

Rhodium-catalysed carbon-carbon bond formation and carbon-sulfur bond functionalisation

Anaïs Bouisseau



St Annes's College, University of Oxford

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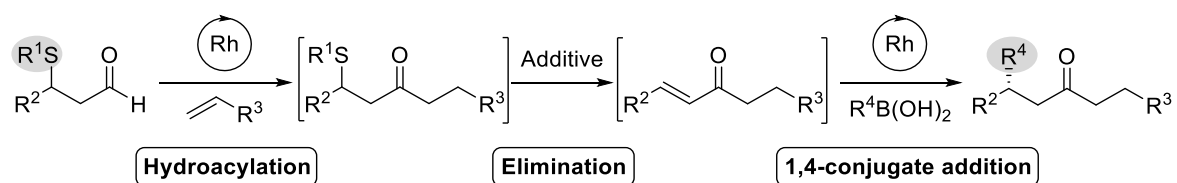
A thesis submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy in Organic Chemistry

Abstract

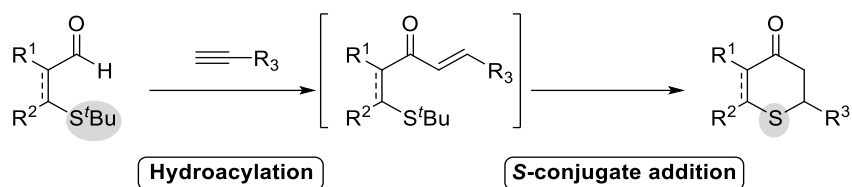
This thesis documents the development of synthetic methodologies utilising rhodium catalysis for the formation of carbon-carbon bonds and the functionalisation of carbon-sulfur bonds.

Chapter 1 provides an overview of the two main areas of research discussed in this thesis that include the key developments in the field of intra- and intermolecular rhodium-catalysed hydroacylation, and the major advances in cross-coupling reactions *via* the catalytic cleavage of carbon-sulfur bonds.

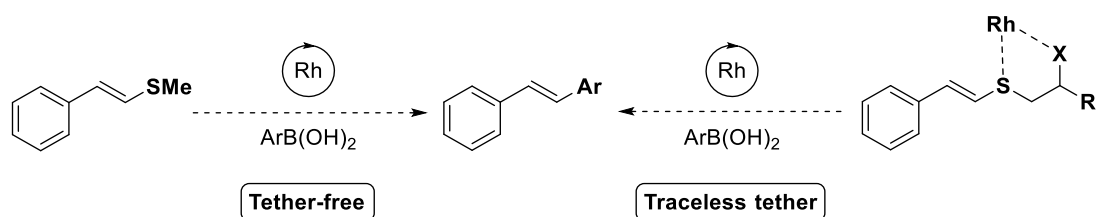
Chapter 2 details the development of a tandem rhodium-catalysed hydroacylation, sulfide elimination and subsequent enantioselective 1,4-conjugate addition sequence allowing the preparation of stereodefined β -substituted ketones. This process enables the formation of two carbon-carbon bonds and offers a general method to access highly functionalised traceless hydroacylation products.



Chapter 3 describes the development of a rhodium-catalysed alkyne hydroacylation, thio-Michael addition sequence in a one-pot fashion. This methodology enables the synthesis of a variety of sulfur-containing heterocycles.



Chapter 4 documents the efforts towards the development of a rhodium-catalysed cross-coupling reaction with alkenyl sulfides and boronic acids *via* C-S bond activation. This study explores both a tether-free and a traceless tether approach.



Chapter 5 summarises the research and the potential future work.

Chapter 6 provides experimental details and data.

Declaration

This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Two of the projects described in this thesis have been developed in collaboration with other students and their contribution to this work will be clearly stated in the text and in the schemes. The products prepared by these students are not described in the experimental section.

In chapter 2, Ming Gao has optimised the hydroacylation step and carried out the alkene scope. In addition, he has prepared several aldehyde substrates and used them for the tandem process. The products he has prepared are mentioned in the thesis (but not in the experimental section).

In chapter 3, Jack Glancy has optimised the tandem reaction and contributed to the alkyne scope, which is acknowledged accordingly.

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Abbreviations and acronyms

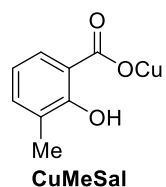
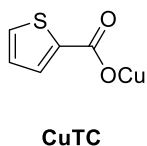
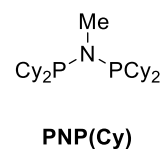
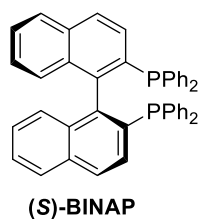
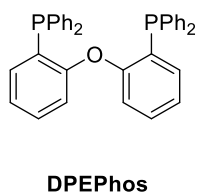
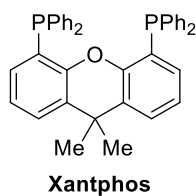
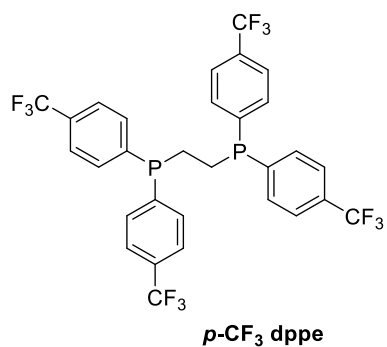
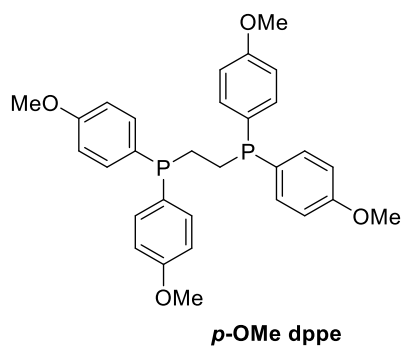
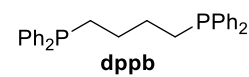
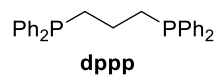
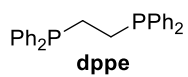
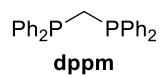
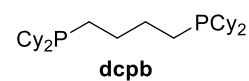
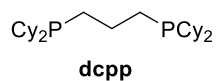
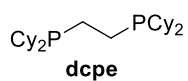
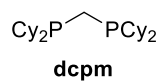
acac	acetylacetone
app.	apparent
Ar	aryl
BAr _F ⁴	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>tert</i> -butoxycarbonyl
br.	broad
Bu	butyl
°C	degrees Celsius
cat.	catalyst or catalytic
CI	chemical ionisation
cod	cyclooctadiene
coe	cyclooctene
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
CuMeSal	copper(I) 3-methylsalicylate
CuTC	copper(I) thiophene-2-carboxylate
cy	cyclohexyl
d	doublet or deuterated
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dcpe	1,1-bis(diphenylcyclohexyl)ethane
dcpm	1,1-bis(diphenylcyclohexyl)methane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminium

Dioxane	1,4-dioxane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMB	dimethoxybenzyl
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPEPhos	<i>bis</i> (2-diphenylphosphinophenyl)ether
dppb	1,4- <i>bis</i> (diphenylphosphino)butane
dppe	1,2- <i>bis</i> (diphenylphosphino)ethane
dppm	1,1- <i>bis</i> (diphenylphosphino)methane
dppp	1,3- <i>bis</i> (diphenylphosphino)propane
dr	diastereomeric ratio
<i>ee</i>	enantiomeric excess
EI	electron impact
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
FI	field ionisation
g	gram
h	hour(s)
Het.	heteroaryl
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
^{<i>i</i>} Pr	<i>iso</i> -propyl
IR	infrared

<i>J</i>	coupling constant
L	ligand or litre
LRMS	low resolution mass spectrometry
M	metal or molar
m	milli (10 ⁻³) or multiplet
M ⁺	parent molecular ion (in mass spectrometry)
<i>m</i>	<i>meta</i>
Me	methyl
MeDuPhos	1,2- <i>bis</i> (2,5-dimethylphospholano)benzene
min	minutes(s)
mol	mole(s)
M.p.	melting point
MS	mass spectrometry
MW	microwave irradiation
<i>m/z</i>	mass to charge ratio
nbd	norbornadiene
ⁿ Bu	normal butyl
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	phenyl
ppm	parts per million
Pr	propyl
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
q	quartet
R	generic group/substituent

rt	room temperature
s	singlet or solid
S _N Ar	nucleophilic aromatic substitution
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
^t Bu	<i>tert</i> -butyl
Tf	trifluoromethanesulfonate/triflate
TFA	trifluoroacetic acid
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
X	(pseudo)halide or generic counterion
Xantphos	4,5- <i>bis</i> (diphenylphosphino)-9,9-dimethylxanthene
δ	chemical shift
μ	micro (10 ⁻⁶)

Ligands and chemical structures

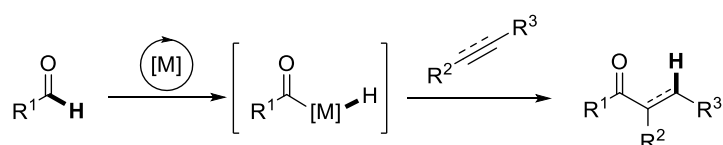


Chapter 1

Introduction

1.1 Overview

Over the last thirty years, the functionalisation of C-H bonds has gained particular importance and allowed new strategic disconnections for the preparation of complex organic molecules.¹ The variety of transformations developed, especially in the area of metal-catalysed C-C bond formation *via* C-H bond activation, highlights the genuine synthetic utility of such processes.² Among the range of reactions explored, the transition metal-catalysed alkene and alkyne hydroacylation reaction has proved to be a powerful method to access highly functionalised ketones and enones from simple aldehydes (Scheme 1.1).³



Scheme 1.1 General scheme for alkyne and alkene hydroacylation

Although several transition metals can be employed for this transformation (including cobalt,⁴ ruthenium,⁵ iridium⁶ and nickel⁷), rhodium catalysts have, since the initial report in 1972, remained the most widely used. The first part of this introduction will be focused on summarising the key developments in the field of rhodium-catalysed hydroacylation reaction.

Despite the high potential of hydroacylation, challenges have remained due to the occurrence of deleterious side reactions. In this context, chelation-controlled strategies have emerged as a successful approach to prevent the main undesired reaction, decarbonylation, and achieve efficient

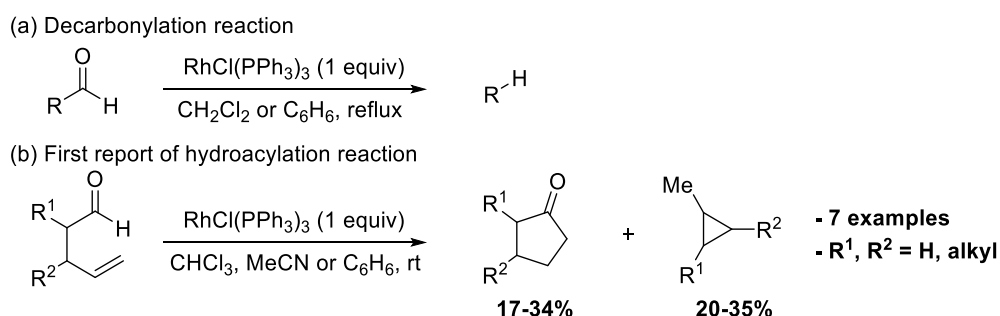
processes under mild reaction conditions. Over the last ten years, the Willis group has widely explored hydroacylation reactions using sulfur tethers, as well as the development of new transformations to remove and functionalise the sulfide chelate after hydroacylation. Some of these methods involve transition metal-catalysed C-S bond activation, which will be the main topic of the second part of this introduction.

1.2 Rhodium-catalysed hydroacylation

Hydroacylation is a transformation that can be either intra- or intermolecular in nature. We will first focus on the developments of the intramolecular version, as it was the first variant to be reported.

1.2.1 Intramolecular hydroacylation: discovery and key developments

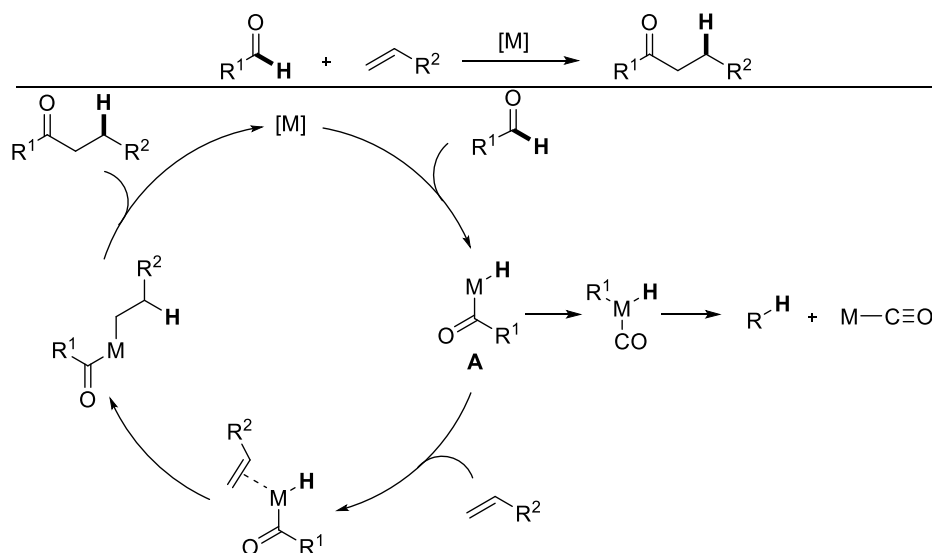
Alkene hydroacylation was first discovered by Sakai in 1972, during studies into rhodium-catalysed decarbonylation reactions.⁸ Whilst Wilkinson's catalyst had already been employed for reductive decarbonylation (Scheme 1.2a),⁹ two unexpected products were isolated when using 4-pentenal derivatives: cyclopentanones, which resulted from the formal addition of the aldehyde across the double bond, and cyclopropanes, which originated from a competitive decarbonylation pathway (Scheme 1.2b).



Scheme 1.2 Decarbonylation reaction and first report of hydroacylation reaction

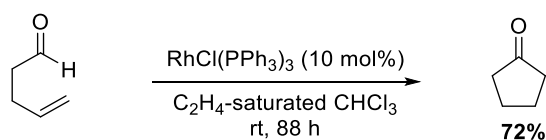
This initial result displayed the high potential of hydroacylation, but also the challenges in overcoming related side reactions. In the following decade, it was understood that rhodium(I) catalysts could insert into an aldehyde C-H bond to give an acyl-rhodium intermediate **A** (Scheme 1.3).^{10,11} From **A**, olefin insertion followed by reductive elimination would lead to the

desired hydroacylation product. On the other hand, **A** could undergo decarbonylation and subsequent reductive elimination to deliver undesired reduced substrate and an inactive metal-carbonyl species. It is this side reaction that has proved to be one of the main obstacles in the development of robust and efficient hydroacylation processes.



Scheme 1.3 General catalytic cycle of alkene hydroacylation reaction

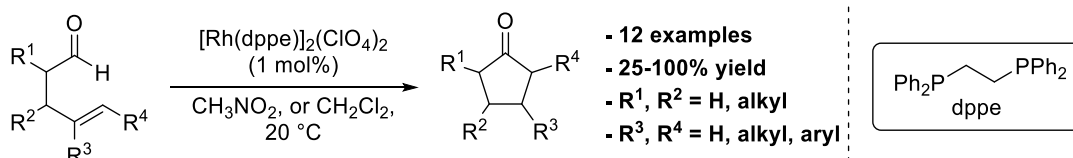
The next significant breakthroughs in the field were achieved by Milstein and Miller, who envisaged stabilising the acyl-rhodium hydride intermediate to prevent decarbonylation. For this purpose, they employed an additional labile alkene making the rhodium-centre coordinatively saturated.^{12,13} Thus, by employing an ethylene-saturated chloroform solution, Miller reported the efficient formation of cyclopentanone with sub-stoichiometric quantities of Wilkinson's catalyst (Scheme 1.4). The desired product of intramolecular hydroacylation was obtained in 72% yield after 88 hours with efficient suppression of the decarbonylation side-reaction.



Scheme 1.4 Miller's use of ethylene for hydroacylation

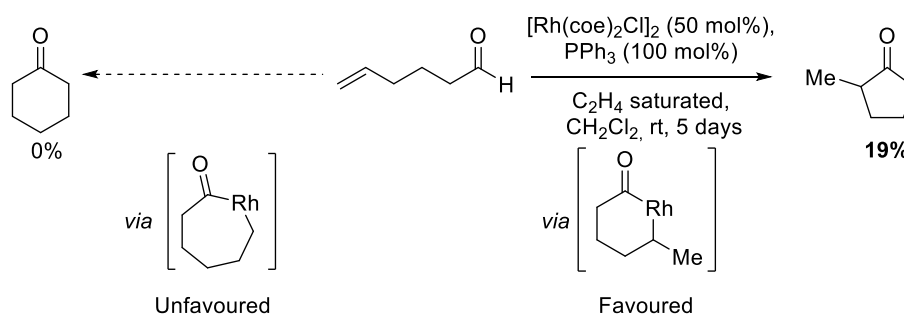
In a separate approach, Bosnich envisioned the development of a new strategy aiming to increase the rate of the hydroacylation steps over the rate of competing side reactions.¹⁴ In this context, a highly electrophilic cationic rhodium *bis*-phosphine complex $[\text{Rh}(\text{dppe})]\text{ClO}_4$ was identified as the

optimal catalyst for intramolecular alkene hydroacylation (Scheme 1.5). This rhodium(I) complex enabled a much faster and more efficient preparation of cyclopentanones with varying substitution patterns in excellent yields, low catalyst loading and with no significant observation of decarbonylation.



Scheme 1.5 Alkene hydroacylation with cationic rhodium *bis*-phosphine complex

Whilst limiting the decarbonylation reaction, these discoveries have enabled more widespread use of hydroacylation and contributed to the expansion of its applications. However, the next challenge in the field was the formation of larger ring systems using intramolecular hydroacylation. Generally, the six-membered metallacycle involved in the case of cyclopentanone formation is favoured. Consequently, if there is any possibility for a cyclic rhodium-acyl intermediate to isomerise to the six-membered rhodacycle, this pathway will usually predominate and prevent the formation of larger rings. For example, when Larock *et al.* employed 5-hexenal substrate, they exclusively isolated the cyclopentanone product (Scheme 1.6).¹⁵

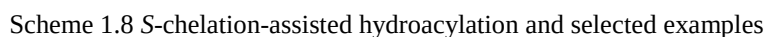


Scheme 1.6 Hydroacylation of 5-hexenal *via* 6-membered rhodacycle

Additionally, the ring closure of cycles larger than cyclopentanones proved slower, hence preventing decarbonylation was more challenging. To overcome these issues, the careful design of suitable substrates was required. In this context, Shair and co-workers developed an elegant method to prepare eight-membered rings *via* intramolecular hydroacylation (Scheme 1.7).¹⁶ By incorporating a cyclopropane ring in the substrate, they envisioned a ring fragmentation and the



A different approach was reported in 2002 by Bendorf *et al.*, who described the preparation of a series of sulfur-containing heterocycles using a chelation-assisted intramolecular hydroacylation (Scheme 1.8).¹⁷ Their strategy was also based on the stabilisation of the acyl-rhodium species, which was achieved by the formation of a metallabicyclic intermediate, hence decreasing reductive decarbonylation. This method enabled the preparation of seven- and eight-membered rings under mild reaction conditions using Wilkinson's catalyst, at room temperature in dichloromethane. Whilst intramolecular alkyne hydroacylation had not been very well explored yet, alkyne-containing substrates could also be employed with this strategy.

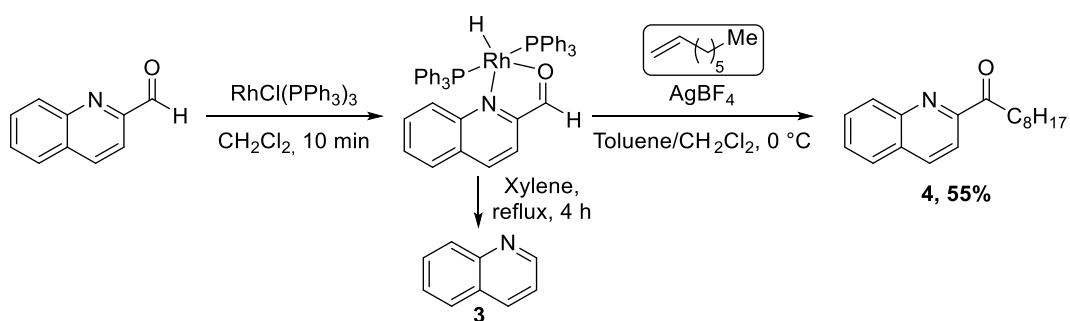


The success of this approach has since led many research groups to investigate other processes based on chelation-control, especially in the area of intermolecular hydroacylation.

1.2.2 Intermolecular hydroacylation and chelation-controlled strategies

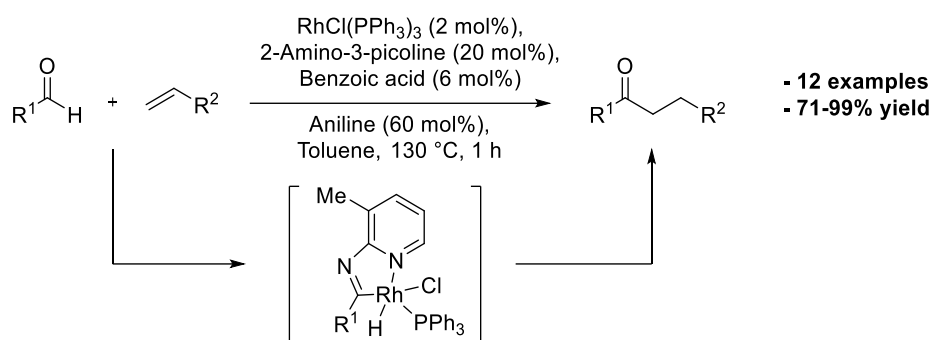
Although great progress had been made in the field of intramolecular hydroacylation, with successful expansion towards the preparation of larger rings, intermolecular processes were found to be more challenging. We have previously mentioned the use of ethylene-saturated chloroform to coordinatively saturate the metal centre and suppress decarbonylation. In the presence of hex-5-enal and pent-4-enal derivatives, the product of intramolecular hydroacylation was predominant compared to the intermolecular product with ethylene.¹³ However, when Milstein employed ethylene gas with benzaldehyde, he observed the formation of propiophenone from the addition of the aldehyde C-H bond across the ethylene double bond.¹² Nevertheless, the combination of low yields and the use of high pressures considerably limited the synthetic utility.

In a separate approach, heteroatom chelation-assisted hydroacylation, first pioneered by Suggs, emerged as a powerful and successful strategy. Discovered while investigating the decarbonylation mechanism of *N*-chelating 8-quinolinecarboxaldehyde with Wilkinson's complex, Suggs was able to isolate an acyl-rhodium(III) species (Scheme 1.9). This intermediate was found to be so stable that four hours in refluxing xylene were required to obtain the decarbonylated product **3**. In addition, the authors found that further treatment of the acyl-rhodium intermediate with 1-octene and silver tetrafluoroborate enabled the preparation of the corresponding ketone **4**, the product of intermolecular hydroacylation.^{18,19}



Scheme 1.9 Isolation of a stable acyl-rhodium species and intermolecular hydroacylation

Following up on Sugg's discoveries, Jun extensively investigated the use of *N*-chelating picolyl imines generated and hydrolysed *in-situ* from benzaldehydes and amines, enabling a traceless intermolecular hydroacylation (Scheme 1.10).²⁰ This method employed low catalyst loading of Wilkinson's complex together with sub-stoichiometric amounts of 2-amino-3-picoline, benzoic acid and aniline additives in refluxing toluene.



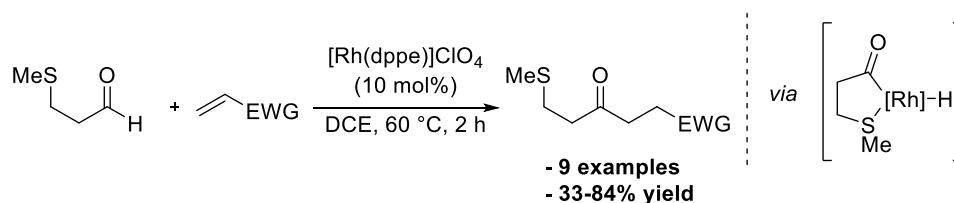
Scheme 1.10 Traceless intermolecular hydroacylation by Jun and co-workers

This optimised system delivered a general method for intermolecular hydroacylation processes, allowing the preparation of a variety of ketones in excellent yields. This method has been covered in a number of articles and was also successfully extended to the preparation of enones *via* alkyne hydroacylation.^{3a,21} At the same time, many other chelation-assisted intermolecular hydroacylations have been investigated and this strategy has become an established approach to deliver efficient intermolecular processes. This transformation can now be performed under mild reaction conditions, with the chelating group located on either the aldehyde or the alkene/alkyne component.²² The reaction was successfully applied to not only nitrogen,²³ but also phosphorus,²⁴ and oxygen²⁵ chelates. Over the last ten years, the Willis group has worked on the development of highly robust alkene and alkyne hydroacylation reactions using sulfur-chelating aldehydes and only these will be further discussed.

1.2.3 Rhodium-catalysed hydroacylation with sulfur-chelating aldehydes

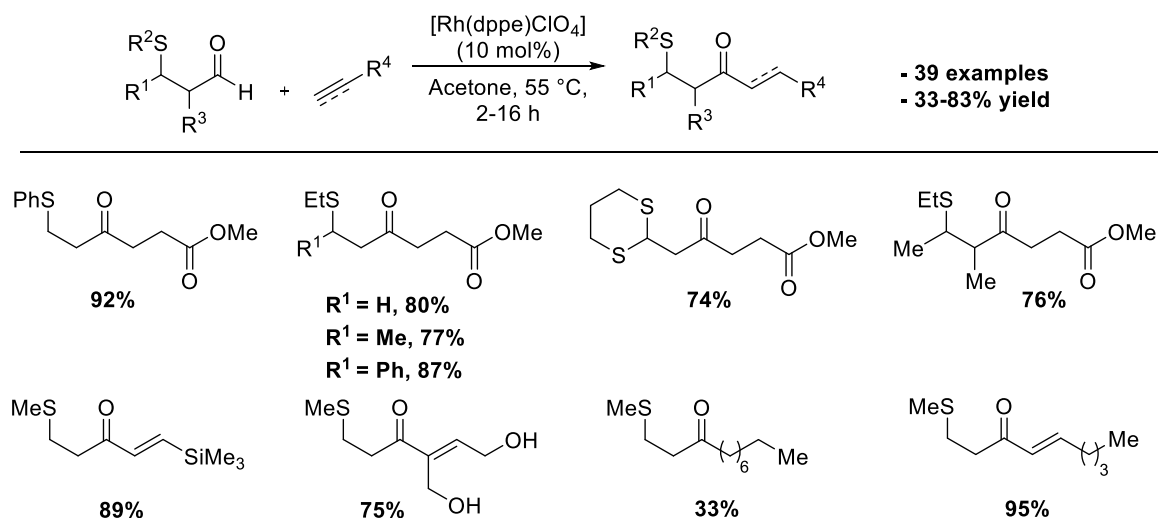
As stated previously, *S*-chelation was first introduced in 2002 by Bendorf and co-workers in an intramolecular process, enabling the formation of both cyclic enones and ketones.¹⁷ Two years later, the Willis group reported the first intermolecular alkene hydroacylation reaction with

β -thiomethyl-substituted aldehydes (Scheme 1.11).²⁶ The authors found that the cationic rhodium *bis*-phosphine complex previously employed by Bosnich delivered the desired ketones in high yields when reacting these aldehydes with electron-poor alkenes. The success of the reaction was attributed to the proposed formation of a cyclic acyl-rhodium species, stabilised by the sulfur heteroatom, thus limiting the decarbonylation pathway from occurring.



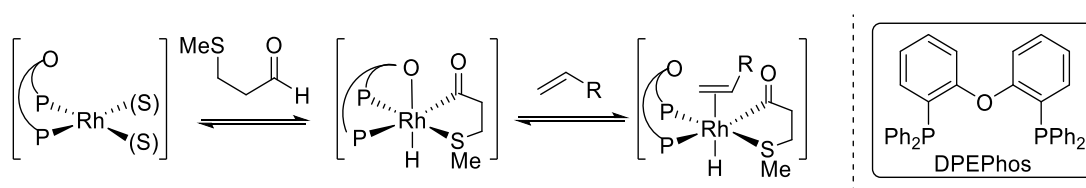
Scheme 1.11 First report of intermolecular hydroacylation with *S*-chelating aldehydes

This work was then extended, with aryl and alkyl thioether chelates, as well as thioacetals all being efficient tethers for hydroacylation (Scheme 1.12), but only with activated alkenes.^{27,28} As shown in the selected examples, the transformation was found to be successful with α - and β - branched aldehyde substrates under mild reaction conditions. In addition, the use of alkynes was also explored, and the reaction proved high yielding even when incorporating functional groups such as silanes and unprotected alcohols. Interestingly, whilst electron-neutral alkenes such as 1-octene delivered reduced yields, 1-hexyne was found to be an excellent substrate.



Scheme 1.12 General hydroacylation developed by Willis and co-workers and selected examples

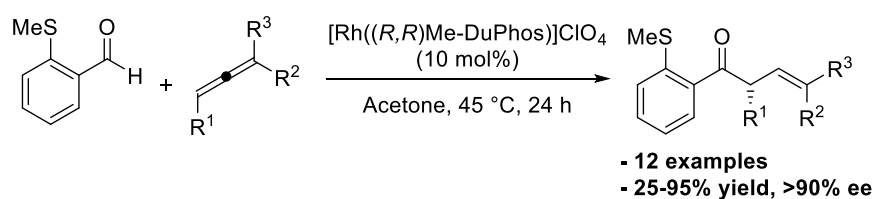
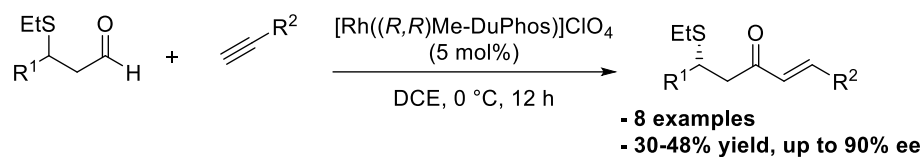
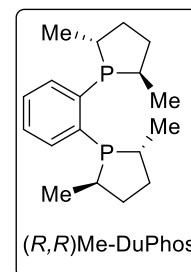
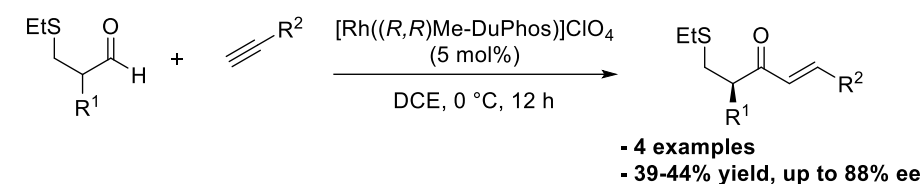
The reduced reactivity observed with unactivated alkenes was overcome by the development of a second-generation catalyst system, reported in 2006 in collaboration with the Weller group.²⁹ The authors envisioned that additional temporary stabilisation of the acyl-rhodium hydride intermediate would result in increased activity (Scheme 1.13). To this end, they employed the *bis*[(2-diphenylphosphino)phenyl] ether (DPEPhos) ligand which incorporates an ether linkage that can reversibly coordinate to the rhodium-centre *cis*-vacant site and thus block decarbonylation. This temporary stabilising effect from the oxygen heteroatom was further confirmed by the characterisation of various intermediates by NMR experiments, mass spectrometry and X-ray crystallography. The use of a hemi-labile ligand enabled less reactive alkenes to undergo hydroacylation with increased yields and under milder reaction conditions compared to the previous system. In addition, the active catalytic species could be generated *in-situ* from commercially available components, thus facilitating the practical aspects of hydroacylation.



Scheme 1.13 Proposed intermediates with hemi-labile DPEPhos ligand

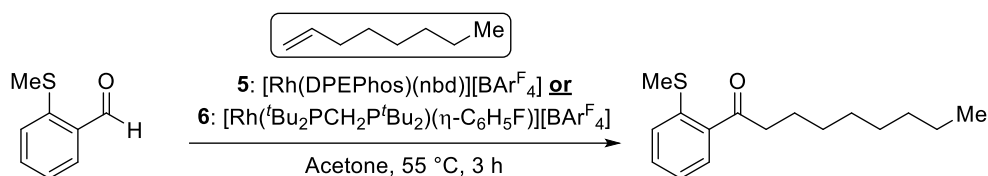
With efficient alkene and alkyne hydroacylation processes in hand, a further advancement was achieved in 2008 with the first asymmetric version of intermolecular hydroacylation using *S*-chelation. After ligand evaluation, the Willis group found that (*R,R*) Me-DuPhos would allow the preparation of β - γ -unsaturated ketones in moderate to excellent yields and good linear/branched selectivities and enantioselectivities starting from aryl aldehydes and substituted allenes (Scheme 1.14a).³⁰ Soon after, a kinetic resolution of racemic β -*S*-aldehydes was reported employing the same rhodium complex for the majority of substrates (Scheme 1.14b and c).³¹

(a) Enantioselective hydroacylation with allenes

(b) Enantioselective formation of β -substituted ketones(c) Enantioselective formation of α -substituted ketones

Scheme 1.14 Enantioselective intermolecular hydroacylation reactions

A further breakthrough in the field came with the study and development of a third generation catalyst which incorporated small bite angle *bis*-phosphine ligands.³² Initially investigated to achieve better linear-selectivity, these so called “PCP” (Phosphorus-Carbon-Phosphorus) ligands were found to be much more efficient than the DPEPhos-derived catalyst, as shown in Table 1.1 when comparing both second (**5**) and third (**6**) generation complexes. When employing unactivated 1-octene, PCP ligand **6** was already found to outperform **5** at a 1 mol% catalyst loading (entries 1 and 2). After optimising the reaction conditions, the activity of catalyst **6** was further increased, resulting in a remarkably efficient system (entries 3 and 4). These PCP ligands have previously shown to favour the formation of rhodium(I) complexes over rhodium(III), and the success of the transformation was attributed to a drastically faster reductive elimination which is the rate-determining step.³³



Entry	Catalyst (mol%)	Concentration (M)	NMR Conversion (%)
1	5 (1)	0.075	12
2	6 (1)	0.075	80
3	5 (0.1)	2	39
4	6 (0.1)	2	100

Table 1.1 Comparison between catalysts **5** and **6**

In summary, from the first generation catalyst incorporating large bite angle ligands to the optimised third generation, continuous efforts in designing robust rhodium complexes have made chelation-controlled intermolecular hydroacylation one of the most robust methods available (Table 1.2). In addition, the stability of these complexes has allowed for conducting thorough mechanistic studies.

	1 st Generation	2 nd Generation	3 rd Generation
Structure (S) = Solvent			
Properties	Large bite angle	Hemi-labile	Small bite angle
Catalyst loading	10 mol%	5-10 mol%	0.1-5 mol%
Characteristics	Activated alkenes only	Slow decarbonylation, alkynes and alkenes but limited scope	Very fast catalysis, broad alkyne and alkene scope

Table 1.2 1st, 2nd and 3rd generation catalysts for hydroacylation

1.2.4 Mechanistic studies

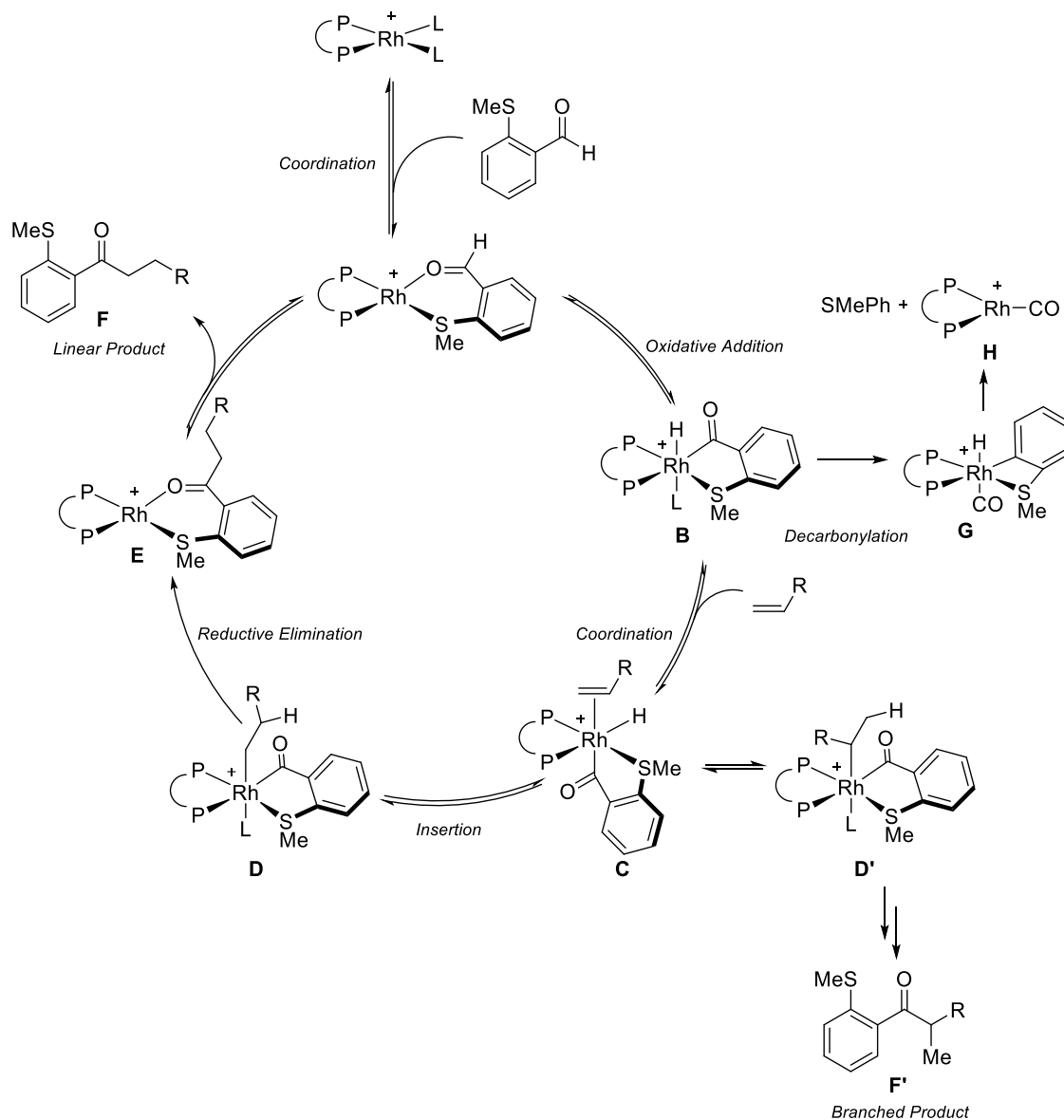
Since the discovery of hydroacylation, an extensive range of experiments have been carried out with a variety of rhodium systems in order to investigate the mechanism. The first isolation of a rhodium-acyl hydride complex by Suggs in 1978 was followed by NMR spectroscopy studies and

deuterium labelling experiments conducted by Miller and Bosnich.^{13,14,18,34} These were among the most important early contributions to the establishment of the proposed Rh(I)/Rh(III) catalytic cycle *via* the acyl-rhodium hydride intermediate. Further studies included computational experiments that investigated the energy profile of side reactions (isomerisation and decarbonylation)³⁵ and NMR experiments with hemi-labile DPEPhos ligand.^{29,36} Additionally, Willis and Weller recently carried out new mechanistic studies with small bite angle *bis*-phosphine ligands, including isolation of key intermediate species, deuterium labelling and kinetic isotope effect experiments.³² The catalytic cycle proposed involves a main pathway that begins with the coordination of the aldehyde to the rhodium(I) catalyst, followed by the oxidative addition of the aldehyde C-H bond to the metal to give the acyl-rhodium hydride intermediate **B** (Scheme 1.15). After coordination of the olefin (**C**), hydride insertion (**D**) followed by reductive elimination (**E**) affords the desired linear product **F**. Hydride insertion into the alkene is the crucial step that controls the outcome of the regioselectivity of the reaction. Both intermediates **D** and **D'** can be formed, delivering either the linear **F** or the branched **F'** product. In the field of intermolecular hydroacylation employing rhodium catalysts and *bis*-phosphine ligands, linear selectivity has normally been predominant. With the hydride insertion step being reversible, the high linear selectivity of the reaction has been attributed to a much faster reductive elimination of intermediate **D**, with a lower energy barrier. Mechanistic studies have shown that this final reductive elimination step was irreversible.

As previously mentioned, the undesired decarbonylation can occur from acyl-rhodium intermediate **B**, due to the presence of a *cis*-vacant site at the metal centre. Intermediate **G** can then undergo irreversible reductive elimination and form both the reduced starting material and an inactive rhodium carbonyl complex **H**.

When studying the reaction in *d*⁶-acetone with 1-octene, the authors showed that the rate of decarbonylation was negligible compared to the rate of formation of the desired ketone. The generation of only trace amounts of decarbonylated adducts thus proved that the major issue to

efficient hydroacylation has been resolved by combining the use of chelating groups and highly robust PCP-based rhodium complexes.

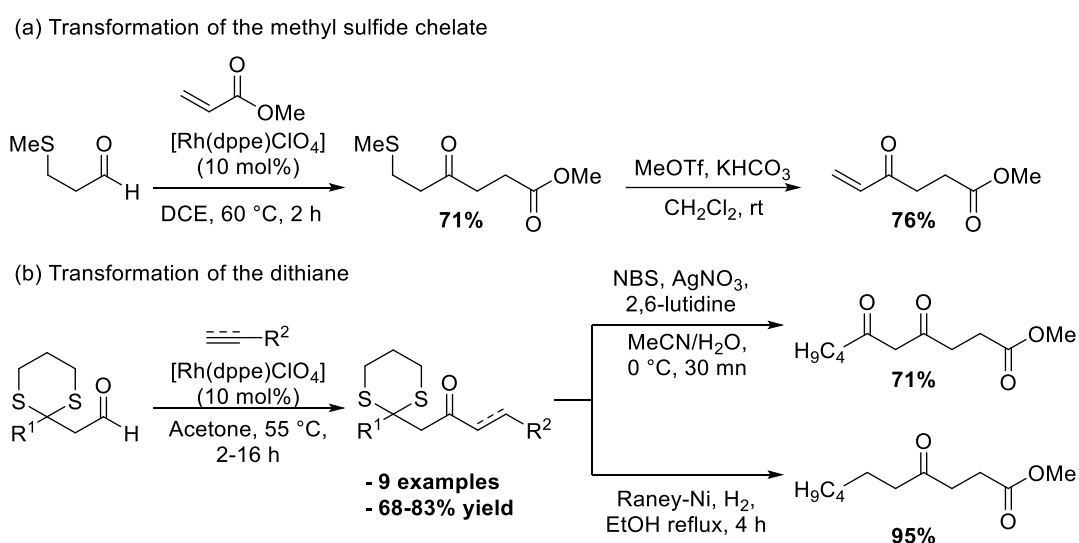


Scheme 1.15 Proposed mechanism for intermolecular hydroacylation

In summary, developments made in the field since the discovery of the hydroacylation reaction have been remarkable, achieving high efficiency, selectivity, and enabling the formation of a wide range of products under mild reaction conditions. The use of chelation-controlled strategies has dramatically improved intermolecular processes and efficiently suppressed the decarbonylation side reaction.

1.2.5 Towards traceless hydroacylation

Even though S-chelating aldehydes have proved to be ideal substrates for the reaction, there is a penalty to pay, in that the heteroatom directing group remains in the final product. For this reason, the Willis group has also focused on the development of methods aiming to eliminate or replace the sulfur directing group after the hydroacylation step as its presence in the final product would substantially reduce the scope of the reaction. Thus, the first report of hydroacylation reaction with β -methylsulfanyl aldehydes also described the elimination of the sulfide tether with methyl trifluoromethanesulfonate to provide the corresponding enone (Scheme 1.16a).²⁶ Similarly, 1,3-dithiane groups could also be derivatised by hydrolysis or reduction, enabling the formation of tether-free products (Scheme 1.16b).²⁸ These transformations, however, were developed from the isolated hydroacylation product enone or ketone, hence requiring an additional step to derivatise the sulfide chelate.

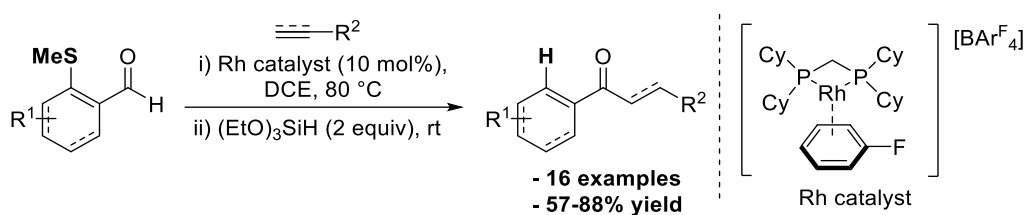


Scheme 1.16 Examples of derivatisation of the sulfide chelate

Although these transformations enabled the removal of the sulfide tether, it was understood that a truly efficient system would allow both the hydroacylation and the derivatisation steps to occur in a one-pot procedure. To this end, the Willis group reported several transformations combining a rhodium-catalysed hydroacylation and a further derivatisation of the tether into more interesting functional groups. Two of these processes stood out from a synthetic perspective as a single

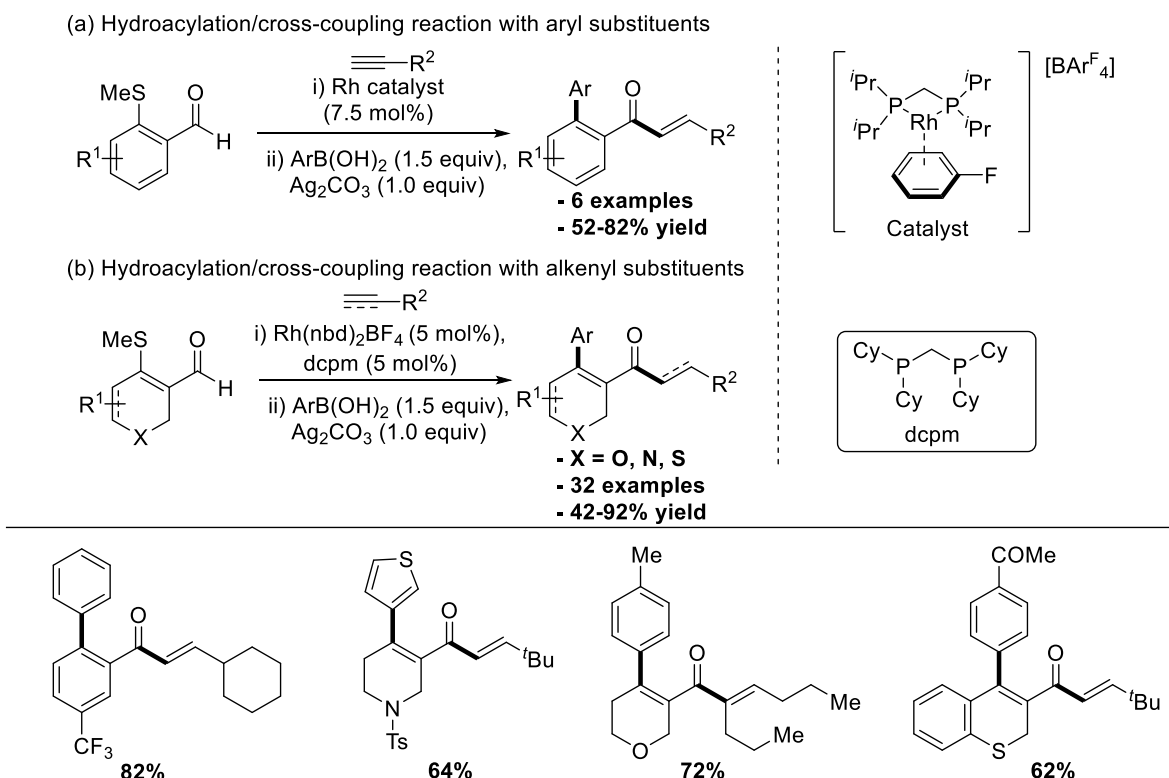
preformed rhodium catalyst played the dual role of performing the hydroacylation first, and further catalysing a second step in a one-pot fashion.

One of these transformations involved a tandem hydroacylation/sulfide reduction to deliver traceless hydroacylation products (Scheme 1.17).³⁷ In this desulfitative process, the rhodium(I) complex catalysed first the C-H activation to perform the hydroacylation, and then the sulfide reduction by means of C-S bond cleavage. Employing a total of 10 mol% of rhodium catalyst, the two steps were combined in a one-pot process under mild reaction conditions, delivering traceless products in good yields.



Scheme 1.17 One-pot hydroacylation/C-S bond reduction

The second transformation also involved the combination of C-H and C-S bond activation processes. However, in this case, the sulfide tether was replaced by another functional group *via* a hydroacylation/cross-coupling sequence with boronic acids, enabling the formation of two new C-C bonds in a single transformation. This methodology was initially developed with 2-methylthio-benzaldehyde derivatives employing a preformed rhodium complex (Scheme 1.18a).³⁸ The reaction was then extended to the use of alkenyl and heterocyclic aldehydes with commercially available and bench stable rhodium(I) pre-catalyst and dcpm ligand (Scheme 1.18b).³⁹



Scheme 1.18 One-pot hydroacylation/cross coupling reaction and selected examples

Since these discoveries, efforts have been focused on expanding the range of similar one-pot processes in order to offer a large panel of transformations available from the hydroacylation product intermediate. Chapters 2 and 3 will show some extension of this work.

In addition, both reactions described in Scheme 1.17 and Scheme 1.18 involve a rhodium-catalysed C-S bond cleavage. The second part of this introduction will summarise the recent advancements in transition metal-catalysed C-C bond formation *via* C-S bond activation and will be further discussed in Chapter 4.

1.3 Recent advances in transition metal-catalysed C-S bond activation

Over the past fifty years, transition metal-catalysed carbon-carbon (C-C) bond formation *via* cross-coupling reactions has had a major impact in both academia and industry.⁴⁰ With a plethora of literature available and constant progress being made in the field, the catalytic formation of new C-C bonds has considerably increased our possibilities to construct more complex molecules and has become a powerful tool for synthetic chemists. This type of

transformation has changed our approach when designing retrosynthetic routes and has proved invaluable for the synthesis of highly functionalised compounds.⁴¹ These reactions generally proceed by oxidative addition of an electrophilic partner to a transition metal-based catalyst, followed by transmetallation with a nucleophilic organometallic reagent and subsequent reductive elimination to provide the cross-coupled product. This general mechanism encompasses a large number of well known reactions, including Suzuki-Miyaura, Sonogashira, Stille, Hiyama, Kumada and Negishi couplings. The emergence of these processes has required the development of catalysts that selectively activated and cleaved certain chemical bonds to enable the combination of two coupling-partners at a determined position. In this context, the use of organohalides has been well explored for cross-coupling reactions, with aryl or vinyl iodides and bromides being the most frequently employed.

However, in an effort to expand the scope of electrophilic coupling partners suitable for C-C formation, the area of carbon-heteroatom activation has gained particular importance, especially with carbon-oxygen (C-O) bonds. Most notably, the use of aryl triflates, mesylates and tosylates has facilitated the catalytic cleavage of C-O bonds, and thus given rise to efficient cross-coupling processes.⁴² Carbon-nitrogen (C-N) bond activation has also been explored,⁴³ with the first Suzuki-Miyaura cross-coupling reaction with aryltrimethylammonium salts having been reported by MacMillan and co-workers in 2003.⁴⁴

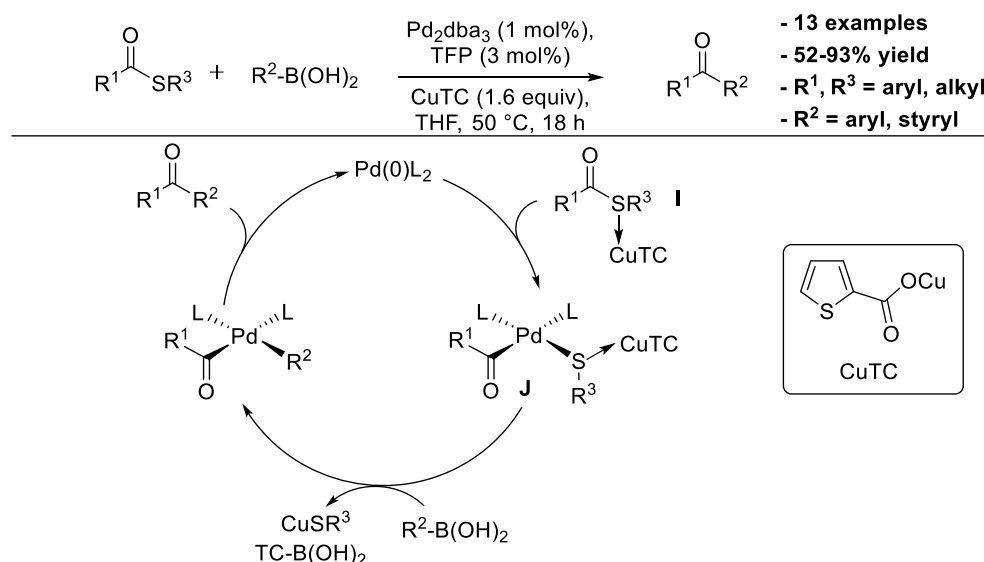
Over the last decade, processes employing thioorganic compounds as electrophilic coupling partners have emerged due to the wide occurrence of S-containing molecules in natural products, pesticides and proteins.⁴⁵ However, general catalytic functionalisations of C-S bonds for the formation of new C-C bonds are still lacking. This is in part explained by the strong tendency of the sulfur atom to poison catalysts by binding to metal centres in an irreversible manner, thus preventing catalytic turn-over.⁴⁶ Although a number of cross-coupling reactions *via* catalytic C-S cleavage has been developed with sulfonyl chlorides,⁴⁷ and sulfones,⁴⁸ this introduction will focus on describing the major advances in C-S activation of thioesters and thioethers only.

$$\text{R}^1-\text{C}(=\text{O})-\text{SEt} \xrightarrow[\text{Various solvents and temperatures}]{\begin{array}{l} [\text{PdCl}_2(\text{PPh}_3)_2] \text{ (5-10 mol\%)} \\ \text{R}^2\text{ZnX (1.5-3.0 equiv)} \end{array}} \text{R}^1-\text{C}(=\text{O})-\text{R}^2$$
 - 29 examples
 - 50-99% yield

$$\text{R}^1-\text{C}(=\text{O})-\text{SEt} \xrightarrow[\text{Alkyne (2.0 equiv), DMF/Et}_3\text{N, 5:1, 50 }^\circ\text{C, 3 h}]{\begin{array}{l} [\text{PdCl}_2(\text{dppf})] \text{ (10 mol\%)} \\ \text{P(2-furyl)}_3 \text{ (25 mol\%)} \\ \text{CuI (1.7 equiv)} \end{array}} \text{R}^1-\text{C}(=\text{O})-\text{C}\equiv\text{C}-\text{R}^2$$
 - 14 examples
 - 64-95% yield

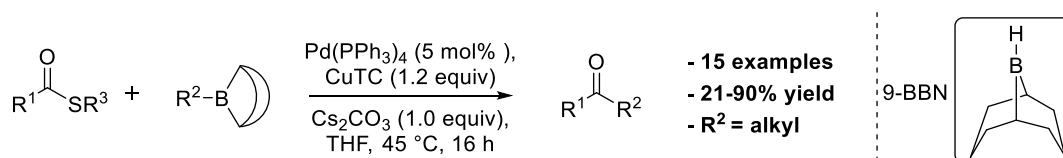
The next significant breakthrough in the field was achieved in 2000 by Liebeskind and Srogl, who reported the first palladium-catalysed copper-mediated cross-coupling protocol to synthesise ketones from thioesters and boronic acids (Scheme 1.20).⁵² The key to promoting catalytic turnover was found to be the use of copper(I) thiophene-2-carboxylate (CuTC) in stoichiometric quantities. This additive enabled the activation of an otherwise stable bond formed between the metal and the soft sulfur atom after oxidative addition. It was proposed that the reaction initiated by the oxidative addition of the CuTC/thioester complex **I** to the active Pd(0) catalyst to form an acylpalladium-thiolate-CuTC intermediate **J**. Transmetallation between the boronic acid and the metal-thiolate followed by reductive elimination led to the formation of the desired ketone, and the regeneration of the active Pd(0) catalyst. Interestingly, both the copper cation and the carboxylate were found to be critical as no reaction would occur when employing either copper(I)-halides, or zinc(II) carboxylate. It was thus proposed that CuTC plays a dual role by: activating the Pd-S bond through coordination to the Cu(I) cation; and activating the boronic acid through coordination of the

carboxylate. The combination of these two factors enabled an efficient transmetallation process, with the stoichiometric amount of CuTC being necessary to scavenge the resulting thiolate species. Aryl, alkenyl and alkyl substituents were all well tolerated and the variety of products obtained under mild, base-free reaction conditions and low catalyst loading demonstrated the robustness of this method.



Scheme 1.20 Liebeskind-Srogl coupling and proposed mechanism

Similarly to the Suzuki-Miyaura coupling, alkylboronic acids were found to deliver low yields when employing these reaction conditions. This issue was overcome with the use of alkyl-9-borabicyclo[3.3.1]nonane (alkyl-9-BBN) instead of boronic acid reagents, enabling the formation of aryl/alkyl and alkyl/alkyl ketones in excellent yields under mild reaction conditions (Scheme 1.21).⁵³

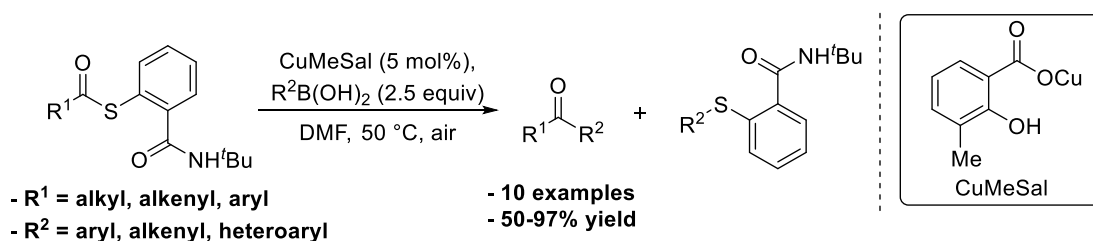


Scheme 1.21 Liebeskind-Srogl coupling with alkyl-9-BBN

In the following years, the so-called “first generation” Liebeskind-Srogl coupling proved its versatility with the possibility to employ other nucleophilic partners such as organostannanes,⁵⁴ which were further explored by Guillaumet for cross-couplings between vinyl and aryl stannanes

with π -electron deficient heteroaryl-thioethers.⁵⁵ Thioesters could also undergo palladium-catalysed C-C bond formation with organoindium and organozinc reagents, delivering ketone products in good yields (55-95%) with the additional benefit of not requiring a copper reagent to mediate the reaction.^{56,57}

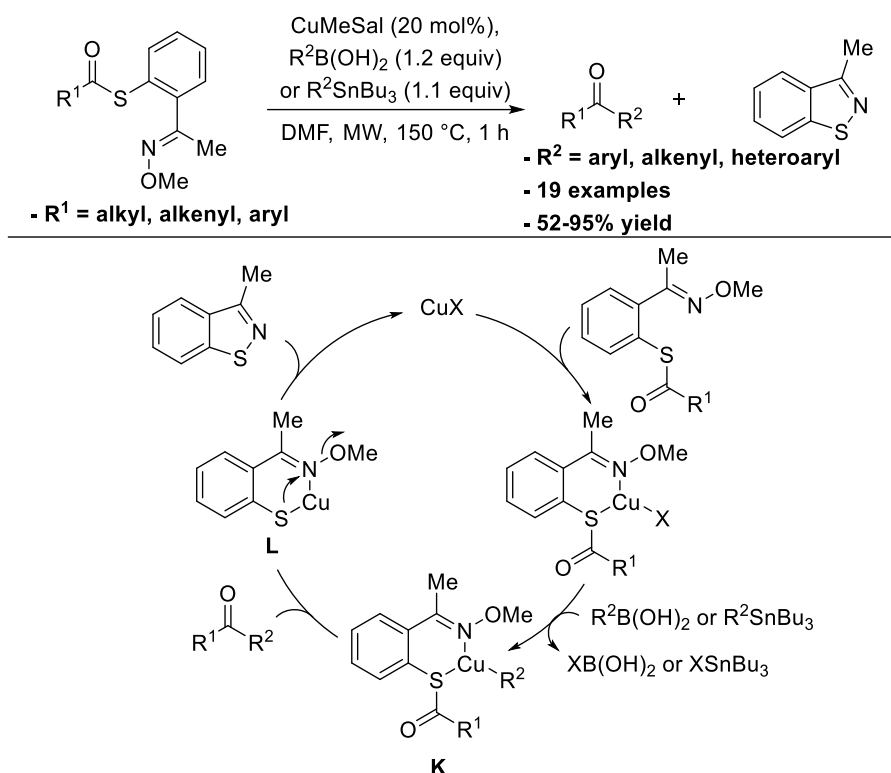
However, the most important breakthrough in the field was reported in 2007, with the development of a mechanistically unprecedented palladium-free copper(I)-catalysed cross-coupling with boronic acids under aerobic conditions.⁵⁸ Preliminary investigations revealed that thioesters possessing a coordinating functional group *ortho* to the sulfur would deliver the desired ketone in the presence of sub-stoichiometric amounts of copper(I) 3-methylsalicylate (CuMeSal) (Scheme 1.22). The reaction was successfully applied to a variety of aryl, alkyl and alkenyl thiosalicylamides. Excess boronic acid was found to be necessary, the sacrificial equivalent rendering the process catalytic by breaking the intermediate copper-thiolate bond and forming the thioether side-product in a 1:1 ratio with the desired ketone. Additionally, and in contrast to the previously reported palladium-catalysed cross-coupling reaction, a variety of copper(I) sources proved to be effective for this transformation, regardless of the nature of the counterion (halide, carboxylate and diphenylphosphinate).



Scheme 1.22 Copper-catalysed cross-coupling of thioesters and boronic acids under aerobic conditions

Finally, in 2011, Liebeskind and co-workers reported the “third generation” anaerobic copper(I)-catalysed desulfurative cross-coupling reaction with boron or tin reagents.⁵⁹ The process outcompeted the previous generations by employing a new ligating functional group in which the *tert*-butyl amide has been replaced by an oxime ether (Scheme 1.23). The proposed mechanism starts with the coordination of the copper(I) complex to the thioester-oxime and is followed by the transmetalation with organoboron or organotin reagents to form intermediate **K**. The authors

suggested that the close proximity of the activated carbon from the thioester and the R^2 group led to the direct reaction of the organocopper intermediate **K**, delivering the desired ketone product. The subsequent copper-thiolate complex **L** could then react with the oxime ether intramolecularly, thus forming benzoisothiazoles and regenerating the catalyst. It is the final step of this cycle which, by efficiently trapping the thiolate *via* an auto-scavenging process, enabled the catalytic turn-over of the reaction without having to employ excess boronic acid.



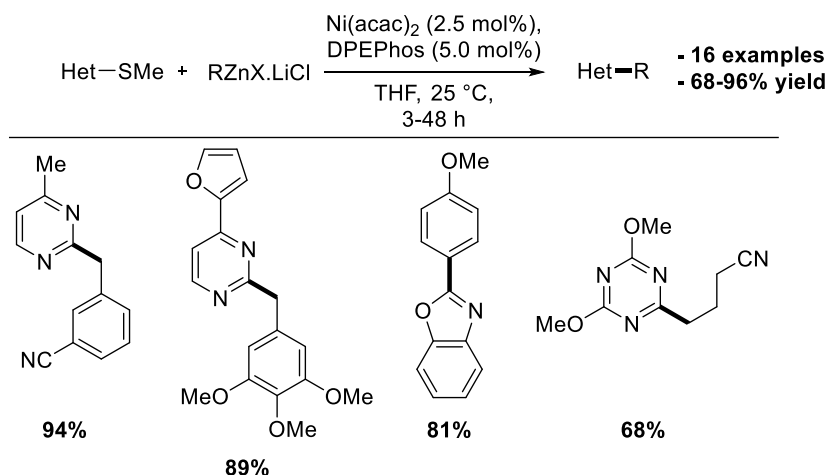
Scheme 1.23 Third generation Liebeskind-Srogl cross-coupling and suggested mechanism

1.3.2 C-C bond formation *via* catalytic C-S bond activation of thioethers

While extensive progress has been made for the development of catalytic C-C bond formation *via* C-S bond cleavage of thioesters, the related C-S activation of thioethers has proved more challenging. Amongst the wide variety of thioether-containing compounds, heteroaryl thioethers have prevailed in the area of C-S cleavage-mediated cross-couplings. Alkenyl-thioether and alkynyl-thioether have also been explored, and a number of significant examples from each group will be next described.

1.3.2.1 Heteroaryl thioethers C-S bond cleavage

Several metal catalysts have shown to be efficient for the activation of C-S bonds found in heteroaryl thioethers, the electron-deficient heteroaromatic core contributing to their enhanced reactivity. In 2010, Gosmini and co-workers reported the activation of thiomethyl *N*-heterocycles using an inexpensive and ligand free cobalt(II) bromide.⁶⁰ The same year, Knochel and co-workers developed an efficient nickel-catalysed cross-coupling reaction between a variety of thiomethyl-containing heterocycles and organozinc reagents (Scheme 1.24).⁶¹ The reaction was successfully applied to a wide range of heteroarenes including pyridines, isoquinolines, pyrimidines, pyrazines, triazines or benzoxazoles.



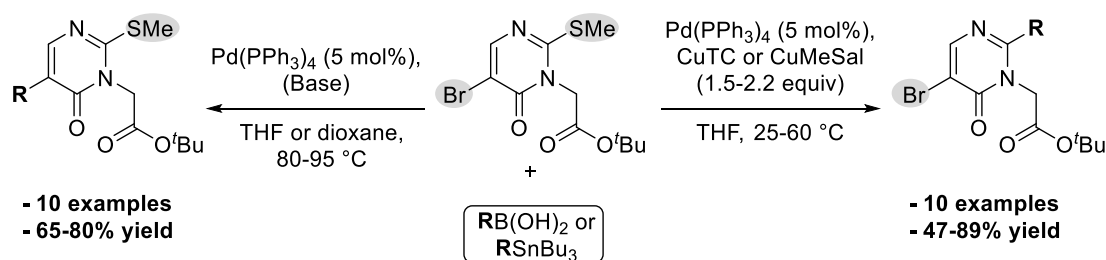
Scheme 1.24 Nickel-catalysed cross-coupling reaction and selected examples

This methodology was then extended to the possibility to employ palladium catalysts and applied to an extensive range of substrates incorporating sensitive functionalities. The robustness of the protocol was demonstrated with several large-scale experiments.^{62,63}

Parallel to their investigations with thioesters, Liebeskind and Srogl also explored cross-coupling reactions with electrophilic partners containing C-S bonds of a different nature. In 2002, they reported a palladium-catalysed copper-mediated reaction of heteroaryl thioethers with boronic acids under their standard “first generation” reaction conditions.⁶⁴ The reaction successfully underwent C-C bond formation and delivered a range of functionalised heteroarenes in good to

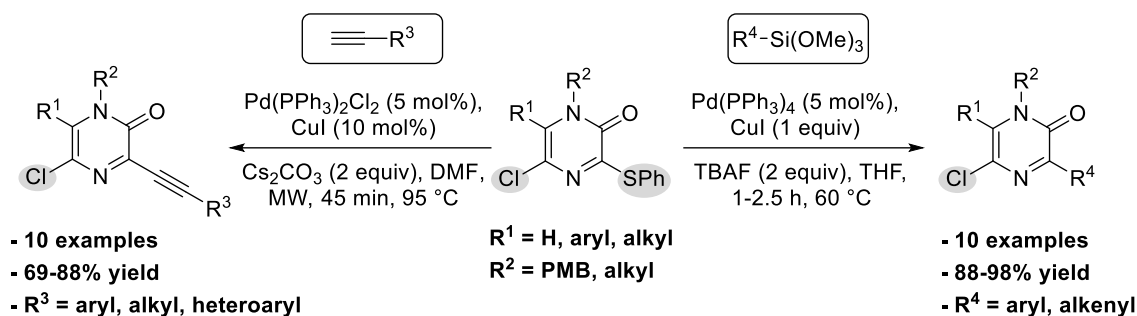
excellent yields. However, simple aryl thioethers proved unreactive under the optimised reaction conditions. This was attributed to a more challenging oxidative addition with these substrates.

One of the major advantages of the base-free C-S activation process developed by Liebeskind and Srogl was demonstrated a year later, with a selective cross-coupling reaction for the synthesis of functionalised pyrimidinones (Scheme 1.25).⁶⁵ A pyrimidinone bearing multiple reactive sites was designed and reacted with a palladium catalyst together with either an organoboronic acid or an organostannane reagent. The authors showed that selective activation of one of the two reactive C-Br or C-SMe bonds was possible by only changing the reaction conditions. On the one hand, standard Suzuki-Miyaura or Stille reaction conditions delivered cross-coupled products at the bromide position, while selective cross-coupling at the thiomethyl position was achieved in the presence of copper additives. The unique selectivity observed in this latter case was explained by the role of the copper(I) salt which facilitated both the oxidative addition by polarising the C-S bond and the transmetalation of the nucleophilic partner to the palladium-thiolate intermediate.



Scheme 1.25 Selective cross-coupling reactions

In 2007, Kappe and co-workers developed a similar methodology with thioamides and thioureas. They showed that cyclic thioamides could undergo different cross-couplings depending on the catalytic system employed, enabling a tunable C-halide or C-S bond activation with boronic acids.⁶⁶ These selective C-S bond cleavages in presence of C-halide bonds were further extended to the Sonogashira and Hiyama-type reactions with pyrazine derivatives, as illustrated by the work developed by Van der Eycken and co-workers (Scheme 1.26).⁶⁷ The authors were able to develop a highly efficient desulfurative alkynylation under microwave irradiation, yielding functionalised pyrazines with no trace of reaction at the chloride position. Similarly, a selective desulfurative Hiyama cross-coupling was also successfully developed.

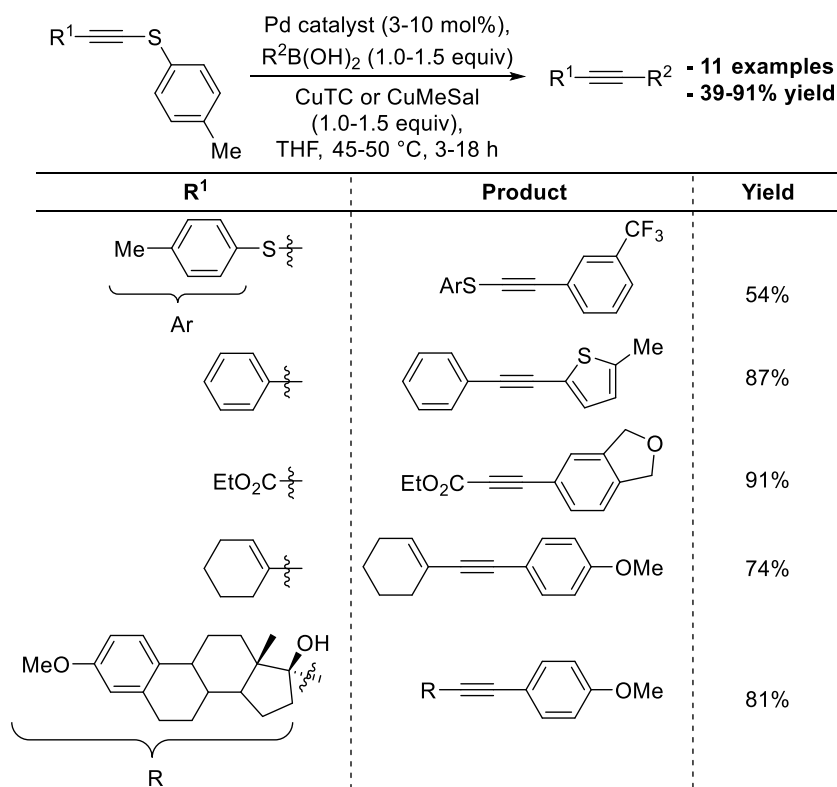


Scheme 1.26 Orthogonal palladium-catalysed cross-coupling reaction with alkynes and alkoxy silanes

In summary, these examples have illustrated the progress made in the field of metal-catalysed cross-coupling reaction *via* C-S bond activation and the development of a number of orthogonal processes. However, the C-S activation of heteroaryl thioethers still suffers from a limited substrate scope and the need to optimise the reaction conditions for each class of heteroaromatic.

1.3.2.2 Alkynyl thioethers C-S bond cleavage

In comparison to heteroaryl thioethers, the C-S activation of alkynyl sulfides has been less explored. However, whilst only specific heteroaryl thioethers could be engaged in the Liebeskind-Srogl C-C formation, this reaction proved efficient for a wide range of alkynyl sulfides, delivering cross-coupled products in moderate to excellent yields (Scheme 1.27).⁶⁸ Although these products could alternatively be easily prepared by Sonogashira cross-couplings, the reaction was versatile and robust, with alkyl, aryl and alkenyl substituents on the alkyne starting material being well tolerated. The boronic acid component allowed the use of heteroaryl, aryl and alkenyl boronic acids. However, alkyl boronic acids could not be employed.



Scheme 1.27 Alkynyl C-S activation and selected examples

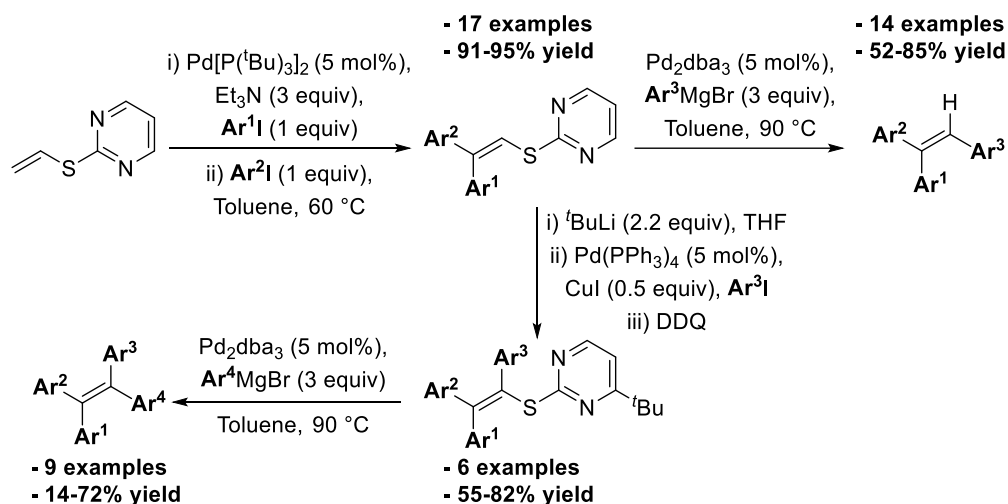
More recently, Knochel and co-workers reported a palladium-catalysed cross-coupling reaction with thiomethyl acetylenes and substituted organozinc reagents. In addition to employing commercially available palladium catalyst and ligand, the reaction tolerated the use of alkyl organozinc reagents.⁶⁹

1.3.2.3 Alkenyl thioethers C-S bond cleavage

The decreased polarisation of the C-S bond of alkenyl sulfides relative to thioesters and heteroaryl thioethers makes their C-S activation more challenging, and hence requires the design of specific substrates. In the 1980s, both Wenkert and Takai reported that the reaction of alkenyl sulfides with Grignard reagents, catalysed by $[\text{NiCl}_2(\text{PPh}_3)_2]$, led to alkenes with retention of the double bond geometry.^{70,71}

In 2004, Yoshida and co-workers reported the synthesis of a library of triaryl- and tetraarylethenes *via* palladium-catalysed cross-coupling reactions with organomagnesium reagents (Scheme 1.28).⁷² Starting from simple vinyl 2-pyrimidyl sulfide, they developed a one-pot double Mizoroki-Heck

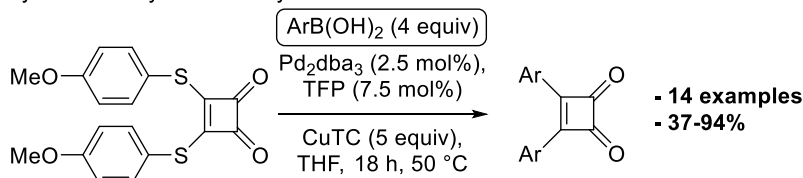
reaction delivering diarylvinyl sulfides. These could undergo either palladium-catalysed C-S cleavage with Grignard reagents to form triaryl alkenes, or be engaged in an α -lithiation/cross-coupling reaction, followed by a second C-C bond formation with Grignard reagents to access tetraaryl alkenes.



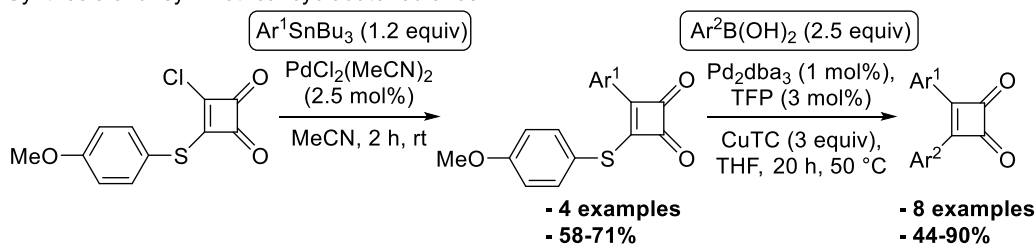
Scheme 1.28 Yoshida's synthesis of highly substituted olefins

In 2007, Aguilar-Aguilar *et al.* reported the synthesis of *bis*-aryl-cyclobutenediones. When employing four equivalents of boronic acid under the Liebeskind-Srogl conditions, *bis*-arylthio-cyclobutenediones delivered symmetrical products (Scheme 1.29a).⁷³ The unsymmetrical synthesis was described the same year by a Stille/Liebeskind-Srogl coupling sequence from chlorothio-cyclobutenedione, enabling the formation of the desired products in moderate to excellent yields (Scheme 1.29b).⁷⁴

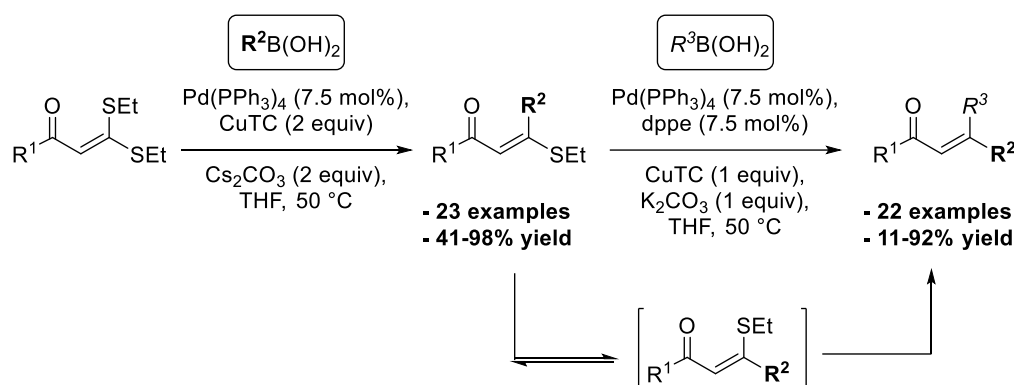
(a) Synthesis of symmetrical cyclobutenediones



(b) Synthesis of unsymmetrical cyclobutenediones

Scheme 1.29 Synthesis of symmetrical and unsymmetrical *bis*-aryl cyclobutenediones

More recently, Jin *et al.* reported a Pd(0)-catalysed, Cu(I)-mediated synthesis of trisubstituted olefins from ketene dithioacetals with aryl and alkenylboronic acids (Scheme 1.30).⁷⁵ The first coupling was either predominantly or exclusively (*E*)-selective, suggesting a strong directing effect from the carbonyl group that facilitated the cleavage of the C-S bond positioned *cis* to the tether. For the second coupling, the authors suggested first an isomerisation of the double bond which promoted the second C-C formation. This methodology provided a range of highly functionalised olefins in good yields and moderate selectivity.

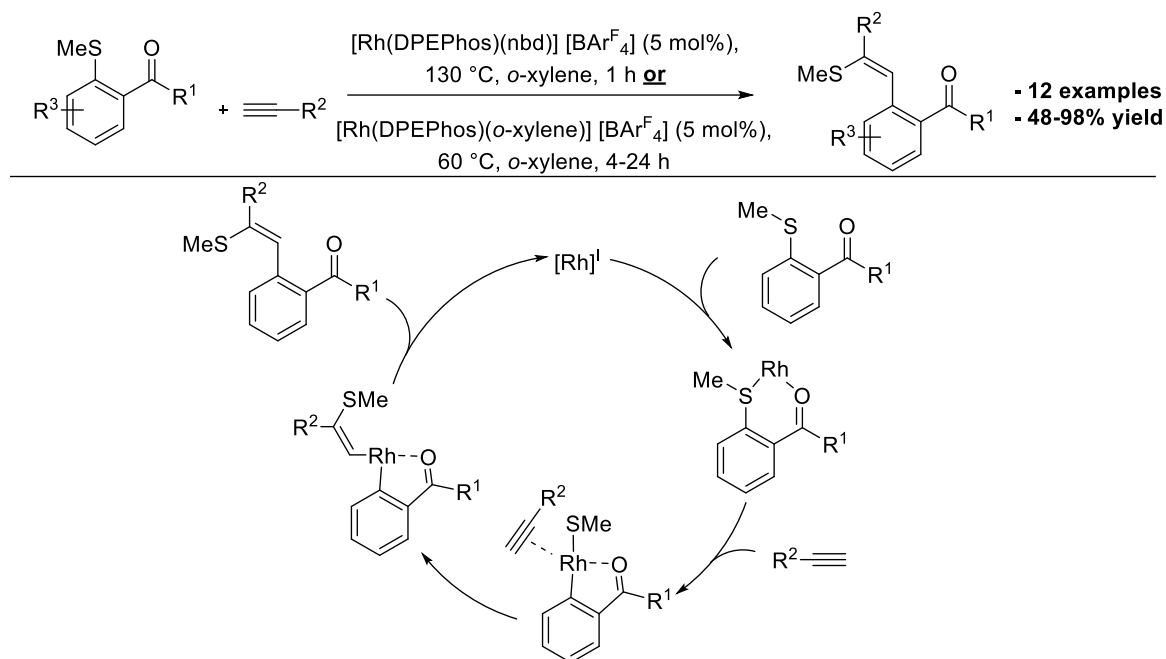


Scheme 1.30 Cross-coupling reaction with ketene dithioacetals and boronic acids

1.3.2.4 Aryl thioethers C-S bond cleavage

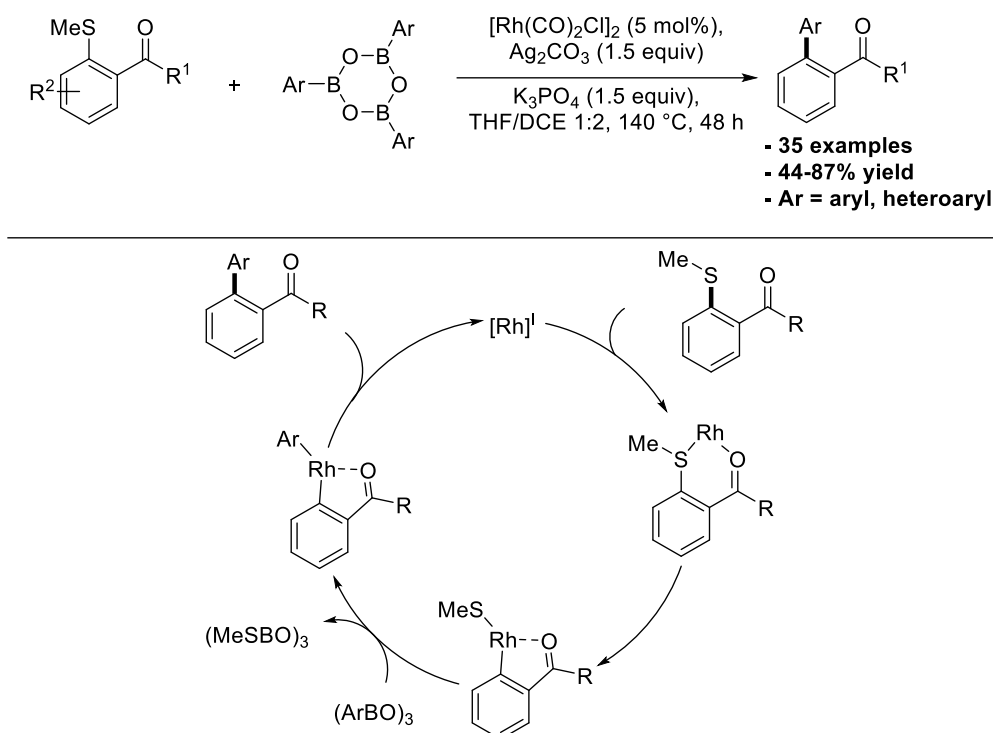
As mentioned previously (see section 1.2.5 page 14), the Willis group has reported several examples of rhodium-catalysed C-C bond formation *via* C-S bond activation of aryl sulfides in order to reutilise the sulfur chelating group employed for the hydroacylation reaction.³⁷⁻³⁹ In 2012, the authors also showed that aryl methyl sulfides and terminal alkynes could be combined to deliver carbothiolation products, a process that incorporates the original methyl sulfide into the product as an alkenyl sulfide.⁷⁶ The process starts with C-S bond activation which is promoted by the presence of the carbonyl directing group, followed by the migration of the methyl sulfide on the alkyne and the reductive elimination (Scheme 1.31). The carbothiolation is a robust process that displays a broad scope and tolerates steric and electronic variations in both coupling partners. The transformation presents several advantages, such as the possibility to combine it with an initial rhodium(I)-catalysed alkene or alkyne hydroacylation in a one-pot fashion, with a single

rhodium(I) catalyst being used to catalyse both steps. Furthermore, carbothiolation products were employed as precursors for the preparation of substituted isoquinolines.⁷⁷



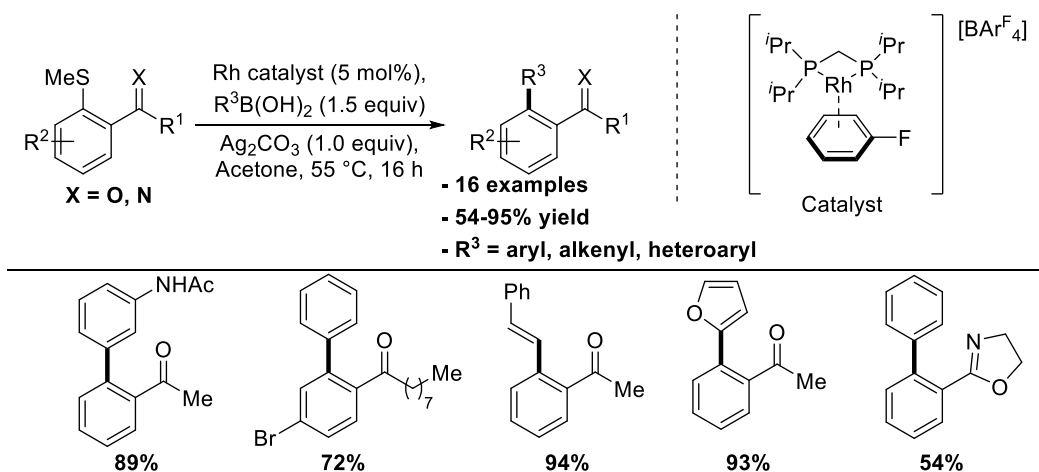
Scheme 1.31 Rhodium-catalysed carbothiolation reaction with aryl sulfides

Even more versatile was the development of a desulfurative rhodium-catalysed cross-coupling reaction with aryl methyl sulfides and organoboron derivatives, reported simultaneously by the groups of Shi and Willis.^{38,78} On the one hand, Shi and co-workers reported a rhodium-catalysed C-C bond formation with a variety of aryl and heteroaryl boroxines (Scheme 1.32). The reaction had the benefit of employing commercially available catalyst, but also required the preparation of the boroxine reagents, as well as long reaction times and high temperatures. The authors suggested a catalytic cycle similar to the one proposed for the Liebeskind-Srogl coupling, involving first coordination of the rhodium(I) catalyst to the starting material, followed by C-S oxidative addition, transmetalation and reductive elimination.



Scheme 1.32 Rhodium-catalysed cross-coupling reaction and suggested mechanism by Shi and co-workers

In the case of the Willis group, a rhodium(I) catalyst incorporating a small bite angle phosphine ligand efficiently promoted C-S bond cleavage and C-C formation with a wide range of boronic acids including aryl, styryl and heteroaryl substituents under mild reaction conditions (Scheme 1.33).³⁸ It is also worth mentioning that the rhodium catalyst displayed orthogonal reactivity towards standard Suzuki-Miyaura reaction since the cross-coupling only occurred at the C-S bond even in the presence of other reactive functional groups such as halides. The use of silver carbonate as a thiophilic inorganic additive proved necessary for promoting the catalytic turnover.



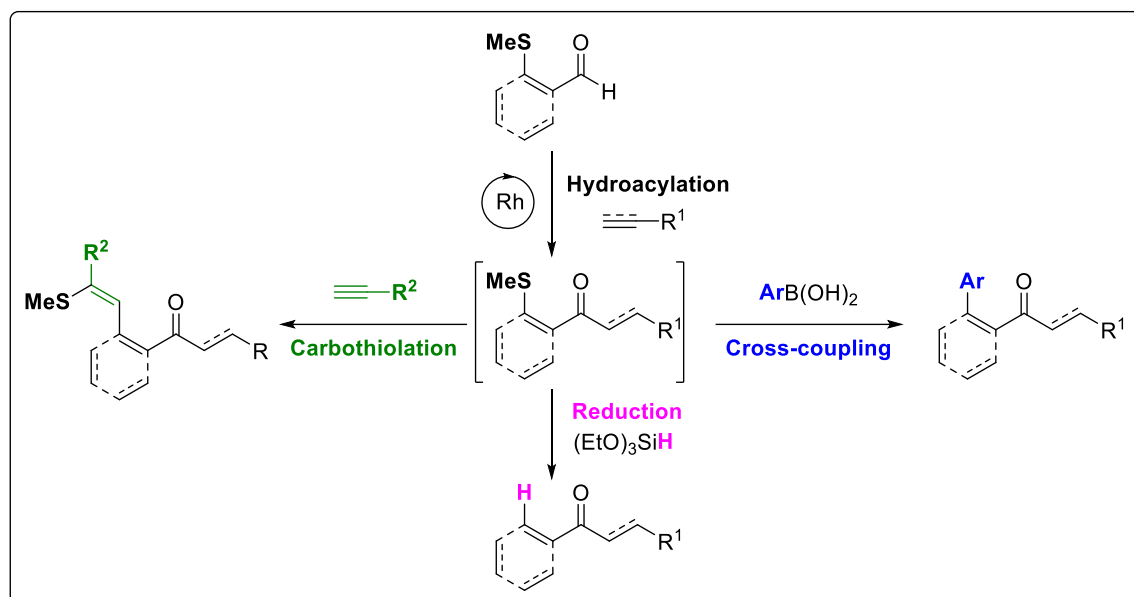
Scheme 1.33 Rhodium-catalysed cross-coupling reaction by Willis and co-workers

The sequential C-H/C-S bond activation enabling the formation of two new C-C bonds was further improved with the possibility to employ commercially available rhodium(I) pre-catalyst and *bis*-phosphine ligand at low catalyst loadings. The process proved versatile, with not only aryl but also alkenyl methyl sulfides being efficient coupling-partners.³⁹ Similar to the carbothiolation, all these processes were also compatible with the rhodium-catalysed hydroacylation, thus enabling a one-pot three-component hydroacylation/Suzuki reaction using a single catalytic system.

However, it is worth mentioning that these reactions were completely shut down in the absence of the carbonyl directing group, thus showing the limitations in terms of substrate scope. Hence these final examples illustrate well both the progress made in the field of C-S activation as well as the future challenges to overcome.

1.4 Summary and overall objectives

The research undertaken around rhodium-catalysed transformations over the last few decades has revealed the potential of this transition metal for the formation of new C-C bonds. Since its initial discovery as a powerful tool for hydroacylation reactions, years of research have now allowed scientists to achieve high yielding and selective reactions with both alkenes and alkynes, in an inter- and intramolecular fashion. Most of these processes have involved the use of chelation-controlled strategies, with the heteroatom tether located on the starting material, and consequently on the product. Overcoming the disadvantage of using a chelate has promoted the development of further transformations to remove, recycle or refunctionalise it. In this context, the Willis group, which has extensively studied S-chelating aldehydes for hydroacylation, has also focused its efforts on developing one-pot processes that delivered tetherless products. Some of these transformations have highlighted the potential of rhodium-based catalysts to efficiently catalyse both hydroacylation and further cleavage of C-S bonds (Scheme 1.34). Nevertheless, there are still limitations with regards to the scope of substrates that can be employed in these processes. The second and third chapters of this thesis will be focused on exploring processes in which the sulfur heteroatom is first exploited to efficiently promote a hydroacylation reaction, and subsequently refunctionalised or recycled.



Scheme 1.34 One-pot processes combining rhodium-catalysed hydroacylation and C-S activation

In addition, the emergence of rhodium(I) as a useful catalyst for C-S activation has encouraged us to further study cross-coupling reactions involving C-S bond cleavage. The last chapter of this thesis will summarise the developments made in the field of rhodium-catalysed cross-coupling reactions using alkenyl sulfides.

Chapter 2

Development of a hydroacylation, elimination, 1,4-conjugate addition sequence from alkyl β -S-aldehydes

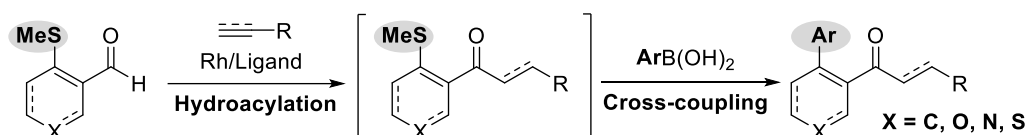
2.1 Introduction and project aims

Over the last decades, attention has been focused on environmental sustainability, particularly within the industrial sector.⁷⁹ Achieving fast and high yielding reactions, as well as reducing catalyst loadings have become a priority for synthetic chemists. In this context, one-pot processes, which combine multi-step transformations into one synthetic operation, have become sought after in contemporary organic chemistry as they allow saving time, energy and also benefit from minimising solvent waste by avoiding work-ups and purifications of intermediates.⁸⁰

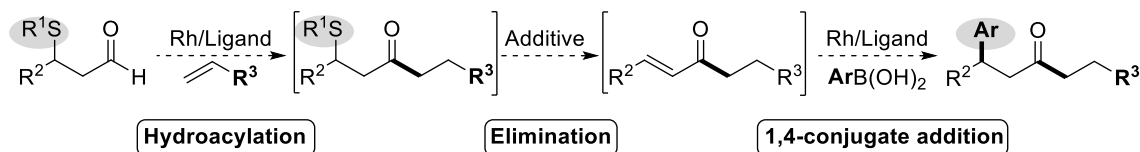
As discussed in chapter 1, the development of chelation-controlled strategies for the rhodium-catalysed hydroacylation has enabled challenging intermolecular processes to occur under mild reaction conditions. In particular, S-chelating groups have proved efficient with a wide range of aryl, alkyl, and alkenyl aldehyde substrates, thus providing powerful and reliable general hydroacylation methods. Nevertheless, the presence of the sulfide chelate in the final product has often been seen as a limitation and processes have emerged to transform the coordinating group. In this context, the Willis group has shown that rhodium-catalysed C-S bond cleavage could allow, after hydroacylation, the replacement of the sulfide tether by more useful functional groups in a tandem fashion.³⁷⁻³⁹ In these examples, the initial constraint of having a directing group has been

turned into an advantage, with the chelate being used as a platform for further functionalisation. Among the transformations developed, the rhodium-catalysed hydroacylation/cross-coupling reaction with boronic acids discussed in chapter 1 stands out as a powerful process, delivering traceless hydroacylation products and enabling the formation of a second C-C bond (Scheme 2.1a). However, these reactions have only been achieved with *aryl* and *alkenyl* thiomethyl sulfides as *alkyl* sulfides have shown to be unreactive cross-coupling partners. To overcome this limitation and extend the utility of the process to *alkyl* aldehydes, our aim was to develop an alternative strategy employing these seemingly non-reactive substrates. For this purpose, we envisioned a one-pot three-step sequence involving an alkene hydroacylation, followed by the elimination of the sulfide group and a subsequent 1,4-conjugate addition of boronic acids (Scheme 2.1b).

(a) Previous work with aryl and alkenyl sulfides



(b) Aim of this work with alkyl sulfides

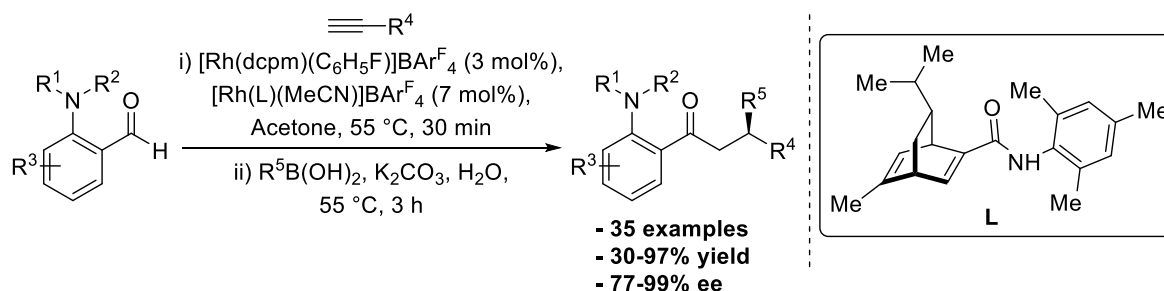


Scheme 2.1 Aim of this work

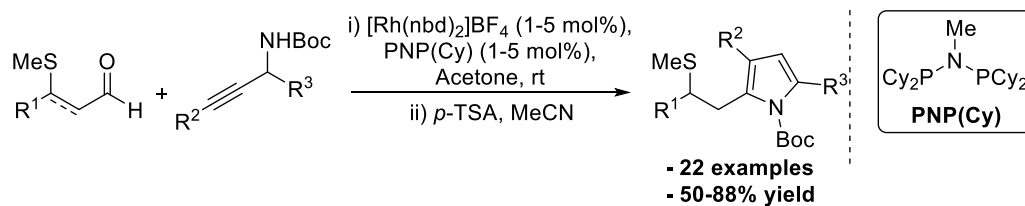
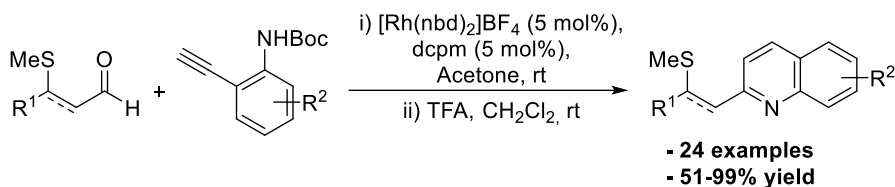
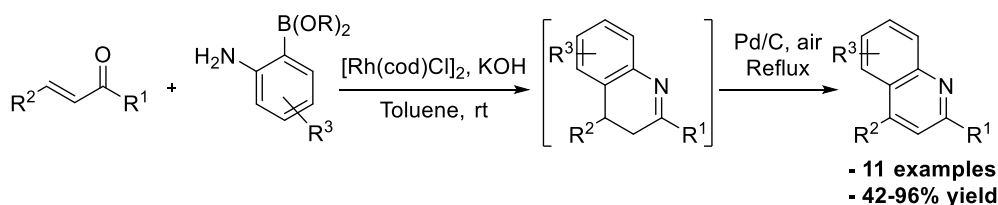
This new strategy would enable the combination of both intermolecular hydroacylation as well as the replacement of the tether by a more useful functional group, thus allowing the formation of two new C-C bonds and a stereogenic centre in a single process. In addition, the large number of commercially available boronic acids would enable the preparation of a wide variety of chiral β -functionalised ketones.

Whilst highly efficient catalytic systems using rhodium(I) complexes have been developed separately for both hydroacylation and 1,4-conjugate addition, only one example combining the two mechanistically distinct reactions has been reported with *N*-chelating aldehydes.⁸¹ This is likely due to the difficulty in finding compatible systems that allow the catalysis of both steps since as a

general trend, hydroacylation is often carried out under anhydrous conditions and is favoured by small bite angle ligands; in contrast, the conjugate addition is promoted by large bite angle ligands and is often carried out in water or methanol in order to generate the catalytically active rhodium(I)-hydroxyl species.⁸² The process developed by Willis and co-workers consisted in the formation of β -substituted ketones from 2-aminobenzaldehydes by a one-pot rhodium-catalysed alkyne hydroacylation and conjugate addition of boronic acids (Scheme 2.2). For the delivery of racemic products, a single preformed $[\text{Rh}(\text{dppe})(\text{C}_6\text{H}_5\text{F})]\text{BAr}^{\text{F}}_4$ complex was found to catalyse both steps efficiently. Furthermore, a preformed chiral rhodium complex, $[\text{Rh}(\text{R,R-MeDuPhos})(\text{C}_6\text{H}_5\text{F})]\text{BAr}^{\text{F}}_4$, successfully allowed the formation of the desired products in good yields and moderate enantioselectivities (33-86% ee). To achieve excellent levels of enantiocontrol (up to >99% ee), two preformed rhodium(I) complexes, both introduced at the start of the reaction sequence, enabled the preparation of the desired products in good yields and high enantioselectivities.

Scheme 2.2 One-pot hydroacylation/conjugate addition with *N*-chelating aldehydes

In a similar manner, our aim was to find suitable reaction conditions which would allow the use of one or two rhodium complexes with an ideal total catalyst loading equal to or less than 10 mol%. Additionally, both the hydroacylation reaction and the 1,4-conjugate addition have been used as tools for the construction of heterocycles such as pyrroles⁸³ and quinolines (Scheme 2.3).⁸⁴ Thus, with the possibility to vary three components in our sequence (aldehyde, alkene and boronic acid), we thought that the tandem reaction could also enable the synthesis of interesting heterocyclic structures.

(a) Pyrrole formation *via* hydroacylation(b) Quinoline formation *via* hydroacylation(c) Quinoline formation *via* conjugate additionScheme 2.3 Synthesis of heterocycles *via* a hydroacylation or conjugate addition

2.2 Results and discussion

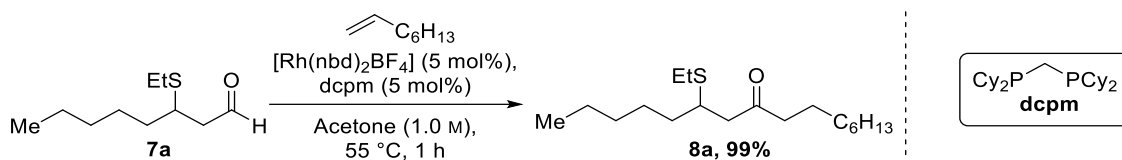
This project was carried out jointly with another DPhil student, Ming Gao, and his contribution is also discussed here for a full understanding of the project. The work he carried out will be clearly stated in the text, but the products he prepared are not included in the experimental section.

2.2.1 Investigations for each individual step

2.2.1.1 Alkene hydroacylation reaction

In order to address the different objectives, we began investigating each step separately. Although successful transformations have already been achieved, rhodium-catalysed hydroacylation has been more challenging with alkenes than with alkynes. Initially only applicable to activated alkenes,^{26,28} the development of a second generation catalyst with the hemi-labile DPEPhos ligand has enabled the use of unactivated alkenes, but long reaction times (16-48 hours) were required.²⁹ Highly effective transformations were then achieved with a preformed rhodium complex incorporating small bite angle *bis*-phosphine ligands.³² Aiming to employ a commercially available pre-catalyst,

DPhil student Ming Gao first studied the hydroacylation step using 3-(ethylthio)octanal **7a** as the standard aldehyde since successful transformations had already been achieved with this substrate (Scheme 2.4).²⁸ Different ligands, concentrations and solvents were thus tested for the intermolecular hydroacylation of **7a** with 1-octene. With three equivalents of alkene, the best catalyst system was found to be an equimolar mixture of bench stable $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ pre-catalyst and dcpm ligand at a 5 mol% catalyst loading. When carried out in acetone at 55 °C, the reaction enabled the formation of ketone **8a** in one hour, which was isolated in 99% yield with no regioselectivity issues. Alternatively, DCE could also be employed instead of acetone, delivering the ketone equally efficiently.

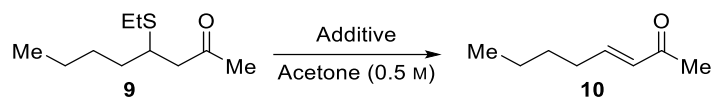


Scheme 2.4 Optimised conditions for hydroacylation reaction

2.2.1.2 Elimination reaction

With the best conditions for hydroacylation having been established, we then turned our attention to the elimination of the sulfide group. This transformation is not well preceded and traditional methods to eliminate sulfides involve the use of 3-chloroperbenzoic acid, sodium periodate, or methyl trifluoromethanesulfonate.⁸⁵ The elimination occurs by the formation of a sulfoxide or a sulfonium ion intermediate which are better leaving groups than the corresponding sulfides. However, we envisaged that these relatively harsh reagents could be detrimental to the rhodium catalyst and inhibit the subsequent conjugate addition if all rhodium sources were added from the start. With a hope to find mild reaction conditions that would be compatible with rhodium catalysts, we initially investigated the development of an E1cB type reaction using weak bases and 4-(ethylthio)octan-2-one **9**, prepared from the corresponding commercially available enone as a model substrate. To avoid using a different solvent than for the hydroacylation step, the transformation was evaluated in acetone but in more dilute concentrations to allow efficient stirring in the presence of inorganic salts. Initially aiming for a single additive that would promote both the elimination of the sulfide and the conjugate addition, we screened organic and inorganic bases that

had already been reported for conjugate additions (Table 2.1). Disappointingly, when mixing one equivalent of potassium carbonate and ketone **9** at 55 °C for 16 h, less than 5% of product **10** was observed under conventional heating or microwave irradiation (entries 1 and 2). Similar results were obtained with sodium carbonate (entries 3 and 4) and triethylamine (entries 5 and 6).



Entry	Additive (equiv)	MW irradiation	Temp., time	NMR conversion
1	K ₂ CO ₃ (1.0)	No	55 °C, 16 h	0%
2	K ₂ CO ₃ (1.0)	Yes	100 °C, 1 h	3%
3	Na ₂ CO ₃ (1.0)	No	55 °C, 16 h	0%
4	Na ₂ CO ₃ (1.0)	Yes	100 °C, 1 h	0%
5	Et ₃ N (1.0)	No	55 °C, 16 h	0%
6	Et ₃ N (1.0)	Yes	100 °C, 1 h	0%
7	CuCl (1.0)	Yes	100 °C, 1 h	0%
8	CuCl (1.0) + K ₂ CO ₃ (1.0)	Yes	100 °C, 1 h	5%
9	Ag ₂ CO ₃ (1.0)	Yes	100 °C, 1 h	11%
10	CuTC (1.0)	Yes	100 °C, 1 h	70%
11	CuMeSal (1.0)	Yes	100 °C, 1 h	100%
12	CuMeSal (1.0)	No	55 °C, 16 h	100%
13	MeOTf (1.1) + K ₂ CO ₃ (1.5)	No	55 °C, 0.5 h	72%
14	MeOTf (1.5) + K ₂ CO ₃ (1.5)	No	55 °C, 1 h	100%

Table 2.1 Additive screening for the elimination reaction

With unsuccessful results using a number of bases that had shown effective for conjugate addition reactions, we next turned our attention to thiophilic additives such as copper and silver salts. These were chosen as they have proved effective for transformations involving thiolates.^{38,39,52,58} Firstly, the use of copper(I) chloride did not deliver any desired product, even when employed in combination with potassium carbonate (entries 7 and 8). However, when using silver carbonate under microwave irradiation, we were pleased to observe 11% conversion to the α - β -unsaturated ketone **10** by analysis of the ¹H NMR spectrum of the crude material (entry 9). A considerable increase in conversion was then achieved when employing copper(I) thiophene-2-carboxylate

(CuTC), which gave a 70% conversion (entry 10), and this result was further improved with copper(I) 3-methylsalicylate (CuMeSal) which afforded full conversion (entries 11 and 12). However, completion of the reaction required stoichiometric amounts of copper with either long reaction times under conventional heating, or short reaction time under microwave irradiation, thus considerably complicating the practical aspect of our envisioned one-pot process. Alternatively, the use of methyl trifluoromethanesulfonate (MeOTf) together with potassium carbonate resulted in clean conversion to the enone **10**, which was isolated in 96% yield (entries 13 and 14).²⁶ The reaction proceeded in only one hour at 55 °C, and could be useful for a one-pot approach in which the second rhodium catalyst would not be added from the start but upon completion of the elimination step.

2.2.1.3 Rhodium-catalysed 1,4-conjugate addition

With the hydroacylation and elimination conditions in hands, we then focused on the last step, aiming to develop a high yielding conjugate addition that would also be compatible with the reaction conditions employed in previous steps.

Miyaura and co-workers first reported the rhodium-catalysed conjugate addition of boronic acids to methyl vinyl ketone with a catalytic amount of neutral rhodium precursor [Rh(acac)(CO)₂] coupled to an achiral bidentate phosphine ligand (Figure 2.1).^{82a} The reaction cleanly delivered the desired Michael addition adduct with excellent yields in a range of solvents (mixture of methanol, DMF or cyclohexane with water). Additionally, they found the bite angle of the ligands to be critical to the reaction conversion with better results obtained from large bite angle values: dppb > dppp > dppe.⁸⁶

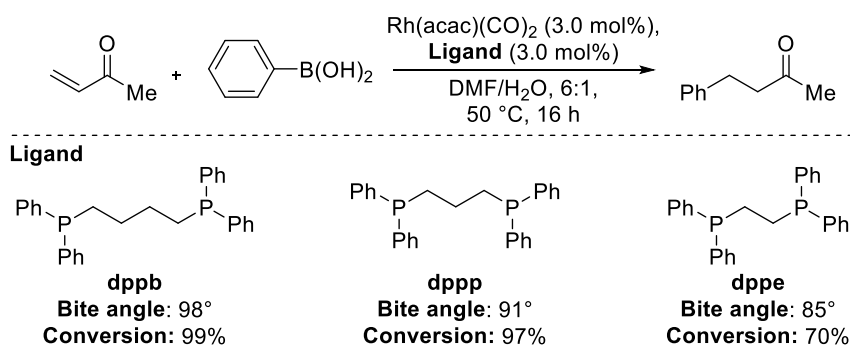
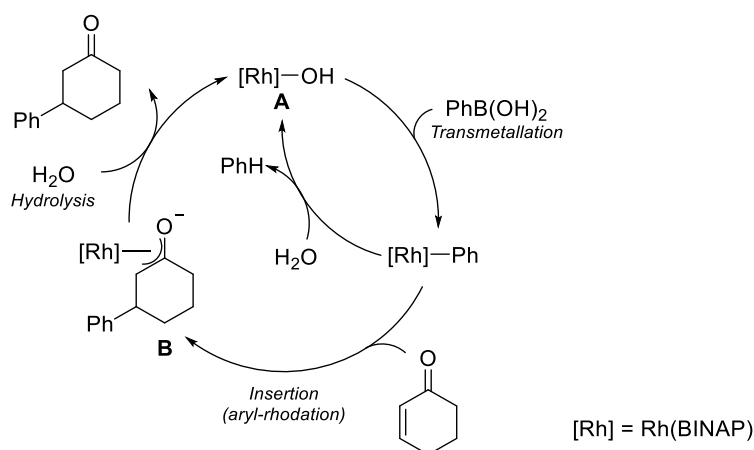


Figure 2.1 Bidentate diphenylalkylphosphine ligands

Only one year later, Hayashi reported the first enantioselective rhodium-catalysed 1,4-addition of aryl and alkenyl boronic acids using BINAP ligands.⁸⁷ This reaction, which has become the benchmark for asymmetric conjugate addition of boronic acids, has proved tolerant to a wide range of electron-rich and electron-poor boronic acids, and of both cyclic and acyclic α,β -unsaturated ketones. The generally accepted mechanism was reported in 2002 by Hayashi and co-workers, who have isolated and characterised the key intermediates of the catalytic cycle using racemic BINAP ligand (Scheme 2.5).⁸⁸ Unlike the hydroacylation reaction, the 1,4-conjugate addition is a neutral redox process whose active species was found to be the rhodium-hydroxyl complex **A**. The catalytic cycle initiates with a transmetallation step, followed by the insertion of the phenyl group into the double bond and the formation of the oxo- π -allylrhodium intermediate **B**. Hydrolysis of **B** delivers the desired product with regeneration of the rhodium catalyst. Excess amounts of boronic acid are often employed as protodeborylation was found to be the main competing side-reaction.



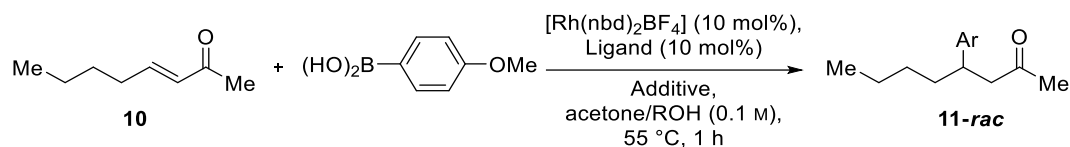
Scheme 2.5 General mechanism of the rhodium-catalysed 1,4-conjugate addition

Over the last fifteen years, numerous asymmetric processes have been developed and many catalytic systems have proved effective for the transformation, with chiral phosphine ligands,⁸⁷ phosphoramidites,⁸⁹ and chiral dienes dominating the field and achieving both excellent yields and high enantioselectivities.⁹⁰

Based on these previous studies, we first investigated the racemic 1,4-conjugate addition of (4-methoxyphenyl)boronic acid with commercially available (*E*)-oct-3-en-2-one **10** using a rhodium(I) catalyst in combination with different ligands and additives. Although acetone has

never been reported as a suitable solvent for this transformation, we employed it in mixture with water or other protic solvents, as these are necessary to the formation of the rhodium-hydroxyl complex and the hydrolysis of the oxo- π -allylrhodium intermediate in the catalytic cycle. We started our additive screening with potassium carbonate which is commonly employed in rhodium-catalysed 1,4-addition reactions. With a 10 mol% catalyst loading, the reaction was found to be successful with racemic BINAP (Table 2.2, entry 1), and full conversion was achieved after four hours at 55 °C. Surprisingly, the small bite angle dcpm ligand delivered the desired ketone product **11-rac** with full conversion of the starting material in a shorter reaction time (entry 2), and the transformation proved as efficient with sub-stoichiometric quantities of K_2CO_3 (entry 3). Disappointingly, when employing CuMeSal as a base, which had been found most efficient for the previous elimination step, no conversion was observed (entry 4). Similarly, CuTC and Ag_2CO_3 did not deliver any product (entries 5 and 6). This could be explained by the poor solubility of copper salts and silver carbonate in semi-aqueous media as clusters of salts were observed in the acetone/water solvent system. With Ag_2CO_3 , CuTC, and CuMeSal not promoting any conjugate addition, it was unlikely that we could use a single additive for both the elimination and the 1,4-addition reactions.

Anticipating that our one-pot sequence would require CuMeSal for the elimination step, and K_2CO_3 for the 1,4-conjugate addition, we next assessed the compatibility of the combination of the two additives. Disappointingly, a low 28% conversion was achieved when the reaction was performed in an acetone/water mixture (entry 7). Here again, we justified this poor reactivity by a lack of solubility of the inorganic salts in the reaction mixture. By replacing water with methanol as the protic source, the conversion was considerably enhanced, enabling us to achieve 87% conversion (entry 8). This result was not further improved by either using additional amounts of K_2CO_3 or changing the acetone/methanol ratio (entries 9 and 10).



Entry	Ligand	Additive (equiv)	ROH (%)	time	NMR conversion
1	<i>rac</i> -BINAP	K ₂ CO ₃ (1.0)	H ₂ O (10%)	4 h	100%
2	dcpm	K ₂ CO ₃ (1.0)	H ₂ O (10%)	1 h	100%
3	dcpm	K ₂ CO ₃ (0.2)	H ₂ O (10%)	1 h	100%
4	dcpm	CuMeSal (1.0)	H ₂ O (10%)	1 h	0%
5	dcpm	CuTC (1.0)	H ₂ O (10%)	1 h	0%
6	dcpm	Ag ₂ CO ₃ (1.0)	H ₂ O (10%)	1 h	0%
7	dcpm	K ₂ CO ₃ (1.0) + CuMeSal (1.0)	H ₂ O (10%)	1 h	28%
8	dcpm	K₂CO₃ (1.0) + CuMeSal (1.0)	MeOH (10%)	1 h	87%
9	dcpm	K ₂ CO ₃ (1.5) + CuMeSal (1.0)	MeOH (10%)	1 h	85%
10	dcpm	K ₂ CO ₃ (1.0) + CuMeSal (1.0)	MeOH (30%)	1 h	76%

Table 2.2 Additive screening for the 1,4-conjugate addition

As the aim of our project also was to develop an enantioselective method, we assessed two chiral diene ligands developed by Hayashi (L1) and Lam (L2) for the asymmetric 1,4-conjugate addition (Table 2.3).^{91,92} These ligands were chosen as excellent enantioselectivities were obtained in the report from the Willis group involving the combination of alkyne hydroacylation and subsequent 1,4-conjugate addition of boronic acids to the resulting β -substituted ketones (see Scheme 2.2).⁸¹ Under the standard conditions using potassium carbonate as the base and preformed [Rh(L)Cl]₂ complexes, full conversion was reached and the desired ketone product **11** was pleasingly isolated in excellent yields and high enantioselectivities with both ligands (entries 1 and 2). When employing a mixture of K₂CO₃ and CuMeSal, **11** was isolated in 88% yield and the enantioselectivity was not affected by the presence of CuMeSal additive (entry 3). This slightly lower conversion obtained when adding CuMeSal had already been observed under the racemic conditions (see Table 2.2, entries 2 and 8); however, when comparing the chiral catalyst system with the racemic one, the conversion was found to be higher (94% vs 87%) even with a lower catalyst loading of 2.5 mol% (5 mol% with respect to rhodium).

Entry	Additive (equiv)	L	NMR conversion	Isolated yield, ee
1	K ₂ CO ₃ (1.0)	L1	100%	94%, 98% ee
2	K ₂ CO ₃ (1.0)	L2	100%	95%, 98% ee
3	K ₂ CO ₃ (1.0) + CuMeSal (1.0)	L2	94%	88%, 98% ee

Table 2.3 Assessment of chiral diene ligands L1 and L2 for the conjugate addition

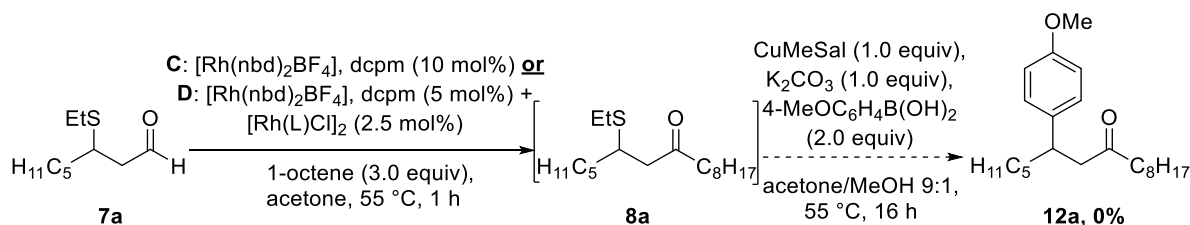
2.2.2 Towards a one-pot procedure

With the optimised reaction conditions established for each individual step, we then turned our attention to combining them in a one-pot procedure. From the results obtained during the optimisation, we thought we could employ: a single catalytic system **C** ([Rh(nbd)₂]BF₄/dcpm) to access racemic products since this complex was found to be effective for both hydroacylation and racemic 1,4-addition; or a combination of two catalytic systems **D** ([Rh(nbd)₂]BF₄/dcpm and [Rh(L)Cl]₂) to prepare the enantioenriched products. Our first aim was thus to find suitable reaction conditions which would allow the use of one or two rhodium complexes added from the beginning of the process, with an ideal catalyst loading equal to or less than 10 mol%.

2.2.2.1 Single addition of rhodium source(s) from the start

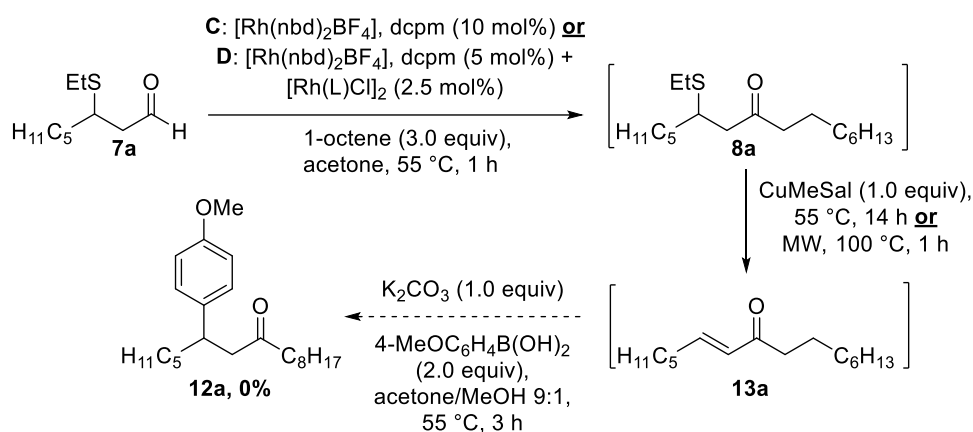
The idea of a single addition of rhodium catalyst(s) at the beginning of the process entailed several options. A major concern that arose during the optimisation of the elimination step was the long reaction time required to achieve completion of the reaction. Therefore, we first assessed the simultaneous addition of both the elimination and the 1,4-conjugate addition reagents to the reaction mixture upon completion of the hydroacylation step (Scheme 2.6). In this case, we thought that the presence of the conjugate addition reagents could aid the progressive consumption of the enone intermediate, and therefore promote the elimination step. Unfortunately, ketone product **12a** was not observed with either catalytic system **C** or **D** when employing 3-(ethylthio)octanal **7a**,

1-octene and (4-methoxyphenylboronic acid); only a mixture of hydroacylation product and α,β -unsaturated ketone was recovered, suggesting that the elimination did not even reach completion under these reaction conditions.



Scheme 2.6 Addition of rhodium sources from beginning, and concomitant elimination-conjugate addition

We next evaluated the tandem process involving the addition of either catalytic system **C** or **D** from the beginning and the sequential addition of all the other reagents into the reaction vial, one step after another (Scheme 2.7). This involved in particular a 14-hour elimination step that could alternatively been carried out in a shorter reaction time under microwave irradiation, before adding the boronic acid and the base necessary to the last step. As expected, this option was quickly abandoned as no conjugate addition product was observed and α,β -unsaturated ketone **13a**, the product of elimination, was systematically recovered. This was likely due to the loss of activity of the catalytic systems upon completion of the first two steps.



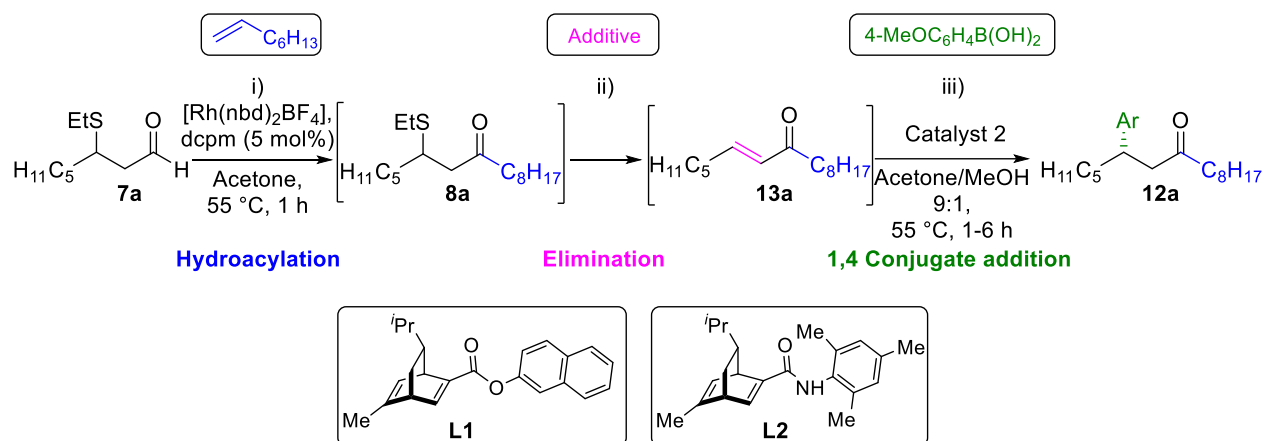
Scheme 2.7 Addition of rhodium sources from the beginning, and sequential elimination-conjugate addition

2.2.2.2 Separate addition of rhodium sources

Based on the disappointing results obtained from a single addition of rhodium catalysts from the beginning, we next focused on their sequential addition, meaning that the conjugate addition

rhodium catalyst was added to the reaction mixture together with the boronic acid after the elimination step, but still in a one-pot fashion. Optimised conditions having been established for the three steps, the advantage of this sequential approach was the possibility to first reach completion of the slowest elimination step before adding a fresh catalyst to promote the final step. Hence, we evaluated different conditions for the sequential process starting with aldehyde **7a** (Table 2.4). When combining the three steps by adding the sets of reagents to the reaction mixture one by one and carrying out the elimination step overnight with CuMeSal, ketone **12a-rac** was isolated in 26% yield with racemic BINAP (entry 1). More encouragingly, the desired product was obtained in 49% yield and 96% ee using [Rh(L2)Cl]₂ for the final step (entry 2). Both TLC and HPLC analysis suggested that the conjugate addition did not reach completion, even though this reaction had previously been optimised in the presence of copper salts. The overall yield under the racemic conditions was further improved to 60% by incorporating an *in-situ* filtration of the reaction mixture through celite under nitrogen between the second and the last step, allowing the removal of inorganic salts (entry 3). This technique was successful with both L1 and L2, delivering the products in even higher yields than under the racemic conditions (entries 4 and 5).

Finally, the use of a mixture of MeOTf and K₂CO₃ for the elimination step without further addition of base during the conjugate addition step enabled the fast combination of the three steps that performed in one hour each without the need of filtering the reaction mixture. Under these reaction conditions, the product **12a** was isolated in 85% yield and 97% ee with L1, which was chosen for the reaction scope over L2 given its commercial availability.



Entry	Elimination			Conjugate addition			Yield (%)	ee (%)
	Additive (equiv)	time	filtration	Catalyst 2 (mol%)	ArB(OH) ₂ (equiv)	K ₂ CO ₃ (equiv)		
1 ^a	CuMeSal (1.0)	14 h	No	Rh(nbd) ₂ BF ₄ / <i>rac</i> -BINAP (5)	2.0	1.0	26	-
2	CuMeSal (1.0)	14 h	No	[Rh(L2)Cl] ₂ (2.5)	2.0	1.0	49	96
3	CuMeSal (1.0)	14 h	Yes	Rh(nbd) ₂ BF ₄ / <i>rac</i> -BINAP (5)	2.0	1.0	60	-
4	CuMeSal (1.0)	14 h	Yes	[Rh(L2)Cl] ₂ (2.5)	2.0	1.0	83	98
5	CuMeSal (1.0)	14 h	Yes	[Rh(L1)Cl] ₂ (2.5)	2.0	1.0	82	98
6	MeOTf (1.5)+ K₂CO₃ (2.5)	1 h	No	[Rh(L1)Cl]₂ (2.5)	1.5	0	85	97

a. Experiment carried out by Ming Gao

Table 2.4 Optimisation of the sequential procedure

2.2.3 Scope of the reaction

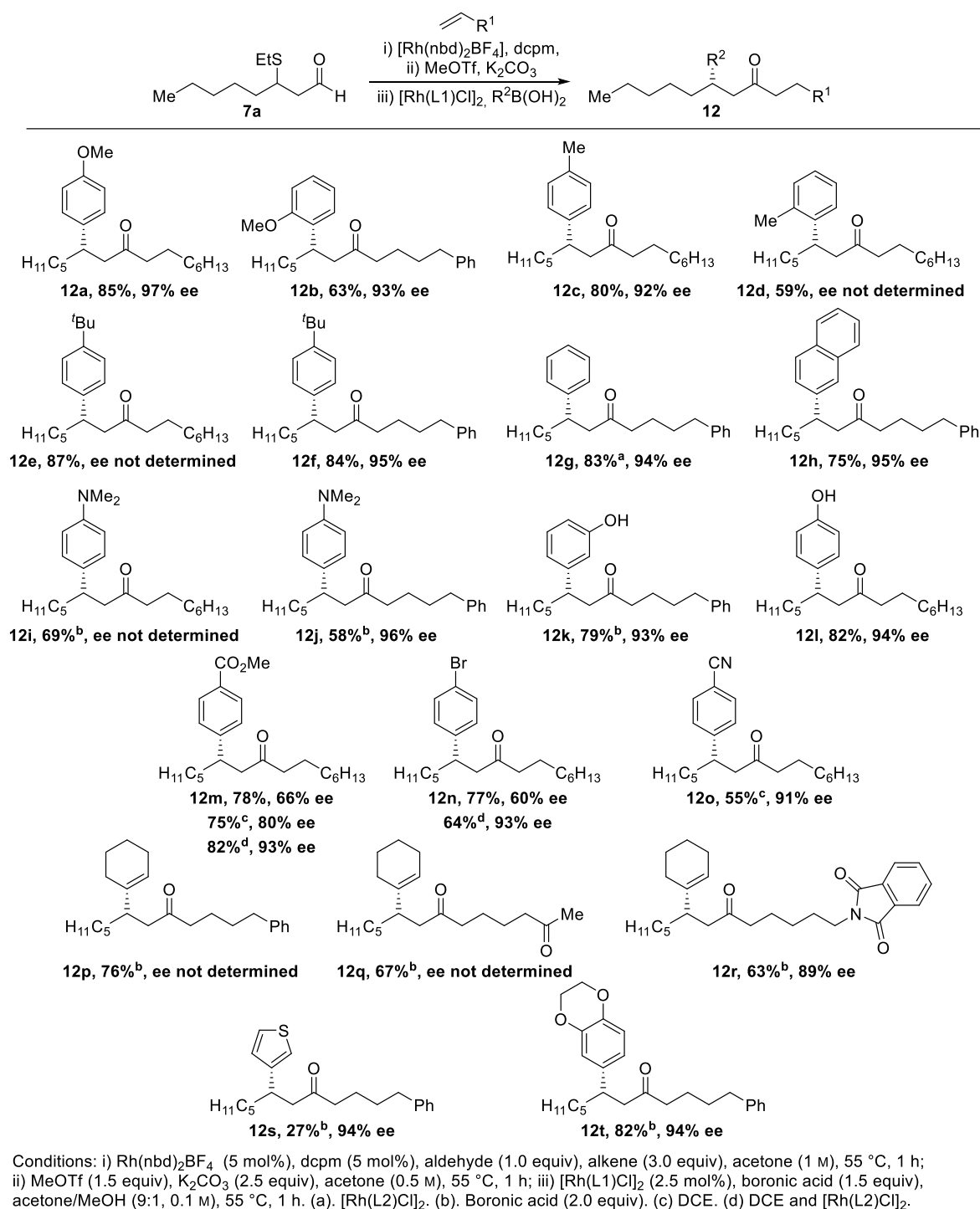
With the optimal reaction conditions in hand, we next investigated the scope of the reaction.

2.2.3.1 Boronic acid scope

The tolerance of the reaction towards a variety of boronic acids was first examined using aldehyde **7a** (Scheme 2.8). 1-Octene was initially selected as the hydroacylation coupling partner. However, 4-phenyl-1-butene was alternatively employed when encountering difficulties in the separation of enantiomers by chiral HPLC, preventing us from determining the enantiomeric excess (ee). For the preparation of racemic products, a large scale tandem hydroacylation/elimination reaction allowed the preparation of the enone intermediate, which was further reacted with a variety of boronic acids using either dcpm or racemic BINAP ligands.

The transformation was successfully applied to diversely substituted arylboronic acids bearing electron-donating groups (**12a-l**), including basic amines (**12i**, **12j**) and unprotected phenols (**12k**, **12l**). The desired products were isolated in good yields (58-87%) and high enantioselectivities (>92% ee). It is worth mentioning that not only *para*- but also *meta*-(**12k**) and *ortho*-(**12b**, **12d**) substituents could be incorporated. On the other hand, electron-withdrawing functional groups on the boronic acid moiety delivered the products in lower enantioselectivities (**12m**, **12n**) under the standard reaction conditions. This issue was overcome by switching the solvent from acetone to 1,2-dichloroethane (DCE) and using [Rh(L2)Cl]₂ instead of [Rh(L1)Cl]₂. Under these modified conditions, **12m** and **12n** were obtained in similar yields but higher enantioselectivities. Reactive groups such as ester (**12m**) and cyano (**12o**) groups were well tolerated. Alkenylboronic acids also showed good reactivity (**12p-r**), with the use of more polar alkenes for the hydroacylation having been necessary to obtain a chromatographic separation by chiral HPLC and determine the enantioselectivity (**12r**). Finally, the tandem sequence involving heteroarylboronic acids was found more challenging. No reactivity was observed when employing 3-furanylboronic acid, and only 27% yield was obtained from 3-thienylboronic acid (**12s**). These substrates have been known to deliver poor conversions under long reaction times, and previous reports have shown that only specific reaction conditions could deliver higher yields.⁹³ However, benzodioxane boronic acid gave **12t** in good yields.

Having achieved yields ranging from 27% to 87% and enantiomeric excesses all above 89%, we next evaluated the scope of the process with respect to the alkene component.

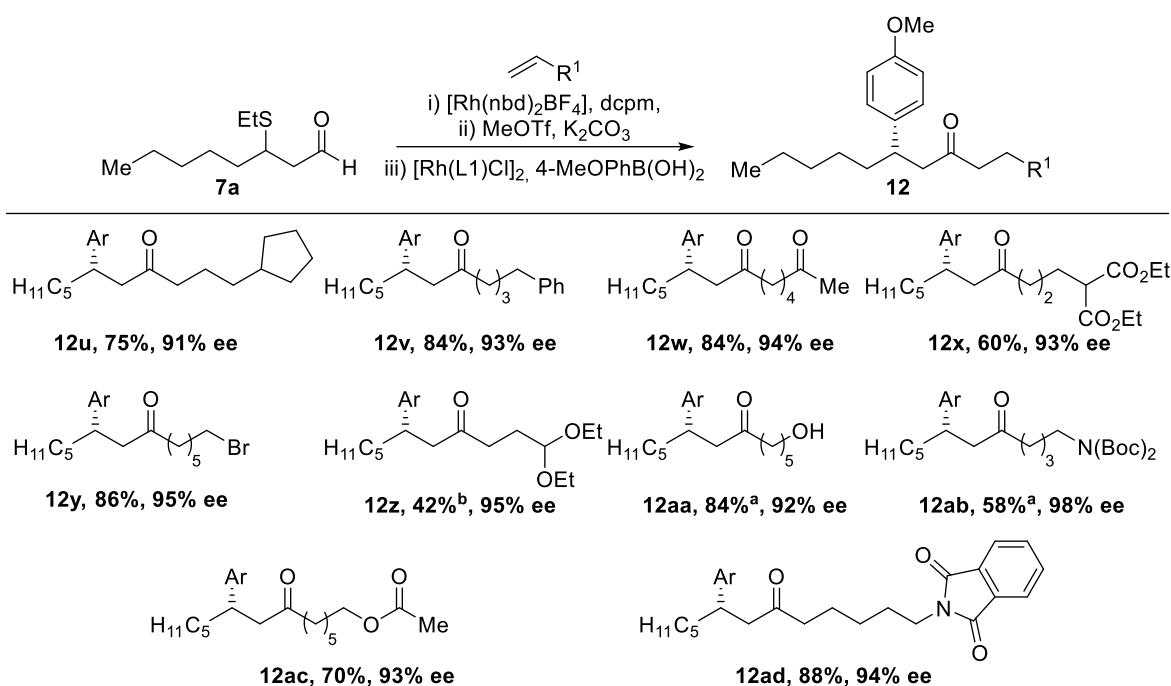


Scheme 2.8 Variation of the boronic acid component

2.2.3.2 Alkene scope

The scope of the alkene component was entirely examined by DPhil student Ming Gao using aldehyde **7a** and *para*-methoxyphenylboronic acid (Scheme 2.9). Alkenes possessing carbocyclic (**12u**), aryl (**12v**) or carbonyl groups (**12w**, **12x**) were well tolerated and yielded the corresponding

ketone products all in good yields and excellent enantioselectivities. Other useful functional groups such as bromo (**12y**) or acetal (**12z**) could be incorporated, and we were also able to carry out a gram-scale reaction with 6-bromo-1-hexene. Starting with 6.0 mmol of aldehyde **7a**, the catalyst loadings for the hydroacylation and conjugate addition steps could be reduced to 2 mol% and 1 mol%, respectively, without any loss of yield or enantioselectivity. Additionally, the use of CuMeSal for the elimination step allowed the use of alkene substrates containing free alcohol and Boc-protected amines (**12aa**, **12ab**). Finally, alkenes incorporating an acetate or phthalimide group were also found to be excellent substrates (**12ac**, **12ad**).



All these products were prepared by Ming Gao

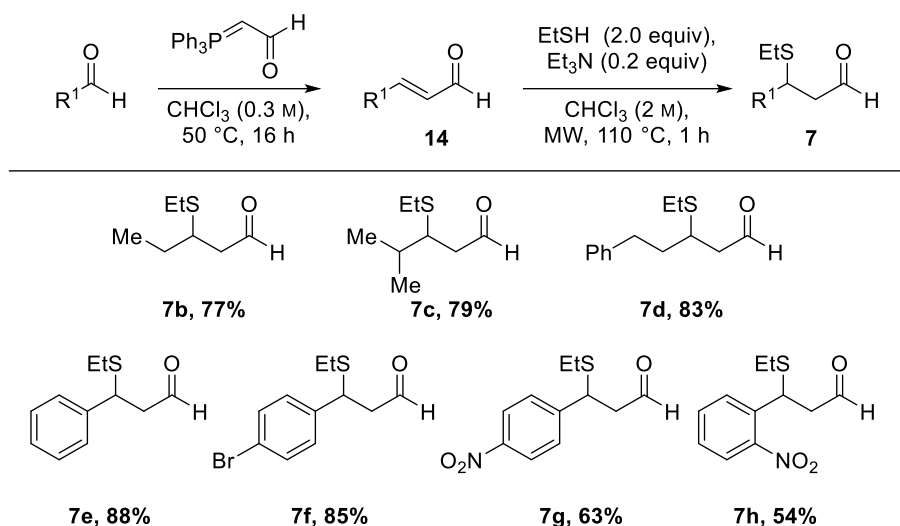
Conditions: i) $\text{Rh}(\text{nbd})_2\text{BF}_4$ (5 mol%), dcpm (5 mol%), aldehyde (1.0 equiv), alkene (3.0 equiv), acetone (1 M), 55 °C, 1 h; ii) MeOTf (1.5 equiv), K_2CO_3 (2.5 equiv), acetone (0.5 M), 55 °C, 1 h; iii) $[\text{Rh}(\text{L1})\text{Cl}]_2$ (2.5 mol%), boronic acid (1.5 equiv), acetone/MeOH (9:1, 0.1 M), 55 °C, 1 h. (a). CuMeSal (1.0 equiv). (b). ArB(OH) $_2$ (3.0 equiv) for 14 h.

Scheme 2.9 Variation of the alkene component

2.2.3.3 Aldehyde synthesis and scope

To finish our study, we finally evaluated the reaction with a series of β -sulfide-containing aldehydes. For this purpose, we first prepared a variety of β -thioethyl-substituted aldehydes **7** by engaging the corresponding α,β -unsaturated aldehydes **14** in a thio-Michael addition with ethyl mercaptan and sub-stoichiometric amounts of triethylamine in chloroform (Scheme 2.10). The enal substrate **14** was either purchased from commercial suppliers, or prepared by Wittig reaction with

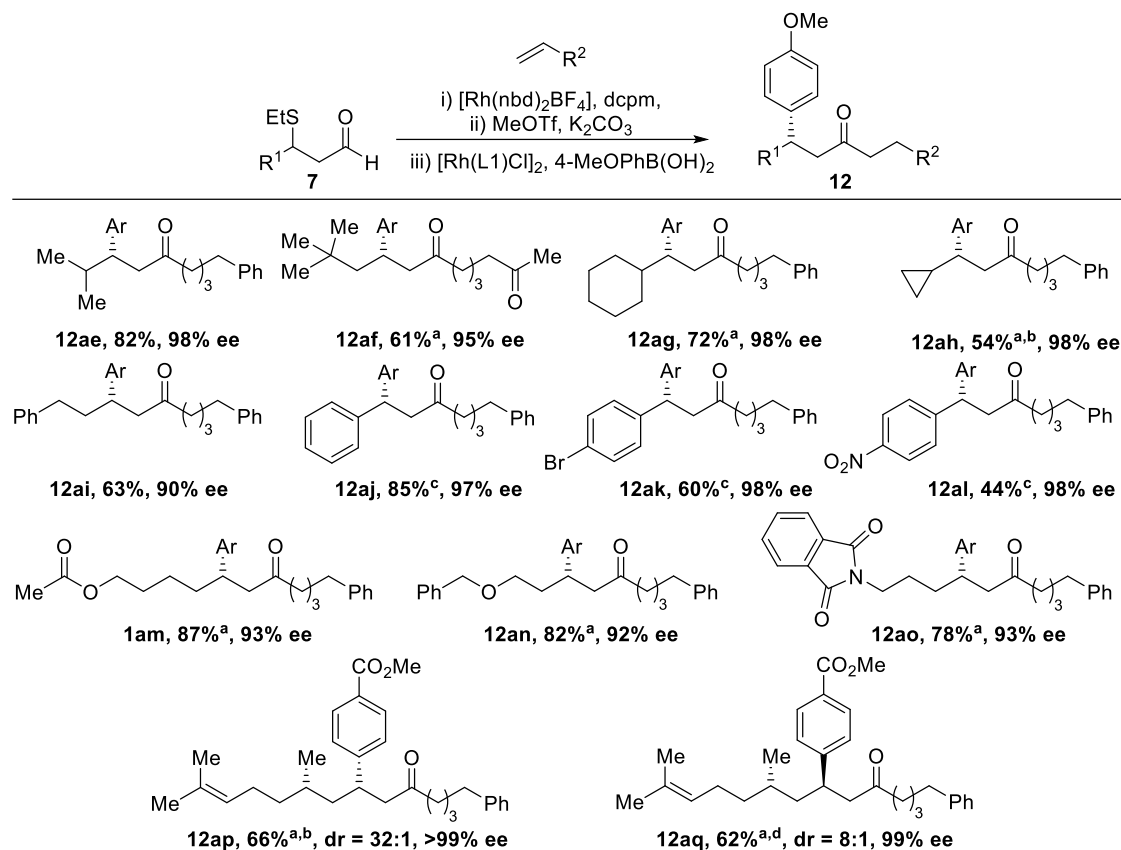
(triphenylphosphoranylidene)acetaldehyde.⁹⁴ The preferred protocol for the subsequent Michael addition was carried out under microwave irradiation at 110 °C for one hour. Alternatively, large scale reactions were set up overnight under conventional heating at 60 °C. This protocol efficiently delivered aldehyde substrates with either alkyl (**7b-d**) or aryl (**7e-h**) substituents. The aldehyde substrates prepared by Ming Gao have not been included in the scheme below.



Scheme 2.10 Preparation of the aldehyde starting materials

We next applied our optimised reaction conditions using the synthesised aldehydes (footnote added on products prepared by Ming Gao, Scheme 2.11). A variety of alkyl groups was successfully introduced, including different levels of steric hindrance and carbocyclic groups (**12ae-ai**). In general, the lower yields were due to a less effective hydroacylation step. Aldehydes containing aromatic rings at the β -position were also applicable to the reaction, allowing excellent levels of stereocontrol (**12aj-al**). The products, however, were obtained in reduced yields, especially with electron-withdrawing substituents. A variety of functional groups on the aldehyde component, including ether, ester and phthalimide were also well tolerated (**12am-ao**). Additionally, an *S*-citronellal moiety was incorporated in the final product (**12ap** and **12aq**), giving *S,S*-ketone **12ap** in a good yield and excellent diastereoselectivity under the standard reaction conditions. The *S,R*-product **12aq** was also obtained using a Rh(I)/(*S*)-BINAP catalyst formed *in-situ* for the conjugate addition step. The reduced diastereoselectivity observed in this case mainly resulted from a decreased selectivity from (*S*)-BINAP ligand compared to the chiral diene ligand since the product

obtained from racemic BINAP displayed a poor diastereomeric ratio of 1:1.5. This indicated that the stereogenic centre present in the aldehyde starting material had a negligible effect on the stereoselectivity observed.



Conditions: i) $\text{Rh}(\text{nbd})_2\text{BF}_4$ (5 mol%), dcpm (5 mol%), aldehyde (1.0 equiv), alkene (3.0 equiv), acetone (1 M), 55 °C, 1 h; ii) MeOTf (1.5 equiv), K_2CO_3 (2.5 equiv), acetone (0.5 M), 55 °C, 1 h; iii) $[\text{Rh}(\text{L}1)\text{Cl}]_2$ (2.5 mol%), boronic acid (1.5 equiv), acetone/MeOH (9:1, 0.1 M), 55 °C, 1 h. (a). Products made by Ming Gao. (b) CuMeSal (1.0 equiv). (c) boronic acid (2.0 equiv). (d) $[\text{Rh}(\text{nbd})_2\text{BF}_4]/\text{S-BINAP}$ (5 mol %), boronic acid (3.0 equiv).

Scheme 2.11 Variation of the aldehyde component

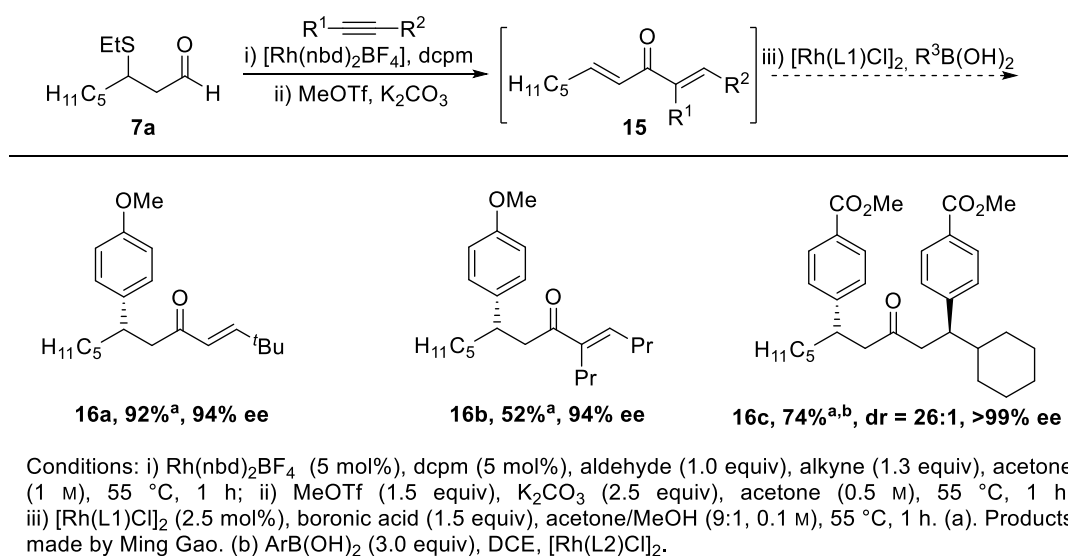
2.2.4 Product derivatisation

With a reasonably wide scope for the boronic acid, alkene, and aldehyde components, we next turned our attention to product derivatisation and application of our methodology.

2.2.4.1 Mono- and double conjugate addition

Anticipating that divinyl ketone intermediates **15** could be accessed *via* an alkyne intermolecular hydroacylation followed by the sulfide elimination, we envisaged the possibility of a substrate-controlled regioselective conjugate addition (Scheme 2.12). Thus, DPhil student Ming Gao investigated the one-pot sequence with three different alkynes. Pleasingly, the introduction of a

sterically encumbering *tert*-butyl group by alkyne hydroacylation completely suppressed the conjugate addition on the adjacent carbon, allowing for a regioselective mono-conjugate addition process delivering **16a** in an excellent yield and high enantioselectivity. Similar regioselectivity could be achieved by utilising an internal alkyne (**16b**), with the presence of an α -substituent significantly decreasing the nucleophilic addition at the adjacent carbon. On the other hand, double conjugate addition was possible when using a less sterically demanding alkyne as the hydroacylation coupling partner, yielding highly functionalised ketone **16c** in a good yield and excellent levels of diastereo- and enantiocontrol.

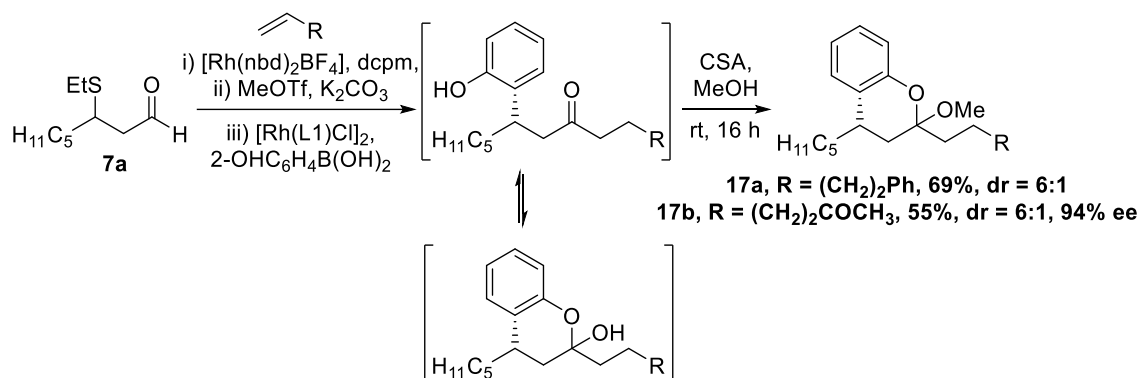


Scheme 2.12 One-pot sequence with alkyne hydroacylation and mono/double conjugate addition

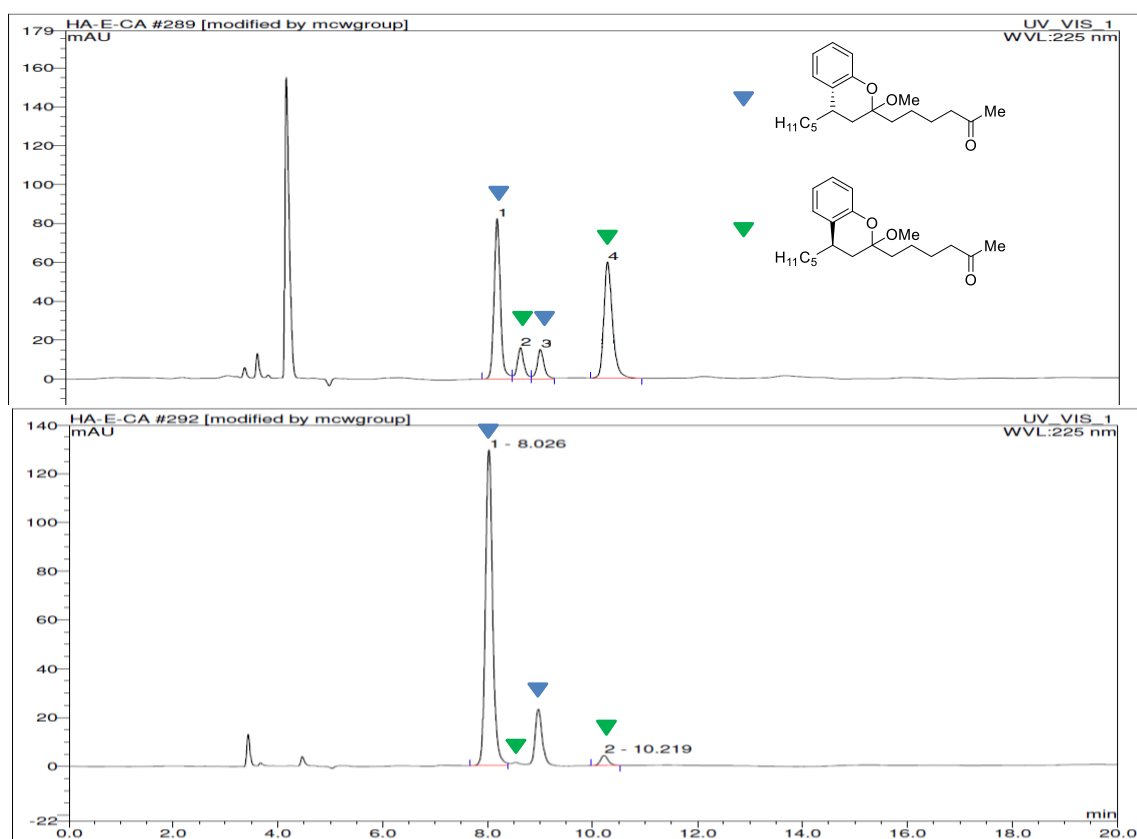
2.2.4.2 Preparation of *O*-containing heterocycles

Having established an efficient methodology for the preparation of a range of functionalised ketones in a single step, we next explored the utility of our methodology for the synthesis of useful heterocyclic motifs and envisioned the preparation of chromane derivatives by applying our methodology with suitable boronic acids. When employing aldehyde **7a** and 2-hydroxyphenylboronic acid, with either 5-hexen-2-one or 4-phenyl-1-butene as the alkene component, mixtures of products were obtained (Scheme 2.13). Analysis of the ^{13}C NMR spectra suggested the presence of both the ketone product and the lactol, which could not be separated by column chromatography. However, upon treatment of the mixture with camphorsulfonic acid in methanol, the corresponding ketal products **17a** and **17b** were isolated in good overall yields for the

four-step process. Both products displayed a diastereomeric ratio of 6:1, and similar diastereoselectivities were obtained with the corresponding racemic products. However, the structure of the products rendered the determination of the relative configuration challenging by NMR experiments.

Scheme 2.13 Sequential formation of ketals **17a** and **17b**

Additionally, the measurement of the enantiomeric excess required the separation of four peaks which was only achieved with compound **17b** (94% ee) (Figure 2.2).

Figure 2.2 Separation of the four isomers of **17b**

The enantiomeric excess of **17a** was obtained by determining the value of a derivatised compound. The ketal **17a** (dr = 6:1) was thus reduced upon treatment with triethylsilane and boron trifluoride diethyl etherate in dichloromethane (Figure 2.3). The reaction enabled the preparation of the chromane derivative **18**, which was isolated in 85% yield with a high level of diastereoselectivity (dr = 25:1). Additionally, NOESY experiments allowed us to determine the relative configuration of chromane **18** thanks to the strong correlation observed between the two protons located on the two stereogenic centres.

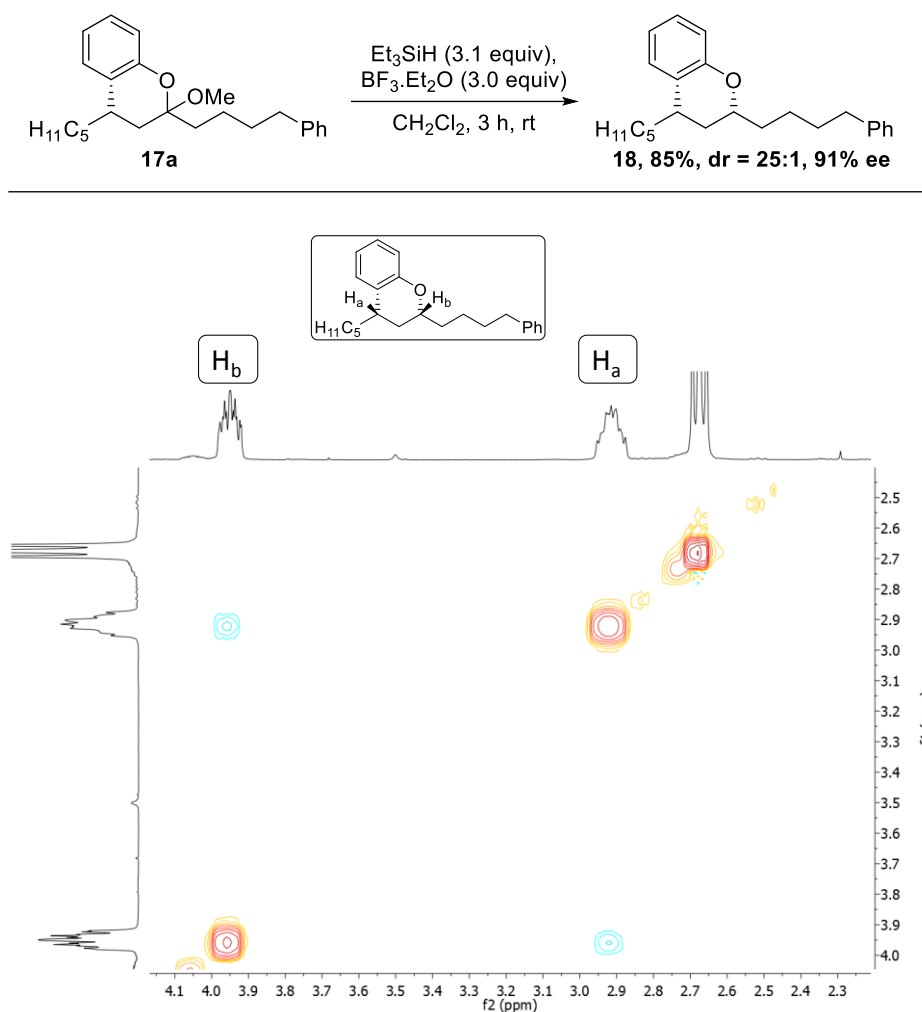
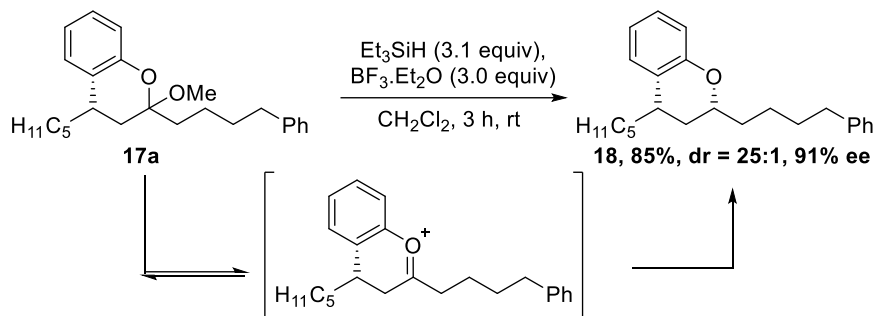


Figure 2.3 NOESY spectrum for the determination of the configuration

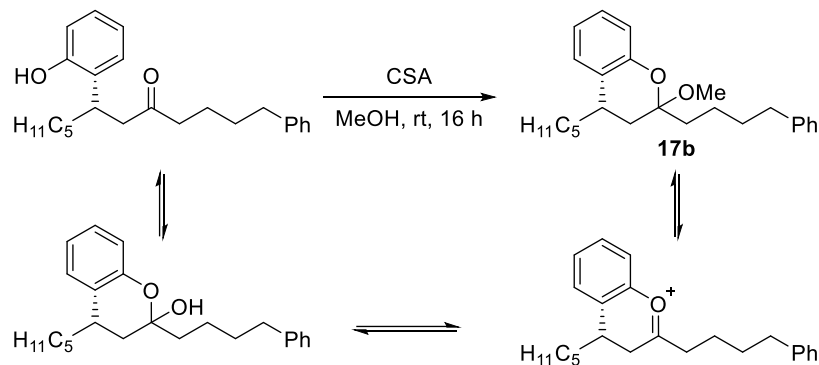
The high level of diastereoselectivity observed compared to ketals **17a** and **17b** could be rationalised by the thermodynamics and kinetics of the formation of the different products **17a**, **17b** and **18**. When reducing **17a**, although the formation of the cyclic oxonium is in an equilibrium, the attack of the hydride nucleophile is irreversible (Scheme 2.14a). In this case, the high

diastereoselectivity could be explained by the important steric effect of the β -stereogenic centre introduced in the conjugate addition step. On the other hand, all the steps leading to the formation of ketals **17a** and **17b** should be reversible (Scheme 2.14b). In this case, the diastereoselectivity is poorer, possibly due to a competitive anomeric effect.

(a) Formation of chromane by reduction

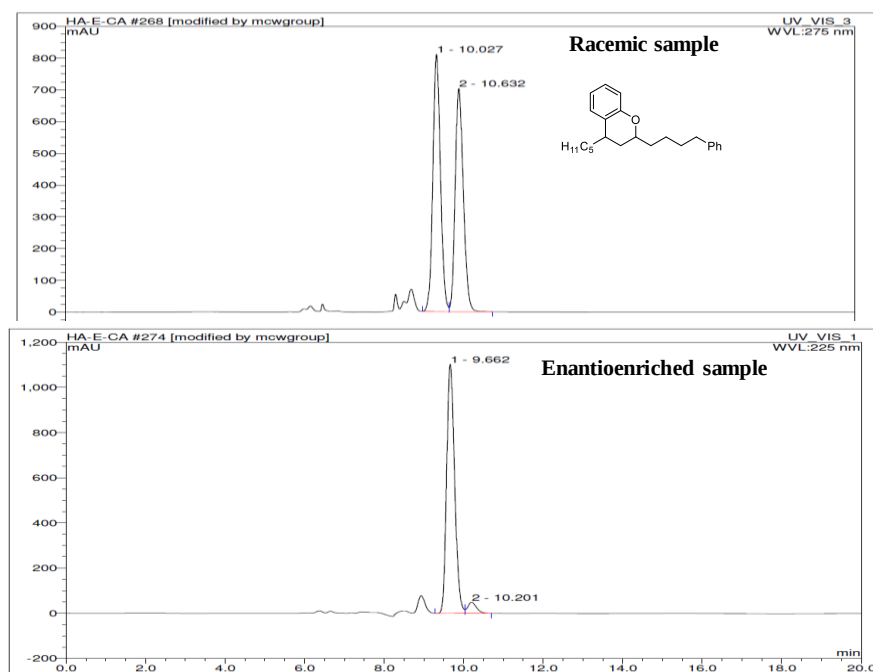


(b) Formation of ketal

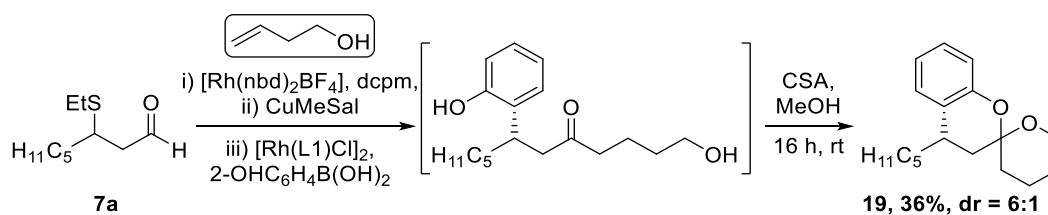


Scheme 2.14 Origins of the different diastereoselectivities observed

Pleasingly, the derivatisation of the ketal into the chromane product **18** enabled us to separate the two enantiomers by chiral HPLC, allowing the determination of the enantiomeric excess (Figure 2.4, 91% ee).

Figure 2.4 Determination of the ee for chromane **18**

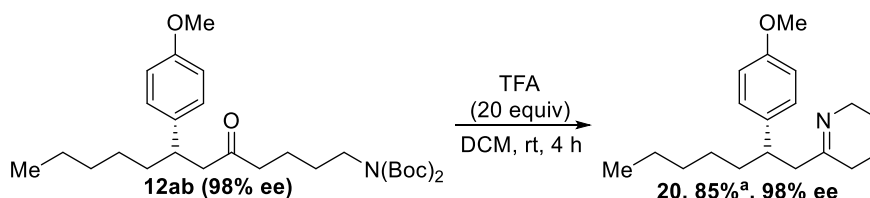
Following these results, we also envisaged the formation of spiro-ketals through intramolecular trapping of oxonium intermediates with an internal hydroxyl functional group, using 3-buten-1-ol as an alternative alkene coupling partner (Scheme 2.15). From the previous evaluation of the alkene scope, we knew that unprotected hydroxyls could be tolerated on the alkene component by employing CuMeSal additive for the elimination of the ethyl sulfide. Thus, we investigated the tandem sequence using aldehyde **7a**, 3-buten-1-ol and 2-hydroxyphenylboronic acid. Attempts in isolating the intermediate (as a mixture of ketone/lactol) only resulted in loss of substrate since the spiro-ketalisation started under the conjugate addition reaction conditions. Direct treatment of the crude material with methanol and CSA enabled the isolation of spiro-ketal **19** in 36% overall yield and a diastereomeric ratio of 6:1. Disappointingly, we were not able to determine the enantiomeric excess of this spiro-ketal by chiral HPLC and the diastereoselectivity was not further improved when heating the reaction mixture, or adding additional equivalents of reagents.



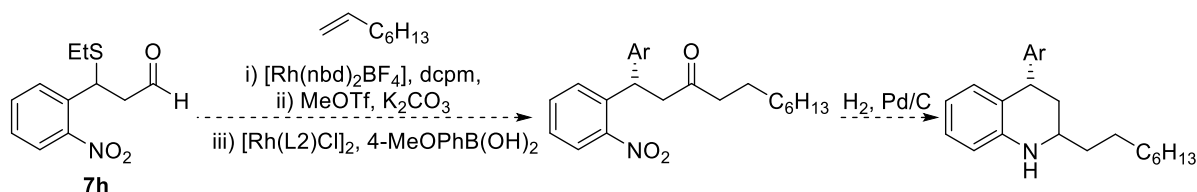
Scheme 2.15 Spiro-ketal preparation

2.2.4.3 Preparation of *N*-containing heterocycles

Several options taking advantage of the tandem sequence were evaluated for the formation of *N*-containing heterocycles. We started our investigation by treating the product **12ab** under acidic conditions and obtained the corresponding tetrahydropyridine **20** in 85% yield with no loss of enantiopurity (Scheme 2.16).

Scheme 2.16 Derivatisation of **12ab** for the formation of tetrahydropyridine derivatives

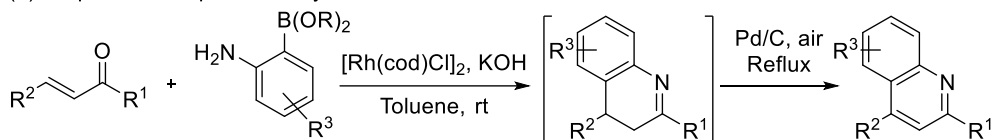
We also assessed our methodology with 2-nitrophenyl aldehyde **7h**, assuming that we could obtain the desired product and further engage it in a reduction/intramolecular cyclisation to form tetrahydroquinolines (Scheme 2.17). Unfortunately, the tandem sequence was found to be unsuccessful, with the hydroacylation not reaching completion and the last 1,4-addition step not proceeding with this substrate.



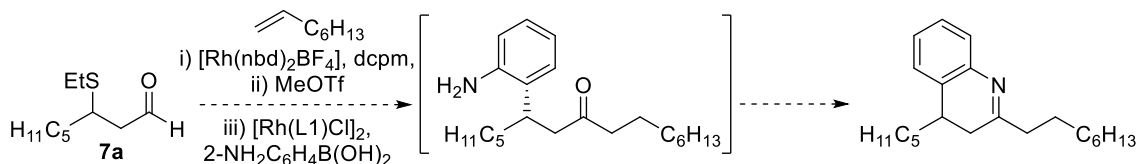
Scheme 2.17 Strategy envisioned for the preparation of tetrahydroquinolines

Inspired by a report from Marsden and co-workers involving the 1,4-conjugate addition of 2-aminophenylboronic acids for the one-pot synthesis of quinolines (Scheme 2.18a),^{84b} we also envisioned accessing *N*-containing heterocycles by applying our methodology with the same strategy (Scheme 2.18b). However, when employing aldehyde **7a** and 1-octene, the rhodium-catalysed 1,4-conjugate addition of 2-aminophenylboronic acid did not occur. This could be explained by the incompatibility of our reaction conditions with the use of unprotected 2-aminophenylboronic acid.

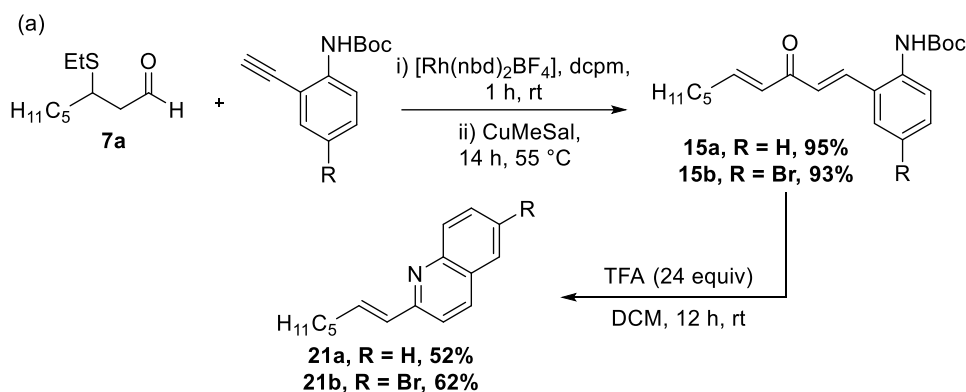
(a) Preparation of quinolines by Marsden and co-workers



(b) Aim with our methodology

Scheme 2.18 Towards *N*-containing heterocycles

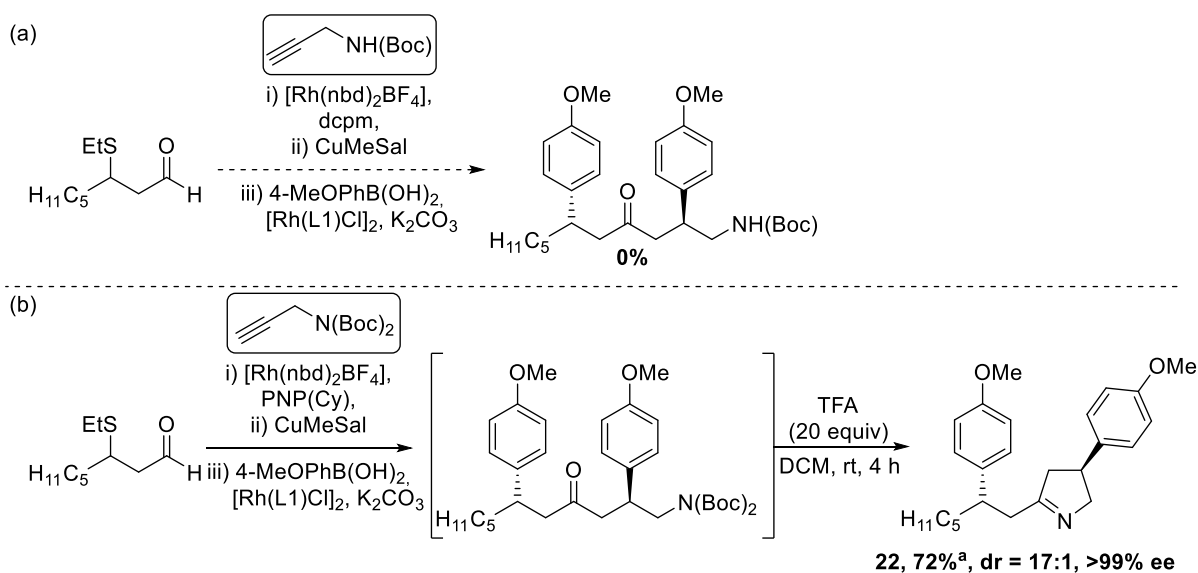
Another strategy envisaged to prepare quinoline derivatives involved changing the alkyne component instead of the boronic acid.^{84a} With aldehyde **7a** and two different alkynyl-anilines, both hydroacylation and copper-mediated sulfide elimination proceeded well. However, no conjugate addition occurred under the standard reaction conditions employing 4-methoxyphenylboronic acid (Scheme 2.19). The 1,4-addition was then assessed using the isolated divinyl ketones **15a** and **15b**, but the reaction still proved unsuccessful. This could be explained by the presence of a mono-protected amine group strongly coordinating to the rhodium, hence decreasing its reactivity. The ketones **15a** and **15b** were still considered as useful traceless hydroacylation products. In this context, we subjected the two divinyl ketones to acidic conditions and obtained the corresponding quinolines **21a** and **21b** in moderate yields. The enantioselective rhodium-catalysed 1,4-arylation of these compounds have previously been reported by Lam and co-workers.⁹¹



Scheme 2.19 Sequential procedure with 2-alkynyl boc-protected anilines

We next assessed the compatibility of our methodology to the recently reported formation of pyrrole derivatives *via* hydroacylation with propargylic amines.⁸³ The preparation of interesting

heterocyclic structures was possible after the modification of certain parameters. Firstly, when employing dcpm ligand for the hydroacylation, completion was not reached and gave a mixture of two products (likely linear and branched, Scheme 2.20a). Secondly, the conjugate addition did not allow the formation of the product, reinforcing the idea that amines needed to be fully protected for the conjugate addition to occur. By changing the ligand and employing a *bis*-Boc-protected propargylic amine, both hydroacylation and elimination proceeded well (Scheme 2.20b). Upon addition of the chiral catalyst and boronic acid, the divinyl ketone intermediate underwent double conjugate addition. Prior to purification, the crude material was then treated with TFA, which allowed the formation of dihydropyrrole **22** in an excellent 72% yield after four steps. Excellent levels of diastereoselectivity and enantioselectivity were achieved.



(a) Product prepared by Ming Gao

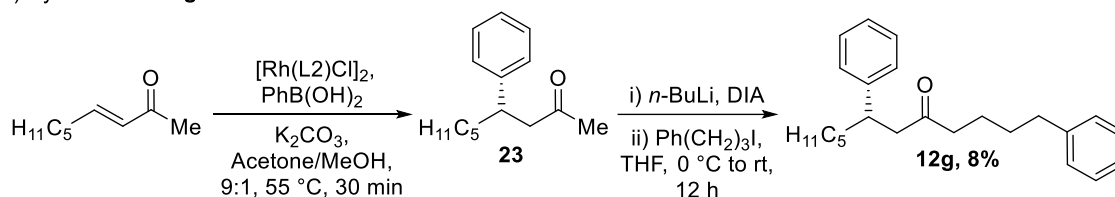
Scheme 2.20 Derivatisation towards several *N*-containing heterocycles

2.2.5 Determination of the absolute configuration

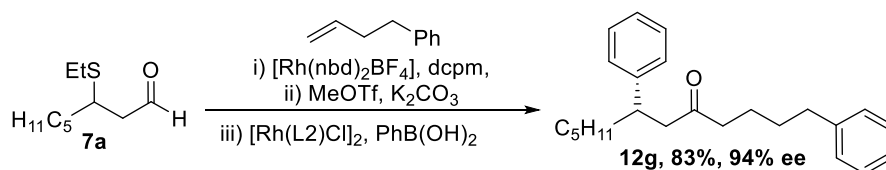
Chiral diene ligands have already been studied and the selectivity exhibited is well understood. Although very similar products to the ones we have prepared have been described in the literature, none of the compounds synthesised during the scope have been previously reported. Thus, we decided to compare the optical rotation of the product **12g** (see Scheme 2.8) with the one alternatively prepared using a method that involved a known chiral intermediate (Scheme 2.21). In this context, we envisioned the alkylation of (*S*)-(phenyl)nonan-2-one **23**, which had been

described in the literature, to form the desired 1,7-diphenyldodecan-5-one **12g**. We first synthesised the reported (*S*)-4-(phenylnonan-2-one) **23** by conjugate addition of phenylboronic acid to (*E*)-non-3-en-2-one with our best rhodium complex $[\text{Rh}(\text{L}2)\text{Cl}]_2$. The comparison of the optical rotations measured with the ones reported confirmed the (*S*) absolute configuration of **23**. Although a poor yield was obtained for the alkylation of (*S*)-4-(phenylnonan-2-one) **23**, we were able to isolate the desired ketone **12g**. Comparison of the optical rotation values and chiral HPLC analysis enabled us to assign the absolute configuration unequivocally.

(a) Synthesis of **12g** via a known chiral intermediate



(b) Synthesis of **12g** using the tandem sequence

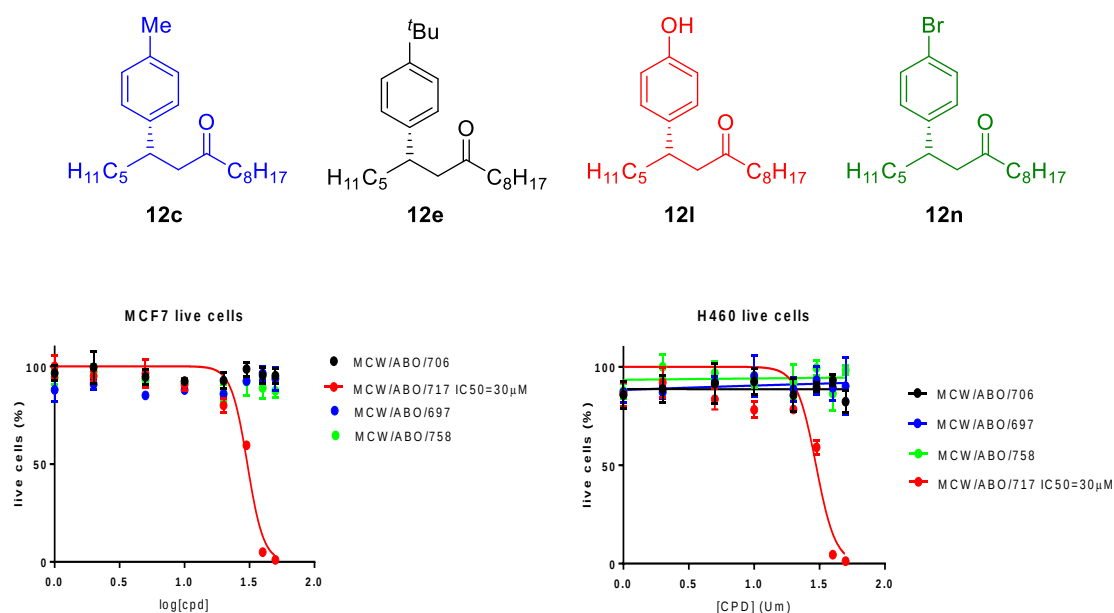


Scheme 2.21 Strategy employed for the determination of the absolute configuration

2.2.6 Biological assays

This PhD has been part of the Oxford Innovative Organic Synthesis for Cancer Research (OxIOSCR) project, an EU-funded doctoral programme established to develop potential anti-cancer compounds. In this context, we had the opportunity to conduct biological assays and test several products prepared in this chapter. In the early screening, it was found that **12c**, **12e**, **12l** and **12n** displayed potential anti-cancer activity against lung, prostate, cervical and breast cancers. These compounds were thus selected for further biological assays in order to determine their IC_{50} with both H460 (lung cancer cell line) and MCF7 (breast cancer). The tests were carried out over five days. Cancer cells are typically kept and constantly grown in a medium that contains a mixture of sugars, proteins, and antibiotics. The first day consisted of the verification of cancer cells' health, the preparation of the plates and the cell counting. During the second day, the compounds were added at different concentrations ranging from 40 to 0.3 μM . The cells were then incubated

for three days, before being analysed by low resolution microscopy. In cell culture, a wide range of stains is available for achieving a good understanding on how the compound affects the cell. In our case, Hoechst 33342, which penetrates cell membranes of both dead and live cells and binds to DNA, was first employed. It enabled the total cell count regardless of the state of the cell. Propidium iodide, which only binds to the DNA of dead cells, was next utilised. The plates were then analysed by low resolution microscopy that differentiated the colours based on the different stains employed and calculated the results. After interpretation of the data by Dr Frances Willenbrock, it was found, as shown in Figure 2.5, that only compound **12l** displayed biological activity. By tracing the curve of live cells as a function of concentration of the compounds used, an IC_{50} of 30 μ M was obtained for **12l**.

Figure 2.5 Determination of the IC_{50}

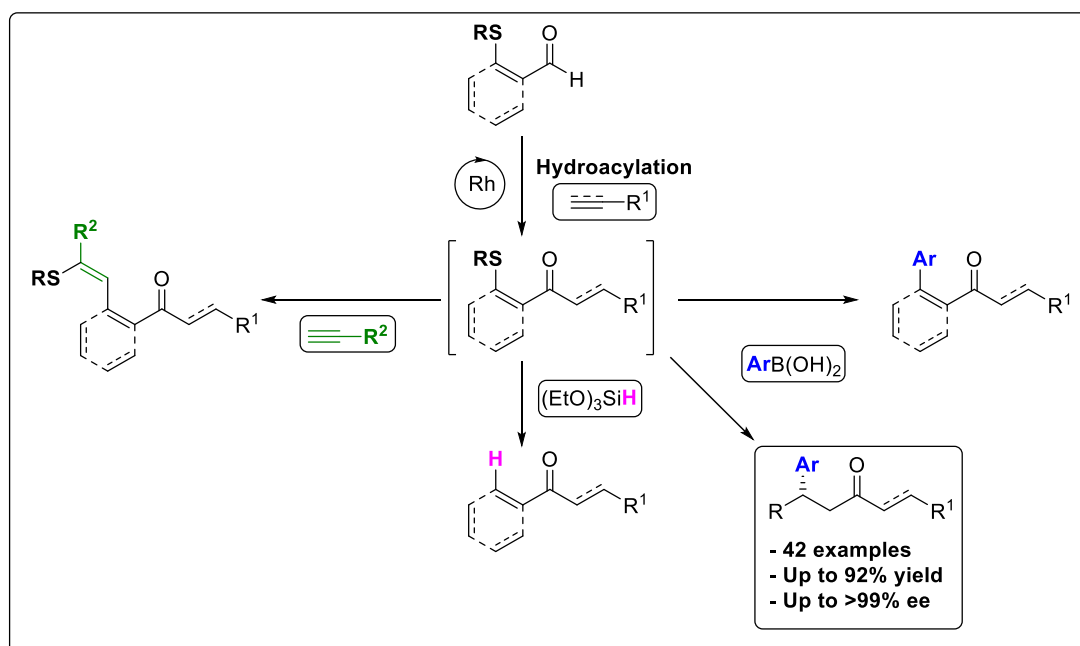
These results will all be triplicated for accuracy, and tested on two other cancer cell lines.

2.3 Conclusions

In conclusion, we have successfully combined a rhodium-catalysed hydroacylation and conjugate addition into a one-pot procedure, leading to highly functionalised ketones with excellent yields and levels of enantiocontrol. This transformation employed easily accessible starting materials and tolerated a broad range of functional groups. We have also shown that the use of

suitable alkynes during hydroacylation enabled regioselective conjugate additions. The utility of our methodology was further demonstrated by the derivatisation of several products into different interesting motifs such as chromanes and dihydropyrroles. The telescoped sequence proved highly flexible, with the variation of many parameters, including solvents, ligands, and unsaturated substrates (alkenes and alkynes) for hydroacylation, all allowing a tuneable tandem sequence. The absolute configuration was determined without ambiguity by optical rotation comparisons. In addition, some of the products prepared with our method displayed anti-cancer activity.

Until now, the formation of traceless hydroacylation products in which the sulfide tether has been replaced by a more useful functional group was only possible with *aryl* and *alkenyl* methyl sulfides, *alkyl* thioethers having proved unreactive. Our new methodology successfully overcomes this limitation (Scheme 2.22).



Scheme 2.22 Summary of the one-pot hydroacylation/elimination/conjugate addition

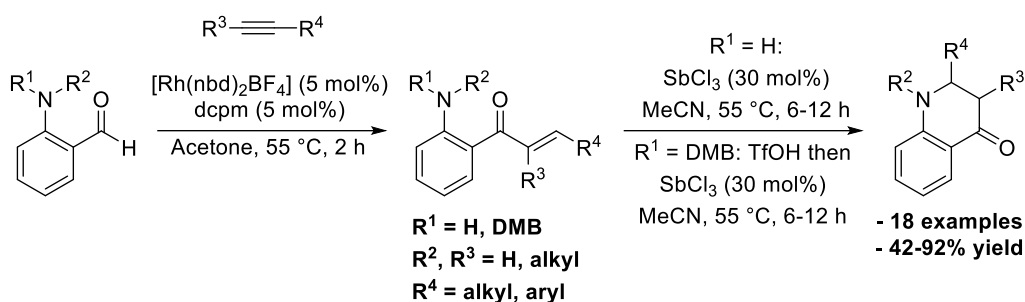
In a constant effort to expand processes that use the sulfide tether for further transformations, we next focused on the preparation of compounds that involved the recycling of the sulfur heteroatom after the hydroacylation step (Chapter 3).

Chapter 3

Synthesis of six-membered S-containing heterocycles *via* alkyne hydroacylation

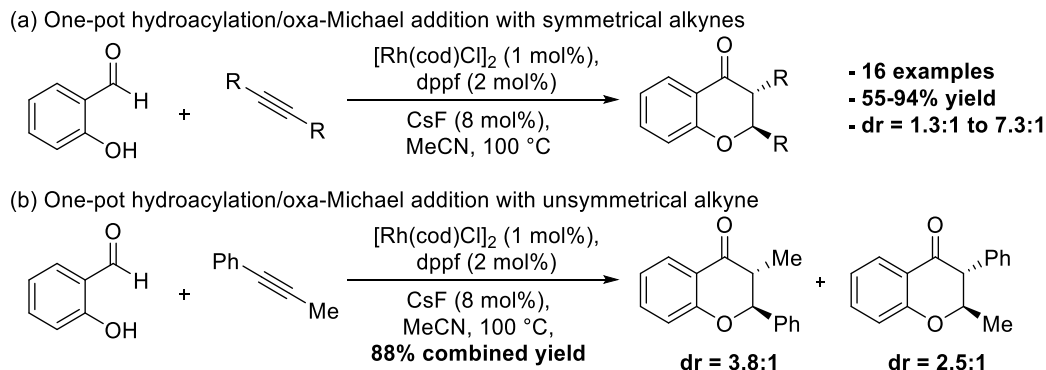
3.1 Introduction

As discussed in chapters 1 and 2, rhodium-catalysed hydroacylation of alkenes and alkynes has become a powerful method to access ketones and enones in an atom-economic manner. The development of chelation-controlled strategies has efficiently limited undesired side reactions and enabled intermolecular processes to occur under mild reaction conditions and with wide functional group tolerance. Although the presence of the heteroatom directing group in the final product is often viewed as a limitation, it can also be a useful platform for further functionalisation. To this end, several tandem and sequential processes have been developed, enabling the combination of both: taking advantage of the remarkably efficient chelation-controlled hydroacylation; and converting the directing group into an alternative functional group *in-situ*.^{37-39,76,77} Of particular interest are transformations that incorporate the directing group in the final product, thus delivering a process that recycles the heteroatom tether. In this context, our group reported in 2013 a stepwise alkyne hydroacylation/aza-Michael addition protocol for the preparation of dihydroquinolones from *N*-chelating aminobenzaldehydes (Scheme 3.1). Although the process could not be conducted in a one-pot manner, it enabled the recycling of the nitrogen tether towards the formation of more complex structures.^{23a}



Scheme 3.1 Stepwise synthesis of dihydroquinolones

Similarly, Stanley and co-workers recently developed a tandem alkyne hydroacylation/oxa-Michael addition sequence to synthesise *trans*-2,3-disubstituted chroman-4-ones from readily accessible salicylaldehydes (Scheme 3.2a).⁹⁵ The reaction employed a commercially available rhodium catalyst and *bis*-phosphine ligand at low catalyst loadings with sub-stoichiometric amounts of caesium fluoride. The desired products were obtained in good to excellent yields in moderate diastereoselectivities. However, unsymmetrical alkynes were found to deliver products displaying low regioselectivity under these reaction conditions (Scheme 3.2b).



Scheme 3.2 One-pot hydroacylation/oxa-Michael addition

Utilising S-containing aldehydes, we sought to develop a tandem hydroacylation/thio-Michael addition for the generation of S-containing heterocycles such as thiochroman-4-ones and tetrahydrothiopyran-4-ones. These molecules often display important antimicrobial, antitumor and antifungal activities, which explains their prevalence in numerous biologically active compounds (Figure 3.1).^{96,97}

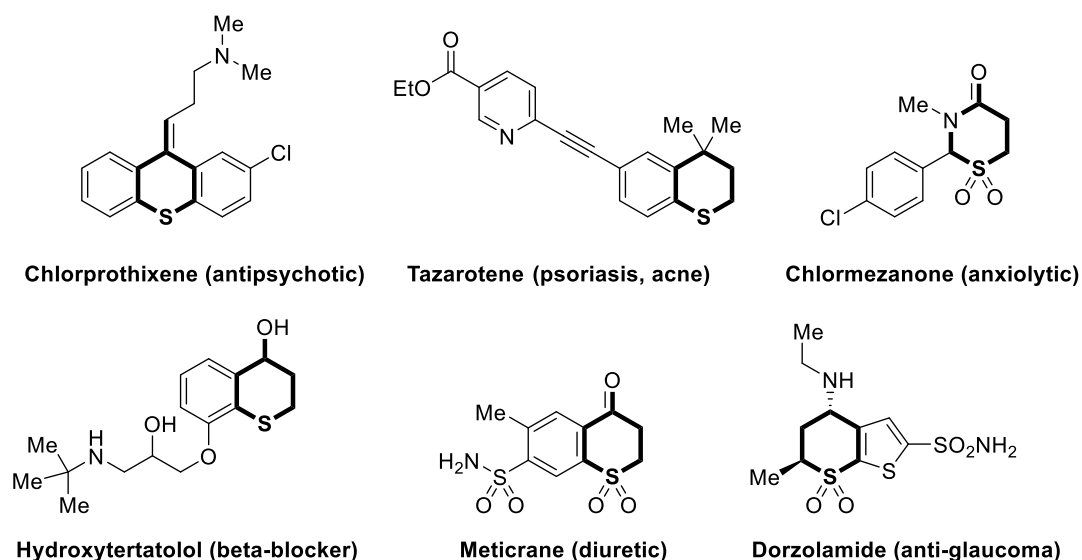
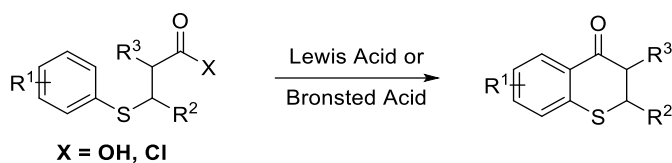


Figure 3.1 S-heterocycles containing drugs

There have been many reports for the synthesis of thiochroman-4-ones that can be divided into two categories:

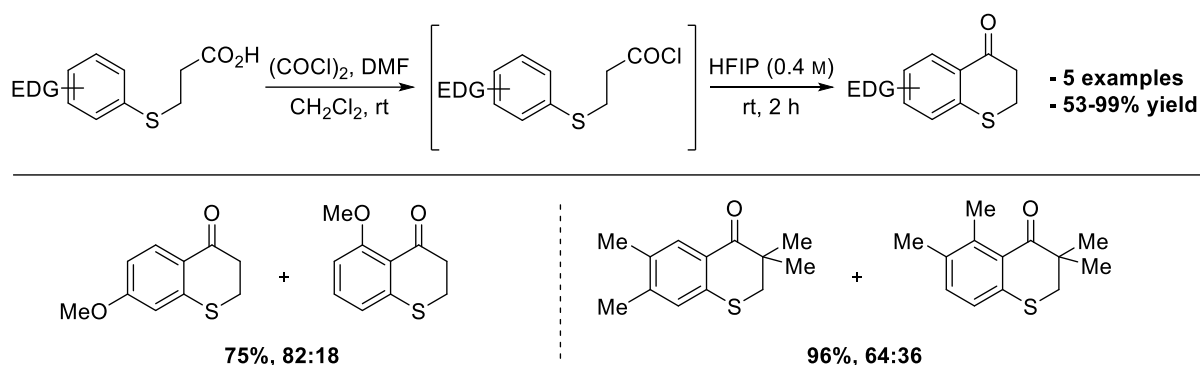
Friedel-Crafts acylation

Cyclisation *via* Friedel-Crafts acylation of (phenylthio)propanoic acid derivatives under acidic conditions utilising either aluminium trichloride,⁹⁸ polyphosphoric acid,⁹⁹ or sulfuric acid¹⁰⁰ has been used widely over the last century (Scheme 3.3). However, there are several limitations to this strategy including restricted functional group tolerance, use of relatively harsh reaction conditions and regioselectivity issues depending on the substituents found on the thiophenol.



Scheme 3.3 General reaction for the Friedel-Crafts acylation

Recently, Motiwala *et al.* reported a mild Friedel-Crafts acylation of simple acyl chlorides in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) with no additional reagent or catalyst (Scheme 3.4).¹⁰¹ Although the simplicity of the procedure was attractive, this method suffered from the potential formation of regioisomers, and therefore judicious choice of substrates was required.

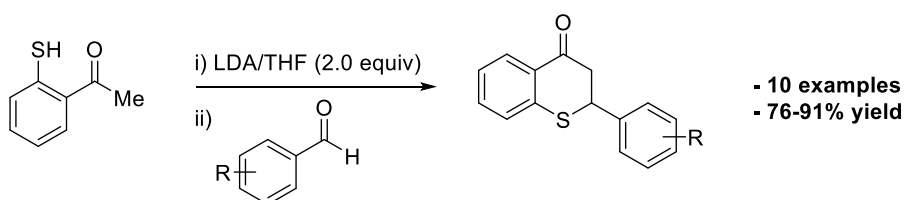


Scheme 3.4 HFIP-promoted Friedel Crafts acylation and selected examples

The second main route to thiochroman-4-one derivatives employs the intramolecular thio-Michael addition.

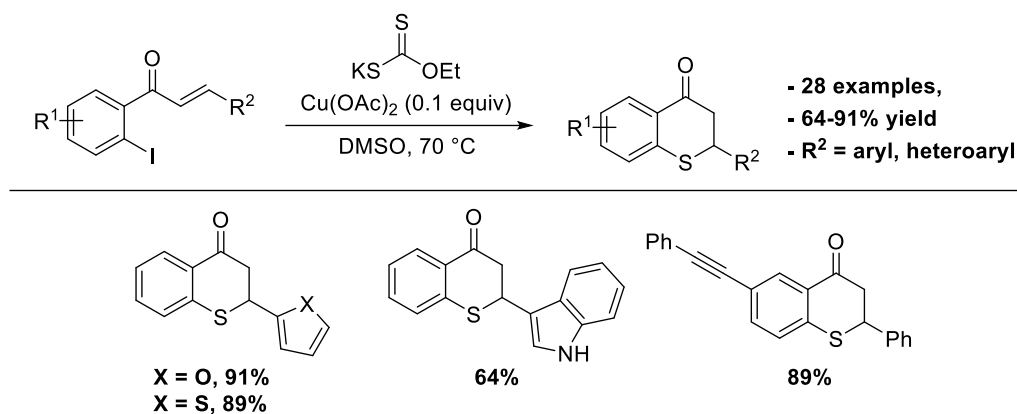
Intramolecular thio-Michael addition

In comparison to the Friedel-Crafts reaction, the thio-Michael addition has the advantage of avoiding the formation of undesired regioisomers.¹⁰² In 2008, Lee reported the development of an efficient tandem aldol condensation/intramolecular conjugate addition from simple thiophenols (Scheme 3.5).^{102a} The two-step sequence enabled access to thiochroman-4-ones in good yields but with a limited scope.



Scheme 3.5 Tandem aldol condensation/Michael addition reported by Lee

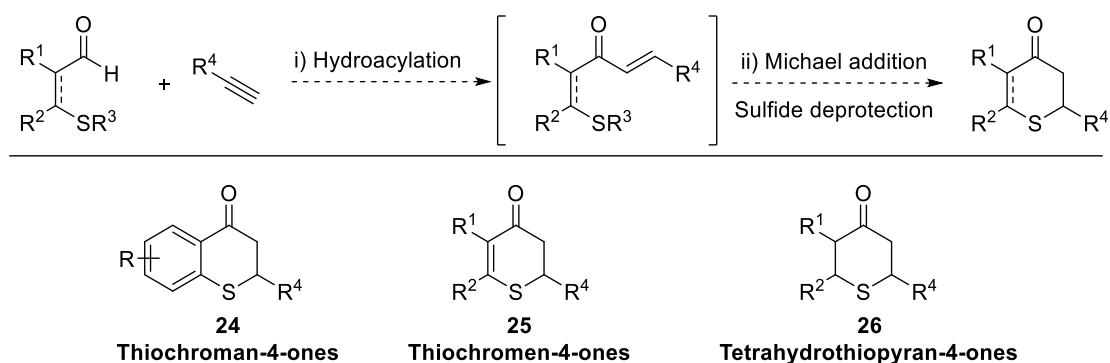
More recently, Sangeetha *et al.* described the formation of 2-arylthiochromanones *via* a copper-catalysed domino process from 2-halochalcones (Scheme 3.6).^{102b} The major advantage of this protocol was the use of xanthate as the sulfur source, which enabled an odourless process by avoiding the use of thiophenol derivatives. However, the scope seemed limited to aryl, heteroaryl and alkenyl substituents on the enone.

Scheme 3.6 Copper-catalysed domino synthesis developed by Sangeetha *et al.* and selected examples

Although the Friedel-Crafts acylation and the thio-Michael addition transformations enable efficient processes, both methodologies are limited to accessing thiochroman-4-ones and different protocols and substrates would have to be employed for the formation of related heterocycles such as tetrahydrothiopyran-4-ones and thiochromen-4-ones. In this context, we thought that a tandem alkyne hydroacylation/S-conjugate-addition reaction could be a new tool for the rapid construction of a variety of sulfur-containing heterocycles using a single strategy.

3.2 Project aims

With the desire to expand multi-component transformations in which the directing group is recycled in the final product, we envisioned the one-pot formation of S-heterocycles *via* an alkyne hydroacylation followed by a concomitant acid-mediated thioether deprotection/thio-Michael addition process (Scheme 3.7). As discussed in chapter 2, S-chelating substrates are some of the most generally employed aldehydes for intermolecular hydroacylation since they tolerate aryl, alkenyl and alkyl substituents on the aldehyde starting material. Therefore, depending on the nature of the aldehyde, a variety of S-containing heterocycles including thiochroman-4-ones **24**, thiochromen-4-ones **25** and tetrahydrothiopyran-4-ones **26**, could be formed from a single procedure. In addition, this strategy would benefit from the ease to scope both alkynes and aldehydes that are either commercially available, or can be prepared from simple procedures.



Scheme 3.7 Project aims for the tandem hydroacylation/acid-mediated thio-Michael addition

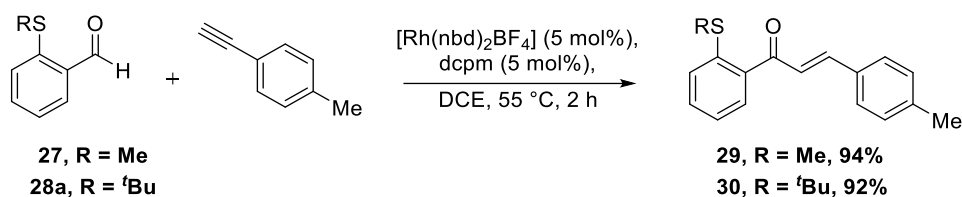
To address these objectives, we started investigating suitable reaction conditions for the two-component assembly of S-heterocycles by a rhodium-catalysed alkyne hydroacylation/acid-mediated thio-Michael addition sequence.

3.3 Results and discussion

This project was carried out jointly with a part II student, Jack Glancy, who developed the optimal reaction conditions and prepared six products which are clearly annotated on the schemes. The products he has prepared are not included in the experimental section.

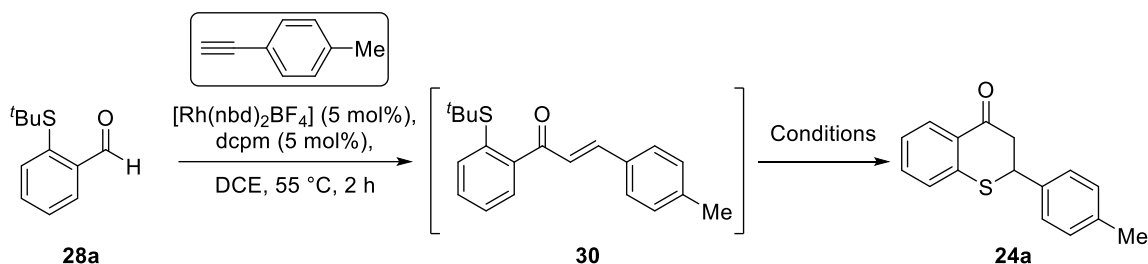
3.3.1. Establishment of the reaction conditions

We began the investigations for the tandem hydroacylation/thio-Michael addition with 2-(methylthio)benzaldehyde **27** and 2-(*tert*-butylthio)benzaldehyde **28a** as we speculated that the *tert*-butyl group might be cleaved more easily under acidic conditions during the thio-Michael addition step. Since *tert*-butyl sulfide tethers had not been employed for hydroacylation before, conditions for this reaction were investigated on a model system using aldehyde **28a** and 4-tolylacetylene. Pleasingly, it was found that the use of conditions previously established led to efficient hydroacylation.^{23a,103} Thus, with pre-catalyst [Rh(nbd)₂]BF₄ and dcpm at a 5 mol% catalyst loading, the desired enones **29** and **30** were isolated in excellent yields in two hours at 55 °C (Scheme 3.8).



Scheme 3.8 Optimal conditions for the intermolecular alkyne hydroacylation

The first attempt at a tandem hydroacylation/thio-Michael addition sequence was carried out by adding trifluoroacetic acid (TFA) directly to the reaction mixture upon completion of the hydroacylation step. Starting from 2-(methylthio)benzaldehyde **27**, a complex mixture of unidentified products was obtained. However, 72% conversion to the desired product **24a** was observed by NMR spectroscopic analysis of the crude material when starting from 2-(*tert*-butylthio)benzaldehyde **28a** (Table 3.1, entry 1). Both higher concentration and temperature improved the conversion (entries 2 and 3). Doubling the number of equivalents of TFA allowed us to reach full conversion to the desired thiochroman-4-one **24a** in one hour at room temperature, delivering the expected product in 84% isolated yield (entry 4).



Entry	TFA (equiv)	Concentration (M)	Time (h)	Temperature	NMR conversion (%) (Isolated Yield, %)
1	5.0	0.35	8	rt	72
2	5.0	0.35	8	50 °C	81
3	5.0	1.0	8	rt	96
4	10.0	1.0	1	rt	100 (84)

a. Conditions: i) Rh(nbd)₂BF₄ (5 mol%), dcpm (5 mol%), aldehyde (1.00 equiv), alkyne (1.05 equiv), DCE (1.0 M), 55 °C, 2 h; ii) TFA, time, temperature, concentration.

Table 3.1 Identification of reaction conditions for the tandem hydroacylation/thio-Michael addition^a

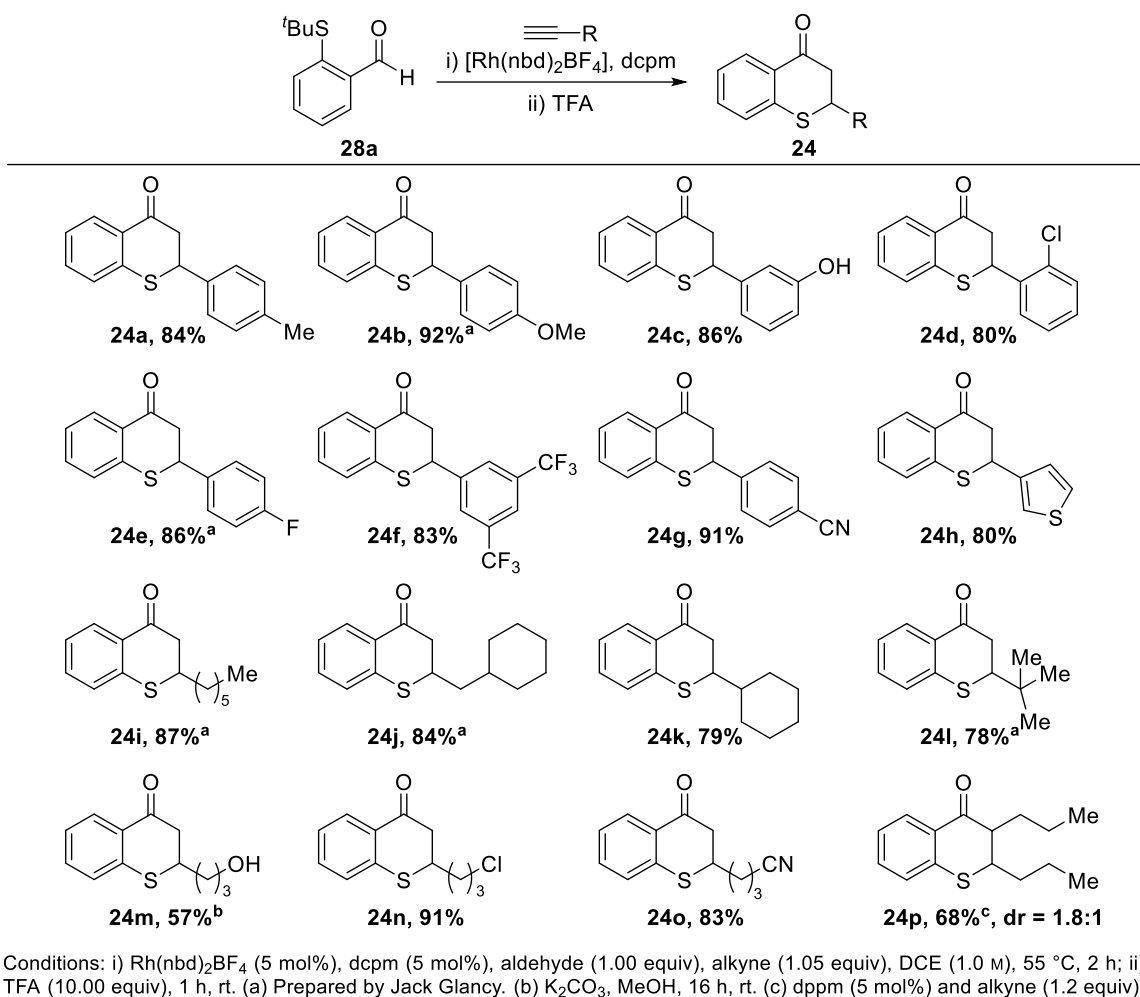
Having established the optimal reaction conditions, we turned our attention to examining the range of alkynes compatible for this reaction.

3.3.2. Alkyne scope

We first evaluated the scope of the reaction using **28a** in combination with a range of alkynes under the optimised reaction conditions (Scheme 3.9). The one-pot process was successfully applied to phenylacetylene derivatives bearing a variety of electron-donating (**24a-c**) and electron-withdrawing groups (**24d-g**), with substituents tolerated at all positions of the benzene ring. Notable amongst these examples was the use of phenol (**24c**), reactive cyano groups (**24g**, **24o**), and thiophene (**24h**). When employing alkynes possessing aliphatic chains, thiochroman-4-ones were also obtained in excellent yields regardless of the level of steric hindrance (**24i-o**). Interestingly, the use of 4-pentyn-1-ol afforded, by NMR spectroscopic analysis of the crude material, a mixture of both product **24m** and its corresponding trifluoroacetate ester. Treatment of the crude reaction mixture with potassium carbonate in methanol cleanly delivered alcohol **24m** in 57% yield over three steps.

When employing 4-octyne under the optimised reaction conditions, poor conversion was observed for the hydroacylation step. After ligand screening, we identified dppm as a more suitable ligand for internal alkynes and obtained 2,3-disubstituted thiochroman-4-one **24p** in 68% yield as a mixture of inseparable diastereomers. The diastereomeric ratio (dr = 1.8:1) was found to be only slightly higher than the corresponding chroman-4-one prepared by Stanley and co-workers (dr = 1.3:1). Despite a few attempts at enolising **24p** under basic conditions, this diastereomeric ratio was not improved further.

Finally, the tandem reaction was found to be applicable on a gram scale using 4-tolylacetylene, with only 1 mol% of rhodium catalyst and ligand, delivering the final product **24a** in 79% yield.

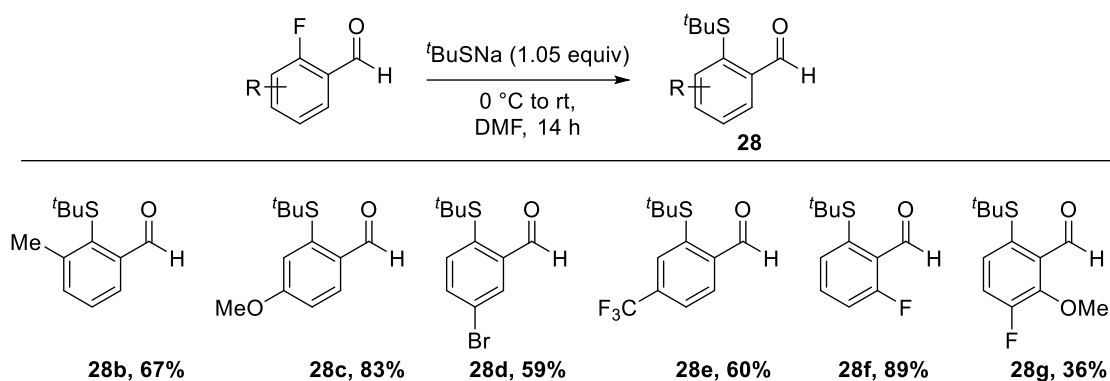


Scheme 3.9 Variation of the alkyne component

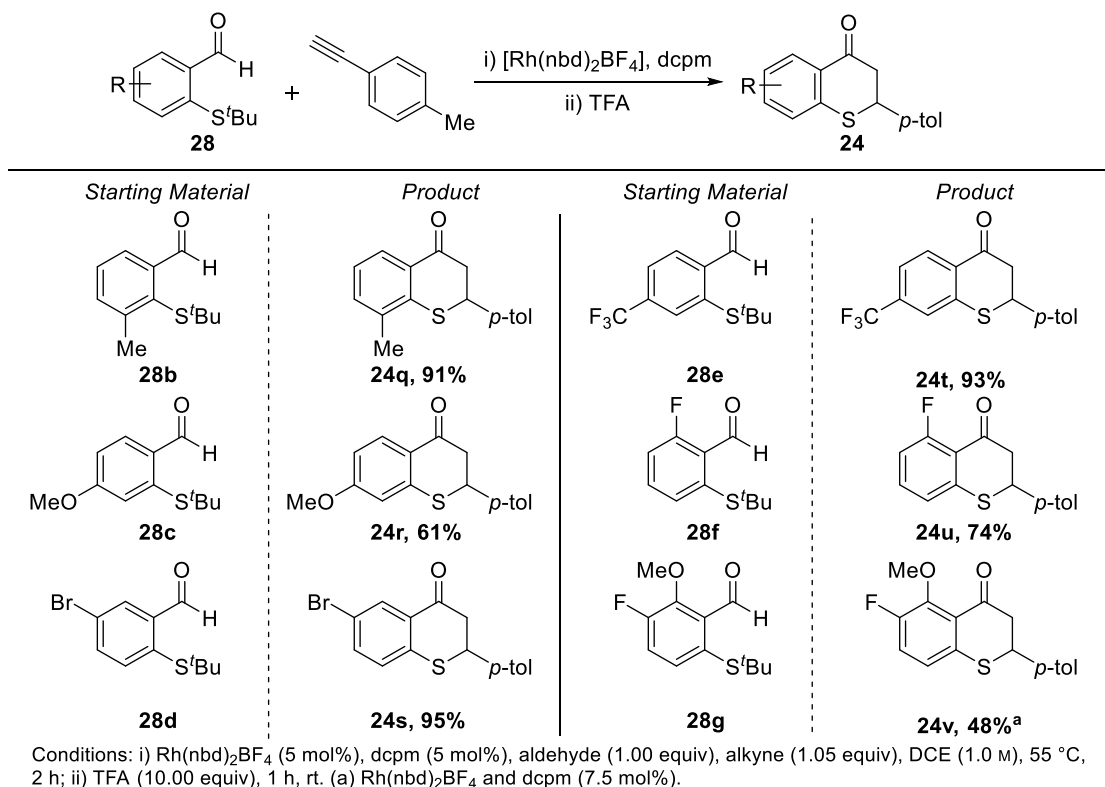
In summary, a library of sixteen different thiochroman-4-ones was obtained using various alkynes, in good to excellent yields. We continued our study of the reaction tolerance by screening different aldehyde starting materials.

3.3.3. Aldehyde scope

To examine the scope of the aldehyde component, several 2-(*tert*-butylthio)benzaldehyde derivatives **28** were prepared by S_NAr reactions from the corresponding 2-fluorobenzaldehydes (Scheme 3.10).

Scheme 3.10 Preparation of the 2-(*tert*-butylthio)benzaldehyde derivatives

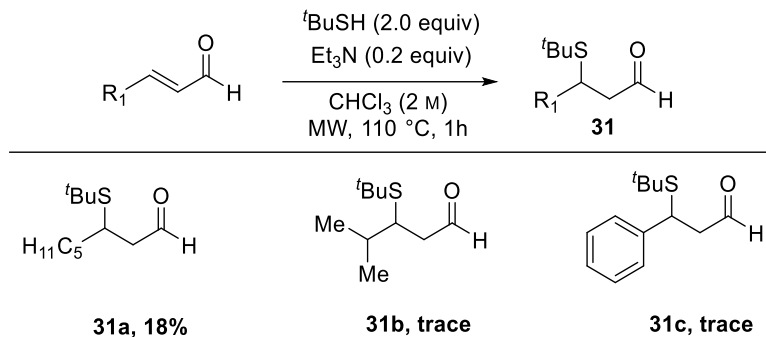
These benzaldehydes were then reacted with 4-tolylacetylene to afford diversely substituted thiochroman-4-ones possessing electron-donating (**24q**, **24r**, **24v**, Scheme 3.11) or withdrawing (**24s-v**) functional groups. Pleasingly, *ortho*-substituted 2-(*tert*-butyl)thiobenzaldehyde **28f** gave the desired product **24u** in 74% yield. However, the more sterically encumbered di-substituted aldehyde **28g** required a higher catalyst loading and was obtained in a lower yield (**24v**).



Scheme 3.11 Variation of the aldehyde component

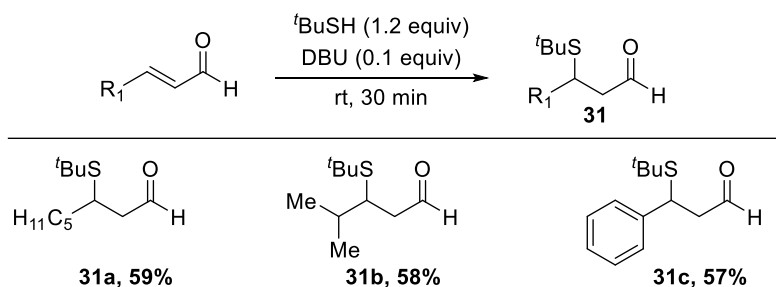
The synthesis of β-S^{*t*}Bu alkyl aldehydes **31** was then pursued. Surprisingly, application of the previously optimised conditions for the preparation of β-SEt-aldehydes in chapter 2 with sub-

stoichiometric amounts of triethylamine and *tert*-butylthiol delivered poor reactivity. Employing different commercially available starting materials, the 1,4-conjugate addition was found slow and low yielding (**31a-c**, Scheme 3.12).



Scheme 3.12 Preparation of alkyl aldehydes by thio-Michael addition

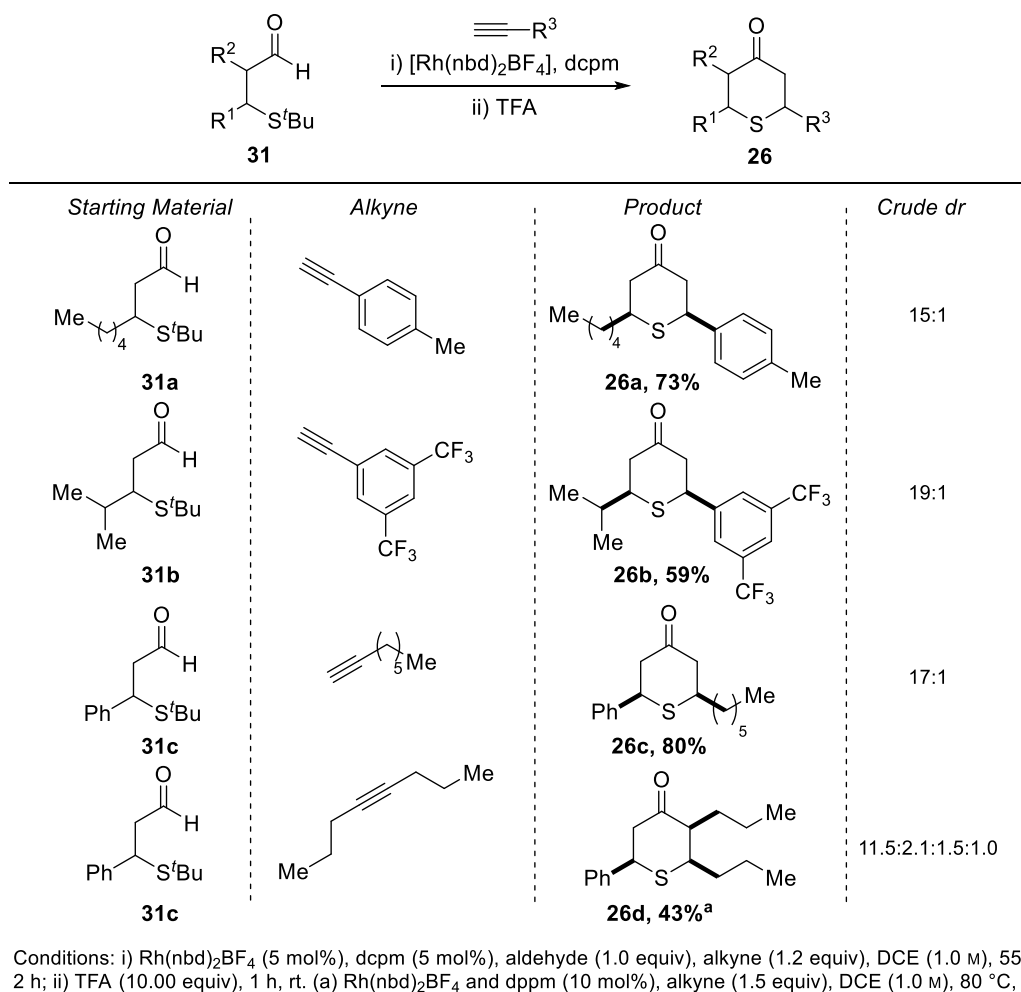
Efficient formation of the desired products was achieved by using sub-stoichiometric amounts of the slightly more basic 1,8-diazabicyclo[5.4.0]undec-7-ene, more commonly known as DBU, under solvent-free conditions at room temperature (Scheme 3.13).¹⁰⁴



Scheme 3.13 Modified reaction conditions for the preparation of S'tBu-alkyl aldehydes

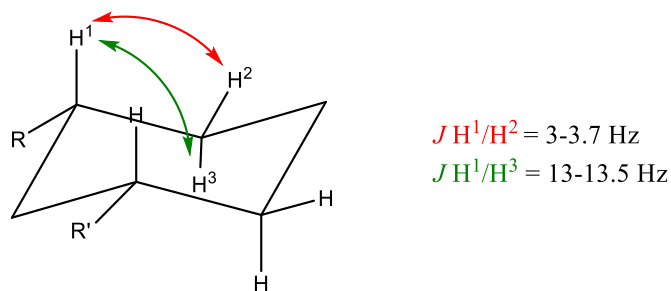
We next subjected these alkyl aldehydes to the one-pot hydroacylation/S-conjugate addition. Pleasingly, aldehydes **31a-c** delivered the corresponding tetrahydrothiopyran-4-ones with various terminal alkynes (**26a-c**) in moderate yields and good diastereoselectivities (Scheme 3.14).

Additionally, the reaction using 4-octyne under the previously modified reaction conditions with 10 mol% of rhodium catalyst and dppm ligand gave one major diastereoisomer by ¹H NMR spectroscopic analysis of the crude material, which was isolated pure in 43% yield (**26d**).

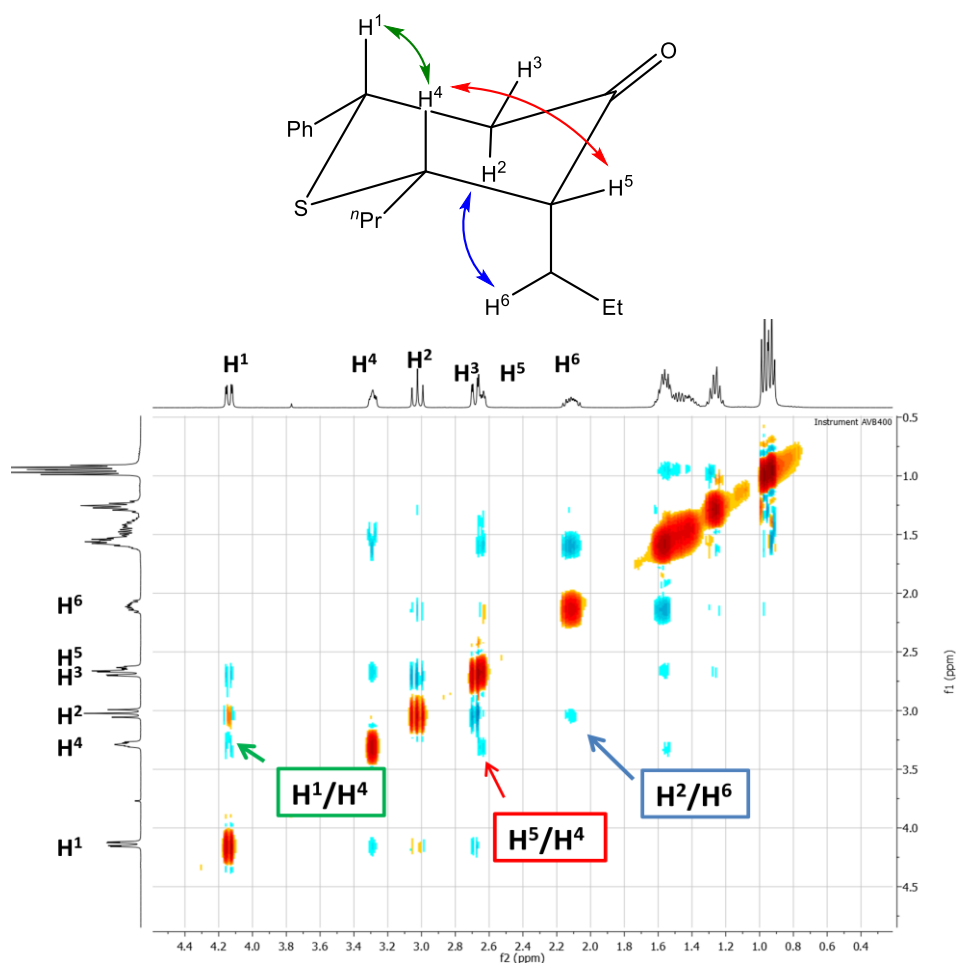


Scheme 3.14 Variation of alkyl-aldehydes

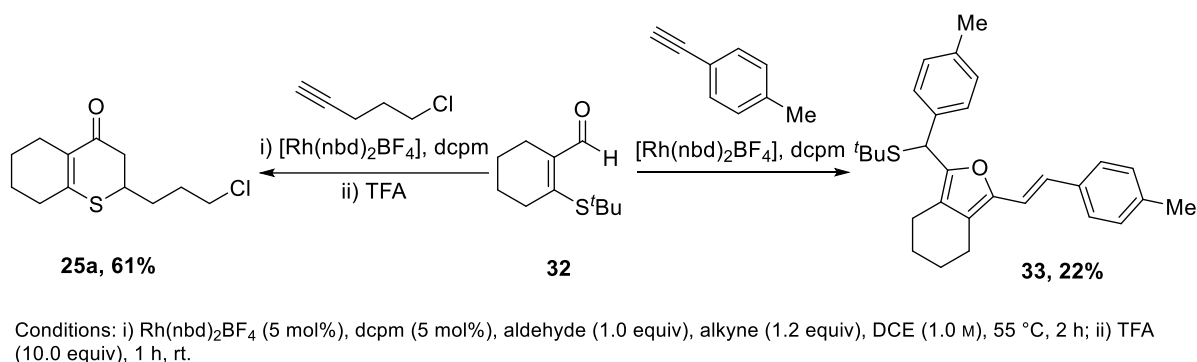
The relative *cis*-configuration of the three di-substituted tetrahydrothiopyran-4-ones **26a**, **26b** and **26c** was determined thanks to the combination of two factors: (a) the strong correlation systematically observed by NOESY experiments between the two protons located on the stereogenic centres; (b) and the comparison of the coupling constants reported for related products.¹⁰⁵ In addition, similar hydrazone derivatives have been studied by X-ray crystallography.¹⁰⁶ It was shown that *cis*-derivatives largely existed in chair conformations with the bulky groups oriented in equatorial position. Hence the coupling constants of the protons adjacent to the sulfur in our case matched the coupling constants described for products that adopt cyclohexane chair or cyclohexene half-chair conformations (Figure 3.2).¹⁰⁷

Figure 3.2 Typical $J_{ax/ax}$ and $J_{ax/eq}$ in chair-like conformations¹⁰⁷

The relative configuration of tri-substituted tetrahydrothiopyran-4-one **26d** was also determined by NOESY experiment. The NOESY spectrum showed a strong correlation between H^1 and H^4 , suggesting these two protons were in *cis*-configuration. In addition, the NOESY correlation between H^4 and H^5 suggested a *cis* axial (H^4)/equatorial (H^5) arrangement. Furthermore, another correlation supporting our assignment was found between H^2 and H^6 .

Figure 3.3 NOESY spectrum of tetrahydrothiopyran-4-one **26d**

Finally, after having employed both alkyl and aryl substituents on the aldehyde component, we prepared alkenyl aldehyde **32** and submitted it to our reaction conditions (Scheme 3.15). When using 4-tolylacetylene for the alkyne component, the hydroacylation delivered a mixture of hydroacylation product, unreacted starting material and an additional product featuring unexpected signals by analysis of the NMR spectra. Isolation of the side-product facilitated its assignment as the furan-derivative **33** and we envisaged that its formation likely arose from a rhodium-catalysed carbthiolation pathway. Alternatively, when employing an alkyne bearing an aliphatic chain, we were able to obtain the desired thiochromen-4-one **25a** in 61% yield.

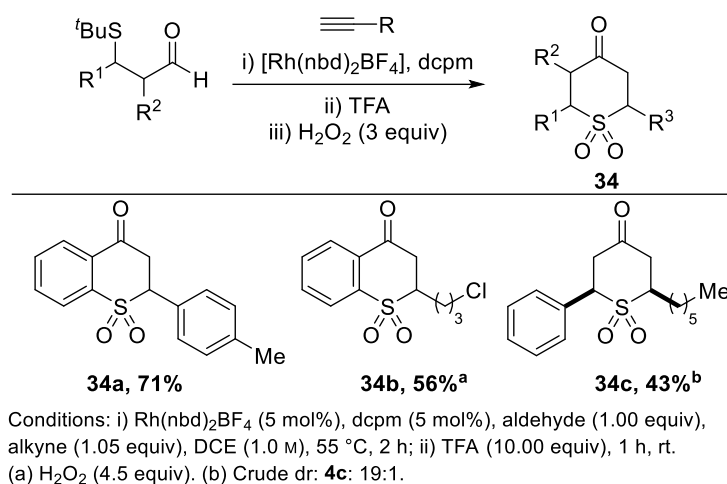


Scheme 3.15 Tandem process using alkenyl aldehyde

In summary, the tandem one-pot hydroacylation/thio-Michael addition sequence was found to be applicable to aldehydes bearing alkyl, aryl and alkenyl substituents, enabling the formation of various S-containing heterocycles from a single method. We next turned our attention to the derivatisation of these compounds.

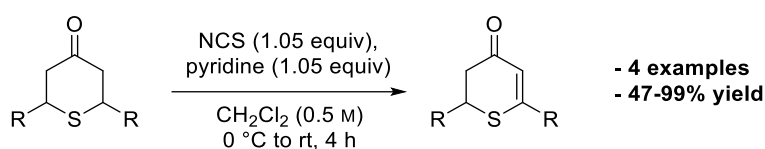
3.3.4. Product derivatisation

Aware that SO₂-containing heterocycles often display a variety of biological activities (see Figure 3.1), we envisioned the one-pot formation of sulfones by direct addition of hydrogen peroxide to the reaction mixture upon completion of the cyclisation step. The desired sulfones **34a-c** were obtained in moderate yields when employing three equivalents of hydrogen peroxide at room temperature (Scheme 3.16). Although hydrogen peroxide itself might have been responsible for some oxidation to the sulfoxide intermediates, it was believed that the main oxidant in the reaction mixture was trifluoroperacetic acid, formed from the excess trifluoroacetic acid.

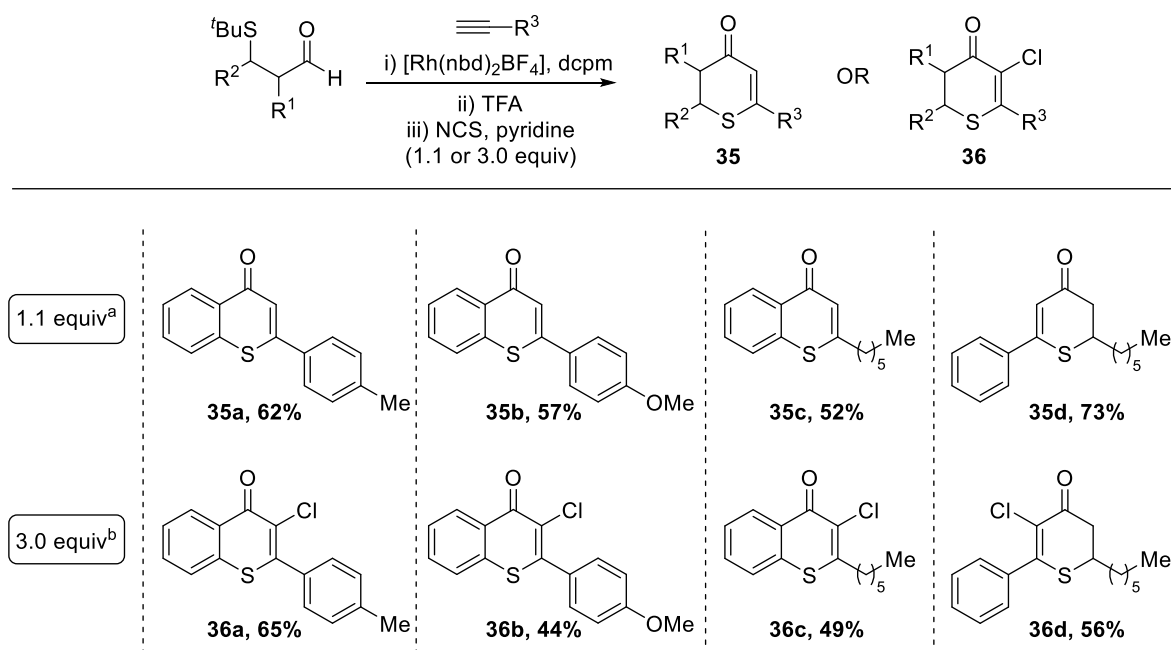


Scheme 3.16 Oxidation of thiochroman-4-one and tetrahydrothiopyran-4-one to sulfone

In addition, following a procedure reported by Chen *et al.* (Scheme 3.17), we envisioned the formation of thiochromen-4-ones and dihydrothiopyran-4-ones from the corresponding aldehyde and alkyne starting materials upon treatment with *N*-chlorosuccinimide (NCS) and pyridine.¹⁰⁸

Scheme 3.17 NCS and pyridine-mediated oxidation of S-containing heterocycles by Chen *et al.*

Due to the need for NCS and pyridine, the presence of an excess amount of TFA in our reaction mixture prevented the development of a one-pot procedure. However, a simple filtration through silica and concentration under reduced pressure was sufficient to remove the excess acid. Direct addition of NCS and pyridine to the crude mixture delivered thiochromen-4-ones and dihydrothiopyran-4-ones in good yields after three steps (**35a-d**, Scheme 3.18). As expected from the work of Chen *et al.*, using excess amounts of NCS and pyridine delivered the α -chloro adducts (**36a-d**), which could be useful intermediates for further transformations. Pleasingly, the *pK_a* difference between the two protons adjacent to the sulfur heteroatom led to the formation of **35d** and **36d** with high regioselectivities.



Scheme 3.18 Sequential synthesis of thiochromen-4-ones and dihydrothiopyran-4-ones

In conclusion, we have developed a one-pot alkyne hydroacylation/thio-Michael addition process to synthesise a library of S-containing heterocycles and their corresponding sulfones from readily accessible starting materials. Moreover, the addition of NCS and pyridine allowed the preparation of thiochromen-4-ones and dihydrothiopyran-4-ones.

3.3.5. Mechanistic investigations

A number of NMR experiments were conducted in order to have a full understanding of the mechanism of the thio-Michael addition reaction. Firstly, the hydroacylation product of the reaction from aldehyde **28a** and 4-tolylacetylene was isolated. The intramolecular thio-Michael addition was then carried out in deuterated chloroform with five equivalents of TFA instead of ten and at a lower concentration in order to slow the reaction and monitor it by NMR spectroscopy. The first ^1H NMR spectra was recorded immediately after addition of TFA and suggested a shift of the *tert*-butyl peak as well as activation of the enone (Figure 3.4).

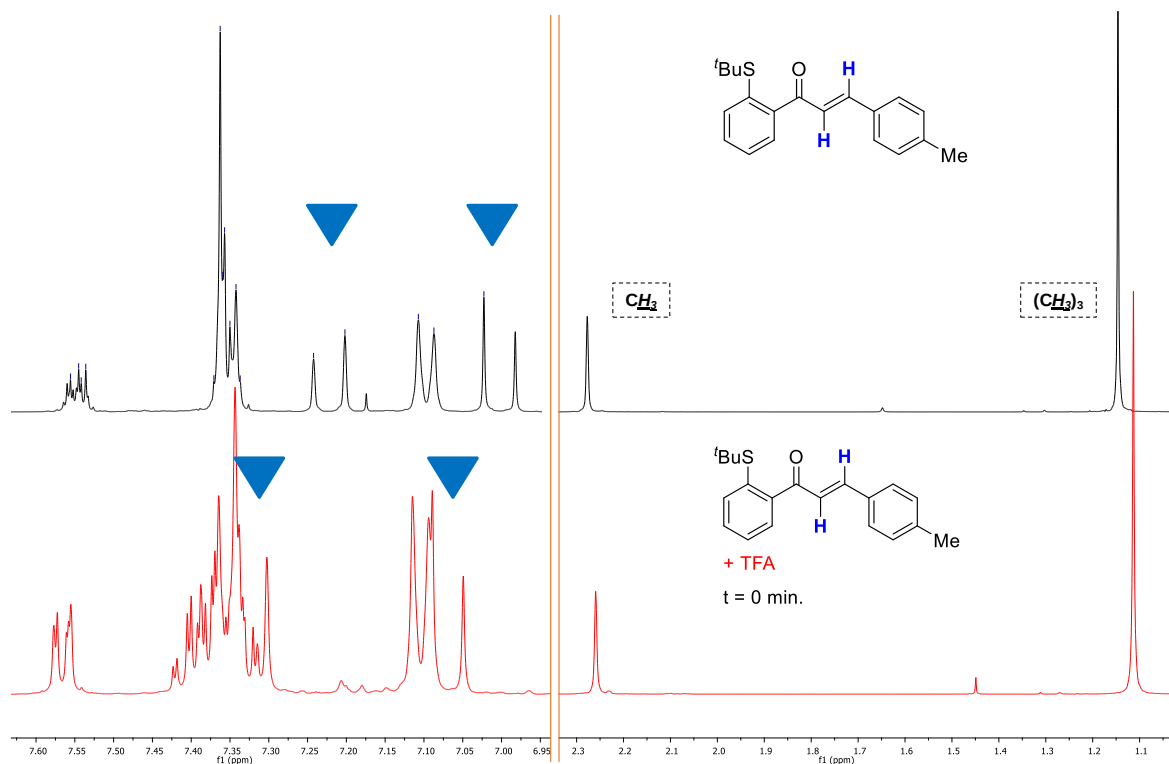


Figure 3.4 ^1H NMR spectra of isolated hydroacylation product and just after addition of TFA

After 45 minutes, in addition to the *tert*-butyl peak found in the “TFA-activated starting material”, a second *tert*-butyl group was observed at 1.54 ppm on the ^1H NMR spectrum (Figure 3.5). The absence of any other peak than starting material, product and this *tert*-butyl group led us to envisage the formation of *tert*-butyl trifluoroacetate.

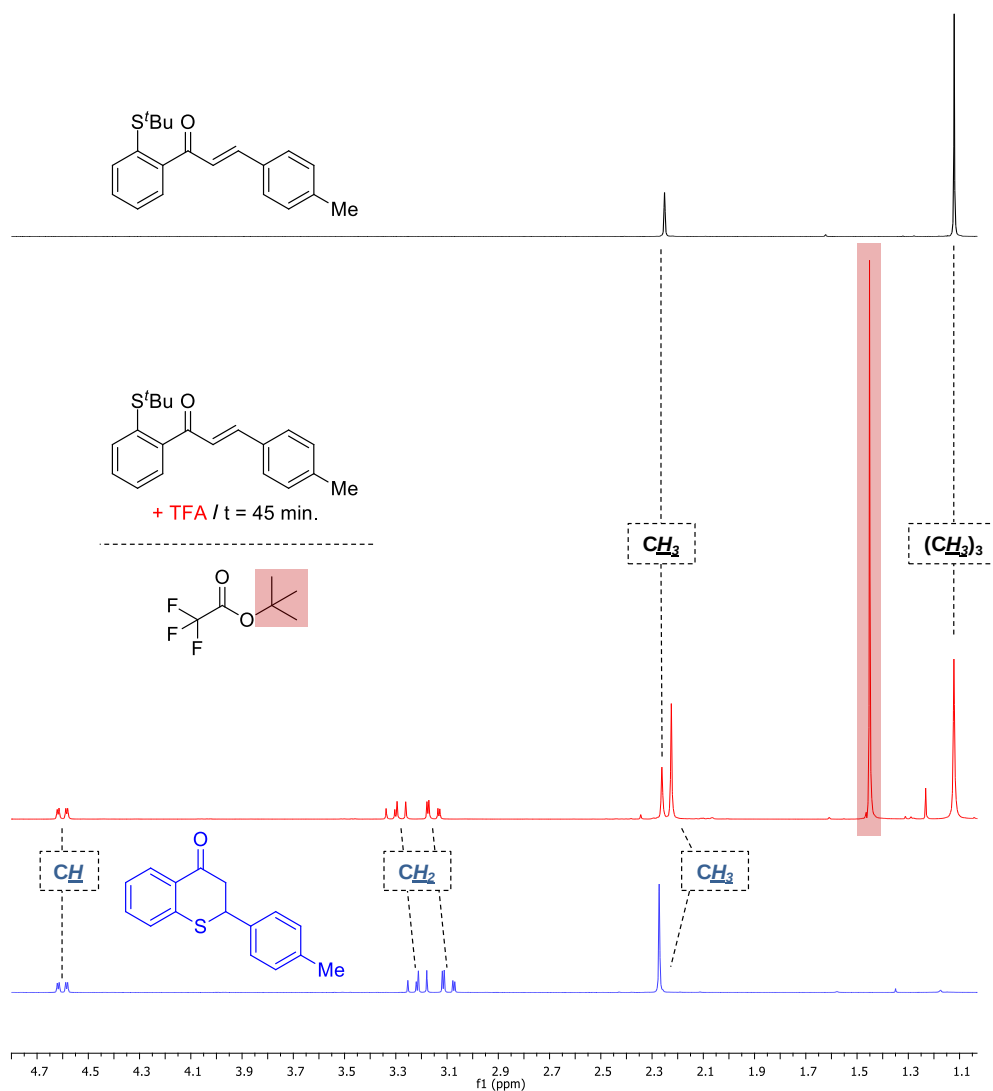
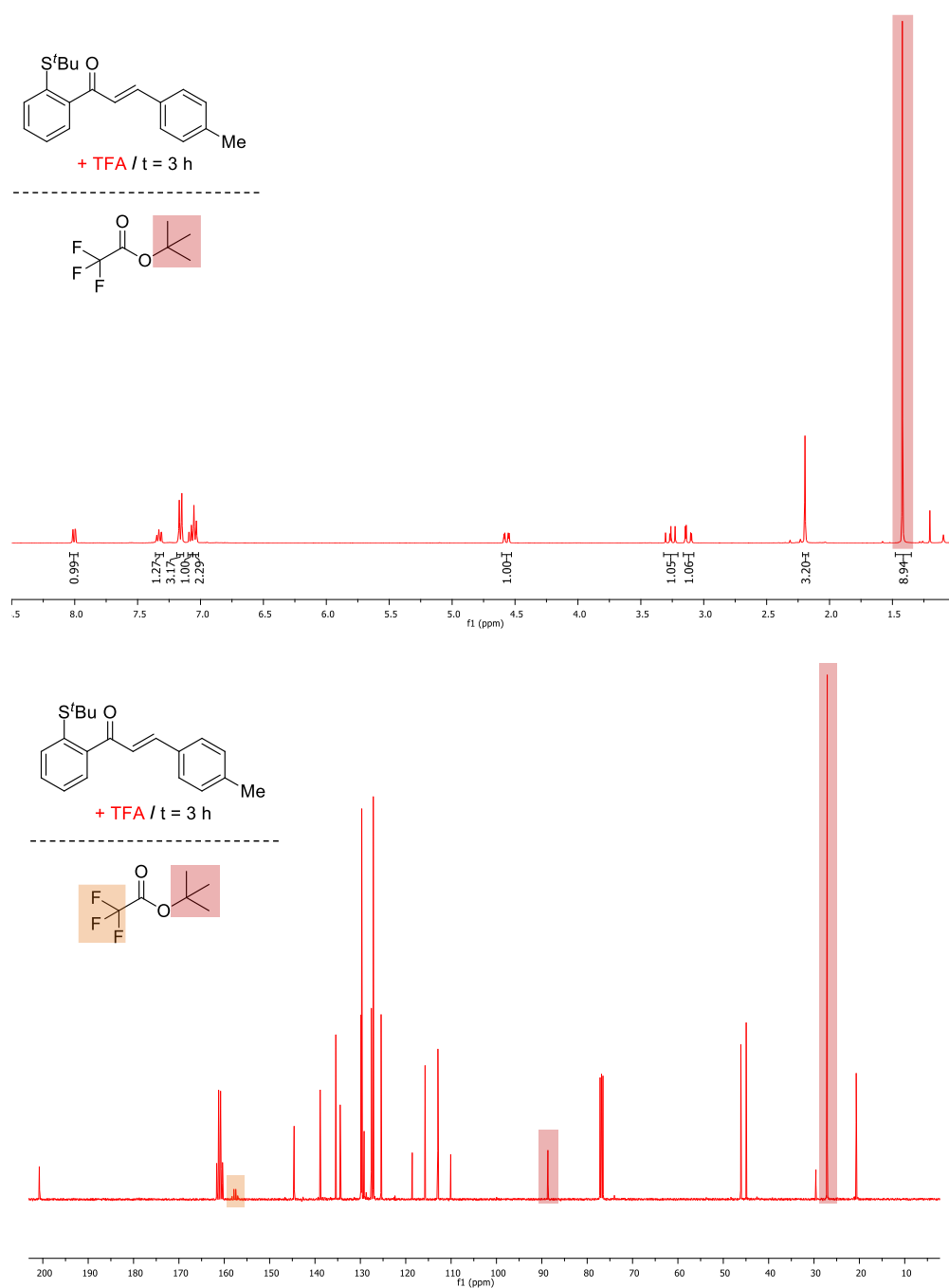


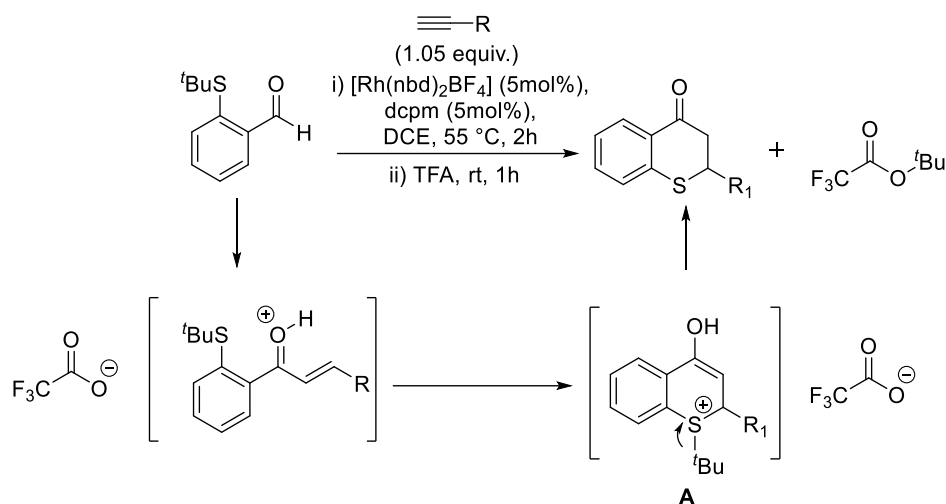
Figure 3.5 ^1H NMR spectra of starting material, reaction mixture at $t = 45$ min and product

Upon completion, comparison of the ^1H and ^{13}C NMR spectra with the literature confirmed the stoichiometric formation of *tert*-butyl trifluoroacetate, whose peak integrated to 9 protons by ^1H NMR spectroscopy (Figure 3.6).¹⁰⁹

Figure 3.6 ^1H and ^{13}C NMR spectra upon completion of the reaction

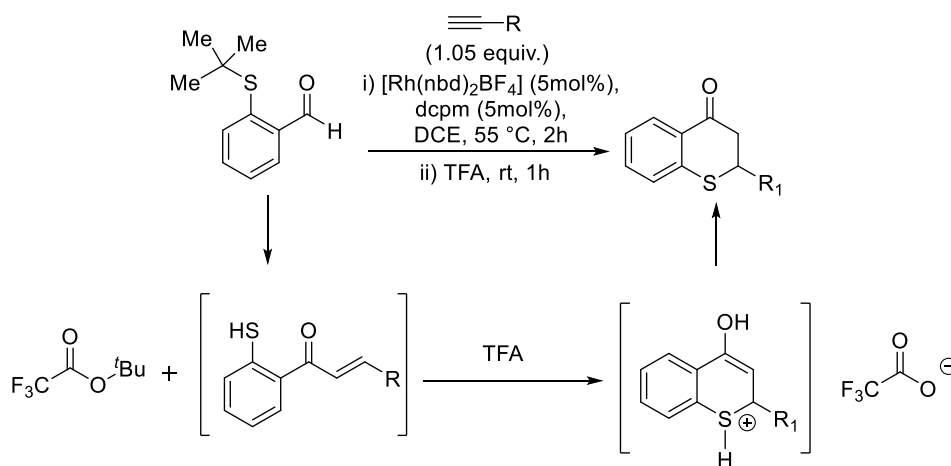
The presence of *tert*-butyl-trifluoroacetate suggested two possible mechanisms:

(a) An intramolecular cyclisation to form the sulfonium trifluoroacetate **A**, which next underwent *tert*-butyl deprotection likely via an $\text{S}_{\text{N}}1$ mechanism to form the product along with the *tert*-butyl-trifluoroacetate by-product (Scheme 3.19).



Scheme 3.19 Pathway (a)

(b) A *tert*-butyl thioether deprotection in TFA via $\text{S}_{\text{N}}1$ mechanism prior to the intramolecular thio-Michael addition (Scheme 3.20).



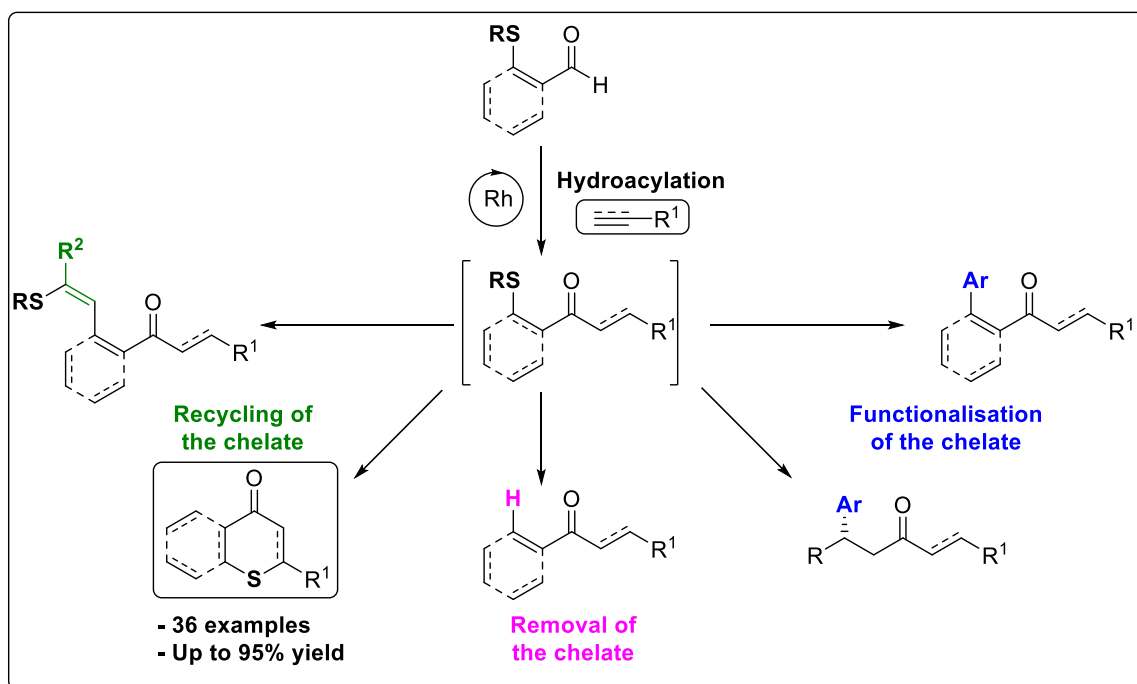
Scheme 3.20 Pathway (b)

In order to determine which pathway the reaction proceeded *via*, we subjected 2-(*tert*-butylthio)benzaldehyde to ten equivalents of TFA in 1,2-dichloroethane and monitored the reaction by ^1H NMR spectroscopy. After stirring for one hour, no change was observed, which indicated that deprotection of the *tert*-butyl moiety was not occurring under these conditions. This information suggested that the thio-Michael addition likely proceeded *via* pathway (a) with the deprotection of the *tert*-butyl group after formation of the sulfonium intermediate. In addition, the proposed mechanism would be consistent with the lack of reactivity observed with the methylthioether analogue. Here also, the intramolecular thio-Michael addition was monitored by ^1H NMR

spectroscopy from the isolated enone. In this case, no desired product was observed, only a complex mixture of products. Despite our efforts, we were not able to isolate any intermediates and only recovered starting material after aqueous treatment. This observation prevented us from drawing any definite conclusion on the mechanism, but may indicate the formation of the sulfonium salt which did not further react in the case of the methyl-thioether.

3.4 Conclusions

In conclusion, we have successfully developed a flexible tandem alkyne hydroacylation/thio-Michael addition sequence that has allowed us to take advantage of the sulfide chelate by using it as a platform for further derivatisation (Scheme 3.21).



Scheme 3.21 Summary of the project

In comparison with previous related reports, this synthetically useful method has enabled the efficient preparation of thiochroman-4-ones, tetrahydrothiopyran-4-ones and thiochromen-4-ones. The process was then extended to the formation of oxidised derivatives, thus allowing us to access a range of S-containing heterocycles using a single strategy (Figure 3.7).

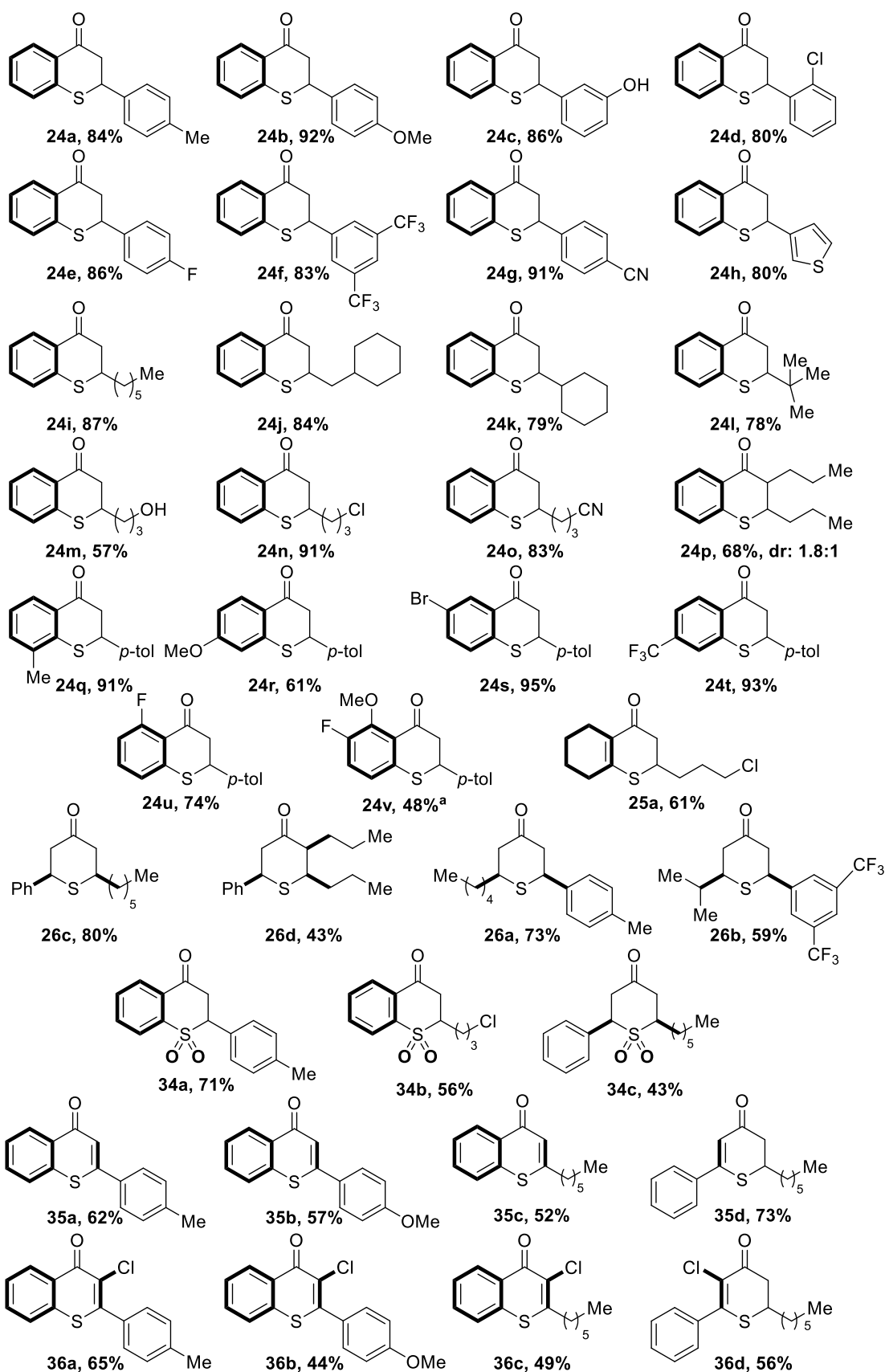


Figure 3.7 S-containing heterocycles prepared by our tandem hydroacylation/Michael addition

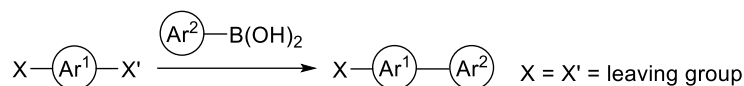
Chapter 4

Rhodium-catalysed cross-coupling reactions via C-S bond activation

4.1 Introduction

Over the last thirty years, the area of transition metal-catalysed cross-coupling reactions has been extensively studied and many key synthetic advances are directly linked to this field. Among the variety of transformations developed, the Suzuki-Miyaura cross-coupling has inarguably played a fundamental role in the formation of carbon-carbon bonds.¹¹⁰ Additionally, recent developments have seen the emergence of modular synthesis and orthogonal reactivity as useful strategies to enable better synthetic flexibility.¹¹¹ In chemistry, orthogonality may be defined by a process involving a multifunctional molecule in which only one functional group will engage in a chemical transformation under certain reaction conditions with a particular reagent.¹¹² The other functional groups will not be affected and may react under different sets of conditions. Although orthogonality is a conceptually powerful tool that improves our capability in assembling synthetic fragments, there have been only limited examples of general systems. For the Suzuki-Miyaura reaction, two main areas have been explored: chemoselective oxidative addition involving a cross-coupling reaction with one electrophile coupling partner in the presence of at least another electrophile (Figure 4.1a); or chemoselective transmetallation based on the differentiation between nucleophilic functional groups (Figure 4.1b) and for which appropriate use of masking groups on boron atoms has played a pivotal role in controlling reactivity.¹¹³

(a) Orthogonal cross-coupling reaction based on chemoselective oxidative addition



(b) Orthogonal cross-coupling reaction based on chemoselective transmetalation

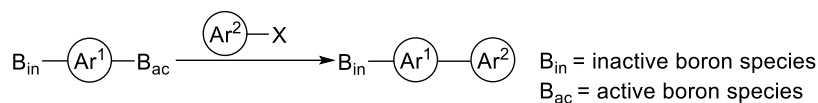
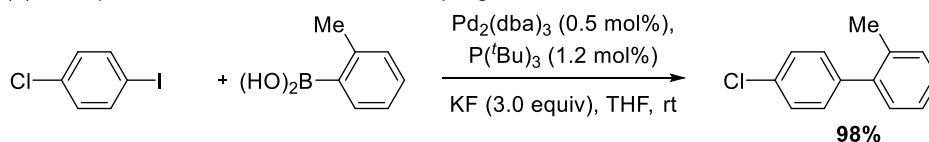


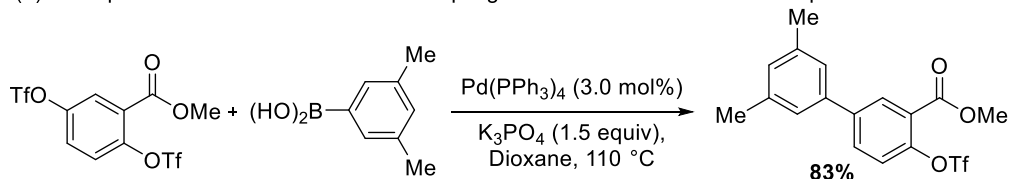
Figure 4.1 Schematic representation of chemoselective cross-couplings

On the one hand, several examples of cross-couplings based on chemoselective oxidative addition have been achieved.¹¹⁴ This strategy benefits from the preparation of intermediates that retain a useful functional handle (X in Figure 4.1a) that can engage in further transformations. In this context, most developments have taken advantage of either the different order of reactivity of (pseudo)halides (Scheme 4.1a),¹¹⁵ or the electronic and steric properties of a specific substrate (Scheme 4.1b).¹¹⁶ Fu, in particular, has exploited general chemoselective Suzuki-Miyura cross-coupling reactions of dihaloarenes under mild reaction conditions and low catalyst loadings. He has also reported a switchable mono-cross-coupling transformation of a bifunctional arene by simply changing the catalytic system (Scheme 4.1c).¹¹⁵

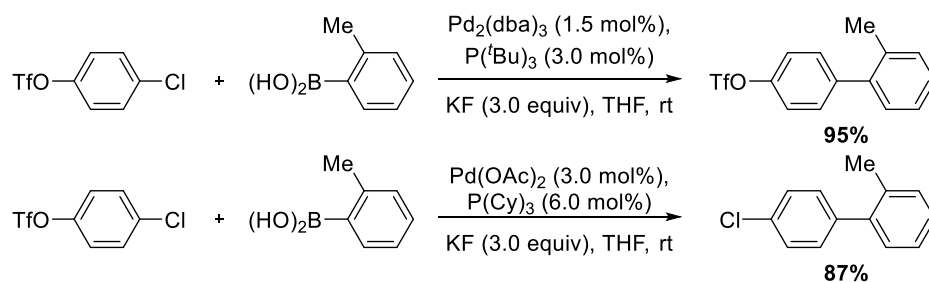
(a) Example of a chemoselective cross-coupling reaction with different halides



(b) Example of a chemoselective cross-coupling reaction with the same electrophile



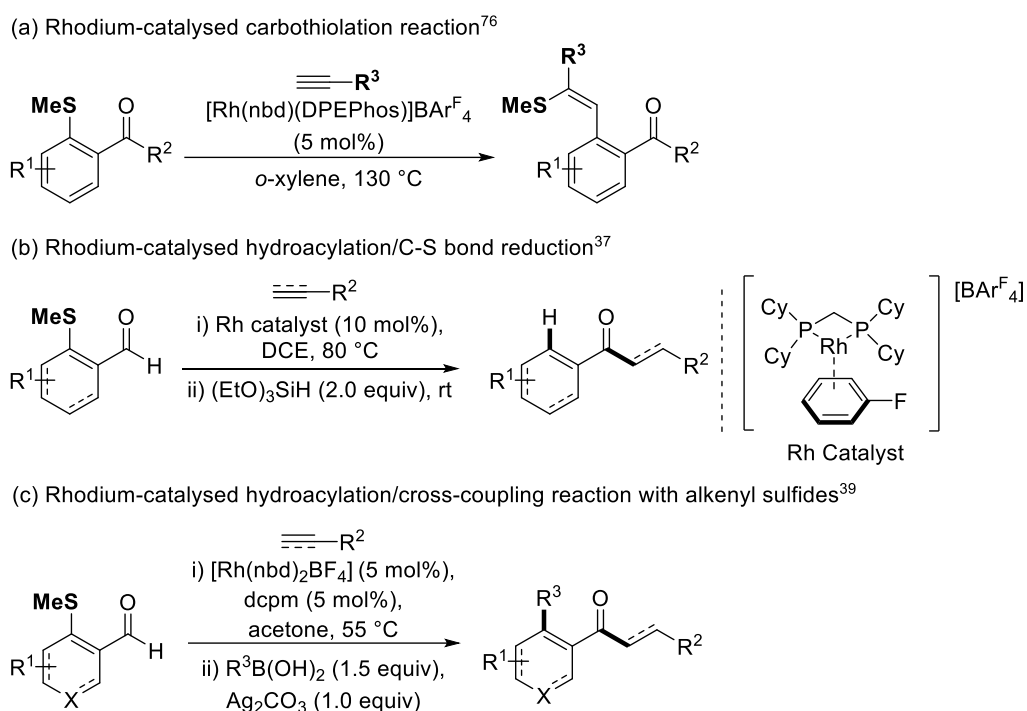
(c) Development of complementary reaction conditions



Scheme 4.1 Chemoselective Suzuki-Miyaura cross-couplings

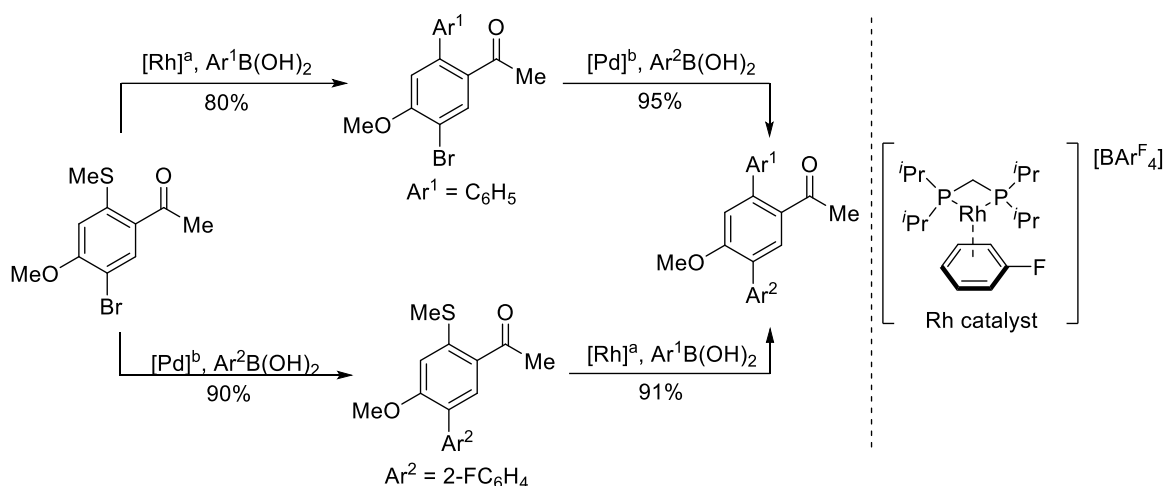
On the other hand, the chemoselective transmetallation strategy has mainly consisted of differentiating boronyl reactive sites and has been independently reported in 2007 by Suginome and Burke.¹¹⁷ The wide commercial availability of boron reagents, coupled to an increased interest in the construction of complex structures such as polyenes and polysubstituted arenes, has since drawn the attention of several research groups.¹¹⁸

As shown in these examples, a number of orthogonal cross-coupling reactions has been reported over the last ten years. However, the regioselectivity of such transformations usually relies on steric and electronic parameters, making most of these processes substrate-specific.¹¹⁹ Another possibility to develop more general site-selective processes as well as discovering new transformations is to explore different activating groups. In an effort to extend the scope of electrophiles suitable for cross-couplings reactions, recent studies have focused on the use of sulfides as activating groups. In the section dedicated to cross-coupling reactions *via* C-S bond activation in chapter 1, it was shown that thioesters and thioethers can engage in cross-coupling reactions, allowing new methods to assemble synthetic fragments. In this field, palladium and nickel catalysts have dominated and few examples of orthogonal cross-coupling reactions have been achieved with a sulfide and a halide group both present in the substrate.^{65-67,74} Recently, methyl sulfide has been successfully employed as an activating group that can undergo rhodium-catalysed C-S bond cleavage. These transformations included a carbothiolation with alkynes which has been developed with aryl methyl sulfides (Scheme 4.2a), and a C-S bond reduction (Scheme 4.2b) or a cross-coupling reaction, which have both been applied to aryl, heteroaryl and alkenyl methyl sulfides (Scheme 4.2c).



Scheme 4.2 Rhodium-catalysed transformations involving C-S bond cleavage

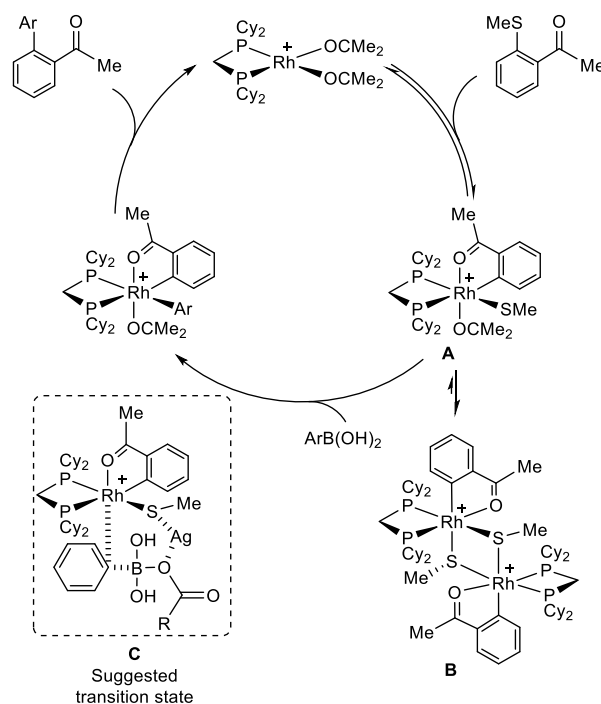
The utility of these processes has been further demonstrated by the possibility of achieving selective transformations in which the rhodium-catalysed cross-coupling reaction was directed at the C-S bond position in the presence of a potentially reactive halide functional group. The methyl sulfide activating group has also been found to be inert to palladium catalysts employed in traditional cross-coupling reactions of aryl halides. This chemoselectivity has allowed cross-coupling reactions to occur selectively at the halide or at the sulfide position, depending on reaction conditions and the transition metal employed. As illustrated in Scheme 4.3, this method has enabled a flexible synthesis of multi-functionalised substrates.



(a) Rh catalyst (5 mol%), Ag₂CO₃ (1.0 equiv), PhB(OH)₂ (1.5 equiv), acetone, 55 °C, 16 h. (b) Pd(OAc)₂ (5 mol%), S-Phos (10 mol%), K₂CO₃ (1.5 equiv), 2-FC₆H₄B(OH)₂ (1.5 equiv), toluene/H₂O, 100 °C, 1 h.

Scheme 4.3 Orthogonal reactivity in rhodium and palladium cross-couplings³⁸

Mechanistic studies including stoichiometric and kinetic experiments have been conducted in order to contribute to a better understanding of the rhodium-catalysed cross-coupling reaction. The proposed mechanism starts with the oxidative addition of the C-S bond to form intermediate **A**, which has already been reported under similar reaction conditions (Scheme 4.4).³⁷ This has also been supported by the characterisation of the catalytically active dimer **B** in acetone when stoichiometric amounts of rhodium catalyst and ketone were employed. Transmetalation of the boronic acid followed by reductive elimination would deliver the product. Of particular importance in this reaction is the presence of silver carbonate, which is necessary to achieve catalyst turn-over. Similar to the mechanism involved in the Liebeskind-Srogl cross-coupling with CuTC,⁵² Willis and co-workers suggested a transition state **C** that takes into account the importance of both the silver cation, which can bind to the sulfur heteroatom, and the counter anion, which can activate the boronic acid. Alternatively, the authors showed that the catalytic cycle could initiate with the transmetalation of the boronic acid to form a complex which was found to be in equilibrium with the dimer **B**.¹²⁰

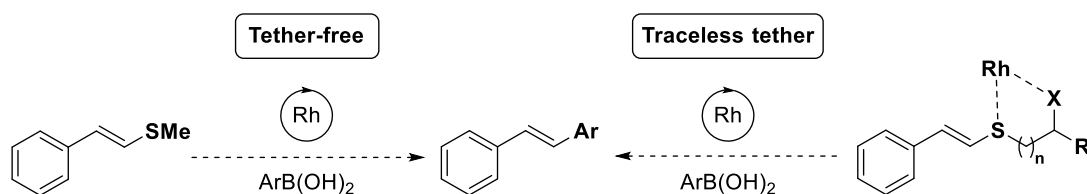
Scheme 4.4 Proposed mechanism for the rhodium-catalysed cross-coupling reaction *via* C-S bond activation

One challenge still to be overcome with the rhodium-catalysed cross-coupling reaction is the removal of the carbonyl directing group, which has so far been essential for the cleavage of the C-S bond to occur. Given the potential exhibited by rhodium catalysts, exploring the reactivity of other sulfide coupling partners could open up new horizons for the development of modular and flexible chemical processes. By extension, this could lead to new methods for the synthesis of polyarenes or polyenes for which efficient and orthogonal synthetic methods are still in demand.

4.2 Project aims

Recent developments achieved in the field of rhodium-catalysed cross-coupling reactions *via* C-S bond activation, together with the orthogonal reactivity observed towards standard Suzuki-Miyaura couplings have encouraged us to further investigate the use of sulfides as activating groups. However, the transformation developed by Willis and co-workers has so far been restricted to aryl and alkenyl sulfides possessing a neighbouring coordinating group, thus limiting the scope of the reaction. Additionally, little work has focused on alkenyl sulfides and we thought that investigating the rhodium catalytic system would potentially enable the development of a new modular synthesis to access tether-free alkenes. To overcome the requirement of a directing group,

we decided to investigate the feasibility of a cross-coupling reaction with tether-free alkenyl sulfides and boronic acid derivatives (Scheme 4.5). If this approach was found unsuccessful, we alternatively envisioned a traceless tether approach, in which a directing group was introduced on the sulfide and cleaved during the catalytic event so that the cross-coupling reaction would still deliver products that did not possess a tether.



Scheme 4.5 Approaches envisioned for the study of cross-coupling reactions with alkenyl sulfides

4.3 Tether-free C-S activation

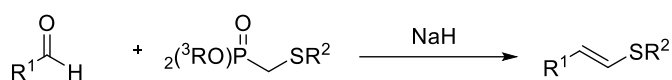
We embarked upon this project by evaluating the more challenging, but tether-free approach. To address our objectives, we first prepared several alkenyl sulfide substrates to test them in a model reaction.

4.3.1 Synthesis of precursors

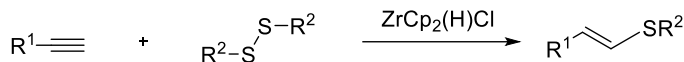
All the transformations developed by Willis and co-workers involving a rhodium-catalysed C-S bond cleavage have employed substrates containing a directing group and utilised *methyl* sulfides as coupling partners.³⁷⁻³⁹ Thus we decided to also prepare alkenyl *methyl* sulfides for assessing the feasibility of our strategy; however these substrates did not incorporate a directing group.

Alkenyl sulfides are usually prepared by three classes of reactions: either by Wittig or Horner-Wadsworth-Emmons strategies from simple aldehydes with S-containing phosphonium ylides or phosphonates (Scheme 4.6a);¹²¹ by hydrozirconation followed by C-S bond formation (Scheme 4.6b);¹²² or by hydrothiolation of an alkyne (Scheme 4.6c). This latter transformation can be radical,¹²³ nucleophilic,¹²⁴ or catalysed by a metal,¹²⁵ but often suffers from regioselectivity issues as the process can deliver three different products: (*E*)-linear **D**, (*Z*)-linear **E** or branched **F**.

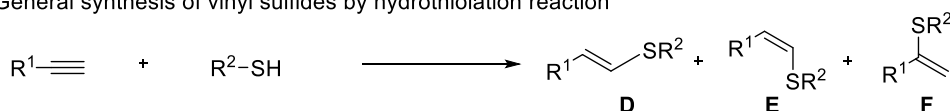
(a) General synthesis of vinyl sulfides by Horner-Wadsworth-Emmons reaction



(b) General synthesis of vinyl sulfides by hydrozirconation/C-S formation

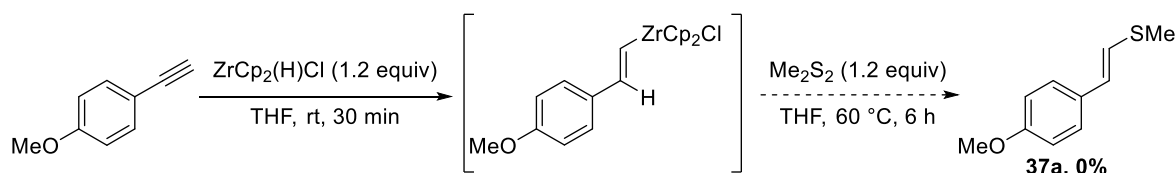


(c) General synthesis of vinyl sulfides by hydrothiolation reaction



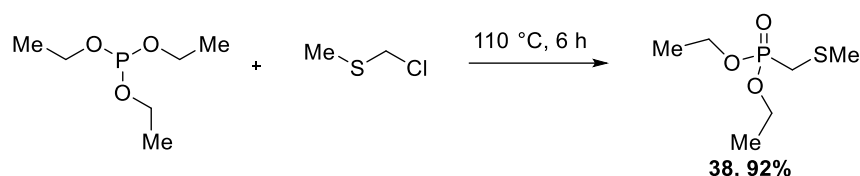
Scheme 4.6 General methods for the preparation of vinyl sulfides

To avoid using methanethiol, we decided to focus on the first two approaches to access vinyl methyl sulfides derivatives: either a Horner-Wadsworth-Emmons reaction or a hydrozirconation reaction with Schwartz's reagent, followed by the addition of dimethyldisulfide. Concerning the latter, a previous report showed that (*E*)-alkenyl sulfides could be accessed in good yields with high selectivities from terminal alkynes and either diphenyl disulfide or dibenzyl disulfide.¹²² When we employed this procedure with 4-ethynylanisole, full consumption of the starting material was observed upon reaction with Schwartz's reagent. However, addition of dimethyl disulfide was found to be unsuccessful (Scheme 4.7).

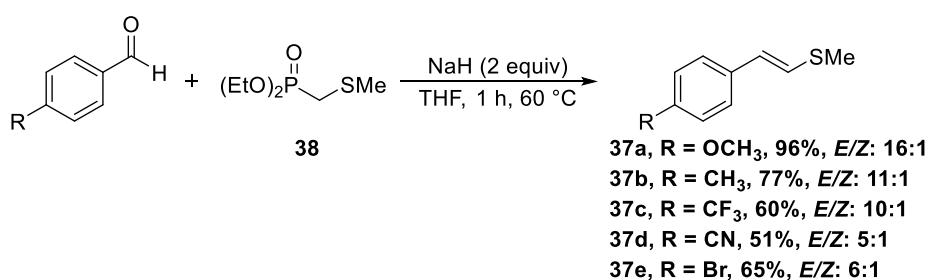


Scheme 4.7 Attempts at synthesising (*E*) alkenyl sulfide **37a** by hydrozirconation

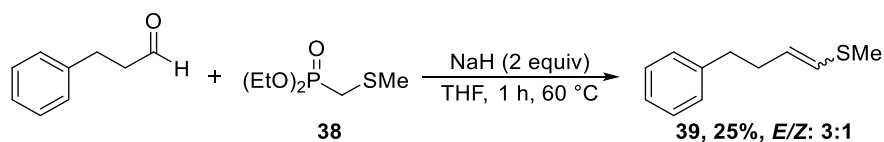
The addition of Lewis acids for the second step, such as silver perchlorate, copper or zinc trifluoromethanesulfonate did not give better results.¹²⁶ Similarly, transmetalation of the organozirconocene intermediate with diethylzinc only afforded trace amounts of the desired product **37a** (< 10% yield).¹²⁷ This hydrozirconation approach was evaluated simultaneously with the Horner-Wadsworth-Emmons-based strategy. For this purpose, we first prepared phosphonate **38** by reacting triethyl phosphite with methylthiomethyl chloride (Scheme 4.8).

Scheme 4.8 Preparation of phosphonate **38**

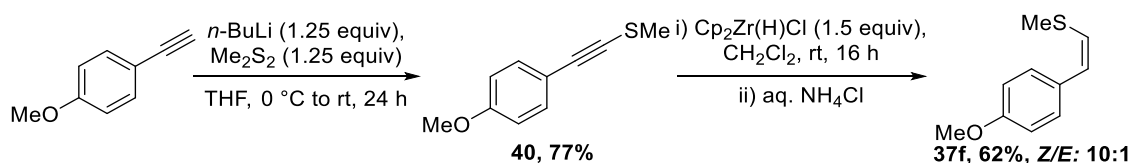
Commercially available benzaldehydes were then reacted with phosphonate **38** and sodium hydride in tetrahydrofuran. This transformation enabled the preparation of alkenyl sulfides (**37a-e**) in moderate to good *E/Z* ratio, although a decreased selectivity was observed with electron-poor aldehydes (Scheme 4.9).

Scheme 4.9 Preparation of (*E*)-alkenyl sulfides via Horner-Wadsworth-Emmons reaction

With hydrocinnamaldehyde, the Horner-Wadsworth-Emmons reaction allowed us to obtain alkenyl sulfide **39** with a *E/Z* ratio of 3:1 (Scheme 4.10).

Scheme 4.10 Preparation of **39** from hydrocinnamaldehyde

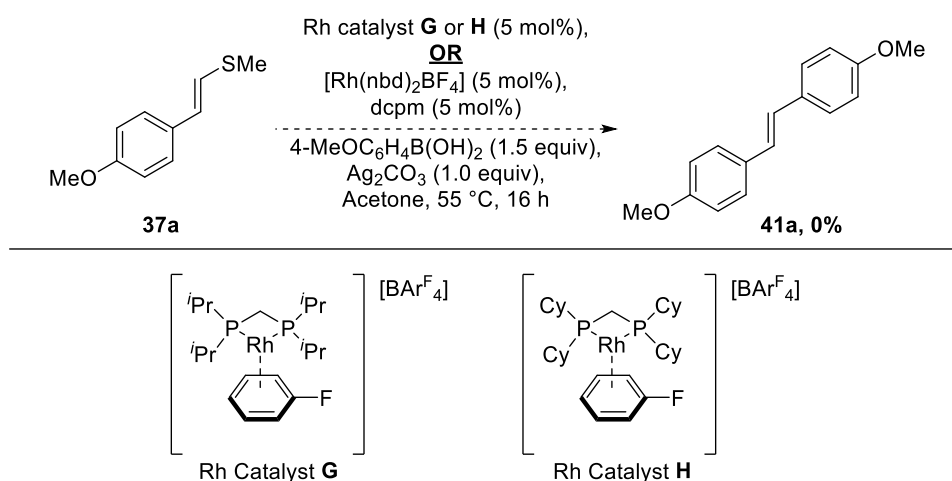
(*Z*)-Alkenyl sulfides could be prepared by reduction of the corresponding alkynyl sulfide. Starting from commercially available 4-methoxyphenylacetylene, we first accessed alkynyl methyl sulfide **40** in a good yield. *Cis*-reduction via hydrozirconation with Schwartz's reagent enabled us to prepare (*Z*)-alkenyl sulfide **37f** in 62% yield (Scheme 4.11).¹²⁸

Scheme 4.11 Preparation of (*Z*) alkenyl sulfide **37f**

Having synthesised a number of alkenyl methyl sulfides, we then turned our attention to the evaluation of the C-C bond formation *via* C-S bond activation.

4.3.2 C-C bond formation *via* C-S bond activation

We first examined the feasibility of the tether-free cross-coupling approach by employing 4-methoxyphenylboronic acid and alkenyl sulfide **37a** that displayed the best *E/Z* ratio and that was easily prepared on a multigram scale *via* the Horner-Wadsworth-Emmons reaction. For the analogous reactions with substrates containing a carbonyl directing group, two different sets of reaction conditions have been reported by Willis and co-workers. Both methods employed boronic acid and silver carbonate in acetone at 55 °C, with either a preformed or an *in-situ* formed rhodium catalyst. Thus, initial attempts were carried out using these previously optimised conditions. In the first report, both preformed rhodium catalysts **G** and **H** had shown to be highly effective for the cross-coupling reaction (Scheme 4.12). Disappointingly, following these conditions with tether-free alkenyl sulfide **37a**, silver carbonate and 4-methoxyphenylboronic acid in acetone at 55 °C did not give any desired product **41a** after 16 hours, and the starting material was recovered. Similarly, the use of a rhodium catalyst formed *in-situ* from commercially available $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ and dcpm was equally unsuccessful.



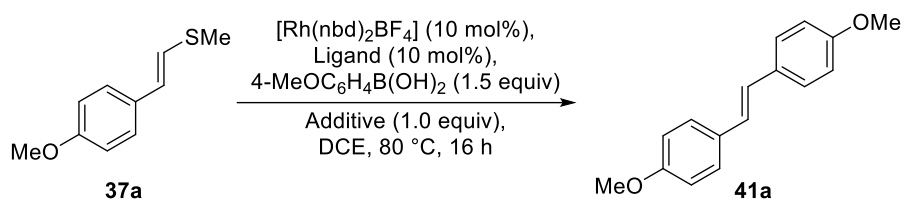
Scheme 4.12 Cross-coupling reaction using previously reported reaction conditions

With a higher catalyst loading of 10 mol%, we next assessed bench-stable pre-catalyst $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ (10 mol%) with various commercially available *bis*-phosphine ligands under the

reaction conditions previously employed. After work-up of the different experiments, complex reaction mixtures were obtained, preventing us from analysing the crude material by NMR spectroscopy. With the desired product being commercially available, we thus turned our attention to HPLC monitoring and analysis of the crude materials. In all cases, no cross-coupling reaction had occurred and various percentages of homocoupling of the boronic acid were measured.

With a complete lack of reactivity using either the preformed or the *in-situ* formed catalyst, an extensive screening of conditions was undertaken exploring a variety of parameters including temperatures, solvents, additives, bases and reagent stoichiometries. Envisaging that higher temperatures might be necessary to achieve the cleavage of the C-S bond, we next selected 1,2-dichloroethane as the solvent of choice since it had already been employed in rhodium-catalysed C-S bond activation. We decided to limit the number of phosphine ligands to Xantphos, dcpe and dppe, and also assessed different additives.

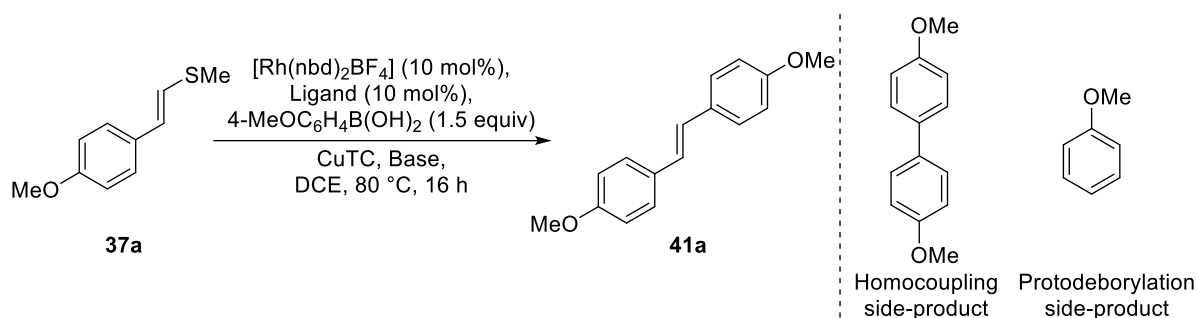
With either silver or sodium carbonate as additive, no product was observed by HPLC monitoring of the reaction mixture (Table 4.1, entries 1-6). When employing potassium carbonate, we were pleasingly able to observe for the first time trace amounts of product (entries 7-9, up to 7% conversion). Considering the success of copper salts as thiophilic agents in several cross-coupling reactions involving C-S bond cleavage,^{52,58} we next assessed copper(I) thiophene-2-carboxylate (CuTC) as an additive (entries 10-12). With Xantphos (entry 10), an encouraging 22% conversion to the desired product was measured. Although the conversion was low, the fact that any cross-coupling was observed at all was promising. However, attempts in isolating the desired product proved unsuccessful.



Entry	Ligand	Additive	HPLC ratio 37a:41a (%)
1	Xantphos	Ag ₂ CO ₃	100:0
2	Dcpe	Ag ₂ CO ₃	100:0
3	Dppe	Ag ₂ CO ₃	100:0
4	Xantphos	Na ₂ CO ₃	98:2
5	Dcpe	Na ₂ CO ₃	100:0
6	Dppe	Na ₂ CO ₃	99:1
7	Xantphos	K ₂ CO ₃	93:7
8	Dcpe	K ₂ CO ₃	99:1
9	Dppe	K ₂ CO ₃	94:6
10	Xantphos	CuTC	78:22
11	Dcpe	CuTC	84:16
12	Dppe	CuTC	85:15

Table 4.1 Additive screening

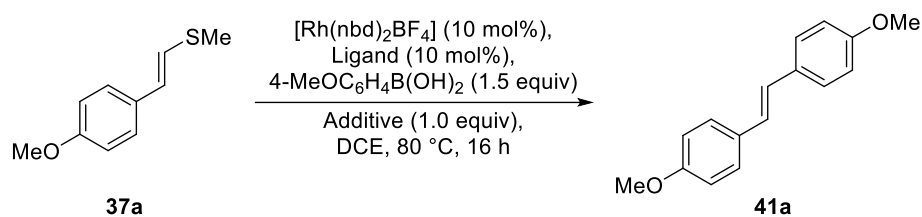
Following these preliminary results, we next attempted to combine CuTC and an inorganic base as reported by Jin *et al.* for the palladium-catalysed cross-coupling reaction of vinyl sulfides (Table 4.2).⁷⁵ The use of one or more equivalents of CuTC with either potassium or cesium carbonate did not offer any observable improvement in conversion (entries 1-9). Additionally, increased percentages of side-products (homocoupling and protodeborylation) were measured.



Entry	Ligand	Additive (equiv)	HPLC ratio 37a:41a (%)
1	Xantphos	CuTC (1) + K ₂ CO ₃ (1)	86:14
2	Dcpe	CuTC (1) + K ₂ CO ₃ (1)	78:22
3	Dppe	CuTC (1) + K ₂ CO ₃ (1)	75:25
4	Xantphos	CuTC (2) + K ₂ CO ₃ (2)	83:17
5	Dcpe	CuTC (2) + K ₂ CO ₃ (2)	88:12
6	Dppe	CuTC (2) + K ₂ CO ₃ (2)	80:20
7	Xantphos	CuTC (2) + Cs ₂ CO ₃ (2)	87:13
8	Dcpe	CuTC (2) + Cs ₂ CO ₃ (2)	82:18
9	Dppe	CuTC (2) + Cs ₂ CO ₃ (2)	81:19

Table 4.2 Different additives and solvents screening

With the first encouraging results emerging from the use of CuTC, we next focused on the evaluation of different commercially available copper sources (Table 4.3). Copper(I) acetate and copper(I) oxide (entries 1-6) showed low to moderate reactivity, with the highest conversion achieved being 24% employing dppe and copper(I) oxide (entry 1). No reaction occurred with copper(II) acetate (entries 7-9) and poor conversions were obtained with copper(I) iodide (entries 10-12), suggesting the importance of both a copper(I) species as well as a suitable counterion. However, the use of copper(I) 3-methylsalicylate (CuMeSal, entries 13-15) allowed us to significantly improve the conversion to 65% with Xantphos (entry 13) and to 70% with dppe (entry 15).



Entry	Ligand	Additive	HPLC ratio 37a:41a (%)
1	Xantphos	CuOAc	85:15
2	Dcpe	CuOAc	99:1
3	Dppe	CuOAc	94:6
4	Xantphos	Cu ₂ O	83:17
5	Dcpe	Cu ₂ O	89:11
6	Dppe	Cu ₂ O	76:24
7	Xantphos	Cu(OAc) ₂	100:0
8	Dcpe	Cu(OAc) ₂	100:0
9	Dppe	Cu(OAc) ₂	100:0
10	Xantphos	CuI	98:2
11	Dcpe	CuI	100:0
12	Dppe	CuI	94:6
13	Xantphos	CuMeSal	35:65
14	Dcpe	CuMeSal	71:29
15	Dppe	CuMeSal	30:70

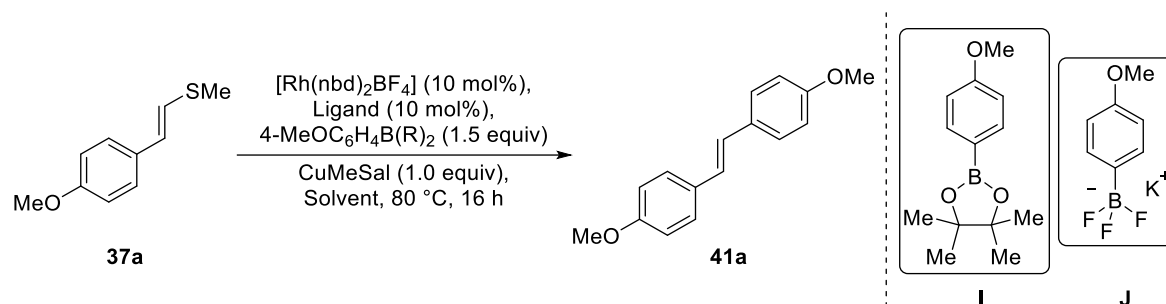
Table 4.3 Screening of different copper sources

Alongside with these promising improvements in the reaction conversion, the percentage of homocoupling and protodeborylation side-products had also increased considerably, preventing us from obtaining accurate NMR spectroscopic analysis of crude materials. Additionally, the purification of the complex mixtures obtained was still troublesome and delivered low yields. Therefore, we thought that additional experiments aiming to suppress the formation of these side-products would be beneficial. In fact, control reactions showed that full consumption of the boronic acid to undesired by-products occurred in eight hours upon treatment with CuMeSal in DCE at 80 °C, suggesting that the presence of copper salts promoted their formation. We therefore decided to screen other boron sources that were less prone to delivering by-products.

Although boronic esters are usually less reactive than their corresponding boronic acids, they dissolve readily in apolar solvents and also withstand a wide variety of reaction conditions.¹²⁹ When assessing the cross-coupling with pinacolboronic ester **I**, only trace amounts of homocoupling and protodeborylation side-products were observed. However, a considerable decrease in the conversion to the desired product was also observed (Table 4.4, entries 1-3).

Alternatively, potassium trifluoroborates **J**, which are air stable electron-deficient sp^3 boron species, are another type of organoboron species that have proved to be highly effective for certain transformations.¹³⁰ These reagents are not the active transmetallating species and require the use of aqueous and/or basic conditions to form the corresponding boronic acid. It is this slow release of the active boronic acid species that allows more effective processes with reduced amounts of side-products. Disappointingly, very little or no reactivity was achieved under the conditions employing CuMeSal in DCE (entries 4-6). Additional reaction conditions were tested including the use of potassium carbonate (entries 7-9) and the variation of the solvent (entries 10-12), but no product was observed in any of these experiments.

Thus, despite the formation of side-products, boronic acids seemed to be the most suitable source of organoboron compounds for the cross-coupling reaction.

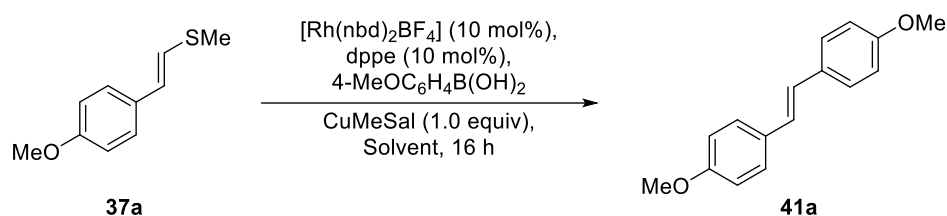


Entry	Ligand	Boron species (I or J)	Base (equiv)	Solvent	HPLC ratio 37a:41a (%)
1	Xantphos	I	-	DCE	97:3
2	Dcpe	I	-	DCE	95:5
3	Dppe	I	-	DCE	90:10
4	Xantphos	J	-	DCE	100:0
5	Dcpe	J	-	DCE	96:4
6	Dppe	J	-	DCE	100:0
7	Xantphos	J	K ₂ CO ₃ (1.0)	DCE	98:2
8	Dcpe	J	K ₂ CO ₃ (1.0)	DCE	99:1
9	Dppe	J	K ₂ CO ₃ (1.0)	DCE	96:4
10	Xantphos	J	K ₂ CO ₃ (1.0)	THF/H ₂ O, 9:1	95:5
11	Dcpe	J	K ₂ CO ₃ (1.0)	THF/H ₂ O, 9:1	97:3
12	Dppe	J	K ₂ CO ₃ (1.0)	THF/H ₂ O, 9:1	95:5

Table 4.4 Evaluation of different organoboron reagents

Taking into account the optimal conditions found so far (dppe with boronic acid and CuMeSal), a new screening was undertaken and each parameter was further explored. This included the variation of ligands, solvents, temperatures and equivalents of reagents, with the most relevant results being summarised in Table 4.5. For the evaluation of solvents and temperatures, similar results than the ones achieved in 1,2-dichloroethane (entry 1) were obtained in refluxing acetone (55 °C, entry 2), tetrahydrofuran (65 °C, entry 3) and chlorobenzene (110 °C, entry 4). However, attempts in purifying these complex mixtures by column chromatography resulted in isolated yields ranging from 24% to 27%. More polar solvents such as 2-propanol and acetonitrile delivered much lower conversions (entries 5 and 6). For the ligand evaluation, the use of an electron-donating substituent on the dppe ligand afforded a slightly higher conversion as opposed to electron-

withdrawing substituent, suggesting that the reaction was more efficient with electron-rich dppe-based ligands (entries 7 and 8). Finally, with commercially available dppe, the best conversion was achieved with two equivalents of boronic acid in 1,2-dichloroethane at 80 °C for 16 hours (entry 9). Under these reaction conditions, 80% conversion of the starting material was measured by HPLC analysis of the crude material; however, the desired product **41a** was isolated in 30% yield. These considerable differences between HPLC conversions and isolated yields were rationalised by the difficulties in separating the various species found in these complex mixtures by column chromatography, which also prevented us from determining the recovered yield of the starting material.



Entry	Ligand	Boronic acid (equiv)	Solvent, Temp. (°C)	HPLC ratio 37a:41a (%)	Isolated yield
1	Dppe	1.5	DCE, 80	30:70	27%
2	Dppe	1.5	Acetone, 55	34:66	24%
3	Dppe	1.5	THF, 65	37:63	26%
4	Dppe	1.5	PhCl, 100	31:69	-
5	Dppe	1.5	2-propanol, 80	78:22	-
6	Dppe	1.5	MeCN, 80	86:14	-
7	<i>p</i> -OMe-dppe	1.5	DCE, 80	25:75	-
8	<i>p</i> -CF ₃ -dppe	1.5	DCE, 80	58:42	-
9	Dppe	2.0	DCE, 80	20:80	30%

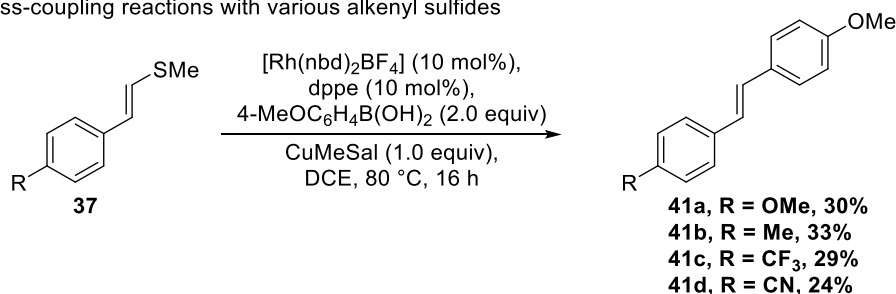
Table 4.5 Evaluation of different ligands, solvents and temperatures

Additionally, the use of microwave irradiation with either acetone or DCE at 100 °C did not allow us to achieve better conversions. Attempts in using freshly prepared CuMeSal delivered a similar result compared to the one obtained with the commercially available copper complex.

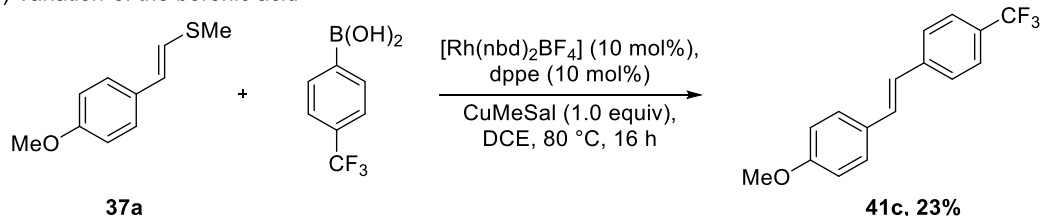
4.3.3 Preliminary scope

Despite not achieving the desired isolated yields, we proved that the tether-free cross-coupling reaction *via* rhodium catalysed C-S activation of alkenyl sulfides was feasible. Thus, we decided to assess the transformation with other alkenyl sulfides **37** and 4-methoxyphenylboronic acid (Scheme 4.13a). Under the optimised reaction conditions, we were able to prepare the desired products (**41a-d**) in modest yields (24-33%), which suggested a negligible influence of the electronics of the *para*- substituent on the reaction conversion. Additionally, in order to assess the effect of the boronic acid, **41c** was alternatively prepared from alkenyl sulfide **37a** with 4-(trifluoromethyl)benzeneboronic acid (Scheme 4.13b). Under the same reaction conditions, the desired product **41c** was isolated in 23% yield, which proved again an insignificant influence of the substituents on the yields, whether they were located on the alkenyl sulfide or the boronic acid.

(a) Cross-coupling reactions with various alkenyl sulfides

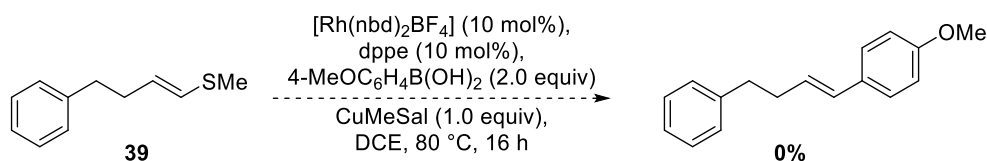


(b) Variation of the boronic acid

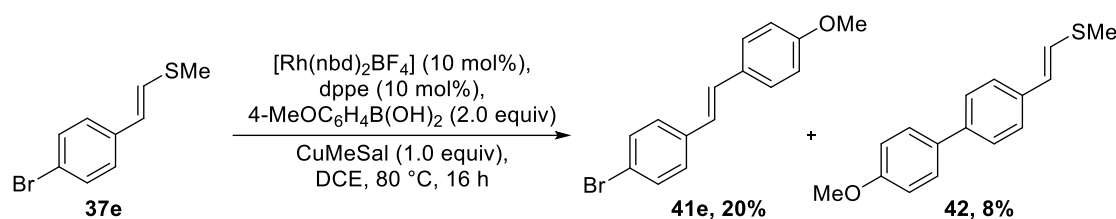


Scheme 4.13 Preliminary scope

Disappointingly, alkenyl sulfide **39** was found to be unreactive (Scheme 4.14), suggesting that the rhodium-catalysed C-S bond cleavage was only effective with styrene derivatives under the optimised reaction conditions.

Scheme 4.14 Evaluation of the transformation with alkenyl sulfide **39**

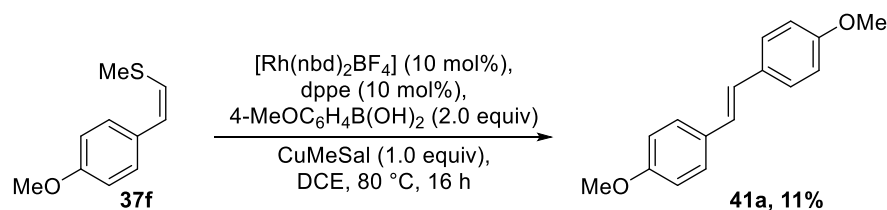
Finally, as the aim of the project was to assess the potential for orthogonal reactivity between C-S and C-halide bonds under rhodium catalysis, the reaction was also carried out with alkenyl sulfide **37e** containing a bromide coupling partner (Scheme 4.15). Although effective monofunctionalisation through rhodium-catalysed cross-coupling had already been achieved with aryl sulfides, the presence of the directing group had played a pivotal role in the selective oxidative addition of the rhodium across the substrate's C-S bond. With tether-free alkenyl sulfide **37e**, we found that the rhodium catalyst employed displayed some chemoselectivity as the desired product **41e** was isolated in 20% yield while the product **42** of cross-coupling reaction occurring at the C-halide bond position was obtained in a lower 8% yield.

Scheme 4.15 Cross-coupling reaction with Br-containing alkenyl sulfide **37e**

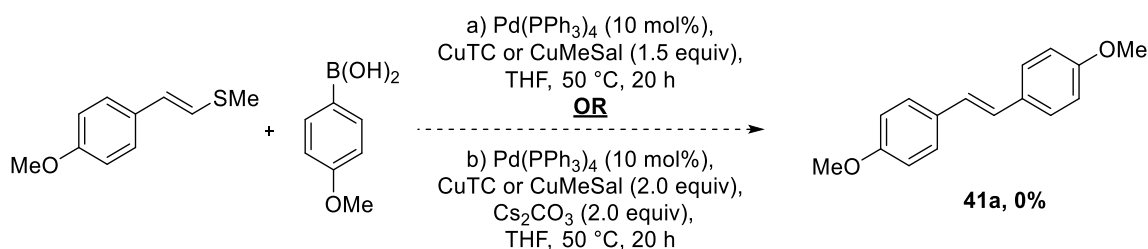
4.3.4 Miscellaneous attempts at a C-S bond activation

In addition to the evaluation of the main cross-coupling reaction of interest, several related transformations have been assessed.

Firstly, the model reaction employing the (*Z*)- instead of the (*E*)-alkenyl sulfide substrate did not deliver the (*Z*)- but the (*E*)-product **41a**, which was isolated in 11% yield (Scheme 4.16). Since the starting material was used as a *Z/E* mixture (10:1), a maximum of 9% yield should have been obtained if the (*E*)-starting material was the only isomer undergoing cross-coupling reaction. This result could potentially suggest that isomerisation of the double bond might have occurred under these reaction conditions, and will be further discussed in the traceless-tether approach.

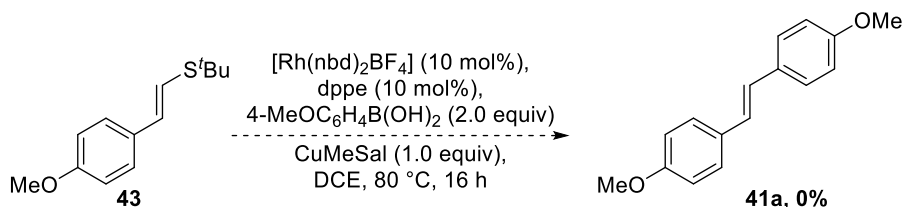
Scheme 4.16 Cross-coupling reaction from (*Z*)-alkenyl sulfide

Additionally, experiments utilising reaction conditions found in similar precedented transformations were carried out, including Liebeskind-Srogl cross-coupling conditions under palladium catalysis (Scheme 4.17)^{68,75} and Negishi-type reaction.¹³¹ All these attempts proved unsuccessful as the desired product was not observed under the different reaction conditions assessed.



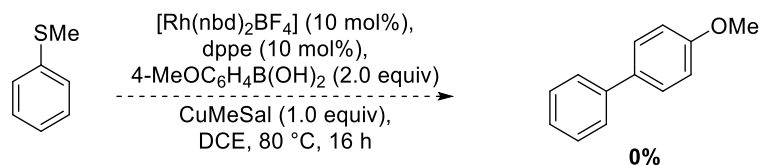
Scheme 4.17 Attempts using reaction conditions reported in the literature for related transformations

Finally, recent developments within the group have shown that aryl *tert*-butyl sulfides (containing an *ortho*-directing group) were more prone to undergoing rhodium-catalysed C-S bond cleavage than their corresponding aryl methyl sulfides.¹⁰³ However, in our case, the *tert*-butyl alkenyl sulfide **43** was found to be unreactive under the optimised reaction conditions (Scheme 4.18).



Scheme 4.18 Cross-coupling reaction with a *tert*-butyl alkenyl sulfide

Although our main focus was the evaluation of cross-coupling reactions with alkenyl sulfides, we also assessed the optimised conditions with tether-free thioanisole substrate (Scheme 4.19). The reaction proved unsuccessful, and the starting material was fully recovered.



Scheme 4.19 Cross-coupling reaction with an aryl sulfide

In conclusion, we have shown that the rhodium-catalysed C-S activation of tether-free alkenyl sulfides could be achieved. It resulted in the isolation of five *trans*-stilbenes with yields ranging from 20% to 33%. Furthermore, partial chemoselectivity was achieved in the presence of a potentially reactive aryl bromide functional group.

4.4 Traceless tether approach

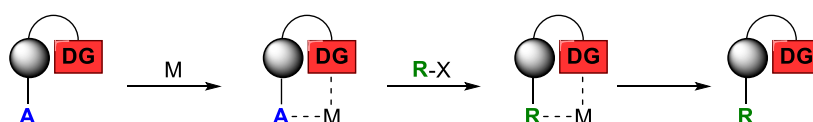
Although we have proved the cross-coupling reaction with tether-free substrates feasible, the yields achieved were not satisfactory. Therefore we wanted to assess another strategy to try improving these results and turned our attention to the use of tether-containing alkenyl sulfides.

In general, methods based on chelation-assisted functionalisation encompass two main strategies: using a directing group incorporated in the substrate and which is also found in the final product (Figure 4.2a). This method covers, among others, various C-H functionalisation reactions including the chelation-assisted hydroacylation explored in our group, as well as the rhodium-catalysed C-S bond activation reactions with the carbonyl tether.¹³²

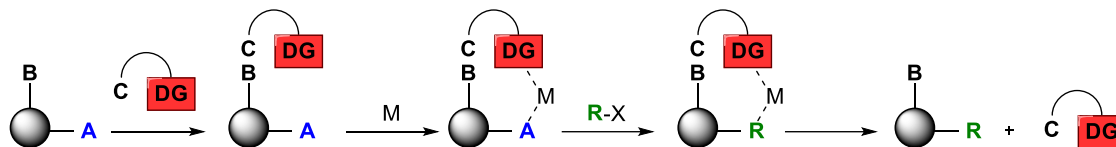
The second approach involves an *in-situ* temporary formation and cleavage of the directing group during the course of the reaction of interest so that the final product will not bear the transient tether (Figure 4.2b).^{20,133} In this case, although the directing group is not found in the final product, its cleavage occurs upon completion of the catalytic event and usually involves the use of additional reagents.

In order to assess a traceless-tether approach, we envisioned a strategy which differed from those previously discussed by employing a substrate incorporating the directing group on the sulfide leaving group (Figure 4.2c). In this approach, the catalytic event itself would concomitantly enable the removal of the directing group. We thought that this strategy would potentially benefit from an overall enhanced reactivity due to the presence of a directing group whilst enabling the preparation of traceless products.

(a) Chelation-assisted functionalisation with the directing group part of the substrate



(b) Chelation-assisted functionalisation with the *in-situ* incorporation and cleavage of the directing group



(c) Our envisioned traceless-tether C-S activation

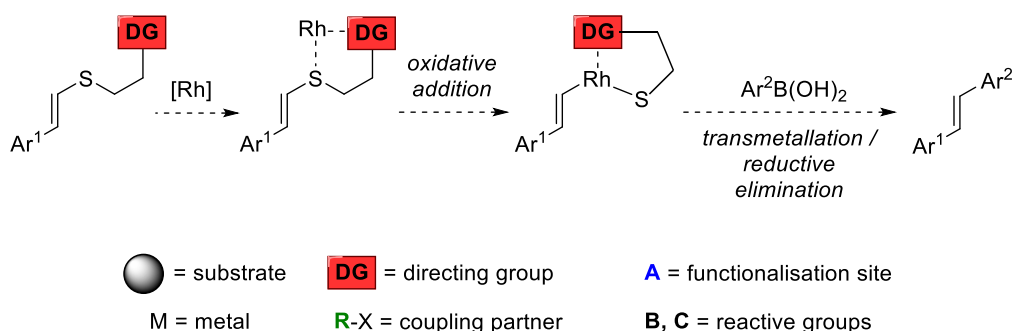
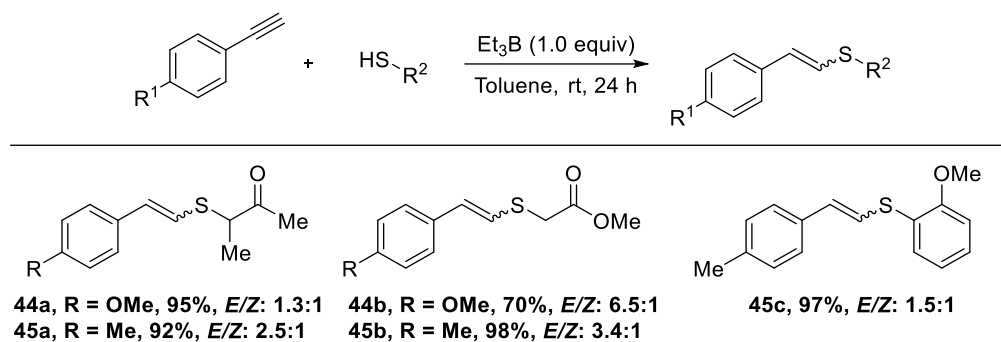


Figure 4.2 Different strategies employing directing groups

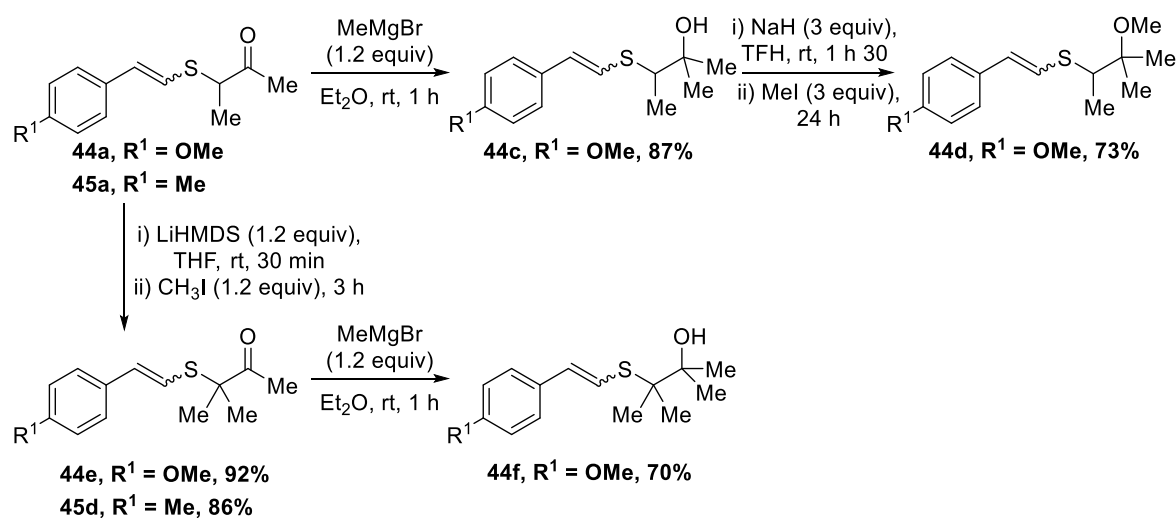
4.4.1 Synthesis of precursors

In order to assess the traceless-tether strategy, we first prepared several alkenyl sulfides incorporating an oxygen-containing directing group. The method previously employed for preparing tether-free (*E*)-alkenyl sulfides was initially considered, however the synthesis of the phosphonate prior to the Horner-Wadsworth-Emmons reaction was impractical and step-intensive. Thus, we turned our attention to the hydrothiolation reaction of simple alkynes with suitable thiols and triethylborane in toluene.¹³⁴ For the thiol component, methyl mercaptoacetate and 3-mercapto-2-butanone were both employed to prepare alkenyl sulfides that incorporated a ketone (**44a**, **45a**, Scheme 4.20) or an ester (**44b**, **45b**) directing group. These sulfides were synthesised in excellent yields at room temperature in 24 hours. However, the selectivities displayed were poor and *E/Z* ratios varied considerably from one experiment to another. An additional product **45c** was prepared in excellent yield with a moderate *E/Z* ratio from a thiophenol derivative displaying a directing group at the *ortho*-position.



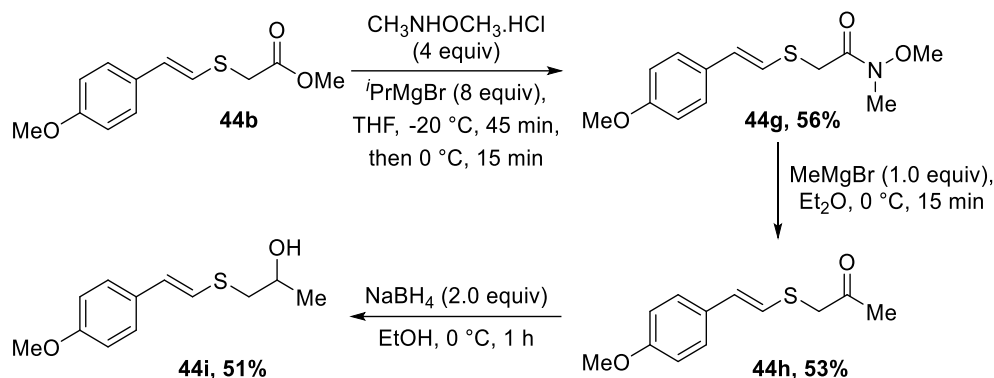
Scheme 4.20 Thiol-yne reaction for the preparation of substrates containing a directing group

From these alkenyl sulfides, simple transformations were carried out in order to access ketone, alcohol, ester and ether-containing substrates. Another parameter taken into account was the level of substitution of each carbon located between the sulfur and the heteroatom coordinating group (Scheme 4.21). Addition of methylmagnesium bromide to **44a** allowed us to prepare **44c** in a good yield, which was further methylated upon treatment with sodium hydride and iodomethane to access the corresponding ether **44d**. On the other hand, methylation of the carbon adjacent to the sulfur heteroatom with lithium hexamethyldisilazane enabled the formation of **44e** and **45d**. Envisaging that increased substitution on the two carbons would be beneficial to coordination of the directing group to the rhodium centre, we finally prepared **44f** which was isolated in 70% yield. As expected, the *E/Z* ratio was not modified by these different transformations (see experimental section).



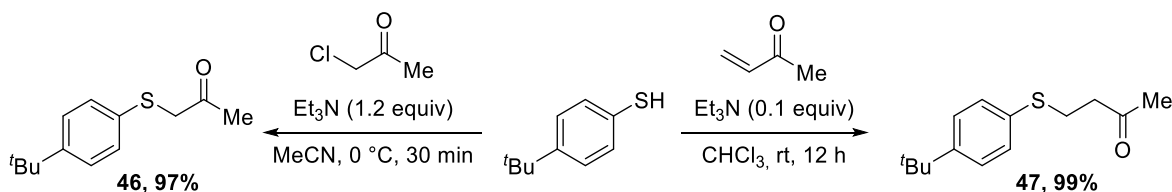
Scheme 4.21 Preparation of oxygen-containing substrates

Additionally, the less sterically encumbered ketone **44h** was prepared from the corresponding Weinreb amide **44g** with methylmagnesium bromide (Scheme 4.22). Treatment of **44h** with sodium borohydride also delivered the corresponding alcohol **44i**.



Scheme 4.22 Preparation of less hindered precursors

In order to also evaluate aryl sulfides for the traceless-tether cross-coupling reaction, we prepared **46** and **47** from 4-(*tert*-butyl)benzenethiol (Scheme 4.23).

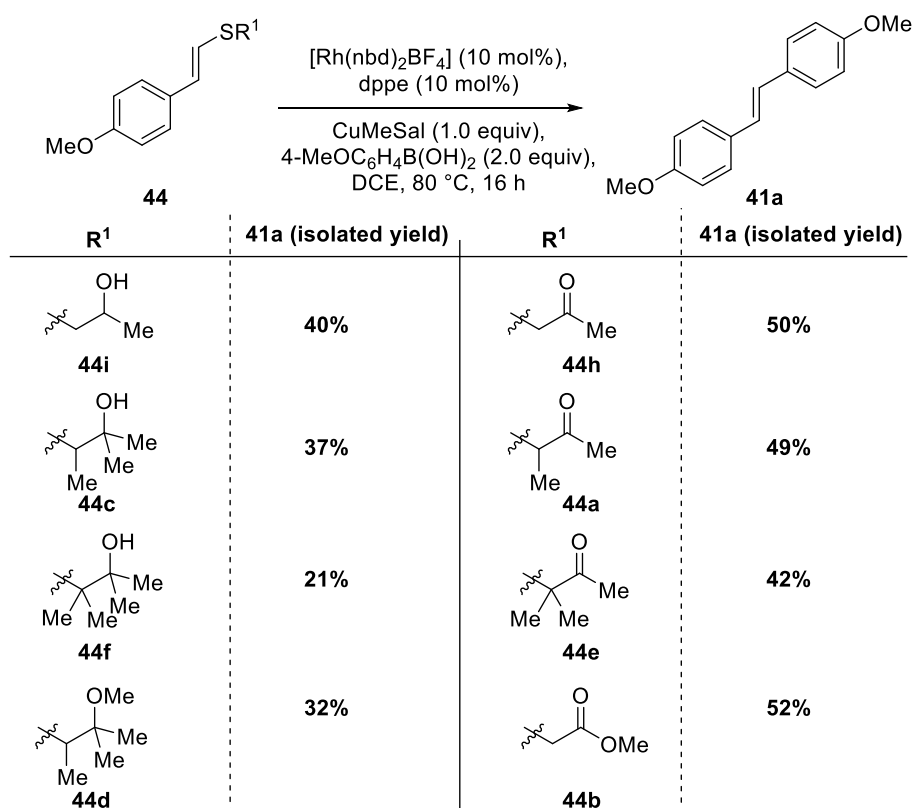


Scheme 4.23 Preparation of directing group-containing aryl sulfides

4.4.2 Cross-coupling reaction with directing group-containing substrates

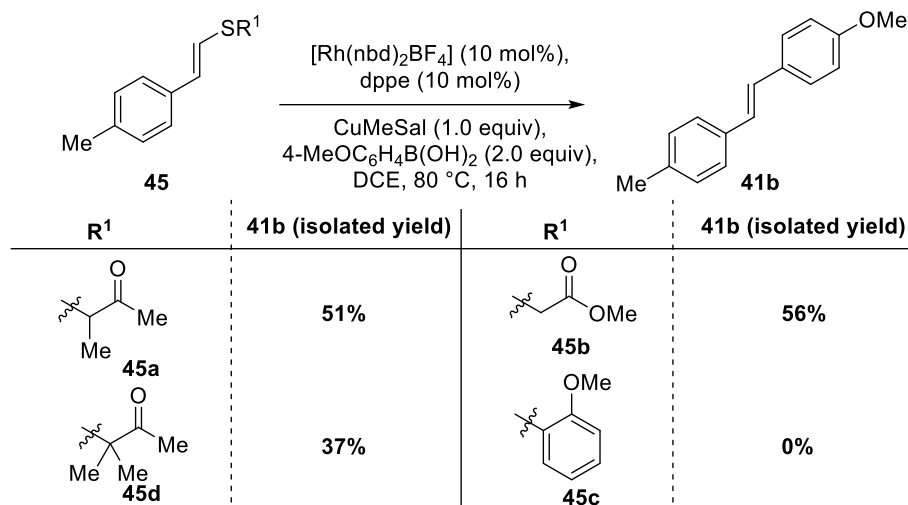
With several precursors in hand, we evaluated whether the rhodium-catalysed cross-coupling reaction was effective in the presence of a directing group. For this purpose, we subjected the different alkenyl sulfide substrates to our previously optimised reaction conditions with CuMeSal and 4-methoxyphenylboronic acid in DCE (Scheme 4.24). With alcohol (**44i**, **44c** and **44f**) and ether (**44d**)-containing substrates, the desired product **41a** was isolated in yields ranging from 21-40%, with three out of the four substrates tested achieving better yields than the tether-free approach (30%). These results suggested that the presence of a directing group on the substrate enhanced the overall reactivity. Although the yields were still modest, the transformations were cleaner and easier to purify in comparison to reactions utilising tether-free substrates. This was mainly due to the diminished formation of side-products as well as the increased polarity of starting

materials, facilitating the separation of the different compounds by column chromatography. The best result was achieved with the less sterically hindered secondary alcohol substrate **44i**. This result was unexpected as we had envisaged that the more substituted substrates would deliver better yields due to an enhanced coordination to the rhodium centre. Additionally, only a small difference of reactivity was observed from alcohol **44c** and its corresponding tertiary methyl-ether **44d**, suggesting that the modest yields were not due to the presence of unprotected alcohols in the reaction mixture. Pleasingly, the transformation proved slightly more successful with ketones (**44h**, **44a** and **44e**), yielding the desired product **41a** in 42% to 50%. Here as well, the *gem*-dimethyl containing substrate **44e** delivered the lowest yield, confirming the detrimental effect of a higher degree of substitution on these carbons. Finally, the best result was achieved with the ester-containing substrate **44b**, delivering the desired product **41a** in a 52% yield.

Scheme 4.24 Cross-coupling reaction *via* a traceless-tether approach

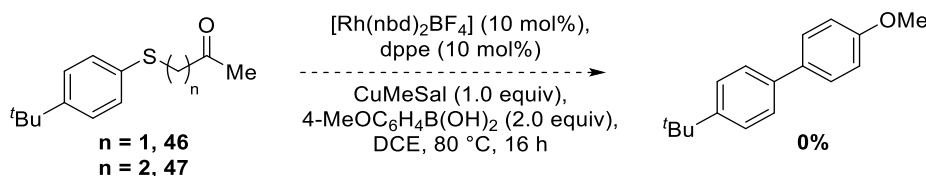
We also assessed a number of *para*-tolyl alkenyl sulfides (Scheme 4.25). Similar observations were made, with the least substituted ketone **45a** delivering the desired product **41b** in 51% yield. When

employing the substrate bearing the ester functional group **45b**, a satisfying 56% yield was achieved. However, no reactivity was obtained from the thiophenol derivative **45c**.



Scheme 4.25 Cross-coupling reaction via a traceless-tether approach

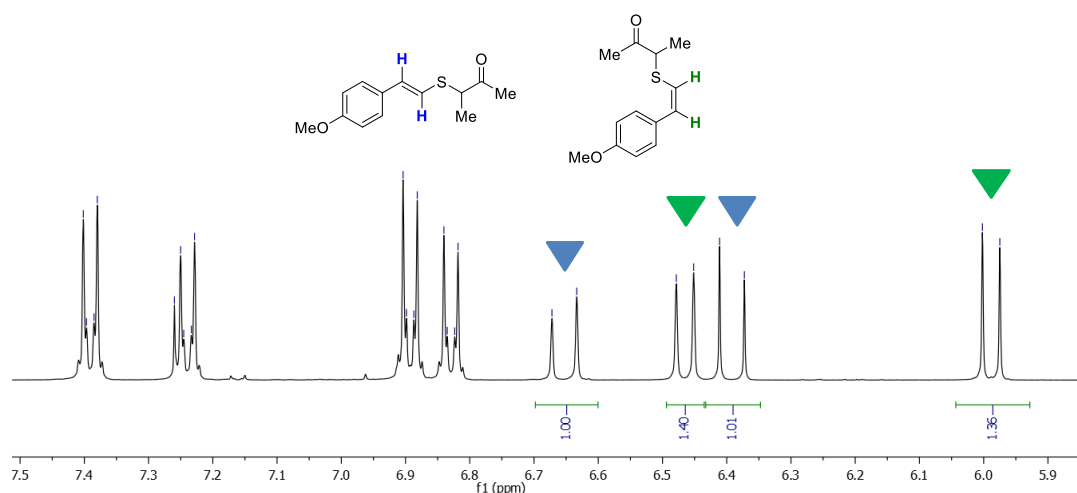
In addition, we also applied the optimised reaction conditions to aryl sulfides **46** and **47** bearing a methyl ketone directing group. The reaction proved unsuccessful, and only the starting material was recovered (Scheme 4.26).



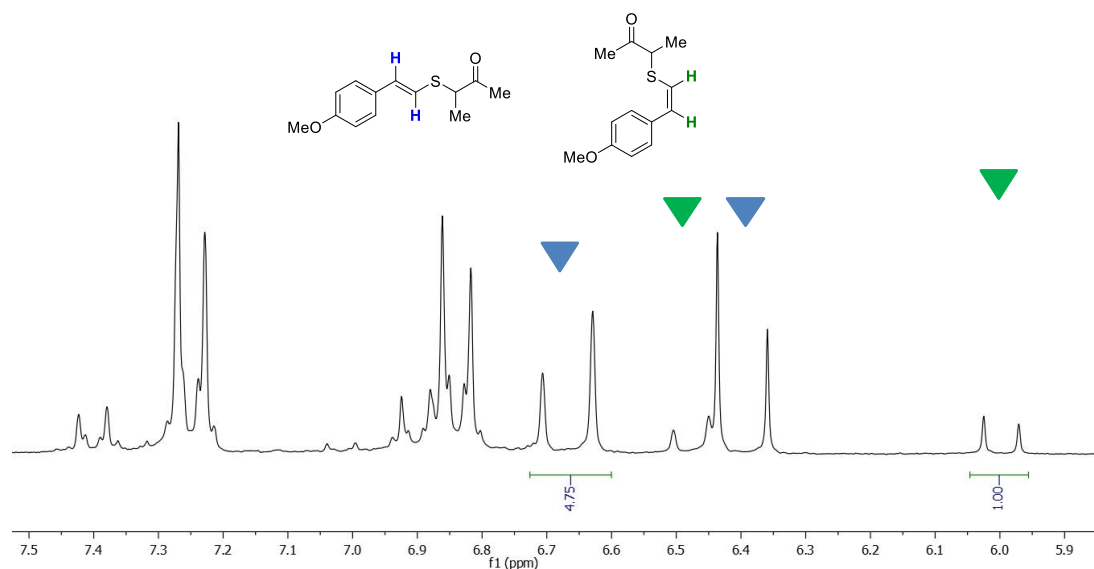
Scheme 4.26 Cross-coupling reaction with aryl sulfides

4.4.3 *E/Z* isomerisation study

It is worth noting that whilst the alkenyl substrates employed for the rhodium-catalysed transformation were used as *E/Z* mixtures, only (*E*)-products have ever been isolated from the cross-coupling reaction. We initially envisioned that isomerisation of the (*Z*)-stilbene product to the (*E*)- was occurring since these compounds are known to easily undergo *E/Z* isomerisation under light and/or heat.¹³⁵ Alternatively, the reaction could be (*E*)-selective; however, this option alone seemed unlikely as yields were found to be relatively similar regardless of the *E/Z* ratio of the alkenyl sulfides. In order to improve our understanding of this process, a number of test reactions were carried out with substrate **44a** displaying a *E/Z* ratio of 1:1.4 (Figure 4.3).

Figure 4.3 Alkenyl sulfide **44a** starting material with an *E/Z* ratio of 1:1.4

When performing the standard reaction overnight employing starting material **44a**, NMR spectroscopic analysis of the crude material showed that only (*E*)-product was formed, and that the *E/Z* ratio of the unreacted starting material had changed, with the (*E*)-isomer dominating. After column chromatography, product **41a** was isolated in 45% yield. Additionally, around 20% of the unreacted starting material **44a** was recovered with a new *E/Z* ratio of 4.75:1 (Figure 4.4).

Figure 4.4 ^1H NMR spectra of the starting material after reaction

These results suggested that isomerisation of the starting material likely occurred under these reaction conditions. To verify this hypothesis, additional test reactions were carried out. To begin with, we stirred a solution of starting material in DCE at 80 °C for 16 hours. By monitoring the

reaction by HPLC, the *E/Z* ratio was found to remain the same under these conditions, thus ruling out the possibility of a thermal isomerisation (Figure 4.5a). Similarly, no change was recorded when employing the rhodium catalyst and ligand at a 10 mol% catalyst loading. Surprisingly, no isomerisation occurred with CuMeSal either, and only upon treatment of the starting material with three equivalents of 4-methoxyphenylboronic acid was the *E/Z* ratio found changed after filtration through a short pad of silica (Figure 4.5b).

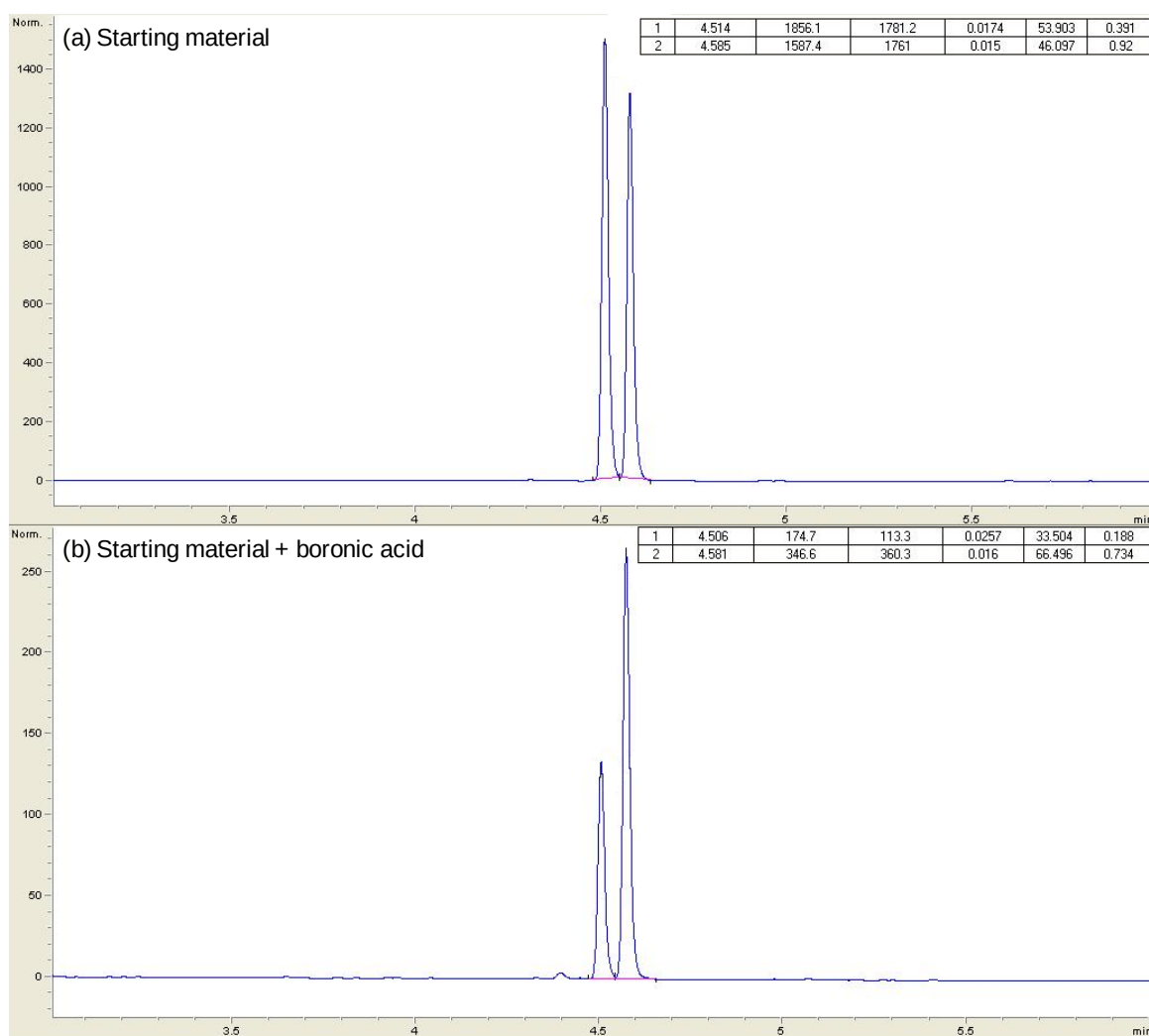


Figure 4.5 *E/Z* isomerisation monitored by HPLC

These results indicated that an acid-mediated isomerisation was likely occurring under these reaction conditions, which was further confirmed by treating the starting material with acetic acid in 1,2-dichloroethane, also resulting in an increase of the *E/Z* ratio.

These experiments indicated that the cross-coupling reaction was likely (*E*)-selective and that isomerisation of the starting material was occurring. With these informations in hands, the process could potentially be related to a dynamic kinetic resolution.

4.5 Conclusions

In summary, achieving the formation of tetherless products by means of rhodium-catalysed C-S bond activation of alkenyl sulfides with boronic acids has been highly challenging. The first approach involving tether-free alkenyl methyl sulfides has shown that the concept was feasible and a number of cross-coupled products could be prepared in modest yields with various electron-donating and electron-withdrawing *para*-substituents. Additionally, partial chemoselectivity was achieved by evaluating the reaction with an alkenyl-sulfide incorporating another reactive functional group.

On the other hand, the traceless-tether approach was found to be more successful. This strategy involved the synthesis of various oxygen-containing alkenyl sulfides, with the directing group located on the leaving group. This method resulted in improved conversions, with yields reaching up to 56%. Alcohol, ether, ketone and ester directing groups all enabled formation of the product, with the best results obtained from the least substituted starting materials.

Chapter 5

Conclusions and future work

The last thirty years have seen major advances in the field of rhodium-catalysed alkene and alkyne hydroacylation reactions. For intermolecular processes, the use of directing groups has become an established approach to stabilise rhodium intermediates and thus prevent undesired side-reactions. Over the last decade, the Willis group has largely contributed to the development of efficient rhodium-catalysed hydroacylations with sulfur-chelates. In addition, to overcome the limitation of having a directing group in the final product, Willis and co-workers have focused their efforts on developing processes that enabled the recycling, the removal or the functionalisation of the chelate.

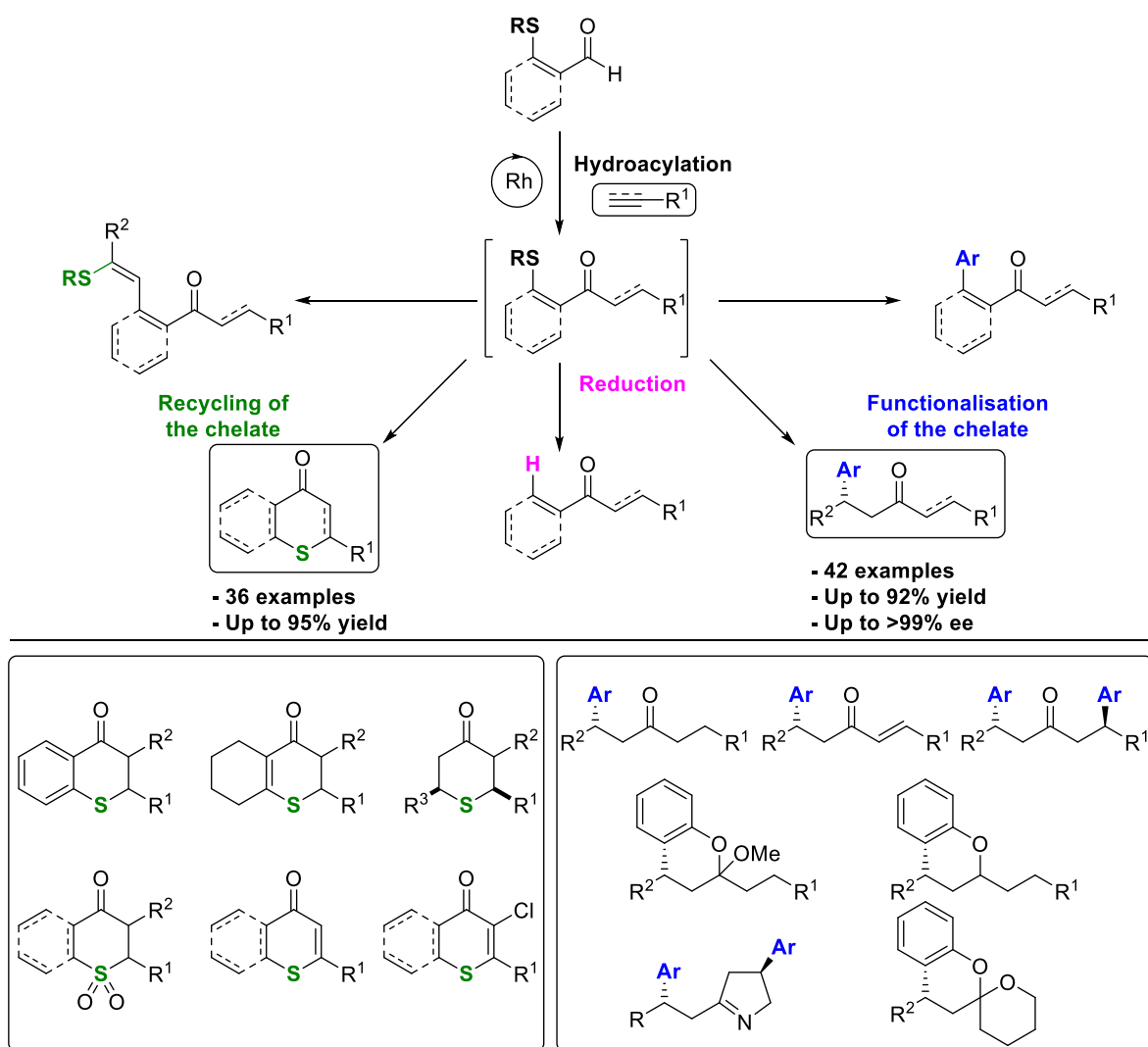
This thesis has illustrated advances made in this field and the new processes developed have been targeted to further improve the synthetic utility of hydroacylation couplings.

The first project of this thesis has described a general method to replace the sulfide tether by a useful functional group when employing alkyl aldehyde substrates. To completely offset the use of a directing group, the three-step transformation involving an alkene hydroacylation, sulfide elimination and 1,4-conjugate addition has been developed in a tandem fashion. This process has enabled the preparation of highly functionalised β -substituted ketones in excellent yields and high enantioselectivities (Scheme 5.1).

The second project shown in this thesis has illustrated a highly efficient process and practical method to access a range of *S*-heterocycles by taking advantage of the presence of the sulfur directing group to further engage it in a thio-Michael addition after the alkyne hydroacylation step.

This synthetically useful transformation has allowed access to a variety of *S*-containing heterocycles, and shown once again great tolerance in the substrate scope (Scheme 5.1).

For these two first projects, further derivatisation of the products has allowed the preparation of valuable heterocyclic structures.



Scheme 5.1 Developing new processes to remove, recycle or functionalise the *S*-chelate

On the other hand, the Willis group has, over the last few years, also engaged sulfide directing groups in a number of rhodium-catalysed transformations involving a C-S bond cleavage. However, the scope of these reactions was limited to substrates containing a neighbouring directing group, necessary to promote the oxidative addition of the rhodium across the C-S bond. In an effort to overcome this limitation and expand the scope of substrates, this thesis has shown, in the final

part, the progress made in the preparation of tether-free olefins by rhodium-catalysed cross-coupling reaction with alkenyl sulfides. In a first approach, the transformation was shown to be feasible with tether-free alkenyl sulfides. However, improved yields and reactivity were achieved from the traceless tether approach, which enabled the formation of the stilbene derivatives in moderate to good yields.

Important future work specific to this chemistry is to conduct further investigations into the traceless-tether approach. The assessment of other heteroatoms (sulfur and nitrogen in particular) and functional groups is crucial to try improving the results obtained and could potentially provide the opportunity to achieve the desired yields. If this screening was successful, the scope of the reaction could be evaluated and the reactivity of rhodium catalysts towards C-S bonds could also be tested in the presence of halides. Additionally, gaining further insight into the different species generated in the catalytic cycle would be of particular interest.

Chapter 6

Experimental section

6.1 General considerations

Reactions were conducted with continuous magnetic stirring under an inert atmosphere of nitrogen (passed through a Drierite® and silica filled drying tube before use) and using dry solvents unless otherwise stated. Glassware was oven-dried (>100 °C), and allowed to cool to room temperature under vacuum once assembled. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Alfa Aesar, Fluorochem Ltd. or Strem Chemicals Inc. and were used as supplied. Alkenes and alkynes were distilled prior to use. 1,2-Dichloroethane was purchased from Rathburn (HPLC grade), distilled over CaH₂ and degassed; acetone was purchased from Fischer (HPLC grade), distilled over Drierite® and degassed. The other solvents were collected fresh from an in-house solvent purification system, which involves passing the solvent through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Microwave conditions were achieved using a CEM Discover-S microwave synthesiser.

Reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminum-backed silica plates (Merck Kieselgel 60 F254). Plates were visualised under ultraviolet light (254 nm) followed by staining with potassium permanganate, vanillin or Seebach's stain (Magic).¹³⁶ Flash column chromatography was carried out using Geduran® Si 60, 40-63 micron silica gel; the compound to be purified was either loaded as oil or pre-absorbed onto silica. Pressure was applied to the column head by hand bellows. Petrol refers to the fraction of light petroleum ether boiling in

the range 40-60 °C. Rhodium complexes were synthesised according to a reported procedure and was weighed out in air and stored in a vial under reduced pressure.^{91,92,137} Diastereomeric ratios (dr) were determined by ¹H NMR on the crude mixture.

¹H NMR spectra were obtained on a Bruker AVIII400 (400 MHz) or AVII500 with He cryoprobe (500 MHz) spectrometers, using the residual solvent as an internal standard. ¹³C NMR spectra were obtained on a Bruker AVIII400 (101 MHz) or AVII500 (126 MHz) spectrometers and ¹⁹F NMR spectra on a Bruker AVIII400 (377 MHz). Acquisitions were carried out at ambient temperature. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (J) were given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (p), multiplet (m), broad (br), apparent (app.). Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, DEPT, nOe data and comparison with spectra of related compounds. Several compounds were isolated as a mixture of isomers. Up to a 5:1 ratio, both isomers were described. Above a 5:1 ratio, only the major isomer was described. Low resolution ESI⁺ mass spectra were recorded on a Waters LCT Premier spectrometer. High resolution mass spectra were recorded either on a Brüker Daltronics MicroTOF spectrometer under electrospray ionisation conditions (ESI⁺) or on a Micromass LCT under the conditions of chemical ionization (CI⁺) or field ionization (FI) by the internal service at Chemistry Research Laboratory, University of Oxford. Samples for mass spectra were prepared at a concentration near 1 mg/mL solution in methanol (LRMS, HRMS-ESI⁺) or submitted neat (HRMS-FI and CI⁺). Values quoted are a ratio of mass to charge in Daltons and relative intensities of peaks observed are quoted as a percentage. High resolution values are calculated to four decimal places from the molecular formula. Reverse phase HPLC analysis was performed on Agilent Zorbax SB-C18 5 μ m column (4.6 $\times$ 150 mm), eluted with a mixture of acetonitrile/water at 1 mL/min (gradient: 10-95% acetonitrile in 6 min). The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Dionex P680 chromatograph with a Dionex UVD170U detector (Daicel Chiralpak AD-H, AS-H, IC, IA-3, ID-3, OD-H, AY-H columns). Infrared spectra were

recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer with internal calibration in the range 4000-600 cm^{-1} . Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1 and optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter.

Important note: products prepared either by DPhil student Ming Gao or Part II student Jack Glancy are not reported in this experimental section.

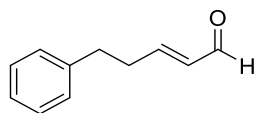
6.2 Chapter 2 data

6.2.1 Starting material synthesis

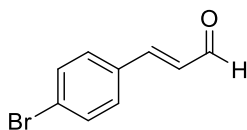
General Procedure A: synthesis of α,β -unsaturated aldehydes

A solution of (triphenylphosphoranylidene)acetaldehyde (1.1 equiv) and aldehyde (1.0 equiv) in CHCl_3 (0.3 M) was heated at 50 $^{\circ}\text{C}$ for 16 h and then concentrated under reduced pressure. Purification by flash column chromatography afforded the desired product.

(*E*)-5-Phenylpent-2-enal **14a**



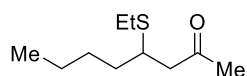
The desired aldehyde was prepared according to general procedure **A** using (triphenylphosphoranylidene)acetaldehyde (0.36 g, 1.1 mmol) and hydrocinnamaldehyde (0.14 mL, 1.0 mmol) in CHCl_3 (3.3 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the desired aldehyde **14a** (0.12 g, 0.70 mmol, 72%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 9.55 (d, J = 8.0 Hz, 1H, CHO), 7.47-7.20 (m, 5H, H_{Ar}), 6.92 (dt, J = 15.5, 6.5 Hz, 1H, $\text{HC}=\text{CH}-\text{CHO}$), 6.20 (ddt, J = 15.5, 8.0, 1.5 Hz, 1H, $\text{HC}=\text{CH}-\text{CHO}$), 2.90 (t, J = 7.5 Hz, 2H, $\text{Ph}-\text{CH}_2-\text{CH}_2$), 2.78-2.69 (m, 2H, $\text{CH}_2-\text{CH}_2-\text{CH}$); ^{13}C NMR (101 MHz, CDCl_3): δ 194.1, 157.5, 140.4, 133.5, 128.7, 128.4, 126.5, 34.4, 34.2; LRMS (ESI $^+$): m/z 183.1 ($[\text{M}+\text{Na}]^+$, 100%). This data is consistent with the literature.¹³⁸

(E)-3-(4-Bromophenyl)acrylaldehyde 14b

The desired aldehyde was prepared according to general procedure **A** using (triphenylphosphoranylidene)-acetaldehyde (1.0 g, 3.3 mmol) and 4-bromobenzaldehyde (0.56 g, 3.0 mmol) in CHCl_3 (3.3 mL). Purification by flash column chromatography (petrol/ Et_2O , 8:2) afforded the desired aldehyde **14b** (0.35 g, 1.7 mmol, 56%) as a yellow powder. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.70 (d, $J = 7.5$ Hz, 1H, CHO), 7.58-7.55 (m, 2H, H_{Ar}), 7.47-7.39 (m, 3H, 2 $\times H_{Ar}$ and $\text{HC}=\text{CH}-\text{CHO}$), 6.69 (dd, $J = 16.0, 7.5$ Hz, 1H, $\text{HC}=\text{CH}-\text{CHO}$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 193.5, 151.3, 133.0, 132.5, 129.9, 129.1, 125.8; **LRMS** (ESI^+): m/z 265.1 ($[^{79}\text{BrM}+\text{MeOH}+\text{Na}]^+$, 50%), 267.1 ($[^{81}\text{BrM}+\text{MeOH}+\text{Na}]^+$, 50%); **M.p.** (Et_2O): 80-82 °C (lit. m.p. 80-81 °C). This data is consistent with the literature.¹³⁹

General procedure B: synthesis of β -S aldehydes and ketones

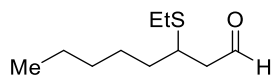
Triethylamine (0.2 equiv) was added to a solution of aldehyde (1.0 equiv) and ethanethiol (2.0 equiv) in CHCl_3 (2.0 M). The resulting mixture was heated under microwave irradiations at 110 °C for 1 h and then concentrated under reduced pressure. Purification by flash column chromatography afforded the aldehyde.

4-(Ethylthio)octan-2-one 9

The desired product was prepared according to general procedure **B**, using triethylamine (0.11 mL, 0.8 mmol), 3-octen-2-one (0.60 mL, 4.0 mmol) and ethanethiol (0.57 mL, 8.0 mmol) in CHCl_3 (2.0 mL). Purification by flash column chromatography (petrol/ Et_2O , 95:5) afforded the *desired ketone 9* (0.68 g, 3.6 mmol, 91%) as a colourless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 3.08 (p, $J = 7.0$ Hz, 1H, $\text{CH}-\text{S}$), 2.70 (dd, $J = 17.0, 7.0$ Hz, 1H, $\text{CH}_a\text{H}_b-\text{CO}$), 2.62 (dd, $J = 17.0, 7.0$ Hz, 1H, $\text{CH}_a\text{H}_b-\text{CO}$), 2.51 (q, $J = 7.5$ Hz, 2H, $\text{S}-\text{CH}_2$), 2.15 (s, 3H, $\text{CO}-\text{CH}_3$), 1.58-1.46 (m, 2H, $\text{CH}-\text{CH}_2-\text{CH}_2$), 1.45-1.25 (m, 4H, 2 $\times \text{CH}_2$), 1.21 (t, $J = 7.5$ Hz, 3H, $\text{S}-\text{CH}_2-\text{CH}_3$), 0.88 (t, $J = 7.0$ Hz, 3H, $\text{CH}_2-\text{CH}_2-\text{CH}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 207.2, 49.8, 40.4, 35.2, 30.9, 29.1, 25.0,

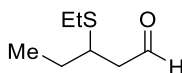
22.6, 14.9, 14.1; **LRMS** (ESI⁺): m/z 211.1 ([M+Na]⁺, 100%), 189.1 ([M+H]⁺, 20%); **HRMS** (ESI⁺): C₁₀H₂₀OSNa requires 211.1127 [M+Na]⁺, found 211.1127; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2958, 2929, 1715, 1358.

3-(Ethylthio)octanal **7a**

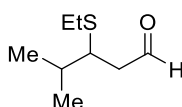


The desired product was prepared according to general procedure **B**, using triethylamine (0.14 mL, 1.0 mmol), *trans*-2-octenal (0.75 mL, 5.0 mmol) and ethanethiol (0.71 mL, 10 mmol) in CHCl₃ (2.5 mL). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired aldehyde **7a** (0.92 g, 4.9 mmol, 98%) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 9.77 (t, J = 2.0 Hz, 1H, CHO), 3.11 (p, J = 6.5 Hz, 1H, CH-S), 2.67-2.60 (m, 2H, CH₂-CO), 2.54 (q, J = 7.5 Hz, 2H, S-CH₂), 1.64-1.55 (m, 2H, CH-CH₂-CH₂), 1.48-1.26 (m, 6H, 3 $\times$ CH₂), 1.24 (t, J = 7.5 Hz, 3H, S-CH₂-CH₃), 0.88 (t, J = 7.0 Hz, 3H, CH₂-CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 201.3, 48.9, 39.4, 35.4, 31.7, 26.6, 24.6, 22.6, 14.9, 14.1; **LRMS** (ESI⁺): m/z 243.1 ([M+MeOH+Na]⁺, 100%). This data is consistent with the literature.³¹

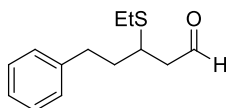
3-(Ethylthio)pentanal **7b**



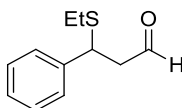
The desired product was prepared according to general procedure **B**, using triethylamine (0.11 mL, 0.80 mmol), *trans*-2-pentenal (0.39 mL, 4.0 mmol) and ethanethiol (0.57 mL, 8.0 mmol) in CHCl₃ (2.0 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired* aldehyde **7b** (0.45 g, 3.1 mmol, 77%) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃): δ 9.76 (t, J = 2.0 Hz, 1H, CHO), 3.09-3.03 (m, 1H, CH-S), 2.67-2.59 (m, 2H, CH₂-CO), 2.53 (q, J = 7.5 Hz, 2H, S-CH₂), 1.69-1.58 (m, 2H, CH-CH₂-CH₃), 1.23 (t, J = 7.5 Hz, 3H, S-CH₂-CH₃), 0.99 (t, J = 7.5 Hz, 3H, CH-CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 201.2, 48.5, 41.0, 28.2, 24.7, 14.9, 11.3; **LRMS** (ESI⁺): m/z 201.1 ([M+MeOH+Na]⁺, 100%); **HRMS** (ESI⁺): C₇H₁₄OSNa requires 169.0658 [M+Na]⁺, found 169.0659; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2966, 2930, 2874, 1721, 1453, 1379, 1265.

3-(Ethylthio)-4-methylpentanal 7c

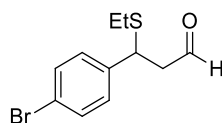
The desired product was prepared according to general procedure **B**, using triethylamine (0.11 mL, 0.80 mmol), 4-methyl-2-pentenal (95%, 0.49 mL, 4.0 mmol) and ethanethiol (0.57 mL, 8.0 mmol) in CHCl_3 (2.0 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired aldehyde 7c* (0.51 g, 3.2 mmol, 79%) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.79 (dd, $J = 2.5, 1.5$ Hz, 1H, CHO), 3.12-2.93 (m, 1H, CH-S), 2.69-2.51 (m, 4H, $\text{CH}_2\text{-CO}$ and S-CH_2), 2.01-1.82 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 1.23 (t, $J = 7.5$ Hz, 3H, $\text{S-CH}_2\text{-CH}_3$), 0.99 (d, $J = 7.0$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 0.97 (d, $J = 7.0$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 201.5, 46.50, 46.48, 32.5, 26.3, 19.5, 19.4, 14.0; **LRMS** (ESI^+): m/z 215.1 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_8\text{H}_{16}\text{OSNa}$ requires 183.0814 $[\text{M}+\text{Na}]^+$, found 183.0816; **IR**: ν_{max} (neat)/ cm^{-1} 2962, 2929, 2872, 1723, 1462, 1284, 1265.

3-(Ethylthio)-5-phenylpentanal 7d

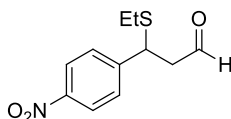
The desired product was prepared according to general procedure **B**, using triethylamine (20 μL , 0.14 mmol), (*E*)-5-phenylpent-2-enal **14a** (0.11 g, 0.70 mmol) and ethanethiol (0.10 mL, 1.4 mmol) in CHCl_3 (0.4 mL, 1.75 M). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired aldehyde 7d* (0.13 g, 0.58 mmol, 83%) as a pale yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.79 (t, $J = 2.0$ Hz, 1H, CHO), 7.38-7.28 (m, 2H, H_{Ar}), 7.28-7.19 (m, 3H, H_{Ar}), 3.16 (p, $J = 7.0$ Hz, 1H, CH-S), 2.89-2.76 (m, 2H, $\text{Ph-CH}_2\text{-CH}_2$), 2.73 (dd, $J = 7.0, 2.0$ Hz, 2H, $\text{CH}_2\text{-CO}$), 2.59 (q, $J = 7.5$ Hz, 2H, $\text{S-CH}_2\text{-CH}_3$), 1.98-1.92 (m, 2H, $\text{Ph-CH}_2\text{-CH}_2$), 1.28 (t, $J = 7.5$ Hz, 3H, $\text{S-CH}_2\text{-CH}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 201.0, 141.4, 128.6, 128.5, 126.2, 49.0, 38.8, 36.9, 33.1, 24.5, 14.9; **LRMS** (ESI^+): m/z 277.1 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{13}\text{H}_{19}\text{OS}$ requires 223.1151 $[\text{M}+\text{H}]^+$, found 223.1153; **IR**: ν_{max} (neat)/ cm^{-1} 3026, 2927, 2360, 1721, 1496, 1454, 1265.

3-(Ethylthio)-3-phenylpropanal 7e

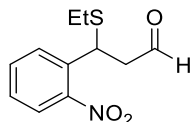
The desired product was prepared according to general procedure **B**, using triethylamine (0.11 mL, 0.80 mmol), *trans*-cinnamaldehyde (0.50 mL, 4.0 mmol) and ethanethiol (0.57 mL, 8.0 mmol) in CHCl_3 (2.0 mL). The resulting mixture was stirred at 22 °C for 12 h. Purification by flash column chromatography (petrol/ CH_2Cl_2 , 1:1) afforded the desired aldehyde **7e** (0.69 g, 3.5 mmol, 88%) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ 9.71 (t, J = 2.0 Hz, 1H, *CHO*), 7.38-7.24 (m, 5H, H_{Ar}), 4.38 (t, J = 7.5 Hz, 1H, *CH-S*), 2.99 (ddd, J = 17.0, 7.5, 2.0 Hz, 1H, $\text{CH}_a\text{H}_b\text{-CO}$), 2.93 (ddd, J = 17.0, 7.5, 2.0 Hz, 1H, $\text{CH}_a\text{H}_b\text{-CO}$), 2.42-2.28 (m, 2H, *S-CH*₂), 1.17 (t, J = 7.5 Hz, 3H, *S-CH*₂-*CH*₃); **^{13}C NMR** (101 MHz, CDCl_3): δ 199.6, 141.4, 128.8, 127.7, 127.6, 49.9, 43.0, 25.3, 14.4; **LRMS** (ESI^+): m/z 249.1 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 100%). This data is consistent with the literature.²⁸

3-(4-Bromophenyl)-3-(ethylthio)propanal 7f

The desired product was prepared according to general procedure **B**, using triethylamine (38 μL , 0.27 mmol), (*E*)-3-(4-bromophenyl)acrylaldehyde **14b** (0.28 g, 1.3 mmol) and ethanethiol (0.19 mL, 2.7 mmol) in CHCl_3 (0.7 mL). Purification by flash column chromatography (petrol/ Et_2O , 85:15) afforded the *desired aldehyde* **7f** (0.31 g, 1.1 mmol, 85%) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ 9.68 (t, J = 1.5 Hz, 1H, *CHO*), 7.48-7.42 (m, 2H, H_{Ar}), 7.25-7.23 (m, 2H, H_{Ar}), 4.33 (t, J = 7.5 Hz, 1H, *CH-S*), 2.93 (dd, J = 7.5, 1.5 Hz, 2H, $\text{CH}_2\text{-CO}$), 2.32 (qd, J = 7.5, 4.5 Hz, 2H, *S-CH*₂-*CH*₃), 1.16 (t, J = 7.5 Hz, 3H, *S-CH*₂-*CH*₃); **^{13}C NMR** (101 MHz, CDCl_3): δ 199.1, 140.7, 131.9, 129.5, 121.3, 49.8, 42.3, 25.3, 14.4; **LRMS** (ESI^+): m/z 327.1 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 50%), 329.2 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 50%); **HRMS** (ESI^+): $\text{C}_{11}\text{H}_{13}\text{OS}^{79}\text{BrNa}$ requires 294.9763 $[\text{M}+\text{Na}]^+$, found 294.9764; **IR**: ν_{max} (neat)/ cm^{-1} 2971, 2928, 2826, 1722, 1487, 1404, 1384, 1315.

3-(Ethylthio)-3-(4-nitrophenyl)propanal 7g

The desired product was prepared according to general procedure **B**, using triethylamine (56 μ L, 0.40 mmol), 4-nitrocinnamaldehyde (0.35 g, 2.0 mmol) and ethanethiol (0.29 mL, 4.0 mmol) in CHCl_3 (1.0 mL). Purification by flash column chromatography (petrol/ CH_2Cl_2 , 1:1) afforded the *desired aldehyde 7g* (0.30 g, 1.3 mmol, 63%) as an orange oil. **^1H NMR** (400 MHz, CDCl_3): δ 9.70 (t, J = 1.0 Hz, 1H, CHO), 8.23-8.10 (m, 2H, H_{Ar}), 7.57-7.52 (m, 2H, H_{Ar}), 4.45 (t, J = 7.5 Hz, 1H, CH-S), 3.06-2.97 (m, 2H, $\text{CH}_2\text{-CO}$), 2.33 (qd, J = 7.5, 3.5 Hz, 2H, S- $\text{CH}_2\text{-CH}_3$), 1.17 (t, J = 7.5 Hz, 3H, S- $\text{CH}_2\text{-CH}_3$); **^{13}C NMR** (101 MHz, CDCl_3): δ 198.2, 149.5, 147.3, 128.9, 124.1, 49.7, 42.1, 25.5, 14.3; **LRMS** (ESI^+): m/z 294.1 ($[\text{M}+\text{MeOH}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{11}\text{H}_{13}\text{O}_3\text{NSNa}$ requires 262.0508 $[\text{M}+\text{Na}]^+$, found 262.0509; **IR**: ν_{max} (neat)/ cm^{-1} 2928, 1721, 1597, 1517, 1452, 1343, 1267.

3-(Ethylthio)-3-(2-nitrophenyl)propanal 7h

The desired product was prepared according to general procedure **B**, using triethylamine (0.21 mL, 1.5 mmol, 0.5 equiv), 2-nitrocinnamaldehyde (0.53 g, 3.0 mmol) and ethanethiol (0.43 mL, 6.0 mmol) in CHCl_3 (1.5 mL). Purification by flash column chromatography (petrol/ Et_2O , 8:2) afforded the *desired aldehyde 7h* (0.39 g, 1.6 mmol, 54%) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ 9.69 (dd, J = 2.0, 1.0 Hz, 1H, CHO), 7.81 (td, J = 8.0, 1.0 Hz, 2H, H_{Ar}), 7.61 (ddd, J = 7.5, 4.5, 1.0 Hz, 1H, H_{Ar}), 7.39 (ddd, J = 8.0, 7.0, 1.5 Hz, 1H, H_{Ar}), 5.13-5.01 (m, 1H, CH-S), 3.02 (ddd, J = 17.5, 7.0, 1.0 Hz, 1H, $\text{CH}_a\text{H}_b\text{-CO}$), 2.93 (ddd, J = 17.5, 8.0, 2.0 Hz, 1H, $\text{CH}_a\text{H}_b\text{-CO}$), 2.48-2.35 (m, 2H, S- CH_2), 1.15 (t, J = 7.5 Hz, 3H, S- $\text{CH}_2\text{-CH}_3$); **^{13}C NMR** (101 MHz, CDCl_3): δ 198.5, 149.5, 136.9, 133.3, 130.1, 128.3, 124.4, 50.2, 37.7, 26.1, 14.4; **LRMS** (ESI^+): m/z 262.1 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{11}\text{H}_{13}\text{O}_3\text{NSNa}$ requires 262.0508 $[\text{M}+\text{Na}]^+$, found 262.0510; **IR**: ν_{max} (neat)/ cm^{-1} 2928, 1720, 1606, 1577, 1522, 1445, 1352.

6.2.2 One-pot formation of β -substituted ketones

General Procedure C: rhodium-catalysed one-pot synthesis of β -substituted ketones from aldehydes, alkenes and boronic acids with methyl trifluoromethanesulfonate

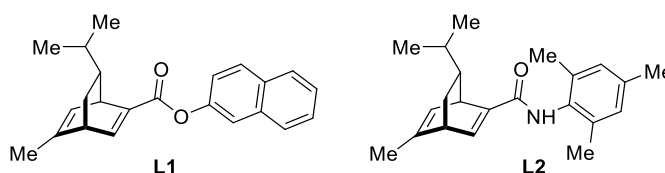
Acetone (~0.5 mL) was added to a microwave reaction vial charged with $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (5.6 mg, 0.015 mmol, 0.05 equiv) and dcpm (6.1 mg, 0.015 mmol, 0.05 equiv) (previously evacuated and back-filled with N_2 gas). The solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until dryness. Acetone (0.30 mL, 1.0 M) was added and the resulting solution was transferred to a N_2 -purged microwave reaction vial containing β -S aldehyde (0.30 mmol, 1.0 equiv). Alkene (0.90 mmol, 3.0 equiv) was added and the reaction mixture was stirred at 55 °C for 1 h. The mixture was allowed to cool to room temperature and transferred to a microwave reaction vial charged with K_2CO_3 (103.7 mg, 0.75 mmol, 2.5 equiv). Acetone (additional 0.30 mL, 0.5 M) then MeOTf (51 μL , 0.45 mmol, 1.5 equiv) were added. The resulting suspension was stirred at 55 °C for 1 h, cooled to room temperature and transferred to a microwave reaction vial charged with boronic acid (0.45 mmol, 1.5 equiv) and $[\text{Rh}(\text{L1})\text{Cl}]_2$ (7.1 mg, 0.0075 mmol, 0.025 equiv) (previously evacuated and back-filled with N_2 gas). Acetone (2.1 mL) and methanol (0.3 mL) (0.1 M) were added and the mixture was stirred at 55 °C for 1 h. Upon completion, the reaction mixture was filtered through a pad of silica and the filtrate concentrated under reduced pressure. Purification by flash column chromatography afforded the desired ketone.

General Procedure D: rhodium-catalysed one-pot synthesis of β -substituted ketones from aldehydes, alkenes and boronic acids with copper(I) 3-methylsalicylate

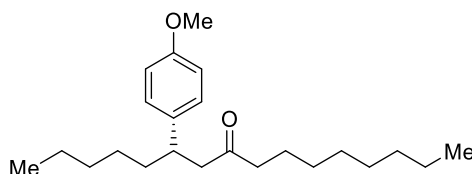
Acetone (~0.5 mL) was added to a microwave reaction vial charged with $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (5.6 mg, 0.015 mmol, 0.05 equiv) and dcpm (6.1 mg, 0.015 mmol, 0.05 equiv) (previously evacuated and back-filled with N_2 gas). The solution was bubbled with H_2 gas for 2 min, followed by N_2 gas until dryness. Acetone (0.30 mL, 1.0 M) was added and the resulting solution was transferred to a N_2 -purged microwave reaction vial containing β -S aldehyde (0.30 mmol, 1.0 equiv). Alkene (0.90 mmol, 3.0 equiv) was added and the reaction mixture was stirred at 55 °C for 1 h. The mixture was allowed to cool to room temperature and transferred to a microwave reaction vial

charged with CuMeSal (64.4 mg, 0.30 mmol, 1.0 equiv). Acetone (additional 0.30 mL, 0.5 M) was added and the resulting suspension was stirred at 55 °C for 14 h, cooled to room temperature and filtered (through a thin Celite® layer under inert atmosphere) into a microwave reaction vial charged with boronic acid (0.60 mmol, 2.0 equiv), K₂CO₃ (41.5 mg, 0.30 mmol, 1.0 equiv) and [Rh(L1)Cl]₂ (7.1 mg, 0.0075 mmol, 0.025 equiv) (previously evacuated and back-filled with N₂ gas). Acetone (2.1 mL) and methanol (0.3 mL) (0.1 M) were added and the mixture was stirred at 55 °C for 1h. Upon completion, the reaction mixture was filtered through a pad of silica and the filtrate concentrated under reduced pressure. Purification by flash column chromatography afforded the desired ketone.

When 1,2-dichloroethane (DCE) is mentioned, it indicates that DCE was used instead of acetone for the whole process (volumes not modified). When [Rh(L2)Cl]₂ is mentioned, it indicates that [Rh(L2)Cl]₂ was used instead of [Rh(L1)Cl]₂ for the conjugate addition step.



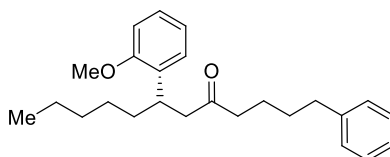
(S)-6-(4-methoxyphenyl)hexadecan-8-one 12a



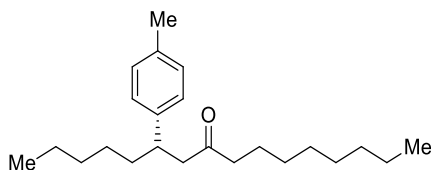
The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 4-methoxyphenylboronic acid (68 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone* **12a** (88 mg, 0.25 mmol, 85%, 97% ee) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.08 (d, *J* = 8.5 Hz, 2H, *H_{Ar}*), 6.81 (d, *J* = 8.5 Hz, 2H, *H_{Ar}*), 3.77 (s, 3H, O-CH₃), 3.10-3.03 (m, 1H, CH-CH₂-CO), 2.66 (dd, *J* = 13.5, 5.0 Hz, 1H, CH-CH_aH_b-CO), 2.61 (dd, *J* = 13.5, 4.5 Hz, 1H, CH-CH_aH_b-CO), 2.31-2.14 (m, 2H, CH₂-CH₂-CO), 1.60-1.40 (m, 4H, 2 × CH₂), 1.29-1.08 (m, 16H, 8 × CH₂), 0.88-0.82 (m, 6H, 2 × CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 210.7, 158.1, 136.9,

128.5, 113.9, 55.3, 50.4, 43.8, 40.6, 36.7, 31.93, 31.86, 31.8, 29.5, 29.2, 27.2, 23.7, 22.8, 22.6, 14.21, 14.16; **LRMS** (ESI⁺): m/z 369.3 ([M+Na]⁺, 100%), 715.6 ([2M+Na]⁺, 50%); **HRMS** (ESI⁺): C₂₃H₃₈O₂Na requires 369.2764 [M+Na]⁺, found 369.2763; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2925, 2855, 1713, 1611, 1512, 1373, 1246; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 9.09 min, τ_{minor} = 9.58 min (97% ee); $[\alpha]_{\text{D}}^{25}$: +20.0 (c = 1.0, CHCl₃).

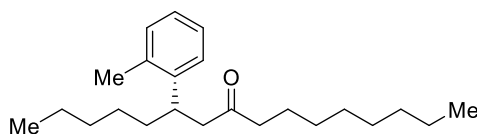
(S)-7-(2-Methoxyphenyl)-1-phenyldodecan-5-one 12b



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 2-methoxyphenylboronic acid (91 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the *desired ketone* **12b** (70 mg, 0.19 mmol, 63%, 93% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.28-7.24 (m, 2H, H_{Ar}), 7.18-7.09 (m, 5H, H_{Ar}), 6.89 (td, J = 7.5, 1.0 Hz, 1H, H_{Ar}), 6.82 (dd, J = 8.0, 1.0 Hz, 1H, H_{Ar}), 3.79 (s, 3H, O-CH₃), 3.58-3.51 (m, 1H, CH-CH₂-CO), 2.71 (dd, J = 15.5, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.63 (dd, J = 15.5, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.55 (t, J = 7.0 Hz, 2H, CH₂-Ph), 2.34-2.29 (m, 2H, CH₂-CH₂-CO), 1.63-1.43 (m, 6H, 3 $\times$ CH₂), 1.26-1.10 (m, 6H, 3 $\times$ CH₂), 0.82 (t, J = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.7, 157.4, 142.4, 132.7, 128.5, 128.4, 128.1, 127.2, 125.8, 120.7, 110.8, 55.4, 49.0, 42.9, 35.8, 35.0, 34.9, 31.9, 31.1, 27.2, 23.4, 22.7, 14.2; **LRMS** (ESI⁺): m/z 367.3 ([M+H]⁺, 40%), 389.3 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₅H₃₅O₂ requires 367.2632 [M+H]⁺, found 367.2635; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2927, 2857, 1711, 1600, 1492, 1455, 1438, 1369, 1240; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 10.27 min, τ_{minor} = 10.95 min (93% ee); $[\alpha]_{\text{D}}^{25}$: +7.8 (c = 1.0, CHCl₃).

(S)-6-(4-Tolyl)hexadecan-8-one 12c

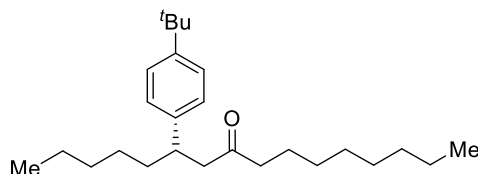
The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 4-tolylboronic acid (61 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the *desired ketone* **12c** (79 mg, 0.24 mmol, 80%, 92% ee) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.09-7.04 (m, 4H, *H*_{Ar}), 3.12-3.04 (m, 1H, CH-CH₂-CO), 2.67 (dd, *J* = 13.5, 5.0 Hz, 1H, CH-CH_aH_b-CO), 2.62 (dd, *J* = 13.5, 4.5 Hz, 1H, CH-CH_aH_b-CO), 2.31 (s, 3H, Ar-CH₃), 2.28-2.16 (m, 2H, CH₂-CH₂-CO), 1.60-1.41 (m, 4H, 2 × CH₂), 1.28-1.09 (m, 16H, 8 × CH₂), 0.87 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃), 0.82 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 210.7, 141.8, 135.8, 129.2, 127.5, 50.3, 43.7, 41.0, 36.6, 32.0, 31.9, 29.5, 29.4, 29.3, 27.2, 23.7, 22.8, 22.6, 21.1, 14.24, 14.19; LRMS (ESI⁺): *m/z* 331.3 ([M+H]⁺, 80%), 353.3 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₂₃H₃₉O requires 331.2995 [M+H]⁺, found 331.2996; IR: ν_{max} (neat)/cm⁻¹ 2955, 2924, 2855, 1714, 1514, 1458, 1313; the ee was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 4.87 min, τ_{minor} = 5.29 min (92% ee); [α]_D²⁵: +18.0 (*c* = 1.0, CHCl₃).

(S)-6-(2-Tolyl)hexadecan-8-one 12d

The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 2-tolylboronic acid (61 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the *desired ketone* **12d** (59 mg, 0.18 mmol, 59%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.21-7.02 (m, 4H, *H*_{Ar}), 3.52-3.39 (m, 1H, CH-CH₂-CO), 2.69 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.63 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.36 (s, 3H, Ar-CH₃), 2.24 (m, 2H, CH₂-CH₂-CO), 1.65-1.39 (m, 4H, 2 × CH₂), 1.35-1.08 (m, 16H, 8 × CH₂), 0.90-0.80 (m, 6H, 2 × CH₃); ¹³C NMR

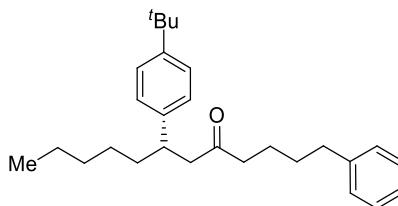
(101 MHz, CDCl₃): δ 210.7, 143.4, 136.2, 130.5, 126.4, 125.9, 125.6, 49.8, 43.8, 43.0, 36.6, 35.7, 32.1, 31.9, 29.5, 29.2, 27.1, 23.7, 22.8, 22.6, 20.0, 14.23, 14.17; **LRMS** (ESI⁺): m/z 331.3 ([M+H]⁺, 70%), 353.3 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₃H₃₈ONa requires 353.2815 [M+Na]⁺, found 353.2813; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2955, 2924, 2855, 1714, 1491, 1463, 1376. The **ee** could not be determined. $[\alpha]_{\text{D}}^{25}$: +12.2 (c = 1.0, CHCl₃).

(S)-6-[4-(*tert*-Butyl)phenyl]hexadecan-8-one 12e



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 4-(*tert*-butyl)phenylboronic acid (80 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone 12e* (97 mg, 0.26 mmol, 87%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.30-7.26 (m, 2H, H_{Ar}), 7.08 (d, J = 8.5 Hz, 2H, H_{Ar}), 3.14-3.01 (m, 1H, CH-CH₂-CO), 2.65 (d, J = 7.5 Hz, 2H, CH-CH₂-CO), 2.31-2.15 (m, 2H, CH₂-CH₂-CO), 1.59-1.52 (m, 2H, CH₂), 1.49-1.40 (m, 2H, CH₂), 1.30 (s, 9H, (CH₃)₃), 1.30-1.11 (m, 16H, 8 $\times$ CH₂), 0.88-0.81 (m, 6H, 2 $\times$ CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.8, 140.0, 141.8, 127.2, 125.4, 50.3, 43.8, 40.9, 36.5, 34.5, 31.9, 31.5, 29.5, 29.27, 29.26, 27.3, 23.7 (2C), 22.8, 22.7, 14.23, 14.20; **LRMS** (ESI⁺): m/z 373.3 ([M+H]⁺, 100%), 395.4 ([M+Na]⁺, 70%); **HRMS** (ESI⁺): C₂₆H₄₄ONa requires 395.3284 [M+Na]⁺, found 395.3280; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2956, 2925, 2856, 1714, 1511, 1463, 1362, 1269. The **ee** could not be determined; $[\alpha]_{\text{D}}^{25}$: +18.0 (c = 1.0, CHCl₃).

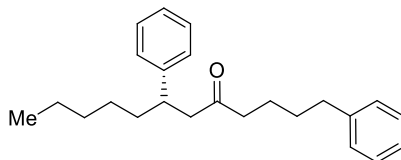
(S)-7-[4-(*tert*-Butyl)phenyl]-1-phenyldodecan-5-one 12f



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 4-(*tert*-butyl)phenylboronic acid

acid (80 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone* **12f** (98 mg, 0.25 mmol, 84%, 95% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.27-7.21 (m, 4H, *H*_{Ar}), 7.16-7.13 (m, 1H, *H*_{Ar}), 7.11-7.09 (m, 2H, *H*_{Ar}), 7.05 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 3.09-3.02 (m, 1H, CH-CH₂-CO), 2.64 (dd, *J* = 13.5, 5.0 Hz, 1H, CH-CH_aH_b-CO), 2.59 (dd, *J* = 13.5, 5.0 Hz, 1H, CH-CH_aH_b-CO), 2.51 (br t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.36-2.15 (m, 2H, CH₂-CH₂-CO), 1.59-1.44 (m, 6H, 3 × CH₂), 1.26 (s, 9H, (CH₃)₃), 1.22-1.07 (m, 6H, 3 × CH₂), 0.80 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.5, 149.0, 142.4, 141.7, 128.5, 128.4, 127.2, 125.8, 125.4, 50.3, 43.4, 40.9, 36.5, 35.8, 34.5, 31.9, 31.5, 31.0, 27.3, 23.3, 22.7, 14.2; **LRMS** (ESI⁺): *m/z* 393.3 ([M+H]⁺, 20%), 415.3 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₈H₄₁O requires 393.3152 [M+H]⁺, found 393.3151; **IR**: ν_{max} (neat)/cm⁻¹ 2954, 2928, 2858, 1713, 1510, 1455, 1362, 1268; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 7.07 min, τ_{minor} = 7.65 min (95% ee); [α]_D²⁵: +18.5 (*c* = 1.0, CHCl₃).

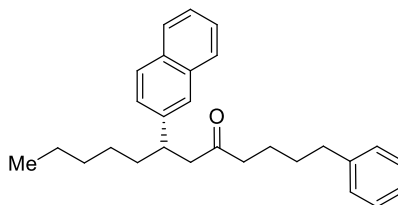
(S)-1,7-Diphenyldodecan-5-one 12g



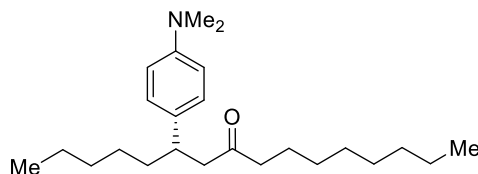
The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (38 mg, 0.20 mmol), 4-phenyl-1-butene (90 μL, 0.60 mmol), phenylboronic acid (49 mg, 0.40 mmol, 2.0 equiv) and [Rh(L2)Cl]₂ (4.6 mg, 0.005 mmol). Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone* **12g** (56 mg, 0.17 mmol, 83%, 94% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.30-7.22 (m, 4H, *H*_{Ar}), 7.19-7.10 (m, 6H, *H*_{Ar}), 3.20-3.01 (m, 1H, CH-CH₂-CO), 2.68 (dd, *J* = 15.0, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.62 (dd, *J* = 15.0, 6.0 Hz, 1H, CH_aH_b-CO), 2.53 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.37-2.15 (m, 2H, CH₂-CH₂-CO), 1.61-1.43 (m, 6H, 3 × CH₂), 1.25-1.07 (m, 6H, 3 × CH₂), 0.81 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.2, 144.9, 142.4, 128.6, 128.5, 128.4, 127.6, 126.4, 125.9, 50.2, 43.5, 41.4, 36.5, 35.8, 31.9, 31.0, 27.2, 23.3, 22.6, 14.2; **LRMS** (ESI⁺): *m/z* 359.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₄H₃₂ONa requires 359.2345 [M+Na]⁺, found 359.2346; **IR**:

$\nu_{\max}$ (neat)/cm⁻¹ 3027, 2927, 2857, 1713, 1453, 1371; the **ee** was determined by HPLC using a Chiralpak IA-3 column (*n*-hexane/*i*-PrOH, 98:2); flow rate 0.5 mL/min; τ_{major} = 11.14 min, τ_{minor} = 11.66 min (94% ee); $[\alpha]_{\text{D}}^{25}$: +17.9 (*c* = 0.5, CHCl₃).

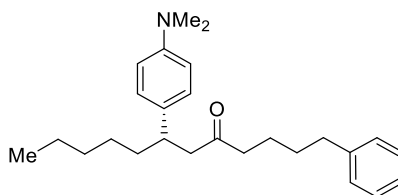
(S)-7-(Naphthalen-2-yl)-1-phenyldodecan-5-one 12h



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 2-naphthaleneboronic acid (77 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired ketone **12h** (87 mg, 0.23 mmol, 75%, 95% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.63-7.59 (m, 3H, *H*_{Ar}), 7.42 (s, 1H, *H*_{Ar}), 7.30-7.23 (m, 2H, *H*_{Ar}), 7.15 (dd, *J* = 8.5, 1.5 Hz, 1H, *H*_{Ar}), 7.08-7.04 (m, 2H, *H*_{Ar}), 6.99-6.96 (m, 1H, *H*_{Ar}), 6.89 (d, *J* = 7.0 Hz, 2H, *H*_{Ar}), 3.12 (p, *J* = 7.0 Hz, 1H, CH-CH₂-CO), 2.61 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.54 (dd, *J* = 16.0, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.31 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.18-2.00 (m, 2H, CH₂-CH₂-CO), 1.51-1.46 (m, 2H, CH-CH₂-CH₂), 1.35-1.24 (m, 4H, 2 × CH₂), 1.10-0.93 (m, 6H, 3 × CH₂), 0.64 (t, *J* = 6.5 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.1, 142.30, 142.26, 133.6, 132.4, 128.5, 128.4, 128.3, 127.74, 127.71, 126.3, 126.1, 125.9, 125.8, 125.4, 50.2, 43.5, 41.5, 36.4, 35.8, 31.9, 30.9, 27.3, 23.3, 22.6, 14.2; **LRMS** (ESI⁺): *m/z* 387.3 ([M+H]⁺, 30%), 409.3 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₈H₃₄ONa requires 409.2502 [M+Na]⁺, found 409.2500; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2927, 2856, 2360, 2341, 1711, 1454; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 8.87 min, τ_{minor} = 9.80 min (95% ee); $[\alpha]_{\text{D}}^{25}$: +19.0 (*c* = 1.0, CHCl₃).

(S)-6-[4-(Dimethylamino)phenyl]hexadecan-8-one 12i

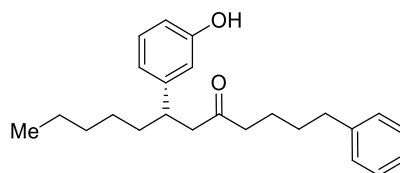
The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 4-(dimethylamino)phenylboronic acid (99 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 97:3) afforded the *desired ketone 12i* (75 mg, 0.21 mmol, 69%) as a yellow oil. **¹H NMR** (500 MHz, CDCl₃): δ 7.06-7.01 (m, 2H, *H_{Ar}*), 6.71-6.65 (m, 2H, *H_{Ar}*), 3.05-2.99 (m, 1H, CH-CH₂-CO), 2.91 (s, 6H, N(CH₃)₂), 2.64 (dd, *J* = 14.0, 6.0 Hz, 1H, CH-CH_aH_b-CO), 2.60 (dd, *J* = 14.0, 6.0 Hz, 1H, CH-CH_aH_b-CO), 2.27 (dt, *J* = 16.5, 7.5 Hz, 1H, CH₂-CH_cH_d-CO), 2.20 (dt, *J* = 16.5, 7.5 Hz, 1H, CH₂-CH_cH_d-CO), 1.64-1.34 (m, 4H, 2 × CH₂), 1.34-1.08 (m, 16H, 8 × CH₂), 0.87 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃), 0.83 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (126 MHz, CDCl₃): δ 211.1, 149.3, 132.9, 128.2, 112.9, 50.6, 43.7, 40.9, 40.6, 36.7, 32.0 (2C), 29.5, 29.28, 29.26, 27.3, 23.7, 22.8, 22.7, 14.23, 14.21; **LRMS** (ESI⁺): *m/z* 360.3 ([M+H]⁺, 100%); **HRMS** (ESI⁺): C₂₄H₄₂ON requires 360.3261 [M+H]⁺, found 360.3261; **IR**: ν_{max} (neat)/cm⁻¹ 2981, 2924, 2854, 1712, 1615, 1520, 1461, 1346. The **ee** could not be determined. [α]_D²⁵: +25.1 (*c* = 0.98, CHCl₃).

(S)-7-[4-(Dimethylamino)phenyl]-1-phenyldodecan-5-one 12j

The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and [4-(dimethylamino)phenyl]boronic acid (99 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired ketone 12j* (66 mg, 0.17 mmol, 58%, 96% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.30-7.26 (m, 2H, *H_{Ar}*), 7.20-7.14 (m, 3H, *H_{Ar}*), 7.04 (d, *J* = 8.5 Hz, 2H, *H_{Ar}*), 6.69 (d, *J* = 8.5 Hz, 2H, *H_{Ar}*), 3.06-2.99 (m, 1H,

CH-CH₂-CO), 2.92 (s, 6H, N(CH₃)₂), 2.66 (dd, *J* = 14.5, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.61 (dd, *J* = 14.5, 6.0 Hz, 1H, CH-CH_aH_b-CO), 2.56 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.34-2.20 (m, 2H, CH₂-CH₂-CO), 1.56-1.47 (m, 6H, 3 × CH₂), 1.27-1.13 (m, 6H, 3 × CH₂), 0.85 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 210.8, 149.3, 142.4, 132.7, 128.5, 128.4, 128.1, 125.8, 112.9, 50.6, 43.5, 40.9, 40.6, 36.7, 35.8, 31.9, 31.0, 27.3, 23.3, 22.7, 14.2; **LRMS** (ESI⁺): *m/z* 380.3 ([M+H]⁺, 100%); **HRMS** (ESI⁺): C₂₆H₃₈ON requires 380.2948 [M+H]⁺, found 380.2940; **IR**: ν_{max} (neat)/cm⁻¹ 2926, 2855, 1710, 1615, 1520, 1453, 1347, 1224; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 98:2); flow rate 1.0 mL/min; τ_{major} = 8.95 min, τ_{minor} = 9.64 min (96% ee); [α]_D²⁵: +25.1 (*c* = 1.0, CHCl₃).

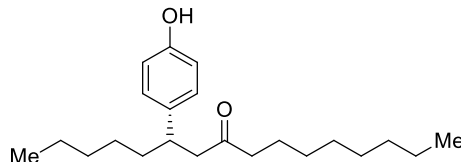
(S)-7-(3-Hydroxyphenyl)-1-phenyldodecan-5-one 12k



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 3-hydroxyphenylboronic acid (83 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired ketone* **12k** (83 mg, 0.24 mmol, 79%, 93% ee) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.22 (m, 2H, *H*_{Ar}), 7.13-7.04 (m, 4H, *H*_{Ar}), 6.65 (d, *J* = 7.5 Hz, 1H, *H*_{Ar}), 6.59-6.56 (m, 2H, *H*_{Ar}), 4.92 (s, 1H, OH), 3.02-2.95 (m, 1H, CH-CH₂-CO), 2.60 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.54 (dd, *J* = 16.0, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.47 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.27-2.14 (m, 2H, CH₂-CH₂-CO), 1.50-1.40 (m, 6H, 3 × CH₂), 1.18-1.03 (m, 6H, 3 × CH₂), 0.75 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 211.2, 155.9, 146.7, 142.3, 129.7, 128.5, 128.4, 125.8, 119.7, 114.7, 113.4, 50.1, 43.6, 41.4, 36.5, 35.8, 31.9, 31.0, 27.2, 23.2, 22.6, 14.2; **LRMS** (ESI⁺): *m/z* 353.3 ([M+H]⁺, 30%), 375.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₄H₃₃O₂ requires 353.2475 [M+H]⁺, found 353.2476; **IR**: ν_{max} (neat)/cm⁻¹ 3379 (br), 2928, 2856, 1699, 1589, 1485, 1454, 1374; the **ee** was determined by HPLC using a Chiralpak AD-H

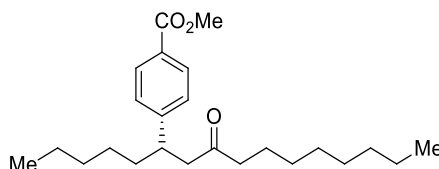
column (*n*-hexane/*i*-PrOH, 94:6); flow rate 1.0 mL/min; $\tau_{\text{major}} = 15.72$ min, $\tau_{\text{minor}} = 19.15$ min (93% ee); $[\alpha]_{\text{D}}^{25}$: +20.1 ($c = 1.0$, CHCl₃).

(S)-6-(4-Hydroxyphenyl)hexadecan-8-one 12l



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 4-hydroxyphenylboronic acid (62 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired ketone 12l* (82 mg, 0.24 mmol, 82%, 94% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.01 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 6.72 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 5.14 (br s, 1H, OH), 3.11-2.99 (m, 1H, CH-CH₂-CO), 2.67 (dd, $J = 13.5, 5.0$ Hz, 1H, CH-CH_aH_b-CO), 2.62 (dd, $J = 13.5, 4.5$ Hz, 1H, CH-CH_aH_b-CO), 2.37-2.13 (m, 2H, CH₂-CH₂-CO), 1.61-1.33 (m, 4H, $2 \times \text{CH}_2$), 1.33-1.02 (m, 16H, $8 \times \text{CH}_2$), 0.86 (t, $J = 7.0$ Hz, 3H, CH₂-CH₃), 0.82 (t, $J = 7.0$ Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 211.7, 154.2, 136.6, 128.6, 115.4, 50.4, 43.7, 40.7, 36.8, 31.94, 31.86, 29.5, 29.3, 29.3, 27.2, 23.7, 22.8, 22.7, 14.24, 14.18; **LRMS** (ESI⁺): m/z 355.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₂H₃₆O₂Na requires 355.2608 [M+Na]⁺, found 355.2606; **IR**: ν_{max} (neat)/cm⁻¹ 3381 (br), 2955, 2925, 2855, 1698, 1614, 1515, 1455, 1375, 1221; the **ee** was determined by HPLC using a Chiralpak IC column (*n*-hexane/*i*-PrOH, 94:6); flow rate 1.0 mL/min; $\tau_{\text{major}} = 7.73$ min, $\tau_{\text{minor}} = 8.75$ min (94% ee); $[\alpha]_{\text{D}}^{25}$: +21.5 ($c = 1.0$, CHCl₃).

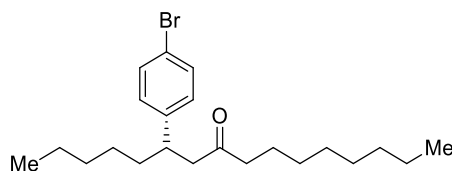
(S)-Methyl 4-(8-oxohexadecan-6-yl)benzoate 12m



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol) and 1-octene (0.14 mL, 0.90 mmol) in DCE. The elimination step was carried out at 22 °C for 1.5 h and the conjugate addition was performed using 4-(methoxycarbonyl)phenylboronic acid (81 mg, 0.45 mmol), [Rh(L2)Cl]₂ (6.9 mg, 0.0075 mmol)

and additional K_2CO_3 (41 mg, 0.30 mmol, 1.0 equiv). Purification by flash column chromatography (petrol/ Et_2O , 96:4) afforded the *desired ketone* **12m** (92 mg, 0.25 mmol, 82%, 93% ee) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.95 (d, J = 8.5 Hz, 2H, H_{Ar}), 7.24 (d, J = 8.5 Hz, 2H, H_{Ar}), 3.89 (s, 3H, CO_2CH_3), 3.24-3.18 (m, 1H, $\text{CH-CH}_2\text{-CO}$), 2.71 (dd, J = 13.5, 4.5 Hz, 1H, $\text{CH-CH}_a\text{H}_b\text{-CO}$), 2.66 (dd, J = 13.5, 4.0 Hz, 1H, $\text{CH-CH}_a\text{H}_b\text{-CO}$), 2.32-2.16 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}$), 1.65-1.54 (m, 2H, $\text{CH-CH}_2\text{-CH}_2$), 1.48-1.40 (m, 2H, CH_2), 1.28-1.05 (m, 16H, $8 \times \text{CH}_2$), 0.86 (t, J = 7.0 Hz, 3H, $\text{CH}_2\text{-CH}_3$), 0.81 (t, J = 7.0 Hz, 3H, $\text{CH}_2\text{-CH}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 209.9, 167.2, 150.6, 129.9, 128.4, 127.7, 52.1, 49.7, 43.7, 41.2, 36.3, 31.9, 31.8, 29.4, 29.2 (2C), 27.1, 23.7, 22.8, 22.6, 14.2, 14.1; **LRMS** (ESI^+): 375.3 ($[\text{M}+\text{H}]^+$, 80%), 397.3 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{24}\text{H}_{39}\text{O}_3$ requires 375.2894 $[\text{M}+\text{H}]^+$, found 375.2893; **IR**: ν_{max} (neat)/ cm^{-1} 2928, 2857, 1715, 1437, 1376, 1281; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 17.95 min, τ_{minor} = 24.03 min (93% ee); $[\alpha]_{\text{D}}^{25}$: +15.3 (c = 1.0, CHCl_3).

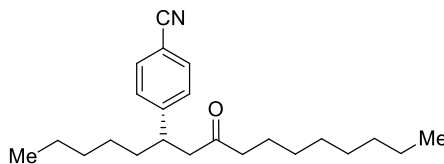
(S)-6-(4-Bromophenyl)hexadecan-8-one 12n



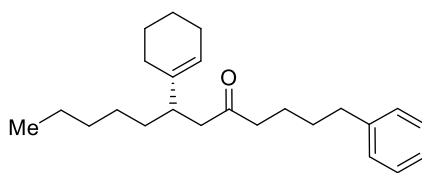
The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol) and 1-octene (0.14 mL, 0.90 mmol) in DCE. The elimination step was carried out at 22 °C for 1.5 h and the conjugate addition step was performed using 4-bromophenylboronic acid (90 mg, 0.45 mmol), $[\text{Rh}(\text{L}2)\text{Cl}]_2$ (6.9 mg, 0.0075 mmol) and additional K_2CO_3 (41 mg, 0.30 mmol, 1.0 equiv). Purification by flash column chromatography (petrol/ Et_2O , 99:1) afforded the *desired ketone* **12n** (76 mg, 0.19 mmol, 64%, 93% ee) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.40-7.37 (m, 2H, H_{Ar}), 7.06-7.03 (m, 2H, H_{Ar}), 3.12-3.08 (m, 1H, $\text{CH-CH}_2\text{-CO}$), 2.64 (d, J = 7.0 Hz, 2H, $\text{CH-CH}_2\text{-CO}$), 2.32-2.16 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CO}$), 1.59-1.41 (m, 4H, $2 \times \text{CH}_2$), 1.30-1.05 (m, 16H, $8 \times \text{CH}_2$), 0.87 (t, J = 7.0 Hz, 3H, $\text{CH}_2\text{-CH}_3$), 0.82 (t, J = 7.0 Hz, 3H, $\text{CH}_2\text{-CH}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 210.0, 144.0, 131.6, 129.4, 120.0, 49.9, 43.8, 40.7, 36.4, 31.9, 31.8, 29.5, 29.3, 29.2, 27.1, 23.7, 22.8, 22.6, 14.2, 14.1; **LRMS** (ESI^+): m/z 395.1 ($[\text{BrM}+\text{H}]^+$,

50%), 397.1 ($[\text{}^{81}\text{BrM}+\text{H}]^+$, 50%), 417.2 ($[\text{}^{79}\text{BrM}+\text{Na}]^+$, 100%), 419.2 ($[\text{}^{81}\text{BrM}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{22}\text{H}_{35}\text{O}^{79}\text{BrNa}$ requires 417.1764 $[\text{M}+\text{Na}]^+$, found 417.1763, $\text{C}_{22}\text{H}_{35}\text{O}^{81}\text{BrNa}$ requires 419.1743 found 419.1741; **IR**: ν_{max} (neat)/ cm^{-1} 2955, 2925, 2855, 2360, 1714, 1485, 1465, 1375; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; $\tau_{\text{major}} = 6.28$ min, $\tau_{\text{minor}} = 6.79$ min (93% ee); $[\alpha]_{\text{D}}^{25}$: +14.1 ($c = 1.0$, CHCl_3).

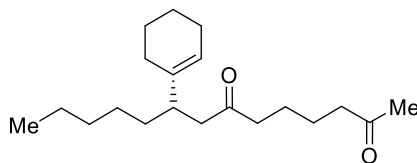
(S)-4-(8-Oxohexadecan-6-yl)benzonitrile 12o



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 1-octene (0.14 mL, 0.90 mmol) and 4-cyanophenylboronic acid (67 mg, 0.45 mmol) in DCE. Purification by flash column chromatography (petrol/ Et_2O , 98:2) afforded the *desired ketone 12o* (56 mg, 0.16 mmol, 55%, 91% ee) as a colorless oil. **^1H NMR** (400 MHz, CDCl_3): δ 7.56 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.28 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 3.12-3.08 (m, 1H, $\text{CH}-\text{CH}_2-\text{CO}$), 2.69 (d, $J = 7.0$ Hz, 2H, $\text{CH}-\text{CH}_2-\text{CO}$), 2.30 (dt, $J = 16.5, 7.5$ Hz, 1H, $\text{CH}_2-\text{CH}_a\text{H}_b-\text{CO}$), 2.21 (dt, $J = 16.5, 7.0$ Hz, 1H, $\text{CH}_2-\text{CH}_a\text{H}_b-\text{CO}$), 1.59-1.41 (m, 4H, $2 \times \text{CH}_2$), 1.30-1.05 (m, 16H, $8 \times \text{CH}_2$), 0.86 (t, $J = 7.0$ Hz, 3H, CH_3), 0.81 (t, $J = 7.0$ Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 209.4, 150.8, 132.4, 128.6, 119.1, 110.2, 49.4, 43.7, 41.1, 36.1, 31.9, 31.7, 29.4, 29.2 (2C), 27.1, 23.7, 22.8, 22.6, 14.2, 14.1; **LRMS** (ESI^+): m/z 364.1 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{23}\text{H}_{35}\text{NONa}$ requires 364.2611 $[\text{M}+\text{Na}]^+$, found 364.2612; **IR**: ν_{max} (neat)/ cm^{-1} 2955, 2926, 2855, 2228, 1713, 1608, 1464, 1375; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; $\tau_{\text{major}} = 17.15$ min, $\tau_{\text{minor}} = 19.09$ min (91% ee); $[\alpha]_{\text{D}}^{25}$: +10.2 ($c = 1.0$, CHCl_3).

(S)-7-(Cyclohex-1-en-1-yl)-1-phenyldodecan-5-one 12p

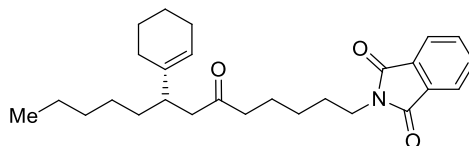
The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and cyclohex-1-en-1-ylboronic acid (76 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone* **12p** (78 mg, 0.23 mmol, 76%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.22 (m, 2H, *H*_{Ar}), 7.16-7.13 (m, 3H, *H*_{Ar}), 5.38-5.36 (m, 1H, C=CH), 2.58 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.43-2.28 (m, 5H, CH-CH₂-CO and CH₂-CH₂-CO), 1.94-1.88 (m, 2H, CH₂), 1.85-1.80 (m, 2H, CH₂), 1.58-1.47 (m, 8H, 4 × CH₂), 1.29-1.13 (m, 8H, 4 × CH₂), 0.84 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 211.0, 142.4, 138.8, 128.5, 128.4, 125.9, 122.9, 47.8, 43.6, 43.1, 35.9, 33.4, 32.0, 31.2, 27.1, 25.3, 24.8, 23.4, 23.1, 22.8, 22.7, 14.2; LRMS (ESI⁺): *m/z* 341.3 ([M+H]⁺, 30%), 363.3 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₂₄H₃₇O requires 341.2839 [M+H]⁺, found 341.2838; IR: ν_{max} (neat)/cm⁻¹ 2925, 2856, 1711, 1497, 1435, 1367. The *ee* could not be determined. [α]_D²⁵: +5.7 (*c* = 1.0, CHCl₃).

(S)-9-(Cyclohex-1-en-1-yl)tetradecane-2,7-dione 12q

The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 5-hexen-2-one (0.10 mL, 0.90 mmol) and cyclohex-1-en-1-ylboronic acid (76 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/ Et₂O, 9:1) afforded the *desired ketone* **12q** (62 mg, 0.20 mmol, 67%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 5.40-5.38 (m, 1H, C=CH), 2.44-2.31 (m, 7H, CH-CH₂-CO, CH₃-CO-CH₂-(CH₂)₂-CH₂-CO), 2.12 (s, 3H, CO-CH₃), 1.96-1.92 (m, 2H, C=CH-CH₂), 1.83-1.80 (m, 2H, HC=C-CH₂), 1.58-1.46 (m, 8H, 4 × CH₂), 1.31-1.15 (m, 8H, 4 × CH₂), 0.85 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 210.7, 208.9, 138.7, 123.0, 47.7, 43.64, 43.61, 43.0, 33.4, 31.9, 30.0, 27.1,

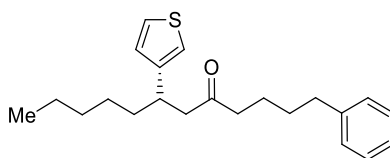
25.3, 24.8, 23.5, 23.13, 23.07, 22.8, 22.7, 14.2; **LRMS** (ESI⁺): m/z 307.3 ([M+H]⁺, 100%); **HRMS** (ESI⁺): C₂₀H₃₅O₂ requires 307.2632 [M+H]⁺, found 307.2631; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2926, 2857, 1712, 1448, 1409, 1307, 1138. The **ee** could not be determined. $[\alpha]_{\text{D}}^{25}$: +6.8 (c = 1.0, CHCl₃).

(S)-2-[8-(Cyclohex-1-en-1-yl)-6-oxotridecyl]isoindoline-1,3-dione 12r



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (38 mg, 0.20 mmol), 2-(pent-4-en-1-yl)isoindoline-1,3-dione (0.13 g, 0.60 mmol), cyclohex-1-en-1-ylboronic acid (50 mg, 0.60 mmol, 2.0 equiv) and [Rh(L2)Cl]₂ (4.6 mg, 0.005 mmol). Purification by flash column chromatography (petrol/EtOAc, 95:5) afforded the *desired ketone 12r* (71 mg, 0.17 mmol, 84%, 89% ee) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.84-7.82 (m, 2H, H_{Ar}), 7.72-7.69 (m, 2H, H_{Ar}), 5.38 (app. s, 1H, C=CH), 3.66 (t, J = 7.5 Hz, 2H, N-CH₂), 2.43-2.30 (m, 5H, CH-CH₂-CO and CH₂-CH₂-CO), 1.98-1.93 (m, 2H, CH₂), 1.88-1.78 (m, 2H, CH₂), 1.66-1.50 (m, 8H, 4 $\times$ CH₂), 1.33-1.16 (m, 10H, 5 $\times$ CH₂), 0.85 (t, J = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.8, 168.5, 138.8, 134.0, 132.3, 123.3, 122.9, 47.7, 43.6, 43.0, 38.0, 33.3, 32.0, 28.6, 27.1, 26.6, 25.3, 24.8, 23.2, 23.1, 22.8, 22.7, 14.2; **LRMS** (ESI⁺): m/z 424.3 ([M+H]⁺, 40%), 446.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₇H₃₈NO₃ requires 424.2846 [M+H]⁺, found 424.2846; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2925, 2856, 1773, 1709, 1466, 1395, 1367; the **ee** was determined by HPLC using a Chiralpak IA-3 column (*n*-hexane/*i*-PrOH, 90:10); flow rate 0.8 mL/min; τ_{major} = 9.69 min, τ_{minor} = 10.20 min (89% ee); $[\alpha]_{\text{D}}^{25}$: +5.5 (c = 1.0, CHCl₃).

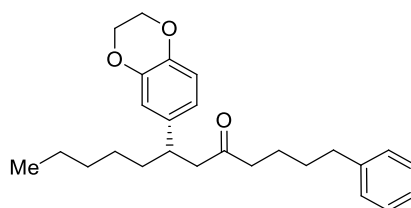
(S)-1-Phenyl-7-(thiophen-3-yl)dodecan-5-one 12s



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 3-thiophenylboronic acid (0.12 g, 0.90 mmol, 3.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 99:1)

afforded the *desired ketone 12s* (28 mg, 0.08 mmol, 27%, 94% ee) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.28-7.22 (m, 3H, *H*_{Ar}), 7.18-7.12 (m, 3H, *H*_{Ar}), 6.91 (d, *J* = 4.0 Hz, 2H, *H*_{Ar}), 3.30-3.23 (m, 1H, CH-CH₂-CO), 2.64 (dd, *J* = 15.0, 6.5 Hz, 1H, CH-CH_aH_b-CO), 2.61-2.53 (m, 3H, CH-CH_aH_b-CO and CH₂-Ph), 2.33-2.19 (m, 2H, CH₂-CH₂-CO), 1.61-1.47 (m, 6H, 3 × CH₂), 1.25-1.12 (m, 6H, 3 × CH₂), 0.83 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.2, 145.6, 142.3, 128.5, 128.4, 126.7, 125.9, 125.6, 120.3, 49.9, 43.5, 36.7, 36.3, 35.8, 31.8, 31.0, 27.1, 23.3, 22.7, 14.2; **LRMS** (ESI⁺): *m/z* 343.2 ([M+H]⁺, 15%), 365.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₂H₃₀OSNa requires 365.1910 [M+Na]⁺, found 365.1910; **IR**: ν_{max} (neat)/cm⁻¹ 2927, 2857, 2361, 1712, 1496, 1454, 1409, 1369; the **ee** was determined by HPLC using a Chiralpak OD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 15.80 min, τ_{minor} = 21.44 min (94% ee); [α]_D²⁵: +14.5 (*c* = 1.0, CHCl₃).

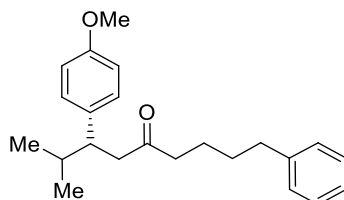
(S)-7-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1-phenyldodecan-5-one 12t



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol), 1,4-benzodioxane-6-boronic acid (82 mg, 0.6 mmol, 2.0 equiv) and [Rh(L2)Cl]₂ (6.9 mg, 0.0075 mmol). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired ketone 12t* (98 mg, 0.25 mmol, 82%, 94% ee) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.23 (d, *J* = 7.5 Hz, 2H, *H*_{Ar}), 7.16-7.10 (m, 3H, *H*_{Ar}), 6.74 (d, *J* = 8.0 Hz, 1H, *H*_{Ar}), 6.64-6.59 (m, 2H, *H*_{Ar}), 4.19-4.17 (m, 4H, O-CH₂-CH₂-O), 3.01-2.94 (m, 1H, CH-CH₂-CO), 2.61 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.58-2.51 (m, 3H, CH-CH_aH_b-CO and CH₂-Ph), 2.32-2.18 (m, 2H, CH₂-CH₂-CO), 1.51-1.42 (m, 6H, 3 × CH₂), 1.22-1.08 (m, 6H, 3 × CH₂), 0.81 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 210.3, 143.4, 142.4, 141.9, 138.2, 128.5, 128.4, 125.8, 120.6, 117.1, 116.0, 64.5, 64.4, 50.3, 43.5, 40.8, 36.6, 35.8, 31.9, 31.0, 27.2, 23.3, 22.6, 14.2; **LRMS** (ESI⁺): *m/z* 417.3 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₆H₃₄O₃Na requires 417.2400 [M+Na]⁺, found 417.2406; **IR**: ν_{max} (neat)/cm⁻¹ 2927, 2360,

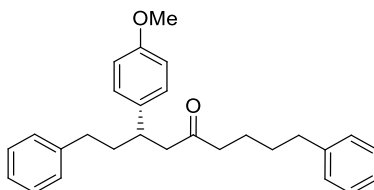
1710, 1590, 1504, 1456, 1306, 1284, 1255; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 98:2); flow rate 1.0 mL/min; $\tau_{\text{major}} = 18.21$ min, $\tau_{\text{minor}} = 17.06$ min (94% ee); $[\alpha]_{\text{D}}^{25}$: +18.3 (*c* = 1.0, CHCl₃).

(R)-7-(4-Methoxyphenyl)-8-methyl-1-phenylnonan-5-one 12ae



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)-4-methylpentanal **7c** (48 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 4-methoxyphenylboronic acid (62 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone* **12ae** (83 mg, 0.25 mmol, 82%, 98% ee) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.25 (d, *J* = 7.5 Hz, 2H, *H*_{Ar}), 7.20-7.09 (m, 3H, *H*_{Ar}), 7.06-7.03 (m, 2H, *H*_{Ar}), 6.83-6.78 (m, 2H, *H*_{Ar}), 3.76 (s, 3H, O-CH₃), 2.90-2.84 (m, 1H, CH-CH₂-CO), 2.72 (d, *J* = 7.5 Hz, 2H, CH-CH₂-CO), 2.51 (br t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.34-2.12 (m, 2H, CH₂-CH₂-CO), 1.78 (dq, *J* = 13.5, 7.0 Hz, 1H, CH(CH₃)₂), 1.48-1.44 (m, 4H, 2 × CH₂), 0.92 (d, *J* = 7.0 Hz, 3H, CH-CH_{3a}), 0.73 (d, *J* = 6.5 Hz, 3H, CH-CH_{3b}); ¹³C NMR (101 MHz, CDCl₃): δ 210.6, 158.0, 142.4, 135.4, 129.3, 128.5, 128.4, 125.8, 113.6, 55.3, 47.5, 47.1, 43.4, 35.8, 33.4, 30.9, 23.2, 20.9, 20.4; LRMS (ESI⁺): *m/z* 361.2 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₂₃H₃₀O₂Na requires 361.2138 [M+Na]⁺, found 361.2136; IR: ν_{max} (neat)/cm⁻¹ 3027, 2834, 1711, 1611, 1511, 1367, 1302, 1247, 1179; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 97:3); flow rate 1.0 mL/min; $\tau_{\text{major}} = 7.73$ min, $\tau_{\text{minor}} = 8.69$ min (98% ee); $[\alpha]_{\text{D}}^{25}$: +31.1 (*c* = 1.0, CHCl₃).

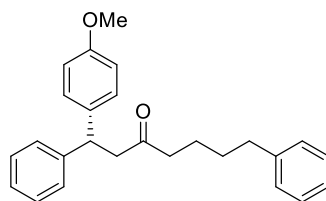
(S)-3-(4-Methoxyphenyl)-1,9-diphenylnonan-5-one 12ai



The desired product was prepared according to general procedure **C**, using 3-(ethylthio)-5-phenylpentanal **7d** (67 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and

4-methoxyphenylboronic acid (68 mg, 0.45 mmol). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the *desired ketone 12ai* (76 mg, 0.19 mmol, 63%, 90% ee) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.20-7.15 (m, 4H, *H*_{Ar}), 7.12-6.98 (m, 8H, *H*_{Ar}), 6.80-6.75 (m, 2H, *H*_{Ar}), 3.70 (s, 3H, O-CH₃), 3.08-2.98 (m, 1H, CH-CH₂-CO), 2.60 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-CH_aH_b-CO), 2.54 (dd, *J* = 16.0, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.45 (t, *J* = 7.0 Hz, 2H, (CH₂)₂-CH₂-Ph), 2.35 (t, *J* = 8.0 Hz, 2H, CH-CH₂-CH₂-Ph), 2.23-2.06 (m, 2H, CH₂-CH₂-CO), 1.90-1.70 (m, 2H, CH-CH₂-CH₂), 1.42-1.39 (m, 4H, 2 × CH₂); **¹³C NMR** (101 MHz, CDCl₃): δ 210.1, 158.3, 142.3, 142.2, 136.2, 128.6, 128.5 (2C), 128.42, 128.40, 125.9, 125.8, 114.1, 55.3, 50.5, 43.5, 40.3, 38.3, 35.8, 33.8, 31.0, 23.3; **LRMS** (ESI⁺): *m/z* 423.3 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₈H₃₂O₂Na requires 423.2295 [M+Na]⁺, found 423.2292; **IR**: ν_{max} (neat)/cm⁻¹ 2930, 2361, 2341, 1710, 1610, 1511, 1368, 1247, 1178; the **ee** was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 94:6); flow rate 1.0 mL/min; τ_{major} = 8.91 min, τ_{minor} = 9.54 min (90% ee); [α]_D²⁵: +15.0 (*c* = 1.0, CHCl₃).

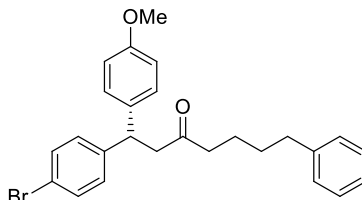
(R)-1-(4-Methoxyphenyl)-1,7-diphenylheptan-3-one 12aj



The desired product was prepared according to general procedure C, using 3-(ethylthio)-3-phenylpropanal **7e** (39 mg, 0.20 mmol), 4-phenyl-1-butene (0.09 mL, 0.60 mmol) and 4-methoxyphenylboronic acid (61 mg, 0.40 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired ketone 12aj* (63 mg, 0.17 mmol, 85%, 97% ee) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.26-7.22 (m, 4H, *H*_{Ar}), 7.18-7.09 (m, 8H, *H*_{Ar}), 6.78 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 4.53 (t, *J* = 7.5 Hz, 1H, CH-CH₂-CO), 3.73 (s, 3H, O-CH₃), 3.08 (d, *J* = 7.5 Hz, 2H, CH-CH₂-CO), 2.51 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.31 (t, *J* = 7.0 Hz, 2H, CH₂-CH₂-CO), 1.55-1.42 (m, 4H, (CH₂)₂-CH₂-Ph); **¹³C NMR** (101 MHz, CDCl₃): δ 209.2, 158.2, 144.4, 142.3, 136.2, 128.8, 128.7, 128.5, 128.4, 127.7, 126.5, 125.9, 114.0, 55.3, 49.1, 45.4, 43.5, 35.8, 30.9, 23.2; **LRMS** (ESI⁺): *m/z* 395.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₆H₂₈O₂Na requires 395.1982 [M+Na]⁺, found 395.1983; **IR**: ν_{max} (neat)/cm⁻¹ 2933, 1712, 1610, 1510, 1495, 1452,

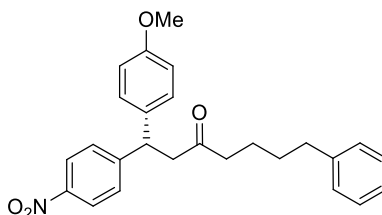
1368, 1302, 1248; the **ee** was determined by HPLC using a Chiralpak ID-3 column (*n*-hexane/*i*-PrOH, 95:5); flow rate 1.0 mL/min; $\tau_{\text{major}} = 11.25$ min, $\tau_{\text{minor}} = 12.12$ min (97% ee); $[\alpha]_{\text{D}}^{25}$: +5.9 (*c* = 1.0, CHCl₃).

(S)-1-(4-Bromophenyl)-1-(4-methoxyphenyl)-7-phenylheptan-3-one 12ak



The desired product was prepared according to general procedure **C**, using 3-(4-bromophenyl)-3-(ethylthio)propanal **7f** (55 mg, 0.20 mmol), 4-phenyl-1-butene (0.09 mL, 0.60 mmol) and 4-methoxyphenylboronic acid (61 mg, 0.40 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired ketone 12ak* (54 mg, 0.12 mmol, 60%, 98% ee) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.29-7.27 (m, 2H, *H*_{Ar}), 7.19-7.15 (m, 2H, *H*_{Ar}), 7.08 (d, *J* = 7.5 Hz, 1H, *H*_{Ar}), 7.03-6.96 (m, 6H, *H*_{Ar}), 6.72-6.70 (m, 2H, *H*_{Ar}), 4.41 (t, *J* = 7.5 Hz, 1H, CH-CH₂-CO), 3.66 (s, 3H, O-CH₃), 2.97 (d, *J* = 7.5 Hz, 2H, CH-CH₂-CO), 2.44 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.24 (t, *J* = 6.5 Hz, 2H, CH₂-CH₂-CO), 1.42-1.38 (m, 4H, 2 × CH₂); **¹³C NMR** (101 MHz, CDCl₃): δ 208.8, 158.4, 143.5, 142.3, 135.6, 131.7, 129.5, 128.7, 128.5, 128.4, 125.9, 120.3, 114.2, 55.4, 48.9, 44.7, 43.5, 35.8, 30.9, 23.3; **LRMS** (ESI⁺): *m/z* 473.1 ([⁷⁹BrM+Na]⁺, 50%), 472.2 ([⁸¹BrM+Na]⁺, 50%); **HRMS** (ESI⁺): C₂₆H₂₇O⁷⁹BrNa requires 473.1087 [M+Na]⁺, found 473.1073; **IR**: ν_{max} (neat)/cm⁻¹ 3026, 2932, 1714, 1609, 1510, 1487, 1249; the **ee** was determined by HPLC using a Chiralpak OD-H column (*n*-hexane/*i*-PrOH, 9:1); flow rate 1.0 mL/min; $\tau_{\text{major}} = 21.36$ min, $\tau_{\text{minor}} = 25.07$ min (98% ee); $[\alpha]_{\text{D}}^{25}$: +9.1 (*c* = 1.0, CHCl₃).

(R)-1-(4-Methoxyphenyl)-1-(4-nitrophenyl)-7-phenylheptan-3-one 12al

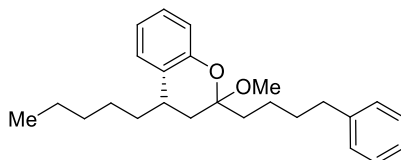


The desired product was prepared according to general procedure **C**, using 3-(ethylthio)-3-(4-nitrophenyl)propanal **7g** (72 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and

4-methoxyphenylboronic acid (91 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 85:15) afforded the *desired ketone 12a* (56 mg, 0.13 mmol, 44%, 98% ee) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 8.14-8.05 (m, 2H, *H*_{Ar}), 7.37-7.32 (m, 2H, *H*_{Ar}), 7.28-7.20 (m, 2H, *H*_{Ar}), 7.18-7.05 (m, 5H, *H*_{Ar}), 6.83-6.78 (m, 2H, *H*_{Ar}), 4.64 (t, *J* = 7.5 Hz, 1H, CH-CH₂-CO), 3.74 (s, 3H, O-CH₃), 3.15 (dd, *J* = 14.0, 4.0 Hz, 1H, CH-CH_aH_b-CO), 3.09 (dd, *J* = 14.0, 4.5 Hz, 1H, CH-CH_aH_b-CO), 2.53 (t, *J* = 7.0 Hz, 2H, CH₂-Ph), 2.35 (t, *J* = 7.0 Hz, 2H, CH₂-CH₂-CO), 1.58-1.41 (m, 4H, 2 × CH₂); ¹³C NMR (101 MHz, CDCl₃): δ 208.2, 158.6, 152.2, 146.6, 142.1, 134.5, 128.8, 128.6, 128.5, 128.4, 125.9, 124.0, 114.4, 55.4, 48.5, 44.9, 43.5, 35.8, 30.9, 23.3; LRMS (ESI⁺): *m/z* 440.2 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₂₆H₄₇O₄NNa requires 440.1832 [M+Na]⁺, found 440.1828; IR: ν_{max} (neat)/cm⁻¹ 2931, 1713, 1605, 1511, 1454, 1344, 1303, 1249; the ee was determined by HPLC using a Chiralpak OD-H column (*n*-hexane/*i*-PrOH, 7:3); flow rate 1.0 mL/min; τ_{major} = 18.00 min, τ_{minor} = 30.61 min (98% ee); [α]_D²⁵: +9.6 (*c* = 1.0, CHCl₃).

6.2.3 Product derivatisation

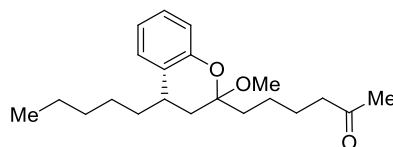
(4S)-2-Methoxy-4-pentyl-2-(4-phenylbutyl)chroman 17a



The desired product was prepared according to general procedure **D**, using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), 4-phenyl-1-butene (0.14 mL, 0.90 mmol) and 2-hydroxyphenylboronic acid (83 mg, 0.60 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 97:3) afforded the ketone/lactol (0.10 g, 0.29 mmol), that was dissolved in methanol (5.8 mL). Camphorsulfonic acid (13 mg, 0.058 mmol, 0.2 equiv) was added and the mixture stirred at 22 °C for 16 h, then diluted with Et₂O (20 mL) and quenched with a saturated aqueous solution of sodium carbonate (10 mL). The aqueous phase was extracted with Et₂O (3 × 20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product 17a* as a mixture of diastereomers (73 mg, 0.20 mmol, 69%, dr = 6:1) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, major

diastereomer described only): δ 7.30-7.23 (m, 3H, H_{Ar}), 7.21-7.16 (m, 3H, H_{Ar}), 7.09 (app. t, $J = 7.5$ Hz, 1H, H_{Ar}), 6.91 (app. td, $J = 7.5, 1.0$ Hz, 1H, H_{Ar}), 6.85-6.81 (m, 1H, H_{Ar}), 3.17 (s, 3H, O-CH₃), 3.04-2.97 (m, 1H, CH-CH₂-CO), 2.68-2.62 (m, 2H, CH₂-Ph), 2.13 (dd, $J = 13.5, 6.0$ Hz, 1H, CH-CH_dH_b-CO), 2.02-1.91 (m, 2H, CH-CH_eH_d-CH₂ and CH₂-CH_eH_f-CO), 1.83-1.63 (m, 3H, CH-CH_eH_f-CH₂ and CH₂-CH₂-Ph), 1.53-1.42 (m, 4H, CH-CH_aH_b-CO, CH₂-CH_cH_d-CO and CH₂-CH₂-CO), 1.29-1.25 (m, 6H, 3 $\times$ CH₂), 0.91-0.88 (m, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃, major diastereomer described only): δ 152.3, 142.6, 128.54, 128.46, 127.2, 127.1, 126.8, 125.9, 120.9, 117.1, 100.2, 48.7, 36.0, 35.7, 35.2, 33.8, 32.4, 31.9, 29.7, 26.0, 23.5, 22.8, 14.3; **LRMS** (ESI⁺): m/z 389.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₅H₃₄O₂N requires 389.2451 [M+H]⁺, found 389.2454; **IR**: ν_{max} (neat)/cm⁻¹ 2928, 2856, 1581, 1487, 1453, 1297, 1223, 1187, 1143, 1050; $[\alpha]_D^{25}$: -2.5 ($c = 0.5$, CHCl₃).

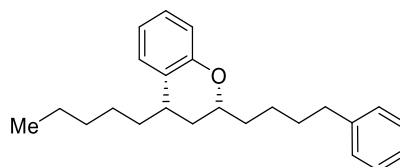
6-[(4S)-2-Methoxy-4-pentylchroman-2-yl]hexan-2-one **17b**



The desired product was prepared according to general procedure **D**, using 3-(ethylthio)octanal **7a** (85 mg, 0.45 mmol), 5-hexen-2-one (0.16 mL, 1.4 mmol) and 2-hydroxyphenylboronic acid (0.12 g, 0.90 mmol, 2.0 equiv). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the ketone/lactol (72 mg, 0.23 mmol), that was dissolved in methanol (4.4 mL). Camphorsulfonic acid (16 mg, 0.069 mmol, 0.3 equiv) was added and the mixture stirred at 22 °C for 16 h, then diluted with Et₂O (20 mL) and quenched with a saturated aqueous solution of sodium carbonate (10 mL). The aqueous phase was extracted with Et₂O (3 $\times$ 20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **17b** as a mixture of diastereomers (82 mg, 0.25 mmol, 55%, dr = 6:1, 93% ee) as a yellow oil. ¹H NMR (400 MHz, CDCl₃, major diastereomer described only): δ 7.27-7.25 (m, 1H, H_{Ar}), 7.10 (app. tdd, $J = 8.0, 1.5, 1.0$ Hz, 1H, H_{Ar}), 6.92 (app. td, $J = 7.5, 1.5$ Hz, 1H, H_{Ar}), 6.82 (dd, $J = 8.0, 1.5$ Hz, 1H, H_{Ar}), 3.18 (s, 3H, O-CH₃), 3.08-2.99 (m, 1H, CH-CH₂-CO), 2.49 (t, $J = 7.5$ Hz, 2H, CH₂-CO-CH₃), 2.16 (s, 3H, CO-CH₃),

2.14-2.11 (m, 1H, CH-CH_aH_b-CO), 2.02-1.91 (m, 2H, CH-CH_cH_d-CH₂ and CH₂-CH_eH_f-CO), 1.81-1.74 (m, 1H, CH₂-CH_eH_f-CO), 1.68-1.61 (m, 2H, CH₂-CH₂-CO-CH₃), 1.50-1.43 (m, 2H, CH-CH_aH_b-CO and CH-CH_cH_d-CH₂), 1.41-1.27 (m, 8H, 4 × CH₂), 0.92-0.88 (m, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃, major diastereomer described only): δ 209.0, 152.2, 127.3, 127.1, 126.8, 121.0, 117.1, 100.0, 48.7, 43.7, 35.7, 35.1, 33.7, 32.3, 30.1, 29.7, 26.1, 24.1, 23.4, 22.8, 14.2; LRMS (ESI⁺): *m/z* 355.2 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₂₁H₃₂O₃Na requires 355.2244 [M+Na]⁺, found 355.2243; IR: ν_{max} (neat)/cm⁻¹ 2930, 2859, 1716, 1581, 1487, 1453, 1297, 1186, 1159. the ee was determined by HPLC using a Chiralpak IA-3 column (*n*-hexane/*i*-PrOH, 99:1); flow rate 0.9 mL/min; τ_{major} = 8.21 min, τ_{minor} = 10.31 min (93% ee); [α]_D²⁵: -4.4 (*c* = 1.0, CHCl₃).

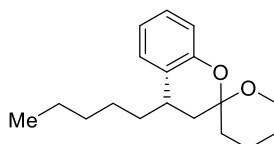
(2*R*,4*S*)-4-Pentyl-2-(4-phenylbutyl)chroman 18



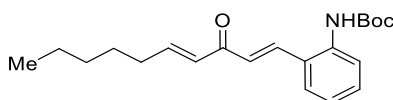
Triethylsilane (59 μL, 0.37 mmol, 3.1 equiv) was added to a solution of (4*S*)-2-methoxy-4-pentyl-2-(4-phenylbutyl)chroman **17a** (44 mg, 0.12 mmol, 1.0 equiv) in anhydrous CH₂Cl₂ (3.0 mL). Boron trifluoride diethyl etherate (44 μL, 0.36 mmol, 3.0 equiv) was then added dropwise and the reaction mixture was stirred at 22 °C for 3 h. The reaction was quenched with a saturated aqueous solution of sodium carbonate (5 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the *desired product* **18** (34 mg, 0.10 mmol, 85%, 91% ee, dr > 25:1) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.28 (m, 2H, *H*_{Ar}), 7.26-7.18 (m, 4H, *H*_{Ar}), 7.11-7.07 (m, 1H, *H*_{Ar}), 6.88 (app.td, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 6.81 (dd, *J* = 8.0, 1.5 Hz, 1H, *H*_{Ar}), 3.98-3.92 (m, 1H, CH-O), 2.93-2.89 (m, 1H, CH-Ar), 2.68 (t, *J* = 7.5 Hz, 2H, CH₂-Ph), 2.05 (ddd, *J* = 13.5, 6.0, 1.5 Hz, 1H, CH-CH_aH_b-CH), 2.02-1.91 (m, 1H, CH-CH_cH_d-(CH₂)₃-CH₃), 1.81-1.64 (m, 4H, CH₂-CH₂-Ph and CH₂-(CH₂)₃-Ph), 1.56-1.40 (m, 4H, CH-CH_aH_b-CH, CH-CH_cH_d-(CH₂)₃-CH₃ and CH₂-(CH₂)₂-Ph), 1.40-1.28 (m, 6H, 3 × CH₂), 0.92 (t, *J* = 6.5 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 155.5, 142.8, 128.6, 128.4, 127.3, 127.1, 126.8, 125.8, 120.3, 116.9, 76.0, 36.04, 36.00, 34.9,

34.44, 34.39, 32.3, 31.7, 26.1, 25.1, 22.8, 14.3; **LRMS** (ESI⁺): m/z 337.2 ([M+H]⁺, 10%), 359.2 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₂₄H₃₂ONa requires 359.2345 [M+Na]⁺, found 359.2344; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2929, 2857, 1606, 1579, 1486, 1454, 1379, 1296, 1233. The **ee** was determined by HPLC using a Chiralpak OD-H column (*n*-hexane/*i*-PrOH, 98:2); flow rate 0.5 mL/min; τ_{major} = 10.63 min, τ_{minor} = 10.03 min (91% ee); $[\alpha]_{\text{D}}^{25}$: +57.0 (c = 1.0, CHCl₃).

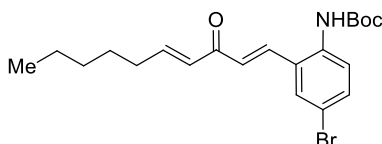
(4S)-4-Pentyl-3',4',5',6'-tetrahydrospiro(chroman-2,2'-pyran) 19



The desired product was prepared according to general procedure **D**, using 3-(ethylthio)octanal **7a** (66 mg, 0.35 mmol), 3-buten-1-ol (90 μ L, 1.05 mmol), 2-hydroxyphenylboronic acid (97 mg, 0.70 mmol, 2.0 equiv). The reaction mixture was then filtered through a pad of silica and concentrated under reduced pressure. Methanol (3.5 mL) and camphorsulfonic acid (81 mg, 0.35 mmol, 1.0 equiv) were added and the solution stirred at room temperature for 12 h, filtered through a pad of celite and concentrated under reduced pressure. Purification by flash column chromatography (from 100% petrol to petrol/Et₂O, 8:2) afforded the *desired product* **19** as a mixture of diastereomers (35 mg, 0.13 mmol, 36%, dr = 6:1) as a colourless oil. **¹H NMR** (400 MHz, C₆D₆): δ 7.25 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.11-7.06 (m, 2H, H_{Ar}), 6.91 (ddd, J = 8.0, 6.5, 2.5 Hz, 1H, H_{Ar}), 3.76 (ddd, J = 12.5, 11.0, 2.5 Hz, 1H, O-CH_dH_b), 3.45-3.40 (m, 1H, O-CH_aH_b), 3.31-3.27 (m, 1H, CH), 2.11 (dt, J = 14.5, 4.0 Hz, 1H, C-CH_cH_d-CH₂), 1.98 (dd, J = 13.0, 6.0 Hz, 1H, CH-CH_eH_f-C), 1.93-1.82 (m, 1H, CH-CH_gH_h-(CH₂)₃), 1.81-1.74 (m, 1H, C-CH_cH_d-CH₂), 1.48-1.37 (m, 5H, CH-CH_eH_f-C, CH-CH_gH_h-(CH₂)₃ and O-CH₂-CH₂-CH_iH_j), 1.31-1.14 (m, 7H, O-CH₂-CH₂-CH_iH_j and 3 $\times$ CH₂), 0.87 (t, J = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 152.1, 127.3, 127.1, 127.0, 120.9, 117.3, 96.3, 61.9, 38.3, 35.3, 34.0, 32.3, 29.7, 26.1, 25.4, 22.8, 18.6, 14.2; **HRMS** (CI⁺): C₁₈H₂₇O₂ requires 275.2011 [M+H]⁺, found 275.1965; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2929, 2857, 1581, 1488, 1453, 1370, 1229, 1216; $[\alpha]_{\text{D}}^{25}$: -17.4 (c = 1.0, CHCl₃).

tert*-Butyl {2-[(1*E*,4*E*)-3-oxodeca-1,4-dien-1-yl]phenyl}carbamate **15a*

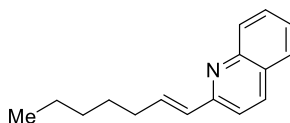
The desired product was prepared according to general procedure **D** following the first two steps only and using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), *tert*-butyl (2-ethynylphenyl)carbamate (70 mg, 0.32 mmol, 1.05 equiv) then copper(I) 3-methylsalicylate (65 mg, 0.30 mmol). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **15a** (99 mg, 0.29 mmol, 95%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.85-7.78 (m, 2H, 1 × *H*_{Ar} and Ar-CH=CH), 7.56 (d, *J* = 7.5 Hz, 1H, *H*_{Ar}), 7.36 (app. t, *J* = 8.0 Hz, 1H, *H*_{Ar}), 7.12 (app. t, *J* = 7.5 Hz, 1H, *H*_{Ar}), 7.07-6.98 (m, 1H, CH₂-CH=CH), 6.96 (d, *J* = 15.5 Hz, 1H, Ar-CH=CH), 6.59 (s, 1H, NH), 6.38 (d, *J* = 15.5 Hz, 1H, CH₂-CH=CH), 2.28 (app. dd, *J* = 14.5, 7.0 Hz, 2H, CH₂-CH), 1.52-1.49 (m, 11H, (CH₃)₃ and CH₂), 1.36-1.29 (m, 4H, 2 × CH₂), 0.90 (t, *J* = 6.5 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 189.0, 153.1, 149.2, 137.6, 137.1, 131.0, 130.1, 127.2, 126.5, 124.4, 123.9 (2C), 81.2, 32.9, 31.5, 28.4, 28.0, 22.6, 14.1; **LRMS** (ESI⁺): *m/z* 266.1 ([M-Boc+Na]⁺, 100%), **HRMS** (CI⁺): C₂₁H₃₀NO₃ requires 344.2226 [M+H]⁺, found 344.2219; **IR**: ν_{max} (neat)/cm⁻¹ 2929, 2858, 1727, 1657, 1627, 1595, 1520, 1454, 1366, 1236, 1158.

tert*-Butyl {4-bromo-2-[(1*E*,4*E*)-3-oxodeca-1,4-dien-1-yl]phenyl}carbamate **15b*

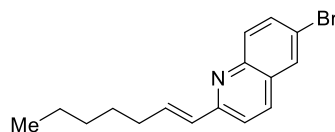
The desired product was prepared according to general procedure **D** following the first two steps only and using 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol), *tert*-butyl (4-bromo-2-ethynylphenyl)carbamate (95 mg, 0.32 mmol, 1.05 equiv) then copper(I) 3-methylsalicylate (65 mg, 0.30 mmol). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **15b** (0.12 g, 0.28 mmol, 93%) as a yellow solid. **¹H NMR** (400 MHz, CDCl₃): δ 7.75 (d, *J* = 9.0 Hz, 1H, *H*_{Ar}), 7.70 (d, *J* = 15.5 Hz, 1H, Ar-CH=CH), 7.66 (d, *J* = 2.5 Hz, 1H, *H*_{Ar}), 7.45 (dd, *J* = 9.0, 2.5 Hz, 1H, *H*_{Ar}), 7.04 (dt, *J* = 15.5, 7.0 Hz, 1H, CH₂-CH=CH), 6.95 (d, *J* = 15.5 Hz, 1H, Ar-CH=CH), 6.57 (s, 1H, NH), 6.35 (dt, *J* = 15.5, 1.5 Hz, 1H, CH₂-CH=CH),

2.31-2.26 (m, 2H, $\text{CH}_2\text{-CH}$), 1.55-1.46 (m, 11H, $(\text{CH}_3)_3$ and CH_2), 1.37-1.27 (m, 4H, $2 \times \text{CH}_2$), 0.92-0.87 (m, 3H, $\text{CH}_2\text{-CH}_3$); ^{13}C NMR (101 MHz, CDCl_3): δ 188.6, 152.8, 149.8, 136.2, 135.8, 133.6, 130.3, 129.8, 127.4, 124.1 (2C), 117.1, 81.6, 32.9, 31.5, 28.4, 27.9, 22.6, 14.1; **LRMS** (ESI^+): m/z 444.1 ($[\text{BrM}+\text{Na}]^+$, 50%), 446.1 ($[\text{BrM}+\text{Na}]^+$, 80%), 455.0 ($[\text{M}+\text{MeOH}+\text{H}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{21}\text{H}_{28}^{79}\text{BrNO}_3\text{Na}$ requires 444.1145 $[\text{M}+\text{Na}]^+$, found 444.1145; **IR**: ν_{max} (neat)/ cm^{-1} 2978, 2958, 2930, 1730, 1658, 1629, 1596, 1513, 1367, 1234, 1155.

(E)-2-(Hept-1-en-1-yl)quinoline 21a



To a solution of *tert*-butyl {2-[(1*E*,4*E*)-3-oxodeca-1,4-dien-1-yl]phenyl}carbamate **15a** (0.14 g, 0.41 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL), was added trifluoroacetic acid (0.78 mL, 10 mmol, 25.0 equiv) at room temperature. The reaction mixture was stirred for 14 h, and then quenched with an aqueous solution of sodium hydroxide (1 M, 15 mL). The product was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/ Et_2O , 95:5) afforded the *desired product* **21a** (48 mg, 0.21 mmol, 52%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 8.06 (d, $J = 8.5$ Hz, 1H, H_{Ar}), 8.03 (d, $J = 8.5$ Hz, 1H, H_{Ar}), 7.75 (d, $J = 8.0$ Hz, 1H, H_{Ar}), 7.67 (ddd, $J = 8.5, 7.0, 1.5$ Hz, 1H, H_{Ar}), 7.53 (d, $J = 8.5$ Hz, 1H, H_{Ar}), 7.49-7.43 (m, 1H, H_{Ar}), 6.83 (dt, $J = 16.0, 6.5$ Hz, 1H, $\text{CH}_2\text{-CH=CH}$), 6.71 (d, $J = 16.0$ Hz, 1H, $\text{CH}_2\text{-CH=CH}$), 2.33 (td, $J = 8.0, 1.0$ Hz, 2H, $\text{CH}_2\text{-CH}$), 1.65-1.46 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}$), 1.40-1.29 (m, 4H, $2 \times \text{CH}_2$), 0.91 (t, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3): δ 156.7, 148.2, 138.2, 136.3, 131.2, 129.7, 129.3, 127.6, 127.3, 126.0, 118.8, 33.2, 31.6, 28.7, 22.7, 14.2; **LRMS** (ESI^+): m/z 226.1 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{16}\text{H}_{20}\text{N}$ requires 226.1590 $[\text{M}+\text{H}]^+$, found 226.1592; **IR**: ν_{max} (neat)/ cm^{-1} 2980, 2889, 1597, 1503, 1461, 1426, 1251, 1152.

(E)-6-Bromo-2-(hept-1-en-1-yl)quinoline 21b

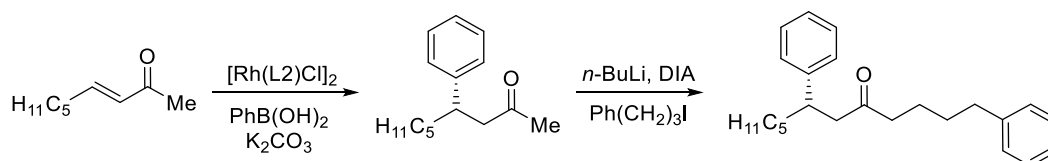
To a solution of *tert*-butyl {4-bromo-2-[(1*E*,4*E*)-3-oxodeca-1,4-dien-1-yl]phenyl}carbamate **15b** (30 mg, 0.07 mmol, 1.0 equiv) in CH₂Cl₂ (1.5 mL), was added trifluoroacetic acid (0.14 mL, 1.8 mmol, 25 equiv) at room temperature. The reaction mixture was stirred for 14 h, and then quenched with an aqueous solution of sodium hydroxide (1 M, 5 mL). The product was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired product* **21b** (13 mg, 0.04 mmol, 62%) as a yellow oil.

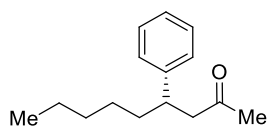
¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 8.5 Hz, 1H, *H*_{Ar}), 7.89 (dd, *J* = 9.0, 5.0 Hz, 2H, *H*_{Ar}), 7.72 (dd, *J* = 9.0, 3.0 Hz, 1H, *H*_{Ar}), 7.52 (d, *J* = 8.5 Hz, 1H, *H*_{Ar}), 6.85 (dt, *J* = 16.0, 7.0 Hz, 1H, CH=CH-Ar), 6.68 (d, *J* = 16.0 Hz, 1H, CH=CH-Ar), 2.32 (td, *J* = 8.0, 1.5 Hz, 2H, CH₂-CH=CH), 1.62-1.47 (m, 2H, CH₂-CH₂-CH), 1.41-1.28 (m, 4H, 2 × CH₂), 0.91 (t, *J* = 7.0 Hz, 3H, CH₃);

¹³C NMR (101 MHz, CDCl₃): δ 157.0, 146.8, 139.0, 135.3, 133.1, 131.0, 130.8, 129.6, 128.3, 119.8, 119.6, 33.2, 31.6, 28.7, 22.7, 14.2; **LRMS** (ESI⁺): *m/z* 304.0 ([⁷⁹BrM+H]⁺, 100%), 306.0 ([⁸¹BrM+H]⁺, 40%); **HRMS** (ESI⁺): C₁₆H₁₉⁷⁹BrN requires 304.0695 [M+H]⁺, found 304.0695; **IR**: ν_{max} (neat)/cm⁻¹ 2956, 2926, 2855, 1650, 1594, 1547, 1488, 1385, 1303, 1231.

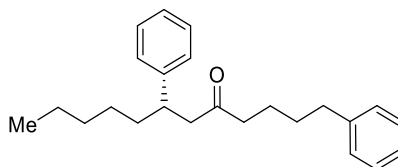
6.2.4 Determination of the absolute configuration

The absolute configuration was determined by first synthesising the reported (*S*)-4-(phenyl)nonan-2-one) **23**. This compound was then alkylated into (*S*)-1,7-diphenyldodecan-5-one. The desired product was also prepared using our sequential procedure (ketone **12g**) and the absolute configuration was determined by comparison of the optical rotation values.



(S)-4-Phenylnonan-2-one 23

A mixture of 3-nonen-2-one (0.14 g, 1.0 mmol, 1.0 equiv), phenylboronic acid (0.24 g, 2.0 mmol, 2.0 equiv), K_2CO_3 (69 mg, 0.50 mmol, 0.50 equiv) and $[Rh(L2)Cl]_2$ (18 mg, 0.02 mmol, 0.02 equiv) in acetone/methanol (10 mL, 9:1) was stirred at 55 °C for 3 h then filtered through a pad of silica and concentrated under reduced pressure. Purification by flash column chromatography (petrol/ Et_2O , 95:5) afforded the desired ketone **23** (0.22 g, 1.0 mmol, 99%, 98% ee) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 7.25-7.21 (m, 2H, H_{Ar}), 7.17-7.11 (m, 3H, H_{Ar}), 3.12-3.02 (m, 1H, $CH-CH_2-CO$), 2.67 (dd, $J = 7.0, 2.0$ Hz, 2H, $CH-CH_2-CO$), 1.97 (s, 3H, $CO-CH_3$), 1.60-1.48 (m, 2H, CH_2), 1.20-1.13 (m, 6H, $3 \times CH_2$), 0.78 (t, $J = 7.0$ Hz, 3H, CH_2-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.2, 144.7, 128.6, 127.6, 126.4, 51.1, 41.4, 36.6, 31.9, 30.8, 27.2, 22.6, 14.2; LRMS (ESI $^+$): m/z 241.1 ($[M+Na]^+$, 100%). This data is consistent with the literature.¹⁴⁰ The ee was determined by HPLC using a Chiralpak OD-H column (*n*-hexane/*i*-PrOH, 92:8); flow rate 0.3 mL/min; $\tau_{major} = 16.3$ min, $\tau_{minor} = 17.4$ min (98% ee). Reported values:¹⁴¹ Chiralpak OD-H column with (*n*-hexane/*i*-PrOH, 100:1), flow rate 0.5 mL/min; $\tau_{major} = 22.0$ min [(*S*)-enantiomer], $\tau_{minor} = 23.1$ min [(*R*)-enantiomer], 98.8% ee. $[\alpha]_D^{25}$: +18.7 ($c = 1.0$, $CHCl_3$); (Reported values: $[\alpha]_D^{20}$: +16.9 ($c = 0.5$, $CHCl_3$, 92% ee for (*S*)-enantiomer)¹⁴²; $[\alpha]_D^{20}$: -17.0 ($c = 1.3$, $CHCl_3$, 92% ee for (*R*)-enantiomer).^{140,143}

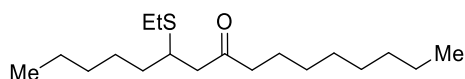
(S)-1,7-Diphenyldodecan-5-one 12g

n-Butyllithium (1.6 M in hexane, 0.26 mL, 0.42 mmol, 1.1 equiv) was added dropwise to a solution of diisopropylamine (70 μ L, 0.48 mmol, 1.2 equiv) in anhydrous THF (1.4 mL) at 0 °C. The mixture was stirred for 15 min and then added dropwise to a solution of (*S*)-4-phenylnonan-2-one **23** (88 mg, 0.40 mmol, 1.0 equiv) in THF (1.0 mL). The reaction mixture was warmed up to room

temperature, stirred for 1 h and cooled down to 0 °C. 1-Iodo-3-phenylpropane (70 μ L, 0.22 mmol, 1.1 equiv) was added dropwise and the solution stirred at 22 °C overnight. A saturated aqueous solution of ammonium chloride was added (5 mL) and the product extracted with Et₂O (3 $\times$ 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 99:1) afforded the *desired ketone* (13 mg, 0.038 mmol, 8%, 98% ee) as a colorless oil. This data is consistent with the one previously described for compound **12g**. The **ee** was determined by HPLC using a Chiralpak IA-3 column (*n*-hexane/*i*-PrOH, 98:2); flow rate 0.5 mL/min; τ_{major} = 11.42 min for [(*S*)-enantiomer], τ_{minor} = 11.95 min [(*R*)-enantiomer] (98% ee); $[\alpha]_{\text{D}}^{25}$: +17.4 (*c* = 0.5, CHCl₃) compared to $[\alpha]_{\text{D}}^{25}$: +17.9 (*c* = 0.5, CHCl₃) obtained for ketone **12g**.

6.2.5 Products isolated during the establishment of optimal conditions

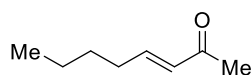
6-(Ethylthio)hexadecan-8-one **8a**



Acetone (~0.5 mL) was added to a microwave reaction vial charged with [Rh(nbd)₂BF₄] (5.6 mg, 0.015 mmol, 0.05 equiv) and dcpm (6.1 mg, 0.015 mmol, 0.05 equiv) (previously evacuated and back-filled with N₂ gas). The solution was bubbled with H₂ gas for 2 min, followed by N₂ gas until dryness. Acetone (0.30 mL, 1.0 M) was added and the resulting solution was transferred to a N₂-purged microwave reaction vial containing 3-(ethylthio)octanal **7a** (56 mg, 0.30 mmol). 1-Octene (0.14 mL, 0.90 mmol) was added and the reaction mixture was stirred at 55 °C for 1 h. The mixture was allowed to cool to room temperature, filtered through a pad of silica and the filtrate concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired product 8* as a colourless oil (89 mg, 0.30 mmol, 99%). **¹H NMR** (400 MHz, CDCl₃): δ 3.18-3.07 (m, 1H, CH-S), 2.68 (dd, *J* = 16.5, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.59 (dd, *J* = 16.5, 7.0 Hz, 1H, CH-CH_aH_b-CO), 2.52 (q, *J* = 7.5 Hz, 2H, S-CH₂-CH₃), 2.41 (td, *J* = 7.0, 1.5 Hz, 2H, CH₂-CH₂-CO), 1.61-1.47 (m, 4H, 2 $\times$ CH₂), 1.46-1.34 (m, 2H, CH₂), 1.33-1.19 (m, 17H, 7 $\times$ CH₂ and S-CH₂-CH₃), 0.88 (m, 6H, 2 $\times$ CH₂-CH₂-CH₃); **¹³C NMR** (101 MHz,

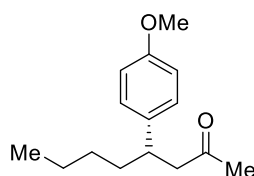
CDCl₃): δ 209.7, 49.0, 44.0, 40.5, 35.6, 32.0, 31.8, 29.5, 29.4, 29.3, 26.6, 25.2, 23.8, 22.8, 22.7, 15.0, 14.2, 14.2; **LRMS** (ESI⁺): m/z 301.3 ([M+H]⁺, 100%), 323.2 ([M+Na]⁺, 25%), 623.5 ([2M+Na]⁺, 40%); **HRMS** (ESI⁺): C₁₈H₃₇OS requires 301.2560 [M+H]⁺, found 301.2560; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2956, 2925, 2855, 1714, 1457, 1408, 1375, 1263.

(E)-3-Octene-2-one **10**



Under nitrogen, acetone (0.4 mL) was added to a vial containing copper(I)-3-methylsalicylate (43 mg, 0.20 mmol, 1.0 equiv) and 4-(ethylthio)octan-2-one **9** (38 mg, 0.20 mmol, 1.0 equiv). The reaction mixture was stirred at 55 °C for 16 h. The resulting suspension was filtered through a pad of silica and then reduced under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the desired product **10** (24 mg, 0.19 mmol, 95%) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃): δ 6.79 (dt, J = 16.0, 7.0 Hz, 1H, HC=CH-CO), 6.05 (dt, J = 16.0, 1.5 Hz, 1H, HC=CH-CO), 2.22 (s, 3H, CO-CH₃), 1.51-1.25 (m, 6H, 3 × CH₂), 0.89 (t, J = 7.0 Hz, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 199.0, 148.9, 131.4, 32.3, 30.3, 26.9, 22.3, 13.90; **LRMS** (ESI⁺): m/z 149.0 ([M+Na]⁺, 100%). This data is consistent with the literature.¹⁴⁴

4-(4-Methoxyphenyl)octan-2-one **11**



Acetone (2.7 mL) and methanol (0.3 mL) were added to a N₂-purged vial containing (E)-3-octene-2-one **10** (44 μ L, 0.30 mmol), [Rh(L1)Cl]₂ (7.1 mg, 0.0075 mmol), potassium carbonate (0.10 g, 0.75 mmol) and 4-methoxyphenylboronic acid (91 mg, 0.60 mmol). The reaction mixture was heated at 55 °C for 1 h. Upon completion, the reaction was filtered through a plug of silica, and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the desired product **11** as a colourless oil (66 mg, 0.28 mmol, 94%). **¹H NMR** (400 MHz, CDCl₃): δ 7.09 (d, J = 8.5 Hz, 2H, H_{Ar}), 6.83 (d, J = 8.5 Hz, 2H, H_{Ar}), 3.78 (s, 3H, O-CH₃), 3.13-2.98 (m, 1H, CH-CH₂-CO), 2.67 (d, J = 7.5 Hz, 2H, CH₂-CO), 2.00 (s, 3H,

CO-CH₃), 1.66-1.42 (m, 2H, CH₂), 1.40-1.03 (m, 4H, 2 × CH₂), 0.82 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 208.4, 158.1, 136.7, 128.5, 113.9, 55.3, 51.3, 40.7, 36.5, 30.8, 29.7, 22.7, 14.1; LRMS (ESI⁺): *m/z* 257.1 ([M+Na]⁺, 100%). The ee was determined by HPLC using a Chiralpak AD-H column (*n*-hexane/*i*-PrOH, 99:1); flow rate 1.0 mL/min; τ_{major} = 8.64 min for [(*S*)-enantiomer], τ_{minor} = 9.21 min [(*R*)-enantiomer] (98% ee); [α]_D²⁵: +15.4 (*c* = 1.0, CHCl₃). This data is consistent with the literature.¹⁴⁵

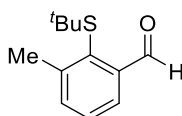
6.3 Chapter 3 data

6.3.1 Starting material synthesis

General procedure E: synthesis of 2-(*tert*-butylthio)benzaldehyde derivatives

A solution of aldehyde (1.0 equiv) in anhydrous DMF (0.8 M) was added dropwise to a suspension of sodium 2-methyl-2-propanethiolate (1.05 equiv) in anhydrous DMF (0.8 M) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 14 h. H₂O (10 mL) was added and the product extracted with Et₂O (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired product.

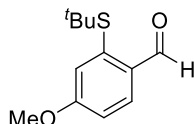
2-(*tert*-Butylthio)-3-methylbenzaldehyde **28b**



The desired aldehyde was prepared according to general procedure E using 2-fluoro-3-methylbenzaldehyde (0.28 g, 2.0 mmol) and sodium 2-methyl-2-propanethiolate (90% technical grade, 0.26 g, 2.1 mmol) in DMF (5.0 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the *desired aldehyde* **28b** (0.28 g, 1.4 mmol, 67%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 10.79 (s, 1H, CHO), 7.81 (dd, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 7.54 (dd, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 7.37 (app. t, *J* = 7.5 Hz, 1H, *H*_{Ar}), 2.59 (s, 3H, Ar-CH₃), 1.23 (s, 9H, C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃): δ 194.8, 146.1, 140.7, 136.1, 135.7, 129.1, 126.1, 49.5, 31.2, 21.6; LRMS (ESI⁺): *m/z* 263.0 ([M+MeOH+Na]⁺, 100%); HRMS (ESI⁺): C₁₂H₁₆OSNa

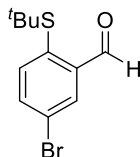
requires 231.0814 $[M+Na]^+$, found 231.0817; **IR**: $\nu_{\max}$ (neat)/ cm^{-1} 2962, 2862, 1681, 1579, 1474, 1363, 1234, 1163.

2-(*tert*-Butylthio)-4-methoxybenzaldehyde **28c**

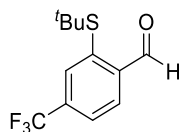


The desired aldehyde was prepared according to general procedure **E** using 2-fluoro-4-methoxybenzaldehyde (0.46 g, 3.0 mmol) and sodium 2-methyl-2-propanethiolate (90% technical grade, 0.40 g, 3.2 mmol) in DMF (7.5 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired aldehyde* **28c** (0.56 g, 2.5 mmol, 83%) as a colourless oil. **^1H NMR** (400 MHz, CDCl_3): δ 10.62 (d, $J = 1.0$ Hz, 1H, CHO), 8.03-7.91 (m, 1H, H_{Ar}), 7.09 (d, $J = 2.5$ Hz, 1H, H_{Ar}), 7.05-6.96 (m, 1H, H_{Ar}), 3.87 (s, 3H, O- CH_3), 1.29 (s, 9H, $\text{C}(\text{CH}_3)_3$); **^{13}C NMR** (101 MHz, CDCl_3): δ 192.4, 163.4, 138.9, 132.9, 130.2, 124.3, 115.6, 55.8, 47.7, 31.1; **LRMS** (ESI^+): m/z 247.0 ($[M+Na]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{12}\text{H}_{17}\text{O}_2\text{S}$ requires 225.0944 $[M+H]^+$, found 225.0946; **IR**: $\nu_{\max}$ (neat)/ cm^{-1} 2963, 1684, 1586, 1475, 1363, 1302, 1275, 1234, 1161.

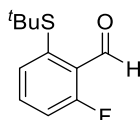
5-Bromo-2-(*tert*-butylthio)benzaldehyde **28d**



The desired aldehyde was prepared according to general procedure **E** using 5-bromo-2-fluorobenzaldehyde (0.41 g, 2.0 mmol) and sodium 2-methyl-2-propanethiolate (90% technical grade, 0.26 g, 2.1 mmol) in DMF (5.0 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired aldehyde* **28d** (0.32 g, 1.2 mmol, 59%) as a colourless oil. **^1H NMR** (400 MHz, CDCl_3): 10.68 (s, 1H, CHO), 8.10 (d, $J = 2.5$ Hz, 1H, H_{Ar}), 7.68 (dd, $J = 8.0$, 2.5 Hz, 1H, H_{Ar}), 7.49 (d, $J = 8.0$ Hz, 1H, H_{Ar}), 1.28 (s, 9H, $\text{C}(\text{CH}_3)_3$); **^{13}C NMR** (101 MHz, CDCl_3): 192.3, 141.5, 140.7, 136.5, 135.6, 131.3, 124.6, 48.1, 31.0; **IR**: $\nu_{\max}$ (neat)/ cm^{-1} 2970, 2862, 1690, 1570, 1454, 1365, 1245, 1182, 1164. This data is consistent with literature.¹⁴⁶

2-(*tert*-Butylthio)-4-(trifluoromethyl)benzaldehyde 28e

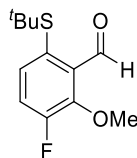
The desired aldehyde was prepared according to general procedure **E** using 2-fluoro-4-(trifluoromethyl)benzaldehyde (0.58 g, 3.0 mmol) and sodium 2-methyl-2-propanethiolate (90% technical grade, 0.40 g, 3.2 mmol) in DMF (7.5 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired aldehyde 28e* (0.46 g, 1.8 mmol, 60%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): 10.80 (d, *J* = 1.0 Hz, 1H, CHO), 8.09 (d, *J* = 8.0 Hz, 1H, *H*_{Ar}), 7.88 (s, 1H, *H*_{Ar}), 7.76 (d, *J* = 8.0 Hz, 1H, *H*_{Ar}), 1.31 (s, 9H, (CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃): δ 192.4, 142.0, 137.7, 136.7 (q, ³*J*_{CF} = 3.5 Hz), 134.9 (q, ²*J*_{CF} = 32.5 Hz), 128.8, 126.5 (q, ³*J*_{CF} = 3.5 Hz), 123.3 (q, ¹*J*_{CF} = 273.0 Hz), 48.5, 31.0; **¹⁹F NMR** (377 MHz, CDCl₃): δ -63.24; **LRMS** (ESI⁺): *m/z* 317.0 ([M+MeOH+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₃H₁₇O₂SF₃Na requires 317.0799 [M+MeOH+Na]⁺, found 317.0793; **IR**: ν_{max} (neat)/cm⁻¹ 2967, 1696, 1476, 1394, 1367, 1198.

2-(*tert*-Butylthio)-6-fluorobenzaldehyde 28f

A solution of sodium-2-methyl-2-propanethiolate (90% technical grade, 0.24 g, 1.9 mmol, 1.0 equiv) in DMF (2.5 mL) was added to 2,6-difluorobenzaldehyde (0.28 g, 2.0 mmol) in DMF (2.5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. H₂O (10 mL) was added and the product extracted with Et₂O (3 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/CH₂Cl₂, 6:4) afforded the *desired aldehyde 28f* (0.36 g, 1.7 mmol, 89%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 10.69 (s, 1H, CHO), 7.51 (app. td, *J* = 8.0, 5.5 Hz, 1H, *H*_{Ar}), 7.42 (d, *J* = 7.5 Hz, 1H, *H*_{Ar}), 7.19-7.14 (m, 1H, *H*_{Ar}), 1.29 (s, 9H, (CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃): δ 191.4, 161.8 (d, ¹*J*_{CF} = 266.0 Hz), 138.2, 135.3 (d, ⁴*J*_{CF} = 4.0 Hz), 134.1 (d, ³*J*_{CF} = 10.0 Hz), 128.1 (d, ²*J*_{CF} = 6.5 Hz), 118.0 (d, ²*J*_{CF} =

22.0 Hz), 48.5, 31.1; **¹⁹F NMR** (377 MHz, CDCl₃): δ -114.2; **HRMS** (CI⁺): C₁₁H₁₄OFS requires 213.0749 [M+H]⁺, found 213.0741; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2980, 2889, 1696, 1590, 1473, 1444, 1384.

6-(*tert*-Butylthio)-3-fluoro-2-methoxybenzaldehyde **28g**

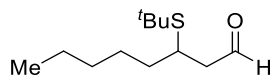


The desired aldehyde was prepared according to general procedure **E** using 3,6-difluoro-2-methoxybenzaldehyde (0.34 g, 2.0 mmol) and sodium 2-methyl-2-propanethiolate (90% technical grade, 0.26 g, 2.1 mmol) in DMF (5.0 mL). Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired aldehyde* **28g** (0.18 g, 0.74 mmol, 36%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 10.59 (m, 1H, CHO), 7.33-7.24 (m, 2H, H_{Ar}), 3.98 (s, 3H, O-CH₃), 1.28 (s, 9H, C(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃): δ 192.4, 156.4 (d, ¹J_{CF} = 253.0 Hz), 147.7 (d, ²J_{CF} = 12.0 Hz), 135.7 (d, ⁴J_{CF} = 2.0 Hz), 135.0 (d, ³J_{CF} = 7.0 Hz), 131.1 (d, ³J_{CF} = 4.0 Hz), 120.3 (d, ²J_{CF} = 20.0 Hz), 62.8 (d, J_{CF} = 5.0 Hz), 48.1, 31.0; **¹⁹F NMR** (377 MHz, CDCl₃): δ -127.1; **HRMS** (ESI⁺): C₁₂H₁₆O₂FS requires 243.0855 [M+H]⁺, found 243.0853; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 1699, 1471, 1437, 1385, 1365, 1271, 1234.

General procedure F: synthesis of β -S alkyl aldehydes

Aldehyde (1.0 equiv) was added dropwise to a solution of 2-methyl-2-propanethiol (1.2 equiv) and 1,8-diazabicycloundec-7-ene (0.1 equiv) and the resulting mixture was stirred for 30 min at room temperature. Purification by flash column chromatography afforded the desired product.

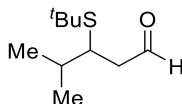
3-(*tert*-Butylthio)octanal **31a**



The desired aldehyde was prepared according to general procedure **F** using *trans*-2-octenal (0.30 mL, 2.0 mmol), 2-methyl-2-propanethiol (0.27 mL, 2.4 mmol) and 1,8-diazabicycloundec-7-ene (30 μ L, 0.20 mmol). Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired product* **31a** (0.25 g, 1.2 mmol, 59%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 9.77 (t, *J* = 1.5 Hz, 1H, CHO), 3.09 (p, *J* = 6.5 Hz, 1H, S-CH), 2.72 (ddd, *J* = 17.0, 6.5, 1.5 Hz, 1H,

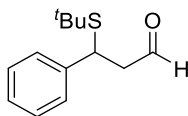
CH-CH_aH_b-CO), 2.65 (ddd, $J = 17.0, 6.5, 2.0$ Hz, 1H, CH-CH_aH_b-CO), 1.62-1.56 (m, 2H, CH-CH₂-CH₂), 1.46-1.35 (m, 2H, CH₂), 1.35-1.25 (m, 13H, $2 \times$ CH₂ and C(CH₃)₃), 0.88 (t, $J = 7.0$ Hz, 3H, CH₂-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 201.8, 50.8, 43.9, 37.7, 37.1, 31.8, 31.6, 26.7, 22.7, 14.2; LRMS (ESI⁺): m/z 271.0 ([M+MeOH+Na]⁺, 100%); HRMS (ESI⁺): C₁₂H₂₅OS requires 217.1626 [M+H]⁺, found 217.1623; IR: $\nu_{\max}$ (neat)/cm⁻¹ 2958, 2929, 2860, 1724, 1679, 1460, 1365.

3-(*tert*-Butylthio)-4-methylpentanal 31b



The desired aldehyde was prepared according to general procedure **F** using (*E*)-4-methylpent-2-enal (0.18 mL, 1.5 mmol), 2-methyl-2-propanethiol (0.20 mL, 1.8 mmol) and 1,8-diazabicycloundec-7-ene (22 μ L, 0.15 mmol). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **31b** (0.16 g, 0.87 mmol, 58%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 9.77 (t, $J = 2.0$ Hz, 1H, CHO), 3.04 (ddd, $J = 7.5, 6.5, 3.5$ Hz, 1H, S-CH), 2.70 (ddd, $J = 17.0, 6.5, 2.0$ Hz, 1H, CH-CH_aH_b-CO), 2.59 (ddd, $J = 17.0, 7.5, 2.0$ Hz, 1H, CH-CH_aH_b-CO), 1.98-1.87 (m, 1H, CH(CH₃)₂), 1.30 (s, 9H, C(CH₃)₃), 0.96 (d, $J = 6.5$ Hz, 3H, (CH-CH₃)_a), 0.92 (d, $J = 7.0$ Hz, 3H, (CH-CH₃)_b); ¹³C NMR (101 MHz, CDCl₃): δ 202.0, 47.6, 43.5, 43.0, 33.7, 31.6, 19.5, 19.0; LRMS (ESI⁺): m/z 243.0 ([M+MeOH+Na]⁺, 100%); HRMS (ESI⁺): C₁₀H₂₀OSNa requires 211.1127 [M+Na]⁺, found 211.1129; IR: $\nu_{\max}$ (neat)/cm⁻¹ 2960, 2900, 2870, 2720, 1722, 1461, 1385, 1365, 1162.

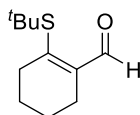
3-(*tert*-Butylthio)-3-phenylpropanal 31c



The desired aldehyde was prepared according to general procedure **F** using *trans*-cinnamaldehyde (0.13 mL, 1.0 mmol), 2-methyl-2-propanethiol (0.14 mL, 1.2 mmol) and 1,8-diazabicycloundec-7-ene (15 μ L, 0.10 mmol). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **31c** (0.13 g, 0.57 mmol, 57%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 9.67 (t, $J = 2.0$ Hz, 1H, CHO), 7.42-7.39 (m, 2H, H_{Ar}), 7.33-7.29 (m, 2H, H_{Ar}), 7.24-7.20 (m, 1H,

H_{Ar} , 4.42 (t, $J = 7.5$ Hz, 1H, S-CH), 2.88 (dd, $J = 7.5, 2.0$ Hz, 2H, CH-CH₂-CO), 1.22 (s, 9H, C(CH₃)₃); ^{13}C NMR (101 MHz, CDCl₃): 199.8, 144.0, 128.8, 127.7, 127.3, 51.8, 44.7, 41.8, 31.4; HRMS (CI⁺): C₁₃H₁₈OS requires 222.1078 [M]⁺, found 222.1078; IR: ν_{max} (neat)/cm⁻¹ 2961, 2898, 2724, 1723, 1492, 1453, 1390, 1162. This data is consistent with literature.¹⁴⁷

2-(*tert*-Butylthio)cyclohex-1-ene-1-carbaldehyde **32**



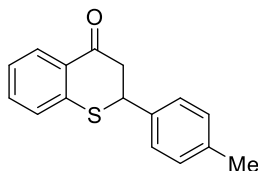
Phosphorous tribromide (2.8 mL, 30 mmol, 3.0 equiv) was added dropwise to a stirred solution of DMF (2.6 mL, 33 mmol, 3.3 equiv) in CHCl₃ (15.6 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, after which cyclohexanone (1.0 mL, 10 mmol, 1.0 equiv) was added. The solution was warmed to room temperature over 16 h. Upon completion, the reaction mixture was poured over ice and neutralised by the slow addition of solid sodium carbonate. Once neutral, the aqueous mixture was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic extracts were washed with brine (20 mL) and a saturated aqueous solution of lithium chloride (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to obtain a dark orange oil. Without further purification, the crude aldehyde was dissolved in DMF (12.5 mL) and stirred at 0 °C, followed by the slow addition of sodium 2-methyl-2-propanethiolate (90% technical grade, 1.7 g, 14 mmol, 1.4 equiv) in DMF (12.5 mL). The solution was warmed to room temperature over 8 h. Water (25 mL) was added to dilute the reaction mixture and the product was extracted with Et₂O (3 × 30 mL). The organic extracts were washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography (petrol/Et₂O, 9:1) to obtain the *desired aldehyde 25a* as a yellow oil (260 mg, 1.3 mmol, 13%). ^1H NMR (400 MHz, CDCl₃): δ 10.40 (s, 1H, CHO), 2.59-2.52 (m, 2H, CH₂-C-CHO), 2.31 (m, 2H, CH₂-C-S), 1.70-1.59 (m, 4H, CH₂-(CH₂)₂-CH₂), 1.36 (s, 9H, C(CH₃)₃); ^{13}C NMR (101 MHz, CDCl₃): δ 193.9, 153.2, 144.9, 48.0, 38.2, 32.1, 24.6, 23.3, 21.4; HRMS (ESI⁺): C₁₁H₁₉OS requires 199.1157 [M+H]⁺, found 199.1078; Rf: 0.3 (petrol/Et₂O, 9:1); IR: ν_{max} (neat)/cm⁻¹ 2938, 2898, 1668, 1588, 1458, 1349, 1268.

6.3.2 One-pot formation of S-heterocycles

General procedure G: synthesis of S-heterocycles by alkyne hydroacylation/thio-Michael addition sequence

DCE (0.2 mL, 1.0 M) was added to a microwave reaction vial charged with [Rh(nbd)₂BF₄] (3.7 mg, 0.01 mmol, 0.05 equiv) and dcpm (4.1 mg, 0.01 mmol, 0.05 equiv) which had previously been evacuated and back-filled with N₂ gas. H₂ gas was then bubbled through the solution until a colour change from deep red to light orange was observed. N₂ gas was then bubbled through the solution until dryness. DCE (0.2 mL, 1.0 M) was added and the solution was transferred to a N₂-purged microwave reaction vial containing aldehyde (0.20 mmol, 1.00 equiv). Alkyne (0.21 mmol, 1.05 equiv) was added and the reaction mixture stirred for 2 h at 55 °C and then cooled to room temperature. TFA (0.15 mL, 2.00 mmol, 10 equiv) was added and the reaction stirred for 1 h at room temperature. The reaction was then filtered through a plug of silica and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired product.

2-(*p*-Tolyl)thiochroman-4-one **24a**

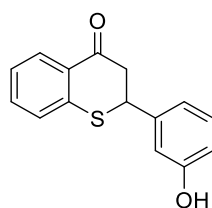


The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 4-ethynyltoluene (27 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/CH₂Cl₂, 7:3) afforded the desired product **24a** (43 mg, 0.17 mmol, 84%) as a beige solid.

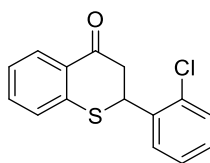
Gram scale: [Rh(nbd)₂BF₄] (18.7 mg, 1 mol%), dcpm (20.4 mg, 1 mol%), 2-(*tert*-butylthio)benzaldehyde (972 mg, 5.00 mmol) and 4-ethynyltoluene (666 μ L, 5.25 mmol) in DCE (2.5 mL, 2 M) at room temperature for 30 min, then TFA (3.8 mL, 50.0 mmol) with additional DCE (2.5 mL, 1 M) at room temperature for 30 min. Purification by flash column chromatography (petrol/CH₂Cl₂, 7:3) afforded the desired product **24a** (1.0 g, 3.9 mmol, 79%) as a beige solid.

¹H NMR (400 MHz, CDCl₃): δ 8.15 (dd, *J* = 8.0, 1.0 Hz, 1H, *H_{Ar}*), 7.41 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, *H_{Ar}*), 7.32 (d, *J* = 8.0 Hz, 2H, *H_{Ar}*), 7.28 (dd, *J* = 8.0, 1.0 Hz, 1H, *H_{Ar}*), 7.23-7.19 (m, 3H, *H_{Ar}*), 4.69 (dd, *J* = 13.0, 3.0 Hz, 1H, S-CH), 3.31 (dd, *J* = 16.5, 13.0 Hz, 1H, CH-CH_aH_b), 3.19 (dd, *J* = 16.5, 3.0 Hz, 1H, CH-CH_aH_b), 2.37 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 194.7, 142.4, 138.4, 135.5, 133.7, 130.5, 129.7, 129.3, 127.4, 127.3, 125.3, 46.9, 45.3, 21.3; **HRMS** (ESI⁺): C₁₆H₁₅OS requires 255.0844 [M+H]⁺, found 255.0844. This data is consistent with literature.¹⁴⁸

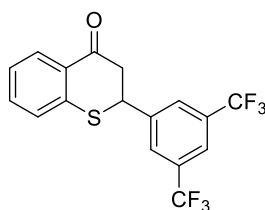
2-(3-Hydroxyphenyl)thiochroman-4-one 24c



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 3-hydroxyphenylacetylene (23 μL, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 6:4) afforded the *desired product* **24c** (44 mg, 0.17 mmol, 86%) as a white solid. **¹H NMR** (400 MHz, CD₃CN): δ 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H, *H_{Ar}*), 7.47 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, *H_{Ar}*), 7.33 (dd, *J* = 8.0, 1.0 Hz, 1H, *H_{Ar}*), 7.27-7.23 (m, 1H, *H_{Ar}*), 7.21 (d, *J* = 8.0 Hz, 1H, *H_{Ar}*), 7.07 (s, 1H, Ar-OH), 6.96-6.94 (m, 1H, *H_{Ar}*), 6.90 (app. t, *J* = 2.0 Hz, 1H, *H_{Ar}*), 6.78 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, *H_{Ar}*), 4.78 (dd, *J* = 12.5, 3.0 Hz, 1H, S-CH), 3.31 (dd, *J* = 16.5, 12.5 Hz, 1H, CH-CH_aH_b), 3.12 (dd, *J* = 16.5, 3.0 Hz, 1H, CH-CH_aH_b); **¹³C NMR** (101 MHz, CD₃CN): δ 194.9, 158.2, 142.7, 141.6, 134.7, 131.4, 131.0, 129.5, 128.1, 126.2, 119.8, 116.1, 115.2, 46.9, 45.6; **LRMS** (ESI⁺): *m/z* 279.0 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₅H₁₃O₂S requires 257.0631 [M+H]⁺, found 257.0632; **IR**: ν_{max} (neat)/cm⁻¹ 3359, 2360, 1663, 1587, 1437, 1400, 1284; **M.p.** (Et₂O): 156-160 °C.

2-(2-Chlorophenyl)thiochroman-4-one 24d

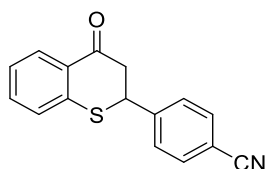
The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 2-chlorophenylacetylene (25 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ CH_2Cl_2 , 7:3) afforded the desired product **24d** (44 mg, 0.16 mmol, 80%) as a yellow solid. **^1H NMR** (400 MHz, CDCl_3): δ 8.14 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H, H_{Ar}), 7.56-7.49 (m, 1H, H_{Ar}), 7.46-7.35 (m, 2H, H_{Ar}), 7.32-7.15 (m, 4H, H_{Ar}), 5.21 (dd, J = 11.5, 3.5 Hz, 1H, S-CH), 3.26 (dd, J = 16.5, 11.5 Hz, 1H, CH- CH_aH_b), 3.18 (dd, J = 16.5, 3.5 Hz, 1H, CH- CH_aH_b); **^{13}C NMR** (101 MHz, CDCl_3): δ 194.1, 141.7, 136.2, 133.9, 133.6, 130.5, 130.3, 129.6, 129.4, 128.4, 127.6, 127.5, 125.5, 45.8, 41.7; **HRMS** (ESI^+): $\text{C}_{15}\text{H}_{12}\text{O}^{35}\text{ClSO}$ requires 275.0292 $[\text{M}+\text{H}]^+$, found 275.0293; $\text{C}_{15}\text{H}_{12}\text{O}^{37}\text{ClSO}$ requires 277.0262 $[\text{M}+\text{H}]^+$, found 277.0263. This data is consistent with literature.¹⁴⁸

2-(3,5-Bis(trifluoromethyl)phenyl)thiochroman-4-one 24f

The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (37 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired product* **24f** (62 mg, 0.16 mmol, 83%) as a white solid. **^1H NMR** (400 MHz, CDCl_3): δ 8.16 (dd, J = 8.0, 1.5 Hz, 1H, H_{Ar}), 7.94-7.84 (m, 3H, H_{Ar}), 7.46 (ddd, J = 8.0, 7.0, 1.5 Hz, 1H, H_{Ar}), 7.34-7.18 (m, 2H, H_{Ar}), 4.84 (dd, J = 12.5, 3.5 Hz, 1H, S-CH), 3.34 (dd, J = 16.5, 12.5 Hz, 1H, CH- CH_aH_b), 3.25 (dd, J = 16.5, 3.5 Hz, 1H, CH- CH_aH_b); **^{13}C NMR** (101 MHz, CDCl_3): δ 193.0, 141.2, 140.6, 134.2, 132.6 (q, $^2J_{\text{CF}}$ = 33.5 Hz), 130.4, 129.6,

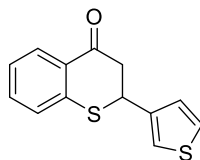
127.9 (q, $^3J_{CF} = 3.5$ Hz), 127.4, 126.0, 123.1 (q, $^1J_{CF} = 273.0$ Hz), 122.7 (q, $^3J_{CF} = 3.5$ Hz), 46.2, 44.7; ^{19}F NMR (377 MHz, CDCl_3): δ -62.91; **LRMS** (ESI^+): m/z 377.0 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{17}\text{H}_{11}\text{OF}_6\text{S}$ requires 377.0284 $[\text{M}+\text{H}]^+$, found 377.0282; **IR**: ν_{max} (neat)/ cm^{-1} 1677, 1585, 1439, 1378, 1276; **M.p.** (CH_2Cl_2): 143-145 °C.

4-(4-Oxothiochroman-2-yl)benzonitrile **24g**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 4-ethynylbenzonitrile (27 mg, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ Et_2O , 8:2) afforded the *desired product* **24g** (48 mg, 0.18 mmol, 91%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.15 (dd, $J = 8.0, 1.0$ Hz, 1H, H_{Ar}), 7.70-7.66 (m, 2H, H_{Ar}), 7.58-7.52 (m, 2H, H_{Ar}), 7.45 (ddd, $J = 8.0, 7.0, 1.5$ Hz, 1H, H_{Ar}), 7.31-7.21 (m, 2H, H_{Ar}), 4.76 (dd, $J = 12.0, 3.5$ Hz, 1H, S-CH), 3.30 (dd, $J = 16.5, 12.0$ Hz, 1H, CH- CH_aH_b), 3.22 (dd, $J = 16.5, 3.0$ Hz, 1H, CH- CH_aH_b); ^{13}C NMR (101 MHz, CDCl_3): δ 193.4, 143.8, 140.9, 134.1, 132.9, 130.4, 129.4, 128.4, 127.4, 125.8, 118.4, 112.5, 46.1, 45.0; **LRMS** (ESI^+): m/z 266.0 ($[\text{M}+\text{H}]^+$, 15%), 288.0 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{16}\text{H}_{11}\text{ONSNa}$ requires 288.0454 $[\text{M}+\text{Na}]^+$, found 288.0454; **IR**: ν_{max} (neat)/ cm^{-1} 2229, 1674, 1587, 1436, 1414, 1285, 1236; **M.p.** (CH_2Cl_2): 130-132 °C.

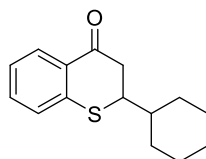
2-(Thiophen-3-yl)thiochroman-4-one **24h**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 3-ethynylthiophene (21 μL , 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ CH_2Cl_2 , 8:2) afforded the *desired product* **24h** (39 mg, 0.16 mmol, 80%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 8.14 (dd, $J = 8.0, 1.0$ Hz, 1H, H_{Ar}), 7.41 (ddd, $J = 8.0, 7.0, 1.5$ Hz, 1H, H_{Ar}), 7.34 (dd,

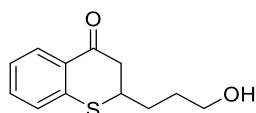
$J = 5.0, 3.0$ Hz, 1H, H_{Ar}), 7.31-7.23 (m, 2H, H_{Ar}), 7.20 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H, H_{Ar}), 7.15 (dd, $J = 5.0, 1.5$ Hz, 1H, H_{Ar}), 4.80 (t, $J = 7.5$ Hz, 1H, S-CH), 3.28 (d, $J = 8.0$ Hz, 2H, CH_2 -CO); ^{13}C NMR (101 MHz, CDCl_3): δ 194.2, 141.6, 139.4, 133.8, 130.6, 129.3, 127.5, 126.9, 126.7, 125.4, 122.8, 46.7, 40.7; HRMS (CI^+): $\text{C}_{13}\text{H}_{11}\text{OS}_2$ requires 247.0251 $[\text{M}+\text{H}]^+$, found 247.0250. This data is consistent with literature.¹⁴⁸

2-Cyclohexylthiochroman-4-one **24k**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), ethynylcyclohexane (27 μL , 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ Et_2O , 95:5) afforded the *desired product* **24k** (39 mg, 0.16 mmol, 79%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 8.06 (ddd, $J = 8.0, 1.5, 0.5$ Hz, 1H, H_{Ar}), 7.37 (ddd, $J = 8.0, 7.0, 1.5$ Hz, 1H, H_{Ar}), 7.27 (ddd, $J = 8.5, 1.5, 0.5$ Hz, 1H, H_{Ar}), 7.15 (ddd, $J = 8.5, 7.0, 1.5$ Hz, 1H, H_{Ar}), 3.38 (ddd, $J = 11.5, 6.5, 3.0$ Hz, 1H, S-CH), 3.03 (dd, $J = 16.0, 3.0$ Hz, 1H, CH- CH_aH_b -CO), 2.87 (dd, $J = 16.0, 11.5$ Hz, 1H, CH- CH_aH_b -CO), 1.93-1.85 (m, 2H, CH_2), 1.81-1.76 (m, 2H, CH_2), 1.70-1.57 (m, 2H, CH_aH_b and S-CH-CH), 1.31-1.07 (m, 5H, CH_aH_b and $2 \times \text{CH}_2$); ^{13}C NMR (101 MHz, CDCl_3): δ 195.5, 142.3, 133.5, 130.8, 129.0, 127.9, 124.9, 47.7, 43.9, 41.6, 30.5, 30.2, 26.3, 26.2 (2C); LRMS (ESI^+): m/z 247.2 ($[\text{M}+\text{H}]^+$, 40%), 269.0 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI^+): $\text{C}_{15}\text{H}_{19}\text{OS}$ requires 247.1162 $[\text{M}+\text{H}]^+$, found 247.1151; IR: ν_{max} (neat)/ cm^{-1} 2924, 2852, 1678, 1589, 1436, 1290, 1234.

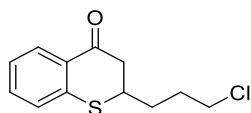
2-(3-Hydroxypropyl)thiochroman-4-one **24m**



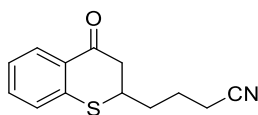
The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), pent-4-yn-1-ol (19 μL , 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). The crude material was solubilised in methanol (2.0 mL). Potassium

carbonate (83 mg, 0.60 mmol, 3.0 equiv) was added and the reaction mixture stirred for 16 h at room temperature and then concentrated under reduced pressure. Saturated aqueous solution of ammonium chloride (2 mL) was added and the product was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/EtOAc, 7:3) afforded the *desired product* **24m** (24.9 mg, 0.11 mmol, 57%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 8.07 (dd, *J* = 8.0, 1.0 Hz, 1H, *H_{Ar}*), 7.38 (td, *J* = 7.5, 1.5 Hz, 1H, *H_{Ar}*), 7.26 (dd, *J* = 8.0, 1.0 Hz, 1H, *H_{Ar}*), 7.18-7.14 (m, 1H, *H_{Ar}*), 3.68 (t, *J* = 6.0 Hz, 2H, CH₂-OH), 3.57-3.50 (m, 1H, S-CH), 3.07 (dd, *J* = 16.5, 3.0 Hz, 1H, CH-CH_aH_b-CO), 2.82 (dd, *J* = 16.5, 11.0 Hz, 1H, CH-CH_aH_b-CO), 1.86-1.69 (m, 4H, CH-(CH₂)₂); **¹³C NMR** (101 MHz, CDCl₃): δ 194.7, 141.5, 133.7, 130.7, 129.0, 127.8, 125.1, 62.3, 46.4, 41.6, 31.0, 29.8; **LRMS** (ESI⁺): *m/z* 223.0 ([M+H]⁺, 40%), 245.0 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₂H₁₅O₂S requires 223.0787 [M+H]⁺, found 223.0788; **IR**: ν_{max} (neat)/cm⁻¹ 3394 (br), 2923, 1673, 1588, 1459, 1436, 1288, 1235.

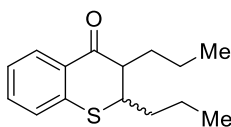
2-(3-Chloropropyl)thiochroman-4-one **24n**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 5-chloropent-1-yne (22 μL, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **24n** (44 mg, 0.18 mmol, 91%) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃): δ 8.08 (dd, *J* = 8.0, 1.5 Hz, 1H, *H_{Ar}*), 7.39 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, *H_{Ar}*), 7.29-7.23 (m, 1H, *H_{Ar}*), 7.17 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, *H_{Ar}*), 3.58-3.48 (m, 3H, S-CH and CH₂-Cl), 3.07 (dd, *J* = 16.5, 3.0 Hz, 1H, CH-CH_aH_b-CO), 2.82 (dd, *J* = 16.5, 11.0 Hz, 1H, CH-CH_aH_b-CO), 2.03-1.83 (m, 4H, CH-(CH₂)₂); **¹³C NMR** (101 MHz, CDCl₃): δ 194.4, 141.1, 133.7, 130.7, 129.1, 127.8, 125.3, 46.3, 44.3, 41.1, 31.7, 29.8; **HRMS** (CI⁺): C₁₂H₁₃O³⁵ClS requires 241.0454 [M+H]⁺, found 241.0455; C₁₂H₁₃O³⁷ClS requires 243.0424 [M+H]⁺, found 243.0424; **Rf**: 0.4 (petrol/Et₂O, 8:2); **IR**: ν_{max} (neat)/cm⁻¹ 2821, 1677, 1590, 1458, 1436, 1287.

4-(4-Oxothiochroman-2-yl)butanenitrile 24o

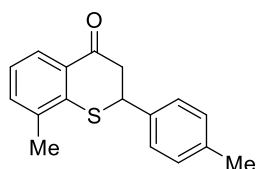
The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 5-hexynenitrile (22 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 1:1) afforded the *desired product* **24o** (38 mg, 0.16 mmol, 83%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 8.08 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.42-7.38 (m, 1H, H_{Ar}), 7.26 (dd, J = 8.0, 0.5 Hz, 1H, H_{Ar}), 7.19 (td, J = 7.5, 0.5 Hz, 1H, H_{Ar}), 3.53-3.46 (m, 1H, S-CH), 3.08 (dd, J = 16.5, 3.0 Hz, 1H, CH-CH_aH_b-CO), 2.83 (dd, J = 16.5, 10.0 Hz, 1H, CH-CH_aH_b-CO), 2.41-2.38 (m, 2H, CH₂-CN), 1.93-1.79 (m, 4H, CH-(CH₂)₂); **¹³C NMR** (101 MHz, CDCl₃): δ 194.0, 140.6, 133.8, 130.7, 129.1, 127.9, 125.4, 119.1, 46.1, 40.9, 33.3, 23.0, 17.0; **LRMS** (ESI⁺): m/z 232.0 ([M+H]⁺, 10%), 254.0 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₃H₁₄ONS requires 232.0791 [M+H]⁺, found 232.0791; **IR**: ν_{max} (neat)/cm⁻¹ 2935, 1675, 1589, 1458, 1436, 1287, 1235.

2,3-Dipropylthiochroman-4-one 24p

The desired product was prepared according to general procedure **G**, using [Rh(nbd)₂BF₄] (3.7 mg, 5 mol%), dppm (3.8 mg, 5 mol%), 2-(*tert*-butylthio)benzaldehyde (39 mg, 0.20 mmol), 4-octyne (35 μ L, 0.24 mmol, 1.2 equiv) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/CH₂Cl₂, 7:3) afforded the *desired product* **24p** (34 mg, 0.14 mmol, 68%, as an inseparable 1.8:1 mixture of diastereoisomers) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.96 (dd, J = 8.0, 1.5 Hz, 1H, H_{Ar}), 7.33-7.25 (m, 1H, H_{Ar}), 7.15-7.11 (m, 1H, H_{Ar}), 7.09-7.04 (m, 1H, H_{Ar}), 3.40 (br s, 0.34H, S-CH_a), 3.06-3.02 (m, 0.66H, S-CH_b), 2.85 (br s, 0.33H, CO-CH_a), 2.60 (td, J = 7.5, 3.5 Hz, 0.62H, CO-CH_b), 1.86-1.38 (m, 6H, 3 $\times$ CH₂), 1.34-1.17 (m, 2H, CH₂), 0.89-0.79 (m, 6H, 2 $\times$ CH₃); **¹³C NMR** (101 MHz, CDCl₃): Major diastereoisomer: δ 197.1, 140.0, 133.6, 129.6, 129.2, 127.5, 124.7, 51.6, 45.8, 36.6, 31.9, 21.0, 20.6, 14.1, 13.7; Minor

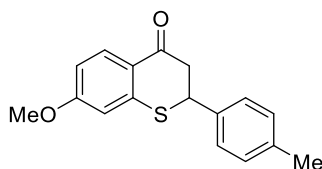
diastereoisomer: δ 197.1, 140.0, 133.3, 129.6, 129.3, 127.3, 124.7, 51.3, 45.2, 36.6, 31.9, 20.9, 20.6, 14.3, 13.8; **LRMS** (ESI⁺): m/z 249.0 ([M+H]⁺, 100%), 271.1 ([M+Na]⁺, 70%); **HRMS** (ESI⁺): C₁₅H₂₁OS requires 249.1308 [M+H]⁺, found 249.1309; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2957, 2872, 1790, 1679, 1590, 1459, 1436.

8-Methyl-2-(*p*-tolyl)thiochroman-4-one **24q**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)-3-methylbenzaldehyde **28b** (42 mg, 0.20 mmol), 4-ethynyltoluene (27 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **24q** (49 mg, 0.18 mmol, 91%) as a yellow solid. **¹H NMR** (400 MHz, CDCl₃): δ 8.05 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H, H_{Ar}), 7.38-7.28 (m, 3H, H_{Ar}), 7.24-7.17 (m, 2H, H_{Ar}), 7.12 (t, J = 7.5 Hz, 1H, H_{Ar}), 4.63 (dd, J = 13.5, 3.0 Hz, 1H, S-CH), 3.30 (dd, J = 16.0, 13.5 Hz, 1H, CH-CH_aH_b), 3.17 (dd, J = 16.0, 3.0 Hz, 1H, CH-CH_aH_b), 2.37 (s, 3H, Ar-CH₃), 2.31 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 195.1, 141.9, 138.5, 135.7, 135.3, 134.9, 130.7, 129.8, 127.5, 127.1, 124.4, 46.3, 44.7, 21.3, 20.1; **LRMS** (ESI⁺): m/z 269.0 ([M+H]⁺, 60%), 291.0 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₇H₁₇OS requires 269.0995 [M+H]⁺, found 269.0996; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 1745, 1675, 1583, 1549, 1449, 1402, 1279; **M.p.** (CH₂Cl₂): 104-107 °C.

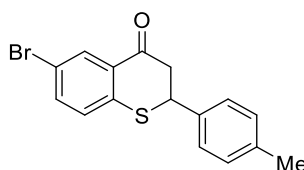
7-Methoxy-2-(*p*-tolyl)thiochroman-4-one **24r**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)-4-methoxybenzaldehyde **28c** (45 mg, 0.20 mmol), 4-tolylacetylene (30 μ L, 0.24 mmol, 1.2 equiv) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/EtOAc, 95:5) afforded the *desired product* **24r** (35 mg, 0.12 mmol, 61%) as a yellow solid. **¹H NMR** (400 MHz, CDCl₃): δ 8.11 (dt, J = 9.0, 1.0 Hz, 1H, H_{Ar}), 7.35-7.28 (m, 2H, H_{Ar}), 7.21-7.14 (m, 2H,

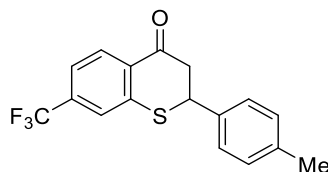
H_{Ar}), 6.77-6.70 (m, 2H, H_{Ar}), 4.68 (dd, $J = 13.0, 3.0$ Hz, 1H, S-CH), 3.84 (s, 3H, O-CH₃), 3.26 (dd, $J = 16.5, 13.0$ Hz, 1H, CH-CH_aH_b), 3.13 (dd, $J = 16.5, 3.0$ Hz, 1H, CH-CH_aH_b), 2.36 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 193.5, 163.7, 144.6, 138.4, 135.6, 131.5, 129.8, 127.4, 124.2, 112.9, 110.5, 55.7, 46.7, 45.6, 21.3; LRMS (ESI⁺): m/z 285.0 ([M+H]⁺, 20%), 307.0 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₁₇H₁₆O₂SNa requires 307.0763 [M+Na]⁺, found 307.0763; IR: ν_{max} (neat)/cm⁻¹ 1668, 1590, 1483, 1438, 1255; M.p. (CH₂Cl₂): 108-110 °C.

6-Bromo-2-(*p*-tolyl)thiochroman-4-one 24s



The desired product was prepared according to general procedure **G**, using 5-bromo-2-(*tert*-butylthio)benzaldehyde **28d** (55 mg, 0.20 mmol), 4-ethynyltoluene (27 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the *desired product* **24s** (63 mg, 0.19 mmol, 95%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 8.26 (d, $J = 2.0$ Hz, 1H, H_{Ar}), 7.50 (dd, $J = 8.5, 2.0$ Hz, 1H, H_{Ar}), 7.30 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.20-7.15 (m, 3H, H_{Ar}), 4.67 (dd, $J = 13.0, 3.0$ Hz, 1H, S-CH), 3.29 (dd, $J = 16.5, 13.0$ Hz, 1H, CH-CH_aH_b), 3.18 (dd, $J = 16.5, 3.0$ Hz, 1H, CH-CH_aH_b), 2.36 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 193.4, 141.3, 138.7, 136.5, 135.1, 131.9, 131.8, 129.4, 129.0, 127.4, 119.0, 46.4, 45.3, 21.3; HRMS (CI⁺): C₁₃H₁₇O⁷⁹BrS requires 332.9949 [M+H]⁺, found 332.9948; Rf: 0.4 (petrol/CH₂Cl₂, 6:4); IR: ν_{max} (neat)/cm⁻¹ 1681, 1575, 1513, 1451, 1387, 1293, 1257, 1231.

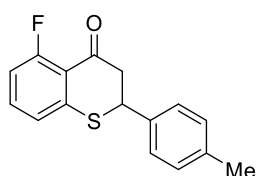
2-(*p*-Tolyl)-7-(trifluoromethyl)thiochroman-4-one 24t



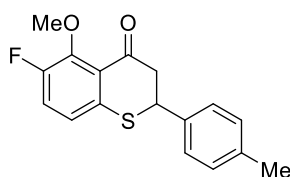
The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)-4-(trifluoromethyl)benzaldehyde **28e** (53 mg, 0.20 mmol), 4-ethynyltoluene (27 μ L, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/CH₂Cl₂, 1:1) afforded the *desired product* **24t** (60 mg, 0.19 mmol, 93%) as a yellow solid. ¹H NMR

(400 MHz, CDCl₃): δ 8.24 (dd, J = 8.5, 1.0 Hz, 1H, H_{Ar}), 7.56-7.52 (m, 1H, H_{Ar}), 7.42 (dd, J = 8.5, 1.5, 1H, H_{Ar}), 7.35-7.29 (m, 2H, H_{Ar}), 7.21 (d, J = 8.0 Hz, 2H, H_{Ar}), 4.73 (dd, J = 13.0, 3.0 Hz, 1H, S-CH), 3.35 (dd, J = 16.5, 13.0 Hz, 1H, CH-CH_aH_b), 3.24 (dd, J = 16.5, 3.0 Hz, 1H, CH-CH_aH_b), 2.37 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 193.7, 143.4, 138.8, 134.9 (q, ² J_{CF} = 33.5 Hz), 134.8, 132.7, 129.92, 129.90, 127.4, 124.5 (q, ³ J_{CF} = 4.0 Hz), 123.2 (q, ¹ J_{CF} = 273.5 Hz), 121.7 (q, ³ J = 3.5 Hz), 46.6, 45.4, 21.3; ¹⁹F NMR (377 MHz, CDCl₃): δ -63.6; HRMS (CI⁺): C₁₇H₁₄F₃OS requires 323.0717 [M+H]⁺, found 323.0714; IR: ν_{max} (neat)/cm⁻¹ 2921, 2851, 1686; 1393, 1321, 1302; M.p. (CH₂Cl₂): 101-103 °C.

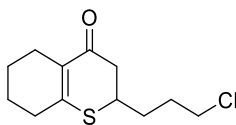
5-Fluoro-2-(*p*-tolyl)thiochroman-4-one **24u**



The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)-6-fluorobenzaldehyde **28f** (43 mg, 0.20 mmol), 4-ethynyltoluene (30 μ L, 0.24 mmol, 1.2 equiv) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **24u** (40 mg, 0.15 mmol, 74%) as a beige solid. ¹H NMR (400 MHz, CDCl₃): δ 7.35 (td, J = 8.0, 5.0 Hz, 1H, H_{Ar}), 7.30 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.19 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.07 (d, J = 8.0 Hz, 1H, H_{Ar}), 6.87 (ddd, J = 11.5, 8.0, 1.0 Hz, 1H, H_{Ar}), 4.68 (dd, J = 13.0, 3.0 Hz, 1H, S-CH), 3.32 (dd, J = 16.0, 13.0 Hz, 1H, CH-CH_aH_b), 3.17 (dd, J = 16.0, 3.0 Hz, 1H, CH-CH_aH_b), 2.36 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 192.9, 163.3 (d, ¹ J_{CF} = 268.0 Hz), 144.4, 138.5, 134.9, 134.3 (d, ³ J_{CF} = 11.0 Hz), 129.7, 127.3, 122.9 (d, ⁴ J_{CF} = 4.0 Hz), 119.9 (d, ² J_{CF} = 6.0 Hz), 113.6 (d, ² J_{CF} = 22.5 Hz), 48.1, 45.0, 21.3; ¹⁹F NMR (377 MHz, CDCl₃): δ -109.0; LRMS (ESI⁺): m/z 273.0 ([M+H]⁺, 50%), 295.0 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₁₆H₁₃OFSNa requires 295.0563 [M+Na]⁺, found 295.0564; IR: ν_{max} (neat)/cm⁻¹ 1685; 1596; 1561; 1513; 1445; 1247; M.p. (CH₂Cl₂): 75-77 °C.

6-Fluoro-5-methoxy-2-(p-tolyl)thiochroman-4-one 24v

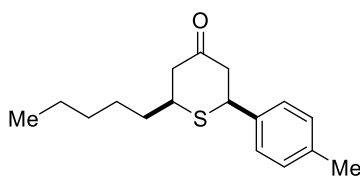
The desired product was prepared according to general procedure **G** using $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (5.6 mg, 7.5 mol%), dcpm (6.1 mg, 7.5 mol%), 6-(*tert*-butylthio)-3-fluoro-2-methoxybenzaldehyde **28g** (48 mg, 0.20 mmol), 4-tolylacetylene (27 μL , 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired product* **24v** (29 mg, 0.10 mmol, 48%) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ 7.28 (dd, $J = 9.0, 7.0$ Hz, 2H, H_{Ar}), 7.22-7.09 (m, 3H, H_{Ar}), 6.97 (dd, $J = 9.0, 4.5$ Hz, 1H, H_{Ar}), 4.64 (dd, $J = 13.0, 3.5$ Hz, 1H, S-CH), 4.00 (s, 3H, O- CH_3), 3.30 (dd, $J = 16.0, 13.0$ Hz, 1H, CH- CH_aH_b), 3.16 (dd, $J = 16.0, 3.5$ Hz, 1H, CH- CH_aH_b), 2.36 (s, 3H, Ar- CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 194.1 (d, $^4J_{\text{CF}} = 2.5$ Hz), 154.2 (d, $^1J_{\text{CF}} = 247.0$ Hz), 149.6 (d, $^2J_{\text{CF}} = 12.0$ Hz), 138.5, 138.0 (d, $^3J_{\text{CF}} = 3.5$ Hz), 135.2, 129.8, 127.4, 126.7, 122.5 (d, $^3J_{\text{CF}} = 7.0$ Hz), 121.4 (d, $^2J_{\text{CF}} = 21.0$ Hz), 62.4 (d, $J_{\text{CF}} = 5.0$ Hz), 48.5, 45.5, 21.3; **^{19}F NMR** (377 MHz, CDCl_3): δ -132.9; **LRMS** (ESI^+): m/z 303.0 ($[\text{M}+\text{H}]^+$, 20%), 325.0 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{17}\text{H}_{16}\text{O}_2\text{FS}$ requires 303.0850 $[\text{M}+\text{H}]^+$, found 303.0851; **IR**: ν_{max} (neat)/ cm^{-1} 1686, 1589, 1467, 1437, 1389, 1267.

2-(3-Chloropropyl)-2,3,5,6,7,8-hexahydro-4H-thiochromen-4-one 25a

The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)cyclohex-1-ene-1-carbaldehyde **32** (40 mg, 0.20 mmol), 5-chloro-1-pentyne (25 μL , 0.24 mmol, 1.2 equiv) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired product* **25a** (30 mg, 0.12 mmol, 61%) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ 3.55 (t, $J = 6.0$ Hz, 2H, $\text{CH}_2\text{-Cl}$), 3.38 (dtd, $J = 12.0, 7.0, 3.5$ Hz, 1H, S-CH), 2.80 (dd, $J = 16.0, 3.5$ Hz, 1H, CH- $\text{CH}_a\text{H}_b\text{-CO}$), 2.58 (dd, $J = 16.0, 12.0$ Hz, 1H, CH- $\text{CH}_a\text{H}_b\text{-CO}$), 2.40-2.26 (m, 4H, CO-C- CH_2 and S-C- CH_2), 1.92-1.78 (m, 4H,

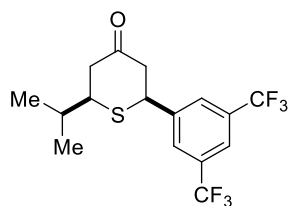
(CH₂)₂-CH₂-Cl), 1.92-1.70 (m, 2H, CH₂), 1.65-1.55 (m, 2H, CH₂); ¹³C NMR (101 MHz, CDCl₃): δ 194.4, 153.5, 128.7, 45.0, 44.4, 41.0, 32.1, 31.5, 29.6, 23.9, 22.6, 22.3; HRMS (CI⁺): C₁₂H₁₈OClS requires 245.0767 [M+H]⁺, found 245.0765; Rf: 0.3 (petrol/Et₂O, 8:2); IR: ν_{max} (neat)/cm⁻¹ 2934, 2859, 1650, 1582, 1361, 1280.

2-Hexyl-6-(*p*-tolyl)tetrahydro-4*H*-thiopyran-4-one 26a



The desired product was prepared according to general procedure **G** using 3-(*tert*-butylthio)octanal **31a** (43 mg, 0.20 mmol), 4-tolylacetylene (24 μL, 0.21 mmol) and TFA (0.15 mL) in DCE (0.2 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product* **26a** (40 mg, 0.15 mmol, 73%, dr = 15:1) as an off-white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.25-7.23 (m, 2H, *H*_{Ar}), 7.15 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 4.13 (dd, *J* = 12.0, 3.0 Hz, 1H, S-CH-Ar), 3.18 (dtd, *J* = 12.0, 7.0, 3.0 Hz, 1H, S-CH-(CH₂)₂), 2.93-2.81 (m, 2H, Ar-CH-CH₂-CO), 2.76 (ddd, *J* = 13.5, 3.0, 1.0 Hz, 1H, (CH₂)₂-CH-CH_aH_b-CO), 2.48 (app. t, *J* = 13.0 Hz, 1H, (CH₂)₂-CH-CH_aH_b-CO), 2.34 (s, 3H, Ar-CH₃), 1.65-1.60 (m, 2H, S-CH-CH₂-CH₂), 1.46-1.42 (m, 2H, S-CH-CH₂-CH₂), 1.33-1.26 (m, 4H, 2 × CH₂), 0.89 (t, *J* = 7.0 Hz, 3H, CH₂-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ 208.9, 137.9, 136.9, 129.7, 127.1, 51.1, 50.3, 47.5, 44.9, 35.9, 31.6, 26.5, 22.6, 21.1, 14.1; HRMS (CI⁺): C₁₇H₂₅OS requires 277.1626 [M+H]⁺, found 277.1623; IR: ν_{max} (neat)/cm⁻¹ 2954, 2927, 1710, 1513, 1251; M.p. (CH₂Cl₂): 41-45 °C. The conformation was determined by comparison with literature¹⁰⁵ and NOESY experiments.

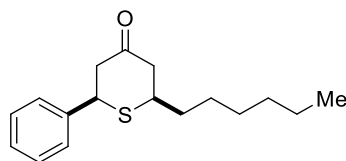
2-[3,5-Bis(trifluoromethyl)phenyl]-6-isopropyltetrahydro-4*H*-thiopyran-4-one 26b



The desired product was prepared according to general procedure **G**, using 3-(*tert*-butylthio)-4-methylpentanal **31b** (38 mg, 0.20 mmol), 1-ethynyl-3,5-bis(trifluoromethyl)benzene (42 μL,

0.24 mmol, 1.2 equiv) and TFA (0.15 mL) in DCE (0.2 mL); crude dr = 19:1. Purification by flash column chromatography (petrol/EtOAc, 97:3) afforded the *desired product 26b* as a single diastereoisomer (44 mg, 0.12 mmol, 59%) as a yellow solid. **¹H NMR** (500 MHz, CDCl₃): δ 7.82 (s, 3H, *H*_{Ar}), 4.24 (dd, *J* = 9.5, 6.0 Hz, 1H, S-CH-Ar), 3.14 (ddd, *J* = 12.5, 5.5, 2.5 Hz, 1H, S-CH-*i*Pr), 2.91-2.88 (m, 2H, Ar-CH-CH₂-CO), 2.82-2.74 (m, 1H, *i*Pr-CH-CH_aH_b), 2.61 (dd, *J* = 13.5, 12.5 Hz, 1H, *i*Pr-CH-CH_aH_b), 1.98-1.92 (m, 1H, CH(CH₃)₂), 1.08-1.05 (m, 6H, CH(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃): δ 207.6, 142.6, 132.4 (q, ²*J* = 34.0 Hz), 127.7 (app d, ³*J*_{CF} = 3.5 Hz), 123.2 (q, ¹*J*_{CF} = 273.0 Hz), 122.4-122.0 (m), 52.0, 50.4, 47.3, 46.6, 32.9, 19.9, 19.6; **¹⁹F NMR** (377 MHz, CDCl₃): δ -62.9; **HRMS** (CI⁺): C₁₆H₂₀ONF₆S requires 388.1170 [M+NH₄]⁺, found 388.1162; **Rf**: 0.3 (petrol/EtOAc, 9:1); **IR**: ν_{max} (neat)/cm⁻¹ 2951, 2928, 1714, 1378, 1279; **M.p.** (CH₂Cl₂): 50-52 °C. The conformation was determined by comparison with literature^{105,149} and NOESY experiments.

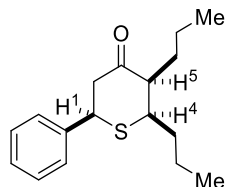
2-Hexyl-6-phenyltetrahydro-4*H*-thiopyran-4-one 26c



The desired product was prepared according to general procedure **G** using [Rh(nbd)₂BF₄] (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%), 3-(*tert*-butylthio)-3-phenylpropanal **31c** (56 mg, 0.25 mmol) and 1-octyne (44 μL, 0.30 mmol, 1.2 equiv) and TFA (0.19 mL) in DCE (0.25 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the *desired product 26c* (55 mg, 0.20 mmol, 80%, dr = 19:1) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.37-7.25 (m, 5H, *H*_{Ar}), 4.16 (dd, *J* = 12.0, 3.5 Hz, 1H, S-CH-Ar), 3.19 (dtd, *J* = 12.0, 7.0, 3.0 Hz, 1H, S-CH-(CH₂)₂), 2.90 (dd, 1H, *J* = 13.5, 12.0 Hz, Ar-CH-CH_aH_b), 2.85 (ddd, *J* = 13.5, 3.5, 1.0 Hz, 1H, Ar-CH-CH_aH_b), 2.77 (ddd, *J* = 13.5, 3.0, 1.0 Hz, 1H, ((CH₂)₂-CH-CH_aH_b-CO), 2.49 (dd, *J* = 13.5, 12.0 Hz, 1H, ((CH₂)₂-CH-CH_aH_b-CO), 1.66-1.60 (m, 2H, CH-CH₂-CH₂), 1.47-1.41 (m, 2H, CH-CH₂-CH₂), 1.32-1.24 (m, 6H, 3 × CH₂), 0.92-0.85 (m, 3H, CH₃); **¹³C NMR** (101 MHz, CDCl₃): 208.8, 139.9, 129.0, 128.1, 127.3, 51.1, 50.3, 47.8, 44.9, 35.9, 31.7, 29.1, 26.8, 22.7, 14.2; **HRMS** (CI⁺): C₁₇H₂₅SO requires 277.1626 [M+H]⁺, found 277.1623; **Rf**: 0.4 (petrol/Et₂O, 8:2); **IR**: ν_{max} (neat)/cm⁻¹ 2926,

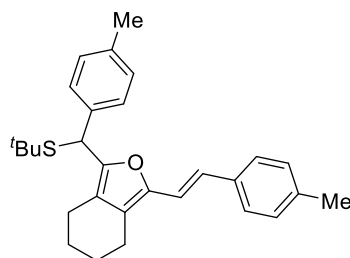
1710, 1496, 1451, 1252. The conformation was determined by comparison with literature¹⁰⁵ and NOESY experiments.

6-Phenyl-2,3-dipropyltetrahydro-4H-thiopyran-4-one **26d**



The desired product was prepared according to general procedure **G** using [Rh(nbd)₂BF₄] (9.4 mg, 10 mol%), dppe (9.6 mg, 10 mol%), 3-(*tert*-butylthio)-3-phenylpropanal **31c** (56 mg, 0.25 mmol), 4-octyne (55 μ L, 0.38 mmol, 1.5 equiv) and TFA (0.19 mL) in DCE (0.25 mL); crude dr = 11.5:2.1:1.5:1.0. Purification by flash column chromatography (gradient from 100% petrol to petrol/Et₂O, 98:2) afforded the *desired product* **26d** as a single diastereoisomer (30 mg, 0.11 mmol, 43%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.26 (m, 5H, *H*_{Ar}), 4.14 (dd, *J* = 12.5, 3.0 Hz, 1H, CH¹), 3.29 (ddd, *J* = 8.5, 6.0, 3.0 Hz, 1H, CH⁴), 3.02 (app. t, *J* = 13.0 Hz, 1H, Ar-CH¹-CH_aH_b), 2.68 (dd, *J* = 13.0, 3.0 Hz, 1H, Ar-CH¹-CH_aH_b), 2.65-2.62 (m, 1H, CH⁵), 2.16-2.06 (m, 1H, CH⁵-CH_cH_d), 1.61-1.39 (m, 5H, CH⁵-CH_cH_d and 2 $\times$ CH₂), 1.31-1.22 (m, 2H, CH₂), 0.97 (t, *J* = 7.0 Hz, 3H, CH_{3e}), 0.93 (t, *J* = 7.0 Hz, 3H, CH_{3f}); ¹³C NMR (101 MHz, CDCl₃): 212.3, 140.1, 129.0, 128.1, 127.3, 55.3, 48.6, 48.3, 47.7, 34.4, 27.6, 20.6, 20.3, 14.3, 14.0; HRMS (CI⁺): C₁₇H₂₅OS requires 277.1626 [M+H]⁺, found 277.1628; **Rf**: 0.3 (petrol/Et₂O, 8:2); **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2957, 2932, 2872, 1706, 1496, 1454. The conformation was determined by comparison with literature¹⁰⁵ and NOESY experiments.

(*E*)-1-[(*tert*-butylthio)(*p*-tolyl)methyl]-3-(4-methylstyryl)-4,5,6,7-tetrahydroisobenzofuran **33**



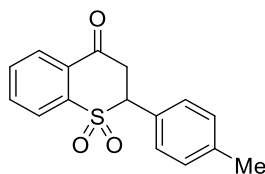
The desired product was prepared according to general procedure **G**, using 2-(*tert*-butylthio)cyclohex-1-ene-1-carbaldehyde **32** (40 mg, 0.20 mmol) and 4-ethynyltoluene (30 μ L,

0.24 mmol, 1.2 equiv) in DCE (0.2 mL) for 2 h at 55 °C. The reaction was then cooled to room temperature, filtered through a plug of silica and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 95:5) afforded the side-product **33** (18 mg, 0.04 mmol, 22%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.42 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.35 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.13 (m, 4H, *H*_{Ar}), 6.87 (d, *J* = 16.5 Hz, 1H, O-C-CH=CH), 6.78 (d, *J* = 16.5 Hz, 1H, O-C-CH=CH), 5.15 (s, 1H, ^tBuS-CH), 2.59-2.41 (m, 4H, 2 × CH₂), 2.34 (s, 3H, CH_{3a}), 2.31 (s, 3H, CH_{3b}), 1.71-1.67 (m, 4H, 2 × CH₂), 1.27 (s, 9H, S(CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃): δ 147.2, 146.4, 137.6, 136.9, 136.8, 135.2, 129.5, 129.3, 128.3, 126.1, 124.7, 121.5, 119.1, 114.9, 44.5, 43.7, 31.2 (2C), 23.2, 23.1, 21.4, 21.22, 21.17, 21.0; **HRMS** (CI⁺): [M-S^tBu]⁺ fragment requires 341.1900 [C₂₅H₂₅O]⁺, found 341.1885; **Rf**: 0.4 (petrol/Et₂O, 9:1); **IR**: ν_{max} (neat)/cm⁻¹ 3022, 2923, 2858, 1509, 1456, 1363.

6.3.3 Product derivatisation

Preparation of SO₂-containing heterocycles

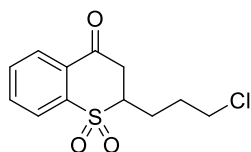
2-(*p*-Tolyl)thiochroman-4-one 1,1-dioxide **34a**



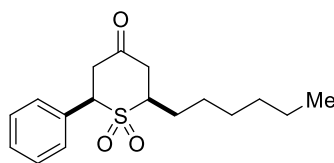
The desired product was prepared according to general procedure **G** using [Rh(nbd)₂BF₄] (9.4 mg, 5 mol%), dcpm (10.2 mg, 5 mol%), 2-(*tert*-butylthio)benzaldehyde **28a** (97 mg, 0.50 mmol), 4-tolylacetylene (67 μL, 0.53 mmol) and TFA (0.38 mL) in DCE (0.5 mL). Upon completion, hydrogen peroxide (30% w/w in H₂O, 150 μL, 1.5 mmol, 3.0 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 15 min then quenched with a saturated aqueous solution of sodium bisulfite (2 mL). The product was extracted with CH₂Cl₂ (3 × 5 mL), dried over anhydrous magnesium sulfate, filtered through a short pad of silica and concentrated under reduced pressure. Purification by flash column chromatography (petrol/EtOAc, 8:2) afforded the *desired sulfone* **34a** (0.10 g, 0.35 mmol, 71%) as a beige solid. **¹H NMR** (400 MHz, CDCl₃): δ 8.22-8.16 (m, 1H, *H*_{Ar}), 8.08 (dd, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 7.83 (td, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 7.76

(td, $J = 7.5, 1.5$ Hz, 1H, H_{Ar}), 7.37 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.27 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 4.85 (dd, $J = 13.0, 3.0$ Hz, 1H, S-CH), 3.95 (dd, $J = 17.5, 13.0$ Hz, 1H, CH-CH_aH_b), 3.40 (dd, $J = 17.5, 3.0$ Hz, 1H, CH-CH_aH_b), 2.39 (s, 3H, Ar-CH₃); ^{13}C NMR (101 MHz, CDCl₃): δ 191.2, 141.6, 140.3, 135.2, 133.5, 130.6, 130.0, 129.8, 128.9, 125.0, 124.6, 63.9, 43.2, 21.4; LRMS (ESI⁺): m/z 309.0 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₁₆H₁₄O₃SN_a requires 309.0556 [M+Na]⁺, found 309.0556; M.p. (CH₂Cl₂): 178-180 °C; IR: ν_{max} (neat)/cm⁻¹ 1687, 1610, 1514, 1440, 1307, 1293.

2-(3-chloropropyl)thiochroman-4-one 1,1-dioxide 34b



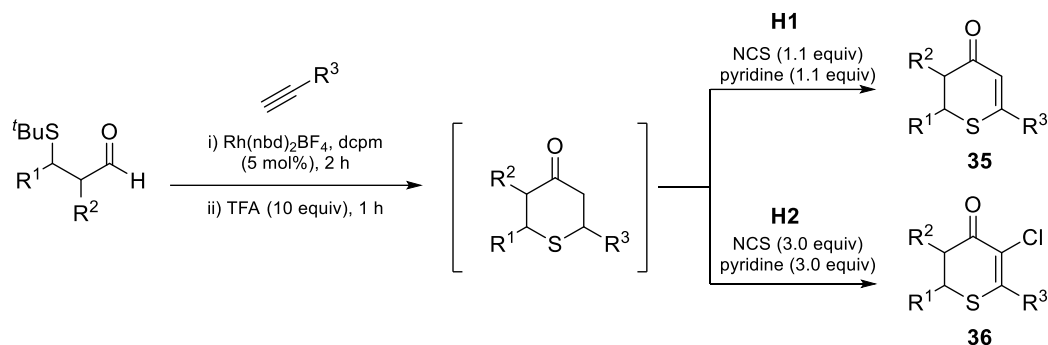
The desired product was prepared according to general procedure **G** using [Rh(nbd)₂BF₄] (5.6 mg, 5 mol%), dcpm (6.1 mg, 5 mol%), 2-(*tert*-butylthio)benzaldehyde **28a** (58 mg, 0.30 mmol) and 5-chloro-pent-1-yne (34 μL , 0.32 mmol) and TFA (0.23 mL) in DCE (0.3 mL). Upon completion, hydrogen peroxide (30% w/w in H₂O, 92 μL , 0.90 mmol, 3.0 equiv) was added dropwise. The reaction mixture was stirred at 55 °C for 2 h. Additional hydrogen peroxide (46 μL , 0.45 mmol, 1.5 equiv) was added and the reaction mixture stirred for 1 h at 55 °C then quenched with a saturated aqueous solution of sodium bisulfite (3 mL). The product was extracted with CH₂Cl₂ (3 $\times$ 5 mL), dried over anhydrous magnesium sulfate, filtered through a short pad of silica and concentrated under reduced pressure. Purification by flash column chromatography (petrol/EtOAc, 8:2) afforded the *desired sulfone 34b* (46 mg, 0.17 mmol, 56%) as a colourless oil. ^1H NMR (400 MHz, CDCl₃): δ 8.12 (dd, $J = 8.0, 1.5$ Hz, 1H, H_{Ar}), 8.05 (dd, $J = 8.0, 1.5$ Hz, 1H, H_{Ar}), 7.84 (td, $J = 7.5, 1.5$ Hz, 1H, H_{Ar}), 7.75 (td, $J = 7.5, 1.5$ Hz, 1H, H_{Ar}), 3.73-3.55 (m, 3H, S-CH and CH₂-Cl), 3.35 (dd, $J = 17.5, 4.5$ Hz, 1H, CH-CH_aH_b-CO), 3.31-3.25 (m, 1H, CH-CH_aH_b-CO), 2.45-2.32 (m, 1H, CH-CH_cH_d-CH₂), 2.13-2.04 (m, 2H, CH-CH₂-CH₂), 1.95-1.84 (m, 1H, CH-CH_cH_d-CH₂); ^{13}C NMR (101 MHz, CDCl₃): δ 190.4, 141.1, 135.2, 133.5, 130.5, 128.7, 124.3, 58.5, 44.0, 42.6, 29.3, 24.6; HRMS (CI⁺): C₁₂H₁₇O₃ClNS requires 290.0612 [M+NH₄]⁺, found 290.0616; IR: ν_{max} (neat)/cm⁻¹ 1693, 1589, 1444, 1302, 1284.

2-Hexyl-6-phenyltetrahydro-4H-thiopyran-4-one 1,1-dioxide 34c

The desired product was prepared according to general procedure **G**, using 3-(*tert*-butylthio)-3-phenylpropanal **31c** (44 mg, 0.20 mmol) and 1-octyne (35 μ L, 0.24 mmol, 1.2 equiv) and TFA (0.15 mL) in DCE (0.2 mL). Upon completion, hydrogen peroxide (30% w/w in H₂O, 61 μ L, 0.60 mmol, 3.0 equiv) was added dropwise. The reaction mixture was stirred at 55 °C for 2 h then quenched with a saturated aqueous solution of sodium bisulfite (3 mL). The product was extracted with CH₂Cl₂ (3 $\times$ 5 mL), dried over anhydrous magnesium sulfate, filtered through a short pad of silica and concentrated under reduced pressure; crude dr = 19:1. Purification by flash column chromatography (petrol/EtOAc, 8:2) afforded the *desired sulfone 34c* (26 mg, 0.086 mmol, 43%) as a white solid. **¹H NMR** (400 MHz, CDCl₃): δ 7.46-7.40 (m, 5H, *H*_{Ar}), 4.39 (dd, *J* = 14.0, 3.5 Hz, 1H, Ar-CH-S), 3.73-3.50 (m, 1H, Ar-CH-CH_dH_b), 3.35 (ddt, *J* = 13.0, 8.5, 4.0 Hz, 1H, S-CH-(CH₂)₂), 2.99 (dd, *J* = 14.5, 13.0 Hz, 1H, CO-CH_cH_d-CH-(CH₂)₂), 2.91-2.81 (m, 2H, CO-CH_cH_d-CH-(CH₂)₂ and Ar-CH-CH_aH_b), 2.29-2.14 (m, 1H, S-CH-CH_eH_f-CH₂), 1.65 (ddd, *J* = 14.0, 10.0, 9.0 Hz, 1H, S-CH-CH_eH_f-CH₂), 1.54-1.25 (m, 8H, 4 $\times$ CH₂), 0.94-0.85 (m, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 202.7, 129.9, 129.7, 129.1, 128.4, 64.4, 59.7, 45.5, 44.8, 31.5, 29.0, 26.1, 26.0, 22.6, 14.2; **LRMS** (ESI⁺): *m/z* 309.0 ([M+H]⁺, 5%), 363.2 ([M+MeOH+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₇H₂₅O₃S requires 309.1519 [M+H]⁺, found 309.1520; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2954, 2929, 2858, 1721, 1456, 1378, 1309; **M.p.** (CH₂Cl₂): 116-118 °C; The conformation was determined by comparison with literature.¹⁴⁹

Preparation of thiochromen-4-ones and dihydrothiopyran-4-ones

General procedure H: synthesis of thiochromen-4-one and dihydrothiopyran-4-ones

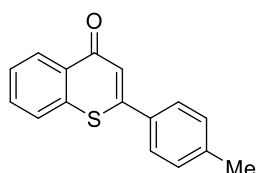


Hydroacylation/thio-Michael addition reactions were carried out following **General Procedure G**. Upon completion, the reaction was then filtered through a plug of silica and concentrated under reduced pressure. DCE (0.5 M) was added and the crude split in two batches.

General Procedure H1. Oxidation to thiochromen-4-one and dihydrothiopyran-4-one derivatives: the crude material (1.0 equiv) in DCE (0.5 M) was added to a vial containing *N*-chlorosuccinimide (NCS) (1.1 equiv) and pyridine (1.1 equiv) which had been evacuated and back-filled with N₂ gas. The reaction mixture was stirred at room temperature for 2 h and directly loaded onto silica. Purification by flash column chromatography afforded the desired product.

General Procedure H2. Oxidation to the α-chloro- derivatives: the crude material (1.0 equiv) in DCE (0.5 M) was added to a vial containing *N*-chlorosuccinimide (NCS) (3.0 equiv) and pyridine (3.0 equiv) which had been evacuated and back-filled with N₂ gas. The reaction mixture was stirred at room temperature for 2 h and then concentrated and directly loaded onto silica. Purification by flash column chromatography afforded the desired product.

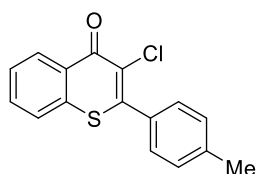
(*p*-Tolyl)-4*H*-thiochromen-4-one 35a



The desired product was prepared according to general procedure **H1** starting with [Rh(nbd)₂BF₄] (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%) and 2-(*tert*-butylthio)benzaldehyde **28a** (49 mg, 0.25 mmol). The crude was then reacted with NCS (37 mg, 0.28 mmol) and pyridine (22 μL,

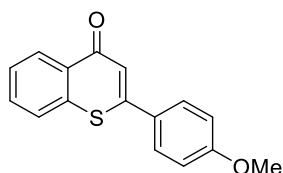
0.28 mmol) in DCE (0.5 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the desired product **35a** (39 mg, 0.15 mmol, 62%) as a beige solid. ¹H NMR (400 MHz, CDCl₃): δ 8.54 (dd, *J* = 8.0, 1.5 Hz, 1H, *H*_{Ar}), 7.70-7.50 (m, 5H, *H*_{Ar}), 7.30 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.23 (s, 1H, CO-CH), 2.42 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 181.0, 153.2, 141.5, 137.8, 133.8, 131.6, 131.1, 130.1, 128.7, 127.8, 126.9, 126.6, 123.0, 21.5; HRMS (CI⁺): C₁₆H₁₃OS requires 253.0687 [M+H]⁺, found 253.0686. This data is consistent with the literature.¹⁵⁰

3-Chloro-2-(*p*-tolyl)-4*H*-thiochromen-4-one **36a**



The desired product was prepared according to general procedure **H2** starting with [Rh(nbd)₂BF₄] (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%) and 2-(*tert*-butylthio)benzaldehyde **28a** (49 mg, 0.25 mmol). The crude was then reacted with NCS (0.10 g, 0.75 mmol) and pyridine (60 μL, 0.75 mmol) in DCE (0.5 mL). Purification by flash column chromatography (petrol/Et₂O, 7:3) afforded the *desired product* **36a** (46 mg, 0.16 mmol, 65%) as a beige solid. ¹H NMR (400 MHz, CDCl₃): δ 8.60 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, *H*_{Ar}), 7.65 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H, *H*_{Ar}), 7.61-7.55 (m, 2H, *H*_{Ar}), 7.45 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.34-7.30 (m, 2H, *H*_{Ar}), 2.44 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 174.9, 148.7, 140.7, 136.7, 132.4, 131.9, 130.5, 129.8, 129.5, 128.9, 128.1, 126.2, 125.7, 21.6; HRMS (CI⁺): C₁₆H₁₁O³⁵ClS requires 287.0297 [M], found 287.0285; C₁₆H₁₁O³⁷ClS requires 289.0268 [M], found 289.0273; IR: ν_{max} (neat)/cm⁻¹ 2921, 1630, 1568, 1462, 1406, 1303; M.p. (CH₂Cl₂): 145-147 °C.

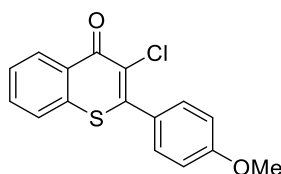
2-(4-Methoxyphenyl)-4*H*-thiochromen-4-one **35b**



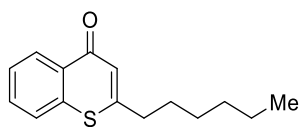
The desired product was prepared according to general procedure **H1** starting with [Rh(nbd)₂BF₄] (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%) and 2-(*tert*-butylthio)benzaldehyde **28a** (49 mg,

0.25 mmol). The crude was then reacted with NCS (37 mg, 0.28 mmol) and pyridine (22 μ L, 0.28 mmol) in DCE (0.5 mL). Purification by flash column chromatography (petrol/Et₂O, 6:4) afforded the desired product **35b** (38 mg, 0.14 mmol, 57%) as a beige powder. **¹H NMR** (400 MHz, CDCl₃): δ 8.56-8.49 (m, 1H, *H*_{Ar}), 7.68-7.57 (m, 4H, *H*_{Ar}), 7.53 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H, *H*_{Ar}), 7.19 (s, 1H, CO-CH), 7.03-6.98 (m, 2H, *H*_{Ar}), 3.87 (s, 3H, O-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 181.0, 162.0, 152.9, 137.7, 131.6, 131.0, 128.9, 128.7, 128.4, 127.8, 126.5, 122.3, 114.8, 55.6; **HRMS** (ESI⁺): C₁₆H₁₂O₂SNa requires 291.0450 [M+Na]⁺, found 291.0450. This data is consistent with the literature.¹⁵⁰

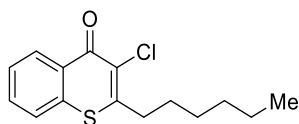
3-Chloro-2-(4-methoxyphenyl)-4H-thiophene-4-one **36b**



The desired product was prepared according to general procedure **H2** starting with [Rh(nbd)₂BF₄] (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%) and 2-(*tert*-butylthio)benzaldehyde **28a** (49 mg, 0.25 mmol). The crude was then reacted with NCS (0.10 g, 0.75 mmol) and pyridine (60 μ L, 0.75 mmol) in DCE (0.5 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the *desired product* **36b** (32 mg, 0.11 mmol, 44%) as a beige powder. **¹H NMR** (400 MHz, CDCl₃): δ 8.59 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1H, *H*_{Ar}), 7.68-7.55 (m, 3H, *H*_{Ar}), 7.54-7.49 (m, 2H, *H*_{Ar}), 7.05-7.00 (m, 2H, *H*_{Ar}), 3.88 (s, 3H, O-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 175.0, 161.2, 148.5, 136.7, 131.9, 130.6, 130.5, 129.9, 128.0, 127.5, 126.1, 125.6, 114.2, 55.6; **LRMS** (ESI⁺): *m/z* 303.0 ([M³⁵Cl+H]⁺, 30%), 305.0 ([M³⁷Cl+H]⁺, 10%), 325.0 ([M³⁵Cl+Na]⁺, 100%), 327.0 ([M³⁷Cl+Na]⁺, 45%); **HRMS** (ESI⁺): C₁₆H₁₁O₂³⁵ClSNa requires 325.0061 [M+Na]⁺, found 325.0061; C₁₆H₁₁O₂³⁷ClSNa requires 327.0031 [M+Na]⁺, found 327.0031; **M.p.** (CH₂Cl₂): 170-172 °C; **IR**: ν_{max} (neat)/cm⁻¹ 1710, 1635, 1605, 1533, 1455, 1265.

2-Hexyl-4H-thiochromen-4-one 35c

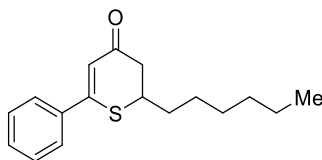
The desired product was prepared according to general procedure **H1** starting with $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%) and 2-(*tert*-butylthio)benzaldehyde **28a** (49 mg, 0.25 mmol). The crude was then reacted with NCS (37 mg, 0.28 mmol) and pyridine (22 μL , 0.28 mmol) in DCE (0.5 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired product* **35c** (32 mg, 0.13 mmol, 52%) as a colourless oil. **^1H NMR** (400 MHz, CDCl_3): δ 8.49 (dt, $J = 8.0, 1.0$ Hz, 1H, H_{Ar}), 7.59-7.54 (m, 2H, H_{Ar}), 7.49 (ddd, $J = 8.5, 5.0, 3.5$ Hz, 1H, H_{Ar}), 6.86 (s, 1H, CO-CH), 2.66 (t, $J = 7.5$ Hz, 2H, S-C- CH_2), 1.72 (p, $J = 7.5$ Hz, 2H, S-C- CH_2 - CH_2), 1.41-1.23 (m, 6H, $3 \times \text{CH}_2$), 0.90-0.86 (m, 3H, CH_2 - CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 180.8, 156.7, 137.9, 131.4, 131.1, 128.6, 127.6, 126.3, 124.2, 37.6, 31.6, 29.9, 28.7, 22.6, 14.2; **LRMS** (ESI^+): m/z 247.2 ($[\text{M}+\text{H}]^+$, 95%), 269.0 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{15}\text{H}_{19}\text{OS}$ requires 247.1151 $[\text{M}+\text{H}]^+$, found 247.1152; **IR**: ν_{max} (neat)/ cm^{-1} 2926, 2856, 1623, 1593, 1461, 1335.

3-Chloro-2-hexyl-4H-thiochromen-4-one 36c

The desired product was prepared according to general procedure **H2** starting with $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (4.7 mg, 5 mol%), dcpm (5.1 mg, 5 mol%) and 2-(*tert*-butylthio)benzaldehyde **28a** (49 mg, 0.25 mmol). The crude was then reacted with NCS (0.10 g, 0.75 mmol) and pyridine (60 μL , 0.75 mmol) in DCE (0.5 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired product* **36c** (34 mg, 0.12 mmol, 49%) as a white solid. **^1H NMR** (400 MHz, CDCl_3): δ 8.53 (dd, $J = 8.0, 1.0$ Hz, 1H, H_{Ar}), 7.65-7.49 (m, 3H, H_{Ar}), 2.91-2.85 (m, 2H, S-C- CH_2), 1.80-1.70 (m, 2H, S-C- CH_2 - CH_2), 1.50-1.39 (m, 2H, CH_2), 1.35-1.30 (m, 4H, $2 \times \text{CH}_2$), 0.92-0.87 (m, 3H, CH_2 - CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 174.4, 151.1, 135.9, 131.7, 130.5, 129.7, 127.9, 126.5, 125.7, 36.8, 31.5, 29.1, 28.7, 22.6, 14.1; **LRMS** (ESI^+): m/z 281.0 ($[\text{M}^{35}\text{Cl}+\text{H}]^+$,

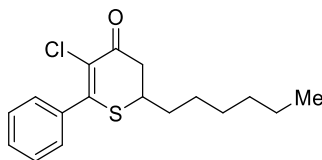
45%), 283.0 ($[M^{37}\text{Cl} + \text{H}]^+$, 15%), 303.0 ($[M^{35}\text{Cl} + \text{Na}]^+$, 100%), 305.0 ($[M^{37}\text{Cl} + \text{Na}]^+$, 30%); **HRMS** (ESI^+): $\text{C}_{15}\text{H}_{18}\text{OS}^{35}\text{Cl}$ requires 281.0761 $[M + \text{H}]^+$, found 281.0763; $\text{C}_{15}\text{H}_{18}\text{OS}^{37}\text{Cl}$ requires 283.0732 $[M + \text{H}]^+$, found 283.0732; **IR**: ν_{max} (neat)/ cm^{-1} 2927, 1632, 1592, 1538, 1321; **M.p.** (CH_2Cl_2): 76-78 °C.

2-Hexyl-6-phenyl-2,3-dihydro-4H-thiopyran-4-one 36d



The desired product was prepared according to general procedure **H1** starting with $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (3.7 mg, 5 mol%), dcpm (4.1 mg, 5 mol%) and 3-(*tert*-butylthio)-3-phenylpropanal **31c** (45mg, 0.20 mmol). The crude was then reacted with NCS (29 mg, 0.22 mmol) and pyridine (18 μL , 0.22 mmol) in DCE (0.4 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1) afforded the *desired product* **35d** (40 mg, 0.15 mmol, 73%) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ 7.64-7.62 (m, 2H, H_{Ar}), 7.48-7.37 (m, 3H, H_{Ar}), 6.46 (s, 1H, CO-CH), 3.56 (dddd, $J = 12.0, 8.0, 6.5, 3.5$ Hz, 1H, S-CH), 2.83 (dd, $J = 16.5, 3.5$ Hz, 1H, CH- CH_aH_b -CO), 2.61 (dd, $J = 16.5, 12.0$ Hz, 1H, CH- CH_aH_b -CO), 1.81-1.74 (m, 2H, S-CH- CH_2 - CH_2), 1.53-1.45 (m, 2H, S-CH- CH_2 - CH_2), 1.36-1.28 (m, 6H, $3 \times \text{CH}_2$), 0.91-0.88 (m, 3H, CH_2 - CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 195.7, 160.2, 137.5, 131.1, 128.9, 127.3, 120.7, 44.1, 42.9, 34.0, 31.7, 29.0, 26.8, 22.7, 14.2; **LRMS** (ESI^+): m/z 275.2 ($[M + \text{H}]^+$, 10%), 297.1 ($[M + \text{Na}]^+$, 100%); **HRMS** (ESI^+): $\text{C}_{17}\text{H}_{23}\text{OS}$ requires 275.1464 $[M + \text{H}]^+$, found 275.1464; **IR**: ν_{max} (neat)/ cm^{-1} 2926, 1650, 1551, 1445, 1267.

5-Chloro-2-hexyl-6-phenyl-2,3-dihydro-4H-thiopyran-4-one 36d



The desired product was prepared according to general procedure **H2** starting with $[\text{Rh}(\text{nbd})_2\text{BF}_4]$ (3.7 mg, 5 mol%), dcpm (4.1 mg, 5 mol%) and 3-(*tert*-butylthio)-3-phenylpropanal **31c** (45 mg, 0.20 mmol). The crude was then reacted with NCS (29 mg, 0.22 mmol) and pyridine (18 μL , 0.22 mmol) in DCE (0.4 mL). Purification by flash column chromatography (petrol/ Et_2O , 9:1)

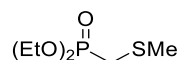
afforded the *desired product* **36d** (35 mg, 0.11 mmol, 56%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.50-7.41 (m, 5H, *H_{Ar}*), 3.58 (dtd, *J* = 12.0, 7.0, 3.0 Hz, 1H, S-CH), 3.09 (dd, *J* = 16.5, 3.0 Hz, 1H, CH-CH_aH_b-CO), 2.88 (dd, *J* = 16.5, 12.0 Hz, 1H, CH-CH_aH_b-CO), 1.82-1.71 (m, 2H, CH-CH₂-CH₂), 1.51-1.39 (m, 2H, CH-CH₂-CH₂), 1.39-1.24 (m, 6H, 3 × CH₂), 0.93-0.86 (m, 3H, CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 188.1, 155.6, 136.2, 130.3, 128.8, 128.5, 120.9, 45.4, 42.1, 33.6, 31.7, 29.0, 26.7, 22.7, 14.2; **LRMS** (ESI⁺): *m/z* 309.0 ([M+H]⁺, 10%), 331.0 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₇H₂₂O³⁵ClS requires 309.1074 [M+H]⁺, found 309.1075; C₁₇H₂₂O³⁷ClS requires 311.1045 [M+H]⁺, found 311.1044; **IR**: *v*_{max} (neat)/cm⁻¹ 2926, 1674, 1535.

6.4 Chapter 4 data

6.4.1 Tether-free approach

6.4.1.1 Starting material synthesis

Diethyl [(methylthio)methyl]phosphonate **38**



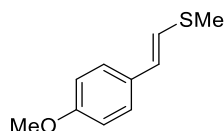
Triethylphosphite (0.87 mL, 5.0 mmol, 1.0 equiv) and (chloromethyl)(methyl)sulfide (0.42 mL, 5.0 mmol, 1.0 equiv) were mixed and heated at 110 °C for 6 h. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure to afford the desired product **38** as a yellow oil (0.91 g, 4.6 mmol, 92%) without further purification. **¹H NMR** (400 MHz, CDCl₃): δ 4.24-4.09 (m, 4H, 2 × O-CH₂), 2.67 (d, *J* = 12.5 Hz, 2H, S-CH₂), 2.27 (s, 3H, S-CH₃), 1.33 (t, *J* = 7.0 Hz, 6H, 2 × CH₂-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 62.6 (d, *J*_{CP} = 6.5 Hz), 27.5 (d, *J*_{CP} = 151.0 Hz), 17.4 (d, *J*_{CP} = 2.5 Hz), 16.5 (d, *J*_{CP} = 6.0 Hz); **LRMS** (ESI⁺): *m/z* 397.0 ([2M+H]⁺, 100%); **IR**: *v*_{max} (neat)/cm⁻¹ 2982, 1246, 1021, 959. This data is consistent with literature.¹⁵¹

General procedure I for the preparation of (*E*)-alkenyl sulfides

Sodium hydride (60 % in mineral oil, 2.0 equiv) was added portionwise to a solution of diethyl[(methylthio)methyl]phosphonate **38** (1.0 equiv) in tetrahydrofuran (0.12 M) and the reaction mixture was stirred for 1 h at 60 °C. Aldehyde (1.0 equiv) was added and the reaction

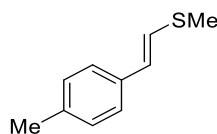
mixture was stirred until completion and then quenched with a saturated solution of ammonium chloride. The product was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and reduced under reduced pressure. The product was purified by flash column chromatography.

(E)-(4-Methoxystyryl)(methyl)sulfane 37a



The desired alkenyl sulfide was prepared according to general procedure **I** using diethyl[(methylthio)methyl]phosphonate **38** (1.8 mL, 10 mmol), sodium hydride (0.80 g, 20 mmol) and 4-methoxybenzaldehyde (1.2 mL, 10 mmol) in tetrahydrofuran (80 mL) for 3 h at 60 °C. Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired product **37a** as an inseparable mixture of geometric isomers (1.7 g, 9.5 mmol, 96%, *E/Z*: 16:1) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.23 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.84 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.62 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.30 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.80 (s, 3H, O-CH₃), 2.37 (s, 3H, S-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 158.7, 130.2, 126.7, 124.9, 123.4, 114.2, 55.4, 15.1; **M.p.** (CH₂Cl₂): 69-71 °C (lit. m.p.¹⁵² 70-71.5 °C). This data is consistent with literature.¹⁵³

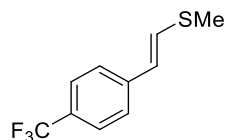
(E)-Methyl(4-methylstyryl)sulfane 37b



The desired alkenyl sulfide was prepared according to general procedure **I** using diethyl[(methylthio)methyl]phosphonate **38** (0.61 mL, 3.5 mmol), sodium hydride (0.28 g, 7.0 mmol) and 4-methylbenzaldehyde (0.41 mL, 3.5 mmol) in tetrahydrofuran (30 mL) for 3 h at 60 °C. Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired product **37b** as an inseparable mixture of geometric isomers (0.44 g, 2.7 mmol, 77%, *E/Z*: 11:1) as a beige residue. ¹H NMR (500 MHz, CDCl₃): δ 7.21 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.12 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 6.73 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.32 (d, *J* = 15.5 Hz, 1H, HC=CH), 2.39 (s, 3H, S-CH₃), 2.34 (s, 3H, Ar-CH₃); ¹³C NMR (126 MHz, CDCl₃): δ 136.6, 134.5, 129.5, 125.4, 125.0,

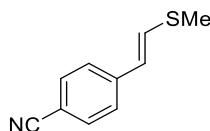
124.7, 21.3, 15.0; **HRMS** (FI^+): $\text{C}_{10}\text{H}_{12}\text{S}$ requires 164.0660 $[\text{M}]^+$, found 164.0656. This data is consistent with literature.¹⁵⁴

(E)-Methyl[4-(trifluoromethyl)styryl]sulfane 37c



The desired alkenyl sulfide was prepared according to general procedure **I** using diethyl[(methylthio)methyl]phosphonate **38** (0.61 mL, 3.5 mmol), sodium hydride (0.28 g, 7.0 mmol) and 4-(trifluoromethyl)benzaldehyde (0.42 mL, 3.5 mmol) in tetrahydrofuran (30 mL) for 3 h at 60 °C. Purification by flash column chromatography (petrol/ Et_2O , 98:2) afforded the *desired product 37c* as an inseparable mixture of geometric isomers (0.46 g, 2.1 mmol, 60%, *E/Z*: 10:1) as a white solid. **^1H NMR** (500 MHz, CDCl_3): δ 7.54 (d, J = 8.5 Hz, 2H, H_{Ar}), 7.37 (d, J = 8.5 Hz, 2H, H_{Ar}), 6.94 (d, J = 15.5 Hz, 1H, $\text{HC}=\text{CH}$), 6.29 (d, J = 15.5 Hz, 1H, $\text{HC}=\text{CH}$), 2.41 (s, 3H, S- CH_3); **^{13}C NMR** (126 MHz, CDCl_3): δ 140.6, 129.3, 128.4 (q, $^2J_{\text{CF}}$ = 32.5 Hz), 125.8 (q, $^3J_{\text{CF}}$ = 4.0 Hz), 125.5, 125.4 (q, $^1J_{\text{CF}}$ = 272.0 Hz), 122.9, 14.8; **HRMS** (FI^+): $\text{C}_{10}\text{H}_9\text{SF}_3$ requires 218.0377 $[\text{M}]^+$, found 218.0384; **IR**: ν_{max} (neat)/ cm^{-1} 1598, 1325, 1120; **M.p.** (CH_2Cl_2): 49-51 °C.

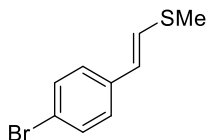
(E)-4-(2-(Methylthio)vinyl)benzonitrile 37d



The desired alkenyl sulfide was prepared according to general procedure **I** using diethyl[(methylthio)methyl]phosphonate **38** (0.39 mL, 2.2 mmol), sodium hydride (0.10 g, 2.6 mmol, 1.3 equiv) and 4-formylbenzonitrile (0.26 g, 2.2 mmol) in tetrahydrofuran (16 mL) for 14 h at room temperature. Purification by flash column chromatography (petrol/ Et_2O , 7:3) afforded the *desired product 37d* as an inseparable mixture of geometric isomers (0.18 g, 1.1 mmol, 51%, *E/Z*: 5:1) as a colourless oil. **^1H NMR** (400 MHz, CDCl_3): δ 7.56-7.53 (m, 2H, H_{Ar}), 7.34-7.35 (m, 2H, H_{Ar}), 7.00 (d, J = 15.5 Hz, 1H, $\text{HC}=\text{CH}$), 6.24 (d, J = 15.5 Hz, 1H, $\text{HC}=\text{CH}$), 2.40 (s, 3H, S- CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 141.5, 132.6, 131.2, 125.7, 122.3, 119.3, 109.5, 14.7;

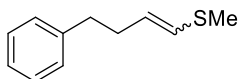
HRMS (FI^+): $\text{C}_{10}\text{H}_9\text{SN}$ requires 175.0456 $[\text{M}]^+$, found 175.0457; **IR**: ν_{max} (neat)/ cm^{-1} 2222, 1590, 1174.

(E)-(4-Bromostyryl)(methyl)sulfane 37e



The desired alkenyl sulfide was prepared according to general procedure **I** using diethyl[(methylthio)methyl]phosphonate **38** (0.18 mL, 1.0 mmol), sodium hydride (80 mg, 2.0 mmol) and 4-bromobenzaldehyde (0.19 g, 1.0 mmol) in tetrahydrofuran (8 mL) for 14 h at room temperature. Purification by flash column chromatography (petrol/ Et_2O , 95:5) afforded the desired product **37e** as an inseparable mixture of geometric isomers (0.15 g, 0.65 mmol, 65%, *E/Z*: 6:1) as a beige solid. **^1H NMR** (400 MHz, CDCl_3): δ 7.42-7.39 (m, 2H, H_{Ar}), 7.17-7.14 (m, 2H, H_{Ar}), 6.80 (d, $J = 15.5$ Hz, 1H, $\text{HC}=\text{CH}$), 6.22 (d, $J = 15.5$ Hz, 1H, $\text{HC}=\text{CH}$), 2.38 (s, 3H, S- CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ 136.2, 131.9, 127.0, 126.9, 123.4, 120.3, 14.9; **M.p.** (CH_2Cl_2): 70-72 $^\circ\text{C}$ (lit. m.p. 71-74 $^\circ\text{C}$). This data is consistent with literature.¹⁵³

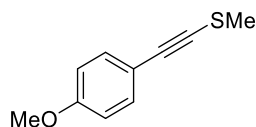
Methyl(4-phenylbut-1-en-1-yl)sulfane 39



The desired alkenyl sulfide was prepared according to general procedure **I** using diethyl[(methylthio)methyl]phosphonate **38** (0.39 mL, 2.2 mmol), sodium hydride (0.10 g, 2.6 mmol, 1.3 equiv) and hydrocinnamaldehyde (0.29 g, 2.2 mmol) in tetrahydrofuran (16 mL) for 14 h at room temperature. Purification by flash column chromatography (petrol/ Et_2O , 98:2) afforded the desired product **39** as an inseparable mixture of geometric isomers (0.10 g, 0.60 mmol, 25%, *E/Z*: 3:1) as a yellow oil. **^1H NMR** (400 MHz, CDCl_3): δ **E**: 7.12-7.24 (m, 5H, H_{Ar}), 6.01 (dt, $J = 15.0, 1.5$ Hz, 1H, $\text{HC}-\text{SMe}$), 5.47 (dt, $J = 15.0, 7.0$ Hz, 1H, $\text{HC}=\text{CH}-\text{SMe}$), 2.70-2.63 (m, 2H, CH_2-Ph), 2.41-2.36 (m, 2H, CH_2-CH), 2.18 (s, 3H, S- CH_3); **Z**: 7.24-7.12 (m, 5H, H_{Ar}), 5.90 (dt, $J = 9.5, 1.5$ Hz, 1H, $\text{HC}-\text{SMe}$), 5.58-5.54 (m, 1H, $\text{HC}=\text{CH}-\text{SMe}$), 2.70-2.63 (m, 2H, CH_2-Ph), 2.41-2.36 (m, 2H, CH_2-CH), 2.21 (s, 3H, S- CH_3); **^{13}C NMR** (101 MHz, CDCl_3): δ **E**: 141.8, 128.6,

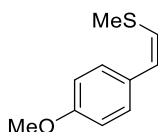
128.5, 126.5, 126.0, 124.6, 36.2, 35.1, 15.2; **Z**: 141.8, 128.6, 128.4, 127.9, 127.6, 126.0, 35.1, 30.8, 17.2; **HRMS** (FI⁺): C₁₁H₁₄S requires 178.0816 [M]⁺, found 178.0812. This data is consistent with literature.¹⁵⁵

[(4-Methoxyphenyl)ethynyl](methyl)sulfane 40



n-Butyllithium (1.6 M/hexane, 2.0 mL, 3.1 mmol, 1.3 equiv) was added dropwise to a solution of 4-ethynylanisole (0.33 mL, 2.5 mmol, 1.0 equiv) in tetrahydrofuran (0.50 mL) at 0 °C. After 30 min, dimethyl disulfide (0.28 mL, 3.1 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction was then quenched with water (5 mL) and extracted with ethyl acetate (2 × 15 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired product **40** (0.34 g, 1.9 mmol, 77%) as pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.37 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 6.82 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 3.80 (s, 3H, O-CH₃), 2.46 (s, 3H, S-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 159.8, 133.5, 115.6, 114.0, 91.7, 79.1, 55.4, 19.6; **LRMS** (ESI⁺): *m/z* 379.1 ([2M+Na]⁺, 100%). This data is consistent with literature.¹⁵⁶

(Z)-(4-Methoxystyryl)(methyl)sulfane 37f



A solution of [(4-methoxyphenyl)ethynyl](methyl) sulfane **40** (89 mg, 0.50 mmol, 1.0 equiv) and bis(cyclopentadienyl) zirconium chloride hydride (0.19 g, 0.75 mmol, 1.5 equiv) in dichloromethane (2 mL) was stirred at room temperature for 15 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (3 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired product **37f** as an inseparable mixture of geometric isomers (56 mg, 0.31 mmol, 62%, *Z/E*

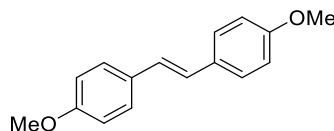
10:1) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.43 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.90 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.40 (d, *J* = 11.0 Hz, 1H, HC=CH), 6.08 (d, *J* = 11.0 Hz, 1H, HC=CH), 3.82 (s, 3H, O-CH₃), 2.40 (s, 3H, S-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 158.3, 130.0, 129.9, 126.5, 125.1, 113.7, 55.4, 18.9; **HRMS** (FI⁺): C₁₀H₁₂OS requires 180.0609 [M]⁺, found 180.0612; **IR**: ν_{max} (neat)/cm⁻¹ 2922, 1605, 1509, 1253, 1033.

6.4.1.2 Cross-coupling reaction with tether-free substrates

General procedure J for the cross coupling reaction of (*E*)-alkenyl sulfides and boronic acids

DCE (2.0 mL) was added to a microwave reaction vial charged with [Rh(nbd)₂BF₄] (11.2 mg, 0.03 mmol, 0.1 equiv) and dppe (12.0 mg, 0.03 mmol, 0.1 equiv) which had previously been evacuated and back-filled with N₂ gas. H₂ gas was then bubbled through the solution until a colour change from deep red to light orange was observed. N₂ gas was then bubbled through the solution until dryness. DCE (3.0 mL, 0.1 M) was added and the solution was transferred to a N₂-purged microwave reaction vial containing (*E*)-alkenylsulfide (0.3 mmol, 1.0 equiv), copper(I) 3-methylsalicylate (0.3 mmol, 1.0 equiv) and boronic acid (0.6 mmol, 2.0 equiv). The resulting reaction mixture was heated at 80 °C for 16 h and then allowed to cool to room temperature. The reaction was filtered through a plug of silica, rinsed with acetone and dichloromethane, and concentrated under reduced pressure. Purification by flash column chromatography afforded the desired product.

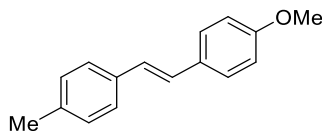
(*E*)-1,2-Bis(4-methoxyphenyl)ethane **41a**



The desired diarylethene was prepared according to general procedure **J** using (*E*)-(4-methoxystyryl)(methyl) sulfane **37a** (54 mg, 0.30 mmol), copper(I) 3-methylsalicylate (64 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91 mg, 0.60 mmol) in DCE (3.0 mL). Purification by flash column chromatography (petrol/Et₂O, 98:2) afforded the desired product **41a** (22 mg, 0.090 mmol, 30%) as a white solid. **¹H NMR** (400 MHz, CDCl₃): δ 7.43 (d, *J* = 9.0 Hz, 4H, *H*_{Ar}),

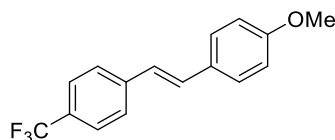
6.93 (s, 2H, $HC=CH$), 6.89 (d, $J = 9.0$ Hz, 4H, H_{Ar}), 3.83 (s, 6H, $2 \times O-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 130.6, 127.6, 126.3, 114.3, 55.5; **HRMS** (FI^+): $C_{16}H_{16}O_2$ requires 240.1148 $[M]^+$, found 240.1150; **M.p.** (CH_2Cl_2): 213-215 °C (lit. m.p. 213-215 °C). This data is consistent with literature.¹⁵⁷

(E)-1-Methoxy-4-(4-methylstyryl)benzene 41b



The desired diarylethene was prepared according to general procedure **J** using (*E*)-methyl(4-methylstyryl)sulfane **37b** (49 mg, 0.30 mmol), copper(I) 3-methylsalicylate (64 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91 mg, 0.60 mmol) in DCE (3.0 mL). Purification by flash column chromatography (petrol/ Et_2O , 98:2) afforded the desired product **41b** (22 mg, 0.10 mmol, 33%) as a beige solid. 1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.39 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.16 (d, $J = 8.0$ Hz, 2H, H_{Ar}), 7.03 (d, $J = 16.5$ Hz, 1H, $HC=CH$), 6.95 (d, $J = 16.5$ Hz, 1H, $HC=CH$), 6.90 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 3.83 (s, 3H, $O-CH_3$), 2.36 (s, 3H, $Ar-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 137.2, 135.0, 130.5, 129.5, 127.7, 127.4, 126.7, 126.3, 114.3, 55.5, 21.4; **HRMS** (FI^+): $C_{16}H_{16}O$ requires 224.1201 $[M]^+$, found 224.1194; **M.p.** (CH_2Cl_2): 154-156 °C (lit. m.p. 165-163 °C). This data is consistent with literature.¹⁵⁸

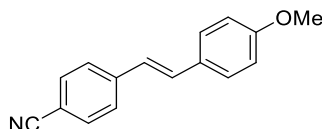
(E)-1-Methoxy-4-[4-(trifluoromethyl)styryl]benzene 41c



The desired diarylethene was prepared according to general procedure **J** using (*E*)-methyl[4(trifluoromethyl)styryl]sulfane **37c** (66 mg, 0.30 mmol), copper(I) 3-methylsalicylate (64 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91 mg, 0.60 mmol) in DCE (3.0 mL). Purification by flash column chromatography (petrol/ Et_2O , 98:2) afforded the desired product **41c** (24 mg, 0.090 mmol, 29%) as a beige solid. 1H NMR (400 MHz, $CDCl_3$): δ 7.60-7.55 (m, 4H, H_{Ar}), 7.48 (d, $J = 9.0$ Hz, 2H, H_{Ar}), 7.15 (d, $J = 16.5$ Hz, 1H, $HC=CH$), 6.98 (d, $J = 16.5$ Hz, 1H, $HC=CH$),

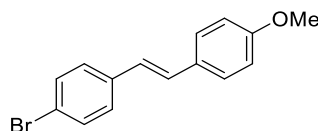
HC=CH), 6.92 (d, $J = 9.0$ Hz, 2H, H_{Ar}), 3.84 (s, 3H, O-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 159.9, 141.3, 130.9, 129.6, 128.9 (q, $^2J_{CF} = 32.5$ Hz), 128.2, 126.4, 125.7 (q, $^3J_{CF} = 3.5$ Hz), 125.1, 123.5 (q, $^1J_{CF} = 271.0$ Hz), 114.4, 55.5; HRMS (FI⁺): C₁₆H₁₃F₃O requires 278.0918 [M]⁺, found 278.0911; M.p. (CH₂Cl₂): 170-172 °C (lit. m.p. 170-172 °C). This data is consistent with literature.¹⁵⁹

(E)-4-(4-methoxystyryl)benzonitrile 41d



The desired diarylethene was prepared according to general procedure **J** using (E)-4-[2-(methylthio)vinyl]benzonitrile **37d** (53 mg, 0.30 mmol), copper(I) 3-methylsalicylate (64 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91 mg, 0.60 mmol) in DCE (3.0 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the desired product **41d** (17 mg, 0.070 mmol, 24%) as a beige solid. ¹H NMR (400 MHz, CDCl₃): δ 7.61 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.54 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.47 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.15 (d, $J = 16.5$ Hz, 1H, HC=CH), 6.97-6.91 (m, 3H, 2 $\times$ H_{Ar} and HC=CH), 3.84 (s, 3H, O-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 160.2, 142.3, 135.6, 132.1, 129.2, 128.4, 126.7, 124.7, 119.3, 114.3, 110.2, 55.4; HRMS (ESI⁺): C₁₆H₁₃NONa requires 258.0889 [M+Na]⁺, found 258.0889; M.p. (CH₂Cl₂): 145-147 °C (lit. m.p. 138-139 °C). This data is consistent with literature.¹⁵⁹

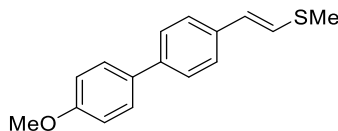
(E)-1-Bromo-4-(4-methoxystyryl)benzene 41e



The desired diarylethene was prepared according to general procedure **J** using (E)-(4-bromostyryl)(methyl)sulfane **37e** (69 mg, 0.30 mmol), copper(I) 3-methylsalicylate (64 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91 mg, 0.60 mmol) in DCE (3.0 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the desired product **41e** (17 mg, 0.060 mmol, 20%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.51-7.40 (m, 4H, H_{Ar}), 7.35 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 7.05 (d, $J = 16.5$ Hz, 1H, HC=CH), 6.92-6.88 (m, 3H, 2 $\times$ H_{Ar} and

HC=CH), 3.83 (s, 3H, O-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 159.7, 136.8, 131.9, 129.9, 129.1, 128.0, 127.9, 125.4, 120.9, 114.3, 55.5; **M.p.** (CH₂Cl₂): 203-205 °C (lit. m.p. 204-205 °C). This data is consistent with literature.¹⁶⁰

(E)-{2-[4'-Methoxy-(1,1'-biphenyl)-4-yl]vinyl}(methyl)sulfane 42

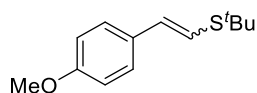


From the reaction employing (*E*)-(4-bromostyryl)(methyl)sulfane **37e** (see procedure above), cross-coupling product **42** was also isolated (6.3 mg, 0.025 mmol, 8%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.45-7.40 (m, 4H, *H*_{Ar}), 7.23 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 7.03 (d, *J* = 16.5 Hz, 1H, HC=CH), 6.94-6.88 (m, 3H, 2 × *H*_{Ar} and HC=CH), 3.83 (s, 3H, O-CH₃), 2.50 (s, 3H, S-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ 159.4, 137.4, 134.8, 130.3, 127.8, 127.0, 126.8, 126.1, 114.4, 114.3, 55.5, 16.1; **HRMS** (FI⁺): C₁₆H₁₆OS requires 256.0922 [M]⁺, found 259.0928; **IR**: ν_{max} (neat)/cm⁻¹ 1606, 1512, 1264, 1031.

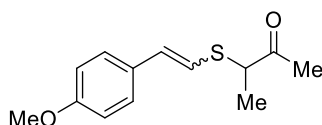
6.4.2 Traceless-tether approach

General Procedure K for the thiol-yne reaction:

Under nitrogen, triethylborane (1.0 M in hexane, 1.0 equiv) was added to a solution of alkyne (1.0 equiv) and thiol (2.0 equiv) in toluene (0.2 M). The reaction mixture was stirred at room temperature for 24 h, and then quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (2 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography.

tert-Butyl(4-methoxystyryl)sulfane 43

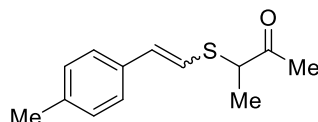
The desired alkenyl sulfide was prepared according to general procedure **K** using triethylborane (2.0 mL, 2.0 mmol), 4-ethynylanisole (0.26 mL, 2.0 mmol) and *tert*-butylthiol (0.45 mL, 4.0 mmol) in toluene (10 mL). Purification by flash column chromatography (petrol/Et₂O, 9:1) afforded the desired product **43** as an inseparable mixture of geometric isomers (0.35 g, 2.0 mmol, 98%, *Z/E*: 2:1) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ **Z**: 7.51-7.43 (m, 2H, *H*_{Ar}), 6.90 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.46 (d, *J* = 11.0 Hz, 1H, HC=CH), 6.33 (d, *J* = 11.0 Hz, 1H, HC=CH), 3.81 (s, 3H, O-CH₃), 1.44 (s, 9H, (CH₃)₃); **E**: 7.30 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.86 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 6.72 (app. s, 2H, HC=CH), 3.81 (s, 3H, O-CH₃), 1.41 (s, 9H, (CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ **Z**: 158.2, 130.1, 130.1, 125.2, 120.9, 113.6, 55.3, 44.4, 30.8; **E**: 159.1, 132.9, 130.0, 127.2, 119.1, 114.1, 55.3, 44.3, 31.0; LRMS (ESI⁺): *m/z* 245.0 ([M+Na]⁺, 100%). This data is consistent with literature.¹⁶¹

3-[(4-Methoxystyryl)thio]butan-2-one 44a

The desired alkenyl sulfide was prepared according to general procedure **K** using triethylborane (5.8 mL, 5.8 mmol), 4-ethynylanisole (0.75 mL, 5.8 mmol) and 3-mercapto-2-butanone (1.2 mL, 12 mmol) in toluene (28 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the desired product **44a** as an inseparable mixture of geometric isomers (1.3 g, 5.5 mmol, 95%, *E/Z* 1.3:1) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ **E**: 7.26-7.23 (m, 2H, *H*_{Ar}), 6.85-6.82 (m, 2H, *H*_{Ar}), 6.65 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.39 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.80 (s, 3H, O-CH₃), 3.62-3.54 (m, 1H, S-CH), 2.31 (s, 3H, CO-CH₃), 1.45 (d, *J* = 7.0 Hz, 3H, HC-CH₃); **Z**: 7.40-7.38 (m, 2H, *H*_{Ar}), 6.90-6.87 (m, 2H, *H*_{Ar}), 6.47 (d, *J* = 11.0 Hz, 1H, HC=CH), 5.99 (d, *J* = 11.0 Hz, 1H, HC=CH), 3.81 (s, 3H, O-CH₃), 3.61-3.55 (m, 1H, S-CH), 2.29 (s, 3H, CO-CH₃), 1.48 (d, *J* = 7.0 Hz, 3H, HC-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ **E**: 205.1, 159.5, 132.9, 129.3,

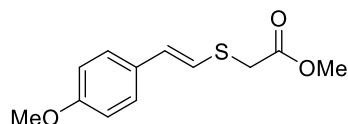
127.5, 117.3, 114.2, 55.4, 49.9, 26.7, 16.0; **Z**: 205.1, 158.7, 130.3, 129.4, 127.5, 119.3, 113.8, 55.4, 50.6, 26.5, 16.1; **LRMS** (ESI⁺): m/z 259.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₃H₁₆O₂SNa requires 259.0763 [M+Na]⁺, found 259.0757; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2932, 2837, 2253, 1707, 1509, 1252.

3-[(4-Methylstyryl)thio]butan-2-one **45a**



The desired alkenyl sulfide was prepared according to general procedure **K** using triethylborane (2.5 mL, 2.5 mmol), 4-ethynyltoluene (0.45 mL, 2.5 mmol) and 3-mercapto-2-butanone (0.51 mL, 5.0 mmol) in toluene (12.5 mL). Purification by flash column chromatography (petrol/Et₂O, 8:2) afforded the *desired product* **45a** as an inseparable mixture of geometric isomers (0.51 g, 2.3 mmol, 92%, *E/Z* 2.5:1) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ **E**: 7.22-7.18 (m, 2H, *H*_{Ar}), 7.12-7.08 (m, 2H, *H*_{Ar}), 6.66 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.50 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.59 (q, *J* = 7.0 Hz, 1H, S-CH), 2.35-2.30 (m, 6H, CO-CH₃ and Ar-CH₃), 1.46 (d, *J* = 7.0 Hz, 3H, HC-CH₃); **Z**: 7.35-7.33 (m, 2H, *H*_{Ar}), 7.18-7.15 (m, 2H, *H*_{Ar}), 6.52-6.48 (m, 1H, HC=CH), 6.06 (d, *J* = 11.0 Hz, 1H, HC=CH), 3.59 (q, *J* = 7.0 Hz, 1H, S-CH), 2.35-2.30 (m, 6H, CO-CH₃ and Ar-CH₃), 1.48 (d, *J* = 7.0 Hz, 3H, HC-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ **E**: 205.2, 137.7, 133.7, 132.6, 129.4, 126.1, 118.9, 49.8, 26.6, 21.3, 16.1; **Z**: 205.1, 137.1, 133.8, 129.1, 128.8, 127.8, 120.7, 50.6, 26.5, 21.4, 16.1; **HRMS** (FI⁺): C₁₃H₁₆OS requires 220.0922 [M]⁺, found 220.0927; **IR**: $\nu_{\max}$ (neat)/cm⁻¹ 2927, 1707, 1510, 1374.

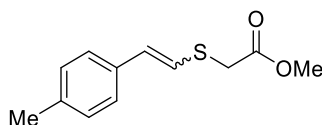
(*E*)-Methyl 2-[(4-methoxystyryl)thio]acetate **44b**



The desired alkenyl sulfide was prepared according to general procedure **K** using triethylborane (5.0 mL, 5.0 mmol), 4-ethynylanisole (0.65 mL, 5.0 mmol) and methyl thioglycolate (0.89 mL, 10 mmol) in toluene (25 mL). Purification by flash column chromatography (petrol/Et₂O, 7:3) afforded the *desired product* **44b** as an inseparable mixture of geometric isomers (0.84 g,

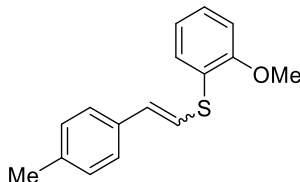
3.5 mmol, 70%, *E/Z* 6.5:1) as a colourless oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.27-7.23 (m, 2H, *H*_{Ar}), 6.86-6.82 (m, 2H, *H*_{Ar}), 6.60 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.56 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.80 (s, 3H, O-CH₃), 3.76 (s, 3H, CO₂CH₃), 3.49 (s, 2H, S-CH₂); **¹³C NMR** (101 MHz, CDCl₃): δ 170.1, 159.2, 130.1, 129.4, 127.2, 120.0, 114.1, 55.3, 52.6, 35.0; **LRMS** (ESI⁺): *m/z* 261.0 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₂H₁₄O₃SNa requires 261.0556 [M+Na]⁺, found 261.0550; **IR**: ν_{max} (neat)/cm⁻¹ 2949, 1735, 1605, 1510, 1437, 1252.

Methyl 2-[(4-methylstyryl)thio]acetate **45b**



The desired alkenyl sulfide was prepared according to general procedure **K** using triethylborane (2.0 mL, 2.0 mmol), 4-ethynyltoluene (0.25 mL, 2.0 mmol) and methyl thioglycolate (0.46 mL, 4.0 mmol) in toluene (10 mL). Purification by flash column chromatography (petrol/CH₂Cl₂, 1:1) afforded the *desired product 45b* as an inseparable mixture of geometric isomers (0.44 g, 2.0 mmol, 98%, *E/Z* 3.4:1) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ **E**: 7.21 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.11 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 6.69 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.59 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.76 (s, 3H, CO₂CH₃), 3.51 (s, 2H, S-CH₂), 2.33 (s, 3H, Ar-CH₃); **Z**: 7.34 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.17 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 6.50 (d, *J* = 11.0 Hz, 1H, HC=CH), 6.26 (d, *J* = 11.0 Hz, 1H, HC=CH), 3.76 (s, 3H, CO₂CH₃), 3.47 (s, 2H, S-CH₂), 2.35 (s, 3H, Ar-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ **E**: 170.2, 137.4, 133.8, 130.0, 129.4, 125.9, 121.6, 52.7, 34.9, 21.3; **Z**: 170.2, 137.0, 133.7, 129.1, 128.8, 127.1, 123.9, 52.7, 36.5, 21.4; **LRMS** (ESI⁺): *m/z* 245.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₂H₁₄O₂SNa requires 245.0607 [M+Na]⁺, found 245.0608; **IR**: ν_{max} (neat)/cm⁻¹ 3022, 1735, 1510, 1435, 1275, 1131.

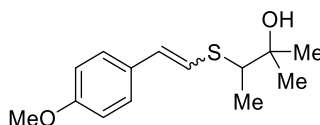
(2-Methoxyphenyl)(4-methylstyryl)sulfane **45c**



A solution of 4-ethynyltoluene (63 μL, 0.50 mmol, 1.0 equiv), 2-methoxybenzenethiol (73 μL, 0.60 mmol, 1.2 equiv) and acetic acid (57 μL, 1.0 mmol, 2.0 equiv) in toluene (1.25 mL) was heated under microwave irradiation at 130 °C for 45 min. Purification by flash column

chromatography (petrol/Et₂O, 95:5) afforded the *desired product* **45c** as an inseparable mixture of geometric isomers (0.13 g, 0.48 mmol, 97%, *E/Z* 1.5:1) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ *E*: 7.37 (dd, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 7.33-7.27 (m, 3H, *H*_{Ar}), 7.17 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.01-6.97 (m, 1H, *H*_{Ar}), 6.96-6.92 (m, 1H, *H*_{Ar}), 6.85 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.80 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.94 (s, 3H, O-CH₃), 2.38 (s, 3H, Ar-CH₃); *Z*: 7.52 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.45 (dd, *J* = 8.0, 1.5 Hz, 1H, *H*_{Ar}), 7.33-7.26 (m, 1H, *H*_{Ar}), 7.23 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.05-7.00 (m, 1H, *H*_{Ar}), 6.96-6.93 (m, 1H, *H*_{Ar}), 6.66 (d, *J* = 10.5 Hz, 1H, HC=CH), 6.44 (d, *J* = 10.5 Hz, 1H, HC=CH), 3.95 (s, 3H, O-CH₃), 2.40 (s, 3H, Ar-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ *E*: 157.0, 137.6, 134.0, 133.0, 130.1, 129.5, 128.0, 126.1, 124.6, 124.1, 120.9, 110.9, 56.0, 21.4; *Z*: 157.3, 137.0, 133.8, 131.0, 129.1, 129.0, 128.5, 128.1, 124.6, 124.2, 121.5, 111.0, 56.1, 21.4; LRMS (ESI⁺): *m/z* 279.1 ([M+Na]⁺, 100%); HRMS (ESI⁺): C₁₆H₁₆OSNa requires 279.0814 [M+Na]⁺, found 279.0820; IR: ν_{max} (neat)/cm⁻¹ 1580, 1510, 1477, 1433, 1274, 1244.

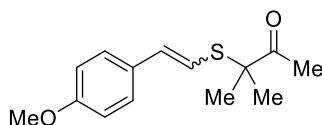
1-[(4-Methoxystyryl)thio]-2-methylpropan-2-ol **44c**



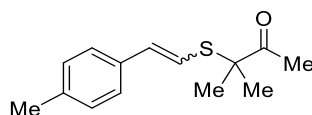
Methylmagnesium bromide (2.6 M in hexane, 1.4 mL, 3.6 mmol, 1.2 equiv) was added dropwise to a solution of 3-[(4-methoxystyryl)thio]butan-2-one **44a** (0.71 g, 3.0 mmol, 1.0 equiv) in diethyl ether (15 mL) and the reaction mixture stirred at room temperature for 30 min. The solution was then cooled to 0 °C and quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (3 × 30 mL) and washed with brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 6:4) afforded the *desired product* **44c** as an inseparable mixture of geometric isomers (0.66 g, 2.6 mmol, 87%, *E/Z* 1.3:1) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ *E*: 7.26-7.22 (m, 2H, *H*_{Ar}), 6.85-6.82 (m, 2H, *H*_{Ar}), 6.63 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.58 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.80 (s, 3H, O-CH₃), 3.07 (q, *J* = 7.0 Hz, 1H, S-CH), 2.29 (s, 1H, OH), 1.40 (d, *J* = 7.0 Hz, 3H, CH-CH₃), 1.33 (s, 3H, CH_{3a}), 1.27 (s, 3H, CH_{3b}); *Z*: 7.47-7.43 (m, 2H, *H*_{Ar}), 6.92-6.88 (m, 2H, *H*_{Ar}), 6.39 (d, *J* = 11.0 Hz, 1H,

HC=CH), 6.19 (d, $J = 11.0$ Hz, 1H, HC=CH), 3.82 (s, 3H, O-CH₃), 3.00 (q, $J = 7.0$ Hz, 1H, S-CH), 2.17 (s, 1H, OH), 1.43 (d, $J = 7.0$ Hz, 3H, CH-CH₃), 1.33 (s, 3H, CH_{3a}), 1.27 (s, 3H, CH_{3b}); ¹³C NMR (101 MHz, CDCl₃): δ **E**: 159.1, 130.2, 130.1, 125.4, 124.5, 113.8, 73.4, 55.9, 55.4, 27.5, 25.7, 18.0; **Z**: 158.4, 130.1, 129.8, 127.1, 122.0, 114.2, 73.4, 58.7, 55.4, 27.5, 25.8, 18.3; **HRMS** (FI⁺): C₁₄H₂₀O₂S requires 252.1184 [M]⁺, found 252.1186; **IR**: ν_{max} (neat)/cm⁻¹ 3448, 2973, 2360, 1606, 1509, 1251.

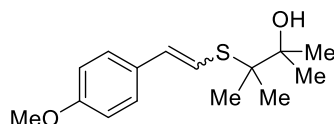
3-[(4-Methoxystyryl)thio]-3-methylbutan-2-one **44e**



Hexamethyldisilazane lithium salt (1.0 M in toluene, 2.2 mL, 2.4 mmol, 1.2 equiv) was added dropwise to a solution of 3-[(4-methoxystyryl)thio]butan-2-one **44a** (0.47 g, 2.0 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) and the reaction mixture was stirred at room temperature for 30 min. Iodomethane (0.15 mL, 2.4 mmol, 1.2 equiv) was added and the resulting mixture stirred for 3 h at room temperature, and then quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (2 × 30 mL), and the organic layer washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 7:3) afforded the *desired product* **44e** as an inseparable mixture of geometric isomers (0.46 g, 1.8 mmol, 92%, *E/Z* 1.3:1) as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ **E**: 7.26-7.23 (m, 2H, *H*_{Ar}), 6.84-6.80 (m, 2H, *H*_{Ar}), 6.68 (d, $J = 15.5$ Hz, 1H, HC=CH), 6.32 (d, $J = 15.5$ Hz, 1H, HC=CH), 3.80 (s, 3H, O-CH₃), 2.33 (s, 3H, CO-CH₃), 1.49 (s, 6H, (CH₃)₂); **Z**: 7.41-7.38 (m, 2H, *H*_{Ar}), 6.90-6.87 (m, 2H, *H*_{Ar}), 6.44 (d, $J = 11.0$ Hz, 1H, HC=CH), 5.88 (d, $J = 11.0$ Hz, 1H, HC=CH), 3.81 (s, 3H, O-CH₃), 2.30 (s, 3H, CO-CH₃), 1.52 (s, 6H, (CH₃)₂); ¹³C NMR (101 MHz, CDCl₃): δ **E**: 206.3, 159.6, 134.3, 129.3, 127.6, 117.1, 114.2, 55.4, 54.9, 24.5, 24.3; **Z**: 206.5, 158.7, 130.3, 129.6, 127.3, 118.9, 113.7, 55.4, 54.9, 24.6, 24.3; **HRMS** (FI⁺): C₁₄H₁₈O₂S requires 250.1028 [M]⁺, found 250.1031; **IR**: ν_{max} (neat)/cm⁻¹ 2980, 2360, 1698, 1607, 1570, 1254.

3-Methyl-3-[(4-methylstyryl)thio]butan-2-one 45d

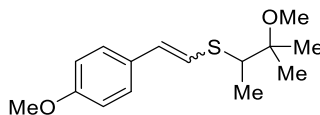
Hexamethyldisilazane lithium salt (1.0 M in toluene, 1.2 mL, 1.2 mmol, 1.2 equiv) was added dropwise to a solution of 3-[(4-methylstyryl)thio]butan-2-one **45a** (0.24 g, 1.0 mmol, 1.0 equiv) in tetrahydrofuran (5 mL) and the reaction mixture stirred at room temperature for 30 min. Iodomethane (0.06 mL, 1.2 mmol, 1.2 equiv) was added and the resulting mixture stirred for 3 h at room temperature, and then quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (2 × 20 mL), and the organic layer washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 7:3) afforded the *desired product* **45d** as an inseparable mixture of geometric isomers (0.20 g, 0.86 mmol, 86%, *E/Z* 2.5:1) as an orange oil. **¹H NMR** (400 MHz, CDCl₃): δ *E*: 7.20 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.10 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 6.69 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.43 (d, *J* = 15.5 Hz, 1H, HC=CH), 2.34 (s, 3H, Ar-CH₃), 2.32 (s, 3H, CO-CH₃), 1.50 (s, 6H, (CH₃)₂); *Z*: 7.34 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.17 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 6.47 (d, *J* = 11.0 Hz, 1H, HC=CH), 5.96 (d, *J* = 11.0 Hz, 1H, HC=CH), 2.35 (s, 3H, Ar-CH₃), 2.31 (s, 3H, CO-CH₃), 1.53 (s, 6H, (CH₃)₂); **¹³C NMR** (101 MHz, CDCl₃): δ *E*: 206.3, 137.9, 134.0, 133.7, 129.4, 126.2, 118.7, 54.8, 24.6, 24.3, 21.3; *Z*: 206.3, 137.0, 133.9, 129.1, 128.9, 127.5, 120.3, 54.9, 24.6, 24.3, 21.4; **HRMS** (FI⁺): C₁₄H₁₈OS requires 234.1078 [M]⁺, found 234.1082; **IR**: ν_{max} (neat)/cm⁻¹ 2980, 2360, 2927, 1699, 1511, 1385, 1252.

3-[(4-Methoxystyryl)thio]-2,3-dimethylbutan-2-ol 44f

Methylmagnesium bromide (2.6 M in hexane, 0.34 mL, 0.89 mmol, 1.2 equiv) was added dropwise to a solution of 3-[(4-methoxystyryl)thio]-3-methylbutan-2-one **44e** (0.18 g, 0.74 mmol, 1.0 equiv) in diethyl ether (3.7 mL) and the reaction mixture was stirred at room temperature for 30 min. The solution was then cooled to 0 °C and quenched with a saturated aqueous solution of ammonium

chloride. The product was extracted with diethyl ether (3 × 15 mL) and washed with brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 6:4) afforded the *desired product 44f* as an inseparable mixture of geometric isomers (0.14 g, 0.52 mmol, 70%, *E/Z* 1.3:1) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ **E**: 7.29-7.26 (m, 2H, *H_{Ar}*), 6.86-6.83 (m, 2H, *H_{Ar}*), 6.77 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.73 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.81 (s, 3H, O-CH₃), 2.14 (m, 1H, OH), 1.43 (s, 6H, (CH_{3a})₂), 1.33 (s, 6H, (CH_{3b})₂); **Z**: 7.51-7.47 (m, 2H, *H_{Ar}*), 6.91-6.88 (m, 2H, *H_{Ar}*), 6.45 (d, *J* = 11.0 Hz, 1H, HC=CH), 6.40 (d, *J* = 11.0 Hz, 1H, HC=CH), 3.82 (s, 3H, O-CH₃), 1.97 (s, 1H, OH), 1.48 (s, 6H, (CH_{3a})₂), 1.33 (s, 6H, (CH_{3b})₂); ¹³C NMR (101 MHz, CDCl₃): δ **E**: 159.3, 133.3, 129.7, 127.3, 119.6, 114.1, 76.1, 57.4, 55.3, 25.6, 25.1; **Z**: 158.3, 130.2, 129.8, 125.7, 121.2, 113.6, 76.2, 57.3, 55.3, 25.6, 24.8; **LRMS** (ESI⁺): *m/z* 289.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₅H₂₃O₂SNa requires 267.1413 [M+Na]⁺, found 267.1411; **IR**: ν_{max} (neat)/cm⁻¹ 3473, 2975, 2359, 1607, 1464, 1252.

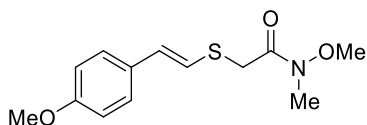
(3-Methoxy-3-methylbutan-2-yl)(4-methoxystyryl)sulfane 44d



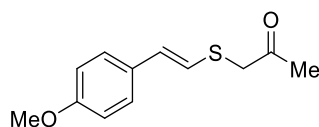
Sodium hydride (60% in mineral oil, 0.12 g, 3.0 mmol, 3.0 equiv) was added to a solution of 1-[(4-methoxystyryl)thio]-2-methylpropan-2-ol **44c** (0.25 g, 1.0 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) and the reaction mixture was stirred at room temperature for 1.5 h. Iodomethane (0.19 mL, 3.0 mmol, 3.0 equiv) was added and the resulting mixture stirred for 24 h at room temperature, and then quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (2 × 15 mL), and the organic layer washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/CH₂Cl₂, 2:3) afforded the *desired product 44d* as an inseparable mixture of geometric isomers (0.19 g, 0.73 mmol, 73%, *E/Z* 1.3:1) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ **E**: 7.26-7.22 (m, 2H, *H_{Ar}*), 6.86-6.81 (m, 2H, *H_{Ar}*), 6.63 (d, *J* = 15.5 Hz, 1H, HC=CH), 6.56 (d, *J* = 15.5 Hz, 1H, HC=CH), 3.80 (s, 3H, Ar-O-CH₃), 3.24 (s, 3H, C-O-CH₃), 3.15 (q,

$J = 7.0$ Hz, 1H, S-CH), 1.38 (d, $J = 7.0$ Hz, 3H, CH-CH₃), 1.31 (s, 3H, C-CH_{3a}), 1.25 (s, 3H, C-CH_{3b}); **Z**: 7.48-7.43 (m, 2H, H_{Ar}), 6.90-6.86 (m, 2H, H_{Ar}), 6.37 (d, $J = 11.0$ Hz, 1H, HC=CH), 6.20 (d, $J = 11.0$ Hz, 1H, HC=CH), 3.81 (s, 3H, Ar-O-CH₃), 3.24 (s, 3H, C-O-CH₃), 3.06 (q, $J = 7.0$ Hz, 1H, S-CH), 1.40 (d, $J = 7.0$ Hz, 3H, CH-CH₃), 1.31 (s, 3H, C-CH_{3a}), 1.25 (s, 3H, C-CH_{3b}); **¹³C NMR** (101 MHz, CDCl₃): δ **E**: 159.0, 130.2, 129.0, 127.0, 122.8, 114.2, 77.5, 55.4, 51.1, 49.5, 22.9, 22.4, 17.2; **Z**: 158.3, 130.2, 130.1, 125.1, 124.6, 113.7, 77.6, 55.4, 54.1, 49.5, 23.0, 22.4, 17.6; **LRMS** (ESI⁺): m/z 289.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₅H₂₂O₂SNa requires 289.1233 [M+Na]⁺, found 289.1226; **IR**: ν_{max} (neat)/cm⁻¹ 2976, 2243, 1606, 1508, 1251.

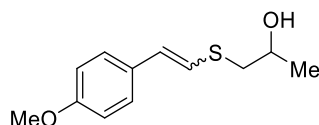
(E)-N-methoxy-2-[(4-methoxystyryl)thio]-N-methylacetamide 44g



A suspension of methyl 2-[(4-methoxystyryl)thio]acetate **44b** (0.36 g, 1.5 mmol, 1.0 equiv) and *N,O*-dimethylhydroxylamine hydrochloride salt (0.20 g, 6.0 mmol, 4.0 equiv) in THF (15 mL) was cooled to -20 °C. Isopropylmagnesium chloride (2 M in Et₂O, 6 mL, 12.0 mmol, 8.0 equiv) was added dropwise over 10 min. The solution was stirred at -20 °C for 45 min then 15 min at 0 °C. The reaction was quenched with a saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The product was extracted with ethyl acetate (2 × 30 mL), and the organic layer washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 3:7) afforded the *desired product 44g* as an inseparable mixture of geometric isomers (0.22 g, 0.84 mmol, 56%, *E/Z* 6.5:1) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.26-7.23 (m, 2H, H_{Ar}), 6.83-6.80 (m, 2H, H_{Ar}), 6.69 (d, $J = 15.5$ Hz, 1H, HC=CH), 6.59 (d, $J = 15.5$ Hz, 1H, HC=CH), 3.79 (s, 3H, O-CH_{3a}), 3.77 (s, 3H, O-CH_{3b}), 3.64 (s, 2H, CH₂), 3.23 (s, 3H, N-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 216.5, 159.1, 130.2, 129.7, 127.2, 120.8, 114.4, 61.7, 55.4, 33.7, 32.5; **LRMS** (ESI⁺): m/z 268.1 ([M+H]⁺, 100%), 290.0 ([M+Na]⁺, 30%); **HRMS** (ESI⁺): C₁₃H₁₇O₃NSNa requires 290.0821 [M+Na]⁺, found 290.0820; **IR**: ν_{max} (neat)/cm⁻¹ 1734, 1605, 1461, 1277.

(E)-1-[(4-Methoxystyryl)thio]propan-2-one 44h

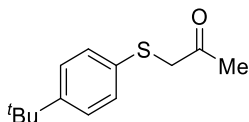
Methylmagnesium bromide (2.6 M in hexane, 0.30 mL, 0.77 mmol, 1.0 equiv) was added dropwise to a solution of (*E*)-*N*-methoxy-2-[(4-methoxystyryl)thio]-*N*-methylacetamide **44g** (0.20 g, 0.77 mmol, 1.0 equiv) in diethyl ether (2.5 mL) at 0 °C. The resulting mixture was stirred for 10 min and then quenched with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered and reduced under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 7:3) afforded the *desired product 44h* as an inseparable mixture of geometric isomers (89 mg, 0.40 mmol, 53%, *E/Z* 6.5:1) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.25-7.21 (m, 2H, *H*_{Ar}), 6.85-6.81 (m, 2H, *H*_{Ar}), 6.56 (d, *J* = 15.5 Hz, 1H, *HC=CH*), 6.45 (d, *J* = 15.5 Hz, 1H, *HC=CH*), 3.80 (s, 3H, O-CH₃), 3.48 (s, 2H, CH₂), 2.32 (s, 3H, CO-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ 203.5, 159.4, 130.4, 130.3, 127.3, 119.6, 114.2, 55.4, 43.5, 28.1; **LRMS** (ESI⁺): *m/z* 245.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₂H₁₄O₂SNa requires 245.0607 [M+Na]⁺, found 245.0602. **IR**: ν_{max} (neat)/cm⁻¹ 1732, 1608, 1522, 1430, 1255.

1-[(4-Methoxystyryl)thio]propan-2-ol 44i

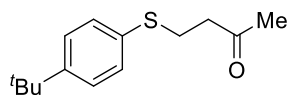
Sodium borohydride (0.11 g, 3.0 mmol, 2.0 equiv) was added portion wise to an ice cold solution of 1-[(4-Methoxystyryl)thio]propan-2-one **44h** (0.33 g, 1.5 mmol, 1.0 equiv) in ethanol (7.5 mL). The reaction mixture was stirred at room temperature for 1 h and then quenched at 0 °C with a saturated aqueous solution of ammonium chloride. The product was extracted with diethyl ether (2 × 30 mL), washed with brine (20 mL) and then concentrated under reduced pressure. Purification by flash column chromatography (petrol/Et₂O, 7:3) afforded the *desired product 44i* as an inseparable mixture of geometric isomers (0.18 g, 0.78 mmol, 51%, *E/Z* 4.6:1) as colourless

oil. **¹H NMR** (400 MHz, CDCl₃): δ **E**: 7.25-7.20 (m, 2H, *H_{Ar}*), 6.87-6.82 (m, 2H, *H_{Ar}*), 6.58 (d, *J* = 15.5 Hz, 1H, *HC=CH*), 6.49 (d, *J* = 15.5 Hz, 1H, *HC=CH*), 4.01-3.93 (m, 1H, *CH*), 3.80 (s, 3H, O-CH₃), 2.94 (dd, *J* = 14.0, 3.5 Hz, 1H, S-CH_aH_b), 2.71 (dd, *J* = 14.0, 8.5 Hz, 1H, S-CH_aH_b), 1.30 (d, *J* = 6.5 Hz, 3H, CH-CH₃); **Z**: 7.47-7.43 (m, 2H, *H_{Ar}*), 6.93-6.89 (m, 2H, *H_{Ar}*), 6.43 (d, *J* = 10.5 Hz, 1H, *HC=CH*), 6.07 (d, *J* = 10.5 Hz, 1H, *HC=CH*), 4.01-3.93 (m, 1H, *CH*), 3.82 (s, 3H, O-CH₃), 2.95-2.91 (m, 1H, S-CH_aH_b), 2.77-2.72 (m, 1H, S-CH_aH_b), 1.33-1.30 (m, 3H, CH-CH₃); **¹³C NMR** (101 MHz, CDCl₃): δ **E**: 159.2, 129.68, 129.66, 127.1, 121.4, 114.2, 66.5, 55.4, 42.7, 22.1; **Z**: 159.2, 130.2, 127.0, 126.5, 124.1, 113.8, 66.9, 55.4, 45.1, 22.1; **LRMS** (ESI⁺): *m/z* 247.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₂H₁₆O₂SNa requires 247.0763 [M+Na]⁺, found 247.0764; **IR**: ν_{max} (neat)/cm⁻¹ 3386, 2930, 1605, 1509, 1250, 1030.

1-([4-(*tert*-Butyl)phenyl]thio)propan-2-one **46**



4-*tert*-Butylbenzenethiol (0.57 mL, 3.3 mmol, 1.1 equiv) was added dropwise to a solution of chloroacetone (0.24 mL, 3.0 mmol, 1.0 equiv) and triethylamine (0.50 mL, 3.6 mmol, 1.2 equiv) in acetonitrile (15 mL) at 0 °C and the reaction mixture was stirred for 30 min. The white suspension was then diluted with dichloromethane. The organic layer was washed with water then brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (petrol/EtOAc, 8:2) afforded the *desired product* **46** (0.65 g, 2.9 mmol, 97%) as a yellow oil. **¹H NMR** (400 MHz, CDCl₃): δ 7.33-7.26 (m, 4H, *H_{Ar}*), 3.63 (s, 2H, CH₂), 2.28 (s, 3H, CO-CH₃), 1.29 (s, 9H, ((CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃): δ 204.0, 150.5, 131.1, 130.0, 126.4, 45.3, 34.7, 31.4, 28.2; **HRMS** (ESI⁺): C₁₃H₁₈OSNa requires 245.0971 [M+Na]⁺, found 245.0969; **IR**: ν_{max} (neat)/cm⁻¹ 2962, 1709, 1490, 1357, 1231, 823.

4-[4-(*tert*-Butyl)phenyl]thio]butan-2-one 47

3-Buten-2-one (0.45 mL, 5.0 mmol, 1.0 equiv) was added to a solution of 4-*tert*-butylthiophenol (0.86 mL, 5.0 mmol, 1.0 equiv) and triethylamine (0.07 mL, 0.5 mmol, 0.1 equiv) in chloroform (5 mL). The reaction mixture was stirred for 12 h at room temperature. Dichloromethane (20 mL) was added and the solution washed with an aqueous solution of hydrochloric acid (1.0 N, 2 × 10 mL), then brine. The organic layer was concentrated under reduced pressure to afford the *desired product 47* as a yellow oil (1.2 g, 4.9 mmol, 99%). **¹H NMR** (400 MHz, CDCl₃): δ 7.33-7.27 (m, 4H, *H*_{Ar}), 3.10 (t, *J* = 7.5 Hz, 2H, S-CH₂), 2.75 (t, *J* = 7.5 Hz, 2H, CH₂-CO), 2.14 (s, 3H, CO-CH₃), 1.30 (s, 9H, (CH₃)₃); **¹³C NMR** (101 MHz, CDCl₃) δ 206.9, 149.9, 132.0, 130.0, 126.2, 43.4, 34.6, 31.4, 30.2, 28.0; **LRMS** (ESI⁺): *m/z* 259.1 ([M+Na]⁺, 100%); **HRMS** (ESI⁺): C₁₄H₂₁OS requires 237.1308 [M+H]⁺, found 237.1307; **IR**: ν_{max} (neat)/cm⁻¹ 2961, 2904, 1714, 1489, 1361, 1121.

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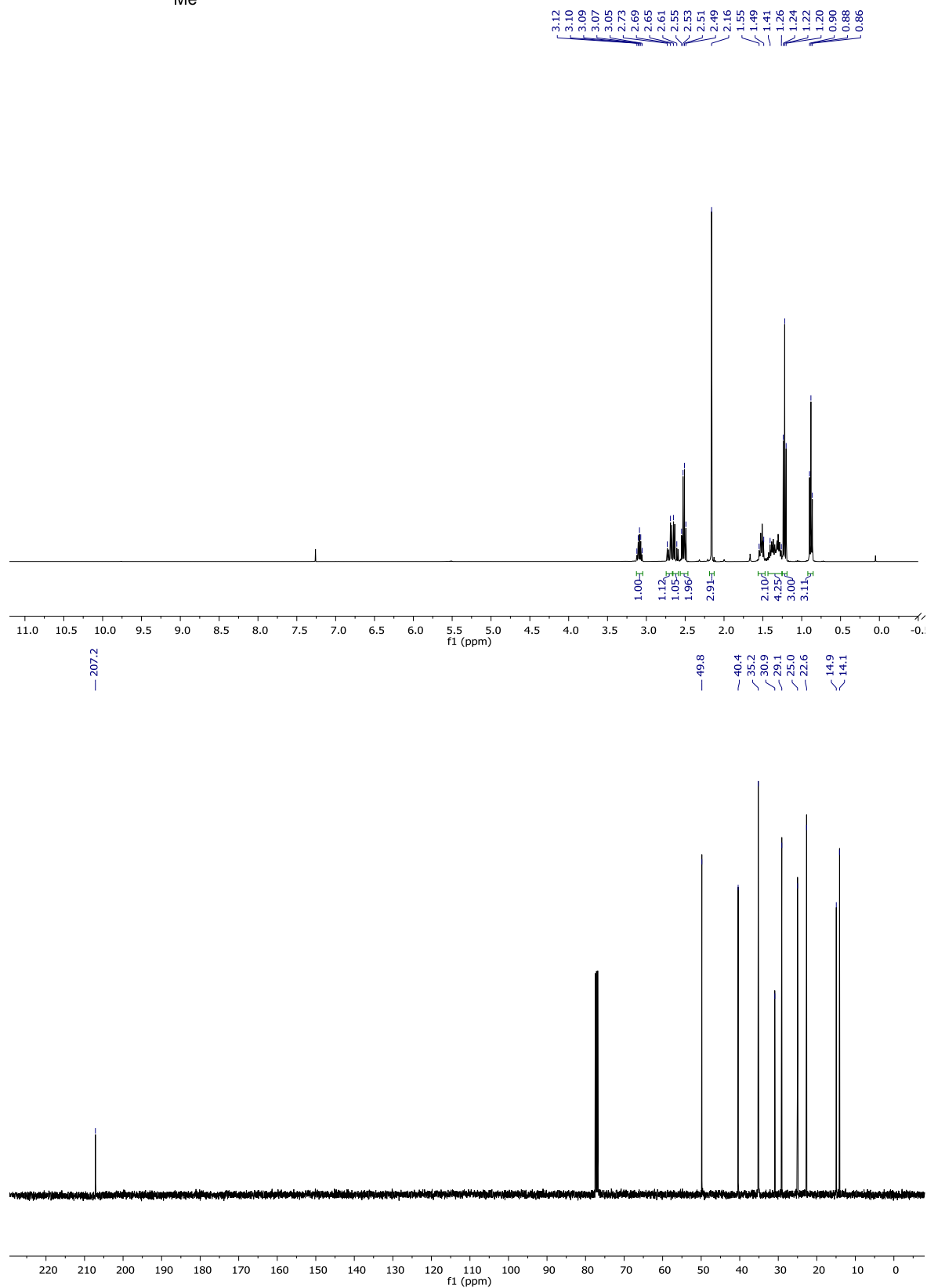
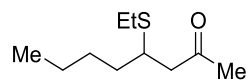
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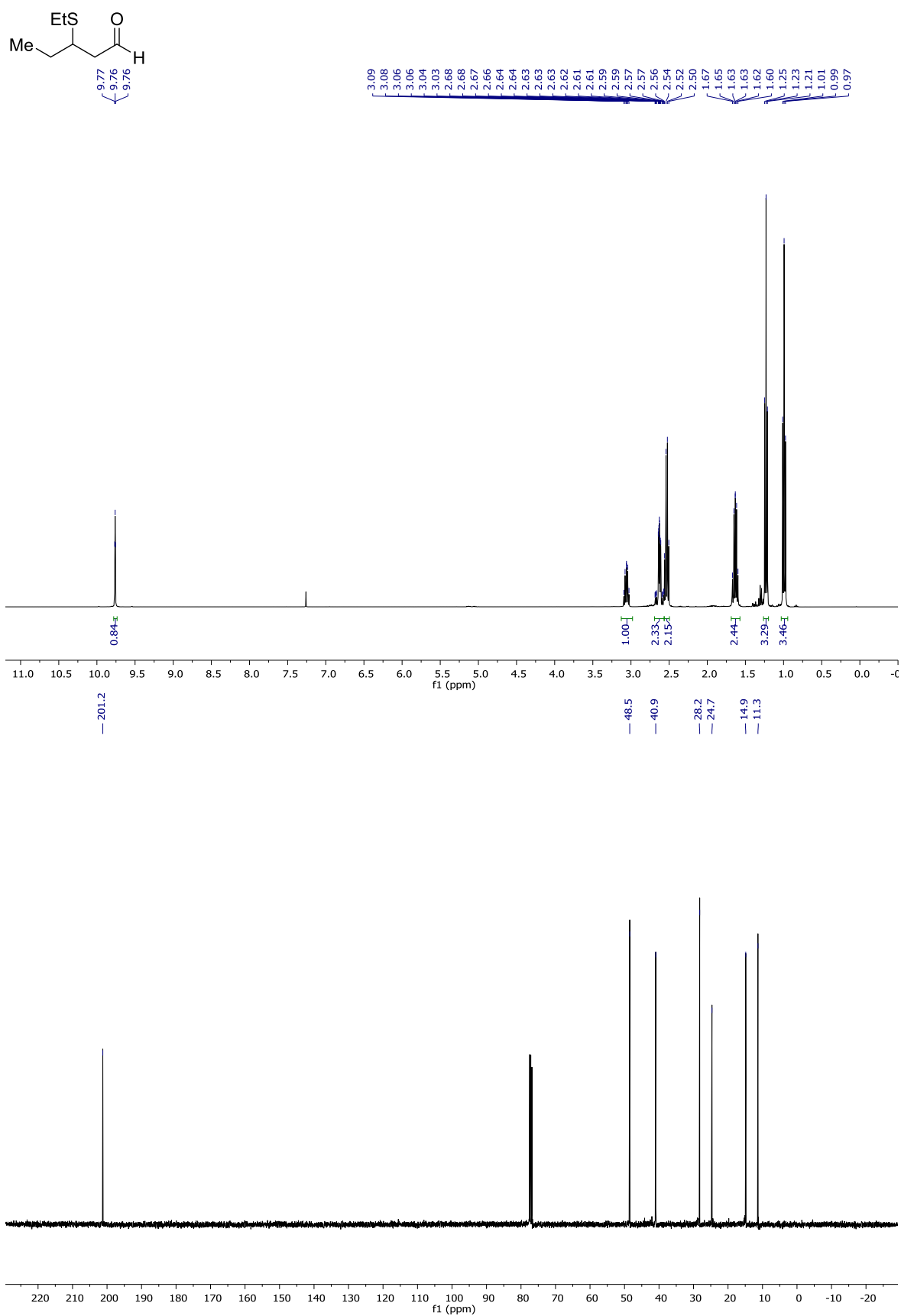
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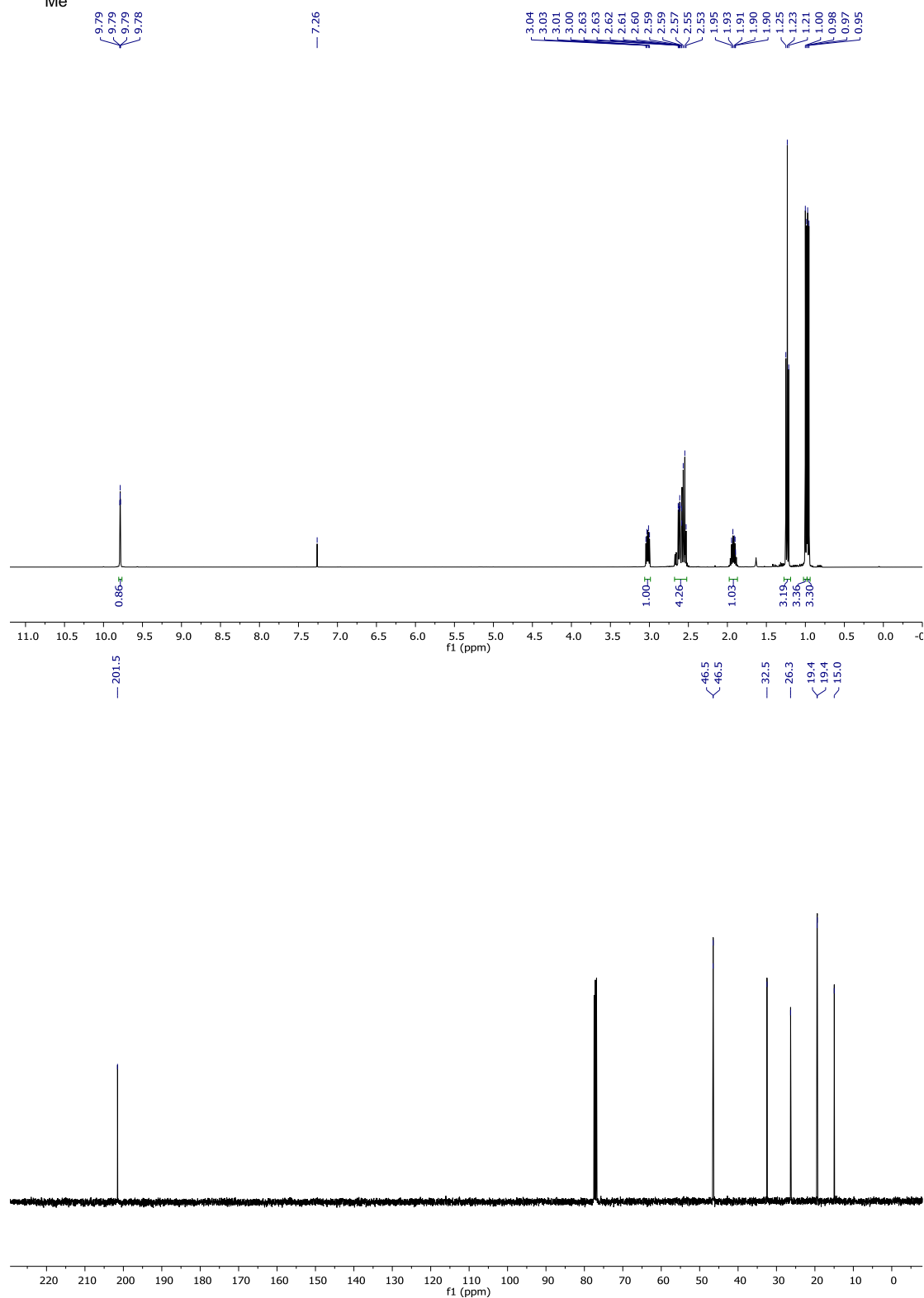
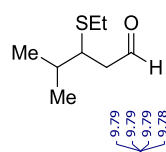
Spectra of novel compounds

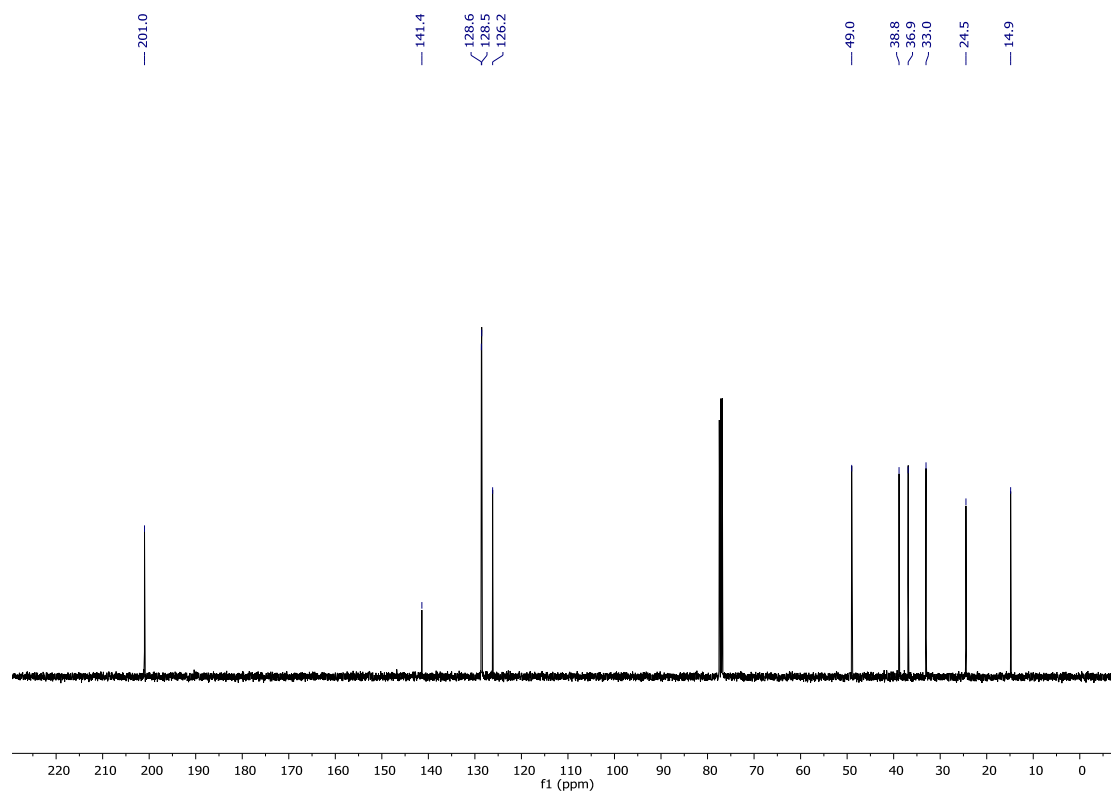
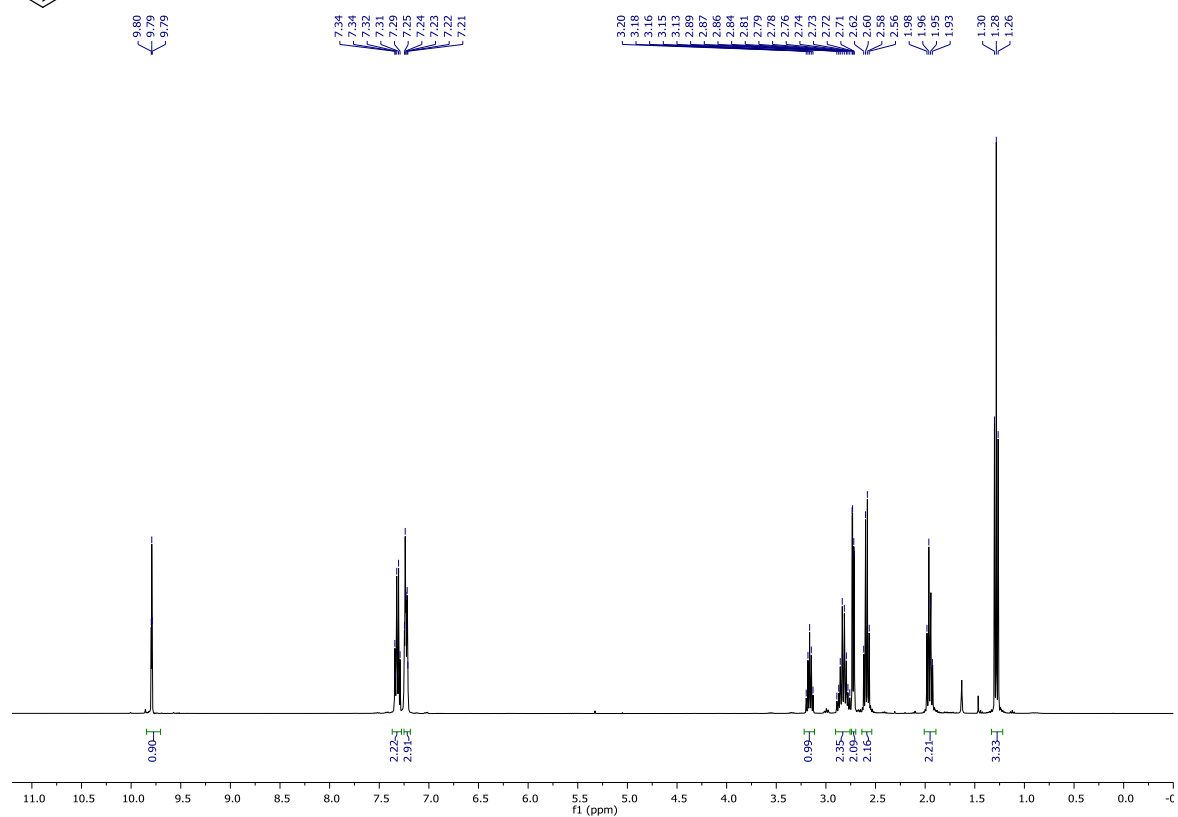
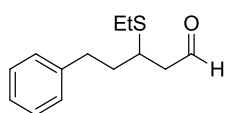
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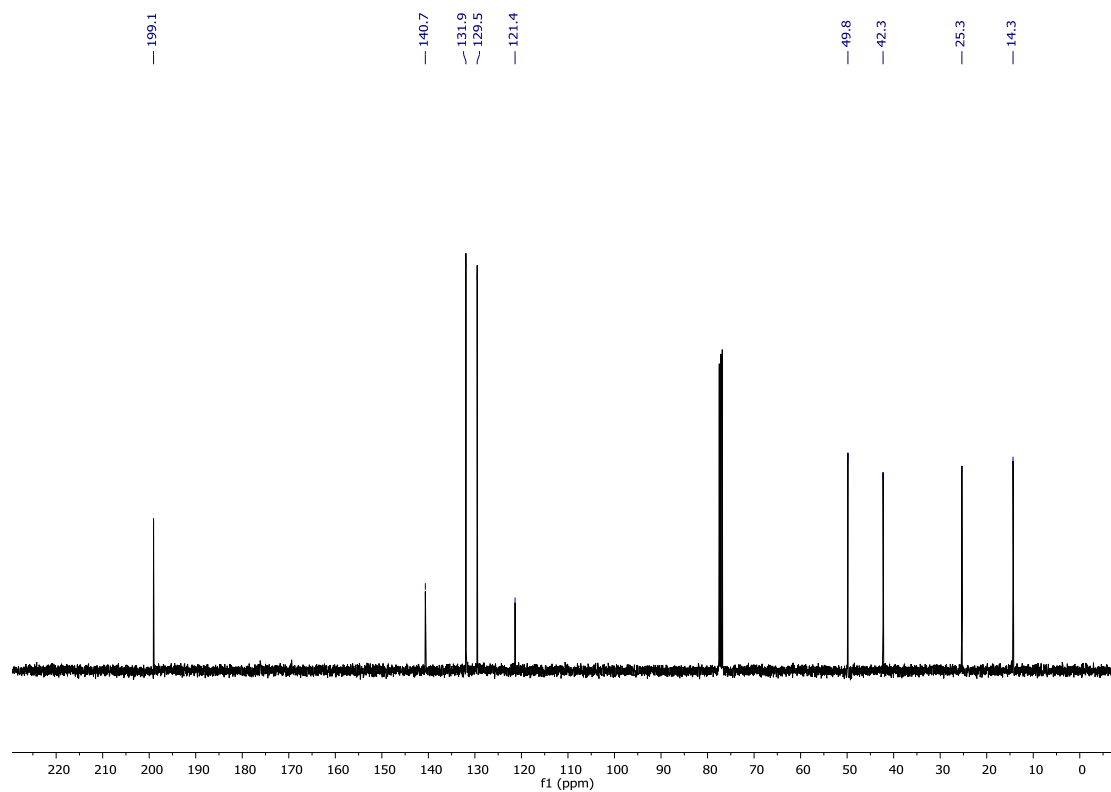
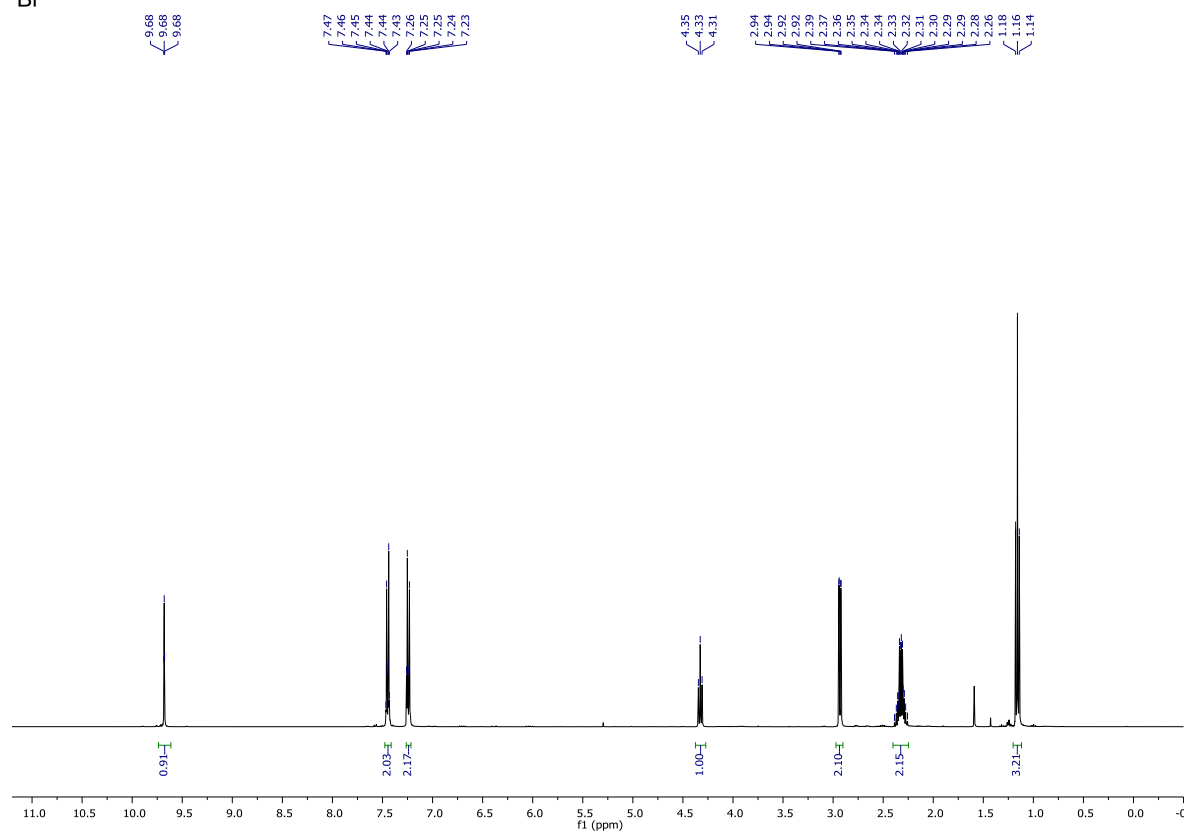
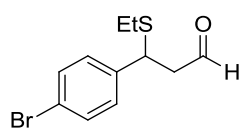


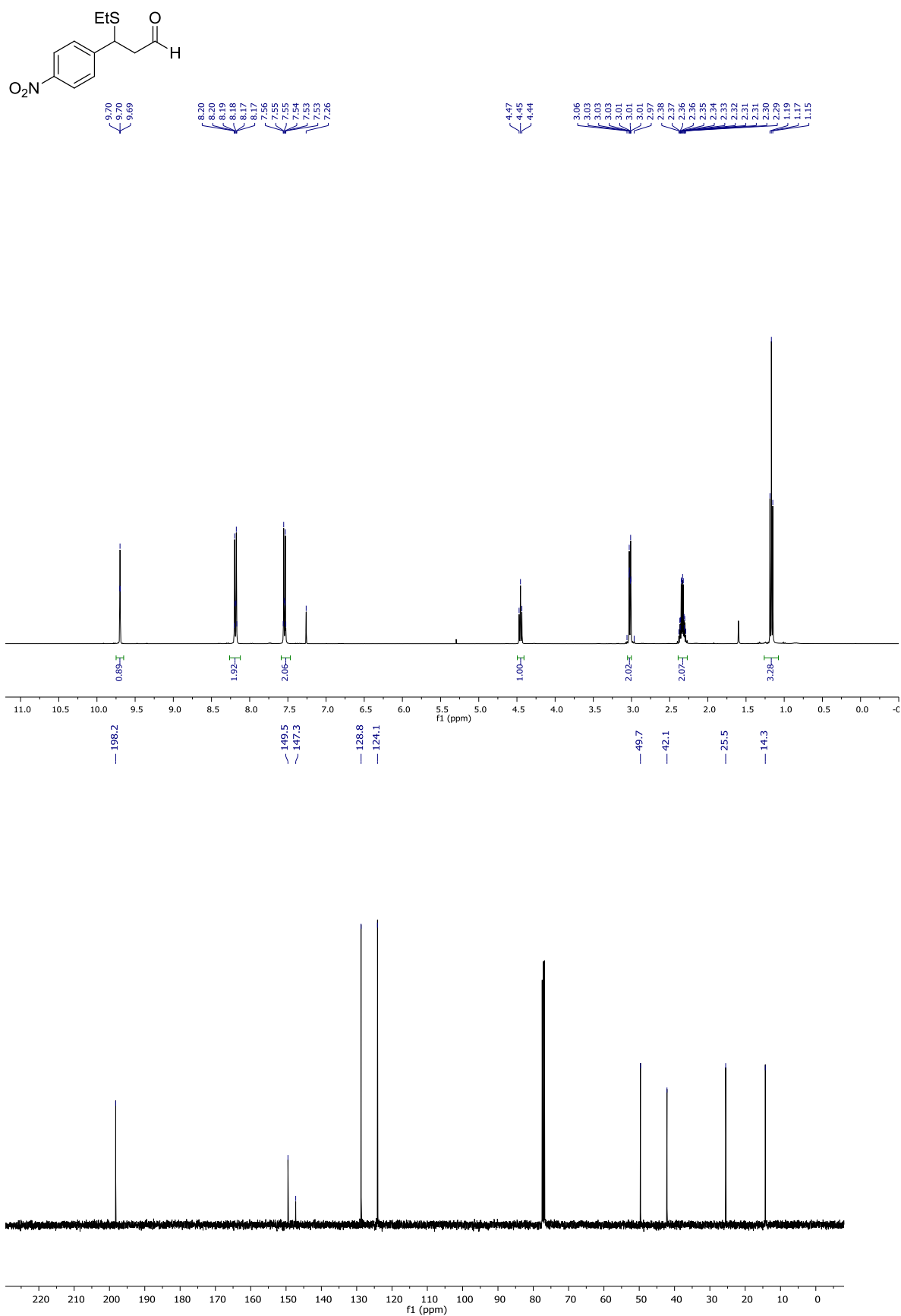
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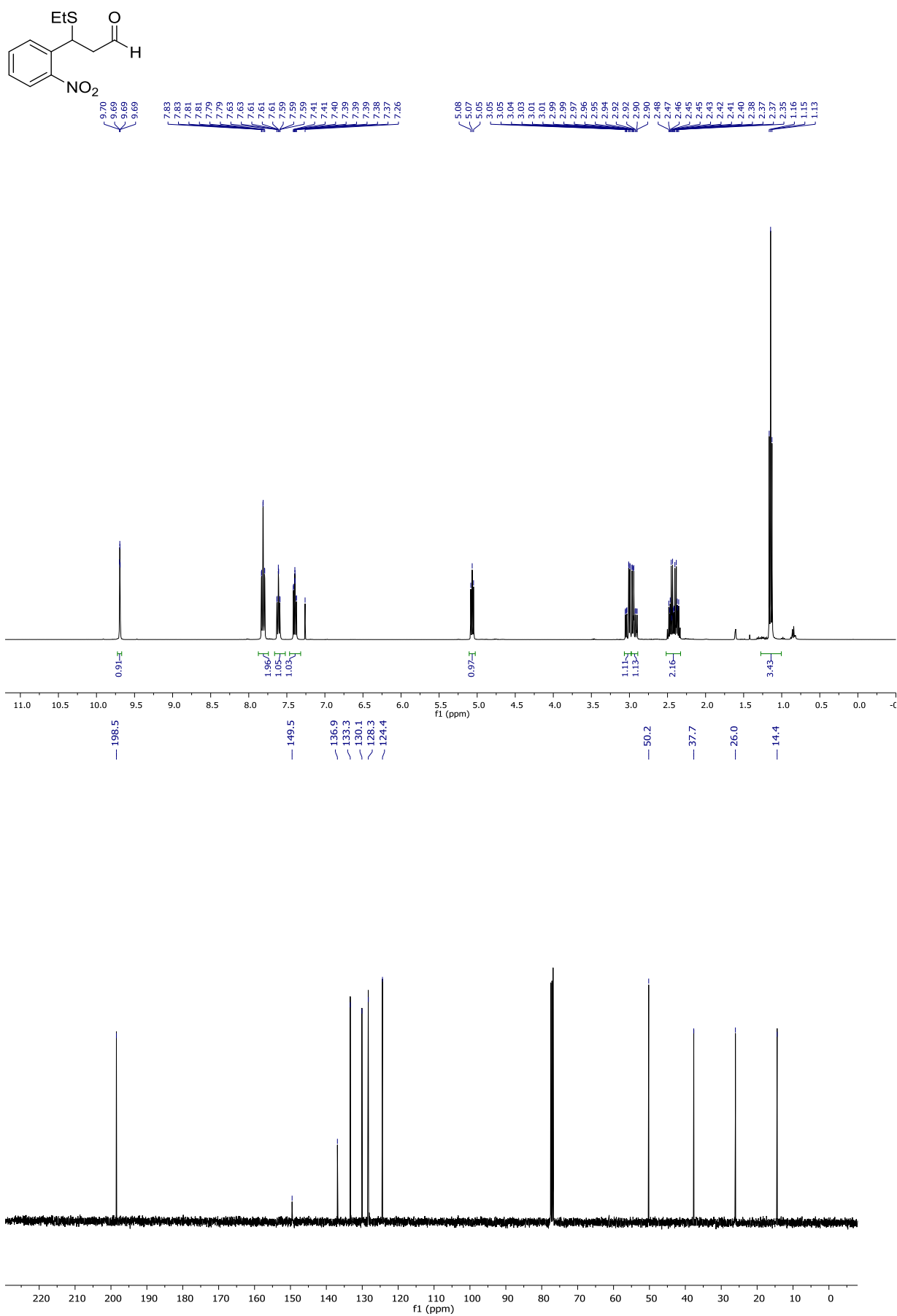


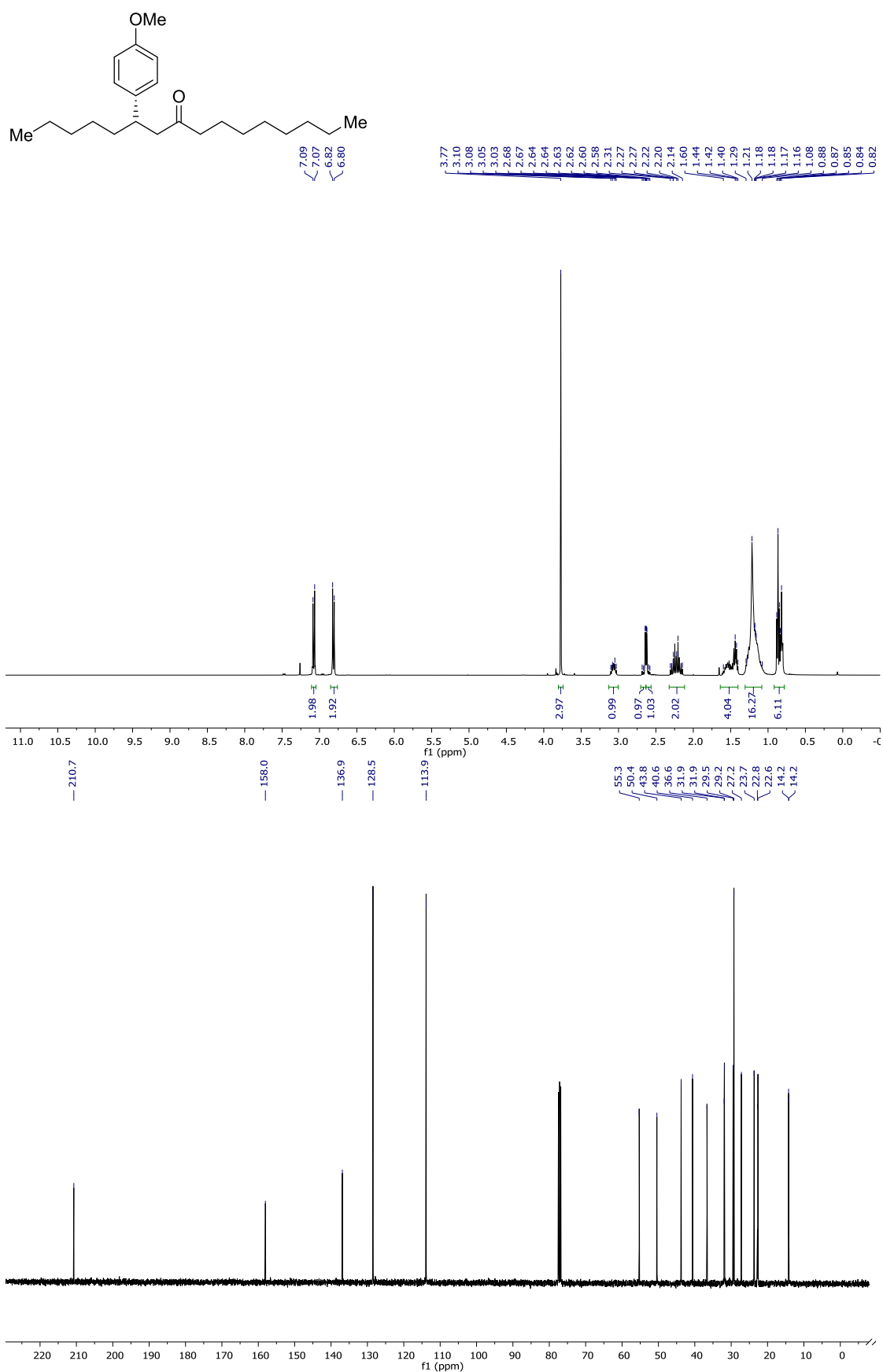
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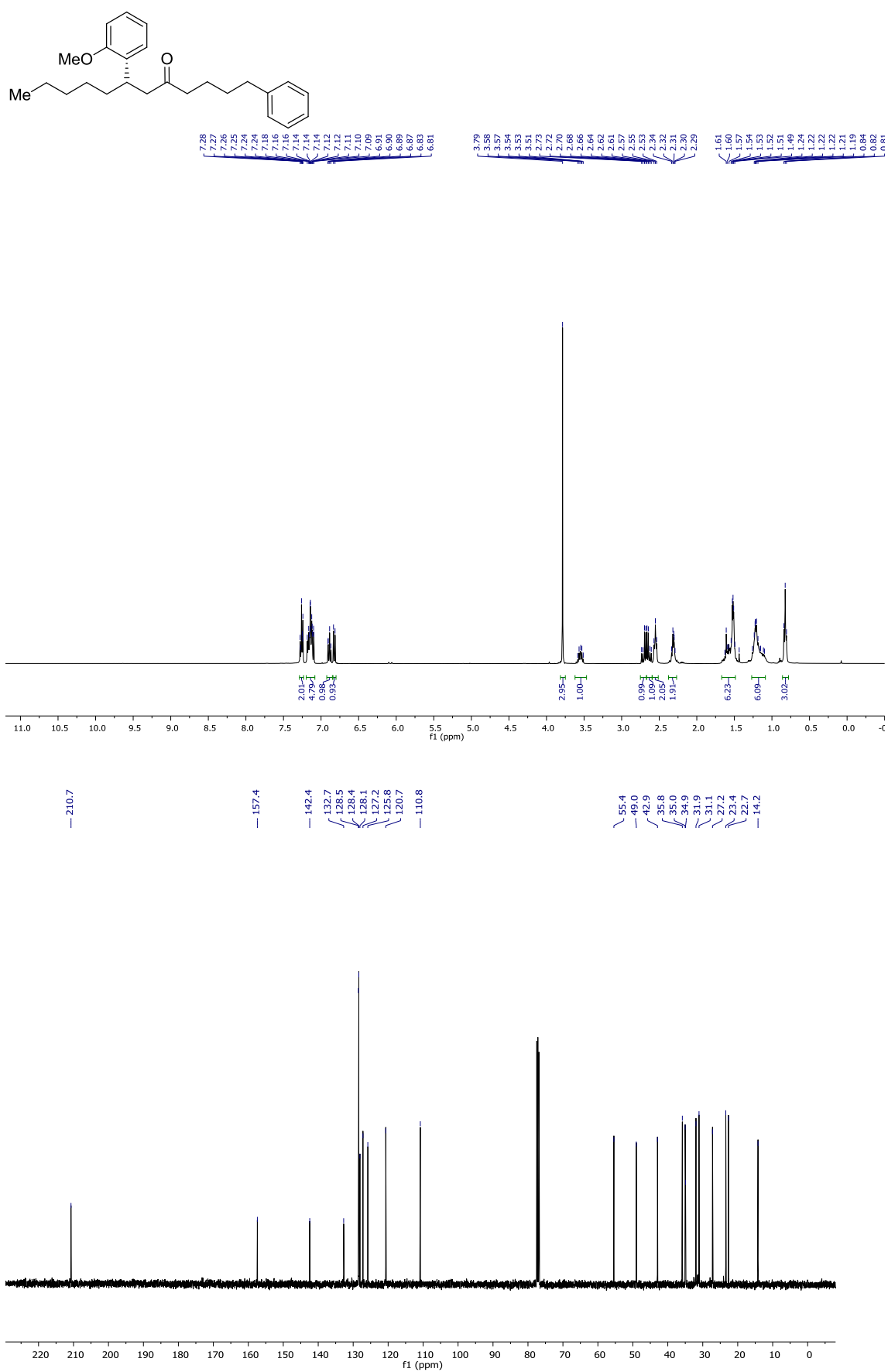
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3-(4-Bromophenyl)-3-(ethylthio)propanal 7f

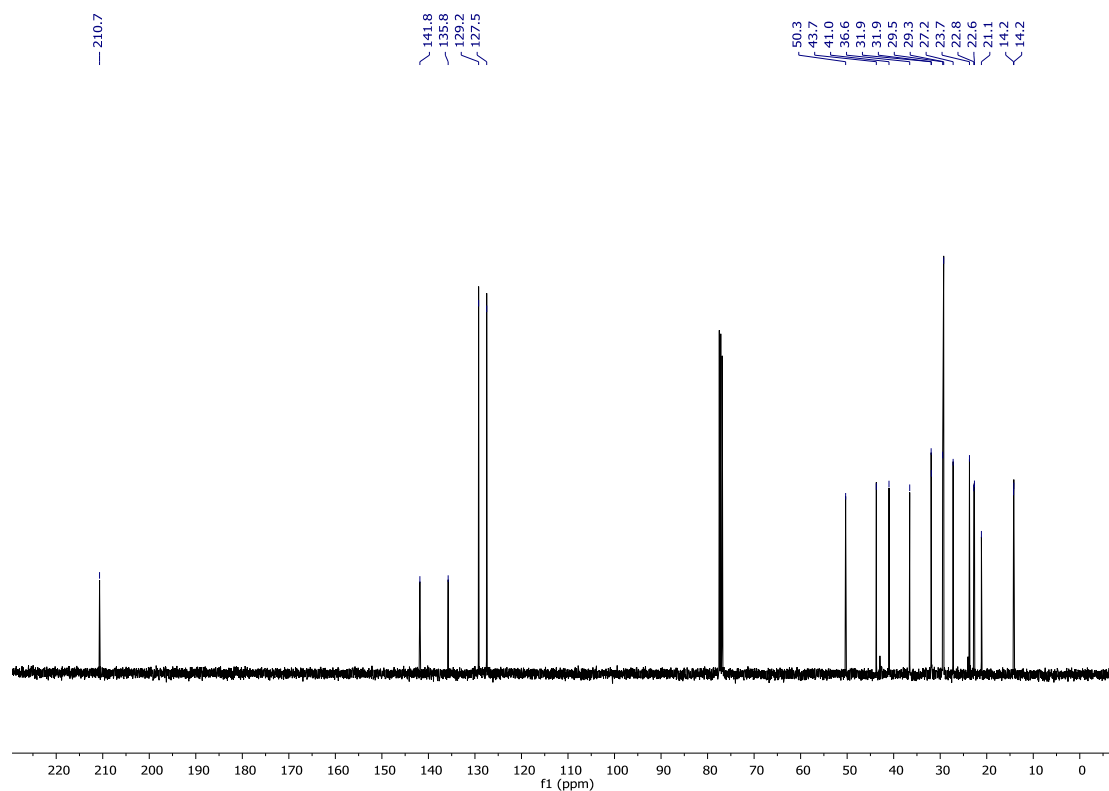
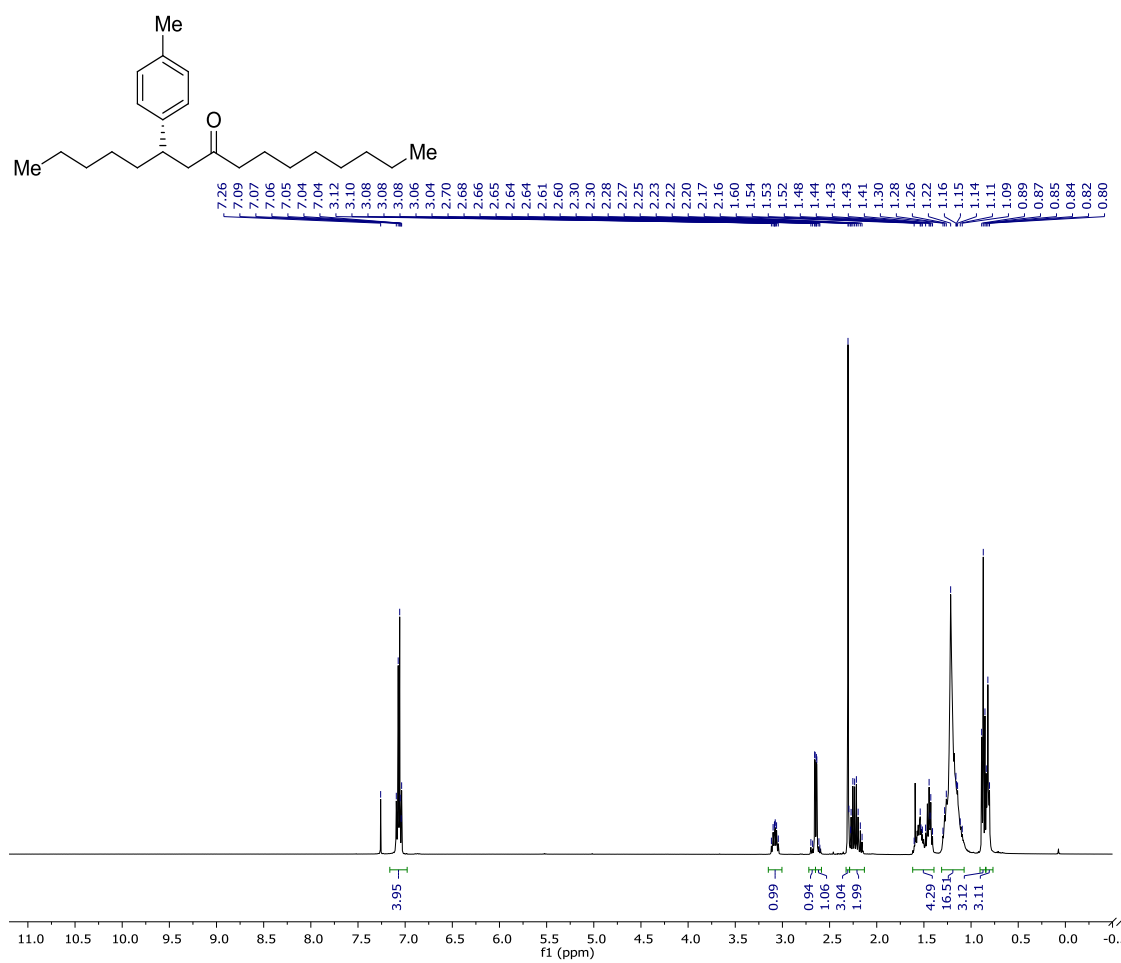
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3-(Ethylthio)-3-(2-nitrophenyl)propanal 7h

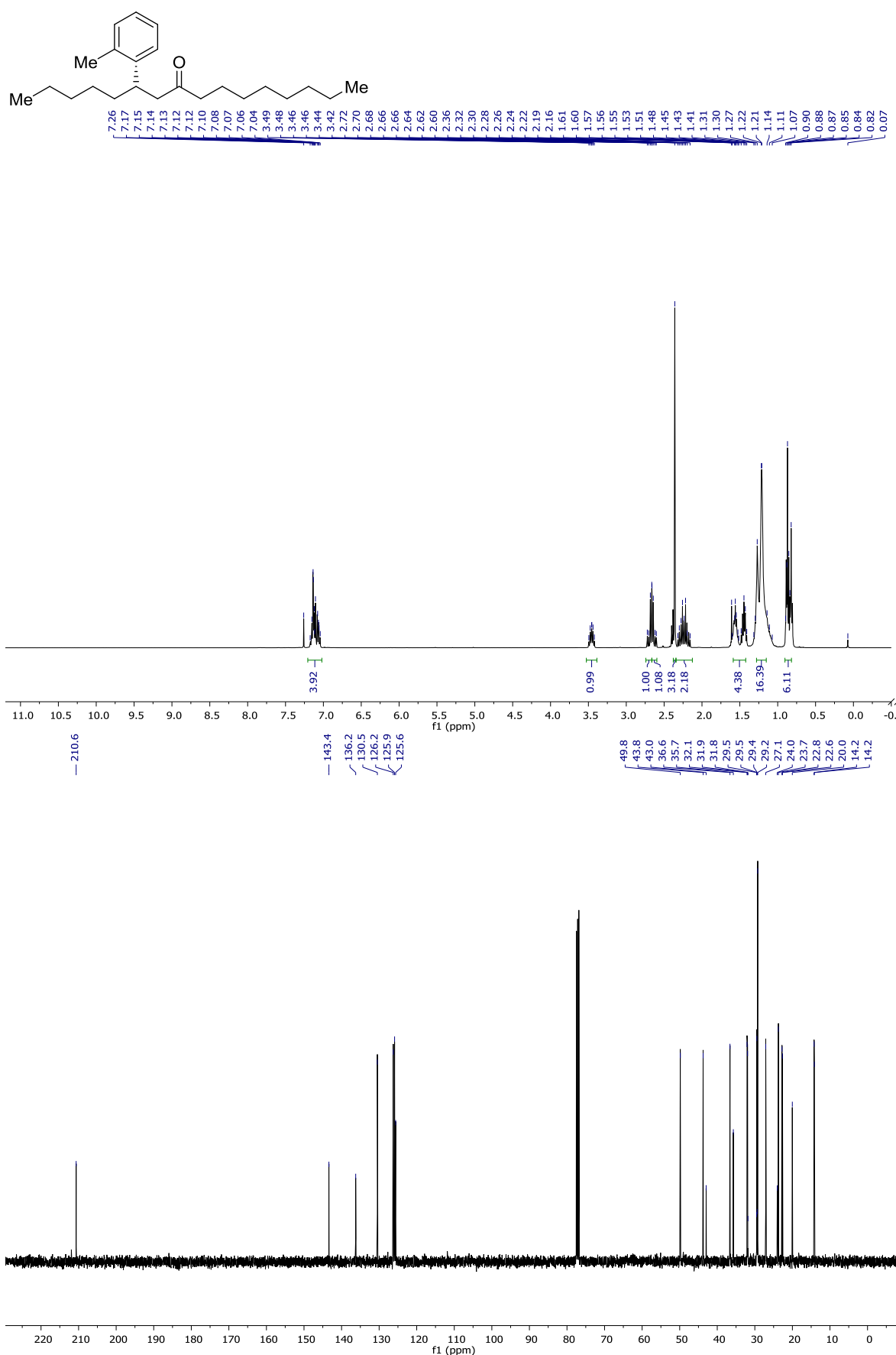
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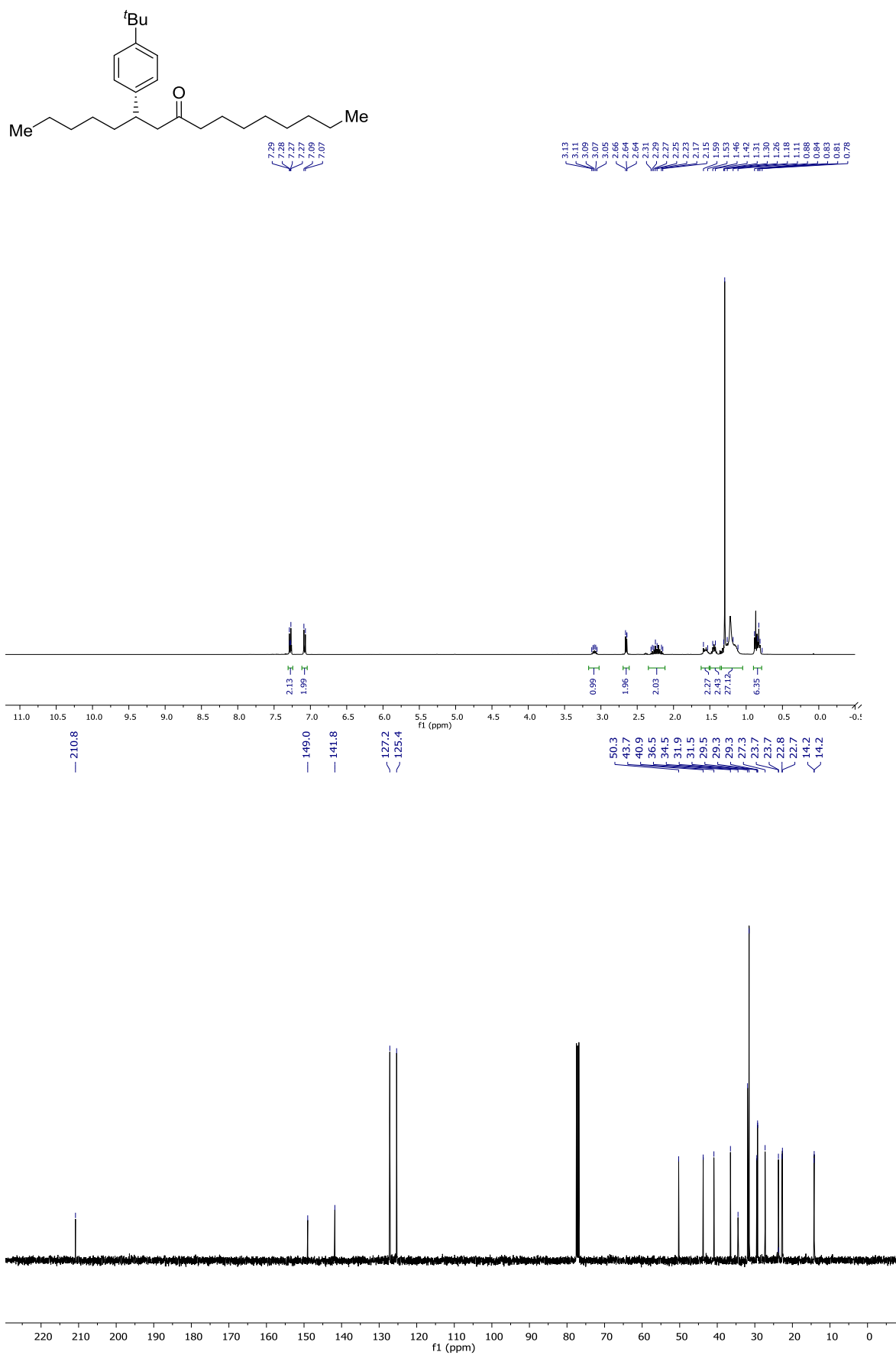
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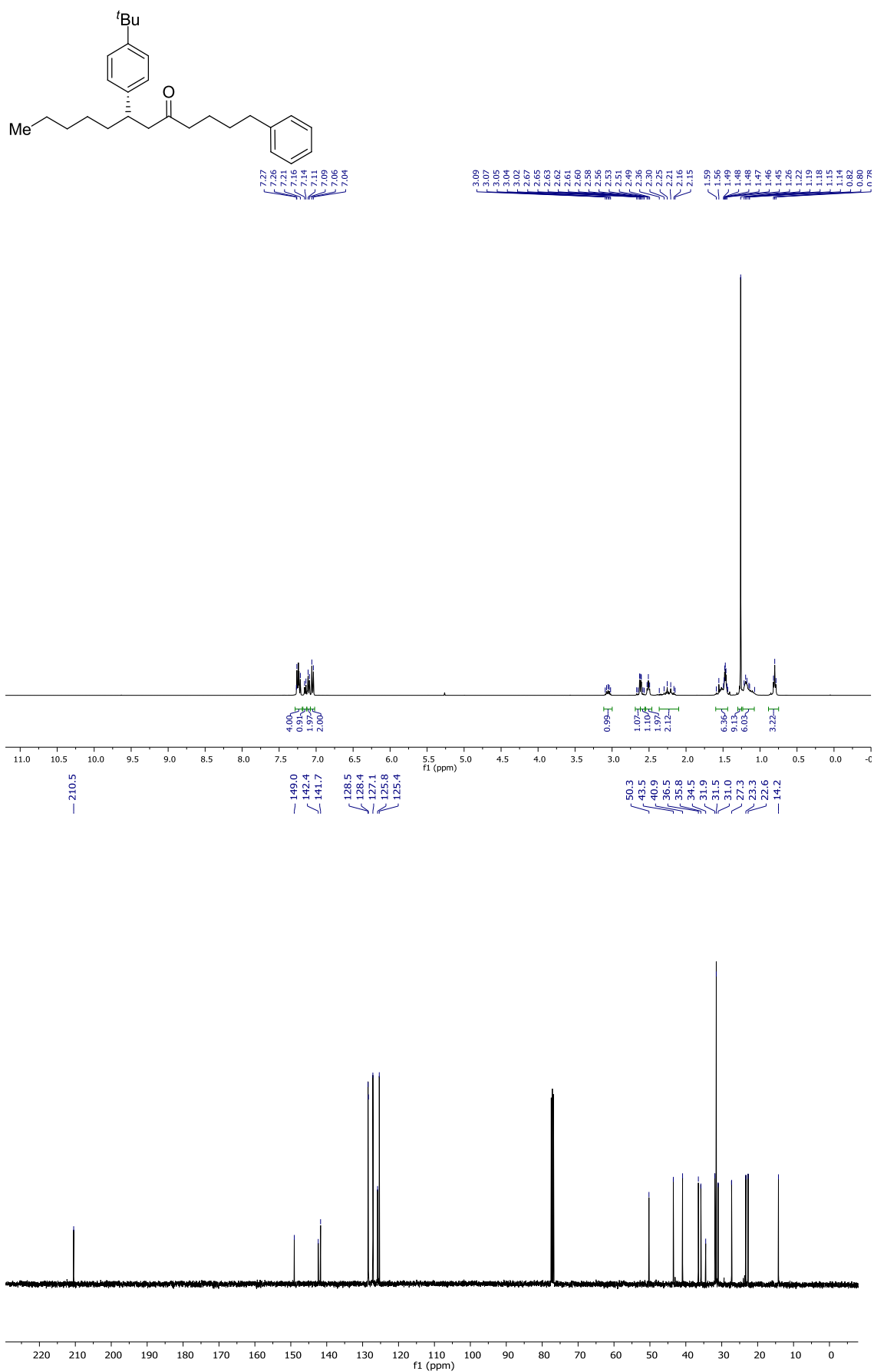
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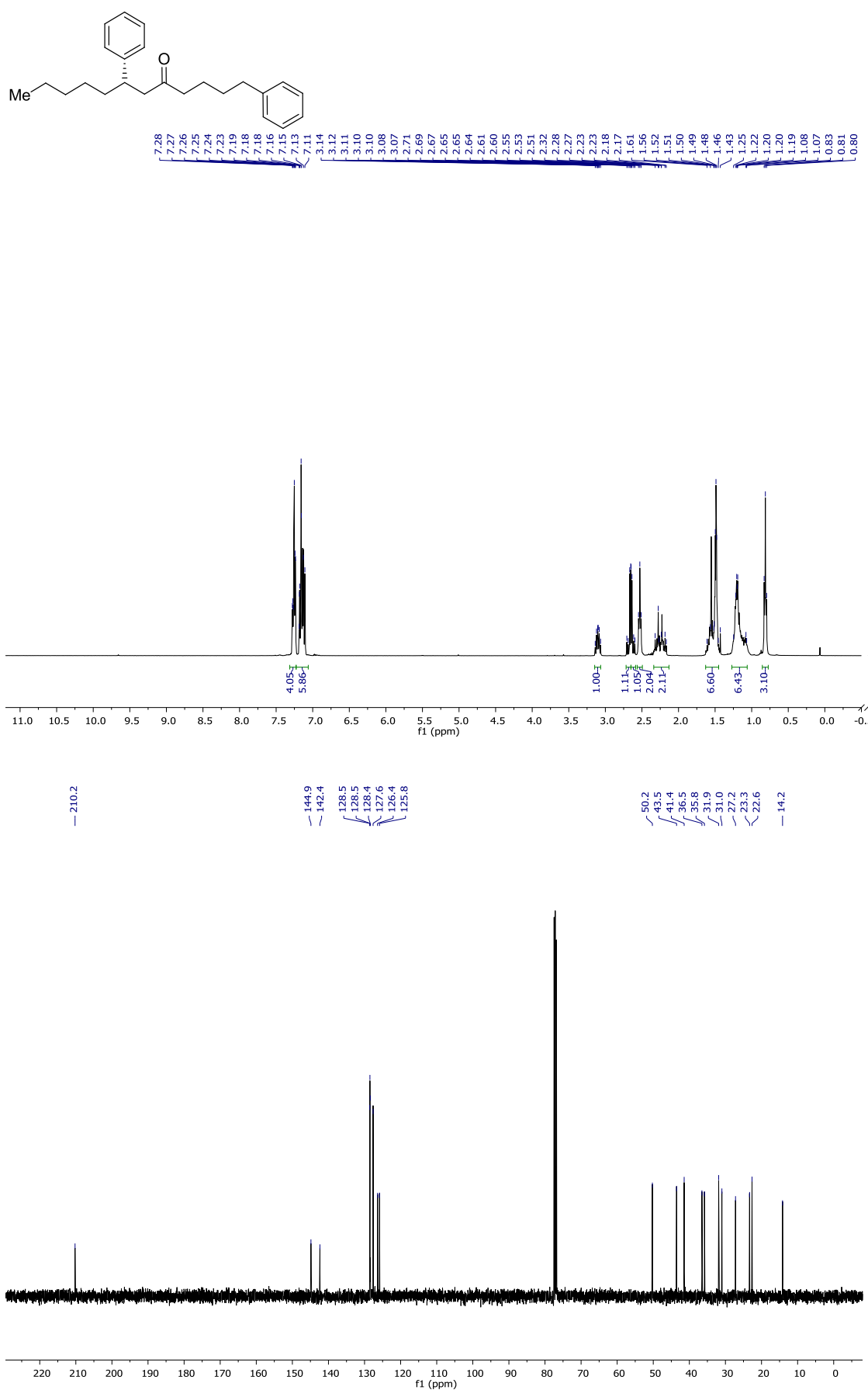


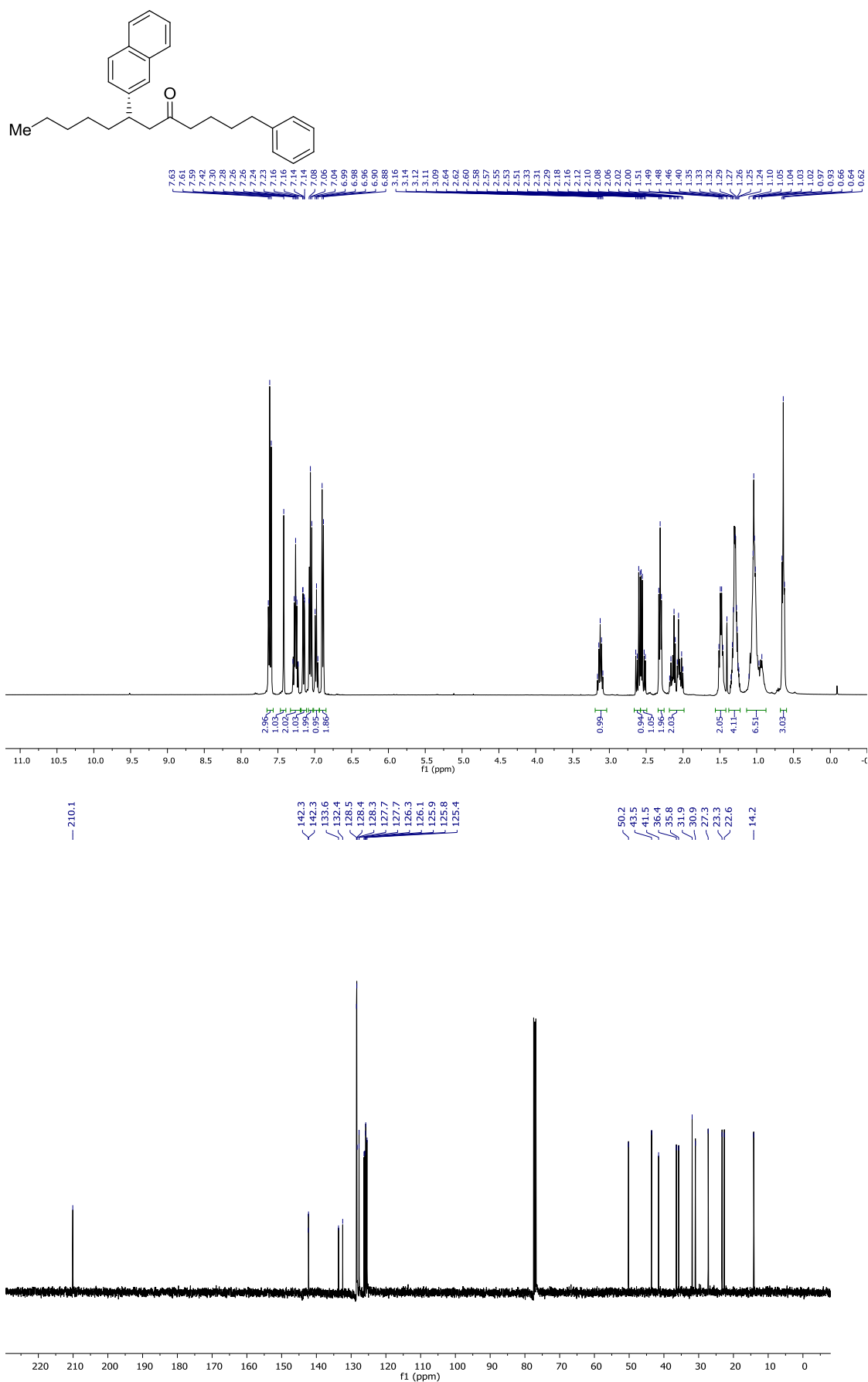
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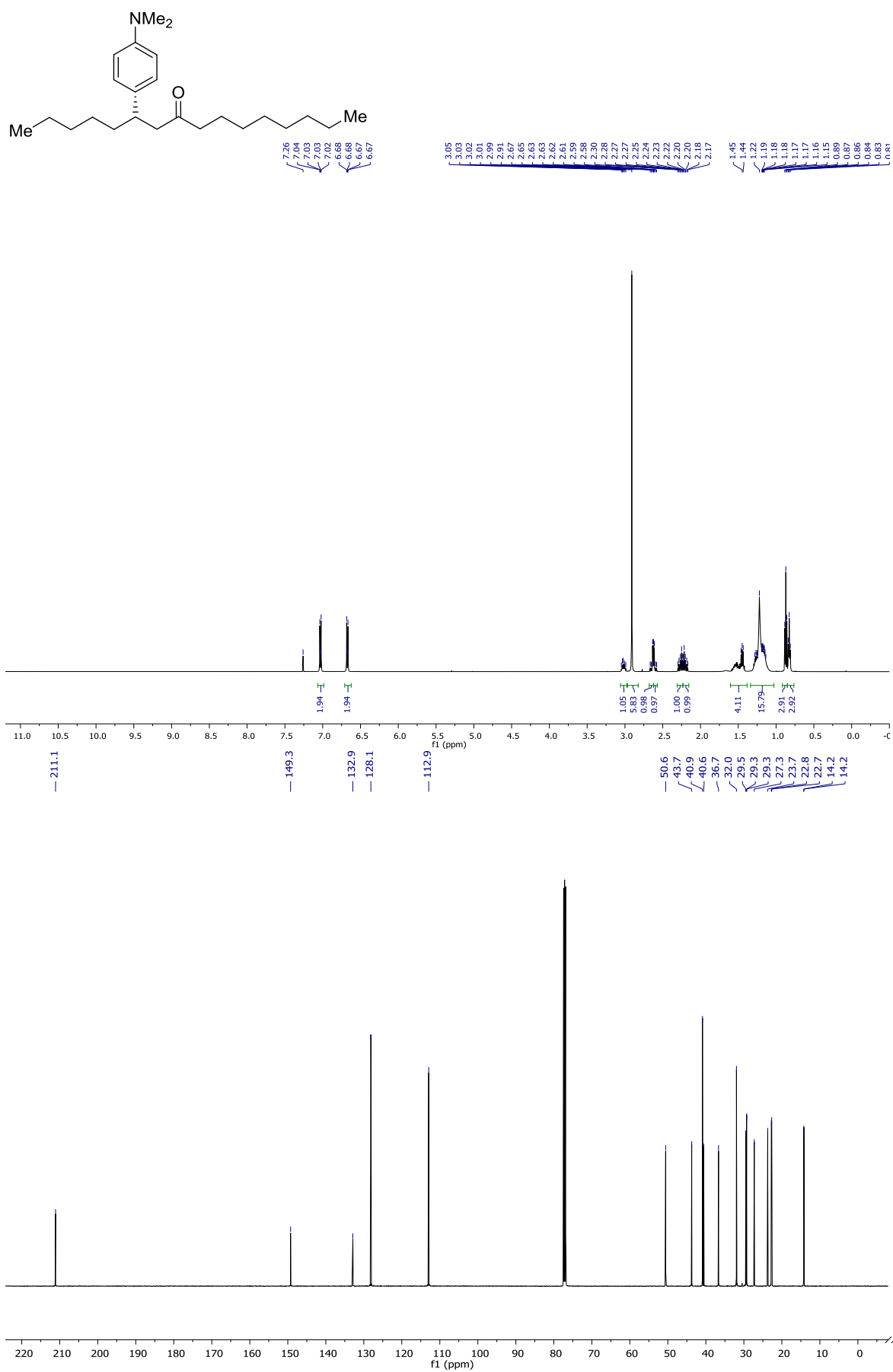
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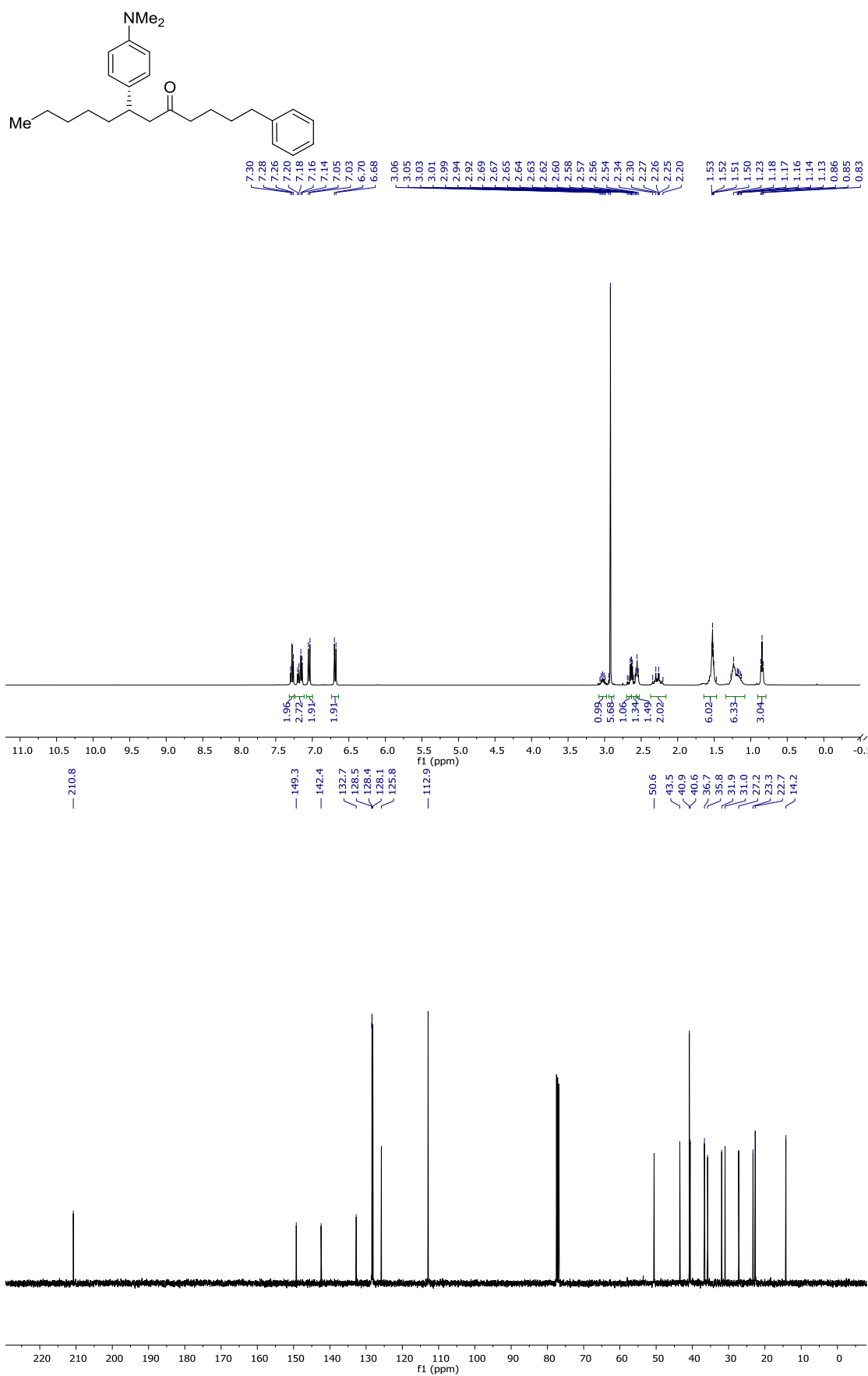
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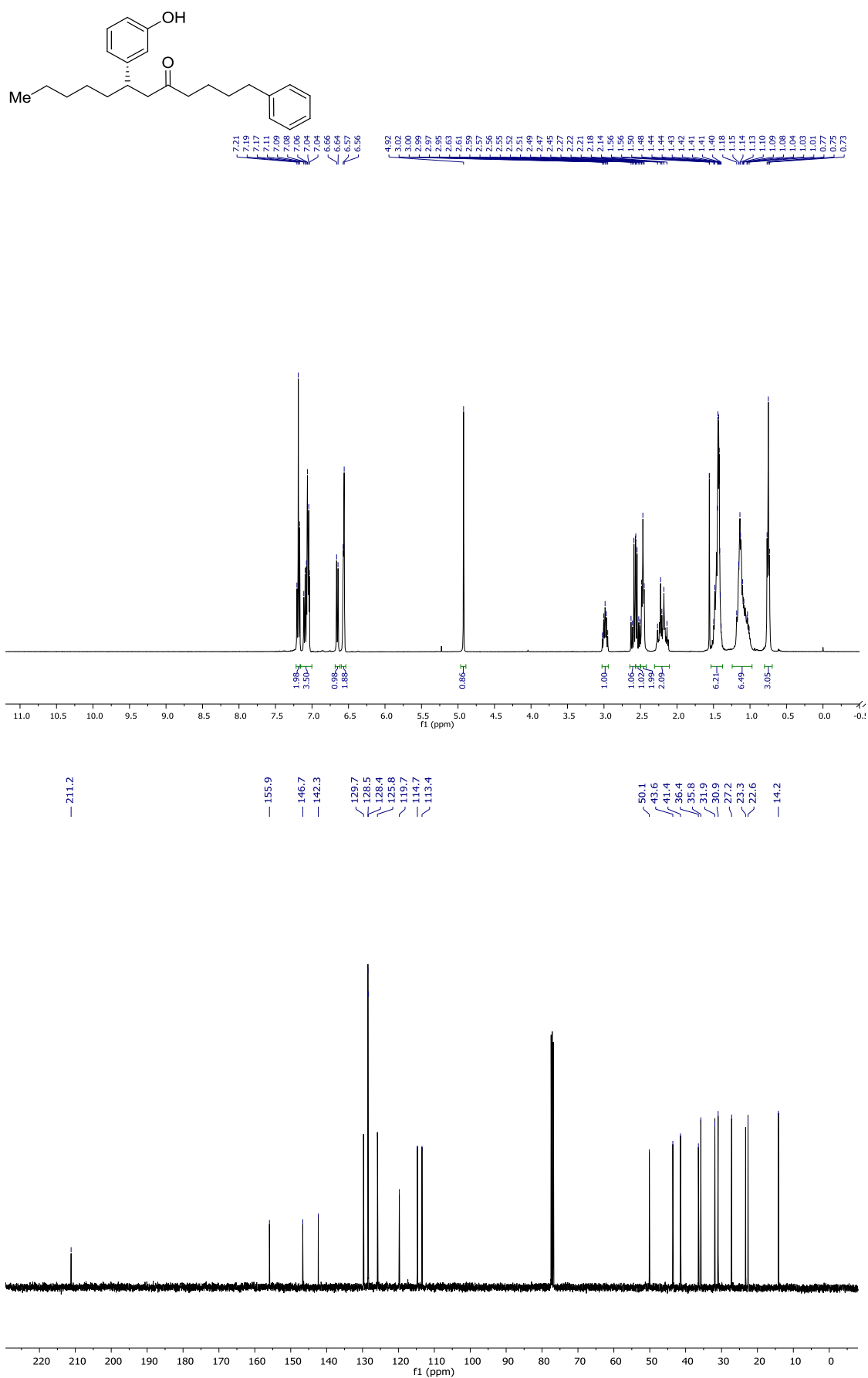
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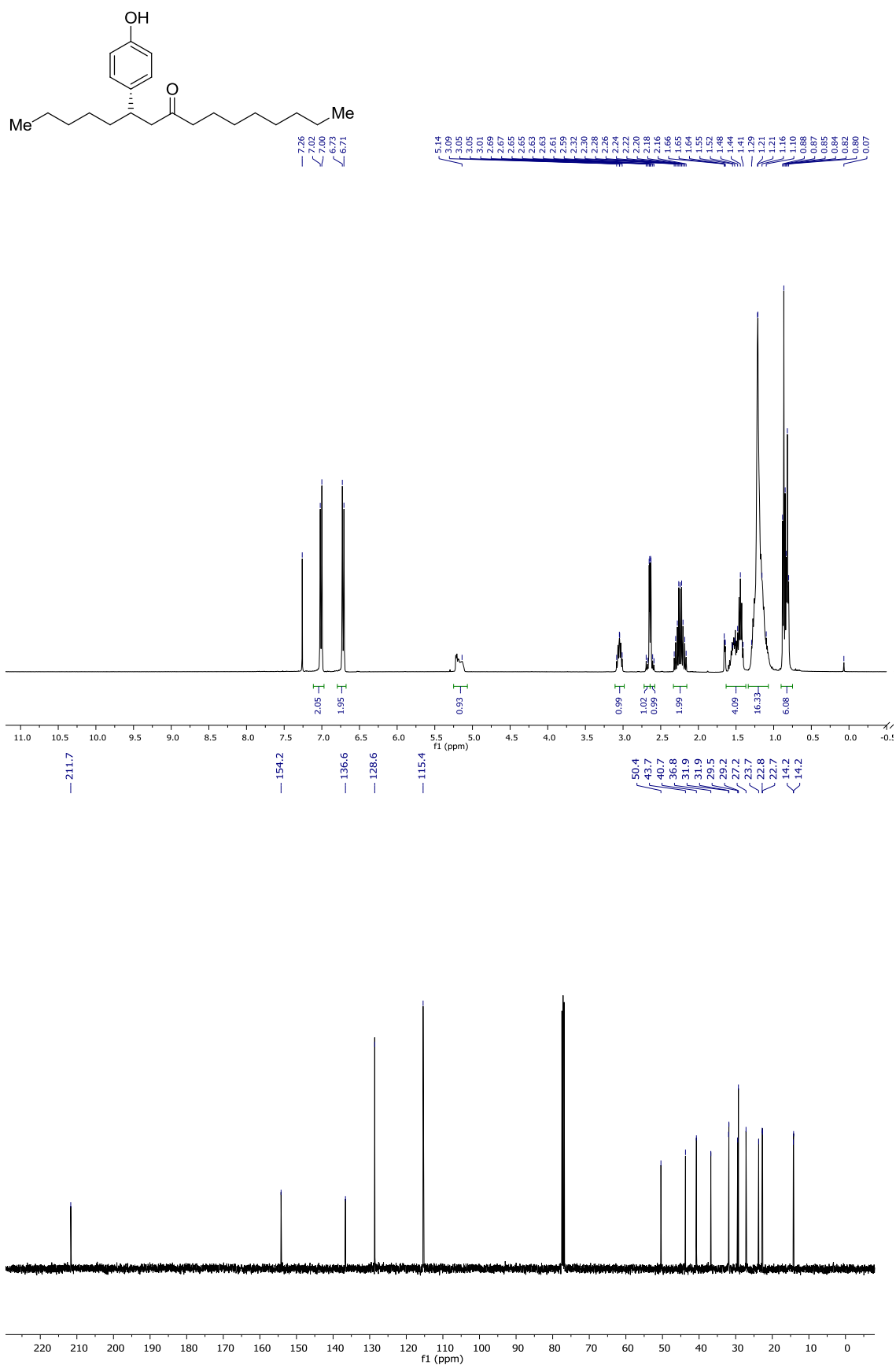
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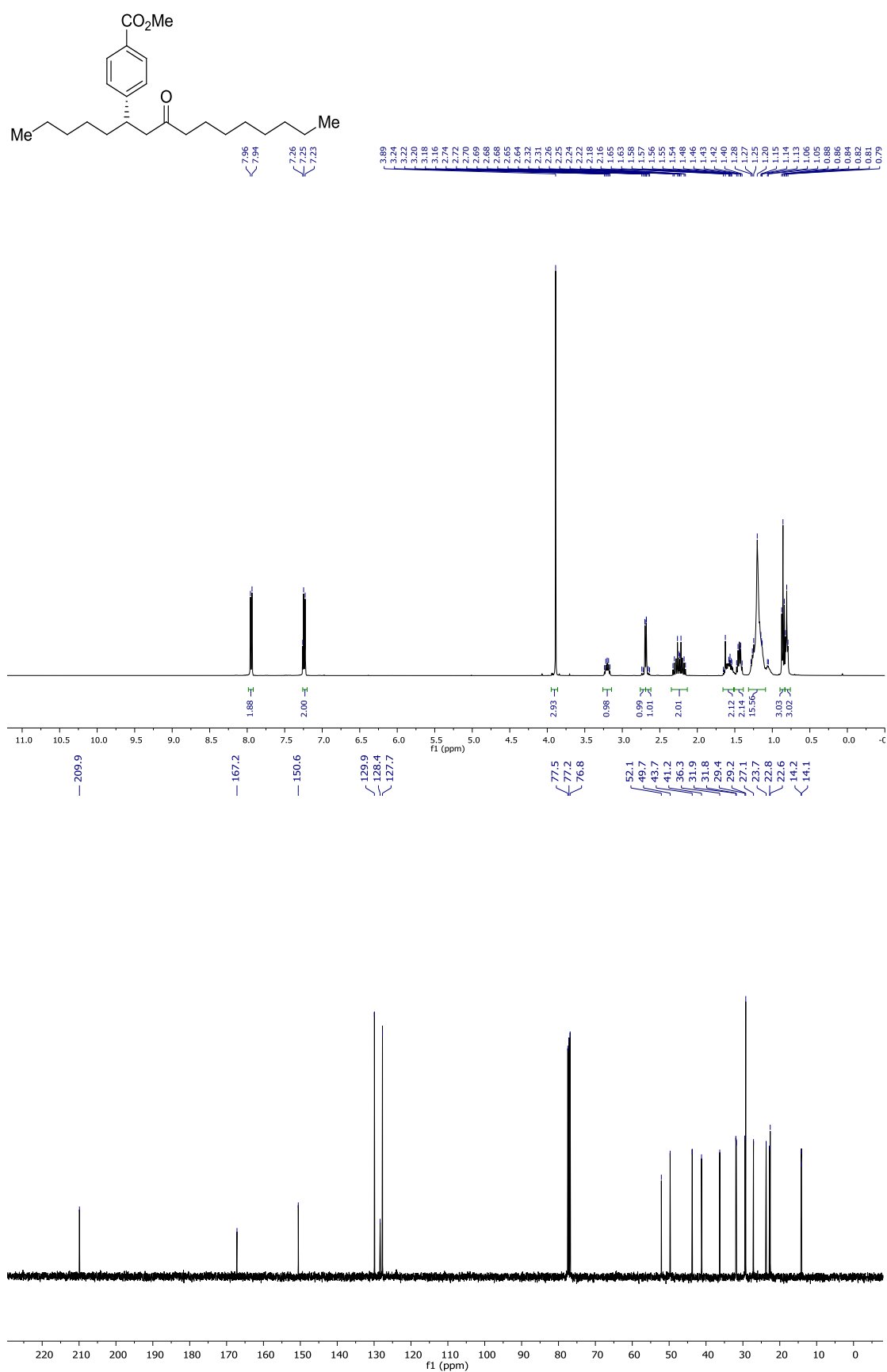
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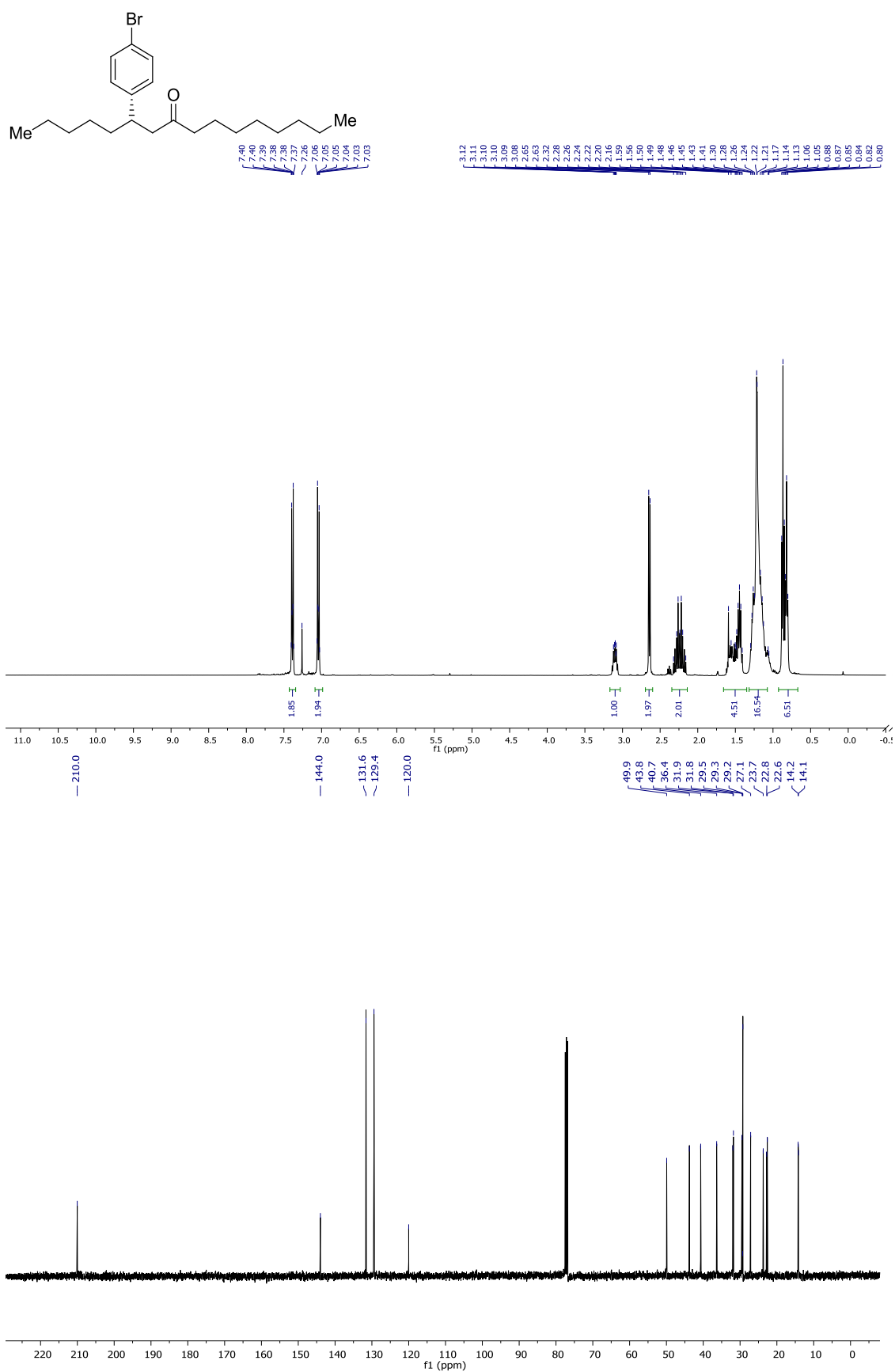


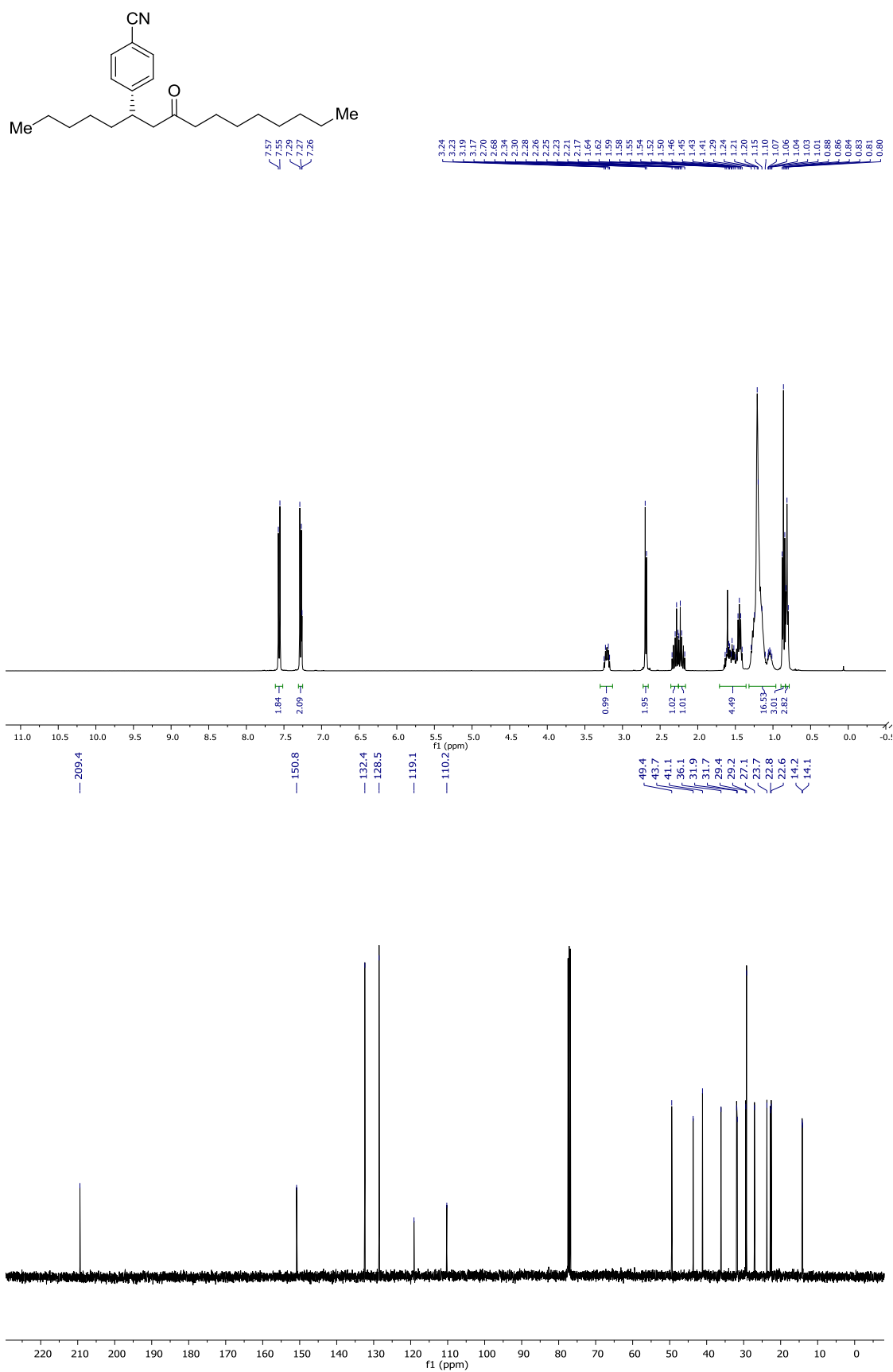
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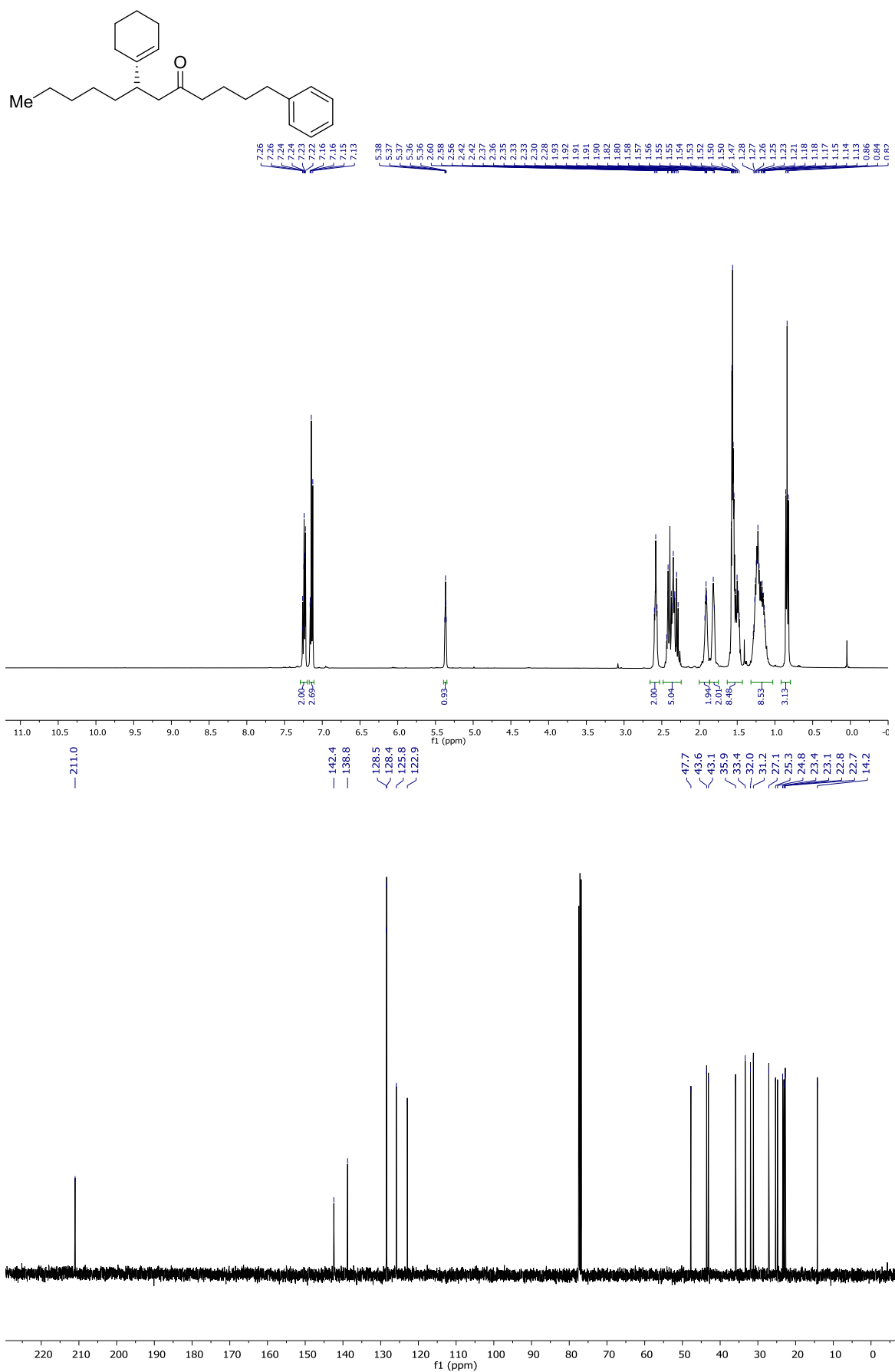
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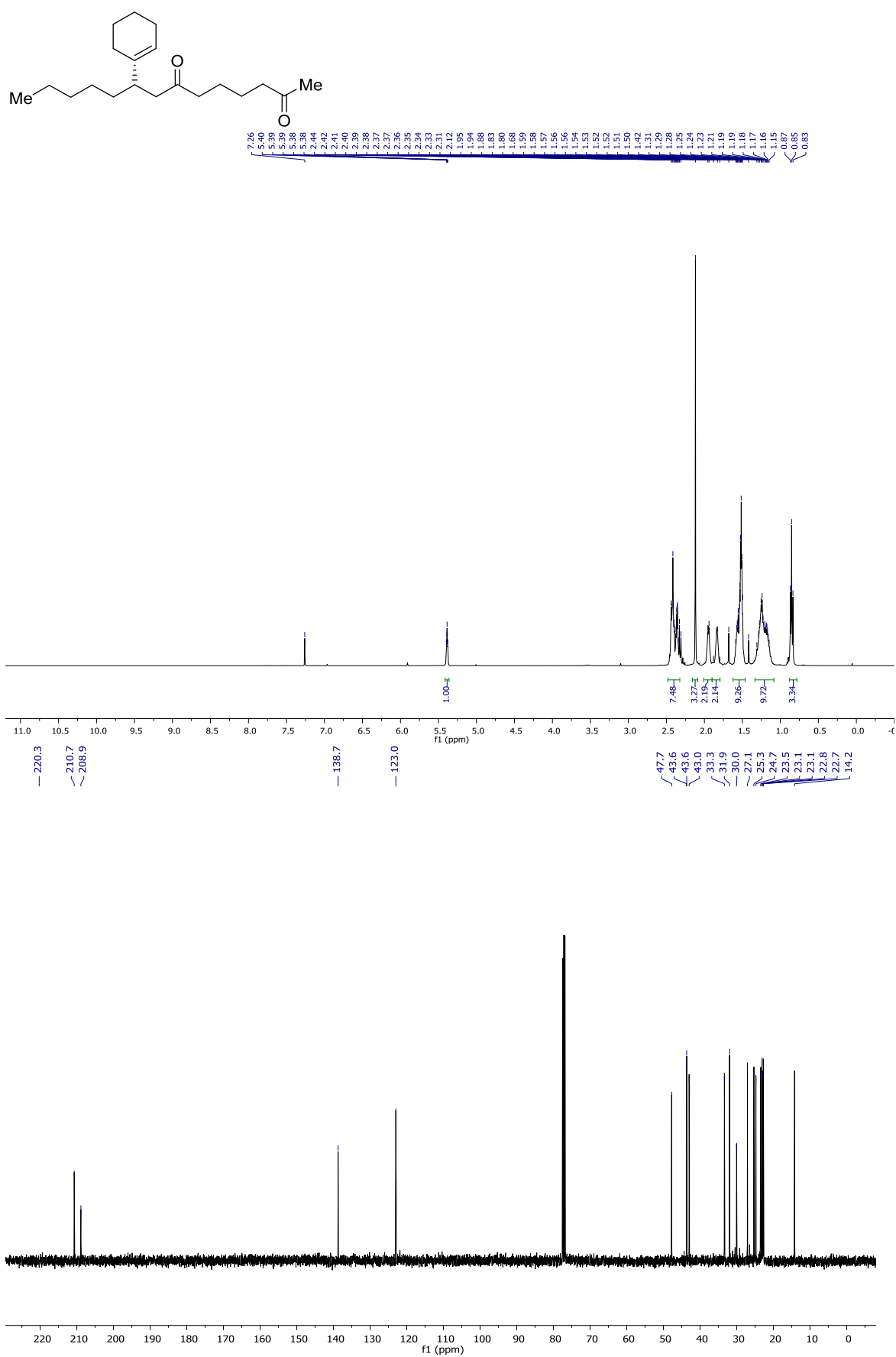
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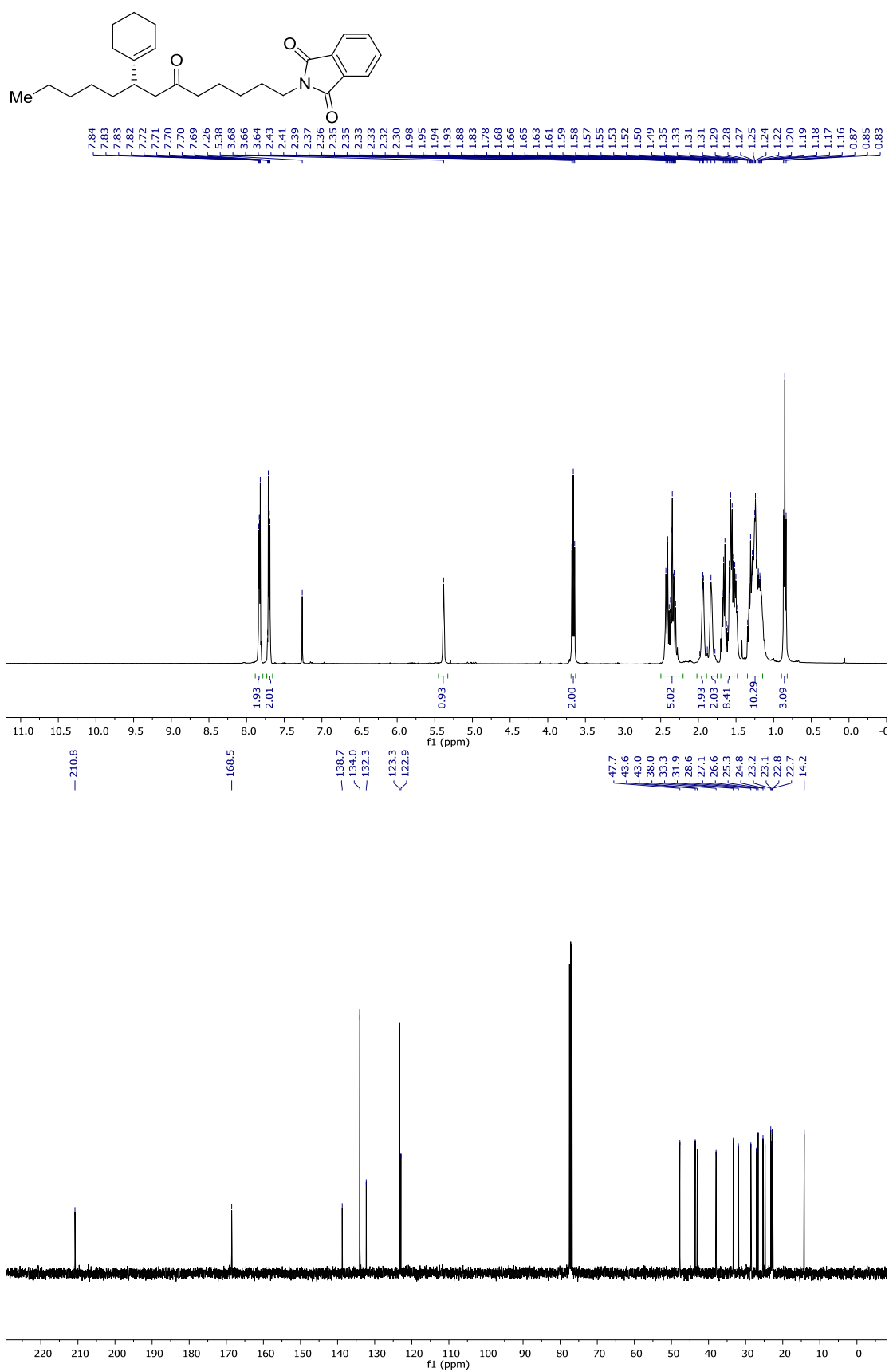
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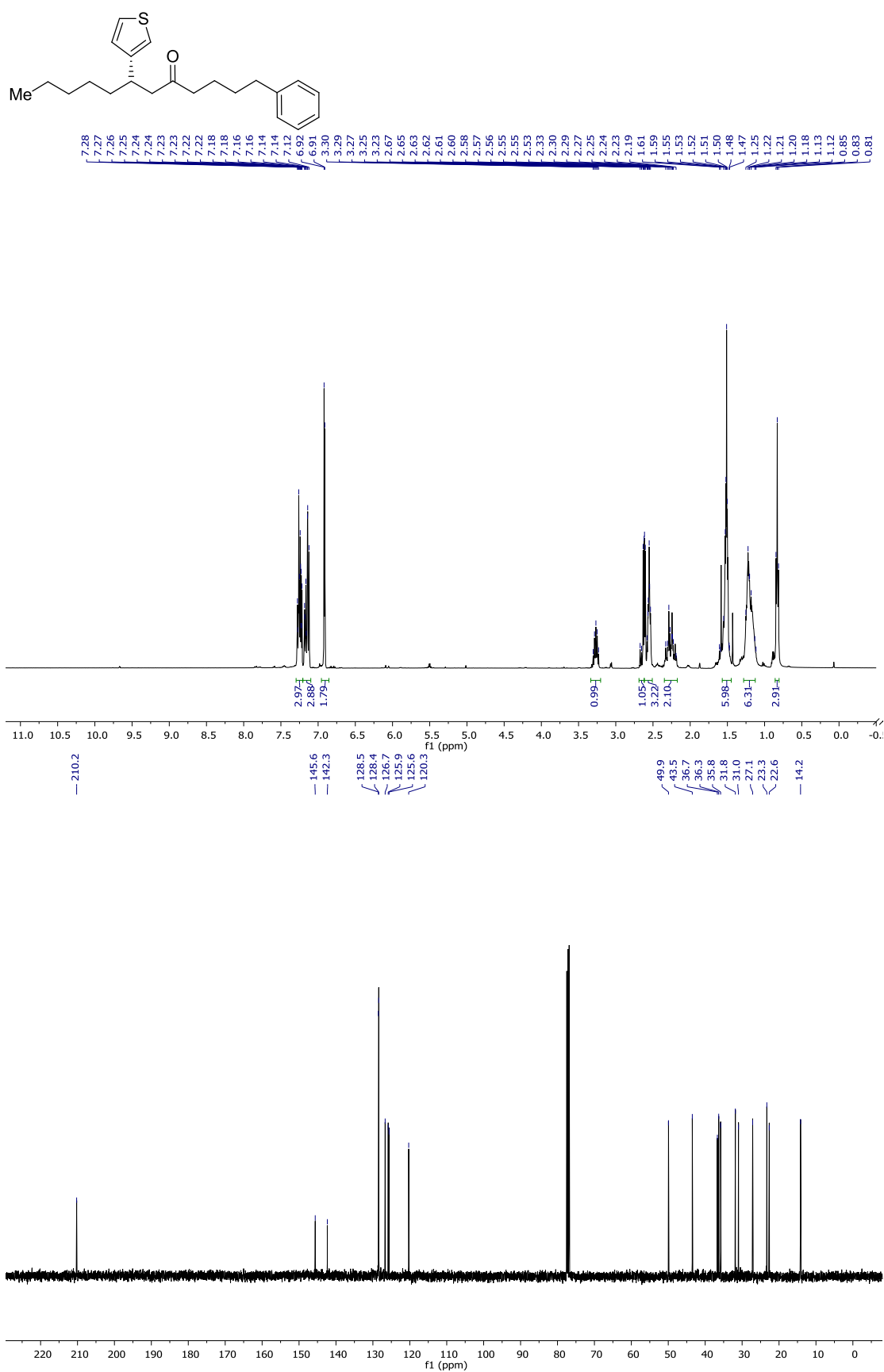
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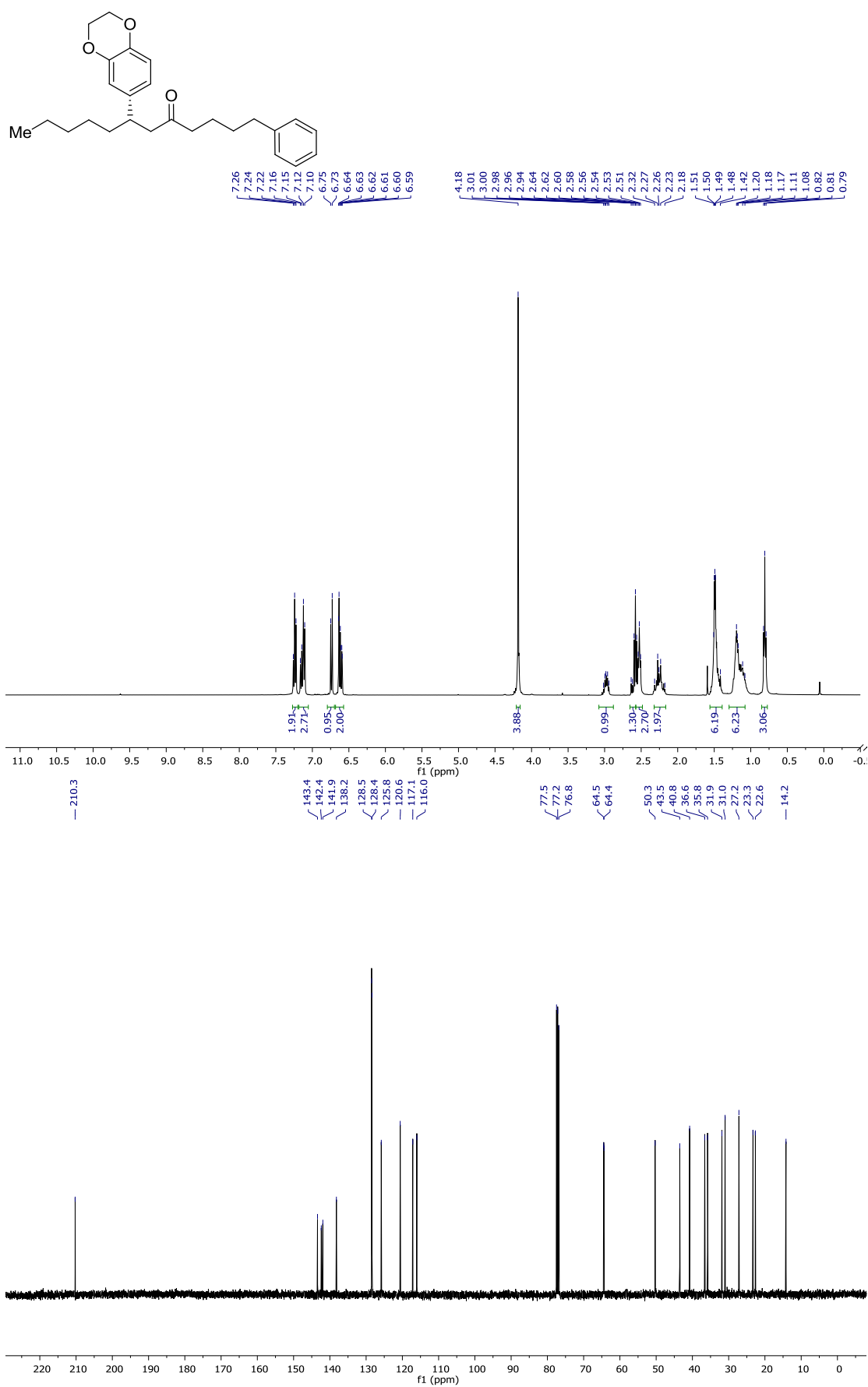
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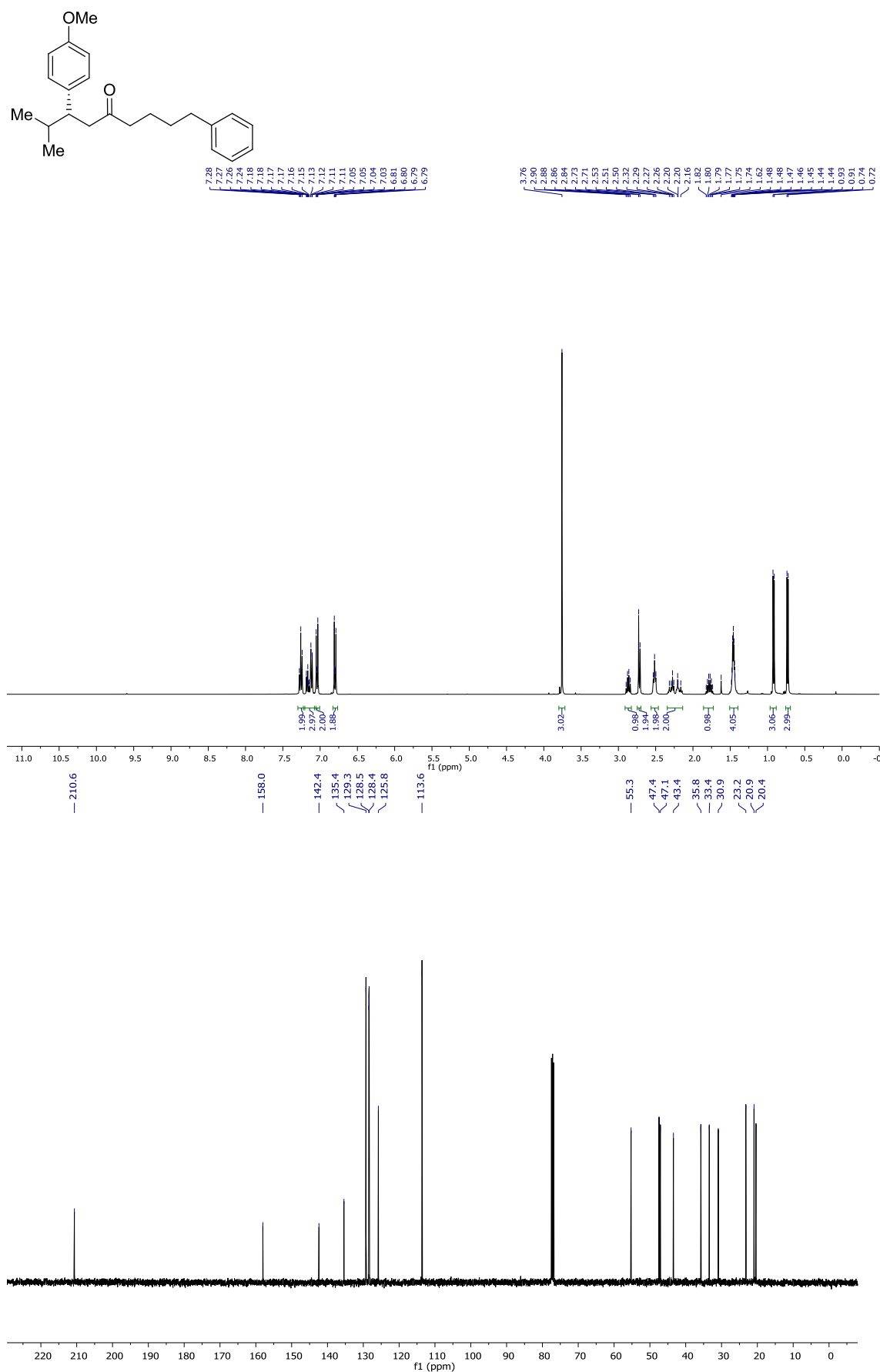
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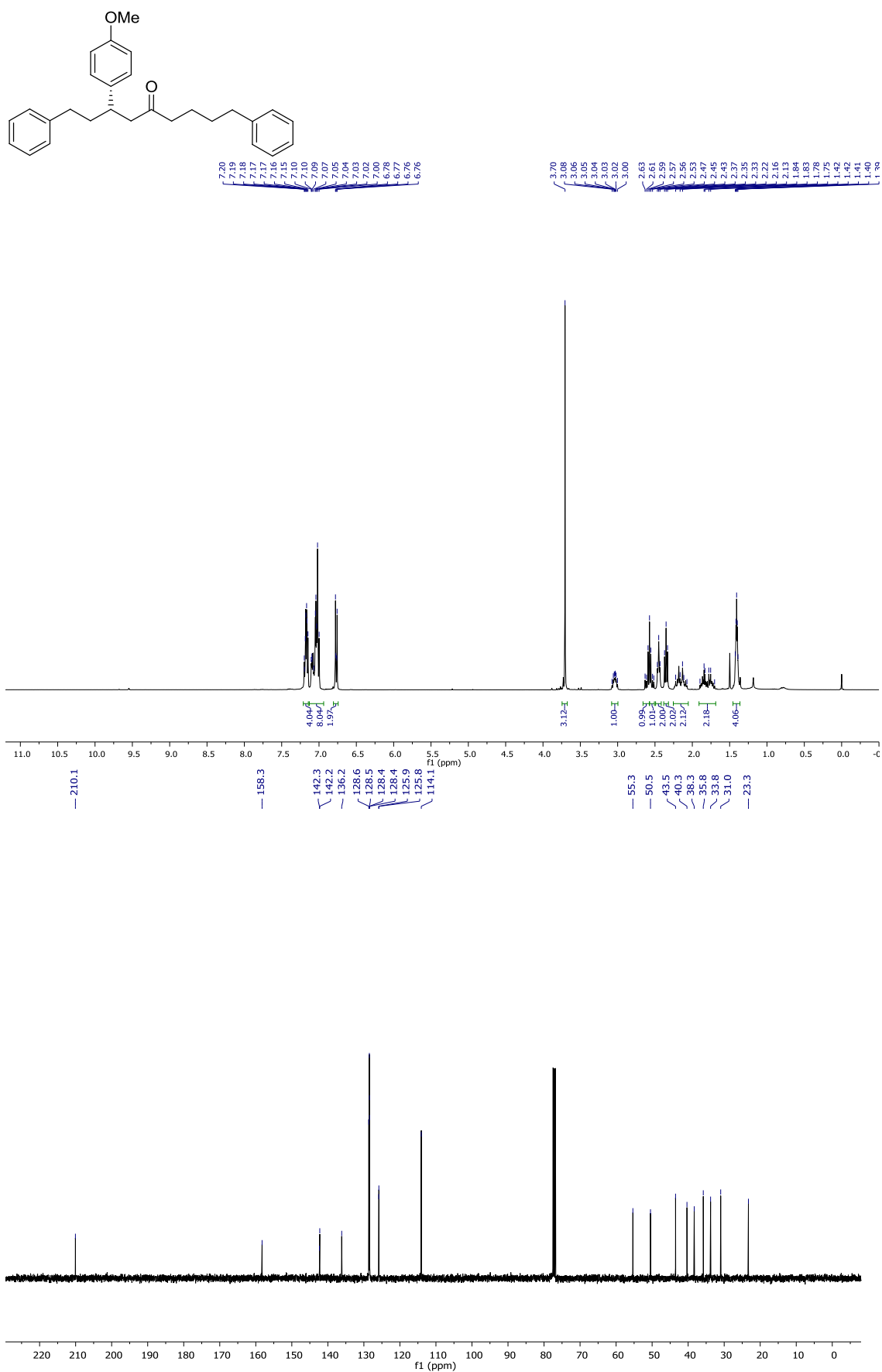
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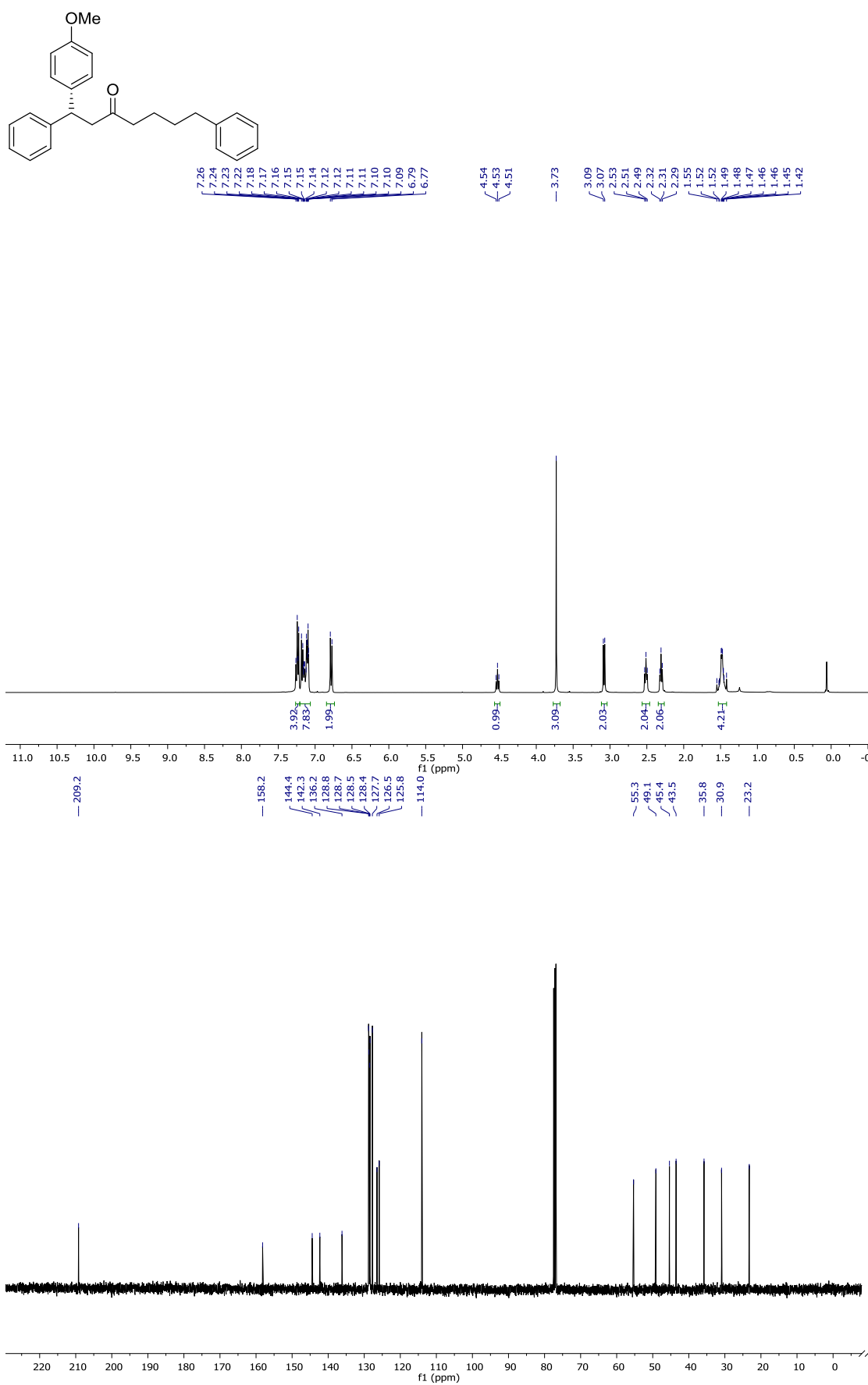
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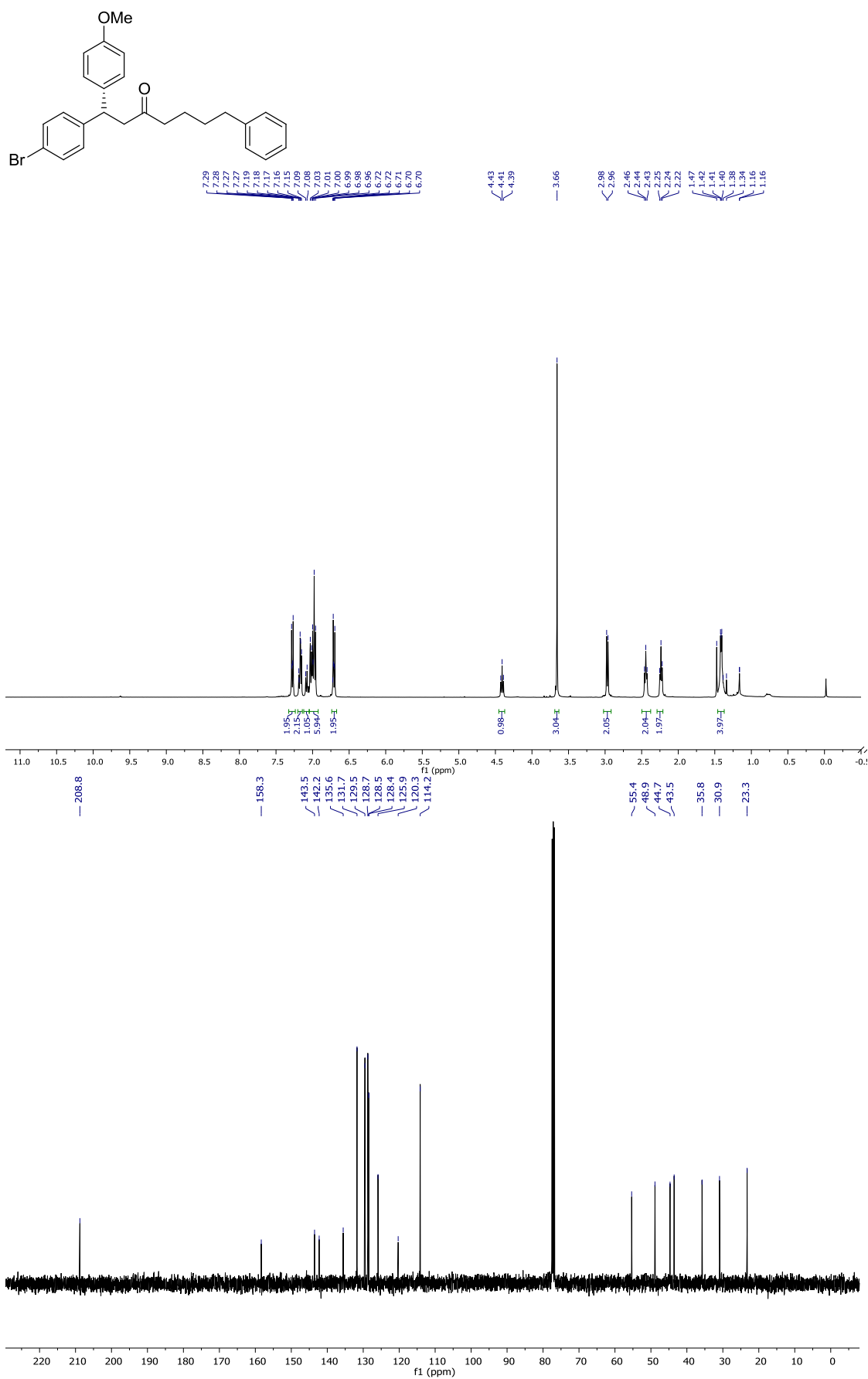
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(R)-7-(4-Methoxyphenyl)-8-methyl-1-phenylnonan-5-one 12ae

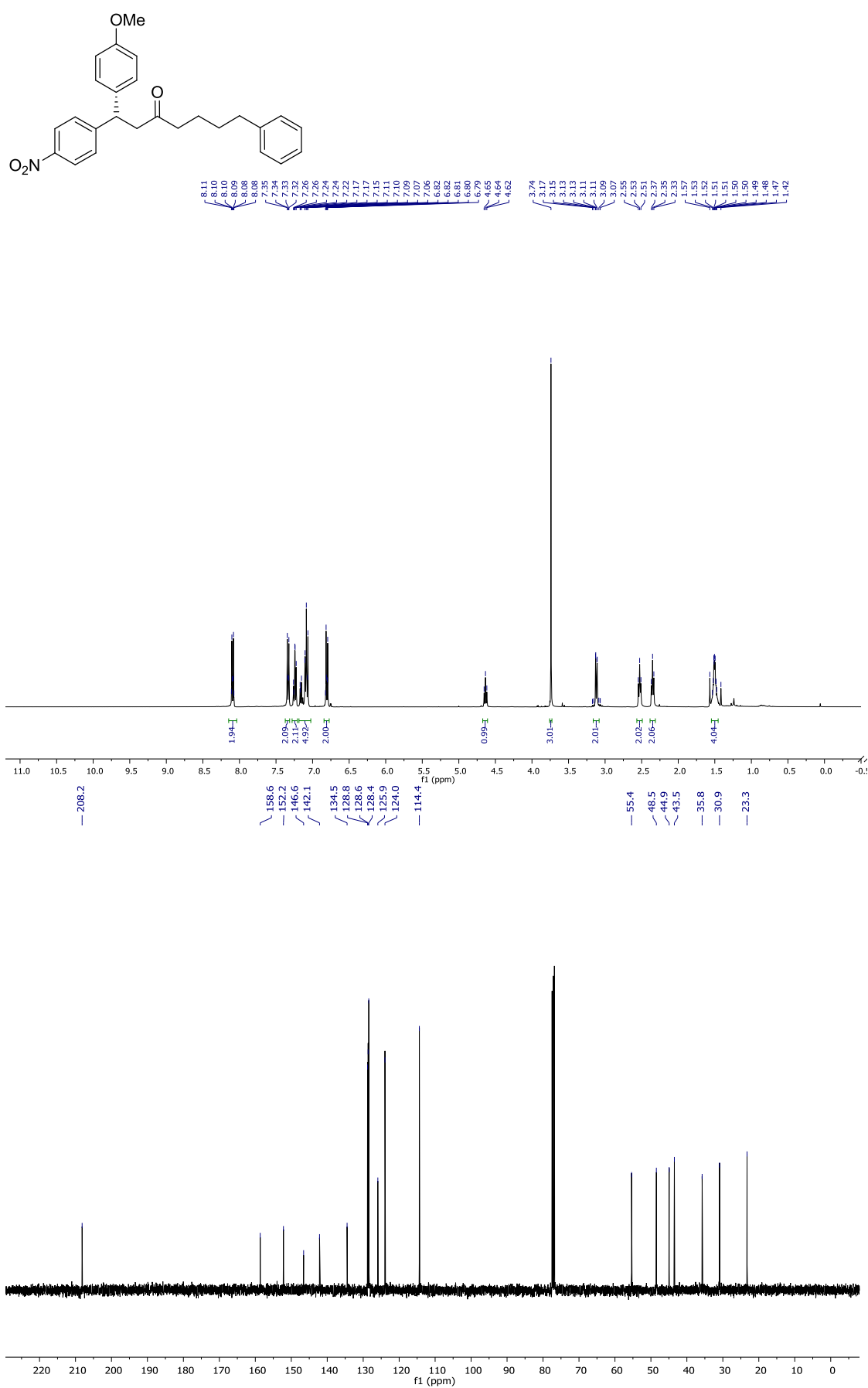


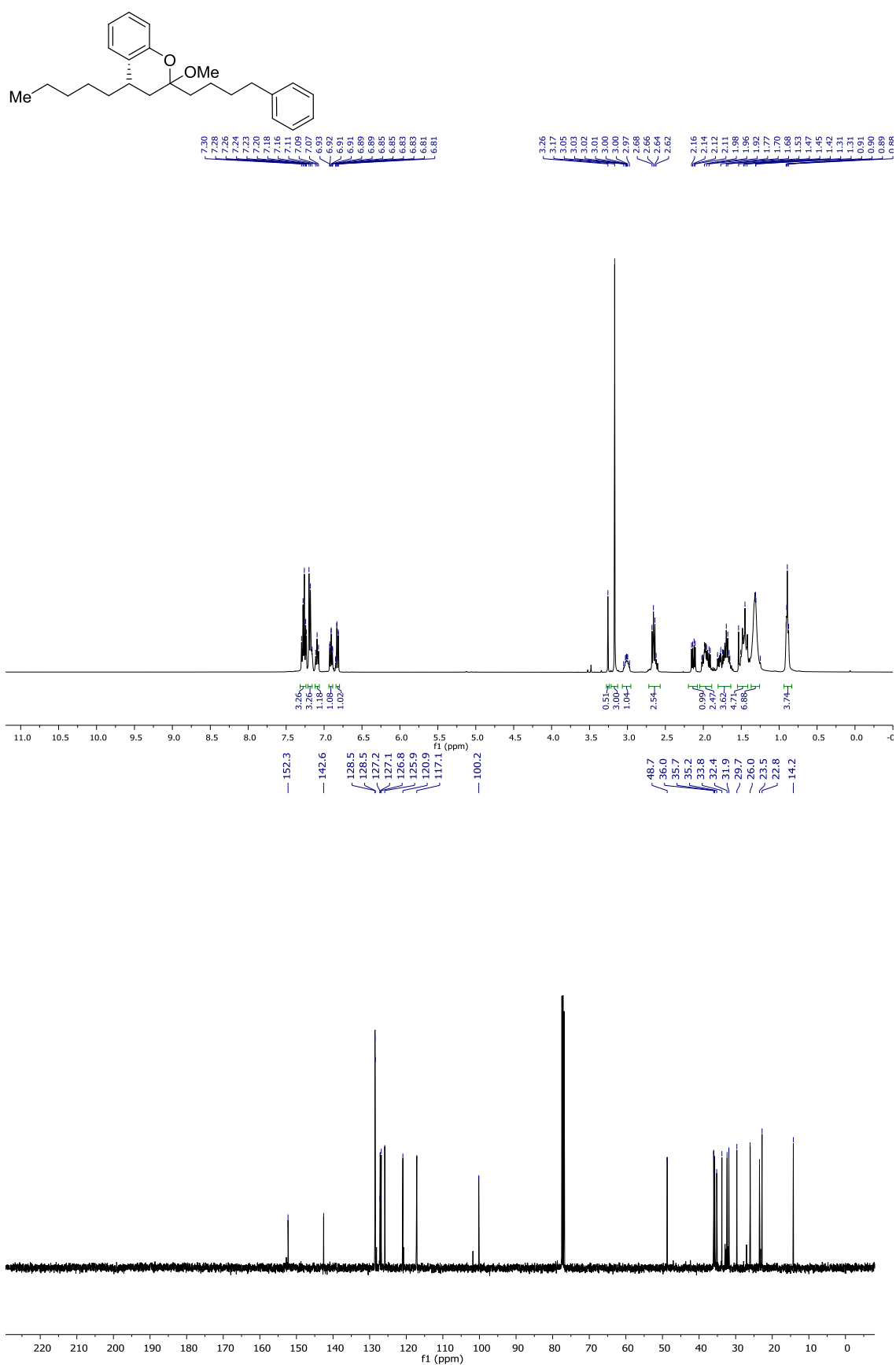
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(R)-1-(4-Methoxyphenyl)-1,7-diphenylheptan-3-one 12aj

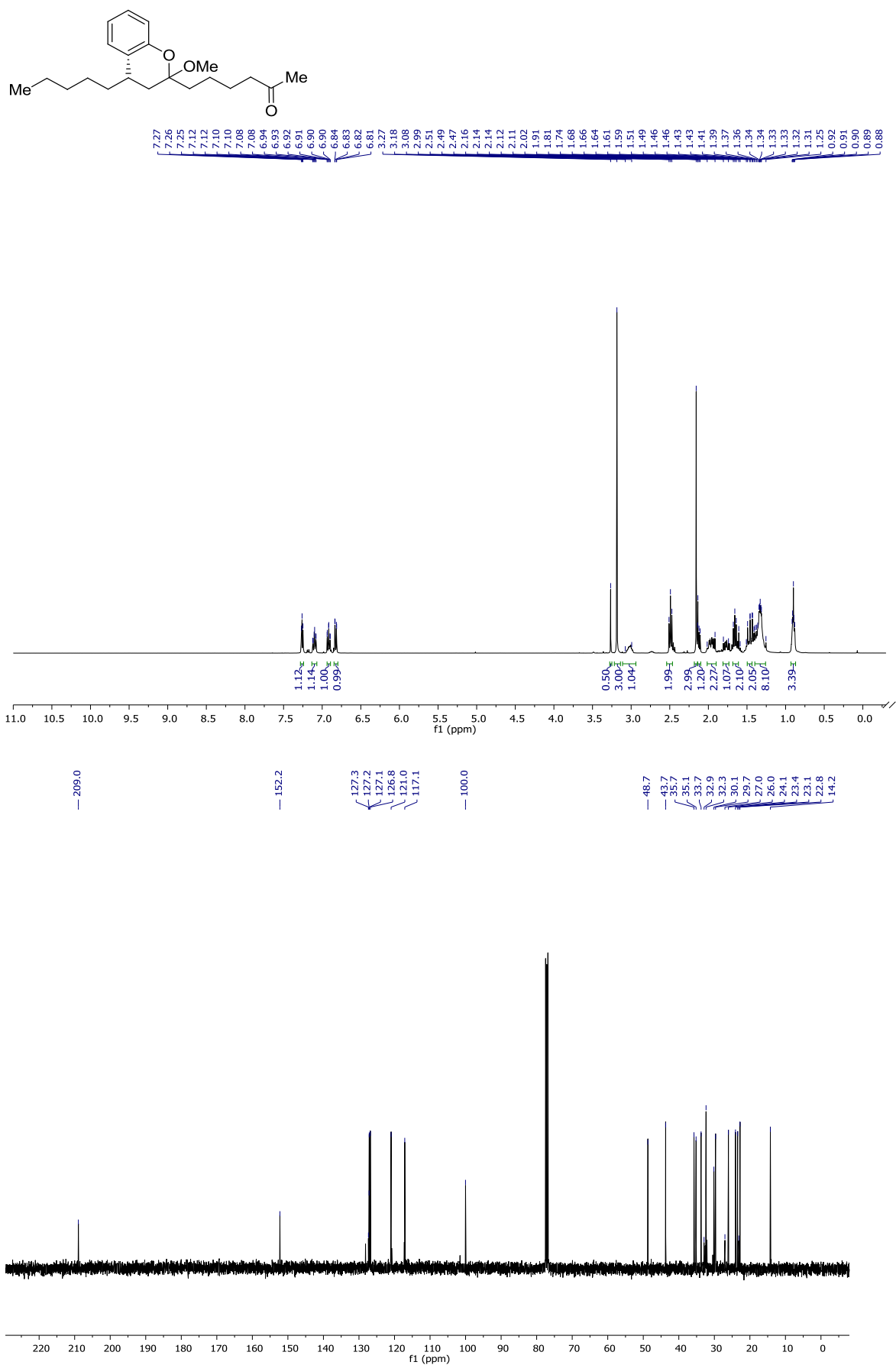
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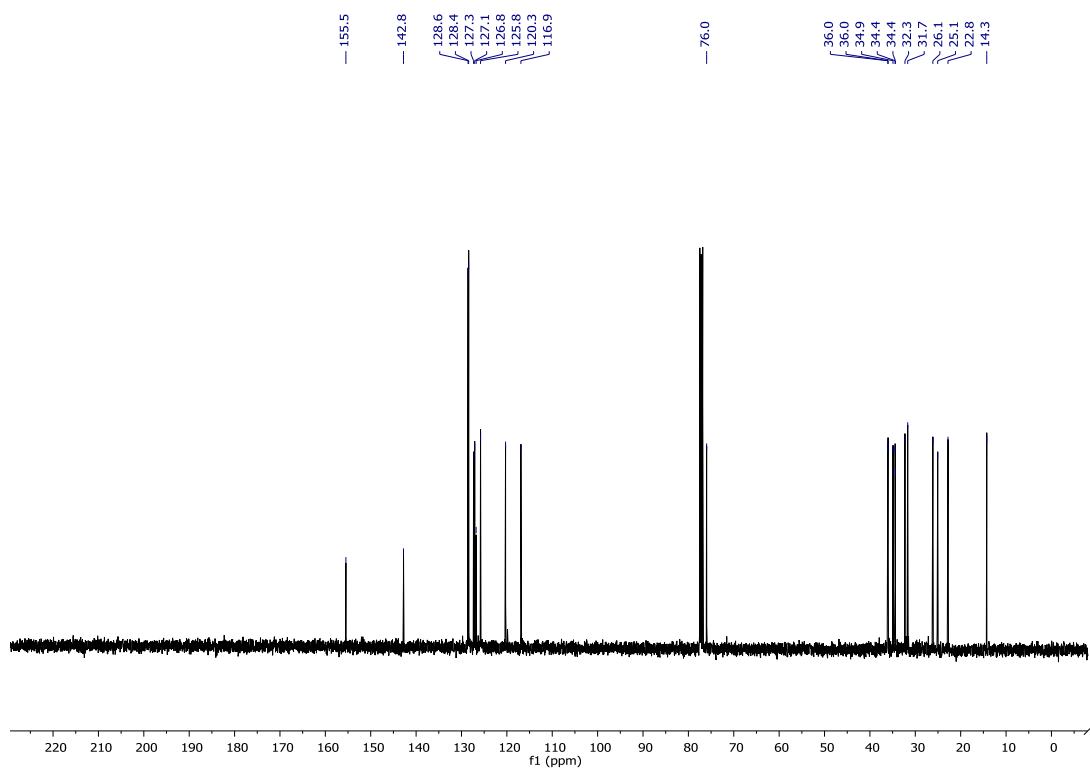
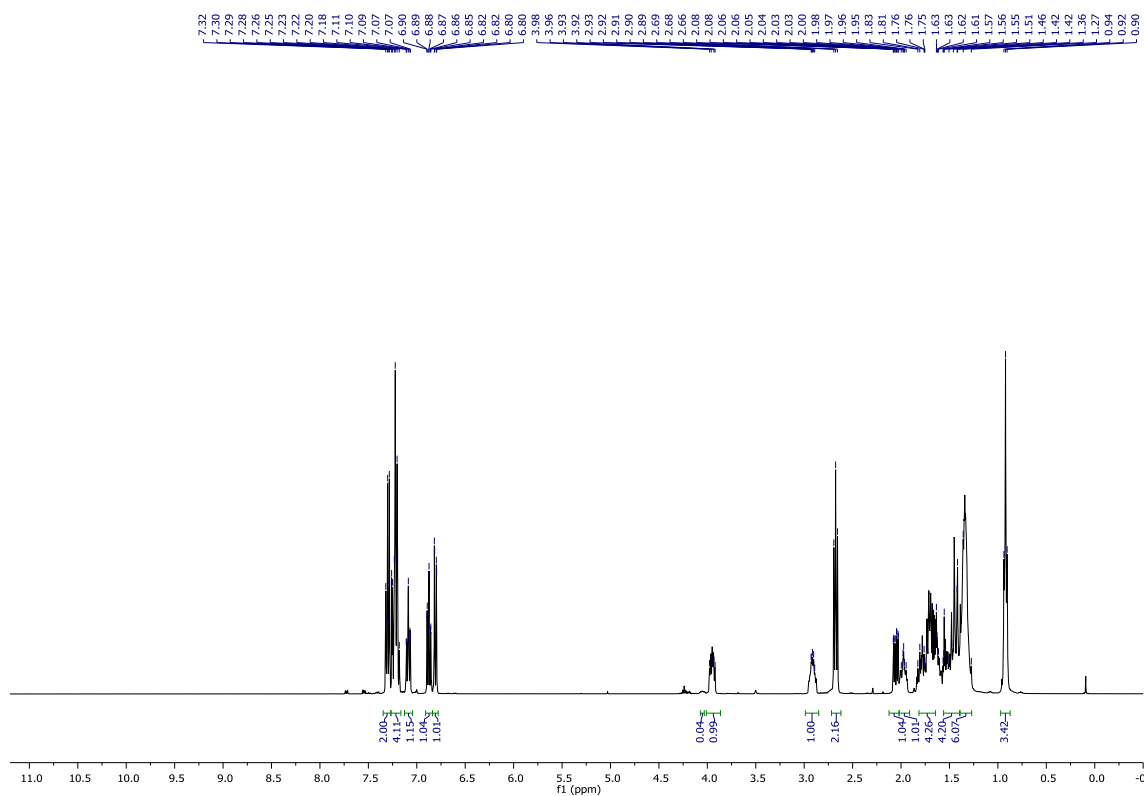
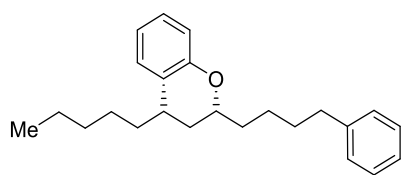
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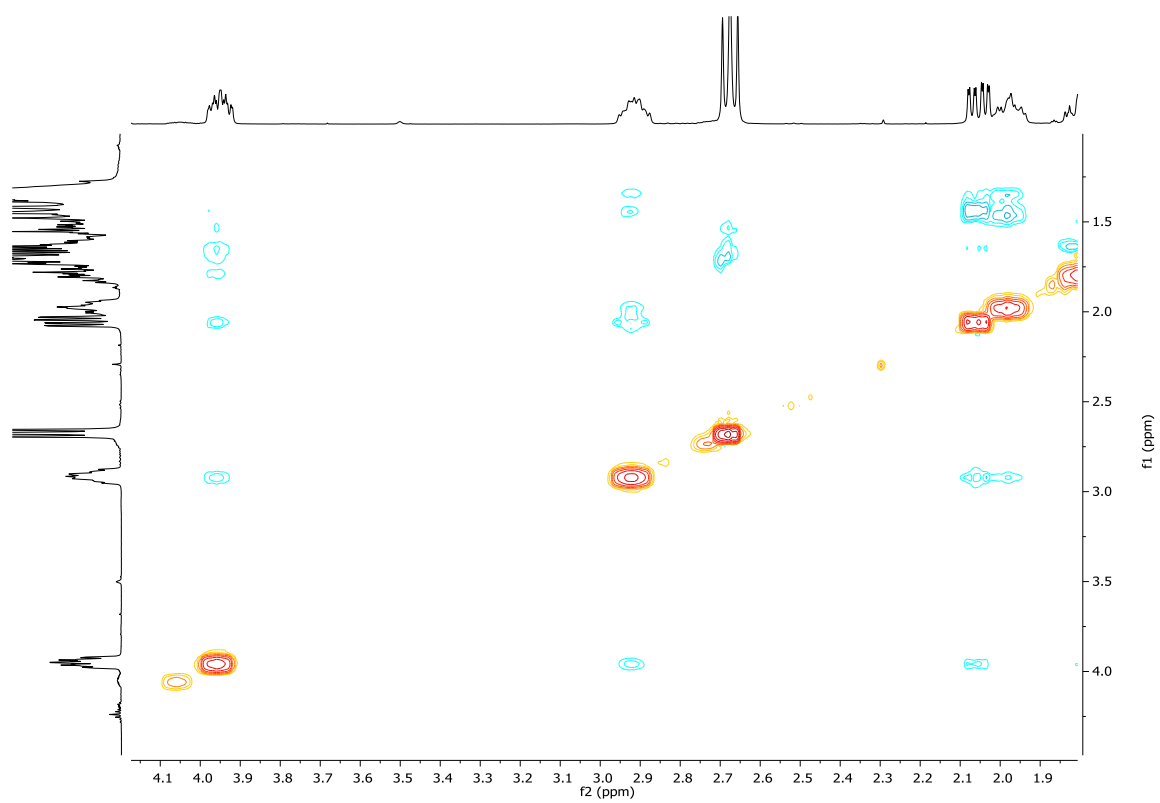


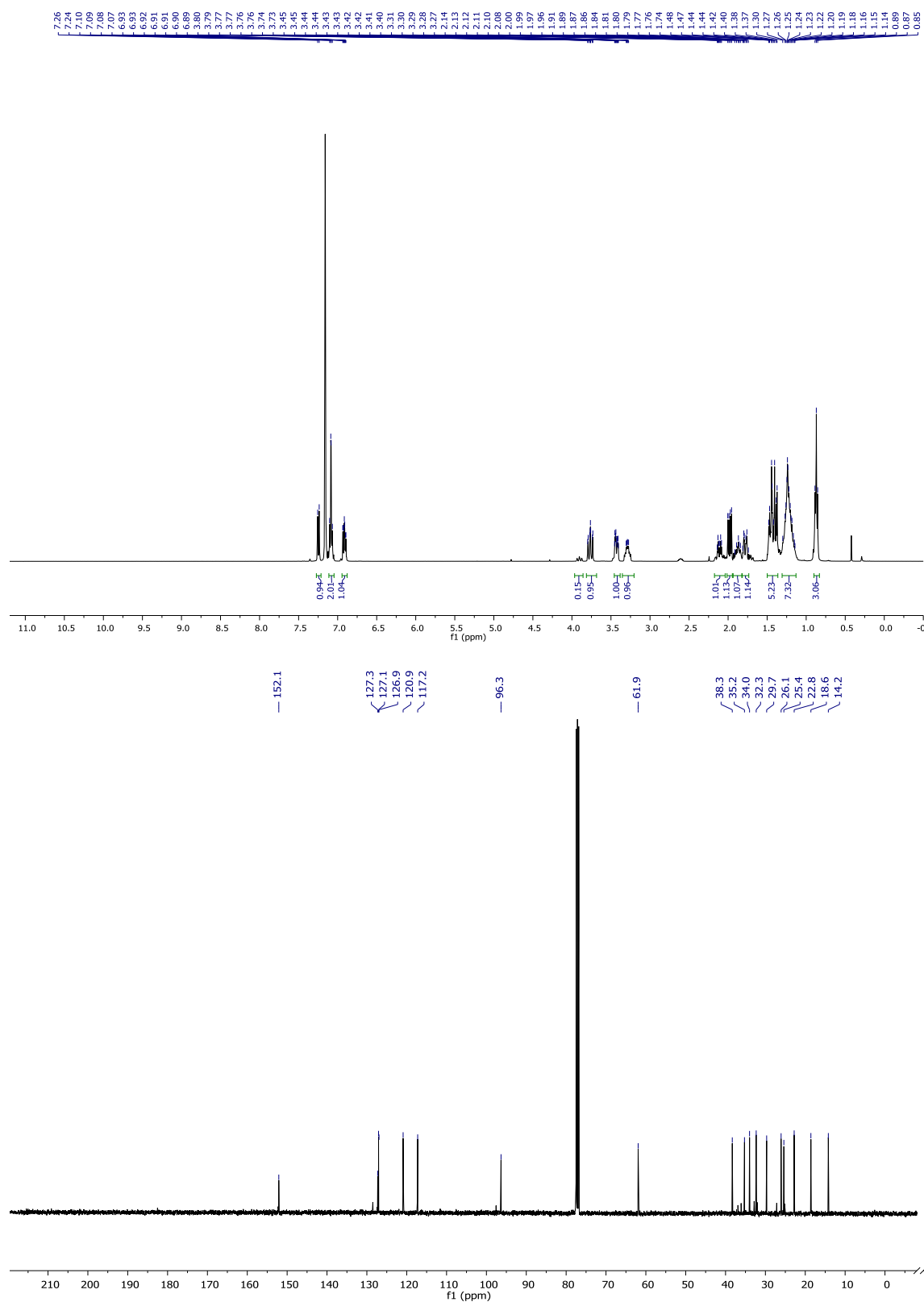
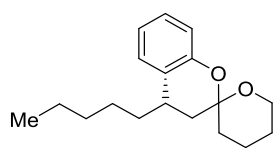
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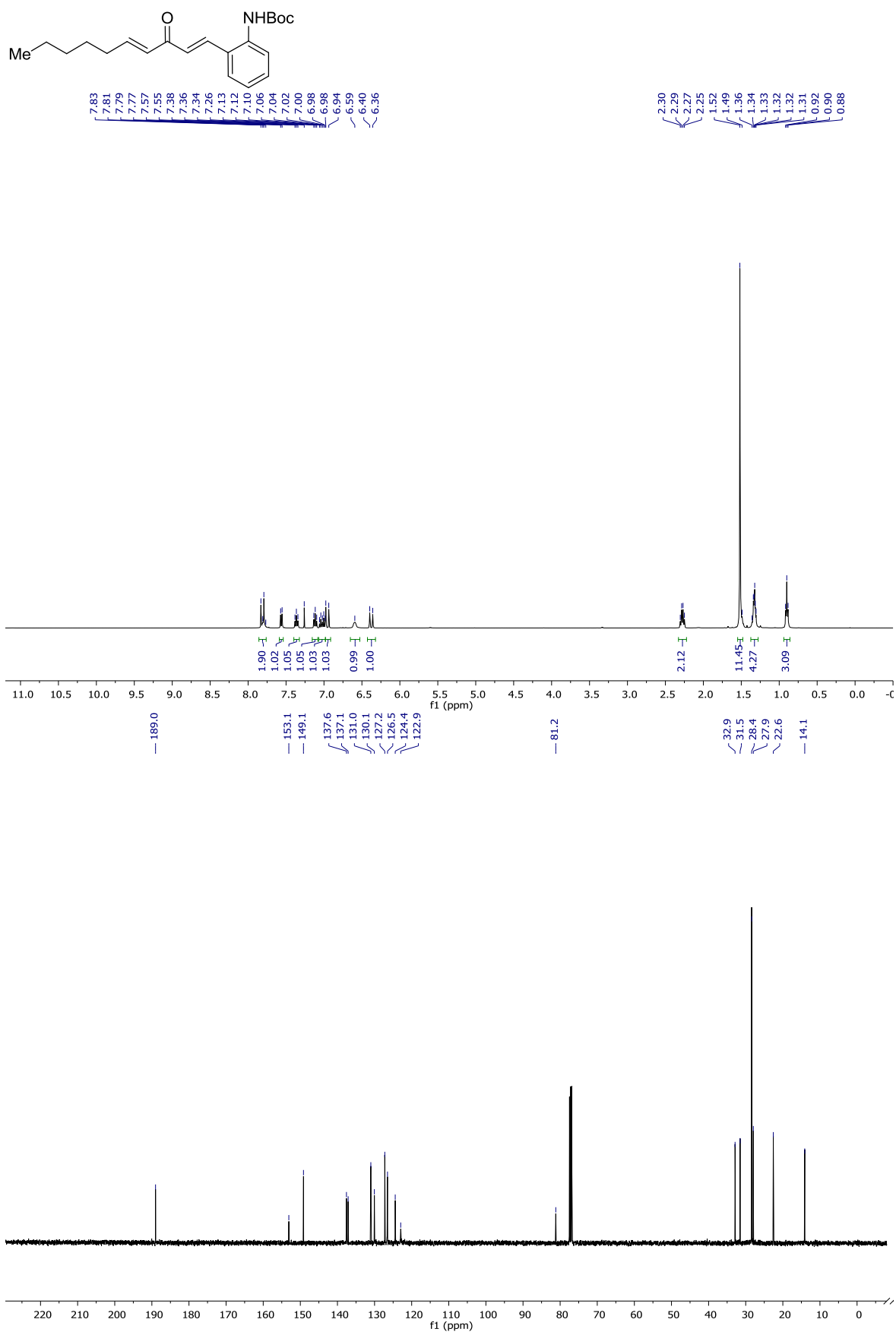
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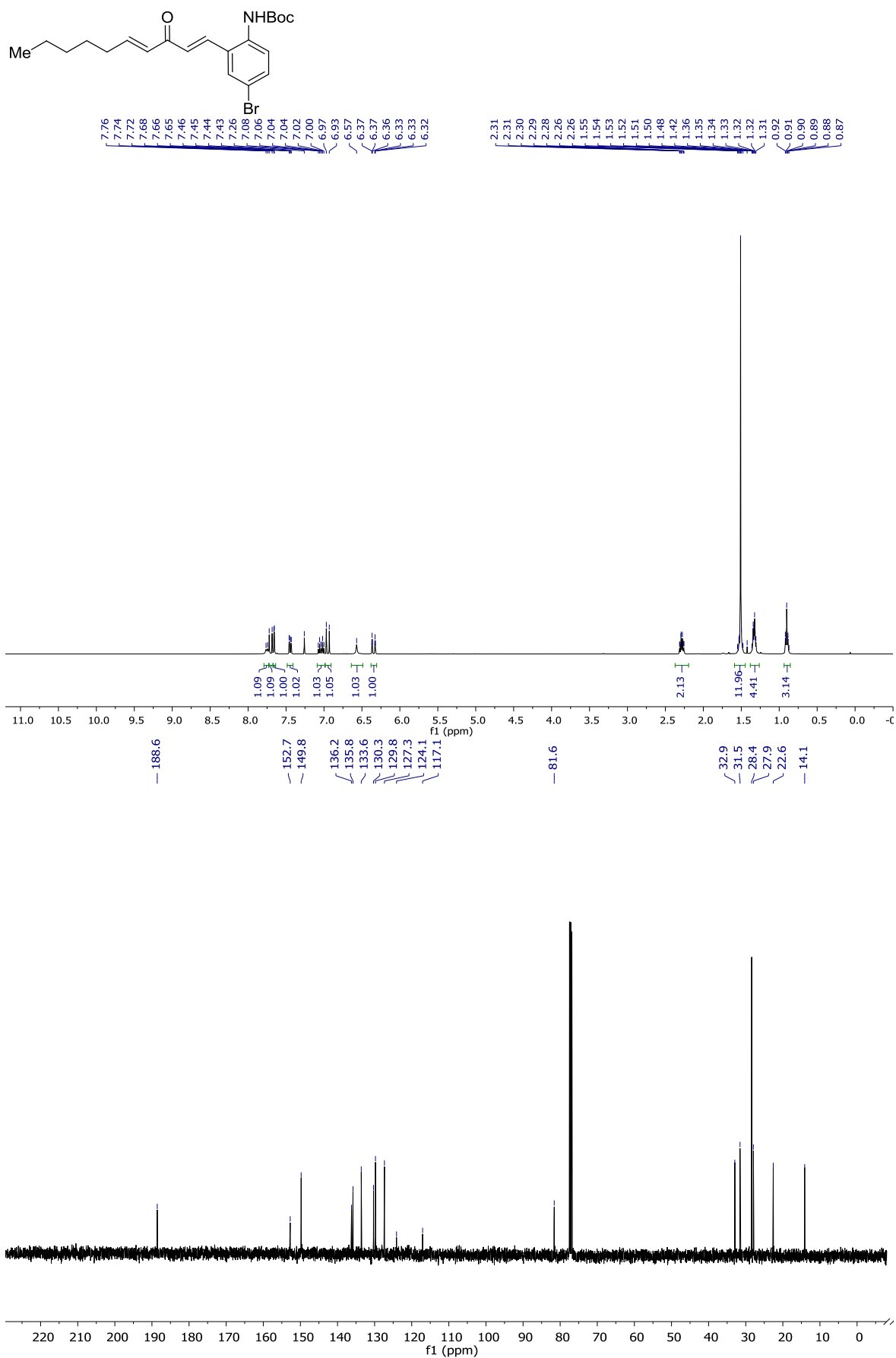


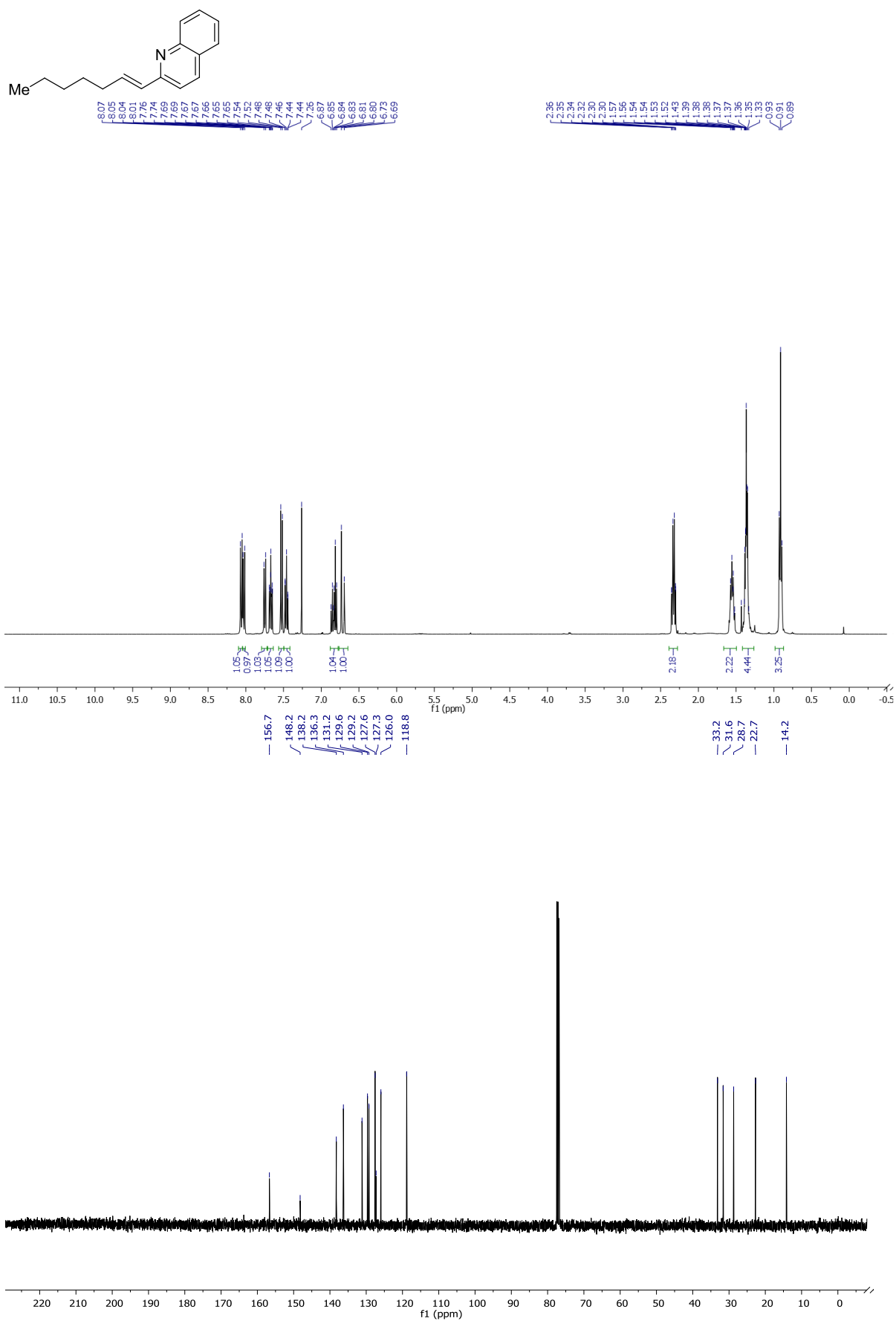
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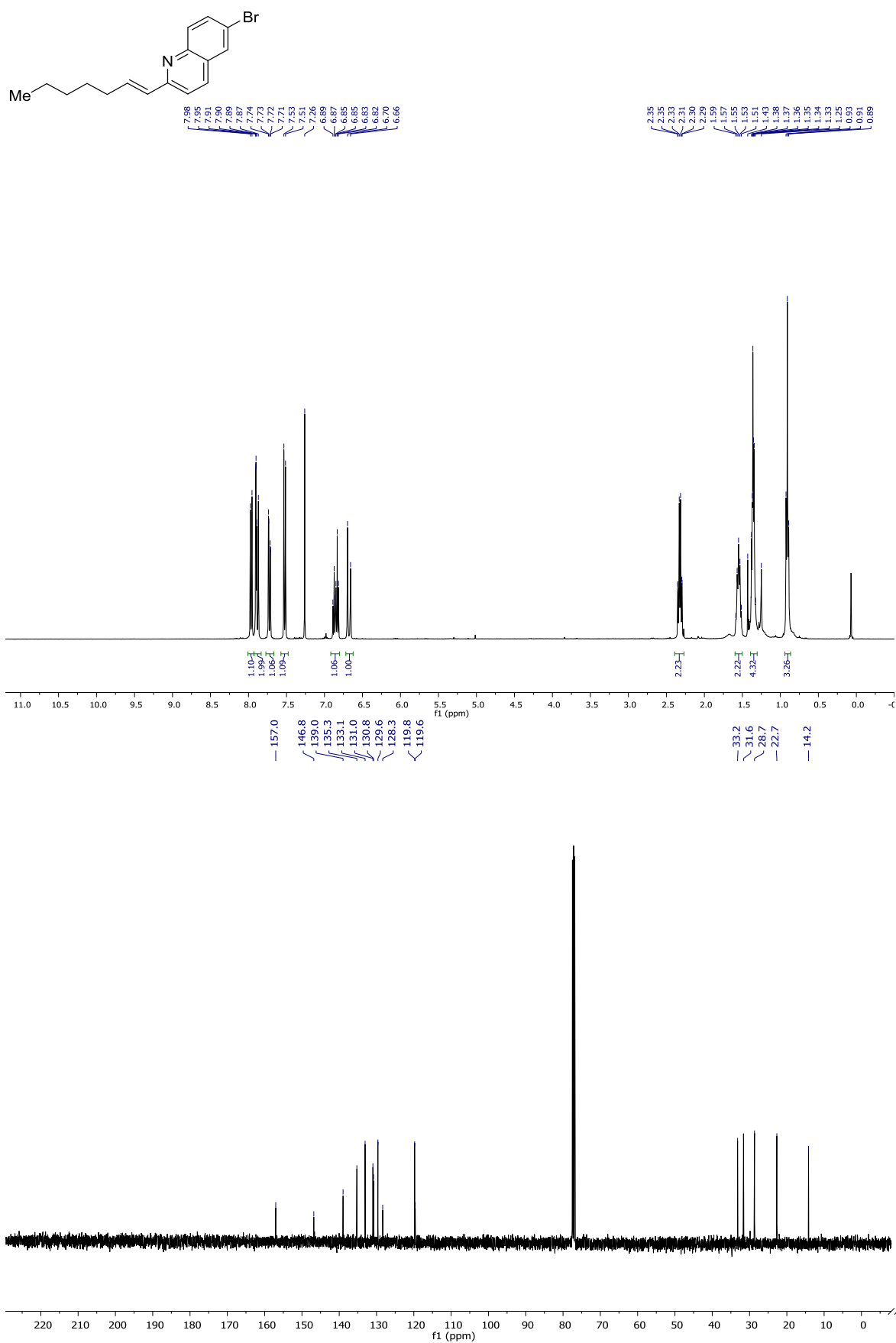


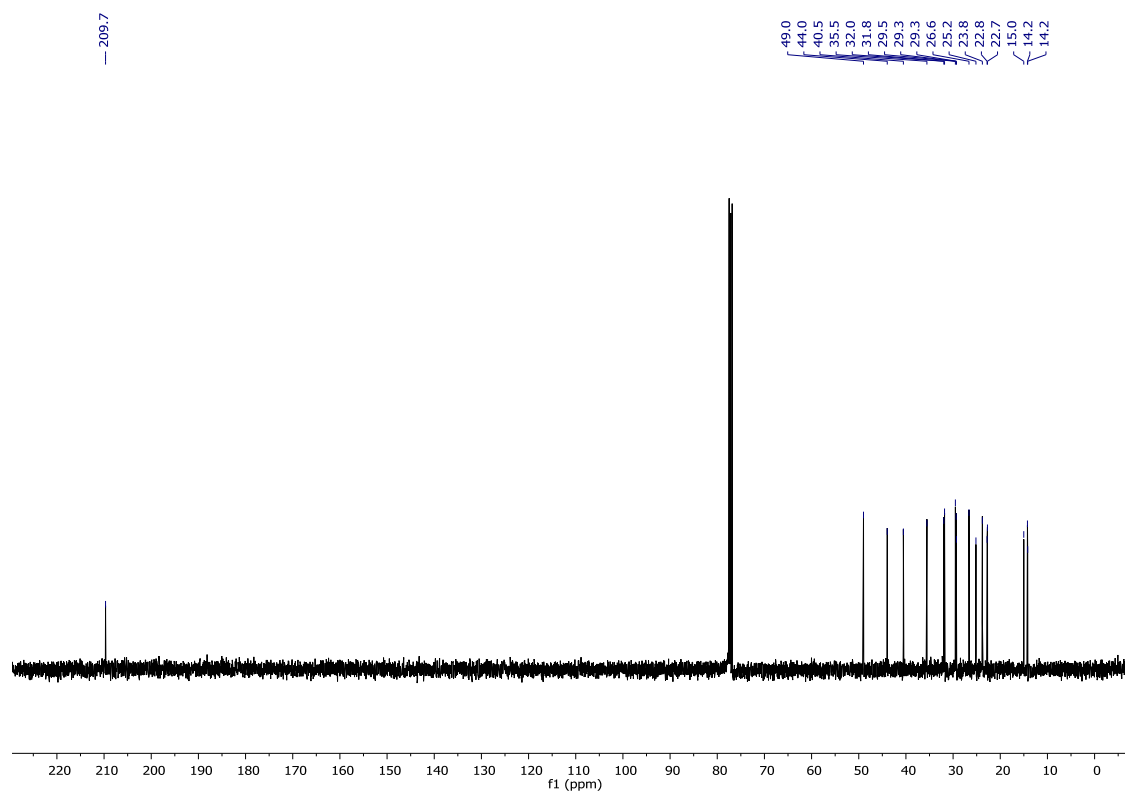
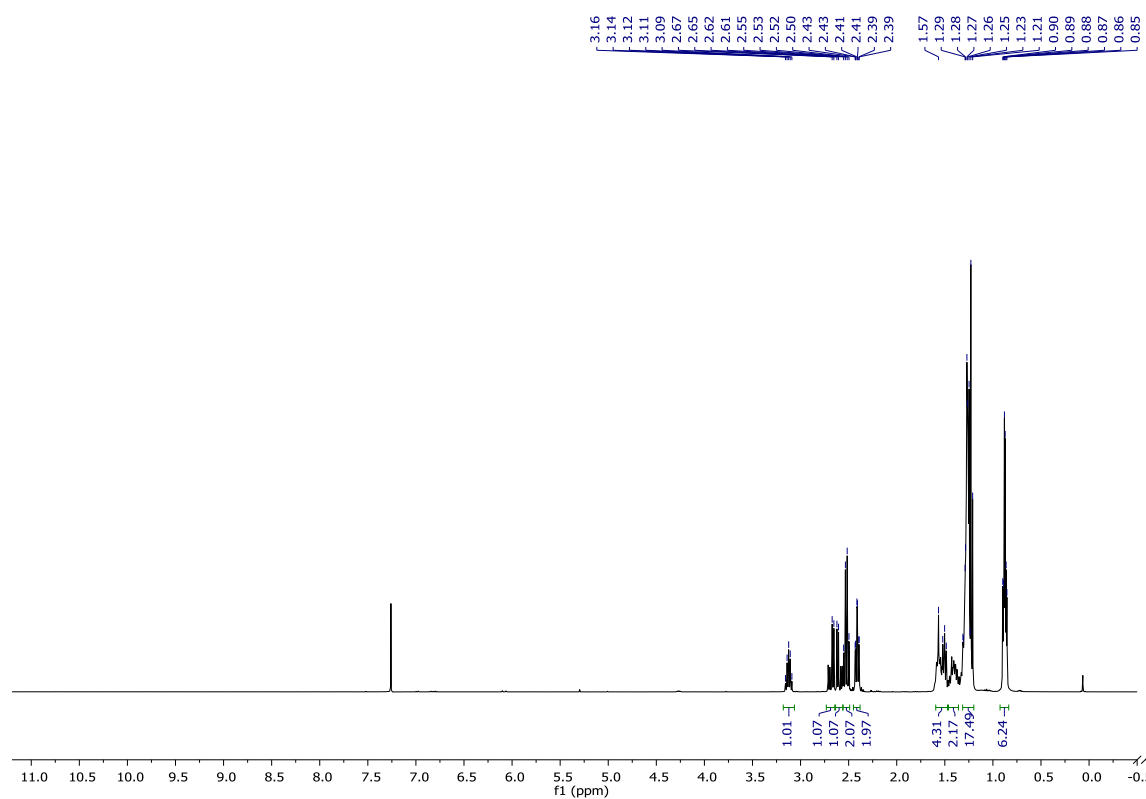
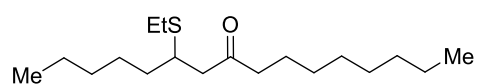
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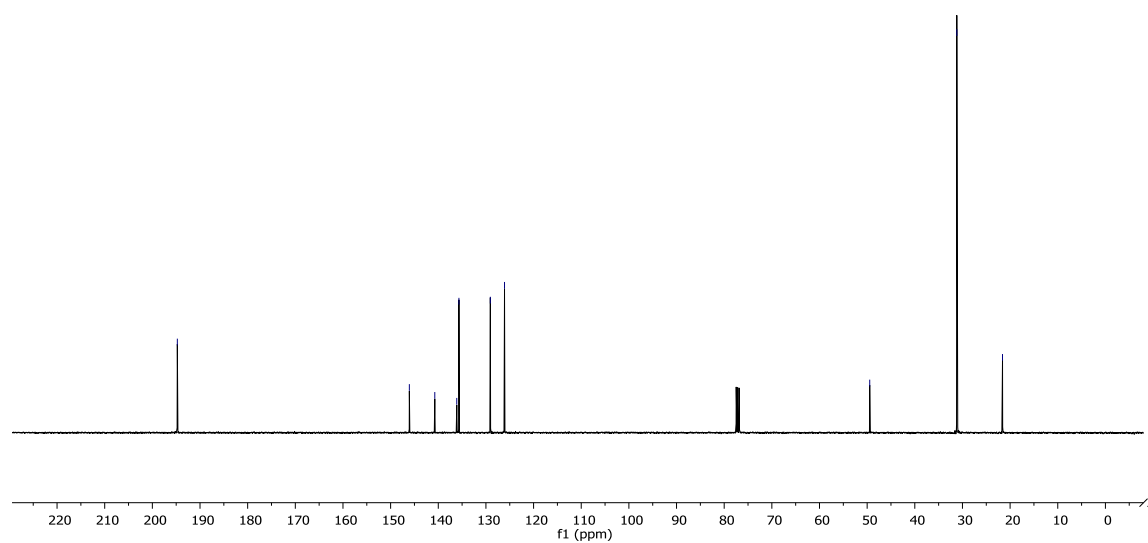
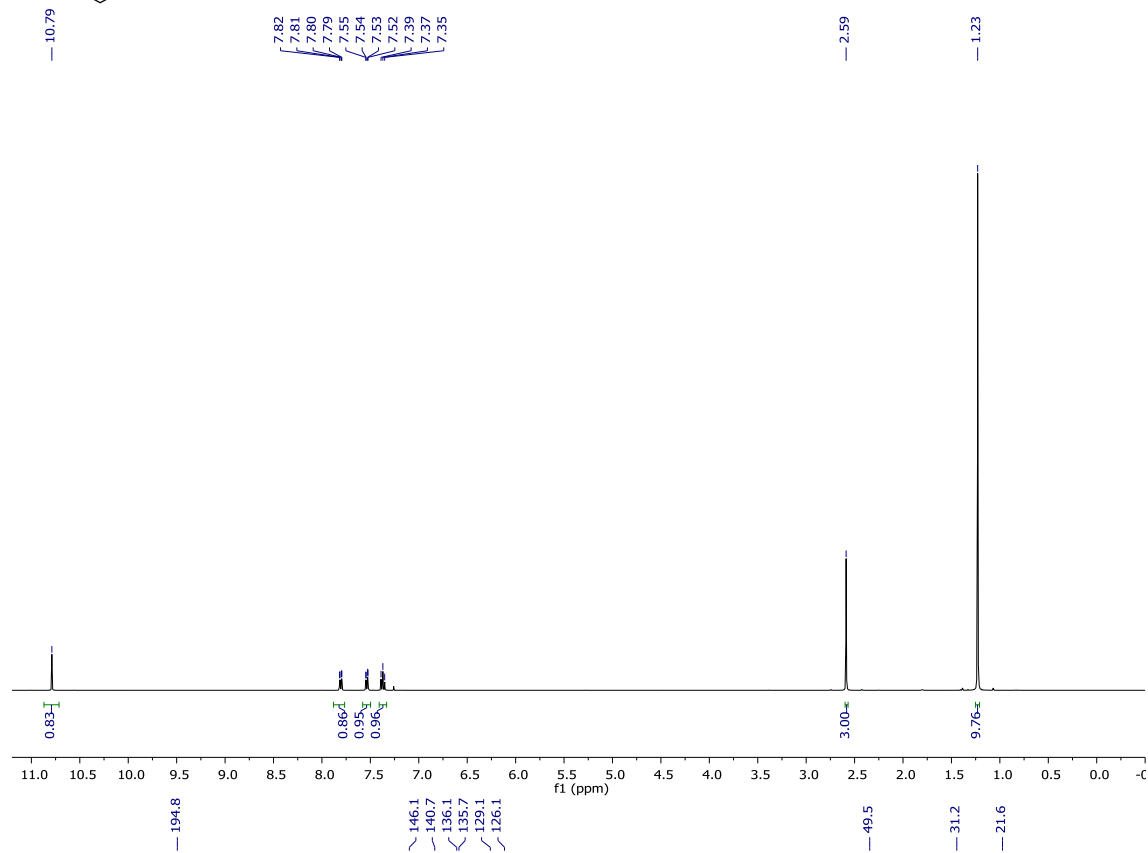
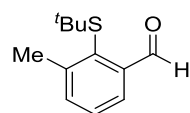
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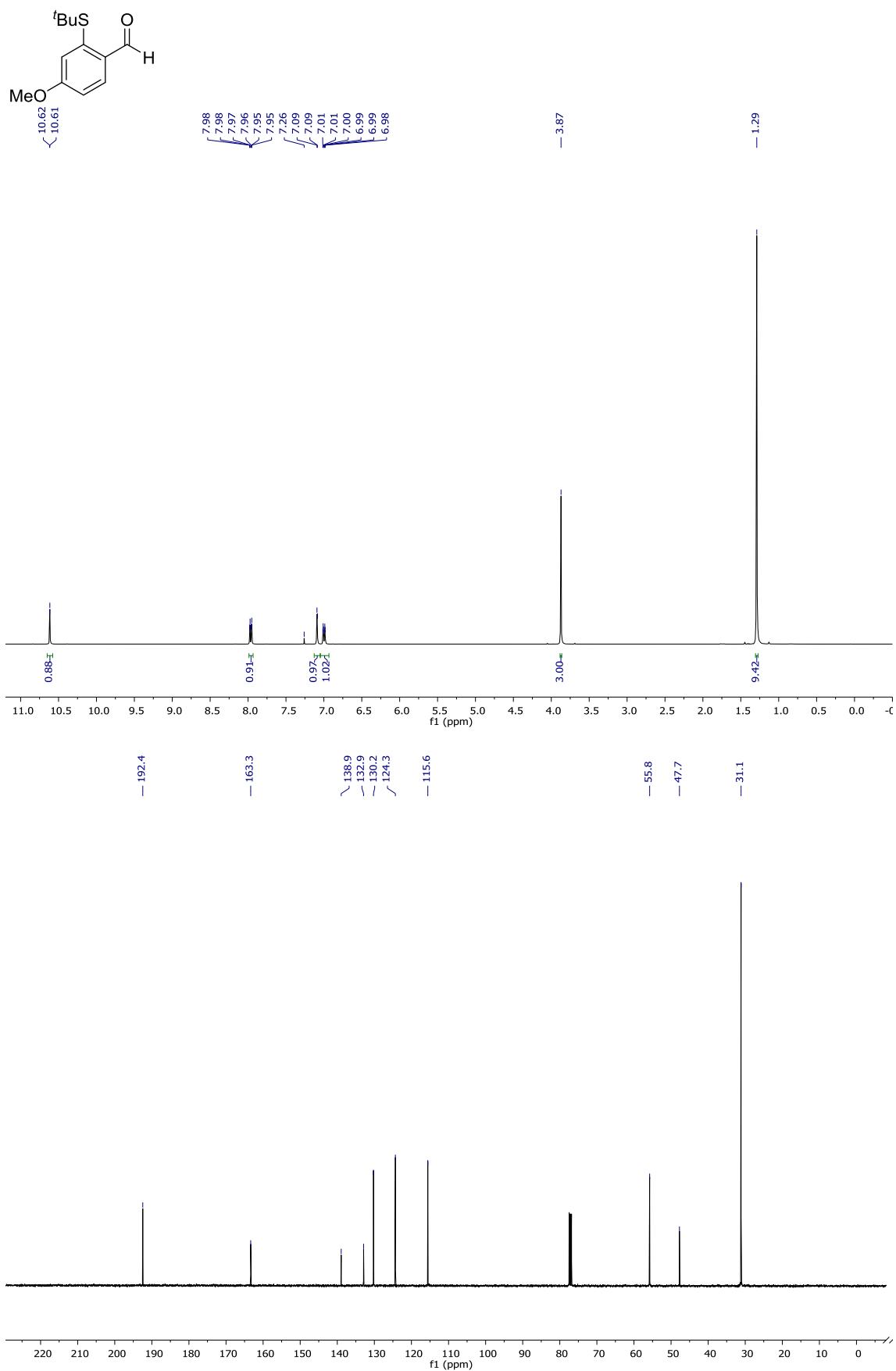
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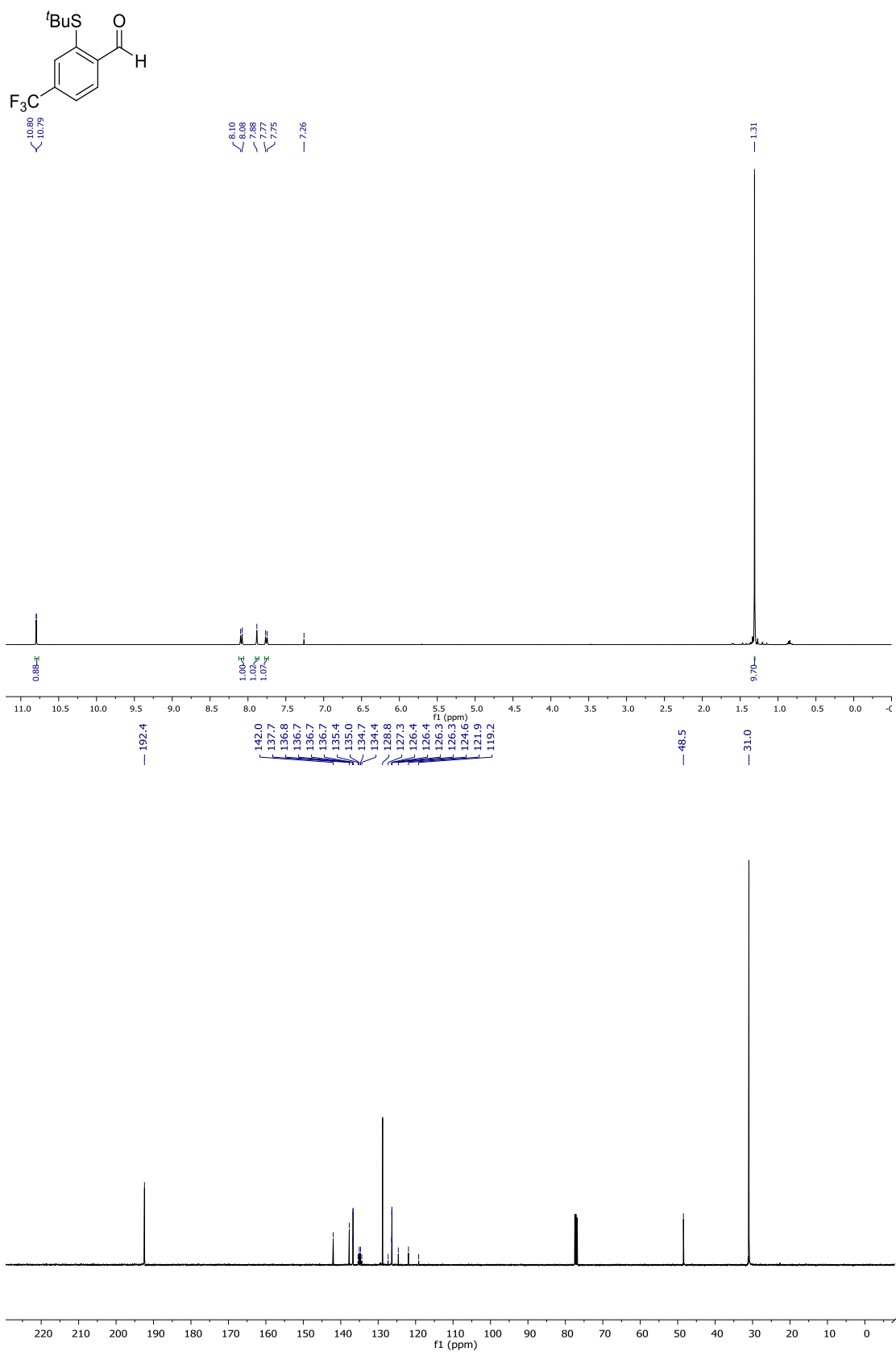
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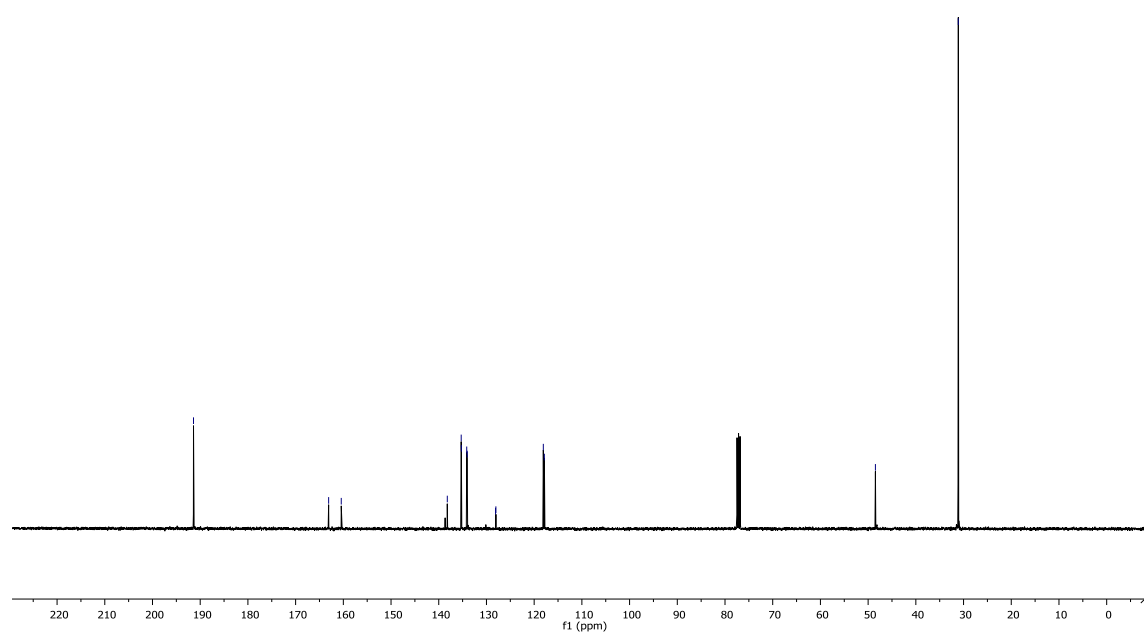
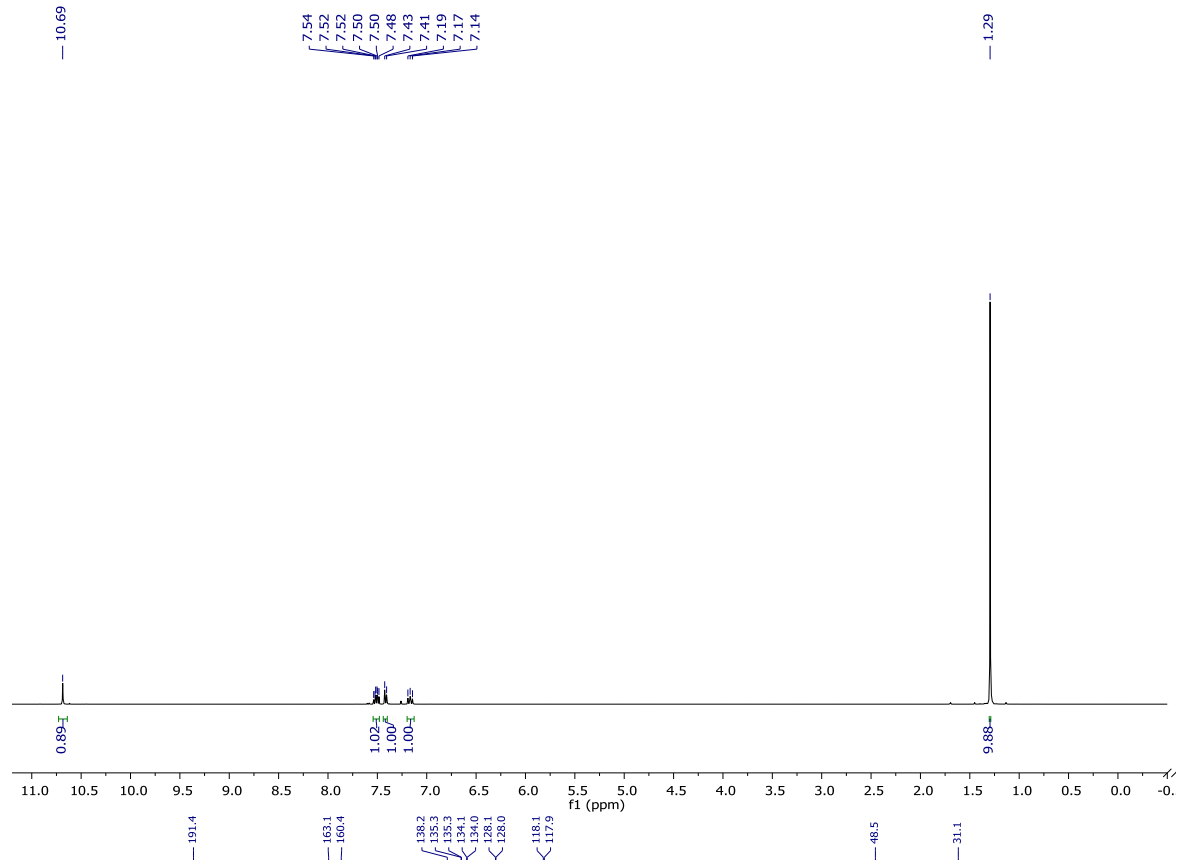
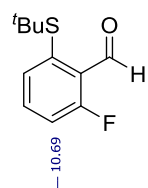
(E)-6-Bromo-2-(hept-1-en-1-yl)quinoline 21b

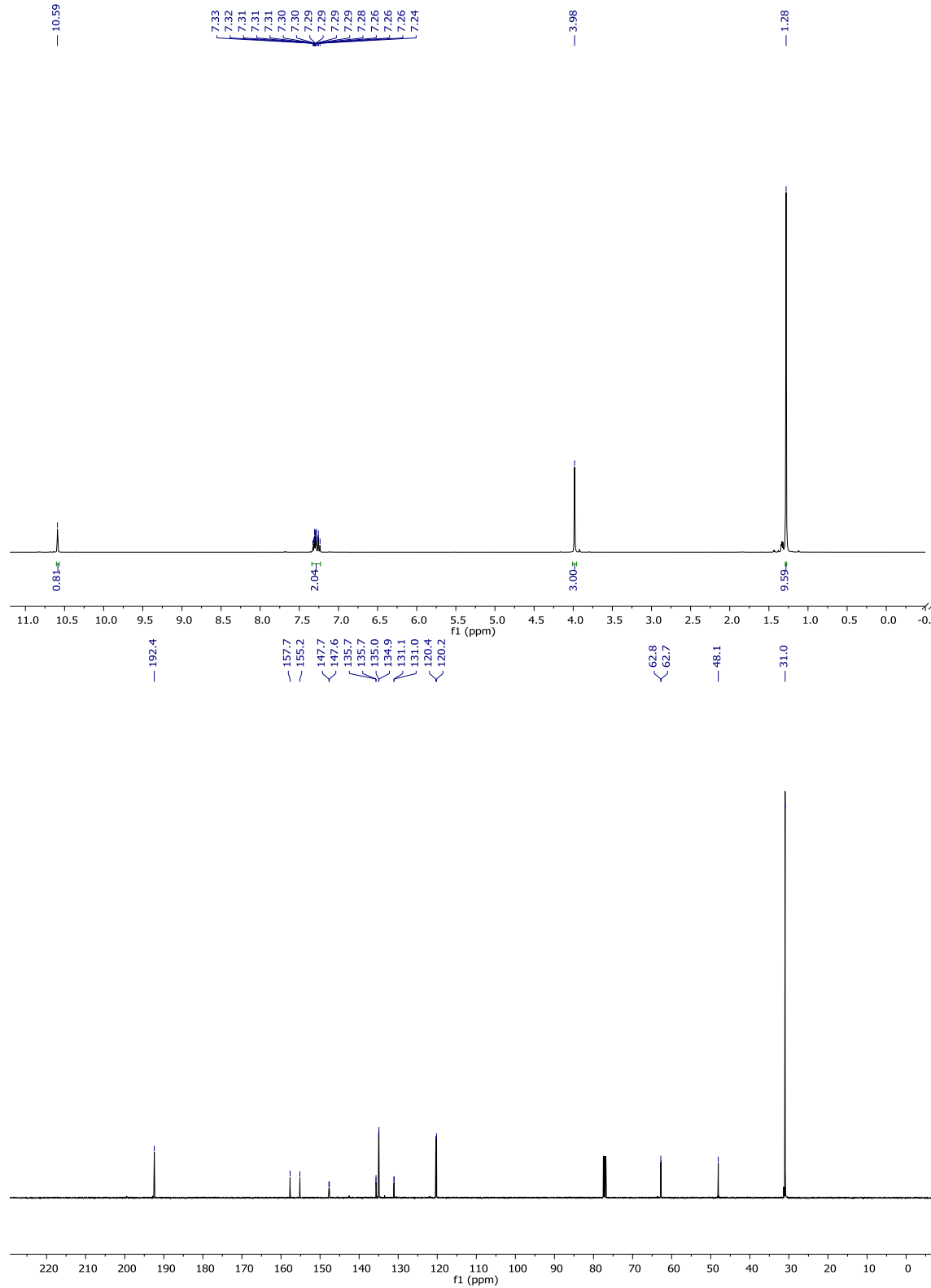
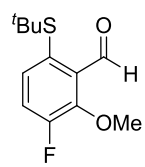
6-(Ethylthio)hexadecan-8-one 8a

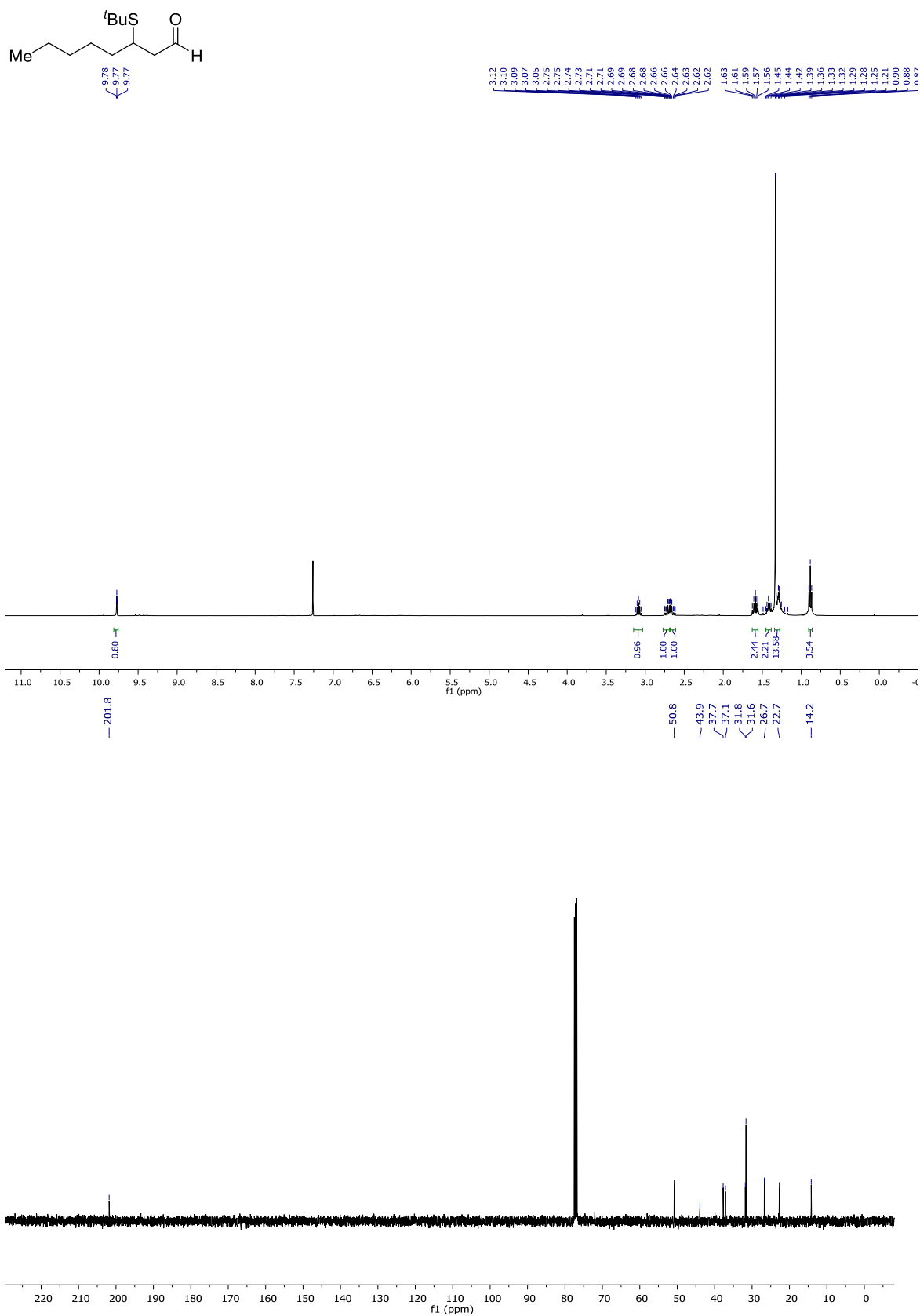
2-(*tert*-Butylthio)-3-methylbenzaldehyde 28b

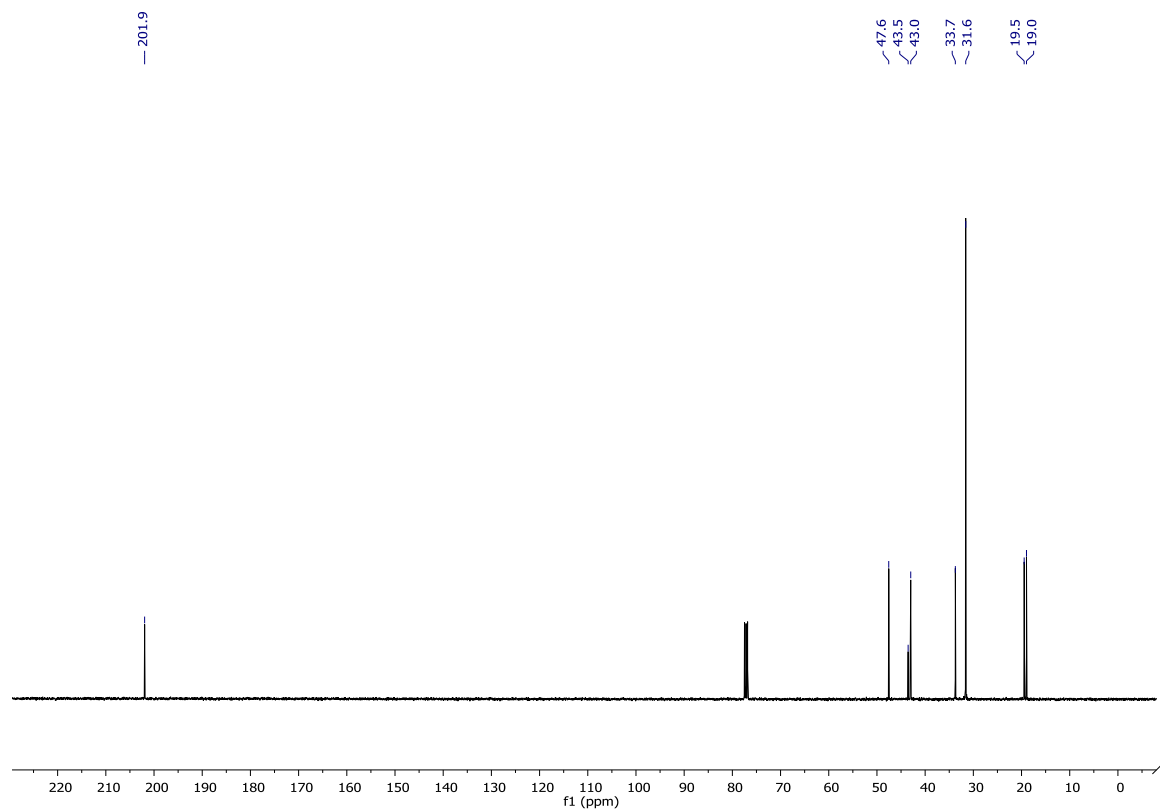
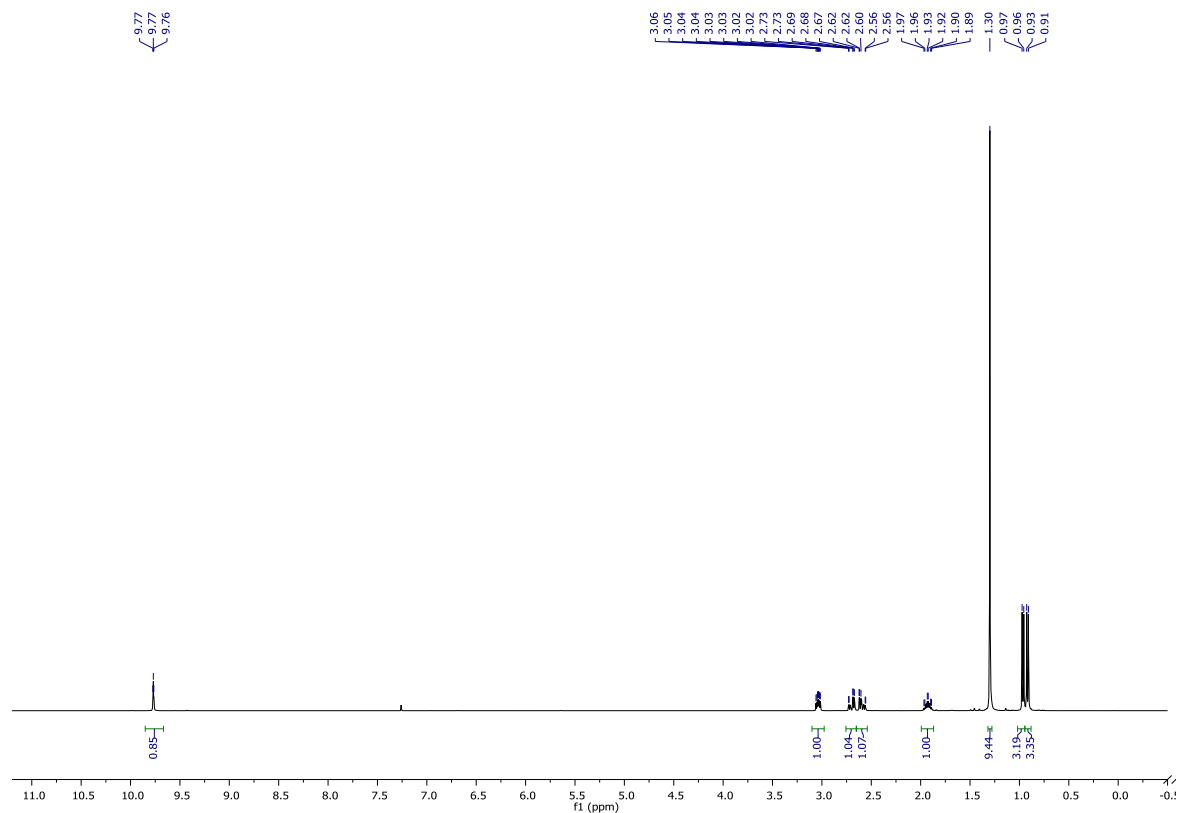
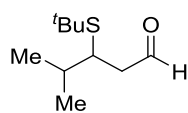
2-(*tert*-Butylthio)-4-methoxybenzaldehyde 28c

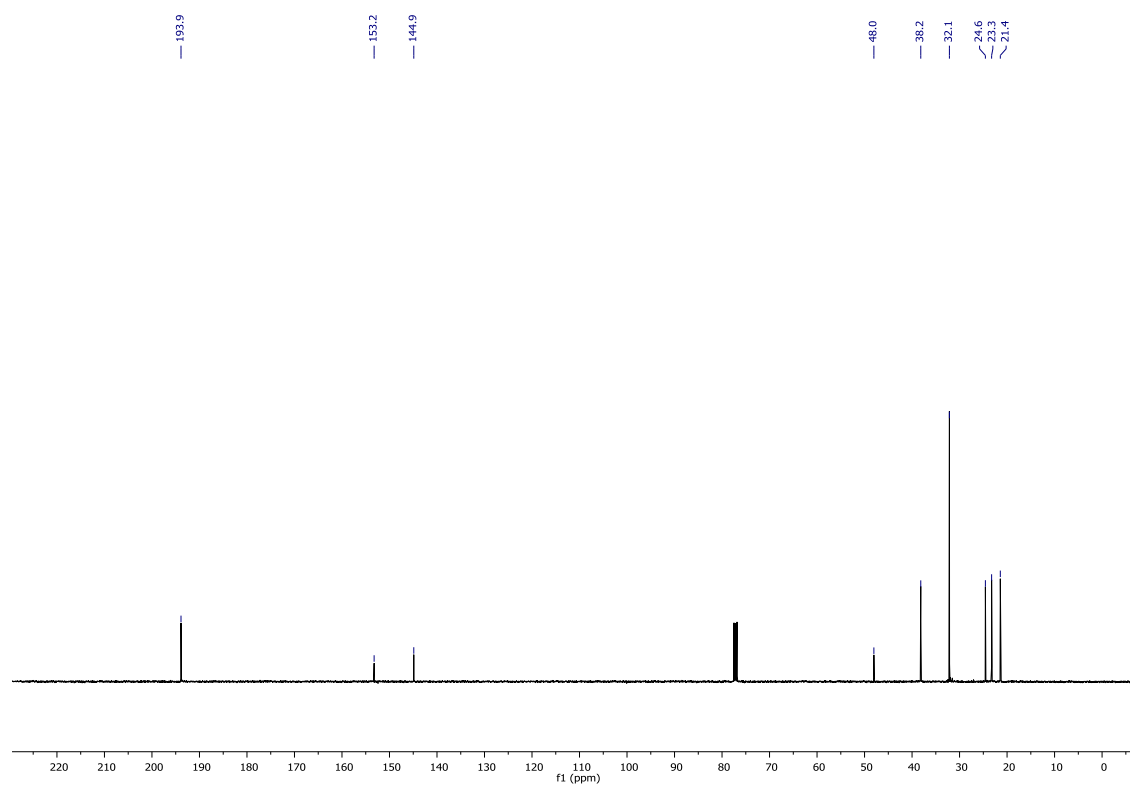
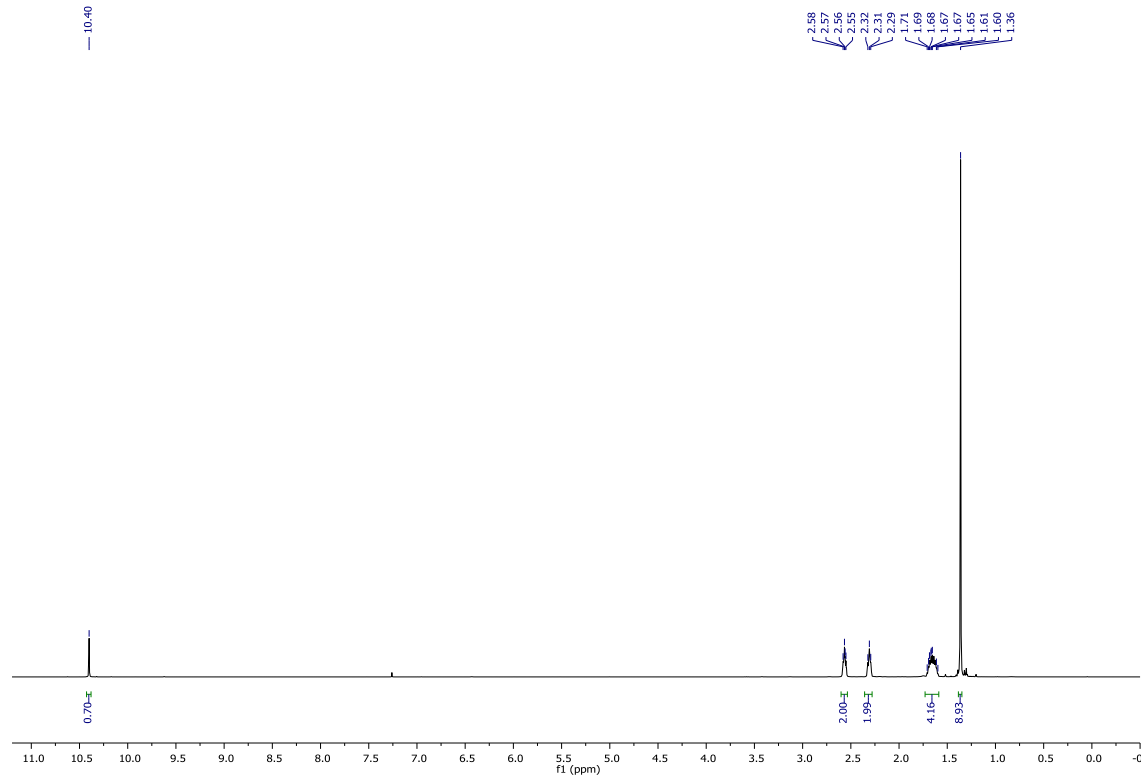
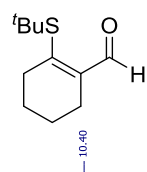
2-(*tert*-Butylthio)-4-(trifluoromethyl)benzaldehyde 28e

2-(*tert*-Butylthio)-6-fluorobenzaldehyde 28f

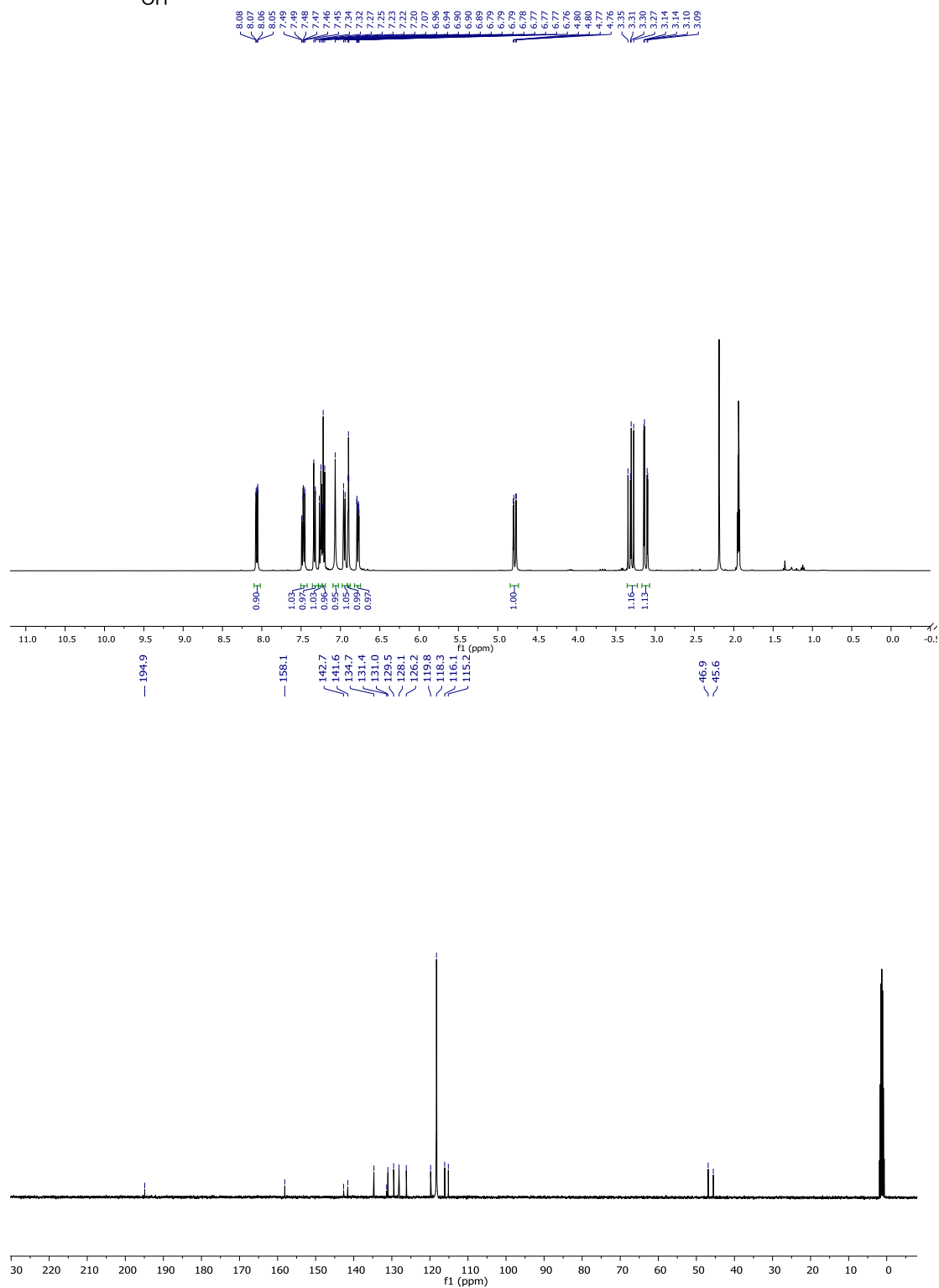
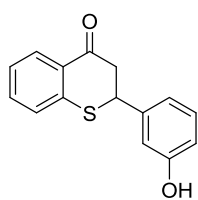
6-(*tert*-Butylthio)-3-fluoro-2-methoxybenzaldehyde 28g

3-(*tert*-Butylthio)octanal 31a

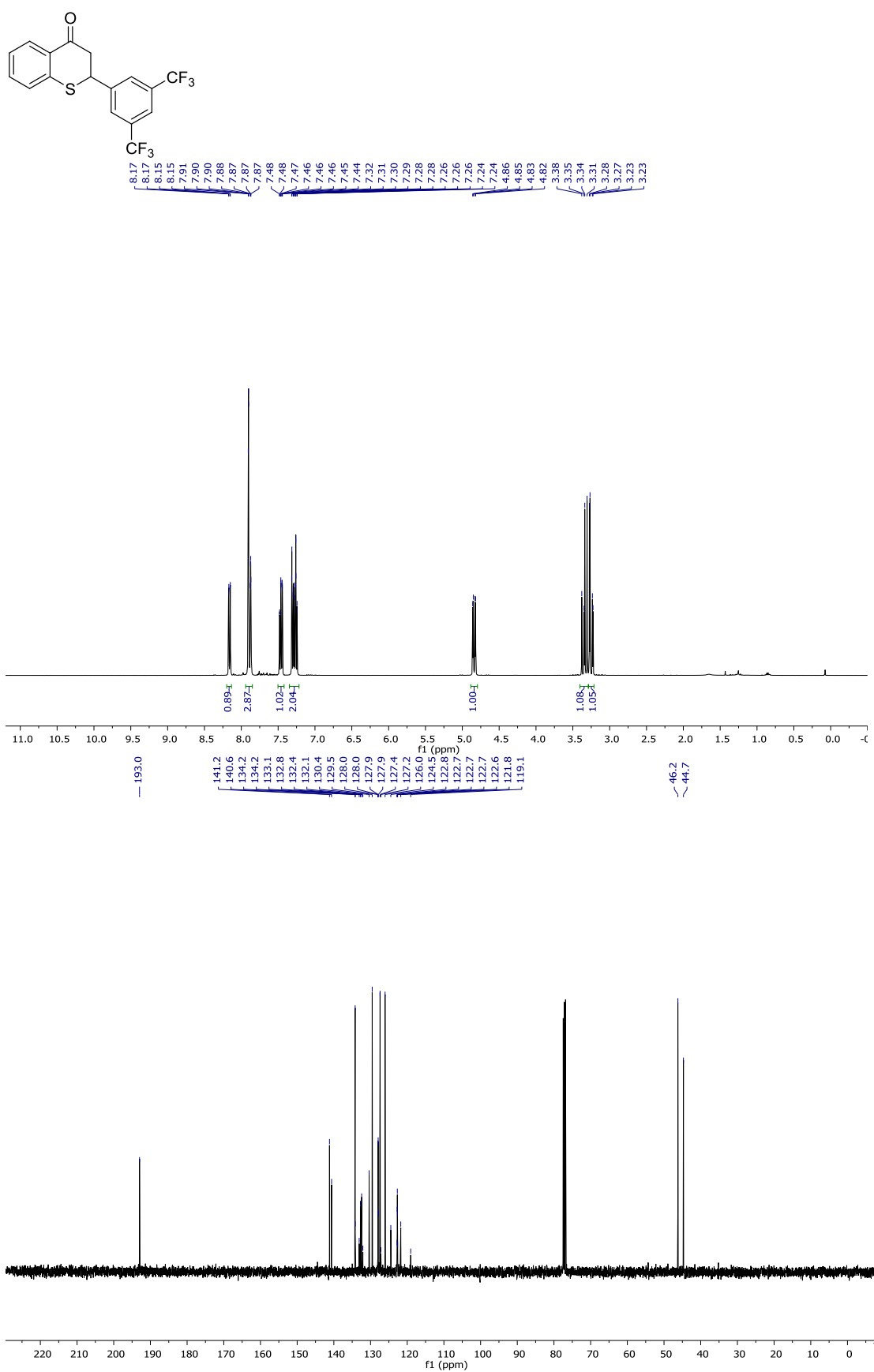
3-(*tert*-Butylthio)-4-methylpentanal 31b

2-(*tert*-Butylthio)cyclohex-1-ene-1-carbaldehyde 32

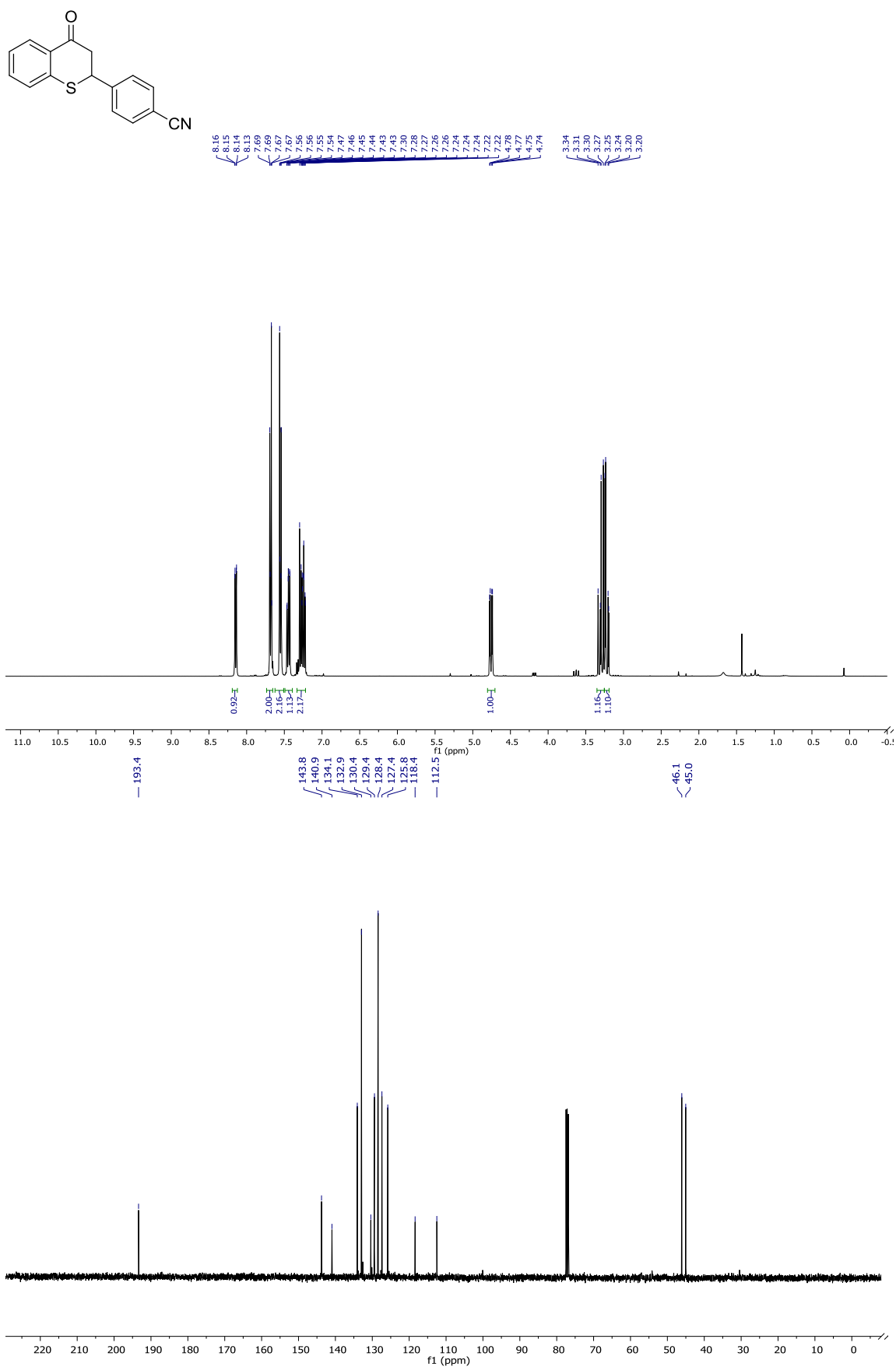
2-(3-Hydroxyphenyl)thiochroman-4-one 24c



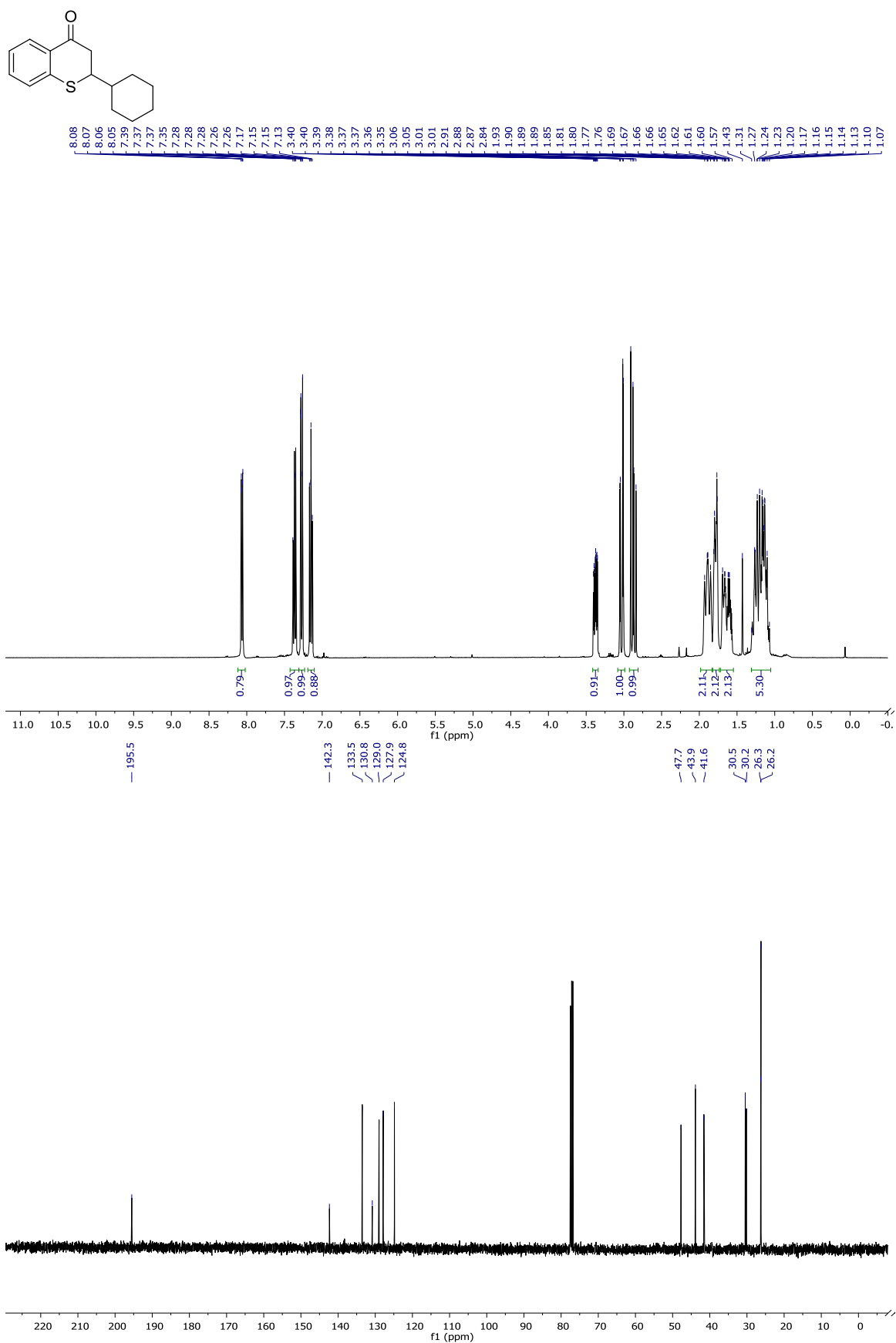
2-(3,5-Bis(trifluoromethyl)phenyl)thiochroman-4-one 24f

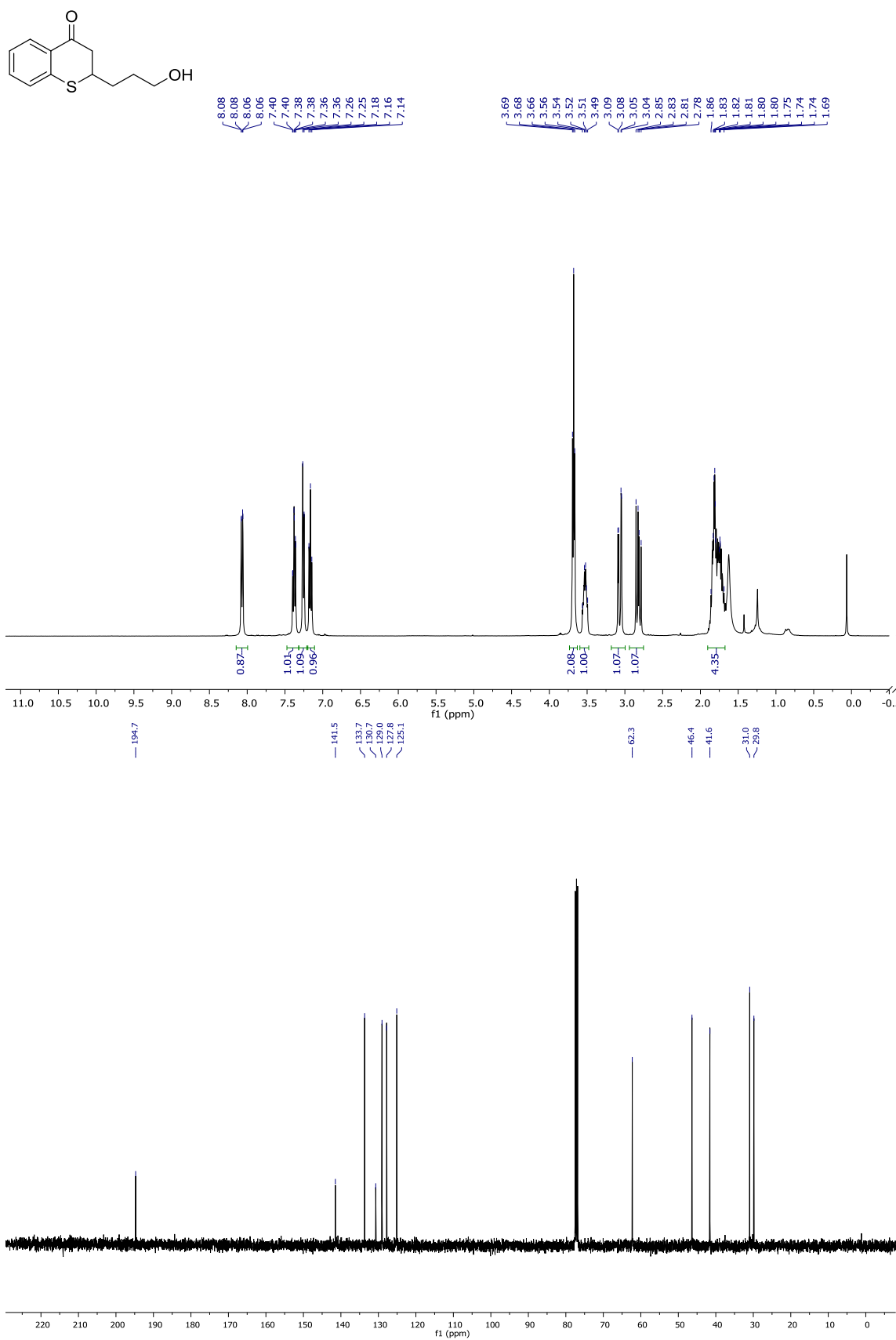


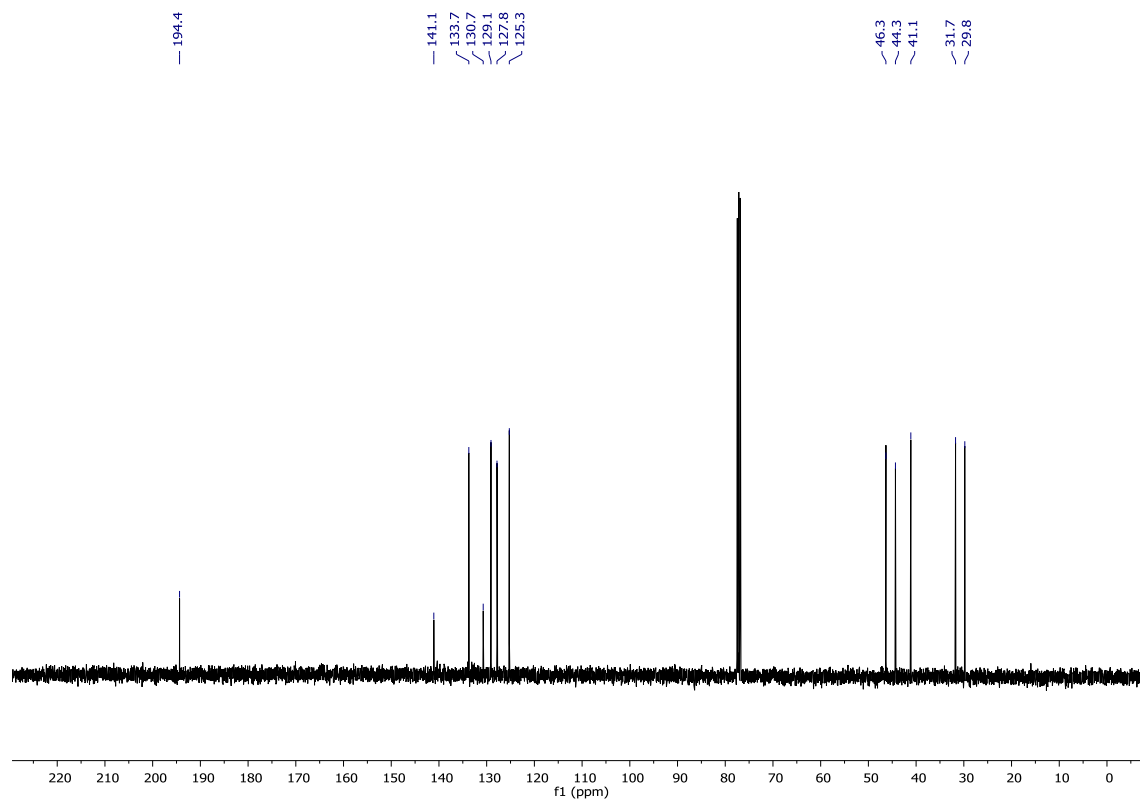
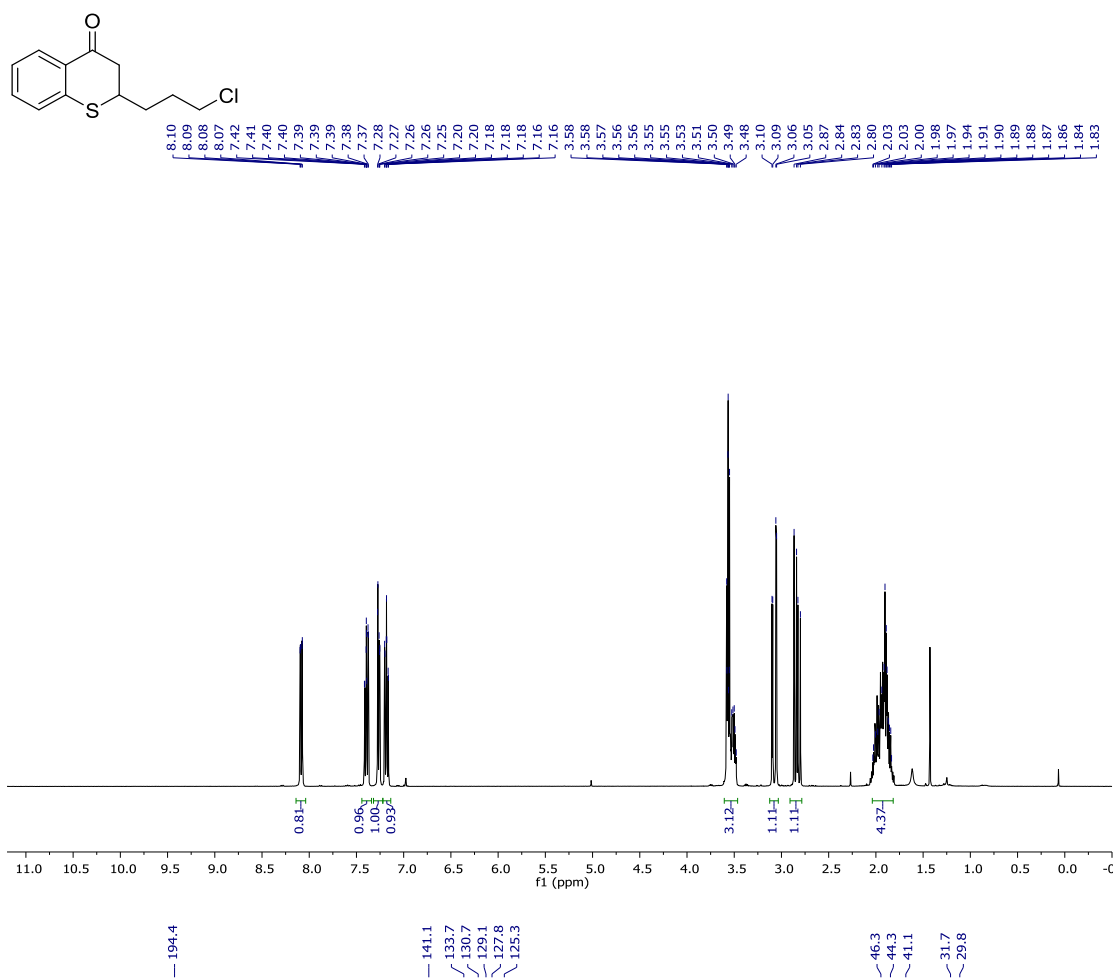
4-(4-Oxothiochroman-2-yl)benzonitrile 24g



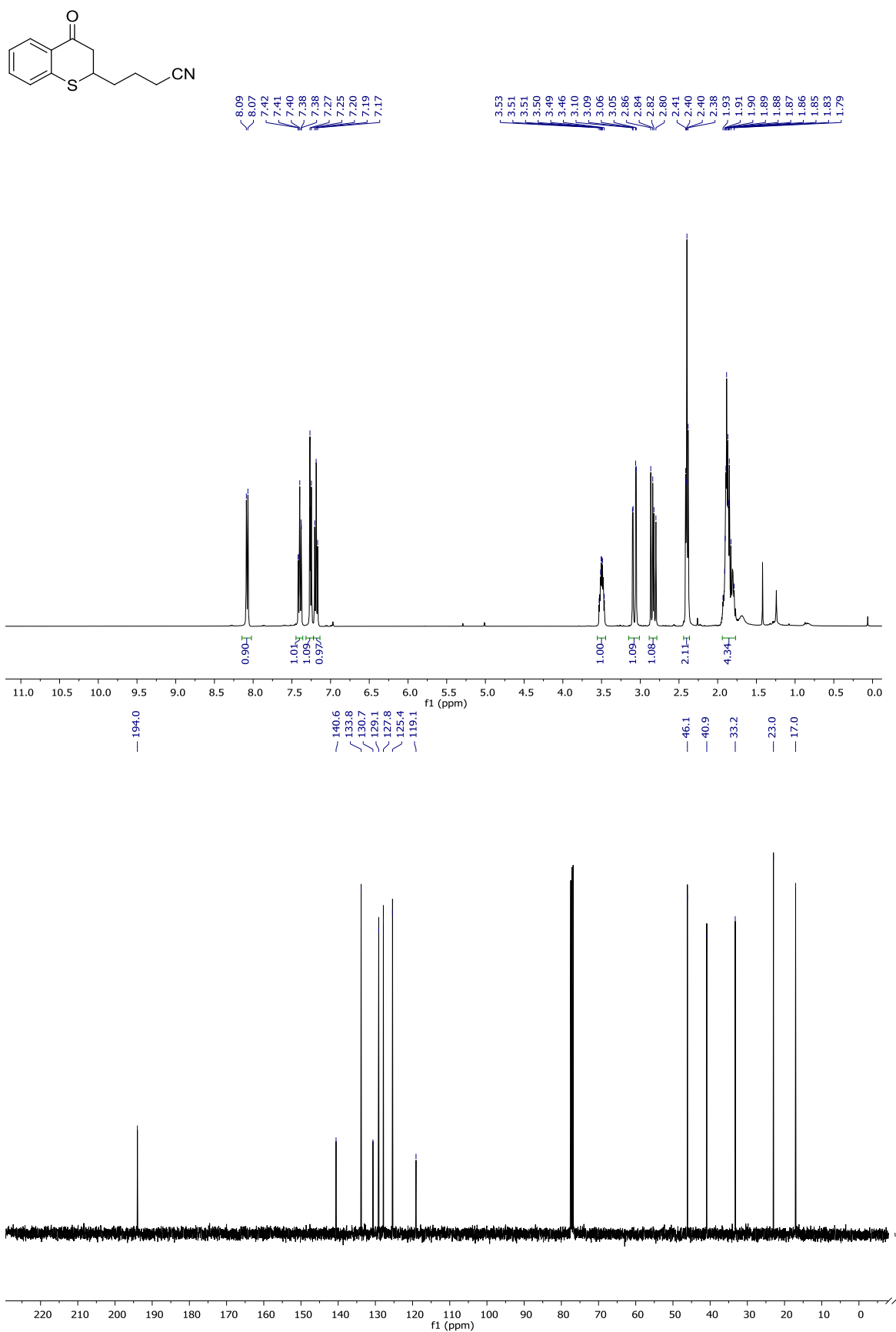
2-Cyclohexylthiochroman-4-one 24k



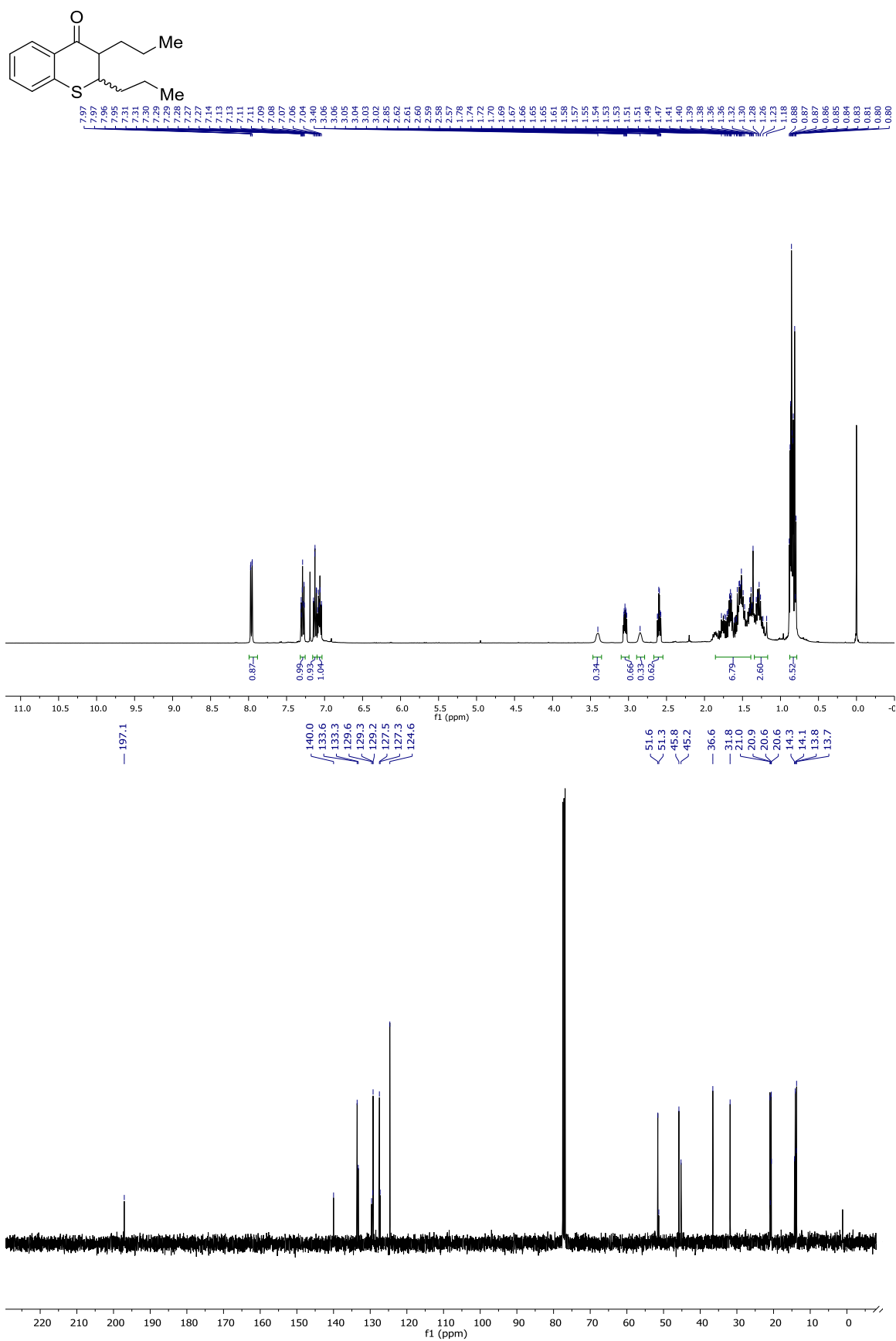
2-(3-Hydroxypropyl)thiochroman-4-one 24m

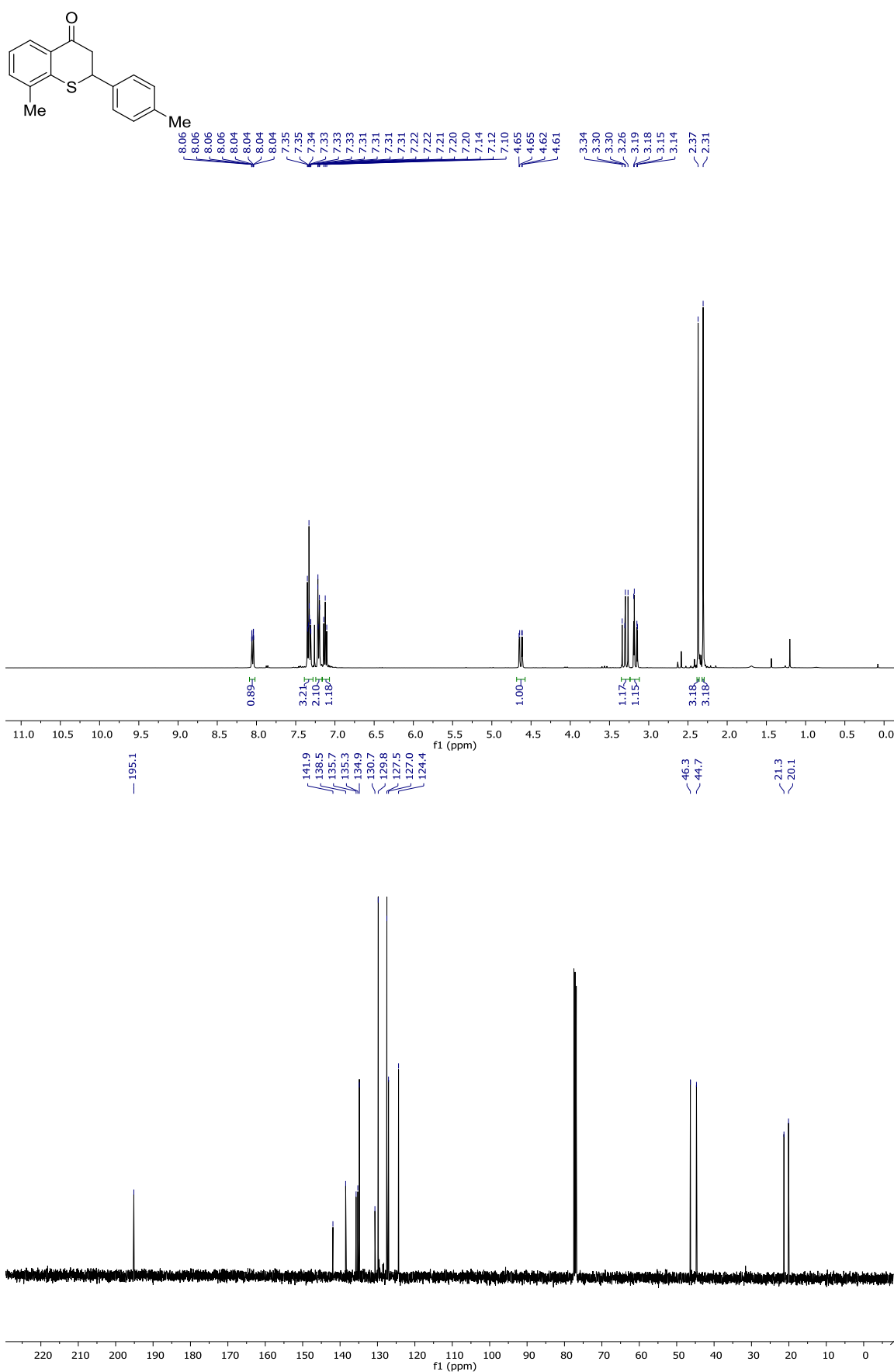
2-(3-Chloropropyl)thiochroman-4-one 24n

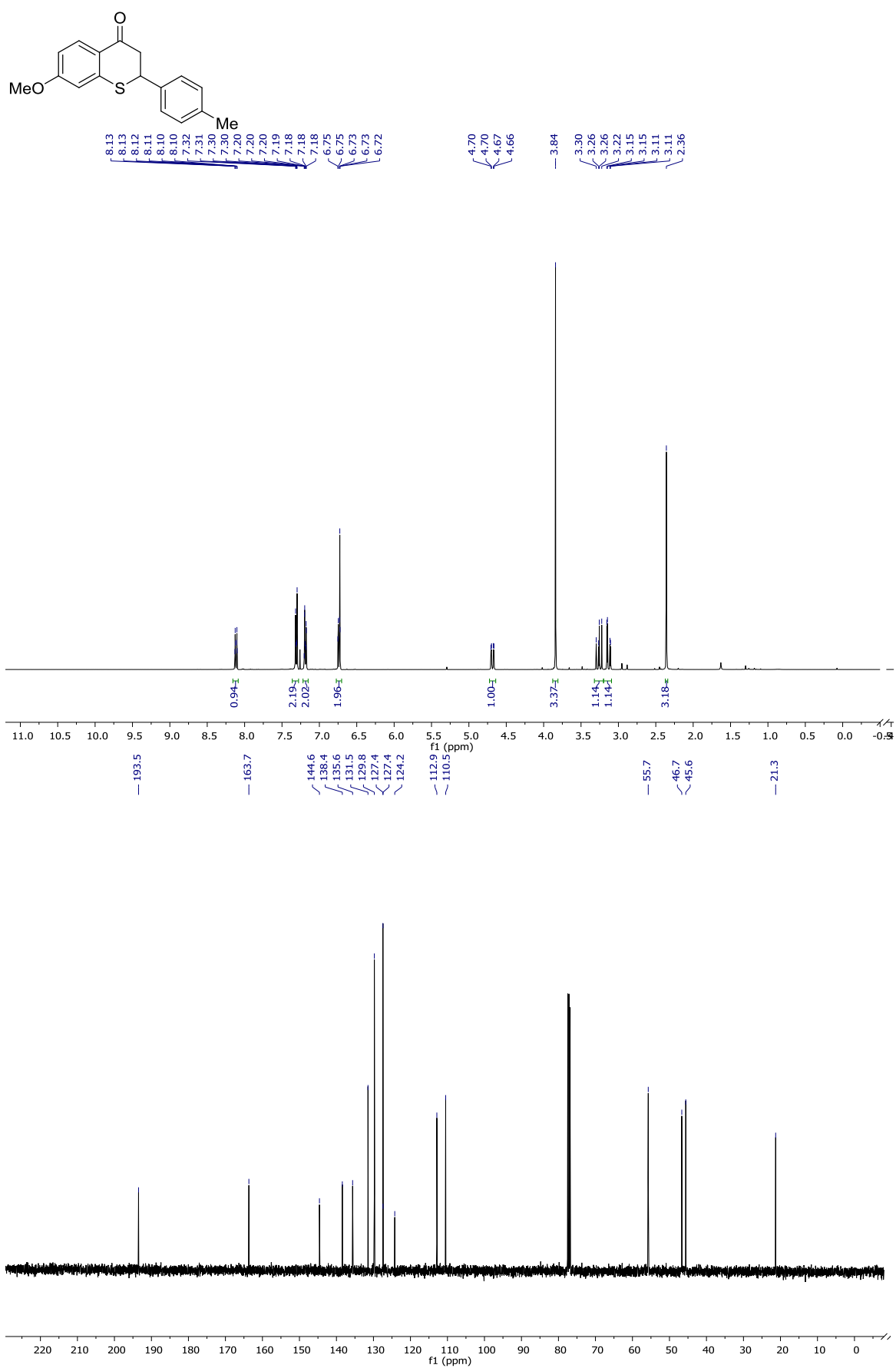
4-(4-Oxothiochroman-2-yl)butanenitrile 24o

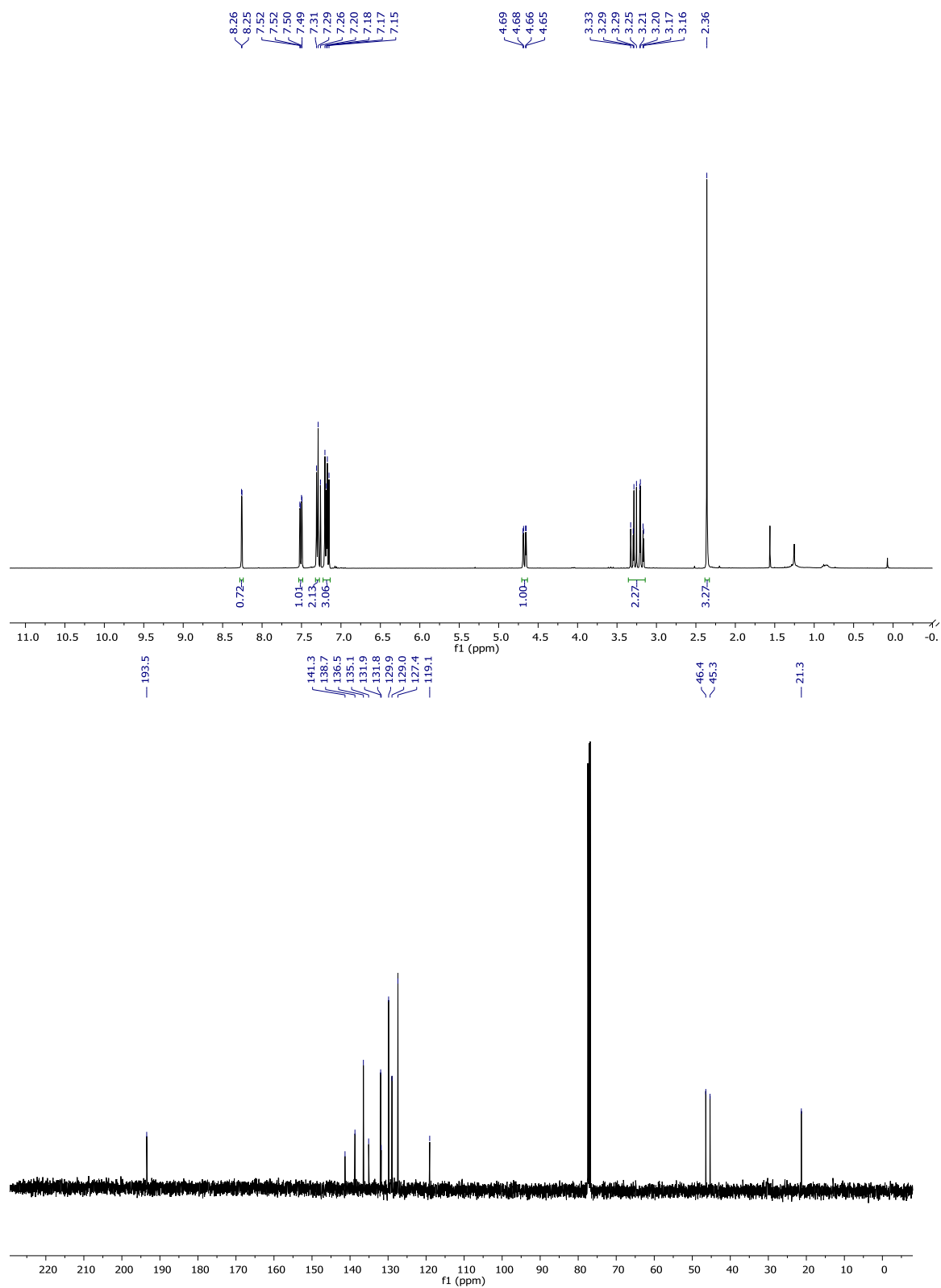
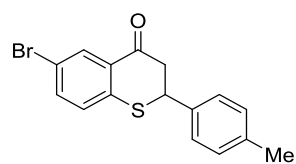


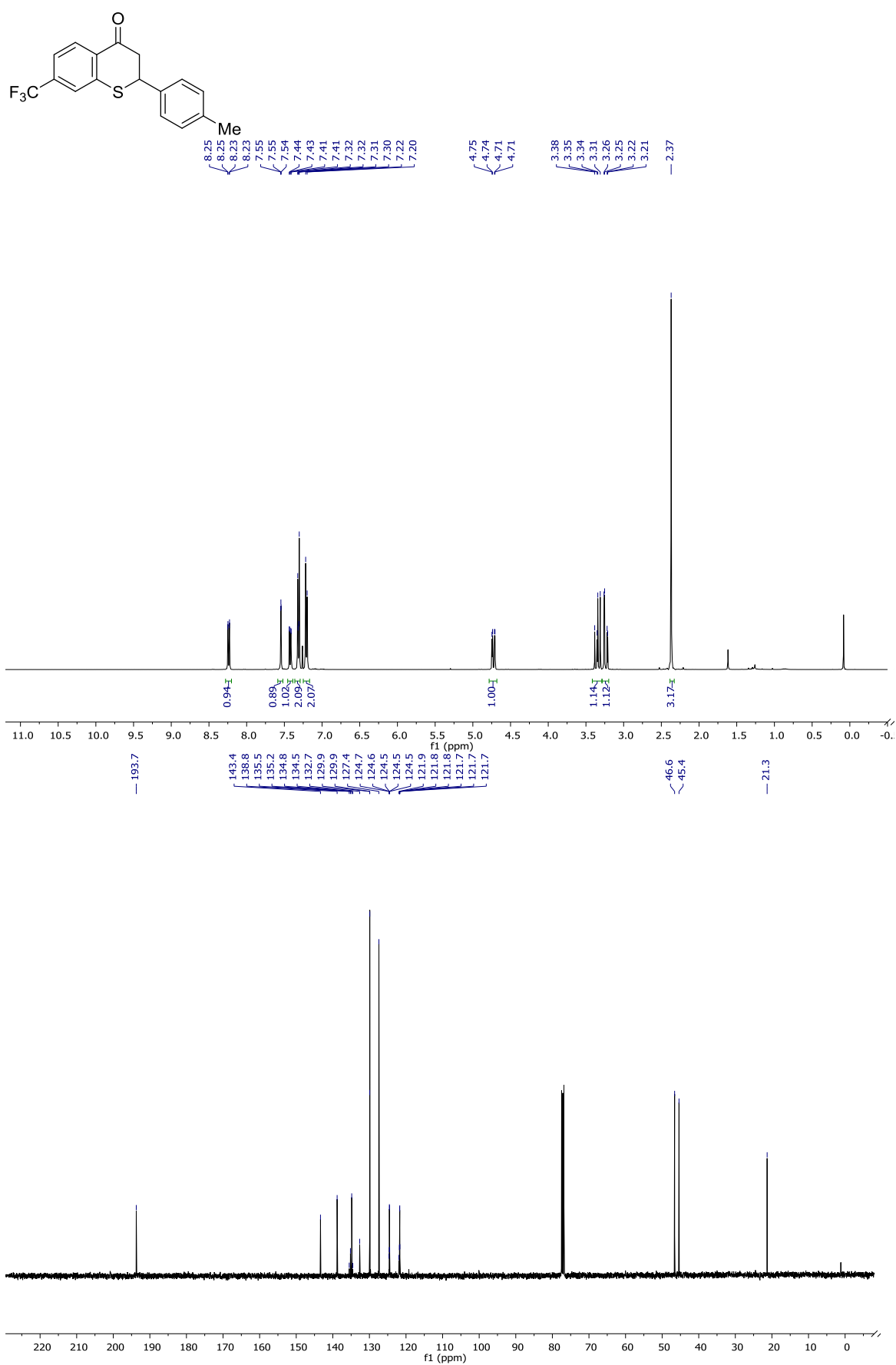
2,3-Dipropylthiochroman-4-one 24p



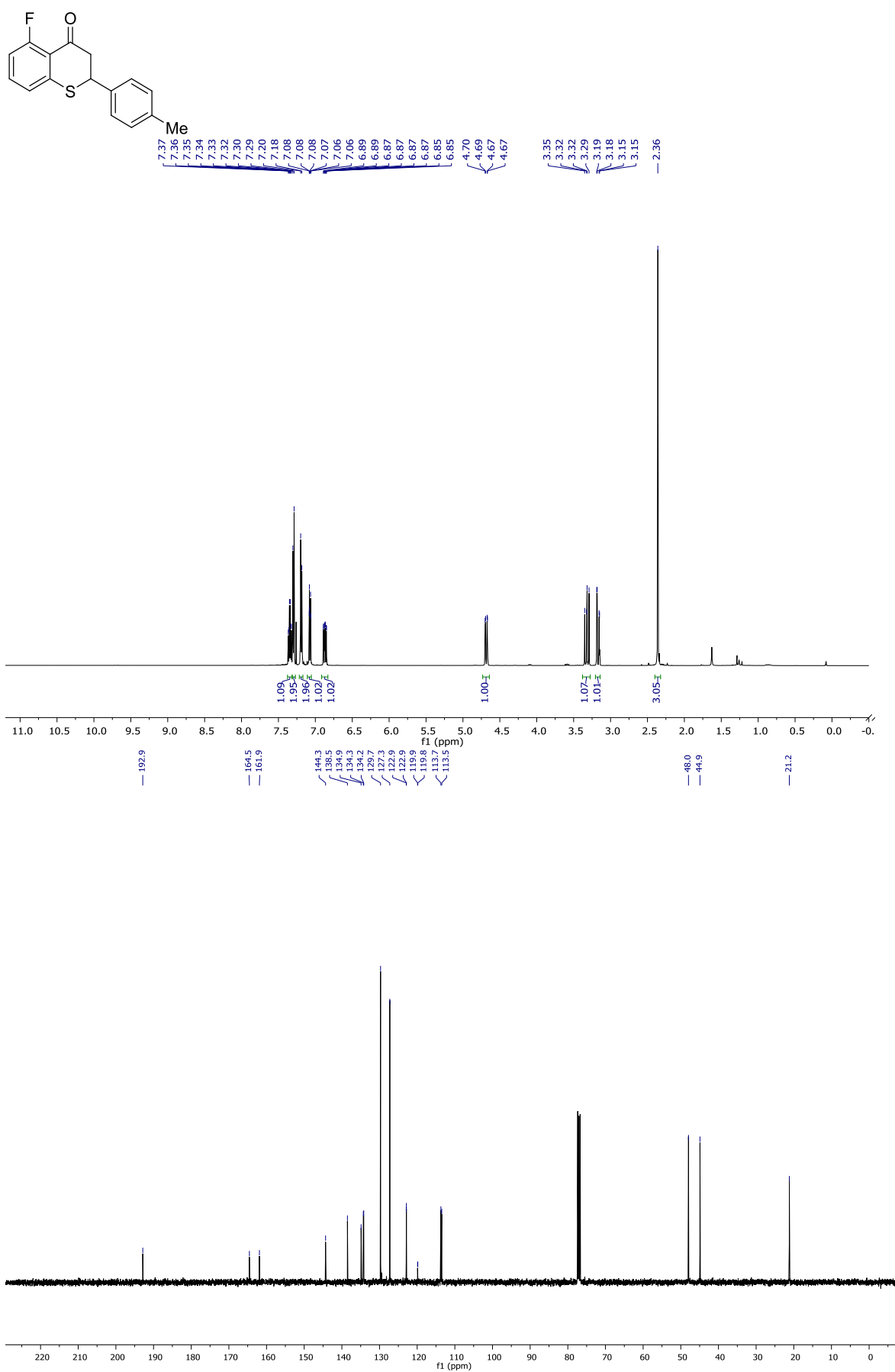
8-Methyl-2-(*p*-tolyl)thiochroman-4-one 24q

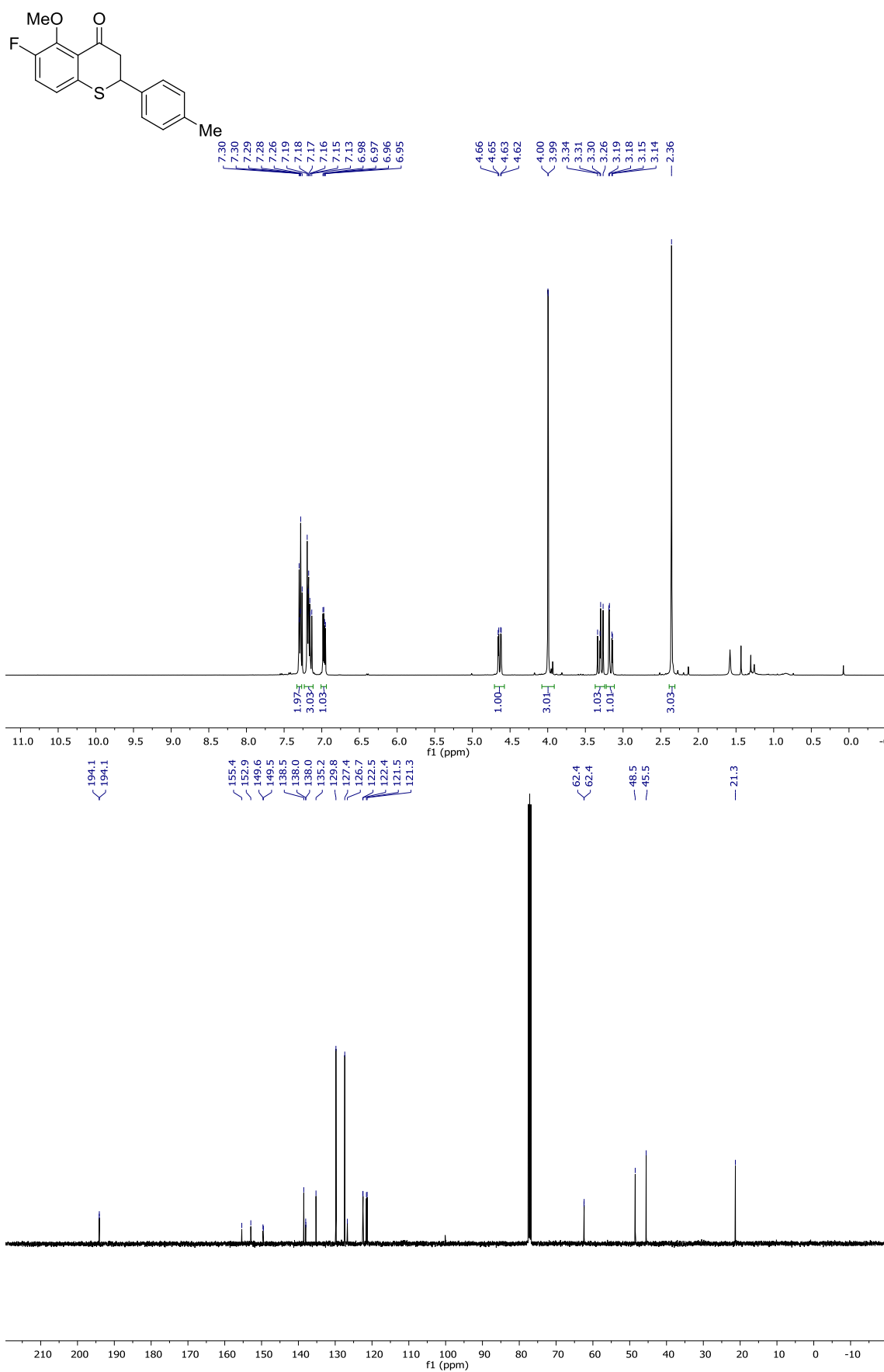
7-Methoxy-2-(p-tolyl)thiochroman-4-one 24r

6-Bromo-2-(p-tolyl)thiochroman-4-one 24s

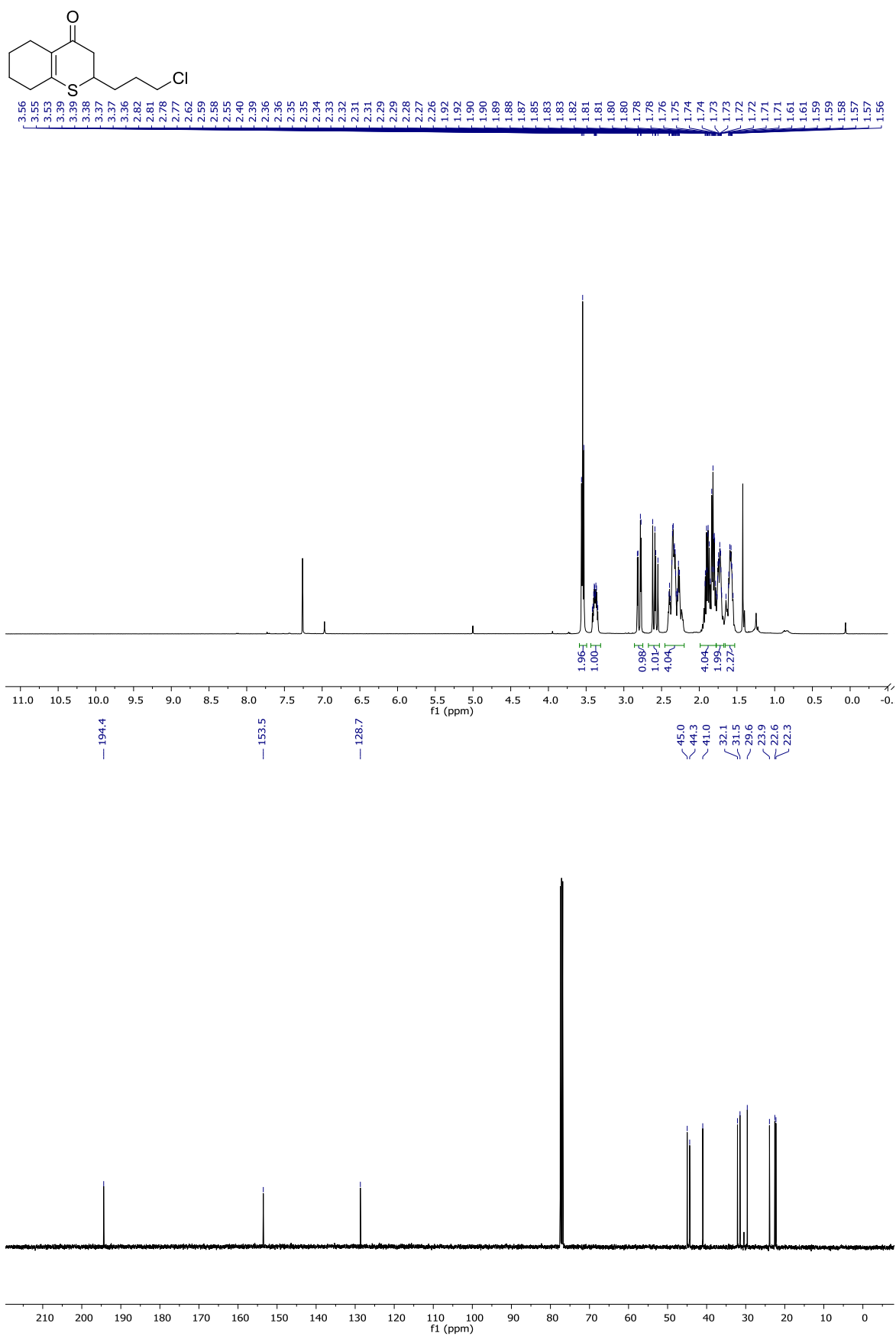
2-(*p*-Tolyl)-7-(trifluoromethyl)thiochroman-4-one 24t

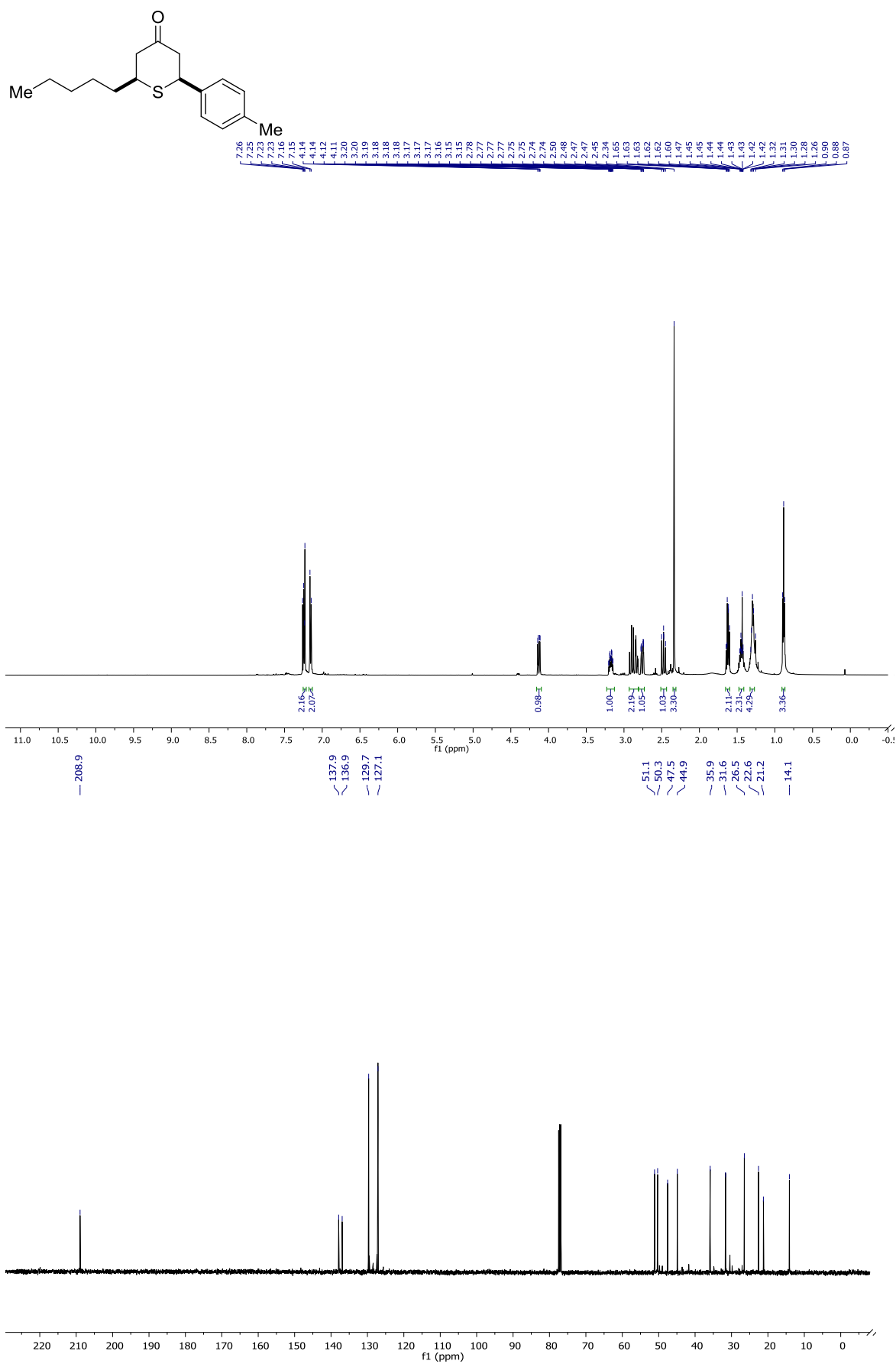
5-Fluoro-2-(p-tolyl)thiochroman-4-one 24u

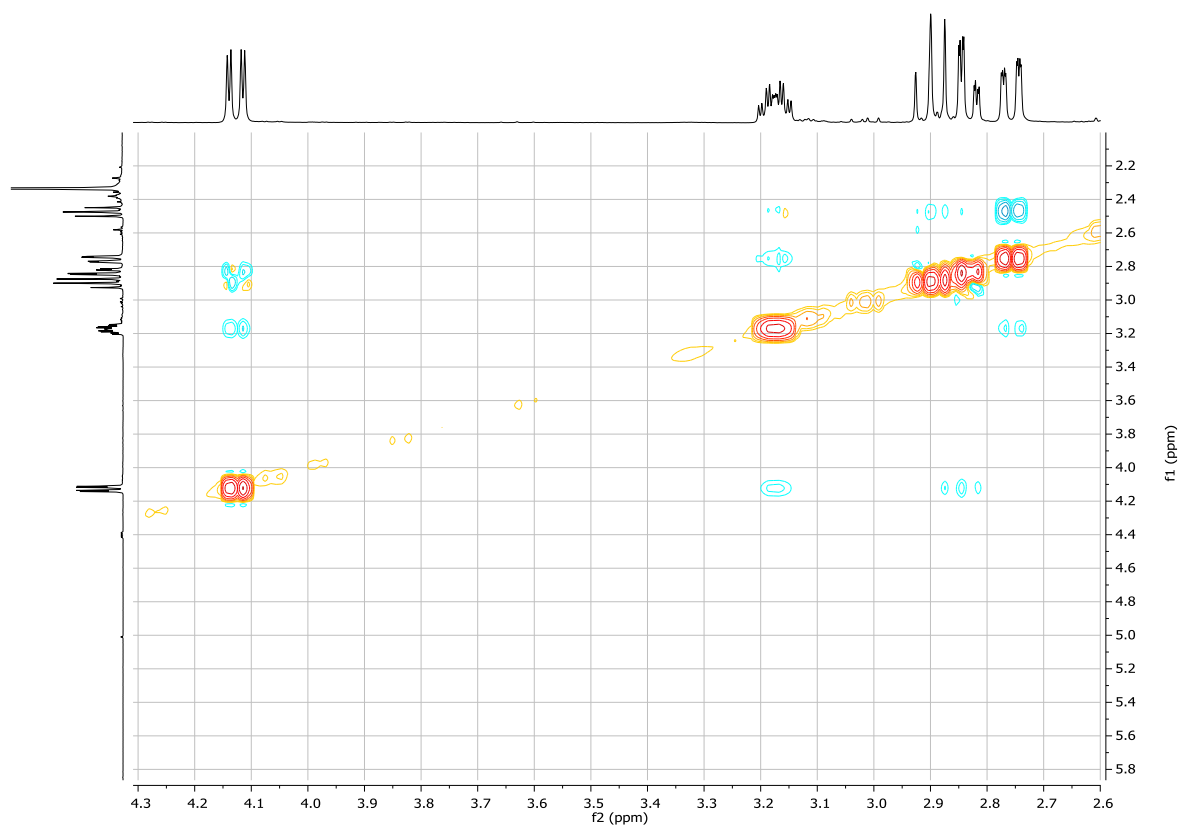


6-Fluoro-5-methoxy-2-(p-tolyl)thiochroman-4-one 24v

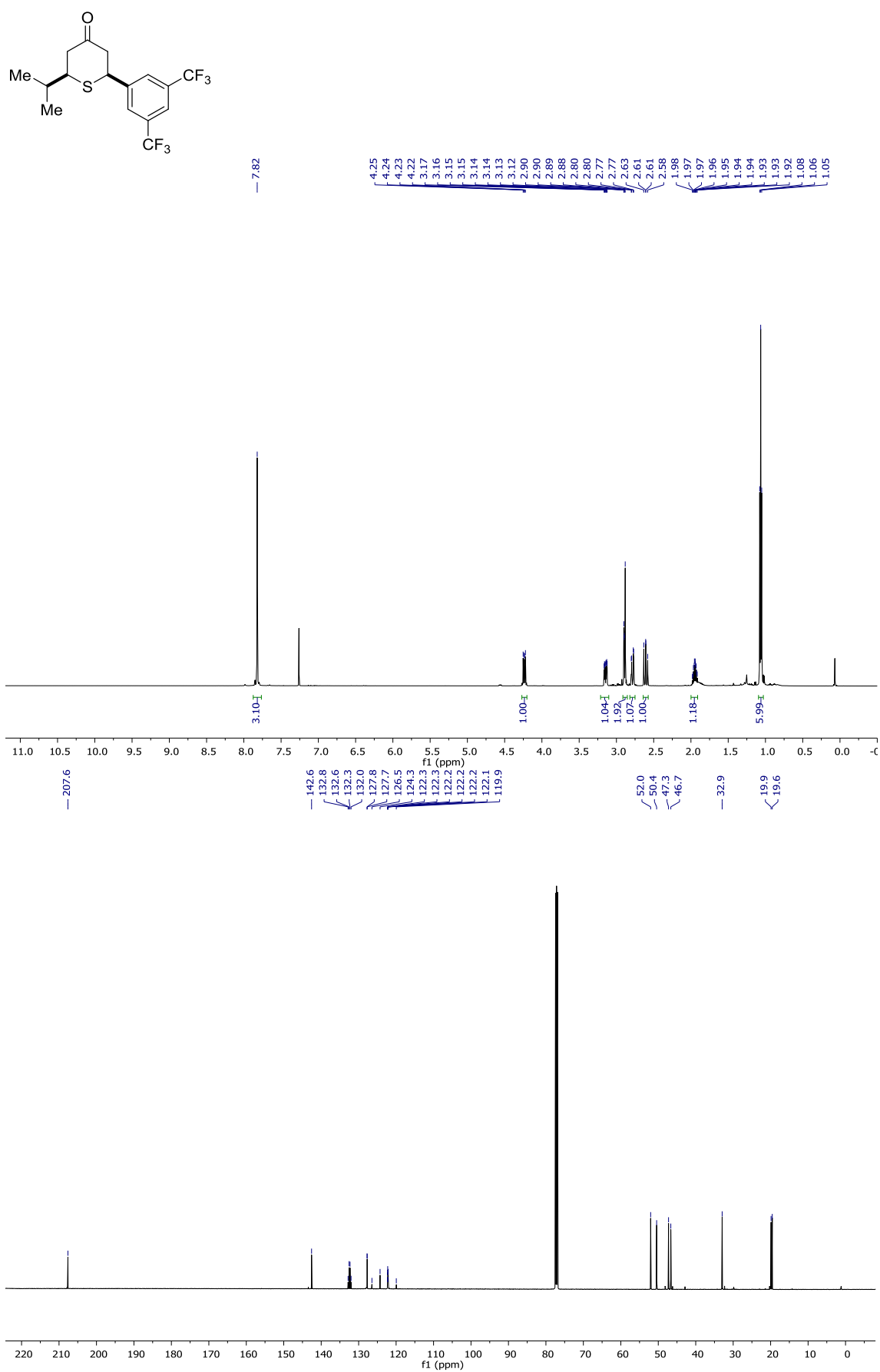
2-(3-Chloropropyl)-2,3,5,6,7,8-hexahydro-4H-thiocrhomen-4-one 25a

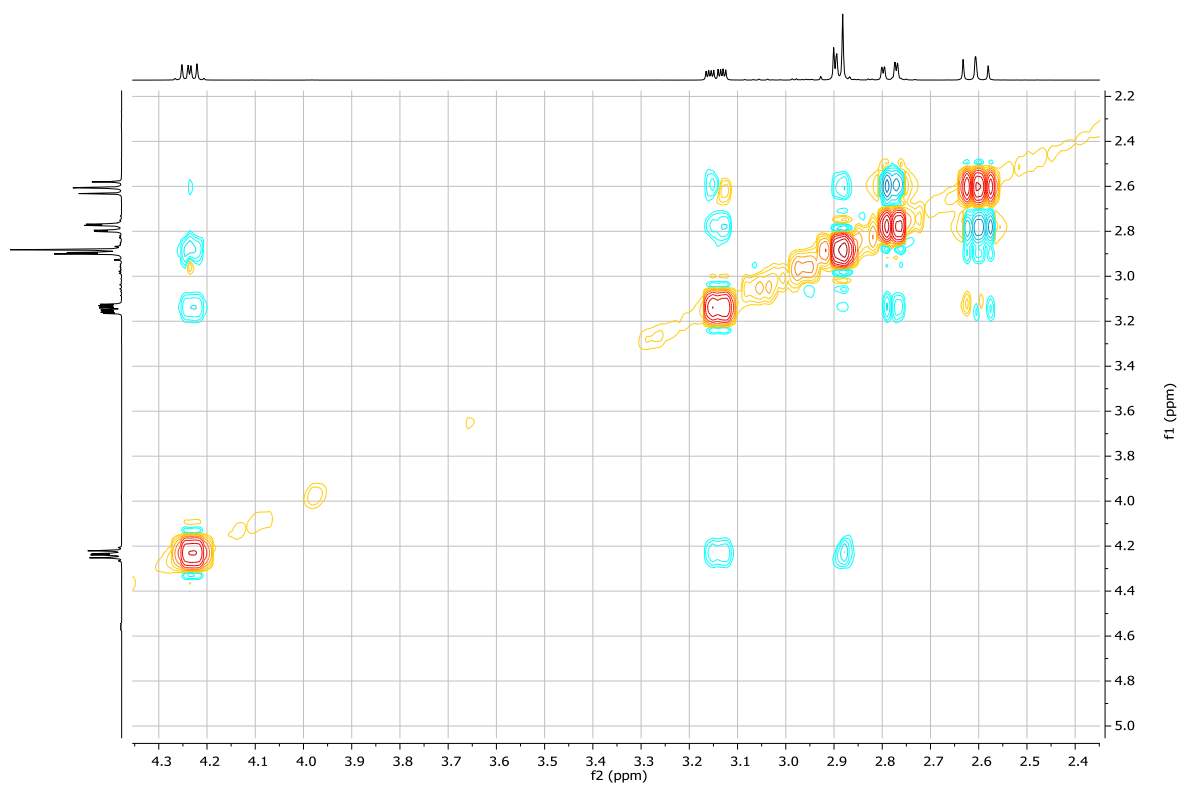


2-Hexyl-6-(*p*-tolyl)tetrahydro-4*H*-thiopyran-4-one 26a

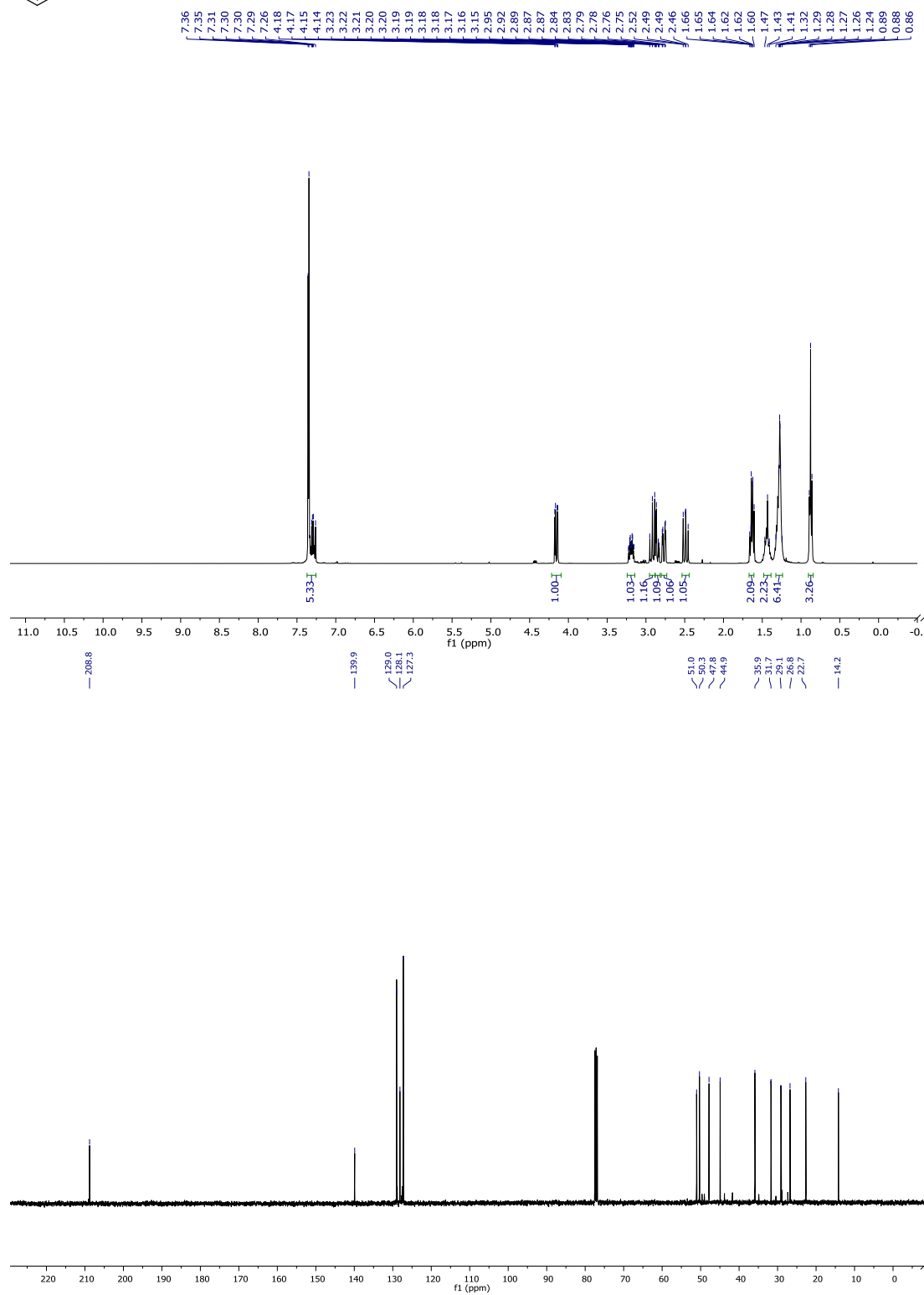
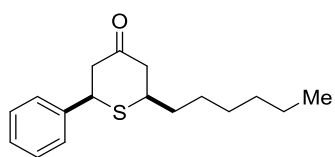


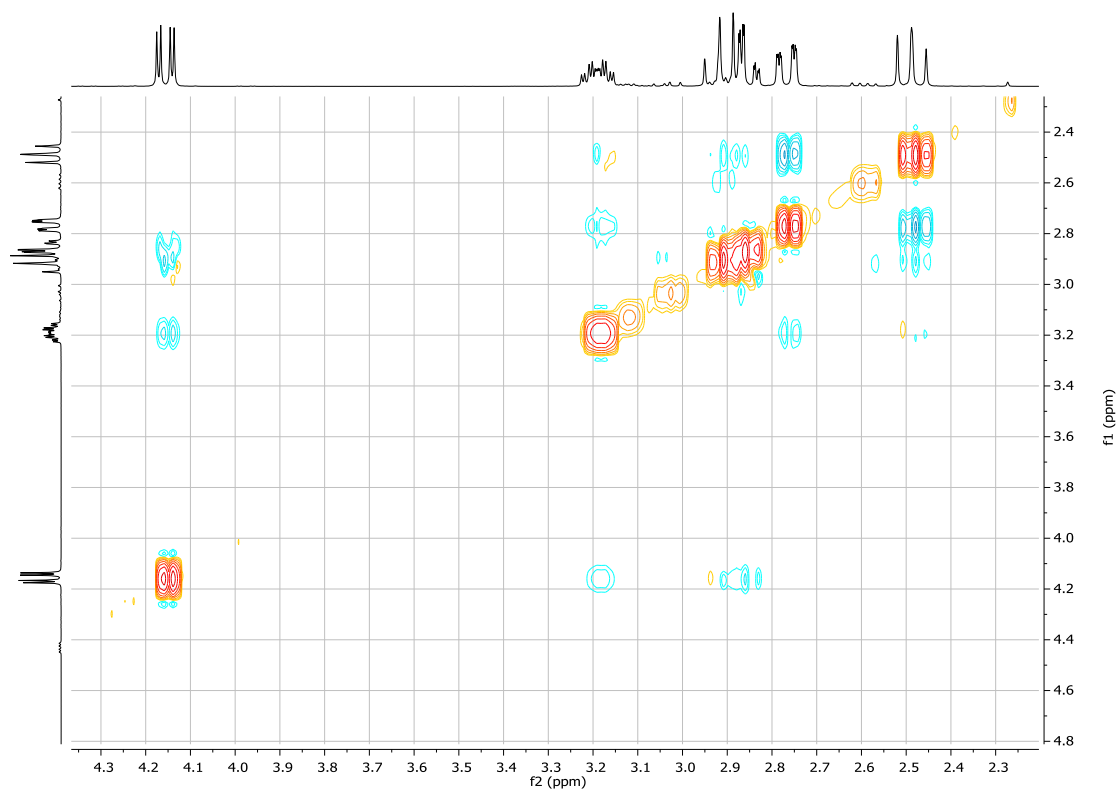
2-[3,5-Bis(trifluoromethyl)phenyl]-6-isopropyltetrahydro-4H-thiopyran-4-one 26b

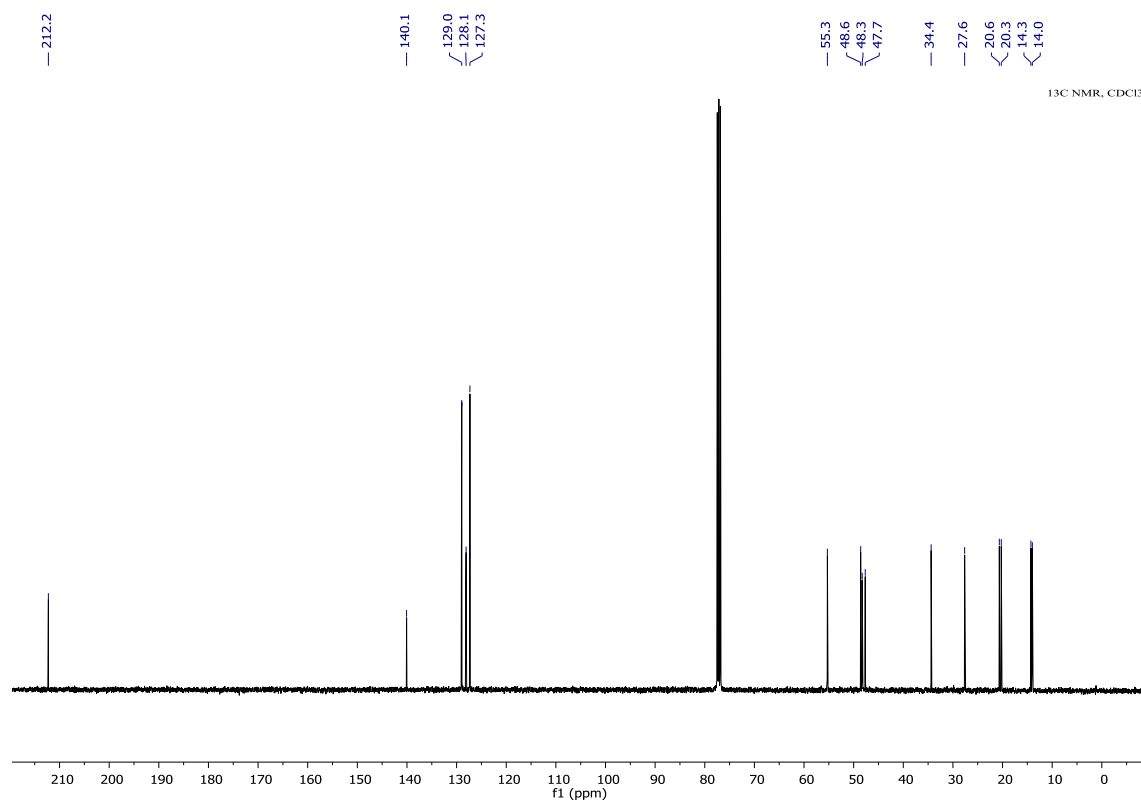
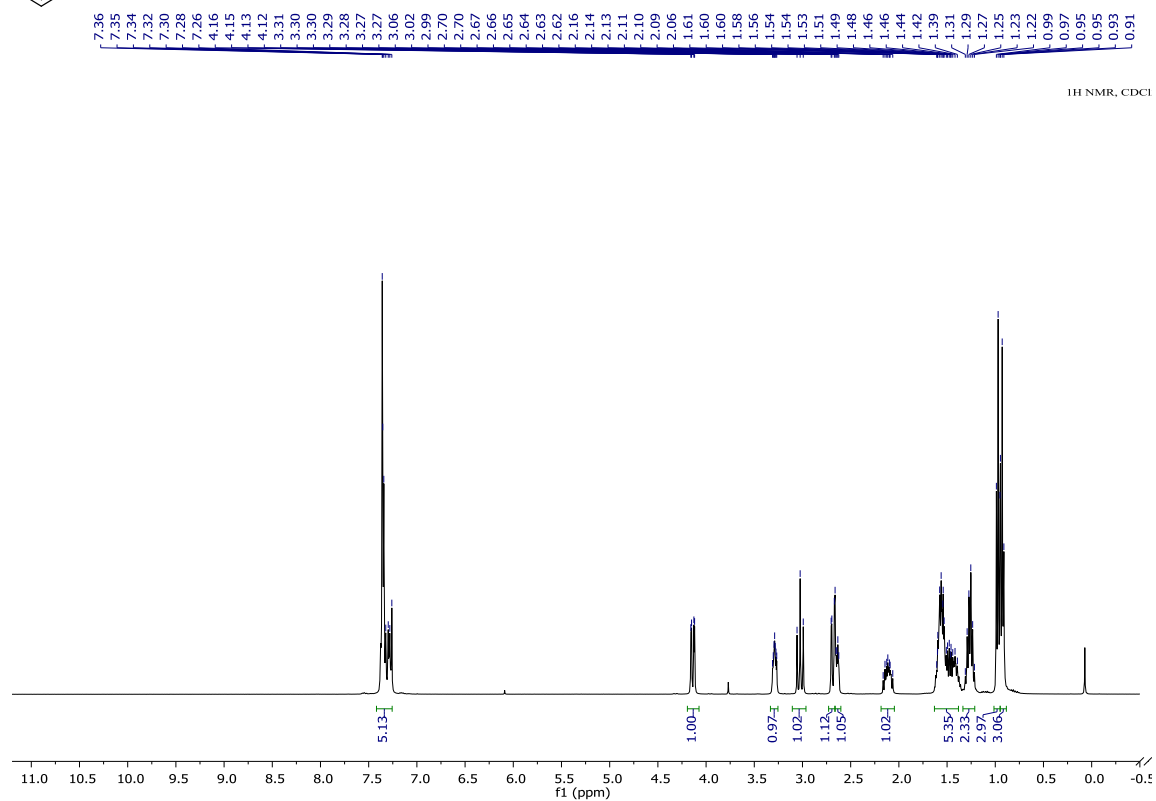
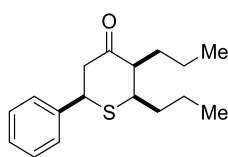




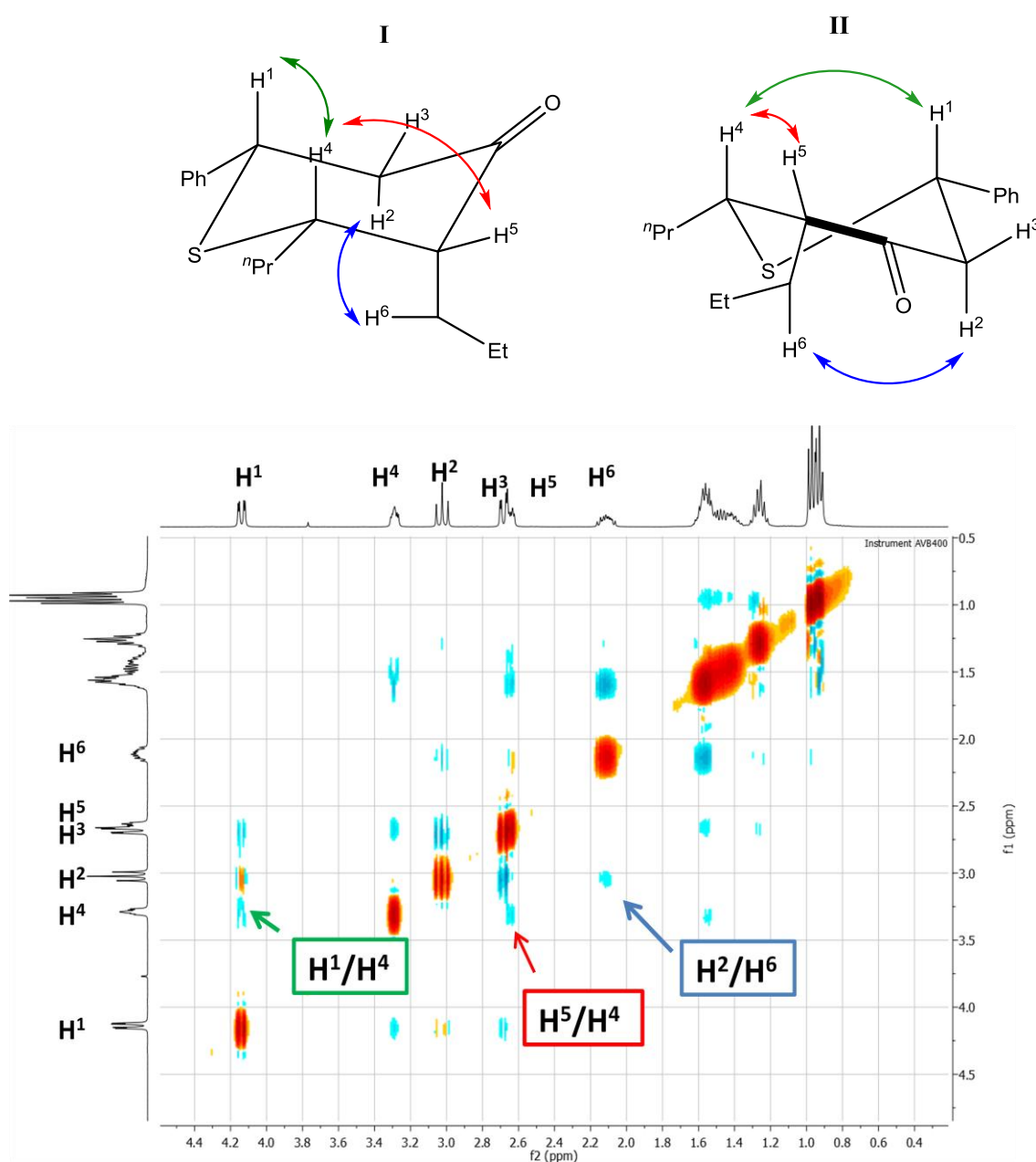
2-Hexyl-6-phenyltetrahydro-4*H*-thiopyran-4-one 26c

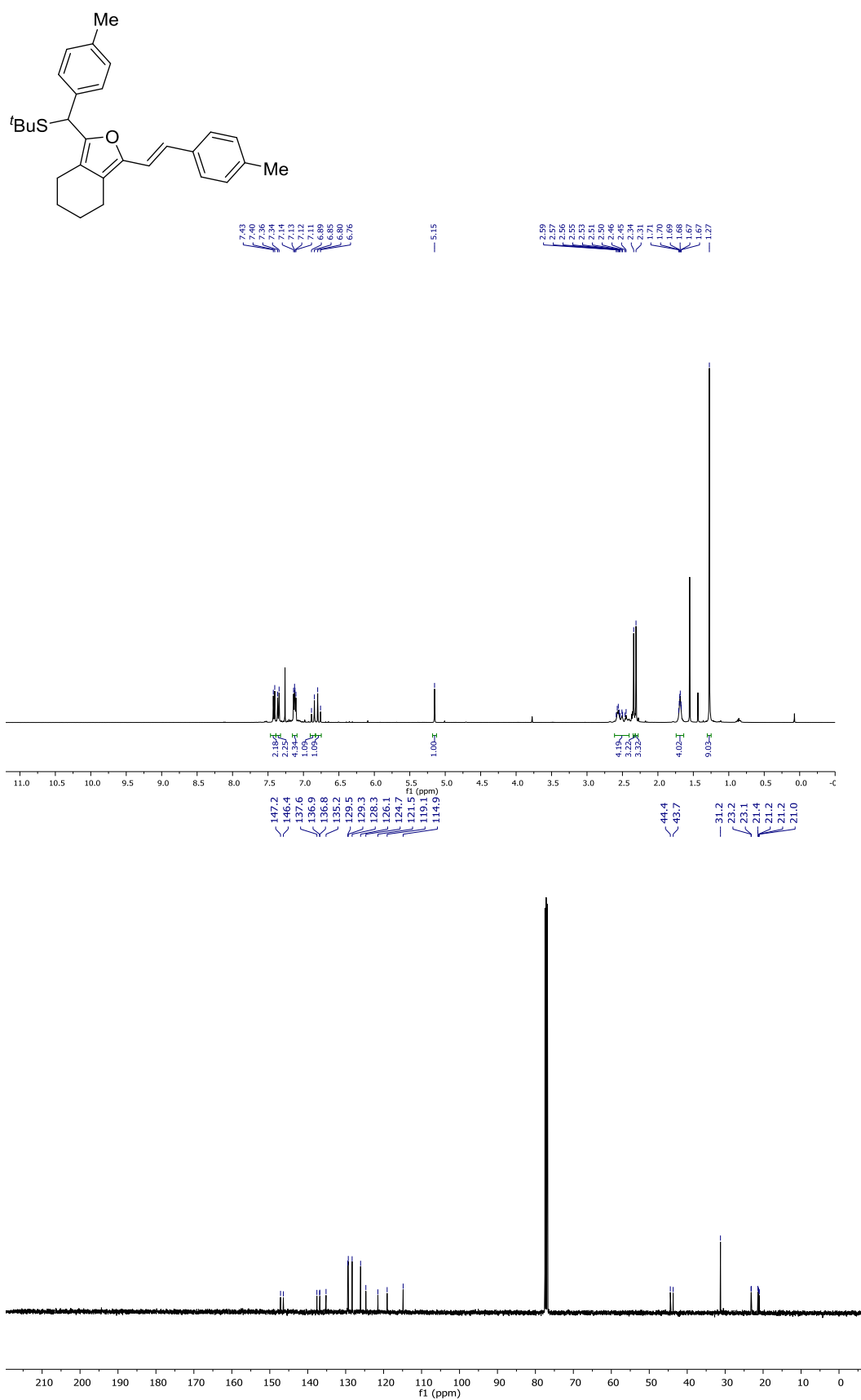


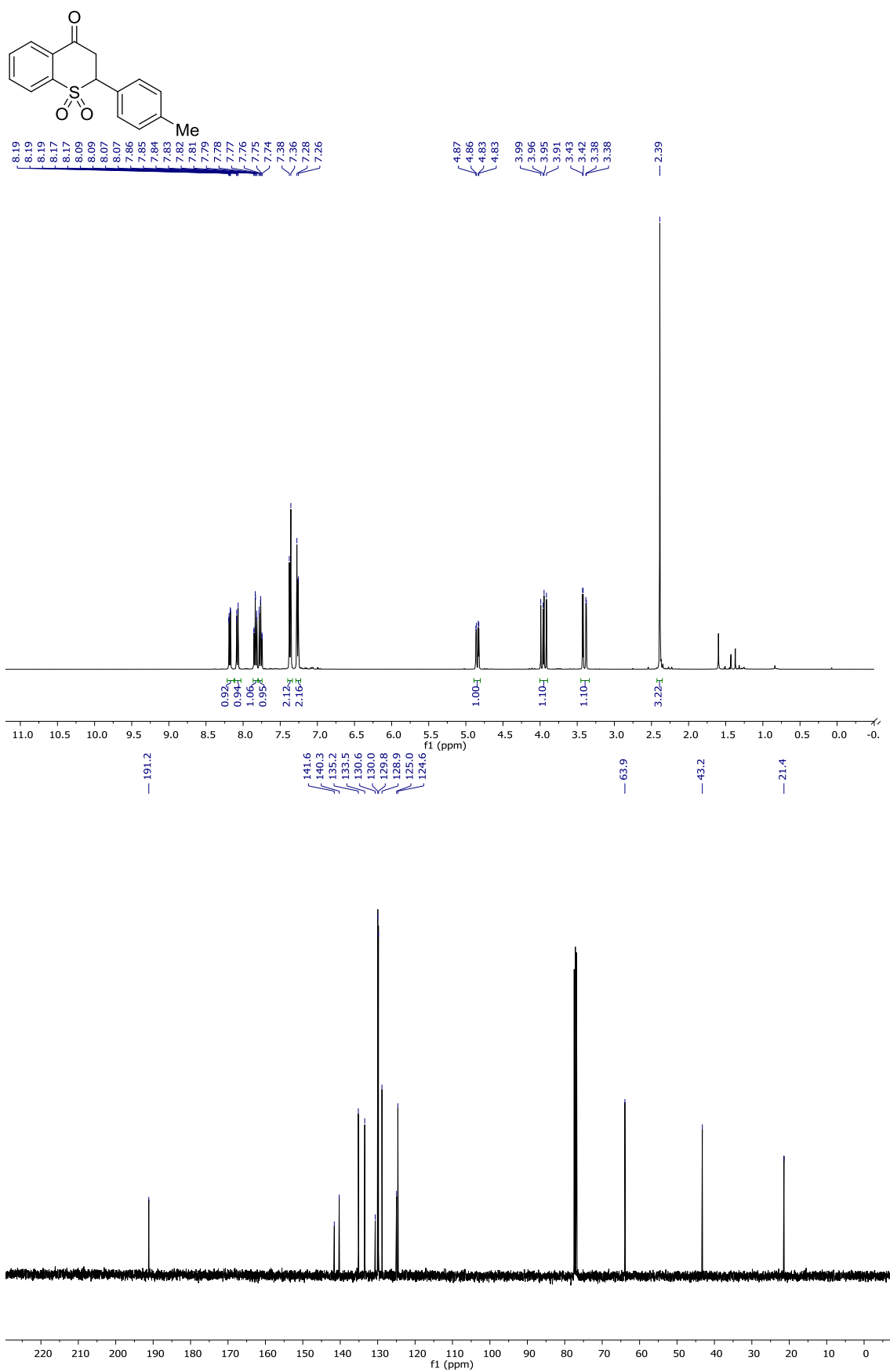


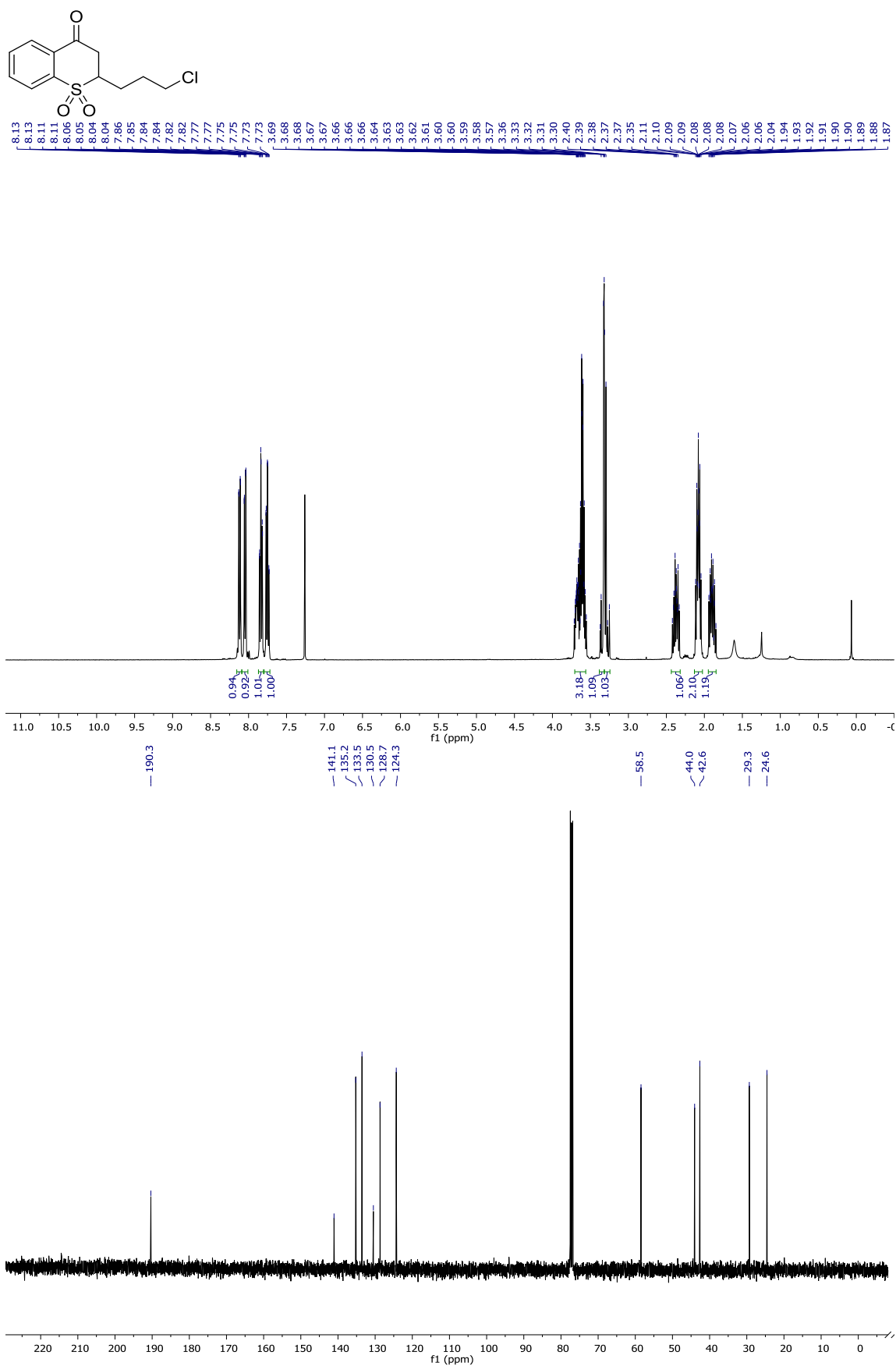
6-Phenyl-2,3-dipropyltetrahydro-4H-thiopyran-4-one 26d

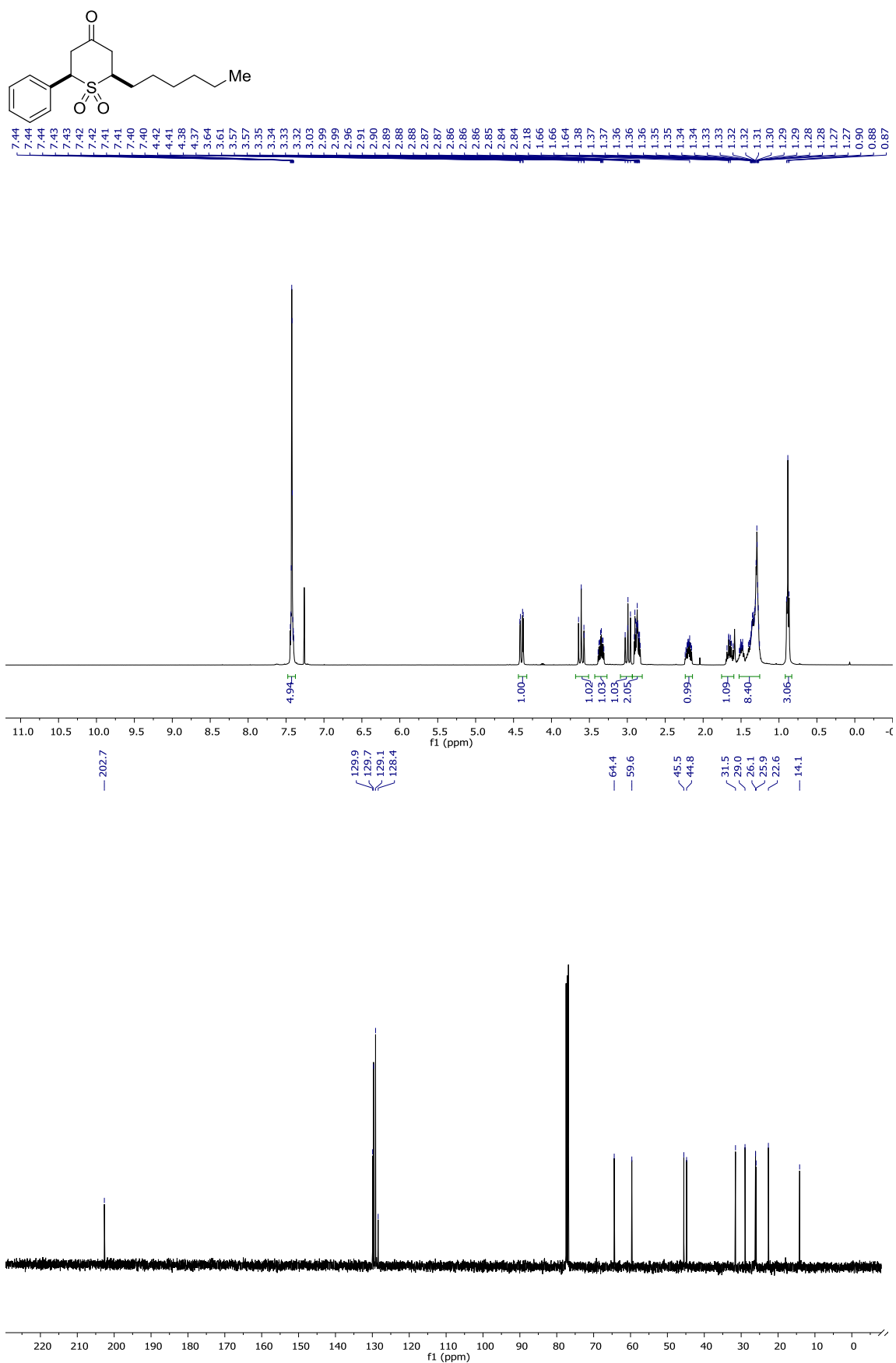
The coupling constants between H^1/H^2 on the one hand and H^1/H^3 on the other hand are typical axial (H^1)/axial (H^2) and axial (H^1)/equatorial (H^3) coupling constants in a chair conformation (**I**).¹⁰⁷ The NOESY spectra shows a strong correlation between H^1 and H^4 , suggesting these are in *cis*-configuration. In addition, the NOESY correlation between H^4 and H^5 also suggest a *cis* axial (H^4)/equatorial (H^5) arrangement. Furthermore, another correlation supporting our assignment was found between H^2 and H^6 . Alternatively, if the molecule exists in a twist chair conformation in solution, as shown in structure **II**, the NOESY data indicates the same relative stereochemistry.

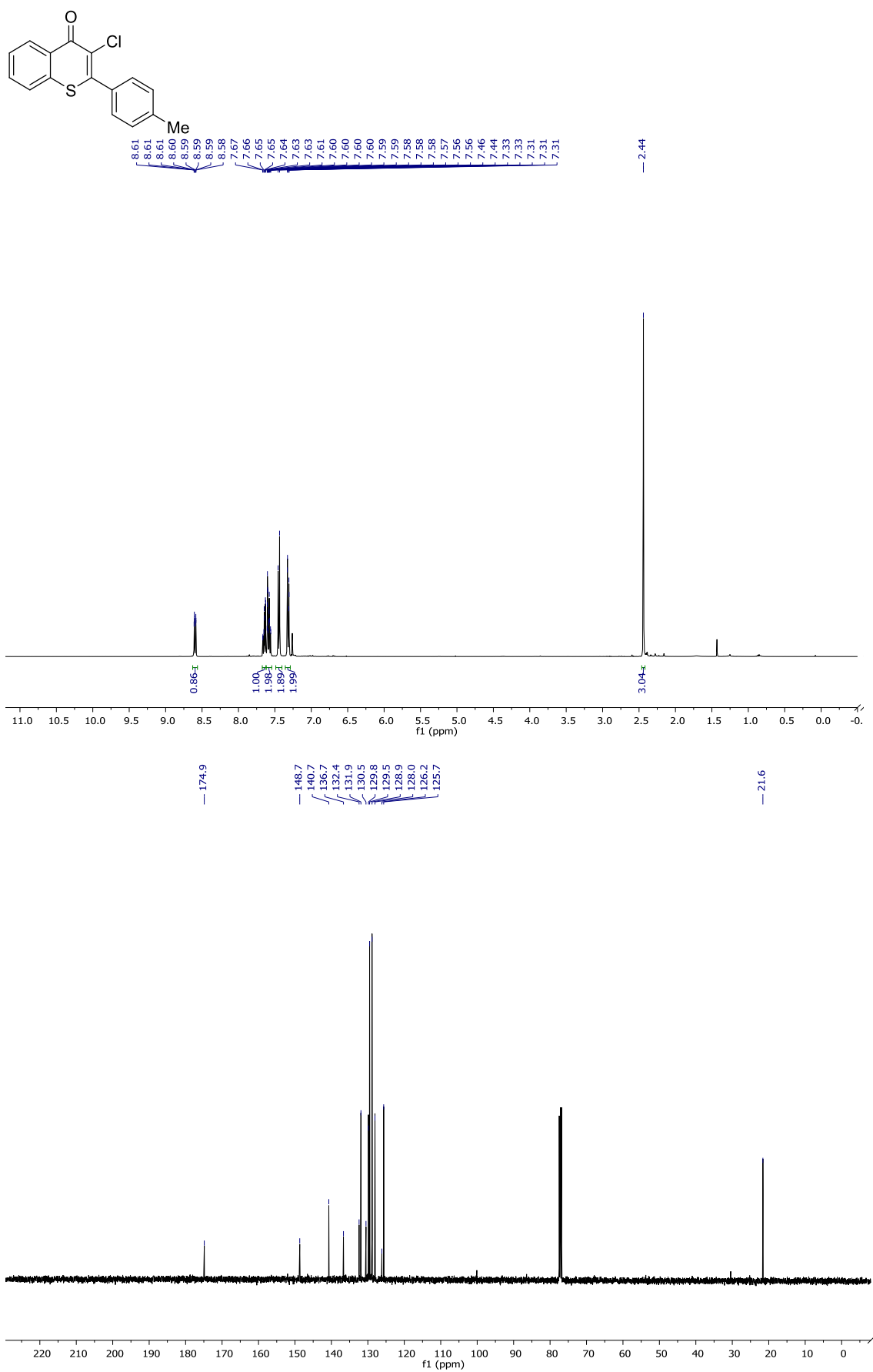


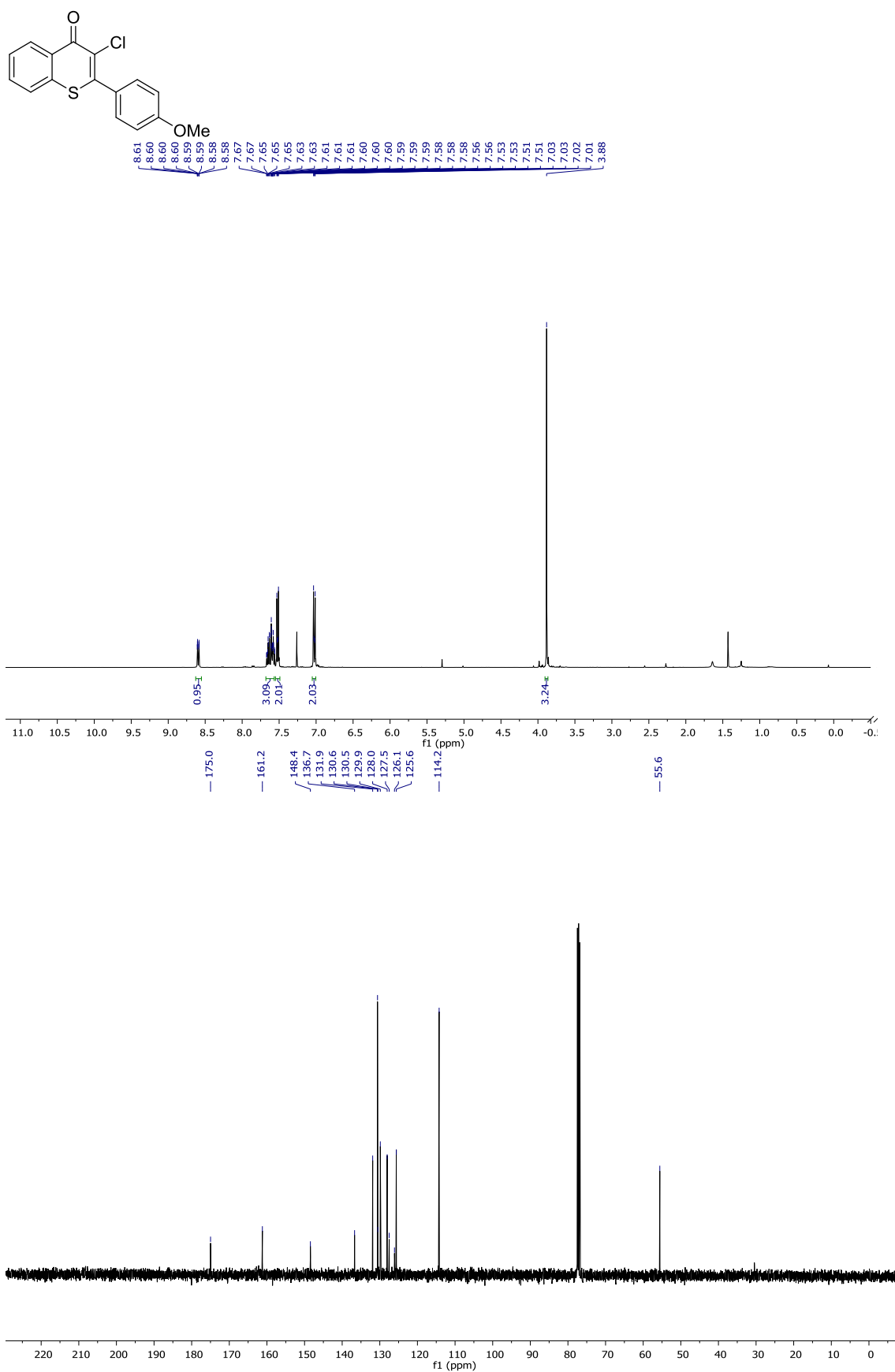
(E)-1-[(*tert*-butylthio)(*p*-tolyl)methyl]-3-(4-methylstyryl)-4,5,6,7-tetrahydroisobenzofuran 33

2-(*p*-Tolyl)thiochroman-4-one 1,1-dioxide 34a

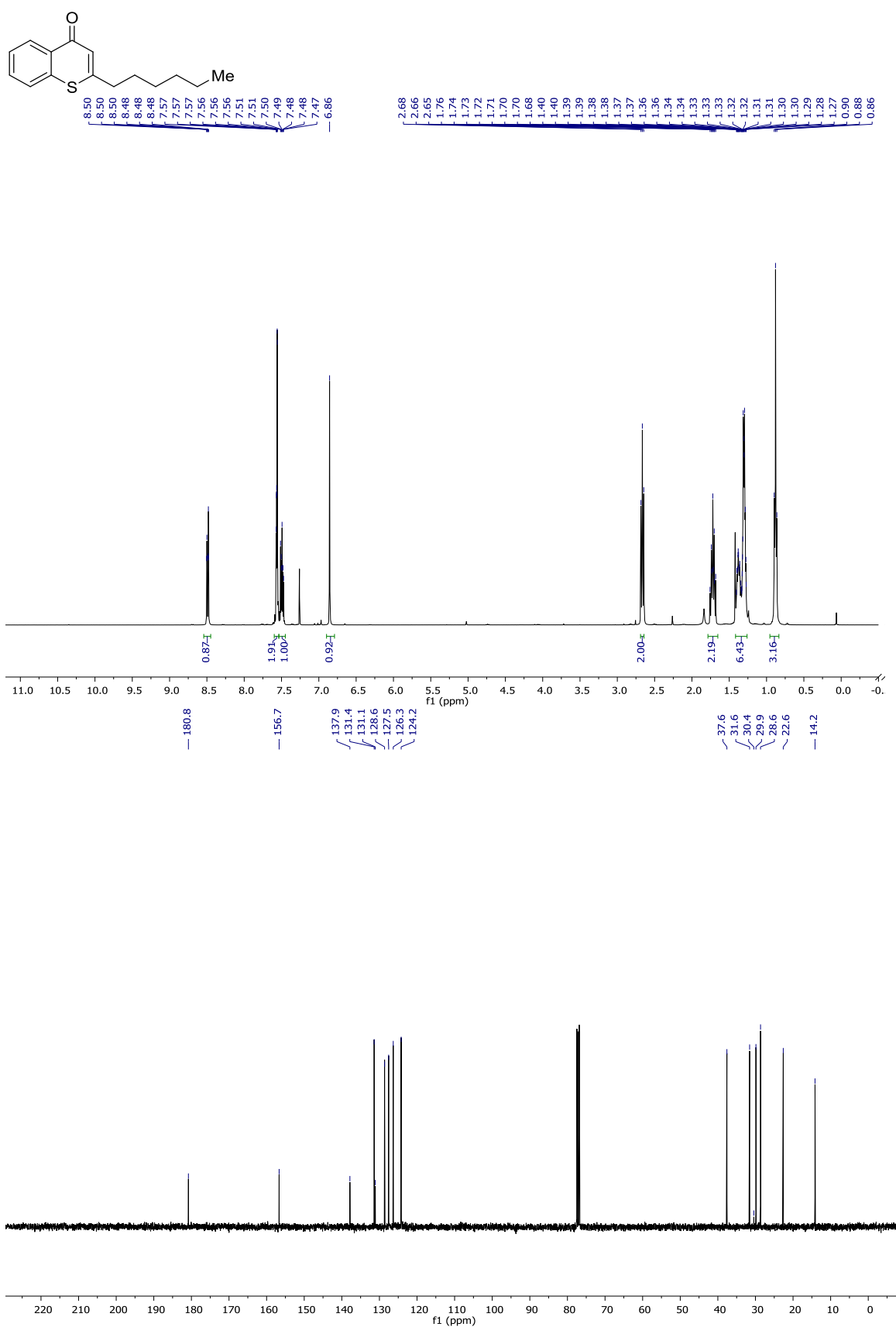
2-(3-chloropropyl)thiochroman-4-one 1,1-dioxide 34b

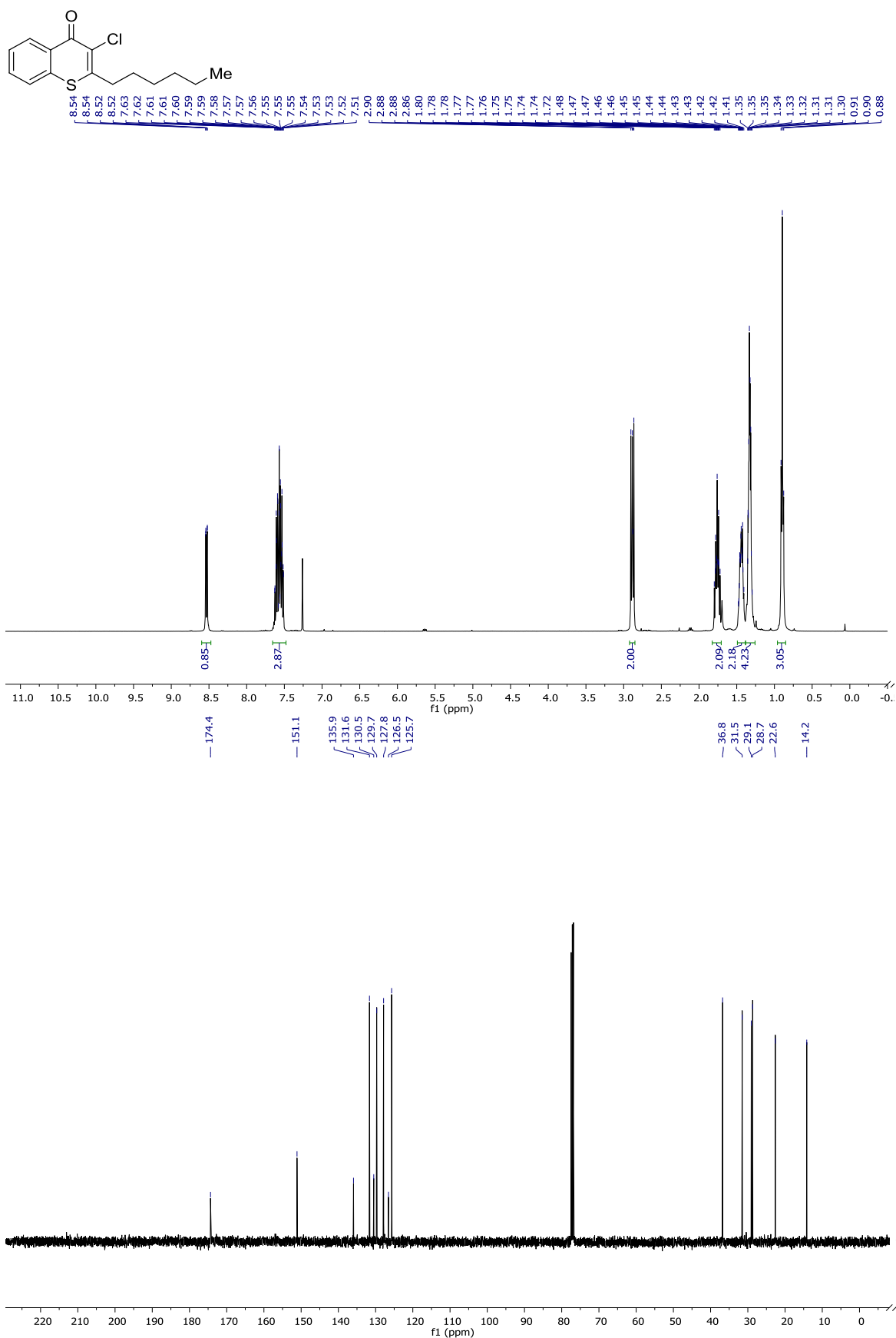
2-Hexyl-6-phenyltetrahydro-4H-thiopyran-4-one 1,1-dioxide 34c

3-Chloro-2-(p-tolyl)-4H-thiophene-4-one 36a

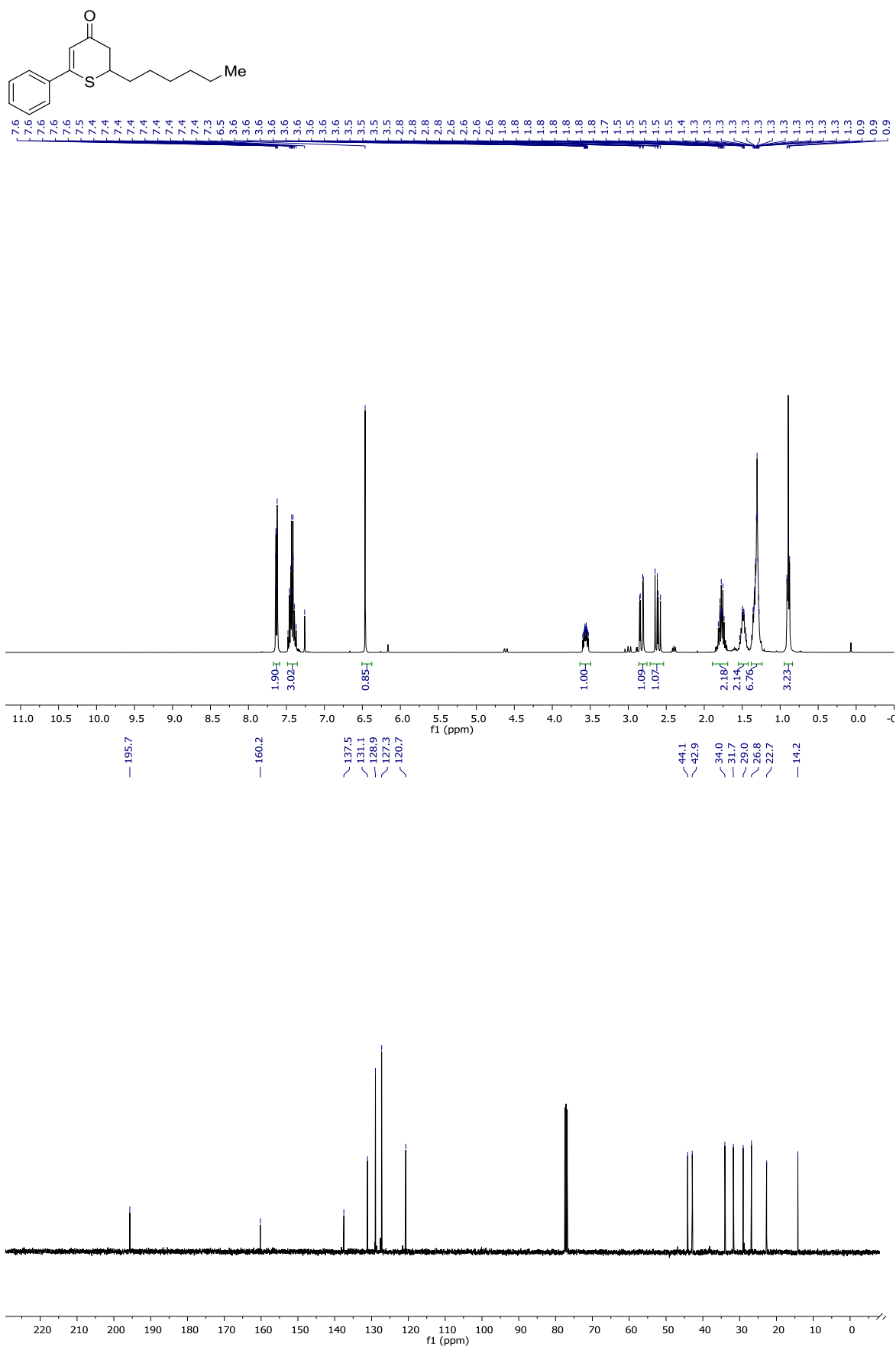
3-Chloro-2-(4-methoxyphenyl)-4H-thiophene-4-one 36b

2-Hexyl-4H-thiochromen-4-one 35c

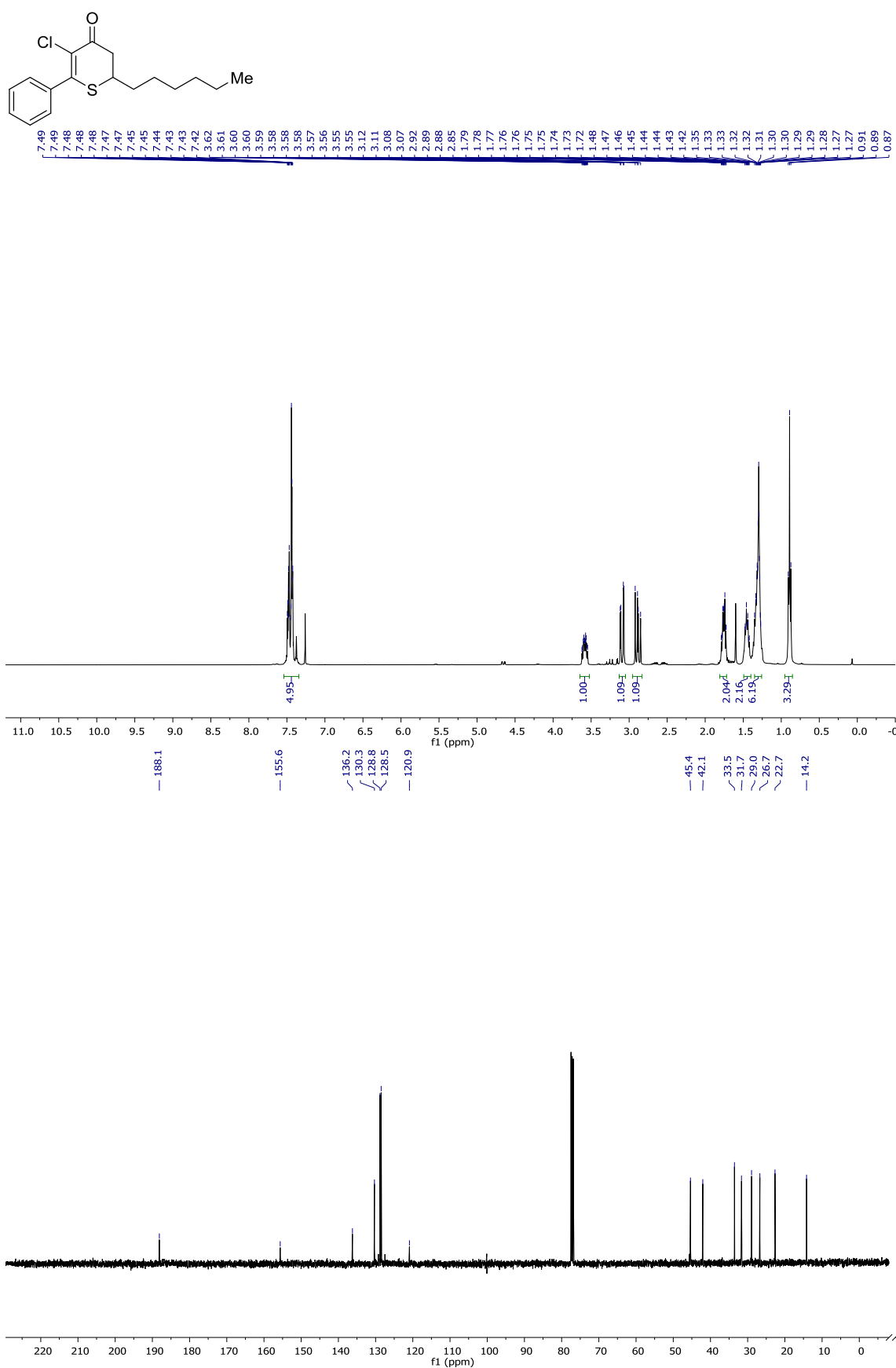


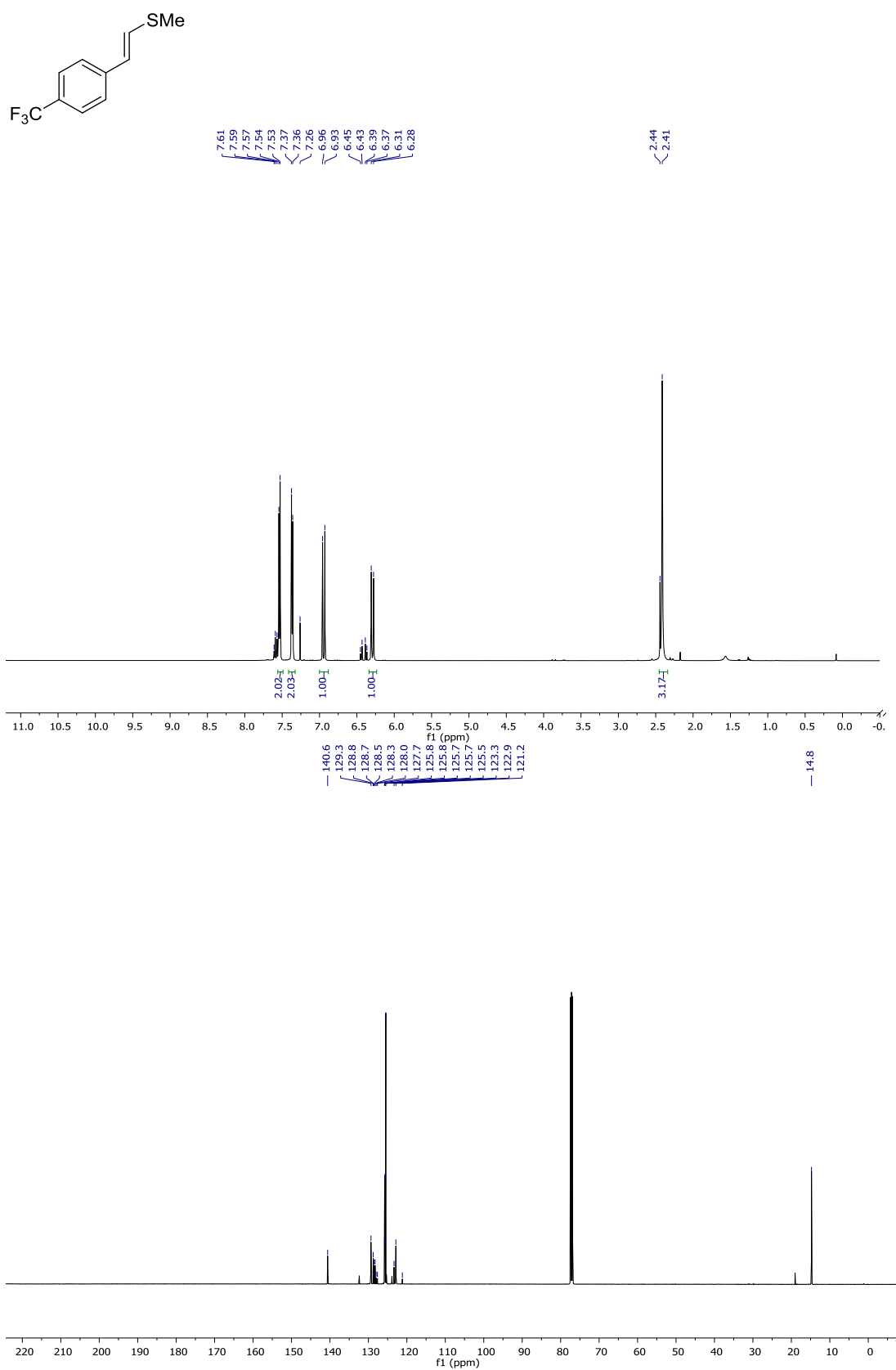
3-Chloro-2-hexyl-4H-thiophene-4-one 36c

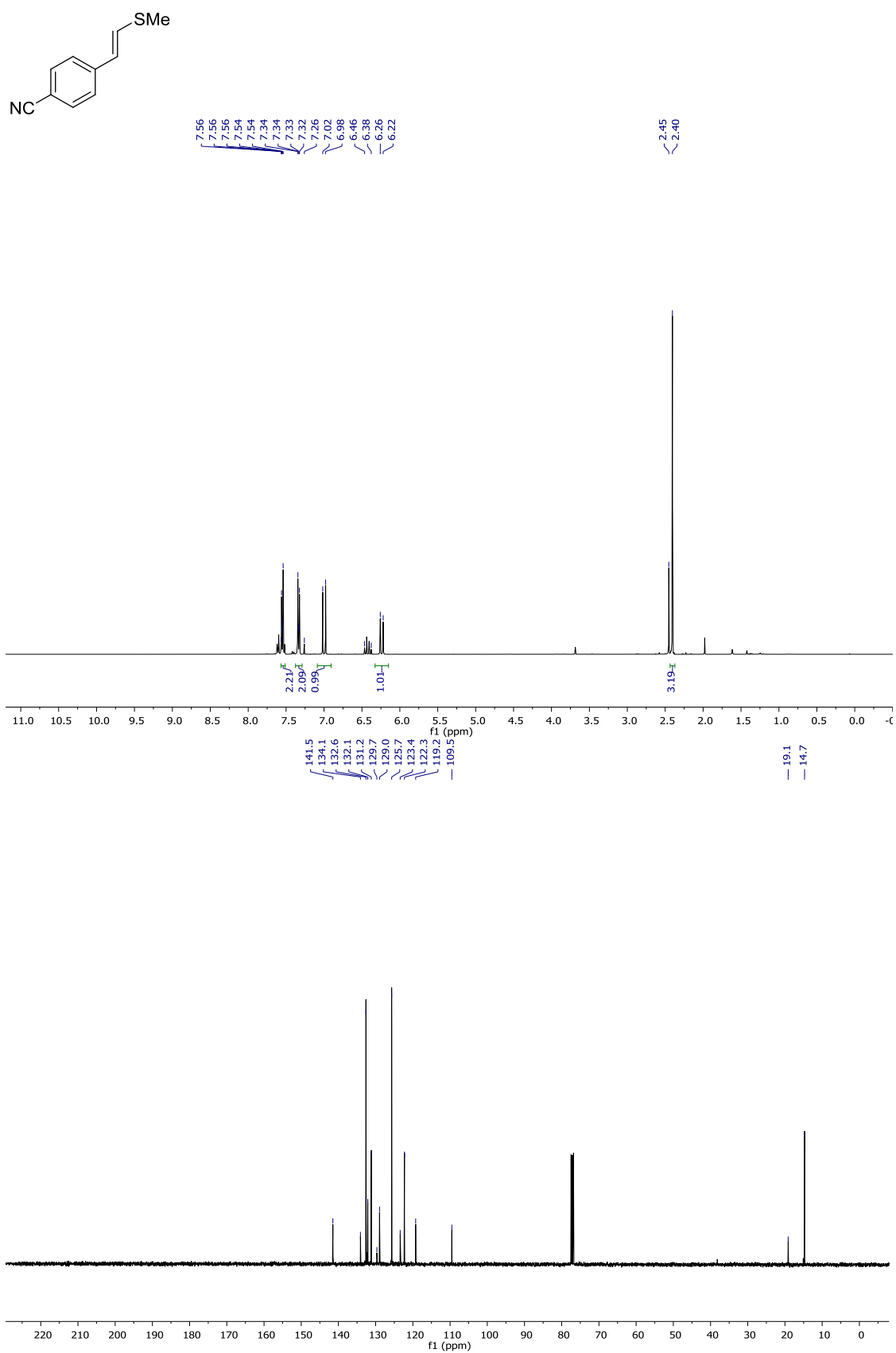
2-Hexyl-6-phenyl-2,3-dihydro-4H-thiopyran-4-one 35d

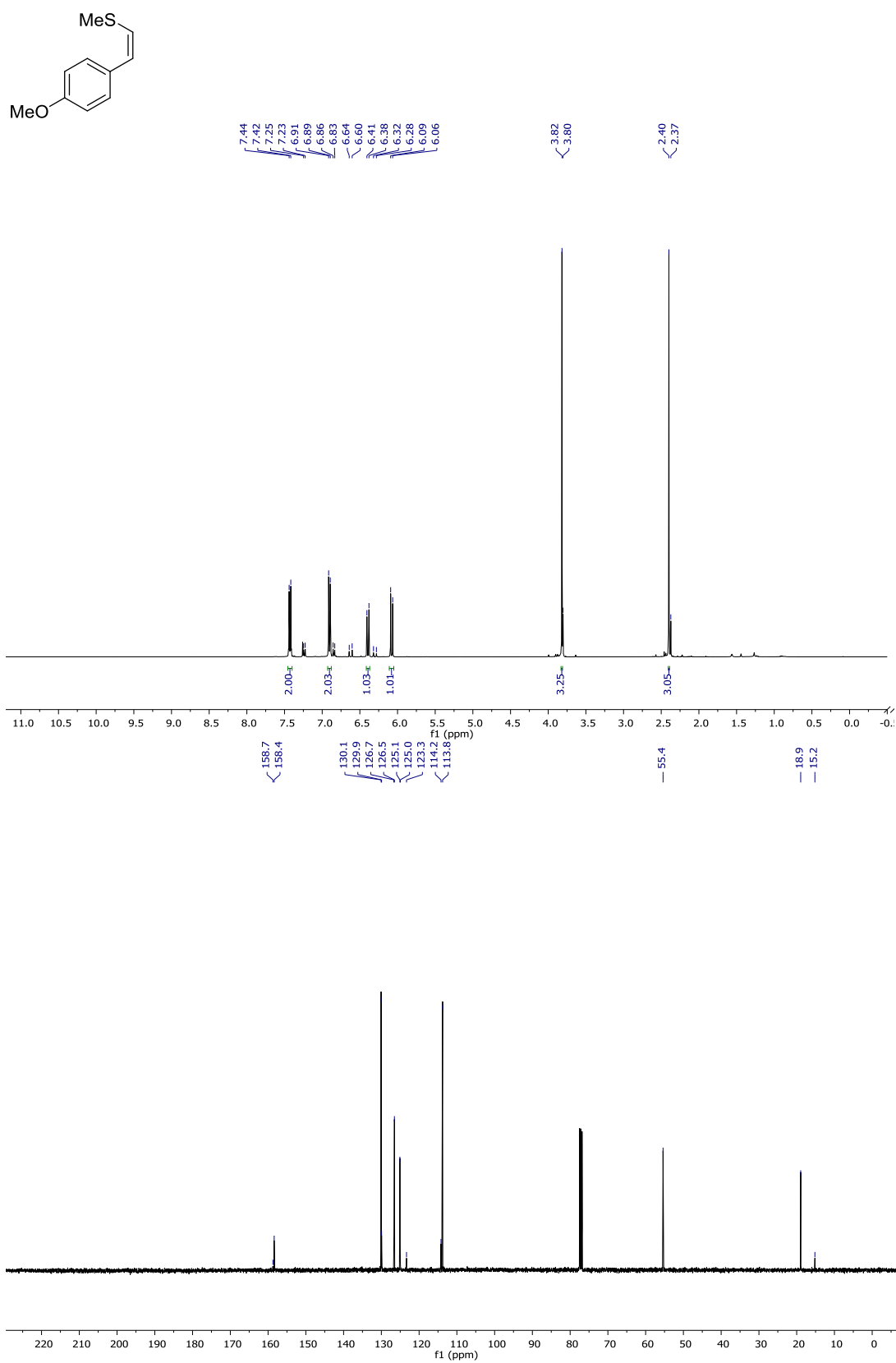


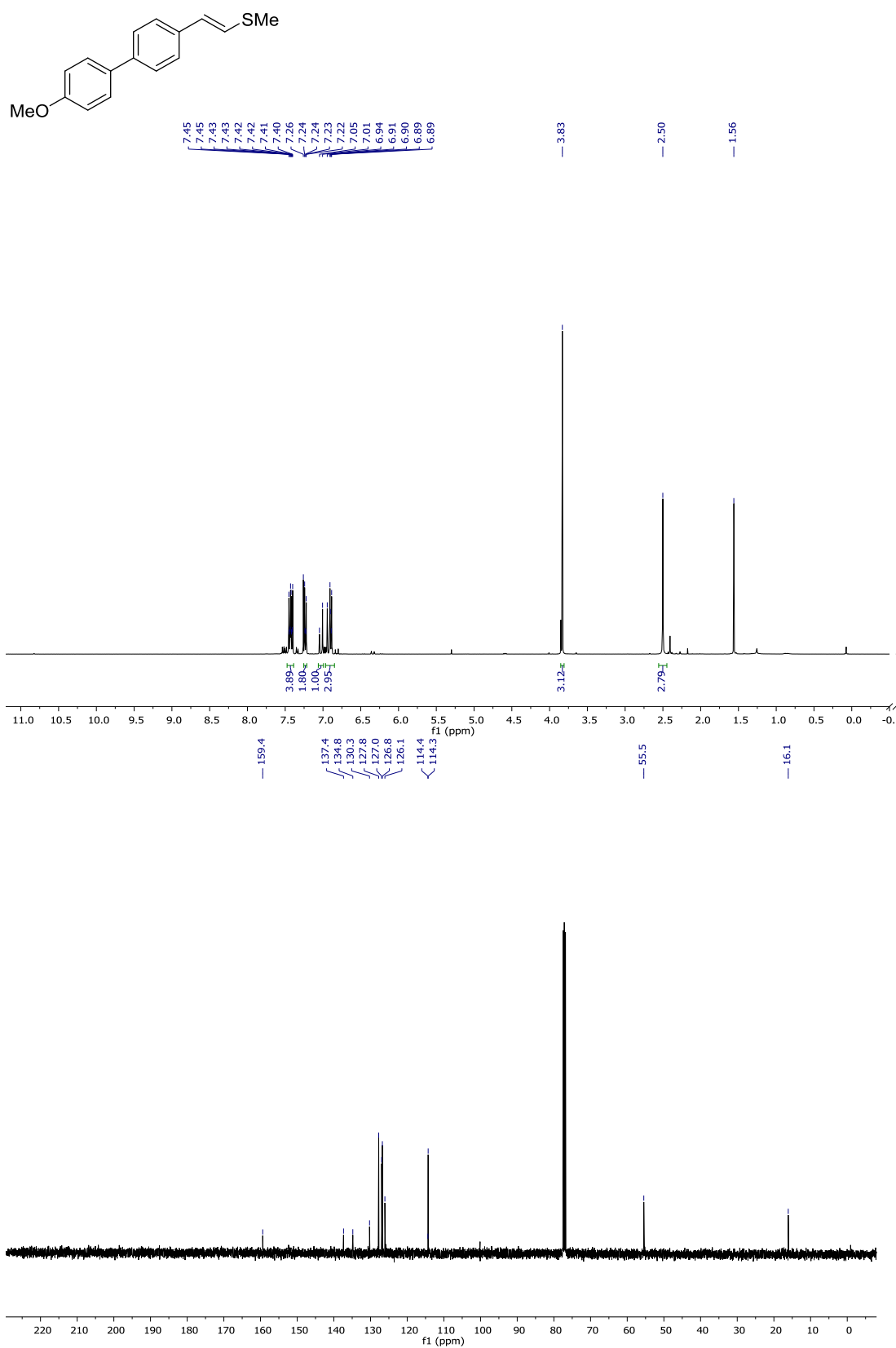
5-Chloro-2-hexyl-6-phenyl-2,3-dihydro-4H-thiopyran-4-one 36d

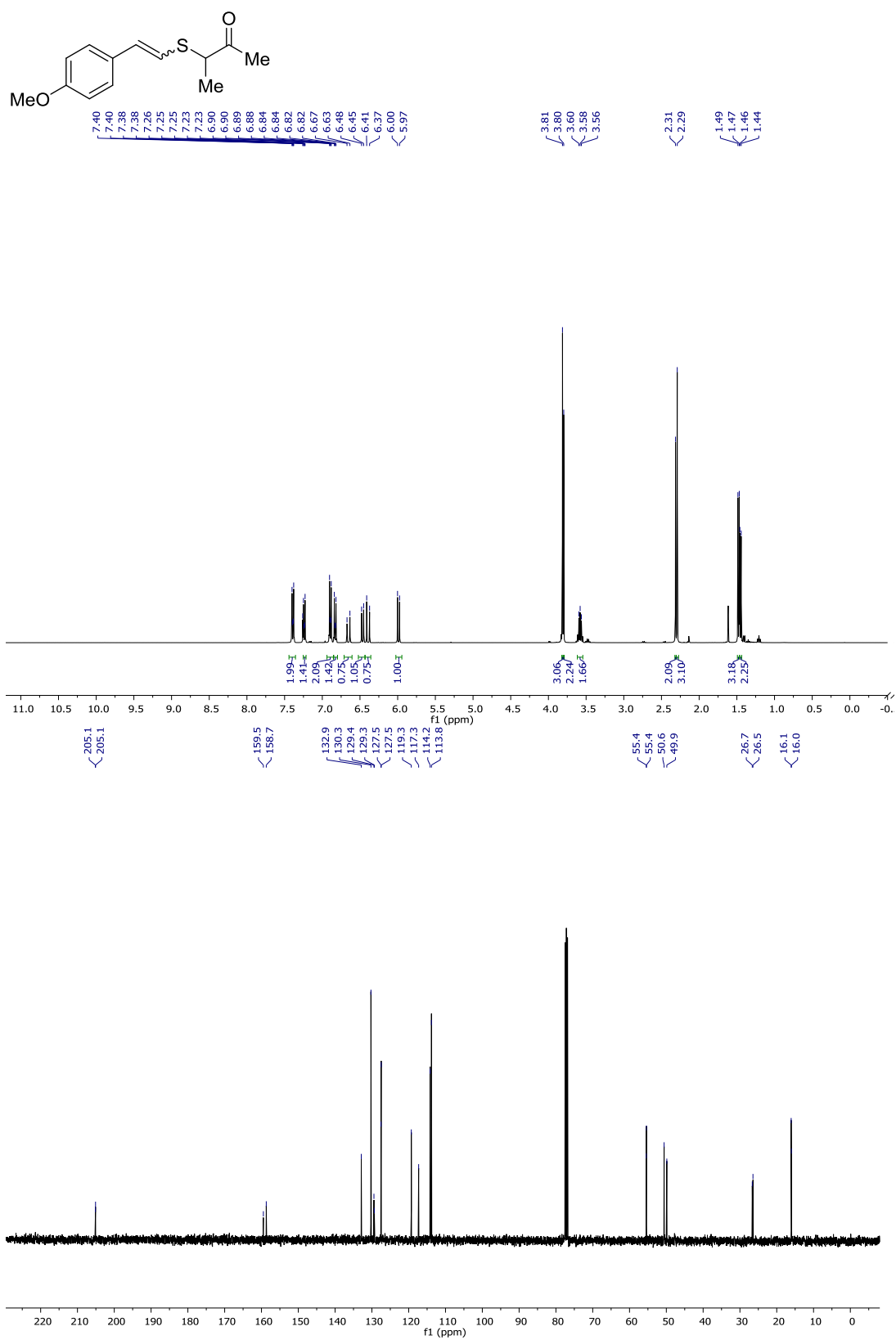


(E)-Methyl[4-(trifluoromethyl)styryl]sulfane 37c

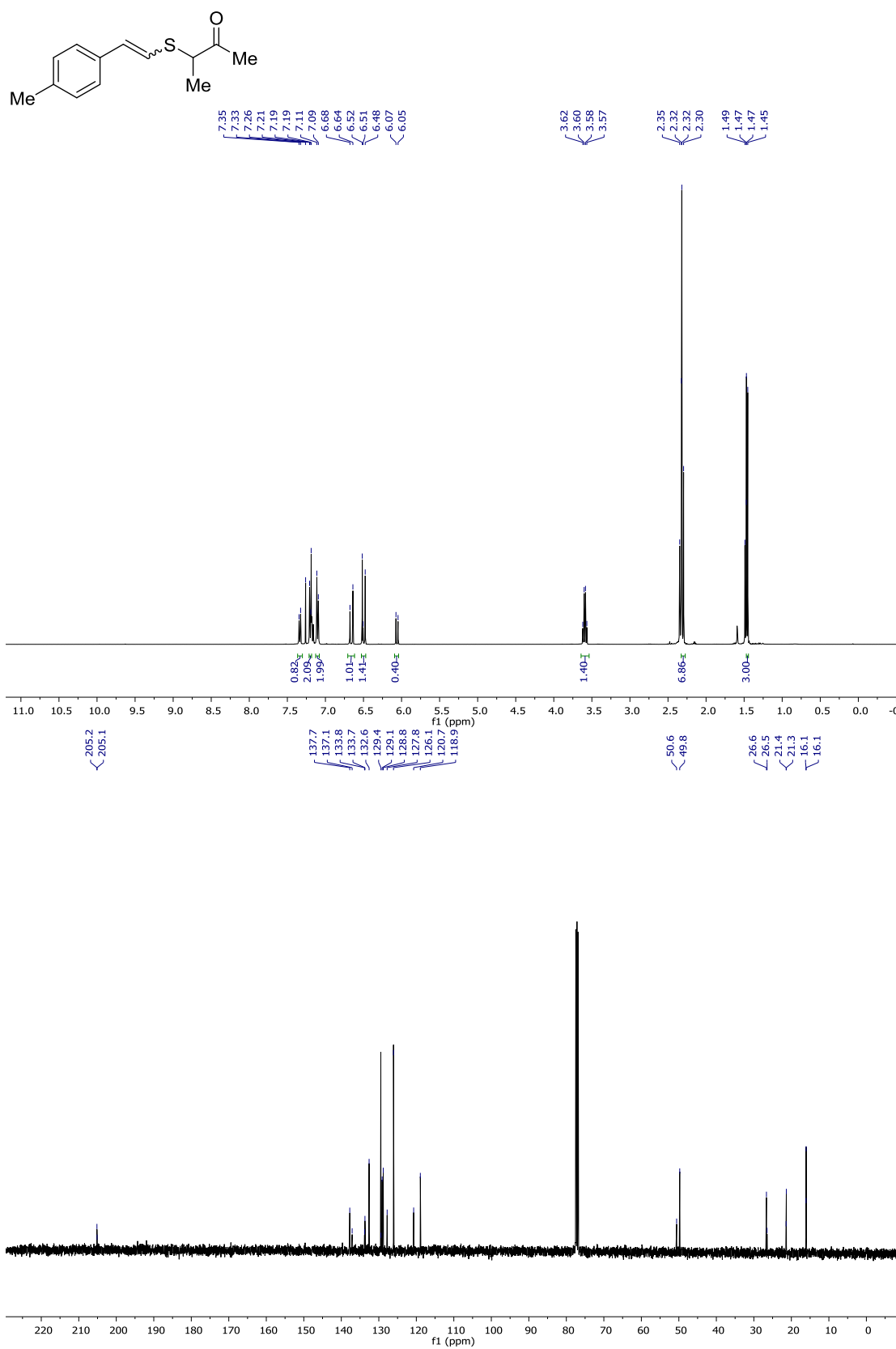
(E)-4-(2-(Methylthio)vinyl)benzonitrile 37d

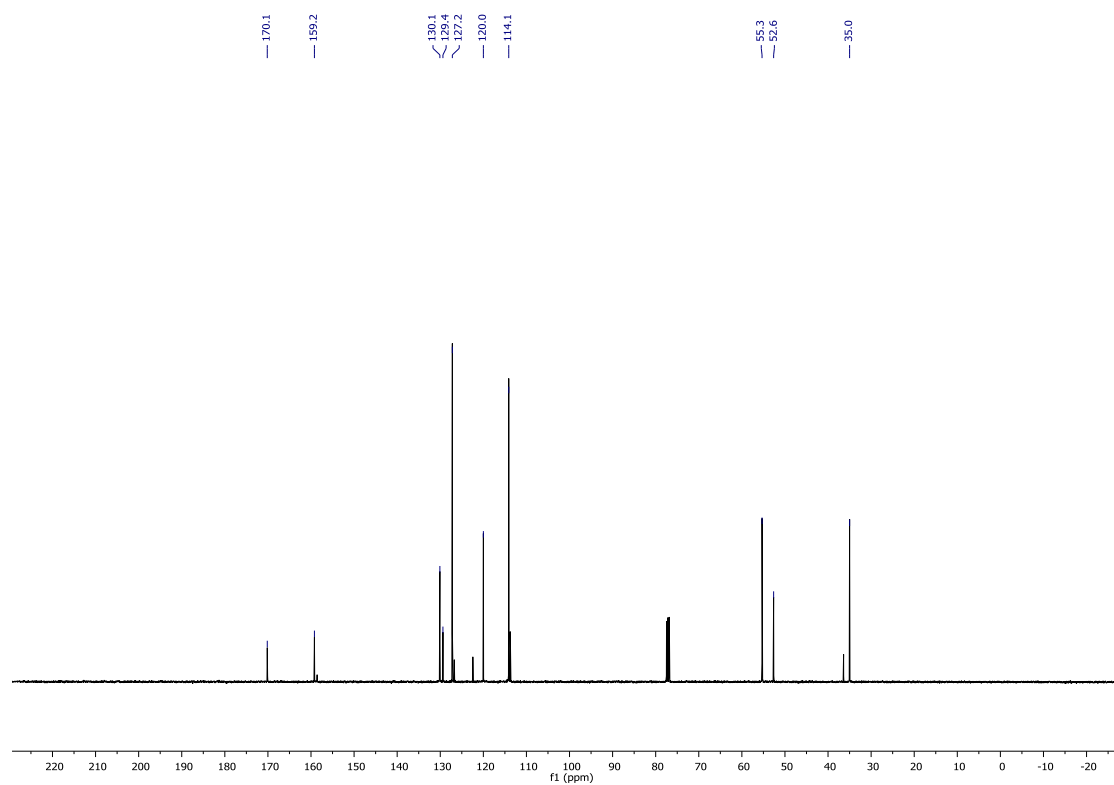
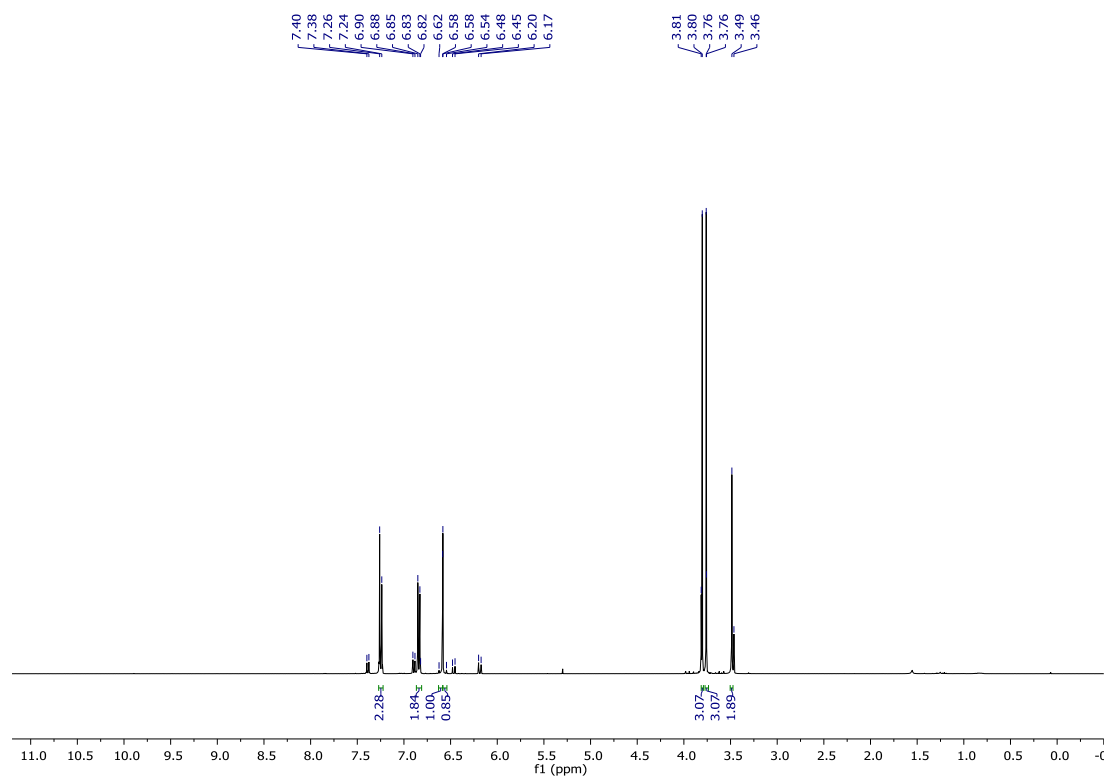
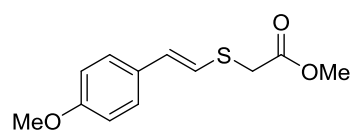
(Z)-(4-Methoxystyryl)(methyl)sulfane 37f

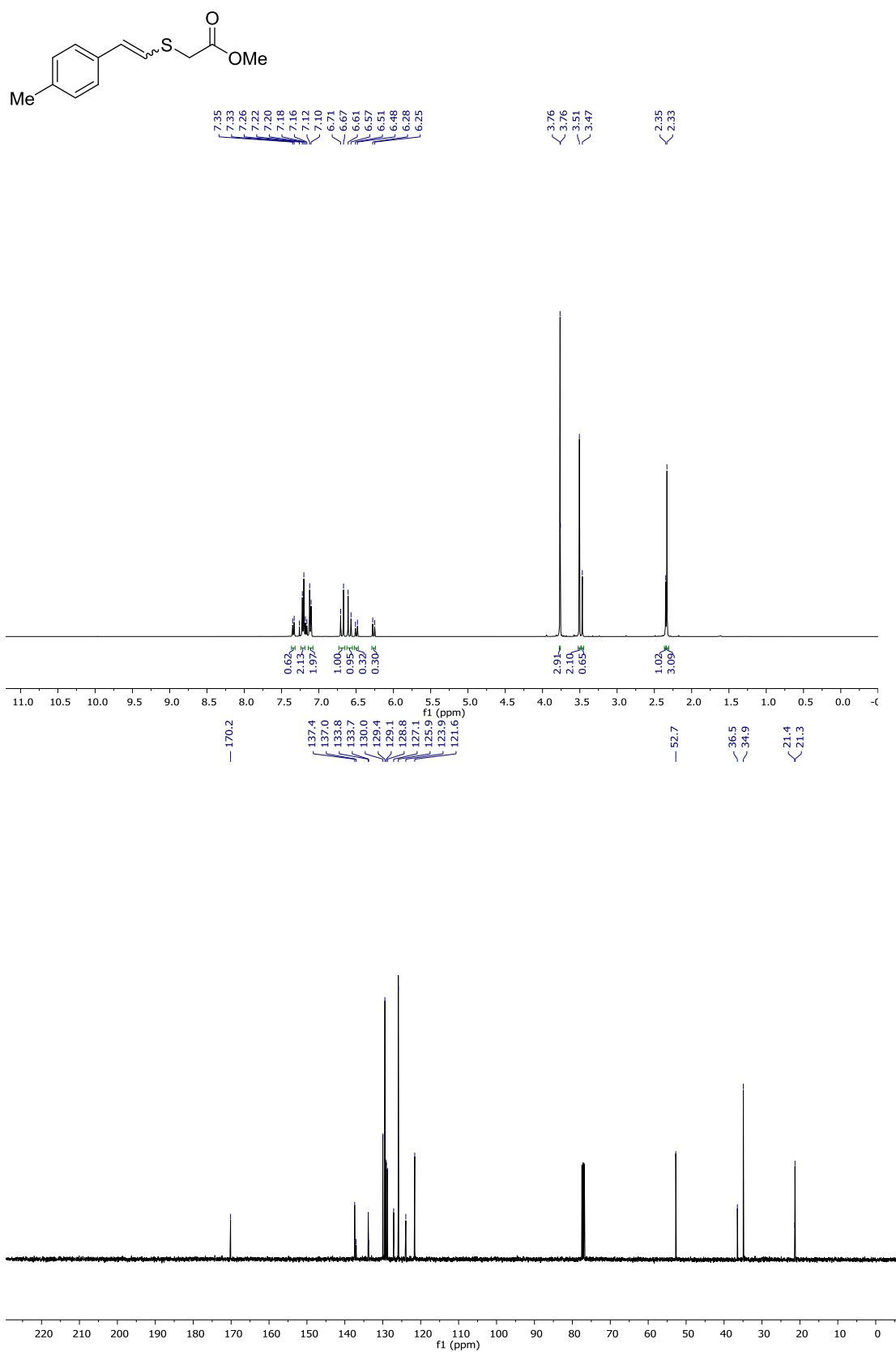
(E)-{2-[4'-methoxy-(1,1'-biphenyl)-4-yl]vinyl}(methyl)sulfane 42

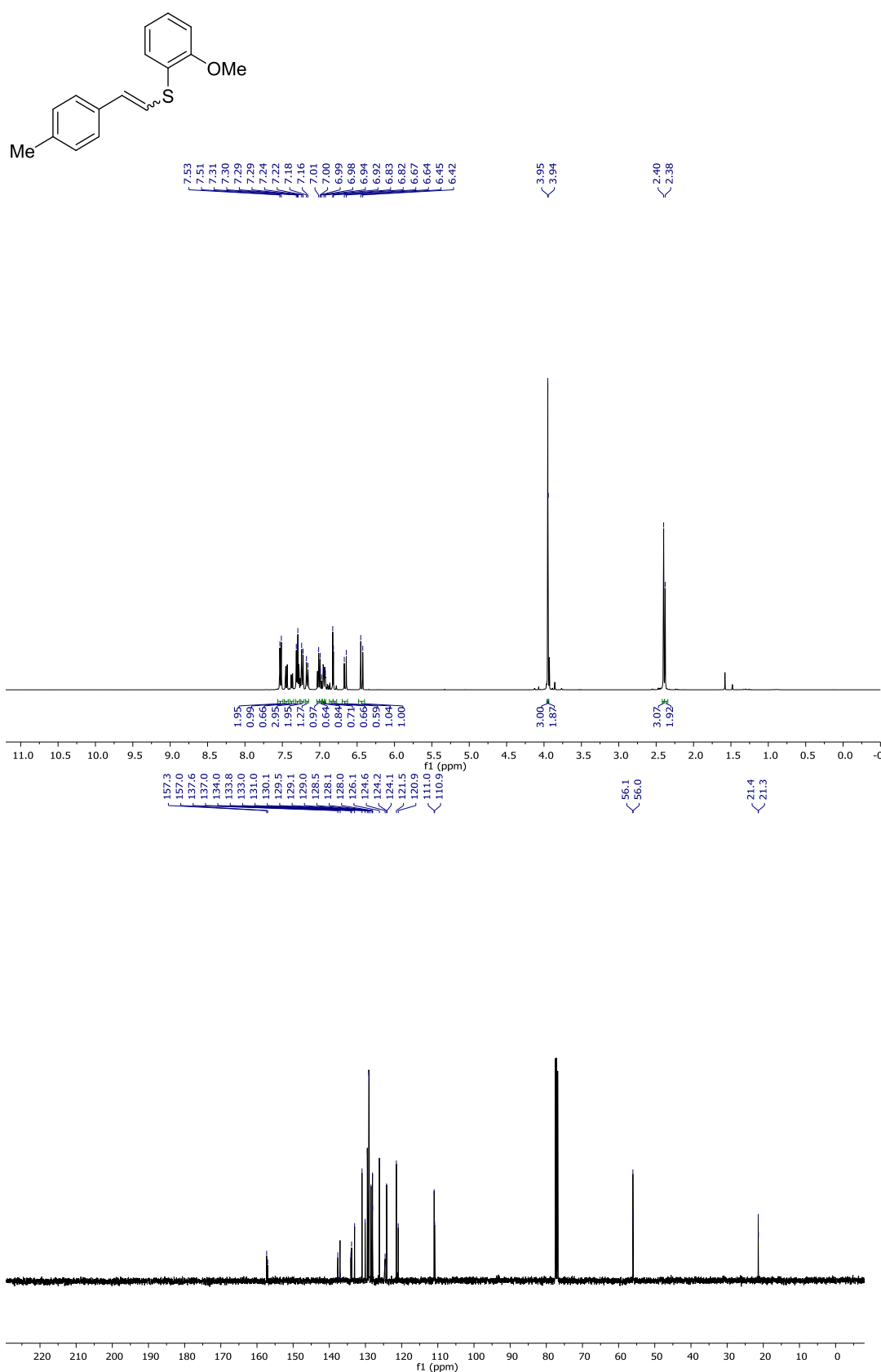
3-[(4-Methoxystyryl)thio]butan-2-one 44a

3-[(4-Methylstyryl)thio]butan-2-one 45a

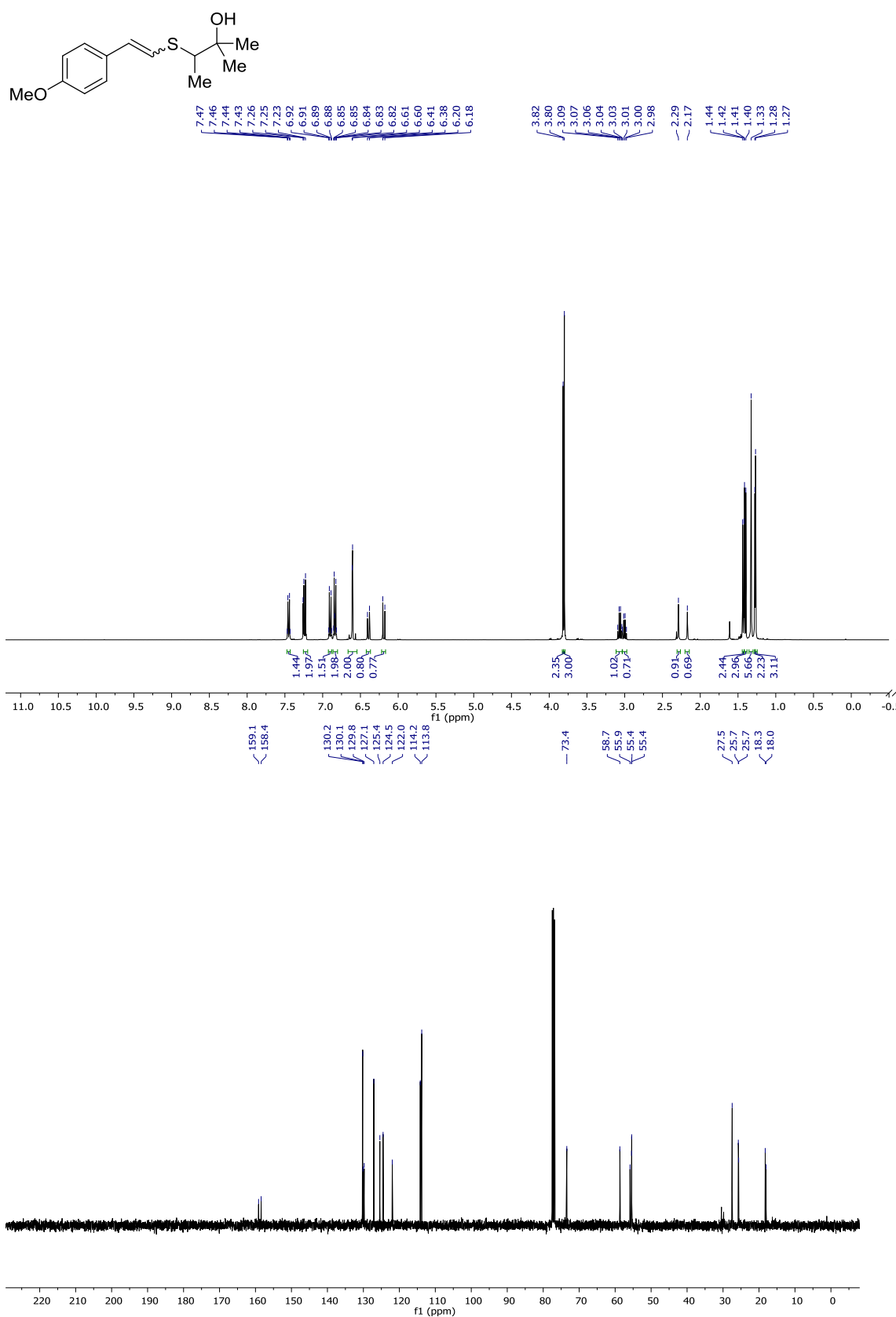


(E)-Methyl 2-[(4-methoxystyryl)thio]acetate 44b

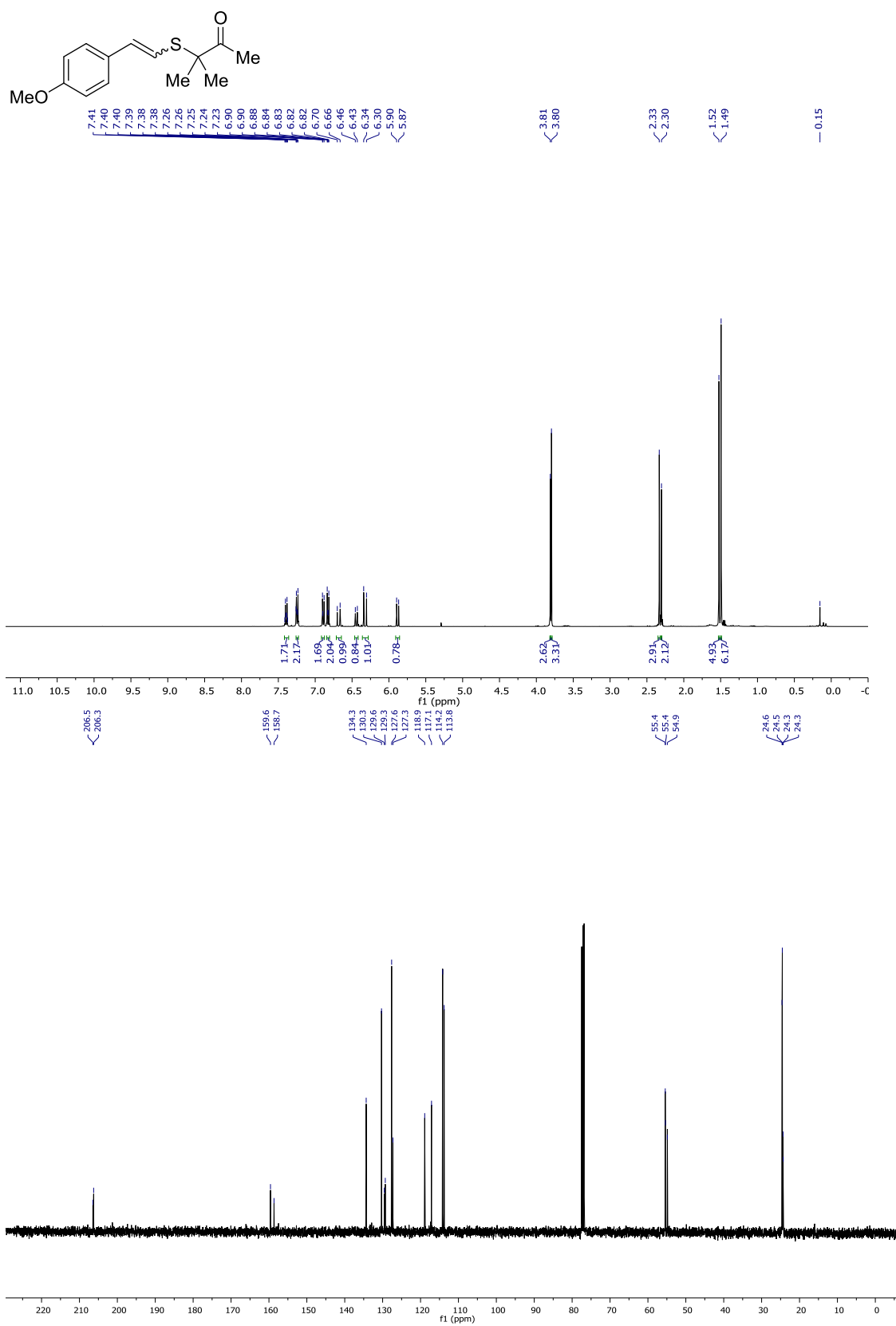
(E)-Methyl 2-[(4-methylstyryl)thio]acetate 45b

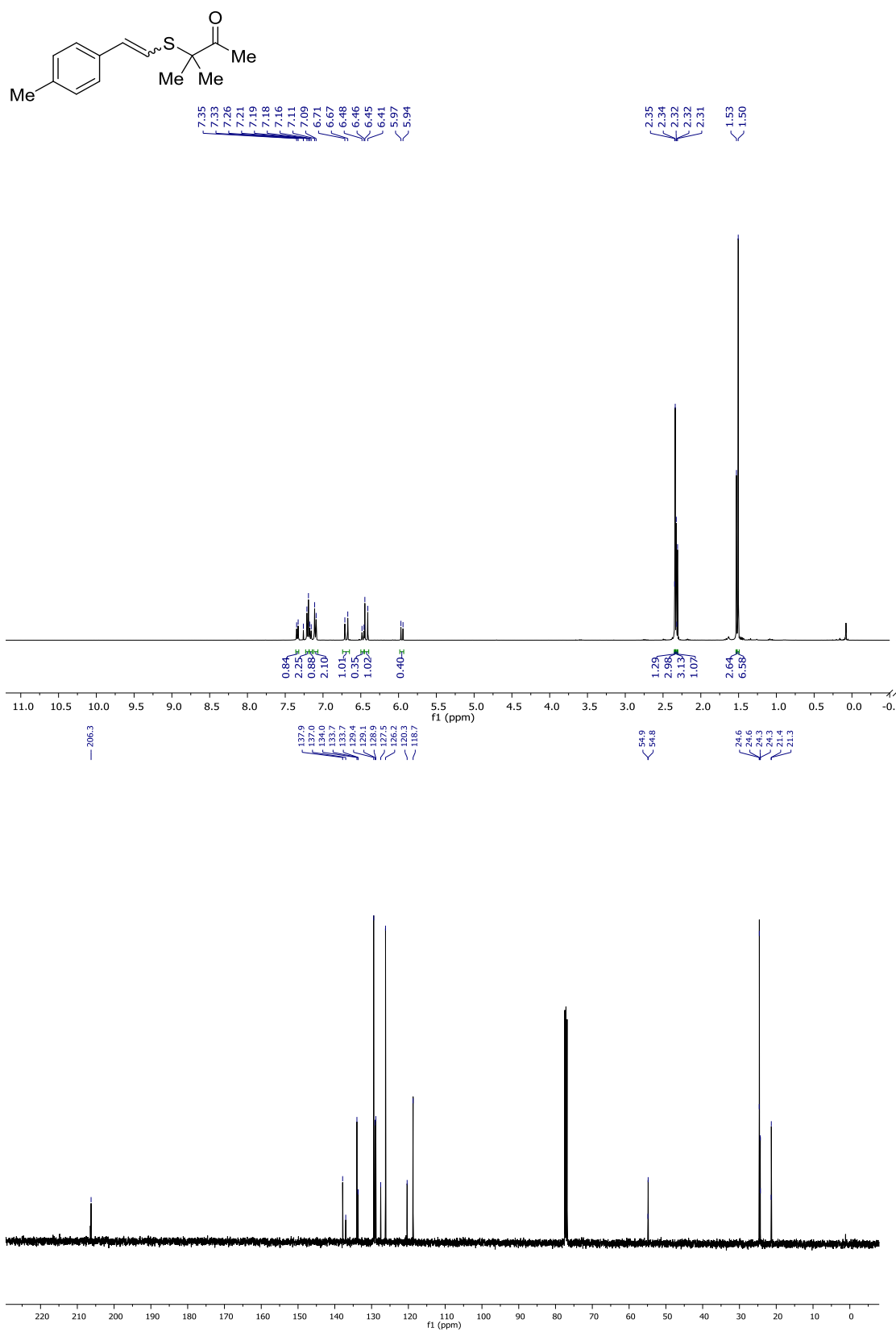
(E)-(2-Methoxyphenyl)(4-methylstyryl)sulfane 45c

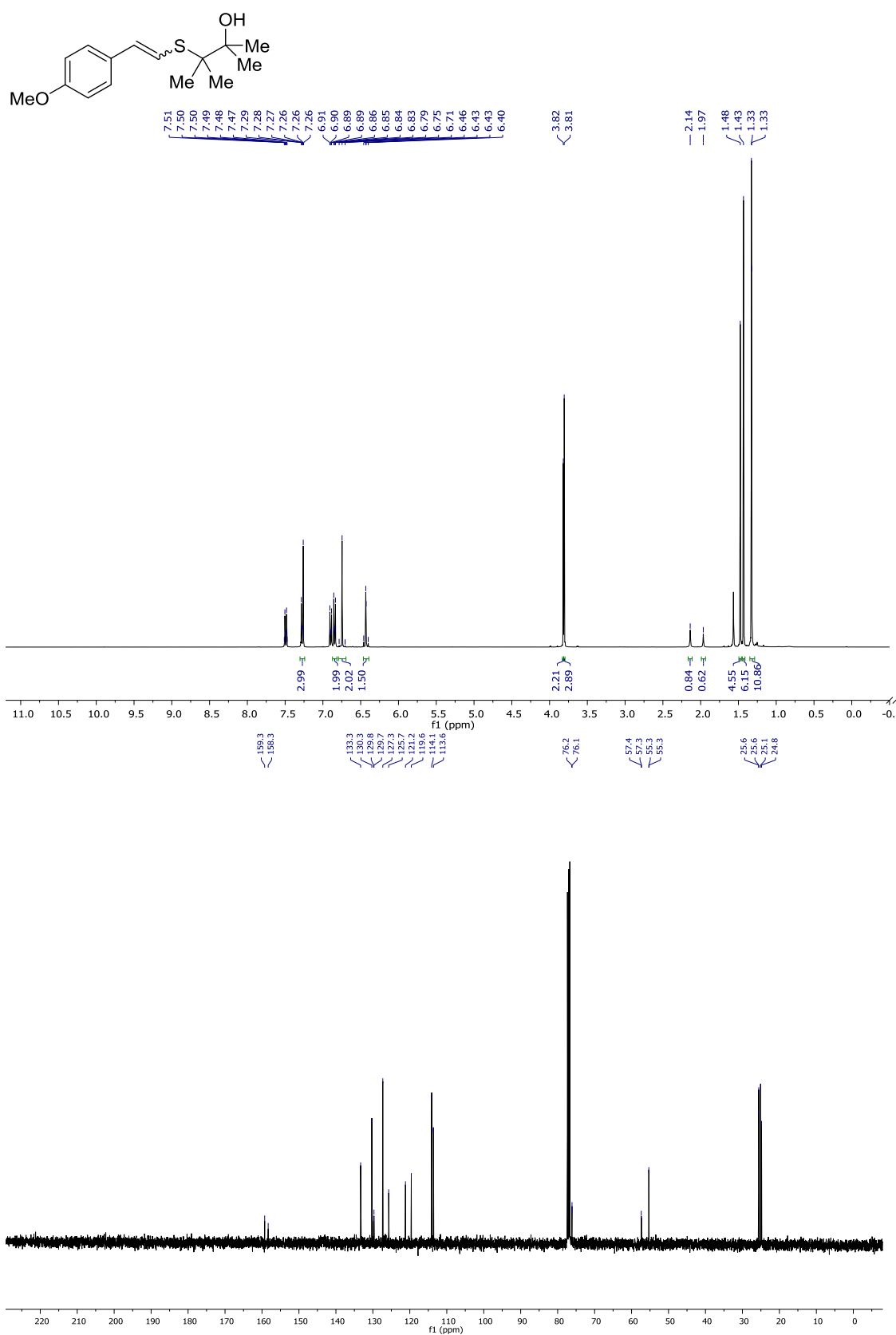
1-[(4-Methoxystyryl)thio]-2-methylpropan-2-ol 44c

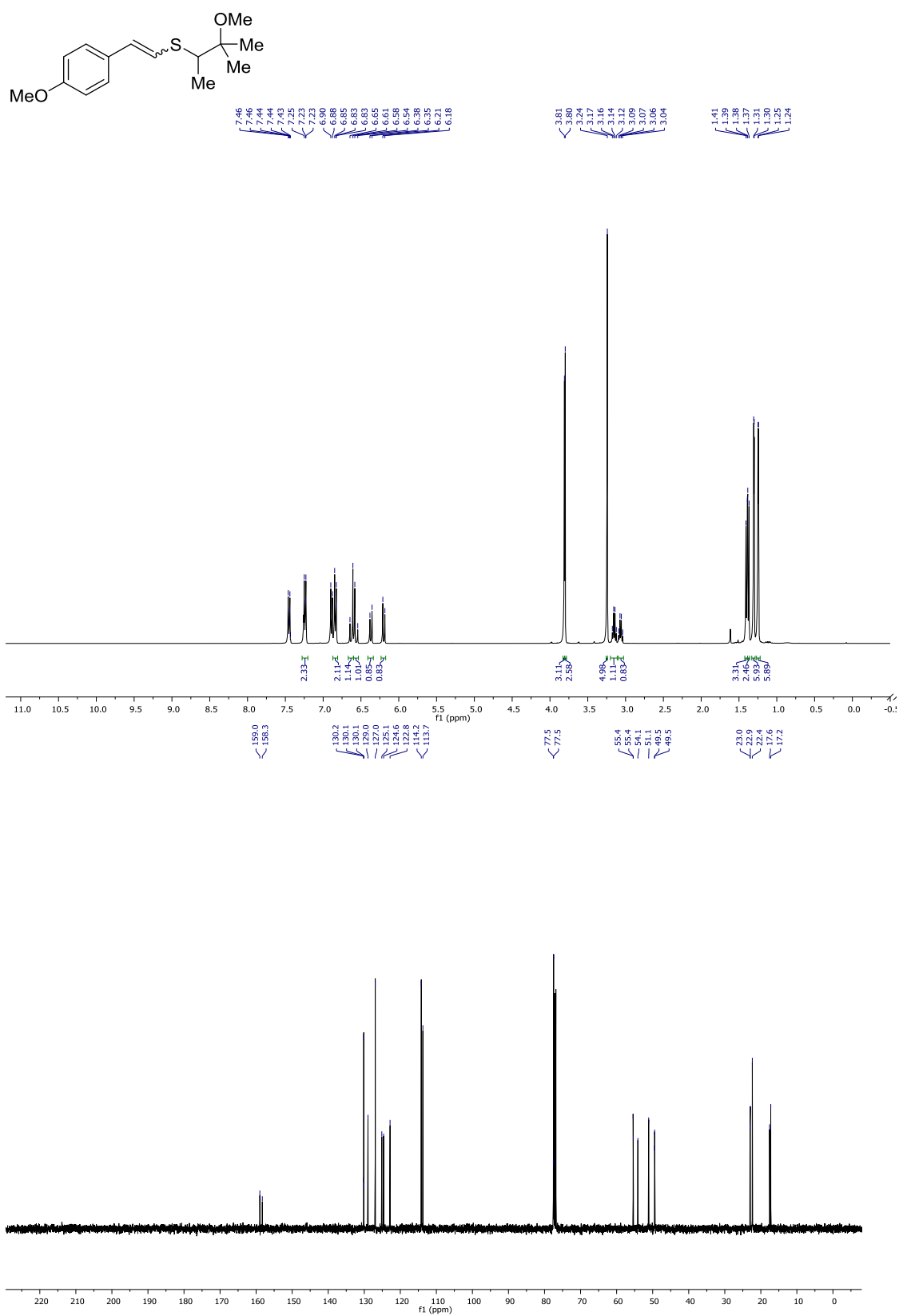


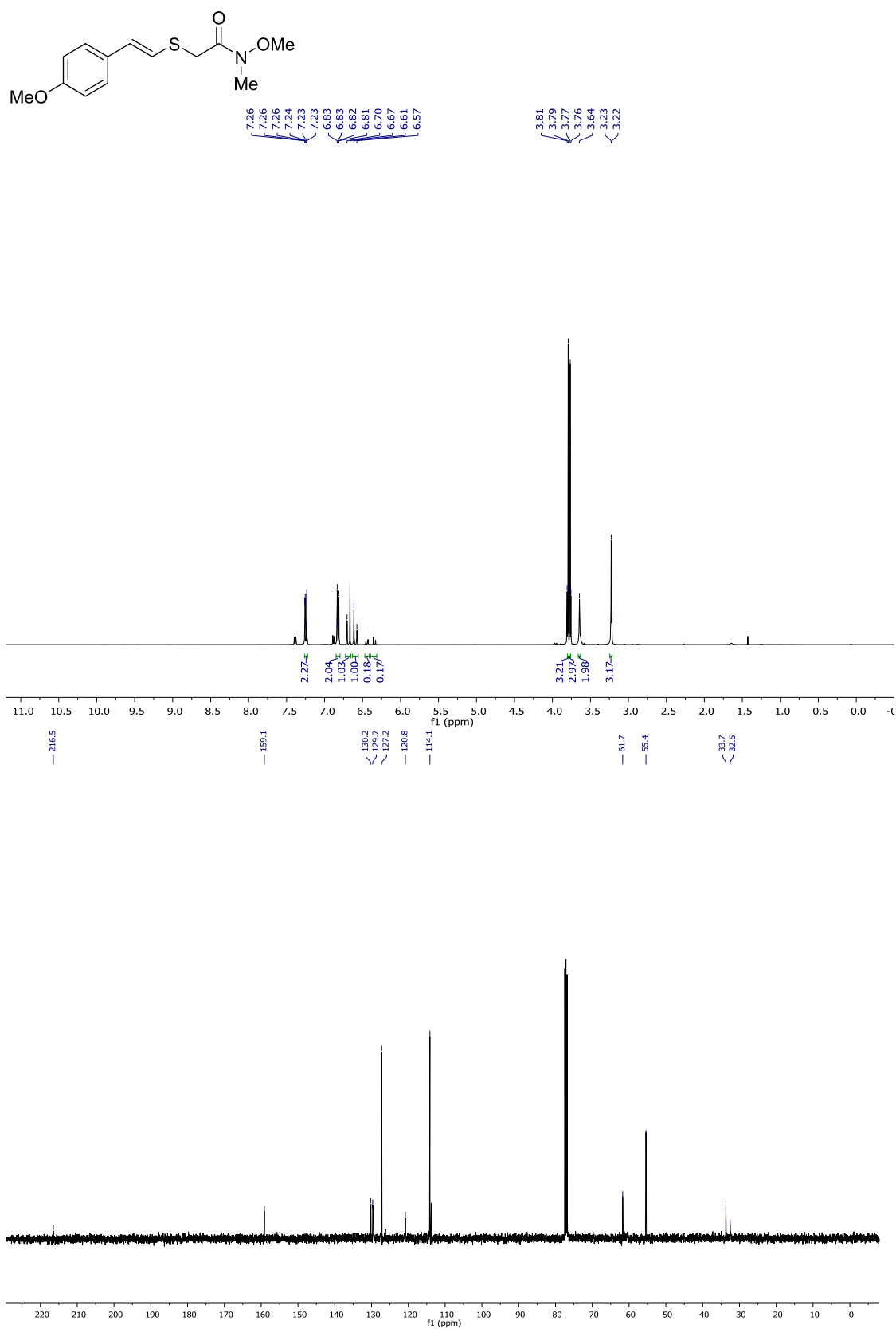
3-[(4-Methoxystyryl)thio]-3-methylbutan-2-one 44e



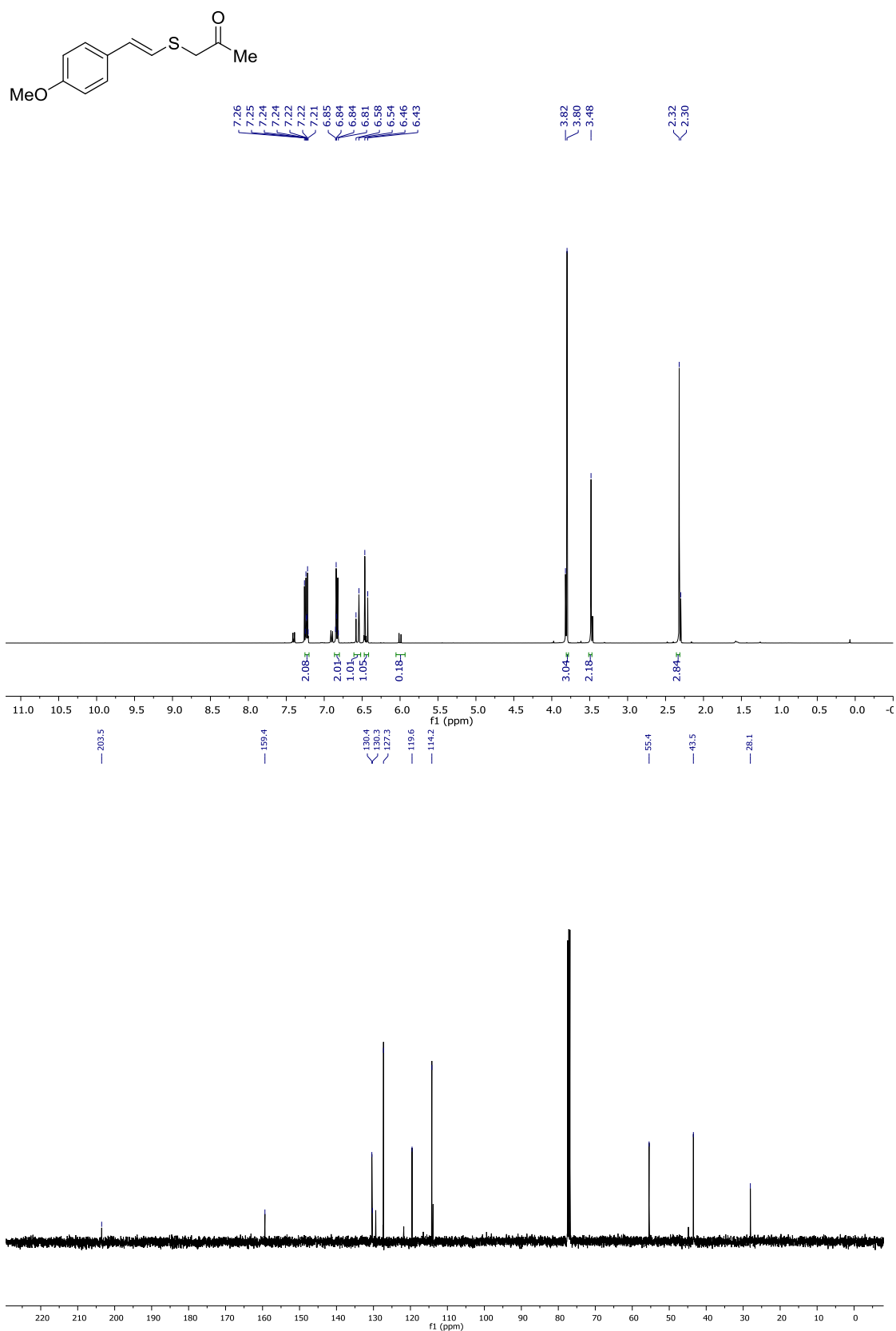
3-Methyl-3-[(4-methylstyryl)thio]butan-2-one 45d

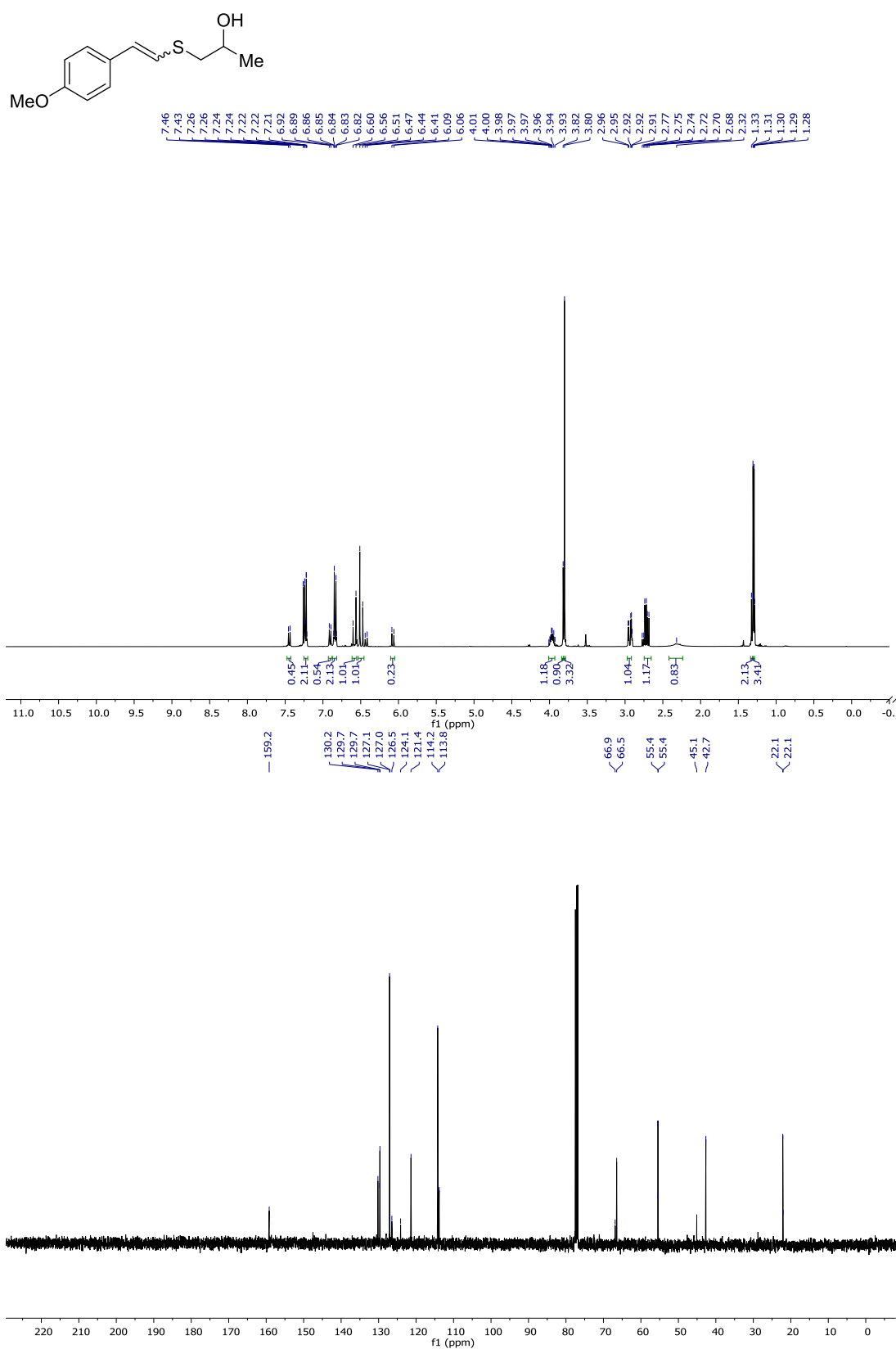
3-[(4-Methoxystyryl)thio]-2,3-dimethylbutan-2-ol 44f

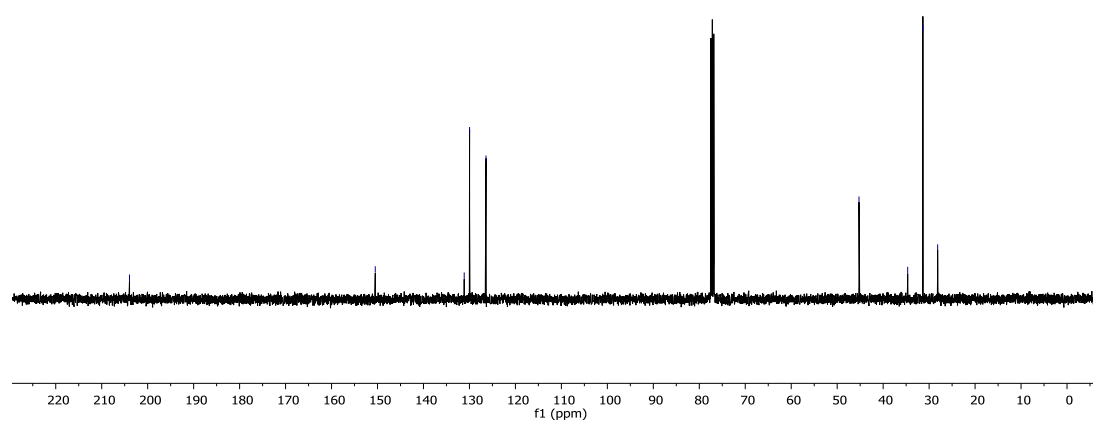
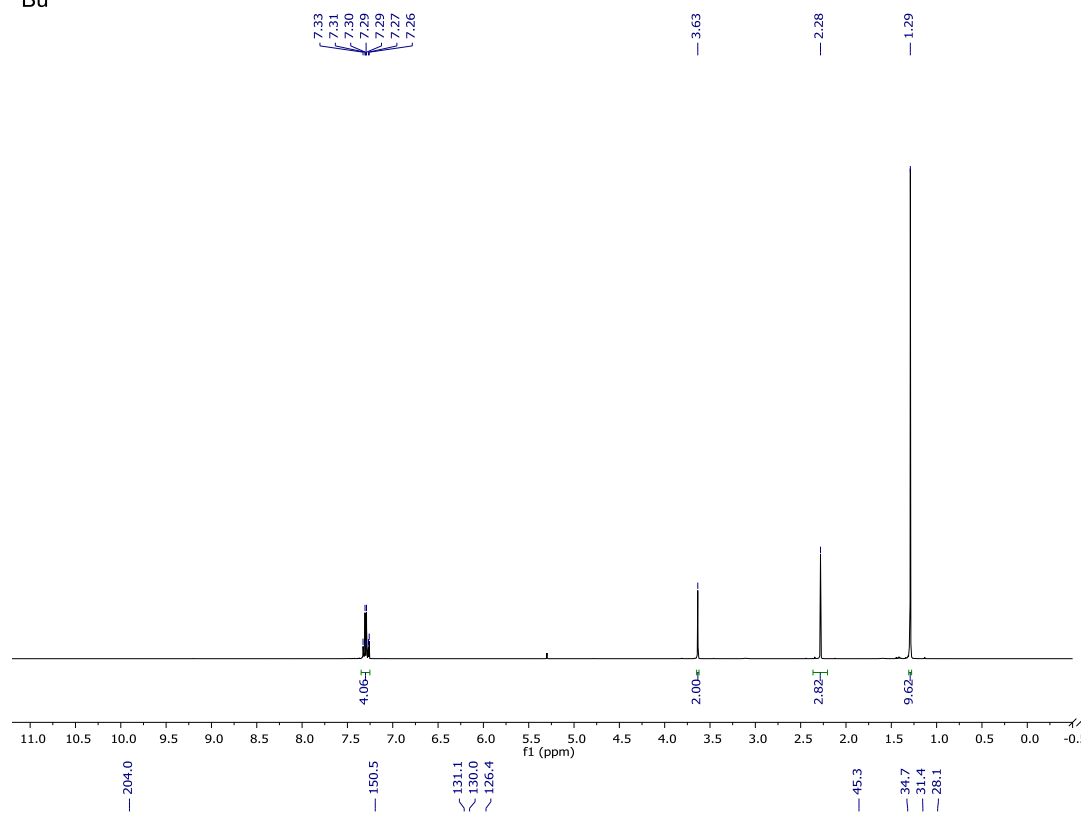
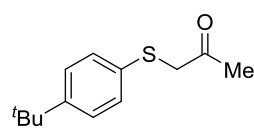
(3-Methoxy-3-methylbutan-2-yl)(4-methoxystyryl)sulfane 44d

(E)-N-methoxy-2-((4-methoxystyryl)thio)-N-methylacetamide 44g

1-[(4-Methoxystyryl)thio]propan-2-one 44h



(E)-1-[(4-Methoxystyryl)thio]propan-2-ol 44i

1-[(4-(*tert*-Butyl)phenyl)thio]propan-2-one **46**

4-[4-(*tert*-Butyl)phenylthio]butan-2-one 47