Studies toward the application and development of rhodium-catalysed hydroacylation reactions

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Trinity Term 2016

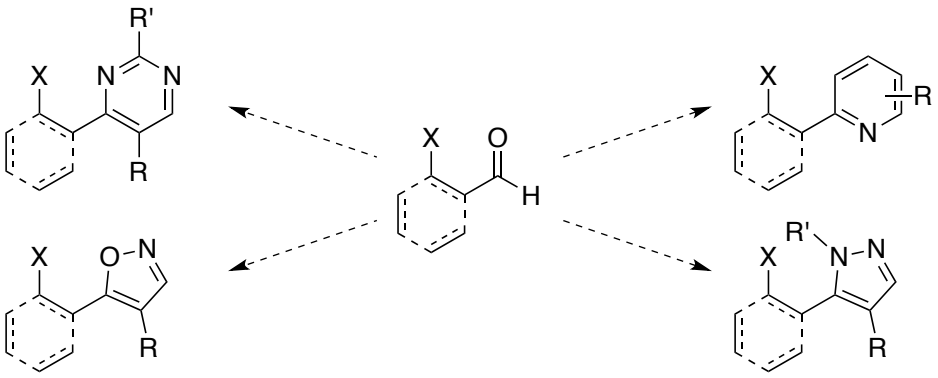
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

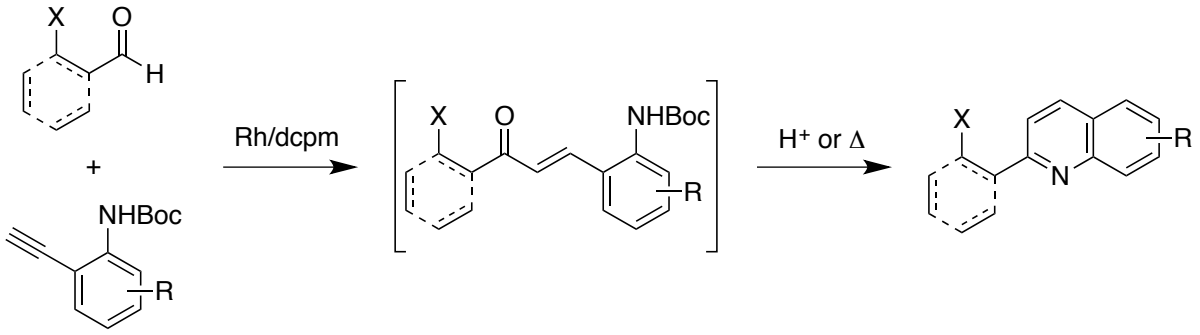
The described in this thesis is primarily concerned with the development of Rh-hydroacylation based approaches to heterocycle synthesis. In addition to investigations on a number of heterocyclic scaffolds, work has been undertaken to increase the synthetic appeal of hydroacylation by expanding the range of functional groups that can be employed as chelating tethers.

Chapter 1 is a literature review surveying the key milestones in the development of efficient, selective intermolecular hydroacylation. The use of chelating tethers, and the development of highly active ligands for their use, is detailed, as well as a summary of attempts to circumvent the requirement for such a tether using Rh and a number of other late transition metals and NHC catalyst systems. The application of a number of Rh-catalysed reactions to the synthesis of heterocycles has been discussed.

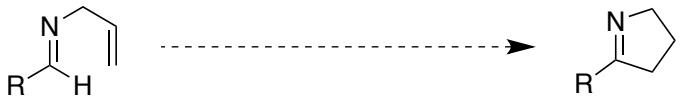
Chapter 2 describes attempts to synthesise 1,3-dicarbonyl analogues, commonly used as intermediates for the synthesis of a number of five- and six-membered heterocycles. In addition, an approach to pyridines featuring a novel disconnection is also detailed.



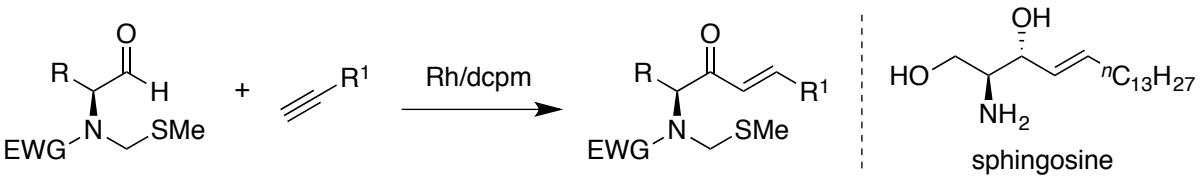
Chapter 3 presents a detailed investigation into the synthesis of diversely substituted quinolines *via* Rh-catalysed hydroacylation. Whilst this approach was successful across a broad range of substrates and substitution patterns, a number of minor limitations were encountered. Methods to overcome each of these drawbacks are detailed, including the synthesis of tether-free quinolines through tandem hydroacylation – C-S functionalisation protocols.



Chapter 4 concerns the synthesis of *N*-containing heterocycles through intramolecular hydroimination. In addition to the conditions employed for intermolecular hydroacylation, a diverse range of hydroacylation catalysts was evaluated.



Chapter 5 documents exploration of the use of the removable MTM-directing group. In addition to extending range of hydroacylation reactions, efforts were made to apply the methodology developed to the synthesis of the natural product sphingosine.



Chapter 6 summarises the research presented and the potential for future work.

Chapter 7 presents the experimental 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

James Neuhaus

June 2016

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First and foremost, I would like to thank Prof. Michael Willis, both for giving me the opportunity to work in his group, but also for being an excellent supervisor to work for. His enthusiasm and technical input into each and every project has been invaluable. In addition, his support and flexibility in allowing me to exercsise my own intellectual freedom is greatly appreciated. I am incredibly thankful for the numerous discussions, both relating to the work in this thesis and other more fanciful ideas. He has been nothing but approachable, friendly and understanding.

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Finally, I would like to dedicate this thesis to my grandparents, in particular my Granny, who was always so proud of everything each of grandchildren achieved, and would have loved to see this moment.

Table of Contents

Chapter 1 – Introduction 1

1.1 The development of Rh-catalysed hydroacylation 2

1.1.1 The use of chelating aldehydes in inter- and intramolecular hydroacylation 6

1.1.2 Ligand development with β-sulfur aldehydes 10

1.1.3 Alternative tethers for chelate-controlled hydroacylation 14

1.1.4 Towards tetherless hydroacylation 16

1.1.5 Alternatives to Rh-catalysed hydroacylation 20

1.2 Rh(I) catalysis in heterocycle synthesis 27

1.2.1 Cycloisomerisation 28

1.2.2 Cycloaddition 29

1.2.3 Hydroacylation 30

1.2.4 Hydroarylation 31

1.2.5 Miscellaneous 33

1.3 Summary 35

Chapter 2 – Intermolecular Rh-catalysed hydroacylation routes to heterocycle synthesis 36

2.1 Introduction 36

2.2 Hydroacylation-based route to 1,3-dicarbonyl analogues 39

2.2.1 Synthesis of ynol ethers and ynol thioethers 40

2.2.2 Hydroacylation optimisation 41

2.3 Hydroacylation for the synthesis of pyridines 44

2.3.1 Prior work in the Willis group 46

2.3.2 Synthesis of homopropargyl sulfonamides 48

2.3.3 Hydroacylation optimisation 49

2.4 Summary 54

Chapter 3 – Diversely substituted quinolines *via* Rh-catalysed alkyne hydroacylation 55

3.1 Introduction 55

3.2 Initial optimisation 58

3.2.1 Hydroacylation optimisation 58

3.2.2 Cyclisation to quinolines 60

3.2.3 Attempted development of tandem/telescoped procedures 61

3.3 Reaction scope 63

3.3.1 Synthesis of *N*-Boc 2-ethynylanilines 63

3.3.2 Scope of the alkyne component 70

3.3.3 Scope of the aldehyde component 75

3.4 Revisited optimisation 79

3.5 Accessing electron-rich quinolines and quinoline *N*-oxides 83

3.6 Accessing tether-free quinolines *via* C-S functionalisation 87

3.7 Accessing substitution at the C(3) and C(4) positions 90

3.7.1 C(3) substitution 91

3.7.2 C(4) substitution 94

3.8 Summary 101

Chapter 4 – Heterocycle synthesis *via* intramolecular hydroimination 102

4.1 Background 102

4.2 Reaction optimisation 105

4.3 Summary 113

Chapter 5 - Expanding the use of the removable MTM directing group 114

5.1 Background 114

5.2 Reaction of MTM-substituted α-amino aldehydes with internal alkynes 120

5.3 Application to the total synthesis of the natural product sphingosine 122

5.3.1 Route 1 – multiple protecting group strategy 124

5.3.2 Route 2 – single cyclic protecting group strategy 126

5.4 Summary 132

Chapter 6 – Future Work and Conclusion 135

6.1 Future Work 135

6.1.1 Further Rh-catalysed hydroacylative routes to heterocycles ... 135

6.1.2 Expanding the range of chelating aldehydes for Rh-catalysed hydroacylation 138

6.2 Conclusion 140

Chapter 7 – Experimental Data and Procedures 143

7.1 General Considerations 143

7.2 Experimental Data for Chapter 2 145

7.2.1 Pyrazole project 145

7.2.2 Pyridine project 150

7.3 Experimental Data for Chapter 3 156

7.3.1 Synthesis of *N*-Boc 2-ethynylanilines 156

7.3.2 Hydroacylation of *N*-Boc 2-ethynylanilines 202

7.3.3 Quinoline-forming cyclisation reactions 232

7.3.4 Use of nitro-substituted alkynes in quinoline synthesis 255

7.3.5 Tandem hydroacylation-Suzuki reactions in quinoline synthesis 267

7.3.6 Functionalisation of the C(3) and C(4) positions 279

7.4 Experimental Data for Chapter 4 288

7.5 Experimental Data for Chapter 5 293

References 305

Spectra S1

Abbreviations and Acronyms

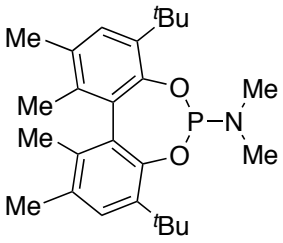
[Br}	brominating agent
[H]	reductant
[O]	oxidant
[α]	specific rotation
Ac	acetyl
acac	acetylacetone
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere(s)
b	branched
$BAr^F{}_4^-$	$[B(3,5\text{-bis}(CF_3)C_6H_3)_4]^-$
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
Bu	butyl
c.	concentrated
c.f.	*confer* (Latin: compare)
cat.	catalyst
Cbz	benzyloxycarbonyl
CI	chemical ionisation
cm	centimetre(s)
cod	1,5-cyclooctadiene
coe	cyclooctene
COSY	correlation spectroscopy
Cpr	cyclopropyl
Cy	cyclohexyl
D	Sodium D line (589 nm)
d	doublet
DABCO	1,3-diazabicyclo-[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DFT	density function theory
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMF.DMA	*N*,*N*-dimethylformamide dimethyl acetal
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E	Entgegen
e.g.	*exemplit gratia* (Latin: for example)

E1cB	unimolecular elimination – conjugate base
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron ionisation
eq.	equivalents
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
Fc	ferrocenyl
FI	field ionisation
g	gram(s) or gas
h	hour(s)
HA	hydroacylation
HMDS	Bis(trimethylsilyl)amine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
L	litre(s) or ligand
l	linear or liquid
LLHT	ligand-to-ligand hydrogen transfer
LRMS	low resultion mass spectrometry
m	meta
M	molar or mega (10^6)
m	multiplet or milli (10^{-3}), e.g. mg = milligram, mL = millilitre
m-CPBA	*m*-chloroperoxybenzoic acid
m.p.	melting point
m/z	mass to charge ratio
MALDI	matrix-assisted laser desorption/ionisation
Me	methyl
min	minute(s)
mol	mole
mol%	mole percentage
Ms	methylsulfonyl
MS	mass spectrometry
MTM	methylthiomethyl
n	normal
N	normal
n/a	not applicable
nbd	norbornadiene
NHC	N-heterocyclic carbene
NIS	*N*-iodosuccinimide
nm	nanometre
NMR	nuclear magnetic resonance
Nu	nucleophile

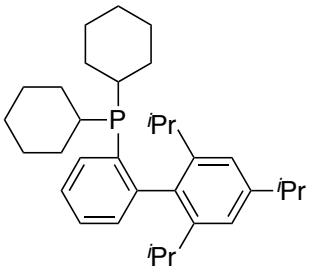
o	ortho
ox. add^{n}.	oxidative addition
p	para
p-TSA	4-toluenesulfonic acid
Ph	phenyl
pin	pinacol
ppm	parts per million
Pr	propyl
q	quartet
quant.	quantitative
R	generic group
r.s.m.	recovered starting material
red. elim^{n}.	Reductive elimination
rr	regioisomeric ratio
RT	room temperature
s	secondary
s	seconds or singlet
sat.	saturated
SEAr	electrophilic aromatic substitution
t	tertiary
t	triplet
TBAI	*tert*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
temp	temperature
Teoc	2-(trimethylsilyl) ethoxycarbonyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
TMS	trimethylsilyl
Tol	tolyl
Ts	toluene-4-sulfonyl
UV	ultraviolet
w/u	workup
wt	weight
X	halide or generic counteranion (unless stated otherwise)
Z	zusammen
δ	chemical shift
μ	micro (10^{-6})
μW	microwave
υ	wavenumber

Ligand Structures

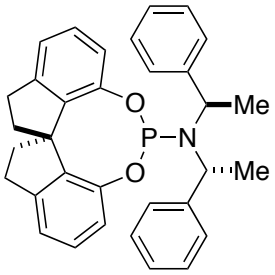
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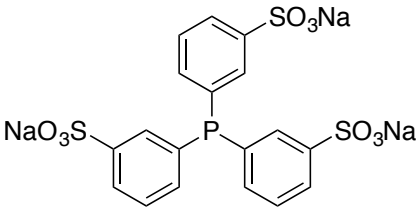
Phosphoramidite L1



XPhos



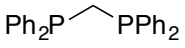
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TPPTS

Bisphosphine ligands

"PCP"-type ligands



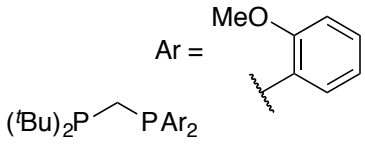
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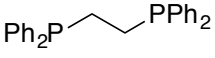


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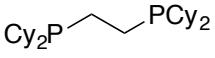


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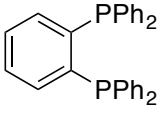
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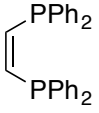
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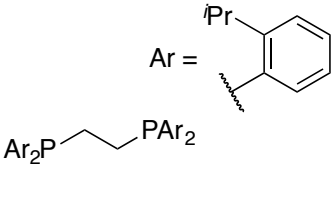
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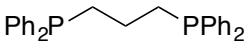


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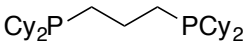


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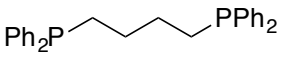
Other achiral bisphosphines



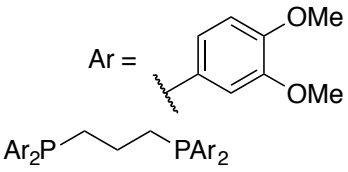
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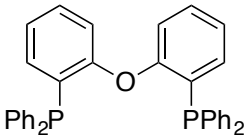
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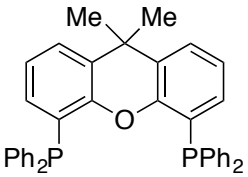
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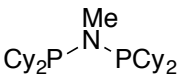
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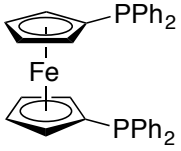
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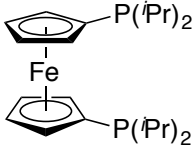
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PNP(Cy)

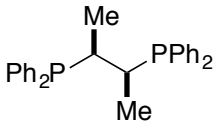


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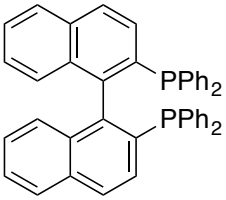


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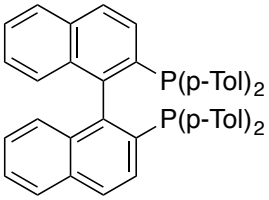
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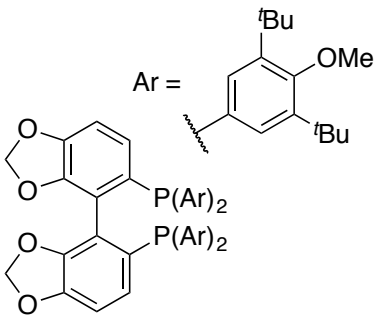
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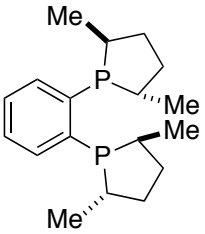
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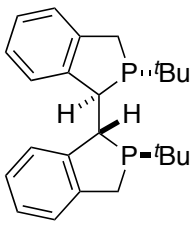
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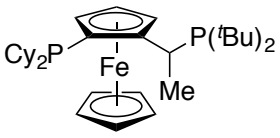
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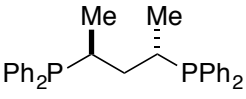
Me-DuPhos



DuanPhos

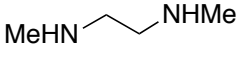


Josiphos SL-J009

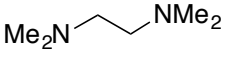


BDPP

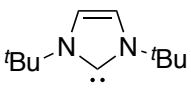
Other ligands



DMEDA



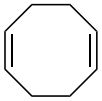
TMEDA



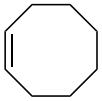
ItBu



nbd



cod



coe

Chapter 1

Introduction

The subject of this thesis is the use and development of rhodium-catalysed hydroacylation reactions and their application to the synthesis of heterocycles.

Hydroacylation brings together aldehydes and alkenes/alkynes for the synthesis of ketones and enones respectively (Figure 1.1), and has the potential to introduce chemical complexity in a 100% atom-economic manner. It is closely related to hydroformylation, which is one of the most important and heavily employed transition metal (TM)-catalysed processes in use globally, and which has been extensively researched and utilised in fields ranging from chemical manufacturing to late stage natural product synthesis.[1, 2] However, whilst there have been concerted efforts to develop and apply hydroacylation in many areas of synthesis, it has yet to enjoy the popularity of alternative TM-catalysed cross-coupling reactions (e.g. Suzuki-Miyaura or Heck reactions).

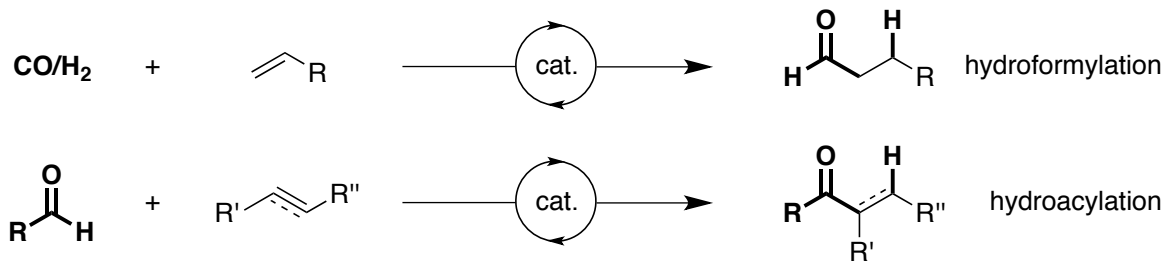


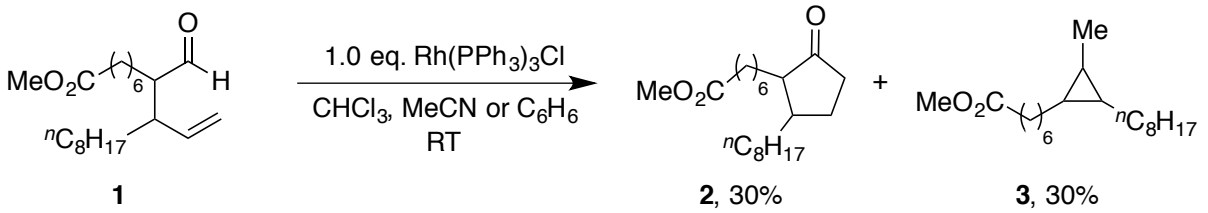
Figure 1.1 The hydroformylation and hydroacylation reactions

There exists a wide range of catalysts that can be used to effect hydroacylation, often based on late-TM complexes. Many such systems have been developed from previously existing decarbonylation catalysts, and the competition between hydroacylation and reductive decarbonylation remains a problem with many of these catalysts. For a more exhaustive summary of individual catalytic systems, a number of reviews on the subject have been published over the last 10 years.[3, 4, 5, 6]

This introductory chapter provides background and context for the work presented in later chapters. In the first section some of the key milestones in the development of highly selective and reactive catalyst systems for hydroacylation are summarised. The second section examines how the beneficial reactivity and selectivity observed in hydroacylation and other Rh(I) catalysed processes have been utilised in the synthesis of heterocycles to date.

1.1 The development of Rh-catalysed hydroacylation

Hydroacylation was first reported in 1972 by Sakai during studies towards the synthesis of prostanoids.[7] He observed that, when treated with Wilkinson's complex, a 4-pentenal-system **1** unexpectedly cyclised to form a mixture of cyclopentanone **2** and cyclopropane **3** (Scheme 1.1).



1 **2**, 30% **3**, 30%

Scheme 1.1 The initial discovery of hydroacylation by Sakai

Following this initial discovery, efforts were made to develop the process into a more efficient, catalytic reaction. However, issues arose due to competitive decarbonylation of the Rh-acyl-hydride intermediate **4** formed upon oxidative addition of the Rh into the aldehydic C-H bond (Figure 1.2).

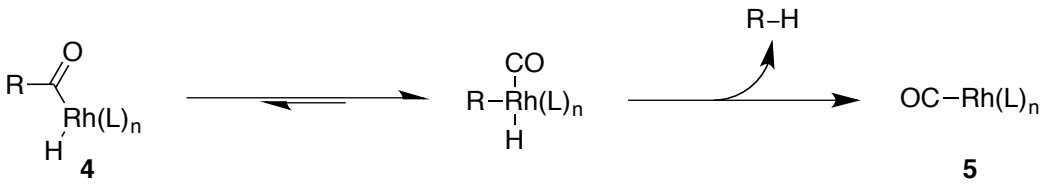
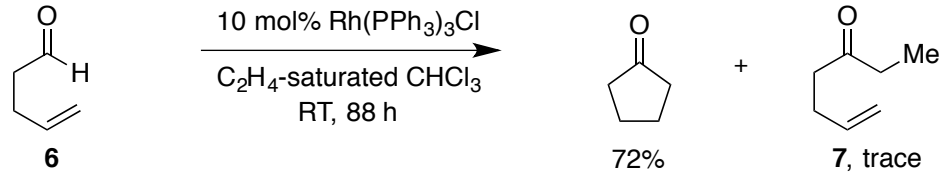


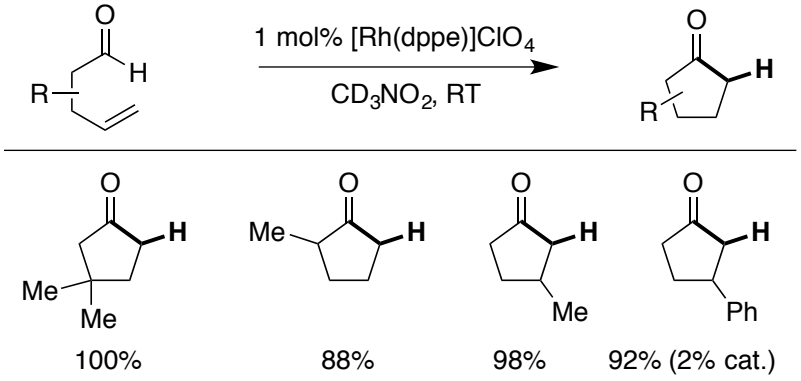
Figure 1.2 Mechanism of decarbonylation

In addition to contributing to decomposition of the starting material, decarbonylation also generates Rh-carbonyl complex **5**, which is completely inactive in hydroacylation, thus degrading the catalyst. The decarbonylation step is known to occur *via* migratory de-insertion of the alkyl chain to an empty binding site on the metal. In order to suppress decarbonylation, Miller saturated his reaction solvent with ethylene gas, which could reversibly bind to the Rh catalyst, blocking the required free site for migratory de-insertion (Scheme 1.2); by doing this he was able to employ catalytic amounts of Rh for the first time in the cyclisation of 4-pentenal **6**.[8] Serendipitously, his isolation of trace quantities of the product (**7**) of hydroacylative coupling between **6** and ethylene also hinted at the possibility of intermolecular hydroacylation.



Scheme 1.2 The use of ethylene saturated solvents in intramolecular hydroacylation

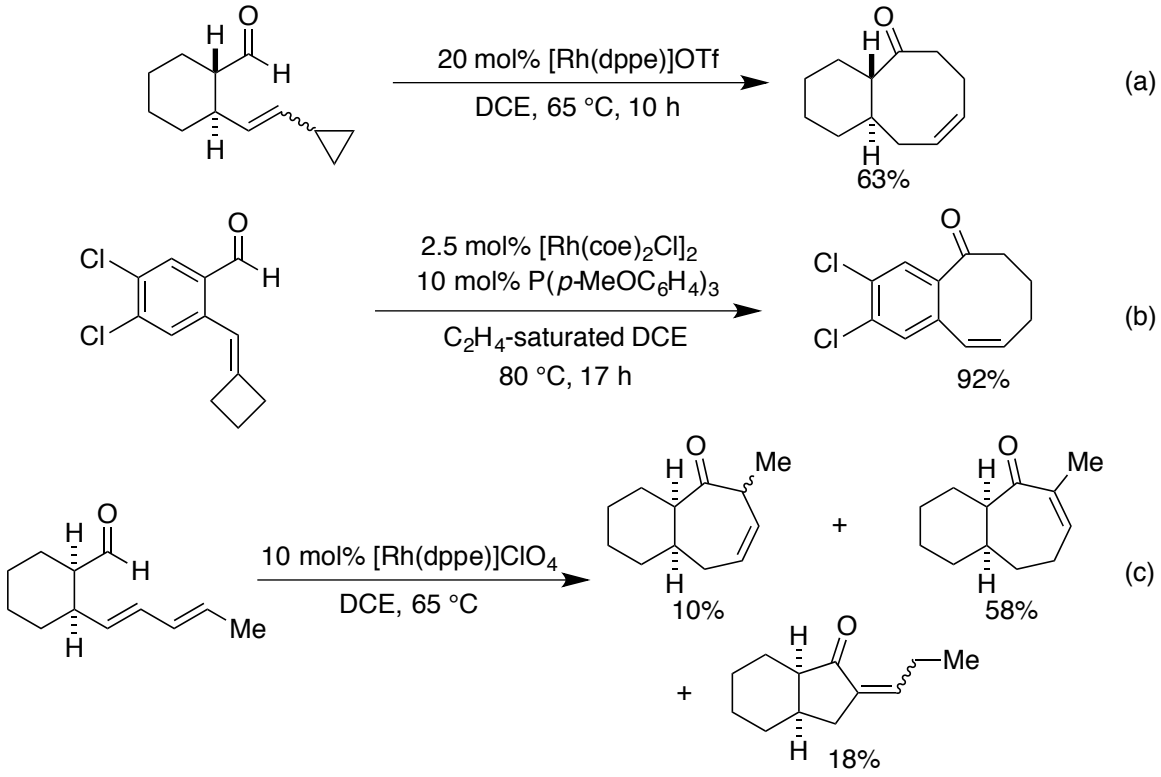
A significant breakthrough in achieving faster, more efficient catalysis came in 1988 with Bosnich's use of highly electrophilic rhodium bis-phosphine complexes (Scheme 1.3).[9, 10] Unlike the neutral rhodium chloride complexes, these high-activity cationic catalysts were able to achieve the cyclisation of 4-pentenal derivatives with loadings of just 1 mol% of Rh complex. As a consequence of this development, the majority of subsequent reports have used similar non-coordinating counteranions.



Scheme 1.3 Non-coordinating counteranions in intramolecular hydroacylation

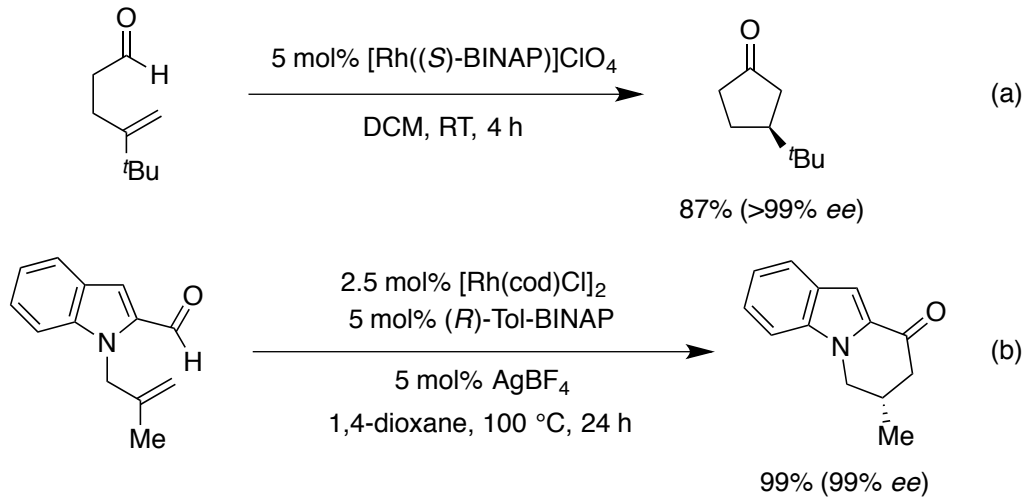
For many years, hydroacylation was limited to intramolecular cyclisations to form cyclopentanones, either through an *endo*-cyclisation of 4-pentenals, or *via exo*-cyclisation of 5-hexenals. In order to expand the utility of the process to the synthesis of medium rings, a number of rearrangement strategies have been developed. By employing either alkenyl cyclopropanes[11] or alkylidenecyclobutanes[12] (Scheme 1.4a and 1.4b) it was possible to synthesise eight-membered rings; alternatively seven-

membered rings could be accessed *via* a Rh-allyl complex generated upon intramolecular hydroacylation of diene substrates (Scheme 1.4c). [13, 14]



Scheme 1.4 Intramolecular hydroacylation for the synthesis of medium-sized rings

In 1992 Sakai demonstrated the first enantioselective hydroacylation reaction by using either enantiomer of BINAP to achieve moderate to high levels of enantiocontrol (Scheme 1.5a).[15] Shortly afterwards, Bosnich evaluated a number of chiral ligands, and found that BINAP, Chiraphos, and DuPhos all generated selective catalysts for certain substrates.[16, 17, 18] Numerous developments have been made towards expanding the scope of these reactions, in particular to enable the synthesis of six-membered rings *via* *endo*-selective hydroacylation (Scheme 1.5b).[19, 20]



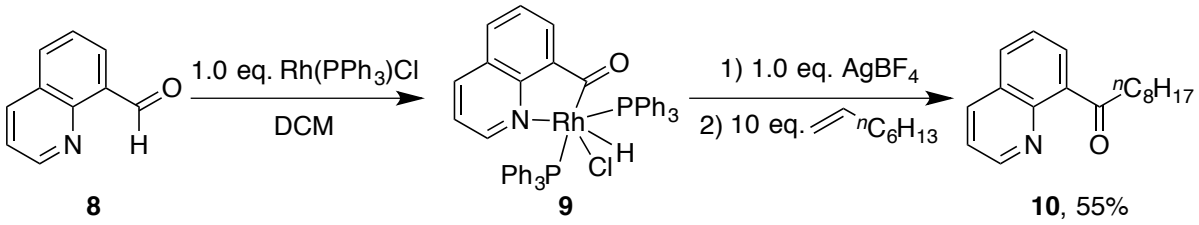
Scheme 1.5 Enantioselective intramolecular hydroacylation

Whilst great strides have been made towards efficient systems for intramolecular hydroacylation, intermolecular hydroacylation is a significantly more complex challenge, and to date there is no effective, broad reaching, general strategy for undertaking these reactions. In order to promote a 2nd order hydroacylative coupling over the 1st order decarbonylation process, various strategies to suppress decarbonylation have been developed.

1.1.1 The use of chelating aldehydes in inter- and intramolecular hydroacylation

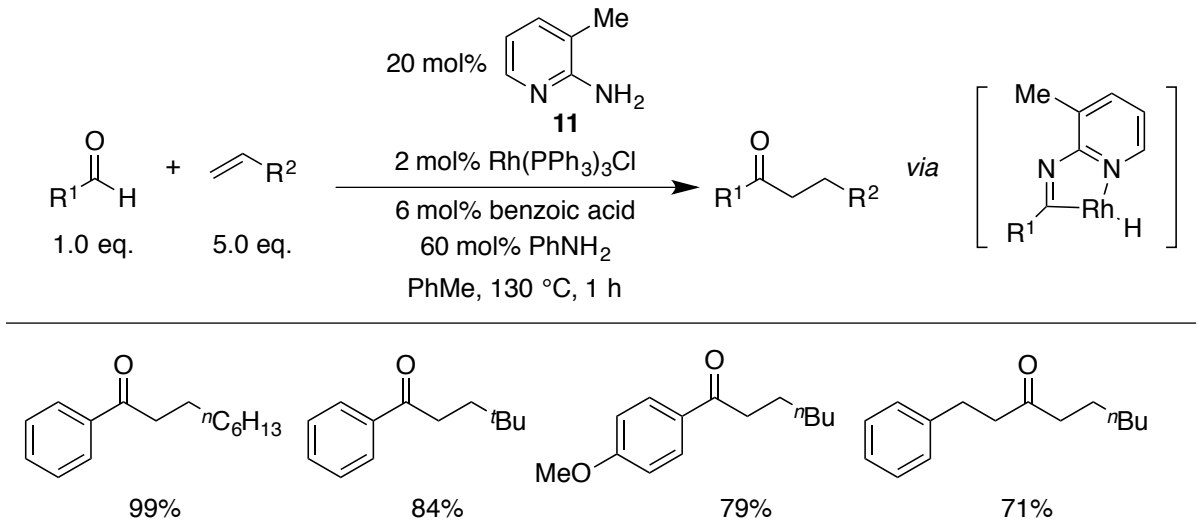
In 1978, Suggs demonstrated that by incorporation of a suitable chelating group within aldehyde starting material **8**, oxidative addition of stoichiometric quantities of Wilkinson's complex into the aldehydic C-H bond affords stable five-membered chelate **9** (Scheme 1.6).[21, 22] For decarbonylation and reductive elimination to occur, the complex had to be refluxed in xylene for four hours, demonstrating remarkable stability. Addition of $AgBF_4$ generated a coordinatively unsaturated complex by removal of the chloride ligand, allowing the complex to react with 1-octene to generate hydroacylation

product **10**. Further experiments with a $[Rh(coe)_2Cl]_2/P(OMe)_3$ catalyst system expanded the alkene scope, although any attempt to make the system catalytic had limited success.[23]



Scheme 1.6 8-Quinolinecarboxaldehyde **8** in intermolecular hydroacylation

Inspired by an approach developed by Suggs as an extension to his previously reported quinolinecarboxaldehyde work,[24] Jun has published extensively on the use of 2-amino-3-picoline **11** as a co-catalyst to generate a chelating imine *in situ*, allowing a wide range of tether-free products to be generated (Scheme 1.7).[25] This method has been subsequently used by a number of groups for a range of applications, and has been covered by a number of reviews.[4, 26]

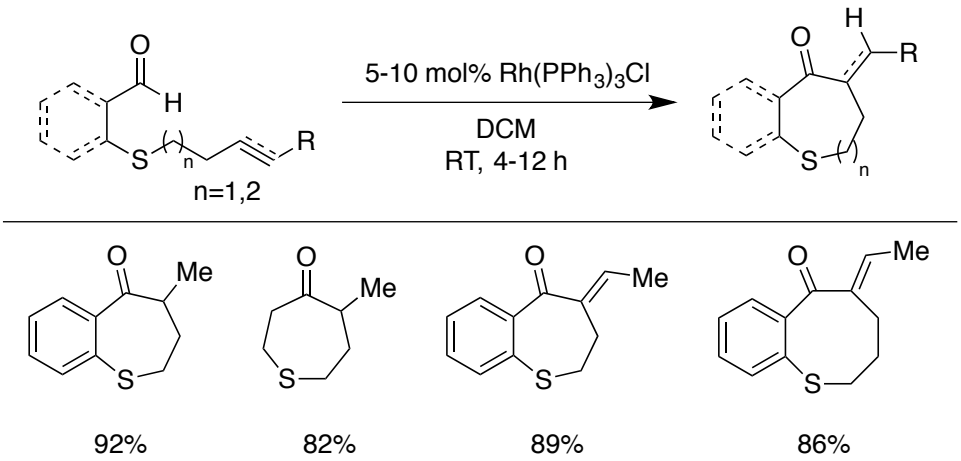


Scheme 1.7 Jun's use of a catalytic picoline tether for intermolecular hydroacylation

Interestingly in this system the neutral Wilkinson's catalyst outperformed Bosnich's cationic catalysts. ^{1}H- and ^{31}P-NMR spectroscopic analysis, coupled with DFT

computational work by Bo and Castillón, suggested that cationic catalysts added endothermically to the imine C-H bond, whereas neutral catalysts underwent an exothermic oxidative addition.[27]

In 2002 Bendorf extended the concept of chelation control to the synthesis of medium sized rings *via* intramolecular hydroacylation (Scheme 1.8).[28] Employing a sulfide tether, she was able to employ either alkenes or alkynes.



Scheme 1.8 Bendorf's use of *S*-tethers in intramolecular hydroacylation

In the absence of the sulfur-tether no reactivity was observed. Analogously to Suggs's quinoline system, the intermediate formed upon oxidative addition (**12**) is a stable five-membered chelate, where decarbonylation would proceed *via* a ring contraction to an energetically disfavoured four-membered chelate (**13**) (Figure 1.3).

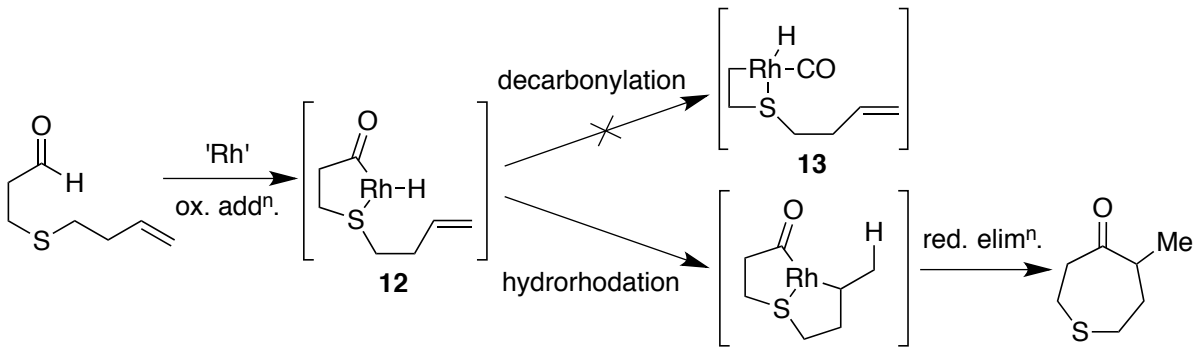
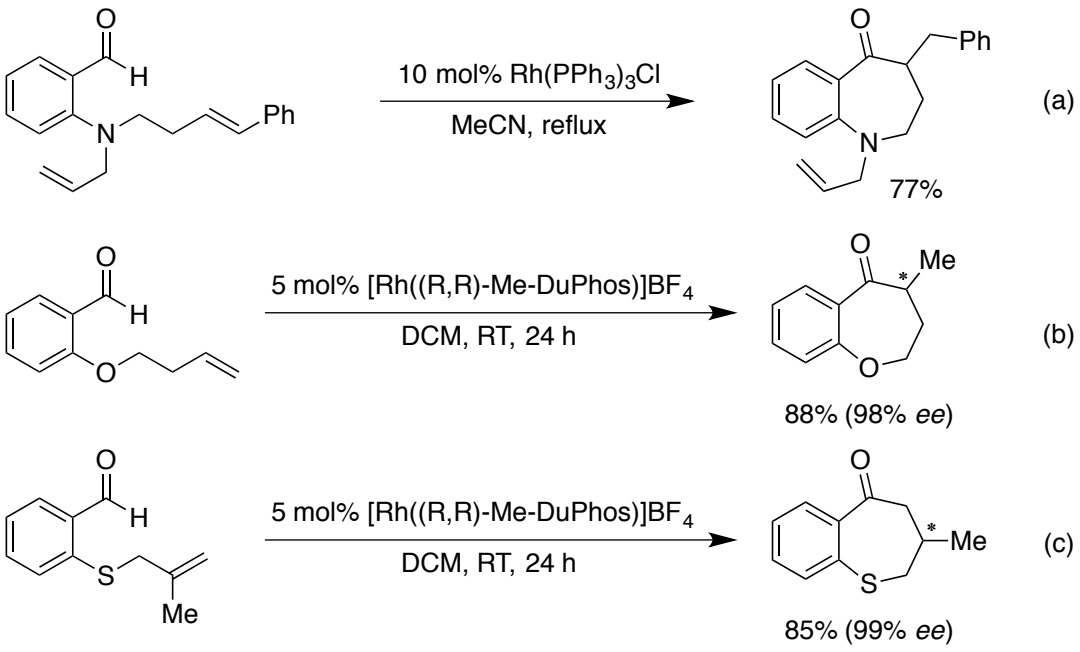


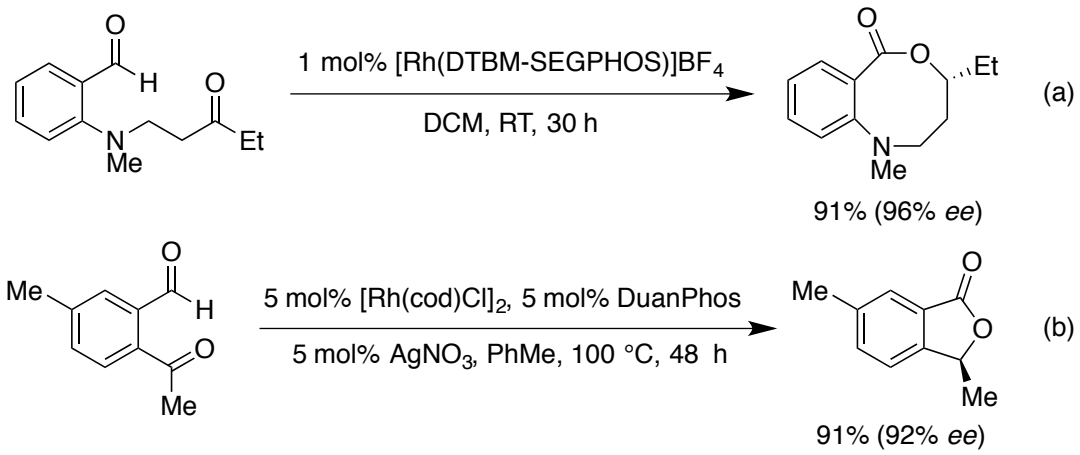
Figure 1.3 Suppression of decarbonylation *via* the use of a *S*-tether

A subsequent publication in 2012 expanded the scope to include *N*-tethers, forming *N*-allyl benzazepanone derivatives in an *exo*-selective fashion (Scheme 1.9a).[29] Interestingly, the identity of the pendant group on the *N*-tether seemed to have a strong effect on the reaction, with *N*-allyl substrates strongly outperforming *N*-methyl or *N*-benzyl, possibly inferring an extra coordinative effect. The Dong group have extended the concept to access enantioenriched α- or β-substituted medium rings by using chiral cationic rhodium-*bis*-phosphine complexes with the aid of either *O*- or *S*-tethers (Scheme 1.9b and 1.9c).[30]



Scheme 1.9 Alternative chelating heteroatoms and enantioselective intramolecular hydroacylation

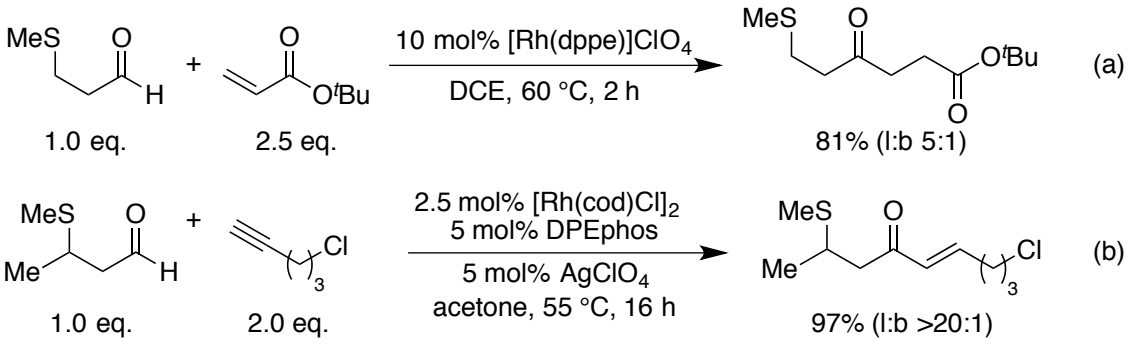
In related procedures, Dong has also shown that similar techniques can be applied to the synthesis of medium-sized lactones *via* carbonyl hydroacylation (Scheme 1.10a).[31, 32, 33] In the absence of a tether it was also possible to access phthalides (Scheme 1.10b),[34] analogously to the cyclopentanone/indanone syntheses found in Section 1.1.



Scheme 1.10 Intramolecular carbonyl hydroacylation

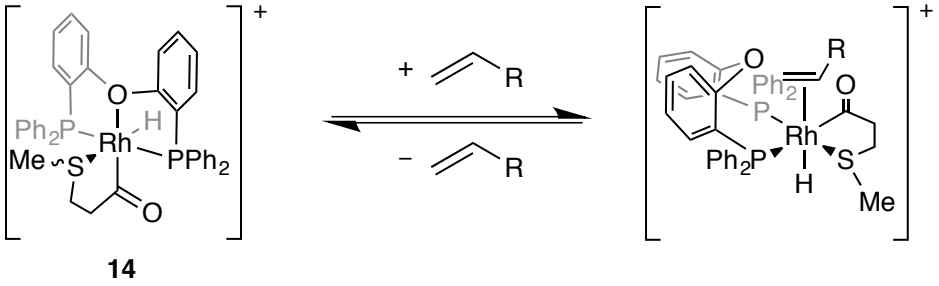
1.1.2 Ligand development with β-sulfur aldehydes

In 2004, Willis reported the first use of sulfur tethers in controlling intermolecular hydroacylation (Scheme 1.11a).[35] By reacting 3-(thiomethyl)propanal derivatives with a range of predominantly electron-deficient alkenes and alkynes he was able to synthesise ketones in moderate to good yields under mild reaction conditions. For this intermolecular hydroacylation, Bosnich-type cationic complexes were again found to be the most suitable, and afforded moderate to good linear:branched (l:b) regioselectivities.



Scheme 1.11 1st and 2nd generation ligands for *S*-directed intermolecular hydroacylation

In collaboration with Weller, work was undertaken in the rational design of new hydroacylation catalysts, and in 2006 a second-generation catalyst was reported (Scheme 1.11b).[36, 37] By utilising the hemilabile ligand DPEphos, they were able to stabilise the acyl-rhodium-hydride intermediate **14** with respect to decarbonylation. This effect is a result of the ability of the ether linkage in the ligand to reversibly coordinate to the rhodium centre, thereby blocking decarbonylation while allowing for less reactive alkene/alkyne substrates to bind and undergo hydroacylation (Figure 1.4).



14

Figure 1.4 Intermediate stabilisation by the hemilabile ligand DPEphos

This effect was confirmed by further mechanistic studies, in which not only was stabilised acyl-hydride complex **15** isolated and characterised, but also the vinyl intermediates (**16** and **17**) preceding reductive elimination.[38] By careful analysis and kinetic studies it was determined that the alkyne insertion was mildly linearly selective (approx. 2:1) and reversible, and that the majority of the linear selectivity with this ligand was due to the relative rates of the irreversible reductive elimination, as shown in the full catalytic cycle in Figure 1.5.

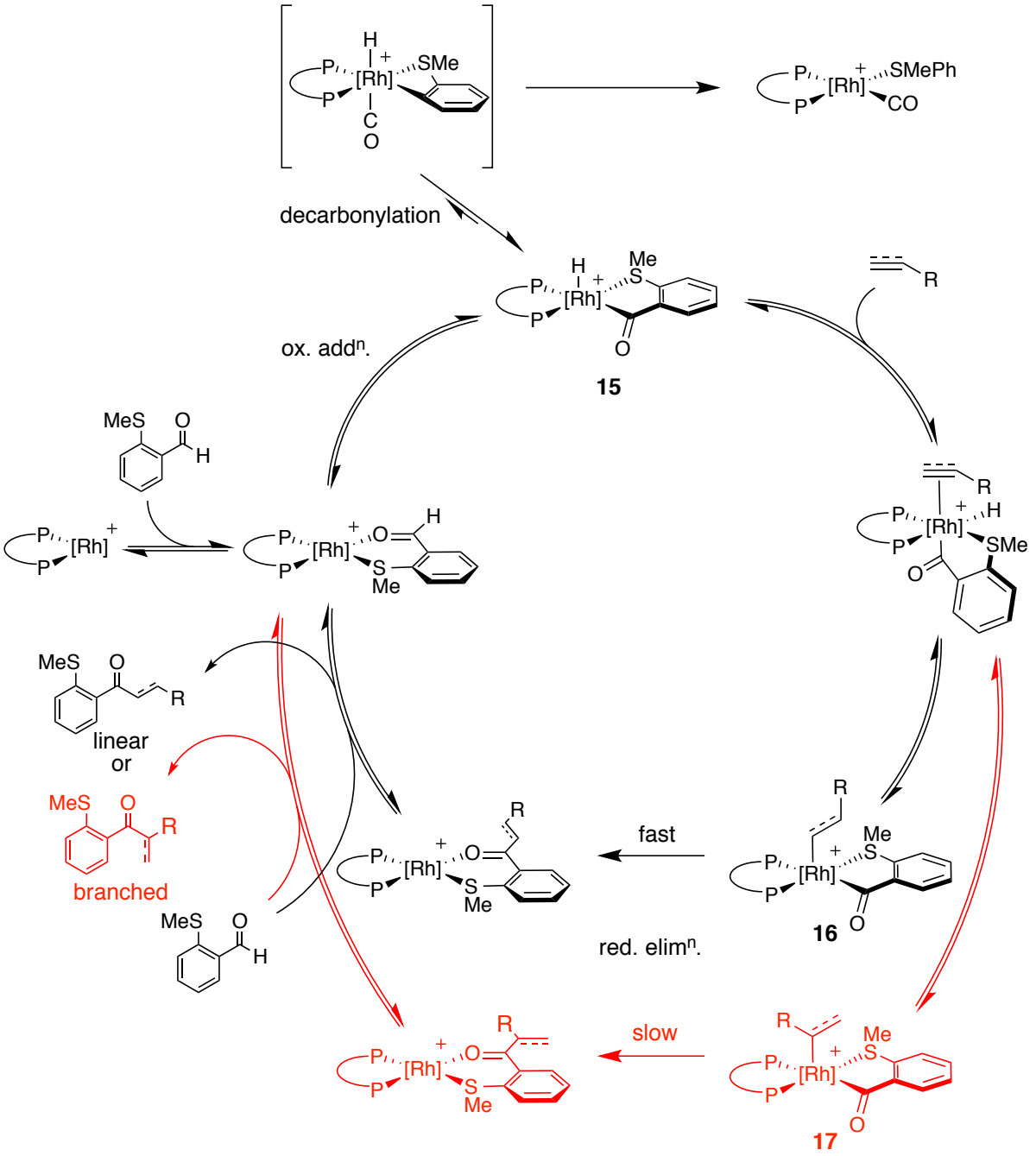
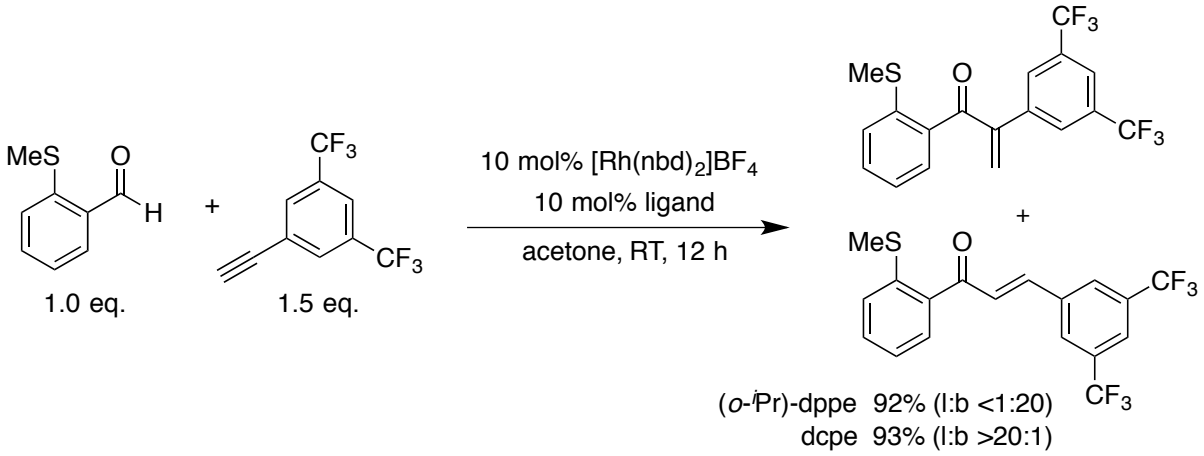


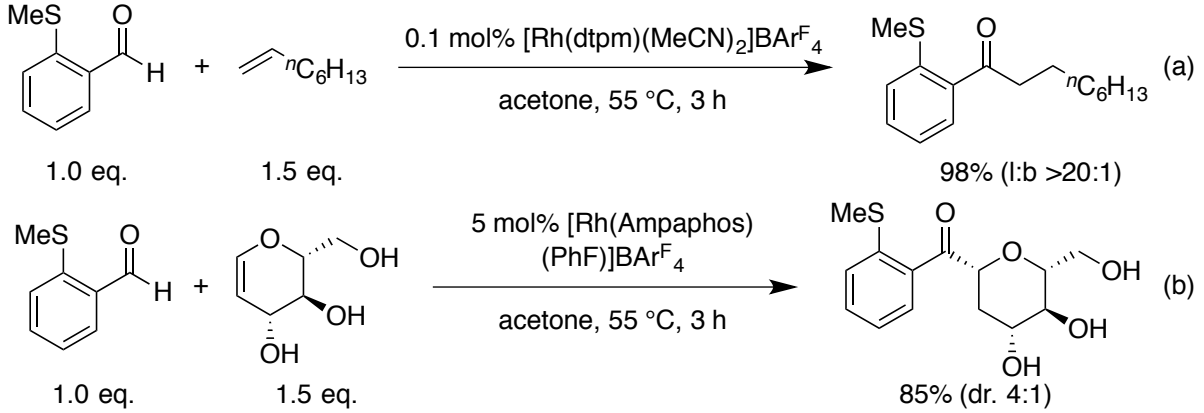
Figure 1.5 Full mechanism of Rh-catalysed, *S*-directed, linear-selective intermolecular hydroacylation

With this insight, it has been possible to design a branched-selective ligand that, due to steric constraints, will favour reductive elimination from branched vinyl intermediate **17**. When applied to hydroacylation, branched-selectivities of over 20:1 have been observed (Scheme 1.12).[39] Using the linear-selective dcpe ligand, full reversal of selectivity can be observed.[40]



Scheme 1.12 Ligand dependent selectivity in intermolecular alkyne hydroacylation

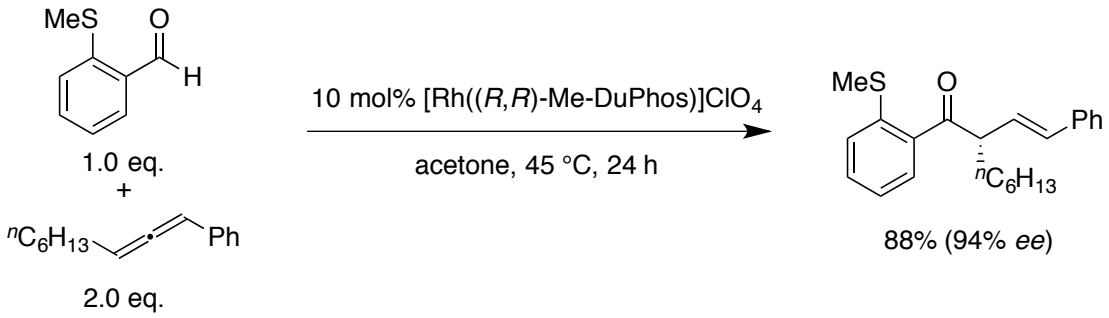
A further advancement was achieved in 2012 by utilising small-bite-angle "PCP"-type ligands (Scheme 1.13a).[41] The key to this system was not the stability of the intermediates to decarbonylation, but a drastically increased rate of reductive elimination, which is normally the rate-determining step in hydroacylation. In addition to greatly expanding the alkene/alkyne scope, reactions that had previously taken days using the second-generation DPEphos system, could now be achieved in hours or minutes, using extremely low catalyst loadings in excellent linear selectivity. This effect of bite-angle was explored further with the development of "PNP"-type ligands, with the decreased bite-angle effecting a noticeable increase in catalyst efficiency and more significantly, linear selectivity.[42]



Scheme 1.13 Small-bite-angle ligands in Rh-catalysed hydroacylation

By combining small-bite-angle "PCP" ligands with the concept of intermediate stabilisation *via* hemilabile coordination, further advances have recently been made in the development of highly active catalysts for the hydroacylation of previously unreactive internal alkenes (Scheme 1.13b).[43]

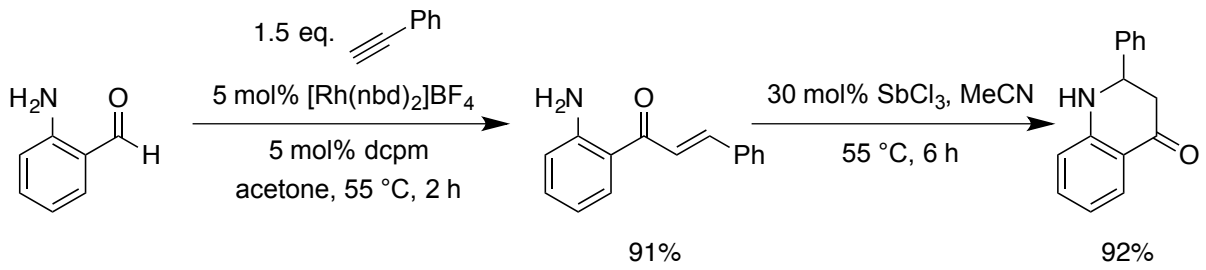
Sulfur based chelate systems have also been employed in enantioselective catalysis, with both the kinetic resolution of racemic allenes (Scheme 1.14),[44] and that of racemic aldehydes with alkynes reported.[45]



Scheme 1.14 Kinetic resolution through enantioselective allene hydroacylation

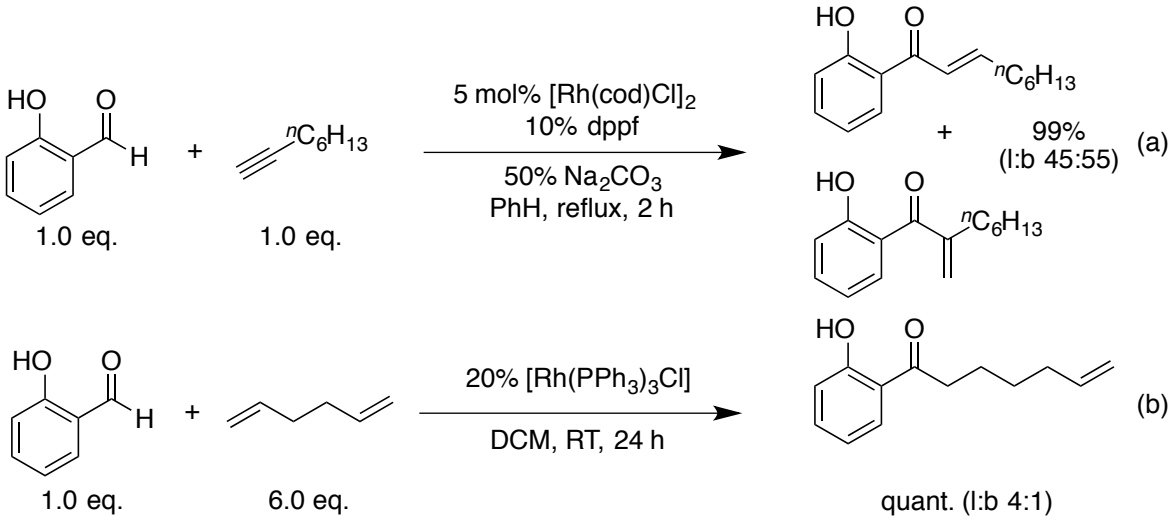
1.1.3 Alternative tethers for chelate-controlled hydroacylation

Alternatives to sulfur-directed hydroacylation have also been reported. Whilst the instability of β-amino-aldehydes to E1cB elimination is a major obstacle to the development of *N*-tethered alkyl aldehydes, in 2013 Willis demonstrated that, by using 2-aminobenzaldehyde derivatives, efficient hydroacylation could be achieved.[46] The resulting enones have been subsequently used in the synthesis of dihydroquinolone derivatives (Scheme 1.15). *N*-chelation has also been recently been used in a Rh(III) catalysed process that proceeds *via* initial metallation-deprotonation, rather than oxidative addition.[47]



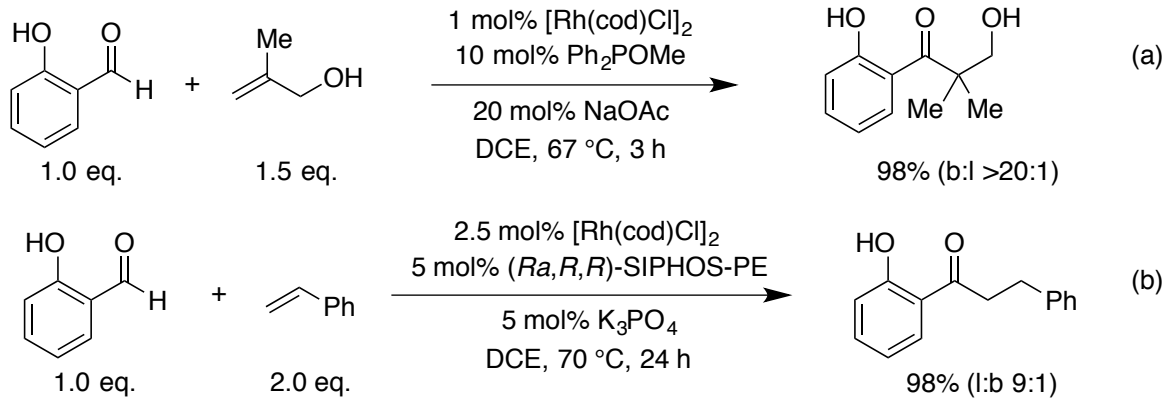
Scheme 1.15 *N*-chelation in intermolecular Rh-catalysed hydroacylation

As early as 1997, it was demonstrated by Miura that salicylaldehydes could be used as *O*-tethered aldehydes in hydroacylation reactions in good to excellent yields (Scheme 1.16a).[48, 49] The employed dppf system suffered from extremely low linear:branched selectivity, ranging from 1:1 to a maximum of 6:1 in a few isolated cases. For the use of symmetrical internal alkynes, this issue was no longer a problem, and the method remains a practical route for the synthesis of such products.[50] In the following years, a number of reports have been published on more selective hydroacylation systems, usually relying on a 'double chelation' strategy. In 2003 Suemune showed that, in combination with diene substrates, salicylaldehyde hydroacylation could be more selective (Scheme 1.16b).[51]



Scheme 1.16 Early *O*-directed intermolecular hydroacylation

More selective still were Dong's double-chelation systems using either alcohol or sulfide tethered alkenes, with high branched-selectivity observed in each case (Scheme 1.17a).[52, 53, 54] It was also shown that activated alkenes without chelating tethers, such as cyclopropenes can undergo enantioselective hydroacylation.[55] In 2012, Dong demonstrated that the use of a SIPHOS-phosphoramidite ligand enabled selective salicylaldehyde hydroacylation of a broad range of unactivated alkenes in a highly linearly selective manner (Scheme 1.17b), as exemplified by the synthesis of a number of octaketide natural products.[56]



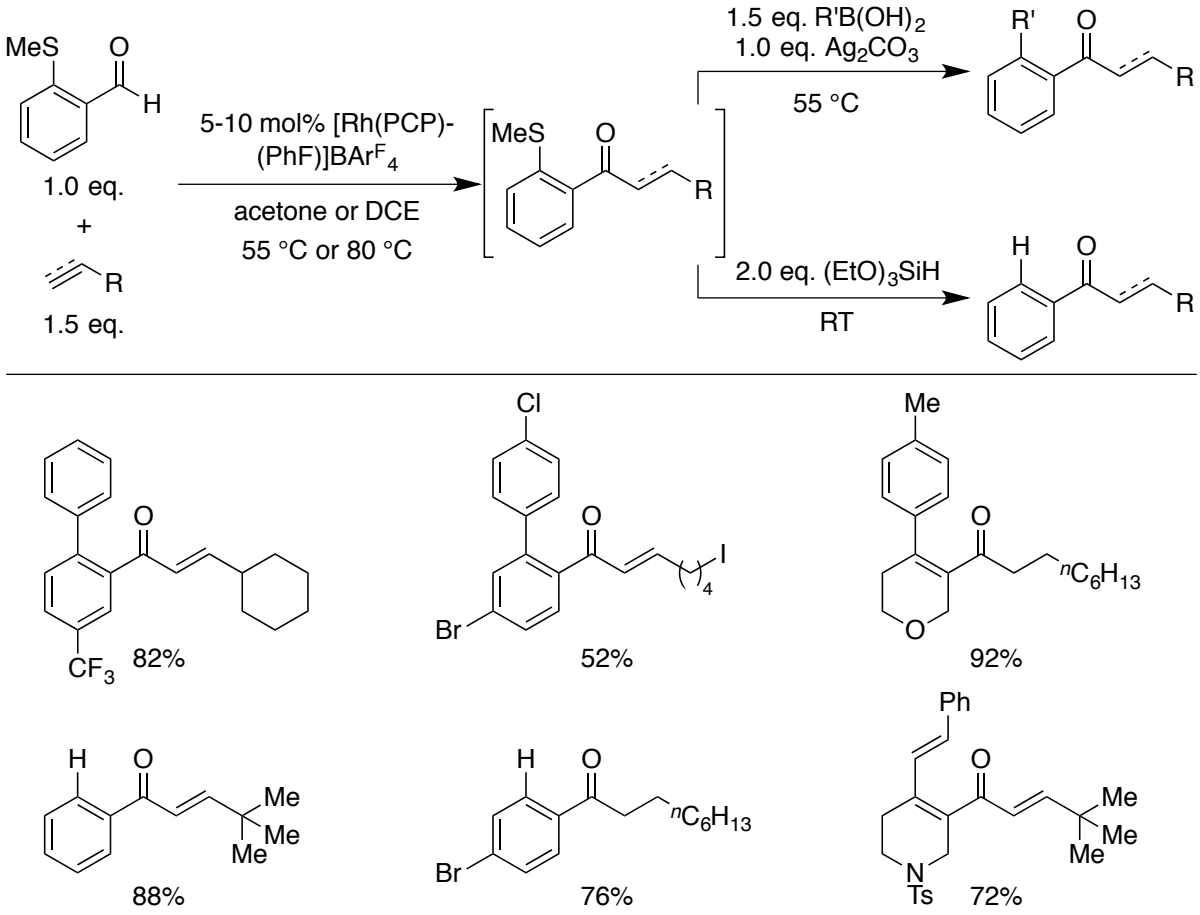
Scheme 1.17 Dong's salicylaldehyde based hydroacylation

Although the use of chelating systems such as those discussed in Sections 1.1.1-1.1.3 results in highly selective, efficient catalysis, the obvious drawback is the consequence that whichever tether is employed is necessarily incorporated in the final product.

1.1.4 Towards tetherless hydroacylation

Whilst not alleviating the requirement for a tether to effect hydroacylation, the Willis group have published a number of traceless-tether hydroacylation reactions *via* tandem hydroacylation-C-S functionalisation reactions, generating sulfide-free products.

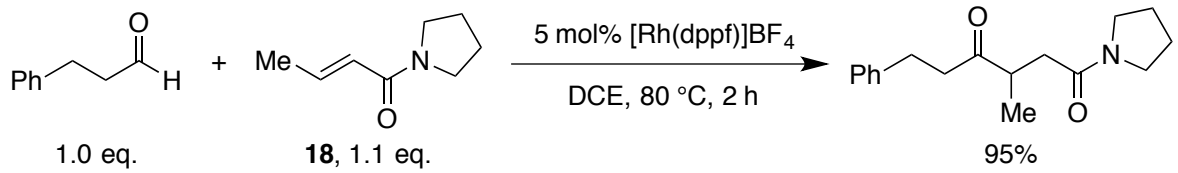
The same small-bite-angle catalyst systems that are so efficient at promoting *S*-directed hydroacylation, can also achieve carbonyl directed C-S activation. Reaction of this C-S activated rhodacycle with suitable coupling partners can result in carbothiolation, C-S reduction and Suzuki-type boronic acid coupling processes (Scheme 1.18).[57, 58, 59, 60]



Scheme 1.18 Tandem hydroacylation – C-S functionalisation reactions

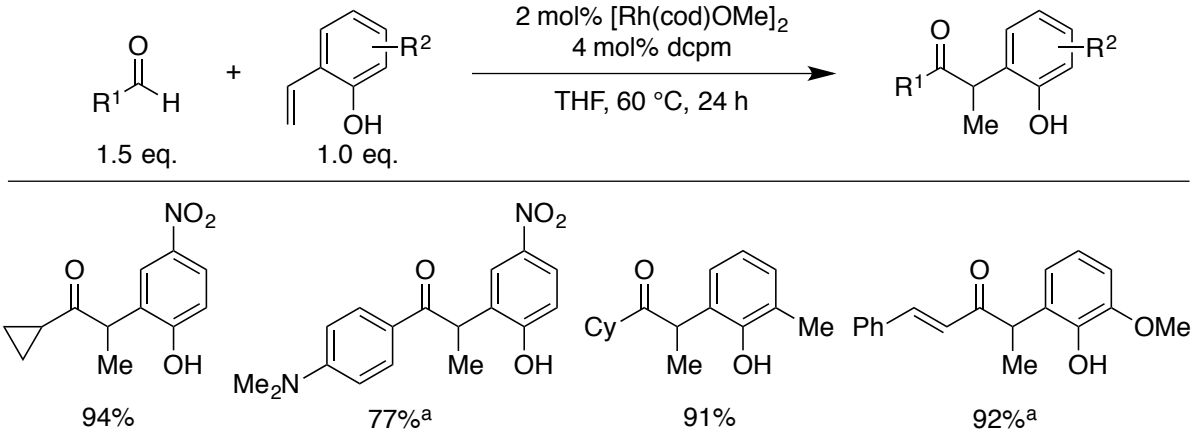
As mentioned in the previous section during the discussion on salicylaldehyde hydroacylation, chelating groups on the alkene/alkyne component can also have a strong influence on hydroacylation. An early demonstration of this can be found in a report by Tanaka in 2007 (Scheme 1.19).[61] The coordination of acrylamide **18** to the cationic rhodium complex can outcompete decarbonylation, allowing for efficient catalysis. It is, however, confined to a narrow range of alkenes, with the less powerfully

chelating acrylates showing a marked decrease in reactivity (55% yield, under more forceful conditions).



Scheme 1.19 Intermolecular acrylamide hydroacylation

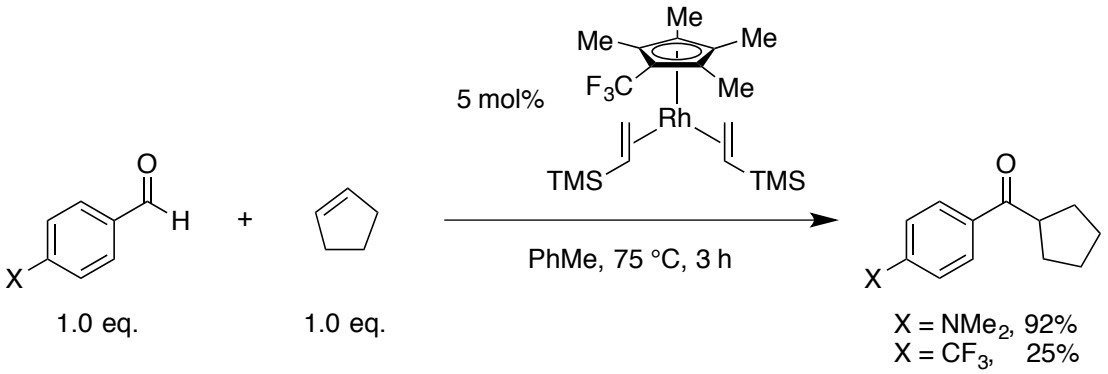
Expanding on her earlier use of alkene-based alcohol-directed branched selective hydroacylations with salicylaldehydes,[53, 54] Dong has shown that by using the high-activity, small-bite-angle ligands developed by Willis, hydroacylation of 2-vinylphenols can be achieved in the absence of chelation control on the aldehyde (Scheme 1.20).[62] In this case, the vinyl-phenolate is present as a ligand on the Rh-centre prior to the rate-determining oxidative addition, leading to efficient hydrometallation/reductive elimination, preventing decarbonylation.[63]



Scheme 1.20 Dong's alkene-based chelation-controlled hydroacylation

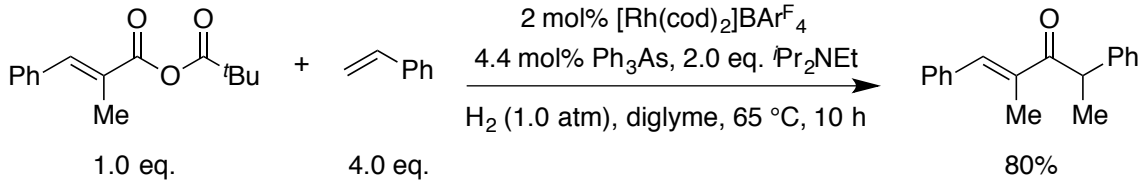
While the above examples rely on alkene-based chelation control rather than aldehyde-based, and are not truly tetherless, Brookhart has shown that in certain cases where the C-C bond to the carbonyl is especially strong, such as in electron-rich

benzaldehydes, an electron-poor Cp-based catalyst can promote efficient catalysis in a completely tetherless process (Scheme 1.21).[64] When treated under the same conditions, alkyl aldehydes undergo a rapid decarbonylation.



Scheme 1.21 Brookhart's tetherless hydroacylation

Taking inspiration from a preliminary study by Miura,[65] Krische has developed a conceptually unique method for generating hydroacylation-type products from symmetrical/mixed anhydrides and alkenes (Scheme 1.22).[66] Using an unusual triphenylarsine ligand, the mechanism involves oxidative addition of cationic Rh(I) to the anhydride to generate an acylrhodium(III) carboxylate.[67]



Scheme 1.22 Reductive hydroacylation from mixed acid anhydrides

Olefin insertion, followed by hydrogenolysis of the carboxylate ligand delivers an alkyl rhodium hydride, which can undergo reductive elimination to generate exclusively the branched hydroacylation product. The authors state that computational studies on similar systems suggest that hydrogenolysis occurs by way of a six-centred transition

state, explaining the superiority of anhydrides over acyl chlorides or fluorides (Figure 1.6).[68, 69, 70]

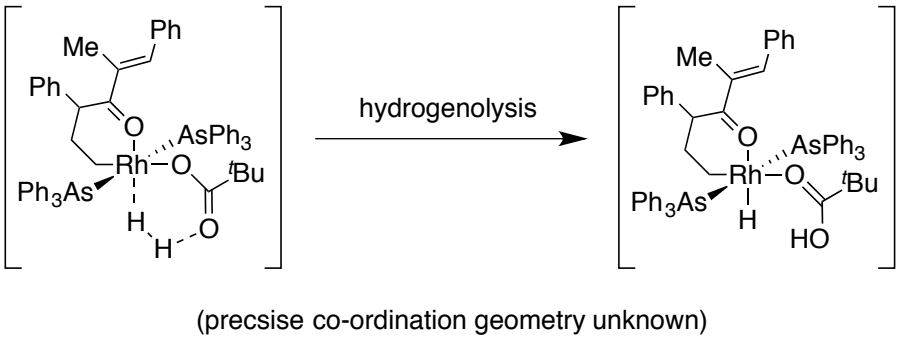
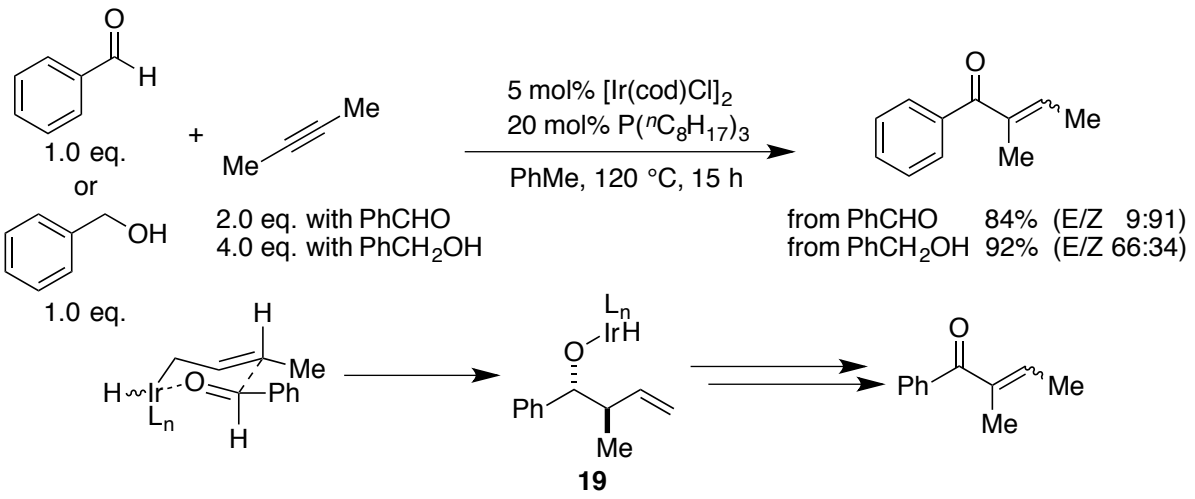


Figure 1.6 Six-membered transition state in Krische's reductive hydroacylation

Whilst the use of rhodium catalysts has provided the bulk of publications in the field, the inherent instability of rhodium-acyl-hydride species towards decarbonylation has fuelled the search for alternative hydroacylation catalysts.[5]

1.1.5 Alternatives to Rh-catalysed hydroacylation

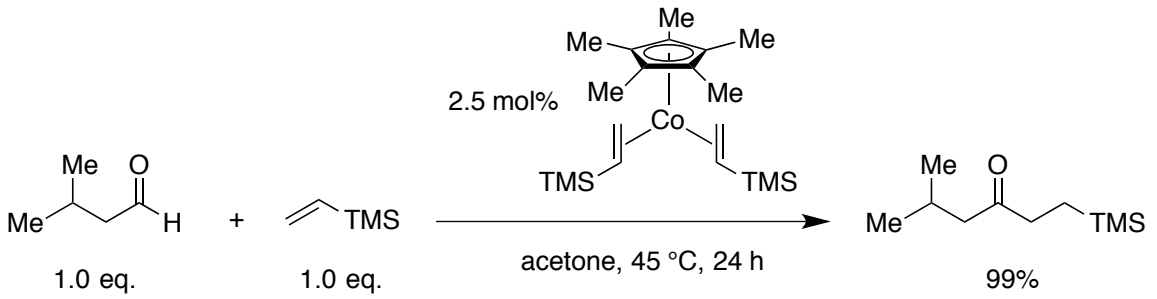
Iridium complexes, often seen as the obvious choices when seeking alternatives to rhodium, have been shown to be effective hydroacylation catalysts. Based on their earlier report of the synthesis of secondary allylic alcohols,[71] Obora and Ishii have demonstrated that alkyne hydroacylation can be achieved by utilising the "hydrogen borrowing" properties of iridium (Scheme 1.23).[72]



Scheme 1.23 Intermolecular iridium-catalysed alkyne hydroacylation

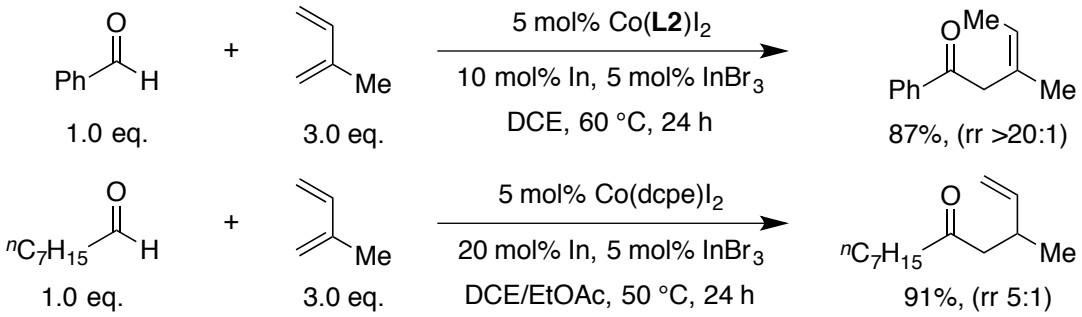
The active catalyst, an iridium dihydride complex is believed to undergo hydrometallation across the alkyne, with the resulting organoiridium compound adding to the aldehyde to afford alcohol intermediate **19**. Reduction/isomerisation of this intermediate then regenerates the active dihydride complex. It is notable that either an aldehyde, or the corresponding alcohol can be used as the initial starting material, and that by avoiding any acyl-metal-complexes, decarbonylation is no longer a potential problem. In a separate development, iridium catalysts have since been shown to effect salicylaldehyde hydroacylation in much the same manner as rhodium, although different selectivities can be observed.[73]

Cobalt, another group IX metal, has potential as a cheaper alternative to rhodium catalysis. Until recently the only reported cobalt mediated hydroacylation was by Brookhart in 1997 involving the use of a cyclopentadienyl-cobalt complex (Scheme 1.24).[74, 75] Although efficient, this system was restricted to the use of vinyl silanes as the coupling partner.



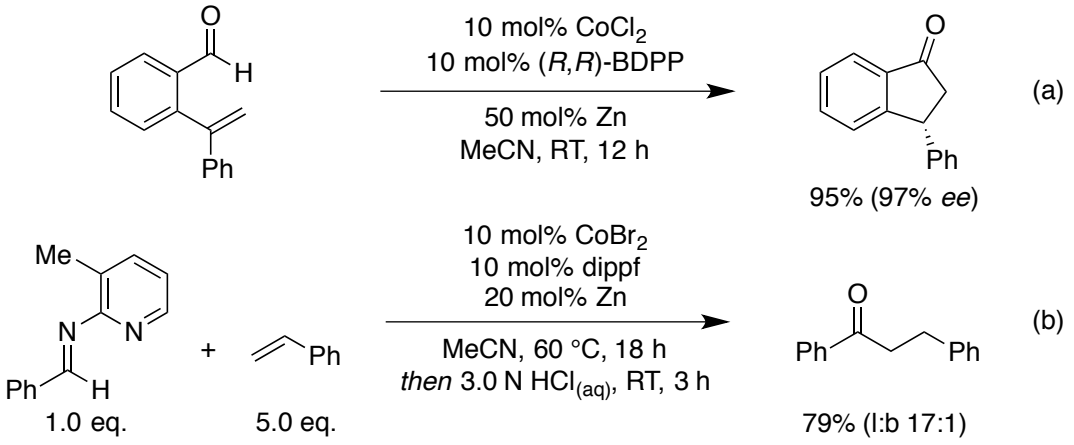
Scheme 1.24 Brookhart's cobalt-catalysed hydroacylation of vinyl silanes

In recent years, however, there has been a renaissance in the development of cobalt-catalysed hydroacylation processes. In 2014, Dong reported that cobalt-bisphosphine complexes can catalyse the hydroacylation of 1,3-dienes (Scheme 1.25).[76] In this report, they propose an oxidative [4+2+1] cyclisation to generate an allyl-alkoxide-bound cobalt centre. β-Hydride elimination, followed by reductive elimination can then generate either the product of formal 1,2-hydroacylation or 1,4-hydroacylation. The authors report that selectivity for the former was observed when alkyl aldehydes are employed, whereas the latter is formed in excellent selectivity when combined with aryl aldehydes.



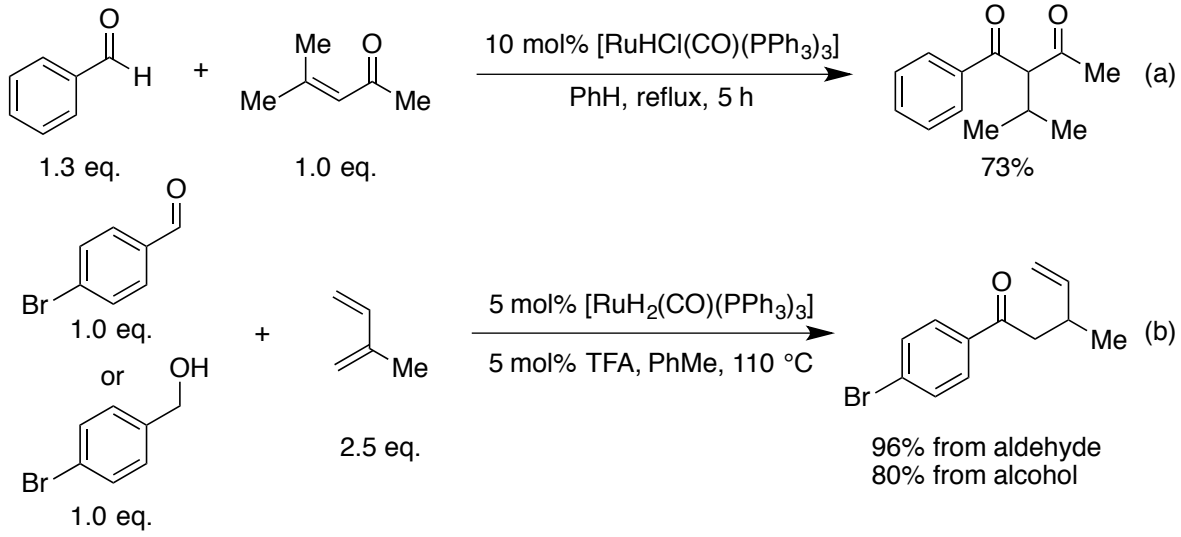
Scheme 1.25 Dong's cobalt-catalysed diene hydroacylation

There have also been several recent reports by Yoshikai (Scheme 1.26) in which he manages to replicate previously reported Rh-catalysed reactions using cobalt, such as the enantioselective intramolecular formation of phthalides and indanones,[77] as well as using Jun's picolyl imine directing groups for intermolecular hydroacylation.[78]



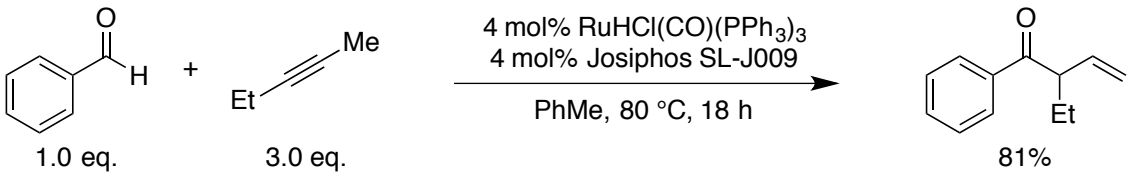
Scheme 1.26 Yoshikai's cobalt hydroacylation systems

Ruthenium-catalysed hydroacylation has also been reported, usually for specific alkene classes. In a mechanism similar to the previously mentioned iridium chemistry by Obora and Ishii,[72] ruthenium hydride complexes can mediate the hydroacylation of either electron-deficient alkenes (Scheme 1.27a),[79] dienes (Scheme 1.27b),[80, 81, 82] or alkynes,[83] *via* stabilised organoruthenium intermediates. Alternatively Ru/CeO_2 combined with Xantphos can react analogously to the previously discussed Rh-bisphosphine systems in alkyne hydroacylation.[84]



Scheme 1.27 Ruthenium in intermolecular hydroacylation

Dong has published an intermolecular hydroacylation of methylalkynes that also proceeds through hydroruthenation processes, generating β,γ-unsaturated ketones (Scheme 1.28).[85] This ruthenium catalyst first mediates a double bond migration to form a terminal allene, before reacting in the same manner as the previously discussed Ru-hydroacylations.



Scheme 1.28 Dong's regioselective hydroacylation/isomerisation process

Although the earliest example of nickel-catalysed hydroacylation, proceeding through a cycloaddition mechanism similar to Dong's cobalt system, was reported in 1990 by Saegusa,[86] it was many years before the subject generated significant interest. The majority of reports invoke a [2+2+1] cycloaddition between the nickel, aldehyde and alkene/alkyne, generating five-membered nickelacycle **20**. β-Hydride elimination, followed by reductive elimination affords hydroacylation product **21** (Figure 1.7).

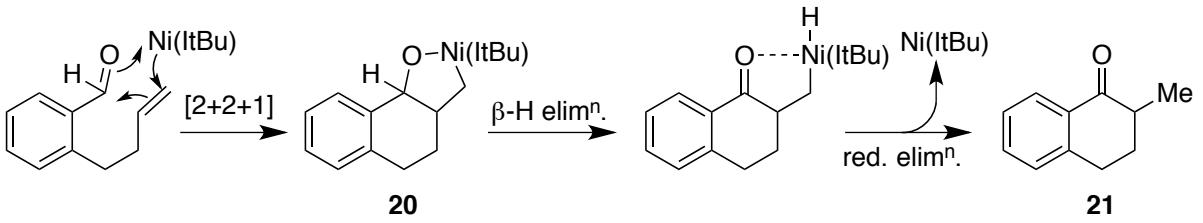
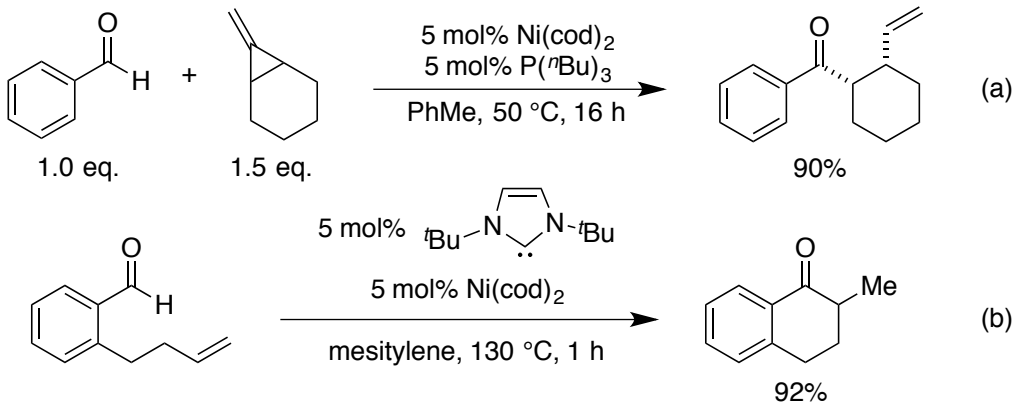


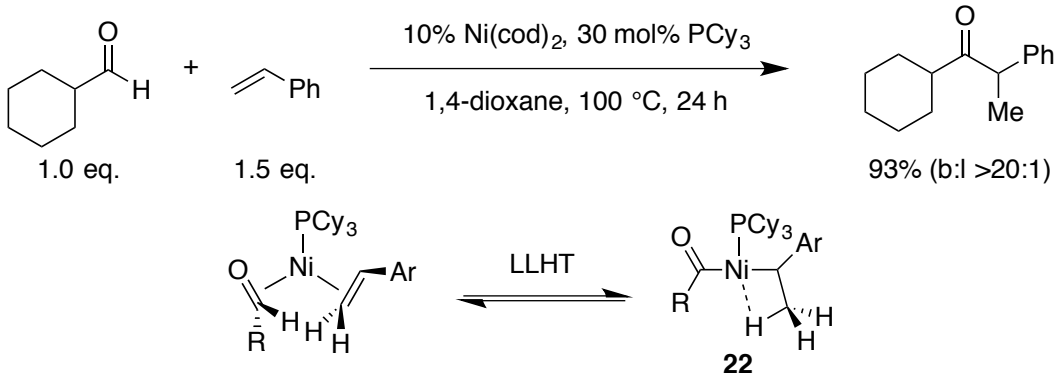
Figure 1.7 Mechanism of Ni-NHC catalysed hydroacylation

This transformation can be achieved either with monophosphine ligands, [87, 88, 89] or with Ni-NHC complexes (Scheme 1.29). [90, 91]



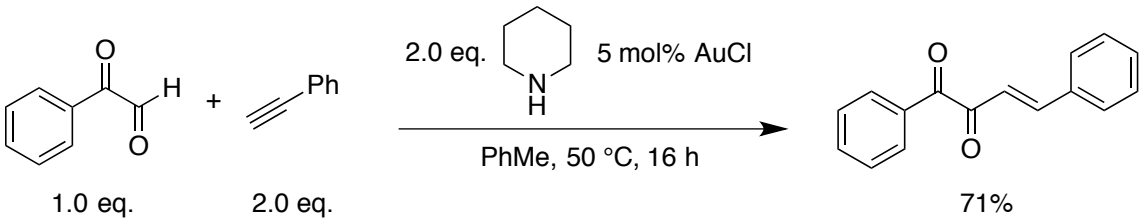
Scheme 1.29 Ni-catalysts in hydroacylation

A new hydroacylation mechanism, supported by DFT calculations, has recently been proposed by Xu and Zhou.[92] In their publication detailing branched selective hydroacylation of styrenes (Scheme 1.30), they invoke a ligand-to-ligand hydrogen transfer (LLHT), which generates acyl-alkyl complex **22** directly, rather than through the intermediacy of an acyl-hydride complex. The use of styrenes as reaction partners helps to prevent decarbonylation at this stage.



Scheme 1.30 Xu and Zhou's LLHT-based intermolecular hydroacylation of styrenes

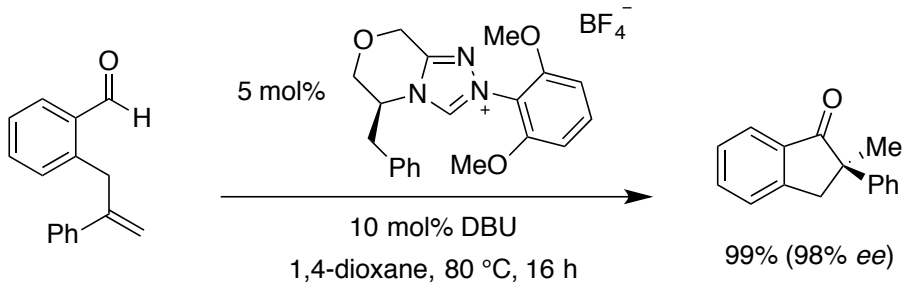
Group XI metals have also been shown to catalyse hydroacylation, with a report on Cu-catalysed hydroacylation by Chen,[93] and an Au-catalysed method by Hashmi[94] (Scheme 1.31) both emerging in 2014. Both employing glyoxal starting materials, these reactions proceed *via* acetylide addition to an activated iminium, followed by hydrolysis/tautomerisation of the resulting propargylic amines to enones.



Scheme 1.31 Hashmi's Au-catalysed hydroacylation

First reported in 1973, the Stetter reaction constituted the first organocatalysed formal hydroacylation,[95] with many reviews having been published on the topic.[96, 97, 98, 99, 100] Whilst highly efficient, enantioselective processes have been developed, extending the process beyond the use of α,β-unsaturated carbonyl systems is a key goal in organocatalytic hydroacylation.[101]

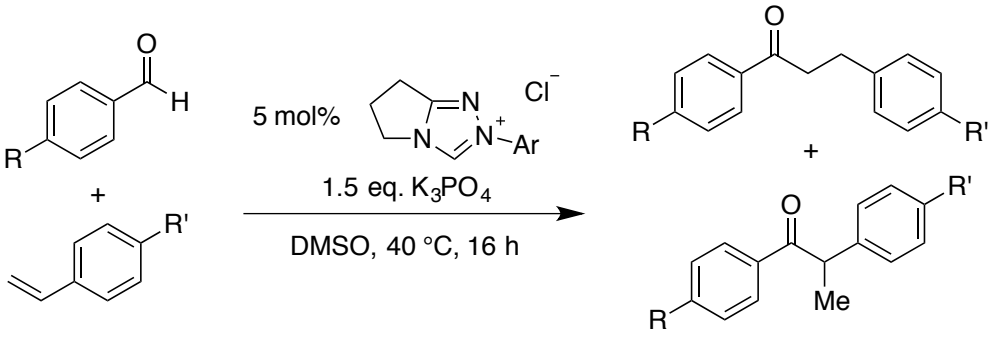
Reported by She in 2006, the first intramolecular system focused on the use of enol ethers as reaction partners.[102, 103] Glorius then extended this to unactivated olefins with a number of reports published.[104, 105, 106, 107, 108] These cover both alkene and alkyne hydroacylation, and robustness screens have been used to test compatibility with a wide range of functional groups. A chiral NHC-catalyst was used in the synthesis of enantioenriched indanones (Scheme 1.32).[108]



Scheme 1.32 Chiral NHC-catalysed intramolecular hydroacylation

Attempts to extend these catalysts to intermolecular hydroacylation have proven successful, with the hydroacylation of arynes,[109] cyclopropenes,[110, 111] and styrenes[112]

reported to date. In the case of styrene hydroacylation, the regioselectivity is determined by the electron density of the coupling partners (Scheme 1.33).



a) R = Me, R' = CN aldehyde:alkene 1.5:1.0 47% (l:b >20:1)
b) R = CF_3, R' = ^{t}Bu aldehyde:alkene 1.0:11.0 42% (l:b <1:20)

Scheme 1.33 Glorius's intermolecular NHC-catalysed styrene hydroacylation

As has been shown, there are a number of alternatives to Rh-catalysed hydroacylation, with strengths and drawbacks associated with each. None of the examples has yet matched the wide reaction scope or mild conditions enjoyed by Rh-catalysed reactions, although by invoking a variety of reaction mechanisms decarbonylation can be attenuated without recourse to chelation-control.

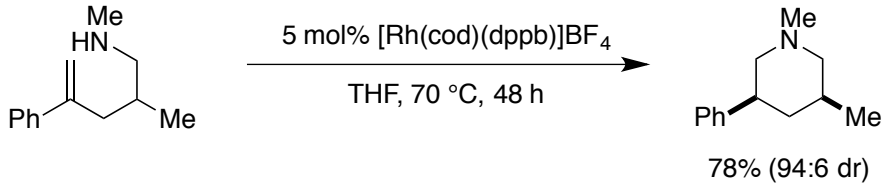
1.2 Rh(I) catalysis in heterocycle synthesis

Rhodium(I) catalysis, as exemplified by hydroacylation in the previous section, is characterised by diverse reactivity, high selectivities and efficient reactions. Such traits show huge potential for application in a number of fields, including heterocycle synthesis. Classical heterocycle syntheses typically involve high temperatures and forcing conditions to reach the thermodynamic products. In the modern age it is often necessary to introduce heterocycles to late-stage intermediates in long syntheses, and also to be able to access highly substituted heterocycles with functional group handles for further derivatisation. This section will summarise briefly the major applications of

Rh(I)-catalysed reactions to the *de novo* synthesis of heterocycles, recently reviewed by Willis.[113] For a more general overview of TM-catalysed heterocycle synthesis, a number of reviews are also available.[114, 115]

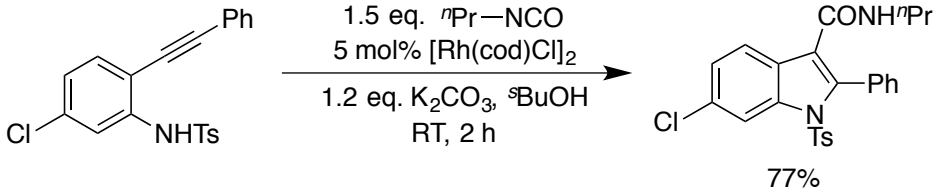
1.2.1 Cycloisomerisation

One of the most conceptually simple transformations for heterocycle formation is the addition of nucleophiles to unactivated alkenes and alkynes. Intramolecular hydroamination and hydroalkoxylation reactions have been used to form a number of small ring systems, for example Hartwig's piperidine synthesis in Scheme 1.34.[116]



Scheme 1.34 Rh-catalysed intramolecular alkene hydroamination

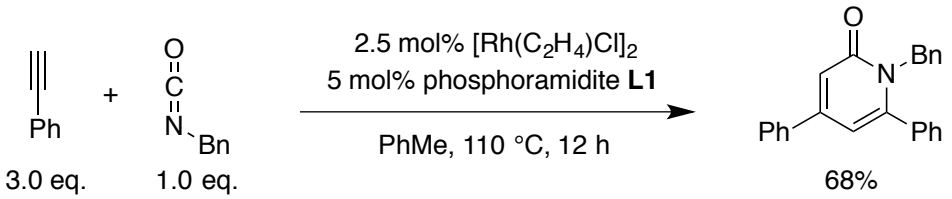
Although this type of reaction can be effected by a number of transition metals, the use of rhodium can allow for the development of tandem catalytic processes. An example of this tactic can be found in a number of indole and benzofuran syntheses from 2-alkynylanilines and phenols respectively,[117, 118, 119] as shown in Scheme 1.35.[120] In these reactions a C(3)-rhodated heteroaromatic intermediate can be trapped by a number of electrophiles.



Scheme 1.35 Domino synthesis of 2,3-disubstituted indoles

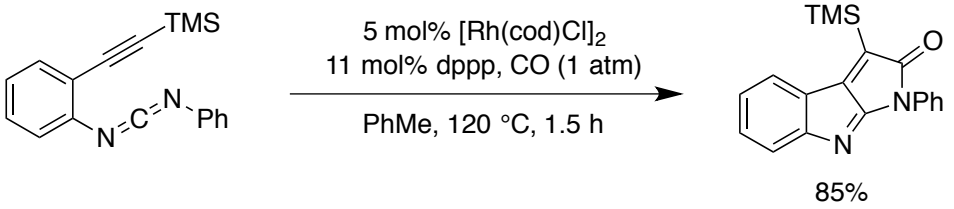
1.2.2 Cycloaddition

Another key application of Rh(I) catalysis is in the field of cyclotrimerisation. While this reaction is most commonly used for the construction of carbocyclic compounds *via* the extensively studied alkyne trimerisation, replacement of one of the alkyne components with a nitrile, isocyanate or similar π-system can generate a range of pyridines, pyridones (Scheme 1.36) and thionopyranimines, which have been summarised in a review by Tanaka.[121] These cross-cyclotrimerisations typically suffer from low regioselectivity, although methods to combat this have been developed.



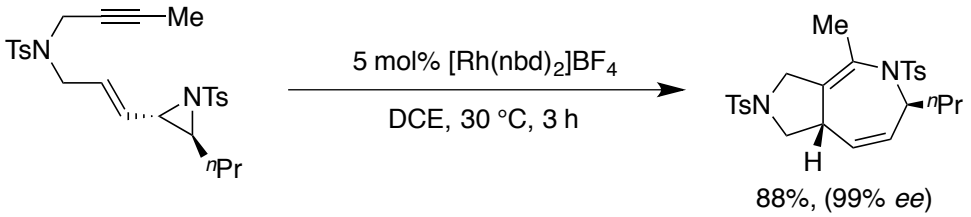
Scheme 1.36 Pyridone synthesis *via* [2+2+2] cross-cyclotrimerisation

Another well-known cycloaddition that has been adapted for heterocycle synthesis is the Pauson-Khand [2+2+1] carbonylation reaction. The first example involved the use of carbodiimides as alkene equivalents (Scheme 1.37),[122] with a number of follow-up reports subsequently published.[123, 124, 125]



Scheme 1.37 [2+2+1] Pausson-Khand reaction applied to heterocycle synthesis

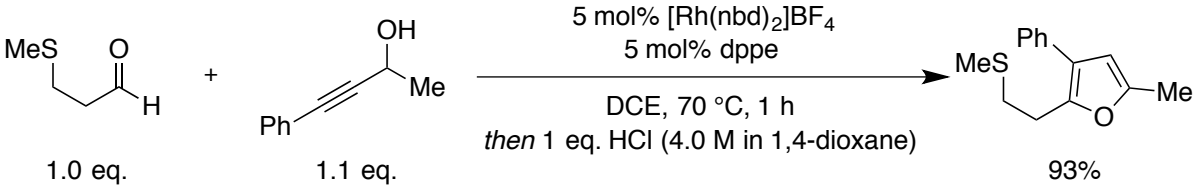
Heterocycle forming [5+2] cycloadditions can also occur, with the key vinylcyclopropane moiety replaced with either a vinyl aziridine[126, 127] as shown in Scheme 1.38,[128] or a cyclopropyl imine.[129]



Scheme 1.38 [5+2] cycloaddition of vinyl aziridines

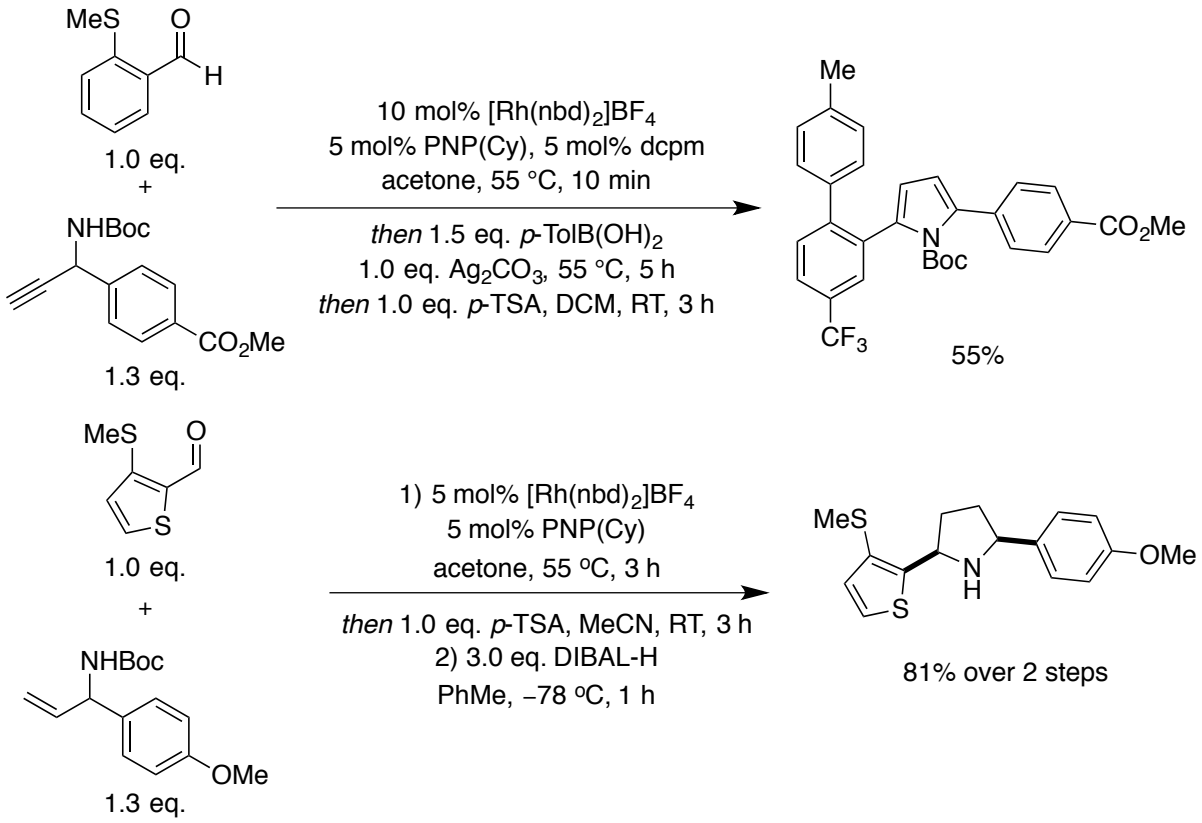
1.2.3 Hydroacylation

Many of the previously detailed chelation-controlled intramolecular hydroacylations generate heterocycles (Schemes 1.8-1.10).[28, 29, 30, 31, 32, 33, 34, 130] We have additionally seen that the chelating tethers involved in intermolecular processes can then be incorporated into heterocycles such as dihydroquinolines (Scheme 1.15)[46] and benzofurans (Scheme 1.20).[62, 63] Willis has targeted a number of key heterocycle precursors by reaction of β-*S*-aldehydes with appropriate alkynes and alkenes. In 2011, a furan synthesis based on the hydroacylation of propargyl alcohols generated a range of di- and tri-substituted products (Scheme 1.39).[131]



Scheme 1.39 Willis's hydroacylation approach to highly substituted furans

Propargylic amines have since been shown to be effective substrates for the synthesis of *N*-Boc pyrroles (Scheme 1.40).[132]



Scheme 1.40 Synthesis of pyrroles, pyrrolines and pyrrolidines via Rh-catalysed hydroacylation

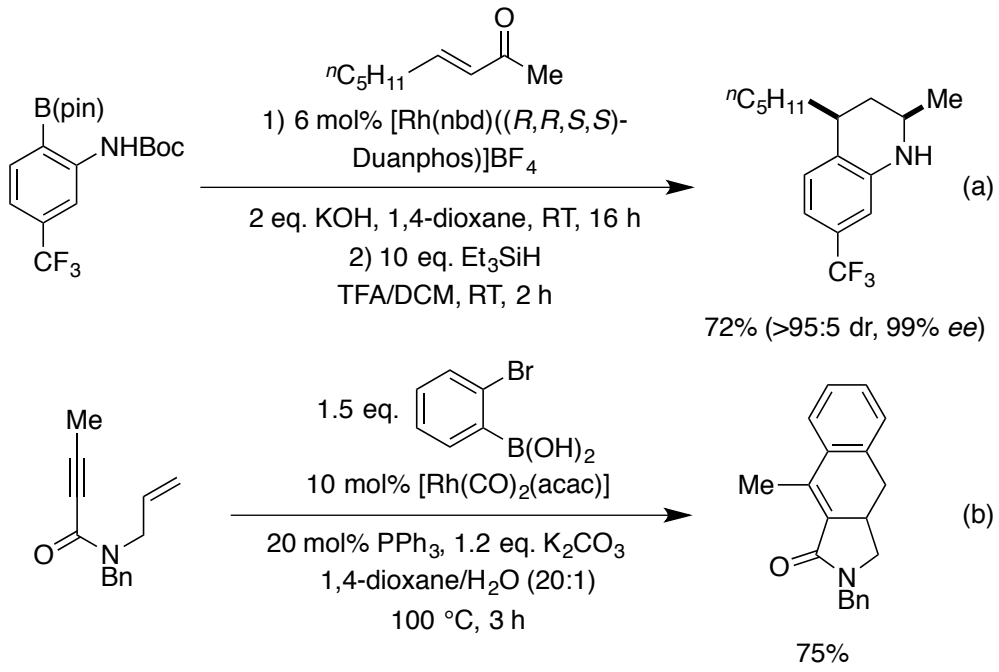
The use of the highly linear-selective PNP(Cy) ligand was required to overcome an initial regioselectivity problem. In the same paper, the synthesis of pyrrolines and pyrrolidines is also discussed.

1.2.4 Hydroarylation

The addition of organometallics across alkenes and alkynes is one of the oldest and most enduring areas of transition metal catalysis. Rhodium(I) complexes have been shown to be highly effective at promoting the reaction of boronic acids with alkenes, alkynes and other π-systems with efficient catalysis and often high enantioselectivity.

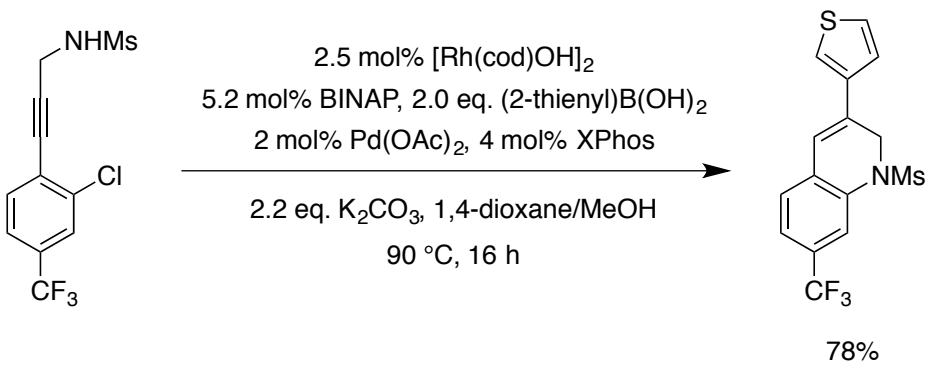
A number of cascade processes that result in heterocycle formation are known, including those in which the hydroarylation forms an intermediate that cyclises under the reaction conditions without the influence of the rhodium catalyst (Scheme 1.41a), or

alternatively the carbometallated intermediate can continue to undergo further domino steps as exemplified in Scheme 1.41b. In Scheme 1.41a the initial reaction generates a dihydroquinoline that can then be reduced in a diastereoselective manner in the second step.



Scheme 1.41 Rh-catalysed hydroarylation in heterocycle synthesis

As well as the cascade processes mentioned above, a number of dual-catalytic systems have been developed by Lautens (e.g. Scheme 1.42), in which the products of Rh-catalysed hydroarylation can be cyclised by Pd-cross coupling reactions.

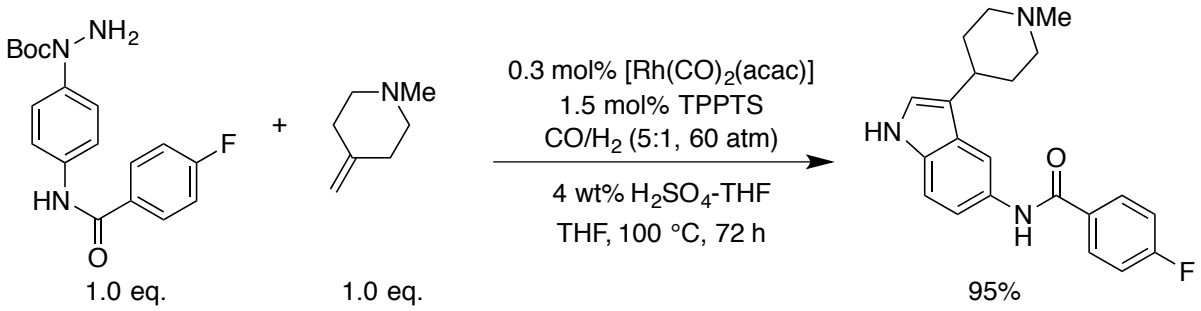


Scheme 1.42 Multicatalytic approach to functionalised heterocycles

1.2.5 Miscellaneous

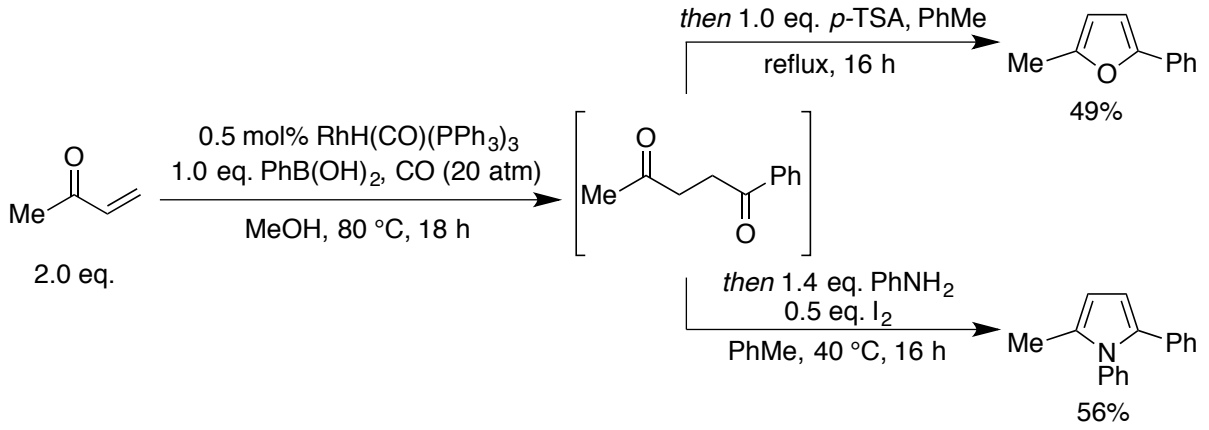
Whilst cycloisomerisation, cycloaddition, hydroacylation and hydroarylation dominate the field of Rh(I)-catalysed heterocycle synthesis, there are many other reactions that could be considered. As mentioned previously, hydroformylation is one of the cornerstones of the petrochemical and fine chemical industries.[2] A number of multicomponent tandem and one-pot hydroformylation reactions have been developed, including a number of heterocycle syntheses.[133]

Eilbracht has used the slow release of aldehydes *via* hydroformylation to overcome the previous requirement for high dilution conditions to prevent aldehyde dimerisation in the Fischer indole synthesis.[134] A number of pharmaceutically relevant indoles have been synthesised in this manner (Scheme 1.43).[135]



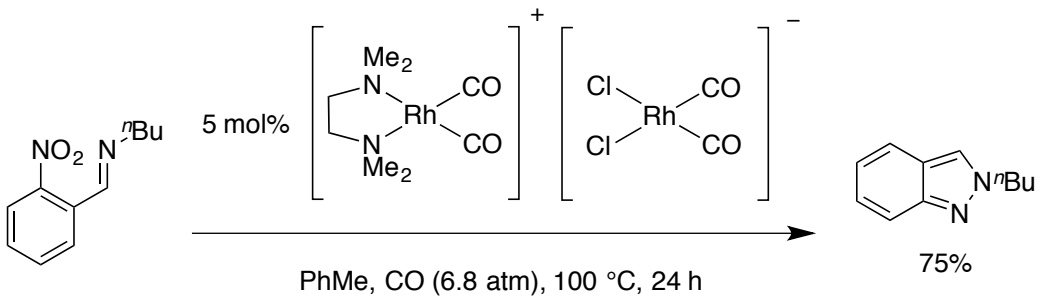
Scheme 1.43 Rh-catalysed hydroformylation-Fischer indole synthesis protocol

The vast majority of classical heterocycle precursors include one or more carbonyl groups, which often undergo dehydrative transformations. As shown in Scheme 1.44,[136] Rh-carbonylation chemistry, coupled with the addition of boronic acid derivatives is a popular method for constructing such substrates.



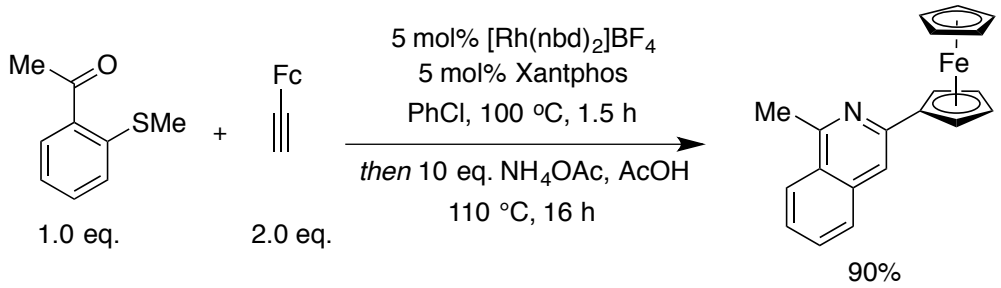
Scheme 1.44 Carbonylative couplings for the synthesis of 1,4-dicarbonyl heterocycle precursors

Carbonylation conditions have also been shown to effect reductive cyclisations, with unusual ionic Rh-diamine catalysts employed in the synthesis of indoles[137] and indazoles (Scheme 1.45). [138]



Scheme 1.45 Indazole formation via reductive cyclisation

As previously mentioned (see Section 1.1.5) Willis has developed a number of carbonyl-directed C-S functionalisation reactions. The earliest of these, alkyne carbothiolation, has been applied to the synthesis of isoquinolines, with a range of substitution well tolerated, as demonstrated by the ferrocenyl group in Scheme 1.46.[57]



Scheme 1.46 Willis's carbothiolation route to isoquinolines

1.3 Summary

Developments in hydroacylation over the last 10 years have provided a range of attractive transformations that benefit from mild conditions, high selectivity and broad functional group tolerance. The main approach to achieving this is through the use of tethers to suppress deleterious carbonylation, a major side reaction in Rh-catalysed hydroacylation. Some efforts have been made to mitigate this limitation, either by expanding the range of tethers available, developing the selective removal of the tether after the hydroacylation reaction, or by utilising other metals with different mechanisms; however chelate-controlled hydroacylation remains the most effective transformation for generating molecular complexity in a single step, or one-pot sequence. The ability of such Rh-catalysed hydroacylation reactions to synthesise a range of heterocycles is still underexplored, and provides a fertile field for further research. Attempts to broaden this approach will form the body of this thesis.

Chapter 2

Intermolecular Rh-catalysed hydroacylation routes to heterocycle synthesis

2.1 Introduction

As demonstrated in Section 1.2, the use of Rh(I) catalysis has been shown to be a practical, if underdeveloped, route to the synthesis of heterocycle precursors. Classical heterocycle syntheses often revolve around the cyclisation of dicarbonyl units, forming a variety of five- and six-membered heterocycles, as summarised in Figure 2.1. Classical syntheses such as the Debus-Radziszewski imidazole synthesis,[139, 140] the Paal-Knorr syntheses of furans, pyrroles and thiophenes,[141, 142] and the Knorr pyrazole synthesis[143] have been used since the 19th century as reliable methods of heterocycle construction.

In addition to simple saturated dicarbonyls, a number of related precursors have more recently been employed. In 2000, while undertaking mechanistic studies on the synthesis of cyclopropanes using phosphonium ylides and 1,2-dioxines, Taylor observed that γ-hydroxy-α,β-enones (**23**) readily cyclised under either acidic or neutral conditions to afford furans.[144]

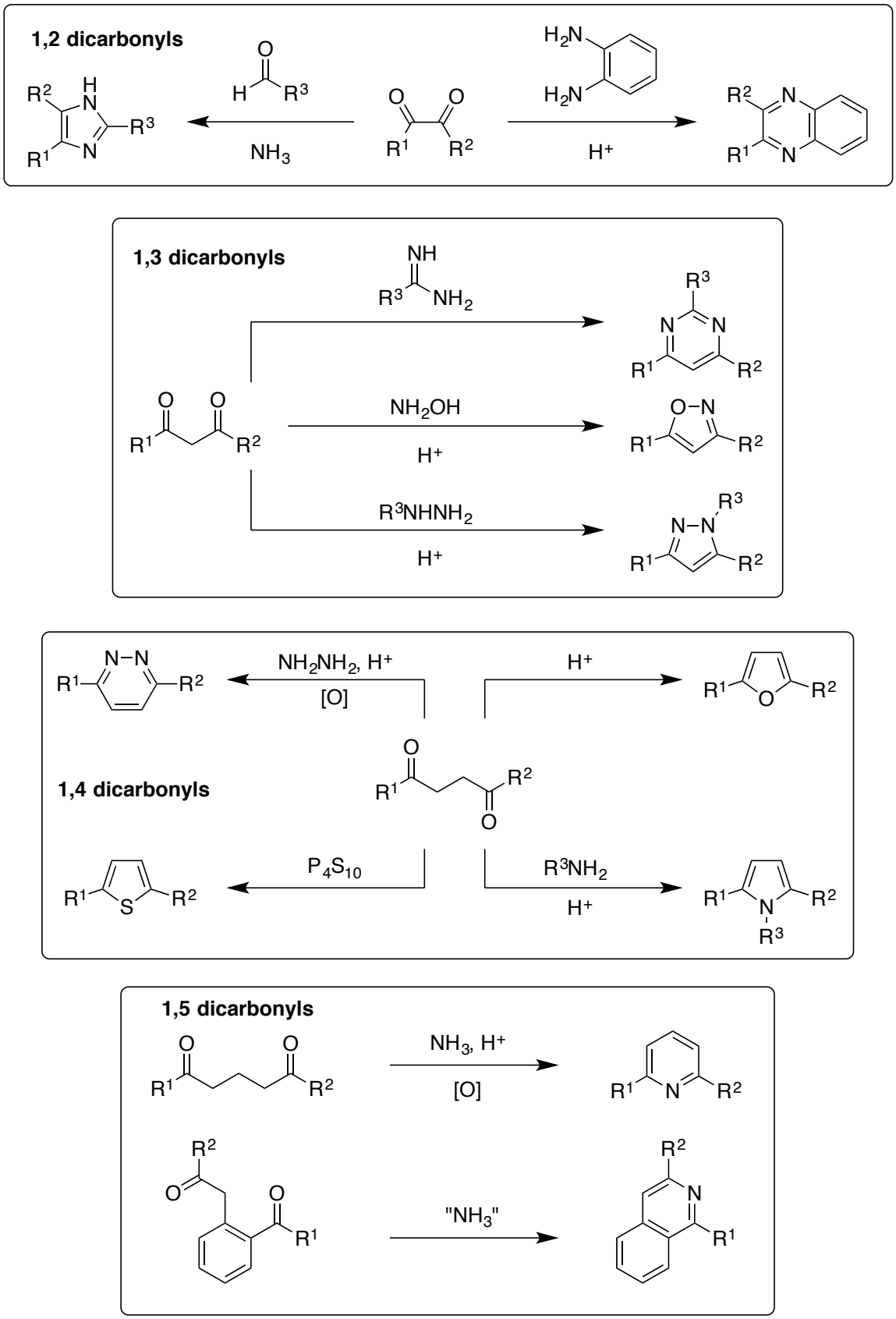


Figure 2.1 Heterocycle synthesis *via* dicarbonyls

This discovery was later exploited by Donohoe in the synthesis of di- and tri-substituted furans *via* a cross metathesis approach.[145, 146] Not only was he able to effect the necessary double bond isomerisation with acid to form di-substituted furans, but also by performing a Heck reaction on the intermediate; the introduction of further substitution was accompanied by the inversion of double bond geometry, with the product *cis*-enone undergoing rapid cyclisation to afford the corresponding furan. This method was later expanded to the synthesis of *N*-protected-pyrroles from γ-amino-α,β-enones (**24**), with the above strategies proving equally effective (Figure 2.2).[147]

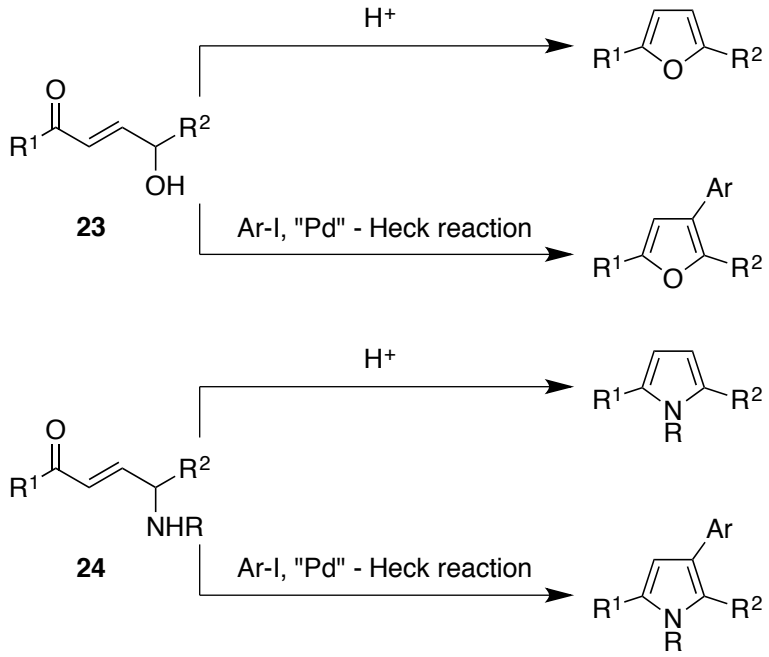


Figure 2.2 Donohoe's double bond isomerisation strategies for furan and pyrrole synthesis

In 2011 (as mentioned in Section 1.2.3) Willis demonstrated that hydroacylation could also be used to synthesise intermediate **23**, and thus a range of furans.[131] Extension of this methodology, undertaken in the group during the period covering the studies described in this thesis, has been shown to be effective in the synthesis of a number of pyrroles, pyrrolines and pyrrolidines.[132] Although hydroacylation had been

shown to be effective at synthesising heterocyclic precursors, it was felt that further developments, targeting other heterocycles would be valuable additions to the field.

2.2 Hydroacylation-based route to 1,3-dicarbonyl analogues

Whilst the synthesis of pyrazoles, isoxazoles and pyrimidines has traditionally been achieved using 1,3-dicarbonyls, such routes often produce mixtures of regioisomers. One of the most common alternative syntheses employed involves the intermediacy of *N*,*N*-dimethyl-β-aminoenones, synthesised *via* condensation chemistry between methylketones and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) (Figure 2.3). These intermediates have been regularly employed in heterocycle synthesis, usually in conjunction with arylmethylketone starting materials.[148, 149, 150, 151, 152, 153]



Figure 2.3 DMF-DMA condensation for the synthesis of a 1,3-dicarbonyl anaologue

It was felt that although the existing methodology for the synthesis of these intermediates was strong in many areas, the high reaction temperatures, low functional group tolerance and poor regioselectivity for more complex ketones would make the development of a mild, functional group tolerant, selective alternative an attractive goal. A simple retrosynthetic analysis of the heterocycle precursor (Figure 2.4) prompted investigation into the hydroacylation of heteroatom-substituted alkynes.

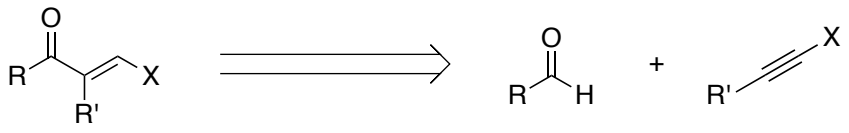
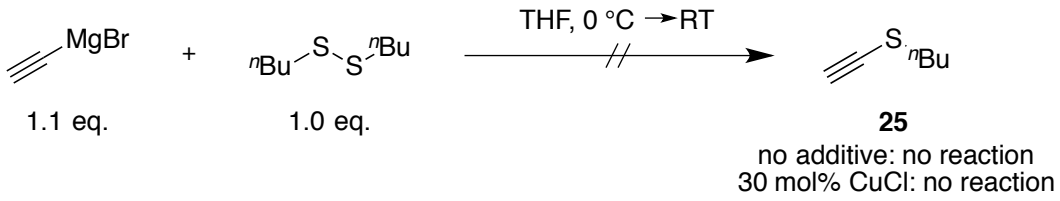


Figure 2.4 Retrosynthetic analysis of 1,3-dicarbonyl analogues

To our knowledge, the hydroacylation of these conjugated alkynes has not been previously attempted.

2.2.1 Synthesis of ynol ethers and ynol thioethers

Only a handful of ynol ethers and ynol thioethers are commercially available, so it was necessary to synthesise the starting materials using previously reported routes. Initial attempts to synthesise ynol thioether **25** *via* the reaction between ethynyl magnesium bromide and dibutyl disulfide proved unsuccessful (Scheme 2.1).

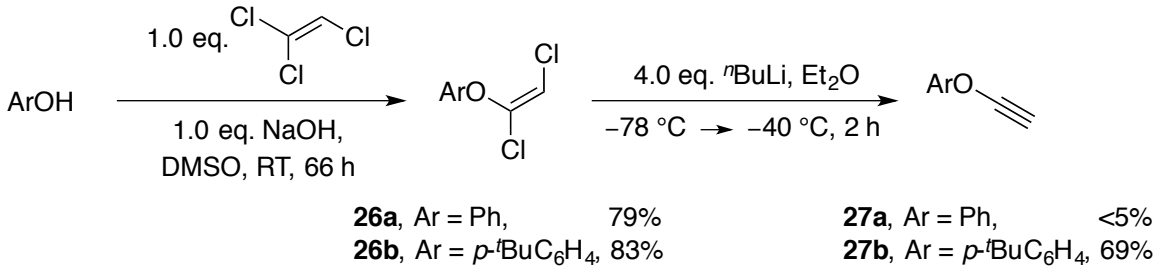


Scheme 2.1 Attempted synthesis of ethynyl sulfides

Instead, it was decided to follow methodology used by Tanaka in the synthesis of aryl ynol ethers (Scheme 2.2).[154] In this report it was mentioned that aryl ynol ethers were much more stable than the corresponding alkyl ynol ethers; therefore it was decided to target these compounds.

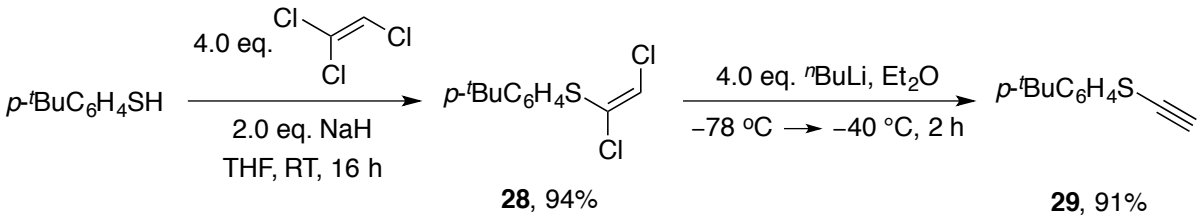
An initial attempt to synthesise *O*-ethynyl phenol **27a** experienced mixed success. The first step afforded 1,2-dichloroenolether **26a** in a 79% yield. Pleasingly, upon treatment with ^{n}BuLi what appeared to be *O*-ethynyl phenol **27a** was formed cleanly. After workup and purification by flash column chromatography the solvent was removed *in vacuo*, and only trace quantities of the product were isolated. Upon investigation, it was found that whilst the reaction was proceeding cleanly, the product (**27a**) was volatile and was being removed *in vacuo*. It was therefore decided to use the

heavier *p*-^{t}Buphenol as a less volatile alternative. This simple swap was sufficient to isolate aryl ynol ether **27b** in 57% yield over two steps (Scheme 2.2).



Scheme 2.2 Synthesis of aryl ynol ethers

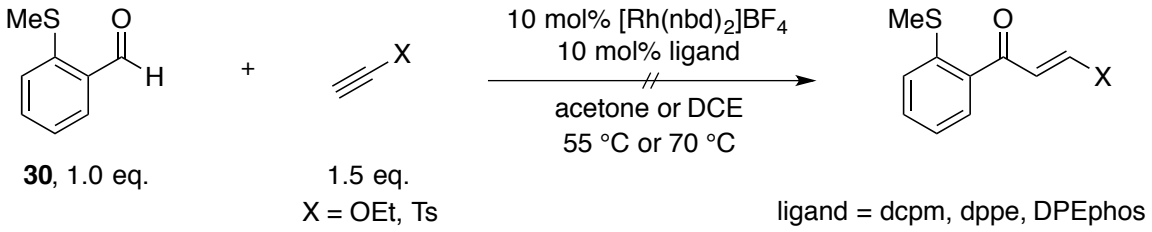
The synthesis of the corresponding ynol thioether (**29**) was also easily achieved in 86% yield over the two steps (Scheme 2.3).



Scheme 2.3 Synthesis of aryl ynol thioether **29**

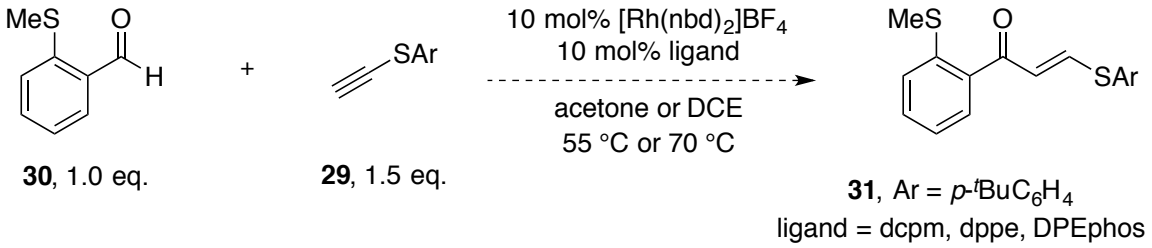
2.2.2 Hydroacylation optimisation

With these simple substrates in hand, their performance in hydroacylation with 2-methylthiobenzaldehyde **30** was evaluated, as well as that of commercially available substrates. Initial studies on the commercial substrates (ethoxyacetylene and *p*-tosylacetylene) with a range of ligands proved unsuccessful (Scheme 2.4); minimal conversion of the aldehyde starting material was observed, with a number of products present in trace quantities.



Scheme 2.4 Attempted hydroacylation on commercially available heteroatom-substituted alkynes

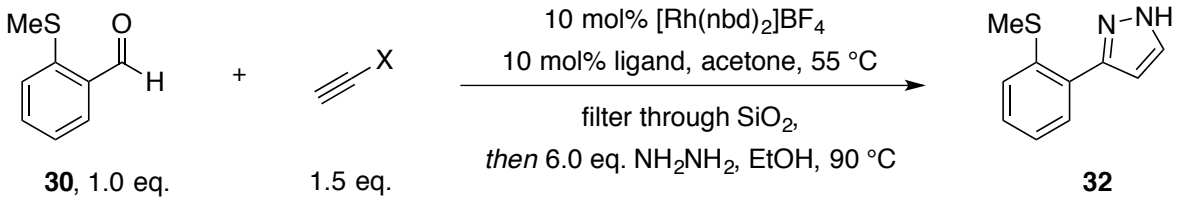
Instead of these highly electron-rich (OEt) or electron-poor (Ts) alkynes, it was decided that the SAr alkyne would be a better substrate due to the poorer overlap between the lone pair orbitals on the sulfur and the alkyne, reducing conjugation in the system (Scheme 2.5). TLC analysis of the initial test reactions appeared to show full consumption of both the aldehyde and alkyne starting materials in almost all cases, the exception being with DPEphos in acetone at 55 °C. The reactions appeared messy and the major product isolated was not definitively identified as the desired product (**31**) by either MS or NMR analyses.



Scheme 2.5 Hydroacylation of aryl ynol thioether **29**

As an alternative method to determine the reaction progress, and to aid separation, which had been an issue for the above system, it was decided to subject the crude reaction mixture, from each reaction, to conditions that should form a mono-substituted pyrazole from the linear product of hydroacylation. The results obtained from this two-step process are summarised in Table 2.1.

Table 2.1 Optimisation of two-step hydroacylation/pyrazole formation



30, 1.0 eq. 1.5 eq. **32**

Entry	X=	Ligand	Reaction conditions	Isolated yield
1	SAr	dcpm	2 h hydroacylation, 2 h cyclisation	55%
2	OAr	dcpm	2 h hydroacylation, 2 h cyclisation	42%
3	SAr	dcpm	2 h hydroacylation, 16 h cyclisation	50%
4	SAr	dcpm	30 min hydroacylation, 2 h cyclisation	48%
5	SAr	dppe	2 h hydroacylation, 2 h cyclisation	13%
6	OAr	dppe	2 h hydroacylation, 2 h cyclisation	trace
7	SAr	DPEphos	2 h hydroacylation, 2 h cyclisation	trace
8	SAr	PNP(Cy)	2 h hydroacylation, 2 h cyclisation	29%

a) Ar = *p*-^{t}BuC$_6$H$_4$

It became apparent that the desired hydroacylation product must be present in the crude mixture obtained after the first step, in order for the second step to produce pyrazole **32**. The yields of pyrazole, however, were never improved beyond the moderate yields indicated above. It was not possible to tell whether this was due to issues with linear:branched selectivity, poor overall yields for the hydroacylation step, or inefficient pyrazole formation. Extending the reaction time for the cyclisation step (Entry 3) didn't show any improvement, indicating that the cyclisation step appears to be complete after two hours. Use of *O*-containing alkyne **27b** resulted in lower yields (Entry 2), as did the use of alternative ligands (Entries 5-8).

Optimisation of this process was put aside while other projects being undertaken simultaneously required more focus (Sections 2.3 and Chapter 3).

2.3 Hydroacylation for the synthesis of pyridines

As described earlier (Section 2.1), one of the major classical routes to the synthesis of pyridines involves the cyclisation of 1,5-dicarbonyls with ammonia (or synthetic equivalents). There are also a number of classical named reactions that rely on the combination of two or more components in which at least one incorporates carbonyl functionality. Examples include the Boger,[155] Bohlmann-Rahtz,[156, 157] Gattermann-Skita,[158] Hantzsch,[159] and Kröhnke[160] syntheses (Figure 2.5).

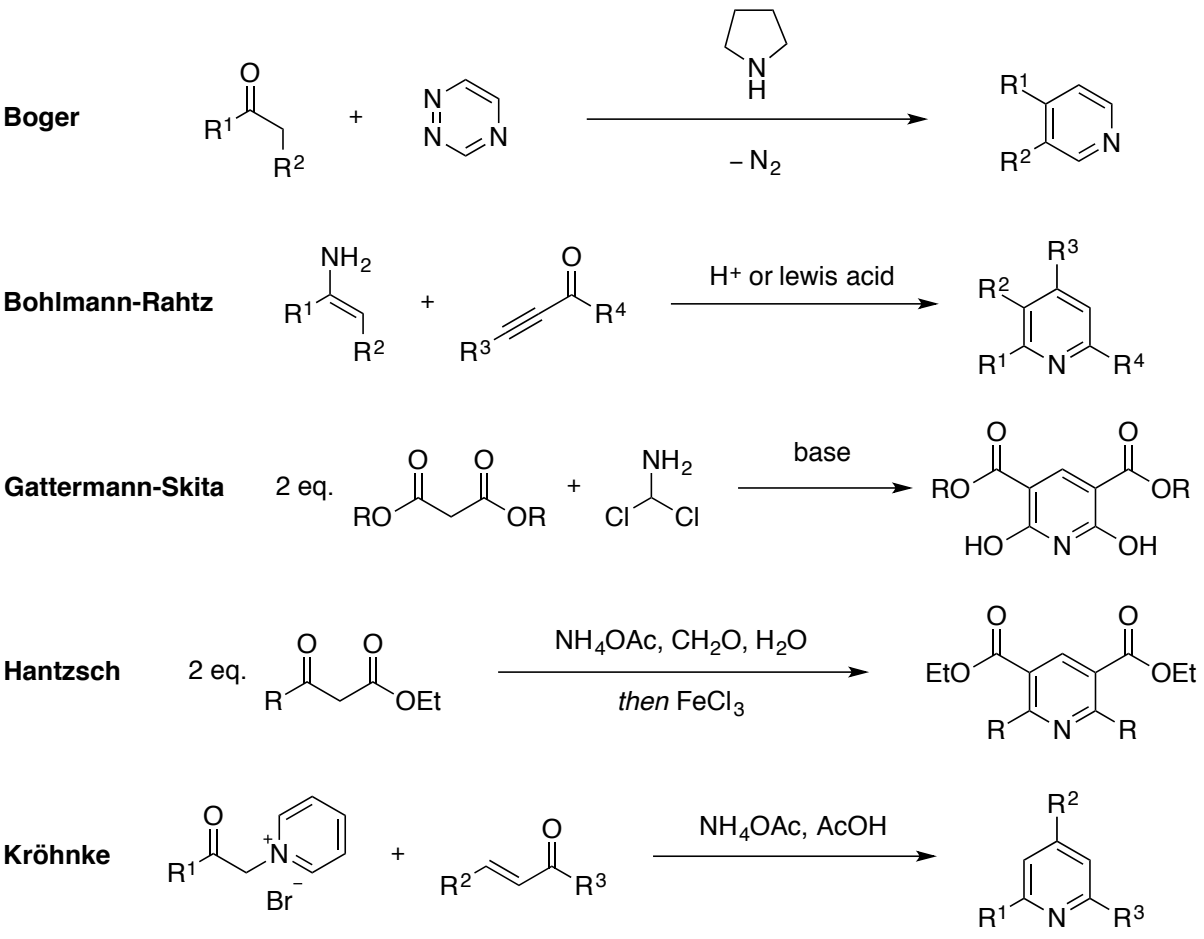
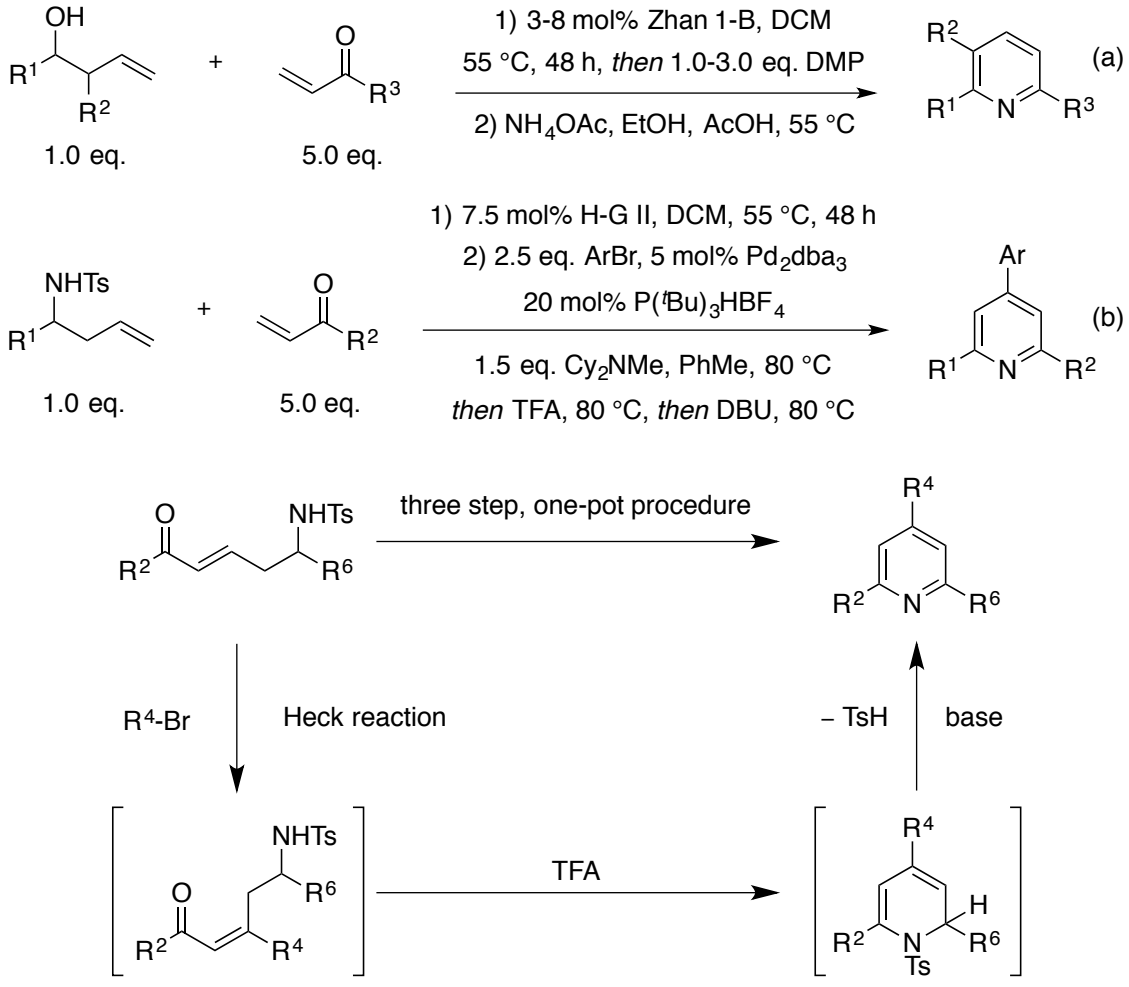


Figure 2.5 Traditional routes to pyridines

In 2011 Donohoe published two novel routes to heterocycles, combining cross-metathesis and palladium-catalysed protocols to introduce a wide range of functionality.[161, 162] One of these methods involved the intermediacy of a

monounsaturated 1,5-dicarbonyl, removing the need for an oxidative cyclisation (Scheme 2.6a). The other achieved aromatisation *via* the elimination of 4-toluenesulfinic acid, again without recourse to either an external oxidant, or an aerobic oxidation. Although these syntheses generated diversely substituted pyridines in good to excellent yields, the initial cross metathesis reaction has many disadvantages. As shown in Scheme 2.6b, a large excess of the vinyl ketone component is required to prevent homodimerisation of the limiting homoallylic alcohol/sulfonamide, generating a considerable amount of waste. The use of highly expensive complexes such as the Zhan 1-B metathesis catalyst is another drawback.



Scheme 2.6 Donohoe's cross metathesis-based pyridine syntheses

2.3.1 Prior work in the Willis group

Given the success of synthesising furans and pyrroles *via* hydroacylation, it was envisaged that at least one of the carbonyl-containing heterocycle precursors previously mentioned would be accessible *via* Rh-catalysed hydroacylation. The Donohoe papers previously mentioned have provided three potential heterocycle precursors that could feasibly be synthesised by Rh-hydroacylation *via* novel disconnections (Figure 2.6).

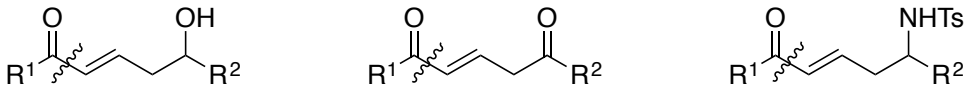
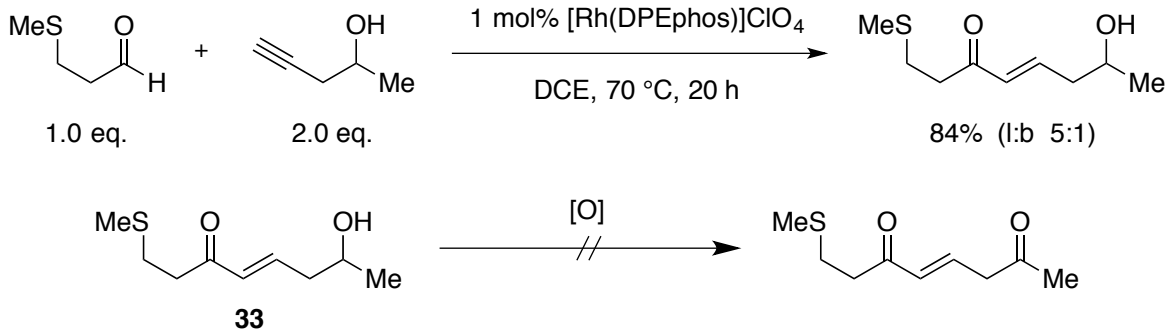


Figure 2.6 Enone-based pyridine precursors

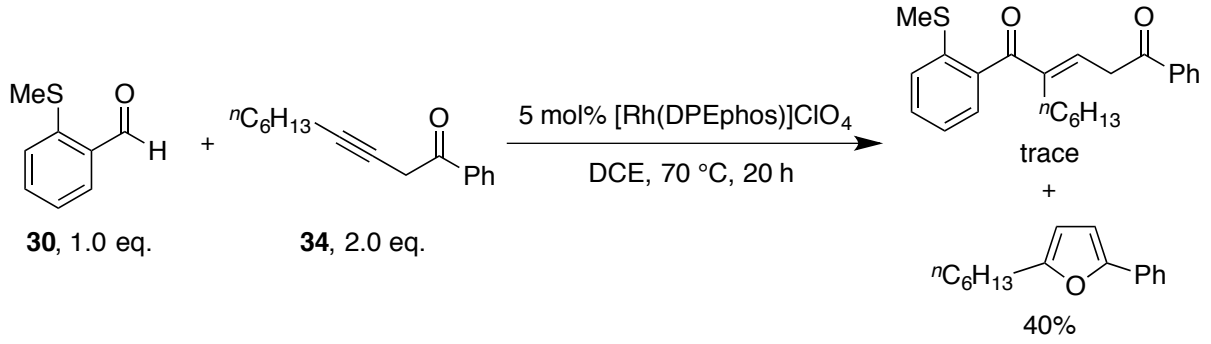
Previous work undertaken in the Willis group had targetted the hydroacylation of homopropargylic alcohols, followed by DMP oxidation.[163] Unfortunately, while the hydroacylation was successful for terminal alkynes, the oxidation of intermediate **33** was unable to be achieved in the presence of the β-sulfur tether, with DMP giving a complex mixture of products (Scheme 2.7).



Scheme 2.7 Attempted hydroacylation-oxidation route to 1,5-dicarbonyl backbone

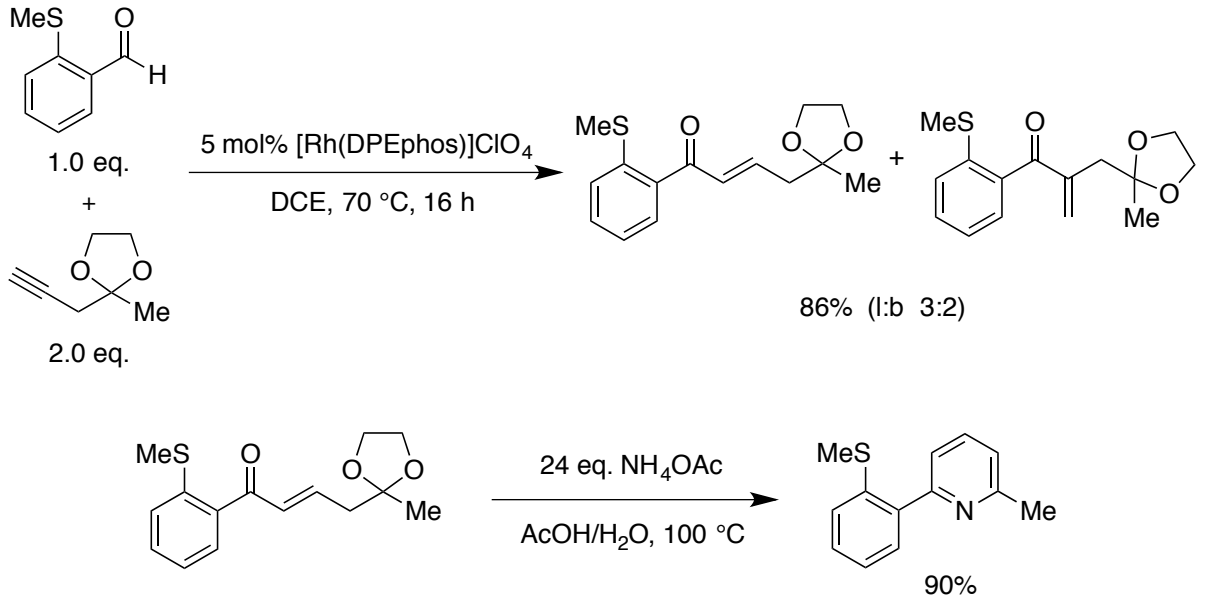
Allenyl esters had previously been shown to be excellent substrates in Rh-catalysed hydroacylation, both in terms of reactivity and regioselectivity of the products.[164] Unfortunately, this reactivity did not appear to be shared by the related

allenyl ketones. Both allenyl and propargyl ketones (e.g. ketone **34**) underwent an intramolecular Rh-promoted cycloisomerisation to form furans (Scheme 2.8). This reaction has been reported with a number of different Lewis acid catalysts.[165, 166, 167, 168]



Scheme 2.8 Hydroacylation of homopropargyl ketone **34**

Protection of the carbonyl functionality as a cyclic ketal enabled the synthesis of pyridines in a two-step hydroacylation-cyclisation procedure (Scheme 2.9). Whilst yields were high for this procedure, the regioselectivity of hydroacylation was poor, affecting the yield of the pyridine product.



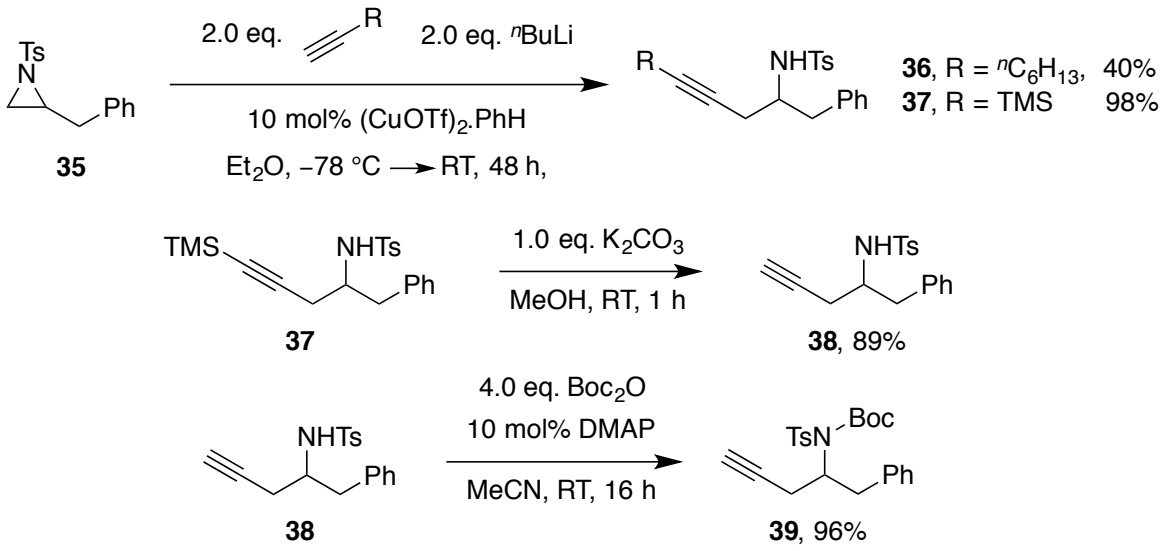
Scheme 2.9 Optimised pyridine synthesis

In addition to the aforementioned limitations of the synthetic route, the synthesis of the starting materials was far from straightforward, and so although a proof of principle had been established, the project was not developed further.

It was at this point that work on pyridine synthesis was first undertaken by the author, as detailed in the following section.

2.3.2 Synthesis of homopropargyl sulfonamides

In order to explore the potential of homopropargyl sulfonamides as hydroacylation partners, a reliable route needed to be established for their synthesis. The addition of propargyl Grignard reagents into imines often results in the formation of a mixture of the homoallenyl and homopropargyl sulfonamides, especially when substituted propargyl Grignards are used.[169, 170, 171] It was therefore decided to synthesise the required homopropargyl sulfonamides from aziridines, using a $[Cu(OTf)]_2$.PhH complex as a catalyst.[172] In this way both terminal and internal alkynes were synthesised (Scheme 2.10). In order to test the effect of *N*-chelation on the regioselectivity of the hydroacylation reaction, an additional *N*-protection was undertaken in the form of a Boc-group. The protection strategy on propargylic amines (used in the pyrrole synthesis – Scheme 1.40) has previously been shown to have a marked effect on linear:branched ratios.



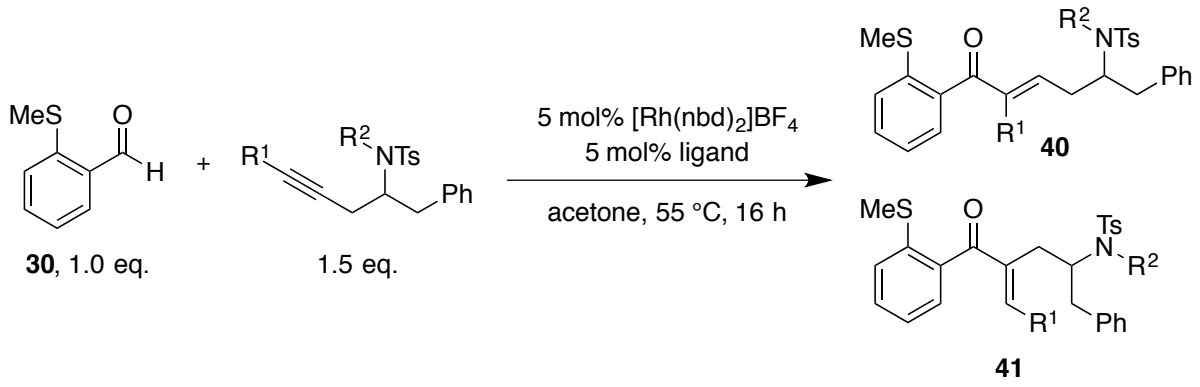
Scheme 2.10 Synthesis of homopropargyl sulfonamides

With these substrates in hand, it was then possible to evaluate their performance in hydroacylation.

2.3.3 Hydroacylation optimisation

Gratifyingly each of the alkynes reacted readily with aldehyde **30**, with each reaction proceeding to completion (Table 2.2). For the case of the terminal alkynes, just two hours was sufficient to achieve full conversion. Whilst the reactivity appeared to be good, the selectivity was less pleasing. For Entry 1, under the group's standard hydroacylation conditions, the *N*-chelation effected a considerable reduction in linear selectivity (c.f. >20:1 for 1-octyne). The use of the highly linear-selective PNP(Cy) ligand however led to an improved selectivity of 8:1 (Entry 2), which enabled isolation of the major product in an 86% yield. While PNP(Cy) is a less attractive ligand choice, relative to the commercially available dcpm, this was a notable increase in selectivity. The addition of extra protection on the nitrogen, afforded no increase in selectivity, and a slight drop in isolated yield to 78%.

Table 2.2 Hydroacylation of homopropargyl sulfonamides



Entry	Alkyne	Ligand	Conversion[a]	**40**:**41**[a]
1	R^1=R^2=H, **38**	dcpm	100%	2.5:1
2	R^1=R^2=H, **38**	PNP(Cy)	100%[b]	8:1
3	R^1=H, R^2=Boc, **39**	PNP(Cy)	100%[c]	8:1
4	R^1=^{n}C$_6$H$_{13}$, R^2=H, **36**	dcpm	100%	1:2.5
5	R^1=^{n}C$_6$H$_{13}$, R^2=H, **36**	PNP(Cy)	100%	1:2.5

a) Determined by ^{1}H-NMR analysis b) Compound **42**, isolated yield of 86% c) Compound **43**, isolated yield of 78%

When internal alkyne **36** was employed, the selectivity appeared to reverse. Steric factors should have little effect; the steric bulk on either end of the alkyne is very similar, with any bulky substitution distant from the alkyne. The directing effect of the *N*-chelation (see Figure 2.7) serves to overcome whatever mild steric selectivity may be present, and the branched isomer is therefore observed as the major product.

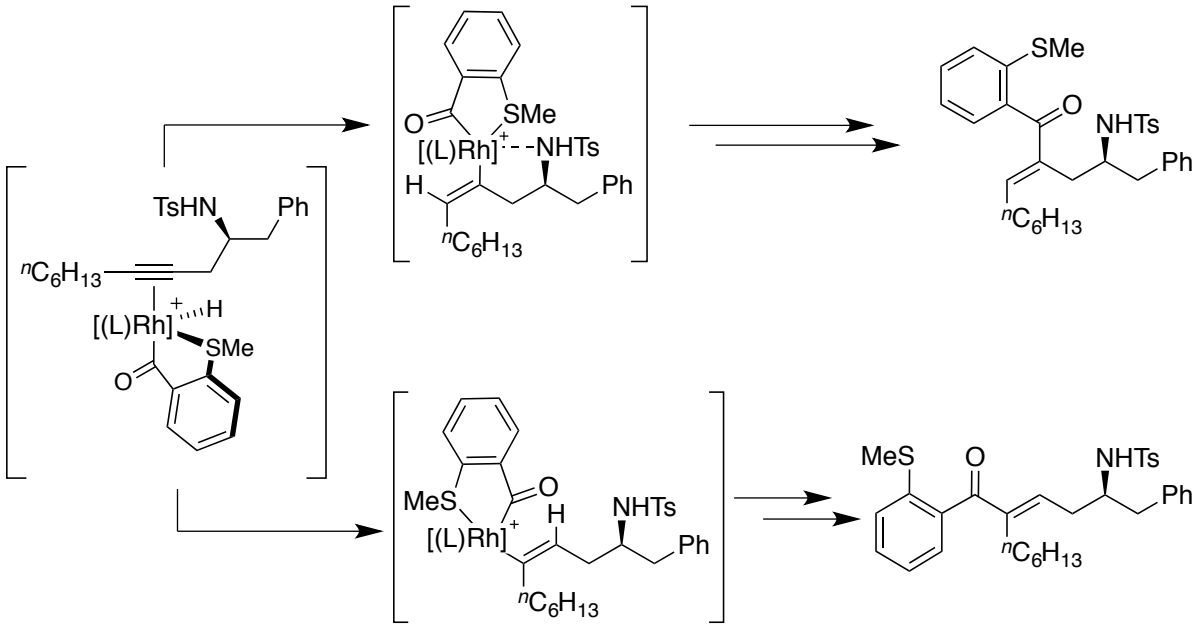
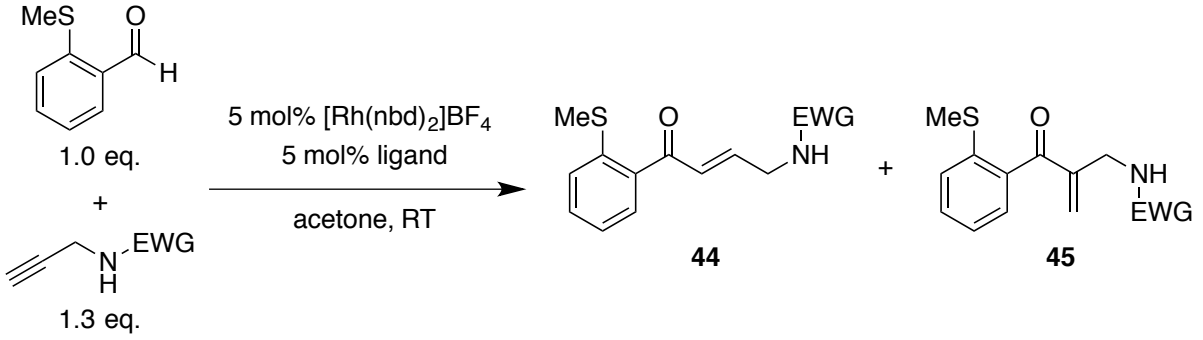


Figure 2.7 The effect of *N*-chelation in hydroacylation regioselectivity

With quantities of hydroacylation product **42** (formed from aldehyde **30** and alkyne **38**) in hand, cyclisation according to Donohoe's procedure was attempted. In their synthesis, a Heck reaction is used to isomerise the enone before an acidic cyclisation. We wanted to ascertain whether it was possible to cyclise the intermediate in the absence of the initial Heck reaction. Unfortunately, it appeared that TFA was ineffective at promoting an isomerisation-cyclisation reaction, with a number of conditions attempted. After discussions with the authors of the original work,[162] it was ascertained that for a number of unpublished examples, it had been impossible to achieve either the acidic cyclisation or the basic elimination, even after Heck-induced enone isomerisation. This meant that this method would be suitable only for 2,4,6-substituted pyridines, however following the entire Heck-cyclisation-elimination sequence would be a low impact repetition of published work, and a general synthesis was of more interest.

In order to circumvent these issues, a number of solutions presented themselves. Firstly, to achieve better linear:branched ratios, it was observed by colleagues working on the pyrrole project (undertaken concurrently with the current work),[132] that protection of the propargylic amines with sulfonyl groups afforded the worst linear:branched selectivities, with carbamates, in particular the Boc group, considerably outperforming them (Table 2.3).

Table 2.3 Effect of *N*-protection on regioselectivity in the synthesis of pyrrole precursors



Entry	EWG	Ligand	**44**:**45**[a]
1	Boc	dcpm	6:1
2	Boc	PNP(Cy)	17:1
3	Cbz	dcpm	4:1
4	Cbz	PNP(Cy)	12:1
5	Ts	dcpm	1:1
6	Ts	PNP(Cy)	4:1

a) determined by ^{1}H-NMR spectroscopy

Such a protection strategy would prevent use of the acidic cyclisation/basic elimination strategy, however an isomerisation/cyclisation following TFA-promoted Boc-deprotection (Figure 2.8) should be more favourable than for the poorly nucleophilic sulfonamide substrate. Oxidation to the pyridine could then be achieved

either with an external oxidant such as DDQ (see Section 3.6), or simply under aerobic conditions.

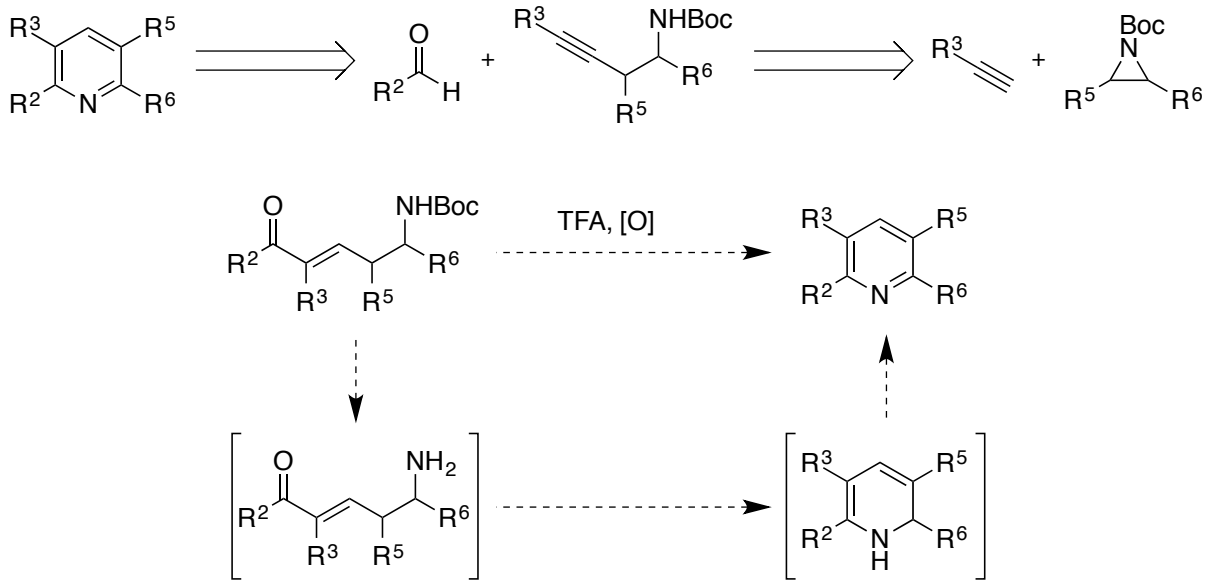


Figure 2.8 An alternative Boc-protection strategy in pyridine synthesis

Another factor that would increase linear selectivity would be to use α-branched alkynes. These could be obtained through the ring opening of 2,3-disubstituted aziridines (Figure 2.8), and would also provide extra substitution on the final pyridine product. Whilst it was envisaged that these modifications should allow for an efficient synthesis of pyridines, they introduced a number of different issues. The major problem now was the synthesis of the starting materials. The synthesis of *N*-Boc aziridines is less well known, especially for 2,3-disubstituted examples, and the ring opening of such substrates would afford mixtures of regioisomers, unless symmetrical systems were employed.

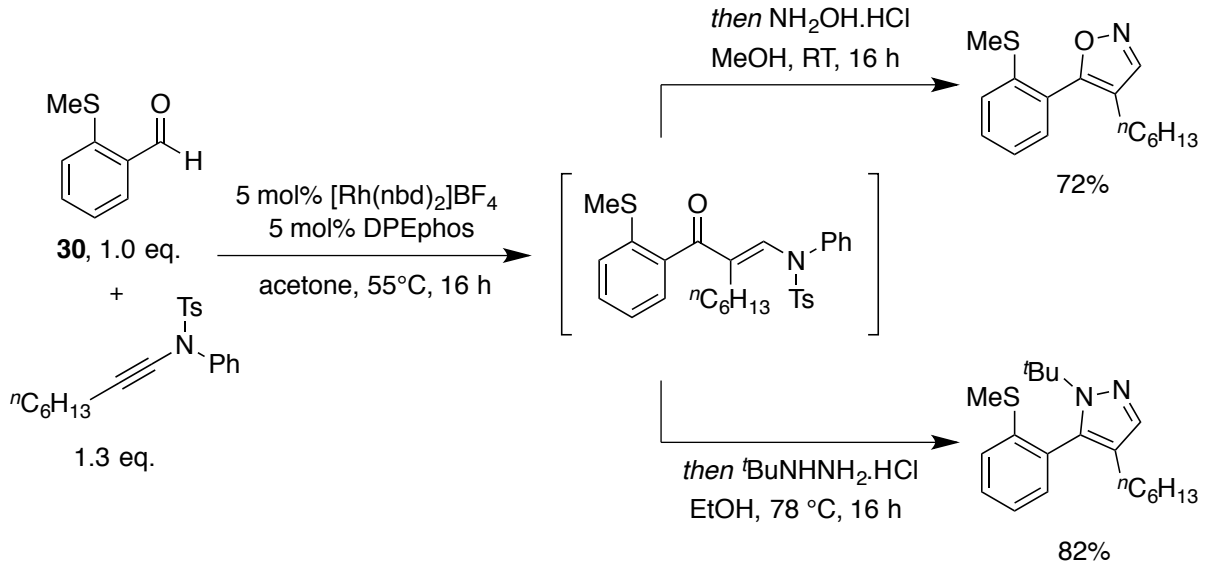
These issues with starting material synthesis would make the process no more attractive than the previously optimised pyridine synthesis, using propargylic ketals (Section 2.3.1). As such it was decided that a protracted exercise in starting material

synthesis would not be a rewarding use of time, given progress in other projects (Chapter 3) and no further investigations were undertaken.

2.4 Summary

To conclude, we have evaluated hydroacylation-based routes to a number of heterocycles. In the case of pyridines, work by the author and others has investigated a number of potential routes to highly substituted pyridines; however, due to protracted starting material syntheses, the processes lacked a general appeal, and were therefore not fully explored. The synthesis of pyrazoles, and potentially other heterocycles from the same intermediates has been demonstrated in moderate yields. Although not a fully developed method, it provides a proof of principle for the use of hydroacylation when targeting 1,3-dicarbonyl analogues.

Since the work detailed herein, advances in the synthesis of ynamides have allowed colleagues in the Willis group to explore their use in hydroacylation and to develop a high yielding, general synthesis of isoxazoles and pyrazoles (Scheme 2.11).[173]



Scheme 2.11 Synthesis of pyrazoles and isoxazoles *via* Rh-catalysed hydroacylation of ynamides

Chapter 3

Diversely substituted quinolines *via* Rh-catalysed alkyne hydroacylation

3.1 Introduction

During the investigation into the synthesis of pyridines (Section 2.3), a route was sought that would not involve either elimination of a sulfinate or an oxidative cyclisation. Whilst such routes are known for dicarbonyl compounds[161] *N*-containing substrates have not been utilised in this way.

It was proposed that δ-aminodienone **46** should be a suitable intermediate for the formation of the required pyridines (Figure 3.1); however, the potential instability of the alkyne required to form such an intermediate *via* hydroacylation meant that this was not investigated. It was realised, however, that an aniline would be a more stable analogue for the enamine fragment. If intermediate **47** could be cyclised, then it would be possible to access a range of quinoline derivatives.

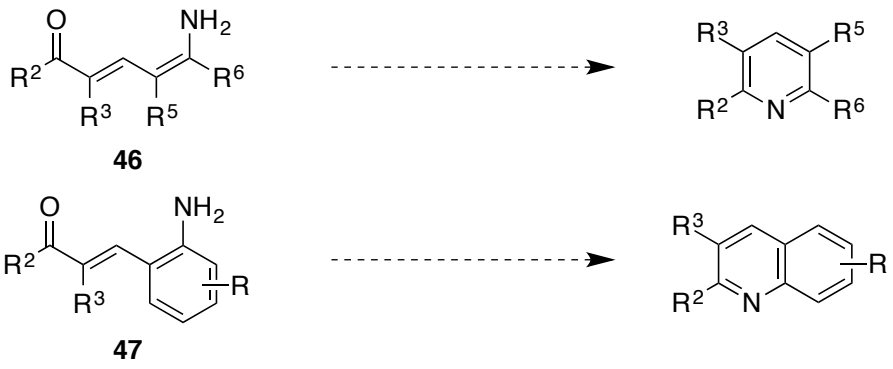


Figure 3.1 Proposed quinoline synthesis

Inspection of the literature revealed that this postulated intermediate (**47**) had been used as a quinoline precursor on a few occasions, although the tactic had not been widely adopted. Existing routes involved isomerisation/cyclisation using either iodine/*N*-iodosuccinimide,[174] or irradiation with UV light.[175] The use of a simple acidic cyclisation was limited to a handful of isolated examples.[176]

Quinolines represent an important class of heterocycle for a number of functions including anticancer, antibacterial, herbicidal and antimalarial agents,[177, 178, 179, 180, 181] with quinine being used as a multipurpose treatment since the 17th century.[182] In addition to their biological properties, quinolines have been used in fields as diverse as organic LEDs and cation sensors.[183, 184, 185, 186] Their synthesis has been of great interest to the synthetic and medicinal chemistry community, as a result. A number of classical syntheses exist such as the Combes,[187, 188] Döbner-von Miller,[189, 190] Friedländer,[191, 192] Knorr,[193, 194] Niementowki,[195, 196] Pfitzinger,[197, 198] Povarov[199, 200] and Skraup[201, 202] syntheses (Figure 3.2). These reactions are characterised by harsh reaction conditions, poor functional group tolerance, and difficulty in achieving good regioselectivity.

The *de novo* synthesis from simple, readily accessible starting materials is an area that has received much attention in recent years, with a number of transition metal catalysed,[203, 204, 205, 206, 207, 208, 209, 210] and transition metal free processes,[211, 212, 213, 214, 215,

[216] although many are limited to simple substituents and specific substitution patterns. Hydroacylation benefits from mild reaction conditions, high selectivity and broad functional group tolerance. It was considered, therefore, that the development of a hydroacylation route to quinolines would be a useful platform from which to demonstrate these characteristics.

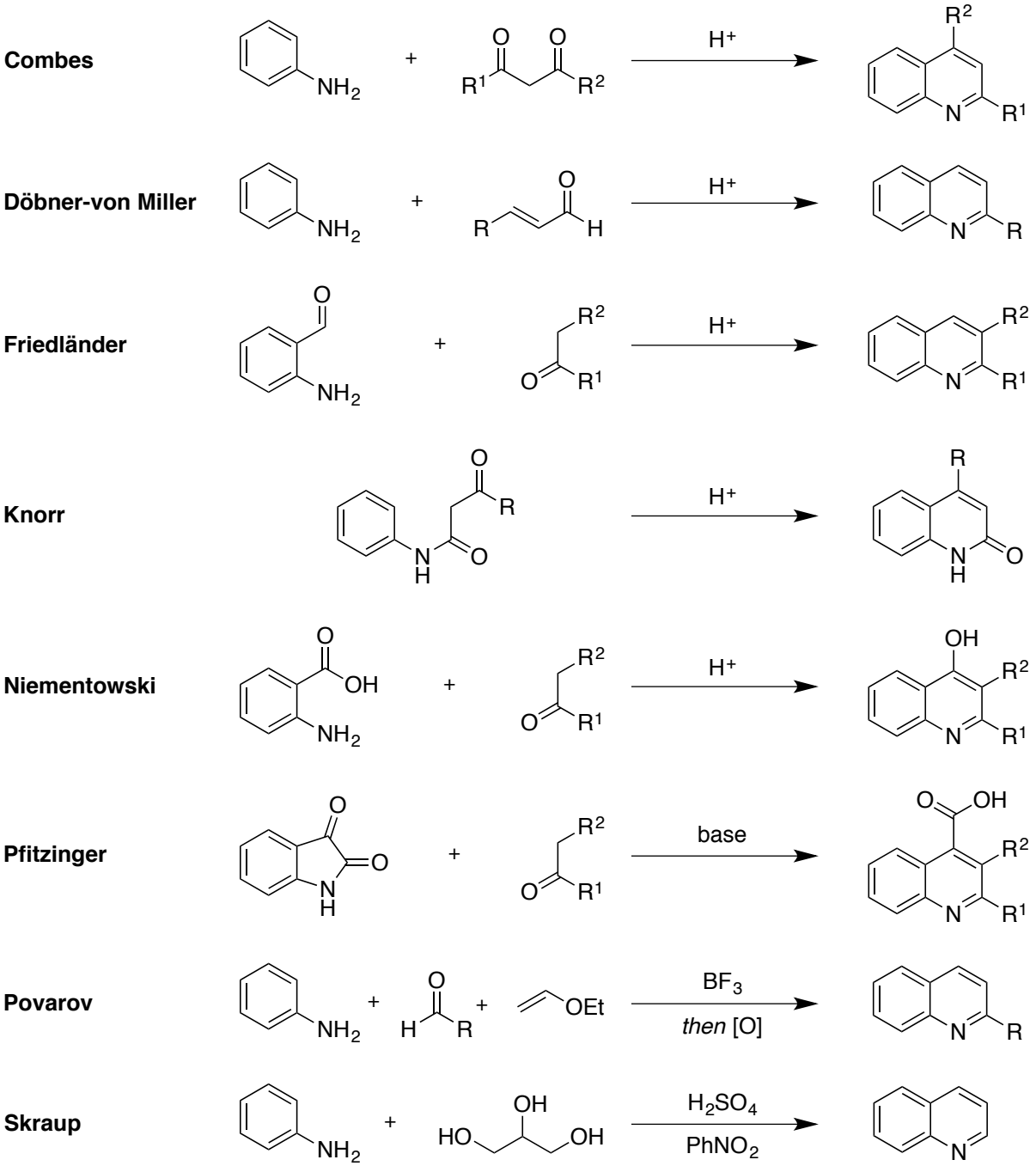


Figure 3.2 Traditional quinoline syntheses

3.2 Initial optimisation

The experiments detailed in this section (3.2) were undertaken by a 4th year undergraduate student under the direct supervision of the author.[217]

3.2.1 Hydroacylation optimisation

The initial retrosynthetic analysis suggested the use of 2-ethynyl aniline (**48**) as a test substrate (Figure 3.3).

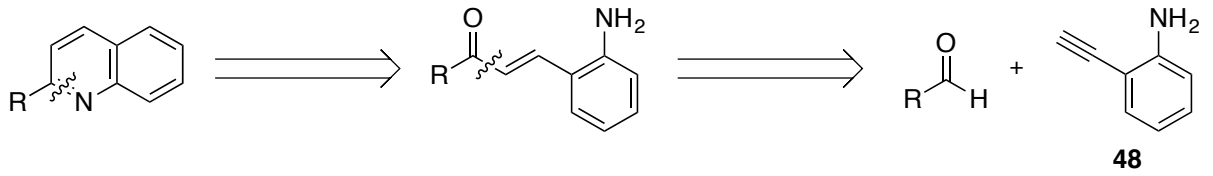
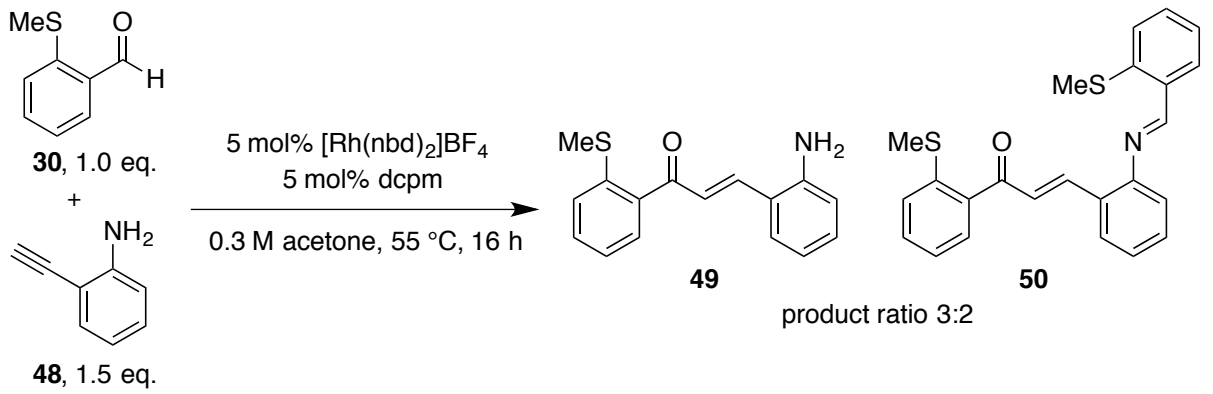


Figure 3.3 Quinoline retrosynthesis

By subjecting the unprotected aniline substrate to the group's standard hydroacylation conditions with aldehyde **30**, full consumption of the aldehyde starting material was observed (Scheme 3.1). The reaction mixture comprised a number of products, the majority corresponding to chalcone **49** and imine **50** in a 3:2 ratio; however, no evidence of the branched HA product was observed by ^{1}H-NMR analysis of the crude reaction mixture.



Scheme 3.1 Initial test reaction

The test reaction on Boc-protected substrate **51a**, initially appeared to be a much cleaner, more efficient reaction (Table 3.1, Entry 1). Gratifyingly, neither imine nor branched product was detected; however upon isolation, the product was found to be an inseparable mixture of chalcone **52a** and carbothiolation product **53**. This carbothiolation process, in which the HA product reacts with excess alkyne present in the reaction mixture (Figure 3.4), has been previously reported by the Willis group.[218]

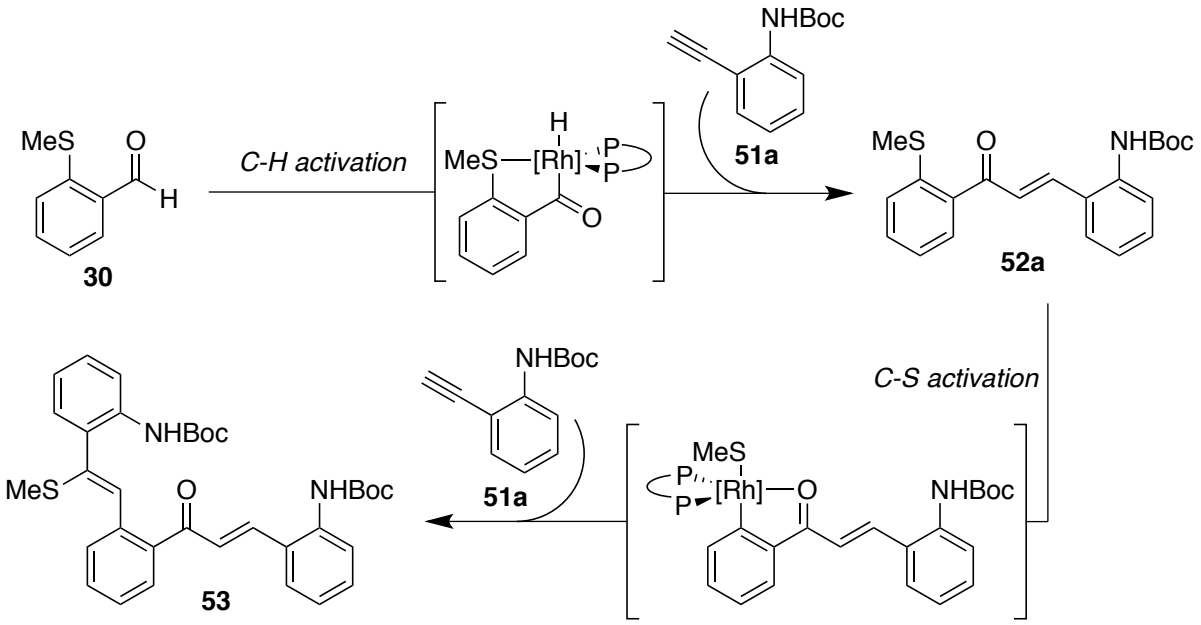
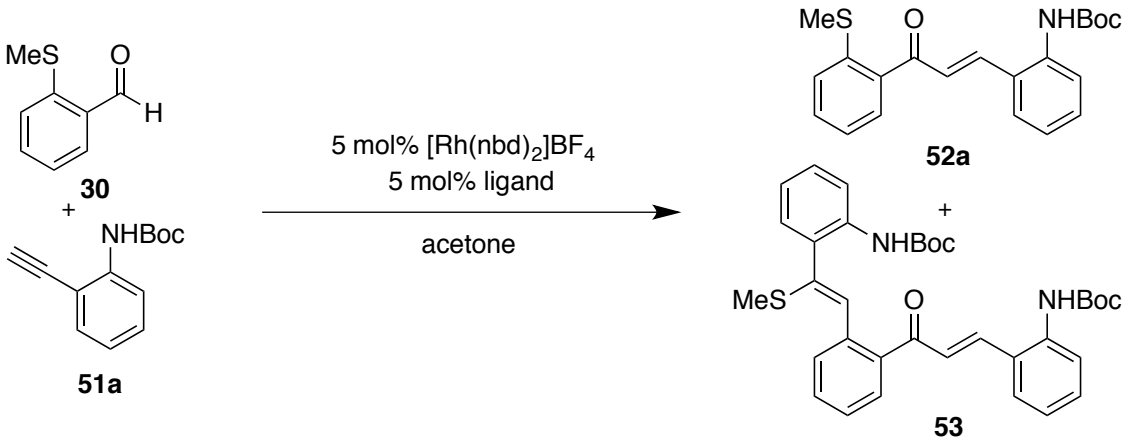


Figure 3.4 Tandem hydroacylation-carbothiolation

Shortening the reaction time to two hours resulted in a more favourable ratio of products, although a considerable quantity of **53** remained (Table 3.1, Entry 2). By adjusting the stoichiometry of the reaction, and by reducing the reaction temperature the formation of carbothiolation product **53** was successfully suppressed. In order to achieve full consumption of the limiting alkyne it was necessary to increase the concentration to 1.0 M, a tactic previously shown to favour the 2nd order hydroacylation reaction over the 1st order decarbonylation reaction.

Table 3.1 Optimisation of the hydroacylation of alkyne **51a**



Entry	**30**:**51a**	Ligand	Reaction conditions	Conversion[a]	**52a**:**53**[a]	Isolated yield[b]
1	1:1.5	dcpm	55 °C, 0.3 M, 16 h	88%	2:1	85%
2	1:1.5	dcpm	55 °C, 0.3 M, 2 h	85%	4:1	81%
3	1.05:1	dcpm	55 °C, 0.3 M, 2 h	100%	19:1	73%
4	1.05:1	dcpm	RT, 0.3 M, 3 h	90%	>25:1	69%
5	**1.05:1**	**dcpm**	**RT, 1.0 M, 3 h**	**100%**	**>25:1**	**96%**
6	1:1.5	dcpm	RT, 1.0 M, 3 h	84%	>25:1	78%

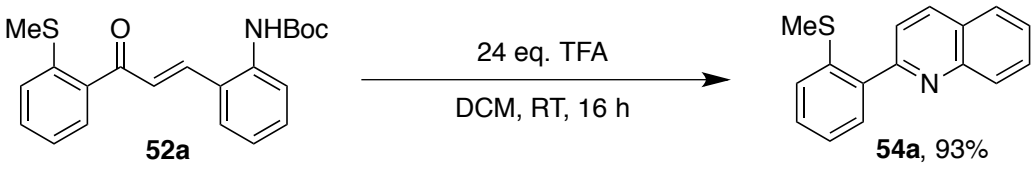
a) Determined by ^{1}H-NMR analysis b) Yield given as a mixture of compounds **52a** and **53**

It should be remarked at this point that alkyne **51a** appears to show unusually high reactivity in the carbothiolation reaction. Subsequent test reactions between chalcone **52a** and alkyne **51a** using Xantphos – the ligand of choice for carbothiolation – afforded **53** in extremely short reaction times. This has been speculated to be a result of *N*-chelation assistance, but this hypothesis has not been further investigated.

3.2.2 Cyclisation to quinolines

It was theorised that an acidic Boc-deprotection would be accompanied by an acidic double bond isomerisation, analogous to those observed for the furan and pyrrole

syntheses (Chapter 1, Schemes 1.39 and 1.40, p. 30-31), affording quinoline **54a** in a single step from hydroacylation product **52a**. To test this hypothesis, chalcone **52a** was exposed to TFA/DCM at room temperature. When the reaction was inspected after sixteen hours, pleasingly the desired quinoline (**54a**) was the only observed product. Following work up and purification, an isolated yield of 93% was obtained (Scheme 3.2).

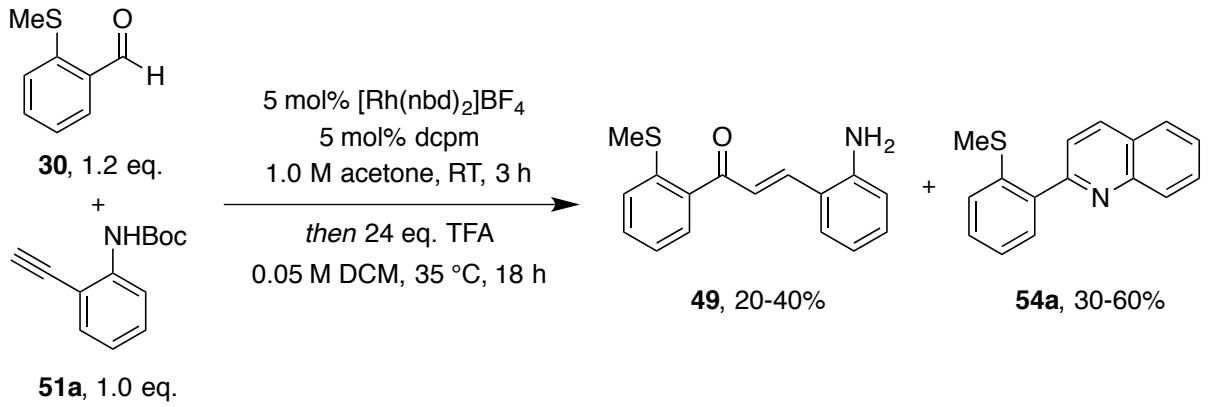


Scheme 3.2 Acid-mediated cyclisation

Increasing the reaction temperature to 35 °C resulted in a markedly faster reaction, with **52a** fully consumed after 40 minutes; however, the isolated yields were often unexpectedly low. It was unclear why this should be the case, but for further experiments the cyclisations were undertaken under ambient conditions. A number of alternative solvents were evaluated for this process, with a view to developing a one-pot hydroacylation/cyclisation procedure; however, complete conversion was only ever observed in chlorinated solvents.

3.2.3 Attempted development of tandem/telescoped procedures

With an optimised two-step synthesis in hand, efforts focussed on the development of a streamlined one-pot operation, in order to cut down on wasteful work-up and purification steps. The addition of TFA/DCM to the crude reaction mixture obtained after three hours resulted in formation of the quinoline; however, on a number of runs the isolated yields varied considerably, between 30% and 60% (Scheme 3.3).



Scheme 3.3 Attempted one-pot hydroacylation/cyclisation protocol

Not only was the cyclisation reaction seemingly retarded by the presence of acetone, Rh-complex or a combination of the two, an additional side product **55** was observed in 5-10% yield. It soon became clear from both NMR and MS analysis that this side product resulted from the reaction of deprotected intermediate **49** with excess aldehyde present from the first step. At this stage of the investigations this compound was not fully identified, though later studies (Section 3.4, p.79) have since elucidated the identity and mechanism of formation of this by-product.

Although the inability to employ alternative solvents for the deprotection step limited the possibilities for optimisation, it was decided that a telescoped procedure that did not involve intermediate purification could be developed. By filtering the crude reaction mixture through a short pad of silica, followed by removal of the initial reaction solvent *in vacuo* and redissolution in TFA/DCM, the reactivity of the system appeared to be restored, and no uncyclised product (**49**) was observed. The isolated yield remained low (50-60% over a number of runs) however, and the previously observed side product (**55**) was isolated in a 10-20% yield. At this stage it was decided that the two-step procedure would be used to evaluate the reaction scope.

3.3 Reaction scope

Within the alkyne scope, seven of the simpler substrates were synthesised and evaluated by a 4th year undergraduate student under the direct supervision of the author.[217] All other experiments for the remainder of this chapter were undertaken by the author.

3.3.1 Synthesis of *N*-Boc 2-ethynylanilines

Whilst it was possible to synthesise the parent alkyne **51a** by Boc-protection of commercially available 2-ethynylaniline **48**, in order to introduce functionality on the carbocyclic quinoline ring, a range of substituted *N*-Boc 2-ethynylanilines had to be synthesised. To this end, it was envisaged that by starting from 2-iodoanilines, the target alkynes could be synthesised in three simple steps (Figure 3.5). A wide range of 2-iodoanilines are commercially available, in part due to their use as starting materials in the Larock indole synthesis,[219] and as such there is a considerable quantity of literature reports on this family of compounds.

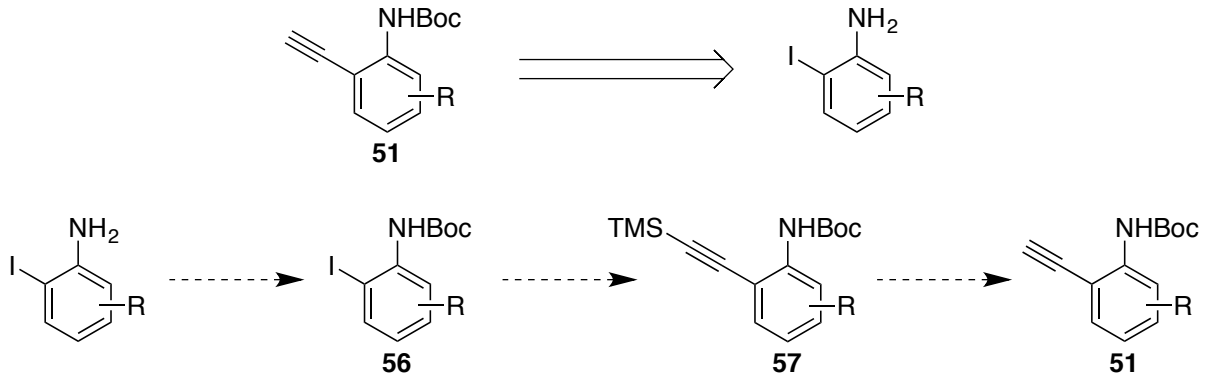
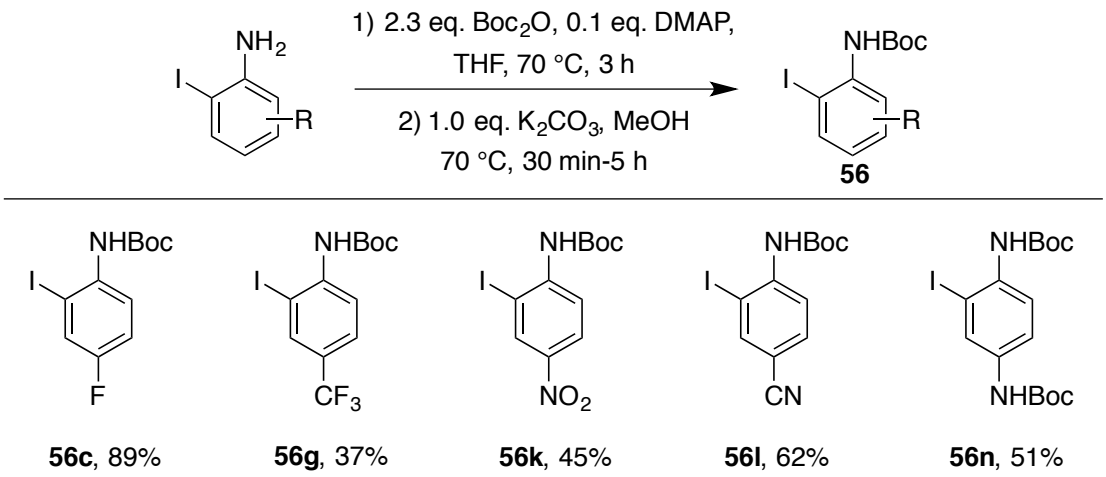


Figure 3.5 Retrosynthetic analysis of *N*-Boc 2-ethynylanilines

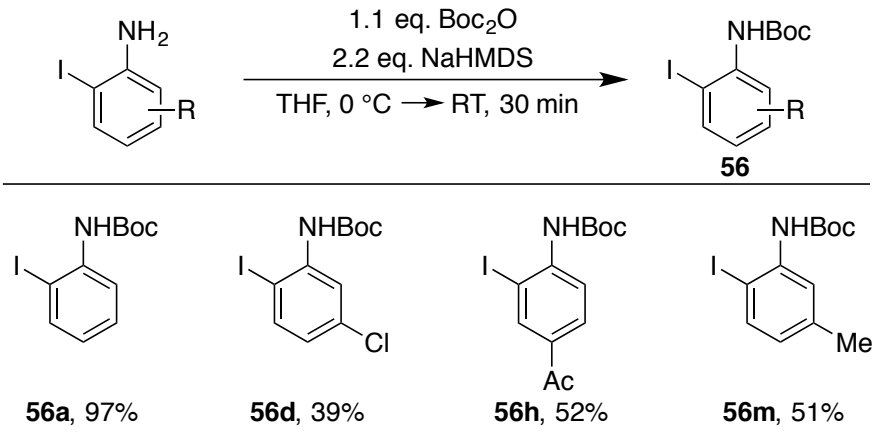
The initial Boc-protection step proved to be the most problematic. Under standard DMAP-catalysed Boc-protection conditions a mixture of unprotected aniline,

mono-protected aniline and di-protected aniline was obtained. This result stems from the increased acidity of the mono Boc-protected compound. Once deprotonated by DMAP or similar weak bases, the aryl carbamate is sufficiently reactive to outcompete the neutral starting aniline. Various literature methods exist to counter this problem, a number of which have been employed in this work. The first option is to carry out an initial double Boc-protection, followed by a selective mono Boc-deprotection under basic conditions. This method was used to synthesise a number of *N*-Boc 2-iodoanilines as shown in Scheme 3.4.



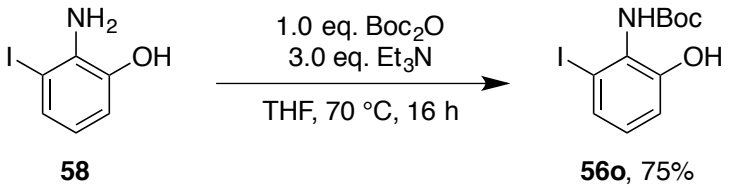
Scheme 3.4 Boc-protection *via* double Boc-protection then mono-deprotection

Another option was to use two equivalents of a strong base such as sodium hexamethyldisilazide. This method has the advantage of shorted reaction times, and less wasted Boc anhydride. This method was used for the synthesis of a further range of *N*-Boc 2-iodoanilines (Scheme 3.5).



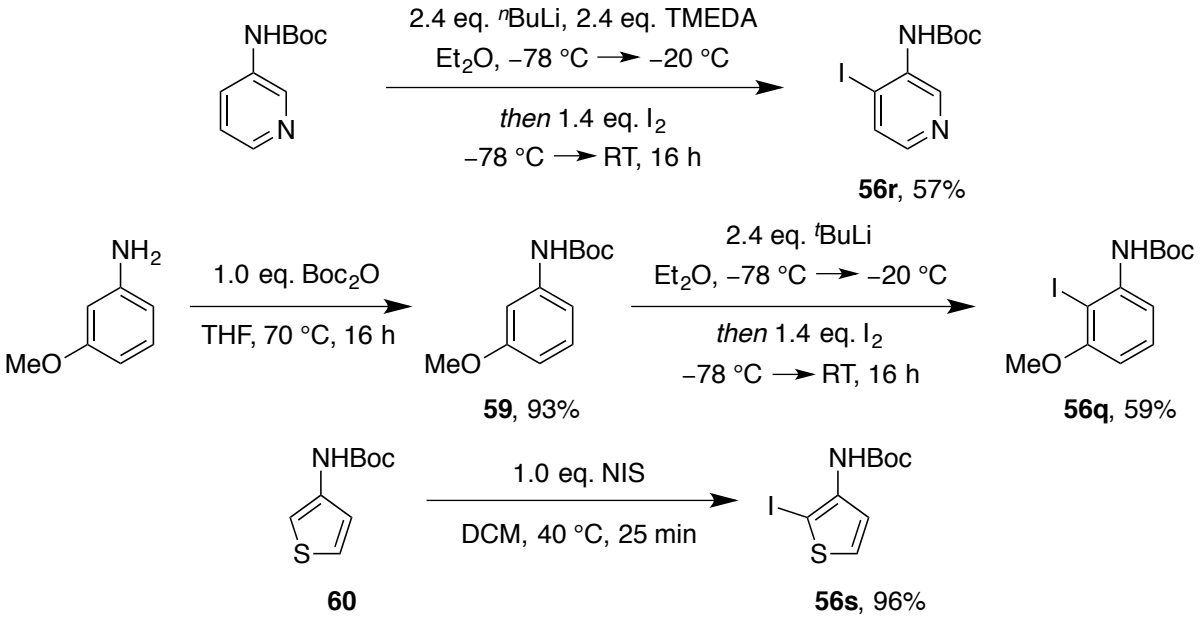
Scheme 3.5 NaHMDS promoted mono-Boc-protection

For the more electron-rich hydroxyaniline **58**, reaction with Boc anhydride in the presence of triethylamine was sufficient to achieve selective mono-protection (Scheme 3.6).



Scheme 3.6 Boc-protection of hydroxyaniline **57**

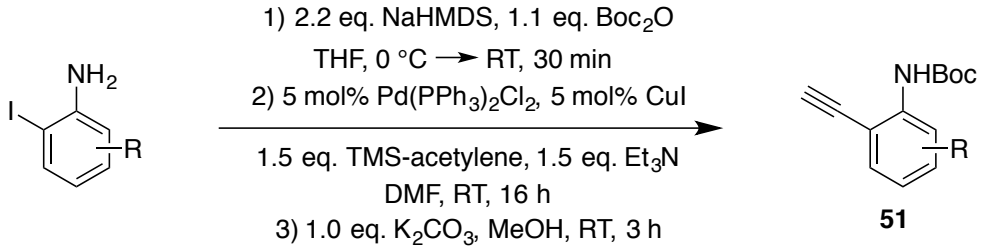
For a number of examples, the required 2-iodoaniline was not commercially available. *N*-Boc anilines are known to be efficient directing groups in *ortho*-lithiation chemistry.[220] By exploiting this reactivity and trapping the resulting lithiated species with iodine, the *N*-Boc 2-iodoanilines were afforded in moderate yields (Scheme 3.7). Reaction with NIS produced the same product in the case of *N*-Boc-3-aminothiophene (**60**) under much milder conditions *via* an S_EAr mechanism.

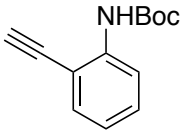


Scheme 3.7 *Ortho*-iodination routes to 2-iodoaniline derivatives

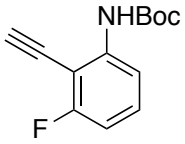
With a range of *N*-Boc 2-iodoanilines in hand, the Sonogashira coupling/TMS-deprotection steps were undertaken. The results of these reactions are summarised in Table 3.2.

Table 3.2 Synthesis of *N*-Boc 2-ethynylanilines

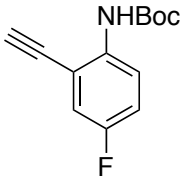




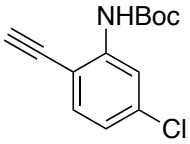
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2) 90%
3) 93%



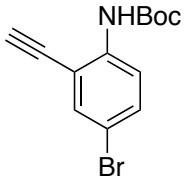
51b
69%[b]



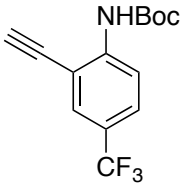
51c
1) 89%[c]
2) 91%
3) 97%



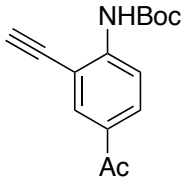
51d
1) 39%
2) 68%
3) 75%



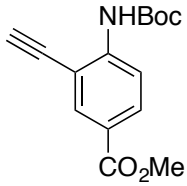
51e
1) and 2) 79%[a]
3) 82%



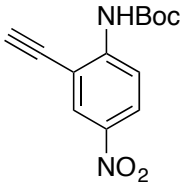
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1) 37%[c]
2) 99%
3) 89%



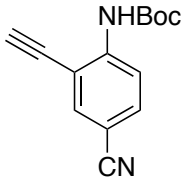
51h
1) 52%
2) and 3) 75%[a]



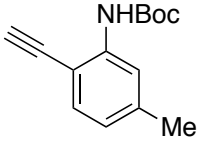
51i
1) and 2) 85%[a]
3) 90%



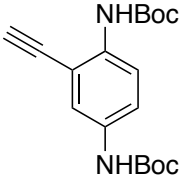
51k
1) 45%[c]
2) 91%
3) 88%



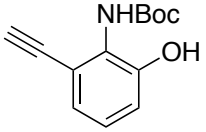
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1) 62%[c]
2) 90%
3) 95%



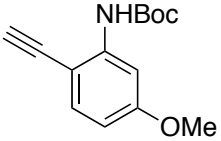
51m
1) 51%
2) 50%
3) 99%



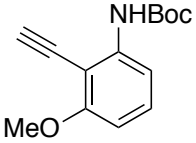
51n
1) 51%[c]
2) 97%
3) 92%



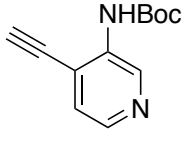
51o
1) 75%[c]
2) 84%
3) 84%



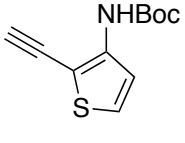
51p
72%[b]



51q
2) 59%
3) 94%



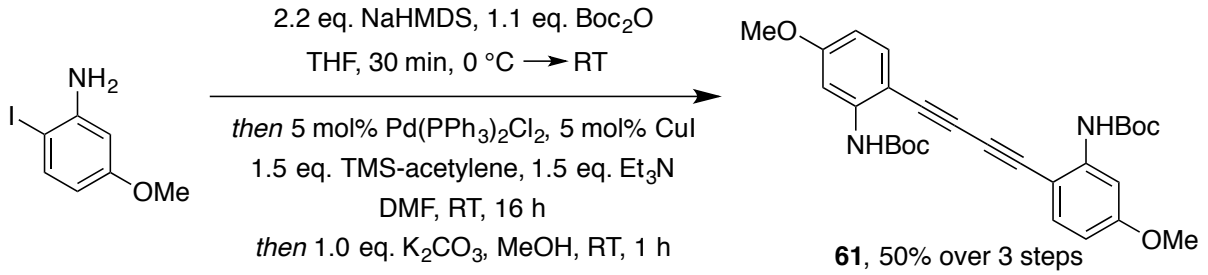
51r
2) 97%
3) 79%



51s
2) 95%
3) 99%

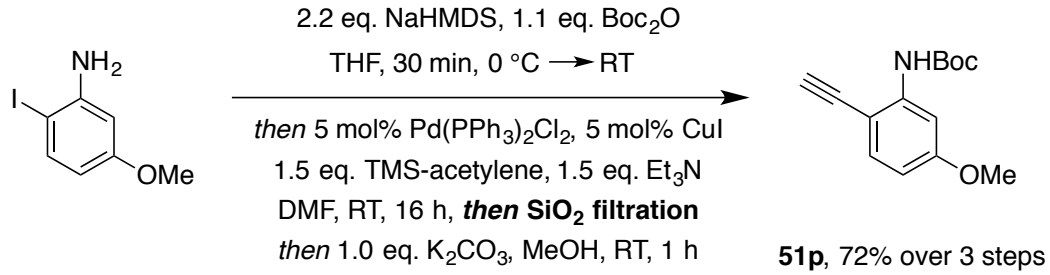
a) Yield given for two-step procedure b) Yield given for three-step procedure c) Alternative Boc-protection conditions used (see Schemes 3.4 and 3.6)

In order to achieve a more streamlined synthesis, a three-step telescoped procedure with no intermediate purification was attempted. This was initially successful, though exposure of the final product to aerobic conditions resulted in the formation of symmetrical dialkyne **61** (Scheme 3.8). It was postulated that this was a consequence of trace quantities of copper remaining from the Sonogashira step effecting a homodimerisation of the terminal alkyne.



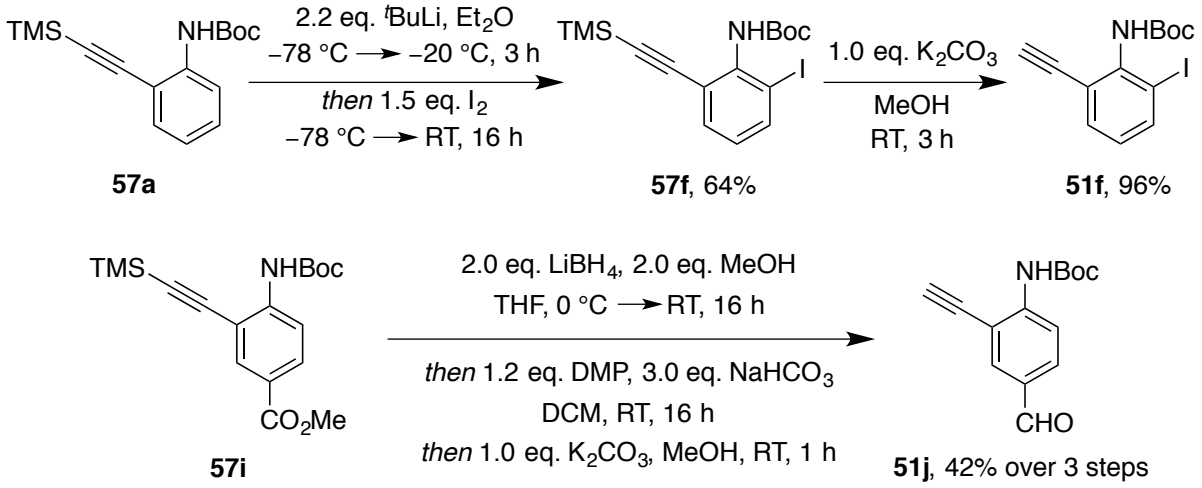
Scheme 3.8 Unexpected dimerisation of terminal alkyne **51p**

A simple filtration through a short pad of silica was sufficient to remove the copper and a three-step procedure with only a single chromatographic step was achieved (Scheme 3.9, and Table 3.2 Examples **51b** and **51p**).



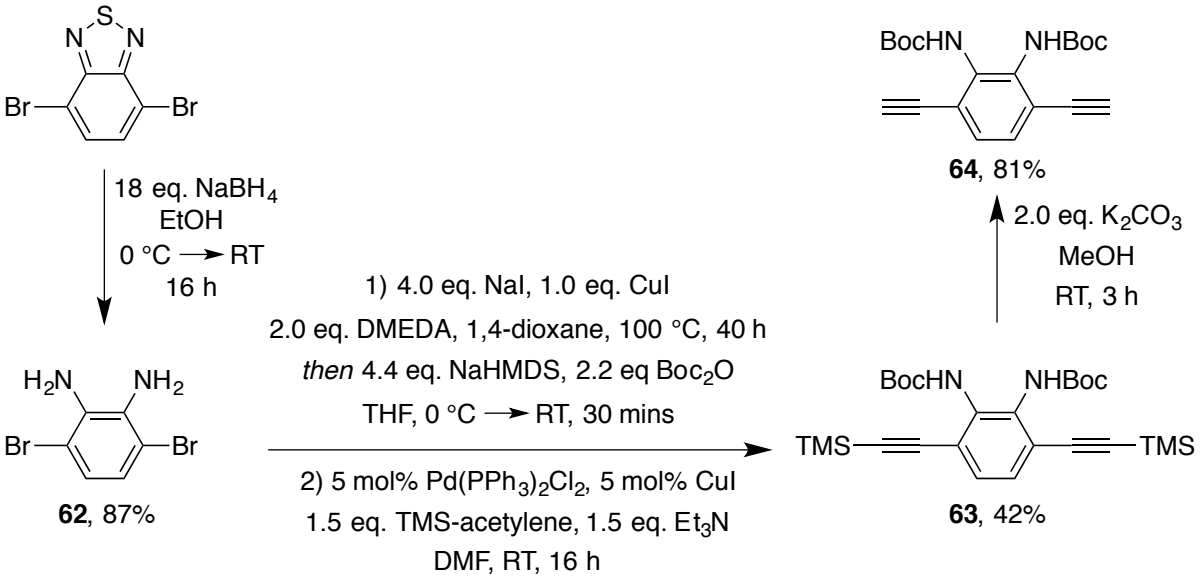
Scheme 3.9 Three-step telescoped procedure for the synthesis of terminal alkyne **51p**

It was possible to access iodo- and formyl-substituted examples by derivatisation of existing intermediates, either by *ortho*-lithiation or by functional group manipulation (Scheme 3.10).



Scheme 3.10 Functional group manipulation to access further substrates

It was also possible to synthesise a dialkyne precursor (**64**) that could potentially be used in the synthesis of phenanthrolines (Scheme 3.11).



Scheme 3.11 Synthesis of dialkyne **64** for phenanthroline synthesis

In summary, a broad range of *N*-Boc 2-ethynylanilines have been synthesised in good yields in a short reaction sequence. The possibility of streamlining the synthesis to require only a single chromatographic purification has also been demonstrated. With these alkynes in hand, it was now possible to explore the scope of the reaction, and to probe the functional group tolerance of the hydroacylation procedure.

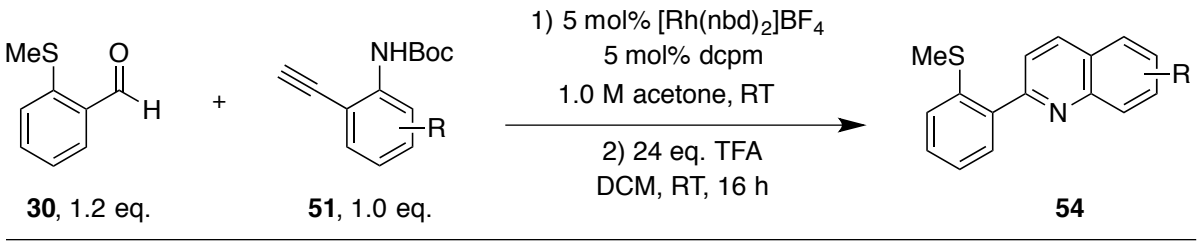
3.3.2 Scope of the alkyne component

By combining aldehyde **30** with the alkynes synthesised in the previous section, it was possible to examine the scope and functional group tolerance of the optimised conditions from Section 3.2. Pleasingly, the yields across almost the entire range of substrates were consistently high (Table 3.3). It was however noted, that the reaction rate exhibited a strong dependence on the electron density of the aryl alkyne. Whilst three hours were required to achieve full conversion when using the standard substrate (**51a**), many of the electron-poor examples were complete in 20-40 minutes, with nitro-substituted alkyne **51k** undergoing an extremely rapid hydroacylation step in just five minutes. With this high reactivity it was possible to incorporate a wide range of functionality onto the quinoline ring. Halide substitution was achieved on every position of the aryl alkyne, providing useful reactive handles for further functionalisation. Methyl ketones and aldehydes (examples **54h** and **54j**) are particularly noteworthy examples due to their incompatibility with many of the classical, aldol-based syntheses. To our knowledge, this is the only example of the *de novo* synthesis of a formyl-substituted quinoline that does not need to protect the aldehyde in any form.

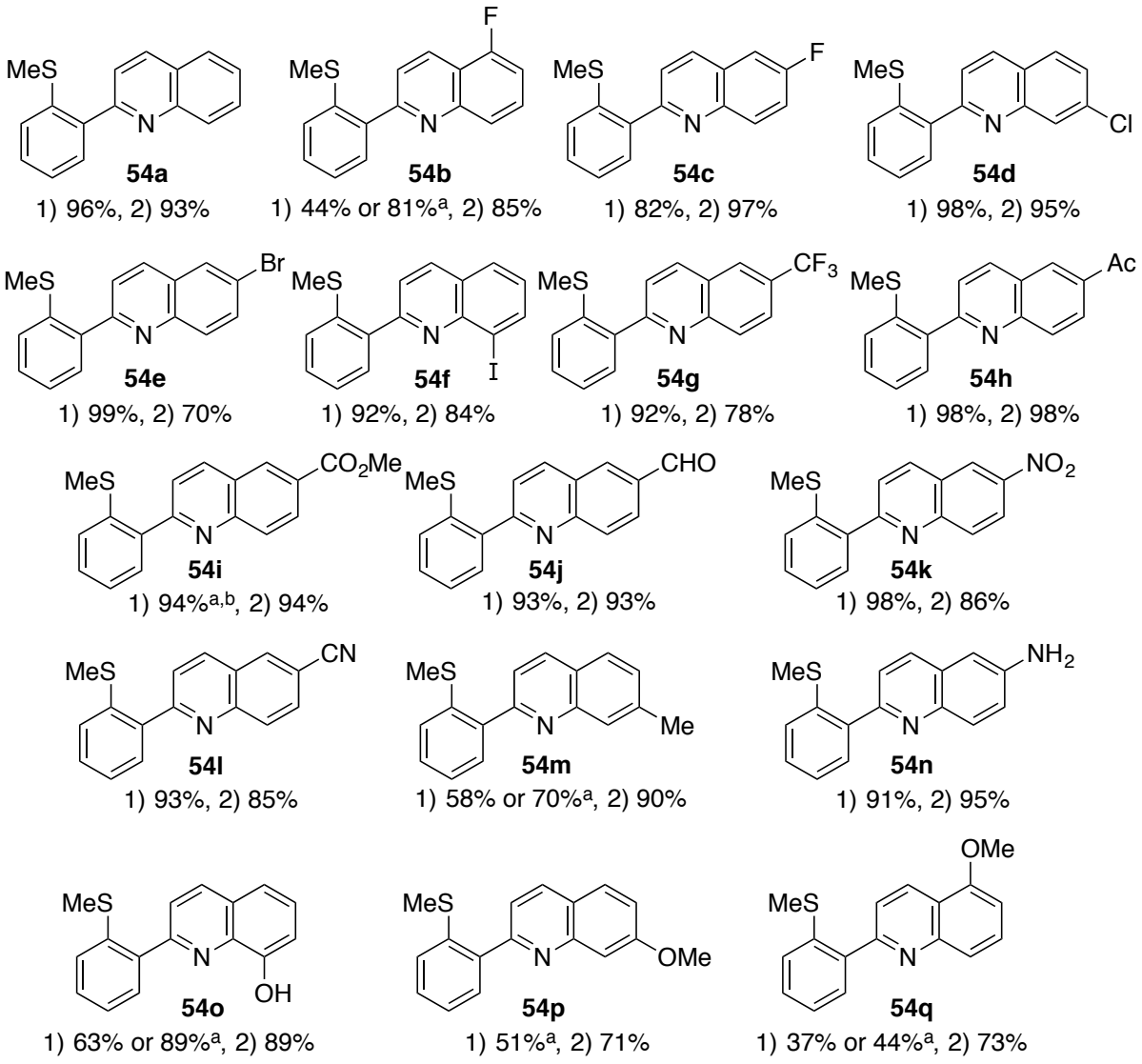
The effect of electron density of the aryl alkyne was seen again in the reduced reactivity of the electron-rich substrates. By heating the reactions that involved methyl and hydroxyl-substituted alkynes at 55 °C it was possible to accelerate the sluggish reactions and achieve full consumption of the starting material, though methoxy-substitution remained problematic.

Encouraged by the broad scope of substituted quinolines, the synthesis of various fused heterocycles was attempted (Table 3.4). As there are numerous reports of

Table 3.3 Two-step quinoline synthesis – alkyne scope



30, 1.2 eq. **51**, 1.0 eq. **54**



54a 1) 96%, 2) 93%

54b 1) 44% or 81%[a], 2) 85%

54c 1) 82%, 2) 97%

54d 1) 98%, 2) 95%

54e 1) 99%, 2) 70%

54f 1) 92%, 2) 84%

54g 1) 92%, 2) 78%

54h 1) 98%, 2) 98%

54i 1) 94%[a,b], 2) 94%

54j 1) 93%, 2) 93%

54k 1) 98%, 2) 86%

54l 1) 93%, 2) 85%

54m 1) 58% or 70%[a], 2) 90%

54n 1) 91%, 2) 95%

54o 1) 63% or 89%[a], 2) 89%

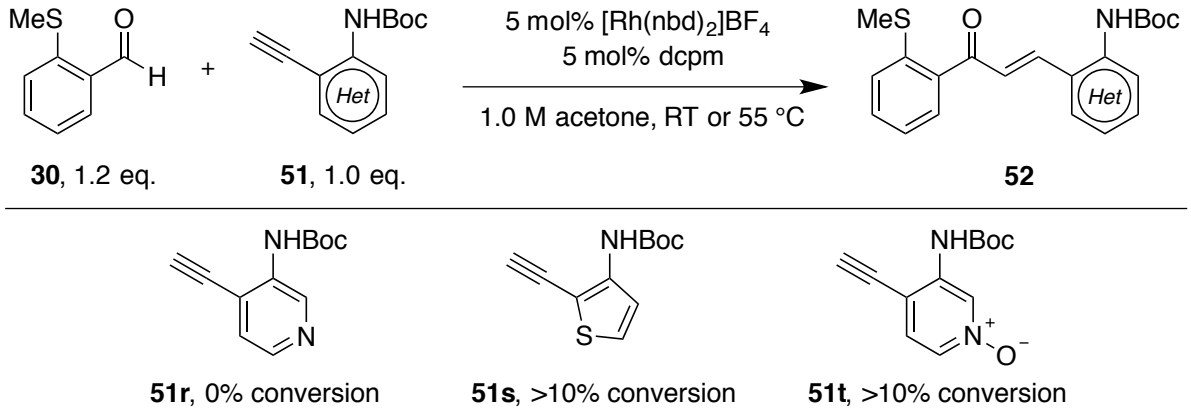
54p 1) 51%[a], 2) 71%

54q 1) 37% or 44%[a], 2) 73%

a) Reaction heated at 55 °C b) DCE used as solvent

the use of thienyl-alkynes in similar hydroacylation procedures, it was surprising that alkyne **51s** did not undergo hydroacylation to any significant extent.

Table 3.4 Attempted hydroacylation of heterocycle-derived alkynes



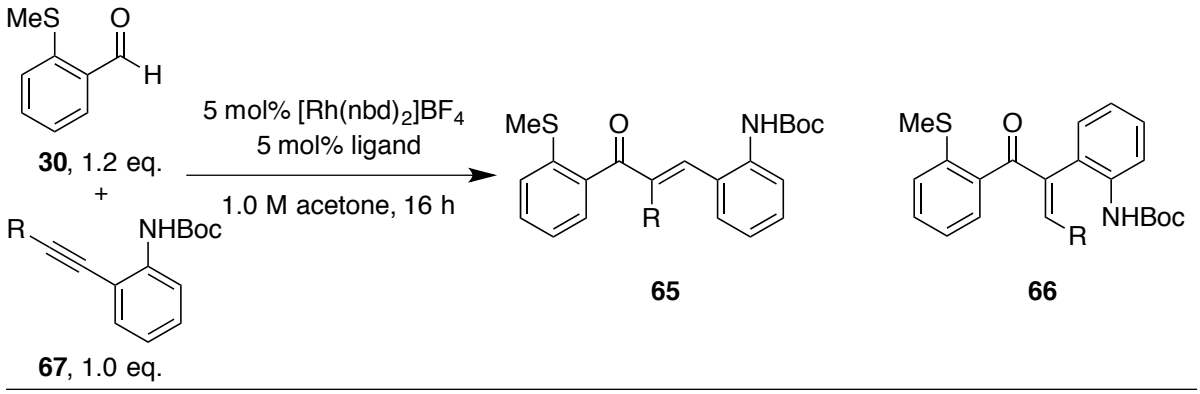
51r, 0% conversion **51s**, >10% conversion **51t**, >10% conversion

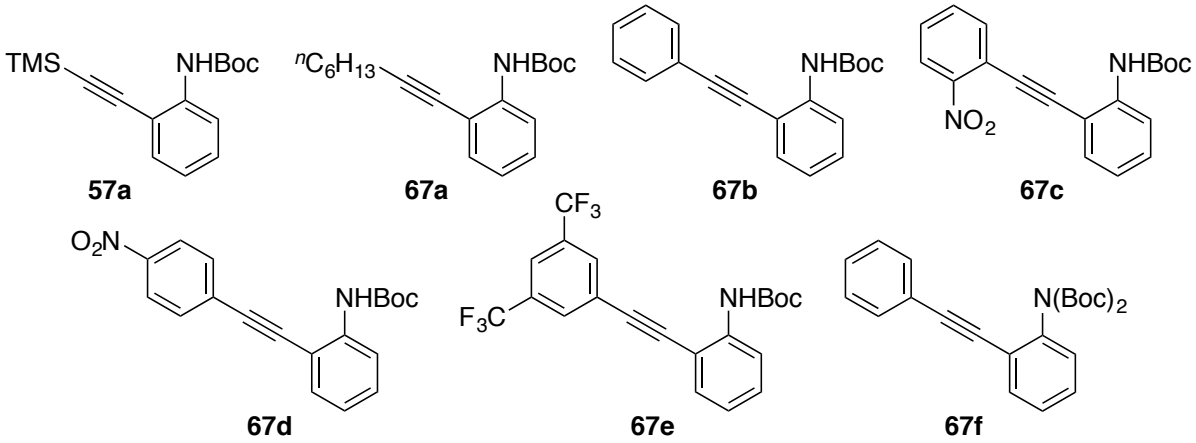
Pyridine and pyridine *N*-oxide examples were similarly unsuccessful, thought to be due to irreversible catalyst coordination and catalyst oxidation respectively.

Thought to derive predominantly through steric factors, hydroacylation of terminal alkynes with small-bite-angle ligands has repeatedly been shown to be highly linearly selective; however, the use of unsymmetrical internal alkynes has often resulted in mixtures of regioisomers. With these more complicated systems, a balance of sterics and electronics must be considered (or in some systems chelation control – Section 2.3.3). Synthesised *via* Sonogashira coupling of *N*-Boc 2-iodoaniline with various terminal alkynes, a number of internal alkynes were tested in hydroacylation. None of the systems employed gave encouraging regioisomeric ratios. In fact the majority of cases exhibited moderate selectivity for the undesired isomer **66** (Table 3.5).

Diarylalkynes appeared most reactive, and were therefore explored in more detail. By modulating the electron density of the system it was possible to obtain moderate selectivity for the desired isomer; however, a combination of an inexplicably poor mass recovery and inability to separate the regioisomers meant that investigations were abandoned. Attempts to suppress *N*-chelation by double Boc-protection resulted in complete suppression of hydroacylation, presumably due to the steric bulk introduced.

Table 3.5 Hydroacylation of internal 2-alkynylanilines



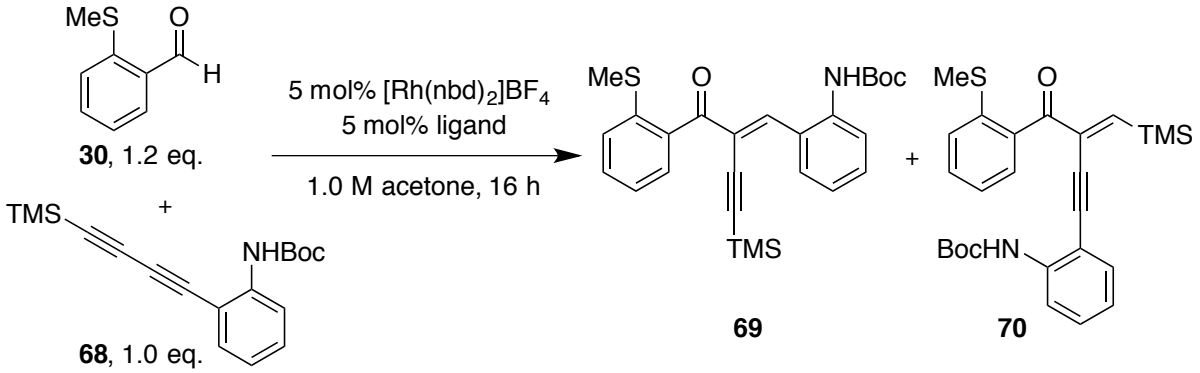


Entry	Alkyne	Reaction conditions	Conversion[a]	**65**:**66**[a]
1	**57a**	dcpm, 55 °C	63%	1:1
2	**67a**	dcpm, 55 °C	72%	<1:10
3	**67b**	dcpm, 55 °C	100%	1:3
4	**67b**	dcpm, RT	60%	1:5
5	**67b**	dppm, 55 °C	78%	1:2
6	**67c**	dcpm, 55 °C	<10%	n/a
7	**67d**	dcpm, 55 °C	100%	3:1
8	**67e**	dcpm, 55 °C	62%	1.5:1
9	**67f**	dcpm, 55 °C	<10%	n/a

a) Determined by ^{1}H-NMR analysis

Reducing the steric bulk of the R substituent by moving from sp^2/sp^3 hybridisation to a linear sp system, it was possible to observe full selectivity for the desired isomer; however, such a strategy introduced new regioisomeric limitations (Table 3.6). It was possible either to observe high conversion (entries 1 and 2) or high selectivity (entries 3 and 4), but not both simultaneously.

Table 3.6 Hydroacylation of dialkyne **68**



Entry	Reaction conditions	Conversion[a]	**69**:**70**[a]
1	dcpm, RT	91%	2:1
2	dcpm, 55 °C	100%	1.3:1
3	dppm, RT	17%	8:1
4	dppm, 55 °C	65%	12:1

a) Determined by ^{1}H-NMR analysis

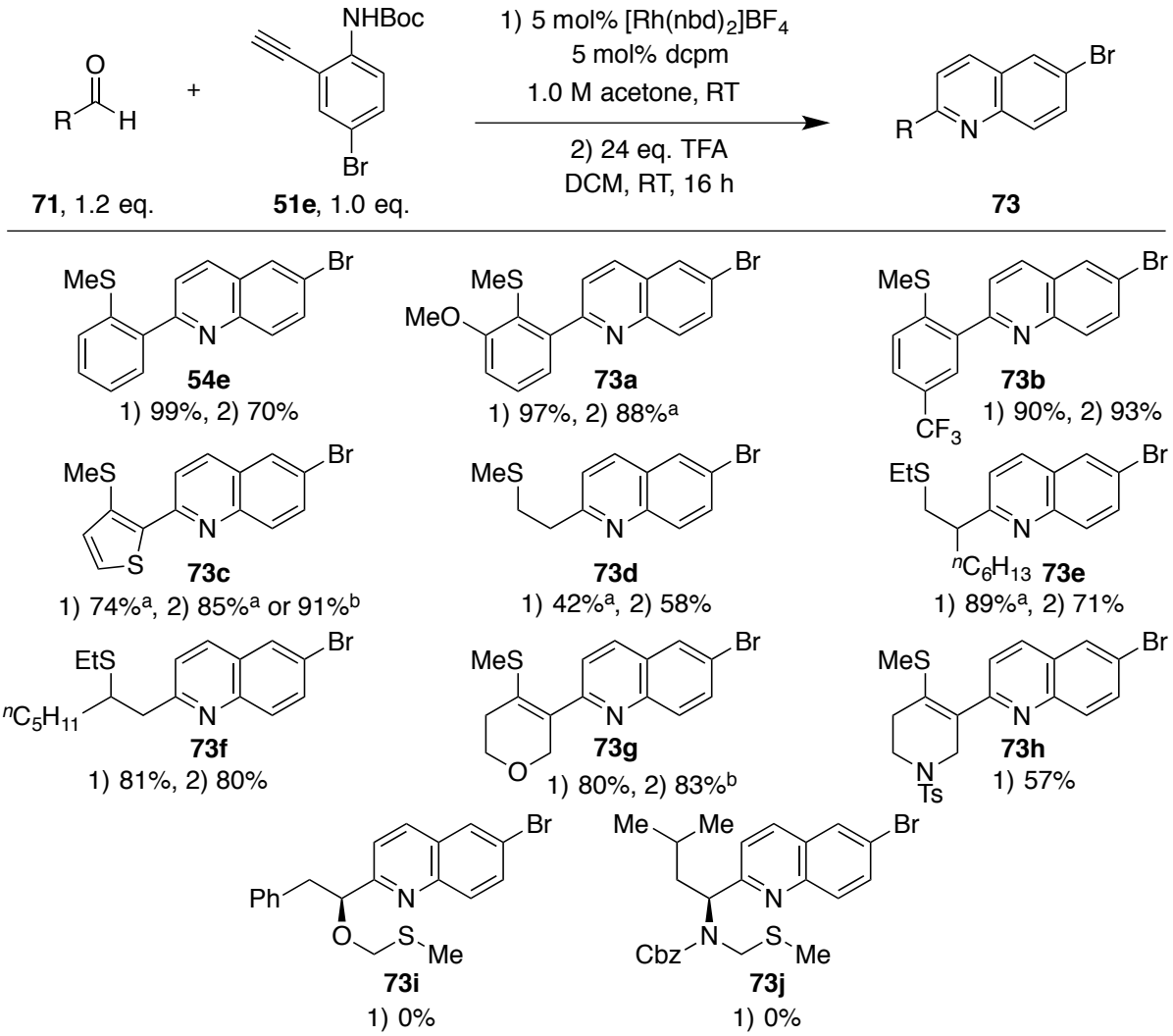
Whilst it may have been possible to find isolated examples where selectivity and yields were high, each new tactic employed increasingly esoteric alkynes, and as such the method would never be general. Attempts were therefore aborted.

3.3.3 Scope of the aldehyde component

In order to assess the reaction scope with respect to the aldehyde component, it was decided that alkyne **51e** would provide a combination of good reactivity (although by no means the most reactive alkyne available), ease of synthesis and the attractive incorporation of a reactive handle for further functionalisation.

A range of aryl (**71a**, **71b**), heteroaryl (**71c**) and alkyl (**71d-f**) aldehydes proved successful substrates (Table 3.7), although the use of 3-methylthiopropional **71d** gave unexpectedly poor results given its ubiquity in previous Willis group reports.

Table 3.7 Two-step quinoline synthesis – aldehyde scope



a) Reaction heated at 55 °C b) Reaction conditions: EtOH/H_20 (1:1), 170 °C μW, 3 h

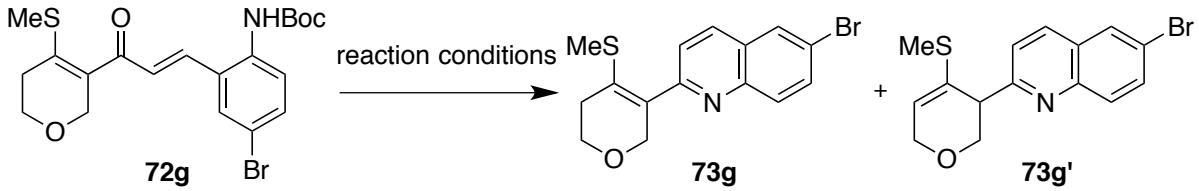
Alkenyl aldehydes **71g** and **71h** were also tested and found to be extremely reactive substrates. Full conversion was observed for both examples shown; however, the loss of yield relative to the aryl substrates reflects the increased reactivity of the products to C-S activation processes. This improved reactivity has previously been explored in the C-S Suzuki-type coupling reaction.[60] Unfortunately, lowering the temperature to 0 °C led to issues with solubility and the generation of a complex mixture of products. MTM-substituted α-hydroxy (**71i**) and α-amino (**71j**) aldehydes (see Chapter 5 for more detail) disappointingly exhibited no reactivity with alkyne **51e**, either at room temperature or 55 °C. Poor reactivity with bulky substrates has been observed in previous studies with these aldehydes; whilst disappointing, this observation is not unusual.

For the quinoline formation step, the previously optimised TFA mediated cyclisation either under ambient conditions or with mild heating was sufficient to cyclise each of the examples; however, for the alkenyl example the quinoline was isolated as a inseparable mixture of regioisomers (**73g** and **73g'**). The cyclisation reaction was repeated at a number of different temperatures, and the conversion and product ratios monitored by HPLC analysis (Table 3.8).

Following a brief optimisation, alternative conditions were developed that enabled quinoline formation under neutral conditions, preventing product isomerisation. By coupling a thermal Boc-deprotection with cyclisation under microwave conditions, (Table 3.8 Entry 5) quinoline **73g** was isolated as a single regioisomer in 83% yield (see Table 3.7). This microwave-mediated cyclisation, complimentary to the previously developed acidic conditions, has been shown to afford

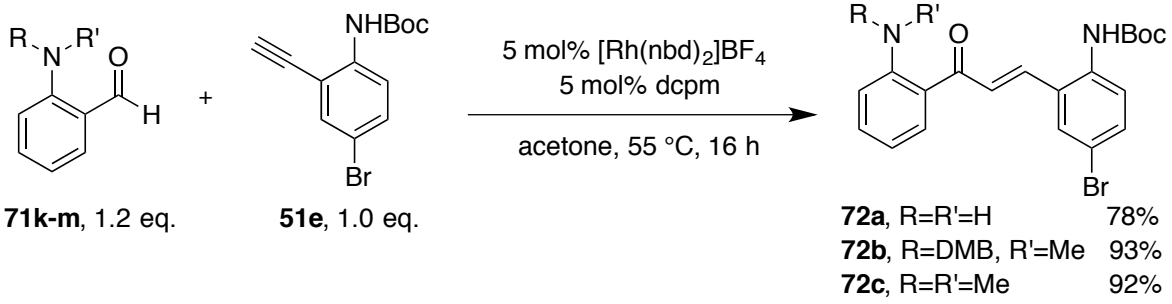
higher quinoline yields in examples where both conditions have been attempted (e.g. examples **73c** and **73m**).

Table 3.8 Cyclisation of intermediate **72g**



Entry	Reaction conditions	Conversion	**73g**:**73g'**[a]
1	24 eq TFA, DCM, RT, 16 h	65%	2.0:1
2	24 eq TFA, DCM, 40 °C, 16 h	80%	1.7:1
3	24 eq TFA, $CHCl_3$, 60 °C, 16 h	100%	1.4:1
4	24 eq TFA, DCE, 70 °C, 16 h	100%	1.3:1
5	EtOH/H_2O (1:1), 170 °C μW, 3 h	100%	1:0

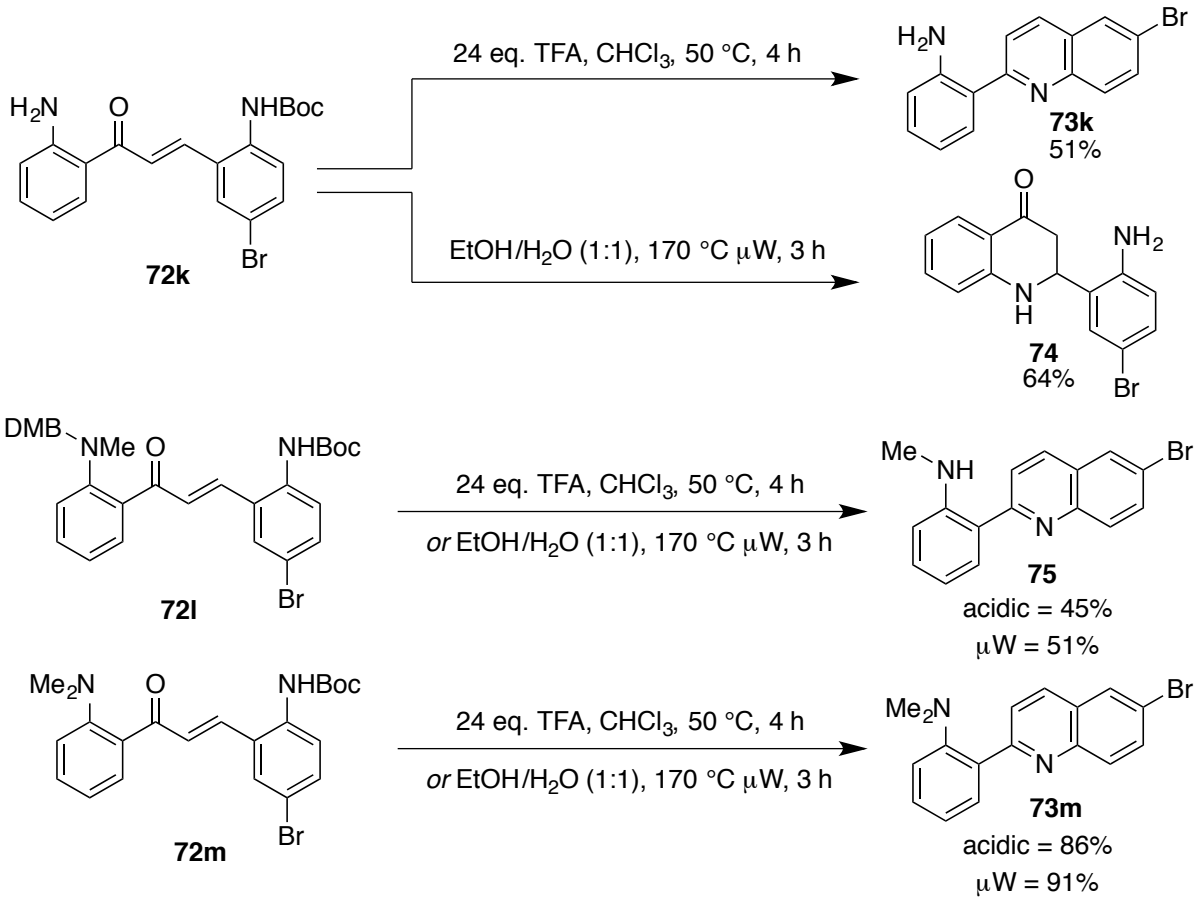
Aniline based aldehydes (as mentioned in Section 1.1.3) were also suitable for the hydroacylation of alkyne **51e**. (Scheme 3.12).



Scheme 3.12 Hydroacylation employing 2-aminobenzaldehydes

The cyclisation of these intermediates was however less straightforward (Scheme 3.13). Under acidic conditions intermediate **52k** underwent the expected cyclisation, although yields were moderate, and a number of other minor products were also observed. Thermal conditions furnished dihydroquinolone **74**, in a 64% yield, *via*

an intramolecular aza-Michael addition, analogously to previously published work.[46] DMB protection was not a suitable strategy for avoiding these side reactions, as both acidic and themal conditions effected DMB deprotection, with only moderate yields of quinoline **75** isolated.

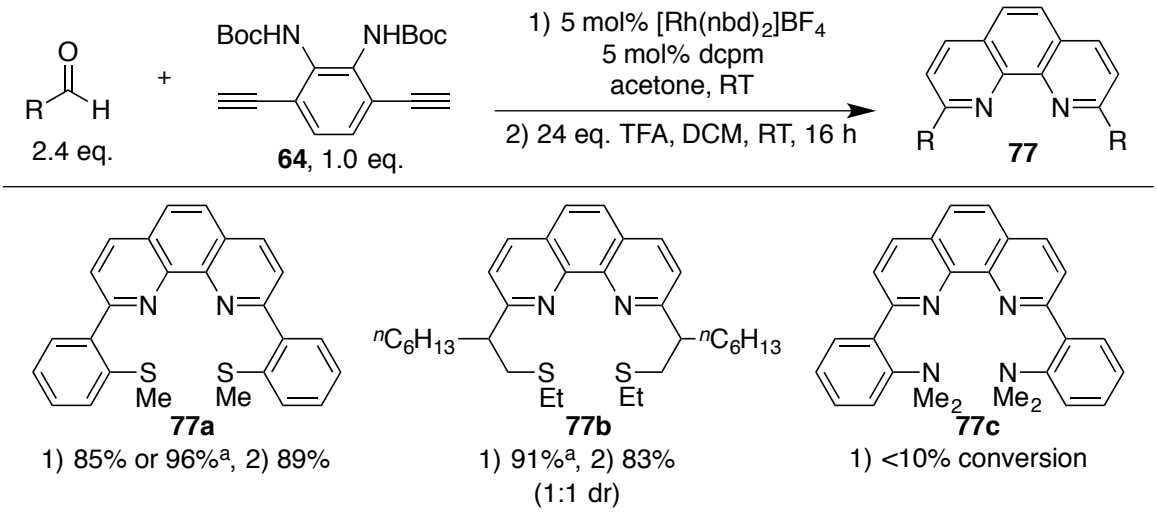


Scheme 3.13 Cyclisation of 2-aminobenzaldehyde-derived intermediates

Cyclisation of 2-(dimethylamino)benzaldehyde-derived chalcone **72m** afforded quinoline **73m** in excellent yields under both acidic and neutral conditions. Again the microwave-mediated reaction outperformed the TFA process in terms of isolated yield.

Using dialkyne **64**, synthesised in Section 3.3.1, it was possible to access a number of interesting phenanthrolines, which could potentially be used as tetradentate ligands. The scope of aldehydes suitable for this process was slightly narrower than that recorded for the simple quinoline examples (Table 3.9).

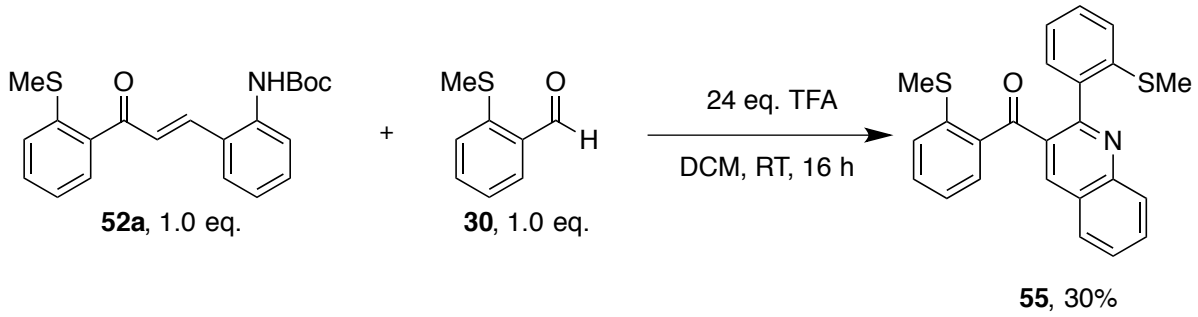
Table 3.9 Phenanthroline synthesis *via* dialkyne **64**



With new insights into both the hydroacylation and cyclisation steps gained through the process of scoping, another attempt to develop a one-pot procedure was undertaken.

3.4 Revisited optimisation

In order to ascertain the identity of the side product observed in the initial optimisation stage, hydroacylation product **52a** was exposed to the standard cyclisation conditions in the presence of stoichiometric aldehyde **30** (Scheme 3.14). A mixture of quinoline **54a** and the side product was obtained. The side product was then characterised as quinoline **55**.



Scheme 3.14 Reaction of enone **52a** with excess aldehyde under acidic cyclisation conditions

Figure 3.6 shows the postulated mechanism of this side reaction. Under acidic conditions, previously isolable (see Section 3.2.1) imine **50** undergoes 6π-electrocyclisation, followed by rearrangement and oxidation to afford quinoline **55**. There are a number of similar transformations reported in the literature, however most reports involve reaction temperatures in excess of 100 °C.[221, 222, 223, 224, 225, 226]

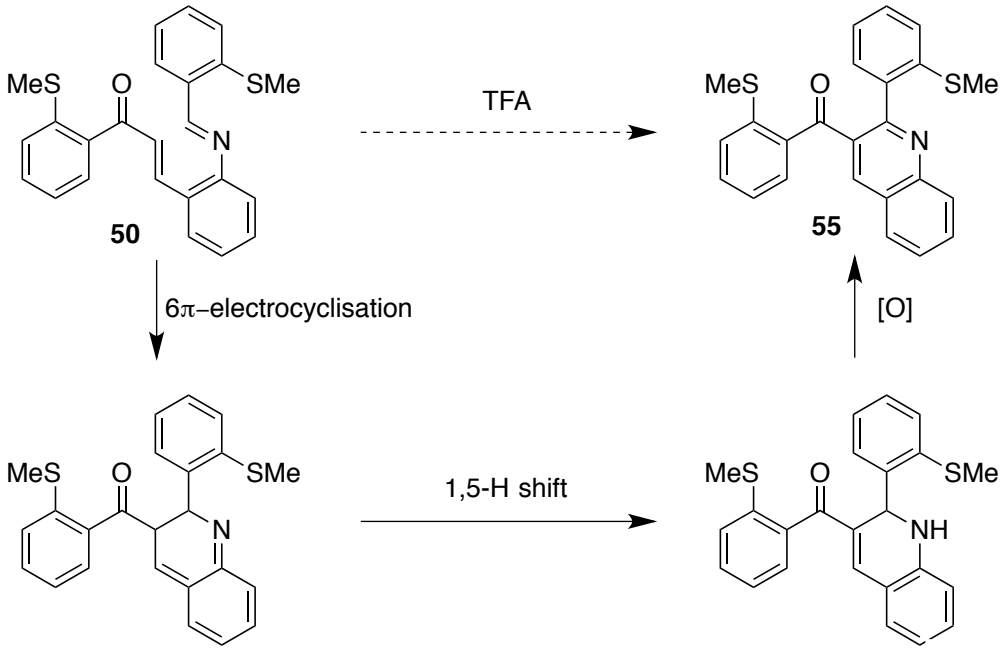
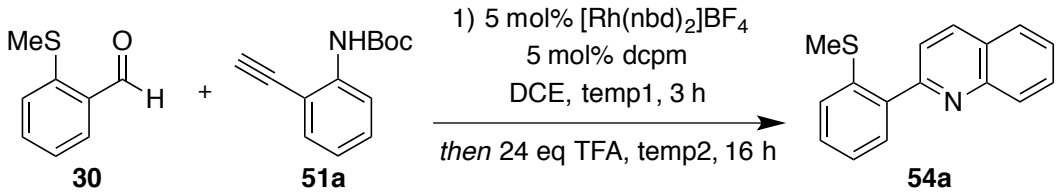


Figure 3.6 Mechanism of formation of quinoline **55**

Unfortunately, more in depth optimisation of tandem conditions did not yield any improvement over the previous isolated yields (Table 3.10). It was found that the best yields were obtained when the alkyne and aldehyde were used in equal stoichiometry, leaving no excess starting material to interfere with the cyclisation step.

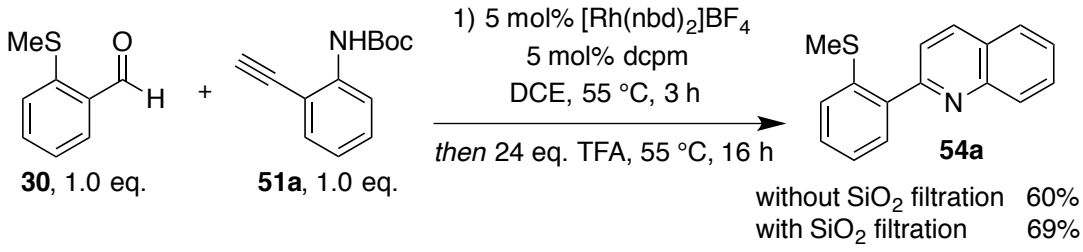
Table 3.10 Attempted one-pot synthesis of quinoline **54a**



30 **51a** **54a**

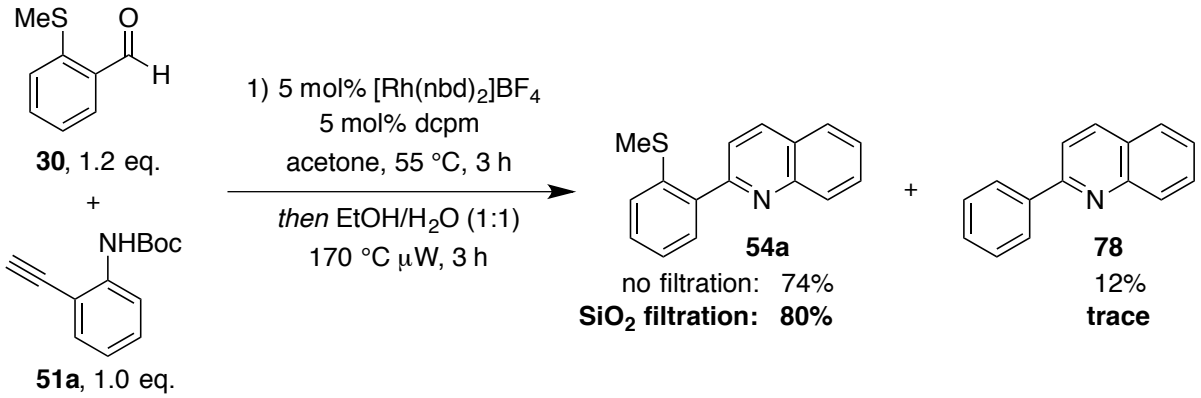
Entry	**30**:**51a**	temp1	temp2	Isolated yield
1	1:1	RT	RT	45%
2	1:1	RT	55 °C	49%
3	1.05:1	RT	55 °C	46%
4	1:1.2	RT	RT	46%
5	1:1.2	RT	55 °C	44%
6	1:1	55 °C	RT	54%
7	**1:1**	**55 °C**	**55 °C**	**60%**
8	1.05:1	55 °C	55 °C	56%
9	1:1.2	55 °C	55 °C	56%

Heating both the hydroacylation and cyclisation steps also appeared mildly beneficial, with a maximum yield of 60% recorded (Entry 7). Removal of the rhodium residues *via* filtration improved the yield to 69% (Scheme 3.15), although this was still lower than for the two-step process used in the reaction scope.



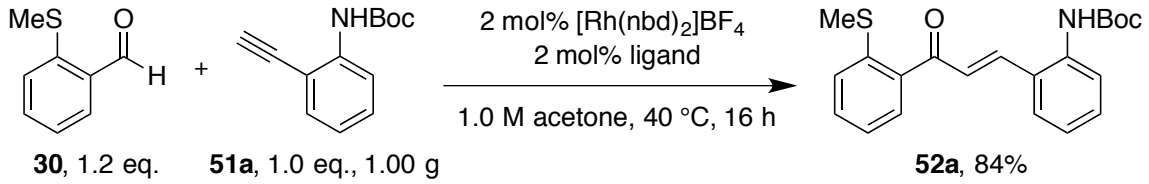
Scheme 3.15 One-pot vs. telescoped quinoline synthesis

When the newly developed thermal deprotection/cyclisation conditions were applied to the one-pot synthesis, no side reaction to form **55** was observed and the yield was improved (Scheme 3.16). What was observed was the product (**78**) of what appeared to be a transfer hydrogenation process resulting in C-S reduction. The reductant for this process was believed to be the ethanol solvent. By removing the rhodium *via* filtration, the side reaction was suppressed and a final optimised yield of 80% for the two-step process was obtained.



Scheme 3.16 Telescoped quinoline synthesis employing microwave mediated cyclisation

By increasing the temperature slightly it was possible to decrease the catalyst loading to 2 mol% whilst maintaining a high yield of hydroacylation product in a gram scale reaction (Scheme 3.17).



Scheme 3.17 Large-scale hydroacylation of alkyne **51a**

As a result of this revisited optimisation, many of the minor issues in the initial process have been addressed. What had yet to be addressed, however, are the disappointing yields obtained when using electron-rich methoxy alkynes.

3.5 Accessing electron-rich quinolines and quinoline *N*-oxides

In order to access methoxy-substituted quinolines an alternative strategy involving the use of 2-ethynyl nitrobenzenes was envisaged. These compounds would be significantly more electron-poor than the *N*-Boc amino substrates,[227] which has been shown to be more beneficial for the HA step in Section 3.3.2. There exist a number of publications detailing the reductive cyclisation of similar nitro-substituted intermediates.[228, 229, 230, 231, 232] By controlling the relative rates of reduction and cyclisation it should be possible to access not just quinolines but also quinoline *N*-oxides[233, 234, 235] and tetrahydroquinolines (Figure 3.7).[236, 237]

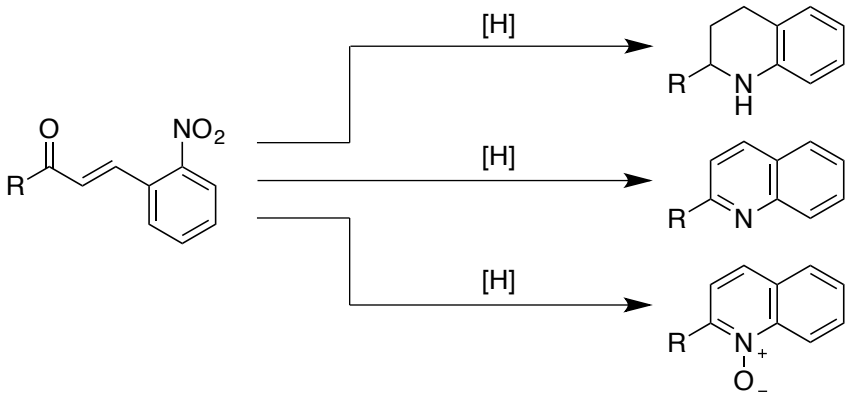
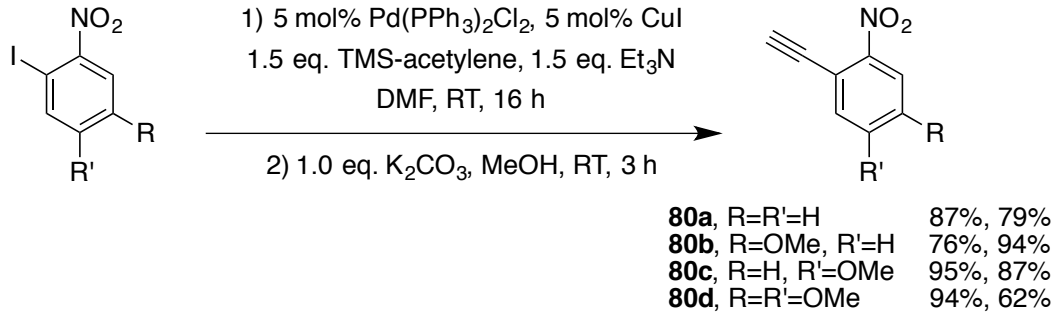


Figure 3.7 Reductive cyclisations for the synthesis of quinoline derivatives

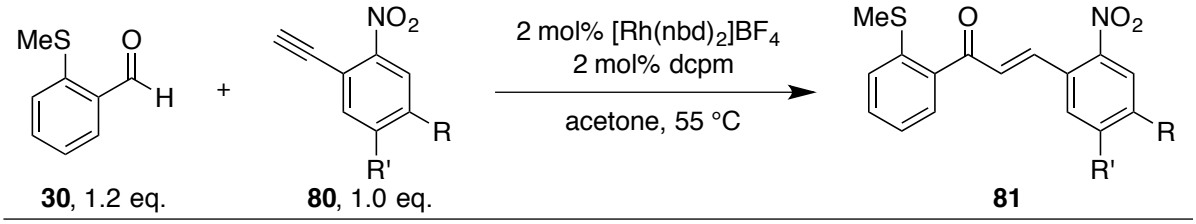
The required alkynes were synthesised from commercially available, or easily accessible 2-iodo nitrobenzenes *via* a Sonogashira/desilylation sequence (Scheme 3.18).



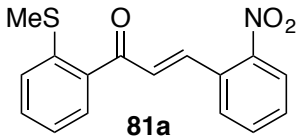
Scheme 3.18 Synthesis of 2-ethynyl nitrobenzenes

In hydroacylation reactions, these substrates proved much more reactive than the corresponding NHBoc substrates, with only 2 mol% catalyst required to obtain excellent yields for examples **81a** and **81b** (Table 3.11).

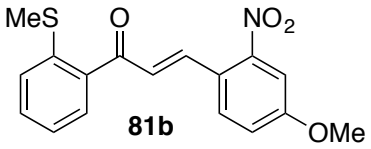
Table 3.11 Hydroacylation of 2-ethynyl nitrobenzenes



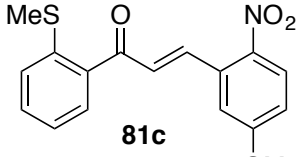
30, 1.2 eq. **80**, 1.0 eq. **81**



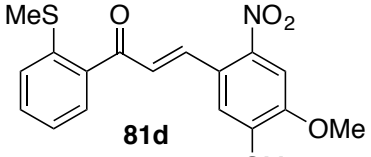
81a
(10 min, 97%)



81b
(15 min, 97%)



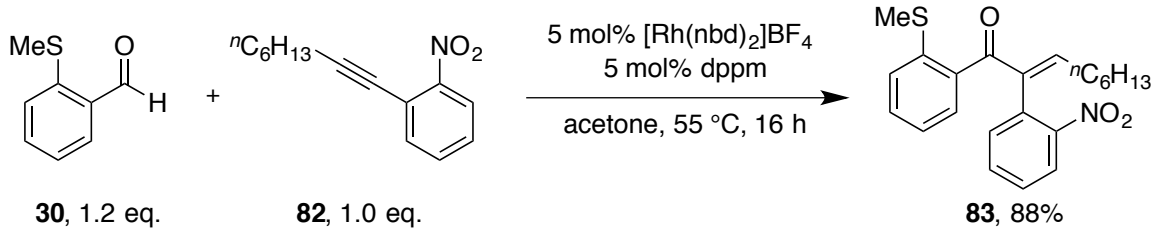
81c
(16 h, trace)



81d
(16 h, trace)

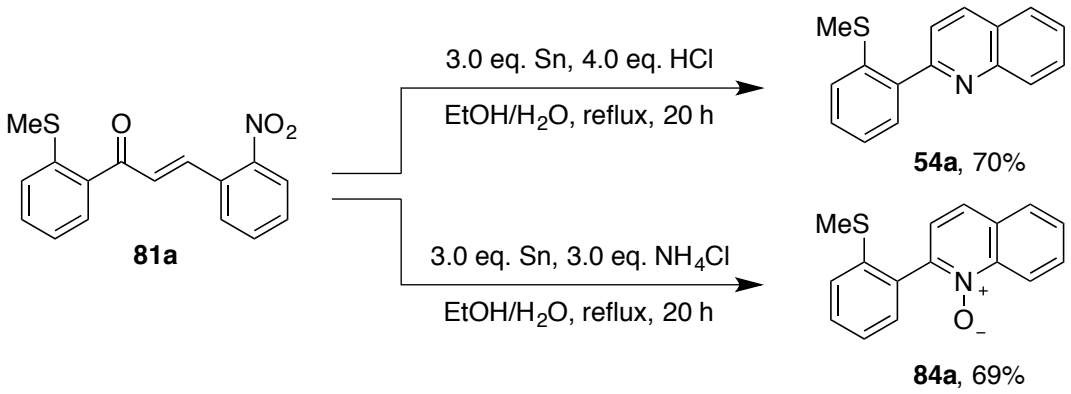
What was surprising was that by changing the substitution pattern from aryl alkyne **81b** to **81c** and **81d** appeared to completely shut the reaction down. Further experiments at 5 and 10 mol% catalyst loadings did not significantly improve the conversion.

Hydroacylation of NO_2-containing internal alkyne **82** was high yielding; however, exclusive formation of isomer **83** was observed (Scheme 3.19).



Scheme 3.19 Hydroacylation of 2-alkynyl nitrobenzene **82**

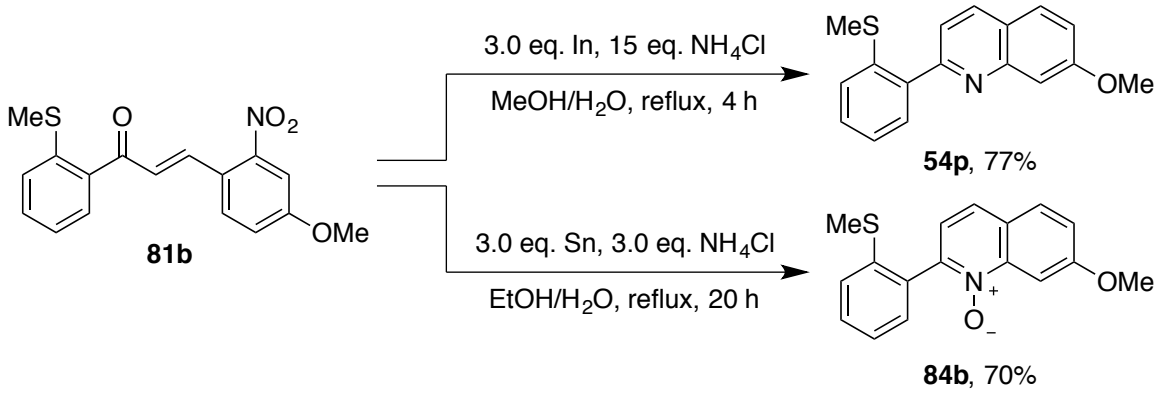
The cyclisation of intermediate **81a** to either quinoline **54a** or quinoline *N*-oxide **84a** was achieved using previously reported literature conditions (Scheme 3.20). The slower reduction observed with Sn/NH_4Cl allows for cyclisation before full reduction takes place. When the reaction is left for a full 72 hours, full reduction to quinoline **54a** is instead observed.



Scheme 3.20 Reductive cyclisations of enone **81a**

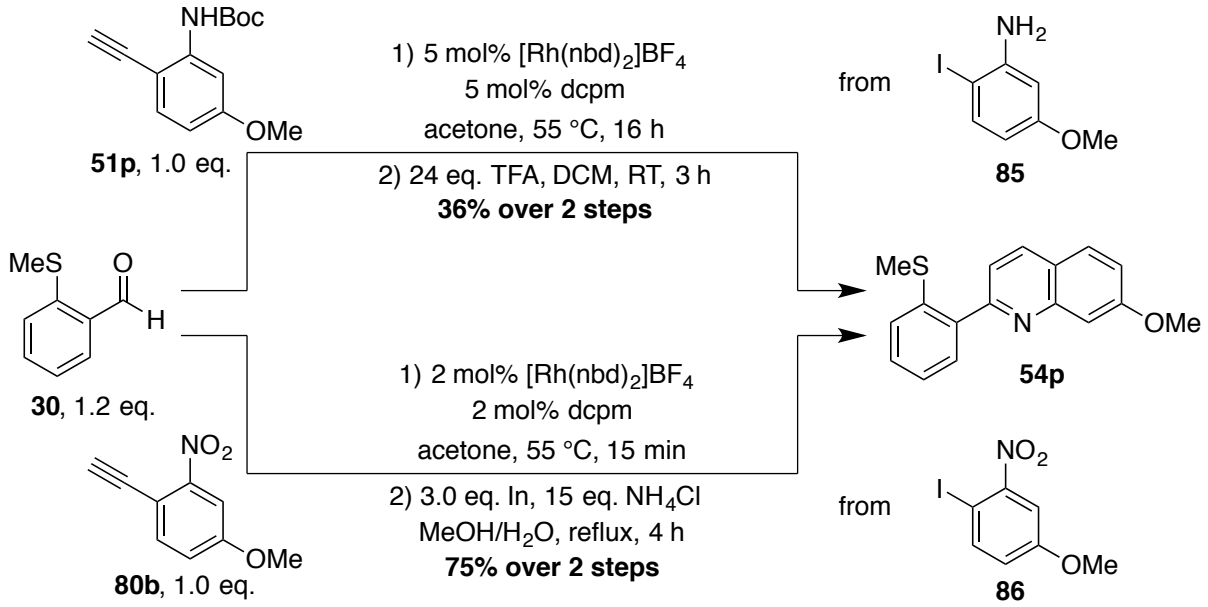
A number of literature precedented reductive cyclisations were attempted; however, only those involving stoichiometric metal reductants were successful. The presence of the sulfide-carbonyl chelate appears to hinder any reaction involving TM-catalysis and as such, the palladium-catalysed cyclisation to the tetrahydroquinoline was repeatedly unsuccessful.

Intermediate **81b** was also cyclised to both quinoline **54p** and quinoline *N*-oxide **84b** in very good yields, although slightly modified cyclisation conditions were required to achieve good yields for quinoline **54p** (Scheme 3.21).



Scheme 3.21 Reductive cyclisations of enone **81b**

The two-step yields for synthesising electron-rich quinoline **54p** *via* this new route is significantly higher than was found to be the case in the original alkyne scope (Scheme 3.22). It is also significant that considerably less rhodium catalyst is required, and the iodo starting material is markedly cheaper (£16 for 5 g of **86** vs. £251 for 5 g of **85** – Fluorochem Ltd in 05/2016).



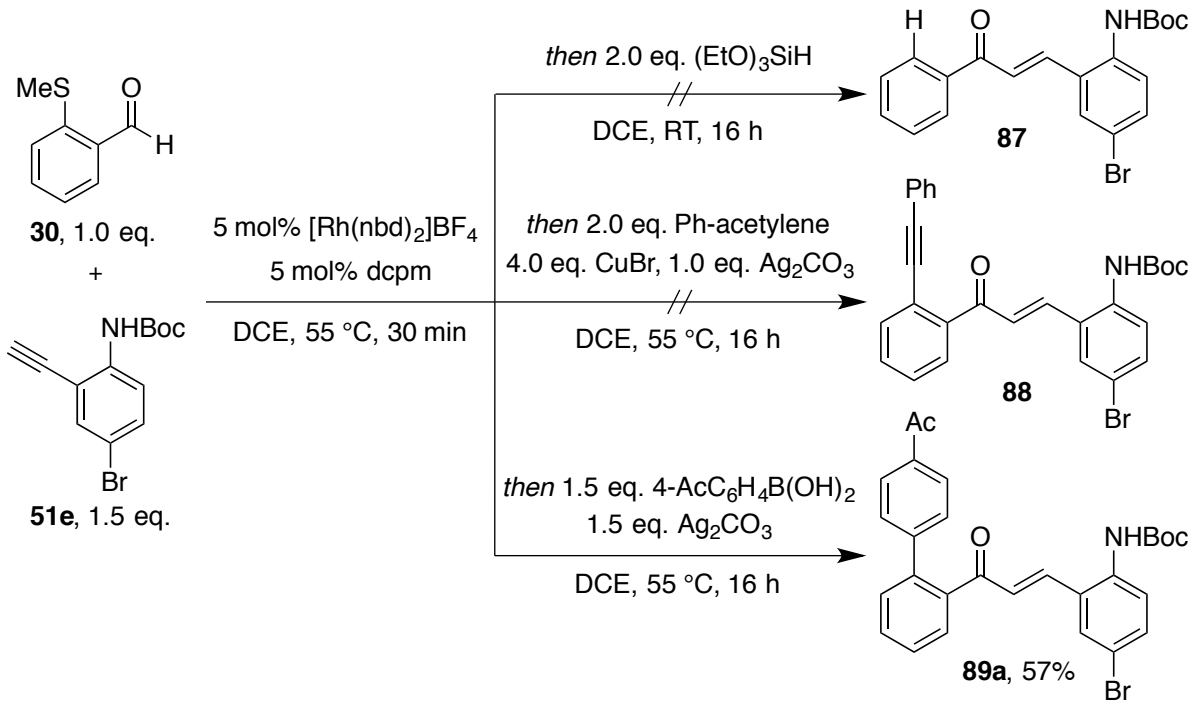
Scheme 3.22 NO_2 vs. NHBoc in the synthesis of quinoline **54p**

Whilst this modification has widened the scope of quinoline derivatives accessible, each of the quinolines yet synthesised necessarily incorporates a β-chelating tether in the 2-substituent originating from the aldehyde.

3.6 Accessing tether-free quinolines *via* C-S functionalisation

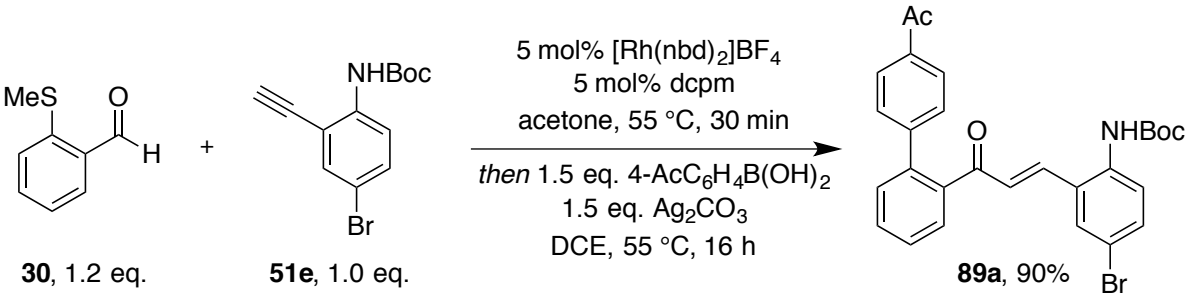
Non-tethered aldehydes proved unsuitable for hydroacylation with these alkynes; however, as mentioned in Section 1.1.4, a number of tandem hydroacylation – C-S functionalisation reactions have been reported by the Willis group.[58, 59, 238]

Using the standard conditions reported in these publications a number of test reactions were attempted (Scheme 3.23). The C-S reduction process was unsuccessful, producing only the product of hydrosilylation. Unpublished conditions to access Sonogashira-coupling products resulted in a complex mixture of products; however, the attempted tandem hydroacylation – C-S Suzuki-coupling did produce tether-free chalcone **89a** in reasonable yield over the two-step process.



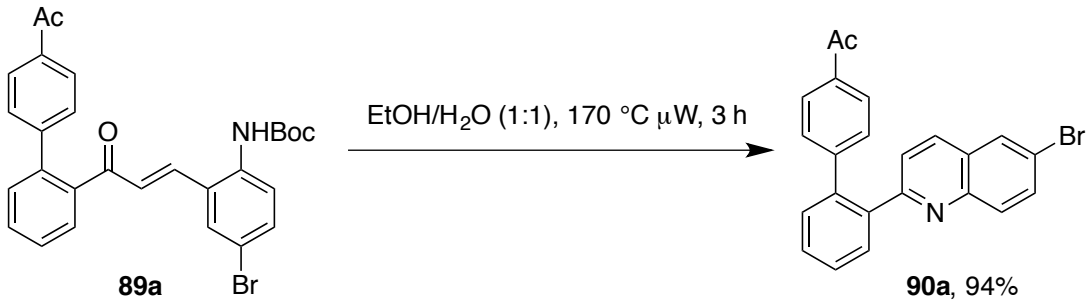
Scheme 3.23 Tandem hydroacylation – C-S functionalisation test reactions

By employing an excess of the aldehyde component, as in the previous sections, the yield was drastically improved (Scheme 3.24), and no further optimisation was necessary. The initial hydroacylation reaction was conducted at 55 °C to enable short reaction times, such that the second step could be carried out before significant catalyst deactivation had occurred.



Scheme 3.24 Optimised hydroacylation – C-S Suzuki coupling reaction

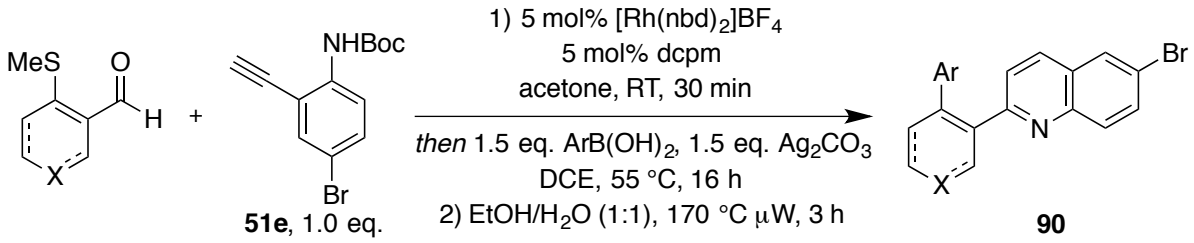
Exposure of enone **89a** to the microwave-mediated deprotection/cyclisation conditions afforded quinoline **90a** in an excellent yield (Scheme 3.25).

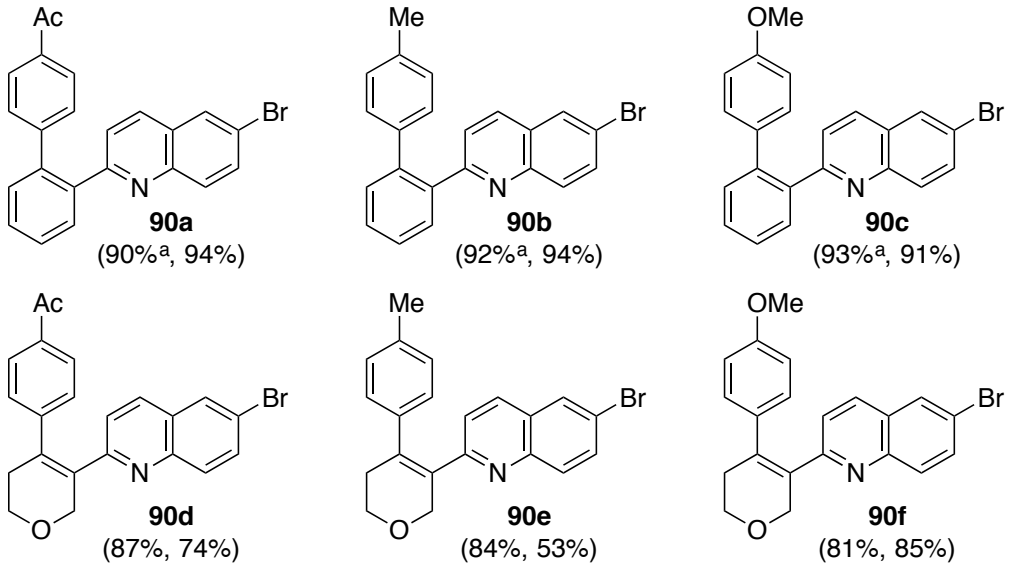


Scheme 3.25 Cyclisation of enone **89a**

With this process optimised, a brief scope was undertaken. As shown in Table 3.12, both electron-poor and electron-rich boronic acids were successfully employed, as was the use of alkenyl β-S aldehyde **71g**. For these substrates, the initial hydroacylation had to be conducted at room temperature to prevent significant carbothiolation; however, the high reactivity of these substrates even under ambient conditions meant that short reaction times were still achieved.

Table 3.12 Three-step, two-pot synthesis of sulfur-free quinolines





a) Reaction heated at 55 °C

It has now been demonstrated that using chelate-controlled hydroacylation does not necessitate incorporation of the tether into the quinoline products. A range of substitution at the C(2) and C(5) to C(8) positions has been accessed; however, no examples of C(3)- or C(4)-substituted quinolines had yet been synthesised.

3.7 Accessing substitution at the C(3) and C(4) positions

Retrosynthetic analysis (Figure 3.8) shows that the C(3) and C(4) positions of the quinoline correspond to the α and β positions of the chalcone respectively.

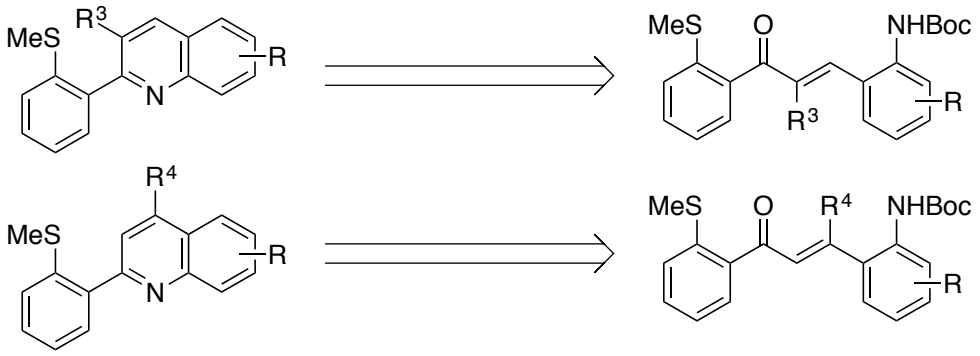


Figure 3.8 Retrosynthetic analysis of C(3)- and C(4)-substitution

By using internal alkynes, it should be possible to access substitution at the *α*-position (Figure 3.9); however, as previously detailed, the selectivity of these reactions can be problematic.

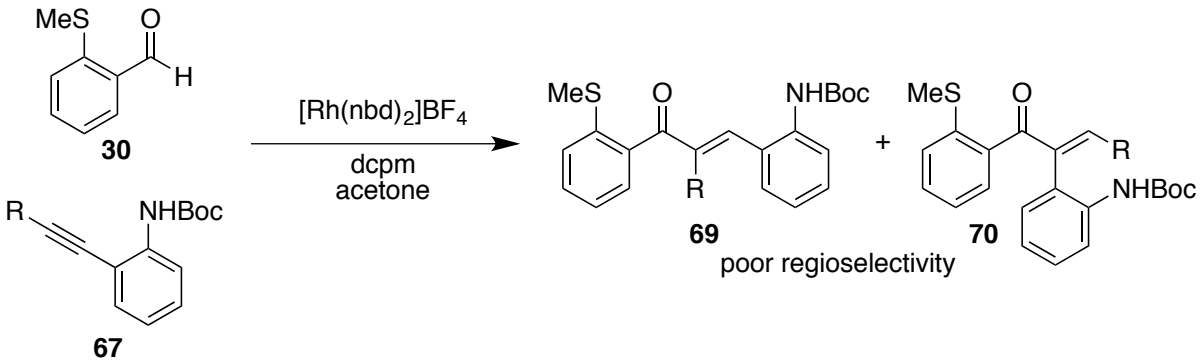


Figure 3.9 Hydroacylation of internal alkynes

It was instead decided that derivatisation of the product of hydroacylation (**52)** would be a logical method for introducing functionality at these positions (Figure 3.10).

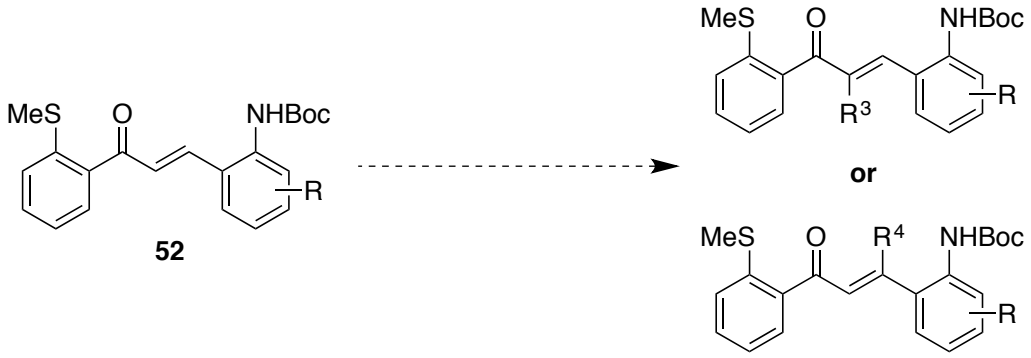


Figure 3.10 Intermediate functionalisation for introducing C(3)- and C(4)-substitution

A number of suitable transformations have been reported in the literature on similar chalcone substrates.

3.7.1 C(3) substitution

In order to introduce α-functionality to the chalcone, the first reaction attempted was an α-bromination process (Figure 3.11).

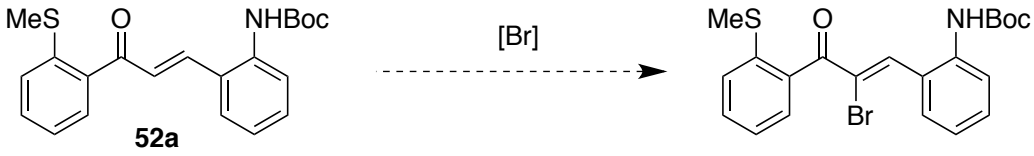
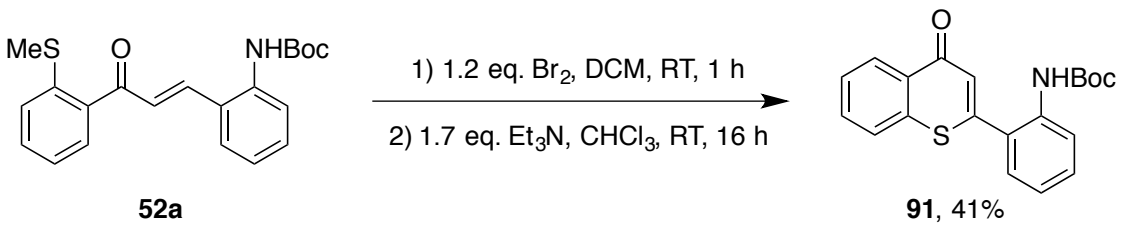


Figure 3.11 Proposed α-bromination of enone **52a**

The standard conditions employed for the synthesis of *α*-bromo chalcones produced a messy mixture of compounds.[239] Whilst a small amount (<10%) of the desired product was isolated, the major product was characterised as thioflavone **91** (Scheme 3.26).



Scheme 3.26 Unexpected synthesis of thioflavone **91**

This unexpected reactivity is thought to proceed *via* a 6-*exo*-tet opening of the bromonium formed in the first step (Figure 3.12). Subsequent demethylation and elimination of HBr would afford the pseudo-aromatic thioflavone. Although it means that the α-bromination of β-sulfide containing enones would be problematic, it is in itself an interesting oxidative cyclisation route to thiochromone derivatives.

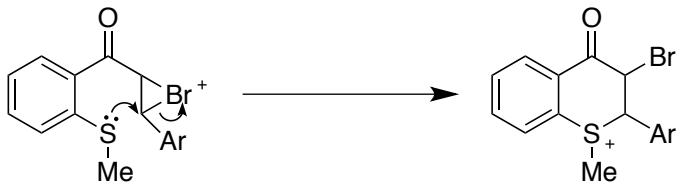
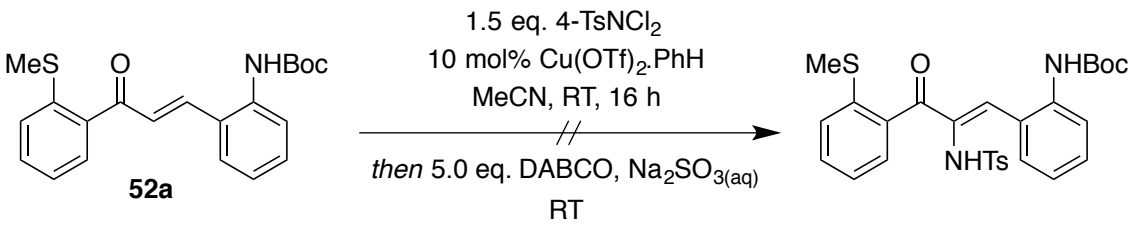


Figure 3.12 6-*exo*-tet opening of bromonium ion

Another transformation attempted was an α-amination reaction reported by Cannon and Li in 2005.[240] On simpler substrates, this reaction is known to proceed *via* initial aminochlorination then elimination of HCl to form the product. Unfortunately, on chalcone **52a**, only a complex mixture of products was obtained (Scheme 3.27).

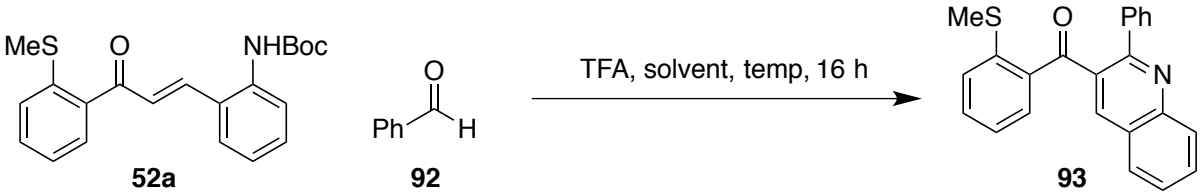


Scheme 3.27 Attempted α-amination of enone **52a**

Whilst α-functionalisation of the intermediate seemed to be beyond reach, this was not the only way that C(3)-substitution could be introduced. Use of the reaction serendipitously discovered during the optimisation (Section 3.2 and 3.4) involving the deprotected intermediate and excess aldehyde would also provide a 2,3-disubstituted quinoline. Switching aldehyde **30** for benzaldehyde **92** did not appear to affect the reaction noticeably (Table 3.13, Entry 1). Optimisation of this process focussed on

attempting to suppress the normal quinoline formation process and to favour the formation of the imine followed by 6π-electrocyclisation. Initially it was thought that the pericyclic reaction would benefit from elevated temperatures; however, this markedly decreased the yield (Entry 2). Increasing the equivalents of aldehyde improved the reproducibility of the reaction, accompanied by a small increase in the yield (Entry 3).

Table 3.13 Optimisation for the synthesis of quinoline **93**

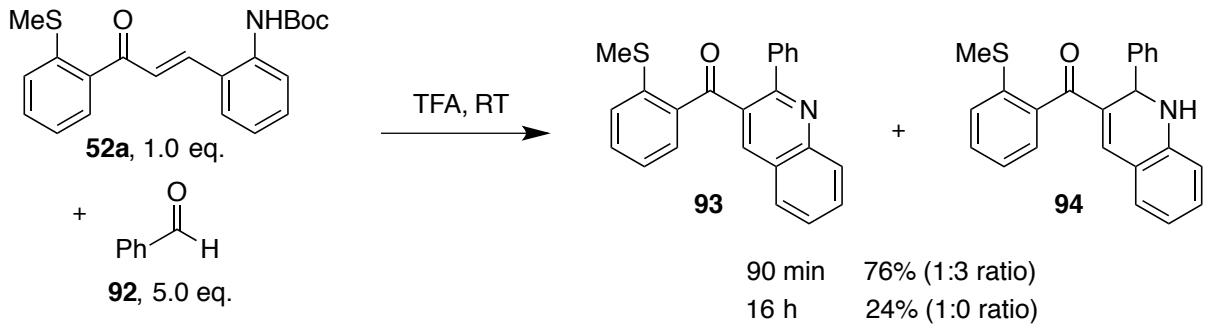


Entry	eq. **92**	eq. TFA	Solvent	Temp.	Isolated yield
1	1.0	24.0	0.05 M DCM	RT	30%
2	1.0	12.0	0.06 M DCE	70 °C	>10% (mostly quinoline **54a**)
3	3.0	12.0	0.06 M DCM	RT	32%
4	5.0	24.0	0.2 M THF	RT	0% (100% r.s.m.)
5	5.0	24.0	0.2 M 1,4-dioxane	RT	0% (100% r.s.m.)
6	5.0	24.0	0.2 M acetone	RT	Complex mixture
7	5.0	24.0	0.2 M MeCN	RT	45%

Conducting the reaction in a number of different solvents proved unsuccessful (entries 4-6), until acetonitrile was tried. (Entry 7). Further experiments varying the concentration and equivalents of aldehyde did not provide any yields higher than 45%.

By conducting the reaction in neat TFA, formation of the 2-aryl quinoline **54a** was completely suppressed, and TLC analysis appeared to show selective product formation. Following purification it was observed that what was thought to be the

product was a 1:3 mixture of product and unoxidised dihydroquinoline **94** (Scheme 3.28). Leaving the reaction longer appeared to result in decomposition of the intermediate and/or product as only a 24% isolated yield was achieved. Further repetition of these reactions gave wildly inconsistent results. The degree to which the aldehyde and chalcone were premixed before TFA addition was thought to have a large impact.



Scheme 3.28 Synthesis of quinoline **93** using TFA as a solvent

Control experiments on the isolated mixture of **93** and **94** showed that oxidation could be achieved with either DDQ or MnO_2; however, addition of either of these reagents to the crude reaction mixture resulted only in a complex mixture of decomposition products. Success in the following section on C(4) substitution curtailed further investigations.

3.7.2 C(4) substitution

In the realm of heterocycle synthesis, there are noticeable precedents for the β-functionalisation of enone intermediates, not least the use of the Heck reaction as demonstrated by Donohoe.[145, 146, 147, 162] Whilst such a tactic had proved successful for the Willis group's furan synthesis, application in the synthesis of pyrroles was not able to be achieved. Unfortunately, this proved again to be the case when applied to enone

52a, with a range of Heck-coupling conditions unable to afford the desired trisubstituted alkene (Figure 3.29). Chalcones are notoriously difficult substrates for Heck reactions, and the use of exotic ligands[241] or coupling reagents[242] is often required.

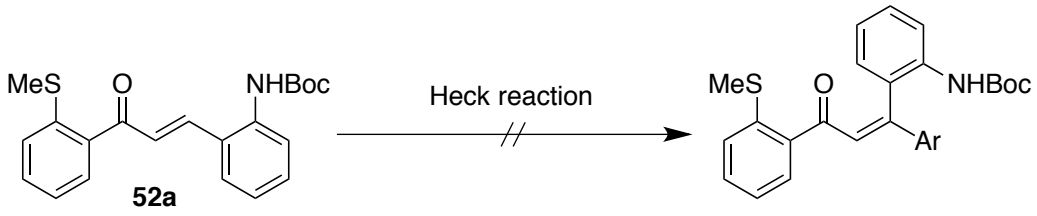
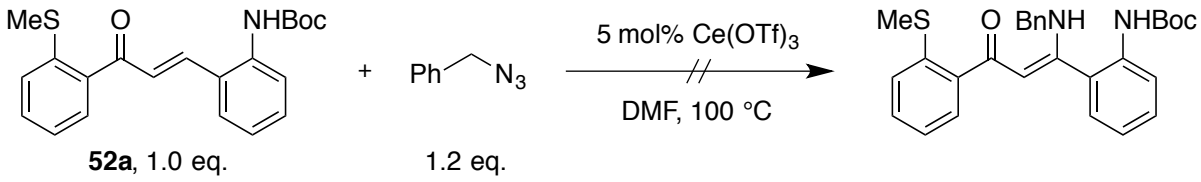


Figure 3.29 Heck reaction of enone **52a**

Another literature-precedented β-functionalisation was a cerium-promoted β-amination reaction, the first step of which involved a [3+2] alkene-azide click-type reaction.[243] A number of experiments returned solely unreacted starting material (Scheme 3.30).



Scheme 3.30 Attempted β-amination of enone **52a**

Having largely exhausted the literature precedents for β-functionalisation of chalcones that would leave the double bond intact, it was theorised that an alternative option would be to effect a conjugate addition reaction, followed by an oxidative cyclisation (Figure 3.14). Whilst such a process might require a separate stoichiometric oxidant, there was significantly greater precedent for the conjugate addition step.

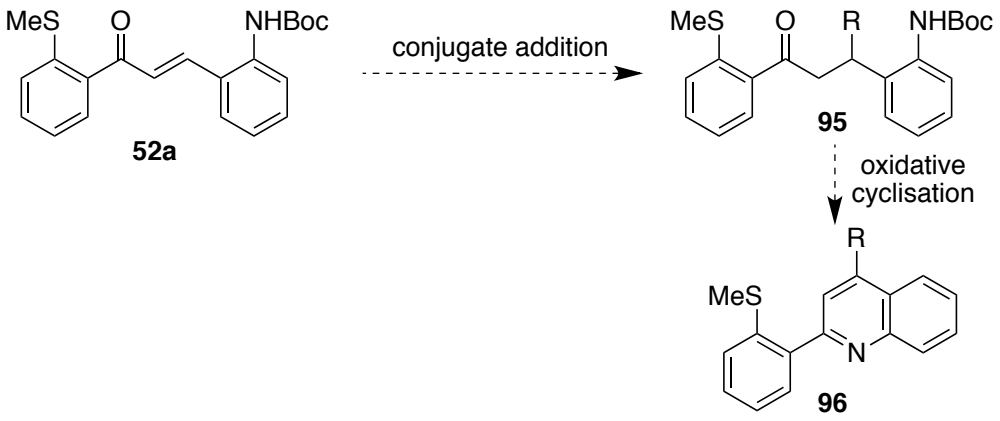
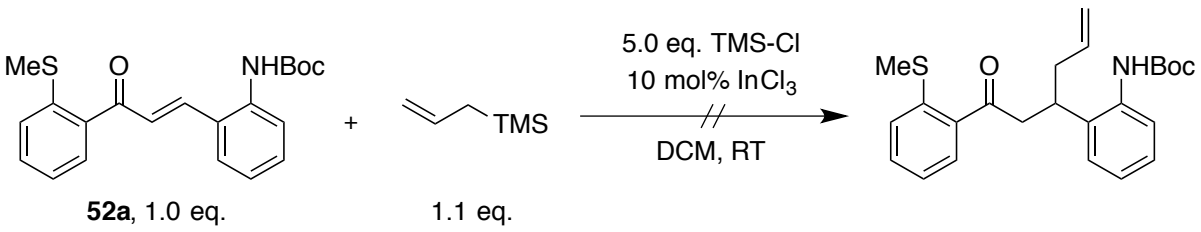


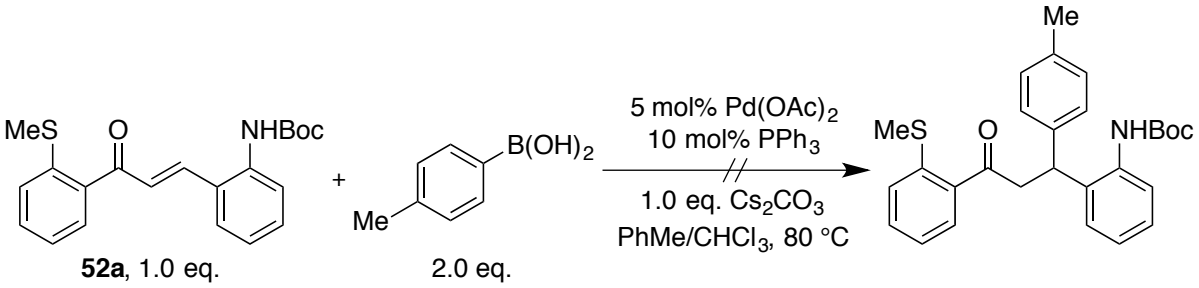
Figure 3.14 Synthesis of C(4)-substituted quinolines *via* conjugate addition and oxidative cyclisation

A number of attempts were made to adapt the Hosomi-Sakurai reaction for this purpose. The reactions returned only the chalcone starting material in all cases (Scheme 3.31).



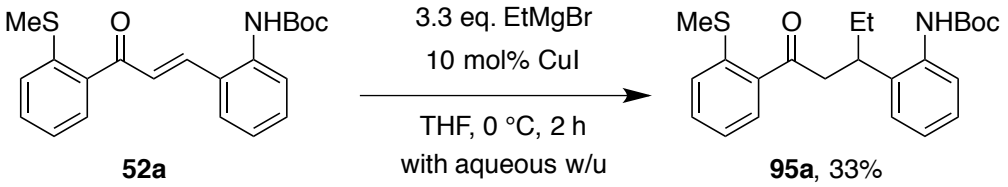
Scheme 3.31 Attempted Hosomi-Sakurai reaction of enone **52a**

Another reaction attempted was a palladium-catalysed hydroarylation reaction (Scheme 3.32). In this instance, some reactivity was observed; however, the crude mixture contained numerous side products in addition to the desired ketone. Although similar rhodium-catalysed conjugate additions are well established, previous work within the Willis group has found that the presence of the sulfide tether suppresses all reactivity.[163]



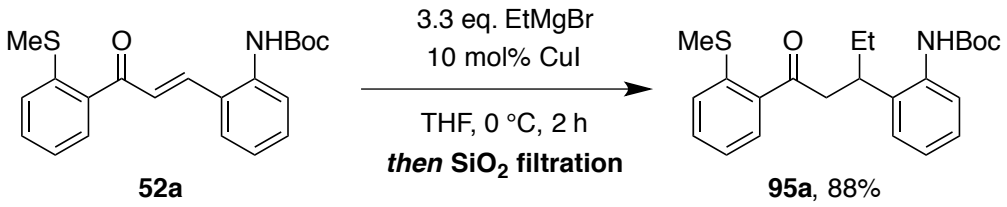
Scheme 3.32 Pd-catalysed hydroarylation of enone **52a**

What appeared to be more successful was the copper-catalysed conjugate addition of Grignard reagents. By HPLC and TLC analysis clean conversion from chalcone **52a** to ketone **95a** was observed over two hours (Scheme 3.33). Following workup and purification the isolated yield was unexpectedly low, and various previously absent side products were also isolated. Whilst not fully identified, the presence of $[M+16+H/Na]^+$ ions in MS analysis indicated that a number of these side products were the result of aerobic oxidation.



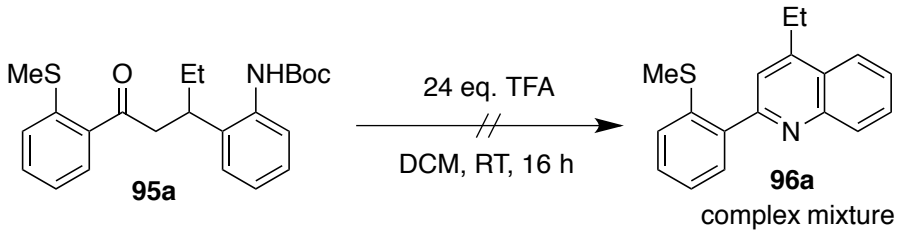
Scheme 3.33 Conjugate addition of EtMgBr to enone **52a**

Since the product proved to be stable to air and column chromatography, it was theorised that the presence of copper salts might be catalysing the oxidation following the workup procedure. By substituting the aqueous workup with a quick SiO_2 filtration in order to remove these residues, this oxidation was suppressed and an isolated yield of 88% achieved (Scheme 3.34).



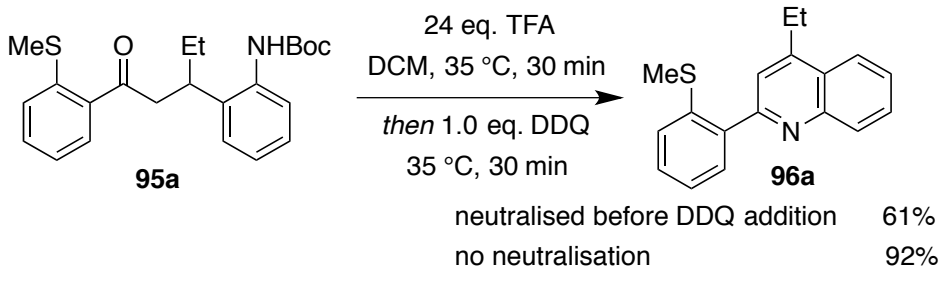
Scheme 3.34 Optimised conjugate addition of EtMgBr to enone **52a**

Exposure of ketone **95a** to acidic cyclisation conditions produced a complex mixture (Scheme 3.35). This reflects the instability of the dihydroquinoline intermediates observed in the previous section.



Scheme 3.35 Acidic cyclisation of ketone **95a** under aerobic conditions

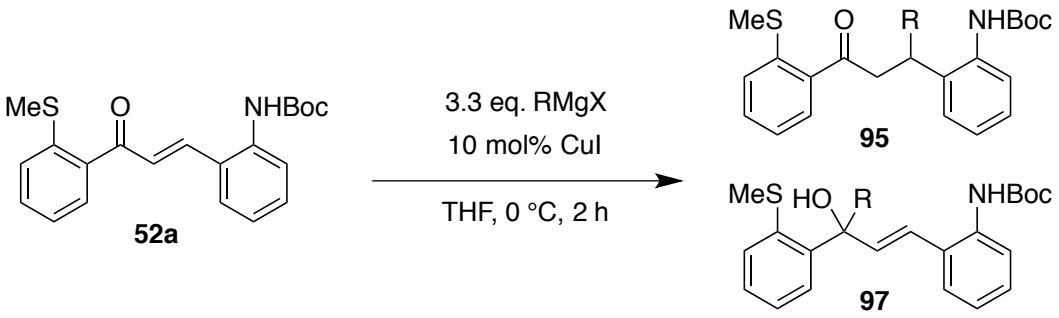
Combining an acidic cyclisation with MnO_2 promoted oxidation, previously shown to be effective in similar cyclisations,[244] resulted in product formation in addition to an unidentified side product. As an alternative oxidant, DDQ proved more applicable to this system. Treatment of the neutralised crude mixture following acidic deprotection/cyclisation with DDQ in DCM afforded the desired quinoline (**96a**) in a good yield (Scheme 3.36). Further optimisation found that a one-pot process was considerably higher yielding, negating the requirement for any intermediate workup.



Scheme 3.36 Acidic cyclisation of ketone **95a** employing stoichiometric oxidant

By expanding this technique to a number of different Grignard reagents, consistently high yields were achieved (Table 3.14). The selectivity for 1,4-addition over 1,2-addition appeared to be Grignard specific, with *p*-tolyl Grignard selective for the desired product, and other Grignard reagents displaying opposite selectivity.

Table 3.14 Grignard scope in Cu-catalysed 1,4-addition to enone **52a**



Entry	Grignard reagent	**95**:**97**[a]	Isolated yield
1	EtMgBr	>20:1	92%
2	*p*-TolMgBr	>20:1	94%
3	allylMgCl	<1:20	99%
4	2-thienylMgBr	<1:20	91%

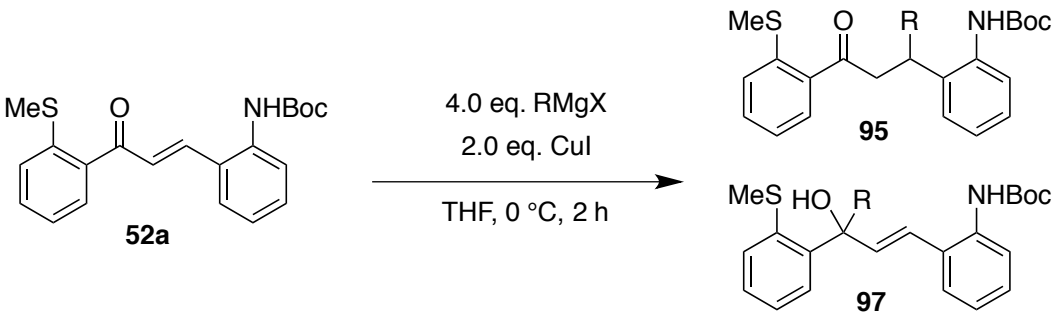
a) Determined by ^{1}H-NMR analysis

The observed ratios were remarkably similar to those recorded in the absence of copper catalyst on related substrates.[245] This observation appeared to fit with the previous observations that substrate **52a** was unsuitable for a number of metal-mediated transformations, potentially due to the presence of the sulfide tether.

In order to circumvent this issue, preformed organocuprates were prepared prior to the addition of chalcone **52a**. Unusually the allyl system appeared to retain a preference for 1,2 reactivity, although some 1,4 product was observed (Table 3.15, Entry 1). A survey of the literature could not identify any examples of a Cu-mediated, 1,4 allylation of enones. The 2-thienyl example exhibited no reactivity at all (Entry 2). In

many organometallic reactions the 2-thienyl group is employed to act as a dummy ligand due to its low migratory aptitude.[246] More successful, however, was the cyclopropyl group, 86% of the desired product isolated (Entry 3).

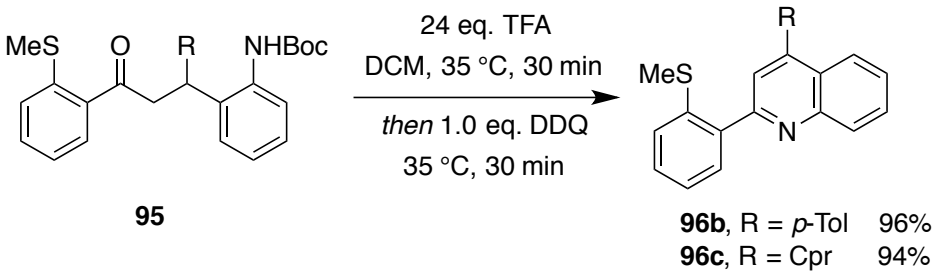
Table 3.15 1,4-addition of preformed cuprates to enone **52a**



Entry	Grignard reagent	**95**:**97**[a]	Isolated yield
1	allylMgCl	1:10	94%
2	2-thienylMgBr	n/a	0%
3	cyclopropylMgBr	>20:1	86%

a) Determined by ^{1}H-NMR analysis

Intermediates **95b** and **95c** were then cyclised in excellent yields to form the corresponding quinolines (Scheme 3.37)



Scheme 3.37 Oxidative cyclisations to form C(4)-substituted quinolines

These examples have been used as a proof of concept for the conjugate addition/oxidative cyclisation route for installing C(4)-functionality. Further progress

could potentially be made when utilising substrates without the chelating tether, such as those synthesised in Section 3.6.

3.8 Summary

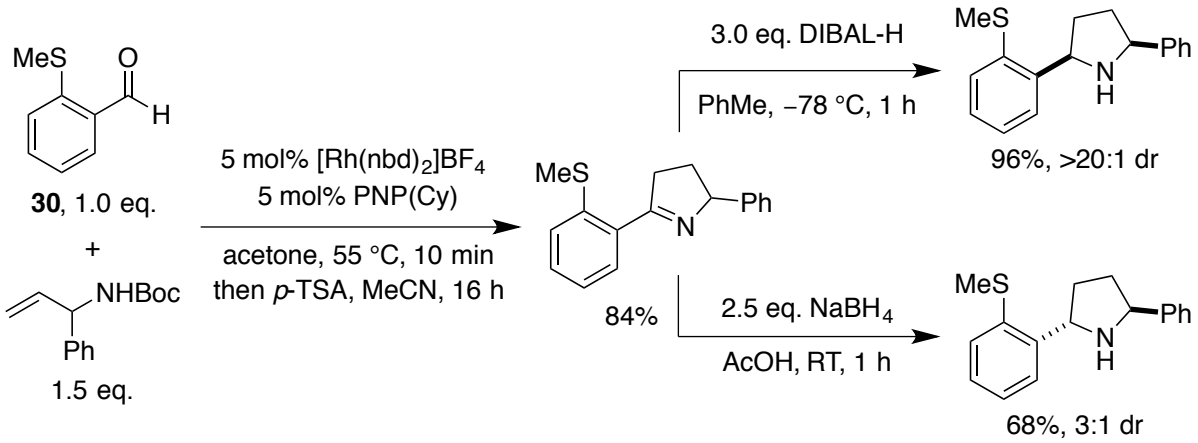
To conclude, the applicability of rhodium-catalysed hydroacylation to the *de novo* synthesis of quinolines has been demonstrated. This method tolerates a broad range of functional groups, many of which can be used as reactive handles for further functionalisation. For electron-rich substrates, shown to be less reactive than the electron-poor variants, an alternative method involving nitro-substituted alkynes was developed, allowing access to both quinolines and quinoline *N*-oxides. Tether free products were obtained by the use of tandem hydroacylation – C-S functionalisation processes, and further substitution of the heterocyclic ring was achieved through functionalisation of the enone intermediate.

Chapter 4

Heterocycle synthesis *via* intramolecular hydroimination

4.1 Background

In Chapters 2 & 3 it has been shown that chelation-controlled hydroacylation represents a powerful transformation for the synthesis of heterocyclic precursors. These intermediates can then undergo condensation to form a number of heteroaromatic compounds. In a related procedure, the synthesis of pyrrolines has also been demonstrated within the Willis group[132]. In this sequence an alkene hydroacylation, followed by an acid catalysed dehydrative cyclisation afforded a range of pyrrolines, which can then be selectively reduced to form either *trans*- or *cis*-2,5-disubstituted pyrrolidines (Scheme 4.1).



Scheme 4.1 Synthesis of trans- and cis-disubstituted pyrrolidines *via* pyrrolines

Whilst it has been shown that the removal of the chelating tether can be effected by rhodium-catalysed C-S functionalisation processes, a method that did not require the use of a tether would have advantages. The use of a tether has clear advantages for intermolecular hydroacylation, whereas intramolecular hydroacylation (as described in Chapter 1) does not suffer from this limitation when synthesising five- and six-membered rings. When the formation of imines in the presence of Rh-catalysts in the previous chapter (Scheme 3.1, p. 68) was observed, it was conceived that an intramolecular hydroacylative route to *N*-containing heterocycles might be an alternative approach (Figure 4.1).

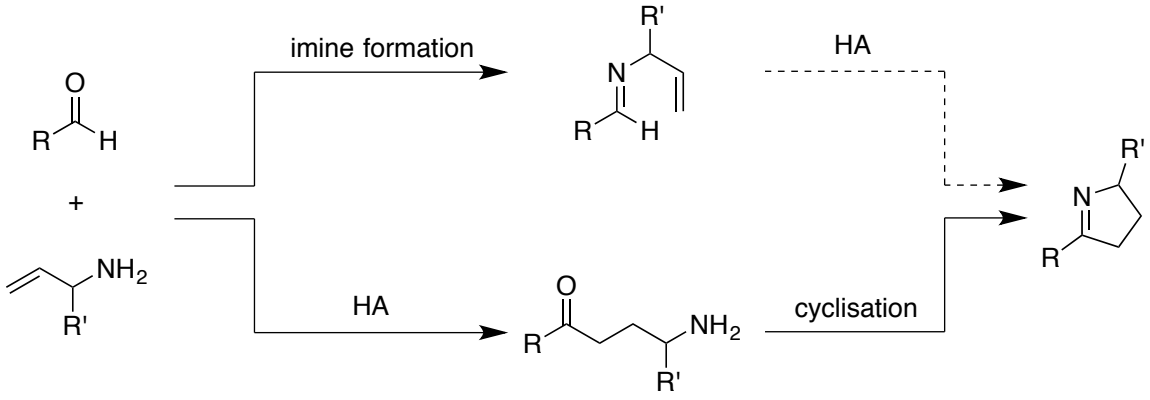


Figure 4.1 Hydroacylative routes to 2,5-disbustituted pyrrolines

It was envisaged that this method would enable the synthesis of a range of five- and six- membered cyclic imines, which could then be further functionalised into diverse heterocycles. To the authors knowledge, intramolecular imine hydroacylation has not been reported in the literature, although a wealth of precedent in chelate-directed intermolecular imine hydroacylation exists (Figure 4.2).[4]

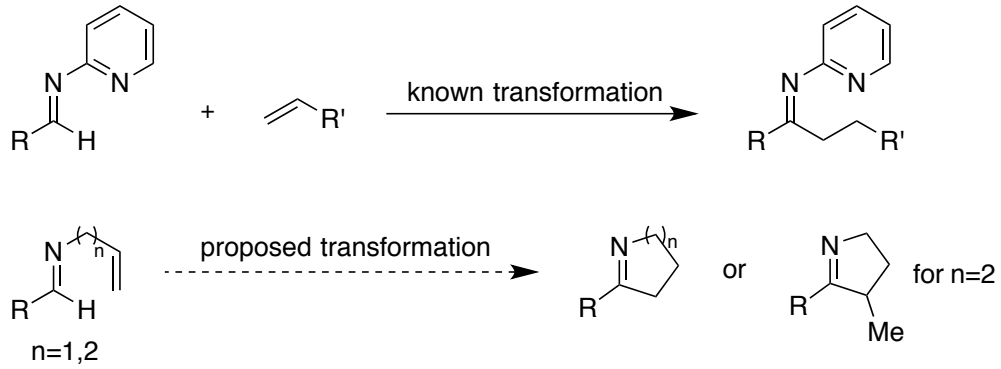
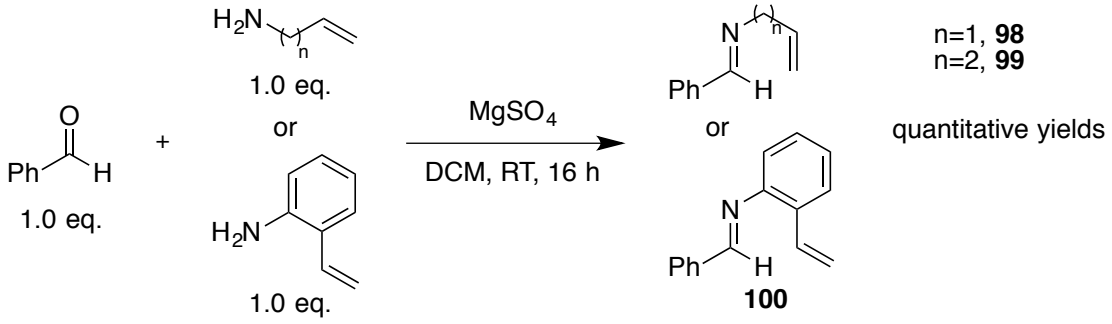


Figure 4.2 Proposed intramolecular hydroimination

The synthesis of imines suitable for this cyclisation procedure was straightforward, involving a simple magnesium sulfate promoted condensation, followed by filtration and removal of the solvent *in vacuo* (Scheme 4.2).



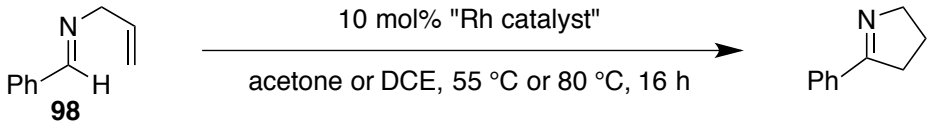
Scheme 4.2 Synthesis of alkene containing imines

The test substrates were derived from allylamine, homoallylamine and 2-aminostyrene. While the allylamine-derived imine **98** would only be able to undergo *endo*-cyclisation, the longer chain length in examples **99** and **100** would enable *exo*-cyclisation, a common mode of reactivity.

4.2 Reaction optimisation

With the imines in hand, a screen of reaction conditions was undertaken for the *endo*-cyclisation of allylamine-derived imine **98**. A range of rhodium precatalyts either with or without ligands were examined. Conversion to the desired product was not observed in any case (Table 4.1).

Table 4.1 Initial reaction screen for intramolecular hydroimination of imine **98**



Entry	Catalyst	Acetone conversion[a]	DCE conversion[a]
1	$[Rh(nbd)_2]BF_4$	Complex mixture	0%
2	1:1 $[Rh(nbd)_2]BF_4$/dcpm	Complex mixture	0%
3	1:1 $[Rh(nbd)_2]BF_4$/dppe	Complex mixture	0%
4	$Rh(PPh_3)Cl$	Complex mixture	0%
5	$[Rh(cod)Cl]_2$	Complex mixture	0%
6	$[Rh(cod)_2]OTf$	Complex mixture	0%

a) Determined by ^{1}H-NMR and HPLC analysis

For the reactions conducted in acetone, full consumption of the starting material was observed, although the major product was that of a Claisen-Schmidt condensation between acetone and the imine, forming enone **101** (Figure 4.3).



Figure 4.3 Claisen-Schmidt condensation between acetone and imine **98**

Similar tests proved unsuccessful for the homoallyl-derived imine **99**. For more extensive screening of potential conditions it was decided to use imine **100**. In the event

of an *exo*-cyclisation the cyclic imine generated (**102**) could undergo a rapid tautomerisation to form indole **103** (Figure 4.4). This indole was easily synthesised using the Fischer indole synthesis, and as such was easily detectable by NMR, TLC and HPLC analysis.

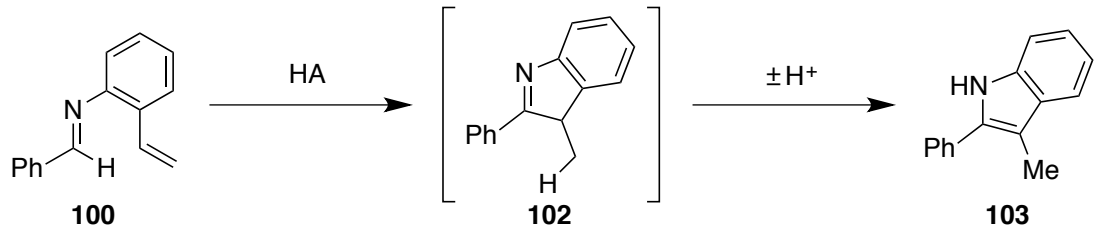


Figure 4.4 Indole formation *via* intramolecular hydroimination

Initial test reactions examined the role of additives. Following the unsuccessful reactions in Table 4.1, it was theorised that coordination to the imine lone pair could be disfavouring oxidative addition into the imine C-H bond, especially if the *E*-configuration was maintained (Figure 4.5).

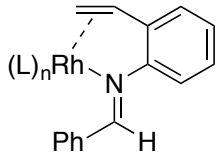
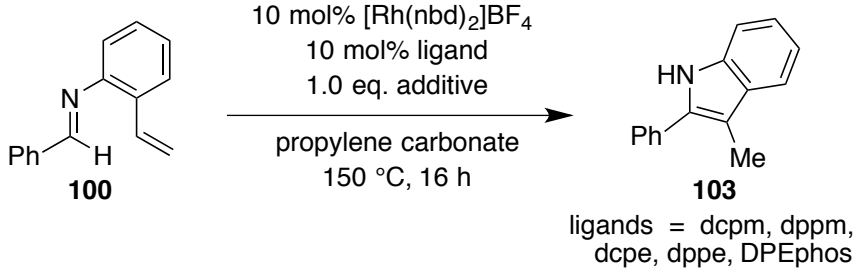


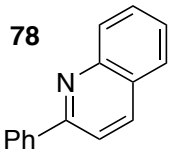
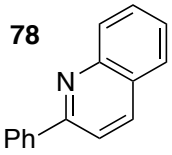
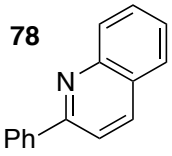
Figure 4.5 Rh-coordination to imine **100**

In order to test this hypothesis a variety of Lewis acids and Brønsted acids were screened as additives with a range of Rh/ligand combinations (Table 4.2). In the absence of additive (Entry 1), no reactivity was observed. For each of the additives, again no indole **103** was detected; however, 2-phenyl quinoline **78** was observed in each case. Whilst this could be rationalised by an *endo*-cyclisation followed by oxidation, the reactions proceeded equally as efficiently in the absence of a rhodium catalyst. This acid catalysed cyclisation therefore is either a result of a 6π-electrocyclisation, or alternatively an aza-Prins-type addition from the alkene into the imine. Given the nature

of the products and intermediates formed, it would be difficult to determine which mechanism is occurring however. The isolated yield of quinoline **78** from the triflic acid promoted cyclisation was 49%, with the remainder of the reaction consisting of a complex mixture of products.

Table 4.2 Additive effect in intramolecular hydroimination



Entry	Additive	Conversion[a]	Side product
1	No additive	0%	n/a
2	BF_3.THF	0%	**78** 
3	$Cu(MeCN)_4BF_4$	0%	**78** 
4	TfOH	0%	**78** 

a) Determined by HPLC analysis

As cationic rhodium complexes did not seem to hold much promise, a screen of conditions using different catalytic systems was attempted (Table 4.3). For each example a citation is given. The precedents for each example are discussed in detail in Chapter 1.

Table 4.3 Diverse reaction conditions for intramoleclular hydroimination



100 **103**

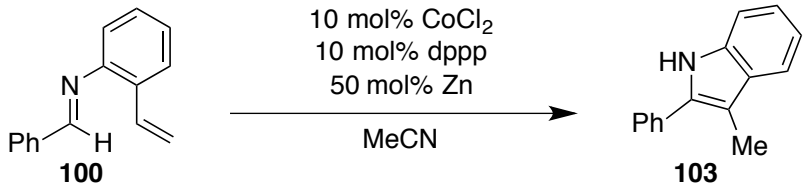
Entry	Reaction conditions	Conversion[a]
1	10 mol% $Rh(PPh_3)Cl$, PhMe, 130 °C, 16 h[4]	0%
2	10 mol% $Ni(cod)_2$, 30 mol% PCy_3, 1,4-dioxane, 100 °C, 40 h[92]	0%
3	10 mol% $CoCl_2$, 10 mol% dppp, 50 mol% Zn powder MeCN, 80 °C, 40 h[77]	31%
4	10 mol% $CoBr_2$, 10 mol% dippf, 50 mol% Zn powder MeCN, 60 °C, 40 h[78]	0%
5	10 mol% $[Rh(nbd)_2]BF_4$, 10 mol% Ampaphos, DCE, 80 °C, 40 h[43]	0%
6	10 mol% $RuHCl(CO)(PPh_3)_3$, 10 mol% Josiphos SL-J009, PhMe, 80 °C, 16 h[85]	0%
7	10 mol% $RuHCl(CO)(PPh_3)_3$, 10 mol% dppf, PhMe, 80 °C, 16 h[85]	0%

a) Determined by HPLC analysis

While the majority of examples showed no improvement from the previous screen, Entry 3, corresponding to Yoshikai's cobalt catalysed intramolecular hydroacylation report, appeared to be proceeding cleanly, albeit slowly, to indole **103**.

The effect of temperature was then explored (Table 4.4). At 80 °C the reaction was sluggish, reaching 36% conversion after 64 hours (Entry 3). This reaction was worked up and an isolated yield of 27% obtained and characterised. Increasing the reaction temperature to 100 °C resulted in a faster reaction (Entry 4), although the maximum conversion appeared to be lower (Entry 5).

Table 4.4 Effect of temperature on the Co-catalysed intramolecular hydroimination

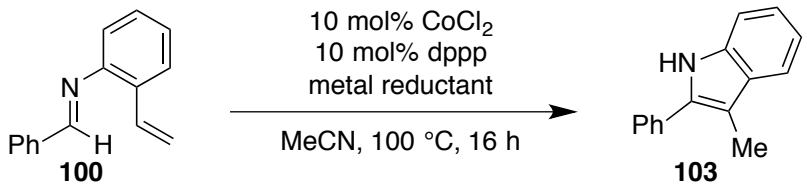


100 **103**

Entry	Reaction conditions	Conversion[a]
1	80 °C, 16 h	8%
2	80 °C, 40 h	30%
3	80 °C, 64 h	36%
4	100 °C, 16 h	20%
5	100 °C, 40 h	26%

a) Determined by HPLC analysis

Table 4.5 Effect of varying metal reductant



100 **103**

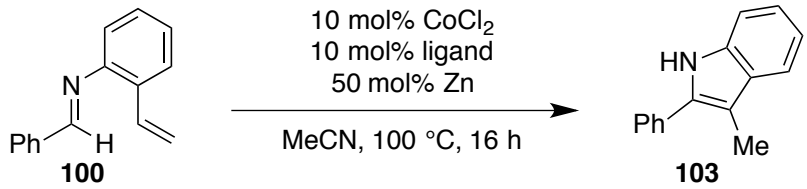
Entry	Reductant	Conversion[a]
1	50 mol% Zn	18%
2	100 mol% Zn	17%
3	20 mol% Zn	7%
4	50 mol% Mn	7%
5	50 mol% In	11%
6	20 mol% In, 10 mol% $InBr_3$	12%

a) Determined by HPLC analysis

Changing the additive employed to reduce the Co(II) prectalyst to Co(I) *in situ*, was unsuccessful (Table 4.5), with both manganese (Entry 4) and indium (Entries 5 & 6) proving less effective.

A ligand screen also showed no further improvement, with the initial large-bite-angle dppp ligand to be the most effective (Table 4.6).

Table 4.6 Ligand screen for the Co-catalysed intramolecular hydroimination

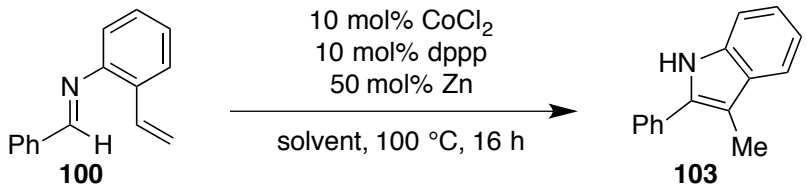


Entry	Ligand	Conversion[a]
1	dcpm	0%
2	dppm	0%
3	dcpe	5%
4	dppe	3%
5	dcpp.HBF_4	0% (major product **78**)
6	dppp	11%
7	dppb	4%
8	dppf	0%
9	dppBz	0%
10	dppEth	4%
11	DPEphos	0%
12	Xantphos	0%
13	BINAP	0%

a) Determined by HPLC analysis

The final screen involved a number of solvents, ranging in polarity and coordinating ability (Table 4.7). Surprisingly, indole **103** was observed in every case, although once again, the initial conditions proved to be the most successful.

Table 4.7 Solvent screen for the Co-catalysed intramolecular hydroimination

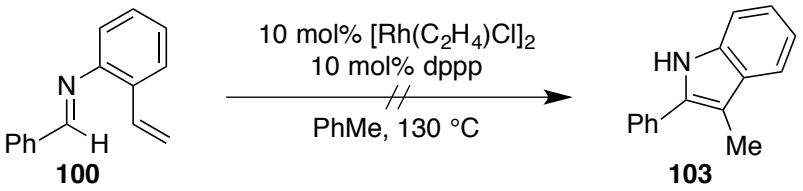


100 **103**

Entry	Solvent	Conversion[a]
1	MeCN	16%
2	DMF	8%
3	acetone	Complex mixture
4	DCE	9%
5	MeOH	3%
6	1,4-dioxane	10%
7	PhMe	6%
8	propylene carbonate	10%
9	THF	6%

a) Determined by HPLC analysis

As mentioned in Chapter 1 (p. 7) a mechanistic study by Bo and Castillón[27] found that for hydroacylation of picolyl imines, neutral complexes such as Wilkinson's catalyst outperformed cationic complexes featuring non-coordinating counteranions. Coupled with the relative success of cobalt chloride complexes, it seemed a logical step that a dppp based, neutral rhodium catalyst system might be a viable catalyst; however, no conversion to the correct product was observed under these conditions (Scheme 4.3).



100 **103**

Scheme 4.3 Neutral Rh-chloride catalysts in intramolecular hydroimination

It was decided to test the reaction conditions on imines **98** and **99**. Unfortunately, complex mixtures of products were observed in each case (Scheme 4.4). The generated cyclic imines are likely to be less stable than the pseudoaromatic indole **103**, and may be decomposing under the reaction conditions.



98,99 complex mixture

Scheme 4.4 Co-catalysed hydroimination of alternative imines

Whilst alkyne based systems have yet to be explored, the lack of further developments made since the initial success have led to reaction optimisation being curtailed.

4.3 Summary

In conclusion, a range of conditions has been screened with the intention of developing an intramolecular, tether-free hydroacylative process for the synthesis of *N*-containing heterocycles. Catalyst systems based on cationic rhodium bisphosphine complexes, shown to be effective at *S*-directed intermolecular hydroacylation, were uniformly ineffective for the proposed transformation. A number of other conditions, based on a range of metals and mechanisms were attempted, and a promising first hit of 31% conversion obtained. Unfortunately, any further optimisation attempts have failed to improve the conversion. There remains potential for further optimisation, for example through the use of alkyne substrates.

Chapter 5

Expanding the use of the removable MTM directing group

5.1 Background

As discussed in Chapter 1, a number of tactics have been employed to reduce the drawbacks associated with the use of chelating aldehydes in intermolecular hydroacylation. Whilst the development of an effective, broad reaching, general strategy for intermolecular hydroacylation remains a major goal in the field, alternative approaches often need to be employed. One method of generating tether-free hydroacylation products that has previously been encountered in this thesis is the use of tandem hydroacylation – C-S functionalisation transformations (Section 1.1.4 and Section 3.6). This strategy has been shown to be effective in the synthesis of a number of sulfide-free ketones and enones (Figure 5.1), although due to the nature of the C(sp^2)-S activation process, only aryl[58, 59, 238] and alkenyl[60] aldehydes can be employed.

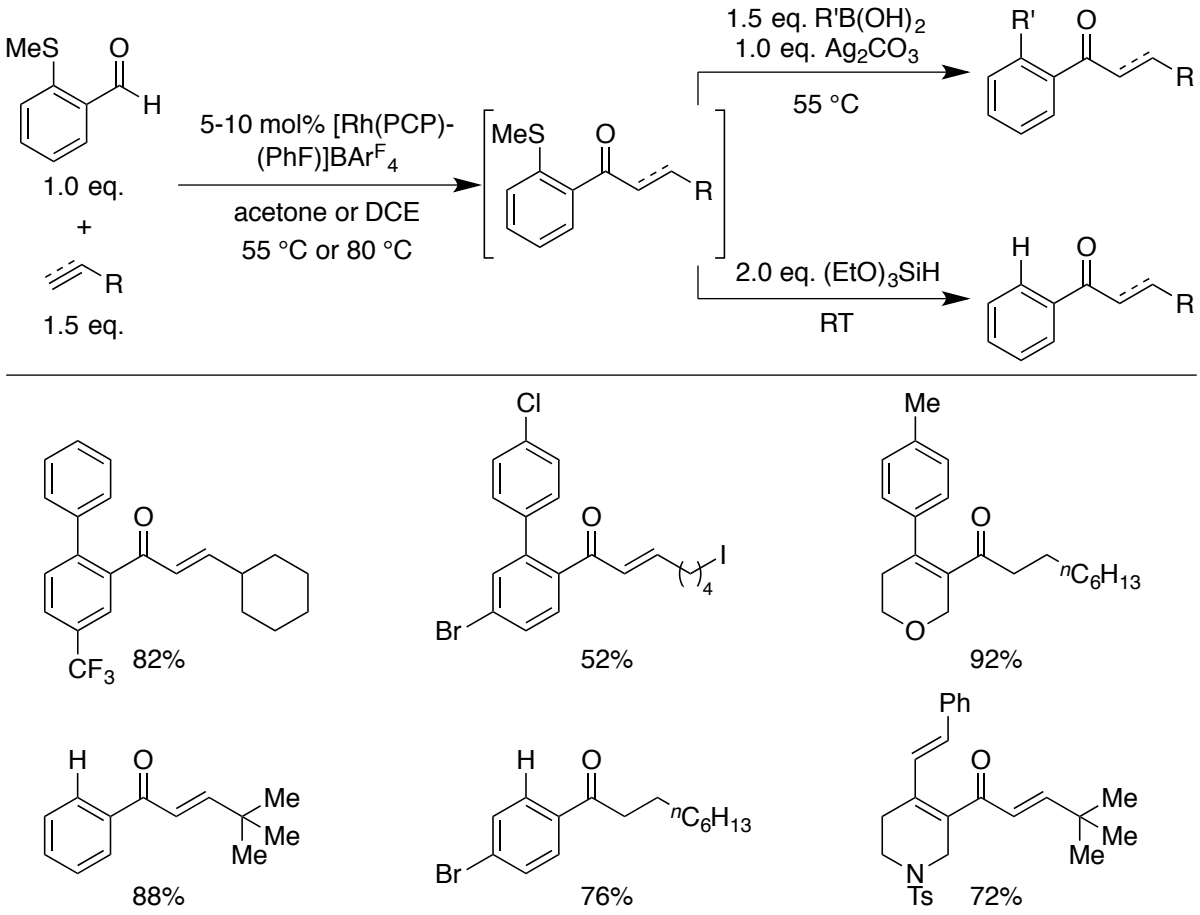
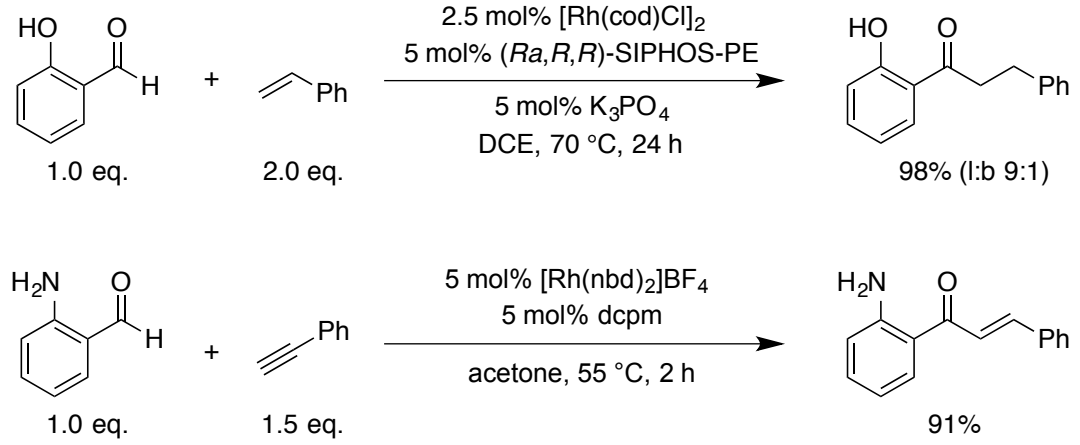


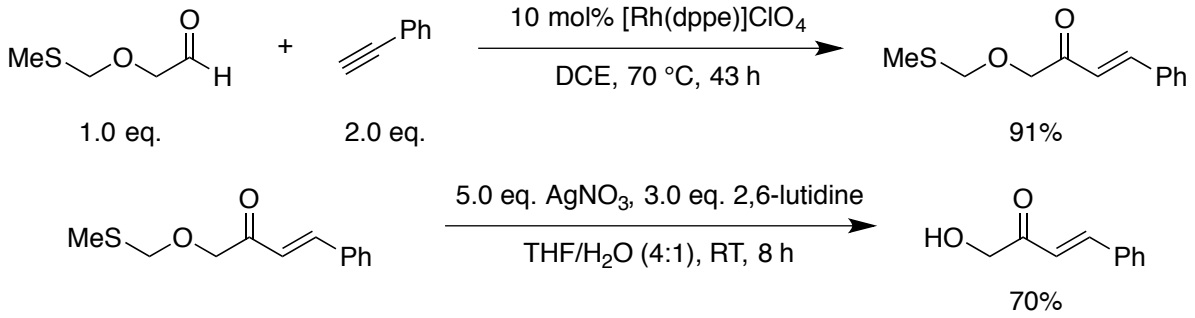
Figure 5.1 Tandem hydroacylation – C-S functionalisation processes

Another approach to reducing the drawbacks associated with chelation-controlled hydroacylation has been to investigate the use of alternative chelating systems. In Section 1.1.3, it was shown that a number of chelate systems exist in addition to the use of β-sulfur containing aldehydes. *O*- and *N*-chelation in the form of salicylaldehydes[56] and aniline derived systems[46] have recently been described (Scheme 5.1).



Scheme 5.1 *O*- and *N*- directed intermolecular hydroacylation

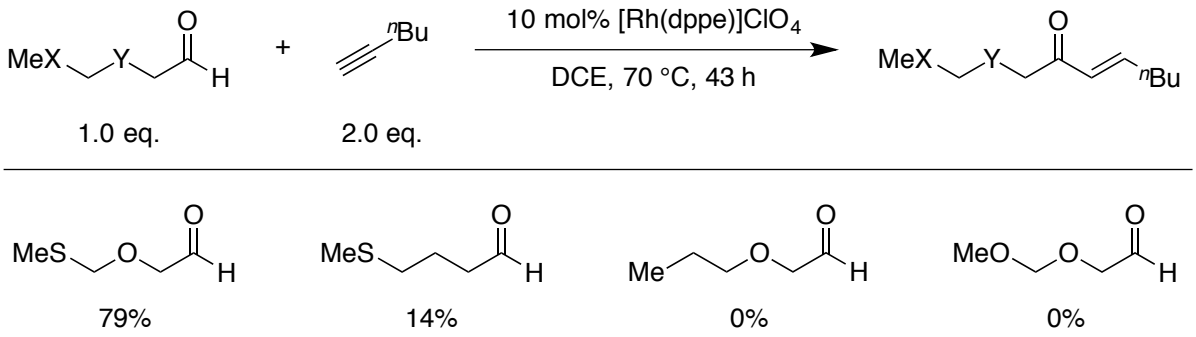
In 2011 Willis reported a new directing group system based on the methylthiomethyl (MTM) functional group.[247] MTM-substituted α-hydroxy aldehydes were shown to undergo hydroacylation in good to excellent yields with a range of aryl and alkyl alkynes (Scheme 5.2). The removal of the MTM group, affording α-hydroxyenones, was easily achieved by employing a thiophilic Lewis acid.



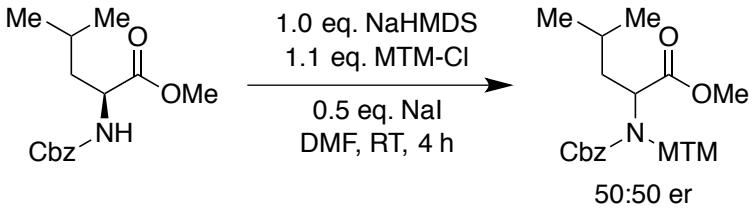
Scheme 5.2 MTM-substituted α-hydroxy aldehydes in intermolecular hydroacylation

A series of control reactions established that the presence of both the sulfur and oxygen atom were required for efficient hydroacylation (Table 5.1). It was theorised that the presence of the α-heteroatom stabilises a reactive conformation; however, any attempts to study the mode of coordination, either through X-ray crystallography, ^{1}H- or ^{31}P-NMR have been unsuccessful.

Table 5.1 *O-S,* cooperativity in chelate controlled hydroacylation



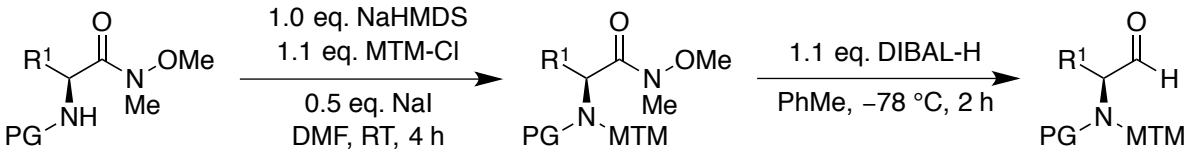
Following the success of this approach it was envisaged that the use of MTM-substituted α-amino aldehydes would likely represent efficient substrates for alkyne hydroacylation. Synthesis of these aldehydes from the corresponding esters was readily achieved by colleagues in the Willis Group. Unfortunately, in the key MTM-incorporation step, they found that the strong base required to deprotonate the carbamate NH resulted in racemisation of the α-stereocentre (Scheme 5.3).

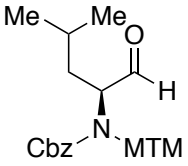


Scheme 5.3 Racemisation in the MTM-incorporation step

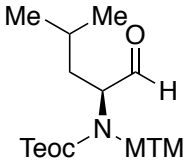
In order to attenuate this racemisation, they designed an alternative route, in which the MTM-incorporation step is carried out on a Weinreb amide derivative. This subtle change reduced the acidity of the α-proton, and a number of highly enantioenriched α-amino aldehydes were synthesised (Table 5.2). Although α-amino aldehydes are notoriously unstable, the presence of an electron-withdrawing group on nitrogen imparts stability to column chromatography and long-term storage.

Table 5.2 Synthesis of enantioenriched MTM-substituted α-amino aldehydes

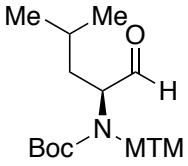




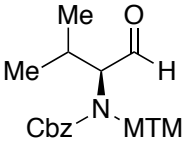
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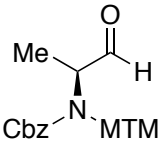
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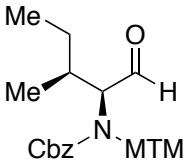
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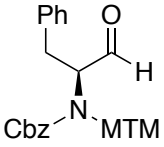
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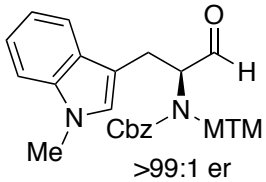
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98:2 er



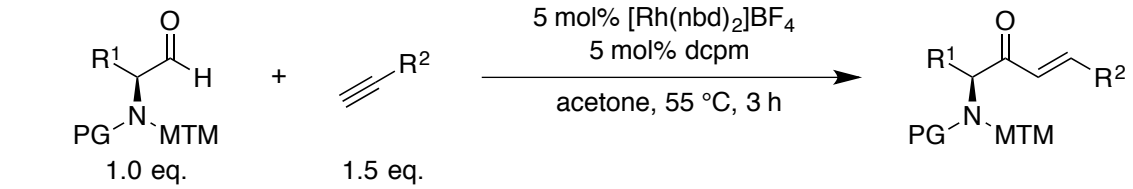
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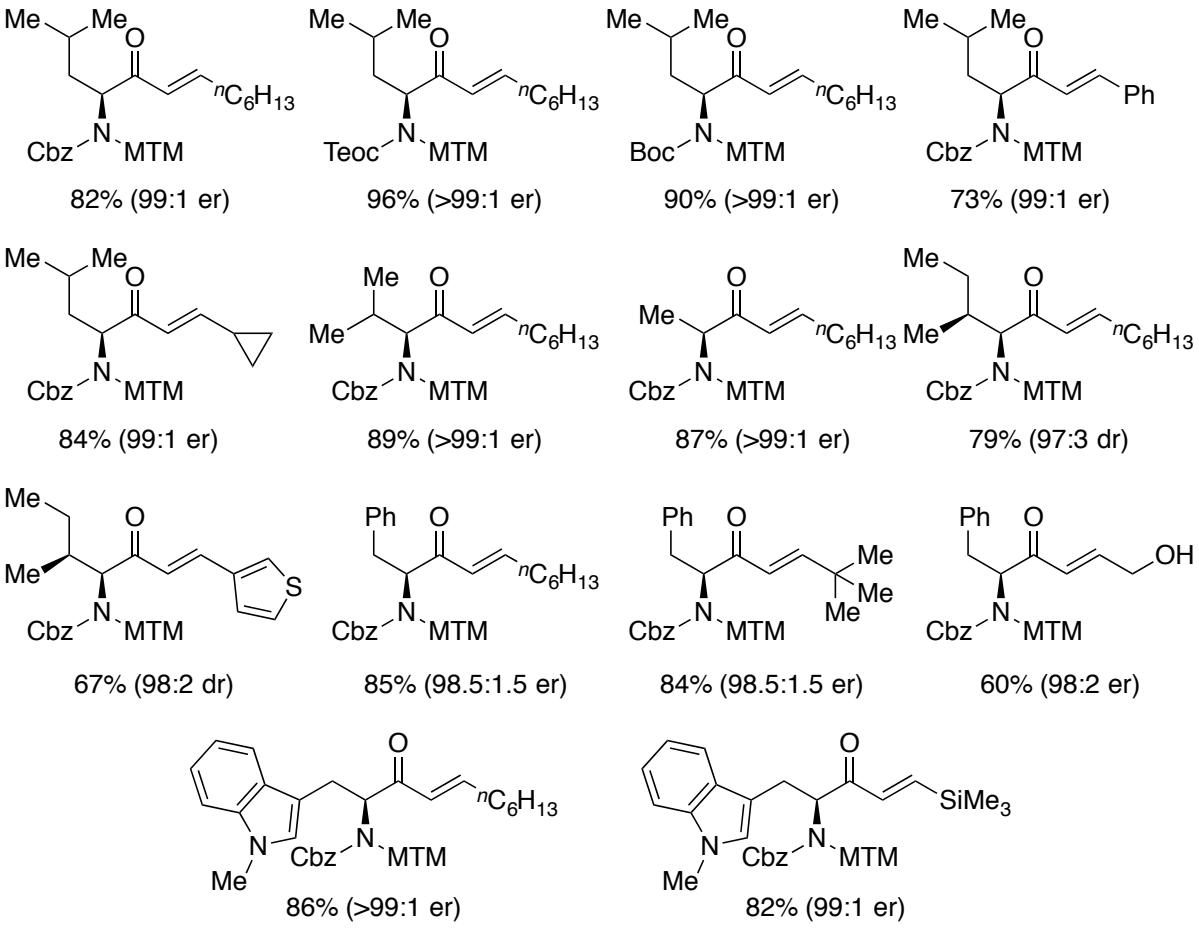


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They then combined these enantiomerically enriched aldehydes with a number of alkynes in good to excellent yields with enantiospecificities ([*ee* of product/*ee* of starting material] × 100%) of 97% or higher (Table 5.3).

Table 5.3 Hydroacylation employing MTM-substituted α-amino aldehydes





In order to complete the investigation into MTM-substituted α-amino aldehydes, an enantiospecific total synthesis of the natural product sphingosine (**104**) was envisaged. By using an appropriately protected serine-derived α-amino aldehyde it was hoped that a concise synthesis could be achieved (Figure 5.2).

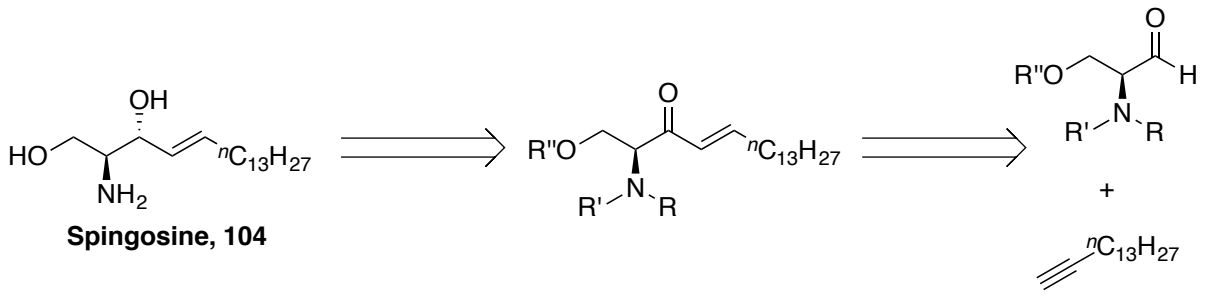


Figure 5.2 Sphingosine retrosynthetic analysis

Before this total synthesis was attempted, there remained a few areas in which the reaction scope could be improved. Previous work had shown that alkenes and allenes were unreactive under the reaction conditions; however, it was thought that internal alkynes could be suitable substrates.

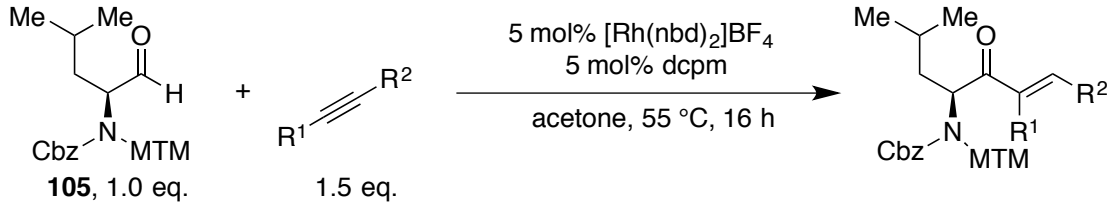
It was at this stage that work on the project was first undertaken by the author.

5.2 Reaction of MTM-subsituted α-amino aldehydes with internal alkynes

The hydroacylation of internal alkynes with the catalysts developed in the Willis group is less straightforward than for terminal alkynes. Issues with both reactivity and regioselectivity are often encountered. In order to avoid these regioselectivity problems, an initial screen was undertaken using the symmetrical alkynes 3-hexyne and diphenylacetylene in combination with leucine-derived aldehyde **105**. Under the standard conditions employed for terminal alkynes, no conversion was observed for the diaryl alkyne (Table 5.4, Entry 1); however, the dialkyl version reached 53% conversion over 16 hours (Entry 2). In order to improve the conversion the concentration was increased, and the reaction reached full conversion in just three hours (Entry 3). Using these conditions, a short scope was attempted. Hydroacylation of 1-phenyl-1-propyne

was achieved in a regioselective manner (Entry 4); however, the reaction employing the slightly more bulky 1-phenyl-1-pentyne was sluggish and less selective (Entry 5).

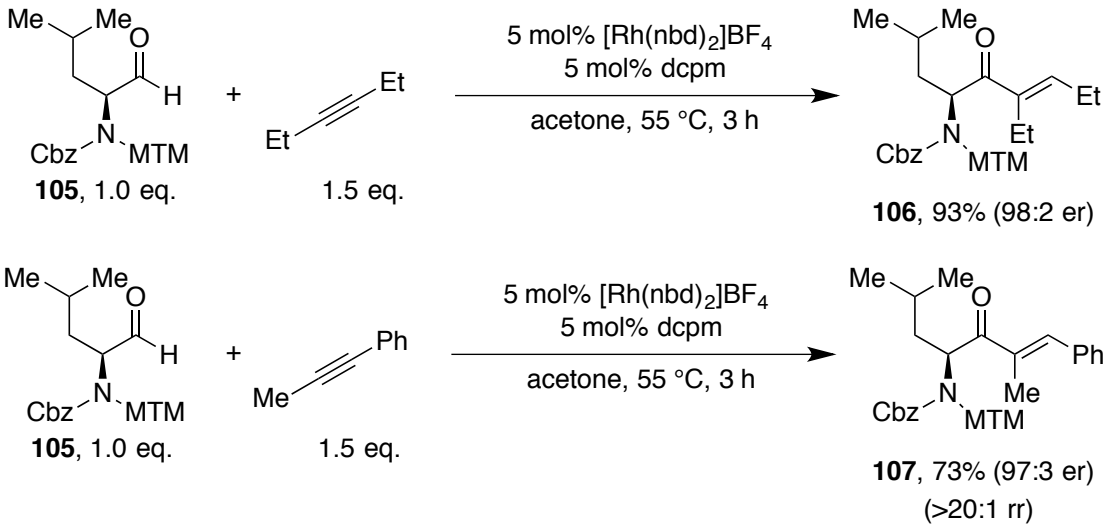
Table 5.4 Optimisation of the hydroacylation of internal alkynes with aldehyde **105**



Entry	Alkyne	Concentration	Conversion[a]	Regioisomeric ratio[a]
1	R^1=R^2=Ph	0.5 M	0%	n/a
2	R^1=R^2=Et	0.5 M	53%	n/a
3	R^1=R^2=Et	1.0 M	100%	n/a
4	R^1=Me, R^2=Ph	1.0 M	100%	>20:1
5	R^1=^{n}Pr, R^2=Ph	1.0 M	63%	3:1

a) Determined by ^{1}H-NMR analysis

The isolated yields of these reactions were very good to excellent, as were the enantiospecificities (Scheme 5.4).

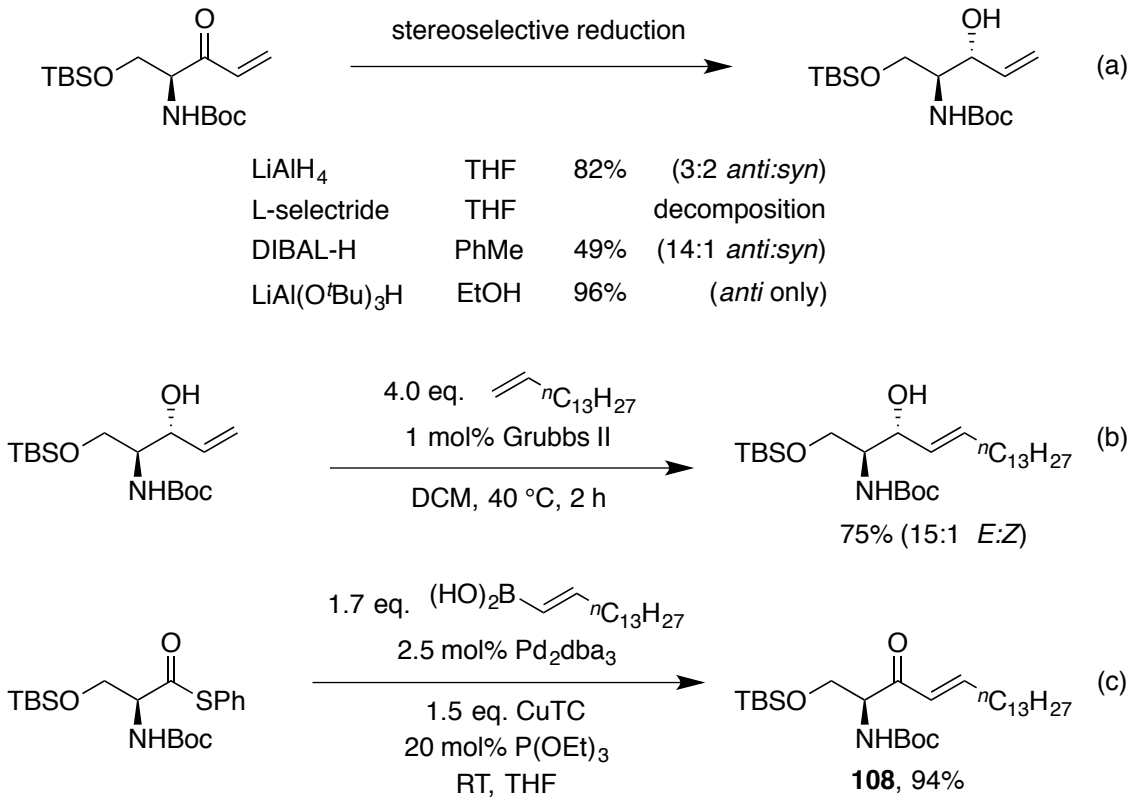


Scheme 5.4 Hydroacylation of internal alkynes with aldehyde **105**

With a satisfactory scope now achieved, attention was focussed on the natural product synthesis.

5.3 Application to the total synthesis of the natural product sphingosine

A number of previous syntheses of sphingosine relied on the diastereoselective reduction of a key enone intermediate (Scheme 5.5a). This reduction was first reported by Katsumura in 2006[248] and has subsequently been utilised in a number of syntheses of sphingosine or other sphingolipids.[249, 250, 251, 252] Notable TM-catalysed examples include Katsumura's original report that utilises a key Ru-catalysed olefin cross metathesis reaction (Scheme 5.5b) and Liebeskind's 2007 route[253] employing a Liebeskind-Srogl coupling[254] as the C-C bond forming step (Scheme 5.5c).



Scheme 5.5 Literature precedent for the synthesis of enantioenriched sphingosine **104**

With these encouraging precedents, in order to avoid having to reoptimise the final steps, it was decided to attempt to intercept intermediate **108** in the Liebeskind synthesis (Figure 5.3). This route would first require the synthesis of serine-derived aldehyde **109**.

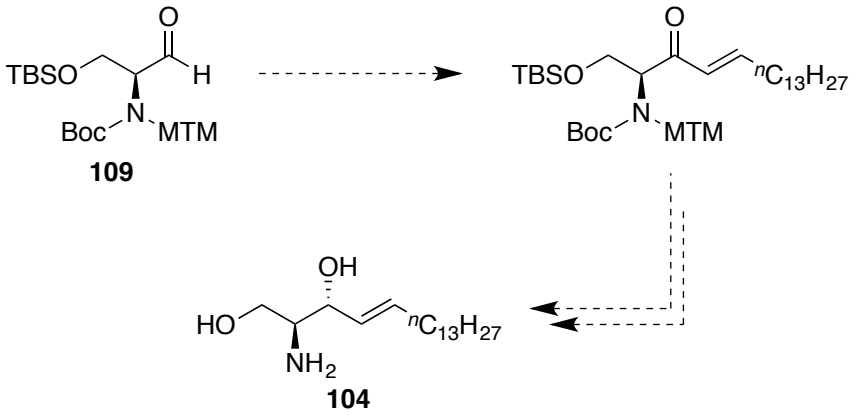
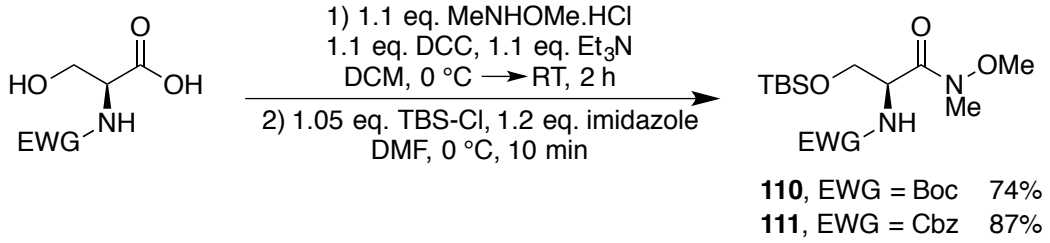


Figure 5.3 Proposed hydroacylative route to sphingosine **104**

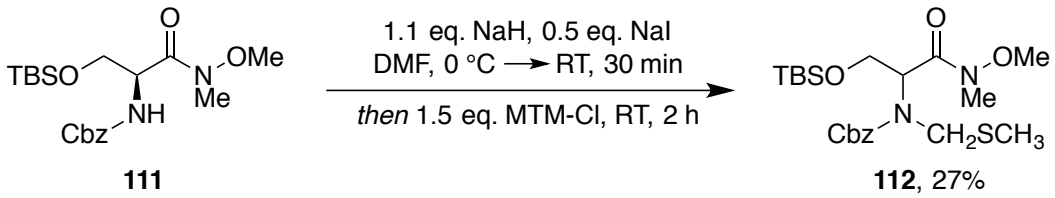
5.3.1 Route 1 – multiple protecting group strategy

The synthesis of aldehyde **109** was attempted using the standard conditions developed previously (Table 5.2). Commercially available Boc-Ser-OH and Z-Ser-OH were transformed into the corresponding silyl-protected Weinreb amides **110** and **111** in very good yields over two steps (Scheme 5.6). Whilst differing from the protection strategy in the previous sphingosine syntheses, the use of Cbz allowed easier analysis of the reaction both by TLC and HPLC.



Scheme 5.6 Synthesis of protected Weinreb amides **110** and **111**

The MTM-incorporation step was less straightforward than for the previously explored examples, due to the potential for an E1cB elimination. An initial test reaction afforded 27% of MTM-substituted compound **112** after two hours (Scheme 5.7).



Scheme 5.7 Test MTM-incorporation reaction

Unfortunately, however, any attempt to repeat this reaction was unsuccessful (Table 5.5). A succession of reaction conditions were screened, varying the base used (Entry 2), equivalents of MTM-Cl (Entries 3 and 4), nucleophilic catalyst employed (Entries 5 and 6) and the effect of additives (Entry 7). The conditions tested were equally ineffective on Boc-protected substrate **110** as Cbz-protected substrate **111**. It

was unclear why the initial conditions were not reproducible, however the mass recovery of the starting Weinreb amide was usually very low, and therefore it was thought that decomposition of the starting material and/or product were responsible for the poor reaction.

Table 5.5 Attempted optimisation of MTM-incorporation on serine-derived Weinreb amides **110** and **111**



EWG = Cbz or Boc

Entry	Reaction conditions	Yield
1	1.1 eq. NaH, 1.5 eq. MTM-Cl, 0.5 eq. NaI	0%
2	1.1 eq. NaHMDS, 1.5 eq. MTM-Cl, 0.5 eq. NaI	0%
3	1.1 eq. NaH, 2.0 eq. MTM-Cl, 0.5 eq. NaI	0%
4	1.1 eq. NaH, 5.0 eq. MTM-Cl, 0.5 eq. NaI	0%
5	1.1 eq. NaH, 1.5 eq. MTM-Cl, 0.5 eq. TBAI	0%
6	1.1 eq. NaH, 1.5 eq. MTM-Cl, 0.5 eq. DMAP	0%
7	1.1 eq. NaH, 1.5 eq. MTM-Cl, 0.5 eq. NaI, 3.0 eq. DMPU, THF	0%

An alternative strategy employed in a number of literature examples involves the interception of an intermediate in the Pummerer reaction (Figure 5.4).

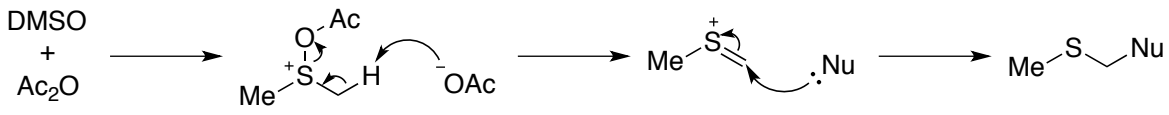
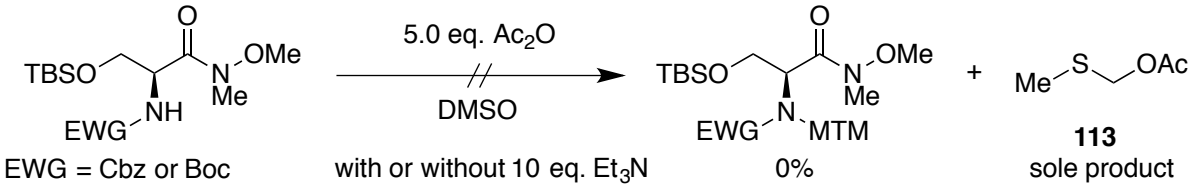


Figure 5.4 Interrupted Pummerer reaction for MTM-incorporation

Unfortunately, this reaction afforded only the product of the uninterrupted Pummerer reaction (**113**), as the carbamate is insufficiently nucleophilic to react in place of the acetate anion (Scheme 5.8).



Scheme 5.8 Attempted interrupted Pummerer reaction for MTM-incorporation

As the use of Weinreb amides **110** and **111** appeared to be ineffective as a means to access an MTM-substituted serine aldehyde, an alternative protecting group strategy was sought.

5.3.2 Route 2 – single cyclic protecting group strategy

By combining the *N*- and *O*-protecting groups into a single cyclic protection strategy, it was postulated that the problems of racemisation and E1cB elimination could be alleviated. Aldehyde **114** was therefore selected as the new target. (Figure 5.5)

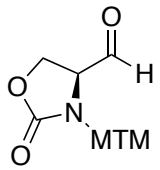


Figure 5.5 Proposed aldehyde **114**

In the case of amides **110** and **111** elimination generates two molecules from a single starting material, and is therefore entropically favourable. No such benefit is immediately possible in this system. Added to this, the rigidity of the system reduces the ability of hyperconjugation to lower the pKa of the α-proton (Figure 5.6).

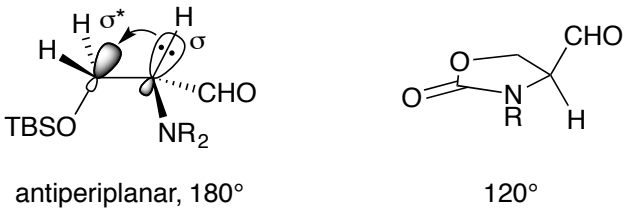
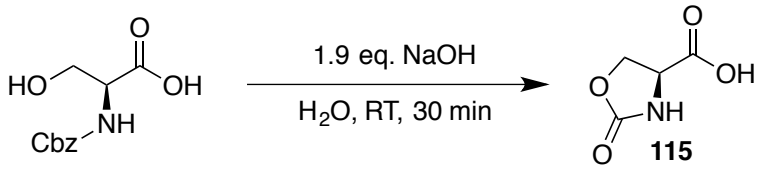


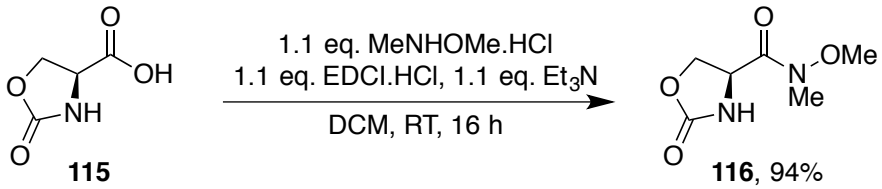
Figure 5.6 The effect of hyperconjugation on the pKa of the α-proton

The synthesis of amino acid **115** was achieved using literature-precedented conditions in good yields (Scheme 5.9).



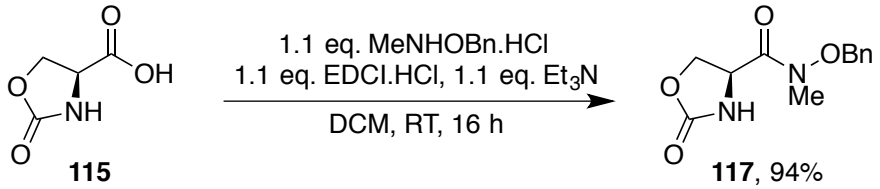
Scheme 5.9 Cyclisation to oxazolidinone-containing amino acid **115**

Formation of the Weinreb amide was initially problematic, due to the high polarity of **116,** preventing the use of an aqueous workup. Column chromatography of the crude reaction mixture failed to remove the DCC-derived dicyclohexylurea after a number of attempts. By replacing the DCC with EDCI.HCl excellent yields were obtained without the requirement for a workup (Scheme 5.10). Purification *via* column chromatography was now straightforward due to the increased polarity of the urea byproduct.



Scheme 5.10 Formation of OMe-Weinreb amide **116**

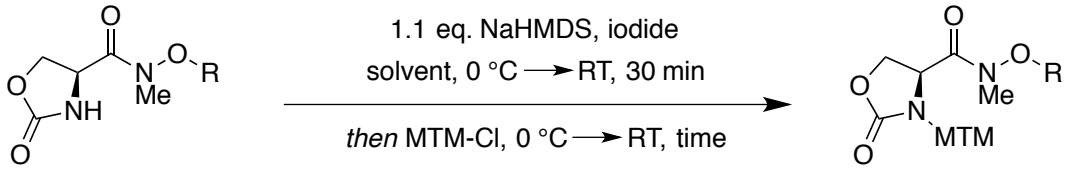
Analogously to the use of the Cbz group in the previous section, it was desirable to insert a chromaphore to enable chiral HPLC analysis of the intermediates. A benzyl variant of Weinreb amide **117** was synthesised in excellent yields (Scheme 5.11).



Scheme 5.11 Formation of OBn-Weinreb amide **117**

The new protecting group strategy appeared to be successful in reducing/preventing elimination, with initial test reactions containing only the product of the reaction in addition to remaining starting material (Table 5.6, entry 1). Yields were still markedly lower than had been achieved in the protection of the simpler amino acid derivatives in the original scope. Table 5.6 details selected reactions from the optimisation.

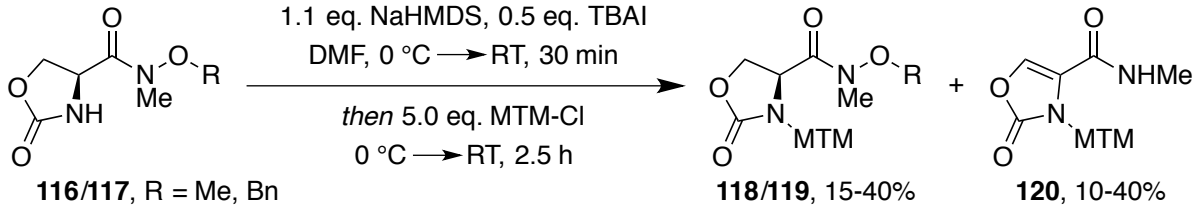
Table 5.6 Optimisation of the MTM-incorporation step



Entry	R =	Reaction conditions	Isolated yield
1	Me	1.5 eq. MTM-Cl, 0.5 eq. NaI, DMF, 16 h	33% (**118**)
2	Me	1.5 eq. MTM-Cl, 0.5 eq. TBAI, DMF, 16 h	48% (**118**)
3	Bn	2.0 eq. MTM-Cl, 0.5 eq. TBAI, DMF, 2 h	49% (**119**)
4	Bn	2.0 eq. MTM-Cl, 0.5 eq. TBAI, DMF, 16 h	61% (**119**)
5	**Bn**	**5.0 eq. MTM-Cl, 0.5 eq. TBAI, DMF, 2.5 h**	**72%** (**119**)
6	Bn	10 eq. MTM-Cl, 0.5 eq. TBAI, DMF, 2.5 h	57% (**119**)
7	Bn	10 eq. MTM-Cl, 1.0 eq. TBAI, DMF, 2.5 h	54% (**119**)
8[a]	Bn	5.0 eq. MTM-Cl, 0.5 eq. TBAI, THF, 2.5 h	45% (**119**)
9[a]	Me	5.0 eq. MTM-Cl, 0.5 eq. TBAI, THF, 2.5 h	57% (**118**)
10	Me	5.0 eq. MTM-Cl, 0.5 eq. TBAI, DMF, 2.5 h	58% (**118**)

It was quickly found that tetrabutylammonium iodide (TBAI) was a more effective nucleophilic catalyst than NaI (Entry 2). An unexpected observation was that the OBn substrate repeatedly afforded yields of as much to 10% higher than when the OMe compound was employed (Entry 4 vs. 2, Entry 5 vs. 10). Increasing the stoichiometry of the methylthiomethyl chloride electrophile from two to five equivalents resulted in improved yields (Entry 5); however, a further increase to ten equivalents saw reduced yields (Entry 6). Increasing the stoichiometry of the iodide additive had minimal effect (Entry 7), and alternative workup conditions involving an isopropyl alcohol quench, followed by dry-loading the crude reaction mixture for column chromatography (Entry 8) showed slightly reduced yields. It was again confirmed (Entries 9 and 10) that use of starting material **116** resulted in lower yields with the updated conditions.

With an isolated yield of 72% achieved on a 0.4 mmol scale, the reaction was scaled up in order to investigate the later steps. Unfortunately, the 72% yield did not appear to be reproducible on an 8.0 mmol scale. In addition to the desired product, a significant amount of oxazolone side-product **120** was also observed.



Scheme 5.12 Scaled-up MTM-incorporation step

Whilst this formation of this oxazolone does appear to be unprecedented in the literature, a similar transformation has been reported by Somfai in 2008, as part of a strategy for the synthesis of unnatural α-amino acids (Figure 5.7).[255, 256, 257]

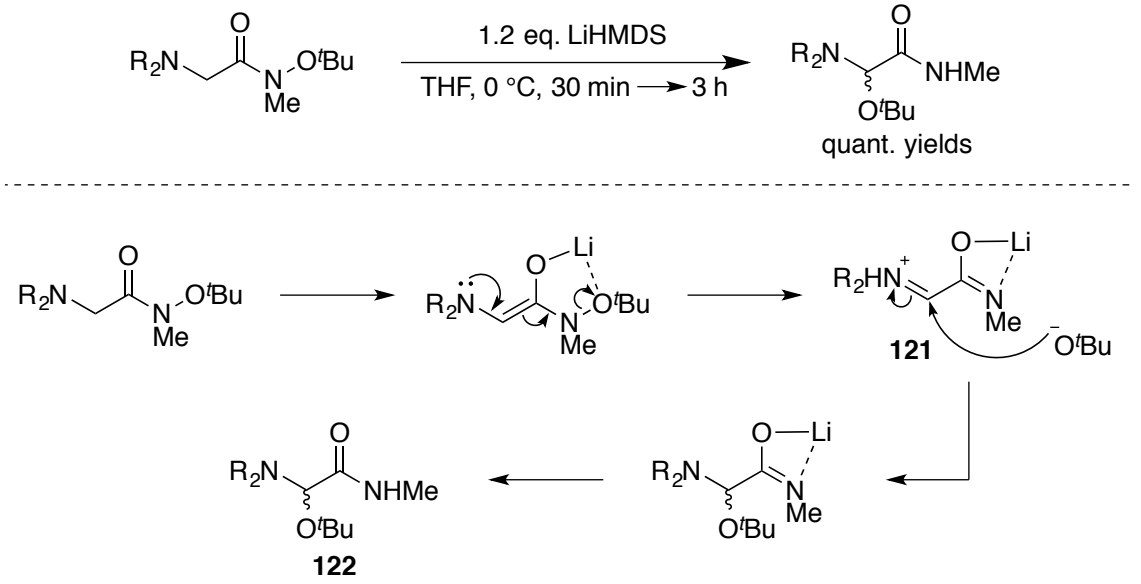


Figure 5.7 Weinreb amide rearrangement reported by Somfai

In his mechanism, he proposes the intermediacy of iminium **121** en route to *N,O*-acetal **122**. In the event of a similar transformation occurring to Weinreb amides **116** and **117** the key iminium can undergo deprotonation to generate the 6π-electron, pseudoaromatic oxazolone **120** (Figure 5.8). Benzyl alcohol was also detected in reactions that employed Weinreb amide **117**, supporting the mechanism suggested.

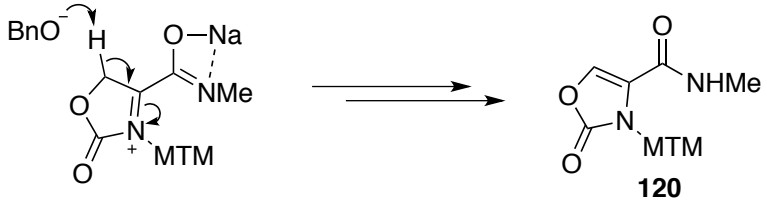
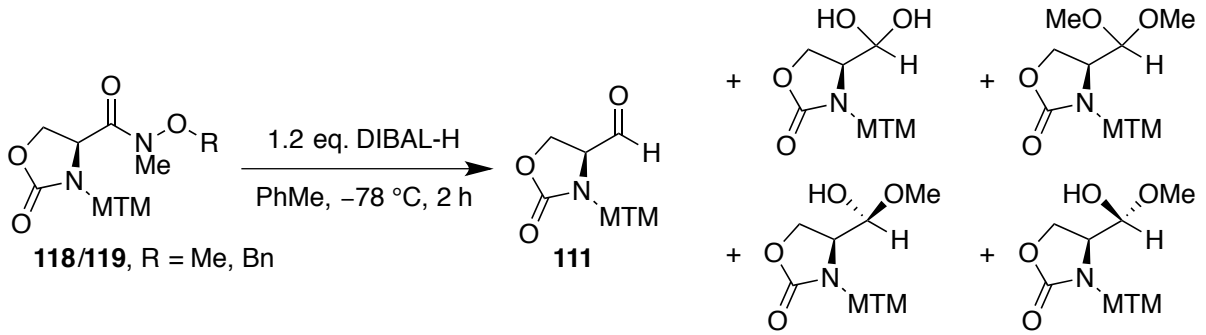


Figure 5.8 Proposed mechanism for formation of oxazolone **120**

The difficulties in accurately controlling reaction temperature on a large scale are likely to be responsible for this side reaction. By exaggerated care with each subsequent addition, the side reaction was reduced, although not completely suppressed. Whilst yields of up to 40% were recorded, upon repetition the yields varied

wildly. Further optimisation was put on hold as sufficient quantities of MTM-substituted amides **118** and **119** had been synthesised to optimise the reduction to aldehyde **114**.

Full consumption was observed under the conditions previously reported (DIBAL-H in toluene at –78 °C); however, NMR analysis of the crude reaction mixture appeared to show a mixture of up to five compounds. After careful analysis of the ^{13}C spectrum of a sample after column chromatography (DCM in MeOH), it was concluded (although not conclusively proved) that the product was present as a combination of the desired aldehyde, hydrate, dimethyl acetal and both diastereomers of the methyl hemiacetal (Scheme 5.13).



Scheme 5.13 Reduction of Weinreb amides **118** and **119**

Use of lithium aluminium hydride as reductant afforded a similar mixture, and alternative chromatography conditions avoiding methanol offered no improvement. Finally, a number of alternative workup procedures known to be of use when handling moisture sensitive compounds were employed, for example the Fieser workup procedure;[258] however, the desired aldehyde (**114**) was never isolated in a pure form. It is hypothesised that the instability of the aldehyde with regards to hydrate and acetal formation may result from the high polarity of the oxazolidinone moiety.

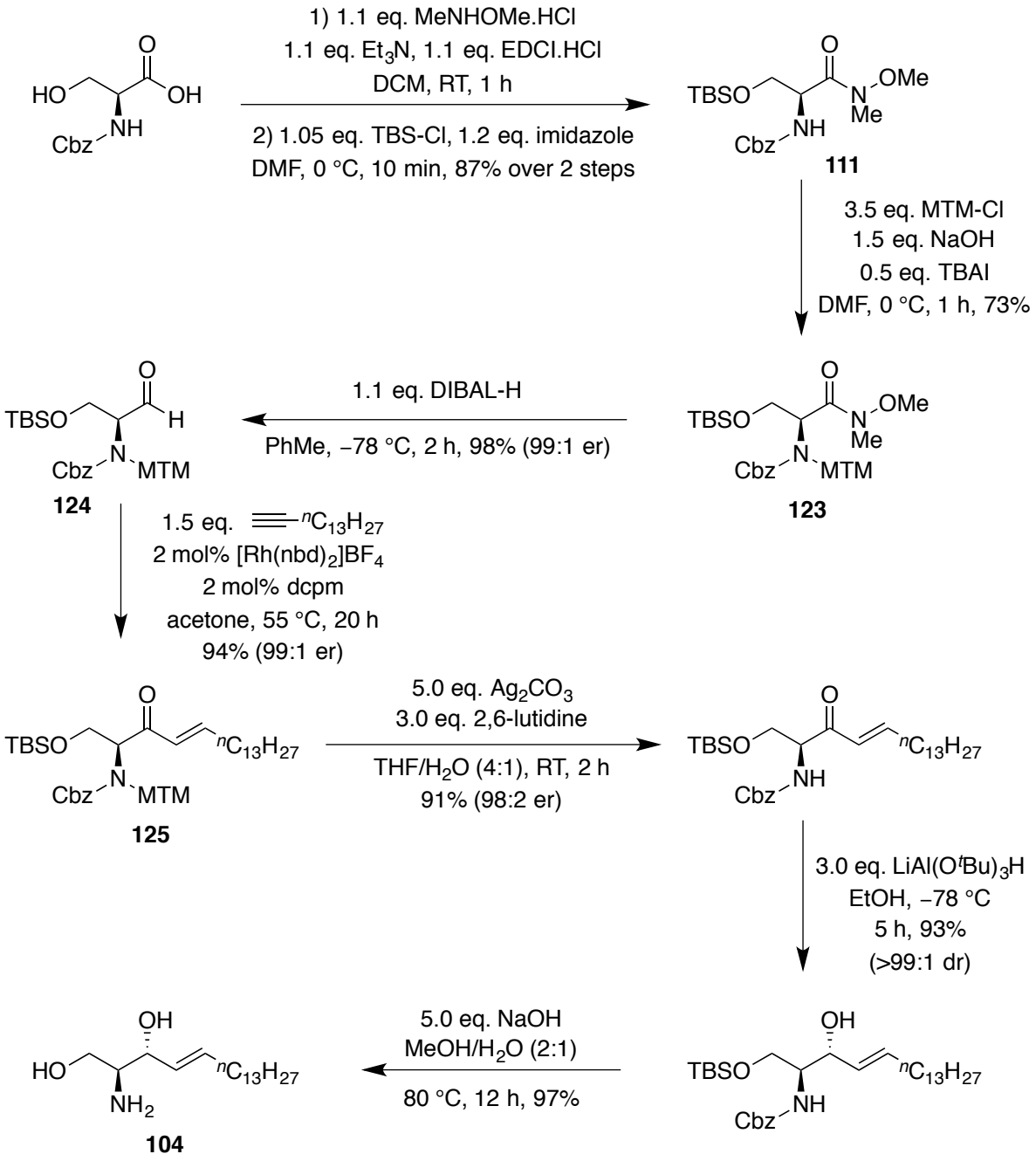
With the desired aldehyde apparently unstable under ambient conditions, this protecting group strategy was now abandoned.

5.4 Summary

In this chapter attempts have been made to expand the scope of Rh-catalysed hydroacylation of alkynes using MTM-substituted α-amino aldehydes. Whilst the hydroacylation of internal alkynes was readily achieved in good to excellent yields, application to the total synthesis of the natural product sphingosine (**104**) has proven difficult, due to the nature of the serine-based aldehyde required for the key hydroacylation step.

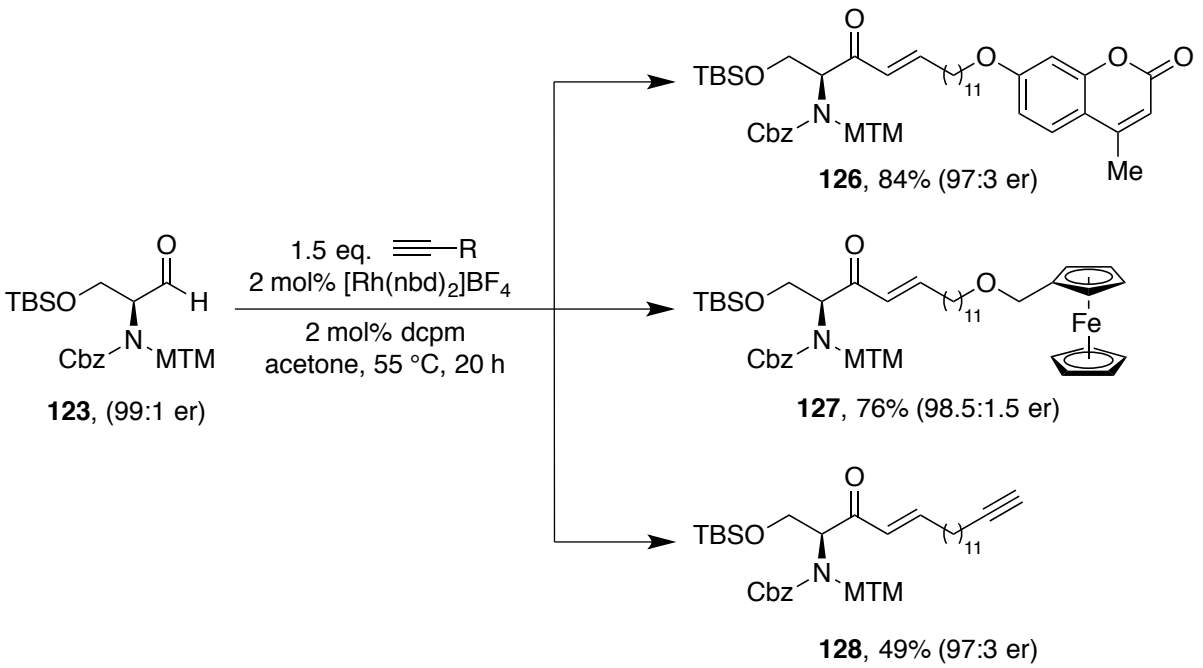
Subsequent follow-up work performed by colleagues within the Willis group has succeeded in synthesising sphingosine **104** *via* Rh-catalysed hydroacylation. By returning to the original carbamate/silyl protecting group combination, optimisation of the MTM-incorporation step was possible. Use of a weaker base in sodium hydroxide, as well as having the electrophile present from the outset allowed for the synthesis of MTM-substituted Weinreb amide **123** in a 73% yield (Scheme 5.14).

Once synthesised, aldehyde **124** underwent efficient hydroacylation to afford enone **125**. The remaining steps, based on literature precedented transformations, were each successful, and sphingosine **104** was synthesised in 48% yield over 8 steps.



Scheme 5.14 Total synthesis of sphingosine

This efficient route has also been shown to be suitable for the straightforward preparation of a range of tagged derivatives. Hydroacylation of aldehyde **124** with functionalised alkynes afforded fluorophore **126**, electrochemically active organometallic **127**, and alkyne **128** (suitable for Huisgen cycloaddition chemistry) in good yields (Scheme 5.15).



Scheme 5.15 Synthesis of tagged sphingsosine derivatives

Chapter 6

Future Work and Conclusion

6.1 Future Work

6.1.1 Further Rh-catalysed hydroacylative routes to heterocycles

The work detailed in Chapters 2-4 has clearly demonstrated the applicability of hydroacylation to a number of heterocycles. Combined with work undertaken by others in the MCW group,[131, 132, 173] a wide range of heterocycles can now be synthesised in good to excellent yields and in short reaction sequences (Figure 6.1). By utilising hydroacylation – C-S functionalisation tandem reactions, the *S*-tether required for efficient hydroacylation need not be present in the heterocyclic product.

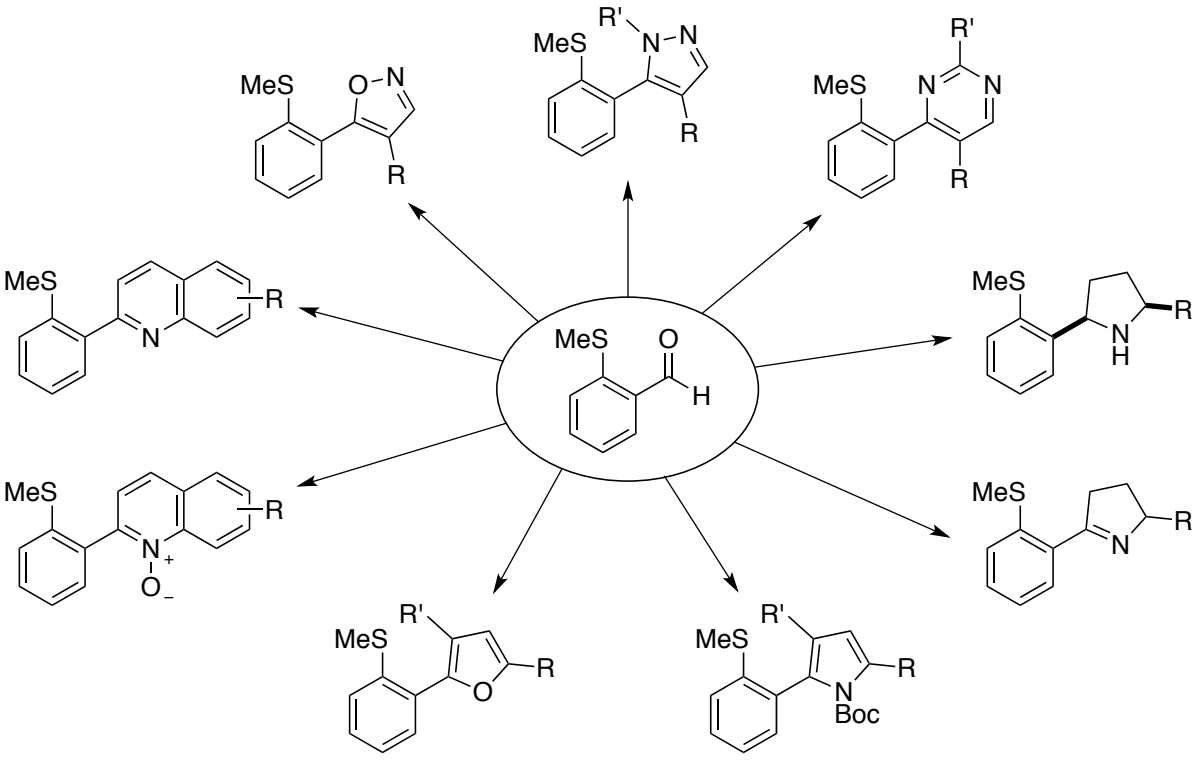


Figure 6.1 Existing hydroacylative routes to heteroaromatic systems

In addition to those syntheses already mentioned, the work detailed in this thesis shows potential for further application to the synthesis of a number of heterocycles. By employing a range of starting materials various partially or fully saturated bicyclic ring systems could potentially be synthesised (Figure 6.2).

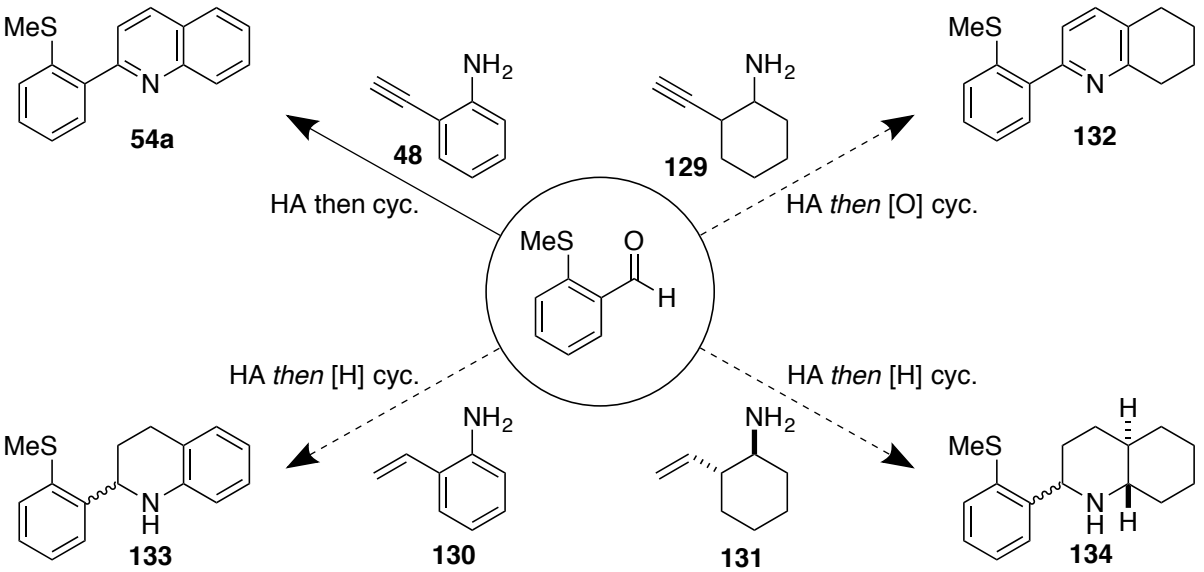


Figure 6.2 Proposed extension of developed methodology

The use of alkyne **129**, followed by an oxidative cyclisation, as suggested in Chapter 2 – Figure 2.8, could afford pyridine derivative **132**. Alternatively, use of alkenes **130** and **131**, followed by cyclisation and reduction could result in tetrahydroquinolines **133** and decahydroquinolines **134**. In the case of decahydroquinolines the rigidity of the transdecalin-type fused ring system should allow for high levels of diastereoselectivity in the reduction step. Alternatively, use of a chiral reducing agent would allow for the synthesis of enantioenriched tetrahydroquinolines. Another route to tetrahydroquinolines would be *via* a literature-precedented diastereoselective reductive cyclisation of intermediate **135**, previously encountered following the conjugate addition reaction detailed in Section 3.7.2.

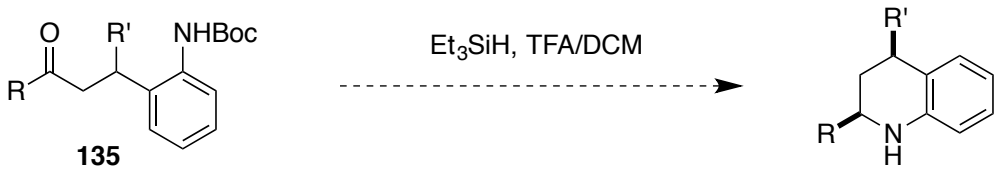
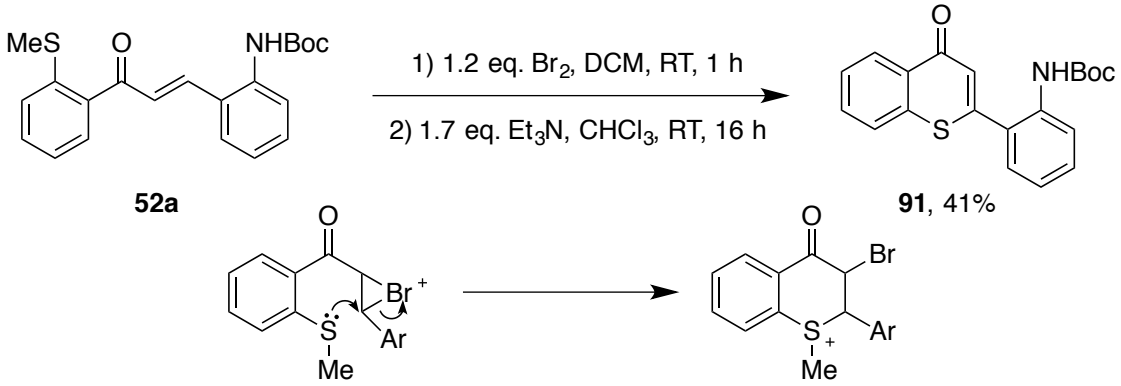


Figure 6.3 Synthesis of 2,4-disbustituted tetrahydroquinolines via reductive cyclisation

The formation of thioflavone derivative **91** serendipitously discovered in Section 3.7.1 is also of interest, as a means to exploit the *S*-tether as useful functionality (Scheme 6.1).



Scheme 6.1 Br-mediated thioflavone synthesis

Optimisation of this procedure would allow access to a broad range of thiochromones (Figure 6.4a). These compounds form the skeleton of numerous biologically or pharmaceutically active compounds.[259, 260, 261, 262, 263, 264, 265] In addition, variants in which the sulfur has been further oxidised are used as human cytomegalovirus protease inhibitors[266] and photolabile protecting groups.[267, 268, 269] Using 2-aminobenzaldehyde derivatives in the hydroacylation step, followed by oxidative cyclisation, could also generate synthetically useful 4-quinolones (**136**) (Figure 6.4b).

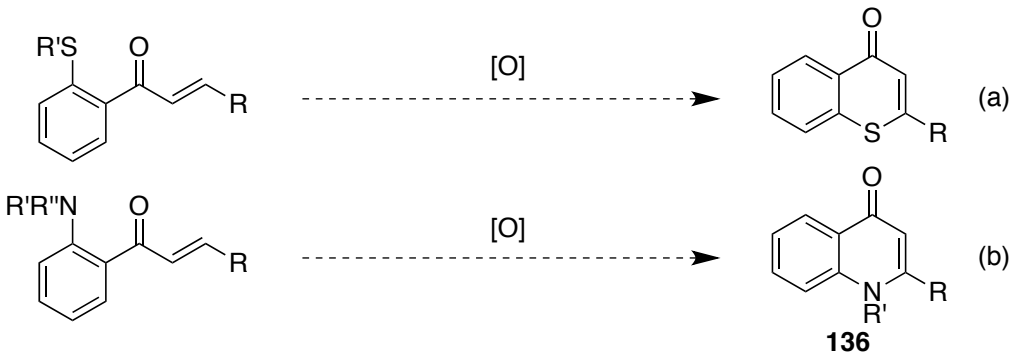


Figure 6.4 Oxidative cyclisations for the synthesis of thiochromenones and 4-quinolones

6.1.2 Expanding the range of chelating aldehydes for Rh-catalysed hydroacylation

In addition to exploring hydroacylative heterocycle syntheses, the work discussed in Chapter 5 has explored the use of alternative chelating aldehydes for controlling decarbonylation. Whilst the use of the methlythiomethyl (MTM) directing group has enabled the synthesis of a number of α-amino enones, the requirement for both an MTM-directing group and an electron-withdrawing protecting group, means that only (protected) primary amino aldehydes can be employed. The use of secondary amino aldehydes, such as prolinal, is not currently possible with the conditions developed.

One tactic in which secondary amines can be employed would be to use *N*-containing heterocyclic aldehydes (Figure 6.5). While serine derivative **114** was insufficiently stable to test this approach, a number of alternative aldehydes, each with an electron-poor nitrogen, could exhibit greater stability. By employing these heterocyclic aldehydes in hydroacylation reactions, a range of functionality-rich, pharmacologically relevant compounds could be synthesised, especially when combined with the existing hydroacylation-based heterocycle syntheses.

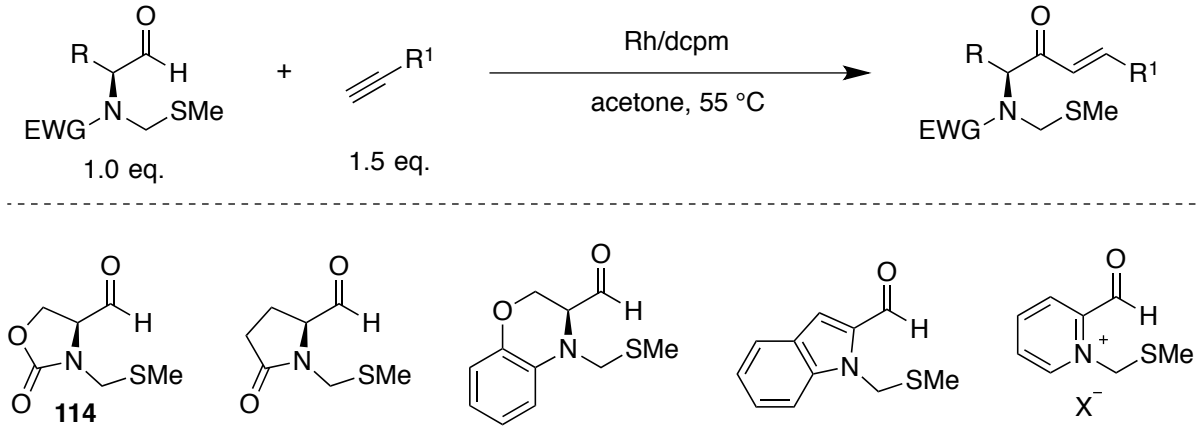


Figure 6.5 MTM-substituted *N*-containing heterocycles for intermolecular hydroacylation

Another tactic that would enable the use of secondary amines would be to combine the stabilisation of the electron-withdrawing group with the directing properties of the *S*-containing MTM functionality (Figure 6.6). By switching the tether system to one of a number of functionalities, for example thiocarbamates, dithiocarbamates or thioureas, could be envisaged to be effective directing groups.

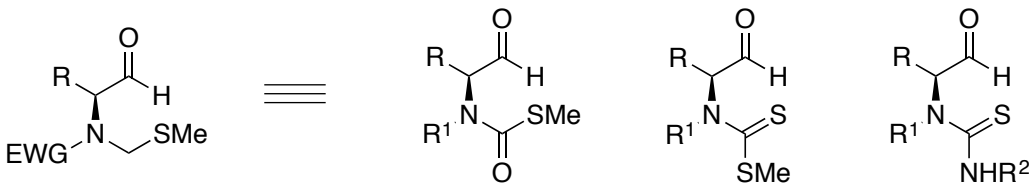


Figure 6.6 Alternative chelating systems for hydroacylation using α-amino aldehydes

In addition to expanding the range of α-amino aldehydes, this tactic should lead to easier incorporation of the directing group, both due to the milder conditions required, and the enhanced nucleophilicity of the secondary amine over the carbamate derivatives required for MTM-incorporation.

6.2 Conclusion

To summarise, the work detailed in this thesis has targeted a number of heterocycles, *via* a novel, key hydroacylative disconnection. The mild reaction conditions and high selectivity of Rh-catalysed hydroacylation using β-chelating aldehydes confers many advantages over traditional condensation approaches.

By targeting analogues of 1,3-dicarbonyls a proof of concept for the synthesis of a range of heterocycles has been established. By reacting the product of hydroacylation of heteroatom-substituted alkynes with hydrazine, pyrrole **32** was synthesised in good yields. The work described herein has since been expanded to encompass the synthesis of multisubstituted pyrroles, isoxazoles and pyrimidines *via* the Rh-catalysed hydroacylation of ynamides.

Other investigations focussed on the synthesis of pyridine precursors. The use of a highly linear-selective "PNP"-type ligand was required to achieve satisfactory levels of regioselectivity, accompanied by high yields. The cyclisation of these intermediates was not straightforward, and although suitable conditions have been proposed, the synthesis of the required starting materials is sufficiently unattractive to render the synthetic route unviable.

By targeting the closely related quinolines, considerably more success has been enjoyed. Boc-protected 2-ethynyl anilines proved to be suitable substrates for

hydroacylation. By reducing the temperature of this process, the formation of carbothiolation by-products has been attenuated. Once isolated, the amino-chalcone derivatives cyclised in excellent yields to form quinolines. A large range of functionalities has been incorporated onto the quinoline ring system, reflecting the high functional group tolerance of the hydroacylation process. Whilst small drawbacks have been identified, these each have been shown to have simple solutions. Electron-rich quinolines can be synthesised in high yields from nitro-substituted substrates, and the *S*-tether required for efficient hydroacylation can be removed using tandem hydroacylation – C-S functionalisation reactions. Finally, functionalisation of the intermediate amino-chalcones allows for the introduction of further functionality on the *N*-containing quinoline ring.

In an effort to target tether-free quinolines, an intramolecular imine-hydroacylation process was investigated. While a number of Rh-catalyst systems proved ineffective, a cobalt-based system showed some promise, with conversions of up to 36%. Further optimisation of these conditions was unfortunately unsuccessful.

In addition to the work undertaken on heterocycle syntheses, efforts to expand the range of tethers employed in hydroacylation have also taken place. In order to enhance an existing study on the use of MTM-substituted α-amino aldehydes, the synthesis of the natural product sphingosine has been attempted. The synthesis of the key serine-derived aldehyde proved problematic due to competitive elimination of the protected alcohol moiety. Following initial studies on a multiple protection group strategy, a route combining *N*- and *O*- protection in a single oxazolidinone system was investigated. Whilst elimination was effective suppressed, the route brought with it a number of new problems, culminating in the instability of the target aldehyde, and the

route was abandoned. Colleagues within the Willis group have since completed the synthesis.

Chapter 7

Experimental Data and Procedures

7.1 General Considerations

Reactions were performed under an inert atmosphere of nitrogen, using anhydrous solvent unless otherwise stated. All glassware was oven dried at >80 °C, and allowed to cool to room temperature under a positive nitrogen pressure. Thin Layer Chromatography (TLC) analysis was carried out on Merck Kieselgel 60 PF254 pre-coated aluminium backed sheets and visualised either by UV fluorescence (254 nm) and/or by staining with potassium permanganate ($KMnO_4$) or Seebach's magic stain. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Fluorochem Ltd., Apollo Scientific Ltd., Acros Organics Ltd., Alfa Aesar Ltd., or Strem Chemicals Inc. and were used as supplied unless otherwise stated. A number of aldehydes were prepared by other members of the Willis group following literature procedures. For these compounds references have been provided. Anhydrous acetonitrile, diethylether, dichloromethane, toluene and tetrahydrofuran were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc.PS-400-7 solvent purification system. Acetone was distilled from Drierite®, and DCE distilled from CaH_2.

'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 °C. Microwave heating was carried out using a CEM Discover-S unit. Flash column chromatography was performed using Apollo scientific silica gel 60 (particle size 0.040-0.063 nm) with the indicated eluents.

NMR spectra were recorded at ambient temperature on a Brüker AV400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s) (as specified). Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Assignments were made on the basis of chemical shifts, coupling constants, DEPT, COSY, HSQC and comparison with spectra of related compounds. Signal multiplicities are denoted as: s,singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad. Multiplicities are reported as observed. Low-resolution ESI mass spectra were recorded on a Fisons Platform spectrometer. High-resolution ESI mass spectrometry measurements were recorded on a Brucker Daltronics microTO (ESI) spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FTIR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

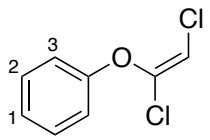
7.2 Experimental Data for Chapter 2

7.2.1 Pyrazole project

General Procedure A for the preparation of Rh/bisphosphine complexes.

$[Rh(nbd)_2]BF_4$ (1 eq.) and ligand (1 eq.) were added to a microwave vial, which was then evacuated and backfilled with $N_{2(g)}$ three times. Then was added distilled and degassed acetone (0.4 mL per 0.01 mmol Rh), and the resulting suspension sonicated in order to solubilise the phosphine ligand. Once the solution was homogenous, $H_{2(g)}$ was bubbled through for 1 minute (or until a noticeable colour change was observed), followed by $N_{2(g)}$ for 30 seconds.

(*E*)-((1,2-Dichlorovinyl)oxy)benzene, 26a

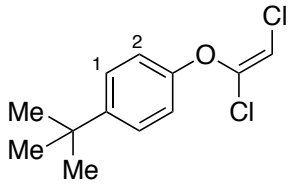


To a solution of phenol (94.0 mg, 1.00 mmol) in DMSO (2.0 mL) was added NaOH (40.0 mg, 1.00 mmol), and left to stir at room temperature for 2 hours. Trichloroethylene (90.0 µL, 1.0 mmol) was then added and the reaction left to stir at room temperature for 66 hours. The reaction was quenched by the addition of H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 2% CH_2Cl_2 in petrol) afforded enol ether **26a** as a colourless oil (151 mg, 79% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.37 (2H, dd, *J* 8.5 and 7.5, C(2)*H*), 7.17 (1H, t, *J* 7.5, C(1)*H*), 7.07 (2H, d, *J* 8.5, C(3)*H*), 5.96 (1H, s, ClC=CCl*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 153.9,

140.1, 129.9, 124.6, 117.2, 103.9; **HRMS** (EI, *m/z*): $C_8H_6Cl_2O$ ($[M]^+$) requires 187.9796, found 187.9792.

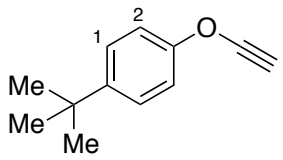
Data consistent with the literature.[270]

(*E*)-1-(*tert*-Butyl)-4-((1,2-dichlorovinyl)oxy)benzene, 26b



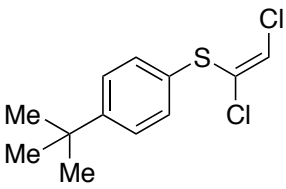
To a solution of 4-(*tert*-butyl)phenol (1.55 g, 10.3 mmol) in DMSO (20 mL) was added NaOH (412 mg, 10.3 mmol), and left to stir at room temperature for 2 hours. Trichloroethylene (0.900 mL, 10.3 mmol) was then added and the reaction left to stir at room temperature for 66 hours. The reaction was quenched by the addition of H_2O (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 2% CH_2Cl_2 in petrol) afforded enol ether **26b** as a colourless oil (2.09 g, 83% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.37 (2H, d, *J* 9.0, C(1)*H*), 6.99 (2H, d, *J* 9.0, C(2)*H*), 5.94 (1H, s, C*H*Cl), 1.32 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.6, 147.5, 126.7 (2 × C), 116.6, 103.6, 34.5, 31.6; **HRMS** (EI, *m/z*): $C_{12}H_{14}Cl_2O$ ($[M]^+$) requires 244.0422, found 244.0421; **IR** ν_{max} (film)/cm^{-1}: 2963, 1632, 1602, 1506, 1365, 1271, 1208, 1170, 1112, 1070, 1015.

1-(*tert*-Butyl)-4-(ethynyloxy)benzene, 27b



To a stirred solution of enol ether **26b** (2.06 g, 8.39 mmol) in Et_2O (42 mL) at –78 °C was added dropwise ^{n}BuLi (21.0 mL, 1.60 M solution in hexanes, 33.5 mmol). The reaction mixture was stirred at –78 °C for 1 hour, then at –40 °C for 2 hours. The reaction was quenched by the addition of ^{i}PrOH (5 mL), and diluted with Et_2O (40 mL), followed by brine (80 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 × 80 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 2% CH_2Cl_2 in petrol) afforded ynol ether **27b** as a colourless oil (1.02 g, 69% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.39 (2H, d, *J* 9.0, C(1)*H*), 7.21 (2H, d, *J* 9.0, C(2)*H*), 2.05 (1H, s, CC*H*), 1.31 (9H, s, $C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 153.4, 147.8, 126.7 (2 × C), 114.6, 89.0, 33.0, 31.6; **HRMS** (EI, *m/z*): $C_{12}H_{14}O$ ($[M]^+$) requires 174.1045, found 174.1044; **IR** ν_{max} (film)/cm^{-1}: 3319, 2963, 2170, 1602, 1505, 1365, 1207, 1170, 1111, 1061, 1014.

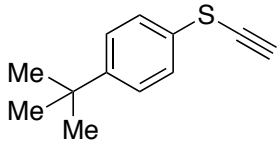
(*E*)-(4-(*tert*-Butyl)phenyl)(1,2-dichlorovinyl)sulfane, 28



To a suspension of NaH (464 mg, 60% suspension in mineral oil, 11.6 mmol) in THF (23 mL) was added 4-(*tert*-butyl)benzenethiol (1.00 mL, 5.80 mmol). After evolution of $H_{2(g)}$ was complete, trichloroethylene (2.10 mL, 23.2 mmol) was added, and the reaction

left to stir at room temperature for 16 hours. The reaction was quenched by the addition of ^{i}PrOH (5 mL), and diluted with Et_2O (100 mL), followed by brine (100 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 × 100 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 2% CH_2Cl_2 in petrol) afforded alkenyl sulfide **28** as a colourless oil (1.43 g, 94% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.38 (4H, s, ArC*H*), 6.53 (1H, s, C*H*Cl), 1.32 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 132.7, 130.5, 126.9, 126.3, 119.6, 34.7, 31.2; **HRMS** (EI, *m/z*): $C_{12}H_{14}Cl_2S$ ([M]$^+$) requires 260.0193, found 260.0196; **IR** ν_{max} (film)/cm^{-1}: 2964, 1489, 1399, 1364, 1268, 1117, 1013.

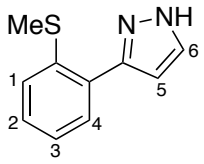
(4-(*tert*-Butyl)phenyl)(ethynyl)sulfane, 29



To a stirred solution of alkenyl sulfide **28** (1.34 g, 5.13 mmol) in Et_2O (25 mL) at –78 °C was added dropwise ^{n}BuLi (12.8 mL, 1.60 M solution in hexanes, 20.5 mmol). The reaction mixture was stirred at –78°C for 1 hour, then at –40 °C for 2 hours. The reaction was quenched by the addition of ^{i}PrOH (5 mL), and diluted with Et_2O (25 mL), followed by brine (40 mL). The layers were separated, and the aqueous layer was then extracted with Et_2O (3 × 50 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 2% CH_2Cl_2 in petrol) afforded alkyne **29** as a colourless oil (887 mg, 91% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.38 (4H, s, Ar*H*), 3.20 (1H, s, CC*H*), 1.31 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 150.4, 127.9, 126.9, 126.6, 86.2. 71.8, 34.7, 31.4; **HRMS** (EI, *m/z*): $C_{12}H_{14}S$ ([M]$^+$)

requires 190.0816, found 190.0816; **IR** ν_{max} (film)/cm^{-1}: 3289, 2963, 2868, 2046, 1498, 1400, 1364, 1268, 1116, 1012.

3-(2-(Methylthio)phenyl)-1*H*-pyrazole, 32

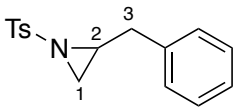


To a catalyst solution ([Rh(nbd)$_2$]BF$_4$ (18.7 mg, 0.05 mmol), dcpm (20.2 mg, 0.05 mmol) in acetone (1.7 mL)) prepared according to General Procedure **A**, was added 2-(methylthio)benzaldehyde **30** (76.1 mg, 0.50 mmol) and alkyne **29** (143 mg, 0.75 mmol). The reaction mixture was left to stir at 55 °C for 2 hours. Upon cooling to room temperature, the crude reaction mixture was passed through a plug of SiO_2, flushed with Et_2O, and concentrated *in vacuo*. The concentrated crude mixture was then dissolved in EtOH (1.3 mL), and hydrazine monohydrate (146 µL, 3.00 mmol) was added before heating at 90 °C for 2 hours. Flash column chromatography (SiO_2, 20-50% EtOAc in petrol) afforded pyrazole **32** as a brown oil (52.3 mg, 55% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 10.97 (1H, br. s, N*H*), 7.55 (1H, d, *J* 2.0, C(6)*H*), 7.52-7.50 (1H, m, C(1)*H*), 7.35-7.30 (2H, m, C(3)*H*, C(4)*H*), 7.20-7.16 (1H, m, C(2)*H*), 6.62 (1H, d, *J* 2.0, C(5)*H*), 2.40 (3H, s, SC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 146.6, 137.2, 133.5, 131.1, 129.9, 128.7, 126.4, 125.1, 105.8, 16.3; **LRMS** (ESI+, *m/z*): 191.1 ([M+H]$^+$).

Data consistent with the literature.[271]

7.2.2 Pyridine project

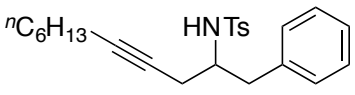
2-Benzyl-1-tosylaziridine, 35



At 0 °C, to a stirred solution of phenylalaninol (5.00 g, 33.1 mmol) and K_2CO_3 (18.3 g, 132 mmol) in MeCN (66 mL) was added portionwise TsCl (13.9 g, 72.8 mmol). The reaction was then stirred at room temperature for 16 hours. Toluene (165 mL) was then added, and a white precipitate observed. The solid was filtered off and the reaction concentrated *in vacuo*. Flash column chromatography (SiO_2, 10% Et_2O in petrol) afforded aziridine **35** as a white solid (5.89 g, 62% yield); **m.p.**: 95-97 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.60 (2H, d, *J* 8.0, Ts*H*), 7.13 (2H, d, *J* 8.0, Ts*H*), 7.09-7.04 (3H, m, Ar*H*), 6.98-6.95 (2H, m, Ar*H*), 2.90-2.84 (1H, tdd, *J* 7.0, 5.0 and 4.5 C(2)*H*), 2.73 (1H, dd, *J* 14.5 and 5.0, C(3)H_AH_B), 2.63 (1H, d, *J* 7.0, C(1)H_AH_B), 2.60 (1H, dd, *J* 14.5 and 7.0, C(3)H_AH_B), 2.35 (3H, s, CH_3), 2.09 (1H, d, *J* 4.5, C(1)H_AH_B); **^{13}C-NMR** (100 MHz, $CDCl_3$): 144.3, 137.0, 134.8, 129.6, 128.7, 128.5, 127.9, 126.5, 41.2, 37.5, 32.8, 21.6; **LRMS** (ESI+, *m/z*): 288.1 ($[M+H]^+$).

Data consistent with the literature.[272]

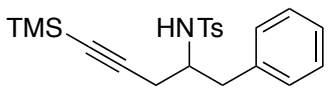
4-Methyl-*N*-(1-phenylundec-4-yn-2-yl)benzenesulfonamide, 36



Under an N_2 atmosphere, to a stirred solution of ^{n}BuLi (1.25 mL, 1.60 M solution in hexanes, 2.00 mmol) in Et_2O (8.0 mL) at –78 °C was added 1-octyne (300 µL,

2.00 mmol). After stirring for 30 minutes at –78 °C the solution was transferred *via* cannula into a flask containing aziridine **35** (287 mg, 1.00 mmol) and Cu(OTf) benzene complex (25.2 mg, 0.05 mmol). The reaction mixture was allowed to warm to room temperature and left to stir for 64 hours. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (4 mL) at 0 °C. The layers were separated, and the aqueous layer extracted with Et_2O (3 × 4 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 15% EtOAc in petrol) afforded alkyne **36** as a colourless oil (162 mg, 40% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.59 (2H, d, *J* 8.5, Ts*H*), 7.17-7.12 (5H, m, Ar*H*, Ts*H*), 7.00 (2H, dd, *J* 8.0 and 2.0, Ar*H*), 4.64 (1H, d, *J* 8.5, TsN*H*), 3.46-3.38 (1H, m, TsNHC*H*), 2.77 (2H, d, *J* 7.0, CH_2Ph), 2.34 (3H, s, ArCH_3), 2.15-2.07 (4H, m, CH_2CCCH_2), 1.47-1.19 (8H, m, 4 × CH_2), 0.83 (3H, t, *J* 7.0, CH_2CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.3, 137.6, 137.1, 129.7, 129.4, 128.6, 127.0, 126.7, 84.4, 74.7, 53.5, 40.1, 31.4, 28.9, 28.7, 24.0, 22.6, 21.5, 18.8, 14.1; **LRMS** (ESI+, *m/z*): 398.3 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{24}H_{31}NNaO_2S$ ($[M+Na]^+$) requires 420.1968, found 420.1959; **IR** ν_{max} (film)/cm^{-1}: 3282, 2929, 2858, 1599, 1496, 1455, 1330, 1160, 1088.

4-Methyl-*N*-(1-phenyl-5-(trimethylsilyl)pent-4-yn-2-yl)benzenesulfonamide, 37

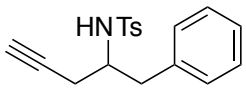


Under an N_2 atmosphere, to a stirred solution of ^{n}BuLi (8.64 mL, 2.06 M solution in cyclohexane, 17.8 mmol) in Et_2O (68 mL) at –78 °C was added TMS-acetylene (2.50 mL, 17.8 mmol). After stirring for 30 minutes at –78 °C the solution was transferred *via* cannula into a flask containing aziridine **35** (2.44 g, 8.50 mmol) and Cu(OTf) benzene

complex (223 mg, 0.440 mmol). The reaction mixture was allowed to warm to room temperature and was left to stir for 64 hours. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (40 mL) at 0 °C. The layers were separated, and the aqueous layer extracted with Et_2O (3 × 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 15% EtOAc in petrol) afforded alkyne **37** as a colourless oil (3.20 g, 98% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.63 (2H, d, *J* 8.0, Ts*H*), 7.24-7.17 (5H, m, Ts*H*, Ar*H*), 7.08-7.06 (2H, m, Ar*H*), 4.77 (1H, d, *J* 8.5, N*H*), 3.58-3.49 (1H, m, C*H*NH), 2.88 (1H, dd, *J* 13.5 and 7.5, CH_AH$_B$Ph), 2.82 (1H, dd, *J* 13.5 and 6.5, CH$_A$$H_B$Ph), 2.41 (3H, s, ArC$H_3$), 2.34 (1H, dd, *J* 17.0 and 6.0, CH_AH$_B$CCR), 2.27 (1H, dd, *J* 17.0 and 4.2, CH$_A$CH_BCCR), 0.19 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.2, 137.5, 136.7, 129.6, 129.3, 128.6, 126.9, 126.7, 101.7, 88.8, 53.1, 39.8, 25.3, 21.5, 0.0; **LRMS** (ESI+, *m/z*): 386.2 ([M+H]$^+$).

Data consistent with the literature.[273]

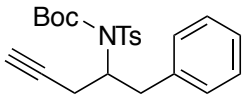
4-Methyl-*N*-(1-phenylpent-4-yn-2-yl)benzenesulfonamide, 38



To a stirred solution of alkyne **37** (363 mg, 0.940 mmol) in MeOH (12 mL) was added K_2CO_3 (156 mg, 1.13 mmol) at room temperature. The reaction was stirred at room temperature for 16 hours. The reaction was then diluted with Et_2O (25 mL), giving a white precipitate. The mixture was filtered through Celite® and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% EtOAc in petrol) afforded terminal alkyne **38** as a white solid (264 mg, 89% yield); **m.p.**: 95-97 °C (crystalised from petrol/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.64 (2H, d, *J* 8.5, Ts*H*), 7.21-7.18 (5H, m,

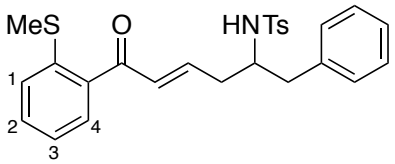
Ar*H*), 7.07-7.05 (2H, m, Ar*H*), 5.22-5.15 (1H, m, N*H*), 3.56 (1H, m, C*H*NH), 2.89 (1H, dd, *J* 13.5 and 7.5, C$H_A$$H_B$Ph), 2.78 (1H, dd, *J* 13.5 and 6.5, CH$_A$$H_B$Ph), 2.39 (3H, s, ArC$H_3$), 2.32-2.30 (2H, m, C$H_2$CCH), 2.08 (1H, t, *J* 2.5, CC*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.3, 137.5, 136.9, 129.7, 129.3, 128.6, 127.0, 126.7, 79.7, 72.1, 53.4, 39.9, 24.3, 21.5; **LRMS** (ESI+, *m/z*): 336.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{18}H_{19}NNaO_2S$ ([M+Na]$^+$) requires 336.1019, found 336.1029; **IR** ν_{max} (film)/cm^{-1}: 3286, 1599, 1496, 1423, 1327, 1158, 1088.

tert-Butyl (1-phenylpent-4-yn-2-yl)(tosyl)carbamate, 39



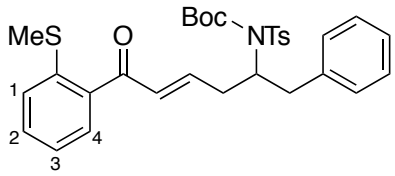
To a stirred solution of sulfonamide **38** (100 mg, 0.319 mmol) and 4-dimethylaminopyridine (12.8 mg, 0.105 mmol) in MeCN (1.0 mL) at room temperature was added Boc_2O (150 µL, 0.638 mmol). After stirring at room temperature for 2 hours, additional Boc_2O (150 µL, 0.638 mmol) was added and the reaction stirred for 16 hours. The reaction mixture was then concentrated *in vacuo*. Flash column chromatography (SiO_2, 15% EtOAc in petrol) afforded alkyne **39** as a colourless oil (126 mg, 96% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.22-7.13 (7H, m, Ar*H*), 6.98 (2H, d, *J* 8.0, Ar*H*), 4.81 (1H, ap. quin, *J* 7.5, BocN(Ts)C*H*), 3.25 (1H, dd, *J* 13.5 and 9.0, PhC$H_A$$H_B$), 3.13 (1H, dd, *J* 13.5 and 6.5, PhCH$_A$$H_B$), 2.86 (1H, ddd, *J* 17.0 8.0 and 2.5, HCCC$H_A$$H_B$), 2.68 (1H, ddd, *J* 17.0, 7.5 and 2.5, HCCCH$_A$$H_B$), 2.28 (3H, s, ArC$H_3$), 1.92 (1H, t, *J* 2.5, CC*H*), 1.28 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 150.6, 143.5, 138.4, 137.0, 129.6, 128.84, 128.76, 128.0, 126.8, 84.4, 81.1, 71.1, 59.8, 38.7, 28.0, 23.4, 21.5; **LRMS** (ESI+, *m/z*): 436.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{27}NNaO_4S$ ([M+Na]$^+$) requires 436.1562, found 436.1553; **IR** ν_{max} (film)/cm^{-1}: 3275, 2969, 1724, 1456, 1342, 1281, 1150, 1089, 1055.

(*E*)-4-Methyl-*N*-(6-(2-(methylthio)phenyl)-6-oxo-1-phenylhex-4-en-2-yl)benzenesulfonamide, 42



To the catalyst ([Rh(nbd)$_2$]BF$_4$ (2.8 mg, 7.5 μmol), PNP(Cy) (3.2 mg, 7.5 μmol)) prepared according to General Procedure **A**, then blown to dryness with $N_{2(g)}$, was added 2-(methylthio)benzaldehyde **30** (22.8 mg, 0.150 mmol) and alkyne **38** (68.9 mg, 0.220 mmol) in acetone (150 μL) at 55 °C. The reaction mixture was left to stir at 55 °C for 2 hours. Upon cooling to room temperature the crude reaction mixture was passed through a plug of SiO_2, flushed with Et_2O, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% EtOAc in petrol) afforded enone **42** as a yellow oil (59.8 mg, 86% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.52-7.48 (3H, m, C(4)*H*, 2 × Ar*H*), 7.39(1H, td, *J* 7.5 and 1.5, C(2)*H*), 7.27 (1H, d, *J* 7.5, C(1)*H*), 7.15-7.09 (6H, m, C(3)*H*, 5 × Ar*H*), 6.94-6.92 (2H, m, Ar*H*), 6.67-6.55 (2H, m, C(O)C*H*C*H*), 4.60 (1H, d, *J* 7.5, TsN*H*), 3.52 (1H, ap. sextet, *J* 6.5, TsNHC*H*), 2.69 (1H, dd, *J* 14.0 and 7.0, PhCH_ACH$_B$), 2.64 (1H, dd, *J* 14.0 and 7.0, PhCH$_A$CH_B), 2.43-2.33 (2H, m, C(O)CHCHCH_2), 2.38 (3H, s, SCH_3), 2.29 (3H, s, ArCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.2, 144.2, 143.4, 140.7, 137.1, 136.6, 136.3, 131.7, 131.7, 129.8, 129.7, 129.3, 128.7, 127.0, 126.9, 126.0, 124.1, 54.2, 40.9, 37.6, 21.5, 16.4; **LRMS** (ESI+, *m/z*): 466.2 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{26}H_{27}NNaO_3S_2$ ([M+Na]$^+$) requires 488.1319, found 488.1325; **IR** ν_{max} (film)/cm^{-1}: 3266, 2922, 1661, 1615, 1495, 1433, 1328, 1155, 1085.

(*E*)-*tert*-Butyl (6-(2-(methylthio)phenyl)-6-oxo-1-phenylhex-4-en-2-yl)(tosyl)carbamate, 43

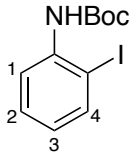


To the catalyst ([Rh(nbd)$_2$]BF$_4$ (2.8 mg, 7.5 μmol), PNP(Cy) (3.2 mg, 7.5 μmol)) prepared according to General Procedure **A**, then blown to dryness with $N_{2(g)}$, was added 2-(methylthio)benzaldehyde **30** (22.8 mg, 0.150 mmol) and alkyne **39** (81.0 mg, 0.200 mmol) in acetone (150 μL) at 55 °C. The reaction mixture was left to stir at 55 °C for 2 hours. Upon cooling to room temperature the crude reaction mixture was passed through a plug of SiO_2, flushed with Et_2O, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% EtOAc in petrol) afforded enone **43** as a yellow oil (66.0 mg, 78% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.48 (1H, dd, *J* 7.5, 1.5, C(4)*H*), 7.36 (1H, ap. td, *J* 7.5 and 1.5, C(2)*H*), 7.26 (1H, d, *J* 8.0, C(1)*H*), 7.23-7.14 (7H, m, Ar*H*), 7.08 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 6.97 (2H, d, *J* 8.0, Ar*H*), 6.76 (1H, ddd, *J* 15.5, 8.0, and 7.0, C(O)CHC*H*CH$_2$), 6.62 (1H, d, J 15.5, C(O)C*H*CHCH$_2$), 4.81 (1H, ap. quin, *J* 7.5, BocN(Ts)C*H*), 3.29 (1H, dd, *J* 13.5 and 8.5, PhC*H*$_A$CH$_B$), 3.07-2.96 (2H, m, PhCH$_A$C*H*$_B$, C(O)CHCHC*H*$_A$CH$_B$), 2.70 (1H, dt, *J* 13.0 and 6.5, C(O)CHCHCH$_A$C*H*$_B$), 2.36 (3H, s, SC*H*$_3$), 2.22 (3H, s, ArC*H*$_3$), 1.29 (9H, s, C(C*H*$_3$)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.6, 150.7, 145.9, 143.6, 140.6, 138.4, 137.4, 136.4, 131.5, 131.3, 129.9, 129.6, 129.1, 128.8, 127.8, 126.8, 126.0, 123.9, 84.5, 60.1, 39.6, 36.6, 28.0, 21.5, 16.4; **LRMS** (ESI+, *m/z*): 588.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{31}H_{35}NNaO_5S_2$ ([M+Na]$^+$) requires 588.1861, found 588.1849; **IR** ν_{max} (film)/cm^{-1}: 2980, 1723, 1663, 1619, 1434, 1352, 1280, 1151, 1087.

7.3 Experimental Data for Chapter 3

7.3.1 Synthesis of *N*-Boc 2-ethynylanilines

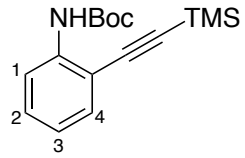
General Procedure B – Boc-protection of anilines using NaHMDS, as exemplified by the synthesis of *tert*-Butyl (2-iodophenyl)carbamate, 56a



Under a $N_{2(g)}$ atomsphere at 0 °C, to a solution of 2-iodoaniline (5.00 g, 22.8 mmol) in THF (25 mL), was added NaHMDS (25.1 mL, 2.00 M solution in THF, 50.2 mmol). The resulting solution was stirred at 0 °C for 30 minutes, before a solution of Boc_2O (5.48 g, 25.1 mmol) in THF (25 mL) was added dropwise. The reaction was stirred for 15 minutes at 0 °C, before being allowed to warm to room temperature over 30 minutes. The reaction was then concentrated *in vacuo*, before being partitioned between EtOAc (200 mL) and 1.0 N $HCl_{(aq)}$ (200 mL). The organic layer was washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. No further purification was necessary and *N*-Boc aniline **56a** was isolated as a dark brown oil (7.06 g, 97% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.98 (1H, dd, *J* 8.0 and 1.0, C(4)*H*), 7.67 (1H, dd, *J* 8.0 and 1.5, C(1)*H*), 7.24 (1H, td, *J* 8.0, 1.0, C(2)*H*), 6.75 (1H, br. s, N*H*), 6.69 (1H, td, *J* 7.5 and 1.5, C(3)*H*), 1.46 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.6, 138.9, 138.8, 129.2, 124.7, 120.2, 88.8, 81.1, 28.3; **LRMS** (ESI+, *m/z):* 342.0 ([M+Na]$^+$).

Data consistent with the literature.[274]

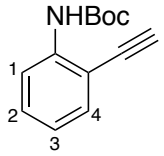
General Procedure C - synthesis of aryl alkynes *via* the Sonogashira reaction, as exemplified by the synthesis of *tert*-Butyl (2-((trimethylsilyl)ethynyl)phenyl) carbamate, 57a



A flask containing aryl iodide **56a** (882 mg, 2.76 mmol), $Pd(PPh_3)_2Cl_2$ (97.0 mg, 0.140 mmol) and CuI (26.3 mg, 0.140 mmol) was evacuated and back filled with $N_{2(g)}$ three times. Then was added sequentially, with stirring, DMF (37 mL), Et_3N (0.580 mL, 4.14 mmol) and TMS-acetylene (0.590 mL, 4.14 mmol). The resulting solution was stirred at room temperature for 16 hours, before quenching with sat. $NH_4Cl_{(aq)}$ (20 mL). The mixture was diluted with EtOAc (50 mL), and washed with 5% $LiCl_{(aq)}$ (3 × 50 mL), then brine (50 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 5% Et_2O in petrol) afforded aryl alkyne **57a** as an orange oil (722 mg, 90% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.96 (1H, d, *J* 8.5, C(1)*H*), 7.23 (1H, dd, *J* 7.5 and 1.0, C(4)*H*), 7.23 (1H, br. s, N*H*), 7.16 (1H, td, *J* 8.0 and 1.5, C(2)*H*), 6.79 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 1.39 (9H, s, C(CH_3)$_3$), 0.15 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.5, 140.4, 131.4, 130.0, 122.0, 117.3, 111.0, 102.14, 100.7, 80.7, 28.4, 0.0; **LRMS** (ESI+, *m/z*): 312.1 ($[M+Na]^+$).

Data consistent with the literature.[275]

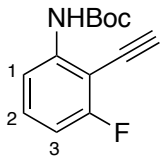
General Procedure D - TMS deprotection of terminal alkynes, as exemplified by the synthesis of *tert*-Butyl (2-ethynylphenyl)carbamate, 51a



To a solution of TMS-protected aryl alkyne **57a** (130 mg, 0.450 mmol) in MeOH (9.0 mL) was added K_2CO_3 (62.2 mg, 0.450 mmol), and the resulting mixture stirred at room temperature for 1 hour. The reaction mixture was diluted with Et_2O (30 mL) and washed with brine. (30 mL). The aqueous layer was then extracted with Et_2O (2 × 30 mL), the organic layers combined then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 5% Et_2O in petrol) afforded terminal alkyne **51a** as an off-white solid (91 mg, 93% yield); **m.p.**: 42-44 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.08 (1H, d, *J* 8.5, C(1)*H*), 7.34 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.25 (1H, td, *J* 8.0 and 1.5, C(2)*H*), 7.20 (1H, br. s, N*H*), 6.88 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 3.41 (1H, s, CC*H)*, 1.46 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.4, 140.3, 132.3, 130.2, 122.0, 117.6, 109.8, 84.1, 80.9, 79.4, 28.3; **LRMS** (ESI+, *m/z*): 240.1 ([M+Na]$^+$).

Data consistent with the literature.[276]

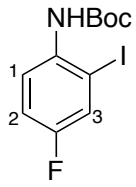
***tert*-Butyl (2-ethynyl-3-fluorophenyl)carbamate, 51b**



Compound **51b** was prepared according to a sequence of General Procedures **B**, **C** and **D** without intermediate isolation, involving a SiO_2 filtration between **C** and **D**, with **C**

conducted at 70 °C, using 3-fluoro-2-iodoaniline (1.00 g, 4.22 mmol), NaHMDS (4.64 mL, 2.00 M solution in THF, 9.28 mmol), Boc_2O (1.01 mg, 4.64 mmol), THF (8.0 mL), $Pd(PPh_3)_2Cl_2$ (147 mg, 0.210 mmol), CuI (40.0 mg, 0.210 mmol), TMS-acetylene (0.90 mL, 6.33 mmol), Et_3N (0.88 mL, 6.33 mmol), DMF (12 mL), K_2CO_3 (583 mg, 4.22 mmol) and MeOH (40 mL). Flash column chromatography (SiO_2, 0-10% Et_2O in petrol) afforded terminal alkyne **51b** as a pale brown solid (693 mg, 69% yield); **m.p.**: 64-66 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.00 (1H, d, *J* 8.5, C(1)*H*), 7.31 (1H, td, *J* 8.5 and 6.5, C(2)*H*), 7.28 (1H, br. s, N*H*), 6.77 (1H, ddd, *J* 9.0, 8.5 and 1.0, C(3)*H*), 3.74 (1H, d, *J* 0.5, CC*H*), 1.56 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 163.5 (d, *J* 251.0), 152.1, 141.8 (d, *J* 3.0), 130.8 (2 × C, ap. d, *J* 9.5), 113.0 (d, *J* 3.0), 108.8 (d, *J* 20.0), 89.1 (d, *J* 4.5), 81.3, 73.2 (d, *J* 3.0), 28.3; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –109.0; **LRMS** (ESI+, *m/z*): 258.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{13}H_{14}FNNaO_2$ ([M+Na]$^+$) requires 258.09008, found 258.09028; **IR** ν_{max} (film)/cm^{-1}: 3407, 3295, 2980, 2934, 1733, 1617, 1580, 1523, 1474, 1436, 1394, 1369, 1313, 1281, 1252, 1231, 1153, 1090, 1065, 1036.

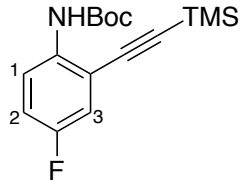
General procedure E – Boc-protection of anilines *via* diBoc aniline as exemplified by the synthesis of *tert*-Butyl (4-fluoro-2-iodophenyl)carbamate, 56c



To a solution of 4-fluoro-2-iodoaniline (2.00 g, 8.44 mmol) in THF (45 mL) was added sequentially Boc_2O (4.24 g, 19.4 mmol) and DMAP (103 mg, 0.84 mmol). The reaction was then heated at reflux for 3 hours. Once cooled to room temperature the solvent was

removed *in vacuo*, and the resulting residue partitioned between 1.0 N $HCl_{(aq)}$ (100 mL) and Et_2O (100 mL). The organic layer was then washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was then dissolved in MeOH (50 mL). K_2CO_3 (3.50 g, 25.3 mmol) was added, and the reaction was stirred at reflux for 1 hour. Once cooled to room temperature the solvent was removed *in vacuo*, and the resulting residue partitioned between 1.0 N $HCl_{(aq)}$ (100 mL) and Et_2O (100 mL). The organic layer was then washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10% Et_2O in petrol) afforded *N*-Boc aniline **56c** as a pale yellow solid (2.52 g, 89% yield); **m.p.**: 59-61 °C (recrystallised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.98 (1H, dd, *J* 7.0 and 3.5, C(1)*H*), 7.49 (1H, dd, *J* 7.5 and 3.0, C(3)*H*), 7.10-7.05 (1H, m, C(2)*H*), 6.71 (1H, br. s, N*H*), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.0 (d, *J* 247.5), 157.7, 135.4 (d, *J* 3.0), 125.3 (d, *J* 25.0), 121.3 (d, *J* 7.0), 115.9 (d, *J* 22.0), 88.4 (d, *J* 6.0), 88.2, 28.3; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –118.2; **LRMS** (ESI+, *m/z*): 360.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{11}H_{13}FINNaO_2$ ([M+Na]$^+$) requires 359.9867, found 359.9876; **IR** ν_{max} (film)/cm^{-1}: 2979, 1729, 1589, 1509, 1392, 1368, 1252, 1226, 1150, 1057, 1020.

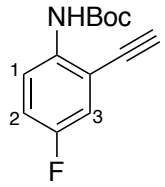
tert-Butyl (4-fluoro-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57c



Compound **57c** was prepared according to General Procedure **C** using aryl iodide **56c** (135 mg, 0.400 mmol), $Pd(PPh_3)_2Cl_2$ (14.1 mg, 20.0 μmol), CuI (3.8 mg, 20.0 μmol), TMS-acetylene (85.0 μL, 0.600 mmol), Et_3N (84.0 μL, 0.600 mmol) and DMF (6.0 mL).

Flash column chromatography (SiO_2, 1% Et_2O in petrol) afforded aryl alkyne **57c** as a pale yellow oil (113 mg, 91% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.89 (1H, dd, *J* 9.0 and 5.0, C(1)*H*), 7.06 (1H, br. s, N*H*), 6.87 (1H, dd, *J* 8.5 and 3.0, C(3)*H*), 6.82 (1H, ap. td, *J* 9.0 and 3.0, C(2)*H*), 1.34 (9H, s, C(CH_3)$_3$), 0.10 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 157.5 (d, *J* 241.5), 152.6, 136.9 (d, *J* 2.5), 119.1 (d, *J* 8.0), 117.7 (d, *J* 24.0), 117.1 (d, *J* 22.0), 112.5 (d, *J* 9.0), 103.3, 99.6 (d, *J* 3.0), 80.9, 28.5, 0.0; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –121.0; **LRMS** (ESI+, *m/z*): 330.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{22}FNNaO_2Si$ ([M+Na]$^+$) requires 330.1296, found 330.1295; **IR** ν_{max} (film)/cm^{-1}: 2977, 2149, 1735, 1517, 1416, 1368, 1280, 1233, 1152, 1105, 1049, 1026.

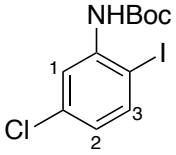
tert-Butyl (2-ethynyl-4-fluorophenyl)carbamate, 51c



Compound **51c** was prepared according to General Procedure **D** using alkyne **57c** (105 mg, 0.340 mmol), K_2CO_3 (47.4 mg, 0.34 mmol) and MeOH (7.0 mL). Flash column chromatography (SiO_2, 0-10% Et_2O in petrol) afforded terminal alkyne **51c** as a pale yellow solid (78.3 mg, 97% yield); **m.p.**: 63-65 °C (crystallised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.04 (1H, d, *J* 9.0 and 5.0, C(1)*H*), 7.08 (1H, br. s, N*H*), 7.04 (1H, dd, *J* 8.5 and 3.0, C(3)*H*), 6.97 (1H, ap. td, *J* 8.5 and 3.0, C(2)*H*), 3.43 (1H, s, CC*H*), 1.45 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 157.2 (d, *J* 242.0), 157.5, 136.7 (d, *J* 2.5), 119.4 (d, *J* 7.0), 118.4 (d, *J* 24.5), 117.2 (d, *J* 22.0), 111.2 (d, *J* 9.0), 84.8, 81.0, 78.3 (d, *J* 3.0), 28.3; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –120.8; **LRMS** (ESI+, *m/z*): 258.0 ([M+Na]$^+$); **HRMS**

(ESI+, *m/z*): $C_{13}H_{14}FNNaO_2$ ($[M+Na]^+$) requires 258.0901, found 258.0910; **IR** ν_{max} (film)/cm^{-1}: 2980, 1728, 1515, 1413, 1393, 1368, 1279, 1234, 1153, 1099, 1049, 1025.

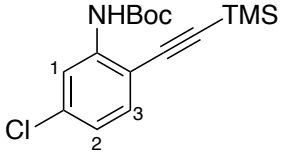
tert-Butyl (5-chloro-2-iodophenyl)carbamate, 56d



Compound **56d** was prepared according to General Procedure **B** using 5-chloro-2-iodoaniline (1.00 g, 3.95 mmol), NaHMDS (3.95 mL, 2.0 M solution in THF, 7.90 mmol), Boc_2O (1.03 g, 4.73 mmol) and THF (14 mL). Flash column chromatography (SiO_2, 5% Et_2O in petrol) afforded *N*-Boc aniline **56d** as an orange oil (548 mg, 39% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.10 (1H, d, *J* 2.5, C(1)*H*), 7.56 (1H, d, *J* 8.5, C(3)*H*), 6.77 (1H, br. s., N*H*), 6.70 (1H, dd, *J* 8.5 and 2.5, C(2)*H*), 1.47 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 139.9, 139.3, 135.5, 124.6, 119.7, 85.1, 81.6, 28.3; **LRMS** (ESI+, *m/z*): 376.0 ($[M(^{35}Cl)+Na]^+$), 378.0 ($[M(^{37}Cl)+Na]^+$).

Data consistent with the literature.[277]

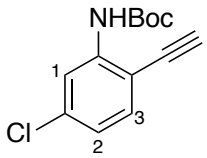
tert-Butyl (5-chloro-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57d



Compound **57d** was prepared according to General Procedure **C** using aryl iodide **56d** (497 mg, 1.40 mmol), $Pd(PPh_3)_2Cl_2$ (49.3 mg, 70.0 μmol), CuI (13.4 mg, 70.0 μmol), TMS-acetylene (0.300 mL, 2.11 mmol), Et_3N (0.290 mL, 2.11 mmol) and DMF (20 mL). Flash column chromatography (SiO_2, 0-3% Et_2O in petrol) afforded aryl alkyne **57d** as

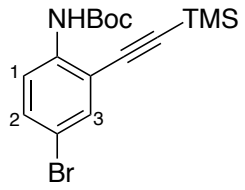
an orange oil (310 mg, 68% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.02 (1H, d, *J* 2.0, C(1)*H*), 7.17 (1H, br. s, N*H*), 7.08 (1H, d, *J* 9.0, C(3)*H*), 6.72 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 1.34 (9H, s, C(CH_3)$_3$), 0.10 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 141.3, 136.1, 132.2, 122.3, 117.5, 109.4, 103.3, 99.7, 81.3, 28.4, 0.0; **LRMS** (ESI+, *m/z*): 346.1 ([M(^{35}Cl)+Na]$^+$), 348.1 ([M(^{37}Cl)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{22}ClNNaO_2Si$ ([M(^{35}Cl)+Na]$^+$) requires 346.1001, found 346.0998; **IR** ν_{max} (film)/cm^{-1}: 2977, 2152, 1737, 1570, 1511, 1452, 1423, 1368, 1281, 1251, 1232, 1152, 1050.

tert-Butyl (5-chloro-2-ethynylphenyl)carbamate, 51d



Compound **51d** was prepared according to General Procedure **D** using alkyne **57d** (260 mg, 0.80 mmol), K_2CO_3 (111 mg, 0.800 mmol) and MeOH (16 mL). Flash column chromatography (SiO_2, 1% Et_2O in petrol) afforded terminal alkyne **51d** as an orange oil (189 mg, 75% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.19 (1H, br. s, C(1)*H*), 7.26 (1H, d, *J* 8.5, C(3)*H*), 7.19 (1H, br. s, N*H*), 6.87 (1H, dd, *J* 8.5 and 2.0, C(2)*H*), 3.44 (1H, s, CC*H*), 1.46 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.1, 141.2, 136.3, 133.0, 122.2, 117.7, 108.1, 84.9, 81.5, 78.5, 28.3; **LRMS** (ESI+, *m/z*): 274.1 ([M(^{35}Cl)+Na]$^+$), 276.0 ([M(^{37}Cl)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{13}H_{14}ClNNaO_2$ ([M(^{35}Cl)+Na]$^+$) requires 274.0605, found 274.0608, ([M(^{37}Cl)+Na]$^+$) requires 276.0577, found 276.0581; **IR** ν_{max} (film)/cm^{-1}: 3404, 3296, 2980, 1733, 1571, 1510, 1451, 1418, 1369, 1280, 1264, 1232, 1153, 1050.

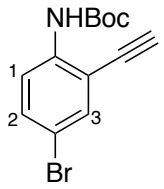
tert-Butyl (4-bromo-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57e



Compound **57e** was prepared according to a sequence of General Procedures **B** and **C** without intermediate isolation, using 4-bromo-2-iodo-aniline (4.88 g, 16.4 mmol), NaHMDS (18.5 mL, 2.00 M solution in THF, 36.9 mmol), Boc_2O (4.04 g, 18.5 mmol), THF (35 mL), $Pd(PPh_3)_2Cl_2$ (590 mg, 0.840 mmol), CuI (160 mg, 0.840 mmol), TMS-acetylene (2.86 mL, 20.2 mmol), Et_3N (2.80 mL, 20.2 mmol) and DMF (50 mL). Flash column chromatography (SiO_2, 0-5% Et_2O in petrol) afforded aryl alkyne **57e** as an orange oil (4.79 g, 79% yield over two steps); **m.p.**: 66-68 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.06 (1H, d, *J* 9.0, C(1)*H*), 7.52 (1H, d, *J* 2.5, C(3)*H*), 7.42 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 7.34 (1H, br. s, N*H*), 1.55 (9H, s, C(CH_3)$_3$), 0.32 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.4, 139.6, 133.9, 133.0, 118.9, 114.1, 113.0, 103.8, 99.2, 81.2, 28.5, 0.0; **HRMS** (ESI+, *m/z*): $C_{16}H_{22}BrNNaO_2Si$ ([M(^{79}Br)+Na]$^+$) requires 390.0495, found 390.0502; ([M(^{81}Br)+Na]$^+$) requires 392.0476, found 392.0481.

Data consistent with the literature.[278]

tert-Butyl (4-bromo-2-ethynylphenyl)carbamate, 51e

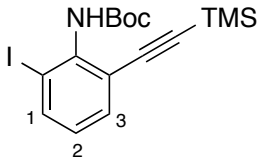


Compound **51e** was prepared according to General Procedure **D** using alkyne **57e** (508 mg, 1.38 mmol), K_2CO_3 (191 mg, 1.38 mmol) and MeOH (30 mL). Flash column

chromatography (SiO_2, 5% Et_2O in petrol) afforded terminal alkyne **51e** as a pale orange solid (333 mg, 82% yield); **m.p.**: 62-64 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (1H, d, *J* 9.0, C(1)*H*), 7.46 (1H, d, *J* 2.5, C(3)*H*), 7.35 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 7.14 (1H, br. s, N*H*), 3.45 (1H, s, CC*H*), 1.46 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 139.5, 134.5, 133.1, 119.1, 113.9, 111.7, 85.3, 81.3, 78.0, 28.3; **LRMS** (ESI+, *m/z*): 318.0 ([M(^{79}Br)+Na]$^+$), 320.0 ([M(^{81}Br)+Na]$^+$).

Data consistent with the literature.[278]

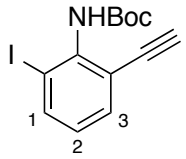
tert-Butyl (2-iodo-6-((trimethylsilyl)ethynyl)phenyl)carbamate, 57f



At –78 °C, to a solution of compound **57a** (800 mg, 2.76 mmol) in Et_2O (6.0 mL) was added dropwise ^{t}BuLi (3.58 mL, 1.70 M in pentane, 6.08 mmol). The reaction mixture was warmed to –20 °C and stirred for 3 hours. The reaction was then cooled to –78 °C and a solution of I_2 (1.05 g, 4.14 mmol) in Et_2O (8 mL) was added dropwise. The reaction was allowed to warm to room temperature over 16 hours, after which time the reaction was quenched by the addition of H_2O (15 mL), and then extracted with Et_2O (3 × 15 mL). The combined organic fractions were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 0-5% EtOAc in petrol) afforded aryl iodide **57f** as a light brown solid (745 mg, 64% yield); **m.p.**: 88-90 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.81 (1H, d, *J* 8.0, C(1)*H*), 7.45 (1H, d, *J* 8.0, C(3)*H*), 6.88 (1H, t, *J* 8.0, C(2)*H*), 6.37 (1H, br. s, N*H*), 1.51 (9H, br. s, C(CH_3)$_3$), 0.25 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.7, 140.6,

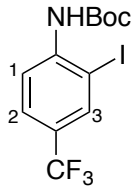
139.6, 132.6, 127.7, 122.5, 101.0, 100.5, 98.5, 80.6, 28.3, –0.1; **LRMS** (ESI+, *m/z*): 438.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{22}INNaO_2Si$ ([M+Na]$^+$) requires 438.03567, found 438.03524; **IR** ν_{max} (film)/cm^{-1}: 3403, 2965, 2899, 2162, 1707, 1481, 1447, 1367, 1247, 1158, 1049, 1023.

tert-Butyl (2-ethynyl-6-iodophenyl)carbamate, 51f



Compound **51f** was prepared according to General Procedure **D** using alkyne **57f** (600 mg, 1.44 mmol), K_2CO_3 (200 mg, 1.44 mmol), and MeOH (30 mL). Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded terminal alkyne **51f** as an off-white solid (477 mg, 96% yield); **m.p.**: 127-129 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.84 (1H, dd, *J* 8.0 and 1.5, C(1)*H*), 7.50 (1H, dd, *J* 8.0 and 1.5, C(3)*H*), 6.91 (1H, t, *J* 8.0, C(2)*H*), 6.28 (1H, br. s, N*H*), 3.31 (1H, s, CC*H*), 1.51 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.8, 140.7, 139.8, 133.3, 127.8, 121.8, 98.7, 82.5, 81.0, 80.1, 28.3; **LRMS** (ESI+, *m/z*): 709.0 ([2M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{13}H_{14}INNaO_2$ ([M+Na]$^+$) requires 365.99614, found 365.99616; **IR** ν_{max} (film)/cm^{-1}: 3294, 2977, 2931, 1703, 1482, 1448, 1392, 1367, 1242, 1158, 1121, 1077, 1049, 1022.

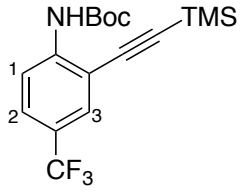
tert-Butyl (2-iodo-4-(trifluoromethyl)phenyl)carbamate, 56g



Compound **56g** was prepared according to General Procedure **E** using 4-amino-3-iodobenzotrifluoride (1.50 g, 5.23 mmol), Boc_2O (2.63 g, 12.0 mmol), DMAP (63.8 mg, 0.52 mmol), THF (35 mL), K_2CO_3 (2.17 g, 15.7 mmol) and MeOH (35 mL) for 16 hours in the second step. Flash column chromatography (SiO_2, 2-3% Et_2O in petrol) afforded *N*-Boc aniline **56g** as a pale yellow solid (753 mg, 37% yield); **m.p.**: 65-67 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.16 (1H, d, *J* 8.5, C(1)*H*), 7.90 (1H, d, *J* 2.0, C(3)*H*), 7.48 (1H, dd, *J* 8.5 and 2.0, C(2)*H*), 6.93 (1H, br. s, N*H*), 1.47 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.1, 142.0, 135.8 (q, *J* 4.0), 126.4 (q, *J* 3.5), 126.0 (q, *J* 33.5), 123.1 (q, *J* 272.0), 118.8, 87.0, 81.9, 28.2; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –62.0; **LRMS** (ESI+, *m/z*): 410.0 ([M+Na]$^+$).

Data consistent with the literature.[279]

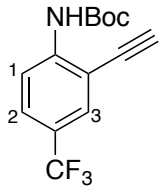
tert-Butyl (4-(trifluoromethyl)-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57g



Compound **57g** was prepared according to General Procedure **C** using aryl iodide **56g** (740 mg, 1.91 mmol), $Pd(PPh_3)_2Cl_2$ (67.1 mg, 0.100 mmol), CuI (18.2 mg, 0.100 mmol), TMS-acetylene (0.410 mL, 2.87 mmol), Et_3N (0.400 mL, 2.87 mmol) and DMF (25 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aryl alkyne **57g** as

a pale yellow solid (677 mg, 99% yield); **m.p.**: 76-78 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.09 (1H, d, *J* 9.0, C(1)*H*), 7.44 (1H, d, *J* 2.0, C(3)*H*), 7.34 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.32 (1H, br. s, N*H*), 1.35 (9H, s, C(CH_3)$_3$), 0.12 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 143.3, 128.7 (q, *J* 4.0), 127.0 (q, *J* 3.5), 124.2 (q, *J* 33.0), 124.1 (q, *J* 271.5), 117.2, 111.4, 104.1, 99.2, 81.7, 28.5, 0.0; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –62.2; **LRMS** (ESI+, *m/z*): 380.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{22}F_3NNaO_2Si$ ([M+Na]$^+$) requires 392.1264, found 392.1275; **IR** ν_{max} (film)/cm^{-1}: 1742, 1586, 1525, 1471, 1421, 1330, 1311, 1287, 1250, 1232, 1150, 1116, 1075, 1050, 1026.

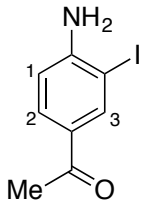
tert-Butyl (2-ethynyl-4-(trifluoromethyl)phenyl)carbamate, 51g



Compound **51g** was prepared according to General Procedure **D** using alkyne **57g** (550 mg, 1.54 mmol), K_2CO_3 (213 mg, 1.54 mmol) and MeOH (30 mL). Flash column chromatography (SiO_2, 10% Et_2O in petrol) afforded terminal alkyne **51g** as a pale yellow solid (392 mg, 89% yield); **m.p.**: 97-99 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.24 (1H, d, *J* 9.0, C(1)*H*), 7.59 (1H, d, *J* 2.0, C(3)*H*), 7.47 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.32 (1H, br. s, N*H*), 3.47 (1H, s, CC*H*), 1.46 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.0, 143.1, 129.3 (q, *J* 4.0), 127.0 (q, *J* 3.5), 124.1 (q, *J* 33.5), 123.7 (q, *J* 271.5), 117.3, 109.9, 85.4, 81.7, 77.9, 28.2; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –62.3; **HRMS** (FI+, *m/z*): $C_{14}H_{14}F_3NNaO_2$ ([M+Na]$^+$) requires 285.0970, found 285.0977; **IR**

ν_{max} (film)/cm^{-1}: 1736, 1589, 1526, 1475, 1419, 1370, 1329, 1253, 1230, 1150, 1118, 1076, 1048, 1024.

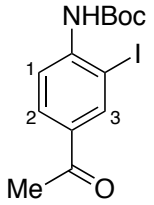
1-(4-Amino-3-iodophenyl)ethan-1-one, 137



To a solution of 4'-aminoacetophenone (2.03 g, 15.0 mmol) in CH_2Cl_2 (30 mL) and H_2O (6.0 mL) was added sequentially $NaHCO_3$ (1.51 g, 18.0 mmol) and I_2 (3.81 g, 15.0 mmol), and the reaction stirred at room temperature for 16 hours. The reaction was quenched by the addition of sat. $Na_2S_2O_{3(aq)}$ (10 mL), and partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, CH_2Cl_2) afforded aryl iodide **137** as a pale brown oil (2.58 g, 66% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.28 (1H, d, *J* 2.0, C(3)*H*), 7.77 (1H, dd, *J* 8.5 and 2.0, C(2)*H*), 6.72 (1H, d, *J* 8.5, C(1)*H*), 4.68 (2H, br. s, NH_2), 2.50 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 195.2, 151.0, 140.3, 130.3, 129.2, 113.1, 82.6, 26.1; **LRMS** (ESI+, *m/z*): 284.0 ($[M+Na]^+$).

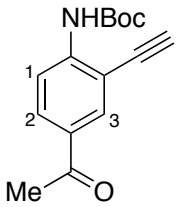
Data consistent with the literature.[280]

tert-Butyl (4-acetyl-2-iodophenyl)carbamate, 56h



Compound **56h** was prepared according to General Procedure **B** using aniline **137** (385 mg, 1.48 mmol), NaHMDS (2.43 mL, 2.00 M solution in THF, 4.86 mmol), Boc_2O (354 mg, 1.62 mmol) and THF (3.0 mL). Flash column chromatography (SiO_2, 0-10% Et_2O in petrol) afforded *N*-Boc aniline **56h** as a cream solid (275 mg, 52% yield); **m.p.**: 42-44 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.38 (1H, d, *J* 2.0, C(3)*H*), 8.24 (1H, d, *J* 8.5, C(1)*H*), 7.91 (1H, dd, *J* 8.5 and 2.0, C(2)*H*), 7.12 (1H, br. s, N*H*), 2.57 (3H, s, C(O)CH_3), 1.57 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 195.6, 152.0, 142.9, 139.3, 133.0, 129.8, 118.1, 87.6, 81.9, 28.2, 26.3; **LRMS** (ESI+, *m/z*): 384.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z)*: $C_{13}H_{16}INO_3$ ([M+Na]$^+$) requires 384.00671, found 384.00668; **IR** ν_{max} (film)/cm^{-1}: 3387, 2978, 2931, 1737, 1681, 1590, 1563, 1516, 1457, 1388, 1368, 1285, 1234, 1151, 1057, 1018.

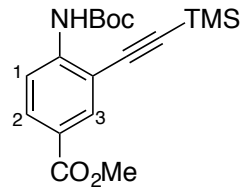
tert-Butyl (4-acetyl-2-ethynylphenyl)carbamate, 51h



Compound **51h** was prepared according to a sequence of General Procedures **C** and **D** without intermediate isolation, with a SiO_2 filtration after step **C**, using aryl iodide **56h** (253 mg, 0.700 mmol), $Pd(PPh_3)_2Cl_2$ (24.6 mg, 35.0 μmol), CuI (6.7 mg, 35.0 μmol), TMS-acetylene (0.150 mL, 1.05 mmol), Et_3N (0.146 mL, 1.05 mmol), DMF (3.5 mL),

K_2CO_3 (96.7 mg, 0.700 mmol) and MeOH (14 mL). Flash column chromatography (SiO_2, 0-10% Et_2O in petrol) afforded terminal alkyne **51h** as a brown solid (137 mg, 75% yield over two steps); **m.p.**: 95-97 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.26 (1H, d, *J* 9.0, C(1)*H*), 8.02 (1H, d, *J* 2.0, C(3)*H*), 7.90 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.46 (1H, br. s, N*H*), 3.56 (1H, s, CC*H*), 2.53 (3H, s, C(O)CH_3), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 196.0, 151.8, 144.1, 132.8, 130.9, 130.5, 116.7, 109.6, 85.1, 81.7, 78.3, 28.2, 26.3; **LRMS** (ESI+, *m/z*): 282.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{15}H_{18}NO_3$ ([M+H]$^+$) requires 260.12812, found 260.12829; **IR** ν_{max} (film)/cm^{-1}: 3401, 3250, 2979, 1733, 1678, 1575, 1517, 1465, 1368, 1283, 1236, 1147, 1047, 1023.

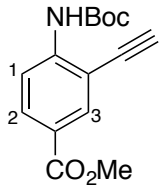
Methyl 4-((*tert*-butoxycarbonyl)amino)-3-((trimethylsilyl)ethynyl)benzoate, 57i



Compound **57i** was prepared according to a sequence of General Procedures **B** and **C** without intermediate isolation, using methyl-4-amino-3-iodobenzoate (2.00 g, 7.22 mmol), NaHMDS (7.94 mL, 2.00 M solution in THF, 15.9 mmol), Boc_2O (1.73 g, 7.94 mmol), THF (15 mL), $Pd(PPh_3)_2Cl_2$ (253 mg, 0.360 mmol), CuI (69.0 mg, 0.360 mmol), TMS-acetylene (1.54 mL, 10.8 mmol), Et_3N (1.51 mL, 10.8 mmol) and DMF (35 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aryl alkyne **57i** as a pale yellow solid (2.14 g, 85% yield over two steps); **m.p.**: 95-98 °C (crystalised from $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.07 (1H, d, *J* 9.0, C(1)*H*), 7.93 (1H, d, *J* 2.0, C(3)*H*), 7.82 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.41 (1H, br. s, N*H*), 3.74 (3H, s, CO_2CH_3), 1.39 (9H, s, C(CH_3)$_3$), 0.15 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 166.3,

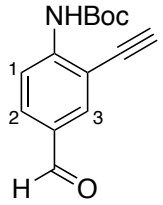
157.1, 144.1, 133.3, 131.6, 123.7, 116.5, 110.9, 103.3, 99.6, 81.5, 52.3, 28.4, 0.0; **LRMS** (ESI+, *m/z*): 370.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{18}H_{25}NNaO_4Si$ ([M+Na]$^+$) requires 370.1445, found 370.1461; **IR** ν_{max} (film)/cm^{-1}: 3392, 2957, 2150, 1740, 1721, 1580, 1520, 1466, 1436, 1413, 1369, 1289, 1235, 1151, 1101, 1049.

Methyl 4-((*tert*-butoxycarbonyl)amino)-3-ethynylbenzoate, 51i



Compound **51i** was prepared according to General Procedure **D** using alkyne **57i** (407 mg, 1.17 mmol), KF (68.0 mg, 1.17 mmol) and MeOH (25 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded terminal alkyne **51i** as a pale yellow solid (289 mg, 90% yield); **m.p.**: 145-147 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.20 (1H, d, *J* 9.0, C(1)*H*), 8.05 (1H, d, *J* 2.0, C(3)*H*), 7.93 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.38 (1H, br. s, N*H*), 3.82 (3H, s, CO_2CH_3), 3.46 (1H, s, CC*H*), 1.47 (9H, s, $C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 166.0, 151.9, 144.1, 134.0, 131.7, 123.7, 116.7, 109.6, 84.9, 81.7, 78.4, 52.1, 28.3; **LRMS** (ESI+, *m/z*): 298.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{15}H_{17}NNaO_4$ ([M+Na]$^+$) requires 298.1050, found 298.1046; **IR** ν_{max} (film)/cm^{-1}: 1719, 1581, 1520, 1469, 1409, 1290, 1242, 1153, 1100, 1049.

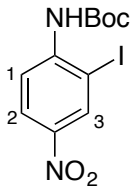
tert-Butyl (2-ethynyl-4-formylphenyl)carbamate, 51j



To a solution of ester **57i** (1.00 g, 2.88 mmol) and MeOH (0.23 mL, 5.76 mmol) in THF (15 mL) at 0 °C, was slowly added $LiBH_4$ (2.88 mL, 2.00 M solution in THF, 5.76 mmol). The reaction was stirred at 0 °C for 15 minutes, then allowed to warm to room temperature. After stirring for 16 hours, the reaction mixture was poured onto 5% citric $acid_{(aq)}$ (100 mL), then extracted with Et_2O (100 mL), washed with sat. $NaHCO_{3(aq)}$ (100 mL), then brine (100 mL), before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude alcohol was then dissolved in dry CH_2Cl_2 (16 mL). Dess Martin Periodinane (1.47 g, 3.46 mmol) and $NaHCO_3$ (726 mg, 8.64 mmol) were then added, and the reaction stirred at room temperature for 16 hours. The reaction was quenched by the addition of sat. $NaHSO_{3(aq)}$, then partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The organic layer was then washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded 551 mg of a mixture of aldehyde **57j** and ester **51i**. This mixture was then dissolved in MeOH (35 mL), and K_2CO_3 added (240 mg, 1.74 mmol). The reaction was stirred at room temperature for 1 hour, and then quenched by the addition of H_2O (200 mL), before extracting with Et_2O (3 × 200 mL). The combined organic layers were then washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aldehyde **51j** as a white solid (300 mg, 42% yield over three steps); **m.p.**: 97-99 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.88 (1H, s,

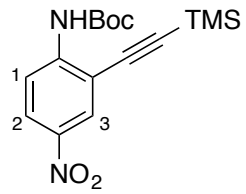
C*H*O), 8.41 (1H, d, *J* 8.5, C(1)*H*), 7.98 (1H, d, *J* 2.0, C(3)*H*), 7.87 (1H, dd, *J* 8.5 and 2.0, C(2)*H*), 7.55 (1H, br. s, N*H*), 3.60 (1H, s, CC*H*), 1.57 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 190.1, 151.8, 145.3, 134.1, 131.8, 130.4, 117.1, 110.2, 85.5, 82.0, 78.0, 28.2; **LRMS** (ESI+, *m/z*): 300.1 ([M+MeOH+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{15}H_{19}NNaO_4$ ([M+MeOH+Na]$^+$) requires 300.12063, found 300.12073; **IR** ν_{max} (film)/cm^{-1}: 3399, 3255, 2979, 2823, 1736, 1693, 1577, 1518, 1465, 1423, 1369, 1310, 1233, 1204, 1150, 1049, 1024.

tert-Butyl (2-iodo-4-nitro-phenyl)carbamate, 56k



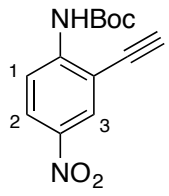
Compound **56k** was prepared according to General Procedure **E** using 2-iodo-4-nitroaniline (2.00 g, 8.33 mmol), Boc_2O (4.18 g, 19.2 mmol), DMAP (102 mg, 0.82 mmol), THF (55 mL), K_2CO_3 (3.46 g, 25.0 mmol) and MeOH (55 mL) for 8 hours in the second step. Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded *N*-Boc aniline **56k** as a pale yellow solid (1.25 g, 45% yield); **m.p.**: 109-111 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.63 (1H, d, *J* 2.5, C(3)*H*), 8.34 (1H, d, *J* 9.0, C(1)*H*), 8.20 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 7.19 (1H, br. s, N*H*), 1.56 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.7, 144.7, 142.6, 134.4, 124.9, 117.7, 85.8, 82.6, 28.2; **LRMS** (ESI+, *m/z*): 387.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{11}H_{13}IN_2NaO_4$ ([M+Na]$^+$) requires 386.98122, found 386.98120; **IR** ν_{max} (film)/cm^{-1}: 3382, 2979, 2932, 1737, 1581, 1527, 1504, 1452, 1391, 1369, 1337, 1307, 1246, 1220, 1145, 1116, 1056, 1034, 1019.

tert-Butyl (4-nitro-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57k



Compound **57k** was prepared according to General Procedure **C** using aryl iodide **56k** (1.00 g, 2.75 mmol), $Pd(PPh_3)_2Cl_2$ (96.0 mg, 0.140 mmol), CuI (26.0 mg, 0.140 mmol), TMS-acetylene (0.586 mL, 4.12 mmol), Et_3N (0.574 mL, 4.12 mmol) and DMF (40 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded aryl alkyne **57k** as a cream solid (837 mg, 91% yield); **m.p.**: 147-149 °C (crystalised from EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.34 (1H, d, *J* 9.5, C(1)*H*), 8.26 (1H, d, *J* 2.5, C(3)*H*), 8.16 (1H, dd, *J* 9.5 and 2.5, C(2)*H*), 7.66, (1H, br. s, N*H*), 1.55 (9H, s, C(CH_3)$_3$), 0.32 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.9, 145.8, 141.9, 127.3, 125.7, 116.8, 111.6, 105.4, 98.2, 82.4, 28.5, 0.0; **LRMS** (ESI+, *m/z*): 357.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{22}N_2NaO_4Si$ ([M+Na]$^+$) requires 357.12410, found 357.12400; **IR** ν_{max} (film)/cm^{-1}: 3381, 2985, 2959, 2150, 1745, 1739, 1581, 1536, 1513, 1478, 1458, 1421, 1394, 1369, 1343, 1319, 1290, 1252, 1234, 1188, 1151, 1088, 1052, 1027.

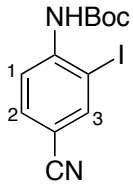
tert-Butyl (2-ethynyl-4-nitrophenyl)carbamate, 51k



Compound **51k** was prepared according to General Procedure **D** using alkyne **57k** (460 mg, 1.38 mmol), KF (80.0 mg, 1.38 mmol), and MeOH (30 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded terminal alkyne **51k** as a

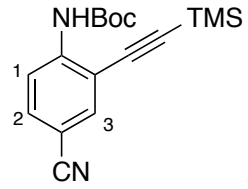
brown solid (318 mg, 88% yield); **m.p.**: 128-130 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.32 (1H, d, *J* 9.5, C(1)*H*), 8.23 (1H, d, *J* 2.5, C(3)*H*), 8.12 (1H, dd, *J* 9.5 and 2.5, C(2)*H*), 7.48 (1H, br. s, N*H*), 3.55 (1H, s, CC*H*), 1.48 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 150.6, 144.6, 140.6, 126.9, 124.7, 115.9, 109.0, 85.3, 81.4, 76.1, 27.1; **LRMS** (ESI+, *m/z*): 285.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{13}H_{14}N_2NaO_4$ ([M+Na]$^+$) requires 285.08458, found 285.08453; **IR** ν_{max} (film)/cm^{-1}: 3402, 3294, 2986, 2936, 1736, 1614, 1580, 1543, 1505, 1471, 1416, 1395, 1370, 1356, 1319, 1253, 1236, 1179, 1155, 1089, 1052, 1027.

tert-Butyl (4-cyano-2-iodo-phenyl)carbamate, 56l



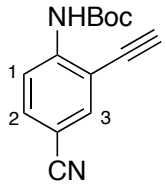
Compound **56l** was prepared according to General Procedure **E** using 4-amino-3-iodobenzonitrile (2.00 g, 8.20 mmol), Boc_2O (4.12 g, 18.9 mmol), DMAP (100 mg, 0.82 mmol), THF (55 mL), K_2CO_3 (3.40 g, 24.6 mmol) and MeOH (55 mL) for 16 hours in the second step. Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded *N*-Boc aniline **56l** as a white solid (1.73 g, 62% yield); **m.p.**: 105-107 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.28 (1H, d, *J* 9.0, C(1)*H*), 8.02 (1H, d, *J* 2.0, C(3)*H*), 7.59 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.08 (1H, br.s, N*H*), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.8, 143.1, 142.2, 133.1, 118.6, 117.4, 107.3, 86.8, 82.4, 28.2; **LRMS** (ESI+, *m/z*): 367.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{12}H_{13}IN_2NaO_2$ ([M+Na]$^+$) requires 366.99139, found 366.99138; **IR** ν_{max} (film)/cm^{-1}: 3386, 2979, 2933, 2227, 1736, 1594, 1558, 1509, 1451, 1390, 1369, 1304, 1277, 1255, 1222, 1148, 1059, 1021.

tert-Butyl (4-cyano-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57l



Compound **57l** was prepared according to General Procedure **C** using aryl iodide **56l** (1.00 g, 2.91 mmol), $Pd(PPh_3)_2Cl_2$ (108 mg, 0.150 mmol), CuI (29.0 mg, 0.150 mmol), TMS-acetylene (0.620 mL, 4.36 mmol), Et_3N (0.607 mL, 4.36 mmol) and DMF (40 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded aryl alkyne **57l** as a cream solid (0.821 g, 90% yield); **m.p.**: 131-133 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.29 (1H, d, *J* 8.5, C(1)*H*), 7.65 (1H, d, *J* 2.0, C(3)*H*), 7.56 (1H, br. s, N*H*), 7.55 (1H, dd, *J* 8.5, 2.0, C(2)*H*), 1.54 (9H, s, C(CH_3)$_3$), 0.31 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.0, 144.1, 135.3, 133.7, 118.7, 117.5, 112.1, 105.4, 105.2, 98.2, 82.1, 28.5, 0.0; **LRMS** (ESI+, *m/z*): 337.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{22}N_2NaO_2Si$ ([M+Na]$^+$) requires 337.13428, found 337.13434; **IR** ν_{max} (film)/cm^{-1}: 3384, 2982, 2227, 2147, 1742, 1735, 1574, 1514, 1457, 1410, 1393, 1369, 1312, 1278, 1265, 1239, 1227, 1151, 1052, 1027.

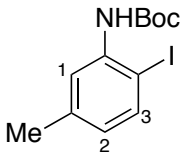
tert-Butyl (4-cyano-2-ethynylphenyl)carbamate, 51l



Compound **51l** was prepared according to General Procedure **D** using alkyne **57l** (700 mg, 2.23 mmol), KF (129 mg, 2.23 mmol), and MeOH (50 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded terminal alkyne **51l** as a cream

solid (510 mg, 95% yield); **m.p.**: 120-122 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.34 (1H, d, *J* 9.0, C(1)*H*), 7.69 (1H, d, *J* 2.0, C(3)*H*), 7.59 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.46 (1H, br. s, N*H*), 3.62 (1H, s, CC*H*), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.6, 144.0, 136.0, 133.7, 118.2, 117.6, 110.5, 105.3, 86.3, 82.1, 77.1, 28.2; **LRMS** (ESI+, *m/z*): 265.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{14}H_{14}N_2NaO_2$ ([M+Na]$^+$) requires 265.09475, found 265.09461; **IR** ν_{max} (film)/cm^{-1}: 3401, 3257, 2980, 2935, 2229, 1734, 1605, 1575, 1512, 1461, 1406, 1394, 1368, 1320, 1280, 1235, 1148, 1049, 1025.

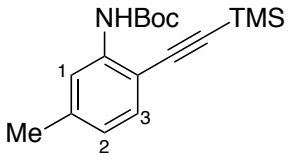
tert-Butyl (2-iodo-5-methylphenyl)carbamate, 56m



Compound **56m** was prepared according to General Procedure **B** using 2-iodo-5-methylaniline (500 mg, 2.15 mmol), NaHMDS (2.15 mL, 2.00 M solution in THF, 4.25 mmol), Boc_2O (562 mg, 2.57 mmol) and THF (14 mL). Flash column chromatography (SiO_2, 25% CH_2Cl_2 in petrol) afforded *N*-Boc aniline **56m** as a yellow oil (365 mg, 51% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.84 (1H, d, *J* 1.0, C(1)*H*), 7.52 (1H, d, *J* 8.0, C(3)*H*), 6.72 (1H, br. s, N*H*), 6.54 (1H, ddd, *J* 8.0, 2.0 and 0.5, C(2)*H*), 2.24 (3H, s, ArCCH_3), 1.47 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.7, 139.5, 138.5, 138.4, 125.8, 120.7, 84.7, 81.0, 28.3, 21.3; **LRMS** (ESI+, *m/z*): 356.0 ([M+Na]$^+$).

Data consistent with the literature.[278]

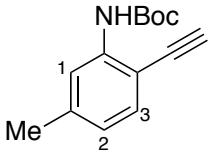
tert-Butyl (5-methyl-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57m



Compound **57m** was prepared according to General Procedure **C** using aryl iodide **56m** (435 mg, 1.04 mmol), $Pd(PPh_3)_2Cl_2$ (36.3 mg, 50 μmol), CuI (9.9 mg, 50 μmol), TMS-acetylene (0.220 mL, 1.55 mmol), Et_3N (0.220 mL, 1.55 mmol) and DMF (14 mL). Flash column chromatography (SiO_2, 2-3% Et_2O in petrol) afforded aryl alkyne **57m** as an orange oil (158 mg, 50% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.83 (1H, br. s, C(1)*H*), 7.22 (1H, br. s, N*H*), 7.12 (1H, d, *J* 8.5, C(3)*H*), 6.62 (1H, ddd, *J* 8.0, 1.5 and 0.5, C(2)*H*), 2.21 (3H, s, (Ar)CC*H*$_3$), 1.40 (9H, s, C(C*H*$_3$)$_3$), 0.15 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.3, 140.6, 140.2, 131.1, 122.9, 117.8, 108.2, 101.3, 100.9, 80.6, 28.4, 22.1, 0.0; **LRMS** (ESI+, *m/z*): 326.2 ([M+Na]$^+$).

Data consistent with the literature.[278]

tert-Butyl (2-ethynyl-5-methylphenyl)carbamate, 51m

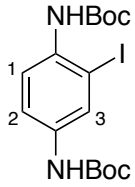


Compound **51m** was prepared according to General Procedure **D** using alkyne **57m** (136 mg, 0.450 mmol), K_2CO_3 (61.8 mg, 0.450 mmol) and MeOH (9.0 mL). Flash column chromatography (SiO_2, 5% Et_2O in petrol) afforded terminal alkyne **51m** as an orange solid (104 mg, 99% yield); **m.p.**: 48-51 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.87 (1H, br. s, C(1)*H*), 7.16 (1H, d, *J* 8.0, C(3)*H*), 7.10 (1H, br. s, N*H*), 6.64 (1H, d, *J* 8.0, C(2)*H*), 3.30 (1H, s, CC*H*), 2.21 (3H, s, ArCC*H*$_3$), 1.39 (9H, s, C(C*H*$_3$)$_3$); **^{13}C-NMR**

(100 MHz, $CDCl_3$): 152.5, 140.8, 140.2, 132.0, 123.0, 118.1, 107.0, 83.4, 80.8, 79.6, 29.7, 22.0; **LRMS** (ESI+, *m/z*): 254.1 ([M+Na]$^+$).

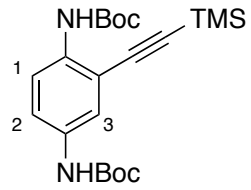
Data consistent with the literature.[278]

tert-Butyl [4-(*tert*-butoxycarbonylamino)-2-iodo-phenyl]carbamate, 56n



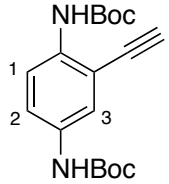
Compound **56n** was prepared according to General Procedure **E** using 2-iodo-1,4-benzenediamine (2.00 g, 8.54 mmol), Boc_2O (8.60 g, 39.3 mmol), DMAP (209 mg, 1.71 mmol), THF (55 mL), K_2CO_3 (4.70 g, 34.2 mmol) and MeOH (55 mL) for 16 hours in the second step. Flash column chromatography (SiO_2, 0-30% EtOAc in petrol) afforded *N*-Boc aniline **56n** as a pale pink solid (1.89 g, 51% yield); **m.p.**: 161-163 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.99 (1H, br. s, C(3)*H*), 7.87 (1H, d, *J* 9.0, C(1)*H*), 7.14 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 6.67 (1H, br. s, N*H*), 6.45 (1H, br. s, N*H*), 1.52 (9H, s, C(CH_3)$_3$), 1.51 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.8, 152.6, 134.7, 134.3, 128.5, 120.6, 119.4, 89.4, 80.9, 80.8, 28.3 (2 × C); **LRMS** (ESI+, *m/z*): 457.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{23}IN_2NaO_4$ ([M+Na]$^+$) requires 457.05947, found 457.05921; **IR** ν_{max} (film)/cm^{-1}: 3328, 2978, 2932, 1697, 1586, 1511, 1477, 1456, 1389, 1293, 1237, 1148, 1062, 1021.

Di-*tert*-butyl (2-((trimethylsilyl)ethynyl)-1,4-phenylene)dicarbamate, 57n



Compound **57n** was prepared according to General Procedure **C** using aryl iodide **56n** (1.50 g, 3.45 mmol), $Pd(PPh_3)_2Cl_2$ (121 mg, 0.170 mmol), CuI (33.0 mg, 0.17 mmol), TMS-acetylene (0.736 mL, 5.18 mmol), Et_3N (0.722 mL, 5.18 mmol) and DMF (50 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded aryl alkyne **57n** as a pale brown solid (1.35 g, 97% yield); **m.p.**: 153-155 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.00 (1H, d, *J* 9.0, C(1)*H*), 7.60 (1H, br. s, N*H*), 7.24 (1H, br. s, C(3)*H*), 7.12 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 6.41 (1H, br. s, N*H*), 1.52 (9H, s, C(CH_3)$_3$), 1.50 (9H, s, (C(CH_3)$_3$), 0.27 (9H, s, Si(CH_3)$_3$**); ^{13}C-NMR** (100 MHz, $CDCl_3$): 152.8, 152.4, 135.8, 132.5, 121.3, 120.3, 117.9, 111.6, 102.0, 100.2, 80.56, 80.48, 28.33, 28.28, –0.2; **LRMS** (ESI+, *m/z*): 427.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{32}N_2NaO_4Si$ ([M+Na]$^+$) requires 427.20236, found 427.20236; **IR** ν_{max} (film)/cm^{-1}: 3400, 3338, 2978, 2933, 2145, 1731, 1709, 1617, 1593, 1533, 1517, 1476, 1476, 1457, 1411, 1393, 1368, 1300, 1276, 1240, 1153, 1056, 1029.

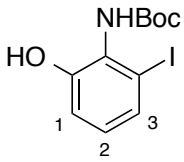
Di-*tert*-butyl (2-ethynyl-1,4-phenylene)dicarbamate, 51n



Compound **51n** was prepared according to General Procedure **D** using alkyne **57n** (1.00 g, 2.47 mmol), K_2CO_3 (342 mg, 2.47 mmol), and MeOH (50 mL). Flash column

chromatography (SiO_2, 0-30% EtOAc in petrol) afforded terminal alkyne **51n** as an off-white solid (759 mg, 92% yield); **m.p.**: 163-165 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.96 (1H, d, *J* 9.0, C(1)*H*), 7.53 (1H, br. s, C(3)*H*), 7.12 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 7.07 (1H, br. s, N*H*), 6.51 (1H, br. s, N*H*), 3.37 (1H, s, CC*H*), 1.45 (9H, s, C(CH_3)$_3$), 1.43 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.8, 151.5, 134.8, 131.7, 121.2, 119.7, 117.4, 109.5, 83.0, 79.8, 79.6, 78.1, 27.3 (2 × C); **LRMS** (ESI+, *m/z*): 355.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{18}H_{24}N_2NaO_4$ ([M+Na]$^+$) requires 355.16283, found 355.16289; **IR** ν_{max} (film)/cm^{-1}: 3409, 3299, 2979, 2933, 1704, 1617, 1593, 1516, 1477, 1407, 1394, 1368, 1297, 1275, 1241, 1151, 1057, 1028.

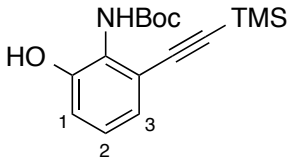
tert-Butyl (2-hydroxy-6-iodo-phenyl)carbamate, 56o



To a solution of 2-amino-3-iodophenol **58** (500 mg, 2.13 mmol) and Et_3N (0.891 mL, 6.39 mmol) in THF (6.0 mL), was added Boc_2O (465 mg, 2.13 mmol). The resulting solution was heated at reflux for 16 hours. Once cooled to 25 °C the solvent was removed *in vacuo*, and the resulting residue partitioned between 1.0 N $HCl_{(aq)}$ and Et_2O. The organic layer was then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 0-25% EtOAc in petrol) afforded *N*-Boc aniline **56o** as an orange oil (532 mg, 75% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.67 (1H, br. s, O*H*), 7.36 (1H, d, *J* 8.0, C(3)*H*), 6.99 (1H, d, *J* 8.0, C(1)*H*), 6.80 (1H, t, *J* 8.0, C(2)*H*), 6.68 (1H, br. s, N*H*), 1.54 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$):155.6, 149.6, 131.1, 128.1, 126.8, 120.6, 93.4, 83.1, 28.2; **LRMS** (ESI+, *m/z*): 358.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{11}H_{14}INNaO_3$ ([M+Na]$^+$) requires 357.99106,

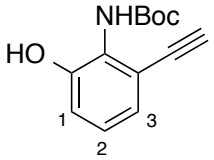
found 357.99094; **IR** ν_{max} (film)/cm^{-1}: 3371, 2979, 2932, 1684, 1571, 1510, 1463, 1392, 1367, 1291, 1249, 1152, 1077, 1052, 1026.

***tert*-Butyl (2-hydroxy-6-((trimethylsilyl)ethynyl)phenyl)carbamate, 57o**



Compound **57o** was prepared according to General Procedure **C** using aryl iodide **56o** (443 mg, 1.32 mmol), $Pd(PPh_3)_2Cl_2$ (46.0 mg, 70 μmol), CuI (13.0 mg, 70 μmol), TMS-acetylene (0.280 mL, 1.98 mmol), Et_3N (0.276 mL, 1.98 mmol) and DMF (19 mL). Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded aryl alkyne **57o** as a brown oil (340 mg, 84% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.50 (1H, br. s, O*H*), 7.30 (1H, br. s, N*H*), 6.98 (3H, s, Ar*H*), 1.54 (9H, s, C(C*H*$_3$)$_3$), 0.29 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 155.9, 148.1, 127.3, 125.5, 123.5, 121.2, 115.2, 102.2, 100.8, 83.0, 28.3, 0.0; **LRMS** (ESI+, *m/z*): $C_{16}H_{23}NNaO_3Si$ ([M+Na]$^+$) 328.1; **HRMS** (ESI+, *m/z*): $C_{16}H_{23}NNaO_3Si$ ([M+Na]$^+$) requires 328.13394, found 328.13399; **IR** ν_{max} (film)/cm^{-1}: 3376, 3119, 2979, 2148, 1690, 1601, 1524, 1474, 1394, 1370, 1305, 1250, 1207, 1153, 1056, 1005.

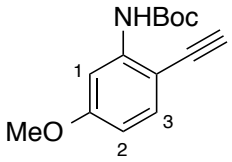
***tert*-Butyl (2-ethynyl-6-hydroxyphenyl)carbamate, 51o**



Compound **51o** was prepared according to General Procedure **D** using alkyne **57o** (297 mg, 0.970 mmol), KF (56.0 mg, 0.970 mmol), and MeOH (30 mL). Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded terminal alkyne **51o** as an off-

white solid (190 mg, 84% yield); **m.p.**: 136-138 °C (crystalised from H_2O/MeCN); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.35 (1H, br. s, O*H*), 7.20 (1H, br. s, N*H*), 7.06-7.00 (3H, m, 3 × Ar*H*), 3.45 (1H, s, CC*H*), 1.54 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 155.7, 148.3, 127.1, 125.6, 124.5, 121.5, 114.2, 84.0, 83.1, 79.5, 28.2; **LRMS** (ESI+, *m/z*): 256.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{13}H_{15}NNaO_3$ ([M+Na]$^+$) requires 256.09441, found 256.09427; **IR** ν_{max} (film)/cm^{-1}: 3319, 3260, 2976, 2931, 2855, 1674, 1598, 1533, 1464, 1393, 1369, 1303, 1275, 1254, 1212, 1156, 1087, 1052, 1031.

tert-Butyl (2-ethynyl-5-methoxyphenyl)carbamate, 51p

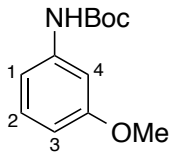


Compound **51p** was prepared according to a sequence of General Procedures **B**, **C** and **D** without intermediate purification, involving a SiO_2 filtration between **C** and **D**, using 2-iodo-4-methoxyaniline **85** (2.00 g, 8.03 mmol), NaHMDS (8.83 mL, 2.00 M solution in THF, 17.7 mmol), Boc_2O (1.93 g, 8.83 mmol), THF (16 mL), $Pd(PPh_3)_2Cl_2$ (281 mg, 0.40 mmol), CuI (76.2 mg, 0.40 mmol), TMS-acetylene (1.71 mL, 12.1 mmol), Et_3N (1.68 mL, 12.1 mmol) and DMF (40 mL), K_2CO_3 (1.11 g, 8.03 mmol) and MeOH (160 mL). Flash column chromatography (SiO_2, 0-10% Et_2O in petrol) afforded terminal alkyne **51p** as a brown solid (1.43 g, 72% yield over three steps); **m.p.**: 57-59 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.85 (1H, d, *J* 2.5, C(1)*H*), 7.35 (1H, d, *J* 8.5, C(3)*H*), 7.31 (1H, br. s, N*H*), 6.54 (1H, dd, *J* 8.5 and 2.5, C(2)*H*), 3.86 (3H, s, OCH_3), 3.45 (1H, s, CC*H*), 1.56 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 161.1, 152.3, 141.8, 133.1, 109.1, 102.4, 101.8, 82.9, 80.9, 79.5, 55.4, 28.3; **LRMS** (ESI+, *m/z*): 270.1

([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{14}H_{17}NNaO_3$ ([M+Na]$^+$) requires 270.11006, found 270.11003; **IR** ν_{max} (film)/cm^{-1}: 3406, 3283, 3126, 2979, 2936, 2837, 2099, 1731, 1613, 1579, 1523, 1469, 1435, 1426, 1393, 1368, 1309, 1288, 1256, 1233, 1212, 1155, 1108, 1049, 1036.

Data consistent with the literature.[278]

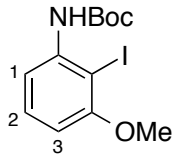
tert-Butyl (3-methoxyphenyl)carbamate, 59



To a solution of 3-anisidine (5.48 g, 44.5 mmol) in THF (70 mL) was added Boc anhydride (9.71 g, 44.5 mmol). The resulting solution was heated at 70 °C for 16 hours. After cooling to room temperature the solvent was removed *in vacuo* and the resulting residue partitioned between Et_2O (200 mL) and 1.0 N $HCl_{(aq)}$ (200 mL). The aqueous fraction was extracted with Et_2O (2 × 100 mL), before the combined organic fractions were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded Boc protected aniline **59** as a white solid (9.21 g, 93% yield); **m.p.**: 51-53 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$):7.17 (1H, t, *J* 8.0, C(2)*H*), 7.10 (1H, br. s, N*H*), 6.83 (1H, d, *J* 8.0, C(1)*H*), 6.58 (1H, dd, *J* 8.0 and 2.5, C(3)*H*), 6.47 (1H, br. s, C(4)*H*), 3.80 (3H, s, OCH_3), 1.52 (9H, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.3, 152.2, 139.6, 129.7, 110.7, 108.9, 104.1, 80.5, 55.3, 28.4; **LRMS** (ESI+, *m/z*): 246.1 ([M+Na]$^+$).

Data consistent with the literature.[281]

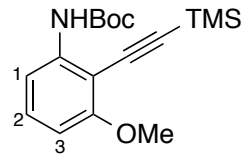
tert-Butyl (2-iodo-3-methoxy-phenyl)carbamate, 56q



At –78 °C, to a solution of compound **59** (1.58 g, 7.08 mmol) in Et_2O (15 mL) was added dropwise ^{t}BuLi (10.0 mL, 1.70 M in pentane, 17.0 mmol). The reaction mixture was warmed to –20 °C and stirred for 3 hours. The reaction was then cooled to –78 °C and a solution of I_2 (2.88 g, 11.3 mmol) in Et_2O (20 mL) was added dropwise. After 16 hours, the reaction was quenched by the addition of H_2O (30 mL), and then extracted with Et_2O (3 × 30 mL). The combined organic fractions were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded aryl iodide **56q** as an off-white solid (1.46 g, 59% yield); **m.p.**: 66-68 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.73 (1H, d, *J* 8.5, C(1)*H*), 7.25 (1H, t, *J* 8.5, C(2)*H*), 7.05 (1H, br. s, N*H*), 6.52 (1H, d, *J* 8.5, C(3)*H*), 3.87 (3H, s, OCH_3), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.3, 152.6, 140.3, 129.7, 112.5, 105.5, 81.1, 81.0, 56.6, 28.3; **LRMS** (ESI+, *m/z*): 372.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{12}H_{16}INNaO_3$ ([M+Na]$^+$) requires 372.00671, found 372.00652; **IR** ν_{max} (film)/cm^{-1}: 3386, 2977, 2932, 1731, 1590, 1574, 1513, 1468, 1406, 1367, 1339, 1288, 1259, 1225, 1149, 1108, 1044, 1025.

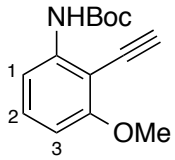
Data consistent with the literature.[277]

tert-Butyl (3-methoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate, 57q



Compound **57q** was prepared according to General Procedure **C** using aryl iodide **56q** (1.00 g, 2.86 mmol), $Pd(PPh_3)_2Cl_2$ (100 mg, 0.14 mmol), CuI (27.0 mg, 0.140 mmol), Et_3N (0.600 mL, 4.30 mmol), TMS-acetylene (0.610 mL, 4.30 mmol) and DMF (40 mL). Flash column chromatography (reverse phase SiO_2, 20-100% MeCN in 10% $NH_4HCO_{3(aq)}$) afforded aryl alkyne **57q** as a pale yellow oil (0.543 g, 59% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.76 (1H, d, *J* 8.5, C(1)*H*), 7.44, (1H, br. s, NH), 7.23 (1H, t, *J* 8.5, C(2)*H*), 6.51 (1H, d, *J* 8.5, C(3)*H*), 3.86 (3H, s, OCH_3), 1.53 (9H, s, C(CH_3)$_3$), 0.31 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.0, 152.3, 141.8, 130.3, 109.7 106.5, 104.2, 100.3, 97.3, 80.5, 55.9, 28.2, 0.0; **LRMS** (ESI+, *m/z*): $C_{17}H_{25}NNaO_3Si$ ([M+Na]$^+$) 342.1; **HRMS** (ESI+, *m/z*): $C_{17}H_{25}NNaO_3Si$ ([M+Na]$^+$) requires 342.14982, found 342.14972; **IR** ν_{max} (film)/cm^{-1}: 3392, 2962, 2840, 2146, 1737, 1585, 1524, 1475, 1431, 1393, 1368, 1289, 1263, 1250, 1233, 1153, 1046, 1028.

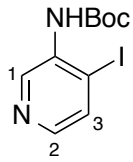
tert-Butyl (2-ethynyl-3-methoxyphenyl)carbamate, 51q



Compound **51q** was prepared according to General Procedure **D** using alkyne **57q** (485 mg, 1.52 mmol), KF (88.0 mg, 1.52 mmol), and MeOH (30 mL). Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded terminal alkyne **51q** as a cream solid (352 mg, 94% yield); **m.p.**: 87-89 °C (crystalised from EtOAc/petrol); **^{1}H-NMR**

(400 MHz, $CDCl_3$): 7.81 (1H, d, *J* 8.5, C(1)*H*), 7.32 (1H, br. s, N*H*), 7.27 (1H, t, *J* 8.5, C(2)*H*), 6.55 (1H, d, *J* 8.5, C(3)*H*), 3.89 (3H, s, OCH_3), 3.74 (1H, s, CC*H*), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.9, 152.4, 141.8, 130.6, 110.1, 104.3, 99.2, 88.3, 80.9, 76.1, 56.0, 28.3; **LRMS** (ESI+, *m/z*): 270.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{14}H_{17}NNaO_3$ ([M+Na]$^+$) requires 270.11006, found 270.10988; **IR** ν_{max} (film)/cm^{-1}: 3403, 3275, 2978, 2937, 1731, 1587, 1522, 1474, 1430, 1393, 1368, 1293, 1264, 1230, 1151, 1114, 1079, 1045, 1027.

tert-Butyl (4-iodopyridin-3-yl)carbamate, 56r

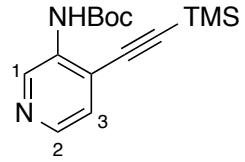


At –78 °C, to a solution of 3-(Boc-amino)pyridine (2.00 g, 10.3 mmol) and TMEDA (3.70 mL, 24.7 mmol) in Et_2O (57 mL) was added dropwise ^{n}BuLi (9.88 mL, 2.50 M solution in hexanes, 24.7 mmol). The resulting solution was warmed to –20 °C and the temperature maintained for 2.5 hours. The reaction was then cooled to –78 °C followed the dropwise addition of I_2 (3.66 g, 14.4 mmol) in Et_2O (8 mL). The resulting solution was gradually allowed to warm to 25 °C. After 16 hours, the reaction was quenched by the addition of H_2O (30 mL), then extracted with Et_2O (3 × 30 mL). The combined organic fractions were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 0-30% EtOAc in petrol) afforded iodopyridine **56r** as a dark brown solid (1.89 g, 57% yield); **m.p.**: 62-64 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.14 (1H, s, C(1)*H*), 7.91 (1H, d, *J* 5.0, C(2)*H*), 7.69 (1H, d, *J* 5.0, C(3)*H*), 6.68 (1H, br. s, N*H*), 1.55 (9H, s, C(CH_3)$_3$);

^{13}C-NMR (100 MHz, $CDCl_3$): 152.1, 144.1, 142.0, 136.5, 133.6, 99.6, 81.9, 28.2; **LRMS** (ESI+, m/z): 321.0 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{10}H_{14}IN_2O_2$ ($[M+H]^+$) requires 321.00945, found 321.00960.

Data consistent with the literature.[278]

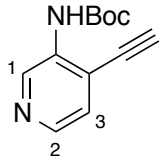
tert-Butyl (4-((trimethylsilyl)ethynyl)pyridin-3-yl)carbamate, 57r



Compound **57r** was prepared according to General Procedure **C** using aryl iodide **56r** (1.00 g, 3.12 mmol), $Pd(PPh_3)_2Cl_2$ (112 mg, 0.160 mmol), CuI (30.0 mg, 0.160 mmol), Et_3N (0.654 mL, 4.69 mmol), TMS-acetylene (0.667 mL, 4.69 mmol) and DMF (45 mL). Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded aryl alkyne **57r** as a dark brown solid (0.877 g, 97% yield); **m.p.**: 60-62 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.38 (1H, s, C(1)*H*), 8.23 (1H, d, *J* 5.0, C(2)*H*), 7.21 (1H, d, *J* 5.0, C(3)*H*), 7.12 (1H, br. s, N*H*), 1.55 (9H, s, C(CH_3)$_3$), 0.31 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 143.3, 140.3, 136.2, 124.7, 118.7, 107.4, 98.0, 81.8, 28.6, 0.0; **LRMS** (ESI+, *m/z*): 291.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{15}H_{23}N_2O_2Si$ ($[M+H]^+$) requires 291.15233, found 291.15235.

Data consistent with the literature.[278]

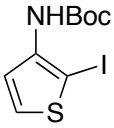
tert-Butyl (4-ethynylpyridin-3-yl)carbamate, 51r



Compound **51r** was prepared according to General Procedure **D** using alkyne **57r** (700 mg, 2.41 mmol), K_2CO_3 (333 mg, 2.41 mmol), and MeOH (50 mL). Flash column chromatography (SiO_2, 0-50% EtOAc in petrol) afforded terminal alkyne **51r** as a dark brown solid (416 mg, 79% yield); **m.p.**: 87-89 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.43 (1H, s, C(1)*H*), 8.25 (1H, d, *J* 5.0, C(2)*H*), 7.28 (1H, d, *J* 5.0, C(3)*H*), 7.12 (1H, br. s, N*H*), 3.71 (1H, s, CC*H*), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.9, 143.0, 140.4, 136.0, 125.2, 117.4, 88.1, 81.7, 76.9, 28.2; **LRMS** (ESI+, *m/z*): 219.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{12}H_{15}N_2O_2$ ([M+H]$^+$) requires 219.11280, found 219.11273.

Data consistent with the literature.[278]

tert-Butyl (2-iodothiophen-3-yl)carbamate, 56s

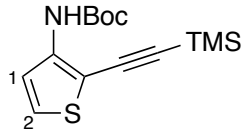


To a refluxing solution of 3-(Boc-amino)thiophene **60** (1.00 g, 5.00 mmol) in CH_2Cl_2 (20 mL) was added portionwise *N*-iodo succinimide (1.13 g, 5.00 mmol). The reaction was heated at reflux for 25 minutes, before cooling to 25 °C. Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded iodothiophene **56s** as a dark brown solid (1.56 g, 96 % yield); **m.p.**: 74-76 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.55-7.43 (2H, m, Ar*H*), 6.50 (1H, br.s, N*H*), 1.53 (9H, s,

C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.3, 140.2, 130.1 (2 × C), 121.7, 81.6, 28.3; **LRMS** (ESI+, *m/z*): 348.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_9H_{12}INNaO_2S$ ([M+Na]$^+$) requires 347.95256, found 347.95275.

Data consistent with the literature.[282]

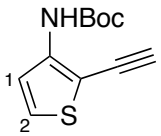
tert-Butyl (2-((trimethylsilyl)ethynyl)thiophen-3-yl)carbamate, 57s



Compound **57s** was prepared according to General Procedure **C** using aryl iodide **56s** (1.00 g, 3.08 mmol), $Pd(PPh_3)_2Cl_2$ (108 mg, 0.150 mmol), CuI (29.0 mg, 0.150 mmol), Et_3N (0.642 mL, 4.61 mmol), TMS-acetylene (0.656 mL, 4.61 mmol) and DMF (45 mL). Flash column chromatography (SiO_2, 0-20% EtOAc in petrol) afforded aryl alkyne **57s** as a dark brown oil (0.861 g, 95% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.61, (1H, br. s, C(2)*H*), 7.13 (1H, d, *J* 5.5, C(1)*H*), 6.88 (1H, br. s, N*H*), 1.53 (9H, s, C(CH_3)$_3$), 0.27 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.9, 141.9, 126.2, 120.3, 104.5, 103.1, 95.1, 81.1, 28.3, 0.0; **LRMS** (ESI+, *m/z*): 318.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{14}H_{21}NNaO_2SSi$ ([M+Na]$^+$) requires 318.09545, found 318.09563.

Data consistent with the literature.[282]

tert-Butyl (2-ethynylthiophen-3-yl)carbamate, 51s

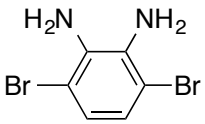


Compound **51s** was prepared according to General Procedure **D** using alkyne **57s** (700 mg, 2.37 mmol), K_2CO_3 (327 mg, 2.37 mmol), and MeOH (50 mL). Flash column

chromatography (SiO_2, 0-50% EtOAc in petrol) afforded terminal alkyne **51s** as a brown oil (526 mg, 99% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.64 (1H, br. s, C(2)*H*), 7.16 (1H, d, *J* 5.5, C(1)*H*), 6.94 (1H, br. s, N*H*), 3.65 (1H, s, CC*H*), 1.52 (9H, s, $C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.9, 142.5, 126.5, 120.4, 101.8, 86.5, 81.2, 74.7, 28.3; **LRMS** (ESI+, *m/z*): 246.1 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{11}H_{13}NNaO_2S$ ($[M+Na]^+$) requires 246.05592, found; 246.05591.

Data consistent with the literature.[282]

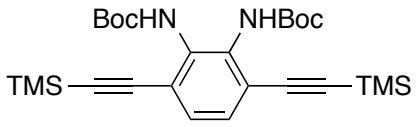
3,6-Dibromobenzene-1,2-diamine, 62



Under a $N_{2(g)}$ atmosphere at 0 °C, to a solution of 4,7-dibromo-2,1,3-benzothiadiazole (5.00 g, 17.0 mmol) in EtOH (600 mL) was added portionwise sodium borohydride (11.6 g, 306 mmol). The reaction was then stirred at 0 °C for 10 minutes, before being allowed to warm to room temperature and stir for 16 hours. The reaction was then cooled to 0 °C, and quenched by the addition of H_2O (150 mL), and then concentrated *in vacuo* to remove the EtOH. The resulting aqueous solution was extracted with Et_2O (2 × 100 mL), then the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude di-aniline **62** as a cream solid (3.94 g, 87 % yield). No further purification was necessary; **m.p.**: 98-100 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.84 (2H, s, Ar*H*), 3.71 (4H, br. s, NH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 133.7, 123.3, 109.7; **LRMS** (ESI+, m/z): 265.0 ($[M(^{79}Br^{79}Br)+H]^+$), 267.0 ($[M(^{79}Br^{81}Br)+H]^+$), 269.0 ($[M(^{81}Br^{81}Br)+H]^+$).

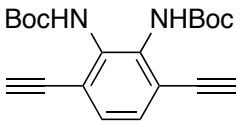
Data consistent with the literature.[283]

Di-*tert*-butyl (3,6-bis((trimethylsilyl)ethynyl)-1,2-phenylene)dicarbamate, 63



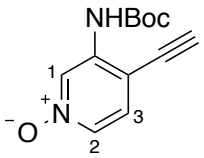
A flask containing compound **62** (4.04 g, 15.2 mmol), CuI (290 mg, 1.52 mmol) and NaI (9.10 g, 60.8 mmol) was evacuated and backfilled with $N_{2(g)}$ three times. Then was added sequentially DMEDA (0.327 mL, 3.04 mmol) and 1,4-dioxane (19 mL). The reaction was then heated at 100 °C for 40 hours. Once cooled to room temperature, the mixture was partitioned between Et_2O (100 mL) and sat. $NH_4Cl_{(aq)}$ (50 mL). The organic layers were then washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a mixture of the di-iodo compound and a bromo-iodo compound. The inseparable crude mixture was then taken on to the Boc-protection step according to General Procedure **B** using NaHMDS (33.4 mL, 2.00 M solution in THF, 66.8 mmol), Boc_2O (7.30 g, 33.4 mmol) and THF (30 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded 4.92 g of a mixture of the di-iodo and bromo-iodo compounds, which were taken on to the Sonogashira step, as described by General Procedure **C** using $Pd(PPh_3)_2Cl_2$ (625 mg, 0.890 mmol), CuI (170 mg, 0.890 mmol), TMS-acetylene (3.75 mL, 26.3 mmol), Et_3N (3.67 mL, 26.3 mmol) and DMF (30 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded dialkyne **63** as a brown oil (3.46 g, 42% yield over three steps); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.28 (2H, s, Ar*H*), 7.12 (2H, br. s, N*H*), 1.51 (18H, s, C(CH_3)$_3$), 0.27 (18H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 153.4, 134.1, 129.4, 101.8, 101.0, 80.5, 77.3, 28.3, –0.1; **LRMS** (ESI+, *m/z*): 523.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{26}H_{40}N_2NaO_4Si_2$ ([M+Na]$^+$) requires 523.24188, found 523.24155; **IR** ν_{max} (film)/cm^{-1}: 3331, 2966, 2901, 2159, 1721, 1599, 1548, 1507, 1485, 1427, 1392, 1367, 1338, 1271, 1248, 1160, 1092, 1061, 1006.

Di-*tert*-butyl (3,6-diethynyl-1,2-phenylene)dicarbamate, 64



Compound **64** was prepared according to General Procedure **D** using dialkyne **63** (1.93 g, 3.85 mmol), K_2CO_3 (1.07 g, 7.71 mmol) and MeOH (40 mL). Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded dialkyne **64** as a pale brown solid (1.11 g, 81% yield); **m.p.**: 159-161 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.36 (2H, s, Ar*H*), 7.09 (2H, br. s, N*H*), 3.43 (2H, s, CC*H*), 1.53 (18H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 153.5, 134.4, 130.1, 120.8, 84.0, 81.0, 79.8, 28.2; **LRMS** (ESI+, *m/z*): 735.3 ([2M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{20}H_{24}N_2NaO_4$ ([M+Na]$^+$) requires 379.16283, found 379.16264; **IR** ν_{max} (film)/cm^{-1}: 3294, 2977, 2931, 1710, 1599, 1555, 1508, 1459, 1393, 1363, 1287, 1271, 1245, 1161, 1085, 1056, 1030.

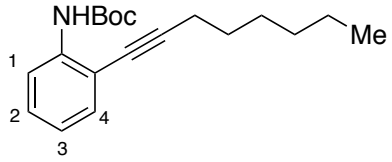
3-((*tert*-Butoxycarbonyl)amino)-4-ethynylpyridine 1-oxide, 51t



To a stirred solution of pyridine **51r** (249 mg, 1.14 mmol) in CH_2Cl_2 (11 mL) was added *m*-CPBA (540 mg, 70-76% in H_2O, 2.28 mmol), and the resulting solution stirred at 25 °C. After 16 hours the reaction was quenched by the addition of saturated $NaHCO_{3(aq)}$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, EtOAc) afforded pyridine *N*-oxide **51t** as an off-white solid (221 mg, 83% yield); **m.p.**: 178-180 °C (crystalised from EtOAc); **^{1}H-NMR** (400 MHz, $(CD_3)_2CO$): 9.00 (1H, d, *J*

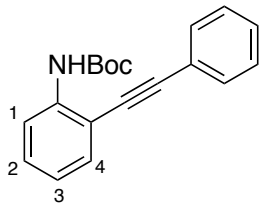
1.5, C(1)*H*), 7.87 (1H, dd, *J* 6.5, 1.5, C(2)*H*), 7.79 (1H, br. s, N*H*), 7.44 (1H, d, *J* 6.5, C(3)*H*), 4.46 (1H, s, CC*H*), 1.53 (1H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $(CD_3)_2CO$): 151.7, 139.0, 133.3, 130.1, 128.2, 106.7, 89.5, 81.6, 76.2, 27.3; **LRMS** (ESI+, *m/z*): 235.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{12}H_{15}N_2O_3$ ([M+H]$^+$) requires 235.10772, found 235.10768; **IR** ν_{max} (film)/cm^{-1}: 3201, 2976, 2932, 2101, 1732, 1610, 1544, 1510, 1479, 1440, 1383, 1368, 1309, 1246, 1183, 1152, 1125, 1055.

tert-Butyl (2-(oct-1-yn-1-yl)phenyl)carbamate, 67a



Compound **67a** was prepared according to General Procedure **C** using aryl iodide **56a** (0.900 g, 2.12 mmol), $Pd(PPh_3)_2Cl_2$ (98.0 mg, 0.140 mmol), CuI (27.0 mg, 0.140 mmol), Et_3N (0.589 mL, 4.23 mmol), 1-octyne (0.624 mL, 4.23 mmol) and DMF (40 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded aryl alkyne **67a** as a pale yellow oil (0.718 g, 84% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.11 (1H, d, *J* 8.0, C(1)*H*), 7.32 (1H, d, *J* 8.0, C(4)*H*), 7.29 (1H, br. s, N*H*), 7.25 (1H, t, *J* 8.0, C(2)*H*), 6.92 (1H, t, *J* 8.0, C(3)*H*), 2.49 (2H, t, *J* 7.0, ArCCCH_2), 1.64 (2H, quintet, *J* 7.0, ArCCCH_2CH_2), 1.53 (9H, s, C(CH_3)$_3$), 1.52-1.46 (2H, m, ArCCCH_2CH$_2$CH_2), 1.37-1.32 (4H, m, CH_2CH_2CH$_3$), 0.91 (3H, t, *J* 6.5, CH$_2$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.5, 139.5, 131.5, 128.8, 121.9, 117.2, 111.9, 97.5, 80.6, 76.0, 31.3, 28.6, 28.3, 27.4, 22.5, 19.6, 14.1; **LRMS** (ESI+, *m/z*): 324.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{27}NNaO_2$ ([M+Na]$^+$) requires 324.19340, found 324.19379; **IR** ν_{max} (film)/cm^{-1}: 3401, 2930, 2859, 1733, 1579, 1515, 1447, 1392, 1367, 1307, 1280, 1236, 1217, 1153, 1117, 1050, 1024.

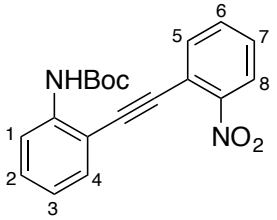
tert-Butyl (2-(phenylethynyl)phenyl)carbamate, 67b



Compound **67b** was prepared according to General Procedure **C** using aryl iodide **56a** (0.900 g, 2.12 mmol), $Pd(PPh_3)_2Cl_2$(98.0 mg, 0.140 mmol), CuI (27.0 mg, 0.140 mmol), Et_3N (0.589 mL, 4.23 mmol), phenylacetylene (0.465 mL, 4.23 mmol) and DMF (40 mL). Flash column chromatography (SiO_2, 0-10% EtOAc in petrol) afforded diaryl alkyne **67b** as a pale orange solid (0.708 g, 86% yield); **m.p.**: 53-55 °C (crystalised from EtOAc/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.17 (1H, d, *J* 8.5, C(1)*H*), 7.57-7.52 (2H, m, Ar*H*), 7.46 (1H, d, *J* 7.5 , C(4)*H*), 7.39-7.35 (3H, m, Ar*H*), 7.34-7.29 (2H, m, N*H*, C(2)*H*), 6.99 (1H, t, *J* 7.5, C(3)*H*), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.5, 139.5, 131.8, 131.6, 129.7, 138.8, 128.6, 122.7, 122.2, 117.6, 111.2, 96.1, 84.6, 80.9, 28.4; **LRMS** (ESI+, *m/z*): 316.1 ([M+Na]$^+$).

Data consistent with the literature.[284]

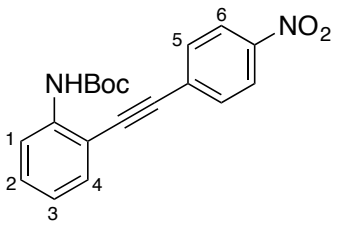
tert-Butyl (2-((2-nitrophenyl)ethynyl)phenyl)carbamate, 67c



Compound **67c** was prepared according to General Procedure **C** using aryl iodide **56a** (319 mg, 1.00 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 50.0 μmol), CuI (9.5 mg, 50 mmol), aryl alkyne **80a** (221 mg, 1.50 mmol, added as a solution in DMF (4.0 mL)), Et_3N (0.210 mL,

1.50 mmol) and DMF (10 mL). Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded aryl alkyne **67c** as an orange solid (126 mg, 37% yield); **m.p.**: 107-109 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.27 (1H, d, *J* 8.5, C(1)*H*), 8.22 (1H, dd, *J* 8.5 and 1.0, C(8)*H*), 7.90 (1H, br. s, N*H*), 7.78 (1H, dd, *J* 8.0 and 1.5, C(5)*H*), 7.67 (1H, td, *J* 7.5 and 1.5, C(6)*H*), 7.55-7.51 (2H, m, C(4)*H*, C(7)*H*), 7.44 (1H, ddd, *J* 8.5, 7.5 and 1.5, C(2)*H*), 7.03 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 1.60 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.8, 148.7, 141.1, 134.5, 133.2, 132.1, 130.9, 128.8, 125.1, 121.9, 118.6, 117.7, 110.0, 93.0, 91.7, 80.8, 28.3; **LRMS** (ESI+, *m/z*): 361.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{18}N_2NaO_4$ ([M+Na]$^+$) requires 361.11588, found 361.11552; **IR** ν_{max} (film)/cm^{-1}: 3380, 2979, 2213, 1729, 1579, 1520, 1482, 1449, 1368, 1341, 1305, 1245, 1225, 1156, 1051.

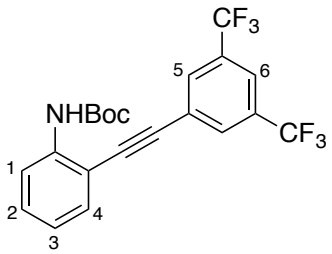
***tert*-Butyl (2-((4-nitrophenyl)ethynyl)phenyl)carbamate, 67d**



Compound **67d** was prepared according to General Procedure **C** using aryl iodide **56a** (319 mg, 1.00 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 50.0 μmol), CuI (9.5 mg, 50 μmol), 4-nitrophenylacetylene (221 mg, 1.50 mmol, added as a solution in DMF (4.0 mL)), Et_3N (0.210 mL, 1.5 mmol) and DMF (10 mL). Flash column chromatography (SiO_2, 10% Et_2O in petrol) afforded aryl alkyne **67d** as a fine yellow crystalline solid (279 mg, 83% yield); **m.p.**: 123-125 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.29 (2H, d, *J* 9.0, C(6)*H*), 8.20 (1H, d, *J* 8.5, C(1)*H*), 7.71 (2H, d, *J* 9.0, C(5)*H*), 7.52 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.41 (1H, ddd, *J* 8.5, 7.5 and 1.5, C(2)*H*), 7.25 (1H, br. s, N*H*), 7.06

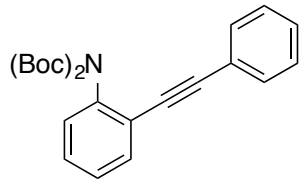
(1H, td, *J* 7.5 and 1.0, C(3)*H*), 1.59 (9H, s, C(C*H*$_3$)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.3, 147.2, 139.8, 132.18, 132.12, 130.8, 129.5, 123.8, 122.4, 118.0, 110.1, 94.1, 89.9, 81.2, 28.3; **LRMS** (ESI+, *m/z*): 361.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{18}N_2NaO_4$ ([M+H]$^+$) requires 361.11588, found 361.11599; **IR** ν_{max} (film)/cm^{-1}: 3411, 2978, 2212, 1733, 1593, 1579, 1517, 1447, 1368, 1342, 1305, 1243, 1222, 1154, 1107, 1050.

tert-Butyl (2-((3,5-bis(trifluoromethyl)phenyl)ethynyl)phenyl)carbamate, 67e



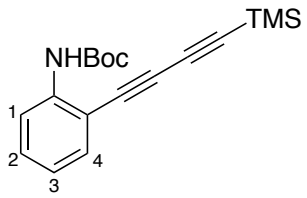
Compound **67e** was prepared according to General Procedure **C** using aryl iodide **56a** (738 mg, 2.00 mmol), $Pd(PPh_3)_2Cl_2$ (70.0 mg, 0.100 mmol), CuI (19.0 mg, 0.100 mmol), 3',5'-bis-trifluoromethylphenyl acetylene (0.530 mL, 3.00 mmol), Et_3N (0.420 mL, 3.00 mmol) and DMF (28 mL). Flash column chromatography (SiO_2, 2-5% Et_2O in petrol) afforded aryl alkyne **67e** as an off-white fluffy solid (705 mg, 82% yield); **m.p.**: 100-102 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.20 (1H, d, *J* 8.5, C(1)*H*), 7.99 (2H, s, C(5)*H*), 7.88 (1H, s, C(6)*H*), 7.51 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.42 (1H, ddd, *J* 8.5, 7.5 and 1.5, C(2)*H*), 7.24 (1H, br. s, N*H*), 7.06 (1H, td, *J* 7.5 and 1.0, C(3)*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.2, 139.9, 132.17 (q, *J* 34.0), 132.01, 131.3 (q, *J* 3.0), 130.8, 125.0, 122.9 (q, *J* 272.5), 122.4, 122.0 (q, *J* 3.5), 118.0, 109.9, 92.9, 88.2, 81.2, 28.3; **^{19}F-NMR** (470 MHz, $CDCl_3$): -63.2; **LRMS** (ESI+, *m/z*): 452.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{17}F_6NNaO_2$ ([M+Na]$^+$) requires 452.10557, found 452.10561; **IR** ν_{max} (film)/cm^{-1}: 3344, 2988, 1698, 1579, 1519, 1481, 1447, 1388, 1282, 1249, 1169, 1131.

_N,N_-DiBoc-2-(phenylethynyl)aniline, 67f



To a solution of mono-Boc protected aniline **67b** (202 mg, 0.688 mmol) in THF (7.0 mL) was added Boc_2O (601 mg, 2.75 mmol) then DMAP (8.6 mg, 70 μmol). The resulting solution was refluxed for 16 hours, and then concentrated *in vacuo*. The resulting residue was dissolved in Et_2O (20 mL) then washed with 1.0 N HCl (2 × 20 mL). The organic fraction was then dried over $MgSO_4$, filtered and concentrated in vacuo. Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded di-Boc protected aniline **67f** as a white solid (247 mg, 91% yield); **m.p.:** 89-91 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.59-7.54 (3H, m, Ar*H*), 7.38-7.30 (5H, m, Ar*H*), 7.21 (1H, dd, *J* 7.5 and 2.0, Ar*H*), 1.39 (18H, s, C(C*H*$_3$)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 151.2, 141.3, 131.7 (2 × C), 128.7, 128.45, 128.39, 128.34, 127.5, 122.9, 122.6, 94.3, 85.5, 82.5, 27.8; **LRMS** (ESI+, *m/z*): 416.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{24}H_{27}NNaO_4$ ([M+Na]$^+$) requires 416.18323, found 416.18245; **IR** ν_{max} (film)/cm^{-1}: 2979, 2933, 1792, 1750, 1725, 1497, 1452, 1368, 1275, 1252, 1152, 1152, 1117, 1097, 1005.

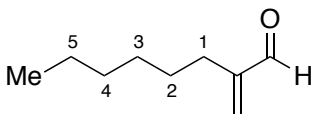
***tert*-Butyl (2-((trimethylsilyl)buta-1,3-diyn-1-yl)phenyl)carbamate, 68**



To a stirred solution of bis-(trimethylsilyl)-1,3-butadiyne (1.22 g, 6.27 mmol) in THF (3.0 mL) under a N_2 atmosphere at 0 °C, was added dropwise methyllithium/lithium

bromide complex (3.13 mL, 2.20 M solution in Et_2O, 6.89 mmol). The resulting solution was stirred at 0 °C for 30 minutes, then warmed to room temperature, and stirred for a further 1 hour. In a separate flask containing $Et_3N.HCl$ (863 mg, 6.27 mmol), aryl iodide **56a** (1.00 g, 3.13 mmol), $Pd(PPh_3)_4$ (181 mg, 0.160 mmol) and CuI (89.5 mg, 0.470 mmol), under a N_2 atmosphere was added Et_3N (6.27 mL). The solution containing the mono-desilylated butadiyne was transfered to this flask *via* cannula, and the resulting solution stirred at room temperature for 18 hours. The reaction mixture was quenched by the addition of $NH_4Cl_{(aq)}$ (50 mL), then extracted with Et_2O (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 2-5% Et_2O in petrol) afforded aryl diyne **68** as a brown solid (685 mg, 70% yield); **m.p.**: 111-113 (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.17 (1H, d, *J* 8.5, C(1)*H*), 7.45 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.36 (1H, dddd, *J* 8.5, 7.5, 1.5 and 0.5, C(2)*H*), 7.16 (1H, br. s, N*H*), 6.97 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 1.58 (9H, s, C(CH_3)$_3$), 0.29 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.3, 141.3, 133.4, 130.7, 122.2, 117.9, 109.3, 92.9, 87.3, 81.2, 80.4, 72.2, 28.3, –0.4; **HRMS** (ammonia CI, *m/z*): $C_{18}H_{24}NO_2Si$ ($[M+H]^+$) requires 313.1498, found 313.1572; **IR** ν_{max} (film)/cm^{-1}: 3412, 2966, 2202, 2102, 1735, 1577, 1513, 1448, 1393, 1368, 1305, 1241, 1220, 1153, 1053, 1015.

2-Methyleneoctanal, 138

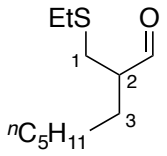


To a solution of octanal (1.60 mL, 10.0 mmol) and formaldehyde (0.700 mL, 37% in H_2O, 10 mmol) in ^{i}PrOH (1.0 mL) was added pyrrolidine (83.0 μL, 1.00 mmol) and propionic

acid (75.0 μL, 1.00 mmol). The reaction mixture was heated at 45 °C for 4 hours, then concentrated *in vacuo*. Flash column chromatography (SiO_2, 5% Et_2O in petrol) afforded aldehyde **138** as a colourless oil (793 mg, 56% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.56 (1H, s, C*H*O), 6.27 (1H, s, C=CH_AH_B), 6.01 (1H, s, C=CH_AH_B), 2.26 (2H, t, *J* 7.5, C(1)H_2), 1.50-1.43 (2H, m, C(2)H_2), 1.37-1.26 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 0.90 (3H, t, *J* 7.5, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.9, 150.5, 133.9, 31.6, 29.0, 27.8, 27.7, 22.6, 14.1; **LRMS** (ESI+, *m/z*): 195.1 ([M+MeOH+Na]$^+$).

Data consistent with the literature.[285]

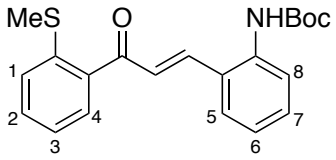
2-((Ethylthio)methyl)octanal, 71e



To a solution of aldehyde **138** (3.48 g, 24.8 mmol) in CH_2Cl_2 (7.0 mL) was added EtSH (2.69 mL, 37.2 mmol) and NEt_3 (0.350 mL, 2.50 mmol). The resulting solution was stirred at room temperature for 16 hours. The solution was concentrated *in vacuo*, and flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aldehyde **71e** as a colourless oil (3.06 g, 61% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 9.66 (1H, d, *J* 2.5, C*H*O), 2.82 (1H, dd, *J* 13.0 and 8.0, C(1)H_AH_B), 2.68 (1H, dd, *J* 13.0 and 6.0, C(1)H_AH_B), 2.56 (2H, q, *J* 7.5, SCH_2CH$_3$), 2.56-2.49 (1H, m, C(2)*H*), 1.76-1.55 (2H, m, C(3)H_2), 1.36-1.25 (8H, m, (CH_2)$_4$), 1.27 (3H, t, *J* 7.5, SCH$_2$CH_3), 0.89 (3H, t, *J* 7.0, (CH$_2$)$_4$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 203.7, 51.6, 31.6, 30.5, 29.3, 28.8, 26.71, 26.57, 22.6, 14.6, 14.0; **LRMS** (ESI+, *m/z*): 257.1 ([M+MeOH+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{12}H_{26}O_2NaS$ ([M+MeOH+Na]$^+$) requires 257.15457, found 257.15471; **IR** ν_{max} (film)/cm^{-1}: 2957, 2916, 2856, 2714, 1725, 1456, 1377, 1264, 1193, 1111, 1052.

7.3.2 Hydroacylation of *N*-Boc 2-ethynylanilines

General Procedure F - hydroacylation of 2-ethynyl aniline derivatives as exemplified by the synthesis of *tert*-Butyl (*E*)-(2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52a



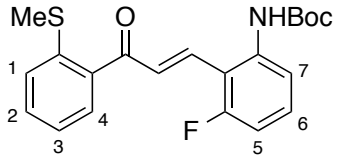
$[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol) and dcpm (4.1 mg, 10 μmol) were added to a microwave vial, which was then evacuated and backfilled with $N_{2(g)}$ three times. Then was added distilled and degassed acetone (0.4 mL), and the resulting suspension sonicated in order to solubilise the phosphine ligand. Once the solution was homogenous, $H_{2(g)}$ was bubbled through for 1 minute, followed by $N_{2(g)}$ until the volume was reduced to approximately 0.1 mL. This resulting solution was transferred by syringe into a microwave vial containing 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol) and alkyne **51a** (43.5 mg, 0.200 mmol). The reaction mixture was stirred at the room temperature for 3 hours. Flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded enone **52a** as a yellow solid (70.8 mg, 96% yield); **m.p.**: 86-88 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.82 (1H, d, *J* 15.5, C(O)CHC*H*), 7.79 (1H, d, *J* 9.5, C(8)*H*), 7.71 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.54 (1H, dd, *J* 8.0 and 1.5, C(5)*H*), 7.42 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.34-7.30 (2H, m, C(1)*H*, C(7)*H*), 7.25 (1H, d, *J* 15.5, C(O)C*H*CH), 7.18 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 7.06 (1H, t, *J* 7.5, C(6)*H*), 6.58 (1H, br. s, N*H*), 2.41 (3H, s, SCH_3), 1.45 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.8, 152.9, 139.5, 137.2, 136.6, 131.9, 131.1, 129.8, 129.4, 128.9, 127.3, 126.3, 126.0,

124.23, 124.16, 122.7, 81.0, 28.3, 16.4; **LRMS** (ESI+, *m/z*): 392.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{23}NNaO_3S$ ([M+Na]$^+$) requires 392.1291, found 392.1296; **IR** ν_{max} (film)/cm^{-1}: 3317, 2978, 1722, 1655, 1595, 1515, 1454, 1367, 1330, 1239, 1209, 1158, 1050, 1026.

Alternatively:

Compound **52a** was prepared according to General Procedure **F** using alkyne **51a** (1.00 g, 4.60 mmol), 2-(methylthio)benzaldehyde **30** (840 mg, 5.52 mmol), $[Rh(nbd)_2]BF_4$ (33.7 mg, 90.0 μmol), dcpm (36.8 mg, 90.0 μmol) and acetone (2.8 mL) for 16 hours at 40 °C. Flash column chromatography (SiO_2, 15-20% Et_2O in petrol) afforded enone **52a** as a yellow solid (1.43 g, 84% yield).

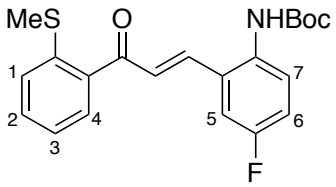
***tert*-Butyl (*E*)-(3-fluoro-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52b**



Compound **52b** was prepared according to General Procedure **F** using alkyne **51b** (47.1 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 4 hours at 55 °C. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded enone **52b** as a yellow solid (62.9 mg, 81% yield); **m.p.**: 127-129 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.81 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.75 (1H, d, *J* 8.5, C(7)*H*), 7.67 (1H, d, *J* 16.0, C(O)CHC*H*), 7.55 (1H, dd, *J* 16.0 and 1.0, C(O)C*H*CH), 7.51 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.40 (1H, d, *J* 8.0, C(1)*H*), 7.32 (1H, ddd, *J* 8.5, 8.0 and 6.5,

C(6)*H*), 7.26 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 6.88 (1H, dd, *J* 10.5 and 8.5, C(5)*H*), 6.79 (1H, br. s, N*H*), 2.49 (3H, s, SCH_3), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.7, 161.3 (d, *J* 251.0), 152.6, 141.7, 138.6 (d, *J* 6.0), 136.1, 133.0, 132.1, 131.0 (d, *J* 11.0), 130.11 (d, *J* 11.0), 130.08, 125.9, 124.1, 117.8 (d, *J* 2.0), 114.7 (d, *J* 14.0), 111.0 (d, *J* 22.5), 81.4, 28.3, 16.4; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –110.5; **LRMS** (ESI+, *m/z*): 410.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{22}FNNaO_3S$ ([M+Na]$^+$) requires 410.11966, found 410.11977; **IR** ν_{max} (film)/cm^{-1}: 3318, 2978, 2925, 1727, 1657, 1597, 1583, 1517, 1472, 1435, 1392, 1367, 1320, 1278, 1247, 1208, 1156, 1081, 1048, 1014.

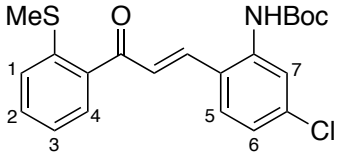
tert-Butyl (E)-(4-fluoro-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52c



Compound **52c** was prepared according to General Procedure **F** using alkyne **51c** (47.1 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 5 hours. Flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded enone **52c** as a yellow solid (63.2 mg, 82% yield); **m.p.**: 118-120 °C (crystallised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.74 (1H, dd, *J* 15.5 and 1.5, C(O)CHC*H*), 7.70-7.65 (2H, m, C(7)*H*, C(4)*H*), 7.41 (1H, app. td, *J* 7.5 and 1.5, C(2)*H*), 7.30 (1H, d, *J* 8.0, C(1)*H*), 7.23 (1H, dd, *J* 9.5 and 3.0, C(5)*H*), 7.22 (1H, d, *J* 15.5, COC*H*CH), 7.17 (1H, ap. td, *J* 7.5 and 1.0, C(3)*H*), 7.01 (1H, ap. tdd, *J* 8.5, 3.0 and 1.0, C(6)*H*), 6.49 (1H, br. s, N*H*), 2.40 (3H, s, SCH_3), 1.43 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 190.3, 158.4 (d, *J* 244.5), 152.1, 140.4,

137.10, 135.2, 132.1 (d, *J* 2.5), 131.0, 128.9, 127.7, 125.9, 124.9, 124.4, 123.1, 116.8 (d, *J* 22.5), 112.0 (d, *J* 23.0), 80.1, 27.3, 15.3; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –117.7; **LRMS** (ESI+, *m/z*): 410.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{22}FNNaO_3S$ ([M+Na]$^+$) requires 410.1197, found 410.1190; **IR** ν_{max} (film)/cm^{-1}: 1704, 1656, 1598, 1511, 1432, 1367, 1332, 1270, 1212, 1156, 1097, 1050, 1016.

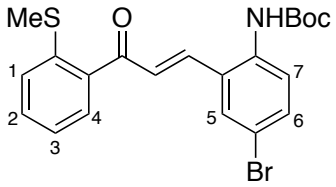
tert-Butyl (_E_)-(5-chloro-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52d



Compound **52d** was prepared according to General Procedure **F** using alkyne **51d** (50.4 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 2 hours at room temperature. Flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded enone **52d** as a yellow oil (78.8 mg, 98% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.93 (1H, br. s, C(7)*H*), 7.72 (1H, d, *J* 15.5, C(O)CHC*H*), 7.69 (1H, dd, *J* 6.5 and 1.5, C(4)*H*), 7.42 (1H, d, *J* 8.5, C(5)*H*), 7.41 (1H, td, *J* 7.0 and 1.5, C(3)*H*), 7.29 (1H, d, *J* 8.0, C(1)*H*), 7.22 (1H, d, *J* 15.5, C(O)C*H*CH), 7.16 (1H, td, *J* 7.5 and 1.0, C(2)*H*), 6.99 (1H, dd, *J* 8.5 and 2.0, C(6)*H*), 6.69 (1H, br. s, N*H*), 2.39 (3H, s, SCH_3), 1.45 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.4, 152.4, 141.4, 138.2, 138.0, 136.9, 136.4, 132.1, 129.9, 128.2, 126.5, 126.0, 124.2, 124.1, 123.9, 121.8, 81.6, 28.3, 16.4; **LRMS** (ESI+, *m/z*): 426.1 ([M(^{35}Cl)+Na]$^+$), 428.1 ([M(^{37}Cl)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{22}ClNNaO_3S$ ([M(^{35}Cl)+Na]$^+$) requires 426.0901, found 426.0895, ([M(^{37}Cl)+Na]$^+$) requires 428.0872,

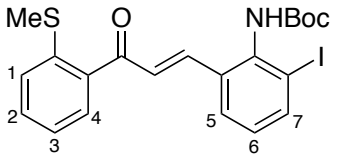
found 428.0865; **IR** ν_{max} (film)/cm^{-1}: 1725, 1655, 1590, 1510, 1462, 1420, 1392, 1367, 1329, 1235, 1209, 1155, 1050, 1013.

tert-Butyl (*E*)-(4-bromo-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52e



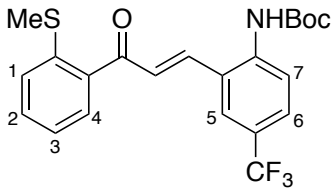
Compound **52e** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), [Rh(nbd)$_2$]BF$_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 20 minutes at room temperature. Flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded enone **52e** as a yellow solid (88.7 mg, 99% yield); **m.p.**: 148-150 °C (crystalised from $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.73-7.69 (3H, m, C(O)CHC*H*, C(7)*H*, C(4)*H*), 7.62 (1H, d, *J* 2.0, C(5)*H*), 7.42 (1H, td, *J* 7.5, 1.5, C(6)*H*), 7.39 (1H, dd, *J* 9.0 and 2.0, C(2)*H*), 7.30 (1H, d, *J* 8.0, C(1)*H*), 7.24 (1H, d, *J* 15.5, C(O)C*H*CH), 7.18 (1H, td, *J* 7.5 and 0.5, C(3)*H*), 6.58 (1H, br. s, N*H*), 2.40 (3H, s, SCH_3), 1.44 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.1, 152.6, 141.7, 137.5, 136.2, 136.1, 133.6, 132.2, 130.0, 129.7, 127.8, 127.1, 125.9, 124.2, 124.0, 116.9, 81.4, 28.3, 16.4; **LRMS** (ESI+, *m/z*): 470.0 ([M(^{79}Br)+Na]$^+$), 472.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{22}BrNNaO_3S$ (^{79}Br, [M+Na]$^+$) requires 470.0396, found 470.0388, (^{81}Br, [M+Na]$^+$) requires 472.0376, found 472.0365; **IR** ν_{max} (film)/cm^{-1}: 2979, 2362, 1703, 1655, 1598, 1508, 1404, 1367, 1327, 1275, 1209, 1158, 1051, 1008.

tert-Butyl (*E*)-(2-iodo-6-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52f



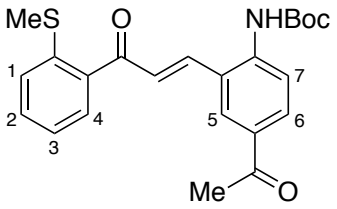
Compound **52f** was prepared according to General Procedure **F** using alkyne **51f** (68.6 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 3 hours at room temperature. Flash column chromatography (SiO_2, 20-40% Et_2O in petrol) afforded enone **52f** as a yellow solid (91.3 mg, 92% yield); **m.p.**: 67-69 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.89 (1H, dd, *J* 8.0 and 1.5, C(7)*H*), 7.78 (1H, d, *J* 16.0, C(O)CHC*H*), 7.73-7.70 (2H, m, C(4)*H*, C(5)*H*), 7.47 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.38 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.25 (1H, d, *J* 16.0, C(O)C*H*CH), 7.23 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 7.03 (1H, t, *J* 8.0, C(6)*H*), 6.26 (1H, br. s, N*H*), 2.46 (3H, s, SCH_3), 1.48 (9H, br. s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.6, 153.3, 141.6, 140.6 (2 × C), 138.1, 137.0, 134.3, 131.6, 129.6, 128.6, 127.4, 126.8, 126.3, 124.2, 100.6, 81.2, 28.3, 16.5; **LRMS** (ESI+, *m/z*): 518.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{22}INNaO_3S$ ([M+Na]$^+$) requires 518.02573, found 518.02586; **IR** ν_{max} (film)/cm^{-1}: 3293,2976, 2924, 1702, 1654, 1597, 1555, 1483, 1450, 1433, 1392, 1367, 1315, 1244, 1207, 1158, 1115, 1082, 1048, 1014.

tert-Butyl (_E_)-(2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)-4-(trifluoromethyl)phenyl)carbamate, 52g



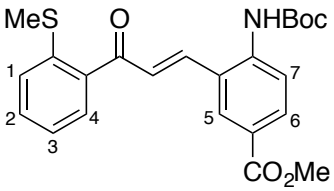
Compound **52g** was prepared according to General Procedure **F** using alkyne **51g** (57.1 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 20 minutes at room temperature. Flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded enone **52g** as a yellow solid (80.6 mg, 92% yield); **m.p.**: 169-171 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.08 (1H, d, *J* 8.5, C(7)*H*), 7.79 (1H, d, *J* 15.5, C(O)CHC*H*), 7.75 (1H, d, *J* 8.0 and 1.0, C(4)*H*), 7.72 (1H, d, *J* 1.0, C(5)*H*), 7.54 (1H, dd, *J* 8.5 and 1.5, C(6)*H*), 7.44 (1H, td, *J* 7.5 and 1.5, C(2)*H*), 7.32 (1H, d, *J* 7.0, C(1)*H*), 7.31 (1H, d, *J* 15.5, C(O)C*H*CH), 7.20 (1H, td. *J* 7.5 and 1.0, C(3)*H*), 6.79 (1H, br. s, N*H*), 2.42 (3H, s, SCH_3), 1.47 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (125 MHz, $CDCl_3$): 189.9, 151.2, 140.7, 139.0, 136.3, 135.0, 131.3, 129.0, 126.8, 126.5 (q, *J* 3.5), 124.9, 124.5 (q, *J* 33.0), 124.1, 123.4 (q, *J* 3.5), 123.2, 122.9 (q, *J* 272.0), 120.2, 80.8, 27.2, 15.3; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –62.2; **LRMS** (ESI+, *m/z*): 460.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{23}NO_3F_3S$ ([M+H]$^+$) requires 438.1345, found 438.1335; **IR** ν_{max} (film)/cm^{-1}: 1703, 1655, 1597, 1519, 1485, 1323, 1271, 1153, 1108, 1006.

tert-Butyl (*E*)-(4-acetyl-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52h



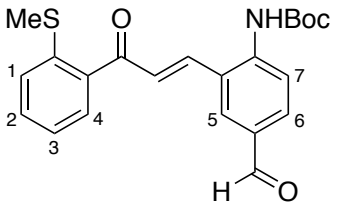
Compound **52h** was prepared according to General Procedure **F** using alkyne **51h** (51.9 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 30 minutes at room temperature Flash column chromatography (SiO_2, 30-60% Et_2O in petrol) afforded enone **52h** as a yellow solid (80.6 mg, 98% yield); **m.p.**: 134-136 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.16 (1H, s, C(5)*H*), 8.12 (1H, d, *J* 8.5, C(7)*H*), 7.92 (1H, d, *J* 8.5, C(6)*H*), 7.84 (1H, d, *J* 15.5, C(O)CHC*H*), 7.80 (1H, d, *J* 7.5, C(4)*H*), 7.48 (1H, t, *J* 7.5, C(2)*H*), 7.40 (1H, d, *J* 15.5, C(O)C*H*CH), 7.35 (1H, d, *J* 8.0, C(1)*H*), 7.23 (1H, t, *J* 7.5, C(3)*H*), 7.09 (1H, br. s, N*H*), 2.58 (3H, s, C(O)CH_3), 2.45 (3H, s, SCH_3), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 196.7, 190.9, 152.2, 141.8, 141.4, 137.9, 135.8, 132.22, 132.03, 131.1, 130.1, 127.6, 127.3, 125.7, 124.7, 124.1, 120.3, 81.7, 28.2, 26.4, 16.3; **LRMS** (ESI+, *m/z*): 434.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{25}NNaO_4S$ ([M+Na]$^+$) requires 434.13965, found 434.13934; **IR** ν_{max} (film)/cm^{-1}: 3313, 2979, 2921, 1727, 1675, 1594, 1574, 1517, 1476, 1433, 1367, 1333, 1284, 1234, 1150, 1048, 1013.

Methyl (*E*)-4-((tert-butoxycarbonyl)amino)-3-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)benzoate, 52i



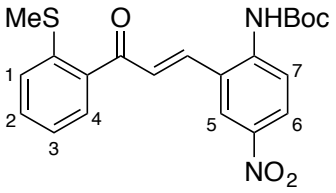
Compound **52i** was prepared according to General Procedure **F** using alkyne **51i** (55.1 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and DCE (0.2 mL) for 30 minutes at 55 °C. Flash column chromatography (SiO_2, 30-50% Et_2O in petrol) afforded enone **52i** as a yellow solid (80.3 mg, 94% yield); **m.p.**: 63-65 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.18 (1H, d, *J* 2.0, C(5)*H*), 8.06 (1H, d, *J* 8.5, C(7)*H*), 7.95 (1H, dd, *J* 8.5 and 2.0, C(6)*H*), 7.89 (1H, d, *J* 15.5, C(O)CHC*H*), 7.76 (1H, dd, *J* 8.5 and 1.5, C(4)*H*), 7.43 (1H, td, *J* 7.5 and 1.5, C(2)*H*), 7.35 (1H, d, *J* 15.5, C(O)C*H*CH), 7.31 (1H, d, *J* 8.0, C(1)*H*), 7.19 (1H, td, *J* 8.0 and 1.0, C(3)*H*), 6.87 (1H, br. s, N*H*), 3.84 (3H, s, CO_2CH_3), 2.41 (3H, s, SCH_3), 1.47 (9H, s, $C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.1, 166.3, 152.2, 141.8, 141.2, 137.7, 136.1, 132.2, 132.1, 130.1, 129.0, 127.3, 125.9, 125.0, 124.5, 124.1, 120.4, 81.8, 52.2, 28.3, 16.4; **LRMS** (ESI+, *m/z*): 450.1 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{25}NNaO_5S$ ($[M+Na]^+$) requires 450.1346, found 450.1331; **IR** ν_{max} (film)/cm^{-1}: 2979, 1717, 1656, 1597, 1518, 1434, 1368, 1288, 1239, 1153, 1049, 1014.

tert-Butyl (*E*)-(4-formyl-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52j



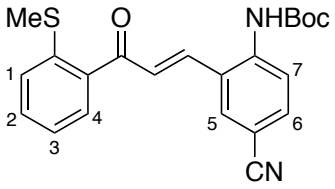
Compound **52j** was prepared according to General Procedure **F** using alkyne **51j** (49.1 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 30 minutes at room temperature. Flash column chromatography (SiO_2, 30-60% Et_2O in petrol) afforded enone **52j** as a yellow solid (73.6 mg, 93% yield); **m.p.**: 155-157 °C (crystalised from Et_2O/petrol**); ^{1}H-NMR** (400 MHz, $CDCl_3$): 9.94 (1H, s, C*H*O), 8.27 (1H, d, *J* 8.5, C(7)*H*), 8.08 (1H, d, *J* 1.5, C(5)*H*), 7.87 (1H, d, *J* 15.5, C(O)C*H*CH), 7.88-7.83 (2H, m, C(4)*H*, C(6)*H*), 7.51 (1H, td, *J* 7.5 and 1.5, C(2)*H*), 7.45 (1H, d, *J* 15.5, C(O)CHC*H*), 7.38 (1H, d, *J* 8.0, C(1)*H*), 7.26 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 7.11 (1H, br. s, N*H*), 2.48 (3H, s, SCH_3), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 190.79, 190.71, 152.0, 142.6, 142.0, 137.3, 135.7, 132.6, 132.3, 131.3, 130.1, 128.7, 127.7, 125.8, 125.0, 124.1, 120.5, 82.0, 28.2, 16.3; **LRMS** (ESI+, *m/z*): 452.1 ([M+MeOH+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{27}NNaO_5S$ ([M+MeOH+Na]$^+$) requires 452.15021, found 452.14972; **IR** ν_{max} (film)/cm^{-1}: 3325, 2979, 2922, 1730, 1689, 1655, 1595, 1576, 1516, 1477, 1431, 1368, 1334, 1228, 1149, 1049, 1014.

tert-Butyl (_E_)-(2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)-4-nitrophenyl)carbamate, 52k



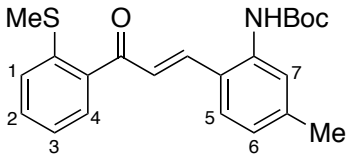
Compound **52k** was prepared according to General Procedure **F** using alkyne **51k** (52.4 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.4 mL) for 20 minutes at room temperature. Flash column chromatography (SiO_2, 0-100% CH_2Cl_2 in petrol) afforded enone **52k** as a yellow solid (81.2 mg, 98% yield); **m.p.**: 174-176 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.47 (1H, d, *J* 2.5, C(5)*H*), 8.35 (1H, d, *J* 9.0, C(7)*H*), 8.25 (1H, dd, *J* 9.0 and 2.5, C(6)*H*), 7.88 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.86 (1H, dd, *J* 15.5, C(O)CHC*H*), 7.56 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.51 (1H, d, *J* 15.5, C(O)C*H*CH), 7.43 (1H, dd, *J* 8.0, 1.0, C(1)*H*), 7.32 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 7.10 (1H, br. s, N*H*), 2.53 (3H, s, SCH_3), 1.58 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (125 MHz, $CDCl_3$): 190.4, 151.8, 142.80, 142.77, 142.1, 136.0, 135.6, 132.6, 130.2, 128.8, 125.92, 125.87, 124.7, 124.2, 123.0, 120.1, 82.5, 28.2, 16.4; **LRMS** (ESI+, *m/z*): 437.1 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{23}N_2O_5S$ ($[M+H]^+$) requires 415.13222, found 415.13226; **IR** ν_{max} (film)/cm^{-1}: 3369, 2959, 2922, 1718, 1656, 1596, 1580, 1534, 1502, 1467, 1340, 1263, 1232, 1216, 1157, 1087, 1050, 1009.

tert-Butyl (*E*)-(4-cyano-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52l



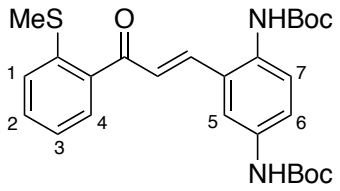
Compound **52l** was prepared according to General Procedure **F** using alkyne **51l** (48.4 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 30 minutes at room temperature. Flash column chromatography (SiO_2, 0-20% EtOAc in CH_2Cl_2) afforded enone **52l** as a yellow solid (73.5 mg, 93% yield); **m.p.**: 172-174 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.26 (1H, d, *J* 8.5, C(7)*H*), 7.86-7.83 (2H, m, C(4)*H*, C(5)*H*), 7.83 (1H, d, *J* 15.5, C(O)CHC*H*), 7.65 (1H, dd, *J* 8.5 and 2.0, C(6)*H*), 7.55 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.42 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.41 (1H, d, *J* 15.5, C(O)C*H*CH), 7.30 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 7.02 (1H, br. s, N*H*), 2.52 (3H, s, SCH_3), 1.57 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 190.6, 151.9, 141.9, 141.1, 136.2, 135.7, 134.1, 132.5, 131.4, 130.2, 128.5, 125.9, 125.3, 124.3, 120.8, 118.5, 106.6, 82.3, 28.2, 16.4; **LRMS** (ESI+, *m/z*): 417.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{22}N_2NaO_3S$ ([M+Na]$^+$) requires 417.12433, found 417.12417; **IR** ν_{max} (film)/cm^{-1}: 3375, 2981, 2924, 2229, 1715, 1655, 1598, 1571, 1508, 1474, 1392, 1368, 1333, 1300, 1273, 1235, 1213, 1160, 1081, 1051, 1011.

tert-Butyl (_E_)-(5-methyl-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52m



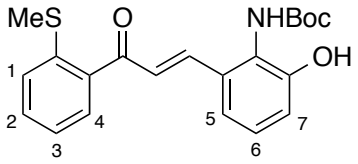
Compound **52m** was prepared according to General Procedure **F** using alkyne **51m** (46.2 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 3 hours at 55 °C. Flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded enone **52m** as a yellow solid (54.6 mg, 71% yield); **m.p.**: 115-117 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.79 (1H, d, *J* 15.5, C(O)CHC*H*), 7.69 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.63 (1H, br. s, C(7)*H*), 7.44 (1H, d, *J* 8.0, C(5)*H*), 7.41 (1H, td, *J* 8.0 and 1.5, C(2)*H*), 7.30 (1H, d, *J* 8.0, C(1)*H*), 7.21 (1H, d, *J* 15.5, C(O)C*H*CH), 7.16 (1H, t, *J* 7.0, C(3)*H*), 6.87 (1H, d, *J* 8.0, C(6)*H*), 6.56 (1H, br. s, N*H*), 2.40 (3H, s, SCH_3), 2.29 (3H, s, ArCH_3), 1.45 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 190.9, 151.9, 141.0, 140.0, 138.4, 136.1, 135.8, 130.7, 128.7, 126.1, 124.9, 124.2, 124.1, 123.1, 122.3, 122.0, 79.9, 27.3, 20.7, 15.4; **LRMS** (ESI+, *m/z*): 406.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{25}NNaO_3S$ ([M+Na]$^+$) requires 406.1447, found 406.1440; **IR** ν_{max} (film)/cm^{-1}: 2922, 2361, 2342, 1726, 1653, 1592, 1523, 1458, 1367, 1243, 1158, 1050.

Di-*tert*-butyl (2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)-1,4-phenylene)(*E*)-dicarbamate, 52n



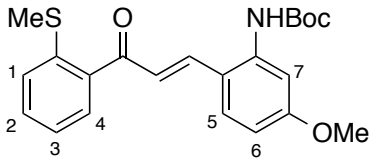
Compound **52n** was prepared according to General Procedure **F** using alkyne **51n** (66.4 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 7 hours at room temperature. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded enone **52n** as a yellow solid (87.1 mg, 90% yield); **m.p.**: 108-110 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.82 (1H, d, *J* 15.5, C(O)CHC*H*), 7.77 (1H, br. s, C(5)*H*), 7.75 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.60 (1H, d, *J* 7.5, C(7)*H*), 7.47 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.36 (1H, dd, *J* 8.0, 1.0, C(1)*H*), 7.27 (1H, d, *J* 15.5, C(O)C*H*CH), 7.24-7.20 (2H, m, C(6)*H*, C(3)*H*), 6.85 (1H, br. s, N*H*), 6.64 (1H, br. s, N*H*), 2.47 (3H, s, SCH_3), 1.52 (9H, s, C(CH_3)$_3$), 1.51 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.9, 153.4, 152.9, 141.1, 139.4, 136.6, 135.3, 132.2, 131.8, 129.9, 127.8, 126.2, 125.9, 124.5, 124.1, 121.5, 116.7, 80.8, 80.6, 28.4, 28.3, 16.4; **LRMS** (ESI+, *m/z*): 507.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{26}H_{32}N_2NaO_5S$ ([M+Na]$^+$) requires 507.19241, found 507.19227; **IR** ν_{max} (film)/cm^{-1}: 3319, 2978, 2925, 1696, 1656, 1588, 1509, 1433, 1417, 1392, 1367, 1279, 1242, 1152, 1059, 1018.

tert-Butyl (_E_)-(2-hydroxy-6-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52o



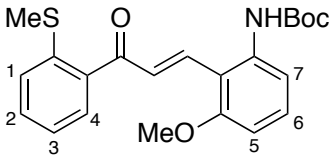
Compound **52o** was prepared according to General Procedure **F** using alkyne **51o** (46.6 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 16 hours at 55 °C. Flash column chromatography (SiO_2, 0-10% EtOAc in CH_2Cl_2) afforded enone **52o** as a yellow solid (69.0 mg, 89% yield); **m.p.**: 95-97 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.25 (1H, br. s, O*H*), 7.87 (1H, d, *J* 15.5, C(O)CHC*H*), 7.76 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.49 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.37 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.29 (1H, d, *J* 15.5, C(O)C*H*CH), 7.26-7.22 (2H, m, C(3)*H*, C(5)*H*), 7.16 (1H, t, *J* 8.0, C(6)*H*), 7.09 (1H, dd, *J* 8.0 and 1.5, C(7)*H*), 6.98 (1H, br. s, N*H*), 2.47 (3H, s, SCH_3), 1.54 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.0, 155.5, 150.8, 141.2, 140.3, 136.4, 132.0, 129.9 (2 × C), 127.1, 126.6, 125.9, 124.6, 124.2, 121.7, 119.6, 82.8, 28.2, 16.3; **LRMS** (ESI+, *m/z*): 408.1 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{23}NNaO_4S$ ($[M+Na]^+$) requires 408.12400, found 408.12404; **IR** ν_{max} (film)/cm^{-1}: 3303, 2978, 2924, 1682, 1654, 1580, 1460, 1368, 1247, 1154, 1050, 1020.

tert-Butyl (_E_)-(5-methoxy-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52p



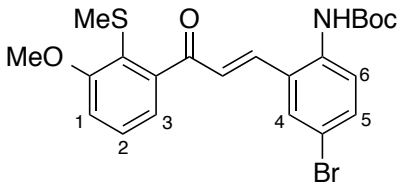
Compound **52p** was prepared according to General Procedure **F** using alkyne **51p** (49.5 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 16 hours at 55 °C. Flash column chromatography (SiO_2, 30-60% Et_2O in petrol) afforded enone **52p** as a yellow oil (41.4 mg, 51% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.87 (1H, d, *J* 15.5, C(O)CHC*H*), 7.78 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.59 (1H, d, *J* 2.5, C(7)*H*), 7.59 (1H, d, *J* 9.0, C(5)*H*), 7.50 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.40 (1H, ddd, *J* 8.0, 1.0 and 0.5, C(1)*H*), 7.26 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 7.26 (1H, d, *J* 15.5, C(O)C*H*CH), 6.78 (1H, br. s, N*H*), 6.70 (1H, ddd, *J* 9.0, 2.5 and 0.5, C(6)*H*), 3.88 (3H, s, OCH_3), 2.50 (3H, s, SCH_3), 1.56 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.8, 162.3, 152.6, 140.9, 139.05, 138.85, 137.1, 131.7, 129.6, 128.5, 125.9, 124.1, 123.5, 117.8, 111.2, 106.1, 81.1, 55.5, 28.3, 16.4; **LRMS** (ESI+, *m/z*): 422.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{25}NNaO_4S$ ([M+Na]$^+$) requires 422.13965, found 422.13953; **IR** ν_{max} (film)/cm^{-1}: 3302, 2976, 2924, 1723, 1651, 1586, 1524, 1478, 1434, 1367, 1306, 1270, 1239, 1207, 1157, 1049, 1016.

tert-Butyl (_E_)-(3-methoxy-2-(3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 52q



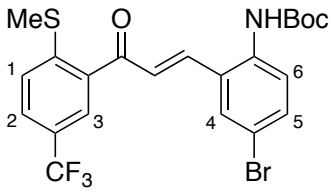
Compound **52q** was prepared according to General Procedure **F** using alkyne **51q** (49.4 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), and acetone (0.1 mL) for 16 hours at 55 °C. Flash column chromatography (SiO_2, 0-10% EtOAc in CH_2Cl_2) afforded enone **52q** as a yellow oil (35.2 mg, 44% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.79 (1H, d, *J* 16.0, C(O)CHC*H*), 7.77 (1H, dd, *J* 7.5 and 1.5 C(4)*H*), 7.57 (1H, d, *J* 8.0, C(7)*H*), 7.54 (1H, d, *J* 16.0, C(O)C*H*CH), 7.50 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.41 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.32 (1H, t, *J* 8.0, C(6)*H*), 7.27 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 6.80 (1H, br. s, N*H*), 6.70 (1H, d, *J* 8.0, C(5)*H*), 3.89 (3H, s, OCH_3), 2.50 (3H, s, SCH_3), 1.54 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 193.0, 158.9, 152.9, 140.8, 138.1, 137.1, 136.8, 131.6, 130.9, 129.8, 129.3, 126.2, 124.3, 115.1, 114.5, 106.2, 80.9, 55.8, 28.3, 16.6; **LRMS** (ESI+, *m/z*): 422.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{25}NNaO_4S$ ([M+Na]$^+$) requires 422.13965, found 422.23973; **IR** ν_{max} (film)/cm^{-1}: 3313, 2975, 2924, 2854, 1724, 1653, 1593, 1514, 1473, 1433, 1392, 1367, 1318, 1261, 1236, 1205, 1155, 1105, 1083, 1047, 1025.

tert-Butyl (_E_)-(4-bromo-2-(3-(3-methoxy-2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72a



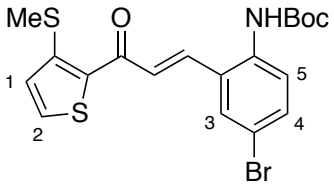
Compound **72a** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 3-methoxy-2-(methylthio)benzaldehyde **71a** (43.2 mg, 0.240 mmol),[132] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 3 hours at room temperature. Flash column chromatography (SiO_2, 40% Et_2O in petrol) afforded enone **72a** as a yellow oil (92.5 mg, 97% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.74 (1H, d, *J* 9.0, C(6)*H*), 7.66 (1H, d, *J* 2.0, C(4)*H*), 7.58 (1H, d, *J* 16.0, C(O)CHC*H*), 7.46 (1H, dd, *J* 9.0 and 2.0, C(5)*H*), 7.40 (1H, t, *J* 8.0, C(2)*H*), 7.04 (1H, d, *J* 16.0, C(O)C*H*CH), 7.03 (2H, ap. d, *J* 8.0, C(1)*H*, C(3)*H*), 6.62 (1H, br. s, N*H*), 3.98 (3H, s, OCH_3), 2.40 (3H, s, SCH_3), 1.52 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 194.5, 160.1, 152.6, 145.9, 136.3, 136.0, 133.5, 130.2, 129.91, 129.78, 128.1, 124.1, 121.5, 119.8, 117.1, 112.7, 81.3, 56.1, 28.3, 18.8; **LRMS** (ESI+, *m/z*): 500.1 ([M(^{79}Br)+Na]$^+$), 502.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{24}BrNNaO_4S$ ([M(^{79}Br)+Na]$^+$) requires 500.05016, found 500.05039, ([M(^{81}Br)+Na]$^+$) requires 502.04812, found 502.04805; **IR** ν_{max} (film)/cm^{-1}: 3310, 3064, 2977, 2926, 2839, 2248, 1721, 1653, 1599, 1568, 1505, 1464, 1424, 1403, 1393, 1367, 1319, 1301, 1262, 1245, 1155, 1117, 1081, 1048, 1026.

tert-Butyl (_E_)-(4-bromo-2-(3-(2-(methylthio)-5-(trifluoromethyl)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72b



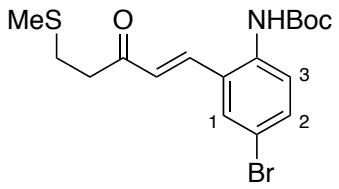
Compound **72b** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 2-(methylthio)-5-(trifluoromethyl)benzaldehyde **71b** (52.8 mg, 0.240 mmol),[132] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 2 hours at room temperature. Flash column chromatography (SiO_2, 40-100% CH_2Cl_2 in petrol) afforded enone **72b** as a yellow solid (92.8 mg, 90% yield); **m.p.**: 169-171 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (1H, d, *J* 1.5, C(3)*H*), 7.87 (1H, d, *J* 15.5, C(O)CHC*H*), 7.83 (1H, d, *J* 9.0, C(6)*H*), 7.76 (1H, d, *J* 2.5, C(4)*H*), 7.75 (1H, dd, *J* 8.5 and 1.5, C(2)*H*), 7.53 (1H, dd, *J* 9.0 and 2.5, C(5)*H*), 7.50 (1H, d, *J* 8.5, C(1)*H*), 7.32 (1H, d, *J* 15.5, C(O)C*H*CH), 6.60 (1H, br. s, N*H*), 2.56 (3H, s, SCH_3), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (125 MHz, $CDCl_3$): 190.1, 152.5, 146.7, 138.8, 136.4, 135.9, 134.0, 129.8, 128.3 (q, *J* 3.5), 127.5, 126.4 (q, *J* 4.0), 126.3 (q, *J* 33.5), 126.1, 125.7, 124.1, 123.8 (q, *J* 272.0), 117.1, 81.6, 28.3, 16.2; **^{19}F-NMR** (470 MHz, $CDCl_3$) {^{1}H}: –62.3; **LRMS** (ESI+, *m/z*): 538.0 ([M(^{79}Br)+Na]$^+$), 540.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{21}BrF_3NNaO_3S$ ([M(^{79}Br)+Na]$^+$) requires 538.02698, found 538.02710, ([M(^{81}Br)+Na]$^+$) requires 540.02494, found 540.02483; **IR** ν_{max} (film)/cm^{-1}: 3358, 2977, 2923, 2852, 1698, 1657, 1593, 1566, 1509, 1467, 1447, 1404, 1393, 1359, 1344, 1314, 1273, 1241, 1201, 1175, 1159, 1116, 1096, 1069, 1054, 1027, 1010.

tert-Butyl (_E_)-(4-bromo-2-(3-(3-(methylthio)thiophen-2-yl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72c



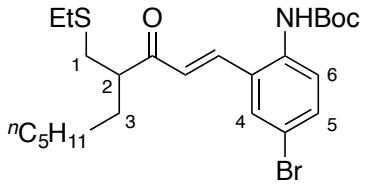
Compound **72c** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 3-(methylthio)thiophene-2-carbaldehyde **71c** (37.9 mg, 0.240 mmol),[132] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.3 mL) for 16 hours at 55 °C. Flash column chromatography (SiO_2, 40-60% Et_2O in petrol) afforded enone **72c** as a yellow solid (67.7 mg, 74% yield); **m.p.**: 183-185 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.89 (1H, d, *J* 15.0, C(O)CHC*H*), 7.86 (1H, d, *J* 9.0, C(5)*H*), 7.72 (1H, d, *J* 2.5, C(3)*H*), 7.67 (1H, d, *J* 5.0, C(1)*H*), 7.49 (1H, dd, *J* 9.0 and 2.5, C(4)*H*), 7.22 (1H, d, *J* 15.0, C(O)C*H*CH), 7.12 (1H, d, *J* 5.0, C(2)*H*), 6.64 (1H, br. s, N*H*), 2.61 (3H, s, SCH_3), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 180.5, 152.5, 148.1, 136.3 (2 × C), 133.6, 131.8, 130.8, 129.6, 127.4, 126.6, 126.5, 123.7, 116.7, 81.4, 28.3, 16.8; **LRMS** (ESI+, *m/z*): 476.0 ([M(^{79}Br)+Na]$^+$), 478.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{20}BrNNaO_3S_2$ ([M(^{79}Br)+Na]$^+$) requires 475.99602, found 475.99584, ([M(^{81}Br)+Na]$^+$) requires 477.99397, found 477.99395; **IR** ν_{max} (film)/cm^{-1}: 3339, 3078, 2970, 2920, 2852, 2101, 1889, 1696, 1646, 1591, 1570, 1510, 1476, 1447, 1400, 1366, 1355, 1316, 1286, 1273, 1242, 1198, 1181, 1161, 1117, 1099, 1080, 1053, 1033.

tert-Butyl (_E_)-(4-bromo-2-(5-(methylthio)-3-oxopent-1-en-1-yl)phenyl)carbamate, 72d



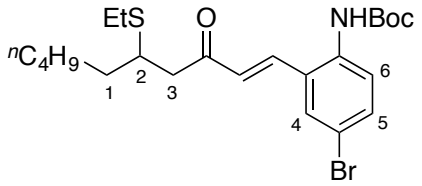
Compound **72d** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 3-(methylthio)propionaldehyde **71d** (25.0 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 16 hours at 55 °C. Flash column chromatography (SiO_2, 30-50% Et_2O in petrol) afforded enone **72d** as a pale yellow oil (33.6 mg, 42% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (1H, d, *J* 9.0, C(3)*H*), 7.68 (1H, d, *J* 16.0, C(O)CHC*H*), 7.66 (1H, d, *J* 2.5, C(1)*H*), 7.48 (1H, dd, *J* 9.0 and 2.5, C(2)*H*), 6.72 (1H, d, *J* 16.0, C(O)C*H*CH), 6.57 (1H, br. s, N*H*), 2.99 (2H, t, *J* 7.0, SCH_2), 2.86 (2H, t, *J* 7.0, C(O)CH_2), 2.18 (3H, s, SCH_3), 1.54 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.7, 152.7, 136.1, 135.9, 133.7, 129.7, 128.2, 127.9, 124.5, 117.3, 81.5, 41.7, 28.3 (2 × C), 15.9; **LRMS** (ESI+, *m/z*): 422.0 ([M(^{79}Br)+Na]$^+$), 424.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{22}BrNNaO_3S$ ([M(^{79}Br)+Na]$^+$) requires 422.03960, found 422.03970, ([M(^{81}Br)+Na]$^+$) requires 424.03755, found 424.03744; **IR** ν_{max} (film)/cm^{-1}: 3309, 2977, 2919, 2254, 1693, 1661, 1607, 1570, 1507, 1403, 1393, 1367, 1286, 1238, 1154, 1118, 1088, 1050, 1024.

tert-Butyl (_E_)-(4-bromo-2-(4-((ethylthio)methyl)-3-oxodec-1-en-1-yl)phenyl)carbamate, 72e



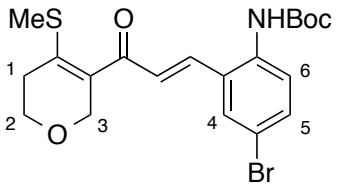
Compound **72e** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), aldehyde **71e** (48.6 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 3 hours at 55 °C. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded enone **72e** as a yellow oil (89.2 mg, 89% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.77 (1H, d, *J* 9.0, C(6)*H*), 7.71 (1H, d, *J* 15.5, C(O)CHC*H*), 7.66 (1H, d, *J* 2.5, C(4)*H*), 7.47 (1H, dd, *J* 9.0 and 2.5, C(5)*H*), 6.78 (1H, d, *J* 15.5, C(O)C*H*CH), 6.63 (1H, br. s, N*H*), 3.02-2.95 (1H, m, C(2)*H*), 2.87 (1H, dd, *J* 13.0 and 8.5, C(1)H_AH_B), 2.69 (1H, dd, *J* 13.0 and 5.5, C(1)H_AH_B), 2.56 (2H, qd, *J* 7.5 and 0.5, SCH_2CH_3), 1.78-1.58 (2H, m, C(3)H_2), 1.53 (9H, s, C(CH_3)$_3$), 1.32-1.24 (11H, m, 4 × CH_2, SCH_2CH_3), 0.88 (3H, t, *J* 7.0, $(CH_2)_4CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 201.5, 152.6, 136.3, 135.8, 133.6, 129.6, 128.0, 127.6, 124.2, 117.0, 81.4, 51.5, 32.9, 32.0, 31.6, 29.3, 28.3, 27.1, 26.8, 22.6, 14.7, 14.1; **LRMS** (ESI+, *m/z*): 520.2 ([M(^{79}Br)+Na]$^+$), 522.2 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{24}H_{36}BrNNaO_3S$ ([M+Na]$^+$) requires 520.14915, found 520.1493; **IR** ν_{max} (film)/cm^{-1}: 3308, 2957, 2926, 2855, 2361, 2342, 1729, 1692, 1603, 1571, 1507, 1456, 1404, 1392, 1367, 1311, 1287, 1234, 1154, 1117, 1083, 1049, 1024.

tert-Butyl (*E*)-(4-bromo-2-(5-(ethylthio)-3-oxodec-1-en-1-yl)phenyl)carbamate, 72f



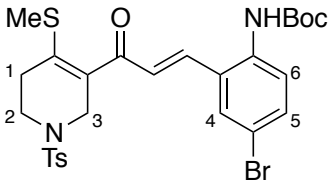
Compound **72f** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 3-(ethylthio)octanal **71f** (45.2 mg, 0.240 mmol),[45] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 3 hours at 55 °C. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded enone **72f** as a yellow oil (78.9 mg, 81% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (1H, d, *J* 9.0, C(6)*H*), 7.66 (1H, d, *J* 15.5, C(O)CHC*H*), 7.65 (1H, d, *J* 2.5, C(4)*H*), 7.46 (1H, dd, *J* 9.0 and 2.5, C(5)*H*), 6.71 (1H, d, *J* 15.5, C(O)C*H*CH), 6.62 (1H, br. s, N*H*), 3.22 (1H, ap. quintet, *J* 6.5, C(2)*H*), 2.96 (1H, dd, *J* 16.5 and 7.0, C(3)H_AH_B), 2.86 (1H, dd, *J* 16.5 and 6.5, C(3)H_AH_B), 2.58 (2H, q, *J* 7.5, SCH_2CH_3), 1.63-1.57 (2H, m, C(1)H_2), 1.53 (9H, s, $C(CH_3)_3$), 1.49-1.43 (2H, m, CH_2), 1.37-1.29 (4H, m, 2 × CH_2), 1.26 (3H, t, *J* 7.5, SCH_2CH_3), 0.90 (3H, t, *J* 7.0, $(CH_2)_3CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.9, 152.7, 136.2, 135.8, 133.6, 129.6, 128.7, 127.9, 124.4, 117.2, 81.4, 48.2, 40.8, 35.4, 31.7, 28.3, 26.5, 25.1, 22.6, 14.9, 14.1; **LRMS** (ESI+, *m/z*): 506.2 ([M(^{79}Br)+Na]$^+$), 508.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{34}BrNNaO_3S$ ([M(^{79}Br)Na]$^+$) requires 506.13350, found 506.13332, ([M(^{81}Br)Na]$^+$) requires 506.13145, found 506.13102; **IR** ν_{max} (film)/cm^{-1}: 3313, 2959, 2928, 2858, 1729, 1695, 1661, 1606, 1571, 1508, 1456, 1404, 1393, 1367, 1320, 1287, 1246, 1157, 1084, 1049, 1024.

tert-Butyl (_E_)-(4-bromo-2-(3-(4-(methylthio)-5,6-dihydro-2_H_-pyran-3-yl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72g



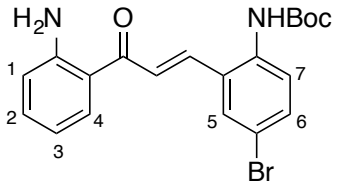
Compound **72g** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde **71g** (38.0 mg, 0.240 mmol),[60] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 30 minutes at room temperature. Flash column chromatography (SiO_2, 40-70% Et_2O in petrol) afforded enone **72g** as a yellow solid (73.0 mg, 80% yield); **m.p.**: 181-183 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.84 (1H, d, *J* 9.0, C(6)*H*), 7.76 (1H, d, *J* 15.0, C(O)CHC*H*), 7.63 (1H, d, *J* 2.5, C(4)*H*), 7.47 (1H, dd, *J* 9.0 and 2.5, C(5)*H*), 6.85 (1H, d, *J* 15.0, C(O)C*H*CH), 6.65 (1H, br. s, N*H*), 4.62 (2H, t, *J* 2.0, C(3)H_2), 3.90 (2H, t, *J* 5.5, C(1)H_2), 2.64 (2H, tt, *J* 5.5 and 2.0, C(2)H_2), 2.36 (3H, s, SCH_3), 1.54 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 186.7, 152.5, 151.0, 136.2, 136.0, 133.4, 129.5, 128.0, 127.7, 126.2, 123.6, 116.6, 81.4, 67.1, 64.1, 29.5, 28.3, 14.5; **LRMS** (ESI+, *m/z*): 476.0 ([M(^{79}Br)+Na]$^+$), 478.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{20}H_{24}BrNNaO_4S$ ([M(^{79}Br)+Na]$^+$) requires 476.05016, found 476.05014, ([M(^{81}Br)+Na]$^+$) requires 478.04812, found 478.04784 (^{81}Br); **IR** ν_{max} (film)/cm^{-1}**:** 3300, 2976, 2926, 2856, 2360, 2341, 1723, 1647, 1592, 1511, 1405, 1392, 1367, 1322, 1288, 1237, 1154, 1116, 1070, 1049, 1020, 1007.

tert-Butyl (_E_)-(4-bromo-2-(3-(4-(methylthio)-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72h



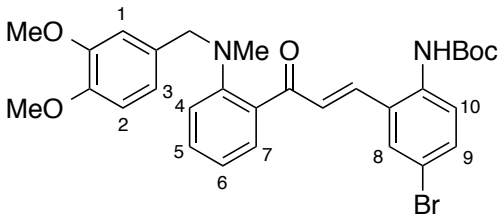
Compound **72h** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 4-(methylthio)-1-tosyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde **71h** (74.7 mg, 0.240 mmol),[60] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), and acetone (0.1 mL). Flash column chromatography (SiO_2, 30% EtOAc in petrol) afforded enone **72h** as an orange oil (69.7 mg, 57% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.83 (1H, d, *J* 9.0, C(6)*H*), 7.74 (2H, d, *J* 8.0, Ts*H*), 7.72 (1H, d, *J* 15.5, C(O)CHC*H*), 7.63 (1H, d, *J* 2.0, C(4)*H*), 7.48 (1H, dd, *J* 9.0 and 2.0, C(5)*H*), 7.37 (2H, d, *J* 8.0, Ts*H*), 6.93 (1H, d, *J* 15.5, C(O)C*H*CH), 6.69 (1H, br. s, N*H*), 4.02 (2H, s, C(3)*H*), 3.31 (2H, t, *J* 5.5, C(1)*H*), 2.70 (2H, t, *J* 5.5, C(2)*H*), 2.46 (3H, s, ArCH_3), 2.32 (3H, s, SCH_3), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 147.1, 142.7, 135.0, 134.8, 132.1, 131.6, 128.5, 128.2, 126.3 (2 × C), 125.5, 125.2, 122.3, 115.3; **LRMS** (ESI+, *m/z*): 629.0 ([M(^{79}Br)+Na]$^+$)), 631.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{27}H_{31}BrN_2NaO_5S_2$ ([M(^{79}Br)+Na]$^+$) requires 629.07500, found 629.07547, ([M(^{81}Br)+Na]$^+$) 631.07295, found 631.07231; **IR** ν_{max} (film)/cm^{-1}: 3336, 2978, 2926, 2855, 2361, 2341, 2254, 1722, 1647, 1594, 1508, 1463, 1404, 1393, 1365, 1342, 1320, 1289, 1236, 1159, 1117, 1094, 1049, 1023.

tert-Butyl (_E_)-(2-(3-(2-aminophenyl)-3-oxoprop-1-en-1-yl)-4-bromophenyl)carbamate, 72k



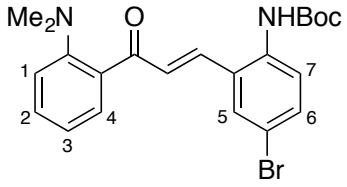
Compound **72k** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 2-aminobenzaldehyde **71k** (29.1 mg, 0.240 mmol),[46] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), and acetone (0.1 mL) at 55 °C. Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded enone **72k** as an orange-yellow solid (65.2 mg, 78% yield); **m.p.:** 172-174 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.87 (1H, dd, *J* 8.5 and 1.5, C(4)*H*), 7.86 (1H, m, C(7)*H*), 7.81 (1H, d, *J* 15.5, C(O)CHC*H*), 7.74 (1H, d, *J* 2.5, C(5)*H*), 7.58 (1H, d, *J* 15.5, C(O)C*H*CH), 7.49 (1H, dd, *J* 9.0 and 2.5, C(6)*H*), 7.34 (1H, ddd, *J* 8.5, 7.0 and 1.5, C(2)*H*), 6.76-6.72 (2H, m, C(1)*H*, C(3)*H*), 6.68 (1H, br. s, N*H*), 6.44 (2H, br. s, NH_2), 1.55 (9H, s, $C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 190.7, 152.7, 151.3, 136.0, 135.6, 134.8, 133.2, 131.0, 129.7, 128.2, 126.7, 123.8, 118.5, 117.4, 116.8, 116.1, 81.4, 28.3; **LRMS** (ESI–, *m/z*): 415.0 ($[M(^{79}Br)-H]^-$), 417.0 ($[M(^{81}Br)-H]^-$); **HRMS** (ESI-, *m/z*): $C_{20}H_{20}BrN_2O_3$ ($[M(^{79}Br)+H]^+$) requires 417.08083, found 417.08093, ($[M(^{79}Br)+H]^+$) requires 419.07879, found 419.07878; **IR** ν_{max} (film)/cm^{-1}: 3735, 3629, 3450, 3331, 2979, 2928, 2853, 2360, 2342, 1716, 1645, 1615, 1577, 1543, 1508, 1484, 1456, 1393, 1368, 1329, 1306, 1289, 1240, 1212, 1158, 1083, 1050, 1024, 1010.

tert-Butyl (_E_)-(4-bromo-2-(3-(2-((3,4-dimethoxybenzyl)(methyl)amino)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72l



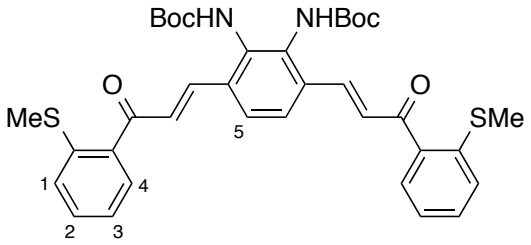
Compound **72l** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 2-((3,4-dimethoxybenzyl)(methyl)amino)benzaldehyde **71l** (68.5 mg, 0.240 mmol),[46] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 3 hours at 55 °C. Flash column chromatography (SiO_2, 20-40% Et_2O in petrol) afforded enone **72l** as an orange-yellow solid (107.8 mg, 93% yield); **m.p.**: 74-76 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.82 (1H, d, *J* 9.0, C(10)*H*), 7.80 (1H, d, *J* 15.5, C(O)CHC*H*), 7.70 (1H, d, *J* 2.5, C(8)*H*), 7.61 (1H, dd, *J* 8.0 and 1.5, C(7)*H*), 7.49 (1H, dd, *J* 9.0 and 2.5, C(9)*H*), 7.46 (1H, ddd, *J* 8.0, 7.0 and 2.0, C(5)*H*), 7.41 (1H, d, *J* 15.5, C(O)C*H*CH), 7.09-7.06 (2H, m, C(4)*H*, C(6)*H*), 6.74 (1H, d, *J* 8.0, C(2)*H*), 6.72 (1H, dd, *J* 8.0 and 1.5, C(3)*H*), 6.61 (1H, br. s, N*H*), 6.56 (1H, s, C(1)*H*), 4.16 (2H, s, CH_2), 3.84 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.74 (3H, s, NCH_3), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 194.2, 152.6, 151.9, 148.7, 148.2, 136.1, 134.5, 133.3, 132.8, 132.3, 130.5, 129.6, 129.5, 129.3, 128.2, 124.0, 121.5, 120.6, 119.1, 116.8, 111.3, 110.8, 81.4, 61.4, 55.80, 55.62, 41.1, 28.3; **LRMS** (ESI+, *m/z*): 581.2 ([M(^{79}Br)+Na]$^+$), 583.2 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{30}H_{33}BrN_2NaO_5$ ([M(^{79}Br)+Na]$^+$) requires 581.16456, found 581.16478, ([M(^{81}Br)+Na]$^+$) requires 583.16251, found 583.16288; **IR** ν_{max} (film)/cm^{-1}: 3323, 2978, 2934, 2835, 1724, 1660, 1597, 1514, 1464, 1452, 1420, 1392, 1367, 1320, 1261, 1236, 1156, 1025.

tert-Butyl (_E_)-(4-bromo-2-(3-(2-(dimethylamino)phenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 72m



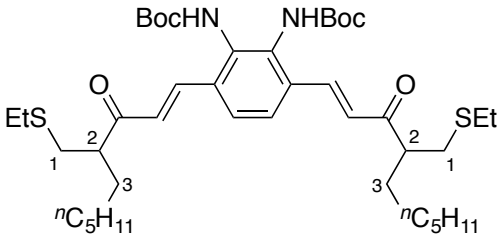
Compound **72m** was prepared according to General Procedure **F** using alkyne **51e** (59.2 mg, 0.200 mmol), 2-(dimethylamino)benzaldehyde **71m** (35.8 mg, 0.240 mmol),[46] $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 1 hour at 55 °C. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded enone **72m** as a yellow-orange solid (82.3 mg, 92% yield); **m.p.**: 118-120 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.83 (1H, d, *J* 7.5, C(7)*H*), 7.82 (1H, d, *J* 15.5, C(O)CHC*H*), 7.66 (1H, d, *J* 2.5, C(5)*H*), 7.58 (1H, dd, *J* 7.5 and 1.5, C(6)*H*), 7.48-7.43 (2H, m, C(2)*H*, C(4)*H*), 7.34 (1H, d, *J* 15.5, C(O)C*H*CH), 7.08 (1H, d, *J* 8.0, C(1)*H*), 7.02 (1H, td, *J* 7.5 and 1.0, C(3)*H*), 6.71 (1H, br. s, N*H*), 2.86 (6H, s, N(CH_3)$_2$), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 194.0, 152.7, 152.6, 136.0, 134.5, 133.1, 132.5, 131.6, 130.6, 129.7, 129.3, 128.2, 123.8, 120.7, 117.1, 116.8, 81.4, 44.7, 28.3; **LRMS** (ESI+, *m/z*): 425.1 ([M(^{79}Br)+H]$^+$), 427.1 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{26}BrN_2O_3$ ([M(^{79}Br)+H]$^+$) requires 445.11213, found 445.11227, ([M(^{81}Br)+H]$^+$) requires 447.11009, found 447.11026; **IR** ν_{max} (film)/cm^{-1}: 3304, 3066, 2978, 2931, 2868, 2841, 2794, 2250, 1726, 1657, 1599, 1571, 1505, 1454, 1433, 1402, 1393, 1367, 1322, 1285 1236, 1155, 1103, 1081, 1050, 1021.

Di-*tert*-butyl (3,6-bis((*E*)-3-(2-(methylthio)phenyl)-3-oxoprop-1-en-1-yl)-1,2-phenylene)dicarbamate, 76a



Compound **76a** was prepared according to General Procedure **F** using dialkyne **64** (71.3 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (73.1 mg, 0.480 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 15 minutes at 55 °C. Flash column chromatography (SiO_2, 0-100% Et_2O in petrol) afforded enone **76a** as a yellow solid (126.5 mg, 96% yield); **m.p.**: 158-160 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.82 (2H, d, *J* 16.0, C(O)CHC*H*), 7.75 (2H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.67 (2H, s, C(5)*H*), 7.49 (2H, td, *J* 7.5 and 1.5, C(2)*H*), 7.39 (2H, d, *J* 7.5, C(1)*H*), 7.34 (2H, d, *J* 16.0, C(O)C*H*CH), 7.25 (2H, td, *J* 7.5 and 1.0, C(3)*H*), 6.87 (2H, br. s, N*H*), 2.47 (6H, s, SCH_3), 1.50 (18H, br. s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.3, 153.9, 140.9, 139.8, 136.7, 134.5, 133.4, 131.7, 129.7, 127.1, 126.1, 125.3, 124.2, 81.2, 28.2, 16.4; **LRMS** (ESI+, *m/z*): 683.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{36}H_{40}N_2NaO_6S_2$ ([M+Na]$^+$) requires 683.22200, found 683.22168; **IR** ν_{max} (film)/cm^{-1}: 3270, 2978, 2922, 1706, 1655, 1597, 1559, 1512, 1468, 1433, 1367, 1323, 1253, 1205, 1167, 1016.

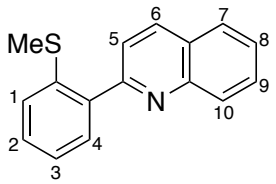
Di-*tert*-butyl (3,6-bis((*E*)-4-((ethylthio)methyl)-3-oxodec-1-en-1-yl)-1,2-phenylene)dicarbamate, 76b



Compound **76b** was prepared according to General Procedure **F** with dialkyne **64** (71.3 mg, 0.200 mmol), aldehyde **71e** (103.9 mg, 0.480 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.3 mL) for 1 hour at 55 °C. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded enone **76b** as a yellow oil (138.7 mg, 91% yield); (isolated as an indistinguishable pair of diasteromers) **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.79 (2H, d, *J* 16.0, C(O)CHC*H*), 7.60 (2H, s, Ar*H*), 6.84 (2H, br. s, N*H*), 6.82 (2H, d, *J* 16.0, C(O)C*H*CH), 3.02 (2H, tt, *J* 8.0 and 6.0, C(2)*H*), 2.85 (2H, dd, *J* 13.0 and 8.0, C(1)H_AH_B), 2.65 (2H, dd, *J* 13.0 and 6.0, C(1)H_AH_B), 2.53 (4H, q, *J* 7.5, SCH_2CH_3), 1.77-1.68 (2H, m, C(3)H_AH_B), 1.64-1.57 (2H, m, C(3)H_AH_B), 1.50 (18H, br. s, $C(CH_3)_3$), 1.31-1.22 (16H, m, $(CH_2)_4CH_3$), 1.24 (6H, t, *J* 7.5, SCH_2CH_3), 0.86 (6H, t, *J* 7.0, $(CH_2)_4CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 201.9, 153.9, 137.6, 134.2, 133.5, 127.9, 125.1, 81.3, 50.7, 33.0, 32.0, 31.6, 29.4, 28.2, 27.0, 26.8, 22.5, 14.7, 14.0; **MS**: no molecular ion was observed in ESI, EI/FI or MALDI experiments; **IR** ν_{max} (film)/cm^{-1}: 3255, 2958, 2927, 2856, 1693, 1604, 1561, 1521, 1471, 1456, 1391, 1367, 1313, 1278, 1254, 1174, 1111, 1072.

7.3.3 Quinoline-forming cyclisation reactions

General Procedure G - acidic cyclisation of 2-aminochalcones to quinolines, as exemplified by the synthesis of 2-(2-(Methylthio)phenyl)quinoline, 54a



To a solution of enone **52a** (740 mg, 2.00 mmol) in CH_2Cl_2 (50 mL) was added TFA (3.67 mL, 48.0 mmol), and the resulting solution stirred at ambient temperature for 16 hours. The reaction was quenched by the addition of 1.0 M $NaOH_{(aq)}$ (100 mL), and extracted three times with CH_2Cl_2 (3 × 100 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded quinoline **54a** as a pale brown solid (466 mg, 93% yield); **m.p.**: 69-71 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.12 (1H, d, *J* 8.0, C(6)*H*), 8.11 (1H, d, *J* 8.0, C(10)*H*), 7.77 (1H, dd, *J* 8.0 and 1.0, C(8)*H*), 7.65 (1H, td, *J* 7.5 and 1.5, C(9)*H*), 7.61 (1H, d, *J* 8.5, C(5)*H*), 7.49-7.45 (2H, m, C(7)*H*, C(4)*H*), 7.35-7.30 (2H, m, C(1)*H*, C(2)*H*), 7.20 (1H, td, C(3)*H*), 2.30 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.7, 147.8, 140.1, 137.8, 136.0, 130.1, 129.7, 129.6, 129.1, 127.6, 127.0, 126.6, 126.5, 125.2, 122.2, 16.7; **LRMS** (ESI+, *m/z*): 252.0 ($[M+H]^+$).

Alternatively:

To a solution of enone **81a** (299 mg, 1.00 mmol) in EtOH (15 mL) was added concentrated $HCl_{(aq)}$ (0.333 mL, 4.00 mmol) and Sn powder (356 mg, 3.00 mmol), and the resulting mixture refluxed for 20 hours. Once cooled to room temperature, the

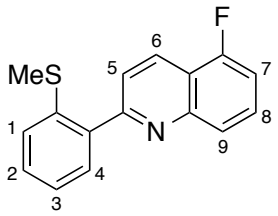
reaction was partitioned between CH_2Cl_2 (200 mL) and 1.0 M $NaOH_{(aq)}$ (200 mL). The organic layer was then washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **54a** as an off-white solid (178 mg, 70% yield).

Alternatively:

$[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol) and dcpm (4.1 mg, 10 μmol) were added to a microwave vial, which was then evacuated and backfilled with $N_{2(g)}$ three times. Then was added distilled and degassed acetone (0.4 mL), and the resulting suspension sonicated in order to solubilise the phosphine ligand. Once the solution was homogenous, $H_{2(g)}$ was bubbled through for 1 minute, followed by $N_{2(g)}$ until the volume was reduced to 0.1 mL. This resulting solution was transferred by syringe into a microwave vial containing 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol) and alkyne **51a** (43.5 mg, 0.200 mmol). The reaction mixture was stirred at the room temperature for 3 hours, then filtered through a short pad of SiO_2 and concentrated *in vacuo*. The resulting residue was dissolved in EtOH (1.5 mL), transferred to a fresh microwave vial, and H_2O (1.5 mL) added. The resulting suspension was heated at 170 °C under microwave conditions for 3 hours. Once the solution had cooled to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (20 mL) and 1.0 M $NaOH_{(aq)}$ (20 mL). The aqueous layer was then washed with CH_2Cl_2 (2 ×10 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **54a** as an off-white solid (40.1 mg, 80% yield).

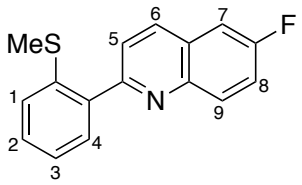
Data consistent with the literature.[279]

5-Fluoro-2-(2-(methylthio)phenyl)quinoline, 54b



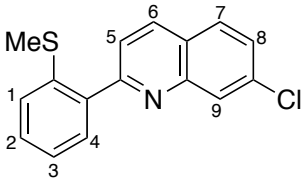
Compound **54b** was prepared according to General Procedure **G** using enone **52b** (80.5 mg, 0.208 mmol), TFA (0.380 mL, 4.98 mmol) and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded quinoline **54b** as a yellow oil (47.3 mg, 85% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.51 (1H, dd, *J* 8.5 and 1.0, C(5)*H*), 8.03 (1H, d, *J* 8.5, C(9)*H*), 7.79 (1H, d, *J* 8.5, C(6)*H*), 7.69 (1H, ddd, *J* 8.5, 8.0 and 6.0, C(8)*H*), 7.59 (1H, ddd, *J* 7.5, 1.0 and 0.5, C(4)*H*), 7.48-7.42 (2H, m, C(1)*H*, C(2)*H*), 7.33 (1H, ddd, *J* 7.5, 6.5 and 2.5, C(3)*H*), 7.25 (1H, ddd, *J* 9.5, 8.0 and 1.0, C(7)*H*), 2.43 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 159.5, 158.2 (d, *J* 254.5), 148.5 (d, *J* 3.0), 139.5, 137.8, 130.1, 129.4, 129.3 (d, *J* 4.5), 129.2 (d, *J* 8.0), 126.6, 125.4 (d, *J* 3.0), 125.2, 122.4, 117.7 (d, *J* 15.5), 110.2 (d, *J* 19.0), 16.7; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –123.0; **LRMS** (ESI+, *m/z*): 270.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{13}FNS$ ([M+H]$^+$) requires 270.07472, found 270.07471; **IR** ν_{max} (film)/cm^{-1}: 3062, 2982, 2920, 2858, 2358, 2234, 1632, 1599, 1565, 1555, 1506, 1470, 1434, 1408, 1376, 1350, 1315, 1273, 1235, 1208, 1157, 1129, 1094, 1059, 1050, 1010.

6-Fluoro-2-(2-(methylthio)phenyl)quinoline, 54c



Compound **54c** was prepared according to General Procedure **G** using enone **52c** (61.3 mg, 0.160 mmol), TFA (0.290 mL, 3.80 mmol) and CH_2Cl_2 (5.0 mL). No further purification was necessary. Quinoline **54c** was obtained as a pale yellow solid (41.6 mg, 97% yield); **m.p.**: 97-99 °C (crystallised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.12 (1H, dd, *J* 9.0 and 5.5, C(9)*H*), 8.08 (1H, d, *J* 8.5, C(5)*H*), 7.64 (1H, d, *J* 8.5 , C(6)*H*), 7.48-7.31 (5H, m, C(1)*H*, C(2)*H*, C(4)*H*, C(6)*H*, C(8)*H*), 7.21 (1H, app. td, *J* 7.0 and 2.0, C(3)*H*), 2.31 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.6 (d, *J* 248.5), 157.9 (d, *J* 2.5), 144.7, 139.5, 137.8, 135.5 (d, *J* 5.0), 132.0 (d, *J* 9.0), 130.1, 129.3, 127.6 (d, *J* 10.0), 126.6, 125.2, 123.0, 119.9 (d, *J* 25.5), 110.6 (d, *J* 21.5), 16.7; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –113.2; **LRMS** (ESI+, *m/z*): 270.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{13}FNS$ ([M+H]$^+$) requires 270.0747, found 270.0736; **IR** ν_{max} (film)/cm^{-1}: 2361, 1625, 1604, 1554, 1500, 1483, 1460, 1435, 1343, 1235, 1219, 1142, 1114, 1046.

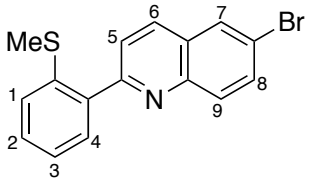
7-Chloro-2-(2-(methylthio)phenyl)quinoline, 54d



Compound **54d** was prepared according to General Procedure **G** using enone **52d** (60.0 mg, 0.150 mmol), TFA (0.27 mL, 3.57 mmol) and CH_2Cl_2 (5.0 mL). No further purification was necessary, with quinoline **54d** isolated as a pale yellow oil (40.3 mg,

94% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.13 (1H, br. s, C(9)*H*), 8.11 (1H, d, *J* 8.5, C(6)*H*), 7.70 (1H, d, *J* 8.5, C(7)*H*), 7.62 (1H, d, *J* 8.5, C(5)*H*), 7.47 (1H, d, *J* 7.0, C(4)*H*), 7.43 (1H, dd, *J* 8.5 and 2.0, C(8)*H*), 7.37-7.31 (2H, m, C(1)*H*, C(2)*H*), 7.21 (1H, td, *J* 7.0 and 2.0, C(3)*H*), 2.32 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 159.6, 147.9, 139.4, 137.9, 136.0, 135.6, 130.1, 129.4, 128.8, 128.5, 127.7, 126.6, 125.4, 125.2, 122.5, 16.7; **LRMS** (ESI+, *m/z*): 286.0 (^{35}Cl, $[M+H]^+$), 288.0 (^{37}Cl, $[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{13}ClNS$ (^{35}Cl, $[M+H]^+$) requires 286.0452, found 286.0450, (^{37}Cl, $[M+H]^+$) requires 288.0422, found 288.0419; **IR** ν_{max} (film)/cm^{-1}: 2920, 1610, 1597, 1497, 1468, 1435, 1405, 1331, 1247, 1134, 1088, 1067, 1046, 1034.

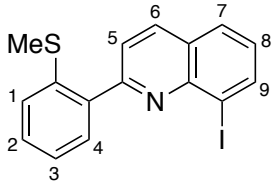
6-Bromo-2-(2-(methylthio)phenyl)quinoline, 54e



Compound **54e** was prepared according to General Procedure **G** using enone **52e** (63.1 mg, 0.140 mmol), TFA (0.260 mL, 3.38 mmol) and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 30% Et_2O in petrol) afforded quinoline **54e** as a pale yellow solid (32.5 mg, 70% yield); **m.p.**: 131-134 °C (crystalised from $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.05 (1H, d, *J* 8.5, C(6)*H*), 8.00 (1H, d, *J* 9.0, C(9)*H*), 7.94 (1H, d, *J* 2.0, C(7)*H*), 7.72 (1H, dd, *J* 9.0 and 2.0, C(8)*H*), 7.65 (1H, d, *J* 8.5, C(5)*H*), 7.48 (1H, dd, *J* 7.5 and 1.0, C(4)*H*), 7.37-7.31 (2H, m, C(1)*H*, C(2)*H*), 7.22 (1H, td, *J* 7.0 and 2.0, C(3)*H*), 2.32 (3H, s, SCH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): 157.9, 145.1, 138.3, 136.8, 134.1, 132.2, 130.1, 129.0, 128.5, 128.4, 127.0, 125.6, 124.2, 122.1, 119.5, 15.6; **LRMS** (ESI+, *m/z*): 330.0 (^{81}Br, $[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{13}BrNS$ (^{79}Br, $[M+H]^+$) requires 329.9947, found

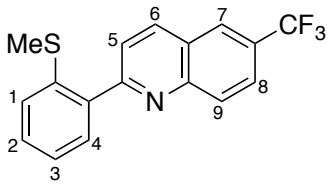
329.9940; (^{81}Br, $[M+H]^+$) requires 331.9926, found 329.9918; **IR** ν_{max} (film)/cm^{-1}: 2917, 1592, 1546, 1490, 1472, 1434, 1305, 1286, 1248, 1187, 1129, 1061, 1045.

8-Iodo-2-(2-(methylthio)phenyl)quinoline, 54f



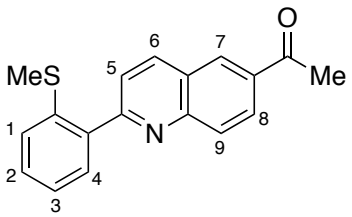
Compound **54f** was prepared according to General Procedure **G** using enone **52f** (92.7 mg, 0.187 mmol), TFA (0.340 mL, 4.49 mmol), and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 50% CH_2Cl_2 in petrol) afforded enone **54f** as a pale yellow oil (59.3 mg, 84% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.39 (1H, dd, *J* 7.5 and 1.5, C(7)*H*), 8.16 (1H, d, *J* 8.5, C(6)*H*), 7.85 (1H, dd, *J* 8.0 and 1.5, C(9)*H*), 7.83 (1H, d, *J* 8.5, C(5)*H*), 7.73 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.49-7.44 (2H, m, C(1)*H*, C(2)*H*), 7.34 (1H, ddd, *J* 7.5, 6.5 and 2.5, C(3)*H*), 7.28 (1H, dd, *J* 8.0 and 7.5, C(8)*H*), 2.47 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 159.3, 146.6, 140.2, 139.3, 138.3, 136.7, 130.9, 129.3, 128.4, 127.64, 127.51, 127.0, 125.1, 123.0, 103.9, 17.3; **LRMS** (ESI+, *m/z*): 378.0 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{12}INNaS$ ($[M+Na]^+$) requires 377.98079, found 377.98080; **IR** ν_{max} (film)/cm^{-1}: 3053, 2919, 2854, 1595, 1534, 1497, 1467, 1435, 1420, 1316, 1288, 1267, 1249, 1199, 1143, 1090, 1058, 1045, 1031.

2-(2-(Methylthio)phenyl)-6-(trifluoromethyl)quinoline, 54g



Compound **54g** was prepared according to General Procedure **G** using enone **52g** (72.6 mg, 0.170 mmol), TFA (0.300 mL, 3.98 mmol) and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 50% Et_2O in petrol) afforded quinoline **54g** as a pale yellow solid (41.5 mg, 76% yield); **m.p.**: 98-101 °C (crystalised from $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.24 (1H, d, *J* 8.5, C(9)*H*), 8.23 (1H, d, *J* 8.0, C(6)*H*), 8.10 (1H, s, C(7)*H*), 7.84 (1H, dd, *J* 9.0 and 2.0, C(8)*H*), 7.75 (1H, d, *J* 8.5, C(5)*H*), 7.50 (1H, dd, *J* 7.5 and 1.0, *C*(4)*H*), 7.39-7.33 (2H, m, C(1)*H*, C(2)*H*), 7.23 (1H, td, *J* 7.0 and 2.0, C(3)*H*), 2.33 (3H, s, SCH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): 159.7, 147.5, 138.1, 136.9, 135.9, 129.6, 129.1, 128.6, 127.4 (q, *J* 32.5), 125.7, 124.9, 125.6-125.4 (2 × C, m), 124.2, 123.0 (q, *J* 272.5), 122.5, 15.7; **^{19}F-NMR** (376 MHz, $CDCl_3$) {^{1}H}: –62.3; **LRMS** (ESI+, *m/z*): 320.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{13}F_3NS$ ($[M+H]^+$) requires 320.0715, found 320.0708; **IR** ν_{max} (film)/cm^{-1}: 2923, 1633, 1601, 1490, 1463, 1436, 1394, 1320, 1302, 1284, 1195, 1164, 1116, 1063.

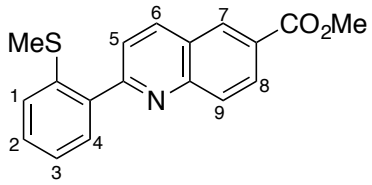
1-(2-(2-(Methylthio)phenyl)quinolin-6-yl)ethan-1-one, 54h



Compound **54h** was prepared according to General Procedure **G** using enone **52h** (78.0 mg, 0.190 mmol), TFA (0.350 mL, 4.56 mmol) and CH_2Cl_2 (4.8 mL). Flash column chromatography (SiO_2, 40-60% Et_2O in petrol) afforded quinoline **54h** as a pale yellow

solid (54.5 mg, 98% yield); **m.p.**: 130-132 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.49 (1H, d, *J* 2.0, C(7)*H*), 8.32 (1H, d, *J* 8.5, C(6)*H*), 8.30 (1H, dd, *J* 9.0 and 2.0, C(8)*H*), 8.24 (1H, d, *J* 9.0, C(9)*H*), 7.79 (1H, d, *J* 8.5, C(5)*H*), 7.59 (1H, dd, *J* 7.5 and 1.0, C(4)*H*), 7.47-7.41 (2H, m, C(1)*H*, C(2)*H*), 7.31 (1H, ddd, *J* 7.5, 6.5 and 2.0, C(3)*H*), 2.76 (3H, s, C(O)CH_3), 2.41 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.5, 160.9, 149.6, 139.3, 138.0, 137.4, 134.8, 130.12, 130.09, 129.58, 129.53, 128.0, 126.6, 126.1, 125.2, 123.1, 26.8, 16.7; **LRMS** (ESI+, *m/z*): 294.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{18}H_{16}NOS$ ([M+H]$^+$) requires 294.09471, found 294.09468; **IR** ν_{max} (film)/cm^{-1}: 3059, 2919, 2850, 1679, 1617, 1595, 1490, 1458, 1434, 1393, 1356, 1291, 1257, 1186, 1046.

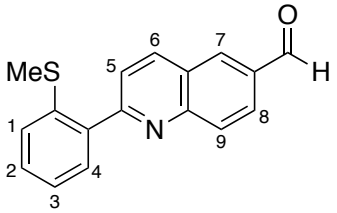
Methyl 2-(2-(methylthio)phenyl)quinoline-6-carboxylate, 54i



Compound **54i** was prepared according to General Procedure **G** using enone **52i** (42.5 mg, 0.100 mmol), TFA (0.180 mL, 2.39 mmol) and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 50% Et_2O in petrol) afforded quinoline **54i** as a pale yellow oil (28.8 mg, 93% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.55 (1H, d, *J* 1.5, C(7)*H*), 8.25 (1H, dd, *J* 9.0 and 2.0, C(8)*H*), 8.24 (1H, d, *J* 8.5, C(6)*H*), 8.16 (1H, d, *J* 9.0, C(9)*H*), 7.71 (1H, d, *J* 8.5, C(5)*H*), 7.51 (1H, d, *J* 7.5, C(4)*H*), 7.38-7.32 (2H, m, C(1)*H*, C(2)*H*), 7.23 (1H, td, *J* 7.0 and 2.0, C(3)*H*), 3.93 (3H, s, CO_2CH_3), 2.33 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 165.6, 159.7, 148.4, 138.2, 136.9, 136.6, 129.7, 129.1, 128.7, 128.5, 128.2, 127.0, 125.6, 125.1, 124.2, 122.0, 51.4, 15.7; **LRMS** (ESI+, *m/z*): 310.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*):

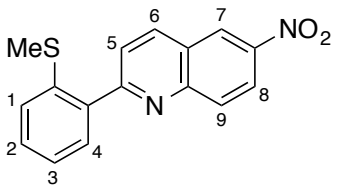
$C_{18}H_{16}NO_2S$ ([M+H]$^+$) requires 310.0896, found 310.0890; **IR** ν_{max} (film)/cm^{-1}: 1720, 1623, 1597, 1459, 1435, 1292, 1265, 1195, 1096.

2-(2-(Methylthio)phenyl)quinoline-6-carbaldehyde, 54j



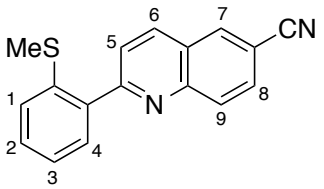
Compound **54j** was prepared according to General Procedure **G** using enone **52j** (69.1 mg, 0.174 mmol), TFA (0.320 mL, 4.18 mmol) and CH_2Cl_2 (4.4 mL). Flash column chromatography (SiO_2, 40-60% Et_2O in petrol) afforded quinoline **54j** as a pale yellow solid (45.2 mg, 93% yield); **m.p.**: 127-129 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 10.22 (1H, s, C*H*O), 8.39 (1H, s, C(7)*H*), 8.38 (1H, d, *J* 8.5, C(6)*H*), 8.29 (1H, d, *J* 8.5, C(9)*H*), 8.23 (1H, dd, *J* 8.5 and 1.5, C(8)*H*), 7.84 (1H, d, *J* 8.5, C(5)*H*), 7.61 (1H, d, *J* 7.0, C(4)*H*), 7.49-7.43 (2H, m, C(1)*H*, C(2)*H*), 7.33 (1H, ddd, *J* 7.5, 7.0 and 2.0, C(3)*H*), 2.43 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 191.6, 161.5, 150.4, 139.2, 138.0, 137.3, 134.3, 133.3, 130.8, 130.1, 129.6, 127.0, 126.7, 126.4, 125.2, 123.4, 16.7; **LRMS** (ESI+, *m/z*): 280.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{14}NOS$ ([M+H]$^+$) requires 280.07906, found 280.07907; **IR** ν_{max} (film)/cm^{-1}: 3059, 2919, 2830, 1696, 1621, 1596, 1495, 1459, 1435, 1226, 1154, 1045.

2-(2-(Methylthio)phenyl)-6-nitroquinoline, 54k



Compound **54k** was prepared according to General Procedure **G** using enone **52k** (78.6 mg, 0.190 mmol), TFA (0.350 mL, 4.56 mmol), and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, CH_2Cl_2) afforded enone **54k** as a yellow solid (48.4 mg, 86% yield); **m.p.**: 185-187 °C (crystalised from CH_2Cl_2); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.86 (1H, d, *J* 2.5, C(7)*H*), 8.53 (1H, dd, *J* 9.0 and 2.5, C(8)*H*), 8.43 (1H, d, *J* 8.5, C(6)*H*), 8.35 (1H, d, *J* 9.0, C(9)*H*), 7.93 (1H, d, *J* 8.5, C(5)*H*), 7.63 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.50 (1H, ddd, *J* 8.0, 7.0 and 1.5, C(2)*H*), 7.46 (1H, dd, *J* 8.0 and 1.5, C(1)*H*), 7.36 (1H, ddd, *J* 7.5, 7.0 and 1.5, C(3)*H*), 2.46 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 162.1, 149.7, 145.5, 138.7, 138.1, 137.7, 131.2, 130.2, 130.0, 126.8, 125.7, 125.3, 124.34, 124.15, 123.2, 16.7; **LRMS** (ESI+, *m/z*): 297.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{13}N_2O_2S$ ($[M+H]^+$) requires 297.06922, found 297.06924; **IR** ν_{max} (film)/cm^{-1}: 3084, 3056, 2925, 2855, 1619, 1606, 1587, 1564, 1553, 1524, 1487, 1453, 1428, 1346, 1334, 1307, 1286, 1248, 1236, 1205, 1154, 1131, 1080, 1045, 1034.

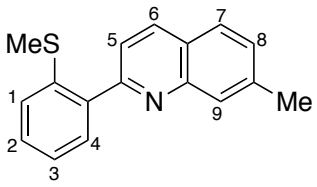
2-(2-(Methylthio)phenyl)quinoline-6-carbonitrile, 54l



Compound **54l** was prepared according to General Procedure **G** using enone **52l** (73.3 mg, 0.186 mmol), TFA (0.340 mL, 4.46 mmol), and CH_2Cl_2 (5.0 mL). Flash column

chromatography (SiO_2, 50-100% CH_2Cl_2 in petrol) afforded quinoline **54l** as an off-white solid (43.3 mg, 85% yield); **m.p.**: 145-147 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.29-8.26 (3H, m, C(6)*H*, C(7)*H*, C(9)*H*), 7.89 (1H, dd, *J* 9.0, 2.0, C(8)*H*), 7.87 (1H, d, *J* 8.5, C(5)*H*) 7.60 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.48 (1H, ddd, *J* 8.0, 7.0, 1.5, C(2)*H*), 7.45 (1H, dd, *J* 8.0 and 1.5, C(1)*H*), 7.34 (1H, ddd, *J* 7.5, 7.0 and 1.5, C(3)*H*), 2.44 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 161.6, 148.6, 138.9, 138.0, 136.2, 133.8, 131.0, 130.4, 130.1, 129.8, 126.7, 126.3, 125.3, 123.9, 118.7, 110.1, 16.7; **LRMS** (ESI+, *m/z*): 277.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{13}N_2S$ ([M+H]$^+$) requires 277.07940, found 277.07934; **IR** ν_{max} (film)/cm^{-1}: 3060, 2920, 2851, 2227, 1619, 1595, 1567, 1556, 1490, 1457, 1433, 1393, 1341, 1310, 1291, 1242, 1160, 1138, 1086, 1045, 1033.

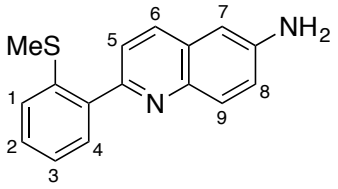
7-Methyl-2-(2-(methylthio)phenyl)quinoline, 54m



Compound **54m** was prepared according to General Procedure **G** using enone **52m** (31.2 mg, 81.3 μmol), TFA (0.150 mL, 1.95 mmol) and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 30% Et_2O in petrol) afforded quinoline **54m** as a pale yellow oil (20.0 mg, 94% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.09 (1H, d, *J* 8.5, C(6)*H*), 7.91 (1H, br. s, C(9)*H*), 7.67 (1H, d, *J* 8.5, C(7)*H*), 7.55 (1H, d, *J* 8.5, C(5)*H*), 7.48 (1H, d, *J* 7.5, C(4)*H*), 7.36-7.31 (3H, m, C(1)*H*, C(2)*H*, C(8)*H*), 7.21 (1H, td, *J* 6.5 and 3.0, C(3)*H*), 2.50 (3H, s, ArCH_3), 2.31 (3H, s, SCH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): 158.6, 147.9, 140.0, 137.8, 135.8, 130.0, 129.1, 128.9, 128.6, 127.2, 126.5, 125.5, 125.09, 125.06, 121.4, 22.0, 16.7; **LRMS** (ESI+, *m/z*): 266.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{16}NS$ ([M+H]$^+$) requires 266.0998,

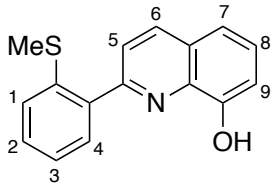
found 266.0996; **IR** ν_{max} (film)/cm^{-1}: 2989, 2361, 1625, 1598, 1508, 1471, 1436, 1311, 1240, 1146, 1086, 1046.

2-(2-(Methylthio)phenyl)quinolin-6-amine, 54n



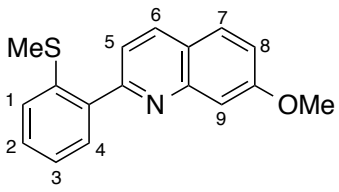
Compound **54n** was prepared according to General Procedure **G** using enone **52n** (87.0 mg, 0.180 mmol), TFA (0.330 mL, 4.30 mmol), and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 20% EtOAc in CH_2Cl_2) afforded enone **54n** as a brown oil (45.3 mg, 95% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (1H, dt, *J* 9.0 and 0.5, C(9)*H*), 7.96 (1H, ddd, *J* 8.5, 1.0 and 0.5, C(6)*H*), 7.59 (1H, d, *J* 8.5, C(5)*H*), 7.57-7.55 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.43-7.39 (2H, m, C(1)*H*, C(2)*H*), 7.29 (1H, ddd, *J* 7.5, 5.5 and 3.0, C(3)*H*), 7.17 (1H, dd, *J* 9.0 and 2.5, C(8)*H*), 6.93 (1H, d, *J* 2.5, C(7)*H*), 4.01 (2H, br. s, NH_2), 2.41 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 155.0, 144.8, 142.8, 140.3, 137.7, 133.8, 130.7, 130.0, 128.7, 128.5, 126.3, 125.0, 122.4, 121.7, 107.3, 16.6; **LRMS** (ESI+, *m/z*): 267.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{15}N_2S$ ([M+H]$^+$) requires 267.09505, found 267.09504; **IR** ν_{max} (film)/cm^{-1}: 3453, 3333, 3210, 3052, 2920, 2854, 1627, 1595, 1556, 1500, 1461, 1434, 1384, 1350, 1317, 1268, 1247, 1175, 1127, 1087, 1045, 1034.

2-(2-(Methylthio)phenyl)quinolin-8-ol, 54o



Compound **54o** was prepared according to General Procedure **G** using enone **52o** (69.0 mg, 0.179 mmol), TFA (0.330 mL, 4.30 mmol), and CH_2Cl_2 (5.0 mL). Flash column chromatography (SiO_2, 20% EtOAc in CH_2Cl_2) afforded quinoline **54o** as a cream solid (42.5 mg, 89% yield); **m.p.**: 108-110 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.44 (1H, br. s, O*H*), 8.25 (1H, d, *J* 8.5, C(6)*H*), 7.81 (1H, d, *J* 8.5, C(5)*H*), 7.70 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.52-7.47 (3H, m, C(1)*H*, C(2)*H*, C(8)*H*), 7.39 (1H, dd, *J* 8.0 and 1.0, C(7)*H*), 7.34 (1H, ddd, *J* 7.5, 6.0 and 3.0, C(3)*H*), 7.25 (1H, dd, *J* 7.5 and 1.0, C(9)*H*), 2.48 (3H, s, (SC*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 155.7, 152.5, 138.5, 138.1, 137.3, 136.4, 130.1, 129.4, 127.9, 127.1, 126.1, 124.8, 122.1, 117.6, 110.3, 16.7; **LRMS** (ESI+, *m/z*): 268.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{13}NNaOS$ ([M+Na]$^+$) requires 268.07906, found 268.07897; **IR** ν_{max} (film)/cm^{-1}: 3379, 3053, 2919, 2851, 1597, 1573, 1557, 1504, 1471, 1434, 1401, 1366, 1327, 1294, 1275, 1245, 1204, 1163, 1085, 1051.

7-Methoxy-2-(2-(methylthio)phenyl)quinoline, 54p



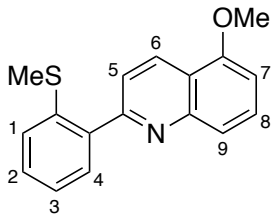
Compound **54p** was prepared according to General Procedure **G** using enone **52p** (41.4 mg, 0.104 mmol), TFA (0.190 mL, 2.48 mmol) and CH_2Cl_2 (2.5 mL). Flash column chromatography (SiO_2, 30-40% Et_2O in petrol) afforded quinoline **54p** as a cream solid

(22.7 mg, 71 % yield); **m.p.**: 180-182 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.16 (1H, d, *J* 8.5, C(6)*H*), 7.76 (1H, d, *J* 9.0, C(7)*H*), 7.58 (1H, d, *J* 8.5, C(5)*H*), 7.56 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.54 (1H, d, *J* 2.5, C(9)*H*), 7.46-7.40 (2H, m, C(1)*H*, C(2)*H*), 7.31 (1H, ddd, *J* 7.5, 6.5 and 2.0, C(3)*H*), 7.24 (1H, dd, *J* 9.0 and 2.5, C(8)*H*), 3.99 (3H, s, OCH_3), 2.43 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.9, 158.9, 149.4, 140.1, 137.7, 135.7, 129.9, 129.0, 128.5, 126.3, 125.0, 122.2, 119.99, 119.85, 107.5, 55.6, 16.6; **LRMS** (ESI+, *m/z*): 282.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{16}NOS$ ($[M+H]^+$) requires 282.09471, found 282.09470; **IR** ν_{max} (film)/cm^{-1}: 3058, 2961, 2919, 2835, 1621, 1599, 1509, 1455, 1434, 1384, 1336, 1274, 1258, 1216, 1174, 1138, 1121, 1028.

Alternatively:

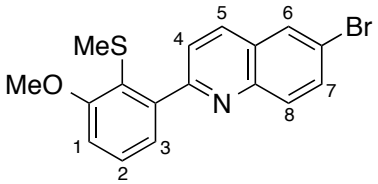
Under a $N_{2(g)}$ atmosphere, to a solution of enone **81b** (83.0 mg, 0.250 mmol) in MeOH (1.5 mL) was added sat. $NH_4Cl_{(aq)}$ (0.5 mL) and In powder (144 mg, 1.25 mmol), and the resulting mixture refluxed for 4 hours. Once cooled to room temperature, the reaction was partitioned between EtOAc (50 mL) and 1.0 M $NaOH_{(aq)}$ (50 mL). The organic layer was then washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 30-40% Et_2O in petrol) afforded quinoline **54p** as a cream solid (53.9 mg, 77% yield).

5-Methoxy-2-(2-(methylthio)phenyl)quinoline, 54q



Compound **54q** was prepared according to General Procedure **G** using enone **52q** (29.3 mg, 73.3 μmol), TFA (0.135 mL, 1.75 mmol), and CH_2Cl_2 (2.0 mL). Flash column chromatography (SiO_2, CH_2Cl_2) afforded quinoline **54q** as a pale yellow oil (15.1 mg, 73% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.66 (1H, dd, *J* 8.5 and 1.0, C(6)*H*), 7.81 (1H, d, *J* 8.5, C(9)*H*), 7.70 (1H, d, *J* 8.5, C(5)*H*), 7.67 (1H, dd, *J* 8.5 and 8.0, C(8)*H*), 7.59 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.46-7.41 (2H, m, C(1)*H*, C(2)*H*), 7.31 (1H, ddd, *J* 7.5, 6.0 and 2.5, C(3)*H*), 6.91 (1H, dd, *J* 8.0 and 0.5, C(7)*H*), 4.06 (3H, s, OCH_3), 2.42 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.9, 155.2, 148.5, 140.0, 137.8, 130.9, 130.1, 129.6, 129.1, 126.5, 125.1, 121.7, 121.3, 119.5, 104.4, 55.8, 16.7; **LRMS** (ESI+, *m/z*): 282.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{16}NOS$ ([M+H]$^+$) requires 282.09471, found 282.09469; **IR** ν_{max} (film)/cm^{-1}: 3059, 3004, 2962, 2919, 2849, 1618, 1594, 1568, 1505, 1471, 1437 1407, 1378, 1347, 1314, 1257, 1248, 1211, 1168, 1152, 1105, 1082, 1069, 1046.

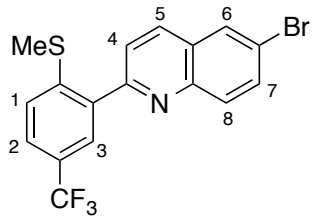
6-Bromo-2-(3-methoxy-2-(methylthio)phenyl)quinoline, 73a



Compound **73a** was prepared according to General Procedure **G** using enone **72a** (63.0 mg, 0.132 mmol), TFA (0.240 mL, 3.17 mmol) and CH_2Cl_2 (3.3 mL) at 55 °C. Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded quinoline **73a** as an off-

white solid (41.6 mg, 88% yield); **m.p.**: 136-138 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.10 (1H, d, *J* 8.5, C(5)*H*), 8.05 (1H, d, *J* 9.0, C(8)*H*), 8.04 (1H, d, *J* 2.5, C(6)*H*), 7.81 (1H, dd, *J* 9.0 and 2.5, C(7)*H*), 7.68 (1H, d, *J* 8.5, C(4)*H*), 7.43 (1H, dd, *J* 8.5 and 7.5, C(2)*H*), 7.22 (1H, dd, *J* 7.5 and 1.5, C(3)*H*), 7.03 (1H, dd, *J* 8.5 and 1.5, C(1)*H*), 4.01 (3H, s, OCH_3), 2.24 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.2, 160.0, 146.3, 146.0, 134.0, 132.9, 131.3, 129.6, 129.3, 128.2, 124.3, 122.9, 122.6, 120.3, 111.4, 56.2, 18.6; **LRMS** (ESI+, *m/z*): 360.0 ([M(^{79}Br)+H]$^+$), 362.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{15}BrNOS$ ([M(^{79}Br)+H]$^+$) requires 360.00522, found 360.00516, ([M(^{81}Br)+H]$^+$) requires 362.00318, found 362.00288; **IR** ν_{max} (film)/cm^{-1}: 3061, 3001, 2959, 2922, 2835, 1595, 1583, 1567, 1546, 1489, 1470, 1457, 1437, 1423, 1374, 1334, 1303, 1259, 1186, 1040.

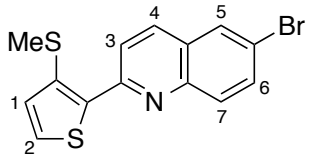
6-Bromo-2-(2-(methylthio)-5-(trifluoromethyl)phenyl)quinoline, 73b



Compound **73b** was prepared according to General Procedure **G** using enone **72b** (70.3 mg, 0.136 mmol), TFA (0.250 mL, 3.26 mmol) and CH_2Cl_2 (3.4 mL). Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded quinoline **73b** as a white solid (50.5 mg, 93% yield); **m.p.**: 102-104 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.18 (1H, d, *J* 8.5, C(5)*H*), 8.07 (1H, d, *J* 9.0, C(8)*H*), 8.06 (1H, d, *J* 2.0, C(6)*H*), 7.85 (1H, dd, *J* 9.0 and 2.0, C(7)*H*), 7.82 (1H, d, *J* 2.0, C(3)*H*), 7.75 (1H, d, *J* 8.5, C(4)*H*), 7.68 (1H, dd, *J* 8.5 and 2.0, C(2)*H*), 7.47 (1H, d, *J* 8.5, C(1)*H*), 2.48 (3H, s, SCH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): 157.5, 146.3, 143.3, 139.1, 135.5, 133.4, 131.3, 129.6, 128.2, 127.0 (q,

J 33.0), 126.7 (q, *J* 4.0), 125.8 (q, *J* 3.5), 125.5, 124.1 (q, *J* 272.0), 122.6, 121.0, 16.1; **^{19}F-NMR** (470 MHz, $CDCl_3$) {^{1}H}: –62.2; **LRMS** (ESI+, *m/z*): 398.0 ([M(^{79}Br)+H]$^+$), 400.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{11}BrF_3NNaS$ ([M(^{79}Br)+Na]$^+$) requires 397.98204, found 397.98200, ([M(^{81}Br)+Na]$^+$) requires 399.98000, found 399.97974; **IR** ν_{max} (film)/cm^{-1}: 2922, 2855, 1610, 1591, 1548, 1490, 1409, 1378, 1339, 1326, 1263, 1235, 1173, 1144, 1121, 1099, 1067, 1060, 1046.

General Procedure H- thermal cyclisation of 2-aminochalcones to quinolines as exemplified by the synthesis of 6-Bromo-2-(3-(methylthio)thiophen-2-yl)quinoline, 73c



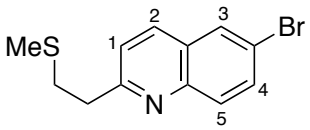
In a microwave vial, to enone **72c** (41.3 mg, 90.9 μmol), was added EtOH (1.5 mL) and H_2O (1.5 mL). The resulting suspension was heated at 170 °C under microwave conditions for 3 hours. Once the solution had cooled to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (20 mL) and 1.0 M $NaOH_{(aq)}$ (20 mL). The aqueous layer was then washed with CH_2Cl_2 (2 ×10 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **73c** as a cream solid (27.7 mg, 91% yield); **m.p.**: 142-144 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.12 (1H, d, *J* 9.0, C(4)*H*), 8.07 (1H, d, *J* 9.0, C(3)*H*), 8.01 (1H, d, *J* 9.0, C(7)*H*), 7.95 (1H, d, *J* 2.0, C(5)*H*), 7.78 (1H, dd, *J* 9.0 and 2.0, C(6)*H*), 7.48 (1H, d, *J* 5.5, C(1)*H*), 7.14 (1H, d, *J* 5.5, C(2)*H*), 2.58 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.9, 146.3, 136.0,

135.4, 134.7, 133.2, 130.8, 129.5, 128.9, 127.6, 127.3, 120.5, 119.9, 18.1; **LRMS** (ESI+, *m/z*): 336.0 ([M(^{79}Br)+H]$^+$), 338.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{14}H_{11}BrNS_2$ ([M(^{79}Br)+H]$^+$) requires 335.95108, found 335.95120, ([M(^{81}Br)+H]$^+$) requires 337.94903, found 337.94882; **IR** ν_{max} (film)/cm^{-1}: 3082, 3058, 2985, 2918, 2855, 1589, 1541, 1501, 1488, 1458, 1439, 1413, 1382, 1351, 1317, 1266, 1236, 1192, 1164, 1128, 1095, 1058.

Alternatively:

Compound **73c** was prepared according to General Procedure **G** using enone **72c** (67.7 mg, 0.149 mmol), TFA (0.270 mL, 3.58 mmol) and CH_2Cl_2 (3.8 mL). Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **73c** as a cream solid (42.6 mg, 85% yield).

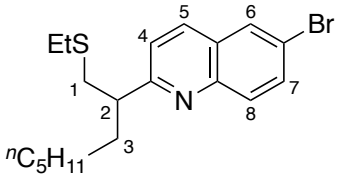
6-Bromo-2-(2-(methylthio)ethyl)quinoline, 73d



Compound **73d** was prepared according to General Procedure **G** using enone **72d** (37.0 mg, 92.4 μmol), TFA (170 μL, 2.20 mmol) and CH_2Cl_2 (2.3 mL). Flash column chromatography (SiO_2, 30% Et_2O in petrol) afforded quinoline **73d** as a pale brown oil (15.0 mg, 58% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.02 (1H, d, *J* 8.5, C(2)*H*), 7.97 (1H, d, *J* 2.0, C(3)*H*), 7.93 (1H, d, *J* 9.0, C(5)*H*), 7.77 (1H, dd, *J* 9.0 and 2.0, C(4)*H*), 7.37 (1H, d, *J* 8.5, C(1)*H*), 3.28 (2H, t, *J* 7.5, ArCH_2), 3.03 (2H, t, *J* 7.5, SCH_2), 2.18 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 161.1, 146.6, 135.3, 132.9, 130.7, 129.6, 128.0, 122.4, 119.7, 38.8, 33.5, 15.8; **LRMS** (ESI+, *m/z*): 282.0 ([M(^{79}Br)+H]$^+$), 284.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+,

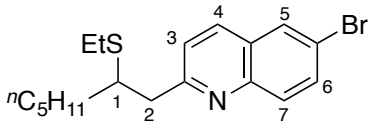
m/z): $C_{12}H_{13}BrNS$ ([M(^{79}Br)+H]$^+$) requires 281.99466, found 281.99479, ([M(^{81}Br)+H]$^+$) requires 283.99261, found 283.99259; **IR** ν_{max} (film)/cm^{-1}: 3053, 2963, 2915, 2266, 2026, 1929, 1596, 1556, 1488, 1462, 1387, 1334, 1301, 1277, 1217, 1186, 1134, 1117, 1059, 1012.

6-Bromo-2-(1-(ethylthio)octan-2-yl)quinoline, 73e



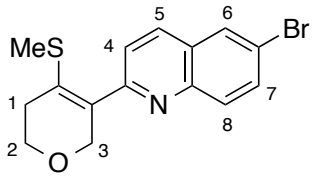
Compound **73e** was prepared according to General Procedure **G** using enone **72e** (62.5 mg, 0.125 mmol), TFA (0.230 mL, 3.00 mmol) and CH_2Cl_2 (3.2 mL). Flash column chromatography (SiO_2, 10% Et_2O in petrol) afforded quinoline **73e** as a pale yellow oil (34.0 mg, 71% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (1H, d, *J* 8.5, C(5)*H*), 7.97-7.94 (2H, m, C(6)*H*, C(8)*H*), 7.76 (1H, dd, *J* 9.0 and 2.0, C(7)*H*), 7.33 (1H, d, *J* 8.5, C(4)*H*), 3.17 (1H, ap. tt, *J* 8.0 and 6.0, C(2)*H*), 3.07 (1H, dd, *J* 12.5 and 8.0, C(1)H_AH_B), 2.95 (1H, dd, *J* 12.5 and 6.0, C(1)H_AH_B), 2.47 (2H, qd, *J* 7.5 and 1.0, SCH_2CH_3), 1.95-1.82 (2H, m, C(3)H_2), 1.31-1.19 (8H, m, 4 × CH_2), 1.21 (1H, d, *J* 7.5, SCH_2CH_3), 0.85 (3H, t, *J* 7.0, $(CH_2)_4CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 164.8, 146.6, 135.0, 132.6, 131.0, 129.5, 128.2, 121.9, 119.5, 48.8, 37.0, 35.0, 31.7, 29.3, 27.4, 26.6, 22.6, 14.7, 14.0; **LRMS** (ESI+, *m/z*): 380.1 ([M(^{79}Br)+H]$^+$), 382.1 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{27}BrNS$ ([M(^{79}Br)+H]$^+$) requires 380.10421, found 380.10435, ([M(^{81}Br)+H]$^+$) requires 382.10216, found 382.10212; **IR** ν_{max} (film)/cm^{-1}: 3053, 2955, 2925, 2854, 2361, 2341, 1912, 1653, 1595, 1555, 1488, 1456, 1388, 1375, 1297, 1264, 1188, 1117, 1059.

6-Bromo-2-(2-(ethylthio)heptyl)quinoline, 73f



Compound **73f** was prepared according to General Procedure **G** using enone **72f** (78.5 mg, 0.160 mmol), TFA (0.300 mL, 3.84 mmol) and CH_2Cl_2 (4.0 mL). Flash column chromatography (SiO_2, 0-10% Et_2O in petrol) afforded quinoline **73f** as a pale brown oil (47.5 mg, 80% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.00 (1H, d, *J* 8.5, C(4)*H*), 7.96 (1H, d, *J* 2.0, C(5)*H*), 7.93 (1H, d, *J* 9.0, C(7)*H*), 7.76 (1H, dd, *J* 9.0 and 2.0, C(6)*H*), 7.38 (1H, d, *J* 8.5, C(3)*H*), 3.30-3.16 (3H, m, C(1)*H*, C(2)H_2), 2.50-2.41 (2H, m, SCH_2CH$_3$), 1.71-1.42 (4H, m, 2 × CH_2), 1.34-1.24 (4H, m, 2 × CH_2), 1.17 (3H, t, *J* 7.5, SCH$_2$CH_3), 0.89 (3H, t, *J* 7.0, (CH$_2$)$_4$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 161.1, 146.5, 134.9, 132.8, 130.7, 129.5, 128.0, 123.3, 119.6, 45.6, 45.2, 35.1, 31.7, 26.4, 24.8, 22.6, 14.9, 14.1; **LRMS** (ESI+, *m/z*): 366.1 ([M(^{79}Br)+Na]$^+$), 368.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{18}H_{24}BrNNaS$ ([M(^{79}Br)+Na]$^+$) requires 366.08856, found 366.08857, ([M(^{81}Br)+Na]$^+$) requires 368.08651, found 368.08634; **IR** ν_{max} (film)/cm^{-1}: 2956, 2927, 2856, 1650, 1594, 1556, 1487, 1457, 1377, 1303, 1263, 1186, 1119, 1059.

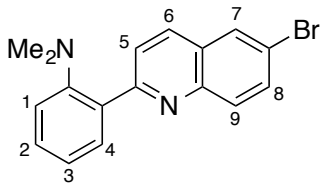
6-Bromo-2-(4-(methylthio)-5,6-dihydro-2*H*-pyran-3-yl)quinoline, 73g



Compound **73g** was prepared according to General Procedure **H** using enone **72g** (45.4 mg, 0.100 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 20% EtOAc in petrol) afforded quinoline **73g** as a pale brown solid (28.0 mg,

83% yield); **m.p.**: 117-119 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.05 (1H, d, *J* 8.5, C(5)*H*), 7.97 (1H, d, *J* 2.0, C(6)*H*), 7.97 (1H, d, *J* 9.0, C(8)*H*), 7.77 (1H, dd, *J* 9.0 and 2.0, C(7)*H*), 7.61 (1H, d, *J* 8.5, C(4)*H*), 4.66 (2H, t, *J* 2.5, C(3)H_2), 4.02 (2H, t, *J* 5.5, C(1)H_2), 2.59 (2H, tt, *J* 5.5 and 2.5, C(2)H_2), 2.23 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 157.0, 146.2, 134.7, 133.6, 132.9, 131.6, 131.0, 129.5, 128.0, 122.7, 120.3, 68.7, 64.8, 29.2, 14.3; **LRMS** (ESI+, *m/z*): 336.0 ([M(^{79}Br)+Na]$^+$), 338.0 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{15}H_{15}BrNOS$ ([M(^{79}Br)+H]$^+$) requires 336.00522, found 336.00532, ([M(^{81}Br)+H]$^+$) requires 338.00318, found 338.00310; **IR** ν_{max} (film)/cm^{-1}: 2959, 2922, 2851, 1589, 1539, 1486, 1421, 1380, 1301, 1240, 1188, 1139, 1121, 1102, 1059, 1017.

2-(6-Bromoquinolin-2-yl)-*N*,*N*-dimethylaniline, 73m



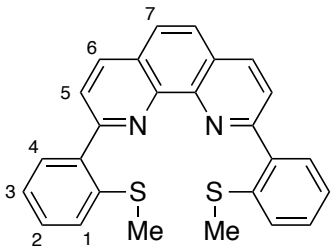
Compound **73m** was prepared according to General Procedure **G** using enone **72m** (81.2 mg, 0.182 mmol), TFA (0.340 mL, 4.38 mmol) and CH_2Cl_2 (4.6 mL). Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded quinoline **73m** as a pale brown solid (51.2 mg, 86% yield); **m.p.**: 92-94 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.06 (1H, d, *J* 9.0, C(9)*H*), 8.05 (1H, d, *J* 8.5, C(6)*H*), 8.03 (1H, d, *J* 8.5, C(5)*H*), 8.00 (1H, d, *J* 2.0, C(7)*H*), 7.79 (1H, dd, *J* 9.0 and 2.0, C(8)*H*), 7.72 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.40 (1H, ddd, 8.0, 7.5, 1.5, C(2)*H*), 7.16-7.12 (2H, m, C(1)*H*, C(2)*H*), 2.63 (6H, s, N(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.7, 151.6, 147.1, 134.3, 132.5, 132.4, 131.9, 131.2, 129.9, 129.4, 128.1, 123.5, 122.1, 119.9, 117.6, 44.0; **LRMS** (ESI+, *m/z*): 327.0 ([M(^{79}Br)+H]$^+$), 329.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{16}BrN_2$ ([M(^{79}Br)+H]$^+$)

requires 327.04914, found 327.04916, ([M(^{79}Br)+H]$^+$) requires 329.04709, found 329.04705; **IR** ν_{max} (film)/cm^{-1}: 3058, 2984, 2941, 2864, 2833, 2785, 1595, 1572, 1546, 1485, 1453, 1432, 1379, 1305, 1188, 1158, 1142, 1126, 1105, 1060, 1034.

Alternatively:

Compound **73m** was prepared according to General Procedure **H** using enone **72m** (46.3 mg, 0.104 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded quinoline **73m** as a pale brown solid (31.0 mg, 91% yield).

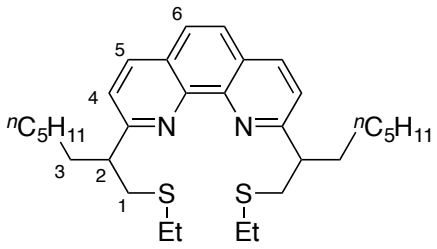
2,9-Bis(2-(methylthio)phenyl)-1,10-phenanthroline, 77a



Compound **77a** was prepared according to General Procedure **G** using enone **76a** (112 mg, 0.169 mmol), TFA (0.310 mL, 4.06 mmol) and CH_2Cl_2 (4.2 mL). Flash column chromatography (SiO_2, 30-40% EtOAc in petrol) afforded phenanthroline **77a** as a pale brown solid (63.7 mg, 89 % yield); **m.p.**: 154-156 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.28 (2H, d, *J* 8.5, C(6)*H*), 8.05 (2H, d, *J* 8.5, C(5)*H*), 7.88 (2H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.81 (2H, s, C(7)*H*), 7.46 (2H, dd, *J* 8.0 and 1.5, C(1)*H*), 7.42 (2H, ddd, *J* 8.0, 7.0 and 1.5, C(2)*H*), 7.33 (2H, ddd, *J* 7.5, 7.0 and 1.5, C(3)*H*), 2.47 (6H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.2, 145.9, 140.4, 138.1, 135.7, 131.1, 129.0, 127.6, 127.1, 126.3, 125.1, 123.8, 17.3; **LRMS** (ESI+, *m/z*): 425.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*):

$C_{26}H_{21}N_2S_2$ ([M+H]$^+$) requires 425.11407, found 425.11386; **IR** ν_{max} (film)/cm^{-1}: 3054, 2981, 2918, 2856, 1619, 1605, 1585, 1562, 1541, 1495, 1466, 1435, 1419, 1357, 1305, 1269, 1245, 1232, 1163, 1144, 1102, 1080, 1042, 1030.

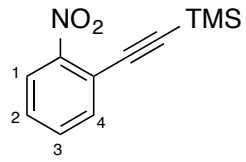
2,9-Bis(1-(ethylthio)octan-2-yl)-1,10-phenanthroline, 77b



Compound **77b** was prepared according to General Procedure **G** using enone **76b** (139 mg, 0.175 mmol), TFA (0.320 mL, 4.20 mmol) and CH_2Cl_2 (4.4 mL). Flash column chromatography (SiO_2, 5-10% Et_3N in petrol) afforded phenanthroline **77b** as a yellow oil (69.1 mg, 83% yield); (isolated as a 1:1 mixture of diastereoisomers) **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.16 (2H, d, *J* 8.0, C(5)*H*), 7.73 (2H, s, C(6)*H*), 7.51 (2H, dd, *J* 8.0 and 1.0, C(4)*H*), 3.40-3.26 (4H, m, C(1)H_AH_B, C(2)*H*), 3.09 (2H, dd, *J* 12.5 and 6.0, C(1)H_AH_B), 2.53 (4H, q, *J* 7.5, SCH_2CH$_3$ (diast)), 2.52 (4H, q, *J* 7.5, SCH_2CH$_3$ (diast)), 2.05-1.98 (4H, m, C(3)H_2), 1.41-1.20 (16H, m, 8 × CH_2), 1.24 (6H, t, *J* 7.5, SCH$_2$CH_3 (diast)), 1.23 (6H, t, *J* 7.5, SCH$_2$CH_3 (diast)), 0.86 (6H, t, *J* 7.0, (CH$_2$)$_4$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 163.8, 145.8, 135.8, 127.4, 125.6, 122.44 (diast), 122.37 (diast), 48.6 (diast), 48.5 (diast), 37.1 (diast), 37.0 (diast), 35.0 (diast), 34.8 (diast), 31.8, 29.50 (diast), 29.48 (diast), 27.5, 26.65 (diast), 26.61 (diast), 22.7, 14.9 (diast), 14.1 (diast); **LRMS** (ESI+, *m/z*): 525.3 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{32}H_{49}N_2S_2$ ([M+H]$^+$) requires 525.33317, found 525.33279; **IR** ν_{max} (film)/cm^{-1}: 3040, 2956, 2926, 2855, 1618, 1608, 1590, 1548, 1495, 1421, 1376, 1299, 1264, 1188, 1144, 1091, 1053.

7.3.4 Use of nitro-substituted alkynes in quinoline synthesis

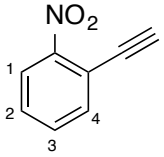
Trimethyl((2-nitrophenyl)ethynyl)silane, 79a



Compound **79a** was prepared according to General Procedure **C** using 2-iodo-nitrobenzene (1.00 g, 4.00 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.200 mmol), CuI (38.0 mg, 0.200 mmol), TMS-acetylene (0.853 mL, 6.00 mmol), Et_3N (0.800 mL, 6.00 mmol) and DMF (20 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aryl alkyne **79a** as a brown oil (765 mg, 87% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.03 (1H, ddd, *J* 8.0, 1.5 and 0.5, C(1)*H*), 7.68 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.58 (1H, td, *J* 7.5 and 1.5, C(3)*H*), 7.47 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 0.31 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 150.1, 135.1, 132.6, 128.8, 124.5, 118.4, 103.7, 99.3, -0.4; **LRMS** (ESI+, *m/z*): 242.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{11}H_{14}NO_2Si$ ([M+H]$^+$) requires 220.07883, found 220.07884.

Data consistent with the literature.[286]

1-Ethynyl-2-nitrobenzene, 80a

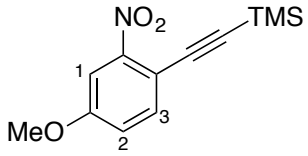


Compound **80a** was prepared according to General Procedure **D** using alkyne **79a** (731 mg, 3.33 mmol), K_2CO_3 (461 mg, 3.33 mmol), and MeOH (40 mL). Flash column chromatography (SiO_2, 5% Et_2O in petrol) afforded terminal alkyne **80a** as a brown

solid (389 mg, 79% yield); **m.p.**: 80-82 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.08 (1H, ddd, *J* 8.0, 1.5 and 0.5, C(1)*H*), 7.73 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.63 (1H, td, *J* 7.5 and 1.5, C(3)*H*), 7.54 (1H, dddd, *J* 8.0, 7.5, 1.5 and 0.5, C(2)*H*), 3.54 (1H, s, CC*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 150.2, 135.5, 132.9, 129.4, 124.6, 117.4, 85.2, 78.5; **HRMS** (EI, *m/z*): $C_8H_5NO_2$ ($[M]^+$) requires 147.0320, found 147.0319.

Data consistent with the literature.[287]

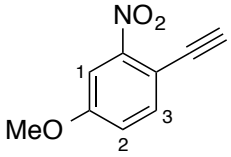
((4-Methoxy-2-nitrophenyl)ethynyl)trimethylsilane, 79b



Compound **79b** was prepared according to General Procedure **C** using 1-iodo-4-methoxy-2-nitrobenzene **86** (2.00 g, 7.16 mmol), $Pd(PPh_3)_2Cl_2$ (251 mg, 0.360 mmol), CuI (69.0 mg, 0.360 mmol), TMS-acetylene (1.54 mL, 10.8 mmol), Et_3N (1.50 mL, 10.8 mmol) and DMF (20 mL). Flash column chromatography (SiO_2, 5-20% Et_2O in petrol) afforded aryl alkyne **79b** as a brown solid (1.36 g, 76% yield); **m.p.**: 68-70 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.57 (1H, d, *J* 8.5, C(3)*H*), 7.53 (1H, d, *J* 2.5, C(1)*H*), 7.10 (1H, dd, *J* 8.5 and 2.5, C(2)*H*), 3.91 (3H, s, OCH_3), 0.29 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 159.6, 151.1, 136.0, 119.5, 110.5, 109.2, 101.4, 99.5, 56.0, -0.3; **LRMS** (ESI+, *m/z*): 272.1 ($[M+Na]^+$).

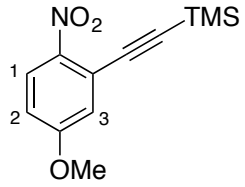
Data consistent with the literature.[288]

1-Ethynyl-4-methoxy-2-nitrobenzene, 80b



Compound **80b** was prepared according to General Procedure **D** using alkyne **79b** (1.28 g, 5.13 mmol), K_2CO_3 (709 mg, 5.13 mmol) and MeOH (50 mL). Flash column chromatography (SiO_2, 5-20% Et_2O in petrol) afforded terminal alkyne **80b** as a brown solid (858 mg, 94 % yield); **m.p.**: 83-85 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.62 (1H, d, *J* 8.5, C(3)*H*), 7.57 (1H, d, *J* 2.5, C(1)*H*), 7.14 (1H, dd, *J* 8.5 and 2.5, C(2)*H*), 3.92 (3H, s, OCH_3), 3.43 (1H, s, CC*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 159.9, 151.2, 136.4, 119.5, 109.5, 109.4, 83.2, 78.6, 56.0; **LRMS** (ESI+, *m/z*): 200.1 ([M+Na]$^+$). Data consistent with the literature.[289]

((5-Methoxy-2-nitrophenyl)ethynyl)trimethylsilane, 79c

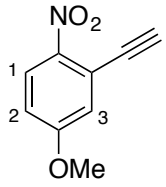


Compound **79c** was prepared according to General Procedure **C** using 2-iodo-4-methoxy-1-nitrobenzene (2.00 g, 7.16 mmol), $Pd(PPh_3)_2Cl_2$ (250 mg, 0.360 mmol), CuI (70.0 mg, 0.360 mmol), TMS-acetylene (1.54 mL, 10.8 mmol), Et_3N (1.50 mL, 10.8 mmol) and DMF (20 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aryl alkyne **79c** as a dark brown solid (1.70 g, 95% yield); **m.p.**: 61-63 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.09 (1H, d, *J* 9.0, C(1)*H*), 7.09 (1H, d, *J* 3.0, C(3)*H*), 6.93 (1H, dd, *J* 9.0 and 3.0, C(2)*H*), 3.91 (3H, s, OCH_3),

0.31 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 162.7, 143.1, 127.0, 120.6, 119.1, 114.9, 103.6, 100.0, 56.0, -0.4; **LRMS** (ESI+, *m/z*): 272.1 ([M+Na]$^+$).

Data consistent with the literature.[288]

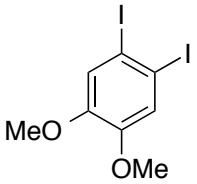
2-Ethynyl-4-methoxy-1-nitrobenzene, 80c



Compound **80c** was prepared according to General Procedure **D** using alkyne **79c** (1.54 g, 6.17 mmol), K_2CO_3 (852 mg, 6.17 mmol) and MeOH (60 mL). Flash column chromatography (SiO_2, 5-20% Et_2O in petrol) afforded terminal alkyne **80c** as a brown solid (952 mg, 87% yield); **m.p.**: 94-96 °C (crystalised from petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.14 (1H, d, *J* 9.0, C(1)*H*), 7.15 (1H, d, *J* 3.0, C(3)*H*), 6.99 (1H, dd, *J* 9.0 and 3.0, C(2)*H*), 3.93 (3H, s, OCH_3), 3.56 (1H, s, CC*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 162.8, 143.1, 127.1, 119.9, 119.7, 115.1, 85.0, 79.1, 56.1; **LRMS** (ESI+, *m/z*): 200.1 ([M+Na]$^+$), **HRMS** (ESI+, *m/z*): $C_9H_7NNaO_3$ ([M+Na]$^+$) requires 200.03181, found 200.03205; **IR** ν_{max} (film)/cm^{-1}: 3289, 3102, 2983, 2953, 2903, 2856, 1610, 1573, 1509, 1480, 1444, 1409, 1373, 1339, 1324, 1288, 1239, 1200, 1161, 1086, 1027.

Data consistent with the literature.[290]

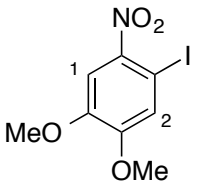
1,2-Diiodo-4,5-dimethoxybenzene, 139



Periodic acid (2.92 g, 12.8 mmol) was dissolved in MeOH (19 mL) and stirred at room temperature for 15 minutes. I_2 (6.38 g, 25.1 mmol) was then added and the solution stirred vigorously for a further 10 minutes. 1,2-dimethoxybenzene (4.34 g, 31.4 mmol) was then added, and the resulting solution refluxed for 4 hours. Heating was then removed, and the hot mixture was poured onto a 10% solution of NaS_2O_5 (100 mL). The resulting precipitate was collected and washed with MeOH, before being dissolved in EtOAc (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. No further purification was necessary to afford di-iodo arene **139** as a peach solid (10.9 g, 89% yield); **m.p.**: 136-138 °C (crystalised from EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.24 (2H, s, 2 × Ar*H*), 3.86 (6H, s, 2 × OCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 149.6, 121.6, 96.1, 56.2; **LRMS** (ESI+, *m/z*): 413.1 ([M+Na]$^+$).

Data consistent with the literature.[291]

1-Iodo-4,5-dimethoxy-2-nitrobenzene, 140

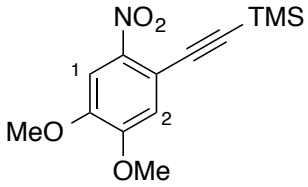


Compound **139** (8.80 g, 23.0 mmol) was added into acetic acid (300 mL), and the mixture was heated to 100 °C to dissolve the solid. The clear mixture was then cooled to room temperature followed by dropwise addition of nitric acid (68-70%, 120 mL). The

reaction mixture was stirred at room temperature for 16 hours and then poured into ice-water (200 mL). The mixture was extracted by CH_2Cl_2 (3 × 100 mL). The combined organic fractions was washed with saturated $NaHCO_3$ solution (200 mL), brine (100 mL), and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded nitro arene **140** as a yellow solid (5.10 g, 73%); **m.p.**: 148-150 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.63 (1H, s, C(1)*H*), 7.42 (1H, s, C(2)*H*), 3.98 (3H, s, OCH_3), 3.96 (3H, s, OCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.7, 149.0, 145.0, 123.1, 109.0, 77.3, 56.7, 56.4; **LRMS** (ESI+, *m/z*): 331.9 ([M+Na]$^+$).

Data consistent with the literature.[292]

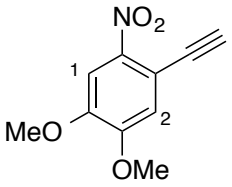
((4,5-Dimethoxy-2-nitrophenyl)ethynyl)trimethylsilane, 79d



Compound **79d** was prepared according to General Procedure **C** using aryl iodide **140** (2.00 g, 6.47 mmol), $Pd(PPh_3)_2Cl_2$ (227 mg, 0.324 mmol), CuI (62.0 mg, 0.324 mmol), TMS-acetylene (1.38 mL, 9.70 mmol), Et_3N (1.35 mL, 9.70 mmol) and DMF (20 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aryl alkyne **79d** as a pale brown solid (1.77 g, 94% yield); **m.p.**: 179-181 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.62 (1H, s, C(1)*H*), 7.01 (1H, s, C(2)*H*), 3.98 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 0.29 (9H, s, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.6, 148.9, 143.2, 115.6, 112.4, 107.4, 102.1, 100.3, 56.52, 56.41, -0.3; **LRMS** (ESI+, *m/z*): 302.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{13}H_{18}NO_4Si$ ([M+H]$^+$) requires 280.09996, found 280.09987; **IR** ν_{max}

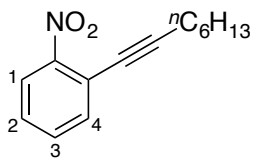
(film)/cm^{-1}: 3011, 2965, 2941, 2900, 2835, 1753, 1712, 1588, 1616, 1590, 1556, 1494, 1479, 1332, 1294, 1269, 1249, 1219, 1185, 1126, 1056.

1-Ethynyl-4,5-dimethoxy-2-nitrobenzene, 80d



Compound **80d** was prepared according to General Procedure **D** using alkyne **79d** (1.73 g, 6.20 mmol), K_2CO_3 (860 mg, 6.20 mmol) and MeOH (60 mL). Flash column chromatography (SiO_2, 10% Et_2O in petrol) afforded terminal alkyne **80d** as a mustard-yellow solid (807 mg, 62% yield); **m.p.**: 140-142 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.66 (1H, s, C(1)*H*), 7.06 (1H, s, C(2)*H*), 3.99 (6H, s, 2 × OCH_3), 3.50 (1H, s, CC*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 152.7, 149.2, 143.3, 116.1, 111.4, 107.5, 83.8, 79.4, 56.6, 56.5; **LRMS** (ESI+, *m/z*): 230.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{10}H_9NNaO_4$ ([M+Na]$^+$) requires 230.04238, found 230.04277; **IR** ν_{max} (film)/cm^{-1}: 3254, 3064, 2940, 2839, 1749, 1711, 1615, 1575, 1519, 1489, 1462, 1439, 1396, 1335, 1267, 1240, 1220, 1170, 1129, 1098, 1063, 1025, 1005.

1-Nitro-2-(oct-1-yn-1-yl)benzene, 82

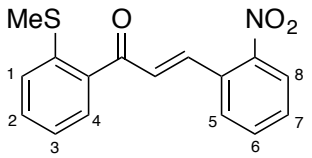


Compound **82** was prepared according to General Procedure **C** using 2-iodo-nitrobenzene (1.00 g, 4.02 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.200 mmol), CuI (38.0 mg, 0.200 mmol), 1-octyne (0.960 mL, 6.00 mmol), Et_3N (0.840 mL, 6.00 mmol) and DMF

(10 mL). Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded aryl alkyne **82** as a brown oil (744 mg, 80% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.99 (1H, ddd, *J* 8.0, 1.5 and 0.5, C(1)*H*), 7.60 (1H, dd, *J* 8.0 and 1.5, C(4)*H*), 7.54 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(3)*H*), 7.41 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 2.50 (2H, t, *J* 7.0, CCCH_2), 1.70-1.62 (2H, m, CH_2), 1.54-1.46 (2H, m, CH_2), 1.39-1.32 (4H, m, 2 × CH_2), 0.93 (3H, t, *J* 7.0, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 150.1, 134.8, 132.5, 127.8, 124.3, 119.4, 99.5, 75.9, 31.3, 28.6, 28.3, 22.5, 19.8, 14.1; **LRMS** (ESI+, *m/z*): 254.1 ([M+Na]$^+$).

Data consistent with the literature.[290]

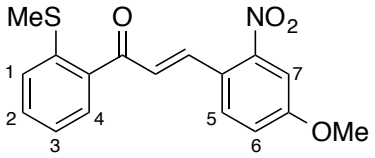
(*E*)-1-(2-(Methylthio)phenyl)-3-(2-nitrophenyl)prop-2-en-1-one, 81a



Compound **81a** was prepared according to General Procedure **F** using alkyne **80a** (2.50 g, 17.0 mmol), 2-(methylthio)benzaldehyde **30** (3.10 g, 20.4 mmol), $[Rh(nbd)_2]BF_4$ (127 mg, 0.340 mmol), dcpm (139 g, 0.340 mmol) and acetone (11.0 mL) for 15 minutes at 55 °C. Flash column chromatography (SiO_2, 20% Et_2O in petrol, followed by 100% CH_2Cl_2) afforded enone **81a** as a yellow solid (4.92 g, 97% yield); **m.p.**: 96-98 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.07 (1H, dd, *J* 8.0 and 1.0, C(8)*H*), 7.99 (1H, dd, *J* 16.0 and 0.5, C(O)CHC*H*), 7.78-7.73 (2H, m, C(4)*H*, C(5)*H*), 7.70 (1H, tdd, *J* 7.5, 1.5 and 0.5, C(6)*H*), 7.57 (1H, ddd, *J* 8.0, 7.0 and 1.5, C(7)*H*), 7.51 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.41 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.27 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 7.18 (1H, d, *J* 16.0, C(O)C*H*CH), 2.49 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.5, 148.4, 140.9, 140.4, 136.2, 133.6, 131.9, 131.2, 130.4, 129.9, 129.7, 129.2, 126.4, 125.0, 124.2, 16.5; **LRMS** (ESI+, *m/z*): 322.1 ([M+Na]$^+$); **HRMS** (ESI+,

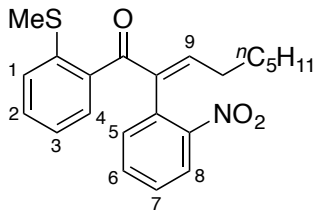
m/z): $C_{16}H_{14}NO_3S$ ([M+H]$^+$) requires 300.06889, found 300.06897; **IR** ν_{max} (film)/cm^{-1}: 3065, 2982, 2920, 2855, 1654, 1602, 1569, 1519, 1462, 1433, 1341, 1297, 1277, 1208, 1141, 1081, 1047, 1009.

(*E*)-3-(4-Methoxy-2-nitrophenyl)-1-(2-(methylthio)phenyl)prop-2-en-1-one, 81b



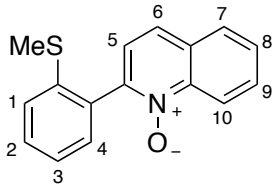
Compound **81b** was prepared according to General Procedure **F** using alkyne **80b** (88.6 mg, 0.500 mmol), 2-(methylthio)benzaldehyde **30** (91.3 mg, 0.600 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.4 mL) for 20 minutes at 55 °C. Flash column chromatography (SiO_2, 20% Et_2O in petrol, followed by 100% CH_2Cl_2) afforded enone **81b** as a yellow solid (159.7 mg, 97% yield); **m.p.**: 146-148 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.92 (1H, dt, *J* 16.0 and 0.5, C(O)CHC*H*), 7.73 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.71 (1H, d, *J* 8.5, C(5)*H*), 7.54 (1H, d, *J* 2.5, C(7)*H*), 7.50 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.41 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.28 (1H, ddd, *J* 7.5, 7.5 and 1.0, C(3)*H*), 7.22 (1H, ddd, *J* 8.5, 2.5 and 0.5, C(6)*H*), 7.12 (1H, d, *J* 16.0, C(O)C*H*CH), 3.94 (3H, s, OCH_3), 2.49 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 193.0, 161.0, 149.5, 140.5, 140.1, 136.7, 131.7, 130.1, 129.7, 128.2, 126.5, 124.3, 123.0, 120.0, 109.6, 56.1, 16.6; **LRMS** (ESI+, *m/z*): 352.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{15}NNaO_4S$ ([M+Na]$^+$) requires 352.06140, found 352.06143; **IR** ν_{max} (film)/cm^{-1}: 2919, 2848, 1721, 1654, 1593, 1559, 1524, 1496, 1463, 1433, 1350, 1291, 1253, 1208, 1186, 1172, 1142, 1084, 1067, 1049, 1030, 1008.

(*E*)-1-(2-(Methylthio)phenyl)-2-(2-nitrophenyl)non-2-en-1-one, 83



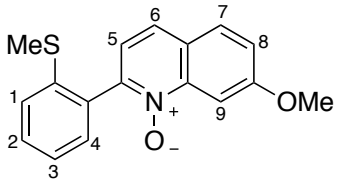
Compound **83** was prepared according to General Procedure **F** using alkyne **82** (46.3 mg, 0.200 mmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol) and acetone (0.1 mL) for 16 hours. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded enone **83** as a pale yellow oil (68.1 mg, 88% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.19 (1H, ddd, *J* 8.5, 1.5 and 0.5, C(8)*H*), 7.71 (1H, td, *J* 7.5 and 1.5, C(6)*H*), 7.63 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.56 (1H, ddd, *J* 8.5, 7.5 and 1.5, C(7)*H*), 7.46 (1H, ddd, *J* 8.0, 7.2 and 1.5, C(2)*H*), 7.41 (1H, dd, *J* 7.5 and 1.5, C(5)*H*), 7.40 (1H, dd, *J* 8.0 and 1.5, C(1)*H*), 7.28 (1H, ddd, *J* 7.5, 7.5 and 1.5, C(3)*H*), 6.54 (1H, t, *J* 7.5, C(9)*H*), 2.47 (3H, s, SCH_3), 2.08 (2H, app. q, *J* 7.5, C(9)HCH_2), 1.38 (2H, app. quintet, *J* 7.0, C(9)HCH$_2$CH_2), 1.28-1.15 (6H, m, 3 × CH_2), 0.85 (3H, t, *J* 7.0, $(CH_2)_4CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 195.6, 149.6, 148.5, 140.6, 138.4, 137.9, 133.3, 133.0, 131.3, 130.5, 129.2, 129.0, 127.3, 124.8 (2 × C), 31.4, 30.3, 28.9, 28.4, 22.4, 17.0, 14.0; **LRMS** (ESI+, *m/z*): 406.2 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{26}NO_3S$ ($[M+H]^+$) requires 384.16279, found 384.16287; **IR** ν_{max} (film)/cm^{-1}: 2954, 2925, 2856, 1655, 1608, 1584, 1573, 1523, 1462, 1433, 1346, 1285, 1247, 1095, 1040.

2-(2-(Methylthio)phenyl)quinoline 1-oxide, 84a



To a solution of enone **81a** (150 mg, 0.500 mmol) in a 1:1 mixture of EtOH (20 mL) and H_2O (20 mL) was added NH_4Cl (80.0 mg, 1.50 mmol) and Sn powder (178 mg, 1.50 mmol), and the resulting mixture refluxed for 20 hours. Once cooled to room temperature, the reaction was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic layer was then washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 50-100% EtOAc in petrol) afforded quinoline *N*-oxide **84a** as a light brown solid (92.8 mg, 69% yield); **m.p.**: 136-138 °C (crystalised from $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.86 (1H, d, *J* 9.0, C(10)*H*), 7.87 (1H, dd, *J* 8.0 and 1.5, C(7)*H*), 7.75 (1H, ddd, *J* 9.0, 7.0 and 1.5, C(9)*H*), 7.73 (1H, d, *J* 8.5, C(6)*H*), 7.63 (1H, ddd, *J* 8.0, 7.0 and 1.0, C(8)*H*), 7.47-7.38 (3H, m, C(1)*H*, C(2)*H*, C(4)*H*), 7.37 (1H, d, *J* 8.5, C(5)*H*), 7.30 (1H, ddd, *J* 7.5, 6.0 and 2.5, C(3)*H*), 2.40 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 145.2, 142.0, 138.9, 133.5, 130.3, 130.0, 129.80, 129.77, 128.6, 128.1, 126.7, 125.4, 124.6, 123.8, 120.3, 16.4; **LRMS** (ESI+, *m/z*): 268.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{16}H_{14}NOS$ ($[M+H]^+$) requires 268.07906, found 268.07892; **IR** ν_{max} (film)/cm^{-1}: 3424, 3057, 2920, 2854, 1560, 1511, 1472, 1449, 1435, 1369, 1340, 1322, 1260, 1242, 1215, 1163, 1135, 1112, 1080, 1048, 1032.

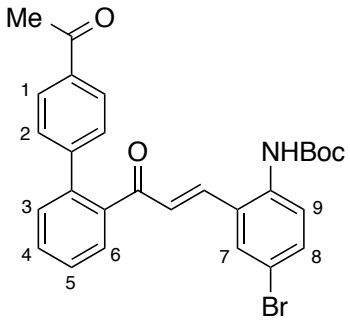
7-Methoxy-2-(2-(methylthio)phenyl)quinoline 1-oxide, 84b



To a solution of enone **81b** (70.0 mg, 0.210 mmol) in a 1:1 mixture of EtOH (8.0 mL) and H_2O (8.0 mL) was added NH_4Cl (34.0 mg, 0.64 mmol) and Sn powder (75.0 mg, 0.64 mmol), and the resulting mixture refluxed for 20 hours. Once cooled to room temperature, the reaction was partitioned between CH_2Cl_2 (30 mL) and H_2O (30 mL). The organic layer was then washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 50-100% EtOAc in petrol) afforded quinoline *N*-oxide **84b** as a white solid (44.5 mg, 70% yield); **m.p.**: 172-174 °C (crystalised from EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.24 (1H, d, *J* 2.5, C(9)*H*), 7.78 (1H, d, *J* 9.0, C(7)*H*), 7.71 (1H, d, *J* 8.5, C(6)*H*), 7.49-7.42 (2H, m, C(1)*H*, C(2)*H*), 7.38 (1H, dd, *J* 7.5 and 1.0, C(4)*H*), 7.33-7.28 (2H, m, C(3)*H*, C(8)*H*), 7.26 (1H, d, *J* 8.5, C(5)*H*), 4.00 (3H, s, OCH_3), 2.42 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 162.0, 145.7, 143.2, 138.9, 133.6, 129.73, 129.69, 129.3, 126.5, 125.26, 125.09, 124.7, 121.6, 121.2, 98.9, 55.9, 16.3; **LRMS** (ESI+, *m/z*): 298.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{17}H_{16}NO_2S$ ($[M+H]^+$) requires 298.08963, found 298.08950; **IR** ν_{max} (film)/cm^{-1}: 3059, 3007, 2968, 2920, 2838, 1624, 1597, 1561, 1522, 1474, 1434, 1382, 1346, 1325, 1272, 1218, 1165, 1021.

7.3.5 Tandem hydroacylation-Suzuki reactions in quinoline synthesis

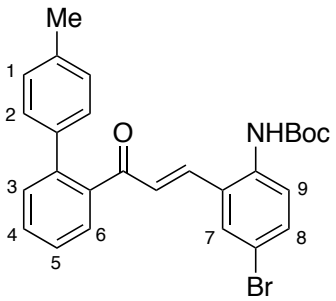
General Procedure I - tandem hydroacylation - C-S functionalisation reaction, as exemplified by the synthesis of *tert*-Butyl (*E*)-(2-(3-(4'-acetyl-[1,1'-biphenyl]-2-yl)-3-oxoprop-1-en-1-yl)-4-bromophenyl)carbamate, 89a



$[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol) and dcpm (4.1 mg, 10 μmol) were added to a microwave vial, which was then evacuated and backfilled with $N_{2(g)}$ three times. Then was added distilled and degassed acetone (0.4 mL), and the resulting suspension sonicated in order to solubilise the phosphine ligand. Once the solution was homogenous, $H_{2(g)}$ was bubbled through for 1 minute, followed by $N_{2(g)}$ until the volume was reduced to 0.1 mL. This resulting solution was transferred by syringe into a microwave vial containing 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol) and alkyne **51e** (59.2 mg, 0.200 mmol). The resulting solution was stirred at the 55 °C for 30 minutes. The resulting mixture was then transferred by syringe into a microwave vial containing Ag_2CO_3 (55.2 mg, 0.200 mmol) and 4-acetylphenylboronic acid (49.2 mg, 0.300 mmol) with the aid of DCE (0.5 mL). The resulting solution was stirred at 55 °C for 16 hours. The reaction mixture was filtered through a pad of SiO_2 (washed with Et_2O), and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20-40% Et_2O in petrol) afforded enone **89a** as a pale brown oil (92.2 mg, 90% yield); **^{1}H-NMR** (400 MHz,

$CDCl_3$): 8.04 (2H, d, *J* 8.5, C(1)*H*), 7.75 (1H, dd, *J* 7.5 and 1.0, C(6)*H*), 7.65 (1H, d, *J* 9.0, C(9)*H*), 7.63 (2H, td, *J* 7.5 and 1.5, C(4)*H*), 7.56-7.46 (5H, m, C(2)*H*, C(O)CHC*H*, C(3)*H*, C(5)*H*), 7.37 (1H, dd, *J* 9.0 and 2.5, C(8)*H*), 6.84 (1H, d, *J* 2.5, C(7)*H*), 6.45 (1H, br. s, N*H*), 6.45 (1H, d, *J* 15.5, C(O)C*H*CH), 2.64 (3H, s, C(O)CH_3), 1.52 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.3, 194.3, 152.5, 145.3, 140.0, 139.3, 136.5, 136.2, 136.0, 133.5, 131.5, 130.2, 129.6, 129.5, 129.4, 129.3, 128.8, 128.4, 127.8, 124.0, 116.8, 81.4, 28.3, 26.8; **LRMS** (ESI+, *m/z*): 542.1 ([M(^{79}Br)+Na]$^+$), 544.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{28}H_{26}BrNNaO_4$ ([M(^{79}Br)+Na]$^+$) requires 542.09374, found 542.09373, ([M(^{81}Br)+Na]$^+$) requires 544.09170, found 544.09171; **IR** ν_{max} (film)/cm^{-1}: 3317, 3062, 2977, 2931, 1724, 1681, 1603, 1509, 1403, 1367, 1324, 1266, 1156, 1050, 1023.

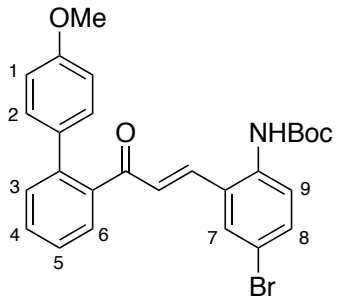
tert-Butyl (_E_)-(4-bromo-2-(3-(4'-methyl-[1,1'-biphenyl]-2-yl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 89b



Compound **89b** was prepared according to General Procedure **I** using [Rh(nbd)$_2$]BF$_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), alkyne **51e** (59.2 mg, 0.200 mmol) and acetone (0.1 mL), 4-methylphenylboronic acid (40.8 mg, 0.300 mmol), Ag_2CO_3 (55.2 mg, 0.200 mmol) and DCE (0.5 mL). Flash column chromatography (SiO_2, 10-30% Et_2O in petrol) afforded enone **89b** as a pale yellow powder (90.4 mg, 92% yield); **m.p.**: 192-194 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.74 (1H, d, *J* 7.5, C(6)*H*), 7.71 (1H, d, *J*

9.0, C(9)*H*), 7.61 (1H, ddd, *J* 8.0, 7.0 and 1.5, C(4)*H*), 7.51-7.46 (2H, m, C(3)*H*, C(5)*H*), 7.44 (1H, d, *J* 15.5, C(O)CHC*H*), 7.37 (1H, dd, *J* 9.0 and 2.5, C(8)*H*), 7.33-7.28 (4H, m, C(1)*H*, C(2)*H*), 6.74 (1H, d, *J* 2.5, C(7)*H*), 6.42 (1H, br. s, N*H*), 6.32 (1H, d, *J* 15.5, C(O)C*H*CH), 2.44 (3H, s, CH_3), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 195.0, 152.5, 141.3, 139.4, 138.5, 137.6, 135.8, 134.6, 133.1, 131.4, 130.3, 130.1, 129.8, 129.7, 129.4, 129.2, 127.9, 127.5, 123.4, 116.5, 81.4, 28.3, 21.4; **LRMS** (ESI+, *m/z*): 514.1 ([M(^{79}Br)+Na]$^+$), 516.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{27}H_{26}BrNNaO_3$ ([M(^{79}Br)+Na]$^+$) requires 514.09883, found 514.09876, ([M(^{81}Br)+Na]$^+$) requires 516.09678, found 516.09679; **IR** ν_{max} (film)/cm^{-1}: 3317, 2977, 2927, 1725, 1663, 1602, 1507, 1401, 1393, 1367, 1324, 1288, 1234, 1206, 1154, 1049, 1020.

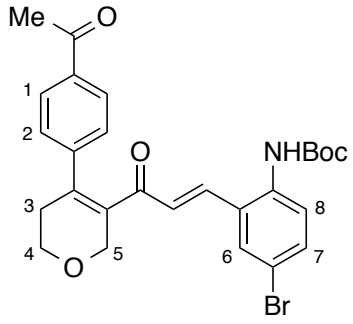
tert-Butyl (_E_)-(4-bromo-2-(3-(4'-methoxy-[1,1'-biphenyl]-2-yl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 89c



Compound **89c** was prepared according to General Procedure **I** using $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), 2-(methylthio)benzaldehyde **30** (36.5 mg, 0.240 mmol), alkyne **51e** (59.2 mg, 0.200 mmol) and acetone (0.1 mL), 4-methoxyphenylboronic acid (45.6 mg, 0.300 mmol), Ag_2CO_3 (55.2 mg, 0.200 mmol) and DCE (0.5 mL). Flash column chromatography (SiO_2, 20-40% Et_2O in petrol) afforded enone **89c** as a fluffy off-white solid (94.2 mg, 93% yield); **m.p.**: 156-158 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (1H, d, *J* 7.5, C(6)*H*), 7.70 (1H, d, *J*

9.0, C(9)*H*), 7.60 (1H, ddd, *J* 8.0, 7.0 and 1.5, C(4)*H*), 7.49-7.45 (2H, m, C(3)*H*, C(5)*H*), 7.44 (1H, d, *J* 15.6, C(O)CHC*H*), 7.37 (1H, dd, *J* 9.0 and 2.5, C(8)*H*), 7.34 (2H, d, *J* 9.0, C(2)*H*), 7.00 (2H, d, *J* 9.0, C(1)*H*), 6.87 (1H, d, *J* 2.5, C(7)*H*), 6.43 (1H, br. s, N*H*), 6.36 (1H, d, *J* 15.5, C(O)C*H*CH), 3.85 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 195.2, 159.8, 152.5, 140.9, 139.3, 135.8, 134.8, 133.2, 132.7, 131.4, 130.6, 130.1, 130.0, 129.7, 129.2, 127.9, 127.3, 123.5, 116.6, 114.3, 81.4, 55.4, 28.3; **LRMS** (ESI+, *m/z*): 530.1 ([M(^{79}Br)+Na]$^+$), 532.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{27}H_{26}BrNNaO_4$ ([M(^{79}Br)+Na]$^+$) requires 530.09374, found 530.09382, ([M(^{81}Br)+Na]$^+$) requires 532.09170, found 532.09177; **IR** ν_{max} (film)/cm^{-1}: 3319, 3008, 2976, 2933, 2837, 1722, 1662, 1604, 1509, 1474, 1401, 1367, 1323, 1289, 1245, 1153, 1035, 1020.

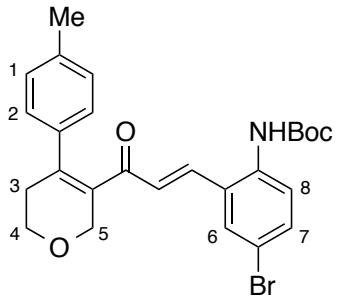
tert-Butyl (_E_)-(2-(3-(4-(4-acetylphenyl)-5,6-dihydro-2_H_-pyran-3-yl)-3-oxoprop-1-en-1-yl)-4-bromophenyl)carbamate, 89d



Compound **89d** was prepared according to General Procedure **I** using [Rh(nbd)$_2$]BF$_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde **71g** (38.0 mg, 0.240 mmol),[60] alkyne **51e** (59.2 mg, 0.200 mmol) and acetone (0.1 mL), 4-acetylphenylboronic acid (49.2 mg, 0.300 mmol), Ag_2CO_3 (55.2 mg, 0.200 mmol) and DCE (0.5 mL) at room temperature for the first step. Flash column chromatography (SiO_2, 10-40% EtOAc in petrol) afforded enone **89d** as a pale brown oil

(91.3 mg, 87% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (2H, d, *J* 8.5, C(1)*H*), 7.62 (1H, d, *J* 8.5, C(8)*H*), 7.40 (1H, d, *J* 15.5, C(O)CHC*H*), 7.39 (2H, d, *J* 8.5, C(2)*H*), 7.31 (1H, dd, *J* 8.5 and 2.5, C(7)*H*), 6.49 (1H, br. s, N*H*), 6.47 (1H, d, *J* 2.5, C(6)*H*), 6.04 (1H, d, *J* 15.5, C(O)C*H*CH), 4.54 (2H, t, *J* 2.5, C(5)H_2), 3.97 (2H, t, *J* 5.5, C(3)H_2), 2.65 (2H, tt, *J* 5.5 and 2.5, C(4)H_2), 2.61 (3H, s, C(O)CH_3), 1.51 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.0, 192.0, 152.5, 145.2, 143.4, 137.3, 137.2, 135.9, 134.2, 133.2, 129.2, 129.1, 128.9, 128.6, 127.8, 123.9, 116.6, 81.4, 66.0, 64.1, 31.0, 28.2, 26.8; **LRMS** (ESI+, *m/z*): 548.1 ([M(^{79}Br)+Na]$^+$), 550.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{27}H_{28}BrNNaO_5$ ([M(^{79}Br)+Na]$^+$) requires 548.10431, found 548.10433, ([M(^{81}Br)+Na]$^+$) requires 550.10226, found 550.10245; **IR** ν_{max} (film)/cm^{-1}: 3306, 2975, 2929, 2855, 1721, 1684, 1650, 1596, 1507, 1402, 1365, 1321, 1261, 1233, 1206, 1153, 1049, 1011.

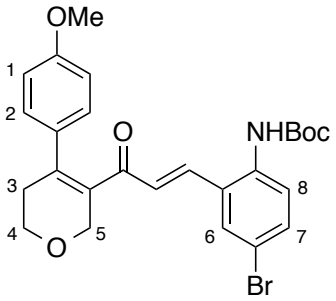
tert-Butyl (_E_)-(4-bromo-2-(3-oxo-3-(4-(_p_-tolyl)-5,6-dihydro-2_H_-pyran-3-yl)prop-1-en-1-yl)phenyl)carbamate, 89e



Compound **89e** was prepared according to General Procedure **I** using $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde **71g** (38.0 mg, 0.240 mmol),[60] alkyne **51e** (59.2 mg, 0.200 mmol) and acetone (0.1 mL), 4-methylphenylboronic acid (40.8 mg, 0.300 mmol), Ag_2CO_3 (55.2 mg, 0.200 mmol) and DCE (0.5 mL) at room temperature for the first step. Flash column chromatography (SiO_2, 20-40% EtOAc in petrol) afforded enone **89e** as a pale yellow

solid (83.6 mg, 84% yield); **m.p.**: 194-196 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.68 (1H, d, *J* 9.0, C(8)*H*), 7.37 (1H, d, *J* 15.5, C(O)CHC*H*), 7.34 (1H, dd, *J* 9.0 and 2.5, C(7)*H*), 7.25 (2H, d, *J* 8.0, C(2)*H*), 7.19 (2H, d, *J* 8.0, C(1)*H*), 6.54 (1H, d, *J* 2.5, C(6)*H*), 6.48 (1H, br. s, N*H*), 6.04 (1H, d, *J* 15.5, C(O)C*H*CH), 4.55 (2H, t, *J* 2.5, C(5)H_2), 3.96 (2H, t, *J* 5.5, C(3)H_2), 2.66 (2H, tt, *J* 5.5 and 2.5, C(4)H_2), 2.44 (3H, s, CH_3), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.4, 152.6, 145.9, 139.8, 137.6, 135.9, 135.8, 132.9, 132.6, 130.0, 129.7, 129.4, 128.4, 128.0, 123.5, 116.4, 81.3, 66.1, 64.3, 31.3, 28.3, 21.5; **LRMS** (ESI+, *m/z*): 520.1 ([M(^{79}Br)+Na]$^+$), 522.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{26}H_{28}BrNNaO_4$ ([M(^{79}Br)+Na]$^+$) requires 520.10939, found 520.10934, ([M(^{81}Br)+Na]$^+$) requires 522.10735, found 522.10713; **IR** ν_{max} (film)/cm^{-1}: 3306, 2976, 2924, 2851, 1726, 1649, 1594, 1509, 1402, 1366, 1321, 1233, 1156, 1049.

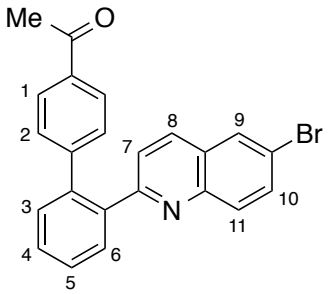
tert-Butyl (*E*)-(4-bromo-2-(3-(4-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-3-yl)-3-oxoprop-1-en-1-yl)phenyl)carbamate, 89f



Compound **89f** was prepared according to General Procedure **I** using $[Rh(nbd)_2]BF_4$ (3.7 mg, 10 μmol), dcpm (4.1 mg, 10 μmol), 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde **71g** (38.0 mg, 0.240 mmol),[60] alkyne **51e** (59.2 mg, 0.200 mmol) and acetone (0.1 mL), 4-methoxyphenylboronic acid (45.6 mg, 0.300 mmol), Ag_2CO_3 (55.2 mg, 0.200 mmol) and DCE (0.5 mL) at room temperature for the first step. Flash column chromatography (SiO_2, 20-30% EtOAc in petrol) afforded enone **89f** as a fluffy

white powder (83.7 mg, 81% yield); **m.p.**: 160-162 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.69 (1H, d, *J* 9.0, C(8)*H*), 7.38 (1H, d, *J* 15.5, C(O)CHC*H*), 7.35 (1H, dd, *J* 9.0 and 2.5, C(7)*H*), 7.22 (2H, d, *J* 9.0, C(1)*H*), 6.95 (2H, d, *J* 9.0, C(2)*H*), 6.65 (1H, d, *J* 2.5, C(6)*H*), 6.47 (1H, br. s, N*H*), 6.08 (1H, d, *J* 15.5, C(O)C*H*CH), 4.55 (2H, t, *J* 2.5, C(5)H_2), 3.96 (2H, t, *J* 5.5, C(3)H_2), 3.84 (3H, s, OCH_3), 2.66 (2H, tt, *J* 5.5 and 2.5, C(4)H_2), 1.53 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 192.5, 160.6, 152.5, 145.4, 135.7, 135.6, 132.9, 132.6, 130.0, 129.9 (2 × C), 129.4, 128.0, 123.5, 116.5, 114.3, 81.3, 66.2, 64.3, 55.4, 31.3, 28.3; **LRMS** (ESI+, *m/z*): 536.1 ([M(^{79}Br)+Na]$^+$), 538.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{26}H_{28}BrNNaO_5$ ([M(^{79}Br)+Na]$^+$) requires 536.10431, found 536.10424, ([M(^{81}Br)+Na]$^+$) requires 538.10226, found 538.10193; **IR** ν_{max} (film)/cm^{-1}: 3296, 2976, 2931, 2838, 1723, 1648, 1593, 1508, 1463, 1392, 1366, 1320, 1292, 1248, 1206, 1154, 1030.

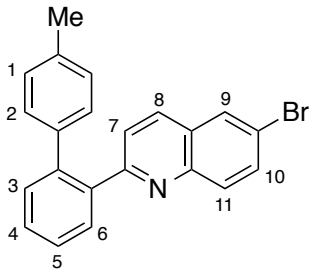
1-(2'-(6-Bromoquinolin-2-yl)-[1,1'-biphenyl]-4-yl)ethan-1-one, 90a



Compound **90a** was prepared according to General Procedure **H** using enone **89a** (59.7 mg, 0.114 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded quinoline **90a** as a colourless oil (43.2 mg, 94% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.01 (1H, d, *J* 9.0, C(11)*H*), 7.92 (1H, d, *J* 2.0, C(9)*H*), 7.87-7.78 (4H, m, C(1)*H*, C(6)*H*, C(10)*H*), 7.77 (1H, d, *J* 8.5, C(8)*H*), 7.60-7.56 (2H, m, C(4)*H*, C(5)*H*), 7.52-7.50 (1H, m, C(3)*H*), 7.30 (2H, d, *J* 8.5, C(2)*H*), 6.99 (1H, d, *J* 8.5,

C(7)*H*), 2.57 (3H, s, C(O)CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.7, 159.7, 146.7, 146.0, 139.6, 139.5, 135.5, 134.2, 133.0, 131.2, 130.9, 130.4, 130.0, 129.5, 129.2, 128.6, 128.3, 127.7, 124.1, 120.4, 26.6; **LRMS** (ESI+, *m/z*): 402.0 ([M(^{79}Br)+H]$^+$), 404.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{16}BrNNaO$ ([M(^{79}Br)+Na]$^+$) requires 402.04990, found 402.04878, ([M(^{81}Br)+Na]$^+$) requires 404.04676, found 404.04670; **IR** ν_{max} (film)/cm^{-1}: 3060, 2923, 2853, 1682, 1603, 1548, 1482, 1403, 1357, 1267, 1185, 1060, 1033, 1005.

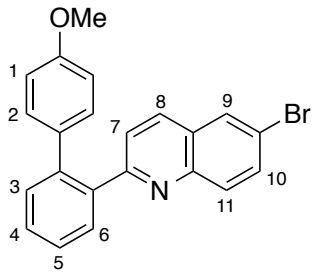
6-Bromo-2-(4'-methyl-[1,1'-biphenyl]-2-yl)quinoline, 90b



Compound **90b** was prepared according to General Procedure **H** using enone **89b** (80.9 mg, 0.164 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **90b** as a colourless oil (57.8 mg, 94% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.07 (1H, d, *J* 9.0, C(11)*H*), 7.92 (1H, d, *J* 2.0, C(9)*H*), 7.87-7.85 (1H, m, C(6)*H*), 7.81 (1H, dd, *J* 9.0 and 2.0, C(10)*H*), 7.73 (1H, d, *J* 8.5, C(8)*H*), 7.55-7.50 (3H, m, C(3)*H*, C(4)*H*, C(5)*H*), 7.11 (2H, d, *J* 8.0, C(2)*H*), 7.05 (2H, d, *J* 8.0, C(1)*H*), 6.99 (1H, d, *J* 8.5, C(7)*H*), 2.34 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.5, 146.8, 140.7, 139.3, 138.0, 136.7, 133.7, 132.7, 131.3, 130.7, 130.6, 129.7, 129.5, 129.1, 129.0, 127.7 (2 × C), 124.5, 120.1, 21.1; **LRMS** (ESI+, *m/z*): 374.1 ([M(^{79}Br)+H]$^+$), 376.1 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{17}BrN$ ([M(^{79}Br)+H]$^+$) requires 374.05389, found 374.05412, ([M(^{81}Br)+H]$^+$) requires 376.05184, found 376.05202; **IR**

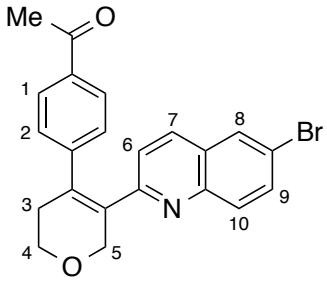
ν_{max} (film)/cm^{-1}: 3056, 3023, 2921, 2864, 1594, 1547, 1517, 1482, 1442, 1378, 1332, 1307, 1292, 1187, 1127, 1059, 1034, 1006.

6-Bromo-2-(4'-methoxy-[1,1'-biphenyl]-2-yl)quinoline, 90c



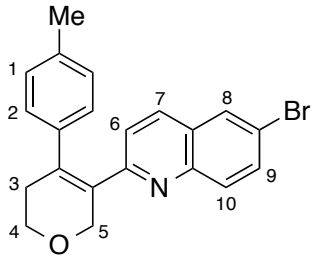
Compound **90c** was prepared according to General Procedure **H** using enone **89c** (88.3 mg, 0.174 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **90c** as a colourless oil (61.6 mg, 91% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.07 (1H, d, *J* 9.0, C(11)*H*), 7.92 (1H, d, *J* 2.0, C(9)*H*), 7.86-7.84 (1H, m, C(6)*H*), 7.80 (1H, dd, *J* 9.0 and 2.0, C(10)*H*), 7.74 (1H, d, *J* 8.5, C(8)*H*), 7.54-7.48 (3H, m, C(3)*H*, C(4)*H*, C(5)*H*), 7.12 (2H, d, *J* 9.0, C(2)*H*), 6.99 (1H, d, *J* 8.5, C(7)*H*), 6.78 (2H, d, *J* 9.0, C(1)*H*), 3.79 (3H, s, OCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.6, 158.8, 146.8, 140.4, 139.2, 133.7, 133.3, 132.7, 131.3, 130.9, 130.8, 130.5, 129.5, 129.1, 127.7, 127.6, 124.5, 120.1, 113.7, 55.2; **LRMS** (ESI+, *m/z*): 390.0 ([M(^{79}Br)+H]$^+$), 392.0 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{17}BrNO$ ([M(^{79}Br)+H]$^+$) requires 390.04880, found 390.04931, ([M(^{81}Br)+H]$^+$) requires 392.04676, found 392.04717; **IR** ν_{max} (film)/cm^{-1}: 3059, 2955, 2933, 2835, 1610, 1594, 1547, 1516, 1482, 1440, 1298, 1246, 1178, 1060, 1038.

1-(4-(5-(6-Bromoquinolin-2-yl)-3,6-dihydro-2*H*-pyran-4-yl)phenyl)ethan-1-one, 90d



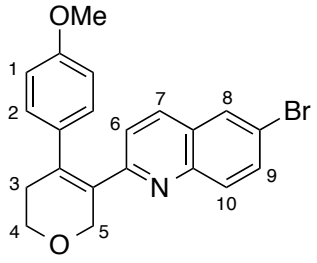
Compound **90d** was prepared according to General Procedure **H** using enone **89d** (90.6 mg, 0.172 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 50-70% Et_2O in petrol) afforded quinoline **90d** as a fluffy white powder (52.0 mg, 74% yield); **m.p.**: 149-151 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.91 (1H, d, *J* 9.0, C(10)*H*), 7.85 (1H, d, *J* 2.0, C(8)*H*), 7.78 (2H, d, *J* 8.5, C(1)*H*), 7.75 (1H, dd, *J* 9.0 and 2.0, C(9)*H*), 7.65 (1H, d, *J* 8.5, C(7)*H*), 7.20 (2H, d, *J* 8.5, C(2)*H*), 6.80 (1H, d, *J* 8.5, C(6)*H*), 4.81 (2H, t, *J* 2.5, C(5)H_2), 4.09 (2H, t, *J* 5.5, C(3)H_2), 2.67 (2H, tt, *J* 5.5 and 2.5, C(4)H_2), 2.54 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 197.5, 157.8, 146.3, 146.0, 136.1, 135.9, 135.3, 134.2, 132.9, 131.0, 129.5, 128.9, 128.4, 127.8, 123.9, 120.4, 68.1, 64.6, 30.6, 26.6; **LRMS** (ESI+, *m/z*): 408.1 ([M(^{79}Br)+H]$^+$), 410.1 ([M(^{79}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{19}BrNO_2$ ([M(^{79}Br)+H]$^+$) requires 408.05937, found 408.05912, ([M(^{81}Br)+H]$^+$) requires 410.05732, found 410.05706; **IR** ν_{max} (film)/cm^{-1}: 3059, 2961, 2923, 2853, 1681, 1602, 1591, 1558, 1544, 1486, 1357, 1303, 1267, 1186, 1141, 1117, 1096, 1060, 1014.

6-Bromo-2-(4-(*p*-tolyl)-5,6-dihydro-2*H*-pyran-3-yl)quinoline, 90e



Compound **90e** was prepared according to General Procedure **H** using enone **89e** (69.1 mg, 0.139 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded quinoline **90e** as a grey solid (28.1 mg, 53% yield); **m.p.**: 157-159 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.93 (1H, d, *J* 9.0, C(10)*H*), 7.84 (1H, d, *J* 2.0, C(8)*H*), 7.75 (1H, dd, *J* 9.0 and 2.0, C(9)*H*), 7.63 (1H, d, *J* 8.5, C(7)*H*), 7.01 (4H, s, C(1)*H*, C(2)*H*), 6.84 (1H, d, *J* 8.5, C(6)*H*), 4.82 (2H, t, *J* 2.5, C(5)H_2), 4.08 (2H, t, *J* 5.5, C(3)H_2), 2.66 (2H, tt, *J* 5.5 and 2.5, C(4)H_2), 2.31 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.7, 146.3, 138.0, 137.2, 136.5, 134.0, 133.7, 132.6, 131.0, 129.4, 129.1, 128.5, 127.7, 124.3, 120.0, 68.1, 64.8, 31.1, 21.2; **LRMS** (ESI+, *m/z*): 380.1 ([M(^{79}Br)+Na]$^+$), 382.1 ([M(^{81}Br)+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{19}BrNO$ ([M(^{79}Br)+H]$^+$) requires 380.06445, found 380.06507, ([M(^{81}Br)+H]$^+$) requires 382.06241, found 382.06290; **IR** ν_{max} (film)/cm^{-1}: 3023, 2959, 2921, 2851, 1641, 1592, 1543, 1511, 1485, 1445, 1382, 1302, 1230, 1187, 1140, 1115, 1096, 1059, 1014.

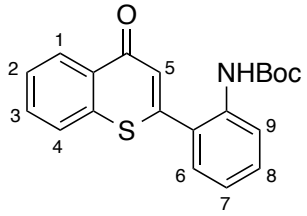
6-Bromo-2-(4-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran-3-yl)quinoline, 90f



Compound **90f** was prepared according to General Procedure **H** using enone **89f** (70.2 mg, 0.136 mmol), EtOH (1.5 mL) and H_2O (1.5 mL). Flash column chromatography (SiO_2, 30-40% Et_2O in petrol) afforded quinoline **90f** as off-white needles (45.8 mg, 85% yield); **m.p.**: 142-144 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.92 (1H, d, *J* 9.0, C(10)*H*), 7.84 (1H, d, *J* 2.0, C(8)*H*), 7.75 (1H, dd, *J* 9.0 and 2.0, C(9)*H*), 7.64 (1H, d, *J* 8.5, C(7)*H*), 7.04 (2H, d, *J* 9.0, C(2)*H*), 6.84 (1H, d, *J* 8.5, C(6)*H*), 6.74 (2H, d, *J* 9.0, C(1)*H*), 4.81 (2H, t, *J* 2.5, C(5)H_2), 4.08 (2H, t, *J* 5.5, C(3)H_2), 3.77 (3H, s, OCH_3), 2.65 (2H, tt, *J* 5.5 and 2.5, C(4)H_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.9, 158.8, 146.3, 136.1, 133.8, 133.6, 133.2, 132.6, 131.0, 129.8, 129.4, 127.7, 124.4, 120.0, 113.8, 68.1, 64.8, 55.2, 31.0; **LRMS** (ESI+, *m/z*): 396.1 ([M(^{79}Br)+H]$^+$) 398.1 ([M(^{81}Br)+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{19}BrNO_2$ ([M(^{79}Br)+H]$^+$) requires 396.05937, found 396.05952, ([M(^{81}Br)+H]$^+$) requires 398.05732, found 398.05739; **IR** ν_{max} (film)/cm^{-1}: 2957, 2928, 2835, 1607, 1591, 1510, 1485, 1462, 1382, 1301, 1247, 1178, 1141, 1113, 1034, 1014.

7.3.6 Functionalisation of the C(3) and C(4) positions

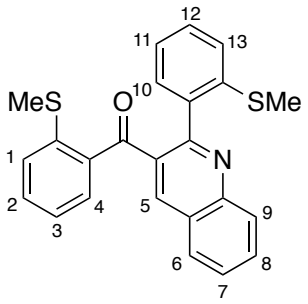
***tert*-Butyl (2-(4-oxo-4*H*-thiochromen-2-yl)phenyl)carbamate, 91**



To a solution of enone **52a** (100 mg, 0.270 mmol) in dry CH_2Cl_2 (0.60 mL) was added Br_2 (17.0 µL, 0.320 mmol), and the reaction stirred for 1 hour at 25 °C. The reaction was then quenched by the addition of 1.0 N $HCl_{(aq)}$ (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was dissolved in $CHCl_3$ (0.5 mL), and then was added Et_3N (64.0 µL, 0.460 mmol). The mixture was stirred at 25 °C for 16 hours. The reaction was then quenched by the addition of 1.0 N $HCl_{(aq)}$ (2 mL) and extracted with $CHCl_3$ (3 × 2 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-40% Et_2O in petrol) afforded thioflavone **91** as a colourless oil (37.5 mg, 41% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.58 (1H, ddd, *J* 8.0, 1.5 and 0.5, C(1)*H*), 8.18 (1H, d, *J* 8.5, C(6)*H*), 7.68-7.63 (2H, m, C(3)*H*, C(4)*H*), 7.59 (1H, ddd, *J* 8.0, 5.5 and 2.5, C(2)*H*), 7.48 (1H, dddd, *J* 8.5, 7.5, 1.5 and 0.5, C(7)*H*), 7.35 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(9)*H*), 7.17 (1H, td, *J* 7.5 and 1.0, C(8)*H*), 7.03 (1H, s, C(5)*H*), 6.85 (1H, br. s, N*H*), 1.49 (9H, s, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 180.3, 152.6, 150.7, 138.3, 135.4, 131.8, 131.0, 130.8, 129.5, 128.7, 128.0, 126.7, 126.4, 125.9, 123.3, 121.0, 81.2, 28.3; **LRMS** (ESI+, *m/z*): 354.1 ([M+H]$^+$); **HRMS** (ammonia CI, *m/z*): $C_{20}H_{20}NO_3S$ ([M+H]$^+$) requires 354.1158, found 354.1159; **IR** ν_{max}

(film)/cm^{-1}: 3265, 2978, 1723, 1616, 1589, 1524, 1443, 1367, 1332, 1298, 1239, 1156, 1101, 1047, 1024.

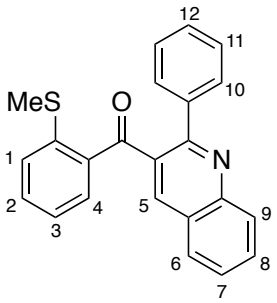
(2-(Methylthio)phenyl)(2-(2-(methylthio)phenyl)quinolin-3-yl)methanone, 55



To a stirred solution of enone **52a** (18.5 mg, 50.1 μmol) in MeCN (0.3 mL) was added 2-(methylthio)benzaldehyde **30** (38.0 mg, 0.250 mmol), then TFA (90.0 μL, 1.20 mmol) and the reaction stirred at room temperature for 1 hour. The reaction was quenched by the addition of 1.0 N $NaOH_{(aq)}$ (10 mL), then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **55** as a pale brown oil (8.2 mg, 41% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.45 (1H, d, *J* 0.5, C(5)*H*), 8.25 (1H, ap. dq, *J* 8.5 and 1.0, C(6)*H*), 7.95 (1H, dd, *J* 8.0 and 1.5, C(9)*H*), 7.86 (1H, ddd, *J* 8.5, 7.0 and 1.5, C(7)*H*), 7.65 (1H, ddd, *J* 8.0, 7.0 and 1.0, C(8)*H*), 7.48 (1H, dd, *J* 8.0 and 1.5, C(4)*H*), 7.33 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.30 (1H, ddd, *J* 7.5, 1.5 and 0.5, C(10)*H*), 7.21 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(12)*H*), 7.18 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.15 (1H, dd, *J* 8.0 and 1.5, C(13)*H*), 7.11 (1H, td, *J* 7.5 and 1.5, C(11)*H*), 6.97 (1H, ddd, *J* 8.0, 7.5 and 1.0, C(3)*H*), 2.39 (3H, s, SCH_3), 2.27 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 195.5, 157.4, 148.0, 142.4, 139.2, 138.4, 137.1, 135.2, 133.6, 132.2, 131.8, 131.4, 130.2, 129.6, 128.7, 128.5, 127.5, 126.7, 126.1, 125.0, 124.9, 122.9, 16.8, 16.0; **LRMS** (ESI+, *m/z*): 402.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{24}H_{20}NOS_2$ ([M+H]$^+$) requires

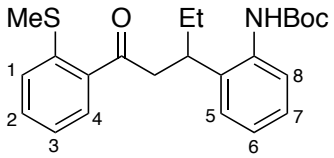
402.09808, found 402.09810; **IR** ν_{max} (film)/cm^{-1}: 3056, 2921, 2853, 1653, 1616, 1586, 1556, 1486, 1460, 1433, 1409, 1372, 1319, 1266, 1229, 1130, 1066, 1042, 1018, 1009.

(2-(Methylthio)phenyl)(2-phenylquinolin-3-yl)methanone, 93



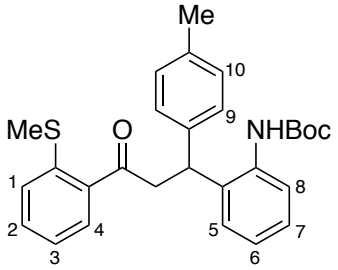
To a stirred solution of enone **52a** (18.5 mg, 50.1 μmol) in MeCN (0.3 mL) was added benzaldehyde **92** (26.0 μL, 0.250 mmol) then TFA (90.0 μL, 1.20 mmol) and the reaction stirred at room temperature for 1 hour. The reaction was quenched by the addition of 1.0 N $NaOH_{(aq)}$ (10 mL), then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% Et_2O in petrol) afforded quinoline **93** as a pale brown oil (8.3 mg, 45% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.43 (1H, d, *J* 0.5, C(5)*H*), 8.26 (1H, dd, *J* 8.5 and 1.0, C(6)*H*), 7.95 (1H, dd, *J* 8.0 and 1.5, C(9)*H*), 7.86 (1H, ddd, *J* 8.5, 7.0 and 1.5, C(7)*H*), 7.66-7.60 (3H, m, C(8)*H*, C(10)*H*), 7.34-7.21 (6H, m, C(1)*H*, C(2)*H*, C(4)*H*, C(11)*H*, C(12)*H*), 6.91 (1H, ddd, *J* 8.0, 7.5 and 1.0, C(3)*H*), 2.46 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 196.6, 157.7, 148.4, 139.9, 138.3, 134.9, 133.3, 132.3, 131.3, 129.6, 129.18, 129.15, 129.07, 128.6, 128.30, 128.19, 127.2, 126.0, 124.9, 123.0, 15.9; **LRMS** (ESI+, *m/z*): 356.0 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{18}NOS^+$ ([M+H]$^+$) requires 356.11036, found 356.11030; **IR** ν_{max} (film)/cm^{-1}: 3059, 2920, 2851, 1715, 1655, 1618, 1588, 1556, 1485, 1458, 1433, 1410, 1372, 1268, 1231, 1130, 1074, 1017.

tert-Butyl (2-(1-(2-(methylthio)phenyl)-1-oxopentan-3-yl)phenyl)carbamate, 95a



At 0 °C, to a suspension of CuI (38.1 mg, 0.200 mmol) in THF (3.0 mL) was added EtMgCl (2.20 mL, 1.47 M solution in THF, 3.30 mmol), and the resulting mixture stirred at 0 °C for 15 minutes. A solution of enone **52a** (370 mg, 1.00 mmol) in THF (3.0 mL) was then added, and the reaction mixture stirred for 2 hours at 0 °C. The reaction was quenched by the addition of MeOH (0.5 mL) under $N_{2(g)}$ and immediately filtered through a SiO_2 pad (washed with Et_2O) to remove the Cu residues. The filtrate was concentrated *in vacuo*, before flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded ketone **95a** as a pale yellow oil (347 mg, 87 % yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.74 (1H, dd, *J* 8.0 and 1.5, C(4)*H*), 7.63 (1H, d, *J* 7.0, C(8)*H*), 7.54 (1H, br. s, N*H*), 7.45 (1H, ddd, *J* 8.0, 7.5 and 1.0, C(2)*H*), 7.31 (1H, d, *J* 8.0, C(1)*H*), 7.20-7.15 (3H, m, C(3)*H*, C(5)*H*, C(7)*H*), 7.09 (1H, td, *J* 7.5 and 1.0, C(6)*H*), 3.55-3.48 (1H, m, C*H*(Ar)Et), 3.40 (1H, dd, *J* 17.5 and 9.0, C(O)CH_AH$_B$), 3.26 (1H, dd, *J* 17.5 and 4.5, C(O)CH$_A$$H_B$), 2.40 (3H, s, SC$H_3$), 1.81-1.69 (2H, m, C$H_2CH_3$), 1.56 (9H, s, C(C$H_3$)$_3$), 0.82 (3H, t, *J* 7.5, CH$_2$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 201.1, 154.2, 142.1, 136.7, 136.3, 134.6, 132.2, 130.0, 126.4, 125.9, 125.3, 124.8, 124.6, 123.6, 79.8, 47.6, 35.1, 29.4, 28.5, 16.0, 12.1; **LRMS** (ESI+, *m/z*): 422.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{29}NNaO_3S$ ([M+Na]$^+$) requires 422.17604, found 422.17588; **IR** ν_{max} (film)/cm^{-1}: 3361, 2967, 2930, 2874, 1721, 1665, 1587, 1510, 1450, 1366, 1232, 1160, 1048, 1024.

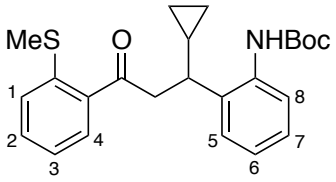
tert-Butyl (2-(3-(2-(methylthio)phenyl)-3-oxo-1-(_p_-tolyl)propyl)phenyl)carbamate, 95b



At 0 °C, to a suspension of CuI (11.4 mg, 60.0 μmol) in THF (0.9 mL) was added *p*-tolylMgBr (1.22 mL, 0.820 M solution in THF, 1.00 mmol), and the resulting mixture stirred at 0 °C for 15 minutes. A solution of enone **52a** (111 mg, 0.300 mmol) in THF (0.9 mL) was then added, and the reaction mixture stirred for 2 hours at 0 °C. The reaction was quenched by the addition of MeOH (0.5 mL) under $N_{2(g)}$ and immediately filtered through a SiO_2 pad (washed with Et_2O) to remove the Cu residues. The filtrate was concentrated *in vacuo*, before flash column chromatography (SiO_2, 15-30% Et_2O in petrol) afforded ketone **95b** as a pale yellow solid (130.6 mg, 94% yield); **m.p.**: 137-139 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.79 (1H, dd, *J* 8.0 and 1.5, C(4)*H*), 7.71 (1H, d, *J* 7.0, C(8)*H*), 7.46 (1H, td, *J* 7.5 and 1.0, C(2)*H*), 7.32 (1H, d, *J* 8.0, C(1)*H*), 7.26-7.18 (3H, m, C(3)*H*, C(5)*H*, C(7)*H*), 7.19 (2H, d, *J* 8.0, C(9)*H*), 7.12 (2H, d, *J* 8.0, C(10)*H*), 7.09 (1H, td, *J* 7.5 and 1.0, C(6)*H*), 7.05 (1H, s, N*H*), 4.98 (1H, t, *J* 7.0, C(O)CH_AH_BC*H*$(Ar)_2$), 3.80 (1H, dd, *J* 17.0 and 7.5, C(O)CH_AH_B), 3.74 (1H, dd, *J* 17.0 and 6.5, C(O)CH_AH_B), 2.40 (3H, s, SCH_3), 2.32 (3H, s, $ArCH_3$), 1.55 (9H, s, $C(CH_3)_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 199.6, 153.7, 142.3, 140.1, 136.2, 135.8, 135.6, 134.7, 132.3, 130.0, 129.5, 127.7, 127.4, 127.0, 125.4, 124.6, 124.2, 123.6, 80.0, 46.0, 39.5, 28.4, 21.0, 16.0; **LRMS** (ESI+, *m/z*): 484.2 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{28}H_{31}NNaO_3S$ ($[M+Na]^+$)

requires 484.19169, found 484.19074; **IR** ν_{max} (film)/cm^{-1}: 3399, 2978 2922, 1720, 1669, 1587, 1510, 1449, 1433, 1366, 1297, 1230, 1155, 1048, 1023.

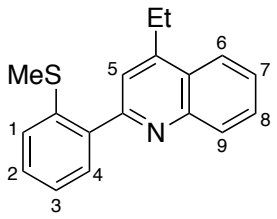
***tert*-Butyl (2-(1-cyclopropyl-3-(2-(methylthio)phenyl)-3-oxopropyl)phenyl)carbamate, 95c**



At 0 °C, to a suspension of CuI (76.2 mg, 0.400 mmol) in THF (0.6 mL) was added cyclopropylMgBr (1.05 mL, 0.760 M solution in THF, 0.800 mmol), and the resulting mixture stirred at 0 °C for 15 minutes. A solution of enone **52a** (73.9 mg, 0.200 mmol) in THF (0.6 mL) was then added, and the reaction mixture stirred for 2 hours at 0 °C. The reaction was quenched by the addition of MeOH (0.5 mL) under $N_{2(g)}$ and immediately filtered through a SiO_2 pad (washed with Et_2O) to remove the Cu residues. The filtrate was concentrated *in vacuo*, before flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded ketone **95c** as an off-white solid (70.7 mg, 86% yield); **m.p.**: 139-141 °C (crystalised from Et_2O/petrol); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.80 (1H, dd, *J* 8.0 and 1.0, C(4)*H*), 7.65 (1H, d, *J* 6.5, C(8)*H*), 7.51 (1H, br. s, N*H*), 7.45 (1H, ddd, *J* 8.0, 7.5 and 1.5, C(2)*H*), 7.34 (1H, dd, *J* 7.5 and 1.5, C(5)*H*), 7.30 (1H, d, *J* 8.0, C(1)*H*), 7.21-7.15 (2H, m, C(3)*H*, C(7)*H*), 7.11 (1H, td, *J* 7.5 and 1.0, C(6)*H*), 3.54 (1H, dd, *J* 17.5 and 9.0, C(O)CH_AH$_B$), 3.45 (1H, dd, *J* 17.5 and 4.5, C(O)CH$_A$$H_B$), 2.87 (1H, td, *J* 9.0 and 4.5, C(O)CH$_A$H$_B$C*H*), 2.39 (3H, s, SCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.23-1.14 (1H, m, Cpr*H*), 0.58 (1H, tt, *J* 9.0 and 4.5, Cpr*H*), 0.43 (1H, tt, *J* 9.0 and 4.5, Cpr*H*), 0.26 (1H, dq, *J* 9.0 and 4.5, Cpr*H*), 0.14 (1H, dq, *J* 9.0 and 4.5, Cpr*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 200.9, 154.1, 142.4,

136.7, 135.7, 134.3, 132.3, 130.2, 126.7, 126.5, 125.2, 124.7, 124.4, 123.5, 79.8, 47.5, 38.9, 28.4, 17.3, 16.0, 5.4, 4.5; **LRMS** (ESI+, *m/z*): 434.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{24}H_{29}NNaO_3S$ ([M+Na]$^+$) requires 434.17604, found 434.17503; **IR** ν_{max} (film)/cm^{-1}: 3356, 2978, 2920, 1719, 1662, 1587, 1509, 1449, 1433, 1366, 1232, 1215, 1156, 1047, 1022.

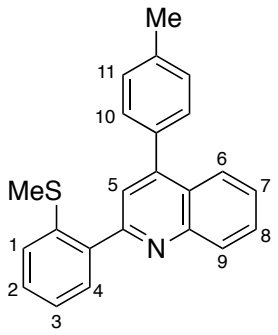
4-Ethyl-2-(2-(methylthio)phenyl)quinoline, 96a



To a solution of ketone **95a** (120 mg, 0.300 mmol) in CH_2Cl_2 (7.5 mL) was added TFA (0.550 mL, 7.20 mmol) and the reaction stirred at 35 °C. After 30 minutes, DDQ (68.1 mg, 0.300 mmol) was added and the reaction stirred at 35 °C for a further 30 minutes. The reaction was quenched by the addition of 1.0 M $NaOH_{(aq)}$ (10 mL), and extracted three times with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded quinoline **96a** as a pale yellow oil (76.5 mg, 92% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.23 (1H, dt, *J* 8.5 and 0.5, C(6)*H*), 8.11 (1H, dd, *J* 8.5 and 1.0, C(9)*H*), 7.75 (1H, ddd, *J* 8.5, 7.0 and 1.5, C(7)*H*), 7.62-7.58 (3H, m, C(4)*H*, C(5)*H*, C(8)*H*), 7.47-7.41 (2H, m, C(1)*H*, C(2)*H*), 7.32 (1H, ddd, *J* 7.5, 6.0 and 2.5, C(3)*H*), 3.21 (2H, qd, *J* 7.5 and 0.5, CH_2CH$_3$), 2.43 (3H, s, SCH_3), 1.47 (3H, t, *J* 7.5, CH$_2$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.5, 149.7, 147.8, 140.3, 137.8, 130.4, 130.0, 129.17, 129.01, 126.3 (3 × C), 125.0, 123.3, 120.8, 25.2, 16.6, 14.0; **LRMS** (ESI+, *m/z*): 280.1 ([M+H]$^+$); **HRMS** (ESI+, m/z): $C_{18}H_{18}NS$ ([M+H]$^+$) requires 280.11545, found

280.11520; **IR** ν_{max} (film)/cm^{-1}: 3060, 2968, 2919, 2874, 1597, 1566, 1552, 1506, 1434, 1351, 1054.

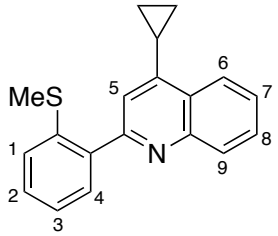
2-(2-(Methylthio)phenyl)-4-(*p*-tolyl)quinoline, 96b



To a solution of ketone **95b** (118 mg, 0.256 mmol) in CH_2Cl_2 (6.4 mL) was added TFA (0.470 mL, 6.14 mmol) and the reaction stirred at 35 °C. After 30 minutes, DDQ (58.1 mg, 0.256 mmol) was added and the reaction stirred at 35 °C for a further 30 minutes. The reaction was quenched by the addition of 1.0 M $NaOH_{(aq)}$ (10 mL), and extracted three times with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20-30% Et_2O in petrol) afforded quinoline **96b** as a pale brown oil (84.2 mg, 96% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.31 (1H, d, *J* 8.5, C(6)*H*), 8.05 (1H, dd, *J* 8.5 and 1.0, C(9)*H*), 7.78 (1H, ddd, *J* 8.5, 7.0 and 1.5, C(7)*H*), 7.71 (1H, s, C(5)*H*), 7.66 (1H, d, *J* 7.0, C(4)*H*), 7.55 (1H, ddd, *J* 8.5, 7.0 and 1.5, C(8)*H*), 7.53 (2H, d, *J* 8.0, C(10)*H*), 7.46-7.43 (2H, m, C(1)*H*, C(2)*H*), 7.38 (2H, d, *J* 8.0, C(11)*H*), 7.33 (1H, ddd, *J* 7.5, 5.0 and 3.5, C(3)*H*), 2.50 (3H, s, ArCH_3), 2.46 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.2, 148.40, 148.35, 139.9, 138.3, 137.9, 135.3, 130.1, 130.0, 129.6, 129.4, 129.3, 129.1, 126.6, 126.4, 125.8, 125.6, 125.1, 122.4, 21.4, 16.7; **LRMS** (ESI+, *m/z*): 342.1 ([M+H]$^+$); **HRMS** (ESI+, *m/z*): $C_{23}H_{20}NS$ ([M+H]$^+$) requires 342.13110, found 342.13087;

IR ν_{max} (film)/cm^{-1}: 3058, 2919, 2859, 1613, 1591, 1567, 1546, 1499, 1473, 1434, 1411, 1357, 1051, 1022.

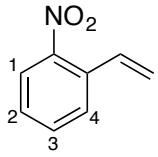
4-Cyclopropyl-2-(2-(methylthio)phenyl)quinoline, 96c



To a solution of ketone **95c** (67.0 mg, 0.163 mmol) in CH_2Cl_2 (4.1 mL) was added TFA (0.300 mL, 3.91 mmol) and the reaction stirred at 35 °C. After 30 minutes, DDQ (37.0 mg, 0.163 mmol) was added and the reaction stirred at 35 °C for a further 30 minutes. The reaction was quenched by the addition of 1.0 M $NaOH_{(aq)}$ (10 mL), and extracted three times with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20-40% Et_2O in petrol) afforded quinoline **96c** as a pale brown oil (44.6 mg, 94% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.38 (1H, d, *J* 8.0, C(6)*H*), 8.23 (1H, d, *J* 8.5, C(9)*H*), 7.76 (1H, ddd, *J* 8.5, 7.0 and 1.0, C(8)*H*), 7.62 (1H, ddd, *J* 8.0, 7.0 and 1.0, C(7)*H*), 7.57 (1H, d, *J* 7.0, C(4)*H*), 7.45-7.40 (2H, m, C(1)*H*, C(2)*H*), 7.37 (1H, s, C(5)*H*), 7.30 (1H, ddd, *J* 7.0, 7.0 and 2.0, C(3)*H*), 2.51 (1H, tt, *J* 9.0 and 5.0, Cpr*H*), 2.41 (3H, s, SCH_3), 1.23-1.19 (2H, m, Cpr*H*), 0.97-0.93 (2H, m, Cpr*H*); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.5, 149.4, 147.7, 140.3, 137.7, 130.18, 129.99, 129.3, 129.0, 127.6, 126.31, 126.28, 125.1, 123.8, 118.3, 16.6, 12.3, 7.9; **LRMS** (ESI+, *m/z*): 292.1 ($[M+H]^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{18}NS$ ($[M+H]^+$) requires 292.11545, found 292.11541; **IR** ν_{max} (film)/cm^{-1}: 3061, 3005, 2919, 2850, 1596, 1551, 1505, 1434, 1376, 1321, 1266, 1050, 1026.

7.4 Experimental Data for Chapter 4

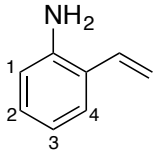
1-Nitro-2-vinylbenzene, 141



Under a N_2 atmosphere, at 0 °C, to a solution of Ph_3PMeBr (11.8 g, 32.8 mmol) in THF (120 mL) was added dropwise ^{n}BuLi (13.1 mL, 2.50 M solution in hexanes, 32.8 mmol). The resulting solution was stirred at room temperature for 1 hour, before the addition of 2-nitrobenzaldehyde (5.00 g, 33.1 mmol). The mixture was then heated at 65 °C for 16 hours. After cooling to room temperature, the reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (30 mL). The crude reaction mixture was partitioned between Et_2O (200 mL) and brine (200 mL), and the aqueous layer washed with Et_2O (2 × 200 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-15% Et_2O in petrol) afforded alkene **141** as a pale yellow oil (3.02 g, 61% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.95 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 7.65 (1H, dd, *J* 8.0 and 1.5, C(4)*H*), 7.61 (1H, dd, *J* 8.0, 7.0 and 1.0, C(3)*H*), 7.44 (1H, ddd, *J* 8.0, 7.0 and 1.5, C(2)*H*), 7.20 (1H, dd, *J* 17.5 and 11.0, C*H*=CH_2), 5.77 (1H, dd, *J* 17.5 and 1.0, CH=C$H_A$$H_B$), 5.51 (1H, dd, *J* 11.0 and 1.0, CH=$CH_A$$H_B$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 147.8, 133.3, 133.1, 132.5, 128.50, 128.36, 124.4, 119.0; **HRMS** (EI, *m/z*): $C_8H_7NO_2$ ($[M]^+$) requires 149.04768, found 149.04822.

Data consistent with the literature.[293]

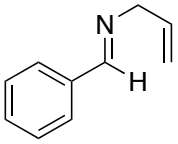
2-Vinylaniline, 130



To a solution of 2-nitrostyrene **141** (2.98 g, 20 mmol) in EtOH (70 mL) was added Fe powder (6.90 g, 124 mmol), followed by HCl (2.00 mL, 12.0 M solution in H_2O, 24 mmol). The resulting solution was refluxed at 85 °C for 5 hours. Once the reaction had cooled to room temperature the mixture was neutralized with Na_2CO_3, then partitioned between Et_2O (400 mL) and H_2O (400 mL). The organic fraction was washed with H_2O (2 × 400 mL), then brine (400 mL), before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20-50% Et_2O in petrol) afforded aniline **130** as a colourless oil (2.30 g, 97% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.33 (1H, ddt, *J* 7.5, 1.5 and 0.5, C(4)*H*), 7.13 (1H, app. td, *J* 7.5 and 1.5, C(2)*H*), 6.81 (1H, dd, *J* 17.5 and 11.0, C*H*CH_2), 6.81 (1H, dddd, *J* 7.5, 7.5, 1.0 and 0.5, C(3)H), 6.72 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 5.67 (1H, dd, *J* 17.5 and 1.5, CHCH_AH_B), 5.36 (1H, dd, *J* 11.0 and 1.5, $CHCH_AH_B$), 3.79 (2H, s, NH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.7, 132.7, 128.7, 127.3, 124.1, 118.9, 116.1, 115.7; **LRMS** (ESI+, *m/z*): 120.2 ($[M+H]^+$).

Data consistent with the literature.[294]

(*E*)-*N*-Allyl-1-phenylmethanimine, 98

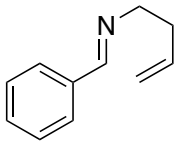


To a solution of allyl amine (3.14 g, 55 mmol) and benzaldehyde **92** (5.31 g, 50 mmol) in CH_2Cl_2 (60 mL) was added anhydrous magnesium sulfate (5.00 g). The resulting

solution was stirred at room temperature for 16 hours. The magnesium sulfate was then removed *via* filtration, and the reaction mixture concentrated *in vacuo,* to afford imine **98** as a colourless oil (7.20 g, 99% yield). No further purification was required; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.33 (1H, s, C(NR)*H*), 7.80-7.78 (2H, m, Ar*H*), 7.48-7.42 (3H, m, Ar*H*), 6.11 (1H, ddt, *J* 17.0, 10.5 and 5.5, C*H*=CH_2), 5.27 (1H, app. dq, *J* 17.0 and 1.5, CH=C$H_A$$H_B$), 5.19 (1H, app. dq, *J* 10.5 and 1.5, CH=$CH_A$$H_B$), 4.30 (2H, app. dq, *J* 5.5 and 1.5, NCH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 162.0, 136.1, 135.9, 130.7, 128.6, 128.1, 116.1, 63.6; **HRMS** (ammonia CI, *m/z*): $C_{10}H_{12}N$ ($[M+H]^+$) requires 146.0964, found 146.0968.

Data consistent with the literature.[295]

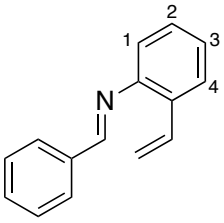
(*E*)-*N*-(But-3-en-1-yl)-1-phenylmethanimine, 99



To a solution of homoallyl amine (625 mg, 8.79 mmol) and benzaldehyde **92** (848 mg, 8.00 mmol) in CH_2Cl_2 (10 mL) was added anhydrous magnesium sulfate (0.80 g). The resulting solution was stirred at room temperature for 16 hours. The magnesium sulfate was then removed *via* filtration, and the reaction mixture concentrated *in vacuo,* to afford imine **99** as a colourless oil (1.26 g, 99% yield). No further purification was required; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.30 (1H, s, NC*H*), 7.77-7.74 (2H, m, Ar*H*), 7.42-7.46 (3H, m, Ar*H*), 5.89 (1H, ddt, *J* 17.0, 10.0 and 7.0, C*H*CH_2), 5.13 (1H, dq, *J* 17.0 and 1.5, CHC$H_A$$H_B$), 5.07 (1H, dq, *J* 10.0 and 1.5, $CHCH_A$$H_B$), 3.71 (2H, td, *J* 7.0 and 1.5, NC$H_2$$CH_2$), 2.50 (2H, qt, *J* 7.0 and 1.5, NCH_2CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 161.3, 136.25, 136.20, 130.6, 128.6, 128.1, 116.2, 61.2, 35.2; **LRMS** (ESI+, *m/z*): 160.2 ($[M+H]^+$).

Data consistent with the literature.[296]

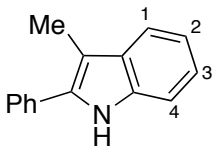
(*E*)-1-Phenyl-*N*-(2-vinylphenyl)methanimine, 100



To a solution of 2-aminostyrene **130** (2.00 g, 16.8 mmol) and benzaldehyde (1.78 g, 16.8 mmol) in CH_2Cl_2 (20 mL) was added anhydrous magnesium sulfate (1.70 g). The resulting solution was stirred at room temperature for 16 hours. The magnesium sulfate was then removed *via* filtration, and the reaction mixture concentrated *in vacuo,* to afford imine **100** as a colourless oil (3.41 g, 98% yield). No further purification was required; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.42 (1H, s, NC*H*), 7.99-7.96 (2H, m, Ar*H*), 7.64 (1H, dd, *J* 7.5 and 1.5, C(4)*H*), 7.55-7.51 (3H, m, Ar*H*), 7.33 (1H, td, *J* 7.5 and 1.5, C(2)*H*), 7.29-7.22 (2H, m, C(3)*H*, C*H*CH_2), 7.00 (1H, dd, *J* 8.0 and 1.0, C(1)*H*), 5.80 (1H, dd, *J* 17.5 and 1.5, CHCH_AH_B), 5.33 (1H, dd, *J* 11.0 and 1.5, CHCH_AH_B); **^{13}C-NMR** (100 MHz, $CDCl_3$): 160.2, 149.9, 136.3, 133.3, 131.42, 131.24, 128.86, 128.80, 128.72, 125.86, 125.69, 118.5, 114.8; **LRMS** (ESI+, *m/z*): 208.2 ($[M+H]^+$).

Data consistent with the literature.[297]

3-Methyl-2-phenyl-1*H*-indole, 103



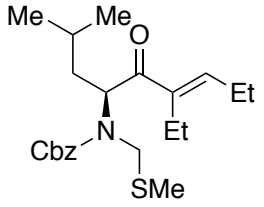
A microwave vial was charged with $CoCl_2$ (3.9 mg, 30 μmol), dppp (12.4 mg, 30 μmol) and Zn powder (9.8 mg, 150 μmol), before being evacuated and backfilled with $N_{2(g)}$ three times. Acetonitrile (0.60 mL) was added, and the resulting solution stirred at

room temperature for 5 minutes. Imine **100** (62.2 mg, 0.300 mmol) in acetonitrile (0.6 mL) was then added, and the reaction heated at 80 °C for 64 hours. Once cooled to room temperature, the reaction mixture was passed through a short pad of SiO_2, washed through with Et_2O, and concentrated *in vacuo*. Flash column chromatography (SiO_2, 5-10% Et_2O in petrol) afforded indole **103** as a colourless oil (16.0 mg, 26% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.08 (1H, s, N*H*), 7.66-7.61 (3H, m, 2 × Ar*H*, C(1)*H*), 7.54-7.49 (2H, m, 2 × Ar*H*), 7.42-7.37 (2H, m, Ar*H*, C(4)*H*), 7.25 (1H, ddd, *J* 8.0, 7.0 and 1.0, C(3)*H*), 7.19 (1H, ddd, *J* 8.0, 7.0 and 1.0, C(2)*H*), 2.51 (3H, s, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 135.8, 134.0, 133.3, 130.0, 128.8, 127.7, 127.3, 122.3, 119.5, 119.0, 110.7, 108.7, 9.7; **HRMS** (ammonia CI, *m/z*): $C_{15}H_{13}N$ ($[M+H]^+$) requires 208.1121, found 208.1119.

Data consistent with the literature.[298]

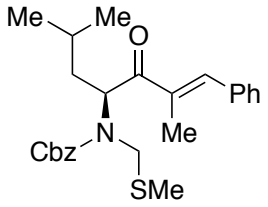
7.5 Experimental Data for Chapter 5

Benzyl (*S*,*E*)-(6-ethyl-2-methyl-5-oxonon-6-en-4-yl)((methylthio)methyl)carbamate, 106



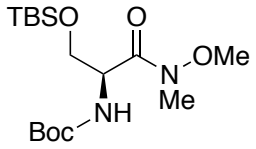
A catalyst solution containing $[Rh(nbd)_2]BF_4$ (2.8 mg, 7.5 μmol) and dcpm (3.0 mg, 7.5 μmol) in acetone (0.30 mL), prepared according to General Procedure **A,** was reduced to dryness by bubbling $N_{2(g)}$ through the solution. A solution of leucine-derived aldehyde **105** (46.0 mg, 0.15 mmol)[299] and 3-hexyne (26.0 μL, 0.23 mmol) in acetone (75 μL) was then added to the dry catalyst. The resulting solution was left to stir at 55 °C for 3 hours, before being filtered through a plug of SiO_2 and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded enone **106** as a colourless oil (53.7 mg, 92% yield); **^{1}H-NMR** (400 MHz, $(CD_3)_2SO$, 363 K): 7.38-7.31 (5H, m, Ar*H*), 6.59 (1H, t, *J* 7.0, C(Et)C*H*(Et)), 5.26 (1H, t , *J* 7.0, C(O)C*H*), 5.16 (2H, s, PhCH_2), 4.44 (1H, d, *J* 14.0, NCH_AH$_B$S), 4.37 (1H, d, *J* 14.0, NCH$_A$$H_B$S), 2.26-2.16 (4H, m, C$H_2CH_3$), 2.08 (3H, s, SC$H_3$), 1.65 (2H, app. t, *J* 7.0, C(O)CH(N)CH_2), 1.58 (1H, app. nonet, *J* 6.5, C*H*$(CH_3)_2$), 0.98 (3H, t, *J* 7.5, CH_2CH_3), 0.92-0.88 (9H, m, CH(CH_3)$_2$, CH_2CH_3); **^{13}C-NMR** (100 MHz, $(CD_3)_2SO$): 199.5, 155.8, 143.3, 141.3, 136.9, 128.8, 128.4, 128.2, 67.7, 56.9, 49.6, 38.4, 25.1, 23.1, 22.4, 21.8, 19.4, 15.8, 13.8, 13.4; **LRMS** (ESI+, *m/z*): 414.2 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{22}H_{33}NNaO_3S$ ($[M+Na]^+$) requires 414.2073, found 414.2078; **IR** ν_{max} (film)/cm^{-1}: 2960, 2934, 2872, 1698, 1668, 1454, 1403, 1367, 1319, 1230, 1177, 1093, 1041, 1002; **$[\alpha]_D^{20}$**: –32.8° (c = 1.0, $CHCl_3$).

Benzyl (*S*,*E*)-(2,6-dimethyl-3-oxo-1-phenylhept-1-en-4-yl)((methylthio)methyl)carbamate, 107



A catalyst solution containing $[Rh(nbd)_2]BF_4$ (2.8 mg, 7.5 μmol) and dcpm (3.0 mg, 7.5 μmol) in acetone (0.30 mL), prepared according to General Procedure **A,** was reduced to dryness by bubbling $N_{2(g)}$ through the solution. A solution of leucine-derived aldehyde **105** (46.0 mg, 0.15 mmol)[299] and 1-phenyl-1-propyne (37.0 μL, 0.23 mmol) in acetone (75 μL) was then added to the dry catalyst. The resulting solution was left to stir at 55 °C for 3 hours, before being filtered through a plug of SiO_2 and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% Et_2O in petrol) afforded enone **107** as a colourless oil (46.0 mg, 73% yield); **^{1}H-NMR** (400 MHz, $(CD_3)_2SO$, 363 K): 7.54 (1H, s, C(Me)C*H*Ph), 7.46-7.30 (10H, m, Ar*H*), 5.40 (1H, t, *J* 7.0, C(O)C*H*), 5.18 (2H, s, PhCH_2), 4.52 (1H, d, *J* 14.0, NCH_AH$_B$S), 4.40 (1H, d, *J* 14.0, NCH$_A$$H_B$S), 2.05 (3H, s, SC$H_3$), 1.98 (3H, s, C(O)C(C$H_3$)CHPh), 1.81-1.56 (3H, m, CH_2C*H*$(CH_3)_2$), 0.94 (6H, t, *J* 6.0, CH(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $(CD_3)_2SO$): 200.5, 155.8, 137.8, 136.8, 136.1, 136.0, 129.9, 128.9 (2C), 128.7, 128.4, 128.2, 67.8, 57.3, 49.5, 38.1, 25.1, 23.2, 22.6, 15.7, 14.0; **LRMS** (ESI+, *m/z*): 448.2 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{25}H_{31}NNaO_3S$ ($[M+Na]^+$) requires 448.1917, found 488.1915; **IR** ν_{max} (film)/cm^{-1}: 2956, 2923, 2869, 1693, 1670, 1625, 1496, 1449, 1404, 1367, 1319, 1229, 1174, 1122, 1094, 1080, 1062, 1028, 1002; **$[\alpha]_D^{20}$**: –62.6° (c = 1.0, $CHCl_3$).

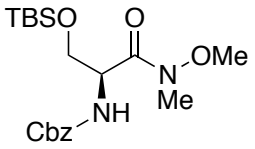
(*S*)-*tert*-Butyl (3,8,8,9,9-pentamethyl-4-oxo-2,7-dioxa-3-aza-8-siladecan-5-yl)carbamate, 110



To a stirred solution of Boc-Ser-OH (5.00 g, 24.4 mmol) in CH_2Cl_2 (240 mL) at 0 ºC, was added triethylamine (3.70 mL, 26.8 mmol) and *N*,*O*-dimethylhydroxylaminehydrochloride (2.61 g, 26.8 mmol). Then was added dicyclohexylcarbodiimide (5.53 g, 26.8 mmol), and the reaction allowed to warm to room temperature over 2 hours before the reaction was then poured onto 1.0 N $HCl_{(aq)}$/ice (200 mL). The layers were then separated, the aqueous layer extracted with CH_2Cl_2 (2 × 200 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. With no further purification the crude Weinreb amide was dissolved in DMF (100 mL) and cooled to 0 ºC. To the resulting solution was added TBS-Cl (3.86 g, 25.6 mmol) and imidazole (1.99 g, 29.2 mmol). The reaction was stirred at 0 °C for 10 minutes before being quenched by the addition of ice. The resulting mixture was extracted with Et_2O (3 × 200 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-20% EtOAc in petrol) afforded Weinreb amide **110** as a colourless oil (6.54 g, 74% yield**); ^{1}H-NMR** (400 MHz, $CDCl_3$): 5.34 (1H, d, *J* 9.0, N*H*), 4.73-4.71 (1H, m, BocNHC*H*), 3.83 (1H, dd, *J* 10.0 and 4.5, TBSOCH_AH_B), 3.76 (1H, dd, *J* 10.0 and 5.0, TBSOCH_AH_B), 3.73 (3H, s, OCH_3), 3.19 (3H, s, NCH_3), 1.41 (9H, s, OC(CH_3)$_3$), 0.83 (9H, s, SiC(CH_3)$_3$), 0.00 (6H, s, Si(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 170.7, 155.4, 79.5, 63.5, 61.5, 52.5, 32.1, 28.3, 25.8, 18.2, –5.5; **LRMS** (ESI+, *m/z*): 385.3 ([M+Na]$^+$); **$[\alpha]_D^{20}$**: +15.2 ° (c = 1.5, $CHCl_3$).

Data consistent with the literature.[300]

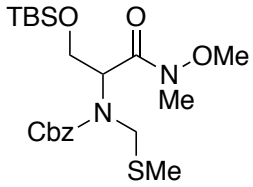
(*S*)-Benzyl (3,8,8,9,9-pentamethyl-4-oxo-2,7-dioxa-3-aza-8-siladecan-5-yl)carbamate, 111



To a solution of carbobenzyloxy-L-serine (5.83 g, 24.7 mmol) in CH_2Cl_2 (240 mL) was added triethylamine (3.73 mL, 26.8 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (2.61 g, 26.8 mmol) at 0 °C. EDCI.HCl (5.14 g, 26.8 mmol) was then slowly added to the reaction mixture over 30 minutes, and the resulting mixture stirred at room temperature for 1 hour. The mixture was poured onto ice/1.0 N HCl(aq) (150 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 125 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. With no further purification the crude Weinreb amide was dissolved in DMF (100 mL) and cooled to 0 ºC. To the resulting solution was added TBS-Cl (3.86 g, 25.6 mmol) and imidazole (1.99 g, 29.2 mmol) at 0 °C. After stirring for 10 minutes at 0 °C, ice was added to the mixture, the organic layer was separated, and the aqueous layer was then extracted with Et_2O (2 × 250 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 50% Et_2O in petrol) to afforded Weinreb amide **111** as a colorless oil (8.42 g, 87% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.38-7.27 (5H, m, Ar*H*), 5.64 (1H, d, *J* 8.5, N*H*), 5.12 (1H, d, *J* 12.5, PhCH_AH_B), 5.06 (1H, d, *J* 12.5, PhCH_AH_B), 4.85-4.73 (1H, m, CBzNHC*H*), 3.87 (1H, dd, *J* 10.0 and 4.5, TBSOCH_ACH_B), 3.80 (1H, dd, *J* 10.0 and 5.0, TBSOC$H_AC H_B$), 3.74 (3H, s, OCH_3), 3.20 (3H, s, NCH_3), 0.84 (9H, s,

C(CH_3)$_3$), 0.00 (6H, s, Si(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 170.3, 156.0, 136.4, 128.5, 128.1, 128.0, 66.9, 63.3, 61.5, 53.1, 32.2, 25.8, 18.3, –5.5; **LRMS** (ESI+, *m/z*): 419.2 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{19}H_{32}N_2NaO_5Si$ ([M+Na]$^+$) requires 419.1973, found 419.1975; **IR** ν_{max} (film)/cm^{-1}: 2930, 2857, 1722, 1661, 1500, 1471, 1391, 1254, 1113, 1047; **$[\alpha]_D^{20}$**: +14.0 ° (c = 1.0, $CHCl_3$).

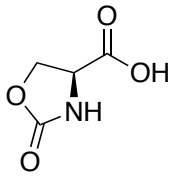
(*S*)-Benzyl ((methylthio)methyl)(3,8,8,9,9-pentamethyl-4-oxo-2,7-dioxa-3-aza-8-siladecan-5-yl)carbamate, 112



To a stirred solution of Weinreb amide **111** (87.0 mg, 0.219 mmol) and NaI (16.5 mg, 0.11 mmol) in DMF (1.4 mL), was added NaH (60% dispersion in mineral oil, 9.6 mg, 0.241 mmol) at 0 °C. The reaction was allowed to warm to room temperature whilst stirring over 30 minutes, before the addition of chloromethyl methyl sulfide (27.6 µL, 0.329 mmol). After 2 hours stirring at room temperature the reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (5 mL). The resulting solution was extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, petrol:EtOAc 10-30% EtOAc) afforded MTM-substituted product **112** as a colourless oil (22.4 mg, 22% yield), in addition to recovered starting material **111** (23.6 mg, 27% yield); **^{1}H-NMR** (500 MHz, $(CD_3)_2SO$, 363 K): 7.41-7.31 (5H, m, Ar*H*), 5.17 (1H, d, *J* 12.5, PhCH_AH_B), 5.13 (1H, d, *J* 12.5, PhCH_AH_B), 5.09 (1H, app. t, *J* 6.5, NC*H*), 4.63 (1H, d, *J* 14.0, SCH_AH_B), 4.54 (1H, d, *J* 14.0, SCH_AH_B), 4.07 (1H, dd, *J* 10.5 and 6.0, OCH_AH_B), 3.92 (1H, dd, *J* 10.5

and 6.5, OCH_AH_B), 3.62 (3H, s, OCH_3), 3.12 (3H, s, NCH_3), 2.12 (3H, s, SCH_3), 0.87 (9H, s, $C(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); **^{13}C-NMR** (125 MHz, $(CD_3)_2SO$, 363 K): 169.6, 156.3, 137.2, 129.1, 128.76, 128.60, 68.0, 62.0, 61.5, 57.4, 49.8, 33.2, 26.5, 18.6, 15.8, –4.72, –4.75; **LRMS** (ESI+, *m/z*): 479.2 ($[M+Na]^+$); **HRMS** (ESI+, *m/z*): $C_{21}H_{36}N_2NaO_5SSi$ ($[M+Na]^+$) requires 479.2006, found 479.2006; **IR** ν_{max} (film)/cm^{-1}: 2928, 1703, 1668, 1402, 1319, 1258, 1115.

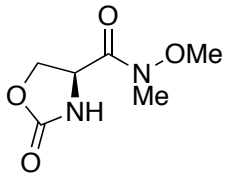
(*S*)-2-Oxooxazolidine-4-carboxylic acid, 115



To a stirred solution of NaOH (4.77 g, 119 mmol) in H_2O (23 mL) was added Z-Ser-OH (15.0 g, 62.7 mmol). The resulting homogenous solution was stirred at room temperature for 30 minutes. The reaction mixture was then washed with Et_2O (3 × 30 mL), acidified to pH 1 by the addition of c. HCl, and then extracted with EtOAc (12 × 60 mL). The combined organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield oxazolidinone **115** as a white solid (6.08 g, 74% yield); **m.p.**: 126-128 °C (crystalised from EtOAc); **^{1}H-NMR** (400 MHz, $(CD_3)_2SO$): 13.09 (1H, br. s, CO_2H), 8.16 (1H, br. s, N*H*), 4.49 (1H, dd, *J* 9.0 and 8.0, CH_AH_B), 4.36 (1H, ddd, *J* 9.0, 4.0 and 1.0, C*H*), 4.30 (1H, dd, *J* 8.0 and 4.0, CH_AH_B); **^{13}C-NMR** (100 MHz, $(CD_3)_2SO$): 173.0, 159.0, 66.8, 53.7; **LRMS** (ESI+, *m/z*): 285.0 ($[2 \times M+Na]^+$); **$[\alpha]_D^{20}$**: –19.6 ° (c = 1.0, H_2O).

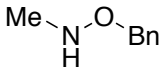
Data consistent with the literature.[301]

(*S*)-*N*-Methoxy-*N*-methyl-2-oxooxazolidine-4-carboxamide, 116



To a solution of carboxylic acid **115** (4.20 g, 32.0 mmol) in CH_2Cl_2 (240 mL) was added sequentially *N*,*O*-dimethylhydroxylaminehydrochloride (3.44 g, 35.2 mmol) and Et_3N (4.91 mL, 35.2 mmol). The solution was then cooled to 0 °C, before a solution of EDCI.HCl (6.75 g, 35.2 mmol) in CH_2Cl_2 (80 mL) was added slowly over 30 minutes. The solution was allowed to warm to room temperature over 16 hours. The reaction mixture was then concentrated *in vacuo* to half of the original volume. The solution was loaded directly onto a SiO_2 column, before flash column chromatography (SiO_2, 60% acetone in petrol) afforded Weinreb amide **116** as a viscous colourless oil (5.26 g, 94 % yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.42 (1H, s, N*H*), 4.63 (1H, dd, *J* 9.5 and 5.5, NHC*H*), 4.56 (1H, dd, *J* 9.5 and 8.5, CH_AH$_B$), 4.36 (1H, dd, *J* 8.5 and 5.5, CH$_A$$H_B$), 3.67 (3H, s, OC$H_3$), 3.17 (3H, s, NC$H_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 170.0, 169.5, 66.7, 61.4, 53.1, 32.5; **LRMS** (ESI+, *m/z*): 371.1 ([2M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_6H_{10}N_2NaO_4$ ([M+Na]$^+$) requires 197.0533, found 197.0528; **IR** ν_{max} (film)/cm^{-1}: 3292, 2981, 2944, 1747, 1662, 1475, 1392, 1326, 1231, 1180, 1120, 1094, 1048; **$[\alpha]_D^{20}$**: −58.4 ° (c = 1.0, $CHCl_3$).

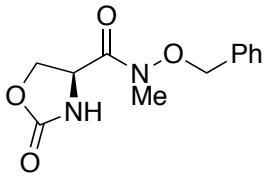
_O_-Benzyl-_N_-methylhydroxylamine, 142



At 0 °C, to a solution of *O*-Benzylhydroxylamine hydrochlorine (10.0 g, 62.7 mmol) in CH_2Cl_2 (125 mL) and H_2O (125 mL) was added portionwise $NaHCO_3$ (11.6 g, 138.0 mmol). Once foaming had ceased, Boc_2O (15.1 g, 69.0 mmol) was added, and the reaction was stirred at 0 °C for 3 hours. The reaction was then quenched by the addition of a saturated solution of $NaHCO_{3(aq)}$ (200 mL). The resulting fractions were separated, and the aqueous fraction extracted with CH_2Cl_2 (2 × 200 mL). The combined organic fractions were dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The crude mixture was then dissolved in DMF (96 mL), and NaH (2.76 g, 60% dispersion in mineral oil, 69.0 mmol) added at room temperature. The resulting solution was stirred for 30 minutes, before the addition of methyl iodide (4.30 mL, 69.0 mmol). The reaction was then stirred at 60 °C for 16 hours. The reaction was quenched by the addition of brine (500 mL), and then extracted with Et_2O (3 × 300 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then added to a stirring solution of TFA (39 mL) and CH_2Cl_2 (117 mL), and stirred for 16 hours. The reaction mixture was basified with 1.0 M $NaHCO_3$ (600 mL), and then extracted with CH_2Cl_2 (3 × 300 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 10-30% EtOAc in petrol) afforded hydroxylamine **142** as a colourless oil (6.90 g, 80% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.42-7.32 (5H, m, Ar*H*), 4.75 (2H, s, CH_2Ph), 2.77 (3H, s, NCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 138.0, 128.41, 128.31, 127.8, 75.6, 39.3; **LRMS** (ESI+, *m/z*): 138.0 ($[M+H]^+$).

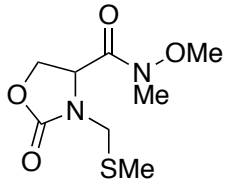
Data consistent with the literature.[302]

(*S*)-*N*-(Benzyloxy)-*N*-methyl-2-oxooxazolidine-4-carboxamide, 117



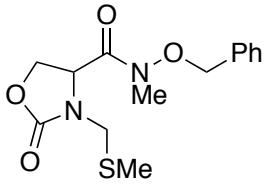
To a solution of carboxylic acid **115** (1.00 g, 7.62 mmol) in CH_2Cl_2 (76 mL) was added sequentially *N*-methyl-*O*-benzylhydroxylamine hydrochloride (1.46 g, 8.39 mmol, hydrochloride salt of compound **142**) and Et_3N (1.17 mL, 8.39 mmol). The solution was then cooled to 0 °C, before EDCI.HCl (1.61 g, 8.39 mmol) was added portionwise over 30 minutes. The solution was allowed to warm to room temperature over 16 hours. The reaction mixture was then concentrated *in vacuo* to half of the original volume. The solution was loaded directly onto a SiO_2 column, before flash column chromatography (SiO_2, 60% acetone in petrol) afforded Weinreb amide **117** as a viscous colourless oil (1.80 g, 94 % yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.46-7.43 (3H, m, Ar*H*), 7.38-7.36 (2H, m, Ar*H*), 6.00 (1H, br. s, N*H*), 4.89 (1H, d, *J* 11.0, PhCH_AH$_B$), 4.84 (1H, d, *J* 11.0, PhCH$_A$$H_B$), 4.347-4.32 (3H, m, C*H*CH_2), 3.31 (3H, s, NCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 170.5, 159.2, 133.5, 129.62, 129.45, 129.1, 76.3, 66.5, 53.0, 33.8; **LRMS** (ESI+, *m/z*): 273.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{12}H_{14}N_2NaO_4$ ([M+Na]$^+$) requires 273.08458, found 273.08425; **IR** ν_{max} (film)/cm^{-1}: 3293, 3063, 2920, 1751, 1664, 1475, 1455, 1391, 1322, 1229, 1182, 1090, 1048; **$[\alpha]_D^{20}$**: −19.6 ° (c = 1.0, $CHCl_3$).

_N_-Methoxy-_N_-methyl-3-((methylthio)methyl)-2-oxooxazolidine-4-carboxamide, 118



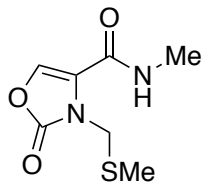
To a solution of Weinreb amide **116** (69.7 mg, 0.400 mmol) and TBAI (73.9 mg, 0.200 mmol) in DMF (2.5 mL) at 0 °C, was added NaHMDS (0.220 mL, 2.0 M solution in THF, 0.440 mmol) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 30 minutes, before cooling back to 0 °C. Methylthiomethyl chloride (168 μL, 2.0 mmol) was then added slowly, and the reaction allowed to warm to room temperature. After 2.5 hours the reaction was quenched by the addition of $LiCl_{(aq)}$ (50 mL, 5% solution), then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% acetone in petrol) afforded MTM-substituted Weinreb amide **118** as a colourless oil (54.4 mg, 58% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 4.99 (1H, dd, *J* 10.0 and 6.5, C(O)C*H*), 4.93 (1H, d, *J* 14.5, NCH_AH_BS), 4.60 (1H, dd, *J* 10.0 and 9.0, OCH_AH_B), 4.21 (1H, dd, *J* 9.0 and 6.6, OCH_AH_B), 4.20 (1H, d, *J* 14.5, NCH_AH_BS), 3.78 (3H, s, OCH_3), 3.24 (3H, s, NCH_3), 2.13 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 168.9, 157.8, 64.4, 61.7, 53.3, 47.5, 32.5, 14.4; **LRMS** (ESI+, *m/z*): 491.2 ([2M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_8H_{14}N_2NaO_4S$ ([M+Na]$^+$) requires 257.0566 , found 257.0577; **IR** ν_{max} (film)/cm^{-1}: 2978, 2921, 1748, 1678, 1480, 1407, 1326, 1276, 1211, 1178, 1081, 1041, 1002.

_N_-(Benzyloxy)-_N_-methyl-3-((methylthio)methyl)-2-oxooxazolidine-4-carboxamide, 119



To a solution of Weinreb amide **117** (100 mg, 0.400 mmol) and TBAI (73.9 mg, 0.200 mmol) in DMF (2.5 mL) at 0 °C was added NaHMDS (0.220 mL, 2.0 M solution in THF, 0.440 mmol) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 30 minutes, before cooling back to 0 °C. Methylthiomethyl chloride (168 μL, 2.0 mmol) was then added slowly, and the reaction allowed to warm to room temperature. After 2.5 hours the reaction was quenched by the addition of $LiCl_{(aq)}$ (50 mL, 5% solution), then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20% acetone in petrol) afforded MTM-substituted Weinreb amide **119** as a colourless oil (89.9 mg, 72% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.43-7.39 (3H, m, Ar*H*), 7.37-7.33 (2H, m, Ar*H*), 4.91 (1H, d, *J* 11.0, CH_AH$_B$Ph), 4.78 (1H, d, *J* 11.0, CH$_A$$H_B$Ph), 4.79 (1H, d, *J* 14.5, NCH_AH$_B$S), 4.78 (1H, dd, *J* 10.0 and 6.5, C(O)C*H*), 4.29 (1H, ap. t, *J* 9.5, OCH_AH$_B$), 4.12 (1H, d, *J* 14.5, NCH$_A$$H_B$S), 4.04 (1H, dd, *J* 9.0 and 6.5, OCH$_A$$H_B$), 3.25 (3H, s, NC$H_3$), 2.05 (3H, s, SC$H_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 169.7, 157.8, 133.5, 129.6, 129.5, 129.1, 76.5, 64.3, 53.4, 47.5, 33.8, 14.5; **LRMS** (ESI+, *m/z*): 333.1 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_{14}H_{18}N_2NaO_4S$ ([M+Na]$^+$) requires 333.08795, found 333.08777; **IR** ν_{max} (film)/cm^{-1}: 2921, 1751, 1671, 1407, 1320, 1276, 1212, 1182, 1079, 1041.

_N_-Methyl-3-((methylthio)methyl)-2-oxo-2,3-dihydrooxazole-4-carboxamide, 120



To a solution of Weinreb amide **117** (2.00 g, 8.00 mmol) and TBAI (1.48 g, 4.00 mmol) in DMF (50 mL) at 0 °C was added NaHMDS (4.40 mL, 2.0 M solution in THF, 8.80 mmol) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 30 minutes, before cooling to 0 °C. Methylthiomethyl chloride (3.36 mL, 40.0 mmol) was then added slowly, and the reaction allowed to warm to room temperature. After 2.5 hours the reaction was quenched by the addition of $LiCl_{(aq)}$ (50 mL, 5% solution), then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, 20-40% acetone in petrol) afforded oxazolone **120** as a colourless oil (420 mg, 26% yield), in addition to MTM-substituted Weinreb amide **119** (650 mg, 25% yield); **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.41 (1H, s, C=C*H*), 7.19 (1H, q, *J* 4.5, N*H*), 5.04 (2H, s, NCH_2S), 2.87 (3H, d, *J* 4.5, NCH_3), 2.15 (3H, s, SCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 158.6, 155.3, 130.1, 122.7, 46.8, 26.2, 15.1; **LRMS** (ESI+, *m/z*): 225.0 ([M+Na]$^+$); **HRMS** (ESI+, *m/z*): $C_7H_{10}N_2NaO_3S$ ([M+Na]$^+$) requires 225.03043, found 225.03033; **IR** ν_{max} (film)/cm^{-1}: 3324, 3129, 2922, 1745, 1656, 1609, 1551, 1418, 1388, 1350, 1291, 1236, 1201, 1122, 1077, 1033.

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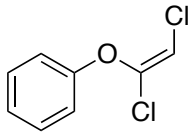
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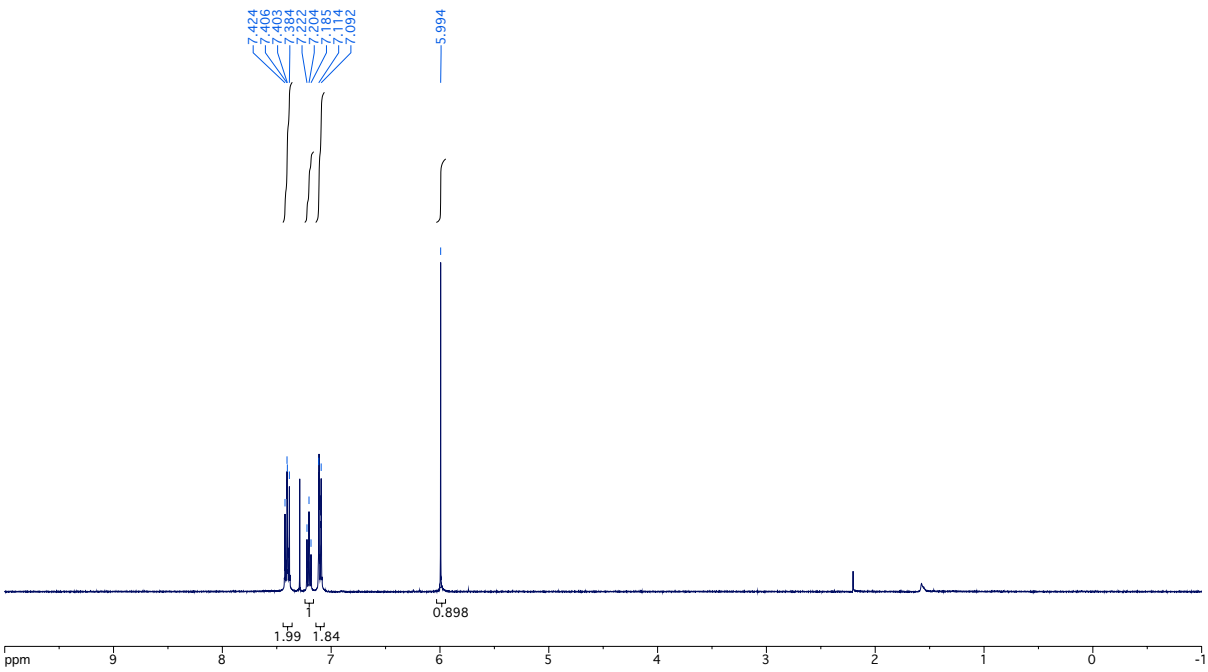
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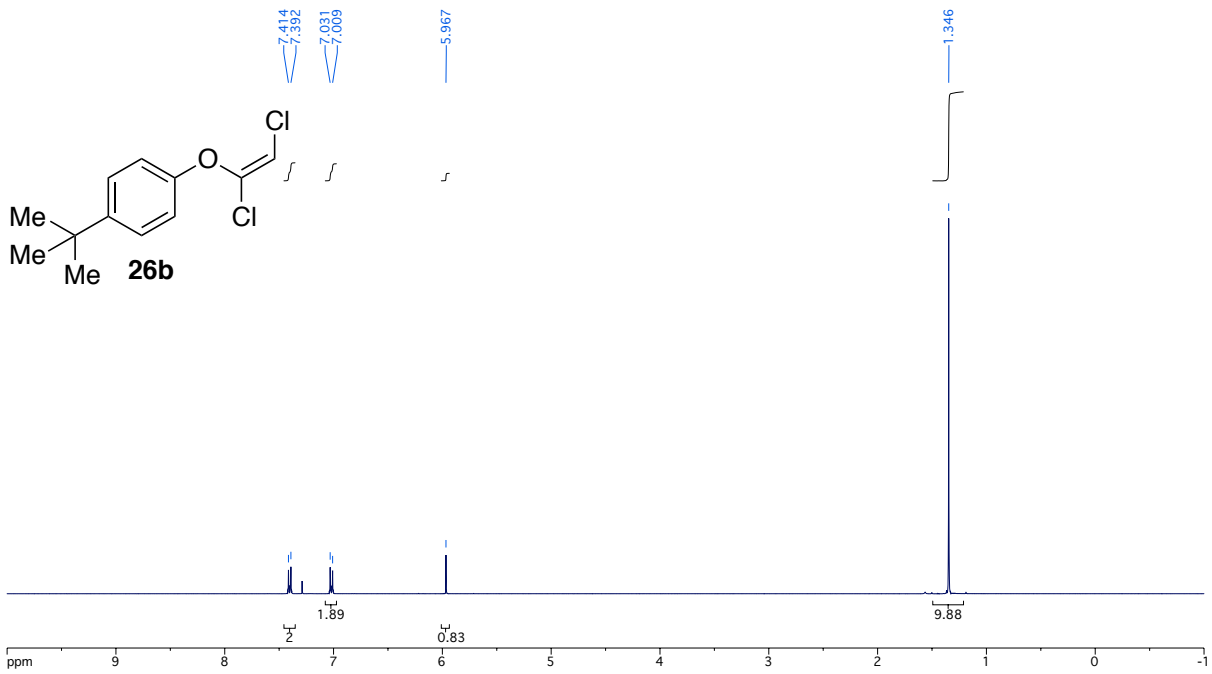
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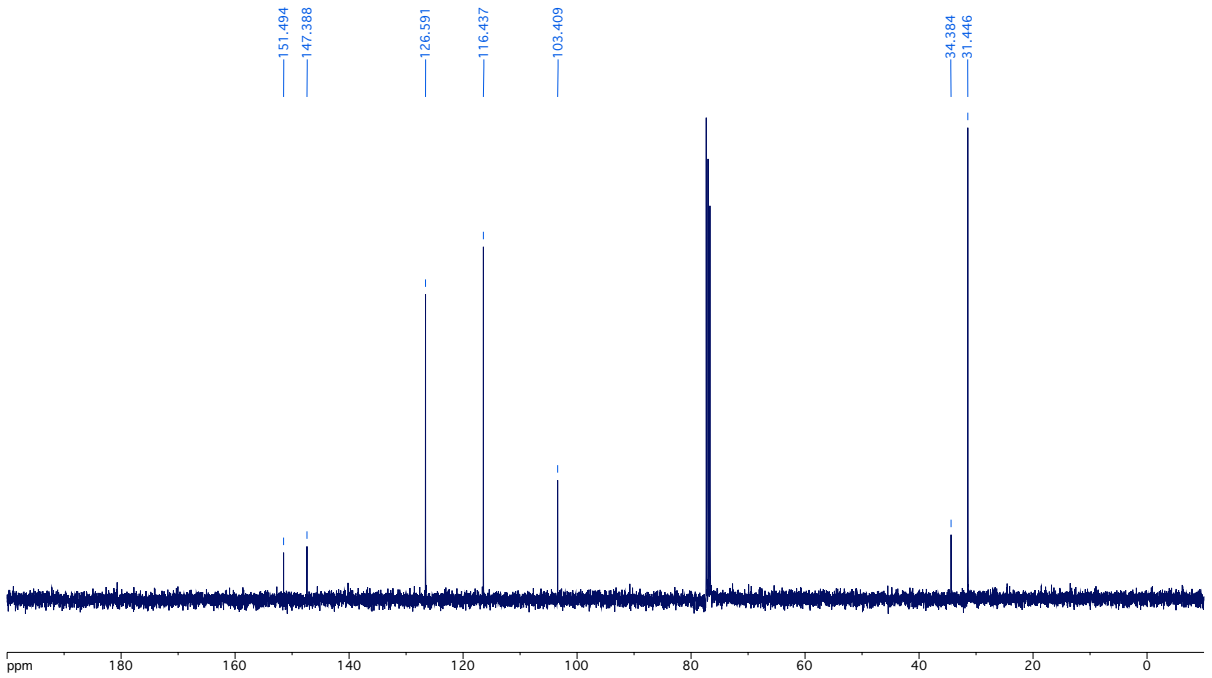

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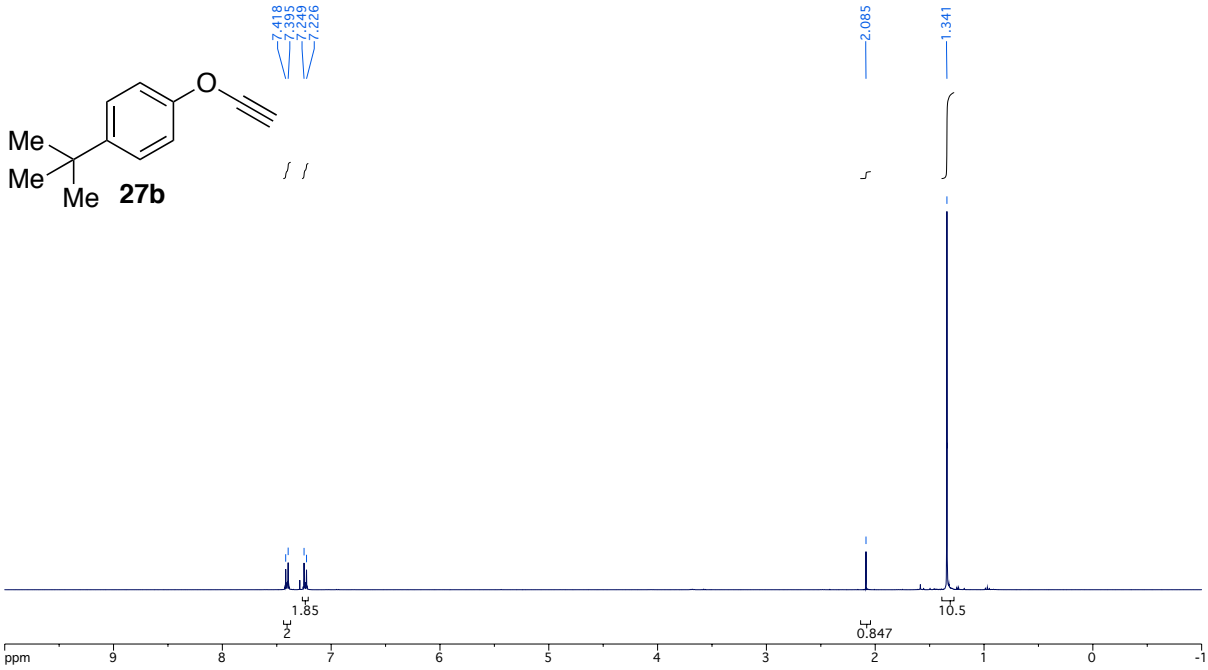
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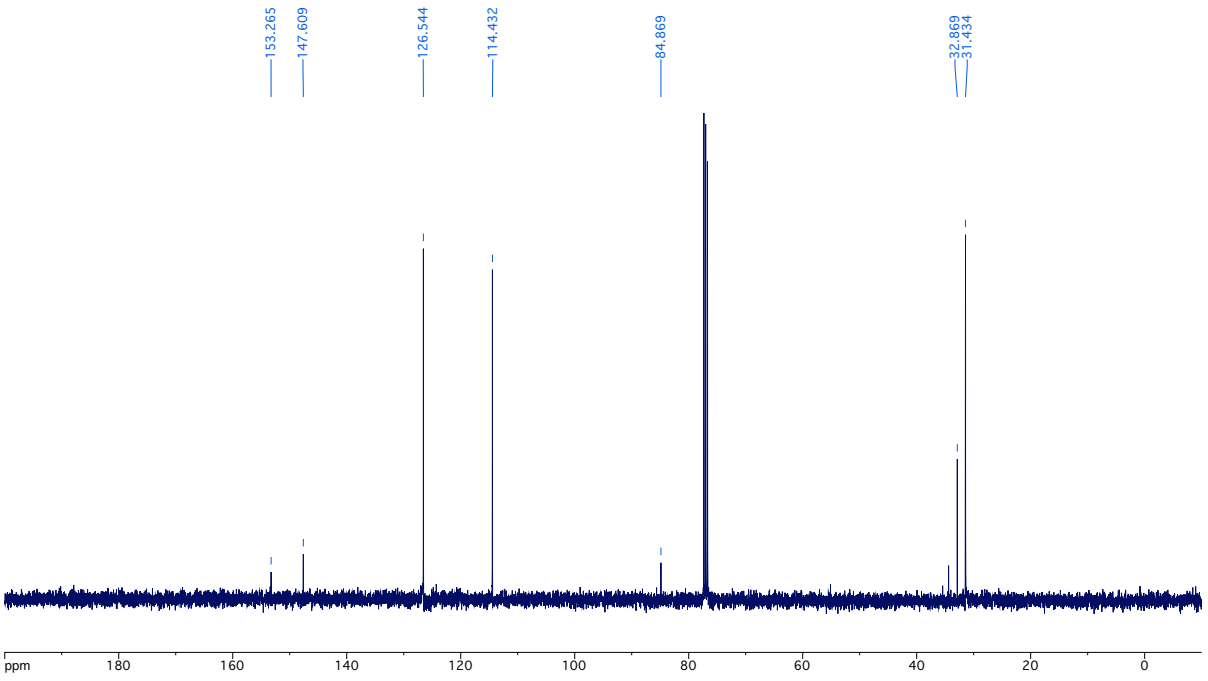
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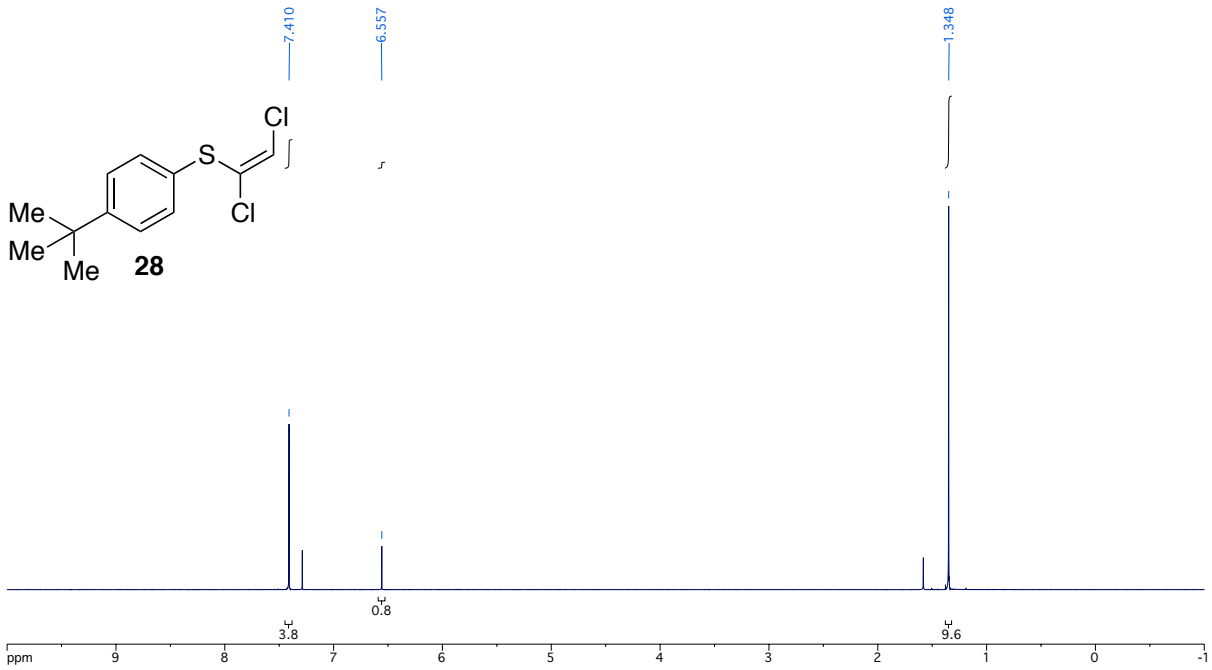

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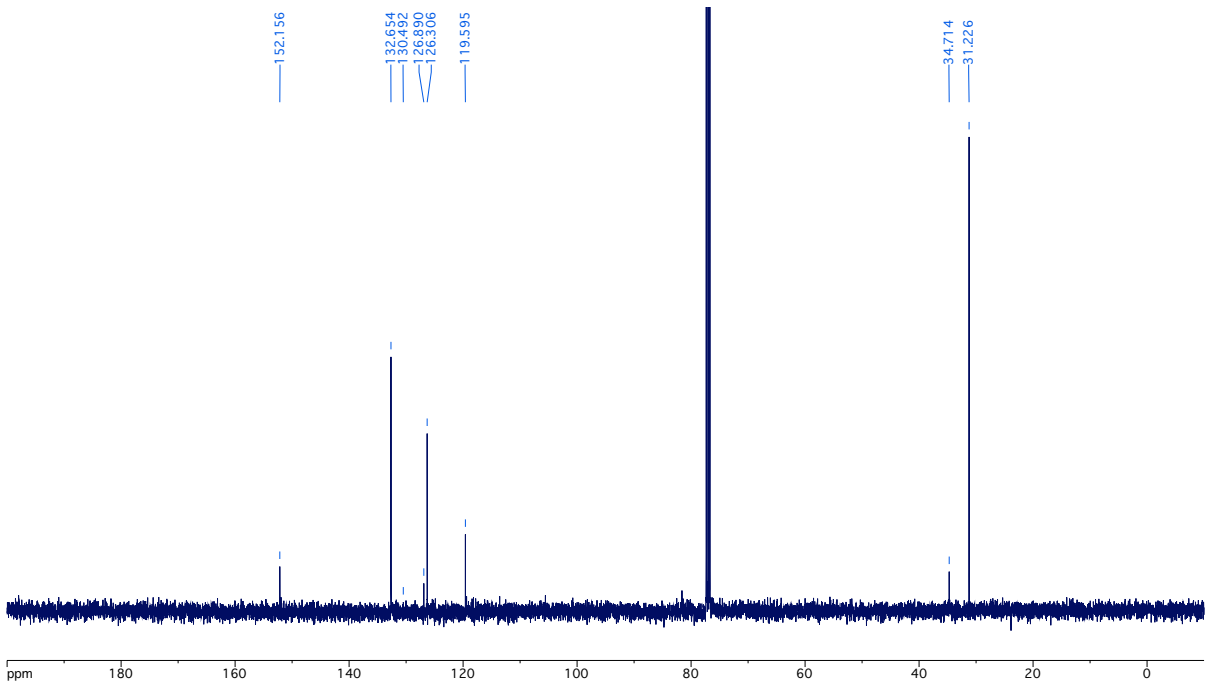

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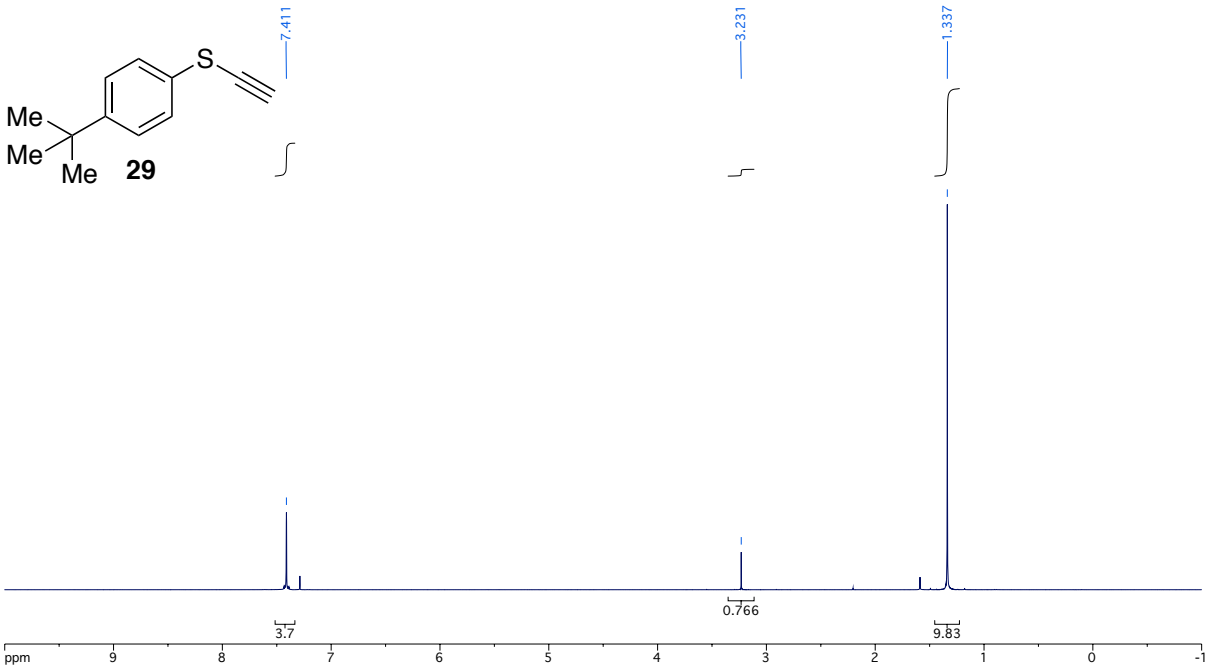

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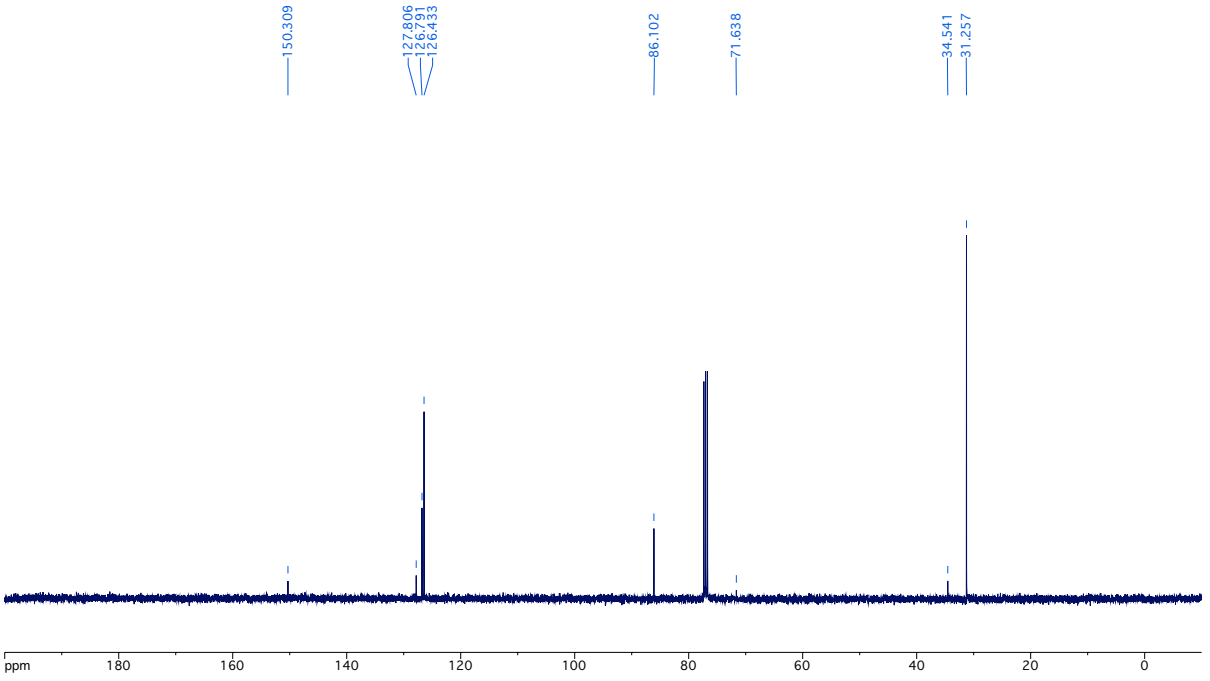

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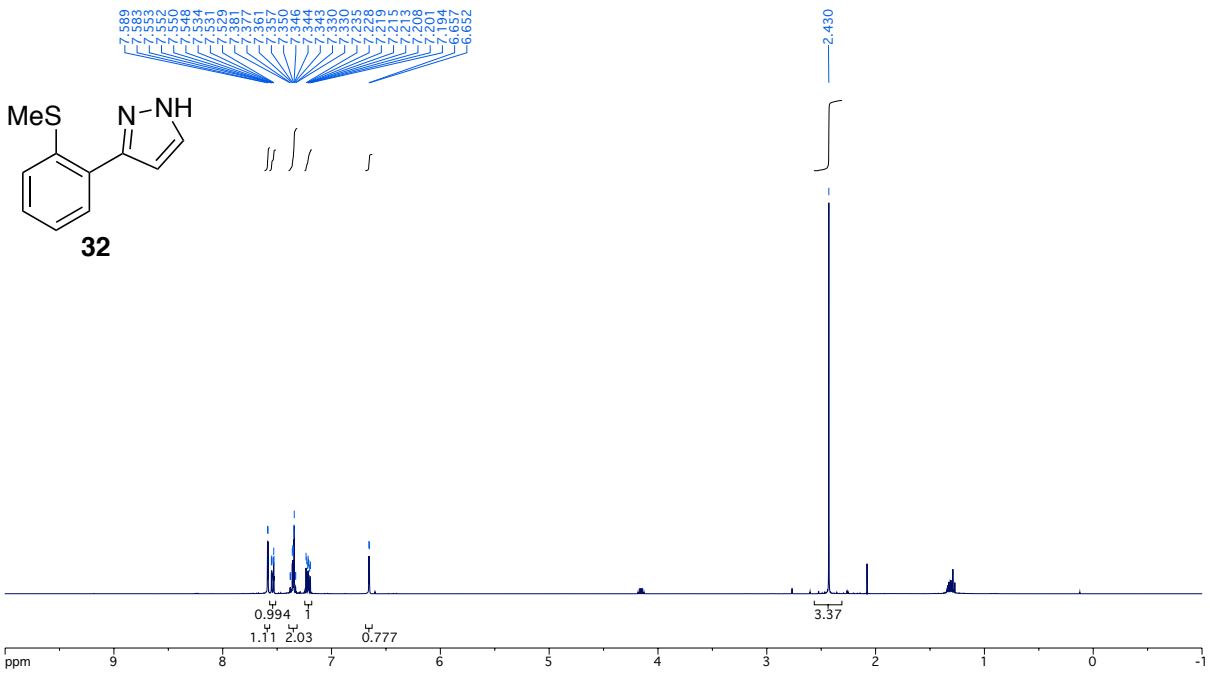

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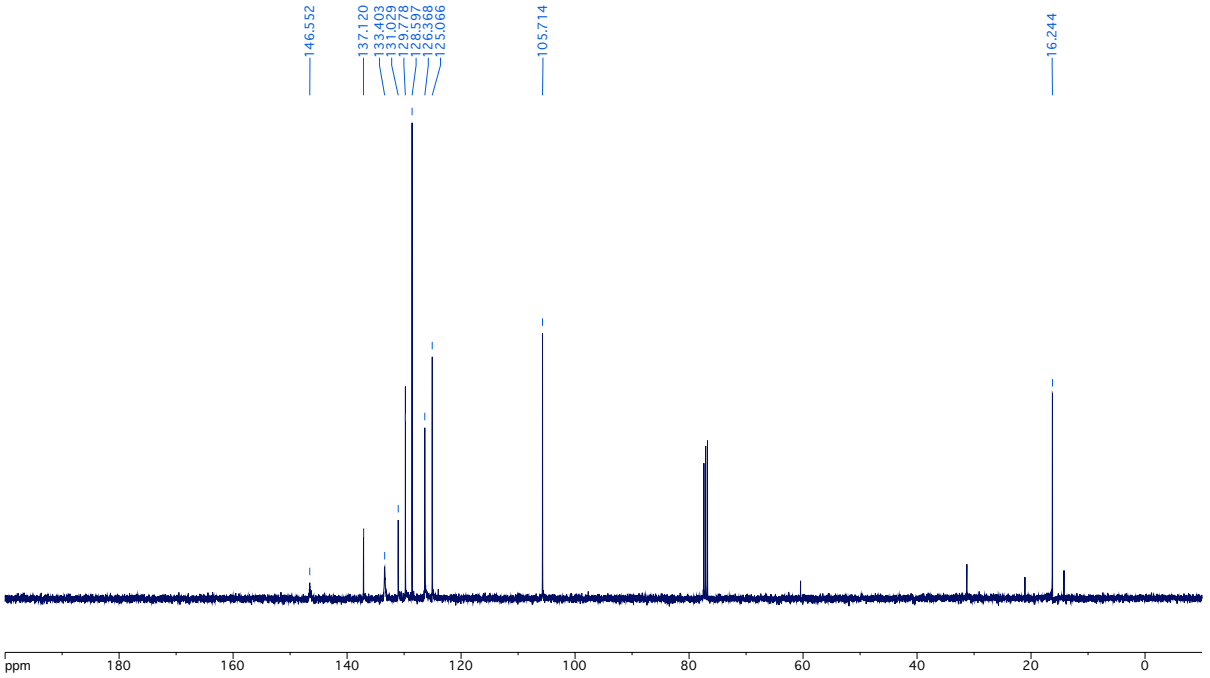

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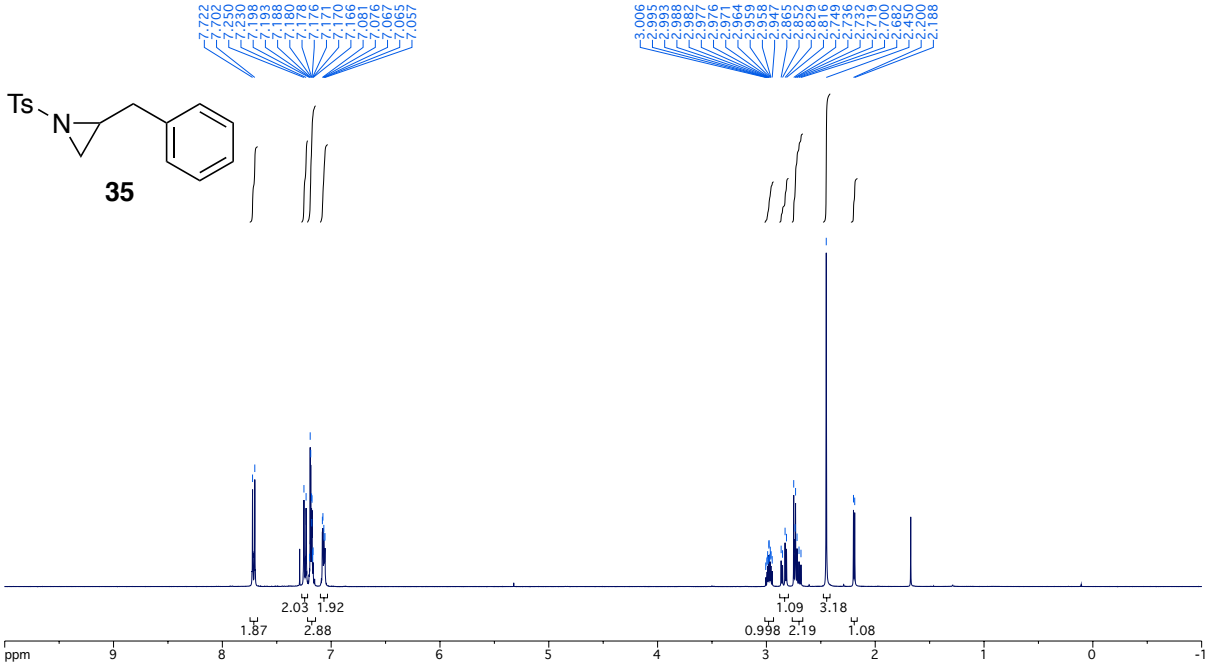

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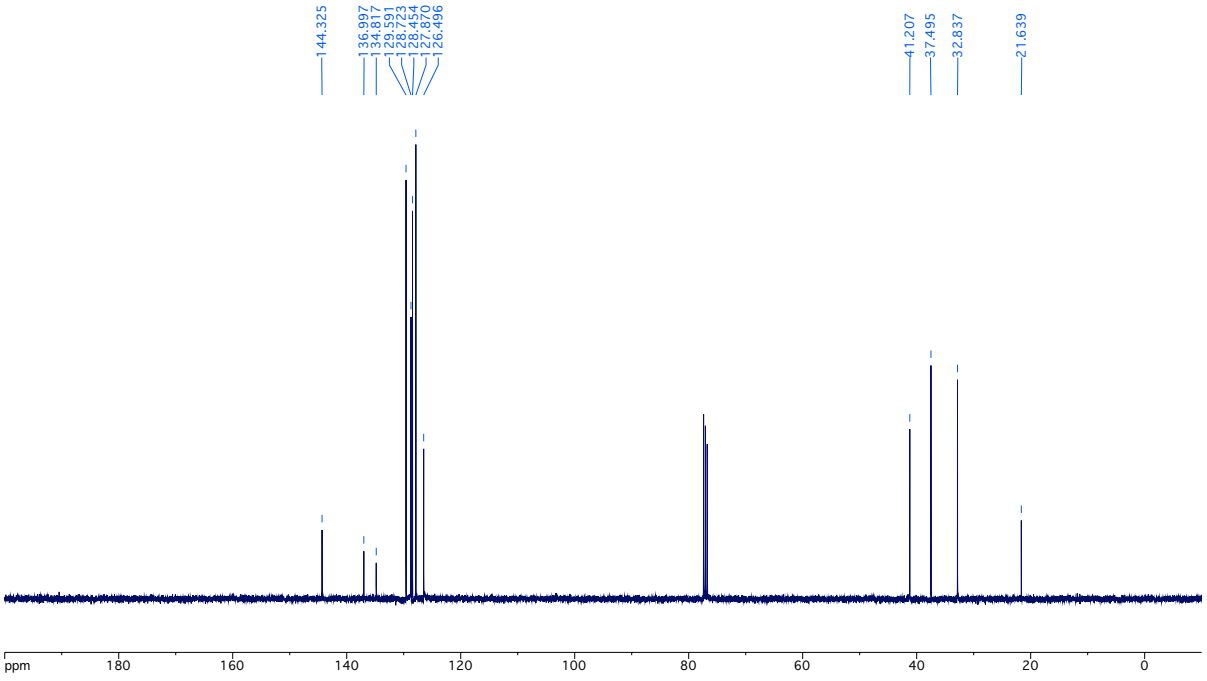

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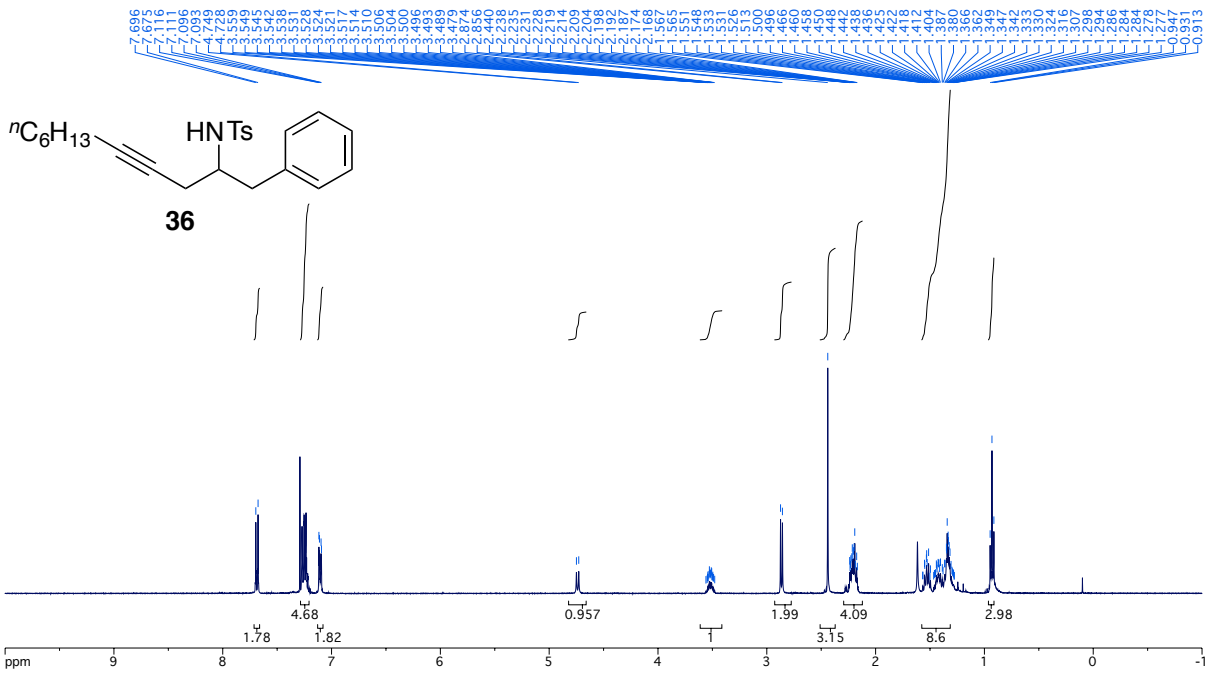

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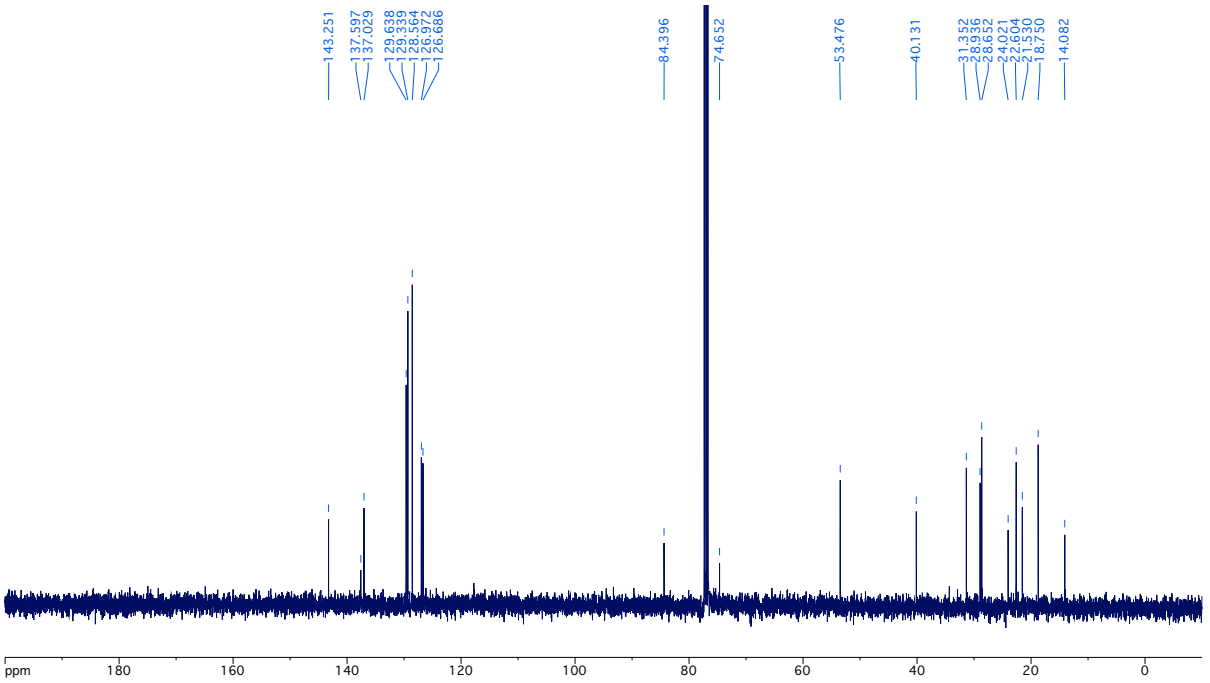

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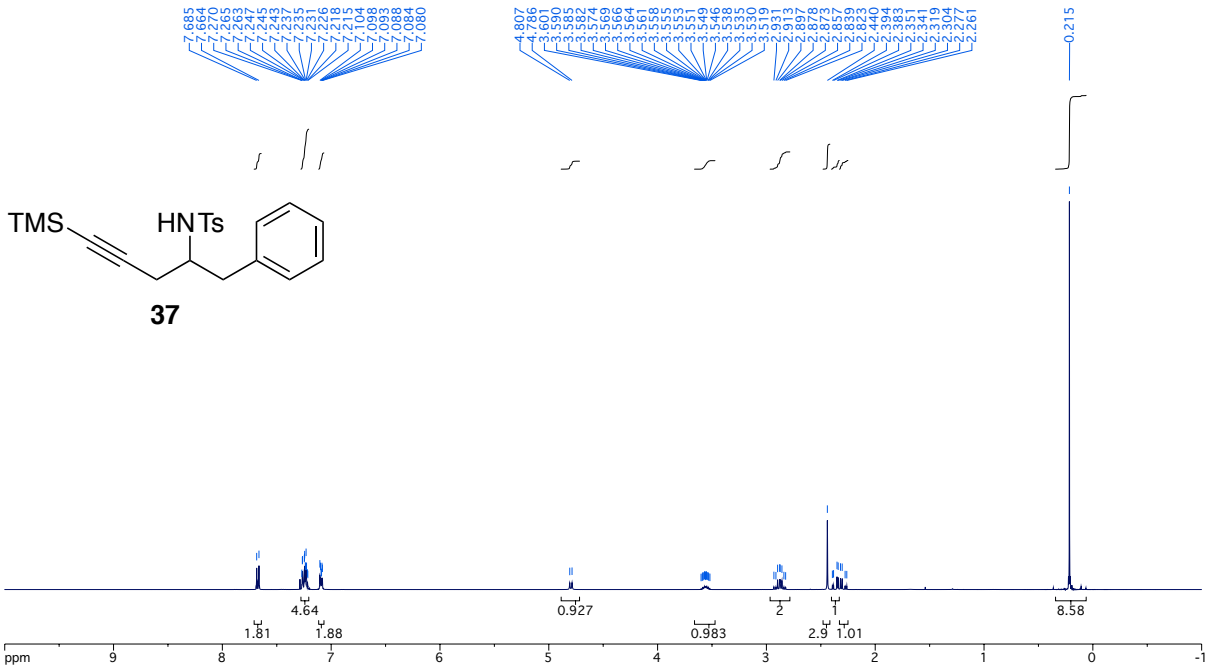

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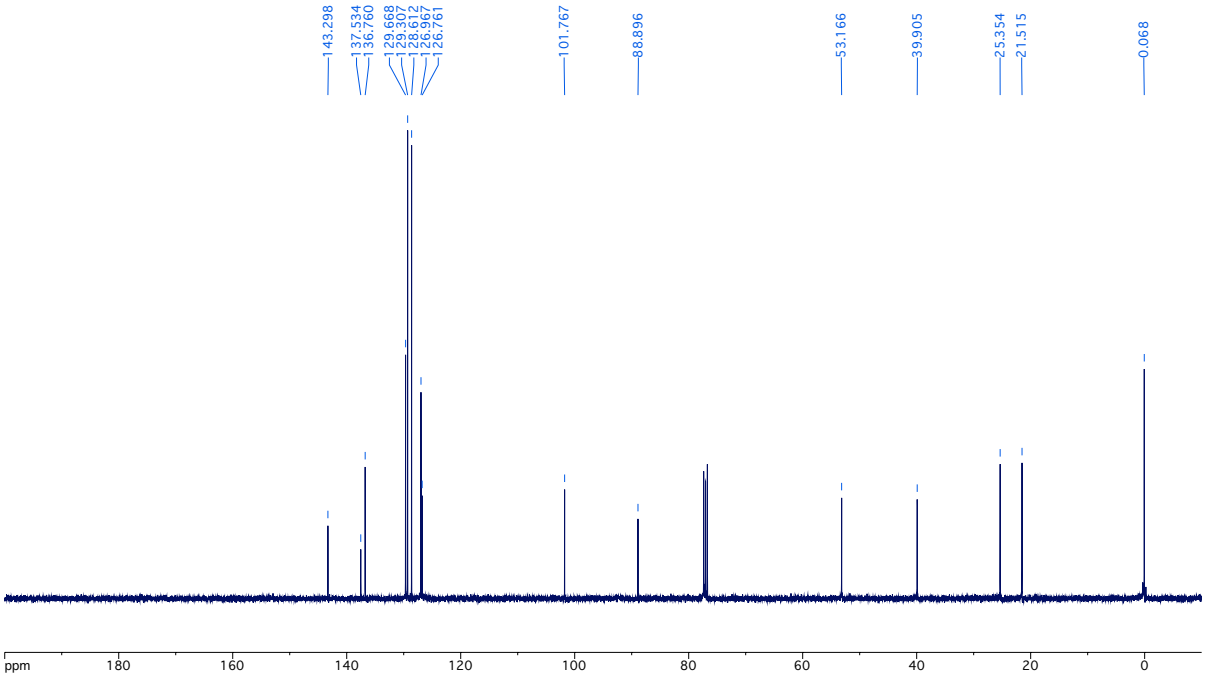

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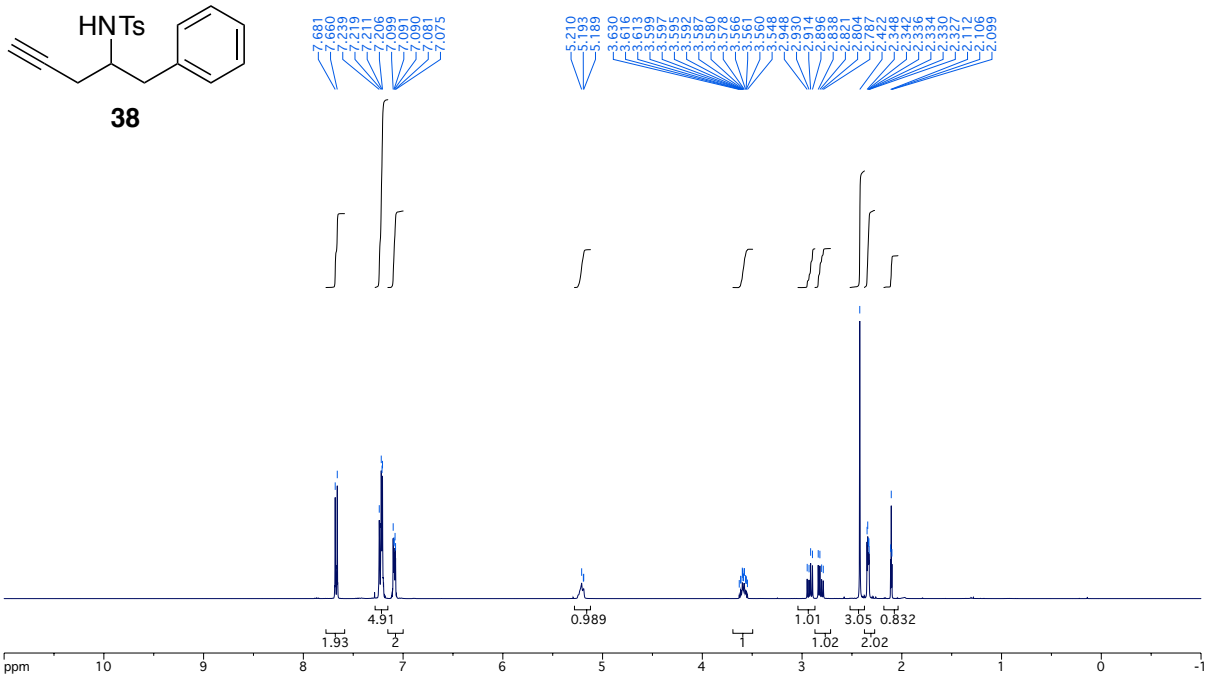

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ppm

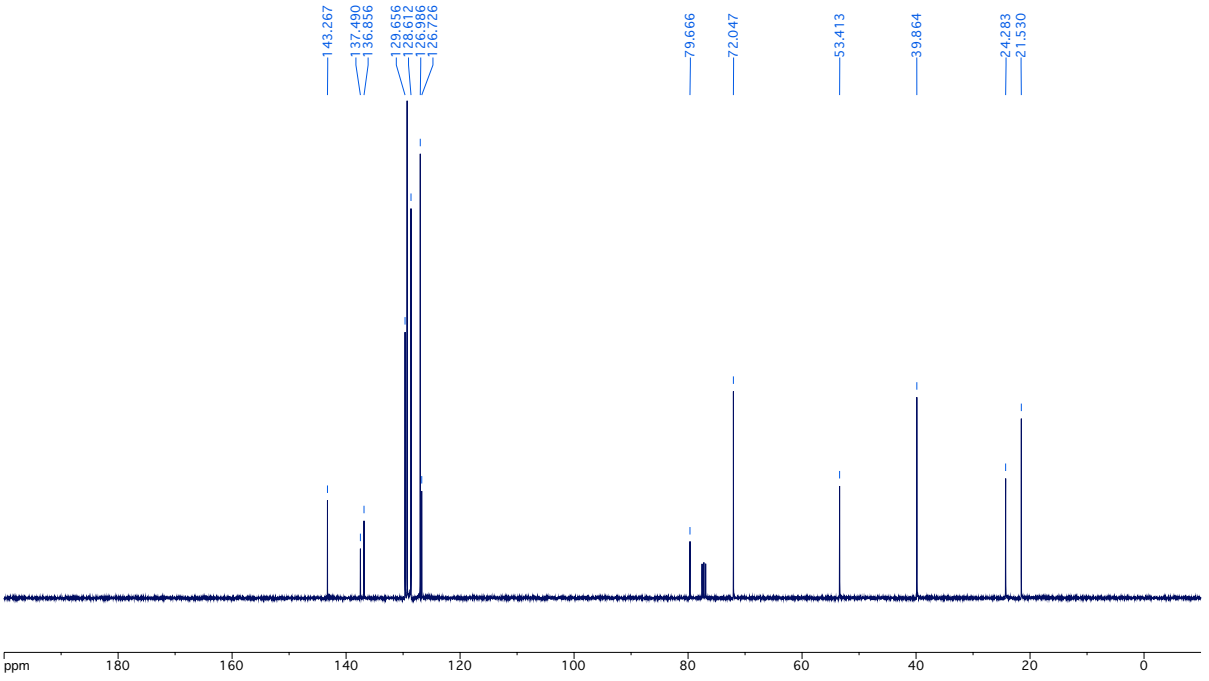

nC6H13
HNTs
36
4.68
1.78
1.82
0.957
1
1.99
4.09
3.15
2.98
8.6
ppm

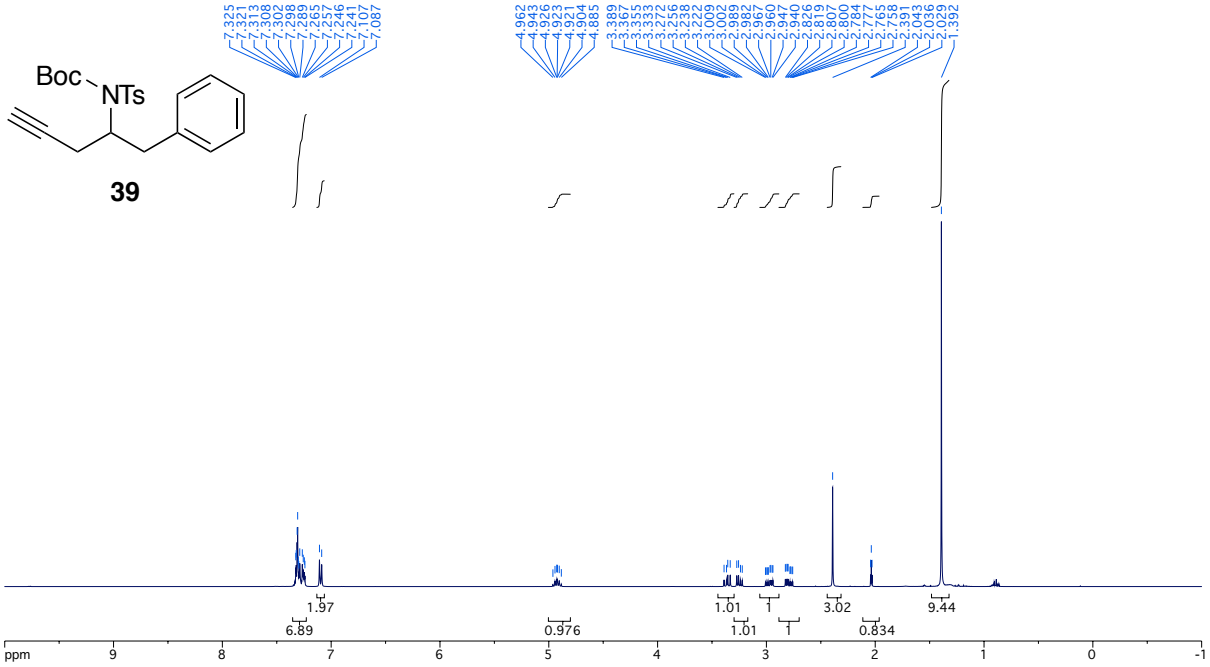

143.251
137.597
137.029
129.638
129.339
128.564
126.972
126.686
84.396
74.652
53.476
40.131
31.352
28.936
28.652
24.021
22.604
21.530
18.750
14.082
ppm

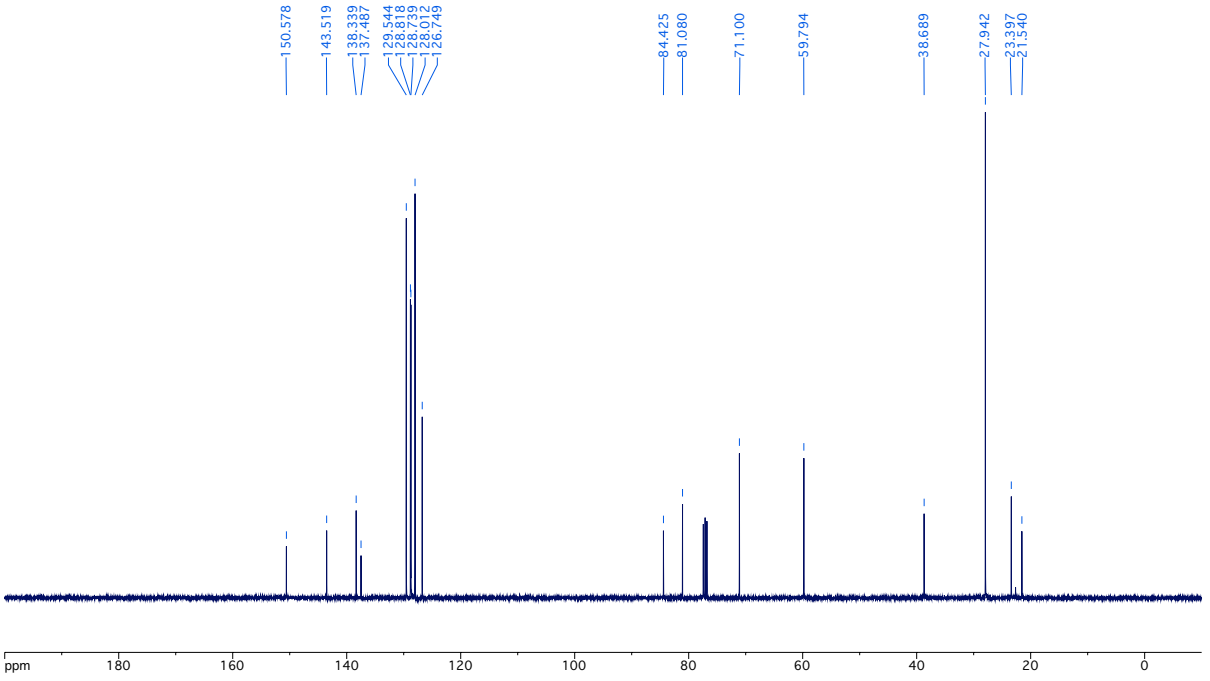

7.685
7.664
7.270
7.265
7.263
7.247
7.245
7.243
7.237
7.235
7.231
7.226
7.218
7.215
7.104
7.098
7.093
7.088
7.084
7.080
4.807
4.786
3.601
3.590
3.585
3.582
3.574
3.569
3.566
3.564
3.561
3.558
3.555
3.553
3.551
3.549
3.546
3.538
3.535
3.530
3.519
2.931
2.913
2.897
2.878
2.873
2.857
2.839
2.823
2.440
2.394
2.383
2.351
2.341
2.319
2.304
2.277
2.261
0.215
TMS
HNTs
37
1.81
4.64
1.88
0.927
0.983
2
2.9
1.01
8.58
ppm

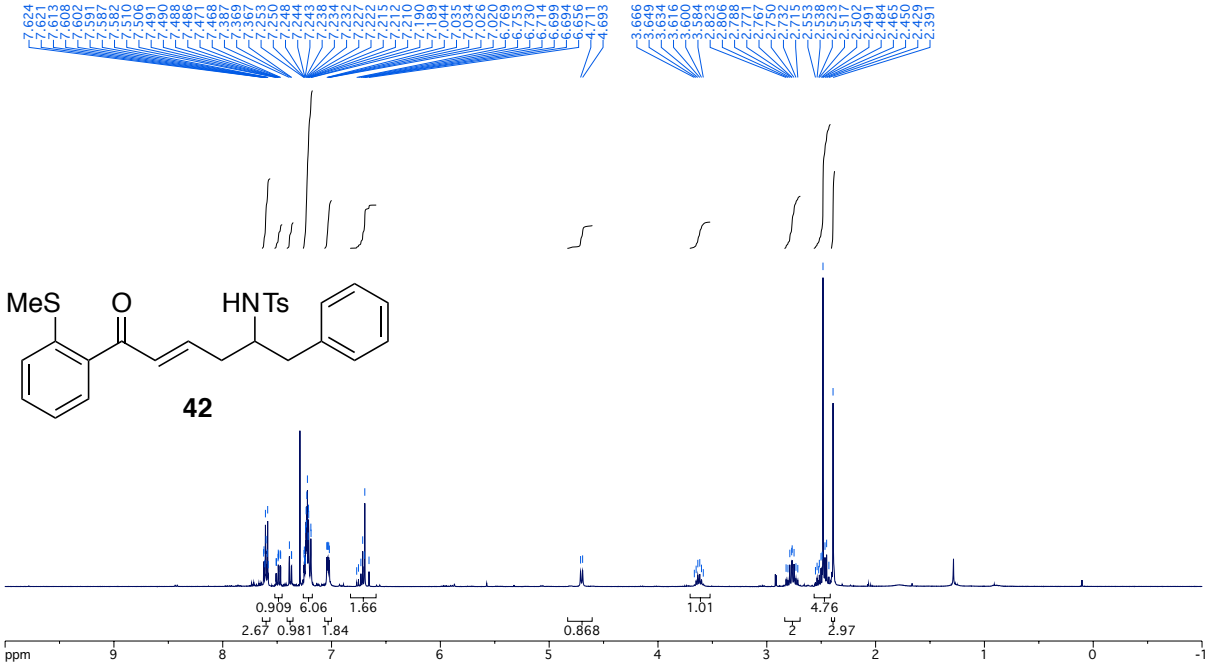

143.298
137.534
136.760
129.668
128.907
128.612
126.967
126.761
101.767
88.896
53.166
39.905
25.354
21.515
0.068
ppm

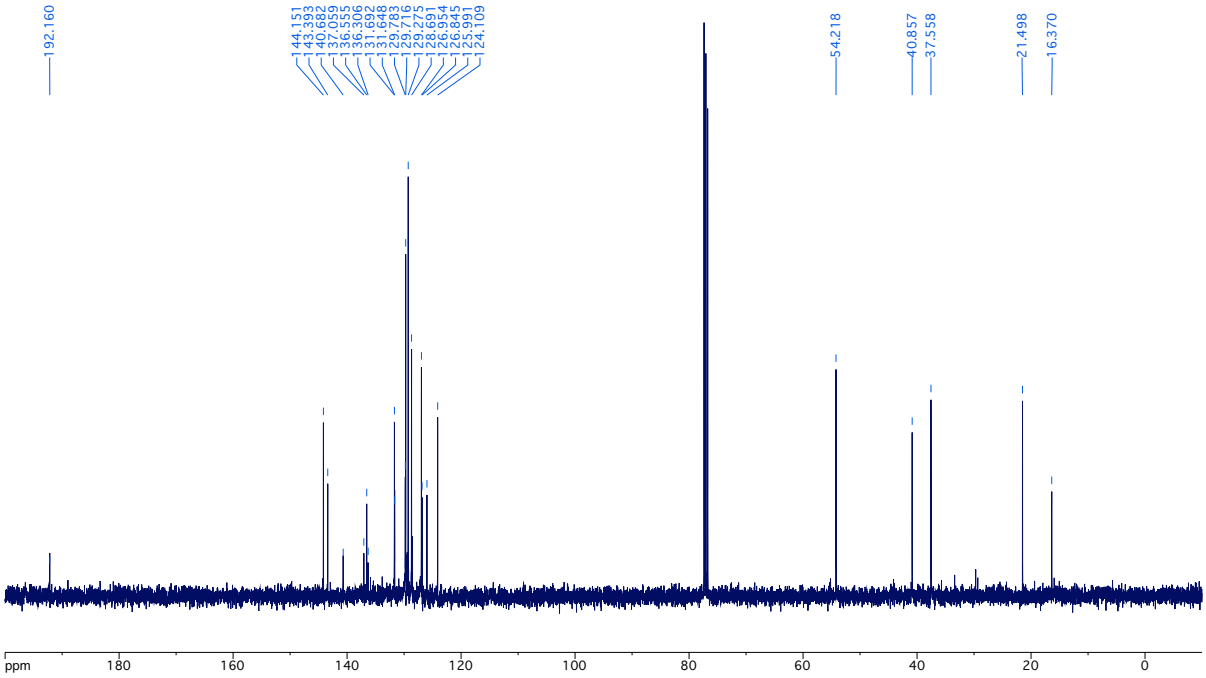

HNTs
38
7.681
7.660
7.239
7.219
7.211
7.206
7.099
7.091
7.090
7.081
7.075
5.210
5.193
5.189
3.630
3.616
3.613
3.599
3.597
3.595
3.592
3.587
3.580
3.578
3.566
3.561
3.560
3.548
3.546
2.930
2.914
2.896
2.838
2.821
2.804
2.487
2.472
2.348
2.342
2.336
2.334
2.330
2.327
2.112
2.106
2.099
4.91
0.989
1.01
3.05
0.832
1.93
2
1
1.02
2.02
ppm

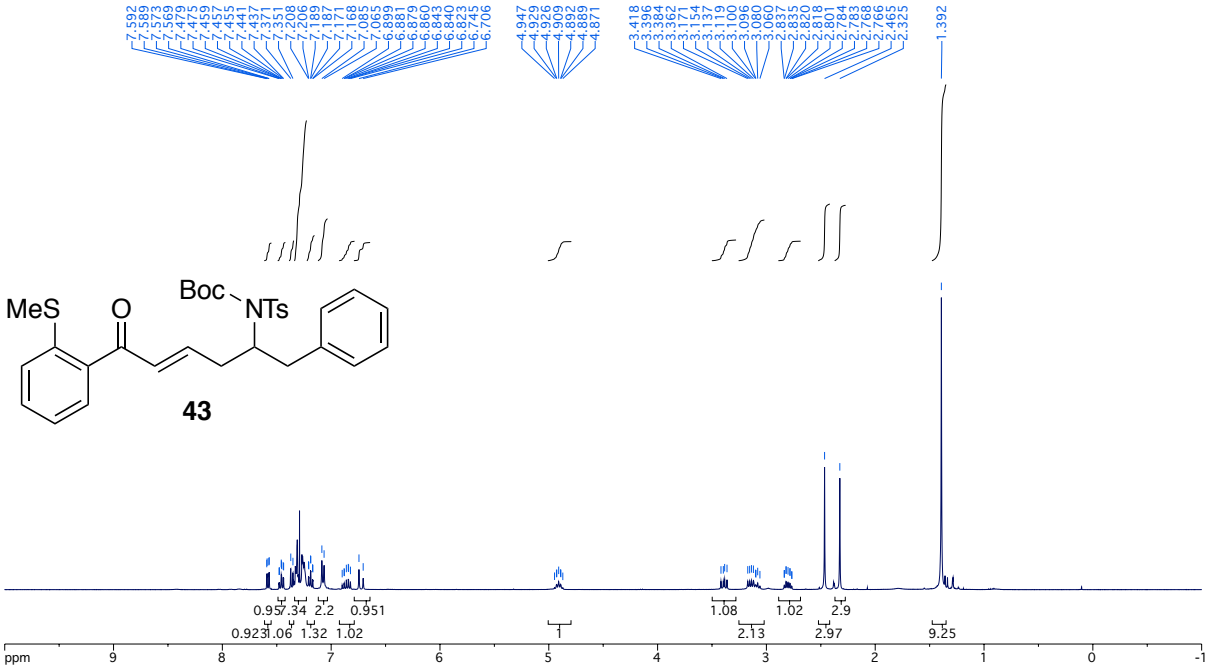

143.267
137.490
136.856
129.656
128.612
128.086
126.726
79.666
72.047
53.413
39.864
24.283
21.530
ppm

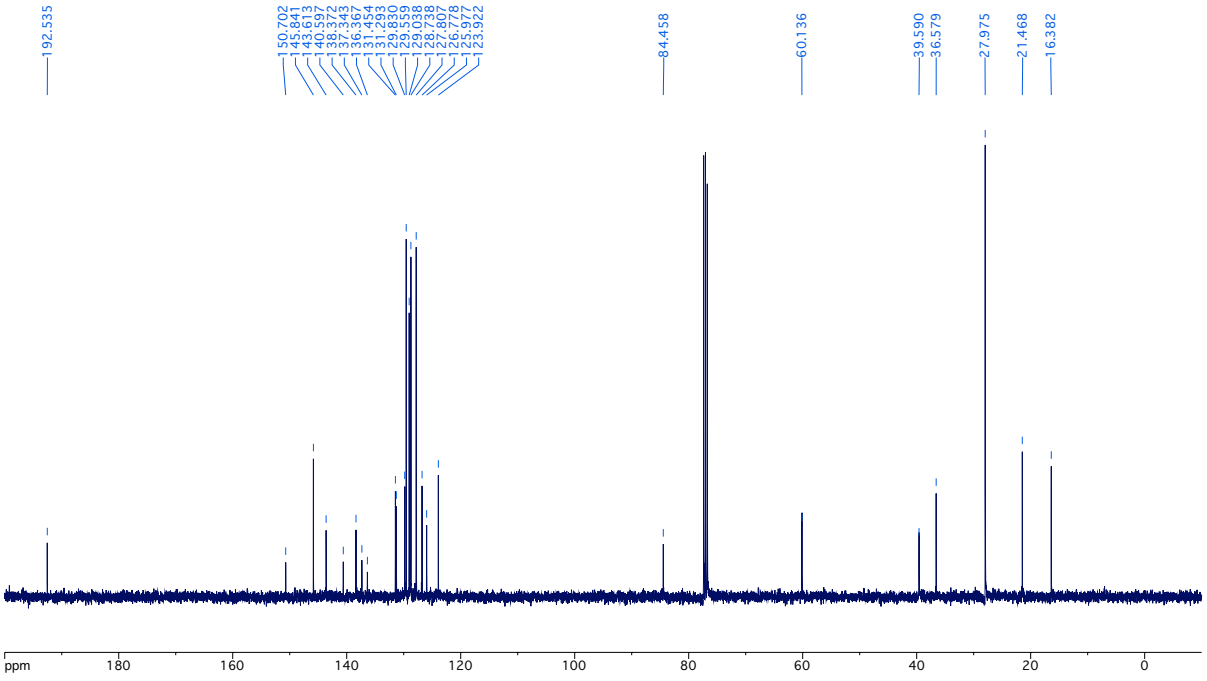

Boc
NTs
39
7.325
7.321
7.313
7.308
7.302
7.289
7.265
7.257
7.246
7.241
7.107
7.087
4.962
4.943
4.926
4.923
4.921
4.904
4.885
3.389
3.367
3.355
3.333
3.272
3.256
3.238
3.222
3.009
3.002
2.989
2.982
2.967
2.960
2.947
2.940
2.826
2.819
2.807
2.800
2.784
2.777
2.765
2.758
2.391
2.043
2.036
2.029
1.392
1.97
6.89
0.976
1.01
1.01
1
1
3.02
0.834
9.44
ppm

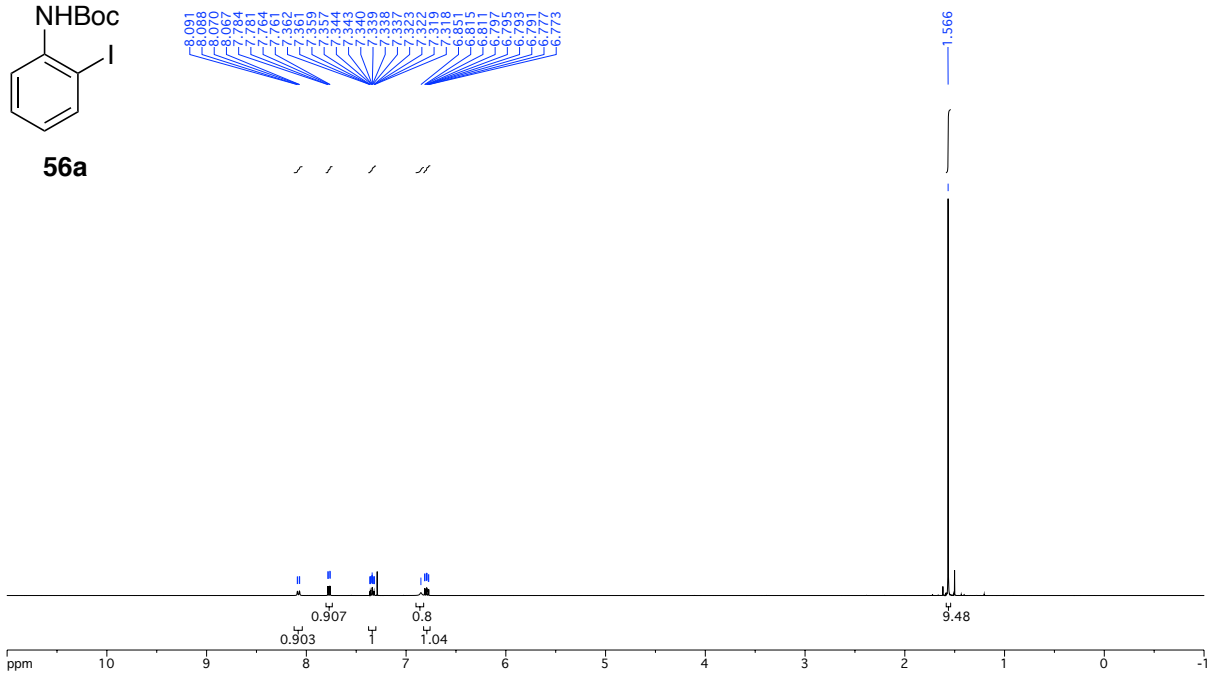

150.578
143.519
138.339
137.487
129.544
128.818
128.739
128.012
126.749
84.425
81.080
71.100
59.794
38.689
27.942
23.397
21.540
ppm

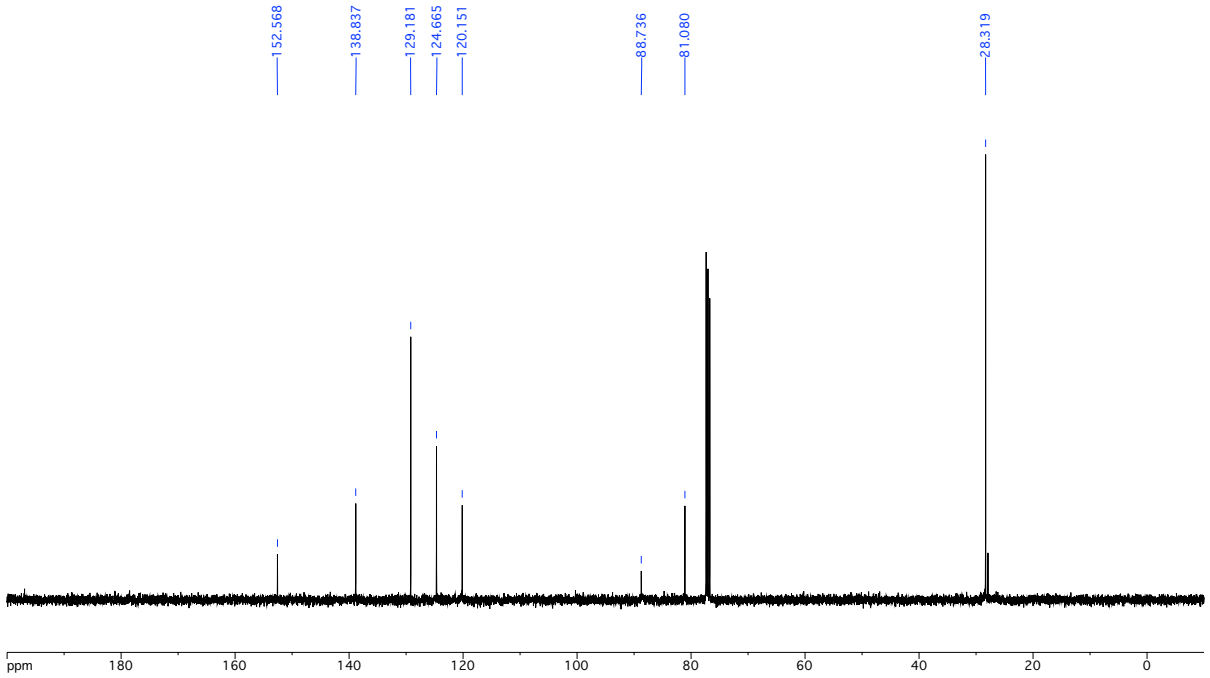

MeS
O
HN Ts
42
0.909
6.06
1.66
1.01
4.76
2.67
0.981
1.84
0.868
2
2.97
ppm

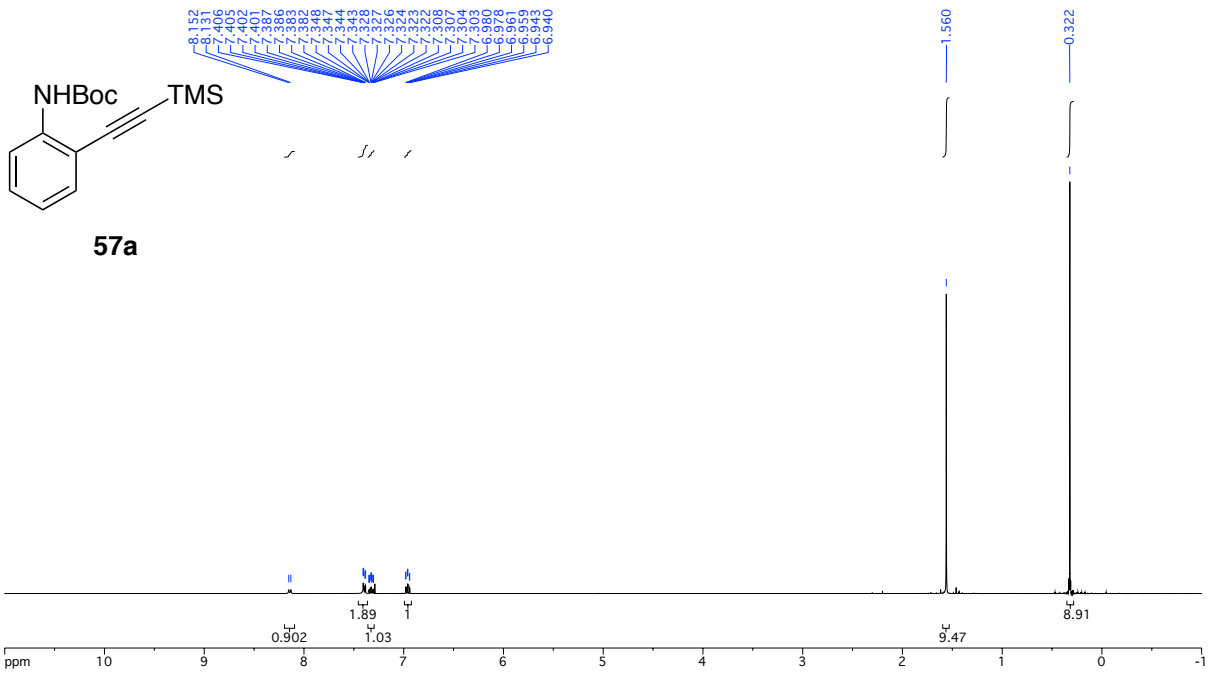

192.160
144.151
143.393
140.682
137.059
136.555
136.306
131.692
131.648
128.783
128.276
129.275
128.691
126.954
126.845
125.991
124.109
54.218
40.857
37.558
21.498
16.370
ppm


MeS
O
Boc
NTs
43
ppm

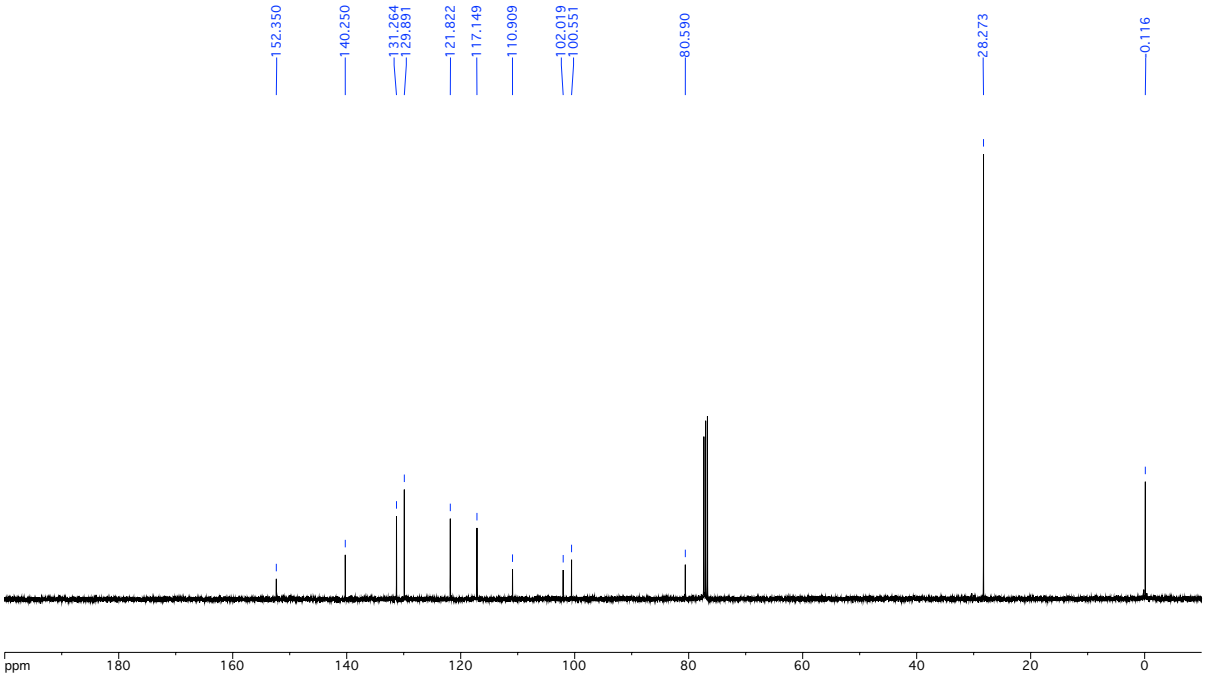

ppm

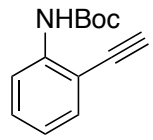

NHBoc
I
56a
8.091
8.088
8.070
8.067
7.784
7.781
7.764
7.761
7.362
7.359
7.357
7.344
7.343
7.340
7.339
7.338
7.337
7.323
7.322
7.319
7.318
6.851
6.815
6.811
6.797
6.795
6.793
6.791
6.777
6.773
1.566
0.903
0.907
1
0.8
1.04
9.48
ppm


152.568
138.837
129.181
124.665
120.151
88.736
81.080
28.319
ppm


NHBoc
TMS
8.152
8.131
7.406
7.405
7.402
7.401
7.387
7.386
7.383
7.382
7.348
7.347
7.344
7.343
7.328
7.327
7.326
7.324
7.323
7.322
7.308
7.307
7.304
7.303
6.980
6.978
6.961
6.959
6.943
6.940
1.560
0.322
0.902
1.89
1.03
1
9.47
8.91
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

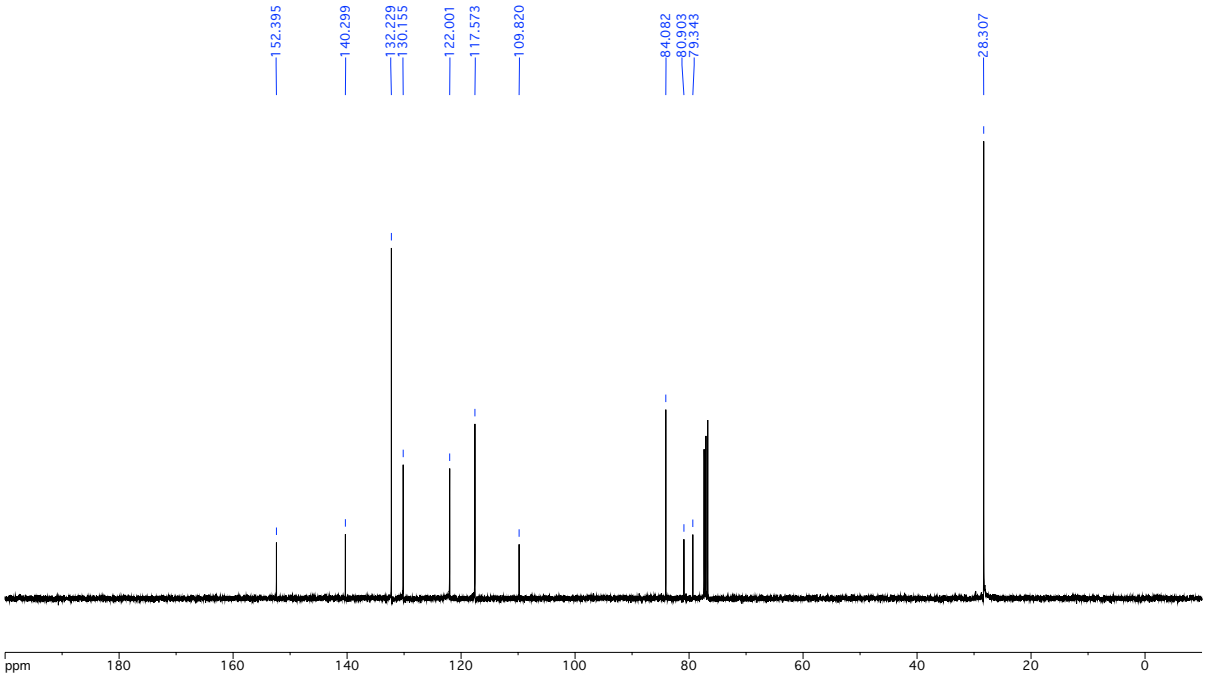
57a

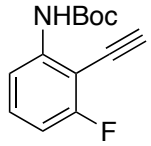

152.350
140.250
131.264
129.891
121.822
117.149
110.909
102.019
100.551
80.590
28.273
0.116
ppm
180
160
140
120
100
80
60
40
20
0


NHBoc

51a

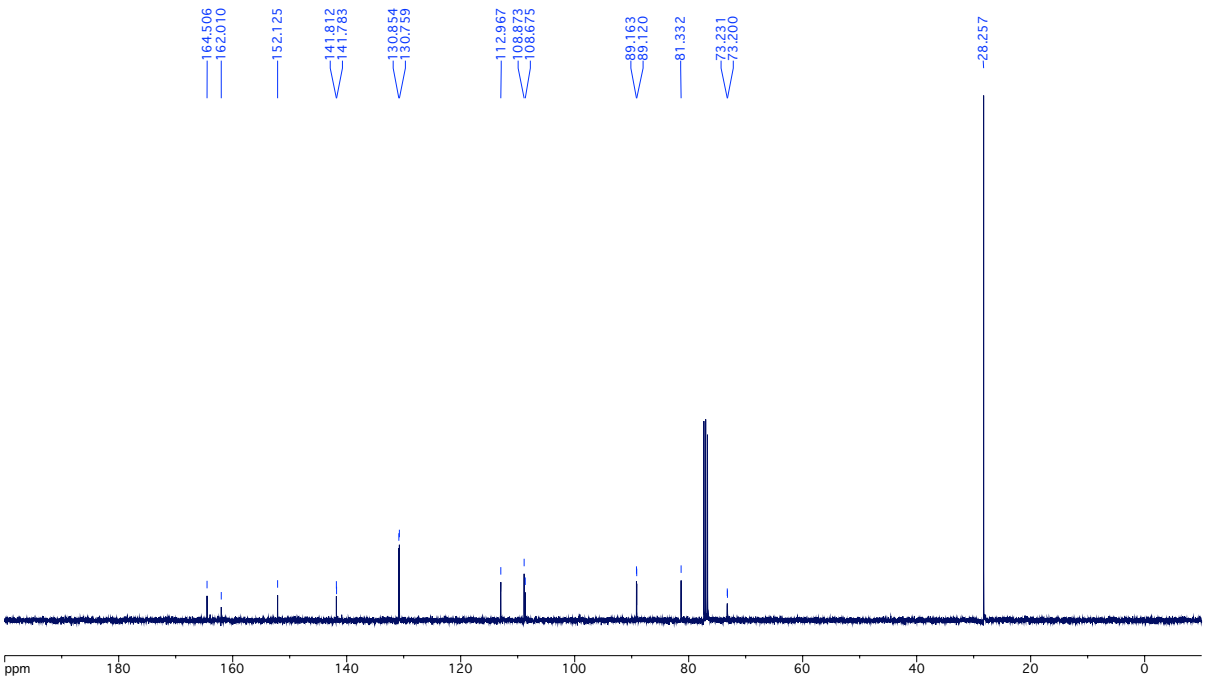
8.199
8.178
7.459
7.456
7.440
7.436
7.381
7.377
7.359
7.341
7.337
7.302
7.007
7.004
6.988
6.985
6.969
6.966
3.511
1.564
0.896
0.942
1.14
1
0.86
9.39
ppm

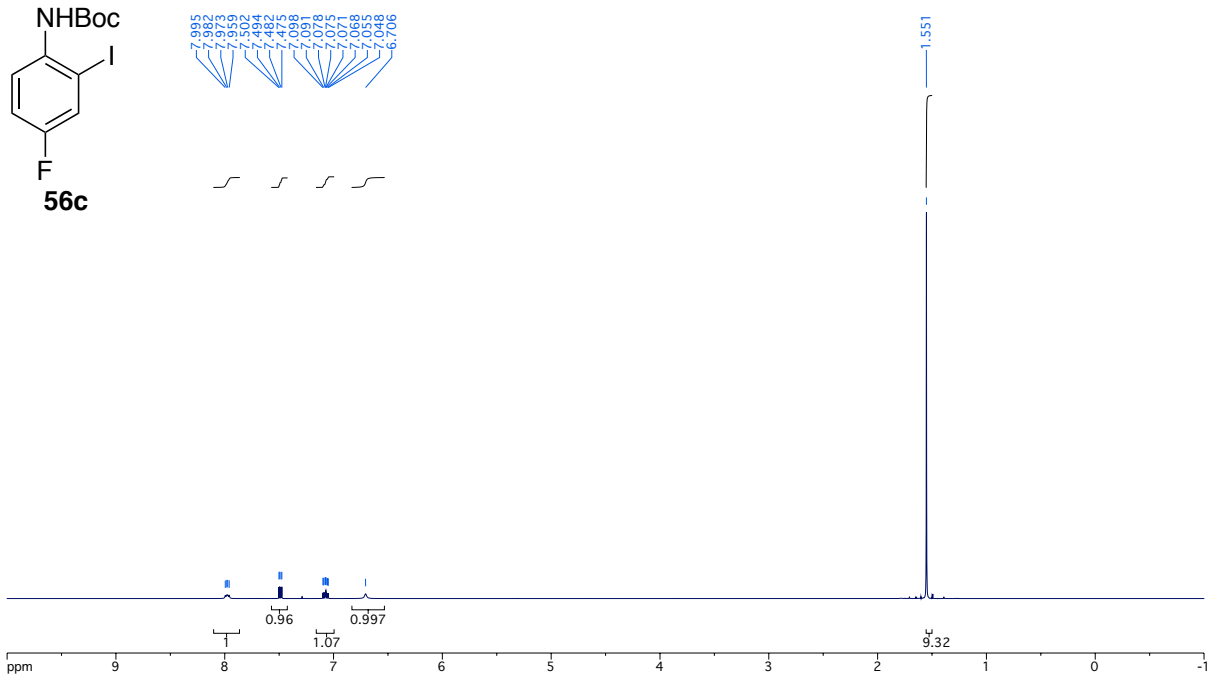

152.395
140.299
132.229
130.155
122.001
117.573
109.820
84.082
80.903
79.343
28.307
ppm

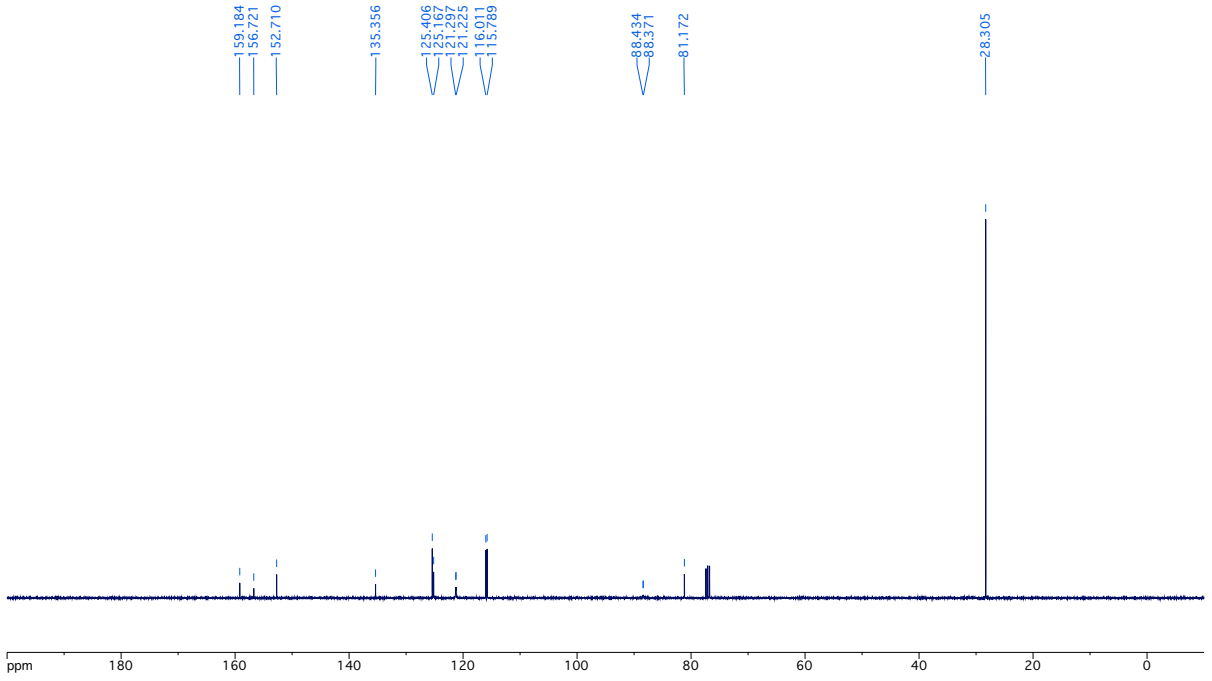

NHBoc
F

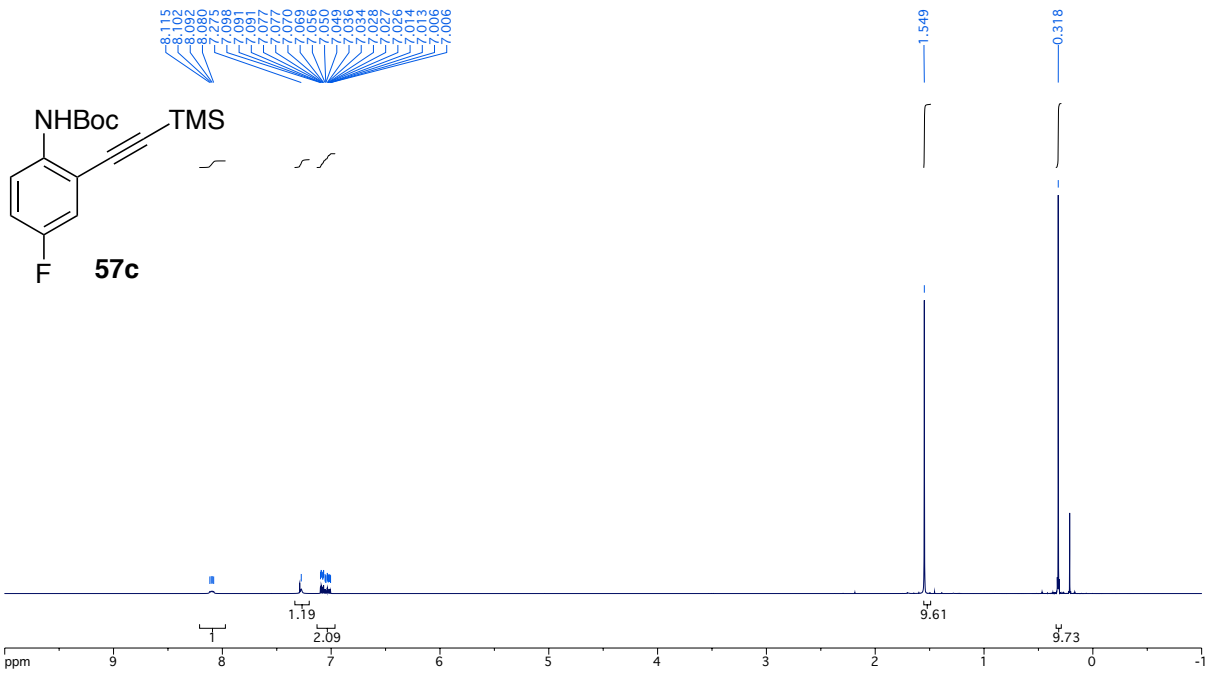
51b

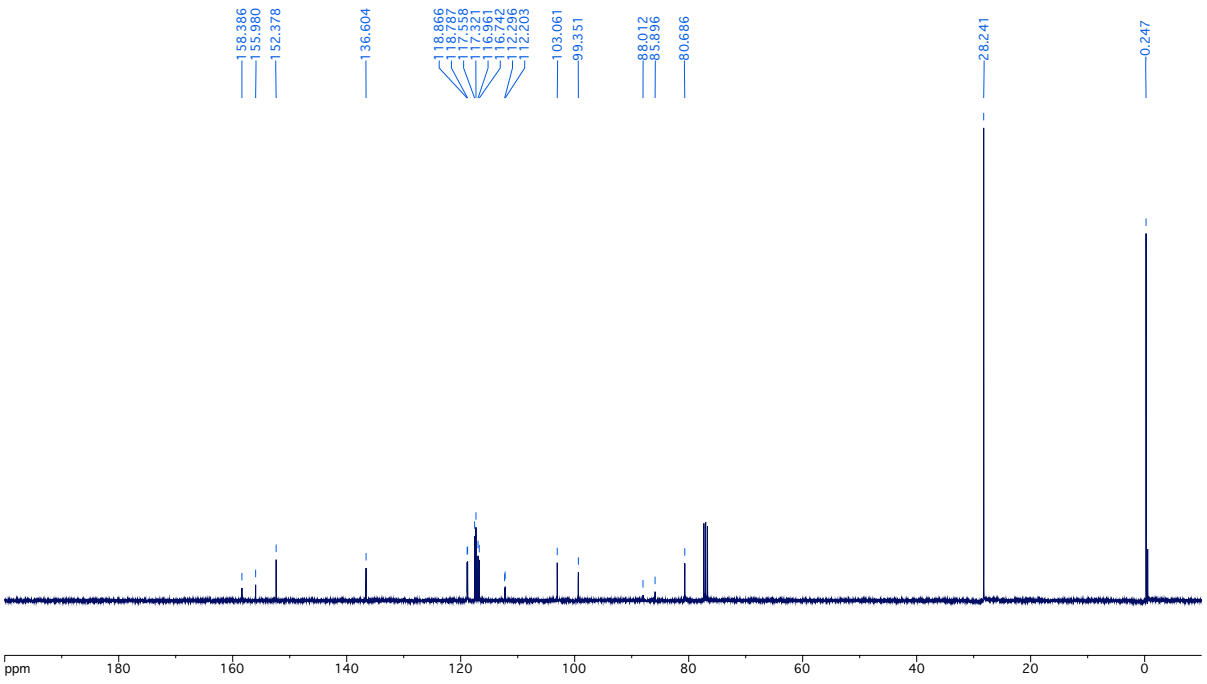
8.015
7.993
7.336
7.320
7.315
7.299
7.294
7.278
6.789
6.786
6.768
6.767
6.765
6.764
6.746
6.743
3.743
3.742
1.563
2.17
0.909
0.974
1
9.12
ppm

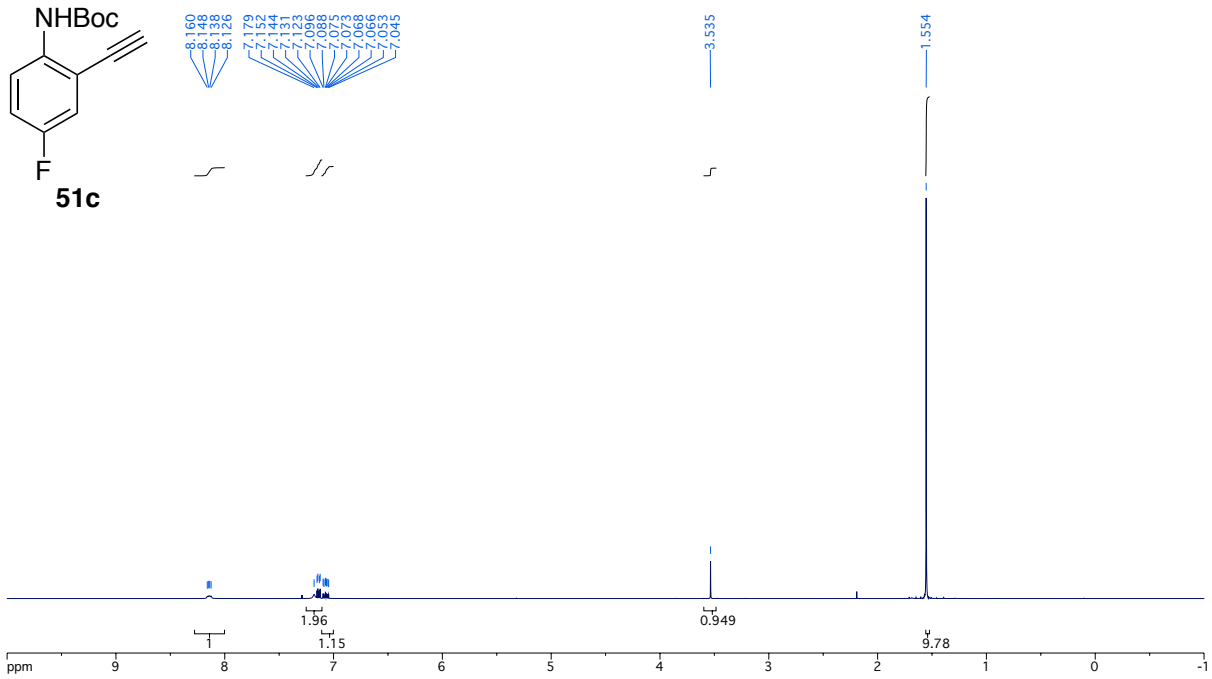

164.506
162.010
152.125
141.812
141.783
130.854
130.759
112.967
108.873
108.675
89.163
89.120
81.332
73.231
73.200
28.257
ppm

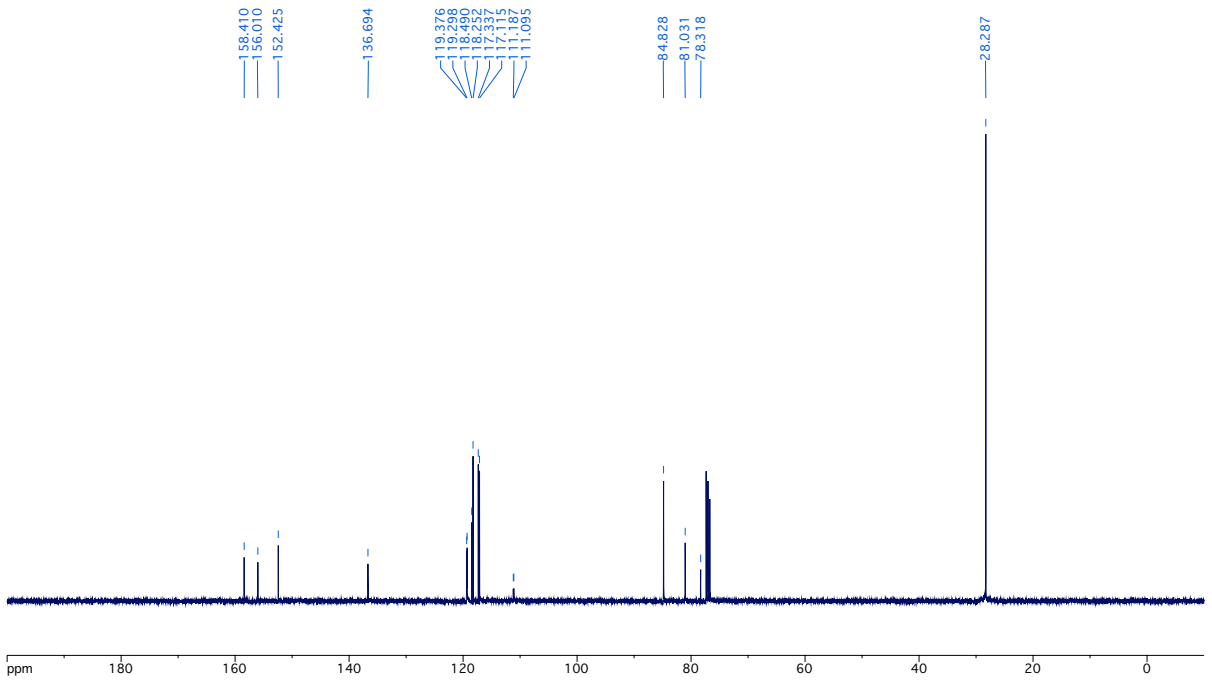

NHBoc
I
F
56c
7.995
7.982
7.973
7.959
7.502
7.494
7.482
7.472
7.098
7.091
7.078
7.075
7.071
7.068
7.055
7.048
6.706
1.551
0.96
0.997
1
1.07
9.32
ppm

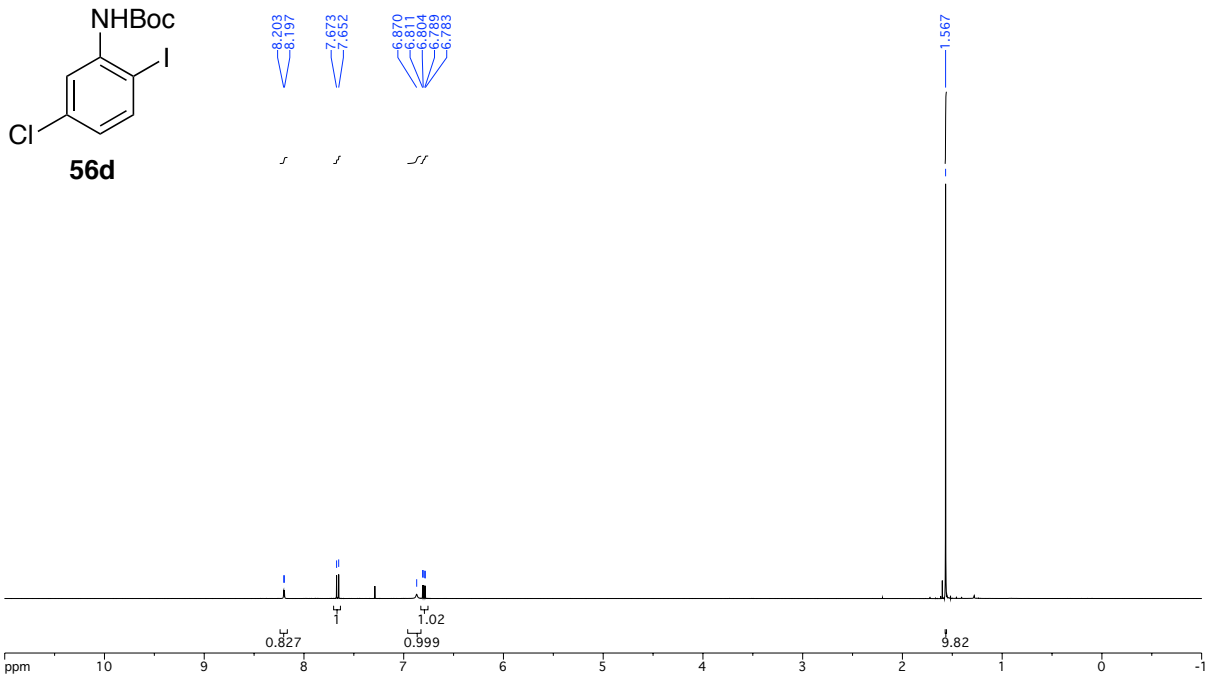

159.184
156.721
152.710
135.356
125.406
125.197
121.367
121.225
116.011
115.789
88.434
88.371
81.172
28.305
ppm

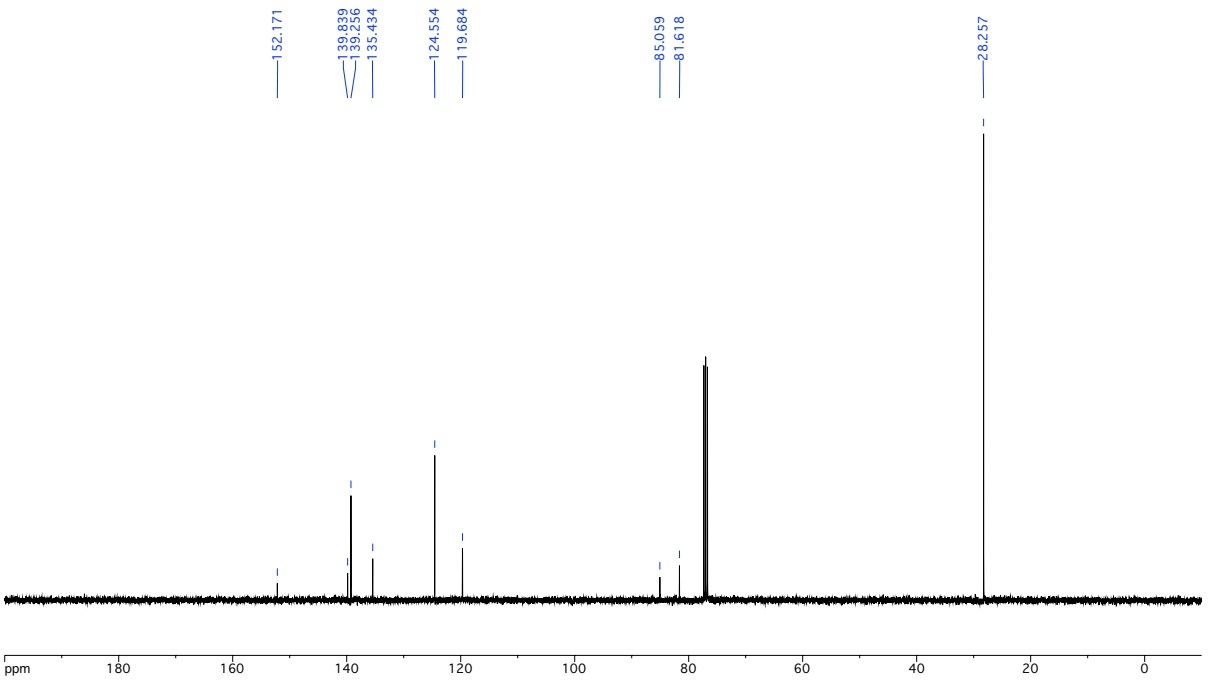

8.115
8.102
8.092
8.080
7.275
7.098
7.091
7.077
7.070
7.069
7.056
7.050
7.049
7.036
7.034
7.029
7.026
7.014
7.013
7.006
7.006
1.549
0.318
NHBoc
TMS
F
57c
1.19
2.09
9.61
9.73
ppm

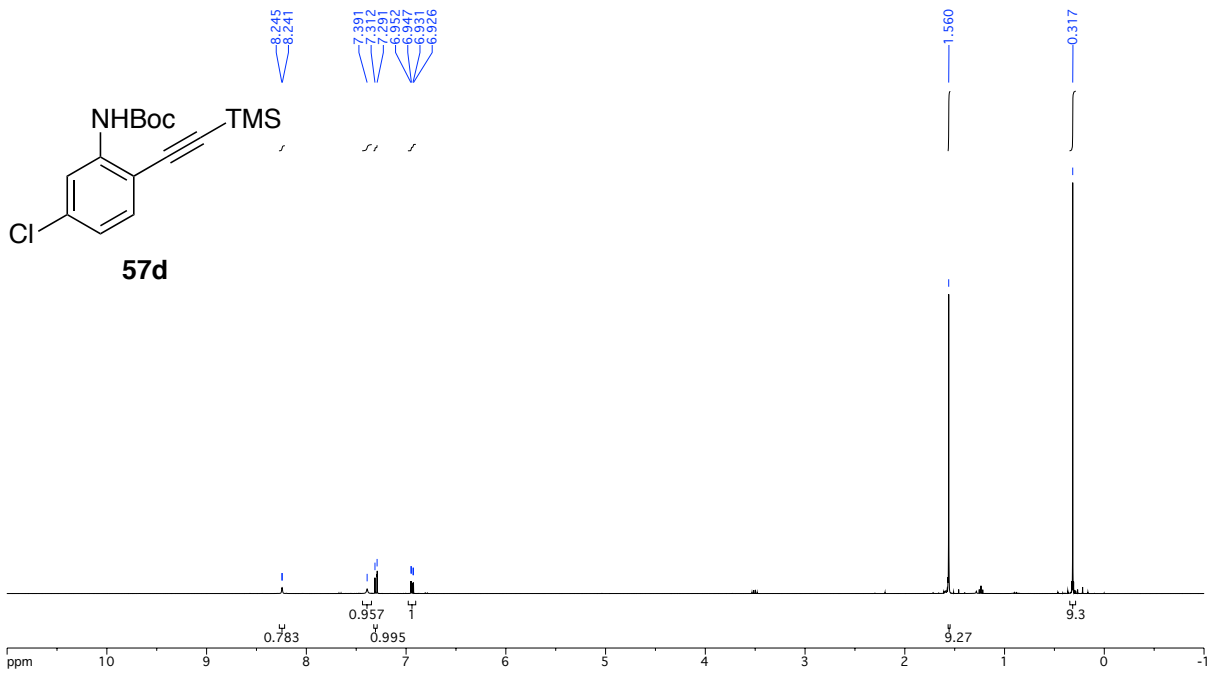

158.386
155.980
152.378
136.604
118.866
118.787
117.558
117.321
116.961
116.744
112.296
112.203
103.061
99.351
88.012
85.896
80.686
28.241
0.247
ppm

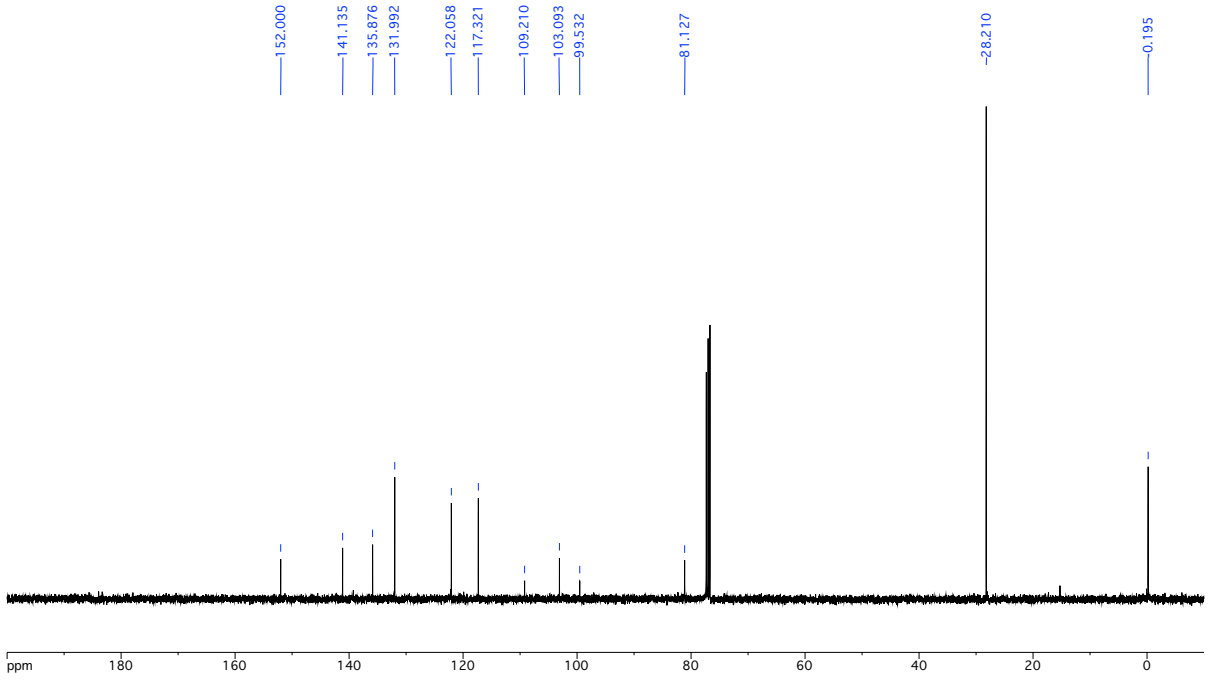

NHBoc
F
51c
8.160
8.148
8.138
8.126
7.179
7.152
7.144
7.131
7.092
7.088
7.075
7.073
7.068
7.066
7.053
7.045
3.535
1.554
1.96
1.15
1
0.949
9.78
ppm

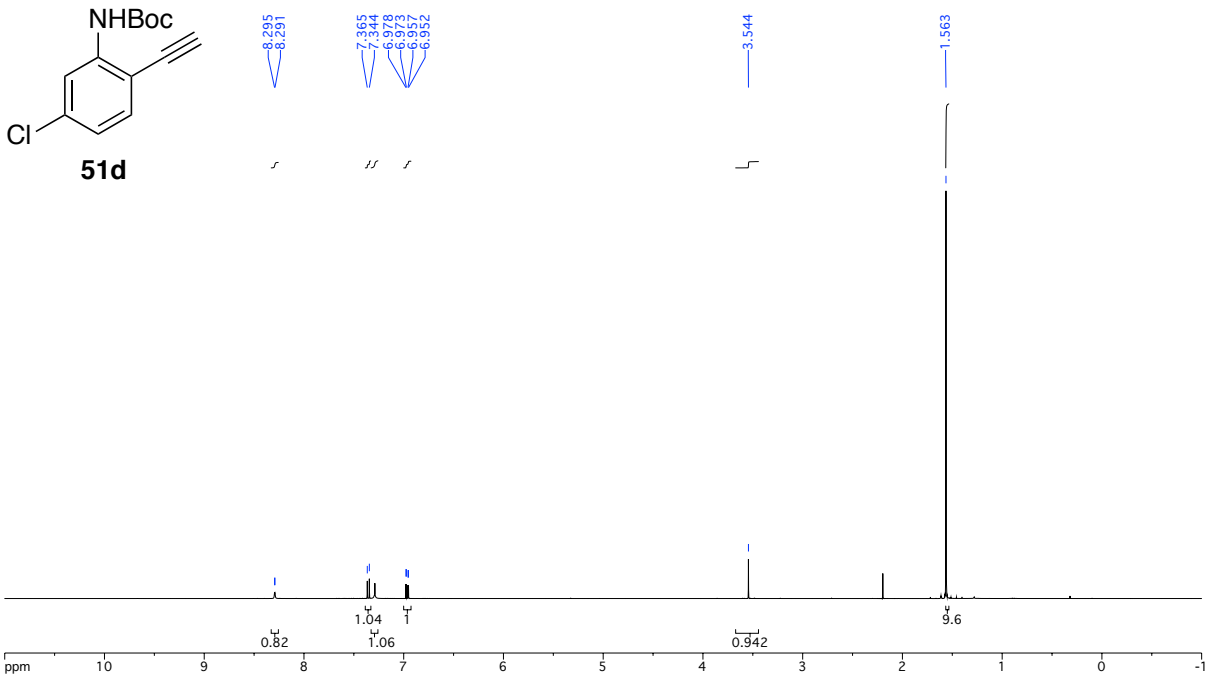

158.410
156.010
152.425
136.694
119.376
119.298
119.290
118.252
117.337
117.115
111.187
111.095
84.828
81.031
78.318
28.287
ppm

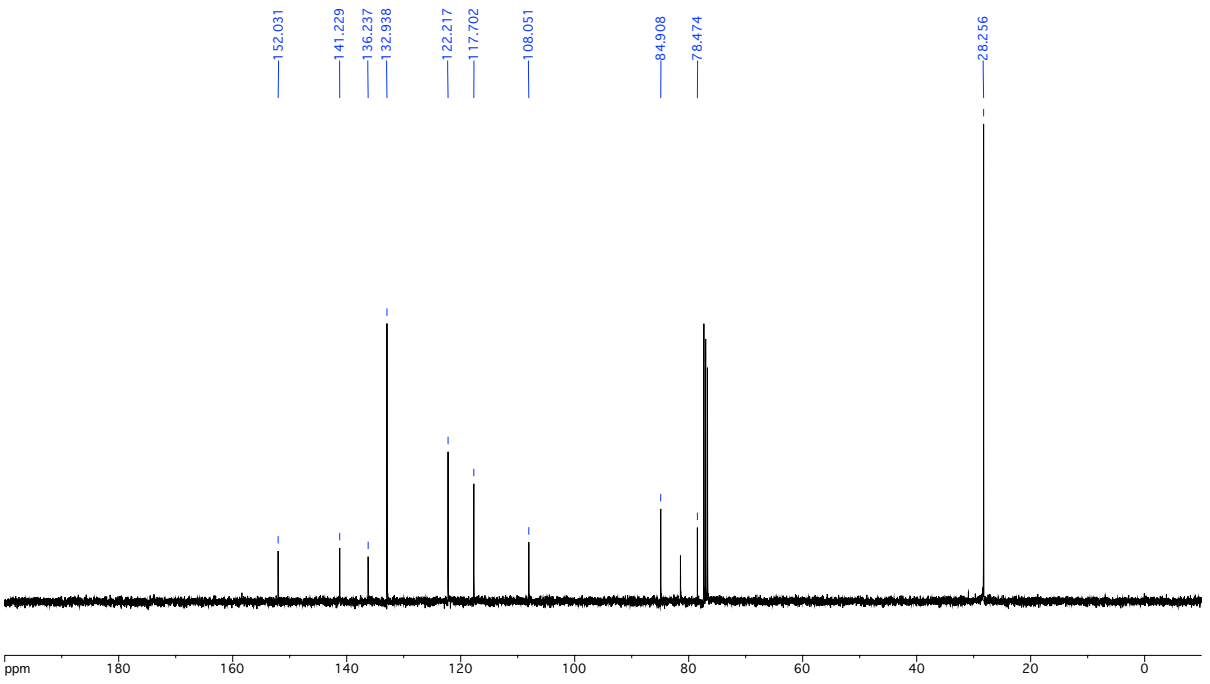

NHBoc
I
Cl
56d
8.203
8.197
7.673
7.652
6.870
6.811
6.804
6.789
6.783
1.567
1
1.02
0.827
0.999
9.82
ppm

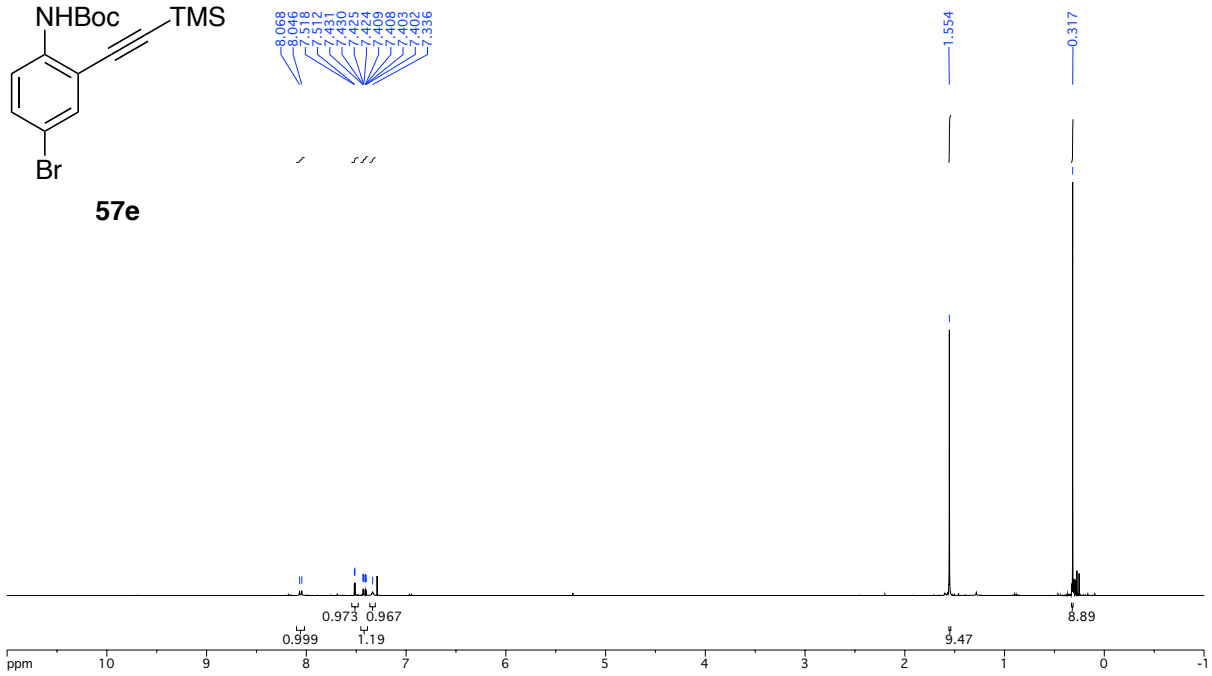

152.171
139.839
139.256
135.434
124.554
119.684
85.059
81.618
28.257
ppm


8.245
8.241
7.391
7.312
7.291
7.252
6.942
6.931
6.926
1.560
0.317
NHBoc
TMS
Cl
57d
0.783
0.957
0.995
1
9.27
9.3
ppm

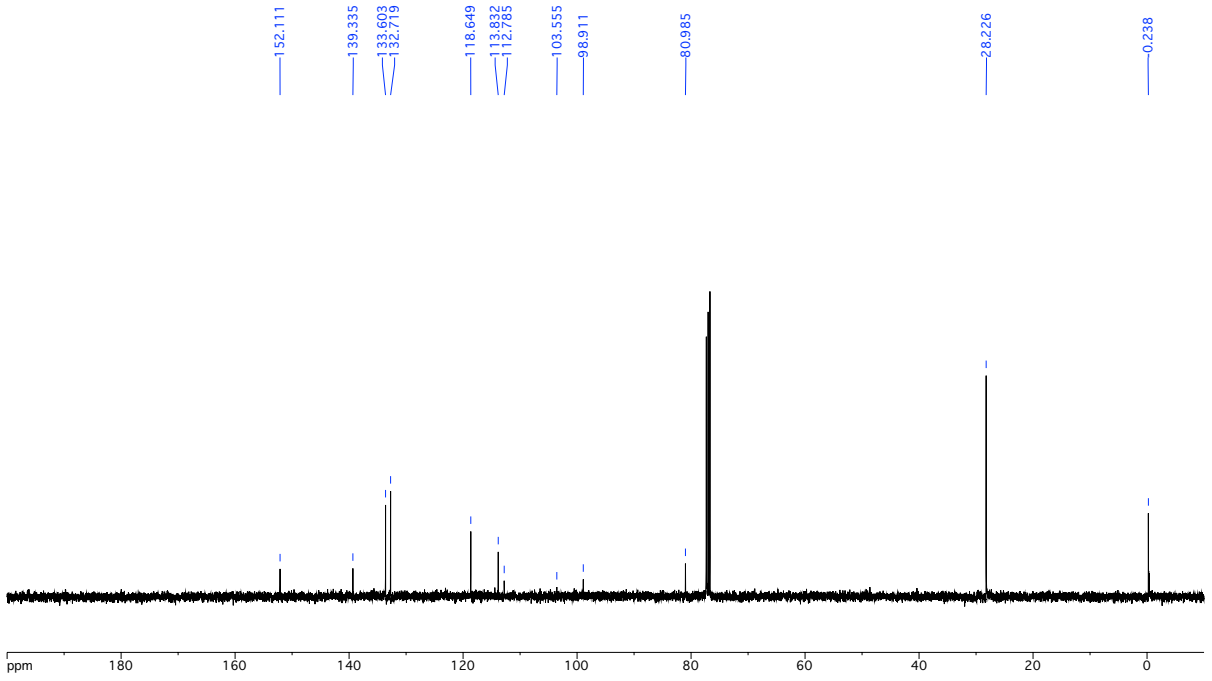

152.000
141.135
135.876
131.992
122.058
117.321
109.210
103.093
99.532
81.127
28.210
0.195
ppm

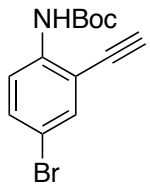

NHBoc
Cl
51d
8.295
8.291
7.365
7.344
6.978
6.957
6.952
3.544
1.563
0.82
1.04
1.06
1
0.942
9.6
ppm


152.031
141.229
136.237
132.938
122.217
117.702
108.051
84.908
78.474
28.256
ppm


NHBoc
TMS
Br
8.068
8.046
7.518
7.512
7.431
7.430
7.425
7.424
7.409
7.408
7.403
7.402
7.336
1.554
0.317
0.973
0.967
0.999
1.19
9.47
8.89
ppm

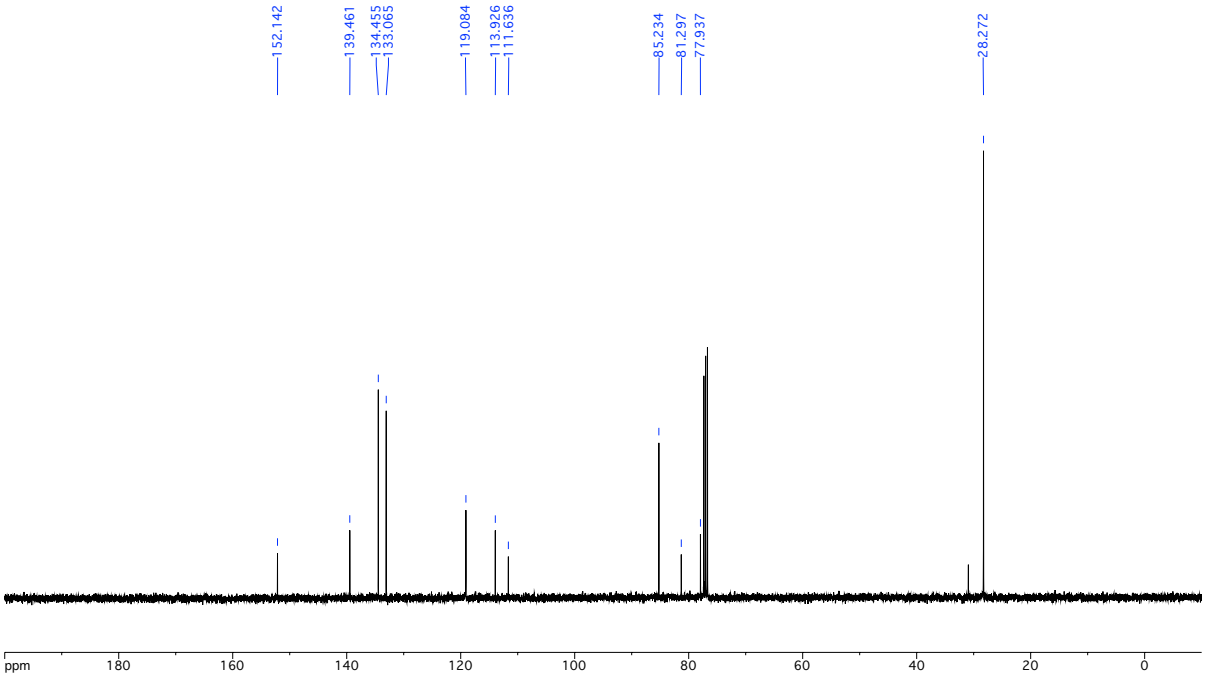
57e

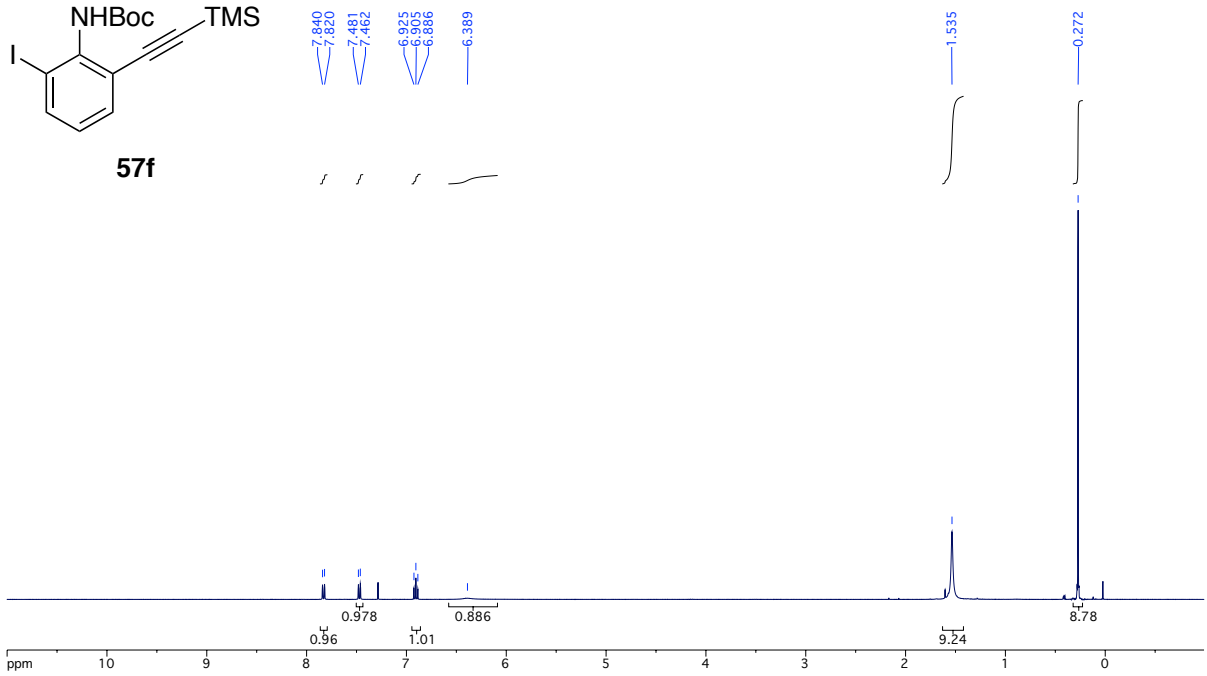

152.111
139.335
133.603
132.719
118.649
113.832
112.785
103.555
98.911
80.985
28.226
0.238
ppm

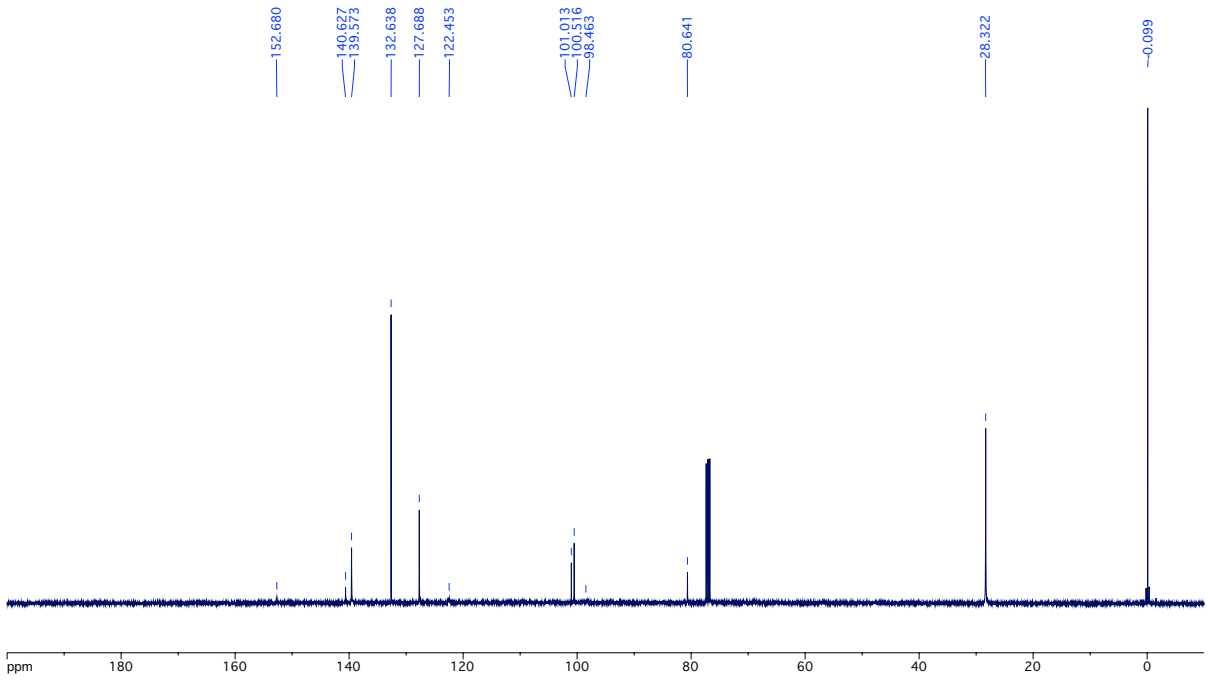

NHBoc
Br

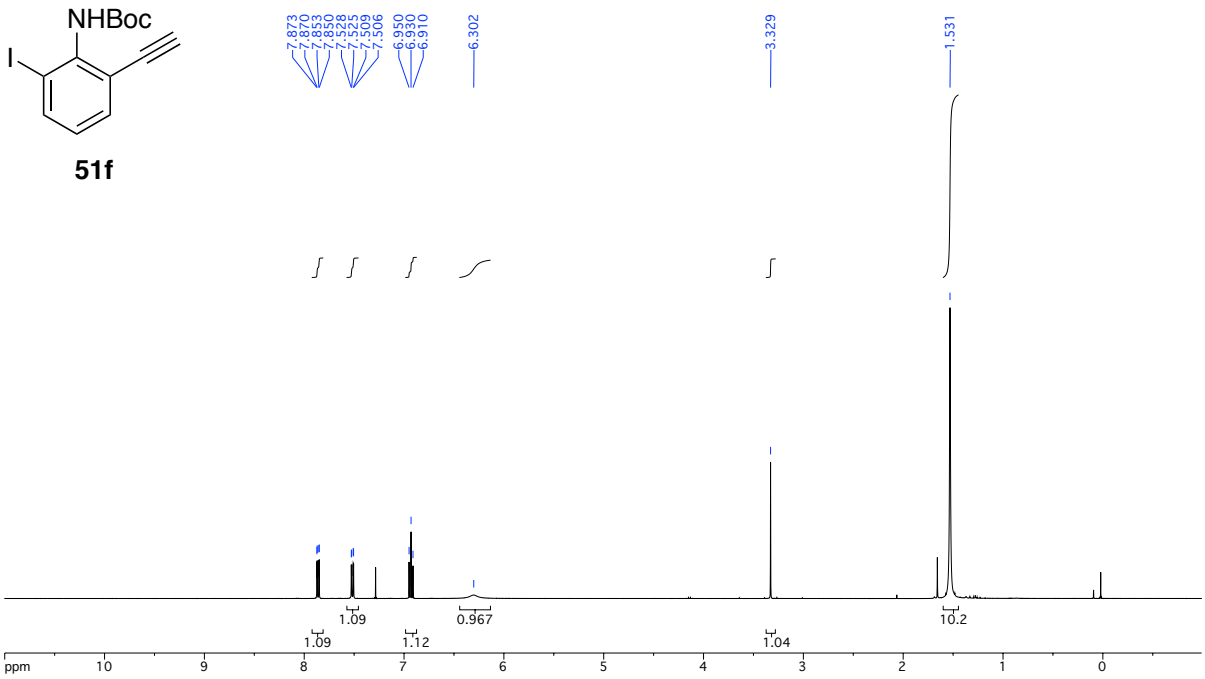
51e

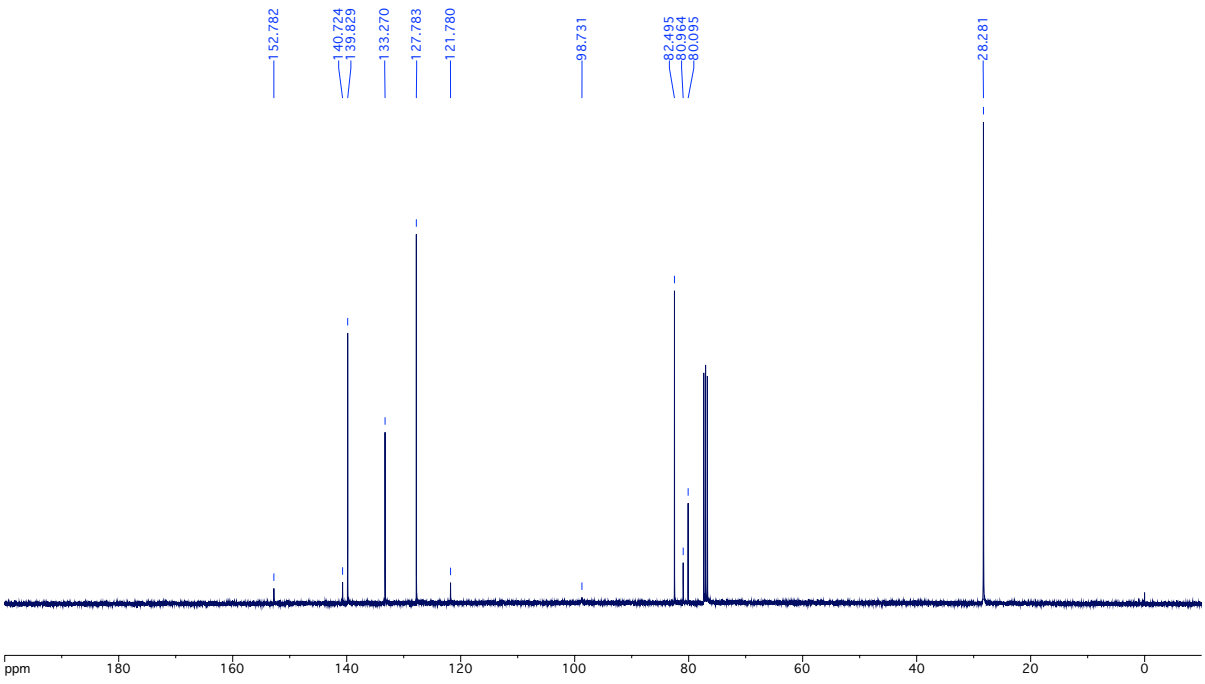
8.115
8.092
7.560
7.554
7.464
7.458
7.442
7.436
7.240
3.550
1.555
0.939
0.844
0.907
0.891
9.47
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

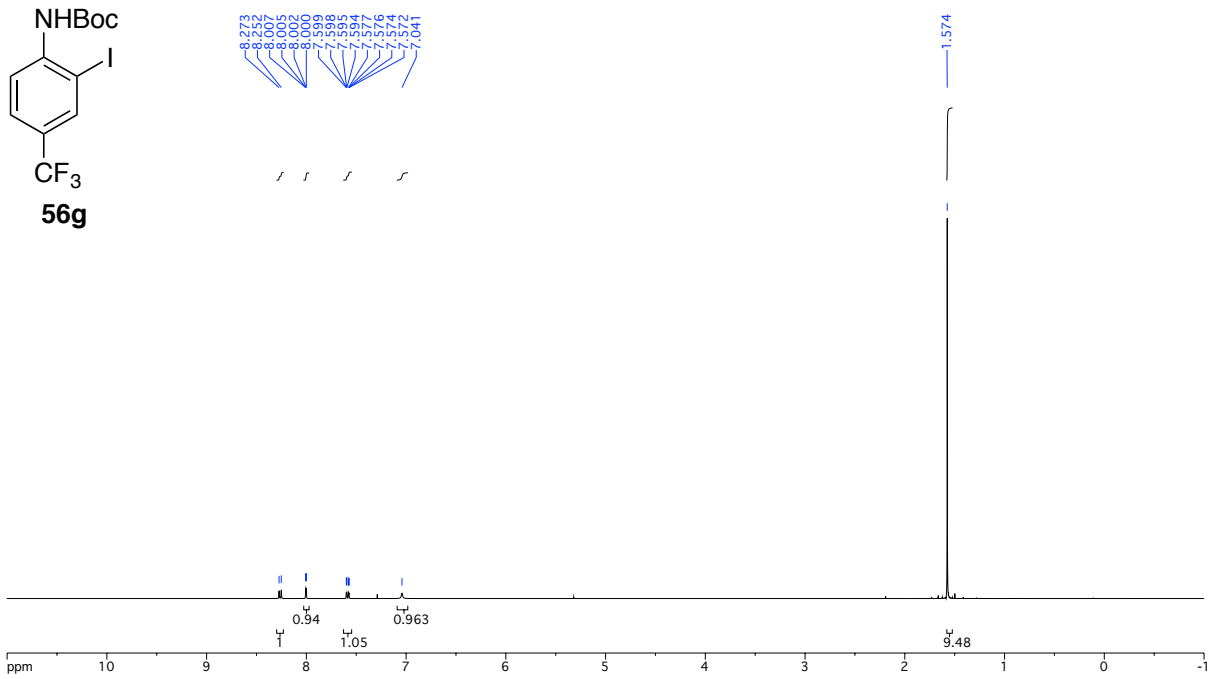

152.142
139.461
134.455
133.065
119.084
113.926
111.636
85.234
81.297
77.937
28.272
ppm
180
160
140
120
100
80
60
40
20
0

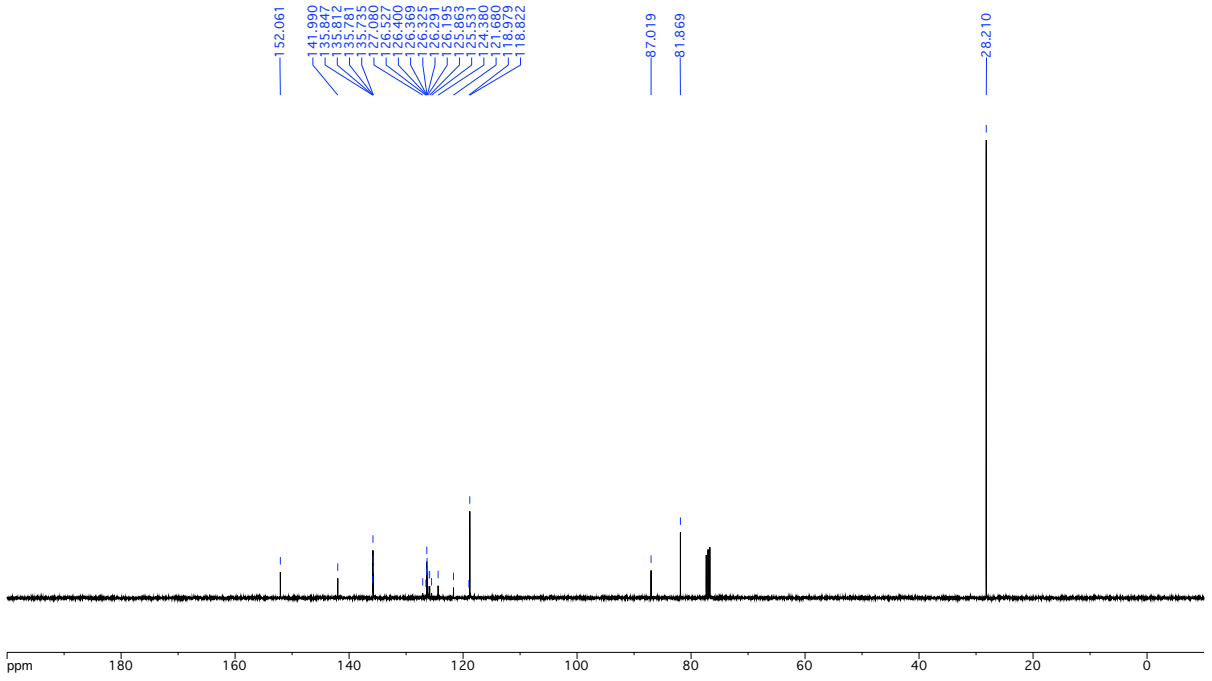

NHBoc
TMS
I
57f
7.840
7.820
7.481
7.462
6.925
6.905
6.886
6.389
1.535
0.272
0.978
0.886
8.78
0.96
1.01
9.24
ppm

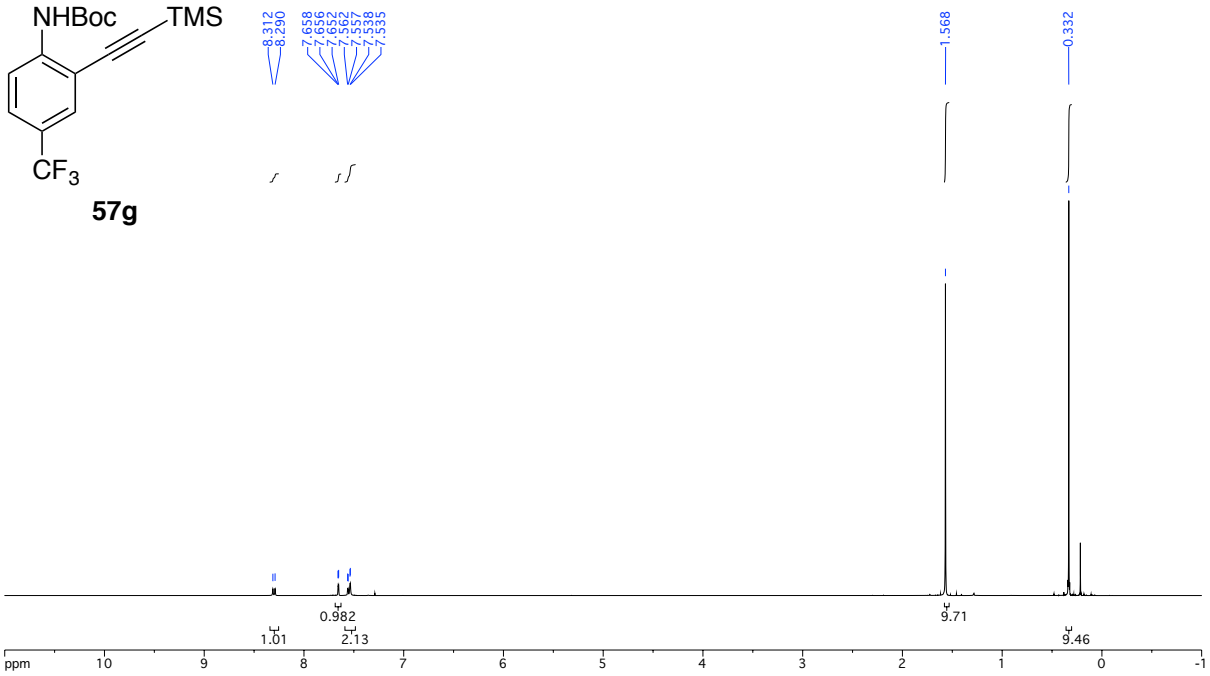

152.680
140.627
139.573
132.638
127.688
122.453
101.013
100.516
98.463
80.641
28.322
0.099
ppm

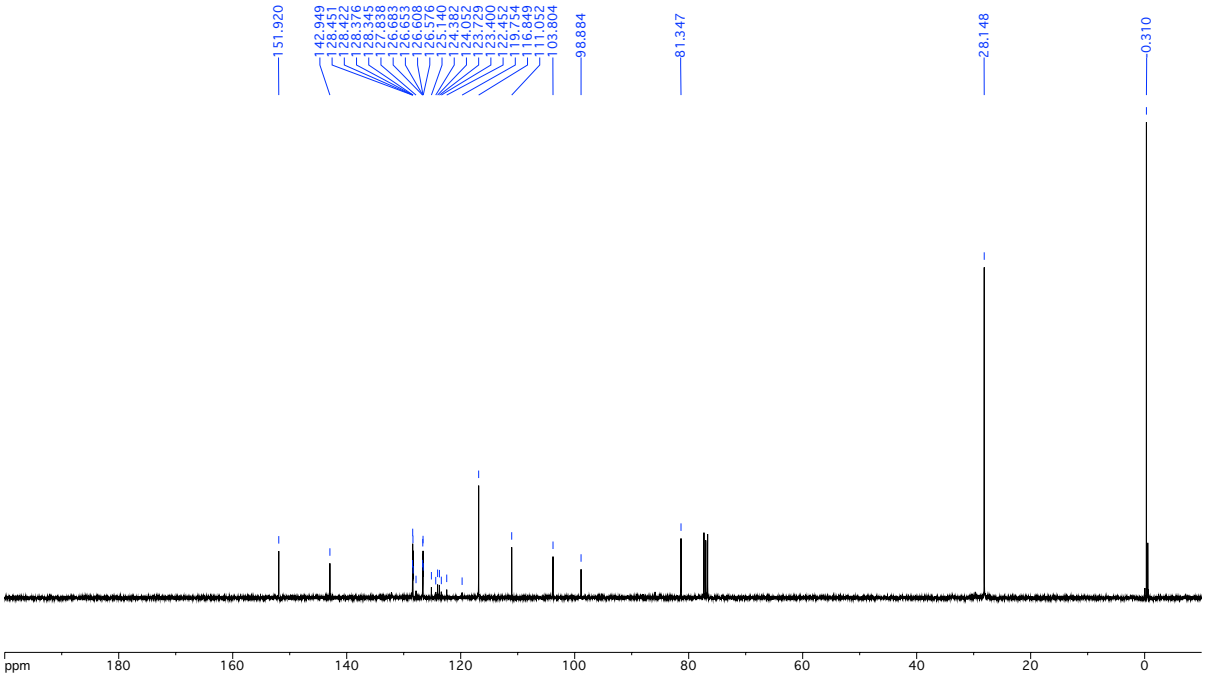

NHBoc
I
51f
7.873
7.870
7.853
7.850
7.528
7.525
7.509
7.506
6.950
6.930
6.910
6.302
3.329
1.531
1.09
0.967
10.2
1.09
1.12
1.04
ppm

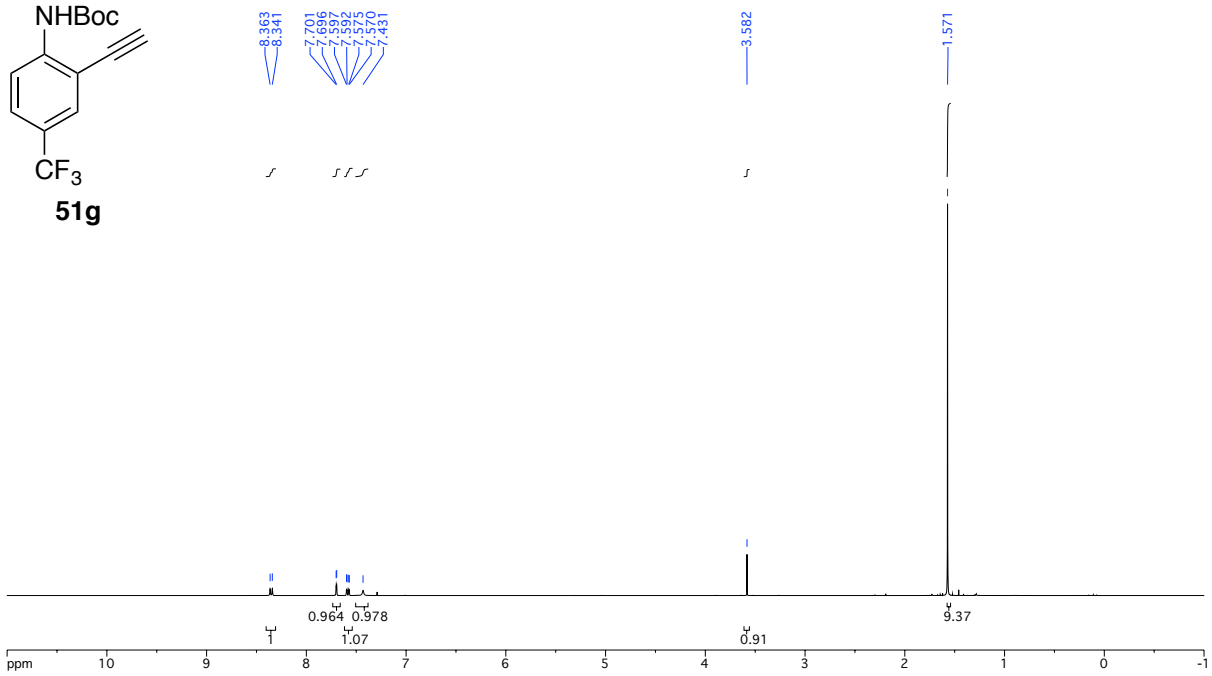

152.782
140.724
139.829
133.270
127.783
121.780
98.731
82.495
80.964
80.095
28.281
ppm

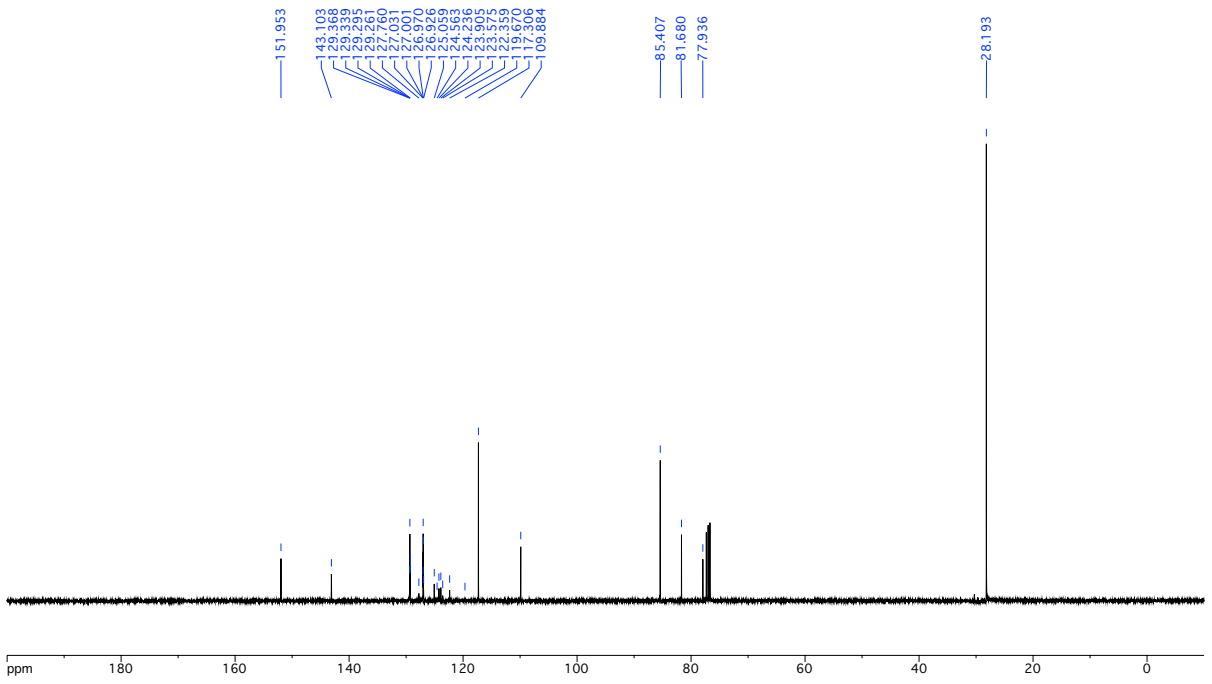

NHBoc
I
CF3
56g
8.273
8.252
8.007
8.005
8.002
8.000
7.599
7.598
7.595
7.594
7.577
7.576
7.574
7.572
7.041
1.574
0.94
1.05
0.963
9.48
ppm

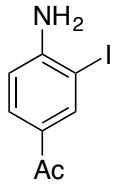

152.061
141.990
141.847
135.812
135.781
135.735
127.080
126.527
126.400
126.369
126.291
126.195
125.863
125.531
124.380
121.680
118.899
118.822
87.019
81.869
28.210
ppm


NHBoc
TMS
CF3
57g
8.312
8.290
7.658
7.656
7.652
7.562
7.557
7.538
7.535
1.568
0.332
1.01
0.982
2.13
9.71
9.46
ppm


151.920
142.949
128.471
128.422
128.376
128.345
127.838
126.683
126.653
126.608
125.676
125.140
124.382
124.052
123.729
123.400
122.452
119.754
116.849
111.052
103.804
98.884
81.347
28.148
0.310
ppm

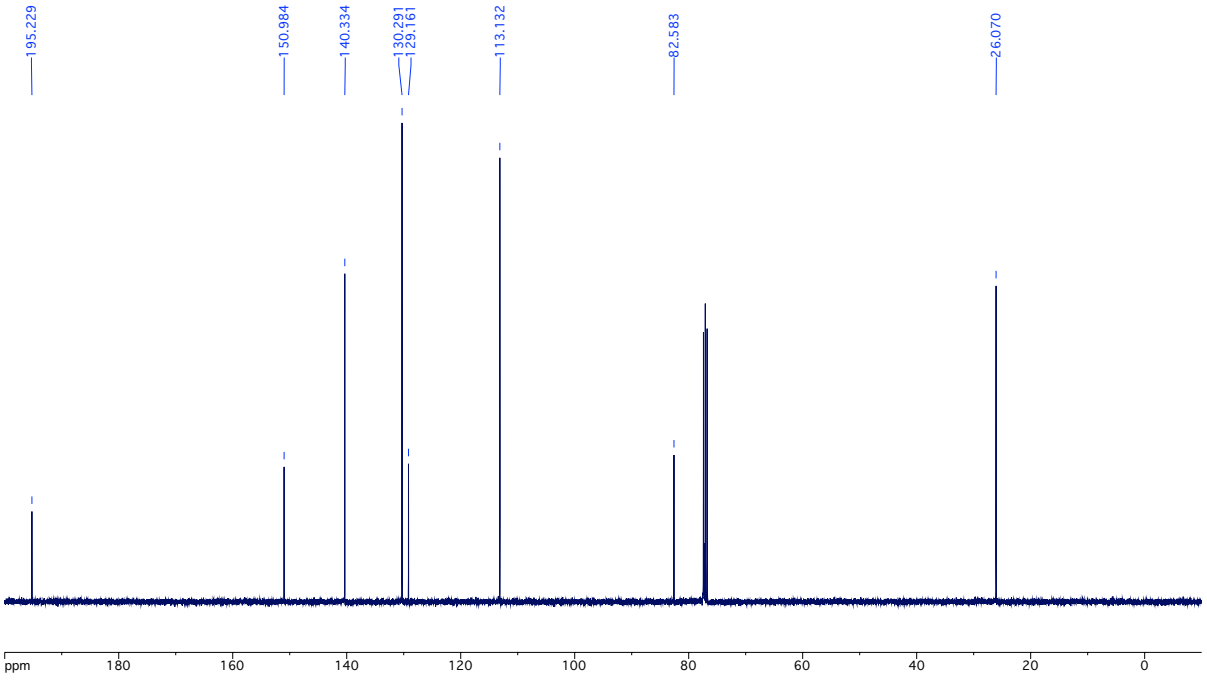

NHBoc
CF3
51g
8.363
8.341
7.701
7.696
7.597
7.592
7.575
7.570
7.431
3.582
1.571
0.964
0.978
1.07
0.91
9.37
ppm

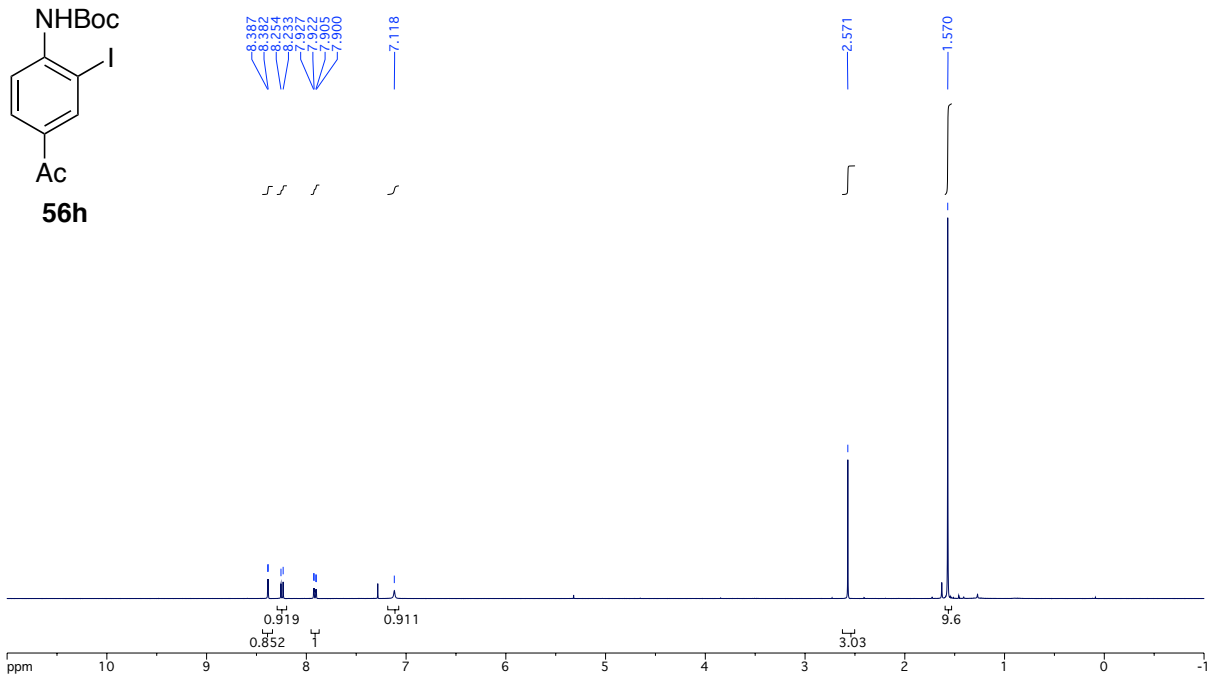

151.953
143.103
129.368
129.339
129.295
129.261
127.060
127.031
127.001
126.970
126.926
125.059
124.563
124.236
123.905
123.375
122.359
119.670
117.306
109.884
85.407
81.680
77.936
28.193
ppm

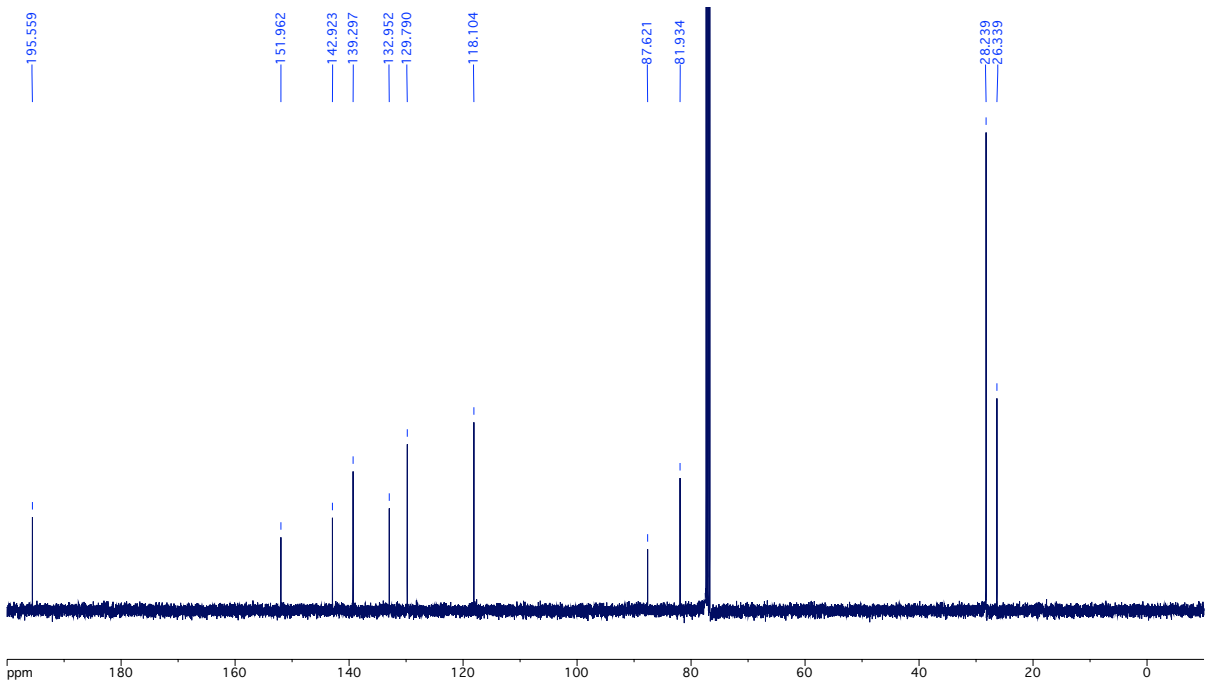

NH2
I
Ac

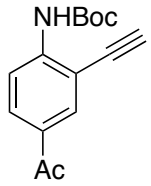
137

8.281
8.276
7.779
7.774
7.758
7.753
6.735
6.713
4.675
2.503
0.859
0.959
1
2.28
3.28
ppm


195.229
150.984
140.334
130.291
129.161
113.132
82.583
26.070
ppm

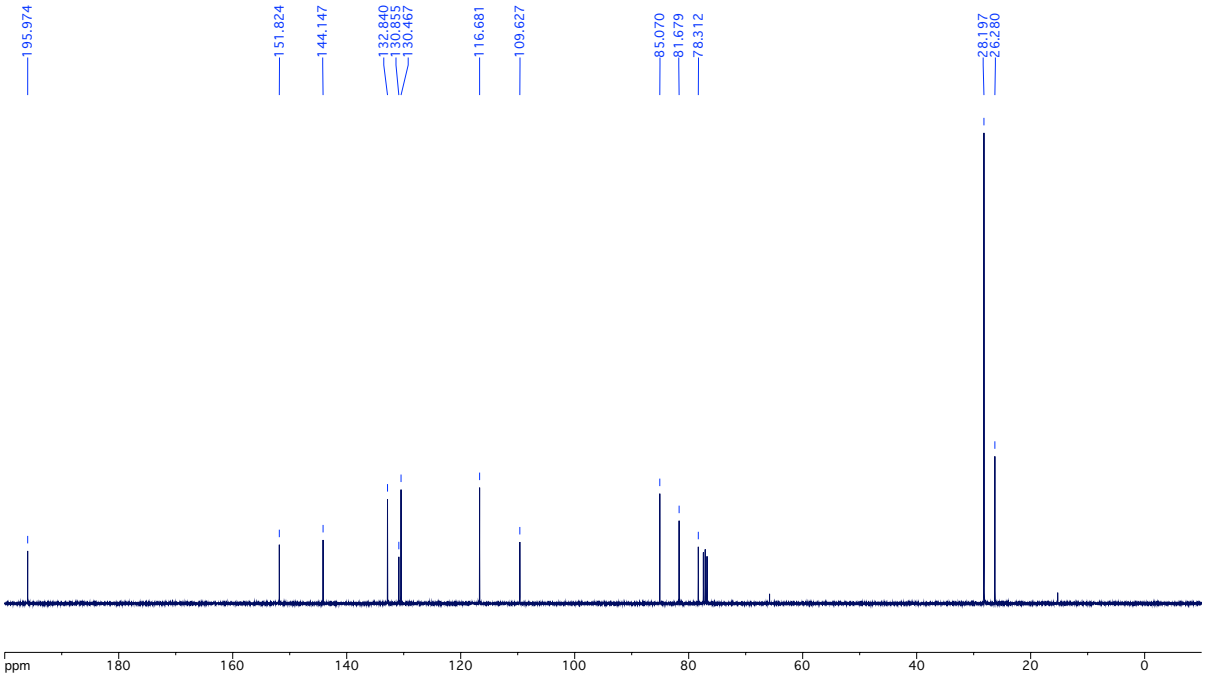

NHBoc
I
Ac
56h
8.387
8.382
8.254
8.233
7.927
7.922
7.905
7.900
7.118
2.571
1.570
0.919
0.852
0.911
3.03
9.6
ppm

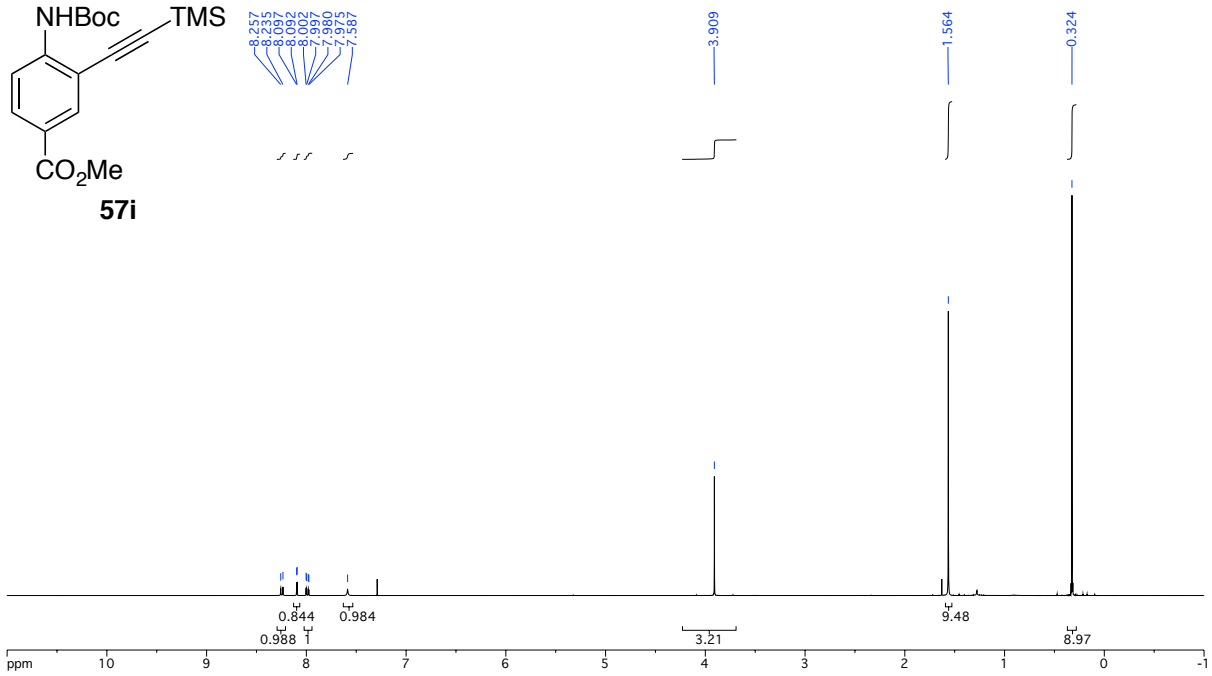

195.559
151.962
142.923
139.297
132.952
129.790
118.104
87.621
81.934
28.239
26.339
ppm

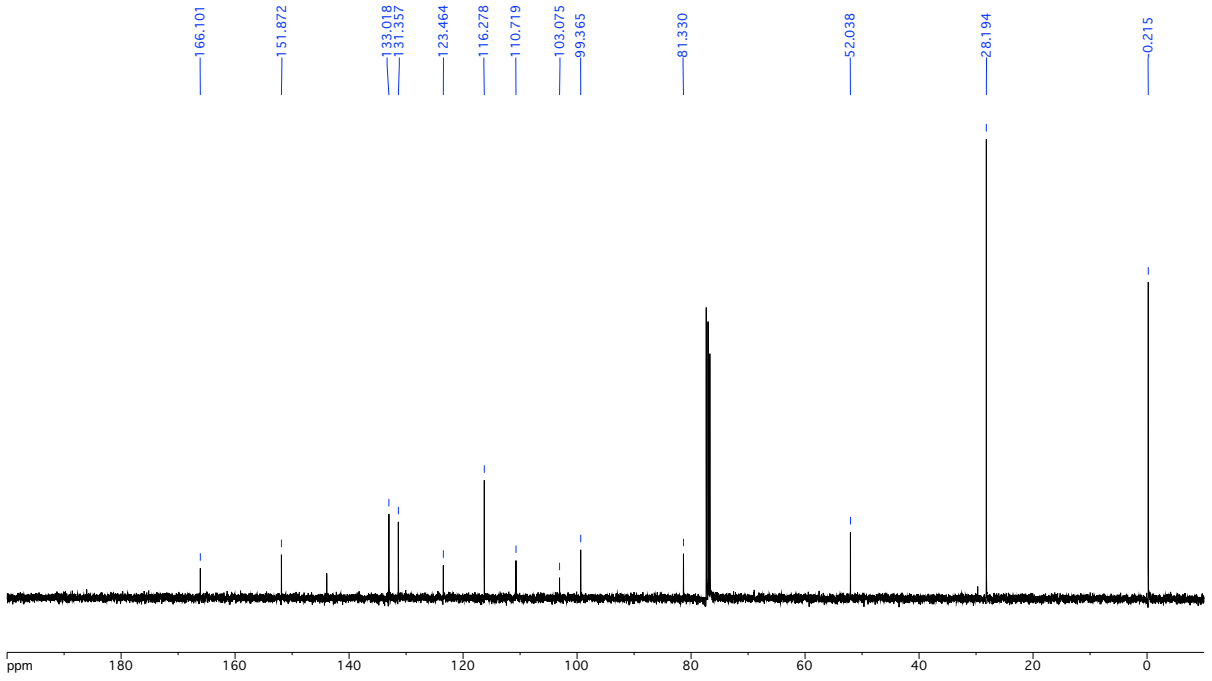

NHBoc
Ac

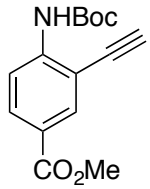
51h

8.276
8.254
8.021
8.016
7.917
7.912
7.895
7.890
7.458
3.562
2.534
1.528
0.936
1.07
0.95
0.842
3.33
9.46
ppm


195.974
151.824
144.147
132.840
130.855
130.467
116.681
109.627
85.070
81.679
78.312
28.197
26.280
ppm

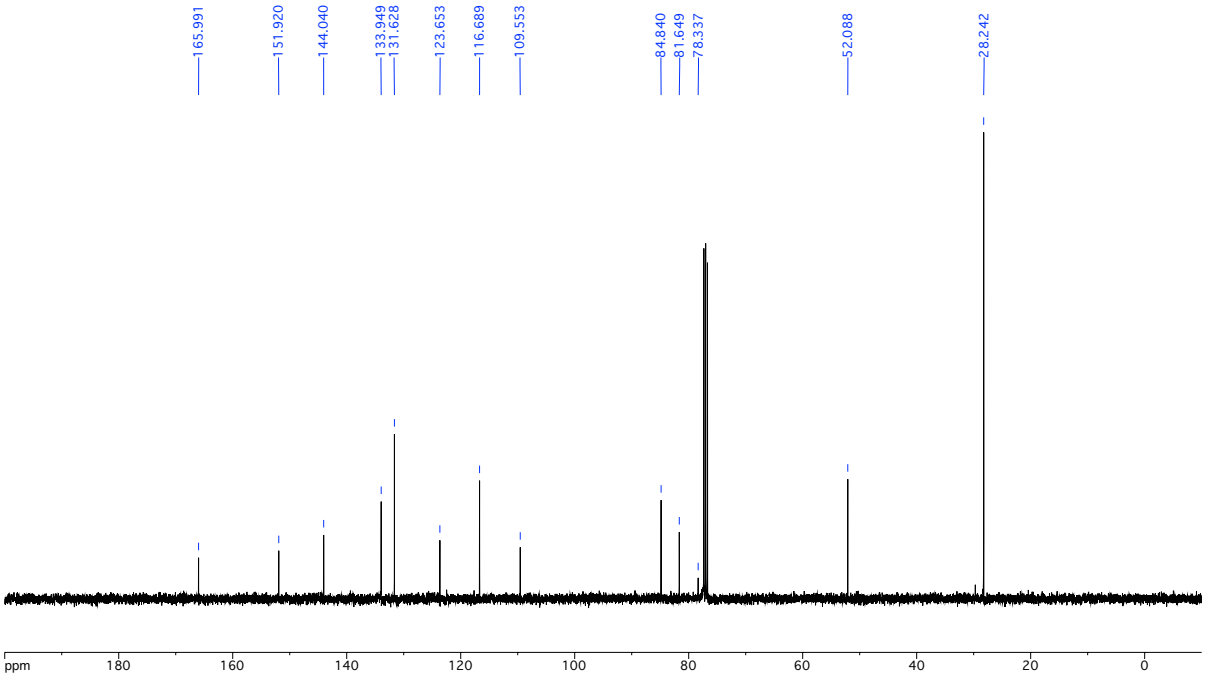

NHBoc
TMS
CO2Me
57i
8.257
8.235
8.097
8.092
8.002
7.997
7.980
7.975
7.587
3.909
1.564
0.324
0.844
0.984
0.988
1
3.21
9.48
8.97
ppm

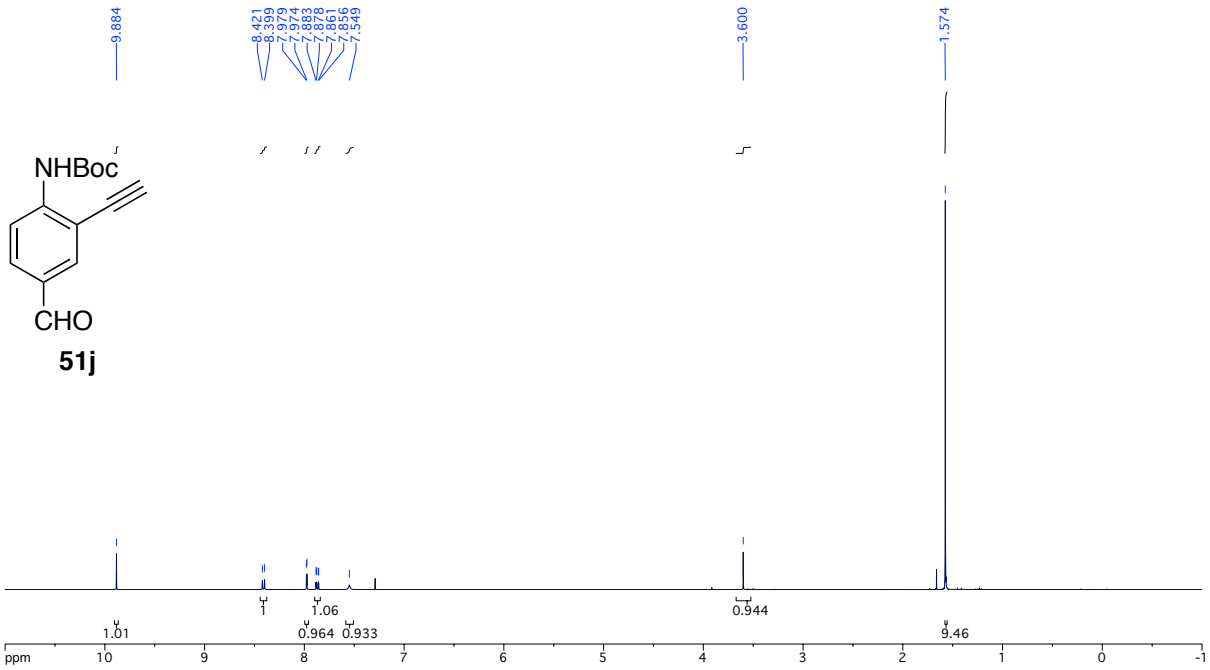

166.101
151.872
133.018
131.357
123.464
116.278
110.719
103.075
99.365
81.330
52.038
28.194
0.215
ppm


NHBoc
CO2Me

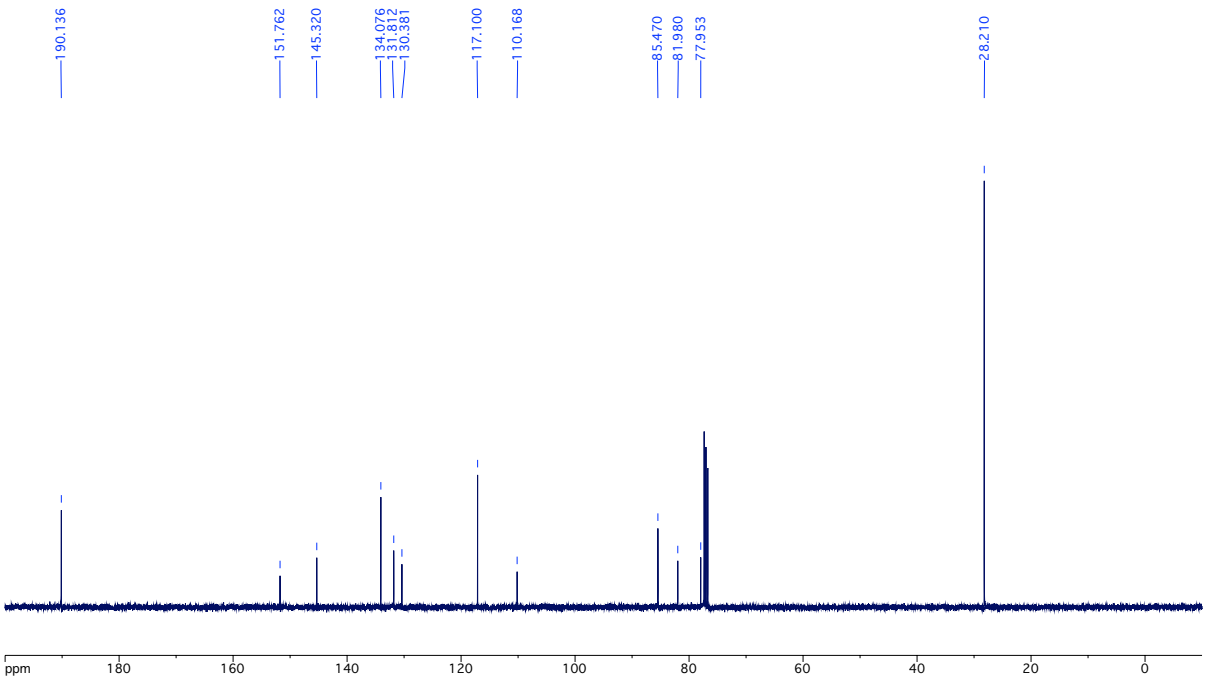
51i

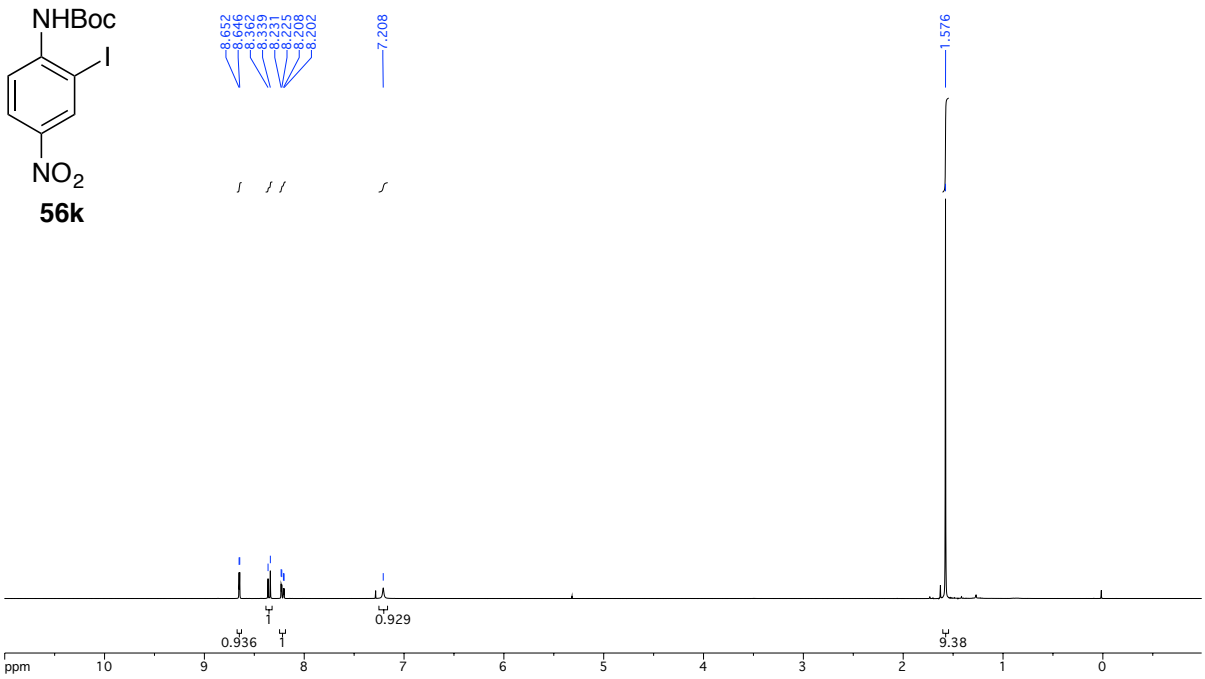
8.308
8.286
8.146
8.140
8.031
8.026
8.026
8.009
8.009
8.004
7.480
3.917
3.553
1.568
0.836
0.997
0.997
1
0.868
3.17
9.62
ppm

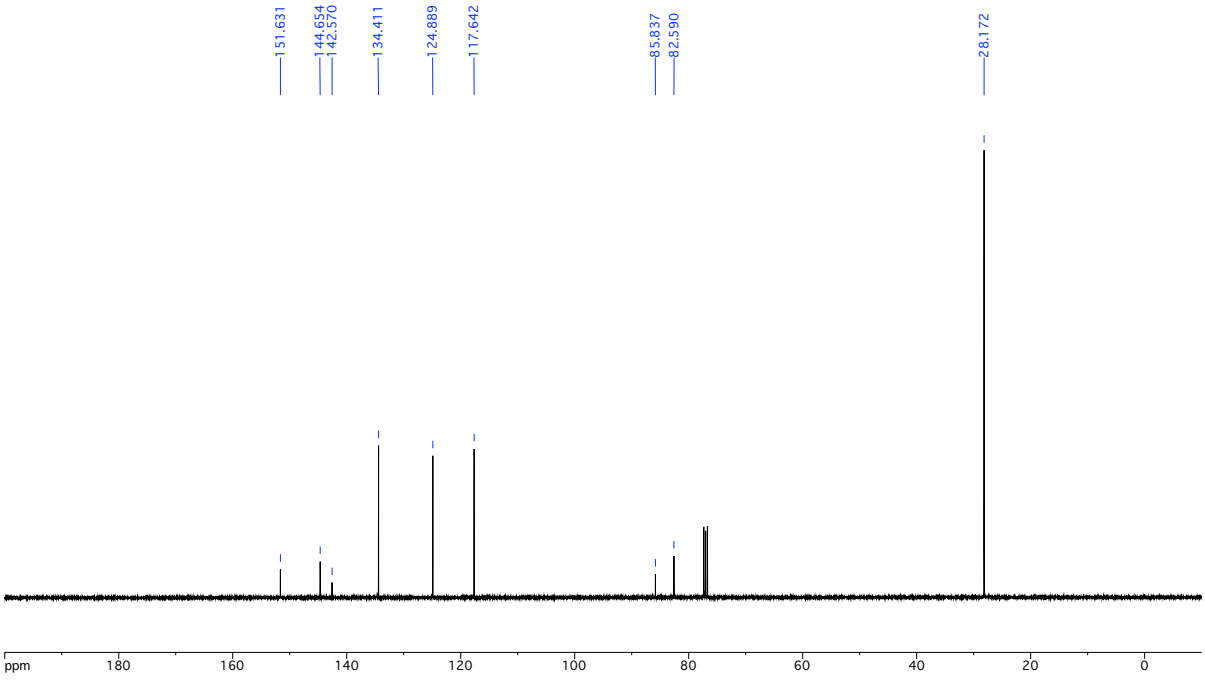

165.991
151.920
144.040
133.949
131.628
123.653
116.689
109.553
84.840
81.649
78.337
52.088
28.242
ppm

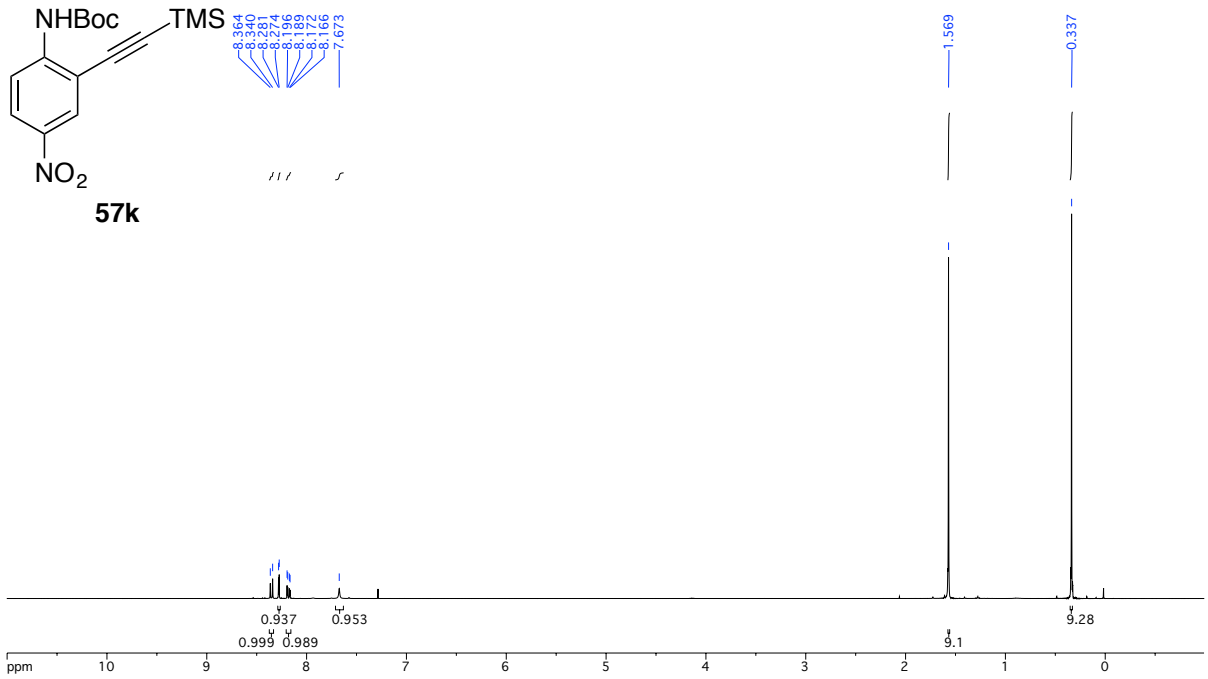

9.884
8.421
8.399
8.379
7.974
7.883
7.878
7.861
7.856
7.549
3.600
1.574
NHBoc
CHO
1.01
1
1.06
0.964
0.933
0.944
9.46
ppm

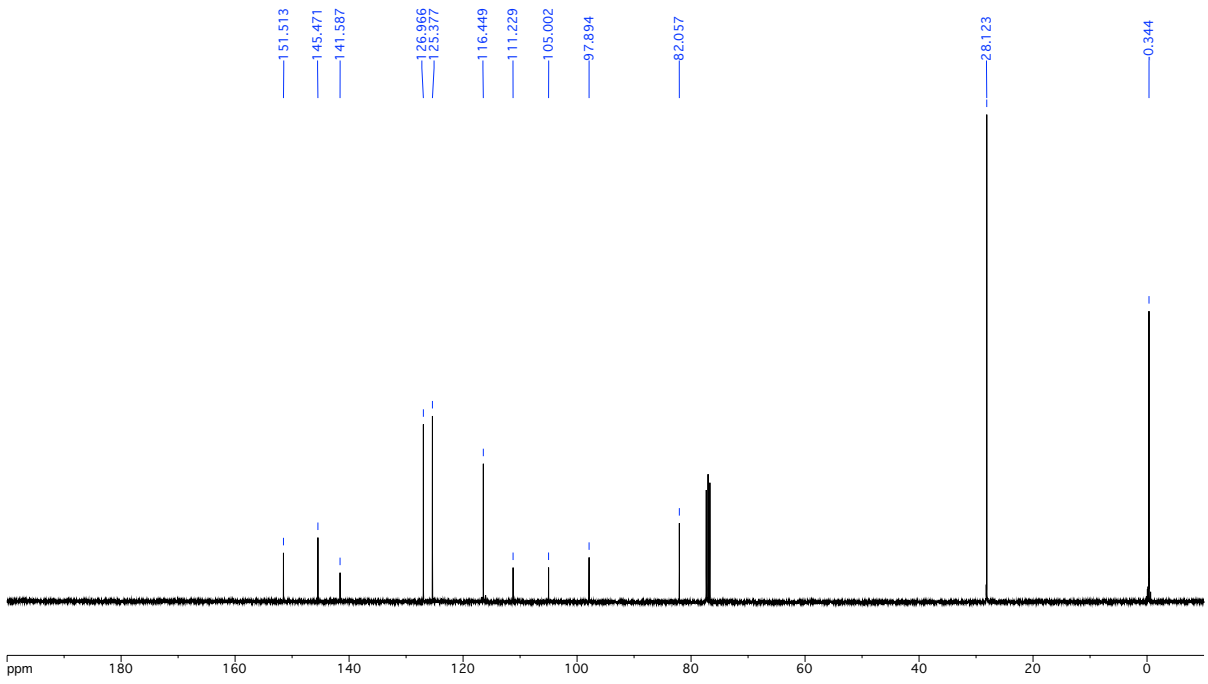
51j

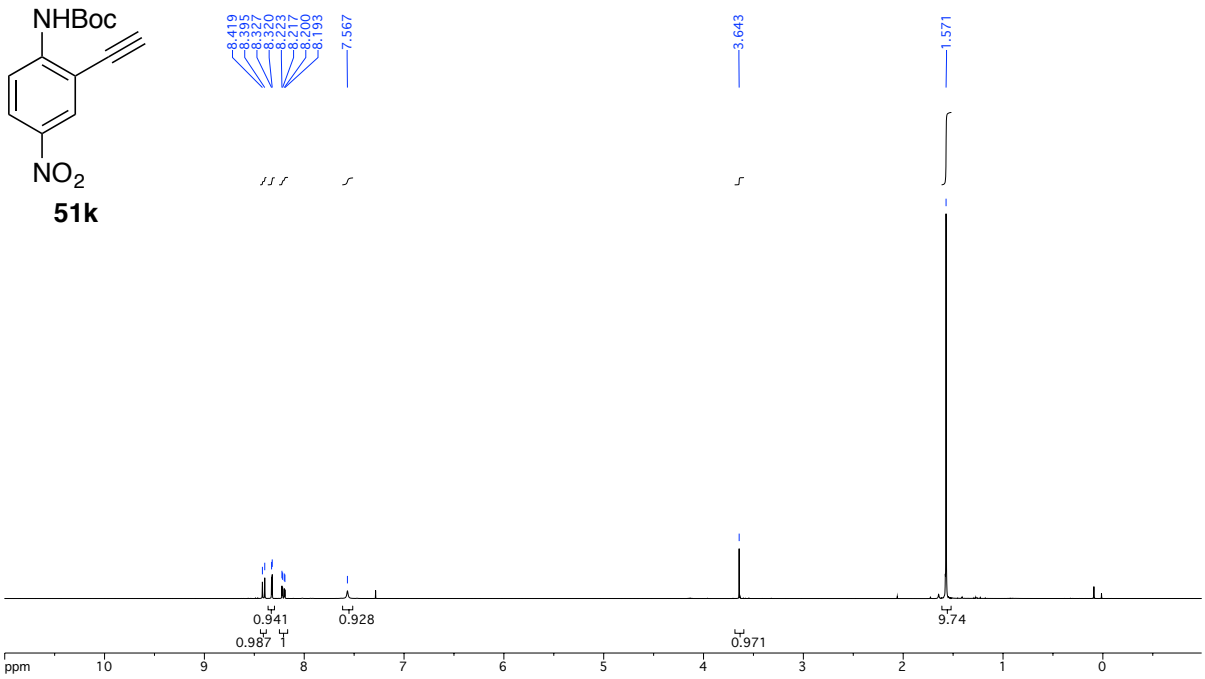

190.136
151.762
145.320
134.076
131.817
130.381
117.100
110.168
85.470
81.980
77.953
28.210
ppm

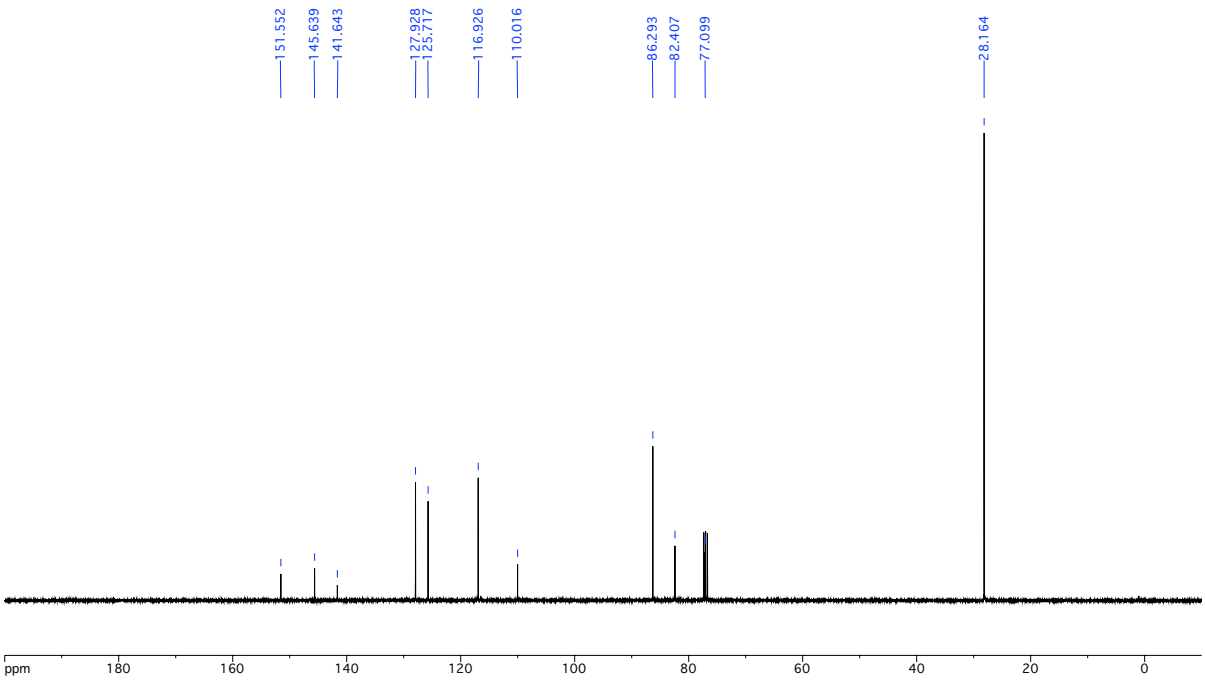

NHBoc
I
NO2
56k
8.652
8.646
8.362
8.339
8.331
8.221
8.208
8.202
7.208
1.576
0.936
1
1
0.929
9.38
ppm
10
9
8
7
6
5
4
3
2
1
0

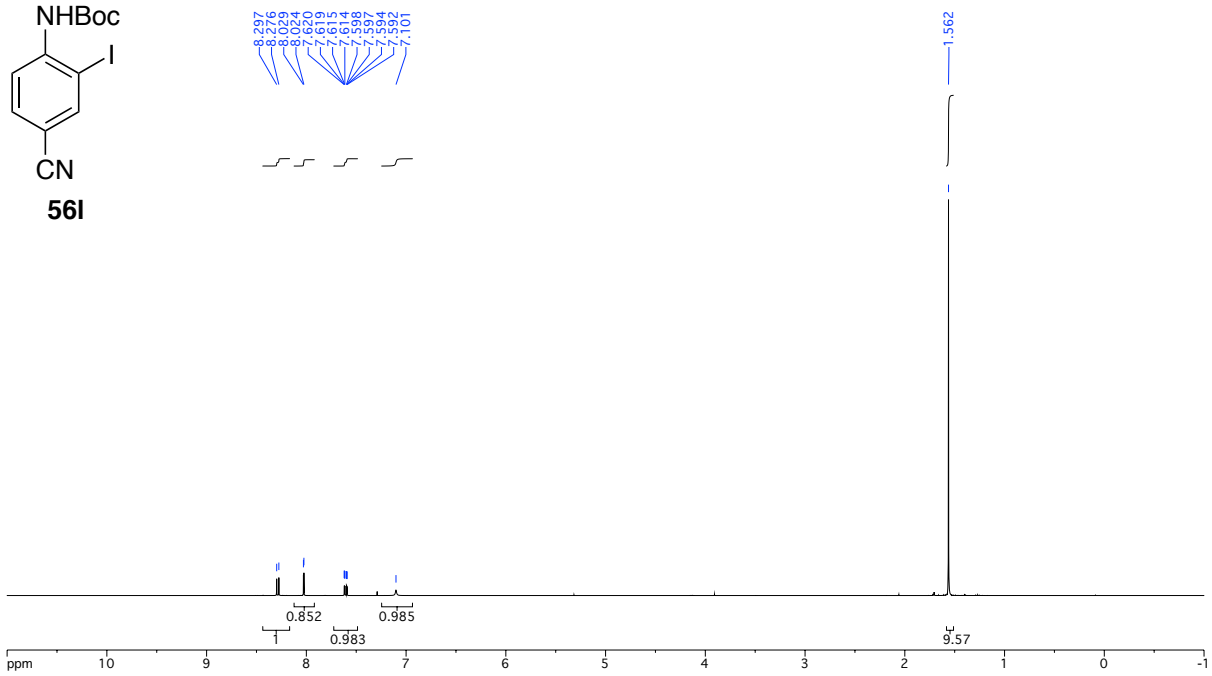

151.631
144.654
142.570
134.411
124.889
117.642
85.837
82.590
28.172
ppm
180
160
140
120
100
80
60
40
20
0

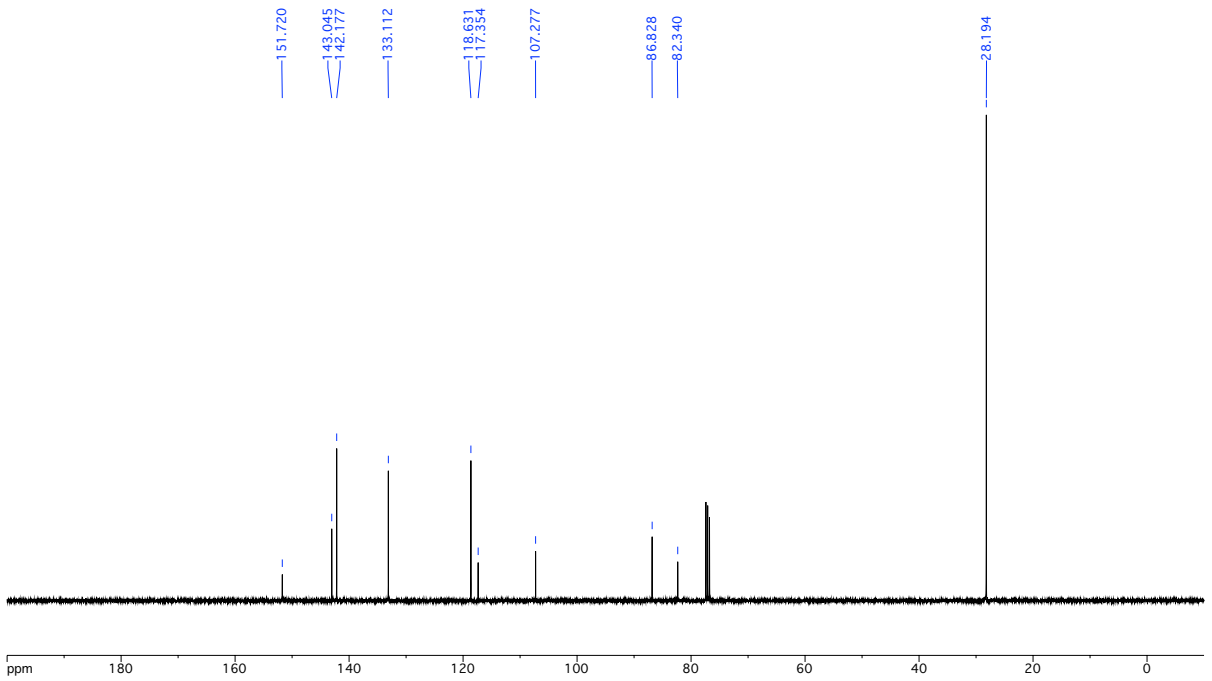

NHBoc
TMS
NO2
57k
8.364
8.340
8.281
8.274
8.196
8.189
8.172
8.166
7.673
1.569
0.337
0.937
0.953
0.999
0.989
9.1
9.28
ppm

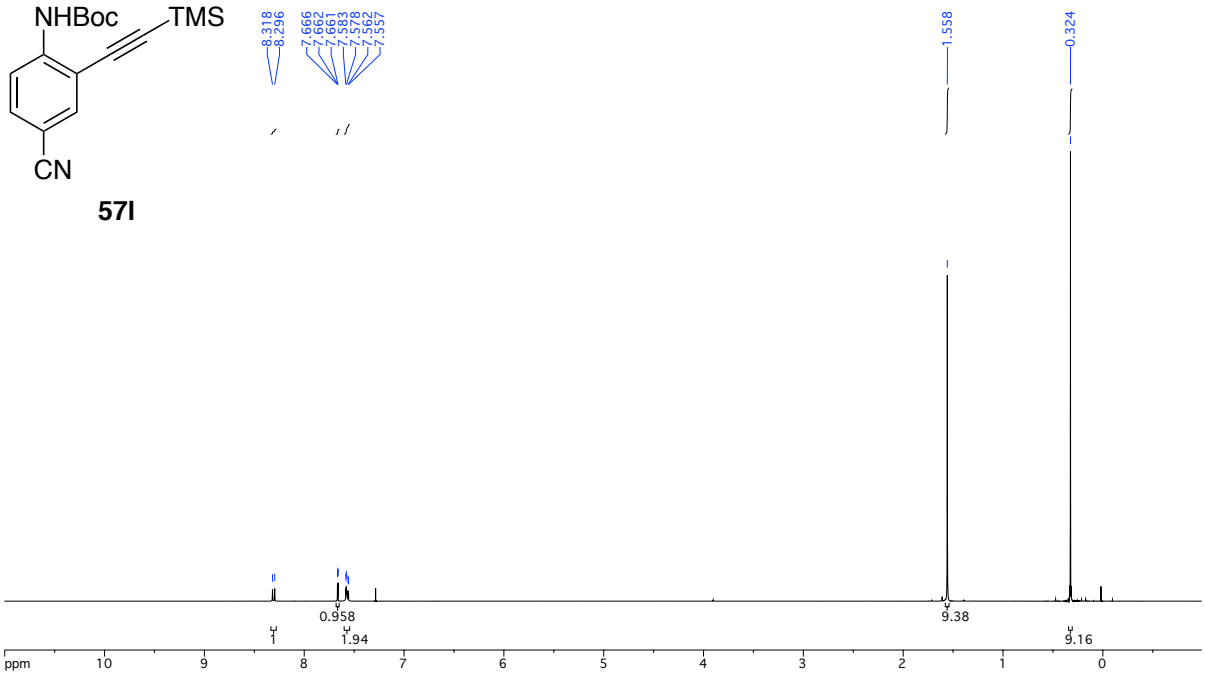

151.513
145.471
141.587
126.966
125.377
116.449
111.229
105.002
97.894
82.057
28.123
0.344
ppm


NHBoc
NO2
51k
8.419
8.395
8.327
8.320
8.223
8.217
8.200
8.193
7.567
3.643
1.571
0.941
0.987
1
0.928
0.971
9.74
ppm
10
9
8
7
6
5
4
3
2
1
0

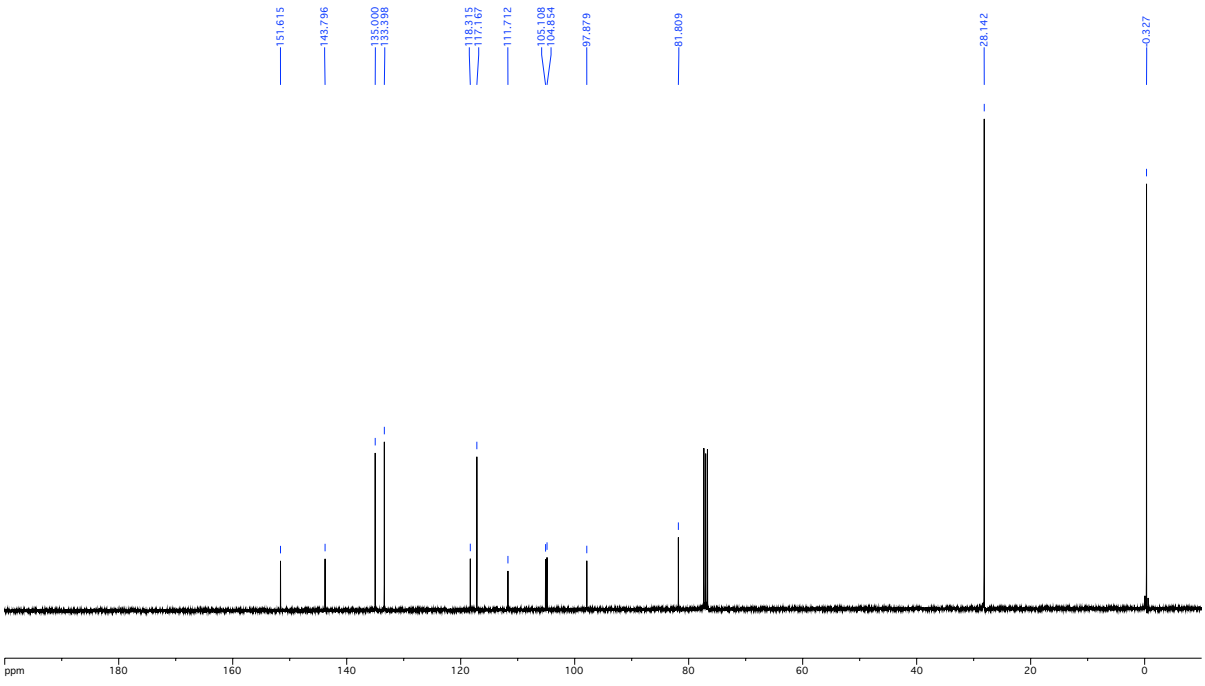

151.552
145.639
141.643
127.928
125.717
116.926
110.016
86.293
82.407
77.099
28.164
ppm
180
160
140
120
100
80
60
40
20
0

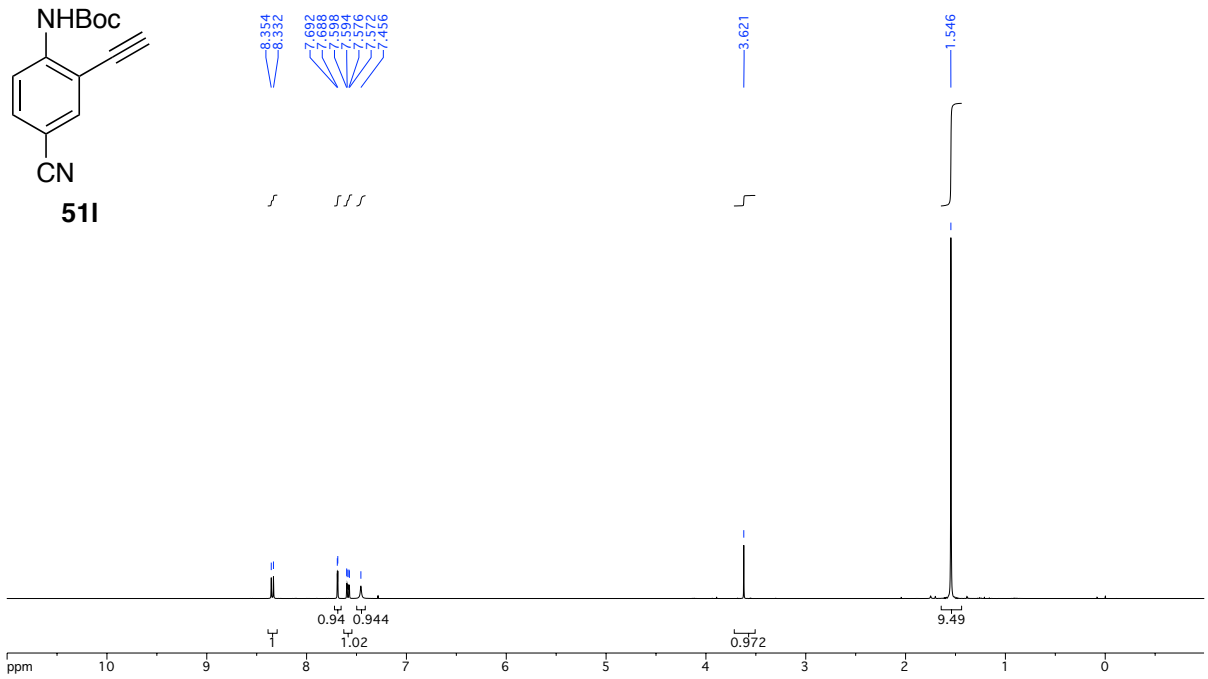

NHBoc
I
CN
56l
8.297
8.276
8.093
8.023
7.620
7.619
7.615
7.614
7.598
7.597
7.594
7.592
7.101
1.562
0.852
0.985
1
0.983
9.57
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

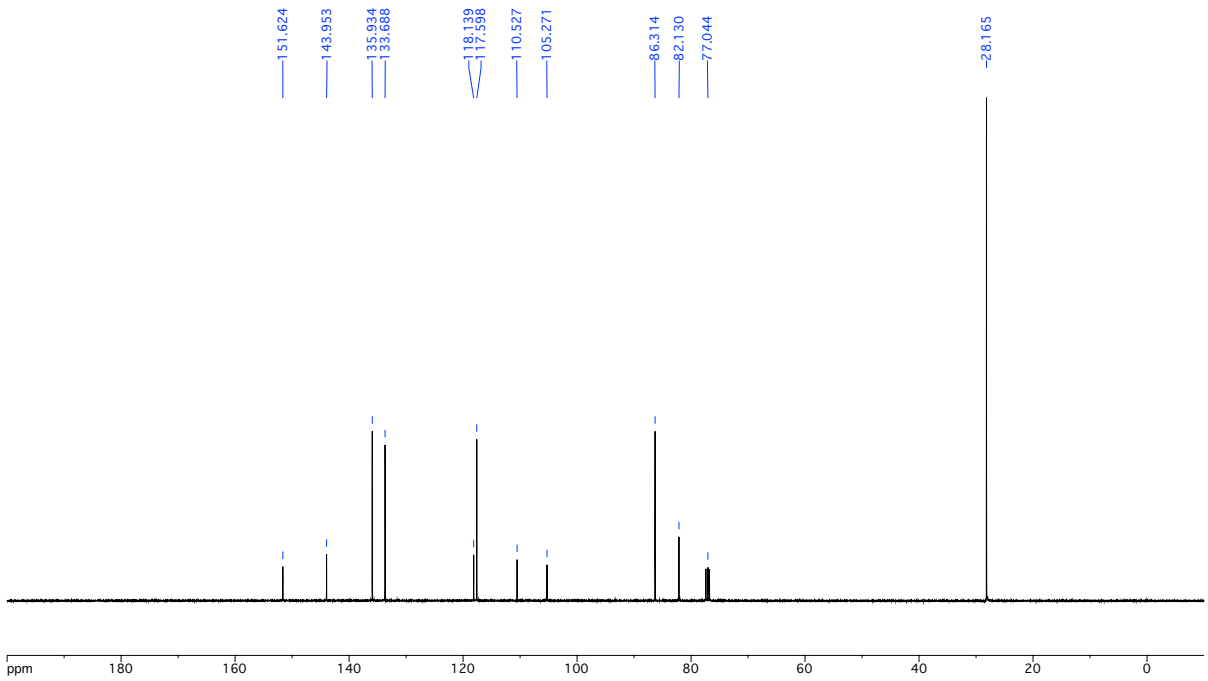

151.720
143.045
142.177
133.112
118.631
117.354
107.277
86.828
82.340
28.194
ppm
180
160
140
120
100
80
60
40
20
0

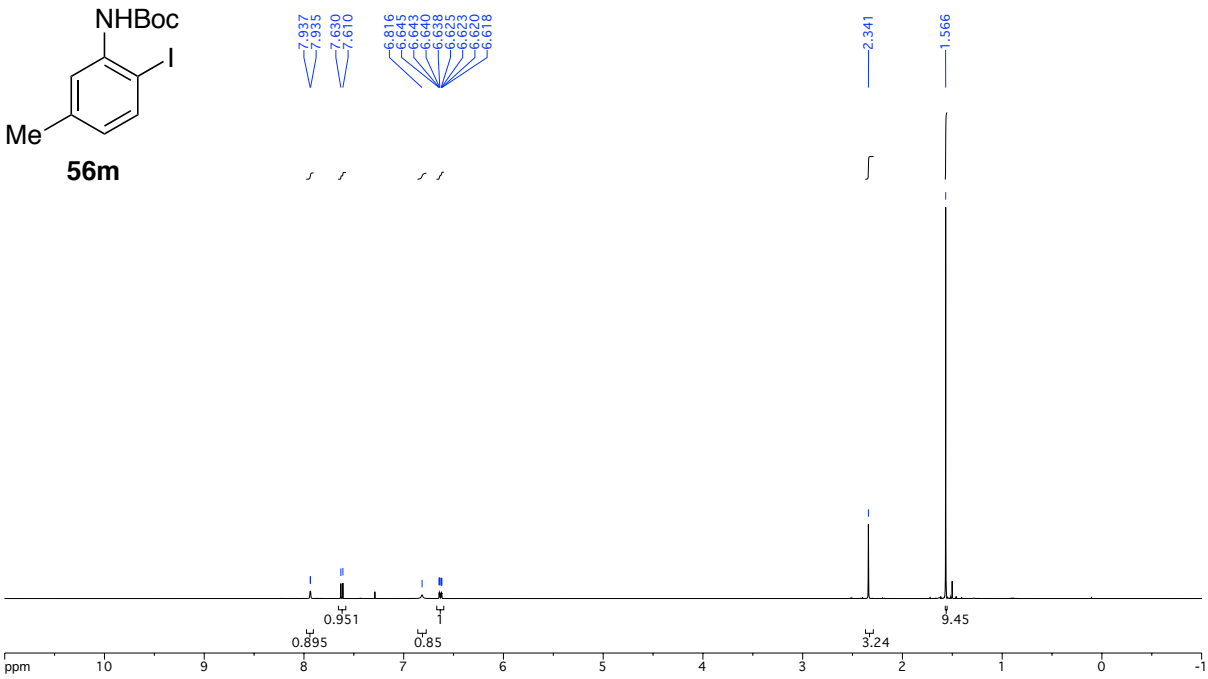

NHBoc
TMS
CN
8.318
8.296
7.666
7.662
7.661
7.583
7.578
7.562
7.557
1.558
0.324
0.958
1.94
9.38
9.16
1
ppm
10
9
8
7
6
5
4
3
2
1
0

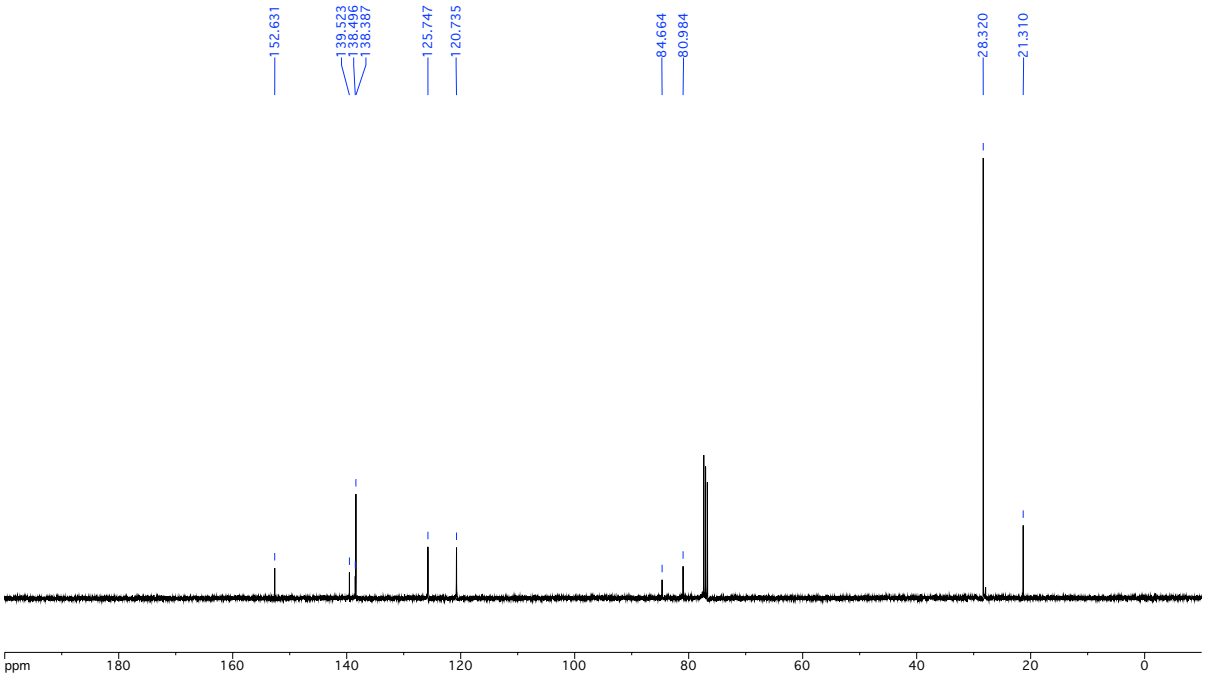
57l

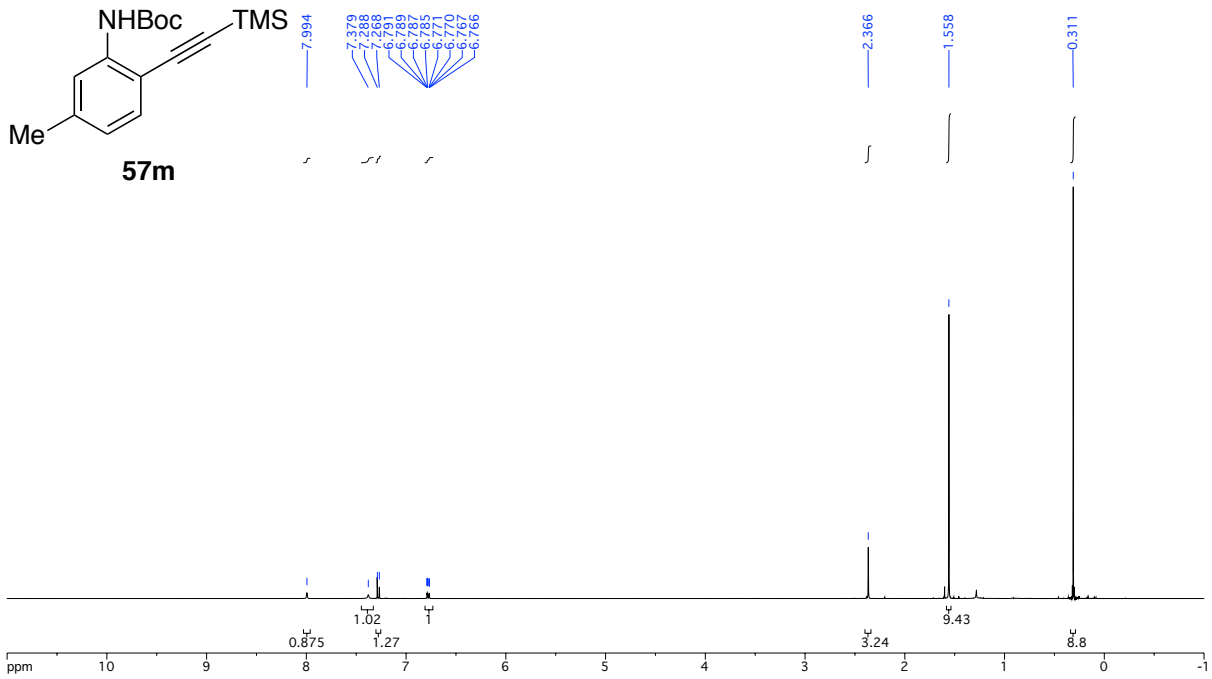

151.615
143.796
135.000
133.398
118.315
117.167
111.712
105.108
104.854
97.879
81.809
28.142
0.327
ppm
180
160
140
120
100
80
60
40
20
0

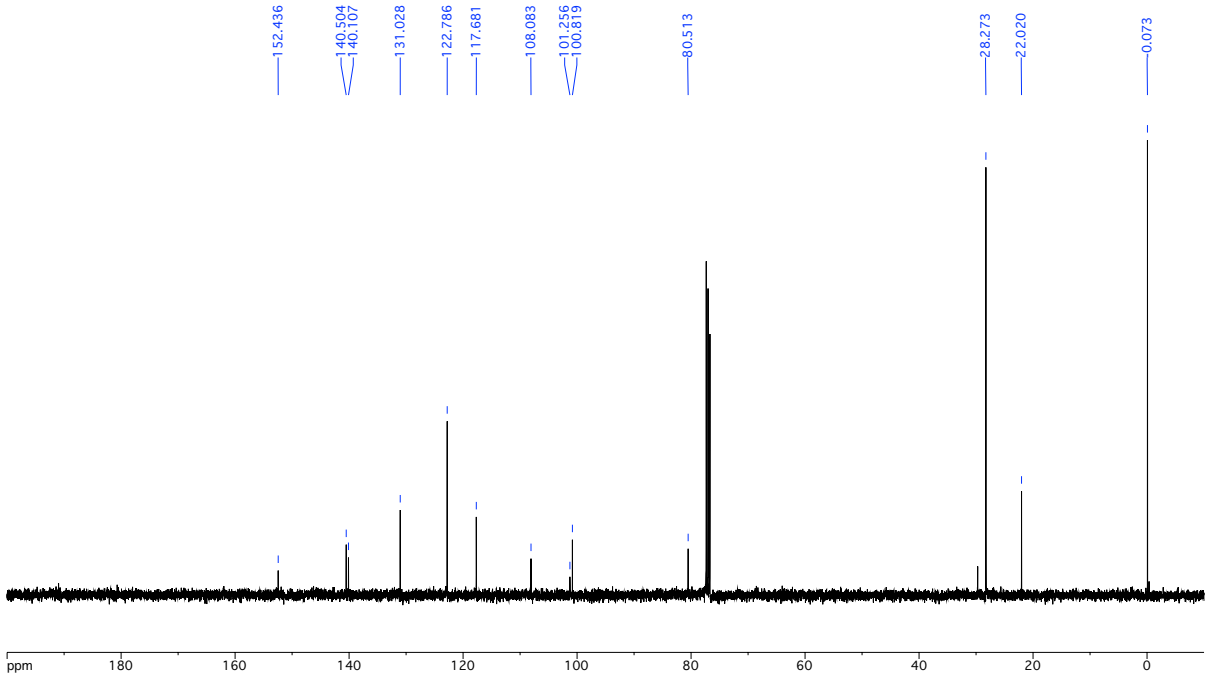

NHBoc
CN
51l
8.354
8.332
7.692
7.688
7.598
7.594
7.576
7.572
7.456
3.621
1.546
0.94
0.944
1.02
0.972
9.49
ppm

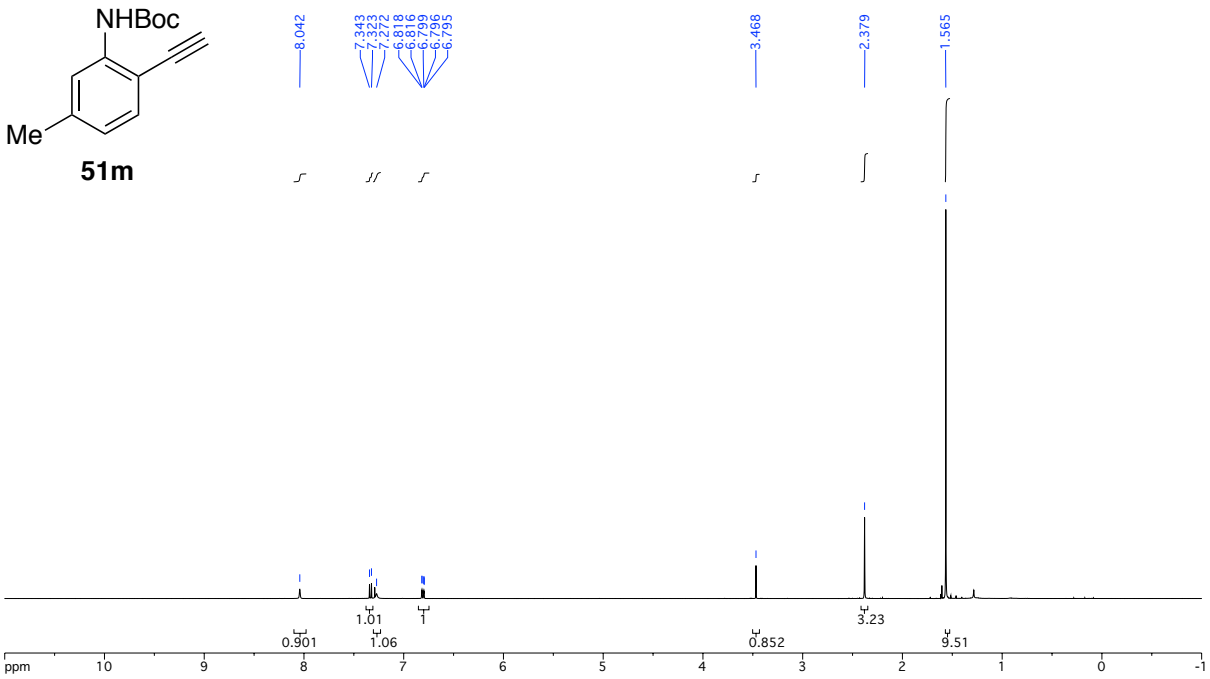

151.624
143.953
135.934
133.688
118.139
117.598
110.527
105.271
86.314
82.130
77.044
28.165
ppm

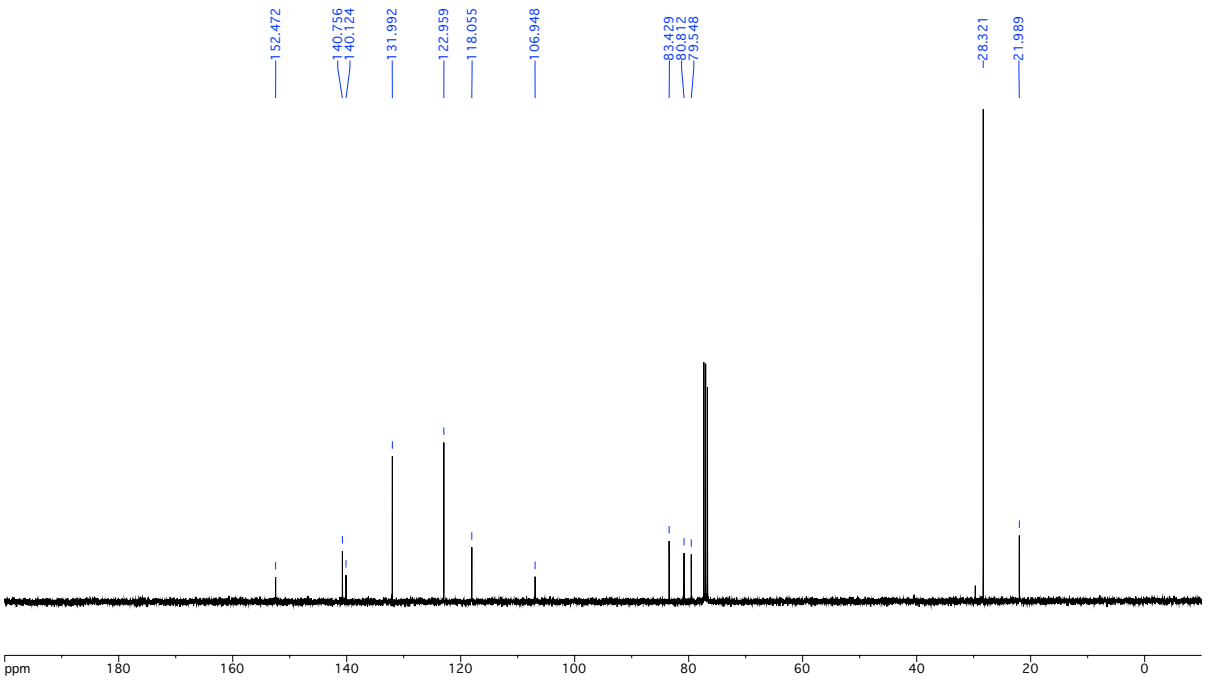

NHBoc
I
Me
56m
7.937
7.935
7.630
7.610
6.816
6.645
6.643
6.640
6.638
6.625
6.623
6.620
6.618
2.341
1.566
0.951
1
9.45
0.895
0.85
3.24
ppm

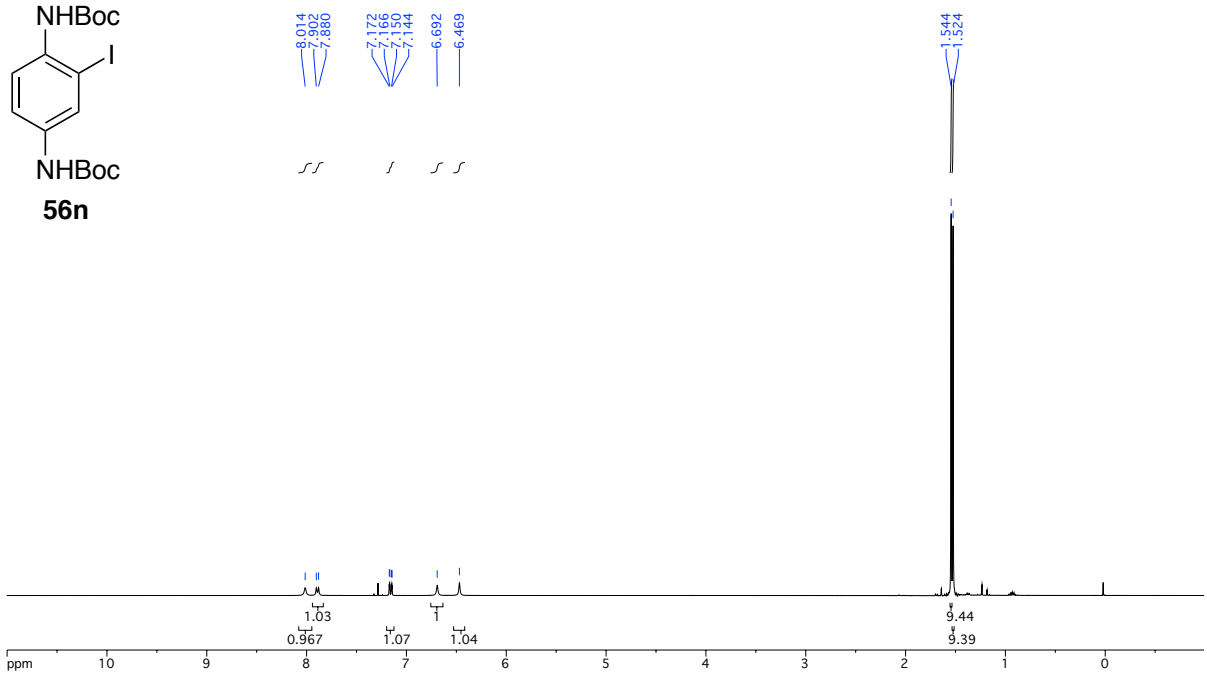

152.631
139.523
138.496
138.387
125.747
120.735
84.664
80.984
28.320
21.310
ppm


NHBoc
TMS
Me
57m
7.994
7.379
7.288
7.268
6.791
6.789
6.787
6.785
6.771
6.770
6.767
6.766
2.366
1.558
0.311
1.02
1
9.43
0.875
1.27
3.24
8.8
ppm

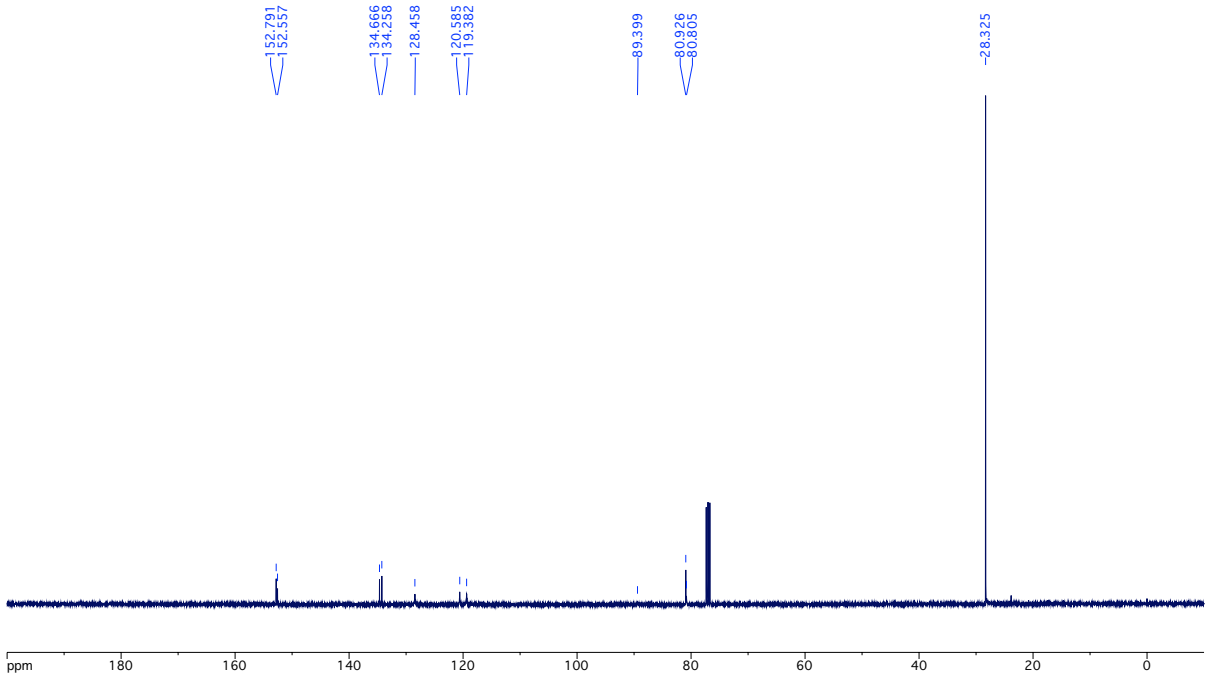

152.436
140.504
140.107
131.028
122.786
117.681
108.083
101.256
100.819
80.513
28.273
22.020
0.073
ppm

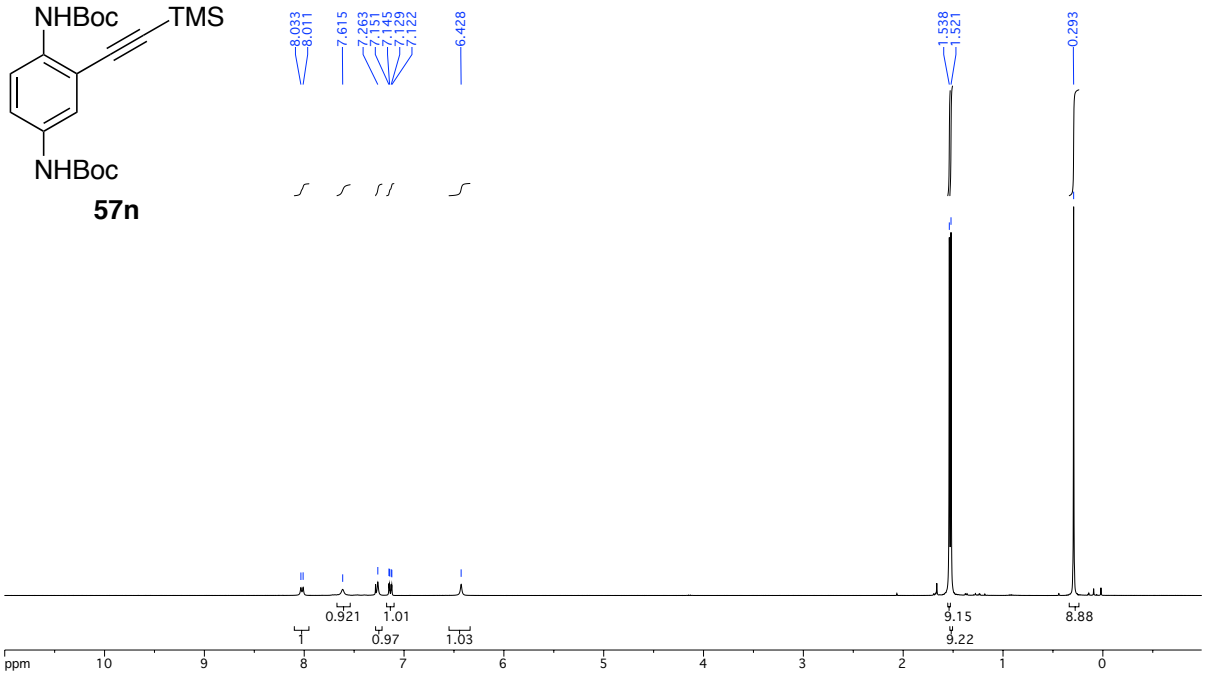

NHBoc
Me
51m
8.042
7.343
7.323
7.272
6.818
6.816
6.799
6.796
6.795
3.468
2.379
1.565
0.901
1.01
1.06
1
0.852
3.23
9.51
ppm

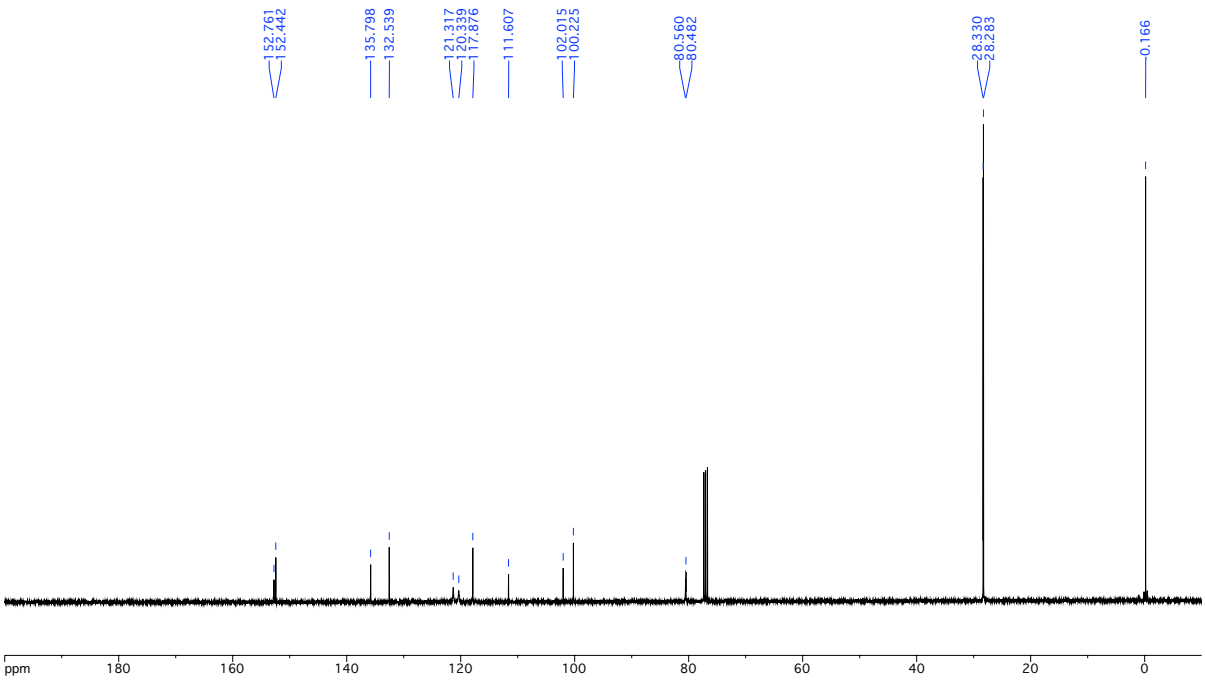

152.472
140.756
140.124
131.992
122.959
118.055
106.948
83.429
80.842
79.548
28.321
21.989
ppm

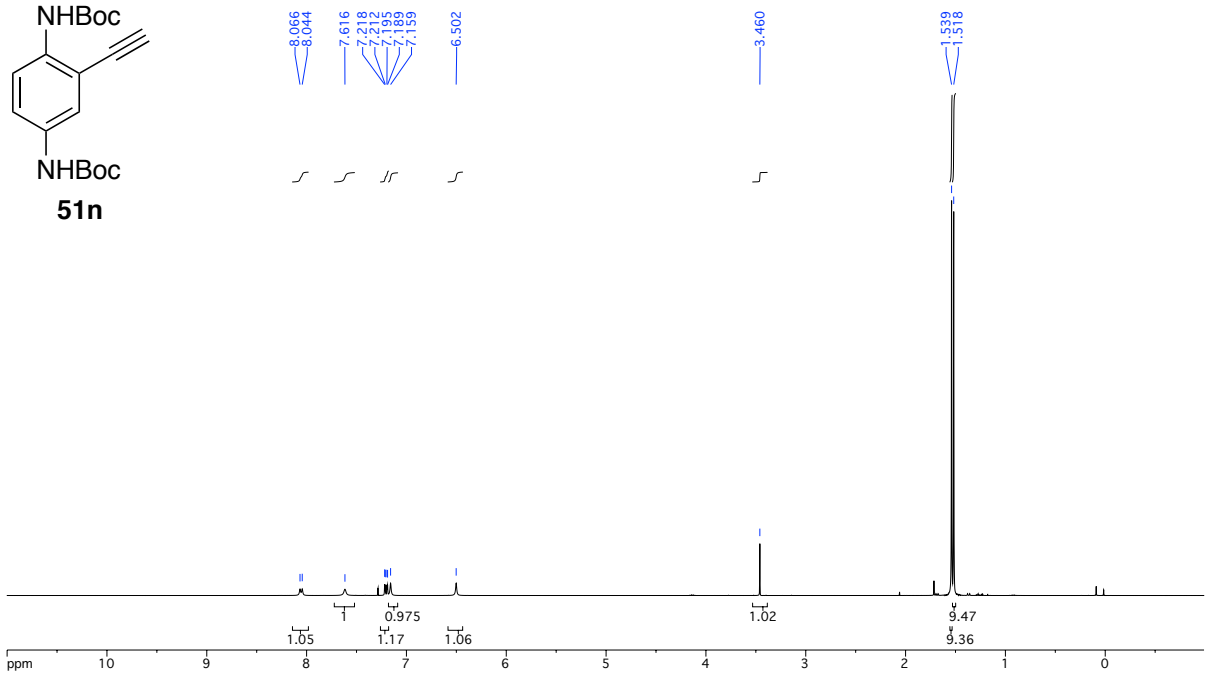

NHBoc
I
NHBoc
8.014
7.902
7.880
7.172
7.166
7.150
7.144
6.692
6.469
1.544
1.524
1.03
0.967
1.07
1.04
9.44
9.39
ppm
10
9
8
7
6
5
4
3
2
1
0

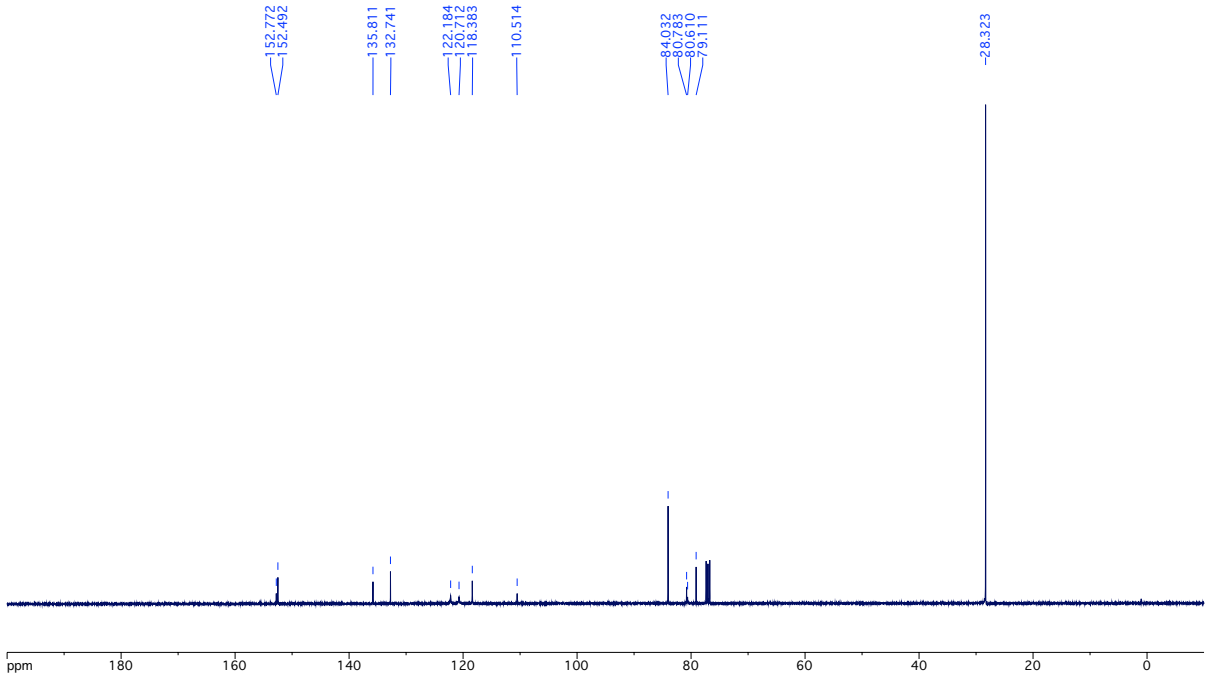
56n

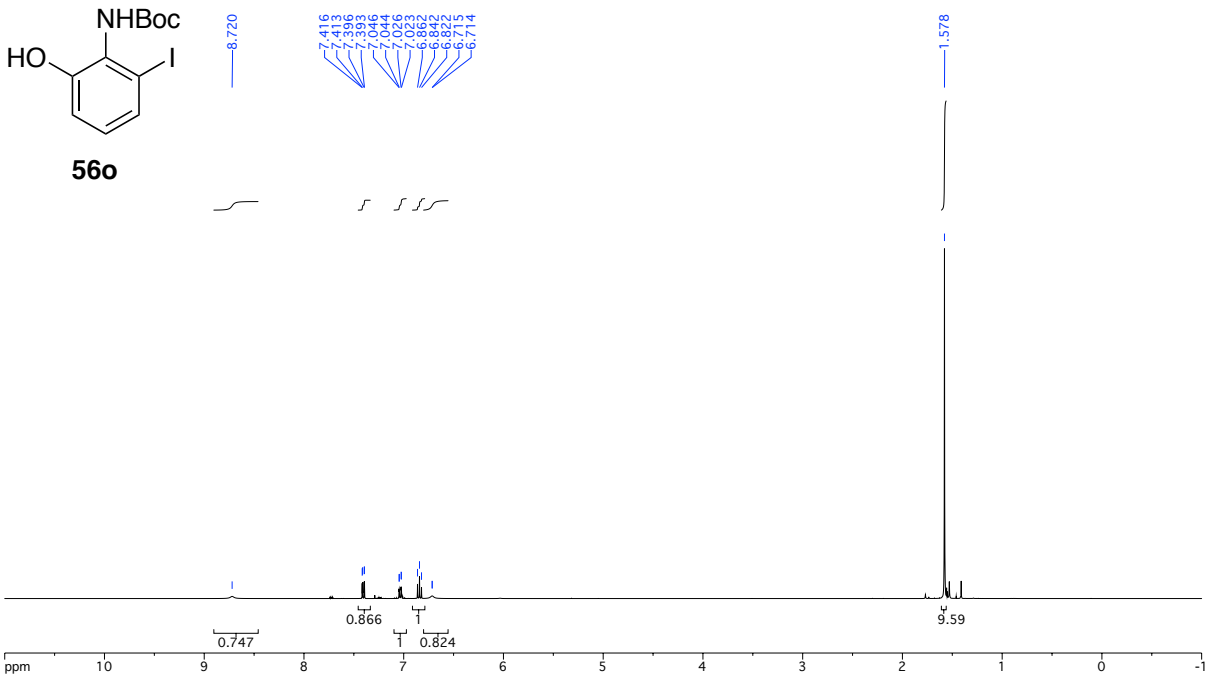

152.791
152.557
134.666
134.258
128.458
120.585
119.382
89.399
80.926
80.805
28.325
ppm
180
160
140
120
100
80
60
40
20
0

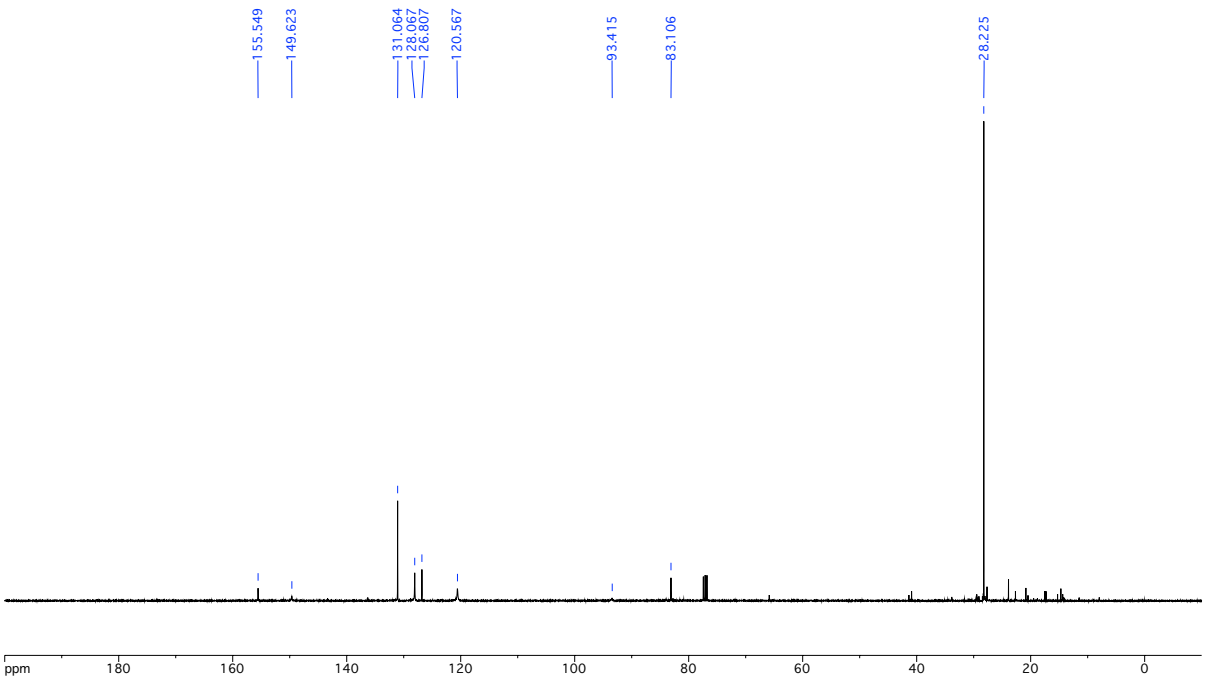

NHBoc
TMS
NHBoc
57n
8.033
8.011
7.615
7.263
7.151
7.145
7.129
7.122
6.428
1.538
1.521
0.293
0.921
1.01
0.97
1.03
9.15
8.88
9.22
ppm

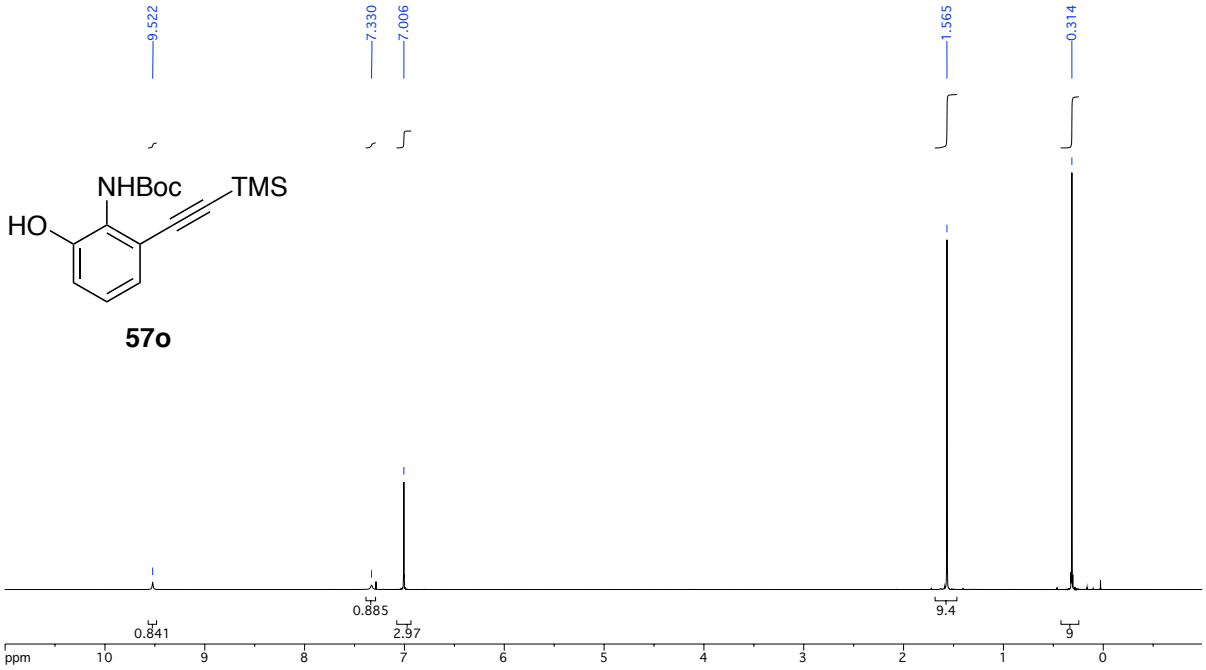

152.761
152.442
135.798
132.539
121.317
120.339
117.876
111.607
102.015
100.225
80.560
80.482
28.330
28.283
0.166
ppm

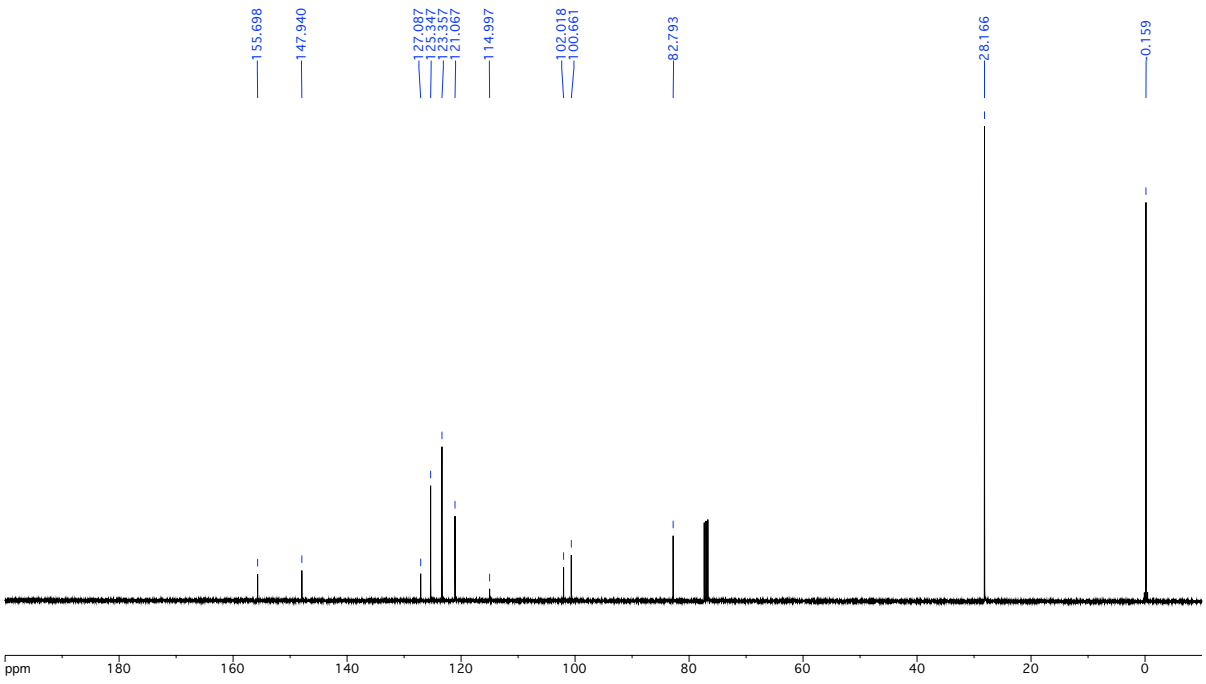

NHBoc
NHBoc
51n
8.066
8.044
7.616
7.218
7.212
7.195
7.189
7.159
6.502
3.460
1.539
1.518
1
0.975
1.02
9.47
1.05
1.17
1.06
9.36
ppm

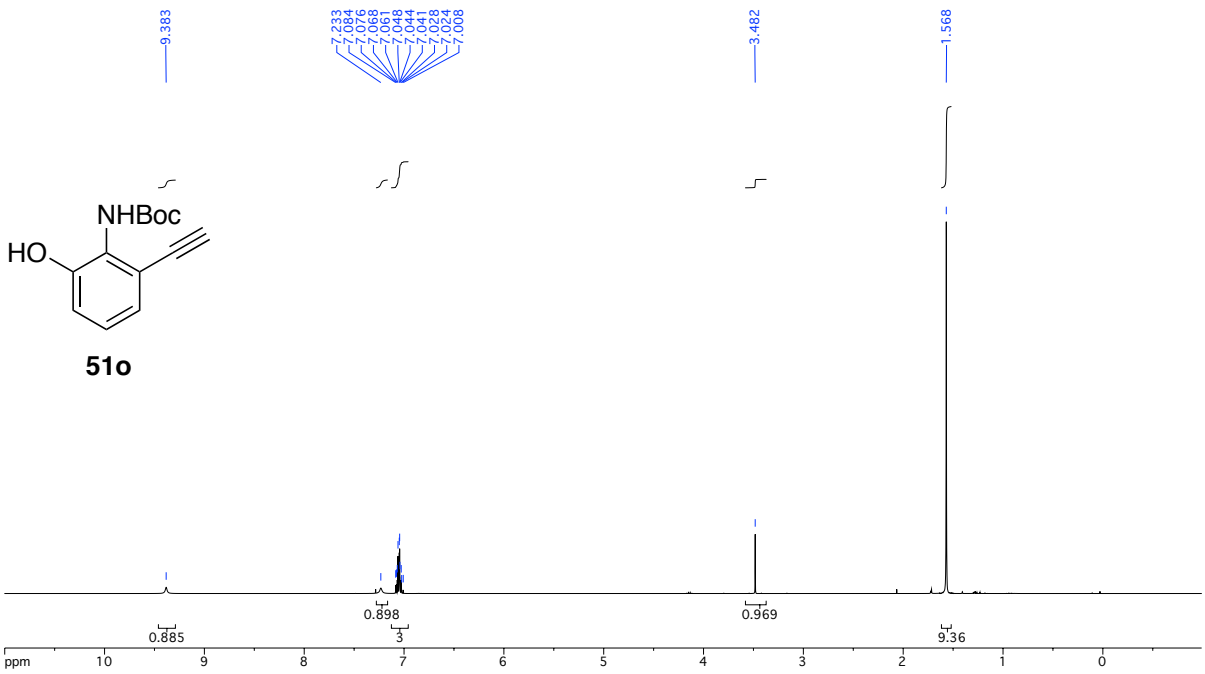

152.772
152.492
135.811
132.741
122.184
120.712
118.383
110.514
84.032
80.783
80.610
79.111
28.323
ppm


NHBoc
HO
I
56o
8.720
7.416
7.413
7.396
7.393
7.046
7.044
7.026
7.023
6.862
6.842
6.822
6.715
6.714
1.578
0.747
0.866
1
0.824
9.59
ppm

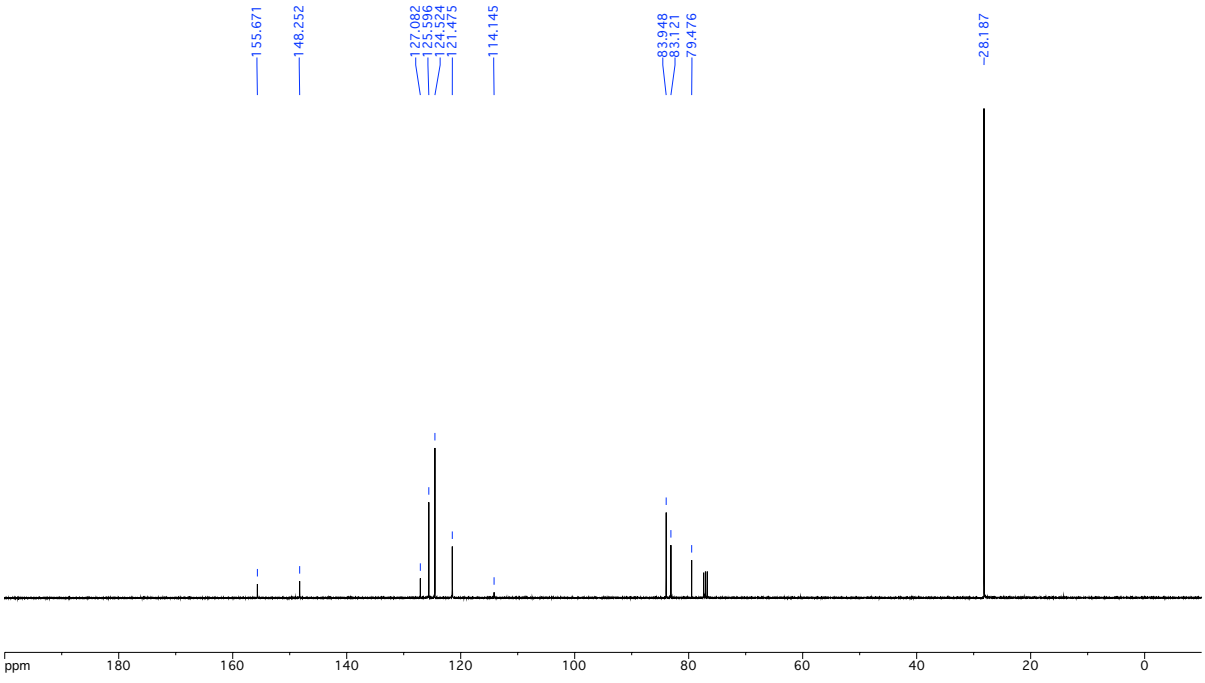

155.549
149.623
131.064
128.067
126.807
120.567
93.415
83.106
28.225
ppm

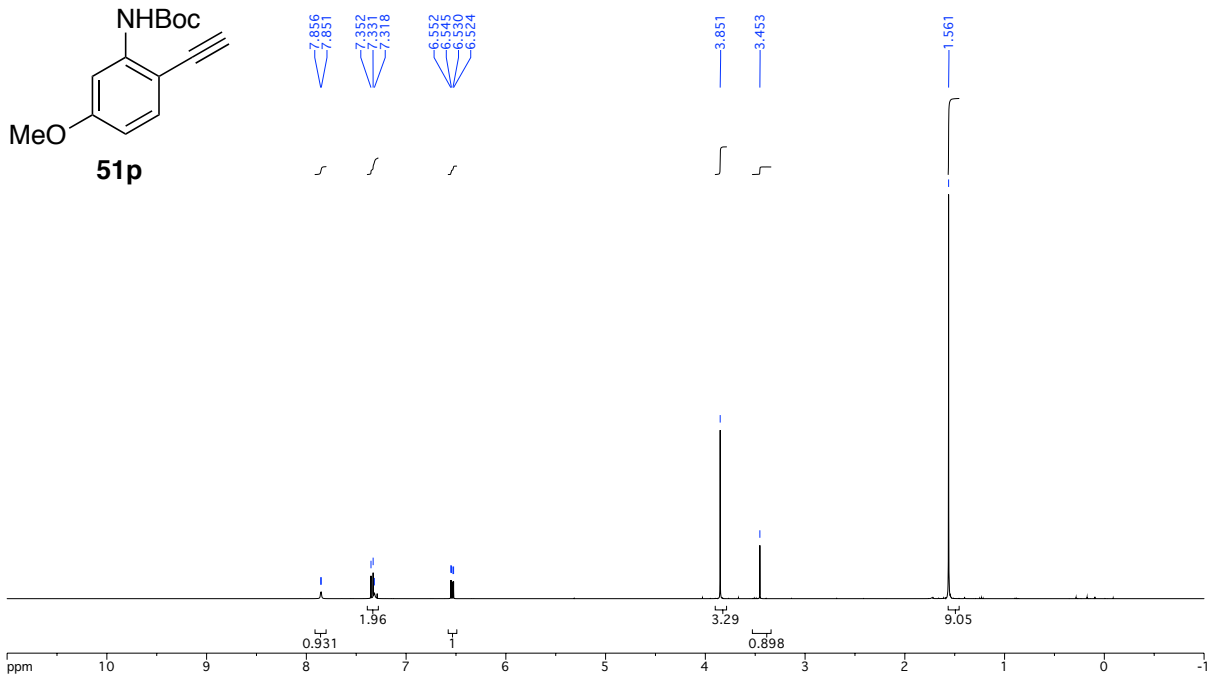

9.522
7.330
7.006
1.565
0.314
NHBoc
TMS
HO
57o
0.841
0.885
2.97
9.4
9
ppm
10
9
8
7
6
5
4
3
2
1
0

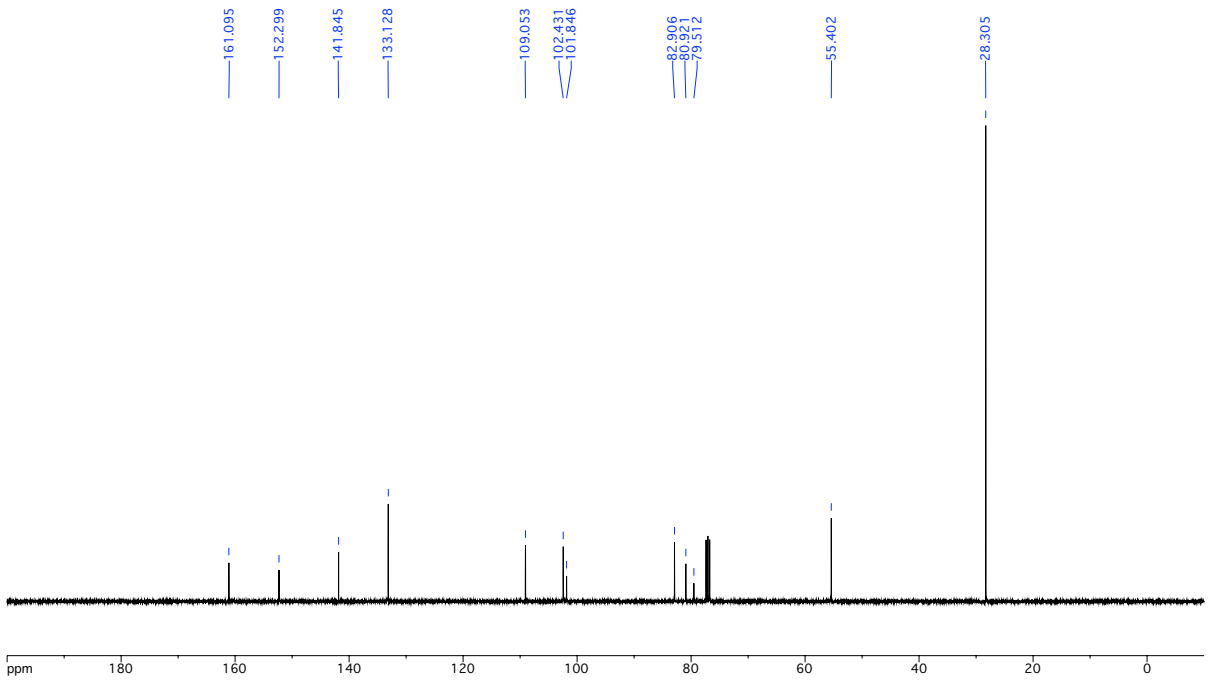

155.698
147.940
127.087
125.347
123.357
121.067
114.997
102.018
100.661
82.793
28.166
0.159
ppm
180
160
140
120
100
80
60
40
20
0

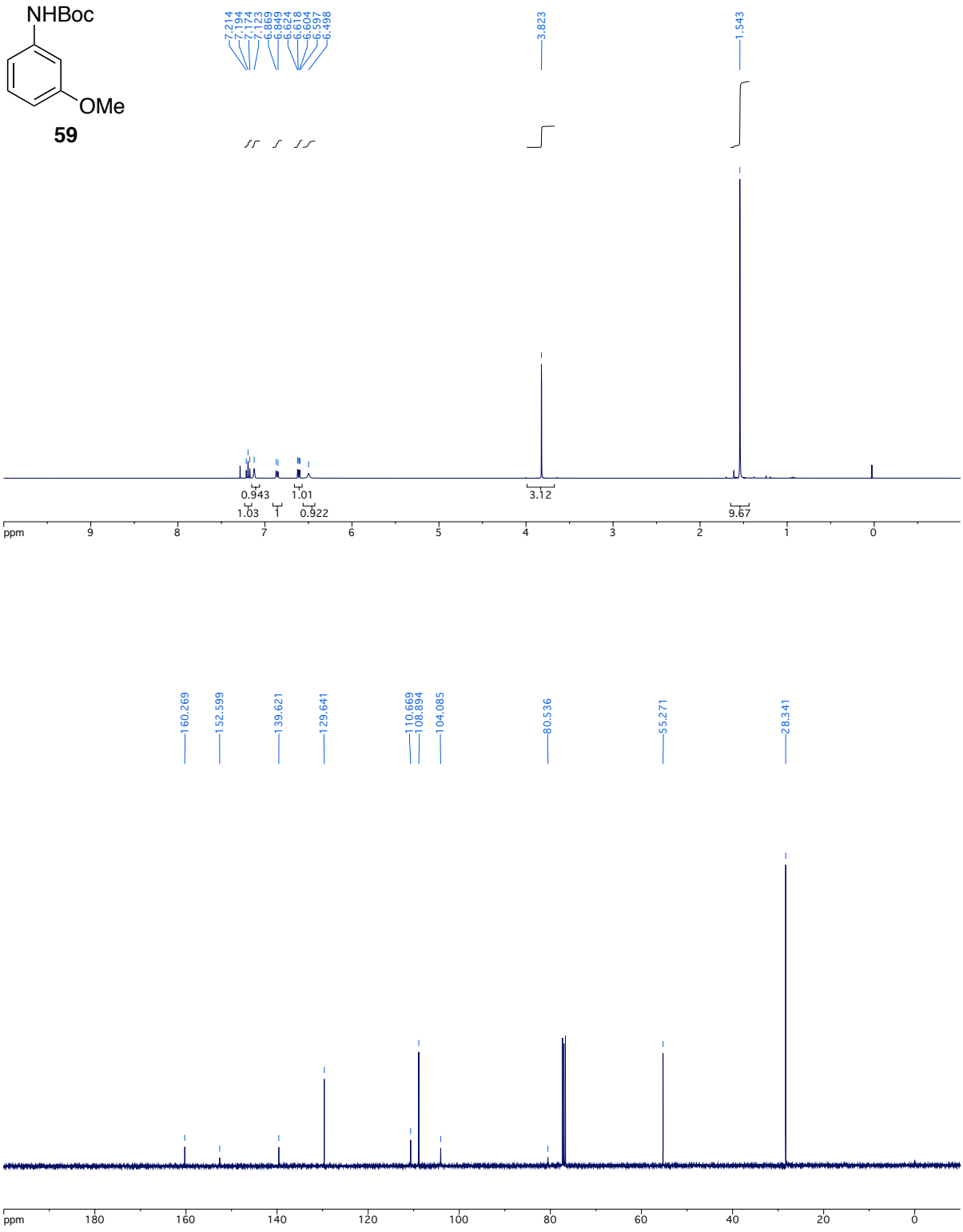

9.383
7.233
7.084
7.076
7.066
7.061
7.048
7.044
7.041
7.028
7.024
7.008
3.482
1.568
NHBoc
HO
0.885
0.898
3
0.969
9.36
ppm

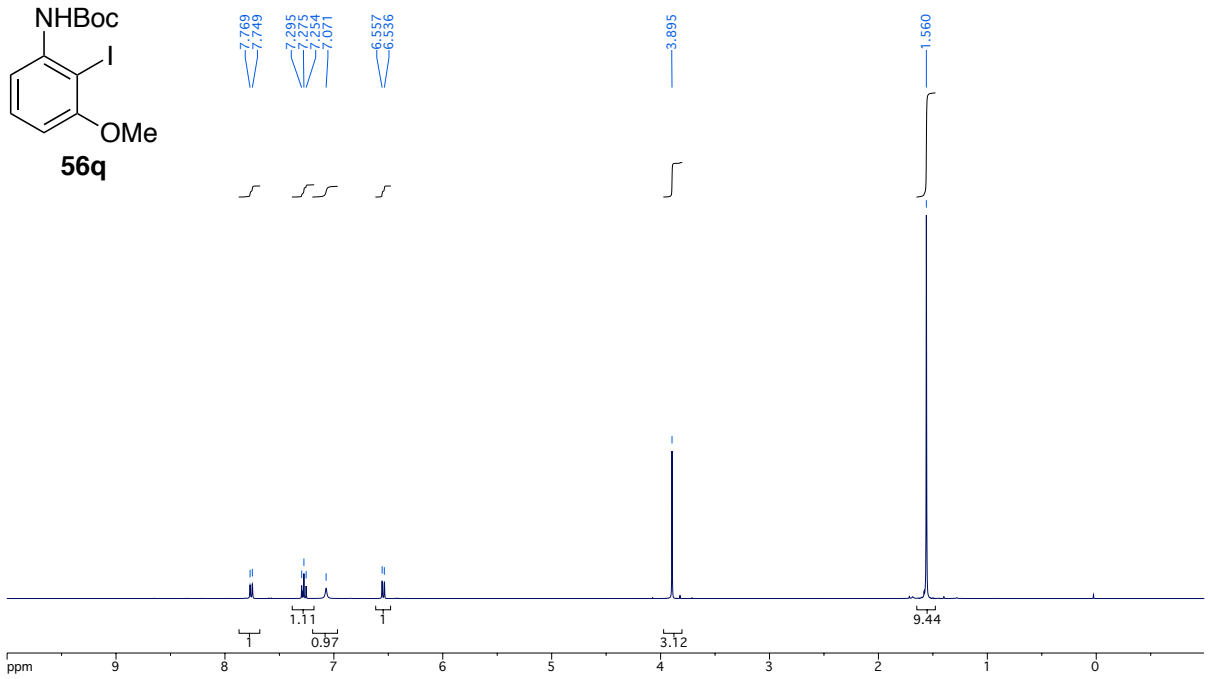
51o

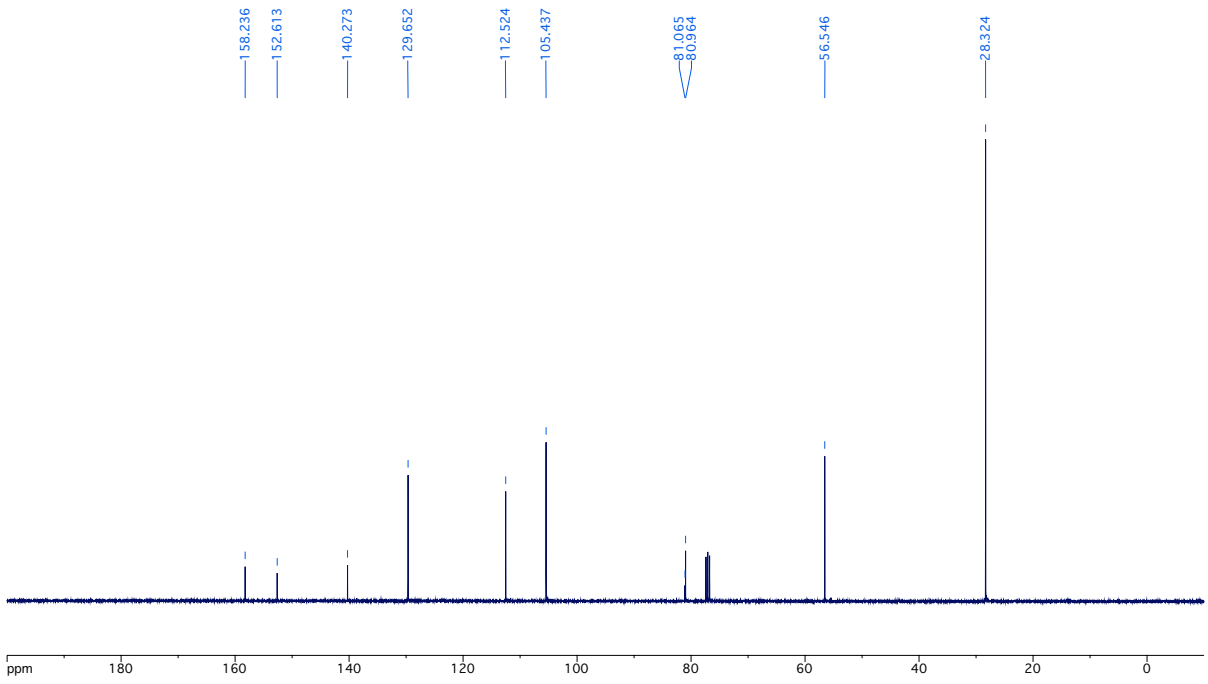

155.671
148.252
127.082
125.596
124.524
121.475
114.145
83.948
83.121
79.476
28.187
ppm

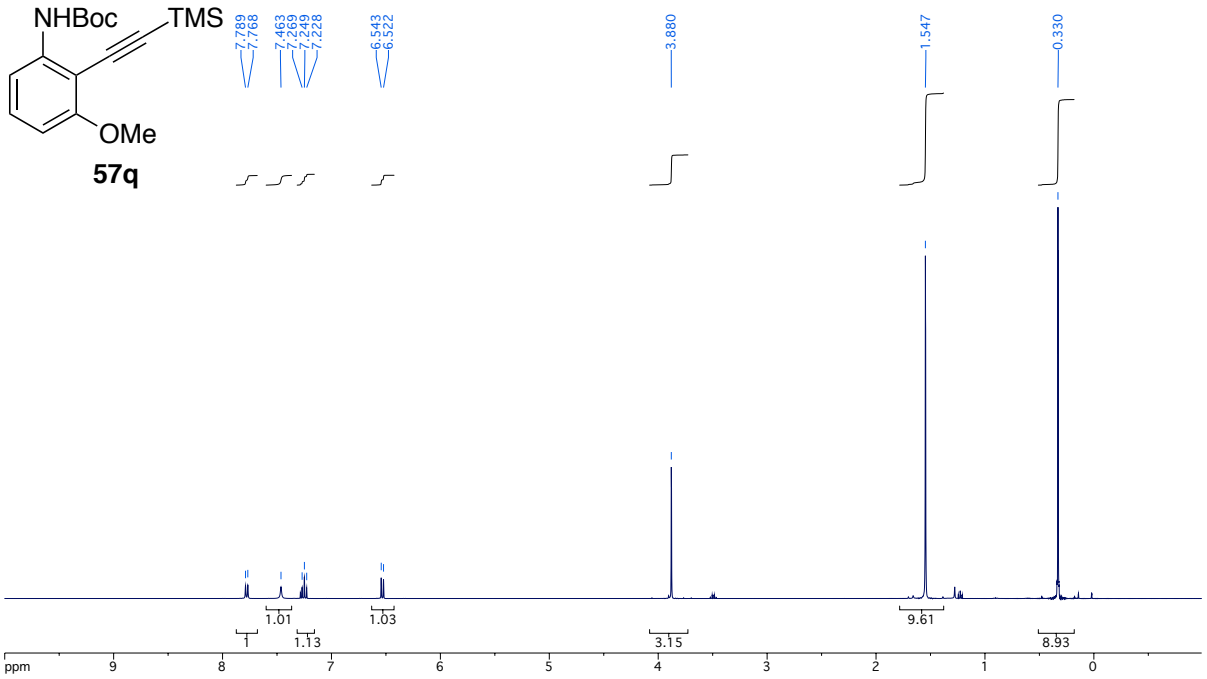

NHBoc
MeO
51p
7.856
7.851
7.352
7.331
7.318
6.552
6.545
6.530
6.524
3.851
3.453
1.561
0.931
1.96
1
3.29
0.898
9.05
ppm

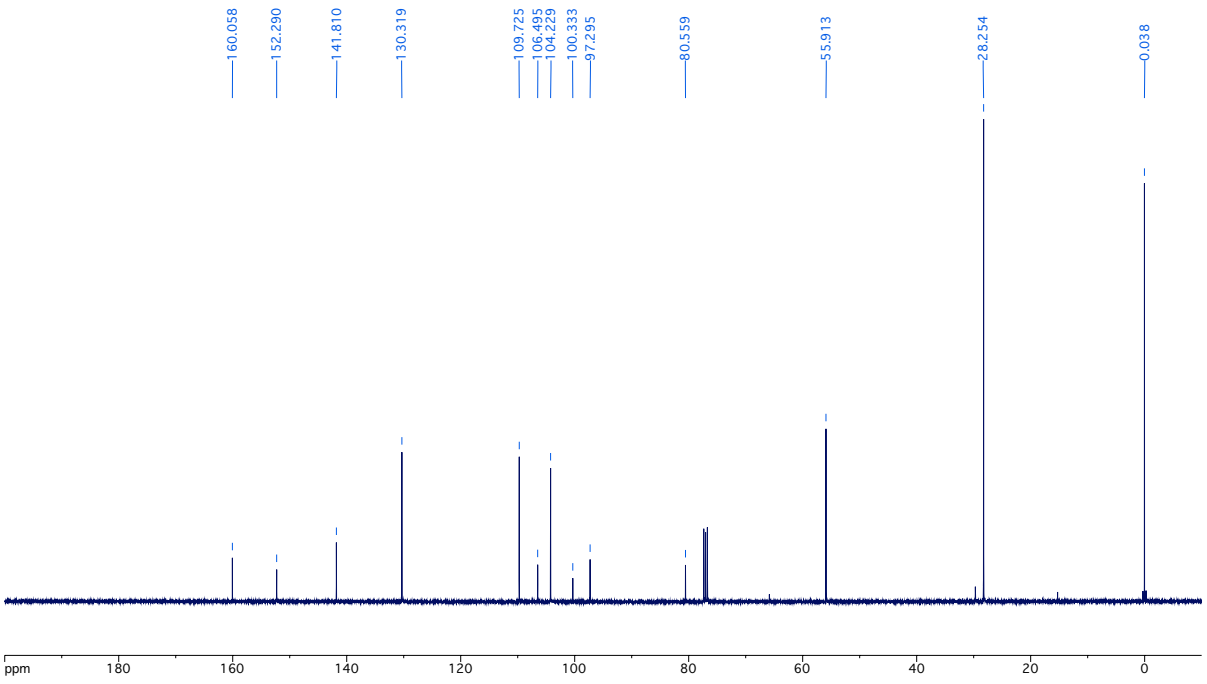

161.095
152.299
141.845
133.128
109.053
102.431
101.846
82.906
80.921
79.512
55.402
28.305
ppm

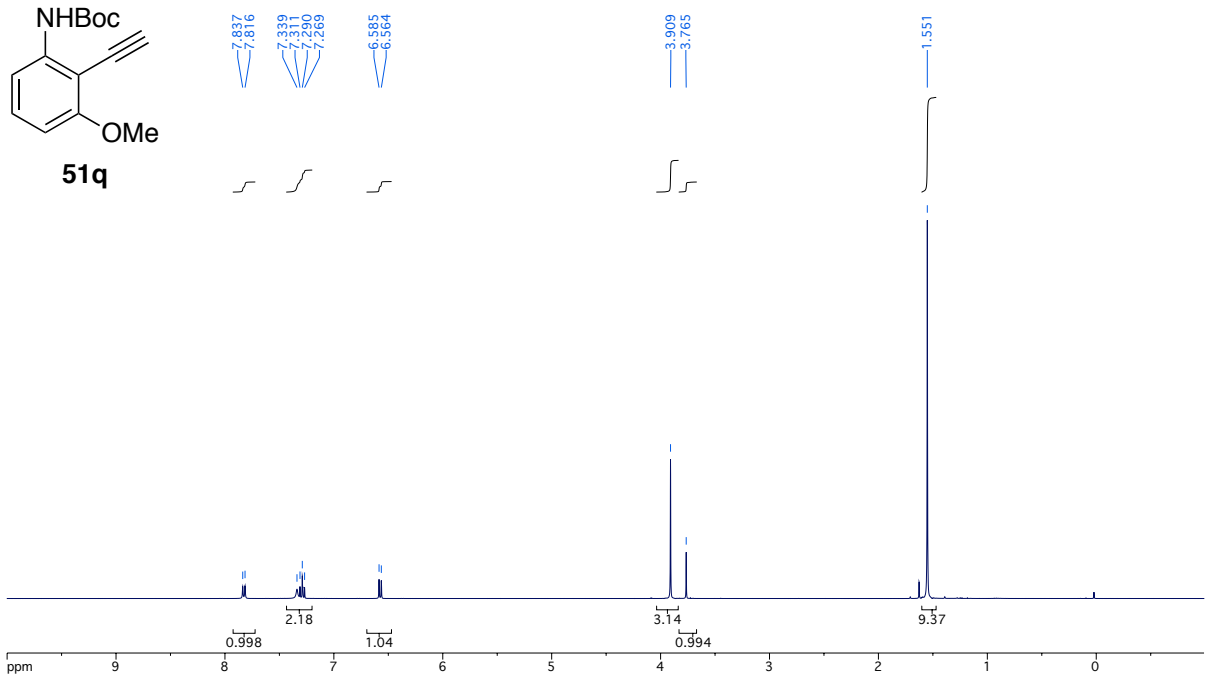

NHBoc
OMe
59
7.214
7.194
7.174
7.123
6.869
6.849
6.624
6.618
6.604
6.597
6.498
3.823
1.543
0.943
1.03
1
1.01
0.922
3.12
9.67
ppm
160.269
152.599
139.621
129.641
110.669
108.894
104.085
80.536
55.271
28.341
ppm

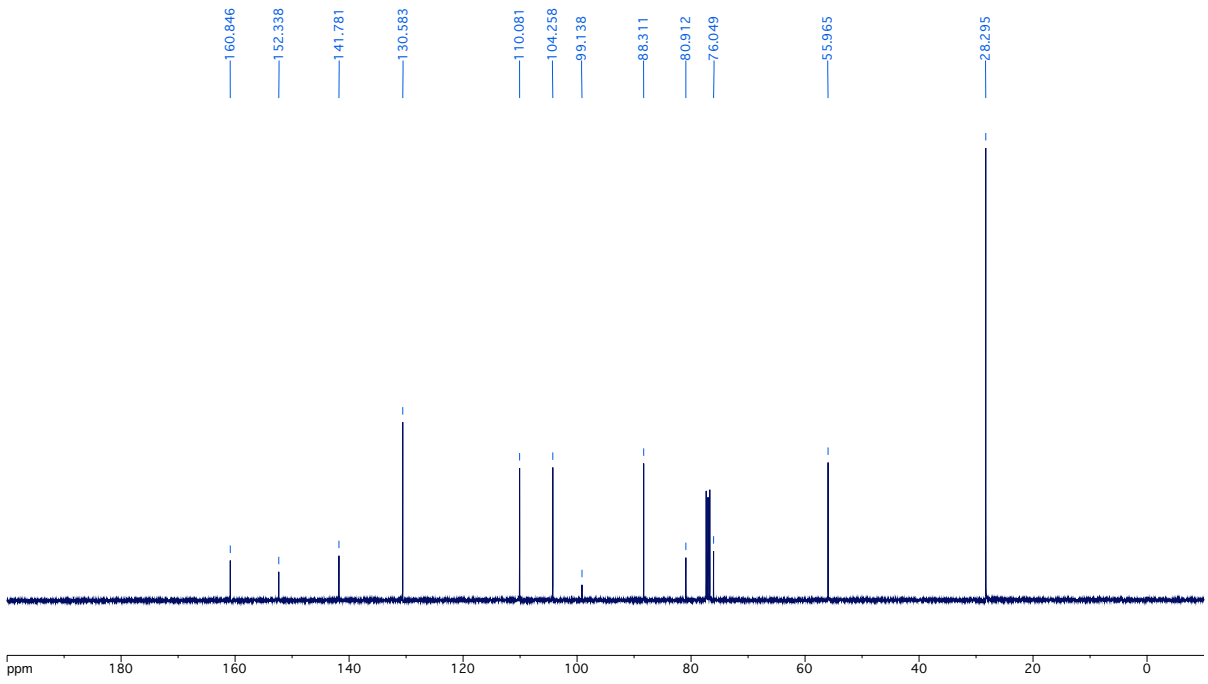

NHBoc
I
OMe
56q
7.769
7.749
7.295
7.275
7.254
7.071
6.557
6.536
3.895
1.560
1
1.11
0.97
1
3.12
9.44
ppm

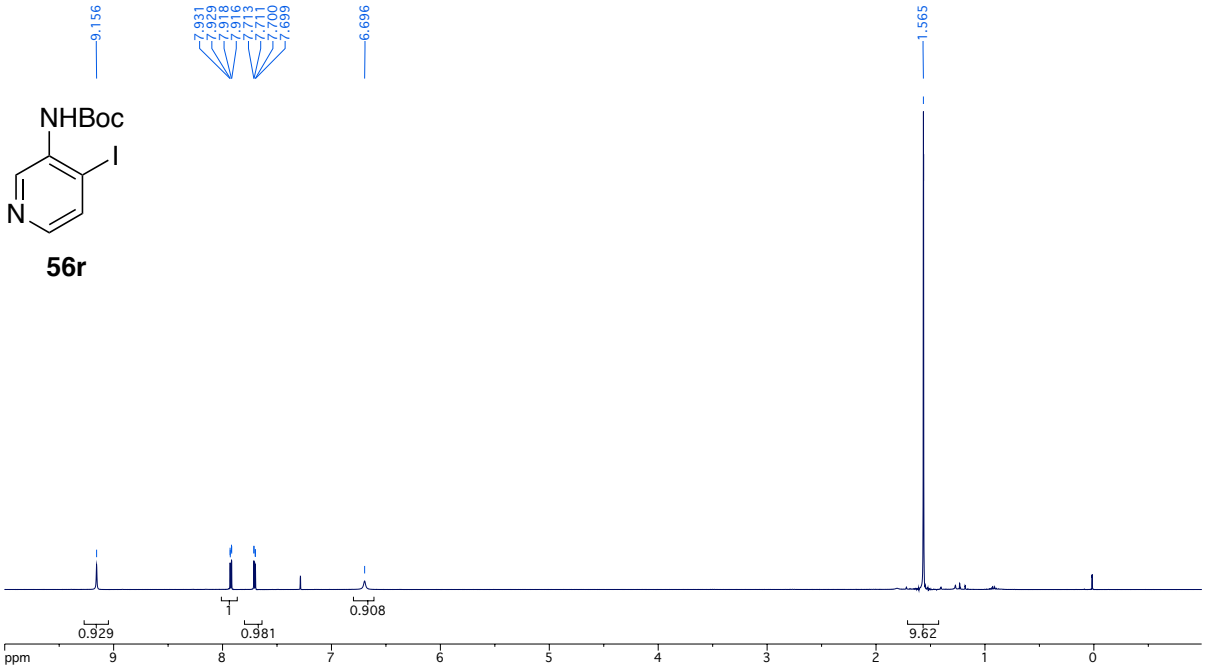

158.236
152.613
140.273
129.652
112.524
105.437
81.065
80.964
56.546
28.324
ppm


NHBoc
TMS
OMe
57q
7.789
7.768
7.463
7.269
7.249
7.228
6.543
6.522
3.880
1.547
0.330
1.01
1.03
9.61
1
1.13
3.15
8.93
ppm

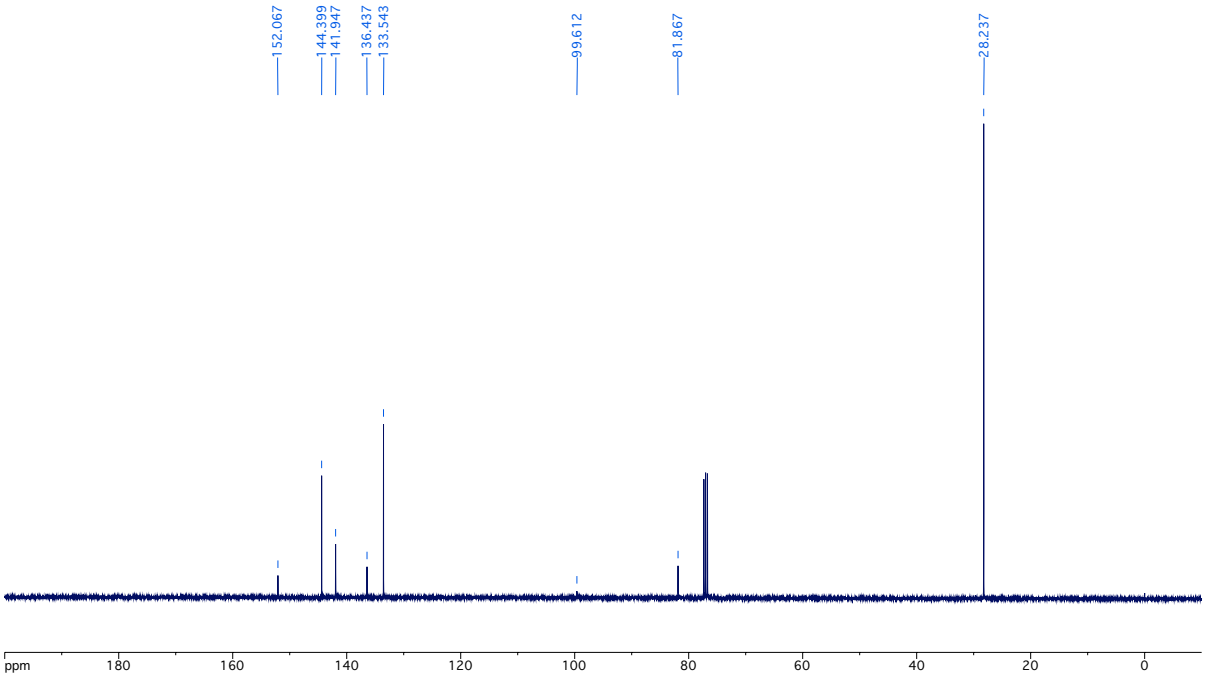

160.058
152.290
141.810
130.319
109.725
106.495
104.229
100.333
97.295
80.559
55.913
28.254
0.038
ppm

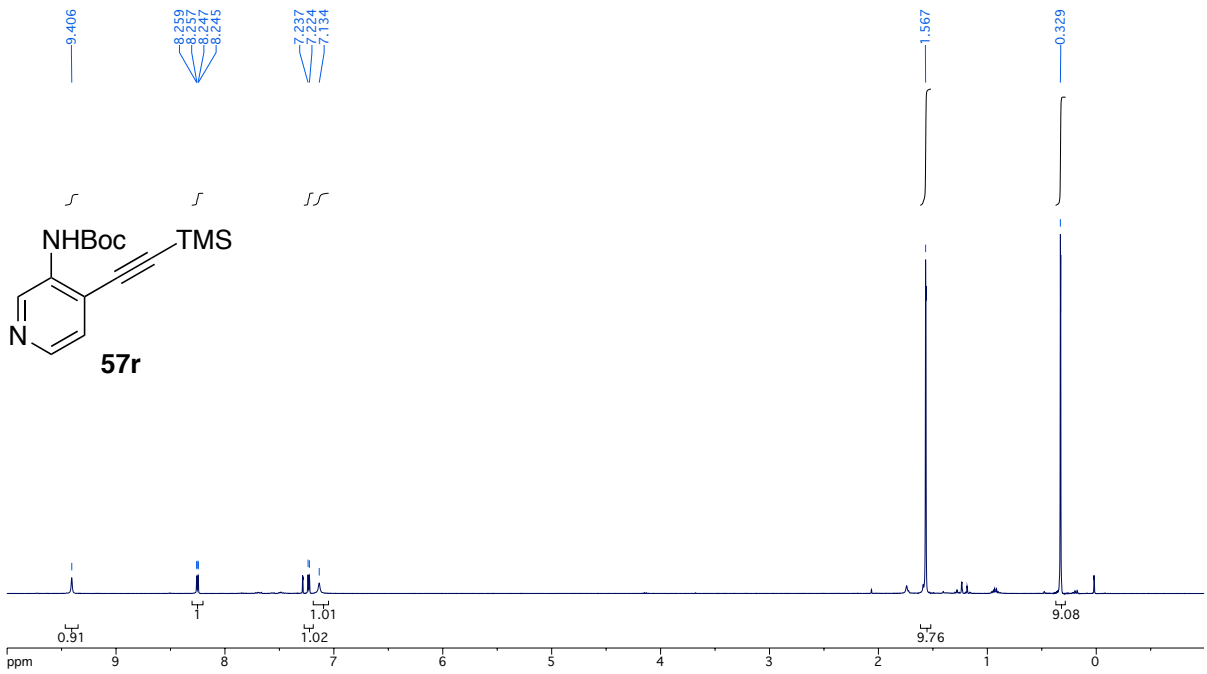

NHBoc
OMe
51q
7.837
7.816
7.339
7.311
7.290
7.269
6.585
6.564
3.909
3.765
1.551
0.998
2.18
1.04
3.14
0.994
9.37
ppm
9
8
7
6
5
4
3
2
1
0

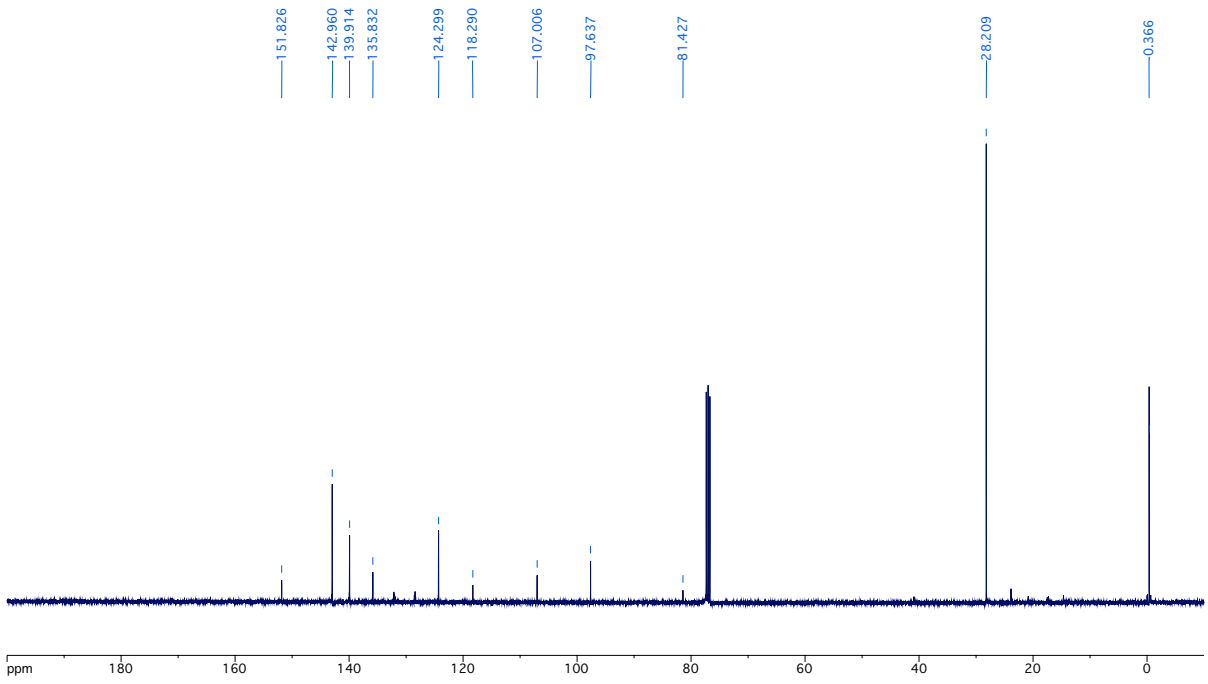

160.846
152.338
141.781
130.583
110.081
104.258
99.138
88.311
80.912
76.049
55.965
28.295
ppm
180
160
140
120
100
80
60
40
20
0

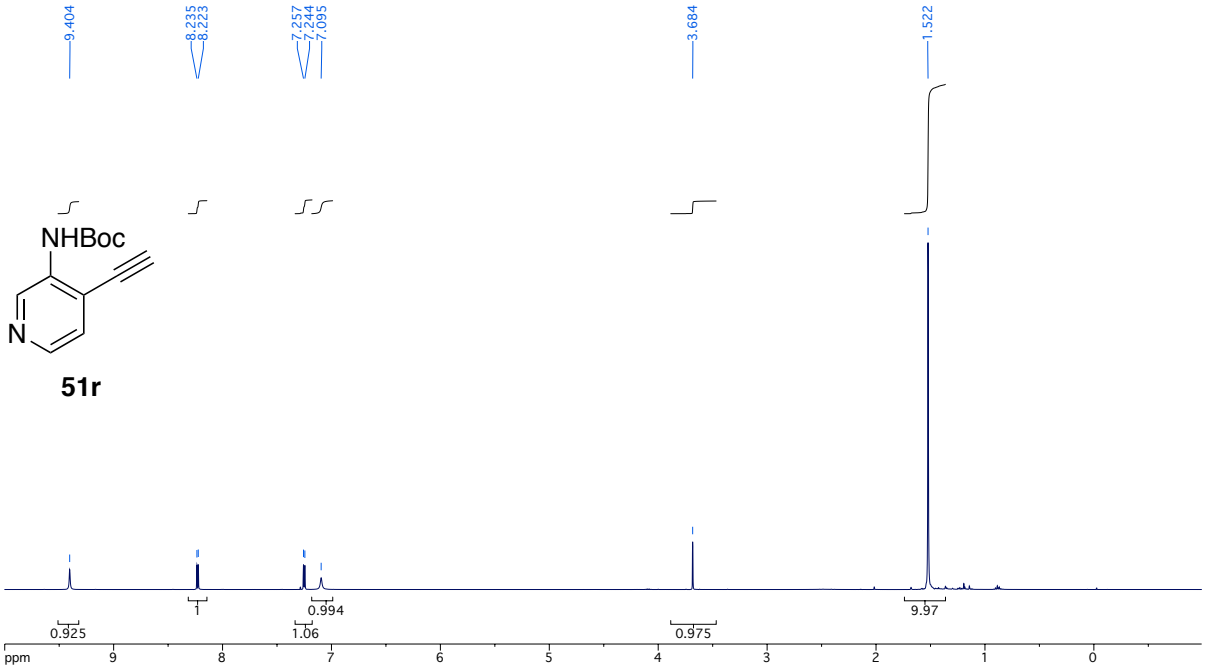

9.156
7.931
7.929
7.918
7.916
7.713
7.711
7.700
7.699
6.696
1.565
NHBoc
I
N
0.929
1
0.981
0.908
9.62
ppm
9
8
7
6
5
4
3
2
1
0

56r

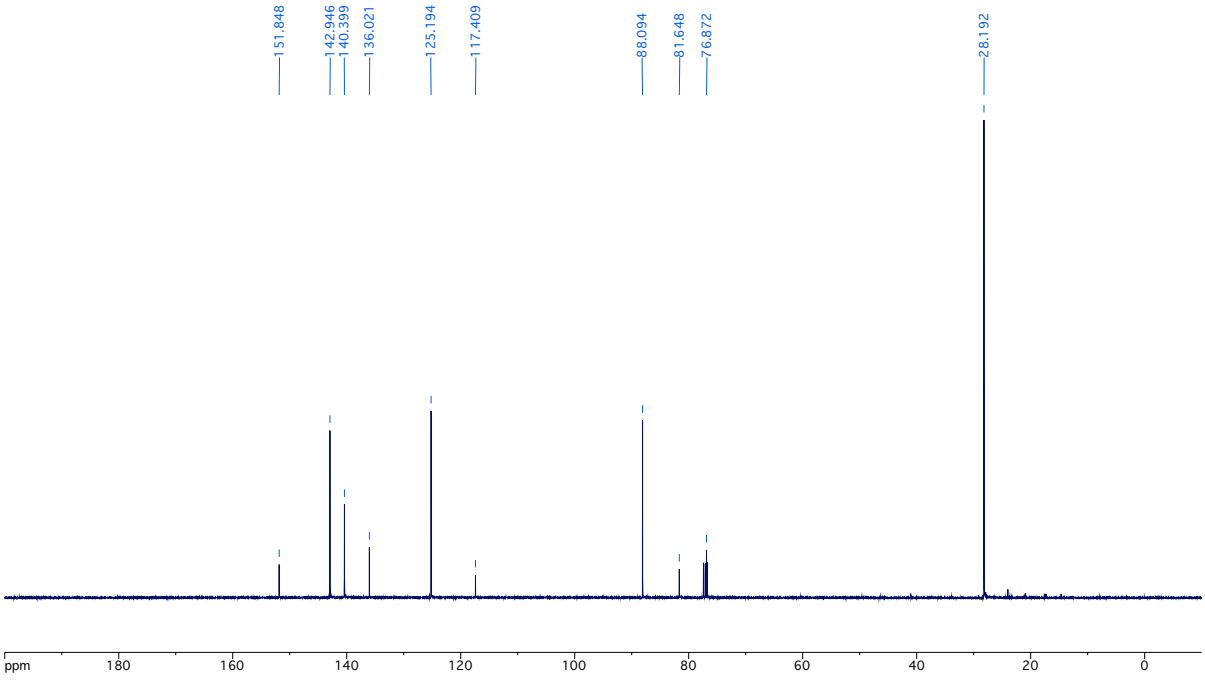

152.067
144.399
141.947
136.437
133.543
99.612
81.867
28.237
ppm
180
160
140
120
100
80
60
40
20
0

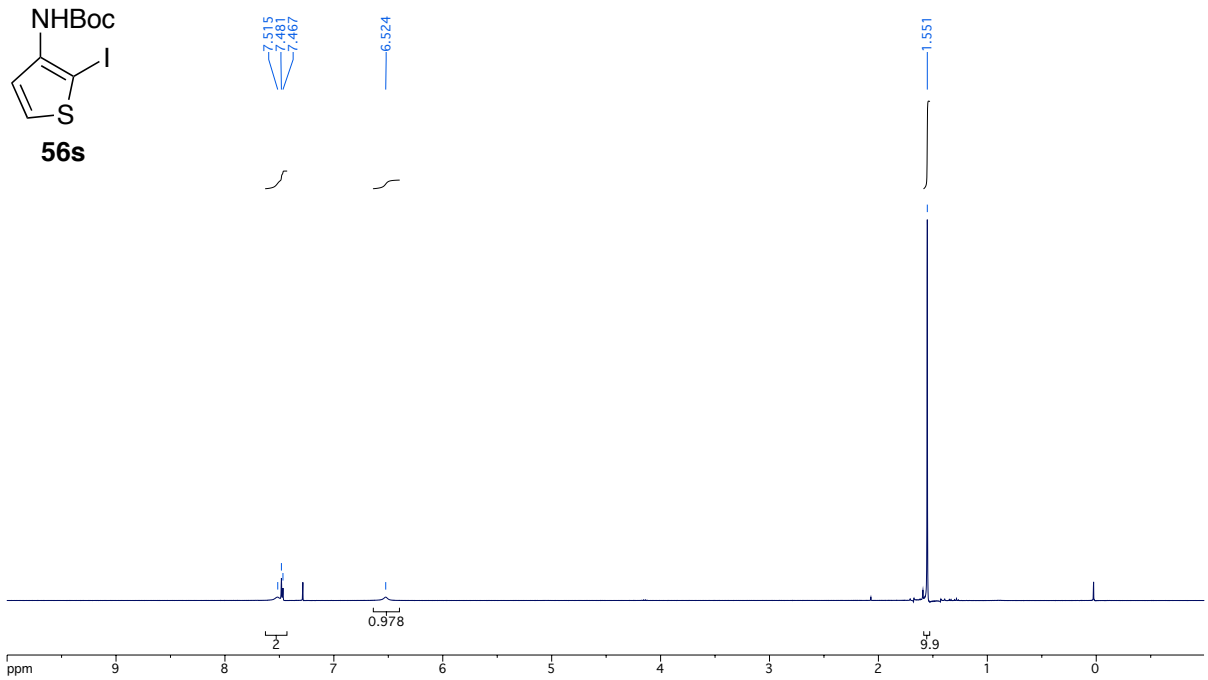

9.406
8.259
8.257
8.247
8.245
7.237
7.234
7.134
1.567
0.329
NHBoc
TMS
N
57r
0.91
1
1.01
1.02
9.76
9.08
ppm

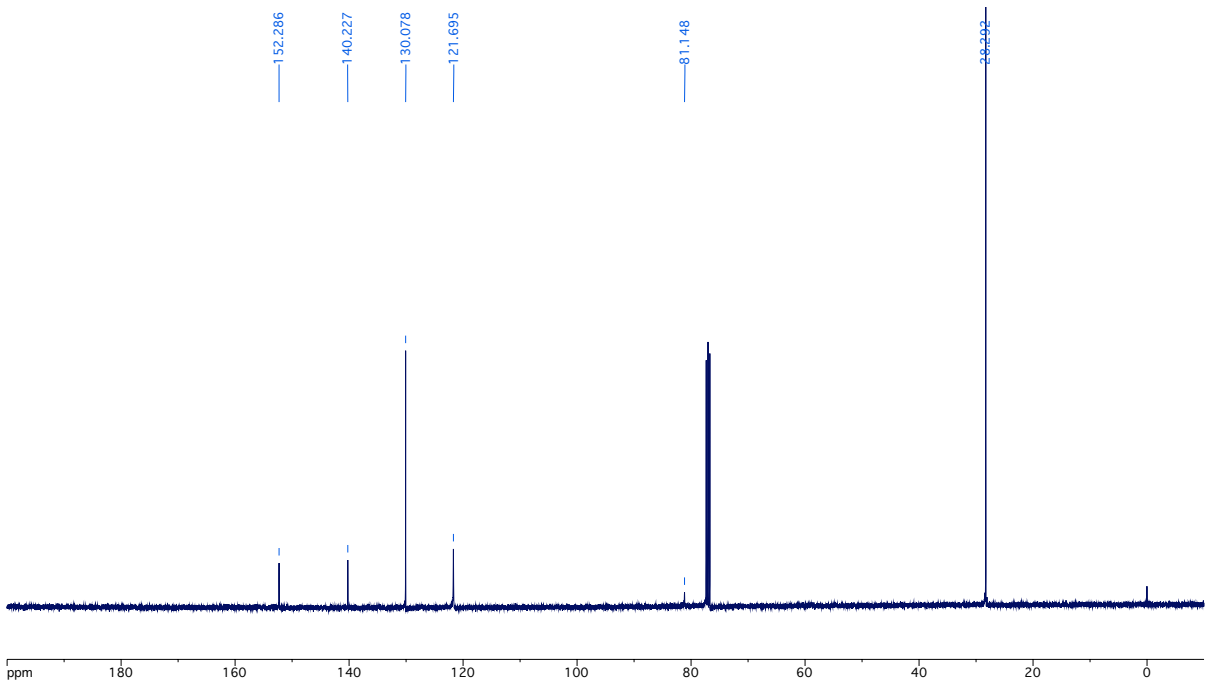

151.826
142.960
139.914
135.832
124.299
118.290
107.006
97.637
81.427
28.209
0.366
ppm

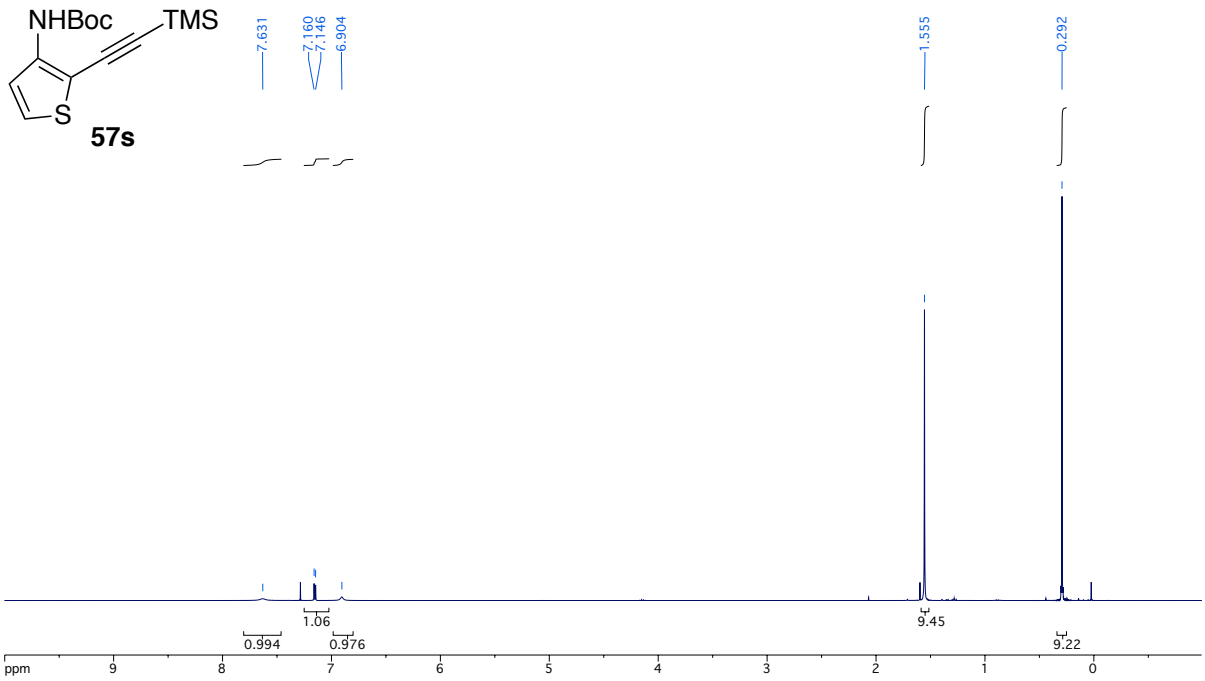

9.404
8.235
8.223
7.257
7.244
7.095
3.684
1.522
NHBoc
N
0.925
1
1.06
0.994
0.975
9.97
ppm

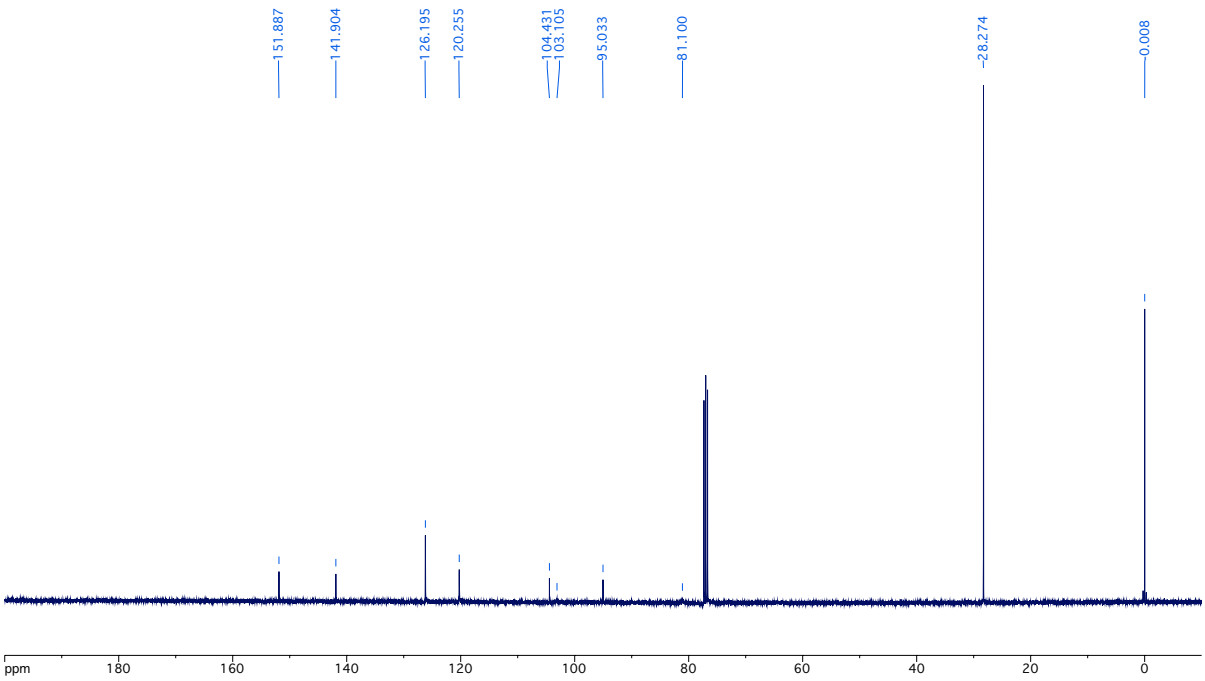
51r

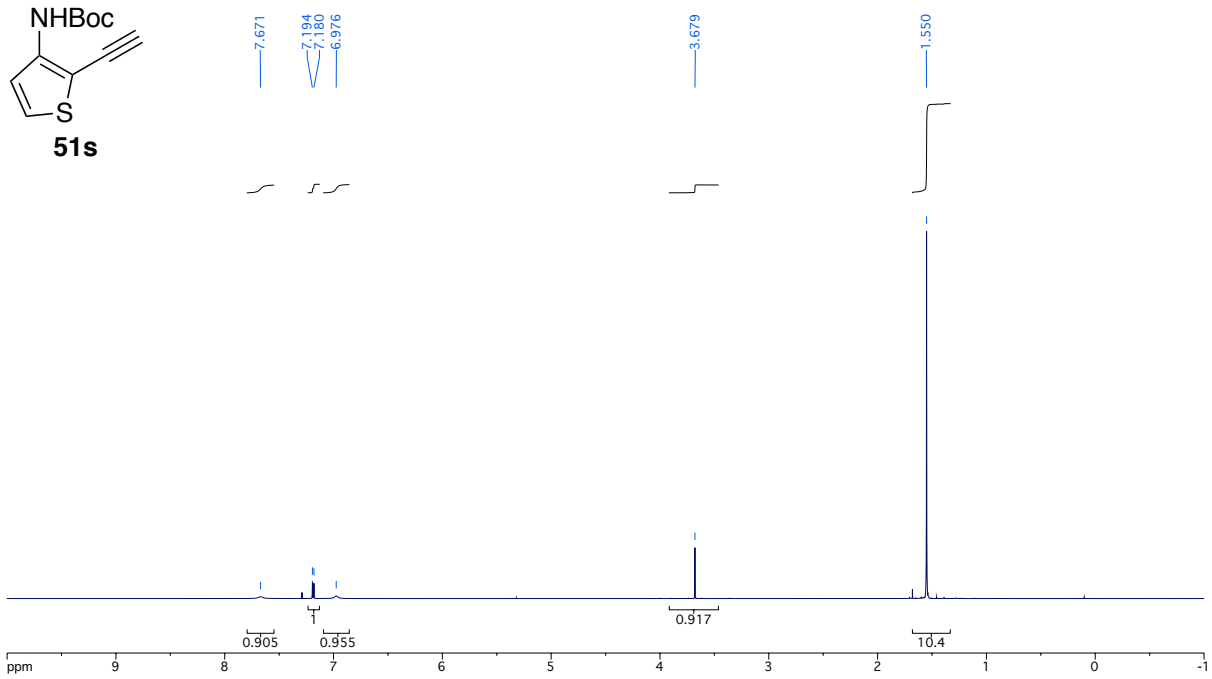

151.848
142.946
140.399
136.021
125.194
117.409
88.094
81.648
76.872
28.192
ppm

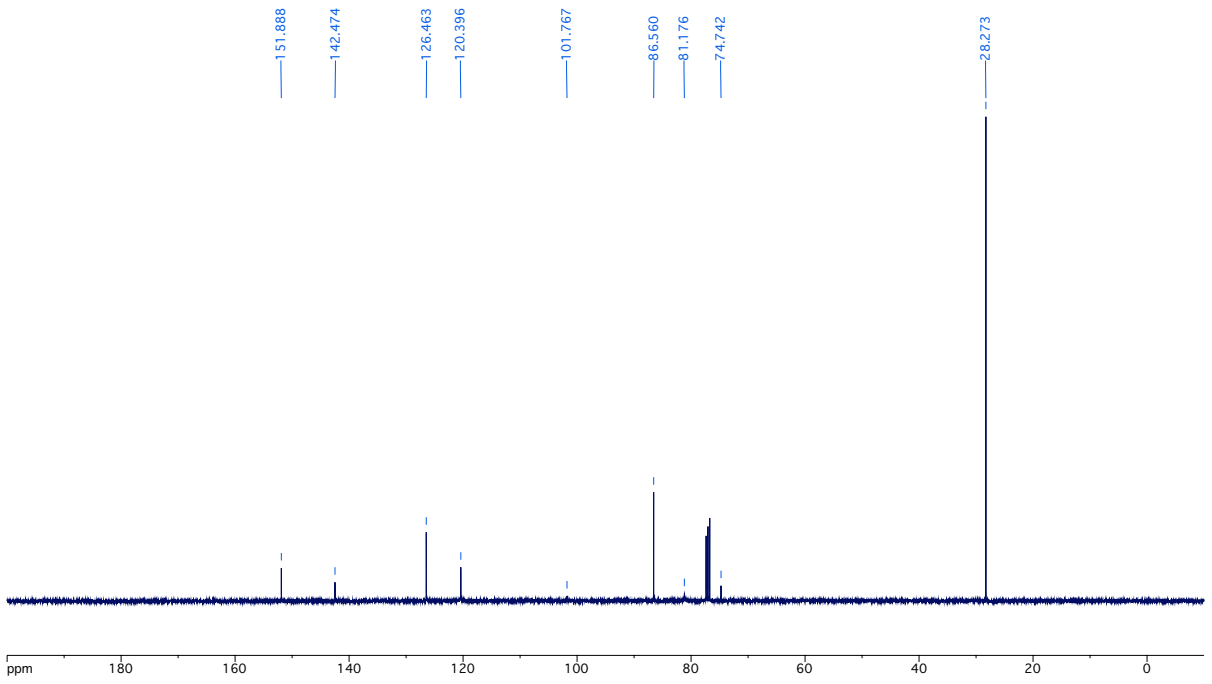

NHBoc
I
S
56s
7.515
7.481
7.467
6.524
1.551
0.978
2
9.9
ppm
9
8
7
6
5
4
3
2
1
0

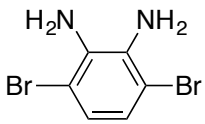

152.286
140.227
130.078
121.695
81.148
28.292
ppm
180
160
140
120
100
80
60
40
20
0


NHBoc
TMS
S
57s
7.631
7.160
7.146
6.904
1.555
0.292
0.994
1.06
0.976
9.45
9.22
ppm


151.887
141.904
126.195
120.255
104.431
103.105
95.033
81.100
-28.274
0.008
ppm

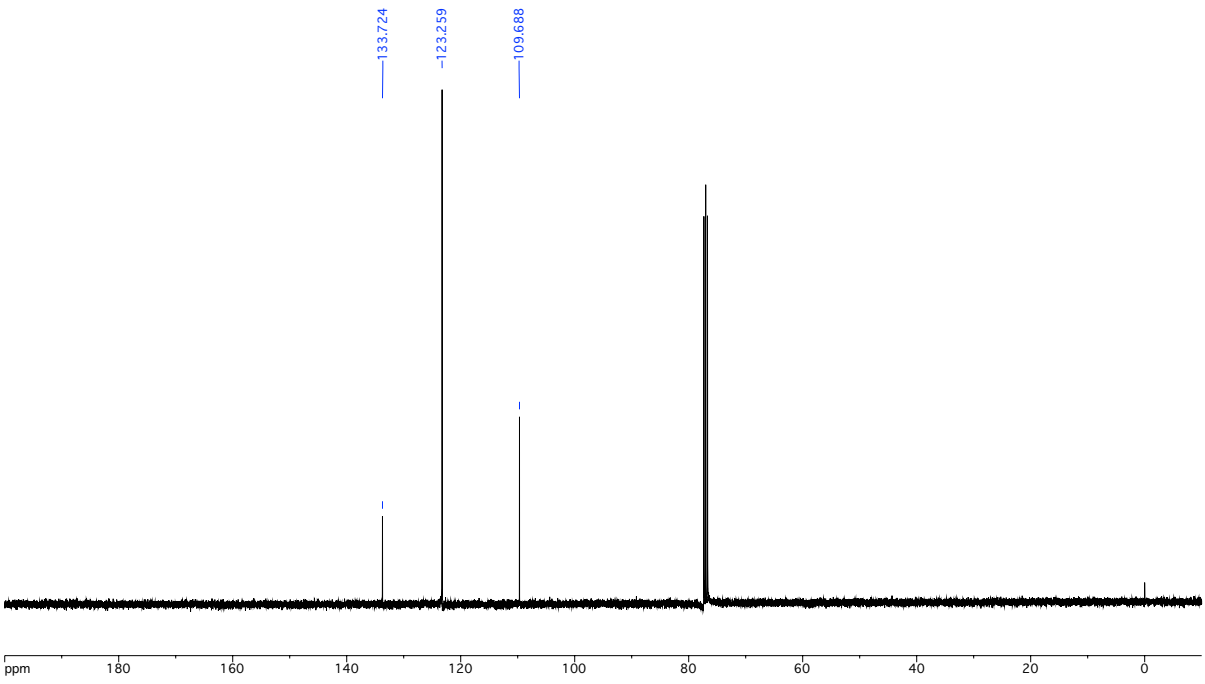

NHBoc
S
51s
7.671
7.194
7.180
6.976
3.679
1.550
0.905
1
0.955
0.917
10.4
ppm
9
8
7
6
5
4
3
2
1
0
-1

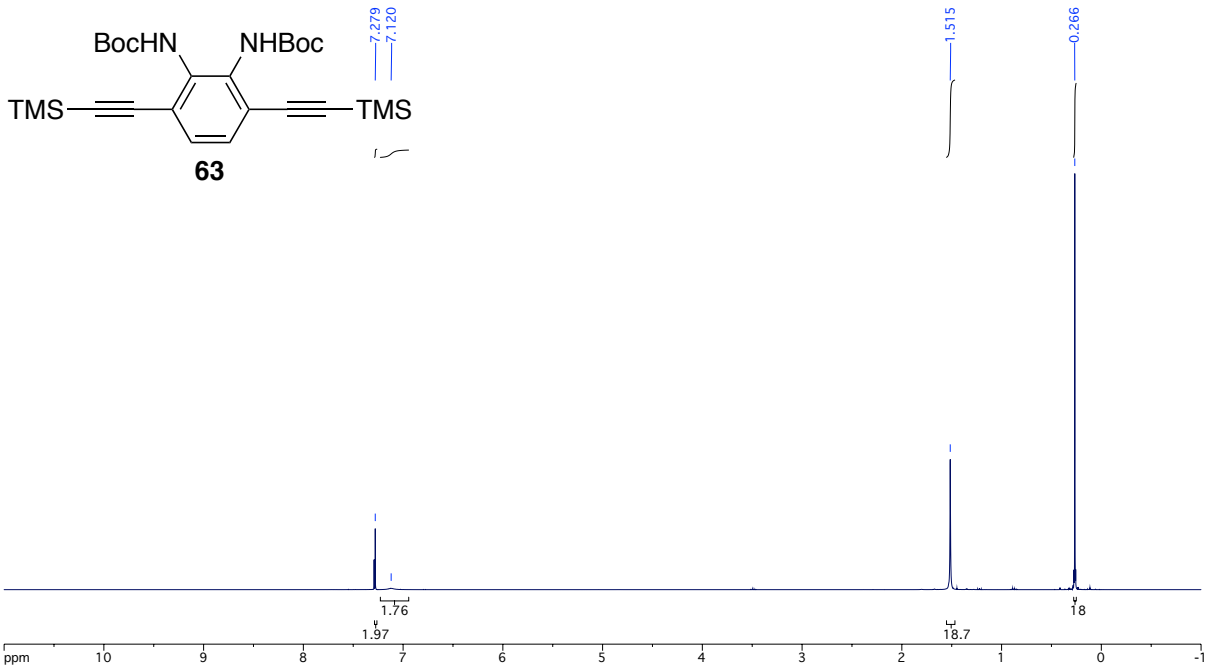

151.888
142.474
126.463
120.396
101.767
86.560
81.176
74.742
28.273
ppm
180
160
140
120
100
80
60
40
20
0

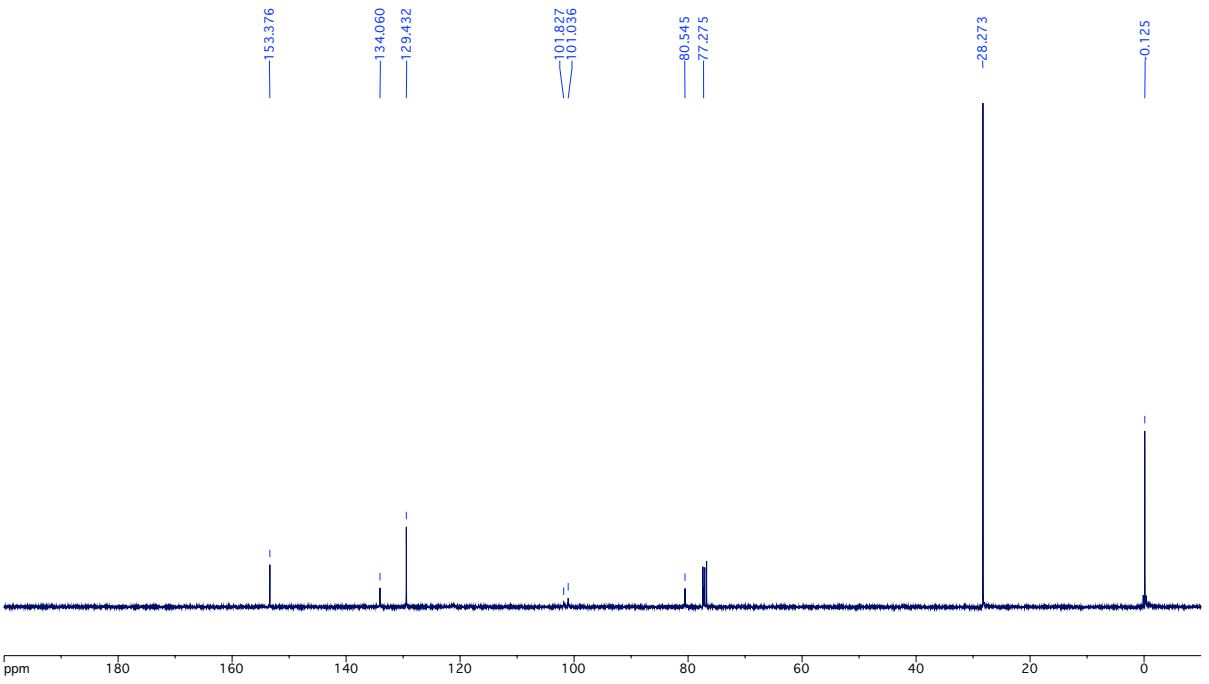

H2N
NH2
Br
Br

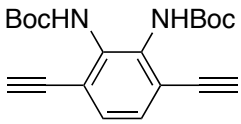
62

6.872
3.744
4.2
2
ppm
10
9
8
7
6
5
4
3
2
1
0


133.724
123.259
109.688
ppm
180
160
140
120
100
80
60
40
20
0

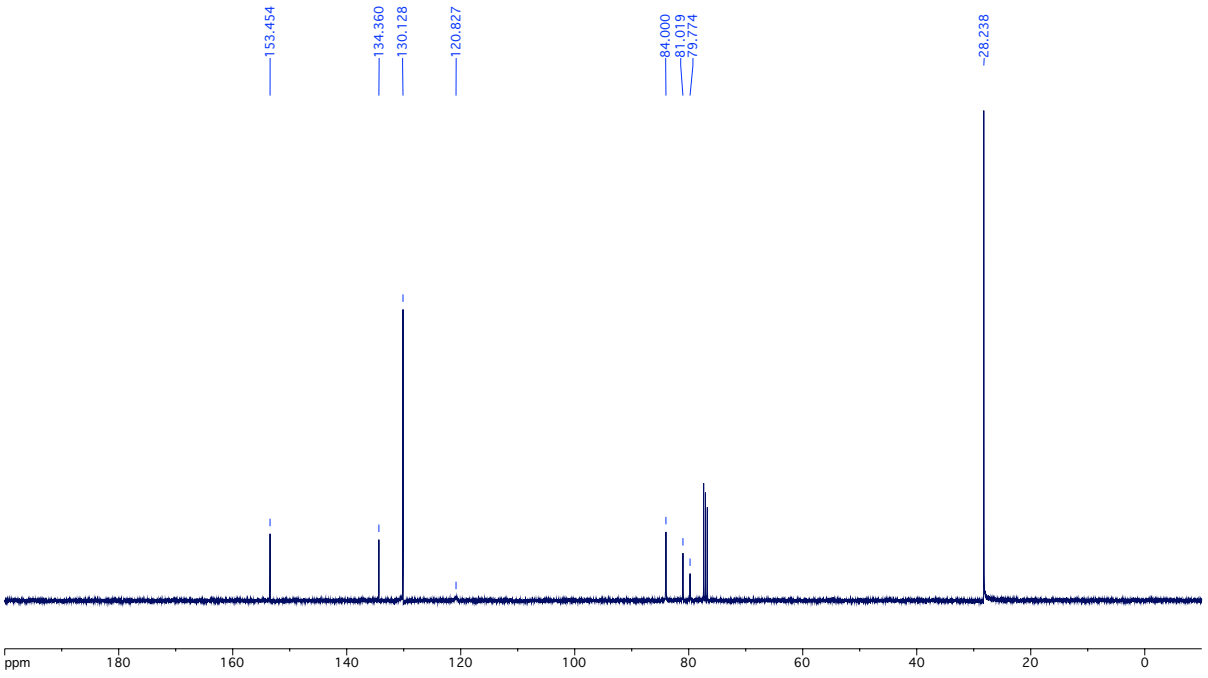

BocHN
NHBoc
TMS
TMS
63
7.279
7.120
1.515
0.266
1.76
1.97
18.7
18
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

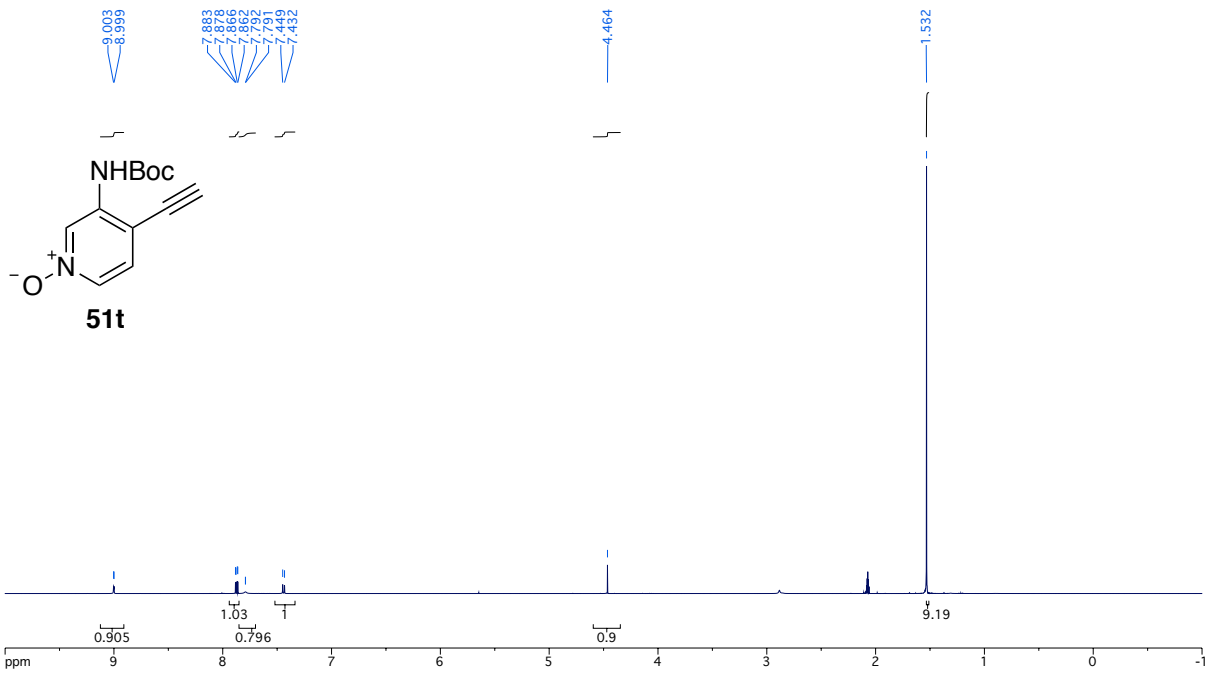

153.376
134.060
129.432
101.827
101.036
80.545
77.275
28.273
0.125
ppm
180
160
140
120
100
80
60
40
20
0

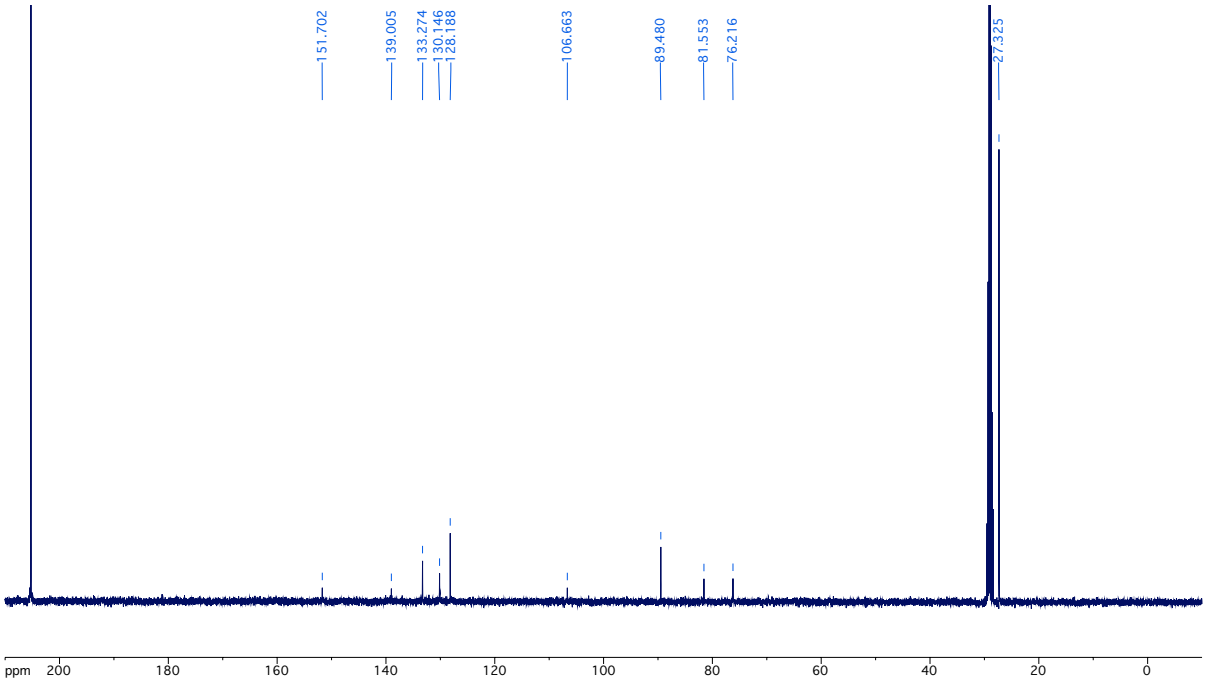

BocHN
NHBoc

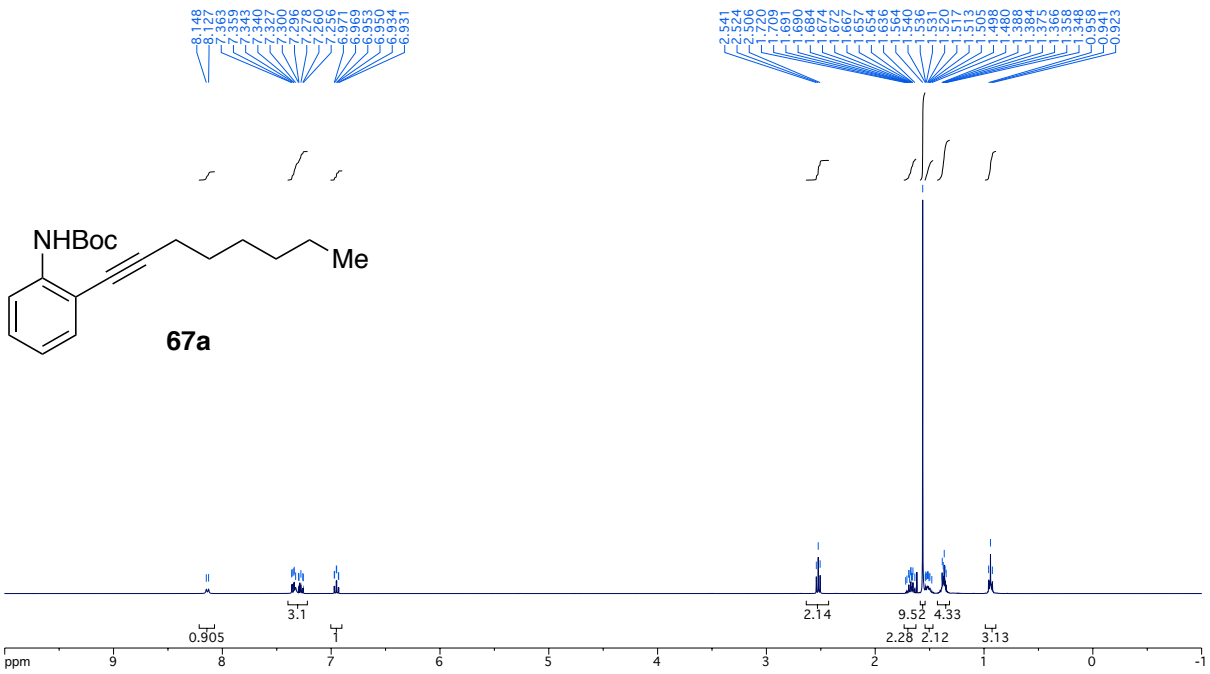
64

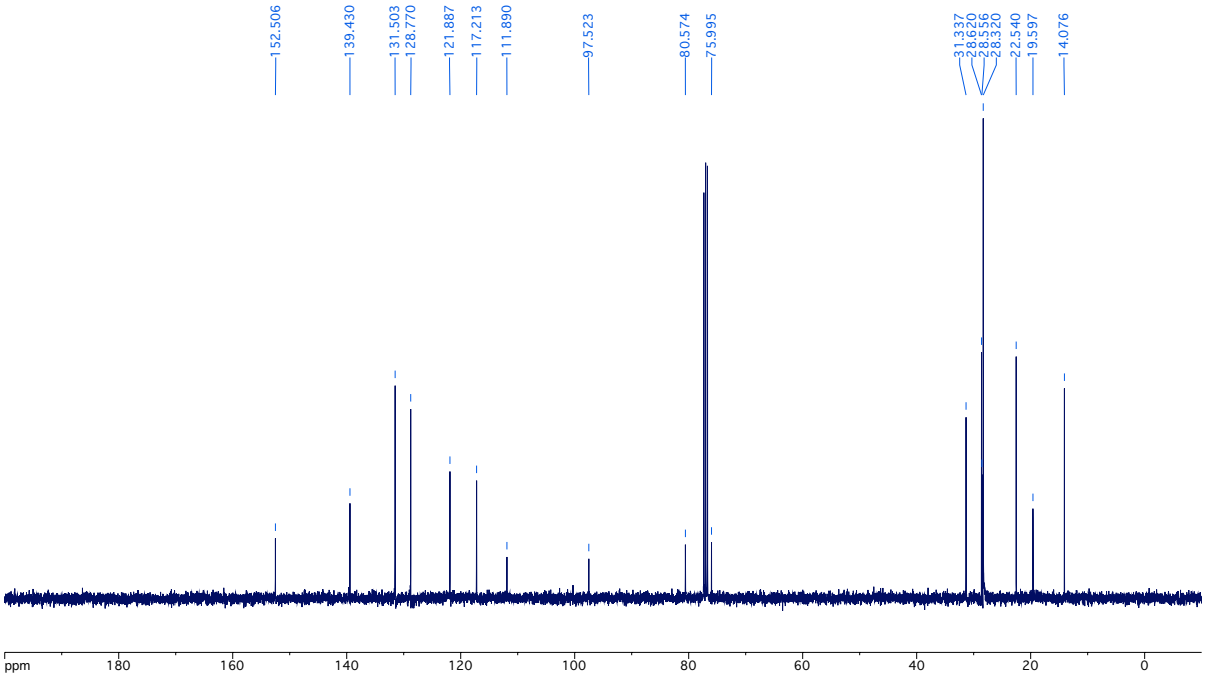
7.360
7.090
3.427
1.531
1.77
1.88
18.2
2
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

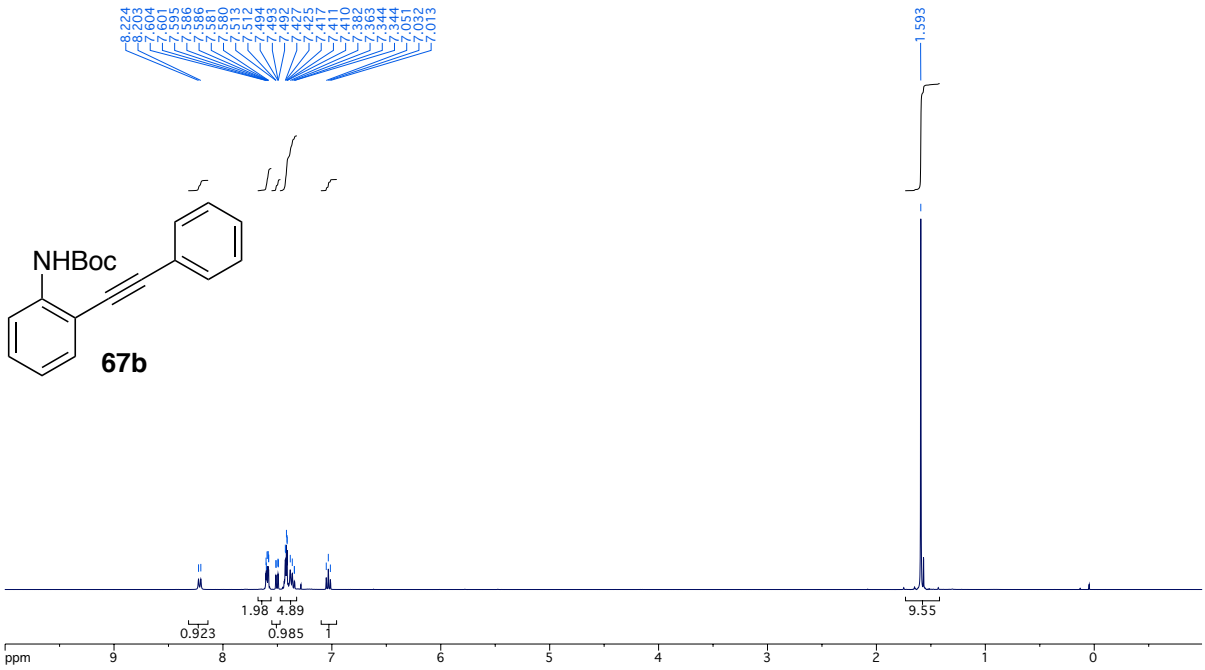

153.454
134.360
130.128
120.827
84.000
81.019
79.774
28.238
ppm
180
160
140
120
100
80
60
40
20
0

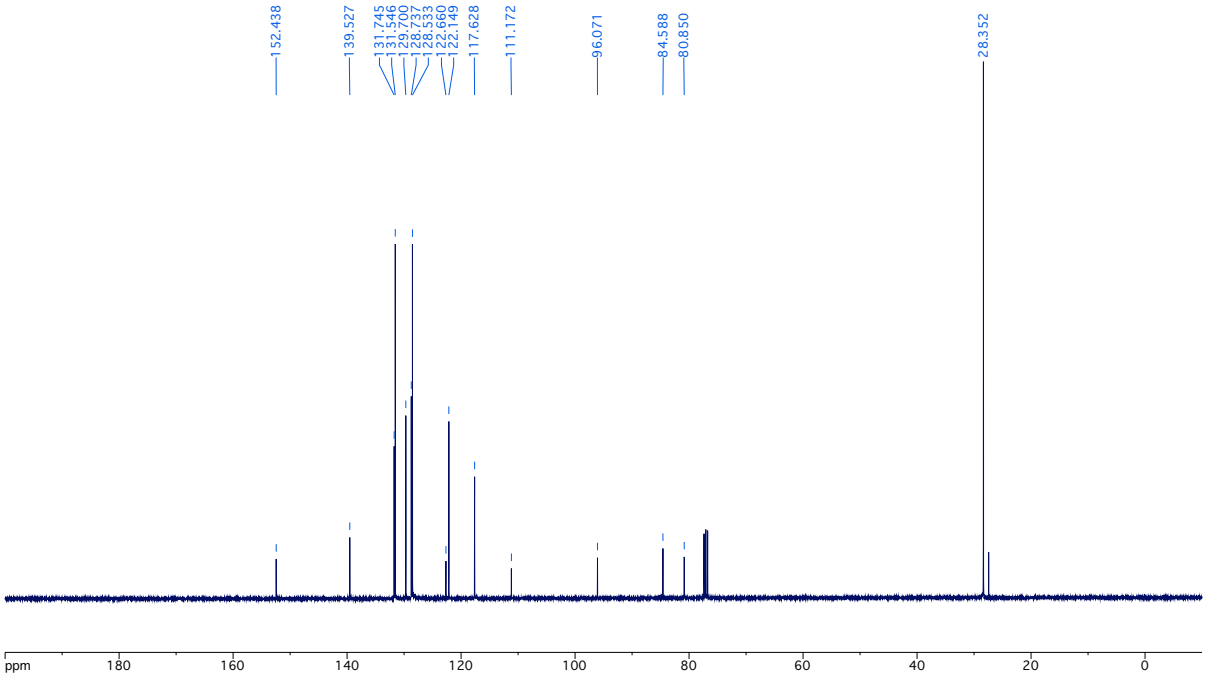

9.003
8.999
7.883
7.878
7.866
7.862
7.792
7.791
7.440
7.432
4.464
1.532
NHBoc
N
O
51t
0.905
1.03
0.796
1
0.9
9.19
ppm
9
8
7
6
5
4
3
2
1
0
-1

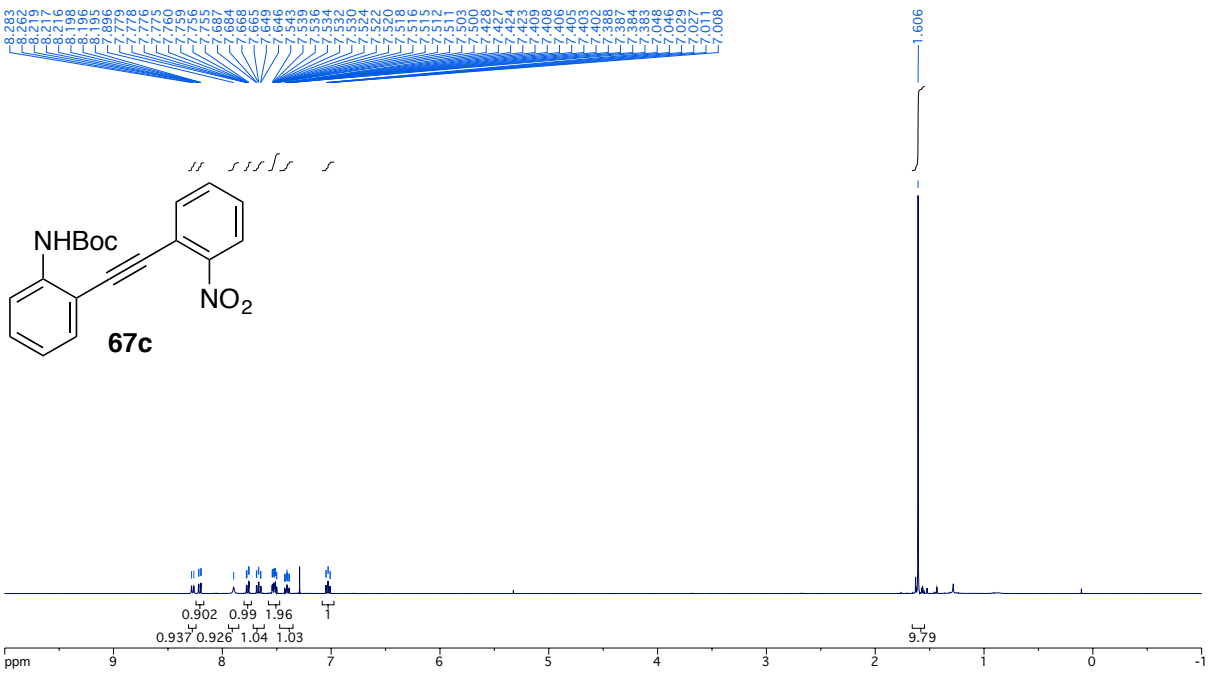

151.702
139.005
133.274
130.146
128.188
106.663
89.480
81.553
76.216
27.325
ppm
200
180
160
140
120
100
80
60
40
20
0

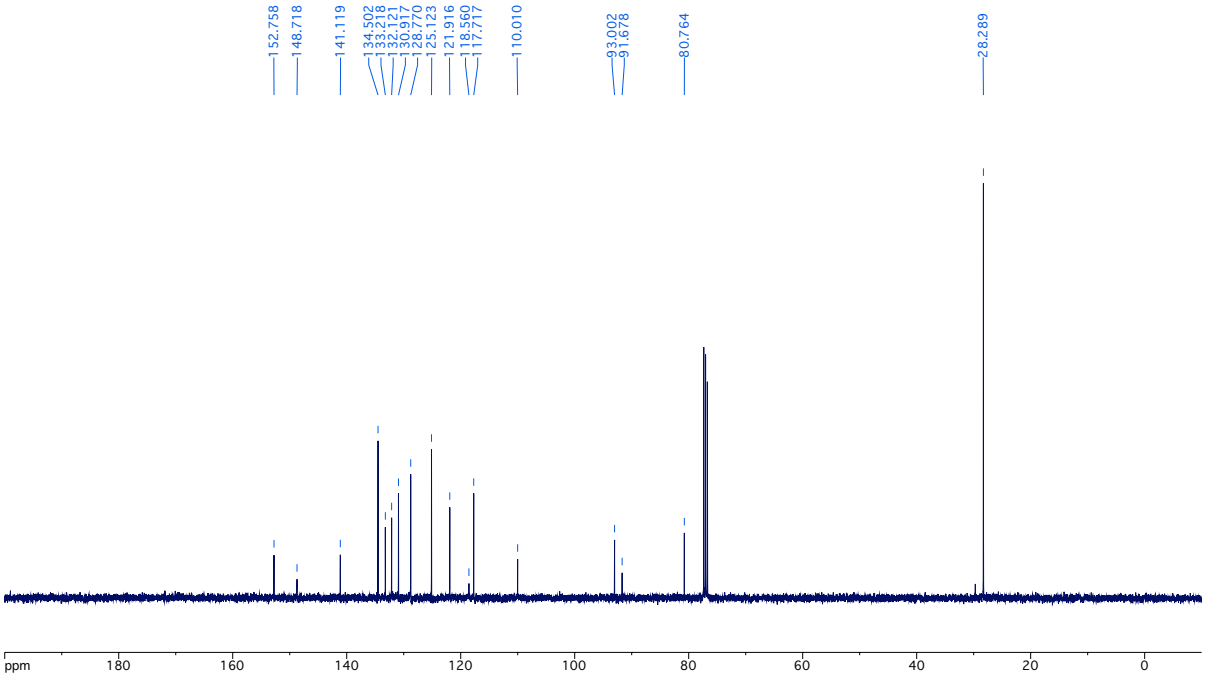

8.148
8.127
7.363
7.359
7.343
7.340
7.327
7.300
7.296
7.278
7.260
7.256
6.971
6.969
6.953
6.950
6.934
6.931
2.541
2.524
2.506
2.488
1.720
1.709
1.691
1.690
1.684
1.674
1.672
1.667
1.657
1.654
1.636
1.564
1.540
1.536
1.531
1.520
1.517
1.513
1.505
1.498
1.480
1.388
1.384
1.375
1.366
1.358
1.348
0.958
0.941
0.923
NHBoc
Me
67a
0.905
3.1
1
2.14
9.52
4.33
2.28
2.12
3.13
ppm
9
8
7
6
5
4
3
2
1
0
-1

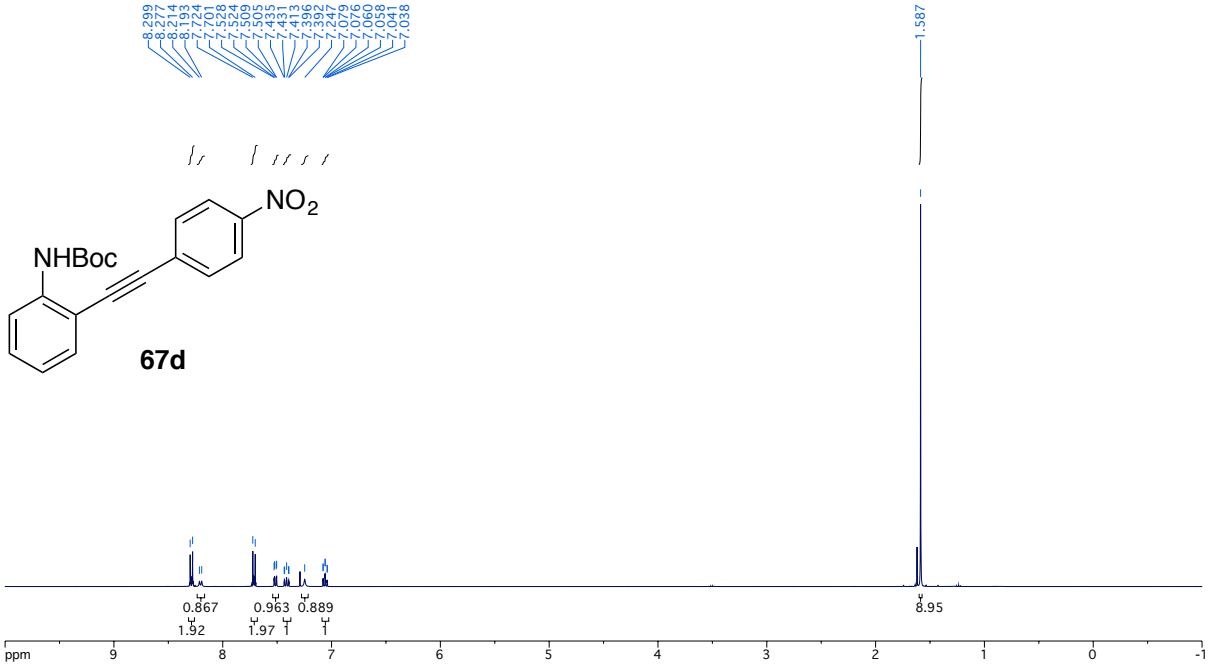

152.506
139.430
131.503
128.770
121.887
117.213
111.890
97.523
80.574
75.995
31.337
28.620
28.556
28.320
22.540
19.597
14.076
ppm
180
160
140
120
100
80
60
40
20
0

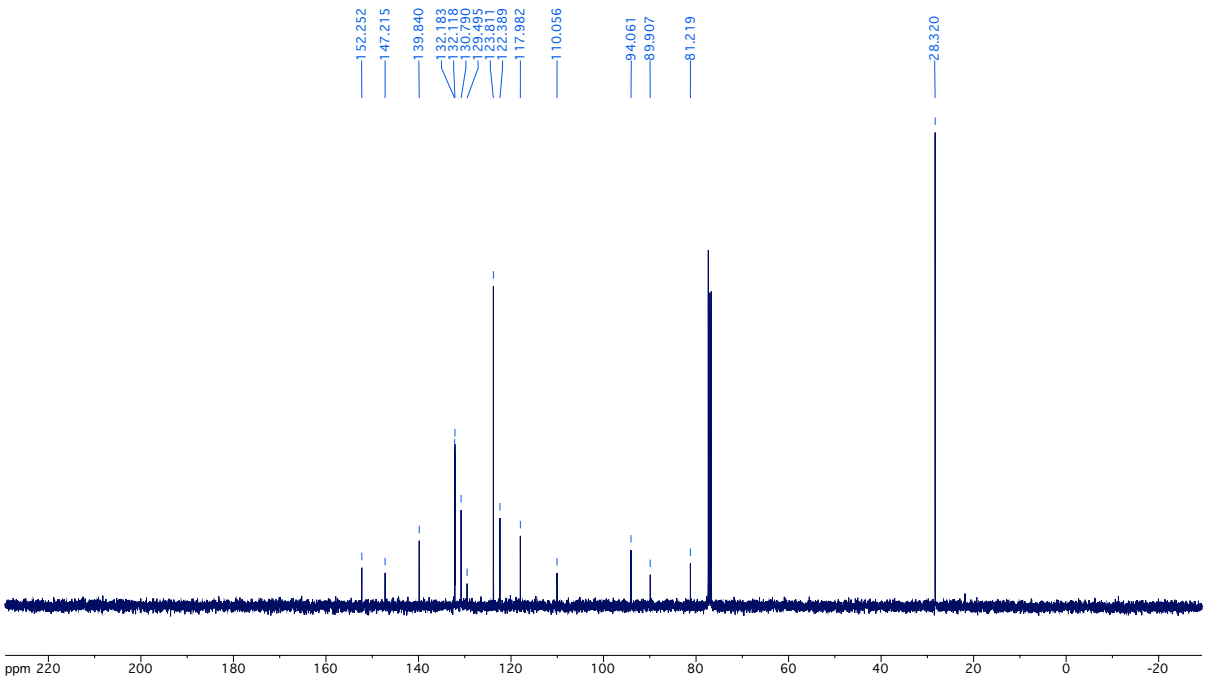

8.224
8.203
7.604
7.601
7.595
7.586
7.581
7.580
7.513
7.512
7.494
7.493
7.492
7.427
7.425
7.417
7.411
7.410
7.382
7.363
7.344
7.341
7.032
7.013
1.593
NHBoc
67b
1.98
4.89
0.923
0.985
1
9.55
ppm

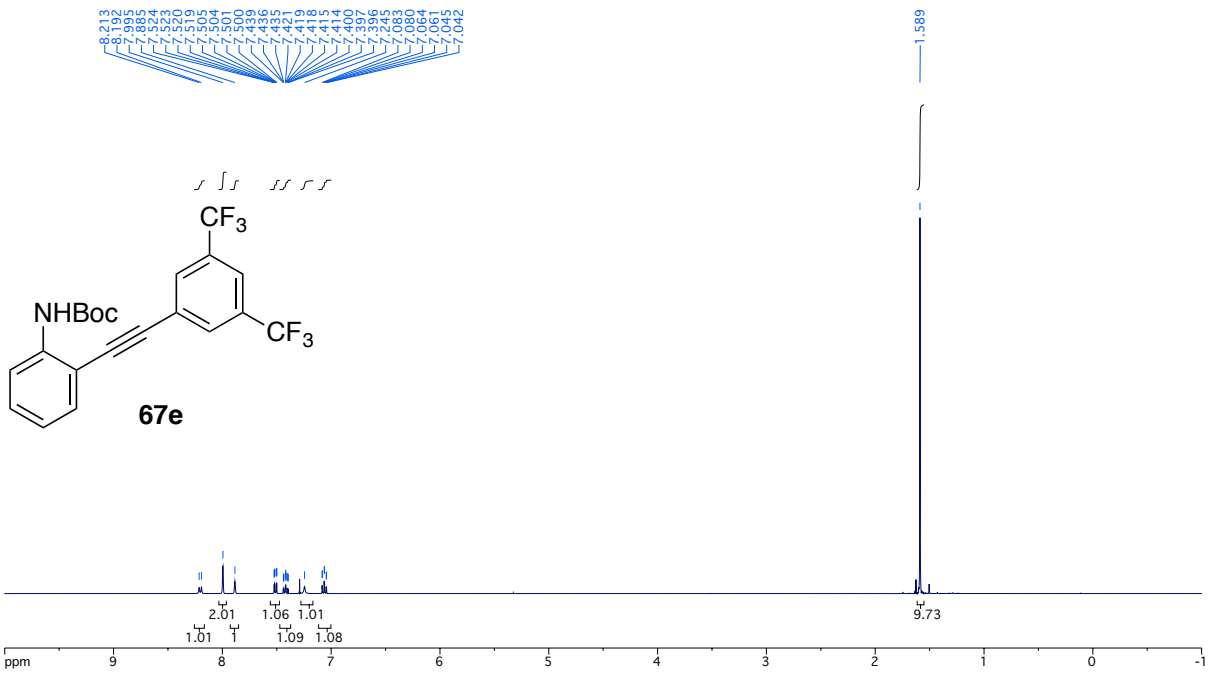

152.438
139.527
131.745
131.546
129.700
128.737
128.533
122.660
122.149
117.628
111.172
96.071
84.588
80.850
28.352
ppm

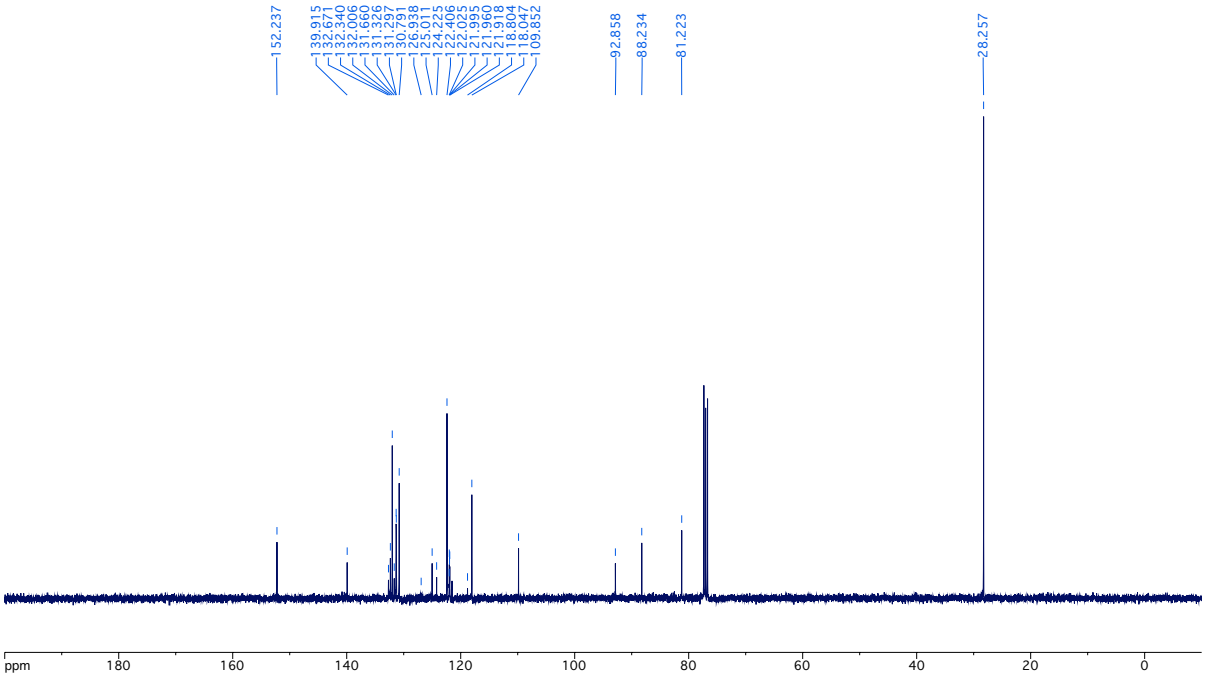

NHBoc
NO2
67c
0.902
0.99
1.96
1
0.937
0.926
1.04
1.03
9.79
ppm

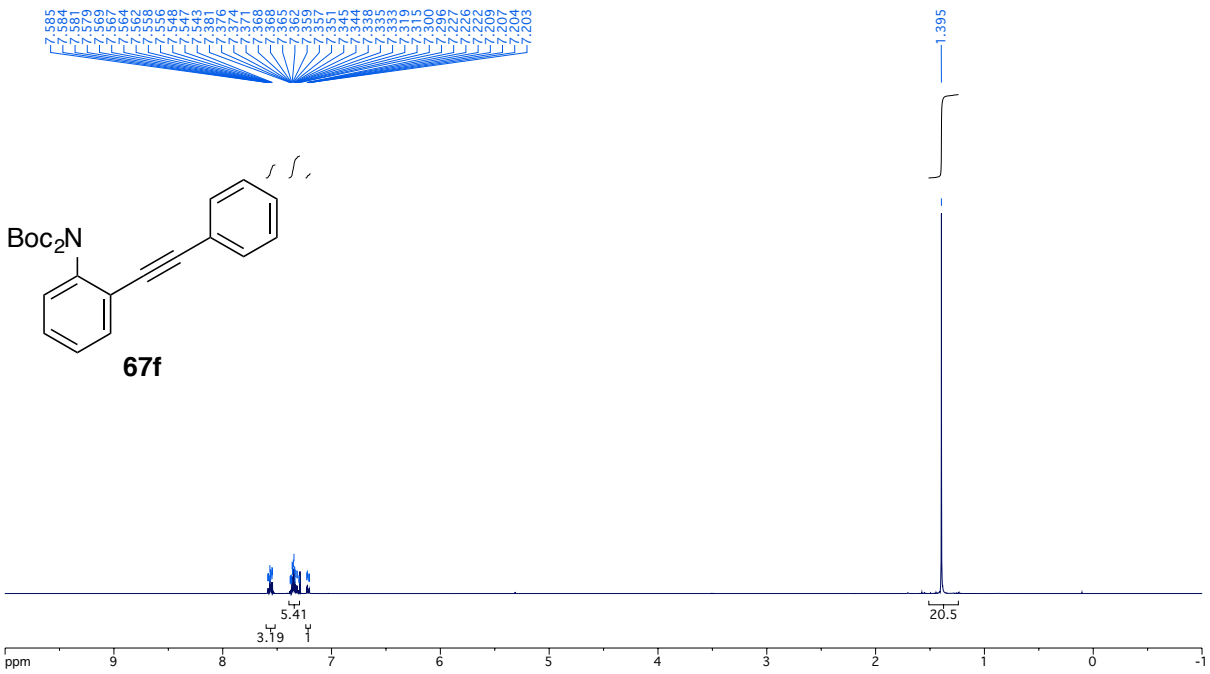

152.758
148.718
141.119
134.502
133.218
132.121
130.917
128.770
125.123
121.916
118.560
117.717
110.010
93.002
91.678
80.764
28.289
ppm

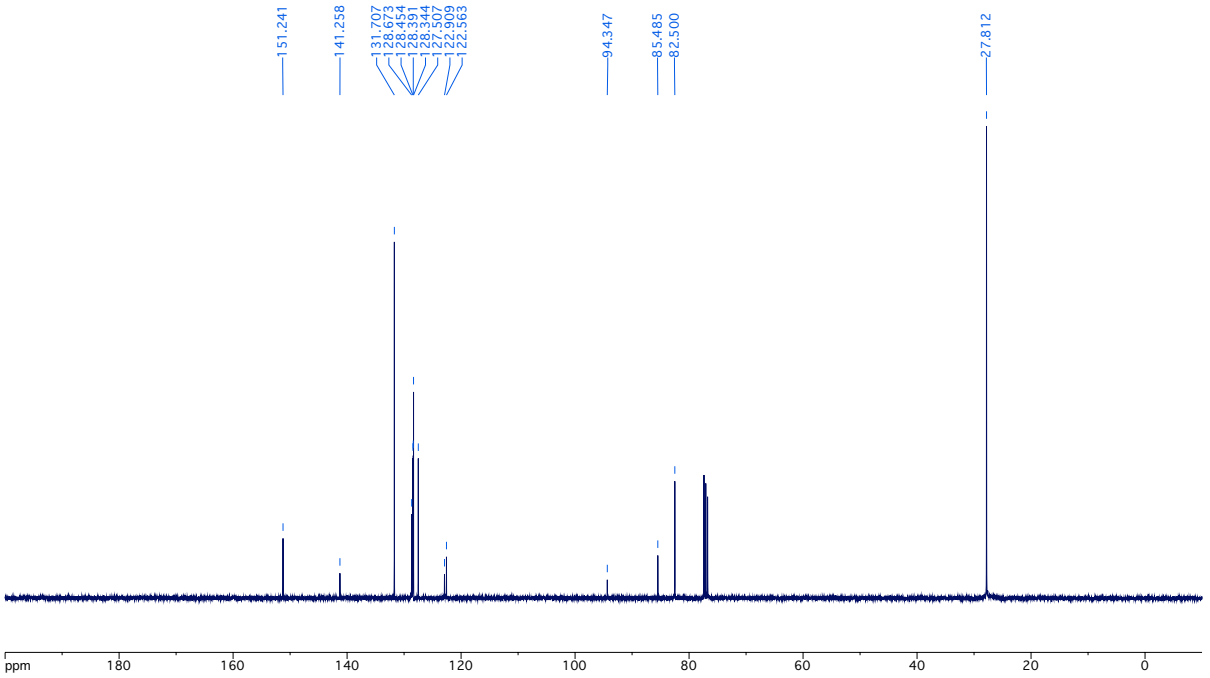

8.299
8.277
8.214
8.193
7.734
7.701
7.528
7.524
7.509
7.505
7.435
7.431
7.413
7.396
7.392
7.247
7.079
7.076
7.060
7.058
7.041
7.038
1.587
NO2
NHBoc
67d
0.867
1.92
0.963
1.97
0.889
1
8.95
ppm

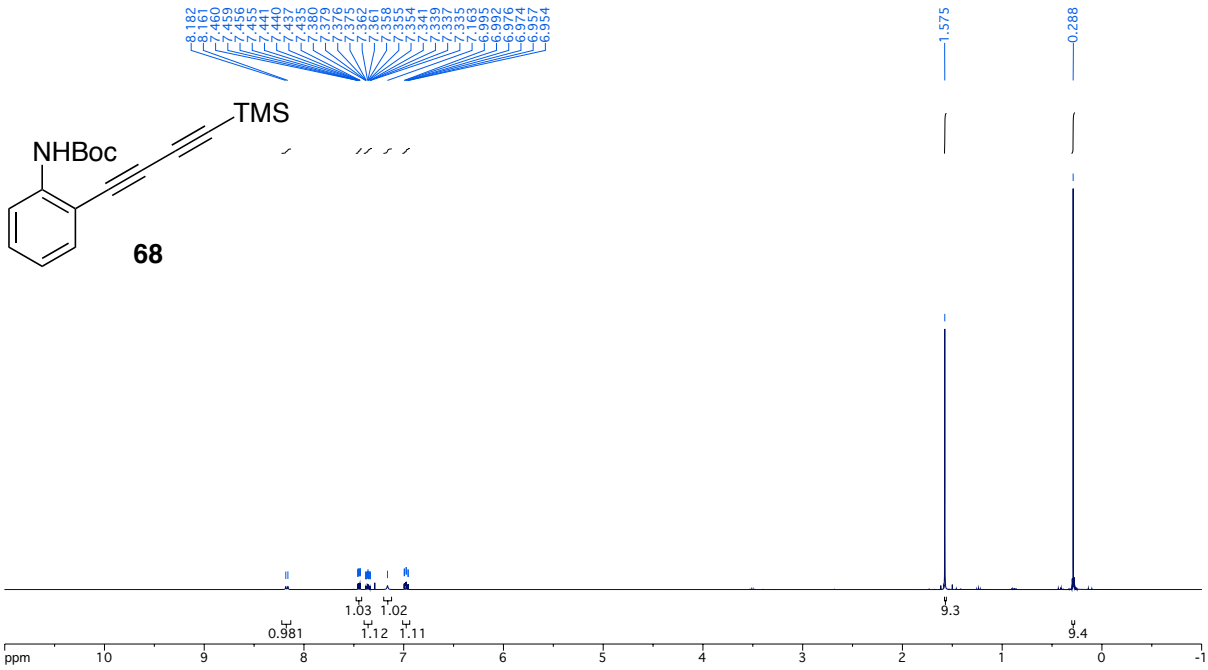

152.252
147.215
139.840
132.183
132.118
130.790
130.495
123.811
122.389
117.982
110.056
94.061
89.907
81.219
28.320
ppm

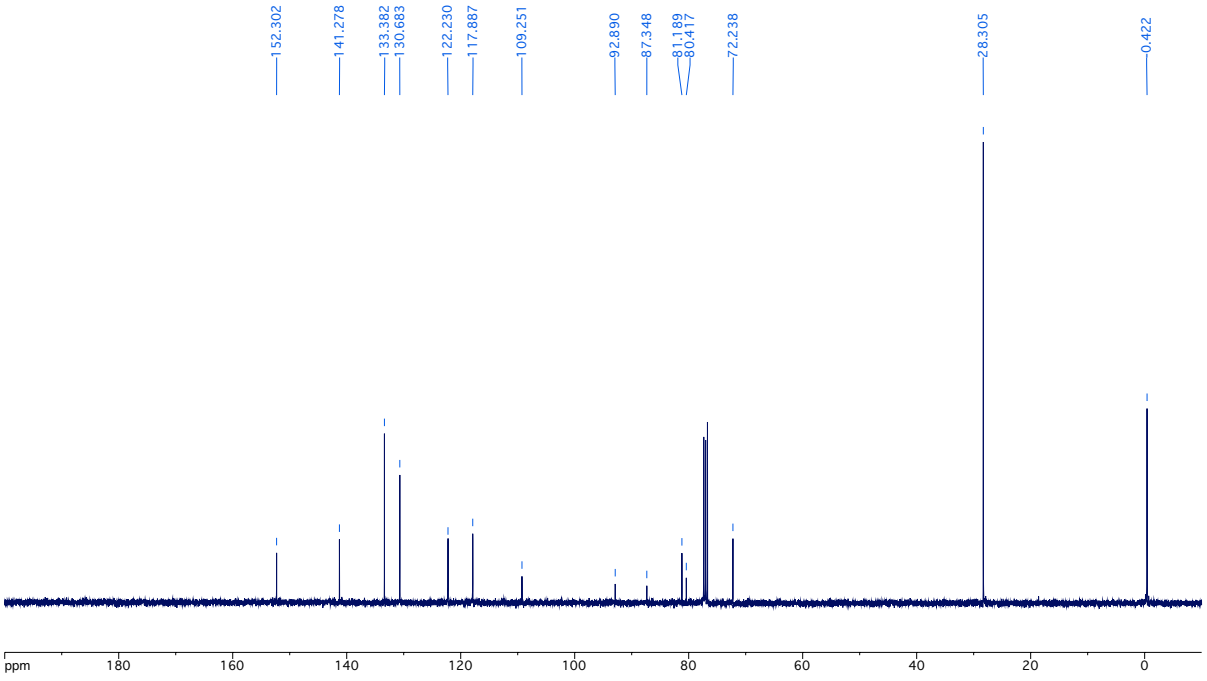

8.213
8.192
7.995
7.885
7.524
7.523
7.520
7.519
7.505
7.504
7.501
7.500
7.439
7.436
7.435
7.421
7.419
7.418
7.415
7.414
7.400
7.397
7.396
7.245
7.083
7.080
7.064
7.061
7.045
7.042
1.589
CF3
NHBoc
CF3
67e
2.01
1.06
1.01
1.01
1.09
1.08
9.73
ppm

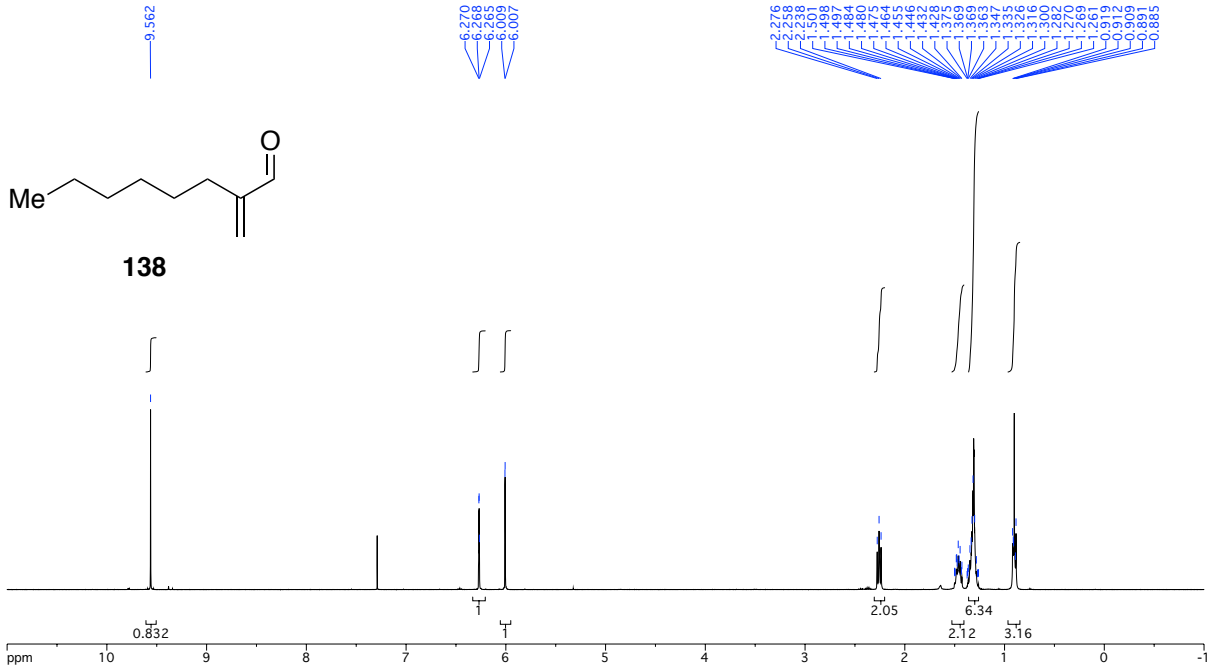

152.237
139.915
133.671
132.340
132.006
131.660
131.326
130.797
130.791
126.938
125.011
124.225
122.406
122.025
121.995
121.960
121.918
118.804
118.047
109.852
92.858
88.234
81.223
28.257
ppm


7.585
7.584
7.581
7.579
7.569
7.567
7.564
7.562
7.558
7.556
7.548
7.547
7.543
7.381
7.376
7.374
7.371
7.368
7.368
7.365
7.362
7.359
7.357
7.351
7.345
7.344
7.338
7.335
7.333
7.315
7.300
7.296
7.227
7.226
7.209
7.207
7.204
7.203
1.395
Boc2N
67f
5.41
3.19
1
20.5
ppm
9
8
7
6
5
4
3
2
1
0
-1

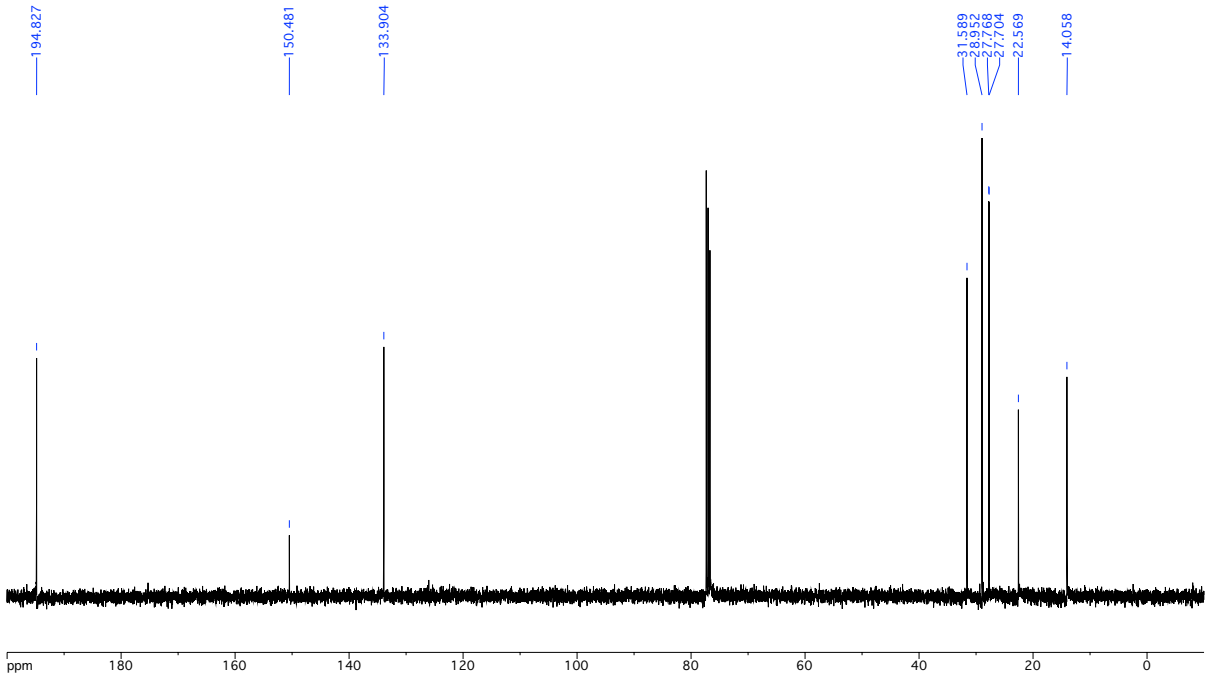

151.241
141.258
131.707
128.673
128.454
128.391
128.344
127.507
127.069
122.563
94.347
85.485
82.500
27.812
ppm
180
160
140
120
100
80
60
40
20
0

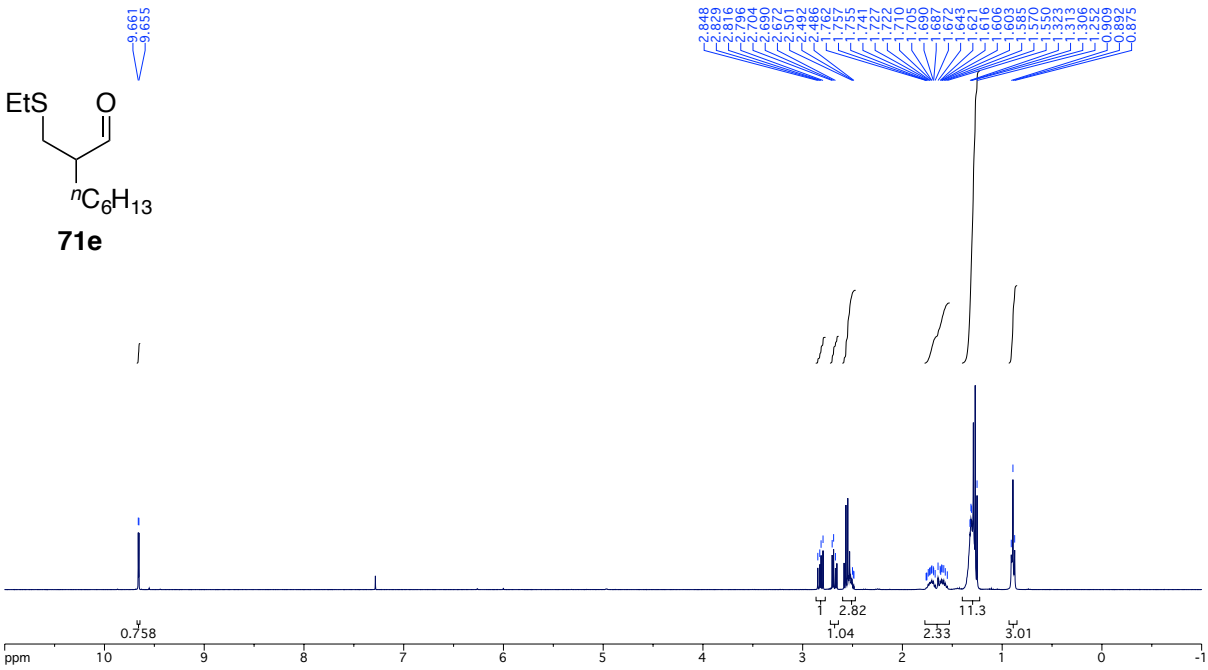

8.182
8.161
7.460
7.459
7.456
7.455
7.441
7.440
7.437
7.435
7.380
7.379
7.376
7.375
7.362
7.361
7.358
7.355
7.354
7.341
7.339
7.337
7.335
7.183
6.995
6.992
6.976
6.974
6.957
6.954
1.575
0.288
TMS
NHBoc
68
1.03
1.02
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1.12
1.11
9.3
9.4
ppm

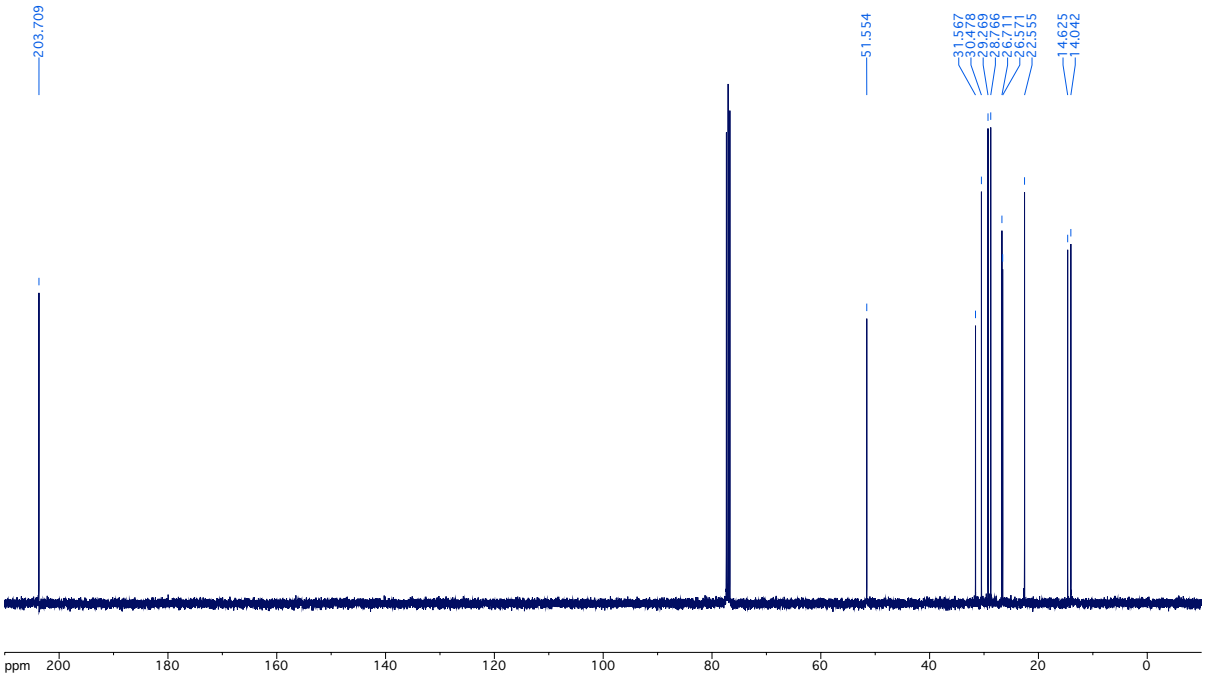

152.302
141.278
133.382
130.683
122.230
117.887
109.251
92.890
87.348
81.189
80.417
72.238
28.305
0.422
ppm

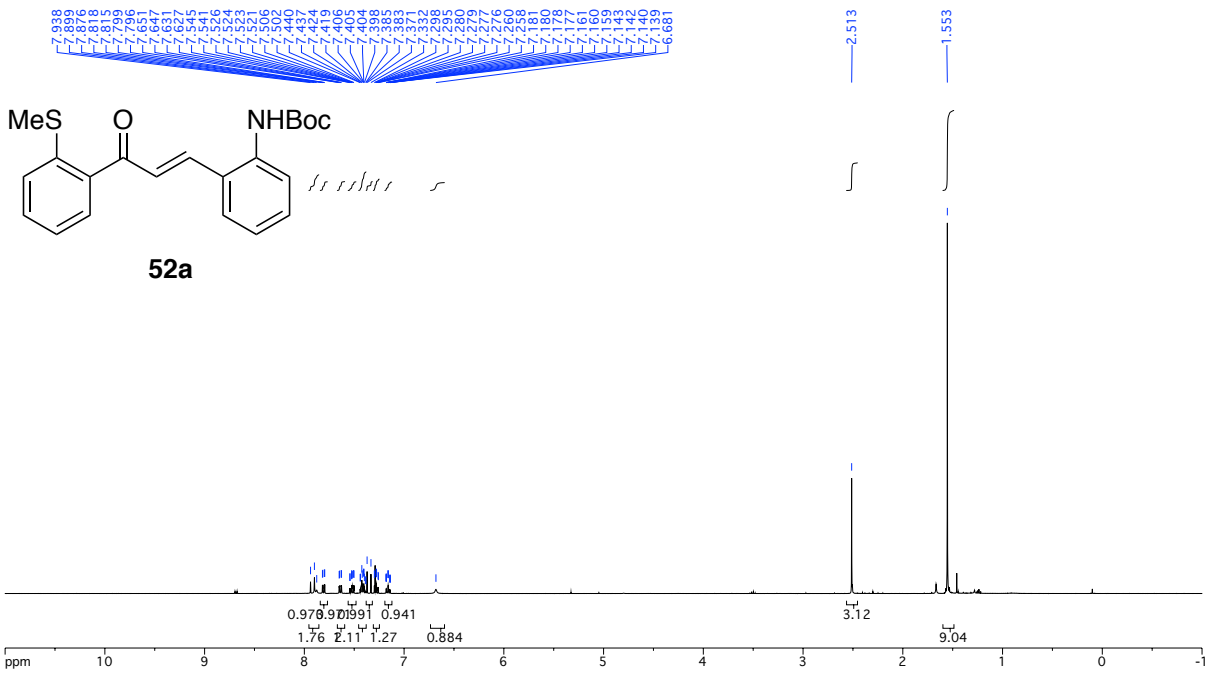

9.562
6.270
6.268
6.265
6.009
6.007
2.276
2.258
2.238
1.501
1.498
1.497
1.484
1.480
1.475
1.464
1.454
1.446
1.432
1.428
1.375
1.369
1.363
1.347
1.335
1.326
1.316
1.300
1.282
1.270
1.261
0.919
0.912
0.909
0.891
0.885
O
Me
0.832
1
1
2.05
2.12
6.34
3.16
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

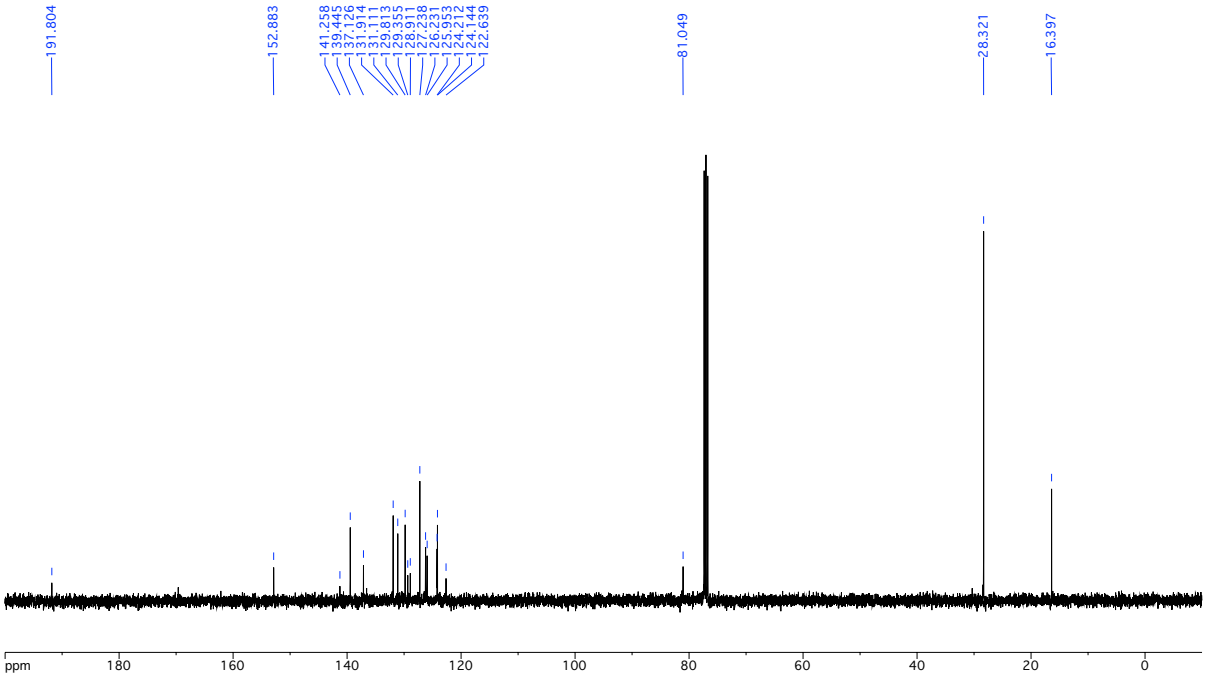
138

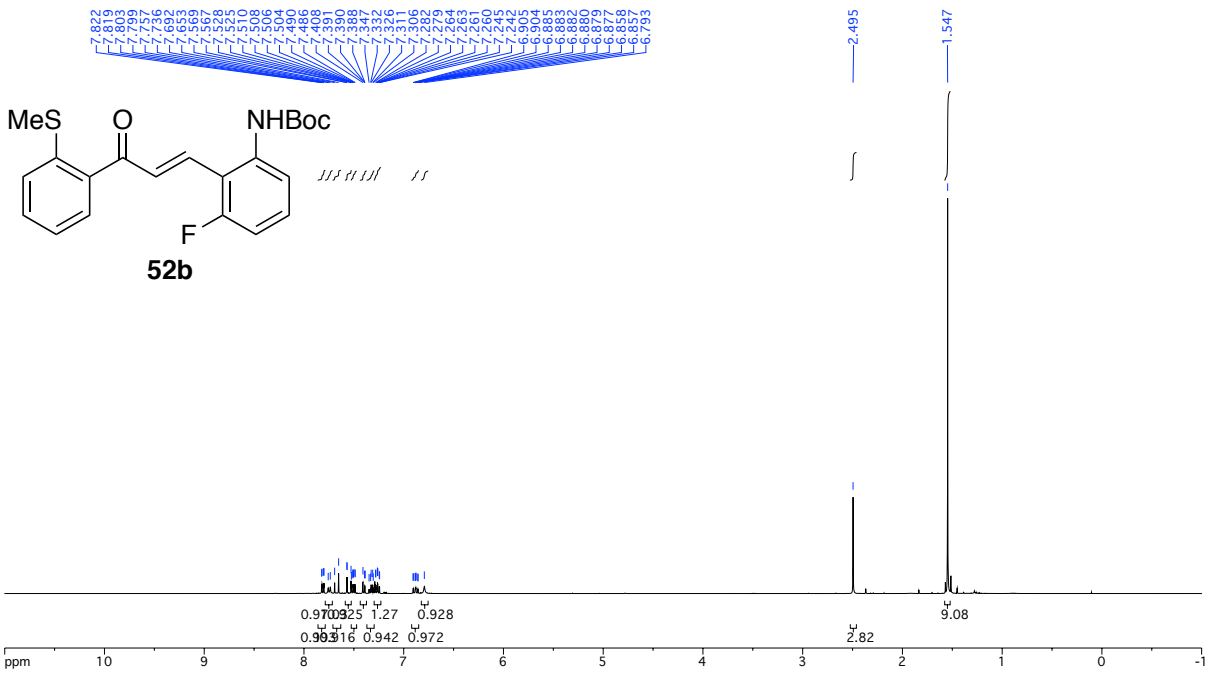

194.827
150.481
133.904
31.589
28.952
27.768
27.704
22.569
14.058
ppm
180
160
140
120
100
80
60
40
20
0

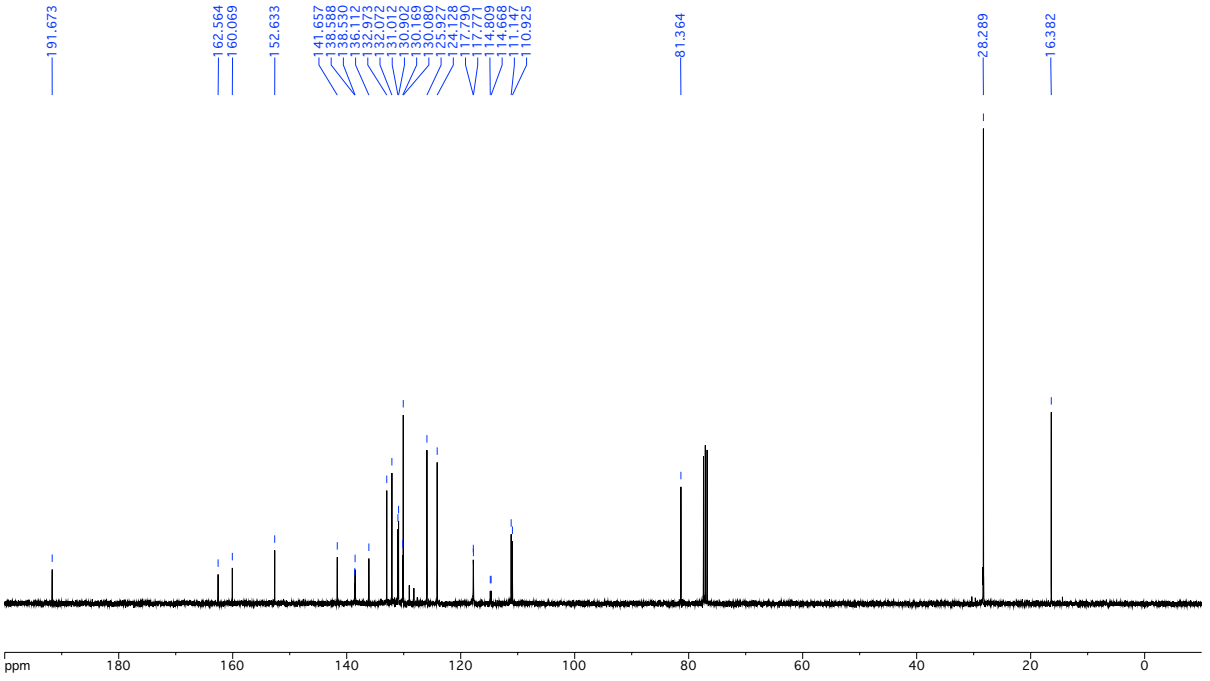

9.661
9.655
2.848
2.829
2.816
2.796
2.784
2.690
2.672
2.501
2.492
2.486
1.762
1.757
1.745
1.741
1.727
1.722
1.710
1.705
1.690
1.687
1.672
1.643
1.621
1.616
1.606
1.603
1.585
1.570
1.520
1.323
1.313
1.306
1.252
0.909
0.892
0.875
EtS
O
nC6H13
71e
0.758
1
2.82
1.04
2.33
11.3
3.01
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

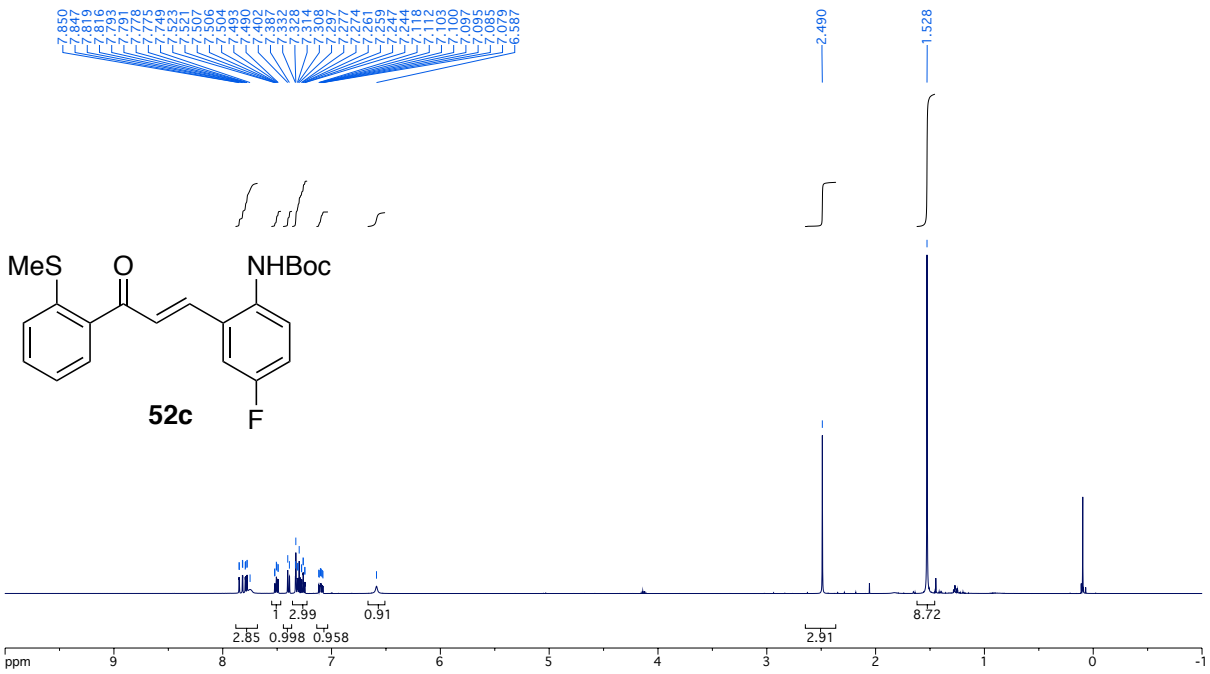

203.709
51.554
31.567
30.478
29.269
28.766
26.711
26.371
22.555
14.825
14.042
ppm
200
180
160
140
120
100
80
60
40
20
0

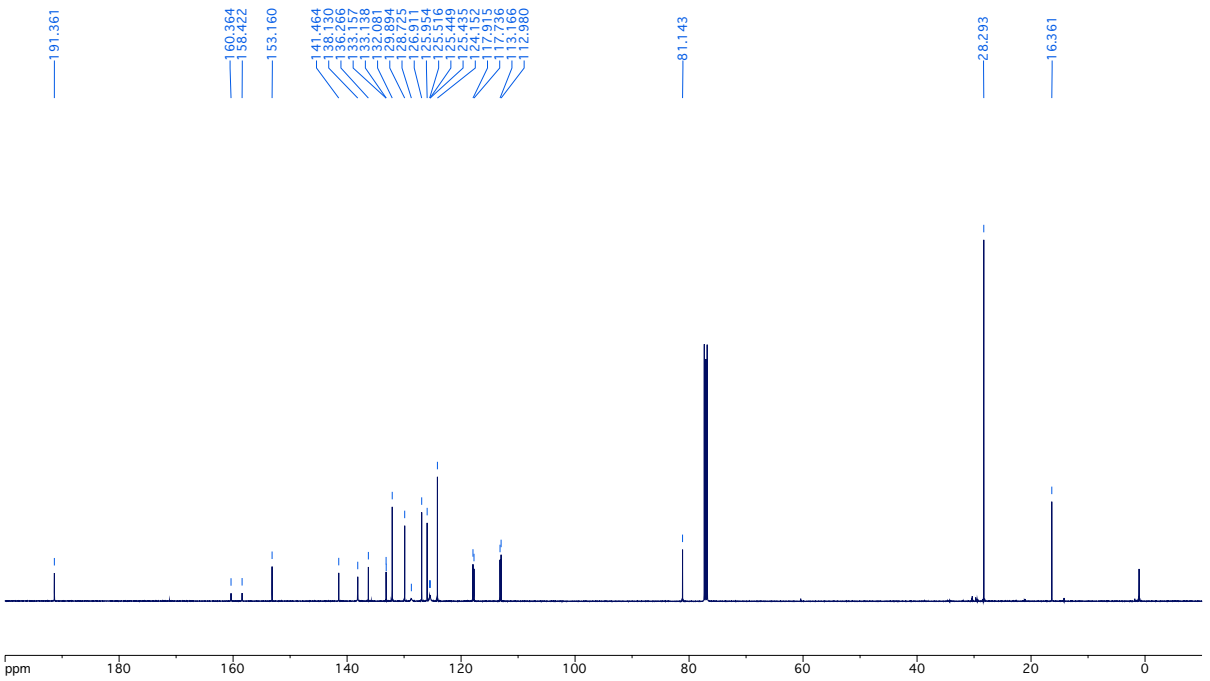

MeS
O
NHBoc
52a
2.513
1.553
3.12
9.04
ppm

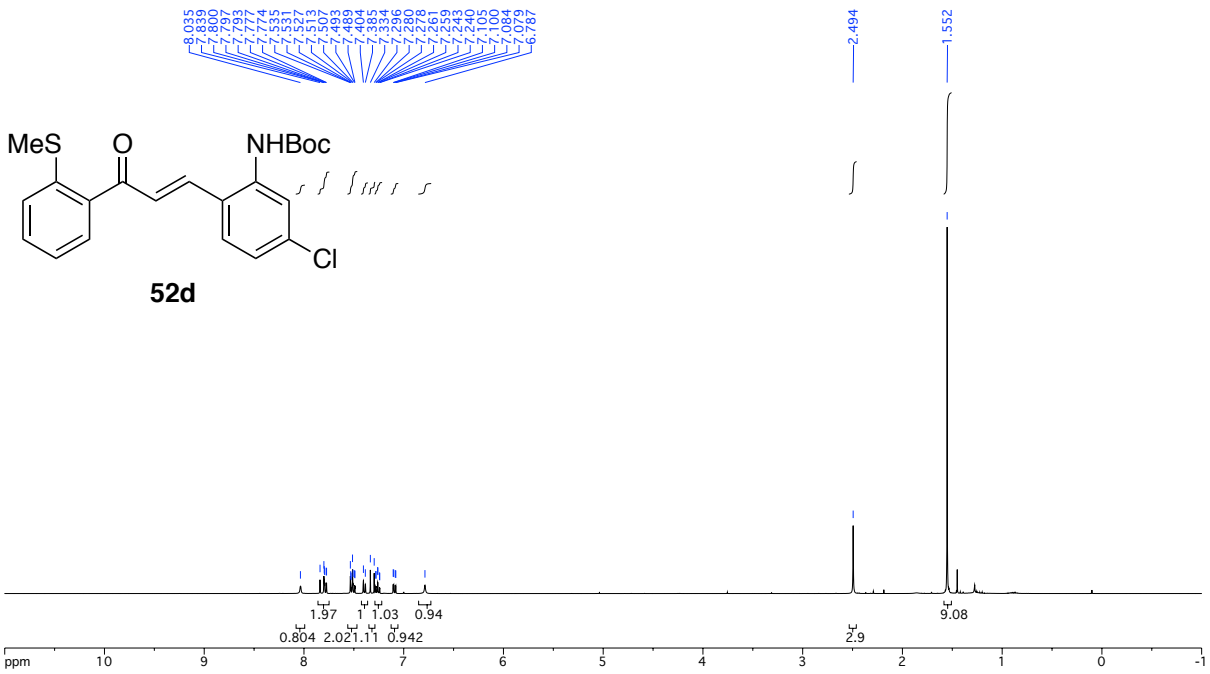

191.804
152.883
141.258
138.445
137.126
131.914
131.111
129.813
129.355
129.111
127.238
126.331
125.953
124.212
124.144
122.639
81.049
28.321
16.397
ppm

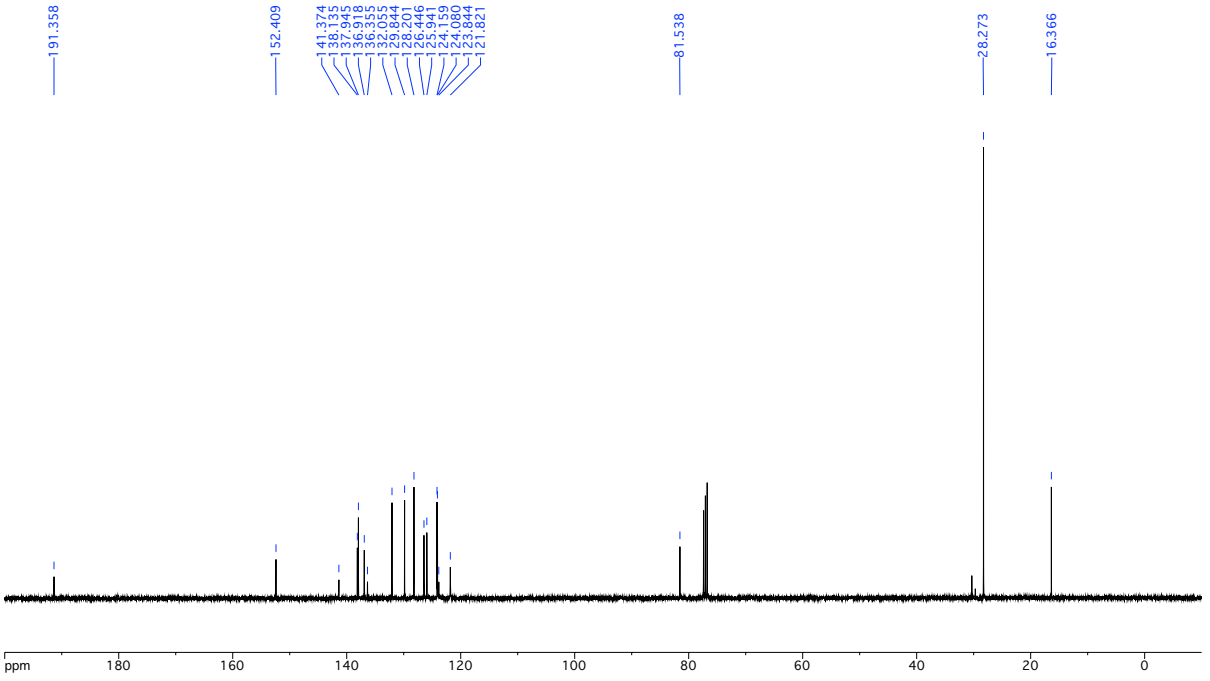

MeS
O
NHBoc
F
52b
2.495
1.547
0.928
9.08
2.82
ppm

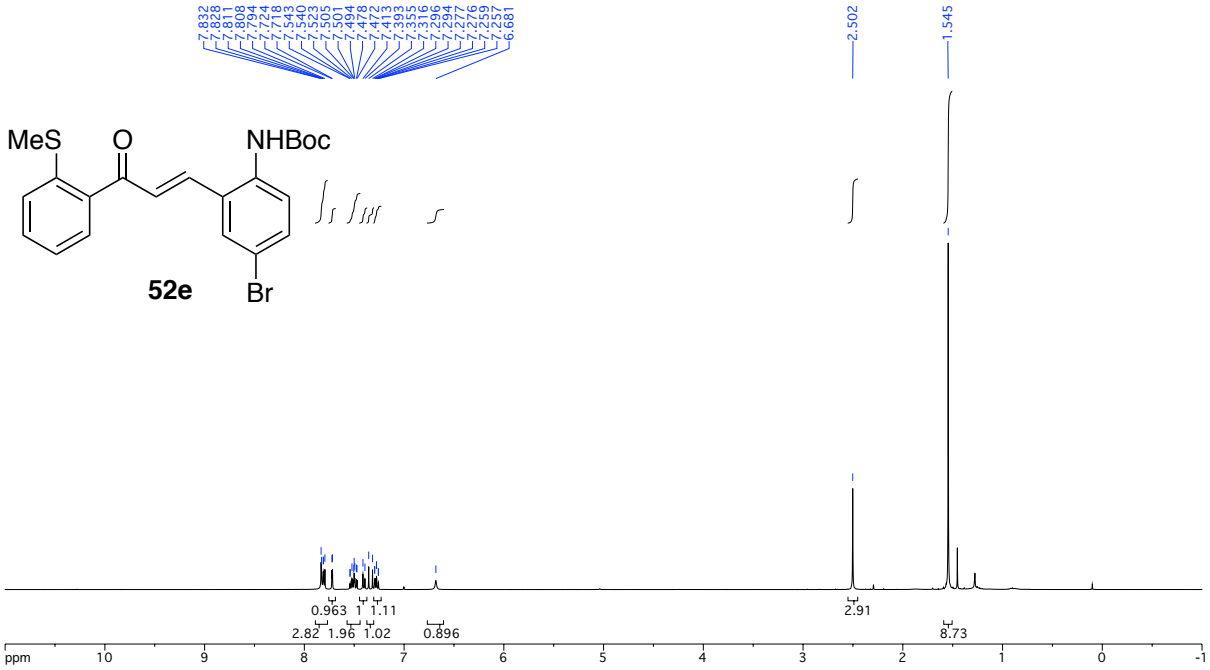

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16.382
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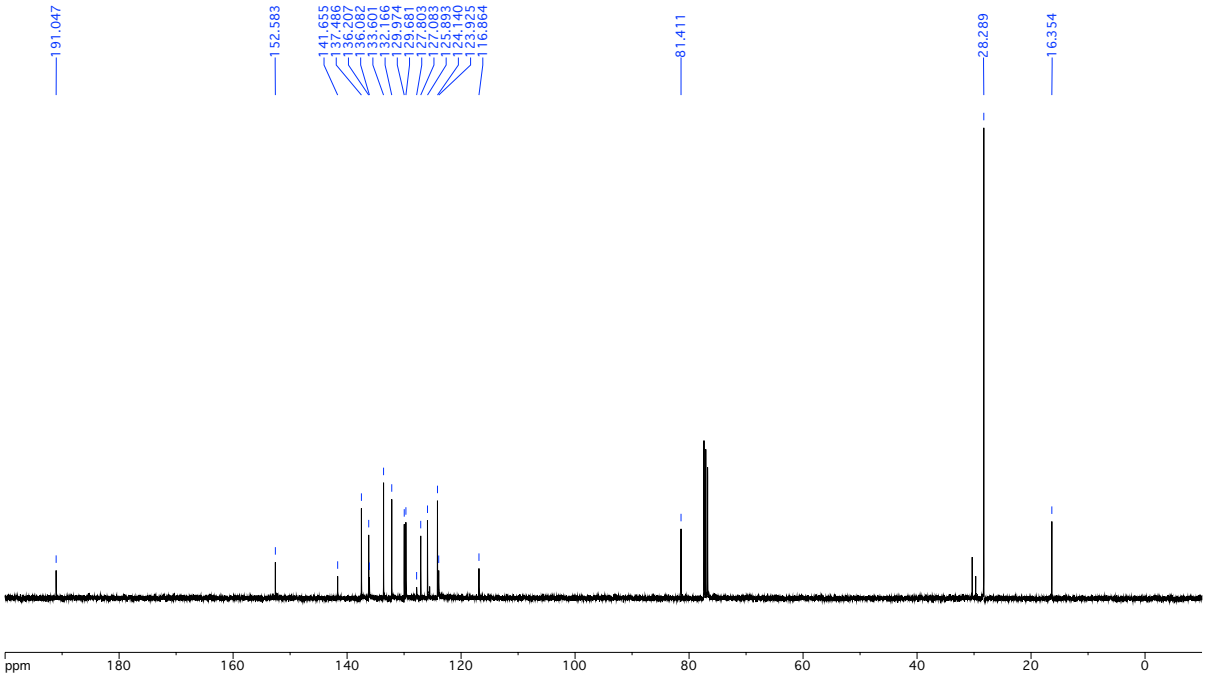

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7.847
7.819
7.816
7.793
7.791
7.778
7.775
7.749
7.523
7.521
7.507
7.506
7.504
7.493
7.490
7.402
7.387
7.332
7.328
7.314
7.308
7.297
7.277
7.274
7.261
7.259
7.247
7.244
7.118
7.112
7.103
7.100
7.097
7.085
7.079
6.587
2.490
1.528
MeS
O
NHBoc
F
52c
1
2.99
0.91
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2.85
0.998
0.958
2.91
ppm

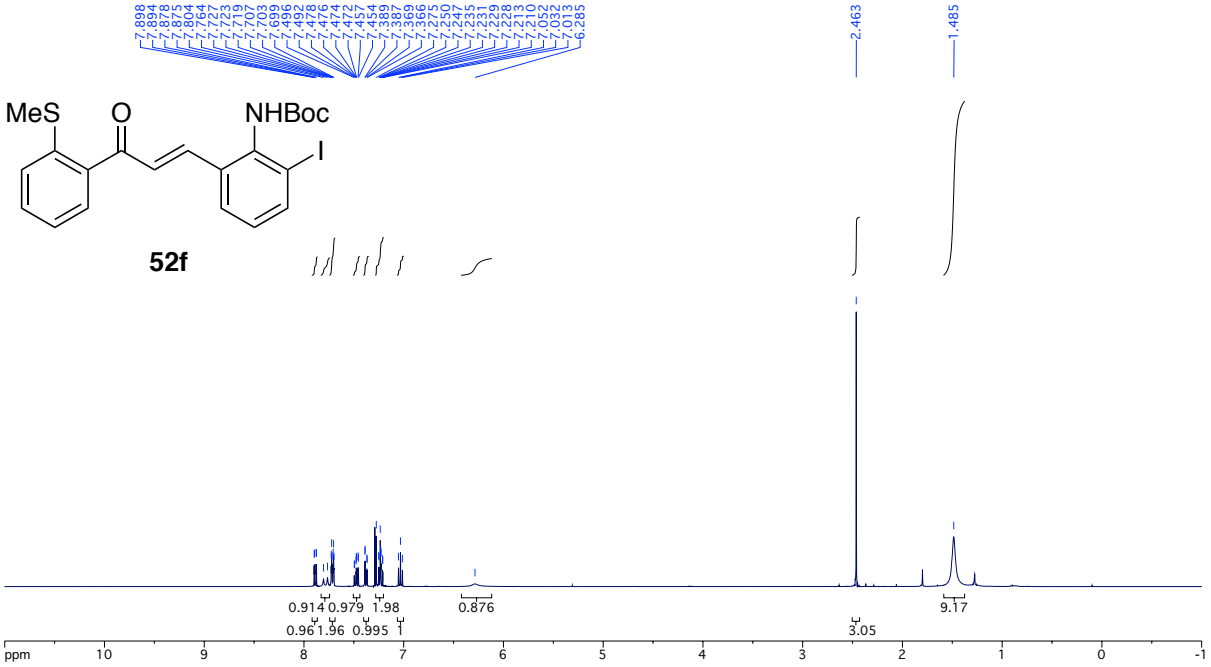

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158.422
153.160
141.464
138.130
136.266
133.137
133.138
132.081
129.894
128.725
126.911
125.954
125.516
125.449
124.435
124.152
117.915
117.736
113.166
112.980
81.143
28.293
16.361
ppm

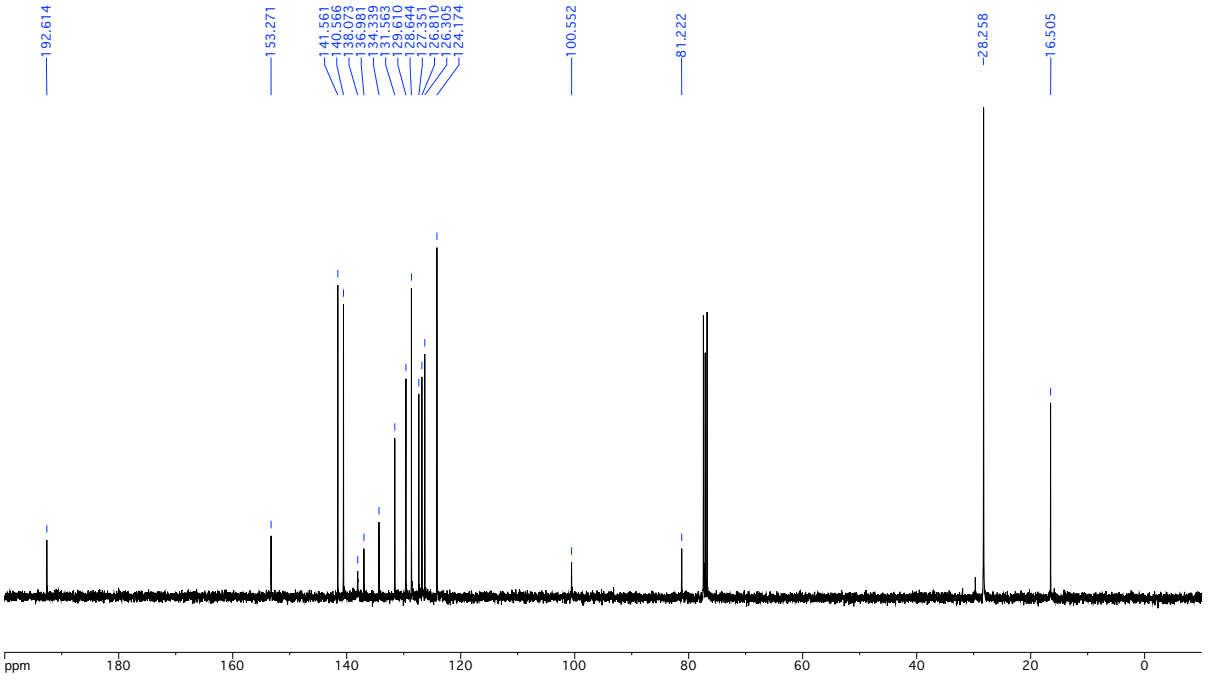

8.035
7.839
7.800
7.797
7.793
7.777
7.774
7.535
7.531
7.527
7.513
7.507
7.493
7.489
7.404
7.384
7.334
7.296
7.280
7.278
7.261
7.239
7.243
7.240
7.105
7.100
7.084
7.079
6.787
2.494
1.552
MeS
O
NHBoc
Cl
52d
1.97
1.03
0.94
0.804
2.02
1.11
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2.9
9.08
ppm
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8
7
6
5
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3
2
1
0
-1

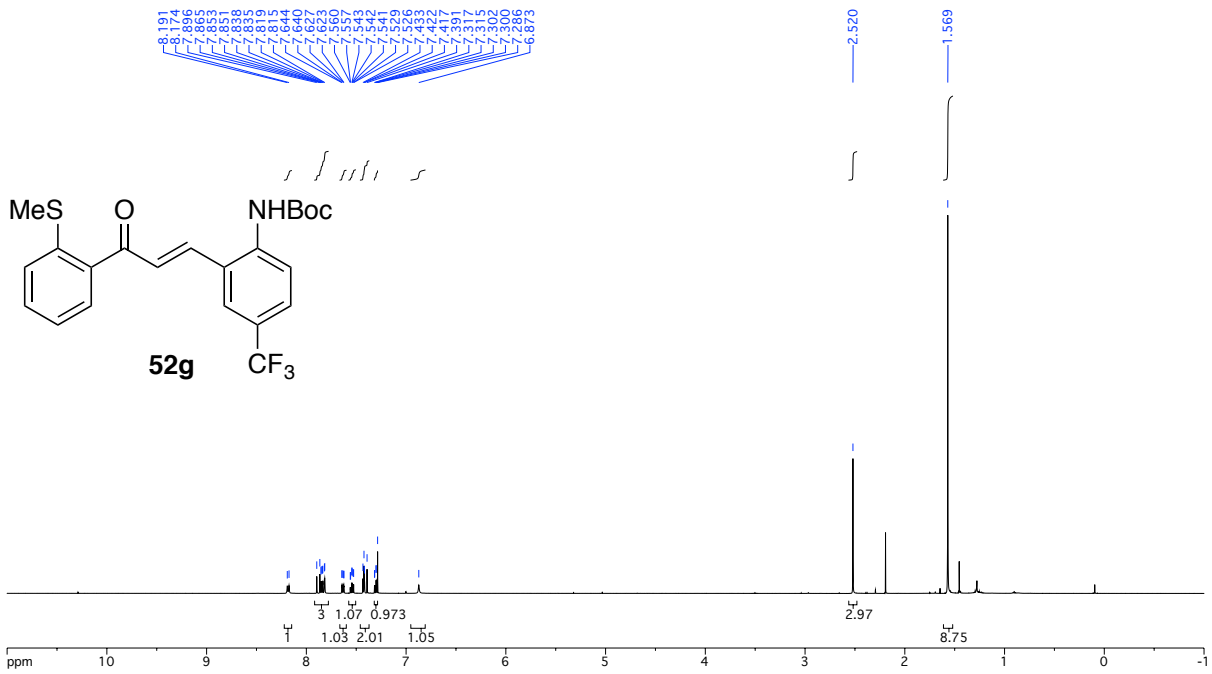

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141.374
139.135
138.944
136.918
136.355
132.055
129.844
128.201
126.446
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123.515
121.080
123.844
121.821
81.538
28.273
16.366
ppm
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140
120
100
80
60
40
20
0

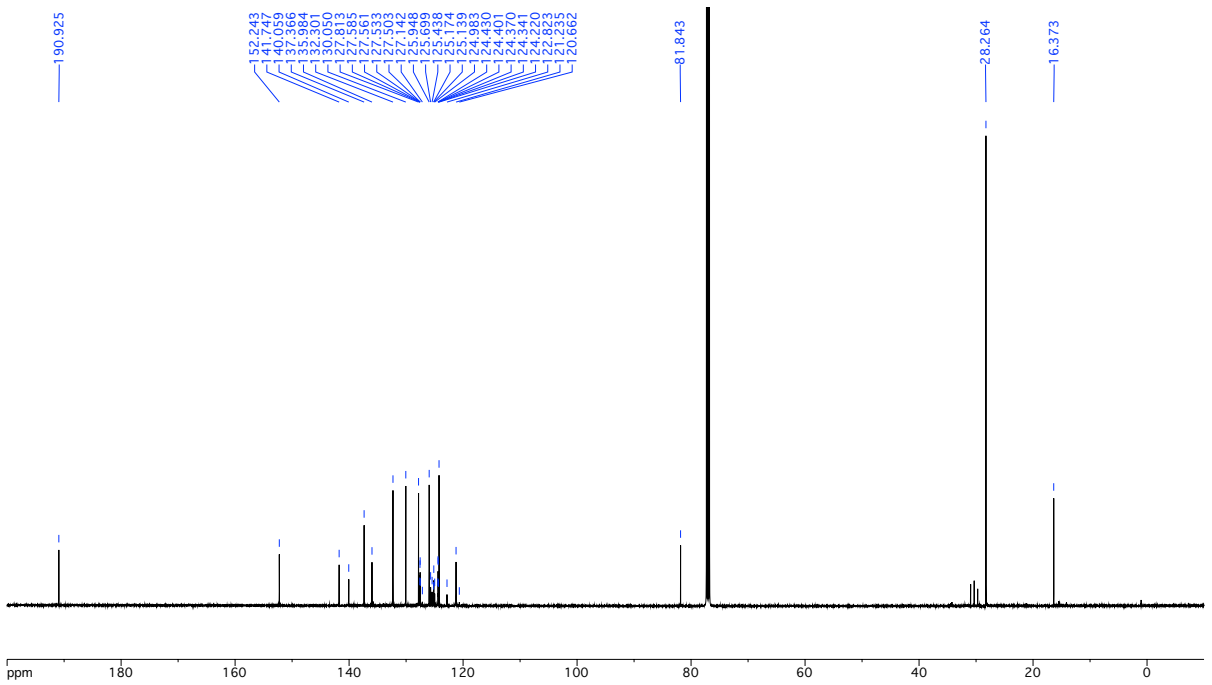

7.832
7.828
7.811
7.808
7.804
7.724
7.718
7.543
7.540
7.523
7.505
7.501
7.494
7.478
7.472
7.413
7.393
7.355
7.316
7.296
7.277
7.276
7.259
7.257
6.681
2.502
1.545
MeS
O
NHBoc
Br
52e
0.963
1
1.11
2.91
2.82
1.96
1.02
0.896
8.73
ppm
10
9
8
7
6
5
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2
1
0
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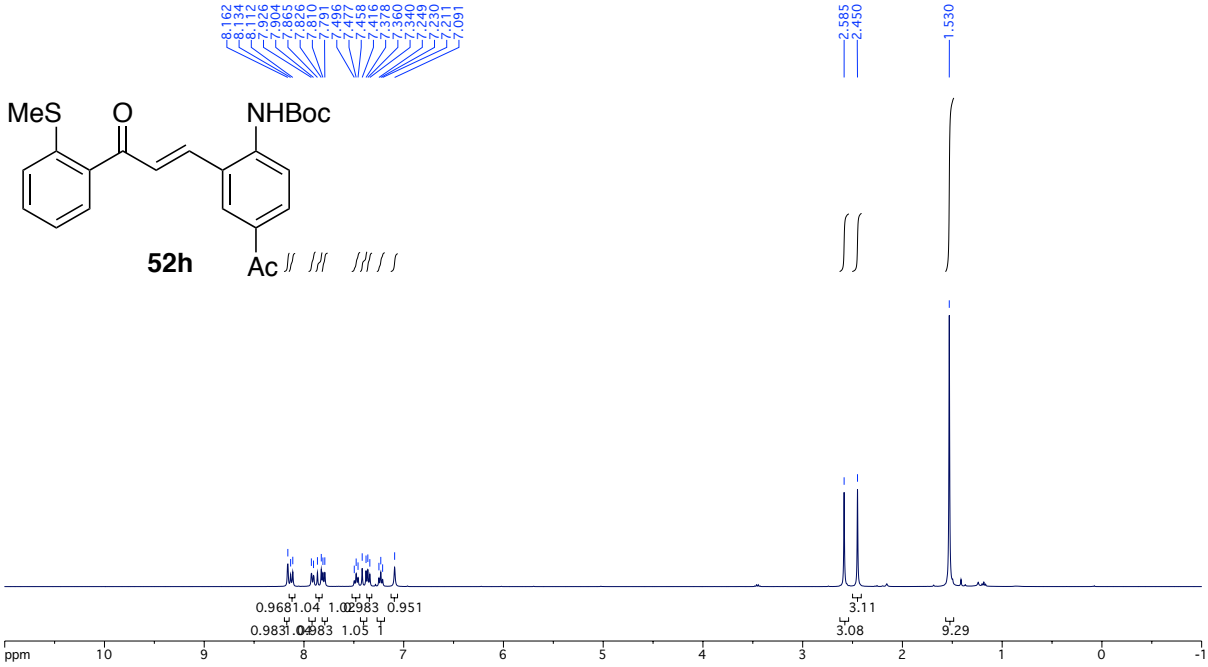

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152.583
141.655
137.486
136.207
136.082
133.601
132.166
129.974
129.881
127.803
127.083
125.893
124.140
123.925
116.864
81.411
28.289
16.354
ppm
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140
120
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80
60
40
20
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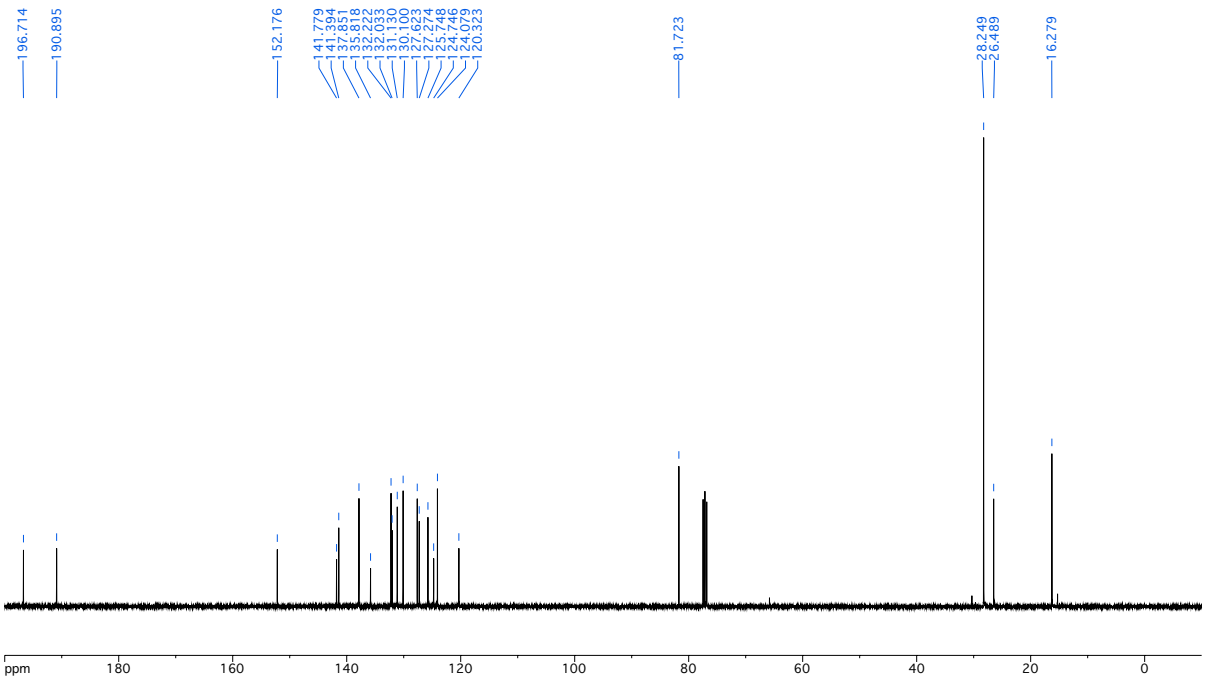

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7.894
7.878
7.875
7.804
7.764
7.727
7.723
7.719
7.707
7.703
7.699
7.496
7.492
7.478
7.476
7.474
7.472
7.457
7.454
7.389
7.387
7.369
7.366
7.275
7.250
7.247
7.235
7.231
7.229
7.228
7.213
7.210
7.032
7.032
7.013
6.285
2.463
1.485
MeS
O
NHBoc
I
52f
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0.979
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0.876
9.17
0.96
1.96
0.995
1
3.05
ppm

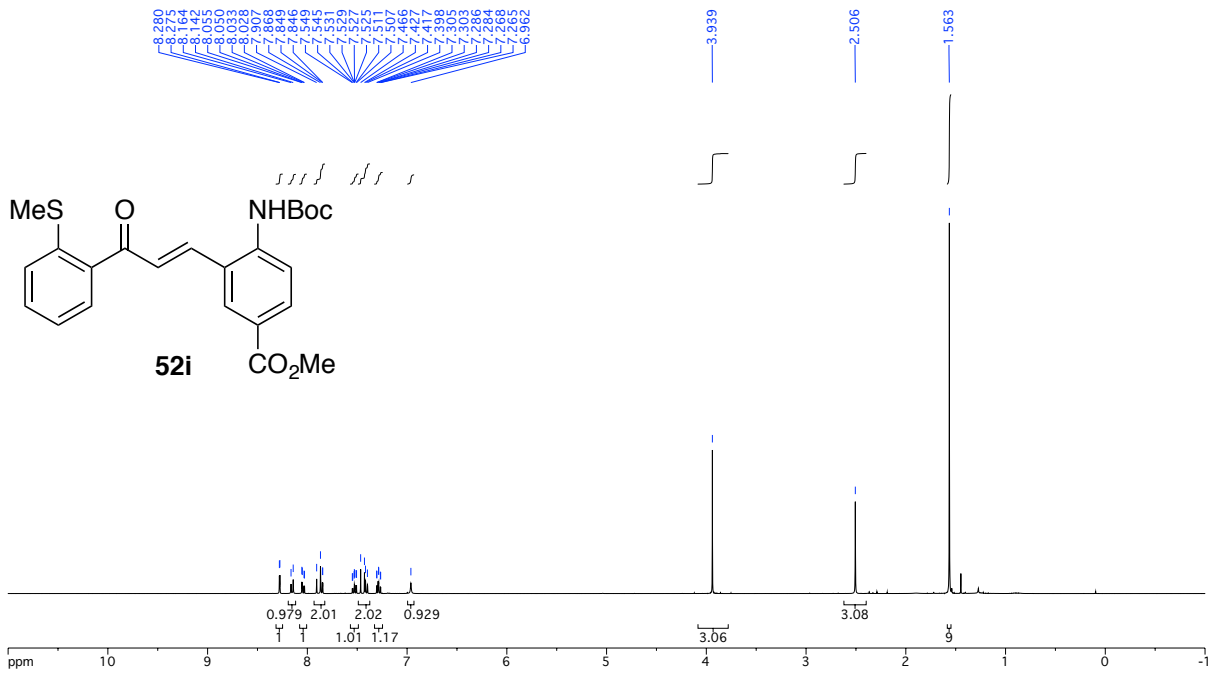

192.614
153.271
141.561
140.566
138.073
136.981
134.381
131.563
129.610
128.644
127.351
126.810
126.305
124.174
100.552
81.222
28.258
16.505
ppm

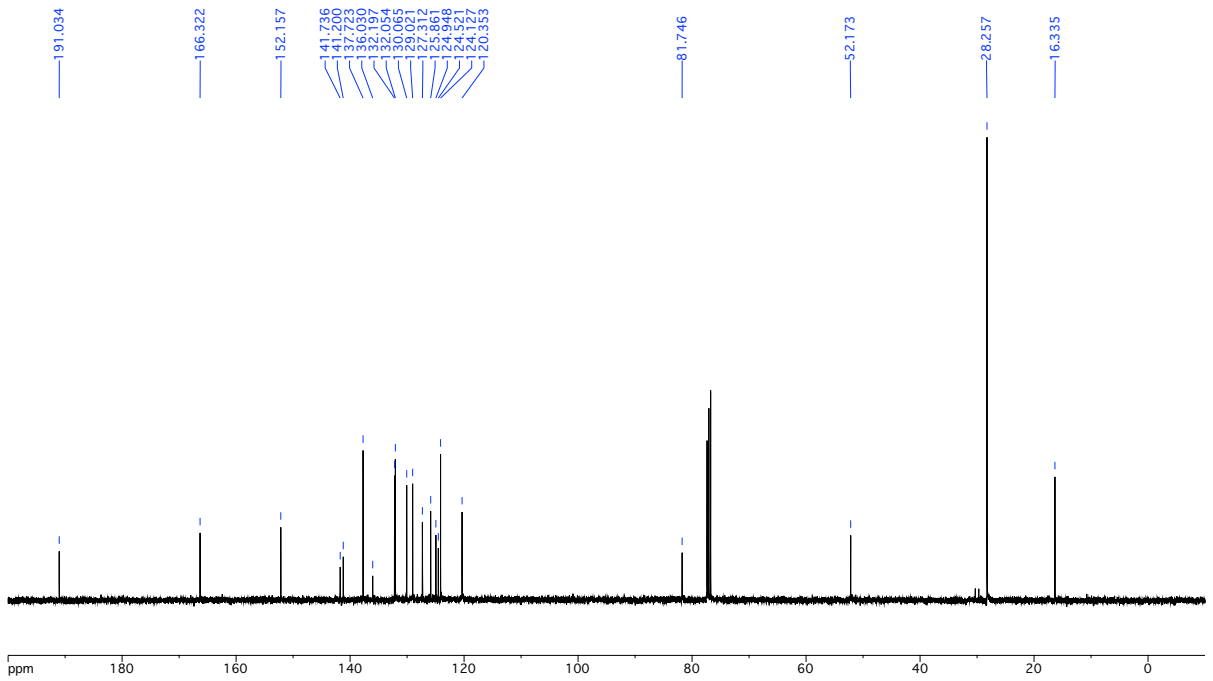

MeS
O
NHBoc
52g
CF3
8.191
8.174
7.896
7.855
7.851
7.838
7.835
7.819
7.815
7.644
7.640
7.627
7.623
7.560
7.557
7.543
7.542
7.541
7.526
7.433
7.422
7.417
7.391
7.317
7.315
7.302
7.300
7.286
6.873
2.520
1.569
3
1.07
0.973
1
1.03
2.01
1.05
2.97
8.75
ppm

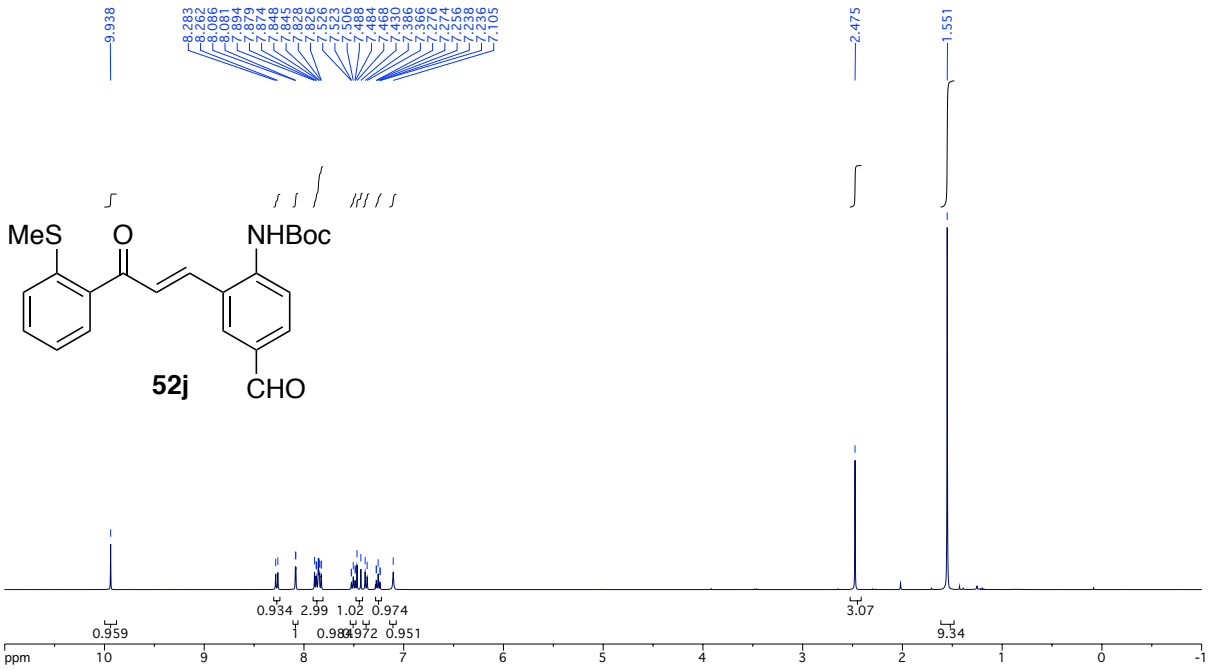

190.925
152.243
141.747
140.059
137.366
135.984
132.301
130.050
129.813
127.561
127.533
127.503
127.142
125.948
125.699
125.474
125.174
125.139
124.983
124.430
124.401
124.370
124.341
122.820
121.235
120.662
81.843
28.264
16.373
ppm

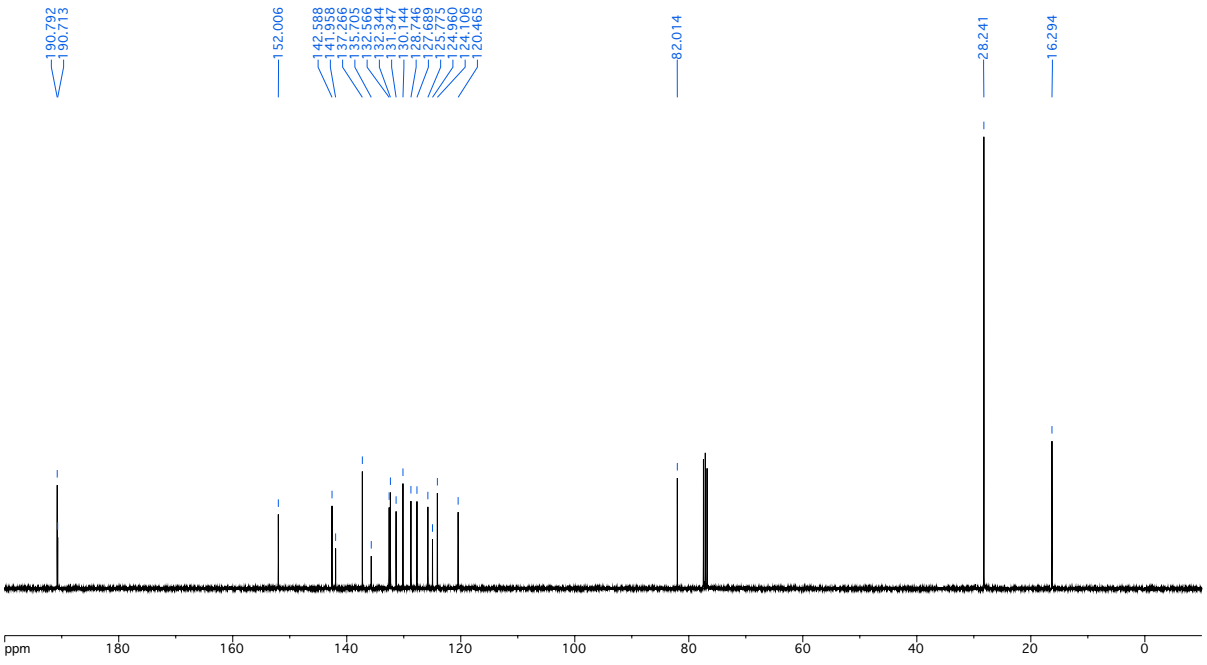

MeS
O
NHBoc
Ac
52h
8.162
8.134
8.112
7.926
7.904
7.865
7.826
7.810
7.791
7.496
7.477
7.458
7.436
7.378
7.360
7.340
7.249
7.230
7.211
7.091
2.585
2.450
1.530
0.968
1.04
1.00
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0.951
0.983
1.04
0.983
1.05
1
3.11
3.08
9.29
ppm

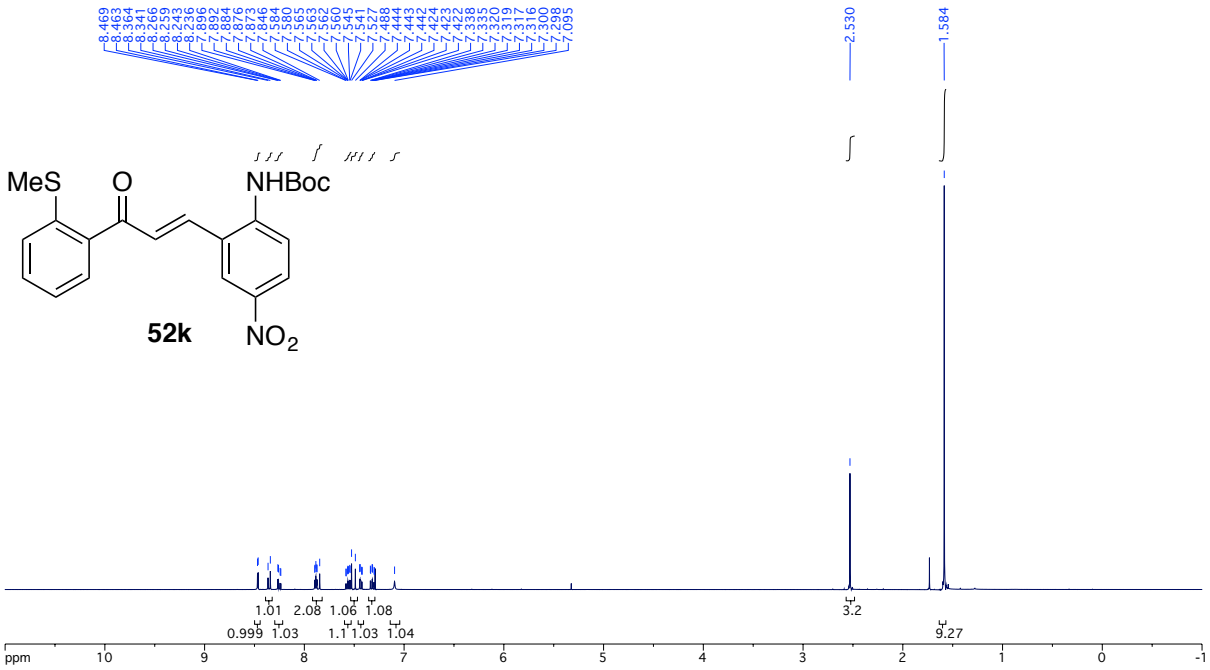

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190.895
152.176
141.779
141.394
137.851
135.818
132.222
132.033
131.130
130.100
127.623
127.274
125.748
124.746
124.079
120.323
81.723
28.249
26.489
16.279
ppm

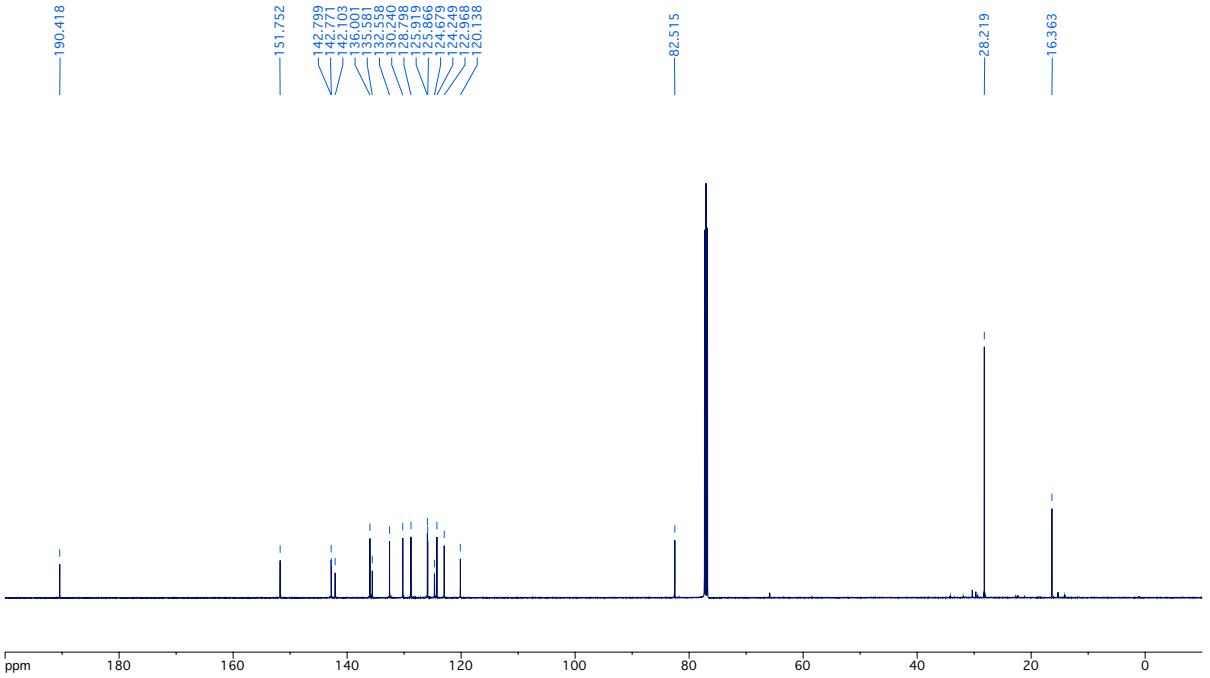

8.280
8.275
8.164
8.142
8.055
8.050
8.033
8.028
7.907
7.868
7.849
7.846
7.549
7.545
7.531
7.529
7.527
7.525
7.511
7.507
7.466
7.427
7.417
7.398
7.305
7.303
7.286
7.284
7.268
7.265
6.962
3.939
2.506
1.563
MeS
O
NHBoc
52i
CO2Me
0.979
2.01
2.02
0.929
1.01
1.17
3.06
3.08
9
ppm

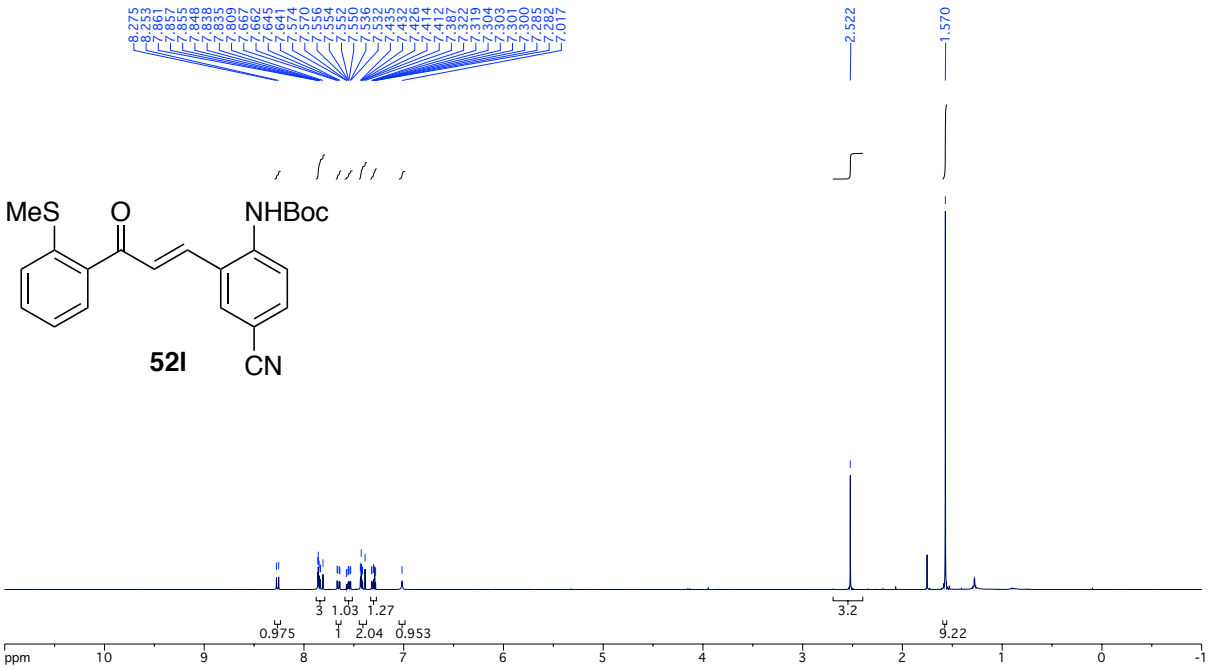

191.034
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141.736
141.200
137.723
136.030
132.197
132.054
130.065
130.021
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125.861
124.948
124.521
124.127
120.353
81.746
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16.335
ppm

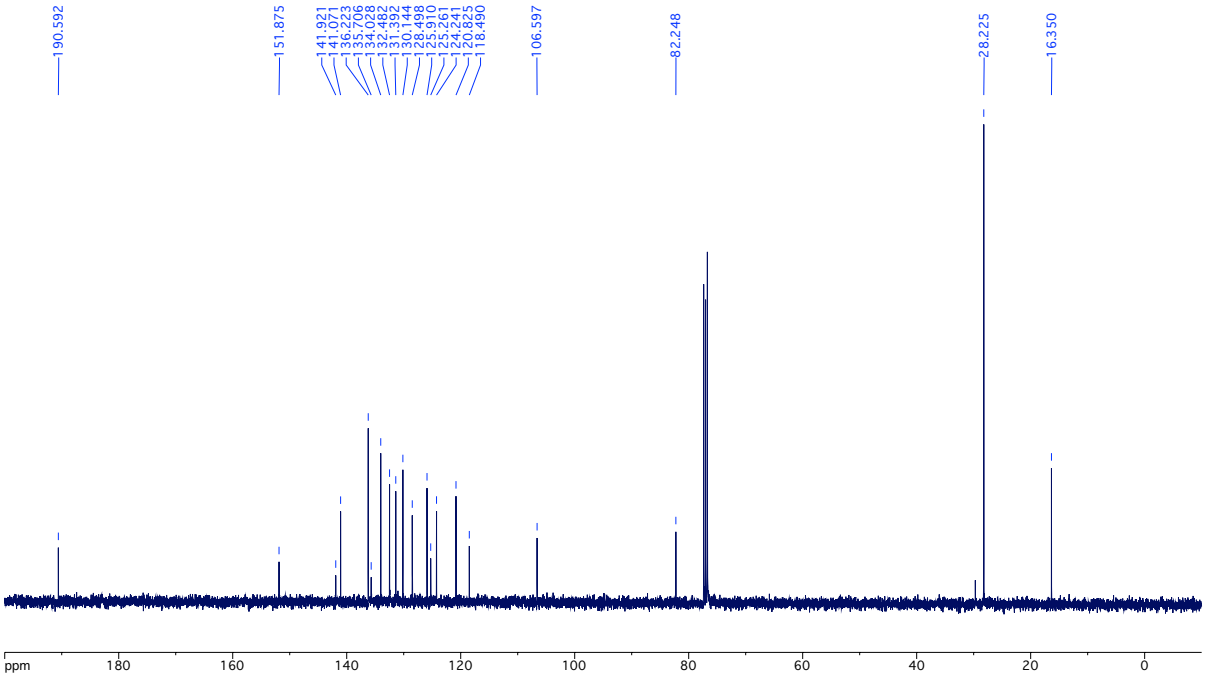

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8.262
8.086
8.081
7.894
7.879
7.874
7.848
7.845
7.828
7.826
7.526
7.523
7.506
7.488
7.484
7.468
7.430
7.386
7.366
7.276
7.274
7.256
7.238
7.236
7.105
2.475
1.551
MeS
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1.02
0.974
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3.07
9.34
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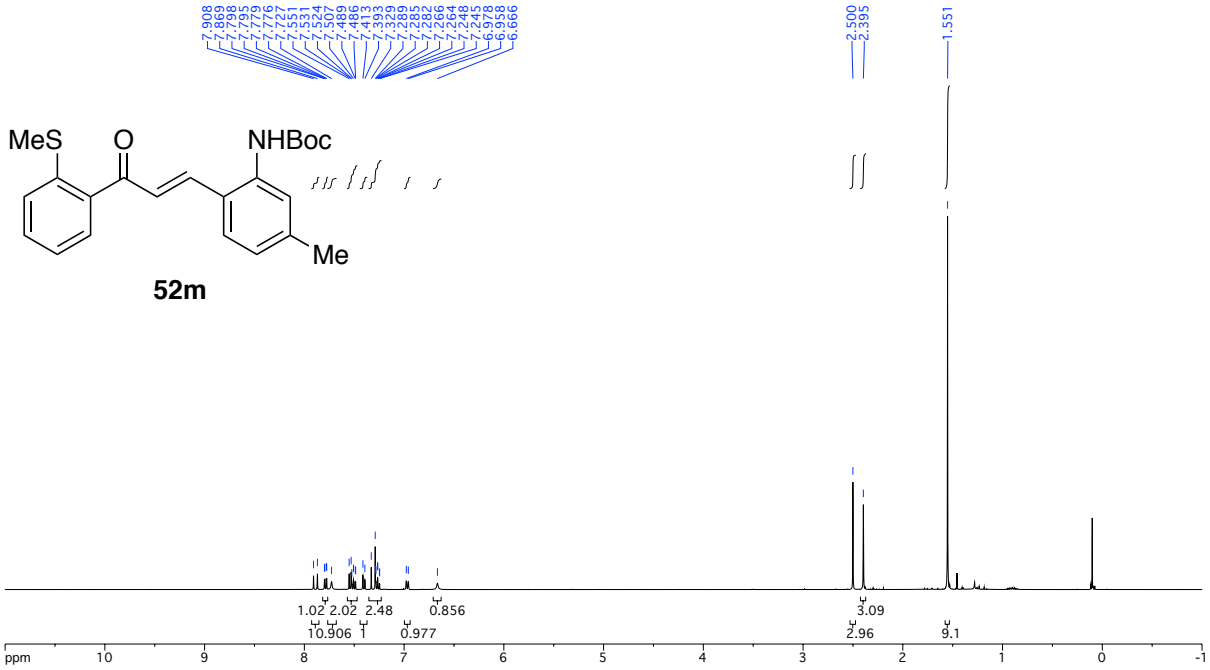

190.792
190.713
152.006
142.588
141.958
137.266
135.705
132.566
132.344
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129.746
129.689
125.775
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120.465
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28.241
16.294
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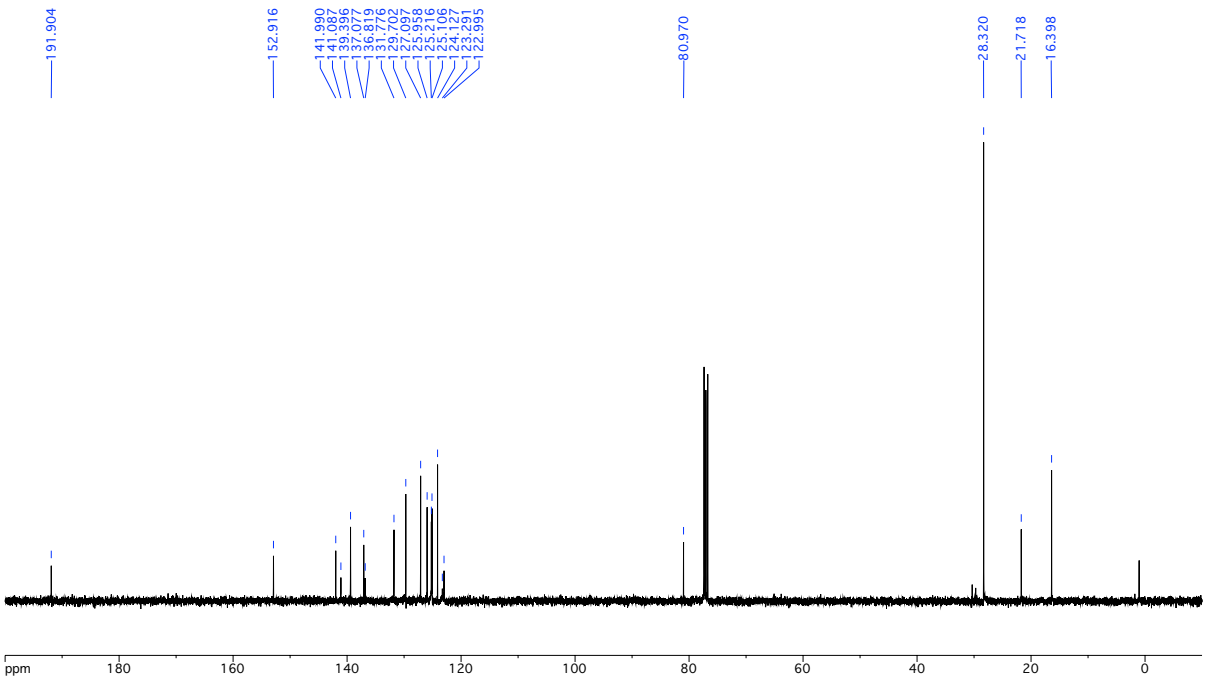

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8.243
8.236
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7.892
7.884
7.876
7.873
7.846
7.584
7.580
7.565
7.563
7.562
7.560
7.545
7.541
7.527
7.488
7.444
7.443
7.432
7.424
7.423
7.422
7.338
7.335
7.320
7.319
7.317
7.316
7.300
7.298
7.095
2.530
1.584
MeS
O
NHBoc
52k
NO2
1.01
2.08
1.06
1.08
0.999
1.03
1.1
1.03
1.04
3.2
9.27
ppm
10
9
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7
6
5
4
3
2
1
0
-1

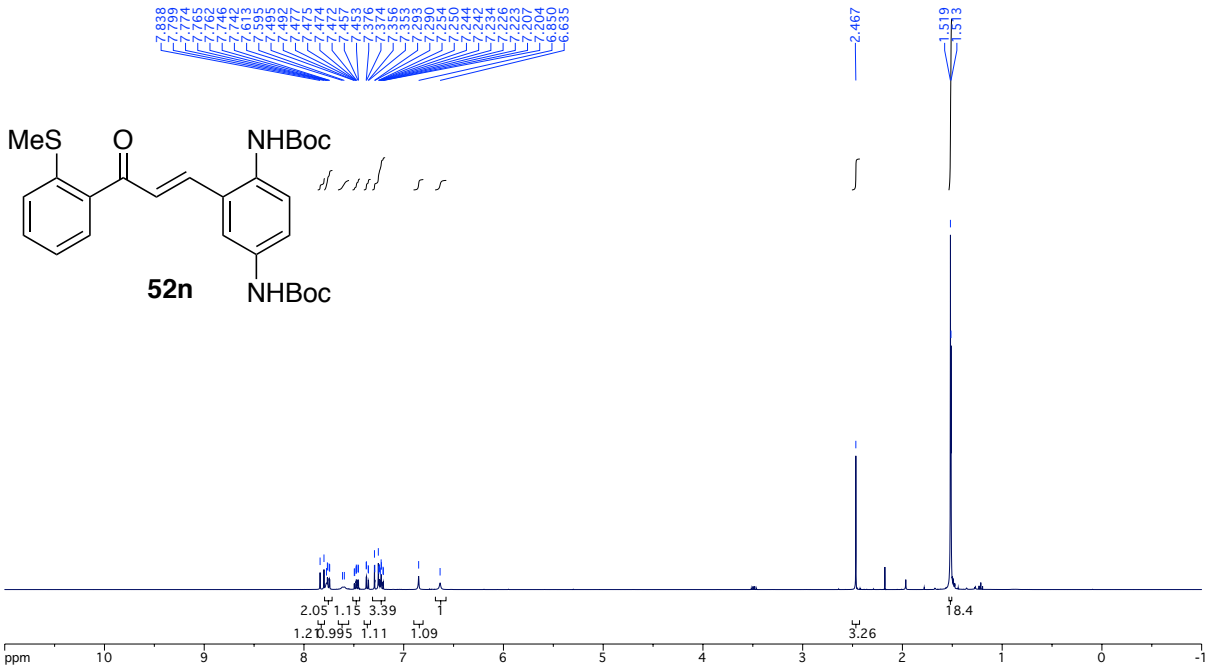

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142.771
142.103
136.001
133.581
133.558
130.240
128.798
125.919
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124.249
122.968
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82.515
28.219
16.363
ppm
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140
120
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60
40
20
0

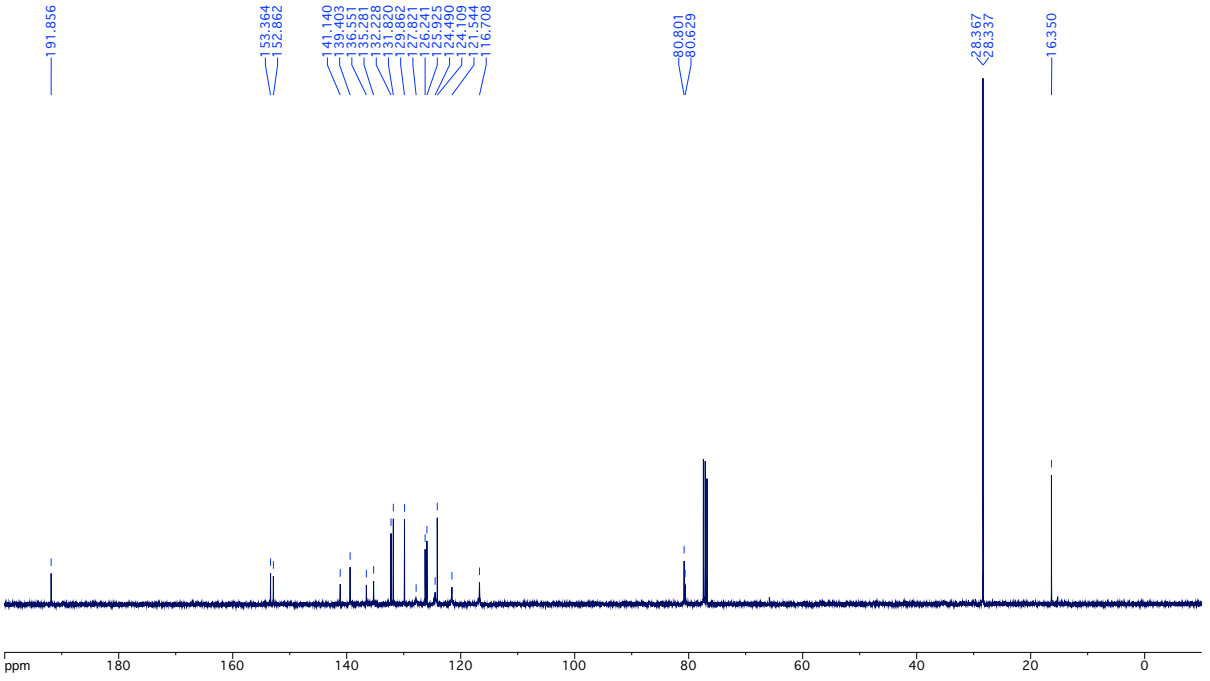

8.275
8.253
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7.848
7.838
7.835
7.809
7.667
7.662
7.645
7.641
7.574
7.570
7.556
7.554
7.550
7.536
7.532
7.435
7.432
7.426
7.414
7.412
7.387
7.322
7.319
7.304
7.303
7.301
7.300
7.285
7.282
7.017
2.522
1.570
MeS
O
NHBoc
CN
52l
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1
2.04
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3.2
9.22
ppm

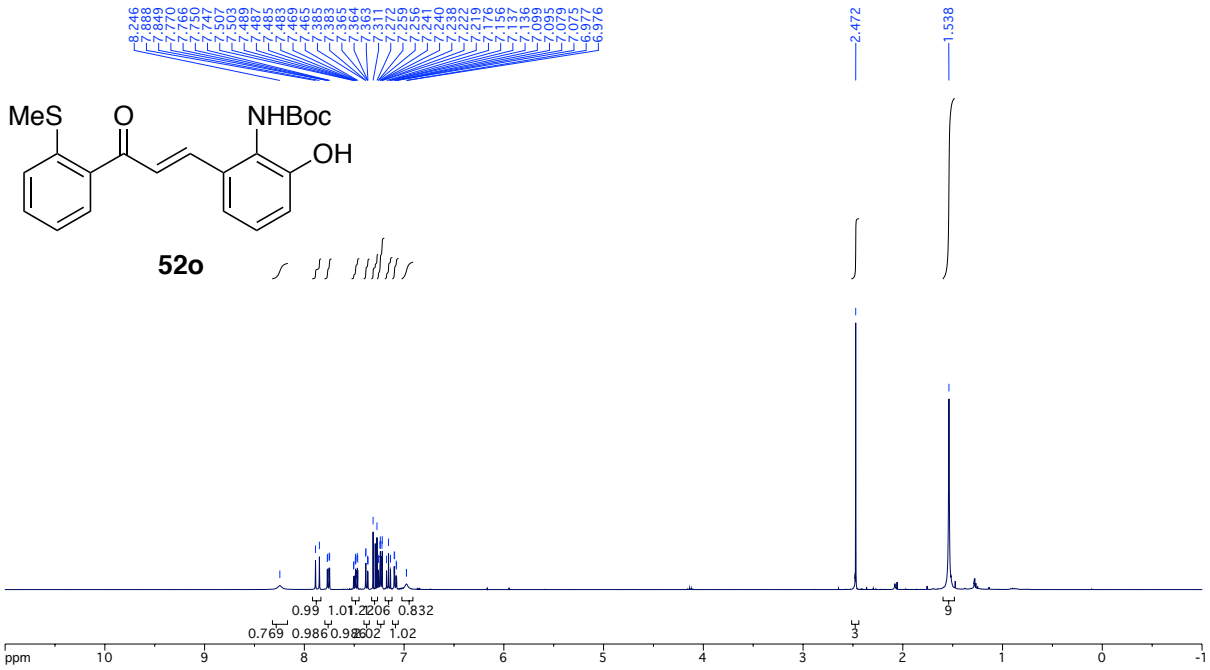

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135.706
134.028
132.482
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125.910
124.261
124.241
120.825
118.490
106.597
82.248
28.225
16.350
ppm

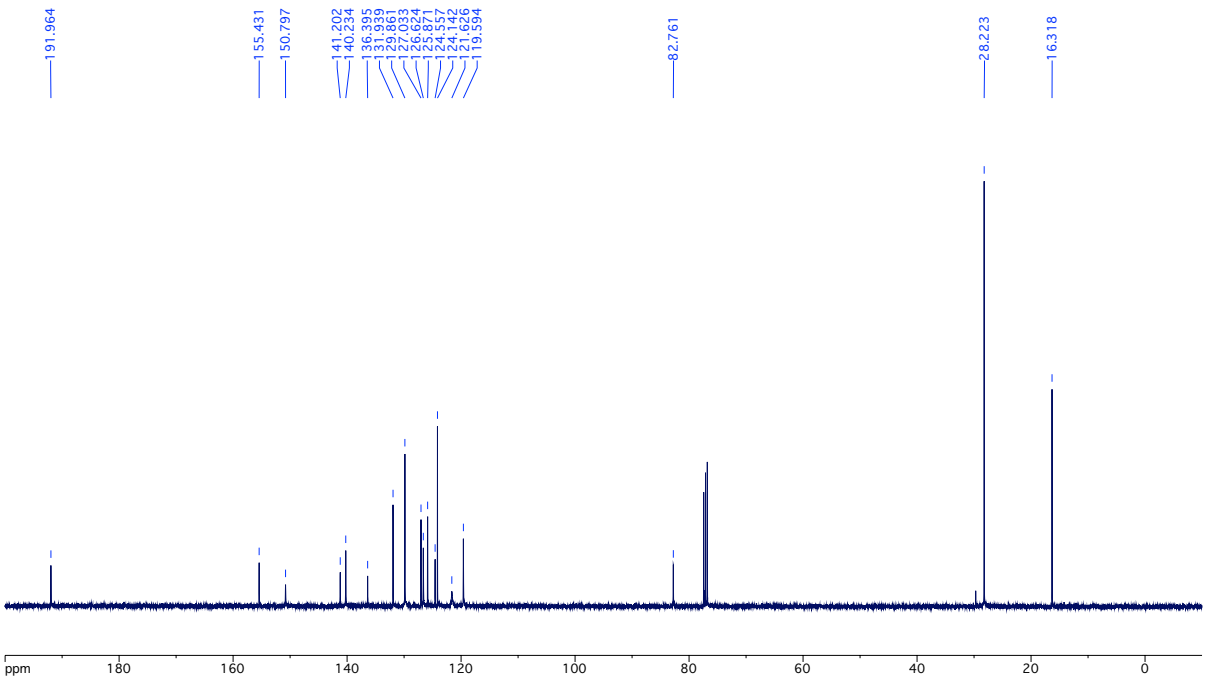

MeS
O
NHBoc
Me
52m
7.908
7.869
7.798
7.795
7.779
7.776
7.551
7.531
7.524
7.507
7.489
7.486
7.413
7.393
7.323
7.289
7.285
7.282
7.266
7.264
7.248
7.245
6.978
6.958
6.666
2.500
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2.02
2.48
0.856
0.906
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0.977
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9.1
ppm

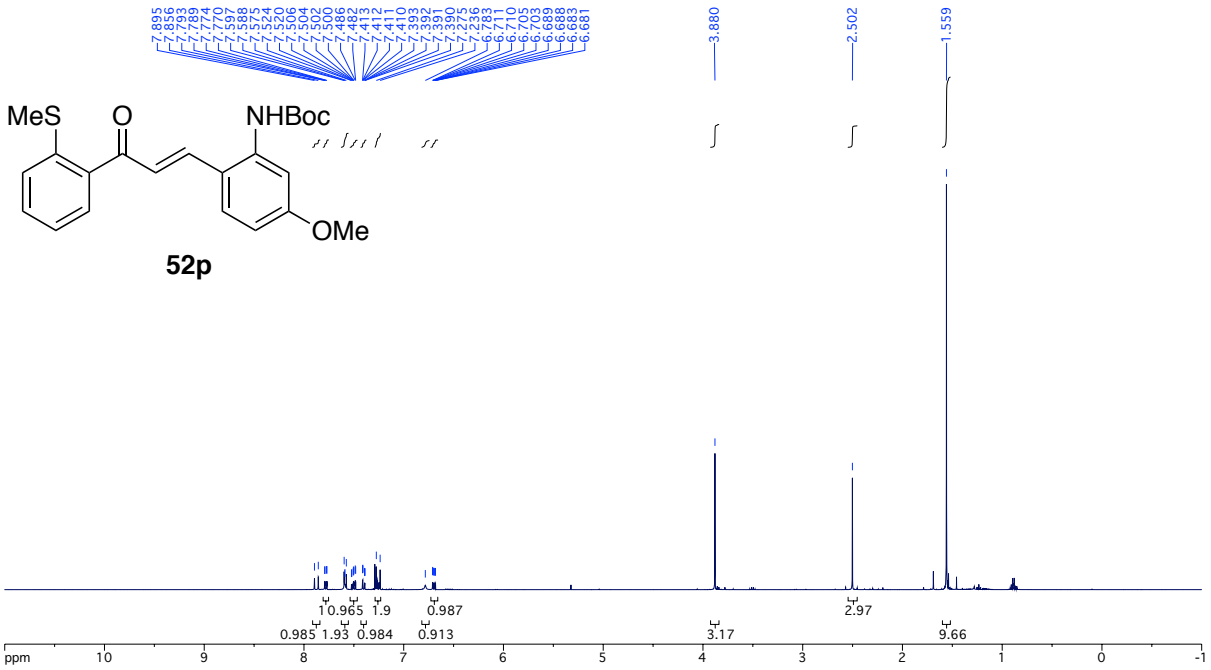

191.904
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141.087
139.396
137.077
136.819
131.776
131.702
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125.216
125.106
124.127
123.291
122.995
80.970
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16.398
ppm

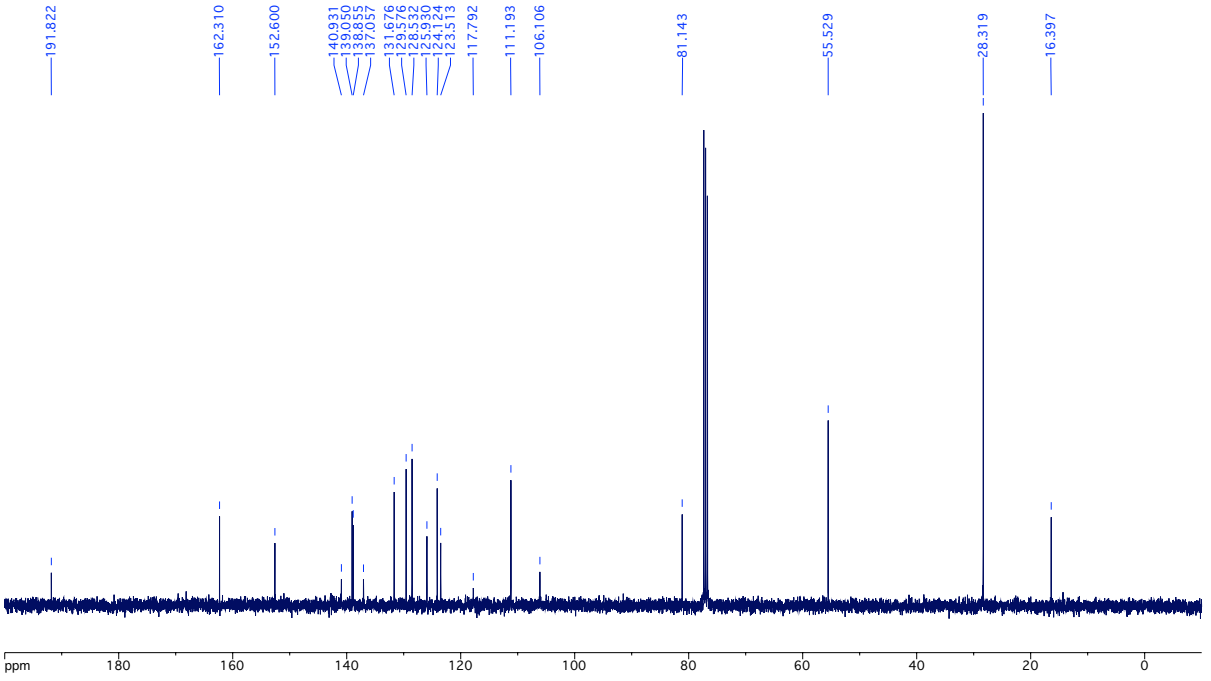

7.838
7.799
7.774
7.765
7.762
7.746
7.742
7.613
7.595
7.495
7.492
7.477
7.475
7.474
7.472
7.457
7.453
7.376
7.374
7.356
7.353
7.293
7.290
7.254
7.250
7.244
7.242
7.234
7.226
7.223
7.207
7.204
6.850
6.635
2.467
1.519
1.513
MeS
O
NHBoc
NHBoc
52n
2.05
1.15
3.39
1
18.4
1.2
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1.11
1.09
3.26
ppm
10
9
8
7
6
5
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3
2
1
0
-1

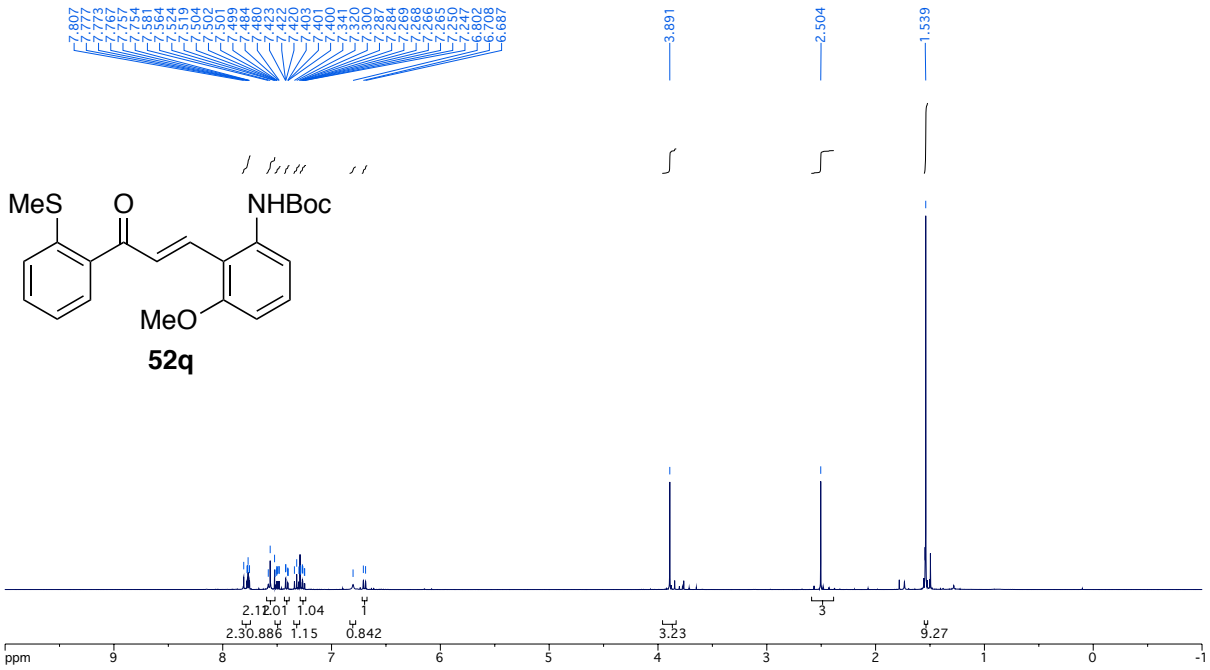

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139.403
136.551
135.281
132.228
131.820
130.862
127.821
126.241
125.925
124.490
124.109
121.544
116.708
80.801
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28.367
28.337
16.350
ppm
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140
120
100
80
60
40
20
0

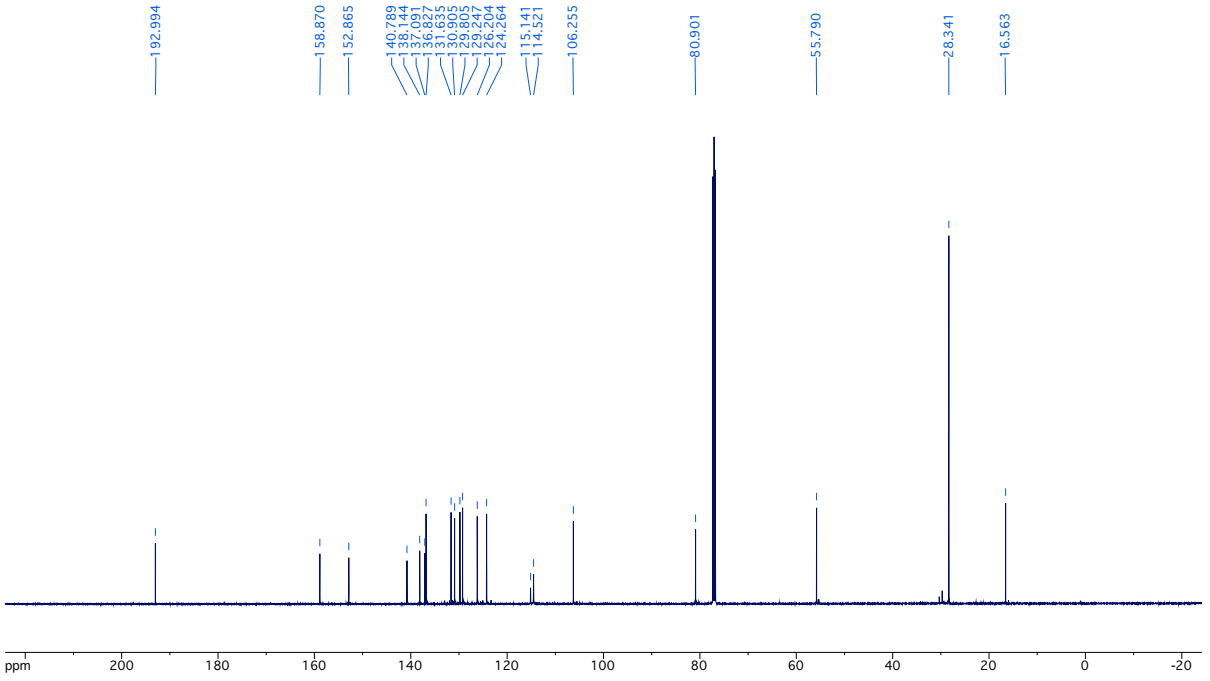

MeS
O
NHBoc
OH
52o
2.472
1.538
ppm

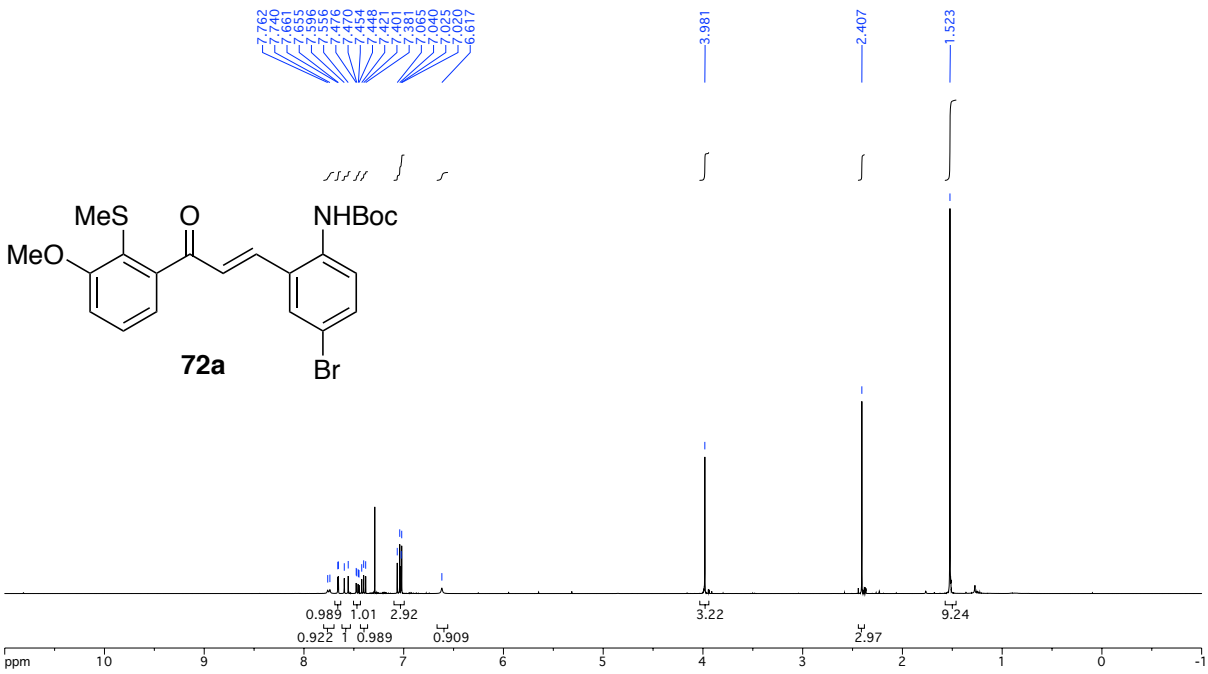

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140.234
136.395
130.339
129.861
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126.624
125.871
124.557
124.142
121.626
119.594
82.761
28.223
16.318
ppm

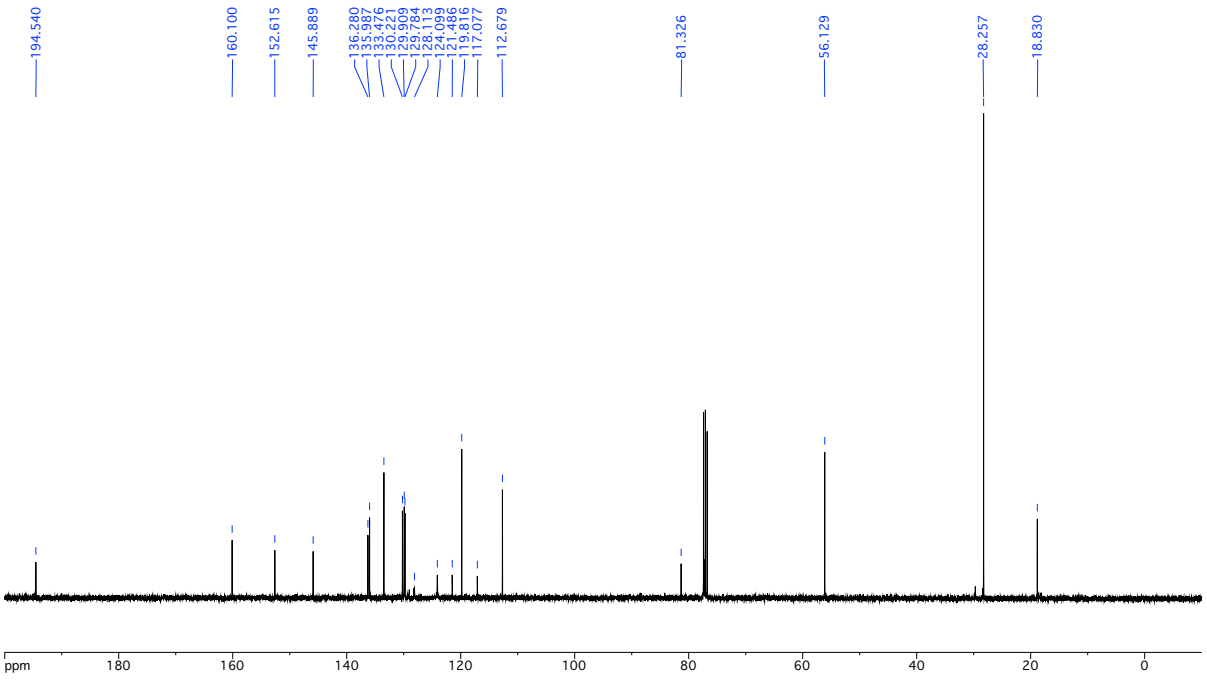

MeS
O
NHBoc
OMe
52p
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7.856
7.793
7.789
7.774
7.770
7.597
7.588
7.575
7.524
7.520
7.506
7.504
7.502
7.500
7.486
7.482
7.413
7.412
7.411
7.410
7.393
7.392
7.391
7.390
7.275
7.236
6.733
6.711
6.710
6.705
6.703
6.689
6.688
6.683
6.681
3.880
2.502
1.559
10.965
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0.987
0.985
1.93
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9.66
ppm

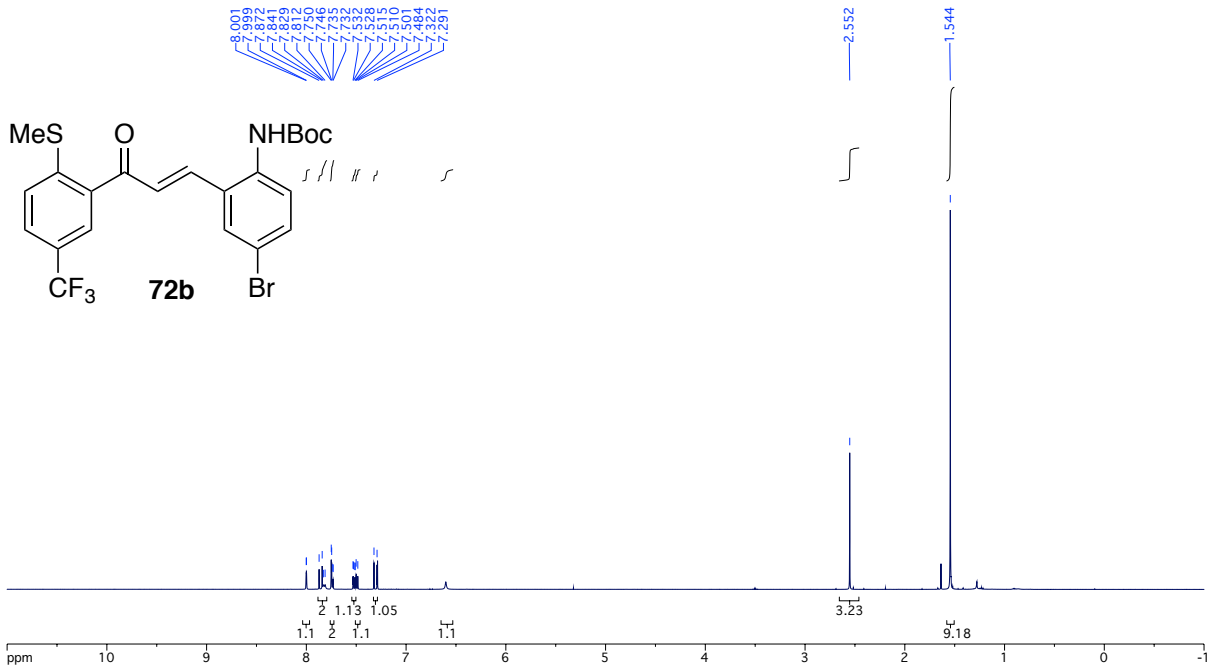

191.822
162.310
152.600
140.931
138.550
138.855
137.057
131.676
131.576
128.532
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124.124
123.513
117.792
111.193
106.106
81.143
55.529
28.319
16.397
ppm

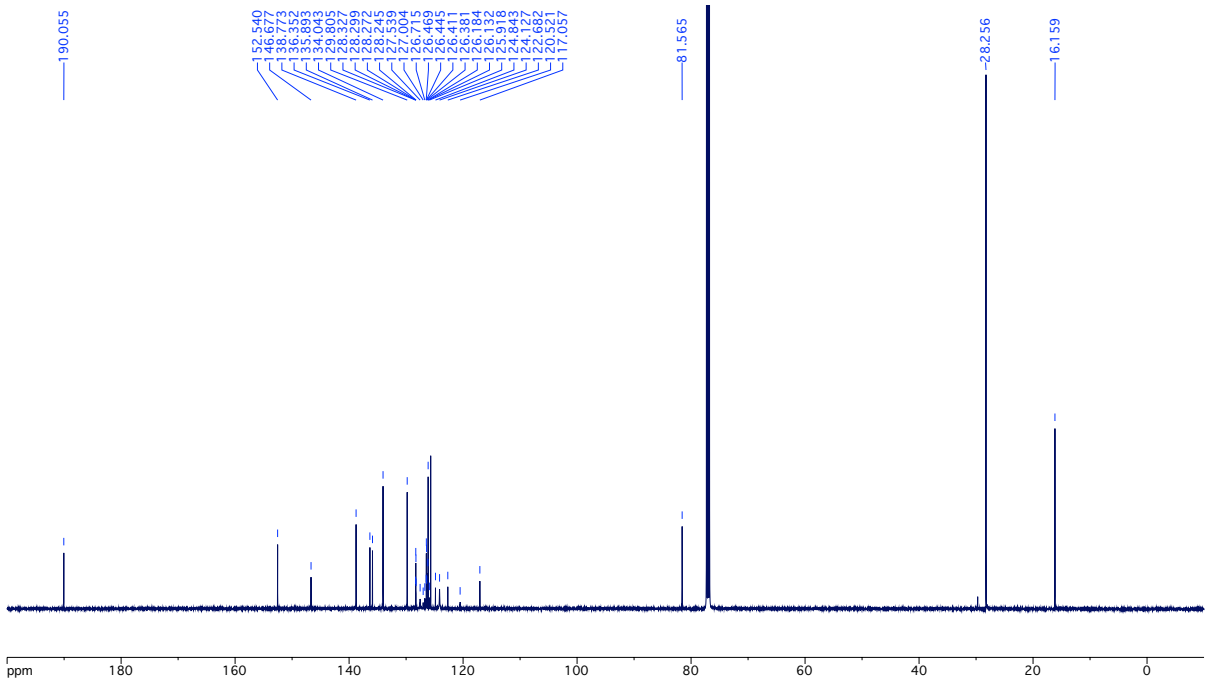

MeS
O
NHBoc
MeO
52q
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7.773
7.767
7.757
7.754
7.581
7.564
7.524
7.519
7.504
7.502
7.501
7.499
7.484
7.480
7.423
7.422
7.420
7.403
7.401
7.400
7.341
7.320
7.300
7.287
7.284
7.269
7.268
7.266
7.265
7.250
7.247
6.802
6.708
6.687
3.891
2.504
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2.01
1.04
1
2.30
0.886
1.15
0.842
3.23
3
9.27
ppm

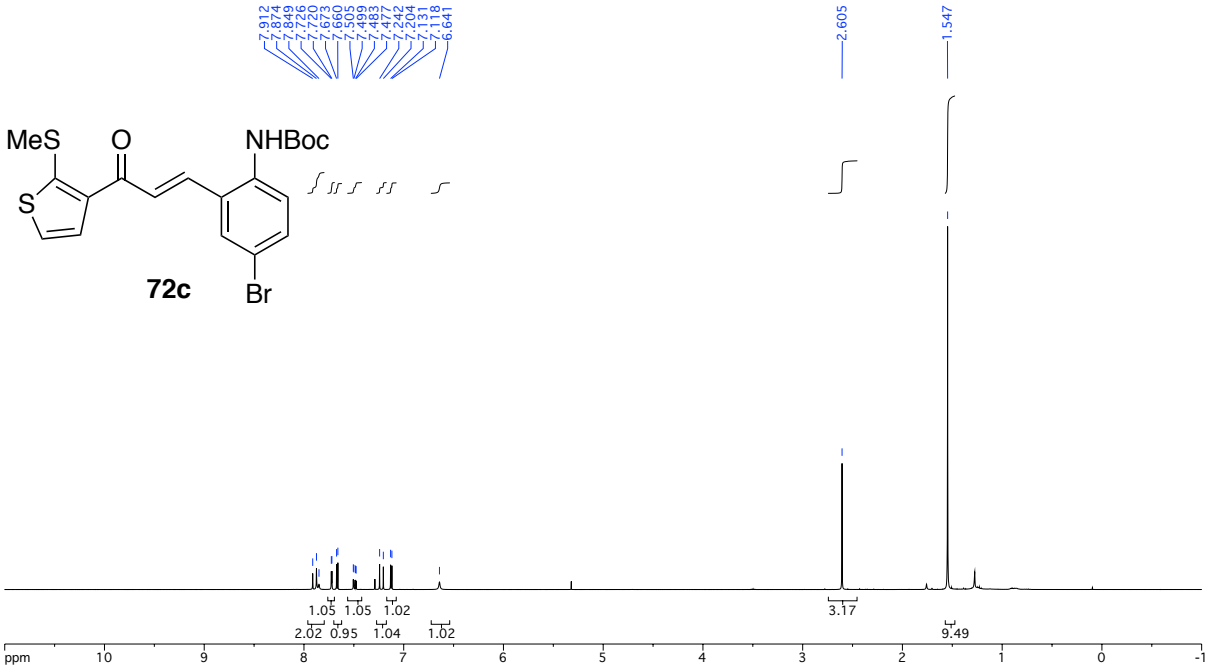

192.994
158.870
152.865
140.789
138.144
137.091
136.827
131.635
130.905
128.805
128.247
126.204
124.264
115.141
114.521
106.255
80.901
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28.341
16.563
ppm

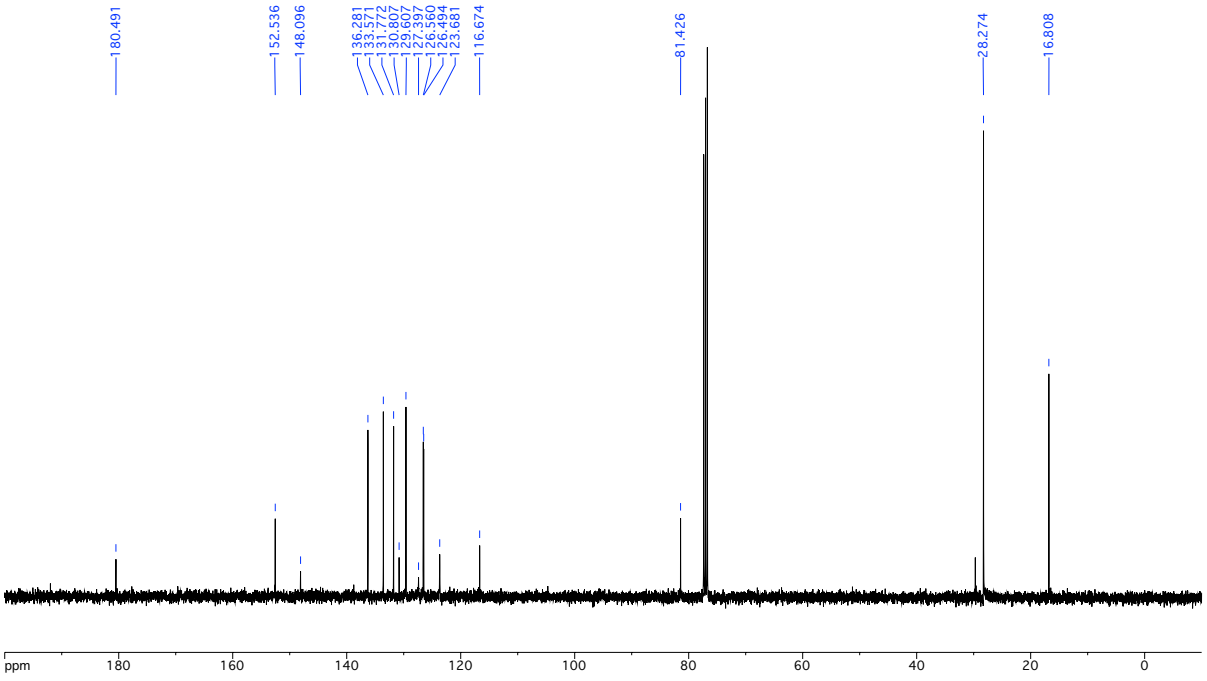

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7.740
7.661
7.655
7.596
7.556
7.476
7.470
7.454
7.448
7.421
7.401
7.381
7.065
7.040
7.025
7.020
6.617
3.981
2.407
1.523
MeS
O
NHBoc
MeO
Br
72a
0.989
1.01
2.92
0.922
1
0.989
0.909
3.22
2.97
9.24
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

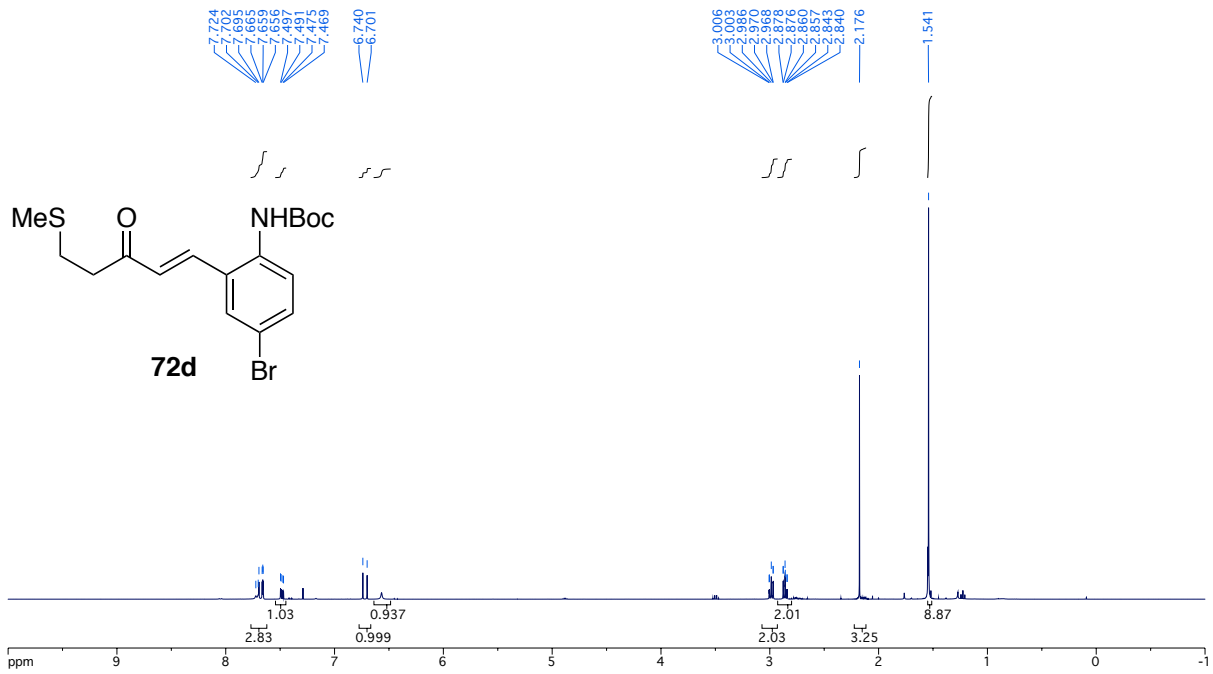

194.540
160.100
152.615
145.889
136.280
135.987
133.476
130.221
129.909
129.784
128.113
124.099
121.486
119.816
117.077
112.679
81.326
56.129
28.257
18.830
ppm
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140
120
100
80
60
40
20
0

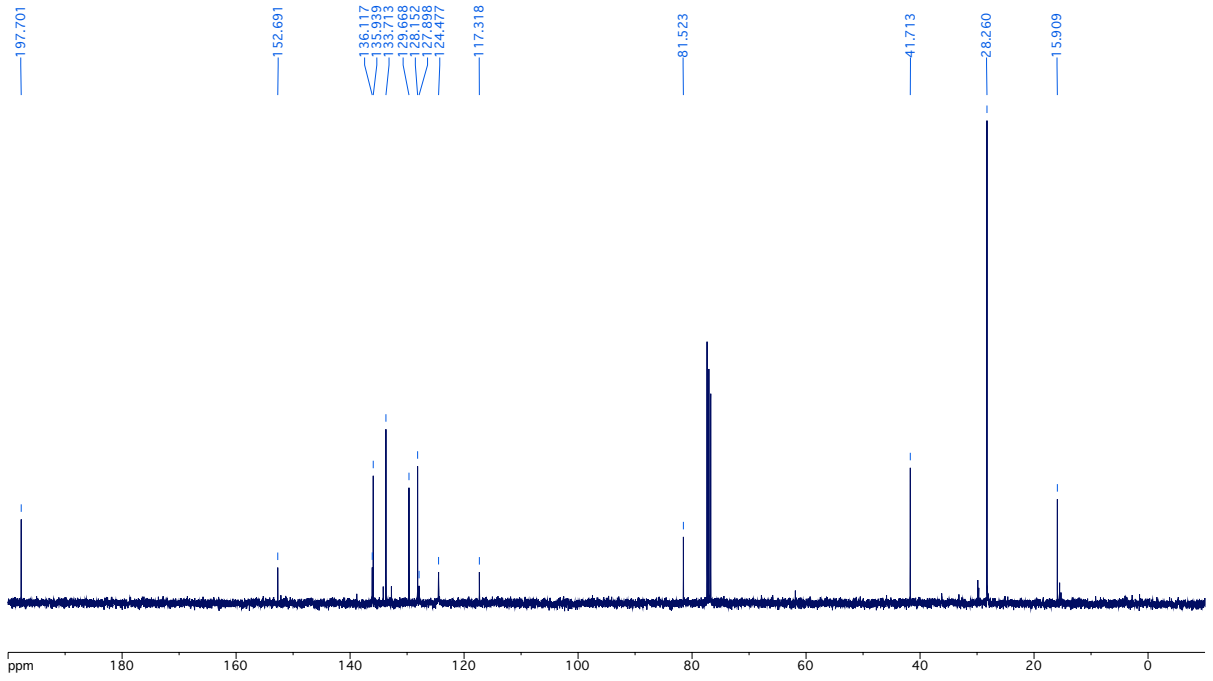

8.001
7.999
7.872
7.841
7.819
7.812
7.750
7.746
7.735
7.732
7.532
7.528
7.515
7.510
7.501
7.484
7.322
7.291
2.552
1.544
MeS
O
NHBoc
CF3
72b
Br
2
1.13
1.05
1.1
2
1.1
1.1
3.23
9.18
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

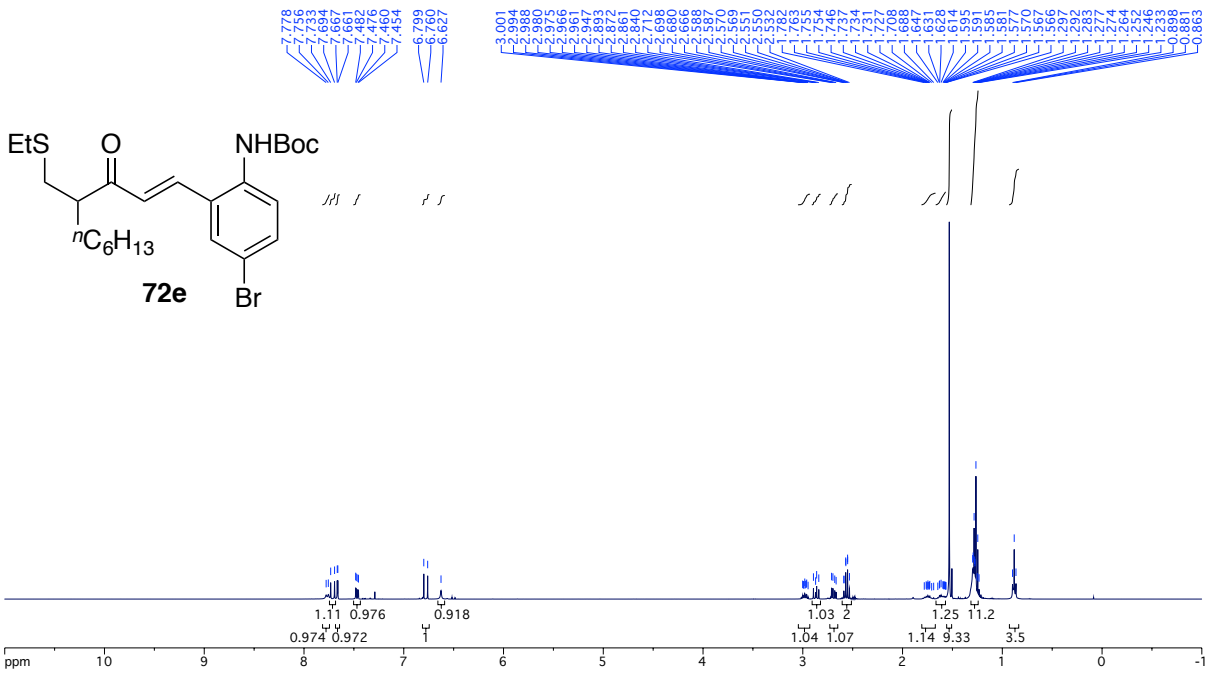

190.055
152.540
146.677
138.773
136.352
135.893
134.043
129.805
128.327
128.299
128.272
128.245
127.539
127.004
126.715
126.469
126.445
126.411
126.381
126.184
126.132
125.918
124.843
124.127
122.682
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81.565
28.256
16.159
ppm
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140
120
100
80
60
40
20
0

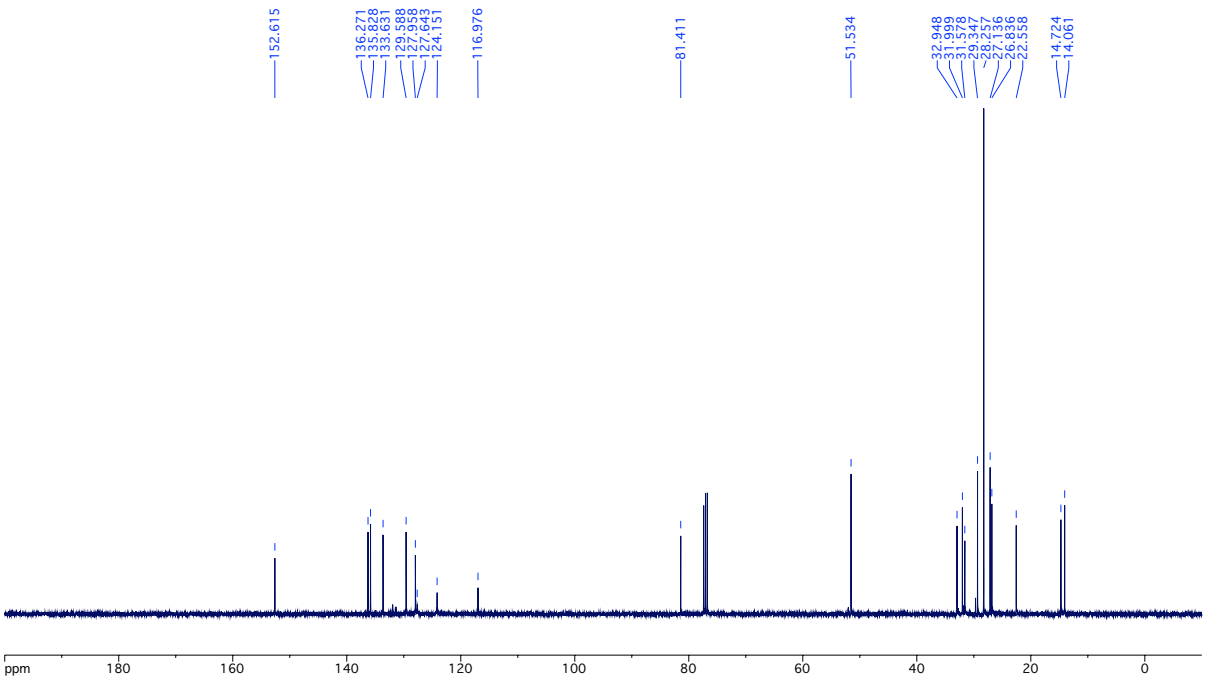

7.912
7.874
7.849
7.726
7.720
7.673
7.660
7.505
7.499
7.483
7.473
7.242
7.204
7.131
7.118
6.641
2.605
1.547
MeS
O
NHBoc
S
Br
72c
1.05
1.05
1.02
2.02
0.95
1.04
1.02
3.17
9.49
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

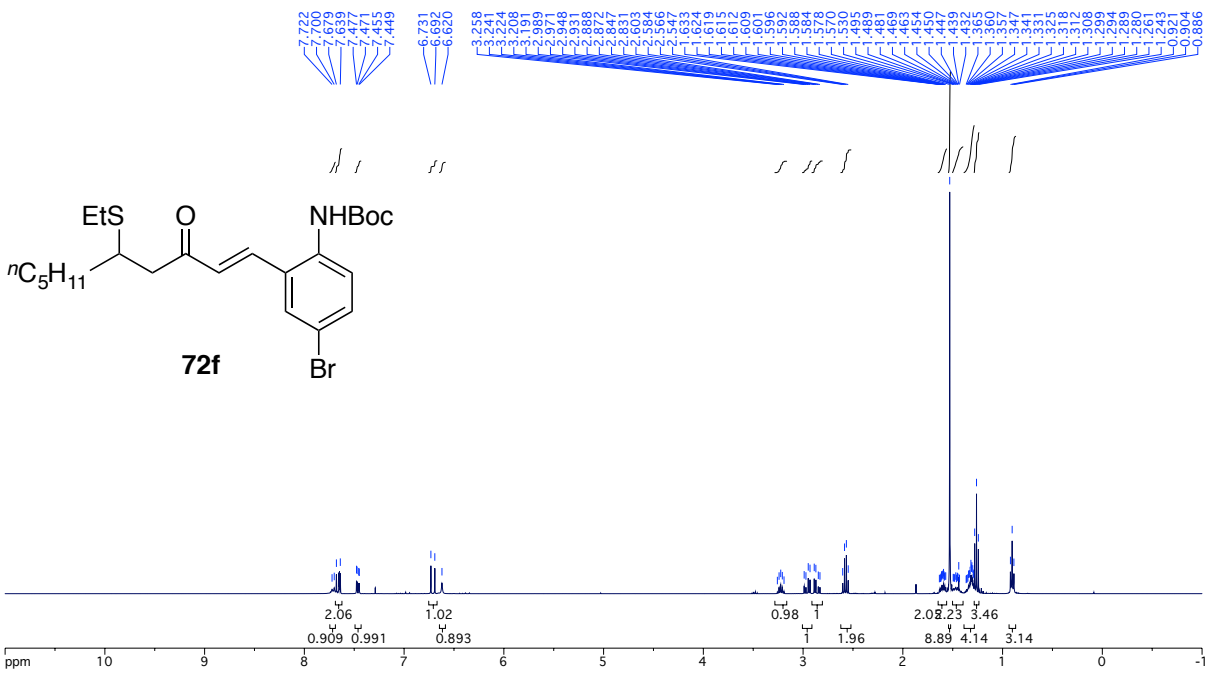

180.491
152.536
148.096
136.281
133.571
131.772
130.807
129.607
127.397
126.960
126.494
123.681
116.674
81.426
28.274
16.808
ppm
180
160
140
120
100
80
60
40
20
0

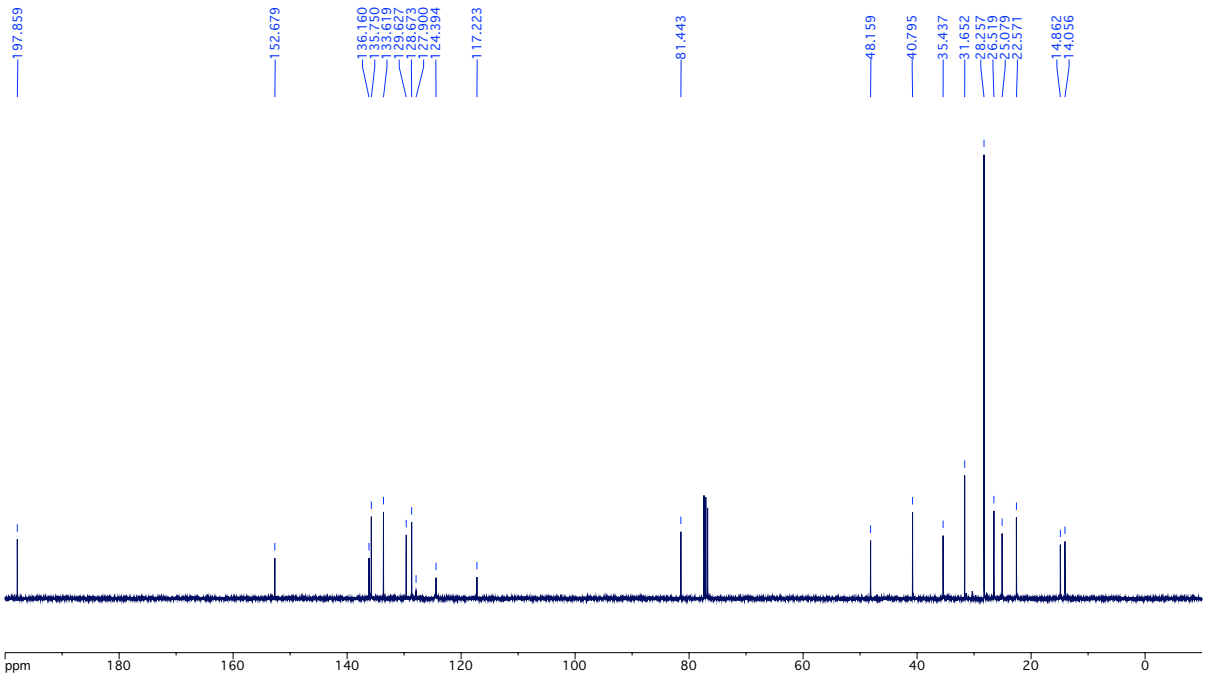

7.724
7.702
7.695
7.665
7.659
7.656
7.497
7.491
7.471
7.469
6.740
6.701
3.006
3.003
2.986
2.970
2.968
2.878
2.876
2.860
2.857
2.843
2.840
2.176
1.541
MeS
O
NHBoc
Br
72d
1.03
0.937
2.01
8.87
2.83
0.999
2.03
3.25
ppm

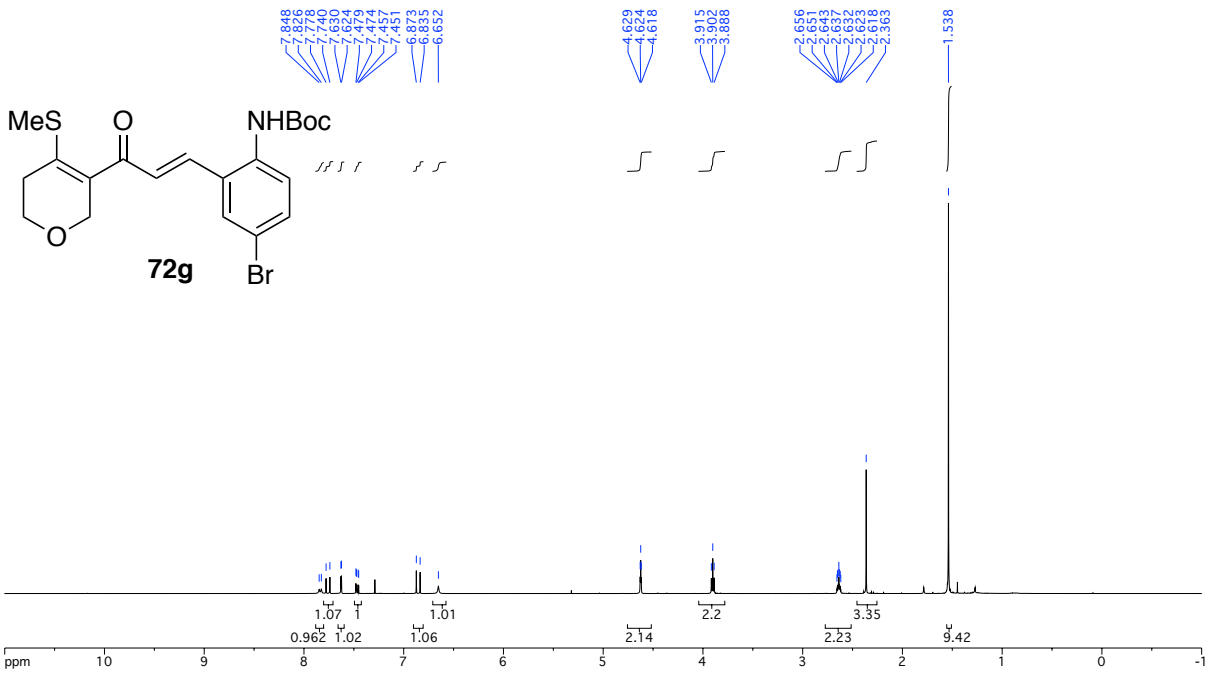

197.701
152.691
136.117
135.939
133.713
129.668
128.152
127.698
124.477
117.318
81.523
41.713
28.260
15.909
ppm

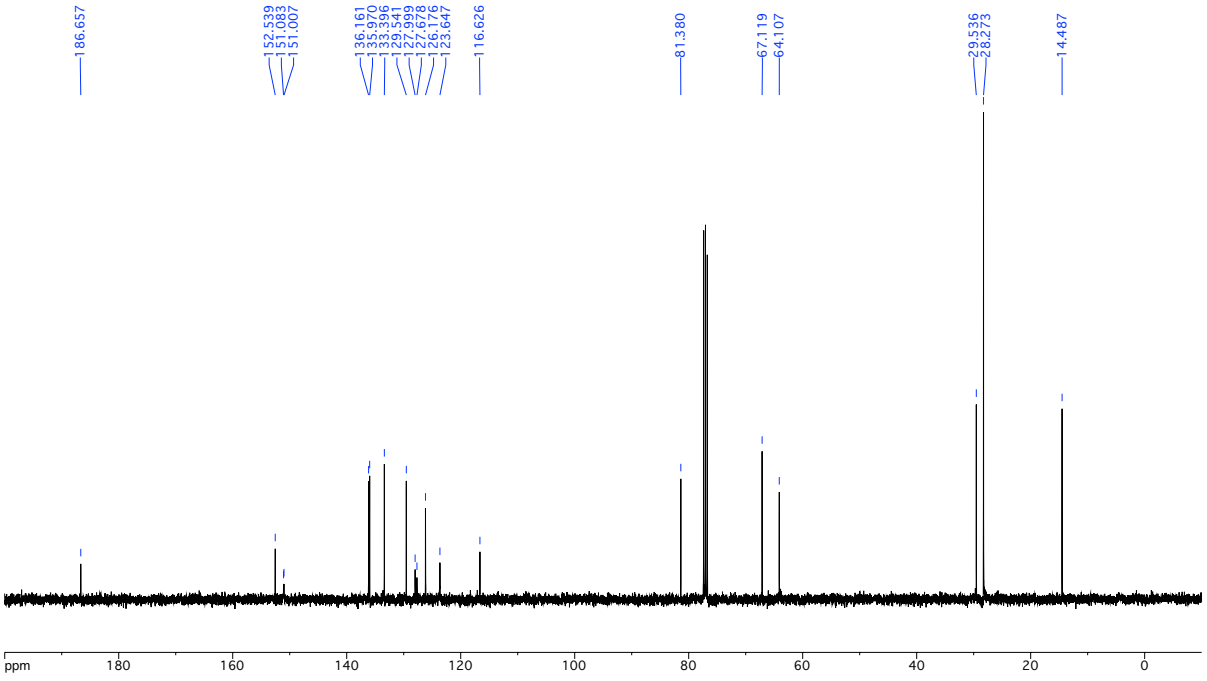

EtS
O
NHBoc
$^{n}C_6H_{13}$
Br
72e
ppm

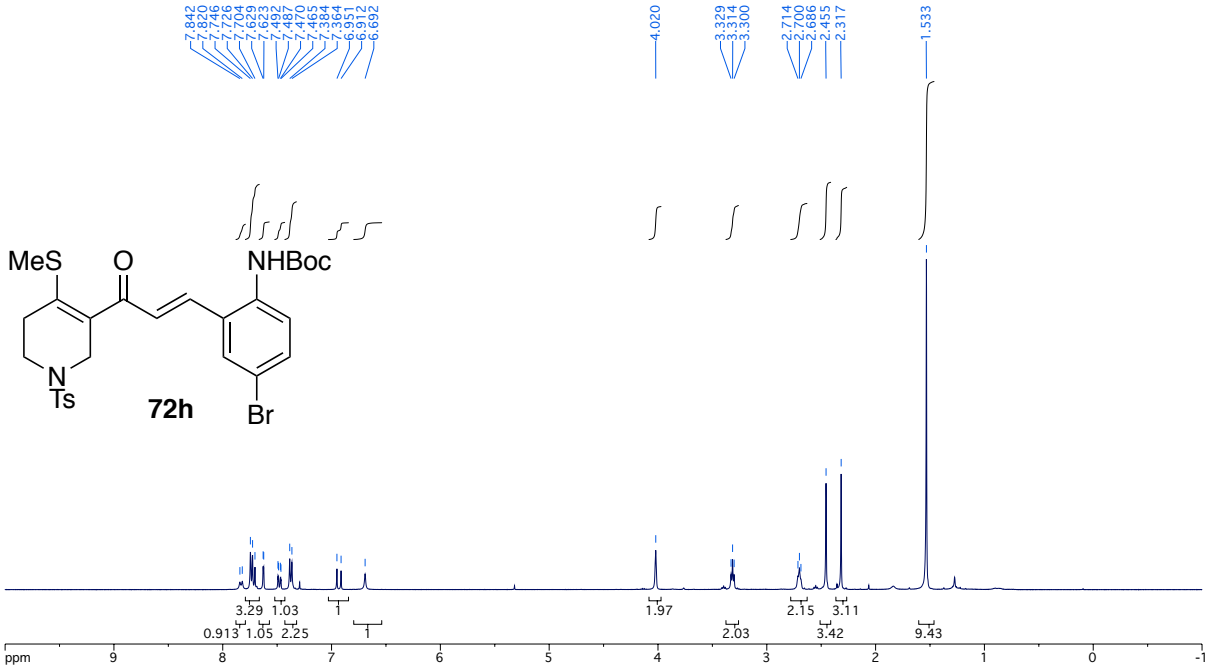

ppm

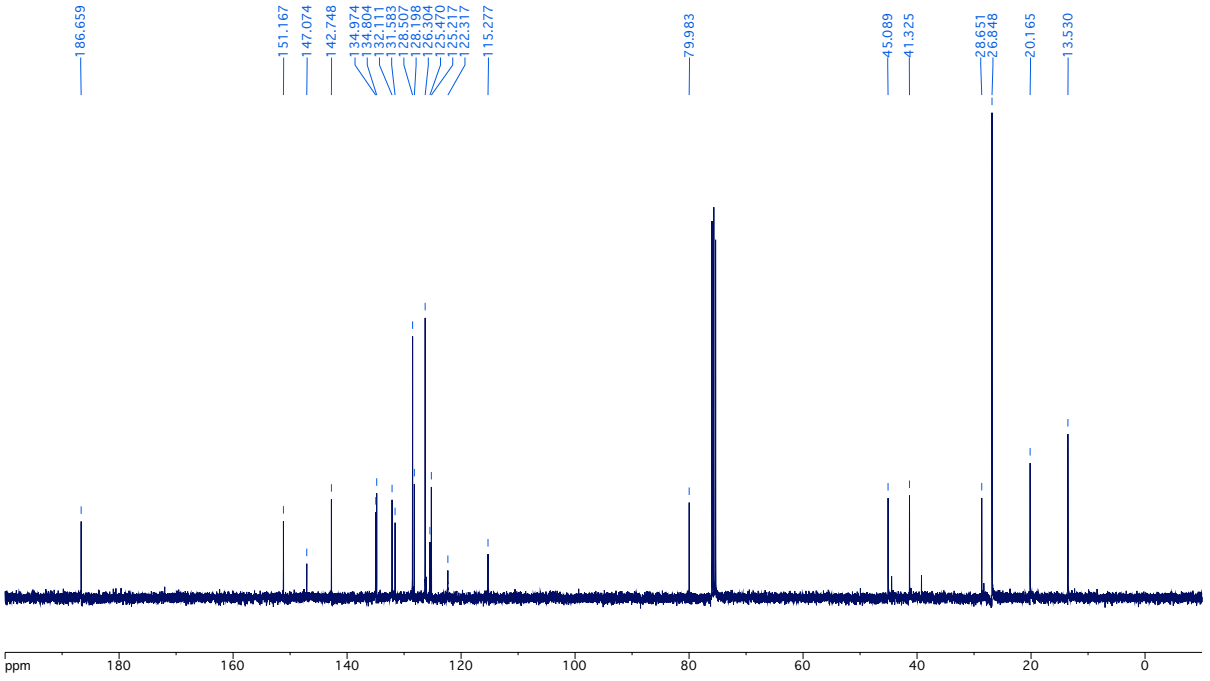

EtS
O
NHBoc
$^{n}C_5H_{11}$
Br
72f
ppm

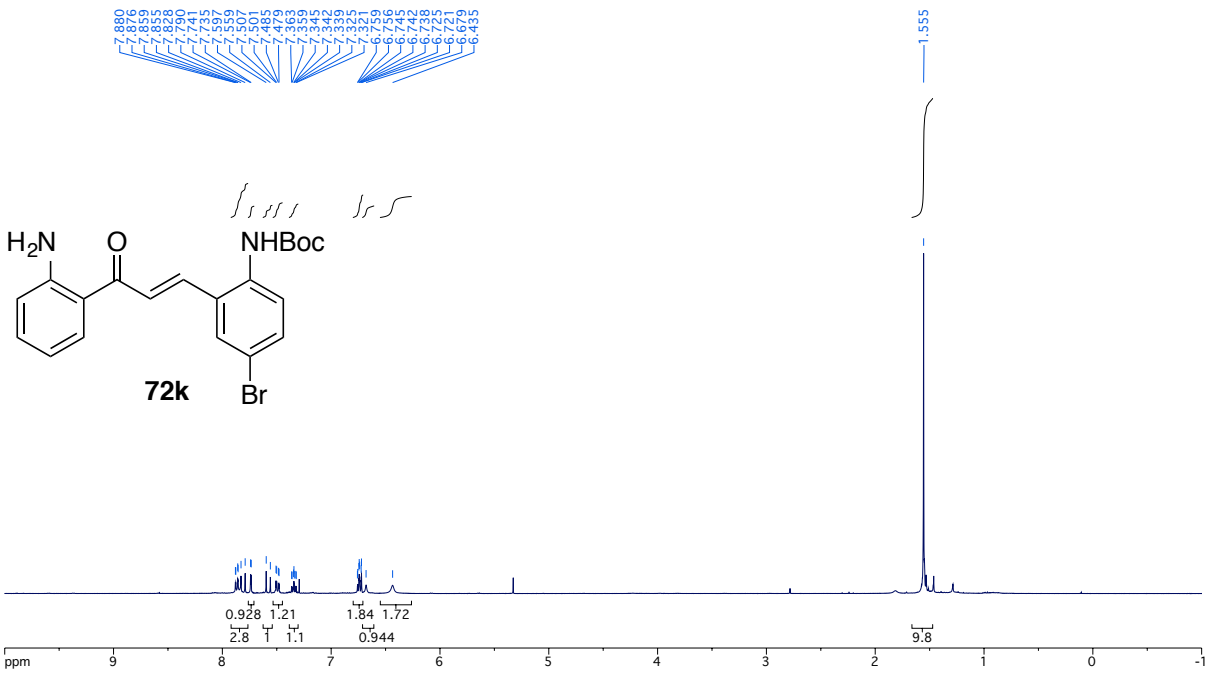

ppm

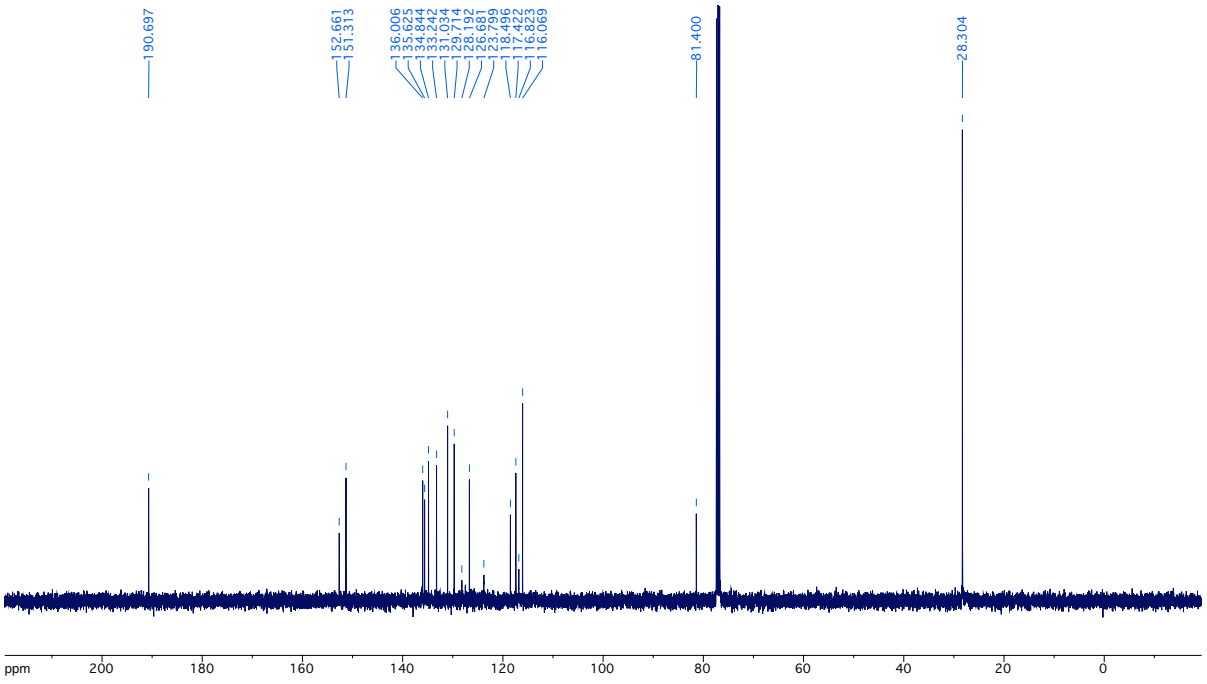

MeS
O
NHBoc
O
Br
72g
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7.826
7.778
7.740
7.630
7.624
7.479
7.474
7.457
7.451
6.873
6.835
6.652
4.629
4.624
4.618
3.915
3.902
3.888
2.656
2.651
2.643
2.637
2.632
2.623
2.618
2.363
1.538
1.07
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1.01
2.2
3.35
0.962
1.02
1.06
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2.23
9.42
ppm

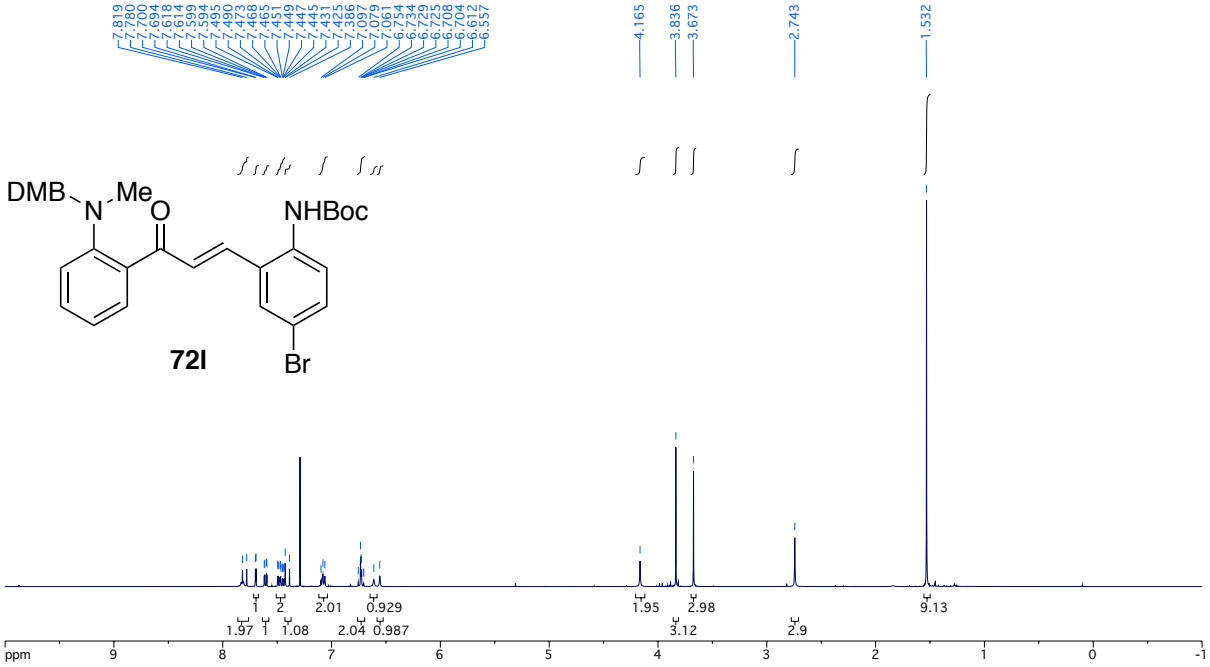

186.657
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151.083
151.007
136.161
135.970
133.396
129.541
127.999
127.678
126.176
123.647
116.626
81.380
67.119
64.107
29.536
28.273
14.487
ppm

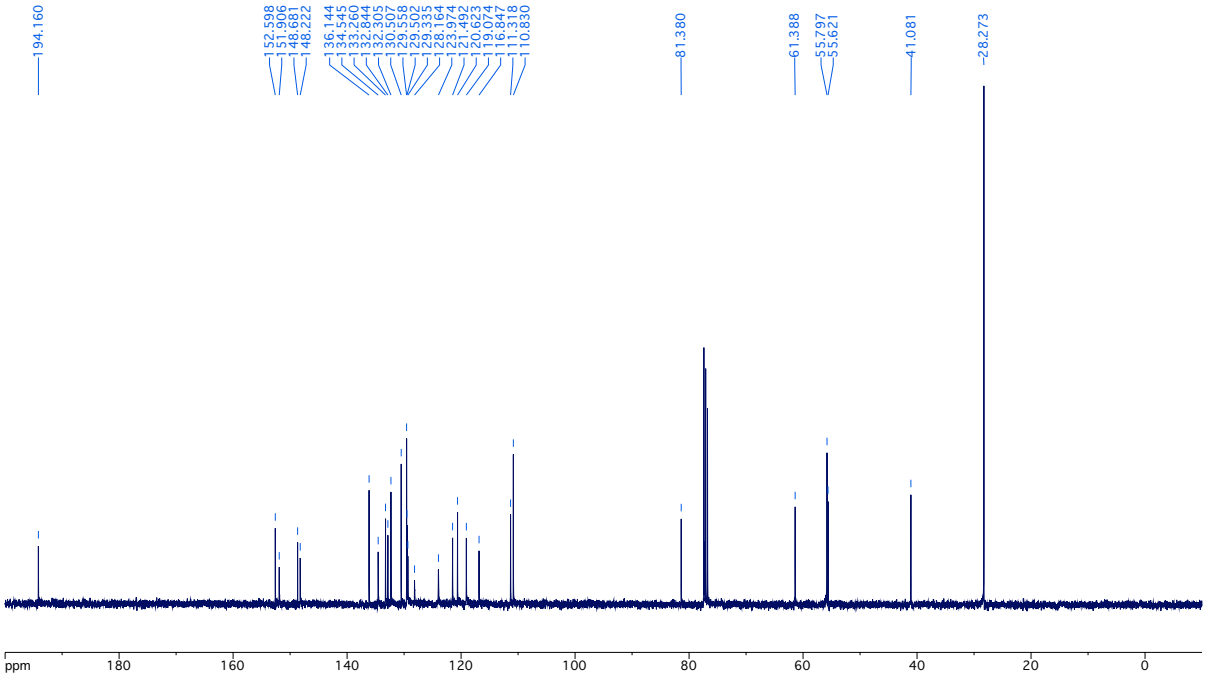

7.842
7.820
7.746
7.726
7.704
7.629
7.623
7.492
7.487
7.470
7.465
7.384
7.364
6.951
6.912
6.692
4.020
3.329
3.314
3.300
2.714
2.700
2.686
2.455
2.317
1.533
MeS
O
NHBoc
N
Ts
Br
72h
3.29
1.03
1
1.97
2.15
3.11
0.913
1.05
2.25
1
2.03
3.42
9.43
ppm

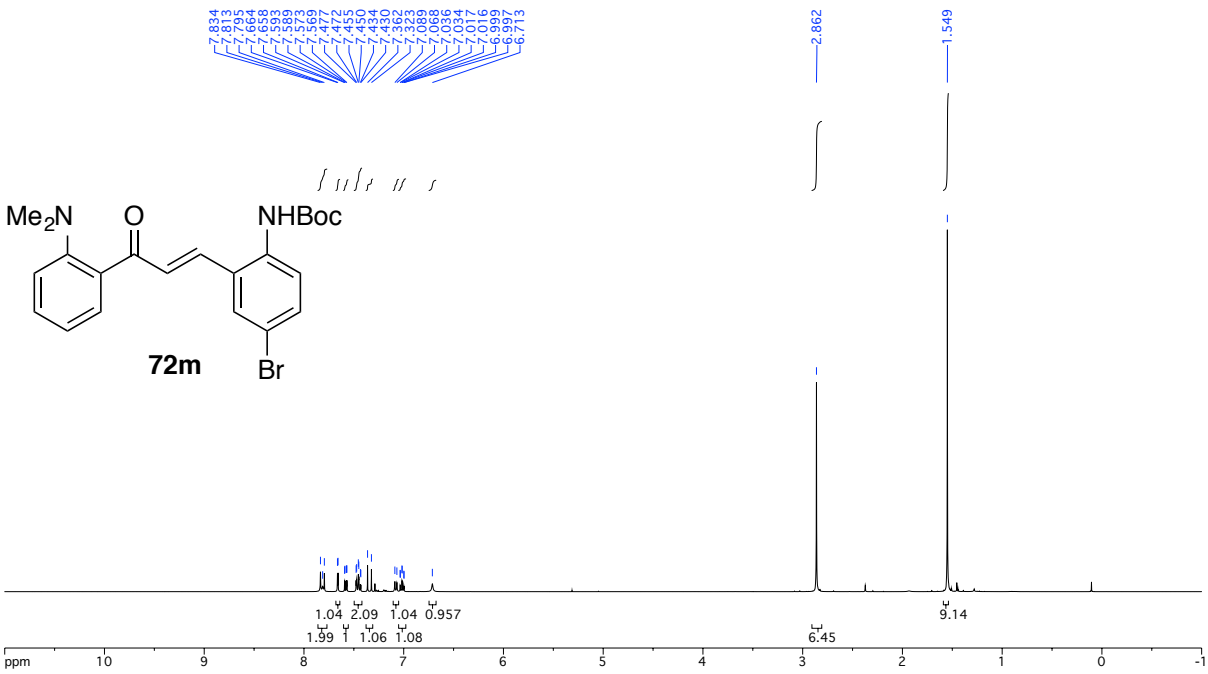

186.659
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147.074
142.748
134.974
134.804
133.711
131.583
128.507
128.198
126.304
125.470
123.217
122.317
115.277
79.983
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28.651
26.848
20.165
13.530
ppm

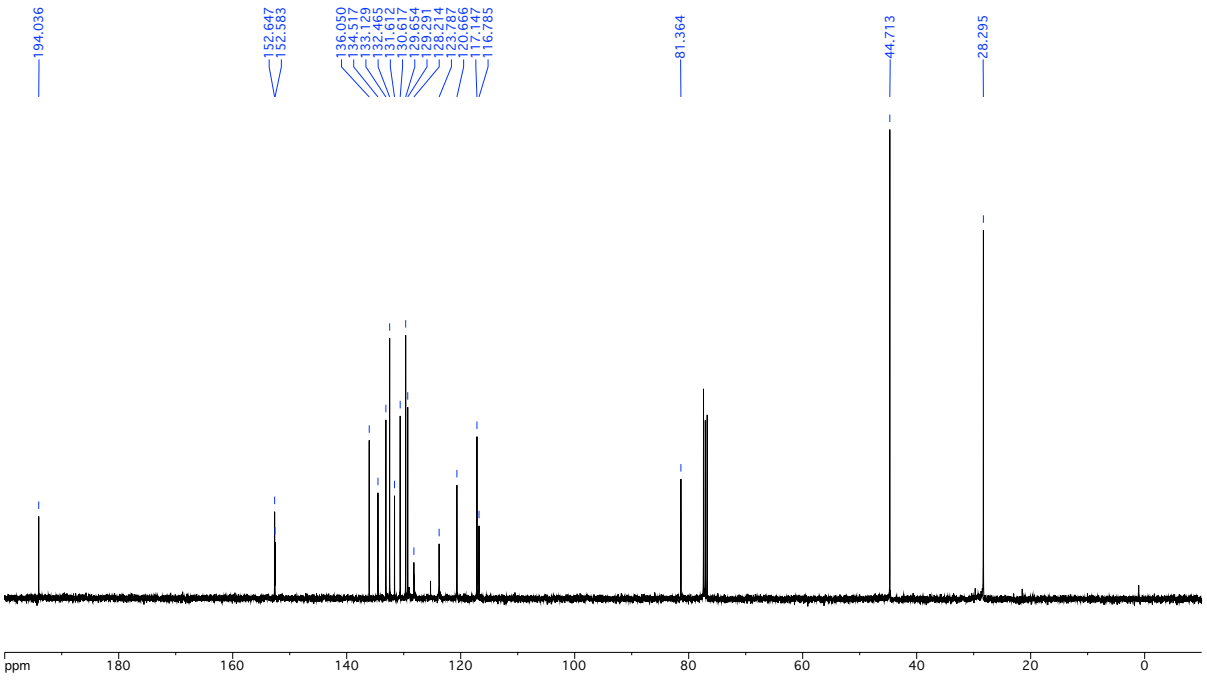

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7.859
7.855
7.828
7.790
7.741
7.735
7.597
7.559
7.507
7.501
7.485
7.479
7.363
7.359
7.345
7.342
7.339
7.325
7.321
6.759
6.756
6.745
6.742
6.738
6.725
6.721
6.679
6.435
1.555
H2N
O
NHBoc
Br
72k
0.928
1.21
1.84
1.72
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1
1.1
0.944
9.8
ppm

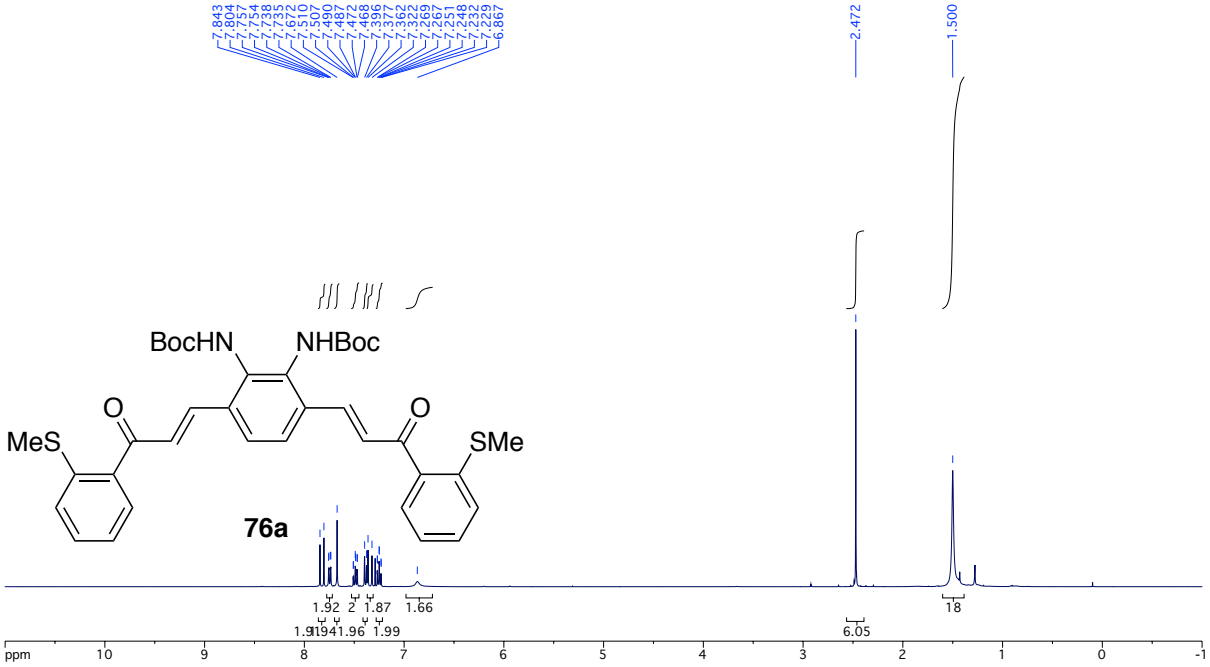

190.697
152.661
151.313
136.006
135.625
134.844
133.242
131.034
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128.192
126.681
123.799
118.496
117.422
116.823
116.069
81.400
28.304
ppm

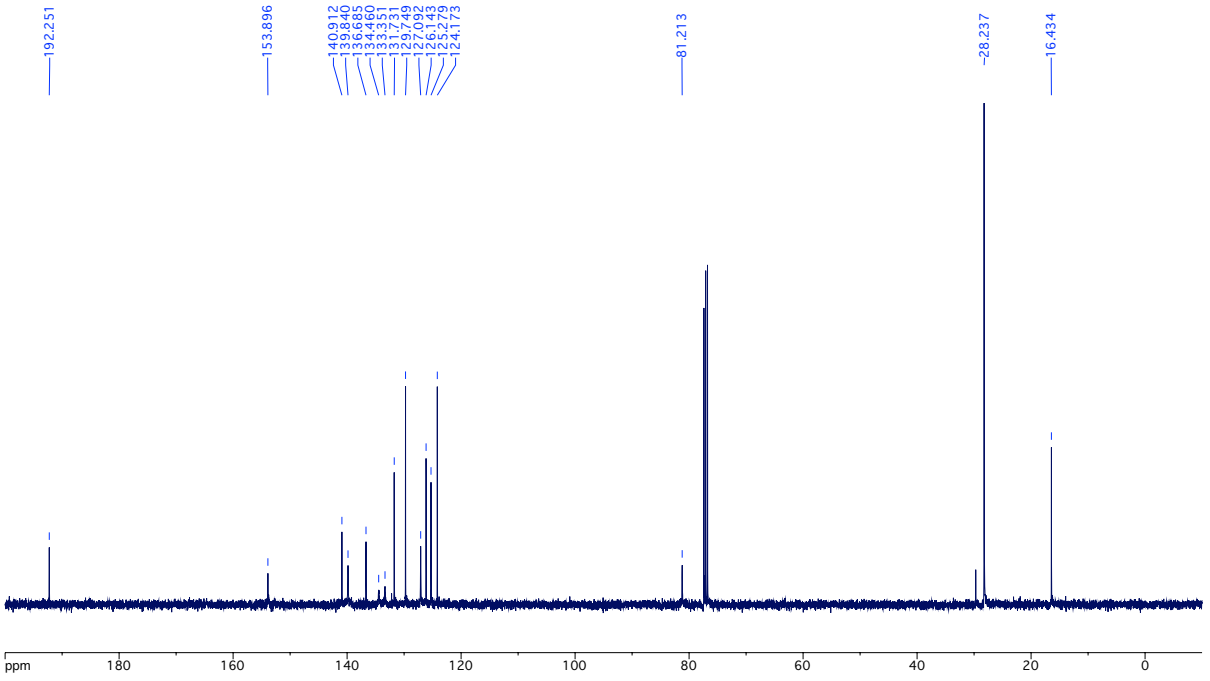

7.819
7.780
7.700
7.694
7.618
7.614
7.599
7.594
7.495
7.490
7.473
7.468
7.465
7.451
7.449
7.447
7.445
7.431
7.425
7.386
7.097
7.079
7.061
6.754
6.734
6.725
6.708
6.704
6.612
6.557
4.165
3.836
3.673
2.743
1.532
DMB
N
Me
O
NHBoc
Br
72l
1
2
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1.95
2.98
9.13
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1.08
2.04
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3.12
2.9
ppm

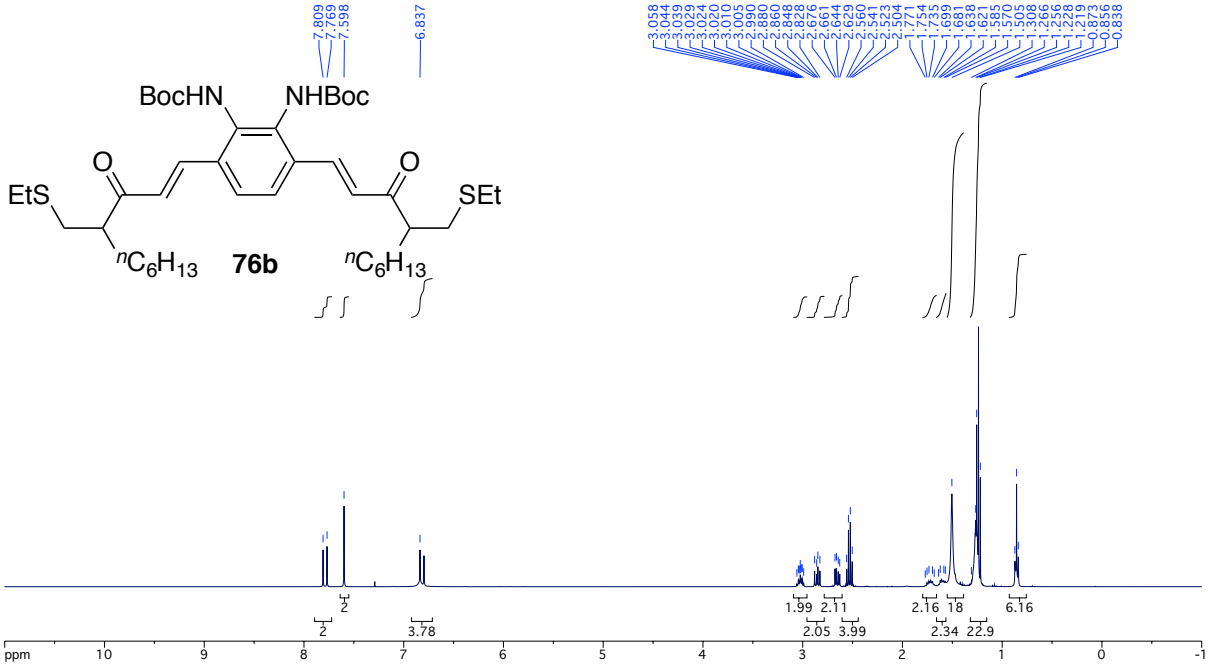

194.160
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151.906
148.681
148.222
136.144
134.545
133.260
133.184
132.305
130.507
129.558
129.502
129.335
128.164
123.974
121.449
120.622
119.074
116.847
111.318
110.830
81.380
61.388
55.797
55.621
41.081
28.273
ppm

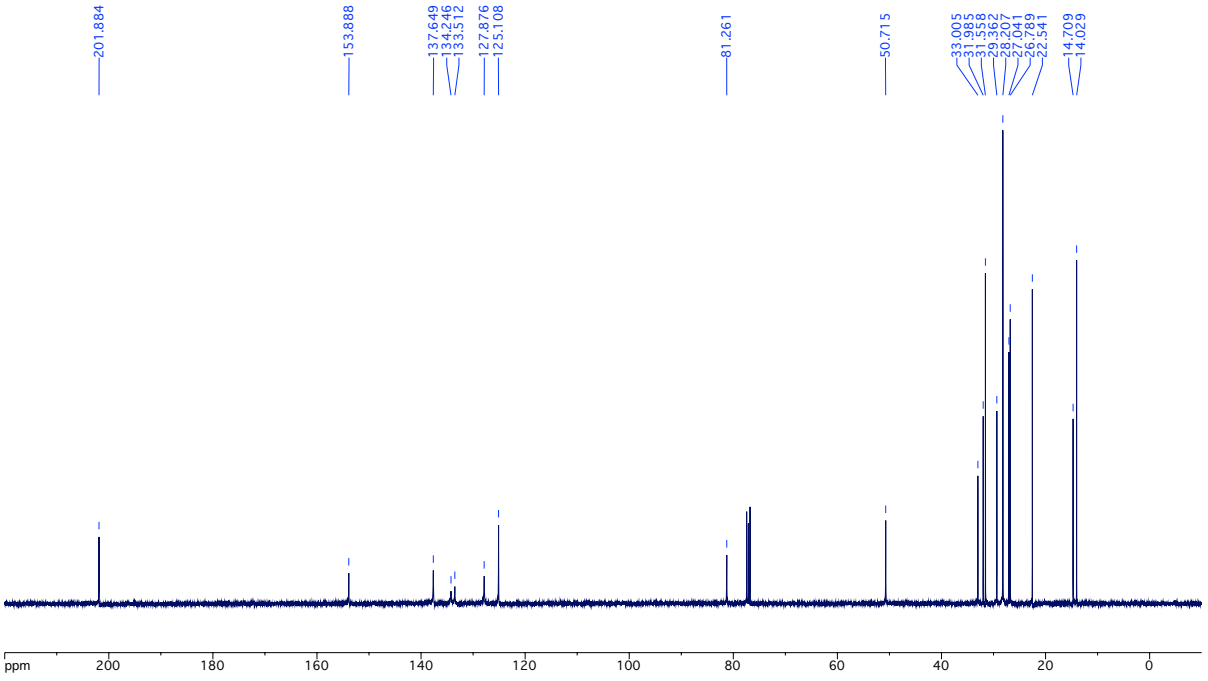

7.834
7.813
7.795
7.664
7.658
7.593
7.583
7.573
7.569
7.477
7.472
7.455
7.450
7.434
7.430
7.362
7.323
7.089
7.068
7.036
7.034
7.017
7.016
6.999
6.997
6.713
2.862
1.549
Me2N
O
NHBoc
Br
72m
1.04
2.09
1.04
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1.99
1.06
1.08
6.45
9.14
ppm

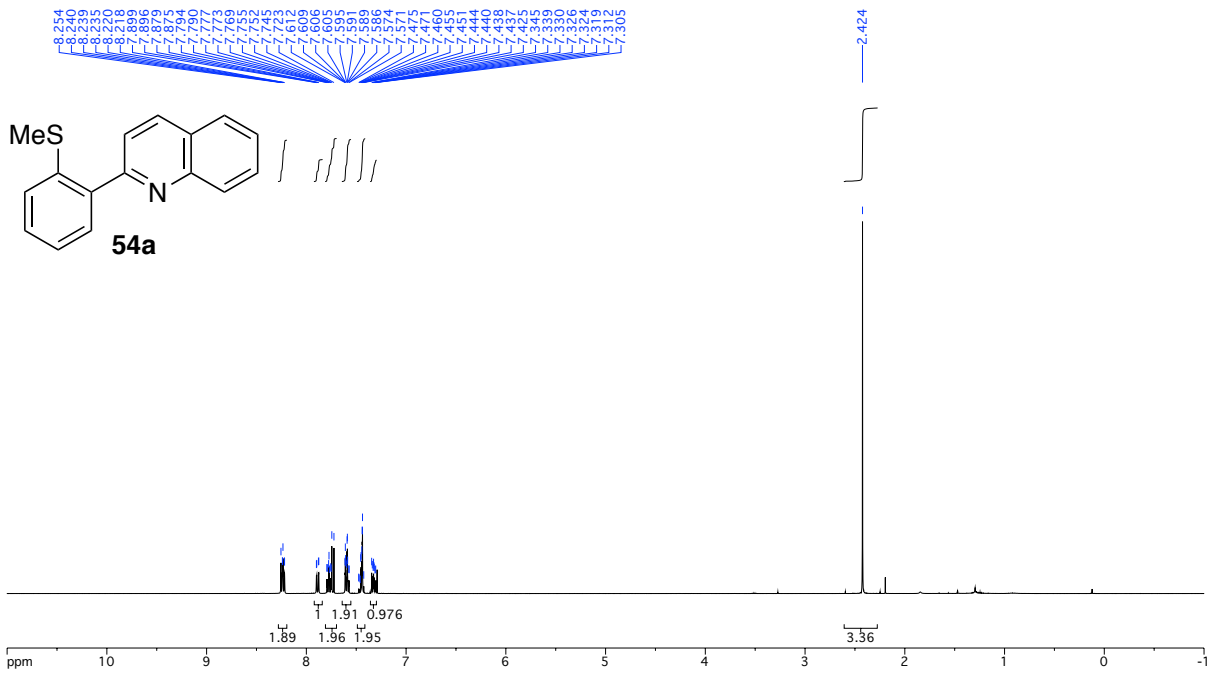

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152.583
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134.517
133.129
132.465
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129.291
128.214
123.787
120.666
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116.785
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ppm

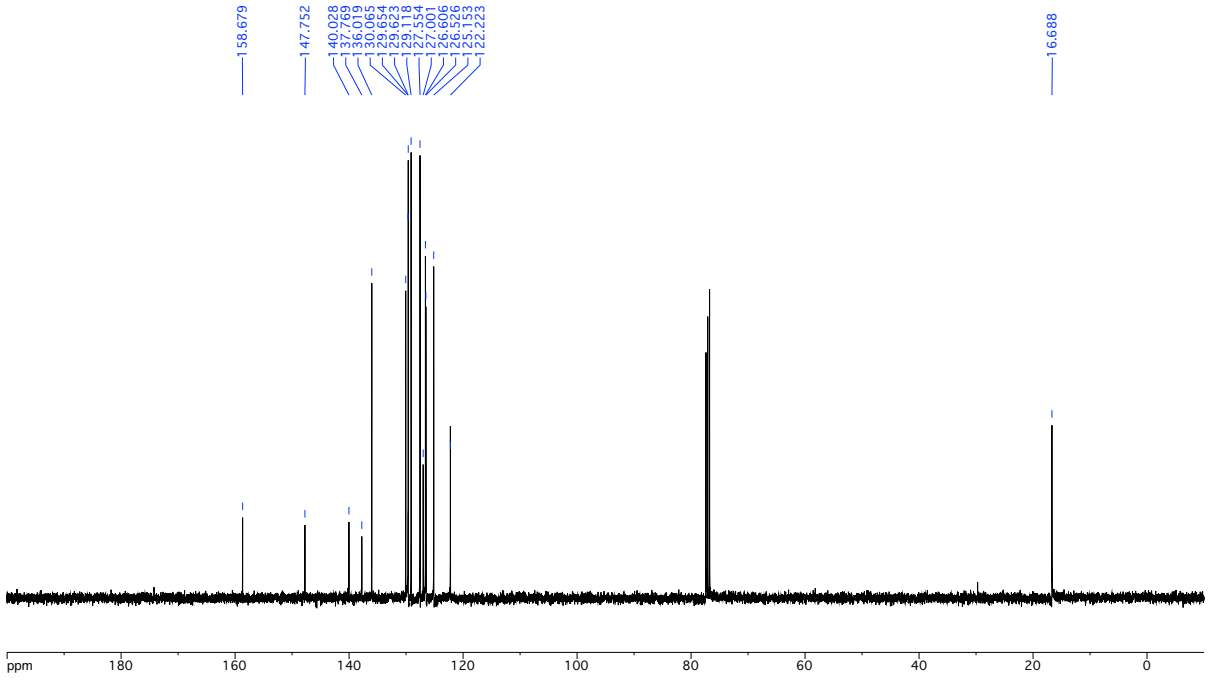

7.843
7.804
7.757
7.754
7.738
7.735
7.672
7.510
7.507
7.490
7.487
7.472
7.468
7.396
7.377
7.362
7.322
7.269
7.267
7.251
7.248
7.232
7.229
6.867
2.472
1.500
BocHN
NHBoc
O
O
MeS
SMe
76a
1.92
2
1.87
1.66
1.91
1.94
1.96
1.99
6.05
18
ppm
10
9
8
7
6
5
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3
2
1
0
-1

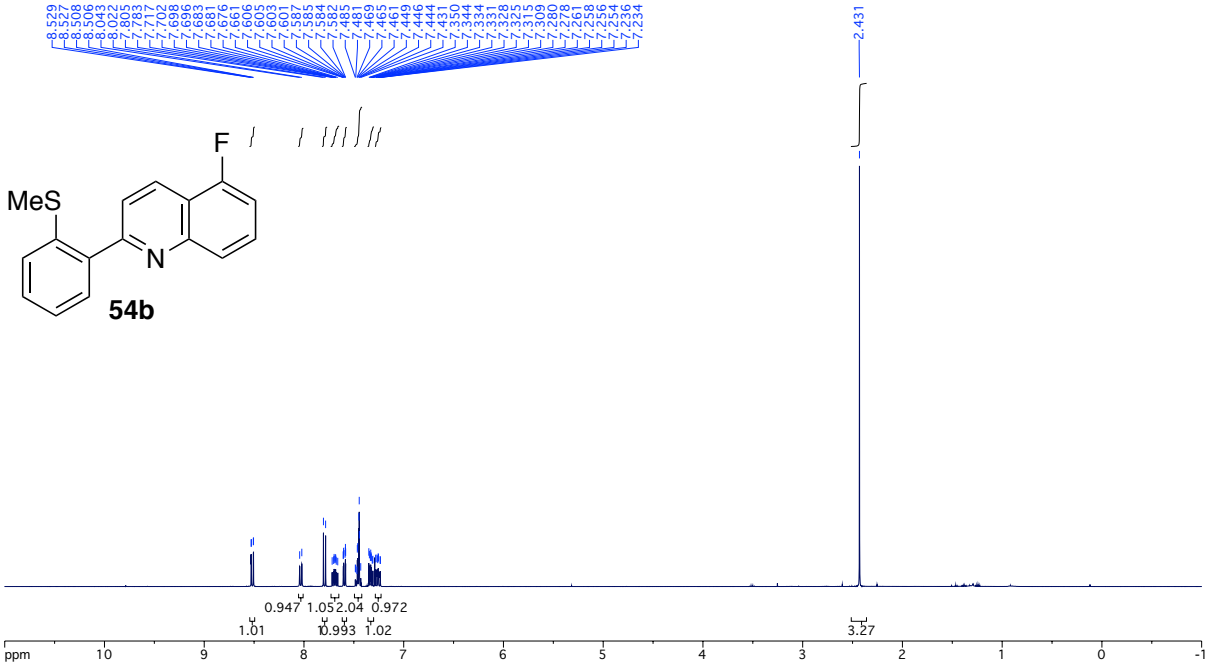

192.251
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136.685
134.460
133.351
133.131
132.749
127.092
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124.173
81.213
28.237
16.434
ppm
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140
120
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80
60
40
20
0

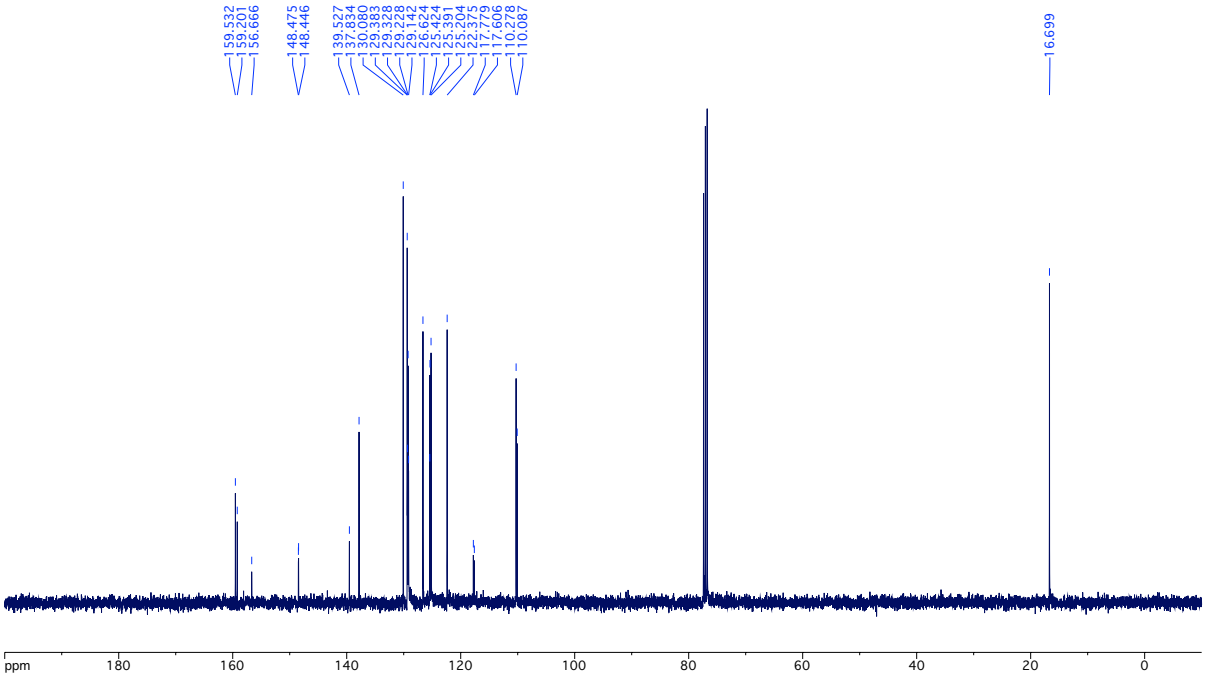

7.809
7.789
7.598
6.837
BocHN
NHBoc
O
O
EtS
SEt
^{n}C$_6$H$_{13}$
76b
^{n}C$_6$H$_{13}$
3.058
3.044
3.039
3.029
3.024
3.020
3.010
3.005
3.000
2.880
2.860
2.848
2.828
2.676
2.661
2.644
2.629
2.560
2.541
2.523
2.504
1.771
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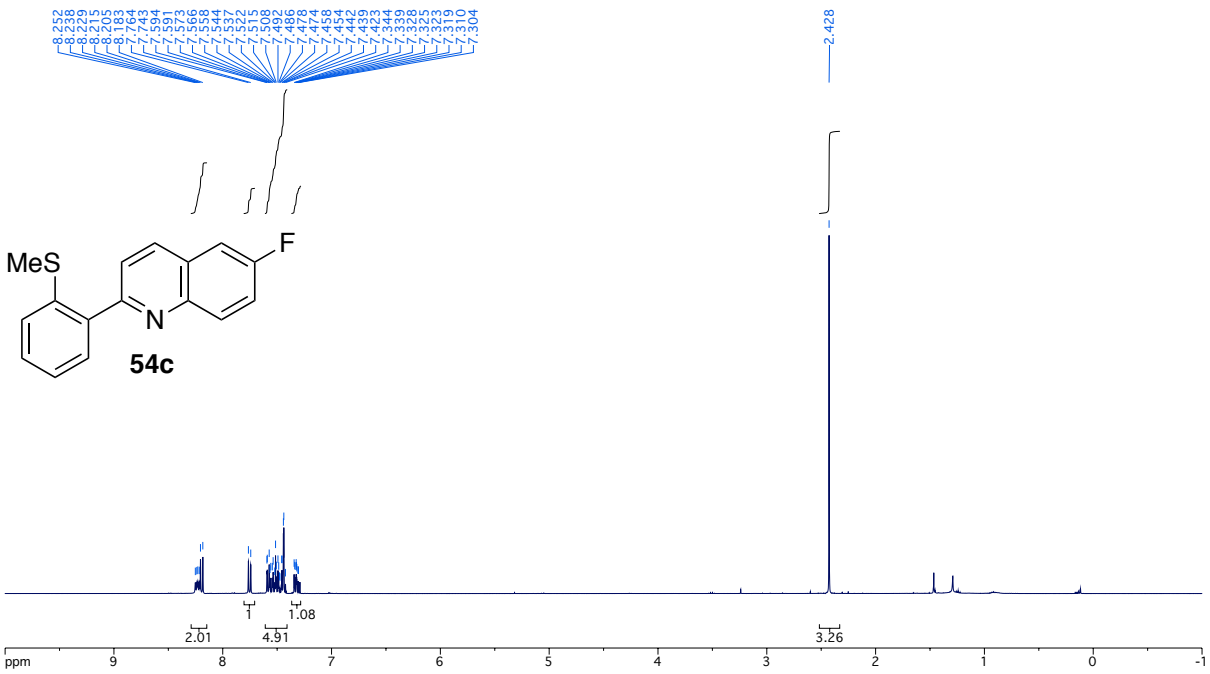

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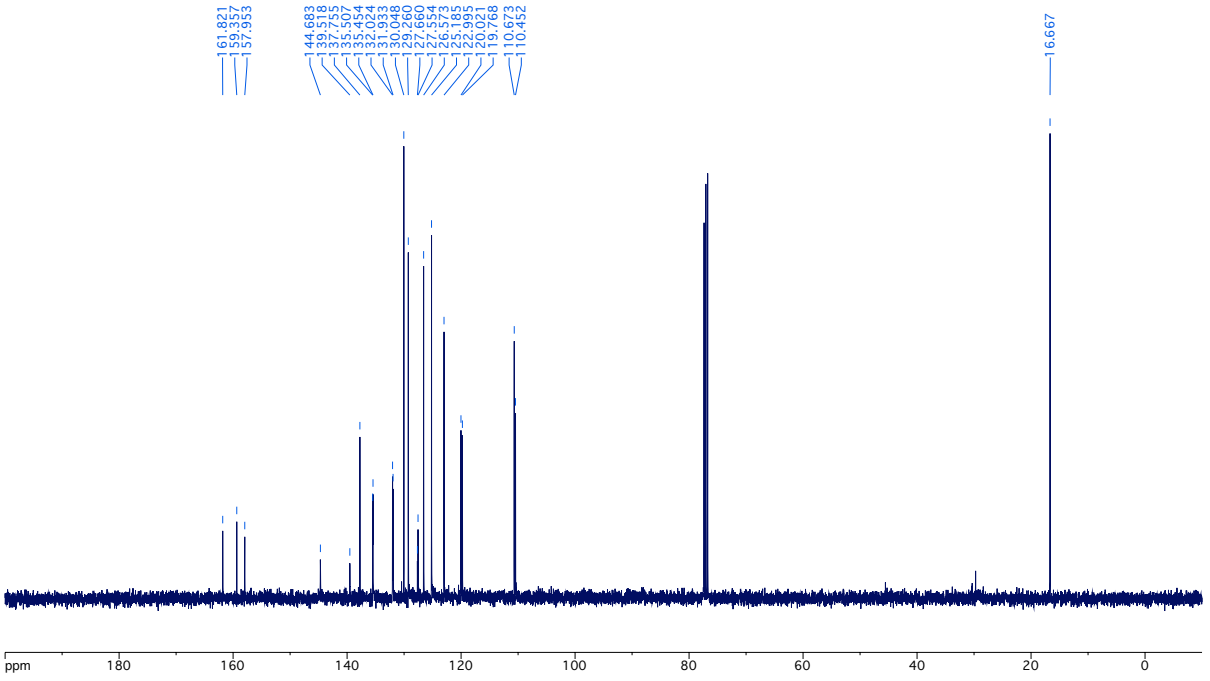

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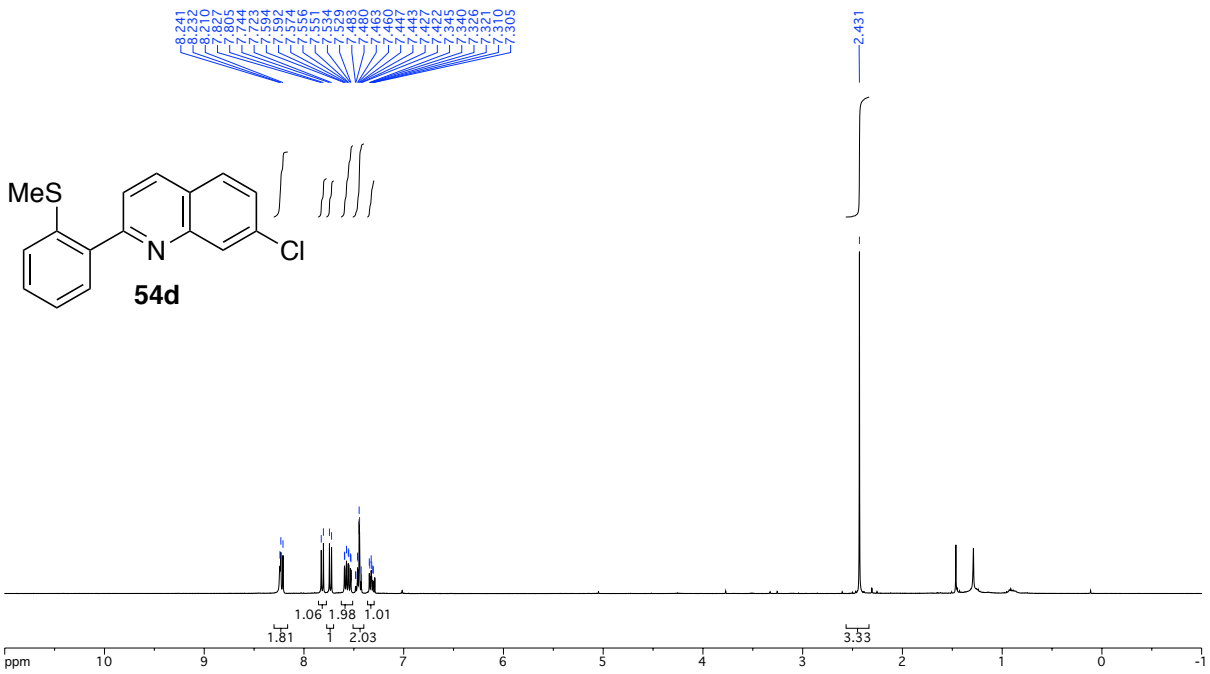

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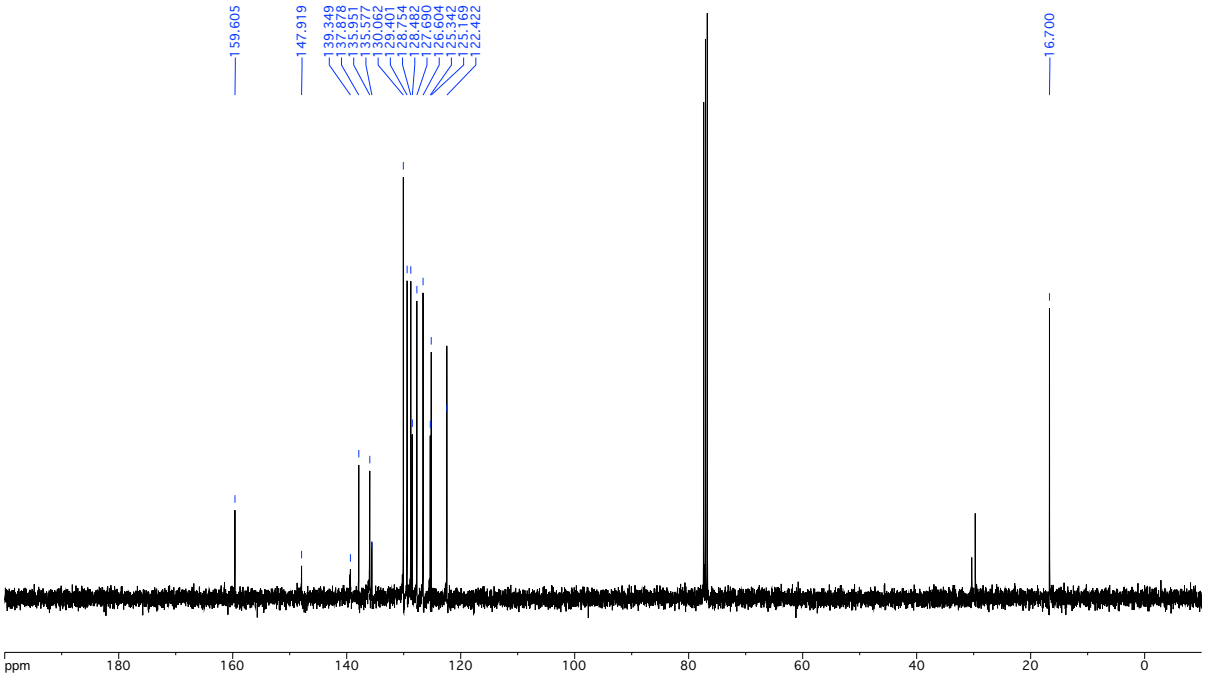

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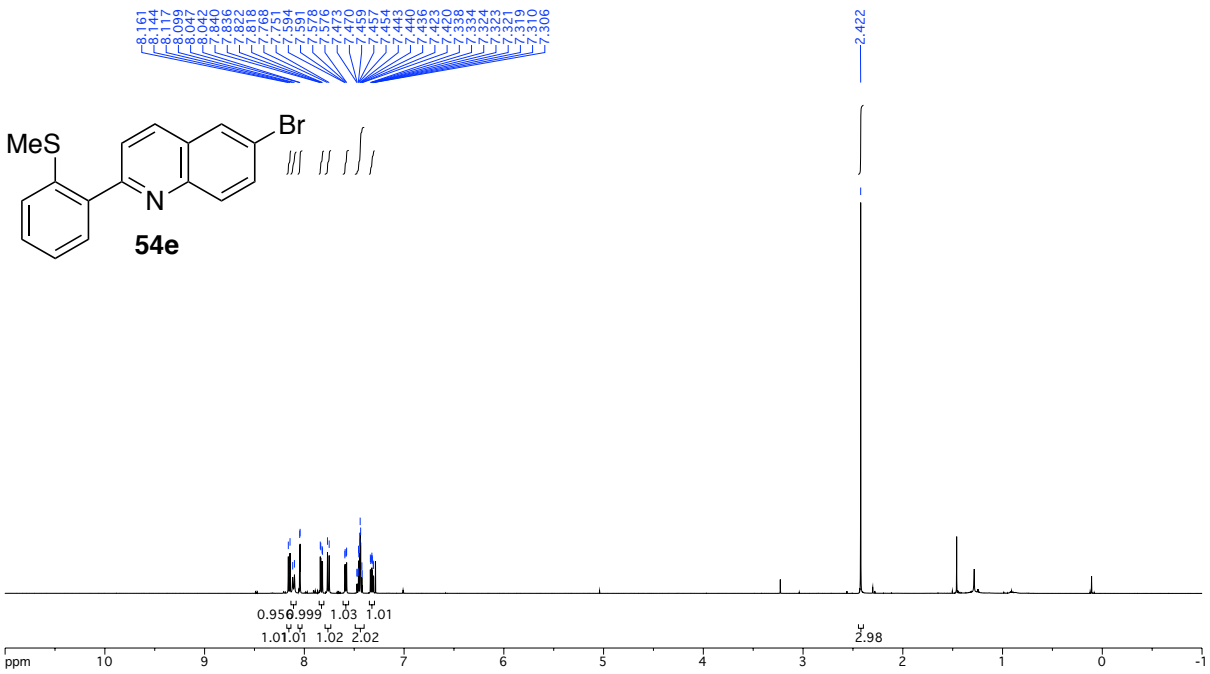

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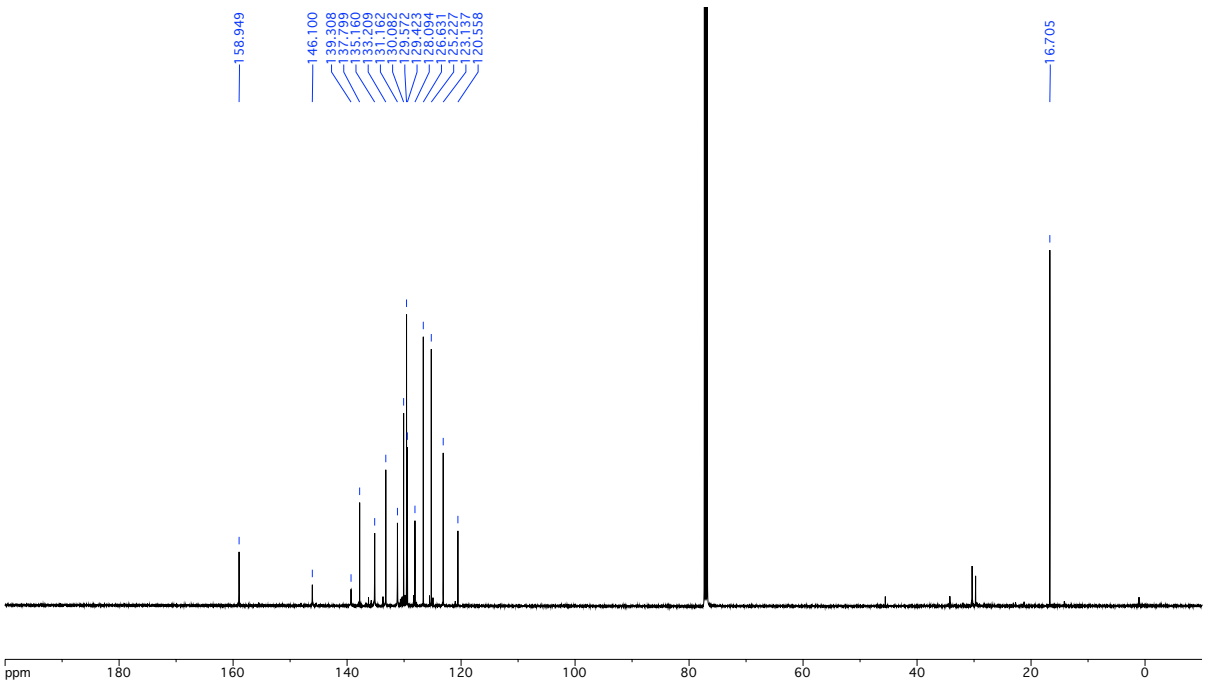

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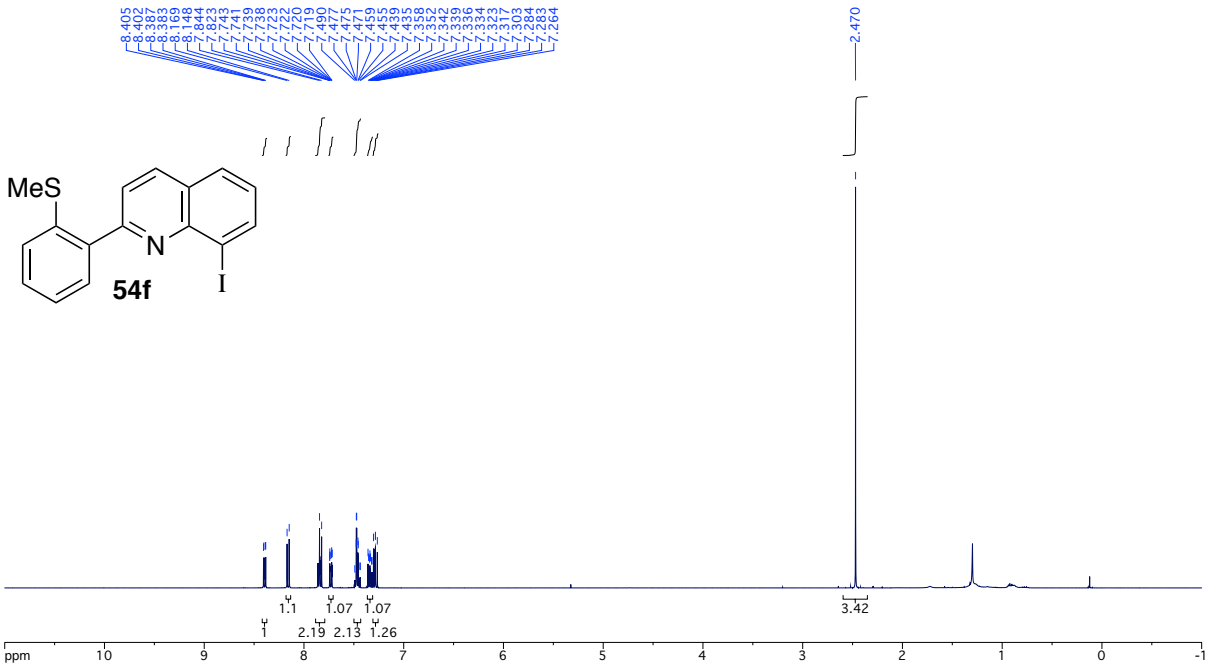

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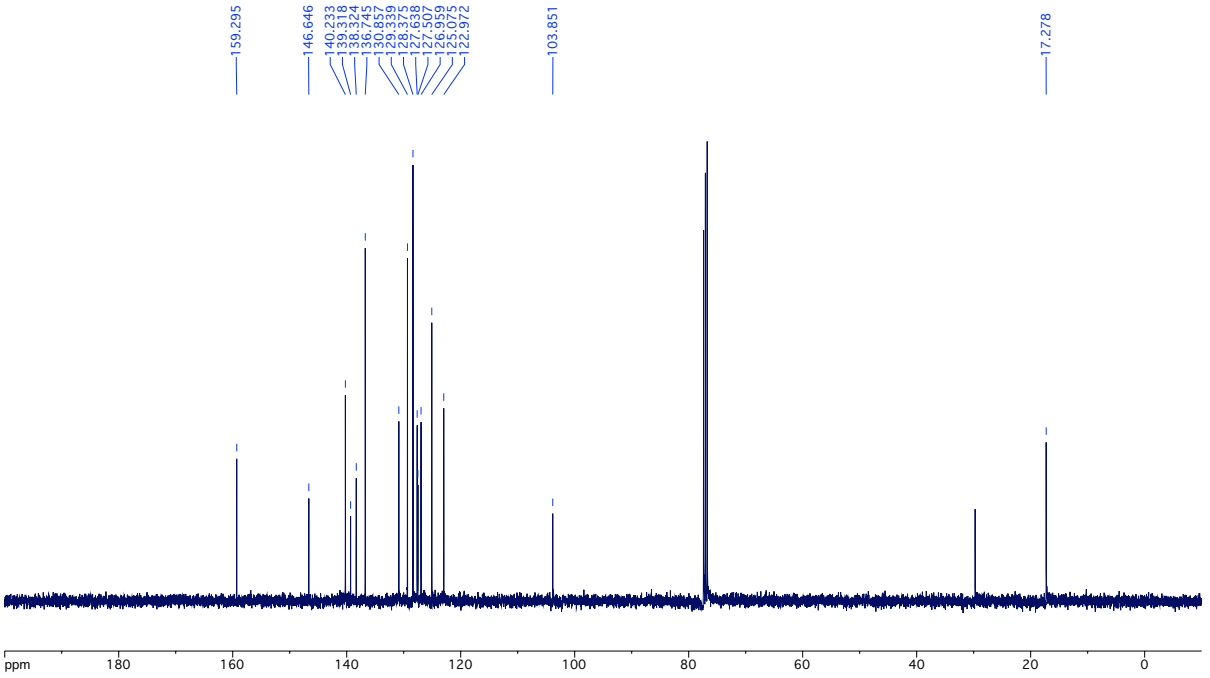

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7.529
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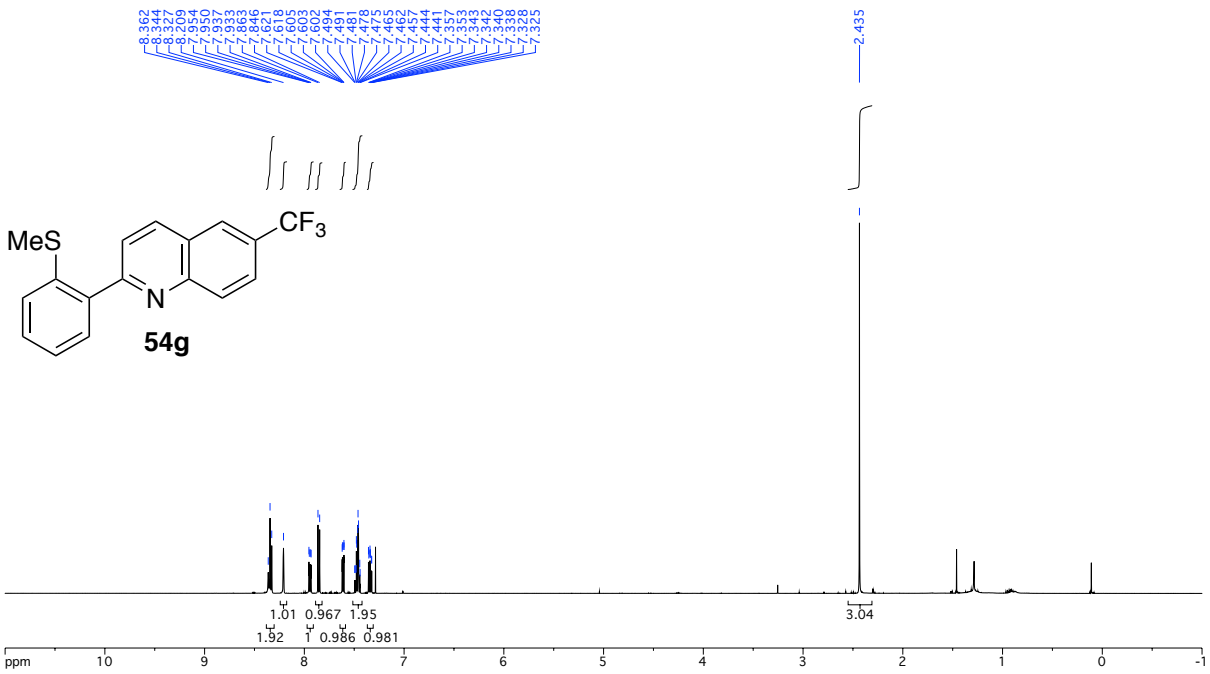

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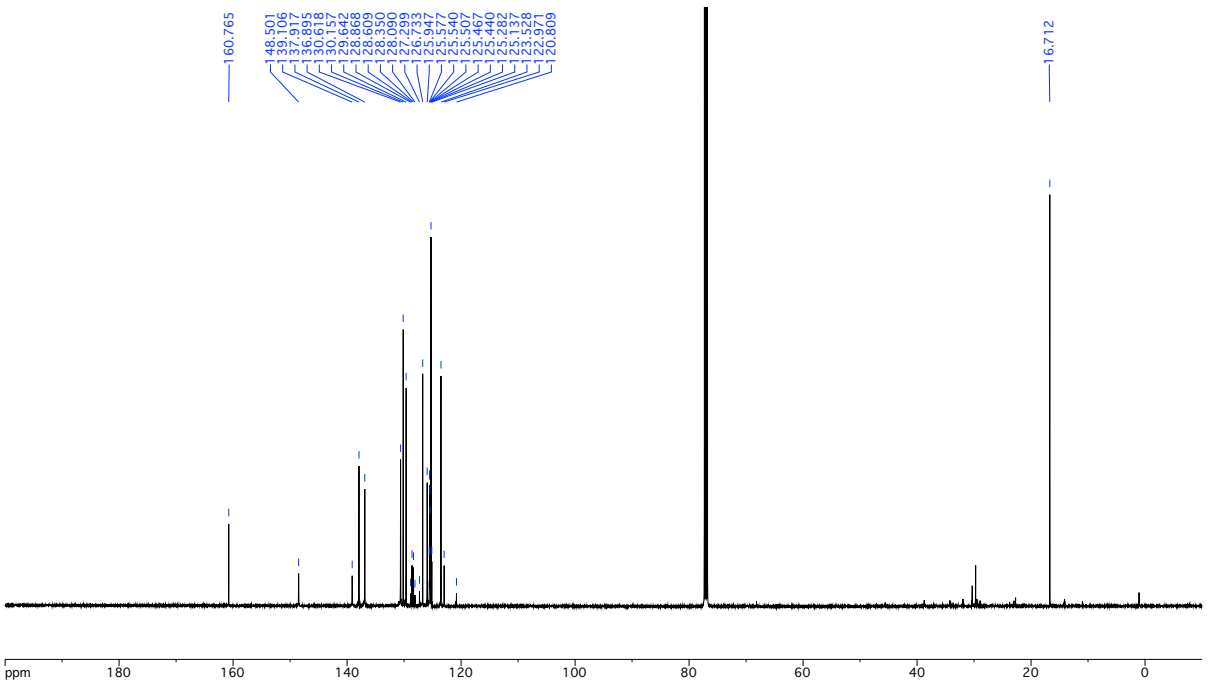

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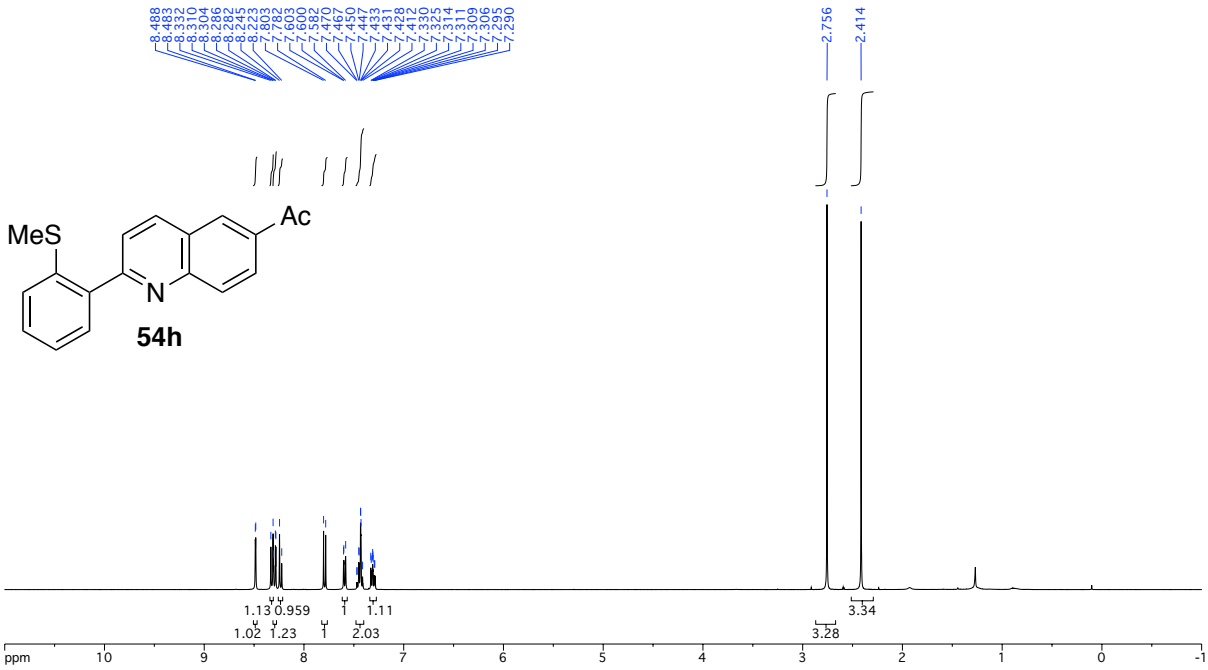

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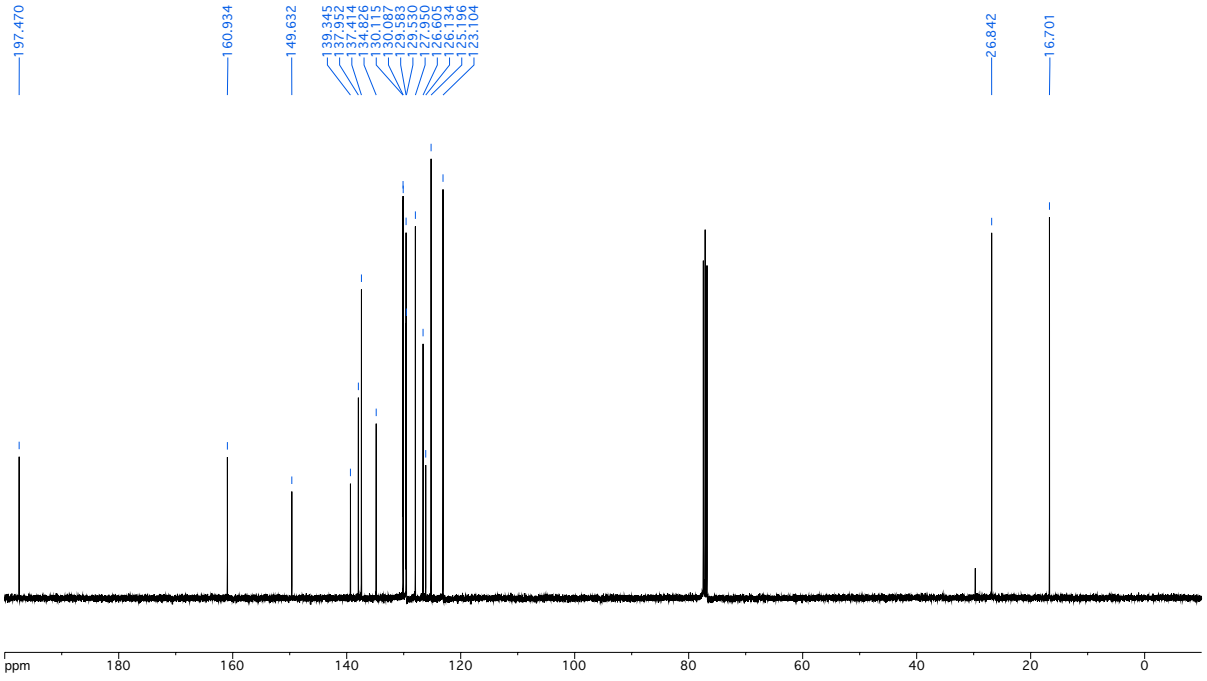

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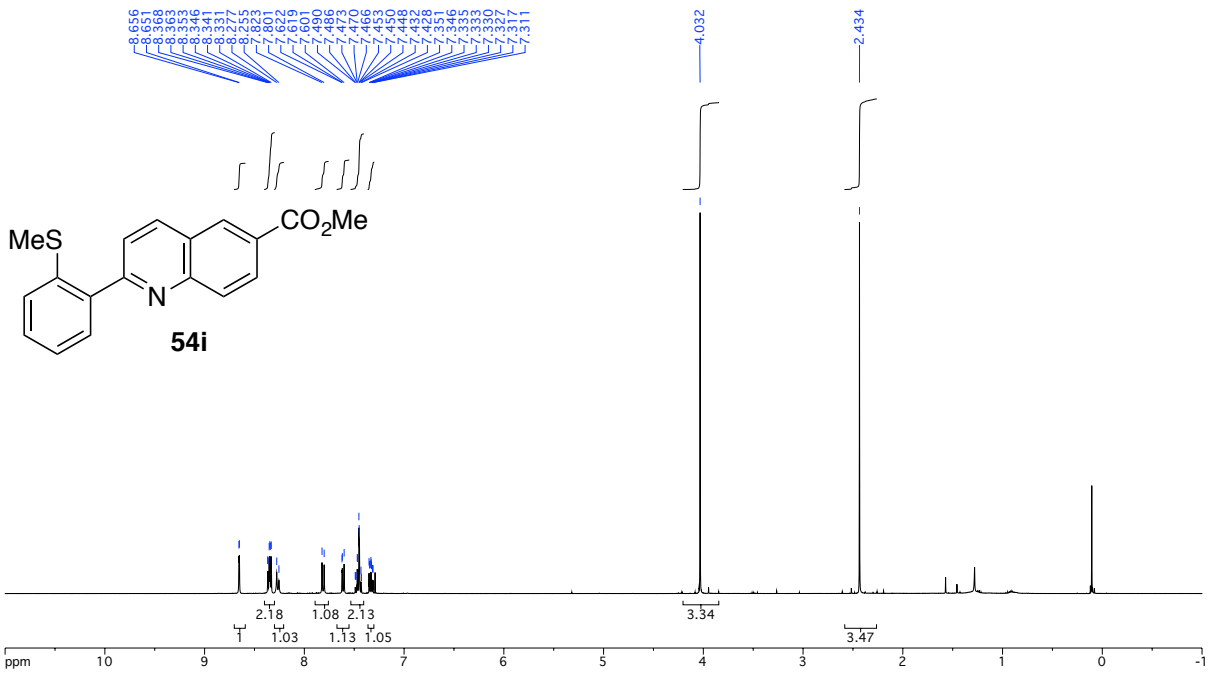

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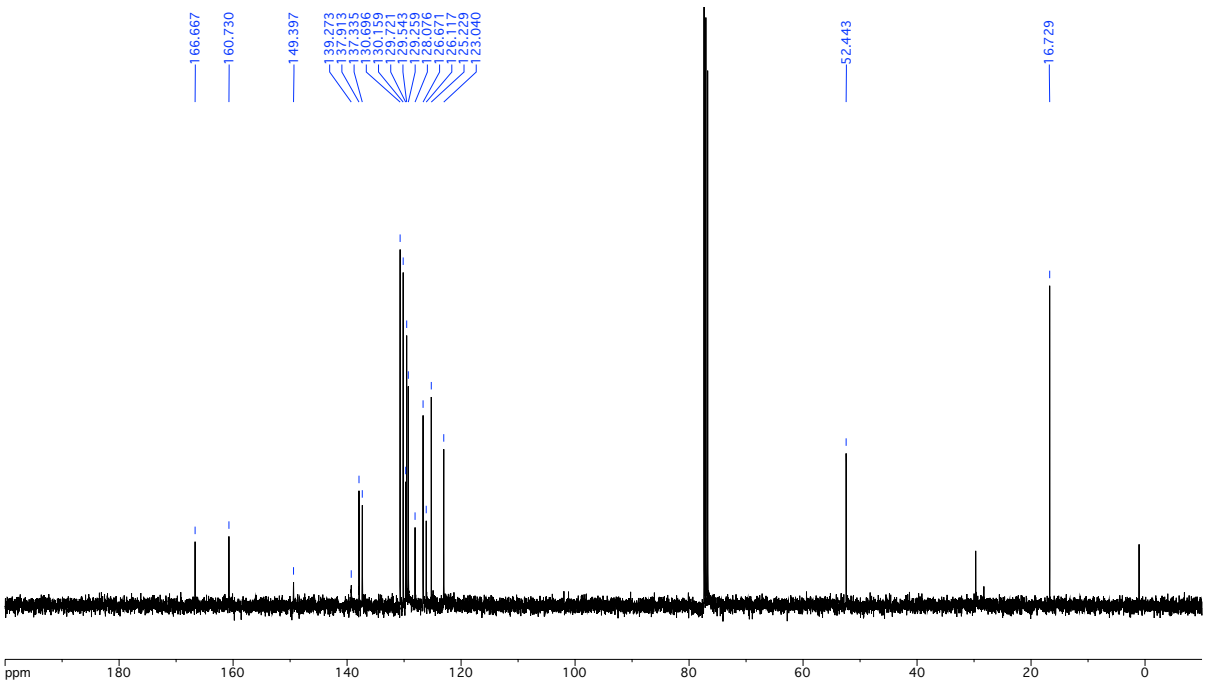

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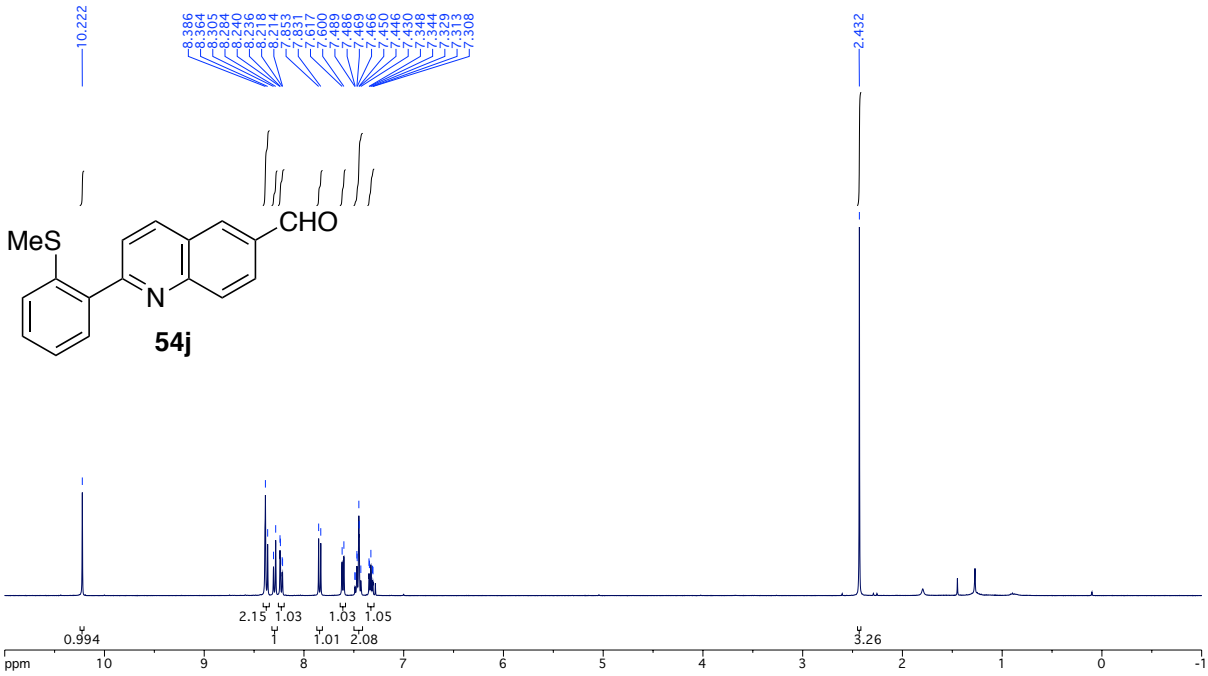

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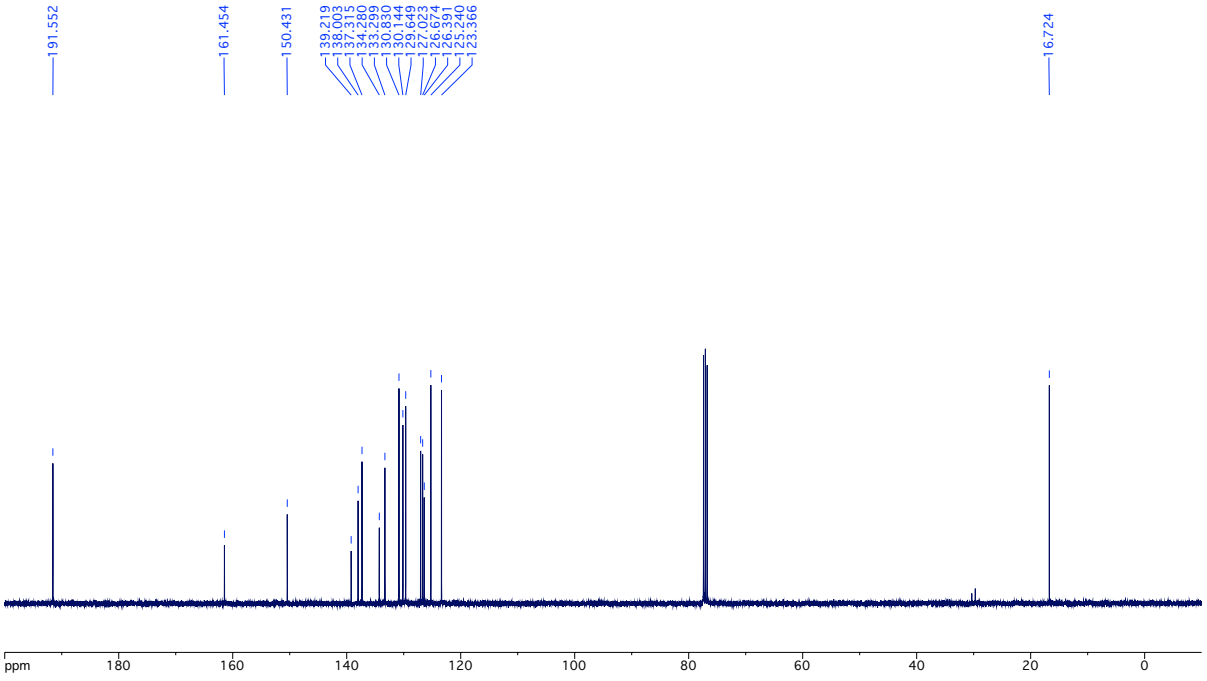

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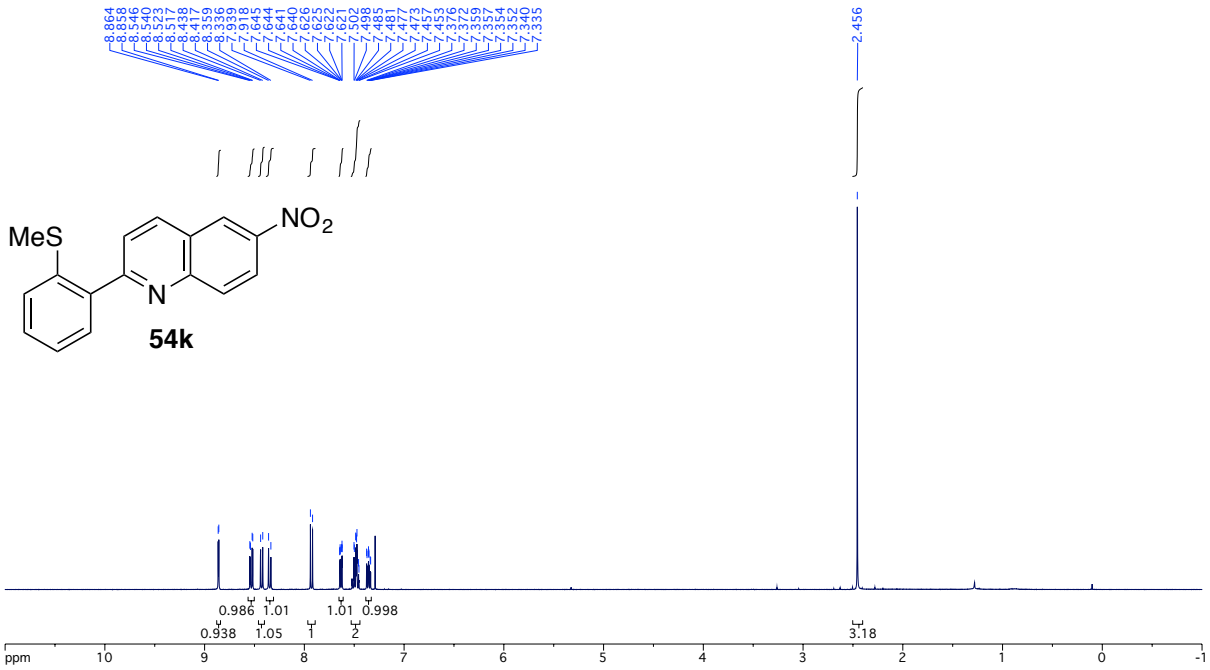

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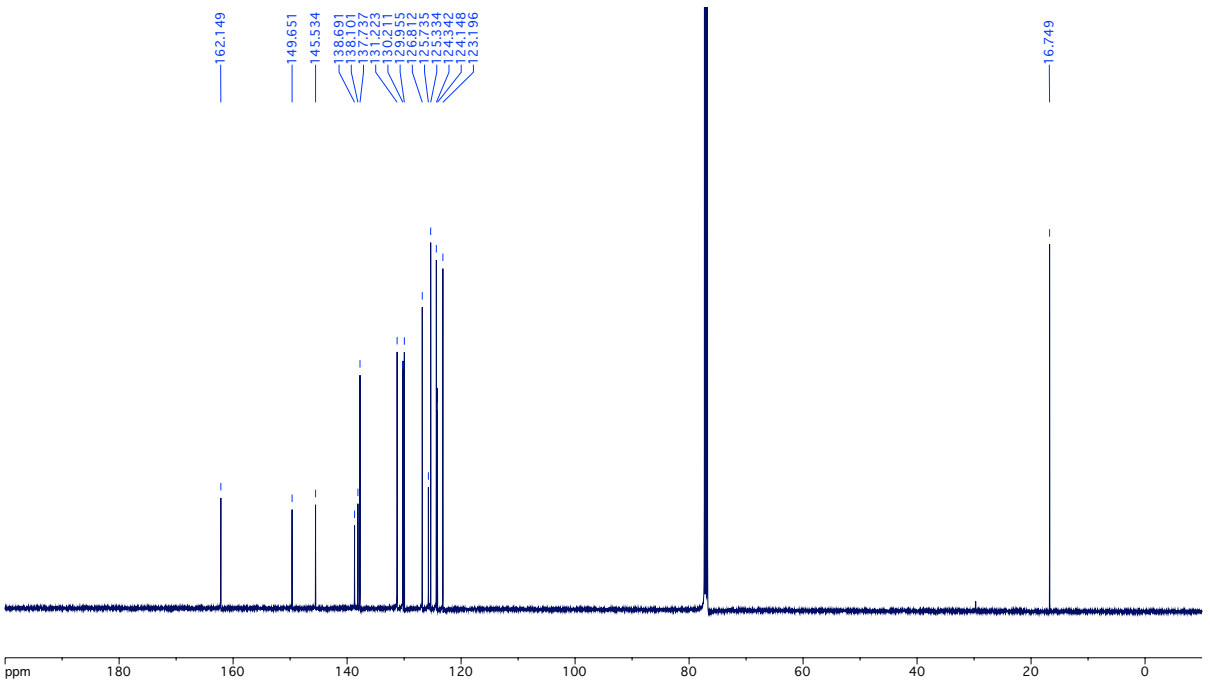

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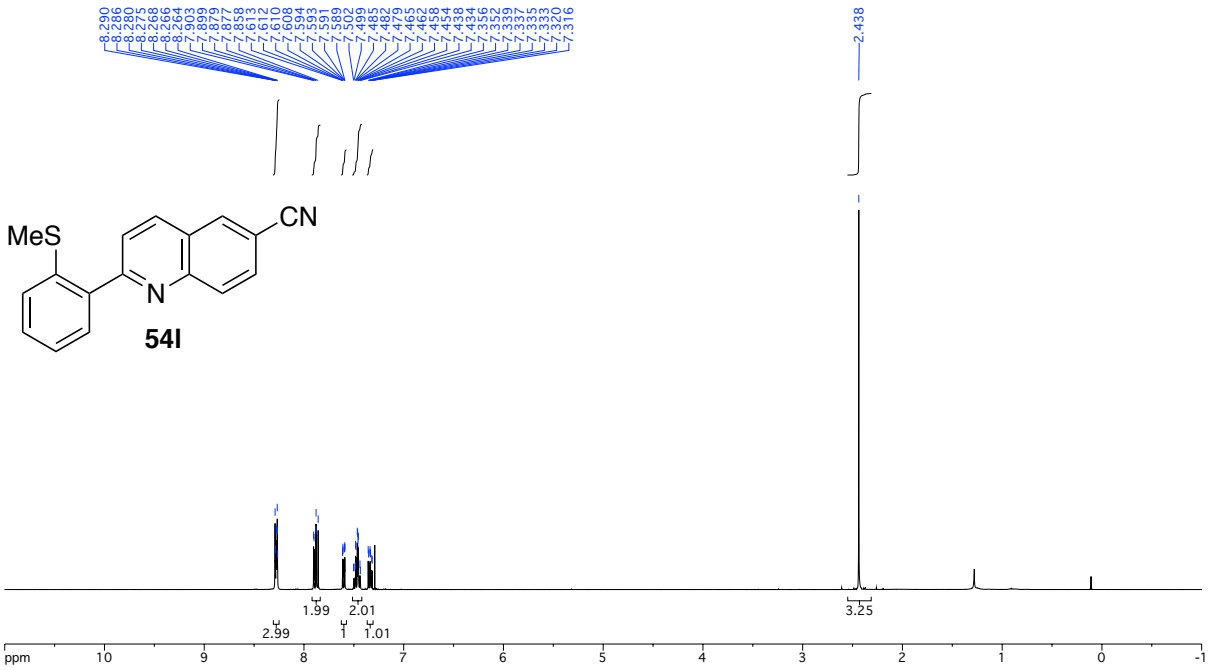

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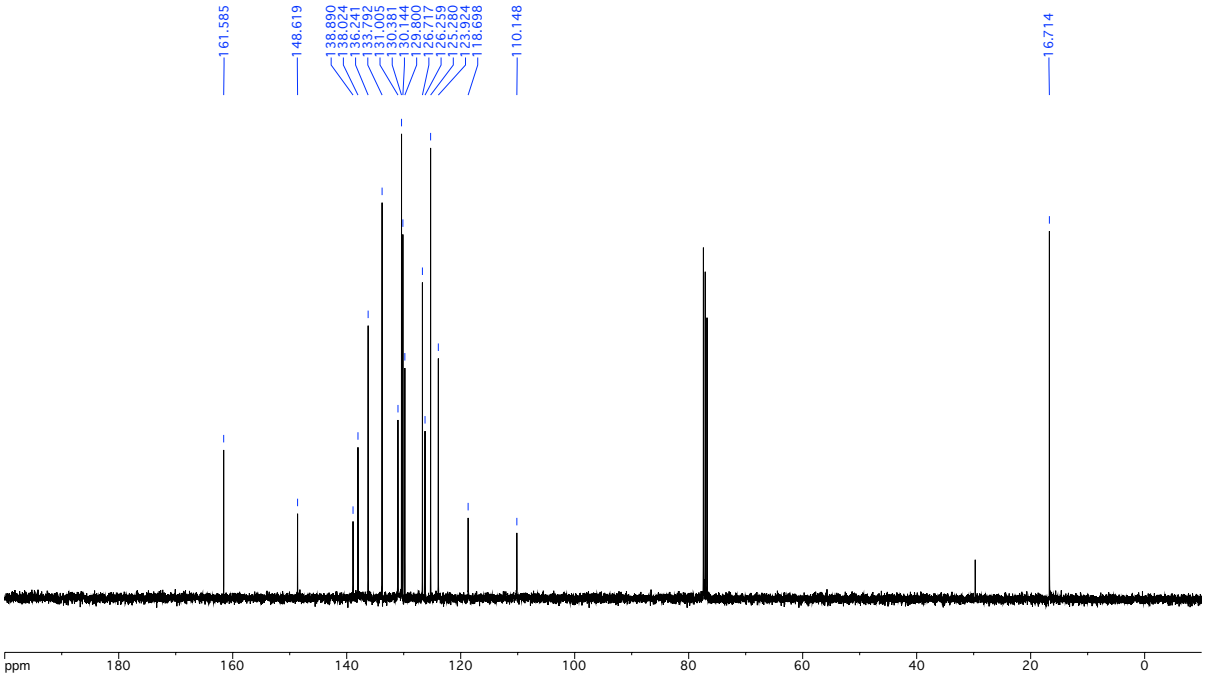

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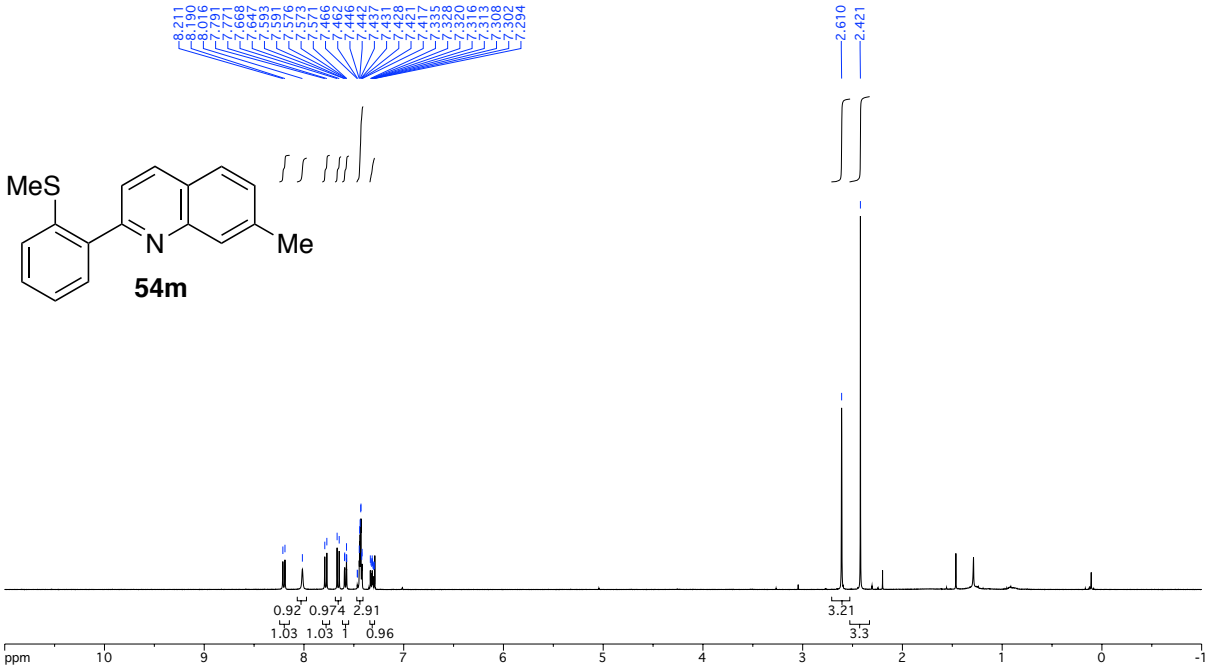

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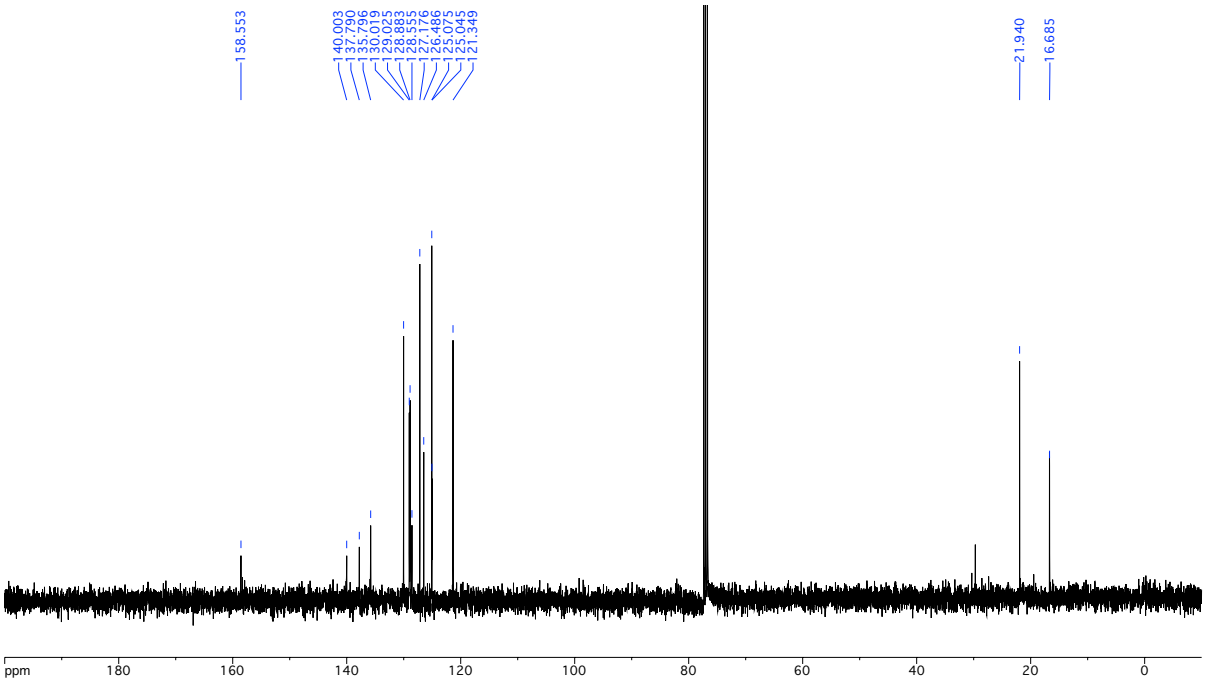

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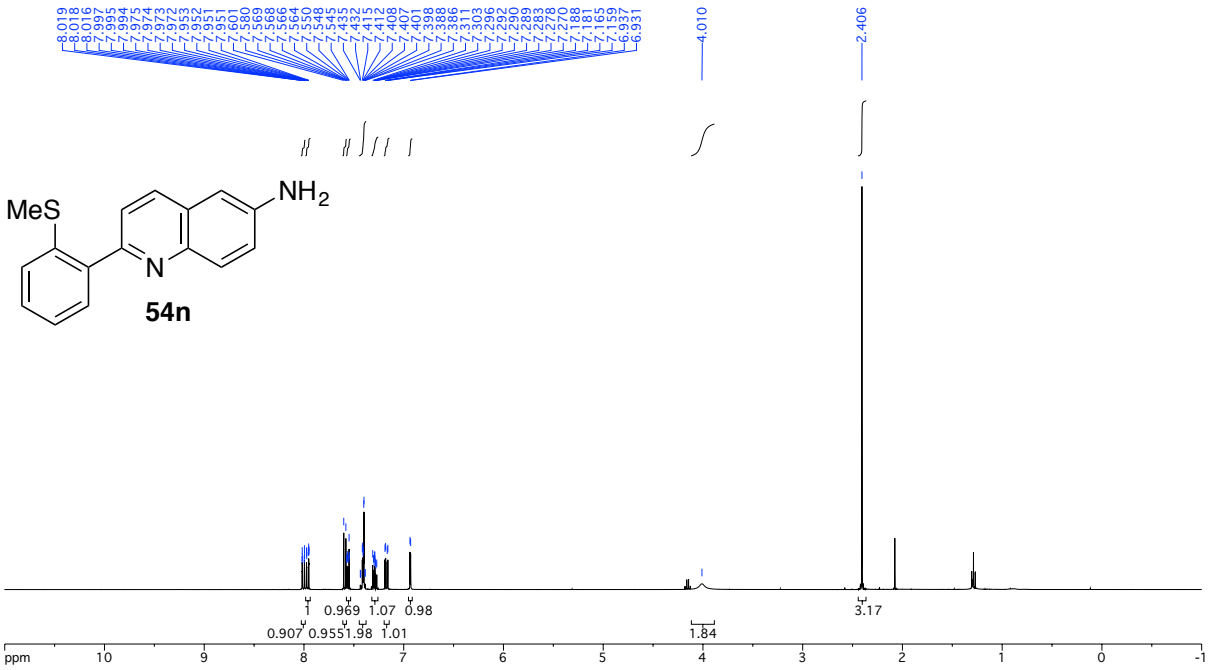

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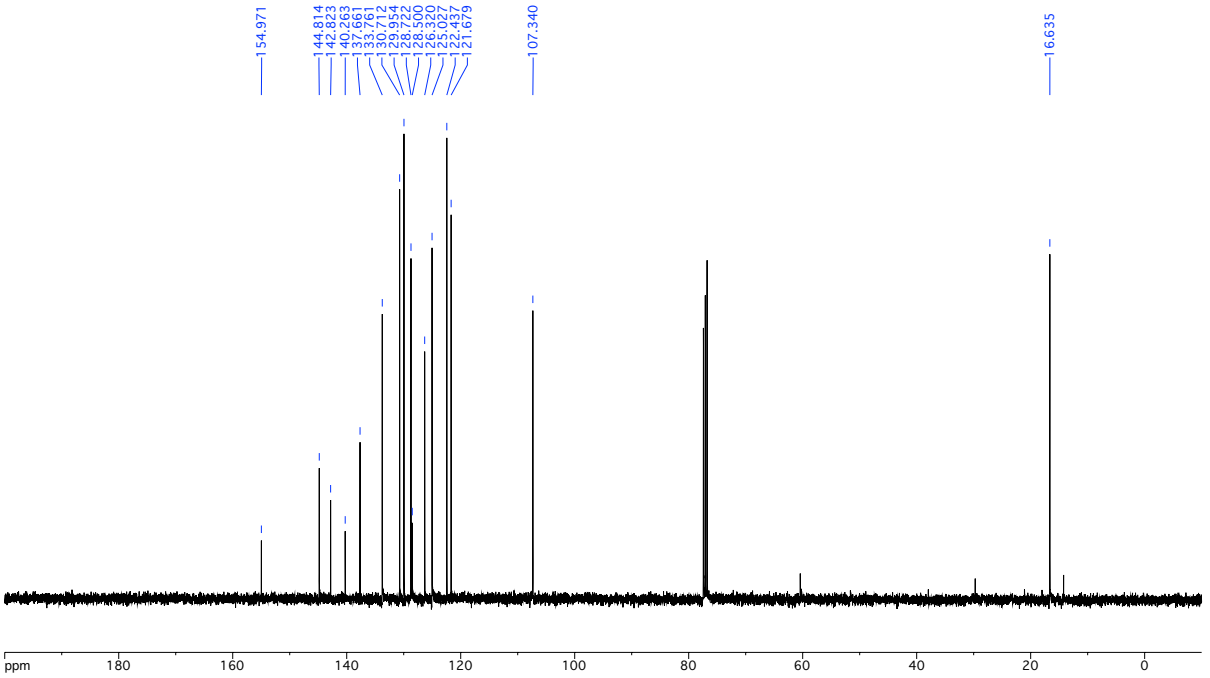

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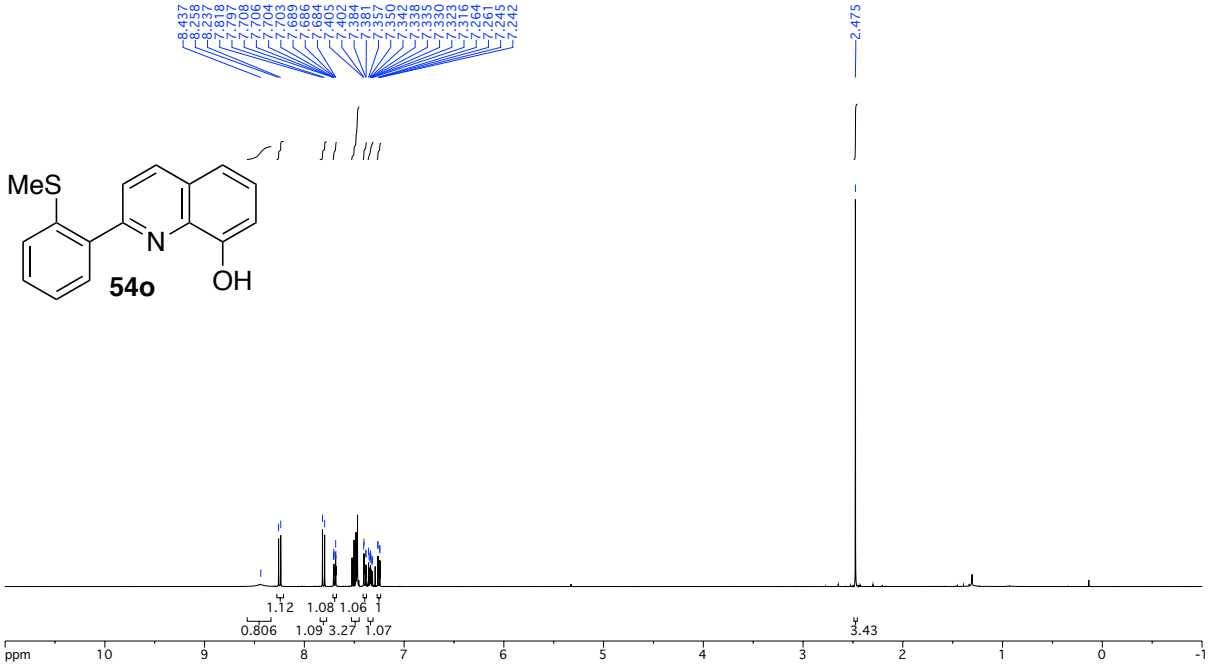

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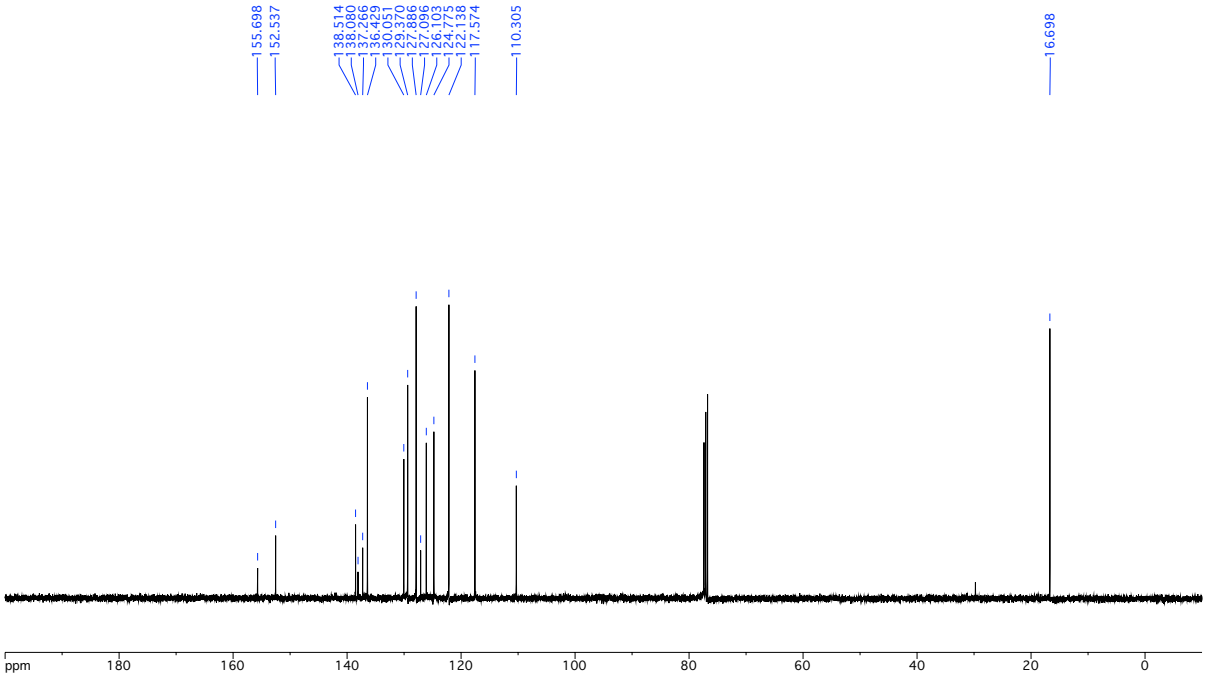

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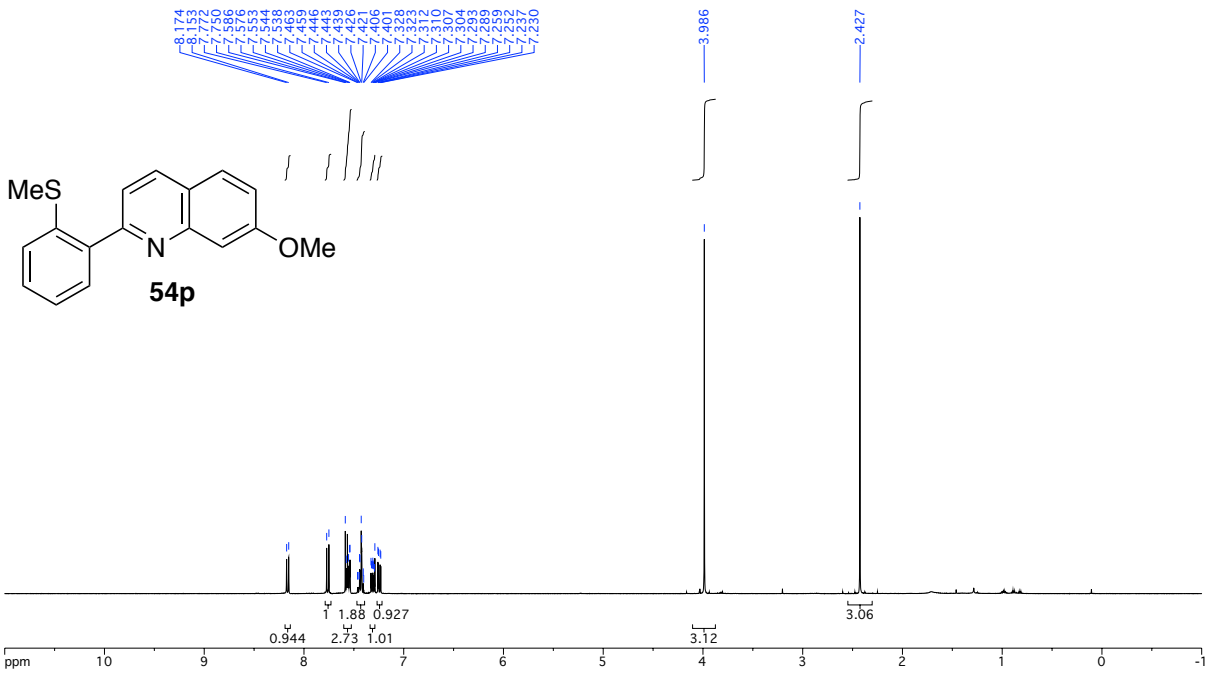

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135.796
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129.013
128.883
128.555
127.176
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125.045
121.349
21.940
16.685
ppm
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140
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60
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20
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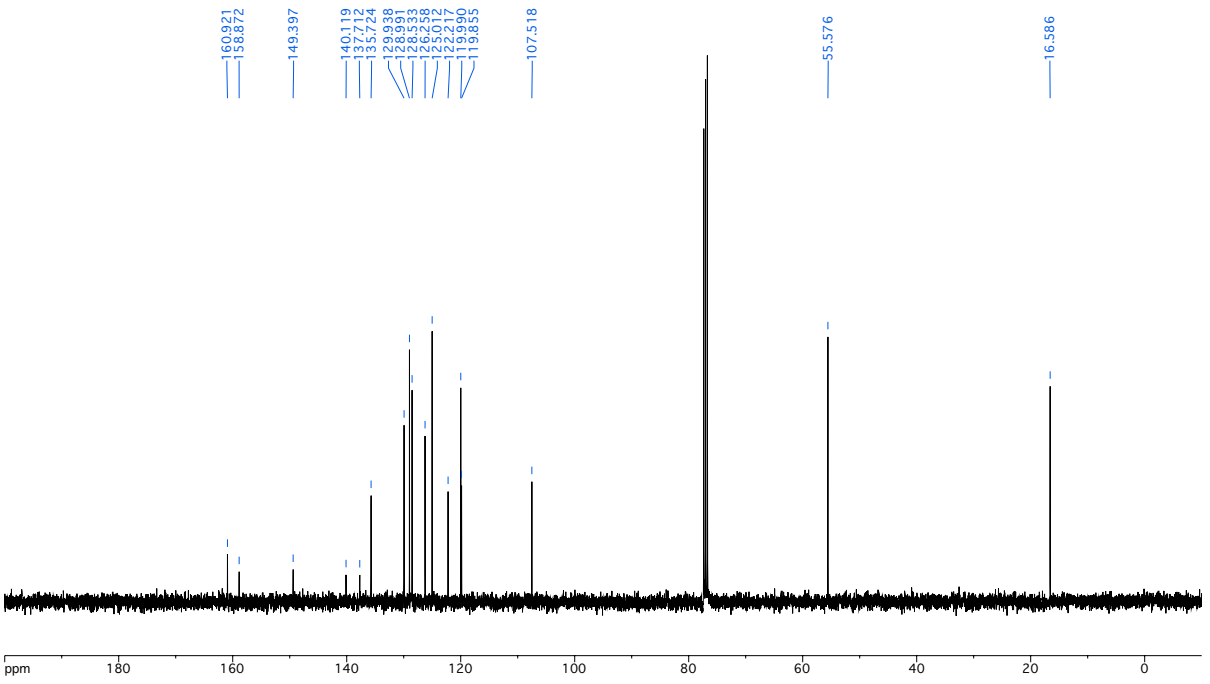

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3.17
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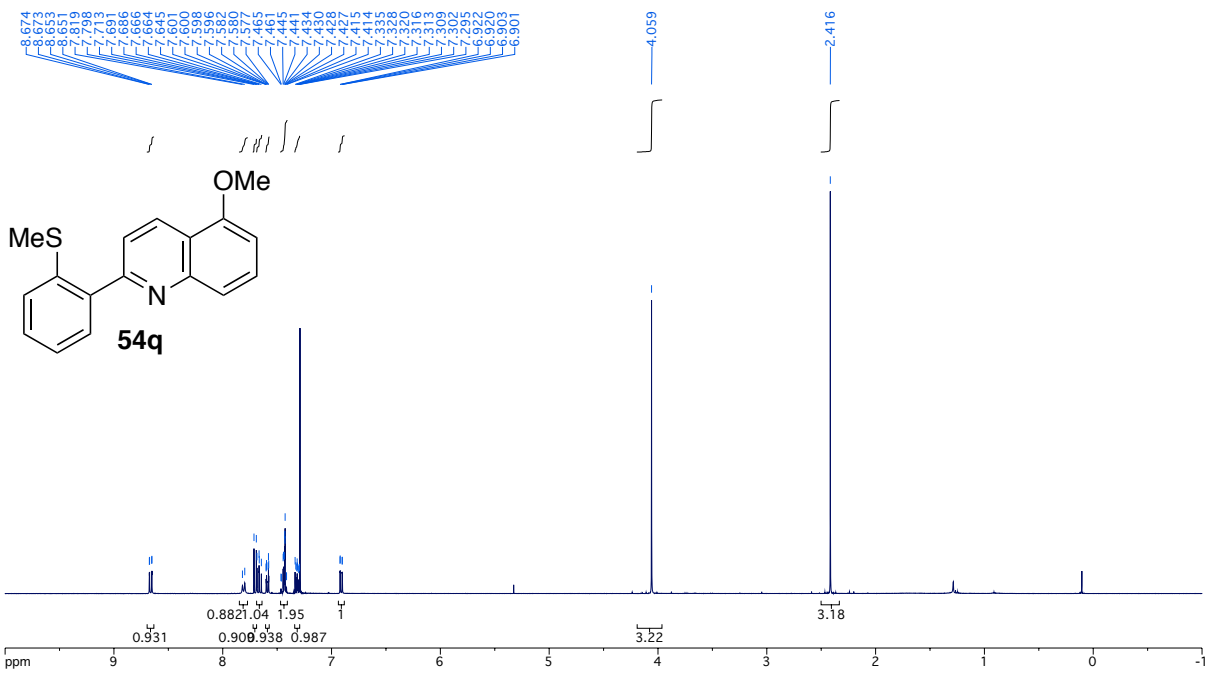

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142.823
140.263
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129.954
128.722
128.500
126.020
125.027
122.437
121.679
107.340
16.635
ppm

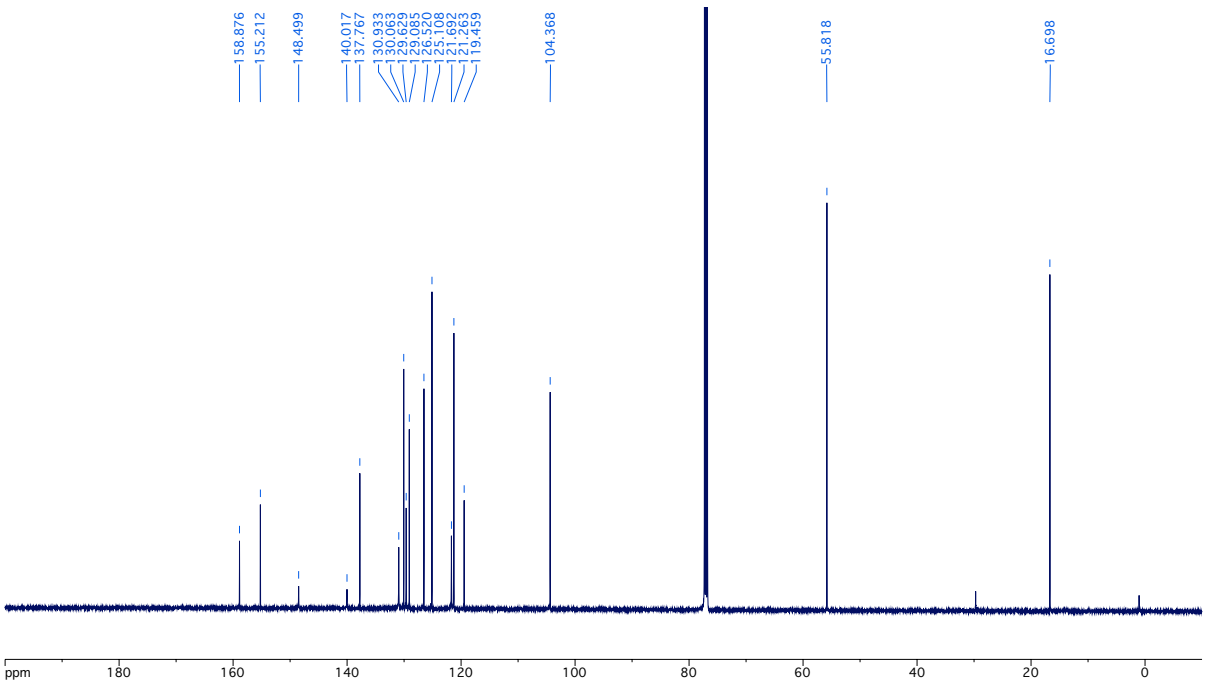

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8.258
8.237
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7.708
7.706
7.704
7.703
7.689
7.686
7.684
7.405
7.402
7.384
7.381
7.357
7.350
7.342
7.338
7.335
7.330
7.323
7.316
7.264
7.261
7.245
7.242
2.475
MeS
N
OH
54o
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1.08
1.06
1
0.806
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1.07
3.43
ppm
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6
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0
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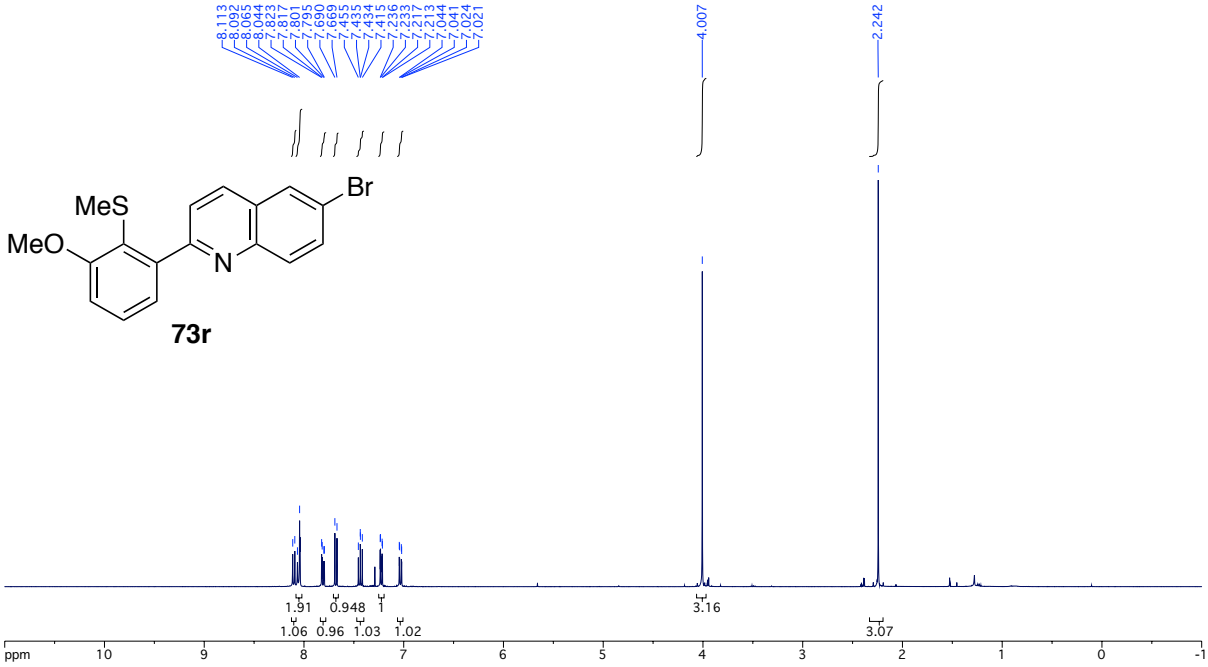

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138.080
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129.370
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127.096
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124.177
122.138
117.574
110.305
16.698
ppm
180
160
140
120
100
80
60
40
20
0


8.174
8.153
7.752
7.750
7.586
7.576
7.553
7.544
7.538
7.463
7.459
7.446
7.443
7.439
7.426
7.421
7.406
7.401
7.328
7.323
7.312
7.310
7.307
7.304
7.293
7.289
7.259
7.252
7.237
7.230
3.986
2.427
MeS
N
OMe
54p
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1.88
0.927
0.944
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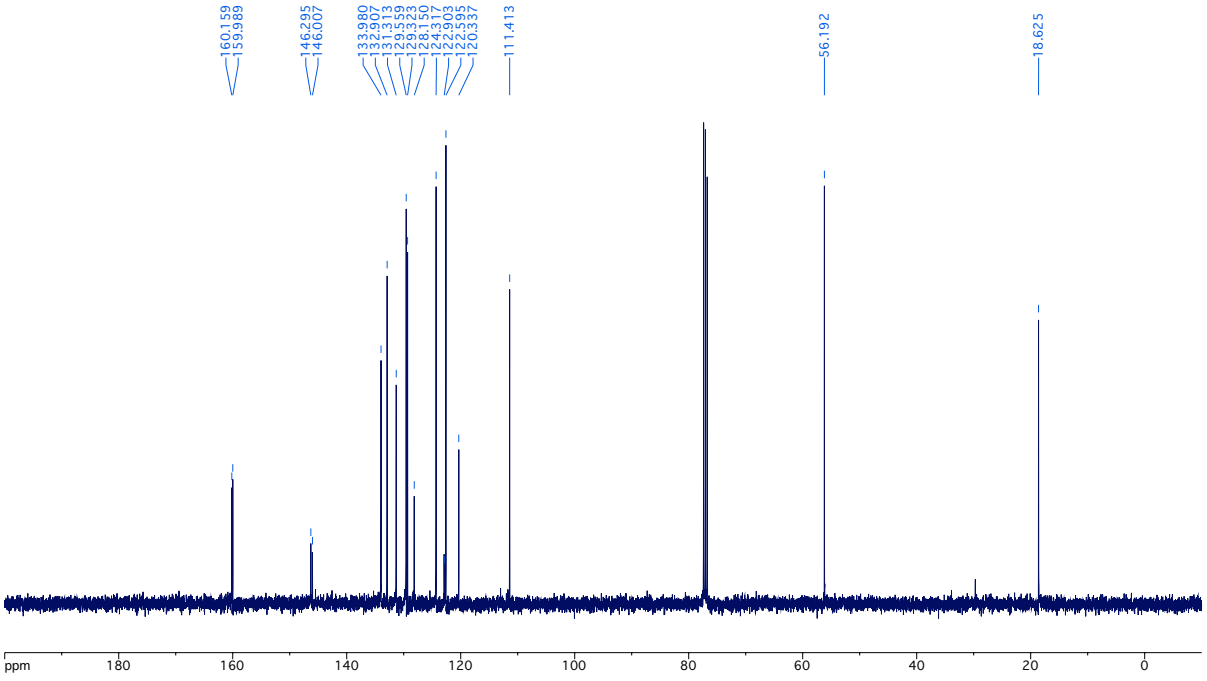

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140.119
137.712
135.724
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126.533
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107.518
55.576
16.586
ppm
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140
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60
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20
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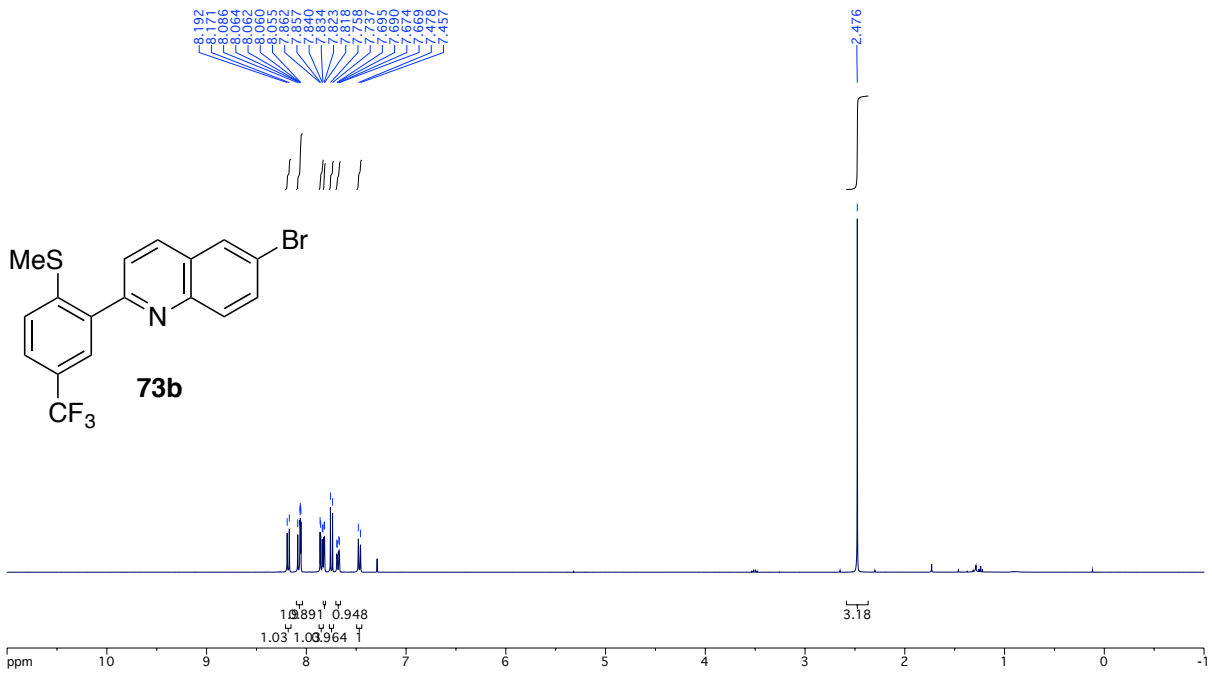

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8.673
8.653
8.651
7.819
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7.793
7.691
7.686
7.666
7.664
7.645
7.601
7.600
7.598
7.596
7.582
7.580
7.577
7.465
7.461
7.445
7.441
7.434
7.430
7.428
7.427
7.415
7.414
7.335
7.328
7.320
7.316
7.313
7.309
7.302
7.295
6.922
6.920
6.903
6.901
4.059
2.416
OMe
MeS
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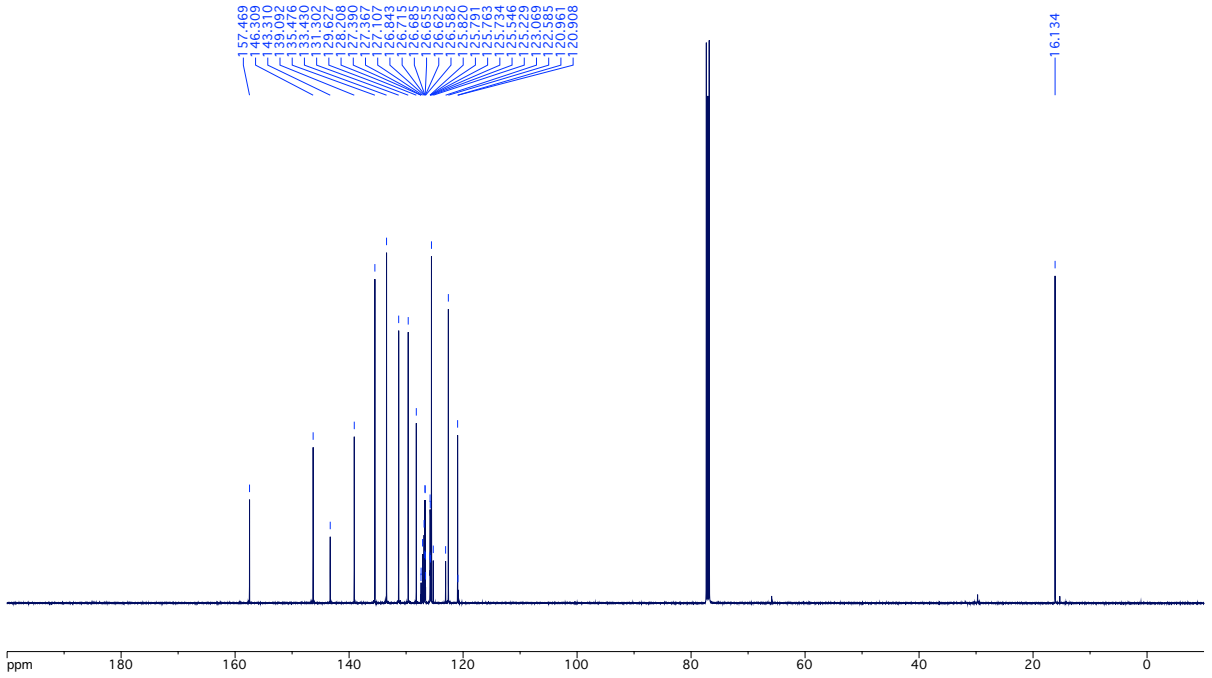

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129.085
126.520
125.108
121.692
121.263
113.459
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55.818
16.698
ppm

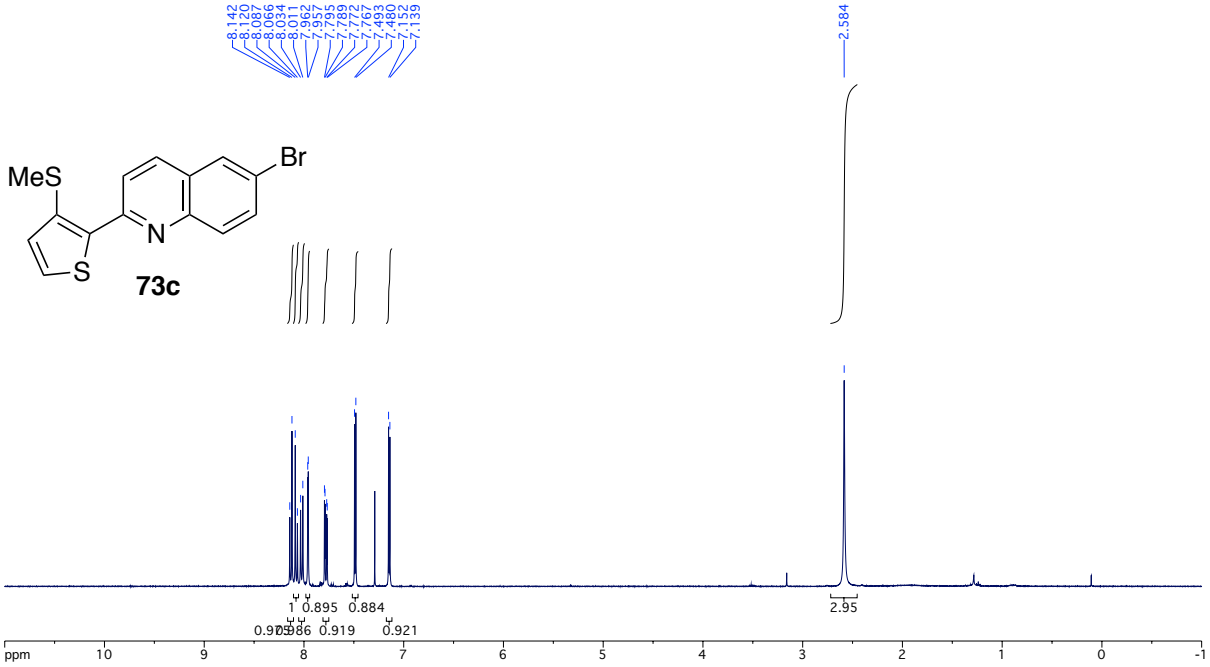

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8.092
8.085
8.044
7.823
7.817
7.801
7.795
7.690
7.669
7.655
7.435
7.434
7.415
7.236
7.233
7.217
7.213
7.044
7.041
7.024
7.021
4.007
2.242
MeS
MeO
Br
N
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0.948
1
3.16
1.06
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1.03
1.02
3.07
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6
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2
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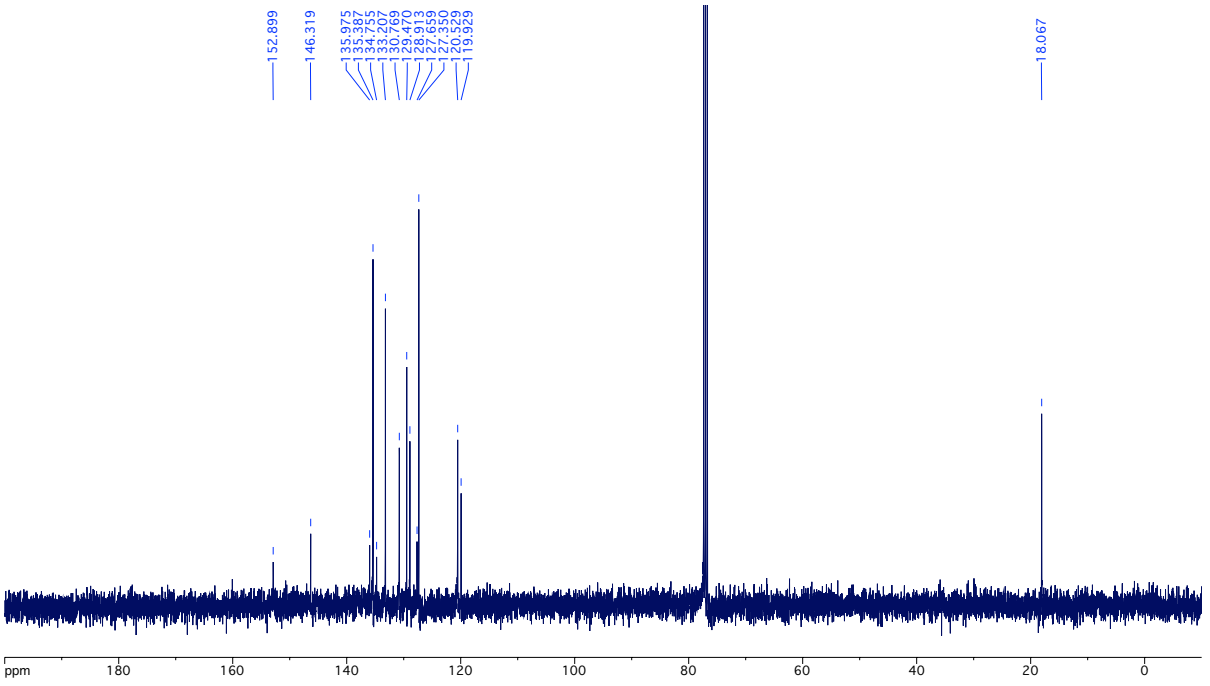
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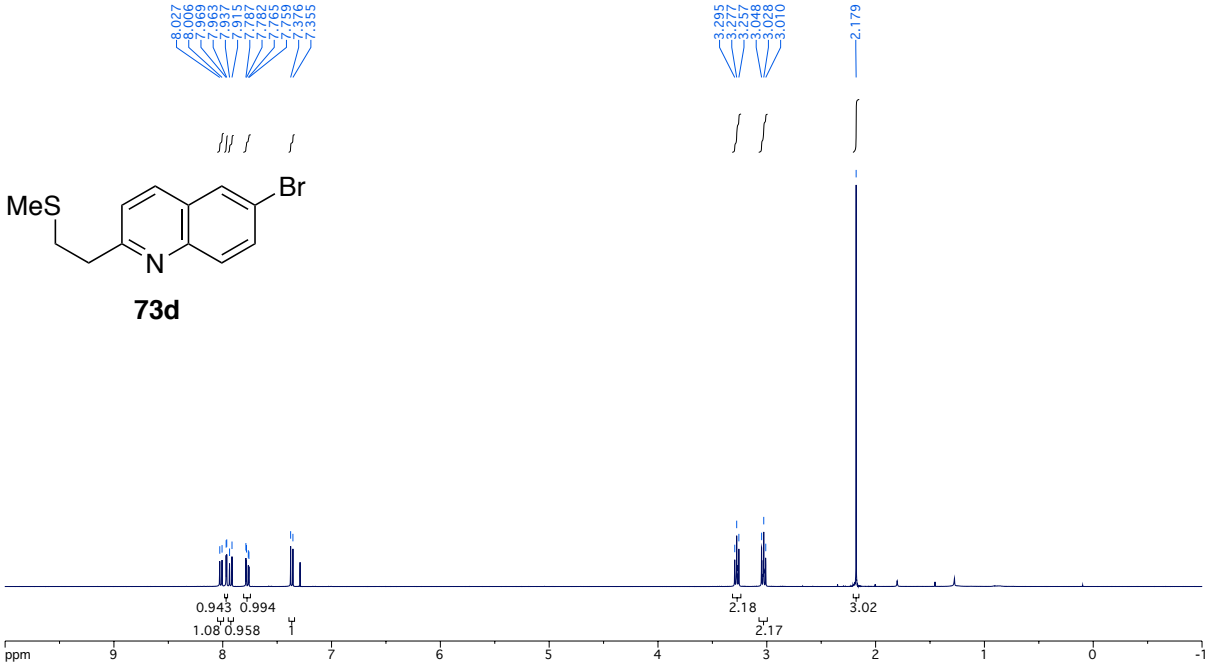

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159.989
146.295
146.007
139.980
133.917
133.113
130.559
129.323
128.150
124.317
122.903
122.595
120.337
111.413
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18.625
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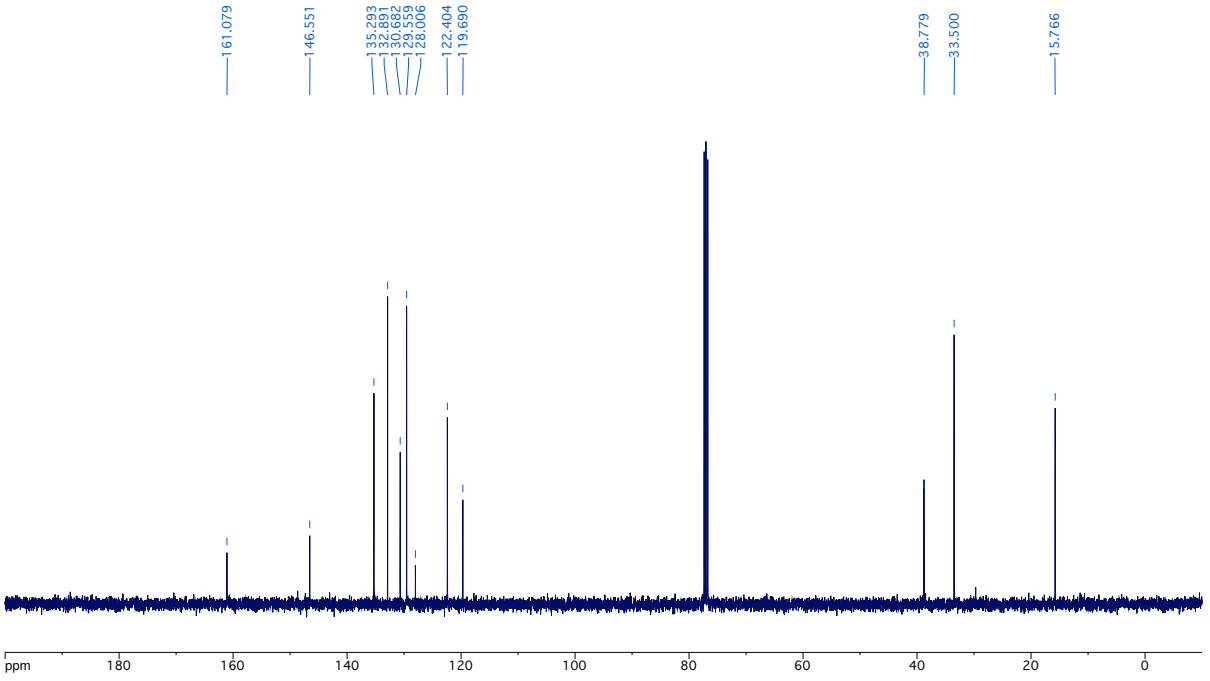

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8.171
8.086
8.064
8.062
8.060
8.055
7.862
7.857
7.840
7.834
7.823
7.818
7.758
7.737
7.695
7.690
7.674
7.669
7.478
7.457
2.476
MeS
Br
N
CF3
73b
1.03
1.00
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3.18
ppm
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6
5
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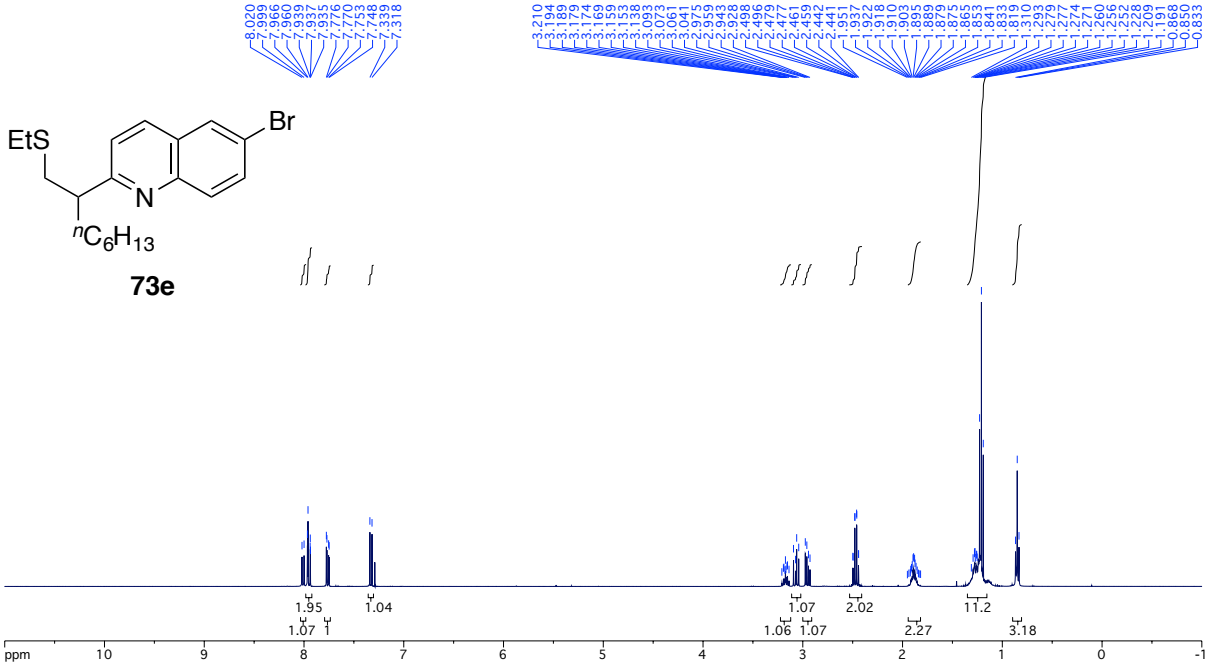

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129.627
129.208
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127.107
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126.715
126.685
126.655
126.625
125.820
125.791
125.763
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125.546
123.229
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20
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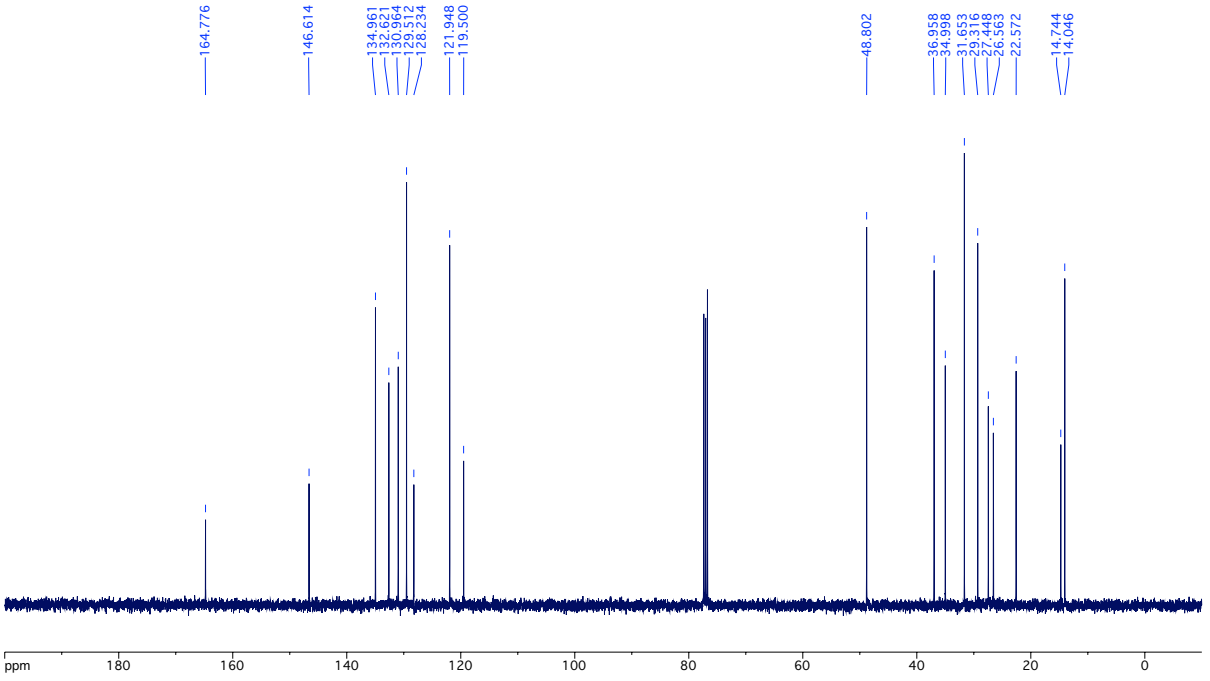

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7.957
7.795
7.789
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7.767
7.493
7.480
7.132
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Br
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S
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2.95
ppm

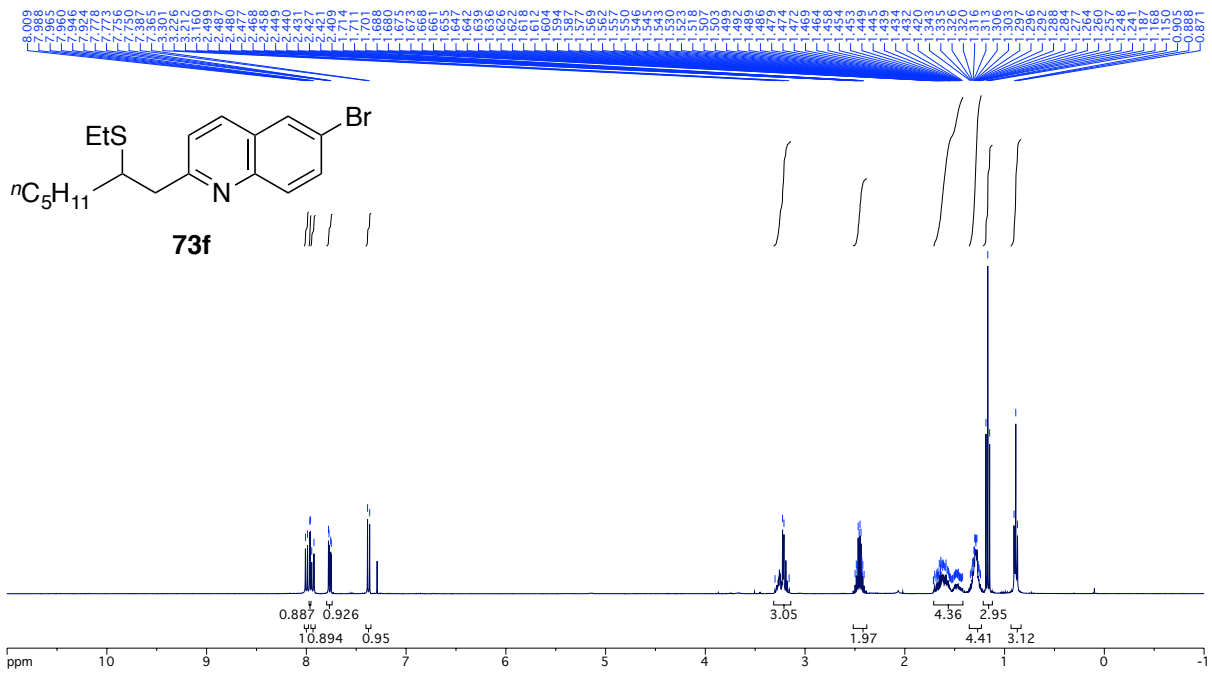

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127.135
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ppm

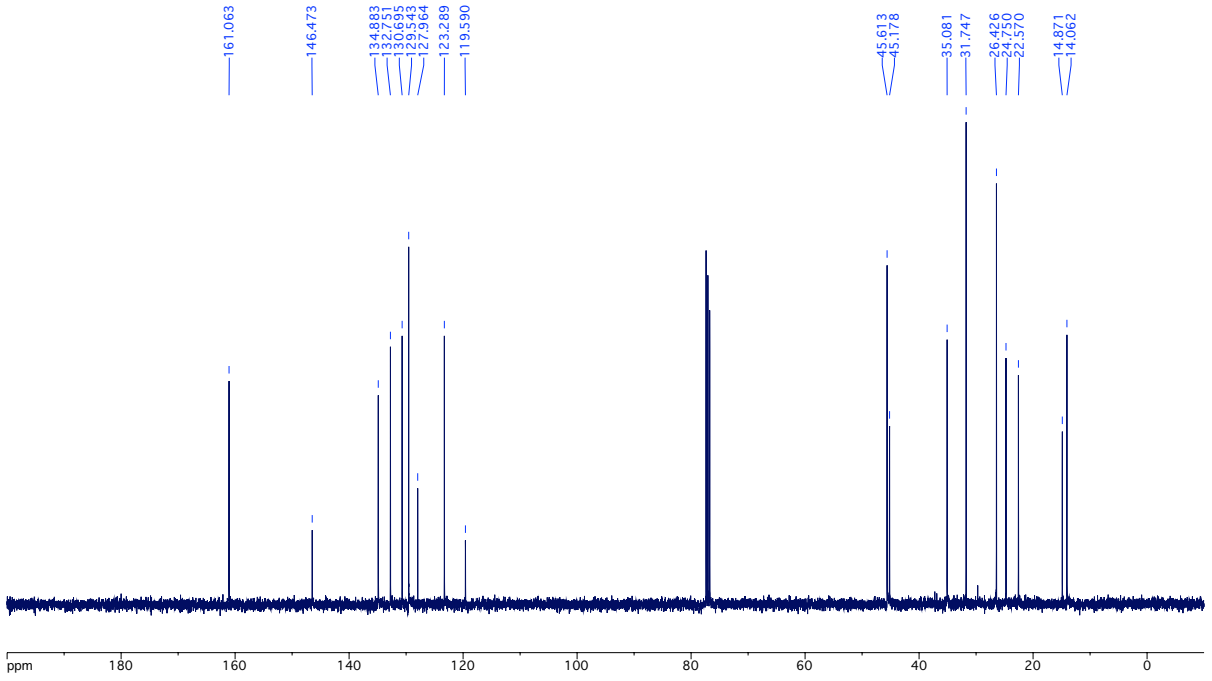

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7.765
7.759
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7.355
3.295
3.277
3.247
3.048
3.028
3.010
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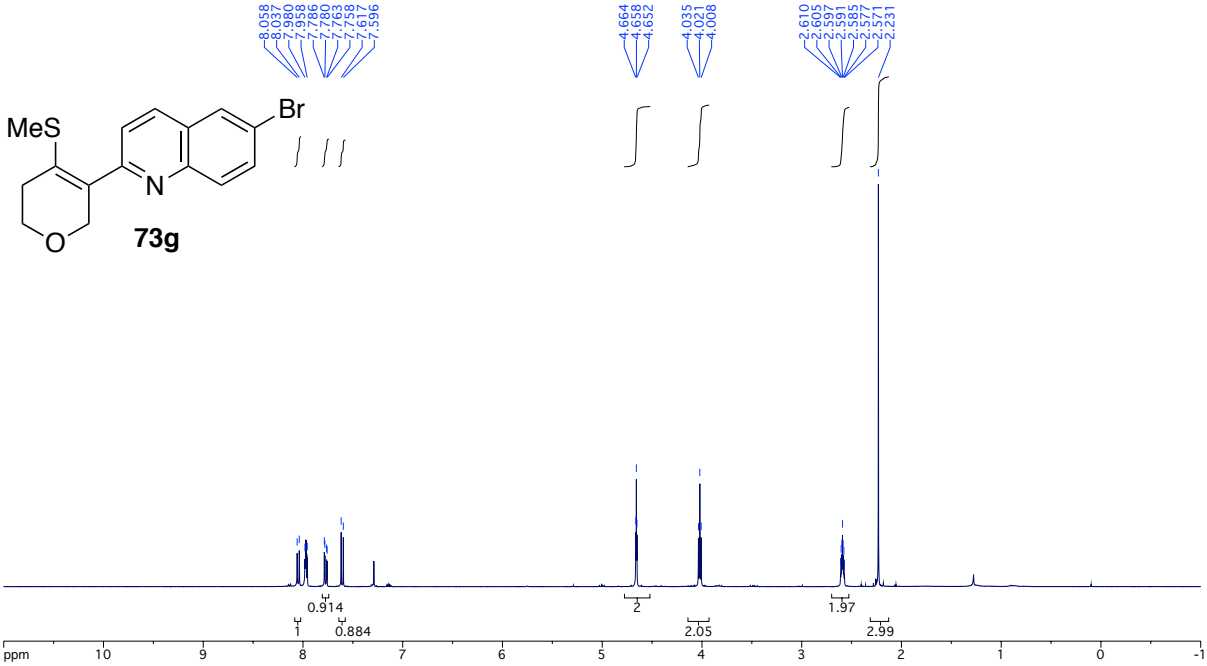

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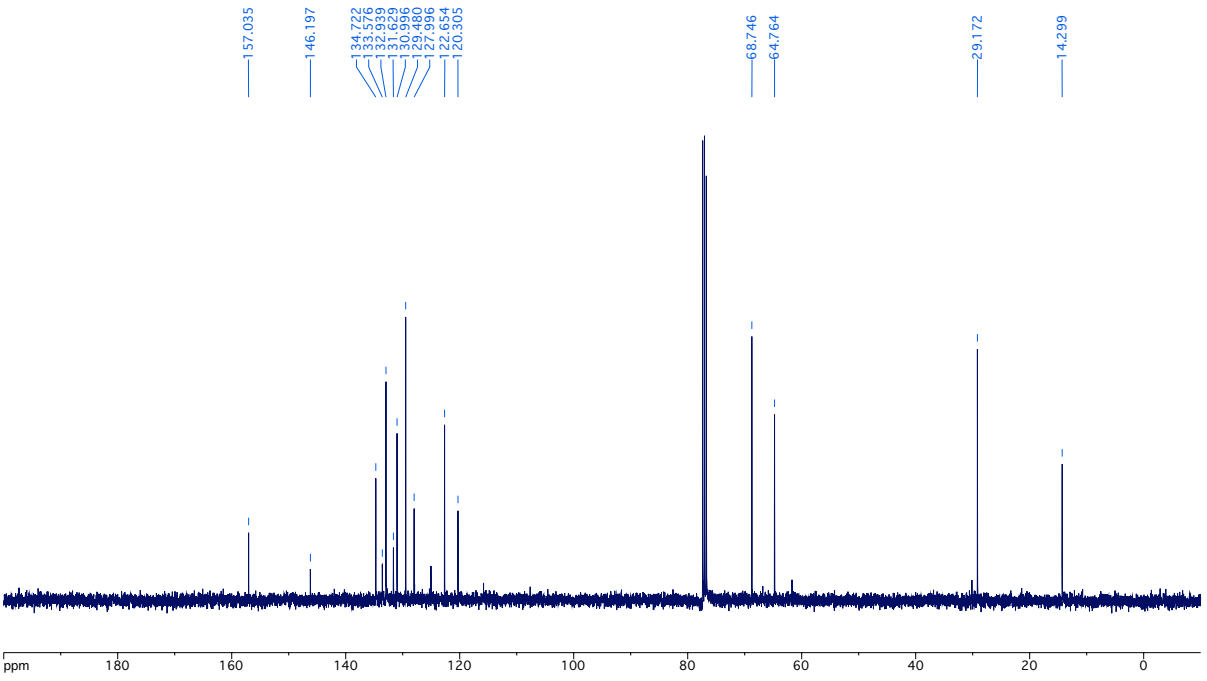

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7.748
7.339
7.318
3.210
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3.189
3.179
3.174
3.169
3.153
3.138
3.093
3.073
3.061
3.041
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1.918
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1.875
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1.853
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1.256
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1.209
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0.850
0.833
EtS
Br
N
nC6H13
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1.07
1
1.04
1.07
1.06
1.07
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6
5
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-1

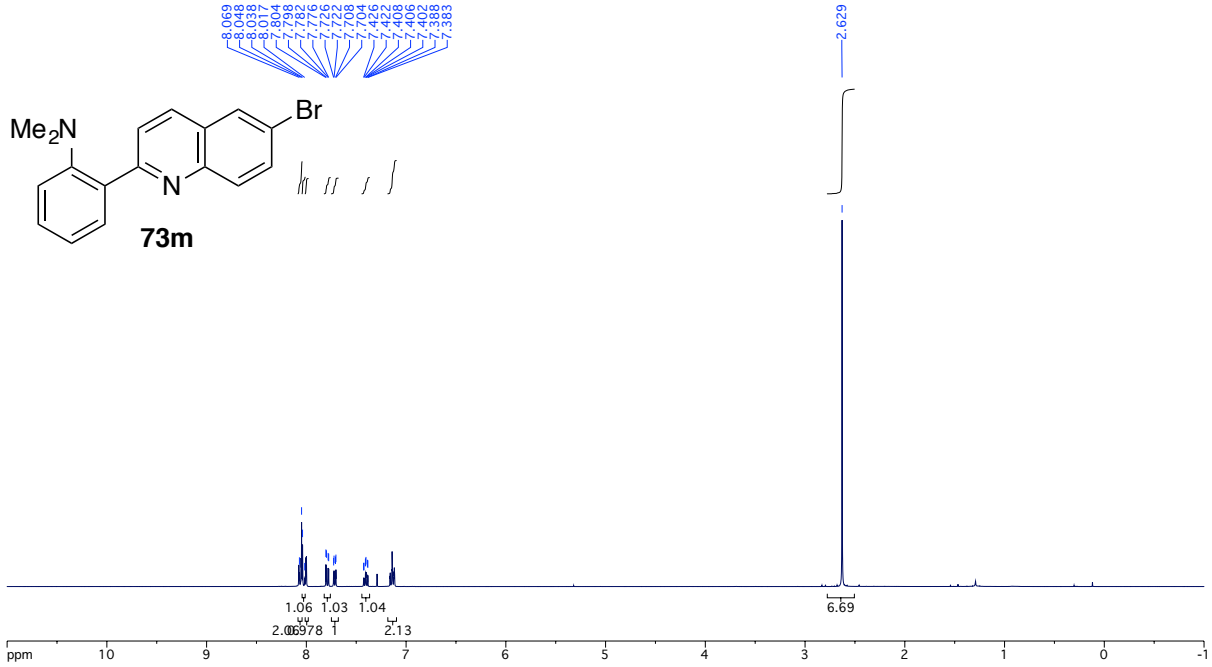

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31.653
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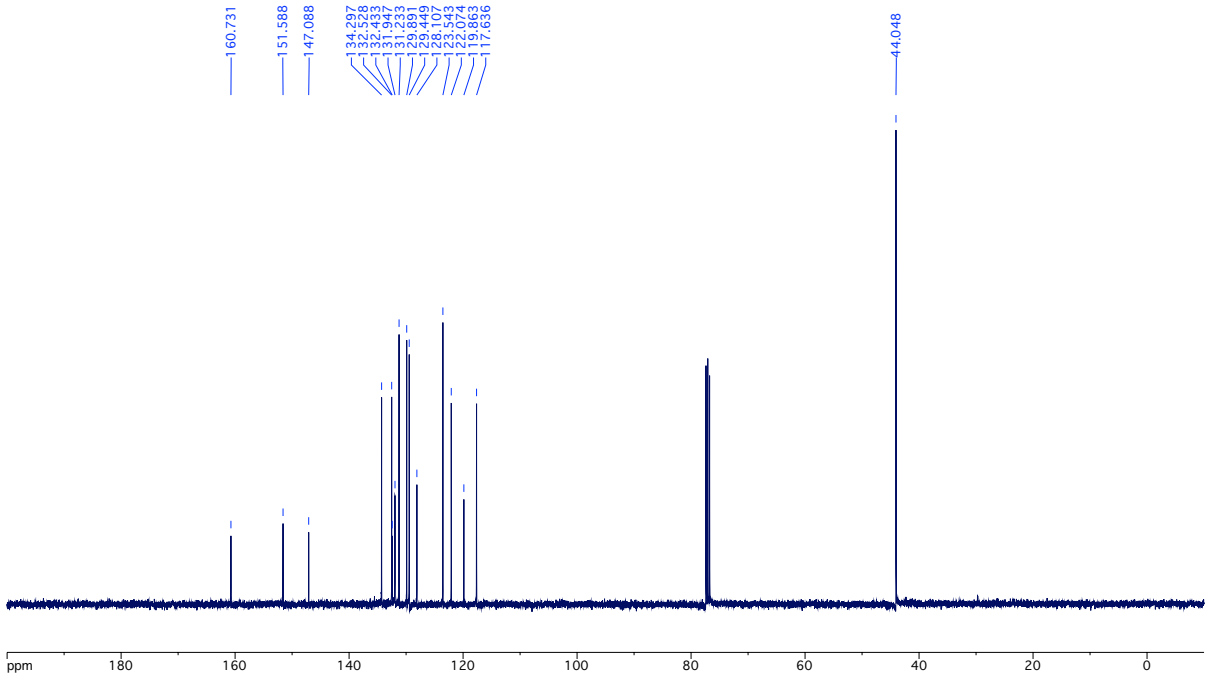

EtS
Br
$^{n}C_5H_{11}$
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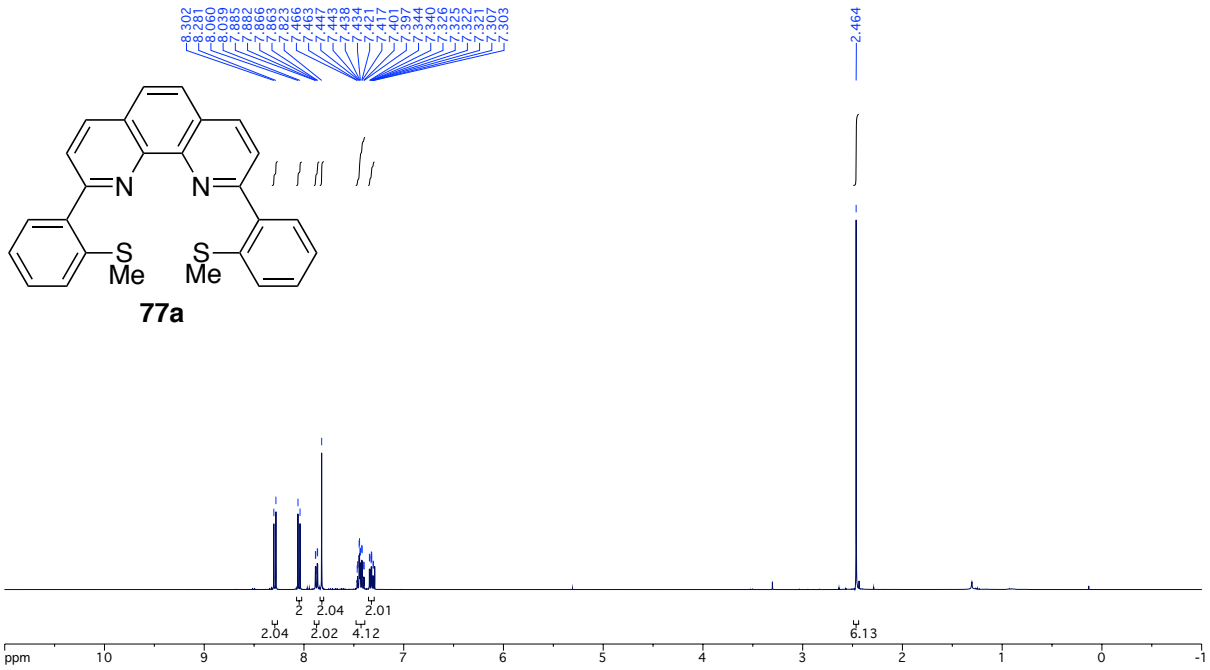

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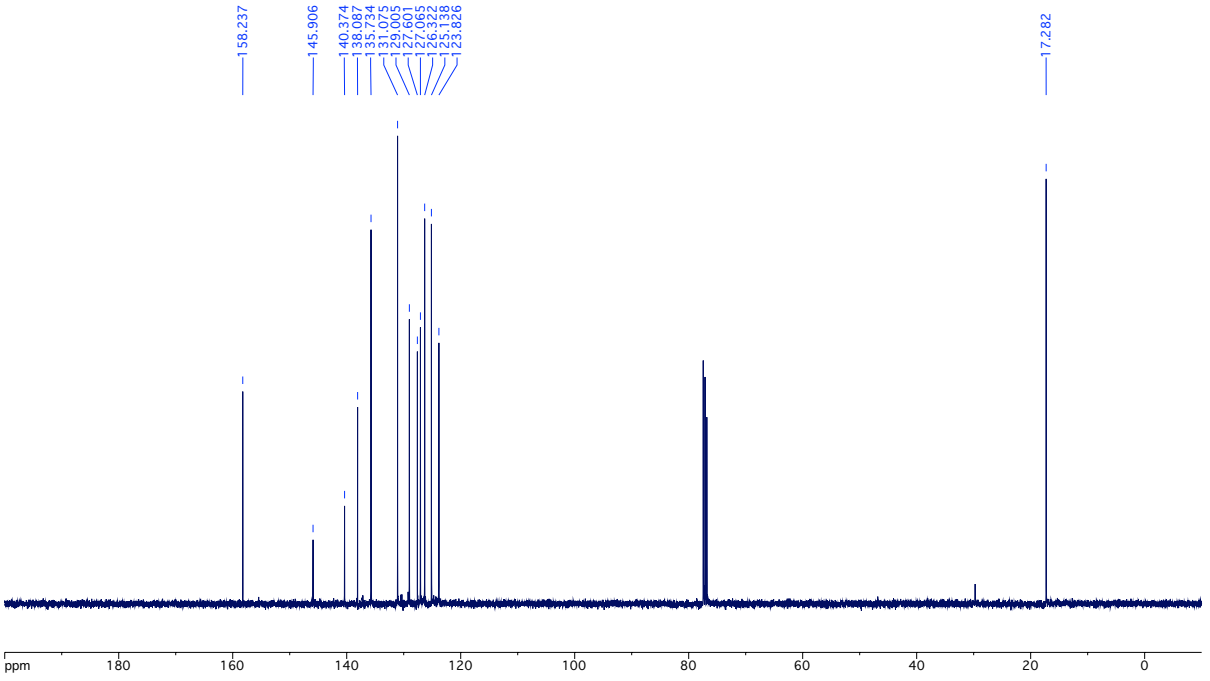

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7.596
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4.652
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4.021
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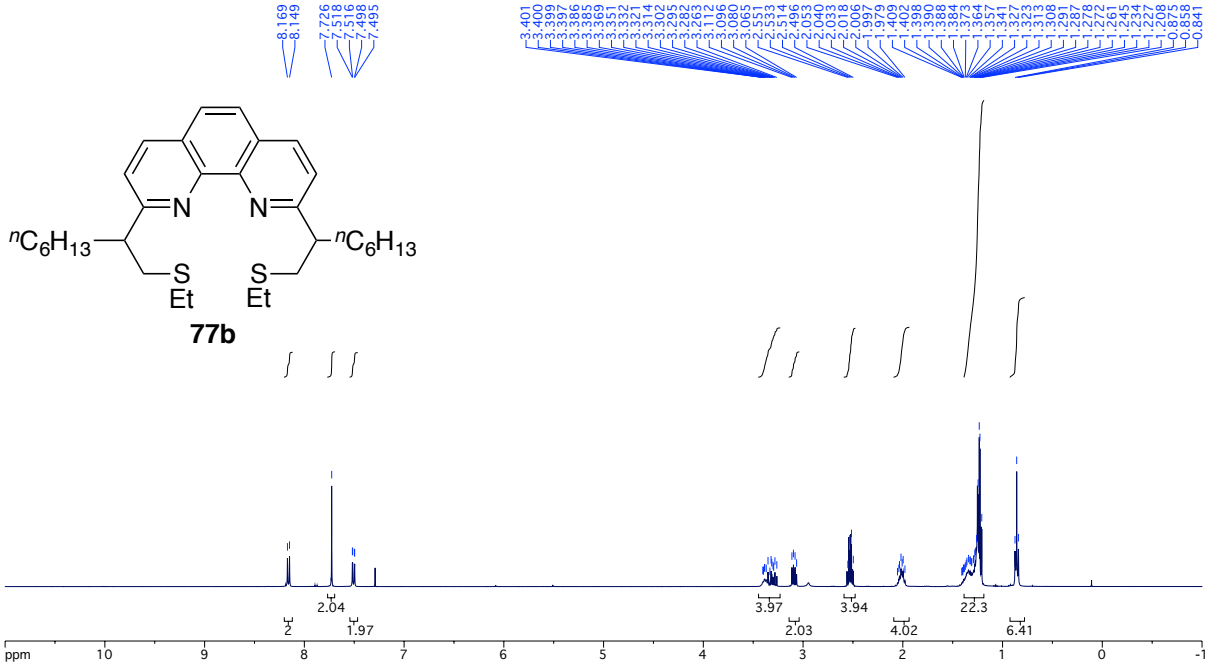

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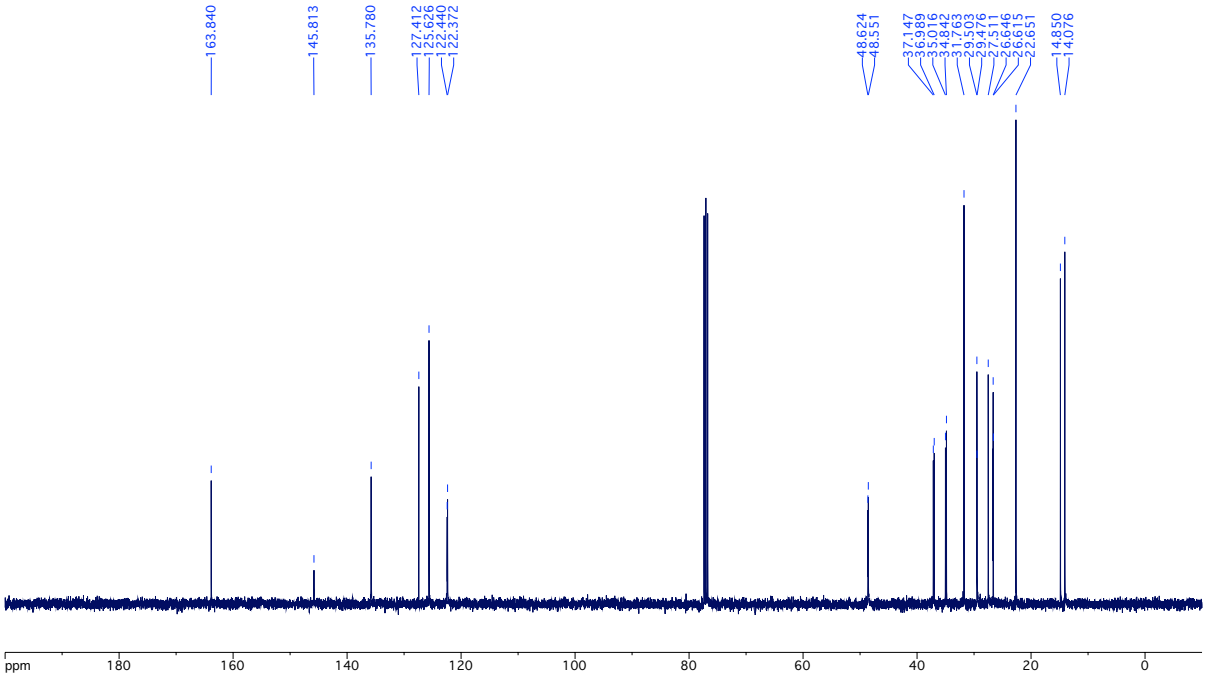

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7.408
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Br
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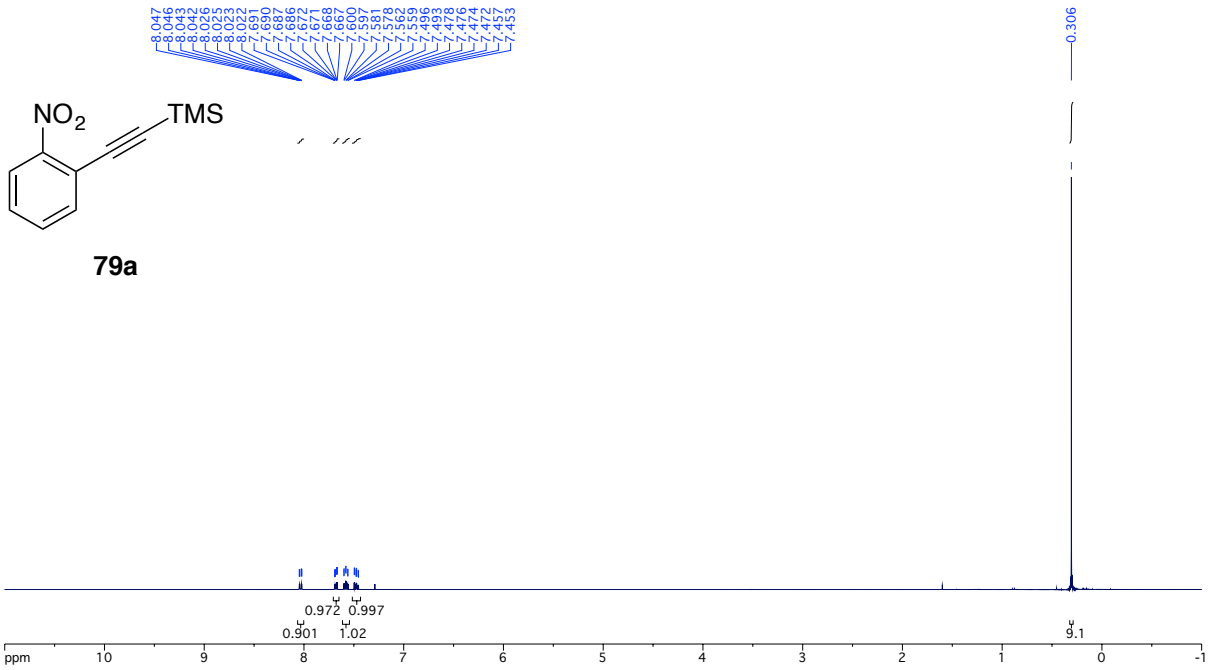

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128.107
123.543
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119.863
117.636
44.048
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8.302
8.281
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8.039
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Me
S
Me
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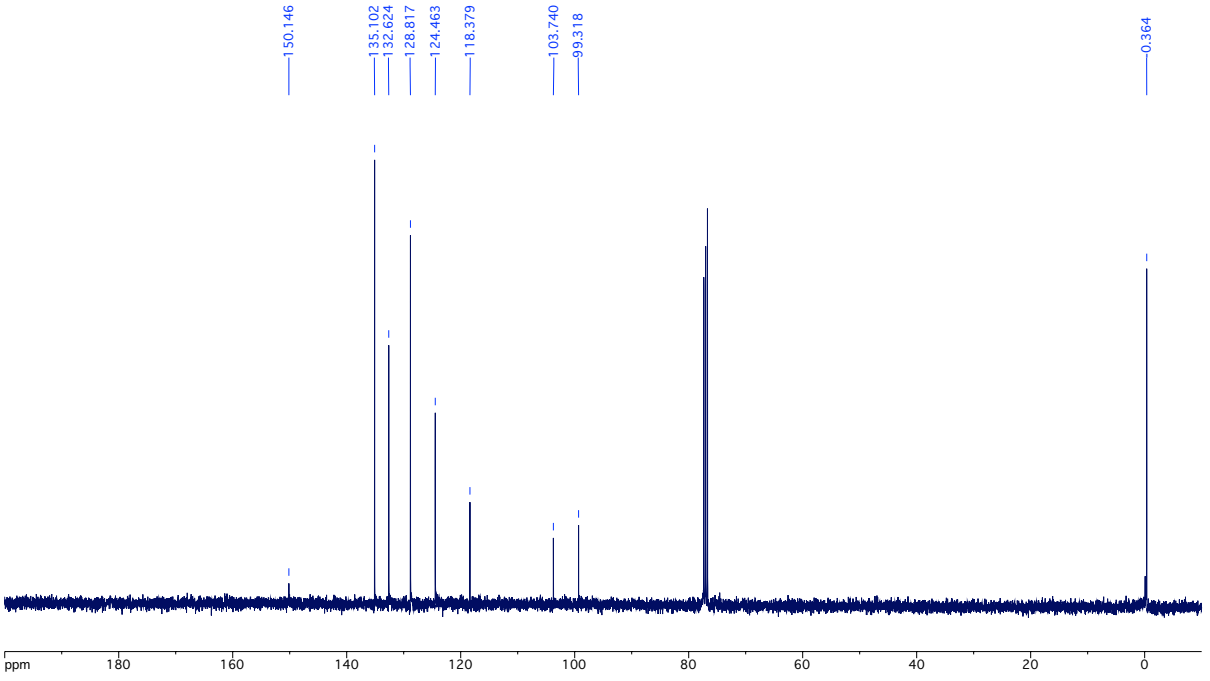

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127.601
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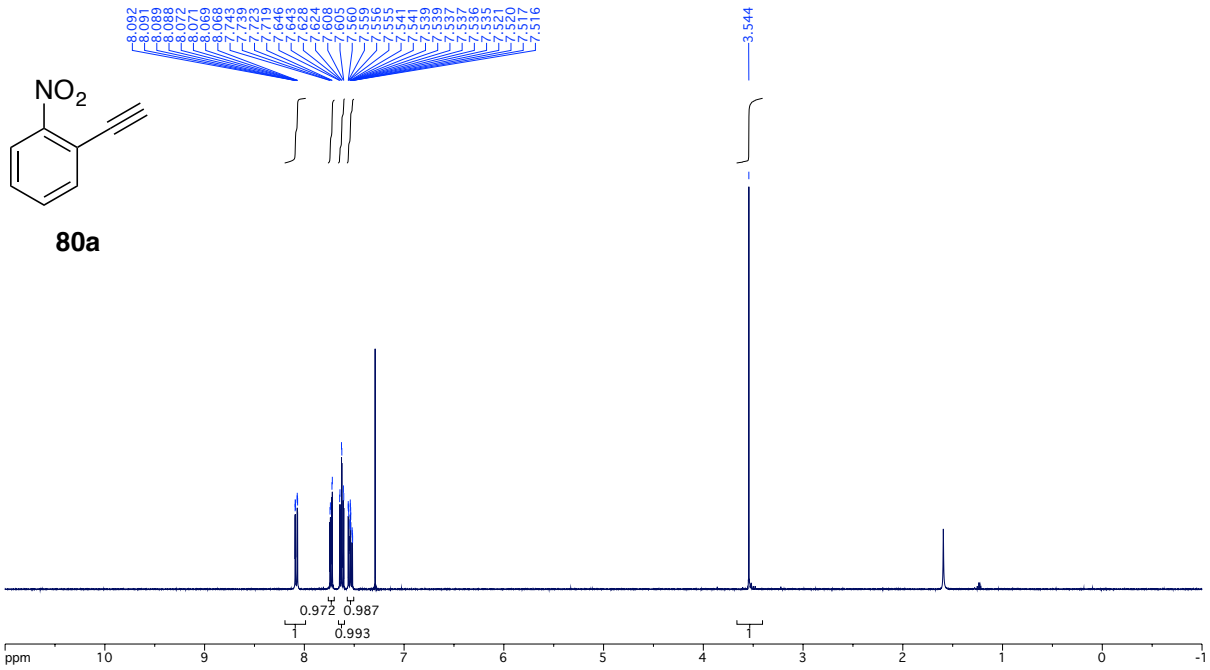

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0.841
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nC6H13
nC6H13
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ppm

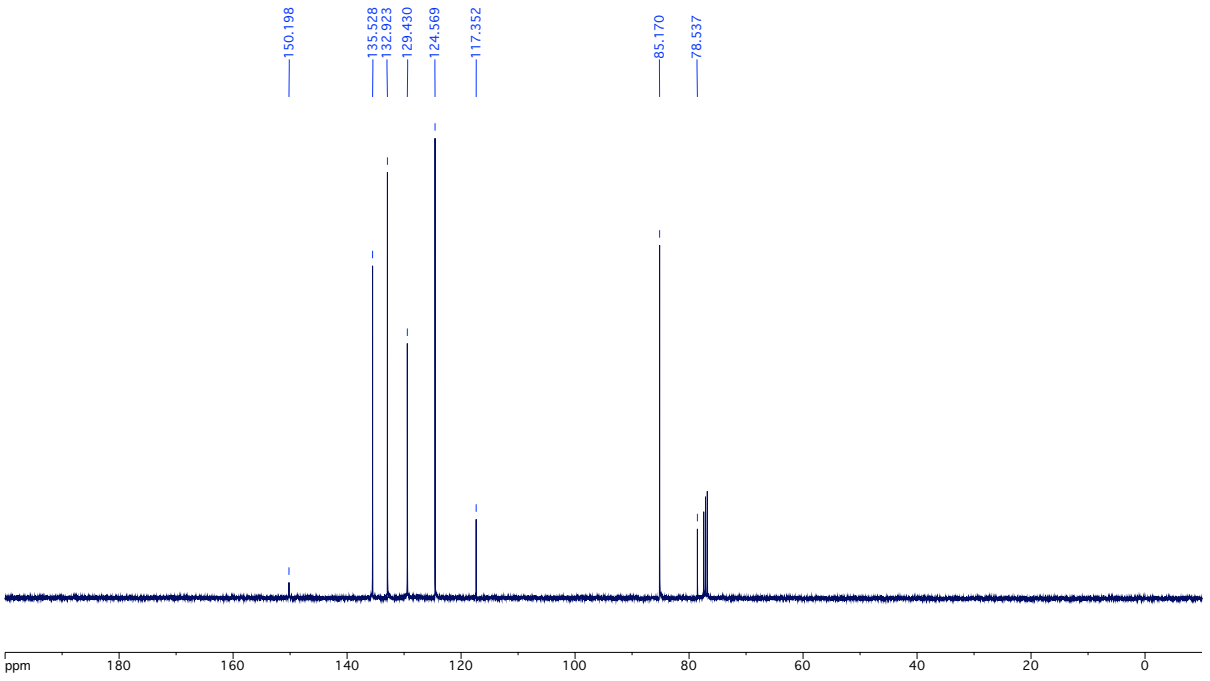

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135.780
127.412
125.626
122.440
122.372
48.624
48.551
37.147
36.989
35.016
34.842
31.763
29.503
29.476
27.511
26.646
26.615
22.651
14.850
14.076
ppm

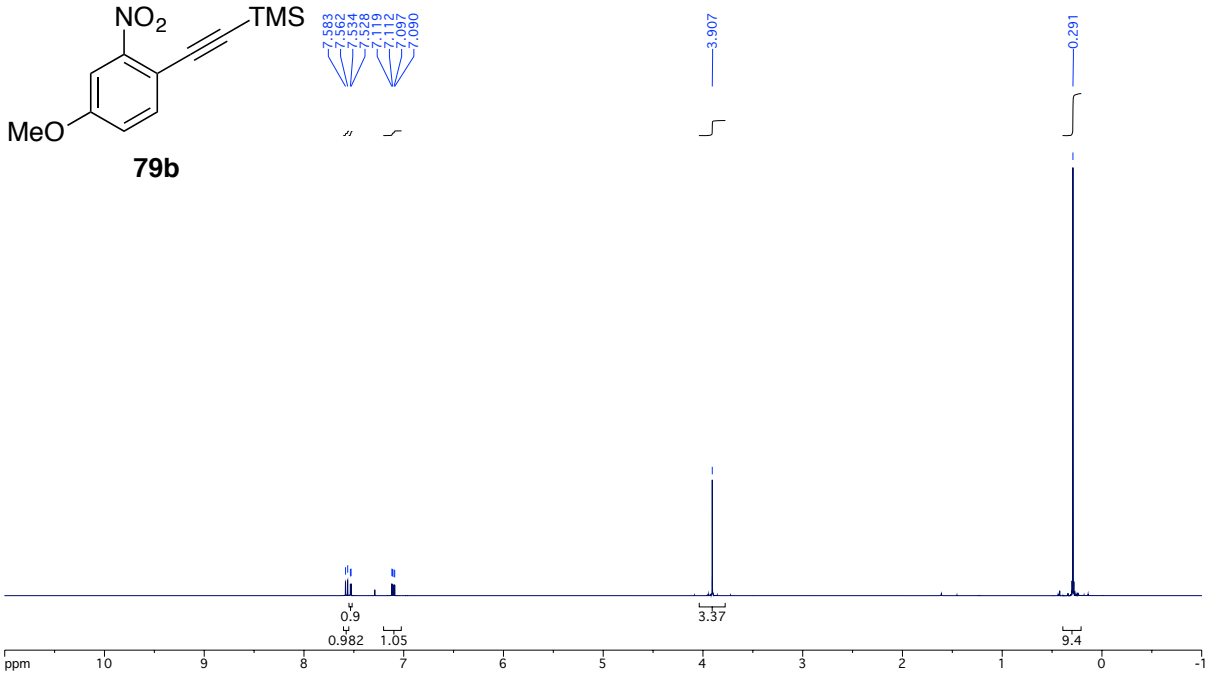

8.047
8.046
8.043
8.042
8.026
8.025
8.023
8.022
7.691
7.690
7.687
7.686
7.672
7.671
7.668
7.667
7.600
7.597
7.581
7.578
7.562
7.559
7.496
7.493
7.478
7.476
7.474
7.472
7.457
7.453
0.306
0.972
0.997
0.901
1.02
9.1
ppm

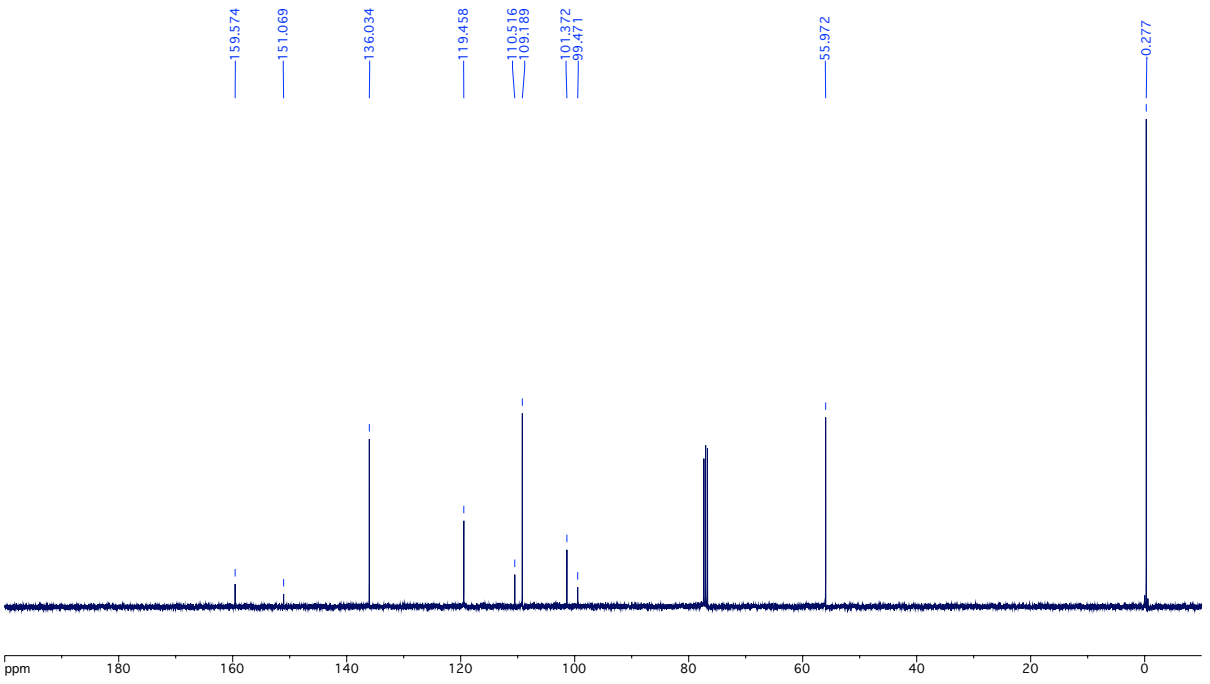
79a

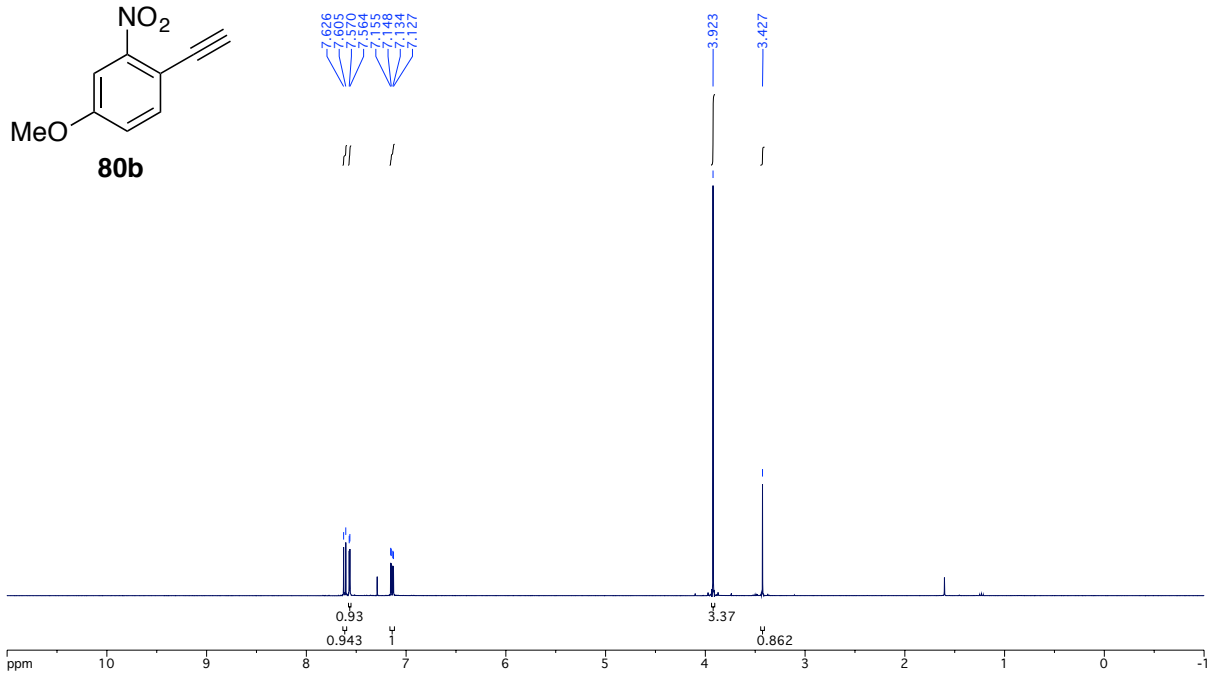

150.146
135.102
132.624
128.817
124.463
118.379
103.740
99.318
0.364
ppm

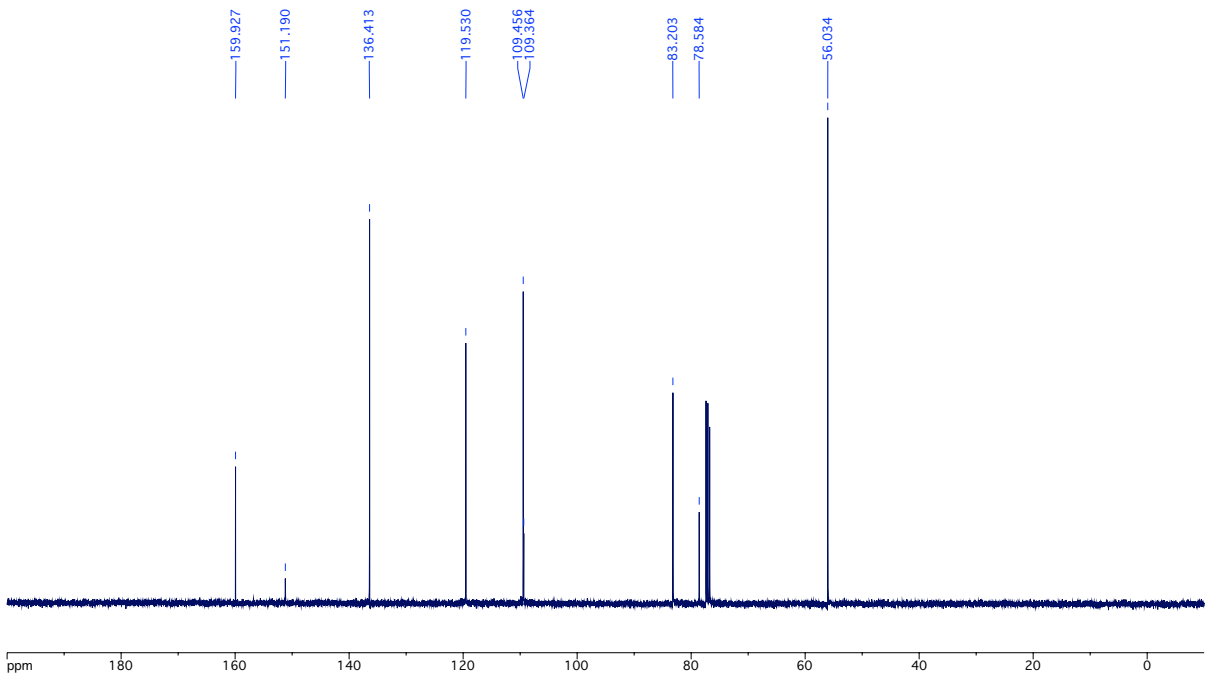

8.092
8.091
8.089
8.088
8.072
8.071
8.069
8.068
7.743
7.739
7.733
7.719
7.646
7.643
7.628
7.624
7.608
7.605
7.560
7.559
7.556
7.555
7.541
7.541
7.539
7.539
7.537
7.537
7.536
7.535
7.521
7.520
7.517
7.516
3.544
NO2
80a
0.972
0.987
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1
1
1
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

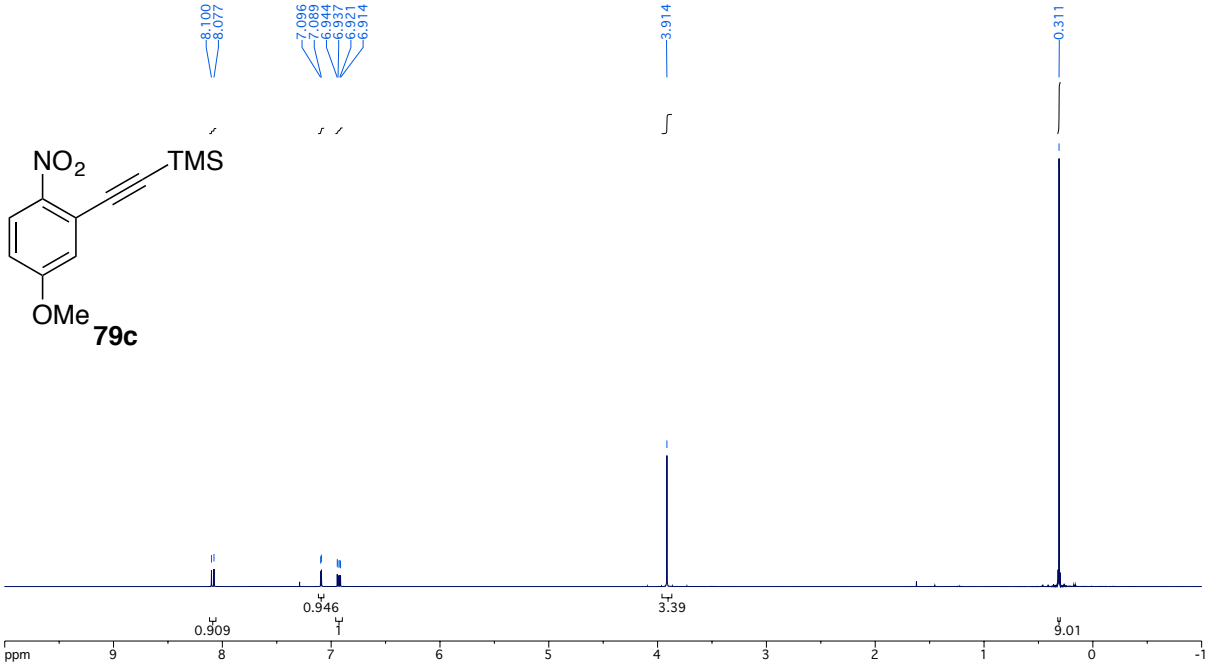

150.198
135.528
132.923
129.430
124.569
117.352
85.170
78.537
ppm
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160
140
120
100
80
60
40
20
0

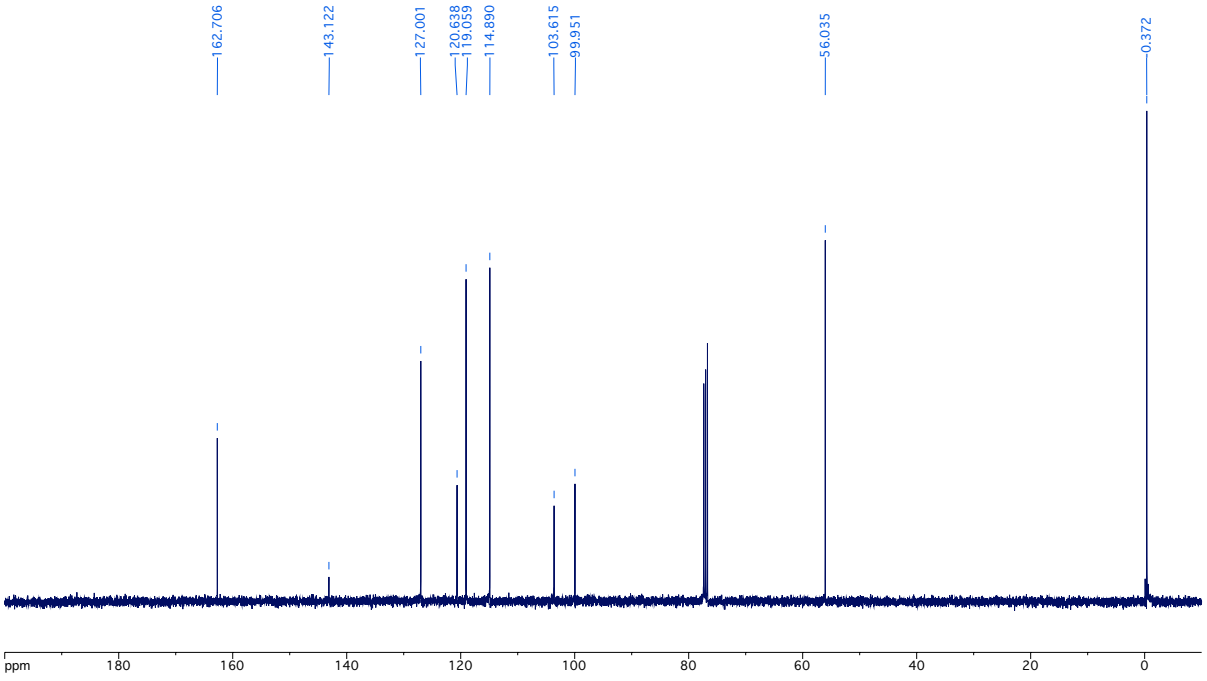

NO2
TMS
MeO
79b
7.583
7.562
7.534
7.528
7.119
7.112
7.092
7.090
3.907
0.291
0.9
0.982
1.05
3.37
9.4
ppm

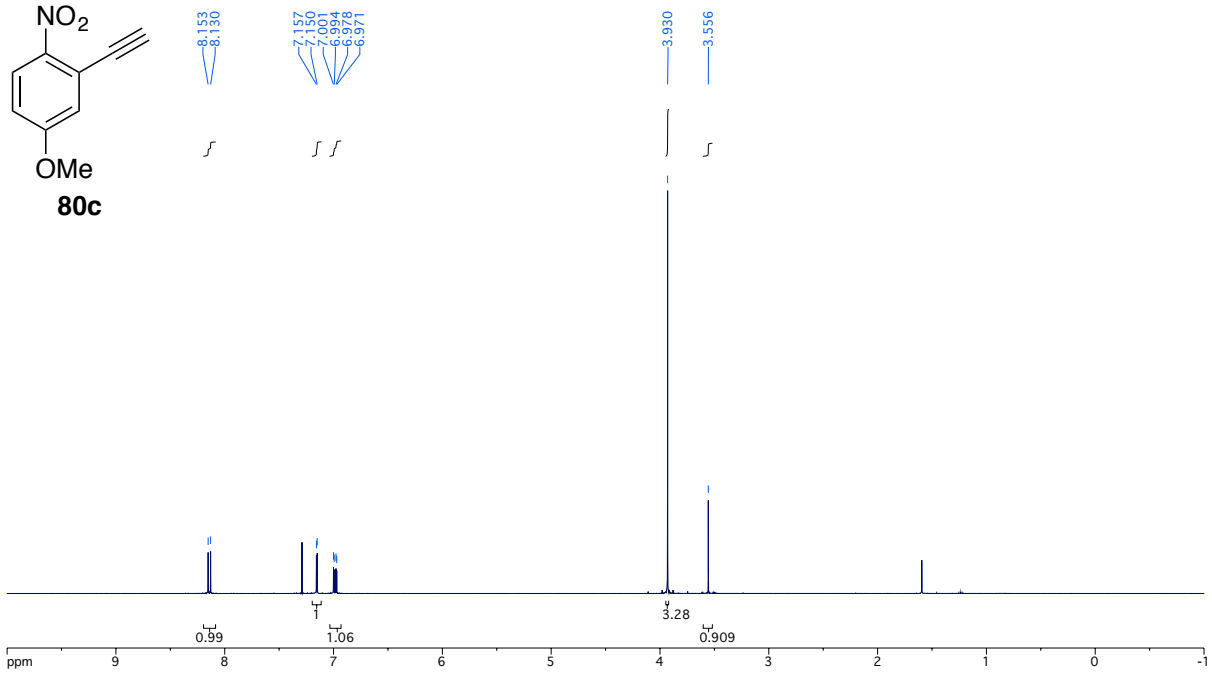

159.574
151.069
136.034
119.458
110.516
109.189
101.372
99.471
55.972
0.277
ppm

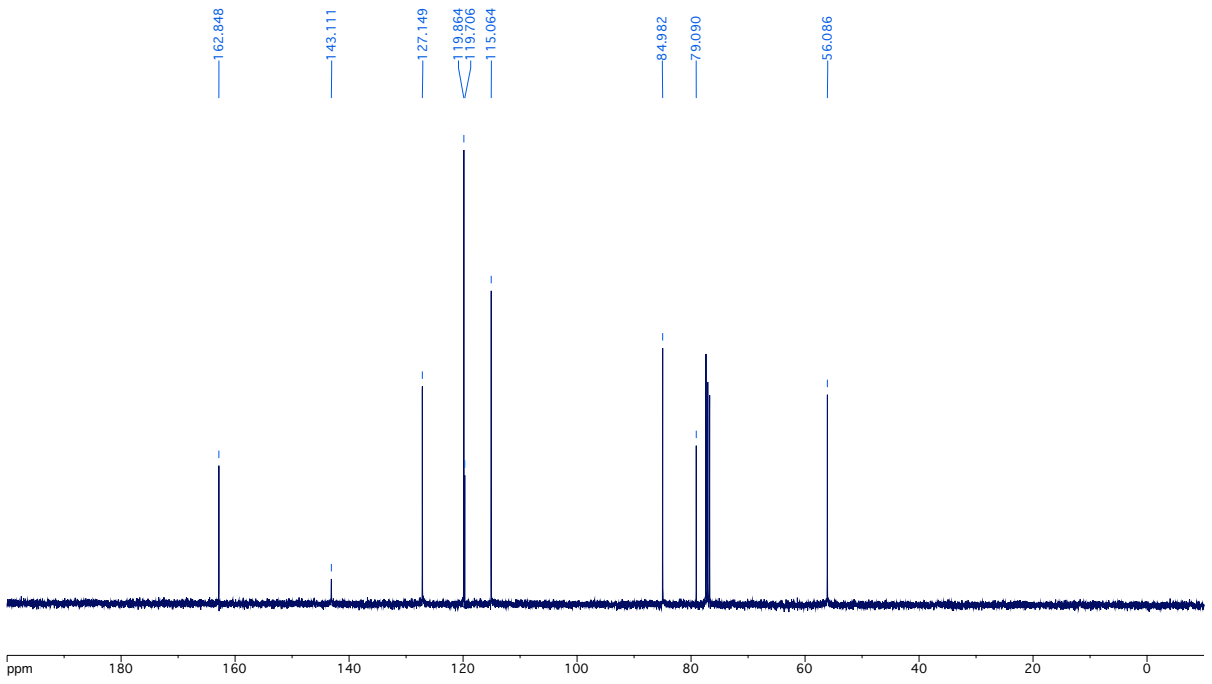

NO2
MeO
80b
7.626
7.605
7.570
7.564
7.155
7.148
7.134
7.127
3.923
3.427
0.93
0.943
1
3.37
0.862
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

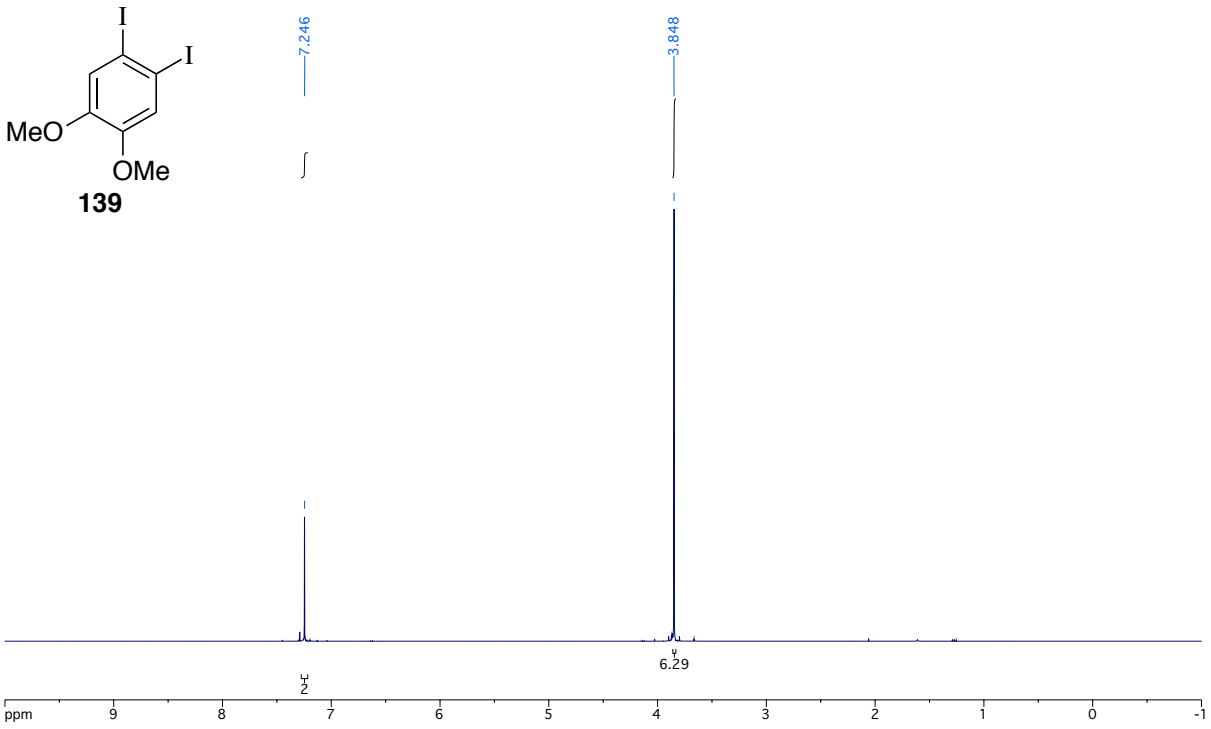

159.927
151.190
136.413
119.530
109.456
109.364
83.203
78.584
56.034
ppm
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140
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60
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20
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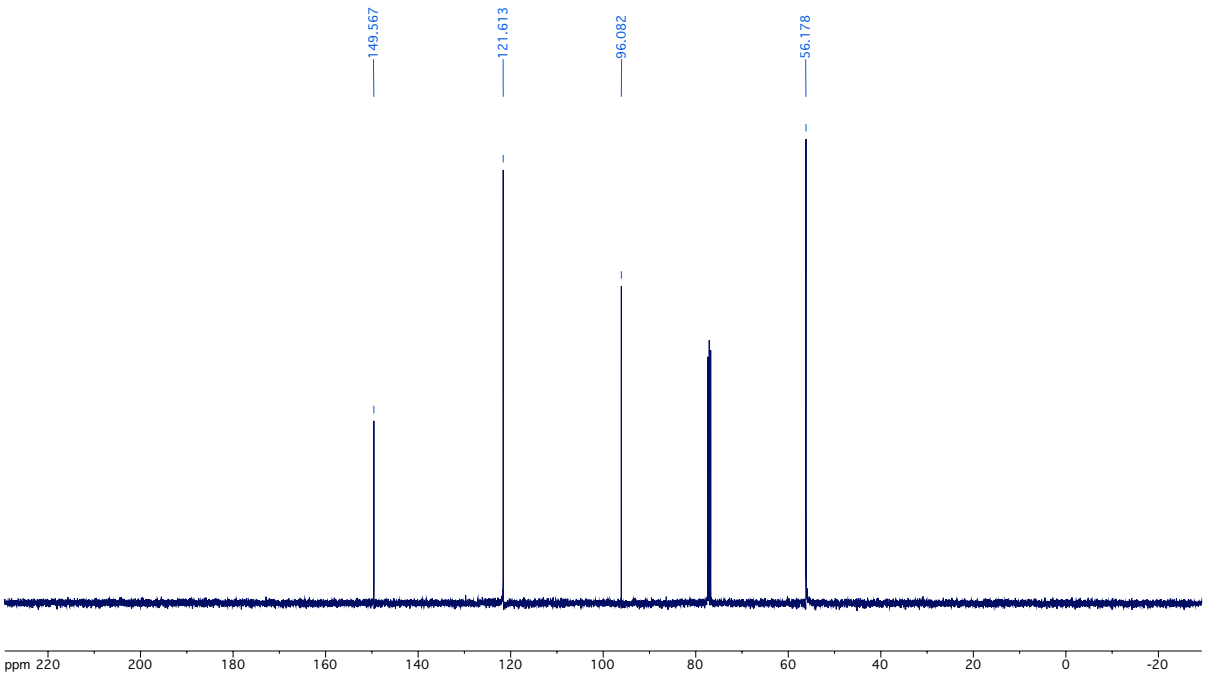

8.100
8.077
7.096
7.089
6.944
6.937
6.921
6.914
3.914
0.311
NO2
TMS
OMe
79c
0.946
3.39
0.909
1
9.01
ppm

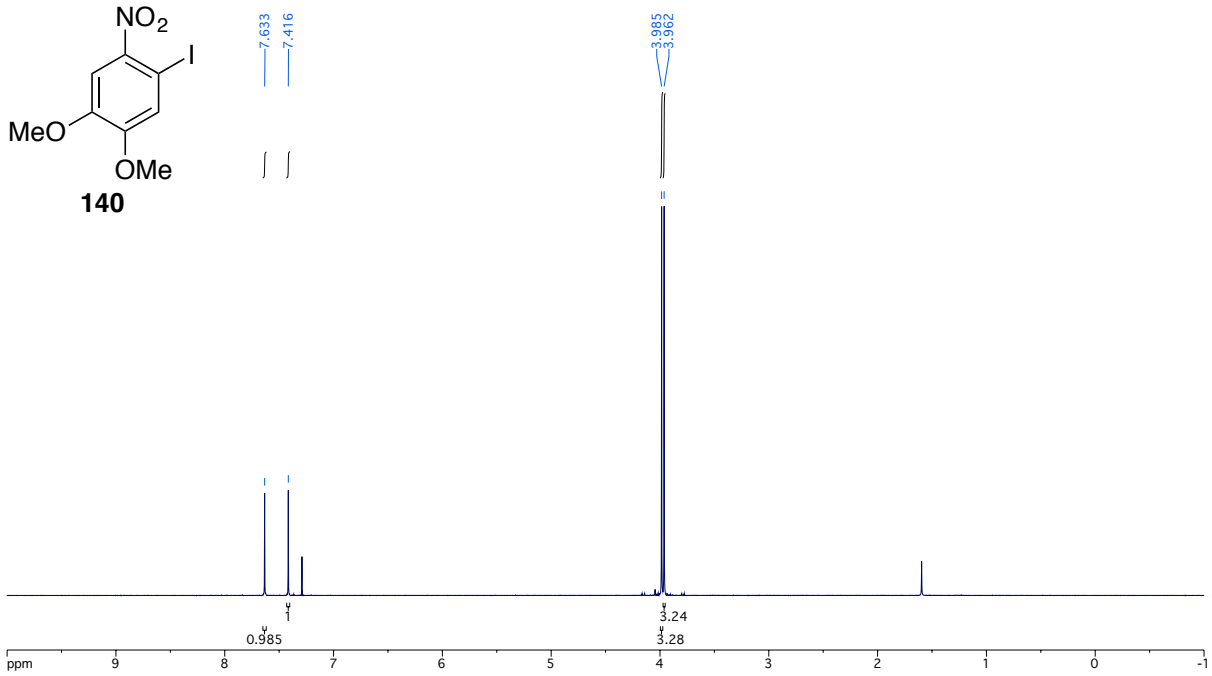

162.706
143.122
127.001
120.638
119.059
114.890
103.615
99.951
56.035
0.372
ppm

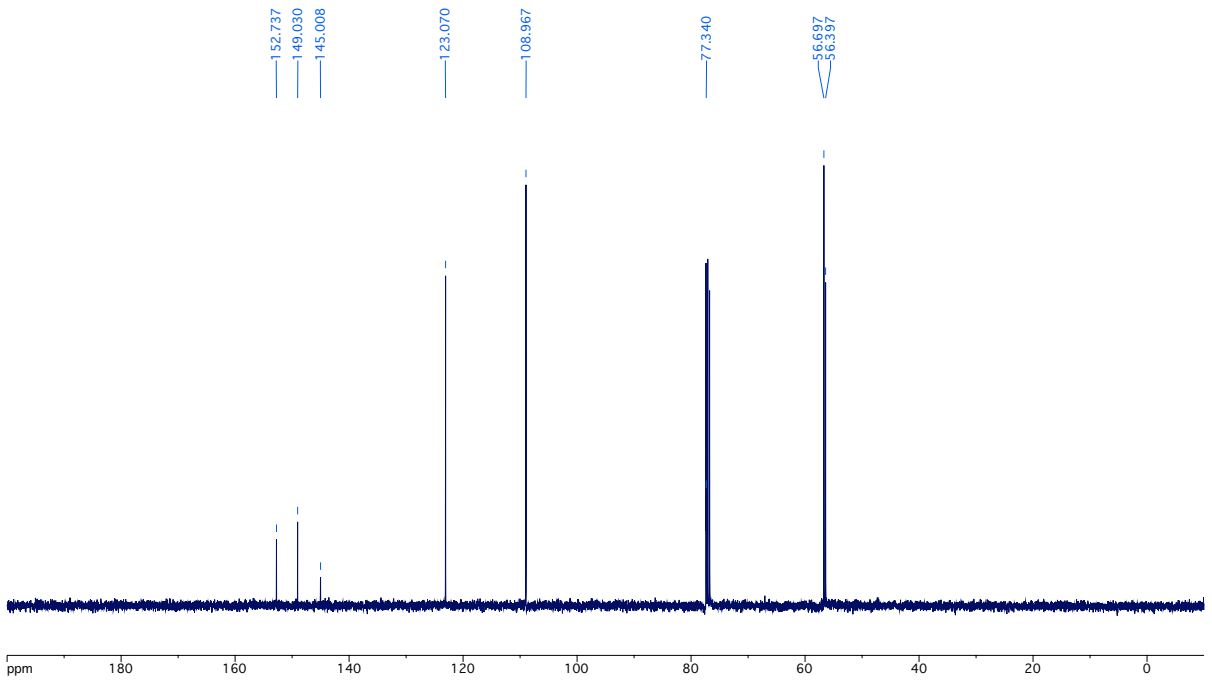

NO2
OMe
80c
8.153
8.130
7.157
7.150
7.001
6.994
6.978
6.971
3.930
3.556
0.99
1
1.06
3.28
0.909
ppm

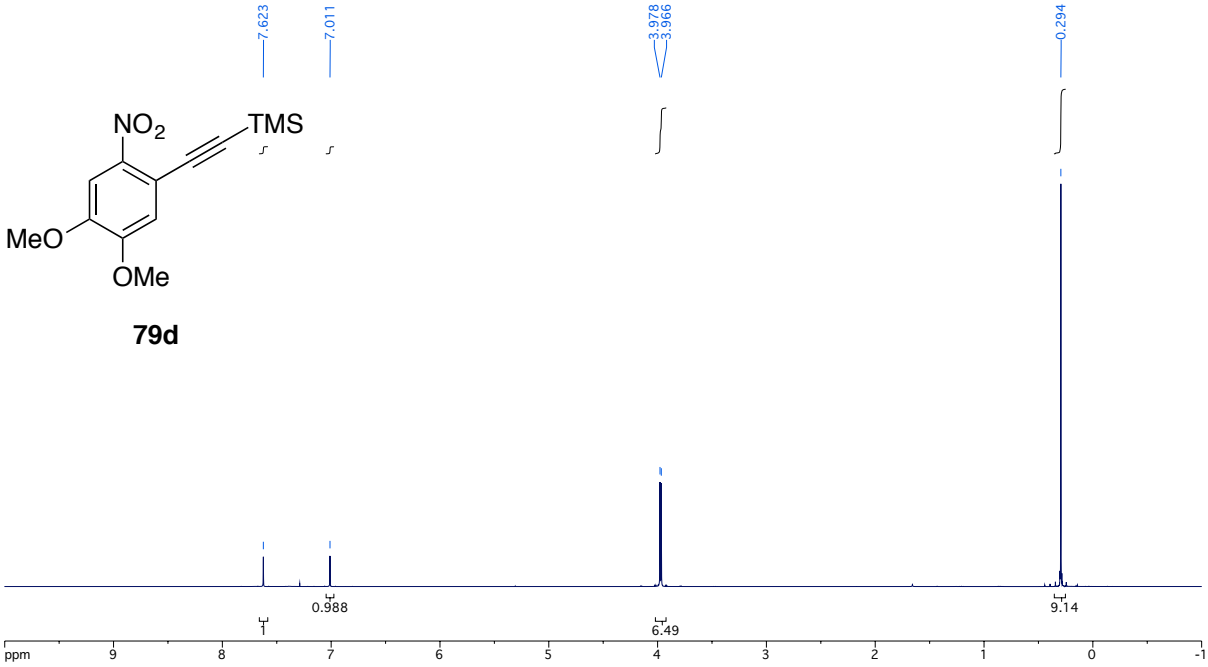

162.848
143.111
127.149
119.864
119.706
115.064
84.982
79.090
56.086
ppm


I
I
MeO
OMe
139
7.246
3.848
6.29
2
ppm 9 8 7 6 5 4 3 2 1 0 -1

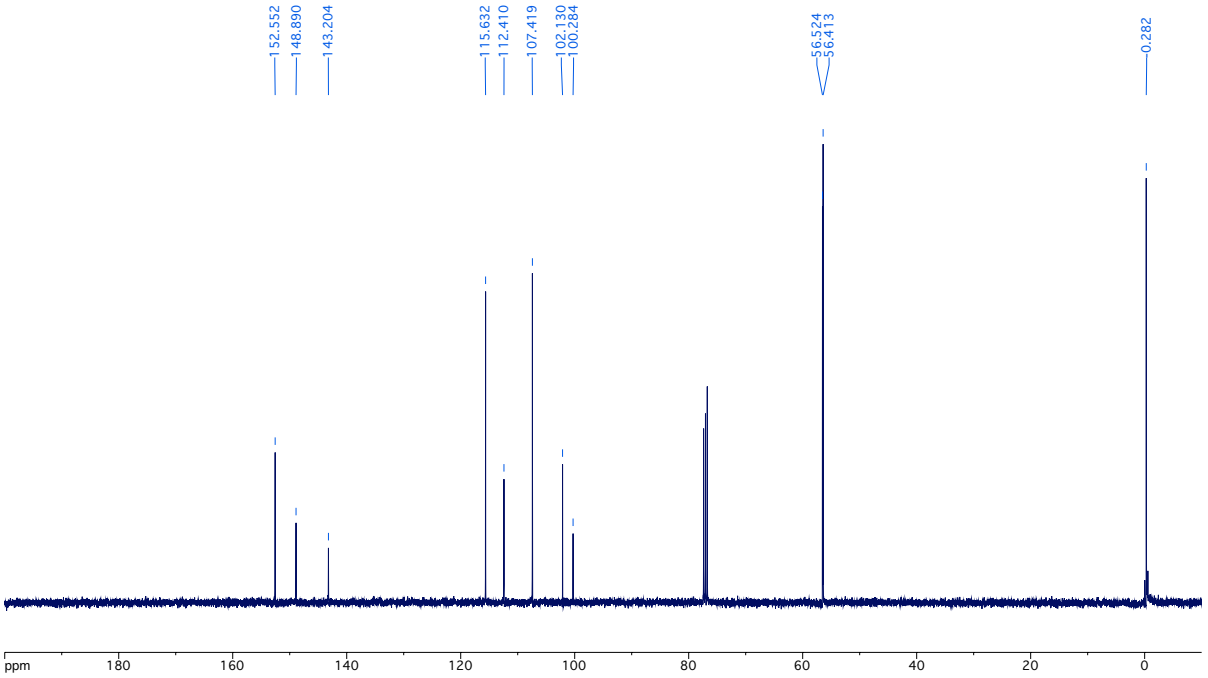

149.567
121.613
96.082
56.178
ppm 220 200 180 160 140 120 100 80 60 40 20 0 -20

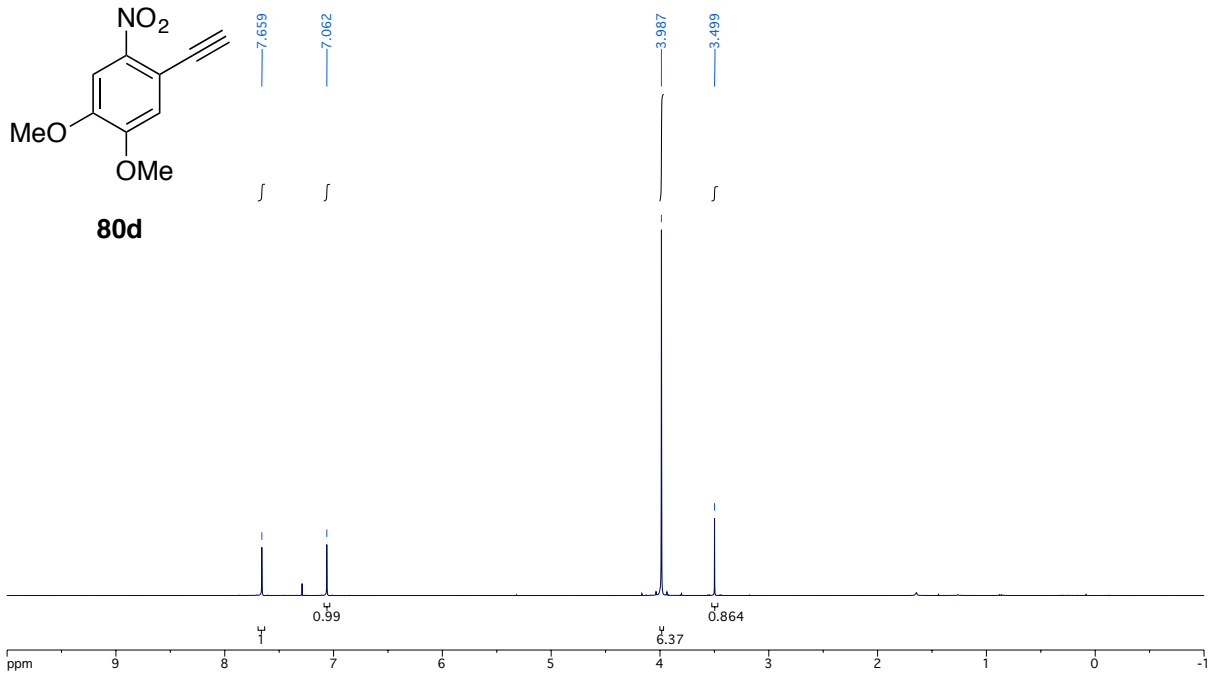

NO2
I
MeO
OMe
140
7.633
7.416
3.985
3.962
1
3.24
0.985
3.28
ppm
9
8
7
6
5
4
3
2
1
0
-1


152.737
149.030
145.008
123.070
108.967
77.340
56.697
56.397
ppm
180
160
140
120
100
80
60
40
20
0

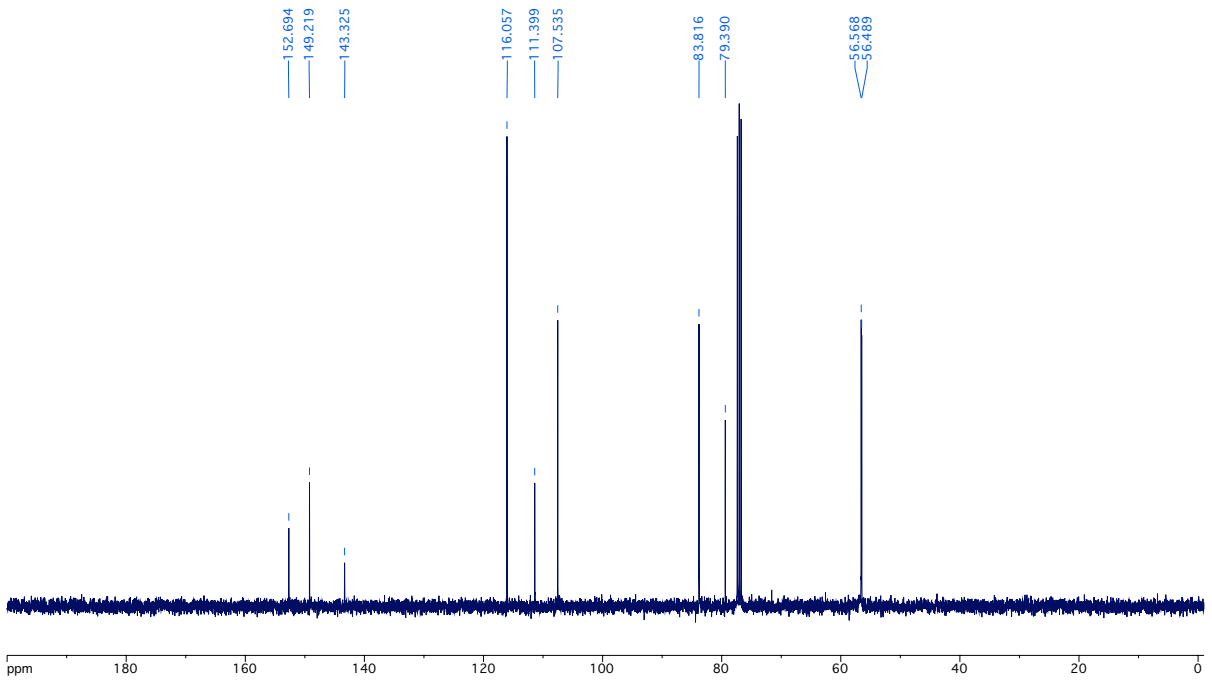

7.623
7.011
3.978
3.966
0.294
NO2
TMS
MeO
OMe
0.988
6.49
9.14
ppm

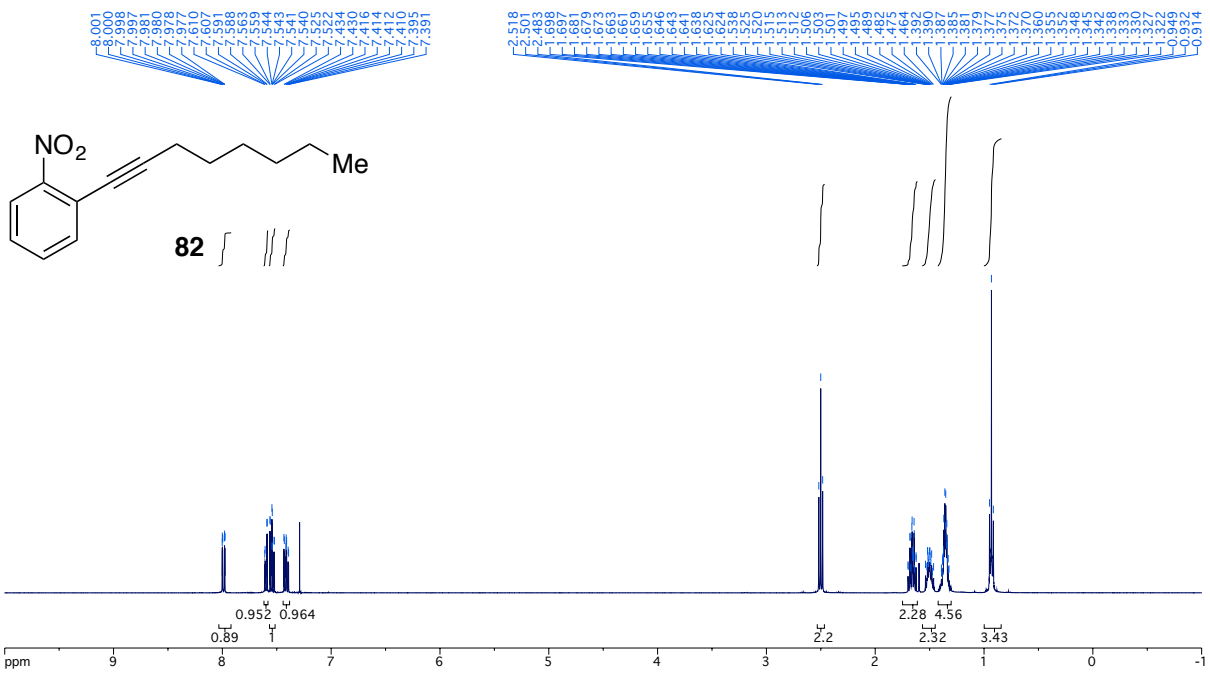
79d

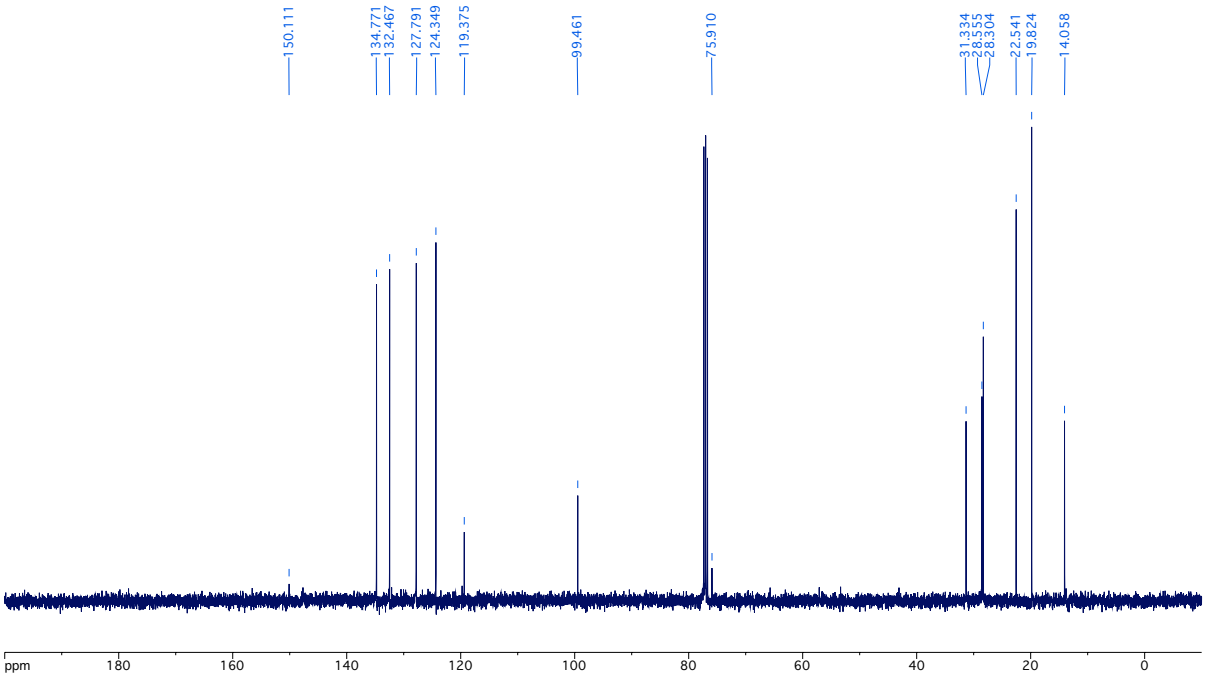

152.552
148.890
143.204
115.632
112.410
107.419
102.130
100.284
56.524
56.413
0.282
ppm

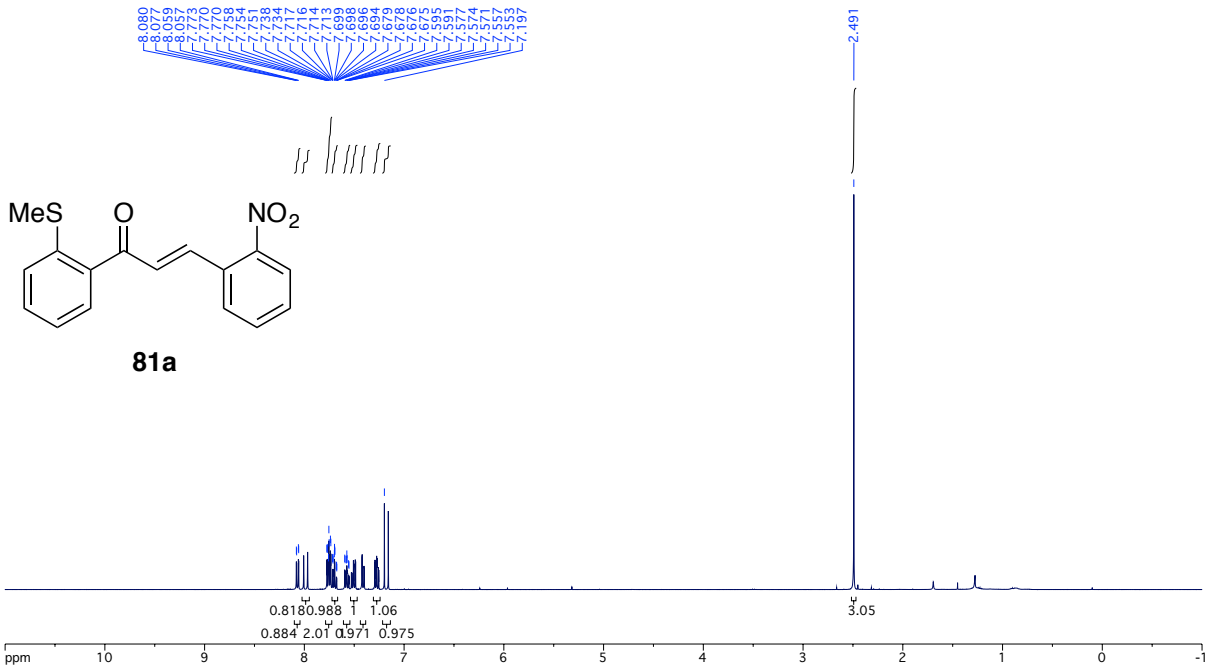

NO2
MeO
OMe
7.659
7.062
3.987
3.499
0.99
6.37
0.864
ppm

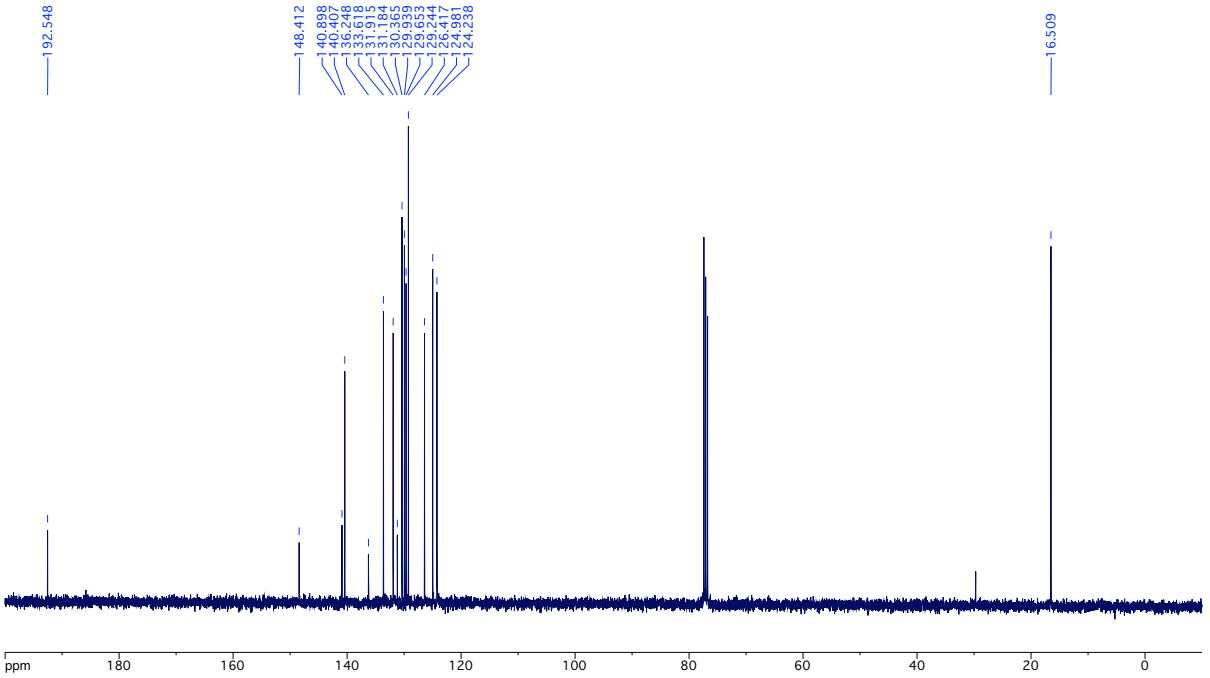
80d

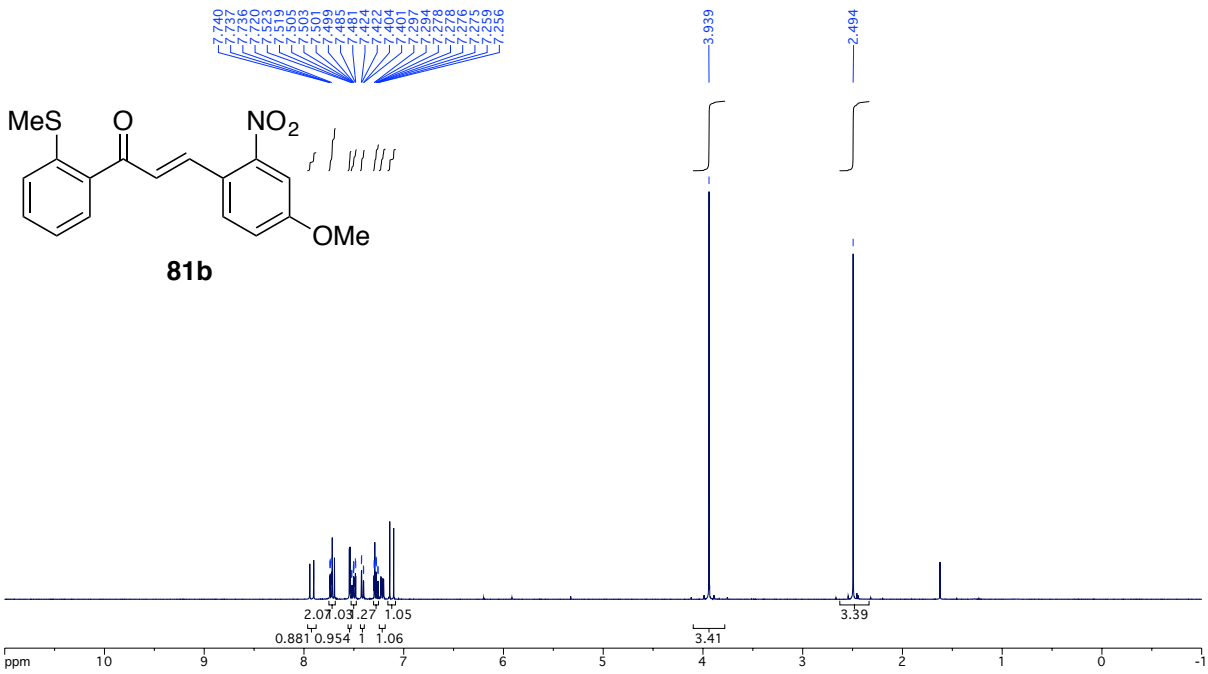

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116.057
111.399
107.535
83.816
79.390
56.568
56.489
ppm

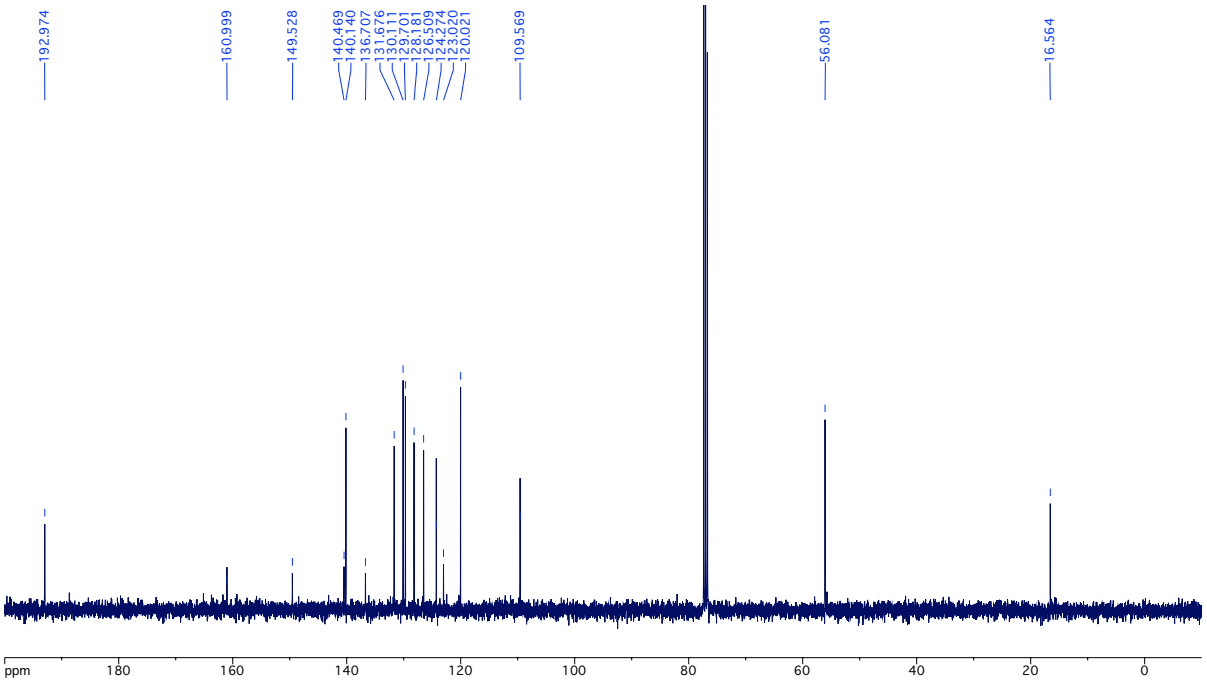

8.001
8.000
7.998
7.997
7.981
7.980
7.978
7.977
7.610
7.607
7.591
7.588
7.563
7.559
7.544
7.543
7.541
7.540
7.525
7.522
7.434
7.430
7.416
7.414
7.412
7.410
7.395
7.391
2.518
2.501
2.483
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1.697
1.681
1.679
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1.659
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1.641
1.638
1.635
1.624
1.538
1.525
1.520
1.515
1.513
1.512
1.506
1.503
1.501
1.497
1.495
1.489
1.492
1.475
1.464
1.392
1.390
1.387
1.385
1.381
1.379
1.377
1.375
1.372
1.370
1.360
1.355
1.352
1.348
1.345
1.342
1.338
1.333
1.330
1.327
1.322
0.949
0.932
0.914
NO2
Me
82
0.89
0.952
1
0.964
2.2
2.28
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4.56
3.43
ppm
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8
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6
5
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2
1
0
-1

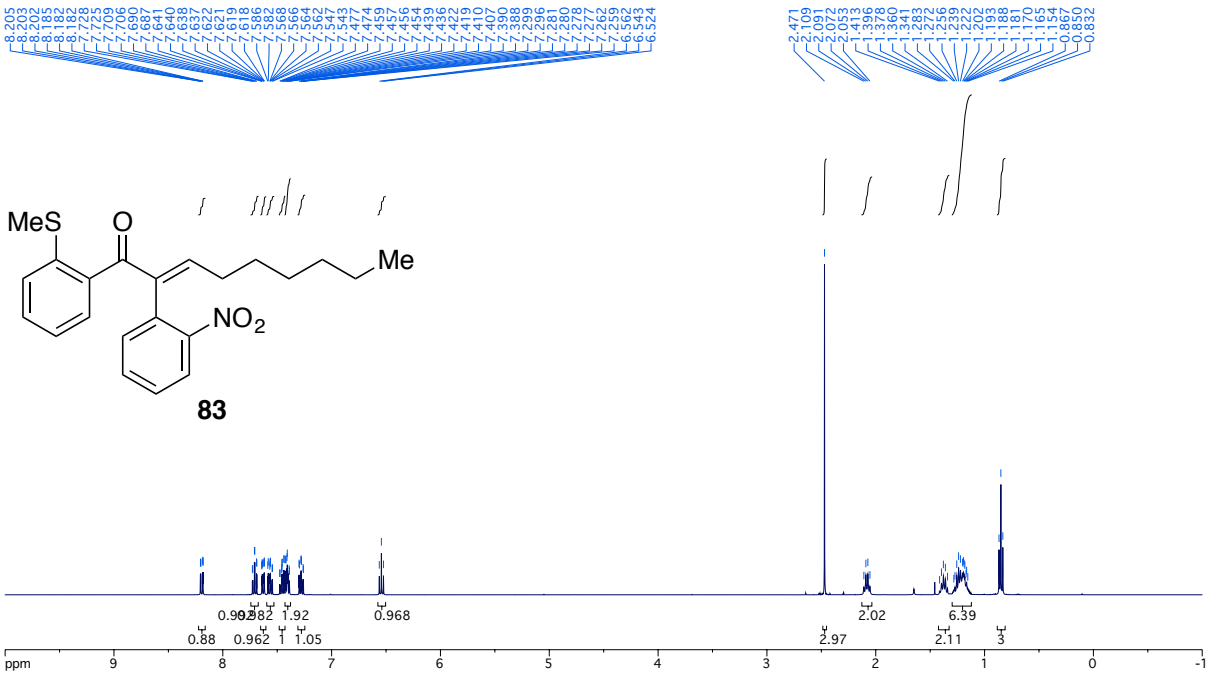

150.111
134.771
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127.791
124.349
119.375
99.461
75.910
31.334
28.555
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22.541
19.824
14.058
ppm
180
160
140
120
100
80
60
40
20
0

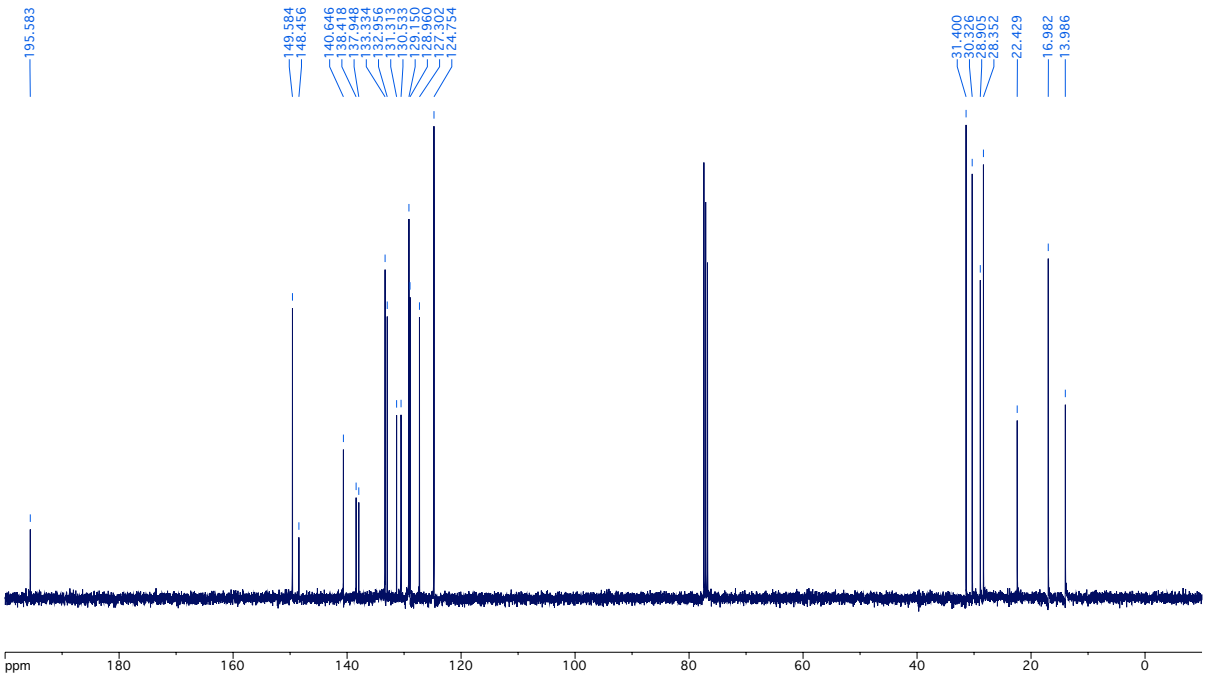

MeS
O
NO2
81a
8.080
8.077
8.059
8.057
7.773
7.770
7.758
7.754
7.751
7.738
7.734
7.717
7.716
7.714
7.713
7.699
7.698
7.696
7.694
7.679
7.678
7.676
7.675
7.595
7.591
7.577
7.574
7.571
7.557
7.553
7.197
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0.818
0.988
1
1.06
0.884
2.01
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0.975
3.05
ppm

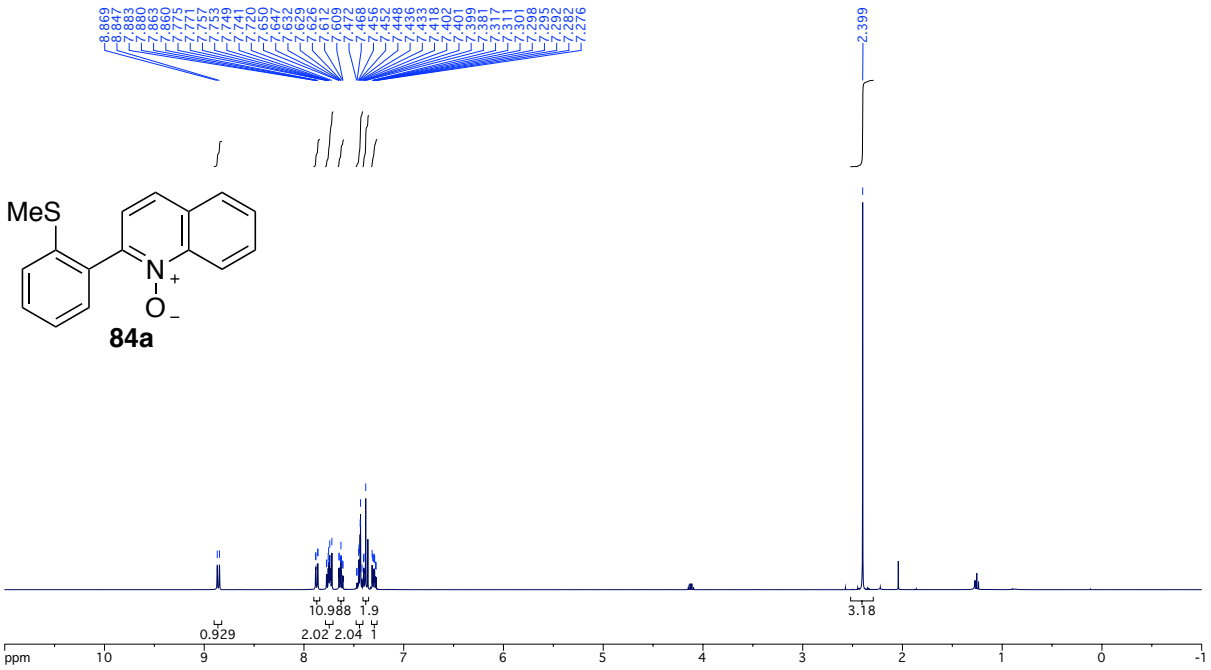

192.548
148.412
140.898
140.407
136.248
133.618
131.915
131.184
130.365
129.939
129.653
129.244
126.417
124.981
124.238
16.509
ppm

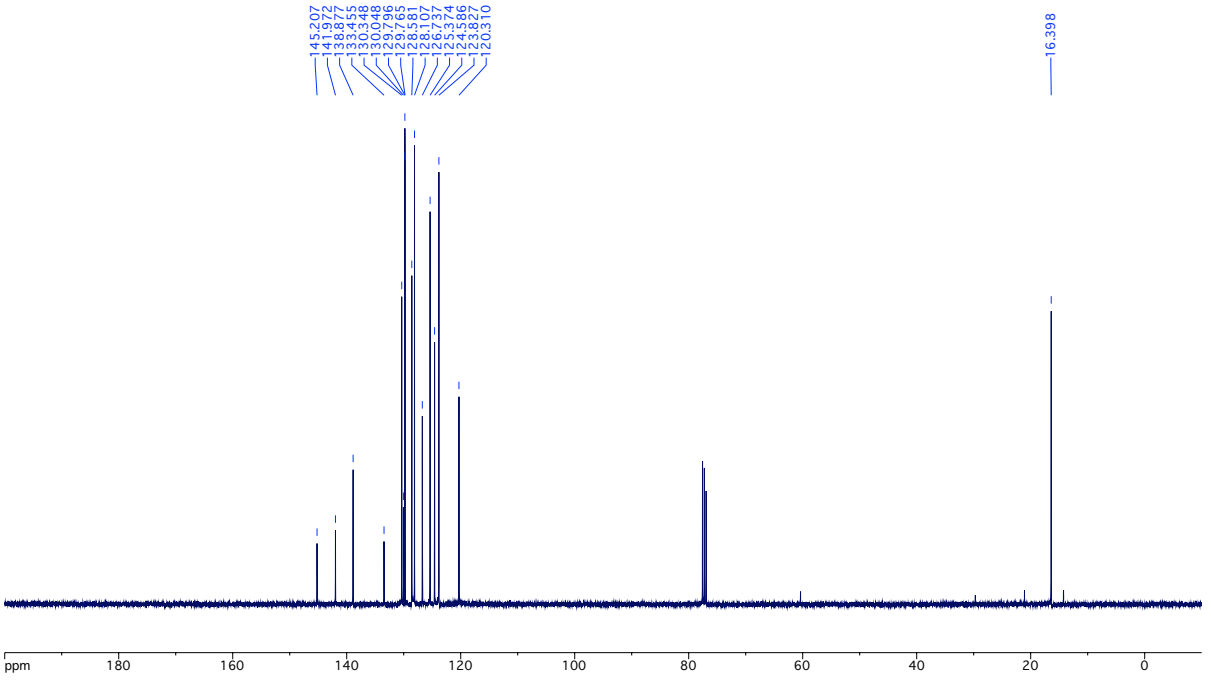

7.740
7.737
7.736
7.720
7.523
7.519
7.505
7.503
7.501
7.499
7.485
7.481
7.424
7.422
7.404
7.401
7.297
7.294
7.278
7.276
7.275
7.259
7.256
3.939
2.494
MeS
O
NO2
OMe
81b
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1.03
3.27
1.05
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1
1.06
3.41
3.39
ppm

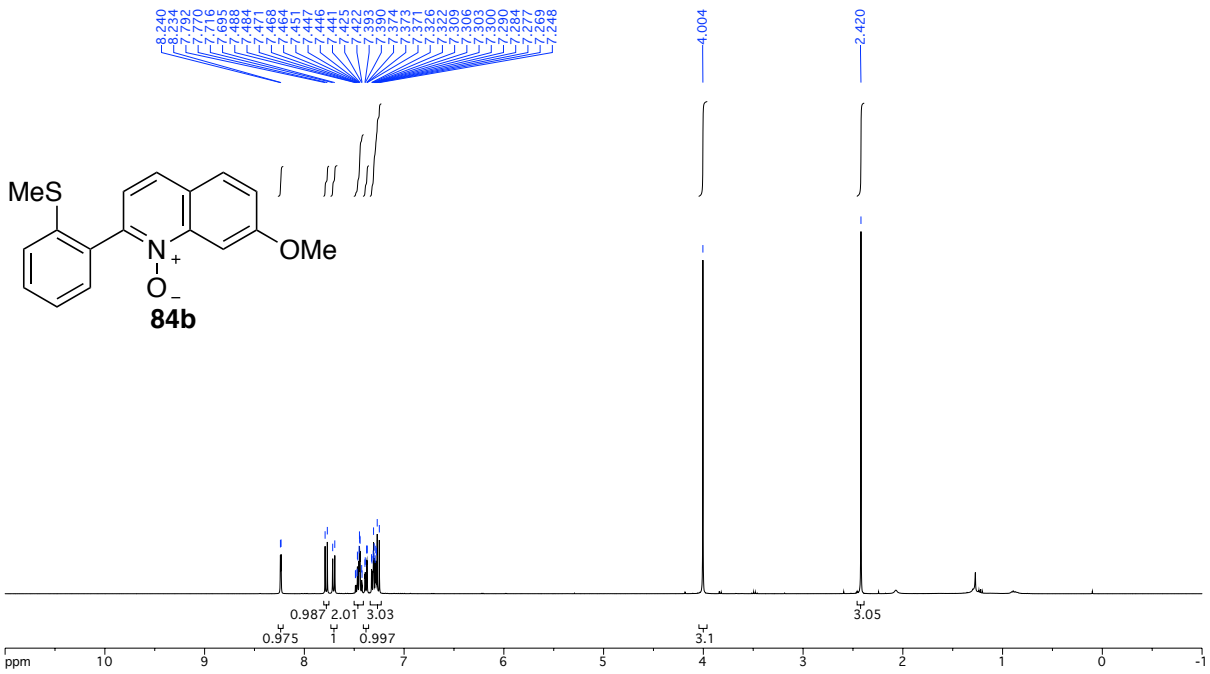

192.974
160.999
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140.469
140.140
136.707
131.676
130.111
129.701
128.387
125.109
124.274
123.020
120.021
109.569
56.081
16.564
ppm

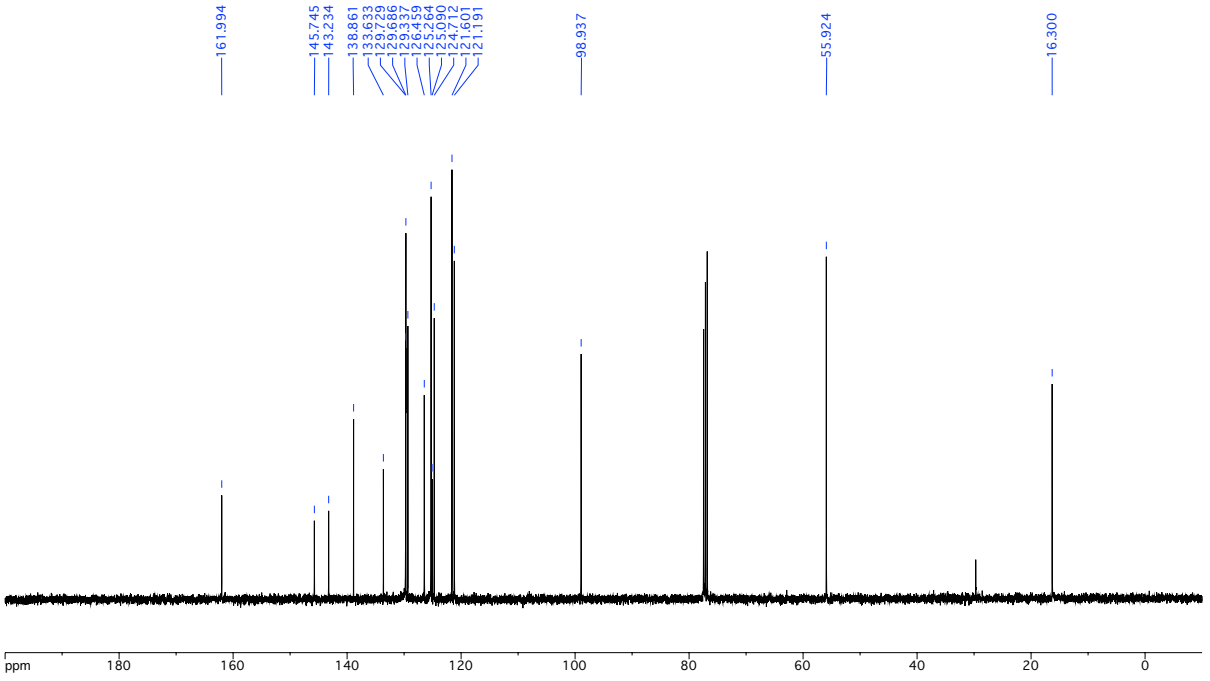

MeS
O
Me
NO2
83
ppm

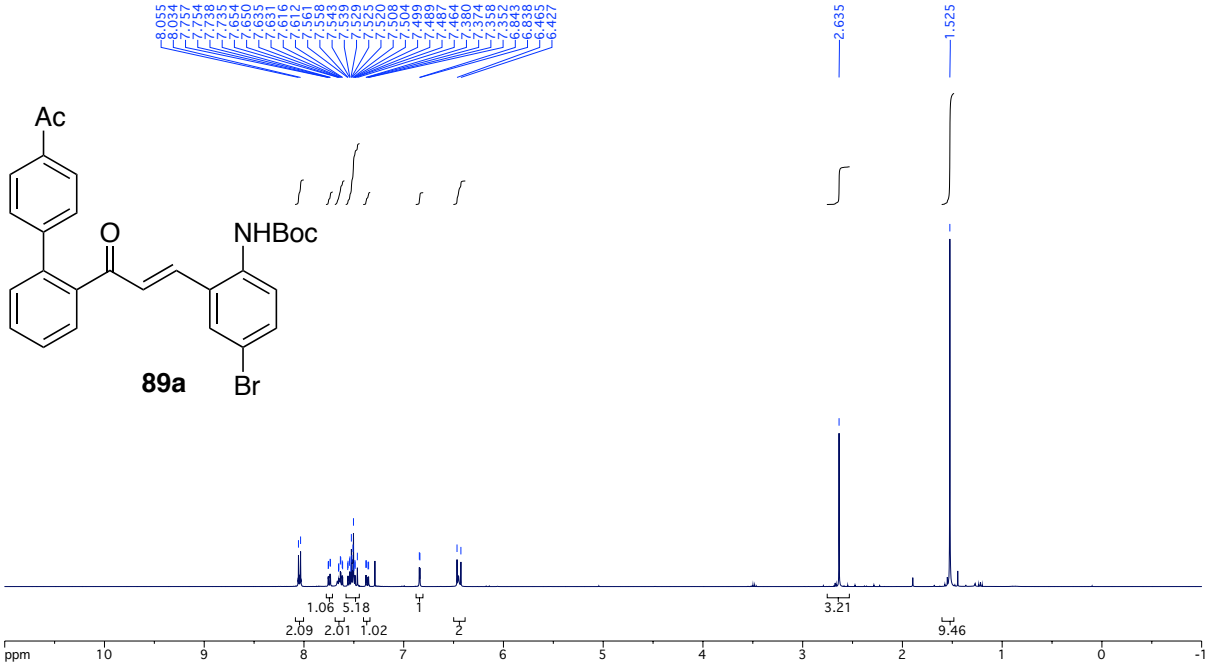

ppm

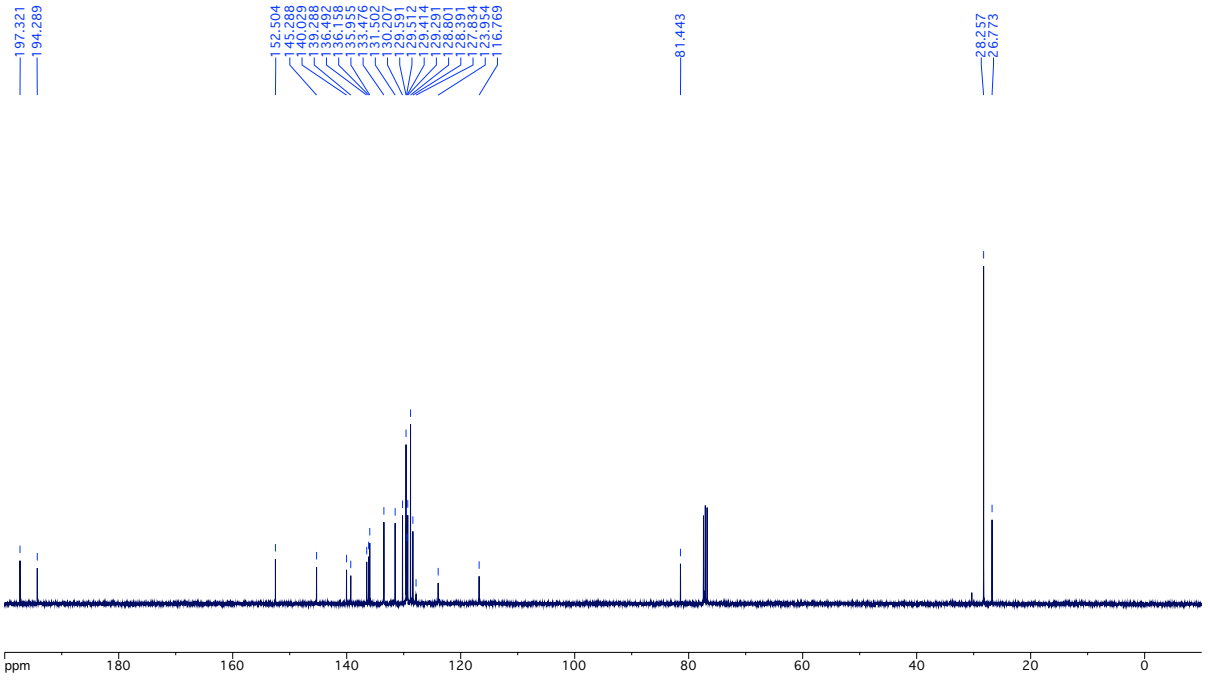

8.869
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7.863
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7.775
7.771
7.757
7.753
7.749
7.741
7.720
7.650
7.647
7.632
7.629
7.626
7.612
7.609
7.472
7.468
7.466
7.452
7.448
7.436
7.433
7.418
7.402
7.401
7.399
7.381
7.317
7.311
7.301
7.298
7.295
7.282
7.276
2.399
MeS
N
O
84a
0.929
10.988
2.02
2.04
1.9
1
3.18
ppm
10
9
8
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6
5
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2
1
0
-1

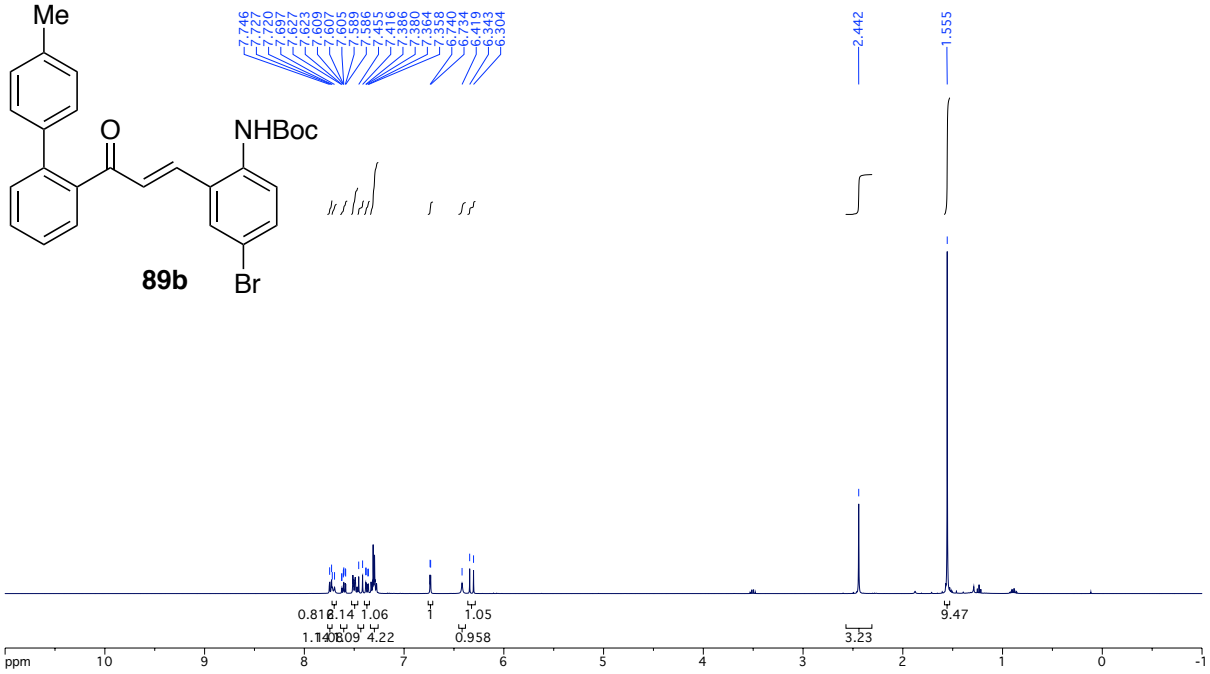

145.207
141.972
138.877
133.455
130.348
130.048
127.966
127.795
126.581
126.107
126.737
125.374
124.586
123.827
120.310
16.398
ppm
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140
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40
20
0

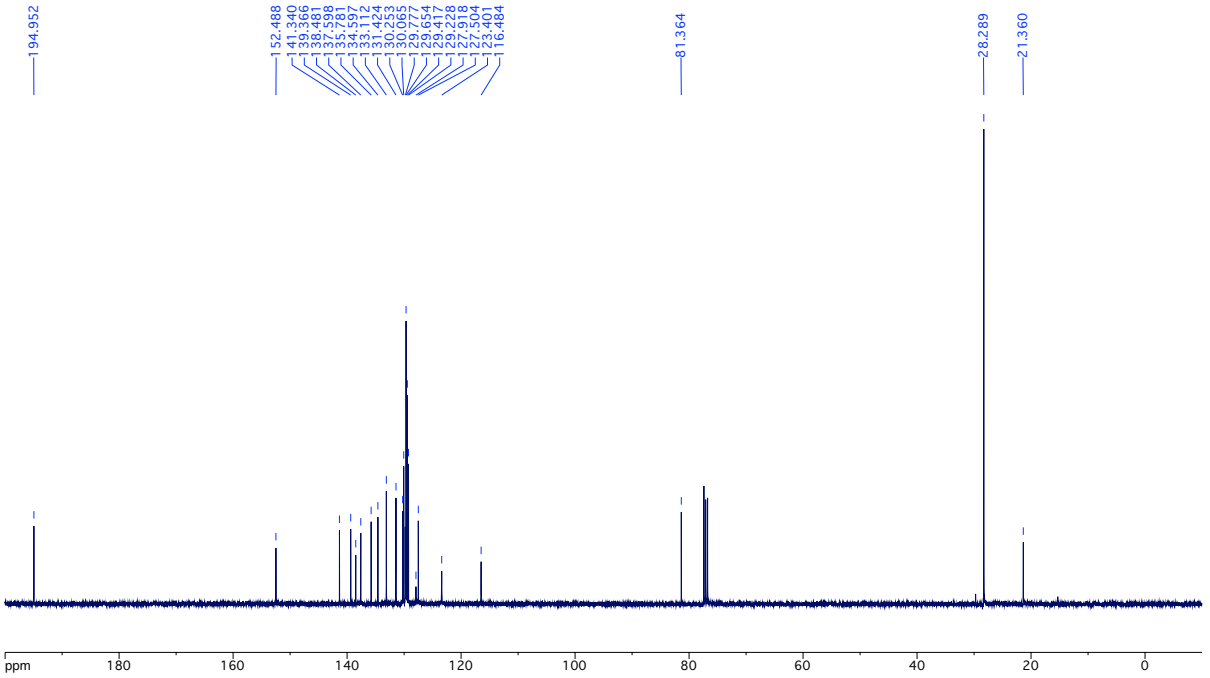

8.240
8.234
7.792
7.770
7.716
7.695
7.488
7.484
7.471
7.468
7.464
7.451
7.446
7.441
7.425
7.422
7.393
7.390
7.374
7.371
7.326
7.322
7.309
7.306
7.303
7.300
7.290
7.284
7.277
7.269
7.248
4.004
2.420
MeS
N
O
OMe
84b
0.975
0.987
1
2.01
1
1
3.03
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3.1
3.05
ppm
10
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8
7
6
5
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-1

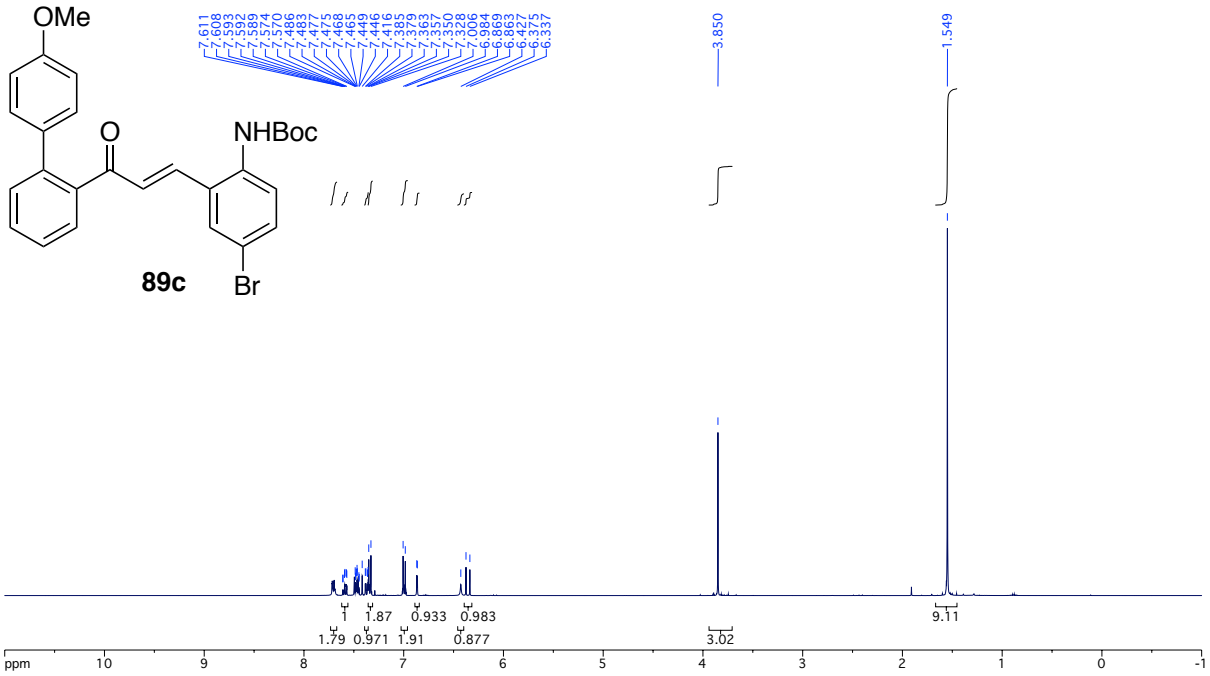

161.994
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138.861
135.533
133.769
132.666
129.337
126.459
125.264
125.090
124.712
121.601
121.191
98.937
55.924
16.300
ppm
180
160
140
120
100
80
60
40
20
0

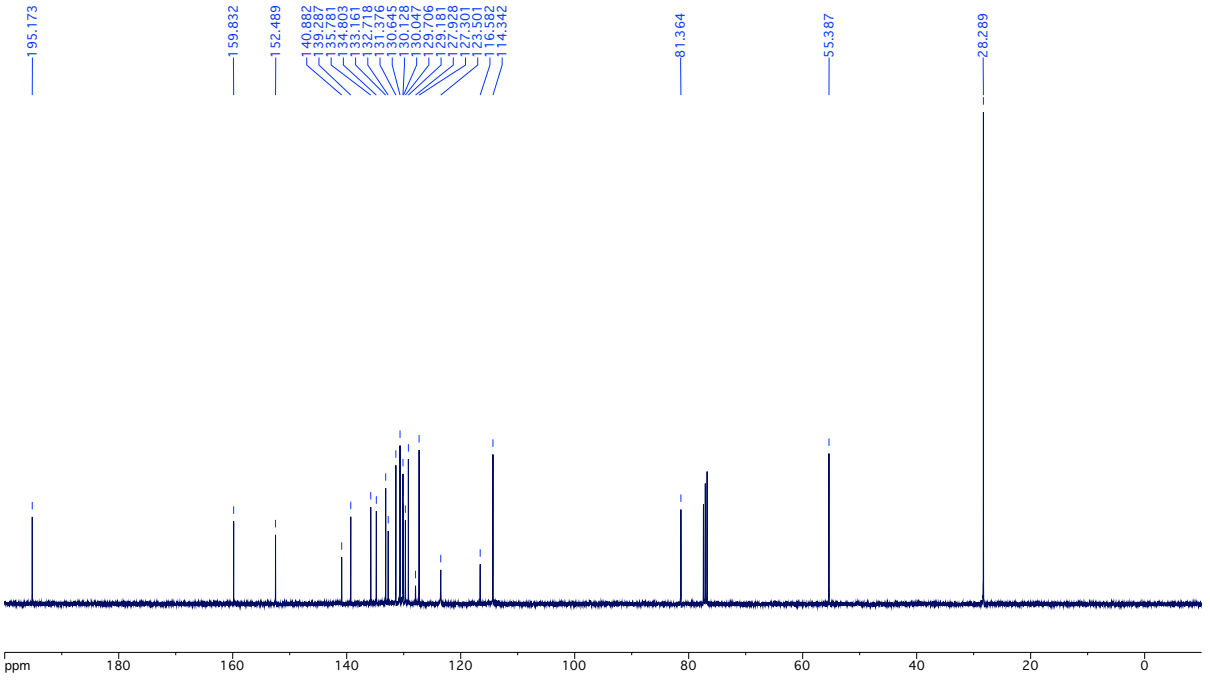

Ac
O
NHBoc
Br
89a
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8.034
7.757
7.754
7.738
7.735
7.654
7.650
7.635
7.631
7.616
7.612
7.561
7.558
7.543
7.539
7.529
7.525
7.520
7.508
7.504
7.499
7.489
7.487
7.464
7.380
7.374
7.358
7.352
6.843
6.838
6.465
6.427
2.635
1.525
1.06
5.18
1
3.21
2.09
2.01
1.02
2
9.46
ppm

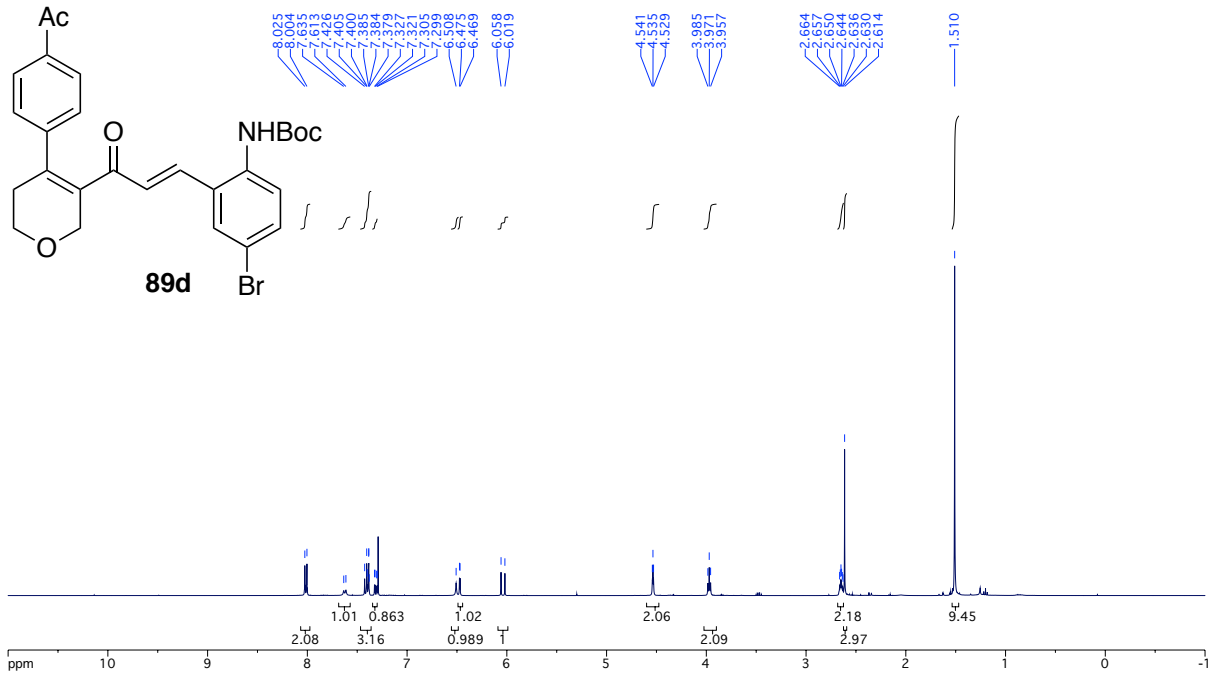

197.321
194.289
152.504
145.288
140.029
139.288
136.492
136.158
135.955
133.476
131.202
130.507
129.591
129.512
129.414
129.291
128.801
128.391
127.834
127.694
116.769
81.443
28.257
26.773
ppm

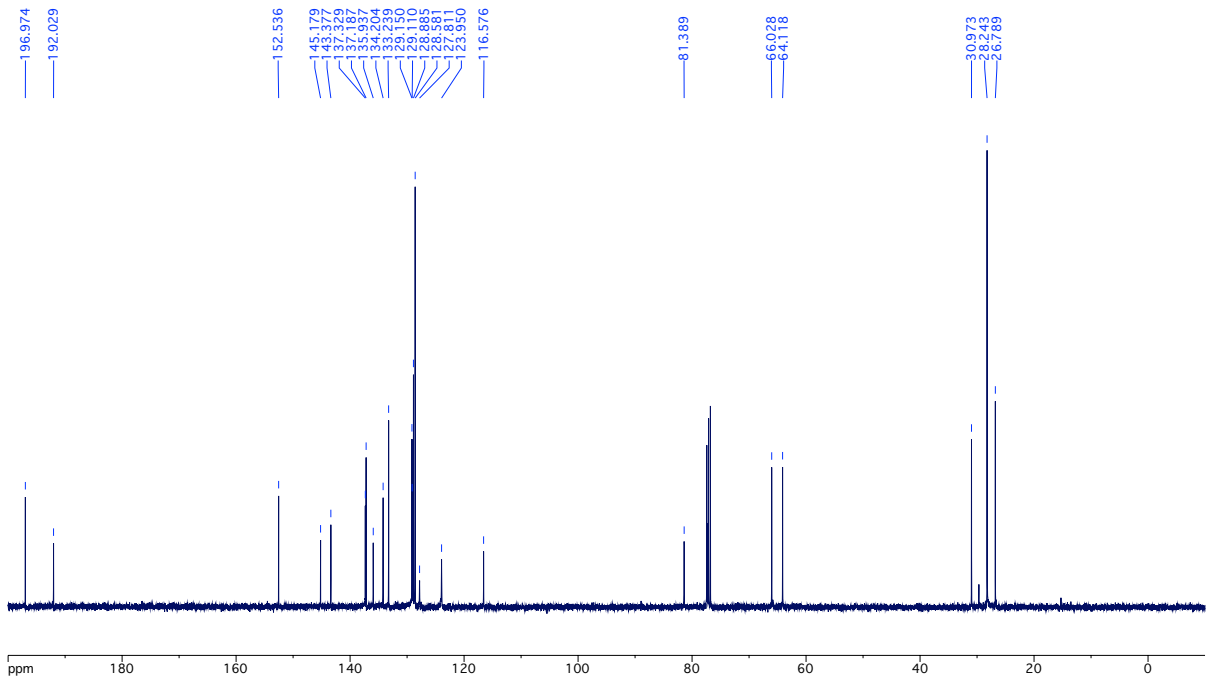

Me
O
NHBoc
Br
89b
7.746
7.727
7.720
7.697
7.627
7.623
7.609
7.607
7.605
7.589
7.586
7.455
7.416
7.386
7.380
7.364
7.358
6.740
6.734
6.419
6.343
6.304
2.442
1.555
0.818
2.14
1.06
1
1.05
1.14
1.09
4.22
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3.23
9.47
ppm

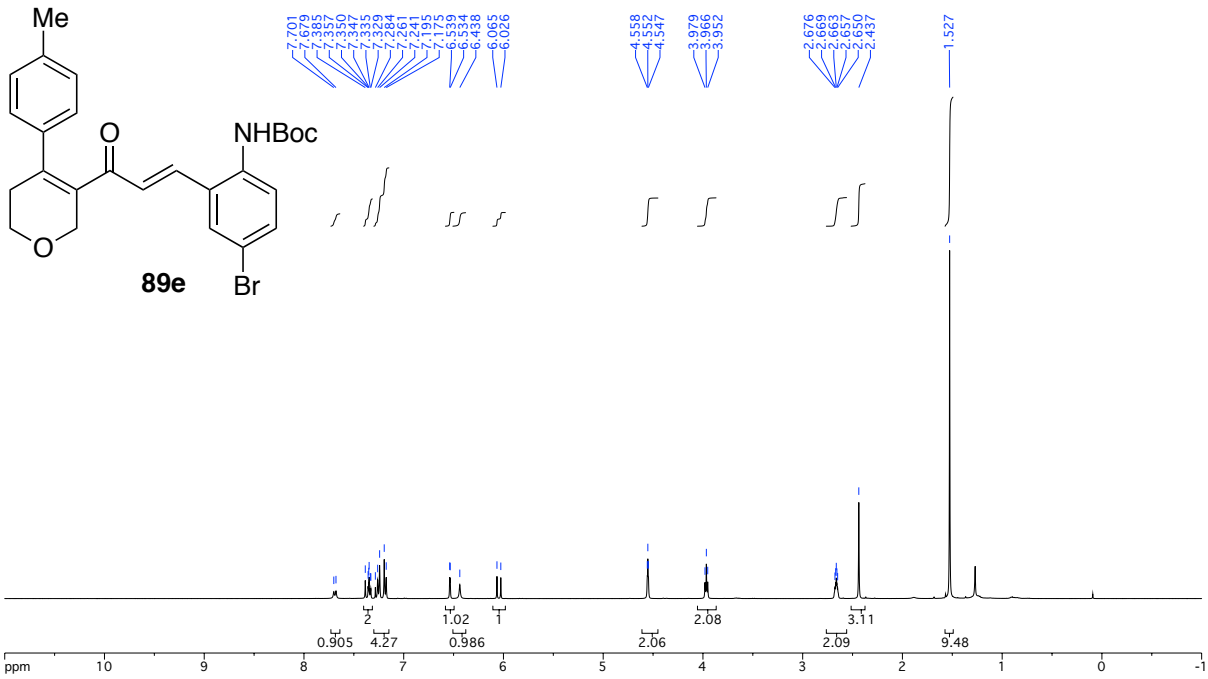

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152.488
141.340
139.366
138.481
137.598
135.781
134.197
134.117
131.424
130.253
130.065
129.777
129.654
129.417
129.228
127.504
123.401
116.484
81.364
28.289
21.360
ppm

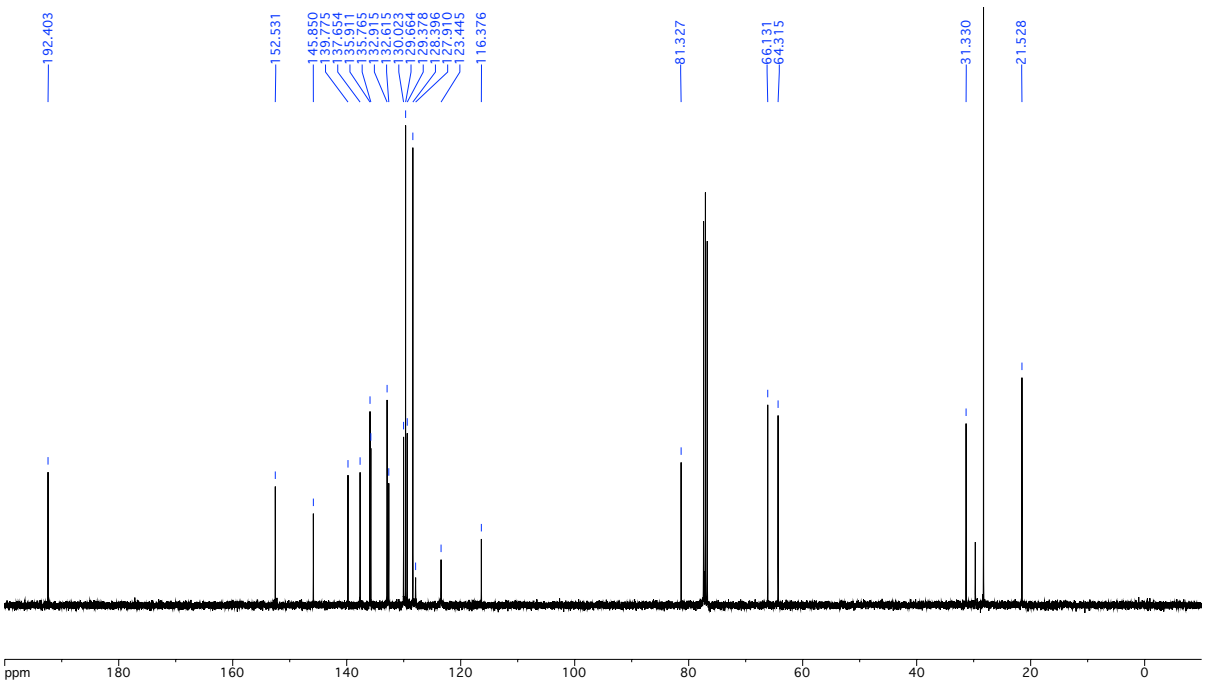

OMe
O
NHBoc
Br
89c
7.611
7.608
7.593
7.592
7.589
7.574
7.570
7.486
7.483
7.477
7.475
7.468
7.465
7.449
7.446
7.446
7.385
7.379
7.363
7.357
7.350
7.328
7.096
7.084
6.869
6.863
6.427
6.375
6.337
3.850
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0.933
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1.79
0.971
1.91
0.877
3.02
9.11
ppm

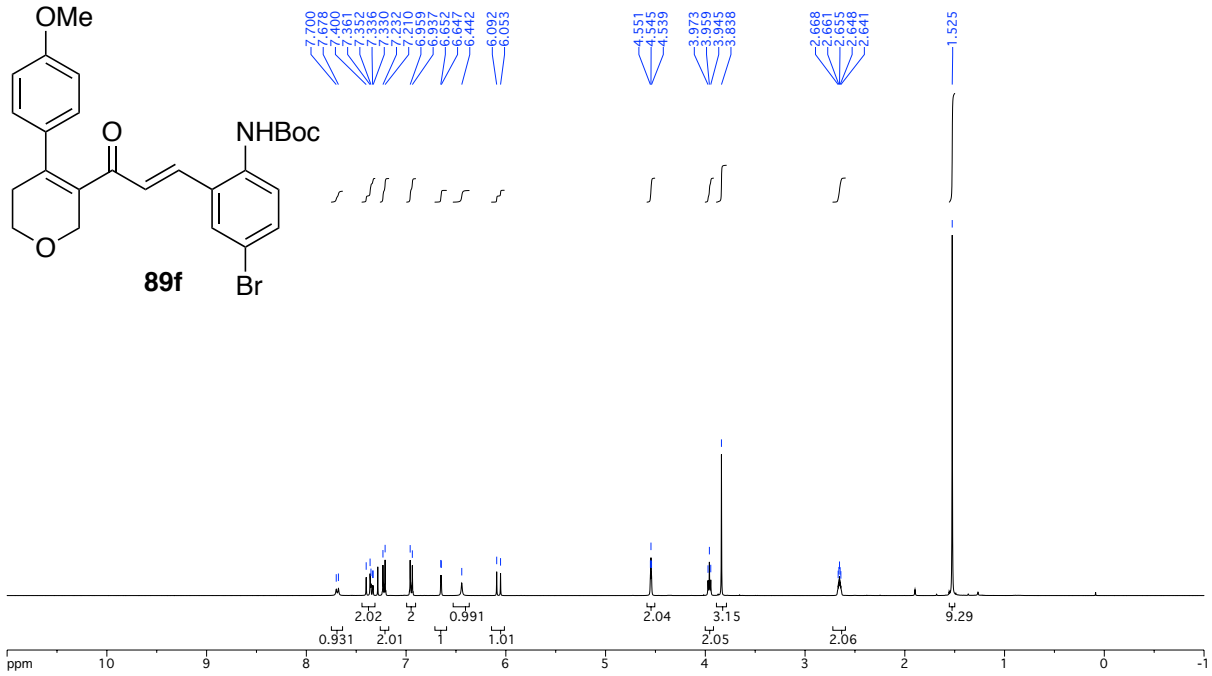

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159.832
152.489
140.882
137.787
137.281
134.803
133.161
132.718
131.376
130.645
130.128
130.047
129.706
129.181
127.928
127.301
123.501
116.582
114.342
81.364
55.387
28.289
ppm

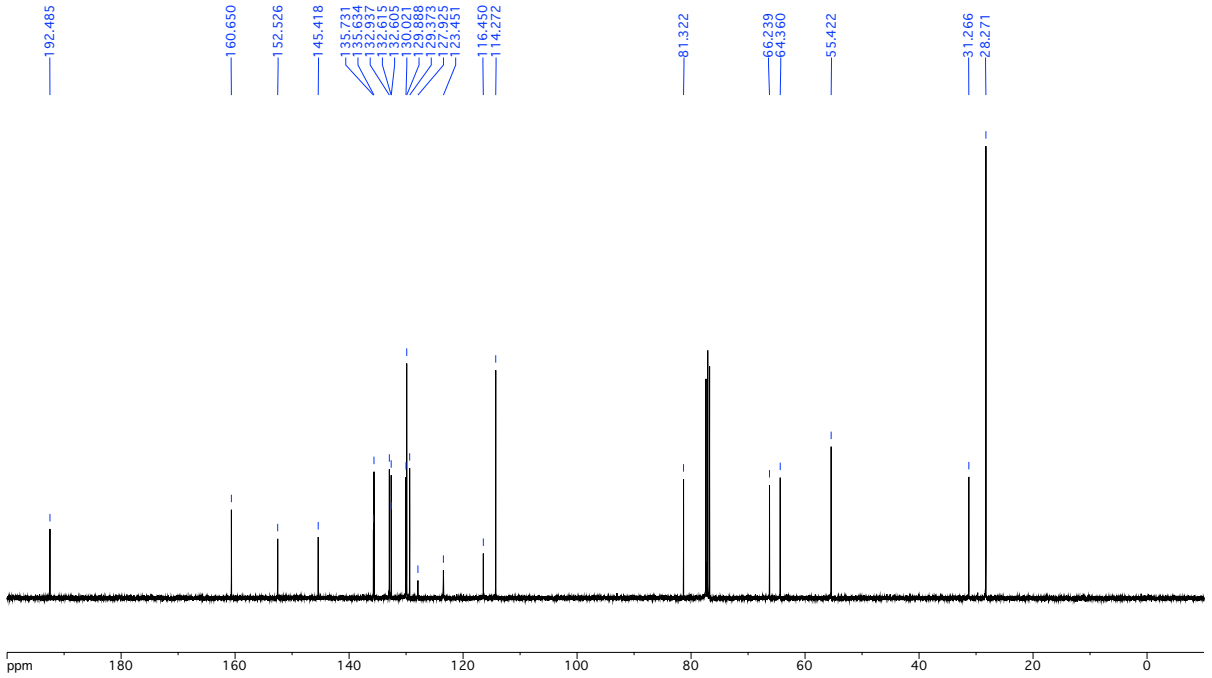

Ac
O
NHBoc
O
Br
89d
8.025
8.004
7.635
7.613
7.436
7.405
7.400
7.385
7.384
7.379
7.327
7.321
7.299
6.508
6.475
6.469
6.058
6.019
4.541
4.535
4.529
3.985
3.971
3.957
2.664
2.657
2.650
2.644
2.636
2.630
2.614
1.510
1.01
0.863
1.02
2.06
2.18
9.45
2.08
3.16
0.989
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2.09
2.97
ppm

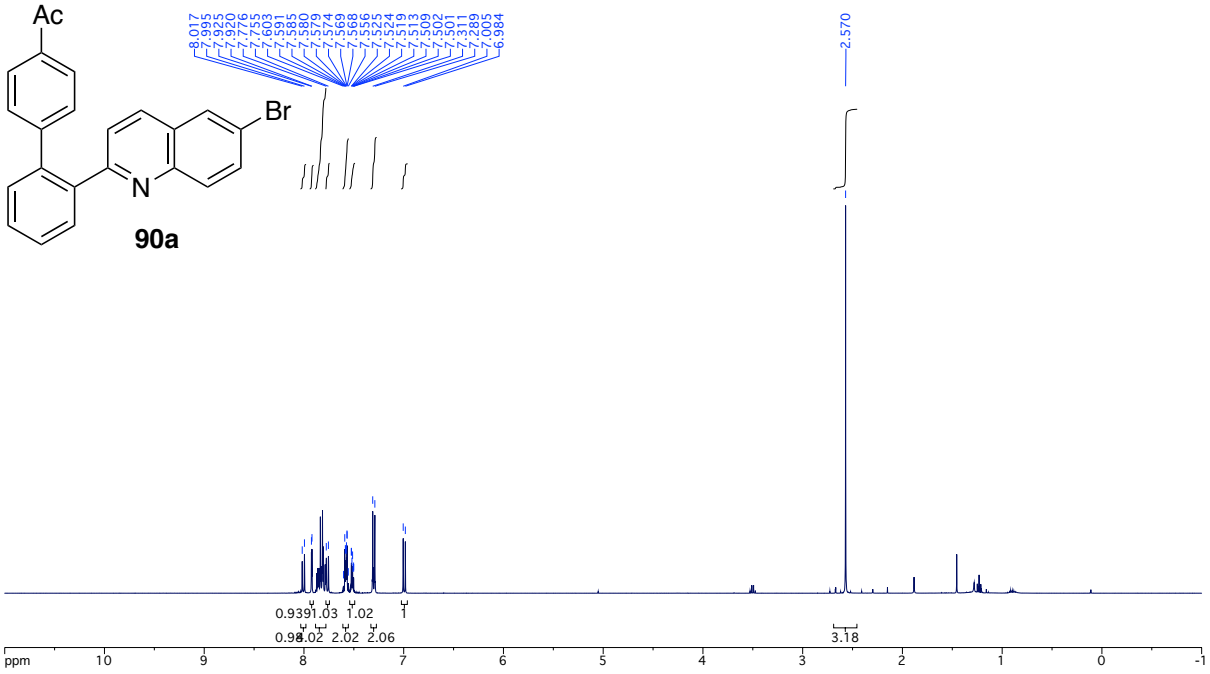

196.974
192.029
152.536
145.179
143.177
137.324
137.187
135.937
134.204
133.239
129.150
128.910
128.885
128.581
127.811
123.950
116.576
81.389
66.028
64.118
30.973
28.243
26.789
ppm

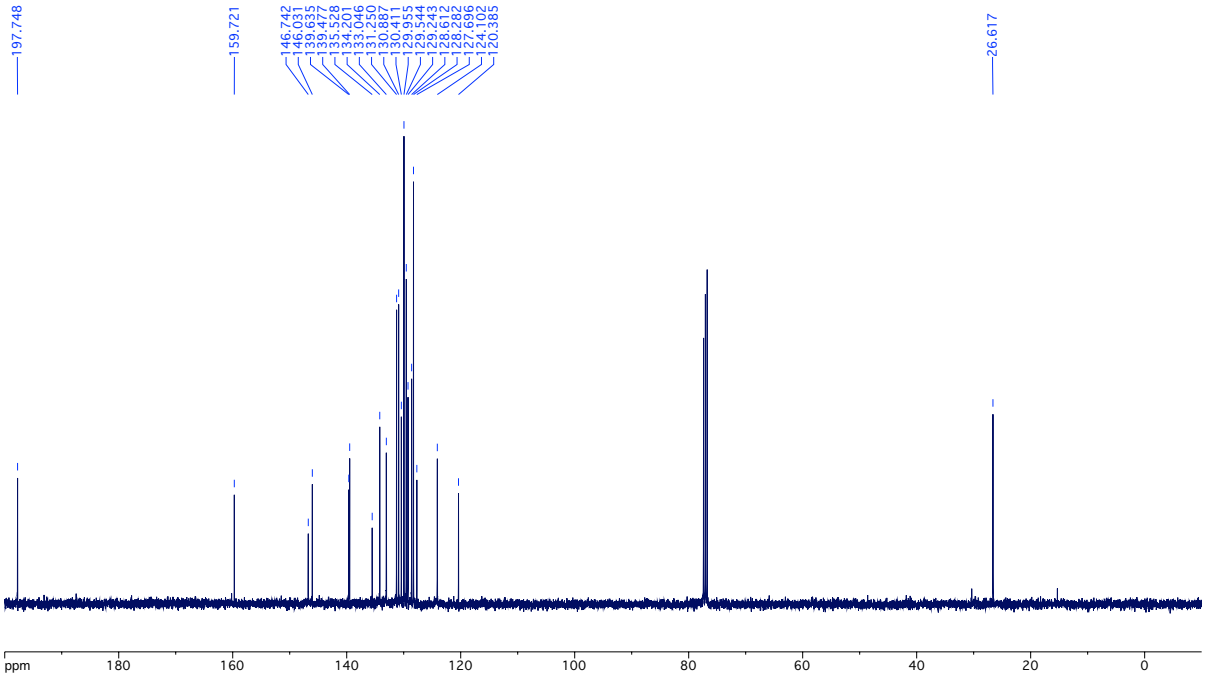

Me
O
NHBoc
O
Br
89e
7.701
7.699
7.685
7.357
7.350
7.347
7.335
7.329
7.284
7.261
7.241
7.195
7.175
6.539
6.534
6.438
6.065
6.026
4.558
4.552
4.547
3.979
3.966
3.952
2.676
2.669
2.663
2.657
2.650
2.437
1.527
2
1.02
1
2.08
3.11
0.905
4.27
0.986
2.06
2.09
9.48
ppm

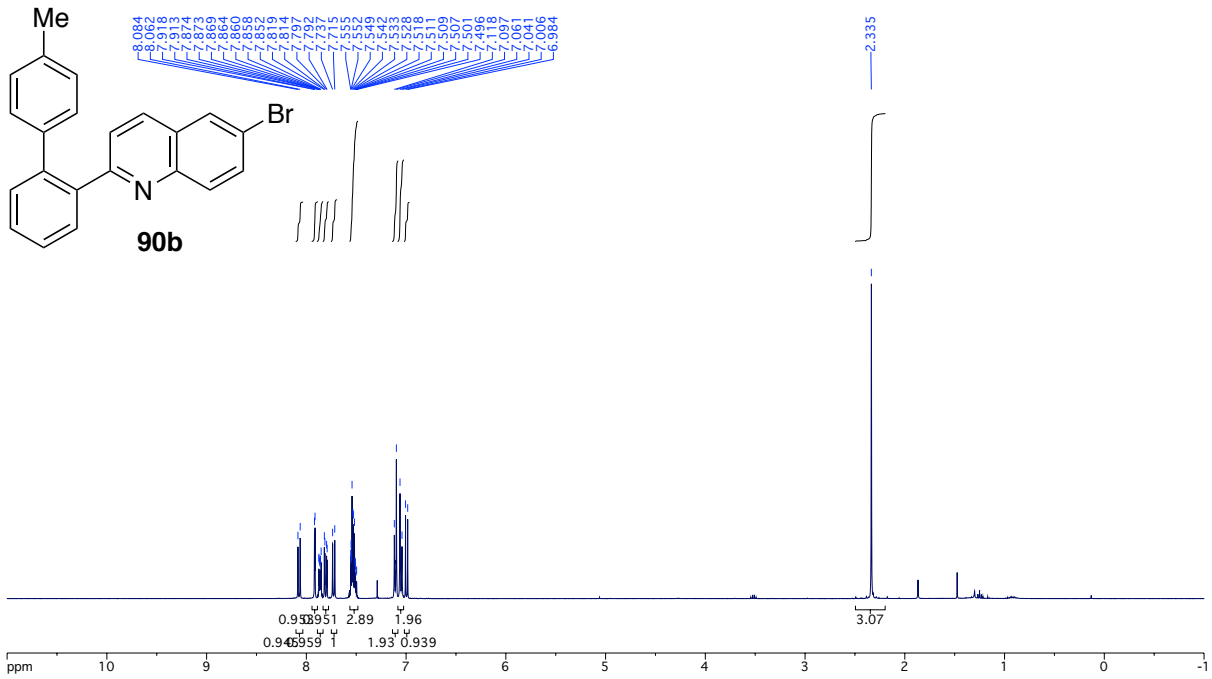

192.403
152.531
145.850
139.775
137.654
135.911
133.765
133.615
130.023
129.664
129.378
128.396
127.910
123.445
116.376
81.327
66.131
64.315
31.330
21.528
ppm

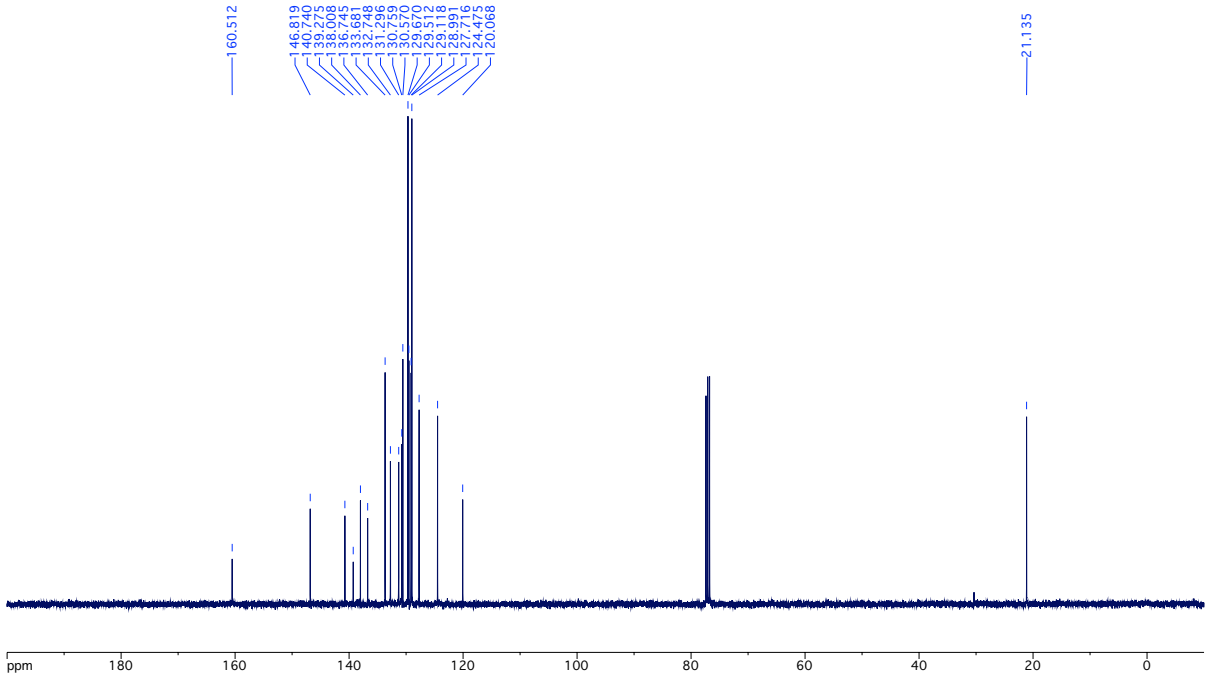

OMe
O
NHBoc
O
89f
Br
7.700
7.678
7.400
7.361
7.352
7.336
7.330
7.312
7.310
6.959
6.937
6.652
6.647
6.442
6.092
6.053
4.551
4.545
4.539
3.973
3.959
3.945
3.838
2.668
2.661
2.655
2.648
2.641
1.525
0.931
2.02
2.01
2
1
0.991
1.01
2.04
3.15
2.05
2.06
9.29
ppm

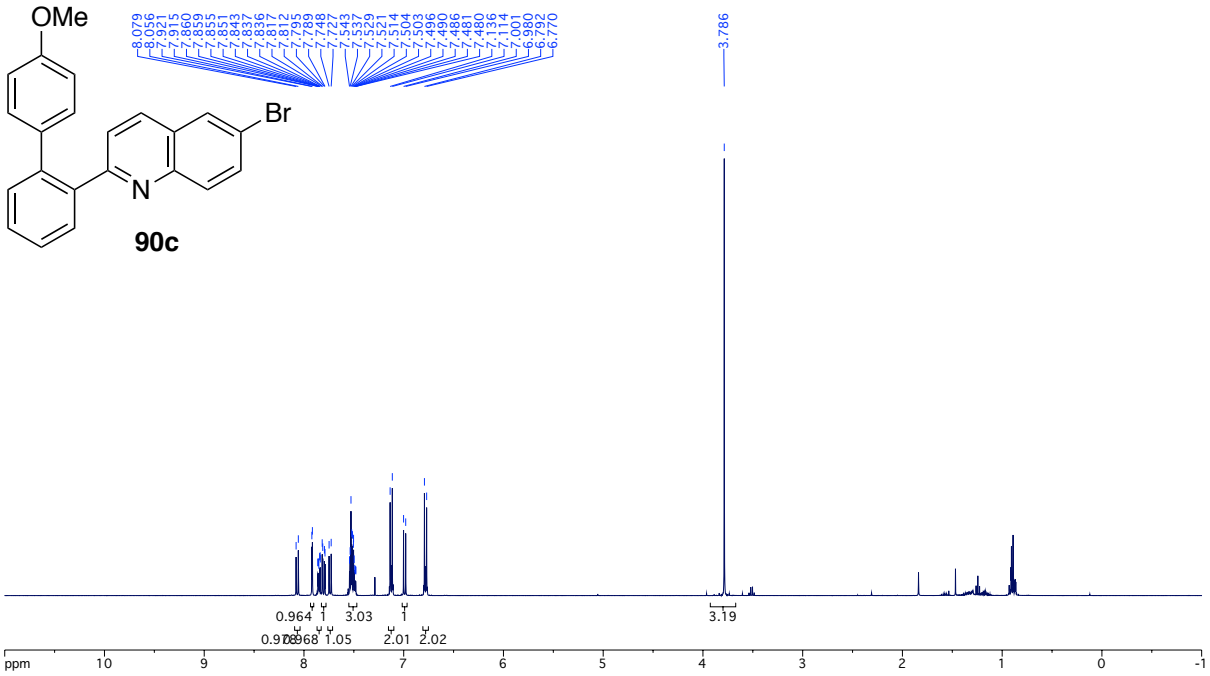

192.485
160.650
152.526
145.418
135.731
135.634
132.937
132.715
132.605
130.021
129.888
129.373
127.925
123.451
116.450
114.272
81.322
66.239
64.360
55.422
31.266
28.271
ppm

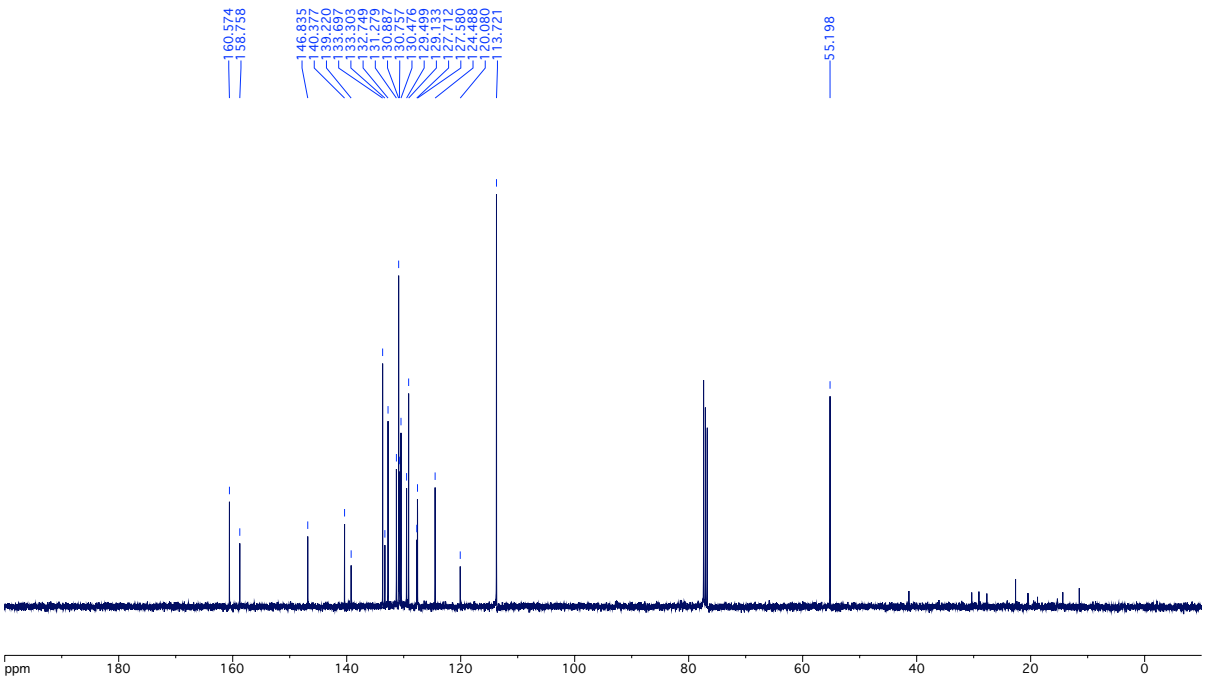

Ac
Br
N
90a
8.017
7.935
7.925
7.920
7.776
7.755
7.603
7.591
7.585
7.580
7.579
7.574
7.569
7.568
7.556
7.525
7.524
7.519
7.513
7.509
7.502
7.501
7.311
7.289
7.095
6.984
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0.93
1.03
1.02
1
0.98
2.02
2.02
2.06
3.18
ppm

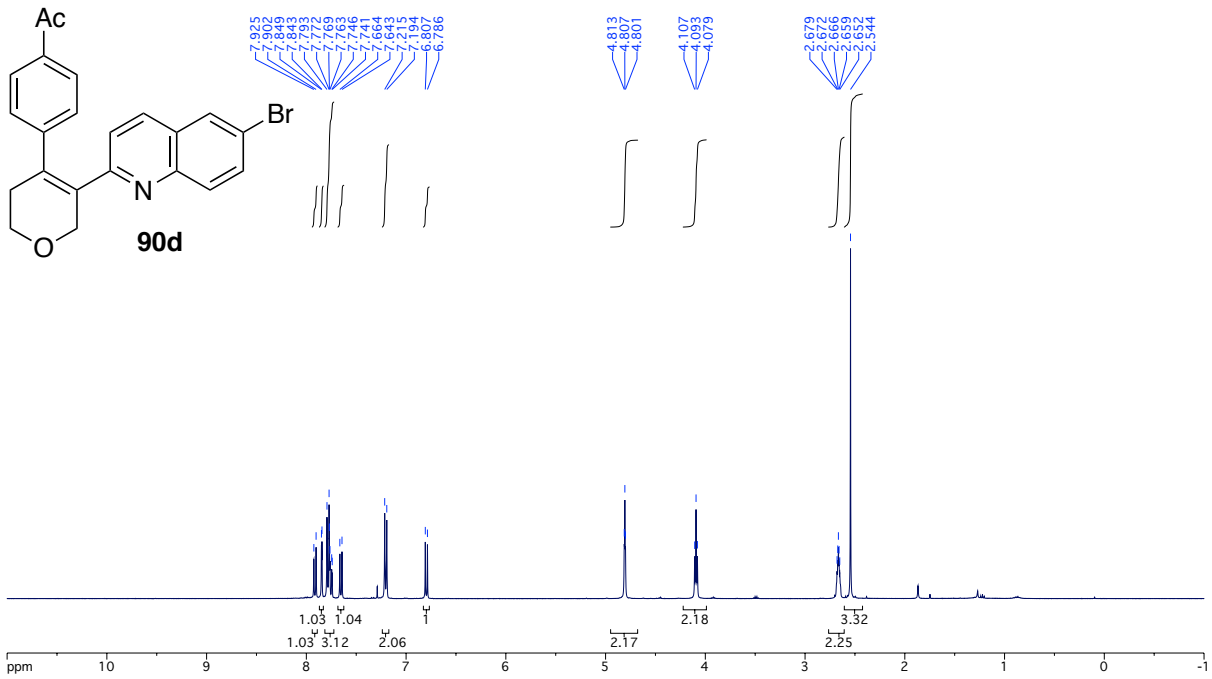

197.748
159.721
146.742
146.031
139.635
139.477
135.528
134.201
134.046
131.250
130.887
130.411
129.955
129.544
129.243
128.612
128.082
127.696
124.102
120.385
26.617
ppm

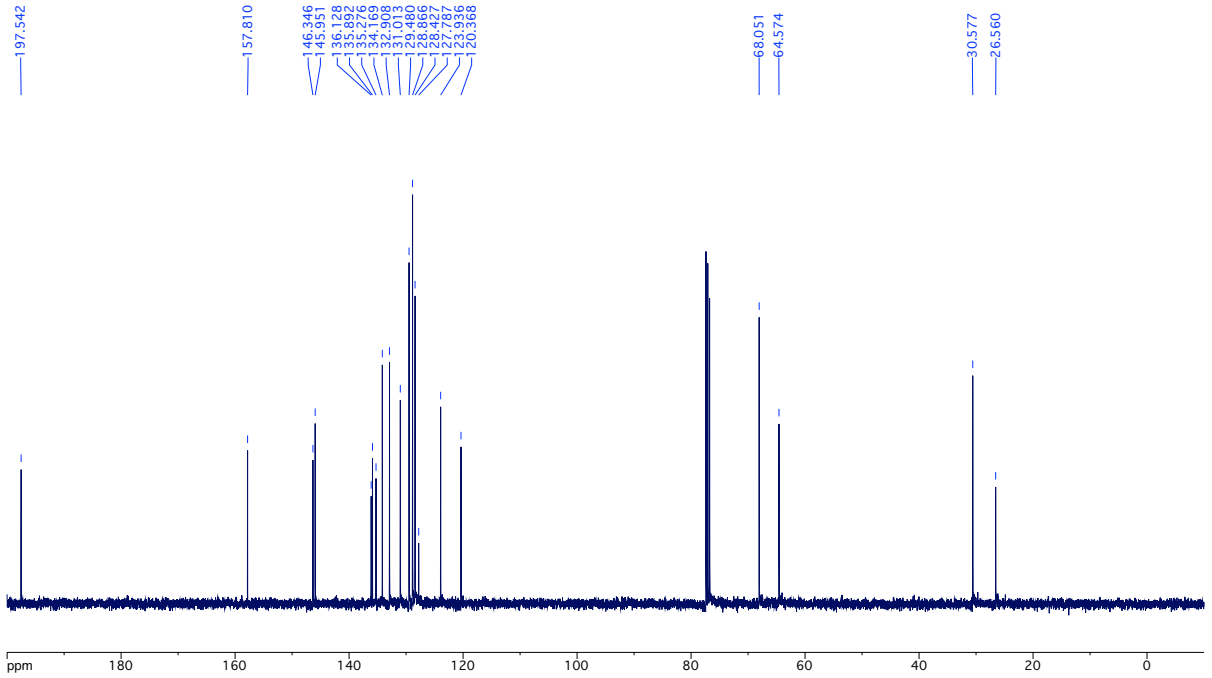

Me
Br
N
90b
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8.062
7.918
7.913
7.874
7.873
7.869
7.864
7.860
7.858
7.852
7.819
7.814
7.797
7.792
7.737
7.715
7.555
7.552
7.549
7.542
7.533
7.528
7.518
7.511
7.509
7.507
7.501
7.446
7.118
7.097
7.061
7.041
7.006
6.984
2.335
0.93
0.95
0.95
0.94
0.95
0.95
1
2.89
1.96
1.93
0.939
3.07
ppm
10
9
8
7
6
5
4
3
2
1
0
-1

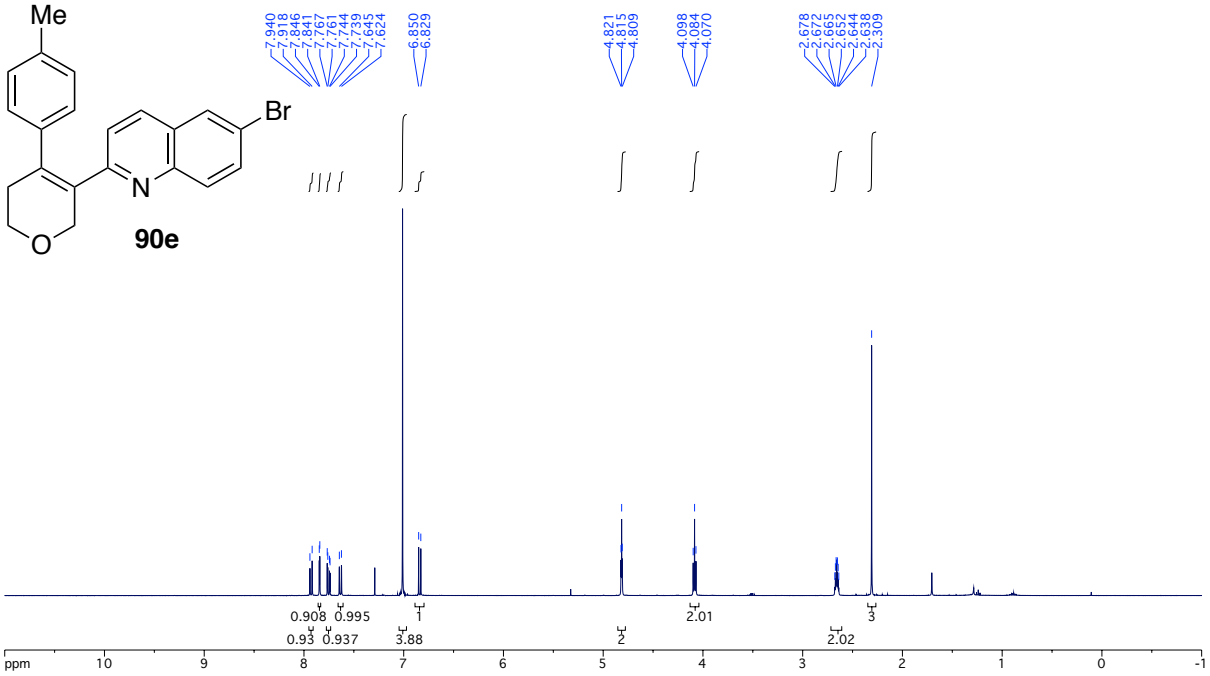

160.512
146.819
140.740
139.275
138.008
136.745
133.681
133.448
131.296
130.759
130.570
129.670
129.512
129.118
129.091
127.716
124.475
120.068
21.135
ppm
180
160
140
120
100
80
60
40
20
0

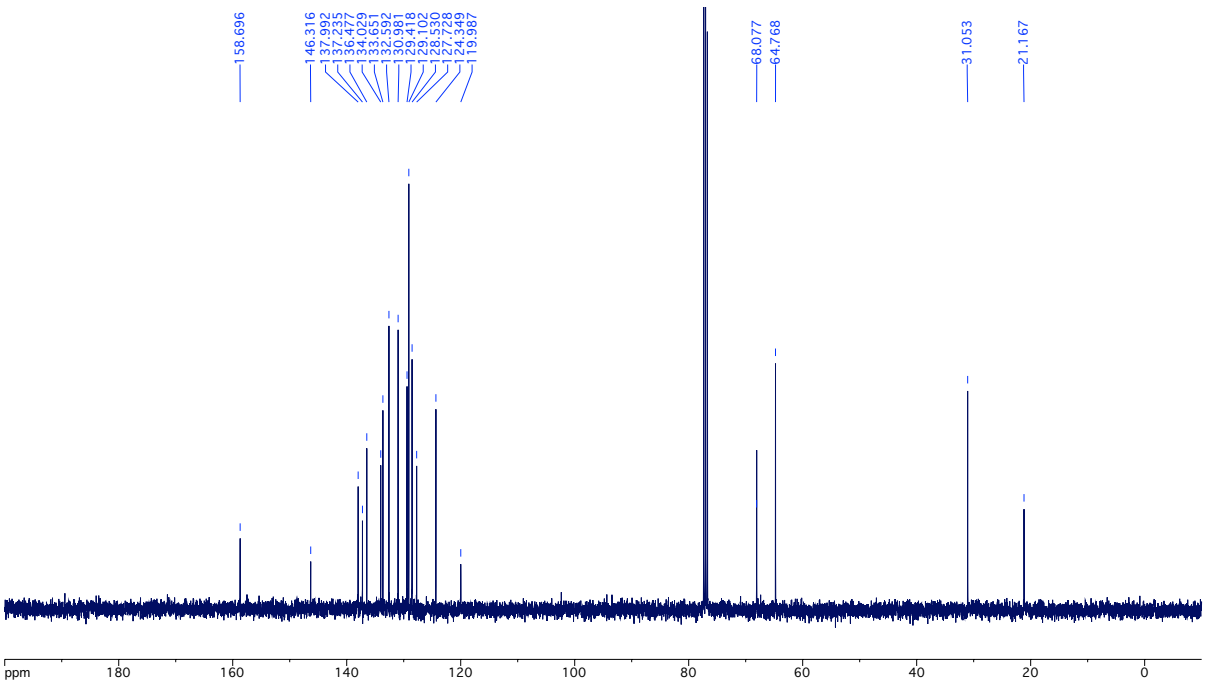

OMe
Br
N
90c
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8.056
7.921
7.915
7.860
7.859
7.855
7.851
7.843
7.837
7.836
7.817
7.812
7.795
7.789
7.748
7.747
7.543
7.537
7.529
7.521
7.514
7.504
7.503
7.496
7.490
7.486
7.481
7.480
7.136
7.114
7.001
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6.892
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3.786
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1.05
3.03
1
2.01
2.02
3.19
ppm

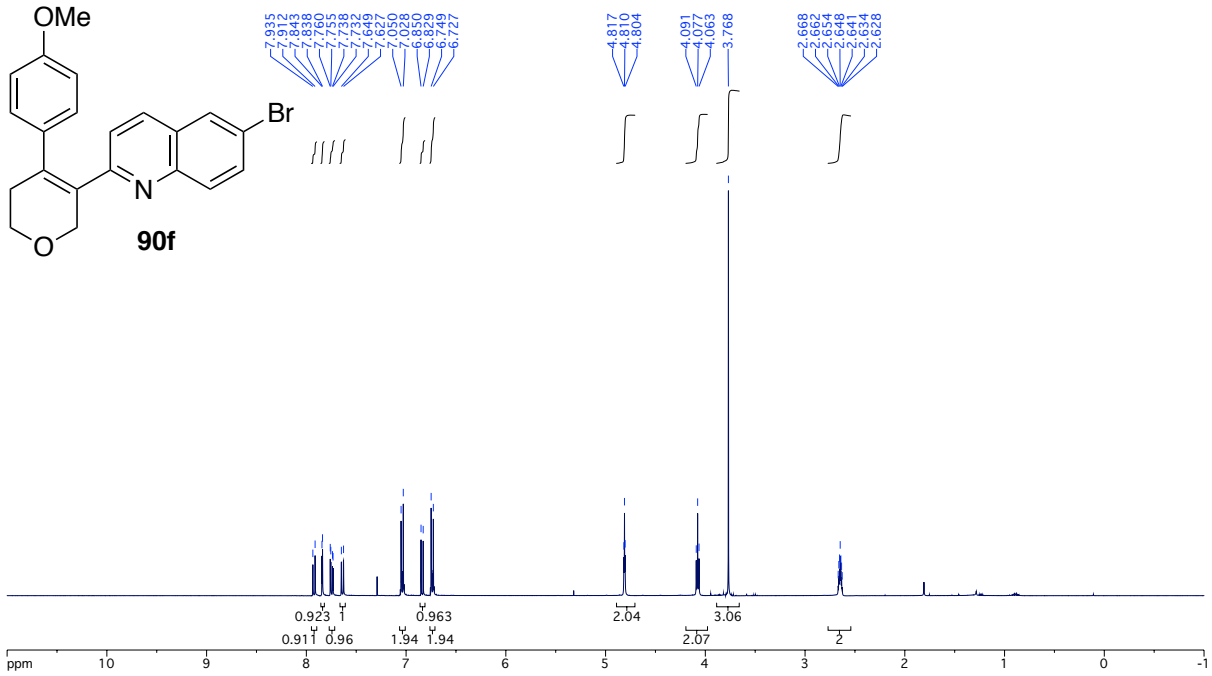

160.574
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139.220
133.697
133.303
132.749
131.879
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130.476
129.499
129.133
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ppm

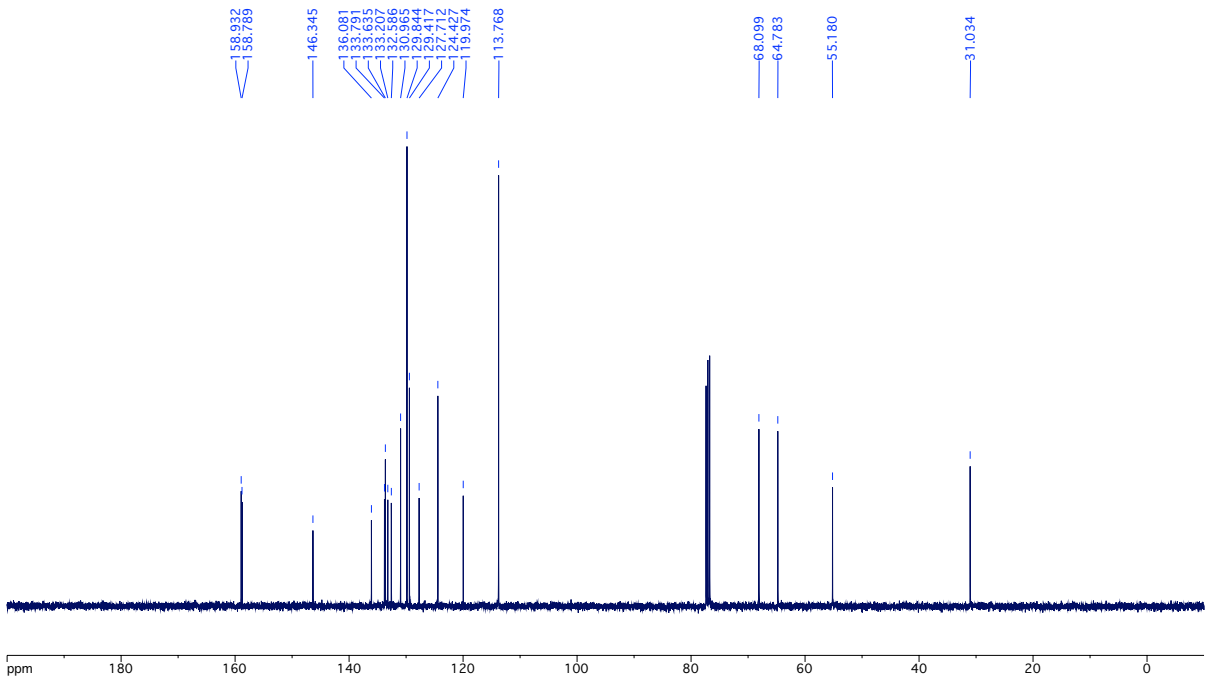

Ac
Br
N
O
90d
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7.902
7.849
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7.769
7.763
7.746
7.741
7.664
7.643
7.215
7.194
6.807
6.786
4.813
4.807
4.801
4.107
4.093
4.079
2.679
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2.659
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1.04
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2.18
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3.12
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2.17
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ppm

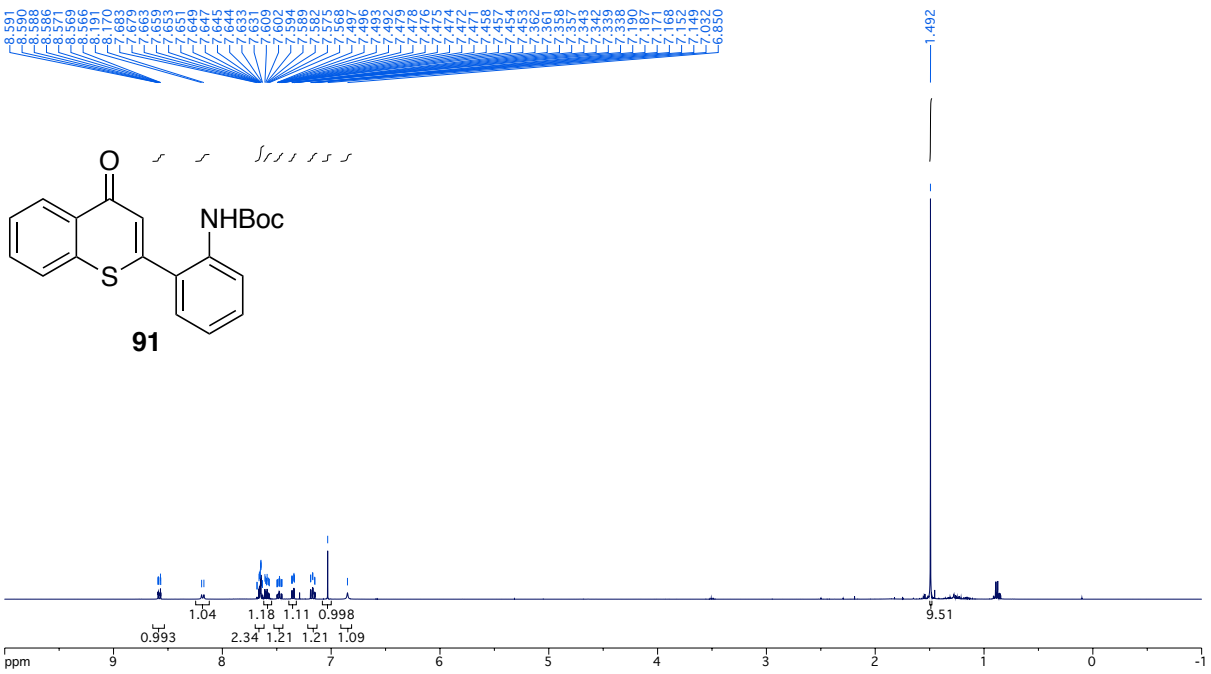

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136.128
135.892
135.276
134.169
132.908
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30.577
26.560
ppm

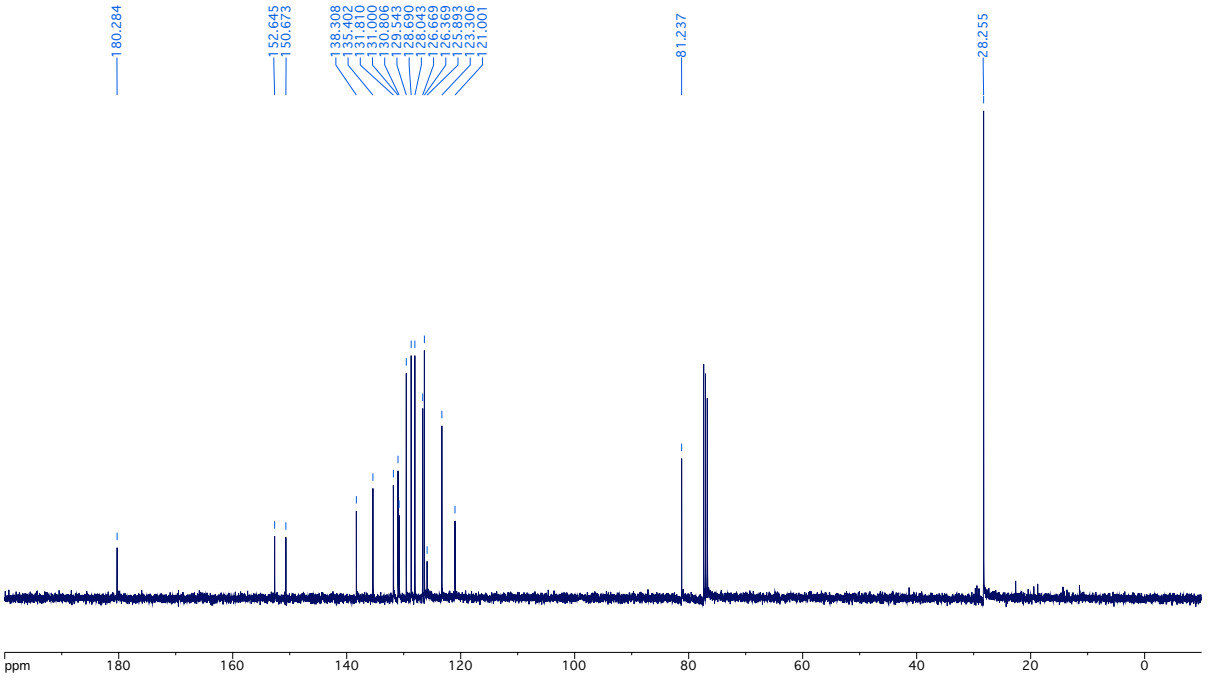

Me
Br
N
O
90e
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7.841
7.767
7.761
7.744
7.739
7.645
7.624
6.850
6.829
4.821
4.815
4.809
4.098
4.084
4.070
2.678
2.672
2.665
2.652
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0.995
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2
2.02
ppm

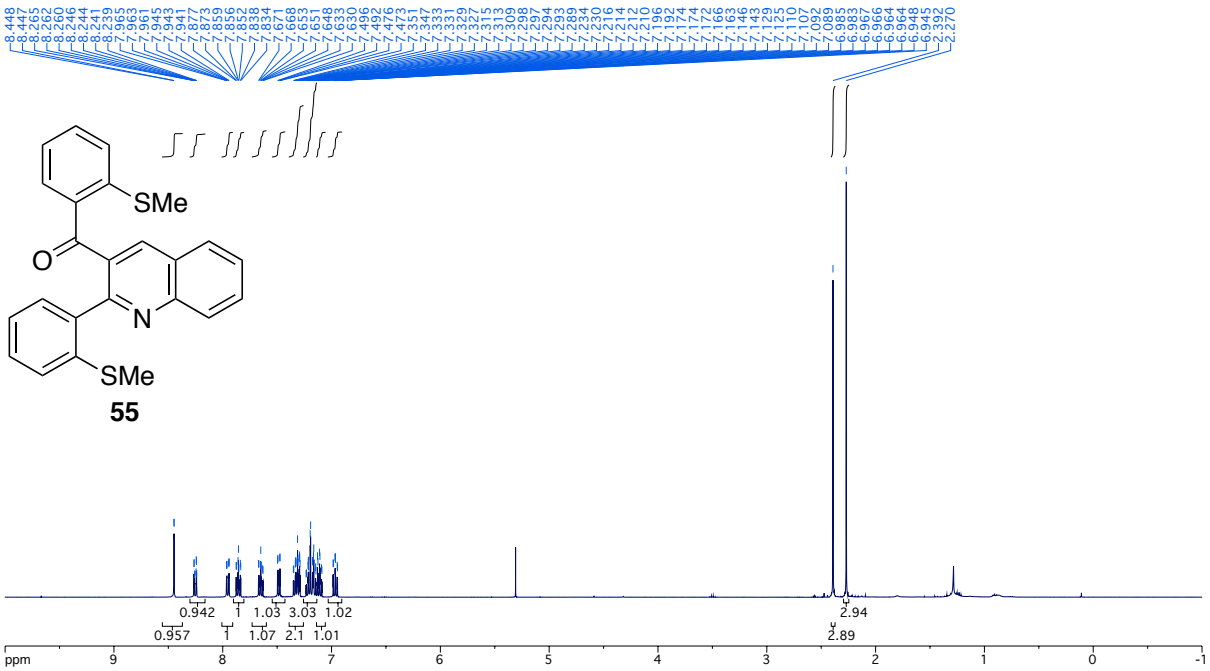

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133.651
133.592
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129.102
128.530
127.728
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21.167
ppm

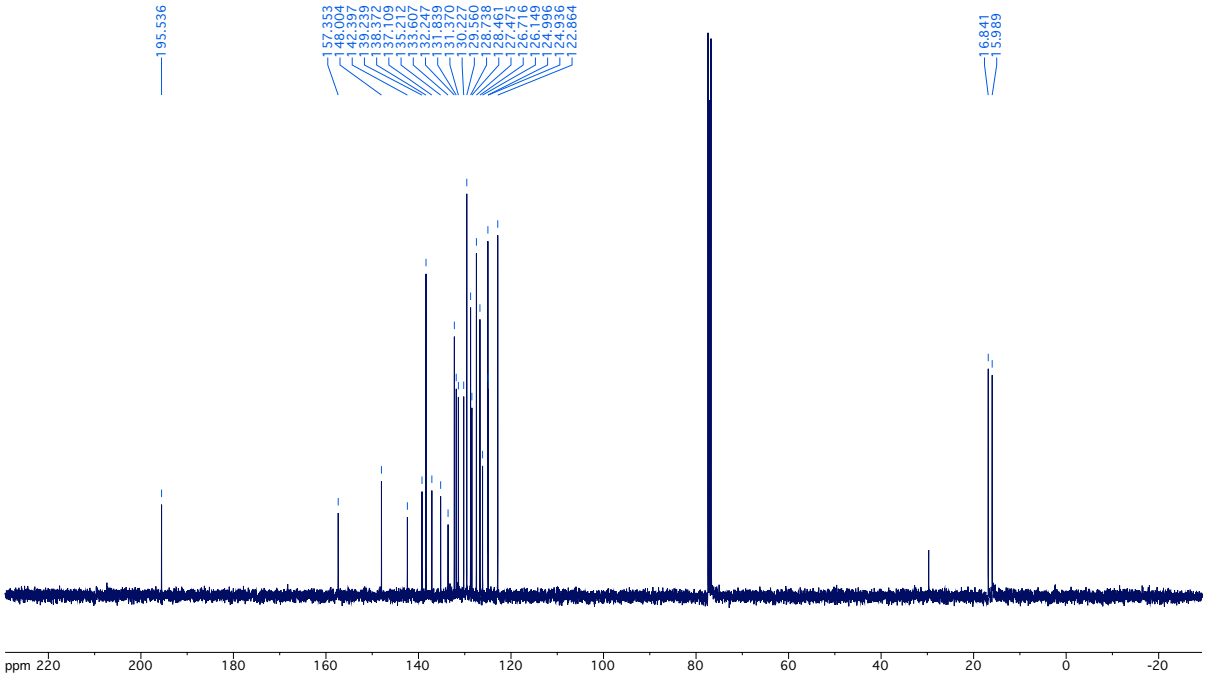

OMe
Br
N
O
90f
7.935
7.912
7.843
7.838
7.760
7.755
7.738
7.732
7.649
7.627
7.050
7.028
6.850
6.829
6.749
6.727
4.817
4.810
4.804
4.091
4.077
4.063
3.768
2.668
2.662
2.654
2.648
2.641
2.634
2.628
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1
0.963
2.04
3.06
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1.94
2.07
2
ppm

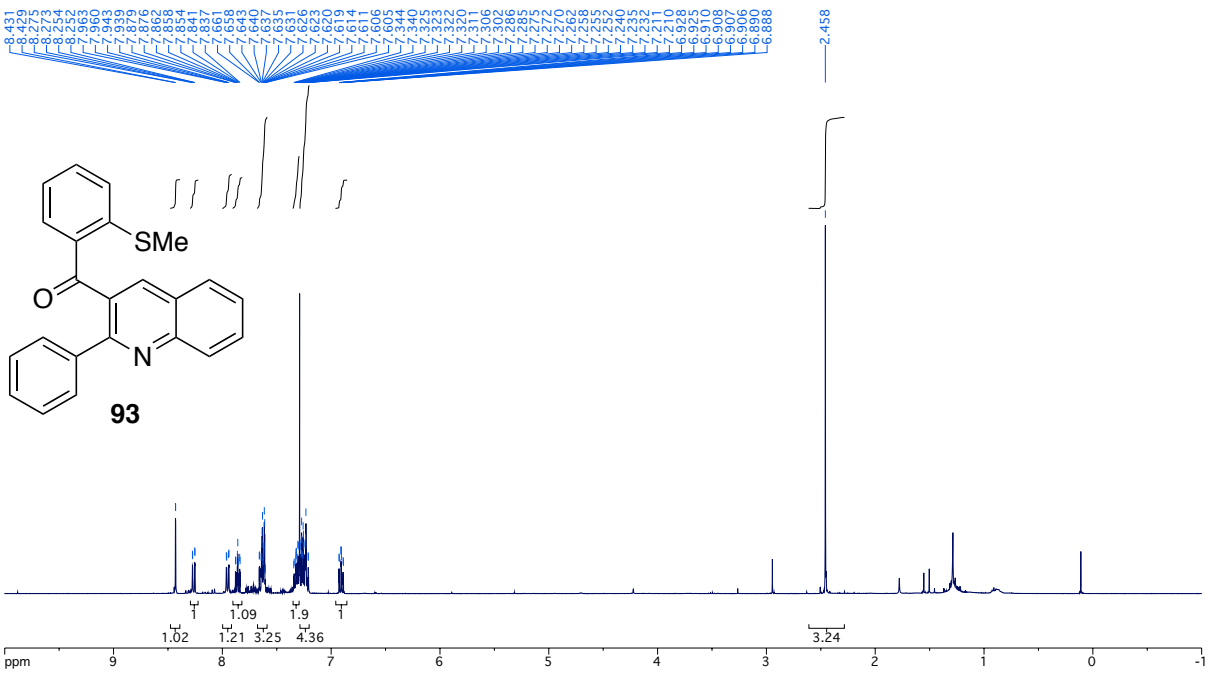

158.932
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133.207
132.586
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129.417
127.712
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119.974
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68.099
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31.034
ppm

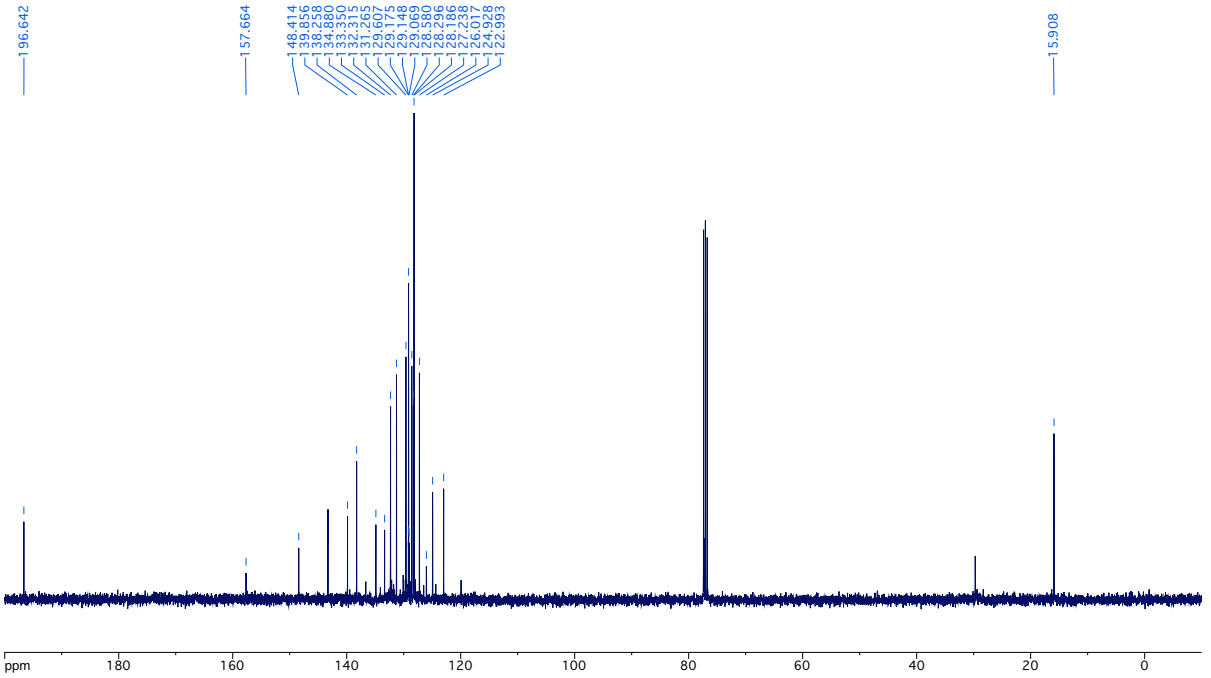

8.591
8.590
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8.586
8.571
8.569
8.566
8.191
8.190
7.683
7.679
7.663
7.659
7.653
7.651
7.649
7.647
7.645
7.644
7.633
7.631
7.609
7.602
7.594
7.589
7.583
7.575
7.568
7.497
7.496
7.493
7.492
7.478
7.476
7.475
7.474
7.472
7.471
7.458
7.457
7.454
7.453
7.362
7.361
7.358
7.357
7.343
7.342
7.339
7.338
7.190
7.187
7.171
7.168
7.152
7.149
7.032
6.850
1.492
O
NHBoc
S
91
1.04
1.18
1.11
0.998
0.993
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1.09
9.51
ppm
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7
6
5
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3
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1
0
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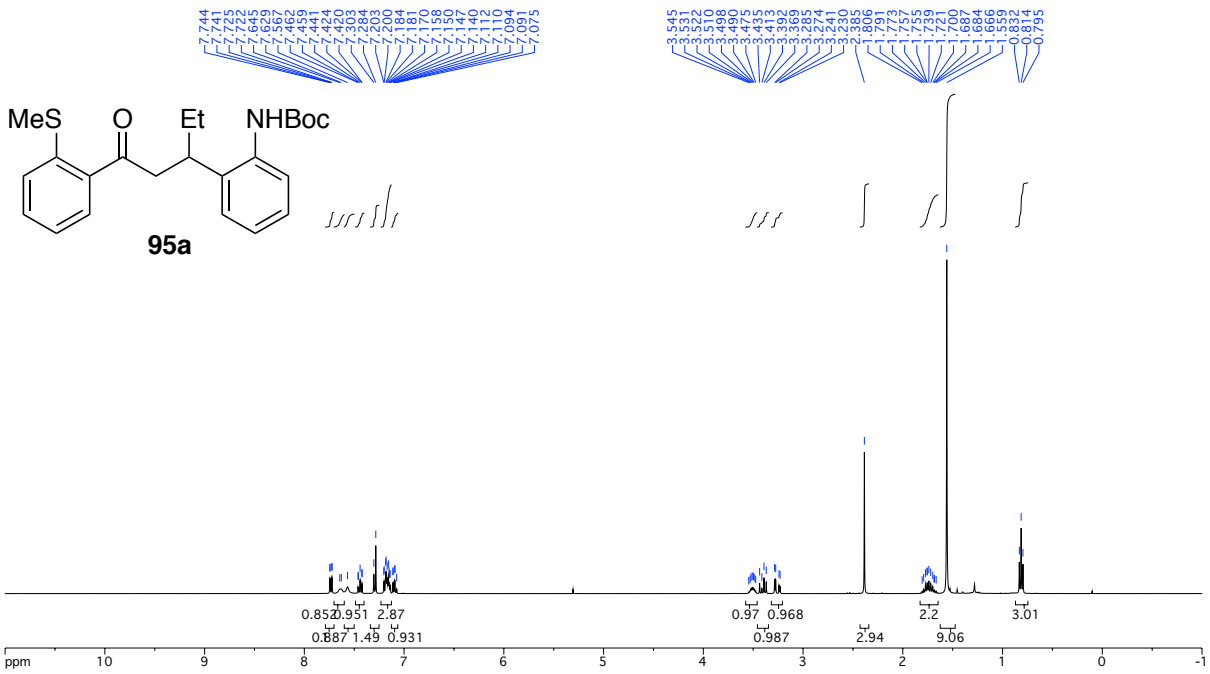

180.284
152.645
150.673
138.308
133.402
131.710
131.000
130.806
129.543
128.690
128.043
126.669
125.869
125.693
123.306
121.001
81.237
28.255
ppm
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140
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80
60
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20
0

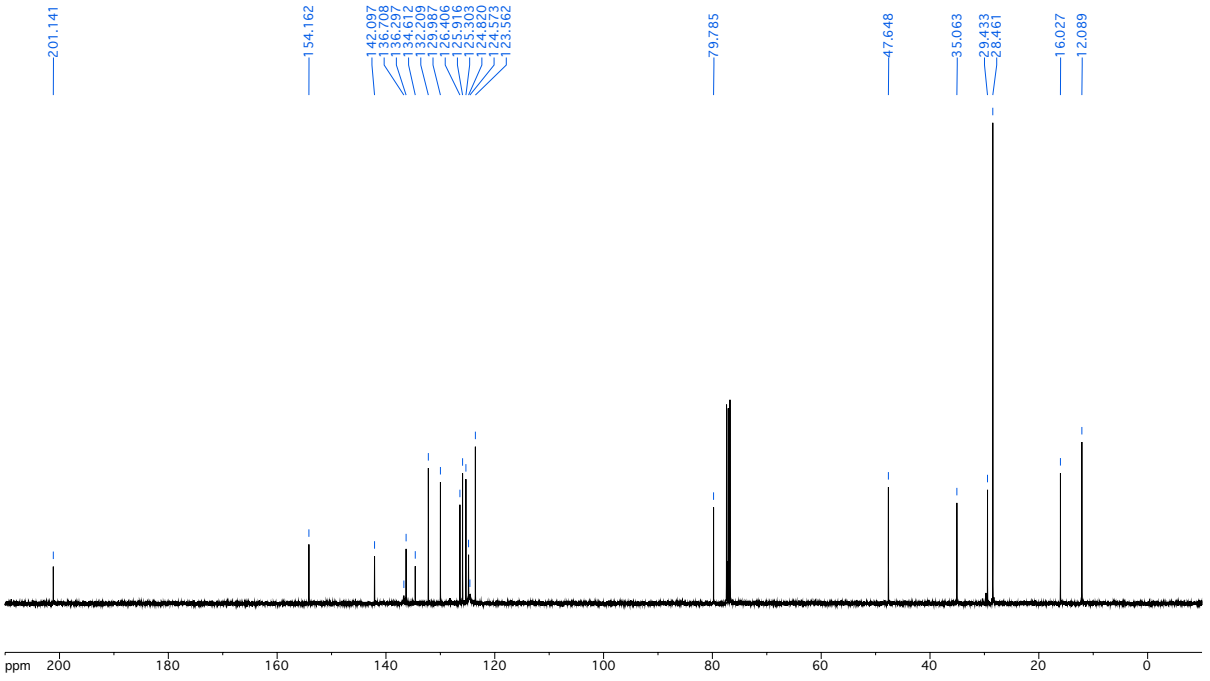

SMe
O
N
SMe
55
0.942
1
1.03
3.03
1.02
2.94
0.957
1
1.07
2.1
1.01
2.89
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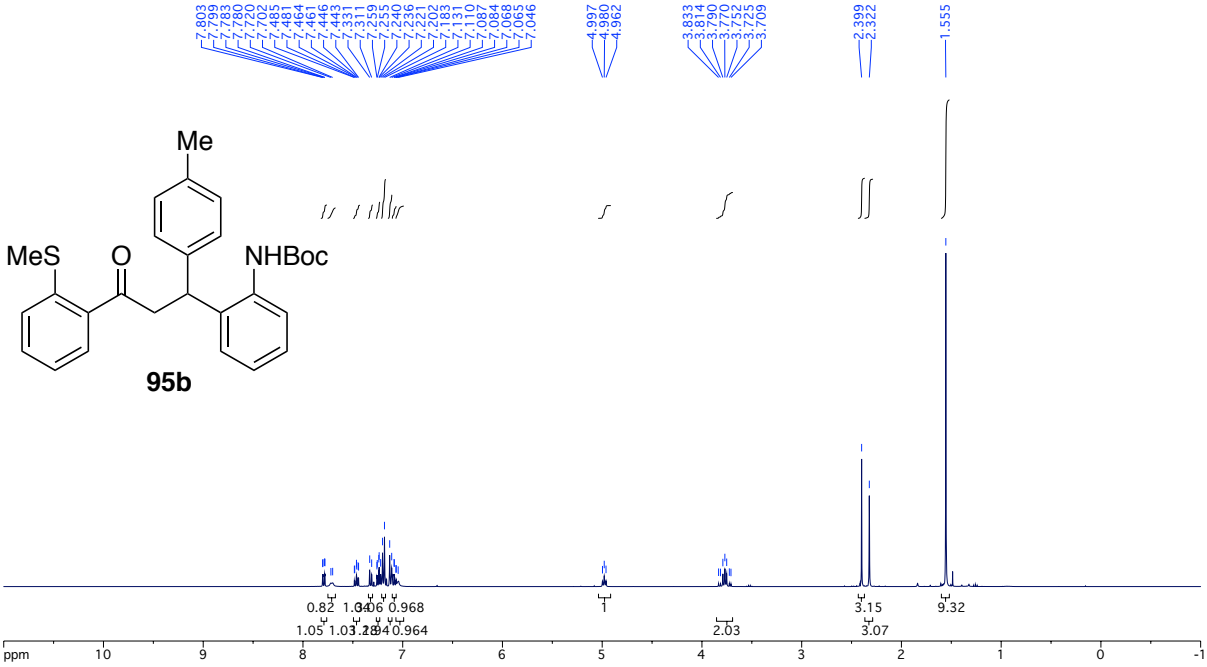

195.536
157.353
148.004
140.397
138.232
137.372
137.109
135.212
133.607
132.247
131.839
131.177
130.227
129.560
128.738
128.461
127.475
126.716
126.449
124.996
122.936
122.864
16.841
15.989
ppm

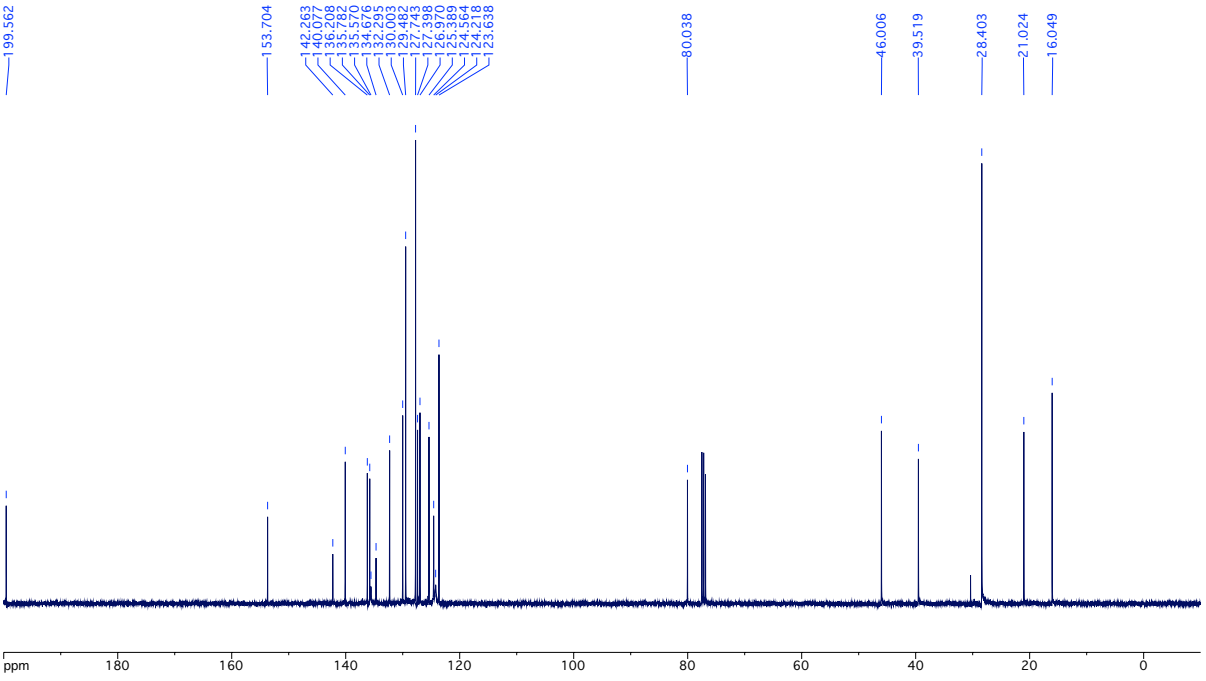

SMe
O
N
93
2.458
1
1.09
1.9
1
1.02
1.21
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4.36
3.24
ppm

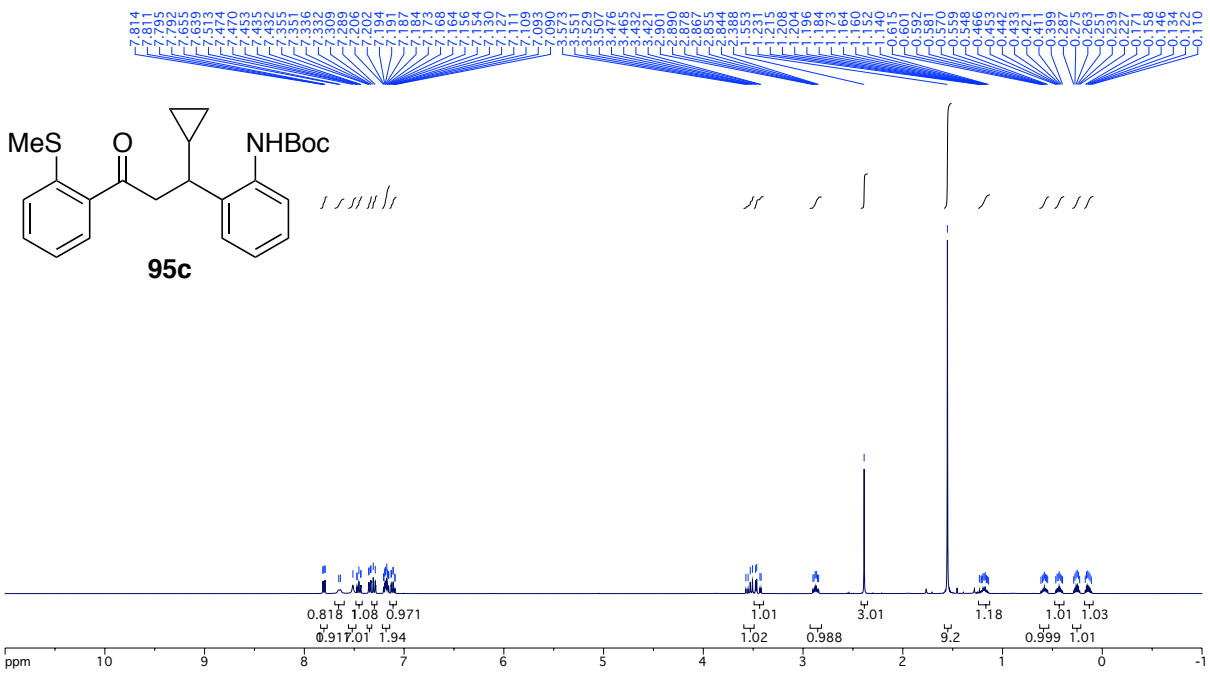

196.642
157.664
148.414
138.856
138.258
134.880
133.350
132.315
131.265
129.607
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128.069
128.580
128.296
128.186
127.238
126.017
124.928
122.993
15.908
ppm

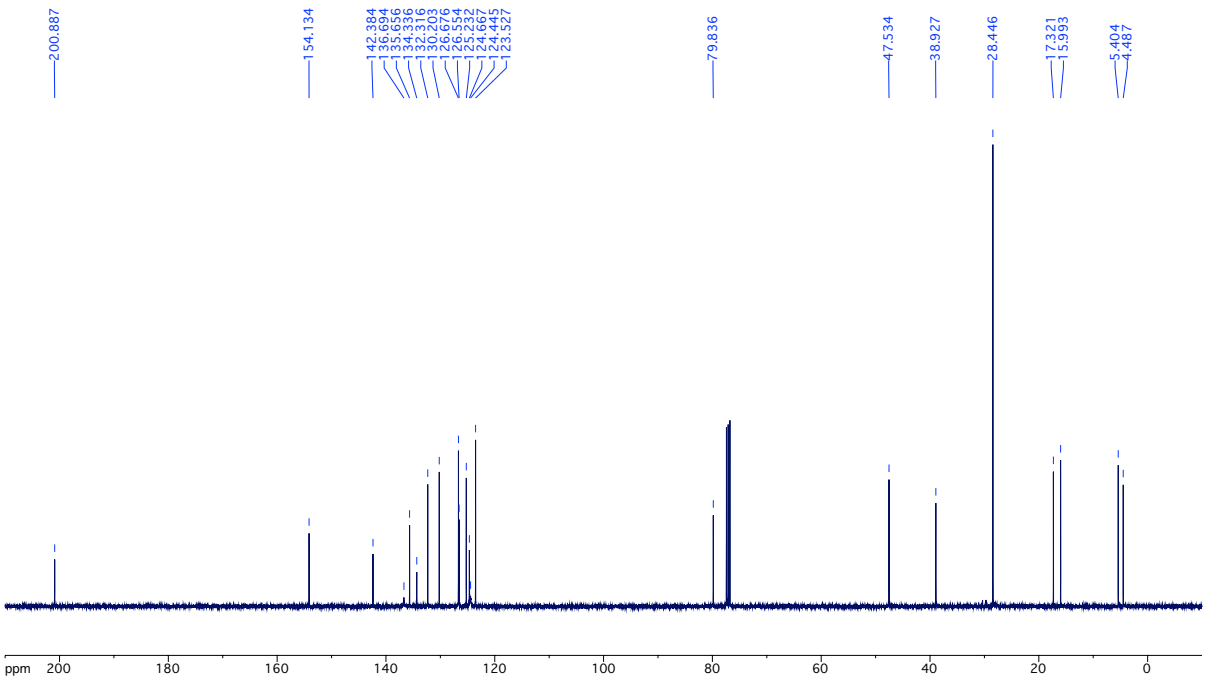

MeS
O
Et
NHBoc
95a
ppm

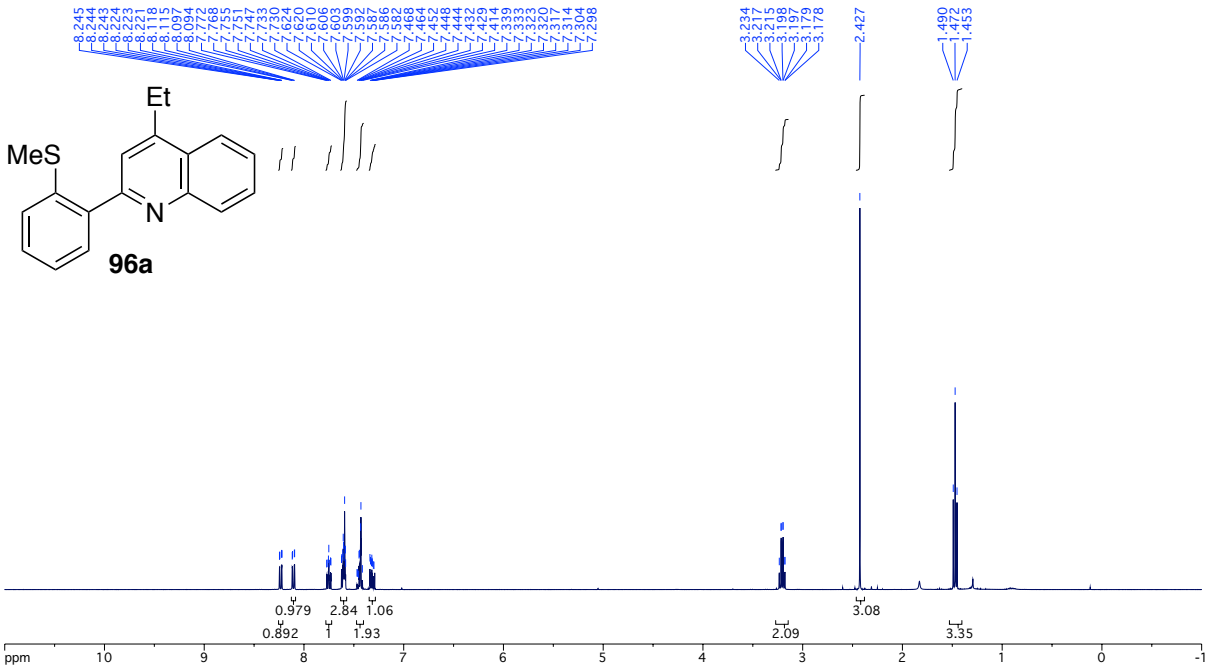

ppm

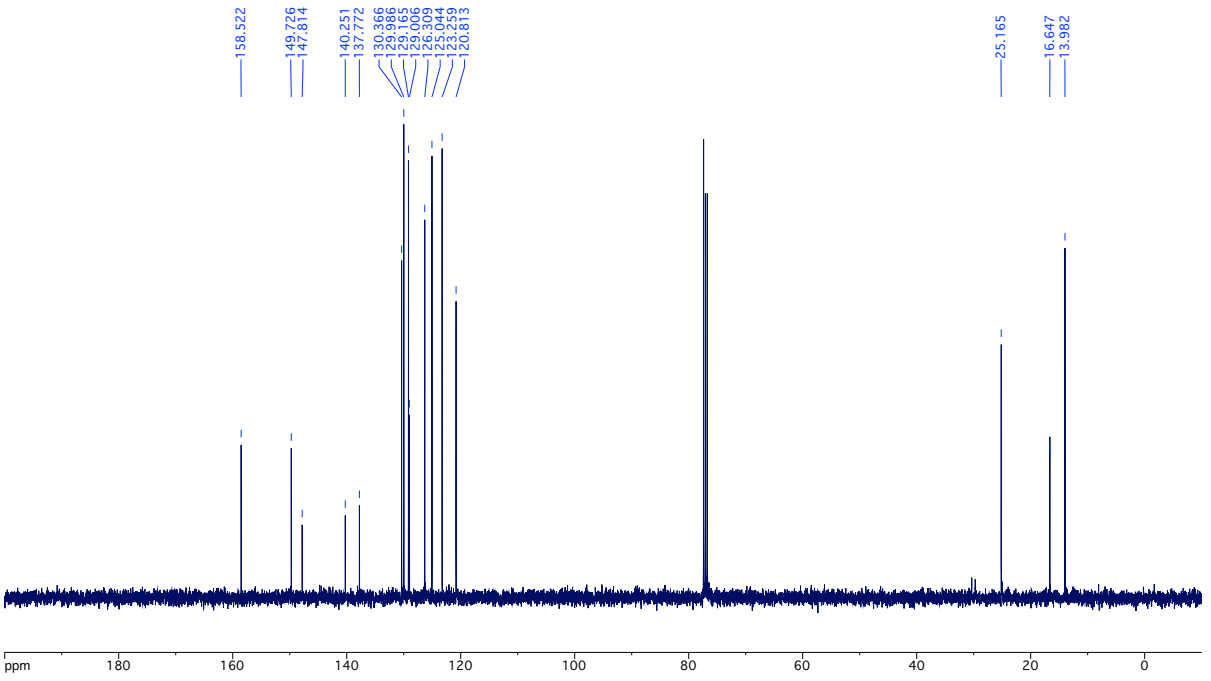

Me
MeS
O
NHBoc
95b
7.803
7.799
7.783
7.780
7.720
7.702
7.485
7.481
7.464
7.461
7.446
7.443
7.331
7.311
7.259
7.255
7.240
7.236
7.221
7.202
7.183
7.131
7.110
7.087
7.084
7.068
7.065
7.046
4.997
4.980
4.962
3.833
3.814
3.790
3.770
3.742
3.725
3.709
2.399
2.322
1.555
0.82
1.05
1.03
1.06
0.968
0.964
1
2.03
3.15
3.07
9.32
ppm

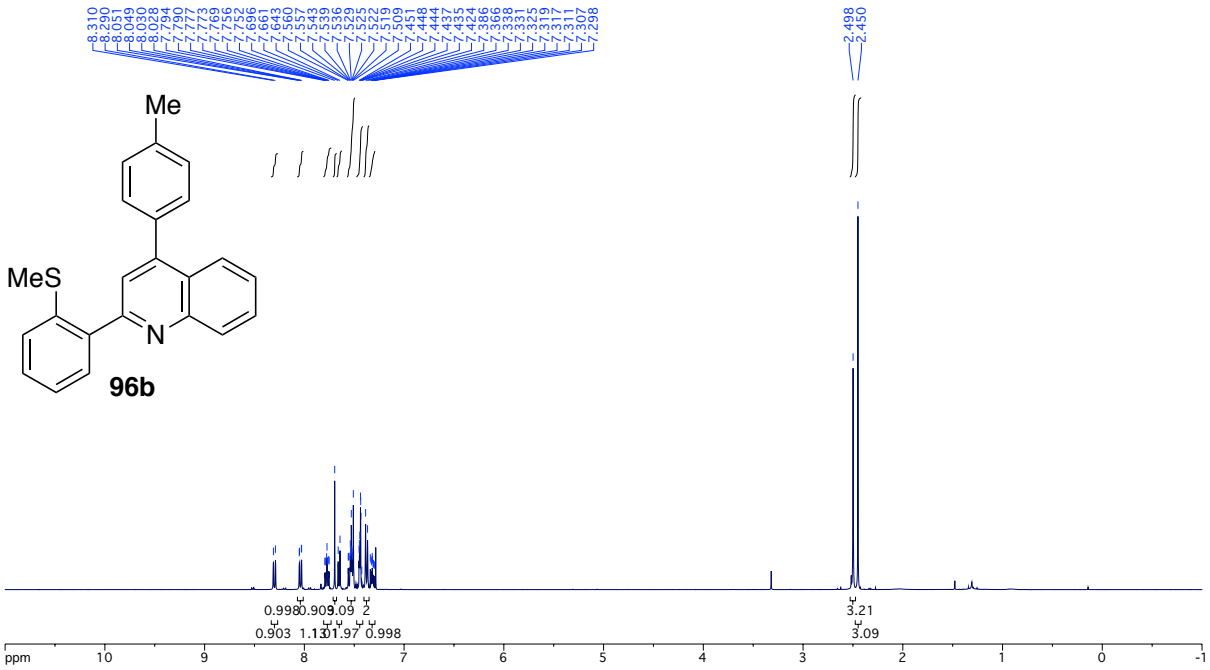

199.562
153.704
142.263
140.017
136.082
135.782
135.570
134.676
132.295
130.003
129.482
127.743
127.348
126.970
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124.564
124.218
123.638
80.038
46.006
39.519
28.403
21.024
16.049
ppm

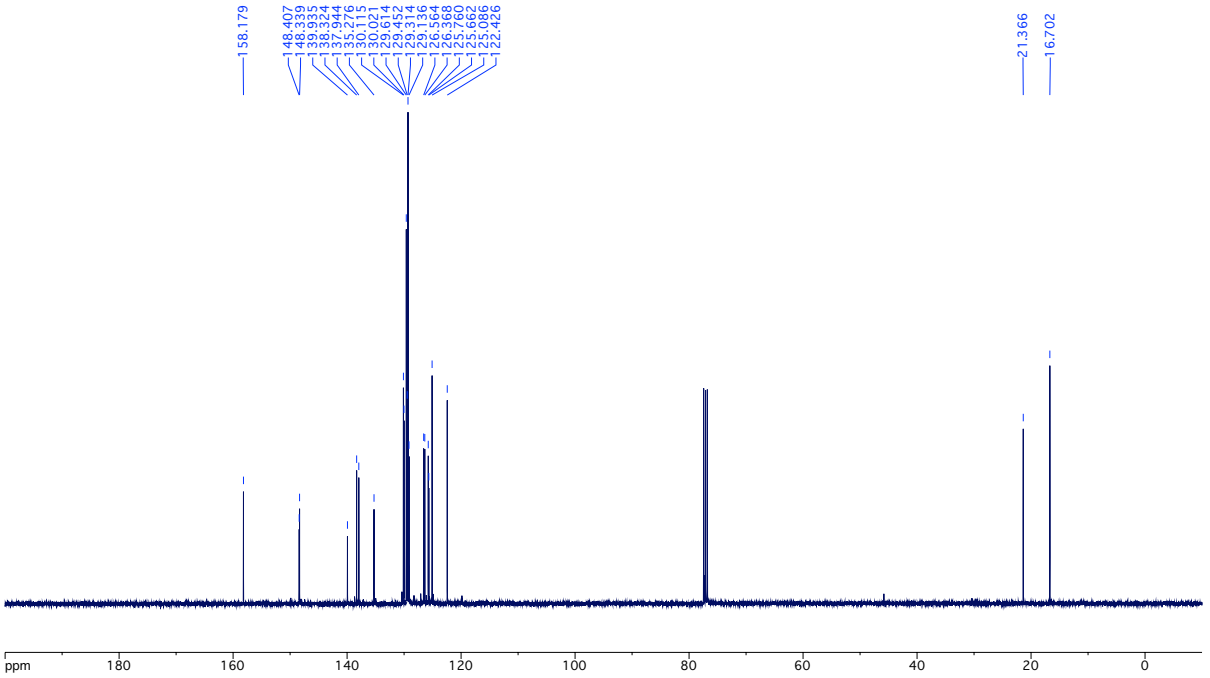

MeS
O
NHBoc
95c
0.818
1.08
0.971
0.917
1.01
1.94
1.01
3.01
1.18
1.01
1.03
1.02
0.988
9.2
0.999
1.01
ppm

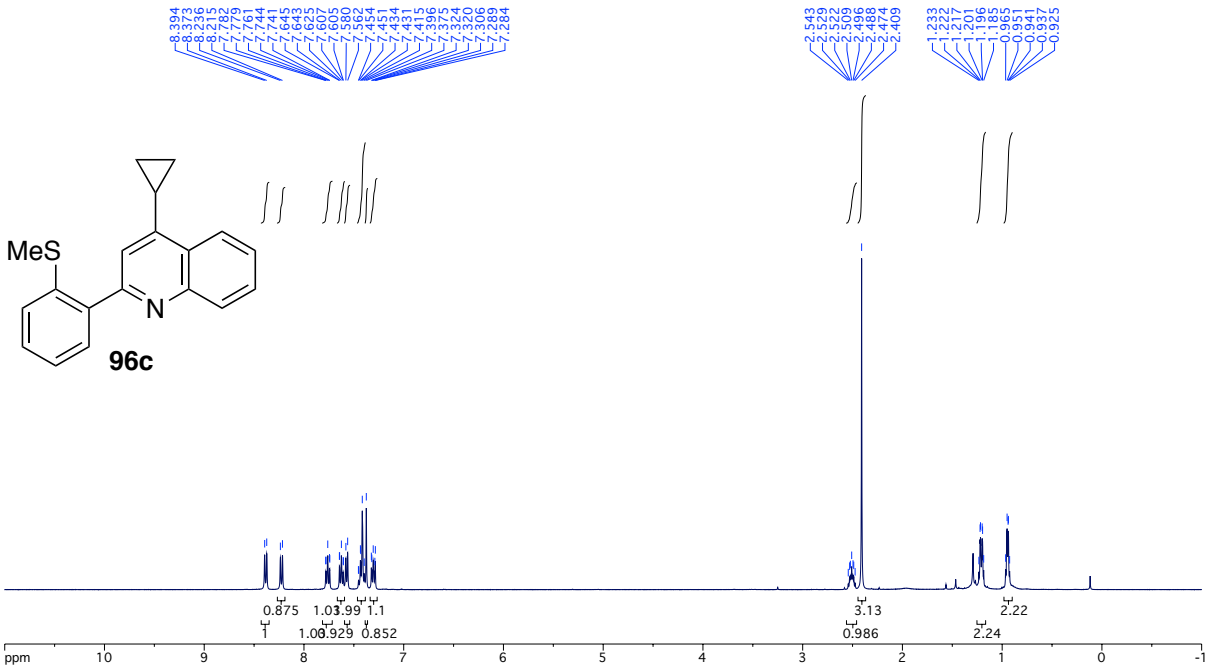

200.887
154.134
142.384
136.694
136.656
133.316
132.336
130.203
126.676
126.554
125.232
124.667
124.445
123.527
79.836
47.534
38.927
28.446
17.321
15.993
5.404
4.487
ppm

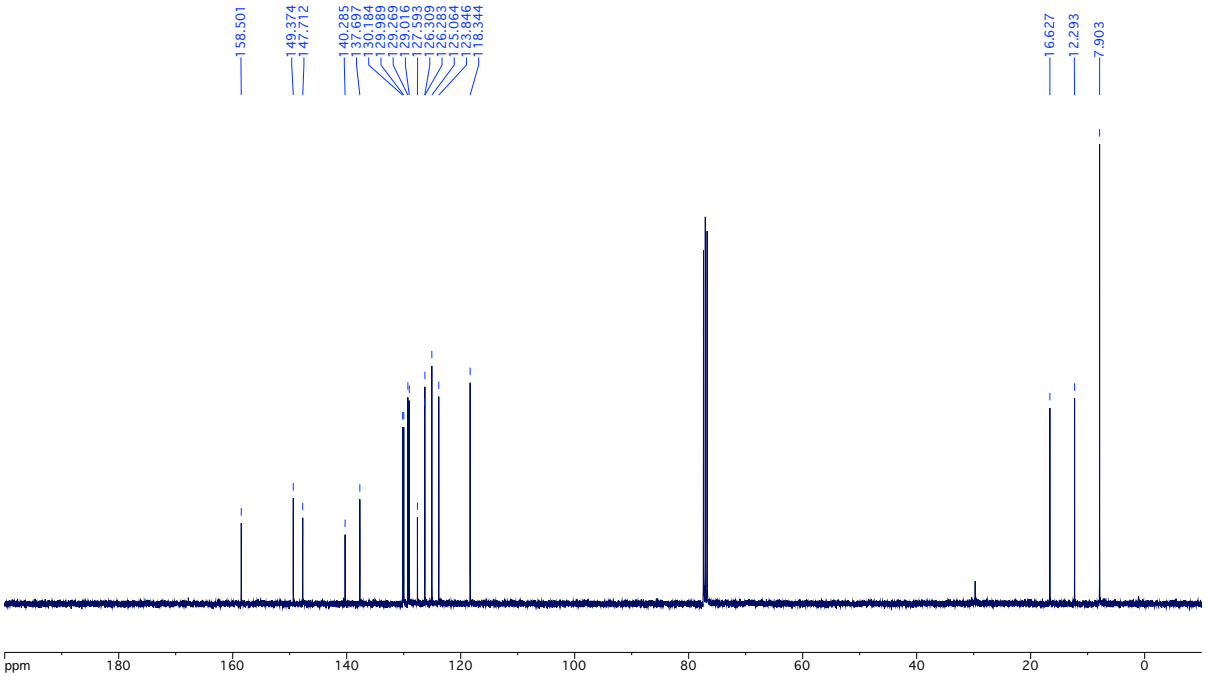

Et
MeS
N
96a
8.245
8.244
8.243
8.224
8.223
8.221
8.118
8.115
8.097
8.094
7.772
7.768
7.755
7.751
7.747
7.733
7.730
7.624
7.620
7.610
7.606
7.603
7.599
7.592
7.587
7.586
7.582
7.468
7.464
7.452
7.448
7.444
7.432
7.429
7.414
7.339
7.333
7.323
7.320
7.317
7.314
7.304
7.298
3.234
3.217
3.215
3.198
3.197
3.179
3.178
2.427
1.490
1.472
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0.979
2.84
1.06
0.892
1
1.93
2.09
3.08
3.35
ppm

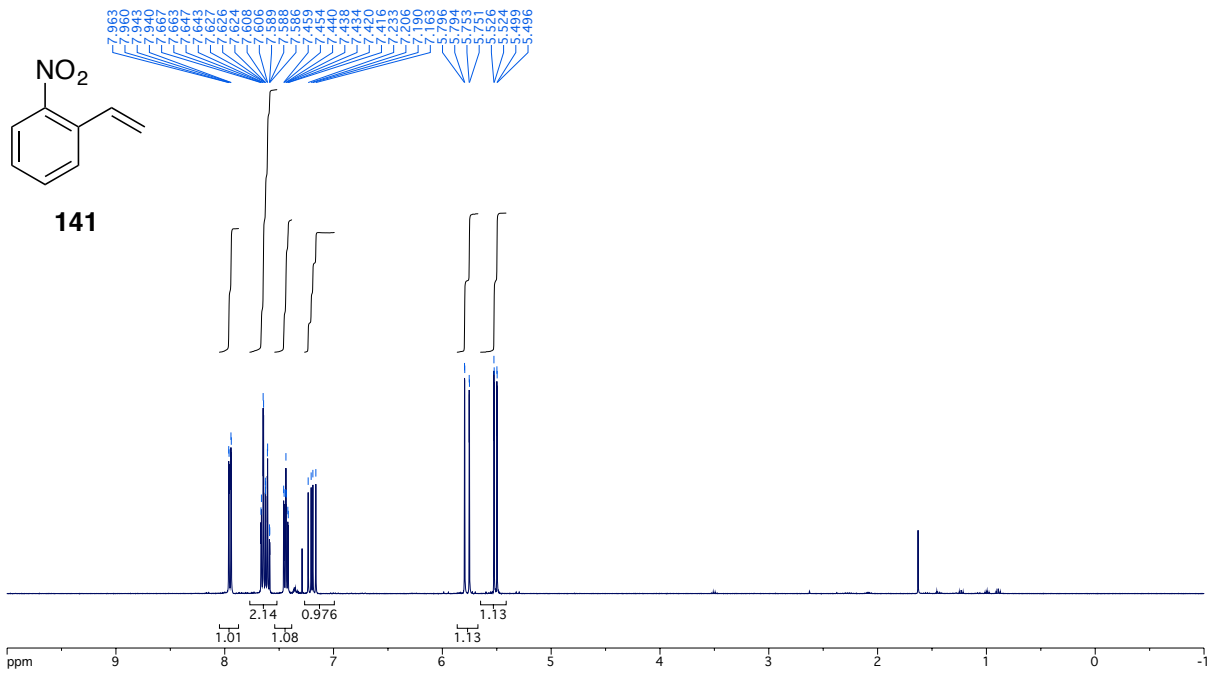

158.522
149.726
147.814
140.251
137.772
130.366
129.986
129.165
129.066
126.309
125.044
123.259
120.813
25.165
16.647
13.982
ppm

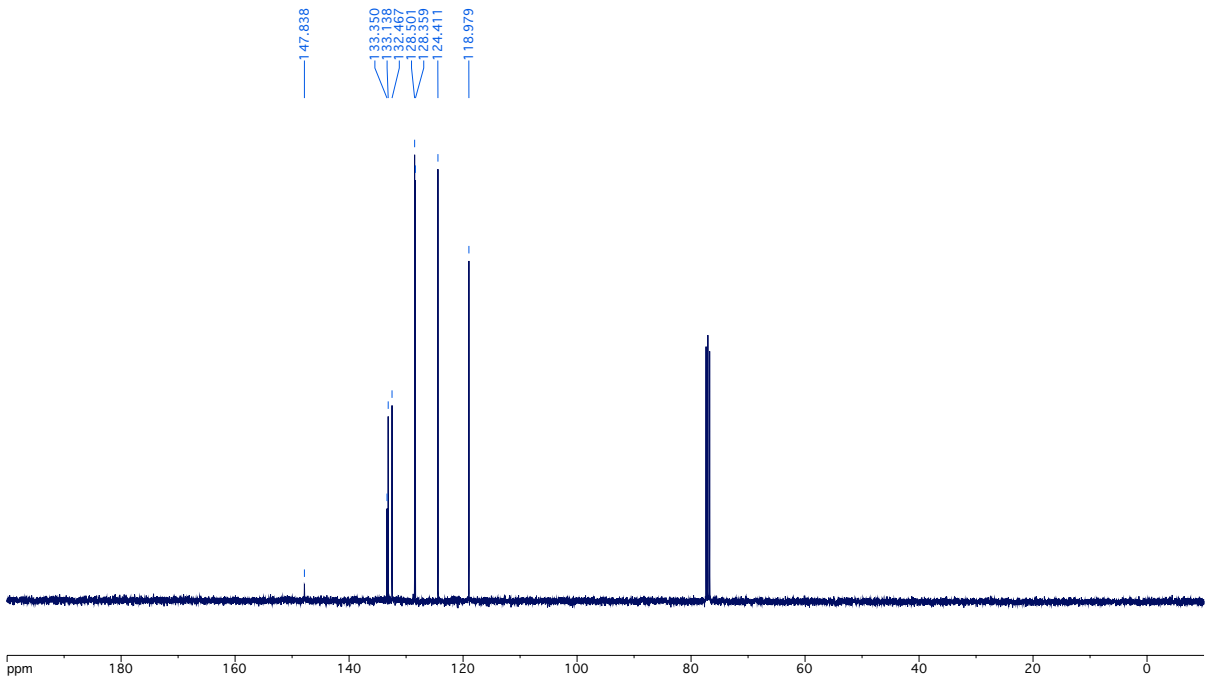

Me
MeS
N
96b
ppm

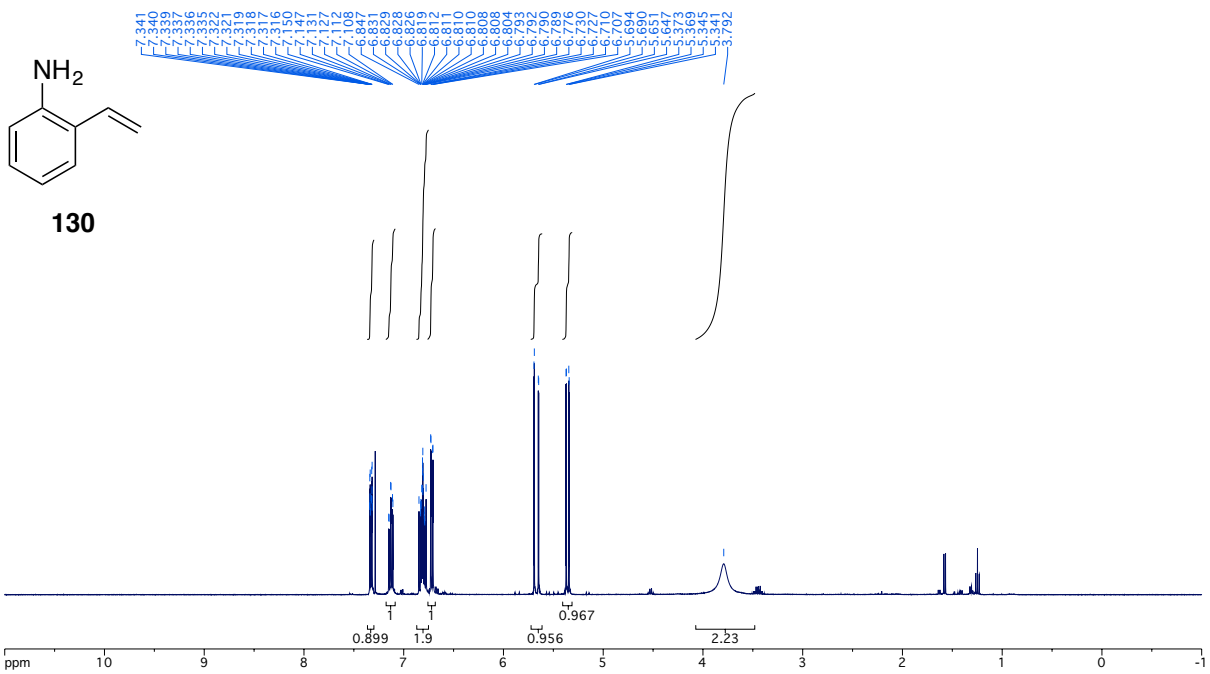

ppm

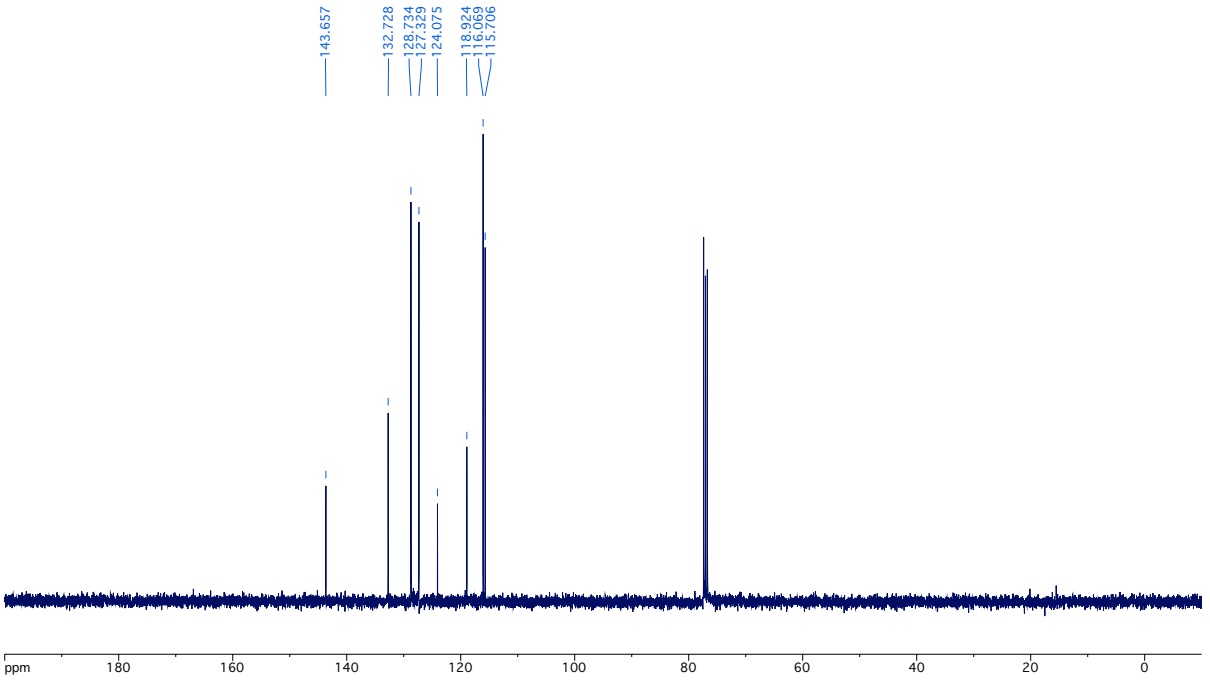

8.394
8.373
8.236
8.215
7.782
7.779
7.761
7.744
7.741
7.645
7.643
7.625
7.607
7.605
7.580
7.562
7.454
7.451
7.434
7.431
7.415
7.396
7.375
7.324
7.320
7.306
7.289
7.284
2.543
2.529
2.522
2.509
2.496
2.488
2.474
2.409
1.233
1.222
1.217
1.201
1.196
1.185
0.965
0.951
0.941
0.937
0.925
MeS
N
96c
0.875
1.03
3.99
1.1
1.00
0.929
0.852
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2.22
2.24
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10
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6
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0
-1

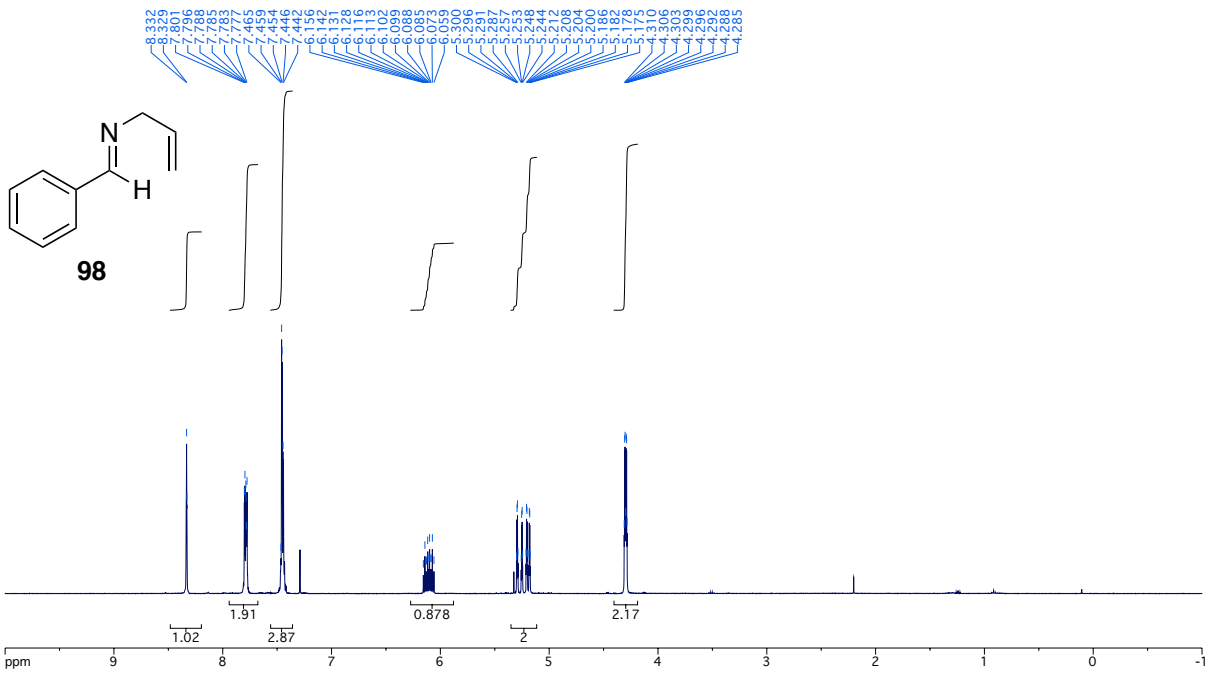

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149.374
147.712
140.285
137.697
130.184
129.989
129.269
129.016
127.593
126.709
126.283
125.064
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20
0

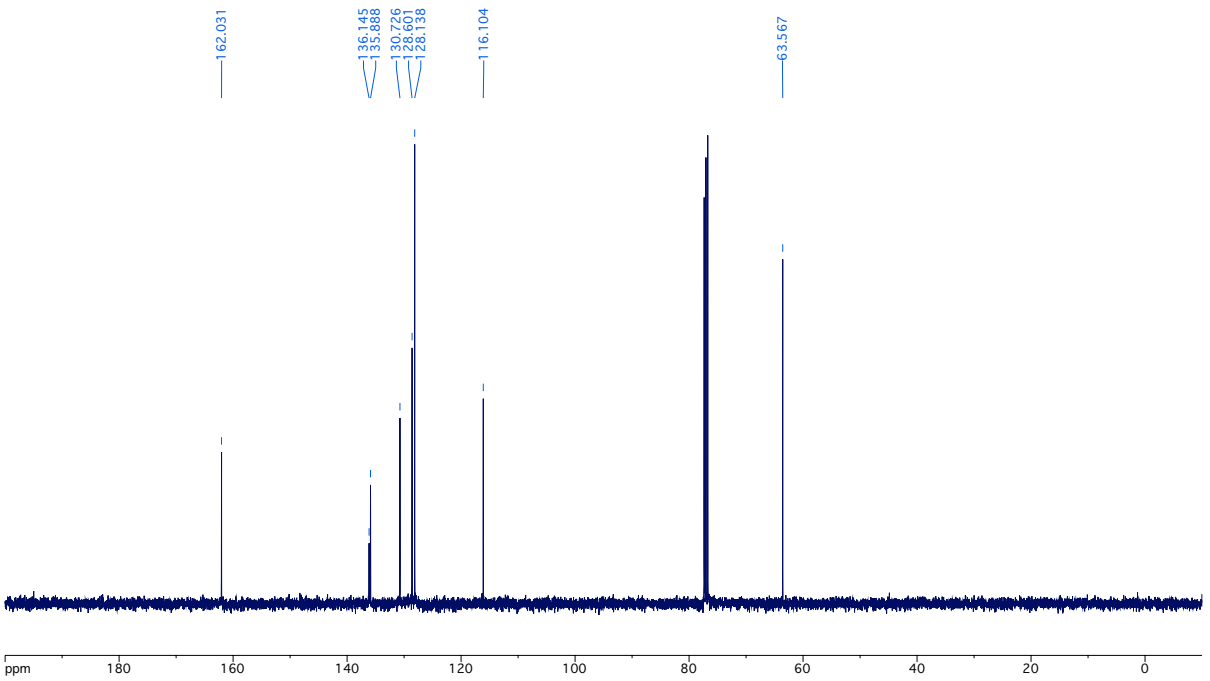

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7.940
7.667
7.663
7.647
7.643
7.627
7.624
7.608
7.606
7.589
7.588
7.586
7.459
7.454
7.440
7.438
7.434
7.420
7.416
7.235
7.206
7.190
7.163
5.796
5.794
5.753
5.751
5.526
5.524
5.499
5.496
NO2
141
2.14
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1.13
1.13
ppm
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8
7
6
5
4
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2
1
0
-1

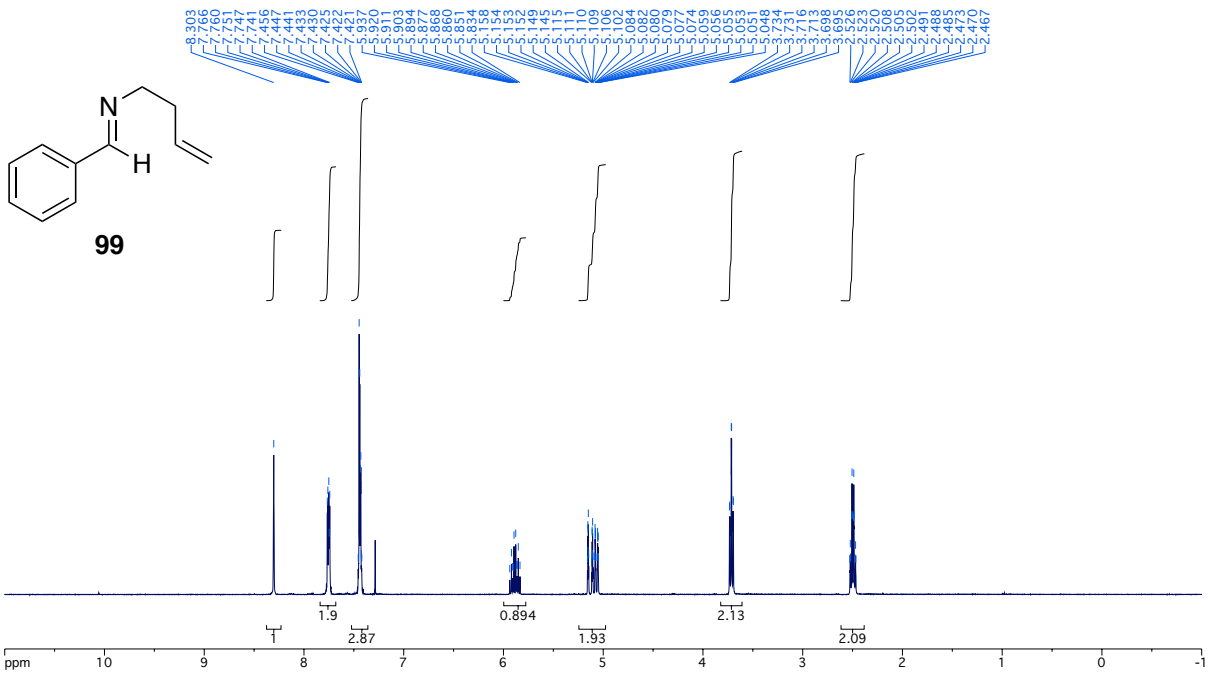

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133.350
133.138
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128.359
124.411
118.979
ppm
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140
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60
40
20
0

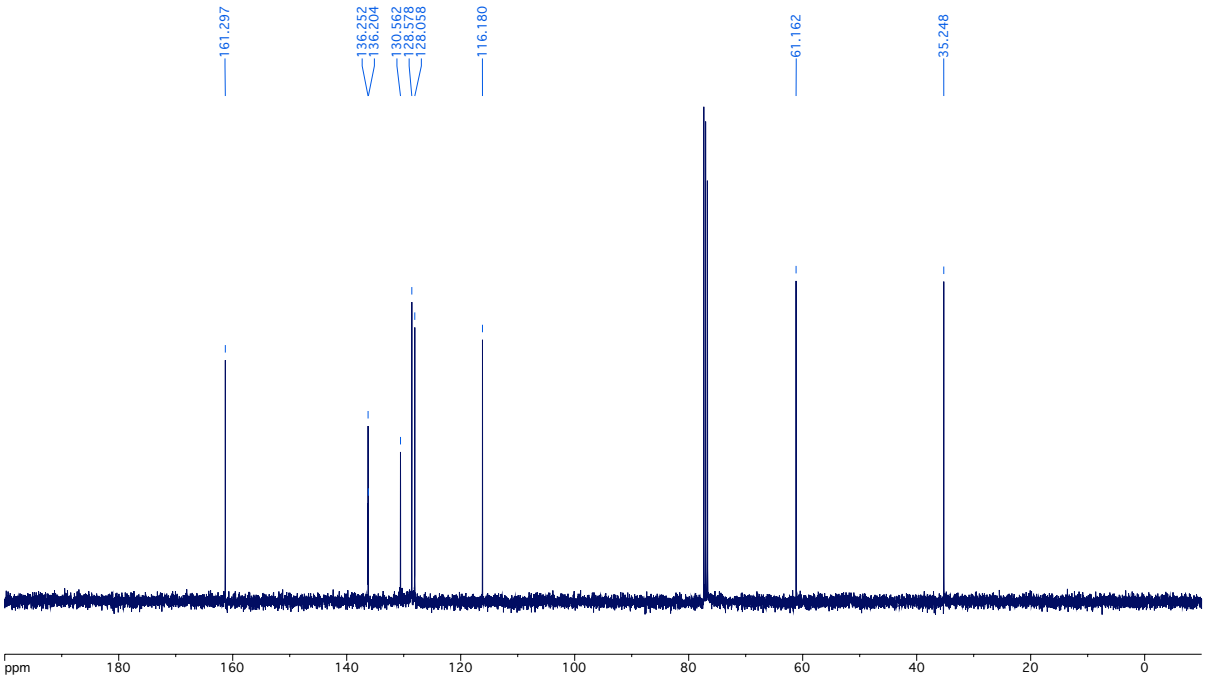

NH2
130
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7.340
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7.335
7.322
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7.319
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7.317
7.316
7.150
7.147
7.131
7.127
7.112
7.108
6.847
6.831
6.829
6.828
6.826
6.819
6.812
6.811
6.810
6.810
6.808
6.808
6.804
6.793
6.792
6.790
6.789
6.776
6.730
6.727
6.710
6.707
5.694
5.690
5.651
5.647
5.373
5.369
5.345
5.341
3.792
0.899
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5
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0
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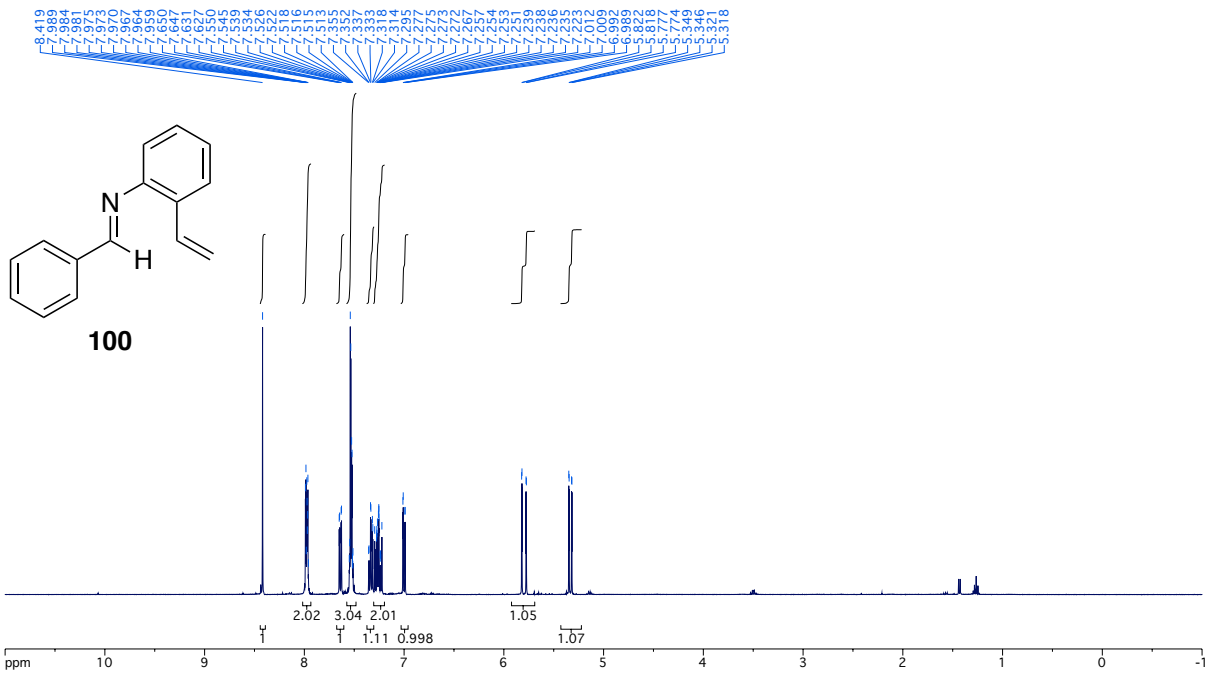

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128.734
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115.706
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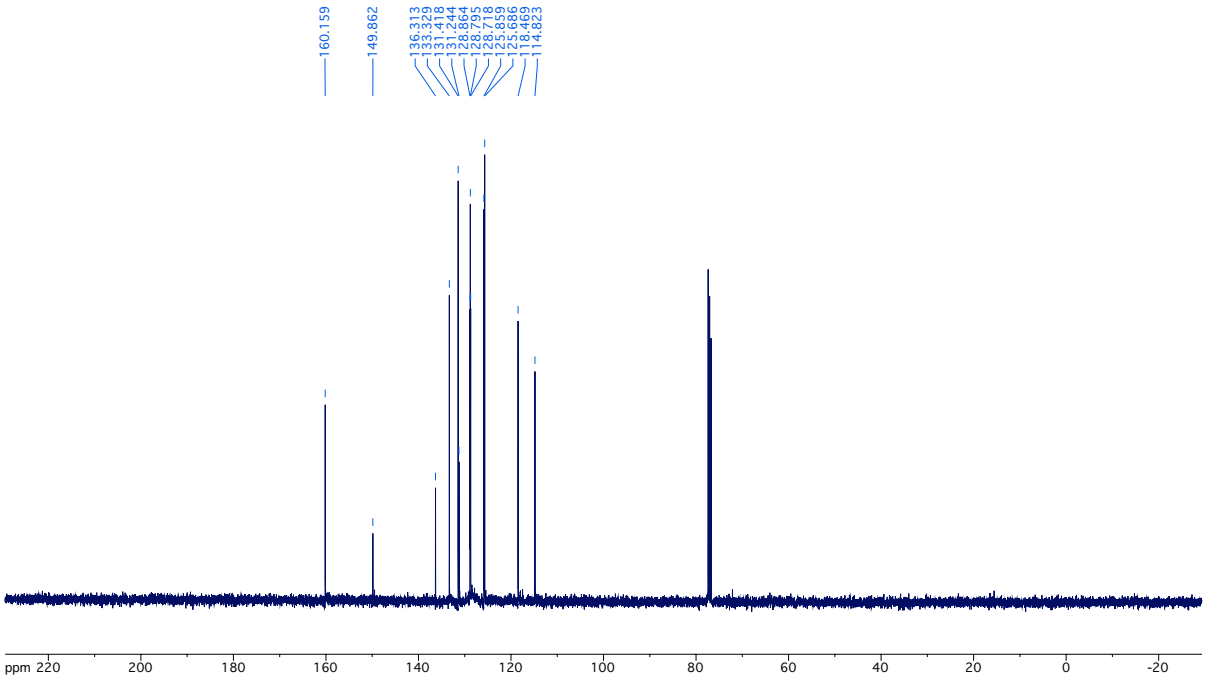

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6.128
6.116
6.113
6.102
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6.088
6.083
6.073
6.059
5.300
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5.248
5.244
5.212
5.208
5.204
5.200
5.196
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4.306
4.303
4.299
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4.285
N
H
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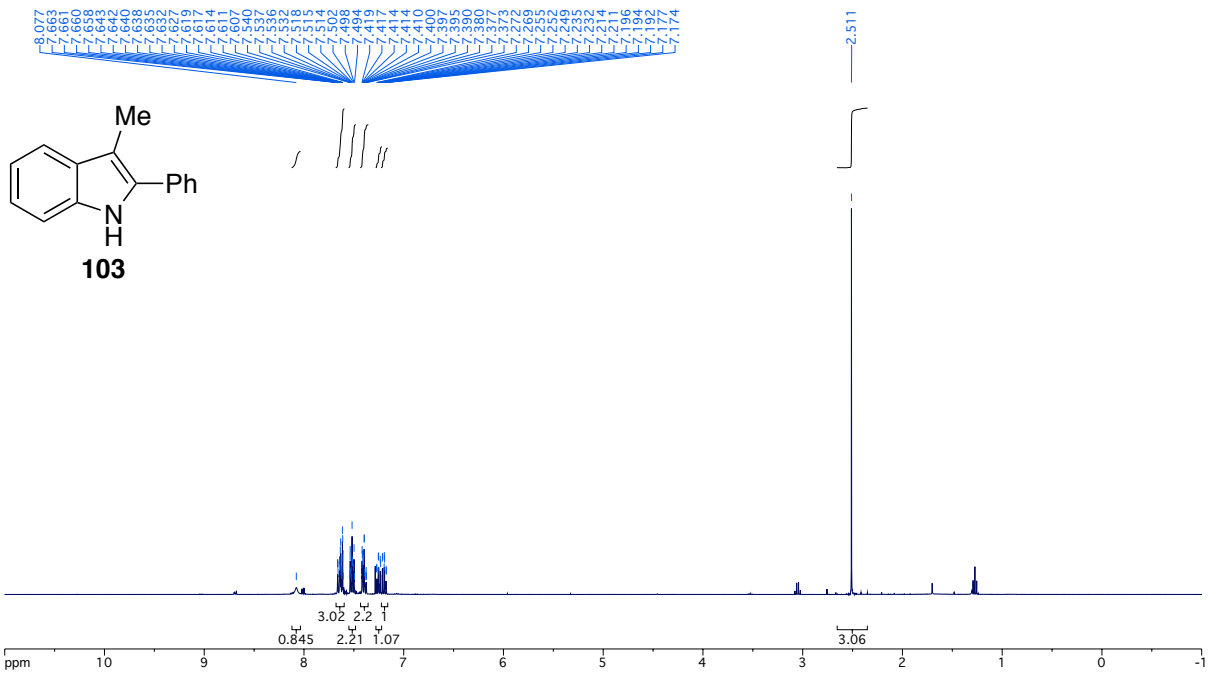

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128.138
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63.567
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40
20
0

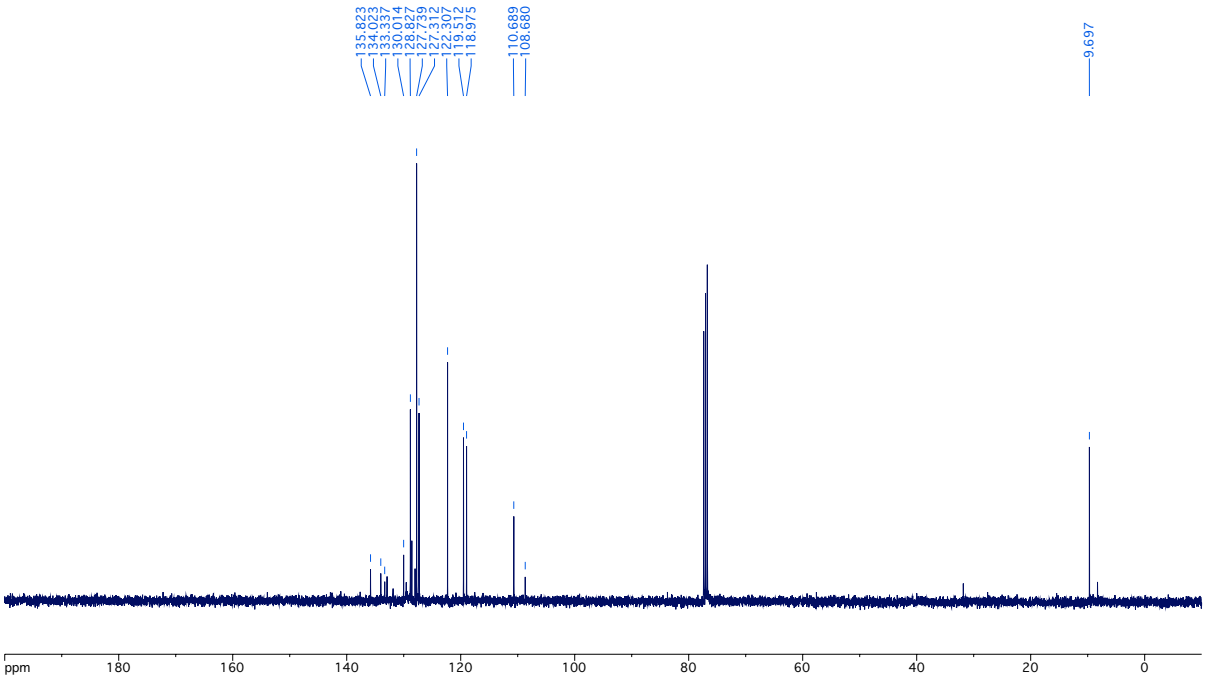

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7.741
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7.441
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7.425
7.422
7.421
5.937
5.930
5.911
5.903
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5.877
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5.860
5.851
5.834
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5.152
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5.145
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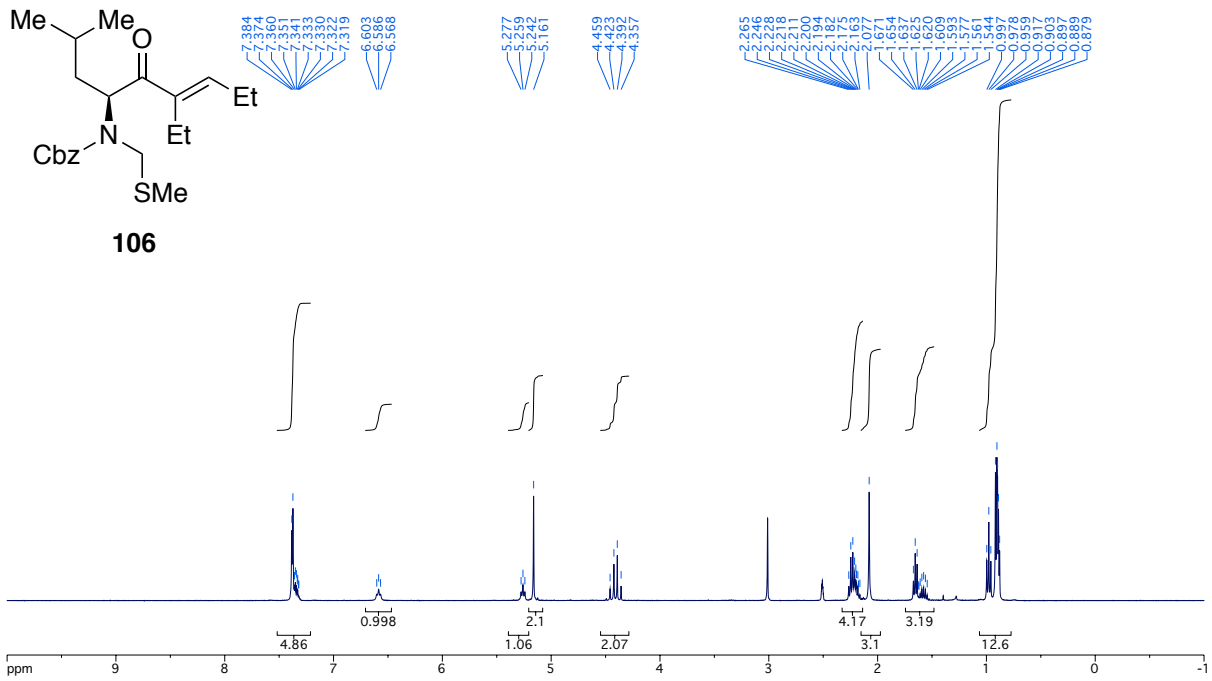

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128.058
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35.248
ppm
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160
140
120
100
80
60
40
20
0


8.419
7.989
7.984
7.981
7.975
7.973
7.970
7.967
7.964
7.959
7.650
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5.318
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H
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3.04
2.01
1.05
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1.07
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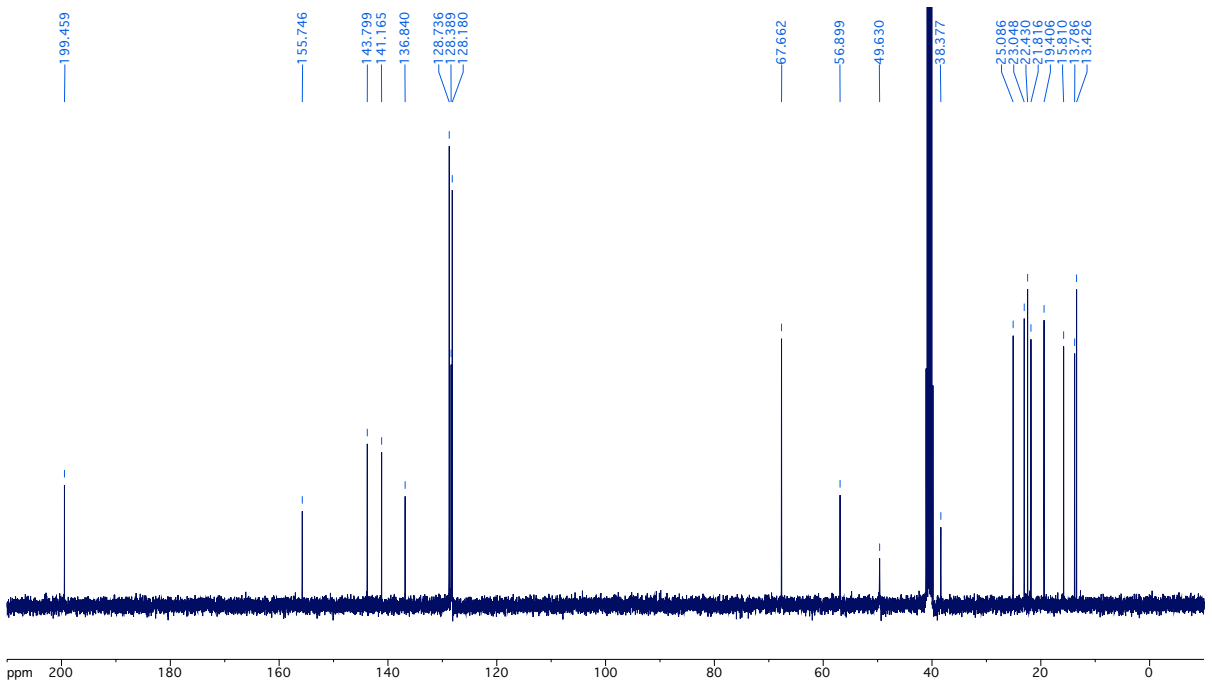

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114.823
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120
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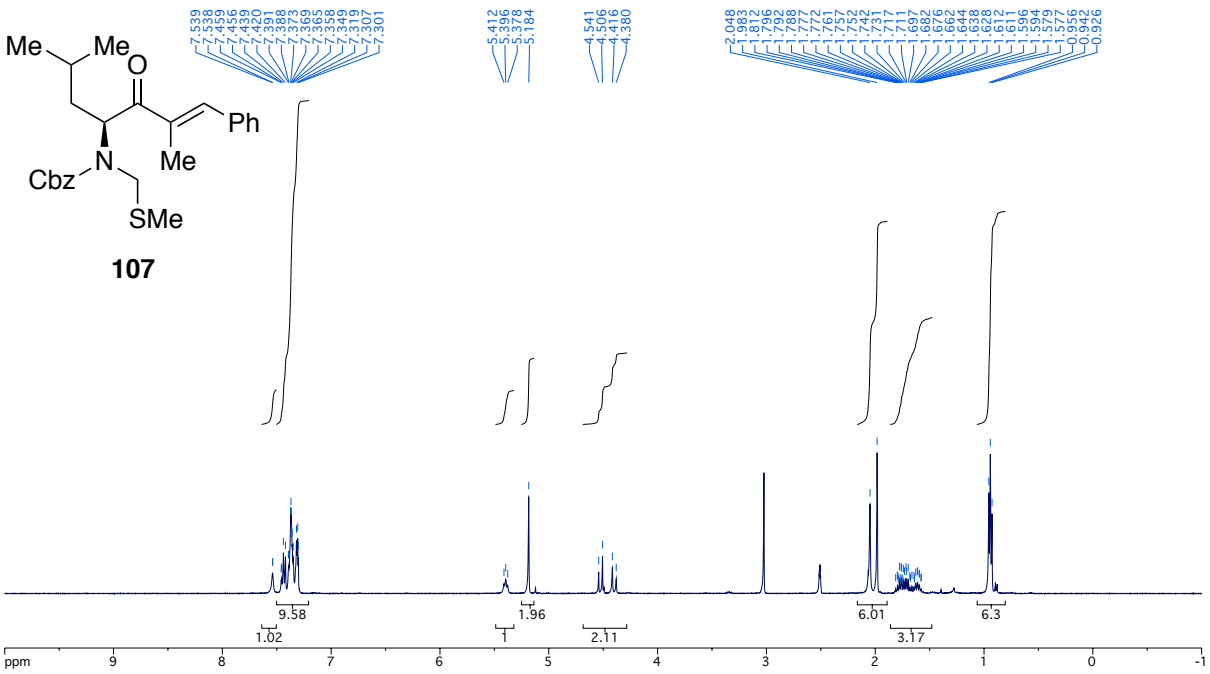

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7.607
7.540
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7.514
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7.174
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Me
Ph
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H
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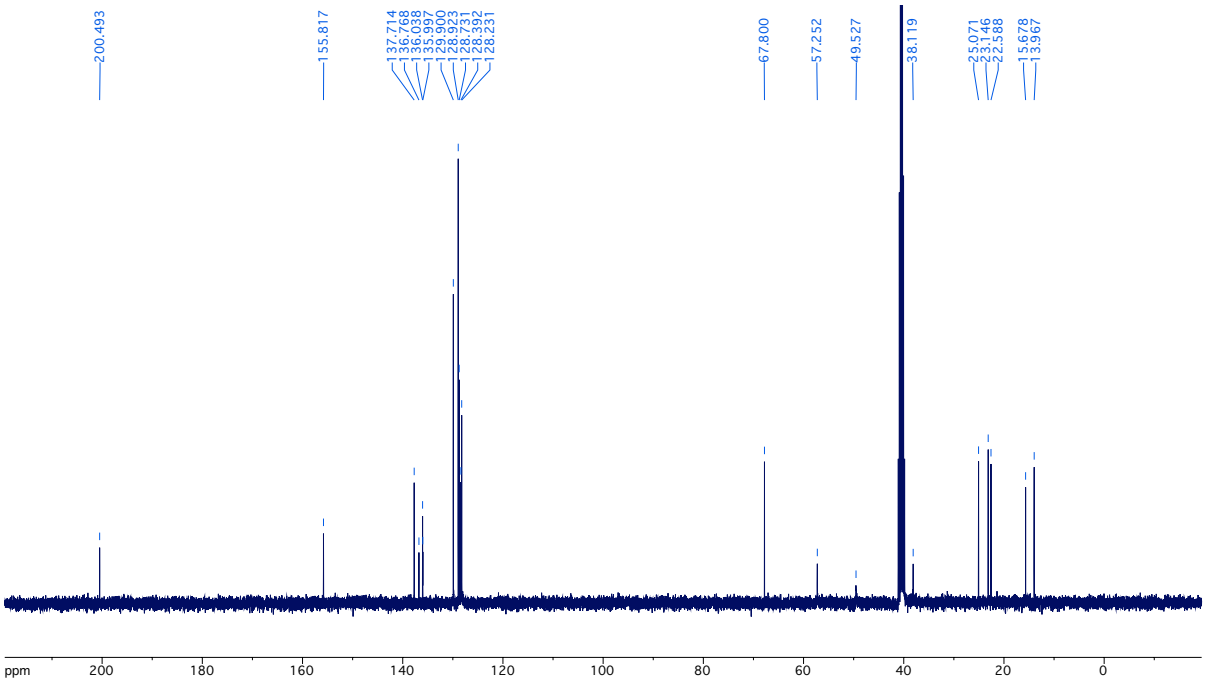

135.823
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127.739
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122.307
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9.697
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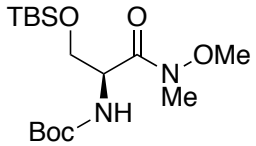

Me
Me
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Et
N
Et
Cbz
SMe
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0.998
1.06
2.1
2.07
4.17
3.1
3.19
12.6
ppm

106


199.459
155.746
143.799
141.165
136.840
128.736
128.389
128.180
67.662
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38.377
25.086
23.048
21.430
21.316
19.406
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13.426
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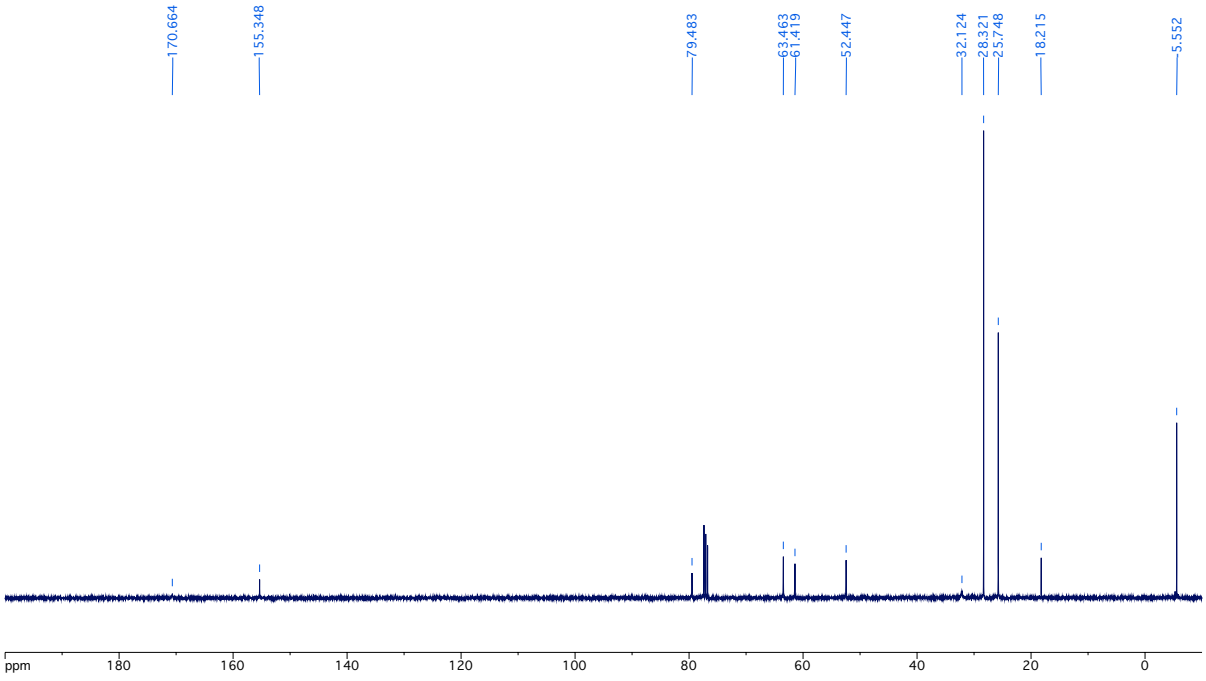

Me
Me
O
Ph
Me
N
Cbz
SMe
107
7.539
7.538
7.455
7.456
7.439
7.420
7.391
7.388
7.373
7.369
7.355
7.355
7.349
7.319
7.307
7.301
5.412
5.396
5.378
5.184
4.541
4.506
4.416
4.380
2.048
1.983
1.812
1.796
1.788
1.777
1.772
1.761
1.757
1.752
1.742
1.731
1.717
1.711
1.697
1.682
1.676
1.662
1.644
1.638
1.628
1.612
1.611
1.596
1.594
1.579
1.577
0.956
0.942
0.926
9.58
1.02
1.96
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ppm
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6
5
4
3
2
1
0
-1

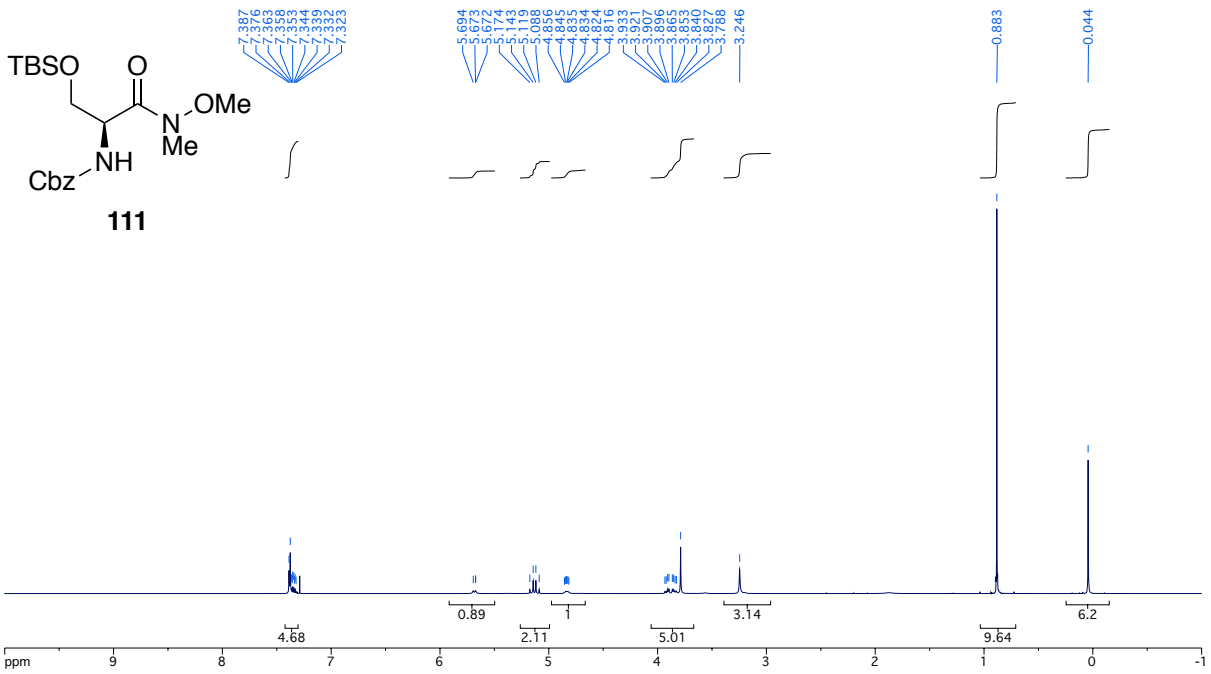

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137.714
136.768
136.039
135.997
129.900
128.923
128.731
128.392
128.231
67.800
57.252
49.527
38.119
25.071
23.146
22.588
15.678
13.967
ppm
200
180
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140
120
100
80
60
40
20
0

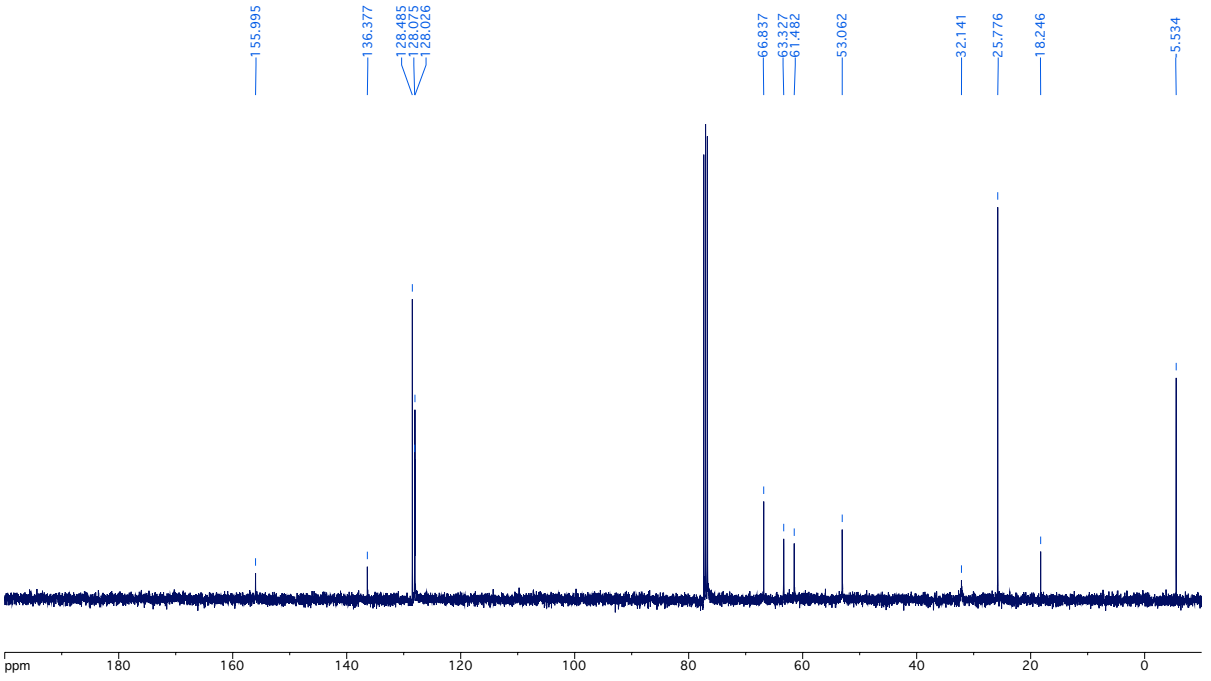

TBSO
O
N
OMe
Me
NH
Boc

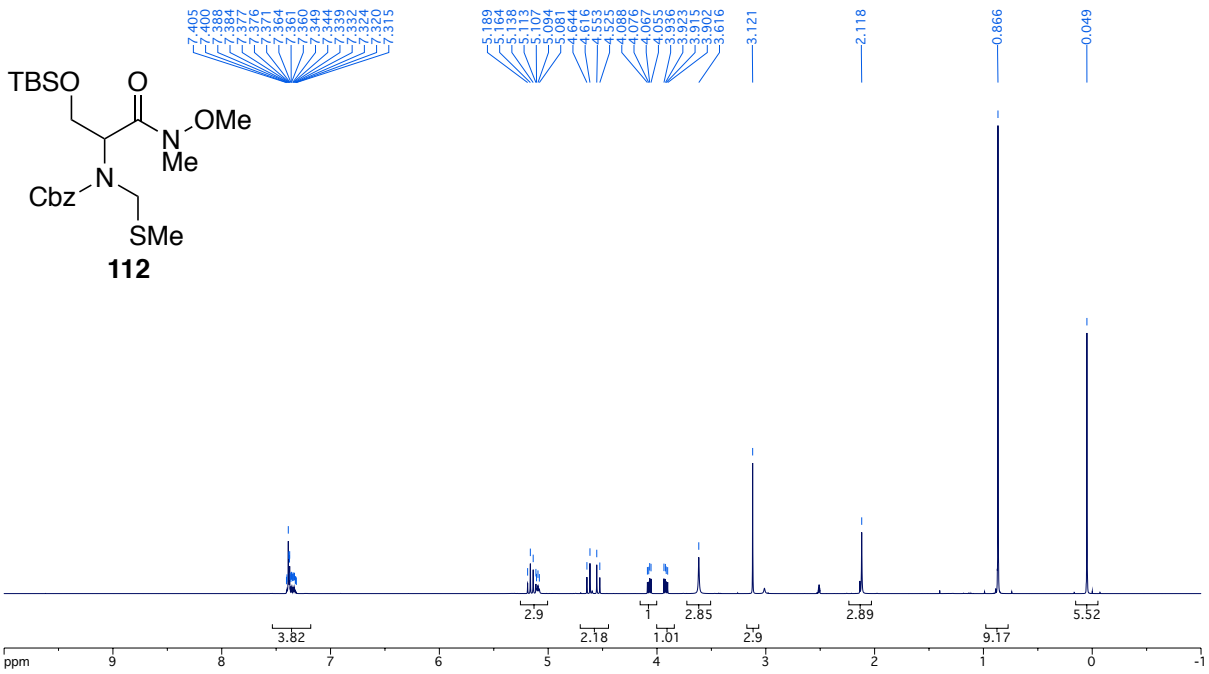
110

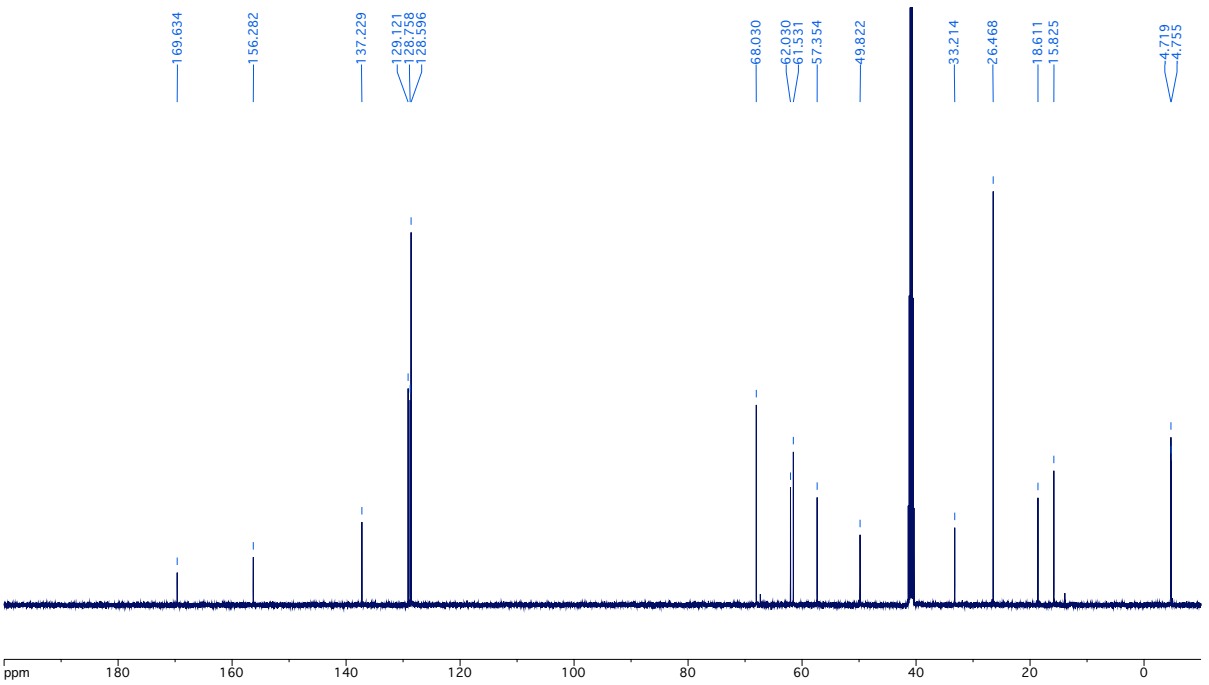
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5.346
4.748
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3.833
3.821
3.794
3.781
3.769
3.756
3.740
3.198
1.421
0.849
0.015
0.013
0.867
2.9
9.2
5.89
0.844
2
2.91
9.17
ppm

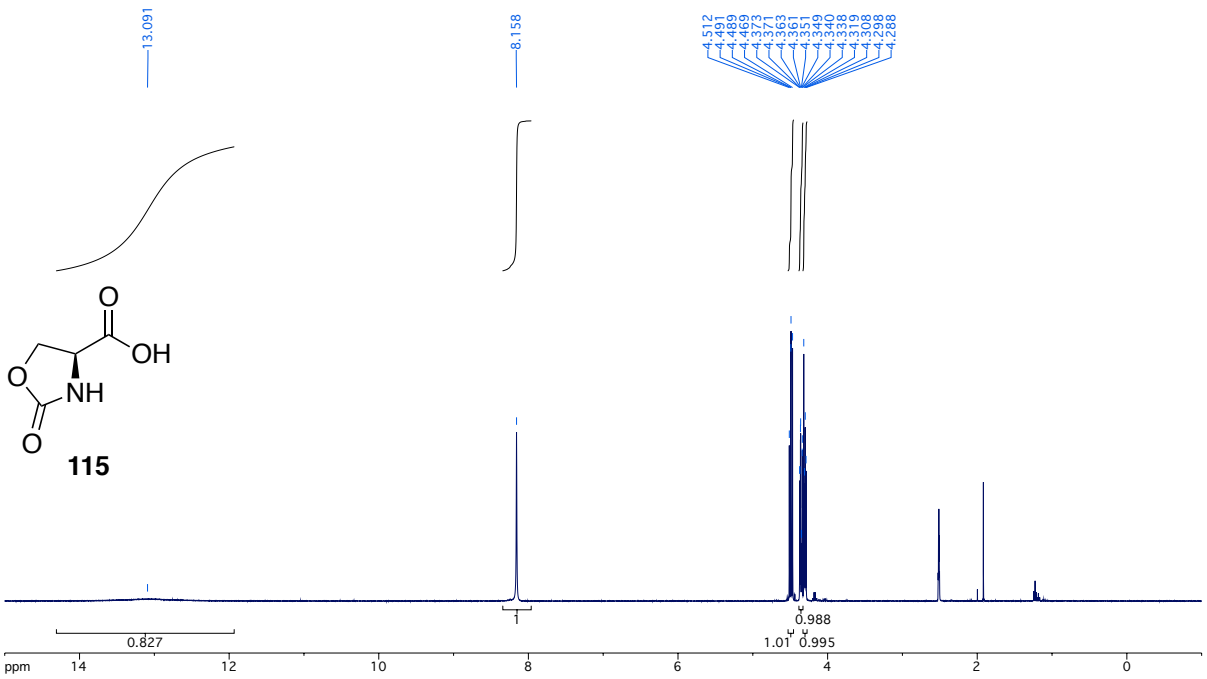

170.664
155.348
79.483
63.463
61.419
52.447
32.124
28.321
25.748
18.215
5.552
ppm

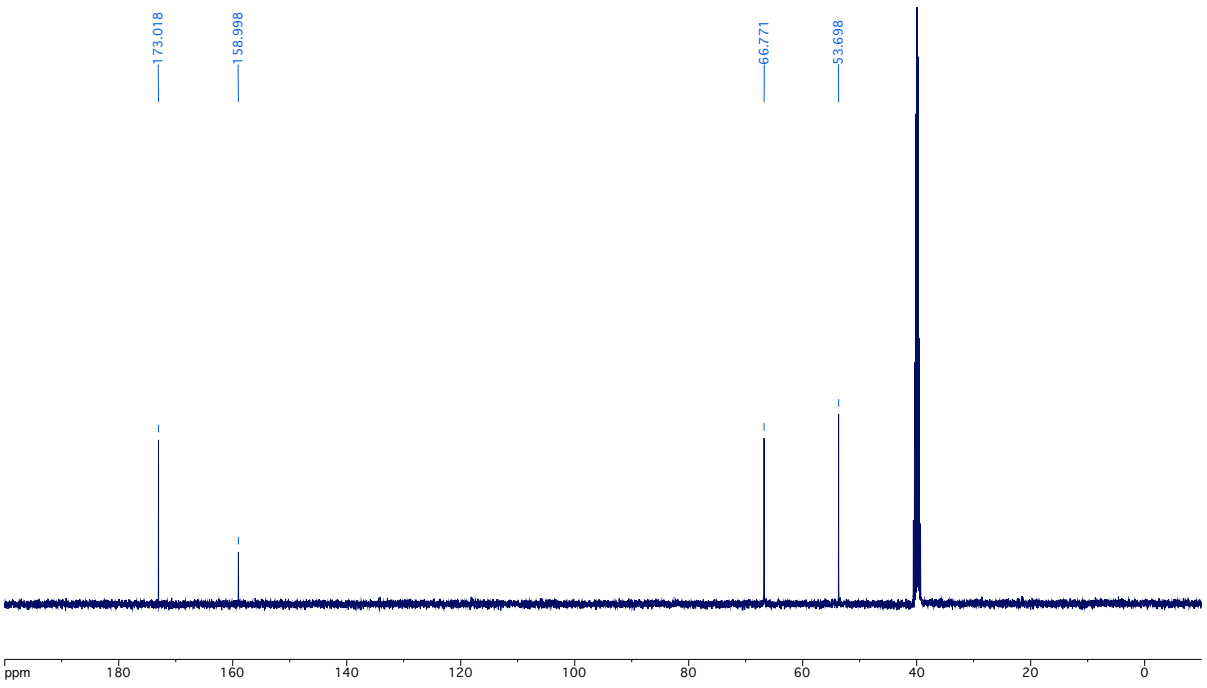

TBSO
O
N
OMe
Me
NH
Cbz
111
7.387
7.376
7.363
7.358
7.353
7.344
7.339
7.332
7.323
5.694
5.673
5.672
5.174
5.143
5.119
5.088
4.856
4.845
4.835
4.834
4.824
4.816
3.933
3.921
3.907
3.896
3.865
3.853
3.840
3.827
3.788
3.246
0.883
0.044
4.68
0.89
2.11
1
5.01
3.14
9.64
6.2
ppm

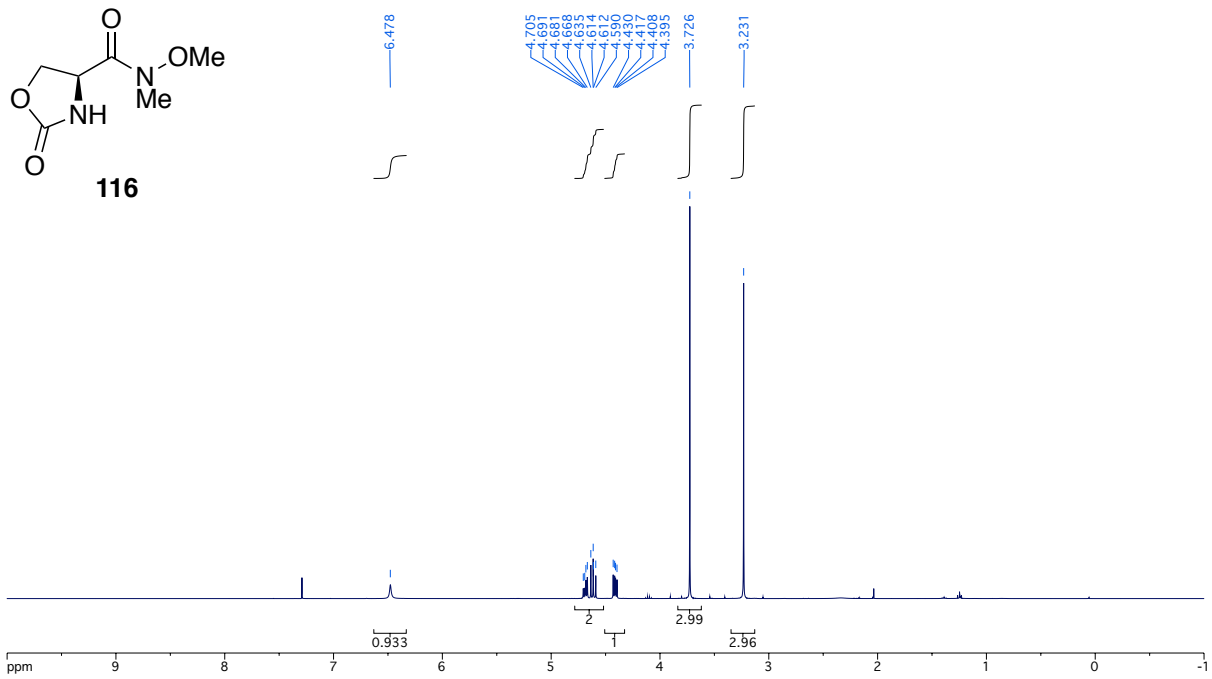

155.995
136.377
128.485
128.075
128.026
66.837
63.327
61.482
53.062
32.141
25.776
18.246
5.534
ppm

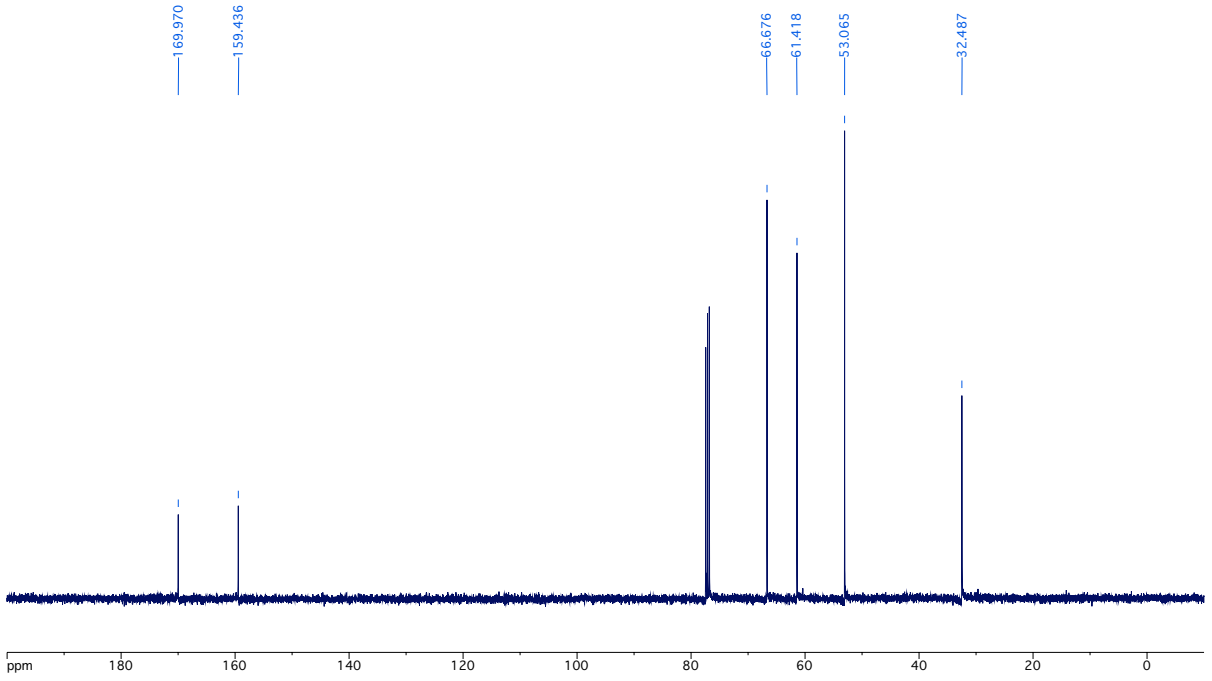

TBSO
O
N
OMe
Me
N
Cbz
SMe
112
7.405
7.400
7.388
7.384
7.377
7.376
7.364
7.361
7.360
7.349
7.344
7.339
7.332
7.324
7.320
7.315
5.189
5.164
5.138
5.113
5.107
5.094
5.081
4.644
4.616
4.553
4.525
4.088
4.076
4.067
4.055
3.936
3.923
3.915
3.902
3.616
3.121
2.118
0.866
0.049
3.82
2.9
2.18
1
1.01
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2.9
2.89
9.17
5.52
ppm

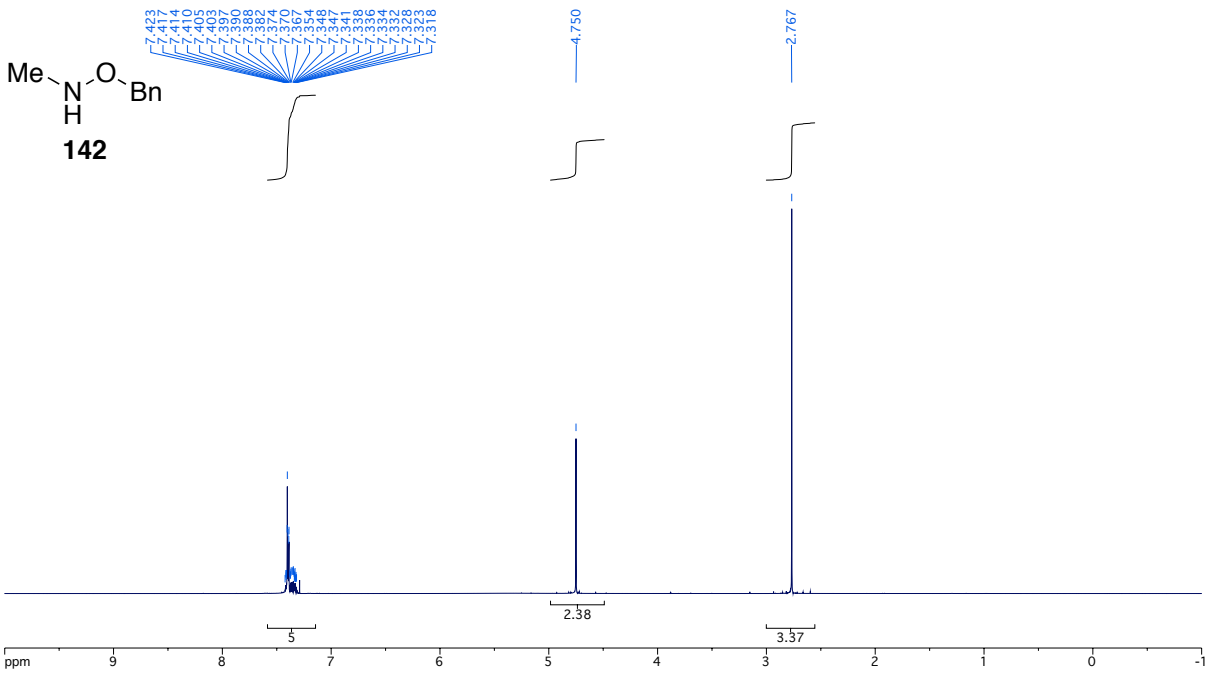

169.634
156.282
137.229
129.121
128.758
128.596
68.030
62.030
61.531
57.354
49.822
33.214
26.468
18.611
15.825
4.719
4.755
ppm

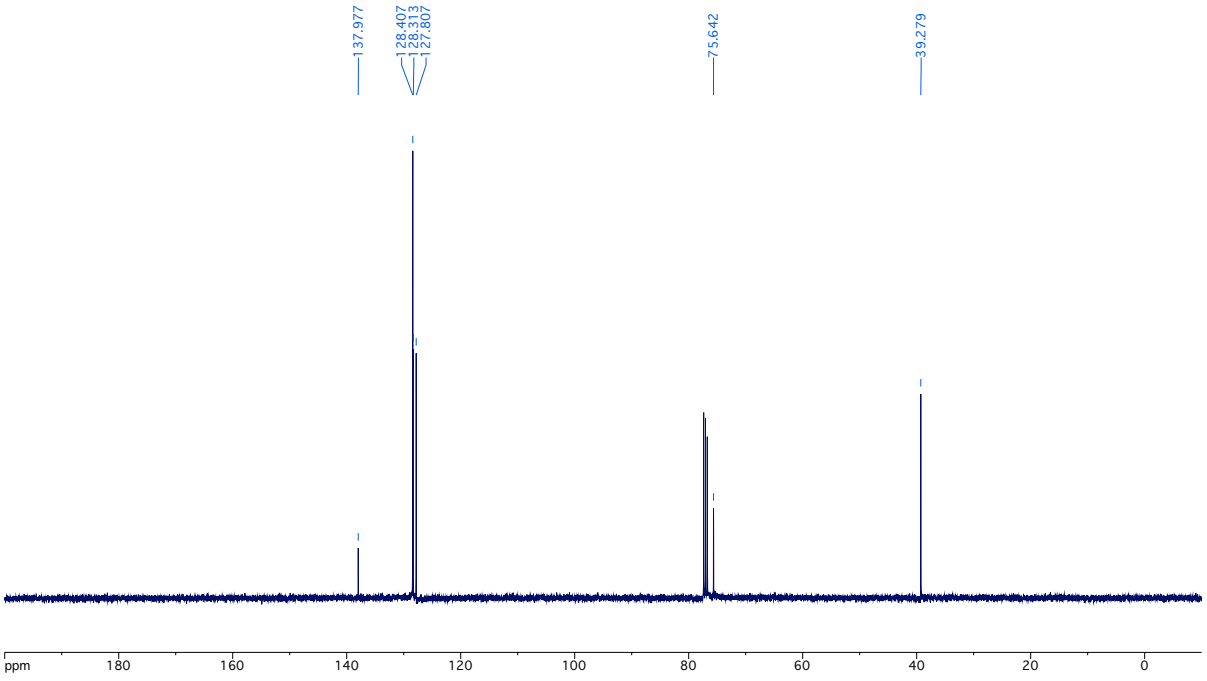

13.091
8.158
4.512
4.491
4.489
4.469
4.373
4.371
4.363
4.351
4.349
4.340
4.338
4.319
4.308
4.288
4.288
O
OH
O
NH
O
115
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1
0.988
1.01
0.995
ppm
14
12
10
8
6
4
2
0

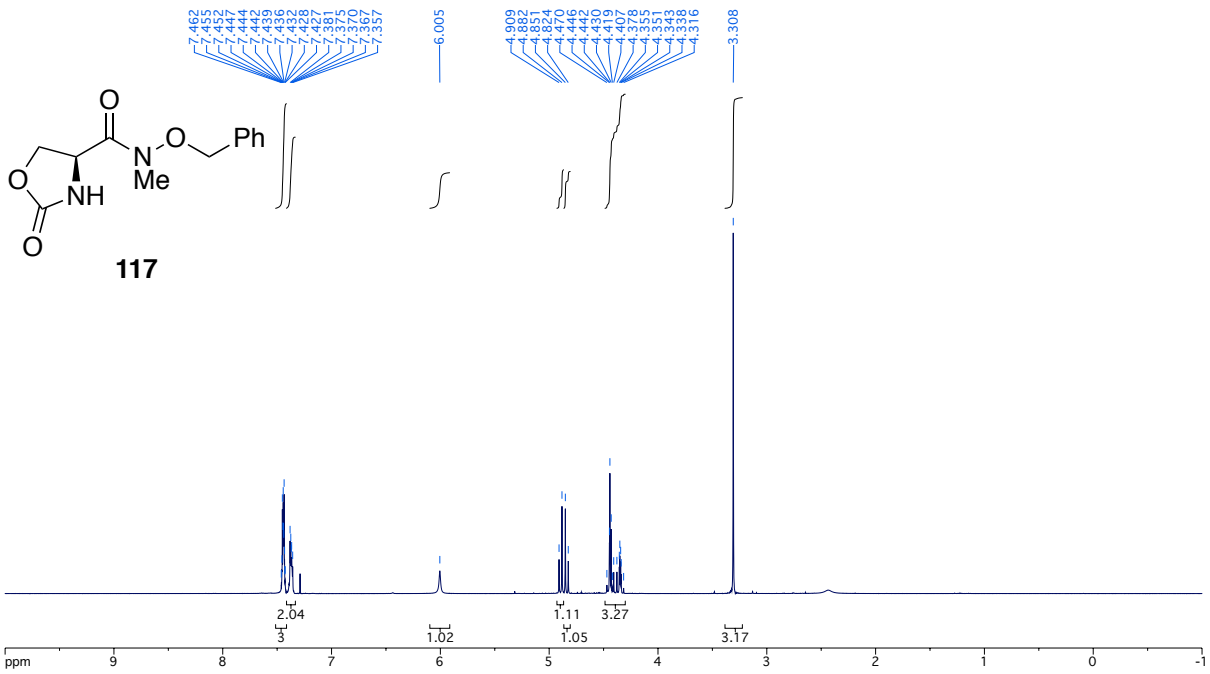

173.018
158.998
66.771
53.698
ppm
180
160
140
120
100
80
60
40
20
0

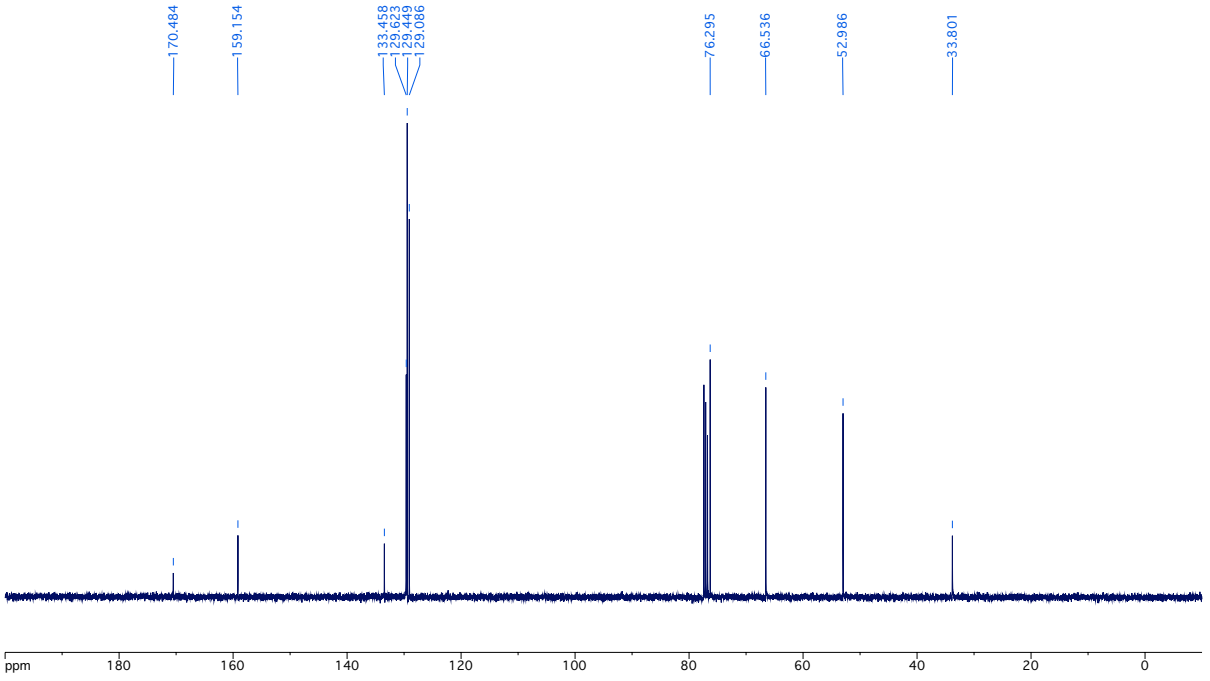

O
OMe
N
Me
O
NH
O
116
6.478
4.705
4.691
4.681
4.668
4.635
4.614
4.611
4.590
4.430
4.417
4.408
4.395
3.726
3.231
0.933
2
1
2.99
2.96
ppm
9
8
7
6
5
4
3
2
1
0
-1

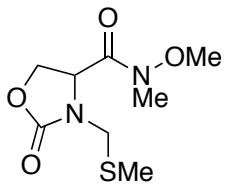

169.970
159.436
66.676
61.418
53.065
32.487
ppm
180
160
140
120
100
80
60
40
20
0


Me
N
H
O
Bn
142
7.423
7.417
7.414
7.410
7.405
7.403
7.397
7.390
7.388
7.382
7.374
7.370
7.367
7.354
7.348
7.347
7.341
7.338
7.336
7.334
7.332
7.328
7.323
7.318
4.750
2.767
5
2.38
3.37
ppm
9
8
7
6
5
4
3
2
1
0
-1


137.977
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128.313
127.807
75.642
39.279
ppm
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140
120
100
80
60
40
20
0

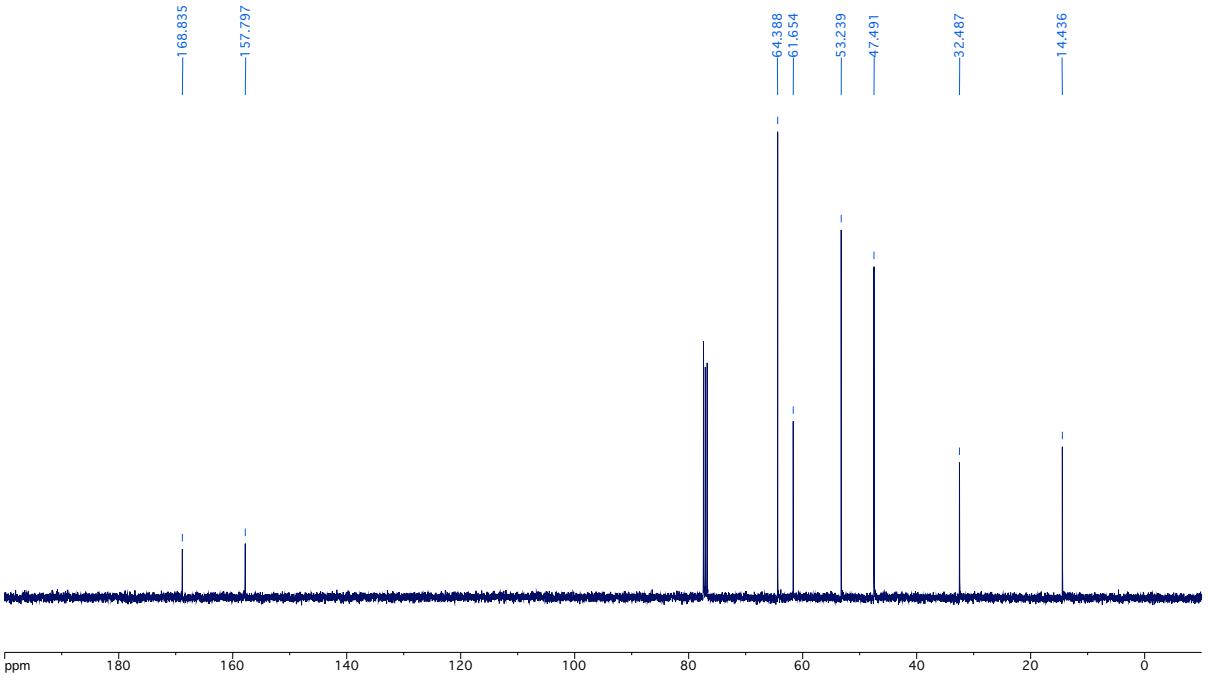

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7.455
7.452
7.447
7.444
7.442
7.436
7.432
7.428
7.427
7.381
7.375
7.370
7.367
7.357
6.005
4.909
4.882
4.851
4.824
4.470
4.446
4.442
4.430
4.419
4.407
4.378
4.355
4.351
4.343
4.338
4.316
3.308
O
O
N
O
Ph
Me
NH
O
117
2.04
3
1.02
1.11
1.05
3.27
3.17
ppm
9
8
7
6
5
4
3
2
1
0
-1

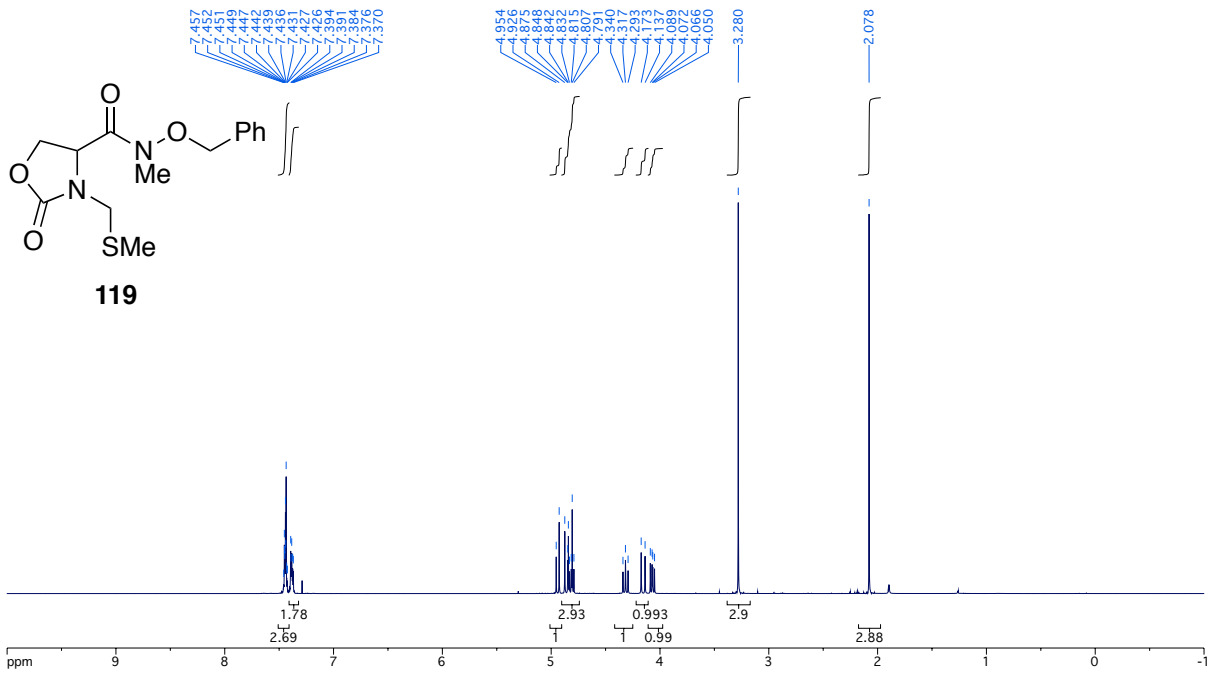

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133.458
129.023
128.449
125.086
76.295
66.536
52.986
33.801
ppm
180
160
140
120
100
80
60
40
20
0


O
N
OMe
Me
O
N
O
SMe

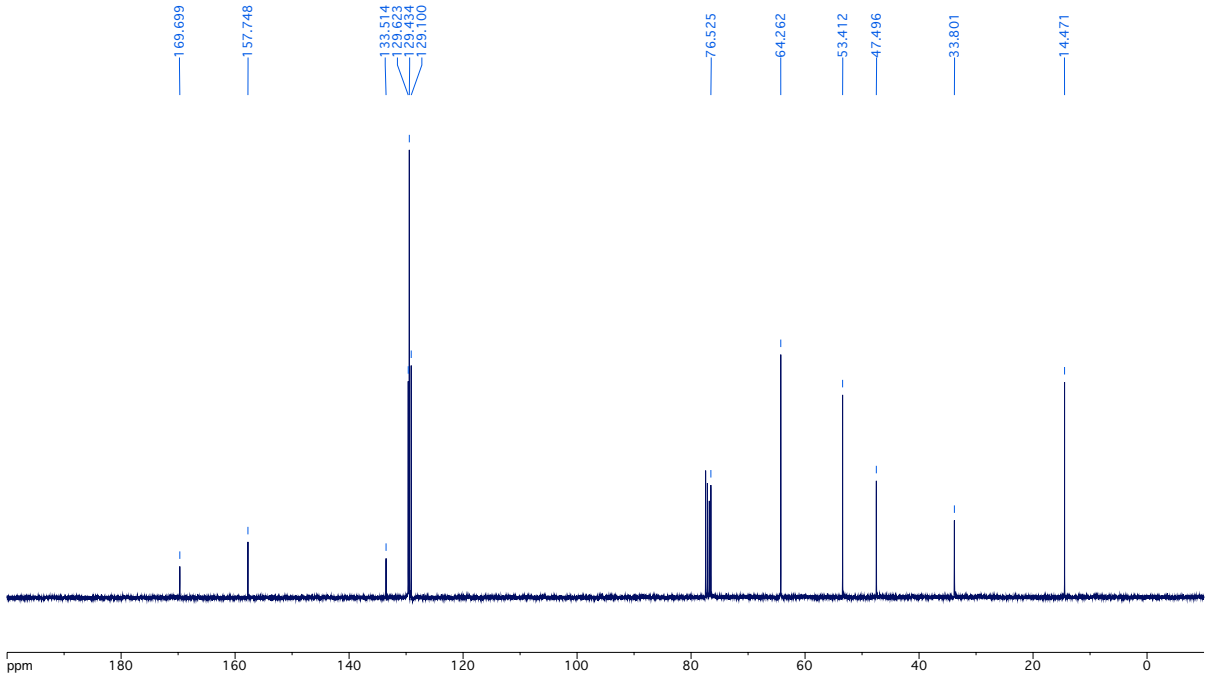
118

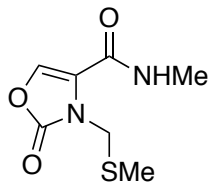
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4.988
4.972
4.945
4.909
4.621
4.599
4.597
4.574
4.234
4.221
4.217
4.211
4.195
4.185
3.775
3.238
2.128
1.9
1.01
2
2.99
2.9
2.94
ppm
9
8
7
6
5
4
3
2
1
0
-1


168.835
157.797
64.388
61.654
53.239
47.491
32.487
14.436
ppm
180
160
140
120
100
80
60
40
20
0


7.457
7.452
7.451
7.449
7.447
7.442
7.436
7.431
7.427
7.426
7.394
7.391
7.384
7.376
7.370
4.954
4.926
4.875
4.848
4.842
4.832
4.815
4.807
4.791
4.340
4.317
4.293
4.137
4.089
4.072
4.066
4.050
3.280
2.078
O
N
O
Ph
Me
O
N
O
SMe
1.78
2.69
2.93
0.993
0.99
2.9
2.88
ppm
9
8
7
6
5
4
3
2
1
0
-1

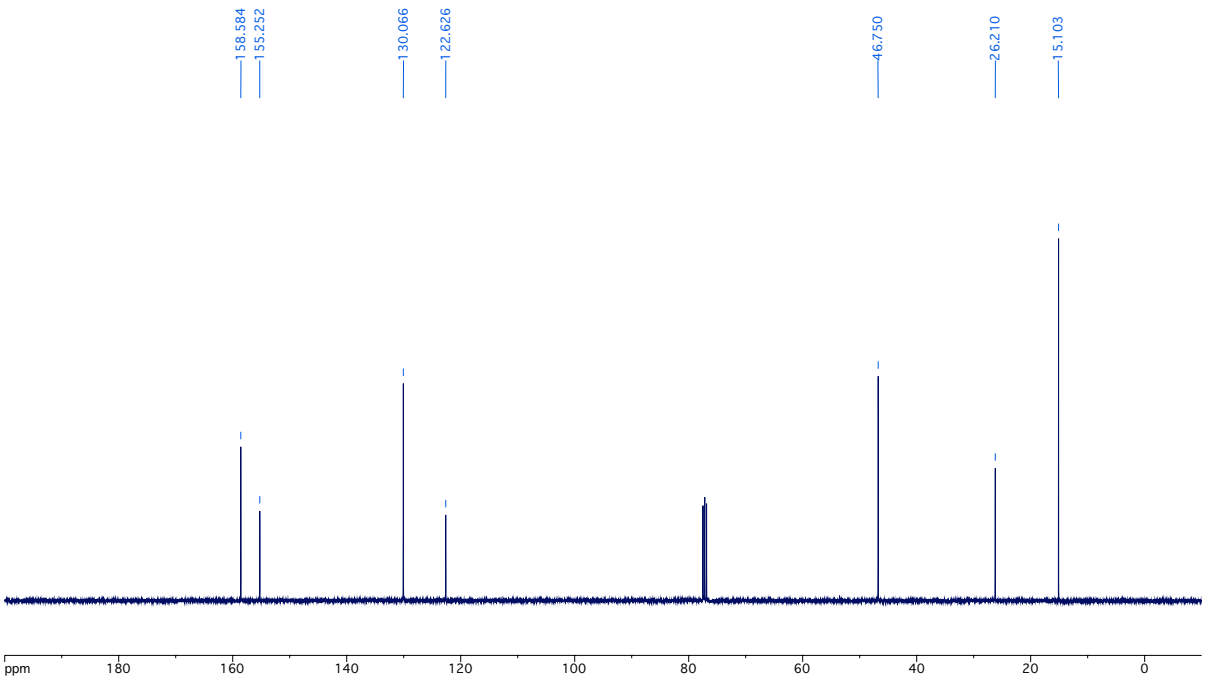
119


169.699
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133.514
129.623
128.434
125.100
76.525
64.262
53.412
47.496
33.801
14.471
ppm
180
160
140
120
100
80
60
40
20
0


O
NHMe
O
N
O
SMe

120

7.406
7.198
7.186
5.036
2.871
2.859
2.146
0.969
0.944
2
2.96
3.03
ppm
9
8
7
6
5
4
3
2
1
0
-1


158.584
155.252
130.066
122.626
46.750
26.210
15.103
ppm
180
160
140
120
100
80
60
40
20
0