7.47 (1H, app t, *J* 7.5, Ar-*H*), 7.37 (1H, d, *J* 7.5, Ar-*H*), 7.21 (1H, app t, *J* 7.5, Ar-*H*), 6.86-6.76 (2H, m, COC*H*C*H*), 4.82 (1H, br s, N*H*), 4.02 (2H, app br s, NHCH_2), 2.46 (3H, s, SCH_3), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 182.1, 155.6, 145.6, 140.8, 136.3, 131.6, 129.7, 127.9, 126.1, 124.0, 79.9, 41.8, 28.4, 16.4; IR: ν_{max} (neat)/cm^{-1} 3370, 2977, 1710, 1514, 1434, 1366, 1250, 1167, 1026; LRMS (ESI$^+$): *m/z* 330 ([M+Na]$^+$, 100%), 308 ([M+H]$^+$, 50%); HRMS (ESI$^+$) found 330.1132 [M+Na]$^+$, $C_{16}H_{21}NO_3SNa^+$ requires 330.1134.

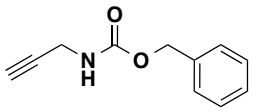
***tert*-Butyl {2-[2-(methylthio)benzoyl]allyl}carbamate, 69b**



Prepared according to general procedure **C** using 2-(methylthio)benzaldehyde **50** (39 μL, 0.30 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (93.1 mg, 0.60 mmol, 2.0 equiv.), $[Rh(nbd)_2]BF_4$ (11.2 mg, 10 mol%) and dppe(*o*-iPr) (17.0 mg, 10 mol%) in acetone (1 mL) for 16 hrs at room temperature. The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to afford title branched *amino enone* **69b** as a pale yellow oil (78.2 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.40-7.38 (2H, m, Ar-*H*), 7.22 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.13 (1H, app s, $NHCH_2CCH_aH_b$), 5.69 (1H, app s, $NHCH_2CCH_aH_b$), 5.10 (1H, br s, N*H*), 4.14 (2H, d, *J* 6.0, NHCH_2), 2.45 (3H, s, SCH_3), 1.45 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 155.6, 145.4, 138.4, 137.9, 131.0, 129.3, 129.2, 127.5, 124.6, 79.4, 41.5, 28.4, 17.0; IR: ν_{max} (neat)/cm^{-1} 3361, 2978, 1695, 1655, 1585, 1513, 1434, 1392, 1367, 1310, 1281, 1251, 1169, 1029; LRMS (ESI$^+$): *m/z* 330 ([M+Na]$^+$, 100%), 308 ([M+H]$^+$, 60%); HRMS (ESI$^+$) found 330.1135 [M+Na]$^+$, $C_{16}H_{21}NO_3SNa^+$ requires 330.1134.

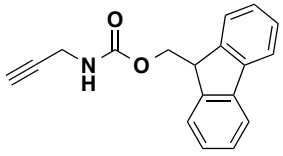
Benzyl prop-2-yn-1-ylcarbamate, 71



Benzyl chloroformate (2.90 mL, 20.4 mmol, 1.1 equiv.) was added dropwise to a solution of propargyl amine (1.20 mL, 18.2 mmol, 1.0 equiv.) and sodium bicarbonate (3.06 g, 36.4 mmol, 2.0 equiv.) in ethanol/water (36 mL, 1:1, v/v) at 0 °C and stirred at this temperature for 1 hr. The solution was then warmed to room temperature over 16 hrs. The reaction mixture was diluted with water (20 mL) and washed with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude brown liquid was purified by flash column chromatography (25-50% Et_2O in petrol) to give propargylic amine **71** as a pale yellow solid (3.02 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.35 (5H, m, Ar-*H*), 5.16 (2H, s, OC*H*$_2$), 5.02 (1H, br s, N*H*), 4.02 (2H, dd, *J* 5.5, 2.5, NHC*H*$_2$), 2.28 (1H, t, *J* 2.5, C*H*CCH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 136.2, 128.6, 128.3, 128.2, 79.7, 71.7, 67.1, 30.9; LRMS (ESI$^+$): *m/z* 212 ([M+Na]$^+$, 100%), 190 ([M+H]$^+$, 45%); mp: 38-40 °C (CH_2Cl_2/petrol) (lit. mp: 39-41 °C). This data is consistent with literature.[257]

(9*H*-Fluoren-9-yl)methyl prop-2-yn-1-ylcarbamate, 72

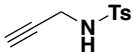


A solution of 9-fluoroenylmethyl chloroformate (2.90 g, 11.3 mmol, 1.05 equiv.) in CH_2Cl_2 (19 mL) was added dropwise to a solution of propargyl amine (0.70 mL, 10.8 mmol, 1.0 equiv) and Et_3N (1.30 mL, 13.0 mmol, 1.2 equiv.) in CH_2Cl_2 (25.2 mL) at −78 °C. The reaction mixture was warmed to room temperature over 16 hrs. Water (20 mL) was added to the reaction mixture and the product was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq.)}$ (20 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white powder. Hexane was added to the powder and the suspension sonicated for 15 mins. The suspension was

filtered to give propargylic amine **72** as a white crystalline solid (2.31 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 7.5, Ar-*H*), 7.62 (2H, d, *J* 7.5, Ar-*H*), 7.46-7.42 (2H, m, Ar-*H*), 7.37-7.33 (2H, m, Ar-*H*), 5.00 (1H, br s, N*H*), 4.46 (2H, d, *J* 7.0, OCH_2), 4.26 (1H, t, *J* 7.0, CO_2CH_2CH), 4.03 (2H, d, *J* 2.5, NHCH_2), 2.29 (1H, t, *J* 2.5, C*H*CCH_2); ^{13}C NMR (101 MHz, $CDCl_3$): 155.9, 143.8, 141.3, 127.8, 127.1, 125.0, 120.0, 79.6, 71.7, 67.1, 47.2, 30.9; LRMS (ESI^+): *m/z* 300 ($[M+Na]^+$, 100%), 278 ($[M+H]^+$, 10%); mp: 126-129 °C (CH_2Cl_2/petrol) (lit. mp: 130-132 °C). This data is consistent with literature.[258]

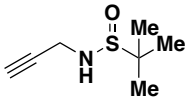
4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide, 73



A solution of *p*-toluenesulfonyl chloride (1.00 g, 5.25 mmol, 1.0 equiv.) in CH_2Cl_2 (6 mL) was added dropwise to a solution of propargyl amine (0.35 mL, 5.51 mmol, 1.05 equiv.) and Et_3N (1.8 mL, 13.1 mmol, 2.5 equiv.) in CH_2Cl_2 (7 mL). The reaction mixture was stirred for 16 hrs at room temperature. Water (15 mL) was added to the reaction mixture and the product was extracted with Et_2O (3 × 10 mL), washed with $HCl_{(aq.)}$ (15 mL, 1 M) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification *via* flash column chromatography (50% EtOAc in petrol) yielded propargylic amine **73** as a white solid (1.00 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 7.0, Ar-*H*), 7.34 (2H, d, *J* 7.0, Ar-*H*), 4.71 (1H, t, *J* 5.0, N*H*), 3.85 (2H, dd, *J* 5.0, 2.5, NHCH_2), 2.46 (3H, s, Ar-CH_3), 2.13 (1H, t, *J* 2.5, C*H*CCH_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.9, 136.5, 129.7, 127.4, 100.6, 73.0, 32.9, 21.6; LRMS (ESI^+): *m/z* 232 ($[M+Na]^+$, 100%), 210 ($[M+H]^+$, 20%); mp: 62-64 °C (CH_2Cl_2/petrol) (lit. mp: 63-64 °C). This data is consistent with literature.[259]

2-Methyl-*N*-(prop-2-yn-1-yl)propane-2-sulfinamide

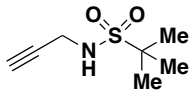


A solution of *tert*-butyl sulfinyl chloride (0.70 mL, 5.60 mmol, 2.0 equiv.) was added dropwise to a solution of propargyl amine (0.18 mL, 2.80 mmol, 1.0 equiv.) and Et_3N

(3.9 mL, 28 mmol, 10.0 equiv.) in CH_2Cl_2 (34 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr. Sat. $NaHCO_{3(aq.)}$ (10 mL) was added to the reaction mixture and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (20-50% EtOAc in petrol) to afford sulfinamide as a colourless oil (0.36 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99-3.87 (2H, m, NHC*H*$_2$), 3.43 (1H, t, *J* 4.0, N*H*), 2.35 (1H, t, *J* 2.5, C*H*CCH$_2$), 1.25 (9H, s, SOC(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 80.0, 72.8, 56.2, 34.7, 22.5; LRMS (ESI$^+$): *m/z* 160 ([M+H]$^+$, 100%), 182 ([M+Na]$^+$, 90%). This data is consistent with literature.[260]

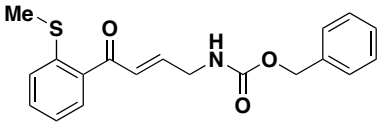
2-Methyl-*N*-(prop-2-yn-1-yl)propane-2-sulfonamide, 74



*m*CPBA (0.74 g, 70-76% in water, 3.30 mmol, 1.5 equiv.) was added to a solution of sulfinamide (2-methyl-*N*-(prop-2-yn-1-yl)propane-2-sulfinamide) (0.35 g, 2.20 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) at room temperature and stirred for 5 mins. Sat. $NaHSO_{3(aq.)}$ (5 mL) was added and the resulting mixture was stirred for a further 10 mins. The product was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with sat. $NaHCO_{3(aq.)}$ (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Propargylic amine **74** was obtained as a white solid and was used without further purification (0.31 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.40 (1H, br s, N*H*), 4.00 (2H, dd, *J* 5.0, 2.5, NHC*H*$_2$), 2.37 (1H, t, *J* 2.5, C*H*CCH$_2$), 1.45 (9H, s, $SO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 79.6, 72.8, 60.2, 33.8, 24.2; LRMS (ESI$^+$): *m/z* 198 ([M+Na]$^+$, 100%); mp: 63-65 °C (CH_2Cl_2/petrol) (lit. mp: 63-64 °C). This data is consistent with literature.[261]

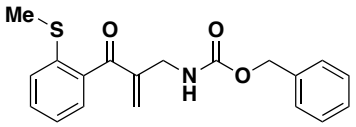
Benzyl (*E*)-{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 76a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (benzyl prop-2-yn-1-ylcarbamate **71**) (42.6 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (88 μL, 1.0 M). After stirring for 30 mins at room temperature the reaction gave a crude mixture of regioisomers (12:1, linear: branched). The compounds were separated by flash column chromatography (5-20% EtOAc in petrol) to yield linear *γ-amino enone* **76a** as a yellow oil (38.8 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (1H, d, *J* 7.5, Ar-*H*), 7.49-7.45 (1H, m, Ar-*H*), 7.38-7.35 (6H, m, Ar-*H*), 7.20 (1H, app t, *J* 7.5, Ar-*H*), 6.87-6.78 (2H, m, COC*H*C*H*), 5.16 (3H, br s, N*H* and CO_2CH_2), 4.09 (2H, dd, *J* 5.5, 3.5, NHCH_2), 2.45 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.3, 156.2, 144.9, 141.0, 136.3, 136.1, 131.7, 129.8, 128.6, 128.3, 128.2, 127.9, 126.0, 124.0, 67.1, 42.2, 16.3; IR: ν_{max} (neat)/cm^{-1} 2919, 2777, 1704, 1667, 1619, 1528, 1249; LRMS (ESI$^+$): *m/z* 342 ([M+H]$^+$, 100%), 364 ([M+Na]$^+$, 95%); HRMS (ESI$^+$) found 364.0979 [M+Na]$^+$, $C_{19}H_{19}NO_3SNa^+$ requires 364.0978.

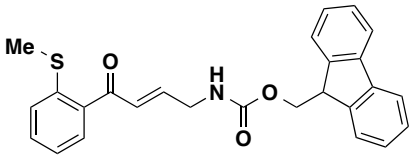
Benzyl {2-[2-(methylthio)benzoyl]allyl}carbamate, 76b



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (benzyl prop-2-yn-1-ylcarbamate **71**) (42.6 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and dcpm (3.1 mg, 5 mol%) in acetone (88 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (4:1, linear: branched). The compounds were separated by flash column chromatography (5-20% EtOAc in petrol) to yield branched *amino enone* **76b** as a cream oil (9.3 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.40-7.35 (7H, m, Ar-*H*), 7.22 (1H, app t, *J* 7.5, Ar-*H*), 6.16 (1H, app s, $NCH_2CCH_aH_b$), 5.71 (1H, app s, $NCH_2CCH_aH_b$), 5.37 (1H, t, *J* 5.5, N*H*), 5.15 (2H, s, CO_2CH_2), 4.22 (2H, d, *J* 6.5, $NHCH_2$), 2.43 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 156.4, 145.0, 138.2, 137.8, 136.5, 131.0, 129.9, 129.1, 128.5, 128.1, 128.0, 127.7, 124.6, 66.8, 41.9, 17.1; IR: ν_{max} (neat)/cm^{-1} 2970, 2931, 1702, 1467, 1378, 1160; LRMS (ESI$^+$): *m/z* 364 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 364.09781 [M+Na]$^+$, $C_{19}H_{19}NO_3SNa^+$ requires 364.09779.

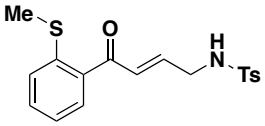
(9*H*-Fluoren-9-yl)methyl-(*E*)-{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 77a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine ((9*H*-fluoren-9-yl)methyl prop-2-yn-1-ylcarbamate, **72**) (63.9 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (67 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (16:1, linear: branched). The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield linear *γ-amino enone* **77a** as a dark yellow oil (44.2 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (2H, d, *J* 7.5, Ar-*H*), 7.62 (2H, d, *J* 7.5, Ar-*H*), 7.46 (1H, dd, *J* 8.0, 7.5, Ar-*H*), 7.49-7.29 (6H, m, Ar-*H*), 7.20 (1H, app t, *J* 7.5, Ar-*H*), 6.86-6.76 (2H, m, COC*HCH*), 5.21 (1H, br s, N*H*), 4.47 (2H, d, *J* 7.0, CO_2CH_2), 4.24 (1H, t, *J* 7.0, CO_2CH_2CH), 4.08 (2H, t, *J* 4.5, $NHCH_2$), 2.45 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.4, 156.3, 144.8, 143.8, 141.3, 136.2, 131.8, 129.8, 128.0, 127.7, 127.1, 126.0, 125.0, 124.0, 120.0, 66.9, 60.4, 47.2, 16.3; IR: ν_{max} (neat)/cm^{-1} 2931, 1660, 1573, 1433, 1351, 1220, 1006; LRMS (ESI$^+$): *m/z* 452 ([M+Na]$^+$, 100%), 430 ([M+H]$^+$, 75%); HRMS (ESI$^+$) found 452.1284 [M+Na]$^+$, $C_{26}H_{23}NO_3SNa^+$ requires 452.1291.

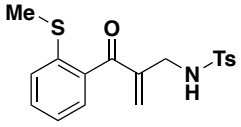
(*E*)-4-Methyl-*N*-{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1yl}benzenesulfonamide, 78a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **73**) (47.1 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (84 μL, 1.0 M). After stirring for 10 mins at room temperature the reaction gave a crude mixture of regioisomers (4:1, linear: branched). The compounds were separated by flash column chromatography (5-20% EtOAc in petrol) to yield linear *γ-amino enone* **78a** as a yellow solid (17.4 mg, 32%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (2H, d, *J* 8.0, Ar-*H*), 7.56 (1H, d, *J* 7.5, Ar-*H*), 7.48 (1H, app t, *J* 7.5, Ar-*H*), 7.35 (3H, dd, *J* 12.5, 8.0, Ar-*H*), 7.21 (1H, app t, *J* 7.5, Ar-*H*), 6.84 (1H, d, *J* 15.5, COC*H*), 6.74-6.69 (1H, m, COCHC*H*), 4.68 (1H, t, *J* 6.0, N*H*), 3.89 (2H, app t, *J* 5.0, NHCH_2), 2.46 (3H, s, SCH_3), 2.44 (3H, s, Ar-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.4, 143.9, 142.4, 141.4, 136.8, 135.6, 132.0, 129.9, 129.7, 128.7, 127.1, 125.9, 123.9, 44.3, 21.6, 16.3; IR: ν_{max} (neat)/cm^{-1} 2941, 2831, 1716, 1554, 1433, 1328, 1159; LRMS (ESI^+): *m/z* 362 ($[M+H]^+$, 100%), 384 ($[M+Na]^+$, 55%); HRMS (ESI^+) found 384.0700 $[M+Na]^+$, $C_{18}H_{19}NO_3S_2Na^+$ requires 384.0699; mp: 107-109 °C (EtOAc/petrol).

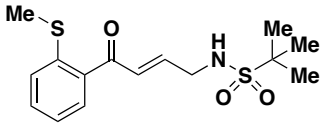
4-Methyl-*N*-{2-[2-(methylthio)benzoyl]allyl}benzenesulfonamide, 78b



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **73**) (47.1 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and dcpm (3.1 mg, 5 mol%) in acetone (84 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (1:1, linear: branched). The compounds were separated by flash column chromatography (5-20% EtOAc in petrol) to yield branched *amino enone* **78b** as a cream oil (21.9 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.78 (2H, m, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.37 (1H, d, *J* 7.5, Ar-*H*), 7.33 (2H, dd, *J* 8.5, 0.5, Ar-*H*), 7.19-7.15 (1H, m, Ar-*H*), 7.15-7.11 (1H, m, Ar-*H*), 6.15 (1H, app s, $NCH_2CCH_aH_b$), 5.68 (1H, app s, $NCH_2CCH_aH_b$), 5.18 (1H, t, *J* 6.5, N*H*), 4.00 (2H, d, *J* 6.5, $NHCH_2$), 2.46 (3H, s, SCH_3), 2.43 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 143.5, 139.4, 138.5, 137.2, 137.1, 131.21, 131.17, 129.8, 129.1, 127.5, 127.2, 124.4, 44.2, 21.6, 16.9; IR: ν_{max} (neat)/cm^{-1} 2923, 2852, 1652, 1598, 1434, 1329, 1184, 1093; LRMS (ESI$^+$): *m/z* 384 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 384.06992 [M+Na]$^+$, $C_{18}H_{19}NO_3S_2Na^+$ requires 384.06989.

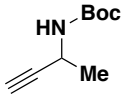
(*E*)-2-Methyl-*N*-{4-[2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}propane-2-sulfonamide, 79a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine **(**2-methyl-*N*-(prop-2-yn-1-yl)propane-2-sulfonamide, **74)** (40.3 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (91 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (7:1, linear: branched) and a NMR conversion of 84%. The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield linear *γ-amino enone* **79a** as a pale yellow oil (25.9 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.48 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.36 (1H, d, *J* 7.5, Ar-*H*), 7.24-7.20 (1H, m, Ar-*H*), 6.98 (1H, dt, *J* 15.5, 1.5, COC*H*), 6.88 (1H, dt, *J* 15.5, 5.0, COCHC*H*), 4.50 (1H, t, *J* 6.5, N*H*), 4.09 (2H, ddd, *J* 6.5, 5.0, 1.5, $NHCH_2$), 2.46 (3H, s, SCH_3), 1.46 (9H, s, $SO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.8, 144.2, 141.4, 135.7, 132.0, 130.0, 128.4, 125.9, 124.0, 60.2, 45.6, 24.3, 16.3; IR: ν_{max} (neat)/cm^{-1} 2977, 1693, 1621, 1434, 1392, 1366, 1249, 1148; LRMS (ESI$^+$): *m/z* 328 ([M+H]$^+$, 100%), 350 ([M+Na]$^+$, 25%); HRMS (ESI$^+$) found 350.0853 [M+Na]$^+$, $C_{15}H_{21}NO_3S_2Na^+$ requires 350.0855.

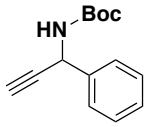
tert-Butyl but-3-yn-2-ylcarbamate, 82



A solution of *n*-butyllithium (1.94 mL, 1.8 M in hexanes, 3.50 mmol, 2.1 equiv.) was added dropwise to a stirring solution of TMS-acetylene (0.48 mL, 3.40 mmol, 2.0 equiv.) in THF (15 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 30 mins. The temperature was lowered to −78 °C and a solution of *α*-amido sulfone (*tert*-butyl (1-tosylethyl)carbamate **122**) (0.50 g, 1.70 mmol, 1.0 equiv.) in THF (5 mL) was added. The mixture was warmed to room temperature over 1 hr. Quick addition of sat. $NH_4Cl_{(aq.)}$ (5 mL) at −78 °C quenched the reaction and the mixture was allowed to warm to room temperature. The product was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. With no further purification, the crude propargyl amine (0.37 g, 1.52 mmol, 1.0 equiv.) was dissolved in MeOH (29 mL). Potassium carbonate (0.21 g, 1.52 mmol, 1.0 equiv.) was added to the solution at room temperature and stirred for 4 hrs. The reaction mixture was diluted with water (15 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (20% EtOAc in petrol) to give title *propargylic amine* **82** as a white solid (0.23 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (1H, br s, N*H*), 4.51 (1H, app br s, NHC*H*), 2.28 (1H, d, *J* 2.5, C*H*CCHNH), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.43 (3H, d, *J* 7.0, NHCH(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 84.6, 79.9, 70.1, 38.2, 28.4, 22.5; IR: ν_{max} (neat)/cm^{-1} 2864, 1691, 1562, 1312, 1293, 1252, 989, 899, 722; LRMS (ESI$^+$): *m/z* 192 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 192.09963 [M+Na]$^+$, $C_9H_{15}NO_2Na^+$ requires 192.09950; mp: 69-70 °C (EtOAc/petrol).

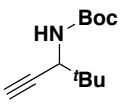
General procedure D for the synthesis of terminal propargylic alkynes as exemplified by the preparation of *tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate, 83:



Following a procedure adapted from Shin *et. al.*,[169] a solution of ethynylmagnesium bromide (20.2 mL, 0.5 M in THF, 9.50 mmol, 2.2 equiv.) was added dropwise to a solution of α-amido sulfone (*tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate **125**) (1.50 g, 4.32 mmol, 1.0 equiv.) in THF (35 mL) at −78 °C. The reaction mixture was warmed to room temperature over 3 hrs. Upon completion the reaction was quenched with sat. $NH_4Cl_{(aq.)}$ (15 mL) at −78 °C and was allowed to warm to room temperature. The product was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give the title *propargylic amine* **83** as a white solid (0.89 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (2H, d, *J* 7.5, Ar-*H*), 7.40-7.33 (3H, m, Ar-*H*), 5.71 (1H, d, *J* 7.0, NHC*H*), 5.24 (1H, br s, N*H*), 2.52 (1H, d, *J* 2.5, C*H*CCHNH), 1.49 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 138.8, 128.7, 128.1, 126.9, 82.2, 80.3, 73.0, 46.1, 28.4; IR: ν_{max} (neat)/cm^{-1} 3305, 2979, 1696, 1495, 1393, 1368, 1246, 1166, 1020, 911, 876, 698; LRMS (ESI$^+$): *m/z* 254 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 254.11523 [M+Na]$^+$, $C_{14}H_{17}NO_2Na^+$ requires 254.11515; mp: 93-95 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

***tert*-Butyl (4,4-dimethylpent-1-yn-3-yl)carbamate, 84**

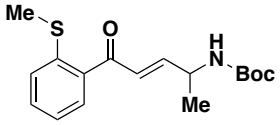


A solution of *n*-butyllithium (3.51 mL, 1.8 M in hexanes, 6.41 mmol, 2.1 equiv.) was added dropwise to a solution of TMS-acetylene (0.86 mL, 6.10 mmol, 2.0 equiv.) in THF (22 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 30 mins. The temperature was lowered to −78 °C and a solution of α-amido sulfone (*tert*-butyl [2,2-dimethyl-1-(phenylsulfonyl)propyl]carbamate **123**) (1.00 g, 3.05 mmol, 1.0 equiv.) in THF (10 mL) was

added to the mixture. The mixture was stirred at −78 °C for 1 hr. Sat. $NH_4Cl_{(aq.)}$ (10 mL) was added and the mixture was warmed to room temperature. The product was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. With no further purification, the crude propargylic amine (0.80 g, 2.80 mmol, 1.0 equiv.) was dissolved in MeOH (53 mL) and potassium carbonate (0.39 g, 2.80 mmol, 1.0 equiv.) was added and the reaction was stirred for 16 hrs at room temperature. Water (15 mL) was added to the reaction mixture and the product was extracted with Et_2O (3 × 10 mL) and washed with brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (5-10% EtOAc in petrol) to give the title *propargylic amine* **84** as a pale yellow solid (0.36 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (1H, d, *J* 8.0, N*H*), 4.27 (1H, d, *J* 8.0, NHC*H*), 2.28 (1H, d, *J* 2.5, C*H*CCHNH), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.01 (9H, s, NHCHC(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.3, 82.5, 79.8, 71.7, 52.2, 35.4, 28.4, 25.8; IR: ν_{max} (neat)/cm^{-1} 3296, 2968, 1692, 1515, 1367, 1249, 1171, 1049, 998, 906, 731, 649; LRMS (ESI$^+$): *m/z* 234 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 234.14666 [M+Na]$^+$, $C_{12}H_{21}NO_2Na^+$ requires 234.14645; mp: 64-65 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

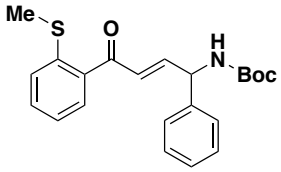
tert-Butyl (*E*)-{5-[2-(methylthio)phenyl]-5-oxopent-3-en-2-yl}carbamate, 85a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl but-3-yn-2-ylcarbamate **82**) (38.0 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (93 μL, 1.0 M). After stirring for 1 hr at room temperature the reaction gave a crude mixture of regioisomers (25:1, linear: branched). The compounds were separated by flash column chromatography (5-10% EtOAc in petrol) to yield linear *γ-amino enone* **85a** as a yellow oil (42.8 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.46 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.36 (1H, d, *J* 7.5, Ar-*H*), 7.20 (1H, app t, *J* 7.5, Ar-*H*), 6.81-6.73 (2H, m, COC*H*C*H*), 4.65 (1H, br s, N*H*), 4.49-4.47 (1H, m, NHC*H*), 2.45 (3H, s, SCH_3), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.32 (3H, d, *J* 7.0, NHCH(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.7, 155.0, 149.9, 141.0, 136.3, 131.7, 129.8, 126.6, 126.0, 123.9, 47.5, 28.4, 27.3, 20.4, 16.4; IR: ν_{max} (neat)/cm^{-1} 3343, 2977, 1694, 1619, 1586, 1511, 1434, 1366, 1247, 1209, 1165, 1049, 1009; LRMS (ESI$^+$): *m/z* 322 ([M+H]$^+$, 10%), 344 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 344.1292 [M+Na]$^+$, $C_{17}H_{23}NO_3SNa^+$ requires 344.1291.

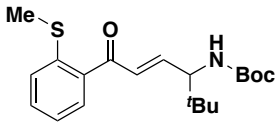
tert-Butyl(*E*)-{4-[2-(methylthio)phenyl]-4-oxo-1-phenylbut-2-en-1-yl}carbamate, 86a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (0.39 mL, 3.0 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **83**) (0.90 g, 3.9 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (11.2 mg, 1 mol%) and PNP(Cy) (14.2 mg, 1 mol%) in acetone (1.7 mL, 1.0 M). After stirring for 15 mins at room temperature the reaction gave the linear γ-amino enone, as the only regioisomer detectable by ^{1}H NMR. The crude reaction mixture was purified by flash column chromatography (10-40% Et_2O in petrol) to yield *γ-amino enone* **86a** as a yellow solid (1.01 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.49-7.45 (2H, m, Ar-*H*), 7.41-7.29 (5H, m, Ar-*H*), 7.21 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.00 (1H, dd, *J* 15.5, 5.0, COCHC*H*), 6.87 (1H, dd, *J* 15.5, 1.5, COC*H*), 5.55 (1H, br s, N*H*), 5.02 (1H, d, *J* 5.0, NHC*H*), 2.46 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.4, 154.8, 147.4, 141.1, 139.3, 136.2, 131.7, 129.9, 129.0, 128.2, 127.3, 126.1, 124.0, 80.2, 55.9, 30.3, 28.4, 16.4; IR: ν_{max} (neat)/cm^{-1} 3343, 2939, 1692, 1619, 1495, 1434, 1366, 1249, 1167, 1025; LRMS (ESI$^+$): *m/z* 384 ([M+H]$^+$, 100%), 406 ([M+Na]$^+$, 25%); HRMS (ESI$^+$) found 406.1444 [M+Na]$^+$, $C_{22}H_{25}NO_3SNa^+$ requires 406.1447; mp: 144-145 °C (CH_2Cl_2/hexane).

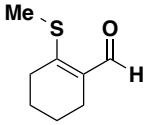
tert-Butyl(*E*)-{2,2-dimethyl-6-[2-(methylthio)phenyl]-6-oxohex-4-en-3- yl}carbamate, 87a



Prepared according to general procedure **B** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (4,4-dimethylpent-1-yn-3-yl)carbamate **84**) (47.5 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (79 μL, 1.0 M). After stirring for 3 hrs at room temperature the reaction gave the linear γ-amino enone, as the only regioisomer detectable by ^{1}H NMR. The crude reaction mixture was purified by flash column chromatography (25% EtOAc in petrol) to yield *γ-amino enone* **87a** as a yellow solid (49.6 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.48 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.38 (1H, d, *J* 7.5, Ar-*H*), 7.23 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.91 (1H, dd, *J* 15.5, 6.0, COCHC*H*), 6.83 (1H, d, *J* 15.5, COC*H*), 4.68 (1H, d, *J* 9.0, N*H*), 4.20 (1H, dd, *J* 9.0, 6.0, NHC*H*), 2.47 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$), 0.99 (9H, s, $NHCHC(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.3, 155.4, 146.5, 141.1, 131.7, 129.8, 128.6, 126.0, 123.9, 79.7, 60.5, 35.0, 28.4, 26.5, 25.4, 16.4; IR: ν_{max} (neat)/cm^{-1} 2968, 1698, 1618, 1501, 1366, 1247, 1169, 1050, 1011; LRMS (ESI$^+$): *m/z* 386 ($[M+Na]^+$, 100%), 364 ($[M+H]^+$, 45%); HRMS (ESI$^+$) found 386.1755 $[M+Na]^+$, $C_{20}H_{29}NO_3SNa^+$ requires 386.1760; mp: 130-131 °C (EtOAc/petrol).

2-(Methylthio)cyclohex-1-enecarbaldehyde, 89

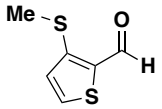


Phosphorous tribromide (17.3 mL, 183 mmol, 3.0 equiv.) was added dropwise to a stirred solution of DMF (15.6 mL, 202 mmol, 3.3 equiv.) in $CHCl_3$ (96 mL) at 0 °C. The reaction mixture was stirred for 1 hr at 0 °C, after which cyclohexanone (6.34 mL, 61.1 mmol, 1.0 equiv.) was added. The solution was warmed to room temperature over 16 hrs. Upon completion, the reaction mixture was poured over ice and neutralised by the slow addition of

solid $NaHCO_3$. Once neutral, the aqueous mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (20 mL) and sat. $LiCl_{(aq.)}$ (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a dark orange oil. Without further purification, the crude aldehyde (23.2 g, 123 mmol, 1.0 equiv.) was dissolved in DMF (50 mL) and stirred at 0 °C, followed by the slow addition of methanethiol sodium salt solution (57.6 mL, 3.0 M in water, 173 mmol, 1.4 equiv.). The solution was warmed to room temperature over 16 hrs. Water (50 mL) was added to dilute the reaction mixture and the product was extracted with Et_2O (3 × 30 mL). The organic extracts were washed with brine (20 mL) and sat. $LiCl_{(aq.)}$ (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid was purified by flash column chromatography (5-25% EtOAc in petrol) followed by recrystalisation (EtOAc/hexane) to obtain the title aldehyde **89** as a white solid (1.65 g, 17%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.30 (1H, s, C*H*O), 2.55 (2H, tt, *J* 6.0, 2.0, CHOCC*H*$_2$), 2.37 (3H, s, SC*H*$_3$), 2.30 (2H, tt, *J* 6.0, 2.0, SCC*H*$_2$), 1.79-1.73 (2H, m, CHOCCH$_2$C*H*$_2$), 1.69-1.63 (2H, m, SCCH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.6, 156.9, 135.0, 30.8, 24.0, 23.0, 21.3, 14.1; LRMS (ESI$^+$): *m/z* 157 ([M+H]$^+$, 100%), 179 ([M+Na]$^+$, 80%); mp: 44-47 °C (EtOAc/hexane), (lit. mp: 45-47 °C). This data is consistent with literature.[105]

3-(Methylthio)thiophene-2-carbaldehyde, 90

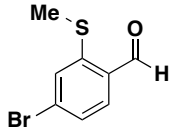


Prepared according to general procedure **A** using methanethiol sodium salt solution (5.80 mL, 3.0 M in water, 17.3 mmol, 1.1 equiv.) and 3-bromothiophene-2-carboxaldehyde (1.70 mL, 15.7 mmol, 1.0 equiv.) in DMF (19 mL). The crude was purified by flash column chromatography (10% Et_2O in petrol) to obtain a brown solid, followed by recrystallisation (CH_2Cl_2/hexane) to afford the title *aldehyde* **90** as white needles (0.91 g, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (1H, s, C*H*O), 7.74 (1H, app dd, *J* 5.0, 1.0, SC*H*), 7.12 (1H, d, *J* 5.0, SCHC*H*), 2.61 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 181.5, 146.0, 135.2, 134.6, 128.1, 17.1; IR: ν_{max} (neat)/cm^{-1} 3101, 2839, 1648, 1478, 1365, 1223, 1777,

907, 665; LRMS (ESI^+): *m/z* 181 ($[M+Na]^+$, 100%), 159 ($[M+H]^+$, 50%); HRMS (ESI^+) found 180.97536 $[M+Na]^+$, $C_6H_6OS_2Na^+$ requires 180.97523; mp: 34-35 °C (CH_2Cl_2/hexane).

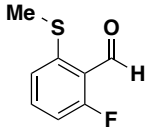
4-Bromo-2-(methylthio)benzaldehyde, 91



Prepared according to general procedure **A** using methanethiol sodium salt solution (5.40 mL, 3.0 M in water, 16.3 mmol, 1.1 equiv.) and 2-fluoro-4-bromobenzaldehyde (3.00 g, 14.8 mmol, 1.0 equiv.) in DMF (18 mL). The crude was purified by flash column chromatography (10-60% Et_2O in petrol) to obtain aldehyde **91** as white needles (0.56 g, 16%).

^1H NMR (400 MHz, $CDCl_3$): δ 10.20 (1H, s, C*H*O), 7.67 (1H, d, *J* 8.0, Ar-*H*), 7.45-7.42 (2H, m, Ar-*H*), 2.52 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 190.2, 145.5, 134.4, 131.4, 129.7, 127.9, 127.5, 15.4; LRMS (ESI^+): *m/z* 255 ($[^{81}Br][M+Na]^+$, 100%), 253 ($[^{79}Br][M+Na]^+$, 95%), 235 ($[^{81}Br][M+H]^+$, 20%), 233 ($[^{79}Br][M+H]^+$, 15%); mp: 80-82 °C (CH_2Cl_2/hexane), (lit. mp: 78 °C). This data is consistent with literature.[262]

2-Fluoro-6-(methylthio)benzaldehyde, 92

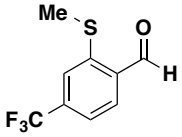


Prepared according to general procedure **A** using methanethiol sodium salt solution (1.52 mL, 3.0 M in water, 15.5 mmol, 1.1 equiv.) and 2,6-difluorobenzaldehyde (1.52 mL, 14.1 mmol, 1.0 equiv.) in DMF (20 mL). The crude oil was purified by flash column chromatography (20-50% CH_2Cl_2 in toluene) to obtain *aldehyde* **92** as a pale yellow solid (0.95 g, 40%).

^1H NMR (400 MHz, $CDCl_3$): δ 10.51 (1H, s, C*H*O), 7.51 (1H, dd, *J* 8.0, 5.0, Ar-*H*), 7.08 (1H, d, *J* 8.0, Ar-*H*), 6.91 (1H, app t, *J* 8.0, Ar-*H*), 2.48 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz,

$CDCl_3$): δ 187.2, 166.7 (d, $^1J_{CF}$ 260.0), 146.1, 134.9 (d, $^2J_{CF}$ 22.0), 120.6 (d, $^3J_{CF}$ 4.0), 119.8 (d, $^3J_{CF}$ 3.5), 110.8 (d, $^2J_{CF}$ 21.5), 15.4; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ -120.3; IR: ν_{max} (neat)/cm^{-1} 2885, 1684, 1560, 1557, 1454, 1323, 1237, 1204, 908, 832, 777, 662; LRMS (ESI$^+$): *m/z* 193 ([M+Na]$^+$, 100%), 171 ([M+H]$^+$, 10%); HRMS (ESI$^+$) found 193.00933 [M+Na]$^+$, $C_8H_7OFSNa^+$ requires 193.00939; mp: 51-53 °C (EtOAc/hexane).

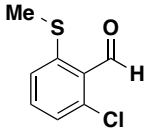
2-(Methylthio)-4-(trifluoromethyl)benzaldehyde, 93



Prepared according to general procedure **A** using methanethiol sodium salt solution (2.30 mL, 3.0 M in water, 12.5 mmol, 1.2 equiv.) and 2-fluoro-4-trifluoromethylbenzaldehyde (1.42 mL, 10.4 mmol, 1.0 equiv.) in DMF (15 mL). The crude was purified by flash column chromatography (5-10% EtOAc in petrol) to obtain aldehyde **93** as a pale yellow solid (1.19 g, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (1H, s, C*H*O), 7.95 (1H, d, *J* 8.0, Ar-*H*), 7.56 (1H, s, Ar-*H*), 7.54 (1H, d, *J* 8.0, Ar-*H*), 2.58 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.2, 144.7, 135.0 (q, $^2J_{CF}$ 32.5), 134.7, 133.4, 123.4 (q, $^1J_{CF}$ 270.5), 121.9 (q, $^3J_{CF}$ 3.5), 120.9 (q, $^3J_{CF}$ 3.5), 15.3; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ -63.4; LRMS (ESI$^+$): *m/z* 243 ([M+Na]$^+$, 100%); mp: 91-93 °C (EtOAc/hexane), (lit. mp: 90-91 °C). This data is consistent with literature.[61]

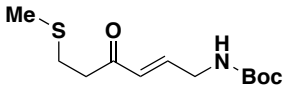
2-Chloro-6-(methylthio)benzaldehyde, 94



Prepared according to general procedure **A** using methanethiol sodium salt solution (2.10 mL, 3.0 M in water, 7.57 mmol, 1.2 equiv.) and 2-fluoro-6-chlorobenzaldehyde (1.00 g, 6.31 mmol, 1.0 equiv.) in DMF (9 mL). The crude was purified by flash column chromatography (10% EtOAc in petrol) to obtain aldehyde **94** as a pale yellow solid (0.55 g, 47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (1H, s, C*H*O), 7.45 (1H, app t, *J* 8.0, Ar-*H*), 7.23 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.24 (1H, d, *J* 8.0, Ar-*H*), 2.48 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.5, 146.8, 140.3, 133.6, 128.1, 125.6, 123.0, 15.5; LRMS (ESI$^+$): *m/z* 209 ([M+Na]$^+$, 100%); mp: 88-90 °C (EtOAc/hexane), (lit. mp: 85-87 °C). This data is consistent with literature.[250]

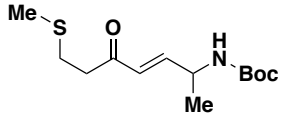
tert-Butyl (*E*)-[6-(methylthio)-4-oxohex-2-en-1-yl]carbamate, 96a



Prepared according to general procedure **B** using 3-(methylthio)propionaldehyde **88** (15 μL, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), [Rh(nbd)$_2$]BF$_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (99 μL, 1.0 M). After stirring for 3 hrs at room temperature the reaction gave a crude mixture of regioisomers (25:1, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **96a** as a yellow oil (24.8 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (1H, dt, *J* 16.0, 5.5, COCHC*H*), 6.22 (1H, d, *J* 16.0, COC*H*), 4.84 (1H, br s, N*H*), 3.96 (2H, app br s, NHC*H*$_2$), 2.90-2.76 (4H, m, SC*H*$_2$C*H*$_2$), 2.13 (3H, s, SC*H*$_3$), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1, 155.6, 143.4, 129.2, 80.1, 41.5, 40.1, 28.4, 28.2, 15.9; IR: ν_{max} (neat)/cm^{-1} 3352, 2978, 1693, 1634, 1513, 1392, 1366, 1248, 1164; LRMS (ESI$^+$): *m/z* 282 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 282.1132 [M+Na]$^+$, $C_{12}H_{21}NO_3SNa^+$ requires 282.1134.

tert-Butyl (*E*)-[7-(methylthio)-5-oxohept-3-en-2-yl]carbamate, 97a

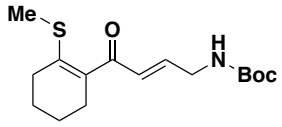


Prepared according to general procedure **B** using 3-(methylthio)propionaldehyde **88** (30 μL, 0.30 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl but-3-yn-2-ylcarbamate **82**) (66 mg, 0.39 mmol, 1.3 equiv.), [Rh(nbd)$_2$]BF$_4$ (5.6 mg, 5 mol%) and PNP(Cy) (6.4 mg, 5 mol%) in acetone (0.2 mL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave the linear *γ*-amino enone, as the only regioisomer detectable by ^{1}H NMR. The crude was purified

by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **97a** as a yellow oil (58 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (1H, dd, *J* 16.0, 5.0, COCHC*H*), 6.20 (1H, dd, *J* 16.0, 1.5, COC*H*), 4.56 (1H, br s, N*H*), 4.44 (1H, app br s, NHC*H*), 2.92-2.87 (2H, m, SCH_2CH_2), 2.82-2.77 (2H, m, SCH_2), 2.15 (3H, s, SCH_3), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.31 (3H, d, *J* 7.0, $NHCHCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.3, 154.9, 147.8, 127.9, 100.0, 47.1, 40.3, 28.4, 28.1, 20.3, 15.9; IR: ν_{max} (neat)/cm^{-1} 3341, 2976, 2919, 1691, 1632, 1514, 1391, 1365, 1246, 1165; LRMS (ESI$^+$): *m/z* 296 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 296.12904 [M+Na]$^+$, $C_{13}H_{23}NO_3SNa^+$ requires 296.12909.

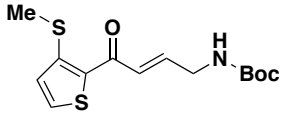
***tert*-Butyl (*E*)-{4-[2-(methylthio)cyclohex-1-en-1-yl]-4-oxobut-2-en-1-yl}carbamate, 98a**



Prepared according to general procedure **B** using 2-(methylthio)cyclohex-1-ene-1-carbaldehyde **89** (23.4 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (91 μL, 1.0 M). After stirring for 15 mins at 0 ºC the reaction gave a crude mixture of regioisomers (12:1, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **98a** as a pale yellow solid (33.2 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (1H, dt, *J* 15.5, 5.0, COCHC*H*), 6.54 (1H, d, *J* 15.5, COC*H*), 4.72 (1H, br s, N*H*), 3.97 (2H, app br s, $NHCH_2$), 2.48 (2H, t, *J* 6.0, $SCCH_2$), 2.41 (2H, t, *J* 6.0, $COCCH_2$), 2.26 (3H, s, SCH_3), 1.76-1.69 (4H, m, $SCCH_2(CH_2)_2$), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.8, 155.6, 145.1, 142.8, 132.4, 127.8, 79.8, 41.8, 29.9, 28.4, 28.3, 23.0, 21.9, 15.0; IR: ν_{max} (neat)/cm^{-1} 2930, 1703, 1609, 1510, 1366, 1250, 1169; LRMS (ESI$^+$): *m/z* 312 ([M+H]$^+$, 100%), 334 ([M+Na]$^+$, 90%); HRMS (ESI$^+$) found 334.1456 [M+Na]$^+$, $C_{16}H_{25}NO_3SNa^+$ requires 334.1447; mp: 99-102 °C (CH_2Cl_2/hexane).

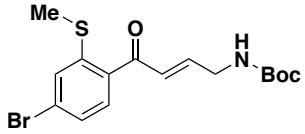
tert-Butyl (_E_)-{4-[3-(methylthio)thiophen-2-yl]-4-oxobut-2-en-1-yl}carbamate, 99a



Prepared according to general procedure **B** using 3-(methylthio)thiophene-2-carbaldehyde **90** (23.7 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (90 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (6:1, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **99a** as a yellow oil (36.2 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (1H, d, *J* 5.0, SC*H*), 7.08 (1H, d, *J* 5.0, SCHC*H*), 7.03 (1H, dt, *J* 15.0, 5.0, COCHC*H*), 6.79 (1H, dt, *J* 15.0, 2.0, COC*H*), 4.84 (1H, br s, N*H*), 4.02 (2H, app br s, NHCH_2), 2.56 (3H, s, SCH_3), 1.49 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.9, 155.6, 143.7, 131.3, 128.6, 126.4, 125.0, 110.5, 83.5, 28.4, 23.9, 16.7; IR: ν_{max} (neat)/cm^{-1} 2978, 2928, 1687, 1655, 1585, 1495, 1402, 1242, 1163, 908; LRMS (ESI$^+$): *m/z* 336 ([M+Na]$^+$, 100%), 314 ([M+H]$^+$, 50%); HRMS (ESI$^+$) found 314.08762 [M+H]$^+$, $C_{14}H_{20}O_3NS_2^+$ requires 314.08791.

tert-Butyl (_E_)-{4-[4-bromo-2-(methylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 100a

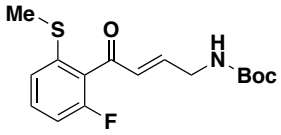


Prepared according to general procedure **B** using 4-bromo-2-(methylthio)benzaldehyde **91** (34.6 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (79 μL, 1.0 M). After stirring for 1 hr at room temperature the reaction gave a crude mixture of regioisomers (18:1, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **100a** as a yellow solid (46.2 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, *J* 8.0, Ar-*H*), 7.44 (1H, d, *J* 1.5, Ar-*H*), 7.33 (1H,

dd, *J* 8.0, 1.5, Ar-*H*), 6.85 (1H, dt, *J* 15.5, 4.0, COCHC*H*), 6.76 (1H, d, *J* 15.5, COC*H*), 4.84 (1H, br s, N*H*), 4.02 (2H, app br s, NHCH_2), 2.46 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.3, 155.6, 146.0, 143.8, 134.4, 131.1, 128.2, 127.3, 126.9, 80.0, 41.8, 28.4, 27.4, 16.3; IR: ν_{max} (neat)/cm^{-1} 2832, 1707, 1573, 1539, 1367, 1281, 1166; LRMS (ESI$^+$): *m/z* 408 ([^{79}Br] [M+Na]$^+$, 100%), 410 ([^{81}Br] [M+Na]$^+$, 95%); HRMS (ESI$^+$) found 408.0235 [[^{79}Br] M+Na]$^+$, 410.0218 [[^{81}Br] M+Na]$^+$, $C_{16}H_{20}O_3N^{79}BrSNa^+$ requires 408.0239, $C_{16}H_{20}O_3N^{81}BrSNa^+$ requires 410.0219; mp: 90-92 °C (CH_2Cl_2/hexane).

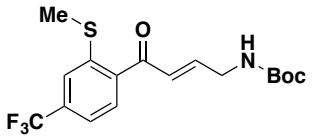
***tert*-Butyl (*E*)-{4-[2-fluoro-6-(methylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 101a**



Prepared according to general procedure **B** using 2-fluoro-6-(methylthio)benzaldehyde **92** (25.5 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (89 μL, 1.0 M). After stirring for 5 mins at room temperature the reaction gave a crude mixture of regioisomers (11:1, linear: branched). The compounds were separated by flash column chromatography (5-15% EtOAc in petrol) to yield linear *γ-amino enone* **101a** as a yellow oil (34.4 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, app td, *J* 8.0, 6.0, Ar-*H*), 7.13 (1H, d, *J* 8.0, Ar-*H*), 6.93 (1H, ddd, *J* 9.0, 8.0, 1.0, Ar-*H*), 6.68 (1H, dt, *J* 15.5, 4.5, COCHC*H*), 6.54 (1H, app dq, *J* 15.5, 1.5, COC*H*), 4.78 (1H, br s, N*H*), 4.01 (2H, app br s, NHCH_2), 2.46 (3H, s, SCH_3), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.5, 160.8, 156.9 (d, $^1J_{CF}$ 286.5), 147.1, 139.8, 131.2 (d, $^2J_{CF}$ 60.0), 130.8 (d, $^2J_{CF}$ 90.0), 126.8 (d, $^3J_{CF}$ 18.5), 122.6 (d, $^3J_{CF}$ 22.0), 107.7, 80.0, 29.7, 28.3, 16.9; IR: ν_{max} (neat)/cm^{-1} 3350, 2925, 1694, 1660, 1621, 1565, 1448, 1250, 1165, 889; LRMS (ESI$^+$): *m/z* 348 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 348.1046 [M+Na]$^+$, $C_{16}H_{20}FNO_3SNa^+$ requires 348.1040.

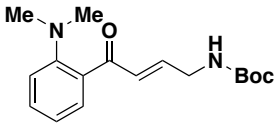
***tert*-Butyl (*E*)-{4-[2-(methylthio)-4-(trifluoromethyl)phenyl]-4-oxobut-2-en-1-yl}carbamate, 102a**



Prepared according to general procedure **B** using 4-trifluoromethyl-2-(methylthio)benzaldehyde **93** (33 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (34.9 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (82 μL, 1.0 M). After stirring for 3 hrs at room temperature the reaction gave a crude mixture of regioisomers (11:1, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield linear *γ-amino enone* **102a** as a pale yellow solid (47.2 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* 8.0, Ar-*H*), 7.56 (1H, br s, Ar-*H*), 7.45 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 6.81 (1H, dt, *J* 15.5, 4.5, COCHC*H*), 6.73 (1H, d, *J* 15.5, COC*H*), 4.86 (1H, br s, N*H*), 4.03 (2H, app br s, NHCH_2), 2.50 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.2, 155.6, 147.2, 141.6, 139.4, 133.1 (q, $^2J_{CF}$ 33.5), 129.5, 127.8, 123.3 (q, $^1J_{CF}$ 279.5), 122.7 (q, $^3J_{CF}$ 3.5), 120.8 (q, $^3J_{CF}$ 3.5), 80.1, 41.8, 28.3, 16.3; IR: ν_{max} (neat)/cm^{-1} 2899, 1706, 1663, 1501, 1241, 1011, 909; LRMS (ESI$^+$): *m/z* 398 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 398.1013 [M+Na]$^+$, $C_{17}H_{20}O_3F_3NSNa^+$ requires 398.1008; mp: 102-103 °C (EtOAc/petrol).

***tert*-Butyl (*E*)-{4-[2-(dimethylamino)phenyl]-4-oxobut-2-en-1-yl}carbamate, 104a**

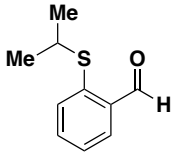


Prepared according to general procedure **B** using 2-(dimethylamino)benzaldehyde **95** (22.4 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (92 μL, 1.0 M). After stirring for 6 hrs at room temperature the reaction gave the linear *γ*-amino enone, as the only regioisomer detectable by ^{1}H NMR. The crude reaction mixture

was purified by flash column chromatography (25% EtOAc in petrol) to yield *γ-amino enone* **104a** as a yellow solid (45.3 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, dd, *J* 7.5, 2.0, Ar-*H*), 7.38 (1H, ddd, *J* 8.0, 7.5, 2.0, Ar-*H*), 6.99 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 6.94 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 6.88 (1H, d, *J* 12.0, COC*H*), 6.82 (1H, dt, *J* 12.0, 2.0, COCHC*H*), 4.81 (1H, br s, N*H*), 3.98 (2H, app br s, NHCH_2), 2.80 (6H, s, N(CH_3)$_2$), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.7, 152.1, 142.7, 132.0, 130.5, 129.0, 119.8, 116.7, 79.7, 44.2, 41.6, 28.4, 21.1, 14.2; IR: ν_{max} (neat)/cm^{-1} 3352, 2978, 1698, 1668, 1619, 1595, 1497, 1433, 1366, 1280, 1250, 1165; LRMS (ESI$^+$): *m/z* 305 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 327.1681 [M+Na]$^+$, $C_{17}H_{24}N_2O_3Na^+$ requires 327.1679; mp: 89-91 °C (CH_2Cl_2/hexane).

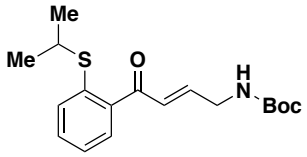
2-(Isopropylthio)benzaldehyde, 105



Prepared according to general procedure **A** using sodium 2-propanethiolate (1.30 g, 13.3 mmol, 1.1 equiv.) and 2-fluorobenzaldehyde (1.27 mL, 12.1 mmol, 1.0 equiv.) in DMF (35 mL). The crude oil was purified by flash column chromatography (20% Et_2O in petrol) to obtain aldehyde **105** as a yellow oil (1.46 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (1H, s, C*H*O), 7.92-7.90 (1H, m, Ar-*H*), 7.56-7.54 (2H, m, Ar-*H*), 7.41-7.36 (1H, m, Ar-*H*), 3.44 (1H, septet, *J* 6.5, SC*H*$(CH_3)_2$), 1.36 (6H, d, *J* 6.5, SCH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 192.1, 140.4, 135.8, 133.9, 132.4, 130.3, 126.7, 38.8, 23.0; LRMS (ESI$^+$): *m/z* 203 ([M+Na]$^+$, 100%), 181 ([M+H]$^+$, 25%). This data is consistent with literature.[263]

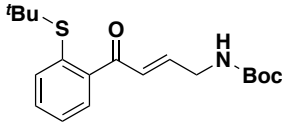
tert-Butyl (*E*)-{4-[2-(isopropylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 108a



Prepared according to general procedure **B** using 2-(isopropylthio)benzaldehyde **105** (27.0 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (35.7 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (90 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave the linear γ-amino enone, as the only regioisomer detectable by ^{1}H NMR. The crude reaction mixture was purified by flash column chromatography (25% EtOAc in petrol) to yield the title *γ-amino enone* **108a** as a dark yellow oil (40.5 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, dd, *J* 7.5, 0.5, Ar-*H*), 7.46-7.40 (2H, m, Ar-*H*), 7.28-7.26 (1H, m, Ar-*H*), 6.70-6.65 (2H, m, COC*H*C*H*), 4.77 (1H, br s, N*H*), 4.01 (2H, d, *J*5.0, NHCH_2), 2.20 (1H, app br d, *J* 0.5, SC*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.29 (6H, d, *J* 7.0, $SCH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.6, 155.5, 145.9, 141.1, 135.5, 131.6, 130.6, 129.5, 128.7, 125.9, 79.9, 41.7, 38.1, 28.4, 22.9; IR: ν_{max} (neat)/cm^{-1} 2973, 2927, 1697, 1660, 1621, 1510, 1433, 1365, 1281, 1165; LRMS (ESI$^+$): *m/z* 336 ($[M+H]^+$, 100%), 358 ($[M+Na]^+$, 90%); HRMS (ESI$^+$) found 336.16268 $[M+H]^+$, $C_{18}H_{26}O_3NS^+$ requires 336.16279.

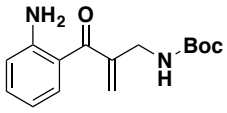
tert-Butyl (*E*)-{4-[2-(*tert*-butylthio)phenyl]-4-oxobut-2-en-1-yl}carbamate, 109a



Prepared according to general procedure **B** using 2-(*tert*-butylthio)benzaldehyde **106** (29.0mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (30.0 mg, 0.195 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (91μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave the linear γ-amino enone, as the only regioisomer detectable by ^{1}H NMR and a NMR conversion of 94%. The crude reaction mixture was purified by flash column chromatography (10-25% EtOAc in petrol) to yield the title *γ-amino enone* **109a** as a dark yellow oil (36.9 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.57 (1H, m, Ar-*H*), 7.45-7.40 (2H, m, Ar-*H*), 7.35 (1H, app dt, *J* 6.5, 3.0, Ar-*H*), 6.57 (1H, d, *J* 16.0, COC*H*), 6.47 (1H, dt, *J* 16.0, 4.5, COCHC*H*), 4.78 (1H, br s, N*H*), 3.96 (2H, app br s, NHCH_2), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.23 (9H, s, $SC(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.4, 155.5, 146.8, 145.1, 138.7, 131.3, 130.0, 129.7, 128.8, 127.9, 79.8, 47.9, 41.6, 31.2, 28.3; IR: ν_{max} (neat)/cm^{-1} 2978, 2862, 1717, 1697, 1622, 1584, 1503, 1391, 1283, 1248, 1167; LRMS (ESI$^+$): *m/z* 372 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 372.16005 [M+Na]$^+$, $C_{19}H_{27}O_3NSNa^+$ requires 372.16039.

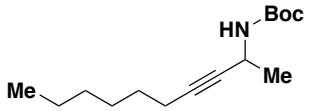
***tert*-Butyl [2-(2-aminobenzoyl)allyl]carbamate, 110b**



Prepared according to general procedure **B** using 2-aminobenzaldehyde **107** (18 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargylamine **59** (30.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (100 μL, 1.0 M). After stirring for 16 hrs at room temperature the reaction gave a crude mixture of regioisomers (1:3, linear: branched). The compounds were separated by flash column chromatography (5% EtOAc in petrol) to yield branched *γ-amino enone* **110b** as a yellow oil (23.5 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.32-7.29 (1H, m, Ar-*H*), 7.08 (1H, d, *J* 8.0, Ar-*H*), 6.88 (1H, app dt, *J* 8.5, 5.5, Ar-*H*), 6.70 (1H, app br s, $NHCH_2CCH_aH_b$), 6.68 (1H, app br s, $NHCH_2CCH_aH_b$), 6.30 (2H, br s, NH_2), 4.77 (1H, br s, N*H*CH_2), 4.04 (2H, br s, NHCH_2), 1.50 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.6, 161.1, 150.5, 134.4, 131.1, 126.4, 117.4, 115.8, 102.2, 101.8, 80.5, 40.1, 28.3; IR: ν_{max} (neat)/cm^{-1} 2979, 1703, 1646, 1616, 1550, 1451, 1260, 1207, 1045; LRMS (ESI$^+$): *m/z* 299 ([M+Na]$^+$, 100%), 277 ([M+H]$^+$, 40%); HRMS (ESI$^+$) found 299.13613 [M+Na]$^+$, $C_{15}H_{20}O_3N_2Na^+$ requires 299.13661.

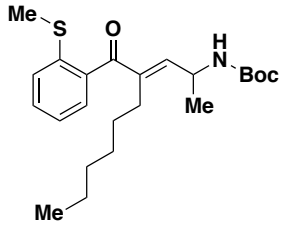
General procedure E for the synthesis of internal propargylic amines as exemplified by the synthesis of *tert*-butyl dec-3-yn-2-ylcarbamate, 111:



A procedure adapted from Shin *et. al*.,[169] a solution of *n*-butyllithium (1.37 mL, 2.5 M in hexanes, 3.43 mmol, 2.05 equiv.) was added dropwise to a solution of 1-octyne (0.49 mL, 3.34 mmol, 2.0 equiv.) in THF (15 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 30 mins. The temperature was lowered to −78 °C and a solution of α-amido sulfone (*tert*-butyl (1-tosylethyl)carbamate **122**) (0.50 g, 1.67 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise. The mixture was allowed to warm to room temperature over 2 hrs. Upon completion, the reaction was quenched by quick addition of sat. $NH_4Cl_{(aq.)}$ at −78 °C and then warmed to room temperature. The product was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-20% EtOAc in petrol) to afford title *propargylic amine* **111** as a colourless oil (297 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (1H, br s, N*H*), 4.47 (1H, app br s, NHC*H*), 2.17 (2H, td, *J* 7.0, 2.0, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.53-1.49 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.47 (9H, s, CO$_2$C(C*H*$_3$)$_3$), 1.39-1.27 (9H, m, (C*H*$_2$)$_3$CH$_3$ and NHCHC*H*$_3$), 0.91 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 154.7, 82.6, 80.7, 31.3, 28.9, 28.6, 28.5, 28.4, 28.0, 23.3, 22.5, 18.6, 14.0; IR: ν_{max} (neat)/cm^{-1} 2932, 2860, 1704, 1495, 1367, 1163, 1053, 908; LRMS (ESI$^+$): *m/z* 276 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) found 276.1934 [M+Na]$^+$, $C_{15}H_{27}O_2NNa^+$ requires 276.1940.

General procedure F for the synthesis of linear *γ*-amino enones *via* rhodium-catalysed hydroacylation of internal alkynes as exemplified by the synthesis of *tert*-butyl (*E*)-{4-[2-(methylthio)benzoyl]dec-3-en-2-yl}carbamate, 112a

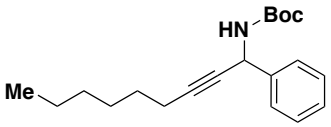


An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%). Once under an inert atmosphere, they were dissolved in acetone (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (74 μL, 1.0 M with respect to aldehyde minus volume or mass of starting materials) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and propargylic amine (*tert*-butyl dec-3-yn-2-ylcarbamate **111**) (57.0 mg, 0.225 mmol, 1.5 equiv.). The reaction mixture, once homogenous (on occasion, sonication was required), was then stirred at room temperature. The reaction was monitored by TLC until complete. After 16 hrs, the reaction mixture was filtered through a plug of silica (acetone, 10 mL) and the solvent removed *in vacuo* to obtain the crude product. The crude product was analysed by ^{1}H NMR spectroscopy to measure the ratio of the linear to branched products (8:1, linear: branched). The regioisomers were then separated by flash column chromatography (5% EtOAc in petrol) to afford title linear *γ-amino enone* **112a** as a pale yellow oil (49.3 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.36 (1H, d, *J* 7.0, Ar-*H*), 7.32 (1H, d, *J* 7.0, Ar-*H*), 7.19 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 5.86 (1H, d, *J* 9.0, COCC*H*), 4.61 (1H, br s, NHC*H*), 4.46 (1H, app br s, N*H*), 2.53 (2H, dd, *J* 9.0, 6.0, $CH_2(CH_2)_4CH_3$), 2.44 (3H, s, SCH_3), 1.61-1.48 (2H, m, $CH_2(CH_2)_3CH_3$), 1.46 (9H, s, $CO_2C(CH_3)_3$), 1.41-1.32 (6H, m, $(CH_2)_3CH_3$), 1.24 (3H, d, *J* 7.0, NHCH(CH_3)), 0.91 (3H, t, *J* 7.0, $(CH_2)_5CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.8, 167.8, 146.7, 141.9, 138.8, 130.4, 129.3, 127.2, 124.5, 100.0, 68.6, 45.1, 31.7, 29.6, 29.2, 28.4, 26.6, 22.6, 21.0, 16.9, 14.1; IR: ν_{max} (neat)/cm^{-1}

2961, 2926, 2855, 1710, 1644, 1492, 1366, 1247, 1166, 1052, 908; LRMS (ESI^+): *m/z* 428 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 406.24124 $[M+H]^+$, $C_{23}H_{36}O_3NS^+$ requires 406.24104.

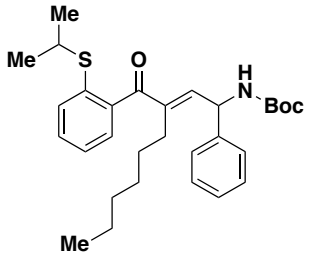
***tert*-Butyl (1-phenylnon-2-yn-1-yl)carbamate, 113**



Prepared according to general procedure **E** using *n*-butyllithium (4.70 mL, 2.5 M in hexanes, 11.8 mmol, 2.05 equiv.), 1-octyne (1.7 mL, 11.5 mmol, 2.0 equiv.) in THF (25 mL) and α-amido sulfone (*tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate **125**) (1.50 g, 5.74 mmol, 1.0 equiv.) in THF (50 mL). The mixture was stirred for 30 mins. The crude product was purified by flash column chromatography (10-30% Et_2O in petrol) to give *propargylic amine* **113** as a colourless oil (1.44 g, 78%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (2H, d, *J* 7.5, Ar-*H*), 7.43-7.35 (2H, m, Ar-*H*), 7.34-7.29 (1H, m, Ar-*H*), 5.67 (1H, app br s, NHC*H*), 5.03 (1H, br s, N*H*), 2.27 (2H, td, *J* 7.0, 2.0, CH_2(CH_2)$_4$$CH_3$), 1.59-1.52 (2H, m, C$H_2$($CH_2$)$_3$$CH_3$), 1.50 (9H, s, CO_2C(CH_3)$_3$), 1.46-1.39 (2H, m, CH_2(CH_2)$_2$$CH_3$), 1.37-1.27 (4H, m, (C$H_2$)$_2$$CH_3$), 0.91 (3H, t, *J* 10.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 140.3, 128.5, 127.7, 126.8, 85.5, 79.9, 78.3, 46.5, 31.3, 29.4, 28.6, 28.4, 22.5, 18.8, 14.0; IR: ν_{max} (neat)/cm^{-1} 2931, 1703, 1493, 1367, 1243, 1167, 1019, 907, 730; LRMS (ESI^+): *m/z* 338 ($[M+Na]^+$, 100%), 653 ($[2M+Na]^+$, 50%); HRMS (ESI^+) found 338.20918 $[M+Na]^+$, $C_{20}H_{29}NO_2Na^+$ requires 338.20905.

***tert*-Butyl-(*E*)-{3-[2-(isopropylthio)benzoyl]-1-phenylnon-2-en-1-yl}carbamate, 114a**

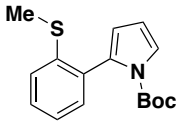


Prepared according to general procedure **F** using 2-(isopropylthio)benzaldehyde **105** (27.0 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylnon-2-yn-1-

yl)carbamate **113**) (71.0 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%) in acetone (52 μL, 1.0 M). After stirring for 2 hrs at 55 ºC the reaction gave the linear *γ-amino enone*, as the only regioisomer detectable by ^{1}H NMR. The crude reaction mixture was purified by flash column chromatography (5-20% Et_2O in petrol) to yield the title *γ-amino enone* **114a** as an off-white oil (63.4 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, d, *J* 8.0, Ar-*H*), 7.40-7.32 (3H, m, Ar-*H*), 7.30-7.24 (5H, m, Ar-*H*), 6.11 (1H, d, *J* 9.0, COCC*H*), 5.69 (1H, s, N*H*), 4.84 (1H, app br s, NHC*H*), 3.30 (1H, septet, *J* 6.5, SC*H*), 2.59 (2H, d, *J* 6.5, $CH_2(CH_2)_4CH_3$), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.38-1.27 (8H, m, $(CH_2)_4CH_3$), 1.22 (6H, app dd, *J* 12.0, 6.5, $SCH(CH_3)_2$), 0.89 (3H, dd, *J* 6.5, 1.5, $(CH_2)_5CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.9, 154.7, 145.0, 143.7, 143.1, 140.4, 133.7, 133.1, 129.6, 128.8, 128.1, 127.8, 126.7, 126.4, 80.0, 52.7, 39.0, 31.7, 29.6, 28.7, 28.3, 26.5, 22.9, 22.6, 14.1; IR: ν_{max} (neat)/cm^{-1} 2959, 2928, 1702, 1654, 1491, 1366, 1240, 1166, 1044, 909; LRMS (ESI^+): *m/z* 496 ($[M+H]^+$, 100%), 518 ($[M+Na]^+$, 70%); HRMS (ESI^+) found 496.28741 $[M+H]^+$, $C_{30}H_{42}O_3NS^+$ requires 496.28799.

General procedure G for the synthesis of *N*-Boc pyrroles as exemplified by the synthesis of *tert*-butyl 2-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 115



a) The one-pot hydroacylation-cyclisation cascade

An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) (for use with terminal alkynes) or dppm (for use with internal alkynes). Once under an inert atmosphere, they were dissolved in acetone (1 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (75 μL, 1.0 M with respect to aldehyde minus the volume or mass of both aldehyde and alkyne) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and *N*-Boc propargylamine **59** (30.2 mg, 0.195 mmol, 1.3 equiv.). The reaction mixture, once homogenous (on occasion,

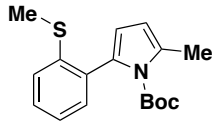
sonication was required), was then stirred at room temperature and monitored by TLC until complete. After 20 mins, the reaction vessel was opened to air followed by the addition of acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.230 mmol, 1.5 equiv.). The reaction mixture was further stirred until complete, after 3 hrs, the solution was diluted with acetonitrile (5 mL) and neutralised by the addition of sat. $NaHCO_{3(aq.)}$ (10 mL) in a separatory funnel. The aqueous mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product and purified by flash column chromatography (5-10% Et_2O in petrol) to afford title *pyrrole* **115** as a colourless oil (35.2 mg, 81%).

b) The direct cyclisation of *γ*-amino enone intermediate

p-TSA (39.9 mg, 0.21 mmol, 1.5 equiv.) was added to a solution of *γ*-amino enone **69a** (46.2 mg, 0.14 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at room temperature, under atmospheric conditions. The reaction was monitored by TLC until complete. Upon completion, after 4 hrs, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and neutralised by the addition of sat. $NaHCO_{3(aq.)}$ (15 mL) in a separatory funnel. The aqueous mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered through a plug of silica. The solvent was removed *in vacuo* to obtain the to obtain the desired *pyrrole,* **115** without further purification as a colourless oil (39.1 mg, 97%). (Overall two-step yield is 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, dd, *J* 3.5, 2.0, NC*H*), 7.35 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.25 (2H, app qd, *J* 3.5, 1.5, Ar-*H*), 7.18 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.31 (1H, app t, *J* 3.5, NCHC*H*), 6.18 (1H, dd, *J* 3.5, 2.0, NCC*H*), 2.38 (3H, s, SC*H*$_3$), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.1, 139.9, 134.2, 132.0, 130.3, 128.3, 124.8, 124.3, 121.7, 114.4, 110.5, 83.1, 27.4, 15.5; IR: ν_{max} (neat)/cm^{-1} 2981, 1738, 1438, 1396, 1370, 1340, 1313, 1152, 1085; LRMS (ESI$^+$): *m/z* 290 ([M+H]$^+$, 100%), 312 ([M+Na]$^+$, 50%); HRMS (ESI$^+$) found 312.1033 [M+Na]$^+$, $C_{16}H_{19}NO_2SNa^+$ requires 312.1029.

tert-Butyl 2-methyl-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 116

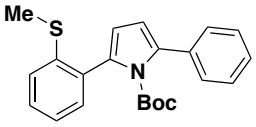


Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl but-3-yn-2-ylcarbamate **82**) (33.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (98 μL, 1.0 M). After stirring for 4 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.230 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **116** as a colourless oil (37.2 mg, 82%).

Prepared according to general procedure **Gb** using γ-amino enone **85a** (25.0 mg, 0.08 mmol, 1.0 equiv.) and *p*-TSA (22.0 mg, 0.12 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 hrs. The crude product was purified by column chromatography on silica (10% EtOAc in petrol) to yield *pyrrole* **116** as a colourless oil (19.1 mg, 83%). (Overall two-step yield is 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (1H, ddd, *J* 8.0, 7.5, 2.0, Ar-*H*), 7.24-7.19 (2H, m, Ar-*H*), 7.16 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.06 (1H, d, *J* 3.0, NC(Ar)C*H*), 6.03 (1H, dq, *J* 3.0, 1.0, NC(CH_3)C*H*), 2.52 (3H, d, *J* 1.0, NC(CH_3)), 2.37 (3H, s, SCH_3), 1.21 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 139.4, 135.0, 132.9, 131.8, 130.2, 128.0, 124.3, 124.2, 112.7, 110.5, 82.8, 27.4, 15.8, 15.3; IR: ν_{max} (neat)/cm^{-1} 2942, 2832, 1742, 1367, 1313, 1149, 1024; LRMS (ESI$^+$): *m/z* 304 ([M+H]$^+$, 100%), 326 ([M+Na]$^+$, 95%); HRMS (ESI$^+$) found 326.1184 [M+Na]$^+$, $C_{17}H_{21}NO_2SNa^+$ requires 326.1185.

tert-Butyl 2-[2-(methylthio)phenyl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 117



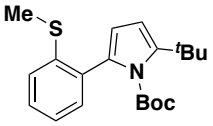
Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (0.41 mL, 3.20 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **83**) (0.96 g, 4.16 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (23.9 mg, 2 mol%) and PNP(Cy)

(30.3 mg, 2 mol%) in acetone (1.8 mL, 1.0 M). After stirring for 30 mins at room temperature, acetonitrile (10 mL) and *p*-TSA (0.61 g, 3.20 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 4 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **117** as a white solid (1.04 g, 88%).

Prepared according to general procedure **Gb** using *γ*-amino enone **86a** (19 mg, 0.05 mmol, 1.0 equiv.) and *p*-TSA (14.3 mg, 0.08 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 4 hrs to yield *pyrrole* **117** as a white solid (17.1 mg, 93%). (Overall two-step yield is 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.45 (2H, m, Ar-*H*), 7.43-7.39 (3H, m, Ar-*H*), 7.38-7.34 (2H, m, Ar-*H*), 7.28 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.23 (1H, app td, *J* 7.5, 1.0, Ar-*H*), 6.33 (1H, d, *J* 3.5, NCC*H*), 6.25 (1H, d, *J* 3.5, NCC*H*), 2.42 (3H, s, SCH_3), 1.16 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.2, 139.8, 136.0, 134.5, 133.9, 133.6, 130.6, 128.8, 128.5, 127.7, 127.0, 124.6, 124.3, 112.9, 112.6, 83.2, 27.1, 15.4; IR: ν_{max} (neat)/cm^{-1} 2980, 1748, 1748, 1482, 1368, 1304, 1147; LRMS (ESI$^+$): *m/z* 366 ([M+H]$^+$, 100%), 388 ([M+Na]$^+$, 25%); HRMS (ESI$^+$) found 388.1338 [M+Na]$^+$, $C_{22}H_{23}NO_2SNa^+$ requires 388.1342; mp: 94-95 °C (CH_2Cl_2/hexane).

tert-Butyl 2-(_tert_-butyl)-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 118

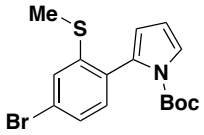


Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (4,4-dimethylpent-1-yn-3-yl)carbamate **84**) (41.2 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (90 μL, 1.0 M). After stirring for 30 mins at room temperature, acetonitrile (1.5 mL) and *p*-TSA (72.5 mg, 0.60 mmol, 4.0 equiv.) were added and stirred at room temperature for a further 3.5 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **118** as colourless oil (42.6 mg, 82%).

Prepared according to general procedure **Gb** using γ-amino enone **87a** (9.90 mg, 0.03 mmol, 1.0 equiv.) and *p*-TSA (8.00 mg, 0.04 mmol, 1.5 equiv.) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 16 hrs to yield *pyrrole* **118** (8.40 mg, 90%) as a colourless oil. (Overall two-step yield is 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.24 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 7.20 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.15 (1H, app td, *J* 7.5, 1.0, Ar-*H*), 6.11 (1H, d, *J* 3.5, NCC*H*), 6.09 (1H, d, *J* 3.5, NCC*H*), 2.36 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.15 (9H, s, NCC$(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.3, 147.0, 144.9, 139.6, 134.2, 130.6, 128.0, 124.2, 124.1, 111.0, 107.4, 83.1, 33.1, 30.4, 27.0, 15.2; IR: ν_{max} (neat)/cm^{-1} 2966, 1748, 1457, 1393, 1368, 1326, 1299, 1257, 1159, 1144, 1084, 1003; LRMS (ESI$^+$): *m/z* 346 ($[M+H]^+$, 100%), 368 ($[M+Na]^+$, 20%); HRMS (ESI$^+$) found 368.1650 $[M+Na]^+$, $C_{20}H_{27}NO_2SNa^+$ requires 368.1655.

***tert*-Butyl 2-[4-bromo-2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 119**



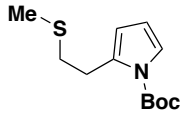
Prepared according to general procedure **Ga** using 4-bromo-2-(methylthio)benzaldehyde **91** (34.6 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargyl amine **59** (30.2 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (80 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **119** as an off-white solid (42.6 mg, 80%).

Prepared according to general procedure **Gb** using γ-amino enone **100a** (14.5 mg, 0.04 mmol, 1.0 equiv.) and *p*-TSA (10.7 mg, 0.06 mmol, 1.5 equiv.) in CH_2Cl_2 (0.8 mL). The reaction mixture was stirred for 2 hrs to yield *pyrrole* **119** (12.6 mg, 93%) as an off-white solid. (Overall two-step yield is 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, dd, *J*, 3.5, 2.0, NC*H*), 7.31-7.30 (2H, m, Ar-*H*), 7.1 (1H, d, *J* 8.5, Ar-*H*), 6.30 (1H, app t, *J* 3.5, NCC*H*), 6.17 (1H, dd, *J* 3.5, 2.0, NCHC*H*), 2.39

(3H, s, SC*H*$_3$), 1.33 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 142.6, 132.6, 131.5, 127.1, 126.8, 126.3, 122.4, 122.0, 114.9, 110.7, 83.5, 27.5, 15.4; IR: ν_{max} (neat)/cm^{-1} 2923, 1740, 1493, 1449, 1399, 1370, 1338, 1312, 1257, 1150, 1082; LRMS (ESI$^+$): *m/z* 392 ([^{81}Br] [M+Na]$^+$, 100%), 390 ([^{79}Br] [M+Na]$^+$, 95%), 370 ([^{81}Br] [M+H]$^+$, 30%), 368 ([^{79}Br] [M+H]$^+$, 25%); HRMS (ESI$^+$) found 390.0131 [[^{79}Br] [M+Na]$^+$], 392.0110 [[^{81}Br] [M+Na]$^+$], $C_{16}H_{18}{}^{79}BrNO_2SNa^+$ requires 390.0134, $C_{16}H_{18}{}^{81}BrNO_2SNa^+$ requires 392.0114; mp: 84-90 °C (Et_2O/petrol).

***tert*-Butyl 2-[2-(methylthio)ethyl]-1*H*-pyrrole-1-carboxylate, 120**

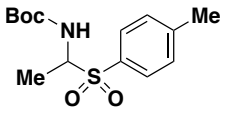


Prepared according to general procedure **Gb** using *γ*-amino enone **96a** (25.7 mg, 0.10 mmol, 1.0 equiv.) and *p*-TSA (28.5 mg, 0.15 mmol, 1.5 equiv.) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 4 hrs to yield *pyrrole* **120** (14.7 mg, 62%) as a colourless oil. (Overall two-step yield is 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (1H, app t, *J* 1.5, NC*H*), 6.13-6.11 (1H, m, NCHC*H*), 6.05 (1H, app br s, NCC*H*), 3.18 (2H, t, *J* 7.5, SCH_2), 2.79 (2H, app td, *J* 7.5, 1.5, SCH_2CH_2), 2.17 (3H, s, SCH_3), 1.63 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.3, 134.0, 121.2, 112.0, 110.0, 83.6, 33.6, 29.1, 28.0, 15.6; IR: ν_{max} (neat)/cm^{-1} 2978, 1738, 1493, 1407, 1370, 1328, 1239, 1143, 1119, 1064; LRMS (ESI$^+$): *m/z* 264 ([M+Na]$^+$, 100%), 242 ([M+H]$^+$, 25%); HRMS (ESI$^+$) found 264.1029 [M+Na]$^+$, $C_{12}H_{19}NO_2SNa^+$ requires 264.1029.

6.3 Chapter 3 Experimental

General procedure H for the synthesis of *α*-amido sulfones, exemplified by the preparation of *tert*-butyl (1-tosylethyl)carbamate, 122

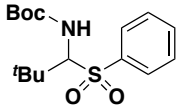


Prepared following a procedure adapted from Petrini *et. al.*,[168] to a stirring solution of *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.) and sodium *p*-toluenesulfinate (3.34 g,

26.6 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (43 mL) was added acetaldehyde (0.80 mL, 14.3 mmol, 1.5 equiv.) and formic acid (0.89 mL, 23.5 mmol, 1.8 equiv.) at room temperature. The mixture was stirred for 16 hrs. The resulting white precipitate was filtered with 10% CH_2Cl_2 in petrol and triturated (10% CH_2Cl_2 in petrol) for 2 hrs. After filtration the white solid was dried under vacuum to afford pure *α*-amido sulfone **122** as a white solid (2.34 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* 8.0, Ar-*H*), 7.35 (2H, d, *J* 8.0, Ar-*H*), 5.04 (1H, br s, N*H*), 4.99-4.95 (1H, m, NHC*H*), 2.44 (3H, s, Ar-CH_3), 1.62 (3H, d, *J* 7.0, NHCH(CH_3)), 1.25 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.4, 144.9, 133.6, 129.7, 129.4, 80.7, 66.7, 27.9, 21.6, 13.0; HRMS (FI^+) found 299.1226 $[M]^+$, $C_{14}H_{21}NO_4S^+$ requires 299.1191; mp: 111-113 °C (EtOAc/hexane), (lit. mp: 110-111 °C). This data is consistent with literature.[264]

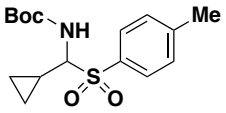
tert-Butyl [2,2-dimethyl-1-(phenylsulfonyl)propyl]carbamate, 123



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.0 g, 8.5 mmol, 1.0 equiv.), sodium phenylsulfinate (2.8 g, 17 mmol, 2.0 equiv.) in H_2O/THF (2:1, v/v) (11.9 mL), trimethylacetaldehyde (1.8 mL, 17 mmol, 2.0 equiv.) and formic acid (3.2 mL, 8.5 mmol, 1.0 equiv.). The mixture was stirred for 72 hrs. Trituration afforded pure *α-amido sulfone* **123** (2.05 g, 74%). Due to rapid decomposition HRMS data was not retrieved and the compound was used directly in propargylic amine synthesis.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (2H, dd, *J* 7.5, 2.0, Ar-*H*), 6.95-6.92 (3H, m, Ar-*H*), 5.20 (1H, d, *J* 11.5, N*H*), 4.84 (1H, d, *J* 11.5, NHC*H*), 1.15 (9H, s, $CO_2C(CH_3)_3$), 1.13 (9H, s, CHC(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9, 139.3, 133.4, 129.1, 128.8, 80.6, 36.7, 28.3, 27.4, 25.3; IR: ν_{max} (neat)/cm^{-1} 3294, 2982, 2030, 1692, 1552, 1516, 1366, 1177, 1048, 997; mp: 86-88 °C (EtOAc/hexane).

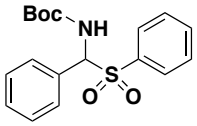
tert-Butyl [cyclopropyl(tosyl)methyl]carbamate, 124



Prepared according to general procedure **H** using *tert*-butyl-carbamate (0.7 g, 6.0 mmol, 1.0 equiv.), sodium *p*-toluenesulfinate (1.18 g, 6.60 mmol, 1.1 equiv.) in H_2O/MeOH (2:1, v/v) (9.5 mL), cyclopropanecarboxaldehyde (0.50 mL, 3.97 mmol, 1.5 equiv.) and formic acid (0.89 mL, 23.5 mmol, 6.5 equiv.). The mixture was stirred for 16 hrs. Trituration afforded pure *α-amido sulfone* **124** (0.69 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (2H, d, *J* 8.0, Ar-*H*), 7.35 (2H, d, *J* 8.0, Ar-*H*), 5.13 (1H, d, *J* 10.0, N*H*), 4.37 (1H, app t, *J* 10.0, NHC*H*), 2.44 (3H, s, Ar-C*H*$_3$), 1.39-1.32 (1H, m, NHCHC*H*), 1.28 (9H, s, $CO_2C(CH_3)_3$), 0.86-0.79 (1H, m, NHCHCHCH_aH$_b$CH$_a$H$_b$), 0.73-0.66 (1H, m, NHCHCHCH$_a$$H_bCH_aH_b$), 0.63-0.59 (1H, m, NHCHCHCH$_a$H$_b$CH_aH$_b$), 0.47-0.41 (1H, m, NHCHCHCH$_a$H$_b$CH$_a$$H_b$); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 153.8, 145.0, 134.5, 129.6, 129.2, 80.5, 74.3, 27.7, 21.3, 9.0, 4.2, 2.0; IR: ν_{max} (neat)/cm^{-1} 2978, 1716, 1597, 1516, 1368, 1163, 1140, 950; HRMS (FI$^+$) found 325.1274 [M]$^+$, $C_{16}H_{23}NO_4S^+$ requires 325.1348; mp: 126-127 °C (EtOAc/hexane).

tert-Butyl [phenyl(phenylsulfonyl)methyl]carbamate, 125

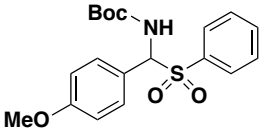


Prepared according to general procedure **H** using *tert*-butyl-carbamate (3.00 g, 25.6 mmol, 1.0 equiv.), sodium phenylsulfinate (8.40 g, 51.2 mmol, 2.0 equiv.) in H_2O/THF (2:1, v/v) (86 mL), benzaldehyde (5.20 mL, 51.2 mmol, 2.0 equiv.) and formic acid (1.80 mL, 0.05 mmol, 0.02 equiv.). The mixture was stirred for 24 hrs. Trituration afforded *α*-amido sulfone **125** as a white solid (7.65 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, *J* 7.5, Ar-*H*), 7.66 (1H, app t, *J* 7.5, Ar-*H*), 7.55 (2H, app t, *J* 7.5, Ar-*H*), 7.48-7.41 (5H, m, Ar-*H*), 5.97 (1H, d, *J* 10.0, N*H*), 5.87 (1H, d, *J* 10.0, NHC*H*), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 153.5, 137.0, 133.9, 130.0, 129.8, 129.5, 129.0, 128.9, 128.7, 81.2, 73.9, 28.0; HRMS (FI$^+$) found 347.1201

$[M]^+$, $C_{18}H_{21}NO_4S^+$ requires 347.1191; mp: 168-170 °C (EtOAc/hexane), (lit. mp: 170 °C). This data is consistent with literature.[168]

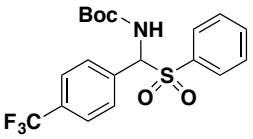
tert-Butyl [(4-methoxyphenyl)(phenylsulfonyl)methyl]carbamate, 126



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (4.30 g, 26.2 mmol, 2.05 equiv.) in H_2O/THF (2:1, v/v) (40 mL), *p*-anisaldehyde (3.10 mL, 25.6 mmol, 2.0 equiv.) and formic acid (0.58 mL, 15.4 mmol, 1.2 equiv.). The mixture was stirred for 48 hrs. Trituration afforded the pure *α*-amido sulfone **126** as a white solid (2.35 g, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, *J* 7.5, Ar-*H*), 7.68-7.65 (1H, m, Ar-*H*), 7.56 (2H, app t, *J* 8.0, Ar-*H*), 7.40 (2H, d, *J* 8.5, Ar-*H*), 6.98-6.95 (2H, m, Ar-*H*), 5.90 (1H, d, *J* 11.0, NHC*H*), 5.77 (1H, br s, N*H*), 3.85 (3H, s, OCH_3), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.8, 153.5, 137.0, 133.9, 130.2, 129.4, 129.0, 121.7, 114.3, 81.2, 73.5, 55.4, 28.0; HRMS (FI$^+$) found 377.1307 $[M]^+$, $C_{19}H_{23}NO_5S^+$ requires 377.1297; mp: 113-114 °C (EtOAc/hexane), (lit. mp: 115-116 °C). This data is consistent with literature.[265]

tert-Butyl [(phenylsulfonyl)[4-(trifluoromethyl)phenyl]methyl]carbamate, 127

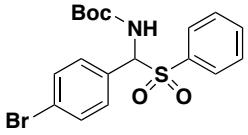


Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.00 g, 8.54 mmol, 1.0 equiv.), sodium phenylsulfinate (2.80 g, 17.1 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (28.5 mL), 4-(trifluoromethyl)benzaldehyde (2.34 mL, 17.1 mmol, 2.0 equiv.) and formic acid (0.59 mL, 15.6 mmol, 1.8 equiv.). The mixture was stirred for 60 hrs. Trituration afforded the pure *α*-amido sulfone **127** as a white powder (1.96 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (2H, d, *J* 7.5, Ar-*H*), 7.70 (3H, d, *J* 8.0, Ar-*H*), 7.60 (4H, dd, *J* 15.5, 8.0, Ar-*H*), 6.03 (1H, br d, *J* 9.0, N*H*), 5.83 (1H, d, *J* 9.0, NHC*H*), 1.28 (9H, s,

$CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.4, 136.5, 134.3, 133.9, 131.9 (q, $^2J_{CF}$ 33.0), 129.5, 129.3, 129.2, 128.5 (q, $^1J_{CF}$ 233.5), 125.7 (q, $^3J_{CF}$ 3.5), 81.6, 73.3, 28.0; ^{19}F NMR (377 MHz, $CDCl_3$, ^1H decoupled): δ -62.9; HRMS (FI^+) found 415.0959 $[M]^+$, $C_{19}H_{20}F_3NO_4S^+$ requires 415.1065; mp: 175-176 °C (EtOAc/petrol), (lit. mp 178-179 °C). This data is consistent with literature.[266]

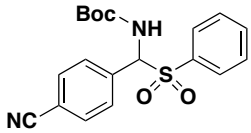
tert-Butyl [(4-bromophenyl)(phenylsulfonyl)methyl]carbamate, 128



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (5.70 g, 32.0 mmol, 2.5 equiv.) in H_2O/MeOH (2:1, v/v) (38.4 mL), 4-bromobenzaldehyde (2.85 mL, 15.4 mmol, 1.2 equiv.) and formic acid (0.96 mL, 25.6 mmol, 2.0 equiv.). The mixture was stirred for 30 hrs. Trituration afforded the pure *α*-amido sulfone **128** as a white powder (1.58 g, 26%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (2H, d, *J* 7.5, Ar-*H*), 7.74 (3H, app t, *J* 7.0, Ar-*H*), 7.64 (4H, dd, *J* 15.5, 7.5, Ar-*H*), 6.05 (1H, d, *J* 10.0, NHC*H*), 5.91 (1H, d, *J* 10.0, N*H*), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 136.6, 134.3, 131.4, 129.4, 129.3, 125.5, 125.4, 125.2, 100.0, 73.2, 27.7; HRMS (FI^+) found 427.0309 $[M]^+$, $C_{18}H_{20}{}^{81}BrNO_4S^+$ requires 427.0277; mp: 170-172 °C (EtOAc/hexane), (lit. mp: 172-173 °C). This data is consistent with literature.[266]

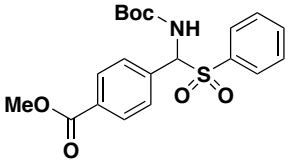
tert-Butyl [(4-cyanophenyl)(phenylsulfonyl)methyl]carbamate, 129



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.20 g, 10.2 mmol, 1.0 equiv.), sodium phenylsulfinate (3.68 g, 20.4 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (33 mL), 4-cyanobenzaldehyde (2.00 g, 15.3 mmol, 1.5 equiv.) and formic acid (7.70 mL, 20.4 mmol, 2.0 equiv.). The mixture was stirred for 60 hrs. Trituration afforded the pure *α*-amido sulfone **129** as a white solid (3.34 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, *J* 7.5, Ar-*H*), 7.73-7.69 (3H, m, Ar-*H*), 7.62-7.57 (4H, m, Ar-*H*), 6.01 (1H, br s, N*H*), 5.88 (1H, d, *J* 20.0, NHC*H*), 1.27 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.4, 136.3, 135.1, 134.4, 132.3, 129.7, 129.4, 129.3, 118.1, 113.7, 81.8, 73.3, 28.0; HRMS (FI^+) found 372.1208 $[M]^+$, $C_{19}H_{20}N_2O_4S^+$ requires 372.1144; mp: 160-161 °C (EtOAc/hexane), (lit. mp: 159-161 °C). This data is consistent with literature.[265]

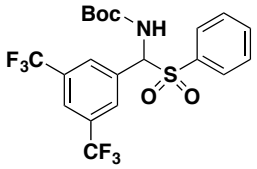
Methyl 4-{[(*tert*-butoxycarbonyl)amino](phenylsulfonyl)methyl}benzoate, 130



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.00 g, 8.54 mmol, 1.0 equiv.), sodium phenylsulfinate (2.80 g, 17.1 mmol, 2.0 equiv.) in H_2O/THF (2:1, v/v) (24.5 mL), methyl 4-formylbenzoate (2.81 g, 17.1 mmol, 2.0 equiv.) and formic acid (0.59 mL, 15.6 mmol, 1.8 equiv.). The mixture was stirred for 60 hrs. Trituration afforded the pure *α*-amido sulfone **130** a white solid (1.03 g, 30%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (2H, d, *J* 8.0, Ar-*H*), 7.93 (2H, d, *J* 8.0, Ar-*H*), 7.68 (1H, app t, *J* 7.5, Ar-*H*), 7.56 (4H, dd, *J* 15.0, 8.0, Ar-*H*), 6.01 (1H, d, *J* 10.0, N*H*), 5.82 (d, *J* 10.0, NHC*H*), 3.96 (3H, s, CO_2CH_3), 1.29 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 153.5, 136.7, 134.7, 134.2, 131.4, 129.8, 129.5, 129.2, 128.9, 81.5, 73.6, 52.3, 28.0; HRMS (FI^+) found 405.1460 $[M]^+$, $C_{20}H_{23}NO_6S^+$ requires 405.1246; mp: 174-176 °C (EtOAc/hexane), (lit. mp: 176 °C). This data is consistent with literature.[267]

***tert*-Butyl [[3,5-bis(trifluoromethyl)phenyl](phenylsulfonyl)methyl]carbamate, 131**

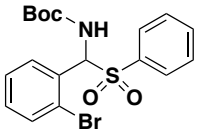


Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (4.30 g, 26.2 mmol, 2.05 equiv.) in H_2O/MeOH (2:1, v/v) (39.4 mL), 3,5-bis(trifluoromethyl)benzaldehyde (4.23 mL, 25.6 mmol, 2.0 equiv.) and

formic acid (0.58 mL, 15.4 mmol, 1.2 equiv.). The mixture was stirred for 48 hrs. Trituration afforded the pure *α-amido sulfone* **131** as a white powder (2.77 g, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.93 (5H, m, Ar-*H*), 7.89 (1H, s, Ar-*H*), 7.74 (1H, app t, *J* 7.5, Ar-*H*), 7.62 (1H,app t, *J* 7.5, Ar-*H*), 6.35 (1H, d, *J* 9.0, N*H*), 5.40 (1H, d, *J* 9.0, NHC*H*), 1.53 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.0, 136.0, 134.6, 132.9, 132.6 (q, $^{1}J_{CF}$ 236.5), 132.1 (q, $^{2}J_{CF}$ 33.5), 131.7, 131.6, 129.4 (q, $^{3}J_{CF}$ 3.5), 129.1 (q, $^{3}J_{CF}$ 3.5), 126.5 (q, $^{3}J_{CF}$ 3.5), 126.0 (q, $^{1}J_{CF}$ 201.0), 124.7 (q, $^{2}J_{CF}$ 31.5), 81.4, 75.2, 28.2; IR: ν_{max} (neat)/cm^{-1} 2988, 1676, 1522, 1501, 1394, 1311, 1221, 1105, 910, 723; HRMS (FI^{+}) found 483.0435 [M]$^{+}$, $C_{20}H_{19}F_6NO_4S^{+}$ requires 483.0539; mp: 181-183 °C (EtOAc/hexane).

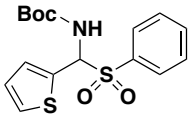
***tert*-Butyl [(2-bromophenyl)(phenylsulfonyl)methyl]carbamate, 132**



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (5.7 g, 32 mmol, 2.5 equiv.) in H_2O/THF (2:1, v/v) (38.4 mL), 2-bromobenzaldehyde (1.80 mL, 15.4 mmol, 1.2 equiv.) and formic acid (0.72 mL, 19.2 mmol, 2.0 equiv.). The mixture was stirred for 60 hrs. Trituration afforded *α-amido sulfone* **132** as a white powder (3.02 g, 55%).

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.97 (2H, d, *J* 8.0, Ar-*H*), 7.69 (1H, app t, *J* 7.5, Ar-*H*), 7.65-7.63 (1H, m, Ar-*H*), 7.61-7.56 (3H, m, Ar-*H*), 7.45 (1H, app td, *J* 7.5, 1.0, Ar-*H*), 7.33-7.30 (1H, m, Ar-*H*), 6.66 (1H, d, *J* 10.5, N*H*), 5.88 (1H, d, *J* 10.5, NHC*H*), 1.31 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, CD_2Cl_2): δ 153.3, 137.2, 134.2, 133.9, 133.2, 131.2, 131.0, 129.4, 129.2, 128.0, 125.8, 81.2, 72.4, 27.7; IR: ν_{max} (neat)/cm^{-1} 2975, 1986, 1704, 1511, 1447, 1276, 1144, 1027, 727; HRMS (FI^{+}) found 427.0262 [M]$^{+}$, $C_{18}H_{20}{}^{81}BrNO_4S^{+}$ requires 427.0277; mp: 163-164 °C (EtOAc/hexane).

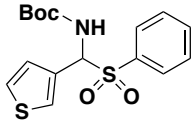
tert-Butyl [(phenylsulfonyl)(thiophen-2-yl)methyl]carbamate, 133



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (4.20 g, 25.6 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (42.8 mL), 2-thiophenecarboxaldehyde (2.39 mL, 25.6 mmol, 2.0 equiv.) and formic acid (0.88 mL, 23.3 mmol, 1.8 equiv.). The mixture was stirred for 60 hrs. Trituration afforded the pure *α*-amido sulfone **133** as an off-white solid (1.12 g, 25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (2H, d, *J* 7.5, Ar-*H*), 7.68 (1H, app t, *J* 7.0, Ar-*H*), 7.57 (2H, d, *J* 7.5, Ar-*H*), 7.45 (1H, dd, *J* 5.0, 1.5, SC*H*), 7.30 (1H, d, *J* 4.0, SCHCHC*H*), 7.10 (1H, dd, *J* 5.0, 4.0, SCHC*H*), 6.21 (1H, d, *J* 11.0, N*H*), 5.67 (1H, d, *J* 11.0, NHC*H*), 1.29 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 136.5, 134.1, 131.5, 129.6, 129.3, 129.1, 127.7, 127.3, 81.4, 70.3, 28.0; HRMS (FI^+) found 353.0756 $[M]^+$, $C_{16}H_{19}NO_4S_2^+$ requires 353.0759; mp: 160-162 °C (EtOAc/hexane), (lit. mp: 172-173 °C). This data is consistent with literature.[265]

tert-Butyl [(phenylsulfonyl)(thiophen-3-yl)methyl]carbamate, 134

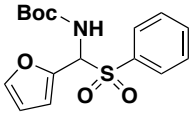


Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.0 g, 8.5 mmol, 1.0 equiv.), sodium phenylsulfinate (2.8 g, 17 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (28.2 mL), 3-thiophenecarboxaldehyde (1.6 mL, 17 mmol, 2.0 equiv.) and formic acid (0.58 mL, 15 mmol, 1.8 equiv.). The mixture was stirred for 16 hrs. Trituration afforded pure *α-amido sulfone* **134** (1.24 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (2H, d, *J* 7.5, Ar-*H*), 7.68 (1H, app t, *J* 7.5, Ar-*H*), 7.59-7.55 (2H, m, Ar-*H*), 7.49 (1H, br s, SC*H*CCH), 7.42 (1H, dd, *J* 5.0, 3.0, SC*H*CH), 7.27 (1H, app dd, *J* 5.0, 1.0, SCHC*H*), 6.08 (1H, d, *J* 9.5, NHC*H*), 5.66 (1H, app br d, *J* 9.0, N*H*), 1.29 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.1, 136.7, 134.0, 130.3, 129.5, 129.1, 127.0, 126.7, 126.4, 100.0, 70.3, 28.0; HRMS (FI^+) found 353.0757 $[M]^+$,

$C_{16}H_{19}NO_4S_2^+$ requires 353.0759; mp: 151-152 °C (EtOAc/hexane).

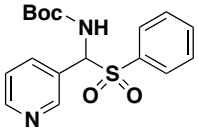
tert-Butyl [furan-2-yl(phenylsulfonyl)methyl]carbamate, 135



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (2.30 g, 12.8 mmol, 1.0 equiv.) in H_2O/THF (2:1, v/v) (18.3 mL), furfural (1.10 mL, 12.8 mmol, 1.0 equiv.) and formic acid (2.40 mL, 64.0 mmol, 5.0 equiv.). The mixture was stirred for 48 hrs. Trituration afforded the pure *α*-amido sulfone **135** as a light brown solid (2.15 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* 8.0, Ar-*H*), 7.68 (1H, d, *J* 7.0, Ar-*H*), 7.56 (2H, app t, *J* 8.0, Ar-*H*), 7.50 (1H, app s, OC*H*), 6.60 (1H, d, *J* 3.0, OCHCHC*H*), 6.46 (1H, dd, *J* 3.0, 2.0, OCHC*H*), 6.05 (1H, d, *J* 10.5, N*H*), 5.84 (1H, d, *J* 10.5, NHC*H*), 1.31 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.3, 144.3, 143.0, 136.6, 134.1, 129.5, 129.1, 112.3, 111.2, 81.4, 69.0, 28.0; HRMS (FI^+) found 337.1081 $[M]^+$, $C_{16}H_{19}NO_5S^+$ requires 337.0984; mp: 160-161 °C (EtOAc/hexane), (lit. mp: 159-161 °C). This data is consistent with literature.[265]

tert-Butyl [(phenylsulfonyl)(pyridin-3-yl)methyl]carbamate, 136

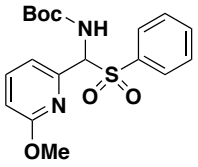


Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.50 g, 12.8 mmol, 1.0 equiv.), sodium phenylsulfinate (4.60 g, 25.6 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (32 mL), 3-pyridinecarboxaldehyde (1.50 mL, 15.4 mmol, 1.2 equiv.) and formic acid (0.72 mL, 19.2 mmol, 1.5 equiv.). The mixture was stirred for 60 hrs. Trituration afforded the pure *α-amido sulfone* **136** as a white powder (1.96 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71-8.70 (2H, m, Ar-*H*), 7.95 (2H, d, *J* 7.5, Ar-*H*), 7.87 (1H, d, *J* 8.0, Ar-*H*), 7.70 (1H, app t, *J* 7.0, Ar-*H*), 7.61-7.57 (2H, m, Ar-*H*), 7.41-7.37 (1H, m, Ar-*H*), 6.01 (2H, app br s, N*H*C*H*), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$):

δ 153.4, 150.9, 150.0, 136.4, 136.3, 134.3, 129.5, 129.2, 126.4, 123.5, 81.6, 71.9, 28.0; IR: ν_{max} (neat)/cm^{-1} 3204, 2978, 1717, 1530, 1308, 1162, 1082, 625; HRMS (FI^+) found 348.1266 $[M]^+$, $C_{17}H_{20}N_2O_4S^+$ requires 348.1144; mp: 152-154 °C (EtOAc/petrol).

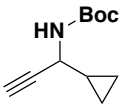
tert-butyl[(6-methoxypyridin-2-yl)-(phenylsulfonyl)-methyl]carbamate, 137



Prepared according to general procedure **H** using *tert*-butyl-carbamate (1.60 g, 13.3 mmol, 1.0 equiv.), sodium phenylsulfinate (4.80 g, 26.6 mmol, 2.0 equiv.) in H_2O/MeOH (2:1, v/v) (34.2 mL), 6-methoxypyridine-2-carbaldehyde (1.93 mL, 16.0 mmol, 1.2 equiv.) and formic acid (1.51 mL, 39.9 mmol, 1.5 equiv.). The mixture was stirred for 60 hrs. Trituration afforded the pure *α-amido sulfone* **137** as a white solid (3.74 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (2H, d, *J* 7.5, Ar-*H*), 7.64 (2H, app t, *J* 7.5, Ar-*H*), 7.53 (2H, app t, *J* 7.5, Ar-*H*), 7.17 (1H, d, *J* 7.0, Ar-*H*), 6.79 (1H, d, *J* 8.0, Ar-*H*), 6.47 (1H, br d, *J* 9.5, N*H*), 5.98 (1H, d, *J* 9.5, NHC*H*), 3.86 (3H, s, OCH_3), 1.34 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 153.7, 145.4, 139.1, 136.8, 133.8, 129.7, 128.8, 118.4, 112.0, 81.0, 74.6, 53.5, 28.1; HRMS (FI^+) found 378.1389 $[M]^+$, $C_{18}H_{22}N_2O_5S^+$ requires 378.1249; mp: 136-137 °C (EtOAc/hexane).

tert-Butyl (1-cyclopropylprop-2-yn-1-yl)carbamate, 138

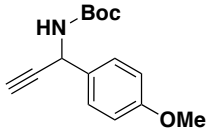


Prepared according to general procedure **D** using ethynylmagnesium bromide (5.05 mL, 0.49 M in THF, 2.02 mmol, 2.2 equiv.) and *α*-amido sulfone (*tert*-butyl [cyclopropyl(phenylsulfonyl)methyl]carbamate **124**) (0.30 g, 0.92 mmol, 1.0 equiv.) in THF (7.5 mL) for 2 hrs. The crude product was purified by flash column chromatography (10-20% Et_2O in toluene) to give *propargylic amine* **138** as a white solid (154 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (1H, br s, N*H*), 4.39 (1H, app br s, NHC*H*), 2.21 (1H,

d, *J* 2.5, C*H*CCHNH), 1.44 (9H, s, $CO_2C(CH_3)_3$), 1.15-1.07 (1H, m, NHCHC*H*), 0.47-0.43 (4H, m, NHCHCH(CH_2)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 154.8, 81.2, 71.1, 45.5, 28.3, 15.1, 2.7, 1.6; IR: ν_{max} (neat)/cm^{-1} 3008, 2978, 1691, 1492, 1366, 1243, 1163, 1045, 1021; LRMS (ESI$^+$): *m/z* 218 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 218.11496 [M+Na]$^+$, $C_{11}H_{17}O_2NNa^+$ requires 218.11515; mp: 64-65 °C (CH_2Cl_2/petrol).

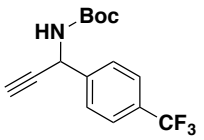
tert-Butyl [1-(4-methoxyphenyl)prop-2-yn-1-yl]carbamate, 139



Prepared according to general procedure **D** using ethynylmagnesium bromide (23.4 mL, 0.5 M in THF, 11.7 mmol, 2.2 equiv.) and α-amido sulfone (*tert*-butyl [(4-methoxyphenyl)(phenylsulfonyl)methyl]carbamate **126**) (2.0 g, 5.3 mmol, 1.0 equiv.) in THF (37 mL) for 1 hr. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **139** as an off-white solid (1.22 g, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (2H, d, *J* 8.5, Ar-*H*), 6.91 (2H, d, *J* 8.5, Ar-*H*), 5.63 (1H, d, *J* 6.0, NHC*H*), 5.05 (1H, br s, N*H*), 3.83 (3H, s, OCH_3), 2.51 (1H, d, *J* 2.5, C*H*CCHNH), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 154.7, 130.9, 128.1, 114.0, 82.4, 80.2, 72.7, 55.3, 45.7, 28.4; IR: ν_{max} (neat)/cm^{-1} 2943, 2253, 1703, 1612, 1511, 1247, 1165, 1035, 909, 732; LRMS (ESI$^+$): *m/z* 284 ([M+Na]$^+$, 100%), 545 ([2M+Na]$^+$, 80%); HRMS (ESI$^+$) found 284.12571 [M+Na]$^+$, $C_{15}H_{19}O_3NNa^+$ requires 284.12571; mp: 94-96 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

tert-Butyl {1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-yl}carbamate, 140

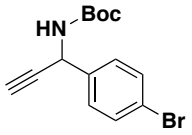


Prepared according to general procedure **D** using ethynylmagnesium bromide (11.3 mL, 0.5 M in THF, 5.30 mmol, 2.2 equiv.) and α-amido sulfone (*tert*-butyl {(phenylsulfonyl)[4-(trifluoromethyl)phenyl]methyl}carbamate **127**) (1.00 g, 2.41 mmol, 1.0 equiv.) in THF (19 mL) for 2 hrs. The crude product was purified by flash column chromatography (5-15%

EtOAc in petrol) to give *propargylic amine* **140** as a white solid (0.426 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.60 (4H, m, Ar-*H*), 5.75 (1H, app br s, NHC*H*), 5.44 (1H, br s, N*H*), 2.55 (1H, d, *J* 2.5, C*H*CCHNH), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 142.9, 130.3 (q, $^{2}J_{CF}$ 32.4), 127.2, 125.6 (q, $^{3}J_{CF}$ 3.5), 124.0 (q, $^{1}J_{CF}$ 272.3), 81.3, 80.6, 73.7, 45.8, 28.2; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): -62.6; IR: ν_{max} (neat)/cm^{-1} 3310, 3100, 1689, 1620, 1496, 1386, 1124, 1018, 909, 732, 661; LRMS (ESI$^+$): *m/z* 322 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 322.10200 [M+Na]$^+$, $C_{15}H_{16}O_2NF_3Na^+$ requires 322.10253; mp: 92-93 °C (EtOAc/petrol).

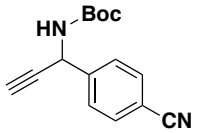
***tert*-Butyl [1-(4-bromophenyl)prop-2-yn-1-yl]carbamate, 141**



Prepared according to general procedure **D** using ethynylmagnesium bromide (8.80 mL, 0.5 M in THF, 4.14 mmol, 2.2 equiv.) and α-amido sulfone (*tert*-butyl [(4-bromophenyl)(phenylsulfonyl)methyl]carbamate **128**) (0.80 g, 1.88 mmol, 1.0 equiv.) in THF (15 mL) for 2 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **141** as a white solid (0.29 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (2H, m, Ar-*H*), 7.43-7.38 (2H, m, Ar-*H*), 5.64 (1H, app br s, NHC*H*), 5.13 (1H, br s, N*H*), 2.53 (1H, d, *J* 2.5, C*H*CCHNH), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 138.0, 131.8, 128.6, 122.1, 81.5, 80.5, 73.4, 45.7, 28.3; IR: ν_{max} (neat)/cm^{-1} 3300, 2978, 1690, 1487, 1367, 1161, 1011, 876, 646; LRMS (ESI$^+$): *m/z* 332 ([^{79}Br] [M+Na]$^+$, 100%), 334 ([^{81}Br] [M+Na]$^+$, 95%); HRMS (ESI$^+$) found 332.02490 [[^{79}Br] M+Na]$^+$, 334.02277 [[^{81}Br] M+Na]$^+$, $C_{14}H_{16}O_2N^{79}BrNa^+$ requires 332.02566, $C_{14}H_{16}O_2N^{81}BrNa^+$ requires 334.02362; mp: 99-100 °C (EtOAc/petrol).

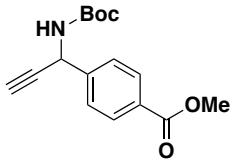
tert-Butyl [1-(4-cyanophenyl)prop-2-yn-1-yl]carbamate, 142



Prepared according to general procedure **D** using ethynylmagnesium bromide (12.6 mL, 0.5 M in THF, 5.90 mmol, 2.2 equiv.) and *α*-amido sulfone (*tert*-butyl ([4-cyanophenyl)(phenylsulfonyl)methyl]carbamate **129**) (1.00 g, 2.68 mmol, 1.0 equiv.) in THF (21 mL) for 2 hrs. The crude product was purified by flash column chromatography (5% EtOAc in petrol) to give *propargylic amine* **142** as a white solid (0.466 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.66 (4H, m, Ar-*H*), 5.73 (1H, d, *J* 6.0, NHC*H*), 5.15 (1H, br s, N*H*), 2.58 (1H, d, *J* 2.5, C*H*CCHNH), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 144.1, 132.5, 127.6, 118.5, 112.0, 80.9, 80.7, 74.2, 45.9, 28.3; IR: ν_{max} (neat)/cm^{-1} 3301, 2980, 1694, 1609, 1504, 1392, 1164, 1020, 733; LRMS (ESI$^+$): *m/z* 279 ([M+Na]$^+$, 100%), 257 ([M+H]$^+$, 10%); HRMS (ESI$^+$) found 279.11003 [M+Na]$^+$, $C_{15}H_{16}O_2N_2Na^+$ requires 279.11040; mp: 106-108 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

Methyl 4-{1-[(*tert*-butoxycarbonyl)amino]prop-2-yn-1-yl}benzoate, 143

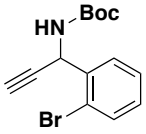


Prepared according to general procedure **D** using ethynylmagnesium bromide (13.9 mL, 0.5 M in THF, 6.51 mmol, 2.2 equiv.) and *α*-amido sulfone (methyl 4-{[(*tert*-butoxycarbonyl)amino](phenylsulfonyl)methyl}benzoate **130**) (1.20 g, 2.96 mmol, 1.0 equiv.) in THF (24 mL) for 2 hrs. The crude product was purified by flash column chromatography (5% EtOAc in petrol) to give *propargylic amine* **143** as a white solid (0.624 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.02 (2H, m, Ar-*H*), 7.58 (2H, d, *J* 8.0, Ar-*H*), 5.73 (1H, app br s, NHC*H*), 5.25 (1H, br s, N*H*), 3.92 (3H, s, CO_2CH_3), 2.54 (1H, d, *J* 2.5, C*H*CCHNH), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 166.7, 154.7, 143.8, 129.9, 129.8,

126.8, 81.4, 80.6, 73.6, 52.2, 45.9, 28.3; IR: ν_{max} (neat)/cm^{-1} 3304, 2984, 1704, 1612, 1509, 1280, 1162, 1019, 910, 732; LRMS (ESI$^+$): *m/z* 312 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 312.11994 [M+Na]$^+$, $C_{16}H_{19}O_4NNa^+$ requires 312.12063; mp: 110-111 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

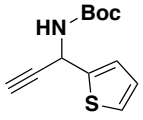
tert-Butyl [1-(2-bromophenyl)prop-2-yn-1-yl]carbamate, 144



Prepared according to general procedure **D** using ethynylmagnesium bromide (12.1 mL, 0.5 M in THF, 5.70 mmol, 2.2 equiv.) and α-amido sulfone (*tert*-butyl [(2-bromophenyl)(phenylsulfonyl)methyl]carbamate **132**) (1.10 g, 2.59 mmol, 1.0 equiv.) in THF (21 mL) for 2 hrs. The crude product was purified by flash column chromatography (5-20% EtOAc in petrol) to give *propargylic amine* **144** as a white solid (0.578 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.55 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.32 (1H, app td, *J* 8.0, 1.0, Ar-*H*), 7.16 (1H, app td, *J* 8.0, 1.5, Ar-*H*), 5.86 (1H, app br s, NHC*H*), 5.37 (1H, br s, N*H*), 2.48 (1H, d, *J* 2.5, C*H*CCHNH), 1.43 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.3, 137.8, 133.3, 129.7, 128.7, 127.8, 123.1, 81.4, 80.3, 73.2, 46.6, 28.3; IR: ν_{max} (neat)/cm^{-1} 3299, 2978, 1696, 1489, 1366, 1159, 1024, 753, 641; LRMS (ESI$^+$): *m/z* 334 ([^{81}Br] [M+Na]$^+$, 100%), 332 ([^{79}Br] [M+Na]$^+$, 95%); HRMS (ESI$^+$) found 332.02503 [[^{79}Br] M+Na]$^+$, 334.02289 [[^{81}Br] M+Na]$^+$, $C_{14}H_{16}O_2N^{79}BrNa^+$ requires 332.02566, $C_{14}H_{16}O_2N^{81}BrNa^+$ requires 334.02362; mp: 96-97 °C (EtOAc/petrol).

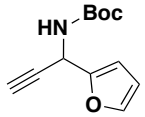
tert-Butyl [1-(thiophen-2-yl)prop-2-yn-1-yl]carbamate, 145



Prepared according to general procedure **D** using ethynylmagnesium bromide (6.60 mL, 0.5 M in THF, 3.10 mmol, 2.2 equiv.) and α-amido sulfone (*tert*-butyl [(phenylsulfonyl)(thiophen-2-yl)methyl]carbamate **133**) (0.50 g, 1.41 mmol, 1.0 equiv.) in THF (11 mL) for 2 hrs. The crude product was purified by flash column chromatography (10% EtOAc in petrol) to give *propargylic amine* **145** as a pale yellow solid (0.154 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (1H, dd, *J* 5.0, 1.0, SC*H*), 7.19 (1H, dd, *J* 3.5, 1.0, SCHCHC*H*), 6.97 (1H, dd, *J* 5.0, 3.5, SCHC*H*), 5.90 (1H, app br s, NHC*H*), 5.26 (1H, br s, N*H*), 2.53 (1H, d, *J* 2.5, C*H*CCHNH), 1.49 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.4, 142.6, 126.7, 125.7, 125.6, 81.5, 80.5, 72.5, 42.1, 28.3; IR: ν_{max} (neat)/cm^{-1} 3304, 2979, 1695, 1488, 1367, 1161, 1018, 909, 864, 731; LRMS (ESI$^+$): *m/z* 260 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 260.07123 [M+Na]$^+$, $C_{12}H_{15}O_2NSNa^+$ requires 260.07157; mp: 58-59 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

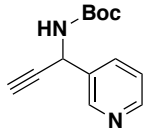
***tert*-Butyl [1-(furan-2-yl)prop-2-yn-1-yl]carbamate, 146**



Prepared according to general procedure **D** using ethynylmagnesium bromide (6.94 mL, 0.5 M in THF, 3.26 mmol, 2.2 equiv.) and *α*-amido sulfone (*tert*-butyl [furan-2-yl(phenylsulfonyl)methyl)]carbamate **135**) (0.50 g, 1.48 mmol, 1.0 equiv.) in THF (6 mL) for 45 mins. The crude product was purified by flash column chromatography (5-15% EtOAc in petrol) to give *propargylic amine* **146** as an off-white solid (0.14 g, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, dd, *J* 2.0, 1.0, OC*H*), 6.39 (1H, dd, *J* 3.0, 1.0, OCHCHC*H*), 6.34 (1H, dd, *J* 3.0, 2.0, OCHC*H*), 5.71 (1H, d, *J* 6.0, NHC*H*), 5.19 (1H, br s, N*H*), 2.44 (1H, d, *J* 2.5, C*H*CCHNH), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.5, 150.8, 142.8, 110.4, 107.4, 80.5, 80.0, 71.9, 40.5, 28.3; IR: ν_{max} (neat)/cm^{-1} 3299, 2980, 1698, 1503, 1392, 1246, 1166, 1012, 862, 740, 656; LRMS (ESI$^+$): *m/z* 244 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 244.09413 [M+Na]$^+$, $C_{12}H_{15}O_3NNa^+$ requires 244.09441; mp: 71-72 °C (EtOAc/petrol). ^{1}H and ^{13}C NMR data is consistent with literature.[169]

***tert*-Butyl [1-(pyridin-3-yl)prop-2-yn-1-yl]carbamate, 147**

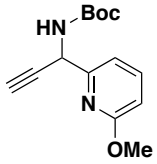


Prepared according to general procedure **D** using ethynylmagnesium bromide (16.1 mL, 0.47 M in THF, 7.57 mmol, 2.2 equiv.) and *α*-amido sulfone (*tert*-butyl

[(phenylsulfonyl)(pyridin-3-yl)methyl]carbamate **136**) (1.20 g, 3.44 mmol, 1.0 equiv.) in THF (27 mL) for 2 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **147** as a brown oil (67.2 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (1H, s, Ar-*H*), 8.55 (1H, d, *J* 4.0, Ar-*H*), 7.82 (1H, app dt, *J* 8.0, 1.5, Ar-*H*), 7.29 (1H, dd, *J* 7.0, 4.5, Ar-*H*), 5.71 (1H, app br s, NHC*H*), 5.55 (1H, br s, N*H*), 2.56 (1H, d, *J* 2.5, C*H*CCHNH), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 154.7, 149.3, 148.5, 134.6, 129.5, 123.4, 80.9, 80.6, 73.9, 44.2, 28.3; IR: ν_{max} (neat)/cm^{-1} 3284, 2999, 1689, 1520, 1249, 1166; LRMS (ESI$^+$): *m/z* 233 ([M+H]$^+$, 100%), 255 ([M+Na]$^+$, 15%); HRMS (ESI$^+$) found 233.12817 [M+H]$^+$, $C_{13}H_{17}O_2N_2^+$ requires 233.12845.

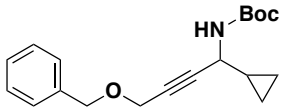
***tert*-Butyl [1-(6-methoxypyridin-2-yl)prop-2-yn-1-yl]carbamate, 148**



Prepared according to general procedure **D** using ethynylmagnesium bromide (17.8 mL, 0.5 M in THF, 8.71 mmol, 2.2 equiv.) and α-amido sulfone (*tert*-butyl [(6-methoxypyridin-2-yl)(phenylsulfonyl)methyl]carbamate **137**) (1.50 g, 3.96 mmol, 1.0 equiv.) in THF (32 mL) for 2 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **148** as a light brown solid (0.522 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (1H, dd, *J* 8.0, 7.5, Ar-*H*), 7.02 (1H, d, *J* 7.5, Ar-*H*), 6.71 (1H, d, *J* 8.0, Ar-*H*), 5.67 (1H, app br s, NHC*H*), 5.58 (1H, br s, N*H*), 3.98 (3H, s, OCH_3), 2.42 (1H, d, *J* 2.5, C*H*CCHNH), 1.50 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 163.9, 154.9, 154.0, 139.5, 113.9, 110.3, 82.3, 80.2, 72.0, 53.5, 47.0, 28.4; IR: ν_{max} (neat)/cm^{-1} 3299, 2931, 1701, 1493, 1167, 908, 731; LRMS (ESI$^+$): *m/z* 263 ([M+H]$^+$, 100%), 285 ([M+Na]$^+$, 35%); HRMS (ESI$^+$) found 285.12029 [M+Na]$^+$, $C_{14}H_{18}O_3N_2Na^+$ requires 285.12096; mp: 42-43 °C (EtOAc/petrol).

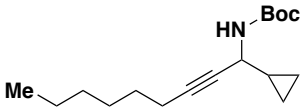
tert-Butyl [4-(benzyloxy)-1-cyclopropylbut-2-yn-1-yl]carbamate, 150



Prepared according to general procedure **E** using *n*-butyllithium (0.56 mL, 2.25 M in hexanes, 1.25 mmol, 2.05 equiv.), [(prop-2-yn-1-yloxy)methyl]benzene (0.18 mg, 1.22 mmol, 2.0 equiv.) in THF (3.0 mL) and α-amido sulfone (*tert*-butyl [cyclopropyl(phenylsulfonyl)methyl]carbamate **124**) (0.20 g, 0.61 mmol, 1.0 equiv.) in THF (4.0 mL). The mixture was stirred for 30 mins. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **150** as a colourless oil (0.134 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.36 (4H, m, Ar-*H*), 7.35-7.33 (1H, m, Ar-*H*), 4.84 (1H, br s, N*H*), 4.60 (2H, s, OCH_2Ar), 4.50 (1H, app br s, NHC*H*), 4.19 (2H, d, *J* 2.0, OCH_2CCCH), 1.49 (9H, s, $CO_2C(CH_3)_3$), 1.19-1.14 (1H, m, NHCHC*H*), 0.54-0.47 (4H, m, NHCHCH(CH_2)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.8, 137.4, 128.4, 128.2, 127.9, 84.0, 78.8, 71.5, 57.3, 45.7, 28.4, 15.4, 2.8, 1.7; IR: ν_{max} (neat)/cm^{-1} 3338, 2979, 1701, 1495, 1366, 1159, 1069, 909, 732; LRMS (ESI$^+$): *m/z* 338 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 338.17132 [M+Na]$^+$, $C_{19}H_{25}O_3NNa^+$ requires 338.17266.

tert-Butyl (1-cyclopropyldec-2-yn-1-yl)carbamate, 151

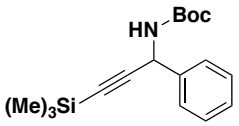


Prepared according to general procedure **E** using ethylmagnesium bromide (2.2 mL, 1.0 M in THF, 2.2 mmol, 2.05 equiv.), 1-octyne (0.32 mL, 2.16 mmol, 2.0 equiv.) in THF (3.8 mL), α-amido sulfone (*tert*-butyl [cyclopropyl(phenylsulfonyl)methyl]carbamate **124**) (0.35 g, 1.08 mmol, 1.0 equiv.) in THF (7.5 mL). The mixture was stirred for 4 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **151** as a colourless oil (0.22 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (1H, app br s, NHC*H*), 4.48 (1H, br s, N*H*), 2.16 (2H, td, *J* 7.0, 2.0, CH_2(CH_2)$_4$$CH_3$), 1.64-1.56 (2H, m, C$H_2$($CH_2$)$_3$$CH_3$), 1.48 (9H, s, $CO_2C(CH_3)_3$),

1.39-1.28 (6H, m, $(CH_2)_3CH_3$), 1.17-1.09 (1H, m, NHCHC*H*), 0.91 (3H, t, *J* 7.0, $(CH_2)_5CH_3$), 0.49-0.42 (4H, m, NHCHCH(CH_2)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 154.9, 83.7, 79.6, 69.8, 31.3, 28.7, 28.4, 22.5, 18.6, 15.4, 14.0, 10.4, 2.6, 1.2; IR: ν_{max} (neat)/cm^{-1} 2928, 2861, 1710, 1494, 1320, 1241, 1017, 912, 732; LRMS (ESI$^+$): *m/z* 302 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 302.20866 [M+Na]$^+$, $C_{17}H_{29}O_2NNa^+$ requires 302.20905.

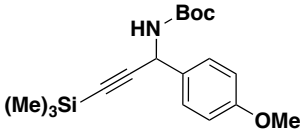
***tert*-Butyl [1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl]carbamate, 152**



Prepared according to general procedure **E** using *n*-butyllithium (3.48 mL, 1.8 M in hexanes, 6.27 mmol, 2.1 equiv.), trimethylsilylacetylene (0.86 mL, 6.12 mmol, 2.0 equiv.) in THF (22 mL) and α-amido sulfone (*tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate **125**) (0.80 g, 3.06 mmol, 1.0 equiv.) in THF (10 mL). The mixture was stirred for 1 hr. The crude product was purified by flash column chromatography (20% EtOAc in petrol) to give *propargylic amine* **152** as a white solid (0.69 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (2H, d, *J* 7.5, Ar-*H*), 7.40-7.36 (2H, m, Ar-*H*), 7.34-7.30 (1H, m, Ar-*H*), 5.70 (1H, app br s, NHC*H*), 5.04 (1H, br s, N*H*), 1.48 (9H, s, $CO_2C(CH_3)_3$), 0.22 (9H, s, $SiC(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 139.4, 128.6, 127.9, 126.9, 103.7, 89.5, 67.9, 46.9, 28.4, –0.10; IR: ν_{max} (neat)/cm^{-1} 2965, 1699, 1494, 1367, 1309, 1249, 1165, 1022; LRMS (ESI$^+$): *m/z* 326 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 326.1536 [M+Na]$^+$, $C_{17}H_{25}NO_2SiNa^+$ requires 326.1547; mp: 94-95 °C (EtOAc/petrol).

***tert*-Butyl [1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-yl]carbamate, 153**

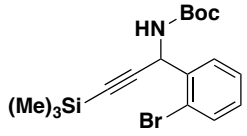


Prepared according to general procedure **E** using *n*-butyllithium (4.36 mL, 2.5 M in hexanes, 10.9 mmol, 2.05 equiv.), trimethylsilylacetylene (1.50 mL, 10.6 mmol, 2.0 equiv.) in THF (3.7 mL) and α-amido sulfone (*tert*-butyl [(4-methoxyphenyl)(phenylsulfonyl)methyl]carbamate **126**) (2.00 g, 5.30 mmol, 1.0 equiv.) in

THF (15.1 mL). The mixture was stirred for 1 hr. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **153** as a white solid (1.67 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (2H, d, *J* 8.5, Ar-*H*), 6.91 (2H, d, *J* 8.5, Ar-*H*), 5.64 (1H, d, *J* 6.0, NHC*H*), 5.01 (1H, br s, N*H*), 3.83 (3H, s, OCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$), 0.22 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 154.7, 131.6, 128.2, 113.9, 103.9, 89.2, 80.0, 55.3, 46.4, 28.4, –0.10; IR: ν_{max} (neat)/cm^{-1} 2964, 2341, 1704, 1612, 1510, 1305, 1249, 1029, 909, 732; LRMS (ESI$^+$): *m/z* 356 ([M+Na]$^+$, 100%), 689 ([2M+Na]$^+$, 20%); HRMS (ESI$^+$) found 356.16504 [M+Na]$^+$, $C_{18}H_{27}NO_3SiNa^+$ requires 356.16524; mp: 89-90 °C (EtOAc/petrol).

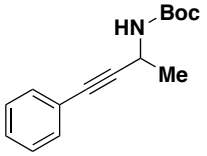
***tert*-Butyl [1-(2-bromophenyl)-3-(trimethylsilyl)prop-2-yn-1-yl]carbamate, 154**



Prepared according to general procedure **E** using ethylmagnesium bromide (4.1 mL, 1.0 M in THF, 4.1 mmol, 2.2 equiv.), trimethylsilylacetylene (0.58 mL, 4.1 mmol, 2.2 equiv.) in THF (5 mL) and *α*-amido sulfone (*tert*-butyl [(2-bromophenyl)(phenylsulfonyl)methyl]carbamate **132**) (0.80 g, 1.88 mmol, 1.0 equiv.) in THF (10 mL). The mixture was stirred for 2 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **154** as a white solid (0.64 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.57 (2H, m, Ar-*H*), 7.35 (1H, app td, *J* 8.0, 1.0, Ar-*H*), 7.19 (1H, app td, *J* 8.0, 1.0, Ar-*H*), 5.84 (1H, app br s, NHC*H*), 5.16 (1H, br s, N*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$), 0.19 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 154.2, 138.3, 133.4, 129.5, 128.8, 127.7, 123.2, 102.7, 89.6, 80.2, 47.5, 28.3, –0.20; IR: ν_{max} (neat)/cm^{-1} 3252, 2985, 1703, 1486, 1250, 1165, 909, 842, 758; LRMS (ESI$^+$): *m/z* 406 ([^{81}Br] [M+Na]$^+$, 100%), 404 ([^{79}Br] [M+Na]$^+$, 95%); HRMS (ESI$^+$) found 404.06437 [[^{79}Br] M+Na]$^+$], 406.06214 [[^{81}Br] M+Na]$^+$], $C_{17}H_{24}O_2N^{79}BrSiNa^+$ requires 404.06519, $C_{17}H_{24}O_2N^{81}BrSiNa^+$ requires 406.06314; mp: 87-88 °C (EtOAc/petrol).

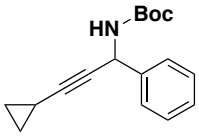
tert-Butyl (4-phenylbut-3-yn-2-yl)carbamate, 155



Prepared according to general procedure **E** using *n*-butyllithium (2.7 mL, 2.5 M in hexanes, 6.7 mmol, 2.05 equiv.), phenylacetylene (0.73 mL, 6.60 mmol, 2.0 equiv.) in THF (25.5 mL), α-amido sulfone (*tert*-butyl (1-tosylethyl)carbamate **122**) (1.0 g, 3.3 mmol, 1.0 equiv.) in THF (8.5 mL). The mixture was stirred for 1.5 hrs. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to give *propargylic amine* **155** as a white solid (0.40 g, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (2H, dd, *J* 7.0, 3.0, Ar-*H*), 7.33-7.31 (3H, m, Ar-*H*), 4.85 (1H, app br s, NHC*H*), 4.75 (1H, br s, N*H*), 1.51 (3H, app s, NHCH(C*H*$_3$)), 1.50 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 131.7, 131.5, 128.2, 122.8, 89.8, 82.1, 79.8, 39.0, 28.4, 22.9; LRMS (ESI$^+$): *m/z* 264 ([M+Na]$^+$, 100%), 242 ([M+H]$^+$, 20%); mp: 84-85 °C (Et_2O/petrol), (lit. mp: 78-80 °C). This data is consistent with literature.[268]

tert-Butyl (3-cyclopropyl-1-phenylprop-2-yn-1-yl)carbamate, 156

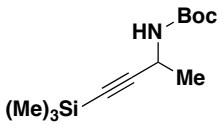


Prepared according to general procedure **E** using ethylmagnesium bromide (3.2 mL, 1.0 M in THF, 3.2 mmol, 2.2 equiv.), cyclopropylacetylene (0.27 mL, 3.2 mmol, 2.2 equiv.) in THF (3.0 mL) and α-amido sulfone (*tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate **125**) (0.50 g, 1.44 mmol, 1.0 equiv.) in THF (8.6 mL). The mixture was stirred for 4 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **156** as a colourless oil (0.22 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (2H, d, *J* 7.5, Ar-*H*), 7.39-7.34 (2H, m, Ar-*H*), 7.33-7.29 (1H, m, Ar-*H*), 5.62 (1H, app br s, NHC*H*), 5.01 (1H, br s, N*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.35-1.28 (1H, m, CCC*H*$(CH_2)_2$), 0.83-0.78 (2H, m, CHC*H*$_2$), 0.74 (2H, dt, *J* 5.0, 3.0, CHC*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 154.8, 140.2, 128.5, 127.7, 126.8, 88.4, 85.2, 73.5,

46.4, 28.4, 8.2, –0.50; IR: ν_{max} (neat)/cm^{-1} 3330, 2978, 1692, 1493, 1367, 1159, 1017, 899, 698; LRMS (ESI$^+$): *m/z* 294 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 294.1467 [M+Na]$^+$, $C_{17}H_{21}O_2NNa^+$ requires 294.1464; mp: 89-90 °C (CH_2Cl_2/petrol).

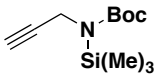
tert-Butyl [4-(trimethylsilyl)but-3-yn-2-yl]carbamate, 157



Prepared according to general procedure **E** using ethylmagnesium bromide (5.40 mL, 1.0 M in THF, 5.39 mmol, 2.2 equiv.), trimethylsilylacetylene (0.76 mL, 5.39 mmol, 2.2 equiv.) in THF (6.5 mL) and α-amido sulfone (*tert*-butyl (1-tosylethyl)carbamate **122**) (0.70 g, 2.45 mmol, 1.0 equiv.) in THF (13.5 mL). The mixture was stirred for 4 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to give *propargylic amine* **157** as a white solid (0.32 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (1H, app br s, NHC*H*), 4.50 (1H, br s, N*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.39 (3H, d, *J* 7.0, CHCH_3), 0.17 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.6, 106.4, 86.4, 79.7, 39.1, 28.4, 22.9, –0.10; IR: ν_{max} (neat)/cm^{-1} 3321, 2980, 1698, 1495, 1250, 1163, 909; LRMS (ESI$^+$): *m/z* 264 ([M+Na]$^+$, 100%), 242 ([M+H]$^+$, 20%); HRMS (ESI$^+$) found 264.13878 [M+Na]$^+$, $C_{12}H_{23}O_2NSiNa^+$ requires 264.13903; mp: 59-60 °C (CH_2Cl_2/petrol).

***tert*-Butyl prop-2-yn-1-yl(trimethylsilyl)carbamate**

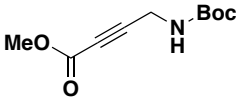


Prepared according to a procedure adapted from Trost *et. al.*[136] A flame-dried flask was charged with *N*-Boc propargyl amine (2.50 g, 16.1 mmol, 1.0 equiv.) and CH_2Cl_2 (32 mL) was added under an inert atmosphere. Et_3N (2.50 mL, 17.7 mmol, 1.1 equiv.) was added to the reaction mixture at 0 °C followed by the dropwise addition of TMS-trifluoromethanesulfonate (3.20 mL, 17.7 mmol, 1.1 equiv.). After 5 mins the reaction mixture was warmed to room temperature and stirred for 30 mins. The reaction was then quenched by the addition of sat. $NaHCO_{3(aq.)}$ (25 mL). The product was extracted in CH_2Cl_2

(3 × 10 mL) and washed with brine (10 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford the *N*-TMS, *N*-Boc propargyl amine (0.75 g, 16%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (2H, app br s, NCH_2), 2.17 (1H, t, *J* 2.5, C*H*CCH_2), 1.51 (9H, s, $CO_2C(CH_3)_3$), 0.31 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 157.7, 82.2, 80.6, 70.0, 33.4, 28.4, 0.5; LRMS (ESI$^+$): *m/z* 250 ([M+Na]$^+$, 100%). This data is consistent with literature.[136]

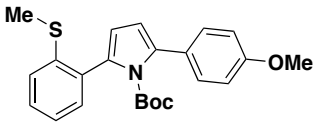
Methyl 4-[(*tert*-butoxycarbonyl)amino]but-2-ynoate, 158



Prepared according to a procedure adapted from Trost *et. al.*[136] Diisopropylamine (0.58 mL, 4.16 mmol, 1.3 equiv.) was dissolved in THF (8 mL) under an inert atmosphere and cooled to 0 °C. *n*-Butyllithium (2.5 mL, 1.6 M in hexanes, 4.0 mmol, 1.25 equiv.) was added and stirred for 30 mins. The reaction mixture was then cooled to −78 °C and *N*-TMS, *N*-Boc propargyl amine (0.73 g, 3.2 mmol, 1.0 equiv.) in THF (7 mL) was added and stirred at −78 °C for 1 hr. Methyl chloroformate (0.25 mL, 3.25 mmol, 1.1 equiv.) was then added in THF (5 mL) *via* cannula. The reaction mixture was warmed to room temperature over 16 hrs. Upon completion, an aqueous solution of HCl (10 mL, 2 M) was added and the biphasic mixture was stirred at room temperature for 1 hr. The phases were separated and the product was extracted with Et_2O (3 × 10 mL) and washed with brine (10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford propargylic amine **158** as a viscous oil, which solidified in the freezer to a waxy solid (0.125 g, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.94 (1H, br s, N*H*), 4.08 (2H, d, *J* 5.0, NHCH_2), 3.77 (3H, s, CO_2CH_3), 1.45 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 155.1, 153.6, 84.3, 80.4, 74.5, 52.8, 30.3, 28.3; LRMS (ESI$^+$): *m/z* 236 ([M+Na]$^+$, 100%); mp: 39-40 °C (CH_2Cl_2/petrol), (lit. mp: 38-39 °C). This data is consistent with literature.[136]

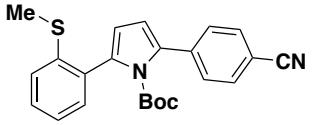
tert-Butyl 2-(4-methoxyphenyl)-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 159



Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(4-methoxyphenyl)prop-2-yn-1-yl]carbamate **139**) (51.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (70 μL, 1.0 M). After stirring for 2 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **159** as colourless oil (46.8 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.35 (3H, m, Ar-*H*), 7.32 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.25 (1H, d, *J* 7.5, Ar-*H*), 7.21 (1H, app t, *J* 7.5, Ar-*H*), 6.94 (2H, d, *J* 8.5, Ar-*H*), 6.25 (1H, d, *J* 3.5, NCC*H*), 6.22 (1H, d, *J* 3.5, NCC*H*), 3.87 (3H, s, OCH_3), 2.40 (3H, s, SCH_3), 1.15 (9H, s $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 149.3, 139.8, 135.9, 134.1, 133.2, 130.6, 130.0, 128.3, 127.0, 124.5, 124.3, 113.2, 112.9, 112.1, 83.1, 55.3, 27.1, 15.4; IR: ν_{max} (neat)/cm^{-1} 2979, 1744, 1613, 1493, 1367, 1302, 1246, 1176, 730; LRMS (ESI$^+$): *m/z* 418 ([M+Na]$^+$, 100%), 396 ([M+H]$^+$, 90%); HRMS (ESI$^+$) found 396.16249 [M+H]$^+$, $C_{23}H_{26}O_3NS^+$ requires 396.16279.

tert-Butyl 2-(4-cyanophenyl)-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 160

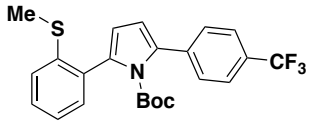


Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(4-cyanophenyl)prop-2-yn-1-yl]carbamate **142**) (50.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (81 μL, 1.0 M). After stirring for 2 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (29 mg, 0.15 mmol, 1.0 equiv.) were added

and stirred at room temperature for a further 16 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **160** as colourless oil (44.6 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.66 (2H, m, Ar-*H*), 7.54-7.51 (2H, m, Ar-*H*), 7.40 (1H, ddd, *J* 8.0, 7.5, 2.0, Ar-*H*), 7.31-7.29 (1H, m, Ar-*H*), 7.26 (1H, d, *J* 7.0, Ar-*H*), 7.22 (1H, app td, *J* 7.5, 2.0, Ar-*H*), 6.40 (1H, d, *J* 3.5, NCC*H*), 6.25 (1H, d, *J* 3.5, NCC*H*), 2.41 (3H, s, SCH_3), 1.15 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 139.8, 138.8, 135.2, 134.1, 133.4, 131.6, 130.5, 129.0, 128.8, 124.5, 124.4, 119.1, 114.5, 113.4, 110.3, 84.0, 27.1, 15.3; IR: ν_{max} (neat)/cm^{-1} 2980, 2226, 1745, 1607, 1454, 1301, 1255, 1146, 909; LRMS (ESI$^+$): *m/z* 413 ([M+Na]$^+$, 100%), 391 ([M+H]$^+$, 20%); HRMS (ESI$^+$) found 413.12903 [M+Na]$^+$, $C_{23}H_{22}O_2N_2SNa^+$ requires 413.12942.

***tert*-Butyl 2-[2-(methylthio)phenyl]-5-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-1-carboxylate, 161**

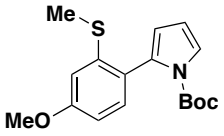


Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl {1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-yl}carbamate **140**) (88.4 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (73 μL, 1.0 M). After stirring for 2 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (28.5 mg, 0.15 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 2 hrs. The crude product was purified by flash column chromatography on silica (5-10% Et_2O in petrol) to afford *pyrrole* **161** as colourless oil (65.0 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* 8.0, Ar-*H*), 7.56 (2H, d, *J* 8.0, Ar-*H*), 7.40 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 7.33 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.27 (1H, d, *J* 8.0, Ar-*H*), 7.25-7.21 (1H, m, Ar-*H*), 6.38 (1H, d, *J* 3.5, NCC*H*), 6.26 (1H, d, *J* 3.5, NCC*H*), 2.42 (3H, s, SCH_3), 1.16 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.0, 139.9, 137.9, 134.6, 134.5, 133.6, 130.6, 128.9 (q, $^2J_{CF}$ 32.5), 128.8, 128.7, 124.7 (q, $^3J_{CF}$ 3.5), 124.5, 124.4, 124.3 (q,

$^{1}J_{CF}$ 272.0), 113.9, 113.2, 83.7, 27.1, 15.3; IR: ν_{max} (neat)/cm^{-1} 2982, 1747, 1618, 1369, 1324, 1147, 1124, 908; LRMS (ESI^{+}): *m/z* 456 ([M+Na]$^{+}$, 100%), 434 ([M+H]$^{+}$, 20%); HRMS (ESI^{+}) found 456.12042 [M+Na]$^{+}$, $C_{23}H_{22}O_2NF_3SNa^{+}$ requires 456.12156.

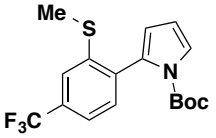
tert-Butyl 2-[4-methoxy-2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 162



Prepared according to general procedure **Ga** using 4-methoxy-2-(methylthio)benzaldehyde (27.3, 0.15 mmol, 1.0 equiv.), *N*-Boc propargyl amine **59** (30.3 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (92 μL, 1.0 M). After stirring for 1 hr at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 1 hr. The crude product was purified by flash column chromatography on silica (5-10% Et$_2$O in petrol) to afford *pyrrole* **162** as colourless oil (31.2 mg, 65%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.42 (1H, dd, *J* 3.5, 2.0, NC*H*), 7.17 (1H, d, *J* 8.5, Ar-*H*), 6.80 (1H, d, *J* 2.5, Ar-*H*), 6.71 (1H, dd, *J* 8.5, 2.5, Ar-*H*), 6.29 (1H, app t, *J* 3.5, NCHC*H*), 6.16 (1H, dd, *J* 3.5, 2.0, NCC*H*), 3.87 (3H, s, OC*H*$_3$), 2.37 (3H, s, SC*H*$_3$), 1.33 (9H, s, CO$_2$C(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 159.8, 149.2, 141.3, 131.7, 131.2, 126.5, 121.6, 114.5, 111.3, 110.4, 108.7, 83.0, 55.4, 27.5, 15.4; IR: ν_{max} (neat)/cm^{-1} 2942, 1735, 1601, 1566, 1460, 1393, 1369, 1254, 839; LRMS (ESI^{+}): *m/z* 342 ([M+Na]$^{+}$, 100%), 320 ([M+H]$^{+}$, 60%); HRMS (ESI^{+}) found 342.1127 [M+Na]$^{+}$, $C_{17}H_{21}O_3NSNa^{+}$ requires 342.1134.

tert-Butyl 2-[2-(methylthio)-4-(trifluoromethyl)phenyl]-1*H*-pyrrole-1-carboxylate, 163

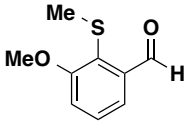


Prepared according to general procedure **Ga** using 2-(methylthio)-4-(trifluoromethyl)benzaldehyde **93** (33.0 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargyl amine **59** (30.3 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (2.8 mg, 5 mol%) and PNP(Cy)

(3.2 mg, 5 mol%) in acetone (87 μL, 1.0 M). After stirring for 2 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 16 hrs. The crude product was purified by flash column chromatography on silica (5-10% Et_2O in petrol) to afford *pyrrole* **163** as colourless oil (33.7 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (1H, dd, *J* 3.5, 2.0, NC*H*), 7.45-7.42 (2H, m, Ar-*H*), 7.36 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 6.33 (1H, app t, *J* 3.5, NCHC*H*), 6.21 (1H, dd, *J* 3.5, 2.0, NCC*H*), 2.43 (3H, s, SCH_3), 1.30 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.5, 148.8, 141.8, 137.3, 130.6 (q, $^2J_{CF}$ 32.5), 130.4, 125.2 (q, $^1J_{CF}$ 272.5), 122.3, 121.0 (q, $^3J_{CF}$ 3.5), 120.8 (q, $^3J_{CF}$ 3.5), 114.9, 110.8, 83.6, 27.4, 15.2; IR: ν_{max} (neat)/cm^{-1} 2944, 1742, 1394, 1370, 1270, 1151, 1081, 976, 845; LRMS (ESI$^+$): *m/z* 380 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 380.08963 [M+Na]$^+$, $C_{17}H_{18}O_2NF_3Na^+$ requires 380.09026.

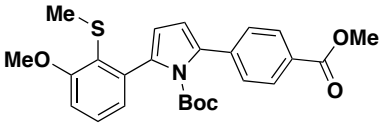
3-Methoxy-2-(methylthio)benzaldehyde



Prepared according to general procedure **A** using methanethiol sodium salt solution (1.28 mL, 3.0 M in water, 3.84 mmol, 1.2 equiv.) and 2-fluoro-3-methoxybenzaldehyde (0.50 g, 3.20 mmol, 1.0 equiv.) in DMF (4 mL). The crude was purified by flash column chromatography (20% Et_2O in petrol) to obtain the title *aldehyde* as a white solid (0.27 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.80 (1H, s, C*H*O), 7.53 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.41 (1H, app t, *J* 8.0, Ar-*H*), 7.14 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 3.98 (3H, s, OCH_3), 2.43 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.6, 160.4, 138.5, 129.4, 128.7, 120.2, 115.8, 56.3, 18.9; IR: ν_{max} (neat)/cm^{-1} 2750, 1691, 1571, 1464, 1264, 1237, 1064, 906; LRMS (ESI$^+$): *m/z* 205 ([M+Na]$^+$, 100%), 183 ([M+H]$^+$, 25%); HRMS (ESI$^+$) found *m/z* 183.04719 [M+H]$^+$, $C_9H_{11}O_2S^+$ requires 183.04743; mp: 59-60 °C (EtOAc/hexane).

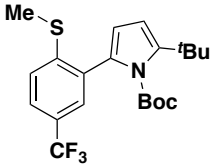
tert-Butyl 2-[3-methoxy-2-(methylthio)phenyl]-5-[4-(methoxycarbonyl)phenyl]-1*H*-pyrrole-1-carboxylate, 164



Prepared according to general procedure **Ga** using 3-methoxy-2-(methylthio)benzaldehyde (24.3 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (methyl 4-{1-[(*tert*-butoxycarbonyl)amino]prop-2-yn-1-yl}benzoate **143**) (56.4 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (66 μL, 1.0 M). After stirring for 2 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 16 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **164** as colourless oil (52.7 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (2H, d, *J* 8.5, Ar-*H*), 7.50 (2H, d, *J* 8.5, Ar-*H*), 7.33 (1H, dd, *J* 8.0, 7.5, Ar-*H*), 7.04-6.97 (2H, m, Ar-*H*), 6.36 (1H, d, *J* 3.5, NCC*H*), 6.18 (1H, d, *J* 3.5, NCC*H*), 3.98 (3H, s, CO_2CH_3), 3.96 (3H, s, $ArOCH_3$), 2.26 (3H, s, SCH_3), 1.16 (9H, s, $CO_2C(CH_3)_3$)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 140.1, 139.2, 134.4, 130.4, 130.0, 129.7, 129.1, 128.3, 128.2, 123.4, 123.0, 120.8, 113.7, 112.7, 110.8, 83.9, 56.0, 52.1, 27.2, 17.9; IR: ν_{max} (neat)/cm^{-1} 2979, 2838, 1607, 1275, 1111, 994; LRMS (ESI$^+$): *m/z* 476 ([M+Na]$^+$, 100%), 454 ([M+H]$^+$, 10%); HRMS (ESI$^+$) found 454.16850 [M+H]$^+$, $C_{25}H_{28}O_5NS^+$ requires 454.16827.

tert-Butyl 2-(_tert_-butyl)-5-[2-(methylthio)-5-(trifluoromethyl)phenyl]-1*H*-pyrrole-1-carboxylate, 165

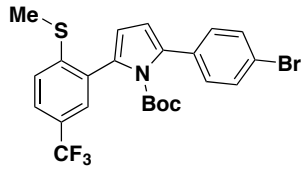


Prepared according to general procedure **Ga** using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **203** (33.3 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (4,4-dimethylpent-1-yn-3-yl)carbamate **84**) (41.2 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (76 μL, 1.0 M).

After stirring for 2 mins at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography on silica (5-10% Et_2O in petrol) to afford *pyrrole* **165** as colourless oil (52.1 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (1H, ddd, *J* 8.5, 2.0, 0.5, Ar-*H*), 7.48 (1H, d, *J* 2.0, Ar-*H*), 7.25 (1H, d, *J* 8.5, Ar-*H*), 6.13 (1H, d, *J* 3.5, NCC*H*), 6.12 (1H, d, *J* 3.5, NCC*H*), 2.41 (3H, s, SCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.15 (9H, s, $NCC(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 151.2, 146.1, 145.6, 134.8, 131.3, 127.5 (q, $^3J_{CF}$ 3.5), 127.1 (q, $^1J_{CF}$ 281.0), 126.6 (q, $^2J_{CF}$ 33.0), 124.9 (q, $^3J_{CF}$ 3.5), 123.6, 112.2, 108.3, 83.8, 33.6, 30.8, 27.4, 15.3; IR: ν_{max} (neat)/cm^{-1} 2970, 1751, 1608, 1394, 1369, 1155, 1125, 1007, 790; LRMS (ESI$^+$): *m/z* 436 ([M+Na]$^+$, 100%), 414 ([M+H]$^+$, 20%); HRMS (ESI$^+$) found 414.17083 [M+H]$^+$, $C_{21}H_{27}O_2NF_3S^+$ requires 414.17091.

tert-Butyl-2-(4-bromophenyl)-5-[2-(methylthio)-5-(trifluoromethyl)-phenyl]-1*H*-pyrrole-1-carboxylate, 166

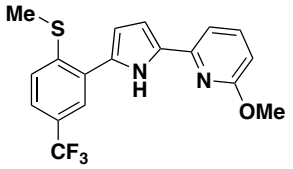


Prepared according to general procedure **Ga** using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **203** (33 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(4-bromophenyl)prop-2-yn-1-yl]carbamate **141**) (60.5 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (57 μL, 1.0 M). After stirring for 2 mins at room temperature, acetonitrile (1.5 mL) and *p*-TSA (51.0 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **166** as a waxy white sold (50.1 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, ddd, *J* 8.5, 2.0, 0.5, Ar-*H*), 7.54-7.51 (3H, m, Ar-*H*), 7.30 (3H, app dq, *J* 9.0, 3.0, Ar-*H*), 6.32 (1H, d, *J* 3.5, NCC*H*), 6.27 (1H, d, *J* 3.5, NCC*H*), 2.45 (3H, s, SCH_3), 1.14 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.7, 145.3, 135.5, 133.7, 133.0, 132.1, 130.9, 130.4, 127.1 (q, $^3J_{CF}$ 3.5), 126.3 (q, $^2J_{CF}$ 33.0), 125.1 (q,

$^{3}J_{CF}$ 3.5), 124.1 (q, $^{1}J_{CF}$ 262.0), 123.4, 121.4, 113.7, 113.3, 83.9, 27.1, 14.9; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −62.1; IR: ν_{max} (neat)/cm^{-1} 2943, 1749, 1609, 1475, 1369, 1171, 1121, 991, 792; LRMS (ESI$^+$): *m/z* 536 ([^{81}Br] [M+Na]$^+$, 100%), 534 ([^{79}Br] [M+Na]$^+$, 90%), 514 ([^{81}Br] [M+H]$^+$, 50%), 512 ([^{79}Br] [M+H]$^+$, 40%); HRMS (ESI$^+$) found 534.03119 [[^{79}Br] M+Na]$^+$, 536.02904 [[^{81}Br] M+Na]$^+$, $C_{23}H_{21}{}^{79}BrNO_2F_3SNa^+$ requires 534.03207, $C_{23}H_{21}{}^{81}BrNO_2SF_3Na^+$ requires 536.03002; mp: 88-89 °C (Et_2O/petrol).

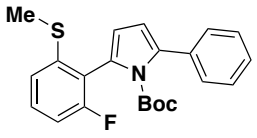
2-Methoxy-6-{5-[2-(methylthio)-5-(trifluoromethyl)phenyl]-1*H*-pyrrol-2-yl}pyridine, 167



Prepared according to general procedure **Ga** using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **203** (33.0 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(6-methoxypyridin-2-yl)prop-2-yn-1-yl]carbamate **148**) (59 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (4.1 mg, 7.5 mol%) and PNP(Cy) (5.2 mg, 7.5 mol%) in acetone (60 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 4 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **167** as pale brown oil (41.0 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (1H, br s, N*H*), 7.76 (1H, app td, *J* 1.5, 0.5, Ar-*H*), 7.59 (1H, dd, *J* 8.0, 7.5, Ar-*H*), 7.50-7.48 (1H, m, Ar-*H*), 7.44 (1H, d, *J* 8.5, Ar-*H*), 7.21 (1H, dd, *J* 7.5, 0.5, Ar-*H*), 6.79 (1H, app dd, *J* 4.0, 2.5, NCC*H*), 6.66 (1H, app dd, *J* 4.0, 2.5, NCC*H*), 6.58 (1H, dd, *J* 8.0, 0.5, Ar-*H*), 4.03 (3H, s, OC*H*$_3$), 2.52 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.5, 147.6, 139.6, 139.3, 132.6, 132.0, 130.2, 127.9 (q, $^{2}J_{CF}$ 32.5), 127.7, 125.3 (q, $^{3}J_{CF}$ 3.5), 124.1 (q, $^{1}J_{CF}$ 272.0), 123.5 (q, $^{3}J_{CF}$ 3.5), 112.0, 110.8, 108.0, 107.6, 53.3, 16.5; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −62.5; IR: ν_{max} (neat)/cm^{-1} 3429, 2923, 1573, 1471, 1423, 1374, 1328, 1260, 1096, 907; LRMS (ESI$^+$): *m/z* 365 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 365.09313 [M+H]$^+$, $C_{18}H_{16}ON_2F_3S^+$ requires 365.09299.

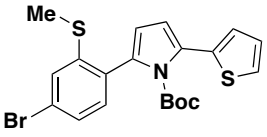
tert-Butyl 2-[2-fluoro-6-(methylthio)phenyl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 168



Prepared according to general procedure **Ga** using 2-fluoro-6-(methylthio)benzaldehyde **92** (25.5 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **83**) (45.1 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (79 μL, 1.0 M). After stirring for 1.5 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.225 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 16 hrs. The crude product was purified by flash column chromatography (10% EtOAc in petrol) to afford *pyrrole* **168** as a cream oil (18.4 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.40 (3H, m, Ar-*H*), 7.39-7.35 (2H, m, Ar-*H*), 7.34-7.31 (1H, m, Ar-*H*), 7.03 (1H, d, *J* 8.0, Ar-*H*), 6.93 (1H, app td, *J* 8.5, 1.0, Ar-*H*), 6.36 (1H, d, *J* 3.5, NCC*H*), 6.33 (1H, d, *J* 3.5, NCC*H*), 2.43 (3H, s, SCH_3), 1.16 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.0, 142.4 (d, $^2J_{CF}$ 62.0), 135.5 (d, $^1J_{CF}$ 245.0), 129.5 (d, $^4J_{CF}$ 7.5), 129.1, 128.7, 127.4 (d, $^2J_{CF}$ 66.0), 127.2, 119.7, 119.6, 114.4, 113.9, 112.9, 112.1 (d, $^3J_{CF}$ 23.0), 111.3 (d, $^3J_{CF}$ 22.5), 83.3, 27.1, 15.6; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −112.7; IR: ν_{max} (neat)/cm^{-1} 2924, 1747, 1565, 1481, 1452, 1304, 1145, 907; LRMS (ESI$^+$): *m/z* 406 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 406.1249 [M+Na]$^+$, $C_{22}H_{22}O_2NFSNa^+$ requires 406.1247.

tert-Butyl 2-[4-bromo-2-(methylthio)phenyl]-5-(thiophen-2-yl)-1*H*-pyrrole-1-carboxylate, 169

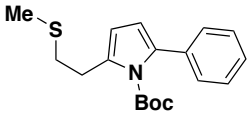


Prepared according to general procedure **Ga** using 4-bromo-2-(methylthio)benzaldehyde **91** (34.7 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(thiophen-2-yl)prop-2-yn-1-yl]carbamate **145**) (46.3 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (69 μL, 1.0 M). After stirring for 2 hrs at room

temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 12 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **169** as white solid (49.2 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.32 (3H, m, Ar-*H*), 7.16-7.13 (2H, m, Ar-*H*), 7.07 (1H, dd, *J* 5.0, 3.5, Ar-*H*), 6.40 (1H, d, *J* 3.5, NCC*H*), 6.21 (1H, d, *J* 3.5, NCC*H*), 2.41 (3H, s, SC*H*$_3$), 1.21 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 142.2, 134.9, 132.7, 132.4, 131.7, 128.4, 127.5, 127.2, 126.7, 126.6, 125.5, 122.5, 114.6, 113.3, 83.8, 27.2, 15.3; IR: ν_{max} (neat)/cm^{-1} 2978, 1747, 1453, 1368, 1299, 1145, 1080, 791; LRMS (ESI$^+$): *m/z* 474 ([^{81}Br] [M+Na]$^+$, 100%), 472 ([^{79}Br] [M+Na]$^+$, 95%); HRMS (ESI$^+$) found 450.01863 [[^{79}Br] M+H]$^+$, 452.01656 [[^{81}Br] M+H]$^+$, $C_{20}H_{21}{}^{79}BrNO_2S_2{}^+$ requires 450.01916, $C_{20}H_{21}{}^{81}BrNO_2S_2{}^+$ requires 452.01711; mp: 85-86 °C (Et_2O/petrol).

***tert*-Butyl 2-[2-(methylthio)ethyl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 170**

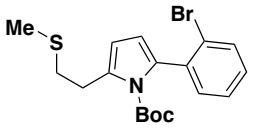


Prepared according to general procedure **Ga** using 3-(methylthio)propionaldehyde (15 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **83**) (45.1 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (90 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (43.0 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 1 hr. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **170** as colourless oil (39.9 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.36 (2H, m, Ar-*H*), 7.34-7.30 (3H, m, Ar-*H*), 6.15 (1H, d, *J* 3.5, NC(Ph)C*H*), 6.10 (1H, dt, *J* 3.5, 1.0, NC($CH_2CH_2SCH_3$)C*H*), 3.20 (2H, app t, *J* 7.5, NCC*H*$_2$), 2.88-2.84 (2H, m, SC*H*$_2$), 2.20 (3H, s, SC*H*$_3$), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 135.5, 135.4, 135.3, 128.4, 127.8, 126.7, 112.2, 110.4, 83.6, 33.9, 29.1, 27.3, 15.6; IR: ν_{max} (neat)/cm^{-1} 2979, 1606, 1526, 1444, 1369, 1144, 908; LRMS

(ESI$^+$): *m/z* 340 ([M+Na]$^+$, 100%), 318 ([M+H]$^+$, 40%); HRMS (ESI$^+$) found 340.13413 [M+Na]$^+$, $C_{18}H_{23}O_2NSNa^+$ requires 340.13417.

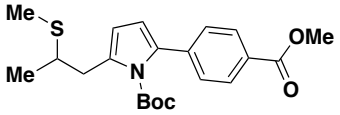
***tert*-Butyl 2-(2-bromophenyl)-5-[2-(methylthio)ethyl]-1*H*-pyrrole-1-carboxylate, 171**



Prepared according to general procedure **Ga** using 3-(methylthio)propionaldehyde (15 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(2-bromophenyl)prop-2-yn-1-yl]carbamate **144**) (60.5 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (75 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (51.0 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 5 hrs. The crude product was purified by flash column chromatography (5-10% Et$_2$O in petrol) to afford *pyrrole* **171** as colourless oil (46.2 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (1H, m, Ar-*H*), 7.36-7.31 (2H, m, Ar-*H*), 7.21 (1H, ddd, *J* 8.0, 6.5, 3.0, Ar-*H*), 6.12 (1H, dt, *J* 3.5, 1.0, NC($CH_2CH_2SCH_3$)C*H*), 6.07 (1H, d, *J* 3.5, NC(Ar)C*H*), 3.23 (2H, app t, *J* 7.5, NCCH_2), 2.85 (2H, t, *J* 7.5, SCH_2), 2.19 (3H, s, SCH_3), 1.23 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 137.5, 135.4, 133.1, 131.9, 131.4, 128.8, 126.9, 125.1, 112.8, 110.5, 83.3, 33.8, 29.6, 27.3, 15.7; IR: ν_{max} (neat)/cm^{-1} 2921, 1742, 1369, 1312, 1148, 908; LRMS (ESI$^+$): *m/z* 418 ([^{79}Br] [M+Na]$^+$, 100%), 420 ([^{81}Br] [M+Na]$^+$, 60%); HRMS (ESI$^+$) found 418.04401 [[^{79}Br] M+Na]$^+$, 420.04180 [[^{81}Br] M+Na]$^+$, $C_{18}H_{22}{}^{79}BrNO_2SNa^+$ requires 418.0.4468, $C_{18}H_{22}{}^{81}BrNO_2SNa^+$ requires 420.04100.

***tert*-Butyl 2-[4-(methoxycarbonyl)phenyl]-5-[2-(methylthio)propyl]-1*H*-pyrrole-1-carboxylate , 172**

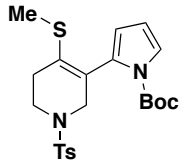


Prepared according to general procedure **Ga** using 3-(methylthio)butanal (18 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **143**) (56.0 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%)

in acetone (76 μL, 1.0 M). After stirring for 4 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 4 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **172** as colourless oil (44.0 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (2H, m, Ar-*H*), 7.38-7.36 (2H, m, Ar-*H*), 6.22 (1H, d, *J* 3.5, NCC*H*), 6.10 (1H, d, *J* 3.5, NCC*H*), 3.96 (3H, s, CO_2CH_3), 3.25 (1H, dd, *J* 14.5, 6.0, $SCH(CH_3)CH_aH_b$), 3.10-3.02 (1H, m, $SCH(CH_3)$), 2.93 (1H, dd, *J* 14.5, 8.0, $SCH(CH_3)CH_aH_b$), 2.14 (3H, s, SCH_3), 1.33 (3H, d, *J* 7.0, $SCH(CH_3)$), 1.28 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 150.3, 140.2, 136.2, 134.6, 129.6, 128.4, 128.3, 113.8, 112.5, 84.6, 52.5, 41.3, 36.4, 27.7, 20.9, 14.0; IR: ν_{max} (neat)/cm^{-1} 2923, 1721, 1609, 1453, 1308, 1276, 1144, 909; LRMS (ESI$^+$): *m/z* 412 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 390.17340 [M+H]$^+$, $C_{21}H_{28}O_4NS^+$ requires 390.17336.

***tert*-Butyl 2-[4-(methylthio)-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl]-1*H*-pyrrole-1-carboxylate, 173**

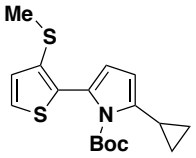


Prepared according to general procedure **Ga** using 4-(methylthio)-1-tosyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde (46.7 mg, 0.15 mmol, 1.0 equiv.), *N*-Boc propargyl amine **59** (34.9 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (68 μL, 1.0 M). After stirring for 5 mins at room temperature, acetonitrile (1.5 mL) and *p*-TSA (57.1 mg, 0.3 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 1.5 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **173** as a white solid (30.0 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (2H, m, Ar-*H*), 7.37-7.33 (3H, m, Ar-*H* and NC*H*), 6.19 (1H, app t, *J* 3.5, NCHC*H*), 6.02 (1H, dd, *J* 3.5, 2.0, NCC*H*), 2.57-2.46 (4H, m, 2 × NCH_2), 2.45 (3H, s, SCH_3), 2.10 (3H, s, Ar-CH_3), 1.66-1.62 (2H, m, $SCCH_2$), 1.59 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 143.7, 132.8, 130.7, 129.7, 129.5,

127.8, 124.7, 122.1, 114.4, 110.5, 84.2, 50.1, 43.2, 29.5, 28.0, 21.5, 14.1; IR: ν_{max} (neat)/cm^{-1} 2926, 1738, 1459, 1370, 1333, 1165, 910; LRMS (ESI$^+$): *m/z* 471 ([M+Na]$^+$, 100%), 449 ([M+H]$^+$, 10%); HRMS (ESI$^+$) found 449.15583 [M+H]$^+$, $C_{22}H_{29}O_4N_2S_2^+$ requires 449.15633.

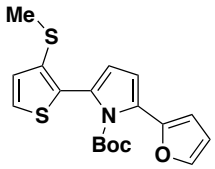
tert-Butyl 2-cyclopropyl-5-[3-(methylthio)thiophen-2-yl]-1*H*-pyrrole-1-carboxylate, 174



Prepared according to general procedure **Ga** using 3-(methylthio)thiophene-2-carbaldehyde **90** (16.3 mg, 0.103 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-cyclopropylprop-2-yn-1-yl)carbamate **138**) (26.2 mg, 0.134 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (1.9 mg, 5 mol%) and PNP(Cy) (2.2 mg, 5 mol%) in acetone (61 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (28.5 mg, 0.15 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 4 hrs. The crude product was purified by flash column chromatography (5-10% Et$_2$O in petrol) to afford *pyrrole* **174** as colourless oil (28.8 mg, 79%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29 (1H, d, *J* 5.5, SC*H*), 7.02 (1H, d, *J* 5.5, SCHC*H*), 6.18 (1H, d, *J* 3.5, NC(Ar)C*H*), 5.92 (1H, dd, *J* 3.5, 1.0, NC(CH(CH$_2$)$_2$)C*H*), 2.32 (3H, s, SC*H*$_3$), 2.29-2.25 (1H, m, NC(C*H*(CH$_2$CH$_2$))), 1.40 (9H, s, CO$_2$C(C*H*$_3$)$_3$), 0.90 (2H, dt, *J* 6.5, 2.0, NC(CH(C*H*$_2$CH$_2$))), 0.69-0.67 (2H, m, NC(CH(CH$_2$*CH*$_2$))); ^{13}C NMR (101 MHz, CDCl$_3$): δ 149.5, 140.4, 132.7, 132.0, 128.6, 124.5, 124.2, 115.0, 108.1, 83.2, 27.5, 17.9, 9.9, 7.0; IR: ν_{max} (neat)/cm^{-1} 3086, 1742, 1369, 1297, 1135, 1090, 971; LRMS (ESI$^+$): *m/z* 336 ([M+H]$^+$, 100%), 358 ([M+Na]$^+$, 90%); HRMS (ESI$^+$) found 358.09025 [M+Na]$^+$, $C_{17}H_{21}O_2NS_2Na^+$ requires 358.09059.

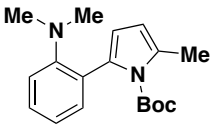
tert-Butyl 2-(furan-2-yl)-5-[3-(methylthio)thiophen-2-yl]-1*H*-pyrrole-1-carboxylate, 175



Prepared according to general procedure **Ga** using 3-(methylthio)thiophene-2-carbaldehyde **90** (23.7 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(furan-2-yl)prop-2-yn-1-yl]carbamate **146**) (43.1 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (83 μL, 1.0 M). After stirring for 3 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 16 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **175** as a light brown oil (32.4 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, dd, *J* 2.0, 1.0, OC*H*), 7.36 (1H, d, *J* 5.5, SC*H*), 7.06 (1H, d, *J* 5.5, SCHC*H*), 6.55 (1H, dd, *J* 3.5, 1.0, OCHC*H*), 6.48 (1H, d, *J* 3.5, NCC*H*), 6.47 (1H, d, *J* 3.5, OCC*H*) 6.36 (1H, d, *J* 3.5, NCC*H*), 2.36 (s, SC*H*$_3$), 1.32 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.7, 146.8, 141.9, 133.3, 131.0, 128.6, 126.8, 126.4, 125.4, 115.5, 113.6, 111.0, 108.7, 83.9, 27.3, 18.0 ; IR: ν_{max} (neat)/cm^{-1} 2923, 2853, 1752, 1458, 1393, 1328, 1258, 1104, 1011, 843, 684; LRMS (ESI$^+$): *m/z* 384 ([M+Na]$^+$, 100%), 362 ([M+H]$^+$, 75%); HRMS (ESI$^+$) found 362.08800 [M+H]$^+$, $C_{18}H_{20}O_3NS^+$ requires 362.08791.

tert-Butyl 2-[2-(dimethylamino)phenyl]-5-methyl-1*H*-pyrrole-1-carboxylate, 176

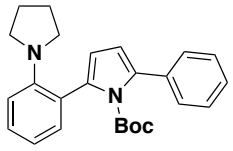


Prepared according to general procedure **Ga** using 2-(dimethylamino)benzaldehyde **95** (22.4 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl but-3-yn-2-ylcarbamate **82**) (33.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (95 μL, 1.0 M). After stirring for 3 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (142.6 mg, 0.75 mmol, 5.0 equiv.) were added and stirred at room

temperature for a further 2 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **176** as pale yellow oil (33.1 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (1H, d, *J* 10.0, Ar-*H*), 7.25-7.23 (1H, m, Ar-*H*), 6.96 (1H, app td, *J* 7.5, 1.0, Ar-*H*), 6.91 (1H, dd, *J* 8.5, 1.0, Ar-*H*), 6.06 (1H, d, *J* 3.0, NC(Ar)C*H*), 5.99 (1H, dt, *J* 3.0, 1.0, NC(CH_3)C*H*), 2.51 (6H, s, N(CH_3)$_2$), 2.48 (3H, d, *J* 1.0, NC(CH_3)CH), 1.29 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 133.2, 132.1, 130.6, 130.4, 128.0, 127.9, 120.8, 116.5, 111.4, 110.1, 82.5, 42.5, 27.5, 15.4; IR: ν_{max} (neat)/cm^{-1} 2922, 2870, 1677, 1599, 1478, 1450, 1260, 1162, 751; LRMS (ESI$^+$): *m/z* 301 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 301.19044 [M+H]$^+$, $C_{18}H_{25}O_2N_2^+$ requires 301.19105.

tert-Butyl 2-methyl-5-[2-(pyrrolidin-1-yl)phenyl]-1*H*-pyrrole-1-carboxylate, 177

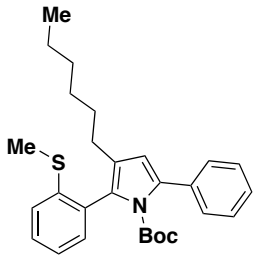


Prepared according to general procedure **Ga** using 2-(pyrrolidin-1-yl)benzaldehyde (26.3 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **83**) (45.1 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (79 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (43.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to afford *pyrrole* **177** as pale yellow oil (40.2 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.36 (4H, m, Ar-*H*), 7.35-7.30 (1H, m, Ar-*H*), 7.28-7.24 (2H, m, Ar-*H*), 6.83 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.76 (1H, d, *J* 8.0, Ar-*H*), 6.27 (1H, d, *J* 3.5, NCC*H*), 6.18 (1H, d, *J* 3.5, NCC*H*), 2.95 (4H, t, *J* 6.0, -CH_2NCH_2-), 1.81-1.78 (4H, t, *J* 6.0, -CH_2CH$_2$NCH$_2$CH_2-), 1.14 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5, 148.5, 135.3, 134.9, 134.2, 132.1, 128.6, 128.5, 127.8, 126.9, 122.1, 117.4, 114.0, 112.3, 112.0, 83.0, 49.4, 31.0, 27.0; IR: ν_{max} (neat)/cm^{-1} 2924, 2853, 1599, 1484, 1366, 1303,

1180, 1027, 978; LRMS (ESI^+): *m/z* 389 ($[M+H]^+$, 100%); HRMS (ESI^+) found 389.22244 $[M+H]^+$, $C_{25}H_{29}O_2N_2^+$ requires 389.22235.

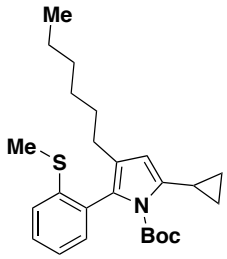
***tert*-Butyl 3-hexyl-2-[2-(methylthio)phenyl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 181**



Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylnon-2-yn-1-yl)carbamate **113**) (61.5 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%) in acetone (70 μL, 1.0 M). After stirring for 4 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (28.5 mg, 0.150 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 4 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **181** as colourless oil (57.0 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (2H, dd, *J* 8.5, 1.5, Ar-*H*), 7.41-7.37 (3H, m, Ar-*H*), 7.34-7.31 (1H, m, Ar-*H*), 7.29-7.20 (3H, m, Ar-*H*), 6.26 (1H, s, NCC*H*), 2.31-2.16 (2H, m, C*H*$_2$$(CH_2)_4CH_3$), 1.55 (2H, app dd, *J* 7.0, 3.5, C*H*$_2$$(CH_2)_3CH_3$), 1.31-1.24 (6H, m, $(CH_2)_3CH_3$), 1.13 (9H, s, $CO_2C(CH_3)_3$), 0.88 (3H, t, *J* 7.0, $(CH_2)_5CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 140.8, 135.3, 134.6, 132.9, 131.3, 129.5, 128.5, 128.4, 127.7, 126.8, 126.2, 124.12, 124.08, 113.9, 82.7, 31.7, 30.2, 29.1, 27.1, 25.7, 22.6, 15.1, 14.1; IR: ν_{max} (neat)/cm^{-1} 3061, 2968, 2855, 1744, 1606, 1484, 1361, 1254, 1074, 991; LRMS (ESI^+): *m/z* 450 ($[M+H]^+$, 100%), 472 ($[M+Na]^+$, 30%); HRMS (ESI^+) found 472.22689 $[M+Na]^+$, $C_{28}H_{35}O_2NSNa^+$ requires 472.22807.

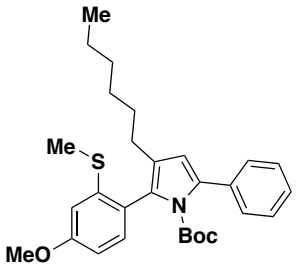
tert-Butyl-5-cyclopropyl-3-hexyl-2-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 182



Prepared according to general procedure **Ga** using 2-(methylthio)benzaldehyde **50** (63 μL, 0.49 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-cyclopropyldec-2-yn-1-yl)carbamate **151**) (178 mg, 0.640 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (9.35 mg, 5 mol%) and dppm (9.61 mg, 5 mol%) in acetone (0.25 mL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (2.0 mL) and *p*-TSA (93.0 mg, 0.49 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 2 hrs. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to afford *pyrrole* **182** as colourless oil (178.3 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (1H, ddd, *J* 8.0, 5.0, 3.5, Ar-*H*), 7.19 (1H, d, *J* 8.0, Ar-*H*), 7.17-7.15 (2H, m, Ar-*H*), 5.85 (1H, s, $NC(CH(CH_2)_2)CH$), 2.35 (3H, s, SCH_3), 2.33-2.29 (1H, m, $NC(CH(CH_2)_2)CH$), 2.18-2.07 (2H, m, $CH_2(CH_2)_4CH_3$), 1.46-1.25 (6H, m, $(CH_2)_3CH_2CH_3$), 1.20 (9H, s, $CO_2C(CH_3)_3$), 0.94-0.83 (6H, m, $(CH_2)_3CH_2CH_3$ and $NCCH(CH_aH_bCH_aH_b)$, 0.75-0.72 (1H, m, $NCCH(CH_aH_bCH_aH_b)$, 0.64-0.58 (1H, m, $NCCH(CH_aH_bCH_aH_b)$, 0.49-0.44 (1H, m, $NCCH(CH_aH_bCH_aH_b)$; ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.8, 145.1, 140.4, 138.4, 133.9, 131.0, 127.8, 127.6, 125.5, 124.0, 109.0, 82.2, 31.6, 30.2, 29.0, 27.4, 25.7, 22.6, 15.0, 14.1, 9.8, 7.2, 6.9; IR: ν_{max} (neat)/cm^{-1} 3085, 2926, 1736, 1590, 1477, 1335, 1158, 1047, 830; LRMS (ESI$^+$): *m/z* 414 ($[M+H]^+$, 100%), 436 ($[M+Na]^+$, 75%); HRMS (ESI$^+$) found 436.22792 $[M+Na]^+$, $C_{25}H_{35}O_2NSNa^+$ requires 436.22830.

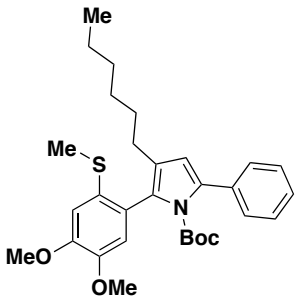
***tert*-Butyl 3-hexanoyl-2-[4-methoxy-2-(methylthio)phenyl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 183**



Prepared according to general procedure **Ga** using 4-methoxy-2-(methylthio)benzaldehyde (27.3 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylnon-2-yn-1-yl)carbamate **113**) (61.5 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%) in acetone (70 μL, 0.9 M). After stirring for 6 hrs at 55 °C, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for 2 hrs. The crude product was purified by flash column chromatography on silica (5-10% Et_2O in petrol) to afford *pyrrole* **183** as colourless oil (59.6 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (2H, app dq, *J* 6.5, 2.0, Ar-*H*), 7.39-7.35 (2H, m, Ar-*H*), 7.32-7.29 (1H, m, Ar-*H*), 7.17 (1H, d, *J* 8.0, Ar-*H*), 6.80 (1H, d, *J* 2.5, Ar-*H*), 6.74 (1H, dd, *J* 8.5, 2.5, Ar-*H*), 6.23 (1H, s, NCC*H*), 3.89 (3H, s, OCH_3), 2.38 (3H, s, SCH_3), 2.29-2.15 (2H, m, CH_2(CH_2)$_4$$CH_3$), 1.55-1.47 (2H, m, C$H_2$($CH_2$)$_3$$CH_3$), 1.30-1.23 (6H, m, ($CH_2$)$_3$$CH_3$), 1.14 (9H, s, $CO_2C(CH_3)_3$), 0.87 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7, 149.5, 142.3, 135.1, 134.8, 132.2, 129.3, 128.4, 127.7, 126.7, 126.4, 125.2, 113.7, 110.7, 108.6, 82.6, 55.3, 31.7, 30.3, 29.1, 27.2, 25.8, 22.6, 15.1, 14.1; IR: ν_{max} (neat)/cm^{-1} 2926, 1742, 1600, 1487, 1467, 1366, 1304, 1155, 729; LRMS (ESI$^+$): *m/z* 480 ([M+H]$^+$, 100%), 502 ([M+Na]$^+$, 30%); HRMS (ESI$^+$) found 480.25529 [M+H]$^+$, $C_{29}H_{38}O_3NS^+$ requires 480.25669.

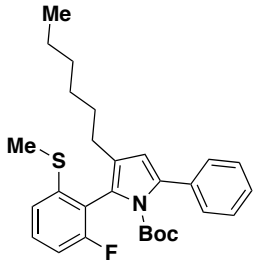
tert-Butyl 2-[4,5-dimethoxy-2-(methylthio)phenyl]-3-hexyl-5-phenyl-1*H*-pyrrole-1-carboxylate, 184



Prepared according to general procedure **Ga** using 4,5-dimethoxy-2-(methylthio)benzaldehyde (31.9 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylnon-2-yn-1-yl)carbamate **113**) (61.5 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%) in acetone (80 μL, 0.9 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (29.0 mg, 0.15 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 2 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford *pyrrole* **184** as colourless oil (65.8 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.36 (4H, m, Ar-*H*), 7.32-7.28 (1H, m, Ar-*H*), 6.92 (1H, s, Ar-*H*), 6.84 (1H, s, Ar-*H*), 6.23 (1H, s, NCC*H*), 3.97 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 2.35 (3H, s, SCH_3), 2.31-2.14 (2H, m, C$H_2(CH_2)_4CH_3$), 1.56-1.48 (2H, m, C$H_2(CH_2)_3CH_3$), 1.31-1.24 (6H, m, $(CH_2)_3CH_3$), 1.15 (9H, s, $CO_2C(CH_3)_3$), 0.87 (3H, t, *J* 7.0, C$H_3(CH_2)_5$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5, 148.9, 146.8, 135.0, 134.7, 131.0, 129.8, 128.4, 127.7, 126.8, 126.7, 126.1, 114.9, 113.6, 111.2, 82.8, 56.1, 31.7, 30.3, 29.7, 29.2, 27.2, 25.9, 22.6, 17.1, 14.1; IR: ν_{max} (neat)/cm^{-1} 2928, 1742, 1497, 1369, 1247, 1207, 1151, 1070, 908; LRMS (ESI$^+$): *m/z* 510 ([M+H]$^+$, 100%), 532 ([M+Na]$^+$, 45%); HRMS (ESI$^+$) found 510.26648 [M+H]$^+$, $C_{30}H_{40}O_4NS^+$ requires 510.26726.

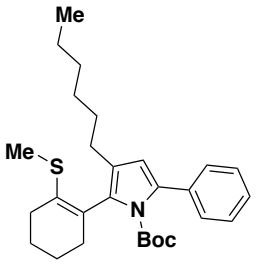
tert-Butyl 2-[2-fluoro-6-(methylthio)phenyl]-3-hexyl-5-phenyl-1*H*-pyrrole-1-carboxylate, 185



Prepared according to general procedure **Ga** using 2-fluoro-6-(methylthio)benzaldehyde **92** (25.5 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylnon-2-yn-1-yl)carbamate **113**) (72.6 mg, 0.23 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%) in acetone (55 μL, 1.0 M). After stirring for 2 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (43 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 4 hrs. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to afford the *pyrrole* **185** as colourless oil (34.0 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.43 (2H, m, Ar-*H*), 7.41-7.35 (3H, m, Ar-*H*), 7.34-7.30 (1H, m, Ar-*H*), 7.02 (1H, d, *J* 8.0, Ar-*H*), 6.94 (1H, app td, *J* 8.5, 1.0, Ar-*H*), 6.29 (1H, s, NCC*H*), 2.42 (3H, s, SCH_3), 2.28-2.18 (2H, m, CH_2(CH_2)$_4$$CH_3$), 1.56-1.49 (2H, m, C$H_2$($CH_2$)$_3$$CH_3$), 1.25 (6H, app td, *J* 10.5, 5.5, (CH_2)$_3$$CH_3$), 1.15 (9H, s, $CO_2C(CH_3)_3$), 0.87 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2, 159.7, 149.1, 143.6, 135.4 (d, $^1J_{CF}$ 190.0), 129.7 (d, $^2J_{CF}$ 19.5), 128.5, 127.7, 126.8, 122.3, 120.5 (d, $^2J_{CF}$ 19.0), 119.2 (d, $^3J_{CF}$ 8.5), 118.2, 114.2, 111.2 (d, $^3J_{CF}$ 8.5), 82.8, 31.6, 29.8, 29.0, 27.1, 25.9, 22.6, 15.3, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −112.3; IR: ν_{max} (neat)/cm^{-1} 2925, 1743, 1605, 1482, 1306, 1153, 989; LRMS (ESI$^+$): *m/z* 468 ([M+H]$^+$, 100%), 490 ([M+Na]$^+$, 50%); HRMS (ESI$^+$) found 468.23627 [M+H]$^+$, $C_{28}H_{35}O_2NFS^+$ requires 468.23670.

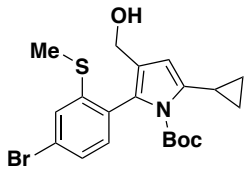
tert-Butyl 3-hexyl-2-[2-(methylthio)cyclohex-1-en-1-yl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 186



Prepared according to general procedure **Ga** using 2-(methylthio)cyclohex-1-enecarbaldehyde **89** (23.5 mg, 0.15 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl (1-phenylnon-2-yn-1-yl)carbamate **113**) (71.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and dppm (2.9 mg, 5 mol%) in acetone (56 μL, 1.0 M). After stirring for 4 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (42.8 mg, 0.23 mmol, 1.5 equiv.) were added and stirred at room temperature for a further 16 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **186** as colourless oil (42.8 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (4H, m, Ar-*H*), 7.28-7.25 (1H, m, Ar-*H*), 6.14 (1H, s, NCC*H*), 2.40 (2H, app d, *J* 3.0, $CH_2(CH_2)_4CH_3$), 2.30 (2H, ddd, *J* 8.5, 7.0, 3.0, $SCCH_2$), 2.14 (3H, s, SCH_3), 1.93-1.88 (2H, m, $CH_2(CH_2)_3CH_3$), 1.78-1.75 (2H, m, $SCCCH_2$), 1.63-1.46 (4H, m, $SCCH_2(CH_2)_2$), 1.39-1.32 (6H, m, $(CH_2)_3CH_3$), 1.31 (9H, s, $CO_2C(CH_3)_3$), 0.91 (3H, t, *J* 7.0, $(CH_2)_5CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6, 135.1, 134.3, 133.0, 132.5, 128.4, 128.2, 127.6, 126.4, 123.6, 113.6, 82.6, 32.8, 31.8, 30.1, 29.4, 29.3, 27.4, 25.9, 23.4, 22.7, 22.6, 22.5, 14.2; IR: ν_{max} (neat)/cm^{-1} 2927, 1742, 1601, 1488, 1467, 1304, 1259, 1155, 729; LRMS (ESI$^+$): *m/z* 454 ([M+H]$^+$, 100%), 476 ([M+Na]$^+$, 90%); HRMS (ESI$^+$) found 476.25847 [M+Na]$^+$, $C_{28}H_{39}O_2NSNa^+$ requires 476.25937.

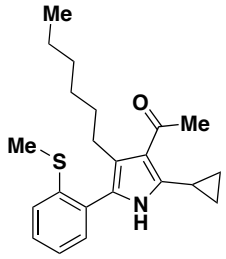
tert-Butyl 2-[4-bromo-2-(methylthio)phenyl]-5-cyclopropyl-3-(hydroxymethyl)-1*H*-pyrrole-1-carboxylate, 187



Prepared according to general procedure **Ga** using 4-bromo-2-(methylthio)benzaldehyde **91** (27.7 mg, 0.12 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [3-(benzyloxy)-1-cyclopropylprop-2-yn-1-yl]carbamate **150**) (48.3 mg, 0.15 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.2 mg, 5 mol%) and dppm (2.3 mg, 5 mol%) in acetone (44 μL, 1.0 M). After stirring for 16 hrs at room temperature, acetonitrile (1.5 mL) and *p*-TSA (46.0 mg, 0.24 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **187** as colourless oil (32.0 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* 2.0, Ar-*H*), 7.26 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 6.99 (1H, d, *J* 8.5, Ar-*H*), 5.77 (1H, s, NC(CH(CH_2)$_2$)C*H*), 3.66 (2H, s, CH_2OH), 2.14 (1H, app ttd, *J* 8.5, 5.5, 1.0, NC(C*H*(CH_2)$_2$)), 1.58 (3H, s, SCH_3), 1.56 (9H, s, CO_2C(CH_3)$_3$), 0.91 (1H, dt, *J* 5.5, 2.0, NC(CHC$H_2$$CH_2$)), 0.69-0.65 (2H, m, NCCH(CH_2CH_2)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3, 141.0, 132.5, 130.9, 129.0, 128.1, 127.2, 125.4, 123.2, 118.5, 106.9, 84.5, 29.7, 27.7, 25.6, 9.3, 6.9; IR: ν_{max} (neat)/cm^{-1} 3285 (br), 2922, 1688, 1557, 1433, 1323, 1156, 1093; LRMS (ESI$^+$): *m/z* 492 ([^{79}Br] [M+MeOH+Na]$^+$, 100%), 494 ([^{81}Br] [M+MeOH+Na]$^+$, 90%), 460 ([^{79}Br] [M+Na]$^+$, 80%), 462 ([^{81}Br] [M+Na]$^+$, 75%); HRMS (ESI$^+$) found 492.00881 [[^{79}Br] [M+MeOH+Na]$^+$], 494.00654 [[^{81}Br] [M+MeOH+Na]$^+$], $C_{21}H_{28}{}^{79}BrNO_4SNa^+$ requires 492.00815, $C_{21}H_{28}{}^{81}BrNO_4SNa^+$ requires 494.00794.

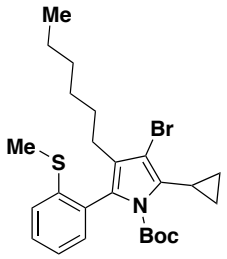
1-[2-Cyclopropyl-4-hexyl-5-(2-(methylthio)phenyl]-1*H*-pyrrol-3-yl)ethan-1-one, 193



Prepared according to a procedure adapted from Frost *et. al*.[182] Pyrrole (*tert*-butyl 5-cyclopropyl-3-hexyl-2-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate **182**) (124 mg, 0.30 mmol, 1.0 equiv.) in nitromethane (0.7 mL) was added dropwise to a solution of indium(III) trifluoromethanesulfonate (16.9 mg, 0.03 mmol, 10 mol%) and lithium perchlorate (31.9 mg, 0.30 mmol, 1.0 equiv.) in nitromethane (0.1 mL) at 50 °C, followed by the addition of acetic anhydride (43 μL, 0.45 mmol, 1.5 equiv.). The reaction mixture was stirred at 50 °C for 16 hrs and then quenched by the addition of water (2 mL). The product was extracted with CH_2Cl_2 (3 × 5 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to yield acylated *pyrrole* **193** as a white solid (84.0 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (1H, br s, N*H*), 7.35 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.28-7.25 (2H, m, Ar-*H*), 7.20 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 2.62 (3H, s, COC*H*$_3$), 2.35 (3H, s, SC*H*$_3$), 2.30 (1H, app dt, *J* 10.0, 4.0, NHCC*H*), 1.48 (2H, app ddd, *J* 10.0, 5.0, 2.0, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.26-1.20 (8H, m, (C*H*$_2$)$_4$CH$_3$), 1.10-1.05 (2H, m, NCCH(C*H*$_2$CH$_2$)), 0.85-0.81 (5H, m, (CH$_2$)$_5$C*H*$_3$ and NCCH(CH$_2$C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.2, 139.0, 138.5, 131.5, 130.7, 128.5, 125.5, 125.07, 125.03, 124.7, 122.1, 31.6, 31.3, 31.1, 29.4, 25.7, 22.7, 15.3, 14.1, 10.3, 7.4; IR: ν_{max} (neat)/cm^{-1} 3249 (br), 2954, 2854, 1622, 1444, 1361, 908; LRMS (ESI$^+$): *m/z* 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 356.20450 [M+H]$^+$, $C_{22}H_{30}OSN^+$ requires 356.20426; mp: 88-89 °C (CH_2Cl_2/hexane).

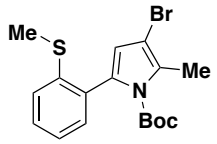
tert-Butyl 3-bromo-2-cyclopropyl-4-hexyl-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 194



Pyrrole (*tert*-butyl 5-cyclopropyl-3-hexyl-2-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate **182**) (62.0 mg, 0.15 mmol, 1.0 equiv.), was dissolved in THF (1 mL) and cooled to −78 °C. *N*-Bromosuccinimide (53.4 mg, 0.30 mmol, 2.0 equiv.) in THF (1.2 mL) was added dropwise to the stirring solution of pyrrole. The reaction mixture was allowed to warm to room temperature for 16 hrs. After which, sat. $NaHCO_{3(aq.)}$ (2 mL) was added at room temperature. The product was extracted with EtOAc (3 × 5 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc in petrol) to yield brominated *pyrrole* **194** as an off-white solid (64.0 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (1H, m, Ar-*H*), 7.20 (1H, d, *J* 8.0, Ar-*H*), 7.18-7.16 (2H, m, Ar-*H*), 2.37 (3H, s, SC*H*$_3$), 2.26-2.09 (2H, m, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.02-1.95 (1H, m, NCC*H*), 1.44-1.37 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.23 (9H, s, CO$_2$C(C*H*$_3$)$_3$), 1.21-1.16 (6H, m, (C*H*$_2$)$_3$CH$_3$), 1.04-0.92 (3H, m, NCCH(C*H*$_2$C*H*$_a$H$_b$)), 0.84 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$), 0.73-0.67 (1H, m, NCCH(CH$_2$CH$_a$*H*$_b$)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.7, 140.5, 132.1, 131.2, 128.4, 127.0, 124.4, 124.1, 124.0, 123.9, 104.5, 82.8, 31.4, 29.6, 29.1, 27.2, 25.2, 22.5, 15.0, 14.1, 8.6, 7.8, 7.3; IR: ν_{max} (neat)/cm^{-1} 2925, 1744, 1577, 1459, 1335, 1155, 1078, 965; LRMS (ESI$^+$): *m/z* 494 ([^{81}Br] [M+H]$^+$, 100%), 492 ([^{79}Br] [M+H]$^+$, 95%), 516 ([^{81}Br] [M+H]$^+$, 50%), 514 ([^{79}Br] [M+Na]$^+$, 48%); HRMS (ESI$^+$) found 514.13841 [[^{79}Br] M+Na]$^+$, 516.13630 [[^{81}Br] M+Na]$^+$, $C_{25}H_{34}{}^{79}BrNO_2SNa^+$ requires 514.13858, $C_{25}H_{34}{}^{81}BrNO_2SNa^+$ requires 516.13654; mp: 99-101 °C (CH_2Cl_2/hexane).

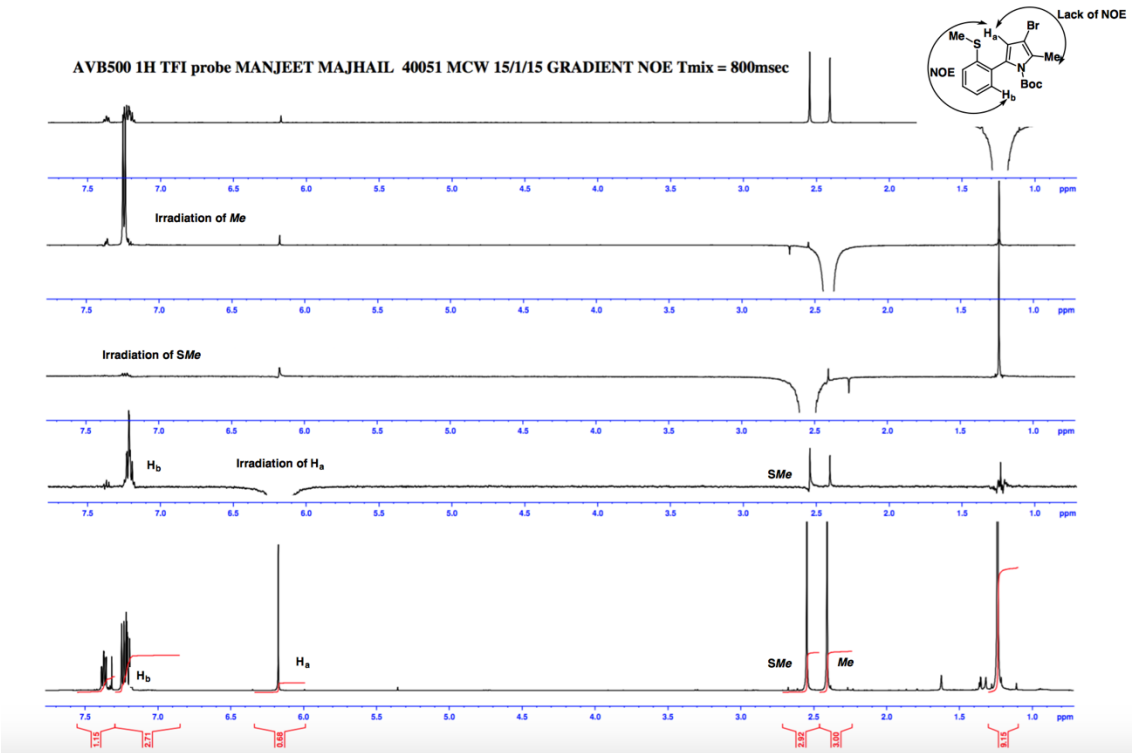
tert-Butyl 3-bromo-2-methyl-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate, 195



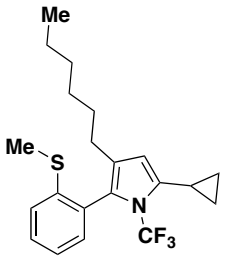
Pyrrole, (*tert*-butyl 2-methyl-5-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate **116**) (52.0 mg, 0.17 mmol, 1.0 equiv.), was dissolved in THF (0.3 mL) and cooled to −78 °C. *N*-Bromosuccinimide (30.3 mg, 0.17 mmol, 1.0 equiv.) in THF (0.5 mL) was added dropwise to the stirring solution of pyrrole. The reaction mixture was allowed to warm to room temperature over 3 hrs. After which, sat. $NaHCO_{3(aq.)}$ (2 mL) was added at room temperature. The product was extracted with EtOAc (3 × 5 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-30% CH_2Cl_2 in petrol) to yield brominated *pyrrole* **195** as a colourless oil (51.0 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (1H, ddd, *J* 8.0, 7.0, 2.0, Ar-*H*), 7.22-7.15 (3H, m, Ar-*H*), 6.15 (1H, s, NCC*H*), 2.52 (3H, s, SCH_3), 2.38 (3H, s, NC(CH_3)), 1.21 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 139.4, 133.8, 131.5, 130.3, 129.9, 128.4, 124.5, 124.4, 115.0, 100.4, 83.6, 27.3, 15.3, 13.8; IR: ν_{max} (neat)/cm^{-1} 2980, 1745, 1435, 1304, 1256, 1158, 1136, 1019, 908; LRMS (ESI$^+$): *m/z* 406 ([^{81}Br] $[M+Na]^+$, 100%), 404 ([^{79}Br] $[M+Na]^+$, 95%); HRMS (ESI$^+$) found 404.02933 [[^{79}Br] $M+Na]^+$, 406.02712 [[^{81}Br] $M+Na]^+$, $C_{17}H_{20}{}^{79}BrNO_2SNa^+$ requires 404.02903, $C_{17}H_{20}{}^{81}BrNO_2SNa^+$ requires 406.02699.

Regioselectivity was confirmed by in-space interactions shown between H_a and H_b upon irradiation of H_a. In addition, irradiation of H_a displayed a lack of in-space interaction with the methyl group displayed, which confirms bromine addition closest to the methyl group on the pyrrole ring.



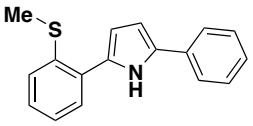
5-Cyclopropyl-3-hexyl-2-(2-(methylthio)phenyl)-1-(trifluoromethyl)-1*H*-pyrrole, 196



An oven-dried reaction vial was charged with pyrrole (*tert*-butyl 5-cyclopropyl-3-hexyl-2-[2-(methylthio)phenyl]-1*H*-pyrrole-1-carboxylate **182**) (50 mg, 0.18 mmol, 1.0 equiv.), (diacetoxyiodo)benzene (116 mg, 0.36 mmol, 2.0 equiv.), trimethyl(trifluoromethyl)silane (53 μL, 0.36 mmol, 2.0 equiv.) and anhydrous DMSO (0.6 mL), under atmospheric conditions. The mixture was stirred at room temperature for 1 min and AgF (5.7 mg, 0.045 mmol, 0.25 equiv.) was slowly added to the stirring mixture. The vial was sealed with a septum cap and the reaction was kept stirring at the same temperature for 20 hrs. The resulting mixture was quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (10% Et_2O in petrol) to yield the *N*-trifluoromethylated *pyrrole* **196** as a colourless oil (15.4 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.38 (2H, m, Ar-*H*), 7.28-7.25 (1H, m, Ar-*H*), 7.22 (1H, ddd, *J* 7.5, 1.5, 0.5, Ar-*H*), 6.80 (1H, s, NC(CH(CH_2)$_2$)C*H*), 2.44 (3H, s, SCH_3), 2.24-2.19 (2H, m, CH_2(CH_2)$_4$$CH_3$), 1.69 (1H, tt, *J* 8.5, 5.0, NC(C*H*(CH_2)$_2$)CH), 1.48-1.42 (2H, m, CH_2(CH_2)$_3$$CH_3$), 1.26-1.21 (6H, m, (C$H_2$)$_3$$CH_3$), 0.86 (3H, t, *J* 7.0, (CH_2)$_5$CH_3), 0.66 (1H, dt, *J* 9.5, 5.0, NC(CH(CH_2C$H_a$$H_b$)), 0.59-0.52 (2H, m, NC(CH(C$H_2$$CH_a$$H_b$)), 0.33 (1H, app dq, *J* 9.5, 5.0, NC(CH($CH_2$$CH_a$$H_b$)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5, 142.2, 136.6, 135.1, 132.2, 132.0, 129.8, 128.6, 127.8, 126.0 ($^1J_{CF}$ 194.5), 125.7, 31.4, 28.6, 28.0, 26.7, 22.4, 17.1, 14.0, 12.1, 1.4, 1.0; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −72.5; LRMS (ESI^+): *m/z* 382 ($[M+H]^+$, 100%), 404 ($[M+Na]^+$, 5%); HRMS (ESI^+) found 382.18043 $[M+H]^+$, $C_{21}H_{27}NF_3S^+$ requires 382.18108.

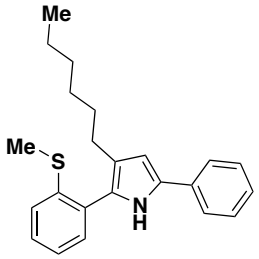
2-[2-(Methylthio)phenyl]-5-phenyl-1*H*-pyrrole, 197



Pyrrole (*tert*-butyl 2-(2-(methylthio)phenyl)-5-phenyl-1*H*-pyrrole-1-carboxylate **117**) (146 mg, 0.40 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL). Trifluoroacetic acid (3.06 mL, 0.04 mmol, 0.1 equiv.) was added to the pyrrole dropwise and stirred at room temperature for 2 hrs. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and neutralised with sat. $NaHCO_{3(aq.)}$. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product required no further purifications and afforded deprotected *pyrrole* **197** as a colourless oil (99 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (1H, br s, N*H*), 7.64-7.60 (3H, m, Ar-*H*), 7.48-7.44 (3H, m, Ar-*H*), 7.33-7.25 (3H, m, Ar-*H*), 6.70-6.67 (2H, m, 2 × NCC*H*), 2.48 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.1, 132.8, 132.6, 132.5, 131.7, 130.5, 129.0, 128.6, 127.0, 126.8, 126.3, 123.8, 110.8, 106.9, 17.6; IR: ν_{max} (neat)/cm^{-1} 3425 (br), 3054, 2919, 1691, 1475, 1456, 1379, 1245, 1099; LRMS (ESI^+): *m/z* 266 ($[M+H]^+$, 100%), 288 ($[M+Na]^+$, 50%); HRMS (ESI^+) found 266.09972 $[M+H]^+$, $C_{17}H_{16}SN^+$ requires 266.09980.

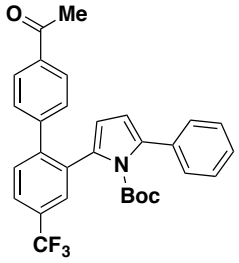
3-Hexyl-2-[2-(methylthio)phenyl]-5-phenyl-1*H*-pyrrole, 198



Pyrrole (*tert*-butyl 3-hexyl-2-[2-(methylthio)phenyl]-5-phenyl-1*H*-pyrrole-1-carboxylate **181**) (30.6 mg, 0.07 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2 mL). Trifluoroacetic acid (0.6 mL, 8.4 μmol, 0.12 equiv.) was added to the pyrrole dropwise and stirred at room temperature for 2 hrs. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and neutralised with sat. $NaHCO_{3(aq.)}$. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product required no further purifications and afforded deprotected *pyrrole* **198** as a colourless oil (23.3 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (1H, br s, N*H*), 7.55-7.52 (2H, m, Ar-*H*), 7.41-7.34 (5H, m, Ar-*H*), 7.26-7.20 (2H, m, Ar-*H*), 6.55 (1H, app d, *J* 3.0, NCC*H*), 2.51 (2H, t, *J* 8.0, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.38 (3H, s, SC*H*$_3$), 1.63 (2H, app t, *J* 7.5, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.37-1.25 (6H, m, (C*H*$_2$)$_3$CH$_{33}$), 0.90 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.2, 132.7, 131.9, 131.3, 131.1, 128.8, 128.0, 127.4, 126.1, 126.0, 124.9, 124.8, 123.5, 106.9, 31.7, 31.1, 29.2, 26.3, 22.7, 15.6, 14.1; IR: ν_{max} (neat)/cm^{-1} 3430 (br), 3057, 2954, 2854, 1606, 1377, 1201, 907; HRMS (FI$^+$) found 349.1862 [M]$^+$, $C_{23}H_{27}SN^+$ requires 349.1864.

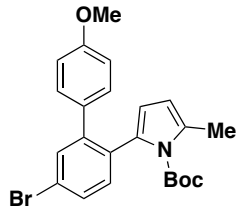
General procedure I for the three-component coupled traceless pyrroles as exemplified by the formation of *tert*-butyl 2-[4'-acetyl-4-(trifluoromethyl)-(1,1'-biphenyl)-2-yl]-5-phenyl-1*H*-pyrrole-1-carboxylate, 200



An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (7.5 mg, 10 mol%), PNP(Cy) (4.2 mg, 5 mol%) and dcpm (4.1 mg, 5 mol%). Once under an inert atmosphere, they were dissolved in acetone (1 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (96 μL, 1.0 M with respect to aldehyde minus the volume or mass of both aldehyde and alkyne) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **203** (44 mg, 0.20 mmol, 1.0 equiv.) and propargylic amine (*tert*-butyl (1-phenylprop-2-yn-1-yl)carbamate **83**) (60.1 mg, 0.26 mmol, 1.3 equiv.). The reaction mixture was then stirred at 55 °C for 5 mins. It was then transferred to an oven-dried microwave vial charged with silver carbonate (55.2 mg, 0.20 mmol, 1.0 equiv.) and 4-acetylphenylboronic acid (49.2 mg, 0.30 mmol, 1.5 equiv.) using acetone (0.47 mL, 0.4 M with respect to aldehyde). The vessel was heated at 55 °C for a further 5 hrs, after which it was cooled to room temperature, opened to air, and filtered through a plug of silica with CH_2Cl_2 (3 mL). *p*-TSA (76.1 mg, 0.40 mmol, 2.0 equiv) was added to the solution and stirred at room temperature until complete. After 6 hrs the solution was diluted with CH_2Cl_2 (5 mL) and neutralised by the addition of sat. $NaHCO_{3(aq.)}$ (10 mL) in a separatory funnel. The aqueous mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product and this was purified by flash column chromatography (5-10% EtOAc in petrol) to afford title *pyrrole* **200** as a light brown solid (51.0 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.93 (2H, m, Ar-*H*), 7.75-7.71 (2H, m, Ar-*H*), 7.58 (1H, d, *J* 8.0, Ar-*H*), 7.40-7.37 (2H, m, Ar-*H*), 7.33-7.32 (3H, m, Ar-*H*), 7.21-7.19 (2H, m, Ar-*H*), 6.17 (1H, d, *J* 3.5, NCC*H*), 6.14 (1H, d, *J* 3.5, NCC*H*), 2.64 (3H, s, COCH_3), 1.01 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.7, 148.7, 145.0, 143.6, 136.8, 135.8, 134.3, 134.2, 133.1, 129.9, 129.8 (q, $^{2}J_{CF}$ 31.5) 129.2, 129.0, 128.1, 127.7, 127.3, 127.2 (q, $^{3}J_{CF}$ 3.5), 124.3 (q, $^{3}J_{CF}$ 3.5), 123.9 (q, $^{1}J_{CF}$ 252.0), 114.7, 113.0, 83.8, 27.1, 26.7; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ –62.3; IR: ν_{max} (neat)/cm^{-1} 2974, 2361, 2169, 1746, 1684, 1397; LRMS (ESI^{+}): *m/z* 528 ([M+Na]$^{+}$, 100%); HRMS (ESI^{+}) found 528.17477 [M+Na]$^{+}$, $C_{30}H_{26}O_3F_3NNa^{+}$ requires 528.17570; mp: 146-147 °C (EtOAc/petrol).

tert-Butyl 2-[5-bromo-4'-methoxy-(1,1'-biphenyl)-2-yl]-5-methyl-1*H*-pyrrole-1-carboxylate, 201

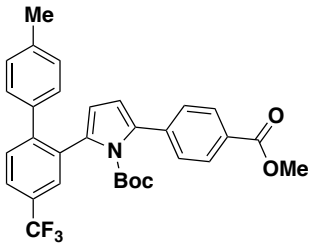


Prepared according to general procedure **I** using 4-bromo-2-(methylthio)benzaldehyde **91** (58 mg, 0.25 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl but-3-yn-2-ylcarbamate **82**) (56 mg, 0.33 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (9.3 mg, 10 mol%), PNP(Cy) (5.3 mg, 5 mol%) and dcpm (5.1 mg, 5 mol%) in acetone (0.14 mL, 1.0 M). After 5 mins at 55 °C it was transferred to silver carbonate (69 mg, 0.25 mmol, 1.0 equiv.) and 4-methoxyphenylboronic acid (50 mg, 0.33 mmol, 1.5 equiv.) using acetone (0.46 mL). After stirring for 4 hrs at 55 °C the reaction was filtered and stirred with CH_2Cl_2 (4 mL) and *p*-TSA (48 mg, 0.25 mmol, 1.0 equiv.) at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (10-40% CH_2Cl_2 in petrol) to afford *pyrrole* **201** as an off-white solid (43.8 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* 2.0, Ar-*H*), 7.45 (1H, dd, *J* 8.0, 2.0, Ar-*H*), 7.21 (1H, d, *J* 8.0, Ar-*H*), 7.12-7.10 (2H, m, Ar-*H*), 6.83-6.81 (2H, m, Ar-*H*), 5.91 (2H, app s, 2 × NCC*H*), 3.82 (3H, s, OCH_3), 2.36 (3H, s, NC(CH_3)), 1.26 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.8, 149.4, 142.3, 133.1, 132.5, 132.4, 132.3, 132.2, 131.8,

129.8, 129.2, 121.3, 113.6, 113.4, 110.6, 83.2, 55.3, 27.6, 16.0; IR: ν_{max} (neat)/cm^{-1} 2979, 1739, 1610, 1513, 1250, 1177, 1093, 983; LRMS (ESI$^+$): *m/z* 444 ([^{81}Br] [M+H]$^+$, 100%), 442 ([^{79}Br] [M+H]$^+$, 95%), 464 ([^{79}Br] [M+Na]$^+$, 80%), 466 ([^{81}Br] [M+Na]$^+$, 70%); HRMS (ESI$^+$) found 464.08330 [[^{79}Br] [M+Na]$^+$], 466.08122 [[^{81}Br] [M+Na]$^+$], $C_{23}H_{24}{}^{79}BrNO_3Na^+$ requires 464.08318, $C_{23}H_{24}{}^{81}BrNO_3Na^+$ requires 466.08113; mp: 133-134 °C (CH_2Cl_2/petrol).

***tert*-Butyl 2-[4-(methoxycarbonyl)phenyl]-5-[4'-methyl-4-(trifluoromethyl)-(1,1'-biphenyl)-2-yl]-1*H*-pyrrole-1-carboxylate, 202**

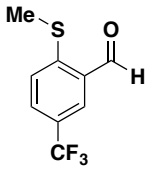


Prepared according to general procedure **I** using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **203** (44 mg, 0.20 mmol, 1.0 equiv.), propargylic amine (methyl 4-{1-[(*tert*-butoxycarbonyl)amino]prop-2-yn-1-yl}benzoate, **143**) (75 mg, 0.26 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (7.5 mg, 10 mol%) , PNP(Cy) (4.2 mg, 5 mol%) and dcpm (4.1 mg, 5 mol%) in acetone (81 μL, 1.0 M). After 5 mins at 55 °C it was transferred to silver carbonate (55 mg, 0.20 mmol, 1.0 equiv.) and 4-tolylboronic acid (41 mg, 0.30 mmol, 1.5 equiv.) using acetone (0.45 mL). After stirring for 6 hrs at 55 °C the reaction was filtered and stirred with CH_2Cl_2 (3 mL) and *p*-TSA (38 mg, 0.20 mmol, 1.0 equiv.) at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford *pyrrole* **202** as a pale brown solid (51.3 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-8.00 (2H, m, Ar-*H*), 7.71-7.68 (2H, m, Ar-*H*), 7.56 (1H, d, *J* 8.5, Ar-*H*), 7.29 (2H, app td, *J* 4.0, 2.0, Ar-*H*), 7.15 (4H, app br s, Ar-*H*), 6.24 (1H, d, *J* 3.5, NCC*H*), 6.16 (1H, d, *J* 3.5, NCC*H*), 3.95 (3H, s, CO_2CH_3), 2.40 (3H, s, ArCH_3), 1.04 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9, 148.5, 144.9, 139.0, 137.2, 137.0, 135.5, 134.9, 133.8, 129.9, 129.0, 128.9 (q, $^2J_{CF}$ 32.5), 128.8, 128.7, 128.6, 128.5, 127.0 (q, $^3J_{CF}$ 3.5), 124.8 (q, $^3J_{CF}$ 3.5), 124.0 (q, $^1J_{CF}$ 270.0), 114.6, 114.0, 84.0, 52.1, 27.1,

21.1; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −62.3; IR: ν_{max} (neat)/cm^{-1} 2931, 1747, 1720, 1611, 1396, 1327, 1169, 1045; LRMS (ESI$^+$): *m/z* 536 ([M+H]$^+$, 75%), 558 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 536.20435 [M+H]$^+$, $C_{31}H_{29}O_4F_3N^+$ requires 536.20432; mp: 128-129 °C (EtOAc/petrol).

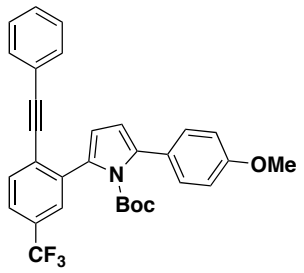
2-(Methylthio)-5-(trifluoromethyl)benzaldehyde, 203



Prepared according to general procedure **A** using methanethiol sodium salt solution (1.90 mL, 3.0 M in water, 5.75 mmol, 1.1 equiv.) and 2-fluoro-5-(trifluoromethyl)benzaldehyde (0.74 mL, 5.20 mmol, 1.0 equiv.) in DMF (10 mL). The crude was purified by flash column chromatography (30% Et_2O in petrol) to afford the title *aldehyde* **203** as a white solid (0.85 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (1H, s, C*H*O), 8.07 (1H, d, *J* 1.5, Ar-*H*), 7.77 (1H, dd, *J* 8.5, 1.5, Ar-*H*), 7.46 (1H, d, *J* 8.5, Ar-*H*), 2.57 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 190.0, 148.4, 130.2 (q, $^3J_{CF}$ 3.5), 129.9 (q, $^3J_{CF}$ 3.5), 127.0, 126.6 (q, $^2J_{CF}$ 30.5), 125.1, 123.6 (q, $^1J_{CF}$ 250.0), 15.2; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): −62.5; IR: ν_{max} (neat)/cm^{-1} 3041, 1686, 1611, 1556, 1350, 1334, 1310, 1262, 1114; LRMS (ESI$^+$): *m/z* 221 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 221.02435 [M+H]$^+$, $C_9H_8OF_3S^+$ requires 221.02425; mp: 102-104 °C (CH_2Cl_2/petrol).

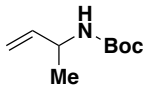
***tert*-Butyl 2-(4-methoxyphenyl)-5-[2-(phenylethynyl)-5-(trifluoromethyl)phenyl]-1*H*-pyrrole-1-carboxylate, 204**



Prepared according to general procedure **I** using 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **203** (44.0 mg, 0.20 mmol, 1.0 equiv.), propargylic amine (*tert*-butyl [1-(4-methoxyphenyl)prop-2-yn-1-yl]carbamate **139**) (67.9 mg, 0.26 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (7.5 mg, 10 mol%) and dcpe (8.5 mg, 10 mol%) in 1,2-DCE (88 μL, 1.0 M). After 2 mins at room temperature the reaction mixture was transferred to silver carbonate (55.0 mg, 0.20 mmol, 1.0 equiv.), copper(I) brominde (114.8 mg, 0.8 mmol, 4.0 equiv.) and phenylacetylene (44 μL, 0.40 mmol, 2.0 equiv.) using 1,2-DCE (0.5 mL). After stirring for 16 hrs at 80 °C the reaction was filtered and stirred with CH_2Cl_2 (3 mL) and *p*-TSA (57 mg, 0.30 mmol, 1.5 equiv.) at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to afford *pyrrole* **204** as an off white solid (56 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.72 (1H, m, Ar-*H*), 7.67 (1H, app dt, *J* 8.0, 1.0, Ar-*H*), 7.61-7.59 (1H, m, Ar-*H*), 7.44-7.41 (2H, m, Ar-*H*), 7.36-7.32 (5H, m, Ar-*H*), 6.96-6.94 (2H, m, Ar-*H*), 6.34 (1H, d, *J* 3.5, NCC*H*), 6.26 (1H, d, *J* 3.5, NCC*H*), 3.88 (3H, s, OCH_3), 1.10 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.1, 149.2, 138.7, 136.5, 132.4 (q, $^2J_{CF}$ 36.0), 131.9, 131.5, 130.5, 130.0, 128.7, 128.6, 127.6 (q, $^1J_{CF}$ 200.5), 127.3, 126.1 (q, $^3J_{CF}$ 3.5), 123.9 (q, $^3J_{CF}$ 3.5), 122.6, 114.6, 113.7, 113.2, 112.5, 94.9, 87.3, 83.7, 55.3, 27.0; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ –62.1; IR: ν_{max} (neat)/cm^{-1} 2980, 2838, 1745, 1581, 1325, 1248, 1172, 1097, 991; LRMS (ESI$^+$): *m/z* 540 ([M+Na]$^+$, 100%), 518 ([M+H]$^+$, 40%); HRMS (ESI$^+$) found 540.17474 [M+Na]$^+$, $C_{31}H_{26}O_3F_3NNa^+$ requires 540.17570; mp: 136-137 °C (Et_2O/petrol).

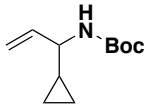
General procedure J for the synthesis of terminal allylic amines as exemplified by the preparation of *tert*-butyl but-3-en-2-ylcarbamate, 205:



Following a procedure adapted from Petrini *et al.*[168] A solution of vinylmagnesium bromide (6.16 mL, 1.0 M in THF, 6.16 mmol, 2.2 equiv.) was added dropwise to a solution of α-amido sulfone (*tert*-butyl (1-tosylethyl)carbamate **122**) (0.80 g, 2.8 mmol, 1.0 equiv.) in THF (26.5 mL) at -20 °C. The reaction mixture was stirred at –20 °C for 30 mins and then warmed to room temperature over 30 mins. Upon completion the reaction was quenched with sat. $NH_4Cl_{(aq.)}$ (15 mL) at –20 °C and was allowed to warm to room temperature. The product was extracted with Et_2O (3 × 10 mL) and washed with brine (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to give title *allylic amine* **205** as a colourless oil (80 mg, 17%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (1H, ddd, *J* 17.0, 10.5, 5.0, CH_2CH), 5.19-5.06 (2H, m, CH_2CH), 4.48 (1H, br s, N*H*), 4.24 (1H, app br s, NHC*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.23 (3H, d, *J* 7.0, NHCH(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.2, 116.4, 113.6, 79.5, 48.2, 28.4, 20.7; HRMS (FI^+) found 171.1258 $[M]^+$, $C_9H_{17}NO_2^+$ requires 171.1259. This data is consistent with literature.[269]

***tert*-Butyl (1-cyclopropylallyl)carbamate, 206**

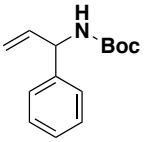


Prepared according to general procedure **J** using vinylmagnesium bromide (3.52 mL, 1.0 M in THF, 3.52 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [cyclopropyl(tosyl)methyl]carbamate **124**) (0.50 g, 1.60 mmol, 1.0 equiv.) in THF (15 mL). The crude product was purified by flash column chromatography (10% Et_2O in petrol) to give *allylic amine* **206** as a colourless oil (160 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (1H, ddd, *J* 17.0, 10.5, 5.5, $CH_2CHCHNH$), 5.21-5.06 (2H, m, $CH_2CHCHNH$), 4.70 (1H, app br s, NHC*H*), 3.58 (1H, br s, N*H*), 1.43 (9H, s,

$CO_2C(CH_3)_3$), 0.89-0.81 (1H, m, NHCH(C*H*$(CH_2)_2$)), 0.53-0.45 (2H, m, NHCH(CH(C$H_2$$CH_2$))), 0.37 (1H, dt, *J* 9.0, 4.5, NHCH(CH($CH_2CH_aH_b$))), 0.27-0.22 (1H, m, NHCH(CH($CH_2CH_aH_b$))); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.3, 137.9, 114.4, 79.2, 56.3, 28.4, 15.6, 2.7; IR: ν_{max} (neat)/cm^{-1} 2979, 1688, 1497, 1390, 1243, 1164, 1018, 989; LRMS (ESI$^+$): *m/z* 220 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 220.13142 [M+Na]$^+$, $C_{11}H_{19}O_2NNa^+$ requires 220.13080.

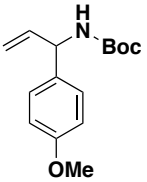
***tert*-Butyl (1-phenylallyl)carbamate, 207**



Prepared according to general procedure **J** using vinylmagnesium bromide (9.5 mL, 1.0 M in THF, 9.5 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [phenyl(phenylsulfonyl)methyl]carbamate **125**) (1.50 g, 4.32 mmol, 1.0 equiv.) in THF (42 mL). The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to give allylic amine **207** as a white solid (0.85 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.36 (2H, m, Ar-*H*), 7.33-7.30 (3H, m, Ar-*H*), 6.02 (1H, ddd, *J* 17.0, 10.5, 5.5, CH_2CH), 5.31 (1H, app br s, NHC*H*), 5.31 (1H, app t, *J* 1.5, $CH_aH_bCHCHNH$), 5.24 (1H, app dt, *J* 3.0, 1.5, $CH_aH_bCHCHNH$), 4.89 (1H, br s, N*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 138.0, 128.7, 127.5, 127.0, 125.7, 115.4, 80.3, 56.6, 28.4; LRMS (ESI$^+$): *m/z* 256 ([M+Na]$^+$, 100%); mp: 64-65 °C (CH_2Cl_2/hexane), (lit. mp: 61 °C). This data is consistent with literature.[168]

***tert*-Butyl [1-(4-methoxyphenyl)allyl]carbamate, 208**

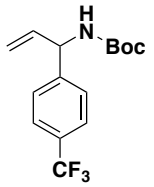


Prepared according to general procedure **J** using vinylmagnesium bromide (1.12 mL, 1.0 M in THF, 1.12 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [(4-methoxyphenyl)(phenylsulfonyl)methyl]carbamate **126**) (0.20 g, 0.53 mmol, 1.0 equiv.) in

THF (5 mL). The crude product was purified by flash column chromatography (15-30% Et_2O in petrol) to give *allylic amine* **208** as a white solid (112 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.22 (2H, m, Ar-*H*), 6.90-6.87 (2H, m, Ar-*H*), 6.00 (1H, ddd, *J* 17.0, 10.0, 5.5, CH_2CH), 5.28-5.21 (3H, m, CH_2CH and NHC*H*), 4.94 (1H, br s, N*H*), 3.80 (3H, s, OCH_3), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 155.0, 138.2, 133.2, 128.2, 115.1, 114.0, 79.5, 56.0, 55.2, 28.4; IR: ν_{max} (neat)/cm^{-1} 2979, 1715, 1612, 1366, 1245, 1108, 1036; LRMS (ESI$^+$): *m/z* 286 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 286.14130 [M+Na]$^+$, $C_{15}H_{21}O_3NNa^+$ requires 286.14136; mp: 74-75 °C (Et_2O/petrol). ^{1}H and ^{13}C data consistent with literature.[270]

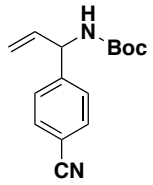
***tert*-Butyl {1-[4-(trifluoromethyl)phenyl]allyl}carbamate, 209**



Prepared according to general procedure **J** using vinylmagnesium bromide (1.32 mL, 1.0 M in THF, 1.32 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [(phenylsulfonyl)[4-(trifluoromethyl)phenyl]methyl]carbamate **127**) (0.25 g, 0.60 mmol, 1.0 equiv.) in THF (5.7 mL). The crude product was purified by flash column chromatography (15-20% Et_2O in petrol) to give *allylic amine* **209** as a white solid (163 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* 8.0, Ar-*H*), 7.43 (2H, d, *J* 8.0, Ar-*H*), 5.98 (1H, ddd, *J* 17.0, 10.5, 6.0, CH_2CH), 5.36 (1H, br s, N*H*), 5.27 (1H, d, *J* 10.5, $CH_aH_bCHCHNH$), 5.22 (1H, d, *J* 17.0, $CH_aH_bCHCHNH$), 5.10 (1H, app br d, *J* 7.0, NHC*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 145.2, 137.1, 129.6 (q, $^2J_{CF}$ 32.5), 127.3, 125.5 (q, $^3J_{CF}$ 3.5), 124.1 (q, $^1J_{CF}$ 275.0) 116.6, 80.0, 56.4, 28.3; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −62.5; IR: ν_{max} (neat)/cm^{-1} 2982, 1700, 1619, 1492, 1367, 1297, 1107, 1067, 990; LRMS (ESI$^+$): *m/z* 324 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 324.1180 [M+Na]$^+$, $C_{15}H_{18}O_2NF_3Na^+$ requires 324.1182; mp: 80-81 °C (Et_2O/petrol). ^{1}H and ^{13}C data consistent with literature.[270]

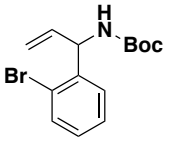
tert-Butyl [1-(4-cyanophenyl)allyl]carbamate, 210



Prepared according to general procedure **J** using vinylmagnesium bromide (4.6 mL, 1.0 M in THF, 4.6 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [(4-cyanophenyl)(phenylsulfonyl)methyl]carbamate **129**) (0.80 g, 2.10 mmol, 1.0 equiv.) in THF (20 mL). The crude product was purified by flash column chromatography (15-30% Et_2O in petrol) to give *allylic amine* **210** as a brown solid (511 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.34 (4H, m, Ar-*H*), 7.38-7.27 (1H, m, N*H*), 7.31 (1H, app dd, *J* 6.0, 3.0, CH_2CH), 6.68 (1H, app d, *J* 10.5, NHC*H*), 5.81-5.77 (2H, m, CH_2CH), 1.47 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1, 136.2, 131.1, 131.0, 128.7, 128.4, 127.4, 126.6, 86.8, 30.3, 28.4; IR: ν_{max} (neat)/cm^{-1} 2979, 2229, 1714, 1642, 1520, 1414, 1305, 1250, 1077; LRMS (ESI$^+$): *m/z* 281 ([M+Na]$^+$, 100%), 259 ([M+H]$^+$, 20%); HRMS (ESI$^+$) found 281.12620 [M+Na]$^+$, $C_{15}H_{18}O_2N_2Na^+$ requires 281.12605; mp: 65-66 °C (Et_2O/petrol).

tert-Butyl [1-(2-bromophenyl)allyl]carbamate, 211

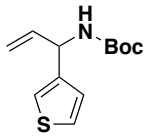


Prepared according to general procedure **J** using vinylmagnesium bromide (4.64 mL, 1.0 M in THF, 4.64 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [(2-bromophenyl)(phenylsulfonyl)methyl]carbamate **132**) (0.90 g, 2.11 mmol, 1.0 equiv.) in THF (20 mL). The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to give *allylic amine* **211** as a white solid (226.3 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (1H, m, Ar-*H*), 7.33-7.31 (2H, m, Ar-*H*), 7.20-7.14 (1H, m, Ar-*H*), 6.03-5.98 (1H, m, CH_2CH), 5.66 (1H, app br s, NHC*H*), 5.28-5.16 (2H, m, CH_2CH), 5.02 (1H, br s, N*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$):

δ 154.8, 140.1, 136.6, 133.2, 128.9, 128.4, 127.6, 123.6, 116.2, 79.7, 56.1, 28.4; IR: ν_{max} (neat)/cm^{-1} 2979, 1698, 1491, 1365, 1170, 1076, 1024; LRMS (ESI^+): *m/z* 334 ([^{79}Br] $[M+Na]^+$, 100%), 336 ([^{81}Br] $[M+Na]^+$, 90%); HRMS (ESI^+) found 334.04150 [[^{79}Br] $M+Na]^+$, 336.03940 [[^{81}Br] $M+Na]^+$, $C_{14}H_{18}O_2N^{79}BrNa^+$ requires 334.04131, $C_{14}H_{18}O_2N^{81}BrNa^+$ requires 336.03927; mp: 78-79 °C (Et_2O/petrol).

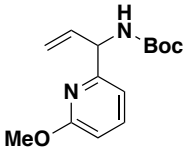
***tert*-Butyl [1-(thiophen-3-yl)allyl]carbamate**, **212**



Prepared according to general procedure **J** using vinylmagnesium bromide (2.5 mL, 1.0 M in THF, 2.5 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl [(phenylsulfonyl)(thiophen-3-yl)methyl]carbamate **134**) (0.40 g, 1.13 mmol, 1.0 equiv.) in THF (11 mL). The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to give *allylic amine* **212** as a white solid (175 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (1H, app ddd, *J* 5.0, 3.0, 2.5, Ar-*H*), 7.13-7.11 (1H, m, Ar-*H*), 7.02-7.00 (1H, m, Ar-*H*), 6.02 (1H, ddd, *J* 17.0, 10.5, 6.0, CH_2CH), 5.36 (1H, app br s, NHC*H*), 5.27-5.20 (2H, m, CH_2CHCHNH), 5.00 (1H, br s, N*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.0, 142.2, 137.6, 126.7, 126.2, 121.6, 115.3, 79.7, 52.5, 28.4; IR: ν_{max} (neat)/cm^{-1} 2971, 1712, 1520, 1416, 1521, 1244, 1077, 794; LRMS (ESI^+): *m/z* 262 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 262.08729 $[M+Na]^+$, $C_{12}H_{17}O_2NSNa^+$ requires 262.08777; mp: 64 °C (Et_2O/petrol).

tert-Butyl [1-(6-methoxypyridin-2-yl)allyl]carbamate, 213

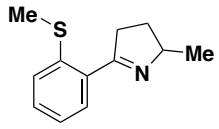


Prepared according to general procedure **J** using vinylmagnesium bromide (4.62 mL, 1.0 M in THF, 4.62 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl[(6-methoxypyridin-2-yl)-(phenylsulfonyl)-methyl]carbamate **137**) (0.80 g, 2.1 mmol, 1.0 equiv.) in THF (20 mL). The crude product was purified by flash column chromatography (5-10% Et_2O in petrol) to give

allylic amine **213** as a white solid (392 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, ddd, *J* 8.5, 7.0, 1.0, Ar-*H*), 6.85 (1H, d, *J* 7.0, Ar-*H*), 6.65 (1H, app dt, *J* 8.5, 1.0, Ar-*H*), 6.01-5.93 (1H, m, CH_2CH), 5.80 (1H, app br s, NHC*H*), 5.32-5.15 (3H, m, CH_2CH and N*H*), 3.96 (3H, s, OCH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 156.4, 155.2, 139.3, 138.2, 115.3, 114.3, 109.2, 79.5, 57.4, 53.3, 28.4; IR: ν_{max} (neat)/cm^{-1} 2983, 1692, 1633, 1520, 1488, 1136, 910; LRMS (ESI$^+$): *m/z* 265 ([M+H]$^+$, 100%), 287 ([M+Na]$^+$, 60%); HRMS (ESI$^+$) found 287.13662 [M+Na]$^+$, $C_{14}H_{20}O_3N_2Na^+$ requires 287.13661; mp: 89-91 °C CH_2Cl_2/hexane).

General procedure K for the synthesis of dihydropyrroles as exemplified by the synthesis of 2-methyl-5-[2-(methylthio)phenyl]-3,4-dihydro-2*H*-pyrrole, 214

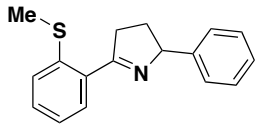


An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%). Once under an inert atmosphere, they were dissolved in acetone (1 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (98 μL, 1.0 M with respect to aldehyde minus the volume or mass of both aldehyde and alkyne) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and allylic amine (*tert*-butyl but-3-en-2-ylcarbamate, **205**) (33.4 mg, 0.195 mmol, 1.3 equiv.). The reaction mixture, once homogenous (on occasion, sonication was required), was then stirred at 55 °C and monitored by TLC until complete. After 3 hrs, the reaction vessel was opened to air followed by the addition of acetonitrile (1.5 mL) and *p*-TSA (30.0 mg, 0.15 mmol, 1.0 equiv.). The reaction mixture was further stirred until complete. After 3 hrs, the solution was diluted with acetonitrile (5 mL) and neutralised by the addition of sat. $NaHCO_{3(aq.)}$ (10 mL) in a separatory funnel. The aqueous mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product and this was purified by flash column

chromatography (10-50% Et_2O in petrol) to afford title *dihydropyrrole* **214** as a colourless oil (18.4 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (1H, m, Ar-*H*), 7.37-7.35 (1H, m, Ar-*H*), 7.31 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.20-7.17 (1H, m, Ar-*H*), 4.47-4.38 (1H, m, NC*H*), 3.11 (1H, dddd, *J* 17.0, 9.5, 5.0, 2.0, NCHCH_aH$_b$), 3.00-2.91 (1H, m, NCCH_aH$_b$), 2.46 (3H, s, SCH_3), 2.25 (1H, dddd, *J* 12.5, 9.5, 7.5, 5.0, NCHCH$_a$$H_b$), 1.61-1.56 (1H, m, NCCH$_a$$H_b$), 1.43 (3H, d, *J* 6.5, NCH(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 139.3, 133.5, 130.2, 129.5, 125.3, 124.0, 69.0, 37.7, 31.0, 22.2, 16.4; IR: ν_{max} (neat)/cm^{-1} 2962, 2924, 1613, 1559, 1470, 1290, 908; LRMS (ESI$^+$): *m/z* 206 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 206.09988 [M+H]$^+$, $C_{12}H_{16}NS^+$ requires 206.09980.

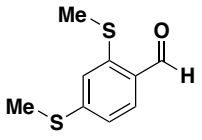
5-[2-(Methylthio)phenyl]-2-phenyl-3,4-dihydro-2*H*-pyrrole, 215



Prepared according to general procedure **K** using 2-(methylthio)benzaldehyde **50** (77 μL, 0.60 mmol, 1.0 equiv.), allylic (*tert*-butyl (1-phenylallyl)carbamate, **207**) (182 mg, 0.78 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (11.2 mg, 5 mol%) and PNP(Cy) (12.7 mg, 5 mol%) in acetone (0.34 mL, 1.0 M). After stirring for 10 mins at 55 °C, acetonitrile (3.0 mL) and *p*-TSA (114 mg, 0.60 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (10% Et_2O in petrol) to afford *dihydropyrrole* **215** as a pale yellow solid (134 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.52-7.49 (2H, m, Ar-*H*), 7.45-7.36 (4H, m, Ar-*H*), 7.32-7.28 (1H, m, Ar-*H*), 7.24 (1H, ddd, *J* 7.5, 7.0, 1.5, Ar-*H*), 5.47 (1H, tt, *J* 8.0, 2.0, NC*H*), 3.23-3.08 (2H, m, NCCH_2), 2.68-2.60 (1H, m, NCHCH_aH$_b$), 2.50 (3H, s, SCH_3), 1.90 (1H, app ddd, *J* 9.5, 9.0, 8.0, NCHCH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2, 144.7, 140.1, 132.9, 129.9, 129.8, 128.4, 126.6, 126.5, 125.2, 123.8, 76.7, 37.9, 32.6, 16.5; IR: ν_{max} (neat)/cm^{-1} 3059, 2918, 1612, 1557, 1470, 1329, 1084; LRMS (ESI$^+$): *m/z* 268 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 268.11560 [M+H]$^+$, $C_{17}H_{18}NS^+$ requires 268.11545; mp: 52-53 °C (Et_2O/petrol).

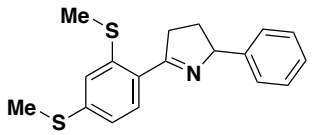
2,4-Bis(methylthio)benzaldehyde



Prepared according to general procedure **A** using methanethiol sodium salt solution (10.4 mL, 3.0 M in water, 31.1 mmol, 2.1 equiv.) and 2-fluoro-4-bromobenzaldehyde (3.00 g, 14.8 mmol, 1.0 equiv.) in DMF (18 mL). The crude purified by flash column chromatography (10-30% Et_2O in petrol) to obtain the title *aldehyde* as off-white needles (0.96 g, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (1H, s, C*H*O), 7.70 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.34-7.22 (1H, m, Ar-*H*), 7.07 (1H, d, *J* 8.0, Ar-*H*), 2.56 (3H, s, *o*-SC*H*$_3$), 2.50 (3H, s, *p*-SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.2, 147.7, 143.8, 133.5, 129.5, 121.3, 120.5, 15.4, 14.7; IR: ν_{max} (neat)/cm^{-1} 2920, 2835, 1675, 1574, 1534, 1286, 1108, 955, 862; LRMS (ESI$^+$): *m/z* 221 ([M+Na]$^+$, 100%), 199 ([M+H]$^+$, 10%); HRMS (ESI$^+$) found 199.02465 [M+H]$^+$, $C_9H_{11}OS_2^+$ requires 199.02458; mp: 64-66 °C (CH_2Cl_2/petrol).

5-[2,4-Bis(methylthio)phenyl]-2-phenyl-3,4-dihydro-2*H*-pyrrole, 216

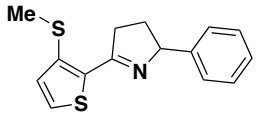


Prepared according to general procedure **K** using 2,4-bis(methylthio)benzaldehyde (29.7 mg, 0.15 mmol, 1.0 equiv.), allylic amine (*tert*-butyl (1-phenylallyl)carbamate **207**) (45.5 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (70 μL, 1.0 M). After stirring for 1 hr at 55 °C, acetonitrile (1.5 mL) and *p*-TSA (57.2 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 2 hrs. The crude product was purified by flash column chromatography (10-20% Et_2O in petrol) to afford *dihydropyrrole* **216** as an off-white solid (40.9 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, *J* 8.0, Ar-*H*), 7.47-7.45 (2H, m, Ar-*H*), 7.40-7.36 (2H, m, Ar-*H*), 7.28-7.25 (1H, m, Ar-*H*), 7.19 (1H, d, *J* 2.0, Ar-*H*), 7.06 (1H, dd, *J* 8.0, 2.0, Ar-*H*), 5.45 (1H, t, *J* 8.0, NC*H*), 3.15-3.07 (2H, m, NCC*H*$_2$), 2.65-2.58 (1H, m, NCHC*H*$_a$H$_b$), 2.56 (3H, s, SC*H*$_3$), 2.49 (3H, s, SC*H*$_3$), 1.90-1.81 (1H, m, NCHCH$_a$*H*$_b$); ^{13}C NMR (101 MHz,

$CDCl_3$): δ 173.4, 144.8, 141.2, 141.1, 130.4, 129.1, 128.4, 126.58, 126.50, 122.1, 120.9, 76.6, 37.6, 32.4, 16.4, 15.4; IR: ν_{max} (neat)/cm^{-1} 2919, 1493, 1473, 1331, 1269, 1114, 1085, 968; LRMS (ESI^+): *m/z* 314 ($[M+H]^+$, 100%); HRMS (ESI^+) found 314.10234 $[M+H]^+$, $C_{18}H_{20}NS_2^+$ requires 314.10317; mp: 73-74 °C (Et_2O/petrol).

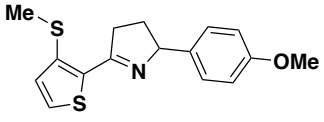
5-[3-(Methylthio)thiophen-2-yl]-2-phenyl-3,4-dihydro-2*H*-pyrrole, 217



Prepared according to general procedure **K** using 3-(methylthio)thiophene-2-carbaldehyde **90** (31.6 mg, 0.20 mmol, 1.0 equiv.), allylic amine (*tert*-butyl (1-phenylallyl)carbamate **207**) (60.6 mg, 0.26 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (3.7 mg, 5 mol%) and PNP(Cy) (4.2 mg, 5 mol%) in acetone (100 μL, 1.0 M). After stirring for 16 hrs at 55 °C, acetonitrile (3.0 mL) and *p*-TSA (57.2 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (10-20% Et_2O in petrol) to afford *dihydropyrrole* **217** as an off-white solid (41.6 mg, 76%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, d, *J* 5.5, SC*H*), 7.37-7.33 (4H, m, Ar-*H*), 7.28-7.25 (1H, m, Ar-*H*), 7.07 (1H, d, *J* 5.5, SCHC*H*), 5.40-5.35 (1H, m, NC*H*), 3.23 (1H, dddd, *J* 14.5, 9.5, 4.5, 2.5, NCC$H_a$$H_b$), 3.14-3.05 (1H, m, NCC$H_a$$H_b$), 2.66-2.59 (1H, m, NCHC$H_a$$H_b$), 2.58 (3H, s, SC$H_3$), 1.91 (1H, dddd, *J* 12.5, 9.5, 8.0, 7.5, NCHC$H_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1, 144.8, 137.6, 130.1, 128.4, 127.9, 127.3, 126.6, 126.5, 75.5, 37.8, 33.0, 17.4; IR: ν_{max} (neat)/cm^{-1} 2921, 1659, 1590, 1494, 1426, 1319, 1260, 1051; LRMS (ESI^+): *m/z* 274 ($[M+H]^+$, 100%); HRMS (ESI^+) found 274.07187 $[M+H]^+$, $C_{15}H_{16}NS_2^+$ requires 274.07187; mp: 57-58 °C (Et_2O/petrol).

2-(4-Methoxyphenyl)-5-[3-(methylthio)thiophen-2-yl]-3,4-dihydro-2*H*-pyrrole, 218

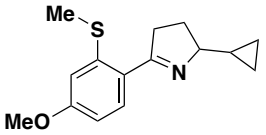


Prepared according to general procedure **K** using 3-(methylthio)thiophene-2-carbaldehyde **90** (31.6 mg, 0.20 mmol, 1.0 equiv.), allylic amine (*tert*-butyl [1-(4-

methoxyphenyl)allyl]carbamate **208**) (79 mg, 0.3 mmol, 1.5 equiv.), $[Rh(nbd_2)]BF_4$ (3.7 mg, 5 mol%) and PNP(Cy) (4.2 mg, 5 mol%) in acetone (89 μL, 1.0 M). After stirring for 16 hrs at 55 °C, acetonitrile (3.0 mL) and *p*-TSA (57.2 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 2 hrs. The crude product was purified by flash column chromatography (10-20% Et_2O in petrol) to afford *dihydopyrrole* **218** as a very pale yellow solid (54.6 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, d, *J* 5.5, SC*H*), 7.29-7.27 (2H, m, Ar-*H*), 7.07 (1H, d, *J* 5.5, SCHC*H*), 6.92-6.88 (2H, m, Ar-*H*), 5.34-5.30 (1H, m, NC*H*), 3.82 (3H, s, OCH_3), 3.22 (1H, dddd, *J* 16.5, 9.5, 4.5, 2.0, NCCH_aH$_b$), 3.12-3.03 (1H, m, NCCH$_a$$H_b$), 2.61-2.56 (1H, m, NCHCH_aH$_b$), 2.58 (3H, s, SCH_3) 1.88 (1H, dddd, *J* 12.5, 9.5, 8.0, 7.5, NCHCH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.8, 137.6, 137.0, 130.2, 129.1, 127.9, 127.5, 127.3, 113.8, 74.9, 55.3, 37.8, 33.1, 17.4; IR: ν_{max} (neat)/cm^{-1} 2953, 2833, 1612, 1511, 1464, 1351, 1319, 1244, 1035; LRMS (ESI$^+$): *m/z* 304 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 304.08220 [M+H]$^+$, $C_{16}H_{18}NOS_2^+$ requires 304.08243; mp: 79-80 °C (Et_2O/petrol).

2-Cyclopropyl-5-[4-methoxy-2-(methylthio)phenyl]-3,4-dihydro-2*H*-pyrrole, 219

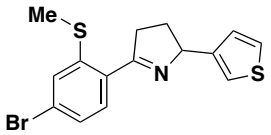


Prepared according to general procedure **K** using 4-methoxy-2-(methylthio)benzaldehyde (36.5 mg, 0.20 mmol, 1.0 equiv.), allylic amine (*tert*-butyl (1-cyclopropylallyl)carbamate **206**) (51.3 mg, 0.26 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (3.7 mg, 5 mol%) and PNP(Cy) (4.2 mg, 5 mol%) in acetone (110 μL, 1.0 M). After stirring for 16 hrs at 55 °C, acetonitrile (2 mL) and *p*-TSA (38 mg, 0.20 mmol, 1.0 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (10-50% Et_2O in petrol) to afford *dihydropyrrole* **219** as a colourless oil (25.1 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, d, *J* 8.5, Ar-*H*), 6.82 (1H, d, *J* 2.5, Ar-*H*), 6.68 (1H, dd, *J* 8.5, 2.5, Ar-*H*), 4.02-3.97 (1H, m, NC*H*), 3.87 (3H, s, OCH_3), 3.01 (1H, dddd, *J* 12.0, 9.5, 4.5, 2.0, NCHCH_aH$_b$), 2.91 (1H, dddd, *J* 16.5, 9.5, 8.0, 1.5, NCCH_aH$_b$), 2.43 (3H, s,

SC*H*$_3$), 2.21-2.18 (1H, m, NCH(C*H*(CH$_2$)$_2$)), 1.74 (1H, app d, *J* 8.5, NCHCH$_a$*H*$_b$), 1.04-1.02 (1H, m, NCCH$_a$*H*$_b$), 0.55-0.45 (4H, m, NCH(CH(C*H*$_2$)$_2$)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 160.4, 142.0, 131.3, 125.9, 111.4, 108.1, 55.3, 37.2, 30.9, 28.8, 16.7, 16.4, 2.5; IR: ν_{max} (neat)/cm^{-1} 3078, 2959, 1593, 1556, 1435, 1332, 1247, 1229, 1045, 907; LRMS (ESI$^+$): *m/z* 262 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 262.12549 [M+H]$^+$, $C_{15}H_{20}NOS^+$ requires 262.12601.

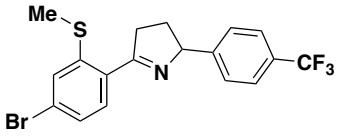
5-[4-Bromo-2-(methylthio)phenyl]-2-(thiophen-3-yl)-3,4-dihydro-2*H*-pyrrole, 220



Prepared according to general procedure **K** using 4-bromo-2-(methylthio)benzaldehyde **91** (45.8 mg, 0.20 mmol, 1.0 equiv.), allylic amine (*tert*-butyl [1-(thiophen-3-yl)allyl]carbamate **212**) (62.2 mg, 0.26 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (3.7 mg, 5 mol%) and PNP(Cy) (4.2 mg, 5 mol%) in acetone (89 μL, 1.0 M). After stirring for 16 hrs at 55 °C, acetonitrile (2 mL) and *p*-TSA (152 mg, 0.80 mmol, 4.0 equiv.) were added and stirred at room temperature for a further 6 hrs. The crude product was purified by flash column chromatography (10-50% Et_2O in petrol) to afford *dihydropyrrole* **220** as an off white solid (58 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, d, *J* 2.0, Ar-*H*), 7.40 (1H, d, *J* 8.0, Ar-*H*), 7.34-7.29 (3H, m, Ar-*H*), 7.15 (1H, dd, *J* 5.0, 1.5, Ar-*H*), 5.50 (1H, t, *J* 7.5, NC*H*), 3.11-3.06 (2H, m, NCC*H*$_2$), 2.61-2.53 (1H, m, NCHC*H*$_a$H$_b$), 2.48 (3H, s, SC*H*$_3$), 1.98-1.90 (1H, m, NCHCH$_a$*H*$_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 145.2, 142.9, 131.3, 131.0, 127.4, 126.7, 126.5, 125.8, 124.5, 120.2, 73.2, 37.4, 31.2, 16.6; IR: ν_{max} (neat)/cm^{-1} 2918, 1573, 1466, 1330, 1273, 1081, 988; LRMS (ESI$^+$): *m/z* 354 ([^{81}Br] [M+H]$^+$, 100%), 352 ([^{79}Br] [M+H]$^+$, 95%); HRMS (ESI$^+$) found 351.98270 [[^{79}Br] M+H]$^+$], 353.98037 [[^{81}Br] M+Na]$^+$], $C_{15}H_{15}{}^{79}BrNS_2^+$ requires 351.98238, $C_{15}H_{15}{}^{81}BrNS_2^+$ requires 352.98033; mp: 59-61 °C (Et_2O/petrol).

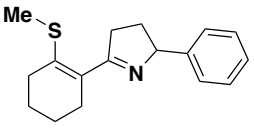
5-[4-Bromo-2-(methylthio)phenyl]-2-[4-(trifluoromethyl)phenyl]-3,4-dihydro-2*H*-pyrrole, 221



Prepared according to general procedure **K** using 4-bromo-2-(methylthio)benzaldehyde **91** (46 mg, 0.20 mmol, 1.0 equiv.), allylic amine (*tert*-butyl {1-[4-(trifluoromethyl)phenyl]allyl}carbamate, **209**) (90 mg, 0.3 mmol, 1.5 equiv.), $[Rh(nbd_2)]BF_4$ (3.7 mg, 5 mol%) and PNP(Cy) (4.2 mg, 5 mol%) in acetone (64 μL, 1.0 M). After stirring for 16 hrs at 55 °C, acetonitrile (3.0 mL) and *p*-TSA (57.2 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 3 hrs. The crude product was purified by flash column chromatography (10-20% Et_2O in petrol) to afford *dihydropyrrole* **221** as a very pale yellow solid (69.6 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (4H, app q, *J* 11.5, Ar-*H*), 7.45-7.42 (2H, m, Ar-*H*), 7.34 (1H, dd, *J* 8.5, 2.0, Ar-*H*), 5.47 (1H, t, *J* 8.0, NC*H*), 3.15-3.10 (2H, m, NCCH_2), 2.66 (1H, dtd, *J* 12.5, 8.0, 4.5, NCHCH_aH$_b$), 2.49 (3H, s, SCH_3), 1.83 (1H, app dq, *J* 12.5, 9.0, NCHCH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 148.5, 143.1, 131.4, 130.6, 128.9 (q, $^2J_{CF}$ 32.5), 127.4, 126.8, 126.7, 126.1 (q, $^1J_{CF}$ 205.5), 125.4 (q, $^3J_{CF}$ 3.5), 124.7, 76.3, 37.7, 32.2, 16.5; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −62.3; IR: ν_{max} (neat)/cm^{-1} 2360, 1618, 1574, 1540, 1325, 1122, 1106; LRMS (ESI$^+$): *m/z* 416 ([^{81}Br] $[M+H]^+$, 100%), 414 ([^{79}Br] $[M+H]^+$, 95%); HRMS (ESI$^+$) found 435.9951 [[^{79}Br] $M+Na]^+$], 437.9929 [[^{81}Br] $M+Na]^+$], $C_{18}H_{15}{}^{79}BrNF_3SNa^+$ requires 435.9953, $C_{18}H_{15}{}^{81}BrNF_3SNa^+$ requires 437.9926; mp: 80-82 °C (Et_2O/petrol).

5-[2-(Methylthio)cyclohex-1-en-1-yl]-2-phenyl-3,4-dihydro-2*H*-pyrrole, 222

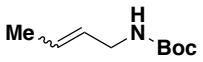


Prepared according to general procedure **K** using 2-(methylthio)cyclohex-1-ene-1-carbaldehyde **89** (31.0 mg, 0.20 mmol, 1.0 equiv.), allylic amine (*tert*-butyl (1-phenylallyl)carbamate, **207**) (70 mg, 0.3 mmol, 1.5 equiv.), $[Rh(nbd_2)]BF_4$ (3.7 mg, 5 mol%)

and PNP(Cy) (4.2 mg, 5 mol%) in acetone (99 μL, 1.0 M). After stirring for 16 hrs at 55 °C, acetonitrile (3.0 mL) and *p*-TSA (57.2 mg, 0.30 mmol, 2.0 equiv.) were added and stirred at room temperature for a further 2 hrs. The crude product was purified by flash column chromatography (10-20% Et_2O in petrol) to afford *dihydopyrrole* **222** as a pale yellow solid (17 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (4H, m, Ar-*H*), 7.27-7.22 (1H, m, Ar-*H*), 5.24-5.19 (1H, m, NC*H*), 3.01-2.94 (1H, m, NCCH_aH$_b$), 2.89-2.80 (1H, m, NCCH$_a$$H_b$), 2.51-2.47 (1H, m, NCHCH_aH$_b$), 2.46-2.41 (3H, m, NCHCH$_a$$H_b$ and SCCH_2), 2.28 (3H, s, SCH_3), 1.78-1.71 (6H, m, SCCH$_2$(CH_2)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 128.3, 127.8, 126.59, 126.53, 126.43, 125.5, 75.6, 38.1, 32.6, 30.3, 29.7, 23.2, 22.2, 14.9; IR: ν_{max} (neat)/cm^{-1} 2967, 1621, 1509, 1455, 1373, 1333, 1250, 998; LRMS (ESI$^+$): *m/z* 272 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 294.12890 [M+Na]$^+$, $C_{17}H_{21}NSNa^+$ requires 294.12869; mp: 70-71 °C (Et_2O/petrol).

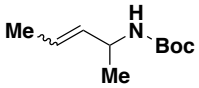
tert-Butyl but-2-en-1-ylcarbamate, 231



Prepared according to general procedure **J** using 1-propenylmagnesium bromide (16.2 mL, 0.5 M in THF, 8.07 mmol, 2.2 equiv.), *tert*-butyl ((phenylsulfonyl)methyl)carbamate (1.00 g, 3.67 mmol, 1.0 equiv.) in THF (35 mL). The crude product was purified by flash column chromatography (10% Et_2O in petrol) to give *allylic amine* **231** as a colourless oil (80 mg, 13%) in a 1:1 mixture of *cis*:*trans*.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64-5.53 (1H, m, *cis* and *trans* CH_3C*H*), 5.47-5.37 (1H, m, NHCH$_2$C*H*), 4.61-4.52 (1H, m, N*H*), 3.85-3.66 (2H, m, NHCH_2), 1.67-1.63 (3H, m, CH_3CH), 1.43 (9H, s, CO_2C(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.9, 127.6, 126.8, 79.1, 42.5 (*trans*), 37.3 (*cis*), 28.4, 17.6 (*trans*), 12.8 (*cis*); IR: ν_{max} (neat)/cm^{-1} 2978, 1690, 1506, 1454, 1391, 1365, 1247, 1163, 1043; LRMS (ESI$^+$): *m/z* 194 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 194.11533 [M+Na]$^+$, $C_9H_{17}O_2NNa^+$ requires 194.11515.

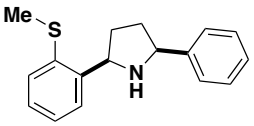
tert-Butyl pent-3-en-2-ylcarbamate, 232



Prepared according to general procedure **J** using 1-propenylmagnesium bromide (12.3 mL, 0.5 M in THF, 6.16 mmol, 2.2 equiv.), α-amido sulfone (*tert*-butyl (1-tosylethyl)carbamate **122**) (0.80 g, 2.8 mmol, 1.0 equiv.) in THF (27 mL). The crude product was purified by flash column chromatography (10% Et_2O in petrol) to give *allylic amine* **232** as a thick white oil (180 mg, 35%) of a 1:1 mixture of *cis*:*trans*.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59-5.50 (0.5H, m, *trans* $CH_3CHCHCHNH$), 5.48-5.35 (1H, m, NHCHC*H*), 5.22 (0.5H, d, *J* 9.5, *cis* $CH_3CHCHCHNH$), 4.54-4.12 (2H, br m, N*H* and NHC*H*), 1.66-1.62 (3H, m, $CH_3CHCHCHNH$), 1.40 (9H, s, $CO_2C(CH_3)_3$), 1.14 (3H, dd, *J* 6.0, 3.0, NHCH(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.1, 133.1, 124.7, 79.0, 47.6 (*trans*), 43.6 (*cis*), 28.4, 21.7, 17.6 (*trans*), 13.1 (*cis*); IR: ν_{max} (neat)/cm^{-1} 2977, 1629, 1497, 1450, 1366, 1241, 1169, 1027; LRMS (ESI$^+$): *m/z* 208 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 186.14911 [M+H]$^+$, $C_{10}H_{10}O_2N^+$ requires 186.14886.

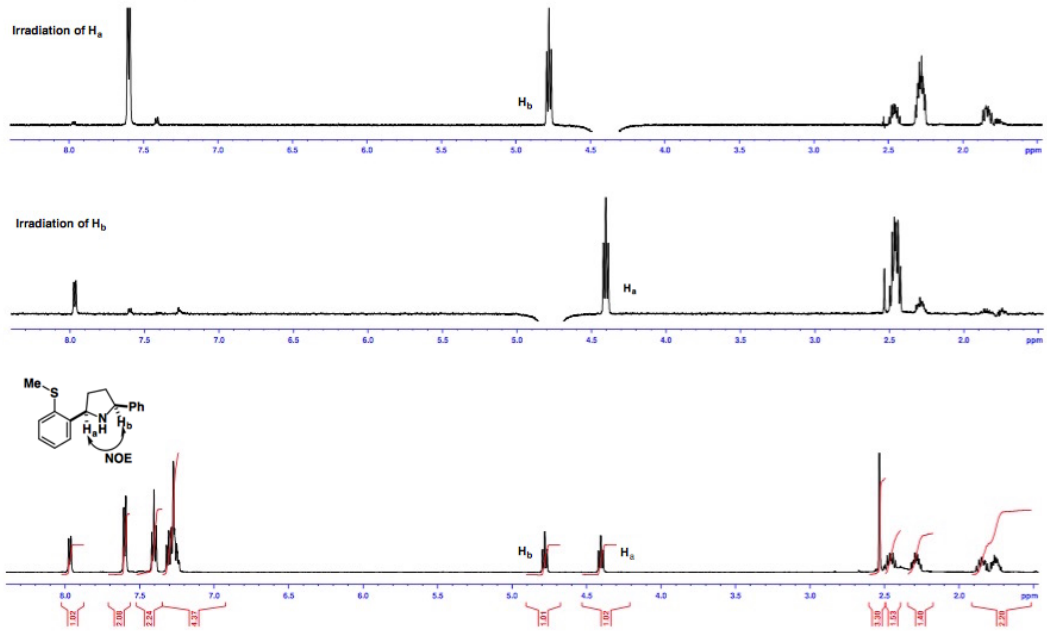
General procedure L for the synthesis of _cis_-pyrrolidines as exemplified by the synthesis of 2-[2-(methylthio)phenyl]-5-phenylpyrrolidine, 233



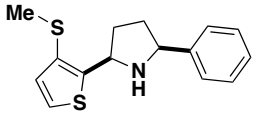
Dihydropyrrole (5-[2-(methylthio)phenyl]-2-phenyl-3,4-dihydro-2*H*-pyrrole **215**) (17.0 mg, 0.06 mmol, 1.0 equiv.), was dissolved in toluene (0.2 mL) and cooled to −78 °C. Diisobutylaluminium hydride (DIBAL-H) solution (0.18 mL, 1.0 M in toluene, 0.18 mmol, 3.0 equiv.) was added dropwise and the solution was stirred at −78 °C for 1 hr. The reaction was then quenched by the addition of sat. $NH_4Cl_{(aq.)}$ (0.16 mL) and warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated i*n vacuo*. The reaction gave the *cis*-diastereoisomer as the only isomer detectable by crude ^{1}H NMR spectroscopy. The crude product was purified by flash column chromatography (5% EtOAc in petrol) to yield title *pyrrolidine* **233** as a colourless oil (15.6 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.98 (1H, m, Ar-*H*), 7.61 (2H, d, *J* 7.5, Ar-*H*), 7.41 (2H, app t, *J* 7.5, Ar-*H*), 7.33-7.25 (4H, m, Ar-*H*), 4.78 (1H, t, *J* 7.5, NHC*H*(*o*SCH_3-C_6H_4)), 4.40 (1H, t, *J* 7.5, NHC*H*(Ph)), 2.54 (3H, s, SCH_3), 2.49-2.44 (1H, m, NHCH(*o*SCH_3-C_6H_4)C$H_a$$H_b$), 2.36-2.25 (2H, m, N*H* and NHCH(Ph)C$H_a$$H_b$), 1.89-1.81 (1H, m, NHCH(Ph)$CH_a$$H_b$), 1.75 (1H, tdd, *J* 11.5, 5.5, 2.5, NHCH(*o*SCH_3-C_6H_4))$CH_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.2, 143.4, 136.2, 128.3, 127.2, 126.9, 126.8, 126.3, 125.4, 125.2, 62.2, 58.4, 34.5, 32.8, 16.1; IR: ν_{max} (neat)/cm^{-1} 3329, 3059, 3026, 2867, 1603, 1491, 1460, 1394, 1124, 907; LRMS (ESI$^+$): *m/z* 270 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 270.13096 [M+H]$^+$, $C_{17}H_{20}NS^+$ requires 270.13110.

Cis-selectivity from a DIBAL-H reduction was confirmed by NOE experiments. The spectra below display in-space interactions between H_a and H_b, which means that both these hydrogens are on the same face of the pyrrolidine ring.



2-[3-(Methylthio)thiophen-2-yl]-5-phenylpyrrolidine, 234

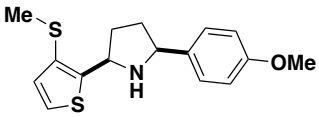


Prepared according to general procedure **L** using dihydropyrrole (5-[3-(methylthio)thiophen-2-yl]-2-phenyl-3,4-dihydro-2*H*-pyrrole **217**), (15 mg, 0.06 mmol, 1.0 equiv.), DIBAL-H solution (0.18 mL, 1.0 M in toluene, 0.18 mmol, 3.0 equiv.) in toluene (0.2 mL). After stirring

for 2 hrs at −78 °C, sat. $NH_4Cl_{(aq.)}$ (0.16 mL) was added and the reaction gave the *cis*-diastereoisomer as the only isomer detectable by crude ^{1}H NMR spectroscopy. The crude product was purified by flash column chromatography (15% Et_2O in petrol) to yield *pyrrolidine* **234** as a colourless oil (14.9 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.56 (2H m, Ar-*H*), 7.38 (2H, dd, *J* 8.0, 7.0, Ar-*H*), 7.29 (1H, app dt, *J* 7.5, 1.5, Ar-*H*), 7.23 (1H, d, *J* 5.0, SC*H*), 7.04 (1H, d, *J* 5.0, SCHC*H*), 4.91-4.87 (1H, m, NHC*H*CS), 4.37 (1H, t, *J* 7.5, NHC*H*(Ph)), 2.45 (3H, s, SCH_3), 2.40-2.34 (1H, m, NHCH(-CS-)CH_aH$_b$), 2.29-2.22 (1H, m, NHCH(Ph)CH_aH$_b$), 1.86 (2H, app tdt, *J* 7.5, 3.5, 2.5, NHCH(-CS-)CH$_a$$H_b$ and NHCH(Ph)CH$_a$$H_b$), 1.29 (1H, br s, N*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 145.1, 129.7, 129.5, 128.3, 126.9, 126.7, 123.2, 62.3, 56.3, 34.7, 34.4, 19.1; IR: ν_{max} (neat)/cm^{-1} 2920, 1491, 1452, 1319, 1246, 1099, 908; LRMS (ESI$^+$): *m/z* 276 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 276.08766 [M+H]$^+$, $C_{15}H_{18}NS_2^+$ requires 276.08752.

2-(4-Methoxyphenyl)-5-[3-(methylthio)thiophen-2-yl]pyrrolidine, 235

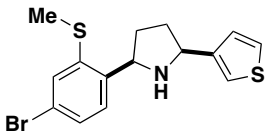


Prepared according to general procedure **L** using dihydropyrrole (2-(4-methoxyphenyl)-5-[3-(methylthio)thiophen-2-yl]-3,4-dihydro-2*H*-pyrrole **218**), (40 mg, 0.13 mmol, 1.0 equiv.), DIBAL-H solution (0.39 mL, 1.0 M in toluene, 0.39 mmol, 3.0 equiv.) in toluene (0.8 mL). After stirring for 1 hr at −78 °C, sat. $NH_4Cl_{(aq.)}$ (0.35 mL) was added and the reaction gave the *cis*-diastereoisomer as the only isomer detectable by crude ^{1}H NMR spectroscopy. The crude product was purified by flash column chromatography (15% Et_2O in petrol) to yield *pyrrolidine* **235** as a colourless oil (35.6 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (2H, m, Ar-*H*), 7.22 (1H, d, *J* 5.0, SC*H*), 7.03 (1H, d, *J* 5.0, SCHC*H*), 6.94-6.90 (2H, m, Ar-*H*), 4.86 (1H, dd, *J* 8.0, 6.0, NHC*H*CS), 4.31 (1H, t, *J* 7.5, NHC*H*(*p*OCH$_3$-C$_6$H$_4$)), 3.84 (3H, s, OCH_3), 2.52 (1H, br s, N*H*), 2.44 (3H, s, SCH_3), 2.39-2.34 (1H, m, NHCH(-CS-)CH_aH$_b$), 2.23-2.16 (1H, m, NHCH(*p*OCH$_3$-C$_6$H$_4$)CH_aH$_b$), 1.88-1.80 (2H, m, NHCH(-CS-)CH$_a$$H_b$ and NHCH(*p*OCH$_3$-C$_6$H$_4$)CH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 150.1, 137.1, 129.7, 127.7, 123.2, 123.0, 113.6, 61.8, 56.1, 55.3, 34.7,

34.4, 19.1; IR: ν_{max} (neat)/cm^{-1} 2965, 2833, 1611, 1584, 1511, 1440, 1244, 1035; LRMS (ESI$^+$): *m/z* 306 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 306.09800 [M+H]$^+$, $C_{16}H_{20}NOS_2^+$ requires 306.09808.

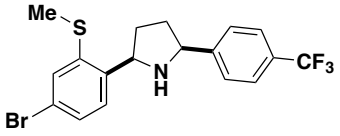
2-[4-Bromo-2-(methylthio)phenyl]-5-(thiophen-3-yl)pyrrolidine, 236



Prepared according to general procedure **L** using dihydropyrrole (5-[4-bromo-2-(methylthio)phenyl]-2-(thiophen-3-yl)-3,4-dihydro-2*H*-pyrrole **220**) (40 mg, 0.11 mmol, 1.0 equiv.), DIBAL-H solution (0.33 mL, 1.0 M in toluene, 0.33 mmol, 3.0 equiv.) in toluene (0.5 mL). After stirring for 2 hrs at −78 °C, sat. $NH_4Cl_{(aq.)}$ (0.3 mL) was added and the reaction gave the *cis*-diastereoisomer as the only isomer detectable by crude ^{1}H NMR spectroscopy. The crude product was purified by flash column chromatography (15% Et_2O in petrol) to yield *pyrrolidine* **236** as a colourless oil (31.1 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (1H, d, *J* 8.0, Ar-*H*), 7.34 (1H, dd, *J* 5.0, 3.0, Ar-*H*), 7.32-7.28 (3H, m, Ar-*H*), 7.21 (1H, dd, *J* 5.0, 1.5, Ar-*H*), 4.63 (1H, app t, *J* 7.5, NHC*H*(-CCHS-)), 4.46 (1H, t, *J* 8.0, NHC*H*(Ar-Br)), 2.51 (3H, s, SCH_3), 2.41 (1H, dtd, *J* 12.0, 8.0, 7.5, NHCH(-CCHS-)CH_aH$_b$), 2.25-2.19 (1H, m, NHCH(Ar-Br)CH_aH$_b$), 1.86-1.77 (1H, m, NHCH(Ar-Br)CH$_a$$H_b$), 1.65 (1H, dddd, *J* 12.0, 9.5, 7.5, 5.0, NHCH(-CCHS-)CH$_a$$H_b$), 1.49 (1H, br s, N*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.6, 142.2, 127.8, 127.7, 127.1, 126.6, 125.7, 120.9, 120.1, 58.1, 57.7, 33.3, 32.6, 28.4, 15.8; IR: ν_{max} (neat)/cm^{-1} 2969, 2920, 1575, 1552, 1492, 1327, 1084, 907; LRMS (ESI$^+$): *m/z* 356 ([^{81}Br] [M+H]$^+$, 100%), 354 ([^{79}Br] [M+H]$^+$, 95%); HRMS (ESI$^+$) found 353.99802 [[^{79}Br] M+H]$^+$], 355.99585 [[^{81}Br] M+H]$^+$], $C_{15}H_{17}{}^{79}BrS_2^+$ requires 353.99803, $C_{15}H_{17}{}^{81}BrNS_2^+$ requires 355.99598.

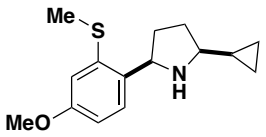
2-[4-Bromo-2-(methylthio)phenyl]-5-[4-(trifluoromethyl)-phenyl]-pyrrolidine, 237



Prepared according to general procedure **L** using dihydropyrrole (5-[4-bromo-2-(methylthio)phenyl]-2-[4-(trifluoromethyl)phenyl]-3,4-dihydro-2*H*-pyrrole **221**) (46 mg, 0.11 mmol, 1.0 equiv.), DIBAL-H solution (0.33 mL, 1.0 M in toluene, 0.33 mmol, 3.0 equiv.) in toluene (0.6 mL). After stirring for 1 hr at −78 °C, sat. $NH_4Cl_{(aq.)}$ (0.3 mL) was added and the reaction gave the *cis*-diastereoisomer as the only isomer detectable by crude ^{1}H NMR spectroscopy. The crude product was purified by flash column chromatography (15% Et_2O in petrol) to yield *pyrrolidine* **237** as a colourless oil (42.1 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (1H, d, *J* 8.0, Ar-*H*), 7.66 (4H, app q, *J* 9.0, Ar-*H*), 7.35-7.29 (2H, m, Ar-*H*), 4.68 (1H, t, *J* 7.5, NHC*H*(Ar-Br)), 4.42 (1H, t, *J* 8.0, NHC*H*(Ar-CF_3)), 2.52 (3H, s, SCH_3), 2.49-2.40 (1H, m, NHCH(Ar-Br)CH_aH$_b$), 2.33-2.26 (1H, m, NHCH(Ar-CF_3)CH_aH$_b$), 2.13 (1H, br s, N*H*), 1.80-1.70 (1H, m, NHCH(Ar-CF_3)CH$_a$$H_b$), 1.70-1.61 (1H, m, NHCH(Ar-Br)CH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 141.9, 138.6, 129.1 (q, $^2J_{CF}$ 32.0), 127.8, 127.7, 127.1, 127.0, 125.2 (q, $^3J_{CF}$ 3.5), 124.2 (q, $^1J_{CF}$ 247.5), 121.0, 61.5, 57.9, 34.4, 32.5, 15.8; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −62.3; IR: ν_{max} (neat)/cm^{-1} 2943, 1619, 1575, 1460, 1324, 1163, 1066; LRMS (ESI$^+$): *m/z* 418 ([^{81}Br] [M+H]$^+$, 100%), 416 ([^{79}Br] [M+H]$^+$, 95%); HRMS (ESI$^+$) found 416.0304 [[^{79}Br] M+H]$^+$], 418.0282 [[^{81}Br] M+H]$^+$], $C_{18}H_{18}{}^{79}BrNF_3S^+$ requires 416.0289, $C_{18}H_{18}{}^{81}BrNF_3S^+$ requires 418.0312.

2-Cyclopropyl-5-[4-methoxy-2-(methylthio)phenyl]pyrrolidine, 238

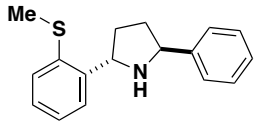


Prepared according to general procedure **L** using dihydropyrrole (2-cyclopropyl-5-[4-methoxy-2-(methylthio)phenyl]-3,4-dihydro-2*H*-pyrrole **219**) (20 mg, 0.08 mmol, 1.0 equiv.), DIBAL-H solution (0.24 mL, 1.0 M in toluene, 0.24 mmol, 3.0 equiv.) in toluene (0.2 mL). After stirring for 2 hrs at −78 °C, sat. $NH_4Cl_{(aq.)}$ (0.22 mL) was added and the reaction gave the *cis*-diastereoisomer as the only isomer detectable by crude ^{1}H NMR

spectroscopy. The crude product was purified by flash column chromatography (15% Et_2O in petrol) to yield *pyrrolidine* **238** as a colourless oil (18.1 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, d, *J* 8.5, Ar-*H*), 6.77 (1H, d, *J* 2.5, Ar-*H*), 6.72 (1H, dd, *J* 8.5, 2.5, Ar-*H*), 4.46 (1H, t, *J* 7.5, NHC*H*(Ar)), 3.83 (3H, s, OCH_3), 2.61 (1H, app q, *J* 7.5, NHC*H*(CH$(CH_2)_2$)), 2.48 (3H, s, SCH_3), 2.24-2.17 (1H, m, NHCH(Ar)CH_aH$_b$), 2.02-1.94 (2H, m, N*H* and NHCH(CH$(CH_2)_2$)CH_aH$_b$), 1.75-1.66 (1H, m, NHCH(CH$(CH_2)_2$)CH$_a$$H_b$), 1.66-1.57 (1H, m, NHCH(Ar)CH$_a$$H_b$), 0.96-0.91 (1H, m, NHCH(C*H*$(CH_2)_2$)), 0.53-0.46 (2H, m, NHCH(CH(CH_2)(CH$_a$H$_b$)), 0.31-0.27 (1H, m, NHCH(CH(CH_2)(CH_aH$_b$)), 0.24-0.19 (1H, m, NHCH(CH(CH_2)(CH$_a$$H_b$)); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 137.6, 135.1, 127.1, 111.7, 109.7, 63.7, 57.9, 55.3, 32.5, 30.7, 16.2, 16.0, 3.1, 2.0; IR: ν_{max} (neat)/cm^{-1} 2999, 2832, 1597, 1571, 1484, 1436, 1290, 1242, 1053; LRMS (ESI$^+$): *m/z* 264 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 264.14158 [M+H]$^+$, $C_{15}H_{22}NOS^+$ requires 264.14166.

2-[2-(Methylthio)phenyl]-5-phenylpyrrolidine, 239

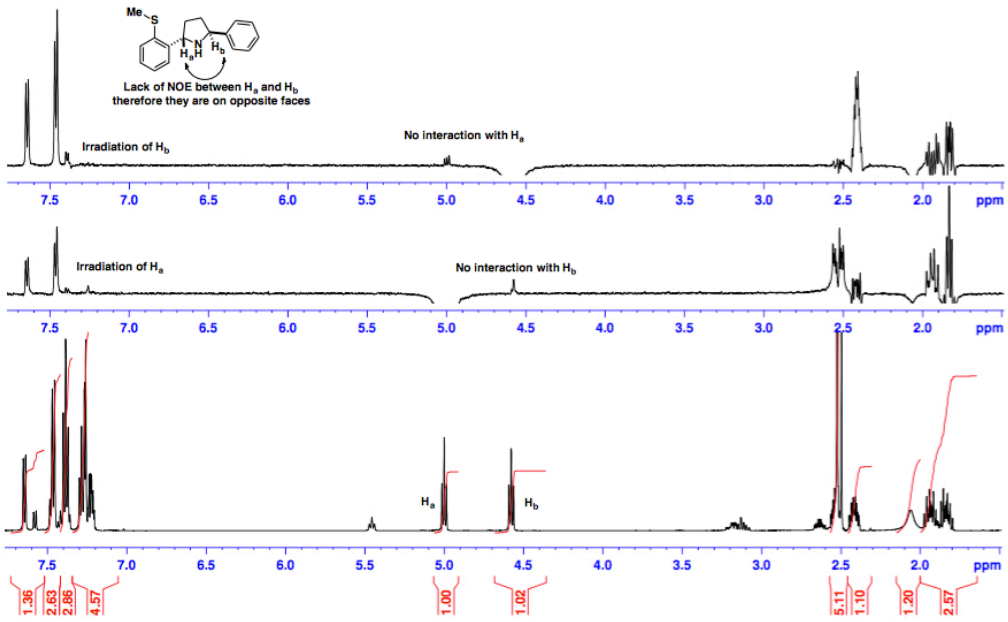


Dihydropyrrole (5-[2-(methylthio)phenyl]-2-phenyl-3,4-dihydro-2*H*-pyrrole **215**) (120 mg, 0.45 mmol, 1.0 equiv.), was dissolved in acetic acid (2.25 mL). Sodium borohydride (42.0 mg, 1.13 mmol, 2.5 equiv.) was added and the solution was stirred at room temperature for 1 hr. The reaction was then quenched by the addition of water (10 mL) and potassium carbonate (0.1 g). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers with washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The reaction gave the *trans*- to *cis*-diastereoisomers in a ratio of 3:1 (*trans*:*cis*) and they were separated by column chromatography (5-20% Et_2O in petrol) to yield *trans-pyrrolidine* **239** as the major diastereoisomer as a colourless oil (83 mg, 68%).

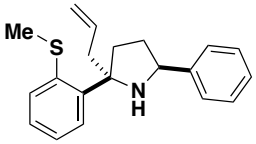
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, dd, *J* 8.5, 1.0, Ar-*H*), 7.48-7.45 (2H, m, Ar-*H*), 7.39 (2H, dd, *J* 8.5, 7.0, Ar-*H*), 7.31-7.28 (1H, m, Ar-*H*), 7.27-7.21 (3H, m, Ar-*H*), 5.00 (1H, t,

J 7.0, NHC*H*(Ar-SCH_3)), 4.57 (1H, t, *J* 7.0, NHC*H*(Ph)), 2.56-2.50 (1H, m, NHCH(Ar-SCH_3)C$H_a$$H_b$), 2.53 (3H, s, SC$H_3$), 2.46-2.38 (1H, m, NHCH(Ph)C$H_a$$H_b$), 2.09 (1H, br s, N*H*), 1.98-1.91 (1H, m, NHCH(Ph)C$H_a$$H_b$), 1.83 (1H, app ddt, *J* 12.0, 9.0, 7.0, NHCH(Ar-SCH_3)C$H_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9, 143.7, 136.4, 128.5, 127.2, 126.8, 126.4, 125.6, 125.4, 125.2, 62.3, 58.8, 35.4, 33.6, 16.1; IR: ν_{max} (neat)/cm^{-1} 2920, 1612, 1586, 1492, 1436, 1272, 1060; LRMS (ESI$^+$): *m/z* 270 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 270.13023 [M+H]$^+$, $C_{17}H_{20}NS^+$ requires 270.13110.

Trans-selectivity from a sodium borohydride reduction was confirmed by NOE experiments, which displayed a lack of in-space interactions between the two hydrogen atoms shown in the spectra below. This indicated that the hydrogens were not on the same face of the pyrrolidine ring and was opposite to the NOE obtained for the *cis*-pyrrolidine.



2-Allyl-2-[2-(methylthio)phenyl]-5-phenylpyrrolidine, 240

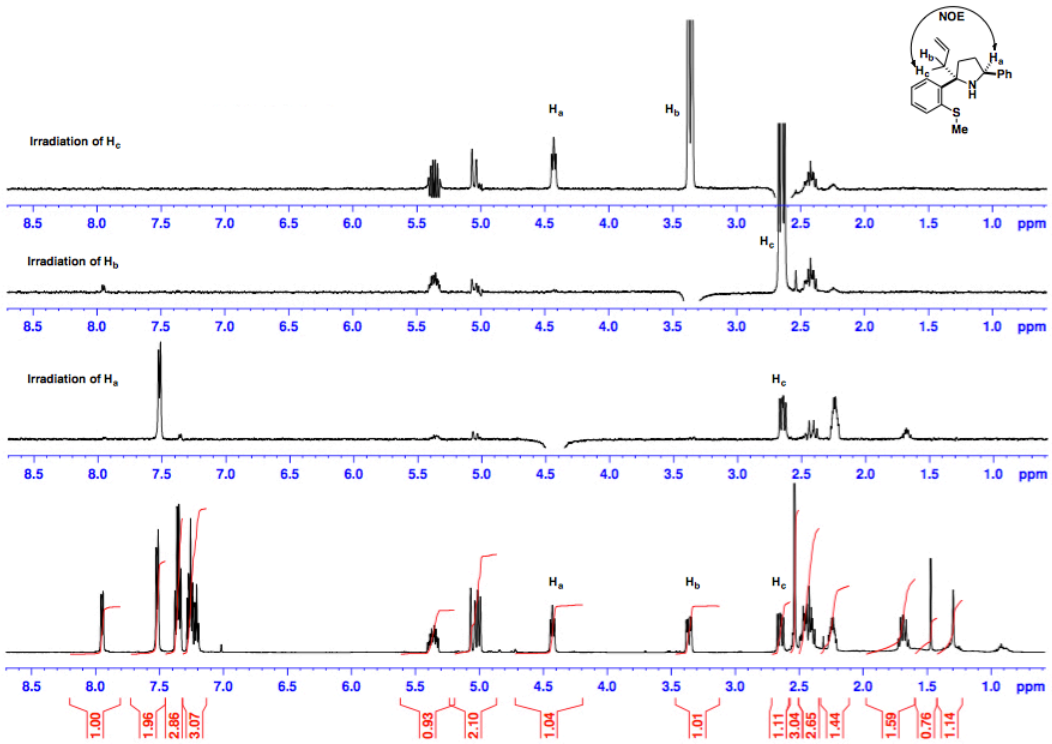


Dihydropyrrole (5-[2-(methylthio)phenyl]-2-phenyl-3,4-dihydro-2*H*-pyrrole **215**) (50 mg, 0.19 mmol, 1.0 equiv.) was dissolved in THF (1.9 mL) and cooled to 0 °C. Allylmagnesium bromide (0.36 mL, 0.8 M in THF, 0.29 mmol, 1.5 equiv.) was added dropwise and the solution

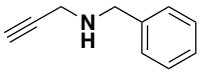
was warmed to room temperature over 30 mins. The reaction was then quenched by the addition of sat. $NH_4Cl_{(aq.)}$ (3 mL), the aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The reaction gave the *cis*- to *trans*-diastereoisomers in a ratio of 25:1 (*cis*:*trans*) and they were separated by column chromatography (20% Et_2O in petrol) to yield title *cis-pyrrolidine* **240** as a colourless oil (53.6 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.95 (1H, m, Ar-*H*), 7.53 (2H, dd, *J* 8.0, 1.0, Ar-*H*), 7.39-7.34 (3H, m, Ar-*H*), 7.29-7.20 (3H, m, Ar-*H*), 5.37 (1H, dddd, *J* 17.0, 10.0, 9.0, 5.5, NHC(CH_2CHCH_2)), 5.09-4.99 (2H, m, NHC(CH_2CHCH_2)), 4.44 (1H, dd, *J* 9.0, 6.5, NHC*H*), 3.37 (1H, dd, *J* 14.0, 5.5, NHC($CH_aH_bCHCH_2$)), 2.65 (1H, dd, *J* 14.0, 9.0, NHC($CH_aH_bCHCH_2$)), 2.54 (3H, s, SCH_3), 2.48-2.38 (3H, m, N*H* and NCH(Ph)CH_2), 2.25 (1H, dddd, *J* 12.0, 7.5, 6.5, 4.5, NC(CH_2CHCH_2)CH_aH_b), 1.69 (1H, app dq, *J* 12.0, 9.0, NC(CH_2CHCH_2)CH_aH_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.9, 145.7, 135.4, 135.2, 128.5, 128.4, 128.2, 126.9, 126.8, 126.7, 124.9, 118.0, 66.6, 60.4, 43.8, 38.1, 35.2, 18.0; IR: ν_{max} (neat)/cm^{-1} 2975, 2922, 1637, 1584, 1435, 1256, 1049; LRMS (ESI$^+$): *m/z* 310 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 310.16204 [M+H]$^+$, $C_{20}H_{24}NS^+$ requires 310.16240.

Cis-selectivity from allylmagnesium bromide addition was confirmed by NOE experiments, which displayed in-space interactions between the two hydrogen atoms shown on the spectra displayed.



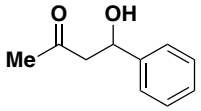
_N_-Benzylprop-2-yn-1-amine, 246



Propargyl bromide (4.0 mL, 80% in toluene, 25.2 mmol, 1.0 equiv.) was added dropwise to benzylamine (16.5 mL, 151.6 mmol, 6.0 equiv.). The reaction was stirred 15 hrs at room temperature and then 2 M NaOH (100 mL) and Et_2O (100 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (100% EtOAc) to give propargylic amine **246** as a pale yellow oil (1.61 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.35 (4H, m, Ar-*H*), 7.32-7.30 (1H, m, Ar-*H*), 3.92 (2H, s, Ar-C*H*$_2$NH), 3.73 (1H, s, N*H*), 3.46 (2H, d, *J* 2.5, NHC*H*$_2$CCH), 2.30 (1H, t, *J* 2.5, C*H*CCH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.4, 129.2, 128.5, 127.2, 82.1, 78.8, 52.3, 37.4; LRMS (ESI$^+$): *m/z* 146 ([M+H]$^+$, 100%). This data is consistent with literature.[271]

4-Hydroxy-4-phenylbutan-2-one, 251

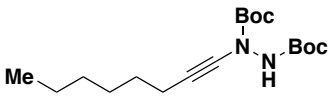


An oven-dried microwave vial was charged with [Rh(nbd)$_2$BF$_4$] (3.7 mg, 5 mol%) and PNP(Cy) (4.2 mg, 5 mol%), once under an inert atmosphere, they were dissolved in acetone (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (0.2 mL, 1.0 M with respect to allylic amine) and this was transferred to a nitrogen-filled microwave vial containing benzaldehyde (26 μL, 0.26 mmol, 1.3 equiv.), allyl amine (15 μL, 0.2 mmol, 1.0 equiv.) and potassium carbonate (3.0 mg, 10 mol%). The reaction mixture was then stirred at 55 °C for 16 hrs and then filtered through a plug of silica (acetone, 10 mL) and the solvent removed *in vacuo*, which was purified by flash column chromatography (5-100% Et_2O in petrol) to afford title aldol product **251** as a thick colourless oil (16.8 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.38 (4H, m, Ar-*H*), 7.33-7.30 (1H, m, Ar-*H*), 5.19 (1H, app dd, *J* 9.0, 3.5, C*H*OH), 3.32 (1H, br s, O*H*), 2.92 (1H, dd, *J* 17.5, 9.0, COCH_aH$_b$), 2.85 (1H, dd, *J* 17.5, 3.5, COCH$_a$$H_b$), 2.23 (3H, s, C$H_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 209.1, 142.7, 128.6, 127.7, 125.6, 69.9, 52.0, 30.8; IR: ν_{max} (neat)/cm^{-1} 3412 (br), 3031, 2924, 1710, 1494, 1453, 1360, 1061, 910; LRMS (ESI$^+$): *m/z* 187 ([M+Na]$^+$, 100%). This data is consistent with literature.[272]

6.4 Chapter 4 Experimental

Di-*tert*-butyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate, 253

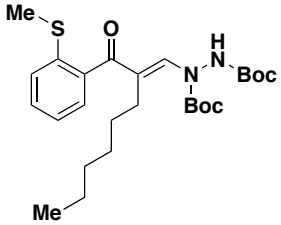


Prepared according to an adapted literature procedure from Batey *et. al*.,[228] a nitrogen flushed round-bottomed flask was charged with 1-octyne (0.59 mL, 4.0 mmol, 1.0 equiv.) in THF (20 mL) and cooled to −78 °C. A solution of *n*-butyllithium (3.0 mL, 1.6 M in hexanes,

4.8 mmol, 1.2 equiv.) was then added dropwise and the resulting mixture was stirred at the same temperature for 15 mins. A solution of di-*tert*-butylazodicarboxylate (1.4 g, 6.0 mmol, 1.5 equiv.) in THF (12 mL) was then added dropwise. The mixture was allowed to warm to room temperature over 3 hrs and then quenched by addition of sat. $NH_4Cl_{(aq.)}$ (15 mL), followed by dilution with EtOAc (100 mL) and water (15 mL). The organic layer was separated and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (10% EtOAc in petrol) to give title ynehydrazide **253** as a yellow oil (0.99 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (1H, br s, N*H*), 2.32 (2H, t, *J* 7.0, CH_2(CH_2)$_4$$CH_3$), 1.56 (2H, app d, *J* 7.0, CH_2(CH_2)$_3$$CH_3$), 1.52 (9H, s, $CO_2C(CH_3)_3$), 1.51 (9H, s, $CO_2C(CH_3)_3$), 1.41 (2H, app dt, *J* 14.5, 7.0, CH_2(CH_2)$_2$$CH_3$), 1.35-1.27 (4H, m, ($CH_2$)$_2$$CH_3$), 0.90 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): 154.1, 153.2, 83.7, 82.1, 77.2, 73.3, 31.4, 28.7, 28.5, 28.1, 27.9, 22.6, 18.5, 14.1; LRMS (ESI^+): *m/z* 363 ([M+Na]$^+$, 100%). This data is consistent with literature.[228]

Di-*tert*-butyl (*E*)-1-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}hydrazine-1,2-dicarboxylate, 254a

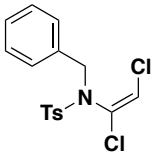


An oven-dried microwave vial was charged with [Rh(nbd)$_2$]BF_4 (5.6 mg, 10 mol%) and PNP(Cy) (6.4 mg, 10 mol%), once under an inert atmosphere, they were dissolved in acetone (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species (colour change from red to pale yellow). The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (0.4 mL, 0.3 M with respect to aldehyde minus the volume or mass of both aldehyde and alkyne) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and ynehydrazide (di-*tert*-butyl 1-(oct-1-yn-1-yl)hydrazine-1,2-dicarboxylate,

253) (66.0 mg, 0.195 mmol, 1.3 equiv.). The reaction mixture was then stirred at 55 °C. The reaction was monitored by TLC until complete. After 16 hrs, the reaction mixture was filtered through a plug of silica (acetone, 10 mL) and the solvent removed *in vacuo* to obtain the crude product. The crude reaction mixture was purified by flash column chromatography (10-40% Et_2O in petrol) to afford title linear *enone* **254a** as a white solid (60.6 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, br s, N(Boc)C*H*), 7.35 (2H, d, *J* 7.5, Ar-*H*), 7.25-7.20 (2H, m, Ar-*H*), 6.54 (1H, br s, N*H*), 2.62-2.60 (2H, m, $CH_2(CH_2)_4CH_3$), 2.44 (3H, s, SCH_3), 1.53 (9H, s, $CO_2C(CH_3)_3$), 1.46 (9H, s, $CO_2C(CH_3)_3$), 1.39-1.33 (8H, m, $(CH_2)_4CH_3$), 0.92 (3H, t, *J* 6.5, $(CH_2)_5CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1, 154.0, 151.7, 139.9, 136.5, 136.4, 129.6, 128.0, 127.7, 124.9, 112.1, 83.1, 82.3, 31.7, 31.4, 30.0, 28.0, 27.7, 26.0, 22.5, 17.1, 14.1; IR: ν_{max} (neat)/cm^{-1} 2977, 2920, 1691, 1623, 1515, 1455, 1366, 1246, 1165; LRMS (ESI$^+$): *m/z* 493 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 493.2728 [M+Na]$^+$, $C_{26}H_{41}N_2O_5S^+$ requires 493.2731; mp: 96-97 °C (Et_2O/petrol).

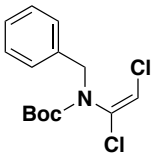
General procedure M for the synthesis of 1,2-dichloroenamides as exemplified by the synthesis of (*E*)-*N*-benzyl-*N*-(1,2-dichlorovinyl)-4-methylbenzenesulfonamide, 255



Prepared according to an adapted literature procedure from Anderson *et. al*.[230] To a stirring suspension of amide (*N*-benzyl-4-methylbenzenesulfonamide **271**) (2.50 g, 9.57 mmol, 1.0 equiv.), powdered Cs_2CO_3 (4.68 g, 14.4 mmol, 1.5 equiv.) and DMF (7.2 mL), at 50 °C, was added trichloroethylene (0.95 mL, 10.5 mmol, 1.1 equiv.) dropwise over 10 mins. The resulting mixture was stirred at 50 ºC until the reaction was complete as shown by TLC analysis. After 2 hrs, upon cooling to room temperature, the mixture was quenched with water (10 mL) and the crude was extracted with EtOAc (20 mL). The organic layer was separated and further washed with brine (10 mL × 3). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (10-40% EtOAc in petrol) to give title dichloroenamide **255** as a white solid (2.86 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (2H, d, *J* 8.5, Ar-*H*), 7.39 (2H, dd, *J* 8.5, 0.5, Ar-*H*), 7.37-7.32 (5H, m, Ar-*H*), 6.30 (1H, s, ClC*H*), 4.34 (2H, br s, NCH_2), 2.50 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): 144.8, 135.1, 133.4, 129.8, 129.4, 129.0, 128.6, 128.5, 128.4, 121.7, 51.8, 21.7; LRMS (ESI$^+$): *m/z* 356 ([M+H]$^+$, 100%), 378 ([M+Na]$^+$, 95%); mp: 140-141 °C (EtOAc/petrol), (lit. mp: 136-137 °C). This data is consistent with literature.[230]

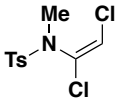
tert-Butyl (*E*)-benzyl(1,2-dichlorovinyl)carbamate, 256



Prepared according to general procedure **M** using NaH (1.90 g, 60% in mineral oil, 50.4 mmol, 2.1 equiv.), instead of Cs_2CO_3, in anhydrous DMF (18 mL), amide (*tert*-butyl benzylcarbamate **267**) (5.0 g, 24 mmol, 1.0 equiv.) in anhydrous DMF (18 mL) and trichloroethylene (2.2 mL, 24 mmol, 1.0 equiv.). The crude was purified by flash column chromatography (5-10% Et_2O in petrol) to give title dichloroenamide **256** as a colourless oil (4.89 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (2H, m, Ar-*H*), 7.37-7.32 (3H, m, Ar-*H*), 6.11 (1H, br s, ClC*H*), 4.85-4.46 (2H, m, NCH_2), 1.52 (9H, s, $CO_2C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 151.4, 135.9, 129.0, 128.8, 128.3, 127.7, 115.4, 82.1, 49.9, 28.1; LRMS (ESI$^+$): *m/z* 324 ([M+Na]$^+$, 100%). This data is consistent with literature.[230]

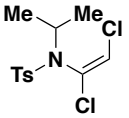
(*E*)-*N*-(1,2-Dichlorovinyl)-*N*,4-dimethylbenzenesulfonamide, 257



Prepared according to general procedure **M** using amide (*N*,4-dimethylbenzenesulfonamide **268**) (2.00 g, 10.6 mmol, 1.0 equiv.), powdered Cs_2CO_3 (5.18 g, 15.9 mmol, 1.5 equiv.) in anhydrous DMF (8 mL) and trichloroethylene (1.10 mL, 11.7 mmol, 1.1 equiv.). The crude was purified by flash column chromatography (50% Et_2O in petrol) to give title *dichloroenamide* **257** as a white solid (2.19 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (2H, d, *J* 7.5, Ar-*H*), 7.36 (2H, d, *J* 7.5, Ar-*H*), 6.42 (1H, s, ClC*H*), 2.97 (3H, s, NCH_3), 2.47 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.6, 134.5, 131.5, 129.7, 128.4, 119.7, 35.2, 21.7; IR: ν_{max} (neat)/cm^{-1} 3029, 1623, 1595, 1354, 1290, 1165, 1087, 908; LRMS (ESI$^+$): *m/z* 302 ([M+Na]$^+$, 100%), 280 ([M+H]$^+$, 10%); HRMS (ESI$^+$) found 279.99624 [M+H]$^+$, $C_{10}H_{12}NO_2{}^{35}Cl_2S^+$ requires 279.99603; mp: 69-70 °C (Et_2O/petrol).

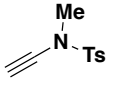
(*E*)-*N*-(1,2-Dichlorovinyl)-*N*-isopropyl-4-methylbenzenesulfonamide, 258



Prepared according to general procedure **M** using amide (*N*-isopropyl-4-methylbenzenesulfonamide **269**) (3.70 g, 17.3 mmol, 1.0 equiv.), powdered Cs_2CO_3 (8.47 g, 26.0 mmol, 1.5 equiv.) in DMF (13 mL) and trichloroethylene (1.70 mL, 19.0 mmol, 1.1 equiv.) The crude was purified by flash column chromatography (20% EtOAc in petrol) to give title *dichloroenamide* **258** as a thick colourless oil (1.45 g, 27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (2H, d, *J* 8.5, Ar-*H*), 7.34 (2H, d, *J* 8.5, Ar-*H*), 6.66 (1H, s, ClC*H*), 4.21 (1H, septet, *J* 7.0, NC*H*), 2.47 (3H, s, Ar-CH_3), 1.30 (3H, d, *J* 7.0, NCH(CH_3)$_a$(CH$_3$)$_b$), 1.13 (3H, d, *J* 7.0, NCH(CH$_3$)$_a$(CH_3)$_b$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.3, 136.8, 129.6, 128.2, 127.9, 123.2, 53.6, 21.7, 21.6, 21.0; IR: ν_{max} (neat)/cm^{-1} 2982, 1597, 1456, 1392, 1306, 1185, 1159, 1019; LRMS (ESI$^+$): *m/z* 330 ([M+Na]$^+$, 100%), 308 ([M+H]$^+$, 99%); HRMS (ESI$^+$) found 330.00928 [M+Na]$^+$, $C_{12}H_{15}NO_2{}^{35}Cl_2SNa^+$ requires 330.00928.

***N*-Ethynyl-*N*,4-dimethylbenzenesulfonamide, 260**

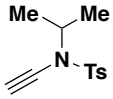


Prepared according to an adapted literature procedure from Anderson *et. al*.,[230] to an oven dried, nitrogen flushed flask was added 1,2-dichloroenamide ((*E*)-*N*-(1,2-dichlorovinyl)-*N*,4-dimethylbenzenesulfonamide **257**) (2.00 g, 7.17 mmol, 1.0 equiv.) and anhydrous THF (71.7 mL), and cooled to –78 °C whilst stirring. A solution of phenyllithium (12.2 mL, 1.29 M in dibutyl ether, 2.79 mmol, 2.2 equiv.) was then added dropwise over 10 mins, and left to

stir at –78 °C. Complete consumption of the starting dichloroenamide was observed by TLC analysis after 1 hr, iodohexane (1.23 mL, 8.6 mmol, 1.2 equiv.) was added at –78 °C and the stirring mixture was allowed to warm to room temperature over 16 hrs. The reaction mixture was quenched with water, followed by extraction with Et_2O (20 mL × 2). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (15-30% Et_2O in petrol) to give title ynamide **260** as a white solid (284 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (2H, d, *J* 8.5, Ar-*H*), 7.40 (1H, app dd, *J* 8.5, 0.5, Ar-*H*), 3.09 (3H, s, NCH_3), 2.71 (1H, s, C*H*CN), 2.49 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.9, 133.2, 129.8, 127.8, 76.7, 57.5, 38.9, 21.7; HRMS (FI^+) found 227.0847 $[M+NH_4]^+$, $C_{10}H_{15}N_2O_2S^+$ requires 227.0847; mp: 74-75 °C (CH_2Cl_2/petrol), (lit. mp: 75-76 °C). This data is consistent with literature.[273]

_N_-Ethynyl-_N_-isopropyl-4-methylbenzenesulfonamide, 261

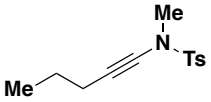


Prepared according to an adapted literature procedure from Anderson *et. al*.,[230] to an oven dried, nitrogen flushed flask was added 1,2-dichloroenamide ((*E*)-*N*-(1,2-dichlorovinyl)-*N*-isopropyl-4-methylbenzenesulfonamide **258**) (0.39 g, 1.27 mmol, 1.0 equiv.) and anhydrous THF (12.7 mL), and cooled to –78 °C whilst stirring. A solution of phenyllithium (2.30 mL, 1.25 M in dibutyl ether, 2.79 mmol, 2.2 equiv.) was then added dropwise over 10 mins, and left to stir at –78 °C. After complete consumption of the starting dichloroenamide was observed by TLC analysis after 1 hr, iodopropane (0.15 mL, 1.52 mmol, 1.2 equiv.) was added at –78 °C and the stirring mixture was allowed to warm to room temperature over 16 hrs. The reaction mixture was quenched with water, followed by extraction with Et_2O (15 mL × 2). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (15-30% Et_2O in petrol) to give title ynamide **261** as a pale yellow solid (112 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.33 (2H, d, *J* 8.5, Ar-*H*), 4.11 (1H, septet, *J* 6.5, NC*H*), 2.80 (1H, s, C*H*CN), 2.43 (3H, s, Ar-CH_3), 1.09 (6H, d, *J* 6.5,

NCH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.5, 135.9, 129.8, 127.4, 61.0, 52.1, 40.0, 21.7, 20.5; LRMS (ESI$^+$): *m/z* 260 ([M+Na]$^+$, 100%), 238 ([M+H]$^+$, 15%); mp: 100-101 °C (Et_2O/petrol), (lit. mp: 95-97 °C). This data is consistent with literature.[274]

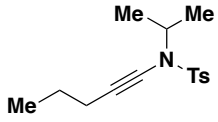
_N_,4-Dimethyl-_N_-(pent-1-yn-1-yl)benzenesulfonamide, 262



To an oven dried, nitrogen flushed flask was added distilled diisopropylamine (0.19 mL, 1.38 mmol, 1.2 equiv.) and anhydrous THF (0.5 mL), and cooled to –78 °C whilst stirring. A solution of *n*-butyllithium (0.55 mL, 2.5 M in hexanes, 1.38 mmol, 1.2 equiv.) was then added dropwise and was removed from the cold bath and left to stir for 15 mins to allow the formation of lithium diisopropylamide (LDA). The flask was re-cooled to –78 °C and ynamide (*N*-ethynyl-*N*,4-dimethylbenzenesulfonamide **260**) (0.24 g, 1.15 mmol, 1.0 equiv.) in THF (2.5 mL) was added to the LDA dropwise and stirred for 1 hr. Subsequently, 1-iodopropane (0.15 mL, 1.50 mmol, 1.3 equiv.) was added and the reaction mixture was warmed to room temperature over 4 hrs. The reaction was quenched with sat. $NH_4Cl_{(aq.)}$ (5 mL), followed by extraction with CH_2Cl_2 (5 mL × 3). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (5-30% EtOAc in petrol) to give title *ynamide* **262** as a colourless oil (119 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.37 (2H, app dd, *J* 8.5, 0.5, Ar-*H*), 3.04 (3H, s, NCH_3), 2.48 (3H, s, Ar-CH_3), 2.24 (2H, t, *J* 7.0, CH_2CH$_2$CH$_3$), 1.52 (2H, app sextet, *J* 7.0, CH_2CH$_3$), 0.97 (3H, t, *J* 7.5, (CH$_2$)$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.5, 133.2, 129.6, 127.8, 75.0, 68.5, 39.4, 22.3, 21.6, 20.4, 13.4; IR: ν_{max} (neat)/cm^{-1} 2963, 2934, 1597, 1455, 1362, 1289, 1170, 1089; LRMS (ESI$^+$): *m/z* 274 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 274.08715 [M+Na]$^+$, $C_{13}H_{17}NO_2SNa^+$ requires 274.08722.

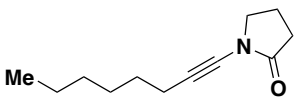
_N_-Isopropyl-4-methyl-_N_-(pent-1-yn-1-yl)benzenesulfonamide, 263



To an oven dried, nitrogen flushed flask was added distilled diisopropylamine (0.16 mL, 1.12 mmol, 1.2 equiv.) and anhydrous THF (0.2 mL), and cooled to –78 °C whilst stirring. A solution of *n*-butyllithium (0.45 mL, 2.5 M in hexanes, 1.12 mmol, 1.2 equiv.) was then added dropwise and was removed from the cold bath and left to stir for 15 mins to allow the formation of lithium diisopropylamide (LDA). The flask was re-cooled to –78 °C and ynamide (*N*-ethynyl-*N*-isopropyl-4-methylbenzenesulfonamide **261**) (0.24 g, 0.99 mmol, 1.0 equiv.) in THF (1 mL) was added to the LDA dropwise and stirred for 1 hr. Subsequently, 1-iodopropane (0.15 mL, 1.49 mmol, 1.5 equiv.) was added and the reaction mixture was warmed to room temperature over 4 hrs. The reaction was quenched with sat. $NH_4Cl_{(aq.)}$ (5 mL), followed by extraction with CH_2Cl_2 (5 mL × 3). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (5-30% EtOAc in petrol) to give title *ynamide* **263** as a colourless oil (69.0 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (2H, d, *J* 8.5, Ar-*H*), 7.35-7.33 (2H, m, Ar-*H*), 4.17 (1H, septet, *J* 6.5, NC*H*), 2.46 (3H, s, Ar-C*H*$_3$), 2.31 (2H, t, *J* 7.0, C*H*$_2$CH$_2$CH$_3$), 1.56 (2H, app sextet, *J* 7.0, C*H*$_2$CH$_3$), 1.09 (6H, d, *J* 6.5, NCH(C*H*$_3$)$_2$), 0.99 (3H, t, *J* 7.5, (CH$_2$)$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0, 136.1, 129.6, 127.4, 72.0, 69.8, 51.9, 22.5, 21.6, 20.63, 20.57, 13.5; IR: ν_{max} (neat)/cm^{-1} 2933, 2873, 1597, 1455, 1358, 1306, 1166, 1087; LRMS (ESI$^+$): *m/z* 280 ([M+H]$^+$, 100%), 302 ([M+Na]$^+$, 30%); HRMS (ESI$^+$) found 280.13657 [M+H]$^+$, $C_{15}H_{22}NO_2S^+$ requires 280.13661.

1-(Oct-1-yn-1-yl)pyrrolidin-2-one, 264

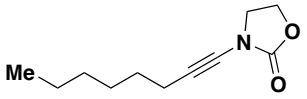


Prepared according to an adapted literature procedure by Evano *et. al*.[233] A round-bottomed flask was successively charged with the pyrrolidin-2-one (2.64 mL, 34.8 mmol, 4.0 equiv.), copper acetylide (oct-1-yn-1-ylcopper) (1.5 g, 8.7 mmol, 1.0 equiv.), and MeCN (17.4 mL).

TMEDA (1.3 mL, 8.7 mmol, 1.0 equiv.) was then added to the bright yellow slurry and the reaction mixture was vigorously stirred at room temperature, under an atmosphere of O_2 (balloon). After complete disappearance of the alkynylcopper reagent (complete dissolution to a deep blue homogeneous reaction mixture after 48 hrs) the crude reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (20% EtOAc in petrol) to give title ynamide **264** as a colourless oil (0.89 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (2H, app td, *J* 7.0, 1.0, NC*H*$_2$), 2.43 (2H, t, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.34 (2H, app td, *J* 7.0, 1.0, COC*H*$_2$), 2.12 (2H, app quintet, *J* 7.5, COCH$_2$C*H*$_2$), 1.54 (2H, app quintet, *J* 7.0, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.39 (2H, app dt, *J* 15.0, 7.5, C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.33-1.28 (4H, m, (C*H*$_2$)$_2$CH$_3$), 0.90 (3H, t, *J* 6.5, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 176.1, 72.7, 71.3, 50.1, 31.3, 29.6, 28.9, 28.6, 22.5, 18.7, 18.6, 14.0; LRMS (ESI$^+$): *m/z* 194 ([M+H]$^+$, 100%). This data is consistent with literature.[233]

3-(Oct-1-yn-1-yl)oxazolidin-2-one, 265

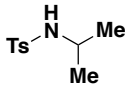


Prepared according to an adapted literature procedure by Evano *et. al*.[233] A round-bottomed flask was successively charged with the oxazolidin-2-one (3.03 g, 34.8 mmol, 4.0 equiv.), copper acetylide (oct-1-yn-1-ylcopper) (1.5 g, 8.7 mmol, 1.0 equiv.), and MeCN (17.4 mL). TMEDA (1.3 mL, 8.7 mmol, 1.0 equiv.) was then added to the bright yellow slurry and the reaction mixture was vigorously stirred at room temperature and under an atmosphere of O_2 (balloon). After complete disappearance of the alkynylcopper reagent (complete dissolution to a deep blue homogeneous reaction mixture after 48 hrs) the crude reaction mixture was concentrated under reduced pressure, and the residue was finally purified by flash column chromatography (20% EtOAc in petrol) to give title ynamide **265** as a very pale yellow oil (1.40 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45-4.41 (2H, m, OC*H*$_2$), 3.91-3.87 (2H, m, NC*H*$_2$), 2.31 (2H, t, *J* 7.0, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.54 (2H, app quintet, *J* 7.5, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.43-1.36 (2H, m, C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.35-1.27 (4H, m, (C*H*$_2$)$_2$CH$_3$), 0.91 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR

(101 MHz, $CDCl_3$): 156.6, 71.3, 70.0, 62.8, 47.0, 31.3, 28.8, 28.5, 22.5, 18.4, 14.1; LRMS (ESI^+): *m/z* 196 ($[M+H]^+$, 100%), 218 ($[M+Na]^+$, 100%). This data is consistent with literature.[233]

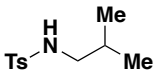
_N_-Isopropyl-4-methylbenzenesulfonamide, 269



NEt_3 (3.80 mL, 37.2 mmol, 1.2 equiv.) was added to a stirring solution of isopropylamine (2.90 mL, 33.8 mmol, 1.0 equiv.) in CH_2Cl_2 (16 mL) at room temperature. Tosyl chloride (7.10 g, 37.2 mmol, 1.2 equiv.) was then added portionwise and stirred for a further 30 mins at room temperature (until the reaction mixture became a white solid). After which, the solution was neutralised with HCl (1 M) and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (20% Et_2O in petrol) to give title amine **269** as a colourless oil that solidifies in the freezer (5.43 g, 75%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.81-7.78 (2H, m, Ar-*H*), 7.33-7.31 (2H, m, Ar-*H*), 4.67 (1H, br d, *J* 7.5, N*H*), 3.51-3.43 (1H, m, NHC*H*), 2.45 (3H, s, Ar-CH_3), 1.09 (6H, d, *J* 6.5, CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 143.2, 138.1, 129.6, 127.0, 46.0, 23.7, 21.5; LRMS (ESI^+): *m/z* 236 ($[M+Na]^+$, 100%); mp: 49-50 °C (Et_2O/petrol), (lit. mp: 50-51 °C). This data is consistent with literature.[275]

_N_-Isobutyl-4-methylbenzenesulfonamide, 270

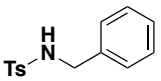


NEt_3 (4.60 mL, 32.8 mmol, 1.2 equiv.) was added to a stirring solution of isobutylamine (2.70 mL, 27.3 mmol, 1.0 equiv.) in CH_2Cl_2 (13 mL) at room temperature. Tosyl chloride (4.60 g, 32.8 mmol, 1.2 equiv.) was then added portionwise and stirred for a further 30 mins at room temperature (until the reaction mixture became a white solid). After which, the solution was neutralised with HCl (1 M) and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated

under reduced pressure. The crude was purified by flash column chromatography (20% Et_2O in petrol) to give title amine **270** as a white solid (5.09 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.76 (2H, m, Ar-*H*), 7.34-7.32 (2H, m, Ar-*H*), 4.70 (1H, br s, N*H*), 2.78-2.74 (2H, m, NHCH_2), 2.45 (3H, s, Ar-CH_3), 1.73 (1H, app dquintet, *J* 13.5, 6.5, NHCH$_2$C*H*), 0.89 (6H, d, *J* 6.5, CH(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 143.3, 137.0, 129.7, 127.1, 50.6, 28.4, 21.5, 19.9; LRMS (ESI$^+$): *m/z* 250 ([M+Na]$^+$, 100%); mp: 54-55 °C (Et_2O/petrol), (lit. mp: 49-50 °C). This data is consistent with literature.[276]

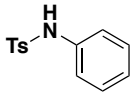
_N_-Benzyl-4-methylbenzenesulfonamide, 271



NEt_3 (7.8 mL, 56 mmol, 1.2 equiv.) was added to a stirring solution of benzylamine (5.10 mL, 46.7 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at room temperature. Tosyl chloride (10.8 g, 56.0 mmol, 1.2 equiv.) was then added portionwise and stirred for a further 30 mins at room temperature (until the reaction mixture became a white solid). After which, the solution was neutralised with HCl (1 M) and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (20% Et_2O in petrol) to give title amine **271** as a white solid (11.8 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (2H, d, *J* 8.5, Ar-*H*), 7.33 (2H, d, *J* 8.5, Ar-*H*), 7.30-7.26 (3H, m, Ar-*H*), 7.23-7.21 (2H, m, Ar-*H*), 4.85 (1H, br s, N*H*), 4.14 (2H, d, *J* 6.0, NHCH_2), 2.46 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): 143.5, 136.8, 136.3, 129.7, 128.7, 127.9, 127.8, 127.2, 47.3, 21.6; LRMS (ESI$^+$): *m/z* 262 ([M+H]$^+$, 100%), 284 ([M+Na]$^+$, 50%); mp: 115-116 °C (EtOAc/hexane), (lit. mp: 118-120 °C). This data is consistent with literature.[277]

4-Methyl-_N_-phenylbenzenesulfonamide, 272

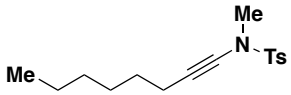


Aniline (9.80 mL, 107 mmol, 1.0 equiv.) was dissolved in anhydrous pyridine (250 mL) and cooled to 0 °C. Tosyl chloride (22.5 g, 118 mmol, 1.2 equiv.) was then added portionwise

and the reaction mixture was allowed to warm to room temperature over 16 hrs. Water (100 mL) was added and the aqueous phase was extracted with EtOAc (2 × 80 mL). The combined organic phase was washed with HCl (1 M, 150 mL), sat. $NaHCO_{3(aq.)}$ (150 mL) and brine (150 mL) and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (10% EtOAc in petrol) to give title amine **272** as a white solid (22.7 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* 8.0, Ar-*H*), 7.27-7.23 (4H, m, Ar-*H*), 7.14-7.09 (3H, m, Ar-*H*), 2.39 (3H, s, Ar-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): 143.9, 136.6, 136.0, 129.7, 129.3, 127.3, 125.2, 121.4, 21.5; LRMS (ESI^+): *m/z* 270 ($[M+Na]^+$, 100%); mp: 95-96 °C (Et_2O/petrol), (lit. mp: 93-96 °C). This data is consistent with literature.[278]

General procedure N for the preparation of internal ynamides as exemplified by the synthesis of *N*,4-dimethyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 273

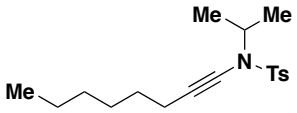


Prepared according to an adapted literature procedure by Stahl *et. al*.[236] In a three-neck round-bottom flask equipped with a stirrer-bar, $CuCl_2$ (26.9 mg, 20 mol%), amide (*N*,4-dimethylbenzenesulfonamide **268**) (0.66 g, 5.0 mmol, 5.0 equiv.) and Na_2CO_3 (0.21 g, 2.0 mmol, 2.0 equiv.) were combined. The reaction flask was purged with O_2 gas for 15 mins. A solution of anhydrous pyridine (0.16 mL, 2.0 mmol, 2.0 equiv.) in anhydrous toluene (5 mL) was added to the reaction flask *via* a syringe. A balloon filled with O_2 gas was connected to the reaction flask and the reaction was heated to 70 °C and stirred for 15 mins. A solution of 1-octyne (0.15 mL, 1.0 mmol, 1.0 equiv.) in anhydrous toluene (5 mL) was added to the flask over 4 hrs using a syringe pump. After the addition of 1-octyne/toluene solution, the reaction mixture was allowed to stir at 70 ºC for another 4 hrs and then cooled to room temperature. The crude mixture was concentrated under vacuum, the reaction mixture was purified by flash column chromatography (10-20% Et_2O in petrol) to yield ynamide **273** as a yellow oil (0.27 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.38-7.36 (2H, m, Ar-*H*), 3.04 (3H, s, NC*H*$_3$), 2.48 (3H, s, Ar-C*H*$_3$), 2.25 (2H, t, *J* 7.0, C*H*$_2$(CH_2)$_4$$CH_3$), 1.49 (2H, app dt, *J* 14.5,

7.0, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.37-1.27 (6H, m, (C*H*$_2$)$_3$CH$_3$), 0.91 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 144.4, 133.2, 129.6, 127.8, 74.8, 68.7, 39.4, 31.4, 28.9, 28.5, 22.6, 21.7, 18.4, 14.1; LRMS (ESI$^+$): *m/z* 316 ([M+Na]$^+$, 100%), 294 ([M+H]$^+$, 40%). This data is consistent with literature.[236]

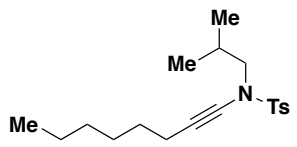
_N_-Isopropyl-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 274



Prepared according to general procedure **N** using CuCl$_2$ (53.8 mg, 20 mol%), amide (*N*-isopropyl-4-methylbenzenesulfonamide **269**) (2.13 g, 10.0 mmol, 5.0 equiv.), Na$_2$CO$_3$ (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 1-octyne (0.3 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (10-20% Et$_2$O in petrol) to yield *ynamide* **274** as colourless oil (89.4 mg, 14%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.82 (2H, d, *J* 8.5, Ar-*H*), 7.34 (2H, app dd, *J* 8.5, 0.5, Ar-*H*), 4.18 (1H, septet, *J* 6.5, NC*H*), 2.46 (3H, s, Ar-C*H*$_3$), 2.33 (2H, t, *J* 7.0, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.43-1.37 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.35-1.23 (6H, m, (C*H*$_2$)$_3$CH$_3$), 1.10 (6H, d, *J* 6.5, NCH(C*H*$_3$)$_2$), 0.91 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$): δ 144.0, 136.2, 129.5, 127.4, 72.1, 69.6, 51.9, 31.3, 29.0, 28.5, 22.6, 21.6, 20.6, 18.6, 14.1; IR: ν_{max} (neat)/cm^{-1} 2928, 2858, 2040, 1696, 1597, 1456, 1355, 1316, 1166, 1085; LRMS (ESI$^+$): *m/z* 344 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 344.16574 [M+Na]$^+$, C$_{18}$H$_{27}$NO$_2$SNa$^+$ requires 344.16547.

_N_-Isobutyl-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 275

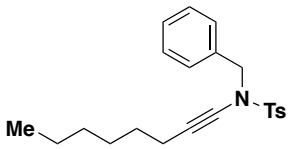


Prepared according to general procedure **N** using CuCl$_2$ (53.8 mg, 20 mol%), amide (*N*-isobutyl-4-methylbenzenesulfonamide **270**) (2.27 g, 10.0 mmol, 5.0 equiv.), Na$_2$CO$_3$ (424 mg, 4.00 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 1-octyne (0.3 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene

(10 mL). The crude mixture was purified by flash column chromatography (10-20% Et_2O in petrol) to yield *ynamide* **275** as colourless oil (74.6 mg, 11%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.36-7.34 (2H, m, Ar-*H*), 3.04 (2H, d, *J* 7.5, NCH_2), 2.47 (3H, s, Ar-CH_3), 2.27 (2H, t, *J* 7.0, CH_2(CH_2)$_4$$CH_3$), 2.03 (1H, app dquintet, *J* 13.5, 7.0, NCH_2CH), 1.52-1.45 (2H, m, CH_2(CH_2)$_3$$CH_3$), 1.38-1.27 (6H, m, ($CH_2$)$_3$$CH_3$), 0.96 (6H, d, *J* 6.5, $NCH_2CH(CH_3)_2$), 0.91 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.1, 134.6, 129.5, 127.6, 73.4, 69.9, 58.7, 31.3, 28.9, 28.4, 27.2, 22.6, 21.6, 19.7, 18.5, 14.0; IR: ν_{max} (neat)/cm^{-1} 2957, 2928, 2048, 1698, 1597, 1494, 1360, 1315, 1166, 1088; LRMS (ESI$^+$): *m/z* 368 ([M+MeOH+H]$^+$, 100%); HRMS (ESI$^+$) found 368.22517 [M+MeOH+H]$^+$, $C_{20}H_{34}NO_3S^+$ requires 368.22539.

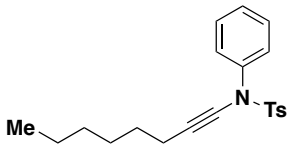
_N_-Benzyl-4-methyl-_N_-(oct-1-yn-1-yl)benzenesulfonamide, 276



Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (*N*-benzyl-4-methylbenzenesulfonamide **271**) (2.61 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (0.42 g, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 1-octyne (0.3 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (10-20% Et_2O in petrol) to yield *ynamide* **276** as a white solid (84.2 mg, 11%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (2H, d, *J* 8.5, Ar-*H*), 7.34-7.31 (7H, m, Ar-*H*), 4.47 (2H, s, NCH_2), 2.47 (3H, s, Ar-CH_3), 2.19 (2H, t, *J* 7.0, CH_2(CH_2)$_4$$CH_3$), 1.40-1.35 (2H, m, C$H_2$($CH_2$)$_3$$CH_3$), 1.30-1.21 (6H, m, ($CH_2$)$_3$$CH_3$), 0.89 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.2, 134.84, 134.76, 129.5, 128.7, 128.4, 128.1, 127.7, 73.3, 70.9, 55.6, 31.3, 28.7, 28.3, 22.6, 21.6, 18.4, 14.1; LRMS (ESI$^+$): *m/z* 392 ([M+Na]$^+$, 100%), 370 ([M+H]$^+$, 20%); mp: 44-45 °C (Et_2O/petrol), (lit. mp: 45-46 °C). This data is consistent with literature.[279]

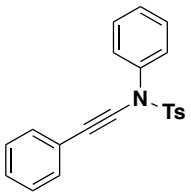
4-Methyl-*N*-(oct-1-yn-1-yl)-*N*-phenylbenzenesulfonamide, 277



Prepared according to general procedure **N** using $CuCl_2$ (29.9 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (1.24 g, 5.00 mmol, 5.0 equiv.), Na_2CO_3 (0.32 g, 3.0 mmol, 3.0 equiv.), anhydrous pyridine (0.16 mL, 2.0 mmol, 2.0 equiv.) in anhydrous toluene (5 mL) and 1-octyne (0.15 mL, 1.0 mmol, 1.0 equiv.) in anhydrous toluene (5 mL). The crude mixture was purified by flash column chromatography (10-20% Et_2O in petrol) to yield ynamide **277** as a pale yellow oil (0.34 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.57 (2H, m, Ar-*H*), 7.37-7.31 (3H, m, Ar-*H*), 7.30-7.27 (4H, m, Ar-*H*), 2.46 (3H, s, Ar-C*H*$_3$), 2.32 (2H, t, *J* 7.0, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.53 (2H, app dt, *J* 14.5, 7.5, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.42-1.28 (6H, m, (C*H*$_2$)$_3$CH$_3$), 0.91 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.6, 139.4, 133.0, 129.3, 128.9, 128.2, 127.8, 126.1, 73.8, 70.4, 31.3, 28.8, 28.5, 22.6, 21.7, 18.5, 14.1; LRMS (ESI$^+$): *m/z* 356 ([M+H]$^+$, 100%), 378 ([M+Na]$^+$, 30%). This data is consistent with literature.[280]

4-Methyl-*N*-phenyl-*N*-(phenylethynyl)benzenesulfonamide, 278

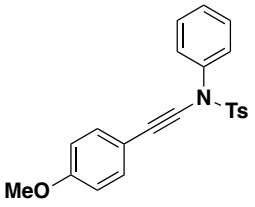


Prepared according to general procedure **N** using $CuCl_2$ (27.0 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (1.85 g, 7.5 mmol, 5.0 equiv.), Na_2CO_3 (0.47 g, 4.5 mmol, 3.0 equiv.), anhydrous pyridine (0.24 mL, 3.0 mmol, 2.0 equiv.) in anhydrous toluene (7.5 mL) and phenylacetyline (0.16 mL, 1.5 mmol, 1.0 equiv.) in anhydrous toluene (7.5 mL). The crude mixture was purified by flash column chromatography (10-20% Et_2O in petrol) to yield ynamide **278** as an off-white solid (398 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (2H, m, Ar-*H*), 7.44-7.41 (2H, m, Ar-*H*), 7.38-7.36 (5H, m, Ar-*H*), 7.34-7.31 (5H, m, Ar-*H*), 2.48 (3H, s, Ar-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$):

δ 145.0, 139.0, 132.9, 131.5, 129.5, 129.3, 129.1, 128.3, 128.2, 128.0, 126.3, 122.6, 83.0, 70.5, 21.7; LRMS (ESI^+): *m/z* 370 ($[M+Na]^+$, 100%); mp: 98-99 °C (Et_2O/petrol), (lit. mp: 88-90 °C). This data is consistent with literature.[281]

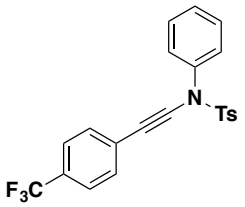
_N_-[(4-Methoxyphenyl)ethynyl]-4-methyl-_N_-phenylbenzenesulfonamide, 279



Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (2.47 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 4-ethynylanisole (0.24 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (60% CH_2Cl_2 in petrol) to yield ynamide **279** as white solid (533 mg, 71%).

^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* 8.5, Ar-*H*), 7.37-7.30 (9H, m, Ar-*H*), 6.87-6.85 (2H, m, Ar-*H*), 3.83 (3H, s, O*C*H_3), 2.47 (3H, s, Ar-*C*H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 144.9, 139.1, 133.4, 133.0, 129.4, 129.0, 128.3, 128.1, 126.2, 114.5, 113.9, 81.5, 70.2, 55.3, 21.7; LRMS (ESI^+): *m/z* 400 ($[M+Na]^+$, 100%); mp: 104-106 °C (CH_2Cl_2/petrol), (lit. mp: 106-108 °C). This data is consistent with literature.[281]

4-Methyl-_N_-phenyl-_N_-{[4-(trifluoromethyl)phenyl]ethynyl}benzenesulfonamide, 280

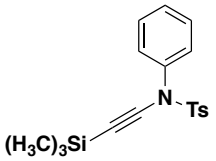


Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (2.47 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 4-trifluoromethylphenyl acetylene (0.33 mL, 2.0 mmol, 1.0 equiv.) in

anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (20-40% EtOAc in petrol) to yield *ynamide* **280** as white solid (314 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.63 (2H, m, Ar-*H*), 7.57 (2H, d, *J* 8.0, Ar-*H*), 7.49 (2H, app dd, *J* 8.5, 1.0, Ar-*H*), 7.41-7.37 (3H, m, Ar-*H*), 7.36-7.31 (4H, m, Ar-*H*), 2.47 (3H, s, Ar-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.3, 138.5, 132.9, 131.1, 129.6, 129.4 (q, $^{2}J_{CF}$ 32.5), 129.2, 128.5, 128.2, 126.7, 126.4, 125.2 (q, $^{3}J_{CF}$ 3.5), 123.9 (q, $^{1}J_{CF}$ 272.0), 85.6, 69.6, 21.7; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ –62.7; IR: ν_{max} (neat)/cm^{-1} 2968, 2918, 2251, 1683, 1602, 1511, 1353, 1122, 1065; LRMS (ESI$^+$): *m/z* 438 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 416.09271 [M+H]$^+$, $C_{22}H_{17}NO_2F_3S^+$ requires 416.09266; mp: 112-113 °C (EtOAc/petrol).

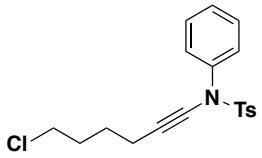
4-Methyl-*N*-phenyl-*N*-[(trimethylsilyl)ethynyl]benzenesulfonamide, 281



Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (2.47 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and ethynyltrimethylsilane (0.28 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (20-40% EtOAc in petrol) to yield ynamide **281** as yellow solid (478 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.58 (2H, m, Ar-*H*), 7.36-7.29 (5H, m, Ar-*H*), 7.27-7.24 (2H, m, Ar-*H*), 2.47 (3H, s, Ar-C*H*$_3$), 0.20 (9H, s, Si(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.9, 138.6, 132.8, 129.3, 129.0, 128.4, 128.2, 126.2, 95.3, 73.2, 21.7, 0.0; LRMS (ESI$^+$): *m/z* 366 ([M+Na]$^+$, 100%), 344 ([M+H]$^+$, 10%); mp: 89-91 °C (EtOAc/petrol), (lit. mp: 88-91 °C). This data is consistent with literature.[282]

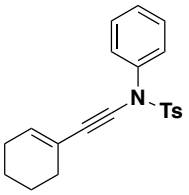
_N_-(6-Chlorohept-1-yn-1-yl)-4-methyl-_N_-phenylbenzenesulfonamide, 282



Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (2.47 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 6-chloro-1-hexyne (0.24 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (20-40% EtOAc in petrol) to yield *ynamide* **282** as colourless oil (646 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (2H, d, *J* 8.5, Ar-*H*), 7.34-7.25 (7H, m, Ar-*H*), 3.58 (2H, t, *J* 7.0, C*H*$_2$Cl), 2.46 (3H, s, Ar-C*H*$_3$), 2.38 (2H, t, *J* 7.0, C*H*$_2$(CH$_2$)$_3$Cl), 1.89 (2H, app dt, *J* 14.5, 7.0, C*H*$_2$CH$_2$Cl), 1.69 (2H, app quintet, *J* 7.5, C*H*$_2$(CH$_2$)$_2$Cl); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.8, 139.2, 132.9, 129.4, 129.0, 128.1, 128.0, 126.1, 74.5, 69.4, 44.6, 31.5, 26.0, 21.7, 17.8; IR: ν_{max} (neat)/cm^{-1} 2952, 2254, 1595, 1488, 1369, 1269, 1174, 1090; LRMS (ESI$^+$): *m/z* 384 ([M+Na]$^+$, 100%), 362 ([M+H]$^+$, 5%); HRMS (ESI$^+$) found 384.07962 [M+Na]$^+$, $C_{19}H_{20}NO_2ClSNa^+$ requires 384.07955.

_N_-(Cyclohex-1-en-1-ylethynyl)-4-methyl-_N_-phenylbenzenesulfonamide, 283

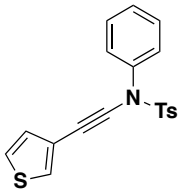


Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (2.47 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 1-ethynylcyclohexene (0.24 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (20-40% EtOAc in petrol) to yield *ynamide* **283** as pale yellow oil (473 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.58 (2H, m, Ar-*H*), 7.35-7.26 (7H, m, Ar-*H*), 6.07 (1H,

tt, *J* 4.0, 2.0, -CH_2CCHCH_2-), 2.46 (3H, s, Ar-CH_3), 2.15-2.09 (4H, m, -$CH_2CHCCCH_2$-), 1.68-1.58 (4H, m, -$CH_2CH_2CH_2CH_2$-); ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.7, 134.6, 132.9, 129.4, 129.0, 128.7, 128.3, 128.0, 126.1, 119.8, 80.4, 77.2, 29.4, 25.7, 22.3, 21.7, 21.5; IR: ν_{max} (neat)/cm^{-1} 2934, 1687, 1596, 1538, 1489, 1360, 1307, 1248, 1170, 1149; LRMS (ESI$^+$): *m/z* 374 ([M+Na]$^+$, 100%), 352 ([M+H]$^+$, 98%); HRMS (ESI$^+$) found 374.11877 [M+Na]$^+$, $C_{21}H_{21}NO_2SNa^+$ requires 374.11852.

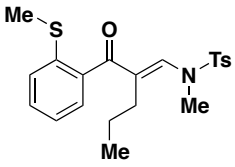
4-Methyl-*N*-phenyl-*N*-(thiophen-3-ylethynyl)benzenesulfonamide, 284



Prepared according to general procedure **N** using $CuCl_2$ (53.8 mg, 20 mol%), amide (4-methyl-*N*-phenylbenzenesulfonamide **272**) (2.47 g, 10.0 mmol, 5.0 equiv.), Na_2CO_3 (424 mg, 4.0 mmol, 2.0 equiv.), anhydrous pyridine (0.32 mL, 4.0 mmol, 2.0 equiv.) in anhydrous toluene (10 mL) and 3-ethynyl thiophene (0.20 mL, 2.0 mmol, 1.0 equiv.) in anhydrous toluene (10 mL). The crude mixture was purified by flash column chromatography (20-40% EtOAc in petrol) to yield *ynamide* **284** as an off white solid (363 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* 8.5, Ar-*H*), 7.43 (1H, dd, *J* 3.0, 1.0, SC*H*CH), 7.37-7.31 (7H, m, Ar-*H*), 7.28 (1H, app q, *J* 2.5, SCHC*H*), 7.10 (1H, dd, *J* 5.0, 1.0, SC*H*C), 2.48 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.0, 138.9, 133.0, 130.2, 129.5, 129.1, 128.9, 128.29, 128.26, 126.3, 125.2, 121.3, 82.3, 65.6, 21.7; IR: ν_{max} (neat)/cm^{-1} 3109, 2241, 1594, 1490, 1371, 1212, 1089, 1027; LRMS (ESI$^+$): *m/z* 376 ([M+Na]$^+$, 100%), 354 ([M+H]$^+$, 5%); HRMS (ESI$^+$) found 376.04389 [M+Na]$^+$, $C_{19}H_{15}NO_2S_2Na^+$ requires 376.04364; mp: 89-90 °C (EtOAc/petrol).

General procedure O for the hydroacylation of ynamides to form amino enones as exemplified by the synthesis of (*E*)-*N*,4-dimethyl-*N*-{2-[2-(methylthio)benzoyl]pent-1-en-1-yl}benzenesulfonamide, 285a

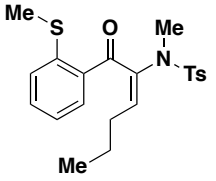


An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%). Once under an inert atmosphere, they were dissolved in acetone (1.0 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species (colour change from orange to dark red). The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (0.15 mL, 1.0 M with respect to aldehyde) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and ynamide (*N*,4-dimethyl-*N*-(pent-1-yn-1-yl)benzenesulfonamide **262**) (56.6 mg, 0.225 mmol, 1.5 equiv.). The reaction mixture was then stirred at 55 °C. The reaction was monitored by TLC until complete. After 16 hrs, the reaction mixture was filtered through a plug of silica (acetone, 10 mL) and the solvent removed *in vacuo* to obtain the crude product. The crude product was analysed by ^{1}H NMR spectroscopy to measure the ratio of the different regioisomers (9:1, *β*-amino enone **285a**: *α*-amino enone **285b**). The regioisomers were then separated by flash column chromatography (5% EtOAc in petrol) to afford title *β-amino enone* **285a** as a colourless oil (48.4 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.51 (2H, m, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.38 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.33-7.30 (2H, m, Ar-*H*), 7.25 (1H, s, NC*H*), 7.28-7.19 (2H, m, Ar-*H*), 3.26 (3H, s, NCH_3), 2.55-2.51 (2H, m, CH_2CH$_2$CH$_3$), 2.46 (3H, s, SCH_3), 2.44 (3H, s, Ar-CH_3), 1.50-1.47 (2H, m, CH_2CH$_3$), 0.95 (3H, t, *J* 8.0, CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.8, 144.6, 143.6, 134.2, 130.1, 130.0, 129.3, 128.1, 127.6, 127.3, 126.3, 125.5, 125.0, 34.9, 26.5, 23.3, 21.6, 17.0, 14.2; IR: ν_{max} (neat)/cm^{-1} 2960, 2871, 1648, 1610, 1432, 1292, 1227, 1164, 979; LRMS (ESI$^+$): *m/z* 426 ([M+Na]$^+$, 100%); HRMS (ESI$^+$)

found 426.11641 $[M+Na]^+$, $C_{21}H_{25}NO_3S_2Na^+$ requires 426.11681.

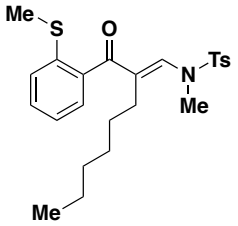
(*E*)-*N*,4-Dimethyl-*N*-{1-[2-(methylthio)phenyl]-1-oxohex-2-en-2-yl}benzenesulfonamide, 285b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (*N*,4-dimethyl-*N*-(pent-1-yn-1-yl)benzenesulfonamide **262**) (56.6 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (1:2.5, β-amino enone **285a**: α-amino enone **285b**). The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *α-amino enone* **285b** as a colourless oil (39.2 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.37-7.34 (2H, m, Ar-*H*), 7.32-7.30 (2H, m, Ar-*H*), 7.25-7.21 (1H, m, Ar-*H*), 6.53 (1H, t, *J* 7.5, COCC*H*), 3.15 (3H, s, NC*H*$_3$), 2.52 (2H, app q, *J* 7.5, C*H*$_2$CH$_2$CH$_3$), 2.44 (3H, s, SC*H*$_3$), 2.43 (3H, s, Ar-C*H*$_3$), 1.51 (2H, app dq, *J* 15.0, 7.5, C*H*$_2$CH$_3$), 0.96 (3H, t, *J* 7.5, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.7, 154.3, 143.3, 139.7, 138.4, 137.6, 136.1, 130.7, 129.3, 128.6, 128.1, 127.4, 124.8, 36.9, 31.4, 21.6, 21.4, 16.9, 14.1; IR: ν_{max} (neat)/cm^{-1} 2961, 2925, 1665, 1630, 1433, 1342, 1226, 1166, 1089; LRMS (ESI^+): *m/z* 404 ($[M+H]^+$, 100%), 426 ($[M+Na]^+$, 50%); HRMS (ESI^+) found 426.11689 $[M+Na]^+$, $C_{21}H_{25}NO_3S_2Na^+$ requires 426.11681.

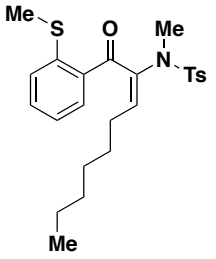
(*E*)-*N*,4-Dimethyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}benzenesulfonamide, 286a



Prepared according to general procedure using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (*N*,4-dimethyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **277**) (66.0 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (9:1, β-amino enone **286a**: α-amino enone **286b**). The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *β-amino enone* **286a** as a pale yellow oil (47.2 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.52 (2H, m, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.38 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.33-7.30 (2H, m, Ar-*H*), 7.26 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.24 (1H, s, NC*H*), 7.20 (1H, ddd, *J* 7.5, 1.5, 1.0, Ar-*H*), 3.26 (3H, s, NCH_3), 2.54 (2H, t, *J* 7.5, CH_2(CH_2)$_4$$CH_3$), 2.46 (3H, s, SC$H_3$), 2.44 (3H, s, Ar-C$H_3$), 1.42-1.26 (8H, m, (C$H_2$)$_4$$CH_3$), 0.89 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.7, 144.6, 143.5, 139.9, 136.8, 134.3, 130.1, 130.0, 128.1, 127.6, 127.2, 126.7, 125.0, 35.0, 31.6, 30.0, 29.4, 24.6, 22.6, 21.6, 17.0, 14.1; IR: ν_{max} (neat)/cm^{-1} 2924, 2855, 1610, 1433, 1358, 1288, 1163, 1059; LRMS (ESI$^+$): *m/z* 468 ([M+Na]$^+$, 100%), 446 ([M+H]$^+$, 5%); HRMS (ESI$^+$) found 446.18257 [M+H]$^+$, $C_{24}H_{32}NO_3S_2^+$ requires 446.18181.

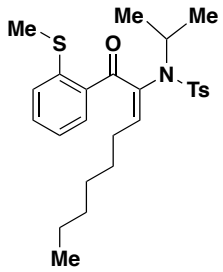
(*E*)-*N*,4-Dimethyl-*N*-{1-[2-(methylthio)phenyl]-1-oxonon-2-en-2-yl}benzenesulfonamide, 286b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (*N*,4-dimethyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **277**) (66.0 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (1:12.5, β-amino enone **286a**: α-amino enone **286b**). The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *α-amino enone* **286b** as a colourless oil (36.9 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* 8.5, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.35 (2H, dd, *J* 8.0, 1.5, Ar-*H*), 7.32-7.30 (2H, m, Ar-*H*), 7.23 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.52 (1H, t, *J* 7.5, COCC*H*), 3.15 (3H, s, NCH_3), 2.52 (2H, app q, *J* 7.5, CH_2(CH_2)$_4$CH$_3$), 2.44 (3H, s, SCH_3), 2.43 (3H, s, Ar-CH_3), 1.48-1.42 (2H, m, CH_2(CH$_2$)$_3$CH$_3$), 1.35-1.28 (6H, m, (CH_2)$_3$CH$_3$), 0.90 (3H, t, *J* 7.0, (CH$_2$)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.7, 154.5, 143.3, 139.5, 138.4, 137.6, 136.1, 130.7, 129.3, 128.6, 128.1, 127.4, 124.8, 36.9, 31.5, 29.5, 29.2, 28.0, 22.5, 21.6, 16.9, 14.0; IR: ν_{max} (neat)/cm^{-1} 2925, 2856, 1665, 1631, 1598, 1433, 1343, 1226, 1157, 944; LRMS (ESI$^+$): *m/z* 468 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 446.18162 [M+H]$^+$, $C_{24}H_{32}NO_3S_2^+$ requires 446.18181.

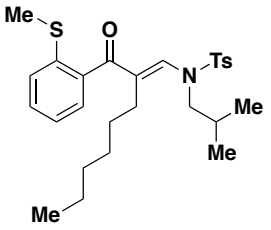
(*E*)-*N*-Isopropyl-4-methyl-*N*-{1-[2-(methylthio)phenyl]-1-oxonon-2-en-2-yl}benzenesulfonamide, 287b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (10 μL, 0.08 mmol, 1.0 equiv.), ynamide (*N*-isopropyl-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **274**) (33 mg, 0.104 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (1.5 mg, 5 mol%) and DPEPhos (2.2 mg, 5 mol%) in acetone (80 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (1:15, β-amino enone: α-amino enone **287b**) and a NMR conversion of 22%. The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *α-amino enone* **287b** as a colourless oil (7.0 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (3H, app td, *J* 6.5, 2.0, Ar-*H*), 7.49 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.38 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.29-7.25 (3H, m, Ar-*H*), 5.96 (1H br s, COCC*H*), 4.24 (1H, septet, *J* 7.0, NC*H*), 2.63 (2H, t, *J* 7.5, $CH_2(CH_2)_4CH_3$), 2.48 (3H, s, SCH_3), 2.42 (3H, s, Ar-CH_3), 1.45-1.39 (2H, m, $CH_2(CH_2)_3CH_3$), 1.35-1.25 (6H, m, $(CH_2)_3CH_3$), 0.97 (6H, d, *J* 7.0, $NCH(CH_3)_2$), 0.88 (3H, t, *J* 7.0, $(CH_2)_5CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 150.2, 143.6, 140.5, 136.88, 136.83, 131.6, 130.8, 129.7, 127.2, 126.3, 124.0, 100.0, 52.3, 31.5, 29.8, 28.1, 27.3, 22.6, 21.5, 20.3, 16.4, 14.1; IR: ν_{max} (neat)/cm^{-1} 2926, 2856, 1656, 1585, 1459, 1433, 1163, 1089; LRMS (ESI$^+$): *m/z* 496 ($[M+Na]^+$, 100%), 474 ($[M+H]^+$, 40%); HRMS (ESI$^+$) found 474.21284 $[M+H]^+$, $C_{26}H_{36}NO_3S_2^+$ requires 474.21311.

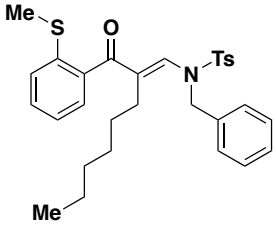
(*E*)-*N*-Isobutyl-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}benzenesulfonamide, 288a



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (*N*-isobutyl-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **275**) (65 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (22:1, β-amino enone **288a**: α-amino enone **288b**) and a NMR conversion of 77%. The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *β-amino enone* **288a** as a pale yellow oil (41.3 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.57 (2H, m, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.38-7.36 (1H, m, Ar-*H*), 7.31-7.27 (3H, m, Ar-*H*), 7.24 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 6.57 (1H, s, NC*H*), 3.17 (2H, d, *J* 7.5, NCH_2), 2.52 (2H, t, *J* 7.0, CH_2(CH$_2$)$_4$CH$_3$), 2.46 (3H, s, SCH_3), 2.44 (3H, s, Ar-CH_3), 1.88-1.80 (1H, m, NCH$_2$C*H*), 1.28-1.22 (8H, m, (CH_2)$_4$CH$_3$), 0.95 (6H, d, *J* 7.0, NCH$_2$CH(CH_3)$_3$), 0.88 (3H, t, *J* 7.0, (CH$_2$)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.7, 144.0, 139.7, 138.9, 137.9, 135.9, 135.6, 130.5, 129.7, 128.8, 127.3, 127.2, 124.7, 55.6, 31.6, 29.4, 28.7, 27.5, 26.1, 22.5, 21.6, 19.7, 16.8, 14.1; IR: ν_{max} (neat)/cm^{-1} 2926, 2856, 1651, 1608, 1465, 1354, 1283, 1164, 1088; LRMS (ESI$^+$): *m/z* 510 ([M+Na]$^+$, 100%), 488 ([M+H]$^+$, 30%); HRMS (ESI$^+$) found 488.22806 [M+H]$^+$, $C_{27}H_{38}NO_3S_2^+$ requires 488.22876.

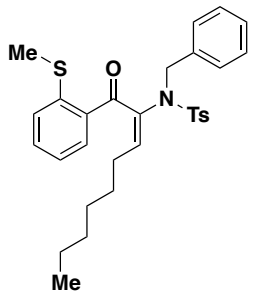
(*E*)-*N*-Benzyl-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}benzenesulfonamide, 289a



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (13 μL, 0.10 mmol, 1.0 equiv.), ynamide (*N*-benzyl-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **276**) (55 mg, 0.15 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (1.9 mg, 5 mol%) and DPEPhos (2.7 mg, 5 mol%) in acetone (100 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave the β-amino enone **289a** as the sole regioisomer and a NMR conversion of 80%. The compound was purified by flash column chromatography (10-15% EtOAc in petrol) to yield *β-amino enone* **289a** as a colourless oil (38.7 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.50 (2H, m, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.37-7.30 (4H, m, Ar-*H*), 7.27 (2H, d, *J* 8.0, Ar-*H*), 7.23 (2H, dd, *J* 8.0, 1.5, Ar-*H*), 7.19 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 7.11 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 6.80 (1H, s, NC*H*), 4.69 (2H, s, NCH_2), 2.45 (3H, s, SCH_3), 2.42 (3H, s, Ar-CH_3), 2.35 (2H, t, *J* 7.5, CH_2(CH_2)$_4$$CH_3$), 1.24-1.15 (8H, m, (C$H_2$)$_4$$CH_3$), 0.86 (3H, t, *J* 7.0, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 144.4, 140.2, 139.0, 137.9, 135.7, 135.0, 133.1, 130.4, 129.8, 128.8, 128.7, 127.8, 127.4, 127.19, 127.16, 124.6, 52.2, 31.6, 29.4, 29.1, 25.6, 22.6, 21.6, 16.8, 14.1; IR: ν_{max} (neat)/cm^{-1} 2924, 2855, 1650, 1512, 1358, 1287, 1186, 1041; LRMS (ESI$^+$): *m/z* 544 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 522.21262 [M+H]$^+$, $C_{30}H_{36}NO_3S_2^+$ requires 522.21311.

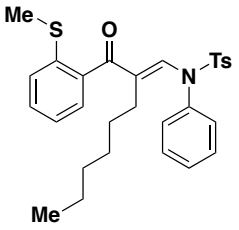
(*E*)-*N*-Benzyl-4-methyl-*N*-(1-(2-(methylthio)phenyl)-1-oxonon-2-en-2-yl)benzenesulfonamide, 289b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (13 μL, 0.10 mmol, 1.0 equiv.), ynamide (*N*-benzyl-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide **276**) (55 mg, 0.15 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (1.9 mg, 5 mol%) and PNP(Cy) (2.1 mg, 5 mol%) in acetone (100 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (1:4, β-amino enone **289a**: α-amino enone **289b**) and a NMR conversion of 69%. The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *α-amino enone* **289b** as a colourless oil (4.2 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (2H, d, *J* 8.5, Ar-*H*), 7.41-7.37 (3H, m, Ar-*H*), 7.36-7.30 (6H, m, Ar-*H*), 7.12 (1H, app td, *J* 7.5, 1.0, Ar-*H*), 6.88-6.87 (1H, m, Ar-*H*), 6.49 (1H, t, *J* 7.5, COCC*H*), 5.01 (1H, app br s, NCH_aH_b), 4.34 (1H, app br s, NCH_aH_b), 2.46 (3H, s, SCH_3), 2.43 (3H, s, Ar-CH_3), 2.25-2.22 (2H, m, $CH_2(CH_2)_4CH_3$), 1.28-1.23 (2H, m, $CH_2(CH_2)_3CH_3$), 1.21-1.08 (6H, m, $(CH_2)_3CH_3$), 0.87 (3H, t, *J* 7.5, $(CH_2)_5CH_3$).; ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.5, 158.9, 143.3, 138.6, 137.4, 136.9, 136.0, 135.8, 130.4, 130.0, 129.3, 128.3, 128.2, 128.1, 128.0, 127.6, 124.6, 52.4, 31.5, 30.3, 29.1, 27.8, 22.5, 21.7, 17.0, 14.0; IR: ν_{max} (neat)/cm^{-1} 2924, 2855, 1664, 1629, 1598, 1287, 1160; LRMS (ESI$^+$): *m/z* 544 ($[M+Na]^+$, 100%); HRMS (ESI$^+$) found 544.19479 $[M+Na]^+$, $C_{30}H_{35}NO_3S_2Na^+$ requires 544.19506.

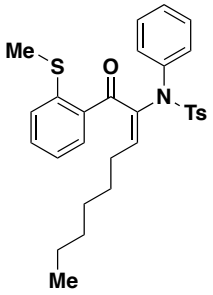
(*E*)-4-Methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}-*N*-phenylbenzenesulfonamide, 290a



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-(oct-1-yn-1-yl)-*N*-phenylbenzenesulfonamide **277**) (80.0 mg, 0.225 mmol, 1.5 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave the β-amino enone **290a** as the sole regioisomer. The compound was purified by flash column chromatography (10-15% EtOAc in petrol) to yield *β-amino enone* **290a** as a pale yellow oil (46.2 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.47 (1H, m, Ar-*H*), 7.49 (1H, s, NC*H*), 7.43-7.41 (2H, m, Ar-*H*), 7.39-7.35 (2H, m, Ar-*H*), 7.33-7.27 (2H, m, Ar-*H*), 7.26-7.23 (4H, m, Ar-*H*), 7.12-7.10 (2H, m, Ar-*H*), 2.46 (3H, s, SCH_3), 2.44 (3H, s, Ar-CH_3), 1.71-1.67 (2H, m, CH_2(CH_2)$_4$$CH_3$), 1.19-1.15 (2H, m, C$H_2$($CH_2$)$_3$$CH_3$), 1.08-1.00 (4H, m, (C$H_2$)$_2$$CH_2CH_3$), 0.90-0.87 (2H, m, ($CH_2$)$_2CH_2CH_3$), 0.83 (3H, t, *J* 7.5, (CH_2)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.7, 144.8, 143.9, 140.1, 137.6, 136.9, 133.9, 130.0, 129.7, 129.6, 129.1, 128.2, 127.9, 127.5, 126.4, 125.2, 120.1, 31.5, 29.3, 27.8, 24.0, 22.5, 21.7, 17.0, 14.1; IR: ν_{max} (neat)/cm^{-1} 2926, 2856, 1694, 1647, 1493, 1433, 1290, 1171, 1128, 1087; LRMS (ESI$^+$): *m/z* 508 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 508.19755 [M+H]$^+$, $C_{29}H_{34}NO_3S_2^+$ requires 508.19746.

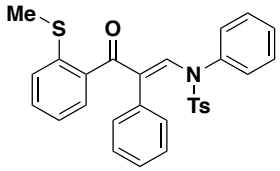
(*E*)-4-Methyl-*N*-{1-[2-(methylthio)phenyl]-1-oxonon-2-en-2-yl}-*N*-phenylbenzenesulfonamide, 290b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-(oct-1-yn-1-yl)-*N*-phenylbenzenesulfonamide **277**) (69.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (1:8, β-amino enone **290a**: α-amino enone **290b**) with a 70% NMR conversion. The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *α-amino enone* **290b** as a colourless oil (36.5 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (3H, ddd, *J* 7.0, 3.5, 1.5, Ar-*H*), 7.57-7.51 (2H, m, Ar-*H*), 7.51-7.45 (1H, m, Ar-*H*), 7.38-7.23 (5H, m, Ar-*H*), 7.17-7.15 (2H, m, Ar-*H*), 6.38 (1H, t, *J* 7.5, COCC*H*), 2.48 (3H, s, SC*H*$_3$), 2.40-2.30 (2H, m, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.36 (3H, s, Ar-C*H*$_3$), 1.25-1.17 (8H, m, (C*H*$_2$)$_4$CH$_3$), 0.86 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.6, 151.4, 143.6, 140.8, 140.5, 138.9, 137.5, 135.7, 131.1, 130.4, 130.1, 129.0, 128.7, 126.4, 126.3, 125.8, 124.3, 31.4, 29.1, 28.8, 27.6, 22.4, 21.6, 16.3, 14.0; IR: ν_{max} (neat)/cm^{-1} 2970, 1632, 1555, 1466, 1378, 1160, 1128; LRMS (ESI$^+$): *m/z* 530 ([M+Na]$^+$, 100%), 508 ([M+H]$^+$, 80%); HRMS (ESI$^+$) found 530.17931 [M+Na]$^+$, $C_{29}H_{33}NO_3S_2Na^+$ requires 530.17941.

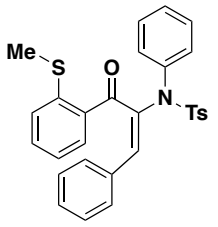
(*E*)-4-Methyl-*N*-{3-[2-(methylthio)phenyl]-3-oxo-2-phenylprop-1-en-1-yl}-*N*-phenylbenzenesulfonamide, 291a



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-phenyl-*N*-(phenylethynyl)benzenesulfonamide **278**) (67.7 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (6:1, *β*-amino enone **291a**: *α*-amino enone **291b**). The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *β-amino enone* **291a** as a pale yellow oil (58.9 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (1H, s, NC*H*), 7.49 (1H, ddd, *J* 8.0, 7.0, 1.5, Ar-*H*), 7.43 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.39-7.37 (1H, m, Ar-*H*), 7.32 (1H, dd, *J* 7.0, 1.5, Ar-*H*), 7.29-7.27 (2H, m, Ar-*H*), 7.24-7.21 (2H, m, Ar-*H*), 7.02-6.98 (1H, m, Ar-*H*), 6.93-6.89 (5H, m, Ar-*H*), 6.83-6.81 (2H, m, Ar-*H*), 6.74-6.71 (2H, m, Ar-*H*), 2.47 (3H, s, SCH_3), 2.46 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.6, 144.9, 143.8, 140.3, 136.9, 135.8, 133.8, 132.6, 130.4, 130.3, 129.8, 129.6, 128.4, 128.33, 128.26, 127.9, 127.6, 127.3, 126.8, 125.42, 125.36, 21.7, 17.2; IR: ν_{max} (neat)/cm^{-1} 2922, 1657, 1614, 1492, 1447, 1324, 1122, 1088; LRMS (ESI$^+$): *m/z* 522 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 500.13361 [M+H]$^+$, $C_{29}H_{26}NO_3S_2^+$ requires 500.13486.

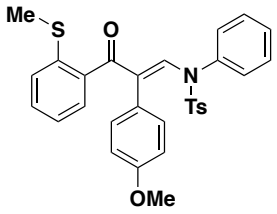
(*E*)-4-Methyl-*N*-{3-[2-(methylthio)phenyl]-3-oxo-1-phenylprop-1-en-2-yl}-*N*-phenylbenzenesulfonamide, 291b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-phenyl-*N*-(phenylethynyl)benzenesulfonamide **278**) (67.7 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and PNP(Cy) (3.2 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (1:1.3, β-amino enone **291a**: α-amino enone **291b**). The compounds were separated by flash column chromatography (10-15% EtOAc in petrol) to yield *α-amino enone* **291b** as a colourless oil (29.9 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (1H, d, *J* 7.5, Ar-*H*), 7.76-7.74 (2H, m, Ar-*H*), 7.69 (2H, d, *J* 8.0, Ar-*H*), 7.55-7.50 (1H, m, Ar-*H*), 7.48 (2H, d, *J* 8.5, Ar-*H*), 7.43 (1H, d, *J* 8.0, Ar-*H*), 7.37-7.34 (3H, m, Ar-*H*), 7.30-7.26 (1H, m, Ar-*H*), 7.17 (2H, d, *J* 8.5, Ar-*H*), 7.12 (2H, app t, *J* 7.5, Ar-*H*), 7.05 (1H, s, COCC*H*), 7.04-7.00 (1H, m, Ar-*H*), 2.54 (3H, s, SCH_3), 2.36 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.6, 143.8, 143.7, 139.8, 139.6, 138.4, 136.9, 135.3, 131.9, 131.5, 131.3, 130.4, 129.1, 128.94, 128.91, 128.6, 128.4, 126.1, 126.0, 125.1, 124.3, 21.6, 16.2; IR: ν_{max} (neat)/cm^{-1} 2922, 1657, 1597, 1447, 1324, 1268, 1122, 1088, 1007; LRMS (ESI$^+$): *m/z* 522 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 500.13459 [M+H]$^+$, $C_{29}H_{26}NO_3S_2^+$ requires 500.13486.

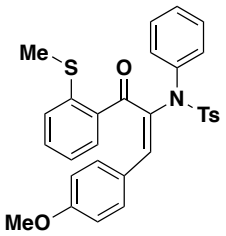
(*E*)-*N*-{2-(4-Methoxyphenyl)-3-[2-(methylthio)phenyl]-3-oxoprop-1-en-1-yl}-4-methyl-*N*-phenylbenzenesulfonamide, 292a



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (*N*-[(4-methoxyphenyl)ethynyl]-4-methyl-*N*-phenylbenzenesulfonamide **279**) (68 mg, 0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (6.3:1, β-amino enone **292a**: α-amino enone **292b**). The compounds were separated by flash column chromatography (5-15% EtOAc in petrol) to yield *β-amino enone* **292a** as a thick white oil (65.2 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, s, NC*H*), 7.49-7.45 (1H, m, Ar-*H*), 7.41 (1H, d, *J* 7.5, Ar-*H*), 7.36 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.31-7.29 (1H, m, Ar-*H*), 7.23 (4H, app q, *J* 9.0, Ar-*H*), 7.02 (1H, app t, *J* 7.5, Ar-*H*), 6.95-6.92 (2H, m, Ar-*H*), 6.74 (4H, d, *J* 8.5, Ar-*H*), 6.45 (2H, d, *J* 8.5, Ar-*H*), 3.66 (3H, s, OCH_3), 2.44 (3H, s, SCH_3), 2.43 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.9, 158.3, 144.9, 143.7, 140.3, 136.9, 135.9, 133.8, 131.5, 130.2, 129.8, 129.6, 128.3, 128.2, 128.1, 127.9, 127.5, 125.4, 125.1, 124.9, 112.9, 55.2, 21.7, 17.1; IR: ν_{max} (neat)/cm^{-1} 2930, 1600, 1511, 1492, 1365, 1289, 1170, 1084; LRMS (ESI$^+$): *m/z* 552 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 530.14438 [M+H]$^+$, $C_{30}H_{28}NO_4S_2^+$ requires 530.14543.

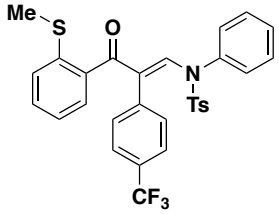
(*E*)-*N*-{1-(4-methoxyphenyl)-3-[2-(methylthio)phenyl]-3-oxoprop-1-en-2-yl}-4-methyl-*N*-phenylbenzenesulfonamide, 292b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **15** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (*N*-[(4-methoxyphenyl)ethynyl]-4-methyl-*N*-phenylbenzenesulfonamide **279**) (68 mg, 0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (6.3:1, β-amino enone **292a**: α-amino enone **292b**). The compounds were separated by flash column chromatography (5-15% EtOAc in petrol) to yield *α-amino enone* **292b** as a colourless oil (9.9 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80-7.77 (3H, m, Ar-*H*), 7.75 (2H, d, *J* 8.5, Ar-*H*), 7.55-7.51 (2H, m, Ar-*H*), 7.50-7.48 (1H, m, Ar-*H*), 7.41 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.26 (1H, dd, *J* 7.5, 1.0, Ar-*H*), 7.19-7.14 (4H, m, Ar-*H*), 7.08 (1H, s, COCC*H*), 7.06-7.02 (1H, m, Ar-*H*), 6.88-6.86 (2H, m, Ar-*H*), 3.82 (3H, s, OC*H*$_3$), 2.52 (3H, s, SC*H*$_3$), 2.36 (3H, s, Ar-C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.7, 161.7, 144.9, 143.8, 139.8, 138.7, 137.8, 135.9, 135.5, 132.9, 131.0, 130.5, 129.0, 128.9, 128.7, 126.3, 125.8, 124.5, 124.4, 124.3, 114.0, 55.3, 21.6, 16.3; IR: ν_{max} (neat)/cm^{-1} 2923, 1655, 1596, 1510, 1491, 1320, 1261, 1177, 1159; LRMS (ESI$^+$): *m/z* 552 ([M+Na]$^+$, 100%), 530 ([M+H]$^+$, 15%); HRMS (ESI$^+$) found 530.14502 [M+H]$^+$, $C_{30}H_{28}NO_4S_2^+$ requires 530.14543.

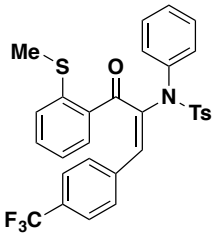
(*E*)-4-Methyl-*N*-{3-[2-(methylthio)phenyl]-3-oxo-2-[4-(trifluoromethyl)phenyl]prop-1-en-1-yl}-*N*-phenylbenzenesulfonamide, 293a



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **19** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-phenyl-*N*-{[4-(trifluoromethyl)phenyl]ethynyl}benzenesulfonamide **280**) (75 mg, 0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (5:1, *β*-amino enone **293a**: *α*-amino enone **293b**). The compounds were separated by flash column chromatography (5-15% EtOAc in petrol) to yield *β-amino enone* **293a** as a white oil (63.6 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, s, NC*H*), 7.54-7.50 (1H, m, Ar-*H*), 7.46-7.44 (1H, m, Ar-*H*), 7.39 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.34 (1H, app td, *J* 7.5, 1.0, Ar-*H*), 7.29-7.26 (2H, m, Ar-*H*), 7.23 (2H, d, *J* 8.0, Ar-*H*), 7.16-7.14 (2H, m, Ar-*H*), 7.02 (1H, app tt, *J* 7.5, 1.5, Ar-*H*), 6.93-6.88 (4H, m, Ar-*H*), 6.69-6.66 (2H, m, Ar-*H*), 2.48 (3H, s, SCH_3), 2.45 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.1, 145.2, 144.8, 138.1 (q, $^1J_{CF}$ 277.5), 136.7, 135.4, 133.6, 130.8, 130.5, 130.0, 129.7, 128.8, 128.5, 128.2, 128.1 (q, $^2J_{CF}$ 34.5), 128.0, 127.6, 125.6, 124.7, 124.0 (q, $^3J_{CF}$ 3.5), 123.2, 122.6, 21.7, 17.2; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ –63.0; IR: ν_{max} (neat)/cm^{-1} 2951, 1605, 1516, 1434, 1406, 1323, 1169, 1122; LRMS (ESI$^+$): *m/z* 590 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 568.12191 [M+H]$^+$, $C_{30}H_{25}NO_3F_3S_2^+$ requires 568.12225.

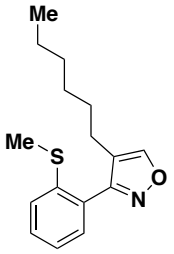
(*E*)-4-Methyl-*N*-{3-[2-(methylthio)phenyl]-3-oxo-1-[4-(trifluoromethyl)phenyl]prop-1-en-2-yl}-*N*-phenylbenzenesulfonamide, 293b



Prepared according to general procedure **O** using 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-phenyl-*N*-{[4-(trifluoromethyl)phenyl]ethynyl}benzenesulfonamide **280**) (75 mg, 0.18 mmol, 1.2 equiv.), $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C the reaction gave a crude mixture of regioisomers (5:1, β-amino enone **293a**: α-amino enone **293b**). The compounds were separated by flash column chromatography (5-15% EtOAc in petrol) to yield *α-amino enone* **293b** as a colourless oil (11 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.78-7.76 (2H, m, Ar-*H*), 7.65-7.62 (2H, m, Ar-*H*), 7.58 (2H, d, *J* 8.0, Ar-*H*), 7.56-7.52 (1H, m, Ar-*H*), 7.43 (1H, d, *J* 7.5, Ar-*H*), 7.40-7.38 (2H, m, Ar-*H*), 7.31-7.29 (1H, m, Ar-*H*), 7.17 (2H, d, *J* 8.0, Ar-*H*), 7.12-7.07 (2H, m, Ar-*H*), 7.04-7.00 (1H, m, Ar-*H*), 6.98 (1H, s, COCC*H*), 2.55 (3H, s, SCH_3), 2.35 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.0, 144.1, 142.5, 140.4, 140.3, 138.6, 137.7 (q, $^1J_{CF}$ 280.0), 134.8, 131.7 (q, $^2J_{CF}$ 35.5), 130.2, 130.0, 129.9, 129.0, 128.9, 128.7, 128.4, 126.4, 125.8, 125.17 (q, $^3J_{CF}$ 3.5), 125.15, 124.5, 124.2, 21.7, 16.1 ; ^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled): δ −63.0; IR: ν_{max} (neat)/cm^{-1} 2925, 1661, 1597, 1491, 1412, 1323, 1160, 1123; LRMS (ESI$^+$): *m/z* 590 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 568.12223 [M+H]$^+$, $C_{30}H_{25}NO_3F_3S_2^+$ requires 568.12225.

General procedure P for the synthesis of isoxazoles as exemplified by the synthesis of 4-hexyl-3-(2-(methylthio)phenyl)isoxazole, 294



c) The direct cyclisation of *β*-amino enone intermediate

Hydroxylamine hydrochloride (5.2 mg, 0.075 mmol, 1.5 equiv.) was added to a solution of *β*-amino enone ((*E*)-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}-*N*-phenylbenzenesulfonamide **290a**) (25 mg, 0.05 mmol, 1.0 equiv.) in anhydrous MeOH (0.08 mL) and the reaction mixture was heated to 55 °C for 24 hrs. After which, the flask was cooled to room temperature and the reaction was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (5% EtOAc in petrol) to give title *isoxazole* **294** as a cloudy white oil (13.7 mg, 99%).

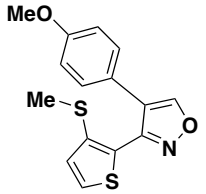
d) The one-pot hydroacylation-cyclisation cascade

An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%). Once under an inert atmosphere, they were dissolved in acetone (1 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (150 μL, 1.0 M with respect to aldehyde) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (19 μL, 0.15 mmol, 1.0 equiv.) and ynamide (4-methyl-*N*-(oct-1-yn-1-yl)-*N*-phenylbenzenesulfonamide **277**) (69.0 mg, 0.195 mmol, 1.3 equiv.). The reaction mixture was then stirred at 55 °C for 16 hrs, after which it was opened to air followed by the addition of MeOH (1.6 mL) and hydroxylamine hydrochloride (16.0 mg, 0.225 mmol, 1.5 equiv.). The reaction mixture was further stirred until complete, after 16 hrs, the solution was diluted with CH_2Cl_2 (10 mL) and neutralised by

the addition of sat. $NaHCO_{3(aq.)}$ (10 mL) in a separatory funnel. The aqueous mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product and purified by flash column chromatography (5% EtOAc in petrol) to afford title *isoxazole* **294** as a cloudy white oil (29.7 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, s, OC*H*), 7.47 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.37 (1H, dd, *J* 8.0, 1.0, Ar-*H*), 7.31 (1H, ddd, *J* 7.5, 1.5, 1.0, Ar-*H*), 7.26 (1H, app td, *J* 7.5, 1.5, Ar-*H*), 2.45 (3H, s, SC*H*$_3$), 2.42 (2H, t, *J* 7.5, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.56-1.53 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.29-1.26 (6H, m, (C*H*$_2$)$_3$CH$_3$), 0.87 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.3, 151.3, 139.8, 130.6, 130.5, 127.0, 126.1, 124.7, 117.3, 31.4, 29.6, 28.8, 22.8, 22.5, 16.0, 14.0; IR: ν_{max} (neat)/cm^{-1} 2925, 2855, 1738, 1452, 1377, 1260, 1143, 1041; LRMS (ESI$^+$): *m/z* 276 ([M+H]$^+$, 100%), 298 ([M+Na]$^+$, 10%); HRMS (ESI$^+$) found 276.14168 [M+H]$^+$, $C_{16}H_{22}NOS^+$ requires 276.14166.

4-(4-Methoxyphenyl)-3-[3-(methylthio)thiophen-2-yl]isoxazole, 296

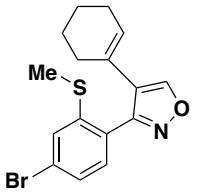


Prepared according to general procedure **Pb** using 3-(methylthio)thiophene-2-carbaldehyde **90** (24.0 mg, 0.15 mmol, 1.0 equiv.), ynamide (*N*-[(4-methoxyphenyl)ethynyl]-4-methyl-*N*-phenylbenzenesulfonamide **279**) (74.0 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL , 1.0 M). After stirring for 16 hrs at 55 °C, MeOH (0.25 mL) and hydroxylamine hydrochloride (16.0 mg, 0.225 mmol, 1.5 equiv.) were added and stirred at 55 °C for a further 5 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford *isoxazole* **296** as pale yellow oil (27.3 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (1H, s, OC*H*), 7.51 (1H, d, *J* 5.5, SC*H*), 7.29-7.27 (2H, m, Ar-*H*), 7.09 (1H, d, *J* 5.5, SCHC*H*), 6.92 (2H, d, *J* 9.0, Ar-*H*), 3.85 (3H, s, OC*H*$_3$), 2.39 (3H, s, SC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 151.0, 131.0, 129.3, 128.51, 128.45,

128.2, 122.1, 121.6, 118.2, 114.3, 55.3, 17.9; IR: ν_{max} (neat)/cm^{-1} 2958, 2919, 1606, 1522, 1491, 1363, 1251, 1176, 1146, 1088; LRMS (ESI$^+$): *m/z* 304 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 304.04612 [M+H]$^+$, $C_{15}H_{14}NO_2S_2^+$ requires 304.04605.

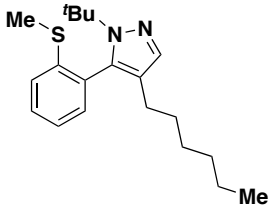
3-[4-Bromo-2-(methylthio)phenyl]-4-(cyclohex-1-en-1-yl)isoxazole, 297



Prepared according to general procedure **Pb** using 4-bromo-2-(methylthio)benzaldehyde **91** (34.6 mg, 0.15 mmol, 1.0 equiv.), ynamide (*N*-(cyclohex-1-en-1-ylethynyl)-4-methyl-*N*-phenylbenzenesulfonamide **283**) (69.0 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF$_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL , 1.0 M). After stirring for 16 hrs at 55 °C, MeOH (0.25 mL) and hydroxylamine hydrochloride (16.0 mg, 0.225 mmol, 1.5 equiv.) were added and stirred at 55 °C for a further 3 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford *isoxazole* **297** as yellow oil (28.6 mg, 54%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.34 (1H, s, OC*H*), 7.42 (1H, d, *J* 1.5, Ar-*H*), 7.37 (1H, dd, *J* 8.0, 1.5, Ar-*H*), 7.21 (1H, d, *J* 8.0, Ar-*H*), 5.85 (1H, app dt, *J* 3.5, 2.0, -CH$_2$CC*H*CH$_2$-), 2.46 (3H, s, SC*H$_3$*), 2.12-2.09 (2H, m, -CH$_2$C*H$_2$*CCHCH$_2$-), 2.04-2.01 (2H, m, -CH$_2$CH$_2$CCH*CH$_2$*-), 1.66-1.58 (4H, m, -CCHCH$_2$C*H$_2$*C*H$_2$*-); ^{13}C NMR (101 MHz, CDCl$_3$): δ 160.9, 149.5, 142.3, 131.9, 128.2, 127.7, 127.5, 127.1, 126.4, 126.3, 125.0, 27.3, 25.5, 22.6, 21.7, 15.9; IR: ν_{max} (neat)/cm^{-1} 2937, 2858, 2832, 1685, 1605, 1571, 1487, 1432, 1334, 1233, 1193; LRMS (ESI$^+$): *m/z* 372 ([^{79}Br] [M+Na]$^+$, 100%), 374 ([^{81}Br] [M+Na]$^+$, 90%), 350 ([^{79}Br] [M+H]$^+$, 30%), 352 ([^{81}Br] [M+H]$^+$, 20%); HRMS (ESI$^+$) found 350.02101 [[^{79}Br] [M+H]$^+$], 352.01890 [[^{81}Br] [M+H]$^+$], $C_{16}H_{17}{}^{79}BrNOS^+$ requires 350.02080, $C_{16}H_{17}{}^{81}BrNOS^+$ requires 352.01883.

General procedure Q for the synthesis of pyrazoles as exemplified by the synthesis of 1-(*tert*-butyl)-4-hexyl-5-[2-(methylthio)phenyl]-1*H*-pyrazole, 298



a) The direct cyclisation of *β*-amino enone intermediate

tert-Butylhydrazine hydrochloride (19 mg, 0.15 mmol, 1.5 equiv.) was added to a solution of *β*-amino enone ((*E*)-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}-*N*-phenylbenzenesulfonamide **290a**) (51 mg, 0.1 mmol, 1.0 equiv.) in EtOH (0.16 mL) and the reaction mixture was heated to 78 °C for 24 hrs. After which, the flask was cooled to room temperature and the reaction was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (5% EtOAc in petrol) to give title *pyrazole* **298** as a colourless oil (28.1 mg, 84%).

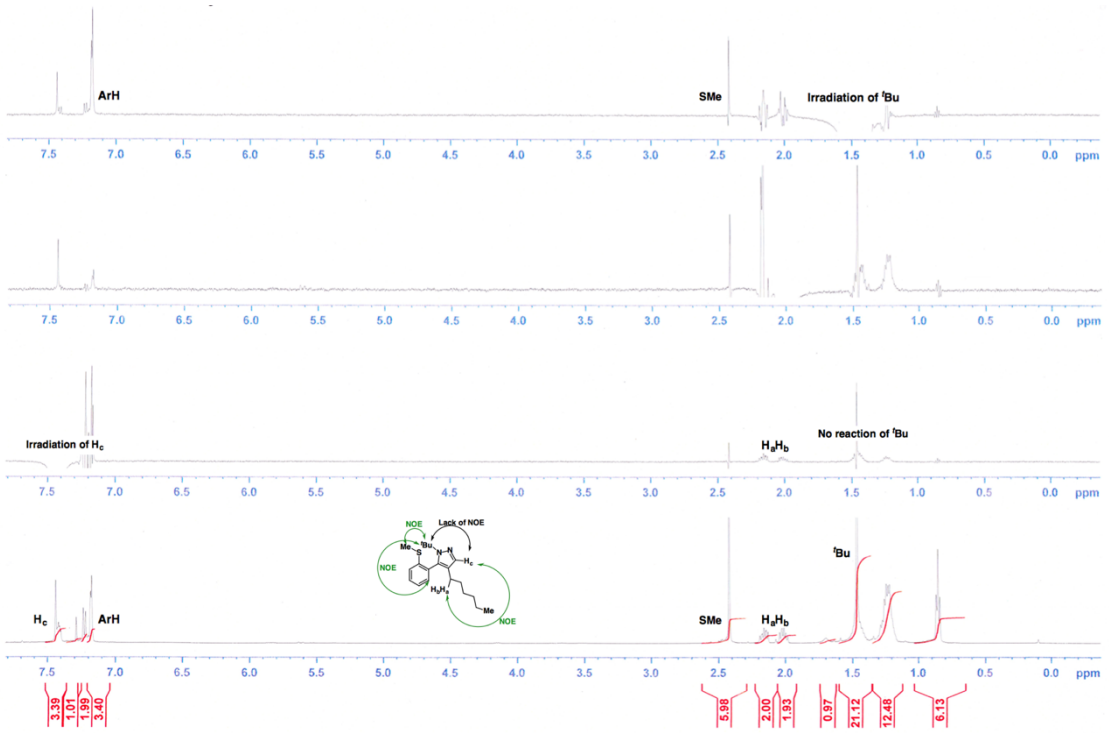
b) The one-pot hydroacylation-cyclisation cascade

An oven-dried microwave vial was charged with $[Rh(nbd)_2]BF_4$ (2.1 mg, 5 mol%) and DPEPhos (3.0 mg, 5 mol%). Once under an inert atmosphere, they were dissolved in acetone (1 mL). Hydrogen gas was bubbled through the solution at room temperature for 1-2 mins in order to generate the active catalyst species. The hydrogen gas was purged using nitrogen gas, and this was bubbled through the catalyst to dryness. The dry catalyst was dissolved in acetone (110 μL, 1.0 M with respect to aldehyde) and this was transferred to a nitrogen-filled microwave vial containing 2-(methylthio)benzaldehyde **50** (14 μL, 0.11 mmol, 1.0 equiv.) and ynamide (4-methyl-*N*-(oct-1-yn-1-yl)-*N*-phenylbenzenesulfonamide **277**) (51.0 mg, 0.143 mmol, 1.3 equiv.). The reaction mixture was then stirred at 55 °C for 16 hrs, after which it was opened to air followed by the addition of EtOH (0.2 mL) and *tert*-butylhydrazine hydrochloride (20.6 mg, 0.165 mmol, 1.5 equiv.). The reaction mixture was then stirred at 78 °C for 16 hrs, the solution was diluted with CH_2Cl_2 (10 mL) and neutralised by the addition of sat. $NaHCO_{3(aq.)}$ (10 mL) in a separatory funnel. The aqueous mixture was extracted with

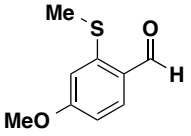
CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product and purified by flash column chromatography (5% EtOAc in petrol) to afford title *pyrazole* **298** as a cloudy white oil (3.0 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, s, NC*H*), 7.43-7.40 (1H, m, Ar-*H*), 7.22 (1H, d, *J* 8.0, Ar-*H*), 7.20-7.16 (2H, m, Ar-*H*), 2.42 (3H, s, SCH_3), 2.16 (1H, app ddd, *J* 14.5, 9.0, 6.0, CH_aH$_b$(CH$_2$)$_4$CH$_3$), 2.07-1.97 (1H, m, CH$_a$$H_b$(CH$_2$)$_4CH_3$), 1.48-1.44 (2H, m, C$H_2$(CH$_2$)$_3CH_3$), 1.46 (9H, s, NC(C$H_3$)$_3$), 1.27-1.19 (6H, m, (C$H_2$)$_3CH_3$), 0.85 (3H, t, *J* 7.0, (CH$_2$)$_5$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 137.1, 136.4, 131.7, 129.2, 123.73, 123.71, 122.2, 119.1, 61.0, 31.6, 30.5, 30.1, 29.1, 23.6, 22.6, 14.8, 14.1; IR: ν_{max} (neat)/cm^{-1} 2957, 2925, 2854, 1433, 1365, 1262, 1080; LRMS (ESI$^+$): *m/z* 331 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 331.22014 [M+H]$^+$, $C_{20}H_{31}N_2S^+$ requires 331.22025.

Regioselectivity of the pyrazole displayed above was confirmed by NOE experiments, which displayed in-space interactions of the *tert*-butyl group with both the SMe protons and an aromatic proton shown below.



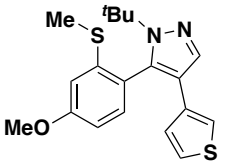
4-Methoxy-2-(methylthio)benzaldehyde, 299



Prepared according to general procedure **A** using methanethiol sodium salt solution (5.60 mL, 3.0 M in water, 16.9 mmol, 1.3 equiv.) and 2-fluoro-4-methoxybenzaldehyde (2.0 g, 13 mmol, 1.0 equiv.) in DMF (18 mL). The crude was purified by flash column chromatography (5-10% EtOAc in petrol) to obtain title *aldehyde* as an off-white solid (2.03 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.11 (1H, s, C*H*O), 7.78 (1H, d, *J* 8.5, Ar-*H*), 6.82-6.78 (2H, m, Ar-*H*), 3.92 (3H, s, OCH_3), 2.49 (3H, s, SCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.7, 164.0, 145.7, 136.2, 126.5, 111.0, 109.1, 55.6, 15.1; IR: ν_{max} (neat)/cm^{-1} 2839, 1671, 1589, 1551, 1278, 1234, 1064, 1035, 891; LRMS (ESI$^+$): *m/z* 205 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 205.02926 [M+Na]$^+$, $C_9H_{10}O_2SNa^+$ requires 205.02937; mp: 84-85 °C (EtOAc/petrol).

1-(*tert*-Butyl)-5-[4-methoxy-2-(methylthio)phenyl]-4-(thiophen-3-yl)-1*H*-pyrazole, 300

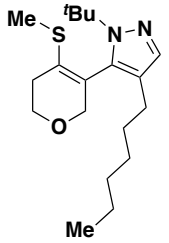


Prepared according to general procedure **Qb** using 4-methoxy-2-(methylthio)benzaldehyde **299** (27.0 mg, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-phenyl-*N*-(thiophen-3-ylethynyl)benzenesulfonamide **284**) (69.0 mg, 0.195 mmol, 1.3 equiv.), [Rh(nbd$_2$)]BF_4 (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL, 1.0 M). After stirring for 16 hrs at 55 °C, EtOH (0.25 mL) and *tert*-butylhydrazine hydrochloride (28.0 mg, 0.225 mmol, 1.5 equiv.) were added and stirred at 78 °C for a further 16 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford *pyrazole* **300** as pale yellow oil (18.3 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (1H, s, NC*H*), 7.19-7.16 (2H, m, Ar-*H*), 6.95 (1H, dd, *J* 5.0, 1.5, Ar-*H*), 6.82 (1H, d, *J* 2.5, Ar-*H*), 6.77 (1H, d, *J* 8.5, Ar-*H*), 6.64 (1H, dd, *J* 3.0, 1.5, Ar-*H*), 3.92 (3H, s, OCH_3), 2.36 (3H, s, SCH_3), 1.52 (9H, s, NC(CH_3)$_3$); ^{13}C NMR

(101 MHz, $CDCl_3$): δ 160.7, 142.7, 136.0, 135.7, 133.5, 132.6, 126.4, 124.7, 123.8, 118.4, 118.2, 111.0, 109.1, 61.7, 55.4, 30.5, 15.0; IR: ν_{max} (neat)/cm^{-1} 2997, 2922, 1599, 1513, 1453, 1397, 1289, 1264, 1146, 1088; LRMS (ESI^+): *m/z* 381 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 359.12468 $[M+H]^+$, $C_{19}H_{23}N_2OS_2^+$ requires 359.12463.

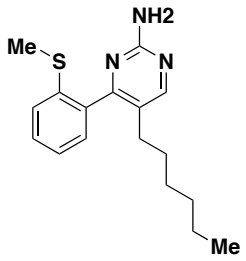
1-(*tert*-Butyl)-4-hexyl-5-[4-(methylthio)-5,6-dihydro-2*H*-pyran-3-yl]-1*H*-pyrazole, 302



Prepared according to general procedure **Qb** using 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde **301** (24.0 mg, 0.15 mmol, 1.0 equiv.), ynamide (4-methyl-*N*-(oct-1-yn-1-yl)-*N*-phenylbenzenesulfonamide **277**) (69.0 mg, 0.195 mmol, 1.3 equiv.), $[Rh(nbd_2)]BF_4$ (2.8 mg, 5 mol%) and DPEPhos (4.0 mg, 5 mol%) in acetone (150 μL , 1.0 M). After stirring for 16 hrs at 55 °C, EtOH (0.25 mL) and *tert*-butylhydrazine hydrochloride (28.0 mg, 0.225 mmol, 1.5 equiv.) were added and stirred at 78 °C for a further 16 hrs. The crude product was purified by flash column chromatography (5-10% EtOAc in petrol) to afford *pyrazole* **302** as pale yellow oil (14.7 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, s, NC*H*), 4.25 (1H, dt, *J* 16.0, 2.0, -C*H*$_a$H$_b$OCH$_c$H$_d$-), 4.08 (1H, app t, *J* 2.5, -CH$_a$*H*$_b$OCH$_c$H$_d$-), 4.06-4.03 (1H, m, -CH$_a$H$_b$OC*H*$_c$H$_d$-), 3.91 (1H, ddd, *J* 11.5, 6.5, 5.0, –CH$_a$H$_b$OCH$_c$*H*$_d$-), 2.49 (2H, dd, *J* 5.0, 2.5, SCC*H*$_2$), 2.29-2.23 (2H, m, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.20 (3H, s, SC*H*$_3$), 1.64 (9H, s, NC(C*H*$_3$)$_3$), 1.59-1.53 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.36-1.29 (6H, m, (C*H*$_2$)$_3$CH$_3$), 0.90 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.9, 134.7, 133.0, 125.5, 121.0, 70.0, 64.8, 60.8, 31.7, 30.4, 30.3, 29.4, 28.2, 23.7, 22.6, 14.1, 12.9; IR: ν_{max} (neat)/cm^{-1} 2957, 2926, 2853, 1465, 1365, 1263, 1145, 1106; LRMS (ESI^+): *m/z* 337 ($[M+H]^+$, 100%); HRMS (ESI^+) found 337.23048 $[M+H]^+$, $C_{19}H_{33}N_2OS_2^+$ requires 337.23081.

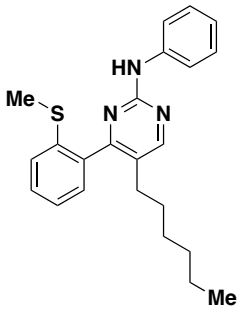
5-Hexyl-4-[2-(methylthio)phenyl]pyrimidin-2-amine, 303



Prepared according to an adapted literature procedure by Peel *et. al.*.[283] Guanidine hydrochloride (9.6 mg, 0.10 mmol, 2.0 equiv.) and potassium carbonate (13.8 mg, 0.10 mmol, 2.0 equiv.) were added to a solution of *β*-amino enone ((*E*)-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}-*N*-phenylbenzenesulfonamide **290a**) (26.0 mg, 0.05 mmol, 1.0 equiv.) in DMF (0.1 mL) and the reaction mixture was heated to 100 °C for 24 hrs. After which, the flask was cooled to room temperature and the reaction was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (20-50% EtOAc in CH_2Cl_2) to give title *pyrimidine* **303** as a colourless oil (8.2 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, s, NC*H*), 7.41-7.38 (1H, m, Ar-*H*), 7.34-7.32 (1H, m, Ar-*H*), 7.26-7.22 (1H, m, Ar-*H*), 7.18-7.16 (1H, m, Ar-*H*), 5.01 (2H, br s, N*H*$_2$), 2.42 (3H, s, SC*H*$_3$), 2.32 (2H, t, *J* 7.5, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.42-1.34 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.23-1.12 (6H, m, (C*H*$_2$)$_3$CH$_3$), 0.83 (3H, t, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 161.2, 159.2, 137.4, 136.6, 129.1, 128.4, 125.9, 124.9, 123.8, 31.4, 30.3, 28.8, 28.7, 22.4, 16.0, 14.0; IR: ν_{max} (neat)/cm^{-1} 2923, 1624, 1542, 1469, 1277, 1260; LRMS (ESI$^+$): *m/z* 302 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 302.16872 [M+H]$^+$, $C_{17}H_{24}N_3S^+$ requires 302.16855.

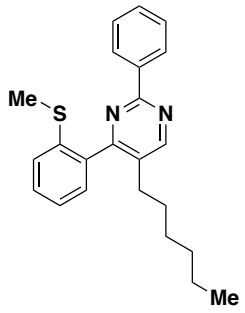
5-Hexyl-4-[2-(methylthio)phenyl]-*N*-phenylpyrimidin-2-amine, 304



Prepared according to an adapted literature procedure by Peel *et. al.*.[283] Phenylguanidine carbonate salt (8.5 mg, 0.063 mmol, 1.5 equiv.) and potassium carbonate (18.0 mg, 0.13 mmol, 3.0 equiv.) were added to a solution of *β*-amino enone ((*E*)-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}-*N*-phenylbenzenesulfonamide **290a**) (21.5 mg, 0.042 mmol, 1.0 equiv.) in DMF (0.38 mL) and the reaction mixture was heated to 120 °C for 24 hrs. After which, the flask was cooled to room temperature and the reaction was diluted with EtOAc (5 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (5 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (20-40% Et_2O in petrol) to give title *pyrimidine* **304** as a colourless oil (7.1 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (1H, s, NC*H*), 7.66 (2H, dd, *J* 8.5, 1.0, Ar-*H*), 7.44 (1H, ddd, *J* 8.0, 7.5, 1.5, Ar-*H*), 7.38-7.33 (3H, m, Ar-*H*), 7.26 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.22-7.20 (1H, m, Ar-*H*), 7.16 (1H, br s, N*H*), 7.04-7.00 (1H, m, Ar-*H*), 2.44 (3H, s, SC*H*$_3$), 2.39 (2H, t, *J* 7.5, C*H*$_2$(CH$_2$)$_4$CH$_3$), 1.43-1.37 (2H, m, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.21-1.17 (6H, m, (C*H*$_2$)$_3$CH$_3$), 0.83 (3H, d, *J* 7.0, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 158.7, 158.2, 139.9, 137.4, 136.8, 129.1, 128.9, 128.5, 126.1, 124.9, 124.8, 122.0, 118.7, 31.4, 30.2, 29.7, 28.9, 28.7, 22.4, 16.1; IR: ν_{max} (neat)/cm^{-1} 3772, 2959, 2919, 2852, 1581, 1553, 1516, 1497, 1444, 1265; LRMS (ESI$^+$): *m/z* 378 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 378.20135 [M+H]$^+$, $C_{23}H_{28}N_3S^+$ requires 378.19985.

5-Hexyl-4-[2-(methylthio)phenyl]-2-phenylpyrimidine, 305



Prepared according to an adapted literature procedure by Caravatti *et. al.*.[284] Benzamidine hydrochloride (7.2 mg, 0.046 mmol, 1.1 equiv.) and sodium hydroxide (2.0 mg, 0.05 mmol, 1.2 equiv.) were added to a solution of *β*-amino enone ((*E*)-4-methyl-*N*-{2-[2-(methylthio)benzoyl]oct-1-en-1-yl}-*N*-phenylbenzenesulfonamide **290a**) (21.5 mg, 0.042 mmol, 1.0 equiv.) in MeOH (0.16 mL) and the reaction mixture was heated to 55 °C for 16 hrs. After which, the flask was cooled to room temperature and the reaction was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (20-40% Et_2O in petrol) to give title *pyrimidine* **305** as a colourless oil (5.9 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (1H, s, NC*H*), 8.48-8.46 (2H, m, Ar-*H*), 7.49-7.46 (3H, m, Ar-*H*), 7.45-7.41 (2H, m, Ar-*H*), 7.31 (1H, dd, *J* 7.5, 1.5, Ar-*H*), 7.28-7.26 (1H, m, Ar-*H*), 2.56-2.52 (2H, m, C*H*$_2$(CH$_2$)$_4$CH$_3$), 2.42 (3H, s, SC*H*$_3$), 1.25-1.19 (8H, m, (C*H*$_2$)$_4$CH$_3$), 0.84 (3H, t, *J* 6.5, (CH$_2$)$_5$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 162.2, 158.1, 137.8, 137.1, 131.5, 130.2, 129.2, 128.9, 128.5, 128.1, 126.7, 125.1, 123.7, 31.4, 30.5, 29.7, 29.5, 28.8, 22.4, 16.5; IR: ν_{max} (neat)/cm^{-1} 2960, 2920, 2850, 2359, 1677, 1648, 1588, 1423, 1292, 1159; LRMS (ESI$^+$): *m/z* 363 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 363.18902 [M+H]$^+$, $C_{23}H_{27}N_2S^+$ requires 363.18895.

References

[1] Dimroth, O. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1029.
[2] Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403.
[3] Chatt, J.; Davidson, J. M. *J. Chem. Soc*. **1965**, 843.
[4] Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.
[5] Lambinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
[6] Bergman, R. G. *Nature* **2007**, *446*, 391.
[7] Brookhart, M.; Green, L. H.; Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.
[8] Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.
[9] Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
[10] Wencel-Delor, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.
[11] Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.
[12] Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.
[13] Colby, D. A.; Tsai, A. S.; Bergman, R. H.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814.
[14] Engle, M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927.
[15] Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wong, J. *Chem. Commun.* **2015**, *51*, 7986.
[16] Motevalli, S.; Sokeirick, Y.; Ghanem, A. *J. Org. Chem.* **2016**, *8*, 1459.
[17] Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wenchel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900.
[18] Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869.
[19] Willis, M. C. *Chem. Rev.* **2010**, *110*, 715.
[20] Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202.
[21] Murphy, S. K.; Dong, V. M. *Chem. Commun.* **2014**, *50*, 13645.
[22] Ghosh, A.; Johnson, K. F.; Vickerman, K. L.; Walker, J. A.; Stanley, L. M. *Org. Chem. Front.* **2016**, *3*, 639.
[23] Trost, B. M. *Science* **1991**, *254*, 1471.
[24] www.sigma-aldrich.com
[25] Seki, T.; Nakajo, T.; Onaka, M. *Chem. Lett.* **2006**, *35*, 824.
[26] Tejel, C.; Ciriano, M. A.; Passarelli, V. *Chem. Eur. J.* **2011**, *17*, 91.
[27] Reynolds, N. T.; Read de Alaniz, J.; Rovis. T. *J. Am. Chem. Soc.* **2004**, *126*, 9518.
[28] Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190.
[29] DiRocco, D. A.; Rovis. T. *Angew. Chem. Int. Ed.* **2011**, *50*, 7982.
[30] Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182.
[31] Janssen-Müller, D.; Schedler, M.; Fleige, M.; Danilius, C. G.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 12492.
[32] Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592.
[33] Esposti, S.; Dondi, D.; Fagnani, M.; Albini, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2531.
[34] Chudasama, V. *RSC Adv.* **2015**, *15*, 44423.
[35] Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120.
[36] Zbieg, J. R.; Yamaguchi, E.; McInturft, E. L.; Krische, M. J. *Science* **2012**, *336*, 324.
[37] Miura, H.; Wada, K.; Hosokawa, S.; Inuoe, M. *Chem. Eur. J.* **2013**, *19*, 861.
[38] Chen, Q.-A.; Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 3157.
[39] Kim, J.; Yi, C. S. *ACS Catal.* **2016**, *6*, 3336.
[40] Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165.
[41] Chen, Q.-A.; Kim, D. K.; Dong, V. M. *J. Am. Chem. Soc.* **2014**, *136*, 3772.

[42] Yang, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 16748.
[43] Yang, J.; Seto, Y. W.; Yoshikai, N. *J. Am. Chem. Soc.* **2015**, *5*, 3054.
[44] Taniguchi, H.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 11298.
[45] Hoshimoto, Y.; Hayashi, Y.; Suzuki, M.; Ohashi, M.; Ogoshi, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 10812.
[46] Ghosh, A.; Walker, J. A.; Ellern, A.; Stanley, L. M. *ACS Catal.* **2016**, *6*, 2673.
[47] Xiao, L.-J.; Fu, X.-N.; Zhou, M.-J.; Xie, J.-H.; Wang, L.-X.; Xu, X.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2957.
[48] Hatanaka, S.; Obora, Y.; Ishii, Y. *Chem. Eur. J.* **2010**, *56*, 1883.
[49] Nagamoto, M.; Nishimura, T. *Chem. Commun,* **2015**, *51*, 1379.
[50] Shi, S.; Wang, T.; Weingand, V.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 1148.
[51] Luchow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281.
[52] Campbell, R. E., Jr.; Luchow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824.
[53] Fairlie, D. P.; Bosnich, B. *Organometallics*, **1988**, *7*, 936.
[54] Hyatt, I. F. D.; Anderson, H. K.; Morehead, A. T.; Sargent, A. L. *Organometallics* **2008**, 135.
[55] Chung, L. W.; Wu, Y. D. *J. Theor. Comput. Chem.* **2005**, *4*, 737.
[56] Gao, J.; Wang, F.; Meng, Q.; Li, M. *Theor. Comput. Chem.* **2008**, *7*, 1041.
[57] Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082.
[58] Moxham, G. L.; Randel-Sly, H.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7618.
[59] Moxham, G. L.; Randel-Sly, H.; Brayshaw, S. K.; Weller, A. S.; Willis, M. C. *Chem. Eur. J.* **2008**, *14*, 8383.
[60] Pawley, R. J.; Huertos, M. A.; Lloyd-Jones, G. C.; Weller, A. S.; Willis, M. C. *Organometallics* **2012**, *131*, 5650.
[61] Chaplin, A. B.; Hooper, J. F.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 4885.
[62] von Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, *134*, 15022.
[63] Osborne, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.
[64] Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, *13*, 1287.
[65] Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H.; Laible-Sands, L. M.; Rheingold, A. L. *Organometallics* **1999**, *18,* 5311.
[66] Kries, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Advan. Synth. Catal.* **2006**, *348*, 2148.
[67] Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206.
[68] Campbell, R. E., Jr.; Miller, R. G. *J. Organomet. Chem.* **1980**, *186*, C27.
[69] Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190.
[70] Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 111492.
[71] Tanaka, K.; Fu, G. C. *Chem. Commun.* **2002**, 684.
[72] Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610.
[73] Crépin, D.; Dawick, J.; Aïssa, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 620.
[74] Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031.
[75] Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932.
[76] Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 3688.
[77] Suggs, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 640.
[78] Suggs, J. W.; Wovkulich, M. J.; Cox, S. D. *Organometallics* **1985**, *4*, 1101.
[79] Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489.

[80] Jun, C.-H.; Lee, P.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem. Int. Ed.* **2000**, *39*, 3070.
[81] Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org Chem.* **1997**, *62*, 1200.
[82] Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Tertahedron Lett.* **1997**, *38*, 6673.
[83] Lee, D.-Y.; Moon, C.-W.; Jun, C.-H. *J. Org. Chem.* **2002**, *67*, 3945.
[84] Jo, E.-A.; Jun, C.-H. *Eur. J. Org. Chem.* **2006**, 2504.
[85] Jo, E.-A.; Jun, C.-H. *Tetrahedron Lett.* **2009**, *50*, 3338.
[86] Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. *Angew. Chem. Int. Ed.* **2002**, *41*, 2146.
[87] Rueda, X. Y.; Castillón, S. *J. Organomet. Chem.* **2007**, *692*, 1628.
[88] Marcé, P.; Godard, C.; Feliz, M.; Yáñez, X.; Bo, C.; Castillón, S. *Organometallics* **2009**, *28*, 2976.
[89] Stemmer, R. T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 1185.
[90] Castaing, M.; Wason, S. L.; Estepa, B.; Hooper, J. F.; Willis, M. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 13280.
[91] Lee, H.; Jun, C.-H. *Bull. Korean Chem. Soc.* **1995**, *16*, 66.
[92] Kuckubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303.
[93] Kuckubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4564.
[94] Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, 1365.
[95] Imai, M.; Tanaka, M.; Tananka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144.
[96] Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330.
[97] Murphey, S. K.; Petrone, D. A.; Coulter, M. M.; Dong, V. M. *Org. Lett.* **2012**, *13*, 6216.
[98] Willis, M. C.; McNally, S. J.; Beswick, P. J, *Angew. Chem. Int. Ed.* **2004**, *43*, 340.
[99] Willis, M. C.; Randell-Sly, H.; Woodward, R. L.; Currie, G. S. *Org. Lett.* **2005**, *7*, 2249.
[100] Willis, M. C.; Randell-Sly, H.; Woodward, R. L; McNally, S. J. Currie, G. S. *J. Org. Chem.* **2006**, *71*, 5291.
[101] Parsons, S. R.; Hooper, J. F.; Willis, M. C. *Org. Lett.* **2011**, *13*, 998.
[102] González-Rodríguez, C.; Parsons, S. R.; Thompson, A. L.; Willis, M. C. *Chem. Eur. J.* **2010**, *16*, 10950.
[103] González-Rodríguez, C.; Willis, M. C. *Pure and Applied Chemistry* **2011**, *83*, 577.
[104] Pawley, R. J.; Moxham, J. L.; Dallanegra, R.; Chaplin, A. B.; Brayshaw, S. K.; Weller, A. S.; Willis, M. C. *Organometallics* **2010**, *29*, 1717.
[105] González-Rodríguez, C.; Pawley, R. J.; Chaplin, A. B.; Thompson, A. L.; Weller, A. S.; Willis, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 5134.
[106] Hofmann, P.; Meier, C.; Hiller, W.; Heckel, M.; Riede, J.; Schmidt, M. U. *J. Organomet. Chem.* **1995**, *490*, 51.
[107] DuBois, D. L.; Blake, D. M.; Miedaner, A.; Curtis, C. J.; DuBois, M. R.; Franz, J. A.; Linehan, J. C. *Organometallics* **2006**, *25*, 4414.
[108] Wilson, A. D.; Miller, A. J. M.; DuBois, D. L.; Labinger, J. A.; Bercaw, J. E. *Inorg. Chem.* **2010**, *49*, 3918.
[109] Manger, M.; Wolf, J.; Teichert, M.; Stalke, D.; Werner, H. *Organometallics* **1998**, *17*, 3210.
[110] Pernik, I.; Hooper, J. F.; Chaplin, A. B.; Weller, A. S.; Willis, M. C. *ACS Catalysis*, **2012**, *2*, 2779.
[111] Hooper, J. F.; Seo, S.; Truscott, F. R.; Neuhaus, J. D.; Willis, M. C. *J. Am. Chem. Soc*. **2016**, *138*, 1630.

[112] Prades, A.; Fernández, M.; Pike, S. D.; Willis, M. C.; Weller. A. S. *Angew. Chem. Int. Ed.* **2015**, *54*, 8520.
[113] Tanaka, K.; Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 1215.
[114] Shibata, Y.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2829.
[115] Murphey, S. K.; Bruch, A.; Dong, V. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 2455.
[116] Murphey, S. K.; Bruch, A.; Dong, V. M. *Chem. Sci.* **2015**, *6*, 174.
[117] Gunatilaka, A. A. L. *J. Nat. Prod.* **2006**, *69*, 509.
[118] Zhan, Y.; Du, X.; Chen, H.; Liu, J.; Zhao, B.; Huang, D.; Li, G.; Xu, Q.; Zhang, M.; Weimer, B. C.; Chen, D.; Cheng, Z.; Zhang, L.; Li, Q.; Li, S.; Zheng, Z.; Song, S.; Huang, Y.; Ye, Z.; Su, W.; Lin, S.-C.; Shen, Y.; Wu, Q. *Nat. Chem. Biol.* **2008**, *4*, 548.
[119] Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*, Wiley, Chichester, **1997**.
[120] Du, X. W.; Stanley, L. M. *Org. Lett.* **2015**, *17*, 3276.
[121] Lenden, P.; Entwistle, D. A.; Willis, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10657.
[122] Fan, H. N.; Peng, J.; Hanmann, M. T.; Hu, J. F. *Chem. Rev.* **2008**, *108*, 264.
[123] Battersby, A. R. *Nat. Prod. Rep.* **2000**, *17*, 507.
[124] Avendaño, C.; Menéndez, J. C.; *Medicinal Chemistry of Anticancer Drugs* Elsevier, Oxford, **2008**.
[125] Raub, T. J. *Mol. Pharmaceutics* **2006**, *3*, 3.
[126] Lazerges, M.; Chane-Ching, K. I.; Aeiyach, S.; Chelli, S.; Peppin-Donnat, B.; Billon, M.; Lombard, L.; Maurel, F.; Jouini, M. *J. Solid State Electrochem.* **2009**, *13*, 231.
[127] Paal. C. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756.
[128] Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863.
[129] Aydogan, F.; Demir, A. S. *Tetrahedron* **2005**, *61*, 3019.
[130] Nair, V.; Vinod, U.; Rajeshi, C. *J. Org. Chem.* **2001**, *66*, 4427.
[131] Rueping, M.; Para, A. *Org. Lett.* **2012**, *12*, 5281.
[132] Imbri, D.; Netz, N.; Kucukdisli, M.; Kammer, L. M.; Jung, P.; Kretzschmann, A.; Optaz, T.; *J. Org. Chem.* **2014**, *79*, 11750.
[133] Khaghninejad, S.; Heravi, M. M. *Advances in Heterocyclic Chemistry* Elsevier, Oxford, **2014**.
[134] Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
[135] Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.
[136] Trost, B. M.; Lumb, J.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740.
[137] Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem, Soc.* **2010**, *132*, 9585.
[138] Michlik, S.; Kempe, R. *Nat. Chem*. **2013**, *5***,** 140.
[139] Wang, L.; Ackermann, L. *Org. Lett.* **2013**, *15*, 176.
[140] Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30.
[141] Ferreira, V. F.; de Souza, M.-C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proc. Int.* **2001**, *33*, 411.
[142] Paulus, O.; Alcaraz, G.; Vaultier, M. *Eur. J. Org. Chem.* **2002**, 2565.
[143] Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *15*, 2283.
[144] Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *18*, 4094.
[145] Ylioja, P. M. Rhodium-Catalysed Hydroacylation Reactions in the Synthesis of Heterocycles, DPhil Thesis, University of Oxford, 2011.
[146] van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.
[147] Saito, A.; Oda, S.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 1517.
[148] Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319.
[149] Shendage, D. M.; Froelich, R.; Haufe, G. *Org. Lett.* **2004**, *6*, 3675.
[150] Wasserman, H. H.; Berger, G. D. *Tetrahedron*, **1983**, *39*, 4969.

[151] Rawal, V. H.; Cava, M. P.; *Tetrahedron Lett.* **1985**, *26*, 6141.
[152] Estevévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Revs.* **2010**, *39*, 4402.
[153] Zhao, W.; Chen, F.-E. *Curr. Org. Synth.* **2012**, *9*, 873.
[154] Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866.
[155] Robinson, R. *J. Chem. Soc., Trans.* **1917**, 762.
[156] O' Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637.
[157] O' Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
[158] Bird, C. W. *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford, **1996**.
[159] Fleurant, A.; Grandjean, C.; Provot, O.; Rosset, S.; Celerier, J. P.; Lhommet, G. *Heterocycles* **1993**, *36*, 929.
[160] Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242.
[161] Race, N. J.; Bower, J. F. *Org. Lett.* **2013**, *15*, 4616.
[162] Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994***, 116*, 8952.
[163] Tang, W.-J.; Zhang, X.-M. *Chem. Rev.* **2003**, *103*, 3029.
[164] Hou, G.-H.; Xie, J.-H.; Yan, P.-C; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366.
[165] Chen, C.; Hou, L.; Cheng, M.; Su, J.; Tong, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 3092.
[166] Chao, D.; Liu, T.-X.; Ma, N.; Zhang, P.; Fu, Z.; Ma, J.; Liu, Q.; Zhange, F.; Zhang, Z.; Zhang, G. *Chem. Commun.* **2016**, *52*, 982.
[167] Zhu, X.; Chiba, S. *Chem. Comuun.* **2016**, *52*, 2473.
[168] Mecozzi, T.; Petrini, M. *J. Org. Chem.***1999**, *64*, 8970.
[169] Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin. S. *Eur. J. Org. Chem.* **2007**, 3503.
[170] Gonzalez, A. Z.; Canales, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 3331.
[171] Kano, T.; Kobayashi, R.; Meruoka, K. *Org. Lett.* **2016**, *18*, 276.
[172] Smith, C. D.; Tchabanenko, K.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron Lett.* **2006**, *47*, 3209.
[173] Huang, X.; Wang, Y.-G. *J. Comb. Chem.* **2007**, *9*, 121.
[174] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
[175] Scaracoglu, N. *Top. Heterocycl. Chem.* **2007**, *11*, 1.
[176] Beck, E. M.; Gaunt, M. J. *Top. Curr. Chem.* **2010**, *292*, 85.
[177] Lopchuck, J. M. *Prog. Heterocycl. Chem.* **2013**, *25*, 137.
[178] Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.
[179] Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2012**, *2*, 20.
[180] Chauhan, K. K.; Frost, C. G. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3015.
[181] Yadav, J.; Reddy, B. S.; Aravind, S.; Kumar, G. N.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 6117.
[182] Chapman, C.; Frost, C. G.; Harley, J.; Whittle, A. *Tetrahedron Lett.* **2001**, *42*, 773.
[183] Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11088.
[184] Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.
[185] Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.
[186] Yu, J.-Q.; Shi, Z. *Top. Curr. Chem.* **2010**, 292.
[187] Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269.
[188] Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2582.
[189] Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *130*, 8172.
[190] Seo, S.; Taylor, J. B.; Greaney, M. F. *Chem. Commun.* **2013**, *49*, 6385.
[191] Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529.
[192] Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
[193] Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506.

[194] Hooper, J. F.; Young, R. D.; Weller, A. S.; Willis, M. C. *Chem. Eur. J.* **2013**, *19,* 3125.
[195] Hooper, J. F.; Young, R. D.; Pernik, I.; Weller, A. S.; Willis, M. C. *Chem. Sci.* **2013**, *4*, 1568.
[196] Niu, J.; Willis, M. C. *Org. Chem. Front.* **2016**, *3*, 625.
[197] Barbero, N.; Martin, R. *Org. Lett.* **2012**, *14*, 796.
[198] Arambasic, M. Carbon-carbon bond formation via rhodium-catalysed C-S activation processes, DPhil Thesis, University of Oxford, 2015.
[199] Sasaki, M.; Andei, K. Y.; *J. Am. Chem. Soc.* **2003**, *125*, 14242.
[200] Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron* **1999**, *55*, 8915.
[201] Milstein, D. *Organometallics* **1982**, *1*, 1549.
[202] Milstein, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1357.
[203] Goikhman, R.; Milstein, D. *Angew. Chem. Int. Ed.* **2001**, *40*, 1119.
[204] Majhail, M. K.; Ylioja, P. Y.; Willis, M. C. *Chem. Eur. J.* **2016**, *22*, 7879.
[205] Neuhaus, J. D.; Morrow, S. M; Brunavs, M.; Willis, M. C. *Org. Lett*. **2016**,*18*,1562.
[206] Quin, L. D.; Tyrell, J. A. *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals.* Wiley, Hoboken, **2010**.
[207] Elasser, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.
[208] Negri, G.; Kascheres, C.; Kascheres, A. J. *J. Heterocyclic Chem.* **2004**, *41*, 461.
[209] Miura, T.; Funakoshi, Y.; Tanaka, T.; Murakami, M. *Org. Lett.* **2014**, *16*, 2760.
[210] Abu-Shanab, F. A.; Sherif, S. M.; Mousa, S. A. S. *J. Heterocyclic Chem.* **2009**, *46*, 801.
[211] Sridharan, V.; Avendaño, C.; Menédez, J. C. *Synlett* **2007**, 2133.
[212] Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815.
[213] Abdulla, R. F.; Brinkmeyer, R. S.; *Tetrahedron* **1979**, *35*, 1675.
[214] Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.
[215] El-Taweel, F. M. A. A.; Elnagdi, M. H. *J. Heterocyclic Chem.* **2001**, *38*, 981.
[216] Lin, Y.-I.; Lang, S. S. *Org. Chem.* **1980**, *45*, 4857.
[217] Kepe, V.; Kocevar, M.; Polanc, S. *J. Heterocyclic Chem.* **1996**, *33*, 1707.
[218] Liu, Y. F.; Wang, C. L.; Bai, Y. J.; Han, N.; Jiag, J. P.; Qi, X. L. *Org. Process Res. Dev.* **2008**, *12*, 490.
[219] Casar, Z.; Bevk, D.; Svete, J.; Stanovinik, B. *Tetrahedron* **2005**, *8*, 541.
[220] Omran, F. A.; Elassar, A. Z. A.; El-Khair, A. A. *Tetrahedron* **2001**, *57*, 10163.
[221] Wagger, J.; Bevk, D.; Meden, A.; Svete, J.; Stanvnik, B. *Helv. Chim. Acta,* **2006**, *89.* 240.
[222] Govindh, B.; Diwakar, B. S.; Murthy, Y. L. N. *Org. Commun,* **2012**, 105.
[223] Kim, S. M.; Lee, D.; Hyeok-Hong, S. *Org. Lett.* **2014**, *16*, 6168.
[224] Yu, X.; Wang, L.; Feng, X.; Bao, M.; Yamamoto, Y. *Chem. Commun.* **2013**, *49*, 2885.
[225] Evano, G.; Coste, A.; Jovin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.
[226] DeKorver, K. A.; Li, H.; Lonse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.
[227] Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560.
[228] Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540.
[229] Chen. Q.-A.; Cruz, F. A.; Dong, V. M.; *J. Am. Chem. Soc.* **2015**, *137*, 3157.
[230] Mansfield, S. J.; Campbell, C. D.; Jones, M. W.; Anderson, E. A. *Chem. Commun.* **2015**, *15*, 3316.
[231] Jouvin, K.; Couly, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272.
[232] Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381.
[233] Jouvin, K.; Heimburger, J.; Evano, G. *Chem. Sci.* **2012**, *3*, 756.

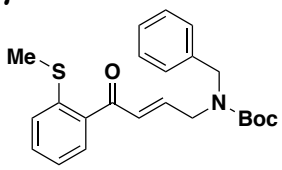
[234] Laroche, C.; Li, J.; Freyer, M. W.; Kerwin, S. M. *J. Org. Chem.* **2008**, *73,* 6462.
[235] Zhang, Y. Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.
[236] Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.
[237] Lin, Y.-I.; Lang, S. A. *J. Org. Chem.* **1980***, 45*, 4857.
[238] Janaki Rama Rao, R.; Bhujanga, Rao, A. K. S.; Sreenivas, N.; Suneel Kumar, R.; Muthy, Y. L. N. *J. Korean Chem. Soc.* **2011**, *53*, 243.
[239] Hamdi, N.; Saud, M.; Ramerosa, A.; Hassan, R. B. *J. Heterocyclic Chem.* **2008**, *45*, 1835.
[240] Mablehot, Y. N.; Al-Majid, A. M.; Barakat, M.; Alshahrani, S.; Siddiqui, Y. *Molecules* **2011**, *27*, 6108.
[241] Carroll, W. A.; Kalvin, D. M.; Medrano, A. P.; Florjanic, A. S.; Wang, Y.; Donelly-Roberts, D. L.; Namovic, M. T.; Grayson, G.; Honoré, P.; Jarvis, M. F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4044.
[242] Busch, M.; Cayir, M.; Niegar, M.; Thiel, W. R.; Bräse, S. *Eur. J. Org. Chem.* **2013**, *27*, 6108.
[243] Balbi, A.; Anzaldi, M.; Macció, C.; Aiello, C.; Mazzeli, M.; Gangemi, R.; Castagnola, P.; Miele, M.; Rosaro, C.; Viale, M. *Eur. J. Med. Chem.* **2011**, *46*, 5293.
[244] Lagoja, I. M. *Chem. Biodivers.* **2005**, *2*, 1.
[245] Rachakonda, V.; Alla, M.; Kotipallis, S. S.; Ummanni, R. *Eur. J. Med. Chem.* **2013**, *70*, 536.
[246] Kaur, N.; Tyagi, R.; Srivastava, M.; Kishore, J. *J. Heterocyclic Chem.* **2014**, *51*, E50.
[247] More, K. N.; Jang, H. W.; Hong, V. S.; Lee, J. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2424.
[248] Stahl, E. *Thin Layer Chromatography*, Springer-Vertag, Berlin, **1969**.
[249] Lee, C. H.; Lee, K.-J. *J. Heterocyclic Chem.* **2009**, *46*, 1023.
[250] Poingdestre, S.-J.; Goodacre, J. D.; Weller, A. S.; Willis, M. C. *Chem. Commun.* **2012**, *48*, 6354.
[251] Roberts, C. F.; Hartley, R. C. *J. Org. Chem.* **2004**, *69*, 6145.
[252] Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.
[253] Paul, A.; Einsiedel, J.; Waibel, R.; Heinemann, F. W.; Meyer, K.; Gmeiner, P. *Tetrahedron* **2009**, *65*, 6156.
[254] Xiong, Y.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 9168.
[255] Marten, S.; Fröhlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Catal.* **2005**, *347*, 754.
[256] Wachenfeidt, H. V.; Paulsen, F.; Sundin, A.; Strand, D. *Eur. J. Org. Chem.* **2013**, 4578.
[257] Teller, H.; Fürstner, A. *Chem. Eur. J.* **2011**, *17*, 7764.
[258] Tong, G.; Lawlor, J. M.; Tregear, G. W.; Haralambidis, J. *J. Org. Chem.* **1993**, *58*, 2223.
[259] Achard, T.; Lepronier, Y. G.; Clavier, H.; Giordano, L.; Tenaglia, A.; Buono, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 3552.
[260] Ye, L.; He, W.; Zhang, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 3236.
[261] Ruano, J. L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008,** *2*, 311.
[262] Arambasic, M.; Hooper, J. F.; Willis, M. C. *Org. Lett.* **2013**, *15*, 5162.
[263] Kost, T.; Sigalov, M.; Goldberg, I.; Ben-Asuly, A.; Lemcoff, N. G. *J. Organomet. Chem.* **2008**, *693*, 2200.
[264] Hernando, E.; Gomez Arryas, R.; Carretero, J. C. *Chem. Commun.* **2012**, *48*, 9622.
[265] Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett*. **2013**, *15*, 2446.
[266] Huang, L.; Wulff, W, D. *J. Am. Chem. Soc*. **2011**, *133*, 8892.

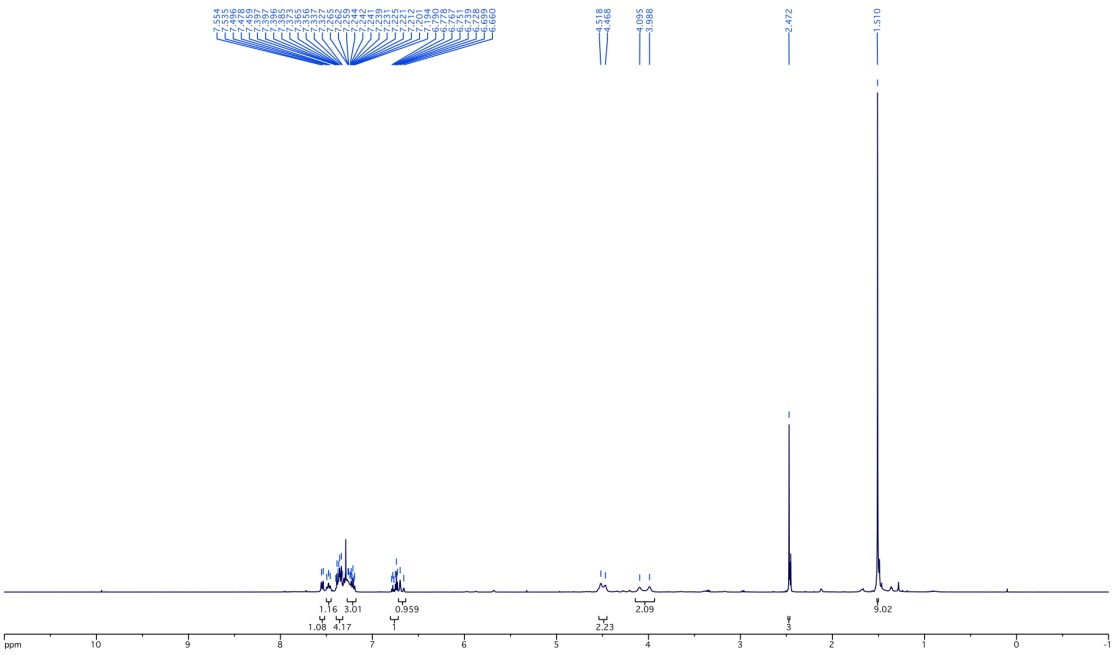
[267] Tsai, S. A.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248.
[268] Schmidt, N. G.; Simon, R. C.; Kroutil, W. *Adv. Synth. Catal.* **2015**, 357, 1815.
[269] Moriwake, T.; Hamano, S.; Saito, S.; Torii, S. *J. Org. Chem.* **1989**, *54*, 4114.
[270] Wiex, D. J.; Marković, D.; Ueda, M.; Hartwig, J. F. *Org. Lett*. **2009**, *11*, 2944.
[271] Hess, W.; Burton, J. W. *Adv. Synth. Catal.* **2011**, *353*, 2966.
[272] Fernandez-Lopez. R.; Kofoed, J.; Machuqueiro, M.; Darbre, T. *Eur. J. Org. Chem.* **2005**, *24*, 5268.
[273] Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852.
[274] Brückner, D, *Tetrahedron* **2006**, *16*, 3809.
[275] Hamura, S.; Oda, T.; Shimizu, Y.; Matsubara, K.; Nagashima, H. *J. Chem. Soc., Dalton Trans.* **2002**, *7*, 1521.
[276] Ruano, J. L. G.; Fernandez-Salas, J. A.; Maestro, M. C.; Parra, A. *Synth. Commun.* **2013**, *2*, 198.
[277] Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 5547.
[278] Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. *Chem. Commun.* **2007**, *10*, 1074.
[279] Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630.
[280] Pan, F.; Shu, C.; Ping, Y.-F.; Pan, Y.-F.; Ruan, P.-P.; Fei, Q.-R.; Ye, L.-W. *J. Org. Chem.* **2015**, *80*, 10009.
[281] Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C. *Tetrahedron* **2006**, *62*, 3843.
[282] Davies, P. W.; Cremonsi, A.; Dunitrescu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8931.
[283] Stevens, K. L.; Jung, D. K.; Alberti, M. J.; Badiang, J. G.; Peckham, G. E.; Veal, J. M.; Cheung, M.; Harris, P. A.; Chamberlain, S. D.; Peel, M. R. *Org. Lett.* **2005**, *7*, 4753.
[284] Furet, P.: Guagano, V.; Fairhurst, R. A.; Imbach-Weese, P.; Bruce, I.; Knapp, M.; Fritsch, C.; Blasco, F.; Blanz, J.; Aichholz, R.; Hamon, J.; Fabbro, D.; Caravatti, G. *Bioorg. Med. Chem. Lett.* **2013**, *23,* 3741.

Appendix: Spectra

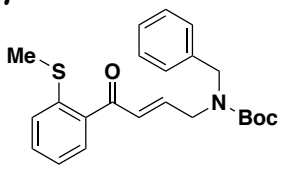
^{1}H and ^{13}C spectra of all novel compounds synthesised in chapters 2, 3 and 4.

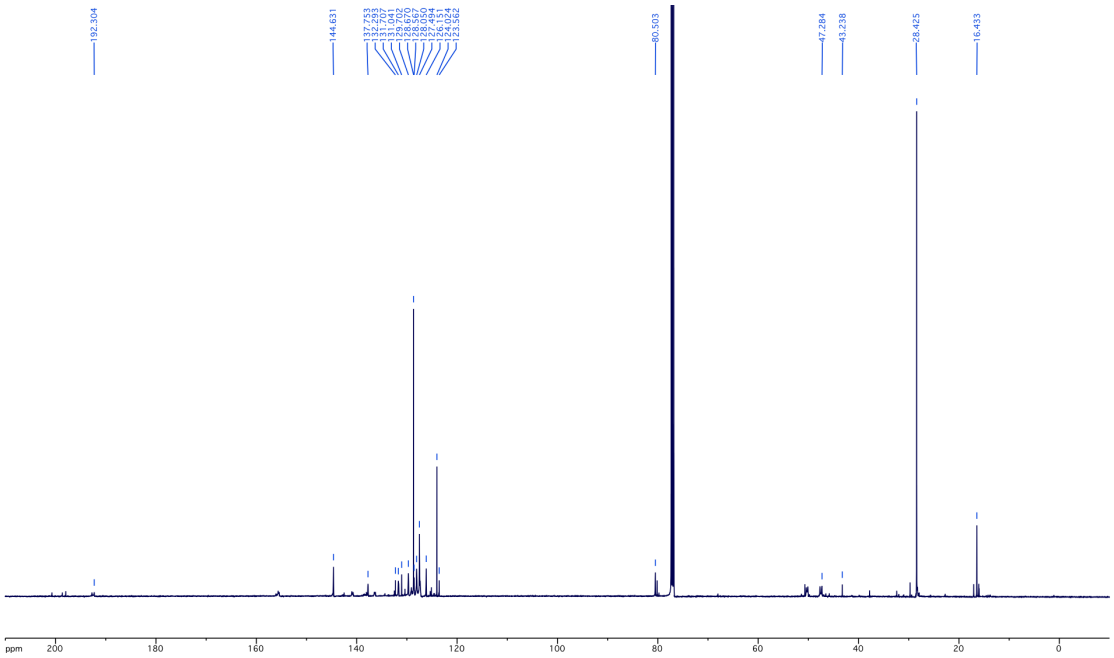
γ-Amino enone 55a: ^{1}H NMR (400 MHz, $CDCl_3$)



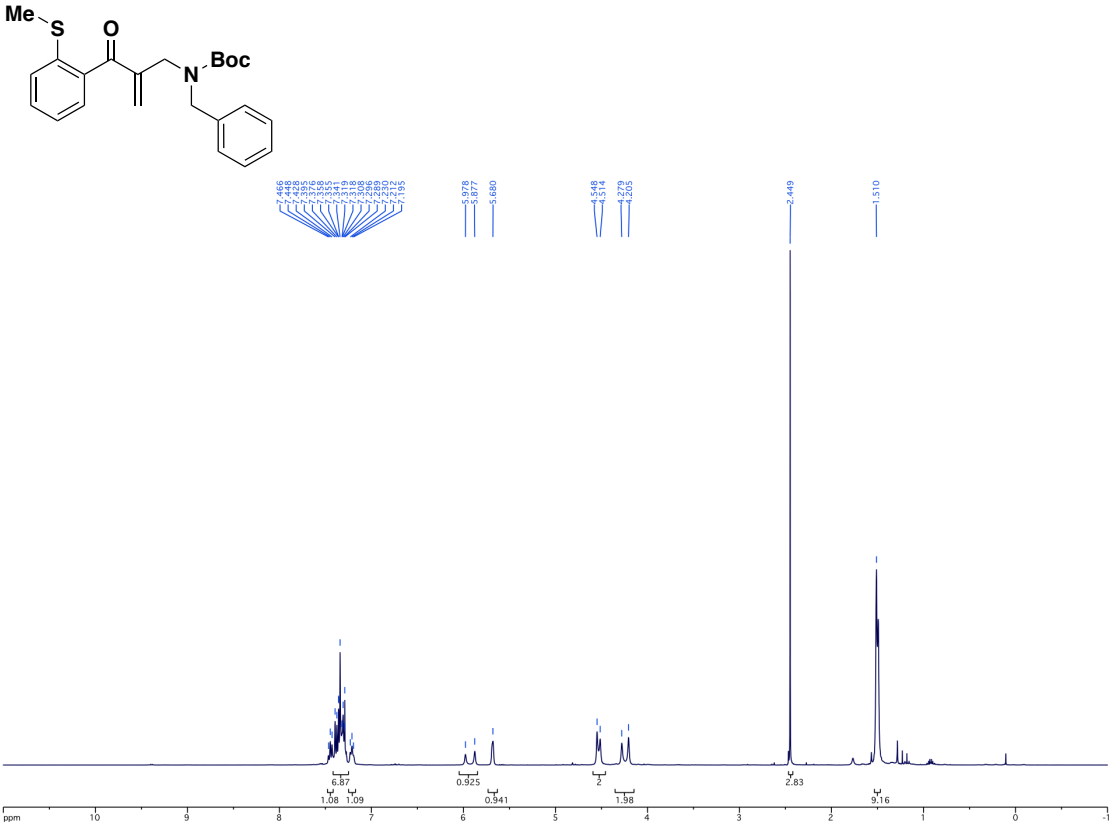


γ-Amino enone 55a: ^{13}C NMR (101 MHz, $CDCl_3$)

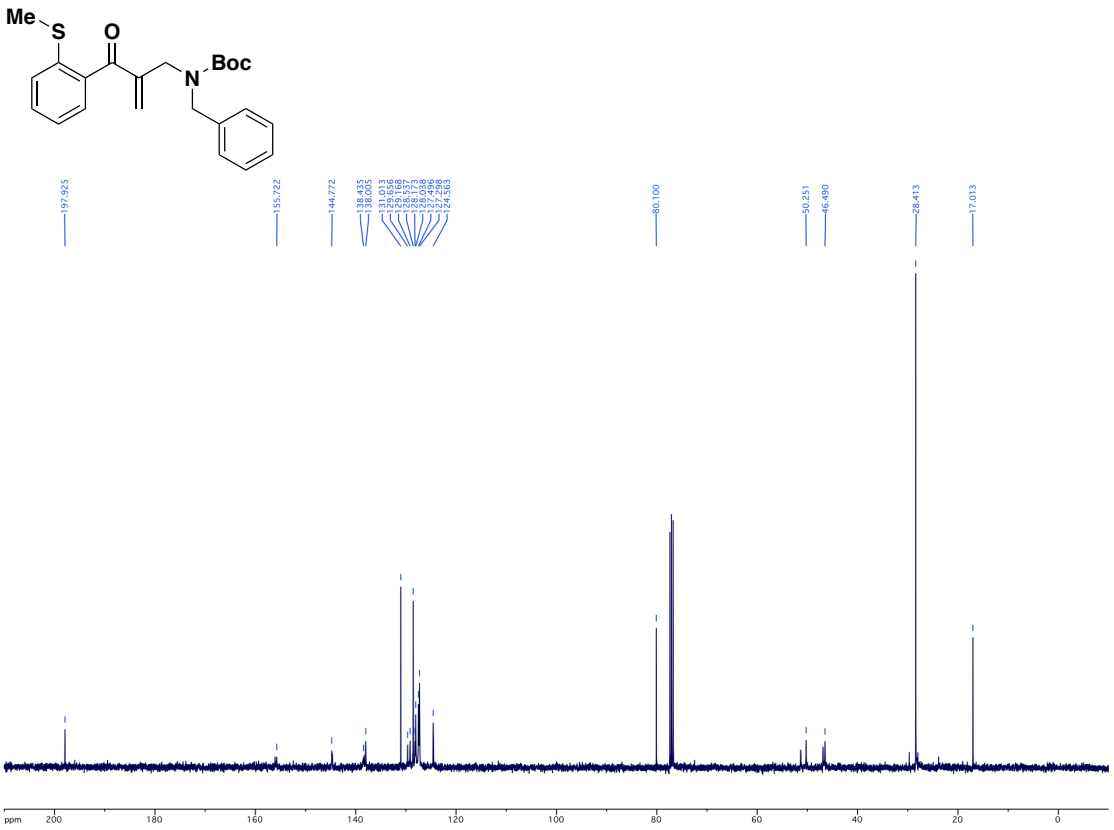




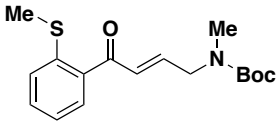
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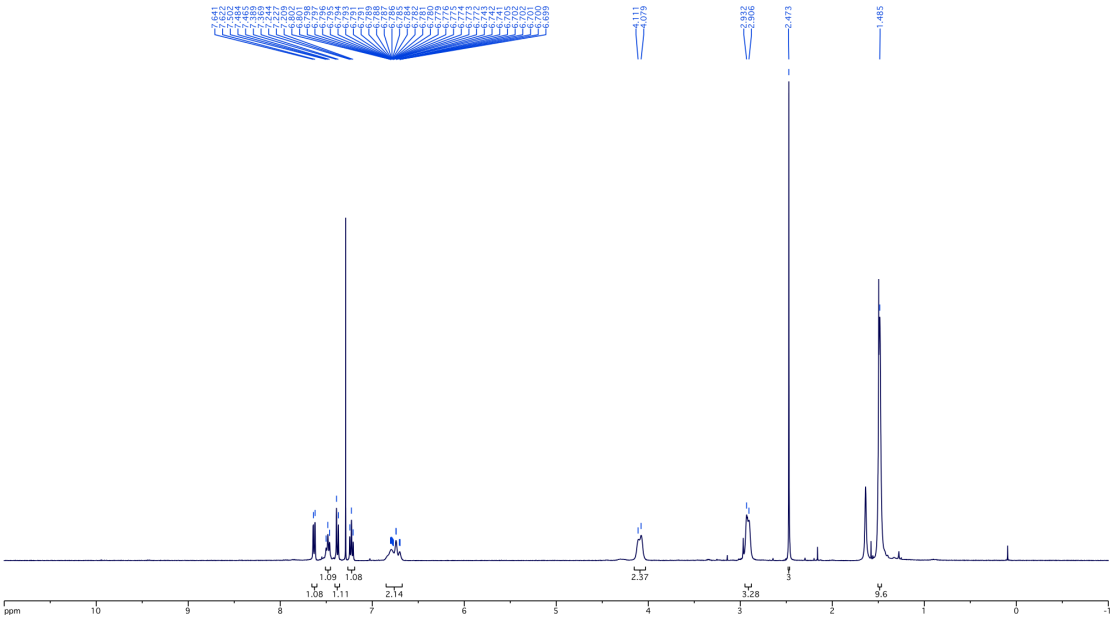


γ-Amino enone 55b: ^{13}C NMR (101 MHz, $CDCl_3$)

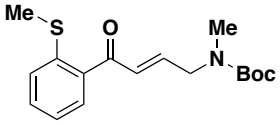


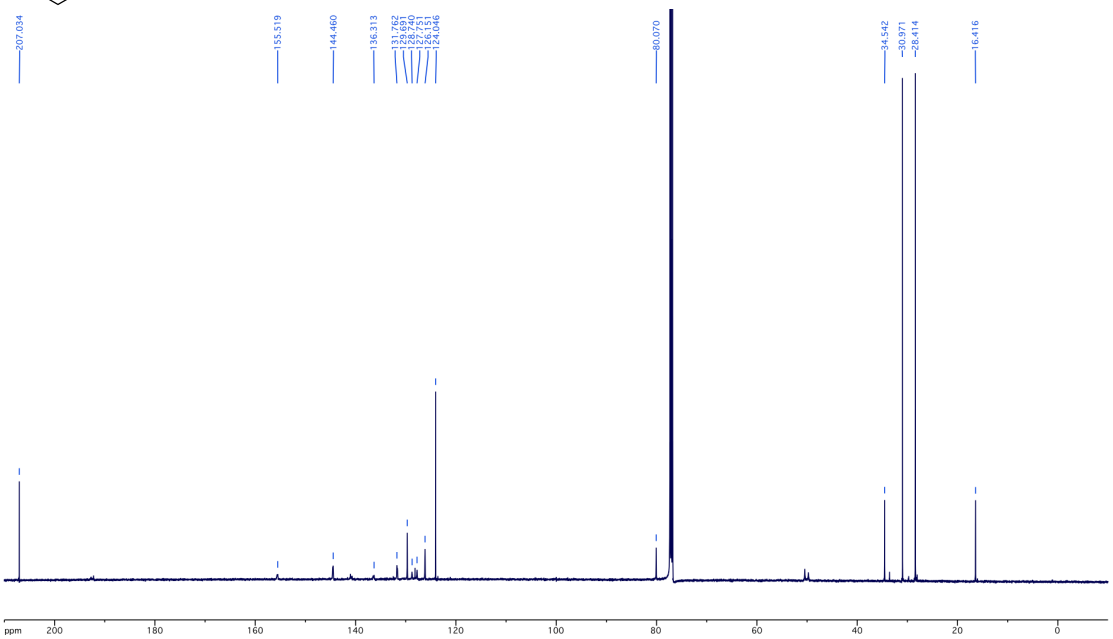
γ-Amino enone 56a: ^{1}H NMR (400 MHz, $CDCl_3$)



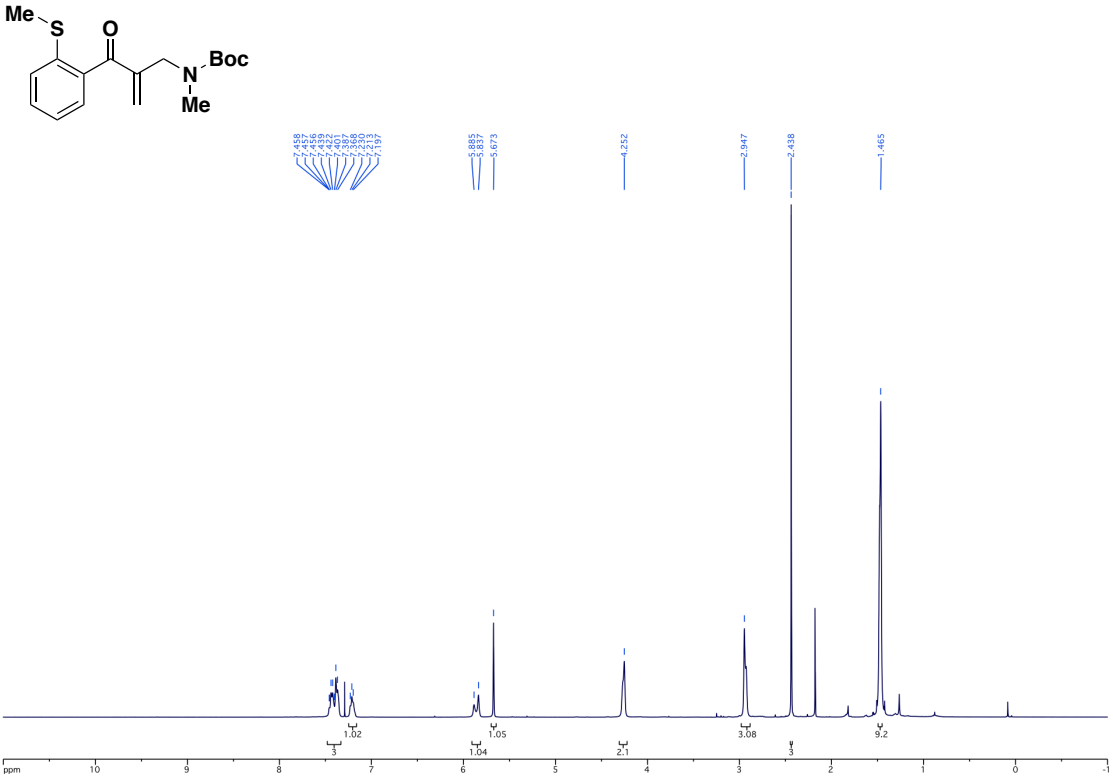


γ-Amino enone 56a: ^{13}C NMR (101 MHz, $CDCl_3$)

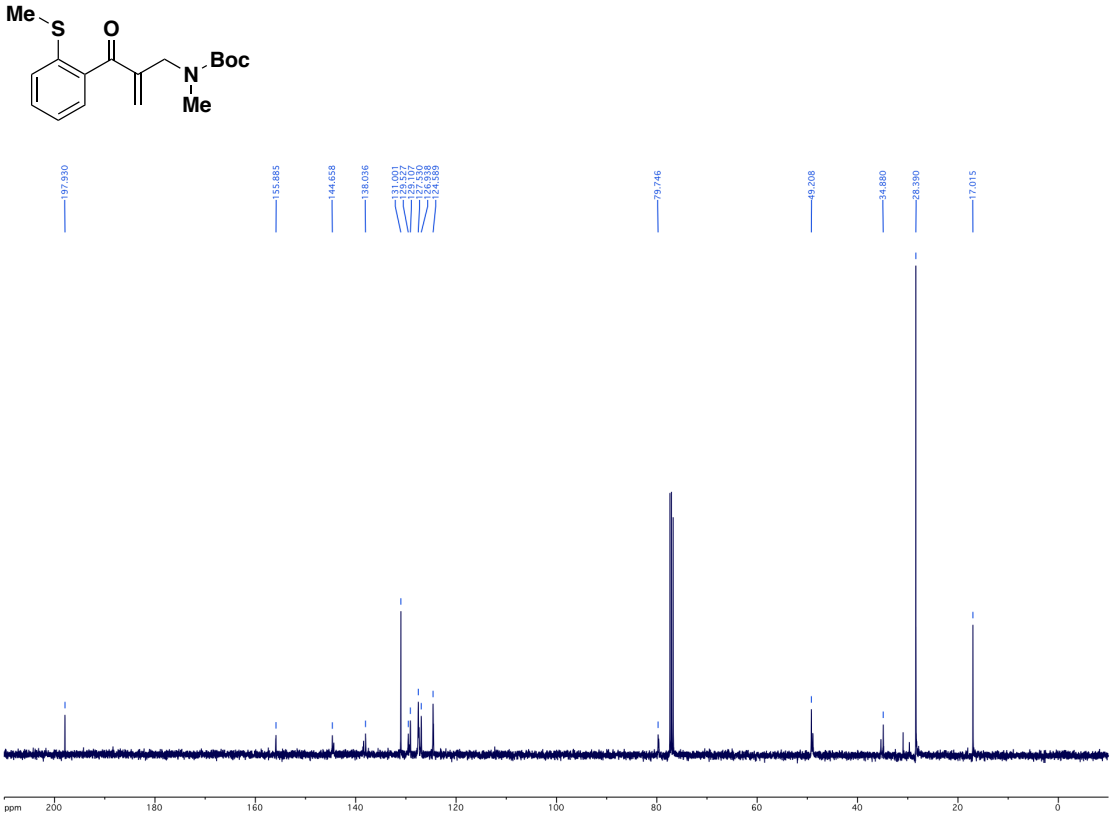




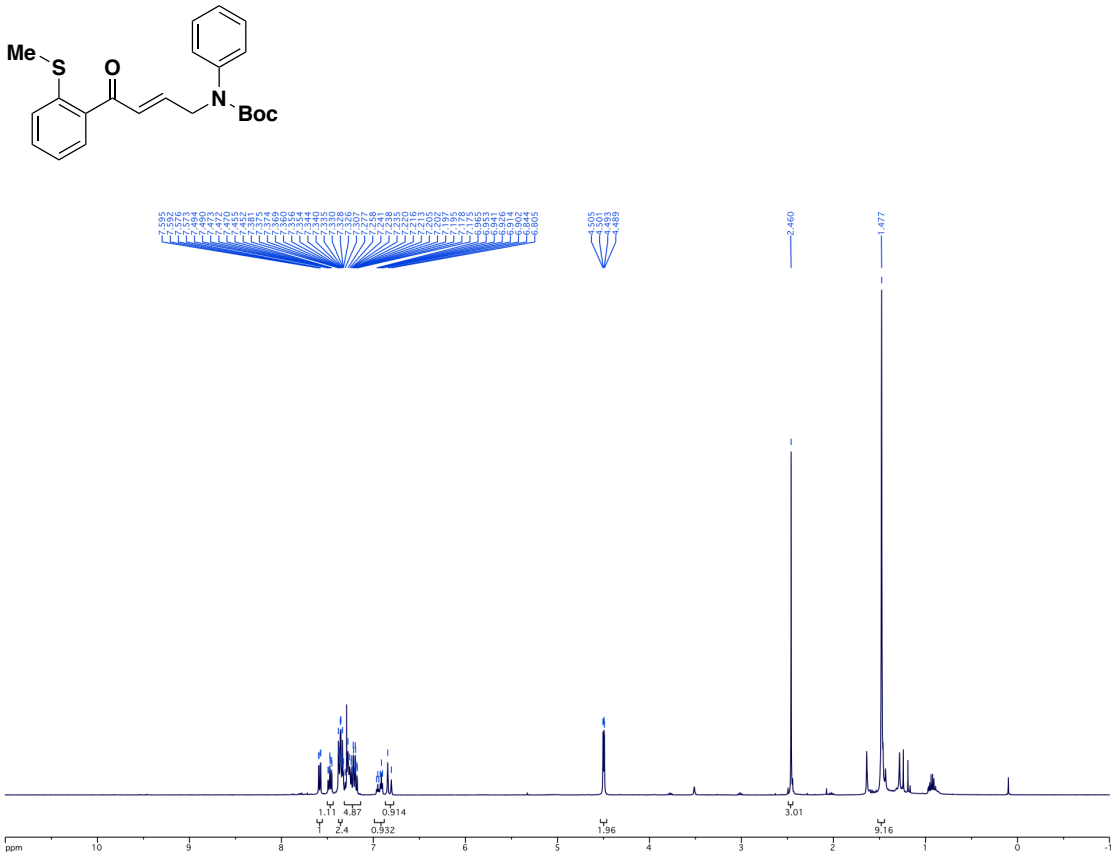
γ-Amino enone 56b: ^{1}H NMR (400 MHz, $CDCl_3$)



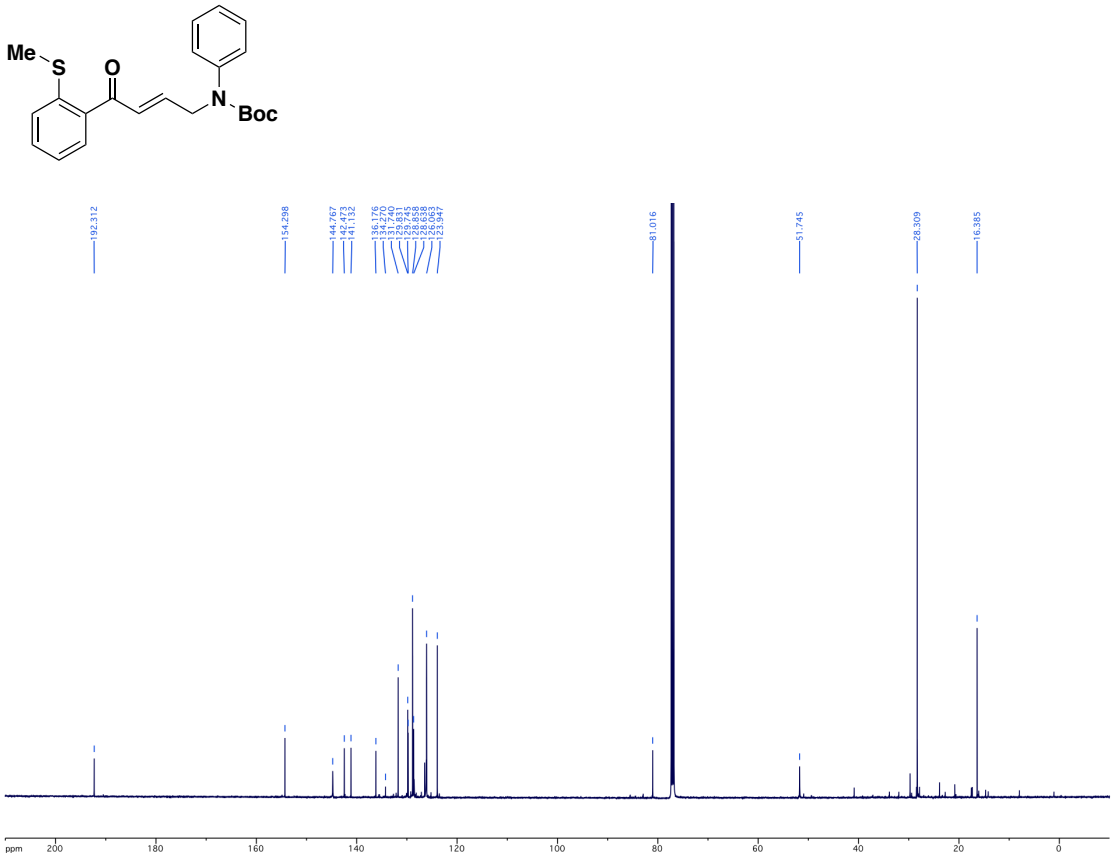
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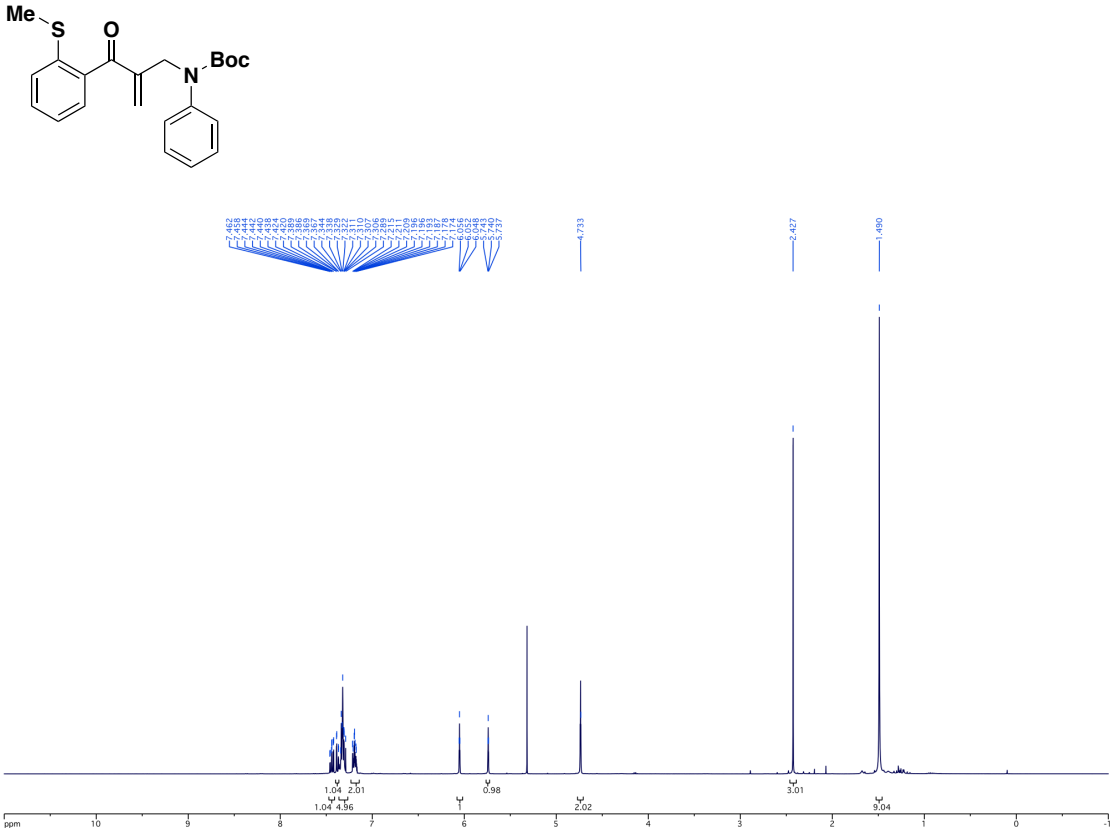
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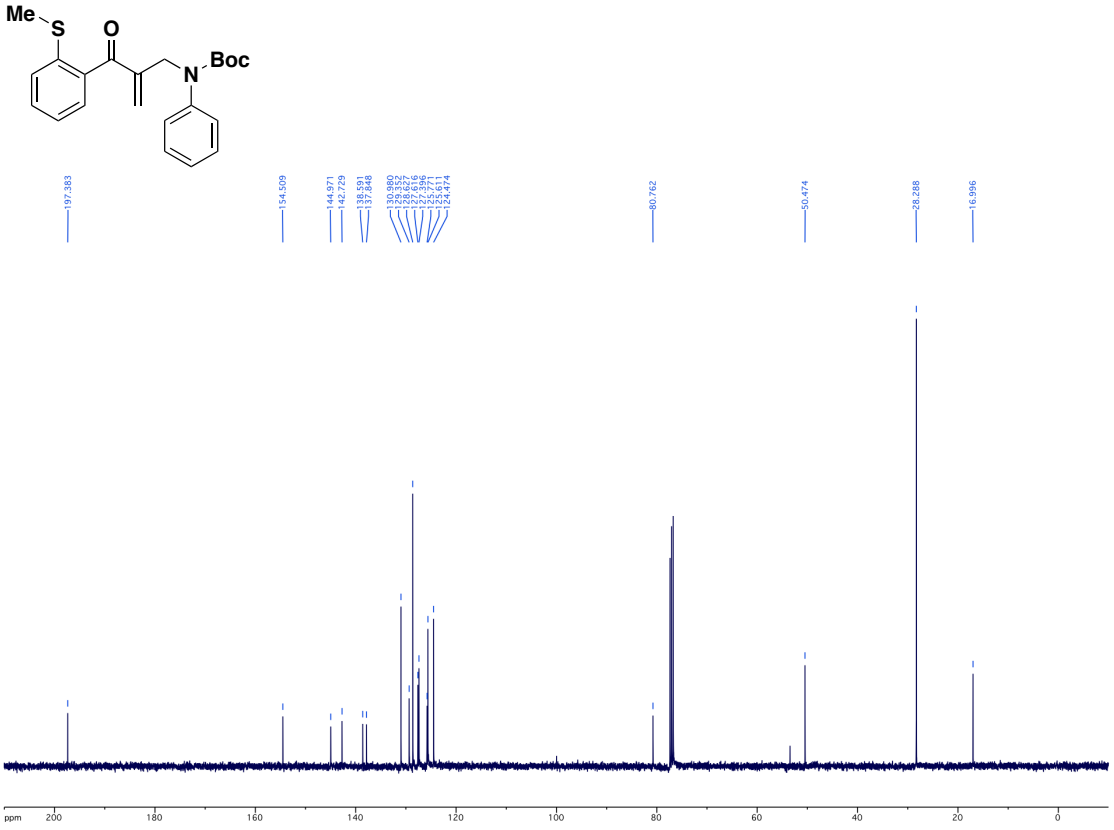
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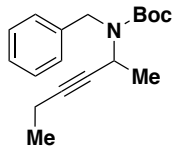
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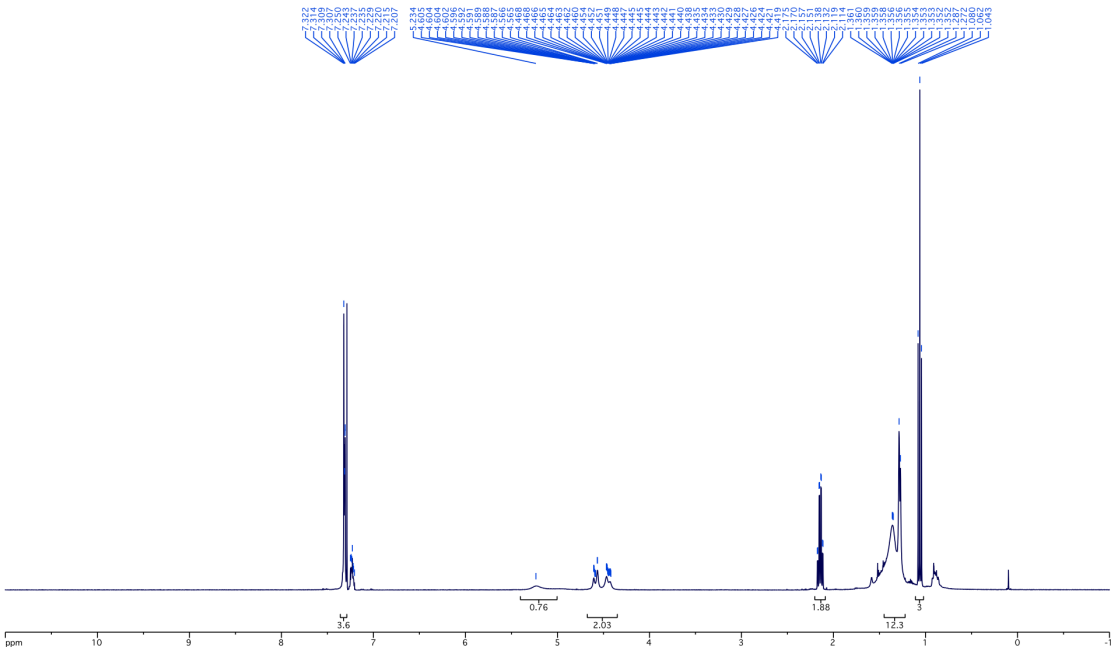


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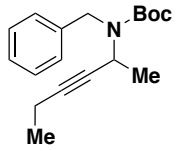


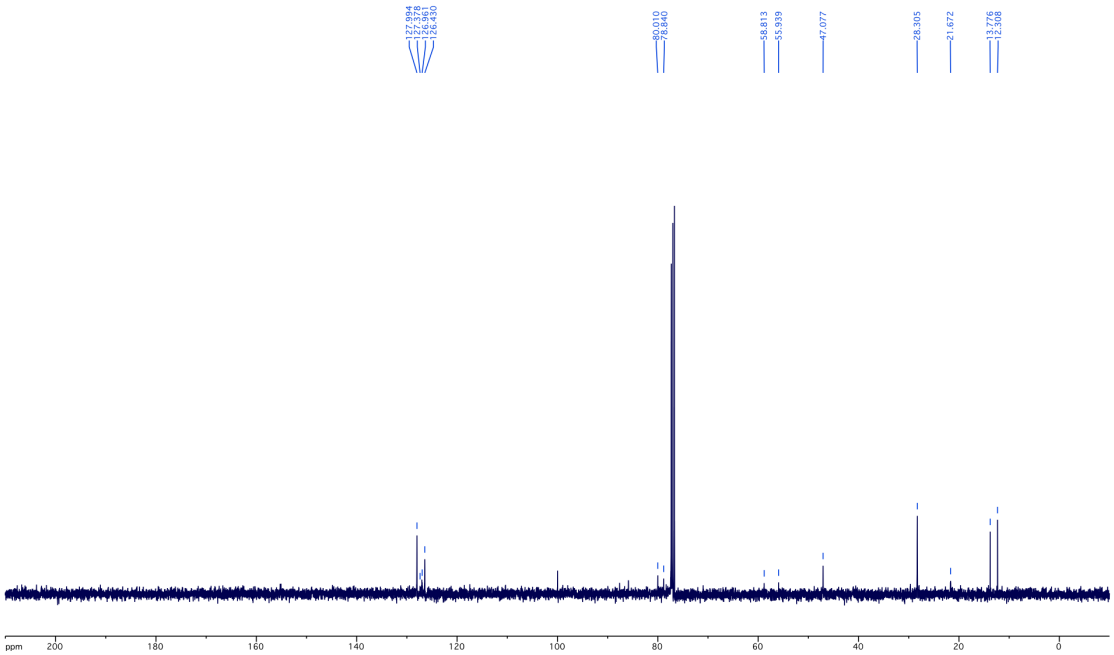
Propargylic amine 61b: ^{1}H NMR (400 MHz, $CDCl_3$)



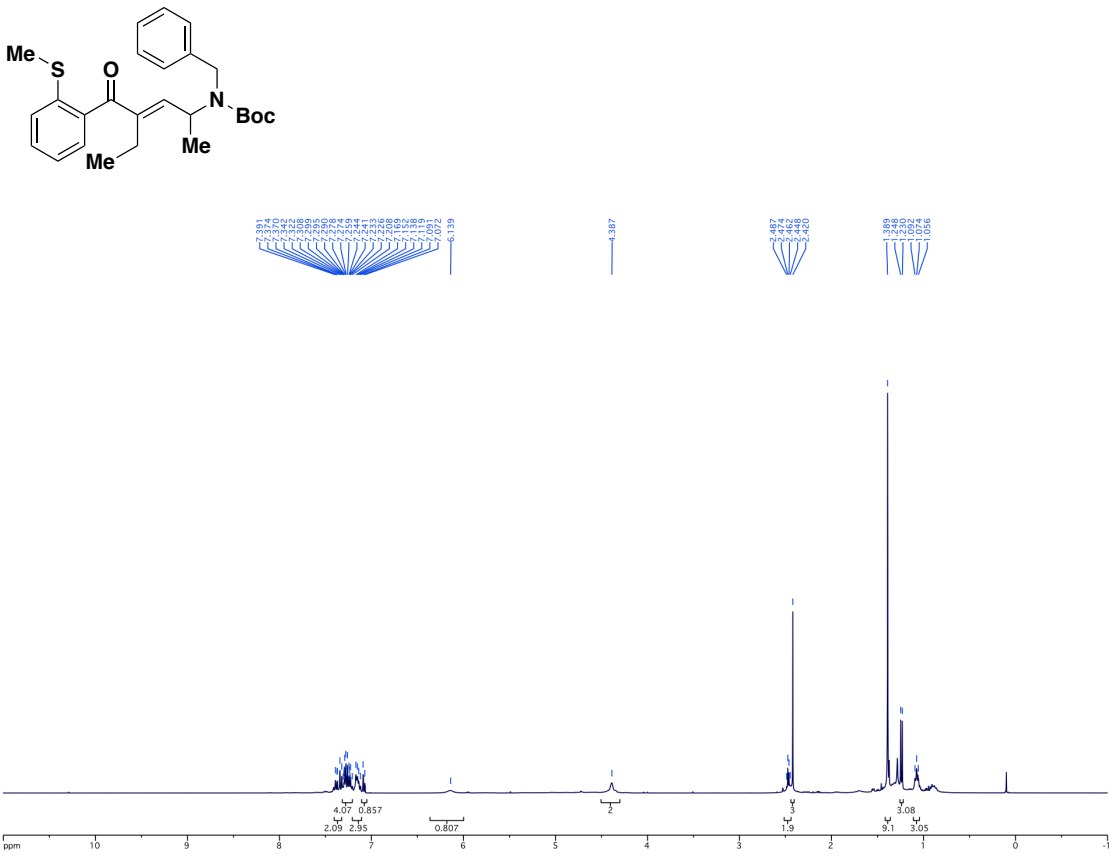


Propargylic amine 61b: ^{13}C NMR (101 MHz, $CDCl_3$)

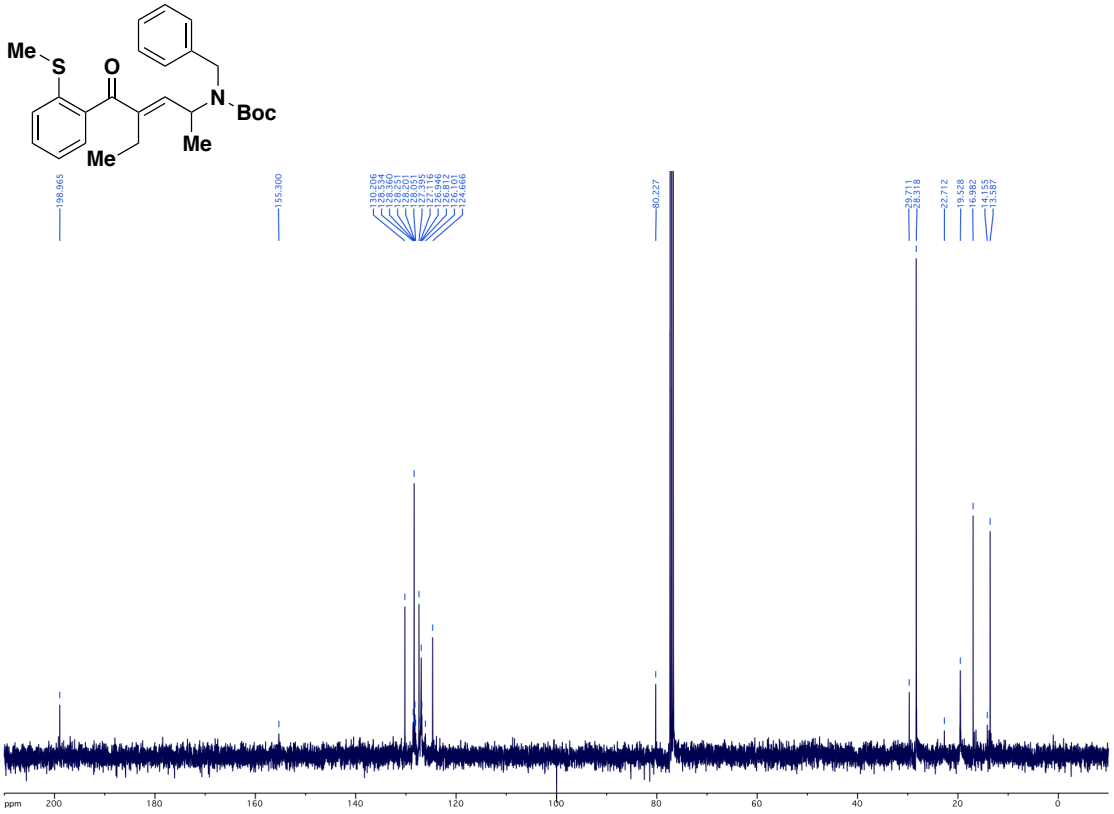




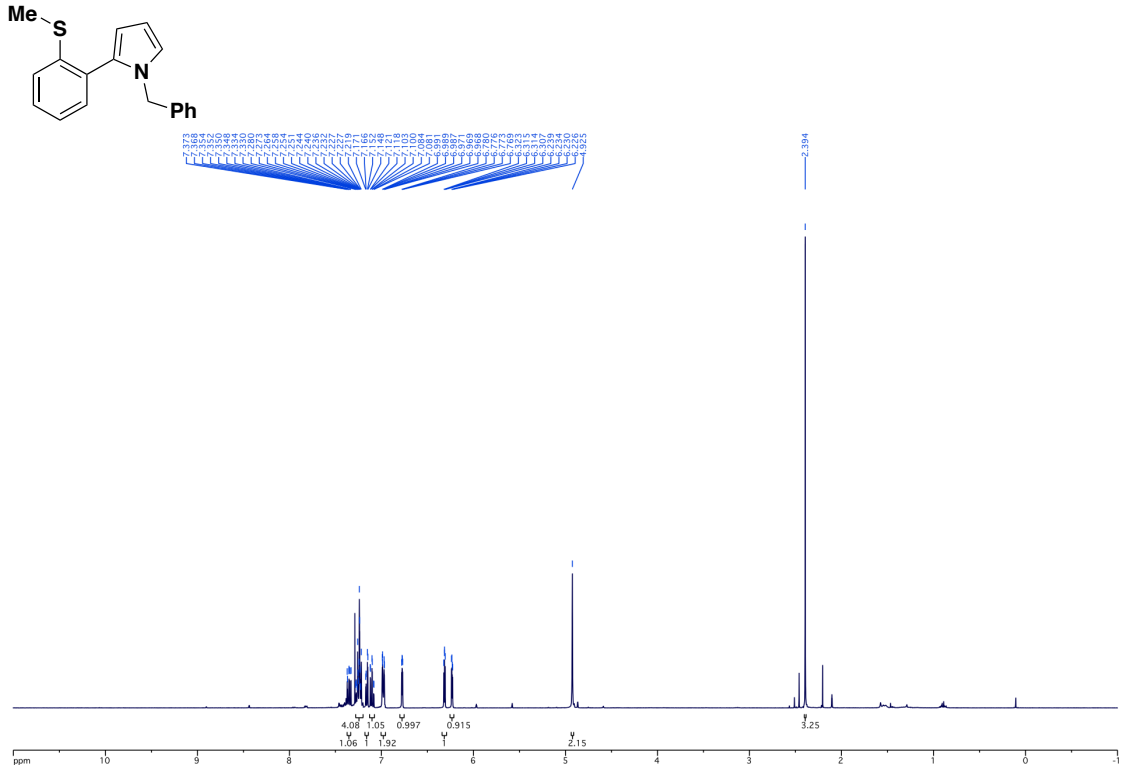
γ-Amino enone 67a: ^{1}H NMR (400 MHz, $CDCl_3$)



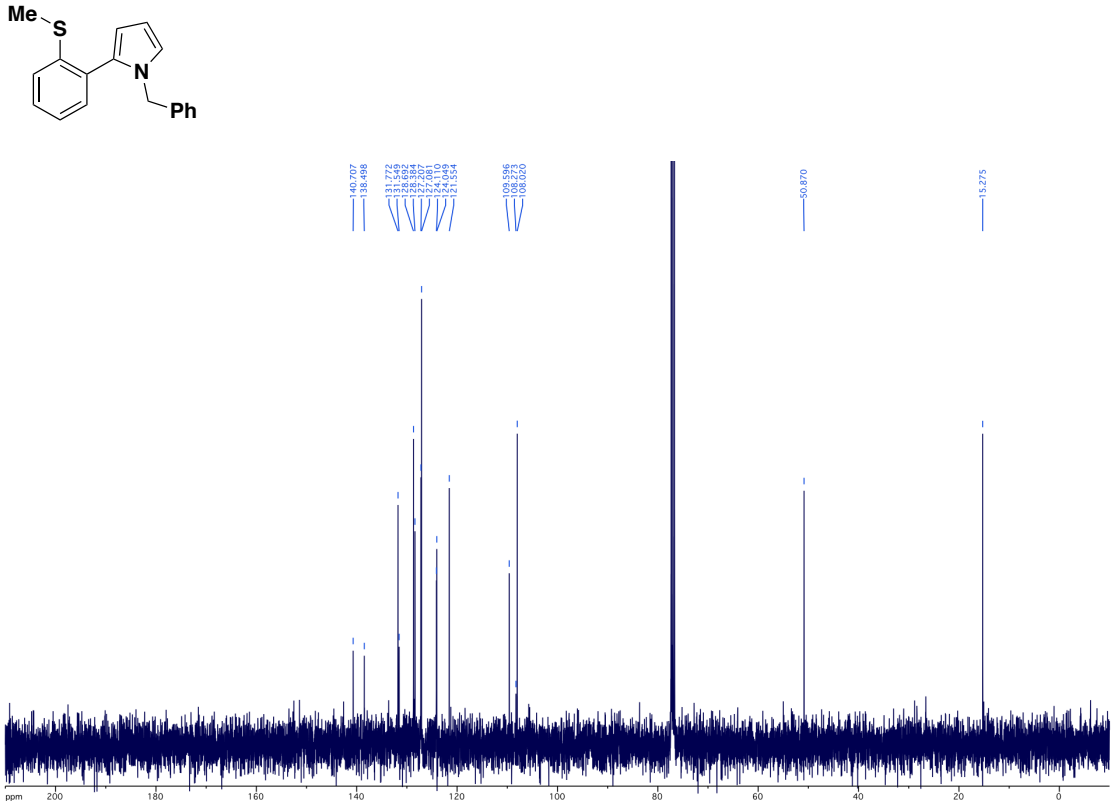
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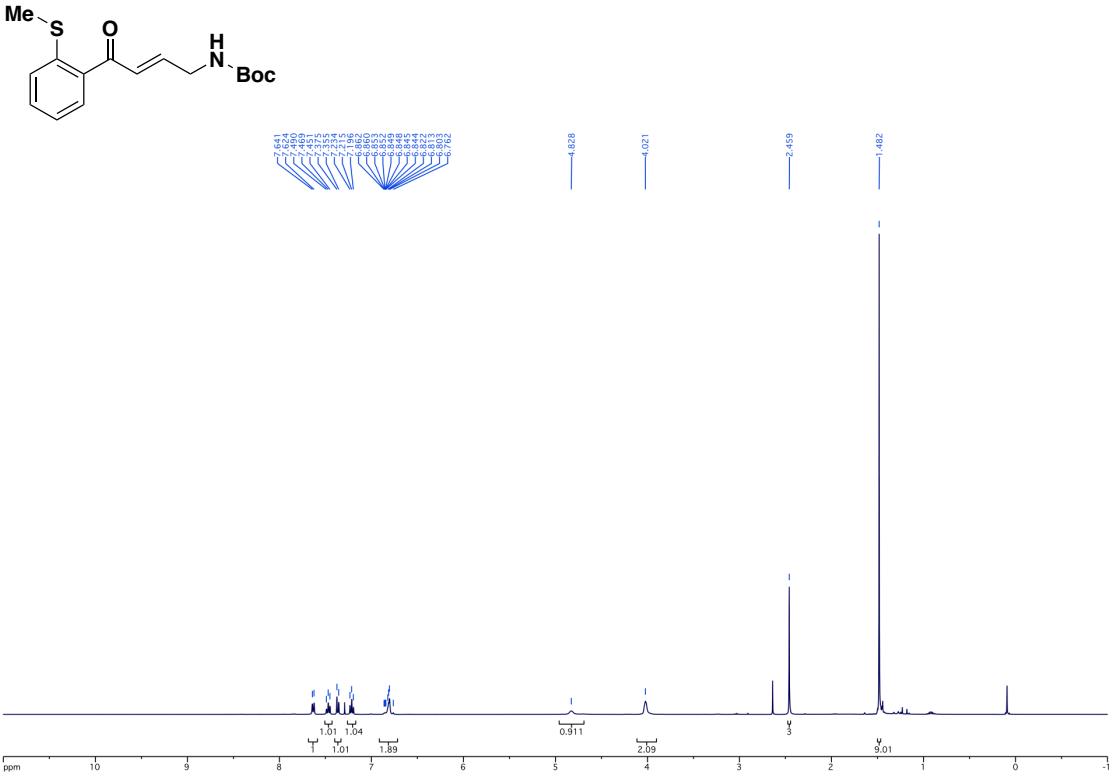
Pyrrole 68: ^{1}H NMR (400 MHz, $CDCl_3$)



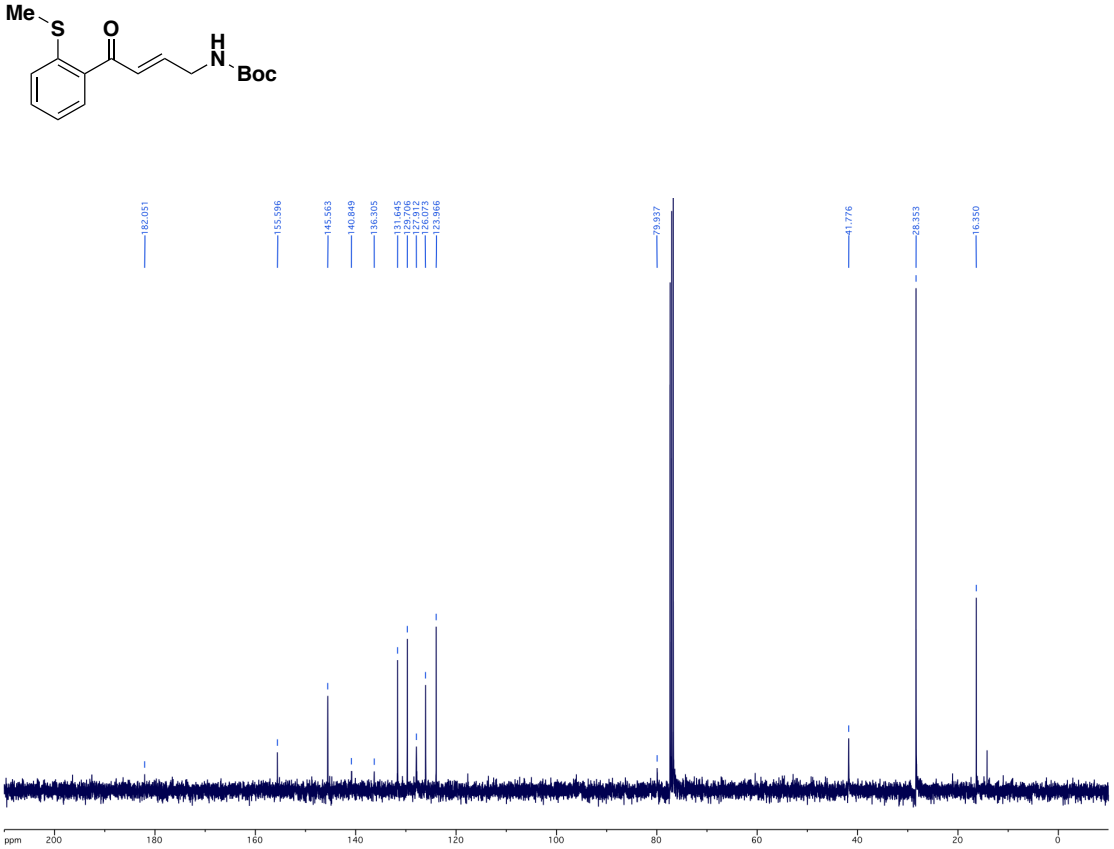
Pyrrole 68: ^{13}C NMR (101 MHz, $CDCl_3$)



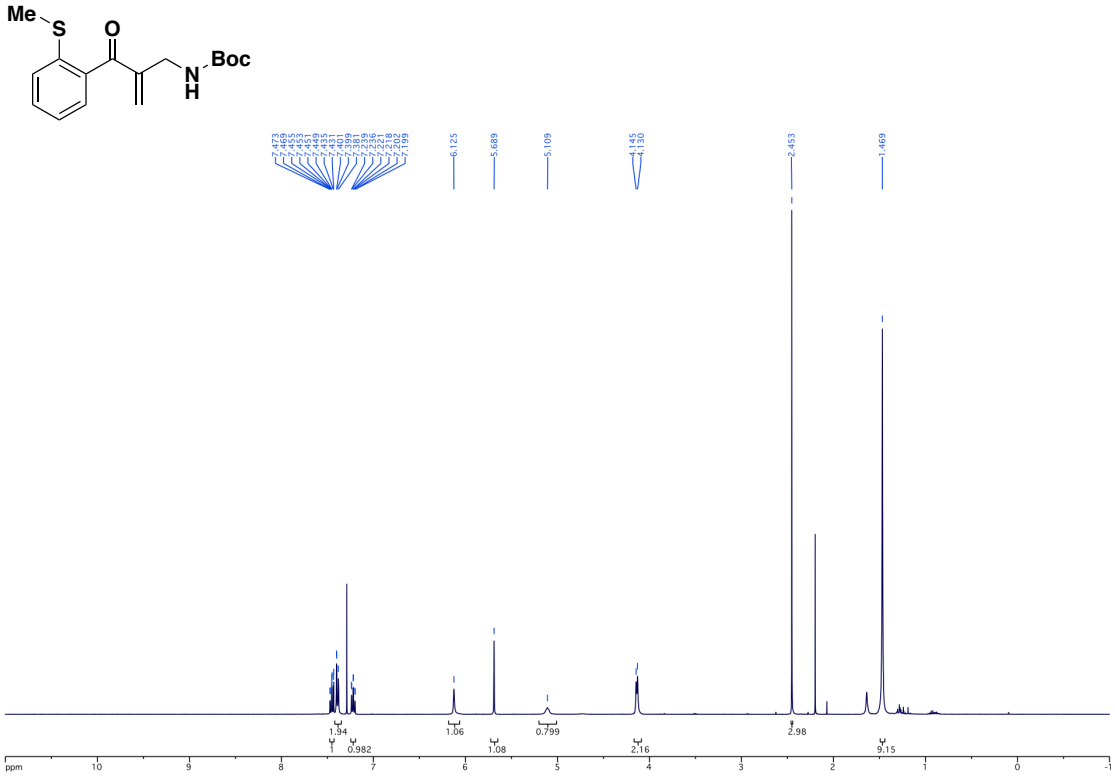
γ-Amino enone 69a: ^{1}H NMR (400 MHz, $CDCl_3$)



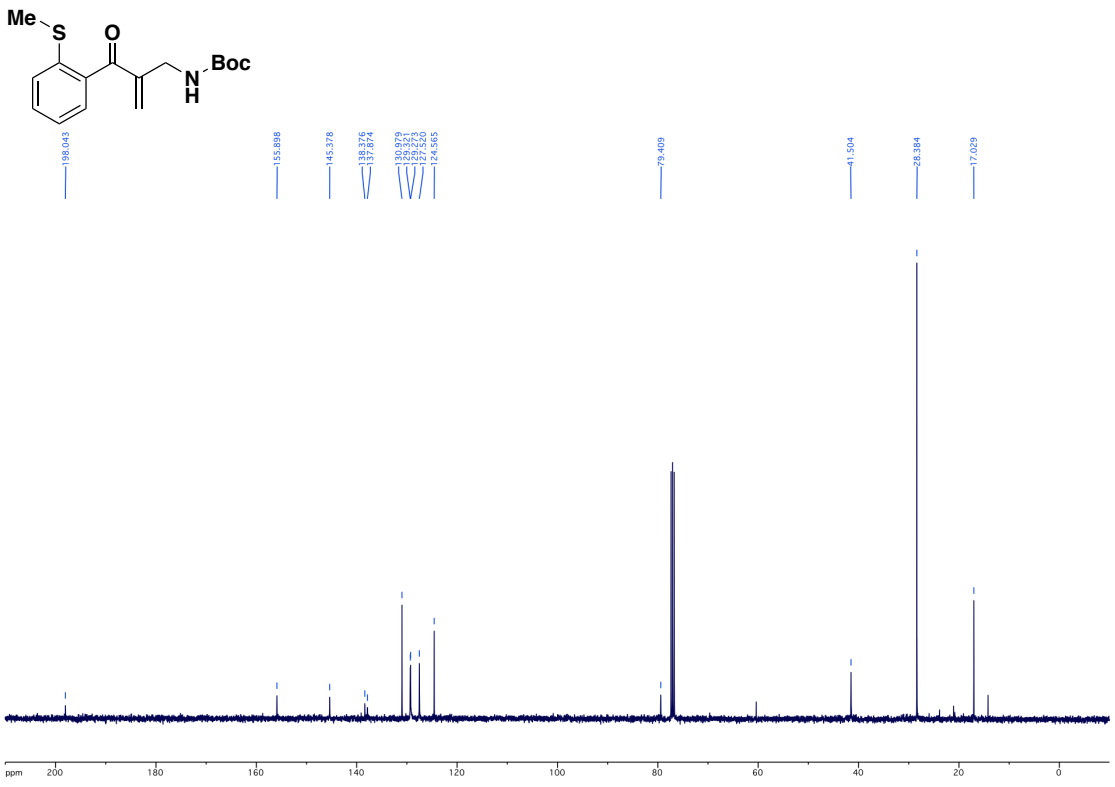
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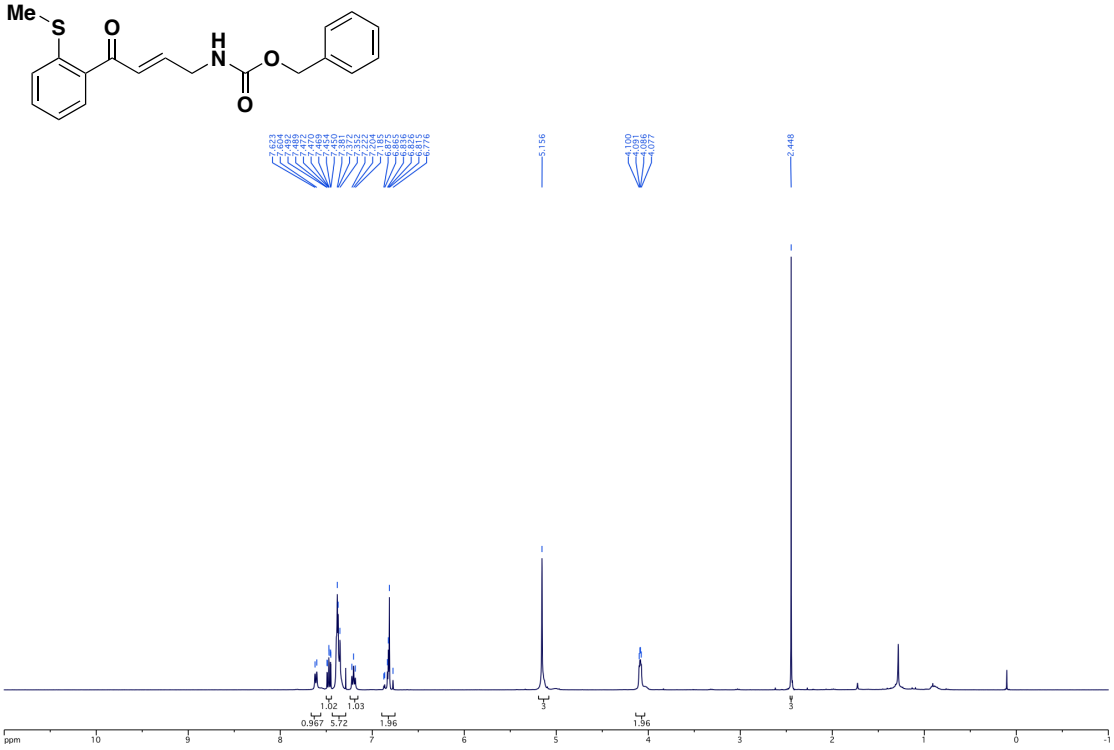
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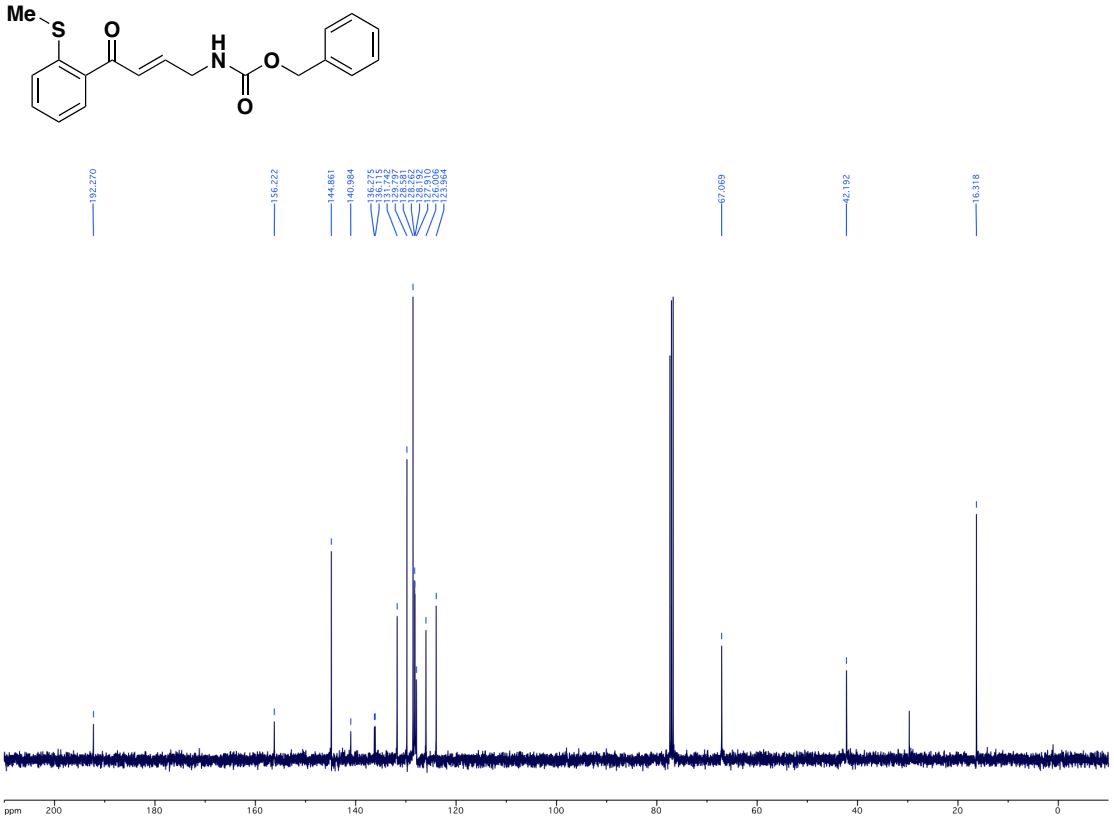
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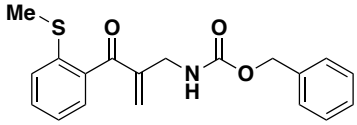
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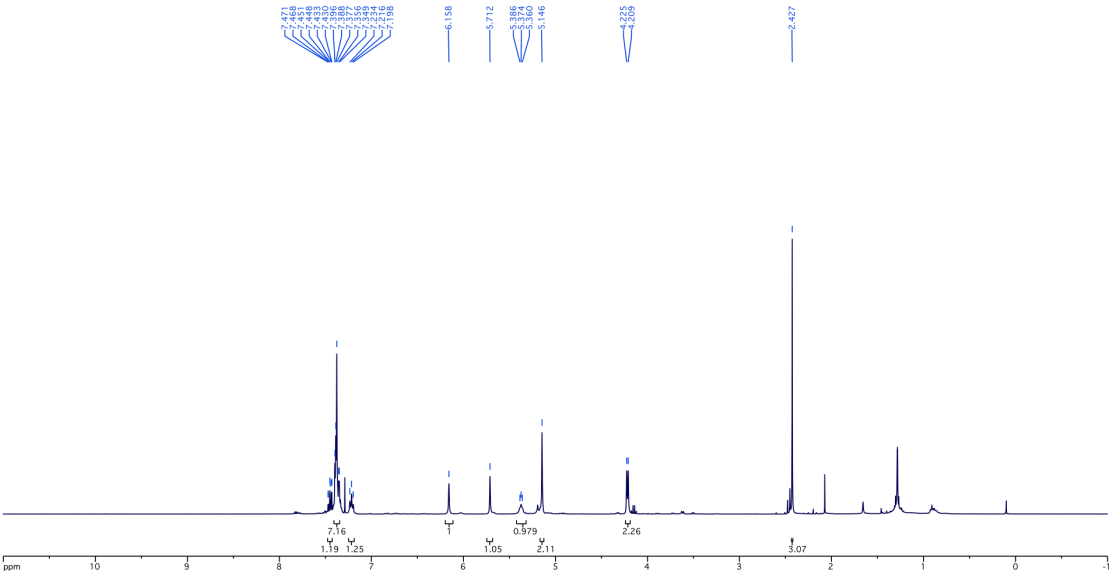


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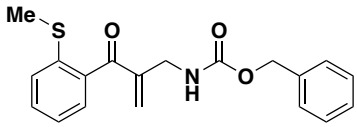


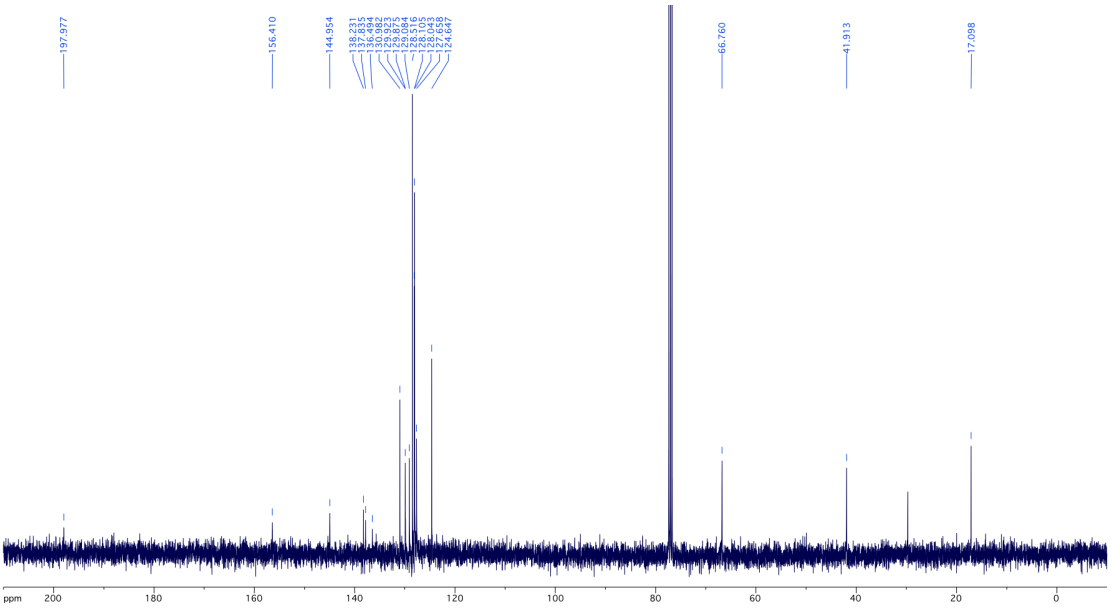
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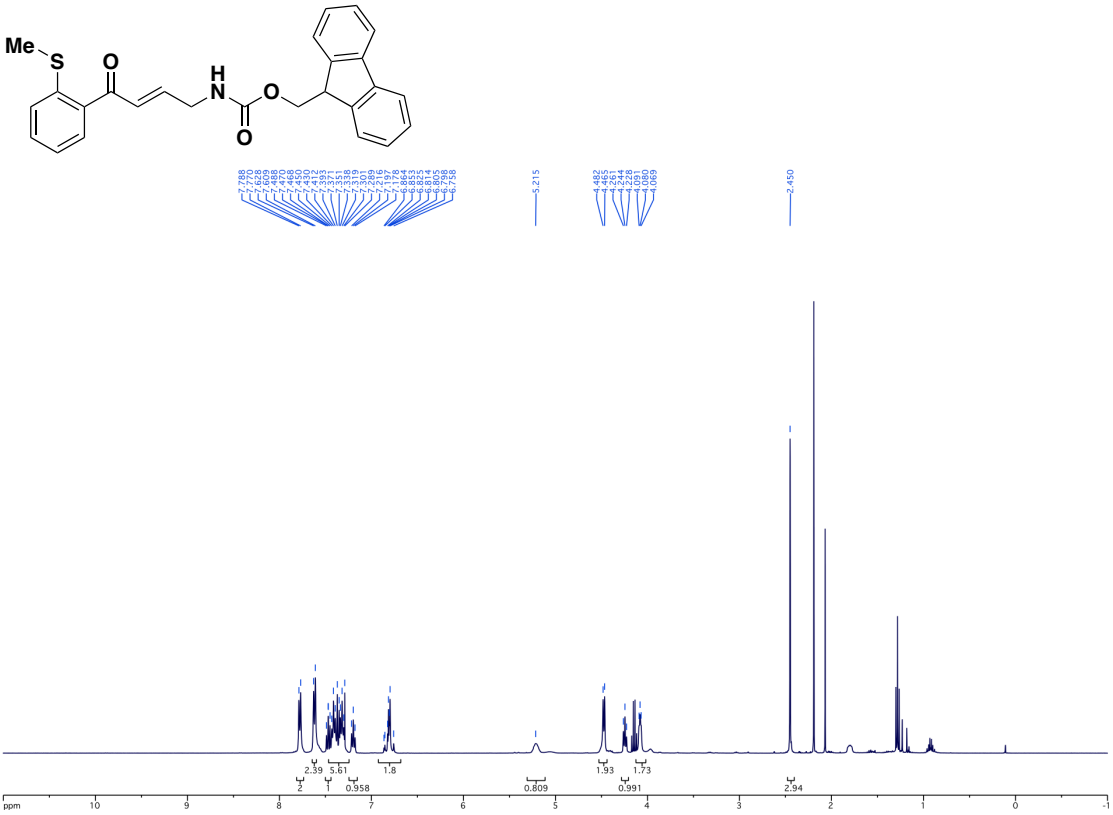


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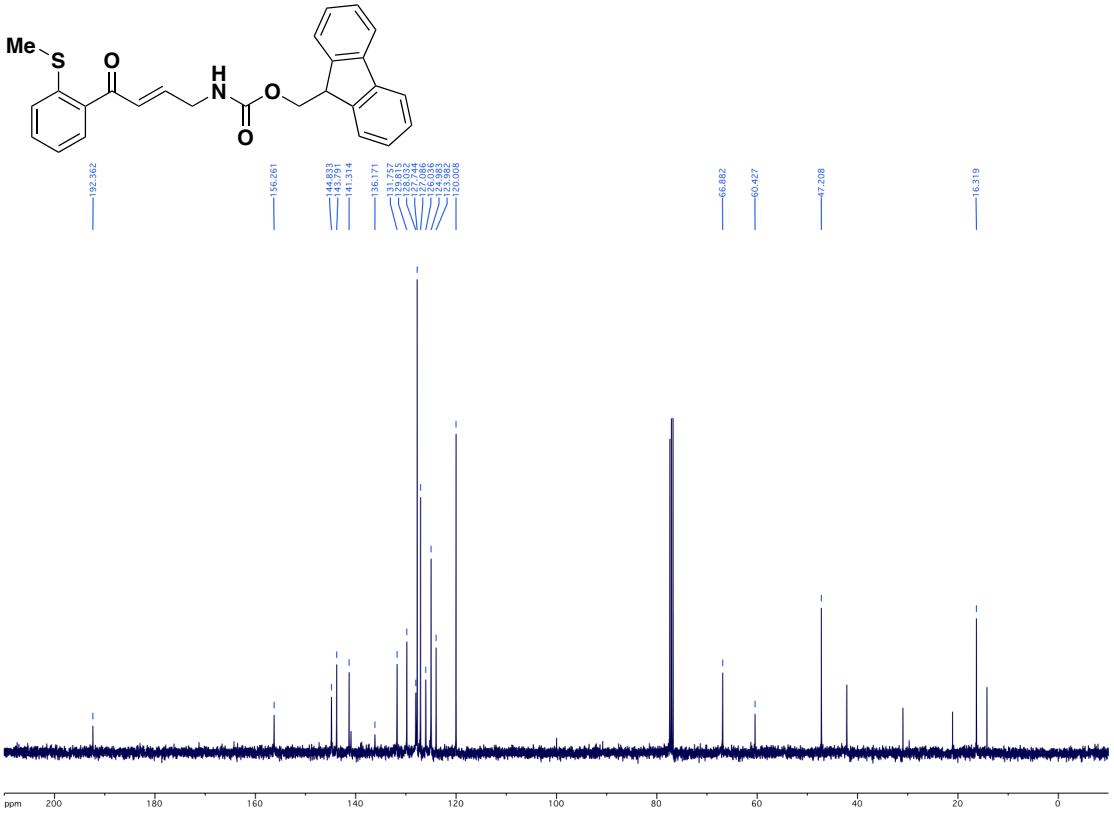




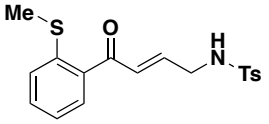
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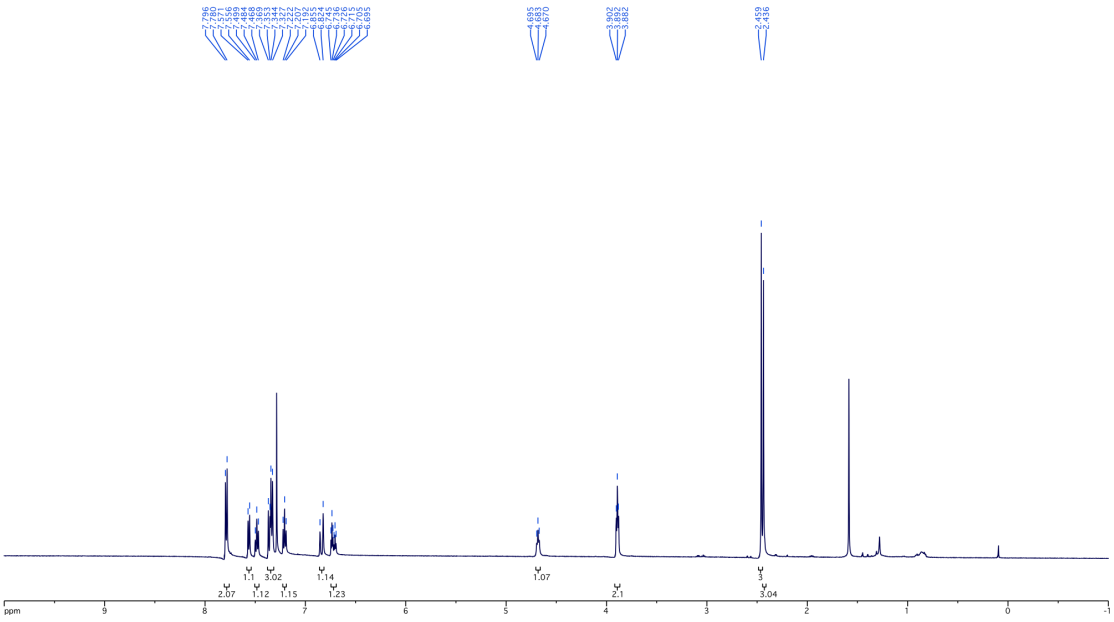


γ-Amino enone 77a: ^{13}C NMR (101 MHz, $CDCl_3$)

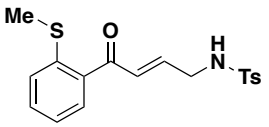


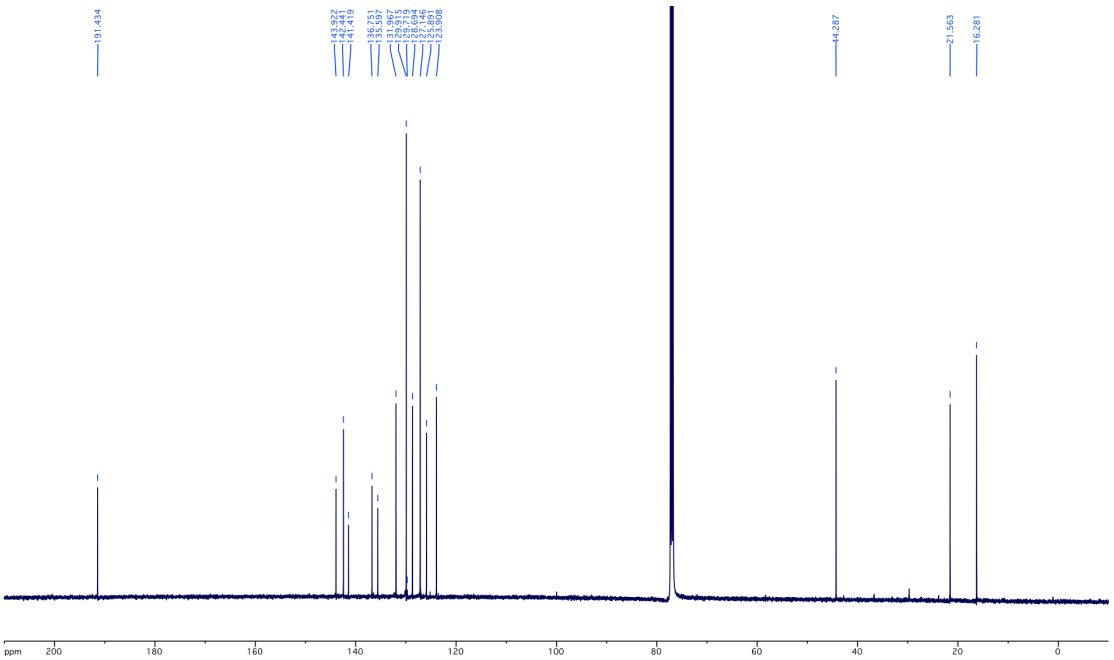
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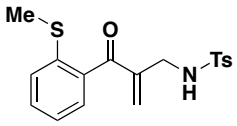


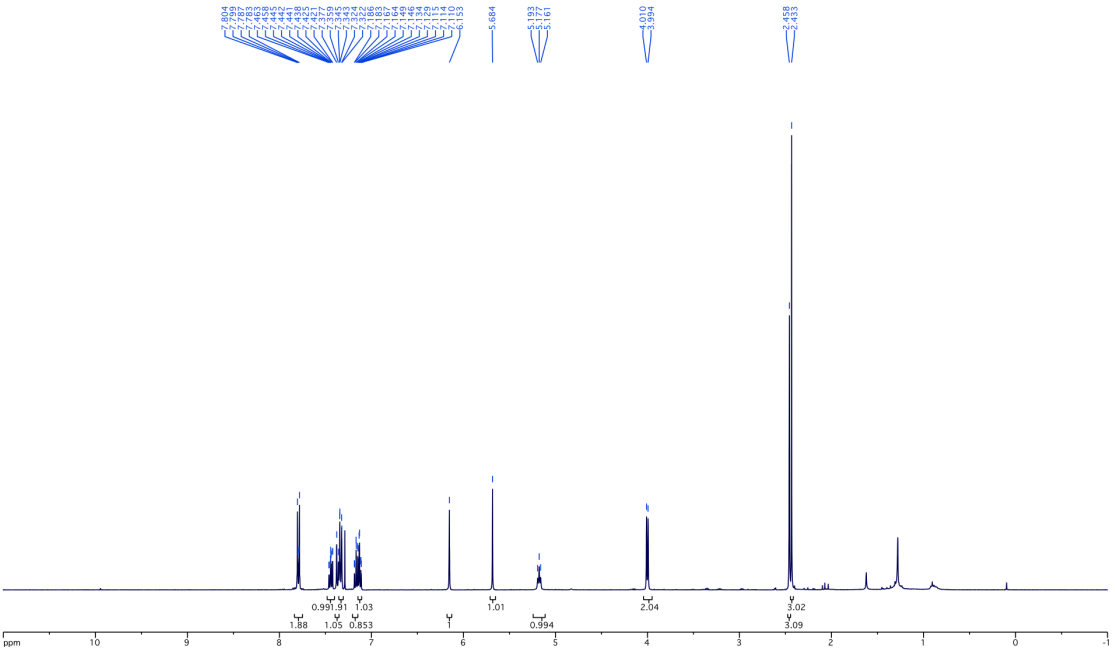
γ-Amino enone 78a: ^{13}C NMR (125 MHz, $CDCl_3$)



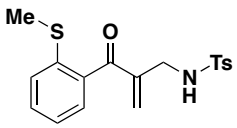


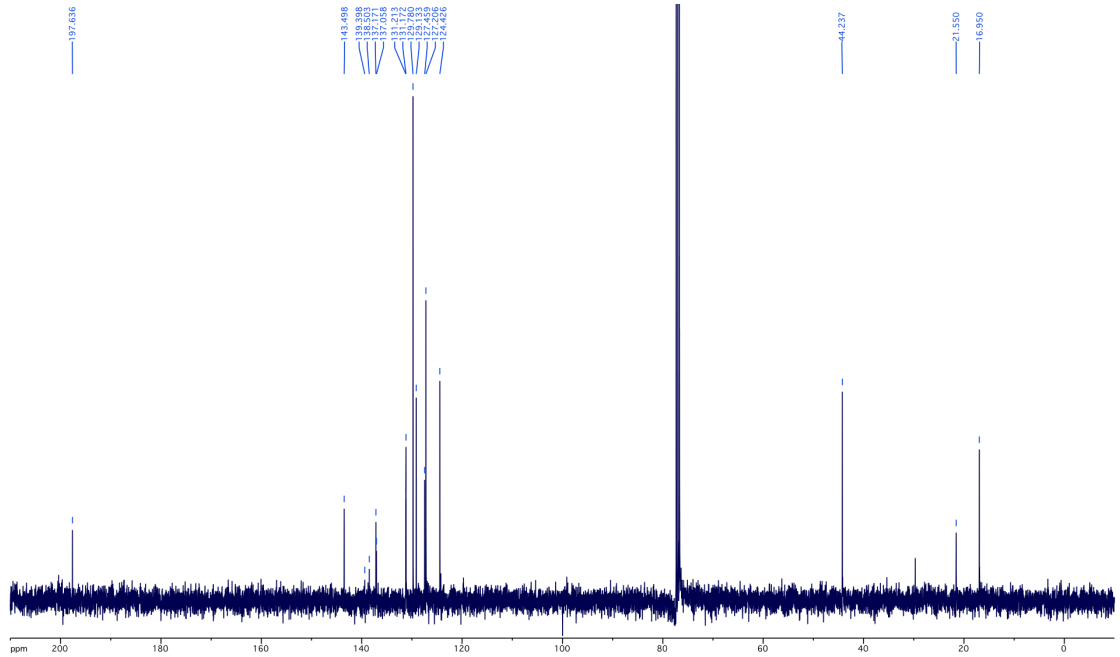
γ-Amino enone 78b: ^{1}H NMR (400 MHz, $CDCl_3$)



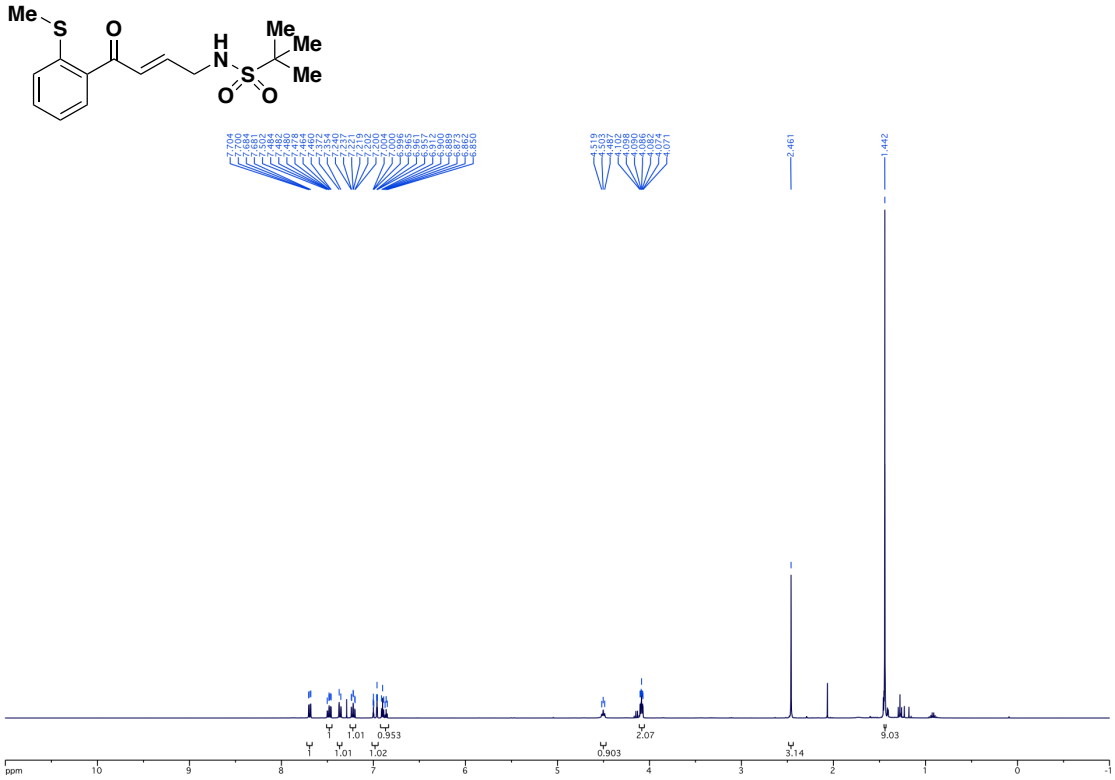


γ-Amino enone 78b: ^{13}C NMR (101 MHz, $CDCl_3$)

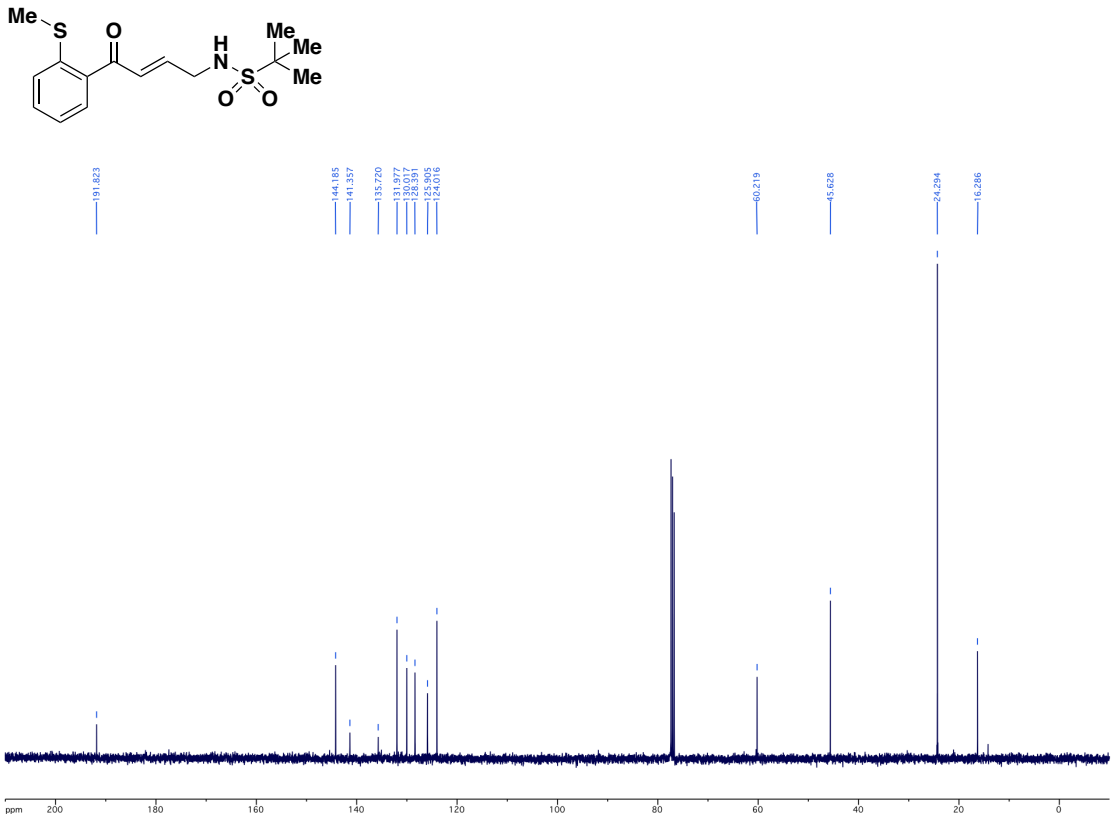




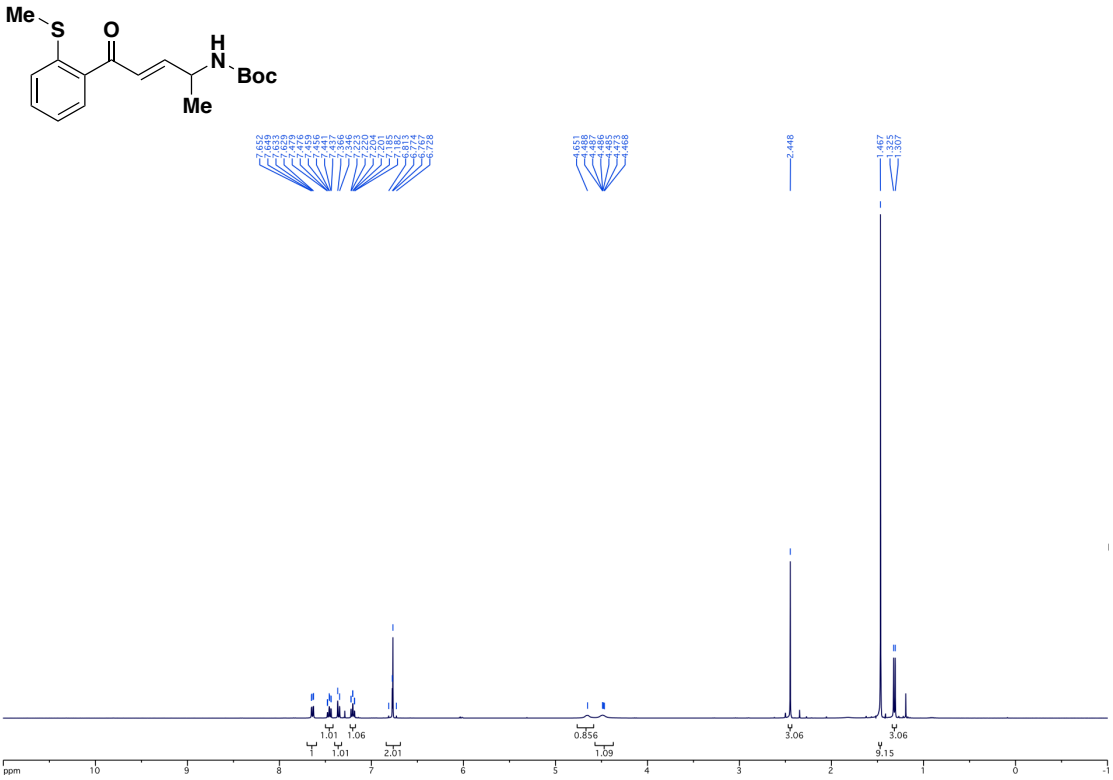
γ-Amino enone 79a: ^{1}H NMR (400 MHz, $CDCl_3$)



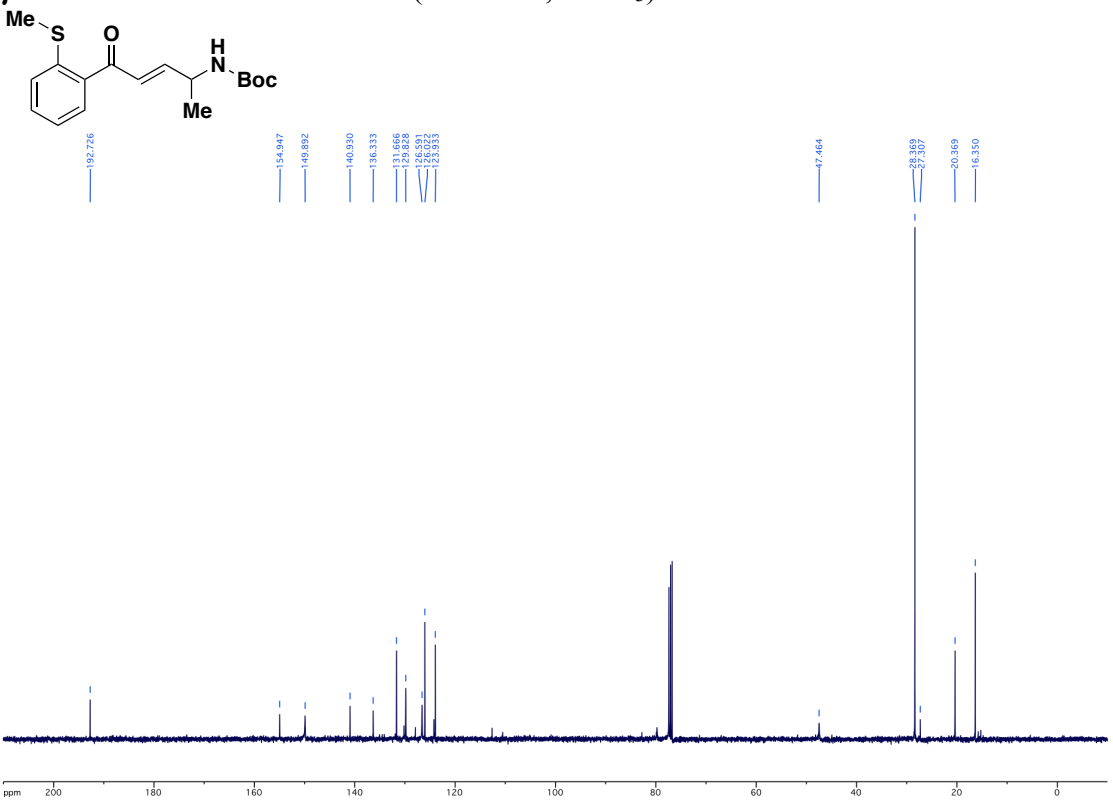
γ-Amino enone 79a: ^{13}C NMR (101 MHz, $CDCl_3$)



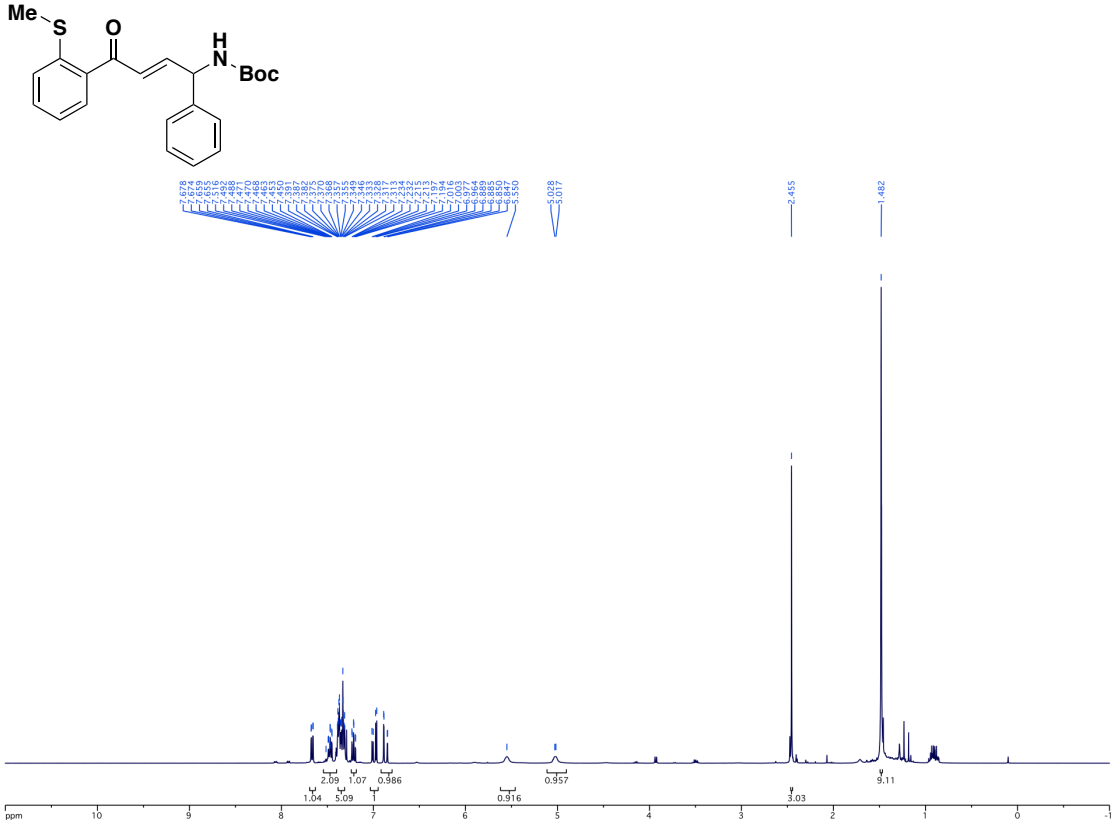
γ-Amino enone 85a: ^{1}H NMR (400 MHz, $CDCl_3$)



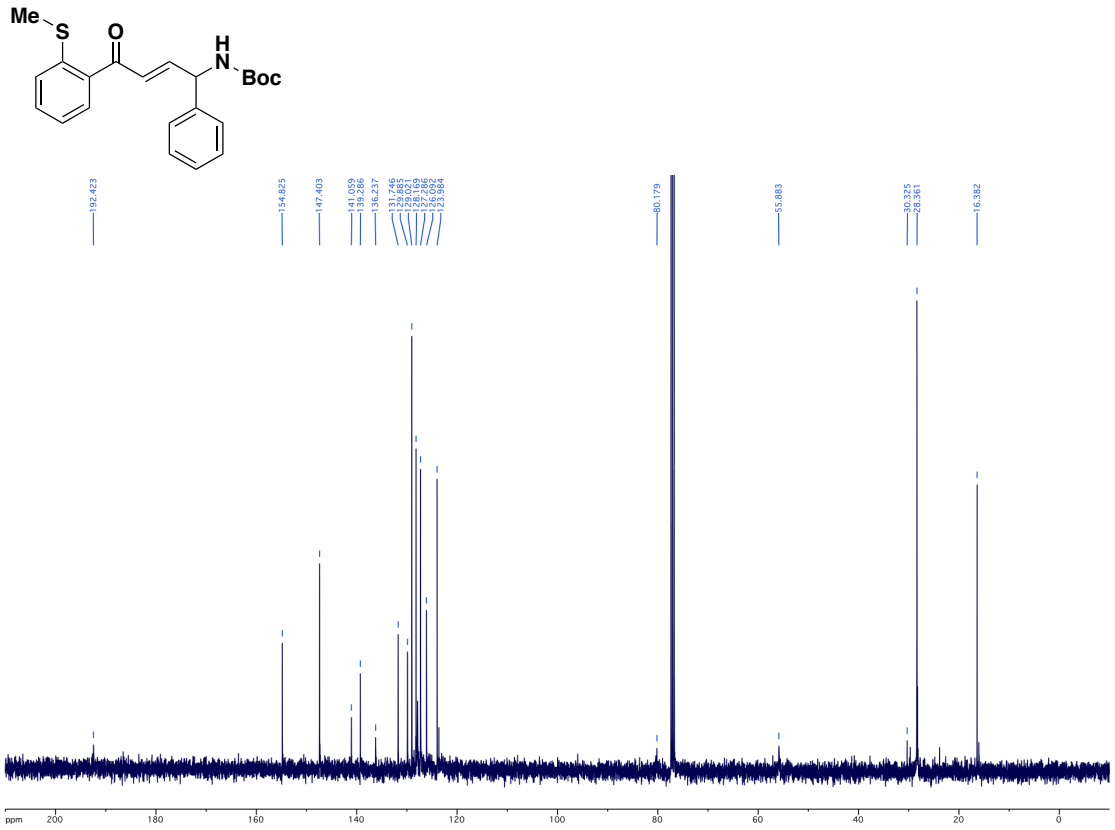
γ-Amino enone 85a: ^{13}C NMR (101 MHz, $CDCl_3$)



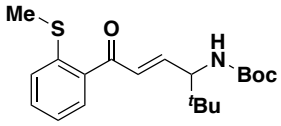
γ-Amino enone 86a: ^{1}H NMR (400 MHz, $CDCl_3$)

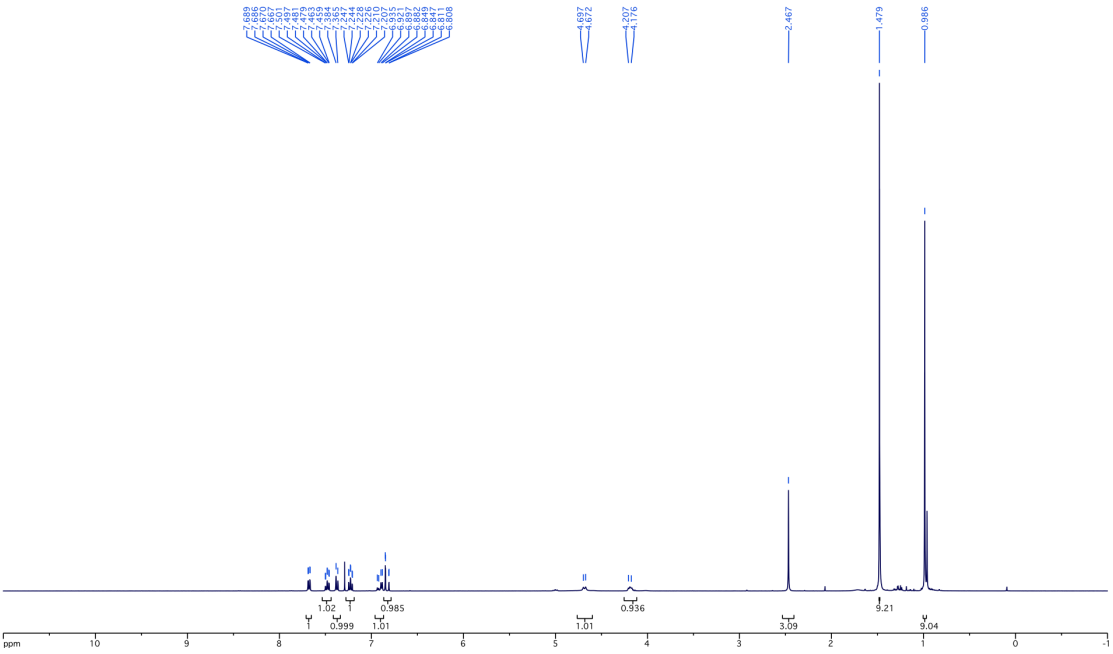


γ-Amino enone 86a: ^{13}C NMR (101 MHz, $CDCl_3$)

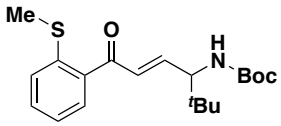


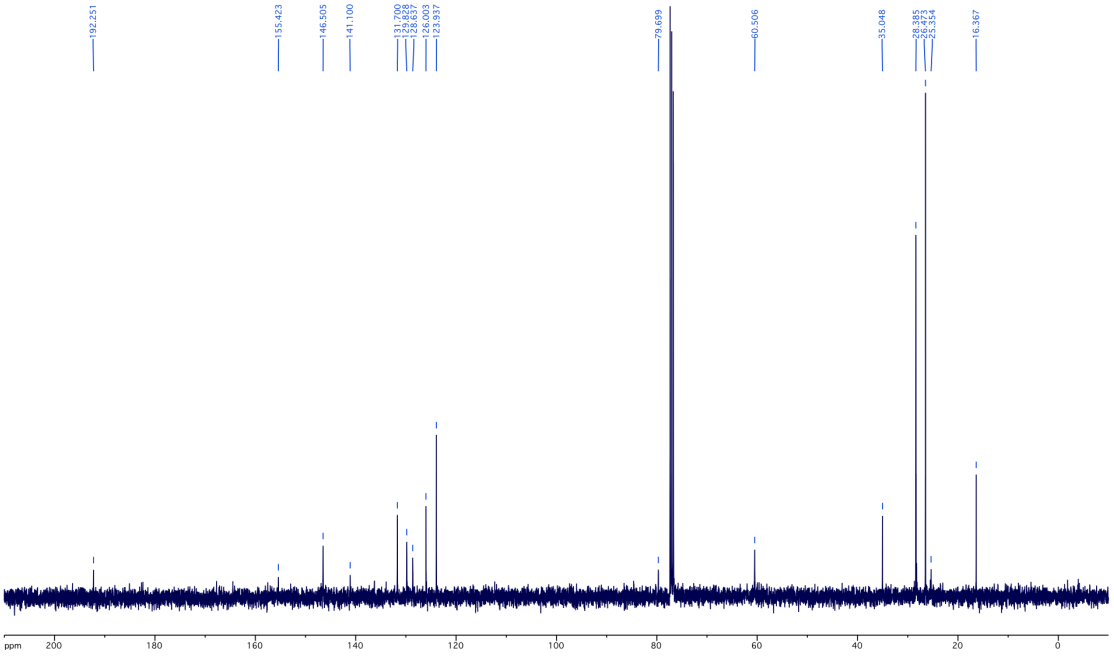
γ-Amino enone 87a: ^{1}H NMR (400 MHz, $CDCl_3$)



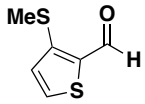


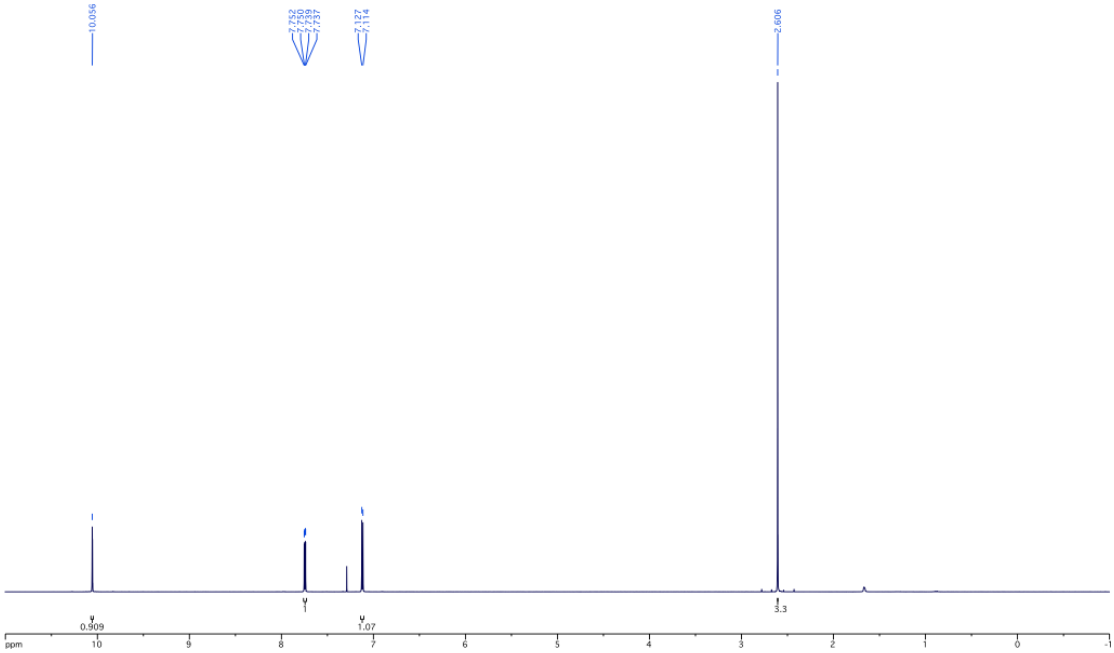
γ-Amino enone 87a: ^{13}C NMR (101 MHz, $CDCl_3$)



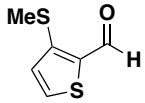


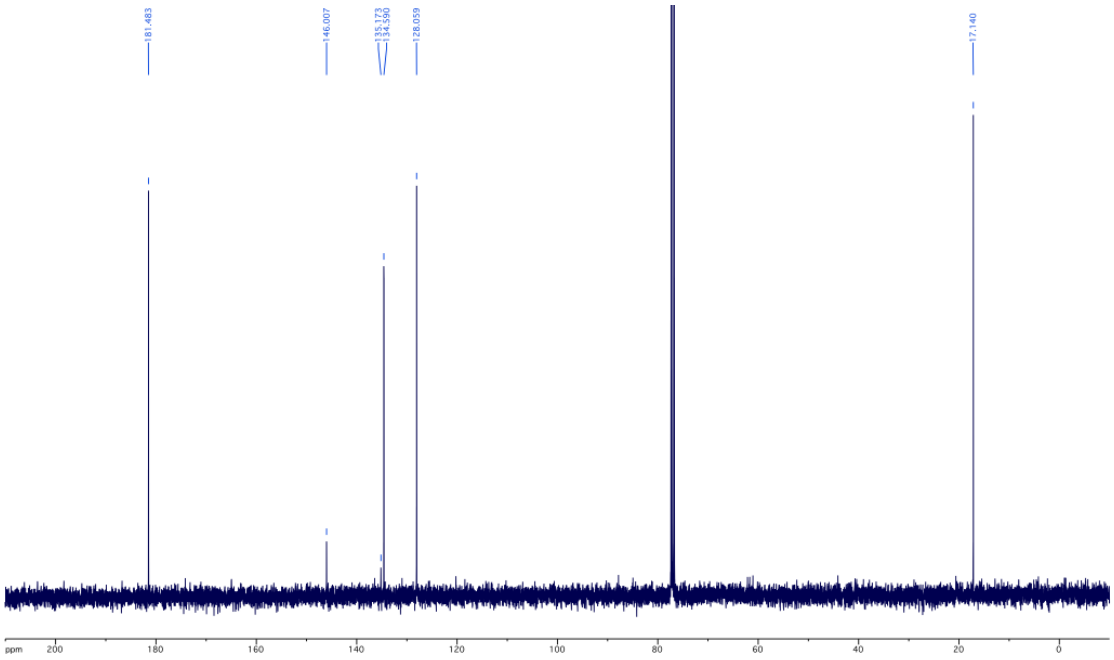
Aldehyde 90: ^{1}H NMR (400 MHz, $CDCl_3$)





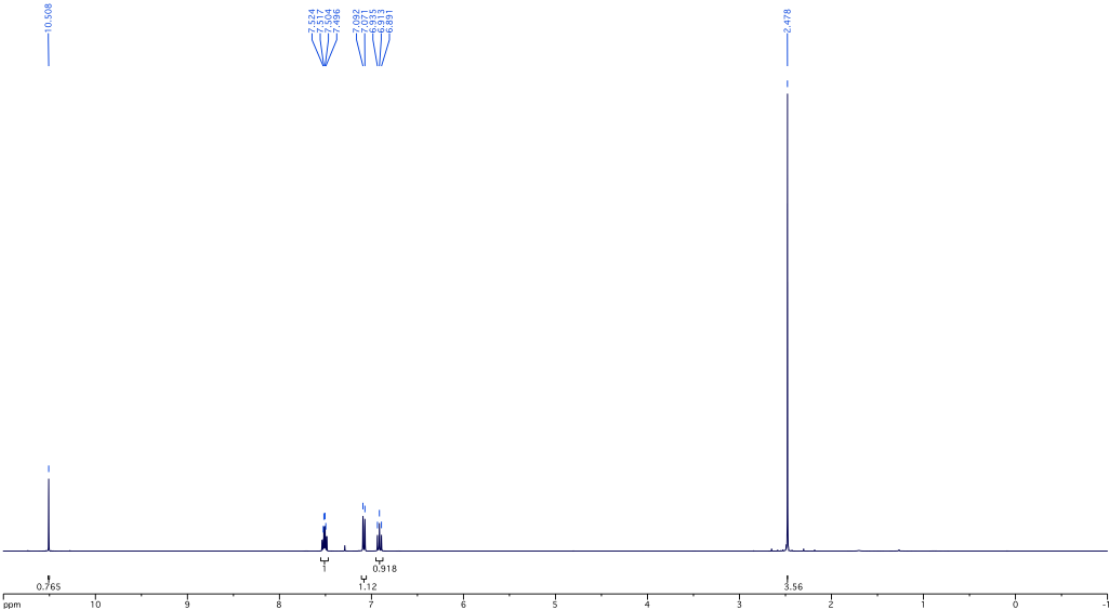
Aldehyde 90: ^{13}C NMR (101 MHz, $CDCl_3$)





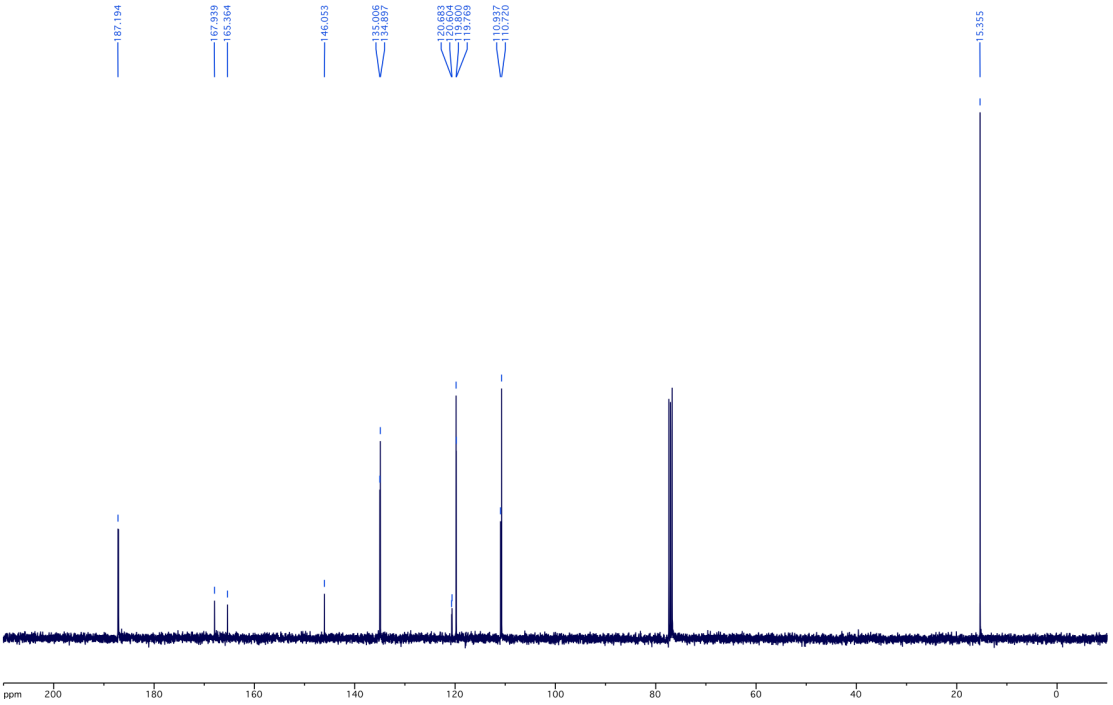
Aldehyde 92: ^{1}H NMR (400 MHz, $CDCl_3$)



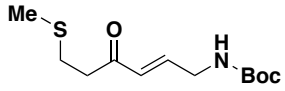


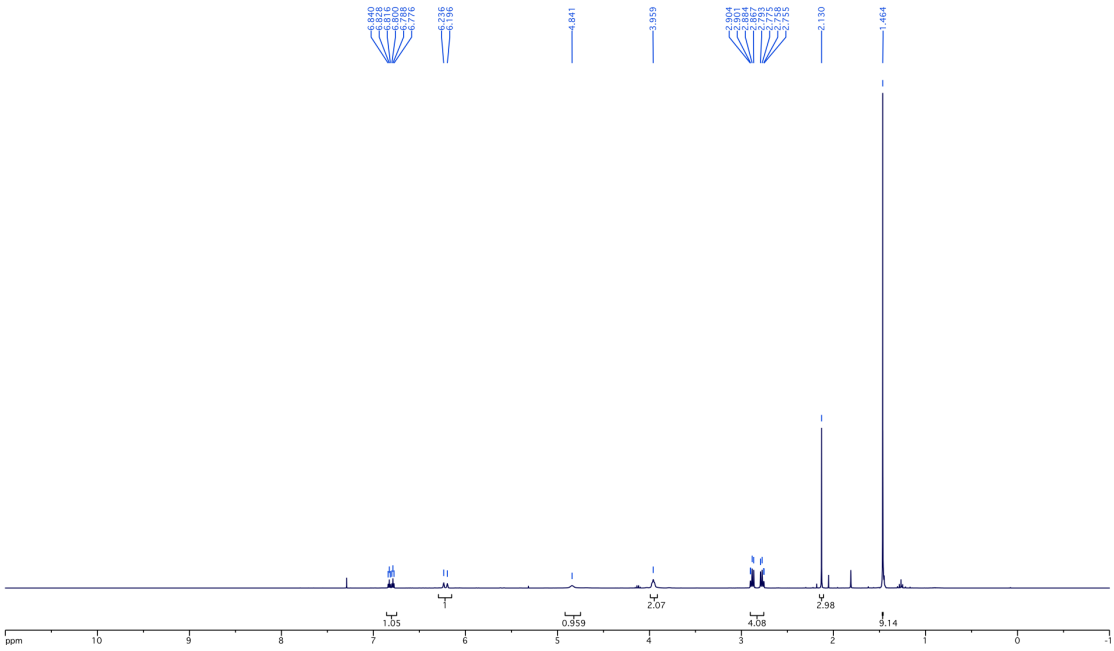
Aldehyde 92: ^{13}C NMR (101 MHz, $CDCl_3$)



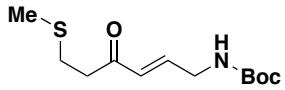


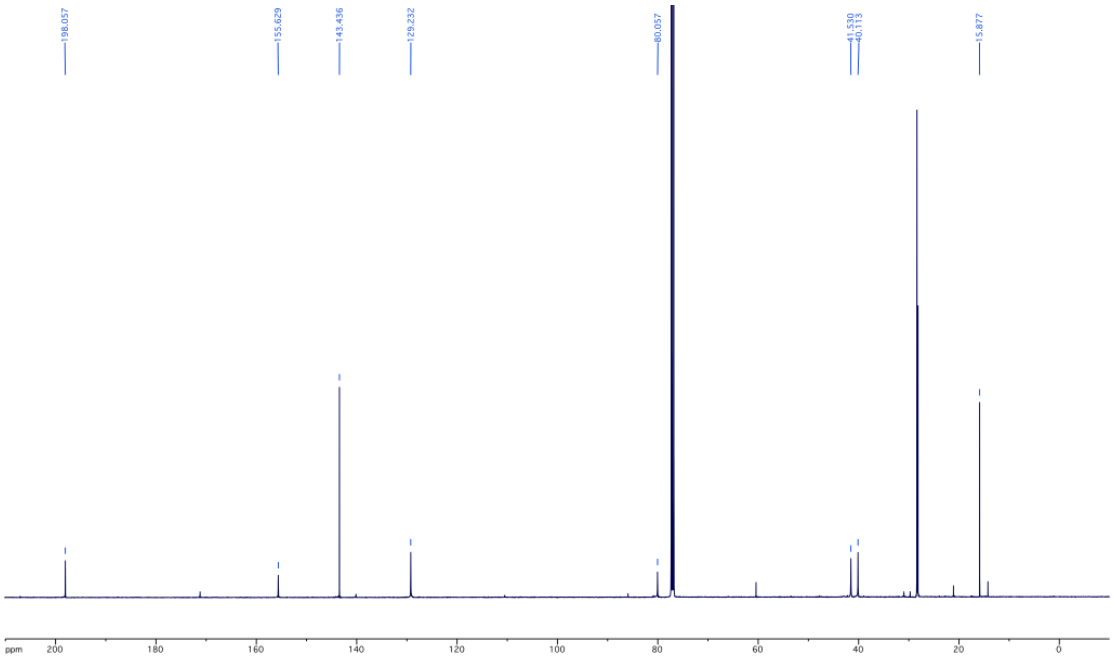
γ-Amino enone 96a: ^{1}H NMR (400 MHz, $CDCl_3$)



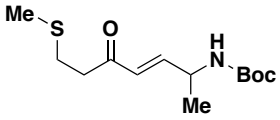


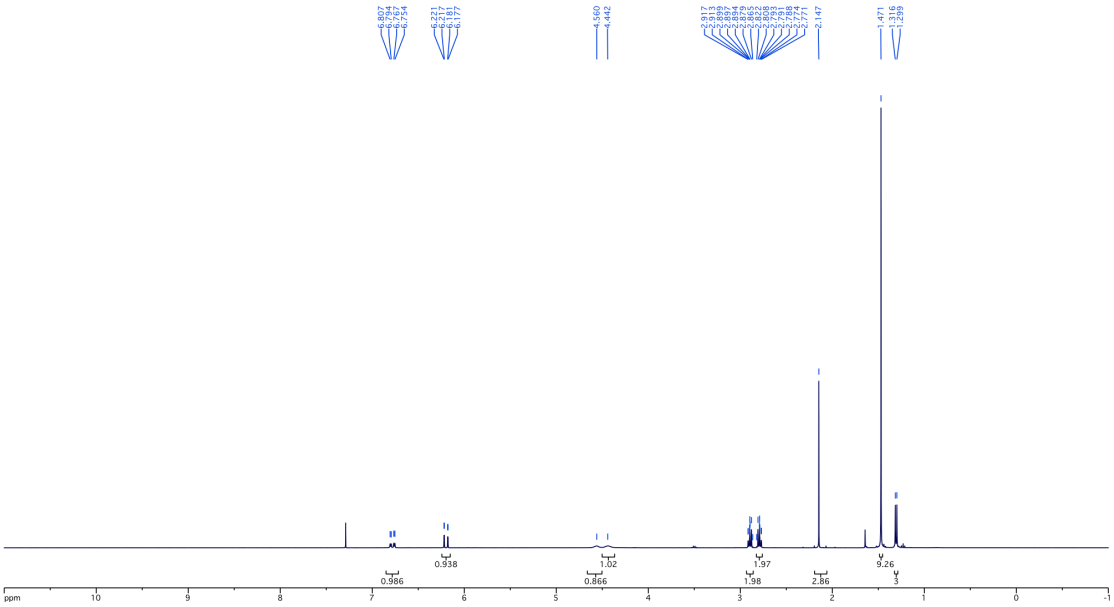
γ-Amino enone 96a: ^{13}C NMR (101 MHz, $CDCl_3$)



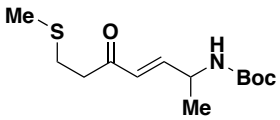


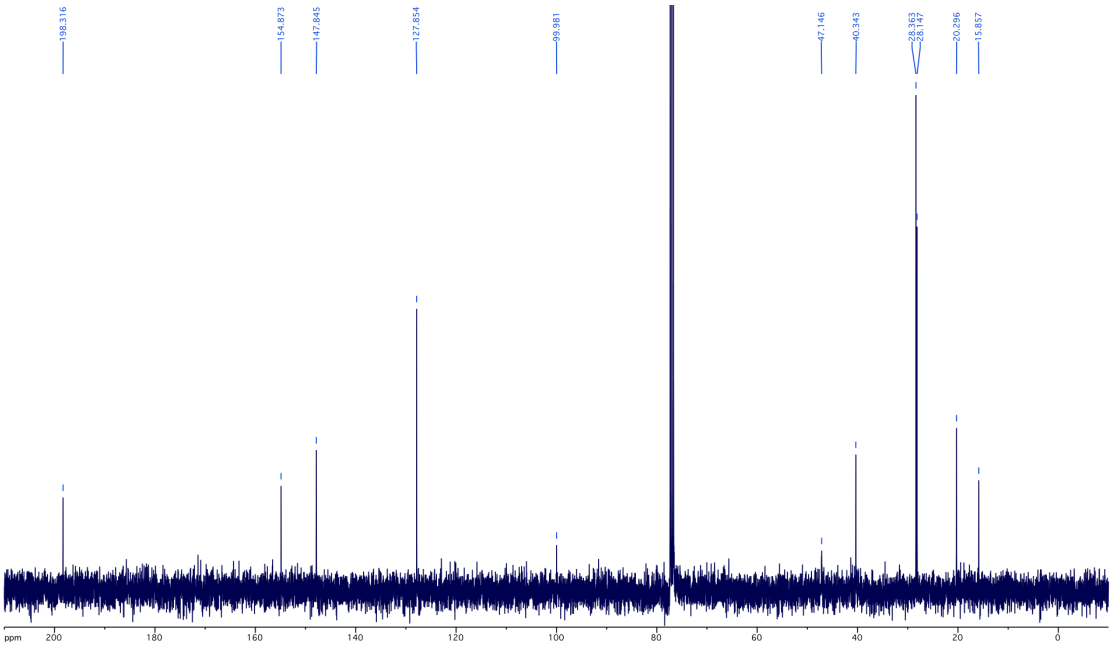
γ-Amino enone 97a: ^{1}H NMR (400 MHz, $CDCl_3$)



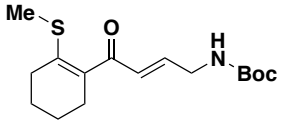


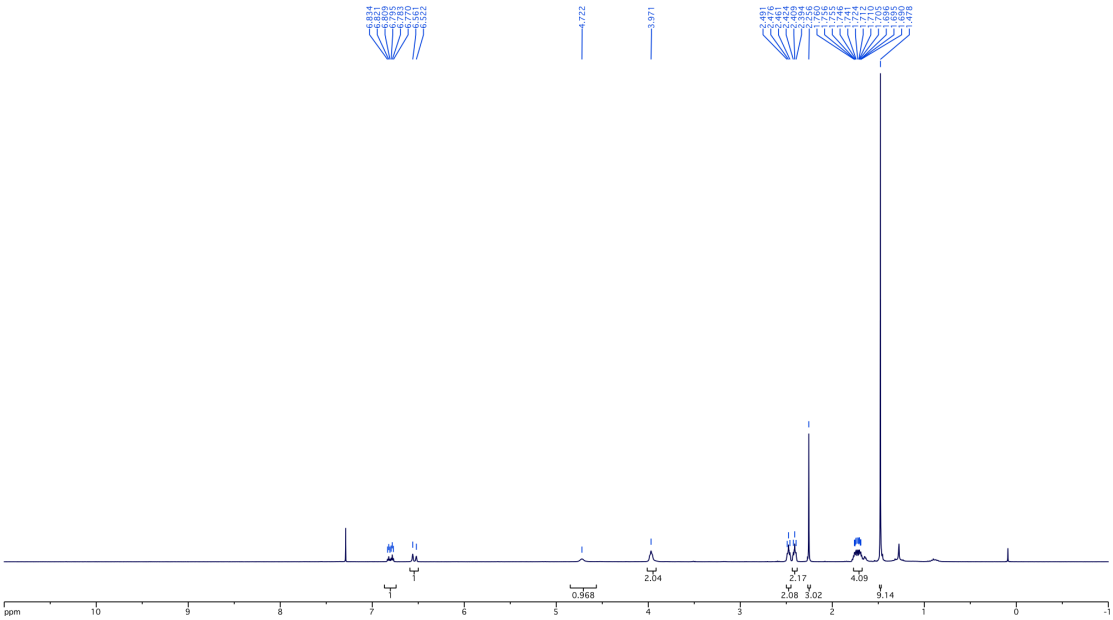
γ-Amino enone 97a: ^{13}C NMR (101 MHz, $CDCl_3$)



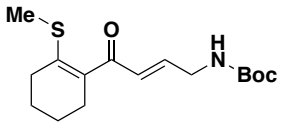


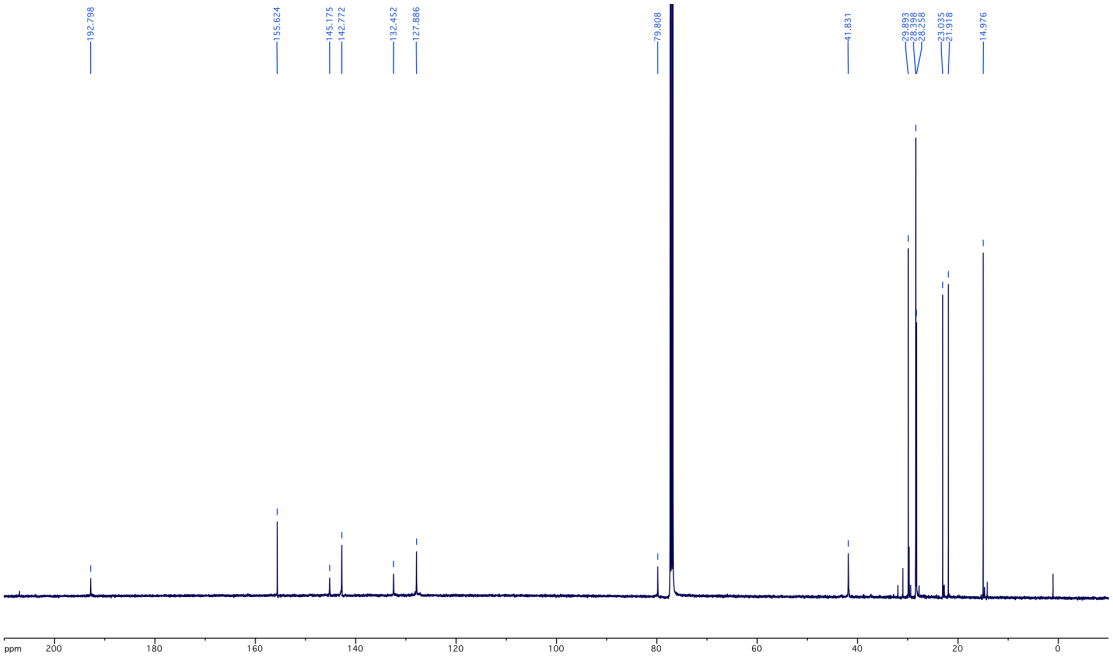
γ-Amino enone 98a: ^{1}H NMR (400 MHz, $CDCl_3$)



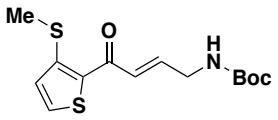


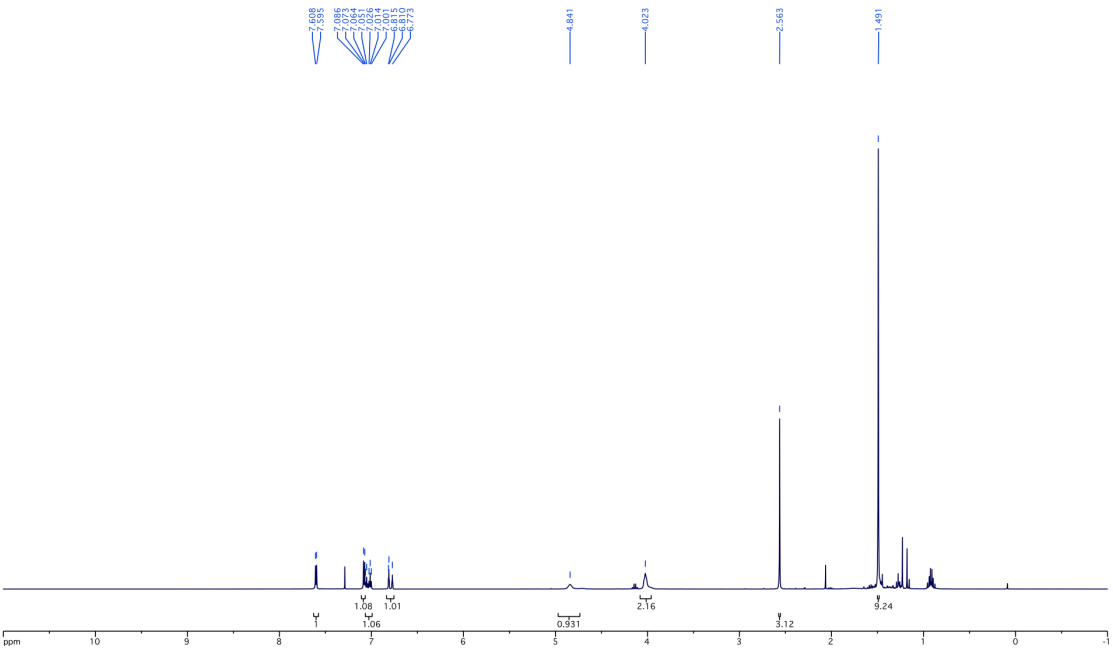
γ-Amino enone 98a: ^{13}C NMR (101 MHz, $CDCl_3$)



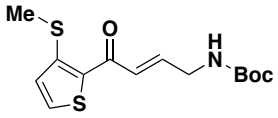


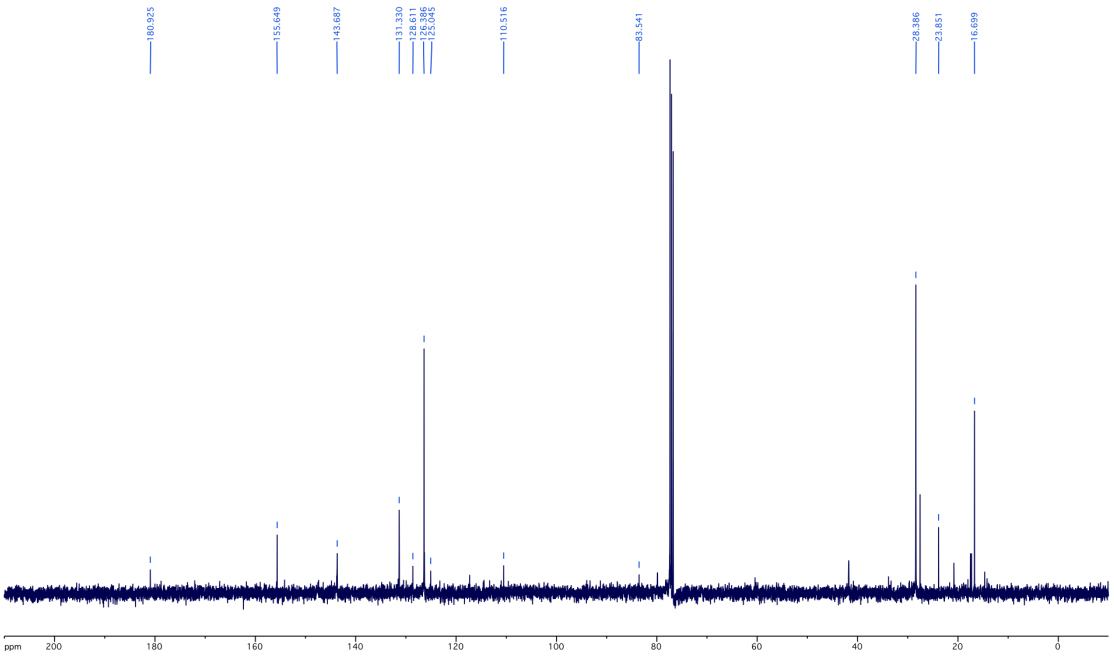
γ-Amino enone 99a: ^{1}H NMR (400 MHz, $CDCl_3$)



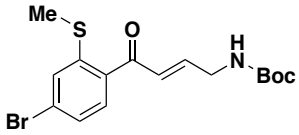


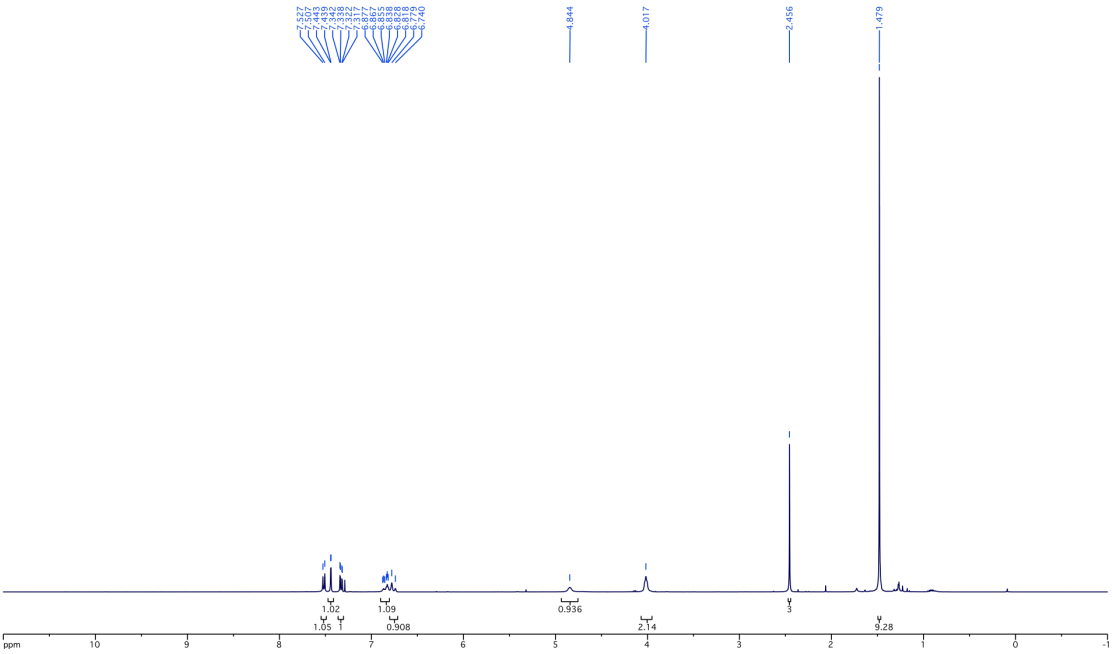
γ-Amino enone 99a: ^{13}C NMR (101 MHz, $CDCl_3$)



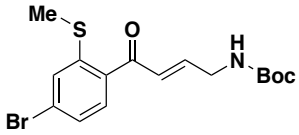


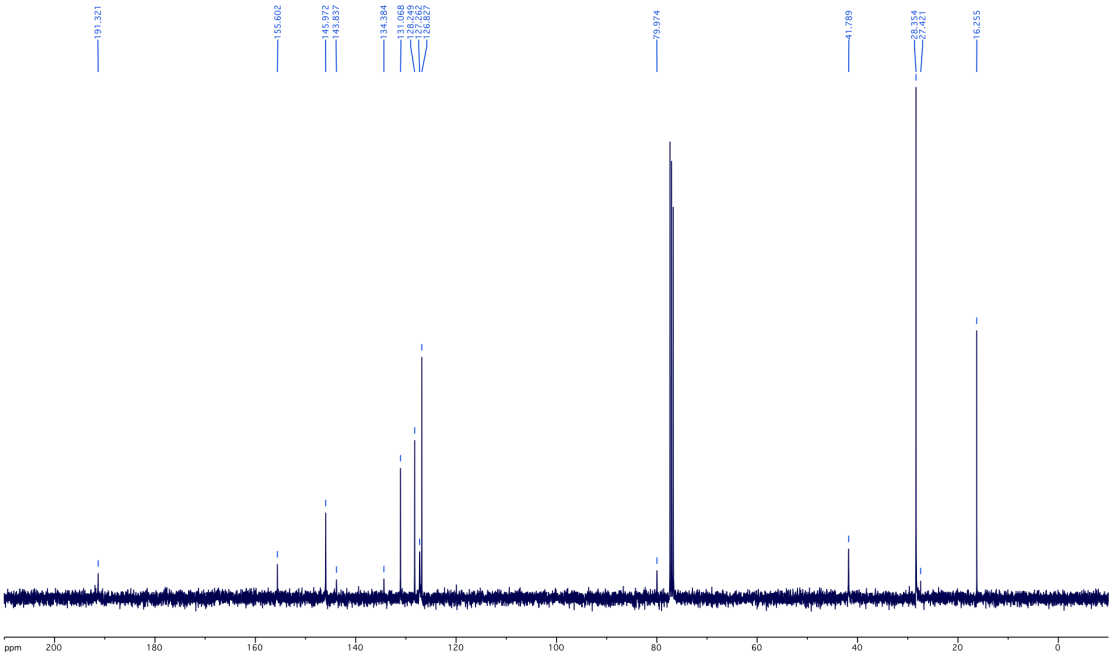
γ-Amino enone 100a: ^{1}H NMR (400 MHz, $CDCl_3$)



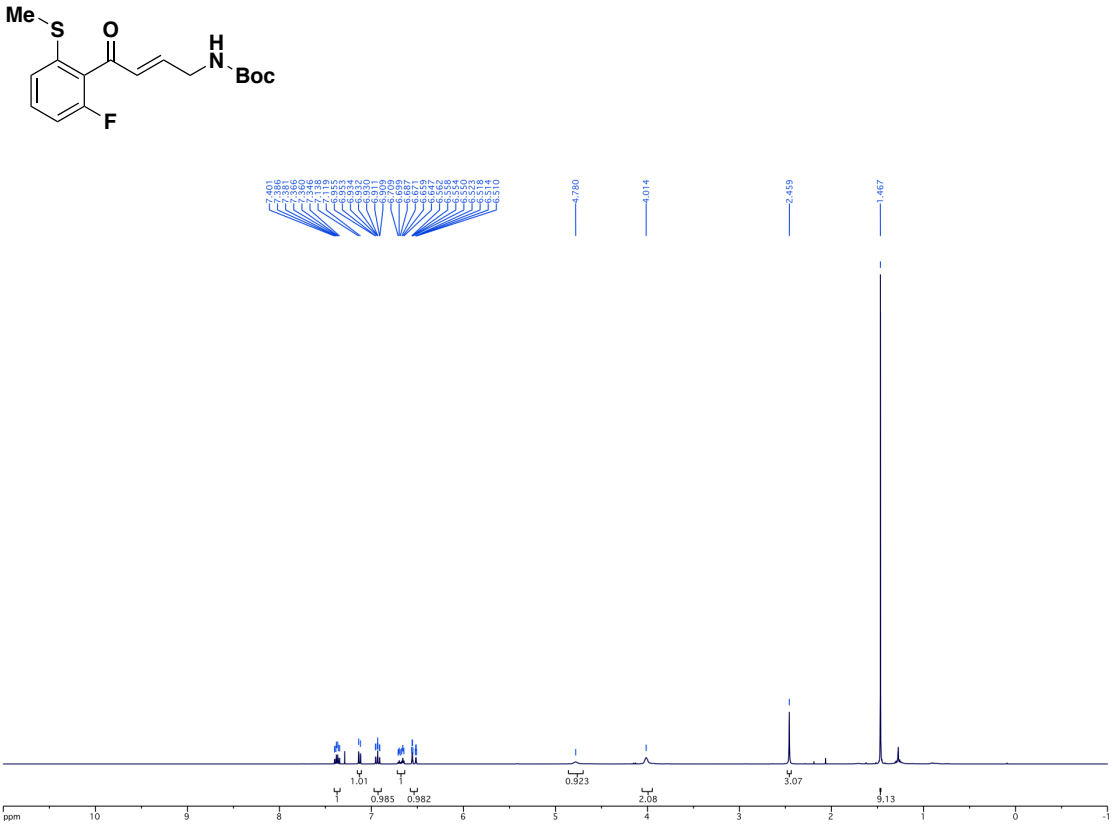


γ-Amino enone 100a: ^{13}C NMR (101 MHz, $CDCl_3$)

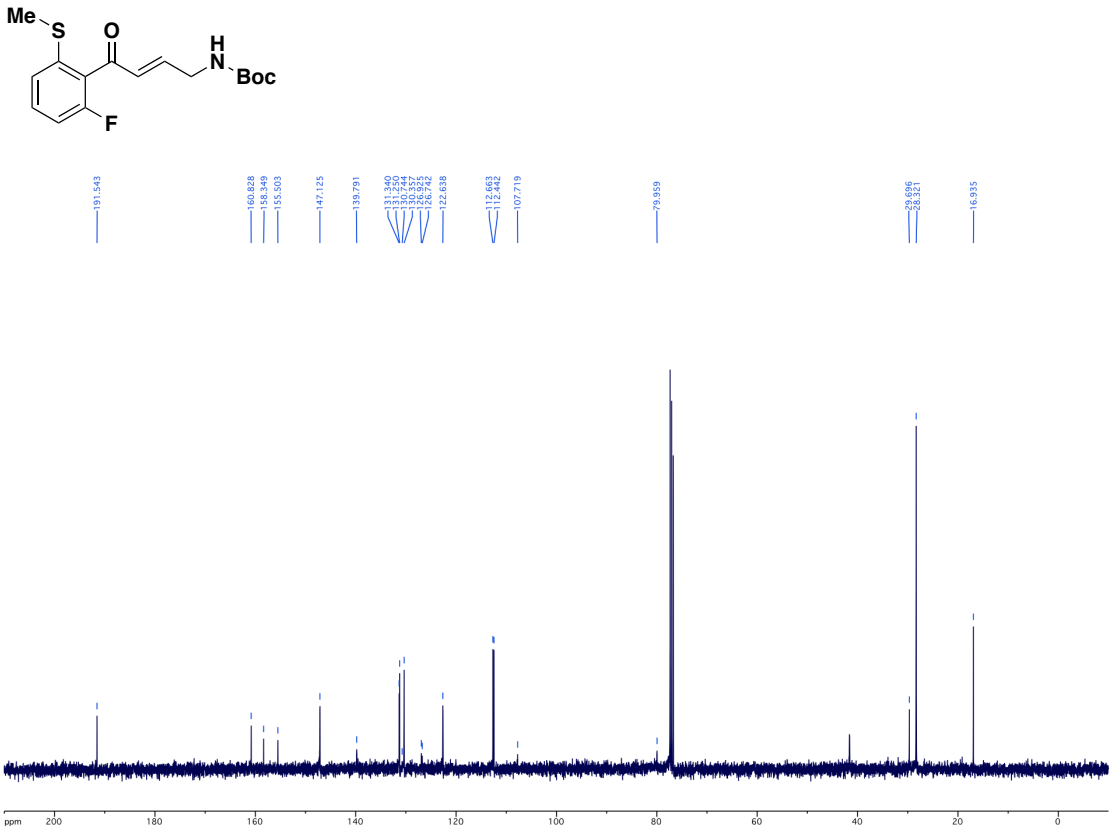




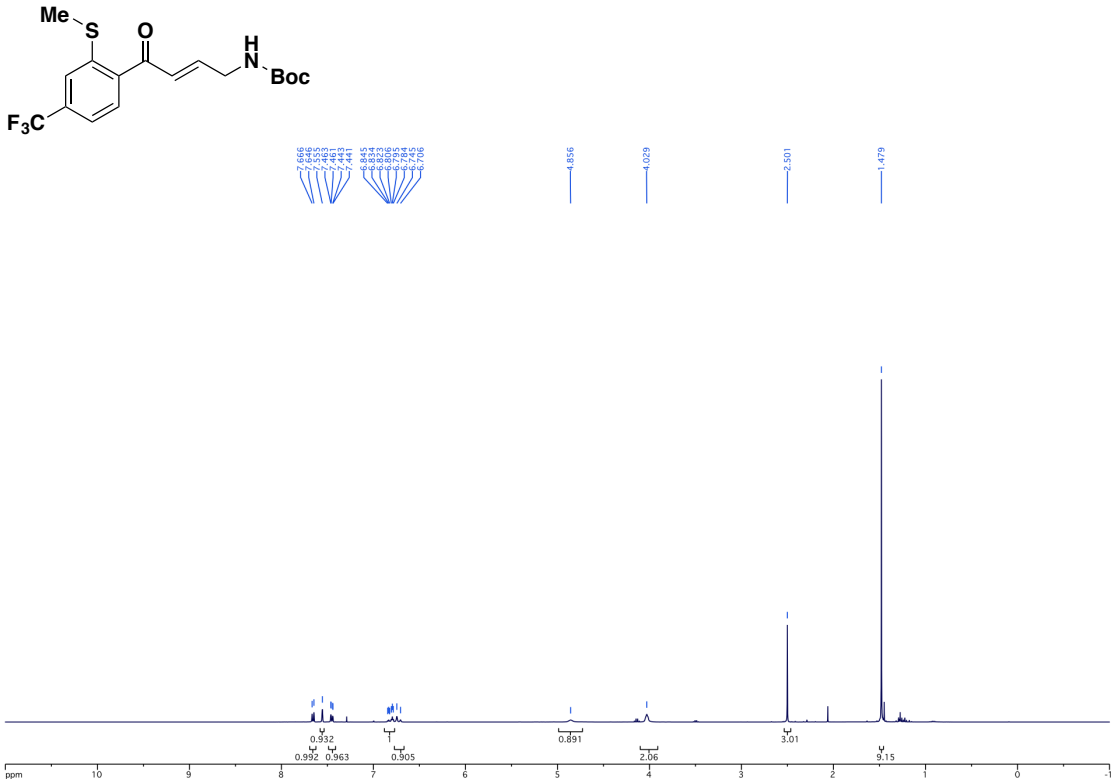
γ-Amino enone 101a: ^{1}H NMR (400 MHz, $CDCl_3$)



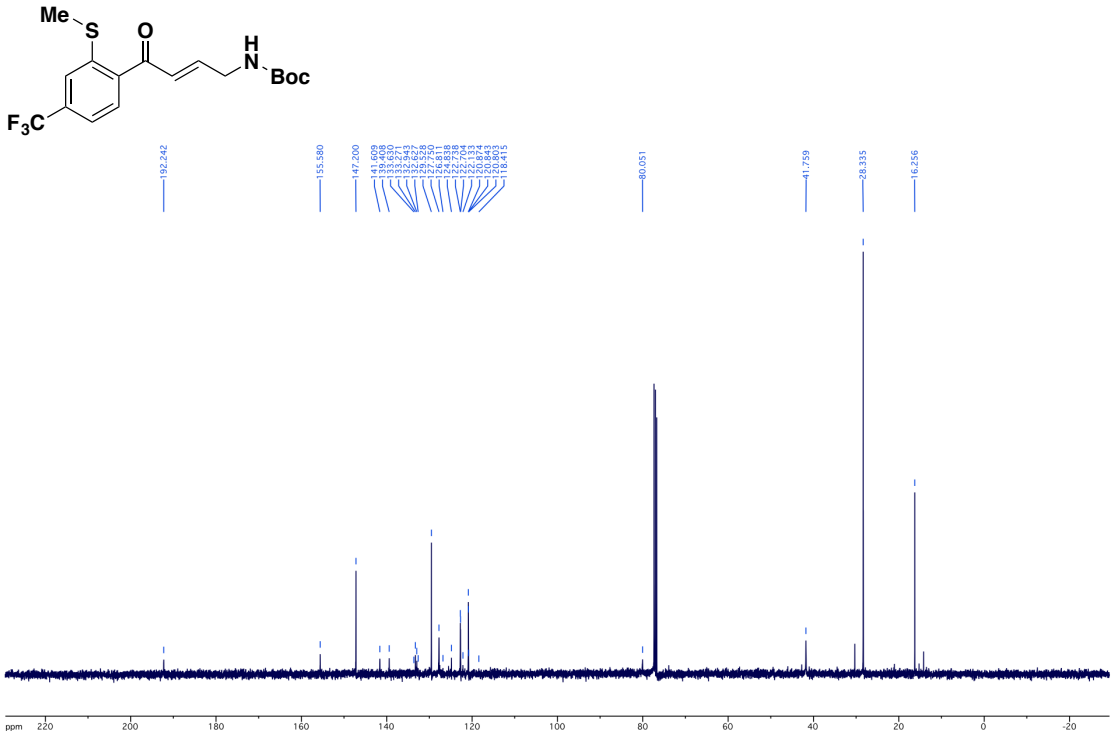
γ-Amino enone 101a: ^{13}C NMR (101 MHz, $CDCl_3$)



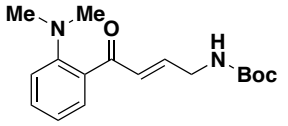
γ-Amino enone 102a: ^{1}H NMR (400 MHz, $CDCl_3$)

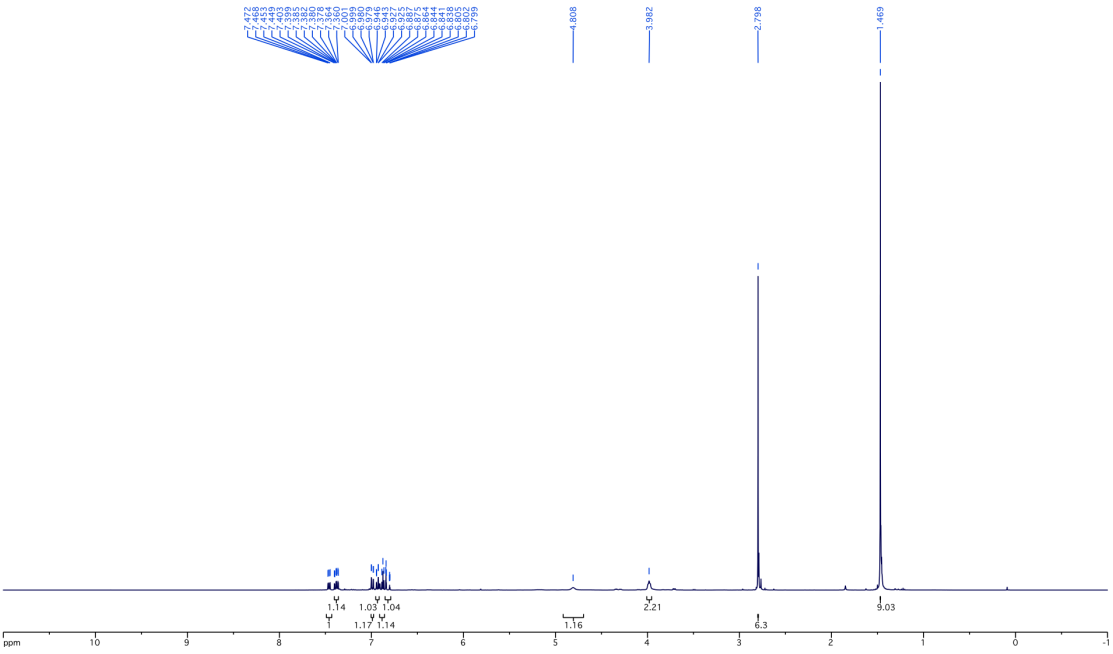


γ-Amino enone 102a: ^{13}C NMR (101 MHz, $CDCl_3$)

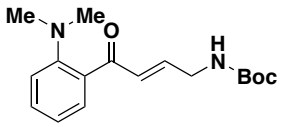


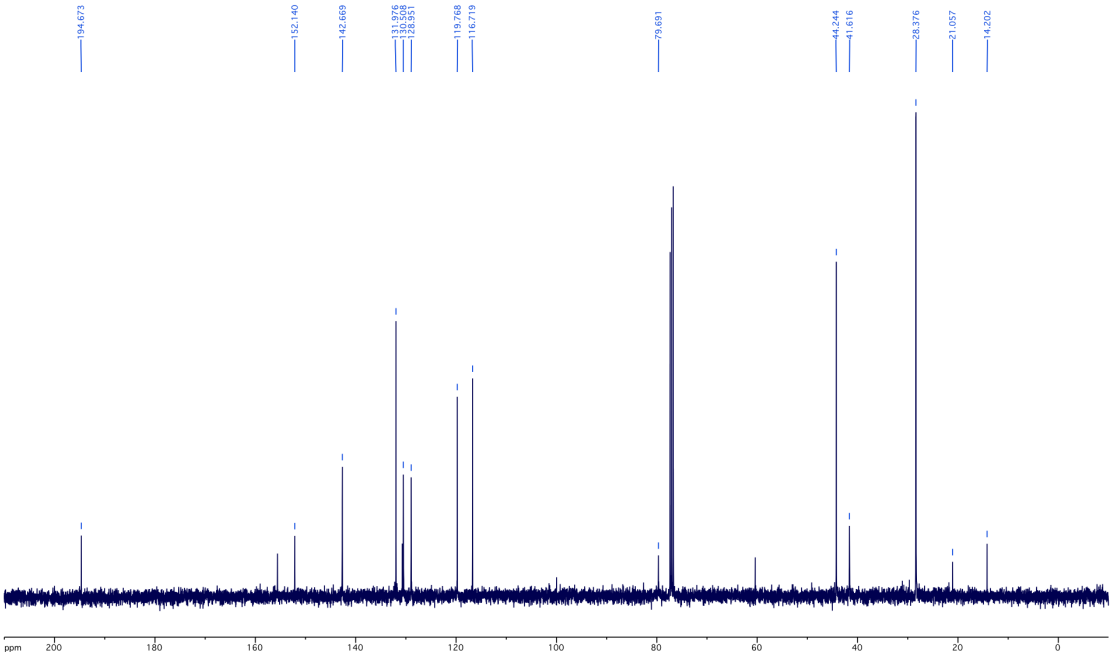
γ-Amino enone 104a: ^{1}H NMR (400 MHz, $CDCl_3$)



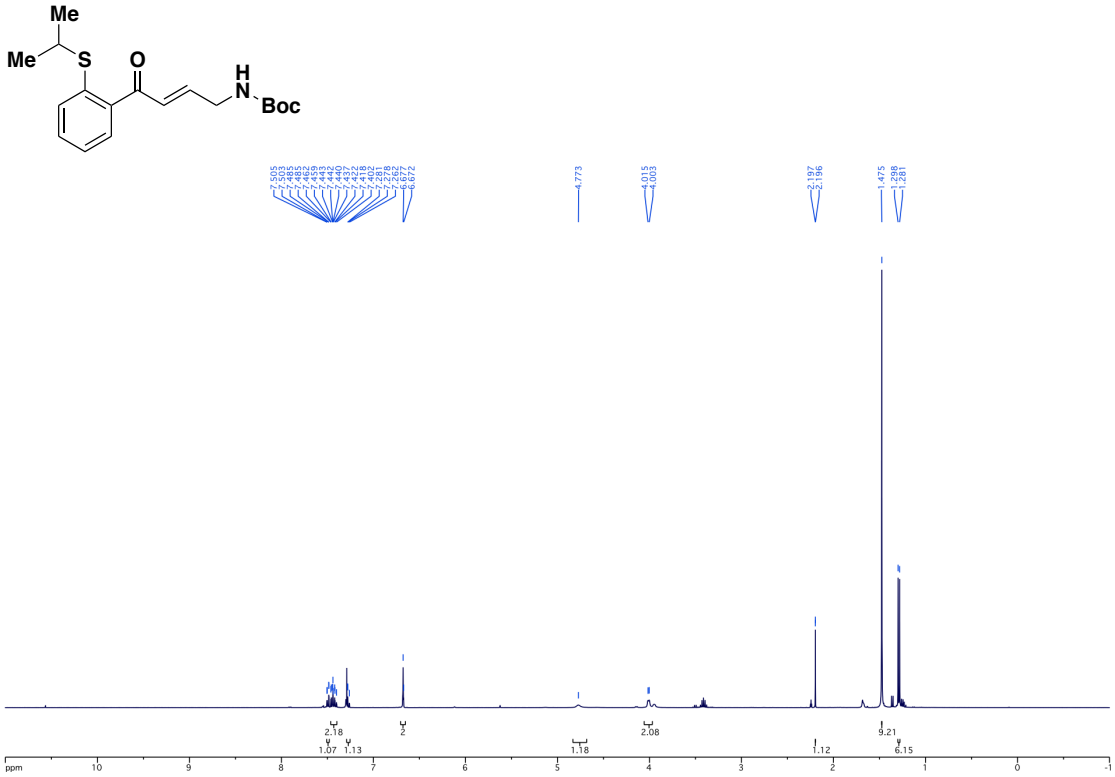


γ-Amino enone 104b: ^{13}C NMR (101 MHz, $CDCl_3$)

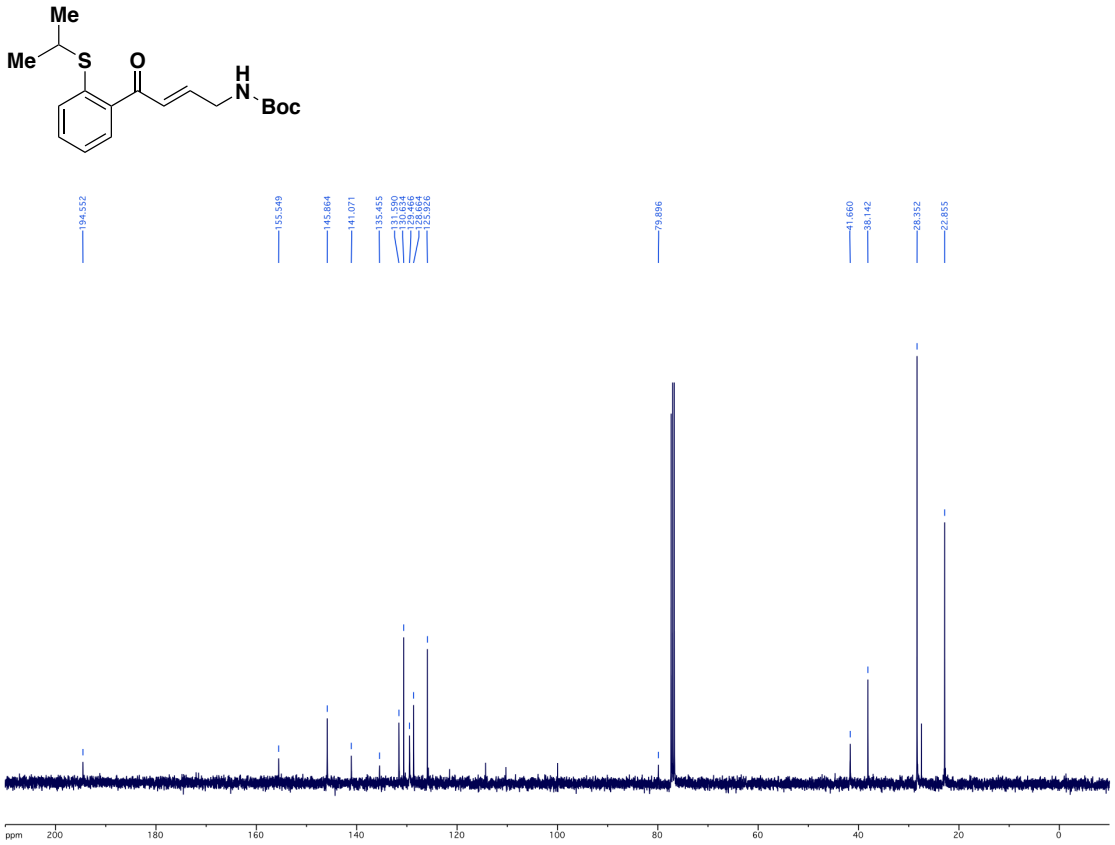




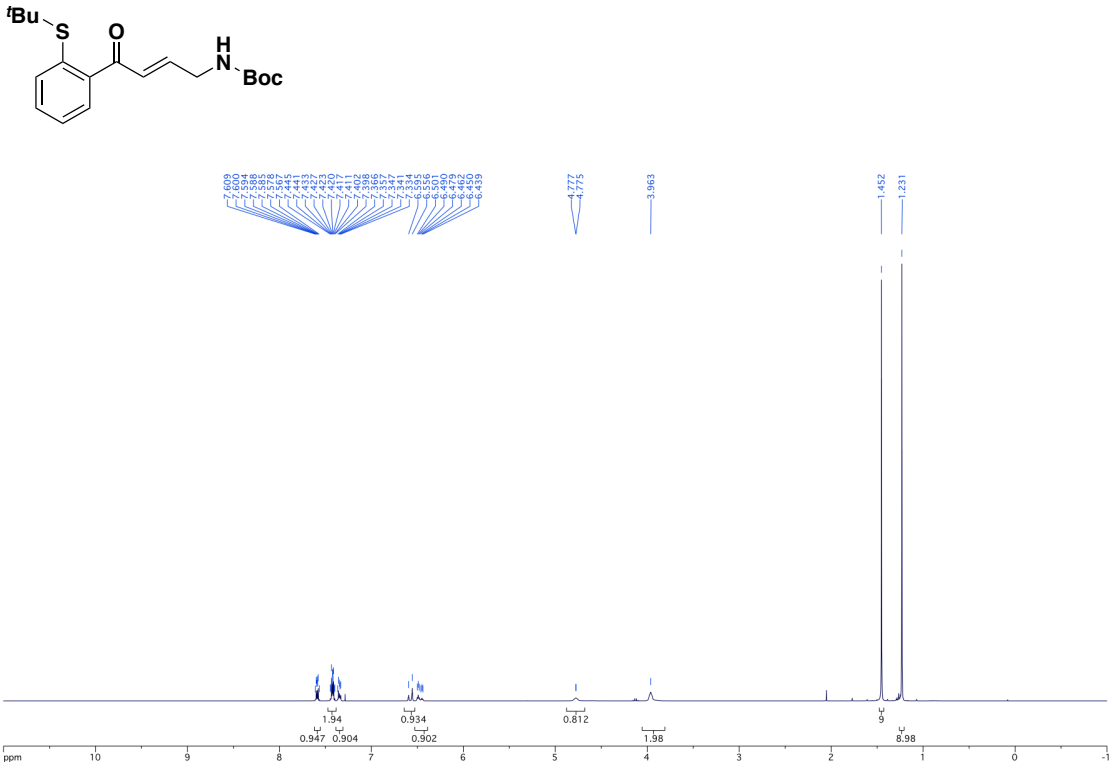
γ-Amino enone 108a: ^{1}H NMR (400 MHz, $CDCl_3$)



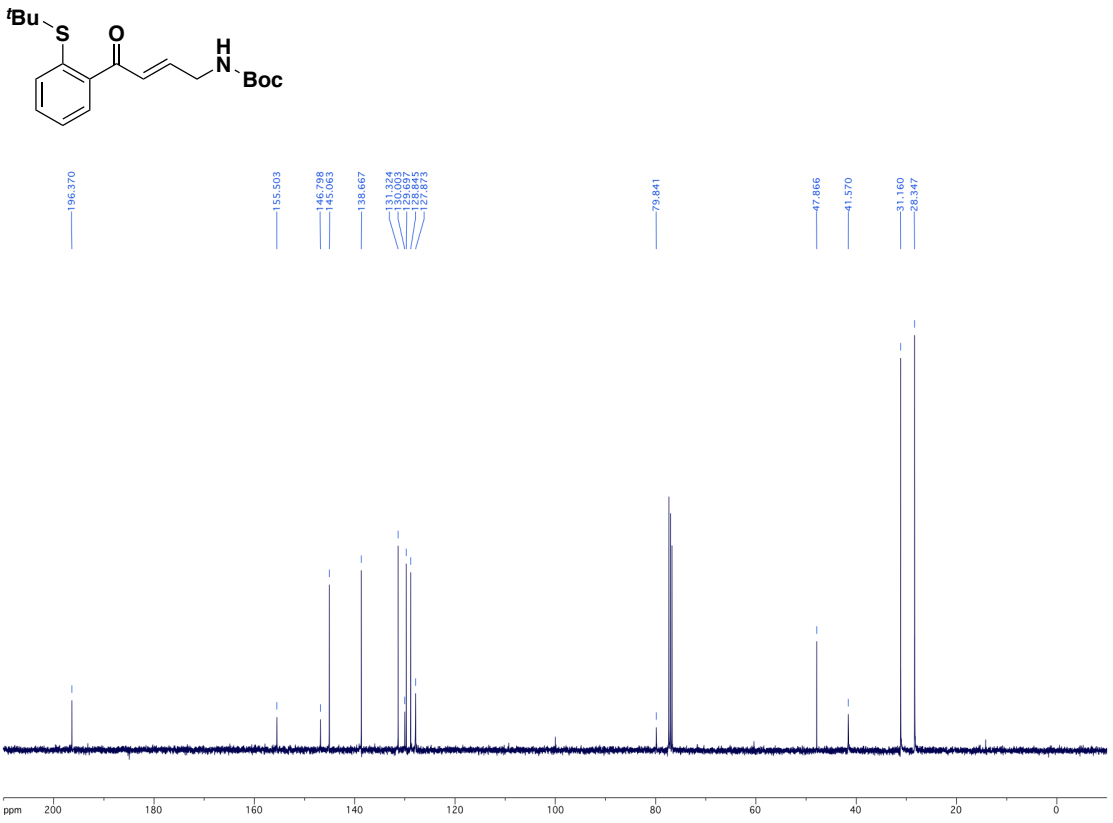
γ-Amino enone 108a: ^{13}C NMR (101 MHz, $CDCl_3$)



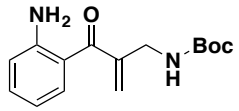
γ-Amino none 109a: ^{1}H NMR (400 MHz, $CDCl_3$)

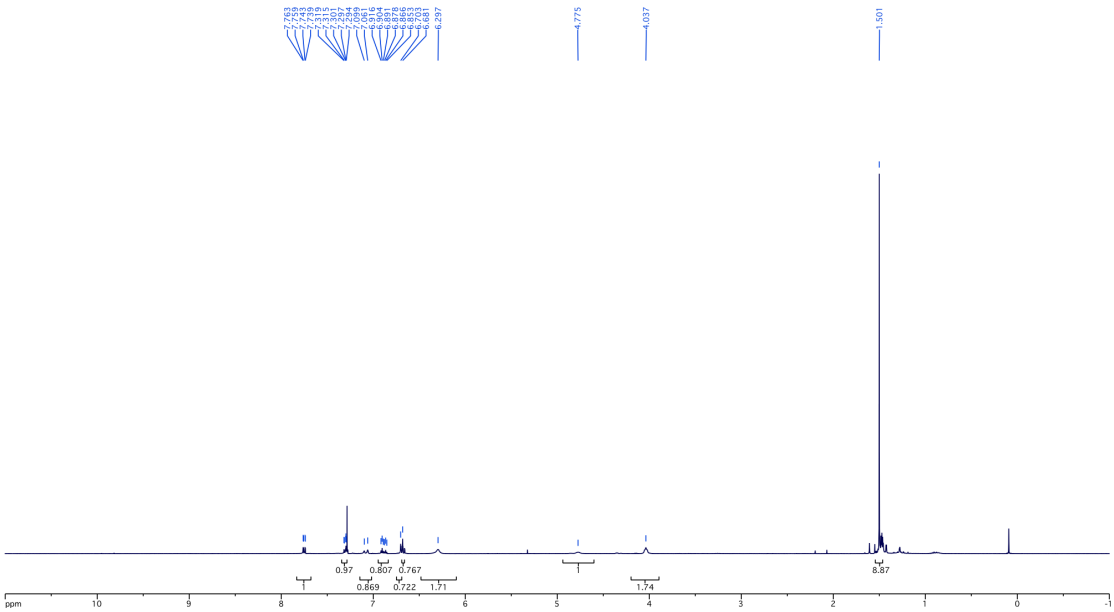


γ-Amino none 109a: ^{13}C NMR (100 MHz, $CDCl_3$)

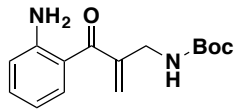


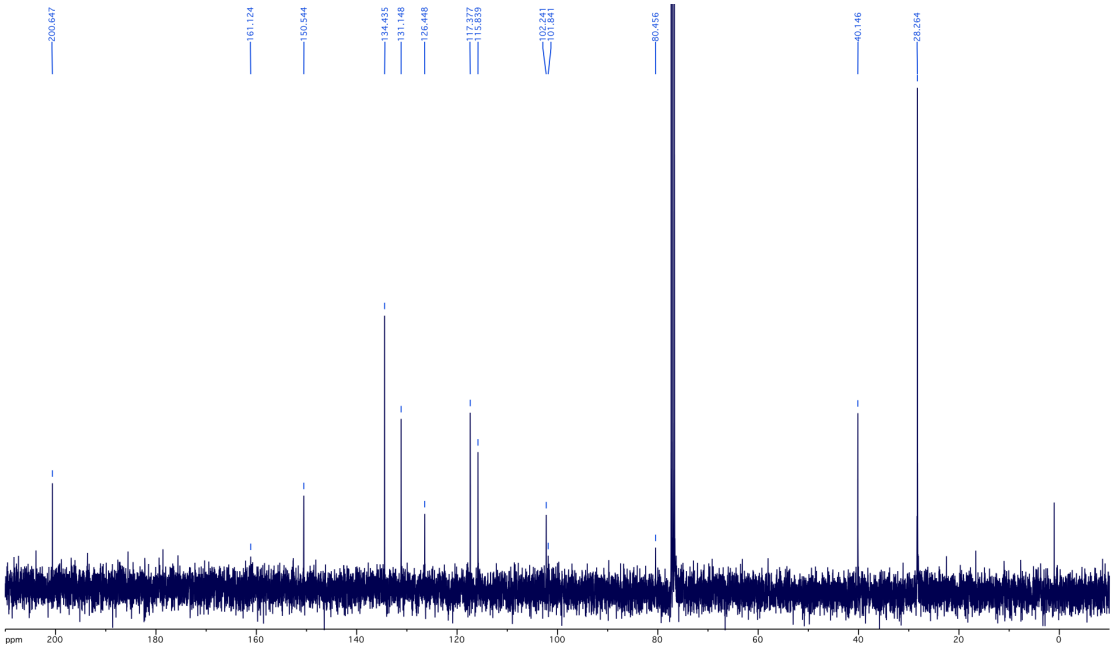
γ-Amino enone 110b: ^{1}H NMR (400 MHz, $CDCl_3$)



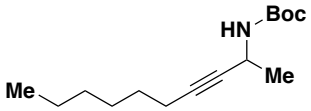


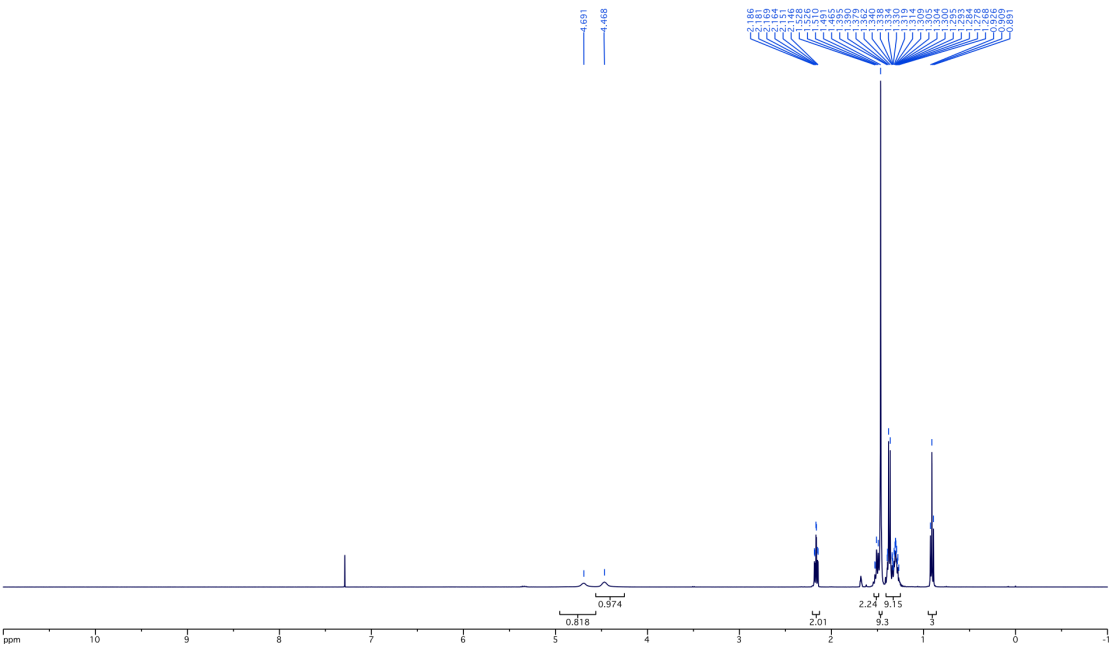
γ-Amino enone 110b: ^{13}C NMR (101 MHz, $CDCl_3$)



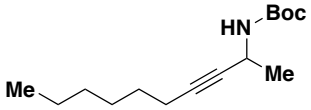


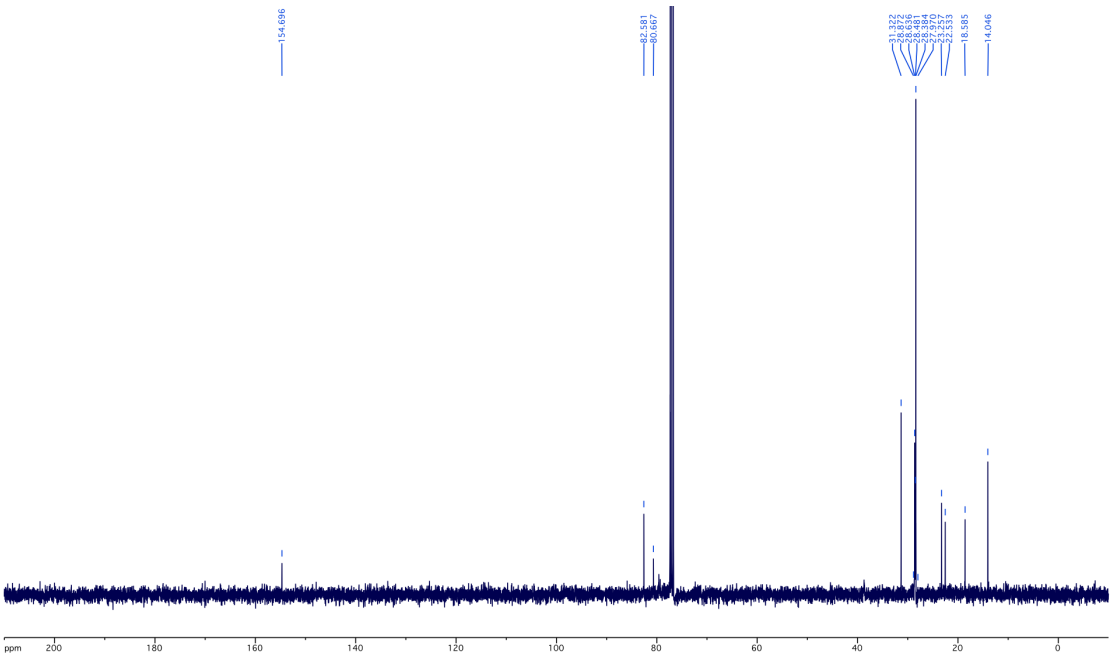
Propargylic amine 111: ^{1}H NMR (400 MHz, $CDCl_3$)



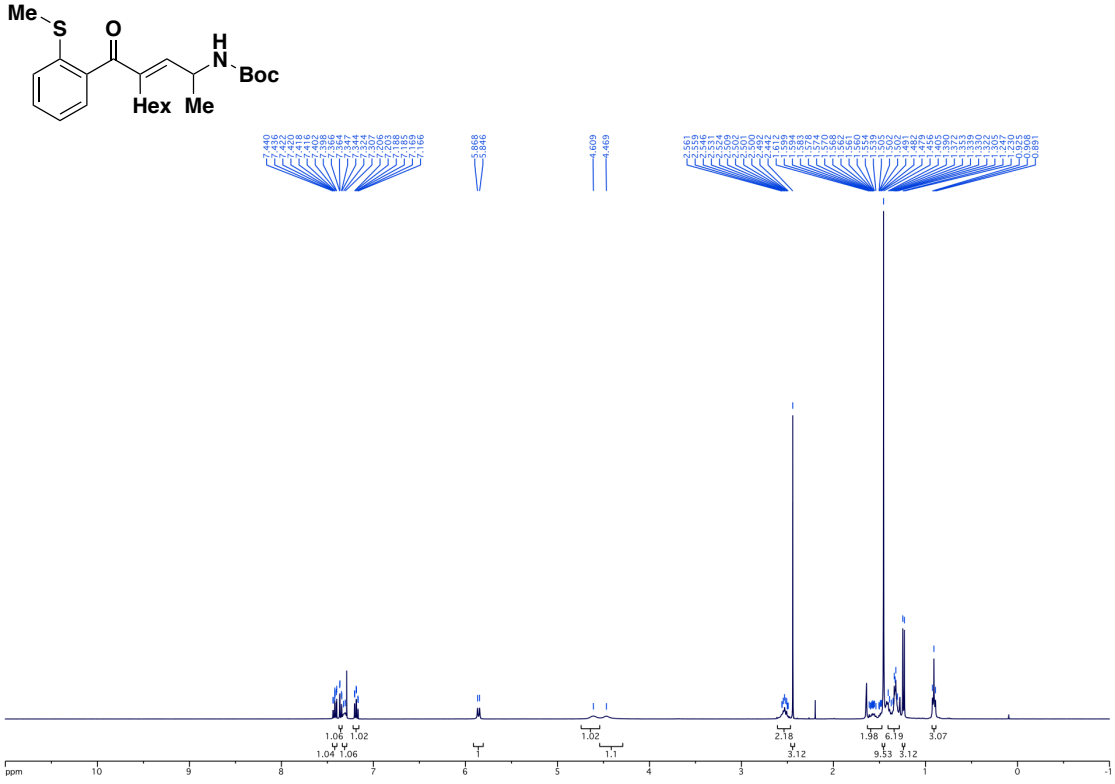


Propargylic amine 111: ^{13}C NMR (101 MHz, $CDCl_3$)

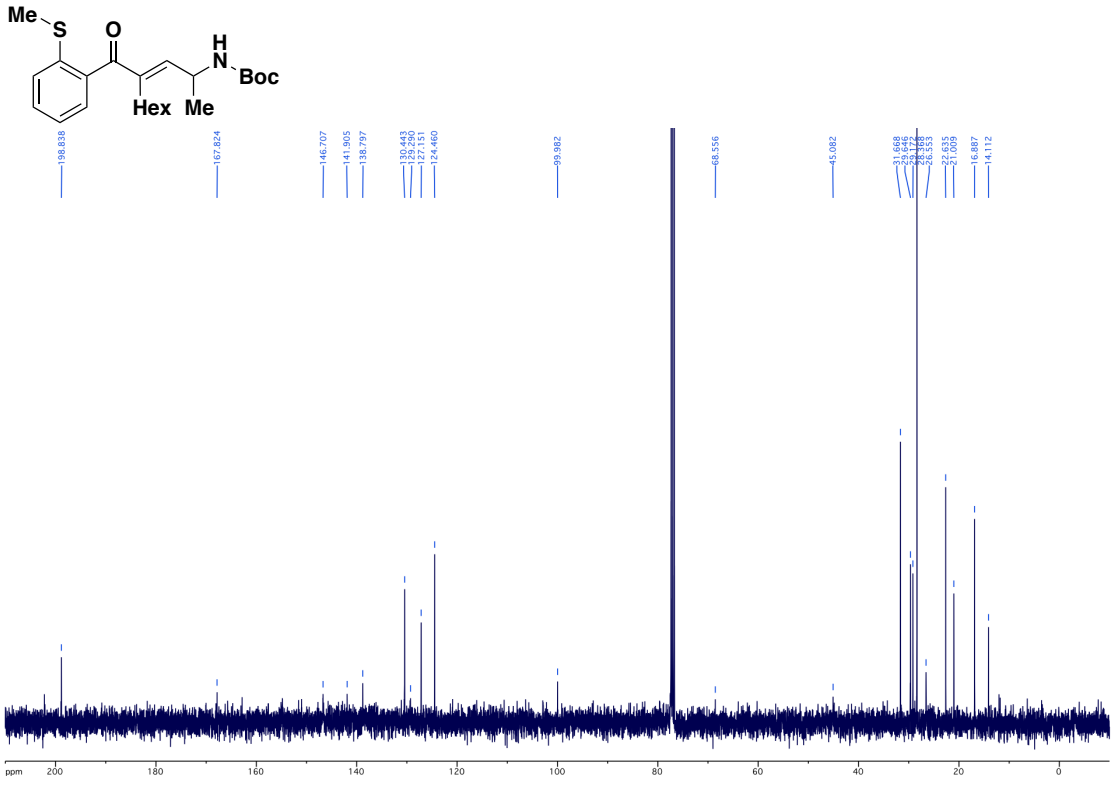




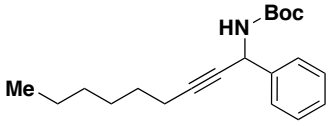
γ-Amino enone 112a: ^{1}H NMR (400 MHz, $CDCl_3$)

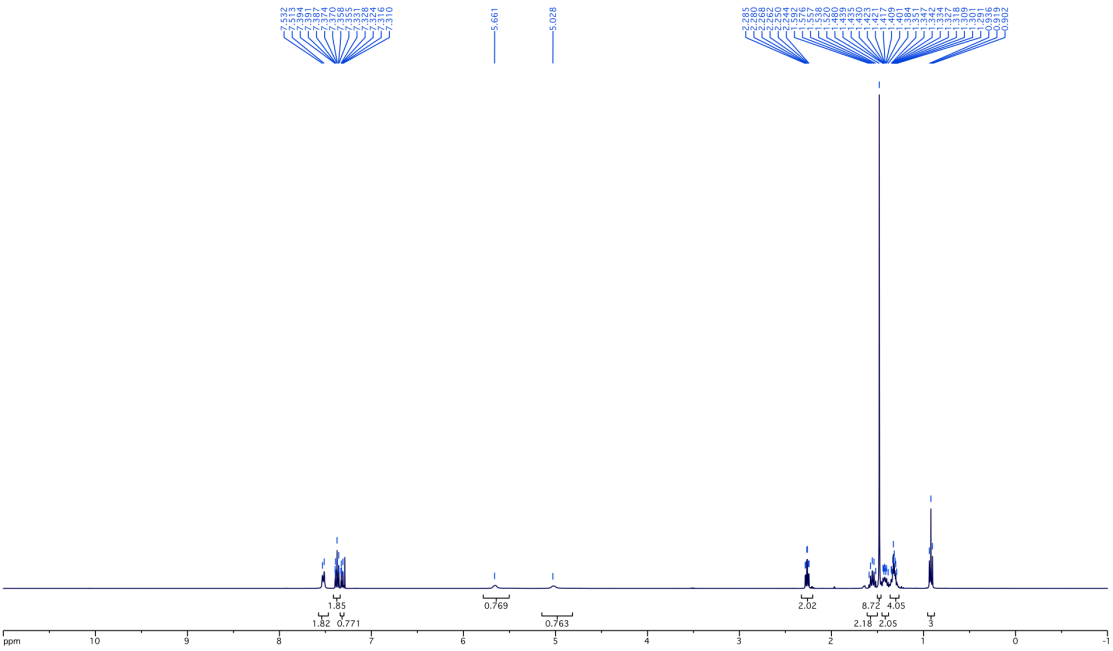


γ-Amino enone 112a: ^{13}C NMR (101 MHz, $CDCl_3$)

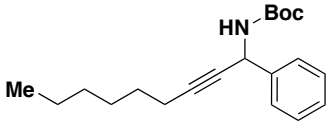


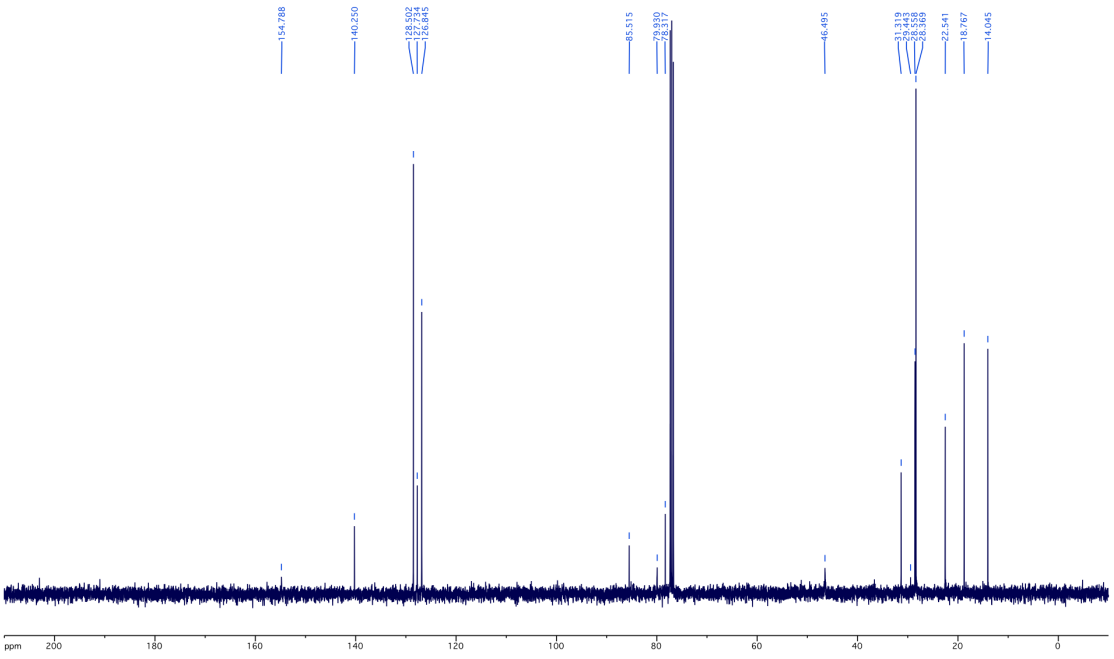
Propargylic Amine 113: ^{1}H NMR (400 MHz, $CDCl_3$)



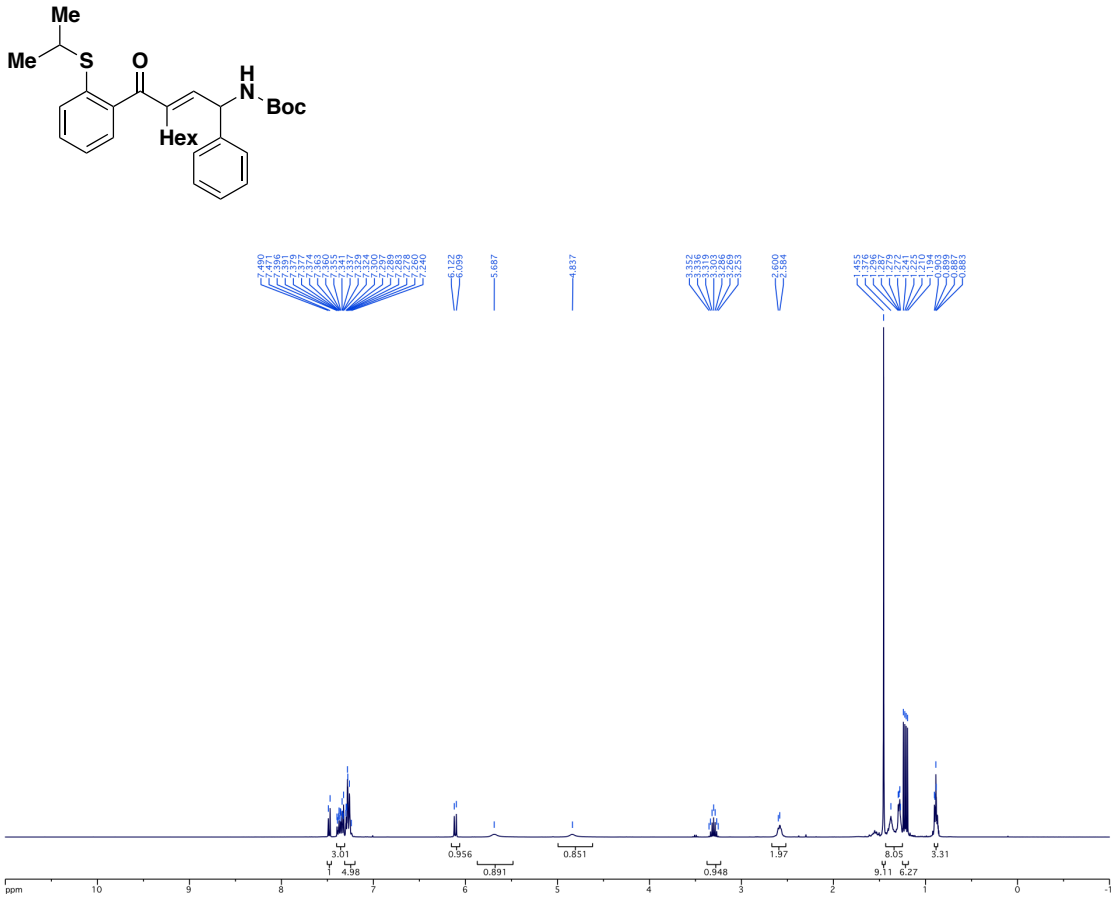


Propargylic Amine 113: ^{13}C NMR (101 MHz, $CDCl_3$)

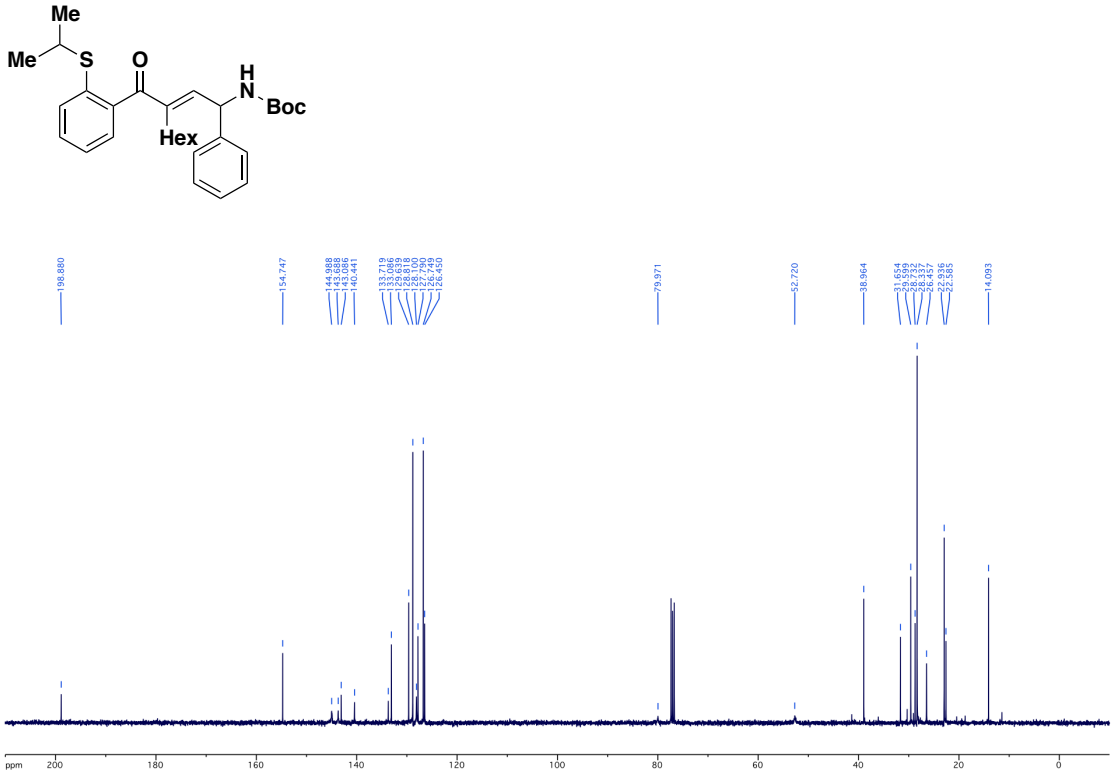




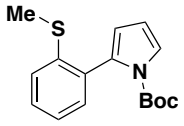
γ-Amino enone 114a: ^{1}H NMR (400 MHz, $CDCl_3$)

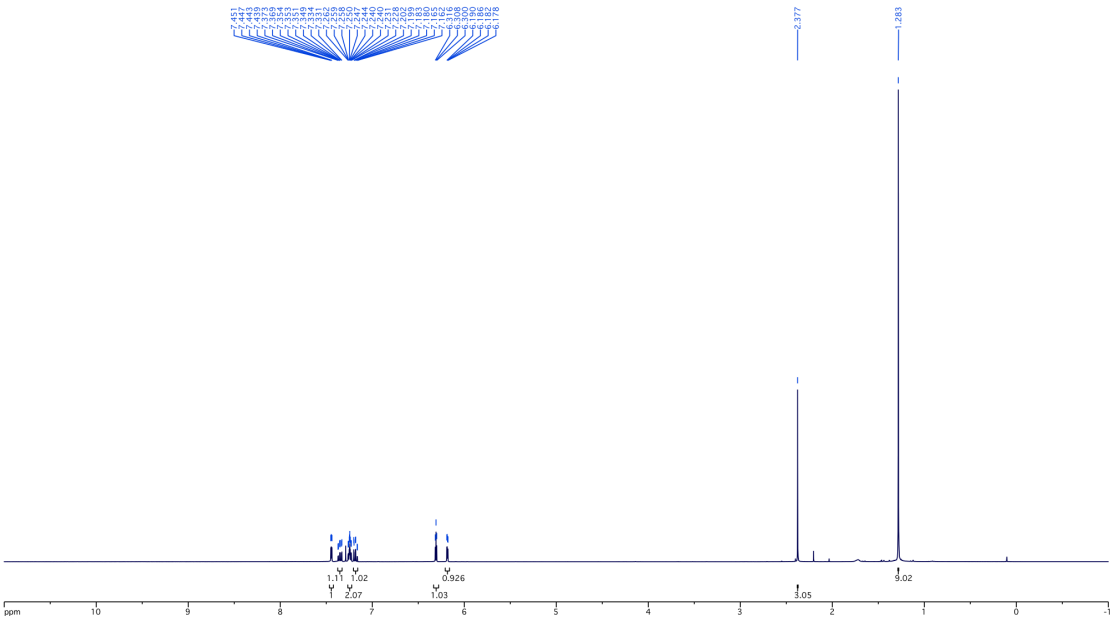


γ-Amino enone 114a: ^{13}C NMR (101 MHz, $CDCl_3$)

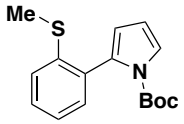


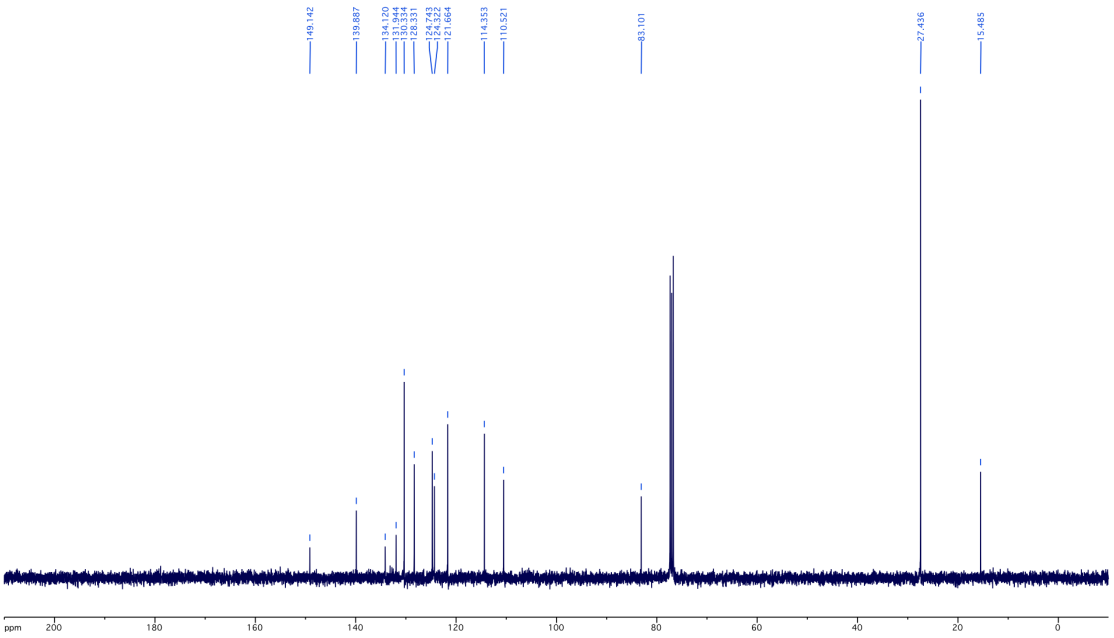
Pyrrole 115: ^{1}H NMR (400 MHz, $CDCl_3$)



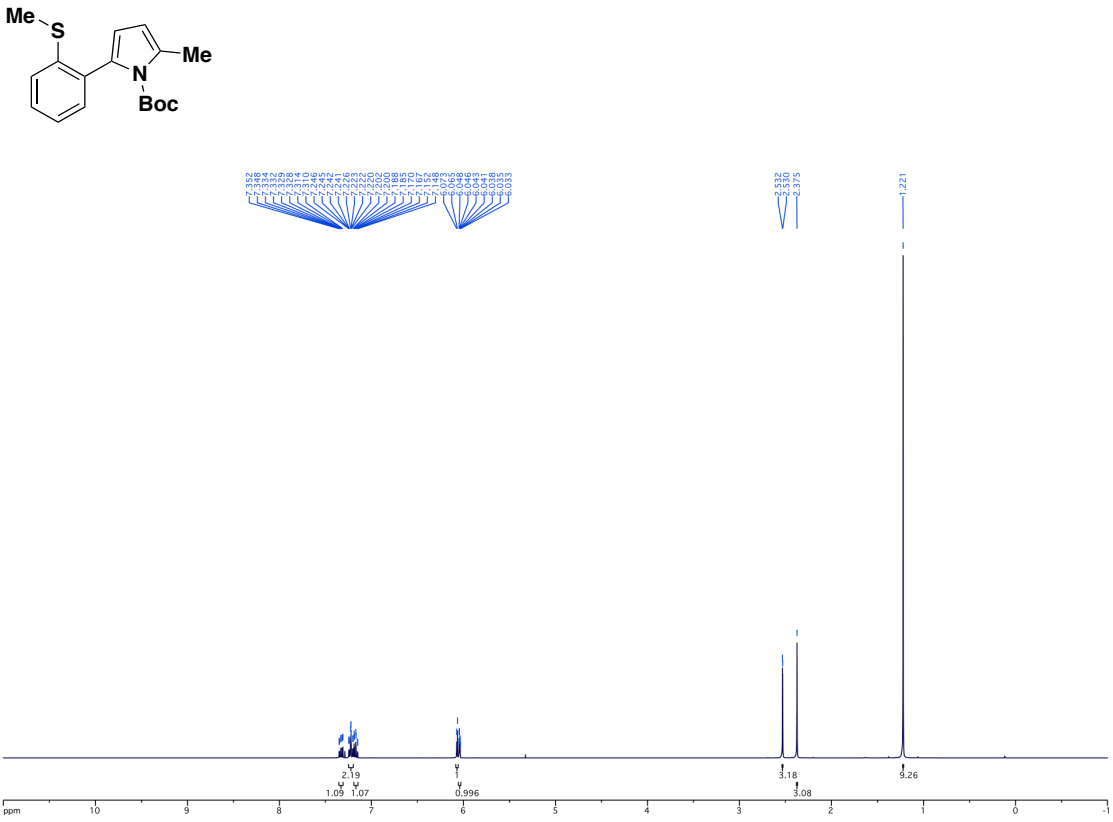


Pyrrole 115: ^{13}C NMR (101 MHz, $CDCl_3$)

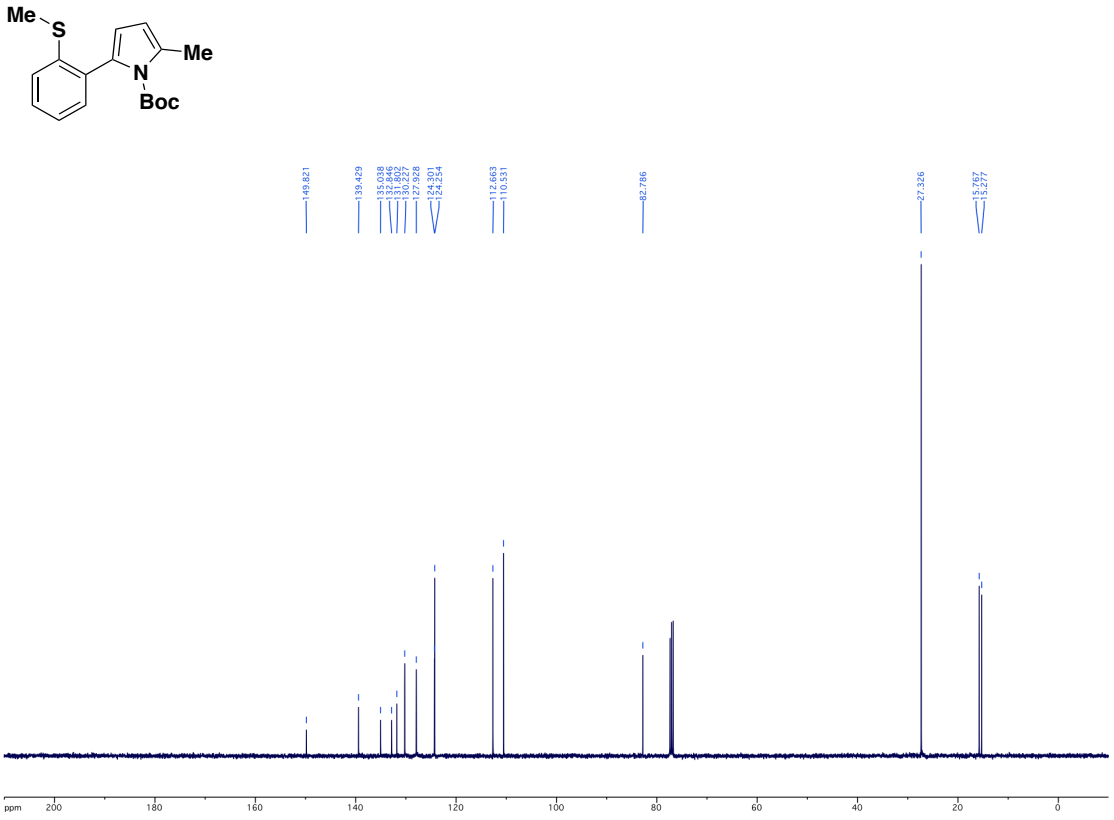




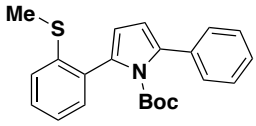
Pyrrole 116: ^{1}H NMR (400 MHz, $CDCl_3$)

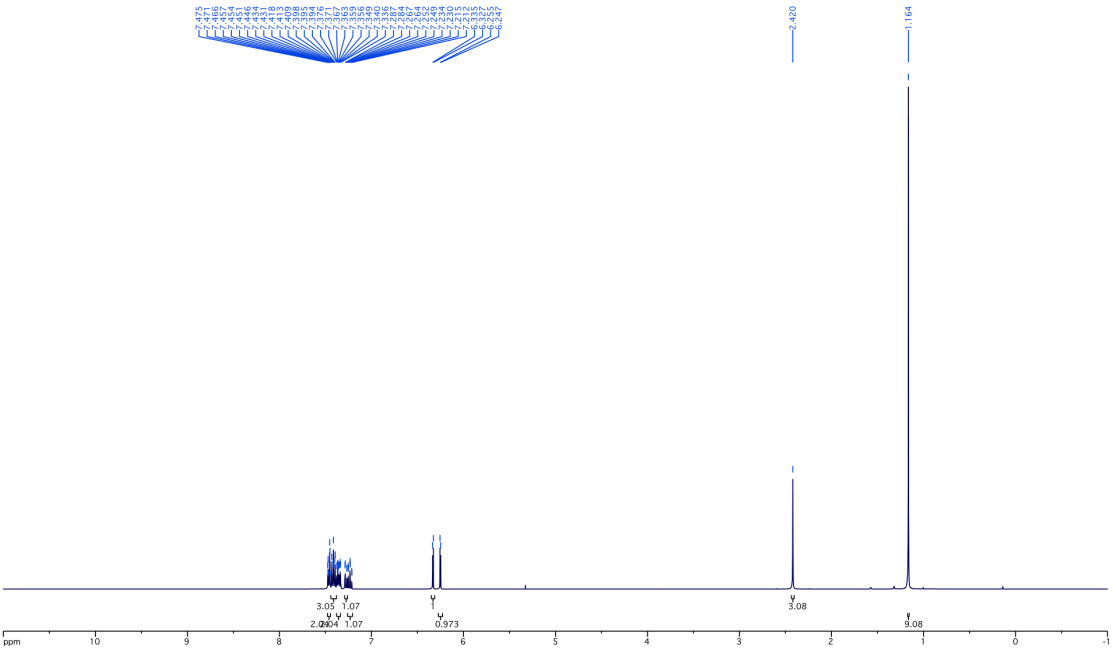


Pyrrole 116: ^{13}C NMR (101 MHz, $CDCl_3$)

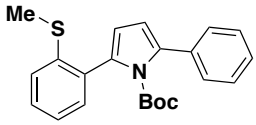


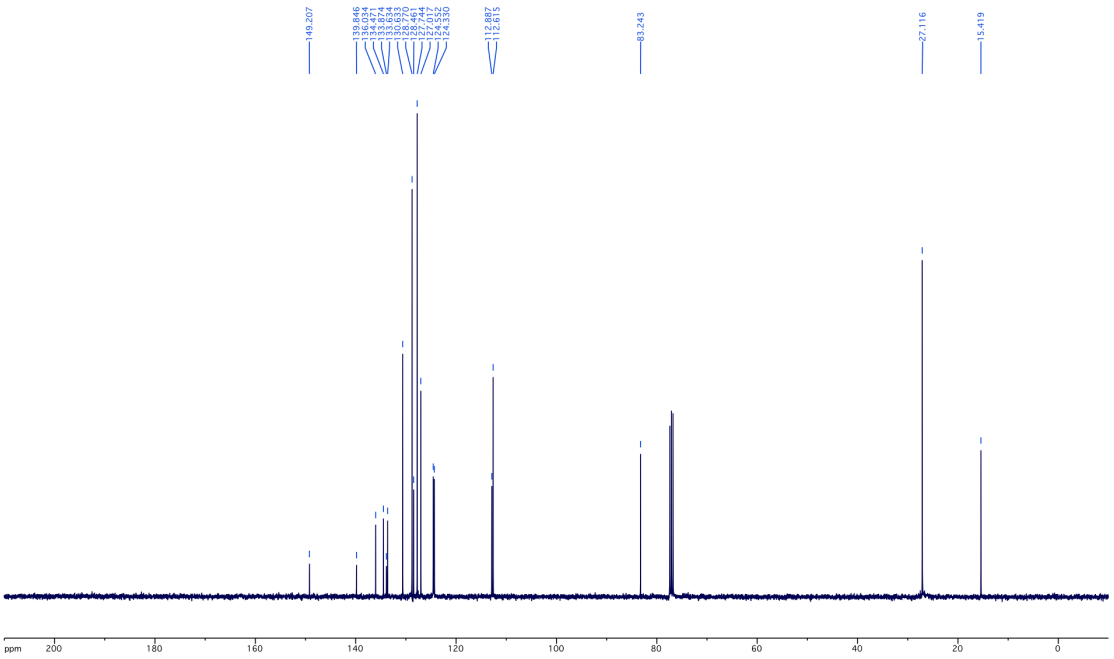
Pyrrole 117: ^{1}H NMR (400 MHz, $CDCl_3$)



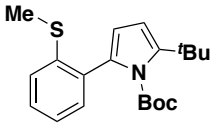


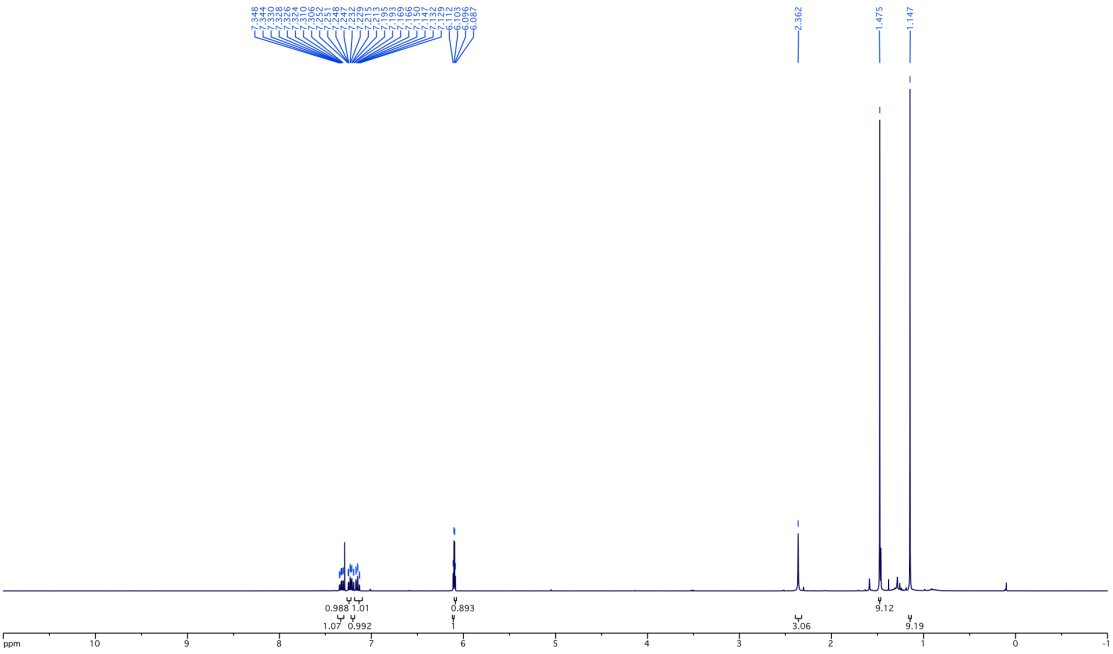
Pyrrole 117: ^{13}C NMR (101 MHz, $CDCl_3$)



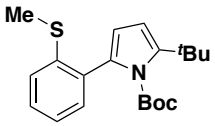


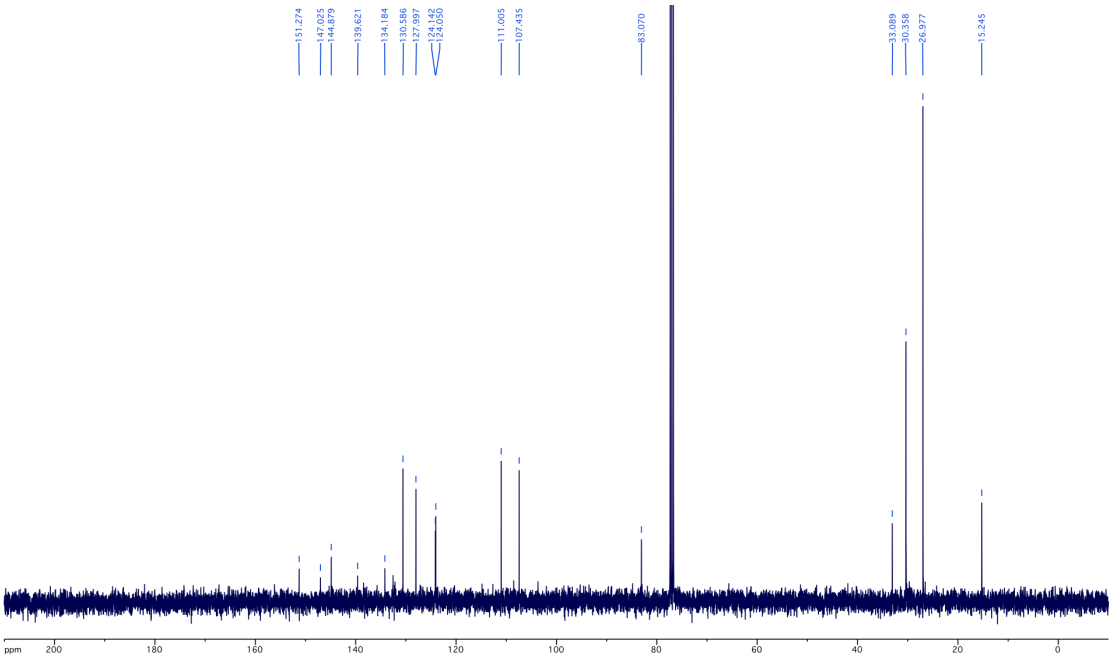
Pyrrole 118: ^{1}H NMR (400 MHz, $CDCl_3$)



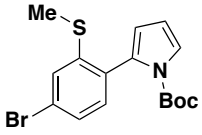


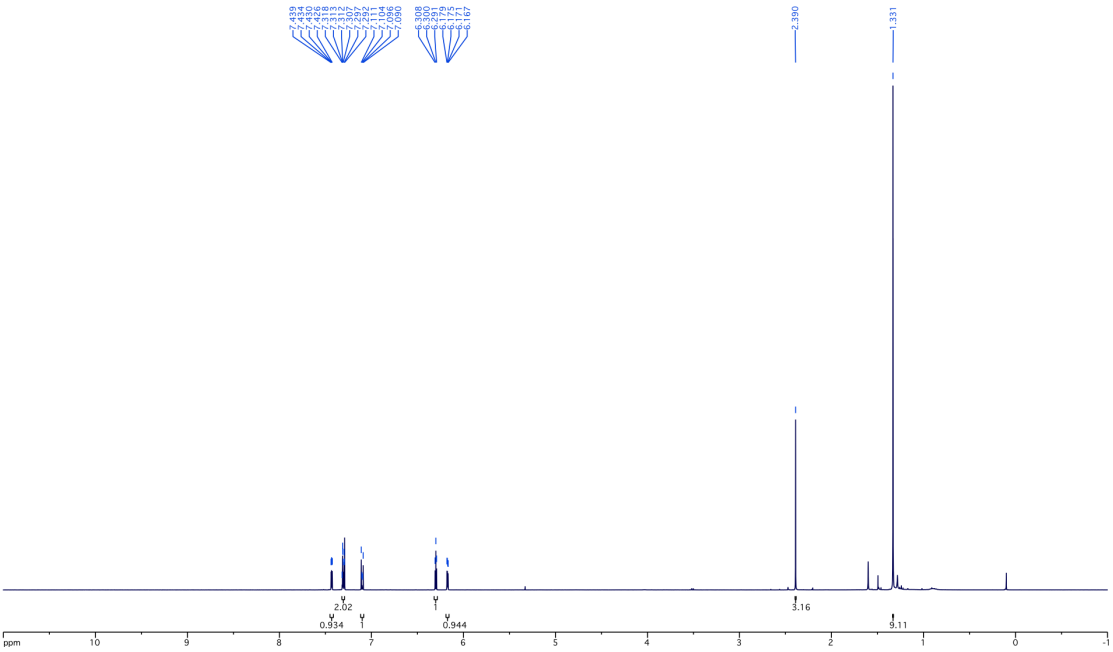
Pyrrole 118: ^{13}C NMR (101 MHz, $CDCl_3$)



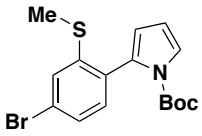


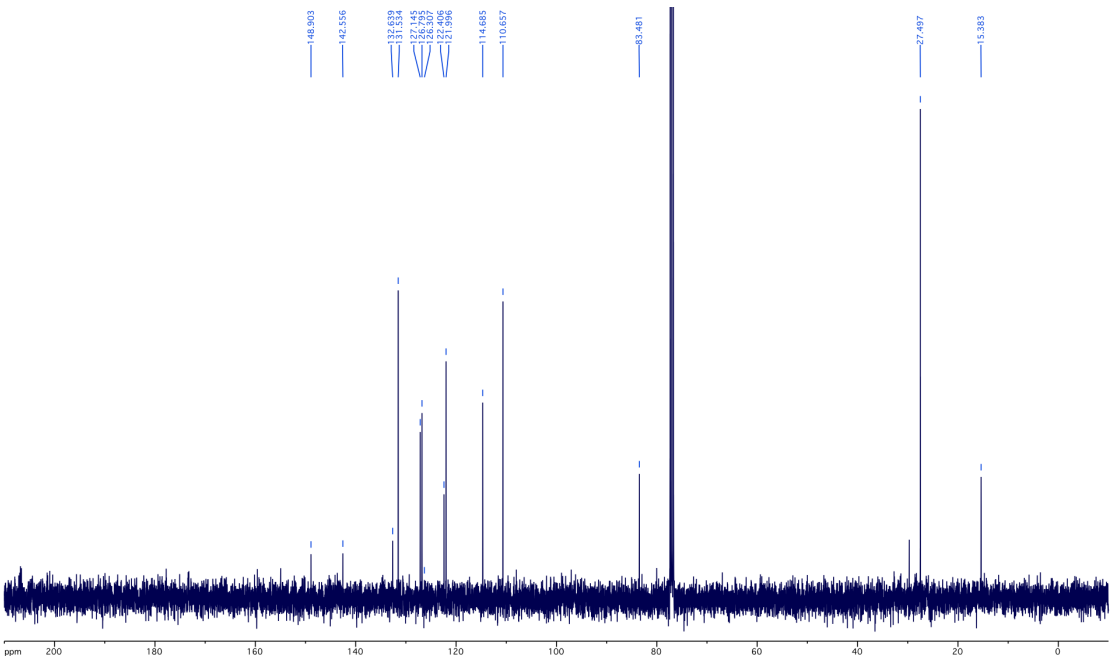
Pyrrole 119: ^{1}H NMR (400 MHz, $CDCl_3$)



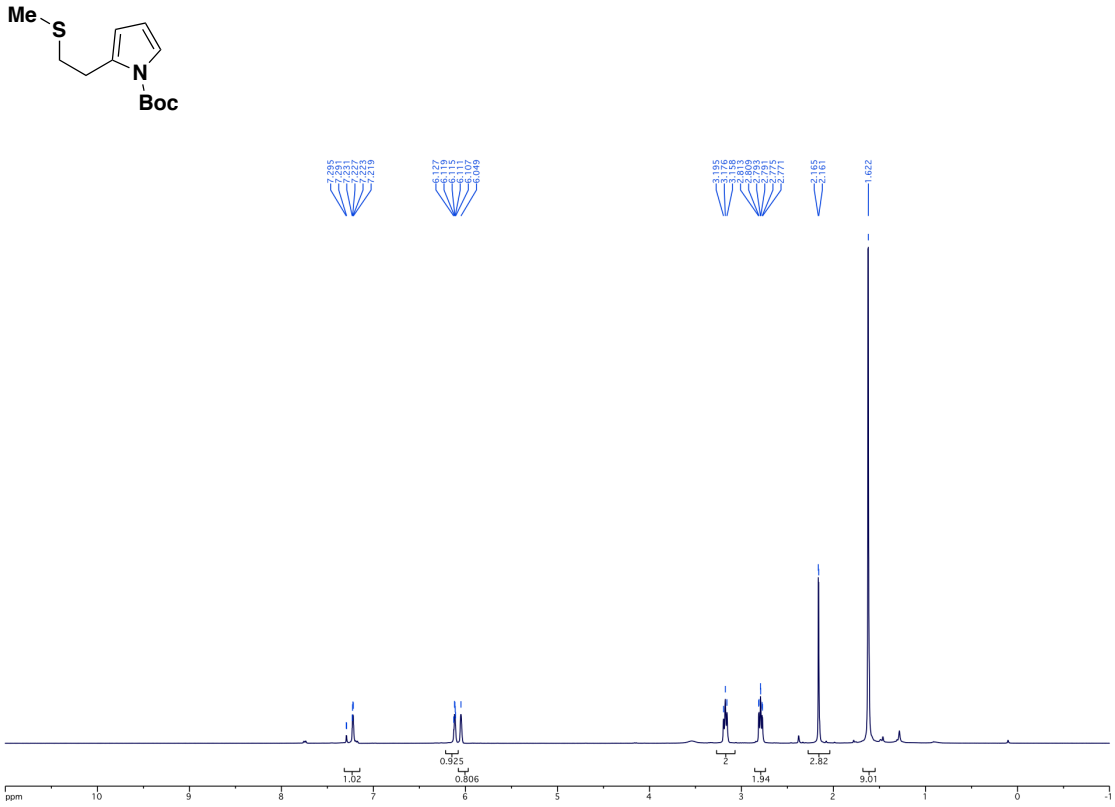


Pyrrole 119: ^{13}C NMR (101 MHz, $CDCl_3$)

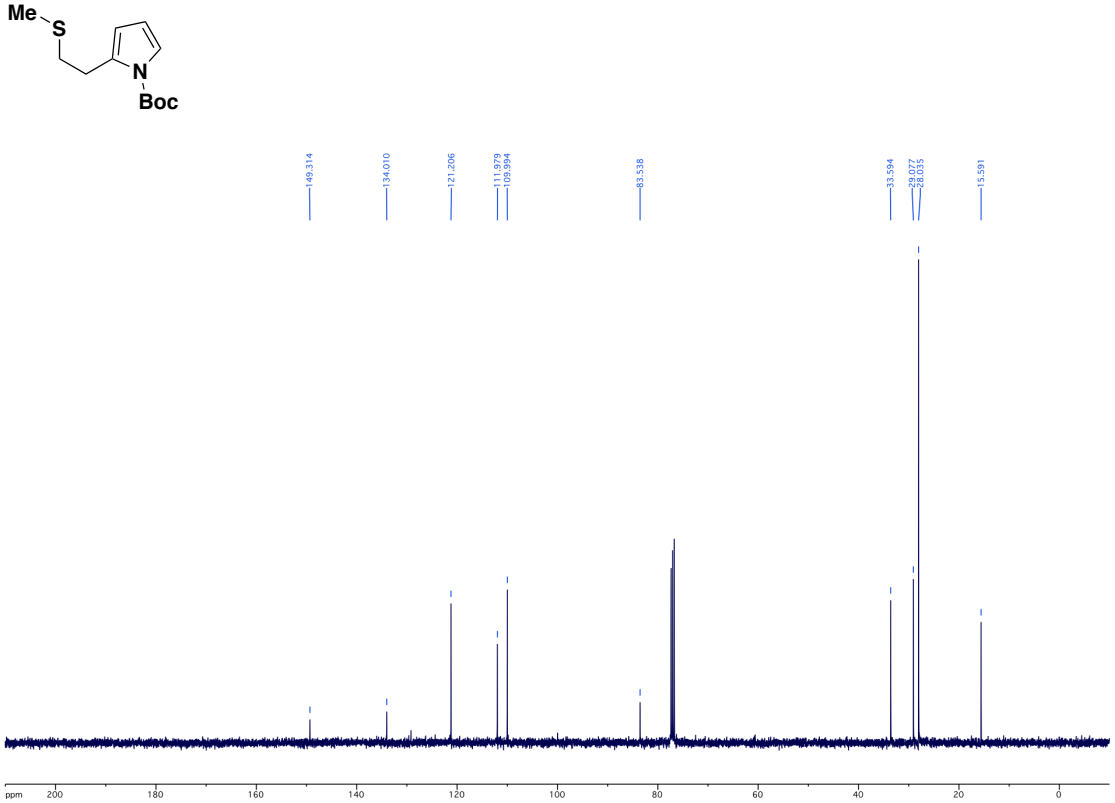




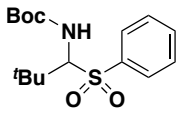
Pyrrole 120: ^{1}H NMR (400 MHz, $CDCl_3$)

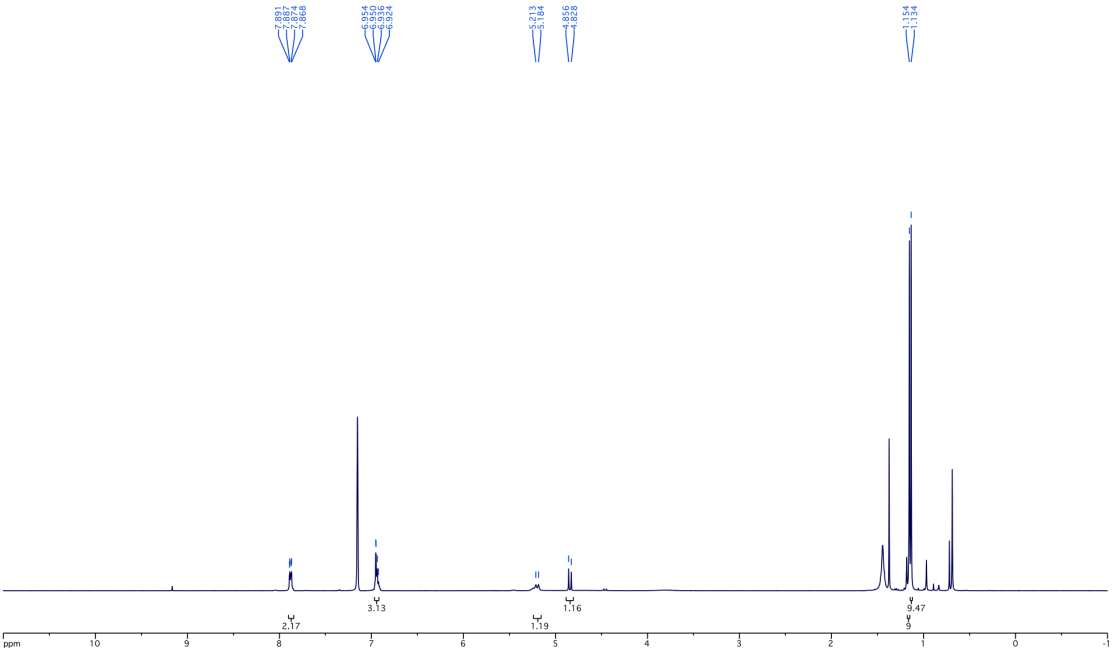


Pyrrole 120: ^{13}C NMR (101 MHz, $CDCl_3$)

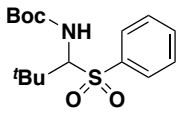


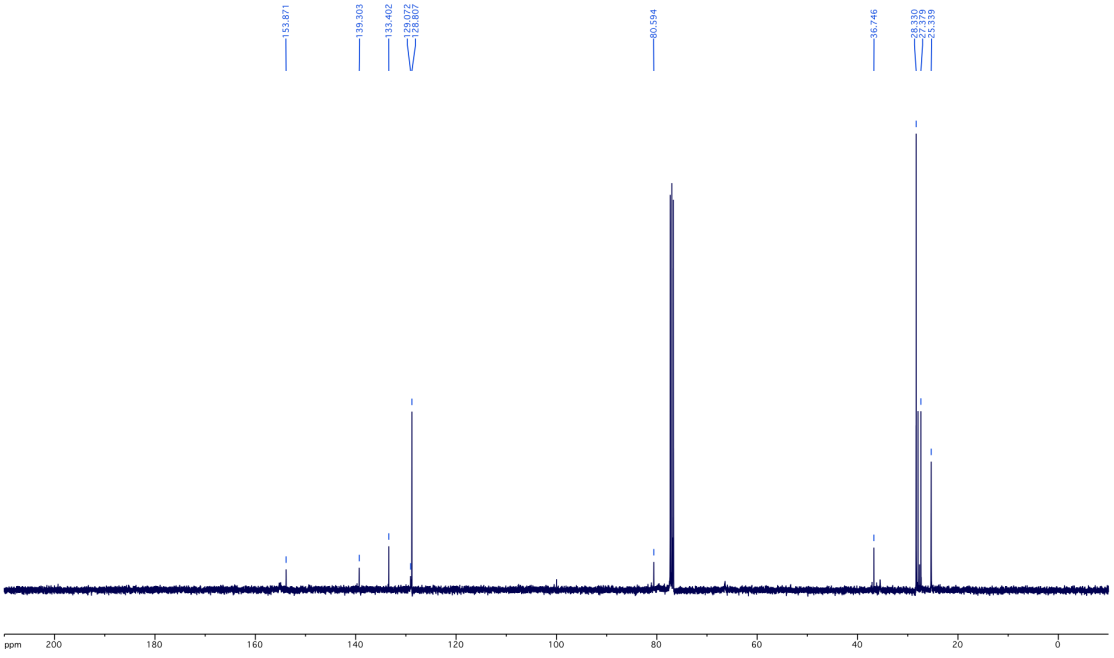
α-Amido sulfone 123: ^{1}H NMR (400 MHz, $CDCl_3$)



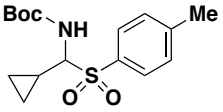


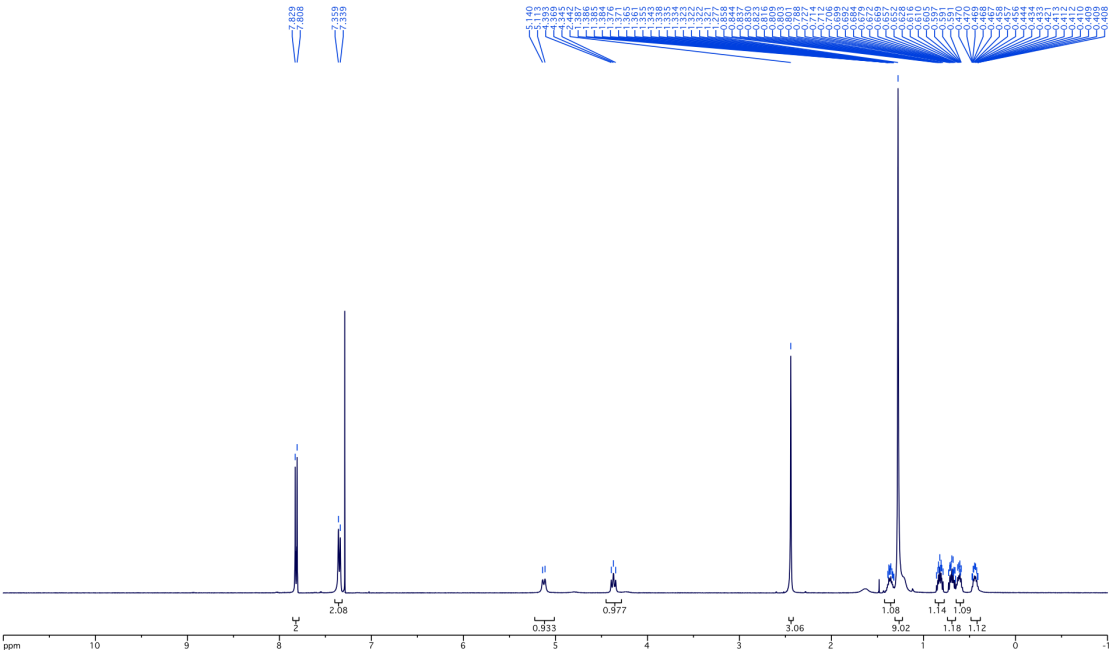
α-Amido sulfone 123:^{13}C NMR (101 MHz, $CDCl_3$)



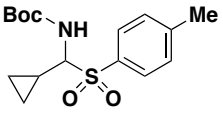


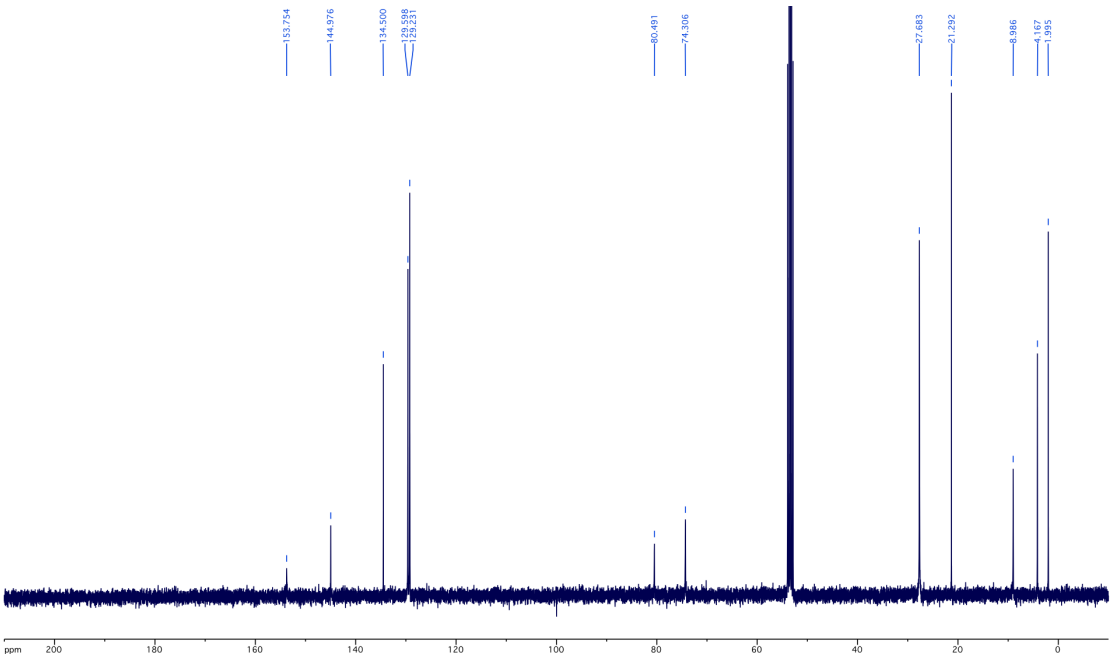
α-Amido sulfone 124: ^{1}H NMR (400 MHz, $CDCl_3$)



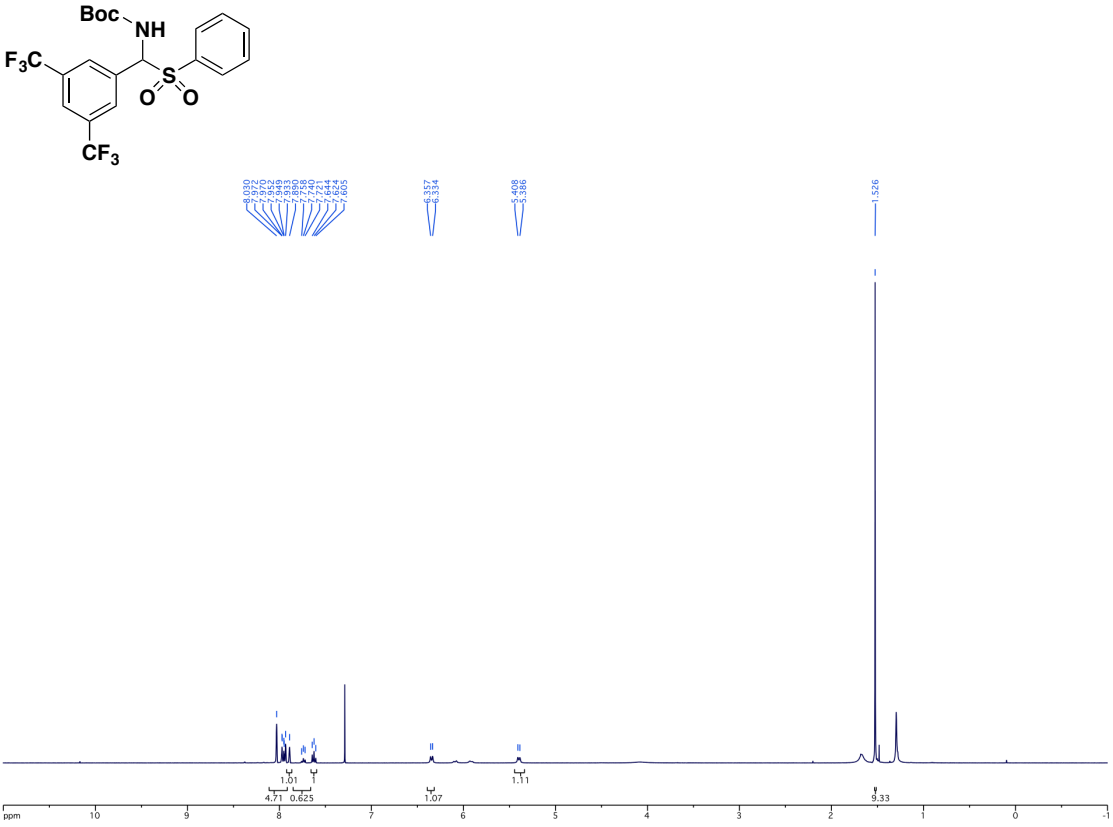


α-Amido sulfone 124: ^{13}C NMR (101 MHz, $CDCl_3$)

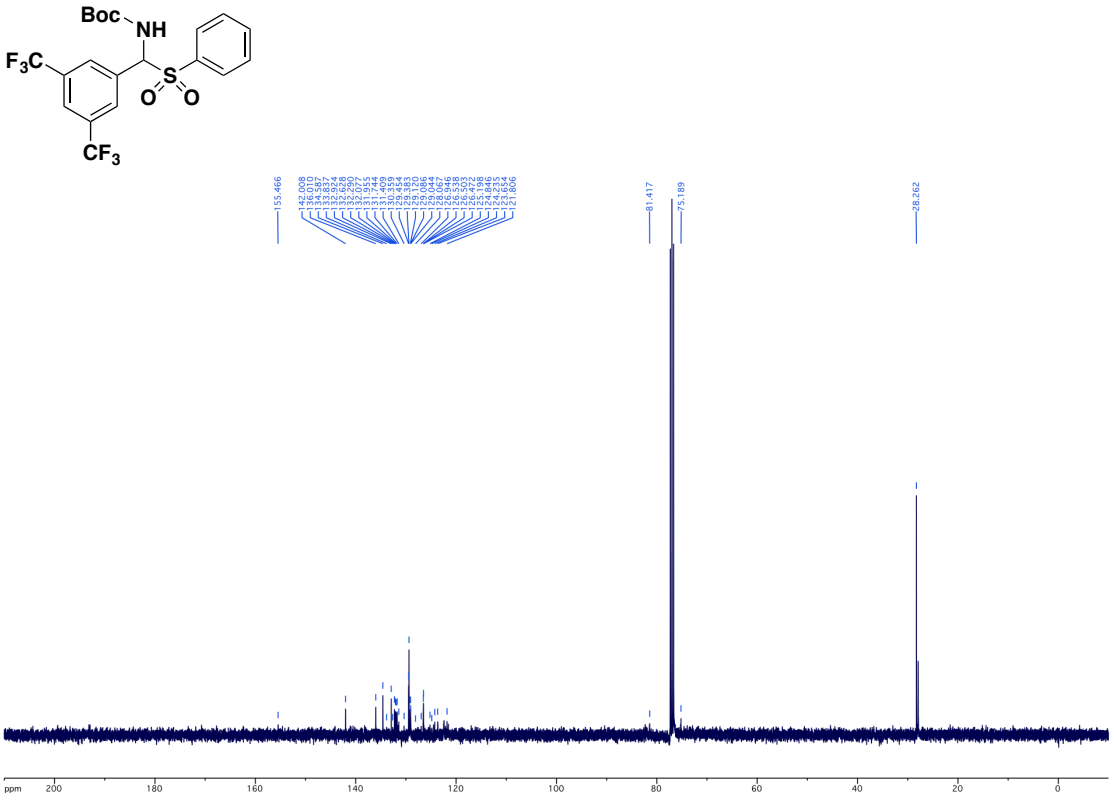




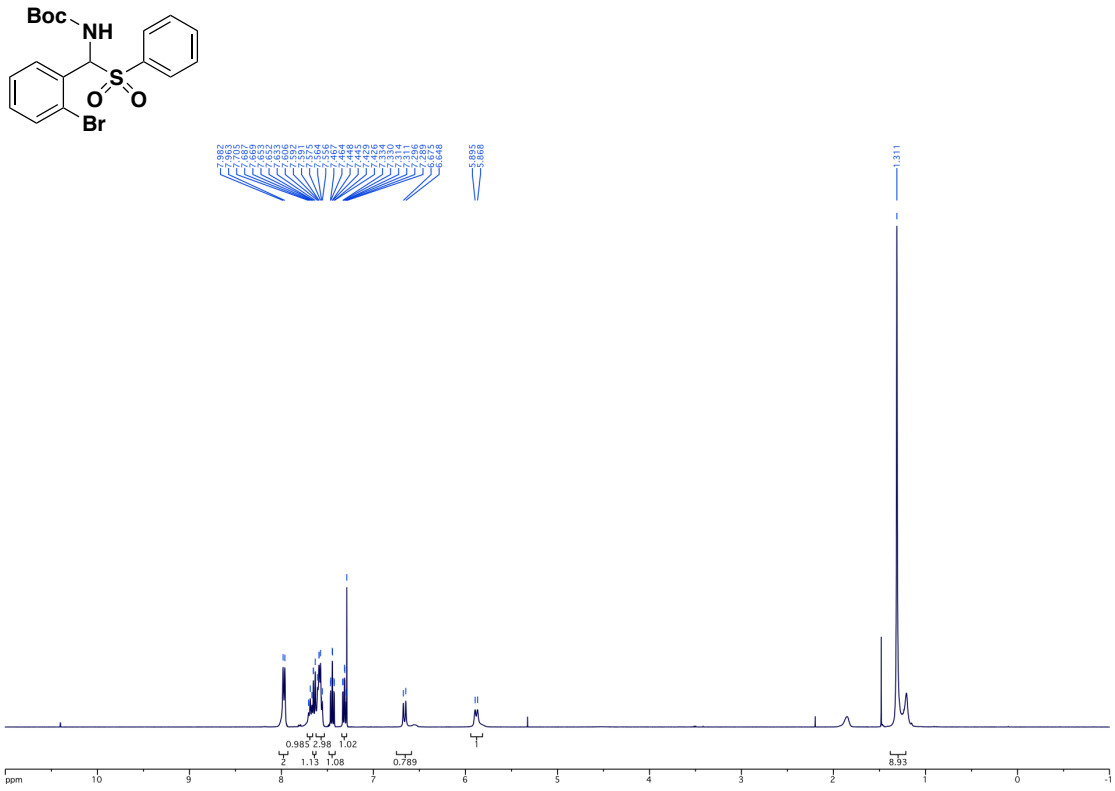
α-Amido sulfone 131: ^{1}H NMR (400 MHz, $CDCl_3$)



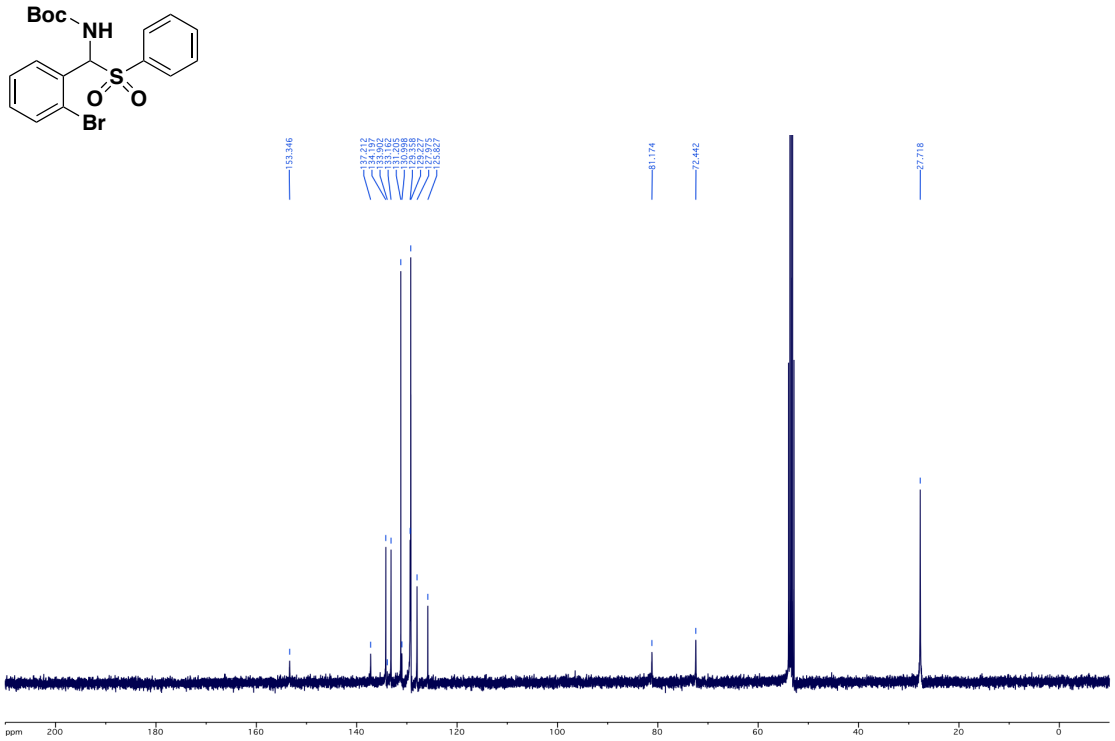
α-Amido sulfone 131:^{13}C NMR (101 MHz, $CDCl_3$)



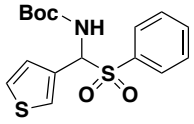
α-Amido sulfone 132: ^{1}H NMR (400 MHz, CD_2Cl_2)

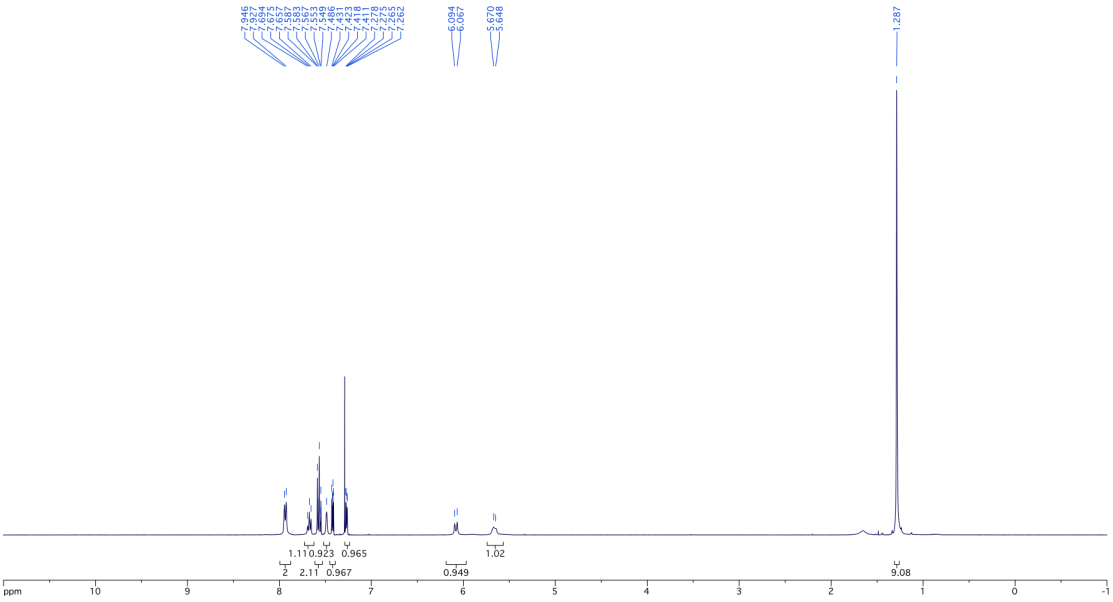


α-Amido sulfone 132: ^{13}C NMR (101 MHz, CD_2Cl_2)

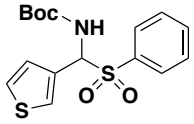


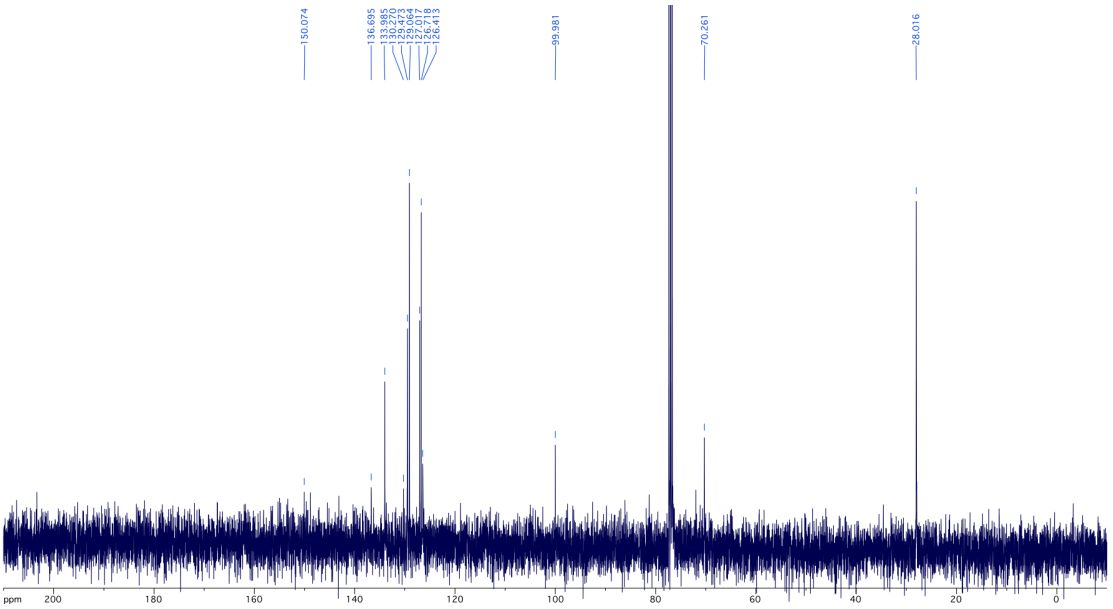
α-Amido sulfone 134: ^{1}H NMR (400 MHz, $CDCl_3$)



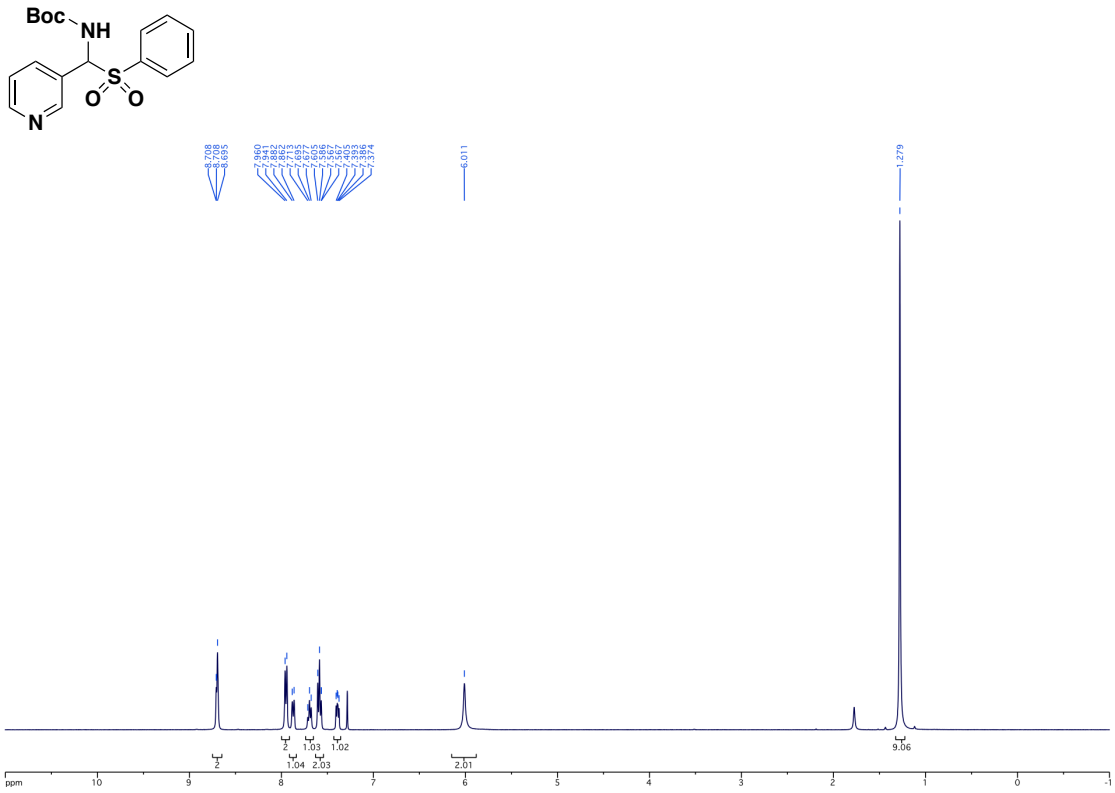


α-Amido sulfone 134:^{13}C NMR (101 MHz, $CDCl_3$)

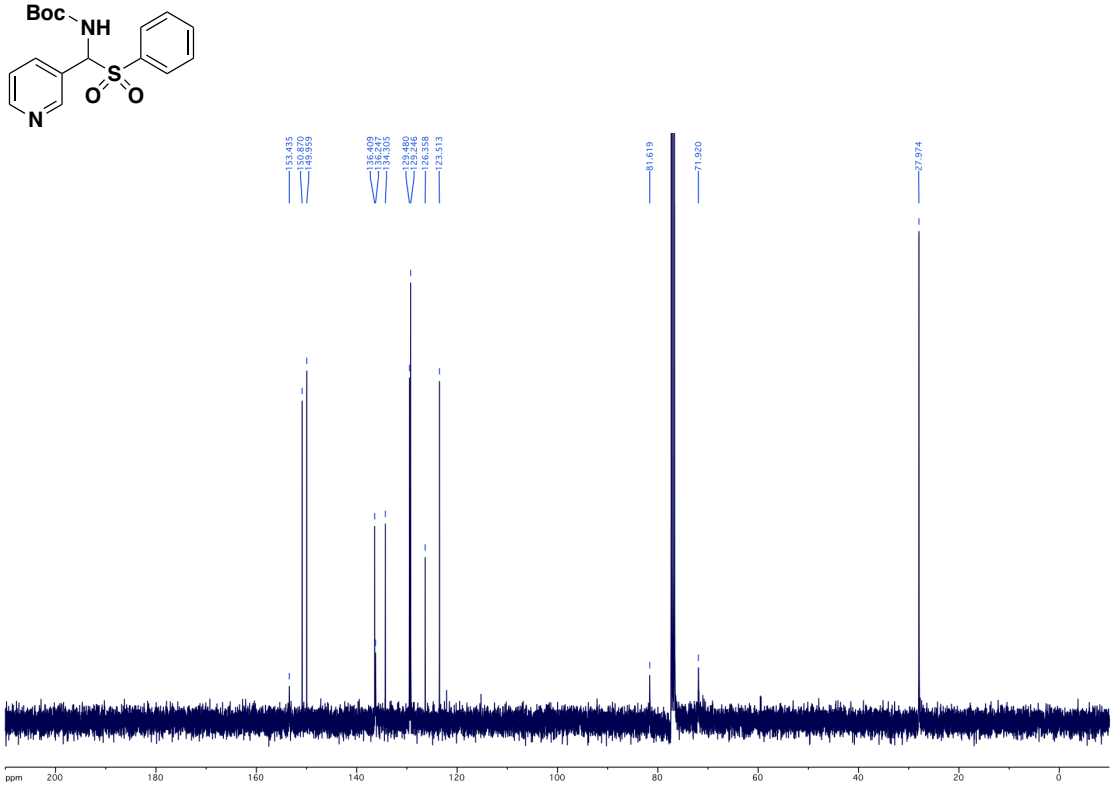




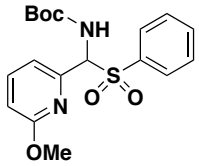
α-Amido sulfone 136: ^{1}H NMR (400 MHz, $CDCl_3$)

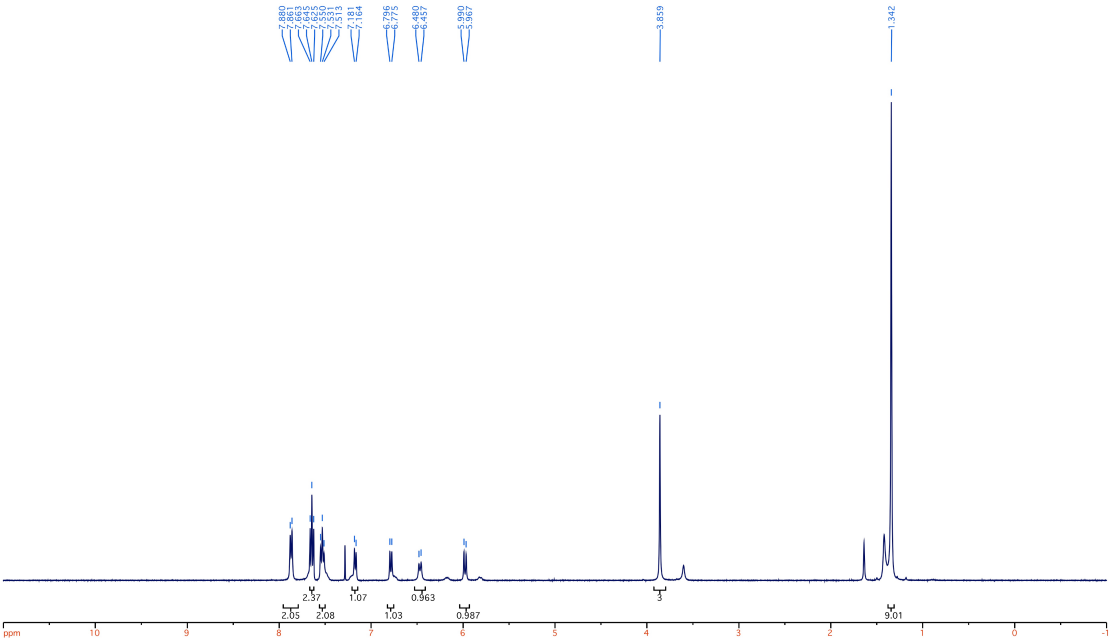


α-Amido sulfone 136:^{13}C NMR (101 MHz, $CDCl_3$)

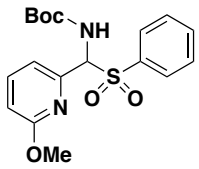


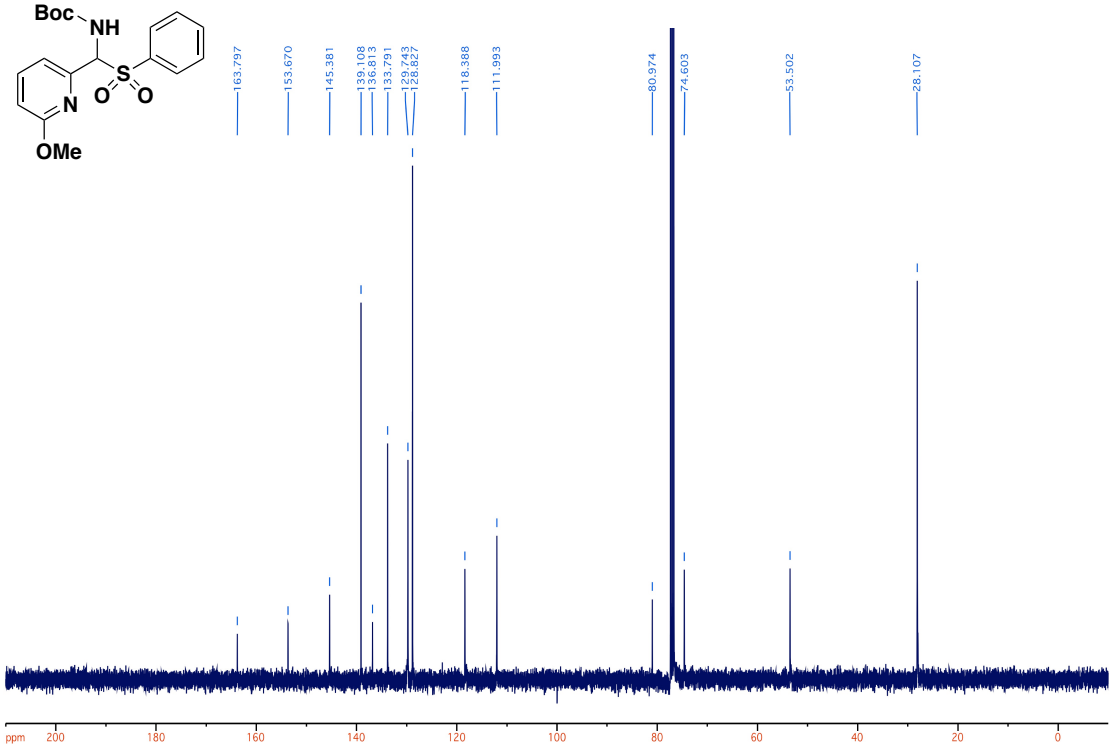
α-Amido sulfone 137: ^{1}H NMR (400 MHz, $CDCl_3$):



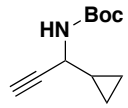


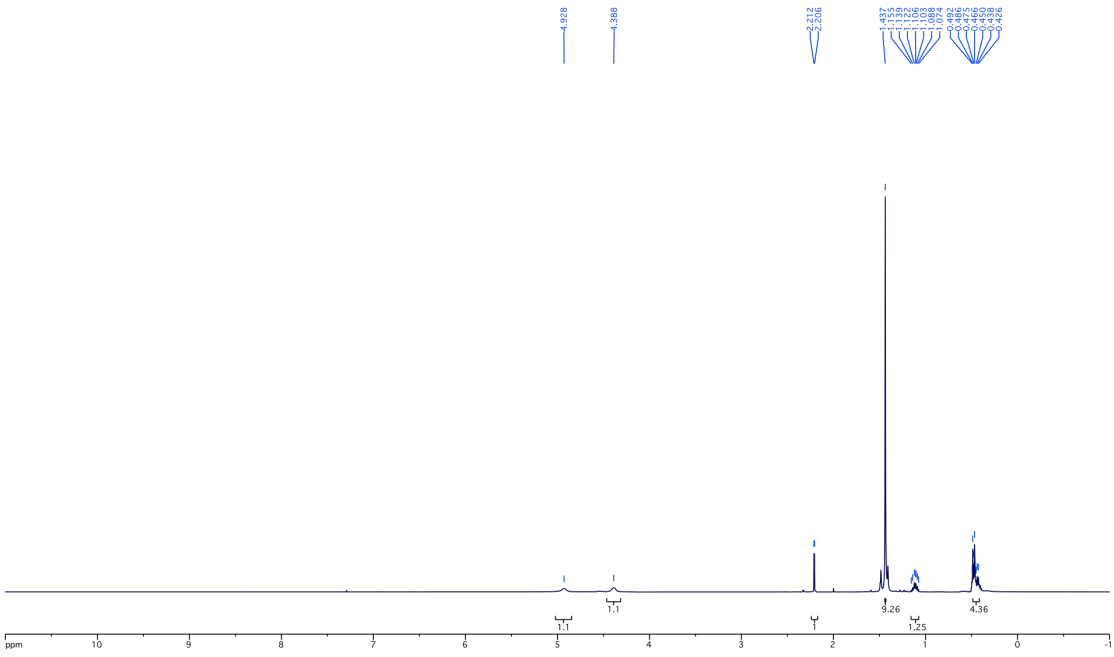
α-Amido sulfone 137: ^{13}C NMR (101 MHz, $CDCl_3$):



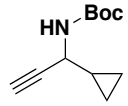


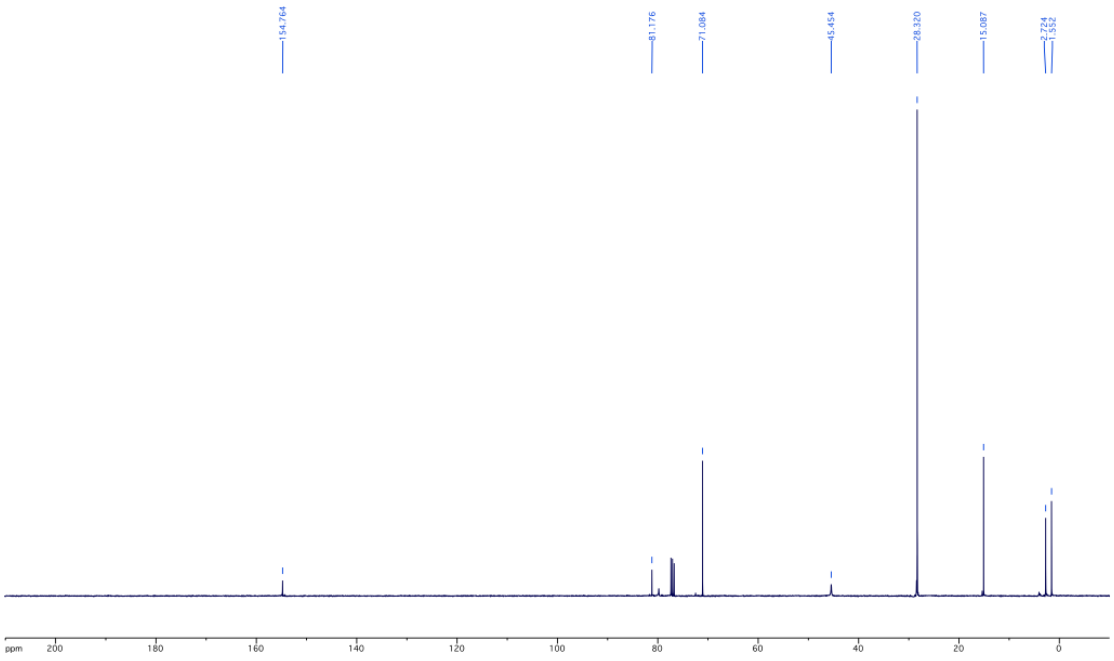
Propargylic amine 138: ^{1}H NMR (400 MHz, $CDCl_3$)



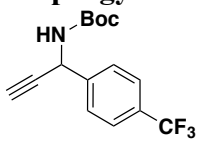


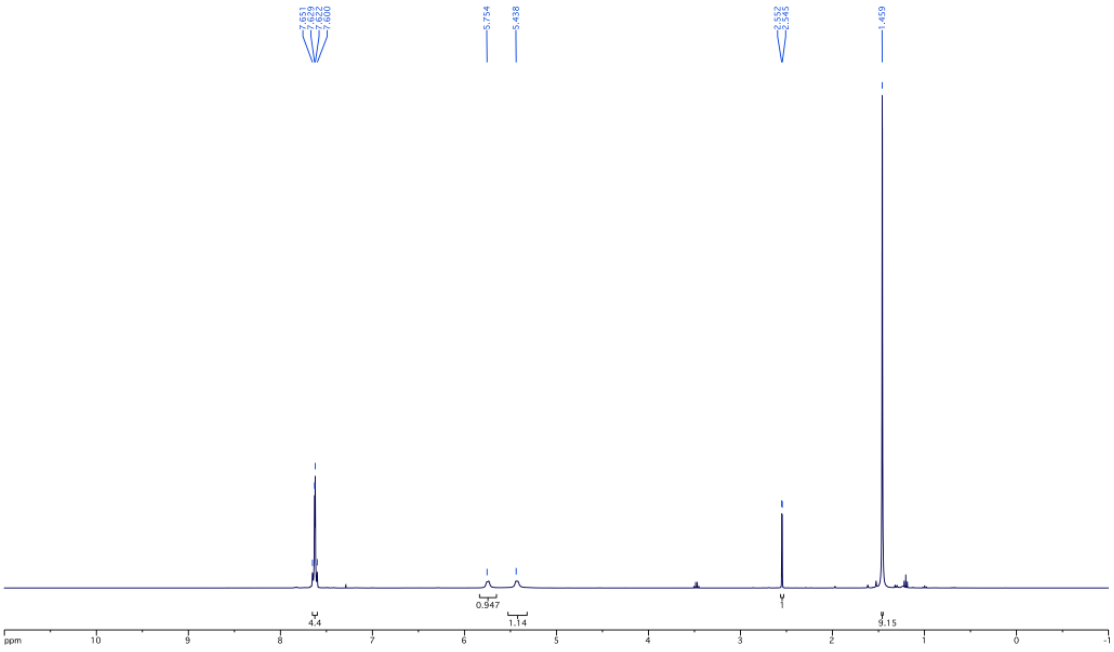
Propargylic amine 138: ^{13}C NMR (101 MHz, $CDCl_3$)



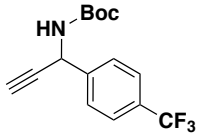


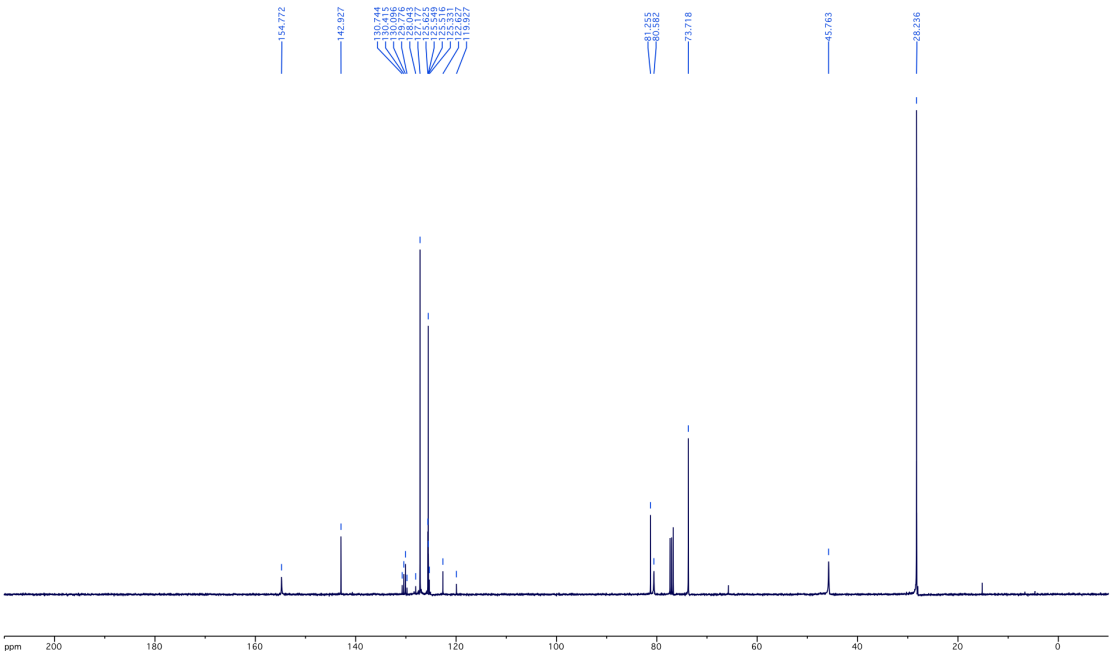
Propargylic amine 140: ^{1}H NMR (400 MHz, $CDCl_3$)



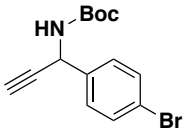


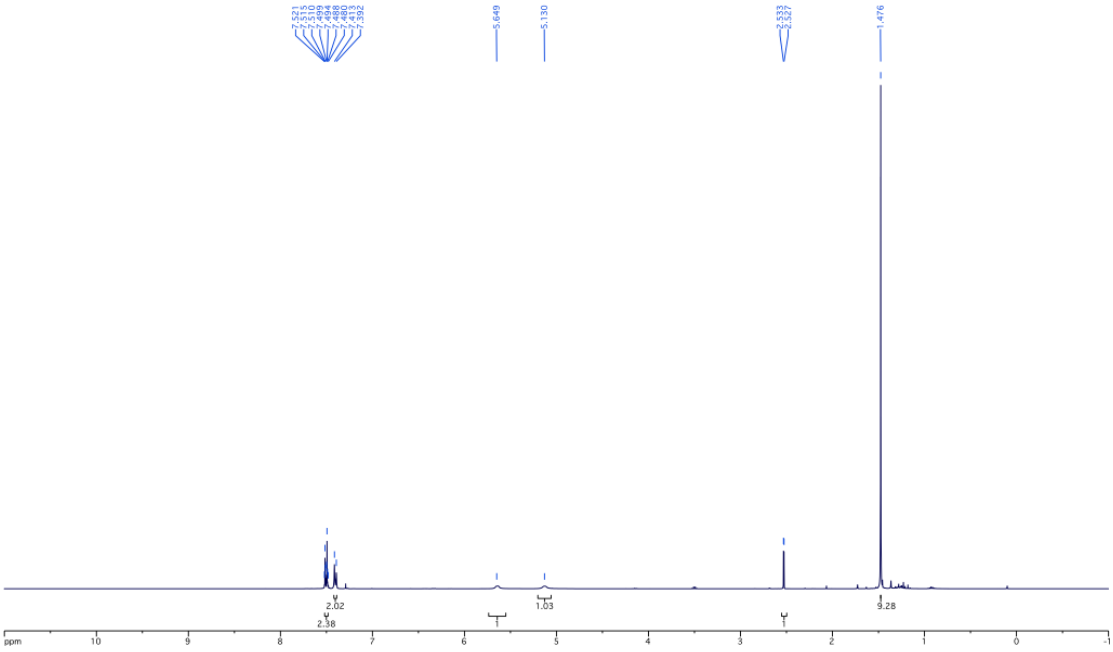
Propargylic amine 140: ^{13}C NMR (101 MHz, $CDCl_3$)



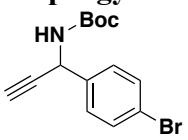


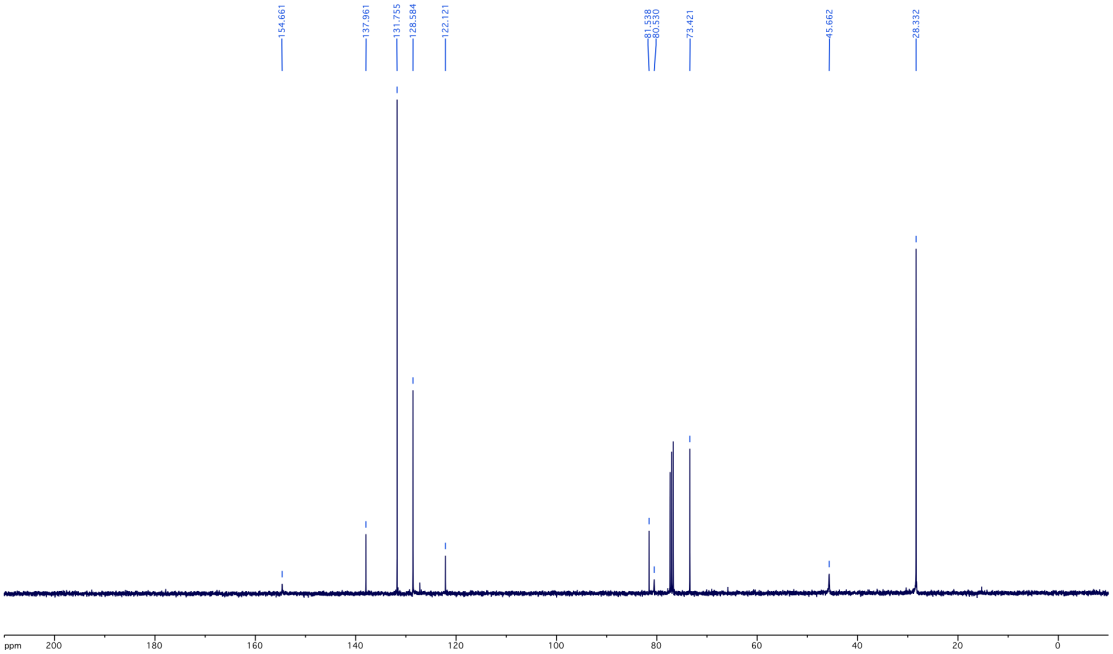
Propargylic amine 141: ^{1}H NMR (400 MHz, $CDCl_3$)



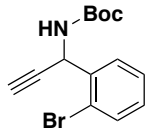


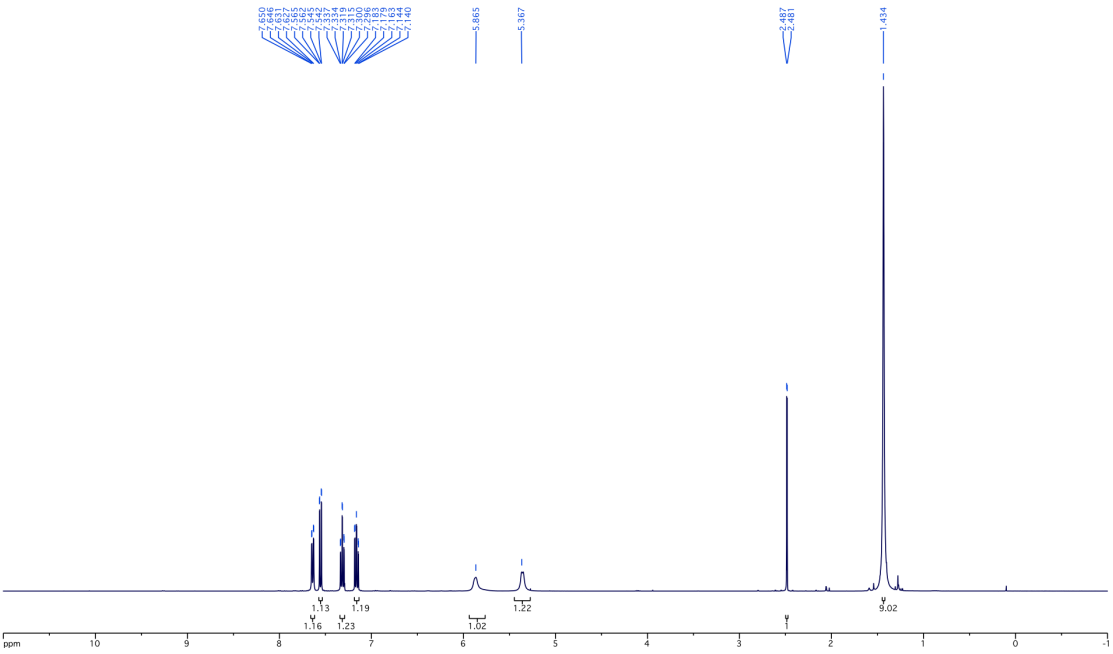
Propargylic amine 141: ^{13}C NMR (101 MHz, $CDCl_3$)



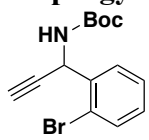


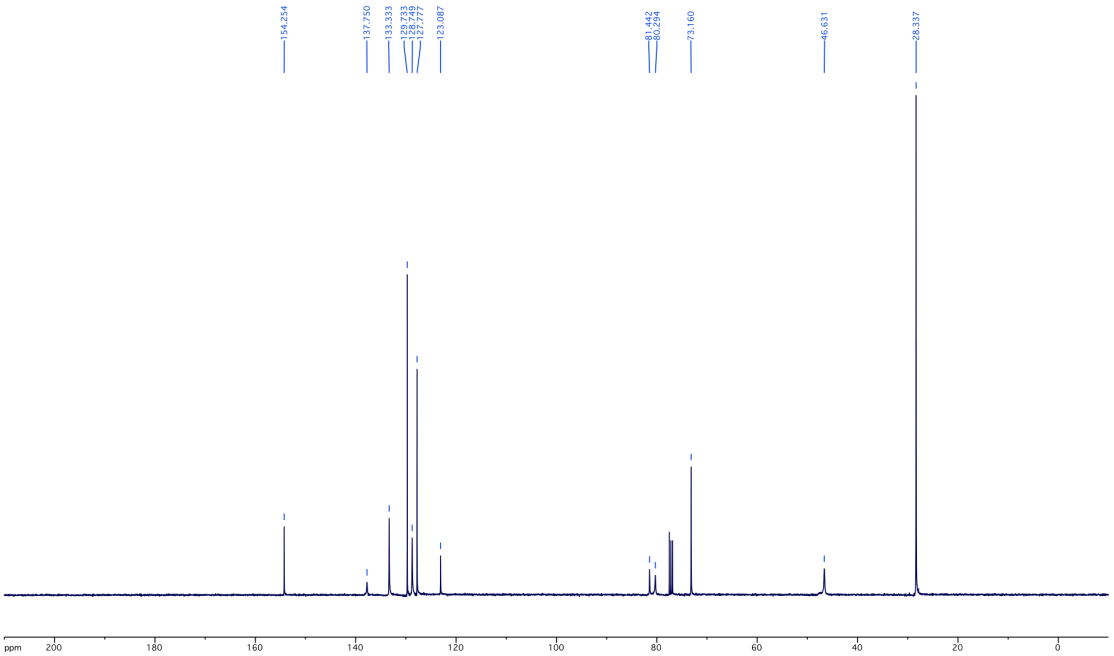
Propargylic amine 144: ^{1}H NMR (400 MHz, $CDCl_3$)



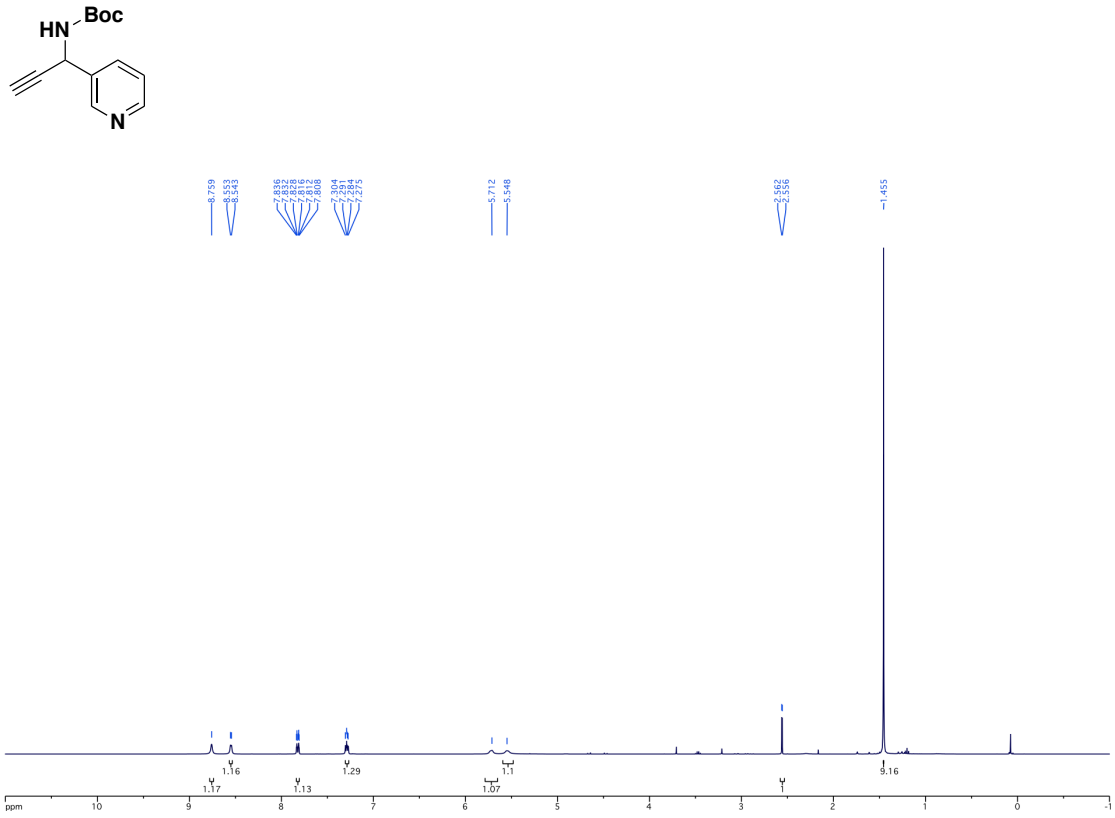


Propargylic amine 144: ^{13}C NMR (101 MHz, $CDCl_3$)

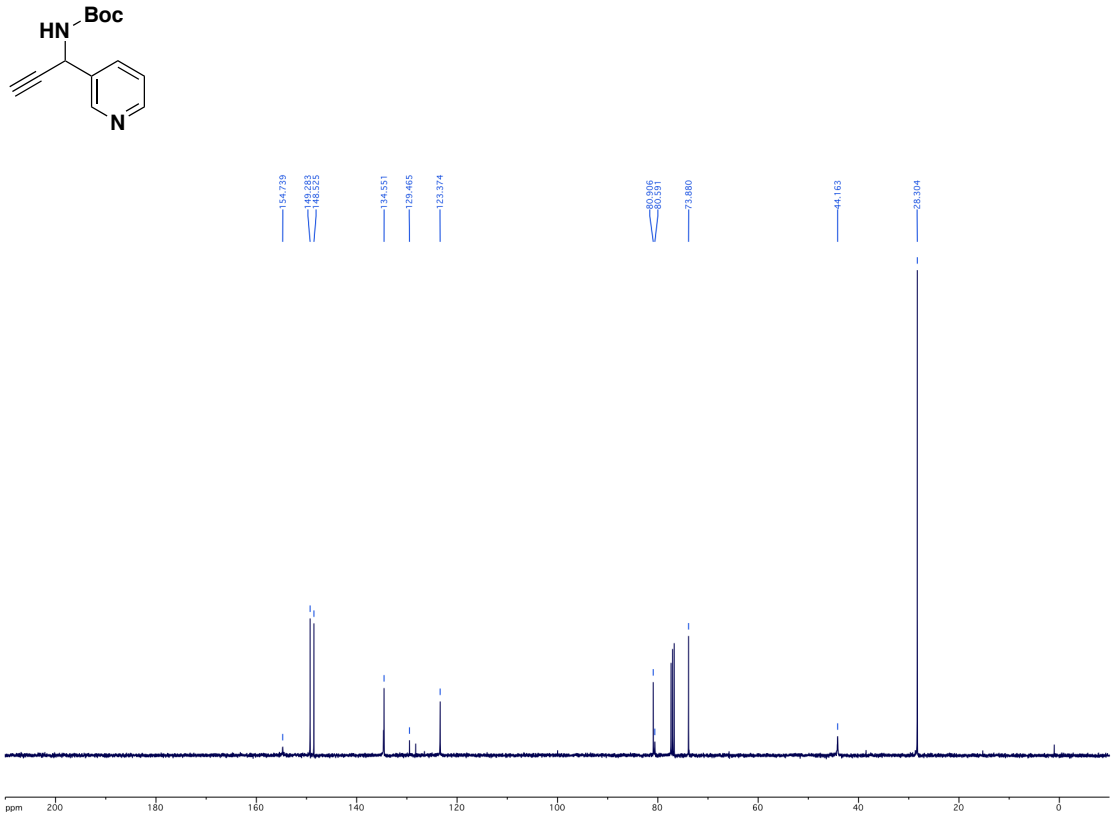




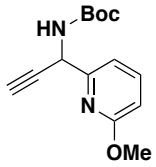
Propargylic amine 147: ^{1}H NMR (400 MHz, $CDCl_3$)

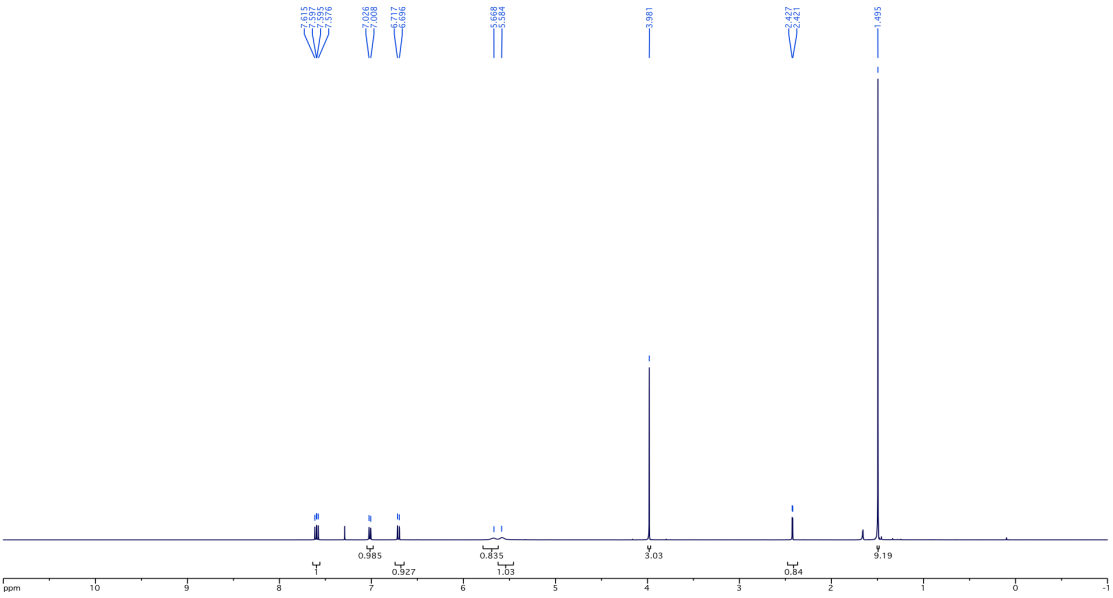


Propargylic amine 147: ^{13}C NMR (101 MHz, $CDCl_3$)

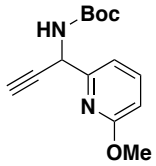


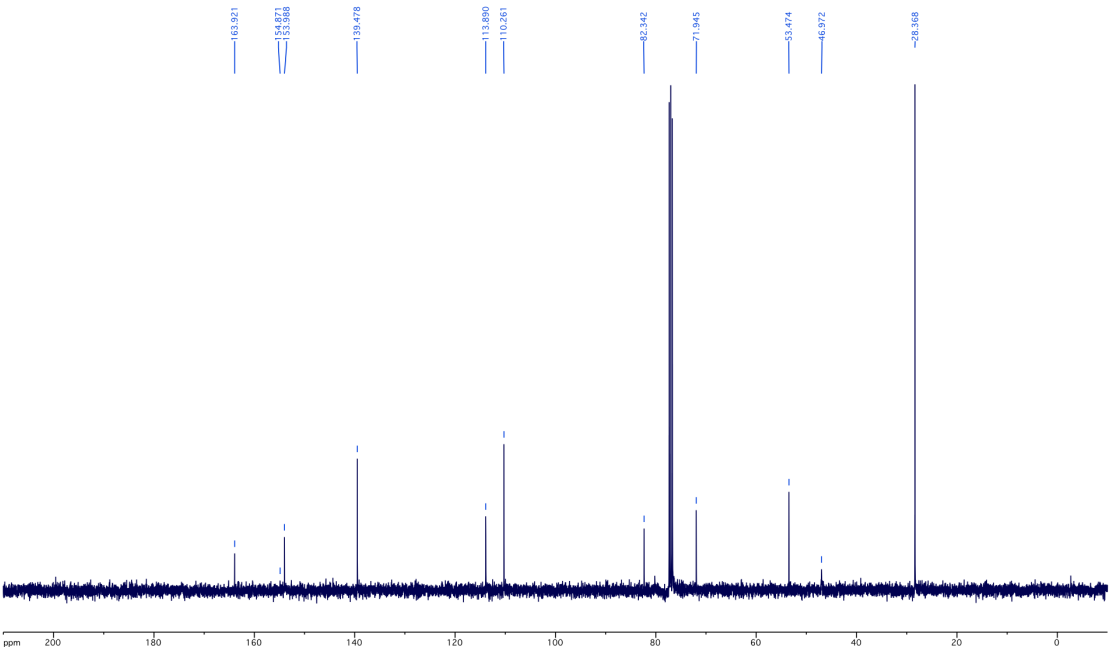
Propargylic amine 148: ^{1}H NMR (400 MHz, $CDCl_3$)



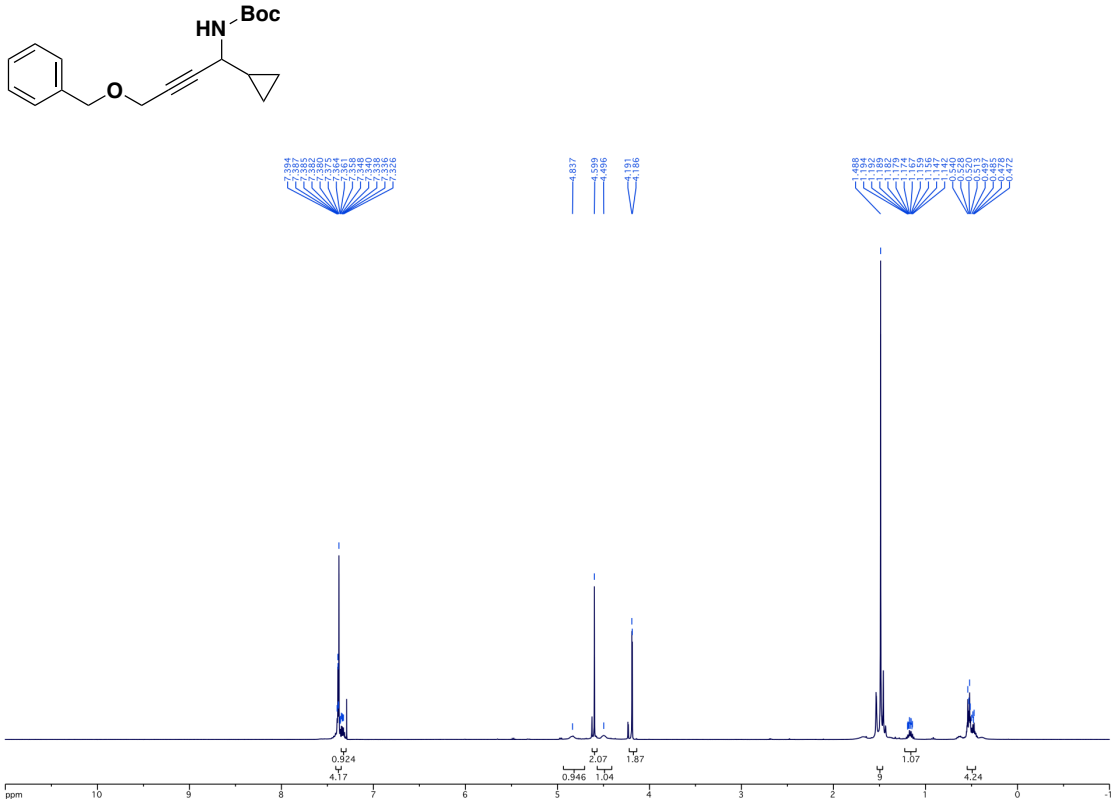


Propargylic amine 148: ^{13}C NMR (101 MHz, $CDCl_3$)

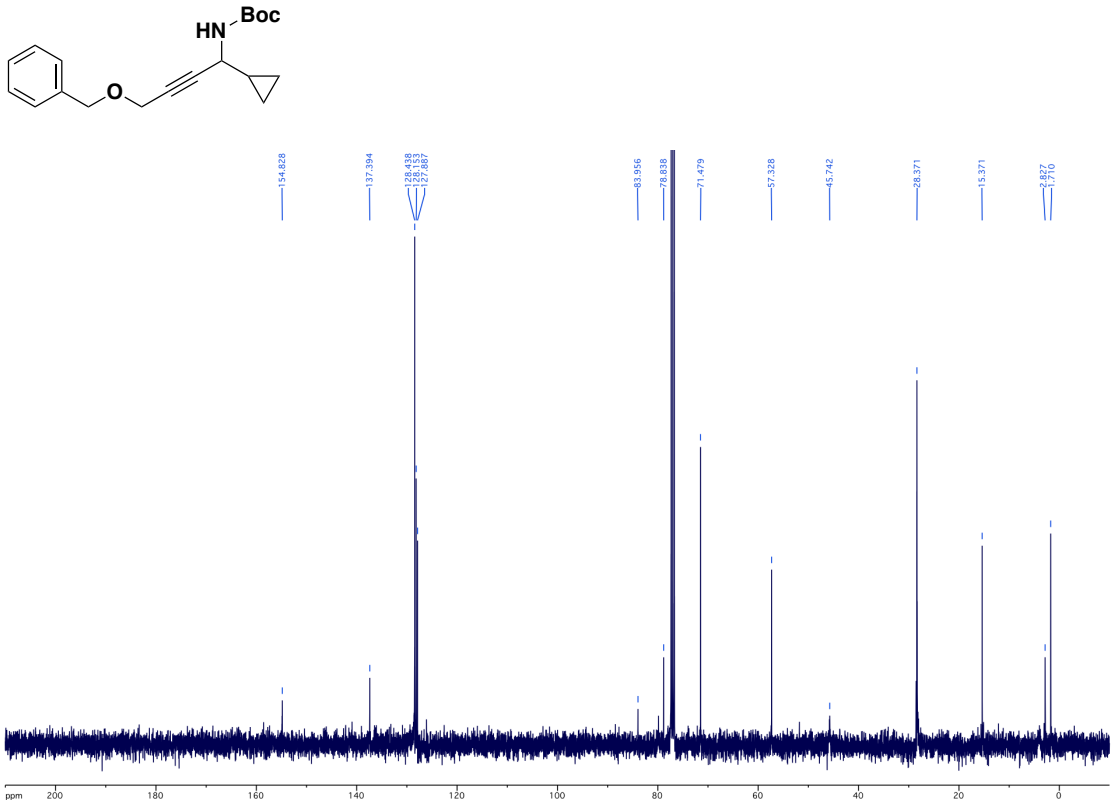




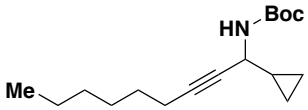
Propargylic amine 150: ^{1}H NMR (400 MHz, $CDCl_3$)

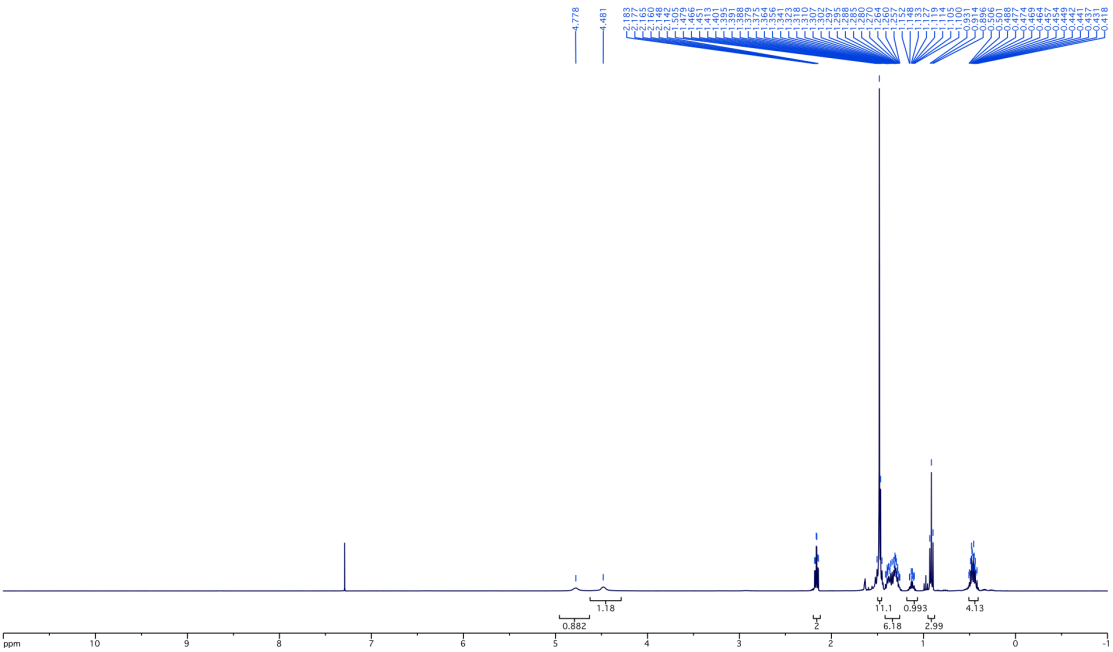


Propargylic amine 150: ^{13}C NMR (101 MHz, $CDCl_3$)

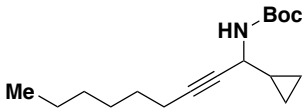


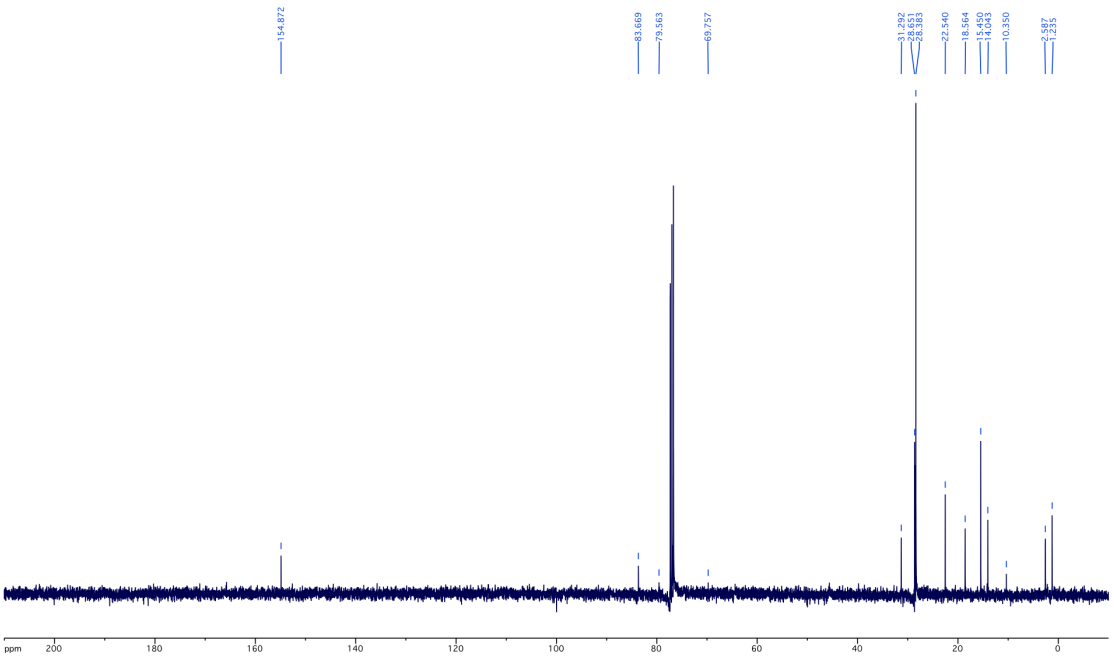
Propargylic amine 151: ^{1}H NMR (400 MHz, $CDCl_3$)



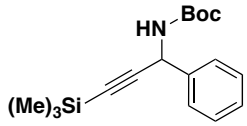


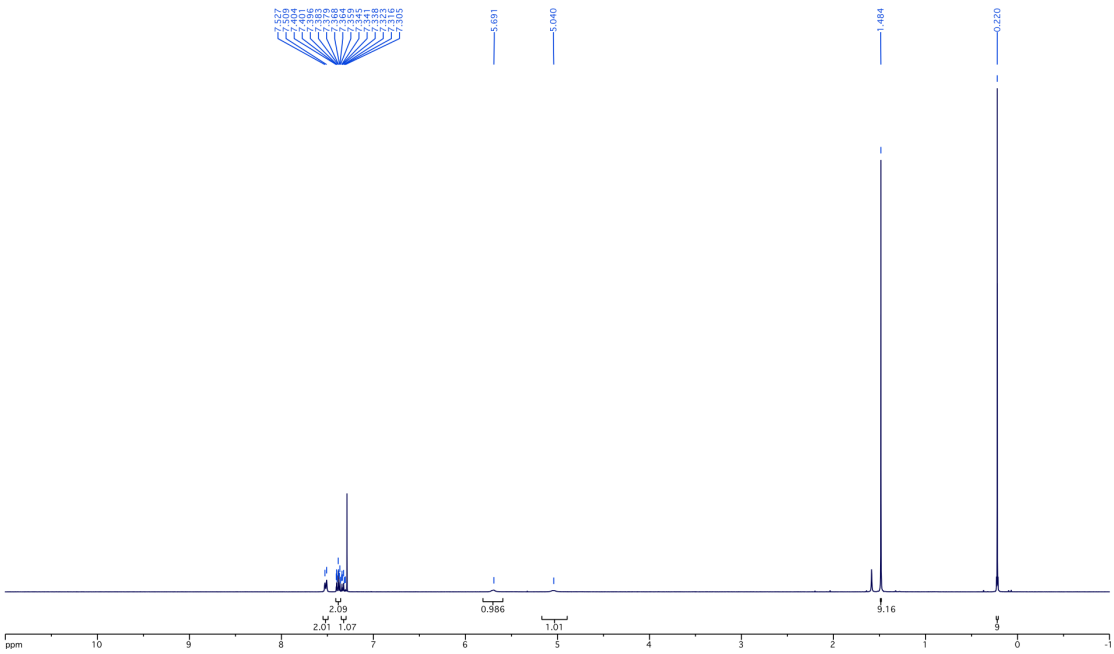
Propargylic amine 151: ^{13}C NMR (101 MHz, $CDCl_3$)



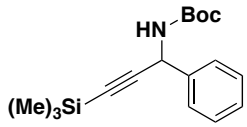


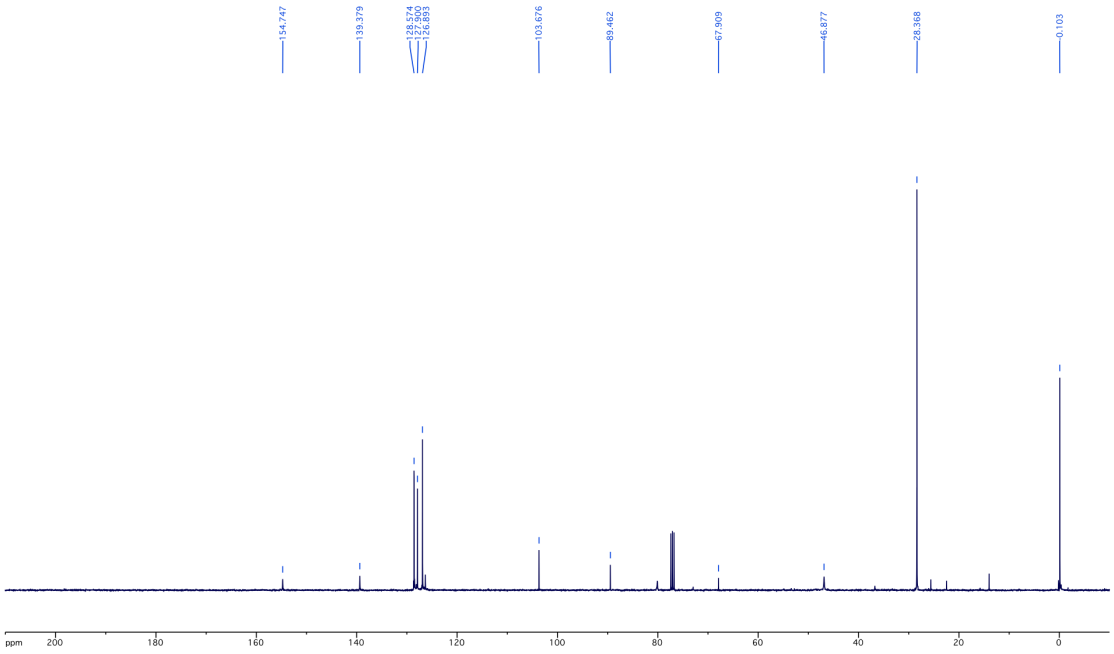
Propargylic amine 152: ^{1}H NMR (400 MHz, $CDCl_3$)



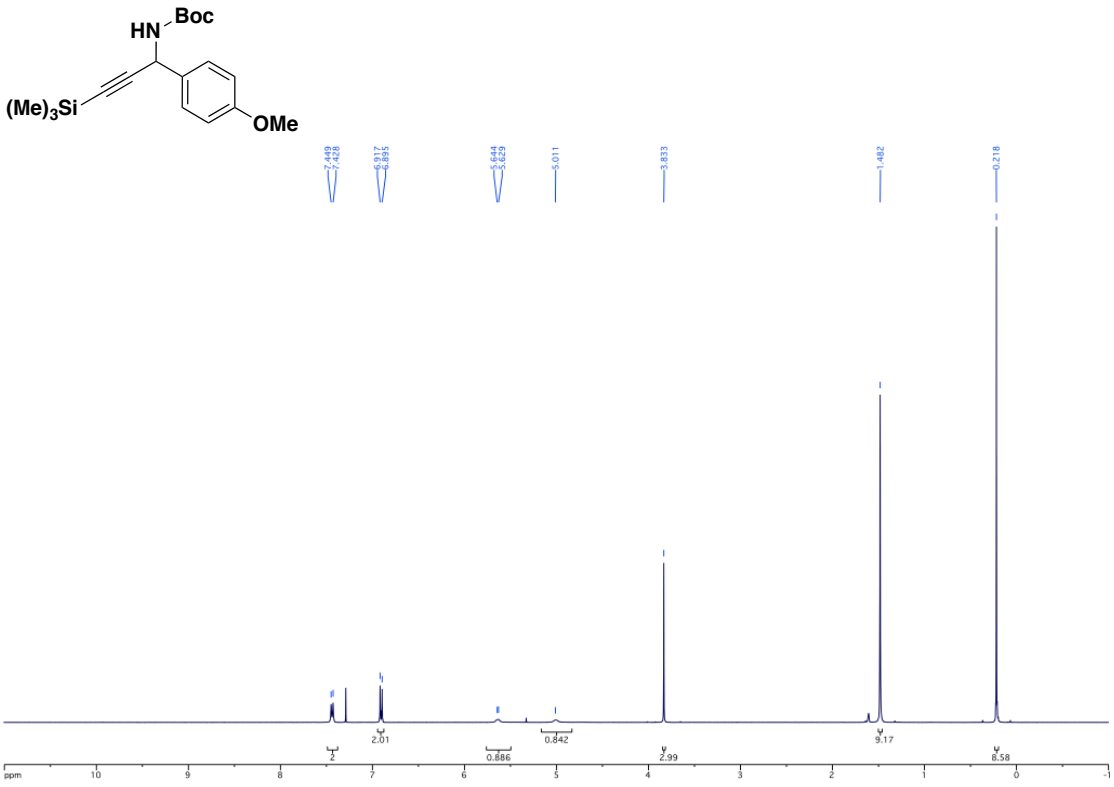


Propargylic amine 152: ^{13}C NMR (101 MHz, $CDCl_3$)

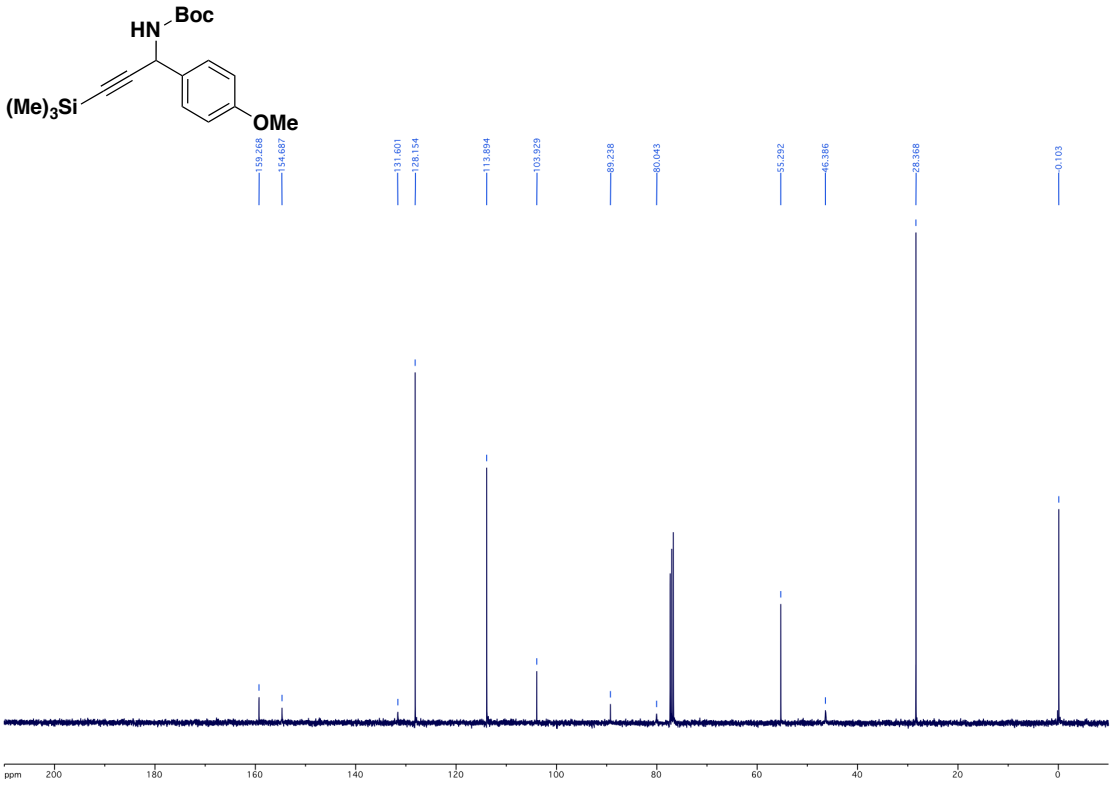




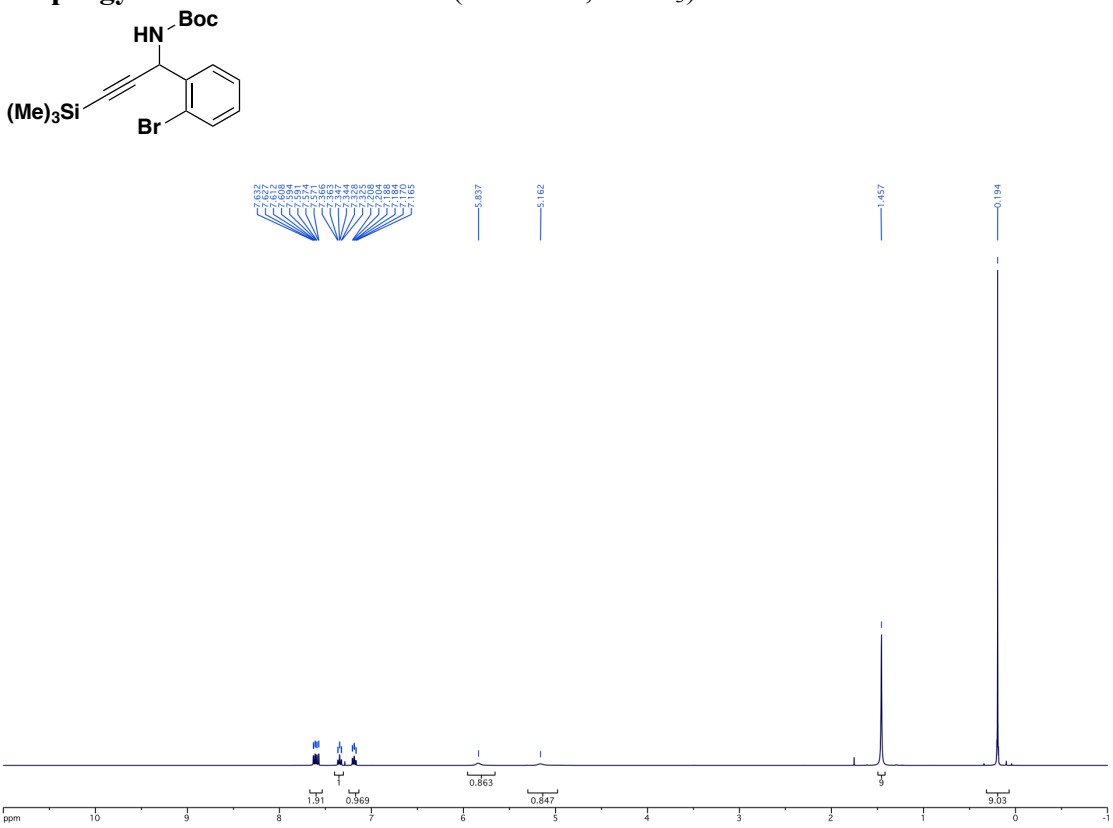
Propargylic amine 153: ^{1}H NMR (400 MHz, $CDCl_3$)



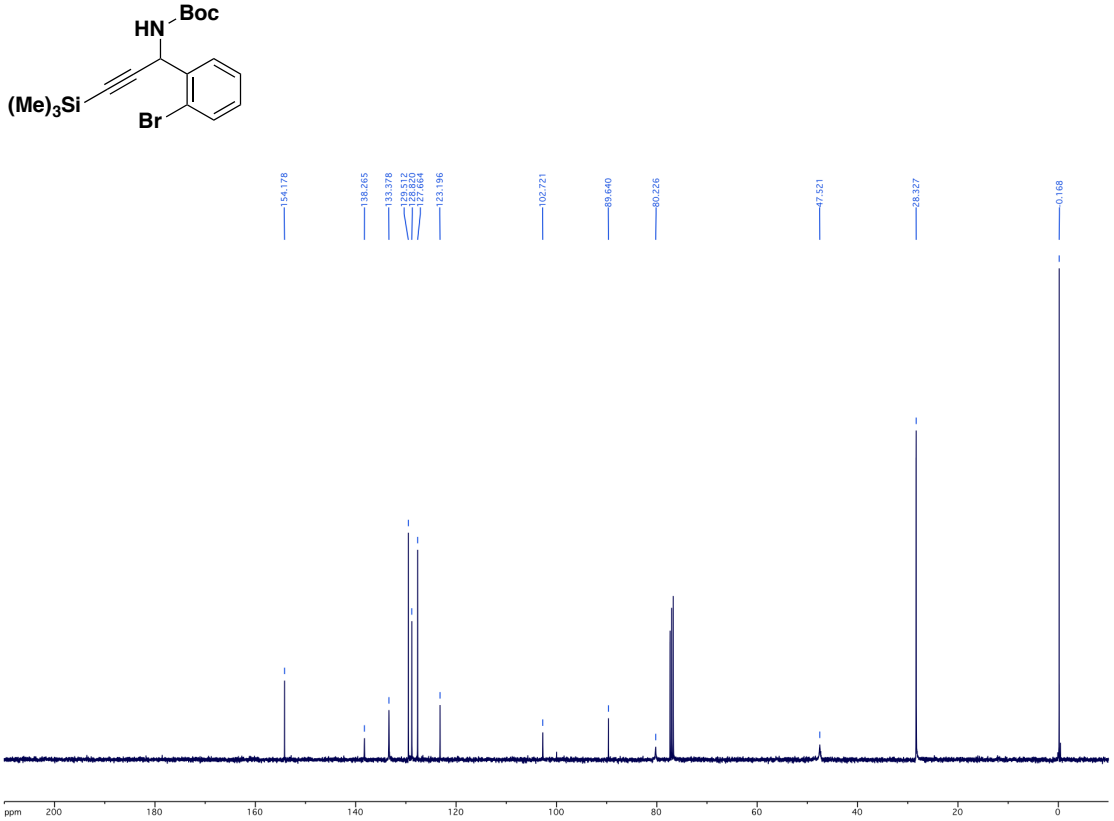
Propargylic amine 153: ^{13}C NMR (101 MHz, $CDCl_3$)



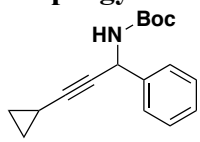
Propargylic amine 154: ^{1}H NMR (400 MHz, $CDCl_3$)

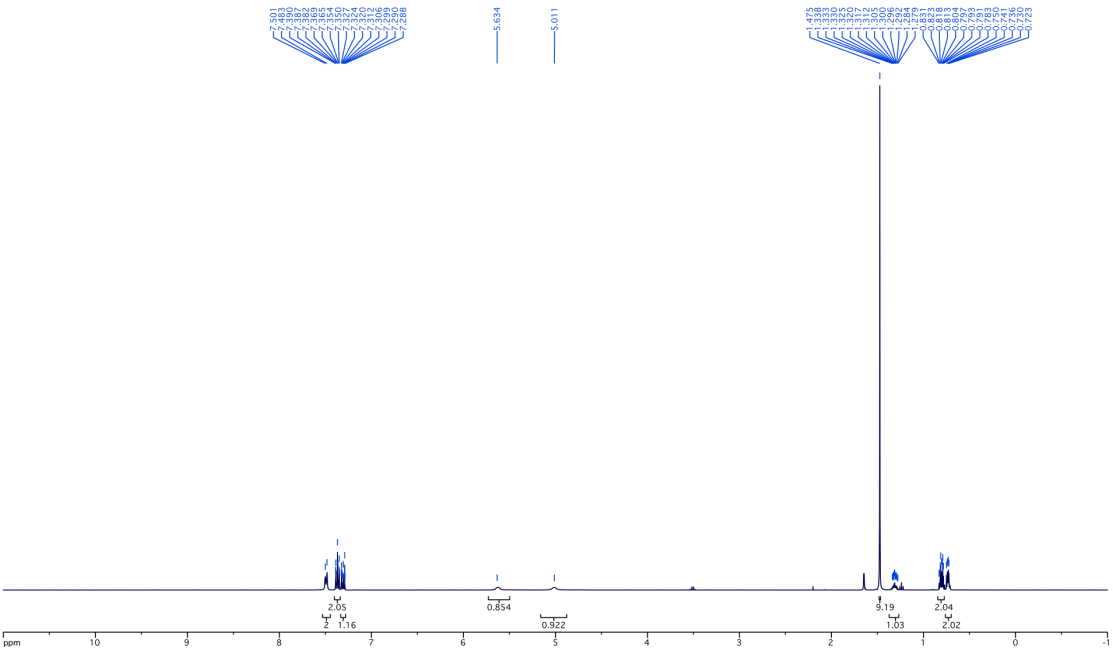


Propargylic amine 154: ^{13}C NMR (101 MHz, $CDCl_3$)

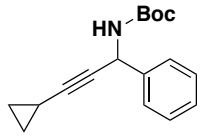


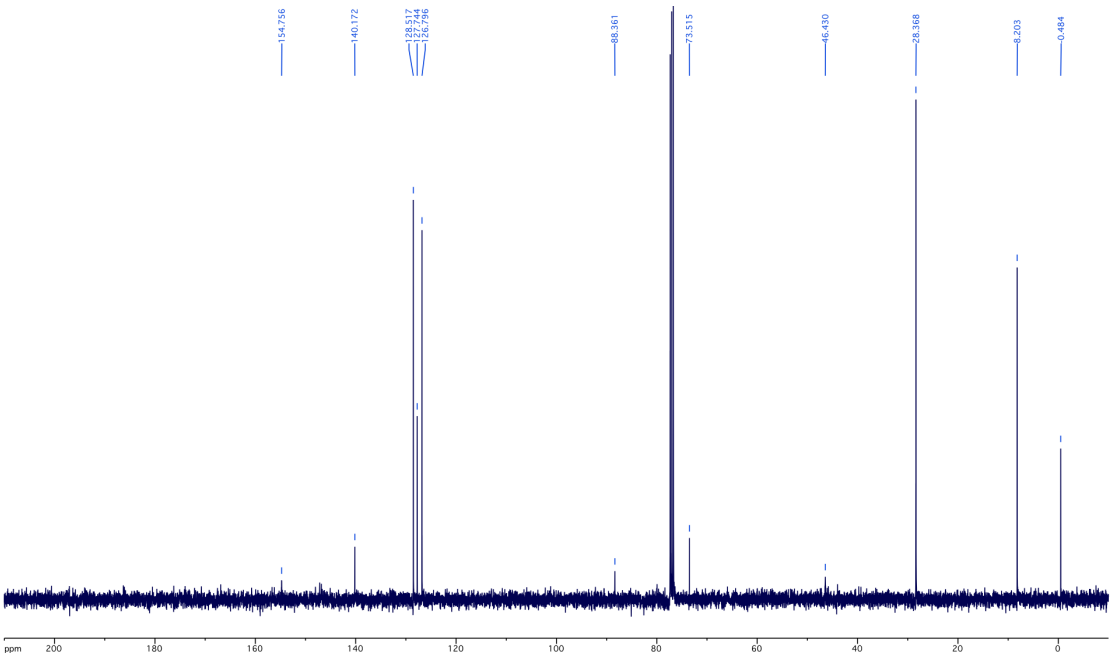
Propargylic amine156: ^{1}H NMR (400 MHz, $CDCl_3$)



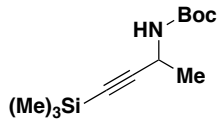


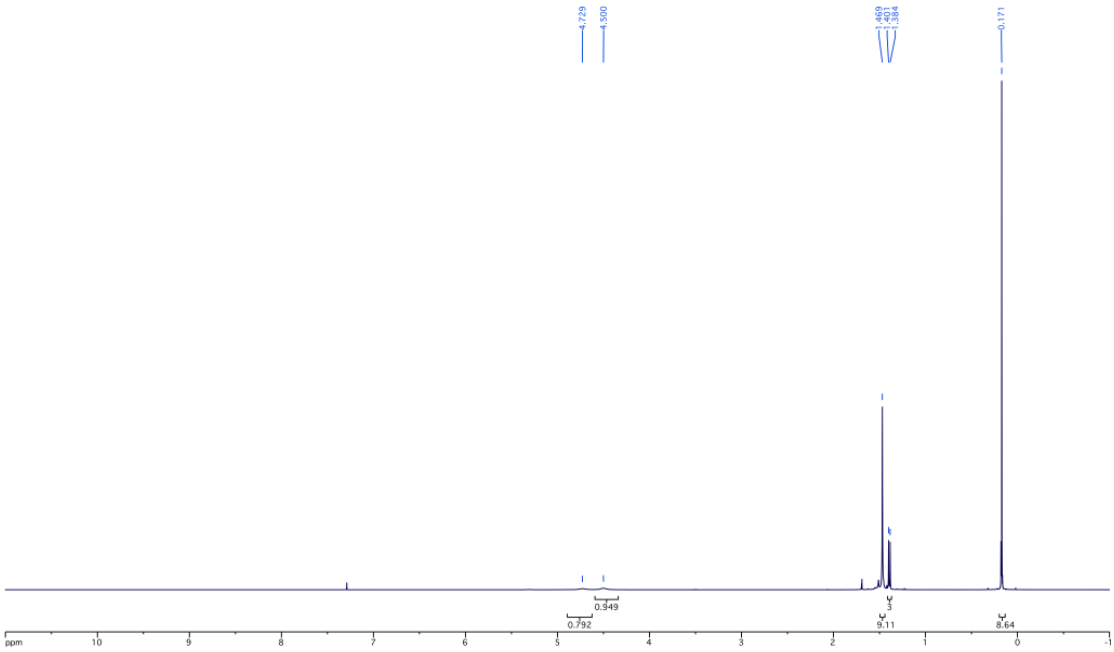
Propargylic amine 156: ^{13}C NMR (101 MHz, $CDCl_3$)



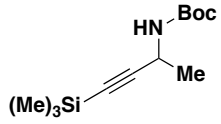


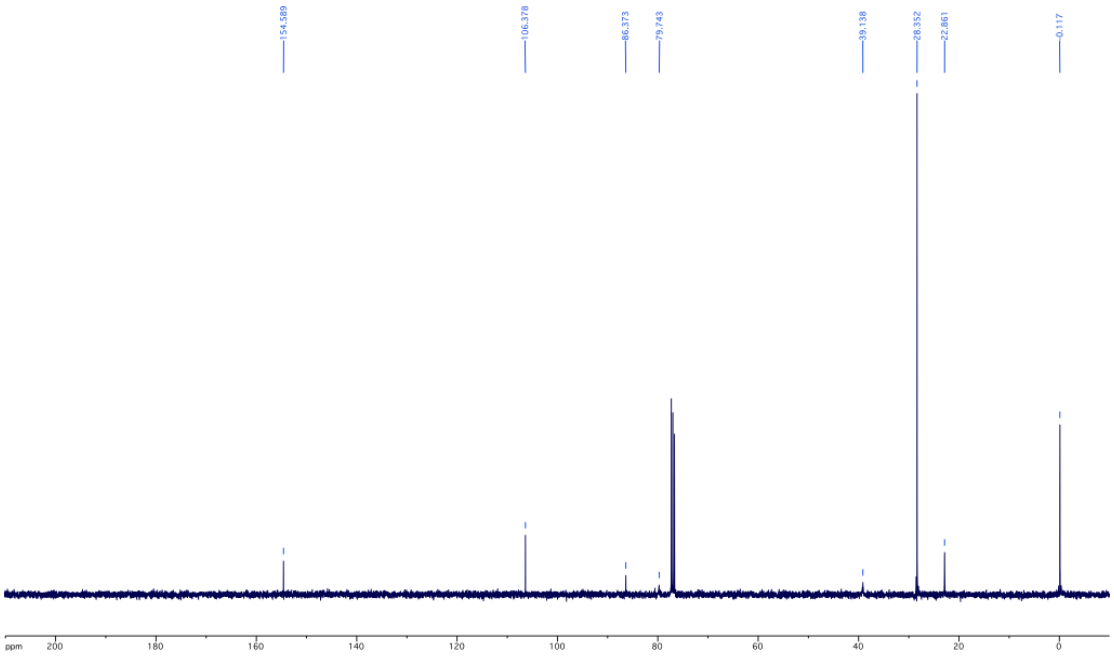
Propargylic amine 157: ^{1}H NMR (400 MHz, $CDCl_3$)



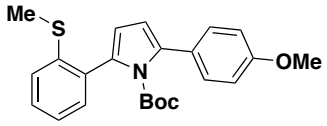


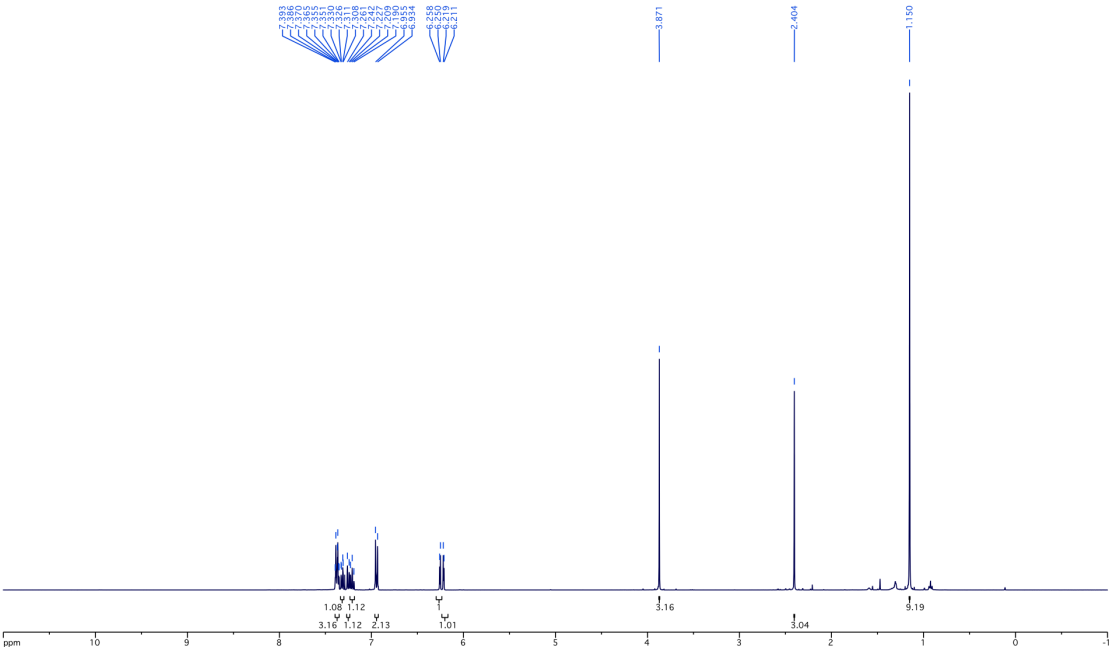
Propargylic amine 157: ^{13}C NMR (101 MHz, $CDCl_3$)



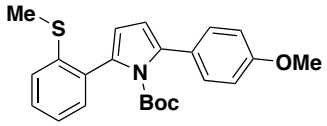


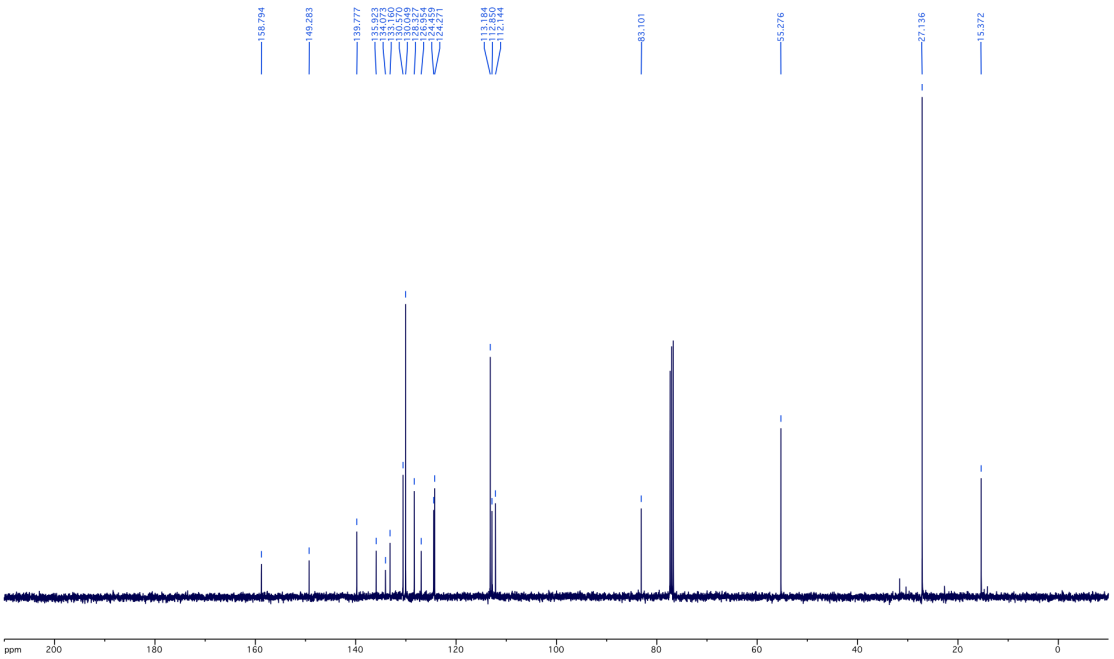
Pyrrole 159: ^{1}H NMR (400 MHz, $CDCl_3$)



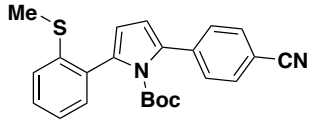


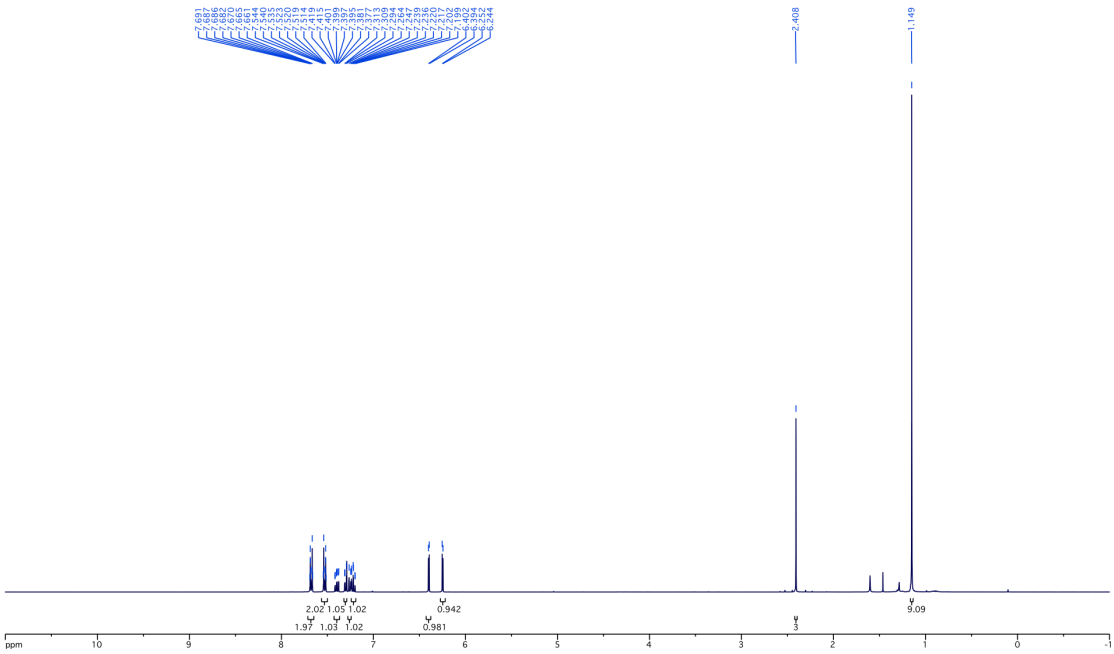
Pyrrole 159: ^{13}C NMR (101 MHz, $CDCl_3$)



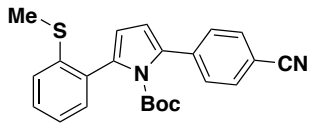


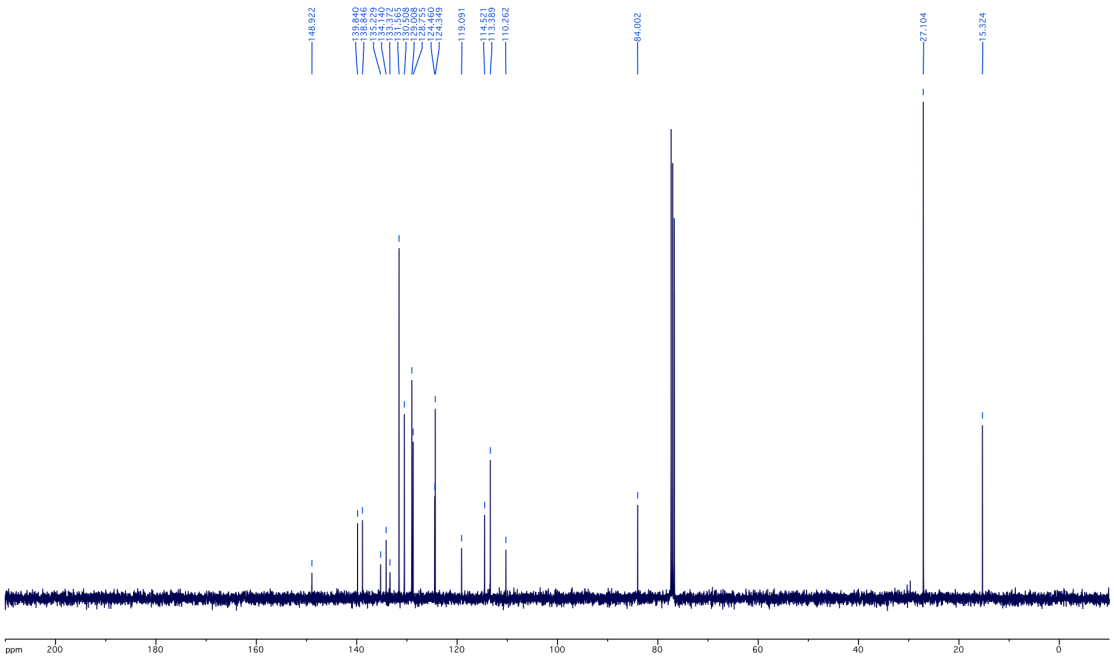
Pyrrole 160: ^{1}H NMR (400 MHz, $CDCl_3$)



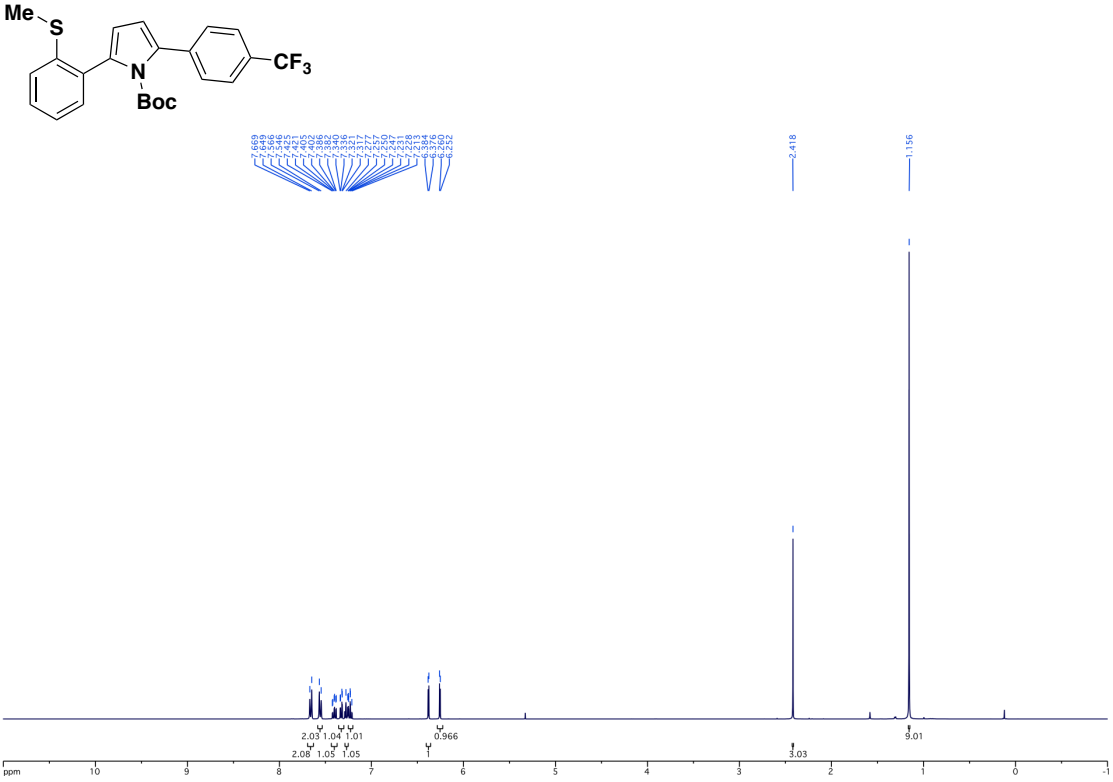


Pyrrole 160: ^{13}C NMR (101 MHz, $CDCl_3$)

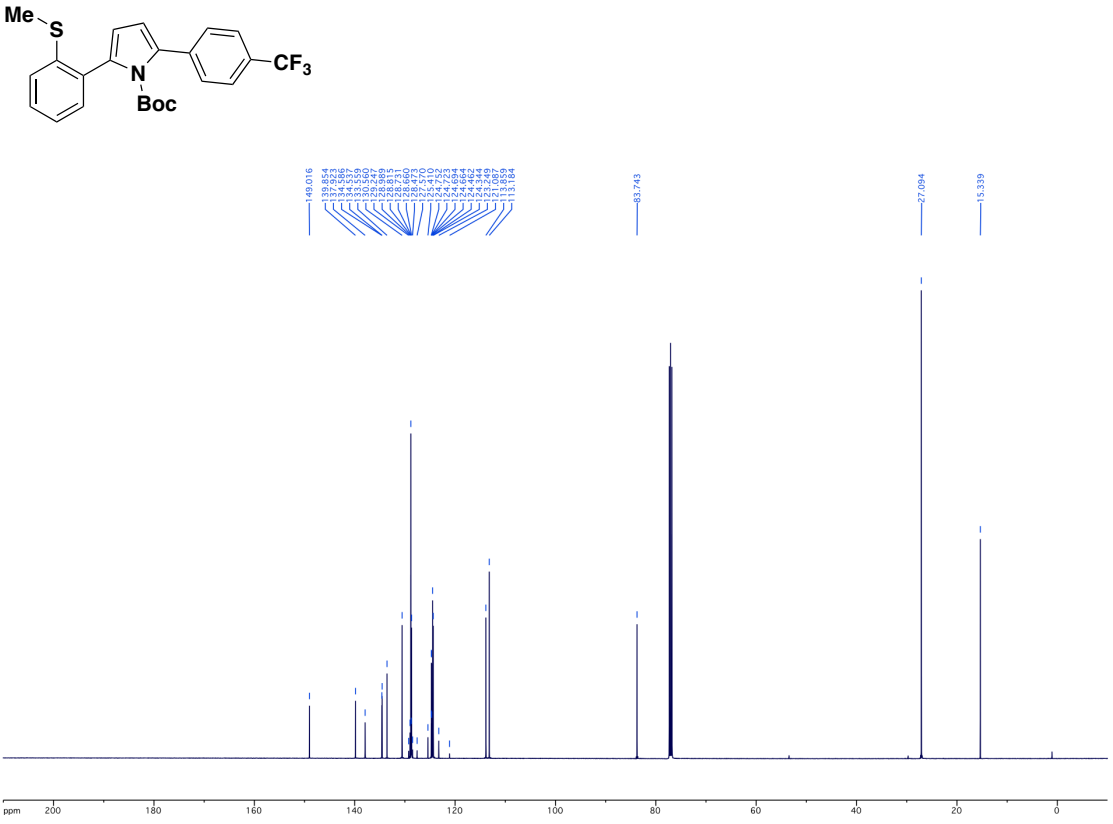




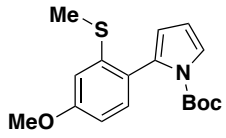
Pyrrole 161: ^{1}H NMR (400 MHz, $CDCl_3$)

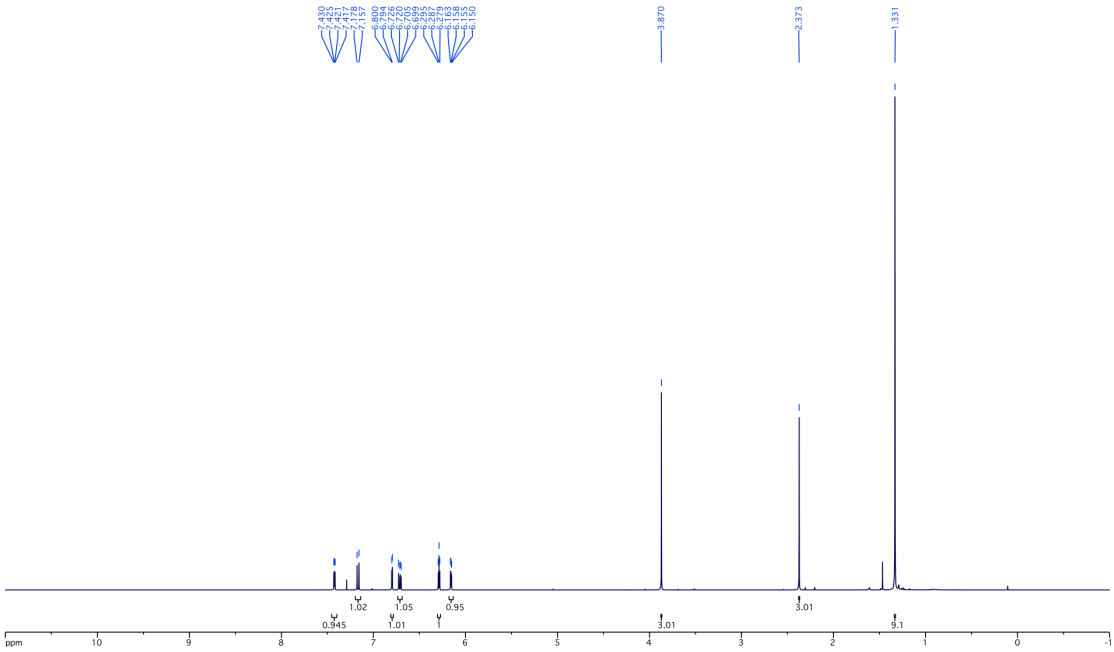


Pyrrole 161: ^{13}C NMR (101 MHz, $CDCl_3$)

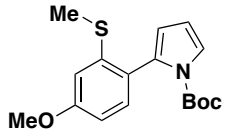


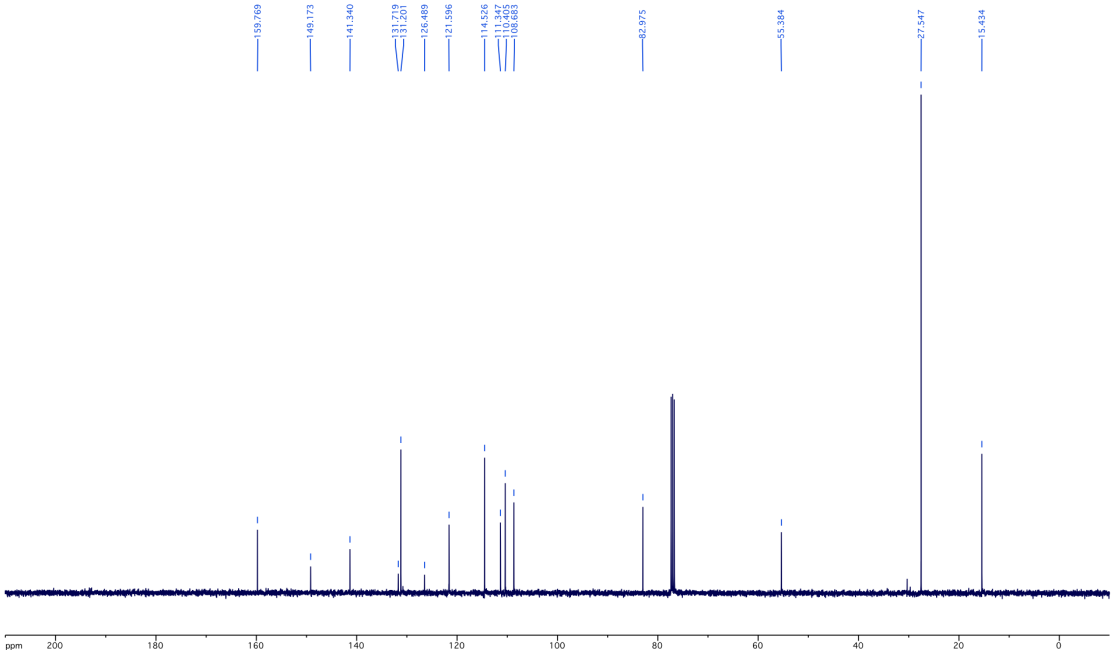
Pyrrole 162: ^{1}H NMR (400 MHz, $CDCl_3$)



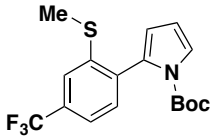


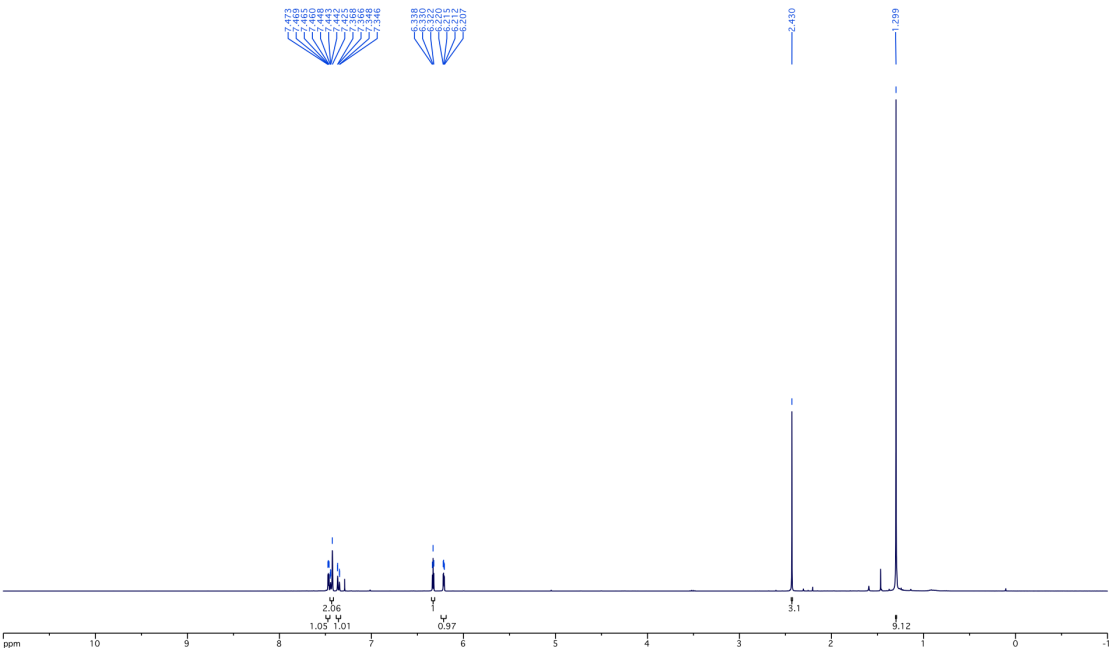
Pyrrole 162: ^{13}C NMR (101 MHz, $CDCl_3$)



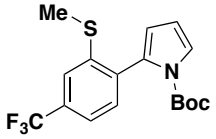


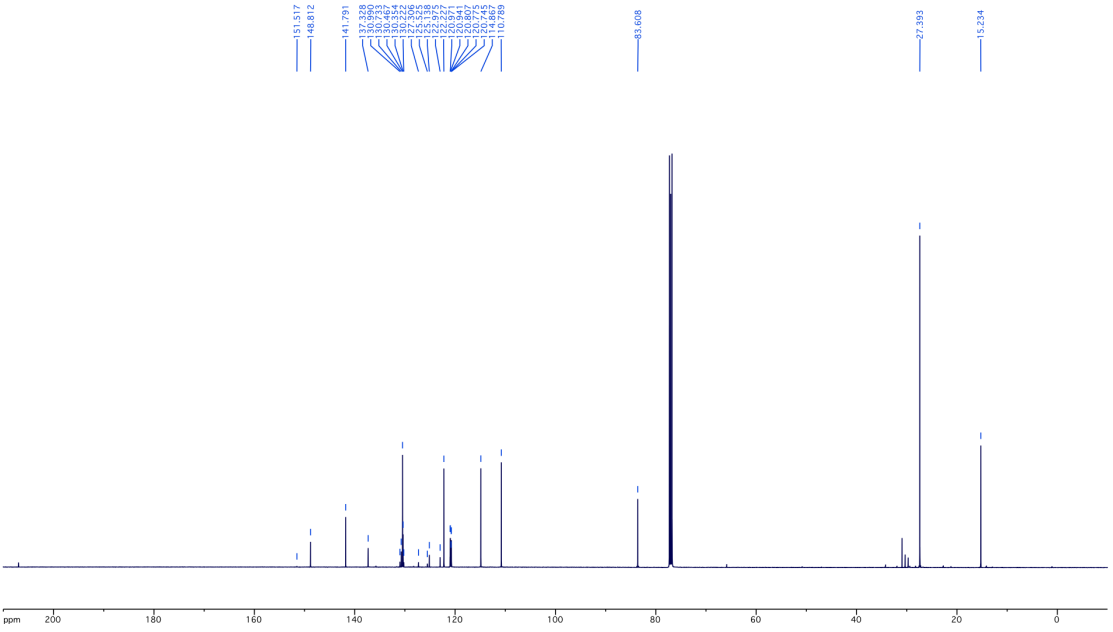
Pyrrole 163: ^{1}H NMR (400 MHz, $CDCl_3$)



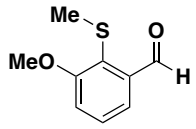


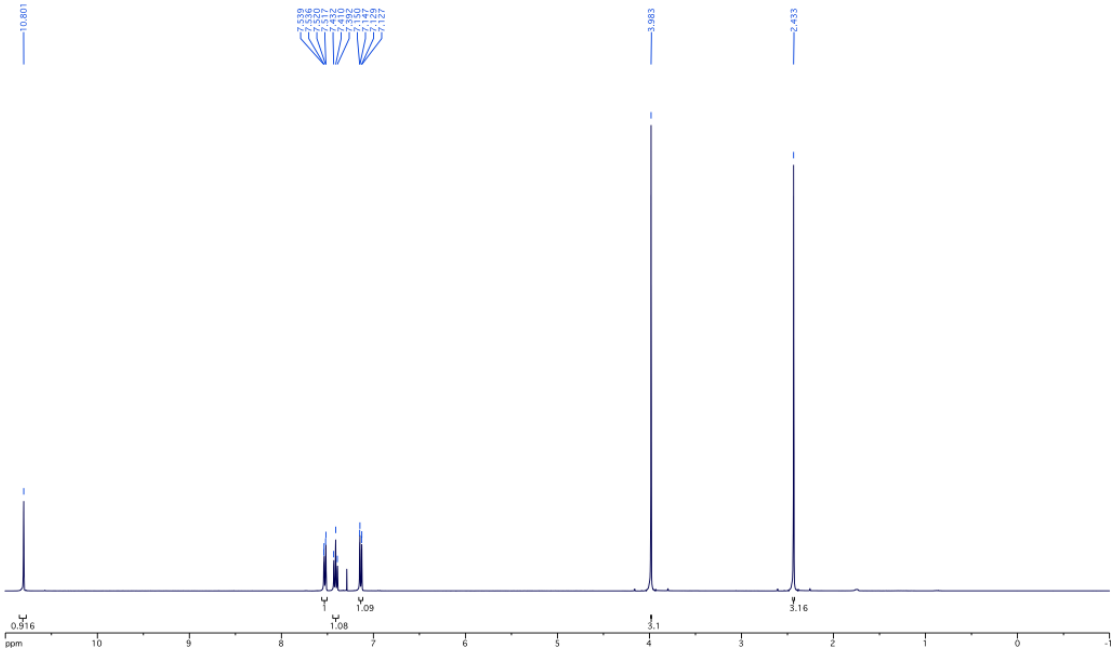
Pyrrole 163: ^{13}C NMR (101 MHz, $CDCl_3$)



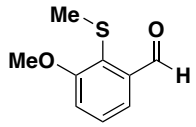


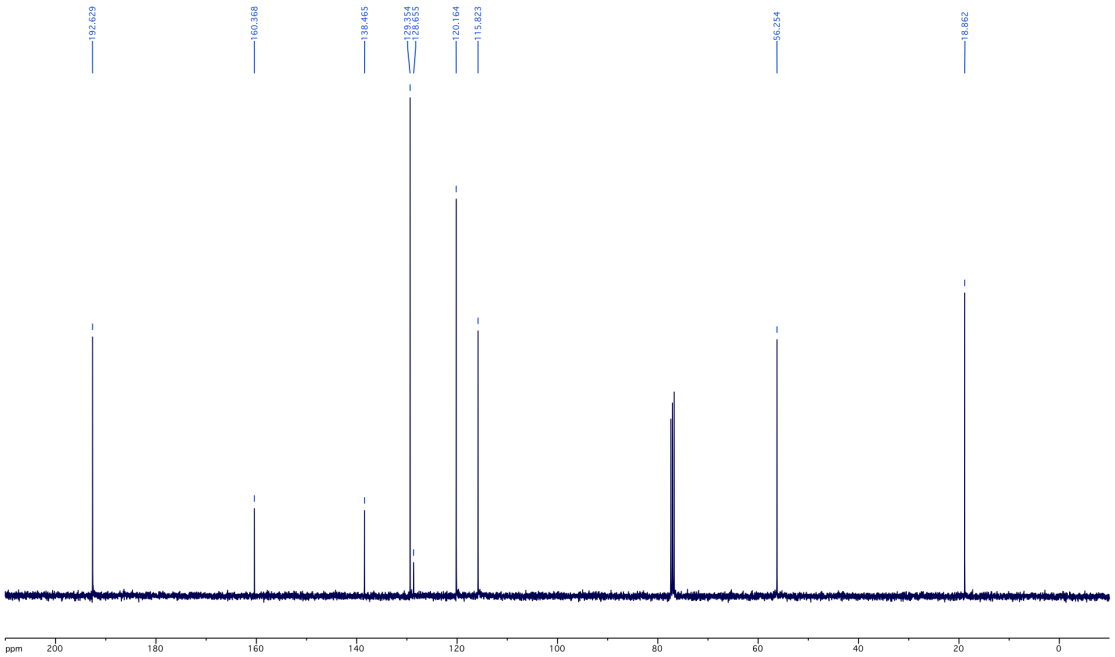
3-Methoxy-2-(methylthio)benzaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$)



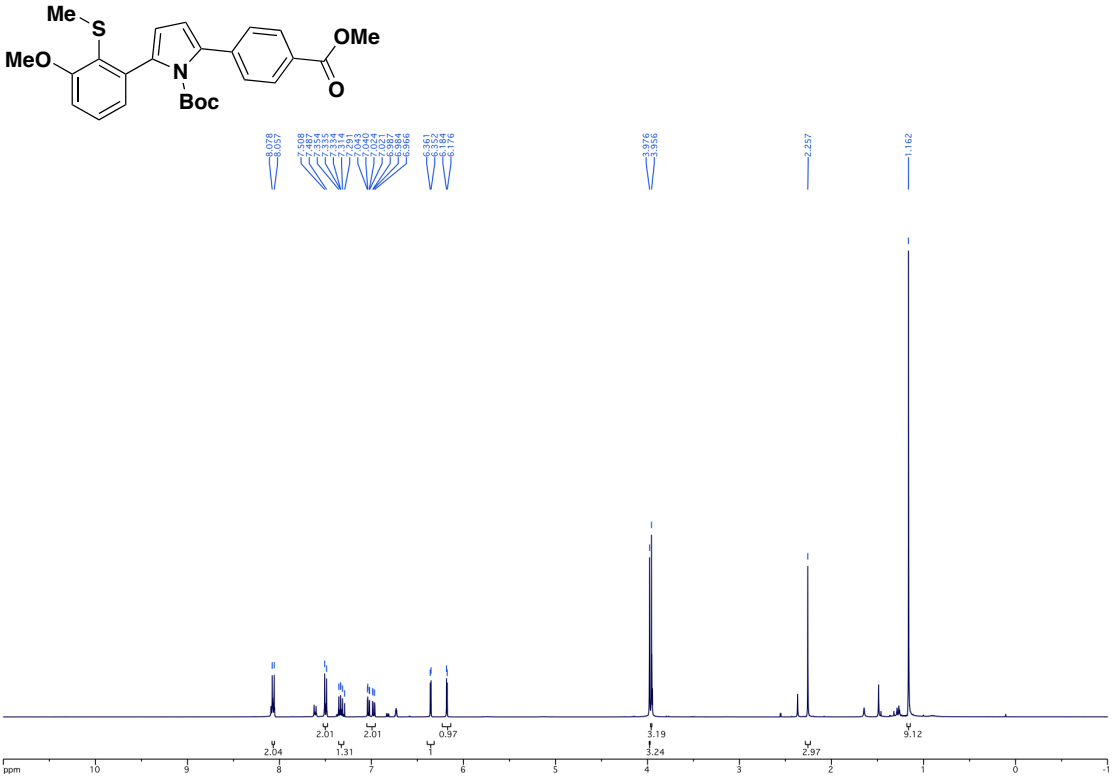


3-Methoxy-2-(methylthio)benzaldehyde: ^{13}C NMR (101 MHz, $CDCl_3$)

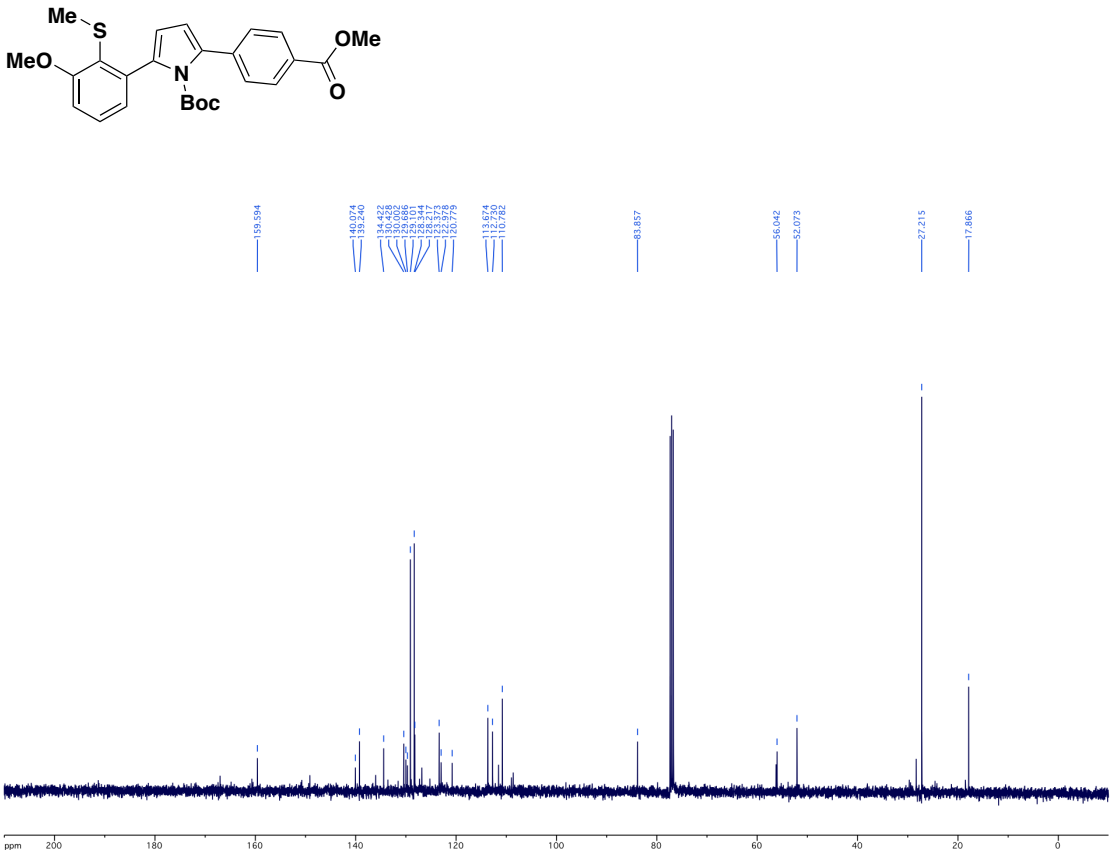




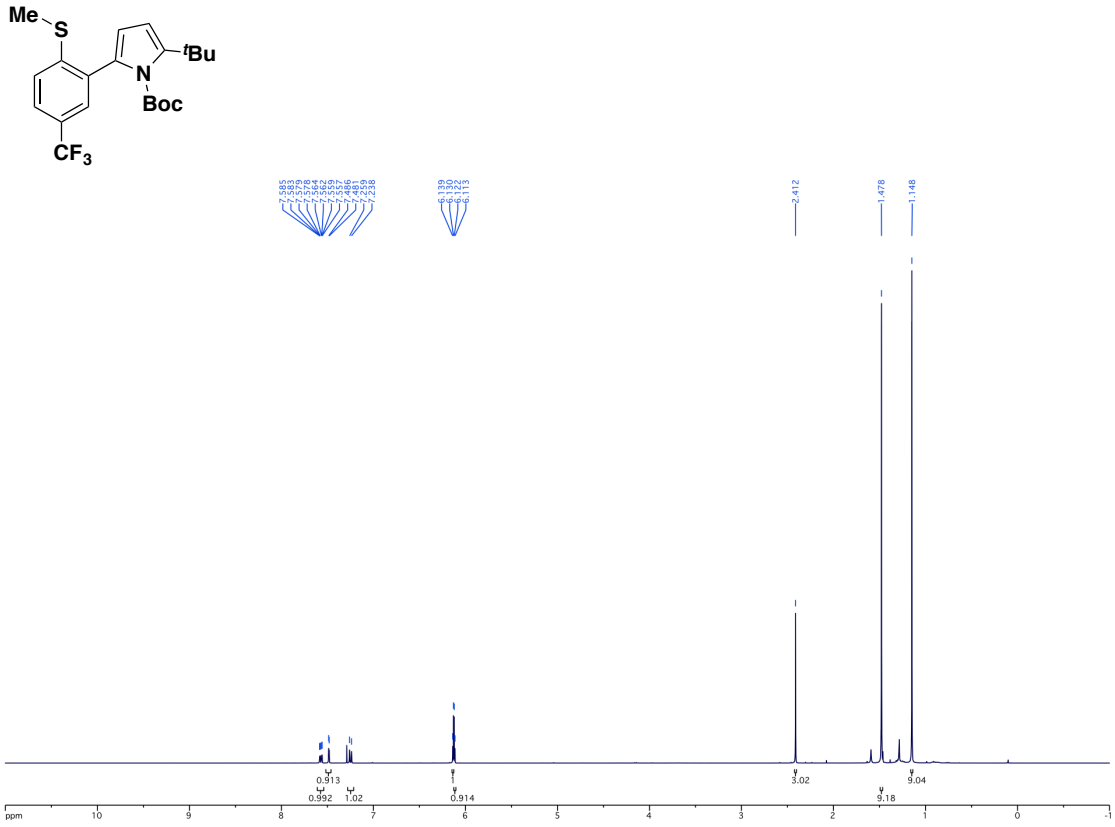
Pyrrole 164: ^{1}H NMR (400 MHz, $CDCl_3$)



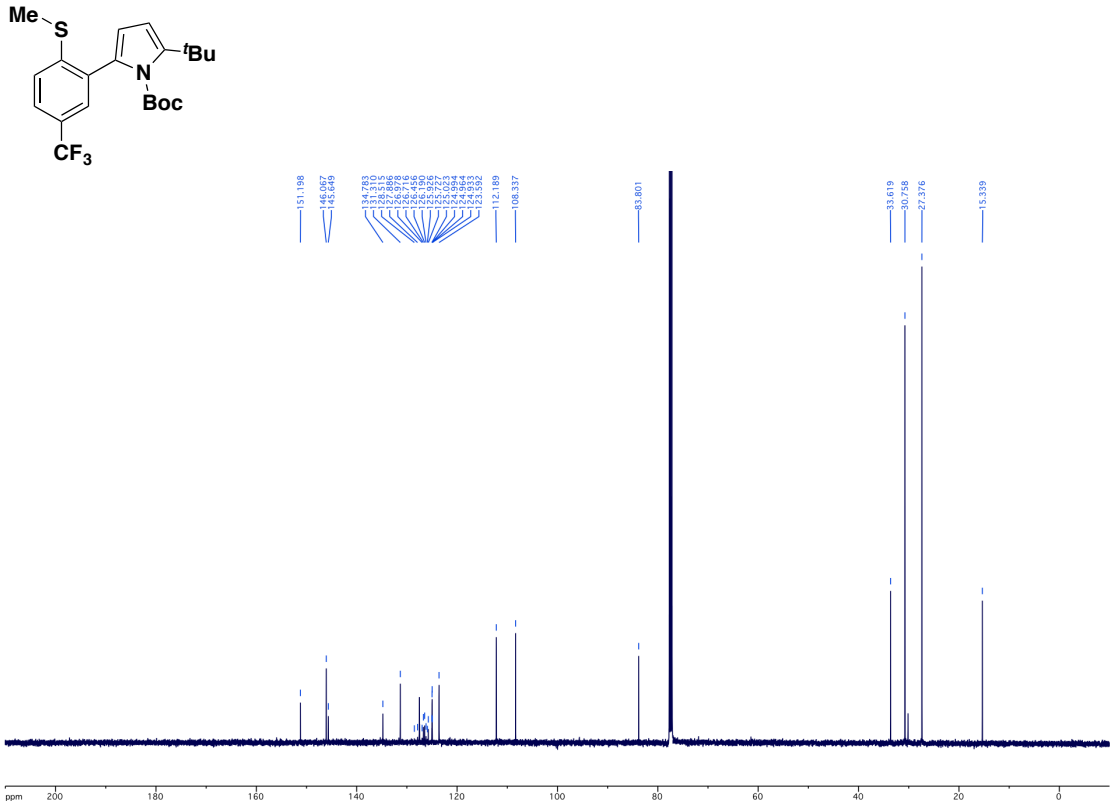
Pyrrole 164: ^{13}C NMR (101 MHz, $CDCl_3$)



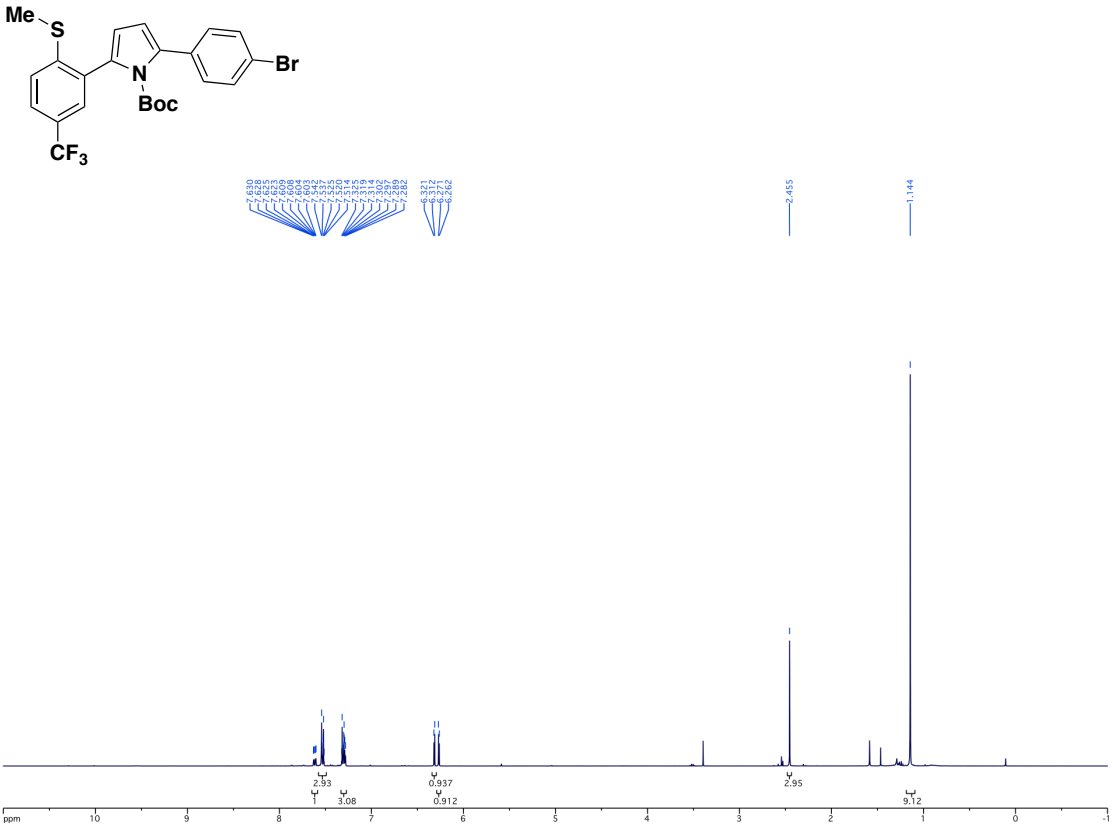
Pyrrole 165: ^{1}H NMR (400 MHz, $CDCl_3$)



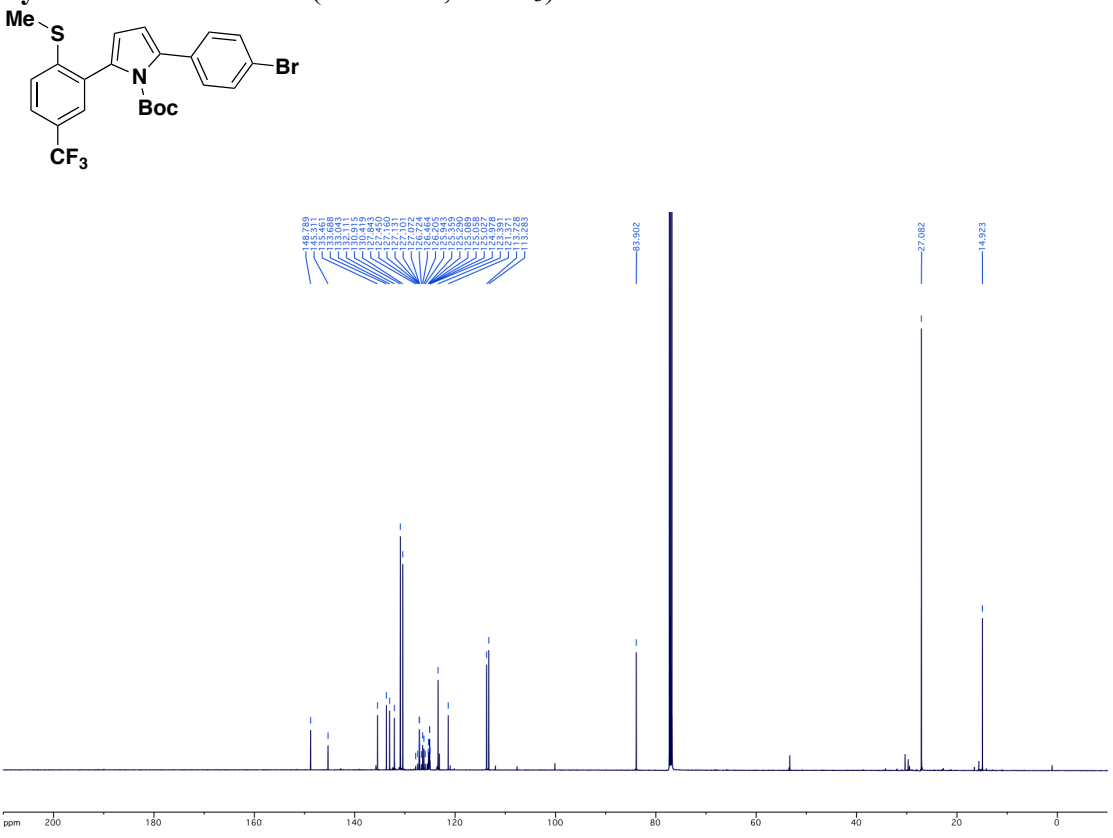
Pyrrole 165: ^{13}C NMR (101 MHz, $CDCl_3$)



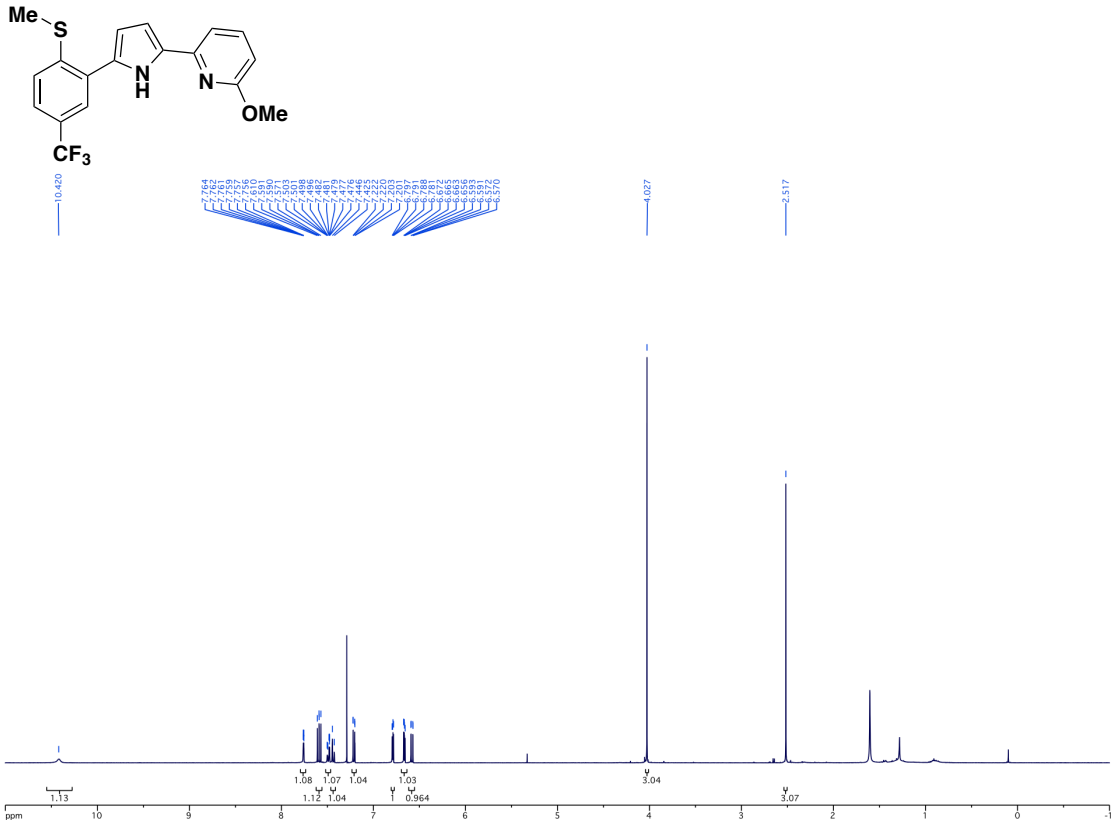
Pyrrole 166: ^{1}H NMR (400 MHz, $CDCl_3$)



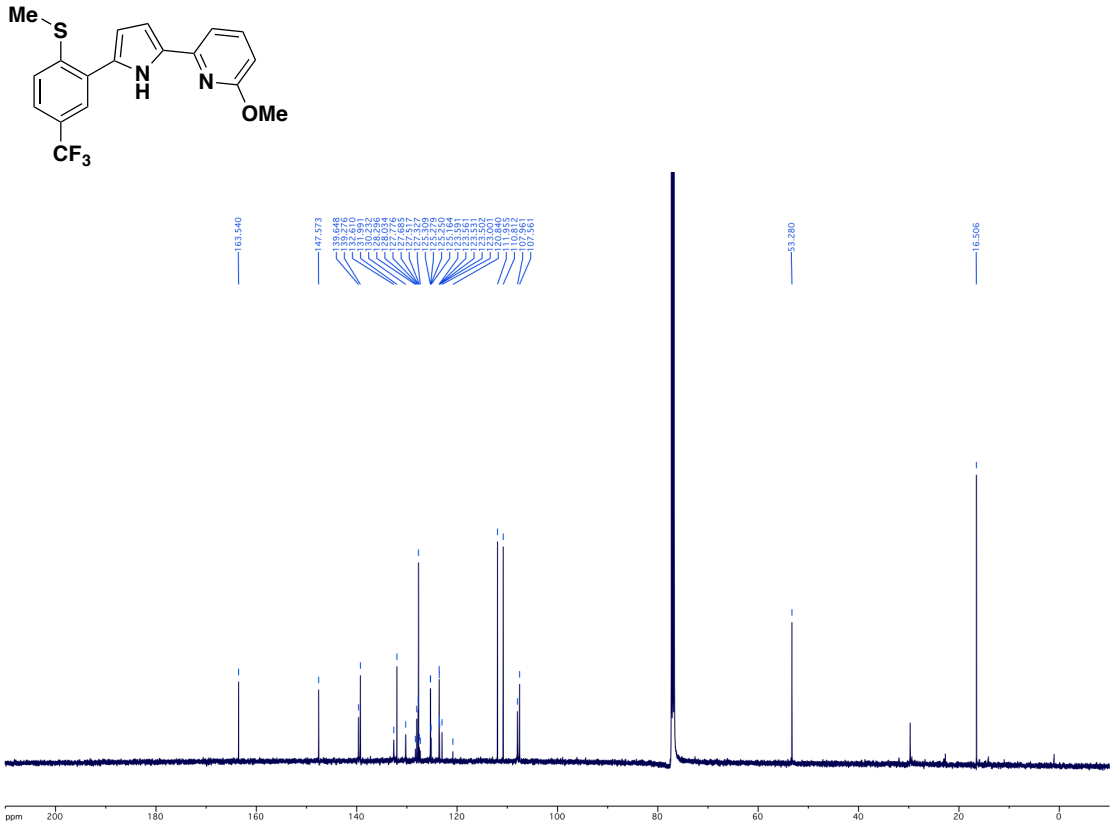
Pyrrole 166: ^{13}C NMR (101 MHz, $CDCl_3$)



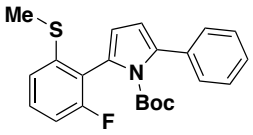
Pyrrole 167: ^{1}H NMR (400 MHz, $CDCl_3$)

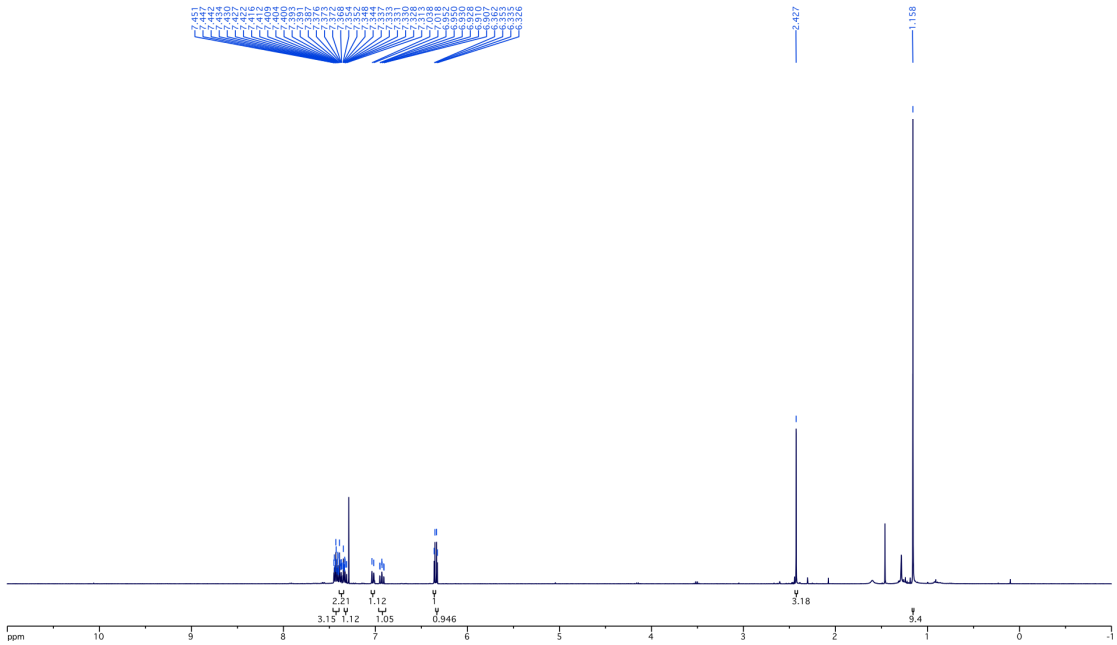


Pyrrole 167: ^{13}C NMR (101 MHz, $CDCl_3$)

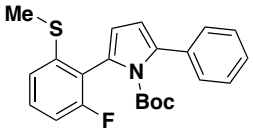


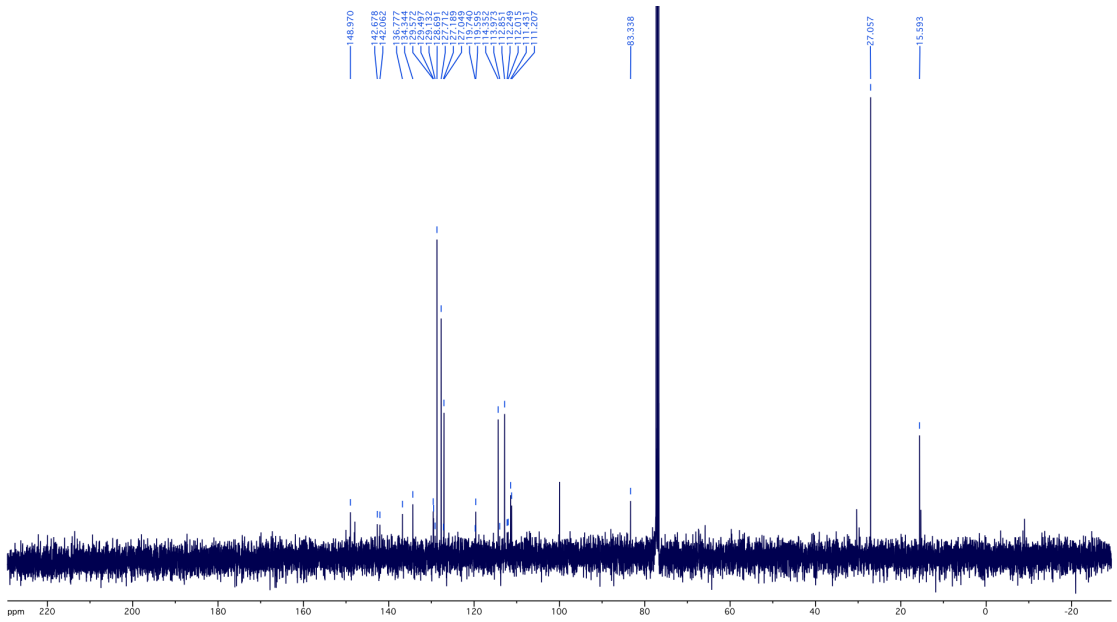
Pyrrole 168: ^{1}H NMR (400 MHz, $CDCl_3$)



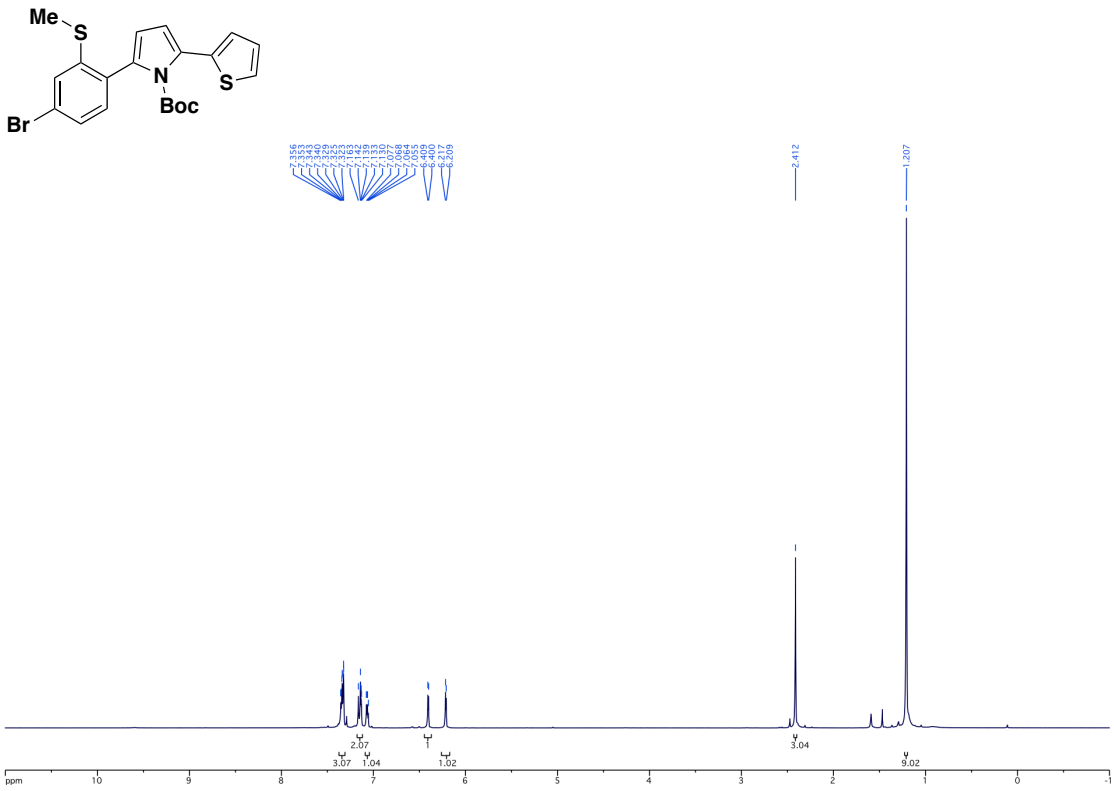


Pyrrole 168: ^{13}C NMR (101 MHz, $CDCl_3$)

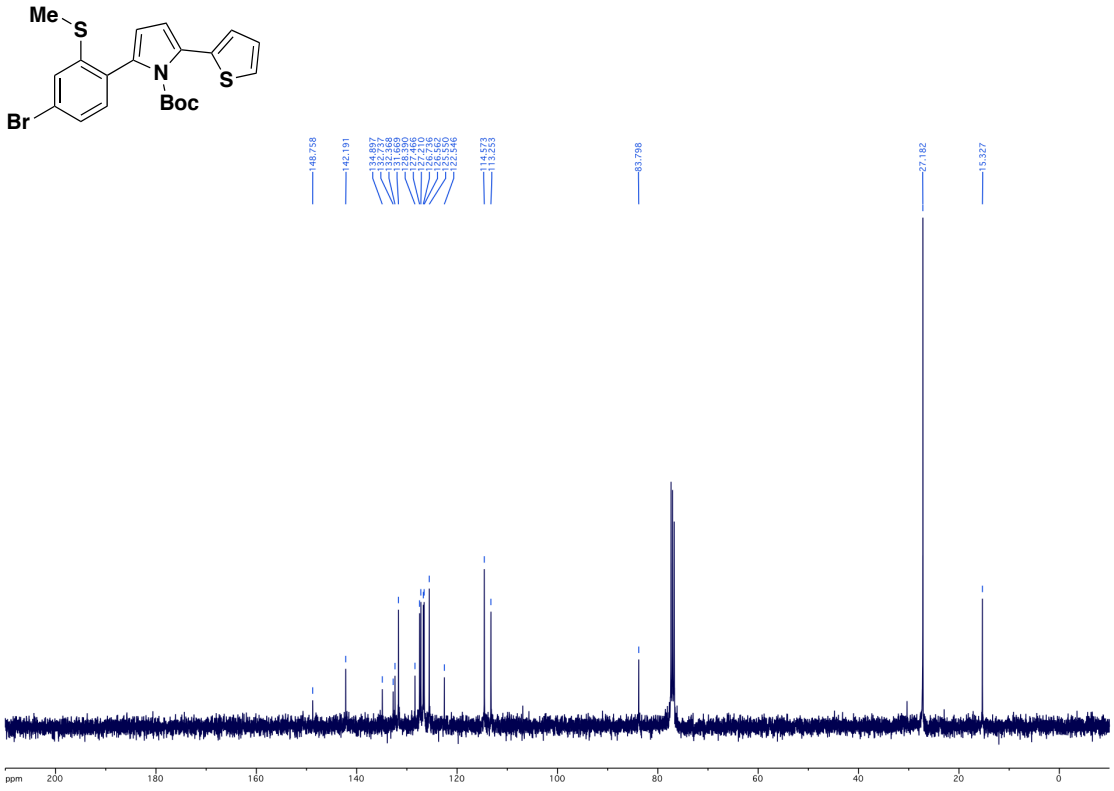




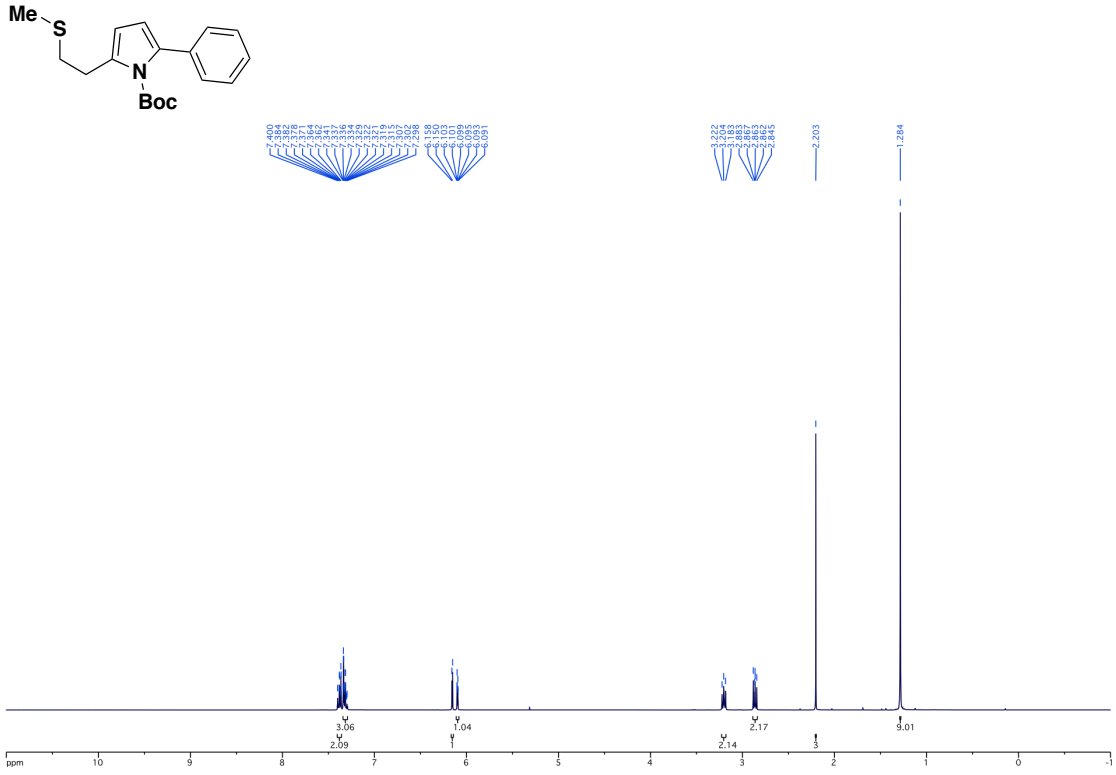
Pyrrole 169: ^{1}H NMR (400 MHz, $CDCl_3$)



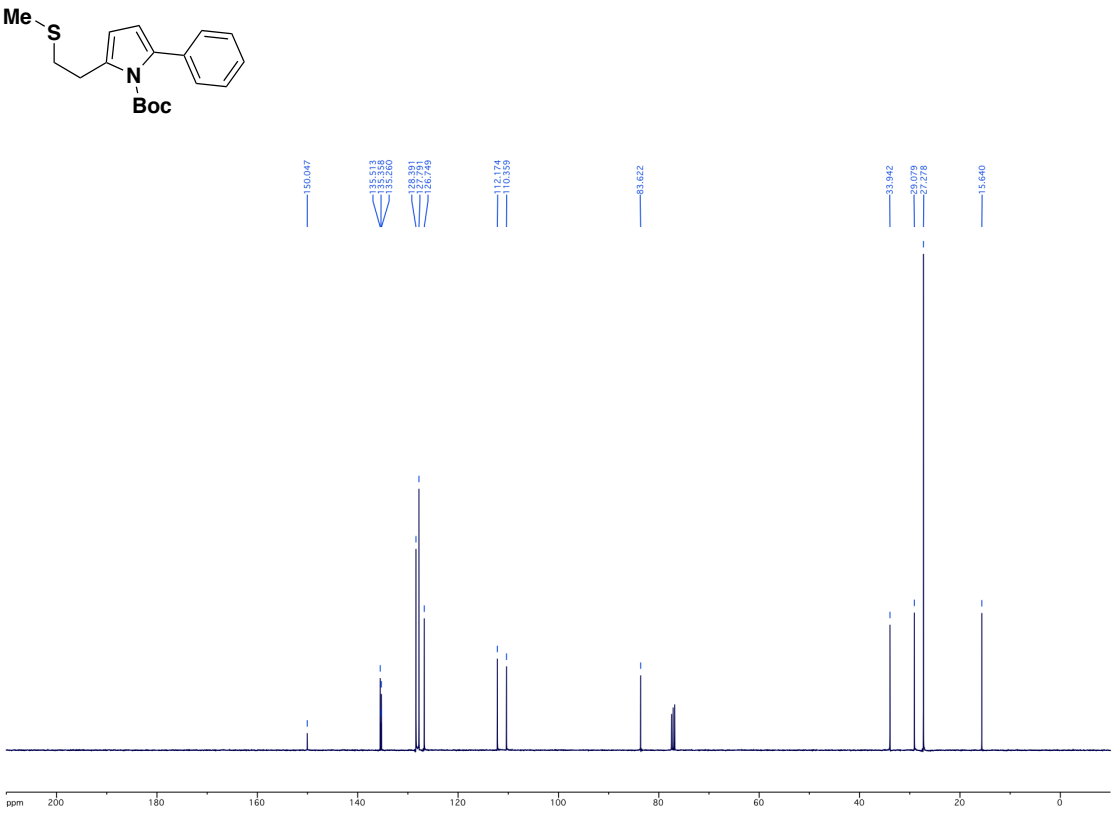
Pyrrole 169: ^{13}C NMR (101 MHz, $CDCl_3$)



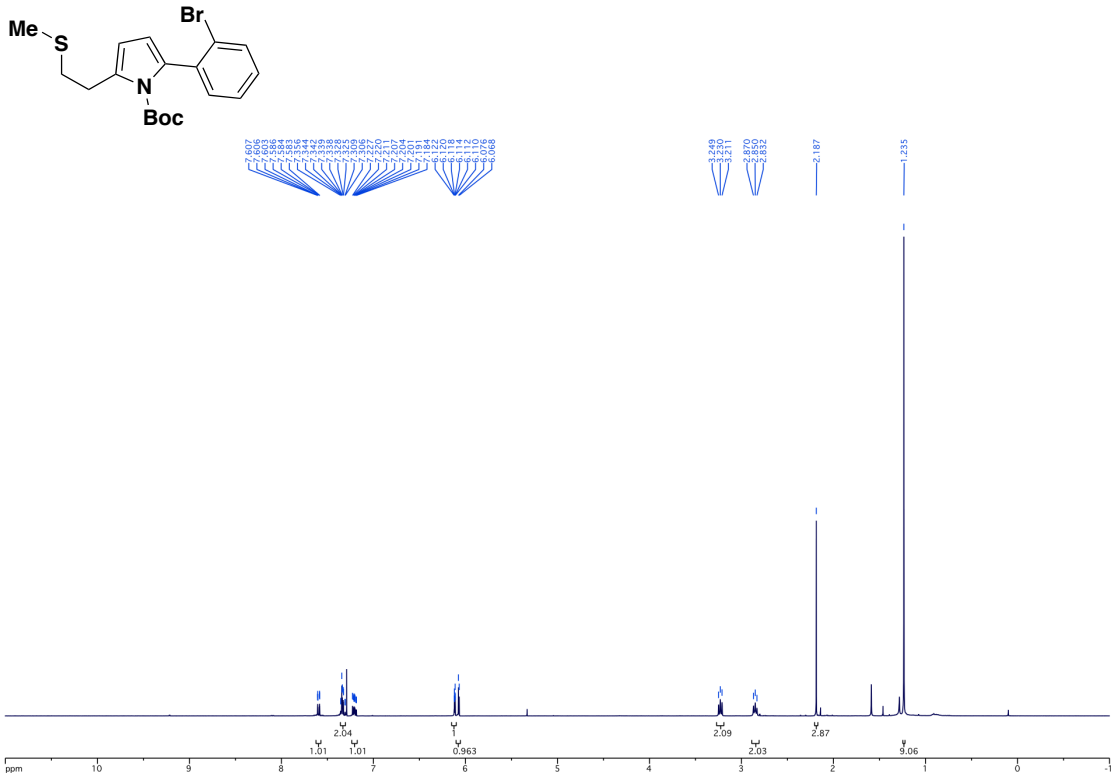
Pyrrole 170: ^{1}H NMR (400 MHz, $CDCl_3$)



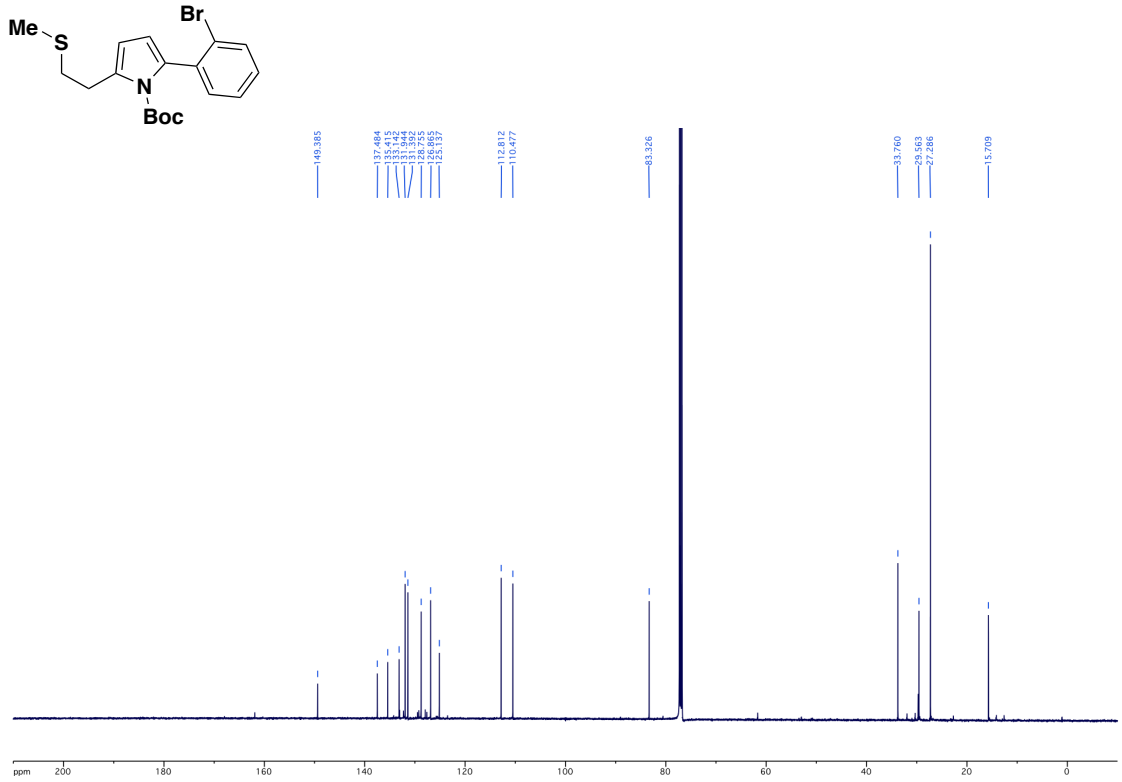
Pyrrole 170: ^{13}C NMR (101 MHz, $CDCl_3$)



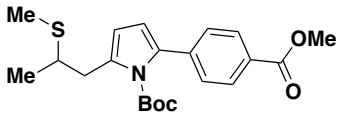
Pyrrole 171: ^{1}H NMR (400 MHz, $CDCl_3$)

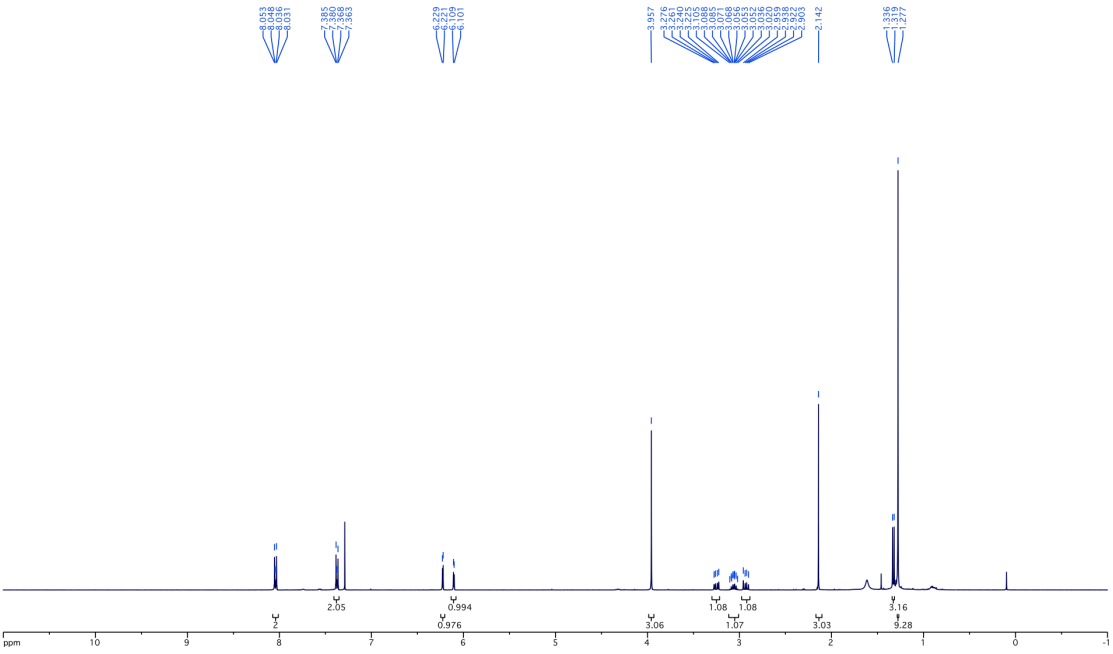


Pyrrole 171: ^{13}C NMR (101 MHz, $CDCl_3$)

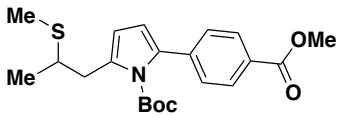


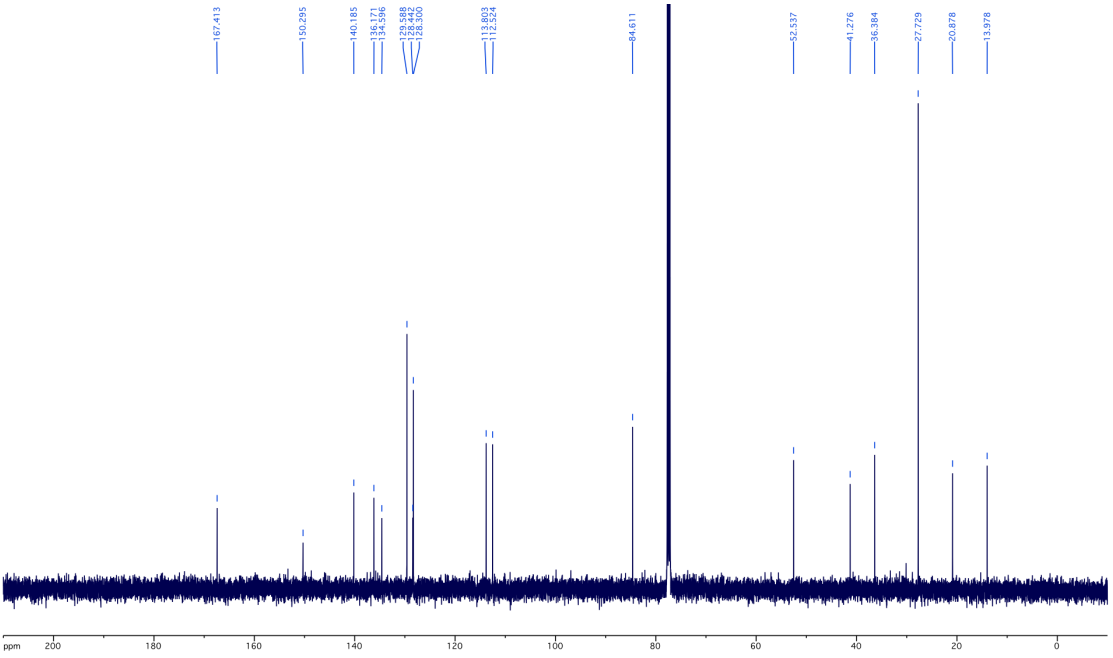
Pyrrole 172: ^{1}H NMR (400 MHz, $CDCl_3$)



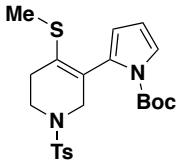


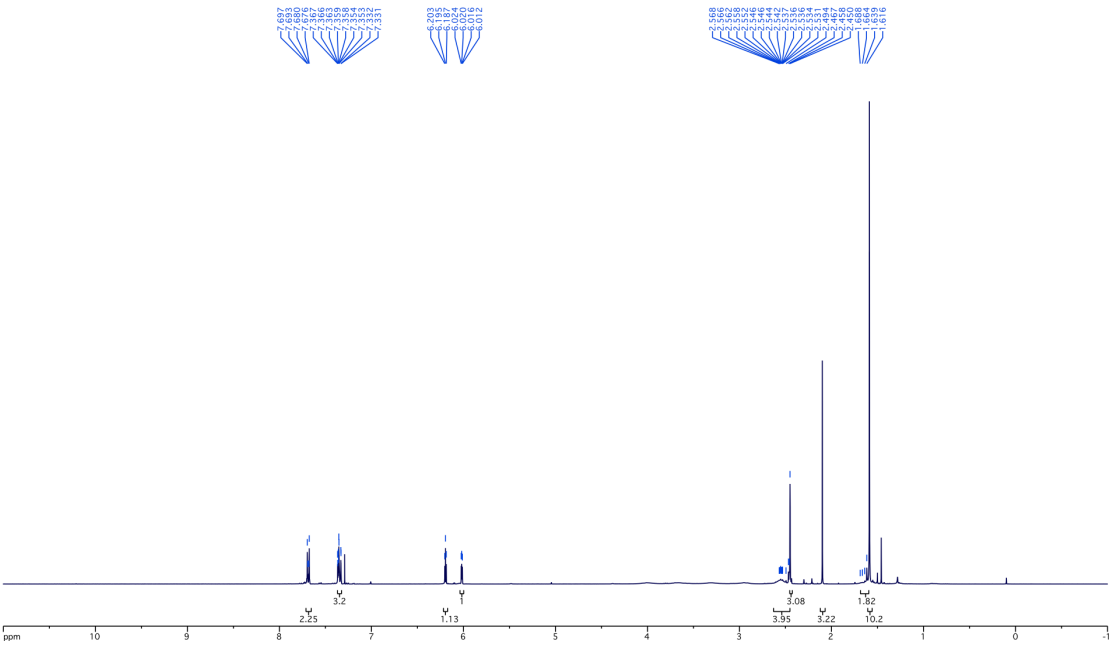
Pyrrole 172: ^{13}C NMR (101 MHz, $CDCl_3$)



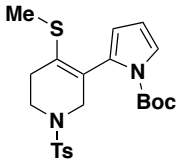


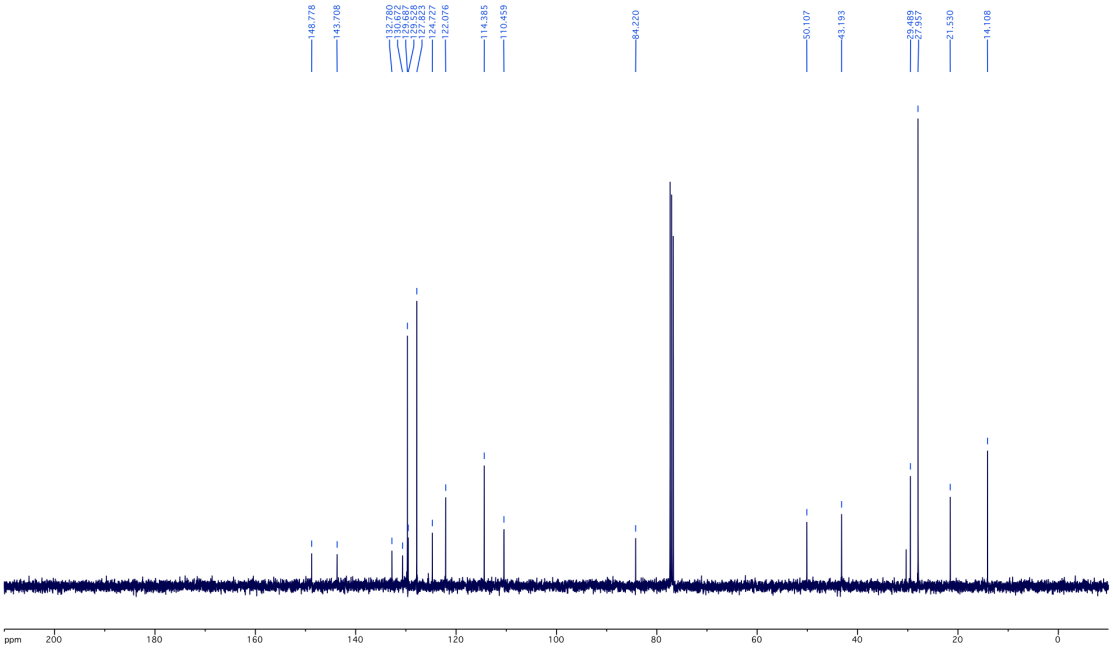
Pyrrole 173: ^{1}H NMR (400 MHz, $CDCl_3$)



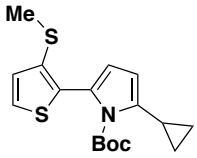


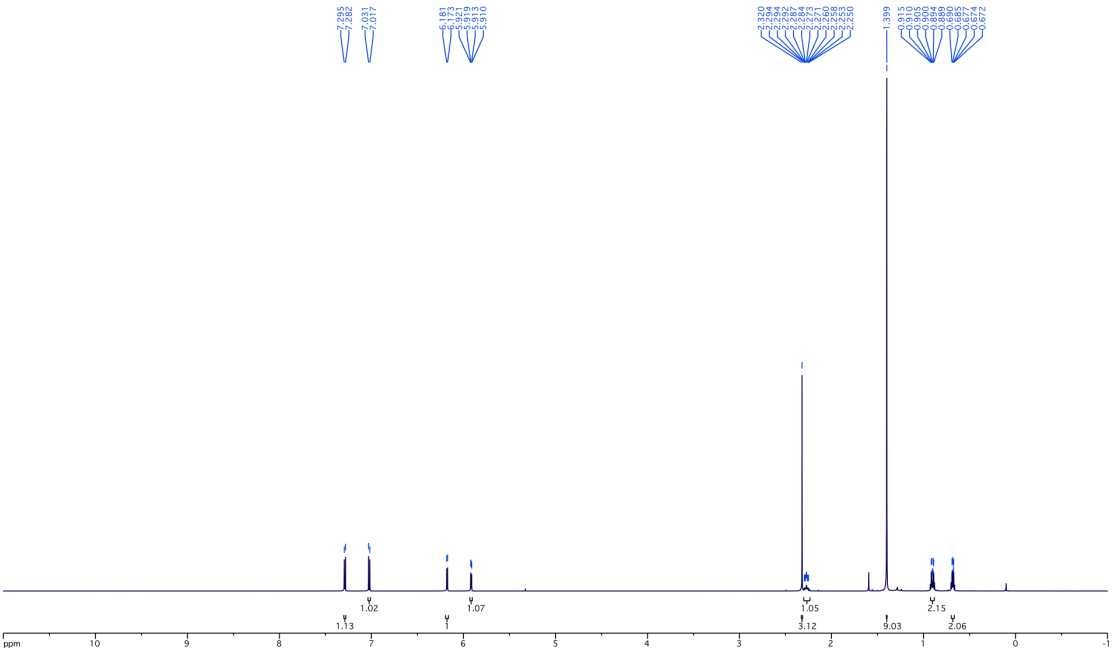
Pyrrole 173: ^{13}C NMR (101 MHz, $CDCl_3$)



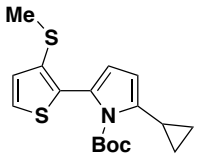


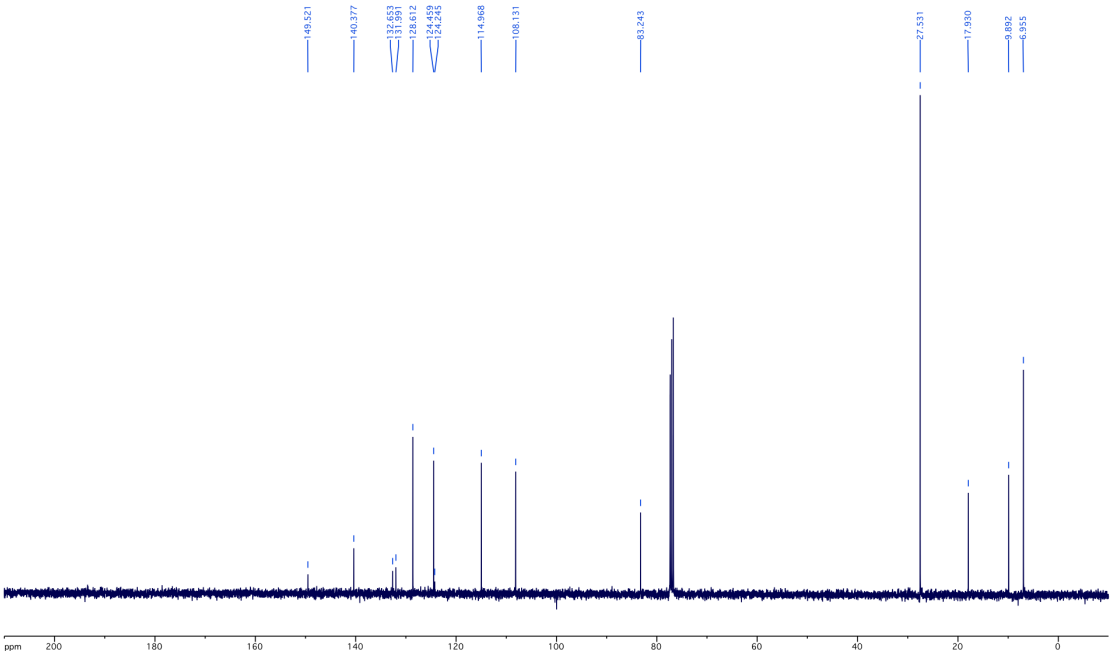
Pyrrole 174: ^{1}H NMR (400 MHz, $CDCl_3$)



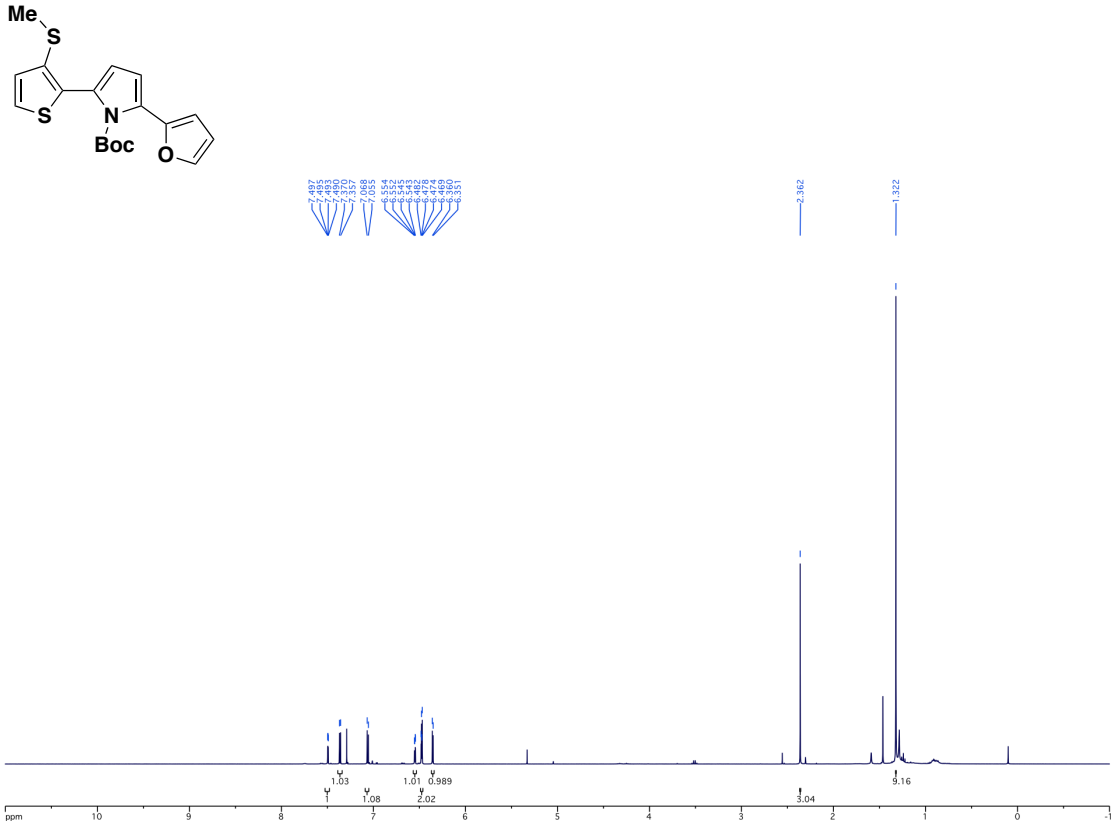


Pyrrole 174: ^{13}C NMR (101 MHz, $CDCl_3$)

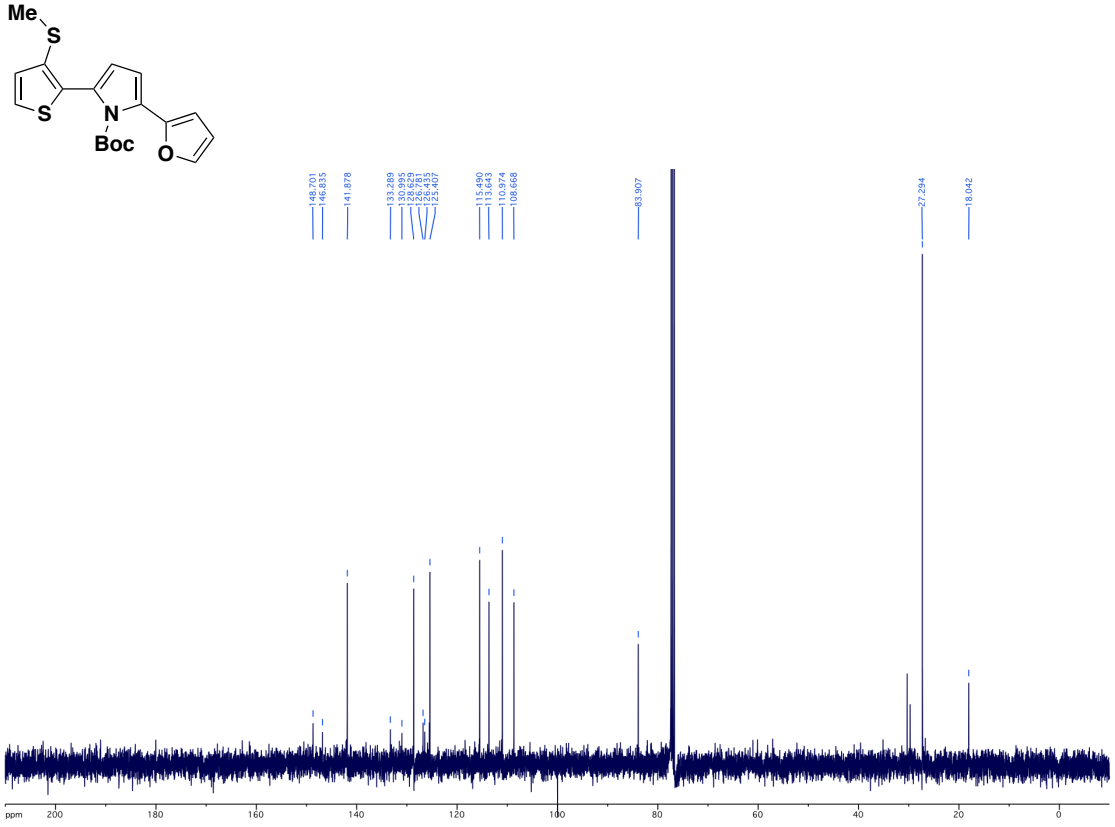




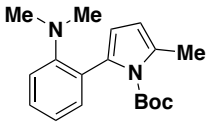
Pyrrole 175: ^{1}H NMR (400 MHz, $CDCl_3$)

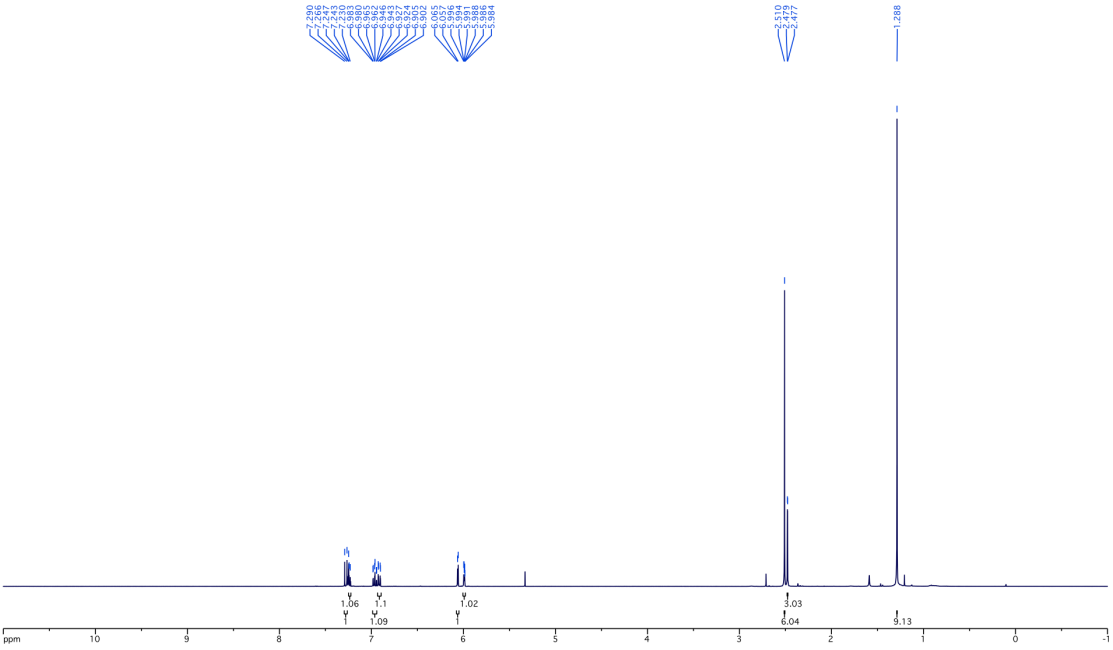


Pyrrole 175: ^{13}C NMR (101 MHz, $CDCl_3$)

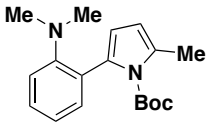


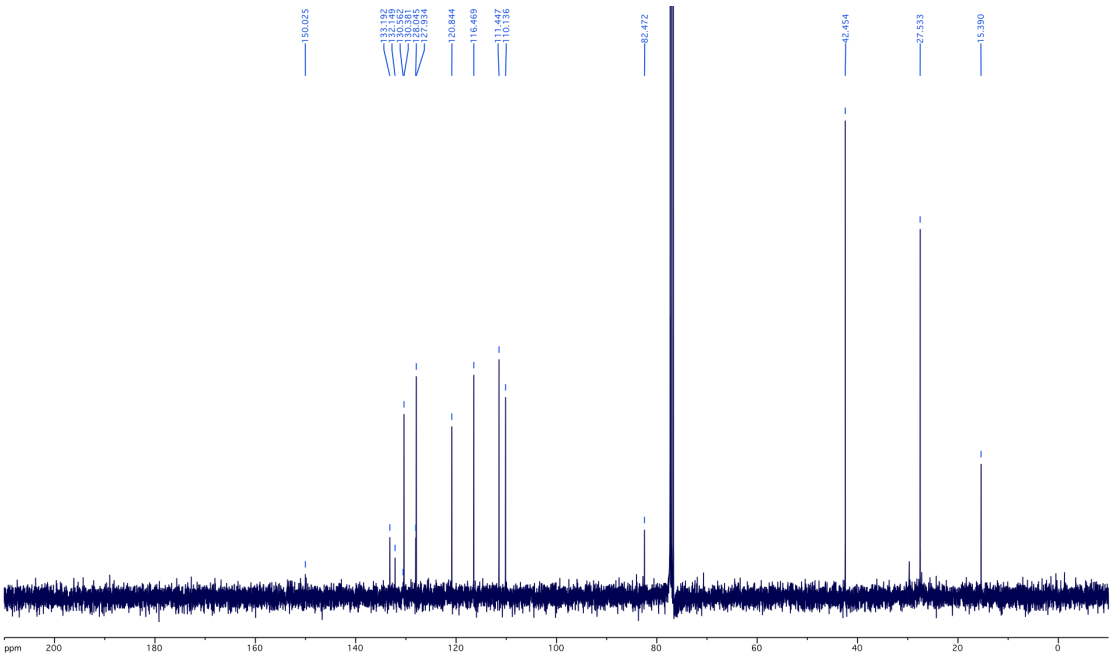
Pyrrole 176: ^{1}H NMR (400 MHz, $CDCl_3$)



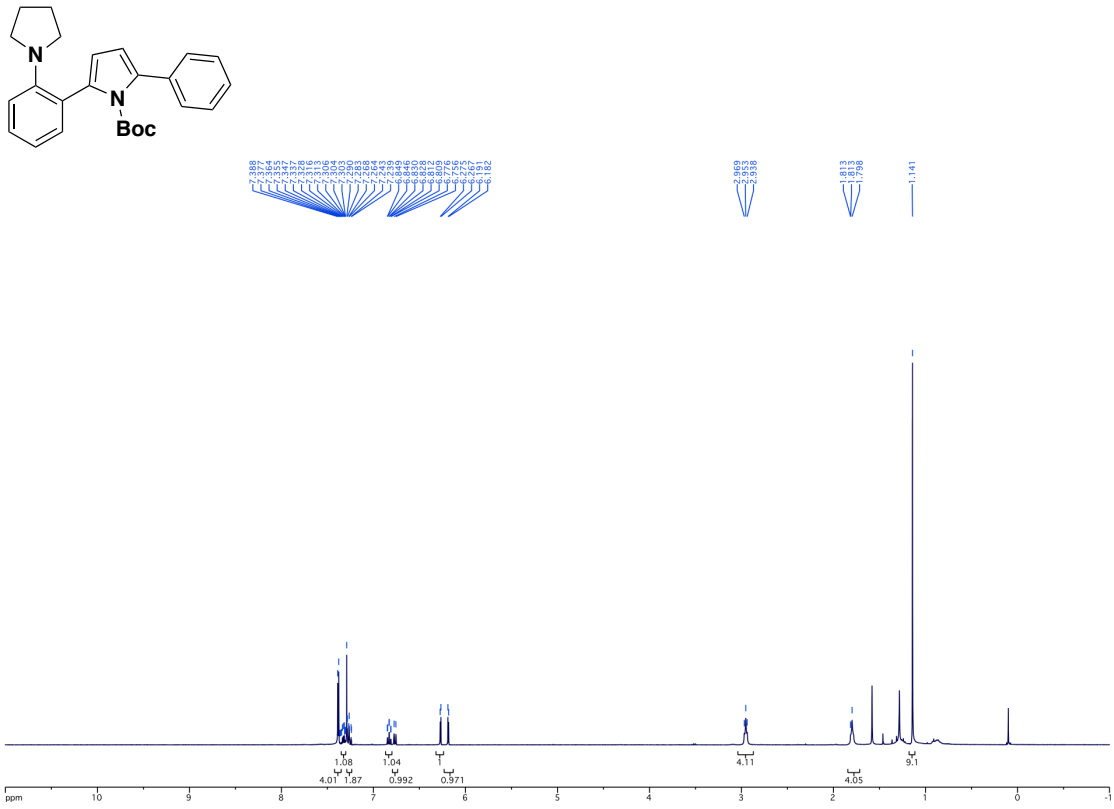


Pyrrole 176: ^{13}C NMR (101 MHz, $CDCl_3$)

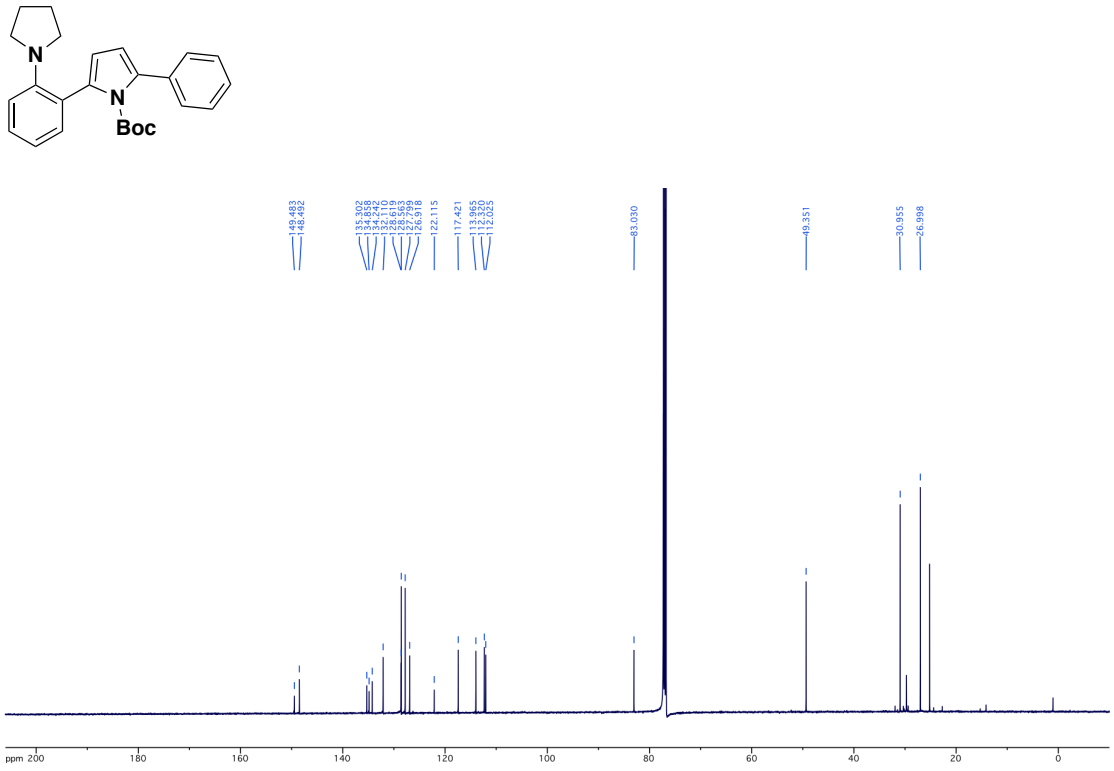




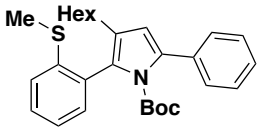
Pyrrole 177: ^{1}H NMR (400 MHz, $CDCl_3$)

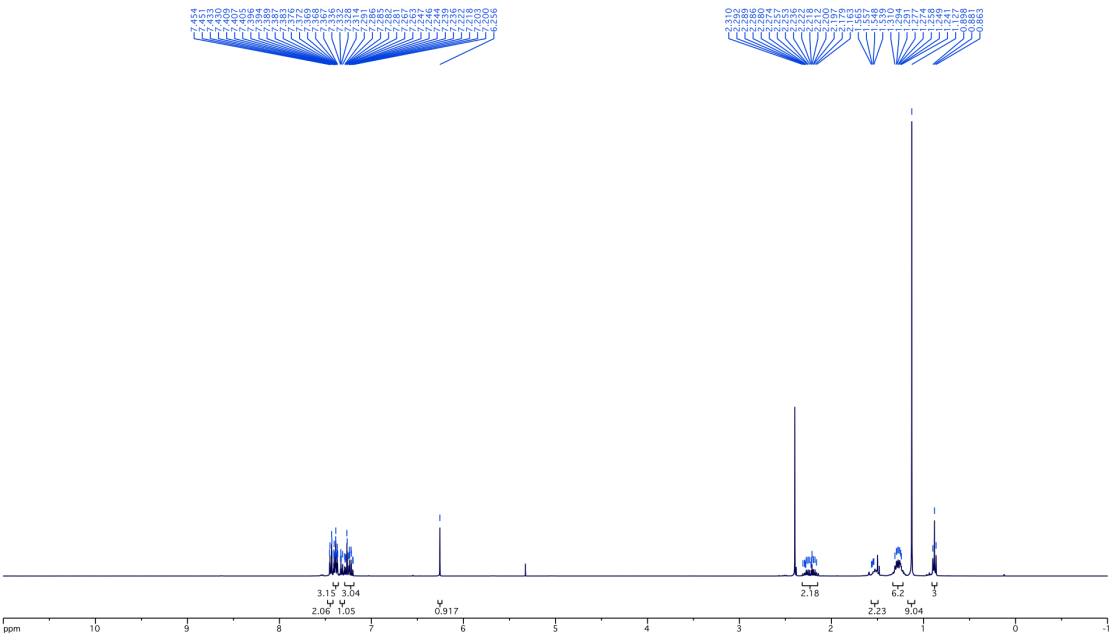


Pyrrole 177: ^{13}C NMR (101 MHz, $CDCl_3$)

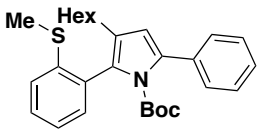


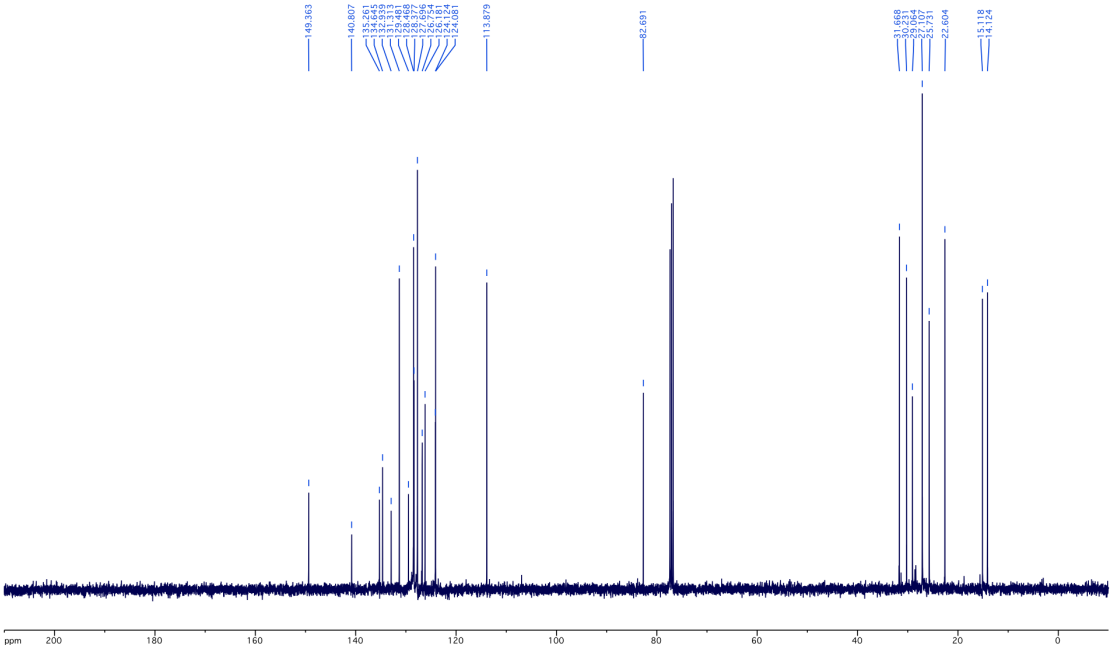
Pyrrole 181: ^{1}H NMR (400 MHz, $CDCl_3$)



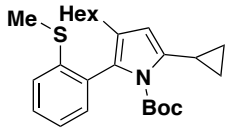


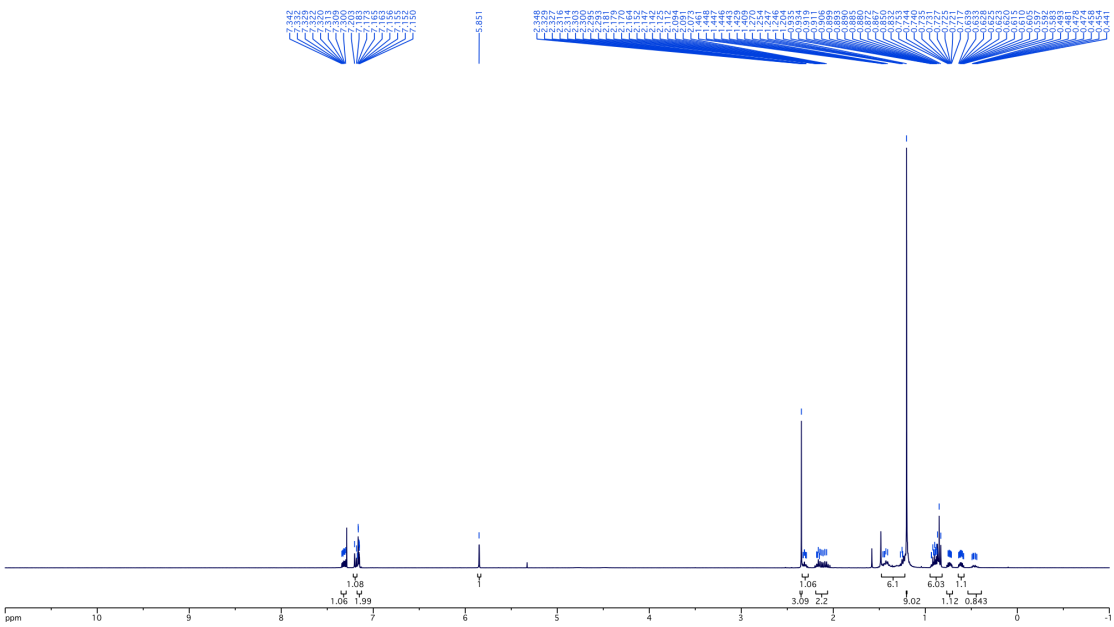
Pyrrole 181: ^{13}C NMR (101 MHz, $CDCl_3$)



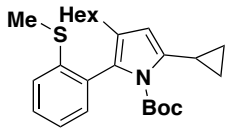


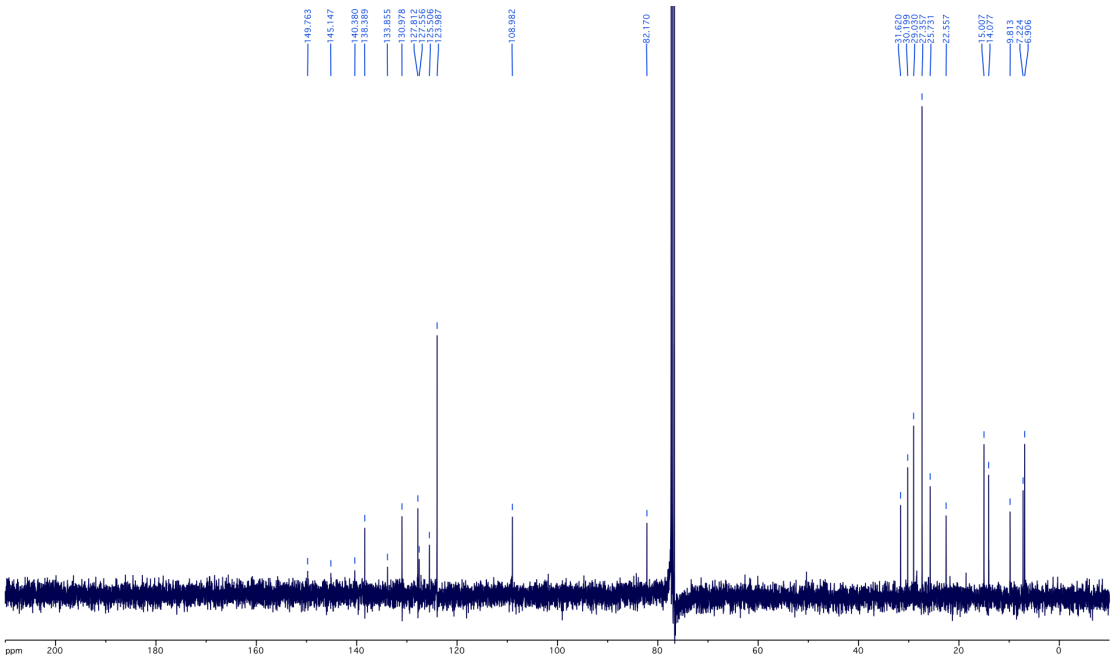
Pyrrole 182: ^{1}H NMR (400 MHz, $CDCl_3$)



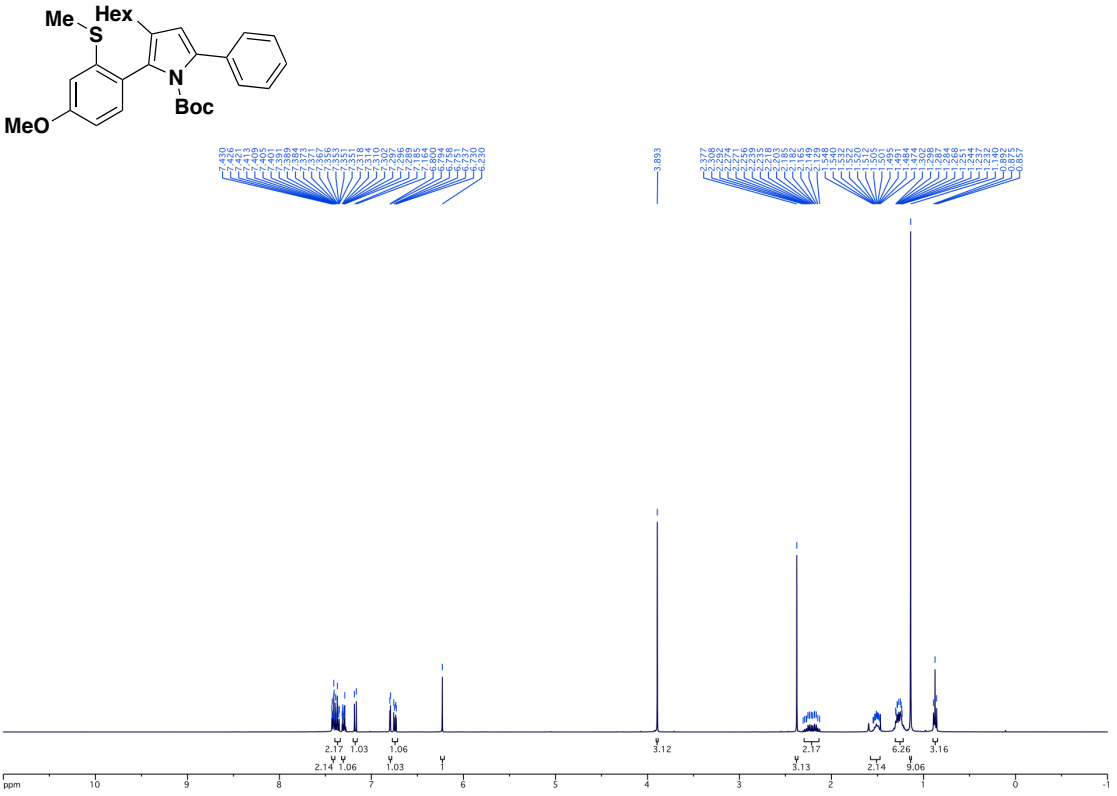


Pyrrole 182: ^{13}C NMR (101 MHz, $CDCl_3$)

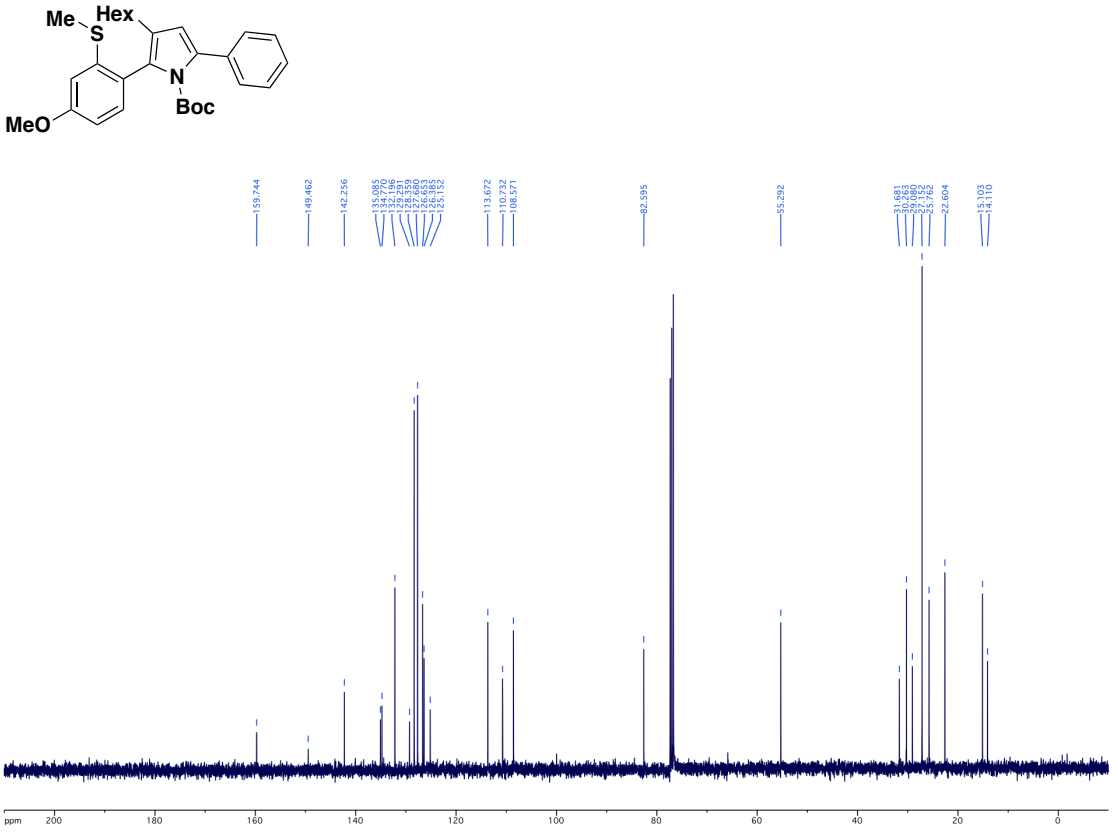




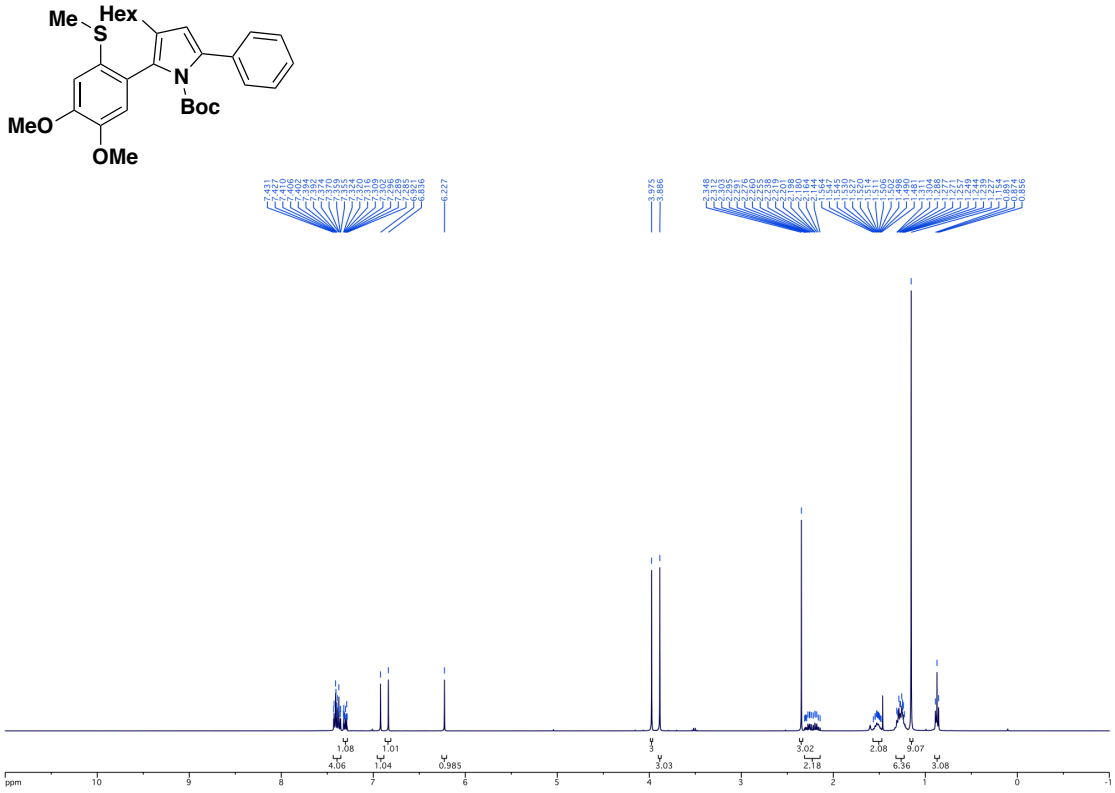
Pyrrole 183: ^{1}H NMR (400 MHz, $CDCl_3$)



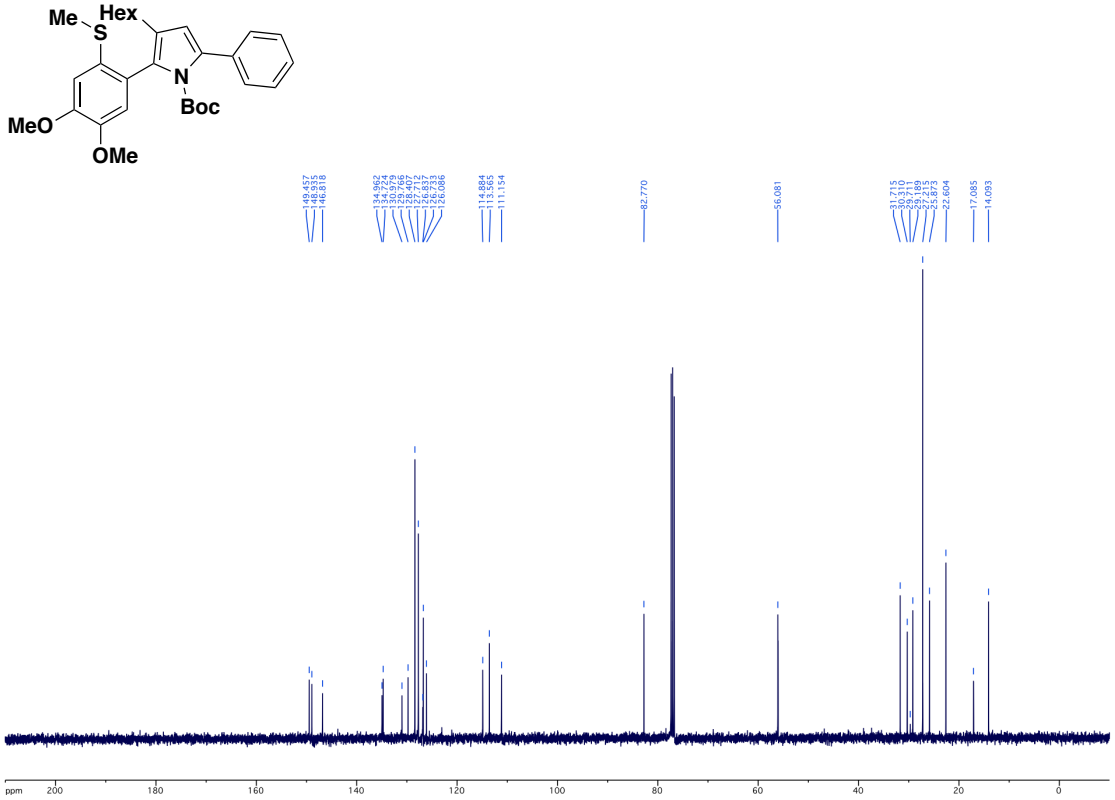
Pyrrole 183: ^{13}C NMR (101 MHz, $CDCl_3$)



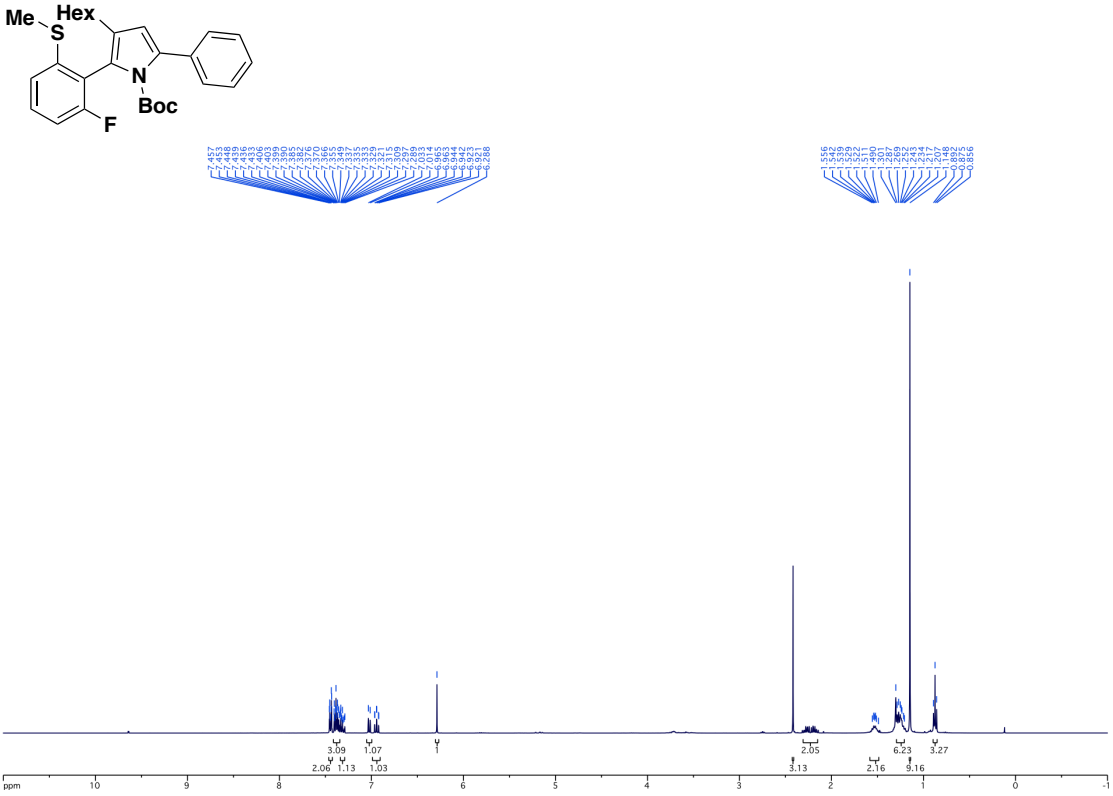
Pyrrole 184: ^{1}H NMR (400 MHz, $CDCl_3$)



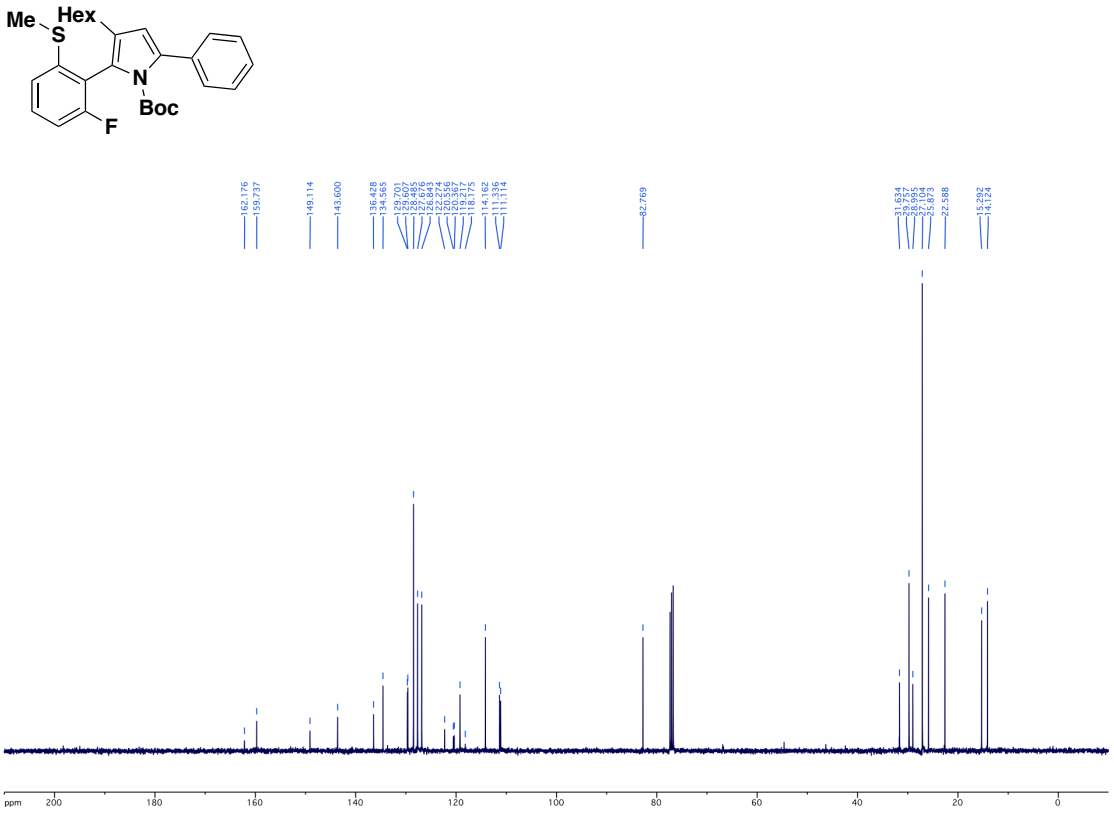
Pyrrole 184: ^{13}C NMR (101 MHz, $CDCl_3$)



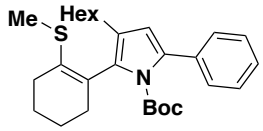
Pyrrole 185: ^{1}H NMR (400 MHz, $CDCl_3$)

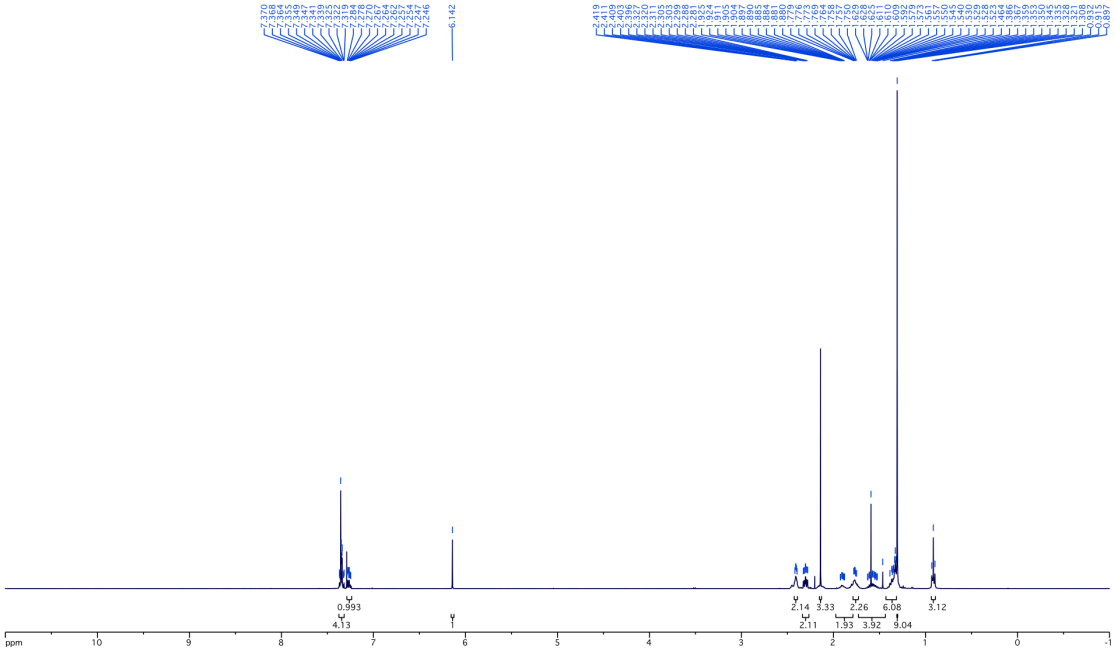


Pyrrole 185: ^{13}C NMR (101 MHz, $CDCl_3$)

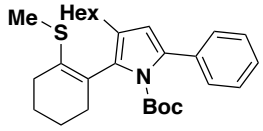


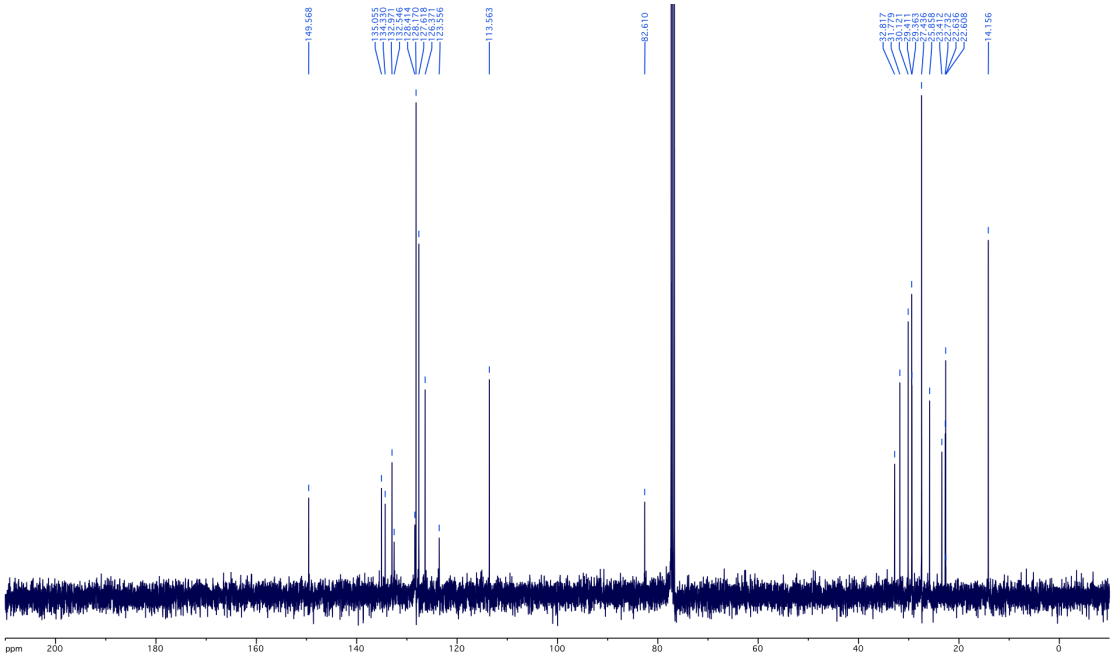
Pyrrole 186: ^{1}H NMR (400 MHz, $CDCl_3$)



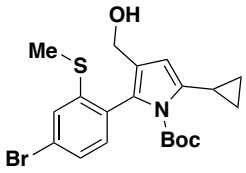


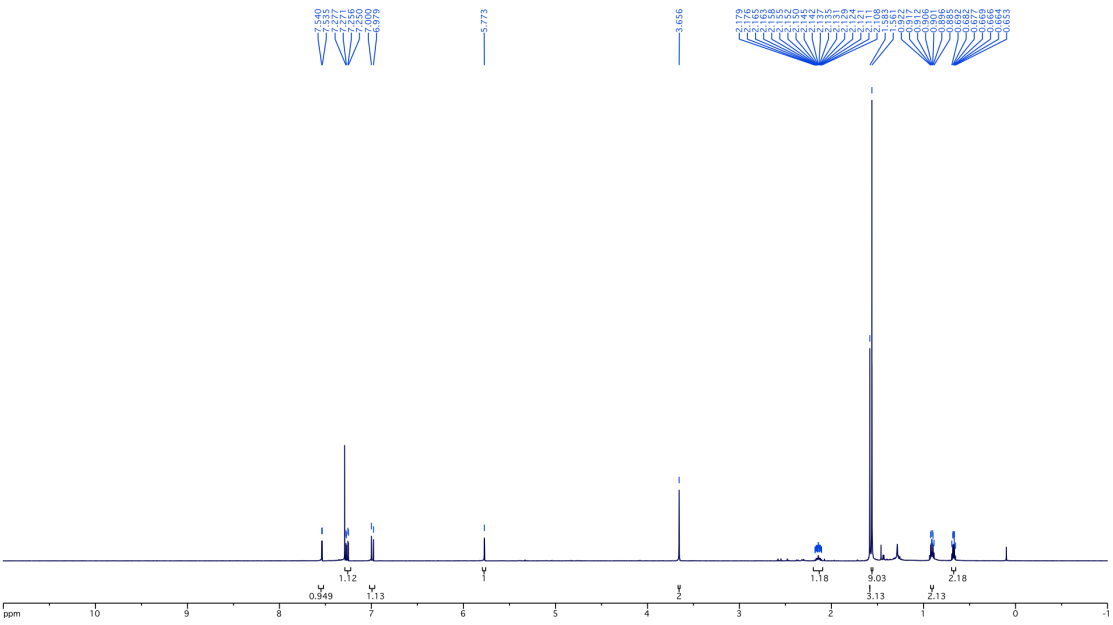
Pyrrole 186: ^{13}C NMR (101 MHz, $CDCl_3$)



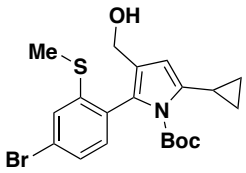


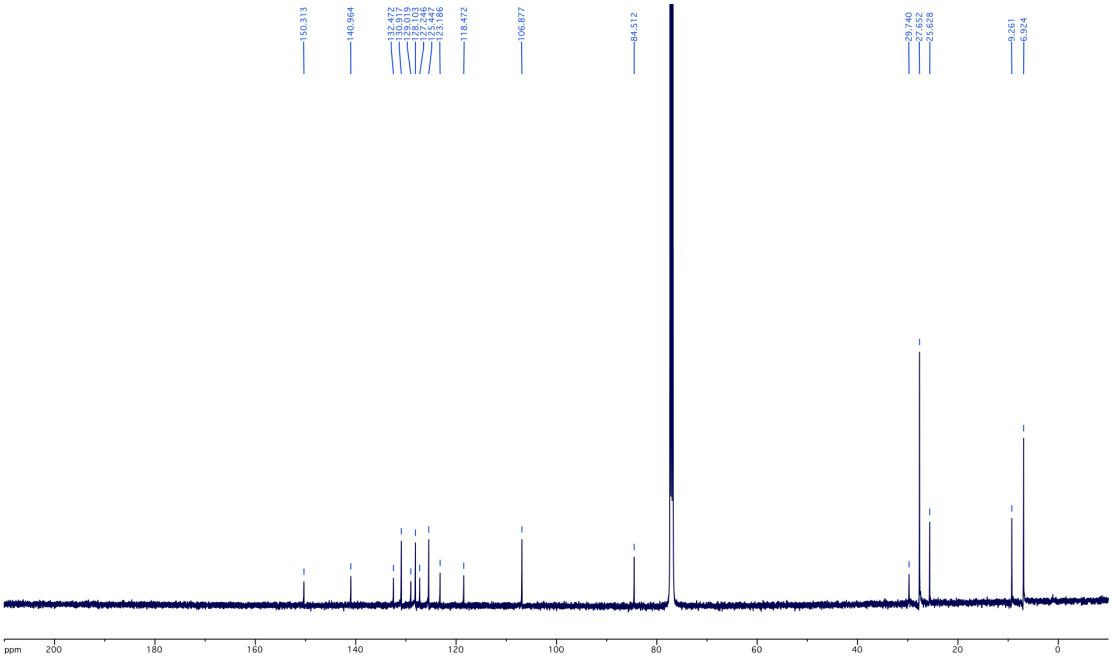
Pyrrole 187: ^{1}H NMR (400 MHz, $CDCl_3$)



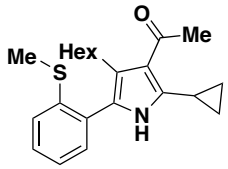


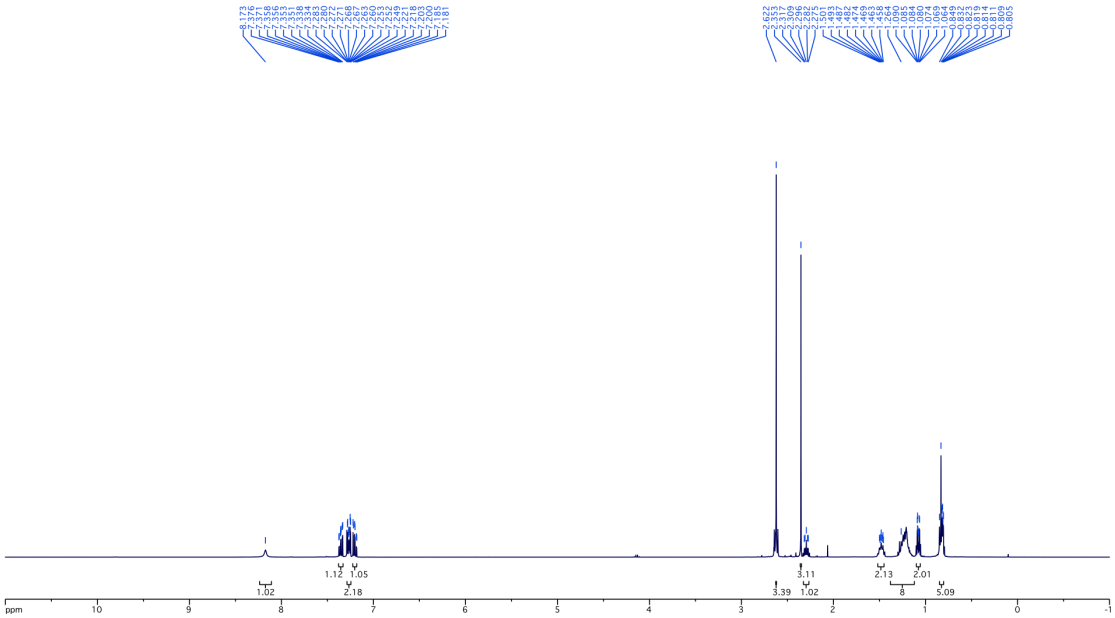
Pyrrole 187: ^{13}C NMR (101 MHz, $CDCl_3$)



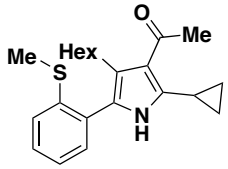


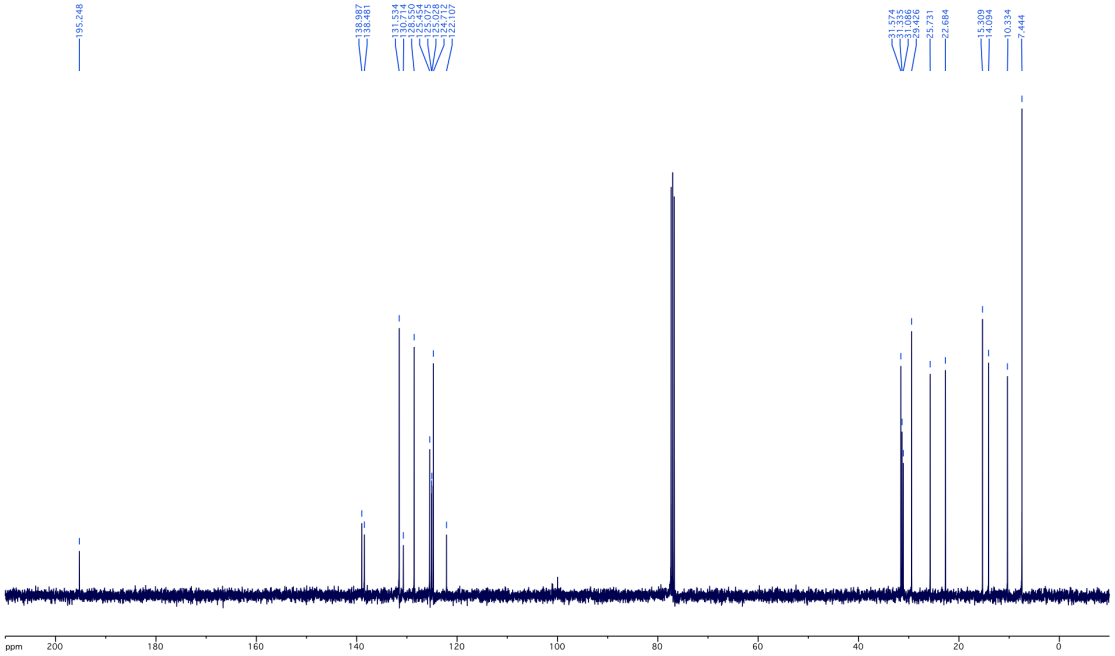
Pyrrole 193: ^{1}H NMR (400 MHz, $CDCl_3$)



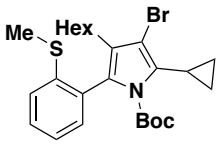


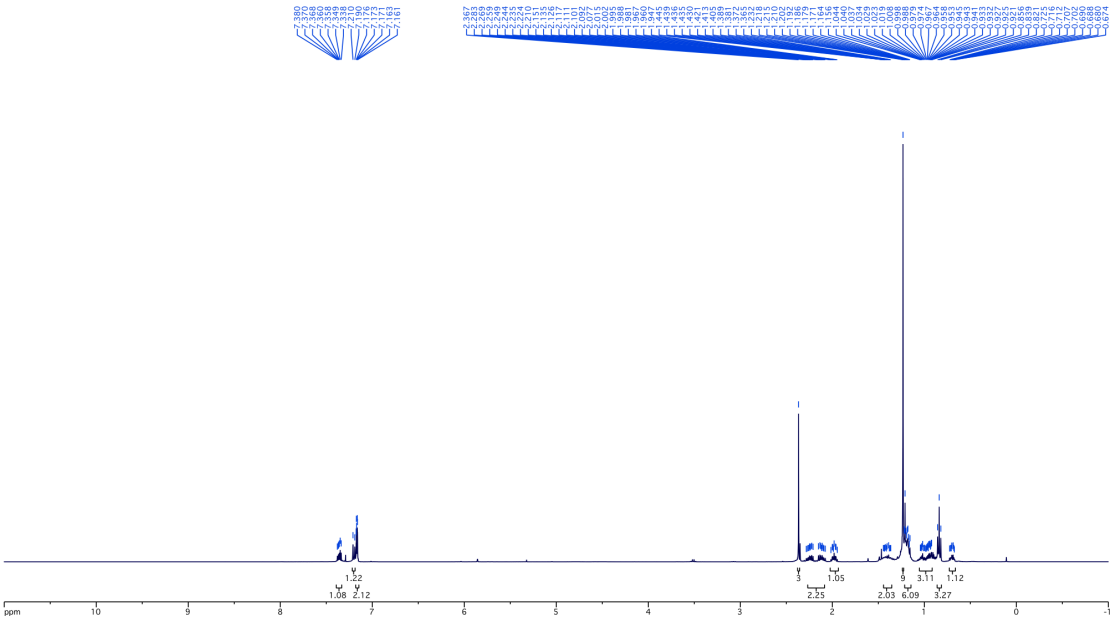
Pyrrole 193: ^{13}C NMR (101 MHz, $CDCl_3$)



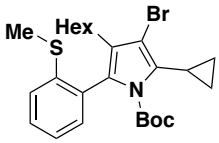


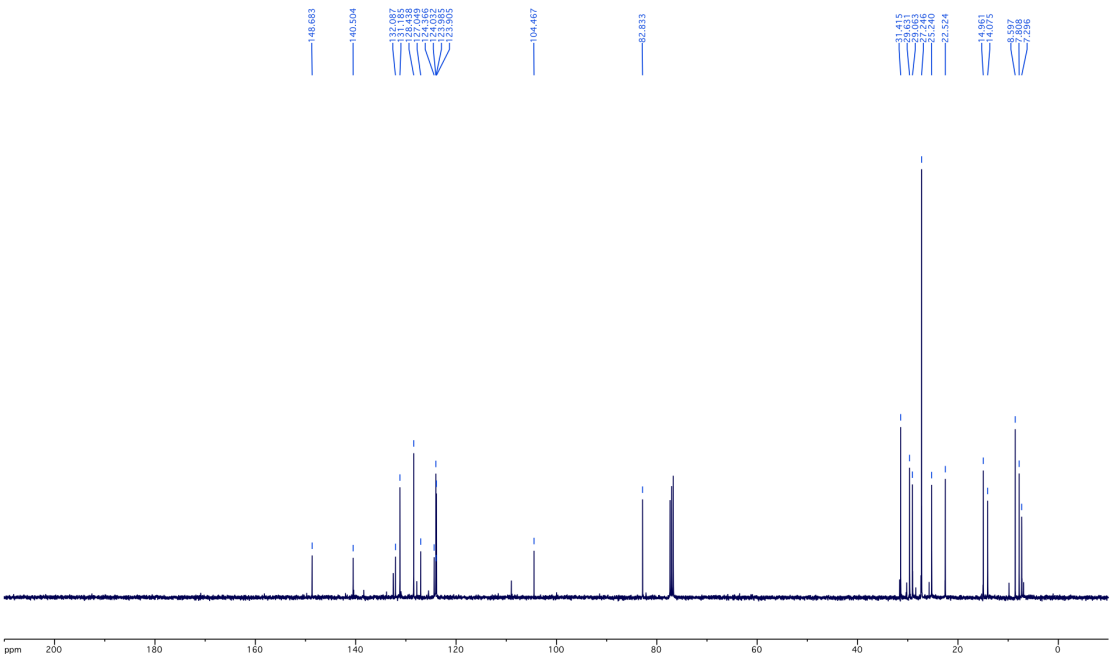
Pyrrole 194: ^{1}H NMR (400 MHz, $CDCl_3$)



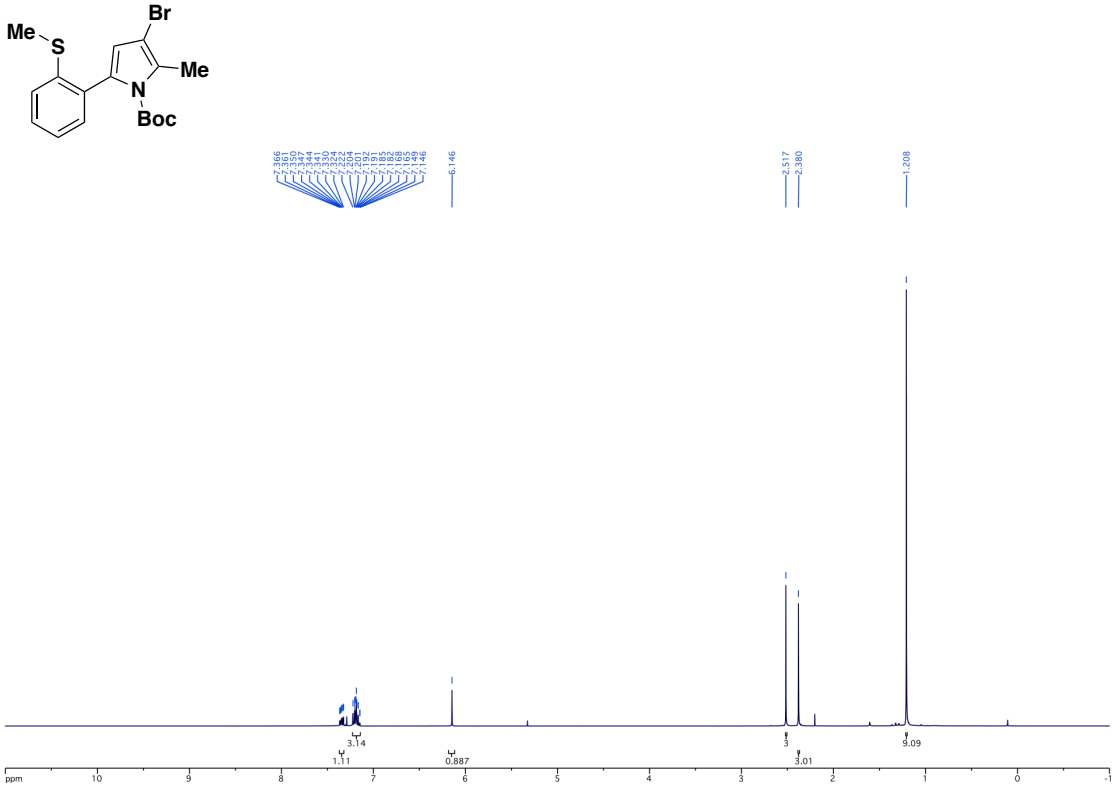


Pyrrole 194: ^{13}C NMR (101 MHz, $CDCl_3$)

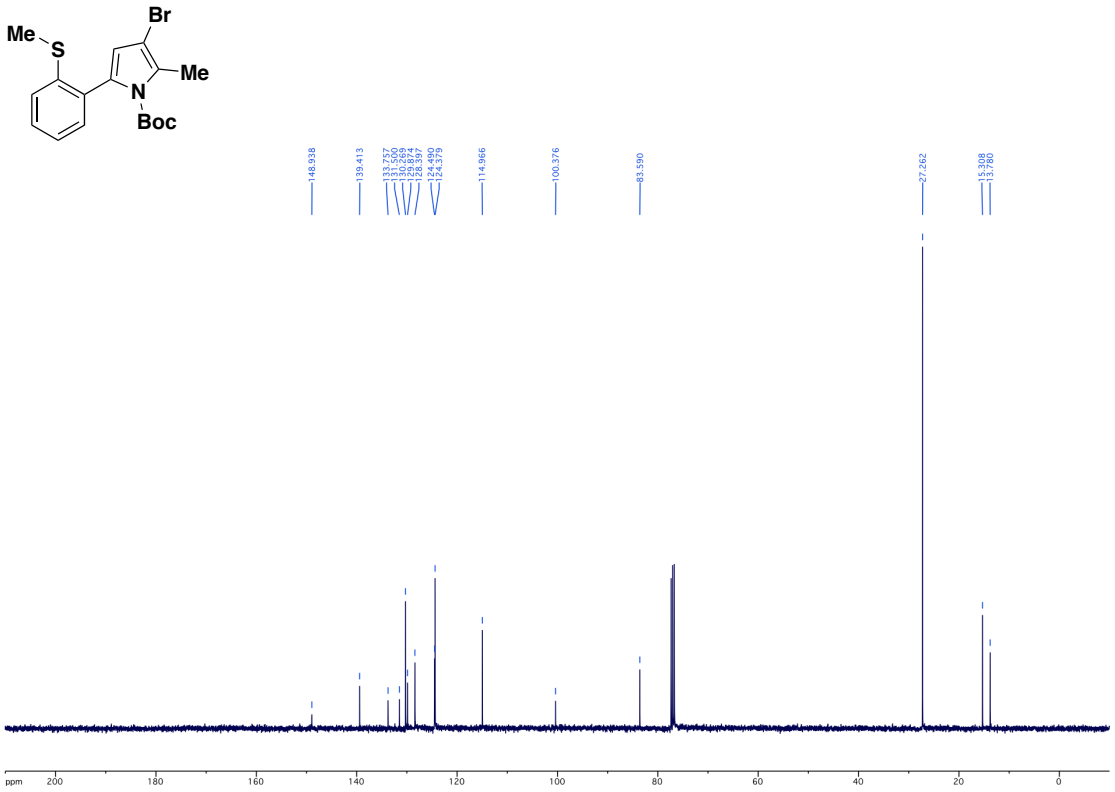




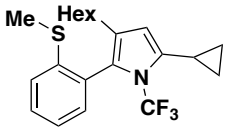
Pyrrole 195: ^{1}H NMR (400 MHz, $CDCl_3$)

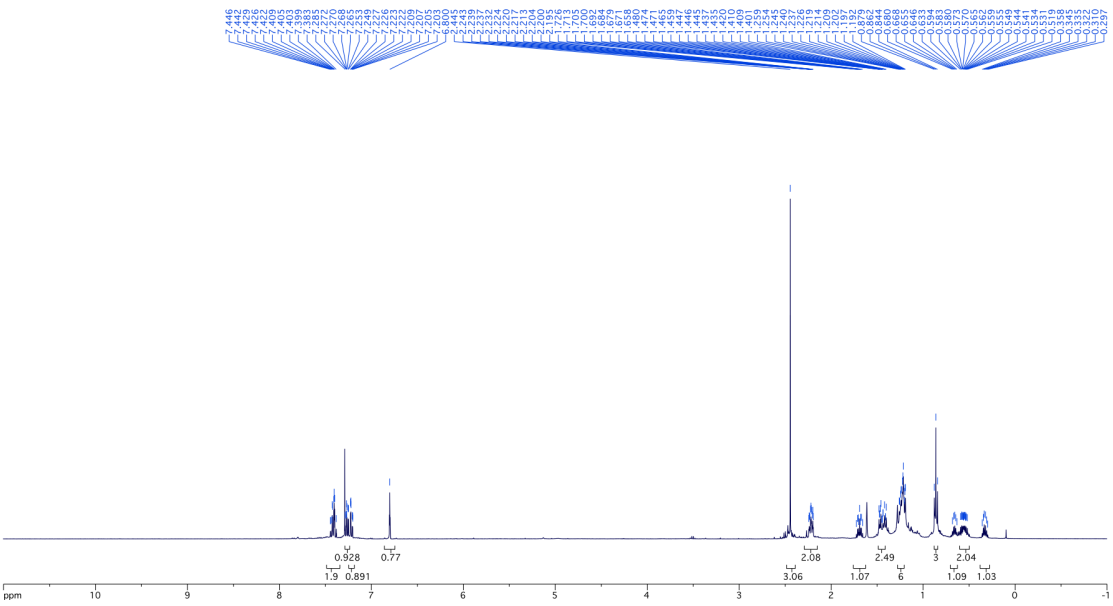


Pyrrole 195: ^{13}C NMR (101 MHz, $CDCl_3$)

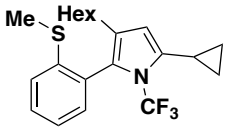


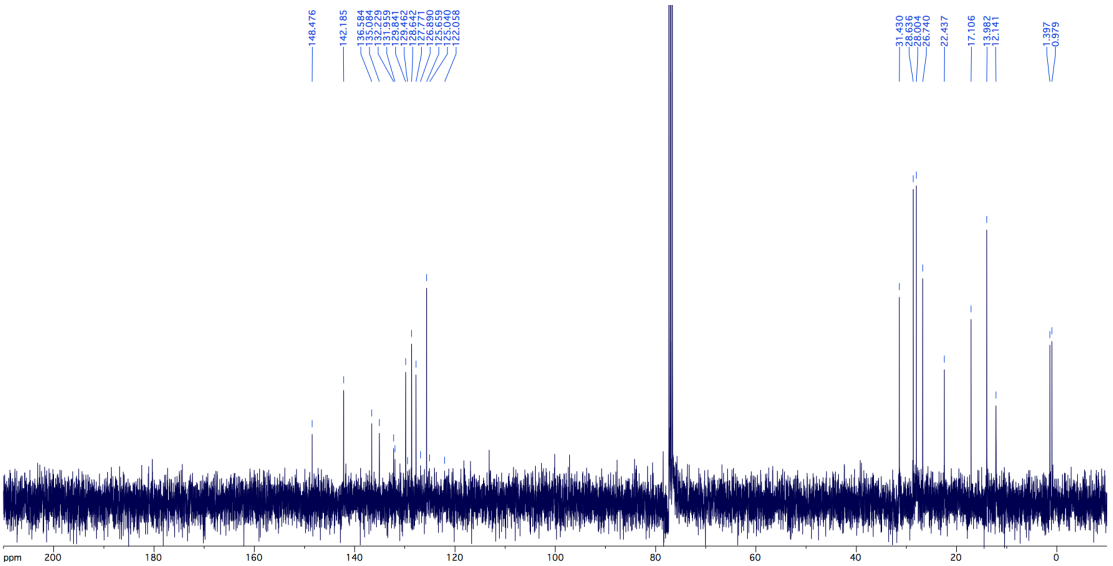
Pyrrole 196: ^{1}H NMR (400 MHz, $CDCl_3$)



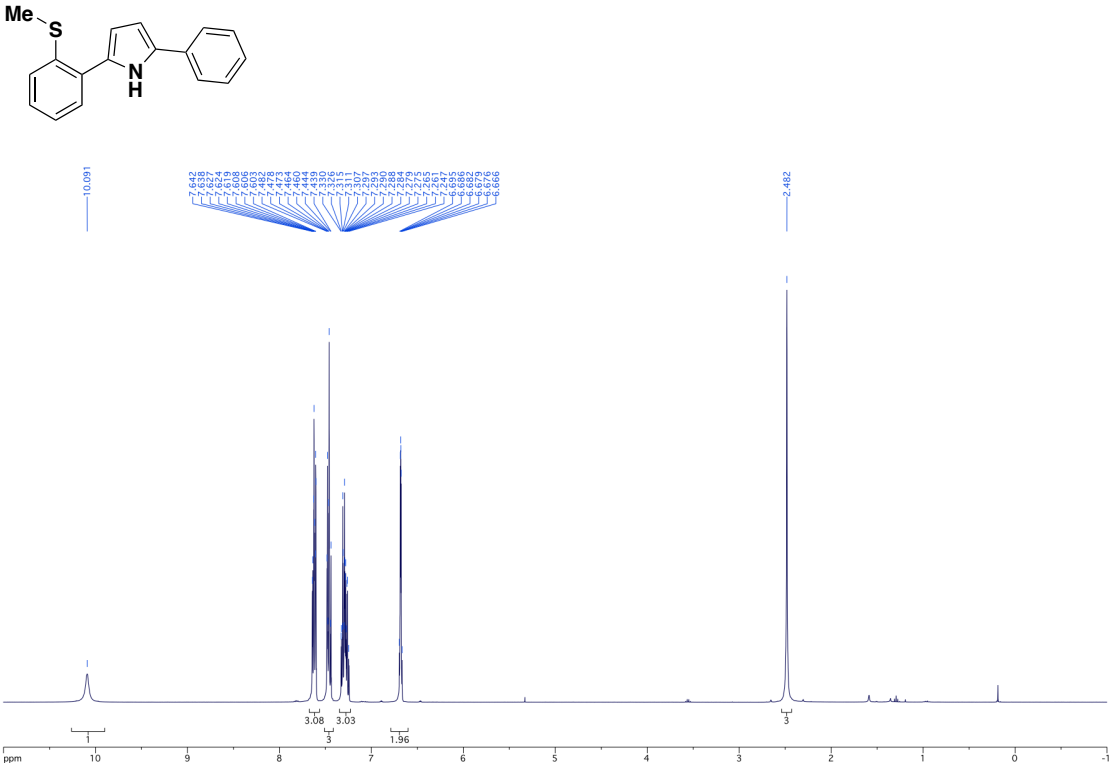


Pyrrole 196: ^{13}C NMR (101 MHz, $CDCl_3$)

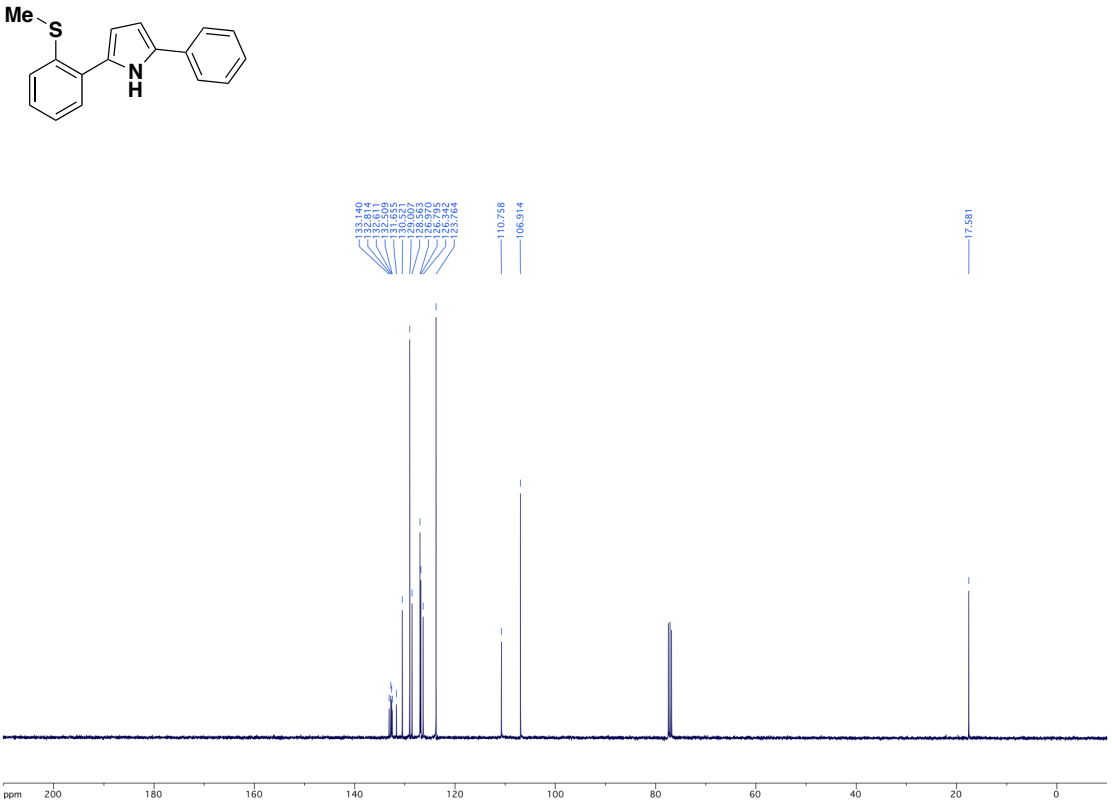




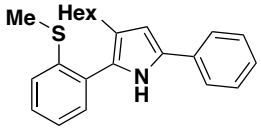
Pyrrole 197: ^{1}H NMR (400 MHz, $CDCl_3$)

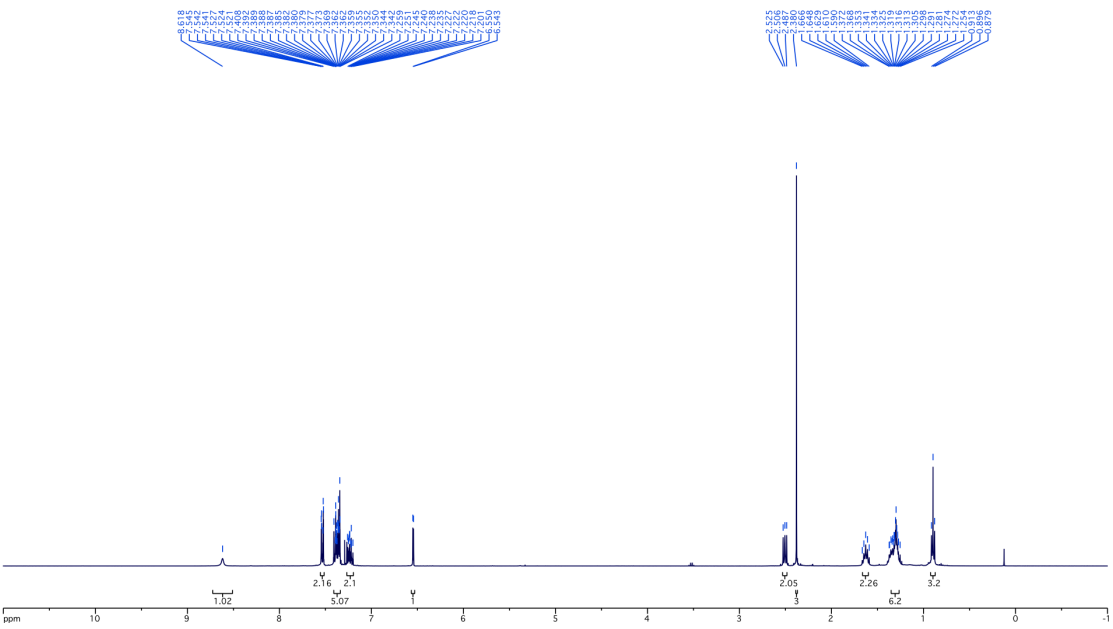


Pyrrole 197: ^{13}C NMR (101 MHz, $CDCl_3$)

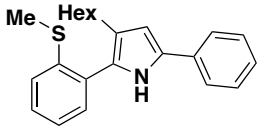


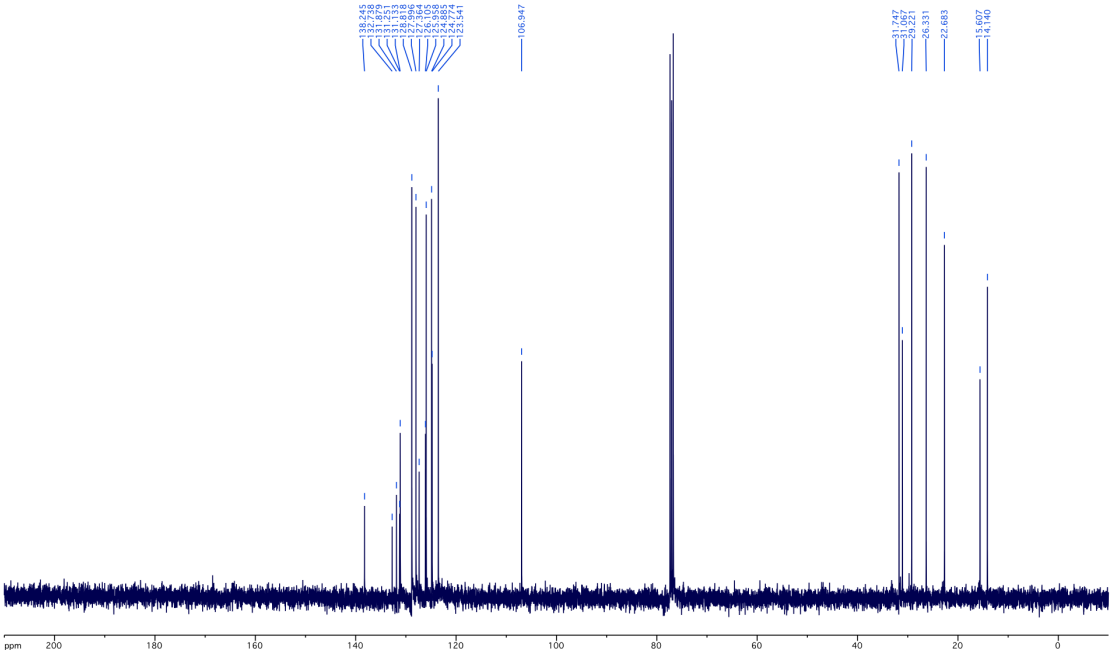
Pyrrole 198: ^{1}H NMR (400 MHz, $CDCl_3$)



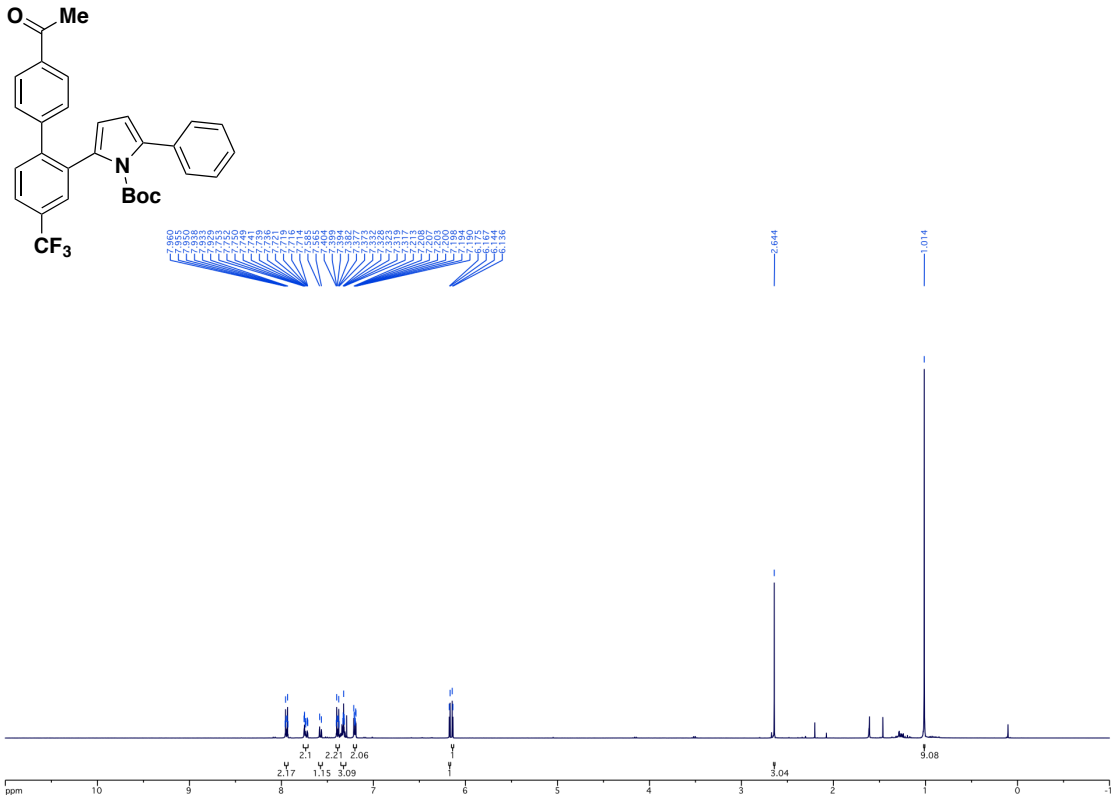


Pyrrole 198: ^{13}C NMR (101 MHz, $CDCl_3$)

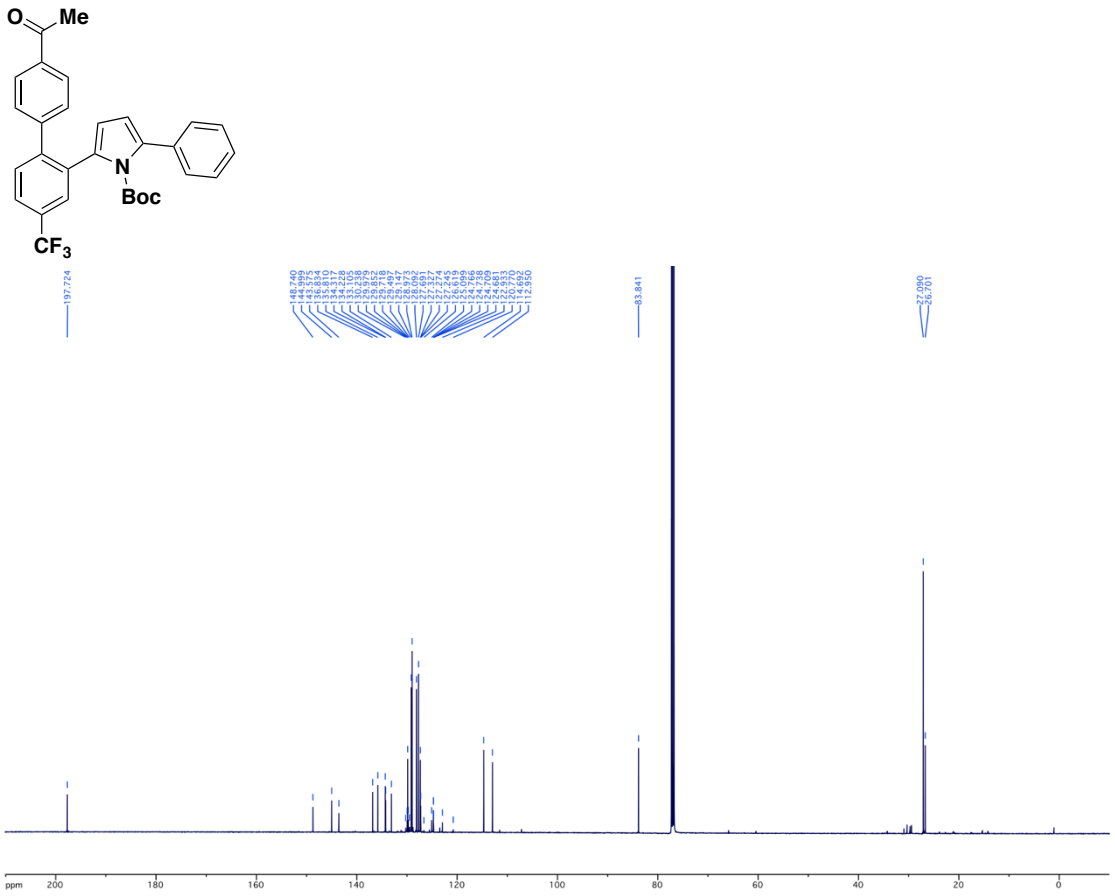




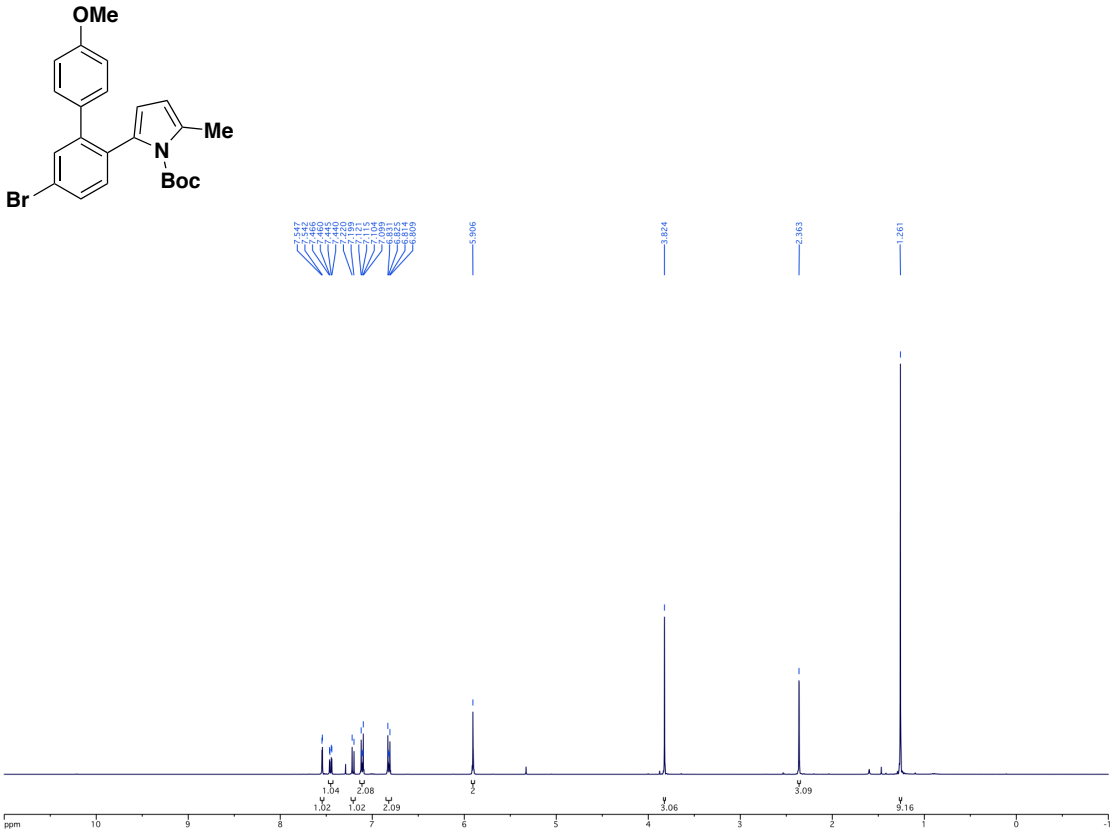
Pyrrole 200: ^{1}H NMR (400 MHz, $CDCl_3$)



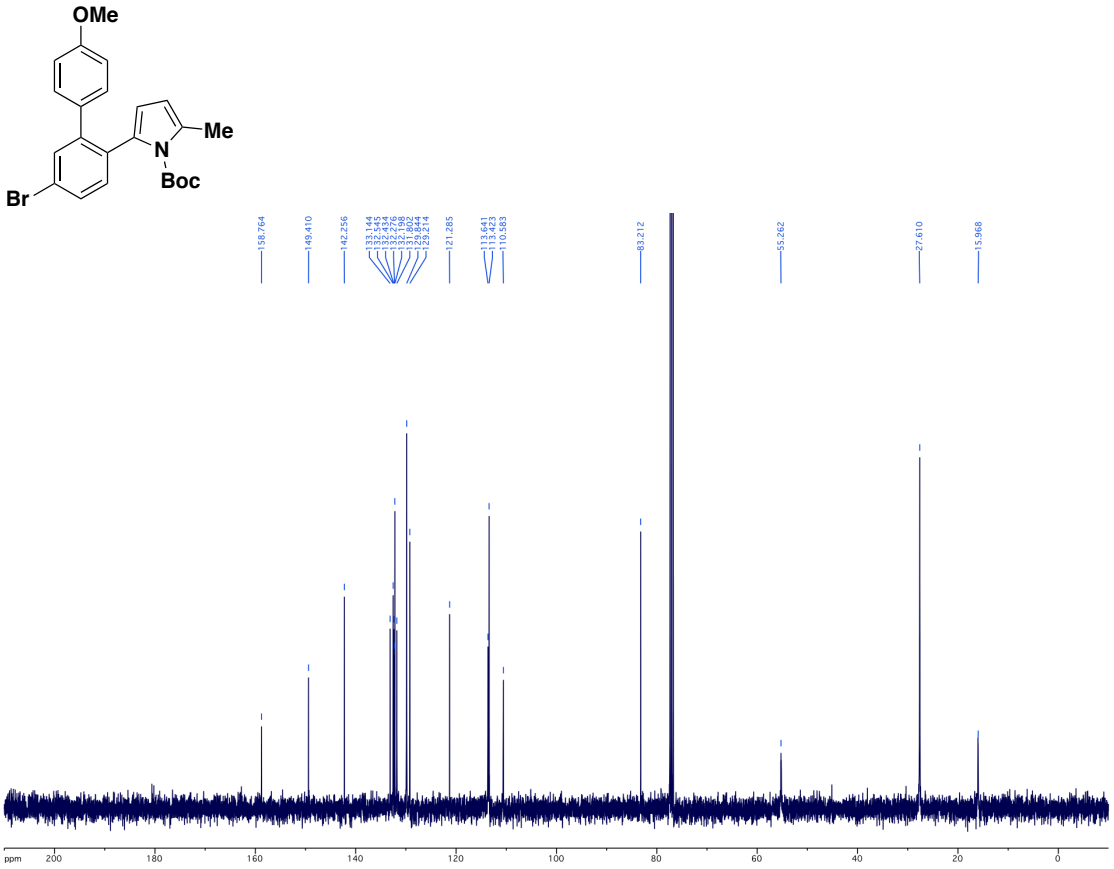
Pyrrole 200: ^{13}C NMR (101 MHz, $CDCl_3$)



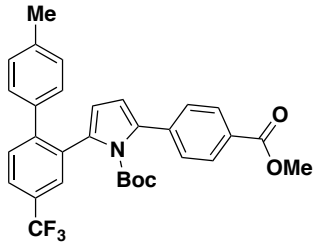
Pyrrole 201: ^{1}H NMR (400 MHz, $CDCl_3$)

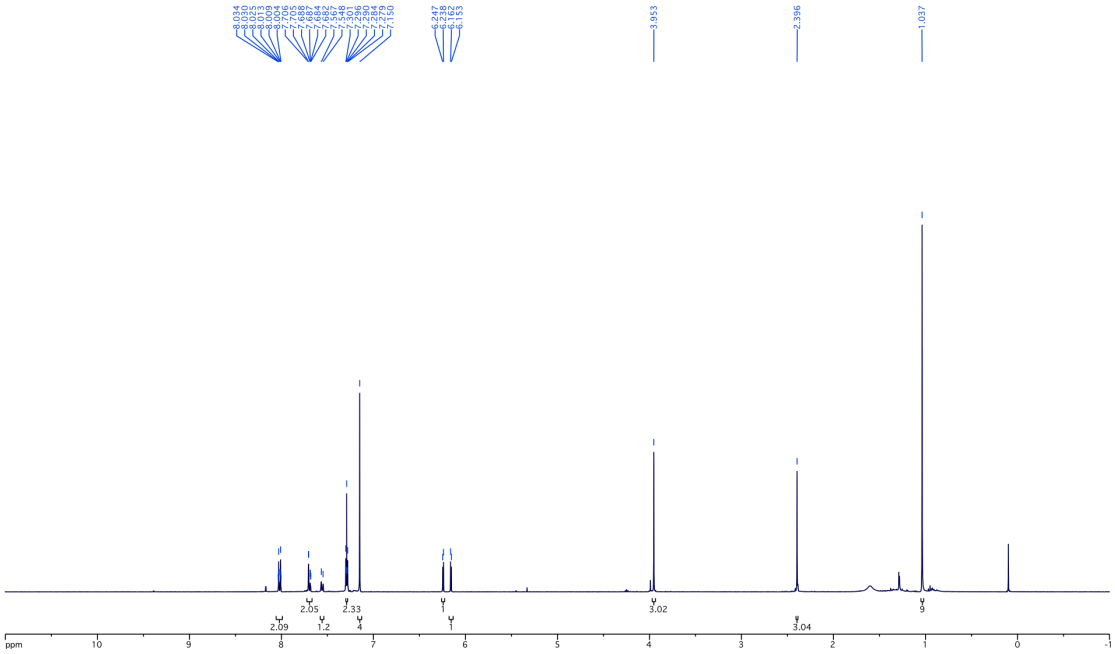


Pyrrole 201: ^{13}C NMR (101 MHz, $CDCl_3$)

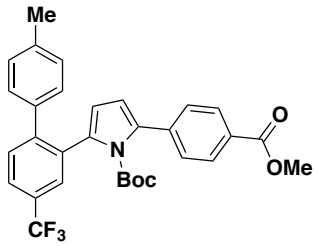


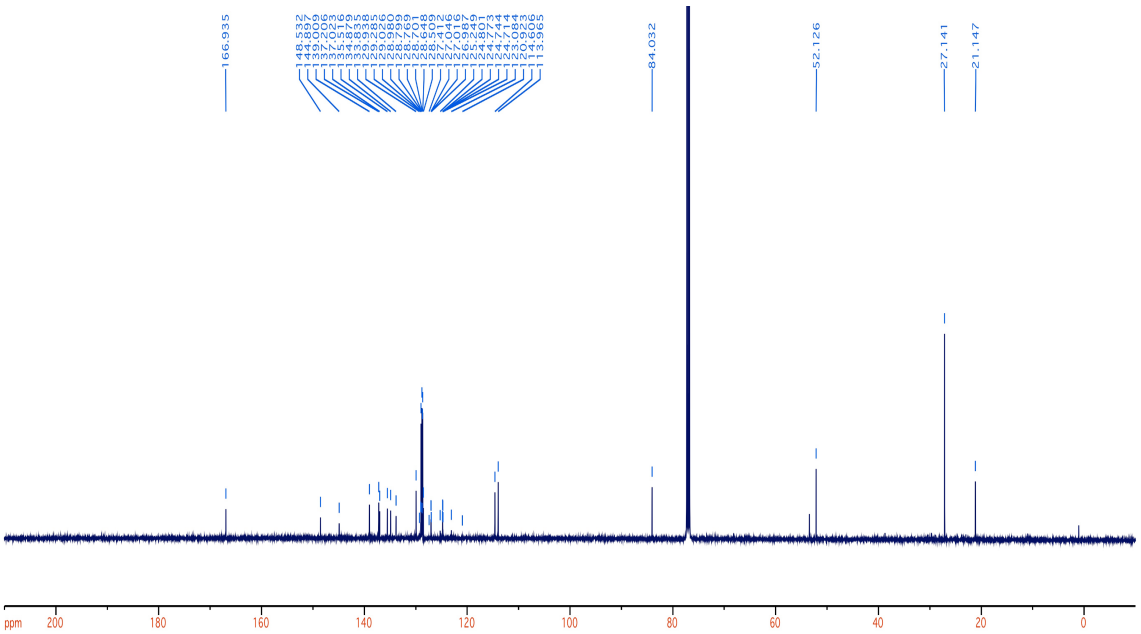
Pyrrole 202: ^{1}H NMR (400 MHz, $CDCl_3$)



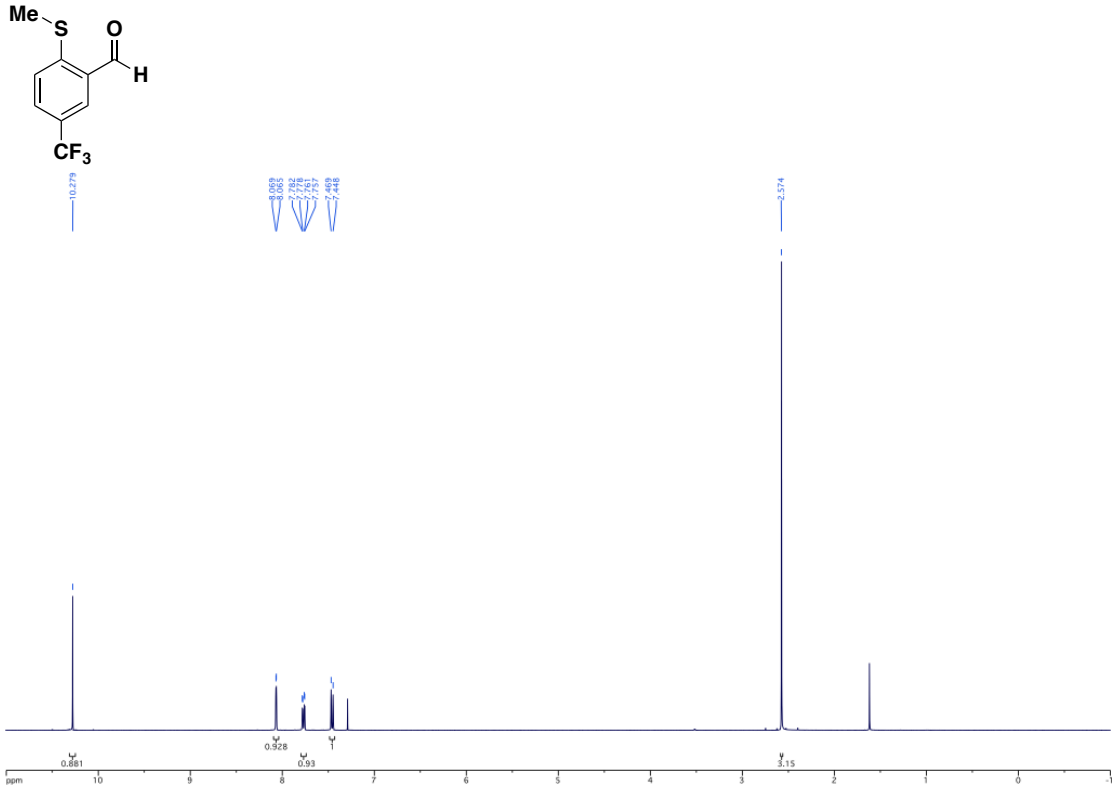


Pyrrole 202: ^{13}C NMR (101 MHz, $CDCl_3$)

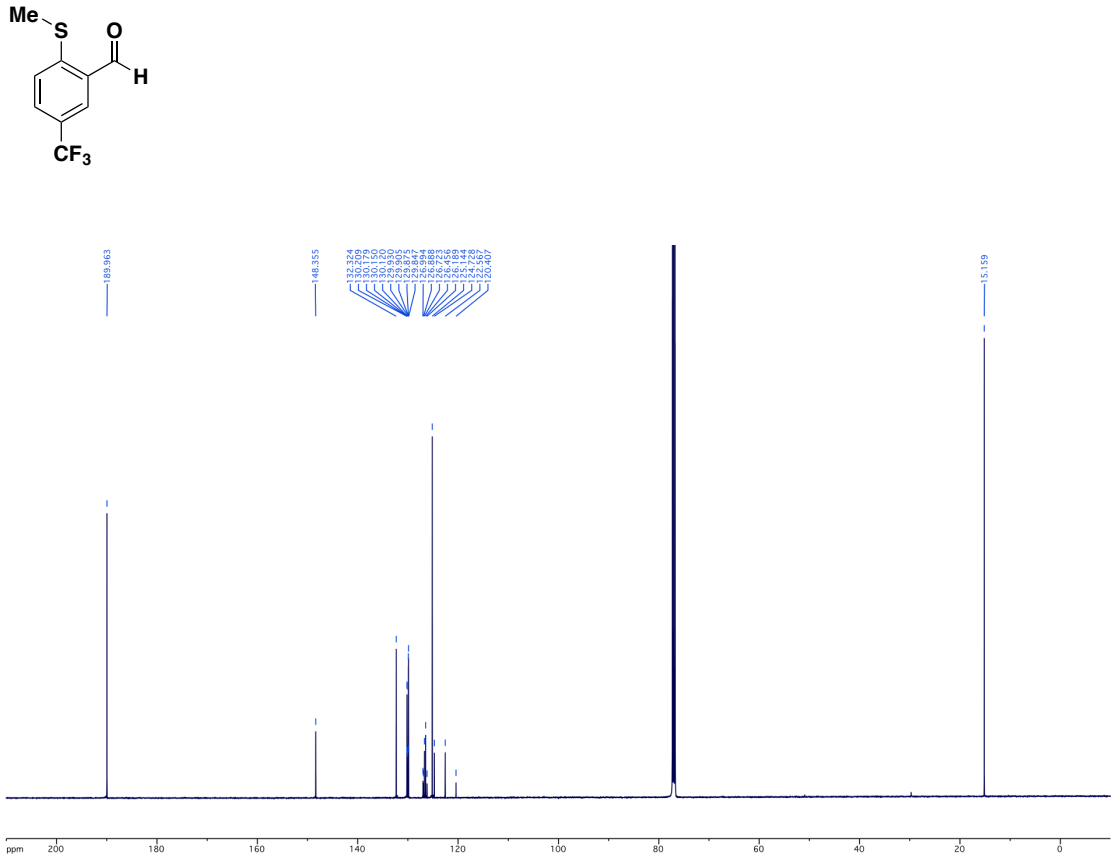




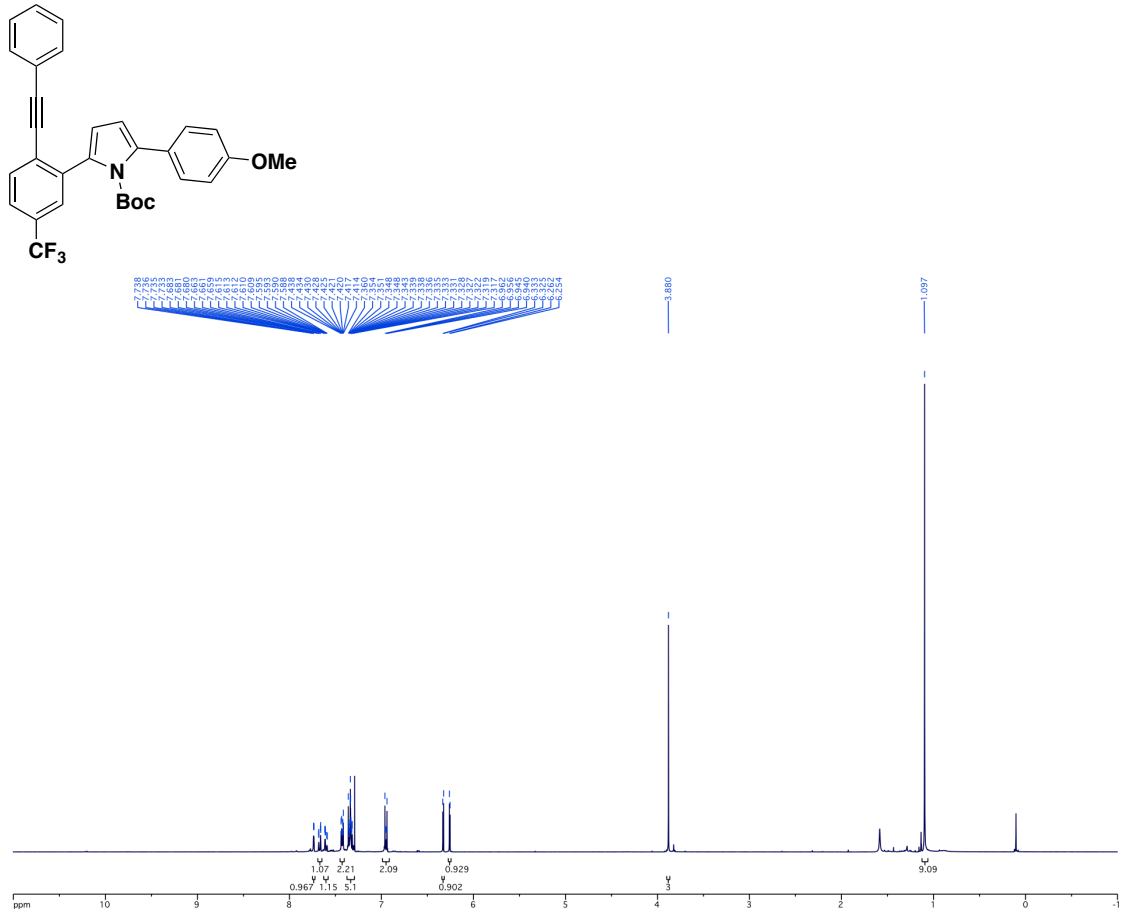
Aldehyde 203: ^{1}H NMR (400 MHz, $CDCl_3$)



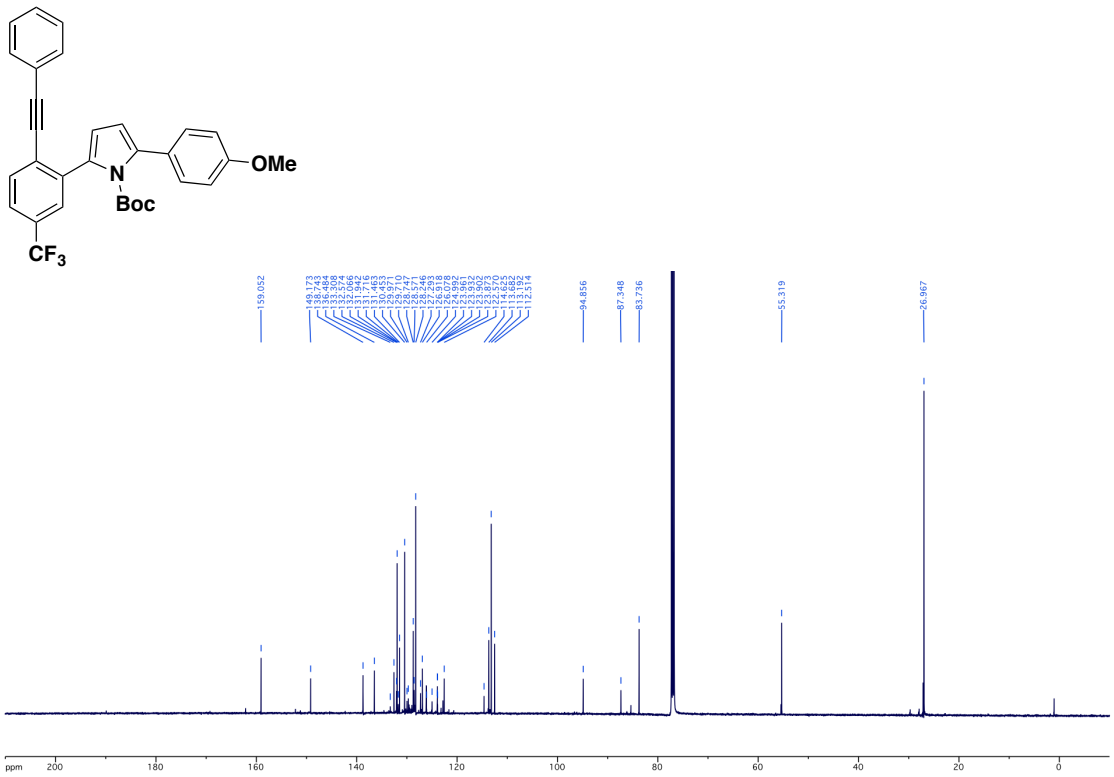
Aldehyde 203: ^{13}C NMR (101 MHz, $CDCl_3$)



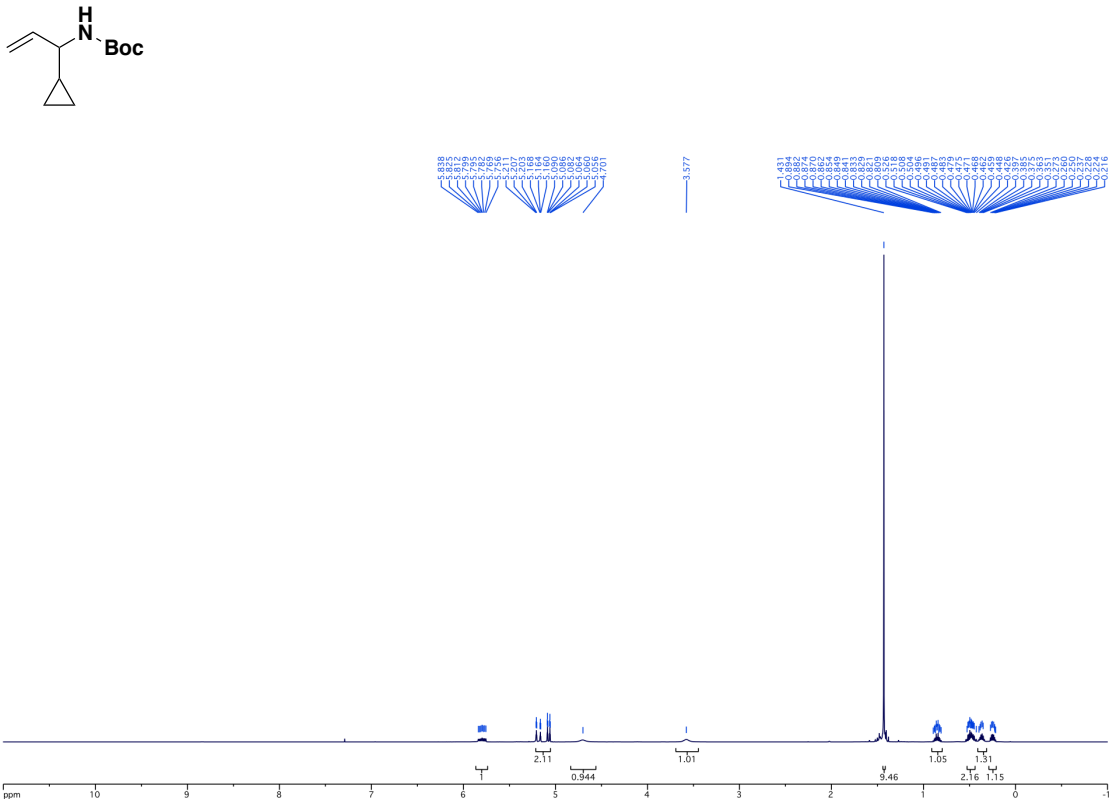
Pyrrole 204: ^{1}H NMR (400 MHz, $CDCl_3$)



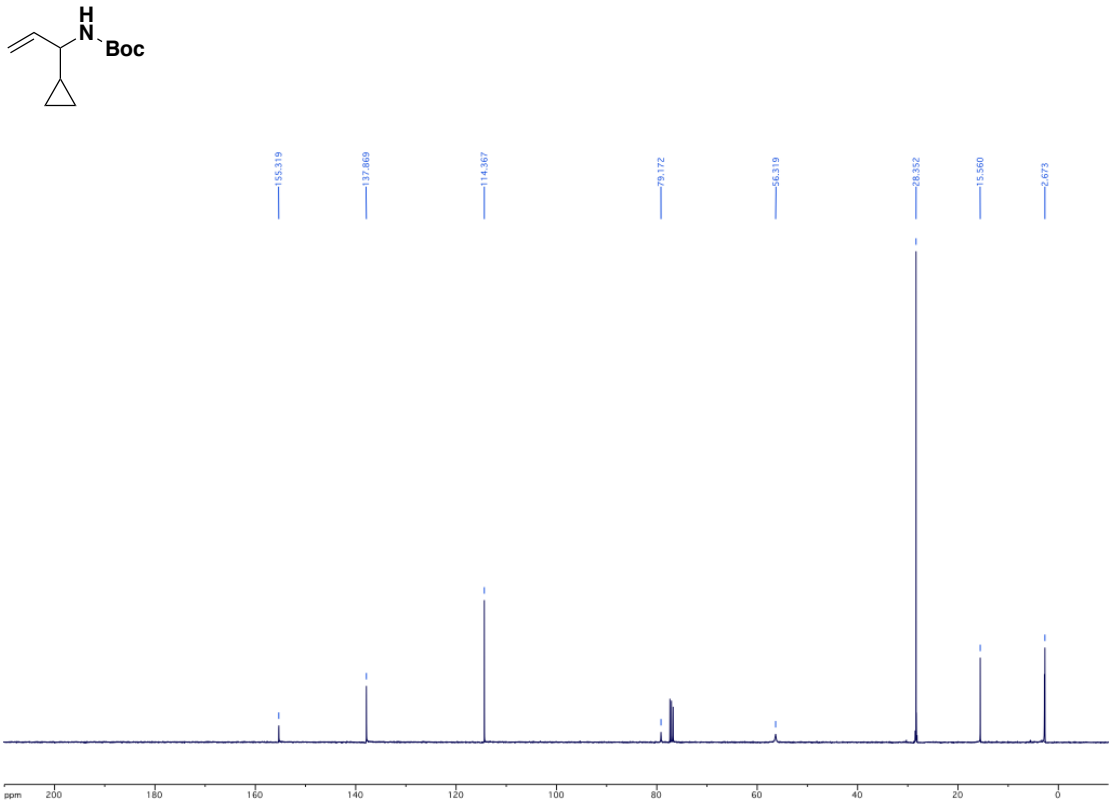
Pyrrole 204: ^{13}C NMR (101 MHz, $CDCl_3$)



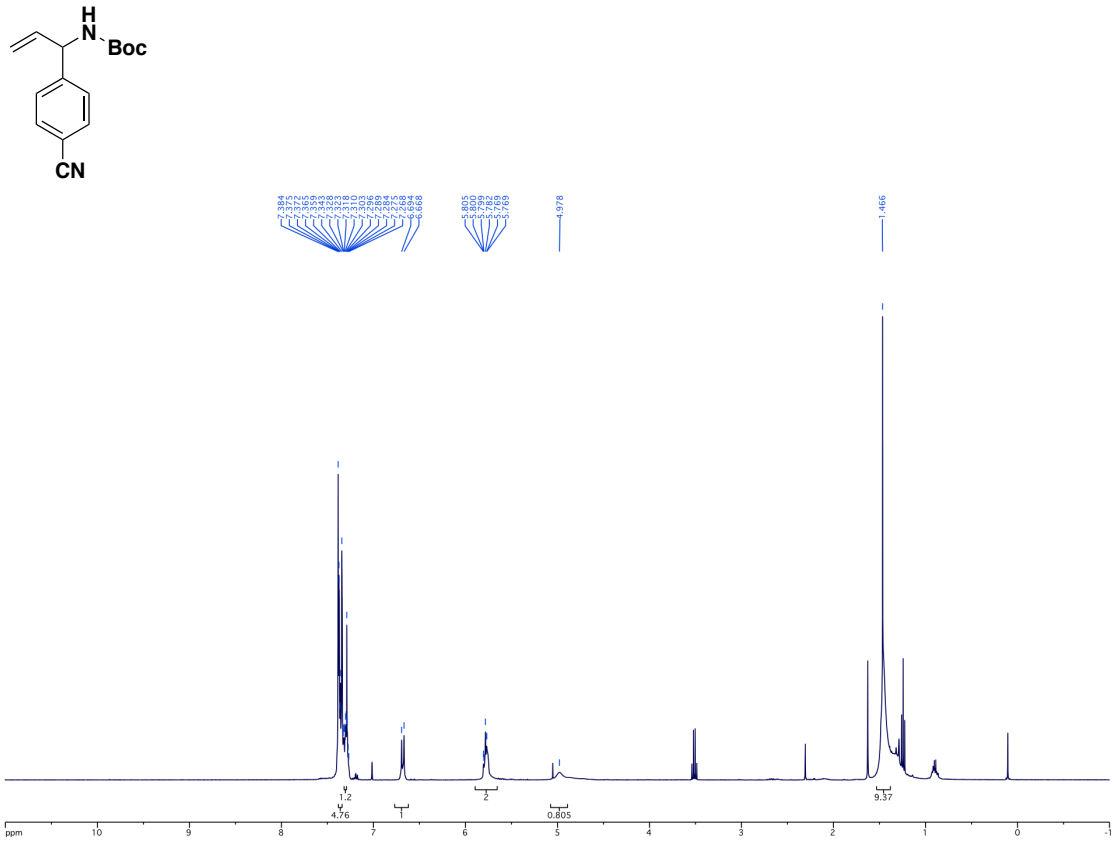
Allylic amine 206: ^{1}H NMR (400 MHz, $CDCl_3$)



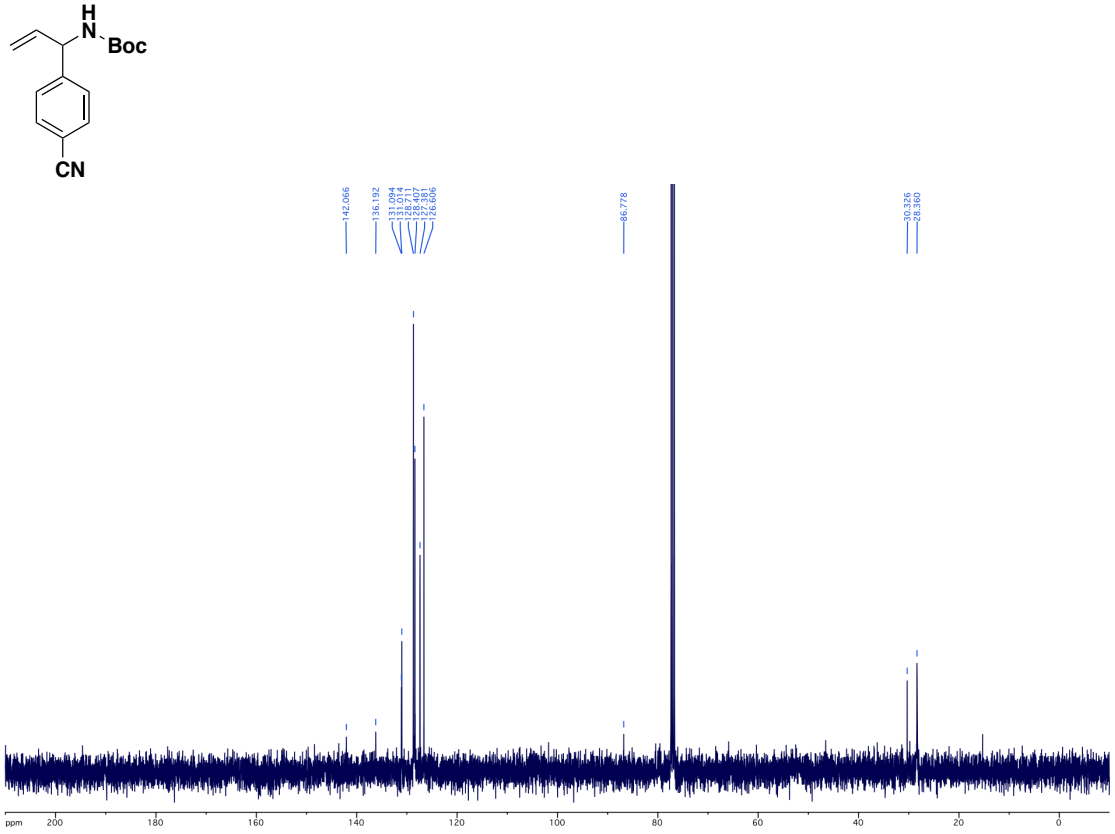
Allylic amine 206: ^{13}C NMR (101 MHz, $CDCl_3$)



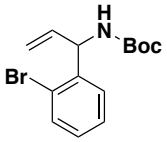
Allylic amine 210: ^{1}H NMR (400 MHz, $CDCl_3$)

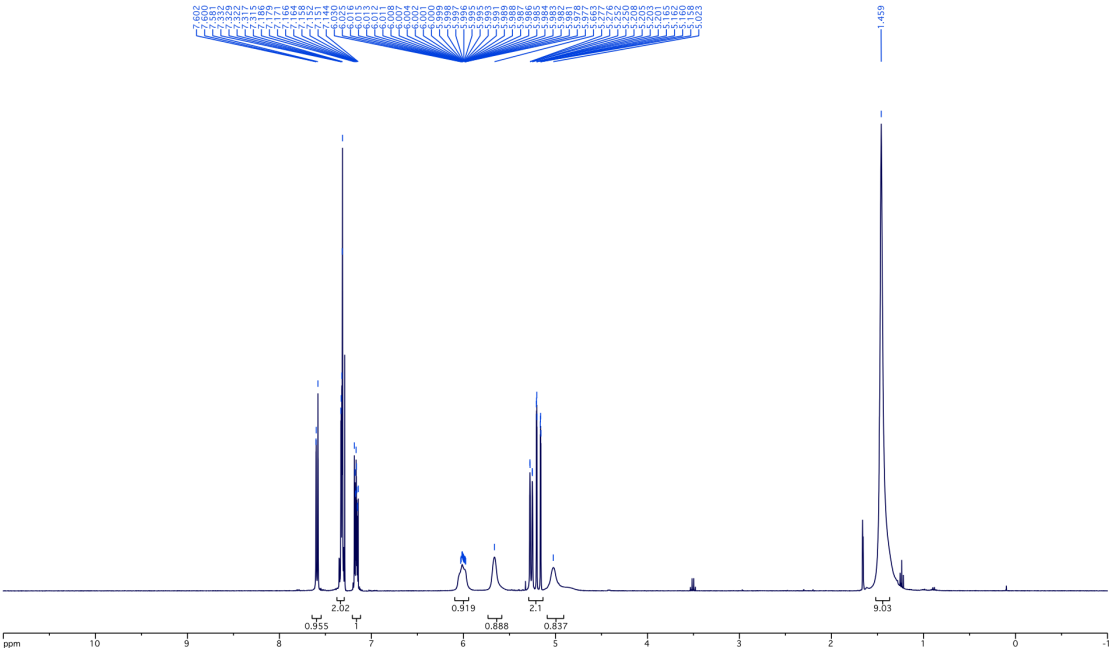


Allylic amine 210: ^{13}C NMR (101 MHz, $CDCl_3$)

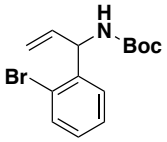


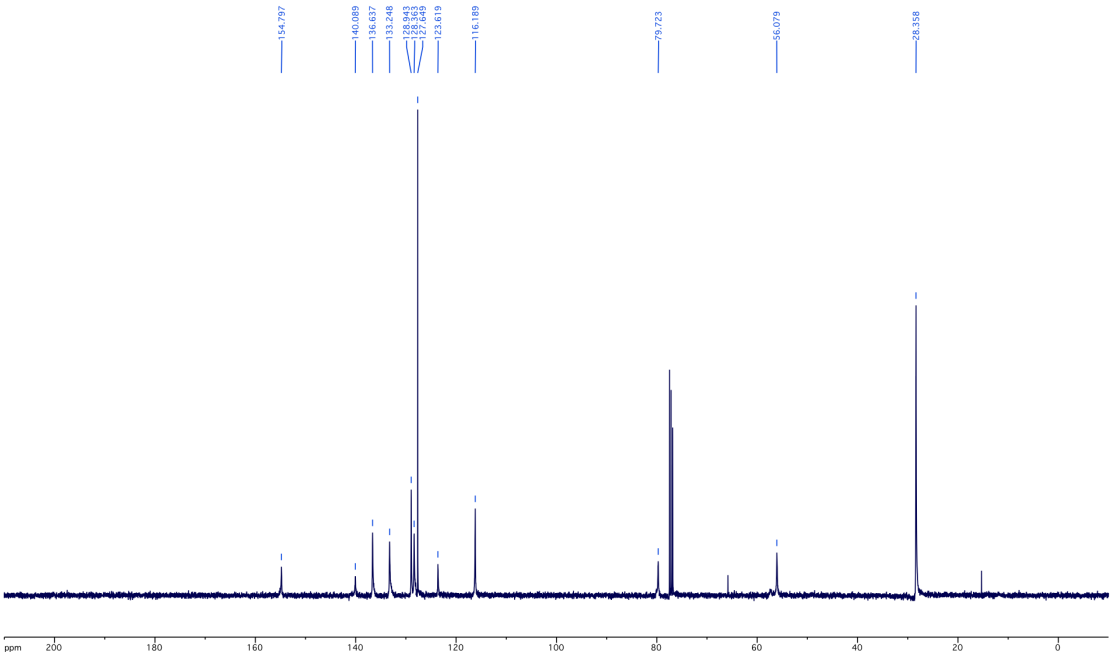
Allylic amine 211: ^{1}H NMR (400 MHz, $CDCl_3$)



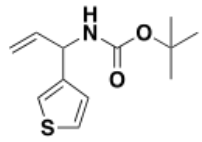


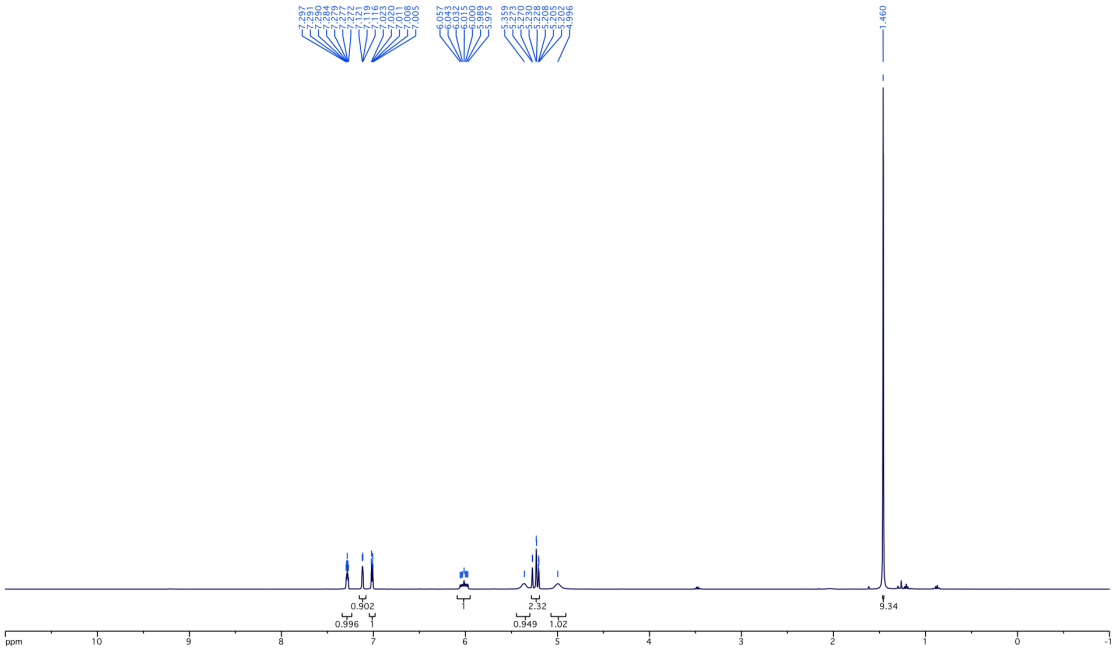
Allylic amine 211: ^{13}C NMR (101 MHz, $CDCl_3$)



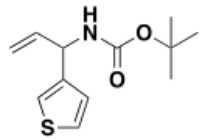


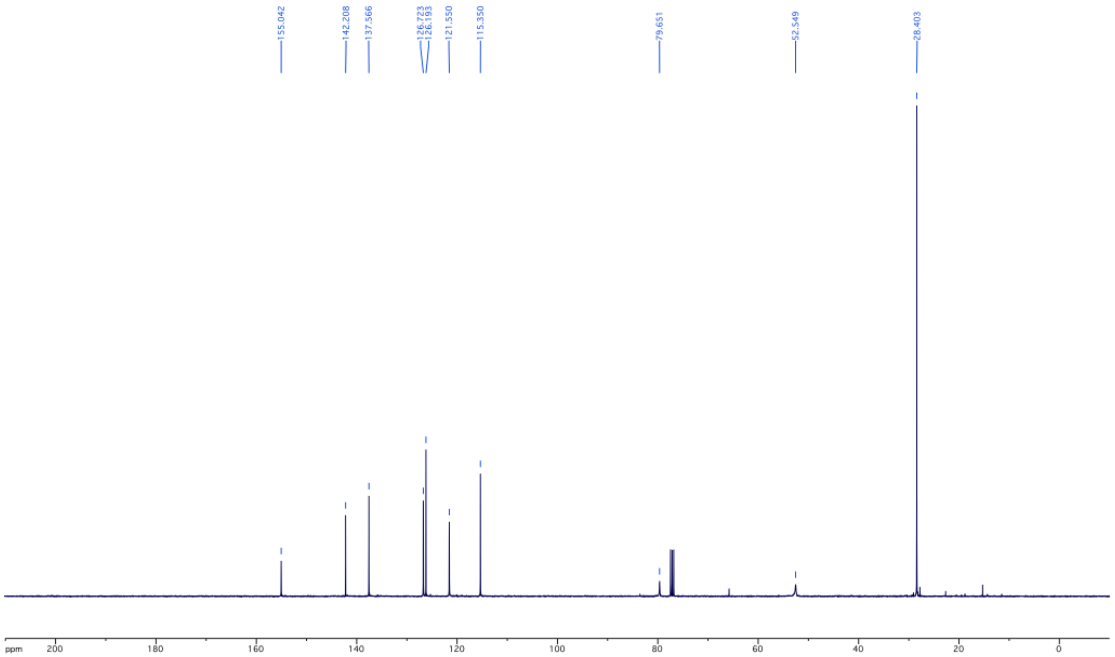
Allylic amine 212: ^{1}H NMR (400 MHz, $CDCl_3$)



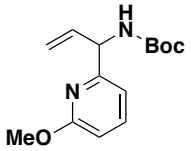


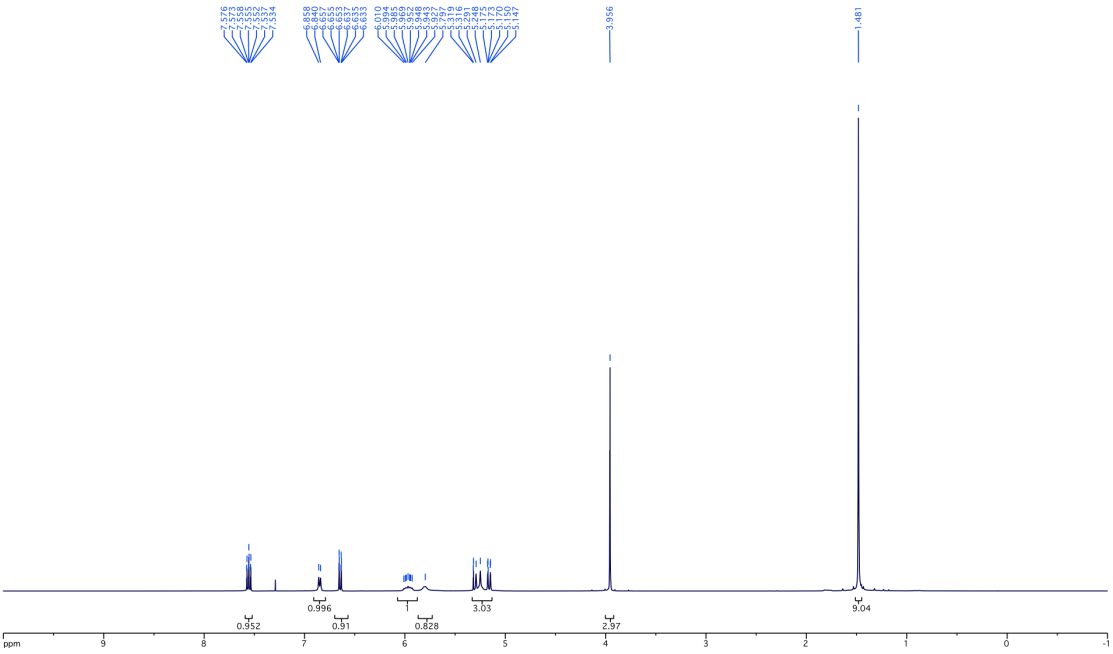
Allylic amine 212: ^{13}C NMR (101 MHz, $CDCl_3$)



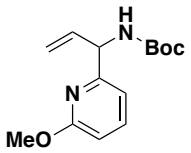


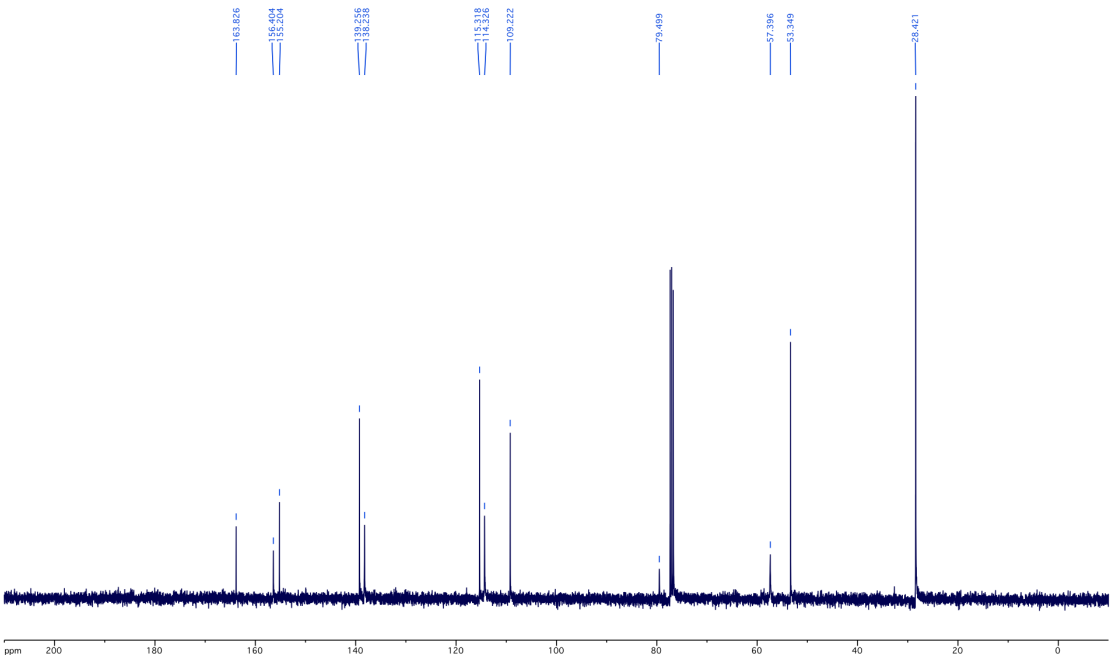
Allylic amine 213: ^{1}H NMR (400 MHz, $CDCl_3$)



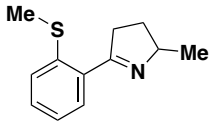


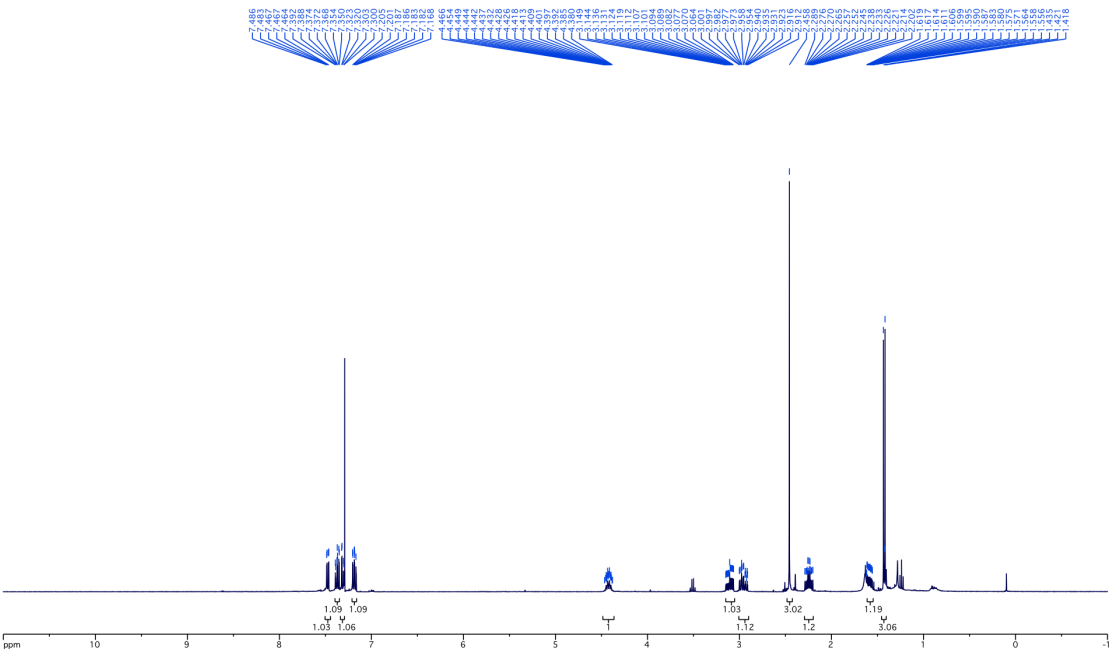
Allylic amine 213: ^{13}C NMR (101 MHz, $CDCl_3$)



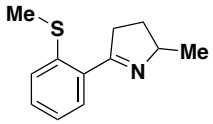


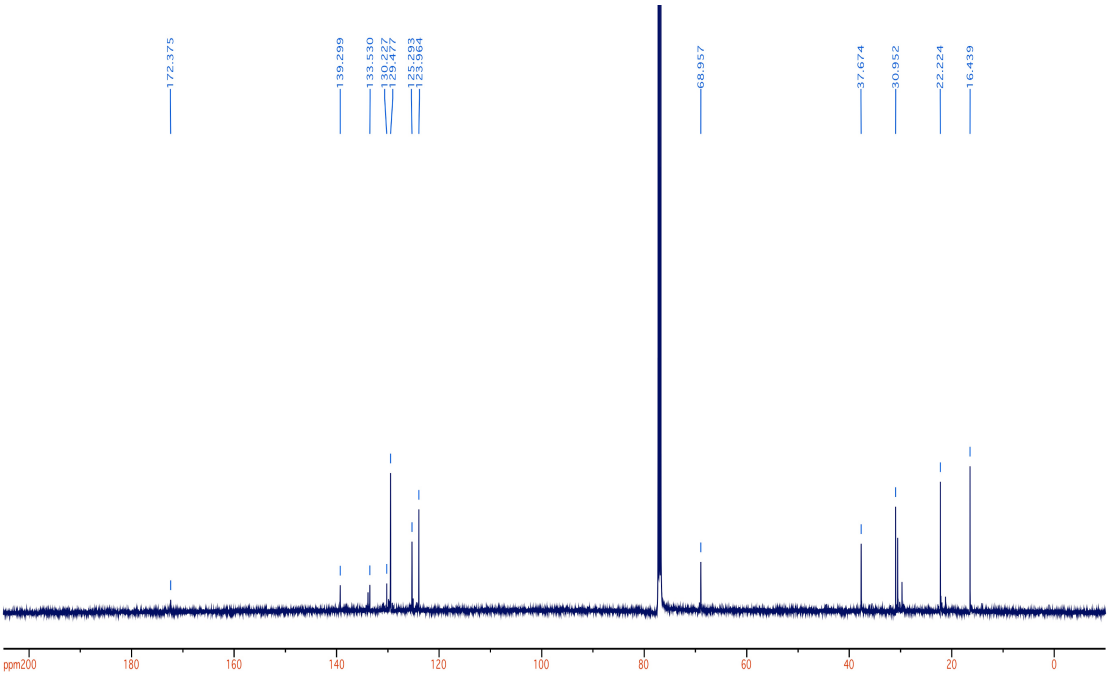
Dihydropyrrole 214: ^{1}H NMR (400 MHz, $CDCl_3$)



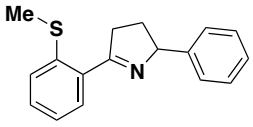


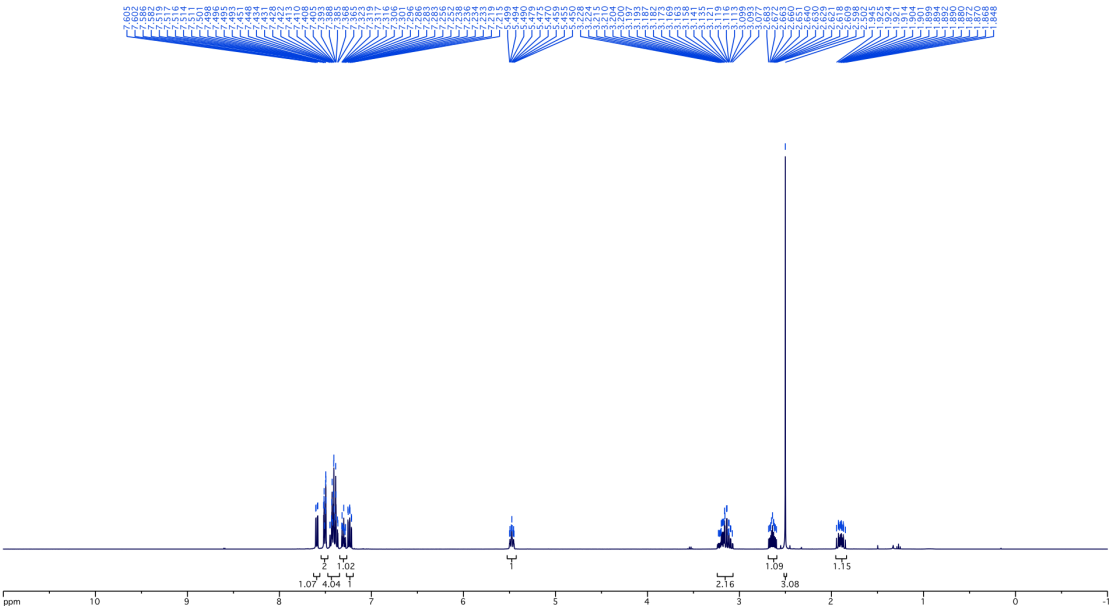
Dihydropyrrole 214: ^{13}C NMR (101 MHz, $CDCl_3$)



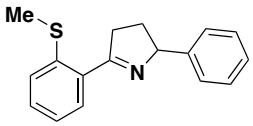


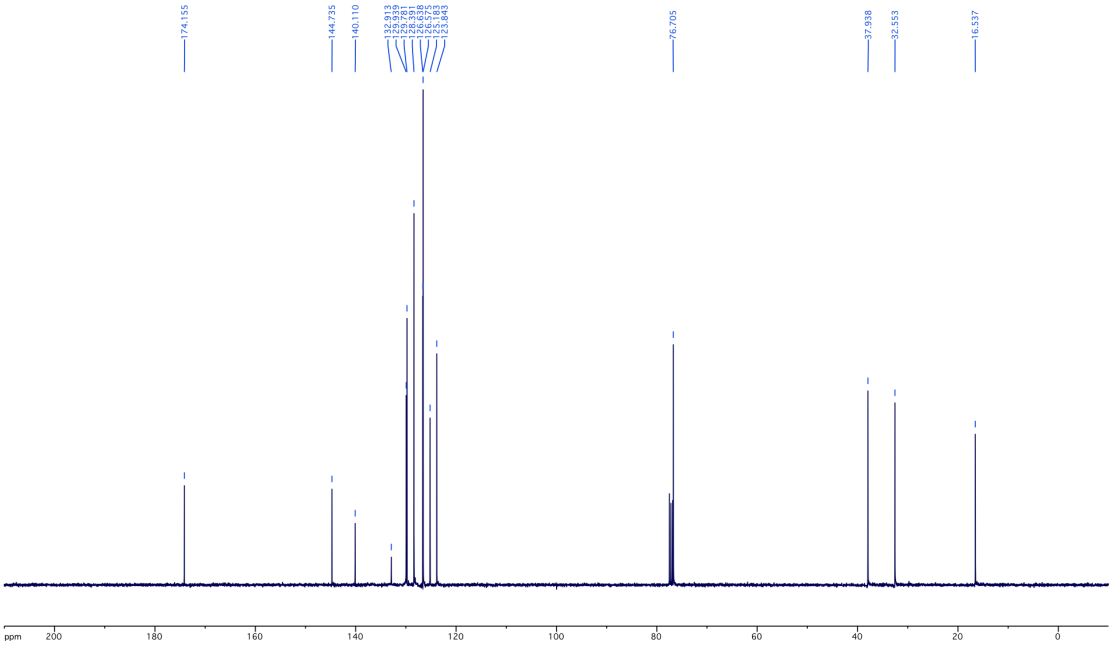
Dihydropyrrole 215: ^{1}H NMR (400 MHz, $CDCl_3$)



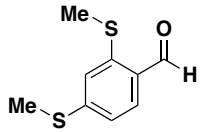


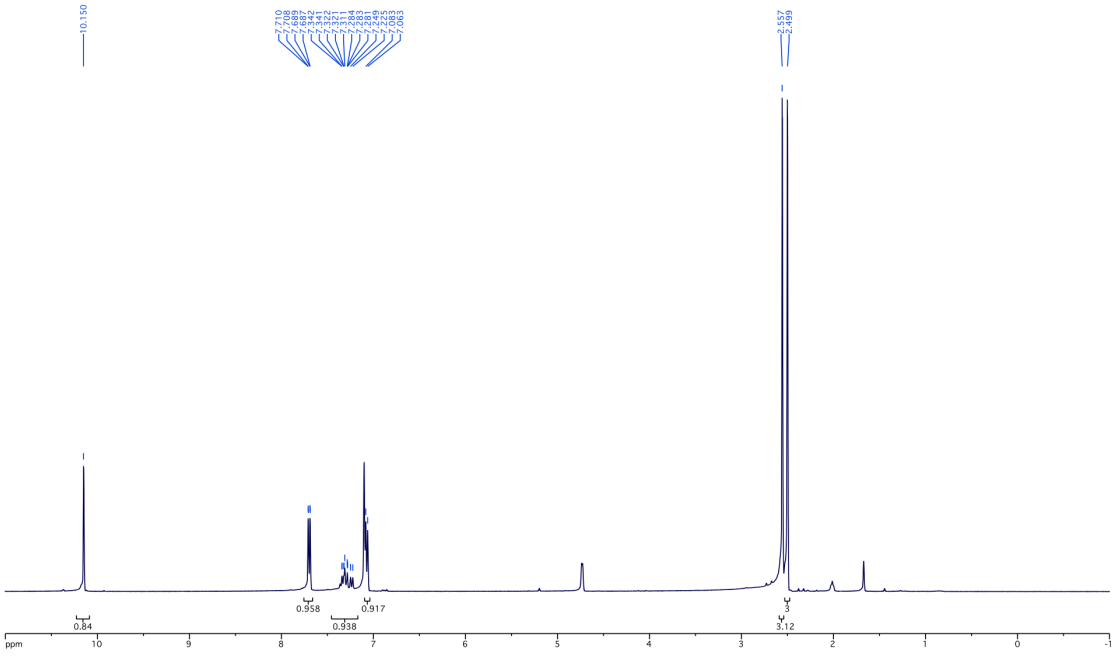
Dihydropyrrole 215: ^{13}C NMR (101 MHz, $CDCl_3$)



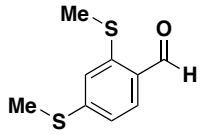


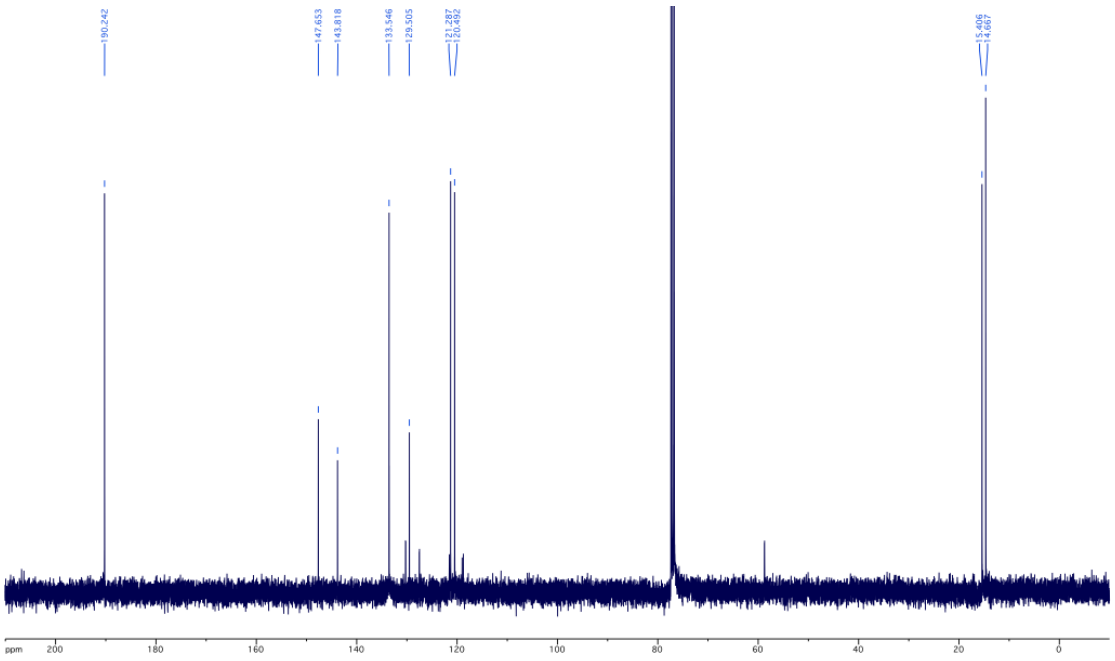
2,4-Bis(methylthio)benzaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$)



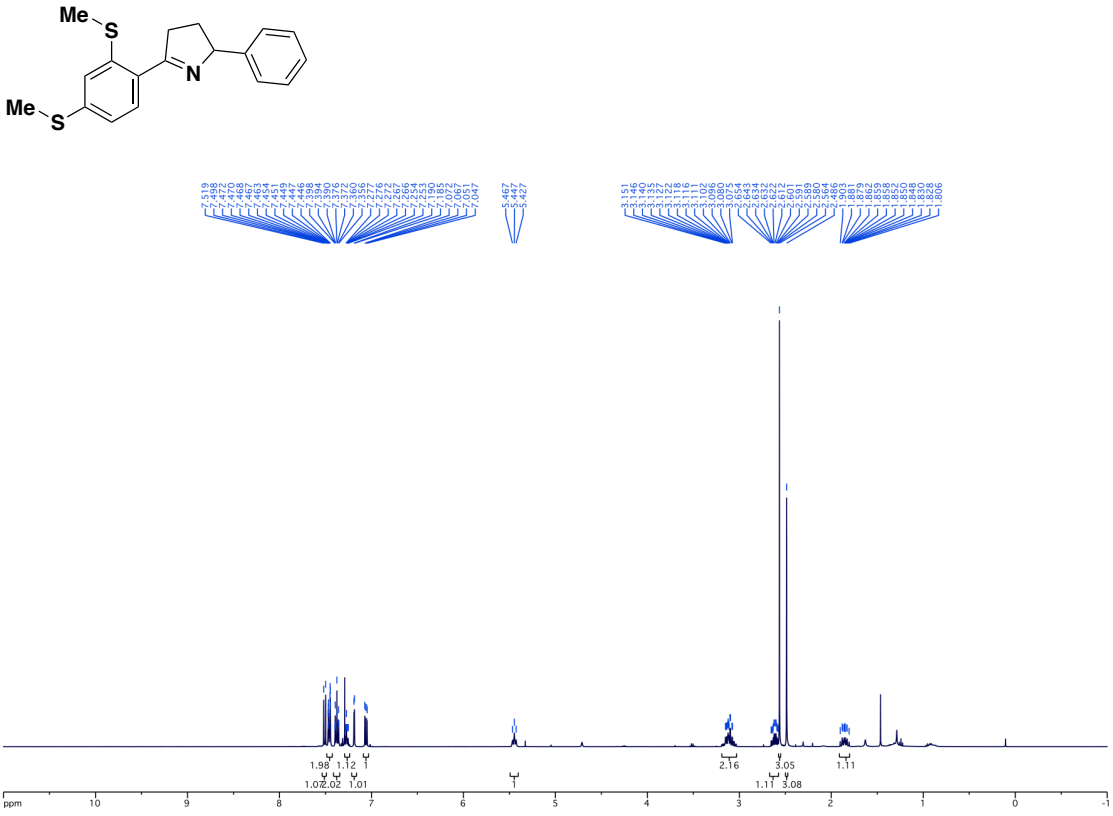


2,4-Bis(methylthio)benzaldehyde: ^{13}C NMR (101 MHz, $CDCl_3$)

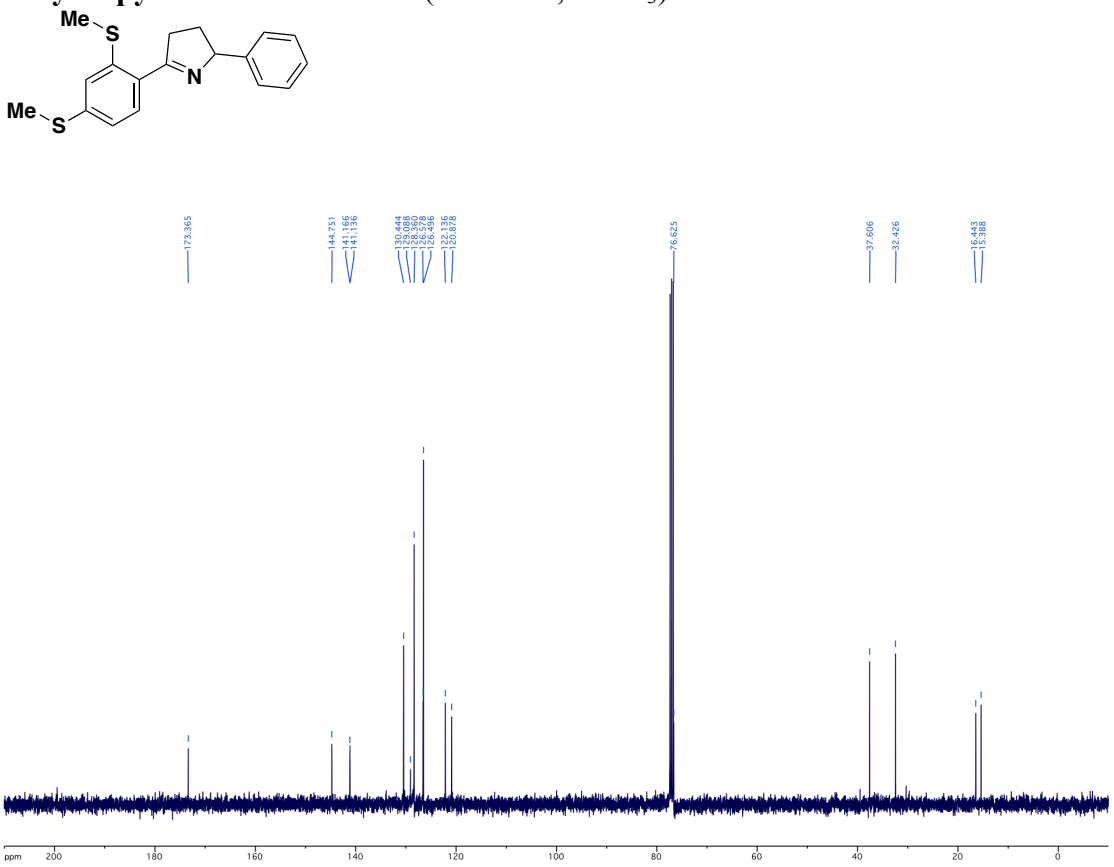




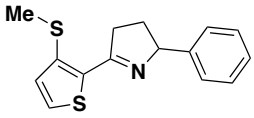
Dihydropyrrole 216: ^{1}H NMR (400 MHz, $CDCl_3$)

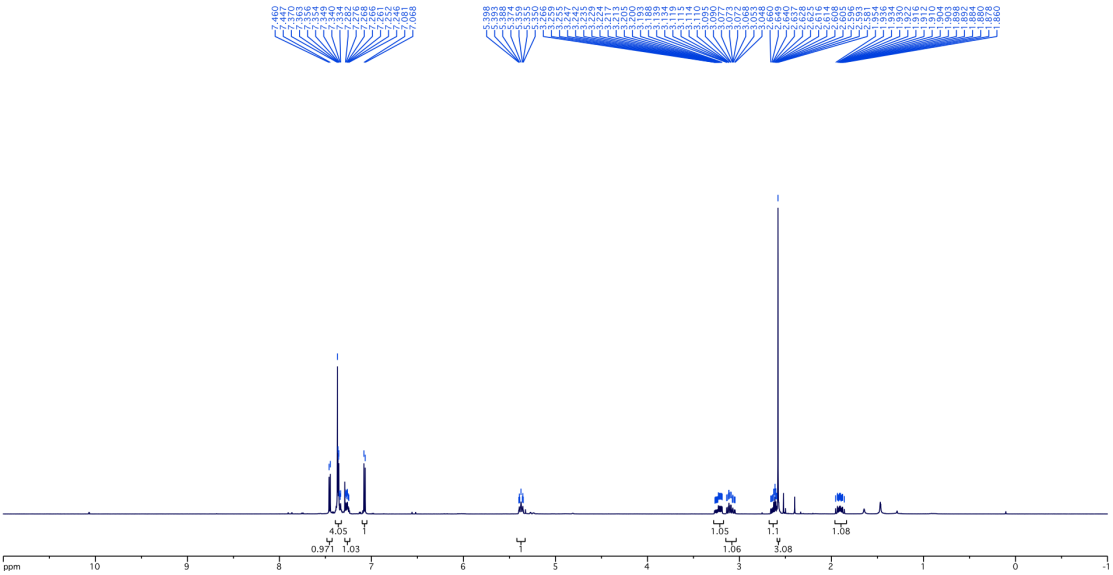


Dihydropyrrole 216: ^{13}C NMR (101 MHz, $CDCl_3$)

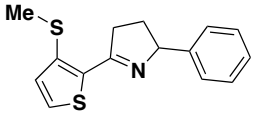


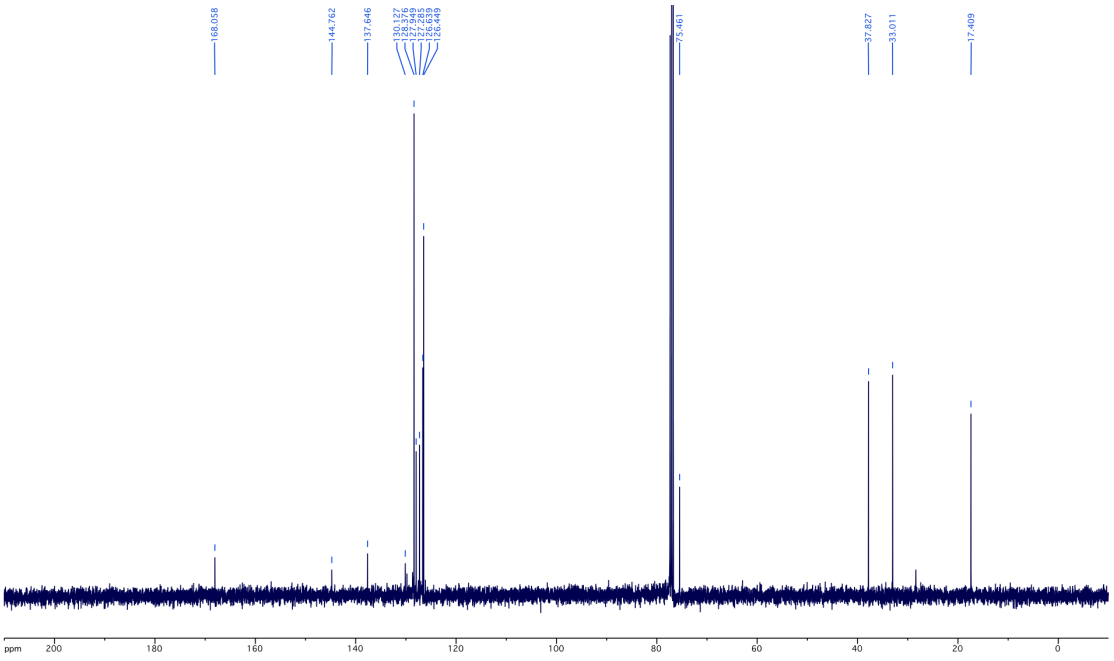
Dihydropyrrole 217: ^{1}H NMR (400 MHz, $CDCl_3$)



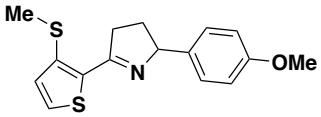


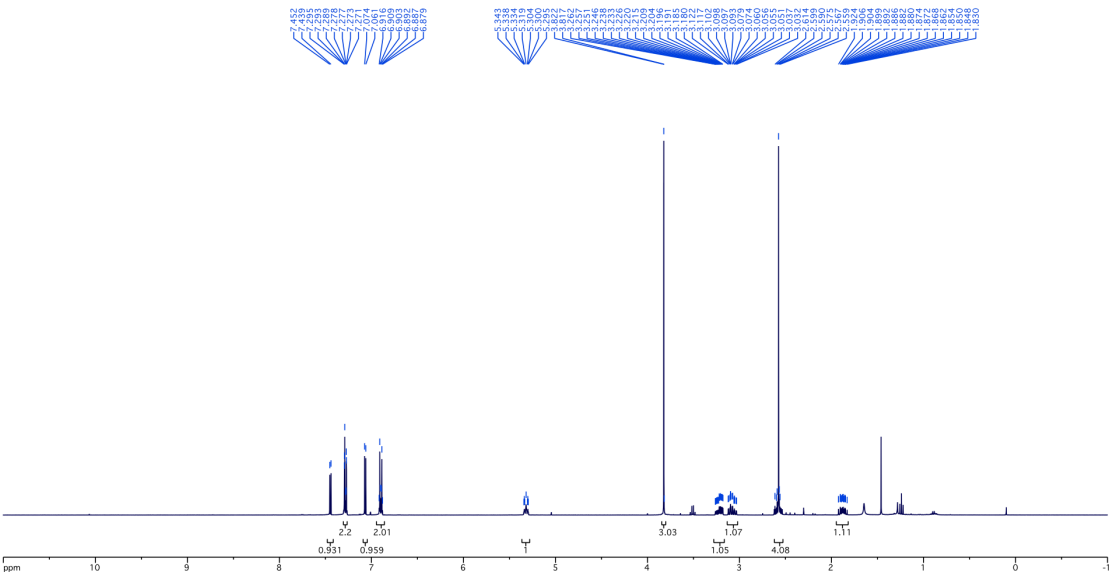
Dihydropyrrole 217: ^{13}C NMR (101 MHz, $CDCl_3$)



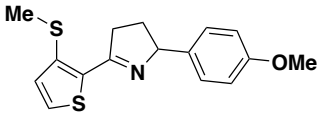


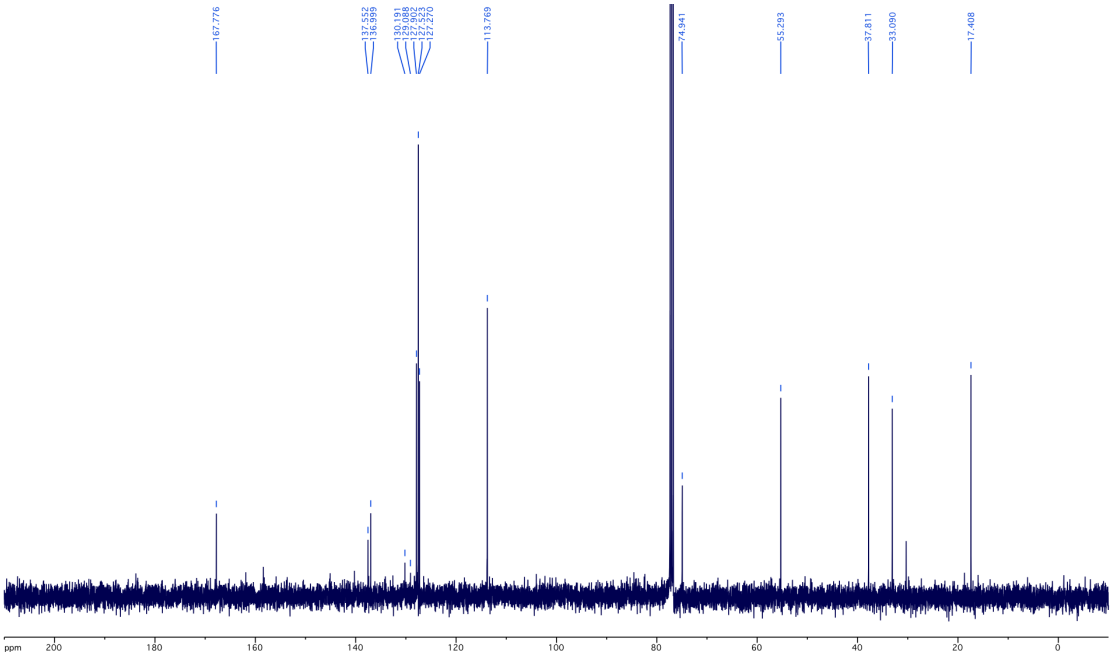
Dihydropyrrole 218: ^{1}H NMR (400 MHz, $CDCl_3$)



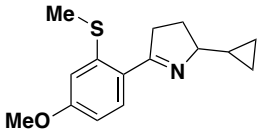


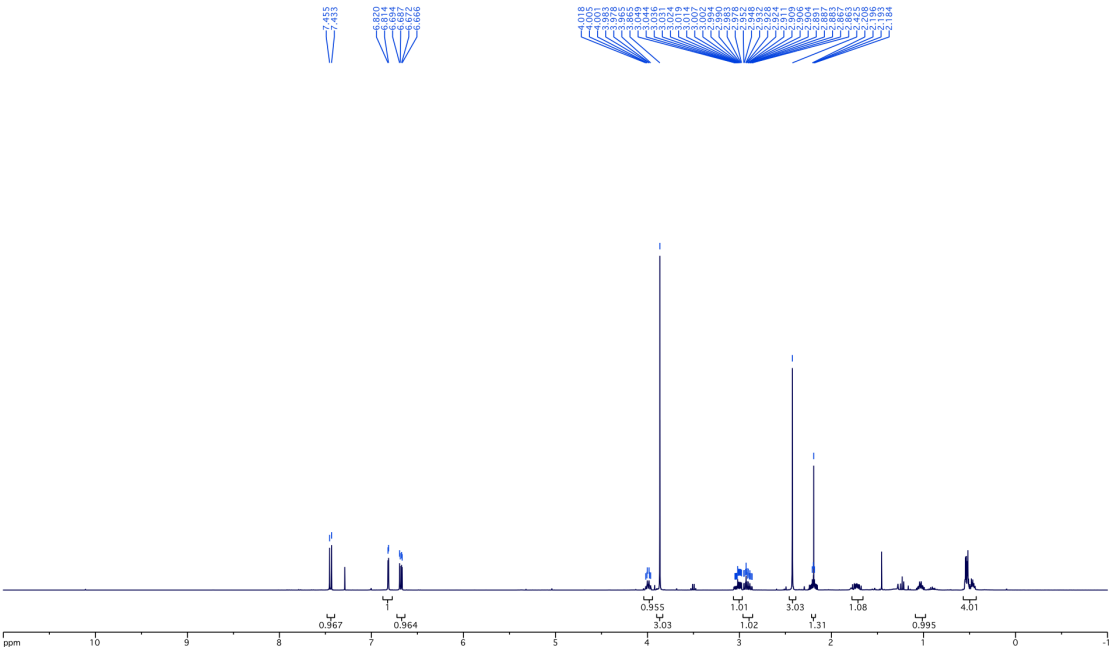
Dihydropyrrole 218: ^{13}C NMR (101 MHz, $CDCl_3$)



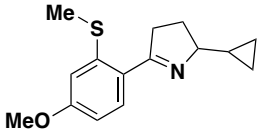


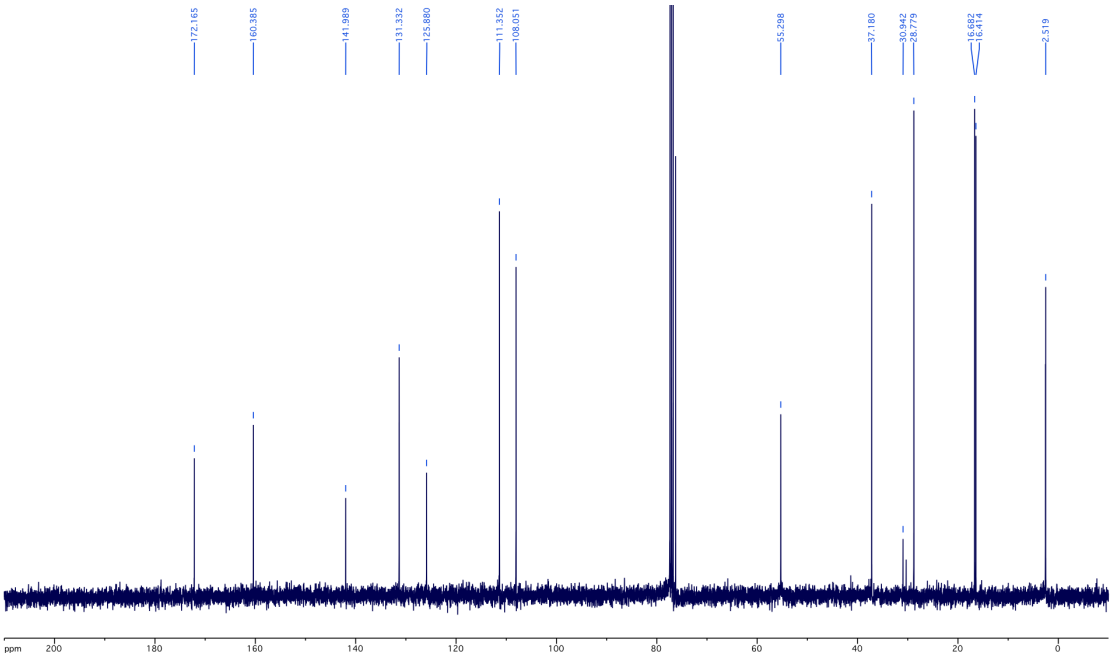
Dihydropyrrole 219: ^{1}H NMR (400 MHz, $CDCl_3$)



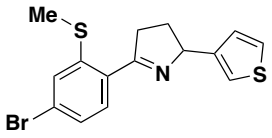


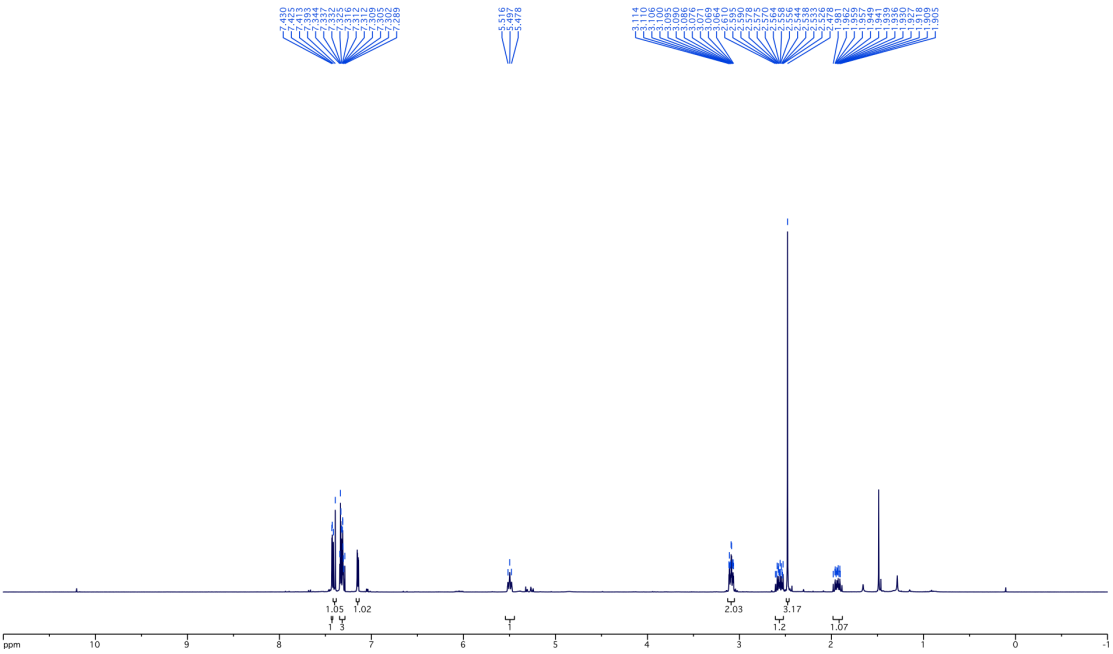
Dihydropyrrole 219: ^{13}C NMR (101 MHz, $CDCl_3$)



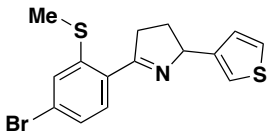


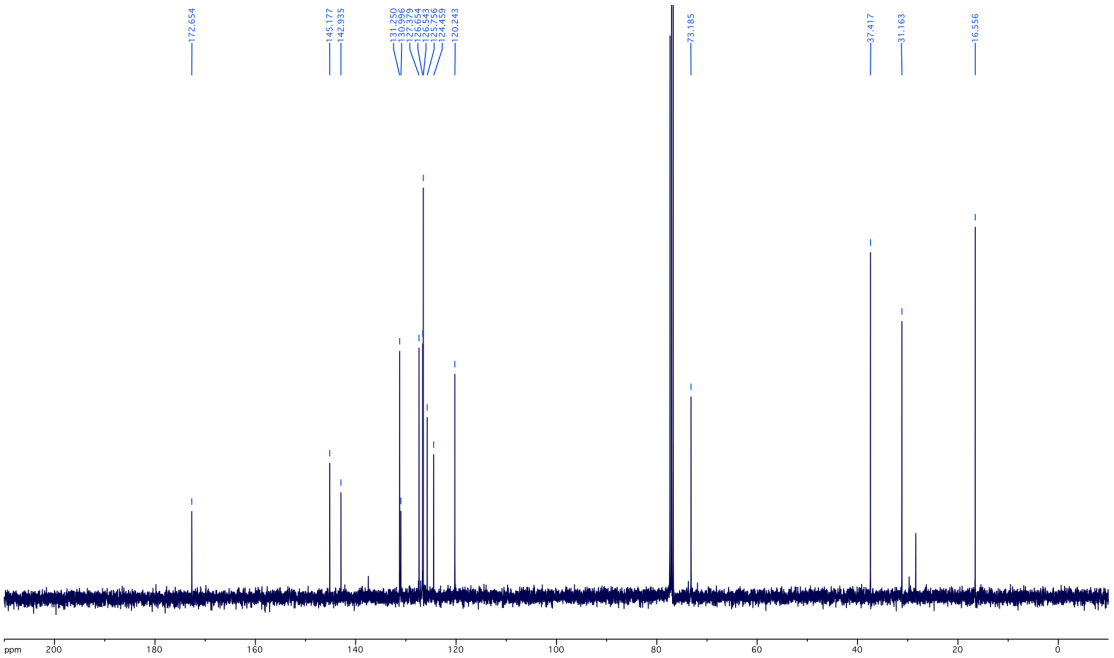
Dihydropyrrole 220: ^{1}H NMR (400 MHz, $CDCl_3$)



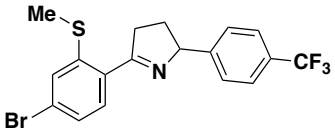


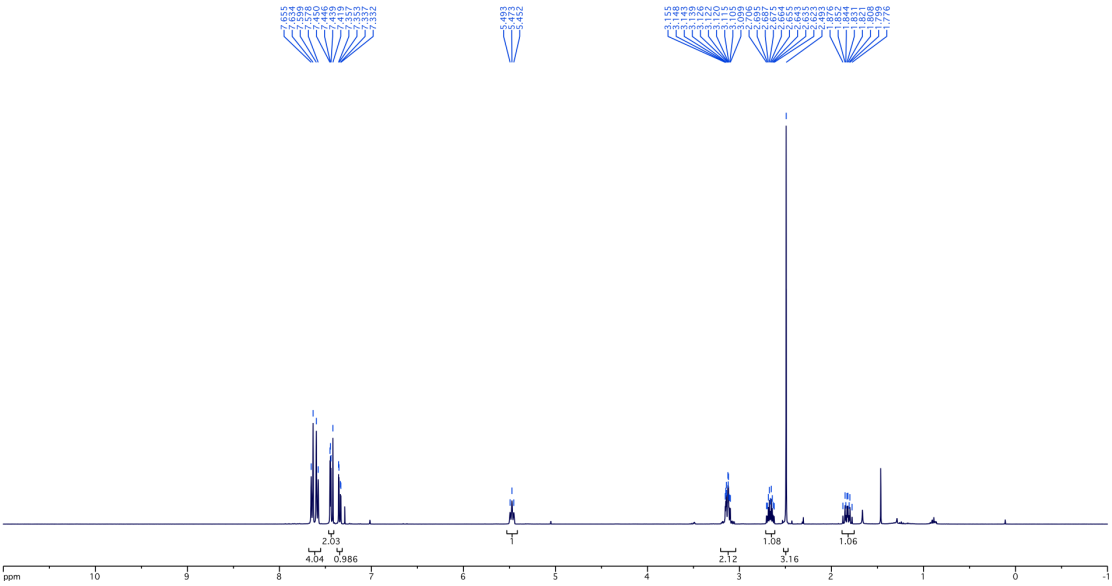
Dihydropyrrole 220: ^{13}C NMR (101 MHz, $CDCl_3$)



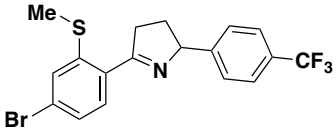


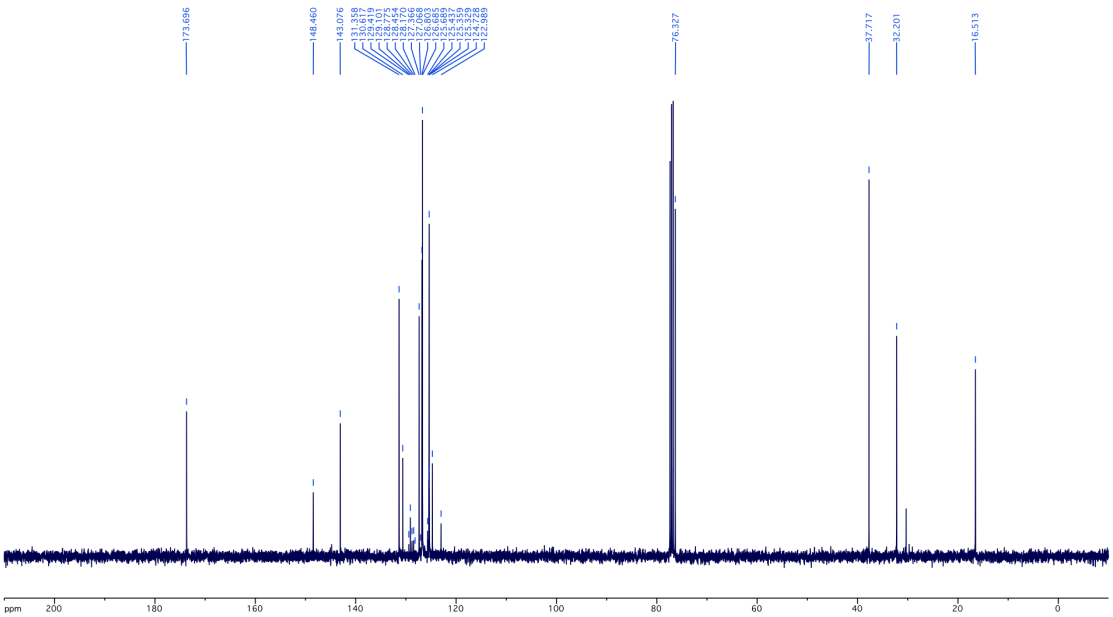
Dihydropyrrole 221: ^{1}H NMR (400 MHz, $CDCl_3$)



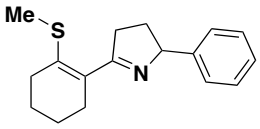


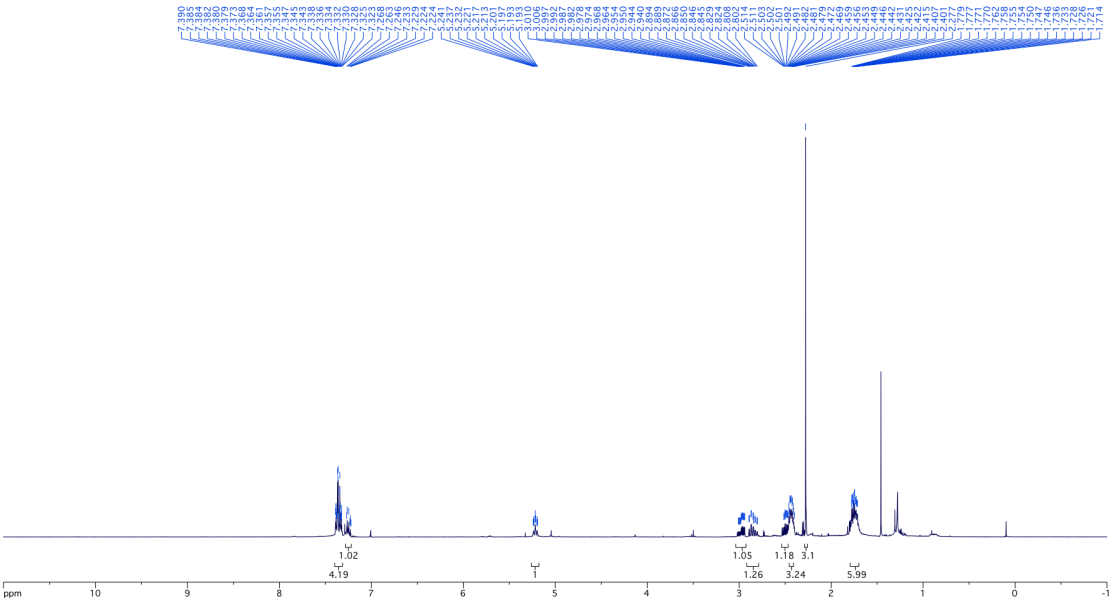
Dihydropyrrole 221: ^{13}C NMR (101 MHz, $CDCl_3$)



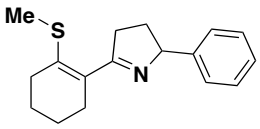


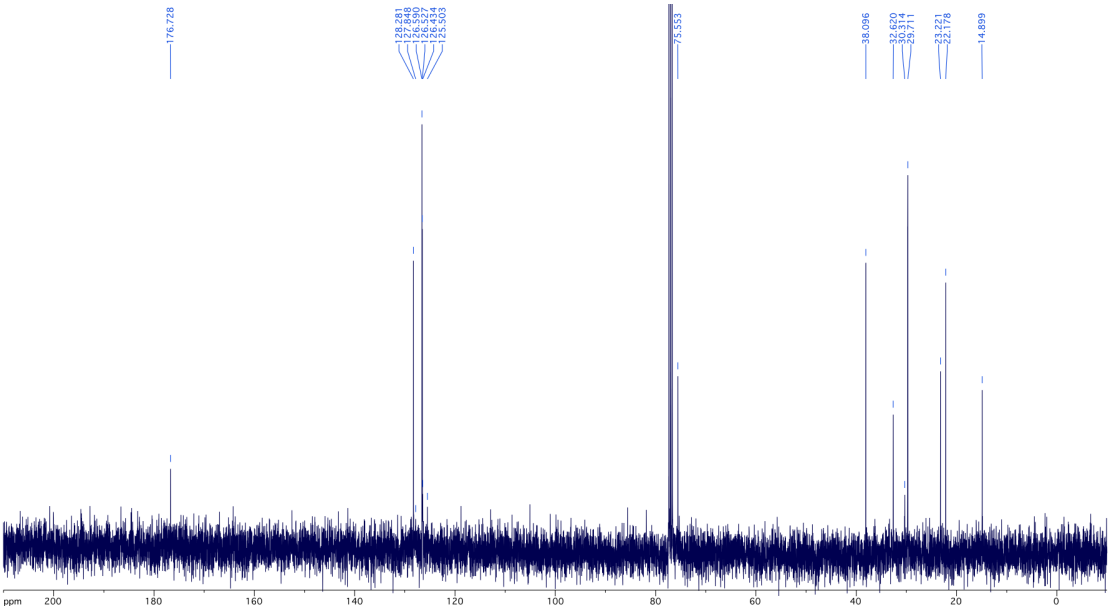
Dihydropyrrole 222: ^{1}H NMR (400 MHz, $CDCl_3$)



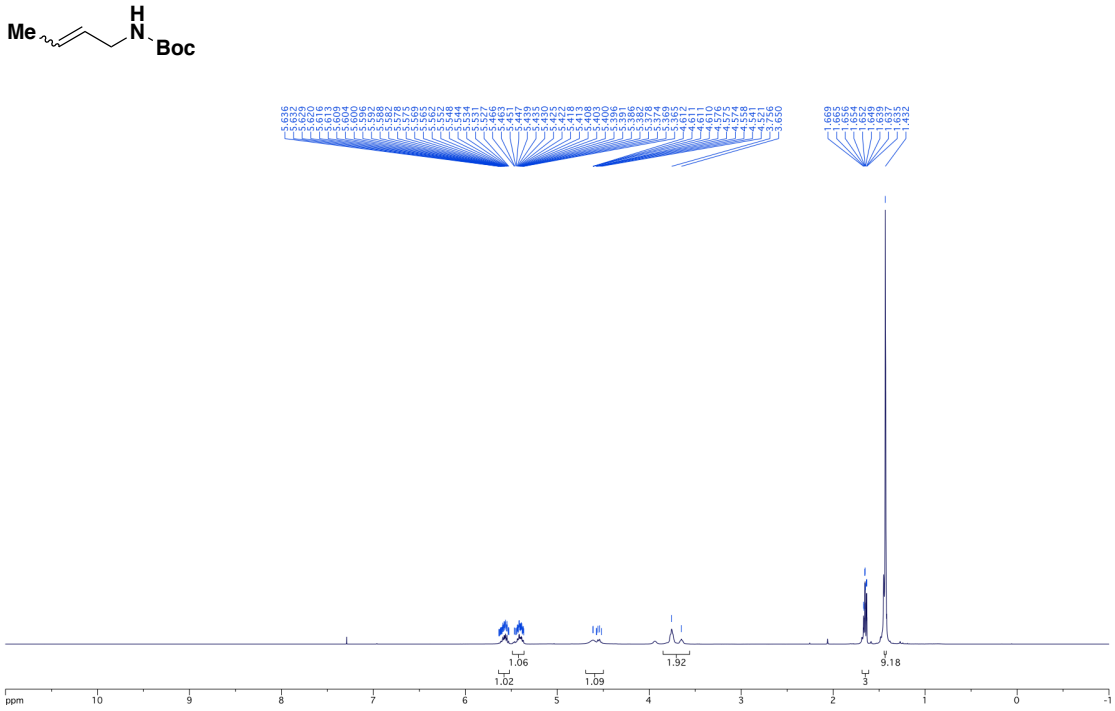


Dihydropyrrole 222: ^{13}C NMR (101 MHz, $CDCl_3$)

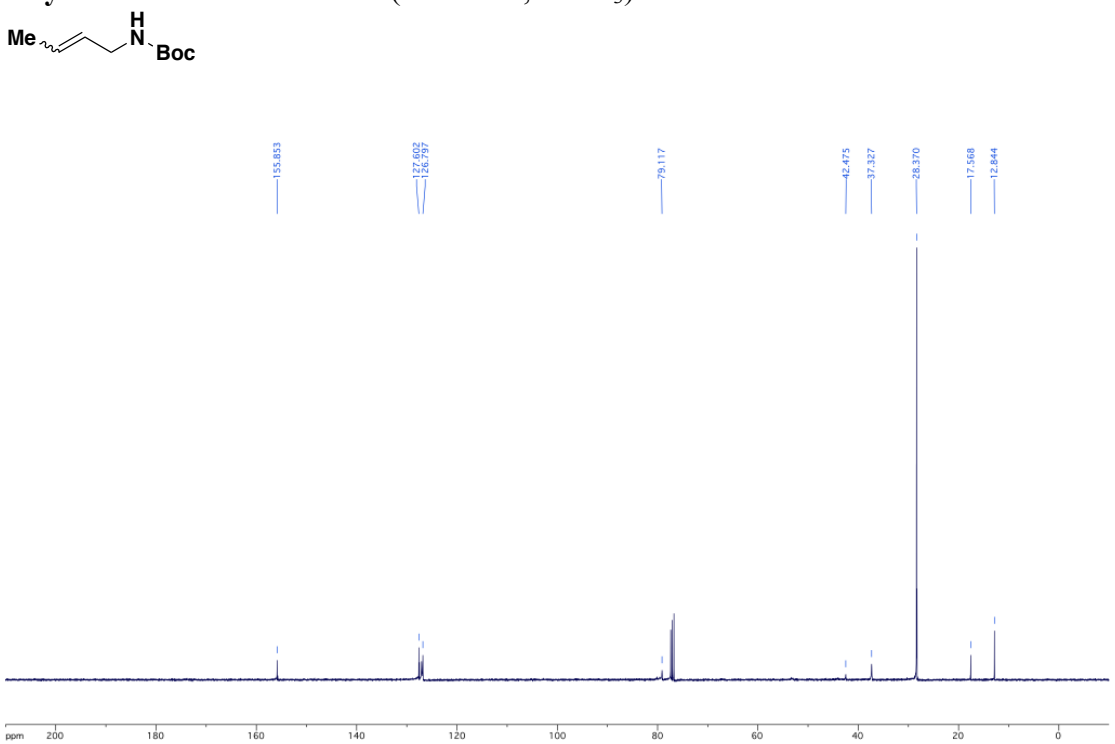




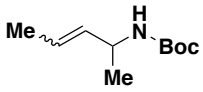
Allylic amine 231: ^{1}H NMR (400 MHz, $CDCl_3$)

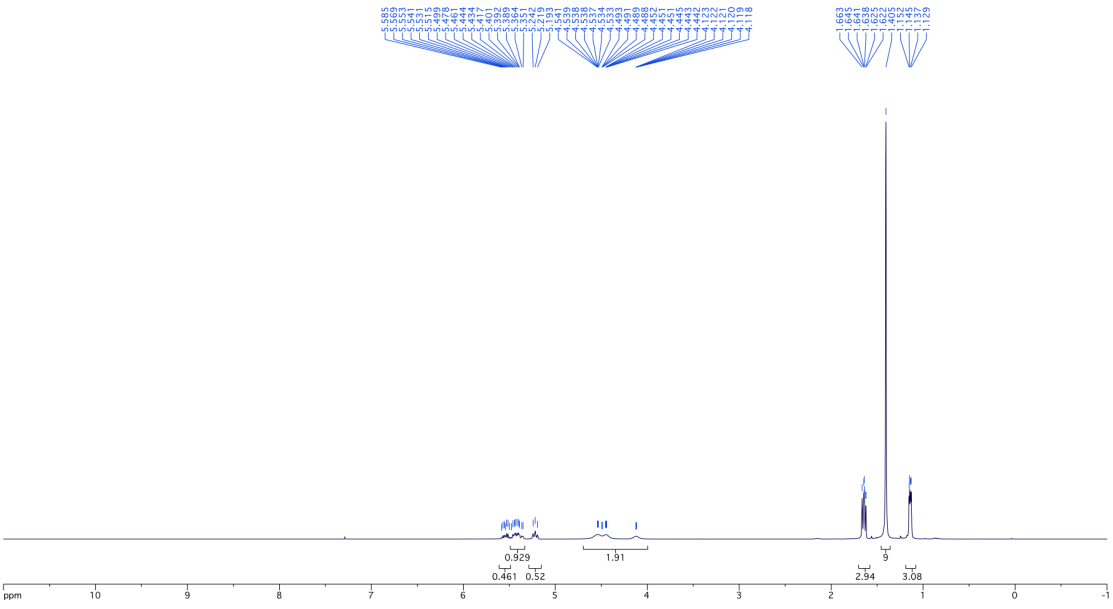


Allylic amine 231: ^{13}C NMR (101 MHz, $CDCl_3$)

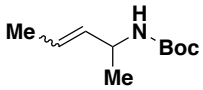


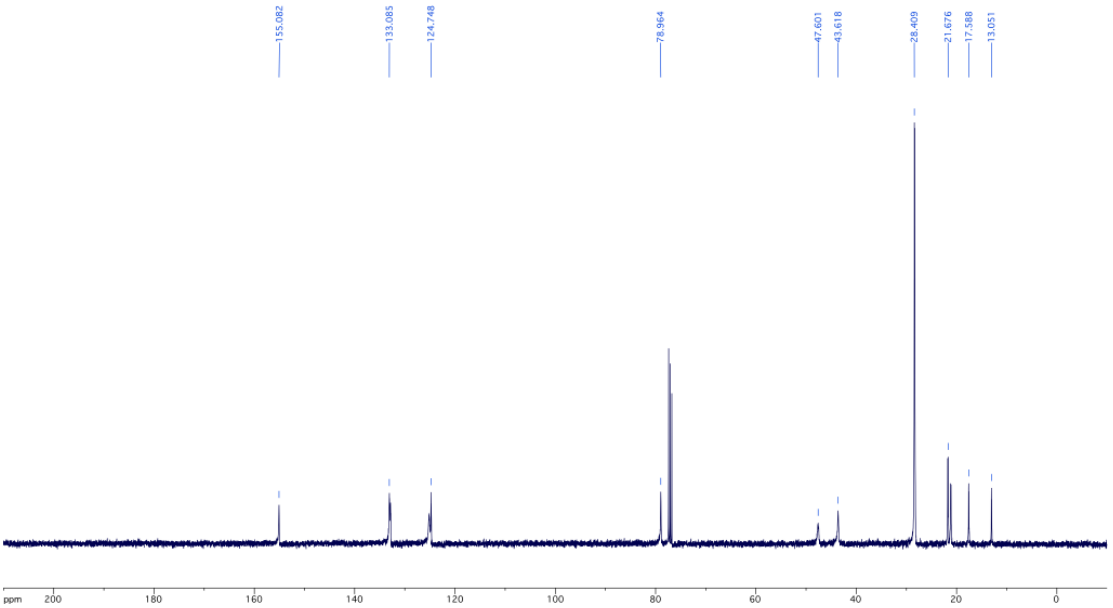
Allylic amine 232: ^{1}H NMR (400 MHz, $CDCl_3$)



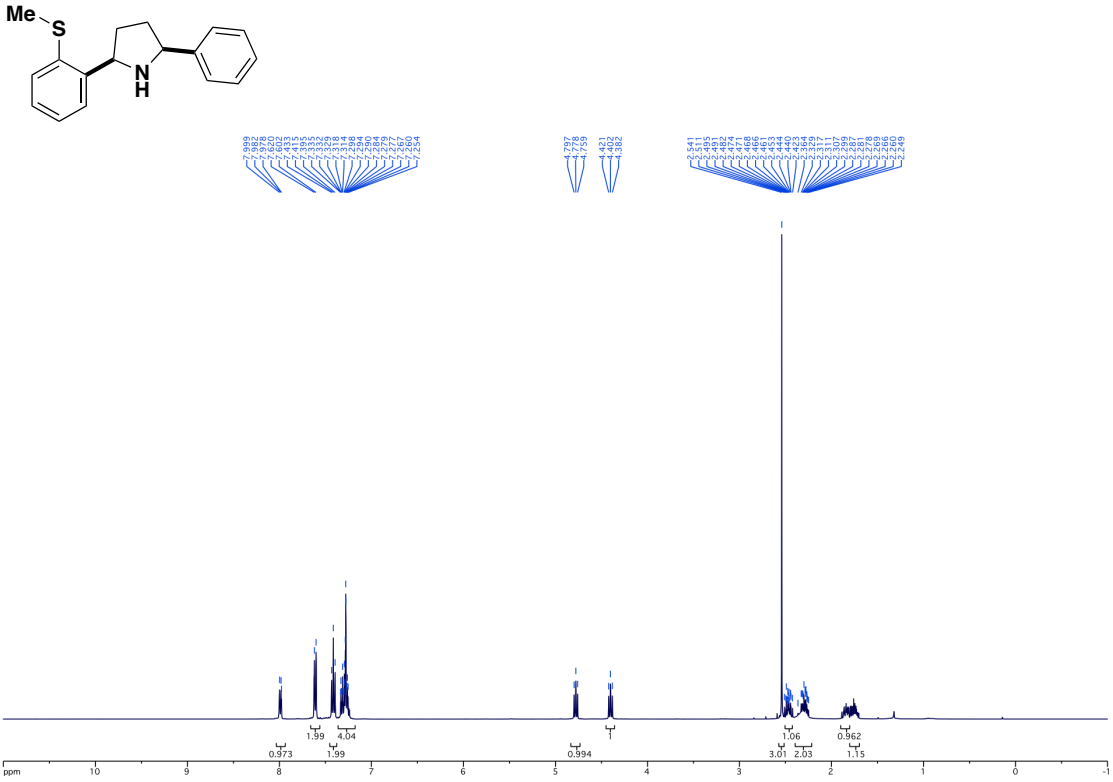


Allylic amine 232: ^{13}C NMR (101 MHz, $CDCl_3$)

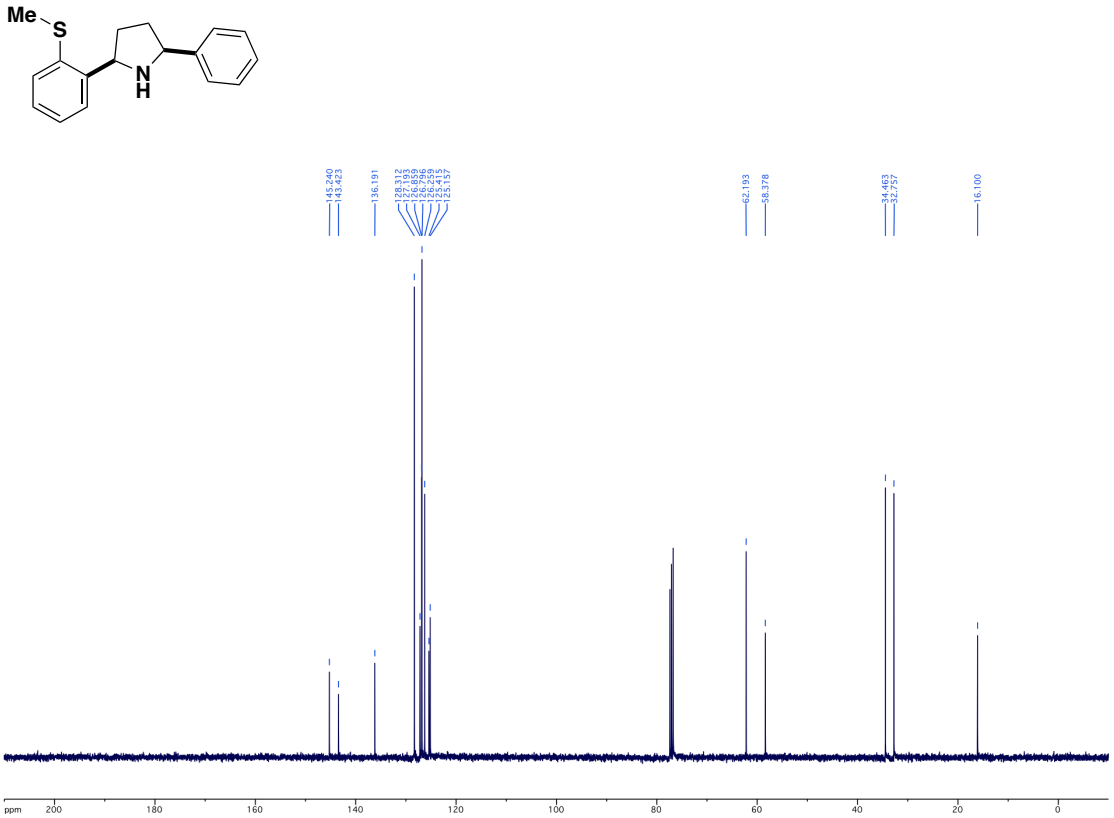




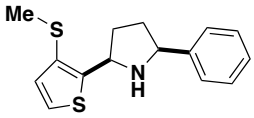
Pyrrolidine 233: ^{1}H NMR (400 MHz, $CDCl_3$)

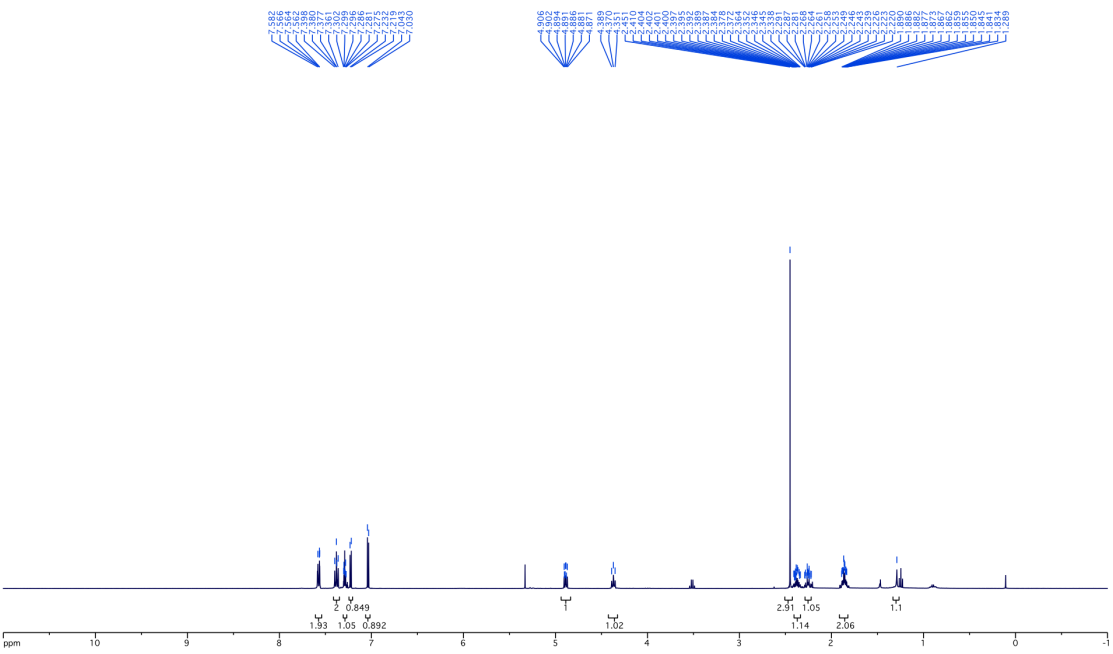


Pyrrolidine 233: ^{13}C NMR (101 MHz, $CDCl_3$)

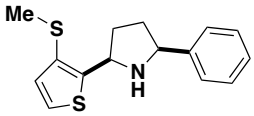


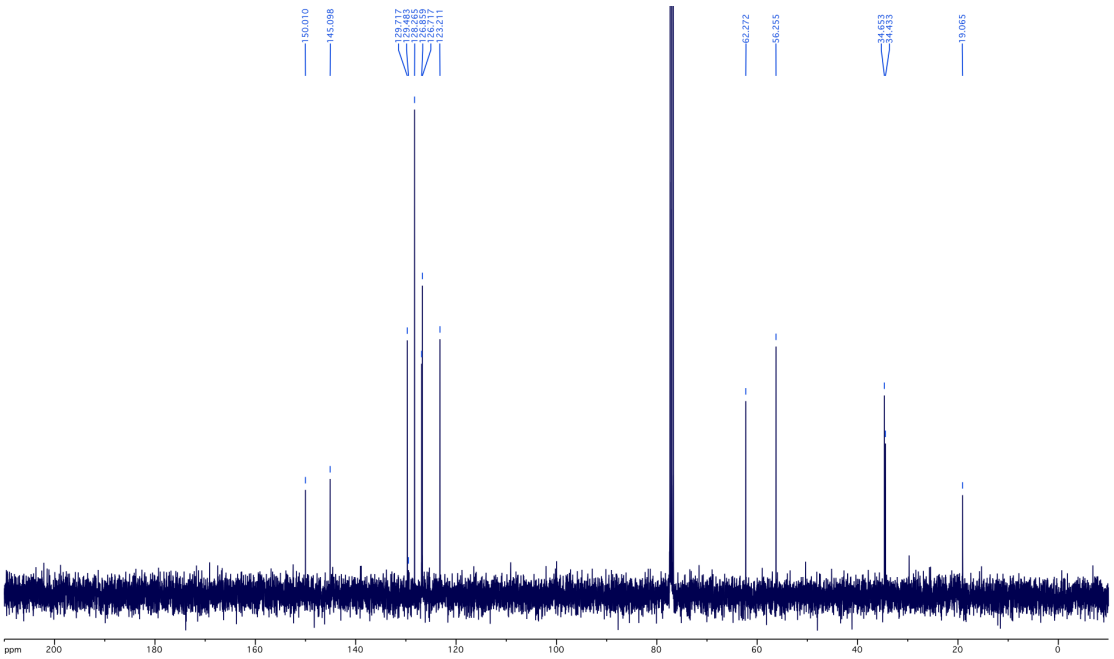
Pyrrolidine 234: ^{1}H NMR (400 MHz, $CDCl_3$)



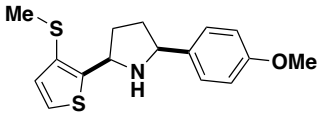


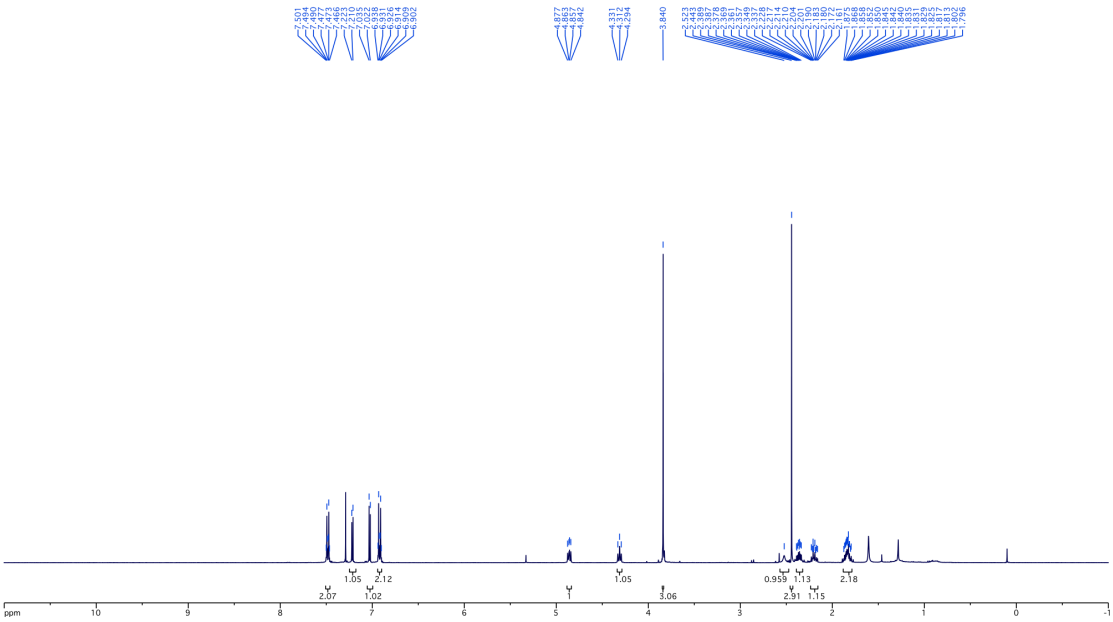
Pyrrolidine 234: ^{13}C NMR (101 MHz, $CDCl_3$)



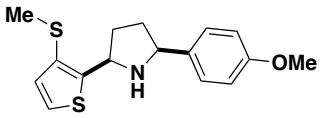


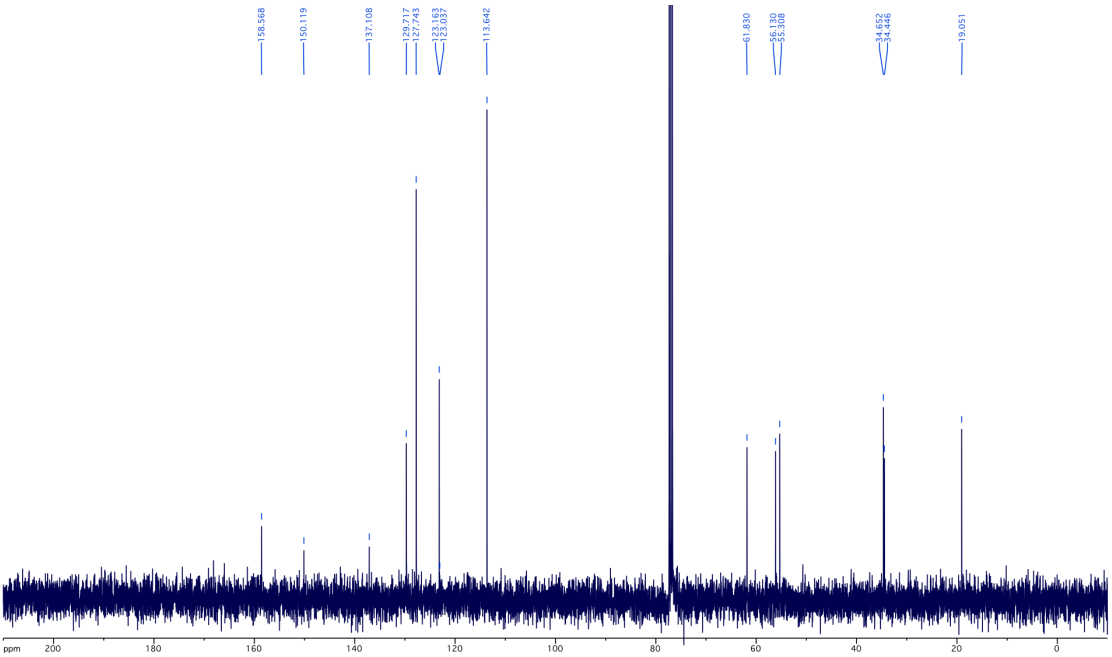
Pyrrolidine 235: ^{1}H NMR (400 MHz, $CDCl_3$)



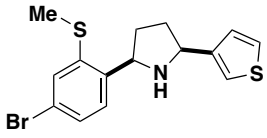


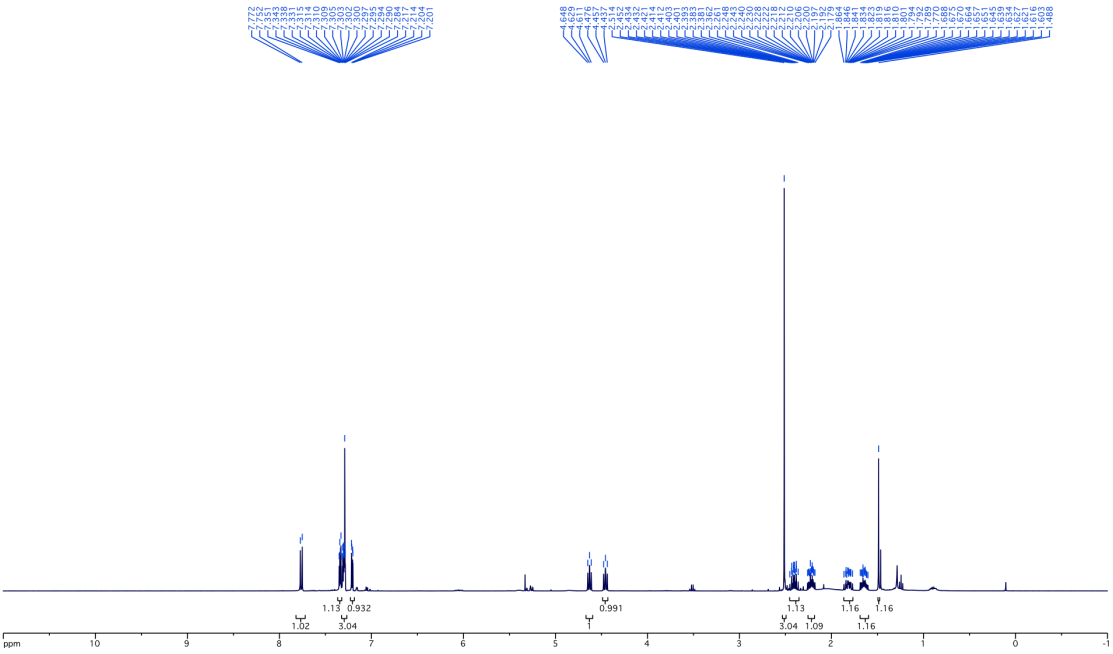
Pyrrolidine 235: ^{13}C NMR (101 MHz, $CDCl_3$)



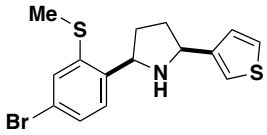


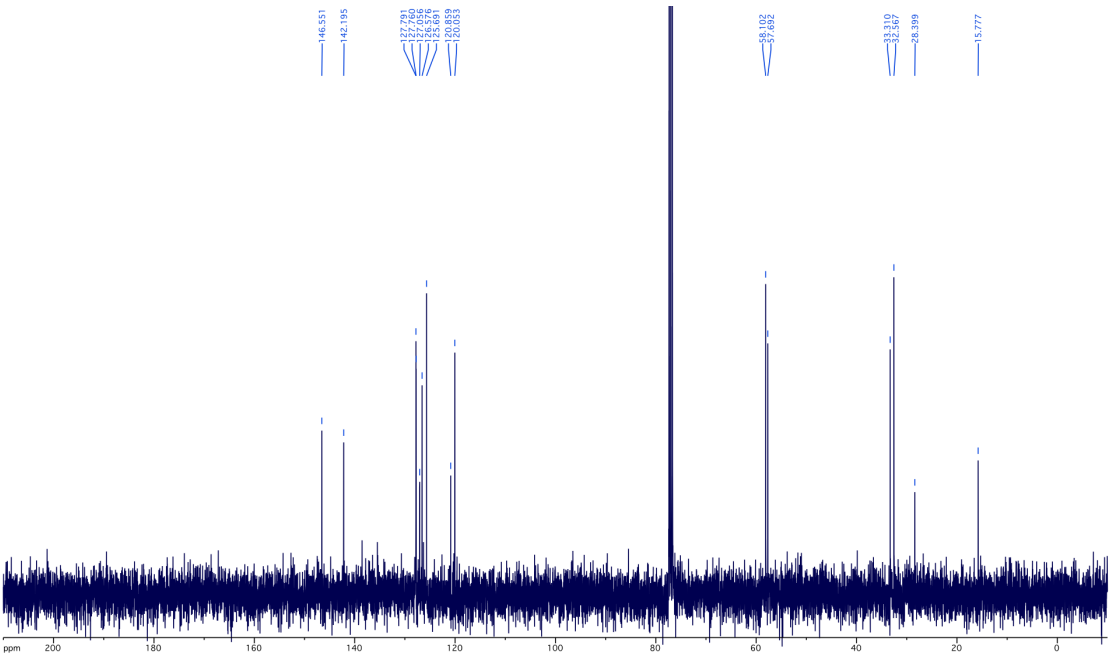
Pyrrolidine 236: ^{1}H NMR (400 MHz, $CDCl_3$)



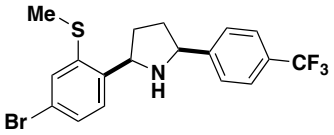


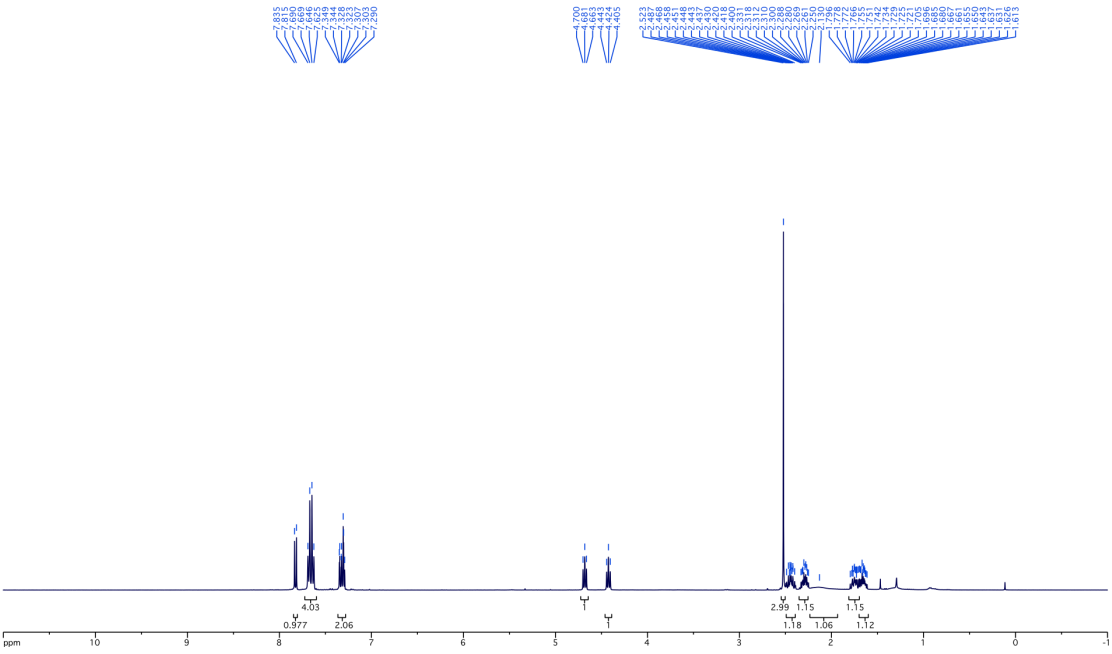
Pyrrolidine 236: ^{13}C NMR (101 MHz, $CDCl_3$)



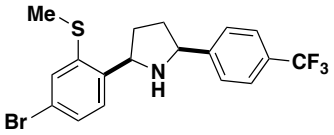


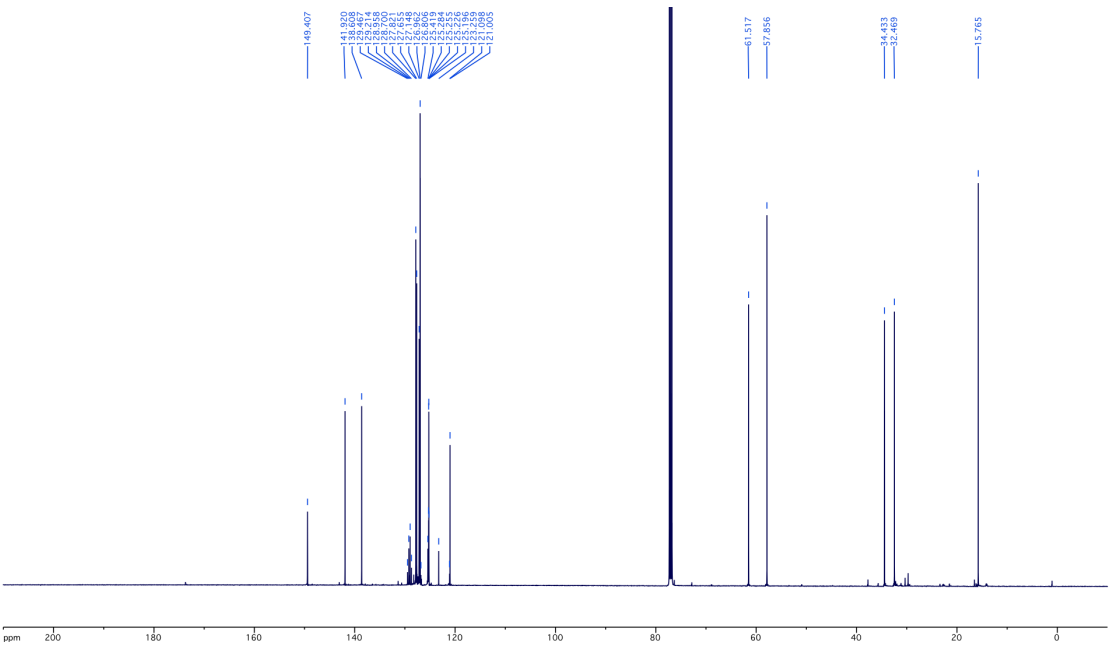
Pyrrolidine 237: ^{1}H NMR (400 MHz, $CDCl_3$)



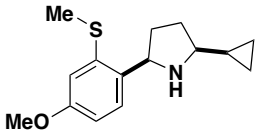


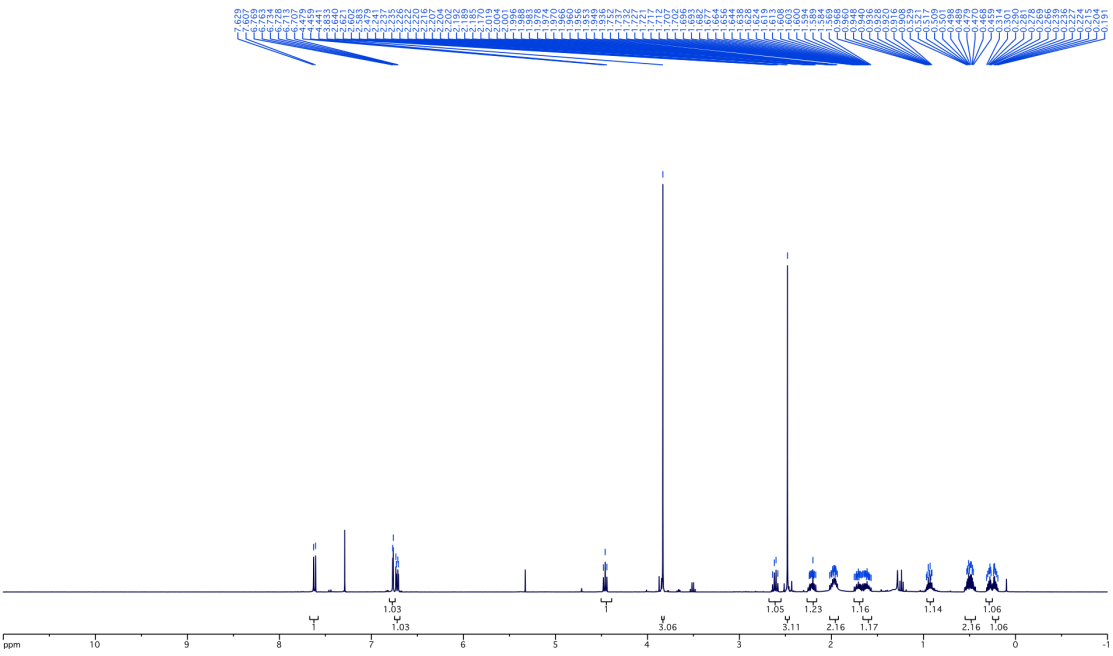
Pyrrolidine 237: ^{13}C NMR (101 MHz, $CDCl_3$)



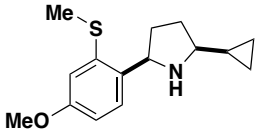


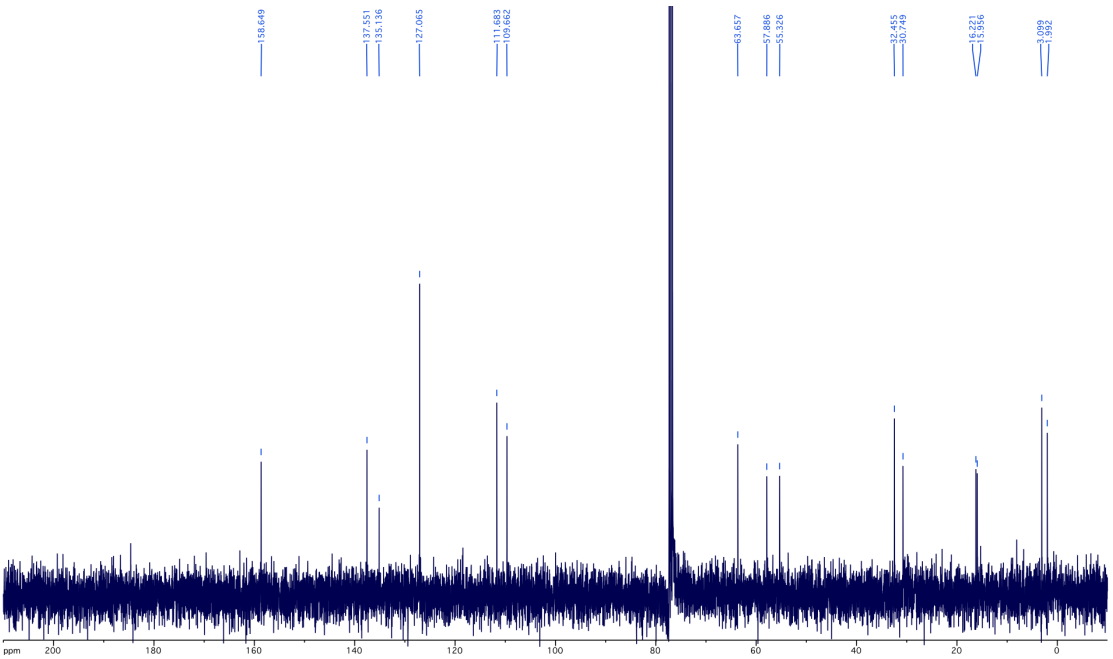
Pyrrolidine 238: ^{1}H NMR (400 MHz, $CDCl_3$)



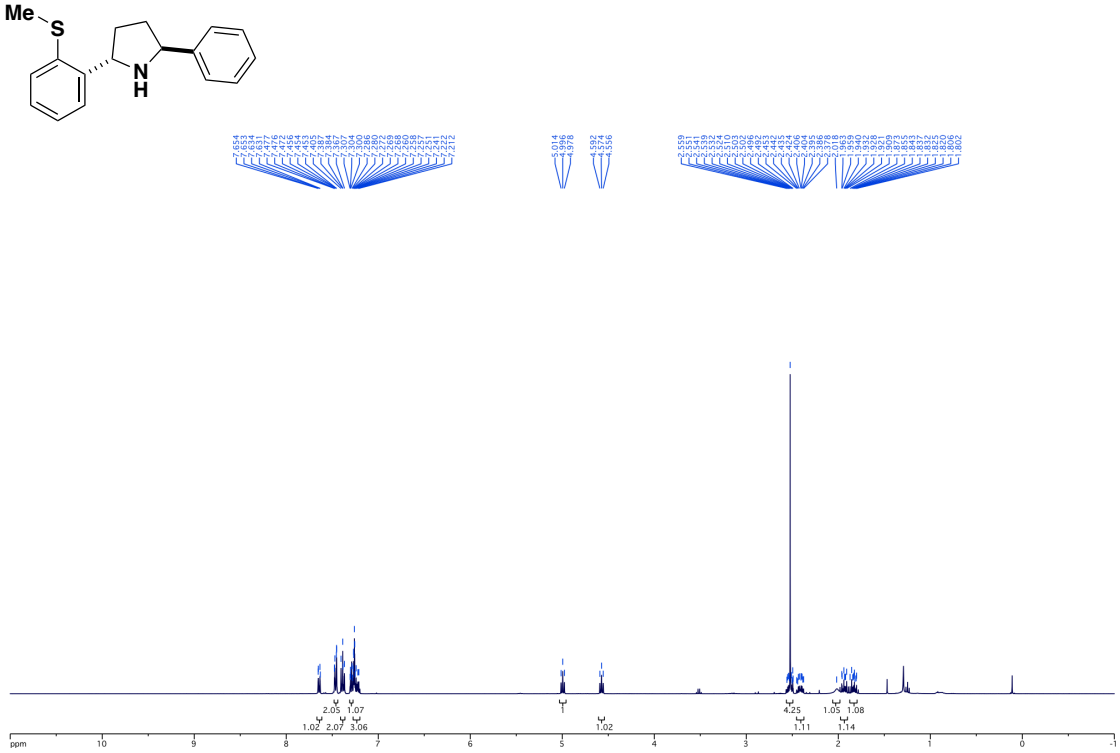


Pyrrolidine 238: ^{13}C NMR (101 MHz, $CDCl_3$)

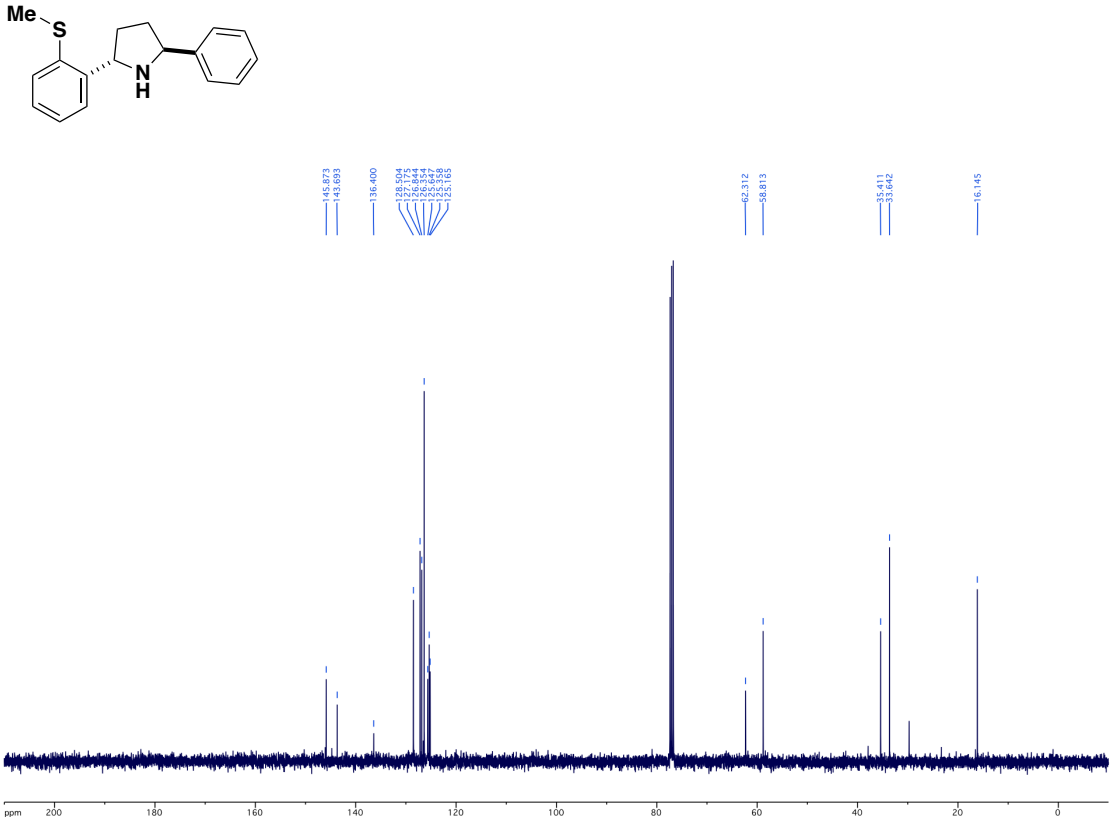




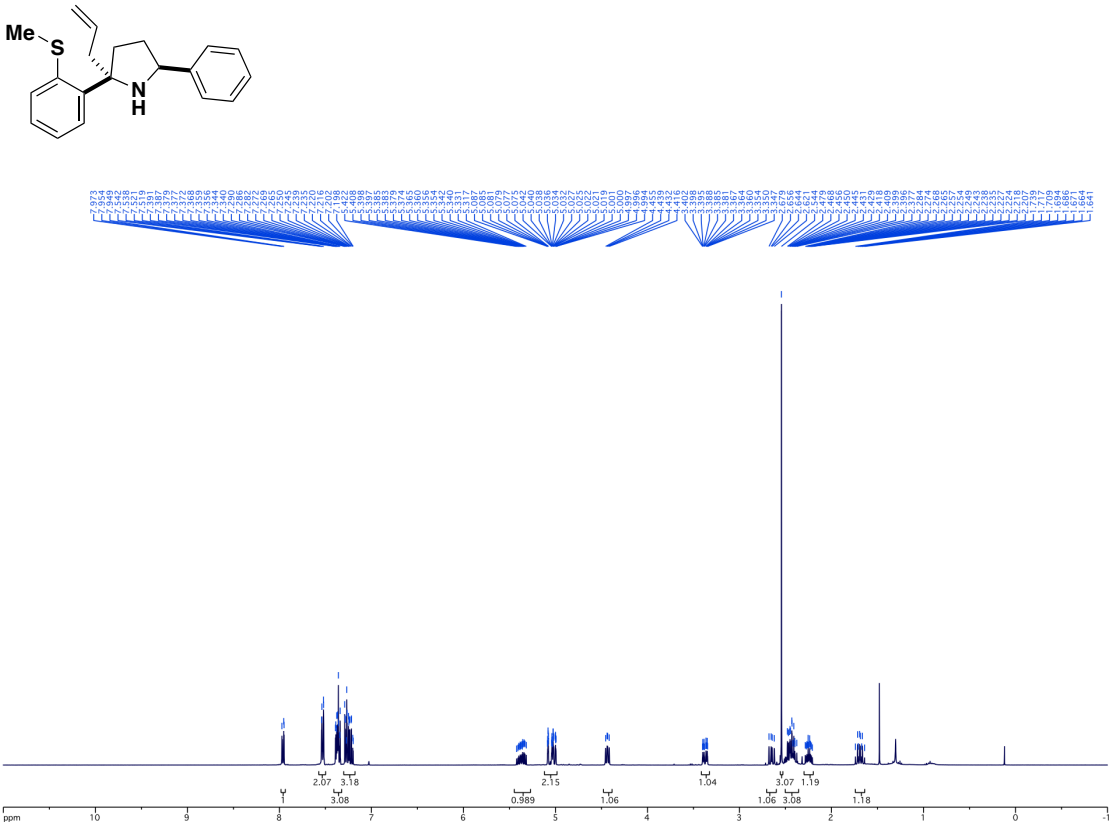
Pyrrolidine 239: ^{1}H NMR (400 MHz, $CDCl_3$)



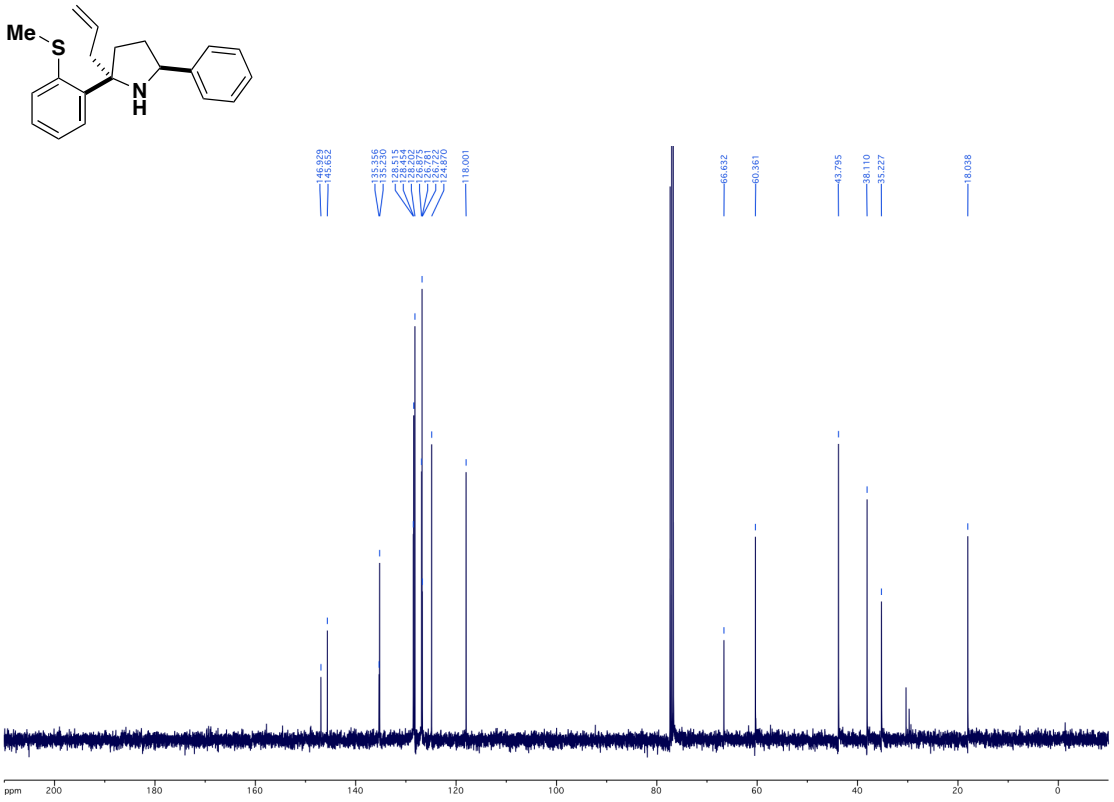
Pyrrolidine 239: ^{13}C NMR (101 MHz, $CDCl_3$)



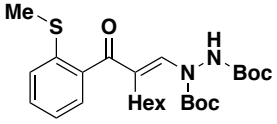
Pyrrolidine 240: ^{1}H NMR (400 MHz, $CDCl_3$)

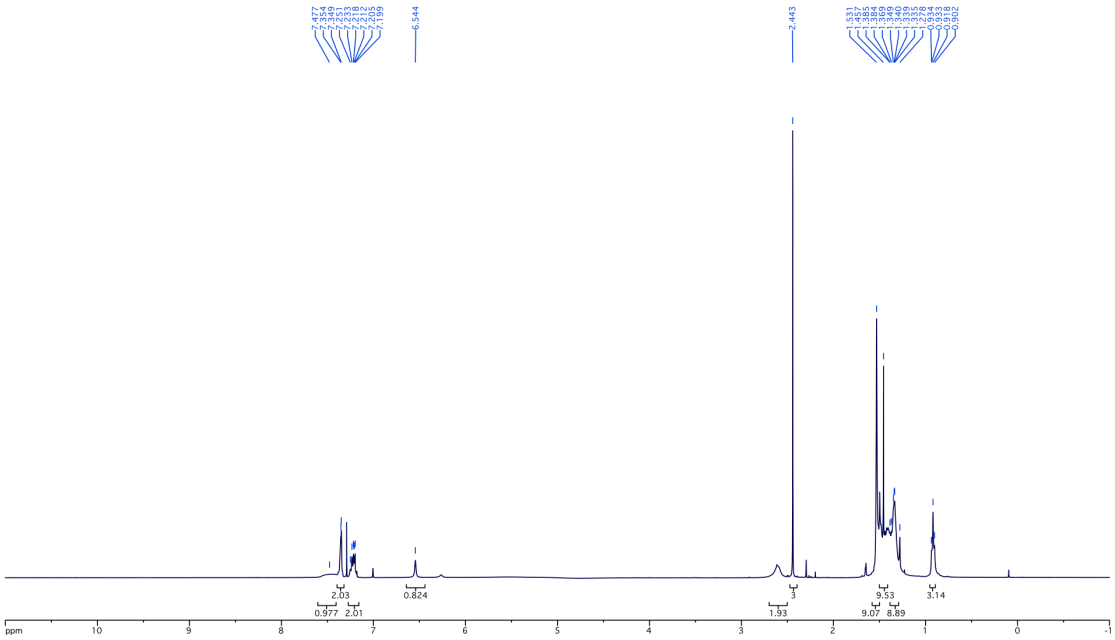


Pyrrolidine 240: ^{13}C NMR (101 MHz, $CDCl_3$)

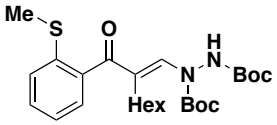


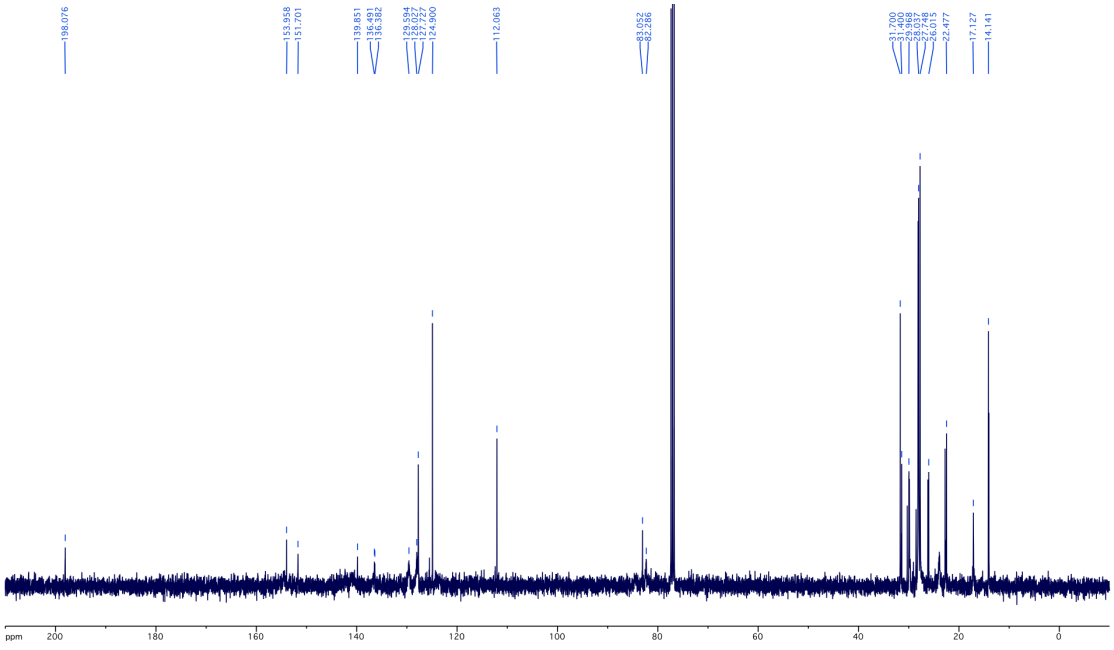
Amino enone 254a: ^{1}H NMR (400 MHz, $CDCl_3$)



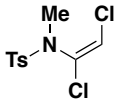


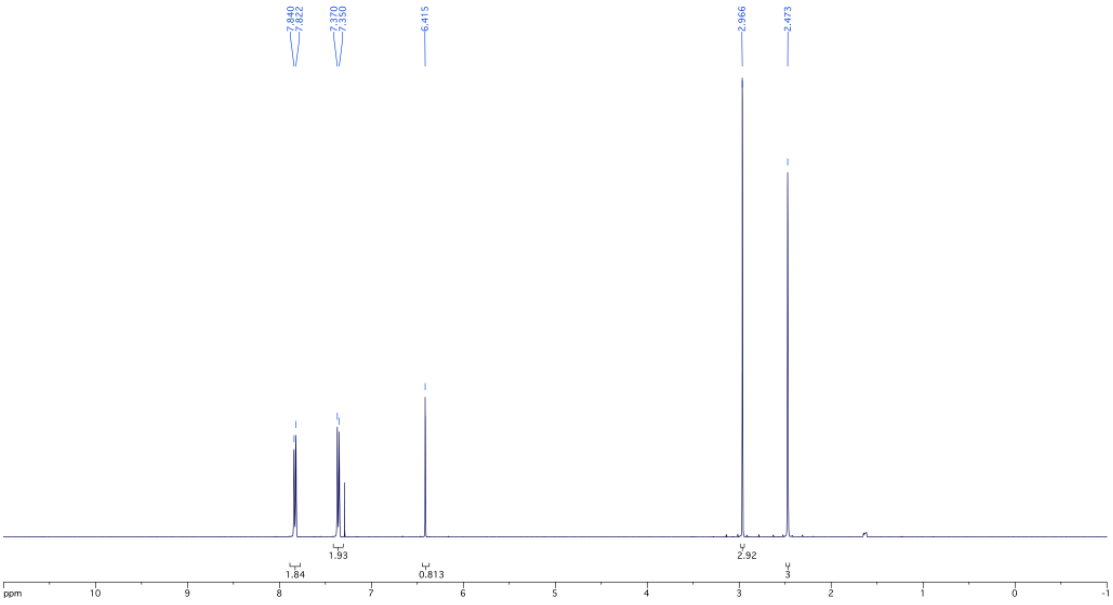
Amino enone 254a: ^{13}C NMR (101 MHz, $CDCl_3$)



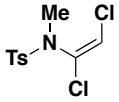


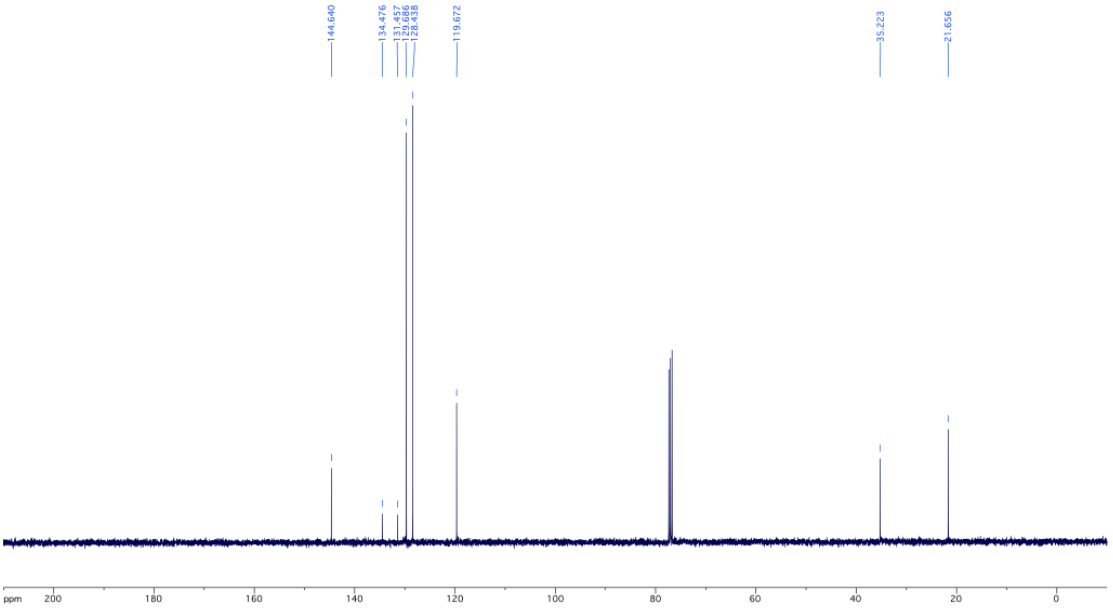
Dichloroenamide 257: ^{1}H NMR (400 MHz, $CDCl_3$)



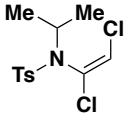


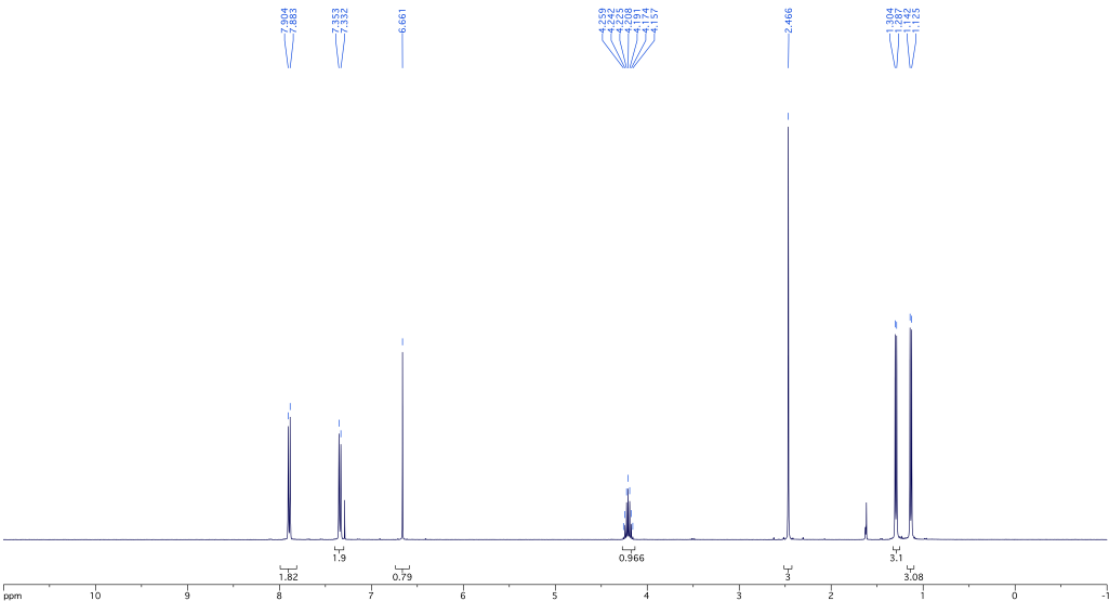
Dichloroenamide 257: ^{13}C NMR (101 MHz, $CDCl_3$)



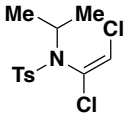


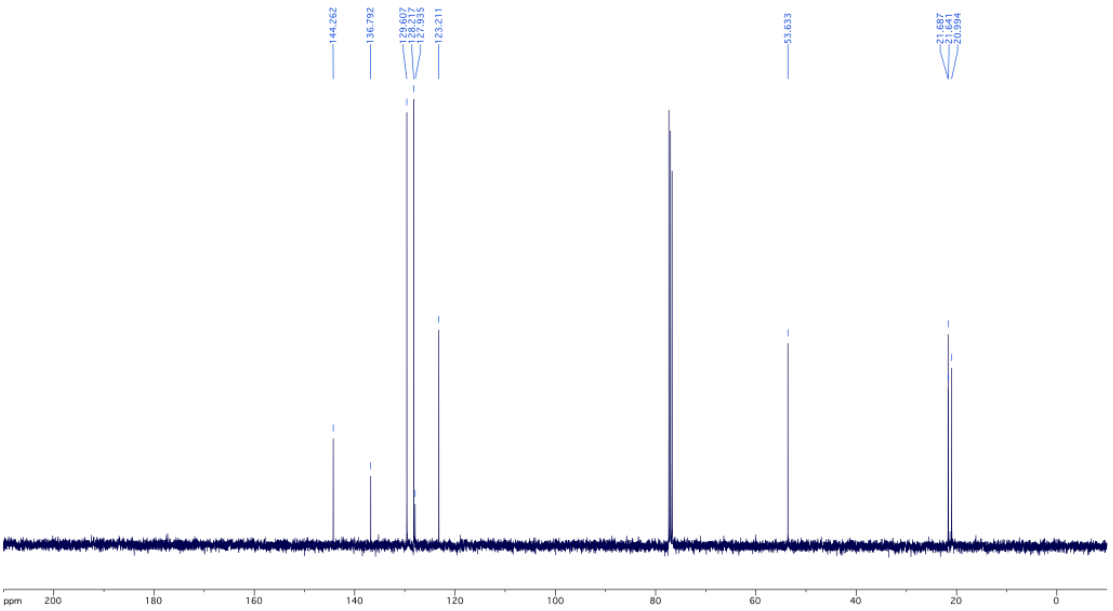
Dichloroenamide 258: ^{1}H NMR (400 MHz, $CDCl_3$)



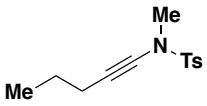


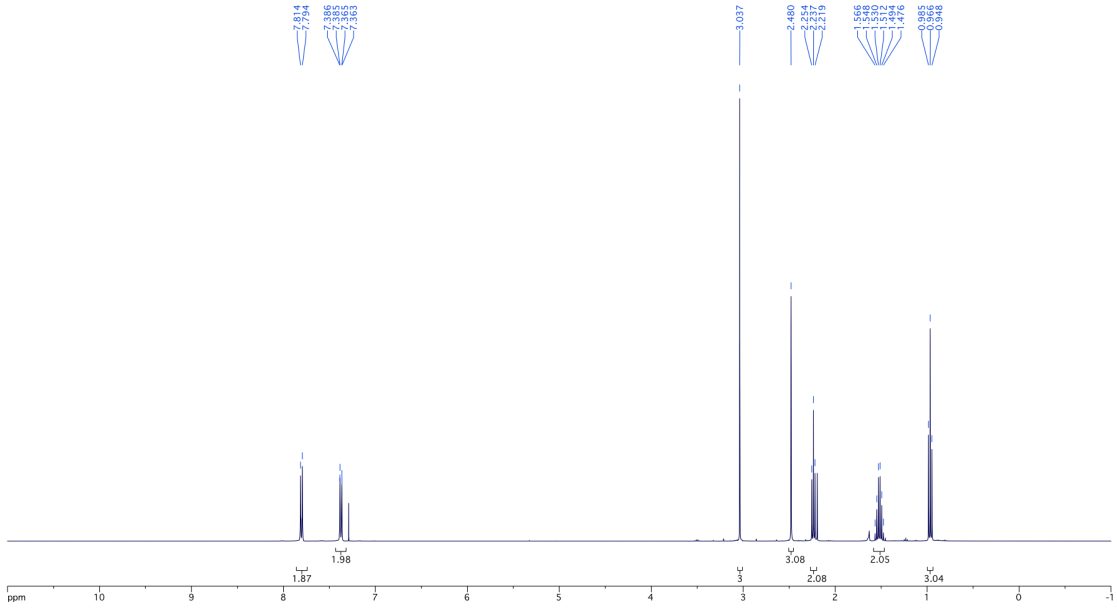
Dichloroenamide 258: ^{13}C NMR (101 MHz, $CDCl_3$)



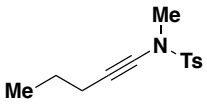


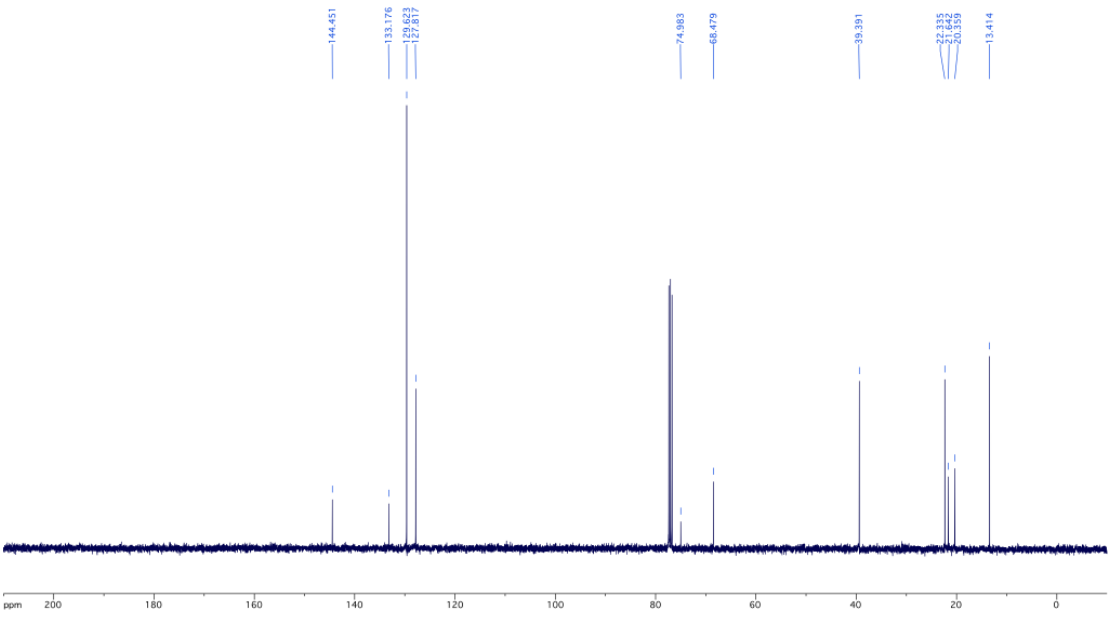
Ynamide 262: ^{1}H NMR (400 MHz, $CDCl_3$)



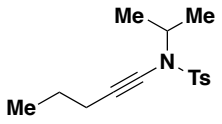


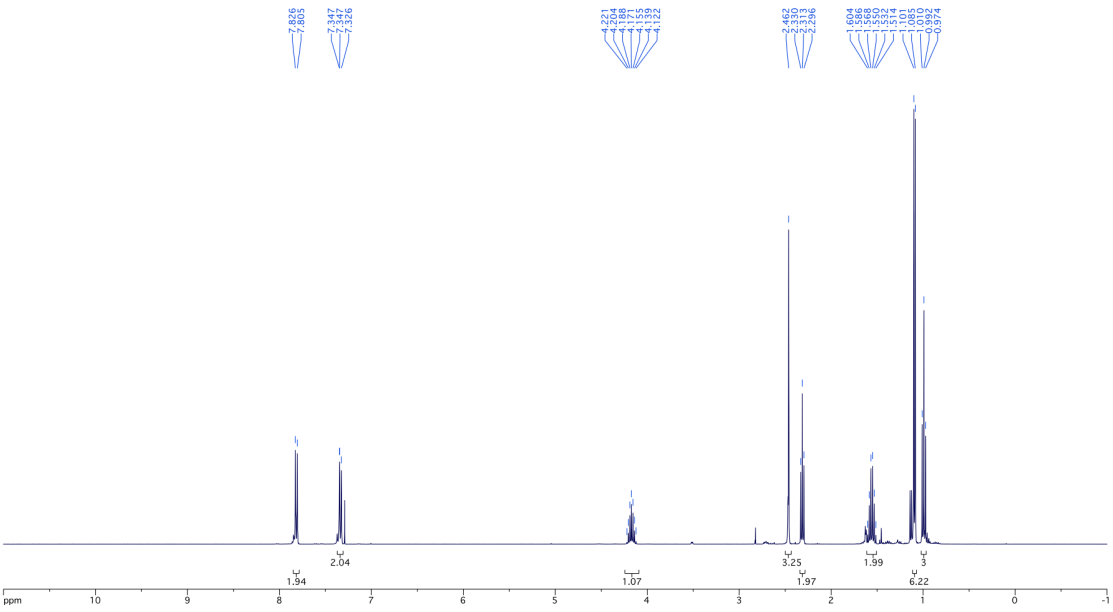
Ynamide 262: ^{13}C NMR (101 MHz, $CDCl_3$)



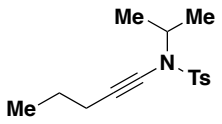


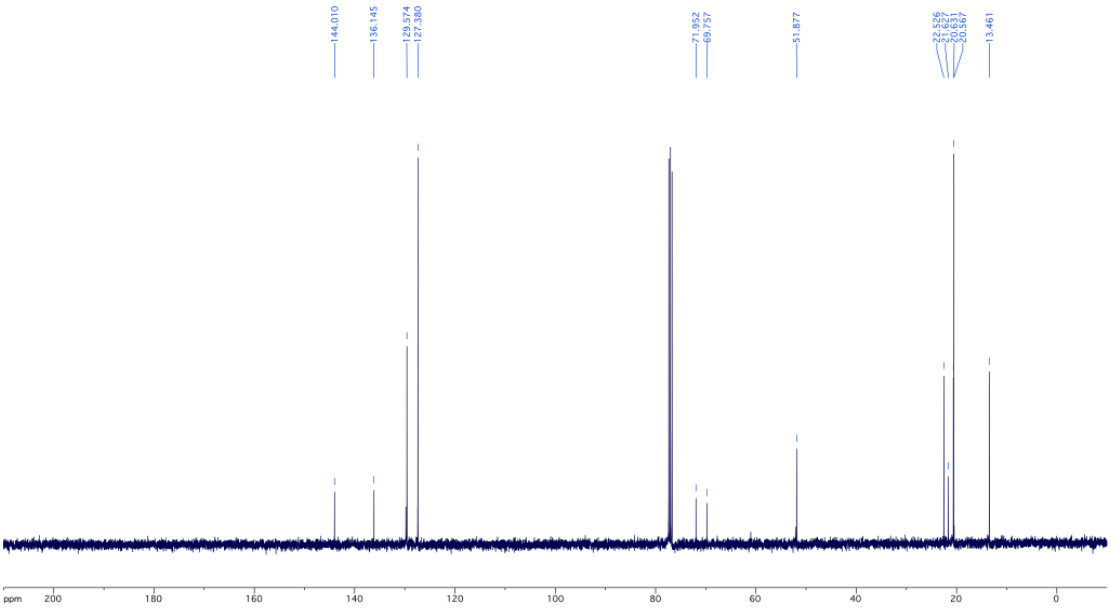
Ynamide 263: ^{1}H NMR (400 MHz, $CDCl_3$)



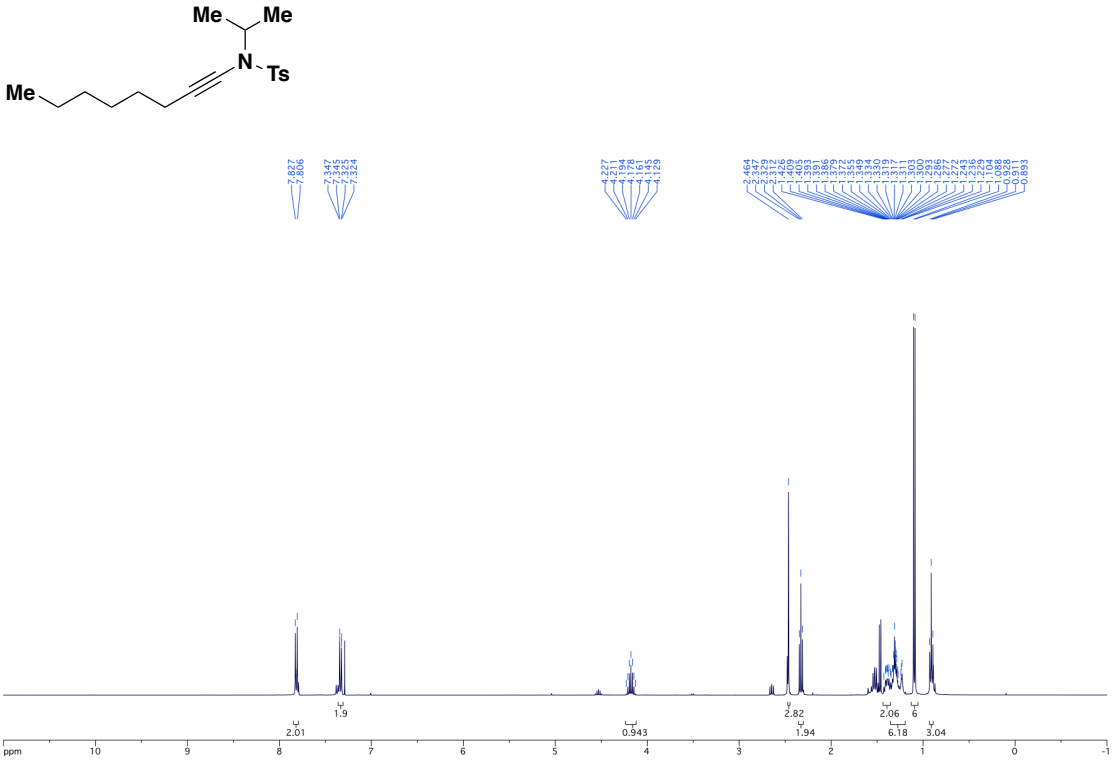


Ynamide 263: ^{13}C NMR (101 MHz, $CDCl_3$)

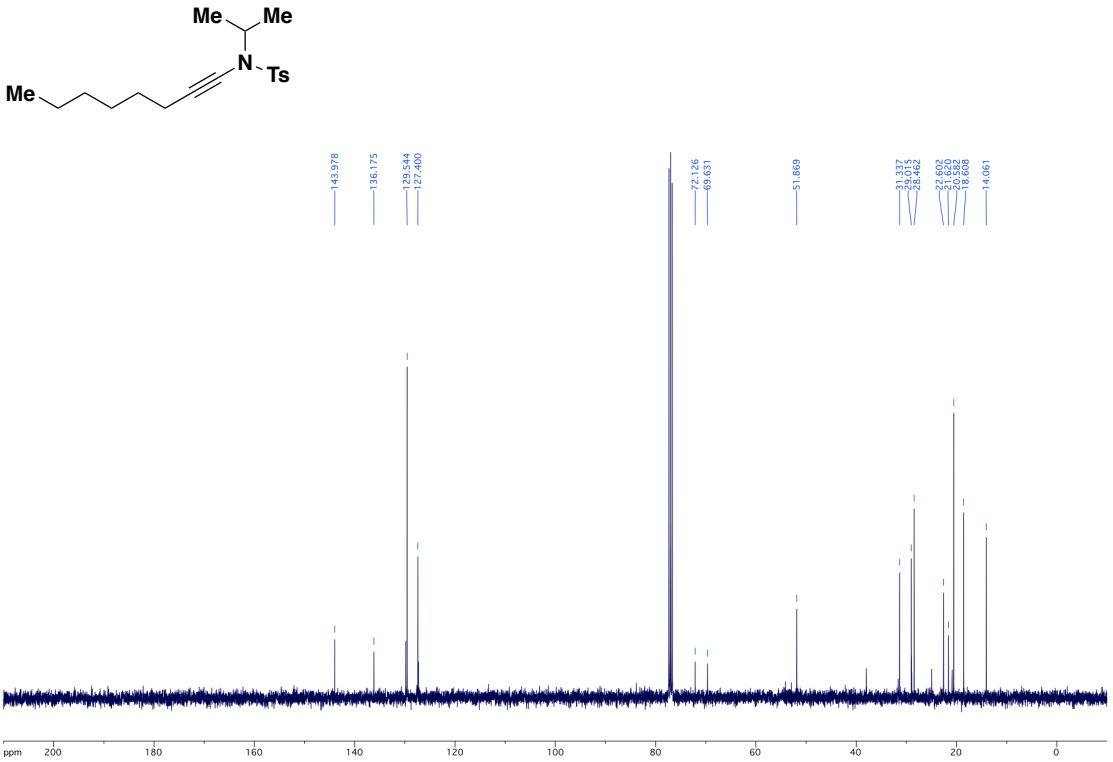




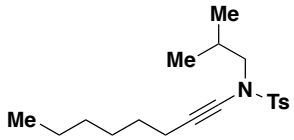
Ynamide 274: ^{1}H NMR (400 MHz, $CDCl_3$)

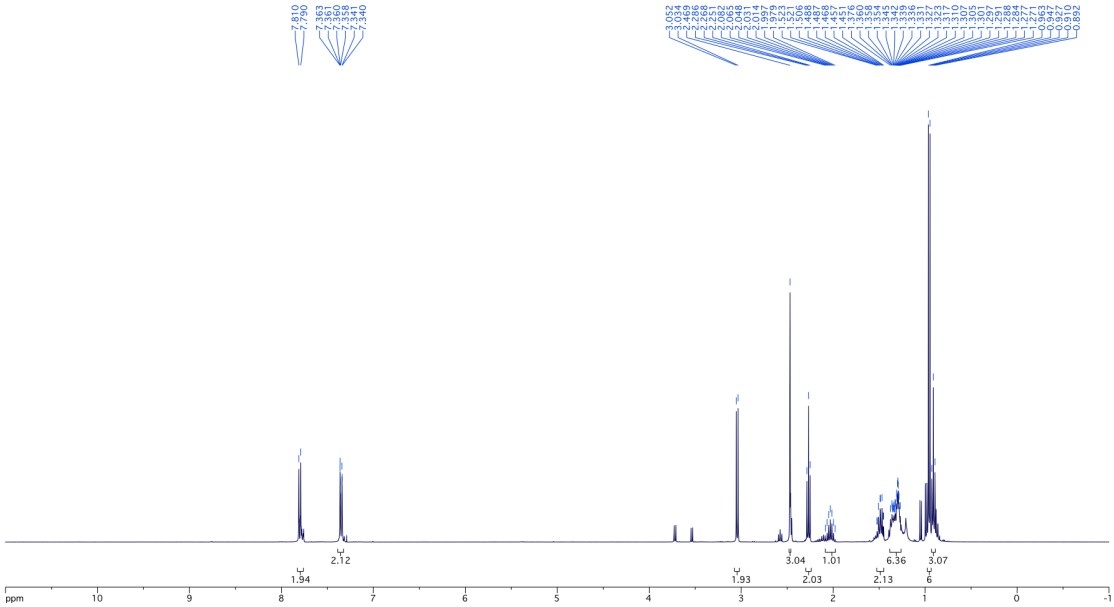


Ynamide 274: ^{13}C NMR (101 MHz, $CDCl_3$)

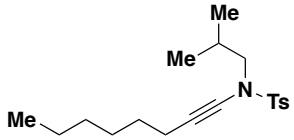


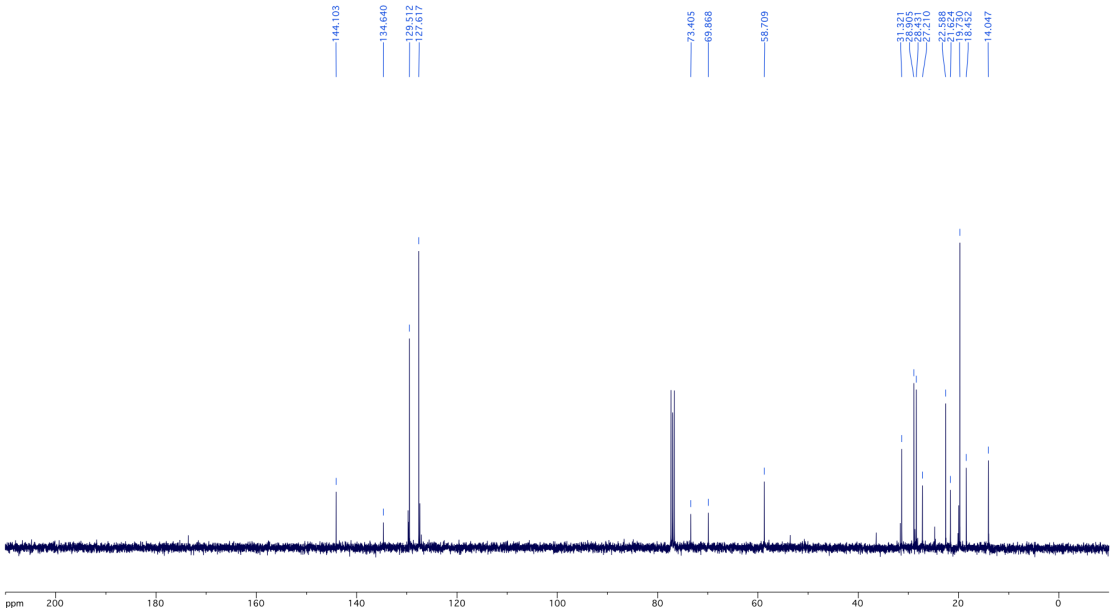
Ynamide 275: ^{1}H NMR (400 MHz, $CDCl_3$)



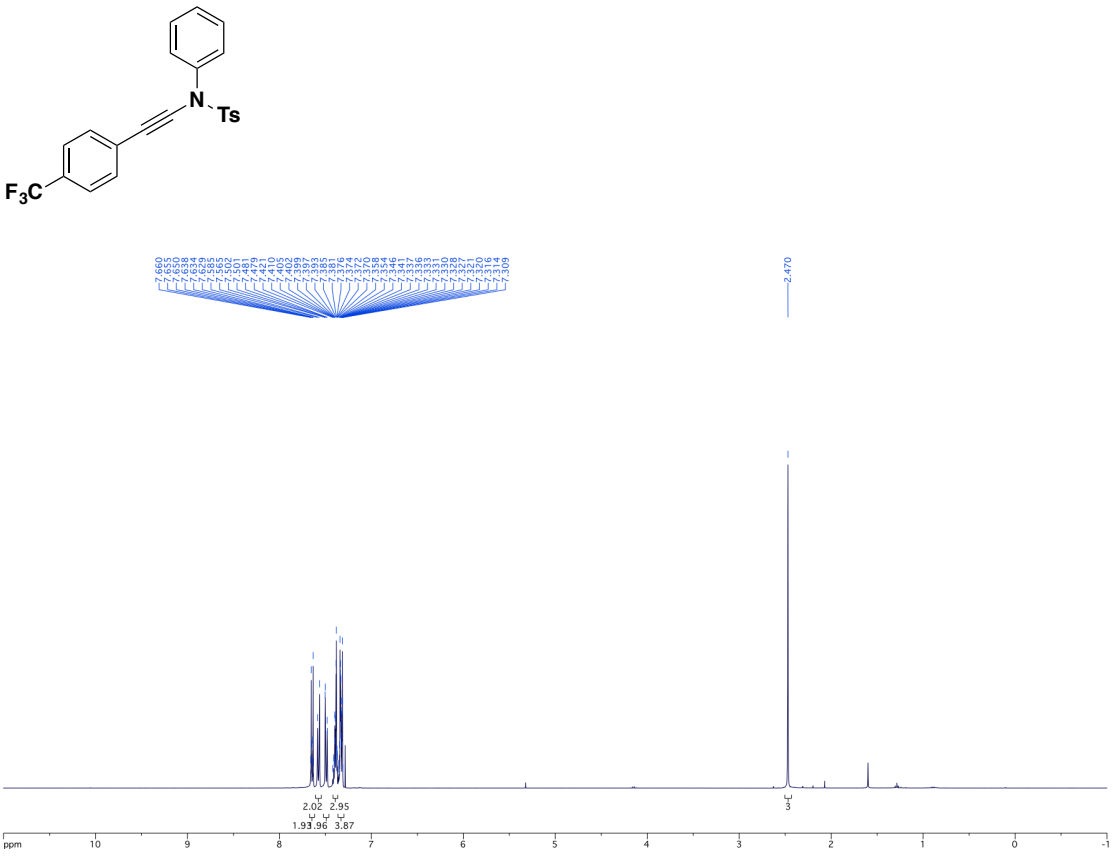


Ynamide 275: ^{13}C NMR (101 MHz, $CDCl_3$)

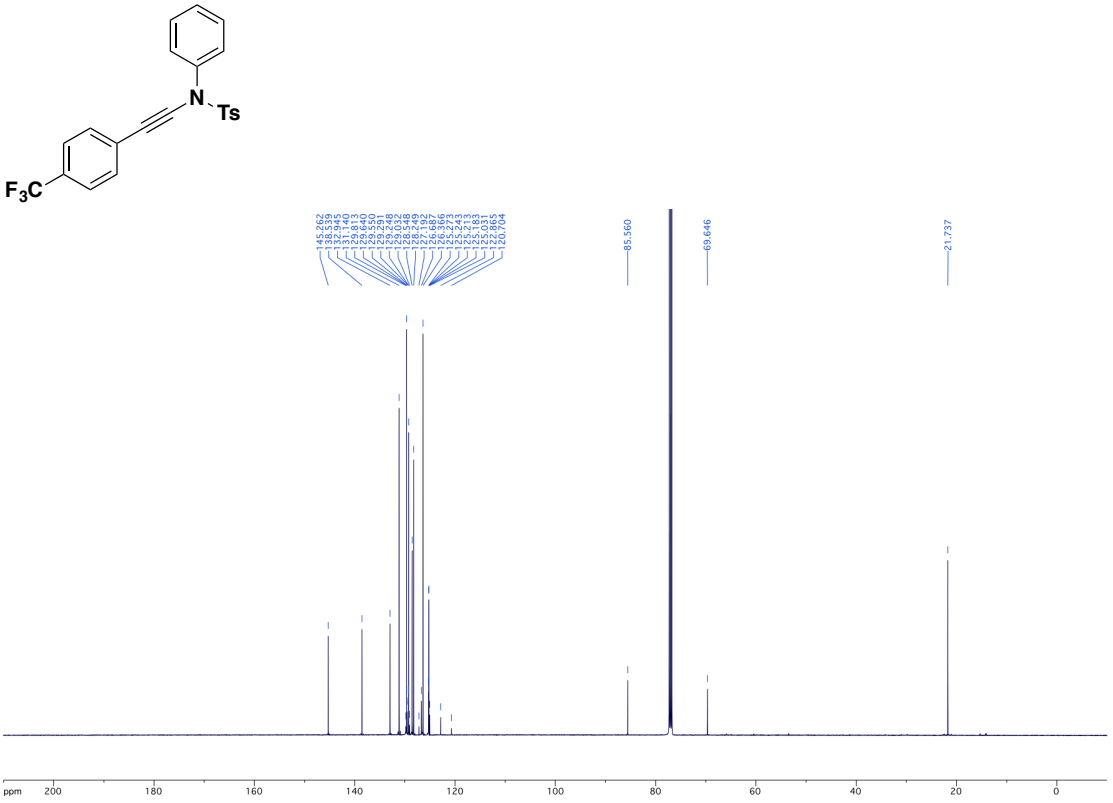




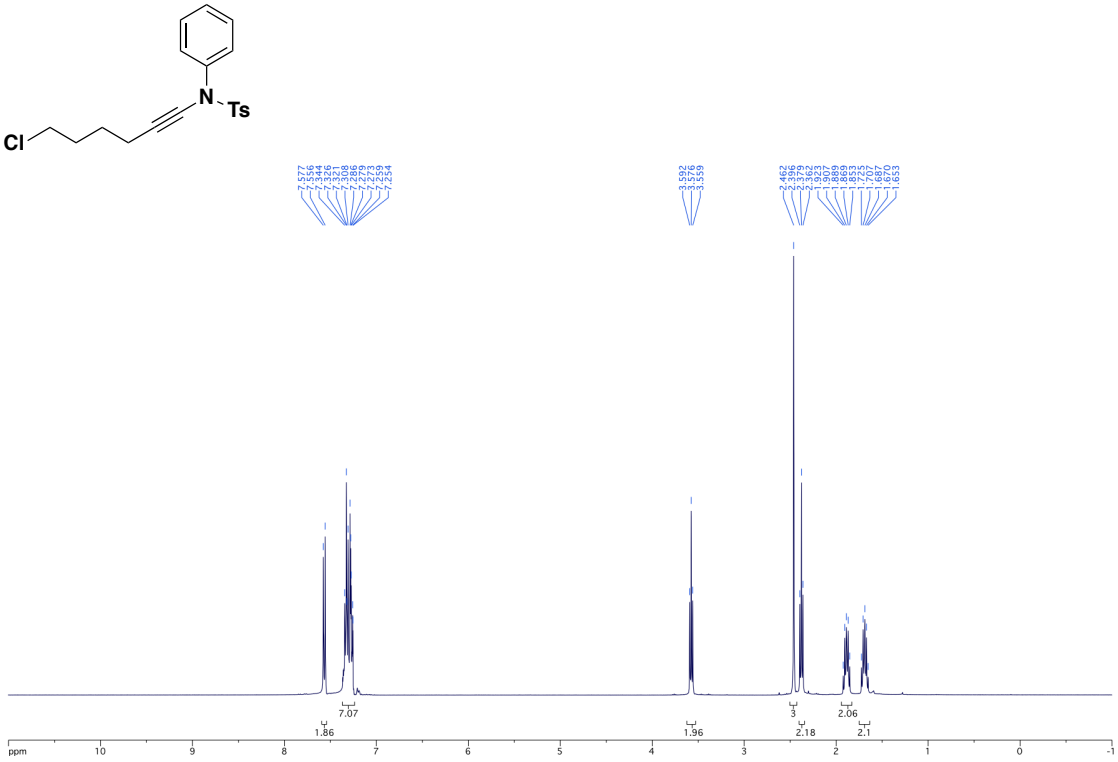
Ynamide 280: ^{1}H NMR (400 MHz, $CDCl_3$)



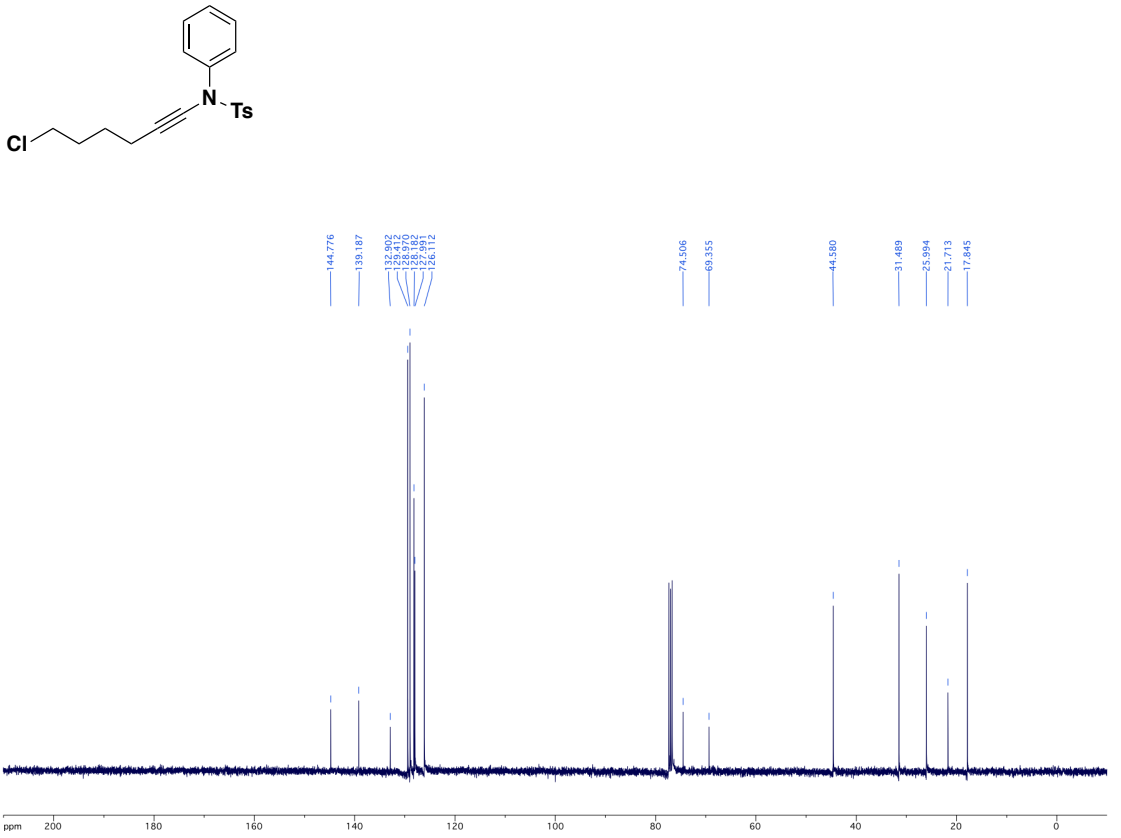
Ynamide 280: ^{13}C NMR (101 MHz, $CDCl_3$)



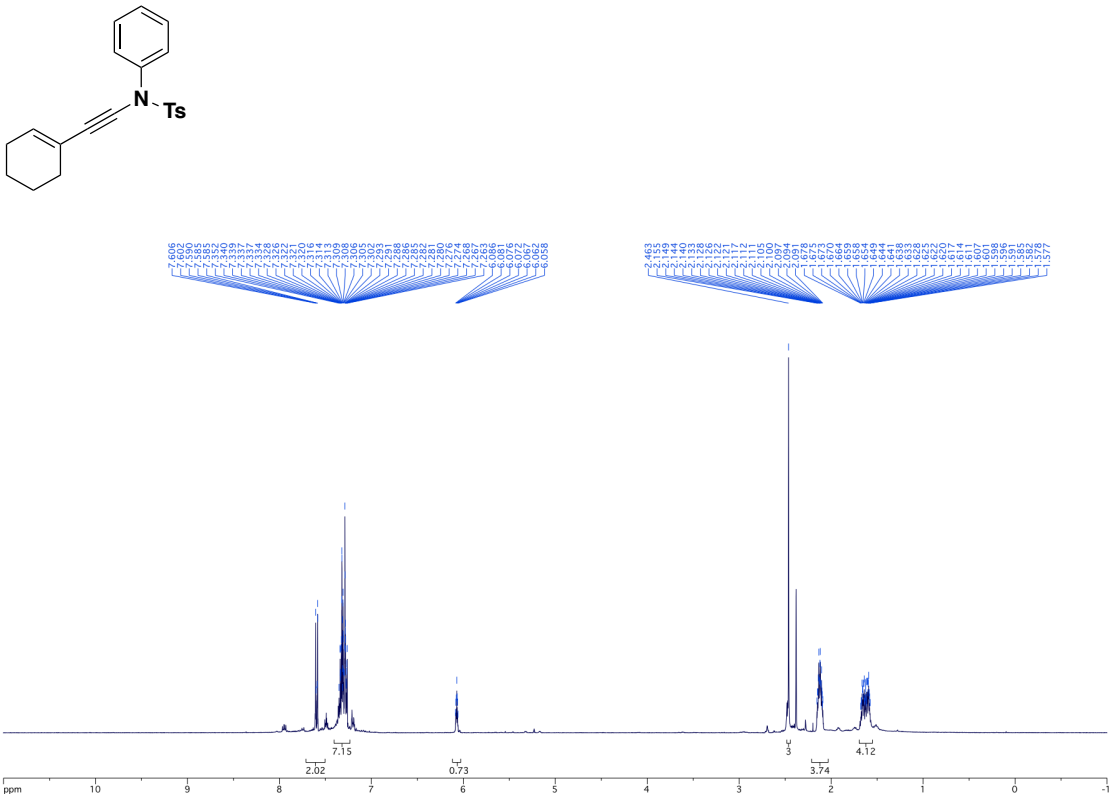
Ynamide 282: ^{1}H NMR (400 MHz, $CDCl_3$)



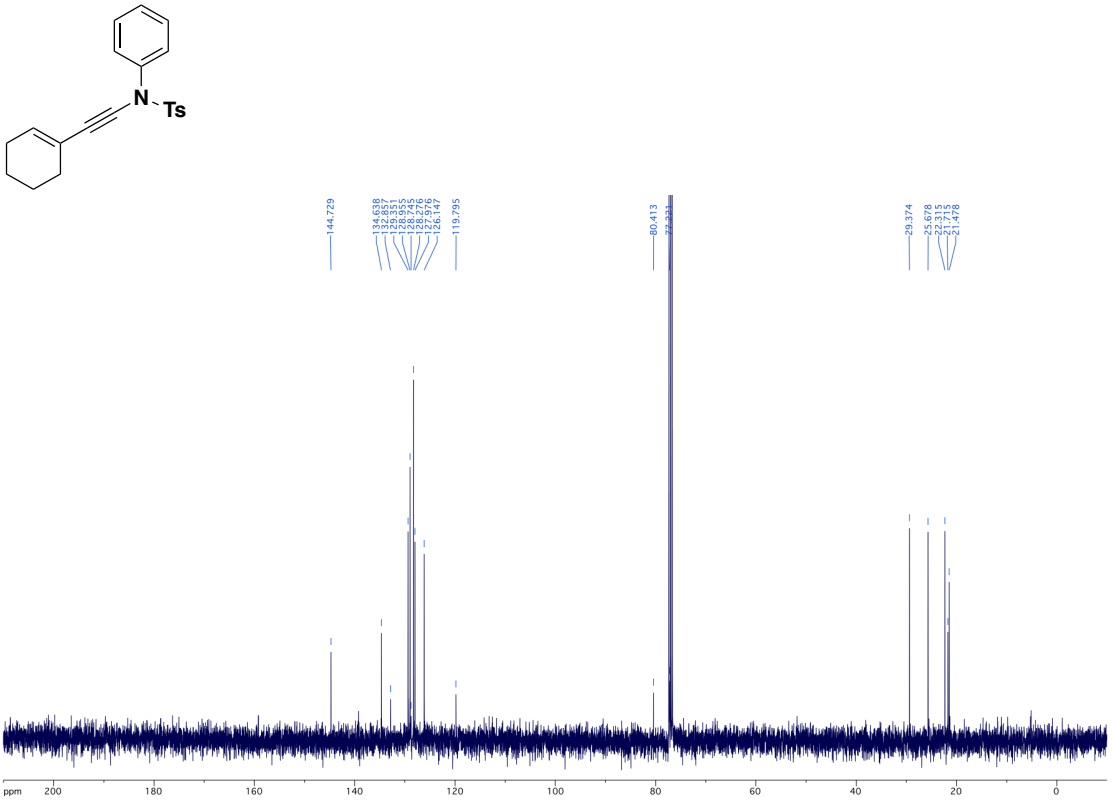
Ynamide 282: ^{13}C NMR (101 MHz, $CDCl_3$)



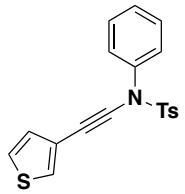
Ynamide 283: ^{1}H NMR (400 MHz, $CDCl_3$)

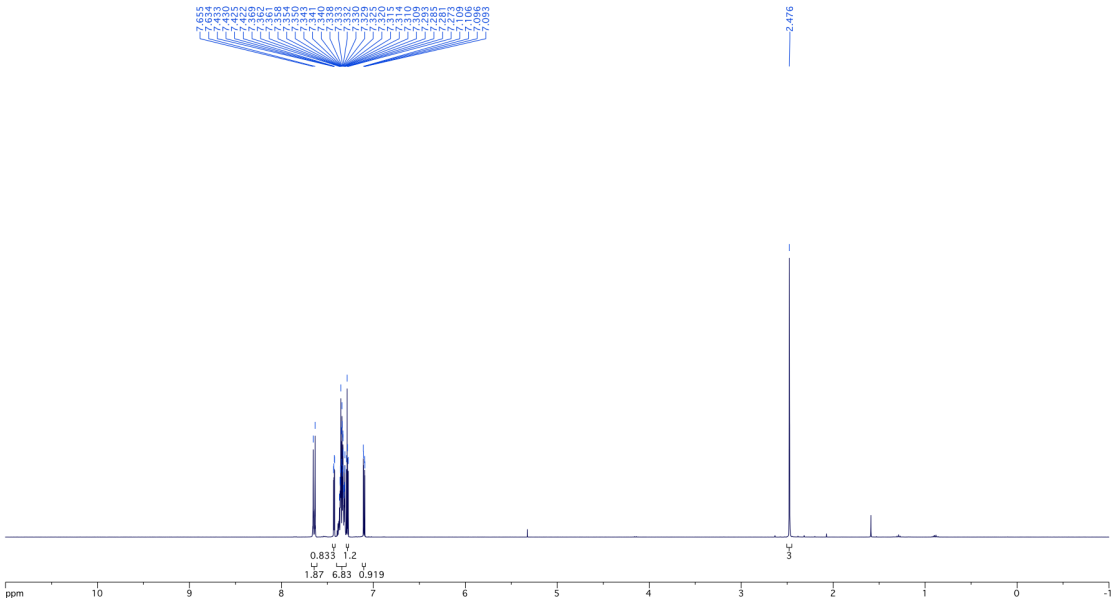


Ynamide 283: ^{13}C NMR (101 MHz, $CDCl_3$)

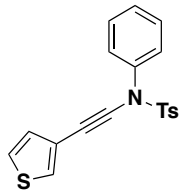


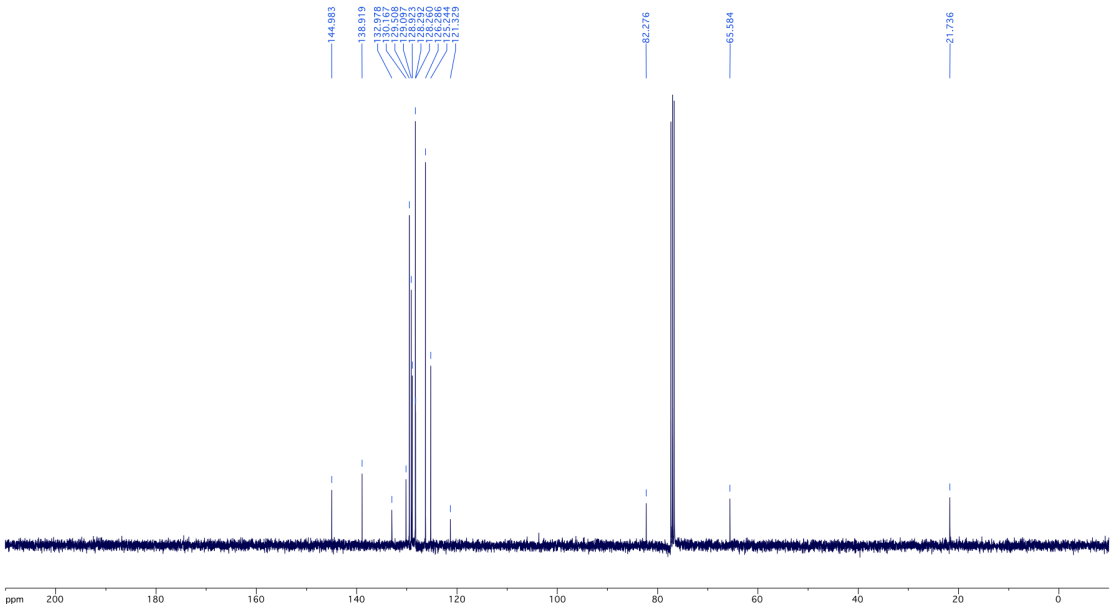
Ynamide 284: ^{1}H NMR (400 MHz, $CDCl_3$)



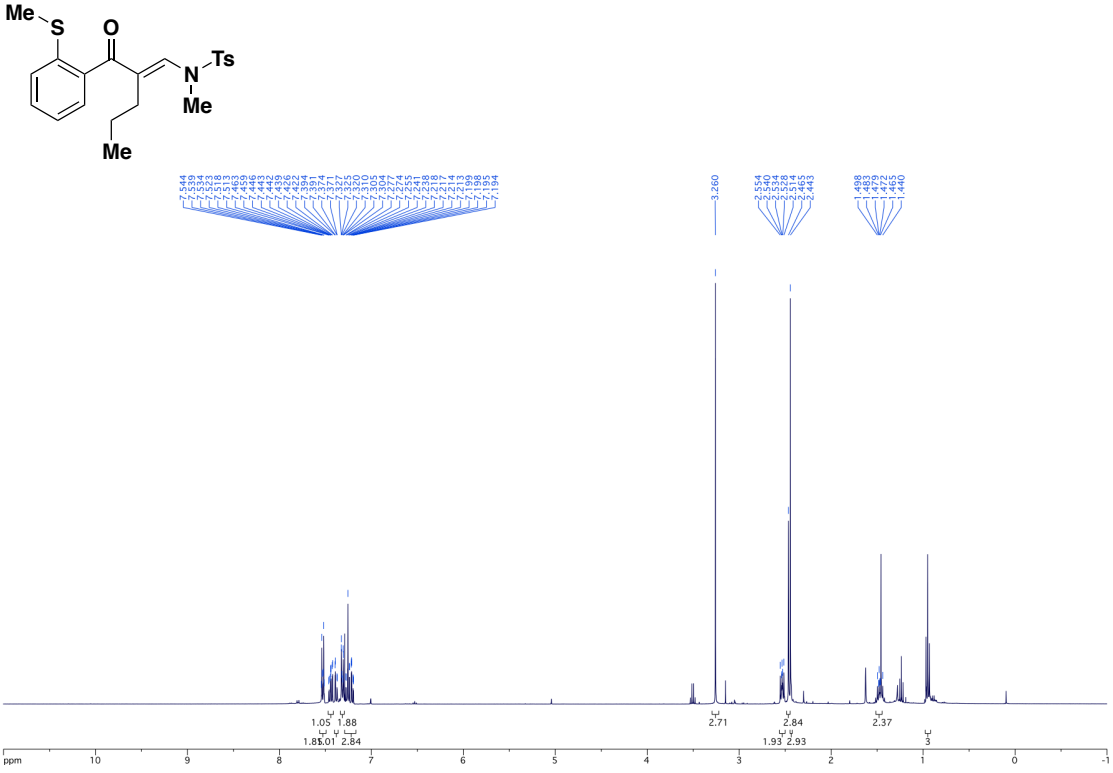


Ynamide 284: ^{13}C NMR (101 MHz, $CDCl_3$)

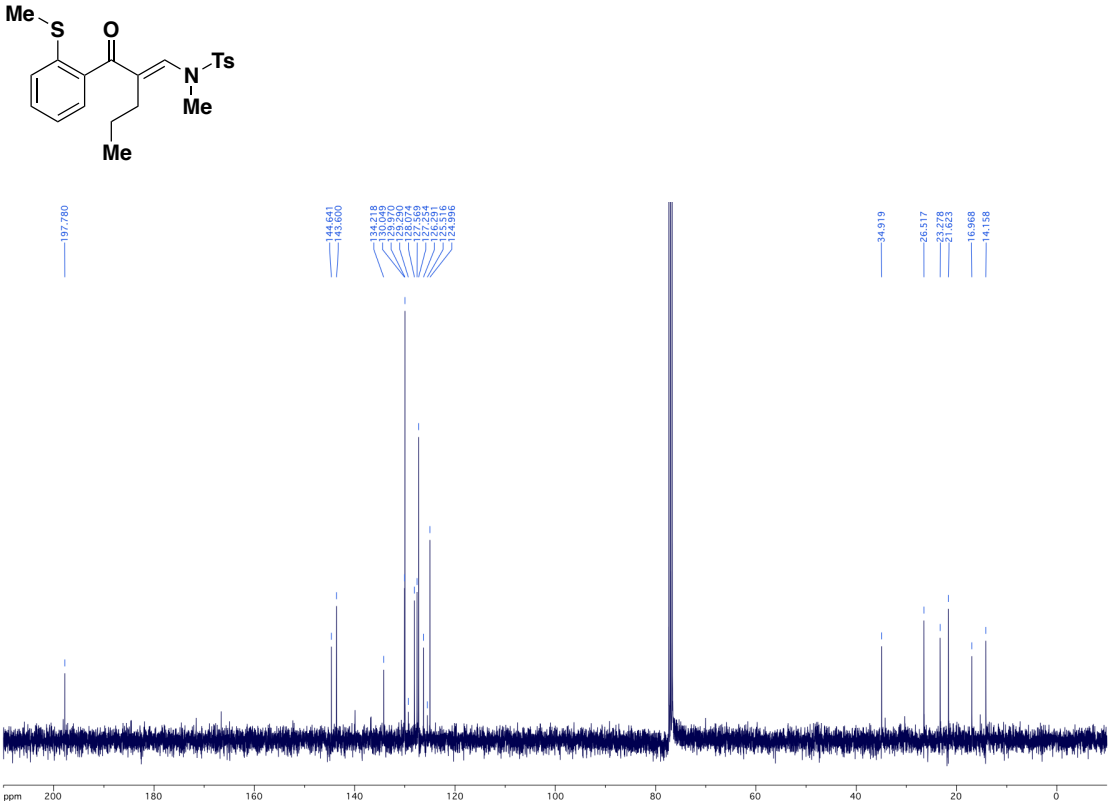




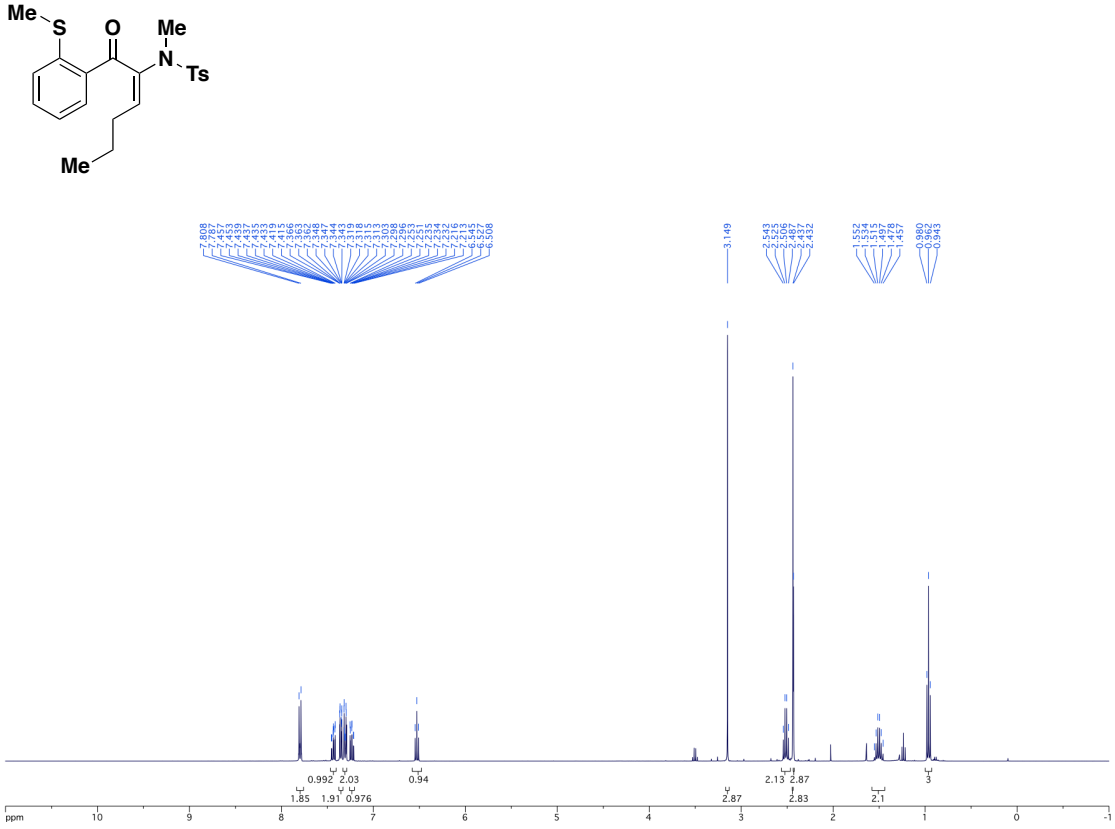
β-Amino enone 285a: ^{1}H NMR (400 MHz, $CDCl_3$)



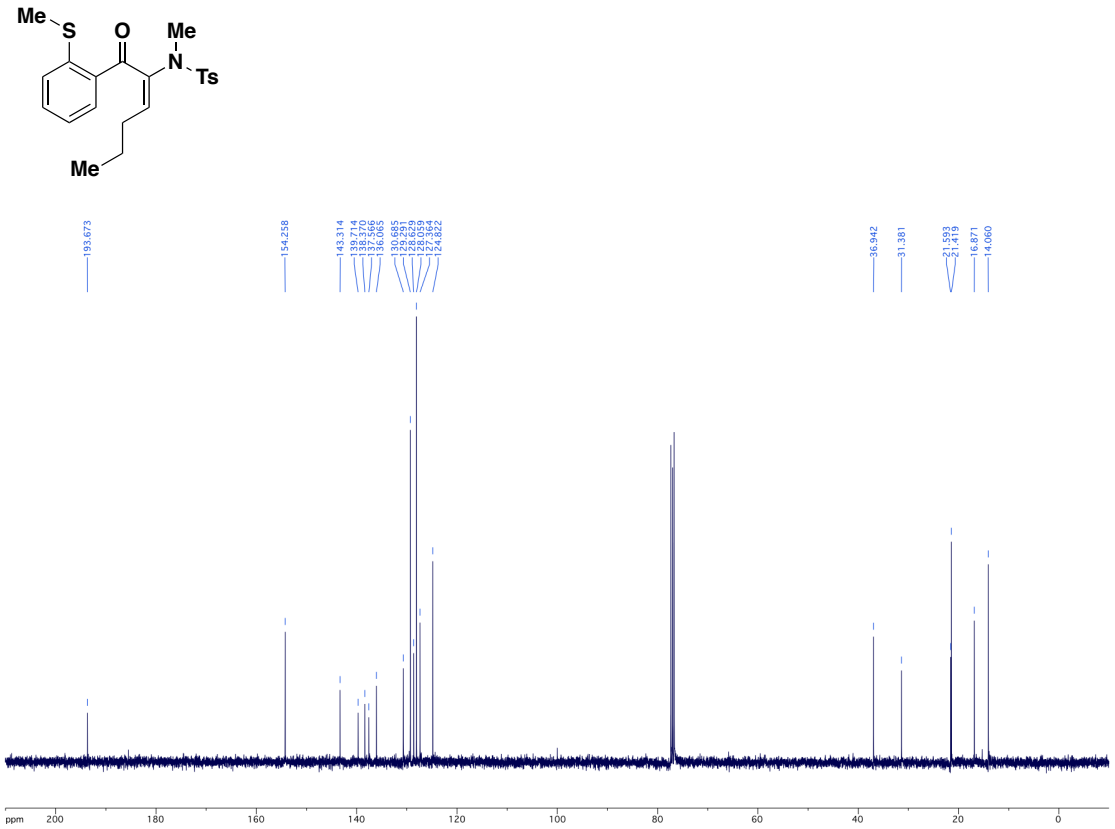
β-Amino Enone 285a: ^{13}C NMR (101 MHz, $CDCl_3$)



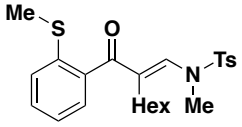
α-Amino enone 285b: ^{1}H NMR (400 MHz, $CDCl_3$)

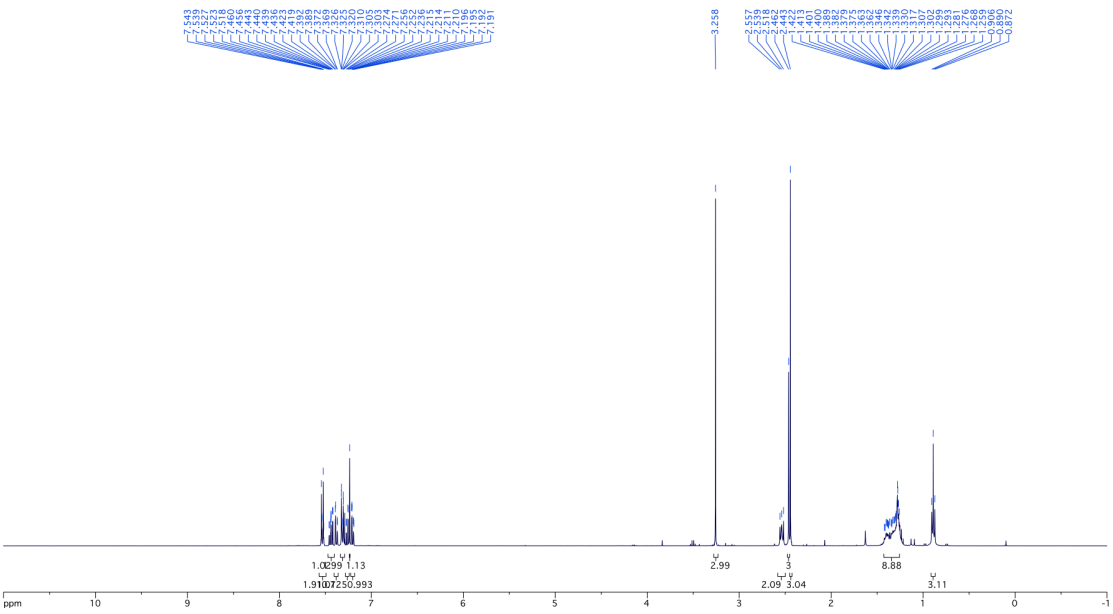


α-Amino enone 285b: ^{13}C NMR (101 MHz, $CDCl_3$)

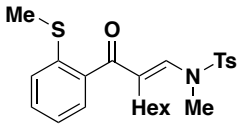


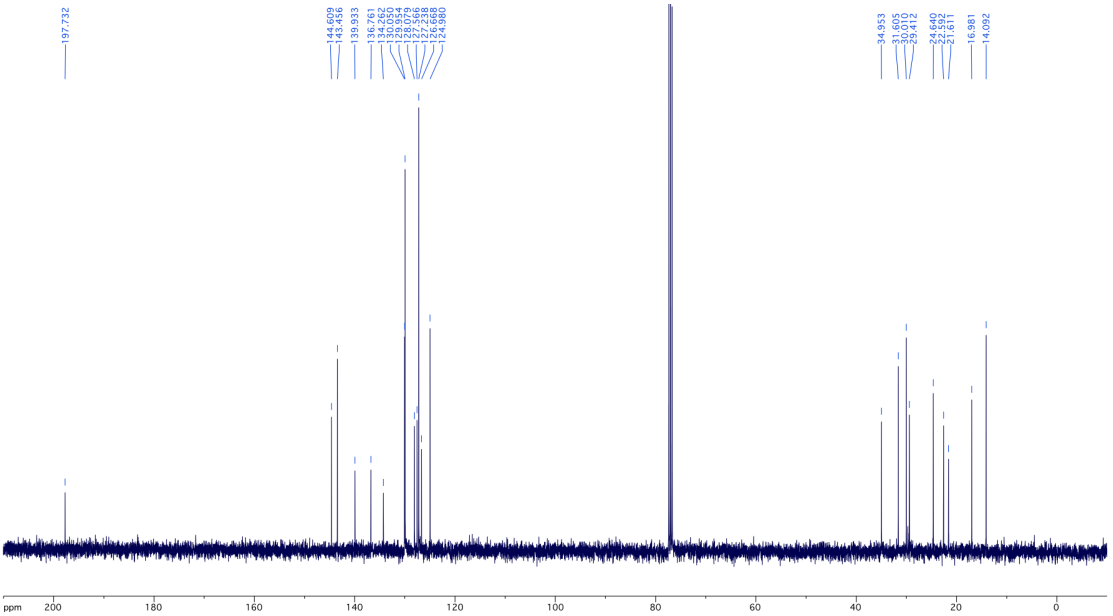
β-Amino enone 286a: ^{1}H NMR (400 MHz, $CDCl_3$)



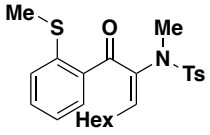


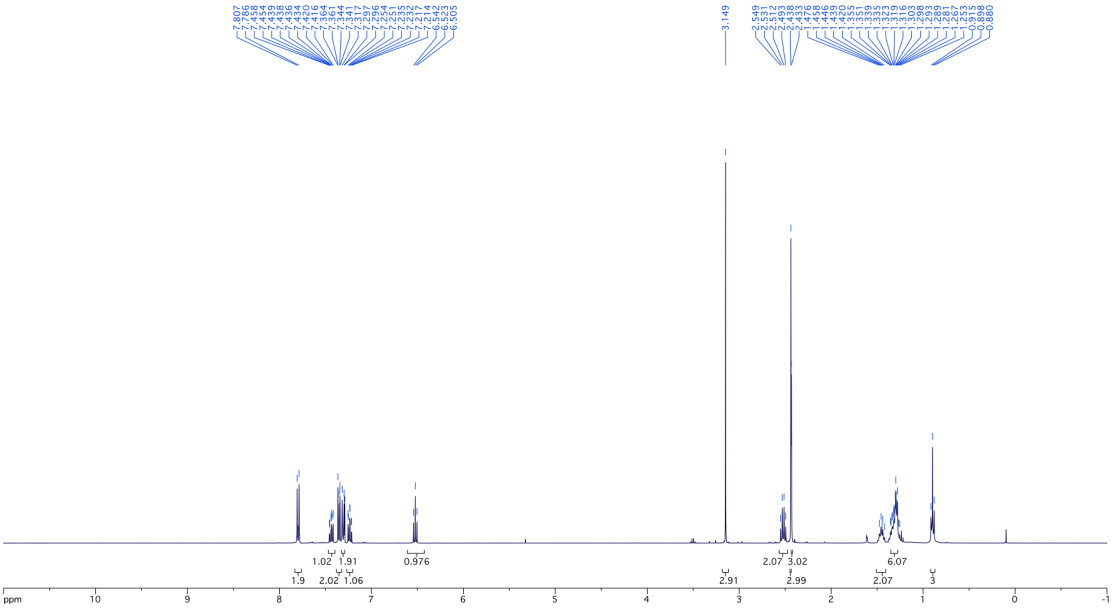
β-Amino enone 286a: ^{13}C NMR (101 MHz, $CDCl_3$)



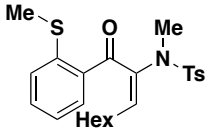


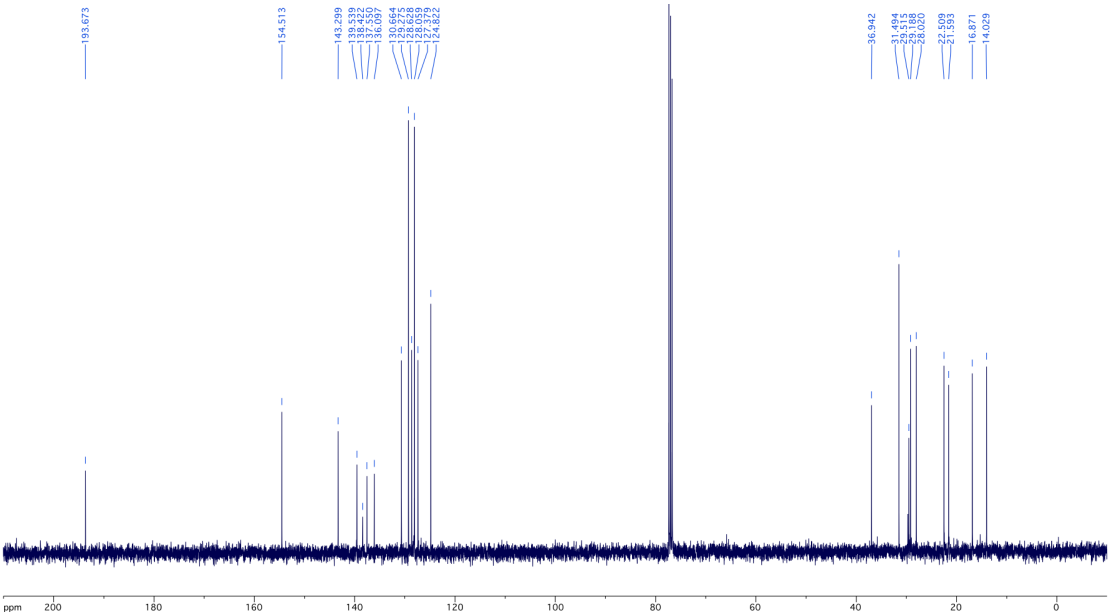
α-Amino enone 286b: ^{1}H NMR (400 MHz, $CDCl_3$)



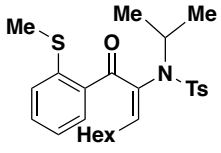


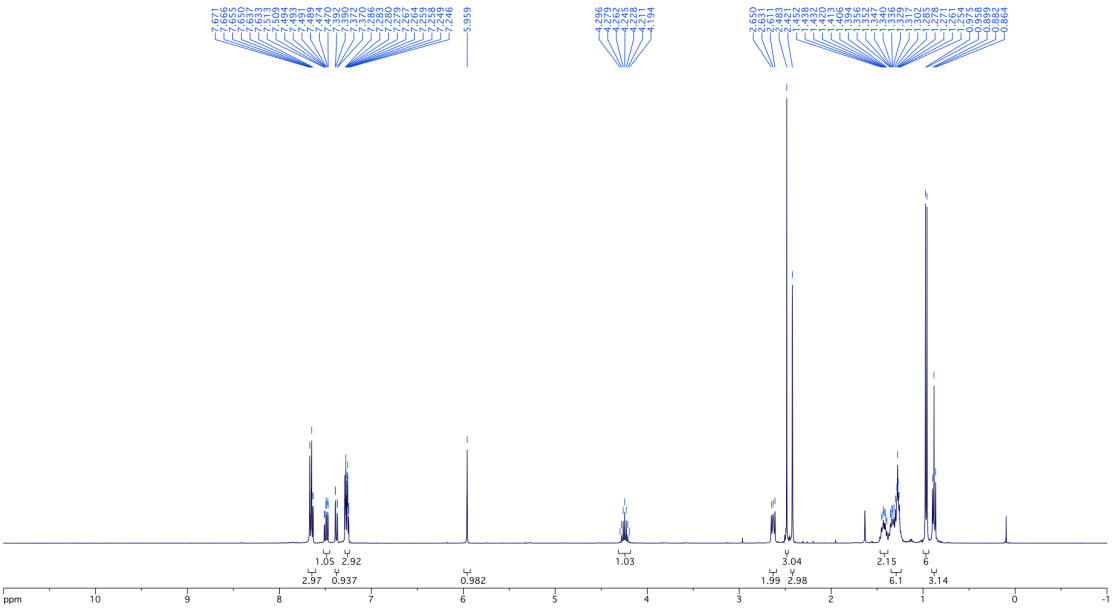
α-Amino enone 286b: ^{13}C NMR (101 MHz, $CDCl_3$)



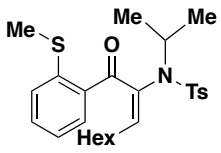


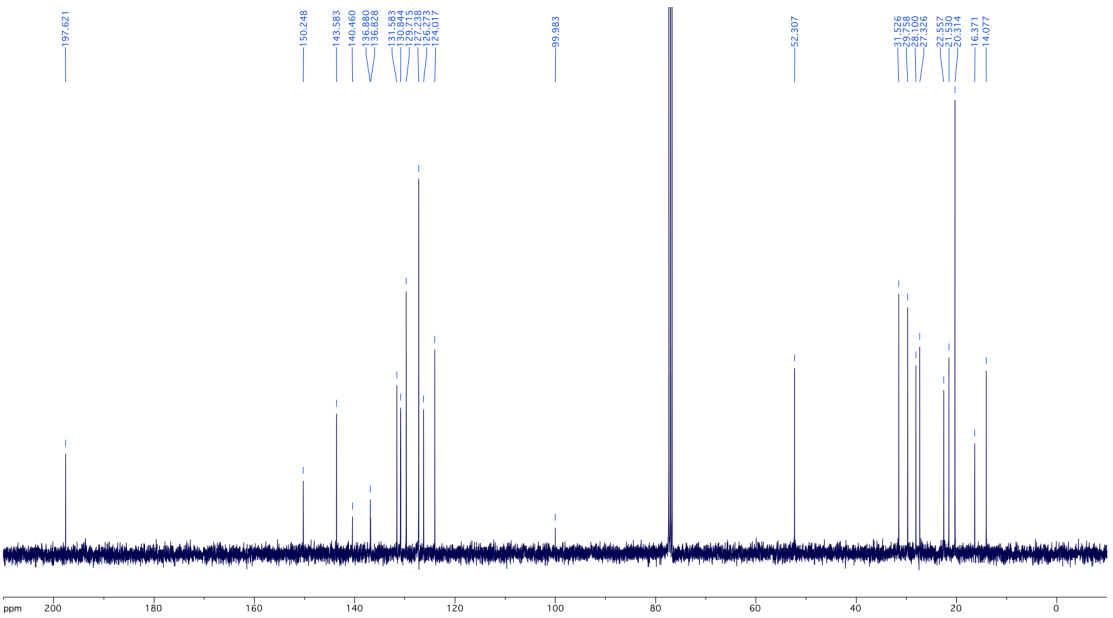
α-Amino enone 287b: ^{1}H NMR (400 MHz, $CDCl_3$)



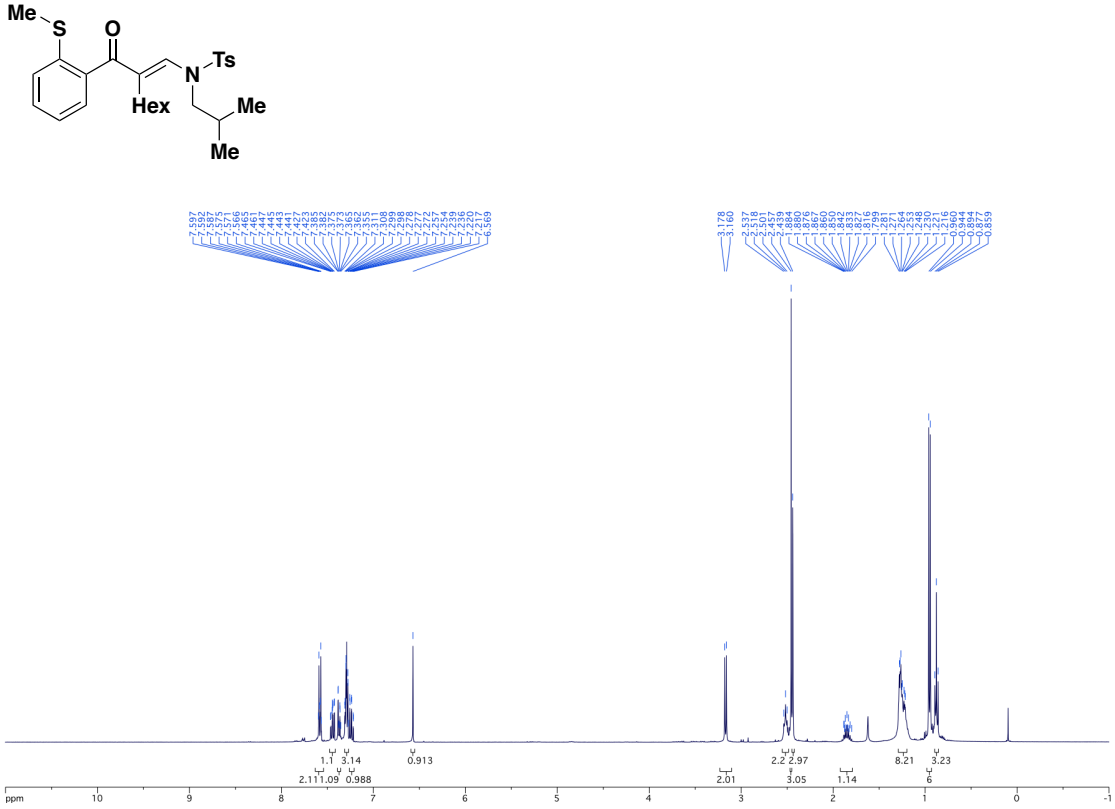


α-Amino enone 287b: ^{13}C NMR (101 MHz, $CDCl_3$)

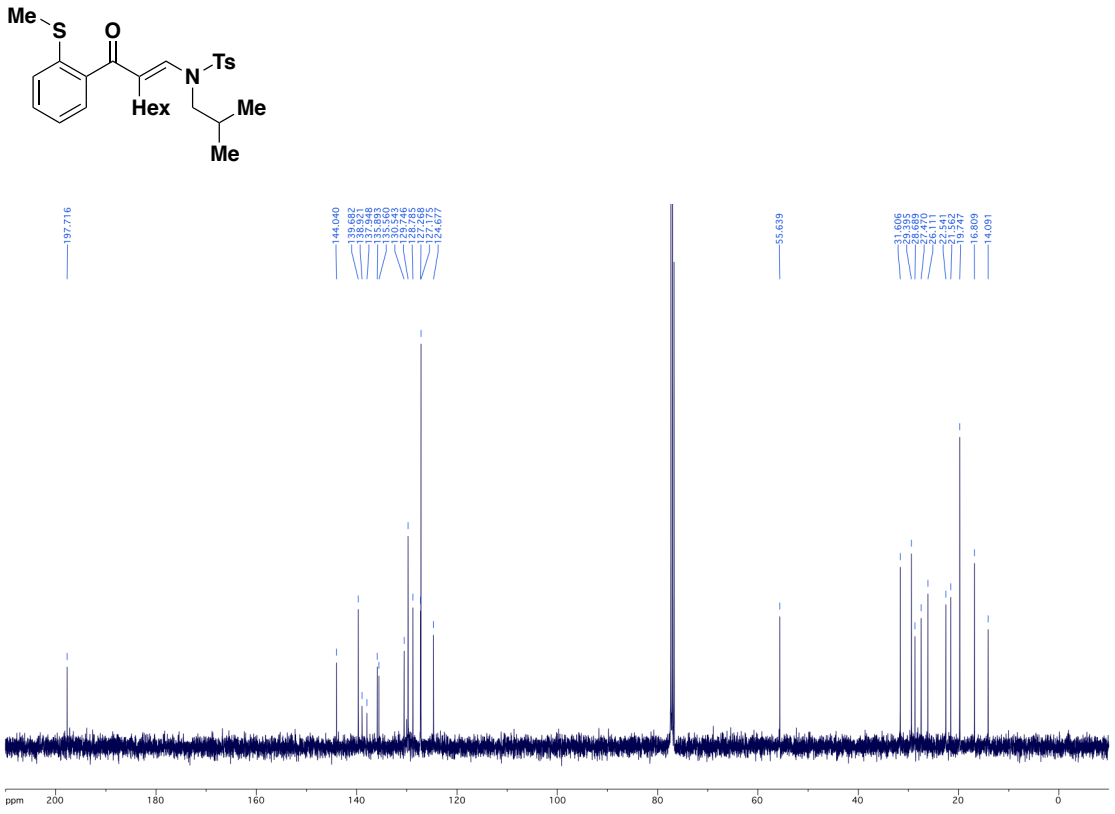



197.621
150.248
143.583
140.460
135.880
131.583
130.844
129.215
127.230
126.273
124.017
99.983
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27.158
27.158
27.158

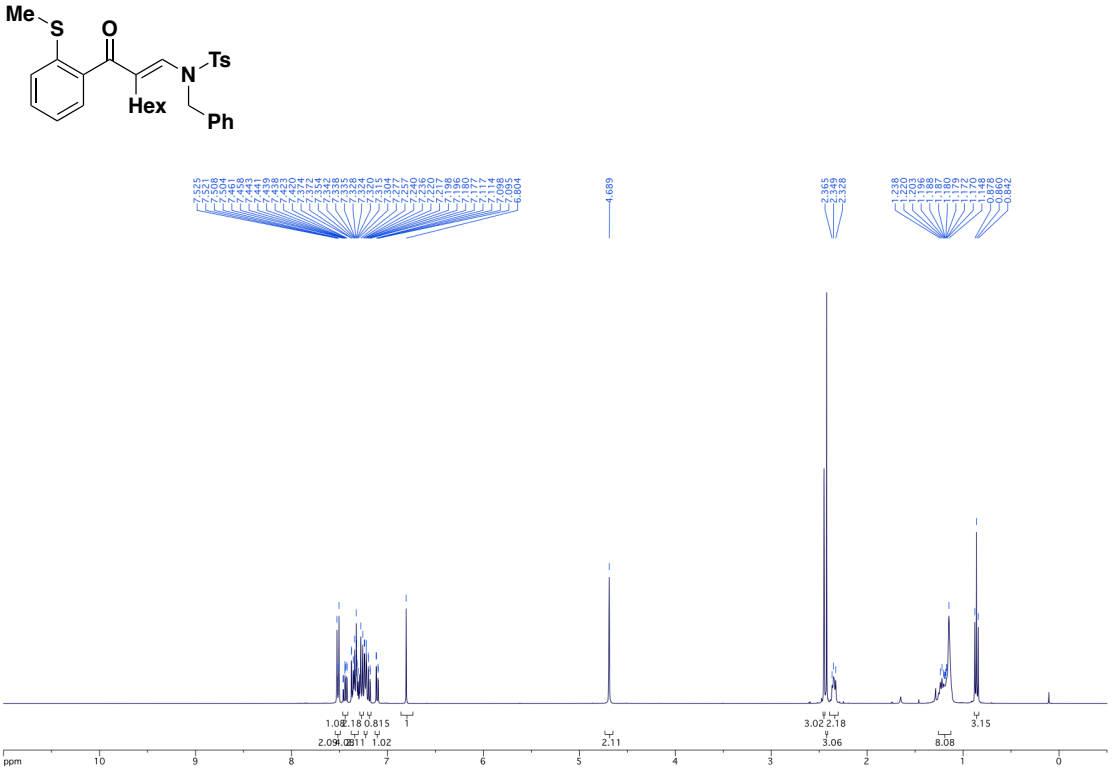
β-Amino enone 288a: ^{1}H NMR (400 MHz, $CDCl_3$)



β-Amino enone 288a: ^{13}C NMR (101 MHz, $CDCl_3$)

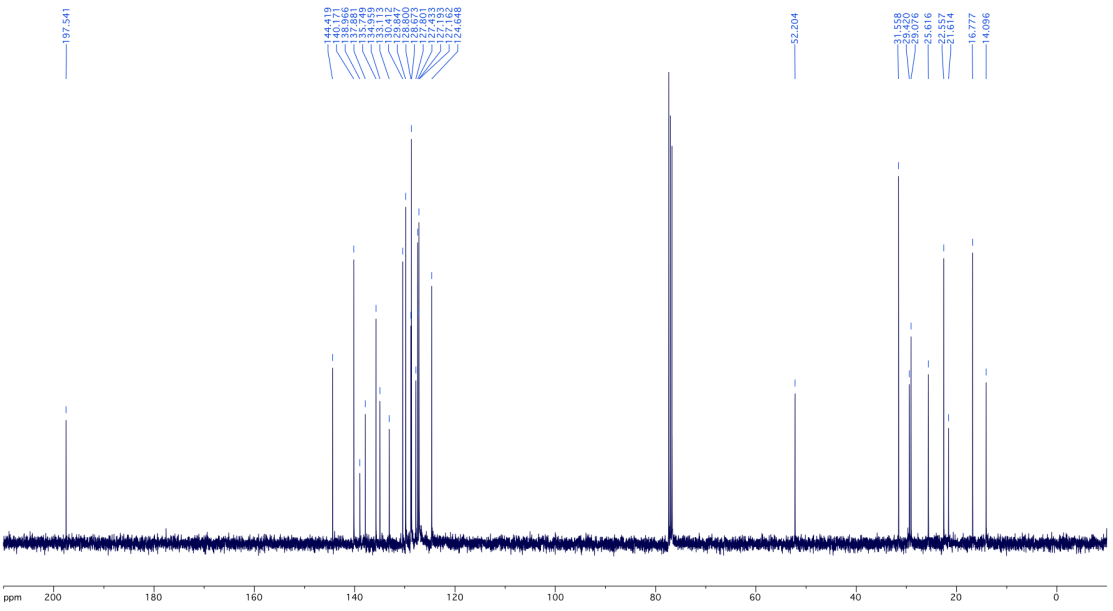


β-Amino enone 289a: ^{1}H NMR (400 MHz, $CDCl_3$)

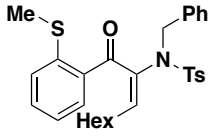


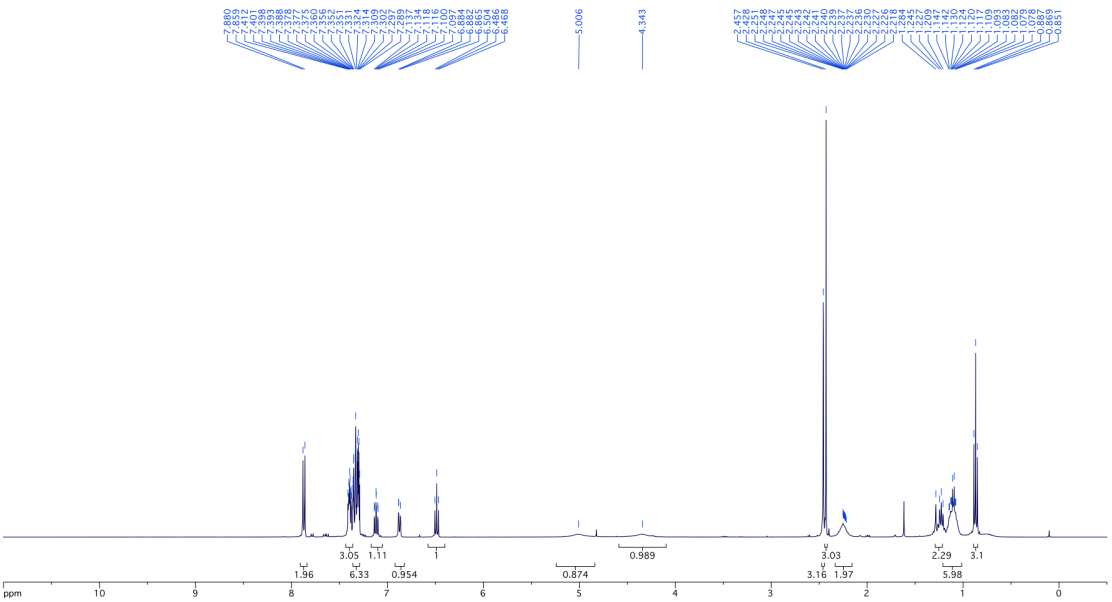
β-Amino enone 289a: ^{13}C NMR (101 MHz, $CDCl_3$)



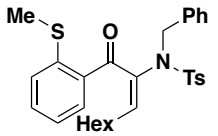


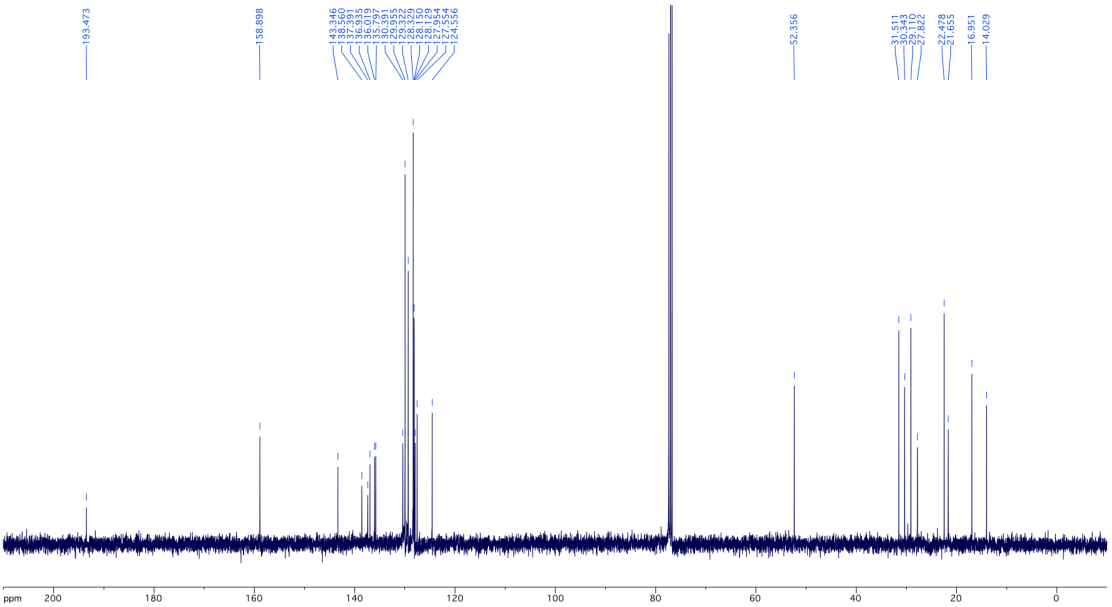
α-Amino enone 289b: ^{1}H NMR (400 MHz, $CDCl_3$)



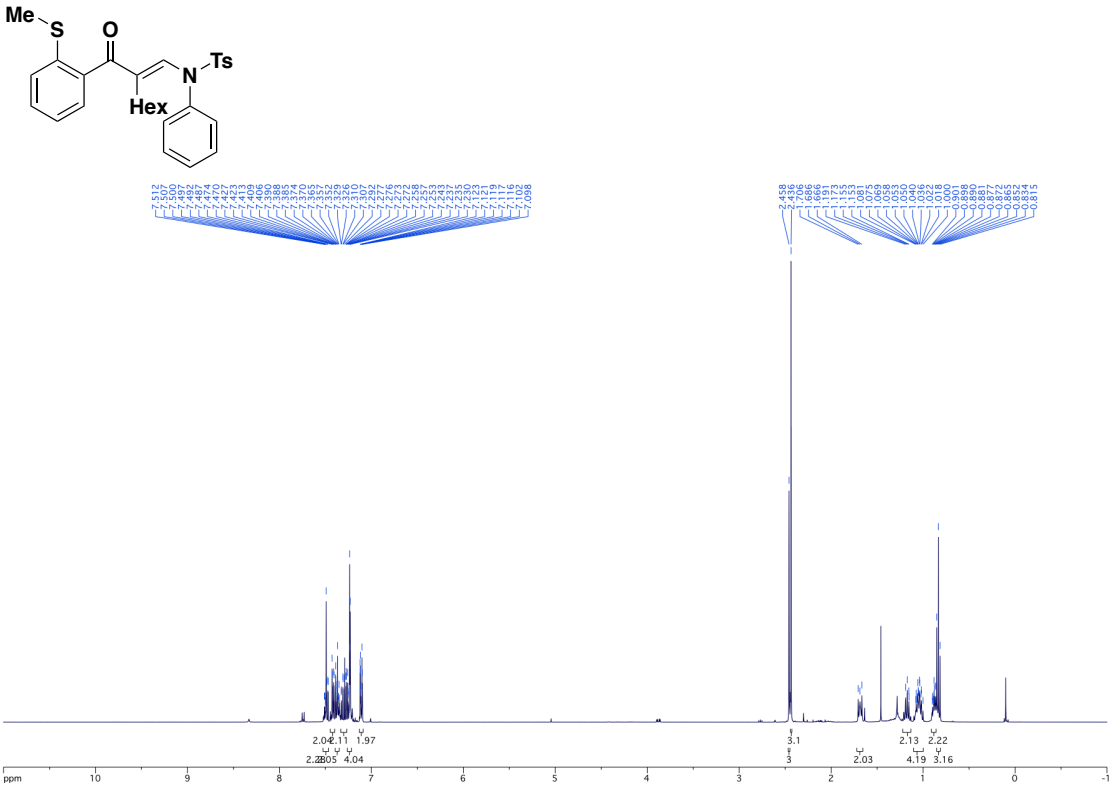


α-Amino enone 289b: ^{13}C NMR (101 MHz, $CDCl_3$)

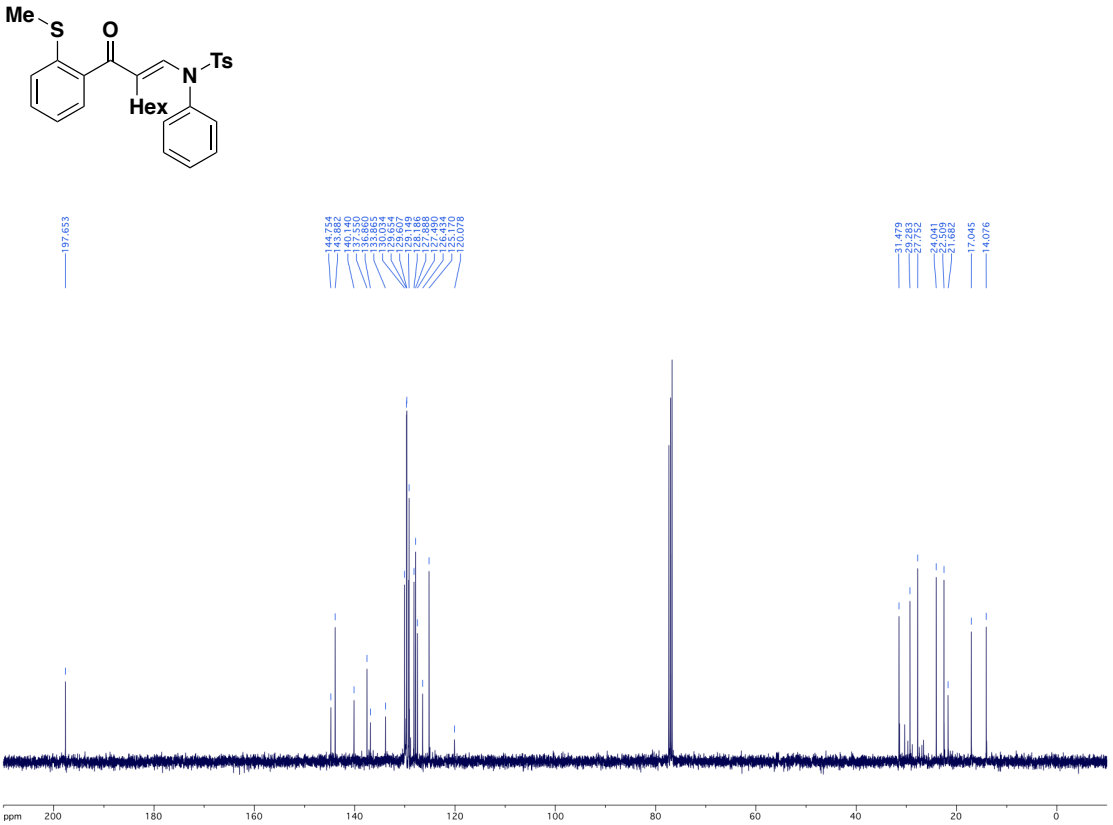




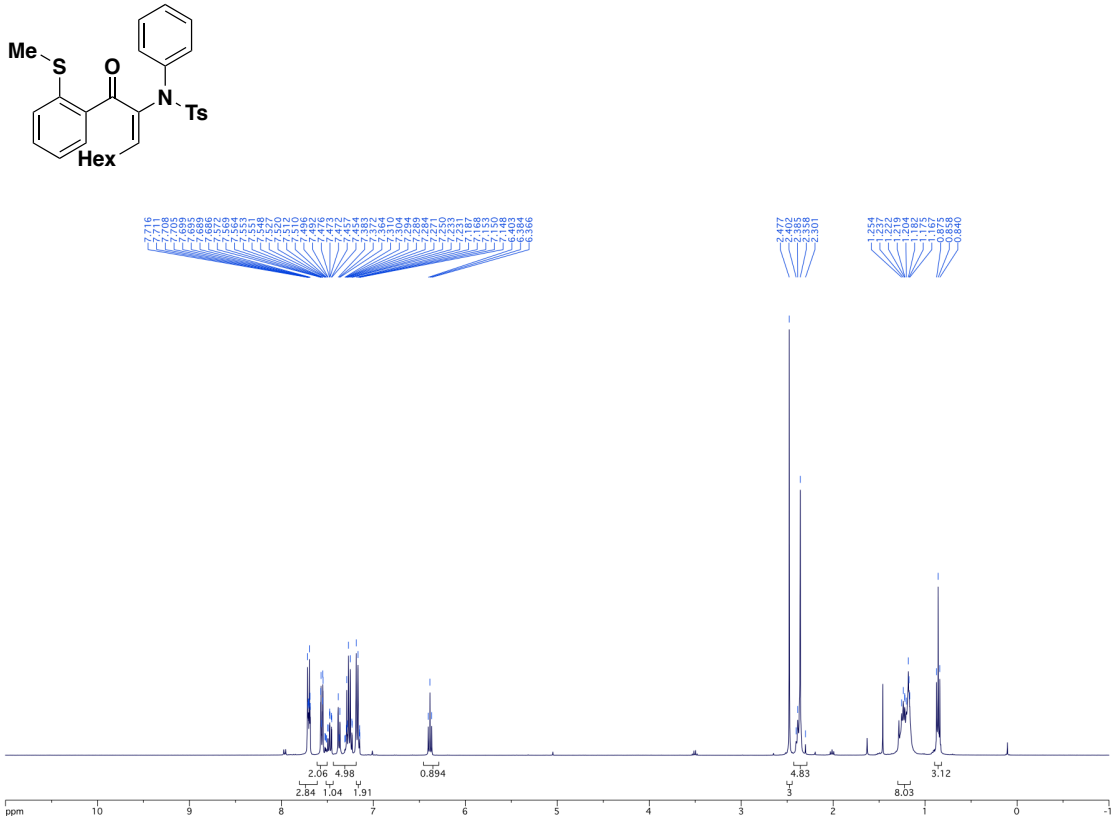
β-Amino enone 290a: ^{1}H NMR (400 MHz, $CDCl_3$)



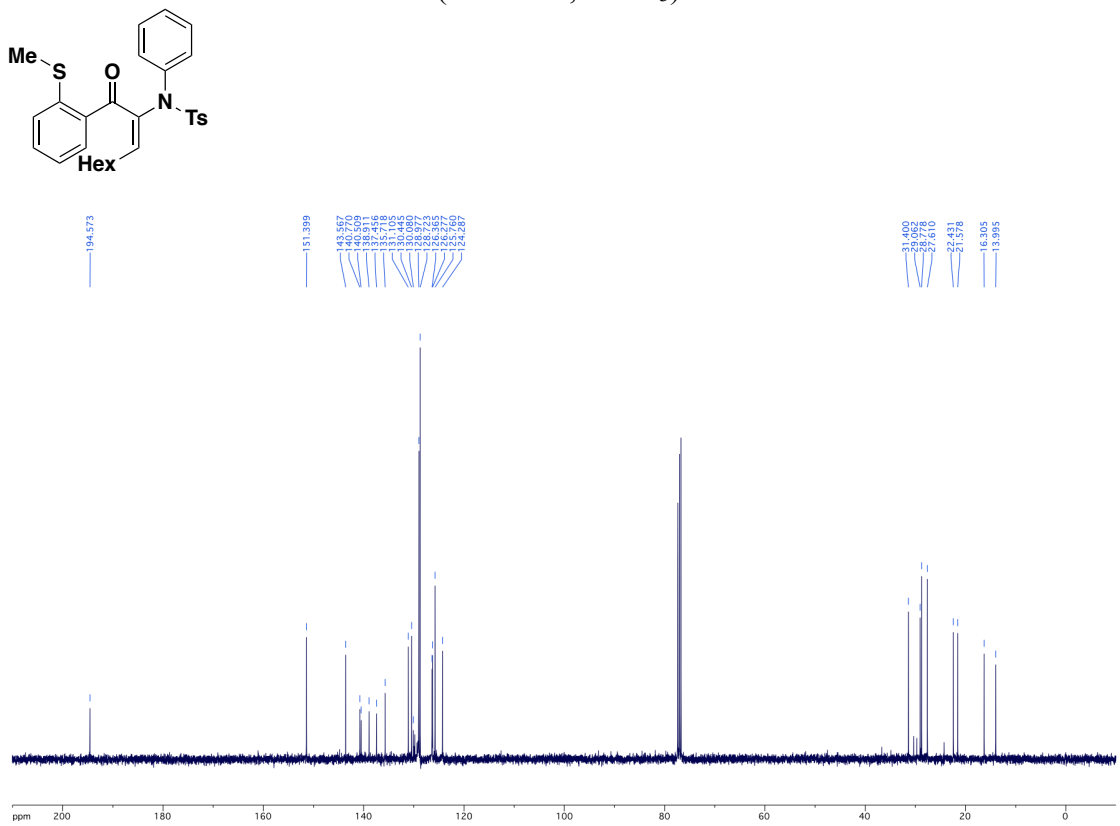
β-Amino enone 290a: ^{13}C NMR (101 MHz, $CDCl_3$)



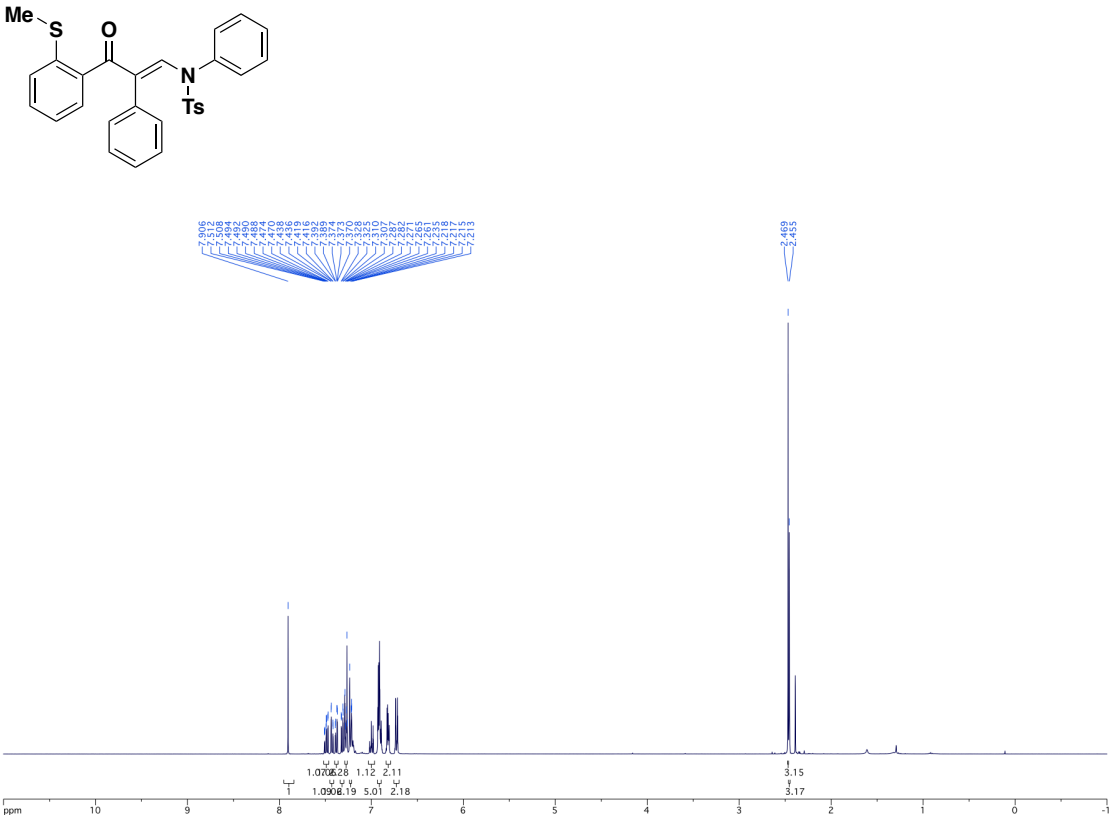
α-Amino enone 290b: ^{1}H NMR (400 MHz, $CDCl_3$)



α-Amino enone 290b: ^{13}C NMR (101 MHz, $CDCl_3$)

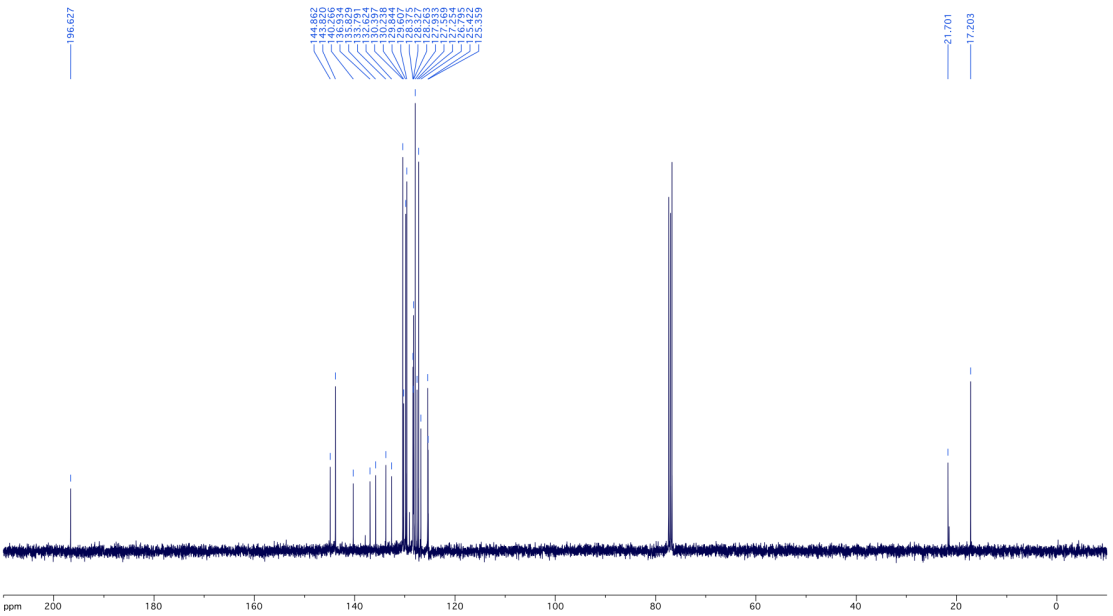


β-Amino enone 291a: ^{1}H NMR (400 MHz, $CDCl_3$)

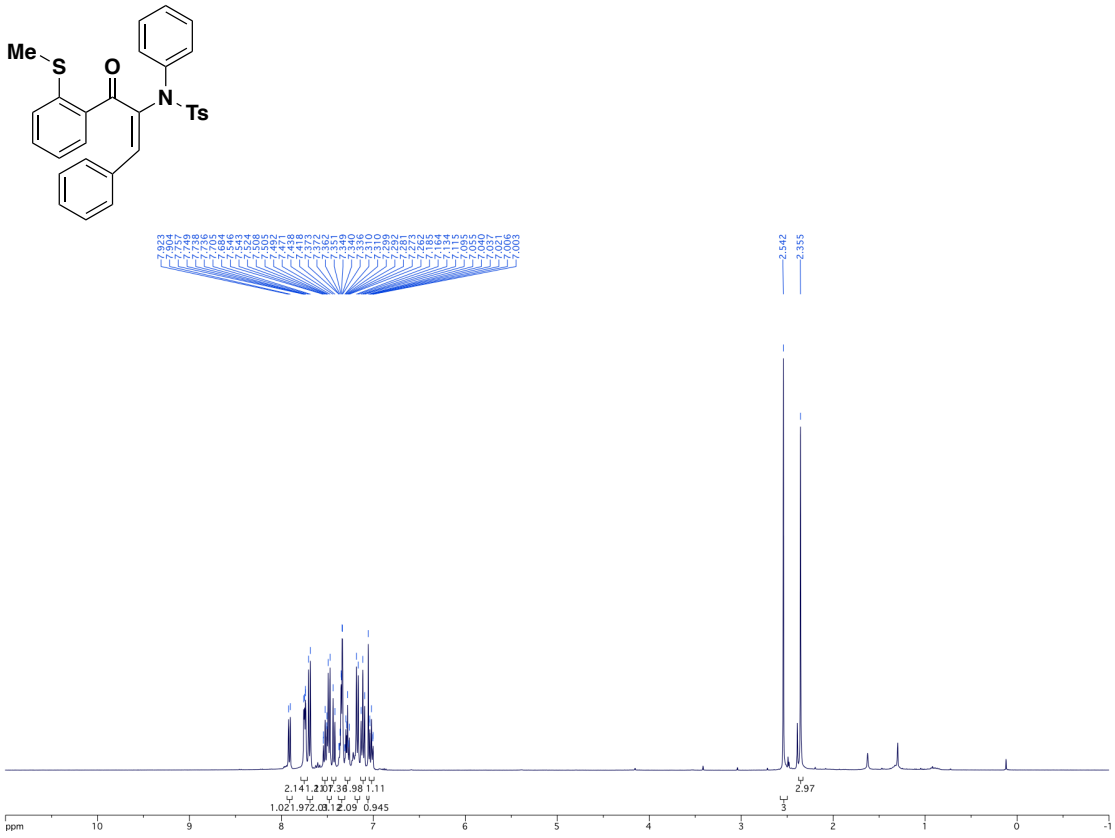


β-Amino enone 291a: ^{13}C NMR (101 MHz, $CDCl_3$)

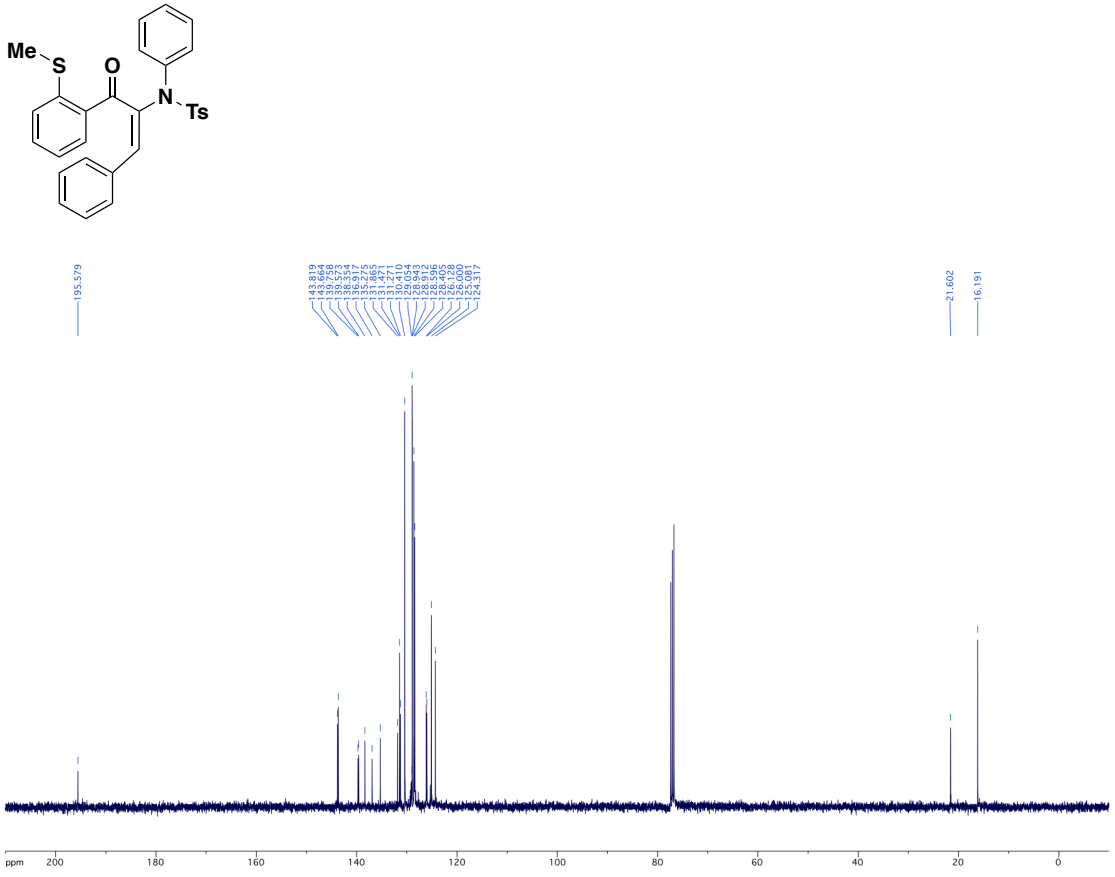




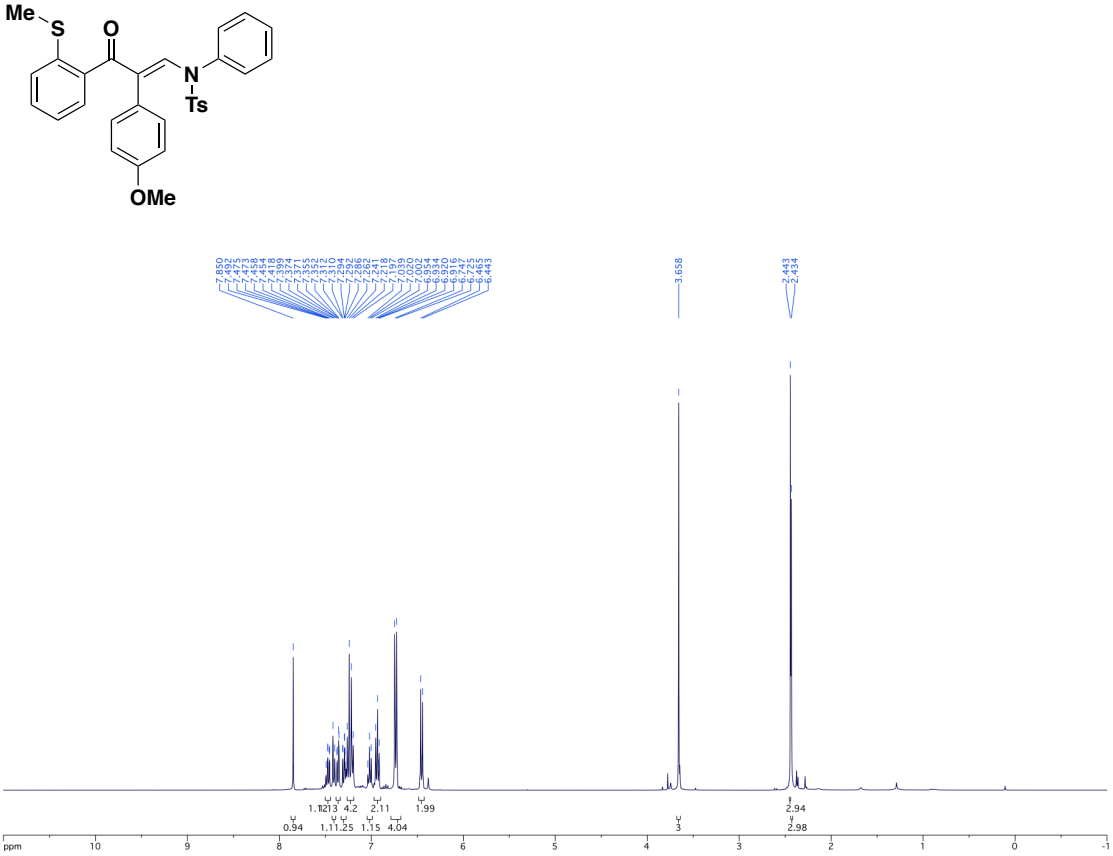
α-Amino enone 291b: ^{1}H NMR (400 MHz, $CDCl_3$)



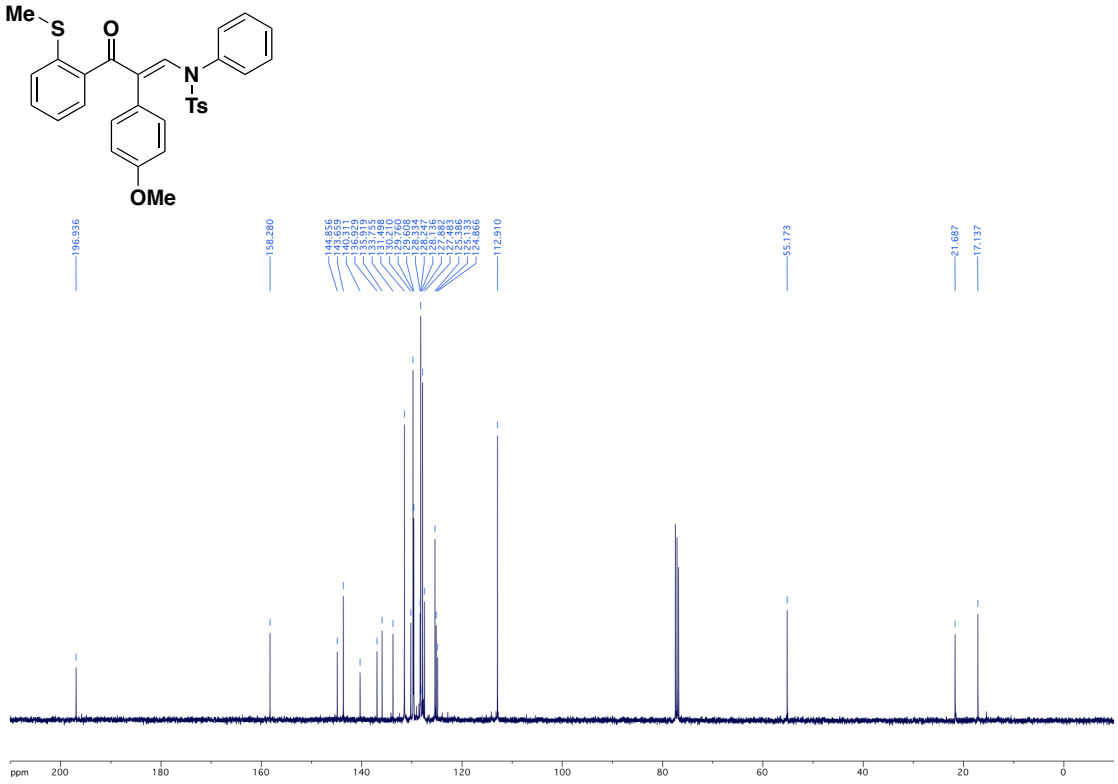
α-Amino enone 291b: ^{13}C NMR (101 MHz, $CDCl_3$)



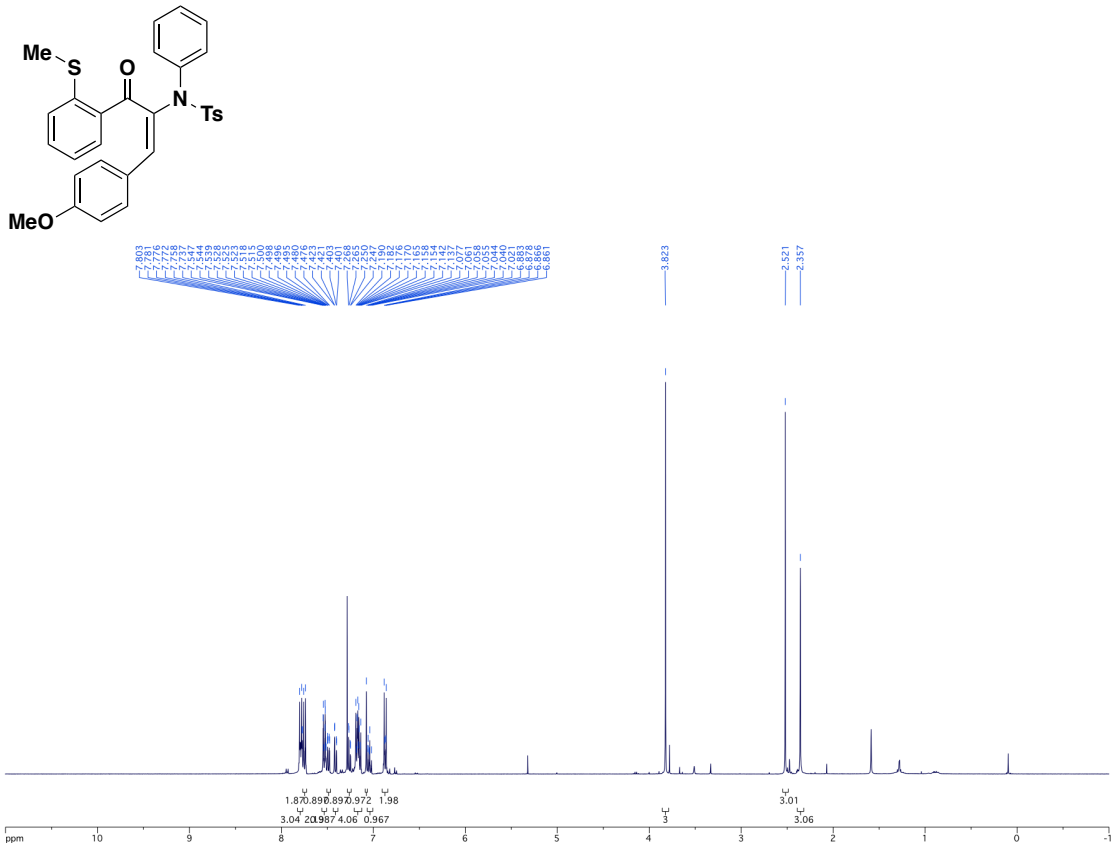
β-Amino enone 292a: ^{1}H NMR (400 MHz, $CDCl_3$)



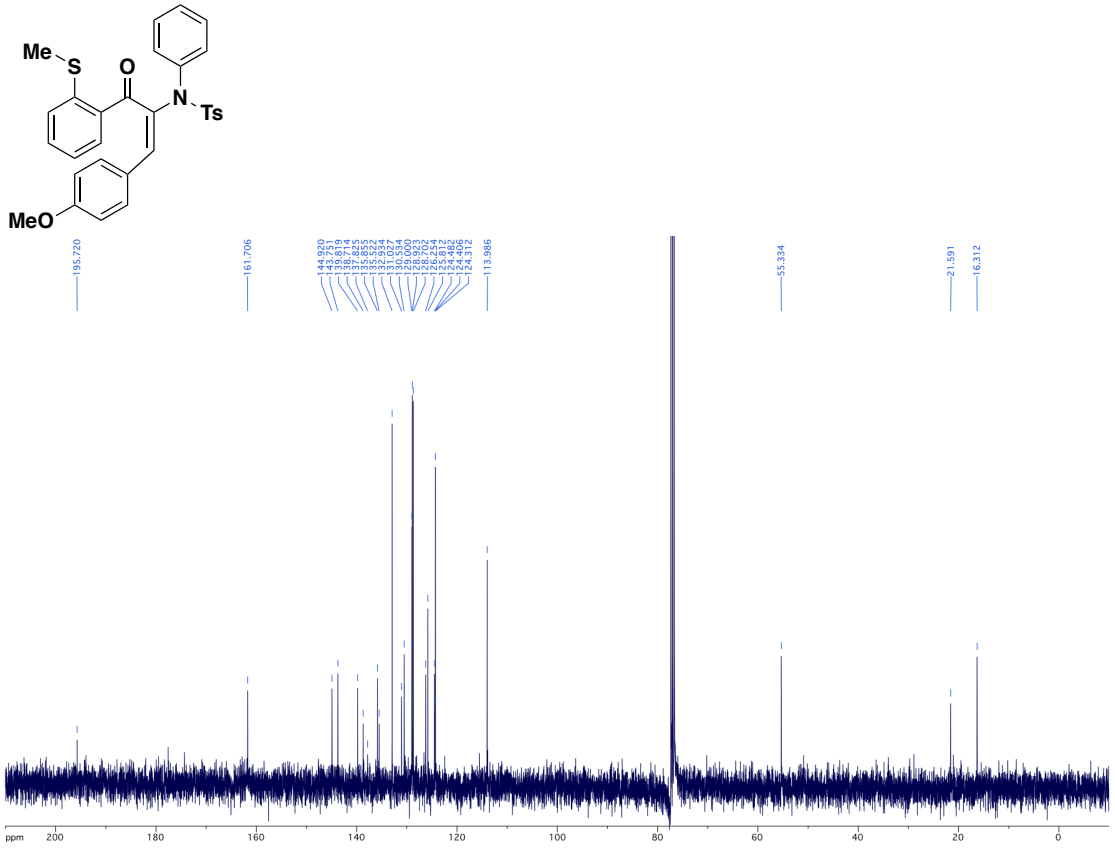
β-Amino enone 292a: ^{13}C NMR (101 MHz, $CDCl_3$)



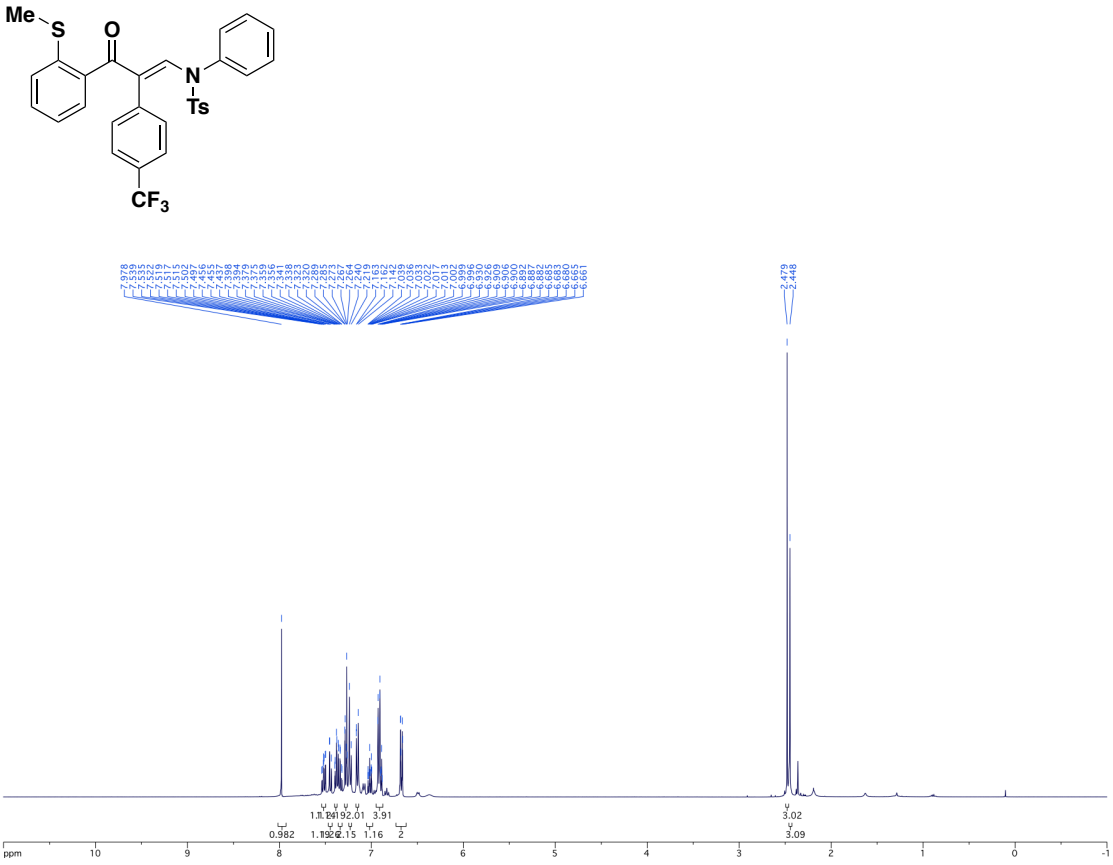
α-Amino enone 292b: ^{1}H NMR (400 MHz, $CDCl_3$)



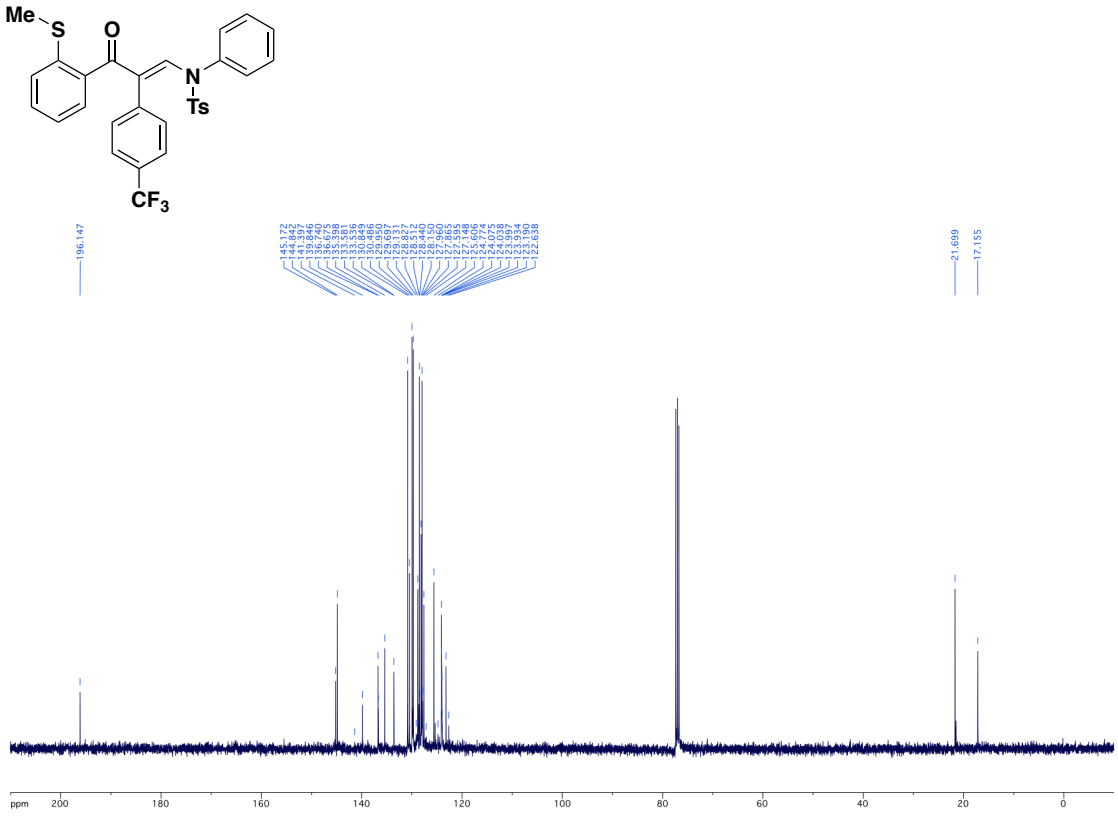
α-Amino enone 292b: ^{13}C NMR (101 MHz, $CDCl_3$)



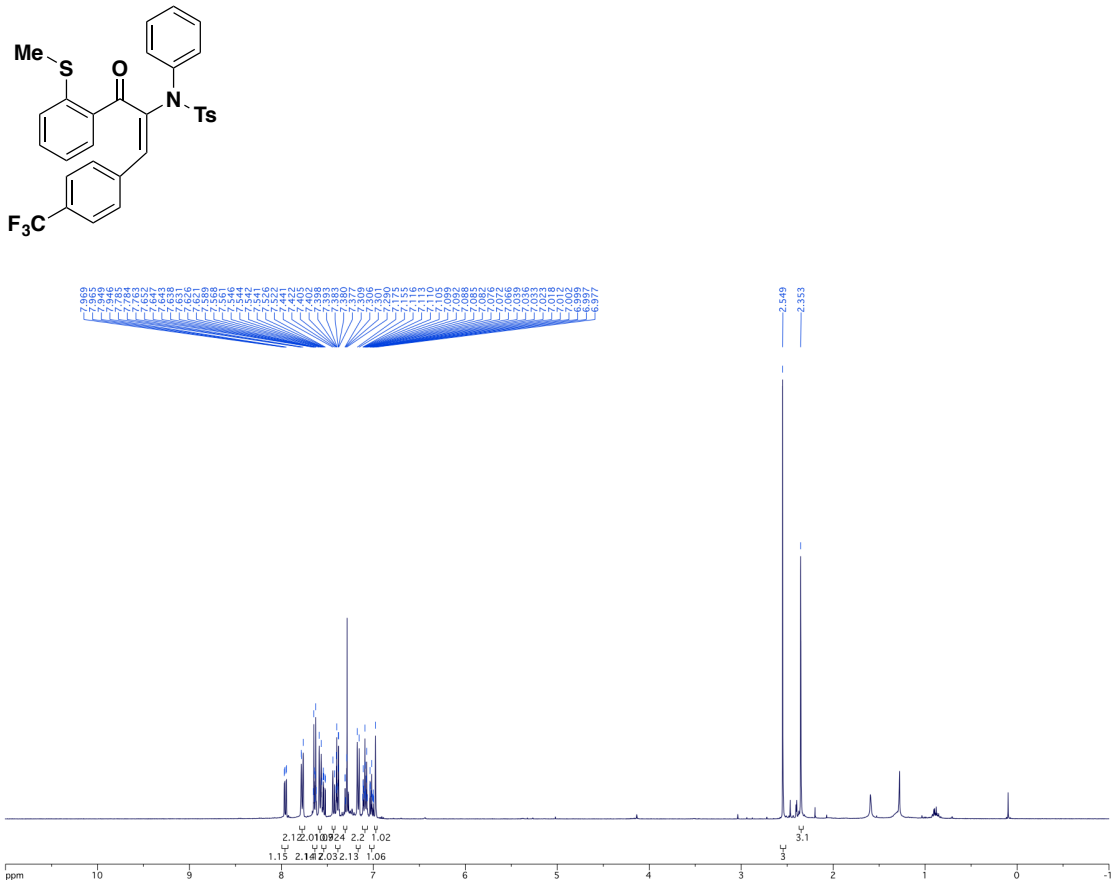
***β*-Amino enone 293a:** ^{1}H NMR (400 MHz, $CDCl_3$)



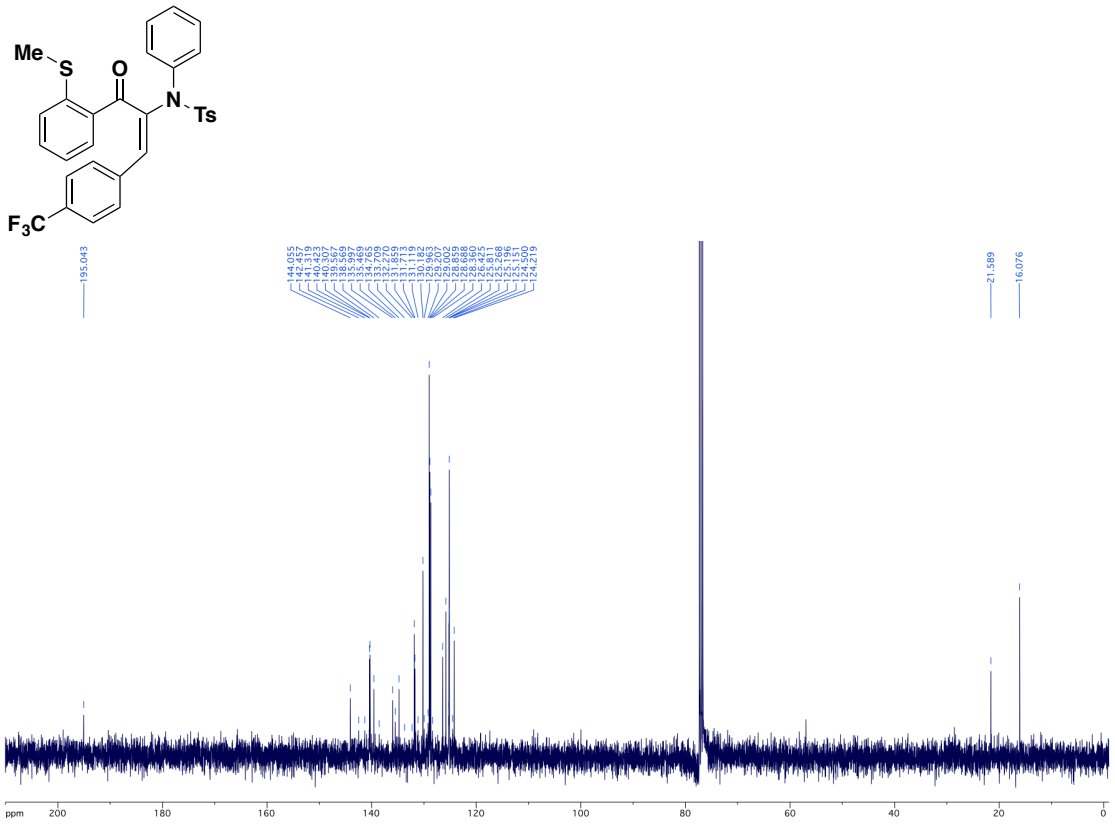
***β*-Amino enone 293a:** ^{13}C NMR (101 MHz, $CDCl_3$)



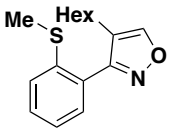
α-Amino enone 293b: ^{1}H NMR (400 MHz, $CDCl_3$)

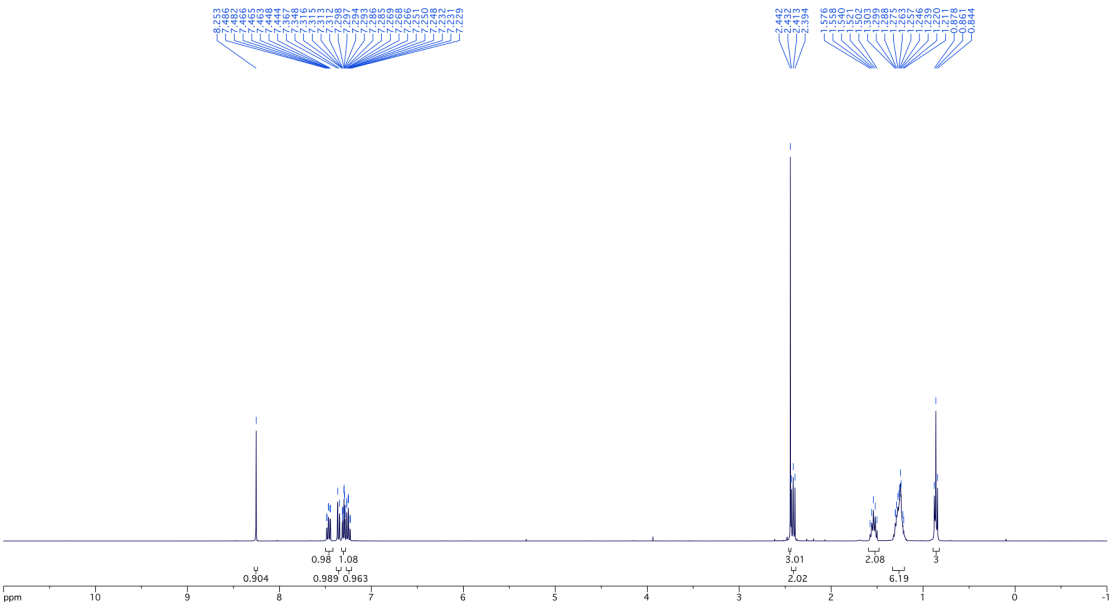


α-Amino enone 293b: ^{13}C NMR (101 MHz, $CDCl_3$)

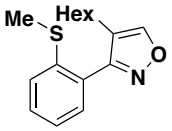


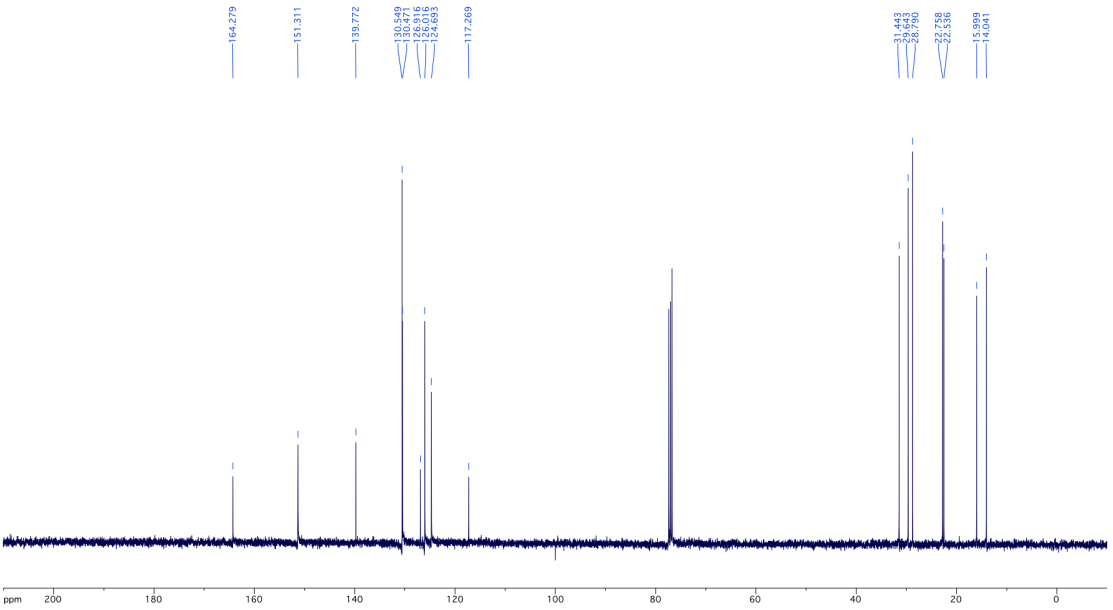
Isoxazole 294: ^{1}H NMR (400 MHz, $CDCl_3$)



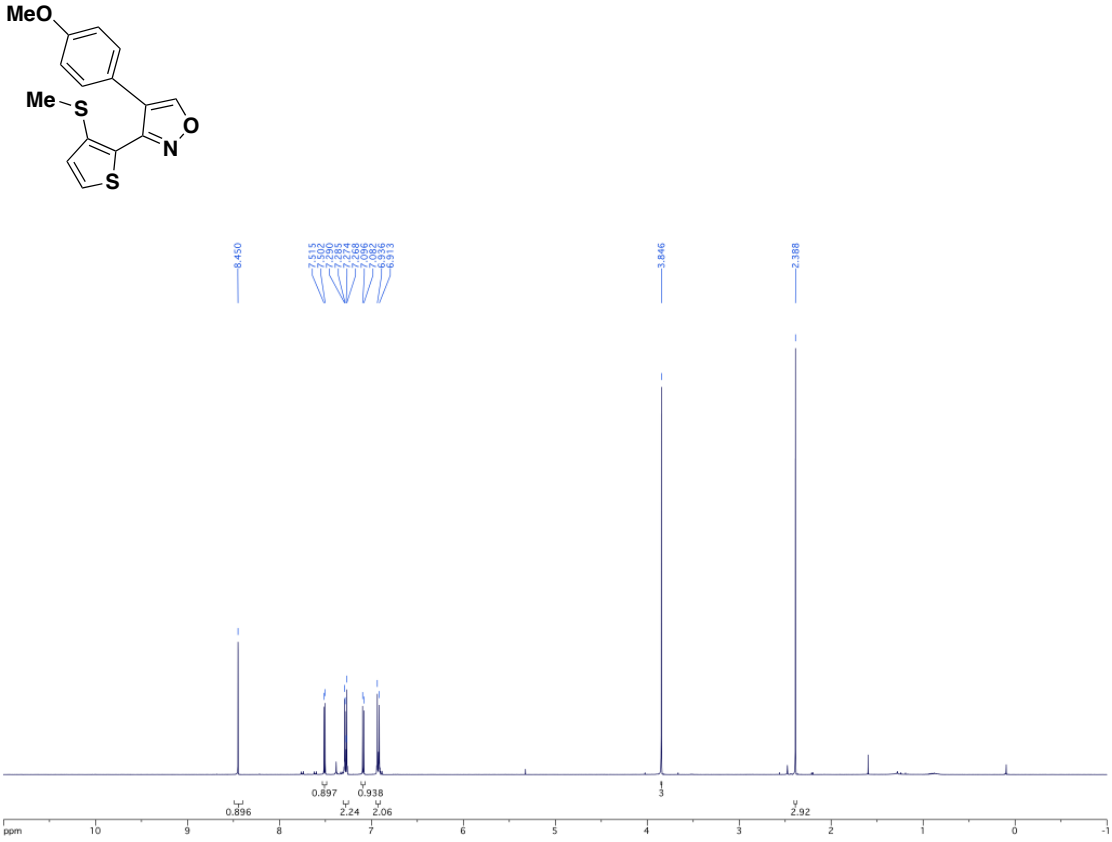


Isoxazole 294: ^{13}C NMR (101 MHz, $CDCl_3$)

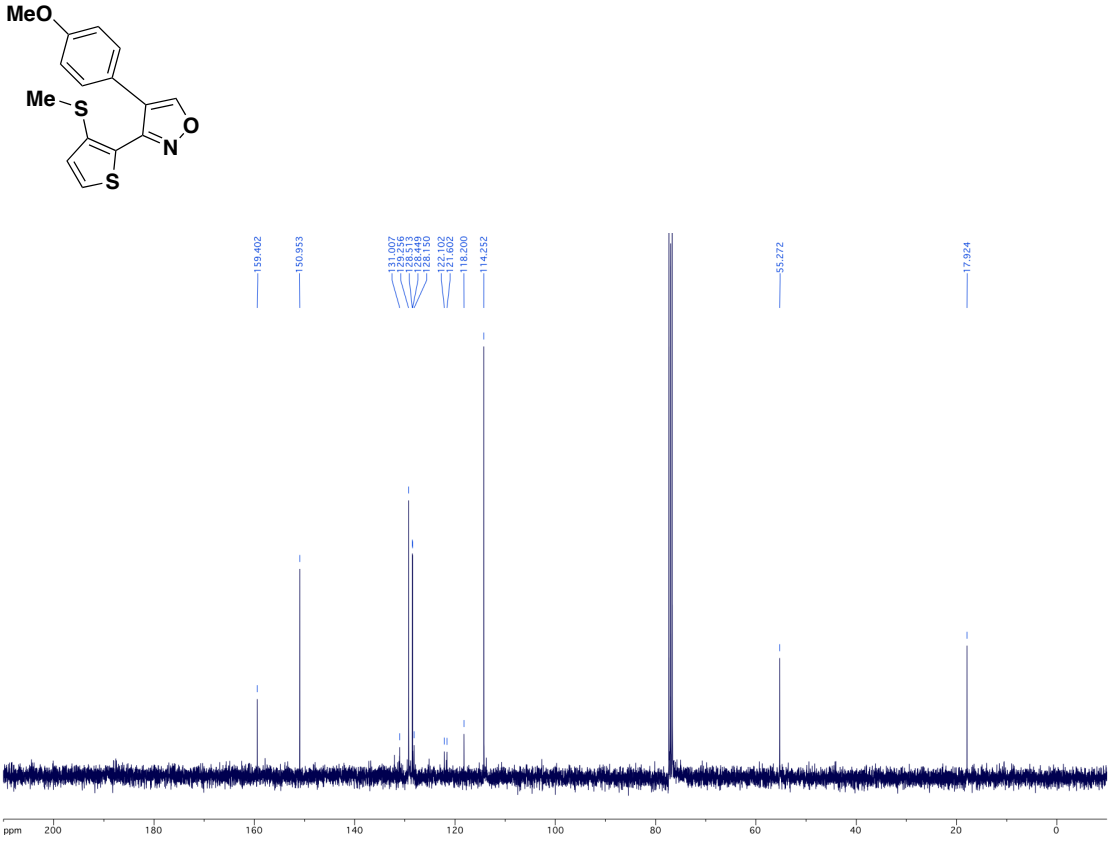




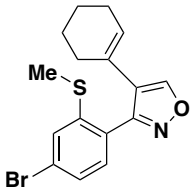
Isoxazole 296: ^{1}H NMR (400 MHz, $CDCl_3$)

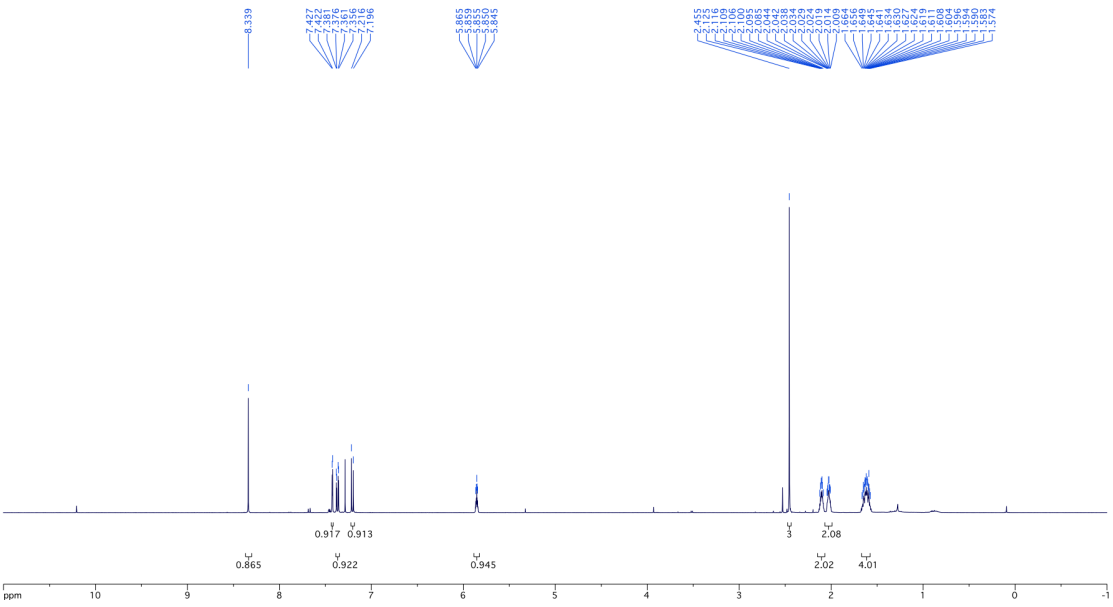


Isoxazole 296: ^{13}C NMR (101 MHz, $CDCl_3$)

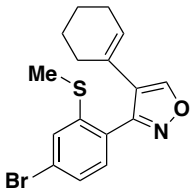


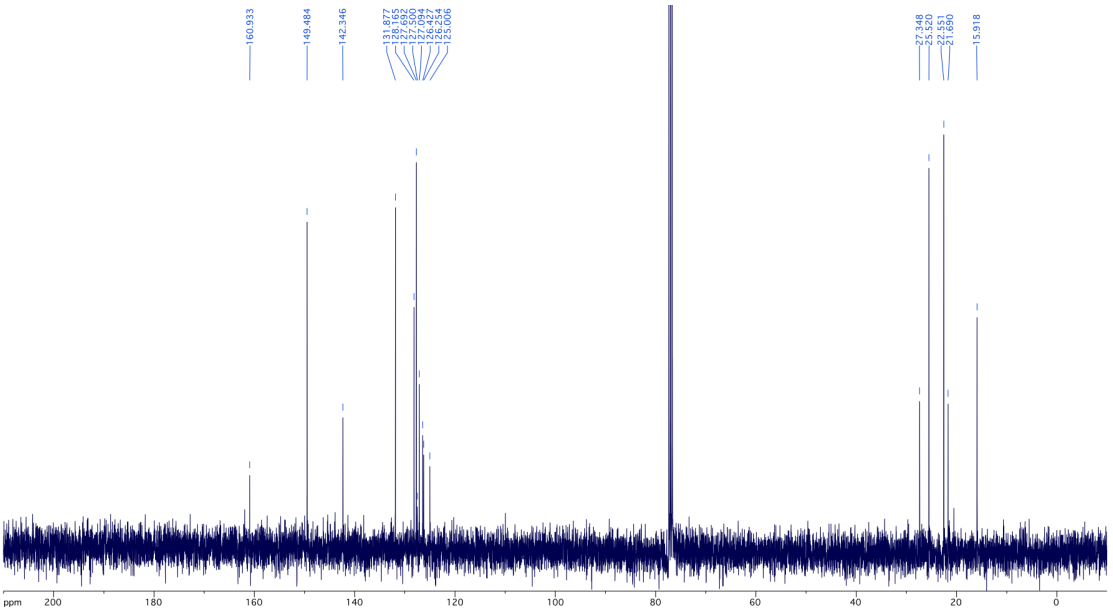
Isoxazole 297: ^{1}H NMR (400 MHz, $CDCl_3$)



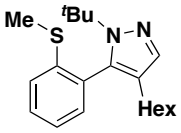


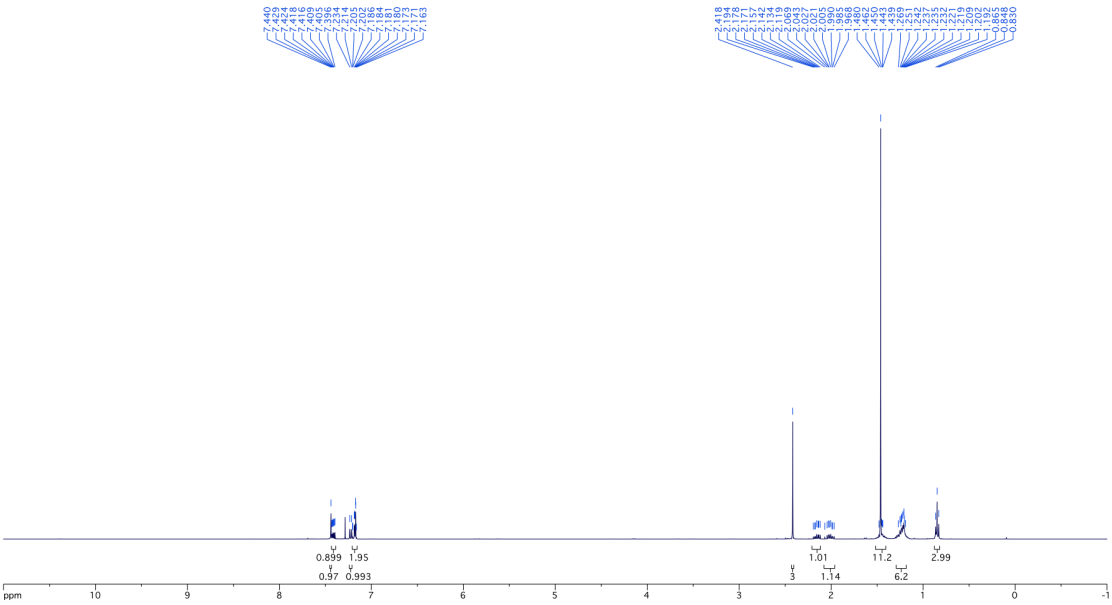
Isoxazole 297: ^{13}C NMR (101 MHz, $CDCl_3$)



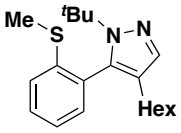


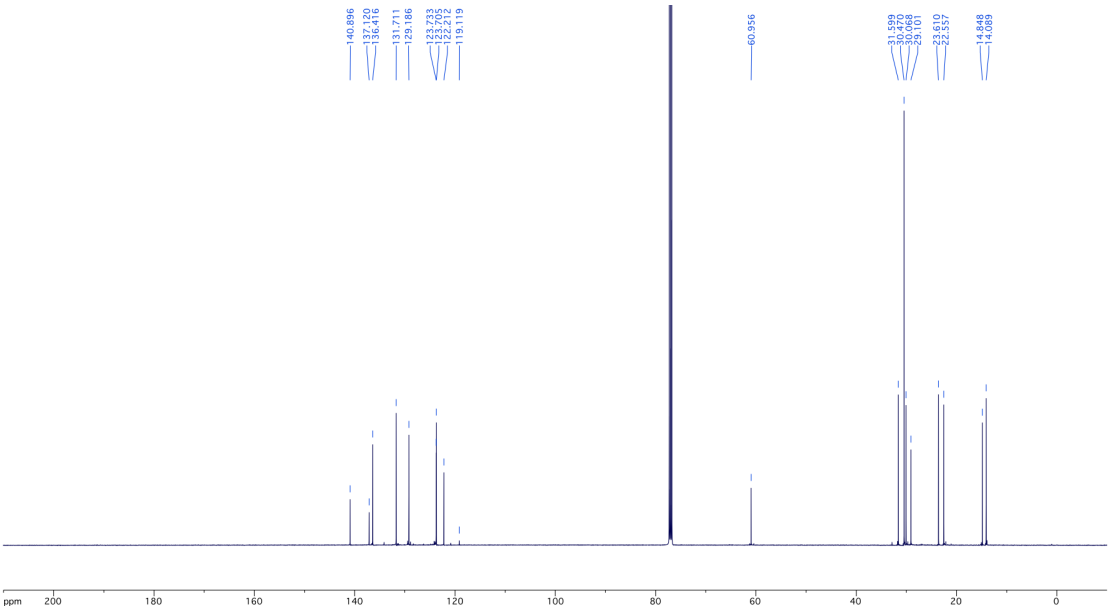
Pyrazole 298: ^{1}H NMR (400 MHz, $CDCl_3$)



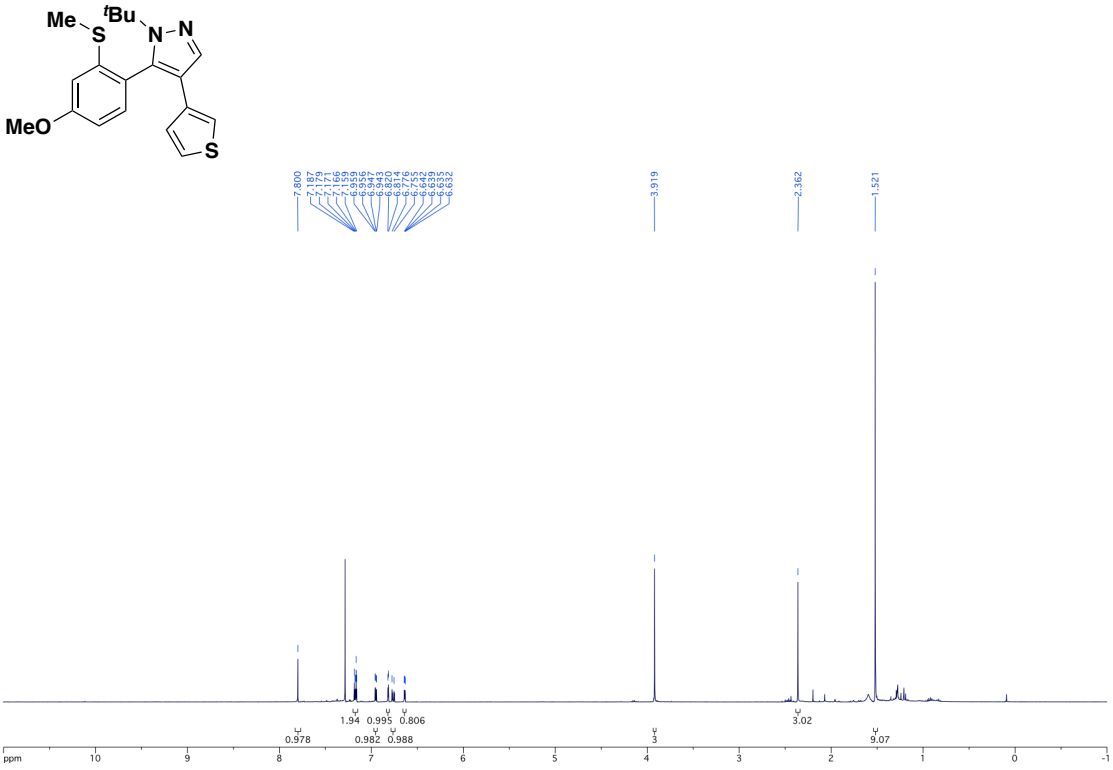


Pyrazole 298: ^{13}C NMR (101 MHz, $CDCl_3$)

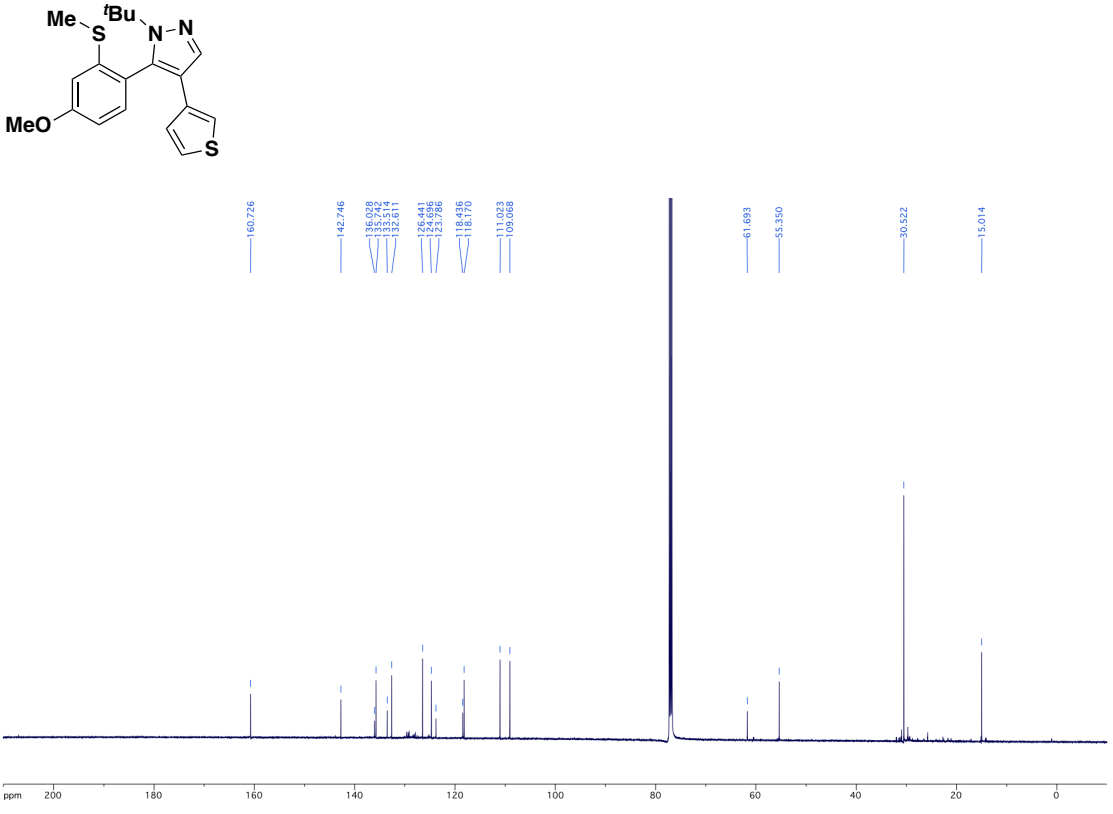




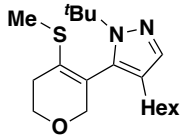
Pyrazole 300: ^{1}H NMR (400 MHz, $CDCl_3$)

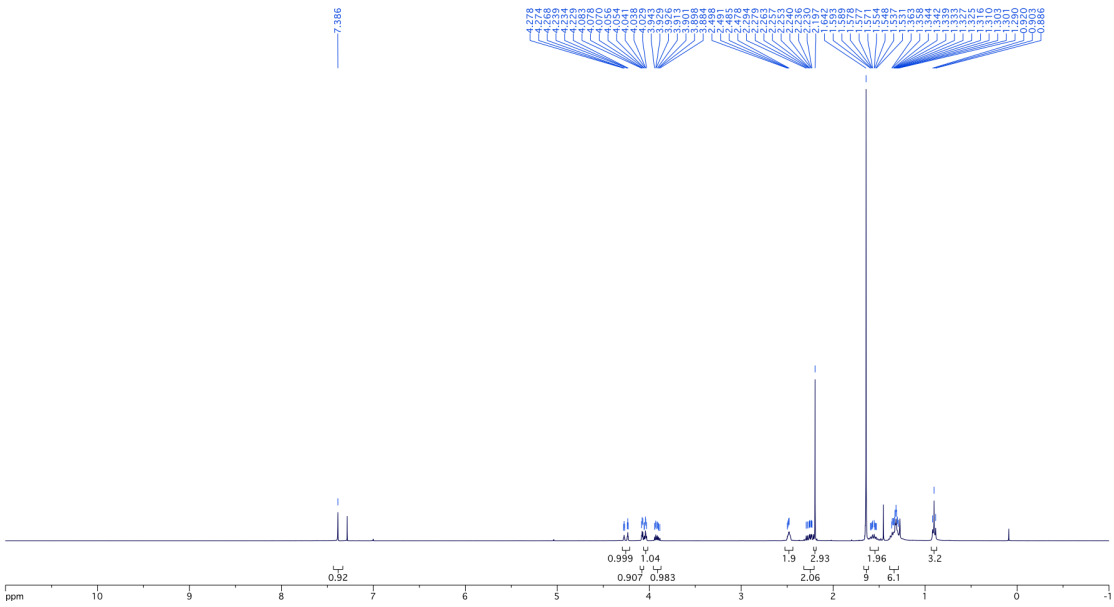


Pyrazole 300: ^{13}C NMR (101 MHz, $CDCl_3$)

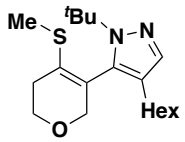


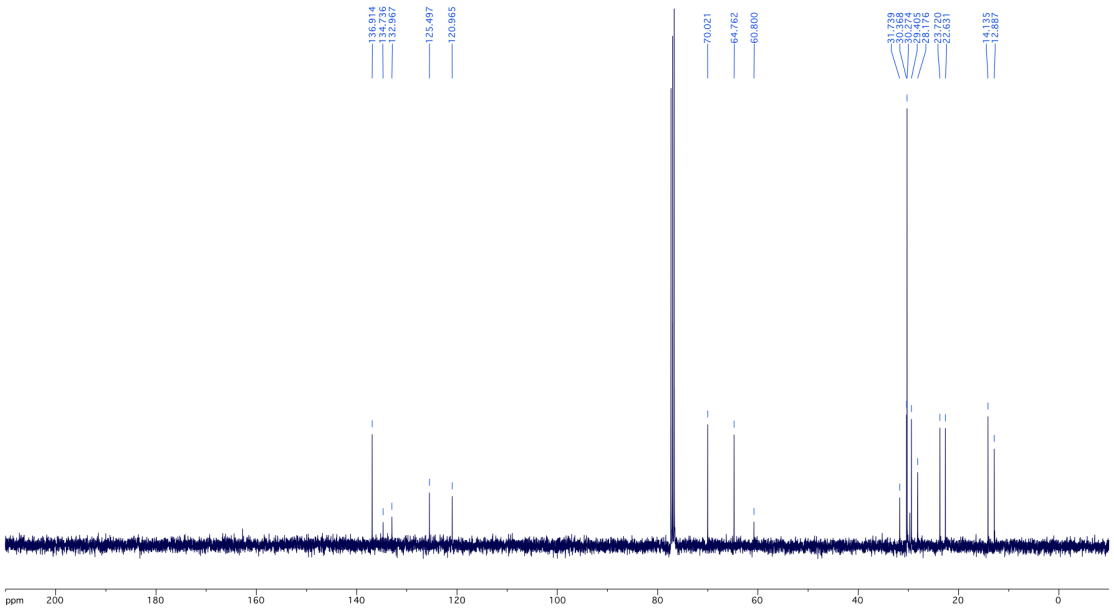
Pyrazole 302: ^{1}H NMR (400 MHz, $CDCl_3$)



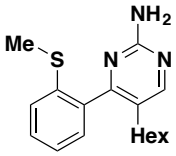


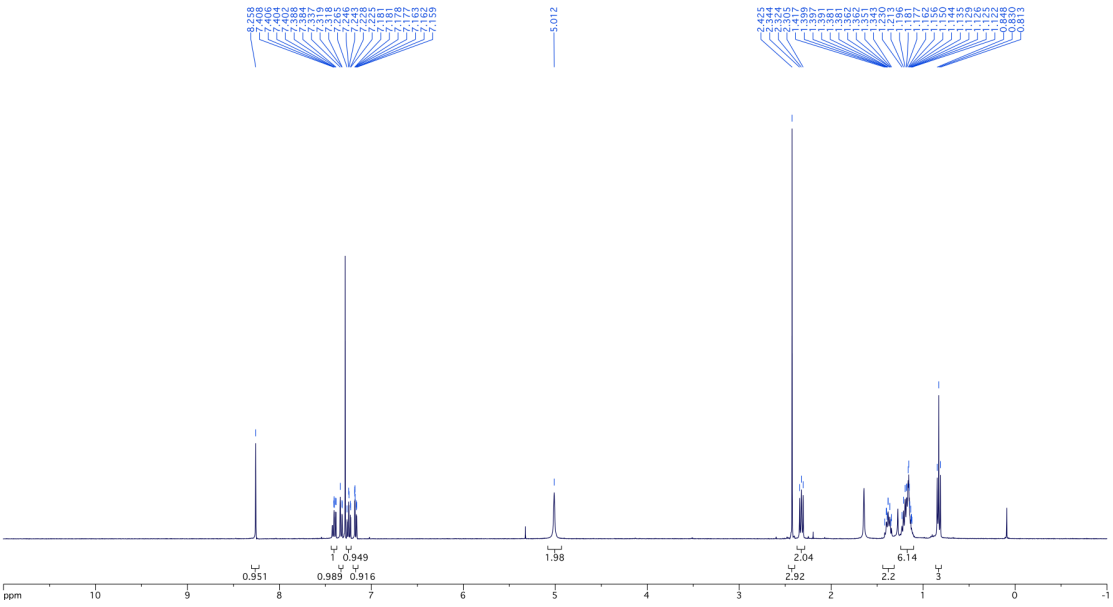
Pyrazole 302: ^{13}C NMR (101 MHz, $CDCl_3$)



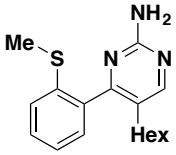


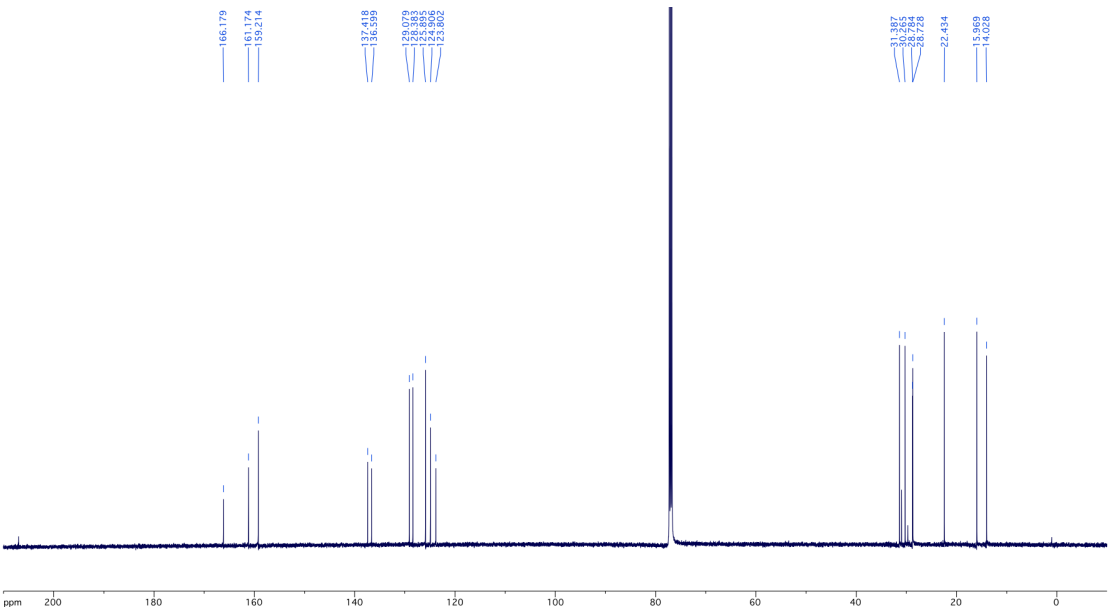
Pyrimidine 303: ^{1}H NMR (400 MHz, $CDCl_3$)



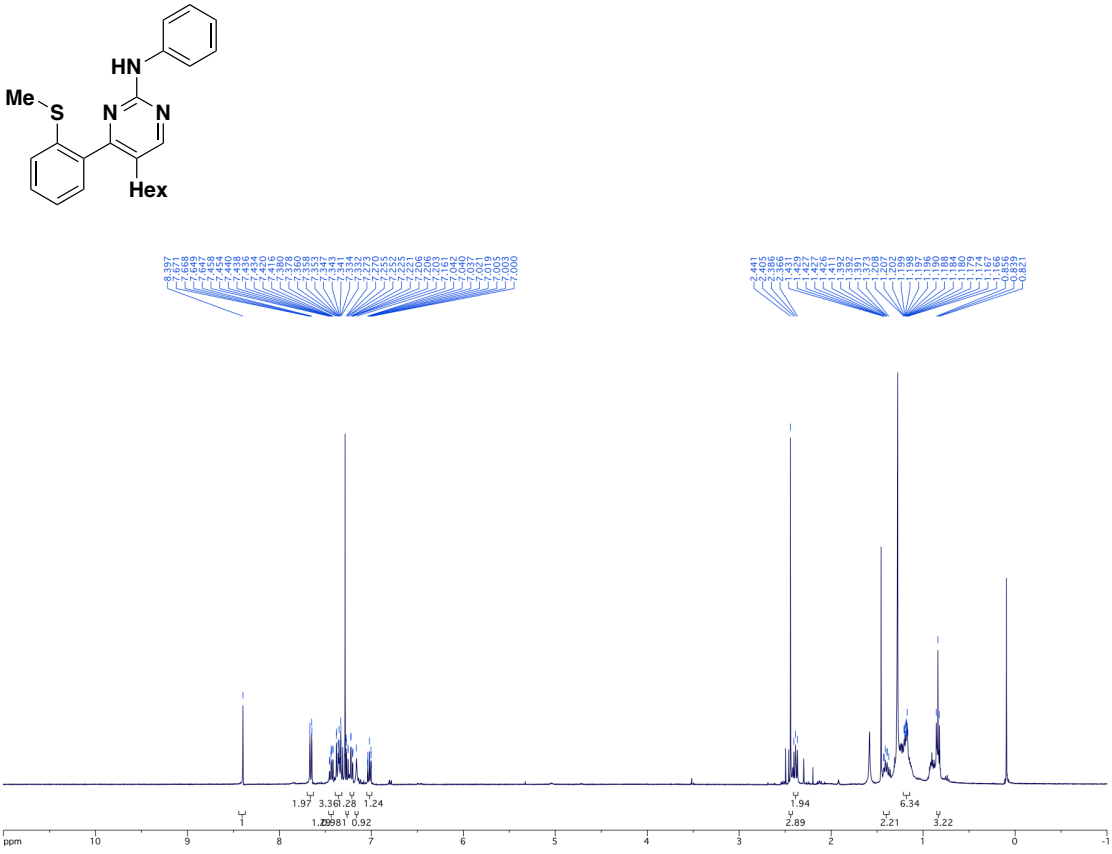


Pyrimidine 303: ^{13}C NMR (101 MHz, $CDCl_3$)

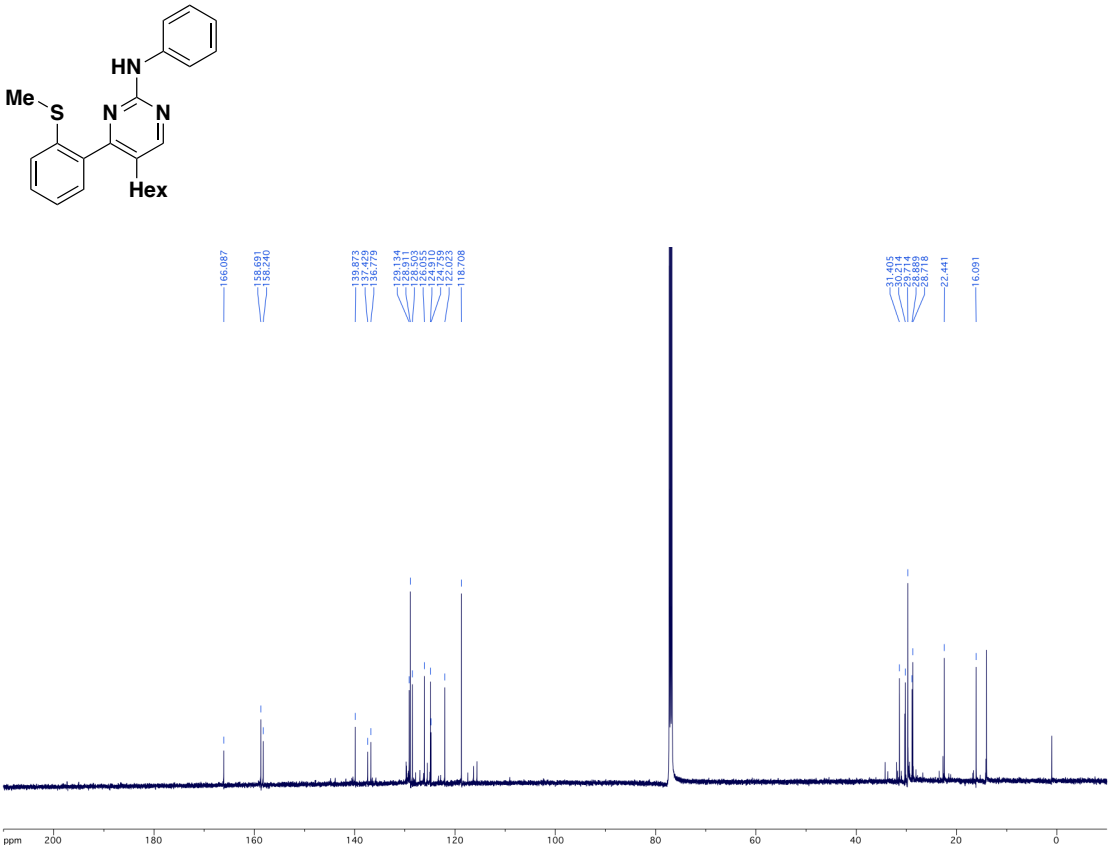




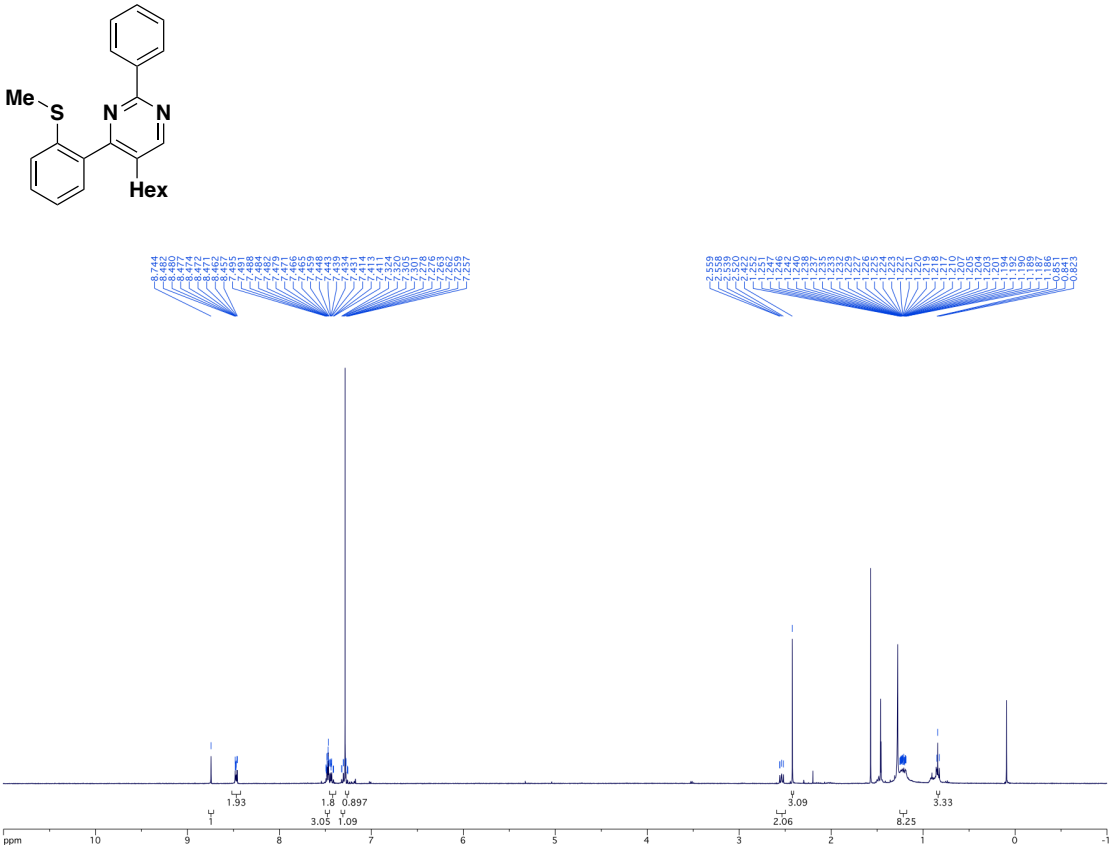
Pyrimidine 304: ^{1}H NMR (400 MHz, $CDCl_3$)



Pyrimidine 304: ^{13}C NMR (101 MHz, $CDCl_3$)



Pyrimidine 305: ^{1}H NMR (400 MHz, $CDCl_3$)



Pyrimidine 305: ^{13}C NMR (101 MHz, $CDCl_3$)

