New Applications of Rhodium-Catalysed Hydroacylation

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

This thesis is dedicated to my mother and grandmother,

Leticia and Fidelia.

‘Give thanks to the Lord, for he is good;

his love endures forever’

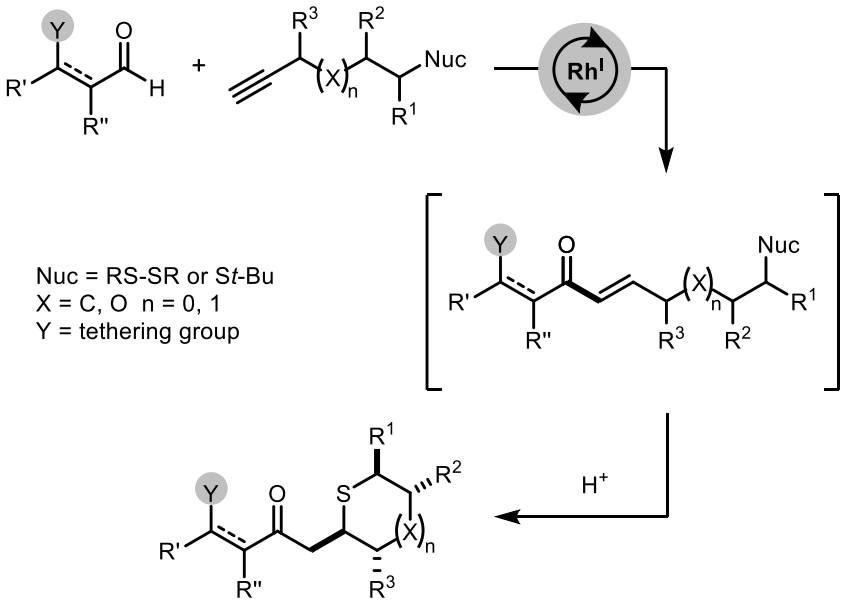
Psalm 118:1

Abstract

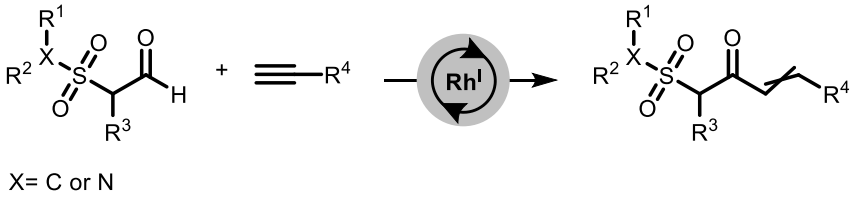
This thesis describes the development of two new rhodium-catalysed hydroacylation methods. The first involves a one-pot hydroacylation/thio-conjugate addition cascade towards the synthesis of fully saturated sulfur heterocycles. The second exploits novel *β*-sulfonyl aldehydes to access *β*-keto-sulfones and sulfonamides.

Chapter 1 delineates a literature review of the evolution of rhodium-catalysed hydroacylation, with focus on catalyst design and chelating groups that hinder decarbonylation. The use of hydroacylation in heterocycle synthesis is also briefly reviewed.

Chapter 2 documents the use of alkynes with pendant sulfur nucleophiles in a highly regioselective rhodium-catalysed hydroacylation reaction, delivering linear *α*,*β*-unsaturated enone intermediates. These adducts are further harnessed in intramolecular cyclisation reactions to access diversely substituted, saturated *S*-heterocycles, in a one-pot fashion.



Chapter 3 outlines initial attempts to develop a rhodium-catalysed hydroacylation methodology for the synthesis of β-keto-sulfones and sulfonamides. The work explores the construction of new β-sulfonyl aldehydes and their use in intermolecular hydroacylation.



X= C or N

Chapter 4 presents the conclusions from the research conducted and future work.

Chapter 5 details the experimental data and procedures.

Declaration

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

Ndidi Iwumene

July 2022

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Finally, I would like to dedicate this thesis to my late mother and grandmother. I deeply miss you both. Thank you for believing in me and for all your sacrifices. I finished this doctorate for you. *Imela*.

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Abbreviations

λ_{max}	maximum wavelength
μL	microlitres
δ	chemical shift
°C	degrees Celsius
Å	angstrom
η	hapticity
ν_{max}	FT-IR absorption maximum
Ac	acetyl
acac	acetylacetonate
Ar	aryl
atm	atmospheres
app.	apparent
aq.	aqueous
b	branched
BAr^{F}_{4}	tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate
binap	2,2’-bis(diphenylphophino)-1,1’-binapthyl
BPhen	bathophenanthroline
bpy	bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
Bz	benzoate

[C]	concentration
calcd.	calculated
Cat.	catalyst
Cbz	carboxybenzyl
cm^{-1}	wavenumber
Cp*	pentamethylcyclopentadiene
CPME	cyclopentyl methyl ether
cod	1,5-cyclooctadiene
coe	cyclooctene
conc.	concentrated
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
dt	doublet of triplets
ddd	doublet of doublet of doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide)
DBU	1,8-biazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide

DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DPEPhos	1,2-bis[(2-diphenylphosphino)phenyl]ether
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dcpe	1,2-bis(dicyclohexylphosphino)ethane
dppf	1,1'-bis(diphosphino)ferrocene
dcpm	1,1-bis(dicyclohexylphosphino)methane
dppm	1,2-bis(diphenylphosphino)methane
dr	diastereomeric ratio
dtpm	1,2-bis(di-*o*-tolylphosphanyl)methane
DuanPhos	2,2′-di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′)biisophosphindolyl
ee	enantiomeric excess
er	enantiomeric ratio
ESI	electrospray ionisation
EI	electron ionisation
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
equiv.	equivalents
EWG	electron withdrawing group
FT-IR	Fourier-transform infrared spectroscopy
g	gram(s)
h	hour(s)
HBcat	catecholborane

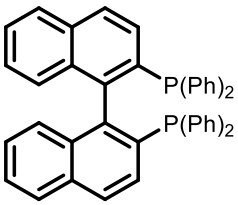
Hex	hexyl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
HMBC	heteronuclear multiple bond correlation
Hz	hertz
i	iso
IR	infrared
IPA	isopropyl alcohol
J	coupling constant
l	linear
LED	light-emitting diode
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet
m	meta
M	molar concentration or mega
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Me-DuPhos	1,2-bis[2,5-dimethylphospholano]benzene
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)

mol	mole(s)
m.p.	melting point
Ms	methanesulfonyl
MTM	methyl thiomethyl
MW	microwave
m/z	mass to charge ratio
n	normal
N	normality
nbd	norbornadiene
n-BuLi	*n*-butyllithium
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
o	ortho
p	para
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PMP	4-methoxy benzyl
ppm	parts per million
Pr	propyl
psi	pounds per square inch
py	pyridine

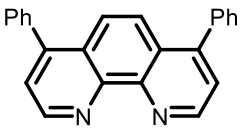
q	quartet
quant.	quantitative
R	generic group
rac	racemic
R_f	retention factor
r.t.	room temperature
s	singlet
sat.	saturated
SM	starting material
SPS	solvent purification system
t	triplet
t	tertiary
T	temperature
TBABr	tetrabutylammonium tribromide
TBS	*tert*-butyldimethylsilyl
TCEP	tris(2-carboxyethyl)phosphine
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
*t*AmOH	2-methyl-2-butanol
TMS	trimethylsilyl

ToF	turnover frequency
Tol	tolyl
ToN	turnover number
Ts	*p*-toluenesulfonyl
TSA	*p*-toluenesulfonic acid
TsOH	*p*-toluenesulfonic acid
UV	ultra-violet
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
wt%	weight percent

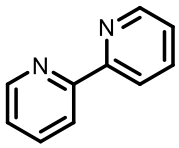
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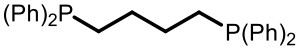
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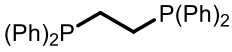
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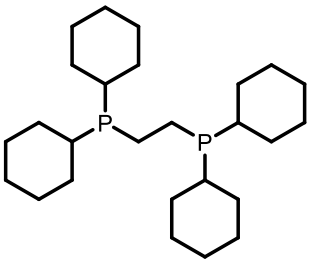
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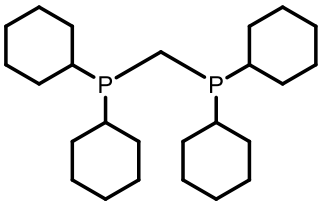
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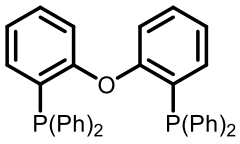
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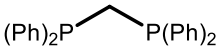
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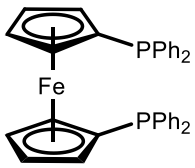
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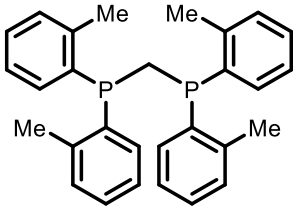
DPEPhos



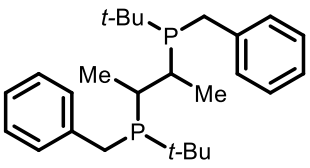
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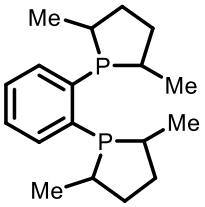
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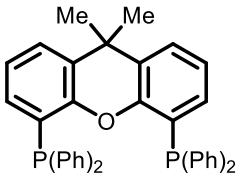
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DuanPhos



Me-DuPhos



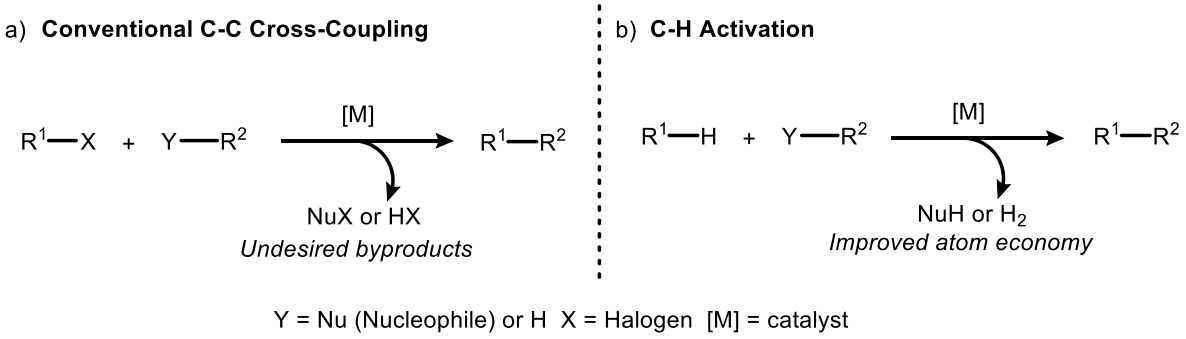
XantPhos

Chapter 1

Rhodium-catalysed hydroacylation

1.1 Introduction

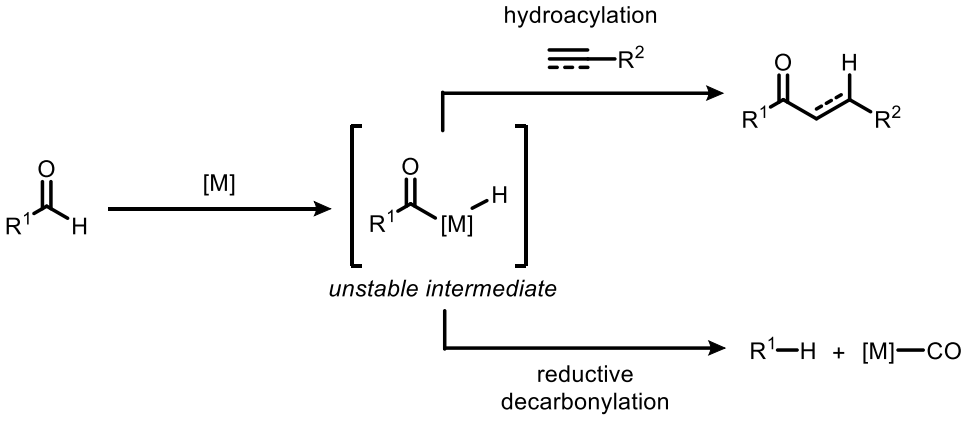
The end of the 20th century saw the birth and explosive growth of metal-catalysed C-C bond cross-coupling reactions.[1-2] Pioneering work from Heck, Negishi, Suzuki, and several others, irrevocably revolutionised organometallic chemistry.[3-4] The high efficiency and chemoselectivity of these mild reactions have resulted in far-reaching practical implications in the synthesis of pharmaceuticals and natural products.[5-6] In 2010, the Chemistry Nobel Prize duly recognised the impact of these transformations on the synthetic chemist's toolbox. Despite this, conventional C-C coupling reactions remain flawed due to the production of salt by-products and their reliance on prefunctionalised coupling partners (Scheme 1.1a).[7-8] Paradoxically, the overuse of these sp^2-sp^2 couplings in drug discovery, has led to drug libraries inundated with 'flat' molecules; thereby restricting chemical diversity.[9]



Scheme 1.1 General metal-catalysed C-C cross coupling reactions a) conventional b) C-H activation

Synthetic chemists have always sought ways of constructing complex molecules in an environmentally benign and cost-effective manner.[10] Their discoveries have since enabled direct functionalisation of—traditionally latent—C-H bonds into C-C bonds.[10-12] These

transformations negate the use of organic- or pseudohalides and organometallic reagents, thus, benefit from high atom and step economy (Scheme 1.1b).[2, 13-14] In the past 15 years, transition metal-catalysed C-H activation has emerged as an attractive tool in complex target synthesis, providing novel retrosynthetic disconnections and operational efficiency.[13, 15] Numerous advancements in reagents and catalysts have culminated in mild, robust, and highly selective methods.[8, 10-11, 13, 16] Evidently, this 'holy grail' of chemistry[17] has been attained, and now has diverse applications in energy, materials science, and late-stage functionalisation.[3, 5, 7, 18] Metal-catalysed hydroacylation—the addition of a formyl C-H bond across an unsaturated C-C bond—is a prime example of a C-H activation process that is rewriting the blueprints of synthetic chemistry.[19-21] The hydroacylative union of an aldehyde and alkene/alkyne is inherently 100% atom economic and delivers versatile ketone/enone products (Scheme 1.2).



Scheme 1.2 General hydroacylation reaction and competing pathway

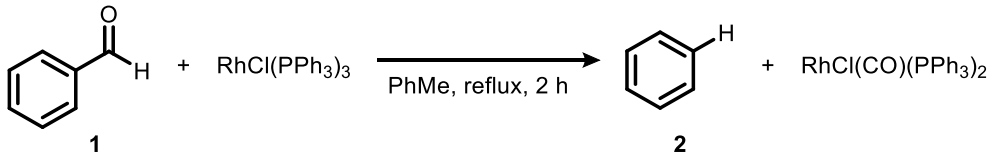
Historically, the success of this intermolecular method has been hampered by reductive decarbonylation of an unstable acyl metal hydride intermediate.[19-20, 22]. A variety of metal catalysts have been utilised in intermolecular hydroacylation: ruthenium[23-25]; cobalt[26-31]; iridium[32]; and nickel[33-35]. However, rhodium(I) catalysts are most commonly employed—and will be the primary focus of discussions herein. This chapter delineates the history of hydroacylation chemistry as well as key synthetic advancements. In particular, the evolution

of catalyst efficiency and substrate scope is presented for intermolecular reactions. A summary of mechanistic insights is also described, along with the application of intermolecular hydroacylation in heterocycle synthesis.

1.2 Intramolecular hydroacylation

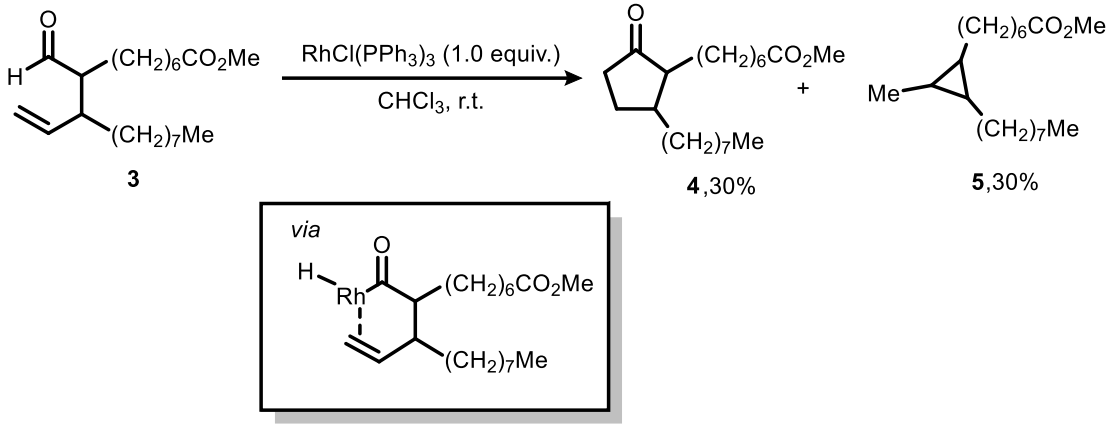
1.2.1 Early Hydroacylation: Cyclopentanone synthesis

In 1965, Tsuji and Ohno described the first reductive decarbonylation of aldehydes using Wilkinson's catalyst (Scheme 1.3).[36] The authors correctly hypothesised that decarbonylation proceeded *via* an acyl hydride intermediate.[37]



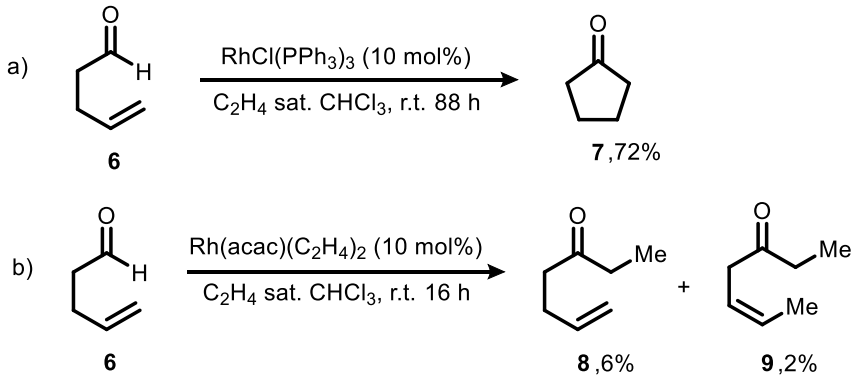
Scheme 1.3 Rhodium-catalysed decarbonylation of benzaldehydes

Some years later, Sakai *et al* disclosed the first example of intramolecular alkene hydroacylation from their studies in prostanoid synthesis.[38] The reaction involved subjecting substituted enals to stoichiometric amounts of Wilkinson's catalyst. This resulted in the formation of cyclopentanones and cyclopropane products (**4** and **5**) in similar amounts (Scheme 1.4). From this, it was clear decarbonylation was facile despite the (later-discovered) stabilising effect of olefins on the intermediate acyl-metal hydride.



Scheme 1.4 First reported example of intramolecular hydroacylation using stochiometric Rh

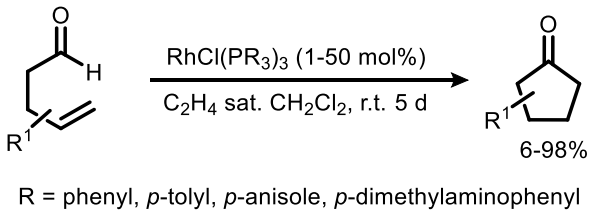
With the potential of intramolecular hydroacylation in mind, the race to subdue decarbonylative side reactions commenced. Lochow and Millner subsequently showed that use of substoichiometric amounts of Wilkinson's complex in ethene-saturated chloroform, yielded cyclopentanone **7** in 72% yield (Scheme 1.5a).[39] Ethene was thought to occupy a vacant Rh coordinate site; hence, significantly suppressed the decarbonylation pathway. The first hints of intermolecular hydroacylation were also discovered from isolation of products **8** and **9**— derived from the coupling of ethene with pentenal (Scheme 1.5b).



Scheme 1.5 Lochow and Millner's catalytic hydroacylations of 4-pentenal

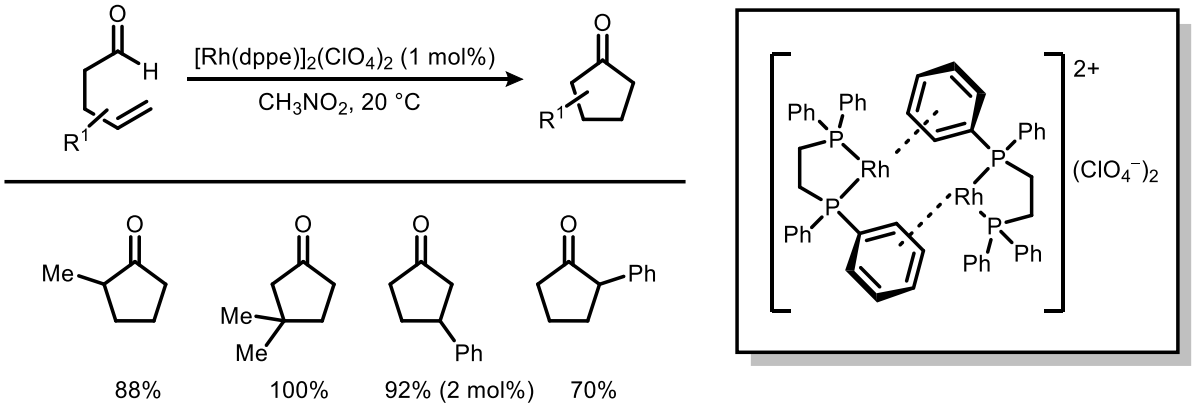
In 1980, Larock utilised a variety of *in situ* generated rhodium monophosphine catalysts to access a more diverse range of cyclopentanones. Nonetheless, high catalyst loadings of

50 mol% and ethylene-saturated solvent were still necessary (Scheme 1.6).[40] Less than a decade later, Bosnich published a significant breakthrough in turn over number (TON) and turn over frequency (TOF) for alkene hydroacylation. The use of cationic rhodium(I) *bis*-phosphine complex $[Rh(dppe)_2[ClO_4]_2$ delivered various substituted cyclopentanones in good yields, using only 1 mol% of catalyst (Scheme 1.7).[41]



Scheme 1.6 Larock's synthesis of cyclopentanones *via* Rh-catalysed intramolecular hydroacylation

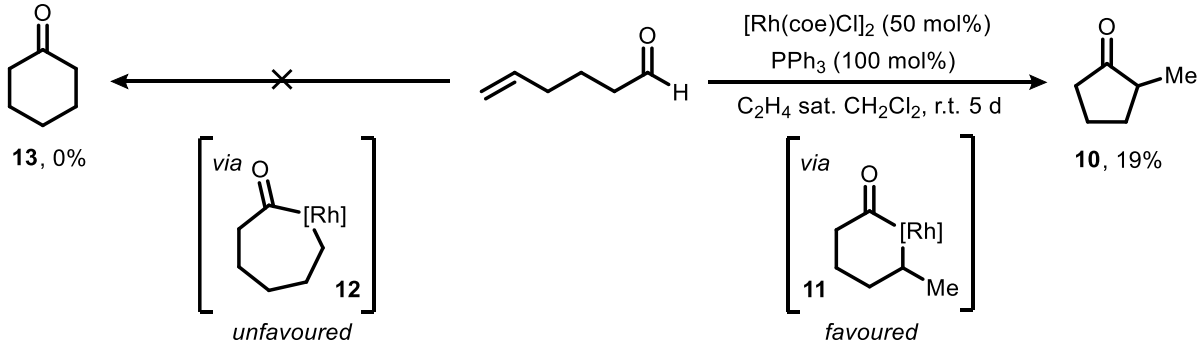
The high catalytic activity was attributed to the cationic nature of the Rh complex, which supposedly promoted formation of coordinatively unsaturated intermediates. Following on from this seminal work, cationic rhodium complexes garnered huge popularity, and have since become the most extensively used systems in intramolecular hydroacylation. To date, research has centred on expanding the reaction scope[42-44] as well as developing efficient catalyst systems[45-48] and asymmetric transformations[49-52]. Significant effort has also been directed towards synthesising larger ring systems.[53-55]



Scheme 1.7 Bosnich's intramolecular hydroacylation using cationic Rh complexes

1.2.2 Larger rings

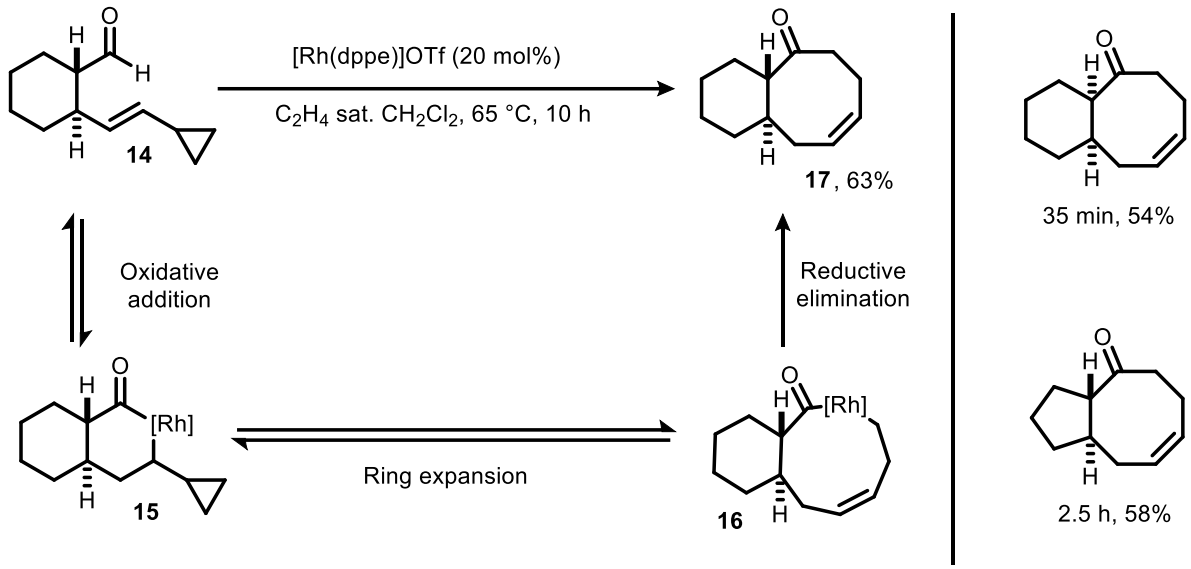
The synthesis of larger-membered cyclic ketones *via* intramolecular hydroacylation is nontrivial since ring closure is kinetically unfavourable. Decarbonylation also prevails as the distance between the olefin and aldehyde increases.[20] Larock's hydroacylation of 5-hexenal first exemplified the difficulty of medium ring construction. Cyclopentanone **10** was obtained in 19% yield instead of desired cyclohexanone **13** (Scheme 1.8).[40] The authors speculated that the formation of six-membered rhodacyle **11** was more favourable than the seven-membered congener; ergo, cyclopentanone **10** was the sole product. The low yield of **10** was put down to extensive decarbonylation. Successive hydroacylation methodologies have succeeded in accessing larger rings by embedding additional functionality into the enal substrate. For instance, Shair and co-workers devised an efficient route to cyclooctenones, exploiting a pendant cyclopropane ring that promoted ring expansion to rhodium acyl intermediate **16** (Scheme 1.9).[56] Subsequent reductive elimination afforded the desired 8-membered rings.



Scheme 1.8 Larock's hydroacylation of 5-hexenal

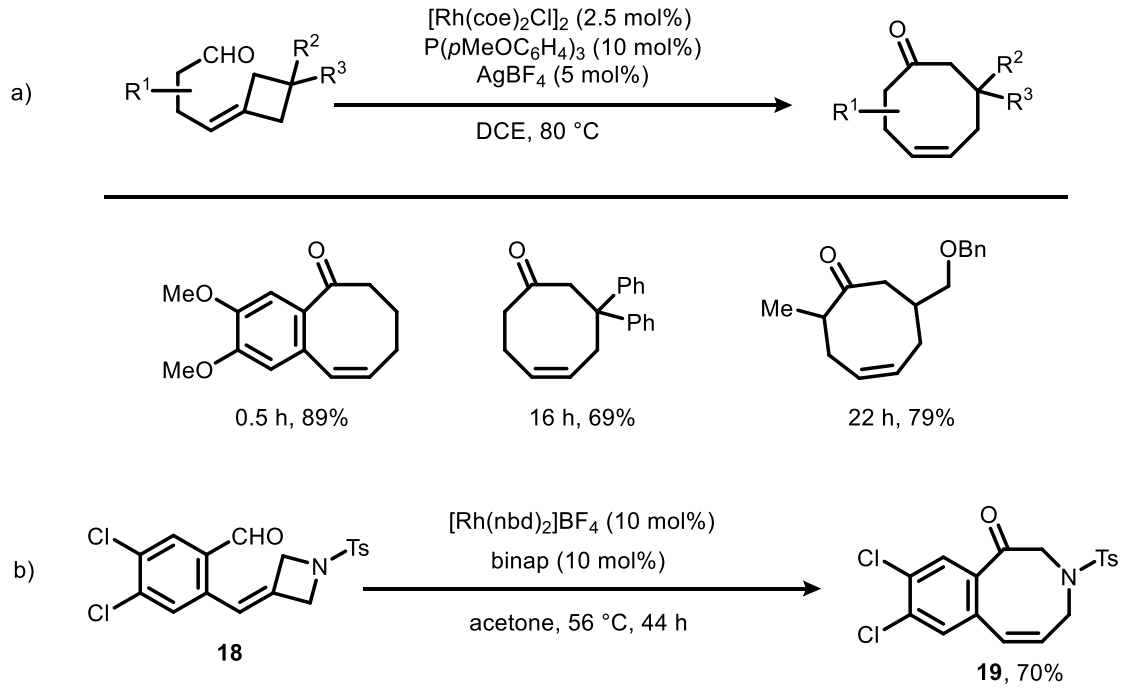
The application of Bosnich's cationic Rh(I) catalyst, alongside a saturated ethylene atmosphere, was essential for obtaining target cyclooctenones in good to moderate yields.

The Aissa group employed a similar ring expansion technique; instead appending cyclobutanes or azetidines onto the starting materials.



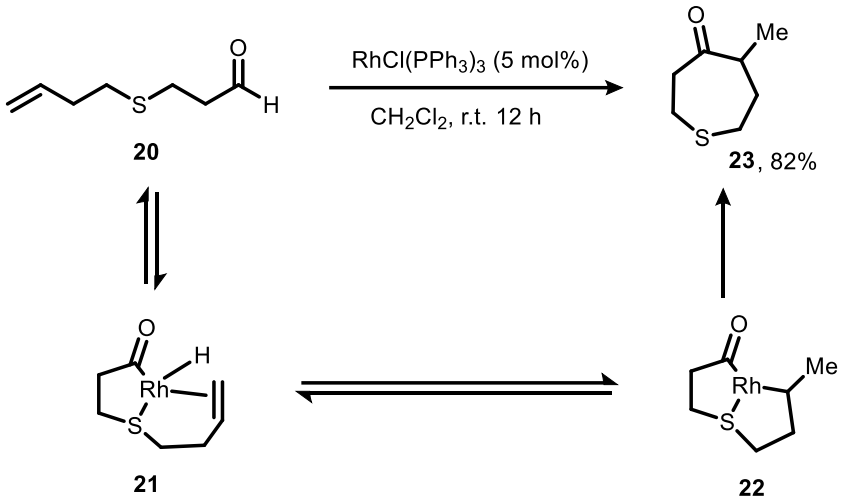
Scheme 1.9 Shair's route to cyclooctenones

The desired 8-membered rings were prepared in excellent yields; without the need for solvent saturated with ethylene (Scheme 1.10).[54]



Scheme 1.10 Aissa syntheses of 8-membered rings

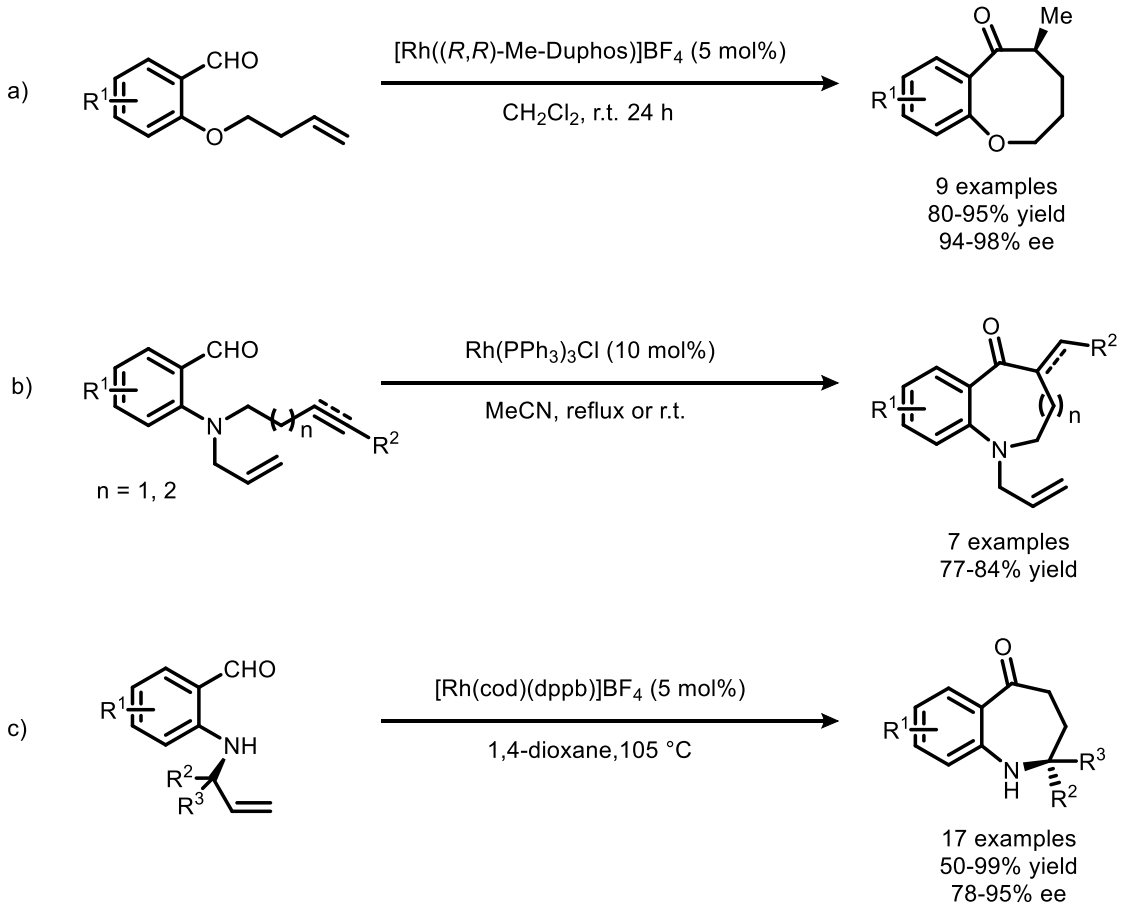
In 2002, heteroatom chelation emerged as an alternative strategy to construct larger rings. The Bendorf group published an elegant chelation-assisted approach to medium-ring sulfur heterocycles (Scheme 1.11).[57] The incorporation of a Lewis-basic sulfur atom into *ω*-alkenals and alkynals enabled formation of chelation-stabilised metallabicycles (**21** and **22**), which were resistant to reductive decarbonylation. However, it was noted that the tether atom must be judiciously positioned relative to the alkene and aldehyde functional groups. Moderate to high yields of an array of seven- and eight-membered rings were isolated—using 5-10 mol% of Wilkinson's catalyst—at room temperature. This report served as the first hydroacylative route to heterocycles and inspired the success of chelation-assisted intermolecular hydroacylation reactions.



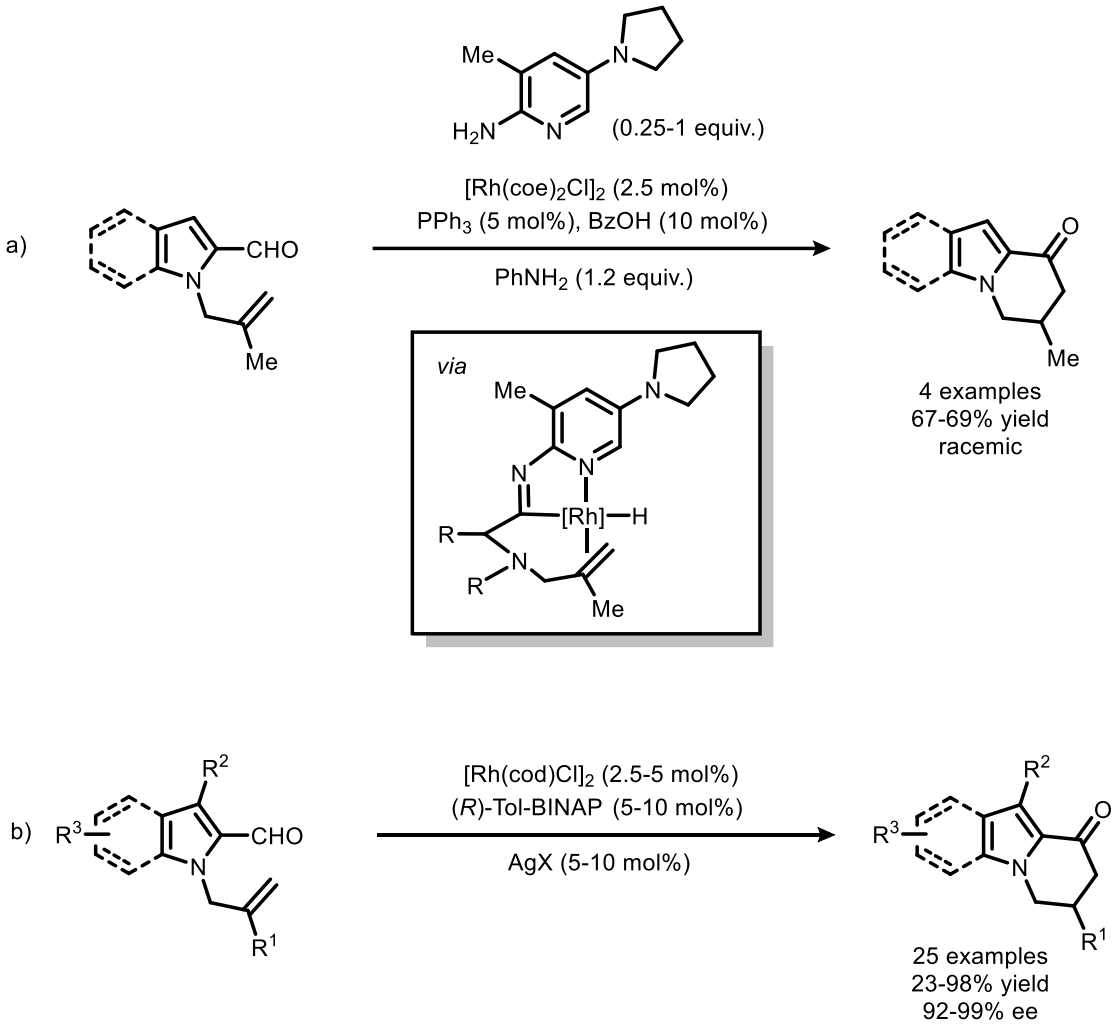
Scheme 1.11 Bendorf's chelation-assisted intramolecular hydroacylation

Dong *et al* eventually extended this method to synthesise analogous *O*-heterocycles with high enantioselectivities (Scheme 1.12a).[58] Since then, Bendorf[59] and Nguyen[53] have, separately, published amine-directed hydroacylations for the synthesis of medium-ring aza-ketones (Scheme 1.12b and c). In general, the requirement of pre-installed chelating groups limits the applicability of these reactions. Having appreciated this, Douglas

developed a cooperative catalysis procedure to prepare six- and seven-membered ring ketones from tetherless substrates (Scheme 1.13a).[46] This method used electron-rich 2-amino-3-picolines to form a transient chelate scaffold on the aldehyde; circumventing degenerative decarbonylation or alkene isomerisation pathways (Scheme 1.13a). The Stanley lab went a step further by completely eliminating the requirement for chelation assistance (Scheme 1.13b).[60-61] This was achieved using *in situ* generated, chiral, non-racemic Rh catalysts. In applying this method, a broad range of polycyclic indole and pyrrole derivatives were synthesised in moderate to high yields, with excellent enantioselectivities.



Scheme 1.12 *N*- and *O*- directed intramolecular hydroacylation: a) Dong b) Bendorf c) Nguyen

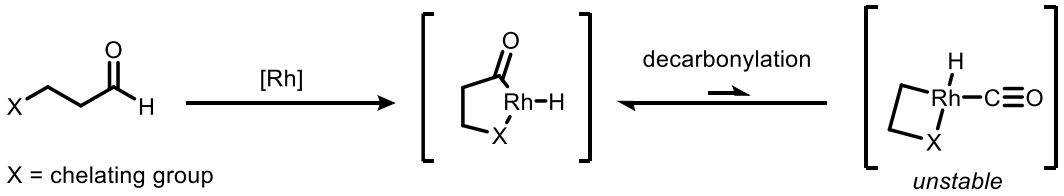


Scheme 1.13 a) Douglas' cooperative catalysis approach to *N*-heterocycles b) Stanley's chelation-free synthesis of *N*-heterocycles

1.3 Intermolecular hydroacylation

Intermolecular hydroacylation reactions are inherently more appealing because they allow divergent synthesis from simple and versatile starting materials. That said, intermolecular processes are more challenging than intramolecular procedures. The crux of the problem remains reductive decarbonylation, which rears its head more emphatically in intermolecular systems.[62] In the absence of olefin coordination, the key acyl rhodium intermediate readily undergoes CO extrusion, which results in catalyst death.[20, 63] To overcome this limitation, chelating groups are employed to stabilise the self-same rhodacyles (Scheme 1.14).[64]

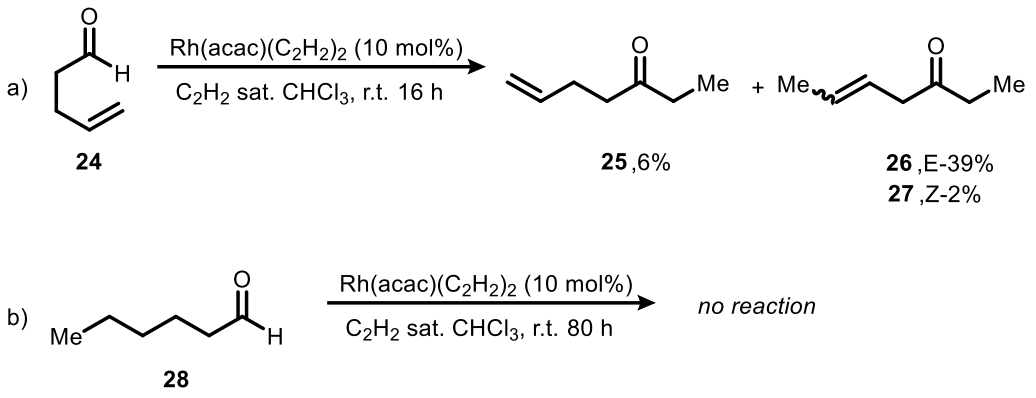
Chelation control is now the most prevalent and effective approach to thwart decarbonylation, although a few non-chelation-controlled strategies have also been reported.[22, 65-66]



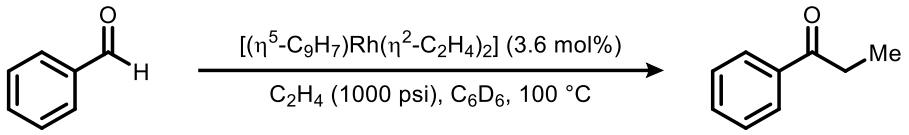
Scheme 1.14 Function of aldehyde-chelating group

1.3.1 Discovery and early work

Lochow and Miller reported the first example of intermolecular hydroacylation in their, aforementioned, intramolecular studies (See Section 1.2.1).[39] They observed that switching to Rh(acac)(C_2H_4)$_2$ with ethylene-saturated chloroform, yielded a mixture of heptanone **25** (6%), and alkene isomerisation products **26** (39%) and **27** (2%). They later established that hexanal (**28**) did not react under the same conditions (Scheme 1.15).[67] This implied that the remote enal olefin functioned as a stabilising tether; thereby, impeding decarbonylation. Thereafter, Marder and Milstein disclosed a modified Rh complex, Rh(η^5-C_9H_7)(η^2-C_2H_4)$_2$, that catalysed the hydroacylation of benzaldehyde with ethylene (Scheme 1.16).[65] However, these reactions required high pressures of ethylene (1000 psi at 25 °C). Overall, these early intermolecular systems suffered from the same inefficiencies as their intramolecular equivalents; namely, low yields and impractical conditions. The desire for improved efficiency eventually invoked the extension of Miller's olefin chelation control to heteroatoms.



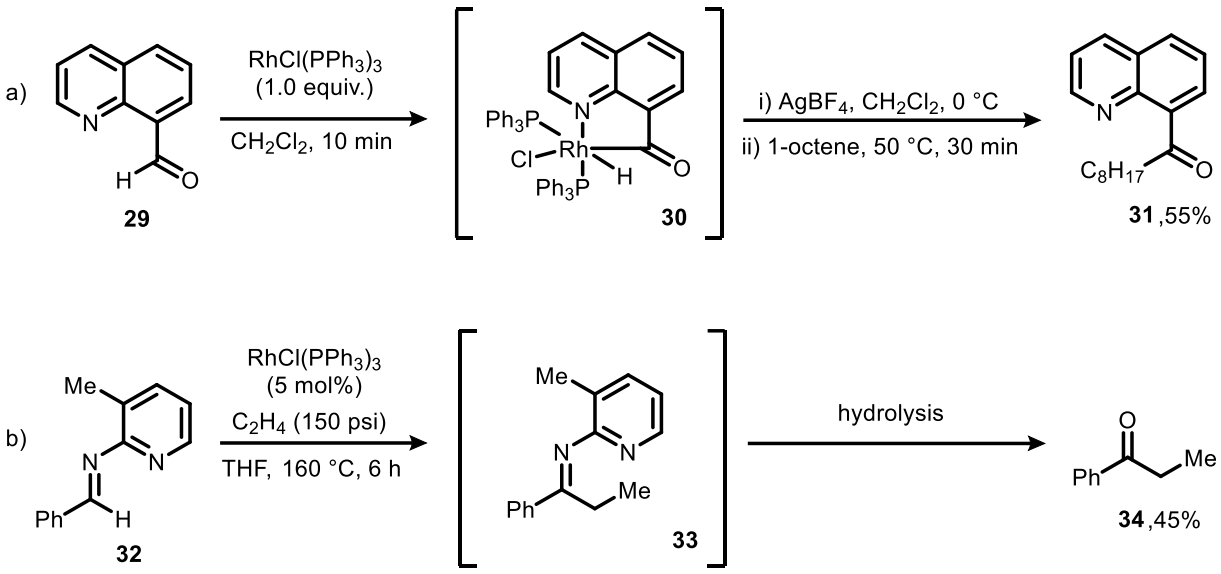
Scheme 3.15 a) Lochow and Millner's intermolecular-hydroacylation of 4-pentenal b) attempted hydroacylation of hexanal



Scheme 1.16 The Marder-Millstein intermolecular hydroacylation

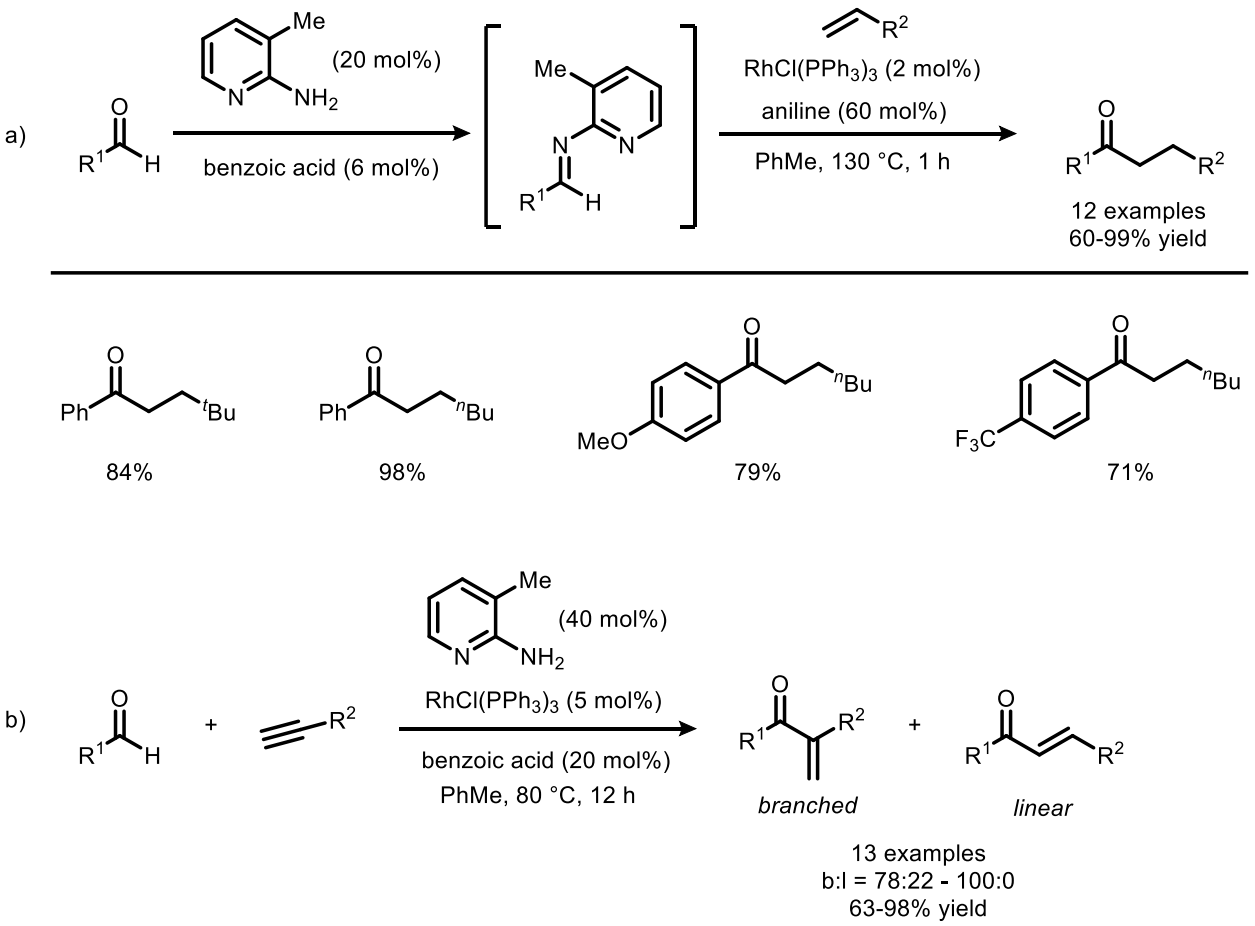
1.3.2 *N*-Chelation

In 1978, Suggs published the first example of heteroatom chelation in intermolecular hydroacylation. Oxidative addition of 8-quinoline carboxaldehyde **29** with stoichiometric Wilkinson's catalyst generated stable acyl rhodium hydride **30** (Scheme 1.17a).[68] This complex then reacted with $AgBF_4$, delivering a coordinatively unsaturated complex that reacted with excess 1-octene, providing hydroacylation adduct **31** in moderate yield. A year later, Suggs achieved catalytic, *N*-chelation-assisted hydroacylation by utilising picolyl imines (Scheme 1.17b).[69] Conveniently, the chelating motif was easily removed, furnishing 'traceless' hydroacylation products. However, the hydroacylation still required high pressures of ethylene. Inspired by Suggs' findings, Jun significantly advanced this strategy by generating imine tethers *in situ*.



Scheme 1.17 a) First example of heteroatom chelation by Suggs b) Suggs' use of picolyl imines in intermolecular hydroacylation

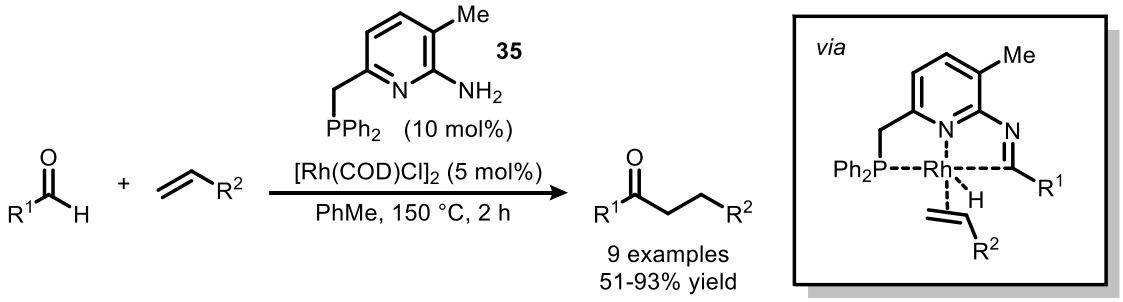
Jun's highly active catalyst system combined: Wilkinson′s complex; aminopicoline; benzoic acid; and aniline cocatalysts that promoted facile transimination (Scheme 1.18a).[70] Employing this method, a variety of 'tether-free' hydroacylation adducts were isolated in excellent yields whilst using notably low loadings of rhodium catalyst. This imine chemistry was further developed by Jun and several other research groups. Particular attention was paid towards broadening substrate scope and improving catalyst turnover.[71-81] Interestingly, extension of the catalytic rhodium/aminopicoline system to terminal alkynes exclusively delivered branched *α,β*-enones (Scheme 1.18b).[82]



Scheme 1.18 a) Jun's 'traceless' intermolecular hydroacylation b) Jun's branched-selective hydroacylation of terminal alkynes

Castillón later illustrated that branched selectivity could be reversed using sterically demanding ligands such as P^{t}Bu$_3$.[83] The Breit group further improved Jun's original catalyst system by removing the need for high loadings of aminopicoline. They devised a novel, bifunctional aminopicoline-phosphine ligand **35**—capable of reversible substrate binding—that facilitated C–H activation, prevented decarbonylation, and controlled chemoselectivity (Scheme 1.19).[45] This protocol allowed efficient intermolecular hydroacylation between various benzaldehydes and terminal alkenes. Altogether, imine-assisted hydroacylation made great strides in advancing the utility of intermolecular couplings. Nevertheless, many of the methodologies required large amounts of amine and additives along with very high reaction temperatures. What's more, mechanistic studies, by

Bo and Castillón, elucidated the incompatibility of picolyl imines with cationic rhodium complexes.[84] And so, there remained a demand for a mild *N*-chelation strategy that could exploit more synthetically useful *N*-based groups.



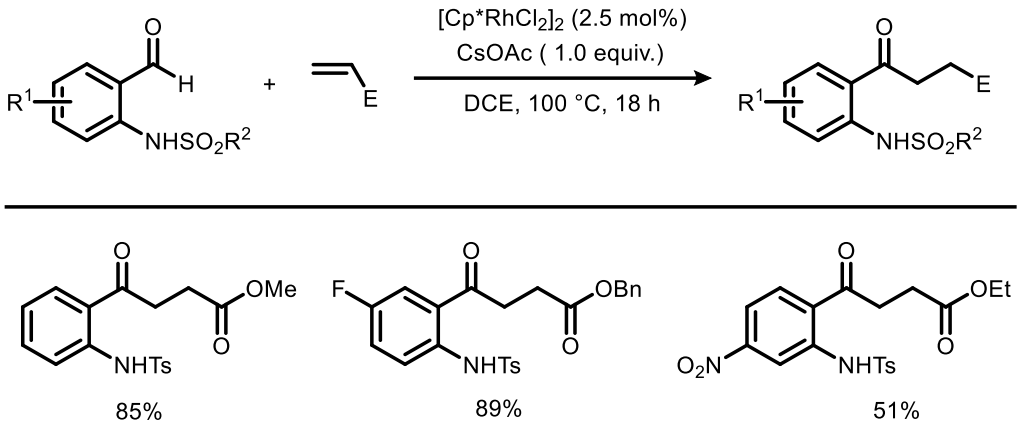
Scheme 1.19 The Breit group's intermolecular hydroacylation employing bifunctional catalyst system

Almost two decades after the first use of imine chelation, the Willis group successfully designed an efficient and versatile *N*-chelation hydroacylation method using *ortho*-aminobenzaldehydes (Scheme 1.20).[85] A simple aniline had already been proven reactive by Bolm and Stemmler,[86] but the Willis group fully cultivated this mode of assistance. Use of a small bite-angle bis-phosphine ligand in a cationic rhodium complex afforded linear hydroacylation adducts in excellent yields and selectivity. The reaction tolerated primary, secondary, or tertiary anilines and required low catalyst loadings and mild temperatures. However, only alkyne substrates were reactive under the conditions.



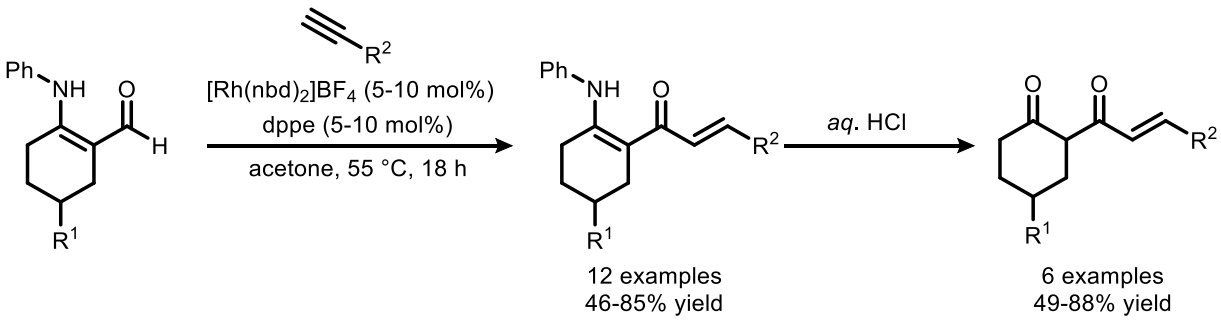
Scheme 1.20 Willis' aniline-directed intermolecular hydroacylation

Soon after, Li and co-workers reported a highly efficient, Rh(III)-catalysed hydroacylation of *N*-sulfonyl 2-aminobenzaldehydes with conjugated and aliphatic olefins (Scheme 1.21).[87]



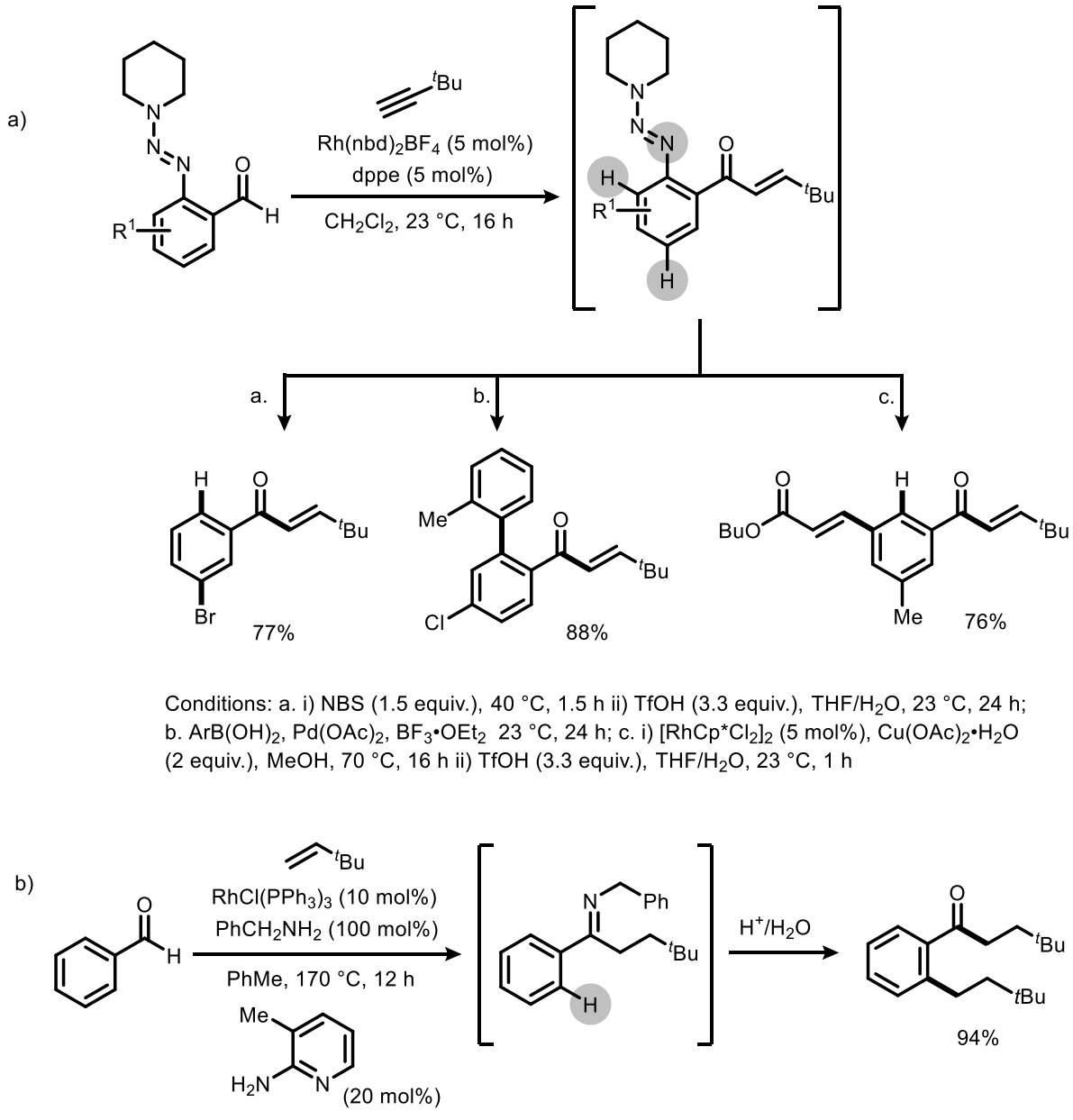
Scheme 1.21 Li's hydroacylation of *N*-sulfonyl-2-aminobenzaldehydes

In 2018, the Willis group showed enamines were efficient directing groups in hydroacylation reactions with alkynes. Utilising a rhodium(I)/dppe catalyst system produced moderate to high yields of the enaminone products as single regioisomers (Scheme 1.22).[88] Subsequent hydrolysis of the enamine functionality generated the corresponding 1,3-dicarbonyl products, which were formerly unattainable using carbonyl-directed hydroacylation (See Section 1.3.5).



Scheme 1.22 The Willis group enamine-controlled intermolecular hydroacylation

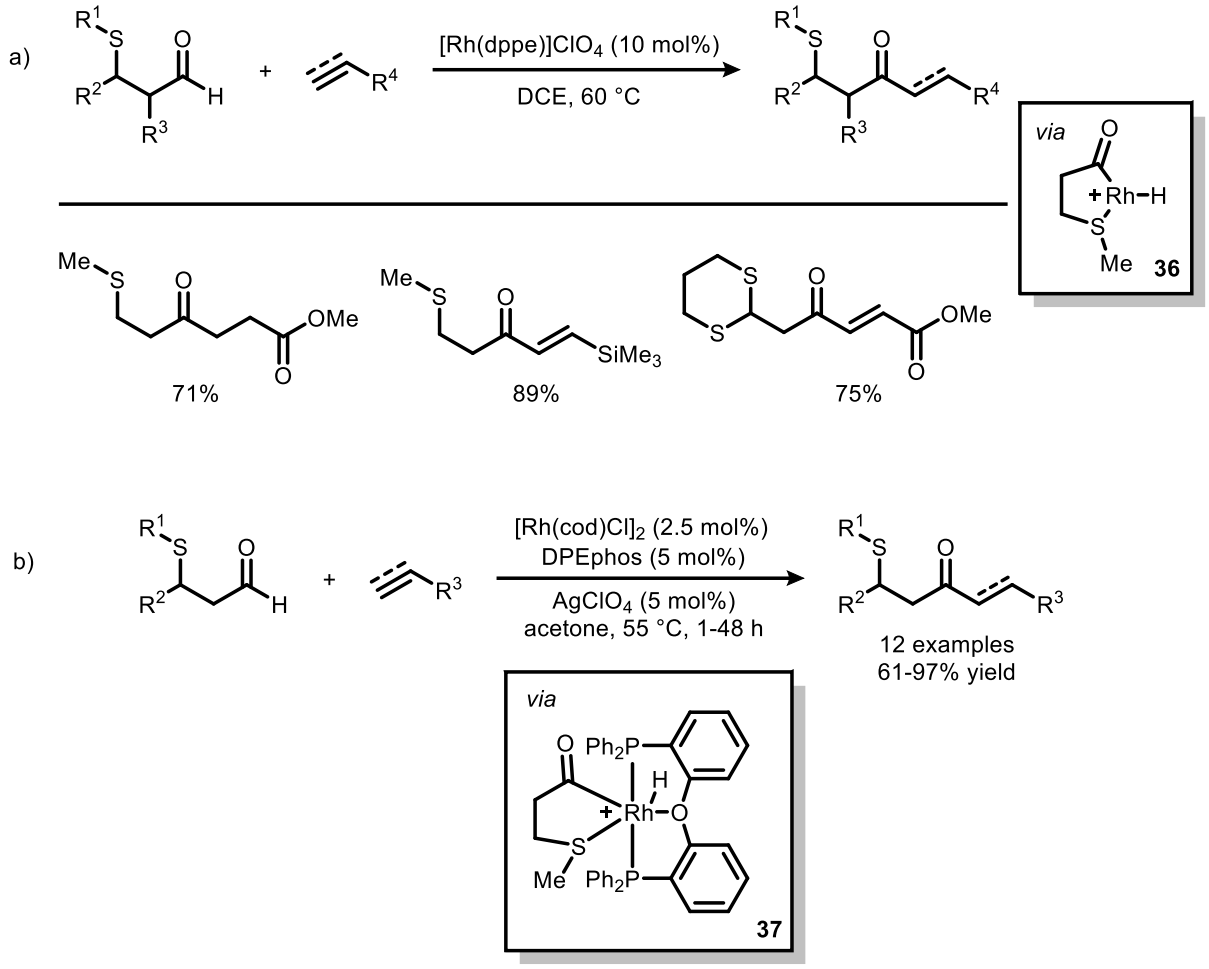
In an attempt to turbocharge the utility of chelating-substituents, Willis *et al* have since developed an efficient aryltriazene-promoted hydroacylation (Scheme 1.23a).[89] In this system, the resulting triazene ketone products can undergo divergent C-H functionalisation reactions, allowing the preparation of diversely substituted benzene cores. Removal and derivatisation of the triazenyl group was also possible, providing a variety of traceless products. As such, this procedure significantly improves on Jun's picolyl-mediated double C-H functionalisation (Scheme 1.23b).[74]



Scheme 1.23 a) Willis' sequential functionalisation of aryltriazenyl aldehydes b) Jun's cascade hydroacylation/*ortho*-C-H alkylation

1.3.3 *S*-chelation

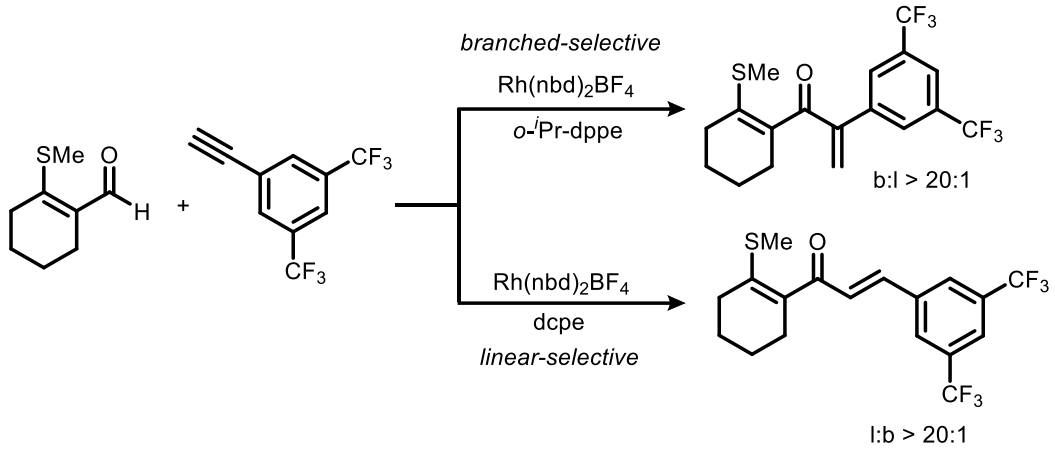
Taking inspiration from Bendorf's *S*-directed intramolecular hydroacylation,[57] the Willis lab spearheaded the use of sulfur-based chelating groups in intermolecular hydroacylation (Scheme 1.24a).[90] Initially, a Bosnich-type, cationic rhodium bis-phosphine complex effectively coupled *β*-*S*-substituted aldehydes with a series of electron-deficient alkenes, producing the corresponding ketones in good yields. The authors discerned that positioning the sulfur atom beta to the aldehyde was necessary to form stable 5-membered Rh-S chelate **36**. However, use of unactivated alkenes led to a marked reduction in reactivity. To address this, Willis and Weller sought to design more active and selective catalysts. A 'second-generation' catalyst was unveiled in 2006, which exploited the hemilabile DPEPhos ligand (Scheme 1.24b).[91] With this catalyst system, simple alkyl-substituted alkenes and alkynes now coupled efficiently at lower temperatures.



Scheme 1.24 a) The Willis group's initial sulfur-directed hydroacylation b) Willis' hydroacylation using hemilabile DPEPhos ligand

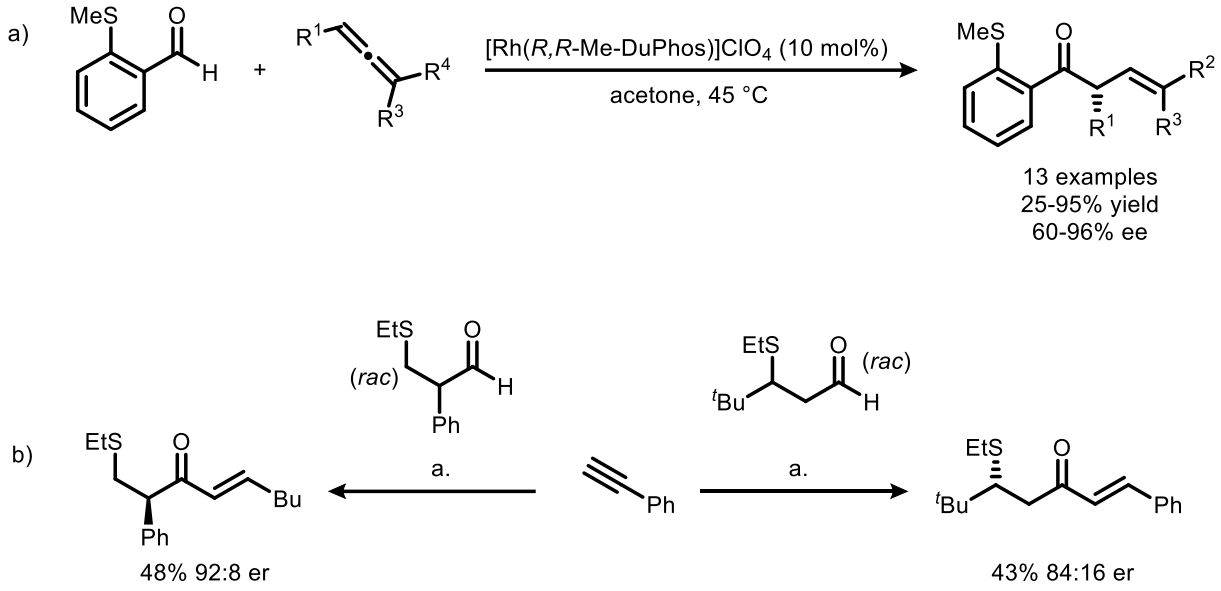
Additional advancements included reduced catalyst loadings, shorter reaction times, and improved practicality. Unlike the earlier system[90]—where the catalyst had to be generated immediately before use—the 'second-generation' catalyst could be prepared *in situ* from $[Rh(cod)Cl]_2$, DPEPhos, and $AgClO_4$. Structural studies credited the observed enhanced reactivity to acyl hydridorhodium species **37**, which was stabilised to decarbonylation by reversible binding of the oxygen atom in the P-O-P ligand. Up to this point, linear adducts were usually preferentially formed in *S*-directed hydroacylation. Then in 2011, the same groups developed branched-selective catalysis by exploiting a bulky *ortho*-^{i}Pr-dppe-derived ligand (Scheme 1.25).[92] They later documented that use of dcpe ligand rendered a complete

reversal of selectivity, providing linear enones in excellent yields.[93] As a result, the authors were able to effect ligand-enforced, regioselectivity switching across a broad range of coupling partners.



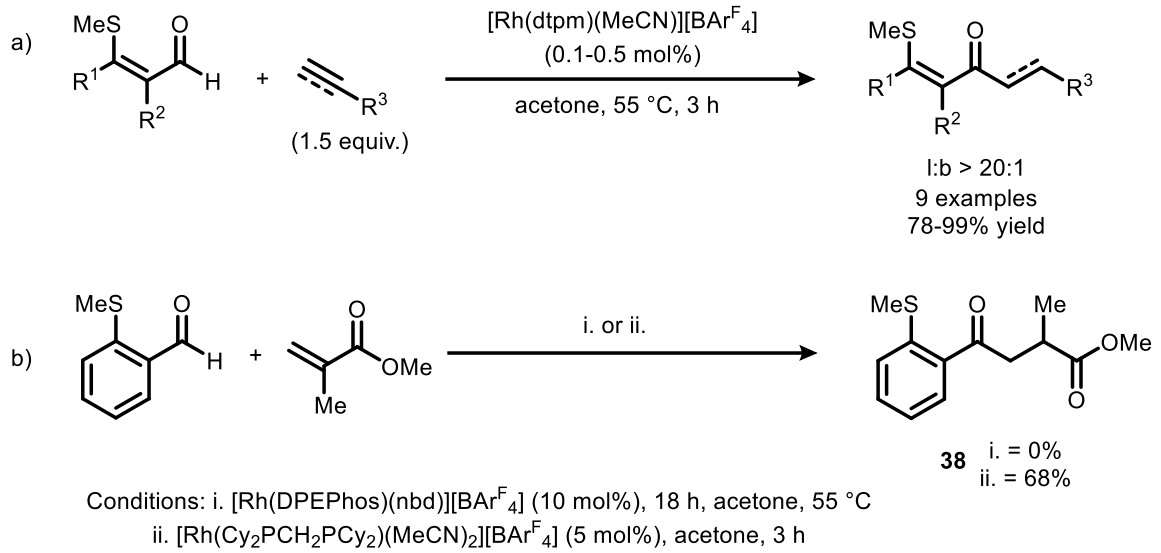
Scheme 1.25 Tuneable regioselectivity in hydroacylation

Highly active, Willis-Weller, cationic Rh(I) catalysts have also facilitated the development of enantioselective transformations. For example, employing a Rh complex with chiral ligand Me-DuPhos allowed efficient coupling of *β*-*S*-substituted benzaldehydes and a range of 1,3-disubstituted allenes (Scheme 1.26a).[94] The resulting non-conjugated enone products were obtained in high yields with excellent ees. A dynamic kinetic asymmetric transformation was suspected to be in operation that entailed racemisation of the allene. Following this, the Willis lab described the first enantioselective intermolecular alkyne hydroacylation. The process involved the kinetic resolution of racemic *α*- and *β*-substituted *S*-chelating aldehydes, generating the corresponding enones with useful levels of enantioselectivity (Scheme 1.26b).[95] Once more, a chiral Me-DuPhos-derived catalyst was optimal for most substrates. Though, for *β*-alkyl-substituted aldehydes the DuanPhos variant displayed superior selectivity.



Scheme 1.26 a) Enantioselective hydroacylation of allenes b) Willis' kinetic resolution method

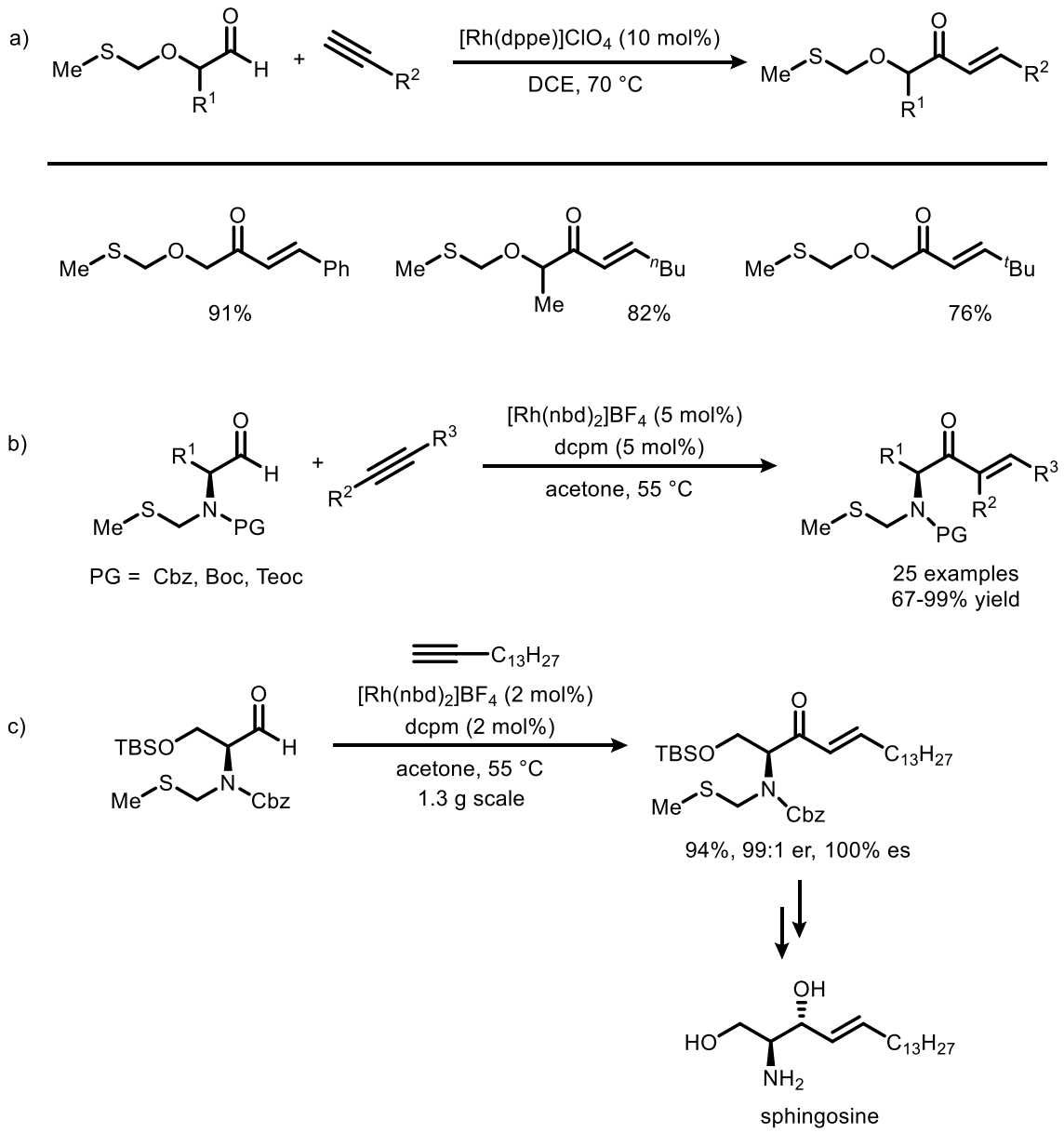
In 2012, Willis and Weller disclosed a 'third generation' catalyst, bolstering catalytic activity by incorporating Hoffmann-esque, small bite-angle ligands. Specifically, employing dtpm (^{t}Bu$_2$PCH$_2$P^{t}Bu$_2$) ligand reduced catalyst loadings to as low as 0.1 mol%, although a higher reaction concentration (2 M) was necessary (Scheme 1.27a).[96] The high activity of these catalysts enabled a broader scope of unactivated alkenes to be incorporated such as, previously challenging, 1,1-disubstituted and 1,2-disubstituted alkenes. When using the 'second-generation' catalyst, hydroacylation of methyl methacrylate was unsuccessful after 18 h (Scheme 1.27b). Contrastingly, employing [Rh(Cy$_2$PCH$_2$PCy$_2$)(MeCN)$_2$][BAr$^F{}_4$] allowed 68% of desired γ-ketoester **38** to be isolated with excellent linear selectivity.[96] The authors proposed that the high reactivity was due to the small bite-angle ligands accelerating the rate-limiting, reductive elimination step of the reaction. A sequent publication confirmed a rhodium catalyst featuring a small bite-angle PNP ligand (^{i}Pr$_2$PNMeP^{i}Pr$_2$) mediated alkyne hydroacylation with high efficiency. This system delivered excellent linear selectivity and an exceptionally high turnover (TON = 100, 5 min).[97]



Scheme 1.27 a) Willis' hydroacylation of unactivated alkenes b) Willis' hydroacylation of disubstituted alkenes

Willis and co-workers further exploited 'third generation' catalysts to improve their use of methylthiomethyl (MTM) as a chelating unit (Scheme 1.28a).[98] Originally, this motif was explored in hydroacylation reactions as it could be easily converted into synthetically useful, free alcohols. In the presence of 'second generation' catalyst [Rh(dppe)]ClO_4, MTM-substituted aldehydes were efficiently coupled to 1-alkynes, producing respective enone products in high yields. This aside, high catalyst loadings (10 mol%) were requisite and internal alkynes were unreactive under the optimised conditions. Guided by these results, the Willis group demonstrated that analogous MTM-protected, enantiomerically enriched α-amino aldehydes were viable hydroacylation substrates. On this occasion, use of a small bite-angle Rh(I)/dcpm complex enabled lower catalyst loadings (5 mol%) and milder conditions than previously reported with second generation catalysis (Scheme 1.28b).[99] More strikingly, internal alkynes now displayed high reactivity. The reaction also exhibited good functional group tolerance, providing a plethora of α-amino enones in excellent yields with retention of enantiomeric purities. The utility of the methodology was validated by its

use for a vital C−C bond forming step in a concise, enantio- and diastereoselective synthesis of natural product sphingosine (Scheme 1.28c).[99]



Scheme 1.28 a) MTM-directed hydroacylation b) *α*-amino aldehydes in hydroacylation c) the Willis group's synthesis of sphingosine

Willis and Weller completed their 'toolset' of catalysts with the design of a complex incorporating novel non-symmetric ligand AmpaPhos ($^{t}Bu_2PCH_2P(^{o}C_6H_4OMe)_2$) (Figure 1.1).[100] The latter combined the benefits of small bite-angle diphosphines with the stabilisation effect of hemilabile *O*-chelation. Accordingly, this 'fourth generation' catalyst

was successfully applied to the hydroacylation of notoriously unreactive substrates; *viz*. internal alkynes and functionalised alkenes. The enhanced reactivity of this system was ascribed to the steric bulk of *ortho*-anisole phosphine substituents that promoted the, formerly retarded, hydride insertion step.[100]

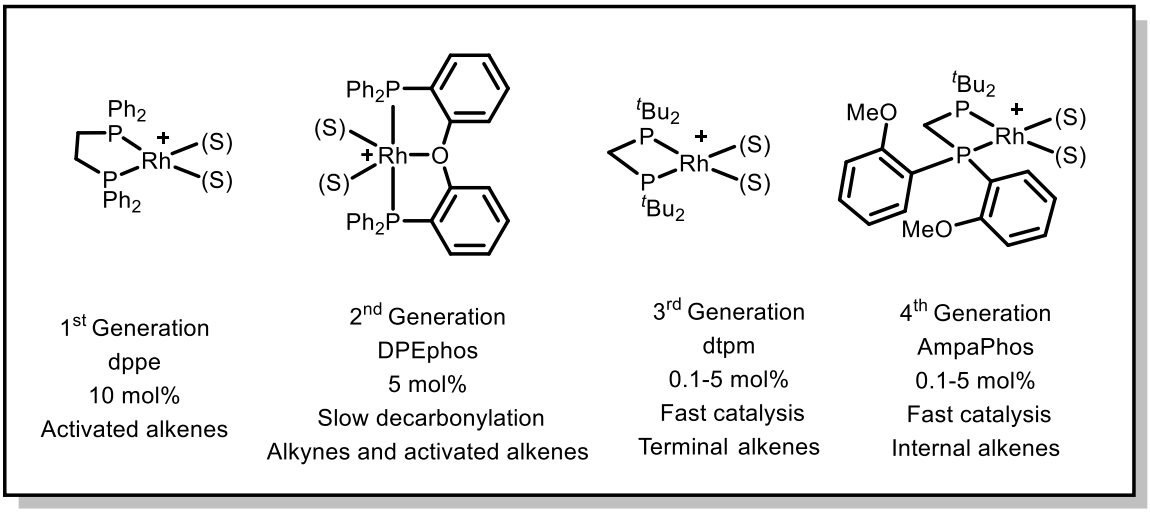
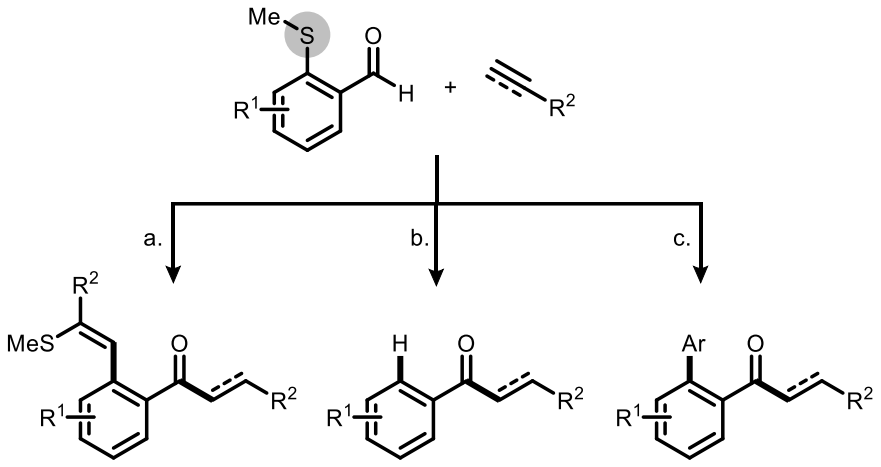


Figure 1.1 Willis-Weller catalyst design for hydroacylation with *β*-*S*-substituted aldehydes

By and large, the Willis-Weller evolution of catalysts for sulfur-directed intermolecular hydroacylation has birthed robust methodologies with vast applications. In spite of this, sulfur-based chelating groups are often synthetically undesirable in final products. 'Traceless' hydroacylation goes someway in addressing this problem by removing or directly functionalising the *S*-motif.[98-99, 101-106] In this context, the Willis group have combined hydroacylation with a number of transformations including carbothiolation[107]; sulfur reduction[102]; and Suzuki-type cross-couplings[103]—to name a few (Scheme 1.29). The same group has also shown that *S*-substituted enones can be converted into different heterocycles in a single step.[108] This approach towards heterocycle synthesis will be reviewed in section 1.3.7.

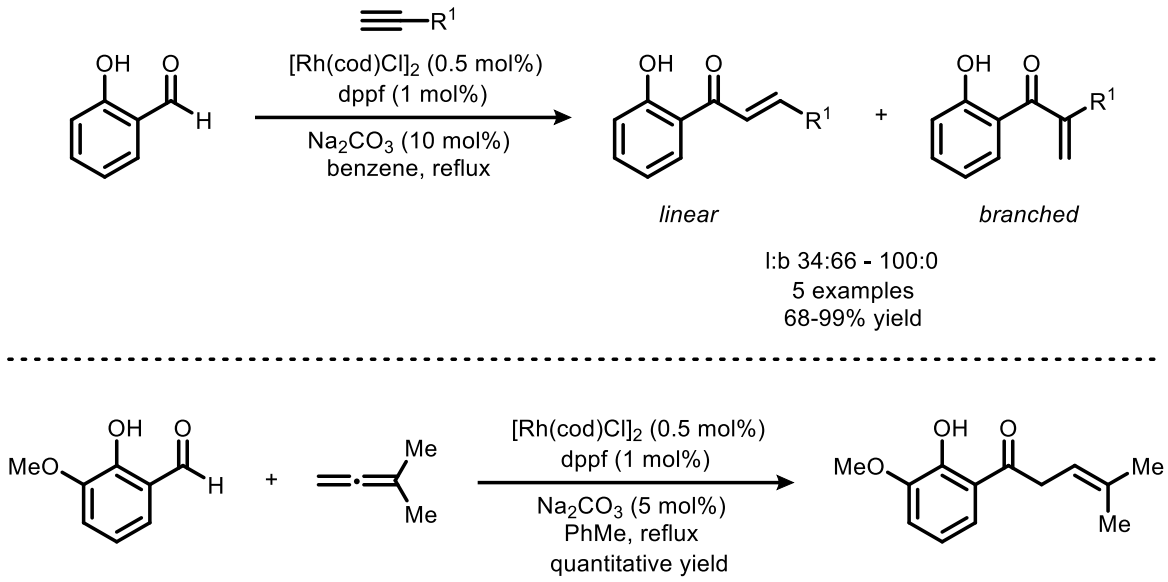


Conditions: a. [Rh(DPEPhos)(*o*-xylene)][BAr^F_4] (5 mol%), 60 °C, 5 h;
b. [Rh($Cy_2PCH_2PCy_2$)(C_6H_5F)][BAr^F_4] (10 mol%), DCE, 80 °C then $(EtO)_3SiH$, 25 °C;
c. [Rh(^{i}PrPCH$_2$P^{i}Pr)(C_6H_5F)][BAr^F_4] (7.5 mol%), acetone, r.t. 5 min then $ArB(OH)_2$, Ag_2CO_3, 55 °C, 16 h

Scheme 1.29 Willis' traceless hydroacylation strategies

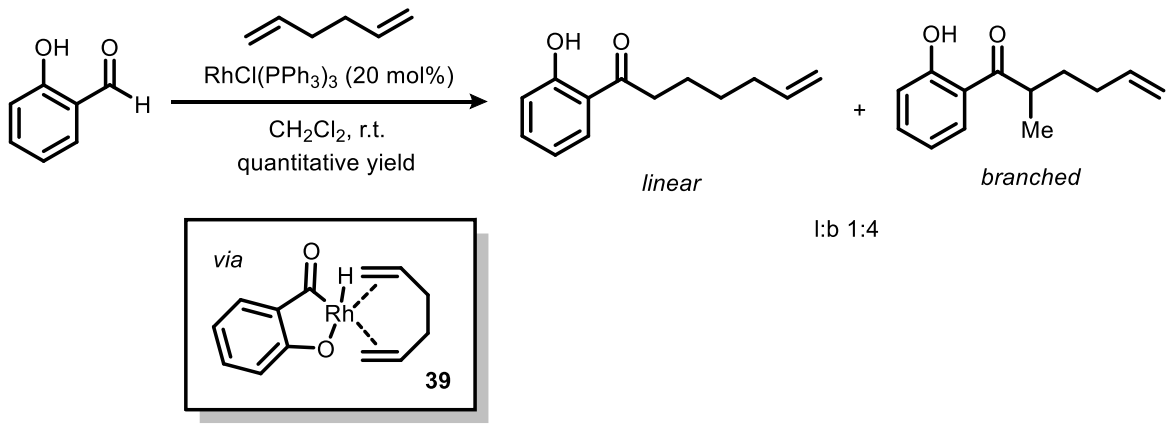
1.3.4 *O*-Chelation

Oxygen tether groups are highly effective at stabilising acyl rhodium intermediates. Miura first established this by using salicylaldehydes in hydroacylation reactions with alkynes and allenes.[109-110] From a synthetic viewpoint, these phenolic derivatives are attractive substrates because their commercial availability evades preinstallation of the tether. Miura's protocol comprised low loadings of $[Rh(cod)Cl]_2$, dppf ligand, and sub-stoichiometric amounts of Na_2CO_3 (Scheme 1.30).[109] The base was deemed essential for deprotonating the alcohol; thereby, promoting the formation of a stable rhodium-phenolate species. In all, only moderate regiocontrol was attained and most alkenes displayed poor reactivity.



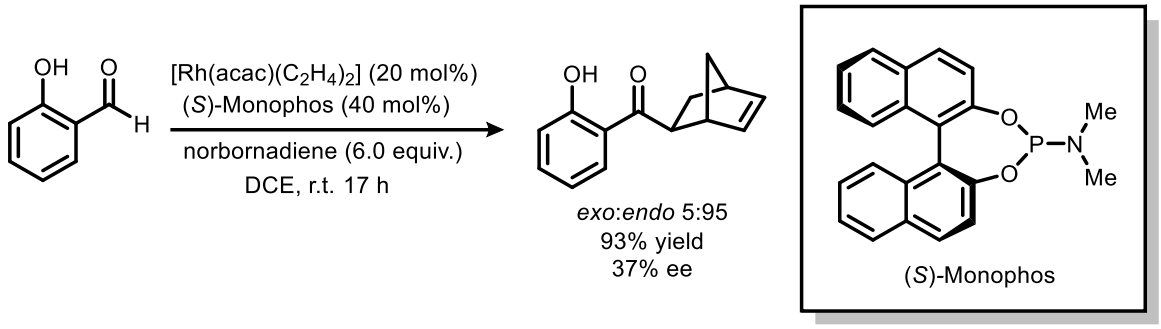
Scheme 1.30 Miura's hydroacylation with salicylaldehydes

Duly, Suemune and co-workers realised mild conditions for coupling salicylaldehydes with 1,4- and 1,5-dienes using Wilkinson's catalyst. The key factor for success was the intermediacy of 'double-chelation' complex **39** where the aldehyde and diene made two-point interactions with rhodium (Scheme 1.31).[111-112] The authors also noticed that the ratio of linear to branched isomers could be tuned by combining different rhodium catalysts with additives.



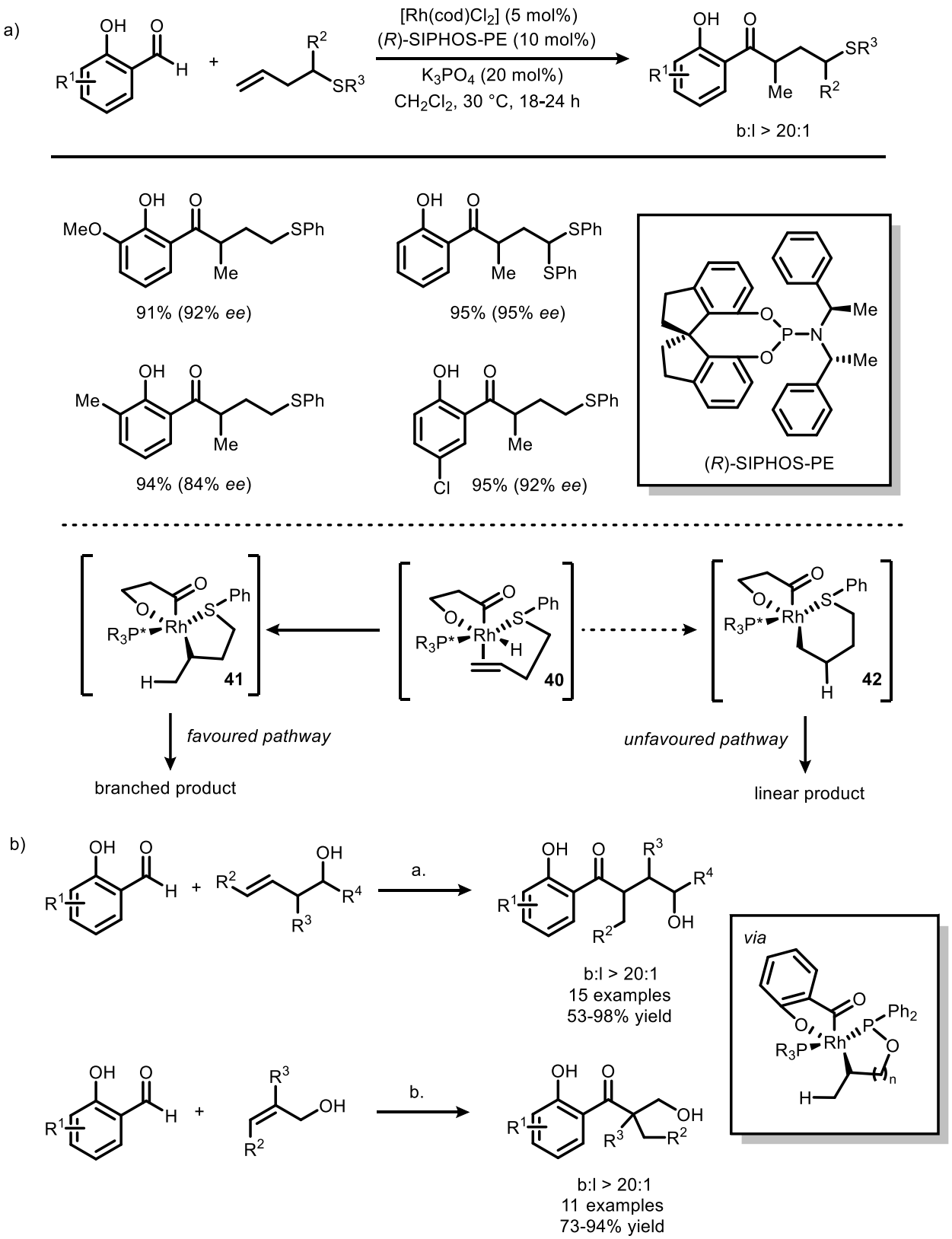
Scheme 1.31 Suemune's hydroacylation of salicylaldehydes and dienes

In subsequent years, several studies leveraged this 'double-chelation' model for the hydroacylation of salicylaldehydes. For example, Bolm described an asymmetric *endo*-selective hydroacylation of norbornadiene using phosphoramidite ligands—which afforded ketone products with moderate enantioselectivities (Scheme 1.32).[86]



Scheme 1.32 Bolm's hydroacylation using norbornadiene

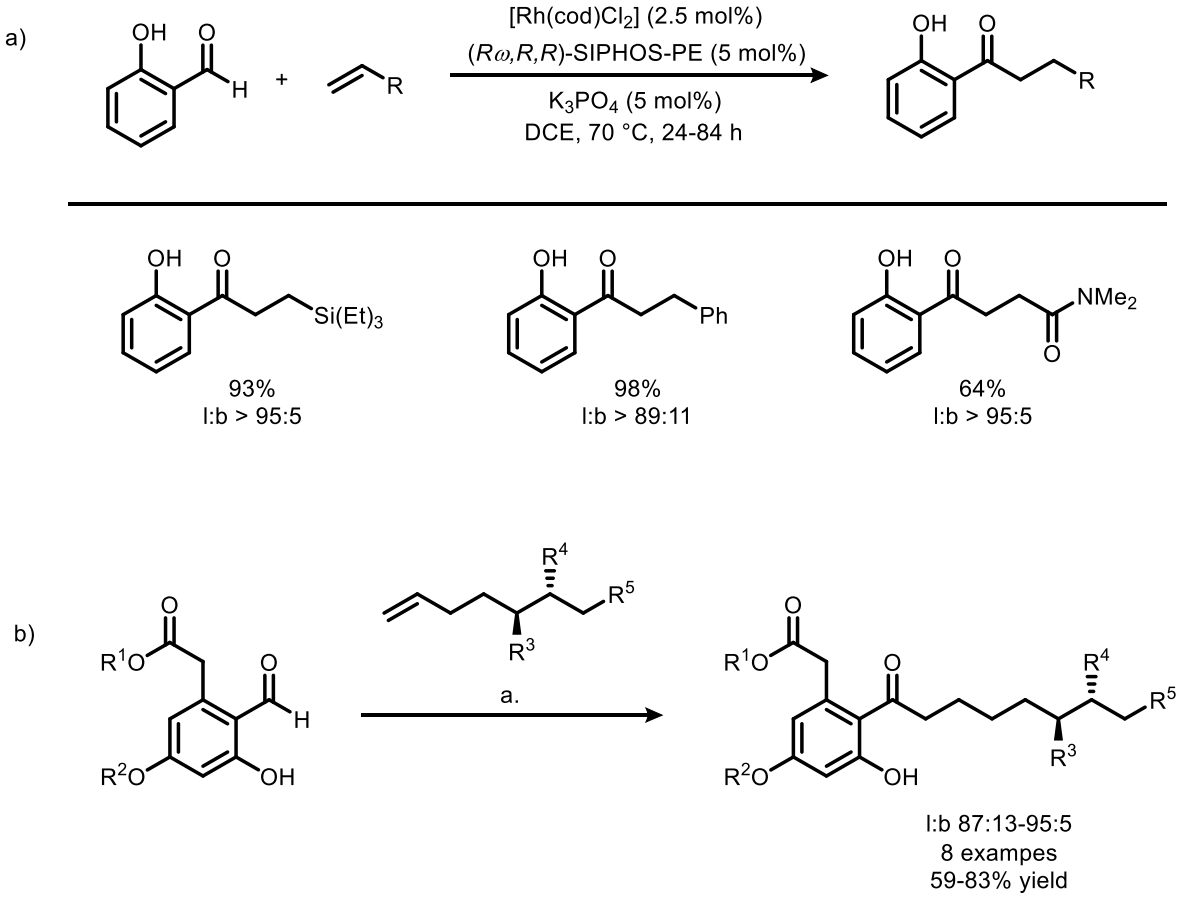
Remaining with salicylaldehyde hydroacylation, Dong and co-workers evolved the double-chelation strategy by replacing a double bond (on the diene coupling partner) with a coordinating sulfide group. In doing so, exceptionally high branched to linear ratios were realised from reactions with various salicylaldehydes and homoallylic sulfides (Scheme 1.33a).[113] The high regioselectivity stemmed from the strong directing potential of the coordinating sulfur atom. It was postulated that Rh(III)-hydride intermediate **40** preferentially undergoes migratory insertion *via* five-membered rhodacycles, rather than 6-membered cognates, providing branched isomers. Excellent enantiocontrol was also achieved using spiro-phosphoramidite ligand SIPHOS-PE. Driven by these results, Dong *et al* expanded this method to allyl and homoallyl alcohols, this time, evoking a 'Jun-like' cooperative catalysis between Rh and Ph_2POMe. The phosphinite was assumed to have two-fold functionality: reversible binding of the alcohol and coordination to the metal centre. In this way, high branch-selectivity for aldol and homoaldol products was obtained (Scheme 1.33b).[114-115]



Conditions: a. $[Rh(cod)Cl_2]$ (2.5 mol%), Ph_2POMe (25 mol%), NaOAc (20 mol%), THF, 70 °C;
b. $[Rh(cod)Cl_2]$ (5 mol%), Ph_2POMe (60 mol%), NaOAc (20 mol%), DCE, 70 °C

Scheme 1.33 a) Dong's enantioselective hydroacylation of homoallylic sulfides b) Dong's hydroacylation employing allylic and homoallylic alcohols

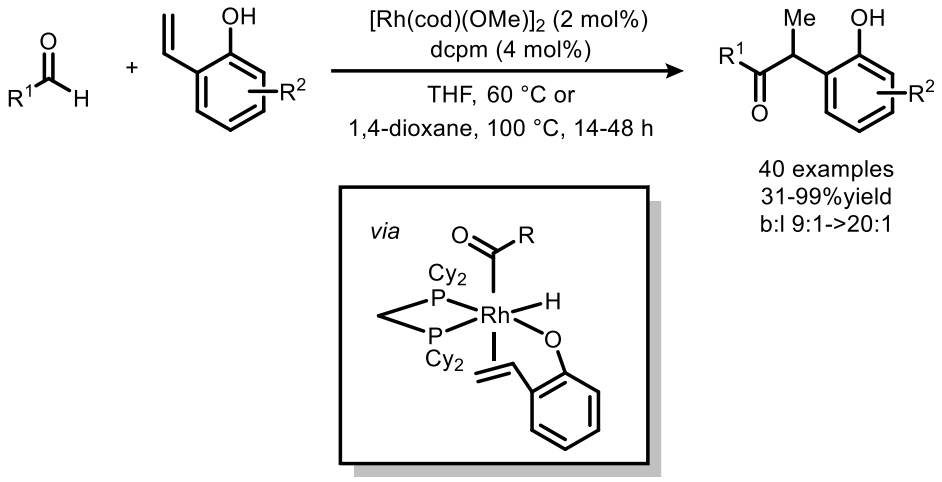
Another strategy to promote hydroacylation with salicylaldehydes is to employ olefins under basic conditions (the base assists in the same manner as described earlier). For example, Dong and co-workers published an efficient hydroacylation method, requiring rhodium loadings as low as 2 mol% and encompassing a broad alkene scope (Scheme 1.34a).[116] In this case, precise quantities of heterogeneous base were critical for enhanced reactivity. The reaction also displayed high linear regioselectivity owing to use of phosphoramidite ligand (*Rω*,*R*,*R*)-SIPHOS-PE, which efficiently suppressed decarbonylation. This procedure was successfully applied to the total synthesis of eight octaketide natural products (Scheme 1.34b).[116]



Conditions: a. $[Rh(cod)Cl_2]$ (5 mol%), (*Rω*,*R*,*R*)-SIPHOS-PE (5-10 mol%), K_3PO_4 (5-10 mol%), DCE, 70 °C, 18-72 h

Scheme 1.34 a) Dong's hydroacylation of salicylaldehyde and unactivated alkenes b) Total synthesis of octaketide natural products

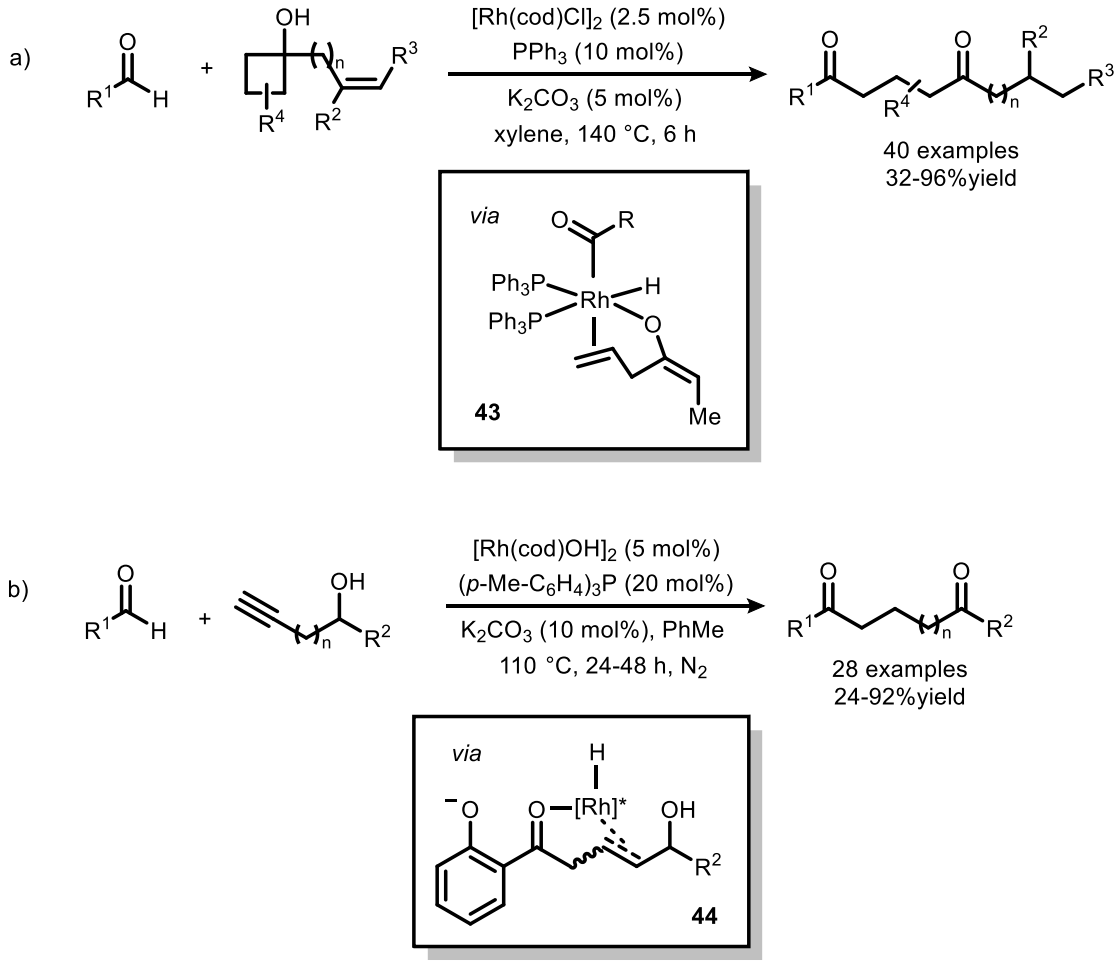
The discussions so far have largely focused on stabilising key acyl rhodium intermediates with chelating aldehydes. However, recent reports have described efficient alkene-tethered hydroacylation reactions with non-chelating aldehydes. The Dong group published a branched-selective protocol for hydroacylation of vinylphenols with aryl, alkenyl, and alkyl aldehydes (Scheme 1.35).[117] Mechanistic studies revealed that strong binding of the vinylphenolate was key to promoting hydroacylation over competitive aldehyde decarbonylation and aldol dehydration. The high reactivity of the neutral rhodium complex was accredited to its electron-rich character and the use of a small bite-angle ligand that promoted oxidative addition.[118]



Scheme 1.35 Vinylphenol hydroacylation with non-chelating aldehydes

Further to this work, Zhang *et al* reported the hydroacylation of vinyl cyclobutanols with non-tethered aldehydes, providing a novel atom-economic route to 1,5 diketones (Scheme 1.36a).[119] Coordination of the vinyl cyclobutanol alkoxide group uniquely induced rhodium-mediated ring-opening. Subsequent transfer hydrogenation afforded a stable rhodium enolate **43** that underwent hydroacylation. The optimised reaction conditions were compatible with both aliphatic and aromatic aldehydes as well as a broad range of alkenyl cyclobutanols. Building on this cascade reactivity, Yan and Li disclosed the

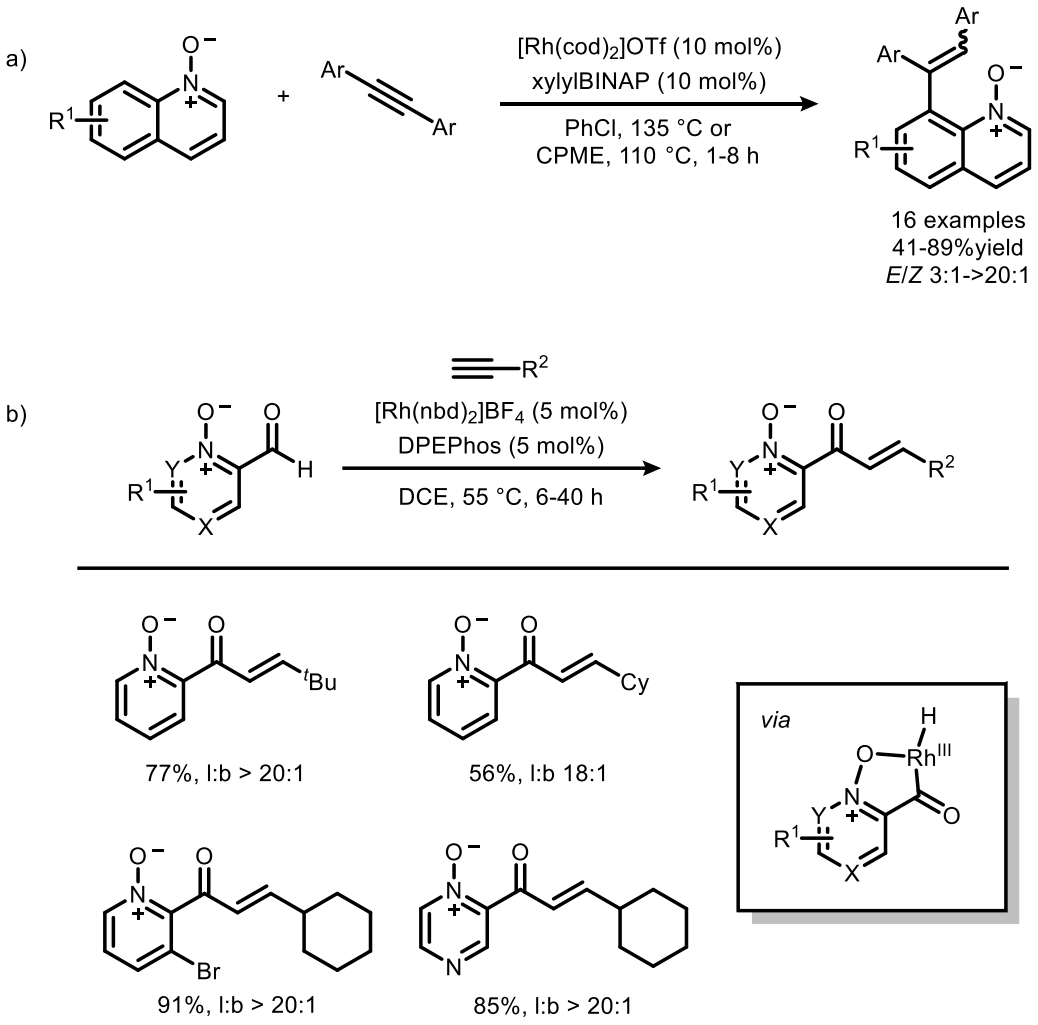
synthesis of 1,4-, 1,5-, and 1,6-diketones by alternatively pairing intermolecular hydroacylation with deconjugative isomerisation (Scheme 1.36b).[120] The requirement of readily accessible alkynols and the broad scope of diketones were noteworthy improvements of Zhang's method. Even so, harnessing ring strain in hydroacylation remains an effective strategy for accessing diverse diketones. In fact, a number of recent methodologies have surfaced that successfully combine salicylaldehyde-directed hydroacylation with ring opening reactions.[121-122]



Scheme 1.36 a) Zhang's synthesis of 1,5 diketones *via* hydroacylation b) Yan and Li's route to diketones *via* hydroacylation

The coordination strength of oxygen can be favourably attenuated by utilising an *N*-oxide as a directing group. Shibata was first to evidence this chelation in a regioselective Rh(I)-catalysed alkenylation of quinoline *N*-oxides (Scheme 1.37a).[123] Inspired by this

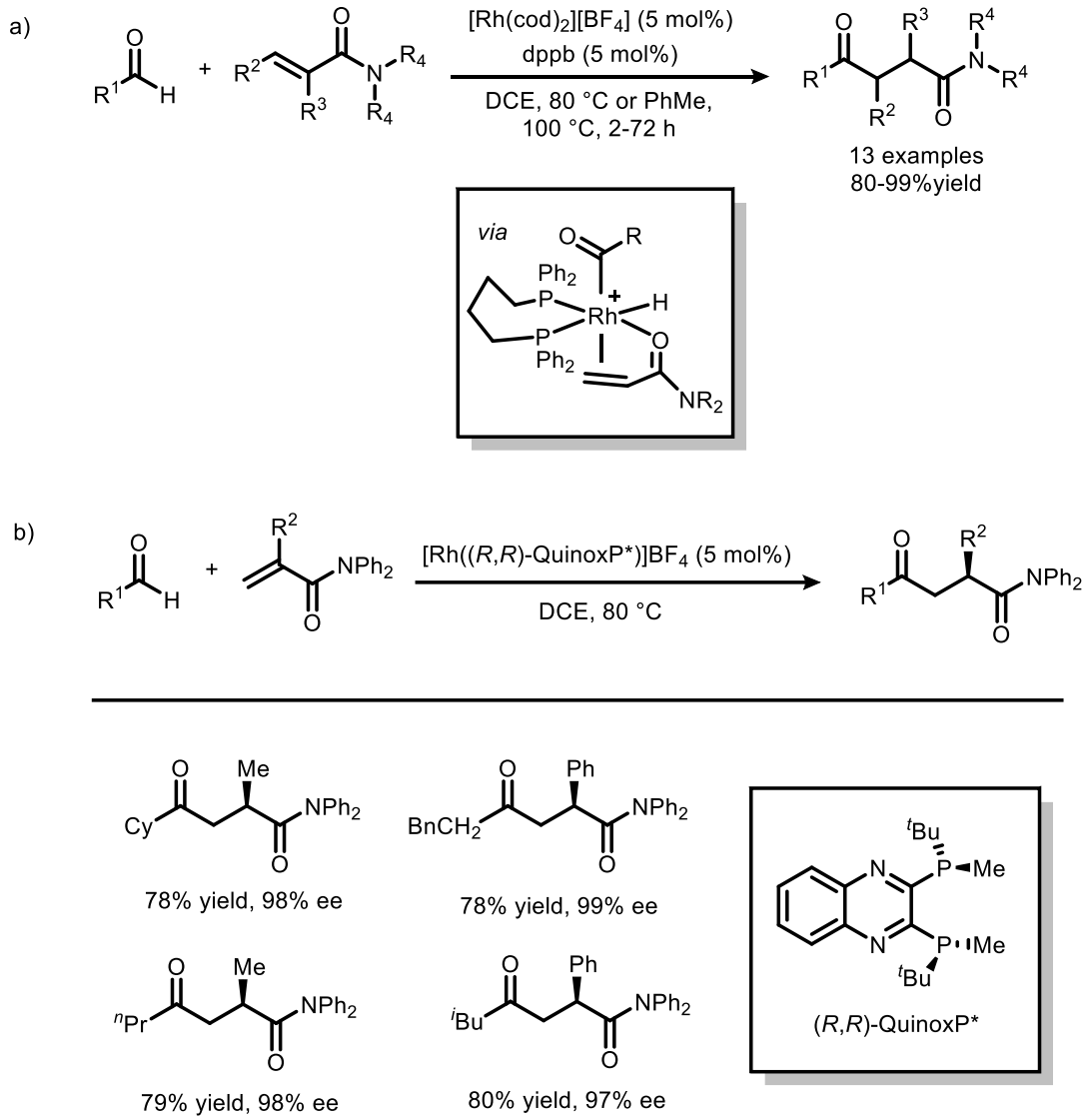
discovery, the Willis group have since shown that azine aldehyde *N*-oxides are highly active substrates in intermolecular hydroacylation (Scheme 1.37b).[124] Notably, the C-H activation occurred under milder conditions and delivered linear enone adducts in good yields.



Scheme 1.37 a) Shibata's *N*-Oxide-directed alkenylation b) Willis' azine-*N*-oxide-directed hydroacylation

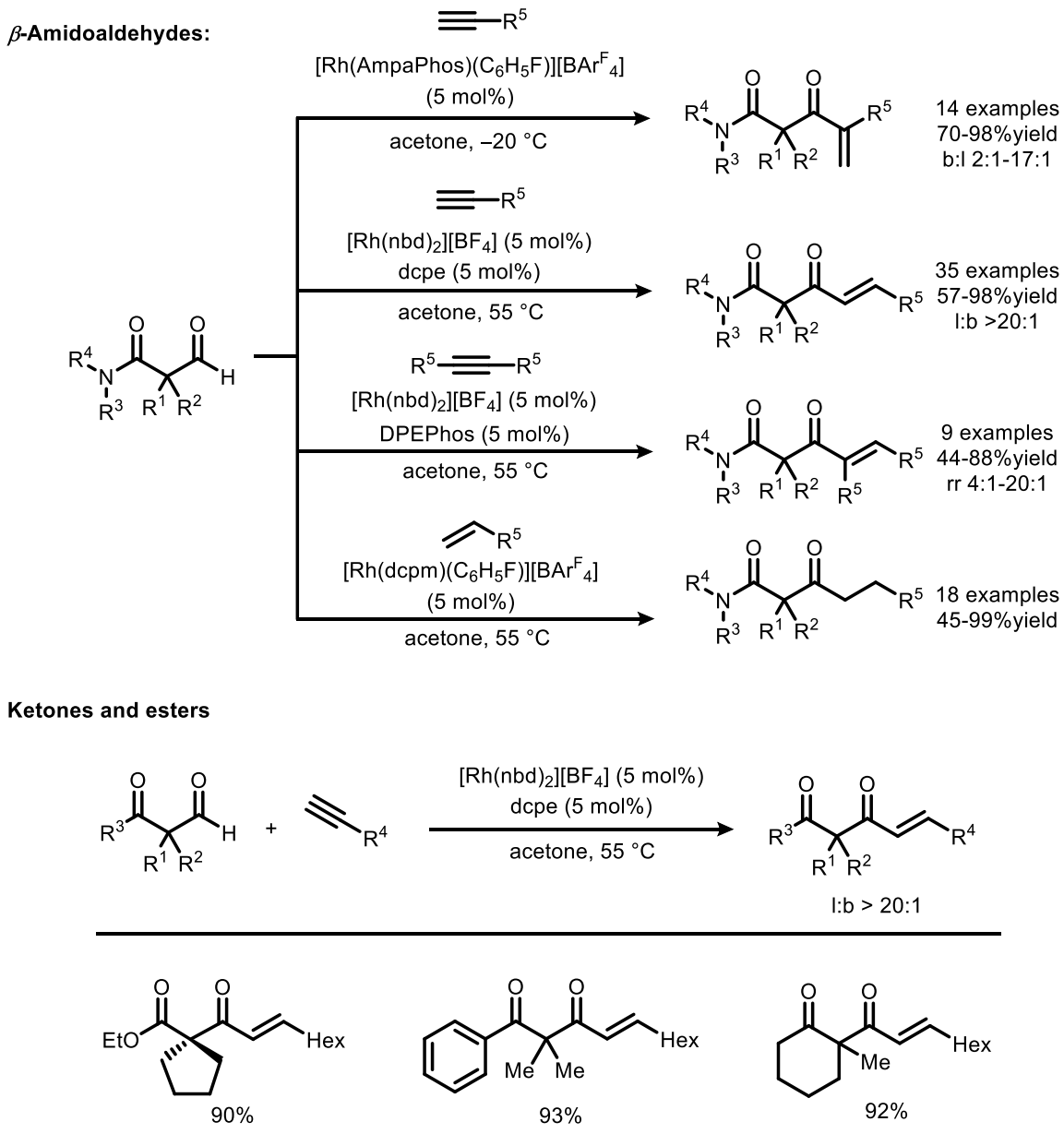
1.3.5 Carbonyl-chelation

The examples highlighted thus far have used chelating groups on alkene or aldehyde partners that can encumber final hydroacylation products. The removal of these tethers—be it through functionalisation or integration into target molecules—is often an afterthought. A simpler approach is to incorporate common, versatile, and useful coordinating groups that are synthetically desirable in the final adducts. A choice example is the carbonyl group, which has ample use in synthetic chemistry. The first suggestion that this motif could be adopted came from Tanaka's acrylamide-directed reaction. Using a cationic rhodium catalyst and wide bite-angle ligand dppb, *γ*-ketoamide products were isolated in high yields and linear selectivity (Scheme 1.38a).[125] It was hypothesised that simultaneous binding of the *N*,*N*-dialkylacrylamide carbonyl and alkene groups stabilises the acyl rhodium hydride; hence, attenuates decarbonylation. Tanaka and Shibata followed up this reaction with an enantioselective variation. The pairing of methyl acrylamides with a cationic rhodium(I)/QuinoxP* complex established an effective hydroacylation with unfunctionalised aldehydes (Scheme 1.38b).[126] The scope of the acrylamide coupling partner was limited, but the desired *γ*-ketoamides were isolated in good yields with excellent enantioselectivities.



Scheme 1.38 a) Tanaka's acrylamide-directed hydroacylation b) Tanaka's enantioselective hydroacylation of acrylamides

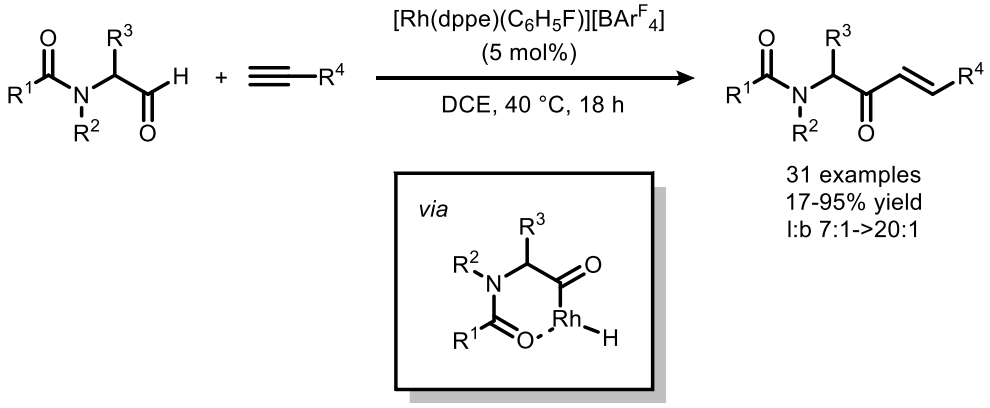
In 2017, Willis *et al* developed an elegant carbonyl-assisted intermolecular hydroacylation procedure. They showcased the exceptional reactivity of *β*-amido, *β*-ester, and *β*-keto aldehydes in the hydroacylation of alkenes and alkynes. By utilising cationic rhodium catalysts with bisphosphine ligands, efficient and selective reactions were realised, providing a remarkable scope of 1,3-dicarbonyl products in excellent yields (Scheme 1.39).[127]



Scheme 1.39 Willis' carbonyl-directed intermolecular hydroacylation

The mild conditions applied are worthy of note as they meant a myriad of functional groups were tolerated. Judicial ligand choice also permitted switchable linear/branched selectivity for alkyne substrates. Nevertheless, ester and ketone-directed reactions necessitated α,α-disubstitution to prevent the formation of enols, which unproductively bound the metal catalyst. Consequently, α-mono-substituted 1,3-dicarbonyl products were inaccessible. The authors later overcame this tautomerisation issue by employing enamines

(See Section 1.3.2). More recently, Willis has presented the first Rh(I)-catalysed hydroacylation reaction mediated by 1,4-dicarbonyl chelation.[128] Readily available *α*-amidoaldehydes were coupled with terminal alkynes using a preformed complex (Scheme 1.40). The latter was integral for achieving high reactivity and regioselectivity because it, supposedly, led to a higher effective catalyst concentration. The authors assumed that the 1,4-dicarbonyl substrates form sufficiently stabilised 6-membered rhodacycle intermediates. As such, the productive hydroacylation pathway outcompetes reductive decarbonylation. This is apparent from the high yields of *α*-amidoketone adducts obtained.

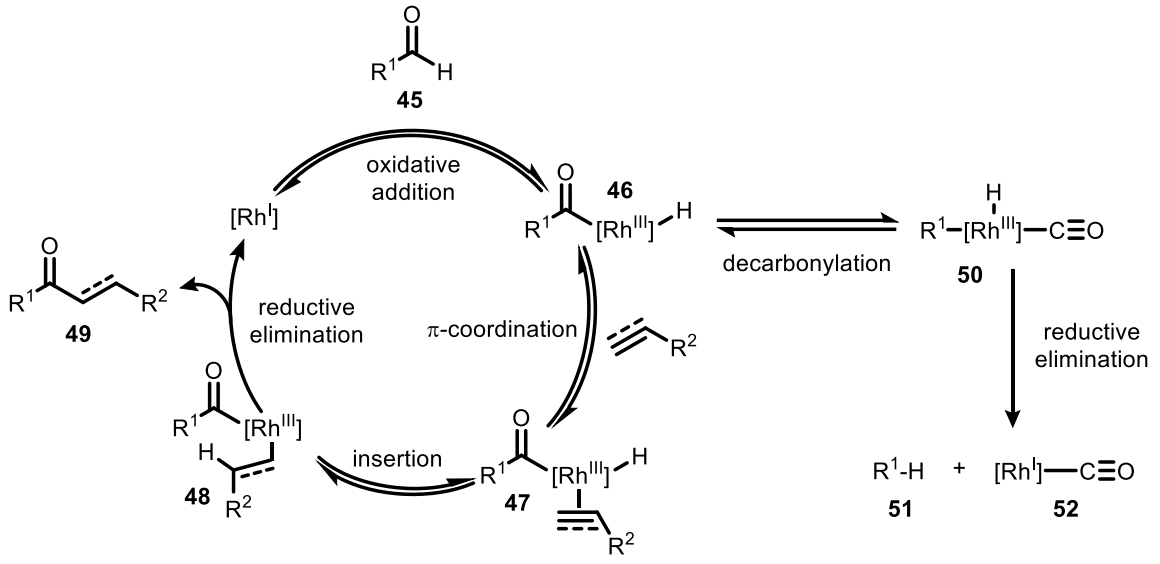


Scheme 1.40 Hydroacylation of *α*-amidoaldehydes with alkynes

1.3.6 Mechanistic studies

Several comprehensive studies have investigated the mechanism of rhodium-catalysed hydroacylation reactions. These monographs are summarised in this section with emphasis on important developments. The earliest study was conducted by Suggs in 1978.[68] In this work, the first stable acyl rhodium(III) hydride complex (*vide supra*) was isolated and established as a key catalytic intermediate. After this, Miller performed deuterium-labelling studies to decipher the mechanism of intermolecular hydroacylation between 4-hexenal and ethylene.[67] The main mechanistic finding was that ethylene promoted the formation of a coordinatively saturated rhodium species; thereby, restricting decarbonylation. This observation was later substantiated by Bosnich's extensive NMR spectroscopy

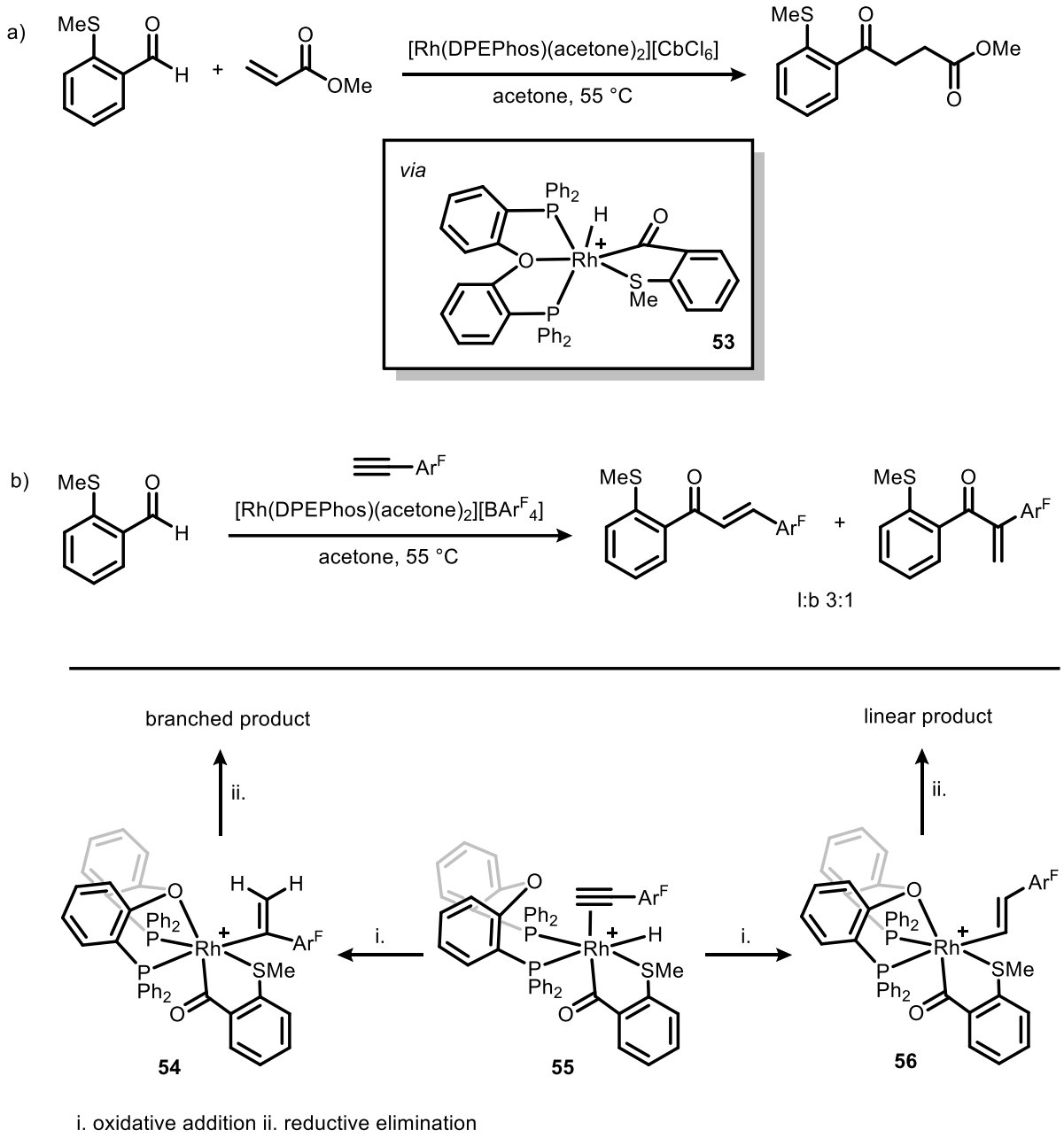
experiments.[129] Interestingly, computational studies led by Morehead and Sargent contested the beneficial impact of alkene coordination.[130] Rather than limiting decarbonylation by coordinative saturation, the authors suggested the binding of excess substrate preferentially lowered the barrier of reductive elimination relative to decarbonylation and resultant catalyst death. Many other groups have delineated mechanistic insights alongside their synthetic studies.[66, 91, 96, 131-132] Taken together, a prototypical hydroacylation mechanism can be presented (Scheme 1.41). Firstly, oxidative addition of aldehyde **45** generates acyl rhodium(III) hydride **46**. Next, coordination of the unsaturated substrate is followed by hydride insertion, giving intermediate **48**. Finally, reductive elimination from **48** produces the hydroacylation adduct whilst regenerating the Rh(I) catalyst. Multiple kinetic and spectroscopic analyses verify that all steps in the catalytic cycle are reversible, except the reductive elimination, which is turnover-limiting. The presence of a *cis*-vacant site in acyl hydride **46** results in carbonyl deinsertion, producing species **50**, which undergoes reductive elimination to form alkane **51**. Brookhart demonstrated that the extrusion of CO was reversible, and that the ensuing Rh-carbonyl species was one of two resting states in the cycle.[66] Accordingly, it is the irreversible reductive elimination of the alkane that ultimately kills the catalyst.



Scheme 1.41 General mechanism for rhodium-catalysed hydroacylation

As previously outlined, repressing decarbonylation has been a major challenge for most rhodium-catalysed hydroacylation methods. Both the reductive decarbonylation and productive reductive elimination steps require a vacant coordination site. The difficulty lies in promoting product formation over the degenerative pathway. Chelation control works to coordinatively saturate the rhodium centre and has proven successful in many intermolecular systems. Willis and Weller have performed mechanistic studies with various *S*-chelating aldehydes and so have characterised several important intermediates involved in the catalytic cycle. Using a DPEPhos-based Rh(I) catalyst and methylacrylate, acyl-hydride intermediate **53** was isolated (Scheme 1.42a).[91, 131] This confirmed dual chelation from the *o*-MeS-benzaldehyde and tethering oxygen atom of the ligand. The latter interaction stabilised **53** against unproductive reductive decarbonylation, providing a longer-lived catalyst. The ability of the ligand to alter its coordination geometry throughout the catalytic cycle was also imperative. This flexibility allowed other coordinated groups (hydride, acyl and alkene), to assume the mutually *cis* orientations required for insertion and reductive elimination. The same catalyst was later used to probe the mechanism of alkyne

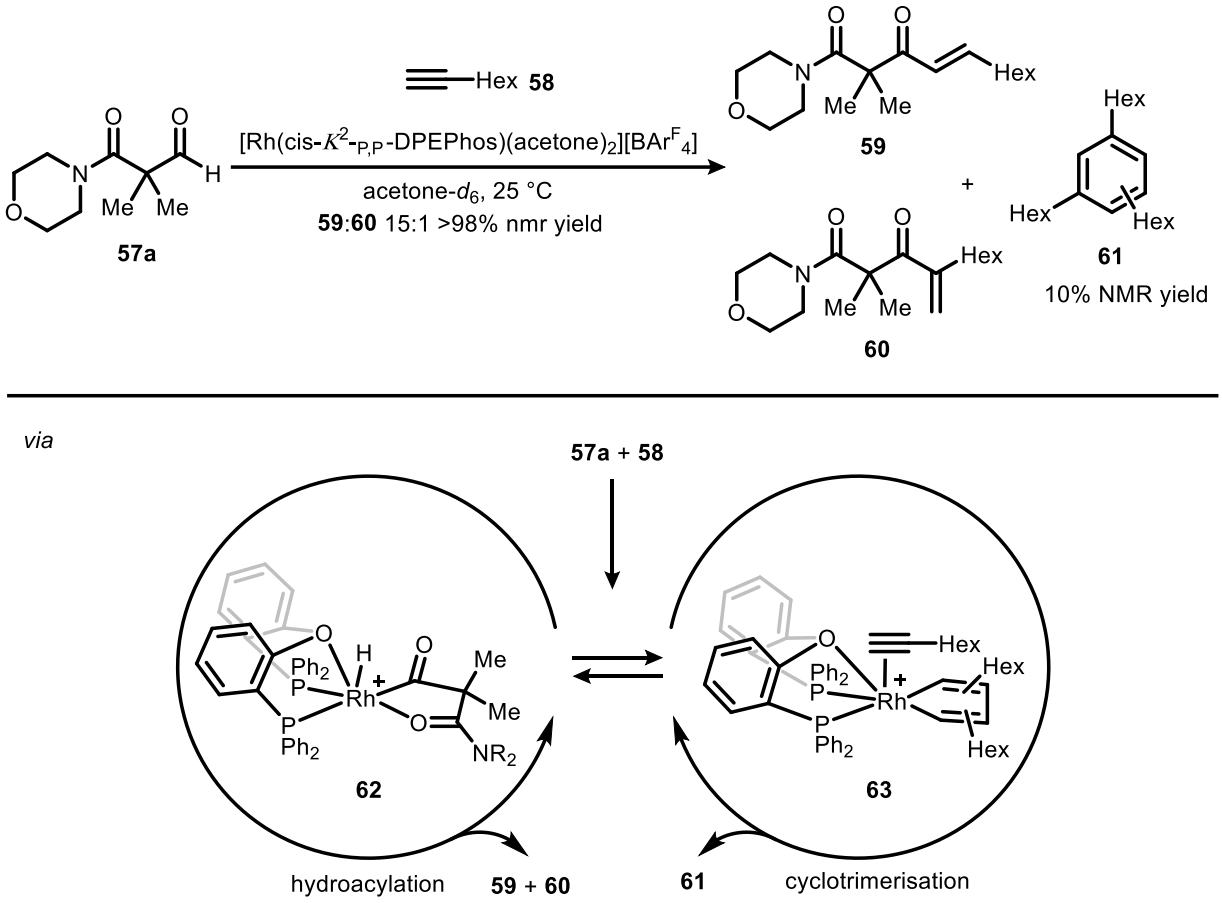
hydroacylation, resulting in the first isolation of branched alkenyl intermediate **54** (Scheme 1.42b).[132] Selective deuteration experiments revealed that in contrast to alkene hydroacylation, hydride insertion into the alkyne was irreversible. Kinetic modelling studies also established putative handles for regiocontrol in the catalytic cycle. Specifically, after alkyne coordination, the hydride can insert into either end of the triple bond, affording both linear and branched adducts. The partitioning of linear and branched pathways, at the hydride insertion step occurred with 2:1 selectivity. Likewise, reductive elimination of the branched isomer was approximately 300 times slower than the linear. This discrepancy in rate was attributed to steric crowding in branched intermediates, which slows C-C reductive elimination.



Scheme 1.42 a) Hydroacylation of *o*-SMe-benzaldehyde and methacrylate b) Linear and branched pathways in alkyne hydroacylation

Recent mechanistic revelations have come from Willis and Weller's research on *β*-carbonyl-assisted hydroacylation.[133] The reaction between *β*-amido-aldehyde **57** and 1-octyne, using $[Rh(DPEPhos)]^+$-based catalysts, involved competing hydroacylation and cyclotrimerisation processes (Scheme 1.43). An acyl Rh(III) hydride fragment **62** was identified as the major resting state of the hydroacylation pathway due to strong binding of

the aldehyde. Notably, when the concentration of free aldehyde neared zero, cyclotrimerisation became competitive. In addition, kinetic experiments proved the migratory insertion step was turnover-limiting and selectivity-determining (in respect to linear/branched products). The above findings drove the discovery of the optimal relative loading of catalyst and starting materials, resulting in a highly efficient hydroacylation protocol (Scheme 1.39).



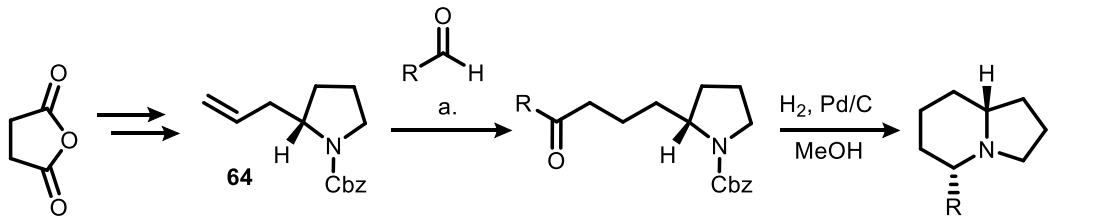
Scheme 1.43 Summary of mechanistic findings of *β*-carbonyl-assisted hydroacylation

1.3.7 Heterocycle synthesis

So far, this chapter has focused on the advancement of intermolecular hydroacylation through chelation control, catalyst design, and mechanistic understanding. In many instances, once a successful methodology is realised, its synthetic utility is exemplified in

the synthesis of heterocycles. Heterocyclic moieties hold a noble status within the fields of medicinal chemistry and natural product synthesis. This, in part, is due to their ubiquity, tuneable polarity, and binding affinity.[134] In general, classical methods for heterocycle construction fall short of sustainable ideals. Conversely, rhodium catalysed hydroacylations are hallmarked by high atom economy and selectivity as well as broad functional group tolerance. These traits are hugely valuable in the context of heterocycle synthesis. Indeed, these intermolecular transformations go further by permitting unorthodox disconnections of target molecules.[134] It is no surprise then, that numerous reports have demonstrated the efficient conversion of hydroacylation adducts into a variety of heterocyclic compounds. The application of intermolecular hydroacylation in the *de novo* synthesis of heterocycles is reviewed herein.

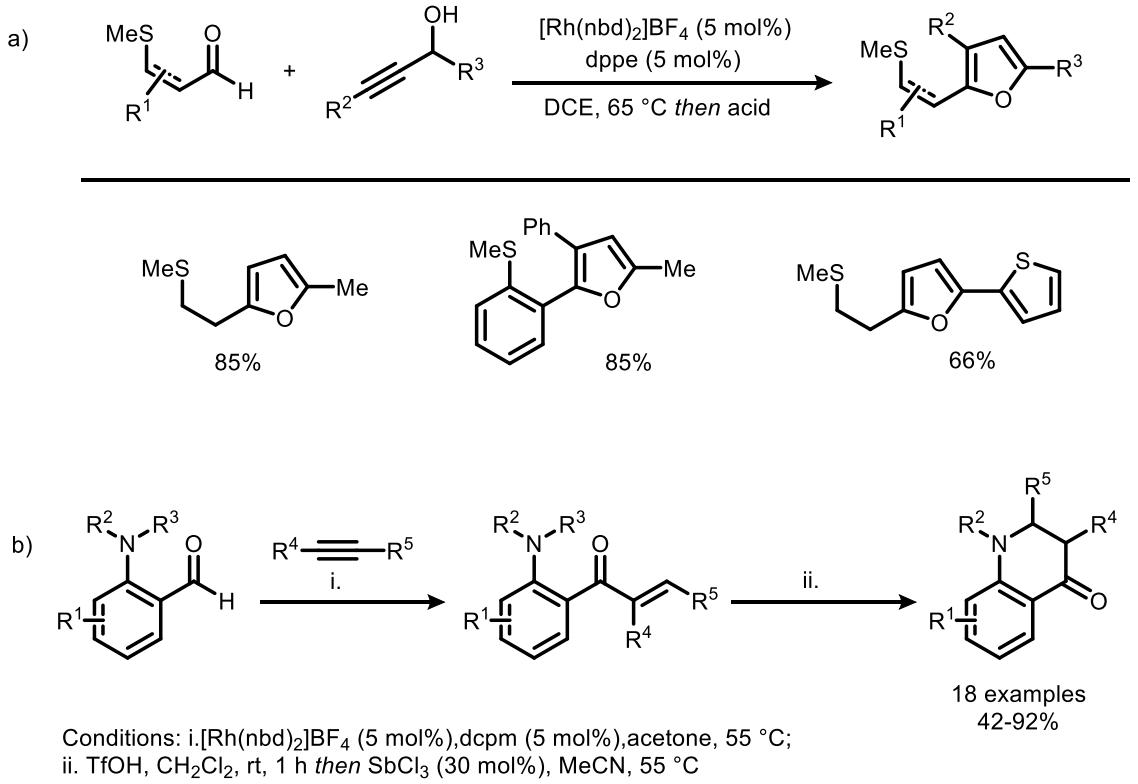
In 2001, Kim and Lee applied Jun's *N*-chelation tactic in the synthesis of gephyrotoxin alkaloids (–)-167B and (–)-209D. Hydroacylation of enantioenriched alkene **64** with alkyl aldehydes provided the corresponding ketone intermediates in modest yields (Scheme 1.44).[80] Subsequent hydrogenation and cyclisation generated the target bicyclic natural products in good yields.



Scheme 1.44 Total synthesis of gephyrotoxin alkaloids *via* hydroacylation

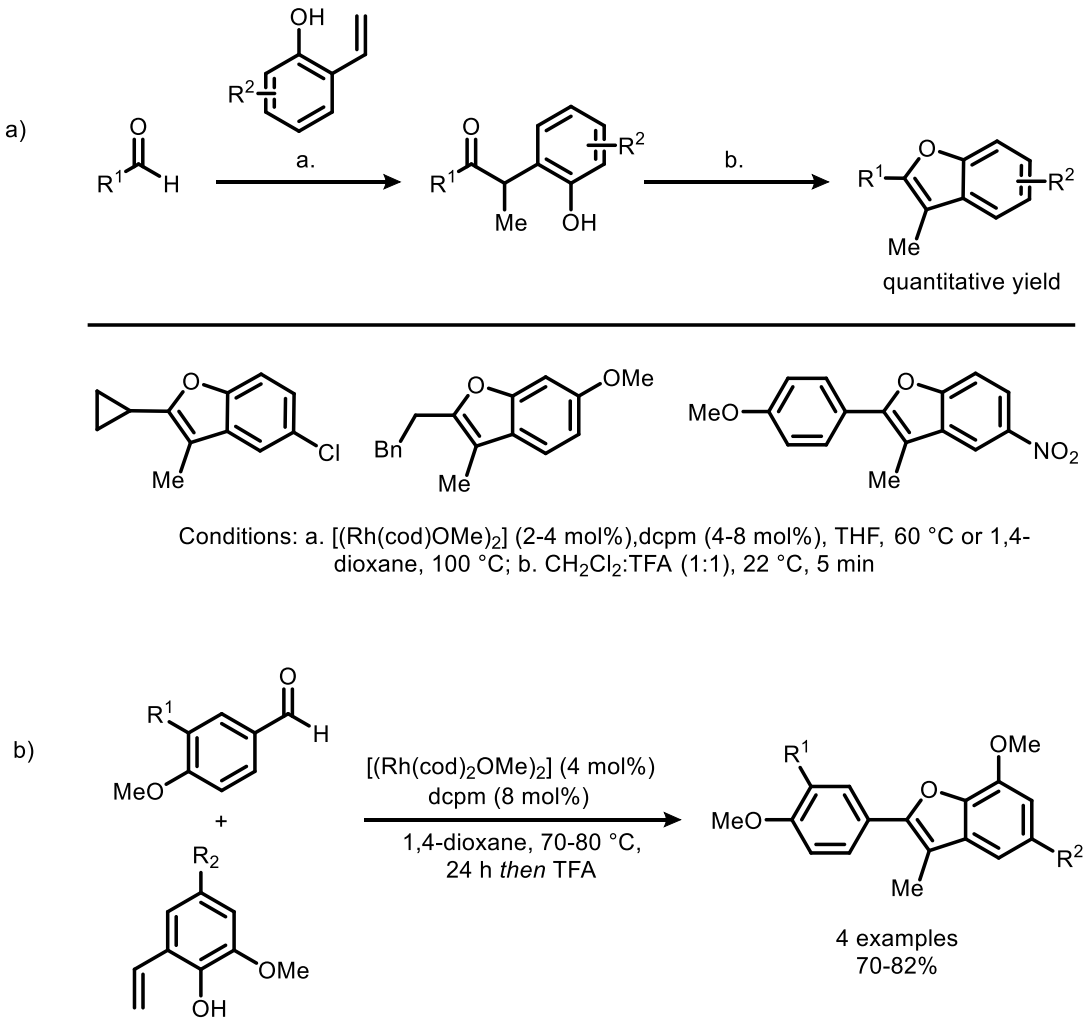
A decade later, the Willis group pioneered the use of alkyne hydroacylation in the assembly of highly substituted furans.[135] Coupling of *S*-chelating aldehydes with propargylic

alcohols delivered γ-hydroxy-α,β-enones that underwent acid-catalysed intramolecular cyclisation, affording the desired furan rings in good to excellent yields (Scheme 1.45a). Despite this, the products still possessed the synthetically unattractive thiomethyl tethering group. This could be avoided by directly integrating the heteroatom tether into the final heterocyclic product. This workaround was implemented in Willis' hydroacylation route to dihydroquinolones (Scheme 1.45b).[85] As aforementioned, this report elegantly advanced *N*-chelation by deviating from Suggs' picolyl imine strategy (See Section 1.3.2). Previously unproductive cationic rhodium complexes now efficiently catalysed the hydroacylation of various alkynes with protected anilines. Sequential treatment of the amino-substituted enone products with antimony trichloride or triflic acid, yielded a selection of dihydroquinolones *via* intramolecular *aza*-conjugate addition.



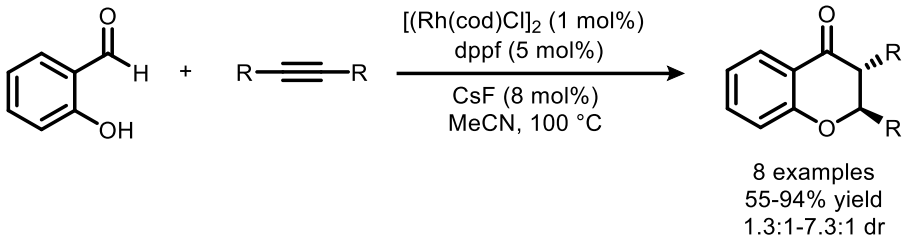
Scheme 1.45 a) Synthesis of furans *via* hydroacylation b) Willis' synthesis of dihydroquinolones

The Dong group employed a similar approach to access benzofurans—except the heteroatom tether was positioned on the unsaturated coupling partner.[117] Their neutral Rh catalysts were highly reactive towards C-H activation of non-chelating aldehydes. Subsequent hydroacylation with vinylphenols provided branched α-aryl ketones in very good yields (Scheme 1.46a). The latter underwent cyclocondensation to give the corresponding benzofurans in quantitative yield. This motivated the authors to apply this method to the synthesis of several bioactive eupomatenoid natural products (Scheme 1.46b). The heterocycles were prepared in a one-pot fashion, but the scope of products was relatively narrow.[117]



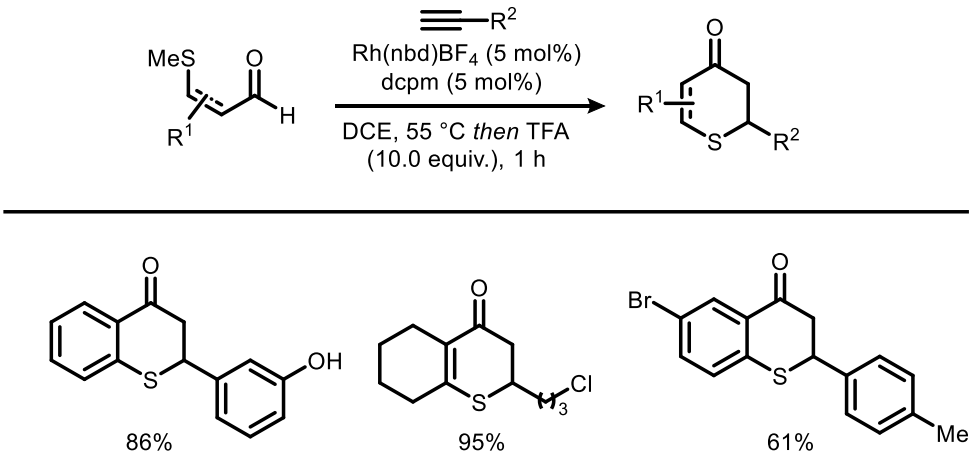
Scheme 1.46 a) The Dong group benzofuran synthesis using non-chelating aldehydes b) Dong's total synthesis of eupomatenoid natural products

Soon after, Stanley and Du synthesised a wider scope of chromanones through a related tandem hydroacylation/cyclisation process.[136] An array of salicylaldehydes were coupled with internal alkynes, using a dppf-derived catalyst and inorganic base. The resulting enones reacted *in situ*, *via* an intramolecular oxa-conjugate addition, forming 2,3-disubstituted chroman-4-ones in high yields and modest diastereoselectivities (Scheme 1.47). Since then, the Li group has also disclosed sequential processes that deliver chromanones from salicylaldehyde precursors.[137-138]



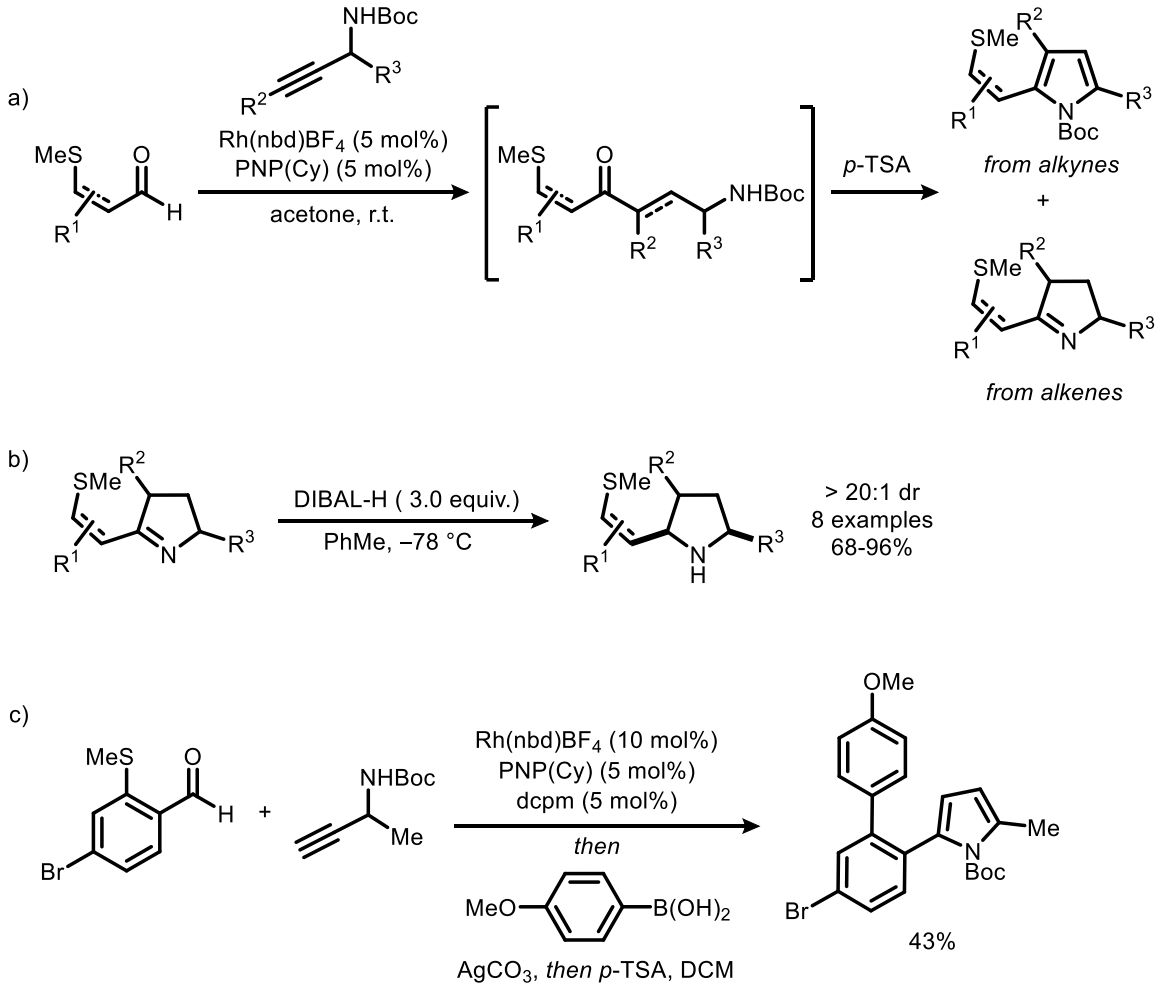
Scheme 1.47 A tandem hydroacylation/Michael addition route to chromanones

In 2016, Willis reported an alkyne hydroacylation/thio-conjugate-addition sequence that delivered thiochroman-4-one derivatives (Scheme 1.48).[108]



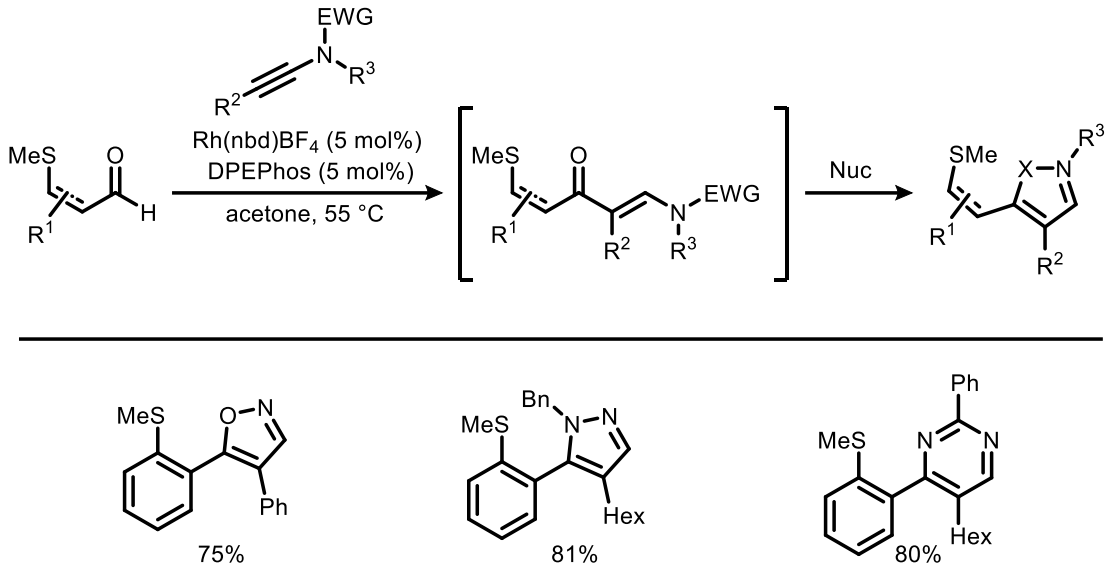
Scheme 1.48 Synthesis of thiochromanones *via* hydroacylation

Willis' combination of β-S-chelating aldehydes with highly active Rh(I)-catalysts has generated an extremely robust hydroacylation protocol that has enabled the synthesis of pyrroles[139], dihydropyrroles[139], and quinolines[140]. These syntheses relied on intermediate, highly electrophilic, α,β-unsaturated enones—which could subsequently cyclise to give different heterocycles. For instance, the hydroacylative union of aldehydes and propargylic amines delivered γ-amino enones, which cyclised to corresponding pyrroles after addition of *p*-TSA (Scheme 1.49a).[139] In this reaction, PNP ligand ($(Cy_2)P_2$)NMe was needed to achieve high linear selectivity. Allylic amines were also compatible substrates, producing functionalised dihydropyrroles that could then be reduced to respective pyrrolidines with excellent *cis*-selectivity (Scheme 1.49b).[139] 'Traceless' pyrrole products were also accessed through telescoped cross-coupling reactions. In this scenario, the methyl sulfide served first as a chelating group, and then as a pseudo-halide (Scheme 1.49c). This method allowed three-component assembly of structurally diverse heterocyclic scaffolds from simple starting materials.[139]



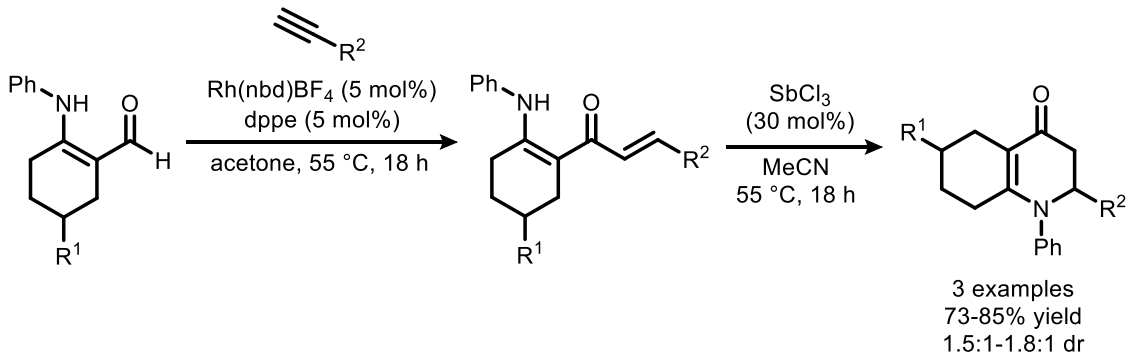
Scheme 1.49 a) Synthesis of pyrroles *via* hydroacylation b) synthesis of dihydropyrroles c) three component couplings leading to 'traceless' hydroacylation products.

The same tandem strategy was extended to the synthesis of alternate *N*-heterocycles by employing ynamides (Scheme 1.50).[141] These were coupled to *β*-*S*-aldehydes, using a commercially available Rh precatalyst and DPEPhos, furnishing linear *β*-enaminone products in high yield and excellent regioselectivity. Exposure of these 1,3-dicarbonyl surrogates to hydroxylamine; *N*-substituted hydrazines; or amidines, yielded isoxazoles; pyrazoles; and pyrimidines, respectively (Scheme 1.50). In this manner, a plethora of functionalised heterocycles were synthesised, in a modular fashion, *via* a one-pot hydroacylation/nucleophilic addition/cyclisation sequence.[141]



Scheme 1.50 Willis's synthesis of heterocycles using ynamide-directed hydroacylation

In a similar way, the success of an enamine-controlled hydroacylation opened up a route to functionalised hexahydroquinolinones.[88] These heterobicycles were synthesised in high yields by treatment of isolated enaminones with catalytic antimony(III) trichloride (Scheme 1.51). However, the *aza*-conjugate addition step relayed low diastereoselectivity.



Scheme 1.51 Willis' route to *N*-heterocycles using enamine-directed hydroacylation

The above literature comprises a reliable blueprint for heterocycle synthesis. Nonetheless, the said routes are constrained by either one of the following caveats, the requisite of highly specific substrates; forcing conditions; or poor 'pot economy'. Most notably, there are no

procedures that deliver fully saturated heterocycles with high regio- and diastereoselective control.

1.4 Summary

As the preceding sections have illustrated, hydroacylation has become a powerful C-C bond forming tool for the synthesis of various ketone products. The development of this method has largely focused on reductive decarbonylation—a mechanistic impasse that has been successfully sequestered using chelation control. Originally, coordinating olefins were frequently employed but they have been superseded by a variety of heteroatom tethers. Extensive mechanistic studies have also advanced catalyst design and as a result regioselective intermolecular processes have been developed. These methods typically require low catalyst loadings, mild conditions, and have a broad substrate scope. Despite this, chelating strategies are inherently limited by the retention of tethering groups in final products. There are three apparent ways to avoid this: the first technique uses 'traceless' protocols i.e., functionalisation and or removal of tethers. This strategy is useful for modular construction of complex structures but ultimately fails to improve the generality of a given hydroacylation reaction. The second approach harnesses coordinating groups in cyclisation reactions; thus, enables the synthesis of several synthetically attractive heterocycles. However, to date, no method delivers fully saturated heterocycles in one pot, and there remains a need for more general, selective, and practical procedures. As such, our aim in Chapter 2 is to explore the synthesis of saturated sulfur heterocycles *via* hydroacylation. The third and final tactic employs chelating groups that are more desirable in final compounds. To this end, our lab has recently shown simple carbonyl groups efficiently direct intermolecular hydroacylation. Building on this, the objective of Chapter 3 is to investigate new synthetically appealing coupling partners for rhodium-catalysed intermolecular hydroacylation.

Chapter 2

Synthesis of saturated *S*-heterocycles *via* hydroacylation

2.1 Introduction

Organosulfur compounds have been used as therapeutic agents since antiquity.[142] Nowadays, a myriad of sulfur-containing motifs are present in numerous natural products and drugs.[142-144] Amongst these, sulfur-containing heterocyclic scaffolds exhibit a wide spectrum of biological activities such as antiviral, antitumor, antimicrobial and anti-inflammatory.[145] Of the 200 top-selling pharmaceutical agents in 2021, 14% contained a sulfur ring.[146] Moreover, oxidation of these moieties uniquely permits access to sulfoxides, sulfones and sulfoximines, providing further handles for structural diversification.[144]

The popularisation of various sp^2-sp^2 couplings in the late 20th century has biased drug discovery towards the assembly of flat aromatic molecules.[147] However, since Lovering's seminal paper,[148] which shed light on the importance of three-dimensionality for clinical success, more emphasis now lies on increasing saturation within drug candidates.[149-151] This is beneficial as the three-dimensionality that saturation confers leads to improved target specificity and solubility.[148, 152] In view of this, synthetic methods that efficiently deliver saturated heterocycles are crucial for advancing the exploration of more diverse chemical space.

Substituted tetrahydrothiophenes and tetrahydrothiopyrans are valuable structural units in medicinal chemistry that display multiple pharmacological activities (Figure 2.1).[153-156] Their chiral analogues also function as versatile ligands and organocatalysts.[154]

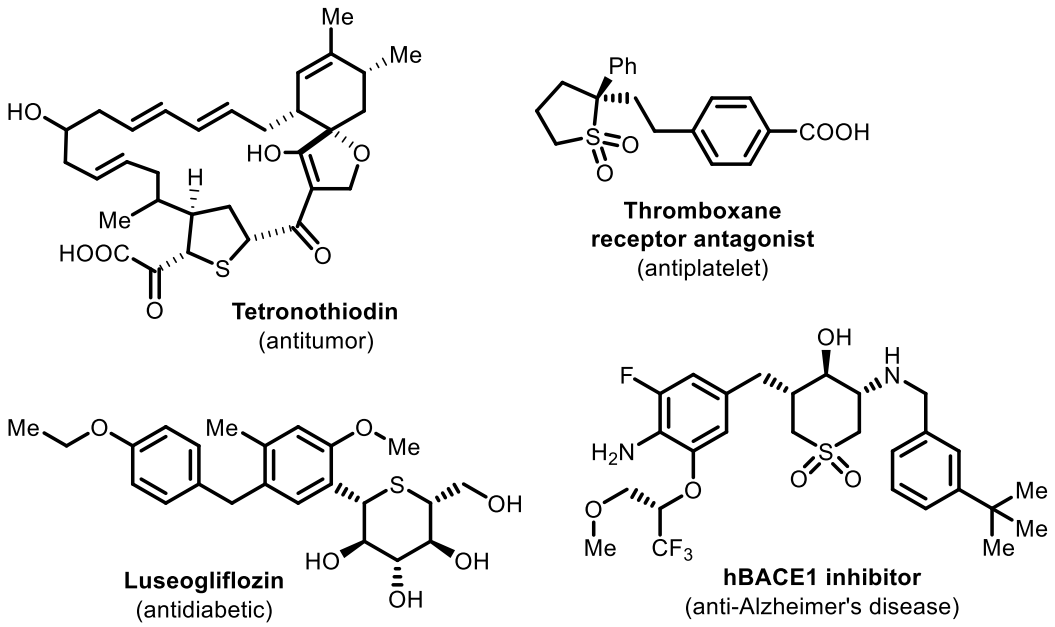
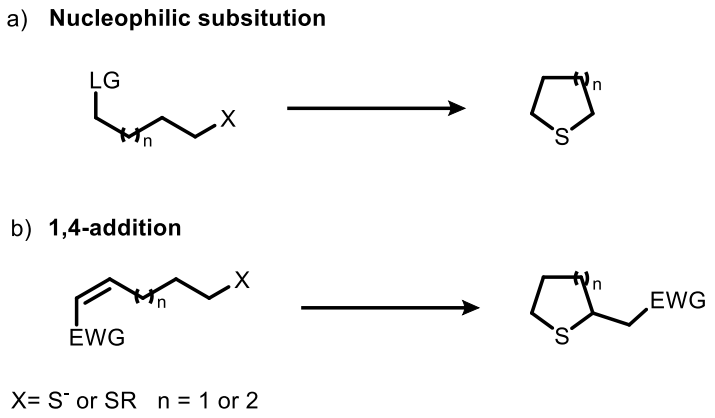


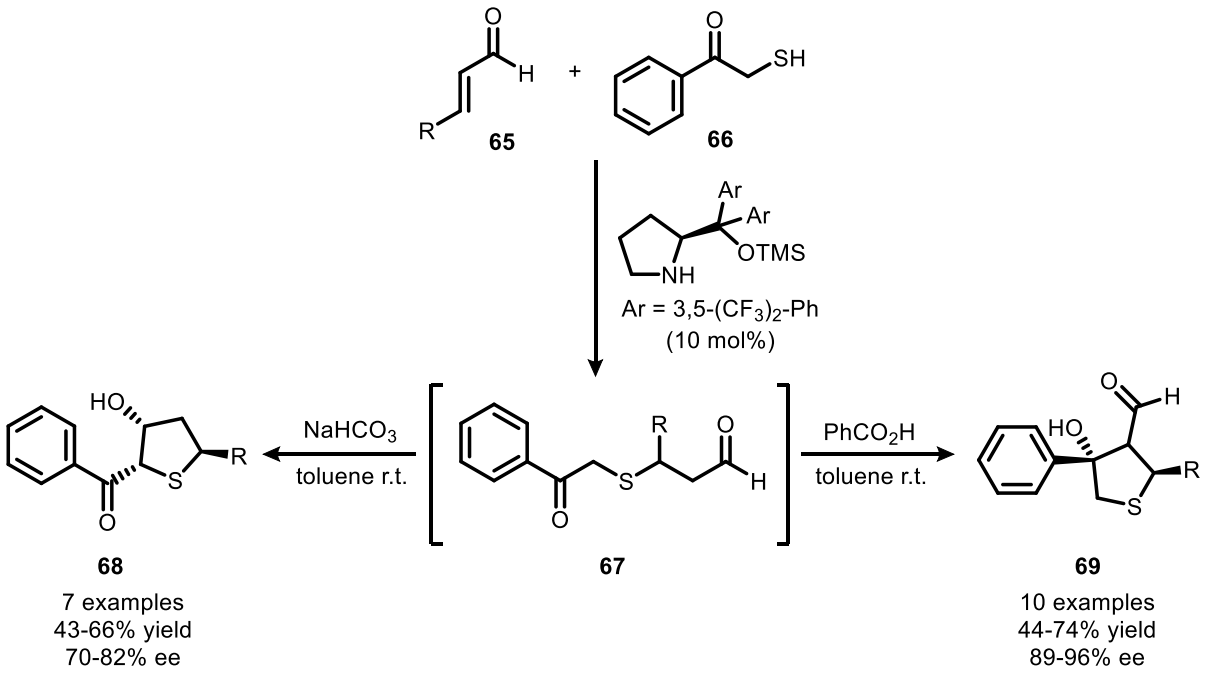
Figure 2.1 Therapeutic agents containing tetrahydrothiophenes and tetrahydrothiopyrans units and their sulfone derivatives

The majority of *de novo* methods to synthesise these 5- and 6-membered sulfides involve nucleophilic C-S bond formation.[157] This is typified by the displacement of leaving groups by a thiolate anion or sulfide (Scheme 2.1a).[157] The 1,4 addition of *S*-nucleophiles to suitable Michael acceptors is another common way to prepare thiolanes and thianes (Scheme 2.1b).[157]



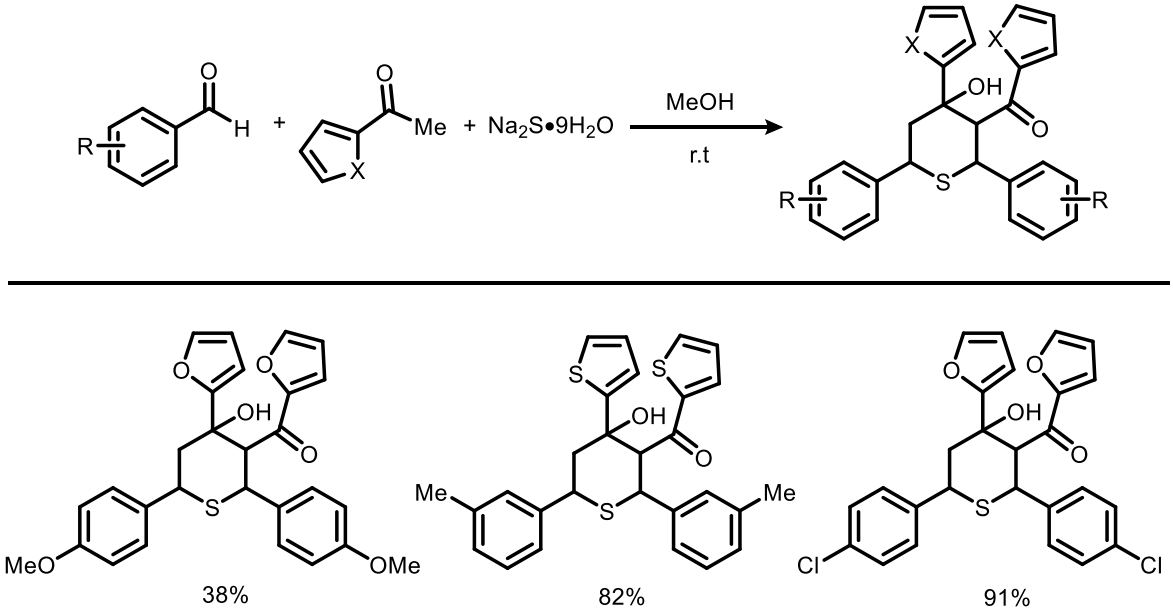
Scheme 2.1 General cyclisation routes to 5 and 6 membered cyclic sulfides

In 2006, the Jørgensen group pioneered the use of organocatalysts for the construction of diastereo- and enantiomerically enriched, functionalised tetrahydrothiophenes (Scheme 2.2).[158] This approach involved asymmetric 1,4-addition of *β*-mercaptoketones to *α*,*β*-unsaturated aldehydes to give dicarbonyls **67**. These in turn can participate in aldol domino reactions, delivering tetrahydrothiophene carbaldehydes **68** or (tetrahydrothiophen-2-yl)phenyl methanones **69** in good yields.[158] This strategy has since been applied to several different Michael acceptors and thia partners.[159-164]



Scheme 2.2 Jørgensen's sulfa-Michael-initiated domino synthesis of chiral thiolanes

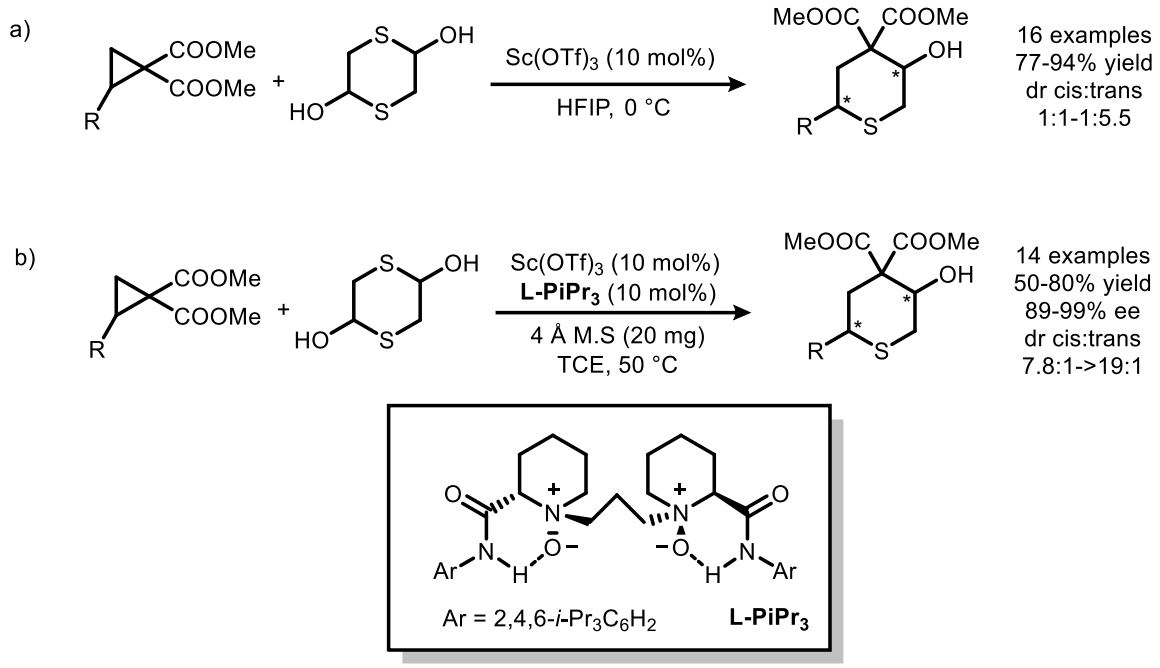
Similar domino processes can also occur without catalysts, as evidenced by Liu and Chen's recent synthesis of tetrahydrothiopyran derivatives (Scheme 2.3).[155] In this case, a stepwise aldol/double Michael addition/aldol reaction cascade from benzaldehydes, 2-acetylfuran/2-acetylthiophene and sodium sulfide provided diverse substituted thianes.[155] This one-pot procedure notably featured mild conditions and readily available substrates.



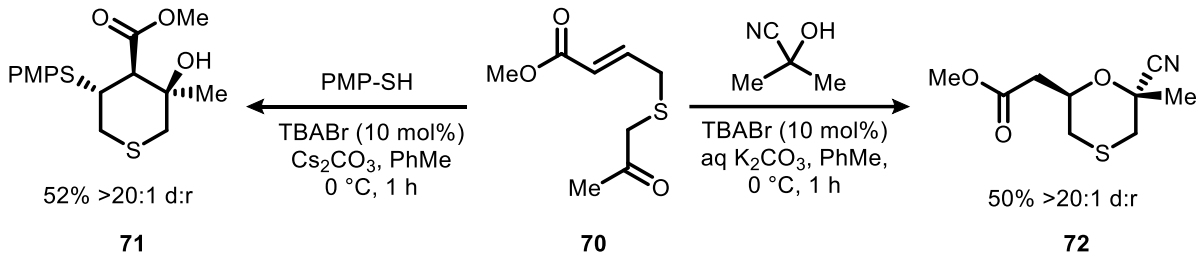
Scheme 2.3 Liu and Chen's domino method towards tetrahydrothiopyran derivatives

Annulation reactions have also enabled expedited syntheses of saturated 5-6 membered *S*-heterocycles.[165-167] In this context, 1,4-dithiane-2,5-diol has emerged as an attractive tool due to its ambiphilicity.[168] For example, Zhang *et al* reported a $Sc(OTf)_3$-catalysed [3+3] annulation of cyclopropane 1,1-diesters with *in situ* generated mercaptoacetaldehyde, furnishing racemic polyfunctionalised tetrahydrothiopyranols in high yields (Scheme 2.4a).[166] The Feng group later devised a highly diastereo- and enantio-selective variation by exploiting a *N*,*N*′-dioxide/scandium(III) catalyst (Scheme 2.4b).[167] In recent years, phase transfer catalysis has been utilised to access enantioenriched thia-heterocycles (Scheme 2.5).[169] This method subjected doubly electrophilic substrate **70**

with thiophenol or cyanide nucleophiles, in the presence of TBABr and base, affording thiane **71** and oxathiane **72** respectively in moderate yields.[169] Interestingly, the choice of nucleophile dictated the chemoselectivity of the reaction, allowing both sulfa-Michael/aldol and cyanide addition/oxa-Michael pathways to be viable.[169]



Scheme 2.4 Catalytic [3+3] annulation processes a) Zhang's method b) Feng's asymmetric procedure



Scheme 2.5 Phase-transfer organocatalytic chemodivergent cascade cyclisations

Thietanes are an equally salient class of aliphatic sulfur heterocycles that are widely found in therapeutic agents and agrochemicals (Figure 2.2).[170-172]

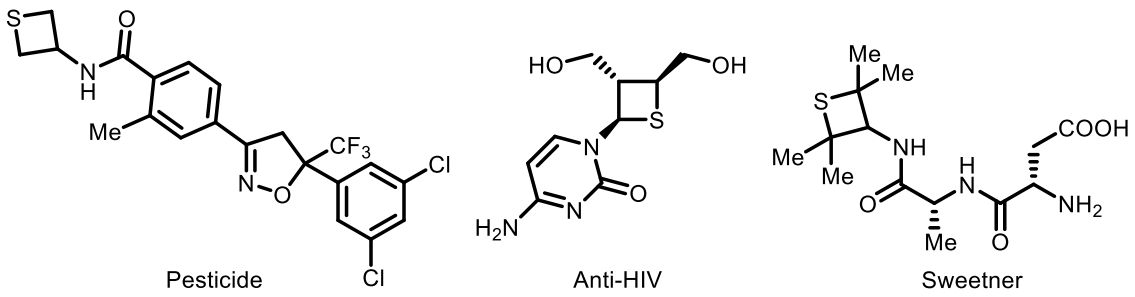
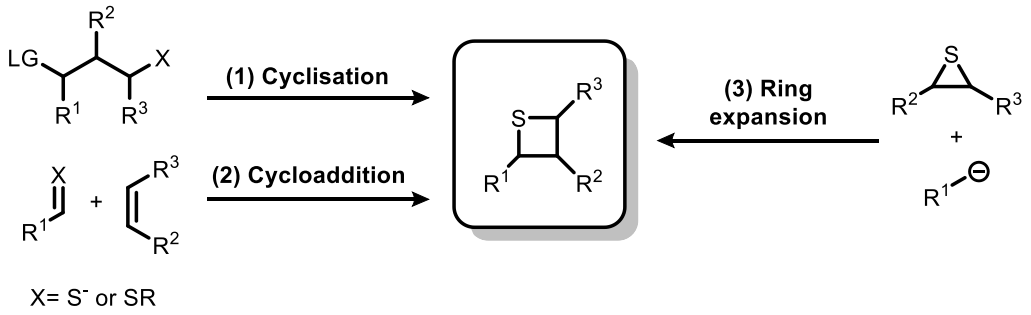
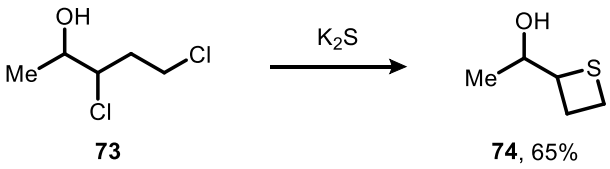


Figure 2.2 Examples of biologically active compounds containing a thietane motif

There are three main routes to thietanes: (1) cyclisation, (2) cycloaddition, and (3) ring expansion (Scheme 2.6).[171] Among cyclisation approaches, the displacement of γ-positioned leaving groups by sulfur nucleophiles, is most common.[157, 171] Early examples of this strategy involved double substitution of 1,3-dihaloalkanes with alkali sulfides. For instance, in 1966 Cerny and Polacek described the synthesis of thietane **74** using 3,5-dichloropentan-2-ol and K_2S (Scheme 2.7).[173] Since then, a number of these thioetherification reactions have been reported.[174-177]

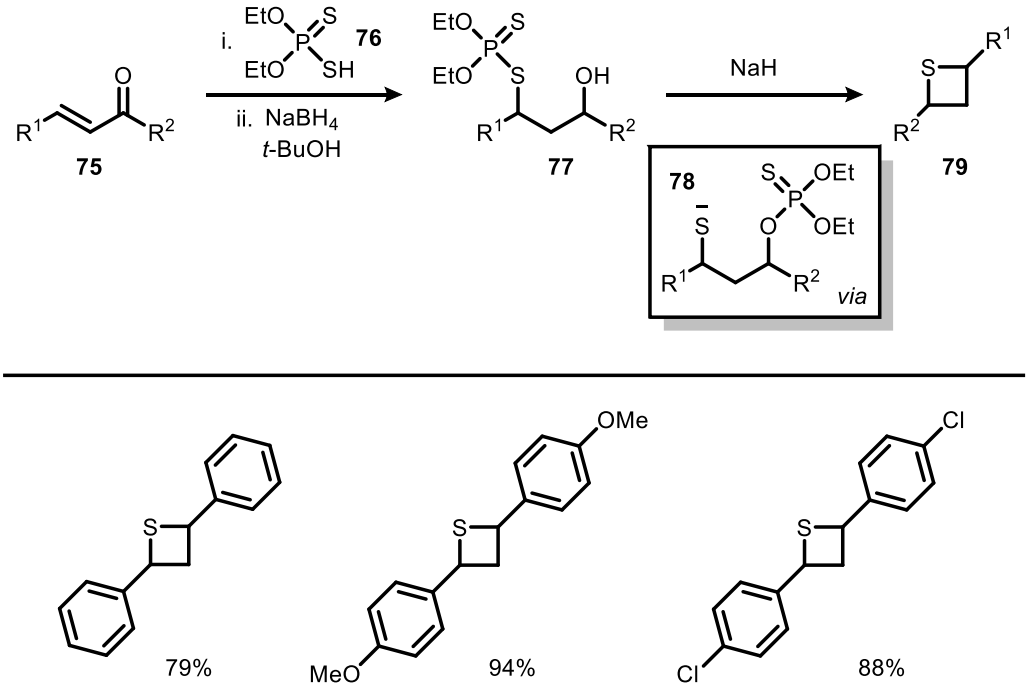


Scheme 2.6 General strategies to prepare 4-membered cyclic sulfides



Scheme 2.7 Cerny and Polacek's synthesis of thietane **74**

A more modern cyclisation route to functionalised thietanes employs phosphorodithioate **76** (Scheme 2.8). Ueno *et al* were the first to use **76** to synthesis 4-membered thiacycles.[178] 1,4-addition of **76** to chalcones **75**, followed by reduction, yielded *β*-hydroxy thiophosphates **77**. Subsequent deprotonation by NaH, triggered thiophosphate ester rearrangement, generating thiolates **78** which cyclised to form thietanes **79**.[178] Following this publication, phosphorodithioate-mediated strategies garnered more interest and have since been applied to the synthesis of distinctly substituted thietanes.[179-181]



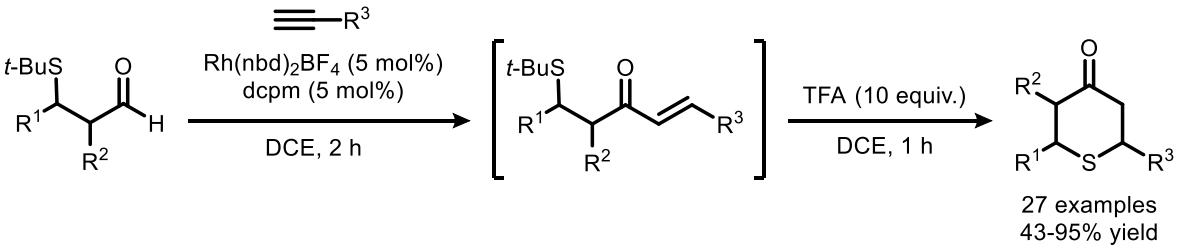
Scheme 2.8 Phosphorodithioate-mediated synthesis of thietanes

Up to now, great efforts have been devoted to the synthesis of saturated *S*-heterocycles. Preparative methods that depend solely on cyclisation are typically less desirable as they produce stoichiometric waste and may require protecting group manipulations or harsh conditions.[171] Conversely, domino processes have been largely successful in building aliphatic thia-heterocycles from simple feedstocks.[155, 169] These cascade reactions often

necessitate mild conditions and are amenable to stereocontrol.[158] Nonetheless, the prerequisite of highly specific substrates limits the generality of such procedures.

2.1.1 Project aims and previous work

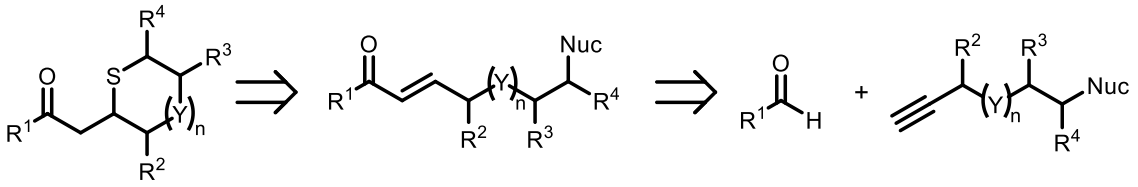
Despite the feats of the methods reviewed above, there remains a need for new approaches to diverse saturated *S*-heterocycles of varied ring size. A hydroacylative route to cyclic sulfides offers the advantage of excellent atom economy and high functional group tolerance. The assembly of unsaturated heterocycles *via* tandem hydroacylation/cyclisation is well established.[85, 88, 108, 135, 139-141] These sequences rely on Rh(I)-catalysed C-C bond formation using a coupling partner bearing a nucleophilic heteroatom. The resulting enone products undergo intramolecular cyclisation, integrating the heteroatom into a ring. Our group utilised this strategy when exploiting *β-tert*-butylthio-substituted aldehydes in *S*-conjugate addition, affording a range of thiochroman-4-ones in very good yields (Scheme 2.9).[108]



Scheme 2.9 Synthesis of thiochromanones *via* hydroacylation/thio-conjugate-addition sequence

Nevertheless, so far, no tandem procedure permits access to fully saturated sulfur rings in one-pot. We hypothesised that complex *S*-heterocycles could be disconnected to enones embedded with *S*-nucleophiles (Scheme 2.10). These, in turn, may be synthesised by the hydroacylative coupling of corresponding aldehydes and terminal alkynes. Such a route may constitute a practical and general strategy to diversely substituted saturated *S*-heterocycles. Initially, two variants of this broader methodology were conceivable. The first could employ

a latent *S*-nucleophile in the form of a disulfide and hence impart high atom economy. The second route may use protecting group chemistry.



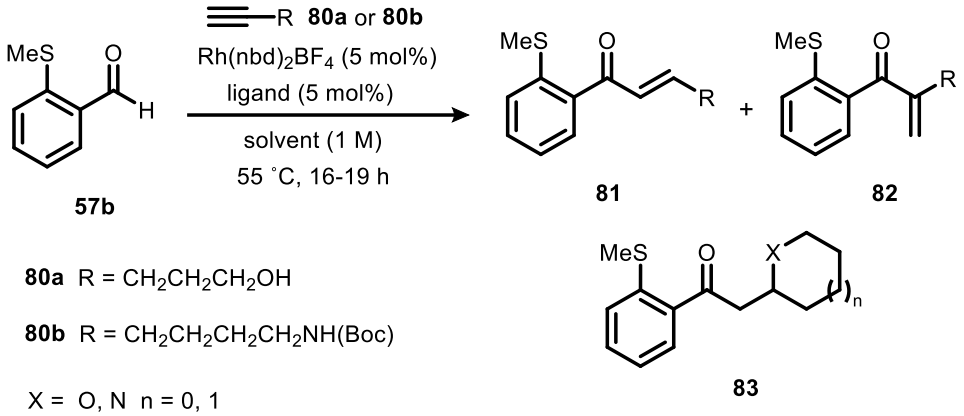
Scheme 2.10 Proposed hydroacylation route to saturated *S*-heterocycles

2.2 Hydroacylation of disulfide alkynes towards saturated sulfur heterocycles

2.2.1 Optimisation of one-pot hydroacylation/cyclisation

We began our studies by investigating the reactivity of alkynes with pendant *O*- and *N*-nucleophiles in hydroacylation. Our lab has previously demonstrated the efficiency and selectivity of Rh(I)-catalysts with small-bite angle diphosphine ligands.[127, 139, 141] Accordingly, a similar catalyst system was applied to the coupling of aldehyde **57b** and 4-pentyn-1-ol (Table 2.1, entry 1). The reaction proceeded with low conversion, but selectivity for the linear isomer was high. Switching from acetone to DCE dramatically increased the conversion (entry 2). Employing dcpe as a ligand was also favourable (entries 3 and 5). Under this optimal catalyst system, tetrahydrofuran products were detected in significant ratios, indicating spontaneous cyclisation of the intermediate enones. This coincides with a serendipitous observation made by our group in a previous study.[99] These initial hydroacylation experiments confirmed the feasibility of a tandem hydroacylation/conjugate addition route to saturated heterocycles. Thus, we set out to construct *S*-heterocycles using alkynes embedded with latent *S*-nucleophiles.

Table 2.1 Preliminary optimisation of hydroacylation with alkynols and alkynamines[a]

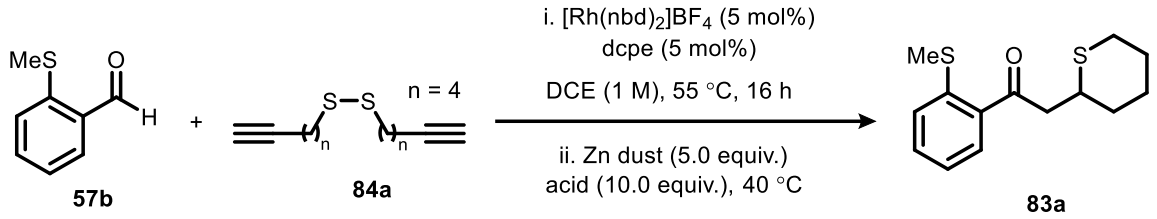


Entry	Alkyne	Solvent	Ligand	Conversion[b]/%	81:82:83
1	**80a**	Acetone	dppe	50	10:2:5
2	**80a**	DCE	dppe	95	10:1:4
3	**80a**	DCE	dcpe	100	10:1:9
4	**80b**	DCE	dppe	85	10:1:2
5	**80b**	DCE	dcpe	100	13:1:2

[a]Reaction conditions: aldehyde (1.0 equiv.), alkyne (1.5 equiv); [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

To begin with, disulfide **84a** was paired with aldehyde **57b** using our newly established conditions (Table 2.2 entry 1). Gratifyingly, full conversion was obtained for the hydroacylation step, with high selectivity for the linear adduct. Subsequent treatment with zinc and TFA mediated S-S cleavage and cyclisation, providing heterocycle **83a** in 45% yield.

Table 2.2 Optimisation of one-pot hydroacylation/*S*-conjugate addition with disulfide alkyne **84a**[a]



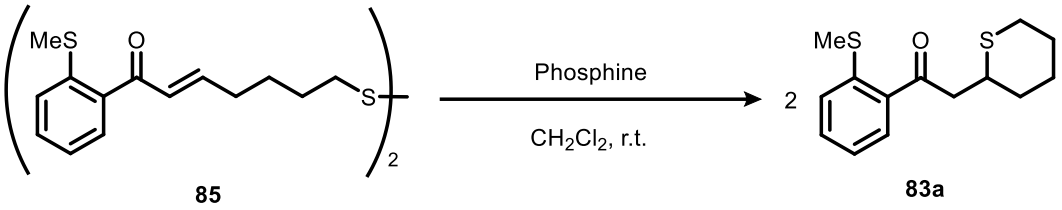
Entry	Time/h	Acid	Solvent	ii. Conversion[b]/%	Yield of 83a/%[c]
1	2	TFA	DCE	86	45
2[d]	2	HCl	Dioxane	86	37
3	4	TSA	DCE	76	39
4	4	TFA	DCE	95	61
5	19	TFA	DCE	94	52
6	4	TFA	MeCN	28	11

[a] Reaction conditions: aldehyde (2.0 equiv.), alkyne (1.5 equiv.), step ii. concentration 4×10^{-3} M, 100% conversion for step (i) based on analysis by ^{1}H NMR spectroscopy; [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [c] NMR yields determined with 1,3,5-trimethoxybenzene as internal standard; [d] 7×10^{-3} M

In order to improve the yield alternate acids were tested (Table 2.2 entries 2 and 3) but they were ineffective. Doubling the reaction time led to a moderate increase in yield, though stirring the reaction overnight did not produce any further enhancement (entries 4 and 5). Use of a more polar solvent significantly decreased the conversion and yield (entry 6). Unfortunately, the highest yielding conditions (entry 4) could not be reproduced most likely because of the heterogeneity of the system. The cyclisation reaction was then examined separately using alternative phosphine reducing agents (Table 2.3). Only trace amounts of thiane **83a** were observed when intermediate **85** was treated with triphenylphosphine (entry 1). However, increasing the nucleophilicity of the phosphine promoted reduction of the sulfide, hence boosted the yield of the cyclised product (entries 2-4). Tris(2-carboxyethyl)phosphine (TCEP) is routinely used to irreversibly cleave S-S bridges

in proteins.[182] When employed in our reaction, as a hydrochloride salt, compound **83a** was generated in moderate yield (entry 4).

Table 2.3 S-S bond cleavage/cyclisation with phosphines[a]

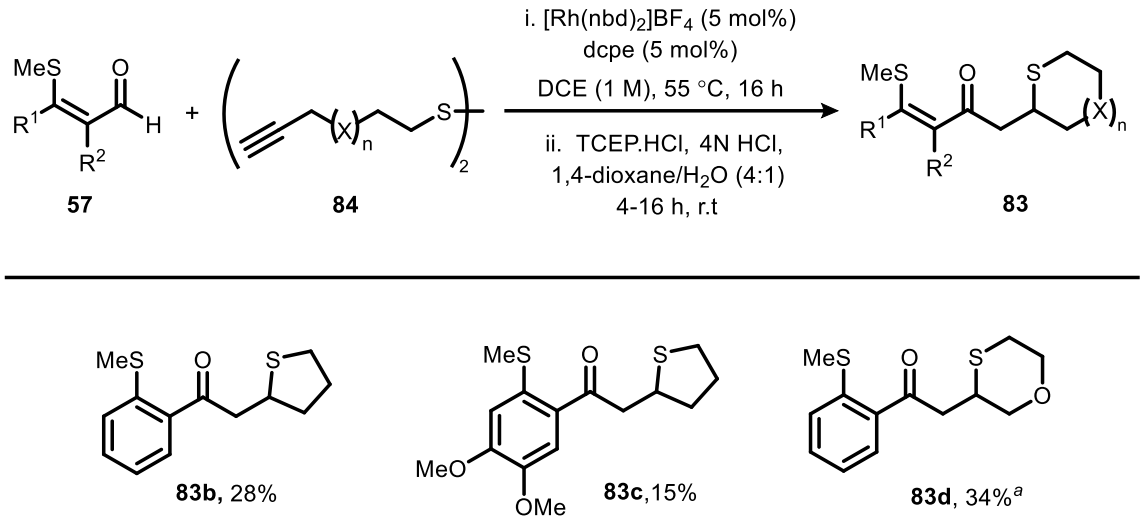


85 **83a**

Entry	Phosphine	Time/h	Yield of 83a/%[b]
1	Ph_3P	19	trace
2	$MePh_2P$	8	30
3	$(n\text{-}Bu)_3P$	16	33
4[c]	TCEP•HCl	16	43

[a] Reaction conditions: enone adduct (1.0 equiv.), phosphine (5.2 equiv.), conc. 6×10^{-3} M;
[b] NMR yields determined with 1,3,5-trimethoxybenzene as internal standard;
[c] reaction conditions: 4:1 1,4-dioxane/H_2O, phosphine (2.0 equiv.), 55 ºC, 8×10^{-3} M

We postulated that the use of additional HCl would improve the yield. However, this was ineffectual when applied to the syntheses of cyclic sulfides **83b**-**83d** (Scheme 2.11).



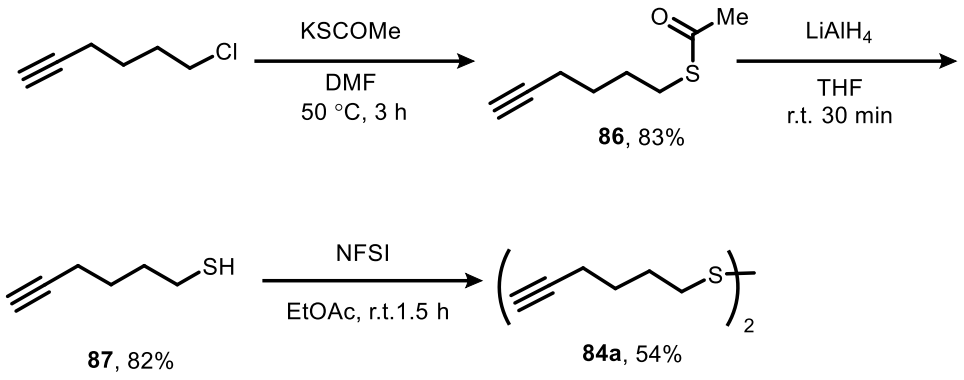
Reaction conditions: i. aldehyde (2.0 equiv.), alkyne (1.5 equiv.), 4×10^{-3} M, ii. TCEP (4.0 equiv.), 4 N HCl (4.0 equiv.); [a] 1,4-dioxane/H_2O (9:1), 55 °C

Scheme 2.11 One-pot hydroacylation/*S*-conjugate addition with disulfide alkynes

In general, enacting tandem S-S cleavage and intramolecular 1,4-addition proved challenging. In most instances, conversions were high, but the desired heterocycles were formed in low yields. It may be the case that the intermediary thiols are relatively unstable. Ultimately, the one-pot hydroacylation/cyclisation reaction using disulfide alkynes could not be fully optimised.

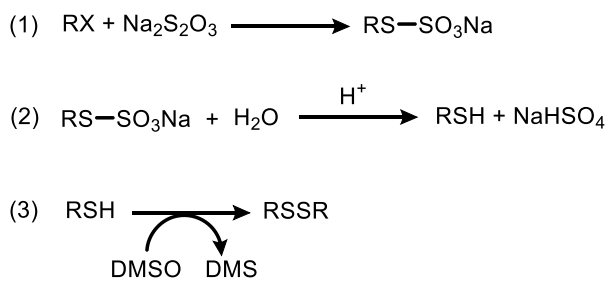
2.2.2 Synthesis of disulfide alkynes

At the outset, disulfide **84a** was prepared in three steps from 6-chlorohex-1-yne (Scheme 2.12). Thiolation with potassium thioacetate was straightforward, yielding sulfide **86** in 83%. **86** was then reduced to thiol **87** using $LiAlH_4$. The target disulfide was then accessed by oxidative coupling of **87** with NFSI. Overall, this approach was constrained by the requirement of multiple redox manipulations, as well as the intermediacy of a malodorous thiol. This left us in pursuit of a more convenient route to symmetrical disulfides.



Scheme 2.12 Initial synthesis of disulfide **84a**

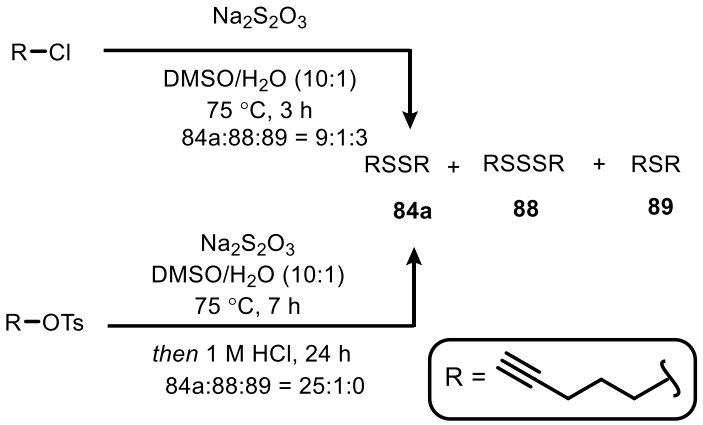
Few literature methods obtain symmetrical disulfides directly from alkyl halides. Abbasi reported a one-pot synthesis of symmetrical disulfides, whereby alkyl halides were reacted with sodium thiosulfate to give *S*-alkyl thiosulfates (Bunte salts) (Scheme 2.13).[183] The latter could be hydrolysed, allowing *in situ* generation of thiols that were subsequently oxidised to disulfides using DMSO.[183]



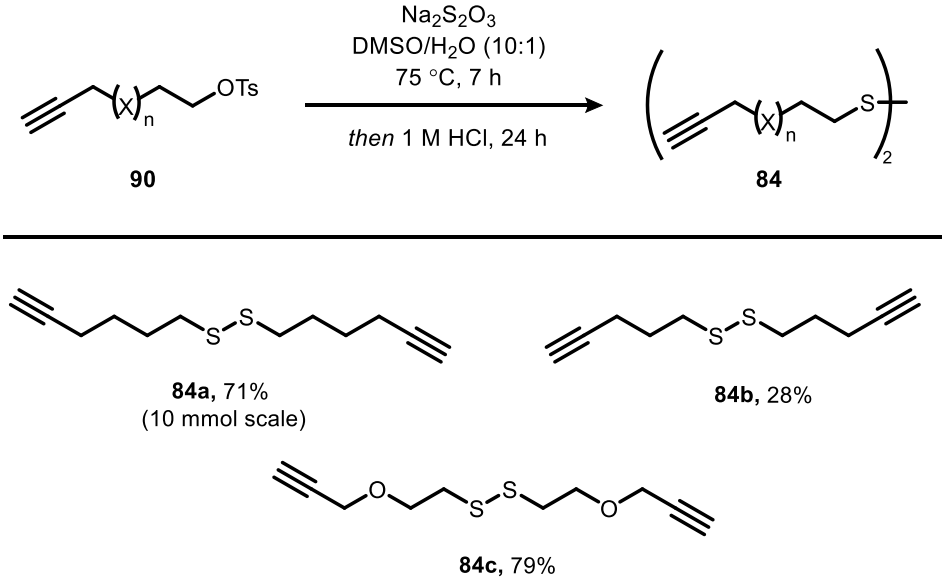
Scheme 2.13 Abbasi's one-pot synthesis of symmetrical disulfides

At first, we attempted to replicate this methodology using 6-chlorohex-1-yne (Scheme 2.14). Disulfide formation was apparent together with coproduction of trisulfide and sulfide contaminants. Utilising a tosylated substrate enabled cleaner conversion to the intermediate Bunte salt. We then decided to add 1 M aqueous HCl, after the tosyl-alkyne had been completely consumed, with the aim of accelerating thiol formation. Pleasingly, this resulted in selective generation of the required disulfide **84a** in 51% yield. Furthermore, the

procedure could be scaled up without loss in yield or selectivity and was later used to prepare alternate disulfides (Scheme 2.15).



Scheme 2.14 Modified synthesis of disulfide **84a**

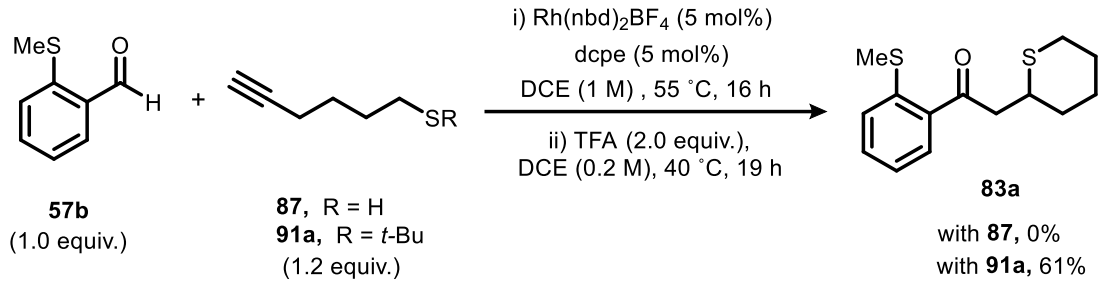


Scheme 2.15 Synthesis of symmetrical disulfide alkynes

2.3 Hydroacylation of *tert*-butyl sulfide alkynes towards saturated sulfur heterocycles

2.3.1 Optimisation of one-pot hydroacylation/cyclisation

Given the aforesaid difficulty of assembling saturated *S*-heterocycles from disulfides, we directed our efforts towards exploiting protecting group chemistry. Initially, we probed the reactivity of alkanethiol **87** by reacting it with aldehyde **57b** under our previously optimised hydroacylation conditions (Scheme 2.16). However, neither the enone intermediate nor the cyclised product were detected after 16 hours. It is possible that chelation of the free thiol to an intermediary rhodium species hindered catalysis. When *tert*-butyl sulfide alkyne **91a** was treated with the same conditions, the hydroacylation proceeded to full conversion with high selectivity for the linear enone (14:1). The subsequent cyclisation occurred readily upon addition of 2.0 equivalents of TFA, furnishing thiane **83a** in 61% yield (Scheme 2.16).

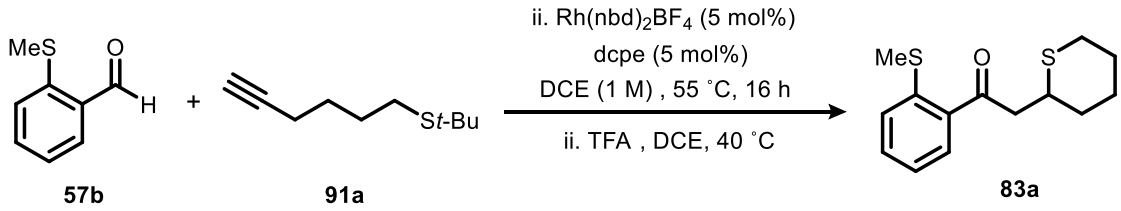


Scheme 2.16 Tandem hydroacylation/*S*-conjugate addition route to thiane **83a**

A thioacetate alkyne was also tested but the hydroacylation reaction was less efficient. We therefore advanced with *t*-Bu-sulfide alkynes as our chosen substrates, focusing on the optimisation of the cyclisation step (Table 2.4). Higher equivalents of acid and longer reaction times depreciated the yield (entries 2 and 3), whereas shortening the reaction time had a marginal effect (entry 4). To our delight, diluting the system favoured the

intramolecular conjugate addition (entries 5 and 6), eventually affording **83a** in 82% yield. Further dilution did not significantly affect the yield (entries 7 and 8). We suspect the cyclisation step occurs *via* a previously proposed, acid-mediated mechanism.[108] First, protonation of the carbonyl intermediate, then thia-conjugate addition, followed by loss of a *tert*-butyl cation.

Table 2.4 Optimisation of one-pot hydroacylation/*S*-conjugate addition with *t*-butyl sulfide alkyne **91a**[a]



57b **91a** **83a**

Entry	Equiv. TFA	Time/h	Concentration/M	Yield of 83a/%[b]
1	2	19	0.2	61
2	5	19	0.2	54
3	10	19	0.2	55
4	2	6	0.2	57
5	2	4	0.5	64
6	2	4	0.1	74(82)
7	2	4	0.05	73
8	2	4	0.025	70

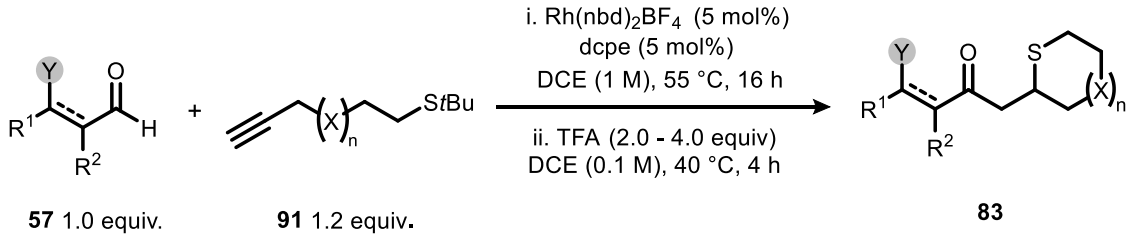
[a] Reaction conditions: aldehyde (1.0 equiv.), alkyne (1.2 equiv.), 100% conversion for step (i) based on analysis by ^{1}H NMR spectroscopy; [b] NMR yields determined with 1,3,5-trimethoxybenzene as internal standard; isolated yields in parentheses

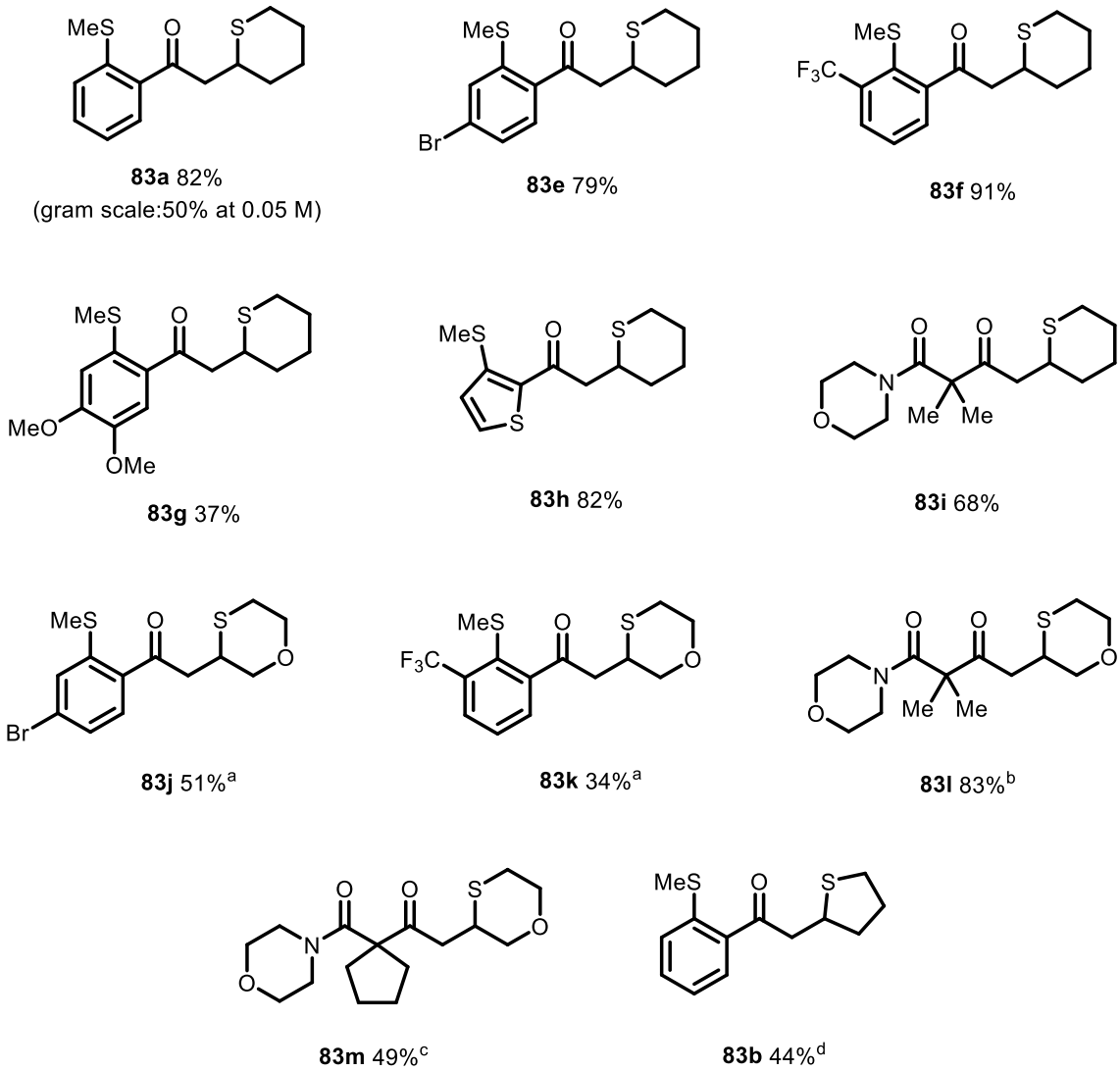
2.3.2 Scope of hydroacylation/cyclisation cascade

2.3.2.1 Unsubstituted heterocycles

With the optimised conditions in hand, the scope of the reaction was examined by pairing different aldehydes with unsubstituted alkynes (Scheme 2.17). Aldehydes with electron

withdrawing groups were well tolerated (**83e** and **83f**). In contrast, those with electron donating groups were less efficient (**83g**). Heteroaromatic and *β*-amido aldehydes also worked well, yielding thianes **83h** and **83i** in 82% and 68% respectively.





[a] 16 h; [b] 22 h, 4.0 equiv. TFA; [c] step (i) 74% conversion based on analysis of ^{1}H NMR [d] 2 h, 1.0 equiv. TFA

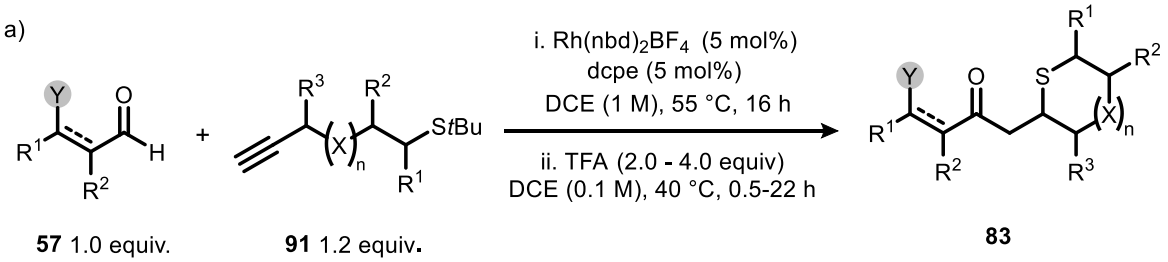
Scheme 2.17 Scope of aldehydes and unsubstituted *t*-Bu sulfide alkynes

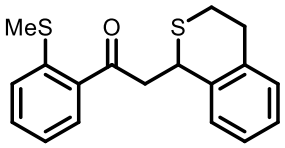
The tandem protocol was also successfully extended to alkynes possessing an oxygen atom linker. Interestingly, when *o*-SMe-benzaldehydes were coupled with these alkynes, the resultant *α,β*-unsaturated enones underwent a competitive 6-*endo*-trig cyclisation, yielding thiochroman-4-ones (See Section 2.3.2.3 for more details). This pathway could be attenuated by incorporating electron-withdrawing groups on the self-same aldehydes. Thus, oxathianes **83j** and **83k** were obtained in moderate yields. Use of *β*-amido chelating aldehydes obviated the aforesaid competing cyclisation (**83l** and **83m**). Originally, application of the developed conditions to the synthesis of tetrahydrothiophene **83b** afforded a low yield (21% by NMR analysis). However, halving the equivalents of acid and reaction time enabled **83b** to be isolated in 44% yield. To illustrate the scalability of the procedure, a gram-scale reaction was performed using 2-(methylthio)benzaldehyde and *tert*-butyl(hex-5-yn-1-yl)sulfane. Deviating from a concentration of 0.1 M to 0.05 M, for the cyclisation step, allowed isolation of sulfide **83a** in 50% yield.

2.3.2.2 Substituted heterocycles

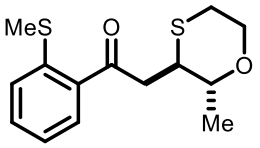
The scope of the reaction was also explored with respect to substituted *t*-Bu sulfide alkynes (Scheme 2.18a). Thiochromane derivative **83n** was isolated in very good yield. Groups on the R^3 position could also be varied. Reacting methyl-substituted alkynes with *o*-SMe aldehydes gave lower yields of the desired heterocycles (**83o** and **83p**) because of the abovementioned, competing 6-*endo*-trig ring closure. Once again, employing a dicarbonyl aldehyde improved the yield, furnishing 1,4-oxathiane **83q** in 81%. For the examples above, the diastereoselectivity (as measure by ^{1}H NMR spectroscopic analysis of the crude reaction mixture) did not exceed 3:1. This contradicted the selectivity achieved with equivalent oxygen heterocycles.[184] It is possible that the length of the forming C-S bond distorts the chair confirmation and alleviates 1,3-diaxial interactions. This may in turn give rise to the low observable diastereoselectivity. Adopting a larger R^3 substituent did not enhance the dr

but instead reduced the yield of cyclic sulfide **83r**. Incorporating acyclic and aliphatic R^2 groups afforded various substituted saturated *S*-heterocycles, in moderate to high yields (**83s**–**v**). Among these structures, 6,5-pyrrolo-1,4-thiazinone **83w** could potentially be leveraged as a versatile framework in medicinal chemistry.[185] Most of the substituted *S*-heterocycles were isolated as an inseparable mixture of isomers. The relative configurations of the major diastereomers were assigned using NMR analysis (See Chapter 5.2.1). We were surprised to discover that an alkyne bearing a cyclopropyl group displayed alternate reactivity, delivering a low yield of oxathiane **83x** and a furan by-product. The latter may arise from the cyclisation of allylic alcohol **93**, which, in turn, may form by elimination from hydroacylation adduct **92y** (Scheme 2.18b). The drs for R^2 substituted compounds remained moderate. Contrastingly, we were pleased to attain excellent selectivity when using a phenyl R^1 group, yielding thiane **83y** as a single diastereoisomer. This higher selectivity may result from the size of the phenyl group and its proximity to the forming stereocentre.

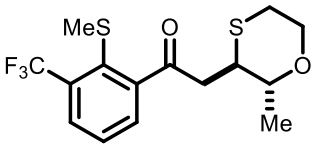




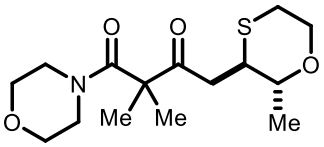
83n 84%



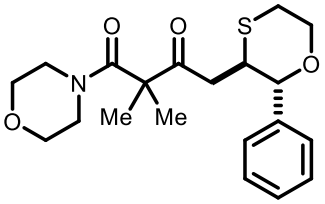
83o 22% 2:1 dr



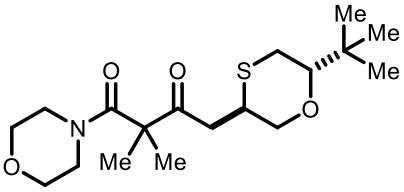
83p 48% 2.4:1 dr



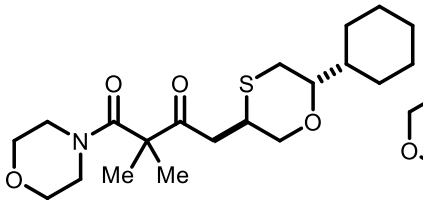
83q 81% 3:1 dr



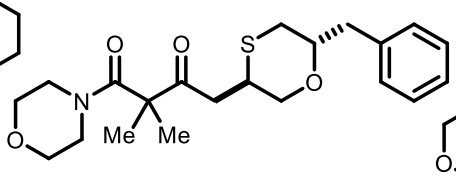
83r 43% 2:1 dr



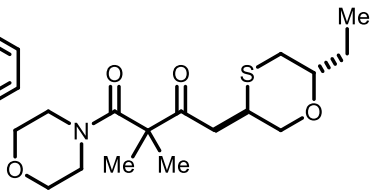
83s 74% 4:1 dr



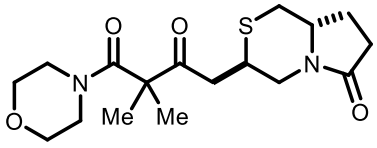
83t 72% 2.6:1 dr



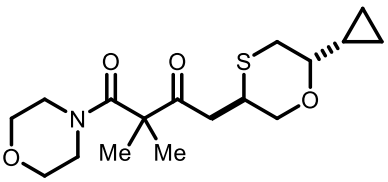
83u 77% 2.6:1 dr



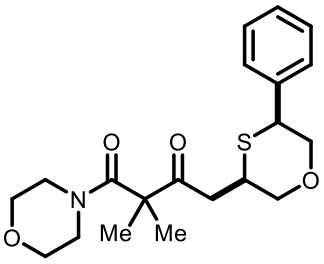
83v 49%[a] 2.6:1 dr



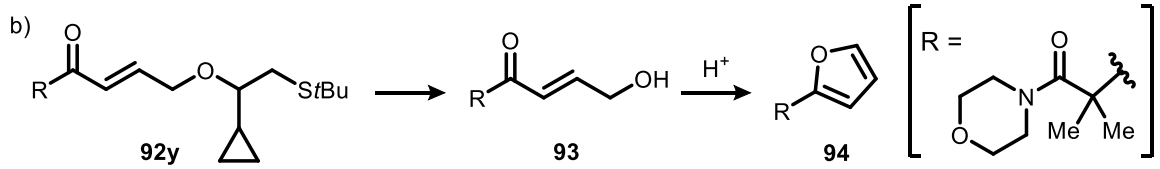
83w 88%[b] 3:1 dr



83x 10% 2.7:1 dr
+42% of furan **94**



83y 58% > 20:1 dr

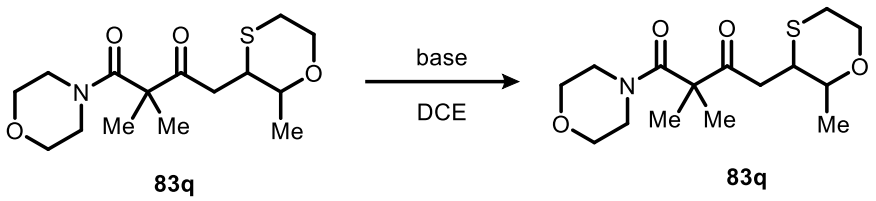


[a] step i. 89% conversion based on analysis of ^{1}H NMR spectrum; [b] 10 equiv. of TFA

Scheme 2.18 a) Scope of aldehydes and substituted *t*-Bu sulfide alkynes b) possible mechanism of competing pathway

Encouraged by this result, we sought to improve the dr of compound **83q** by inducing epimerisation. As such, diastereoisomeric mixtures of **83q** were exposed to stoichiometric quantities of weak base (Table 2.5, entries 1-3). Disappointingly, this resulted in epimerisation of the product.

Table 2.5 Epimerisation of oxathiane **83q** with base



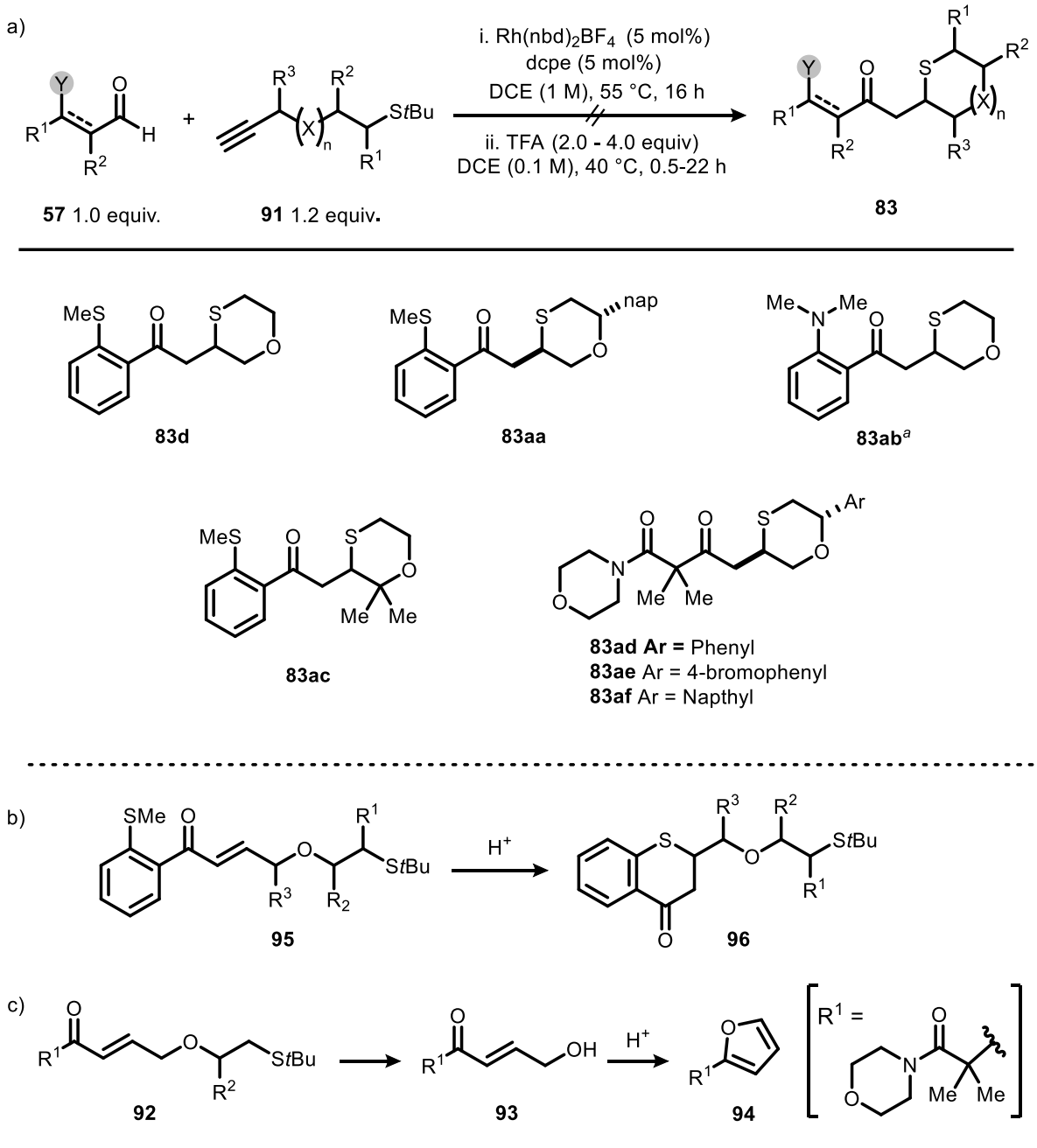
83q **83q**

Entry	Base	Time/h	Temperature/°C	dr start	dr end
1[b]	DBU	6	40	3:1	2.5:1
2	DBU	16	80	2.5:1	1.35:1
3	Cs_2CO_3	16	80	3.6:1	1.1:1

[a] Reaction conditions: base (2.0 equiv.), 0.1 M; [b] 1.0 equiv. of DBU; diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture

2.3.2.3 Inaccessible heterocycles

Overall, the developed methodology displayed good functional group tolerance. That said, certain heterocycles could not be synthesised because of unexpected side reactions (alluded to above) (Scheme 2.19a). For example, enone products derived from *o*-SMe aldehydes and alkynes with oxygen atom linkers (**95**) were more prone to cyclise to form thiochromanone derivatives (**96**) along with complex mixtures of products (Scheme 2.19b). Therefore, cyclisations to give sulfides **83d** and **83aa** did not occur. For compounds **83ab** and **83ac**, the hydroacylation step proceeded with low conversion. This may be because tertiary amines are known to be less efficient directing groups in hydroacylation in the absence of additives.[85] Additionally, the presence of a bulky quaternary centre beta to the alkynyl hydrogen, could have a retarding effect.



[a] dcpm (10 mol%), acetone (0.15 M)

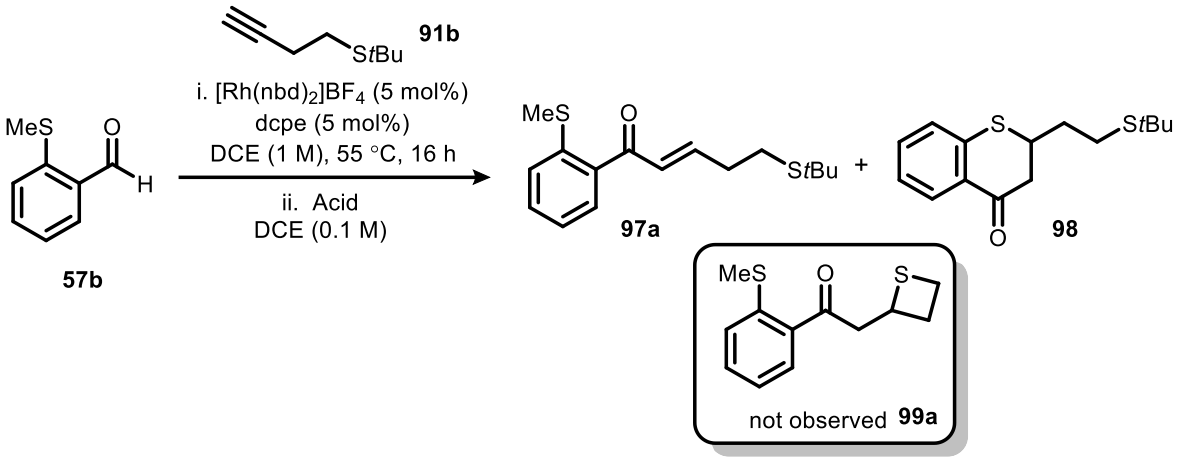
Scheme 2.19 a) Inaccessible heterocycles b) side reaction with *o*-SMe-aldehydes c) possible mechanism of competing pathway

Cyclic sulfides bearing aromatic groups at the R^2 position (**83ad**–**83af**) were not generated under the optimised conditions. Upon addition of acid to their enone precursors, a furan byproduct rapidly formed, most likely *via* the mechanism proposed earlier (Scheme 2.19c).

2.3.3 Synthesis of four-membered rings

In an effort to extend the utility of the cascade method, we attempted to construct four-membered sulfur rings. At the start, aldehyde **57b** and alkyne **91b** were subjected to the previously optimised conditions (Table 2.6, entry 1). Unfortunately, only the intermediate hydroacylation adduct was recovered.

Table 2.6 Attempts to synthesise four-membered *S*-heterocycles[a]



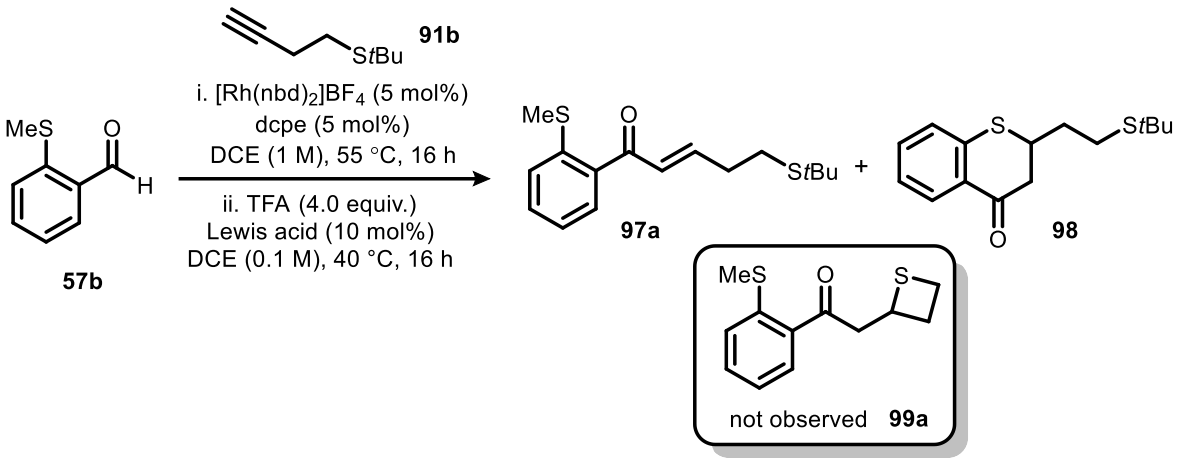
Entry	Acid	Equiv. Acid	Time	T/°C	Product (yield %)[b]
1[c]	TFA	2.0	4 h	40	**97a**
2	TFA	10.0	2 d	80	**98** (37%)
3[d]	TsOH	4.0	2 d	100	**97a**

[a] Reaction conditions: aldehyde (1.0 equiv.), alkyne (1.2 equiv.); 100% conversion for step i. based on analysis by ^{1}H NMR spectroscopy; [b] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures; isolated yields in parentheses [c] 60% conversion for step i. [d] 1,4-dioxane(0.1 M)

Applying more forcing conditions *viz* higher temperature and equivalents of TFA (Table 2.6, entry 2) gave rise to thiochromanone byproduct **98**. This suggests nucleophilic attack of the thiomethyl was more favorable than the desired 4-*exo*-trig cyclisation. Employing a stronger acid (entry 3) also failed to generate thietane **99a**. We reasoned that the presence of a Lewis acid may assist 1,4-addition. Hence, different Lewis acidic additives were screened (Table 2.7, entries 1-5) but none mediated the formation of **99a**. Instead, the aforesaid

competing cyclisation was accelerated, affording a product mixture of **97a** and **98** in similar proportions.

Table 2.7 Lewis-acid-mediated synthesis of 4-membered *S*-heterocycles[a]

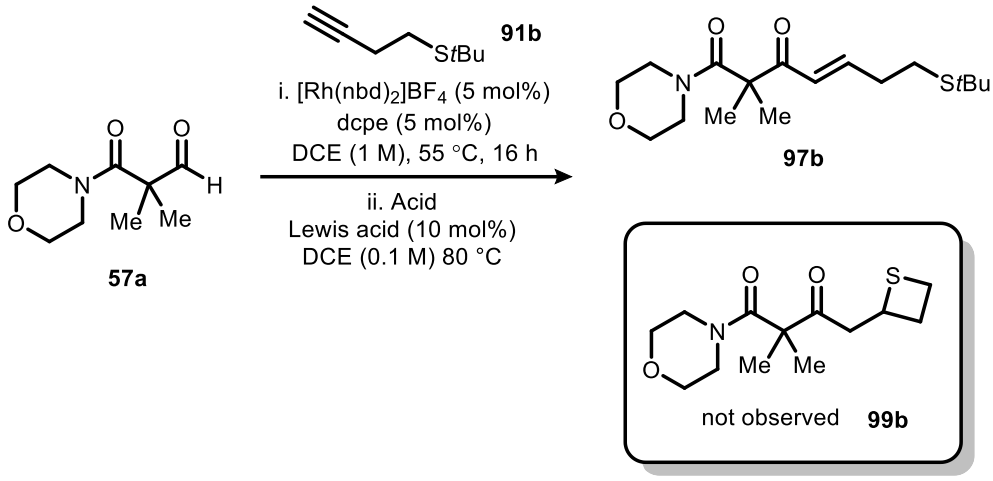


Entry	Lewis Acid	Yield of 97a/%[b]	Yield of 98/%[b]
1	$AlCl_3$	(27)	(14)
2	AgOTf	24	18
3	$Sc(OTf)_3$	21	24
4	$FeCl_3$	18	21
5	$Zn(OTf)_2$	24	15

[a] Reaction conditions: aldehyde (1.0 equiv.), alkyne (1.2 equiv.); >97% conversion for step i. based on analysis by ^{1}H NMR spectroscopy; [b] NMR yields determined with 1,3,5-trimethoxybenzene as internal standard; isolated yields in parentheses

Considering the observed alternate reactivity exhibited by the aryl thiomethyl motif, we substituted 2-(methylthio)benzaldehyde for aldehyde **57a** and explored additional conditions (Table 2.8). In this case, the hydroacylation reaction proceeded with good conversion however, the ensuing cyclisation could not be induced. Extended heating of the crude hydroacylation product with excess TFA did not promote the formation of **99b** (entry 1). Treatment with a selection of stronger acids led to decomposition of the linear enone (entries 2-4).

Table 2.8 Attempt synthesis of 4-membered *S*-heterocycles using aldehyde **57a**[a]



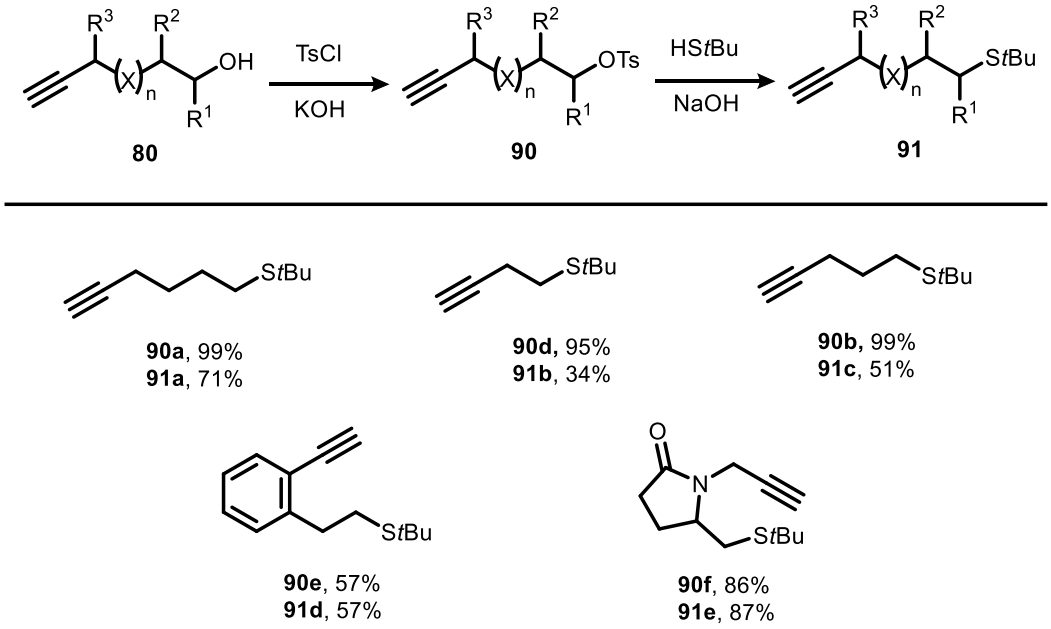
Entry	Acid	Equiv. of acid	Lewis Acid	Time/ h	Product[b]
1	TFA	10.0	-	16	**97b**
2[c]	HCl	10.0	-	16	CM
3	MsOH	6.0	-	3	Degradation
4	TfOH	6.0	-	3	Degradation
5[d]	TFA	4.0	$FeCl_3$	16	**97b**
6[e]	TFA	4.0	$Sc(OTf)_3$	16	**97b**

[a] Reaction conditions: aldehyde (1.0 equiv.), alkyne (1.2 equiv.); >87% conversion for step i. based on analysis by ^{1}H NMR spectroscopy; [b] Determined by ^{1}H NMR spectroscopy of crude reaction mixtures; CM = complex mixture [c] 69% conversion for step i. [d] 62% conversion for step i.; step ii. 40 ºC; [e] step ii. 40 ºC

The aforementioned Lewis acid strategy was also repeated using a lower temperature and fewer equivalents of TFA (Table 2.8, entries 5 and 6). These conditions were also unsuccessful; only the enone intermediate was recovered. Thereafter, investigations into thietane synthesis were discontinued.

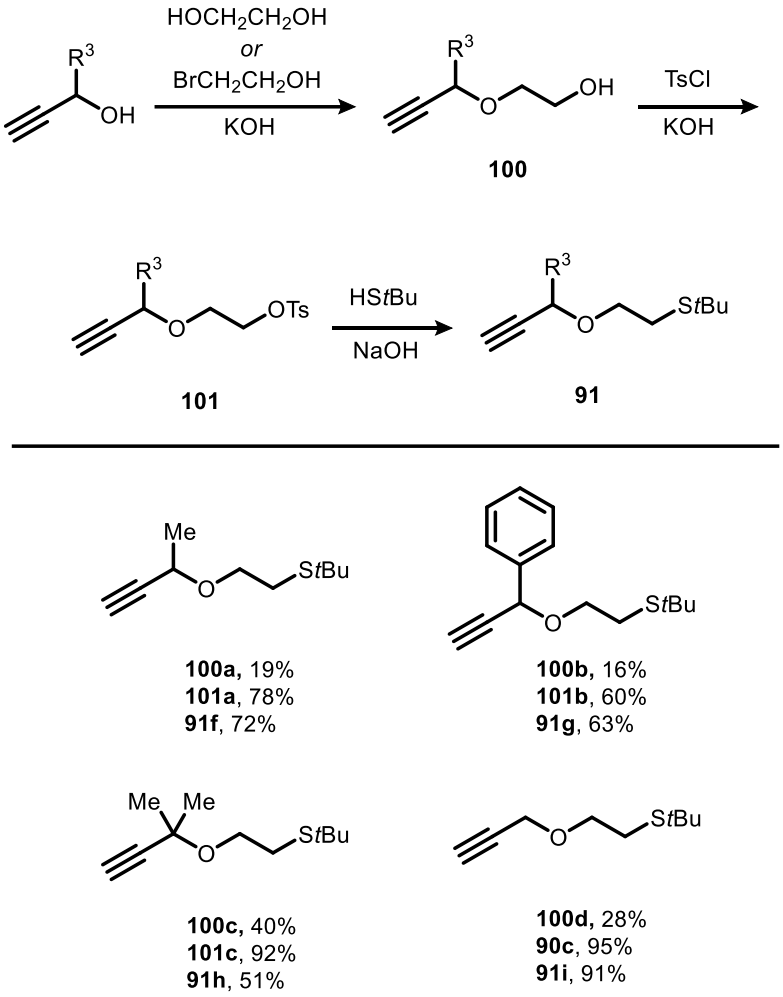
2.3.4 Synthetic routes to *tert*-butyl sulfide alkynes

In order to illustrate the practicality of our hydroacylative route to *S*-heterocycles it was necessary to design a convenient and high-yielding synthesis of *tert*-butyl sulfide alkynes. Unsubstituted alkynes and those with fused rings were prepared from alkynols **80** in two steps; tosylation followed by nucleophilic substitution with *tert*-butylthiol (Scheme 2.20). Attempts to attain the target alkynes directly from the corresponding chloroalkynes were unproductive. As such, the intermediacy of tosylated compounds was essential.



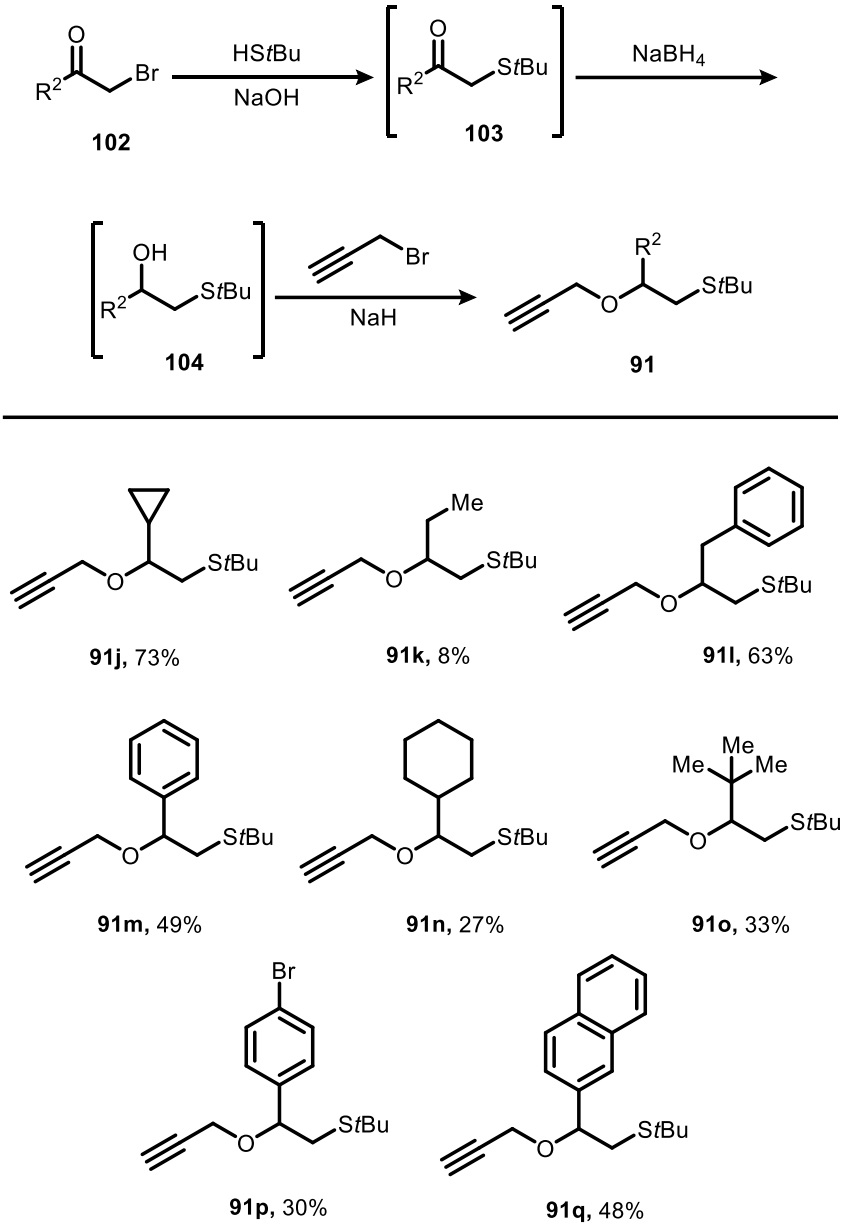
Scheme 2.20 Synthesis of unsubstituted and fused *tert*-butyl sulfide alkynes

R^3-substituted substrates and alkyne **90c** were targeted in a similar manner, except an additional step was requisite (Scheme 2.21). This involved coupling appropriate propargylic alcohols with ethylene glycol or 2-bromoethanol, generating alcohols **100**.



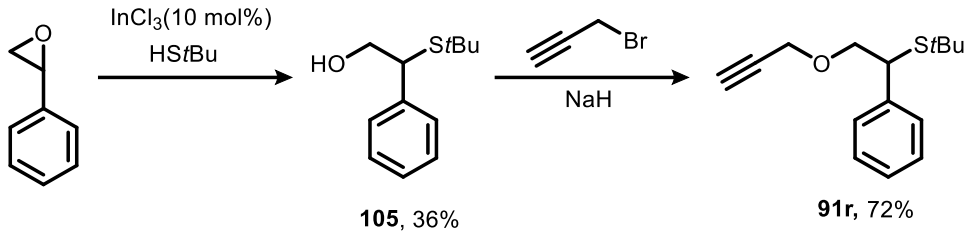
Scheme 2.21 Synthesis of R^3-substituted *tert*-butyl sulfide alkynes

To synthesise *tert*-butyl alkynes with substituents at the R^2 position, we developed a three-step sequence, encompassing a single purification (Scheme 2.22). The first step involved thiolation of *α*-bromoketones **102** to give *tert*-butylsulfide congeners. Subsequent reduction with $NaBH_4$ afforded alcohols **104** which underwent propargylation, delivering the desired substrates. Using this procedure, a variety of substituted *tert*-butyl alkynes were prepared in good yields.



Scheme 2.22 Synthesis of R^2-substituted *tert*-butyl sulfide alkynes

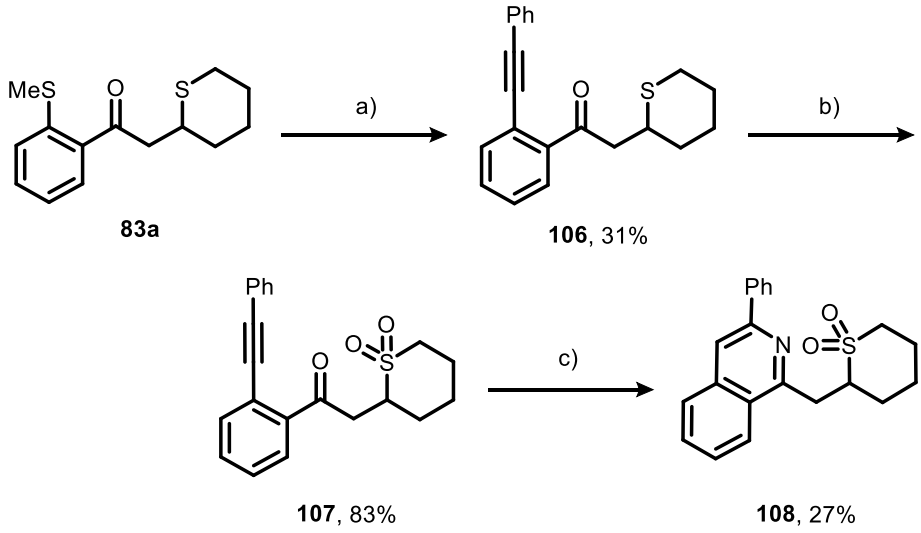
R^1-substituted alkyne **91r** was obtained from styrene oxide in two steps. Firstly, $InCl_3$ catalysed ring-opening with *tert*-butylthiol, yielded *tert*-butylthioethanol **105**. Subsequent treatment of **105** with propargyl bromide and NaH, afforded **91r** in good yield (Scheme 2.23).



Scheme 2.23 Synthesis of *tert*-butyl sulfide alkyne **91r**

2.3.5 Construction of isoquinoline derivative

Having accessed a wide range of diversely substituted saturated *S*-heterocycles, we sought to demonstrate the synthetic utility of the sulfides through derivatisation reactions. To this end, we endeavoured to synthesise isoquinoline **108** from product **83a** using a multi-step sequence (Scheme 2.24).



(a) $Rh(nbd)_2BF_4$ (5 mol%), dcpe (5 mol%), CuBr (2.0 equiv.), Ag_2CO_3 (1.0 equiv.), phenylacetylene (2.0 equiv.), DCE (0.075 M), 80 ºC, 16 h; (b) *m*-CPBA (3.0 equiv.), DCM (0.16 M), r.t, 3h; (c) NH_4OAc (5.5 equiv.), $AgNO_3$ (0.8 equiv.), *t*-BuOH, 60 ºC, 16 h

Scheme 2.24 Synthesis of isoquinoline derivative

Firstly, the thiomethyl motif was exploited as a 'late-stage' lynchpin in a rhodium-catalysed Sonogashira-type coupling, affording adduct **106** in 31% yield. Subsequent oxidation of **106**, using *m*-CPBA, gave sulfone **107**. Finally, using a modified literature procedure,[186] isoquinoline **108** was generated *via* annulation of **107** with ammonium acetate.

2.4 Summary

In conclusion, we have developed a one-pot hydroacylation/thia-conjugate addition cascade for the synthesis of diverse, fully saturated sulfur heterocycles. A robust rhodium(I)/dcpe catalyst system has been established, boasting excellence functional group tolerance and high regioselectivity. The intramolecular cyclisation of *tert*-butyl sulfide enones proceeds with low diastereoselectivity which could not be enhanced. Additionally, two deleterious cyclisation pathways have been characterised. Nonetheless, a broad range of 5- and 6-membered cyclic sulfides have been accessed in good to excellent yields. Despite attempts, 4-membered thia-rings could not be prepared using the devised methodology. The *S*-heterocycles have also been exploited in the modular assembly of a pharmaceutically attractive isoquinoline scaffold. This research has been recently published.[184]

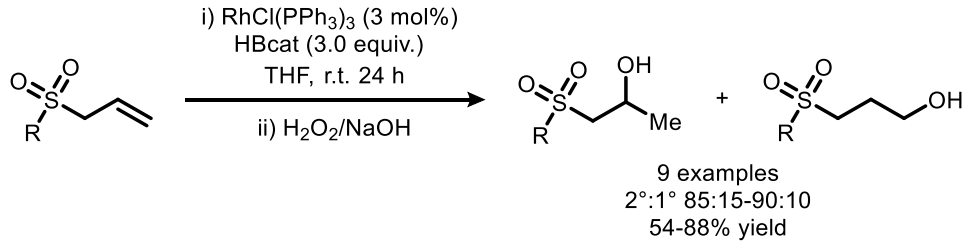
Chapter 3

New sulfonyl aldehydes in rhodium-catalysed hydroacylation

3.1 Introduction

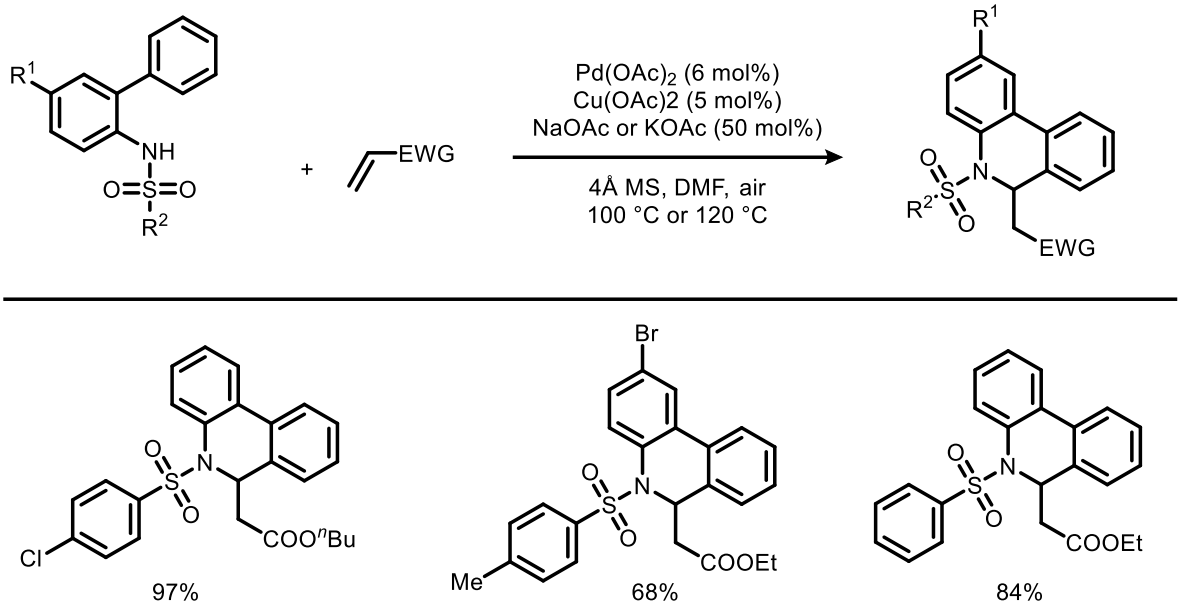
3.1.1 Sulfonyl-directed rhodium catalysed C-H activation

There are limited examples of the use of sulfone and sulfonamide groups as directing groups in C-H activation. However, these transformations have recently garnered more attention. In 1993, Dai and Hou reported the first sulfone promoted rhodium-catalysed hydroboration (Scheme 3.1).[187] A series of allyl sulfones reacted with catecholborane in the presence of Wilkinson's catalyst, furnishing high ratios of secondary alcohols post oxidation.



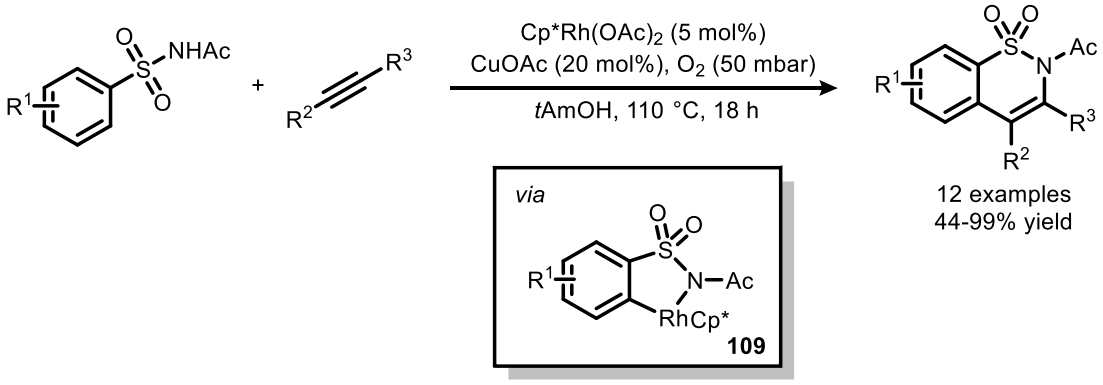
Scheme 3.1 Rh-catalysed hydroboration of allyl sulfones

A few years later, the Miura group disclosed the first example of sulfonamide promoted C-H activation.[188] They coupled *N*-(2′-phenylphenyl)benzenesulfonamides with activated olefins using $Pd(OAc)_2$; $Cu(OAc)_2$; base; and air, yielding diverse phenanthridine derivatives (Scheme 3.2). Since then, the directing effect of sulfonamide moieties has received more focus; it has been particularly earmarked for the construction of heterocyclic compounds. Among the latter, sultam cores stand out as privileged motifs in drug discovery.[189]



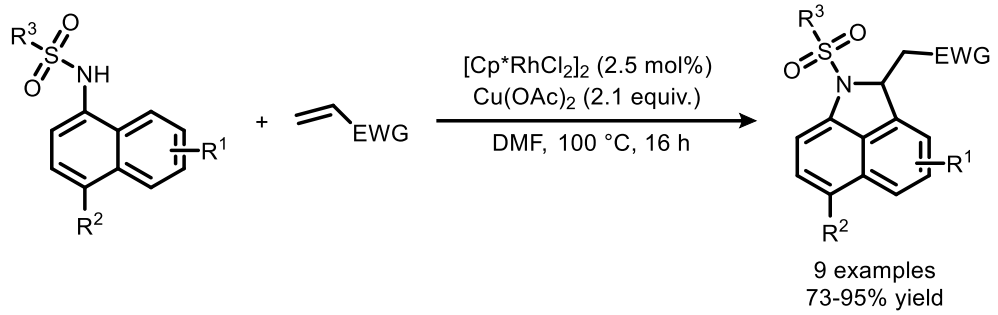
Scheme 3.2 First sulfonamide directed C-H activation

In 2012, Cramer *et al* published the first Rh(III)-catalysed C-H activation/annulation route to sultams, starting from simple acylated sulfonamides (Scheme 3.3).[190] This seminal work showed the attenuated directing character of sulfonamides resulted in key cyclometalated intermediates **109**, which readily reacted with a broad scope of internal alkynes.[190] Thereafter, similar Rh(III)-catalysed sequences allowed access to five[191] and eight-membered[189] cyclic sulfonamides.



Scheme 3.3 Cramer's synthesis of sultams *via* C-H activation/annulation

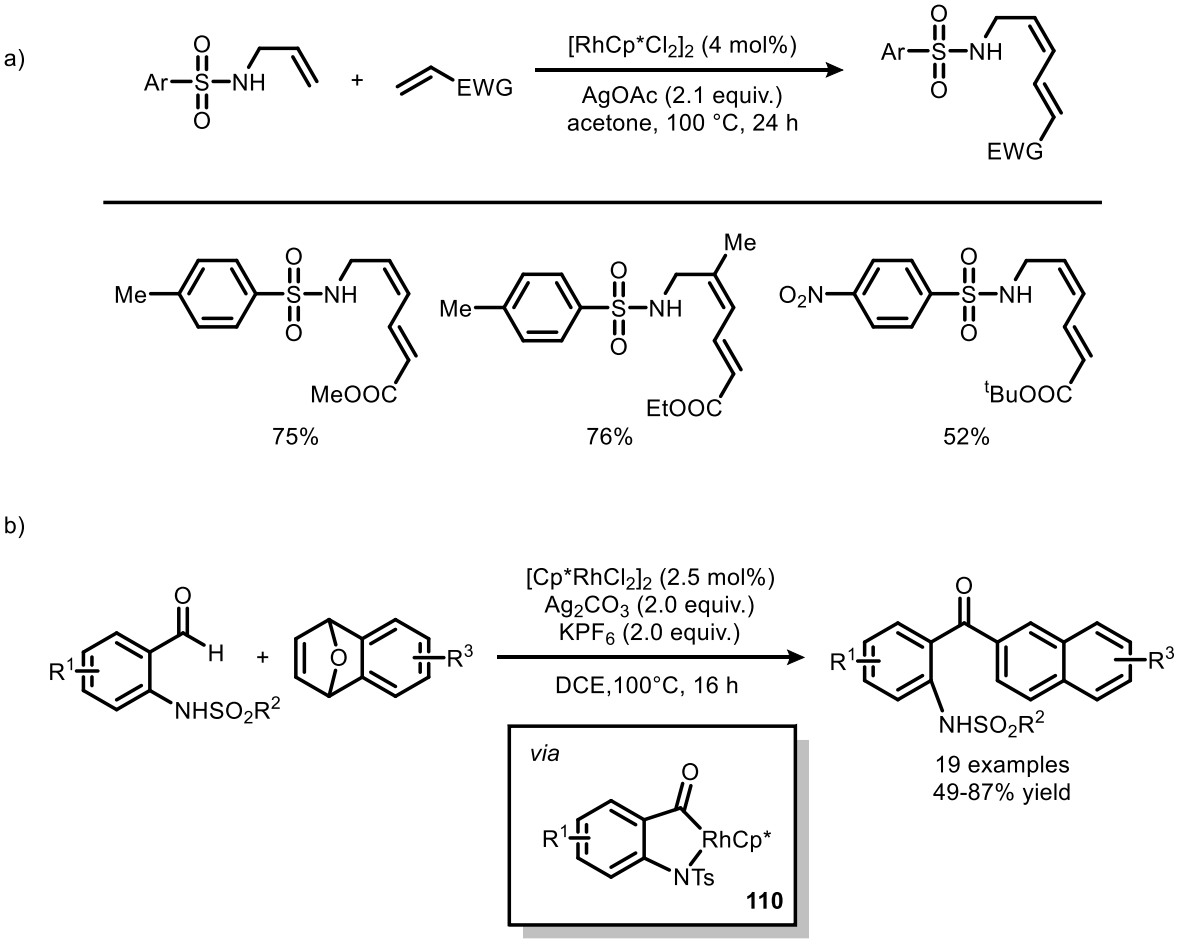
Arylsulfonamides have also been utilised to synthesise alternative heterocycles. For example, the Li group developed a Rh(III)-catalysed oxidative olefination/hydroamination of *N*-(1-naphthyl)sulfonamides with acrylates, affording various benzoindole products in good to excellent yields (Scheme 3.4).[192] Analogous tandem approaches have recently been applied to the synthesis of isoindolinones,[193] indolines,[194] naphthylamides[195] and lactams.[196]



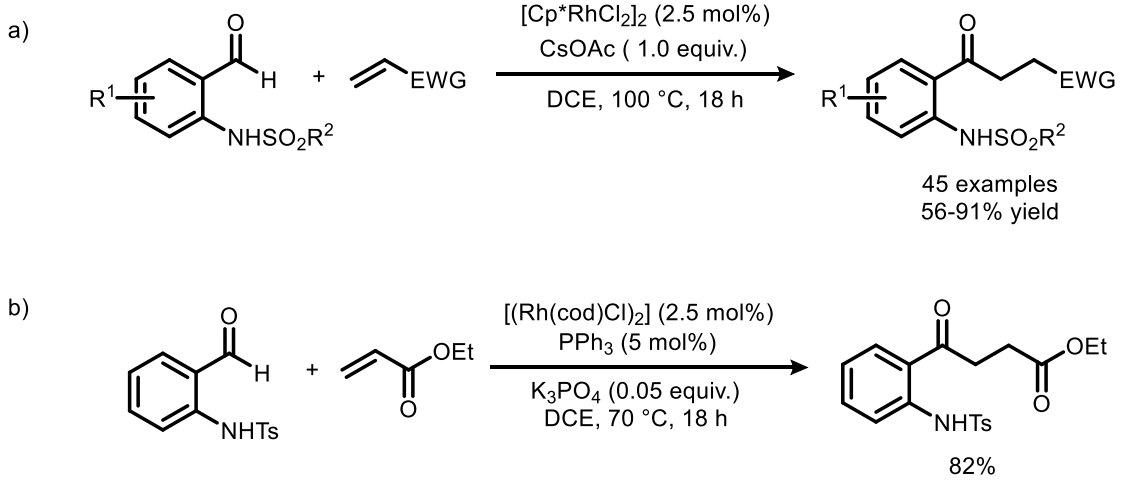
Scheme 3.4 Oxidative olefination of sulfonamides

Beyond heterocycle synthesis, Rh(III) catalysts have been employed in other sulfonamide or sulfone assisted C-C couplings.[191, 196-198] For instance, Li and coworkers described a rhodium(III)-catalysed oxidative coupling of *N*-allyl sulfonamides with activated olefins (Scheme 3.5a).[197] A variety of sulfonamide groups were tolerated and reactions with acrylates proceeded with high stereoselectivity. Later, this group successfully applied the same Rh(III)Cp* catalyst to a redox-neutral coupling of *N*-sulfonyl 2-aminobenzaldehydes with oxygenated allylic olefins (Scheme 3.5b).[196] The authors confirmed the intermediacy of C-H activation by preparing catalytically active, rhodacyclic acyl complex **110** involving *N*-chelation. In an earlier publication (See Section 1.3.2), complex **110** efficiently catalysed the hydroacylation of *N*-sulfonyl 2-aminobenzaldehydes with olefins.[87] In this case, using $[RhCp^*Cl_2]_2$ and stoichiometric base enabled the synthesis of a wide scope of aryl ketones in very good yields (Scheme 3.6a). Interestingly, a Rh(I) catalyst also displayed high activity in the hydroacylation reactions (Scheme 3.6b).[87] Mechanistic studies of the Rh(III) system

revealed C-H activation proceeds *via* a concerted metalation–deprotonation mechanism. This contrasts Rh(I) catalysis where C-H oxidative addition is operational.[87]

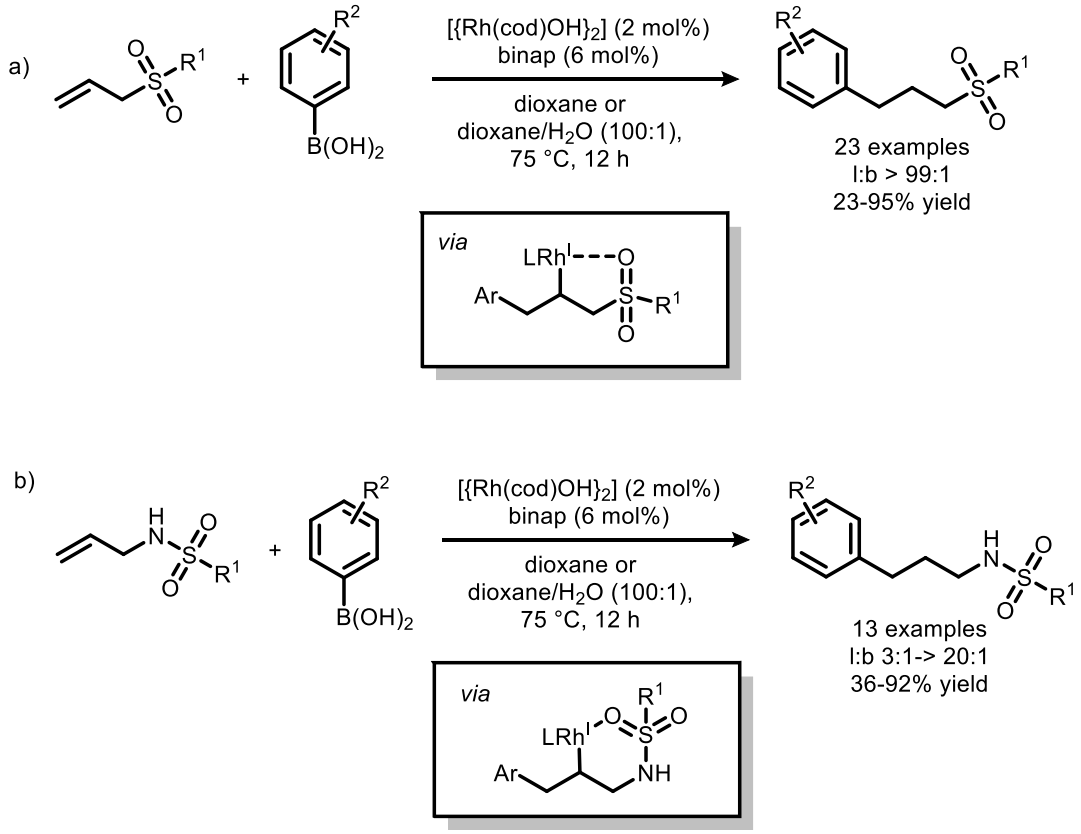


Scheme 3.5 The Li group's sulfonamide directed oxidative coupling with a) *N*-allyl sulfonamides b) *N*-sulfonyl 2-aminobenzaldehydes



Scheme 3.6 Hydroacylation of *N*-sulfonyl 2-aminobenzaldehydes using Rh catalysts a) Rh(III) b) Rh(I)

In general, Rh(I)-catalysed C-C alkene addition reactions have seldom been promoted by sulfonamide or sulfone moieties. Building on Dai and Hou's work (*vide supra*), Lautens *et al* established regioselective hydroarylation reactions of allyl sulfonamides and sulfones (Scheme 3.7).[199-200] Both protocols were thought to involve stabilisation of Rh(I) intermediates by coordination of an S=O group. Notably, this directing effect concomitantly controlled the regioselectivity of the alkene insertion, favouring formation of linear addition products.[199-200] Similar activating effects have also been reported for hydroformylation processes.[201-202]



Scheme 3.7 Lautens' Rh(I)-catalysed hydroarylation using a) allyl sulfones b) allyl sulfonamides

Overall, the above literature provides precedence for the coordinating ability of sulfonamide and sulfones in Rh catalysed C-H functionalisations. Presently, procedures typically employ Rh(III) catalysts under high temperatures (> 100 °C) and have reaction scopes limited to aryl sulfonamides and activated olefins.

3.1.2 Synthesis of *β*-ketosulfonyl compounds

3.1.2.1 *β*-ketosulfones

The *β*-ketosulfone functionality is found in several pharmaceuticals and agrochemicals (Figure 3.1).[203-204] In recent times, *β*-ketosulfones have gained considerable interest due to their favourable biological activities and chemical reactivity.[203-204] Several reports have exploited *β*-ketosulfones as versatile intermediates for the synthesis of diverse classes of organic compounds.[205-207] In view of these utilities, the preparation of *β*-ketosulfones has been extensively explored and now constitutes an expanding branch of organosulfur chemistry.[208]

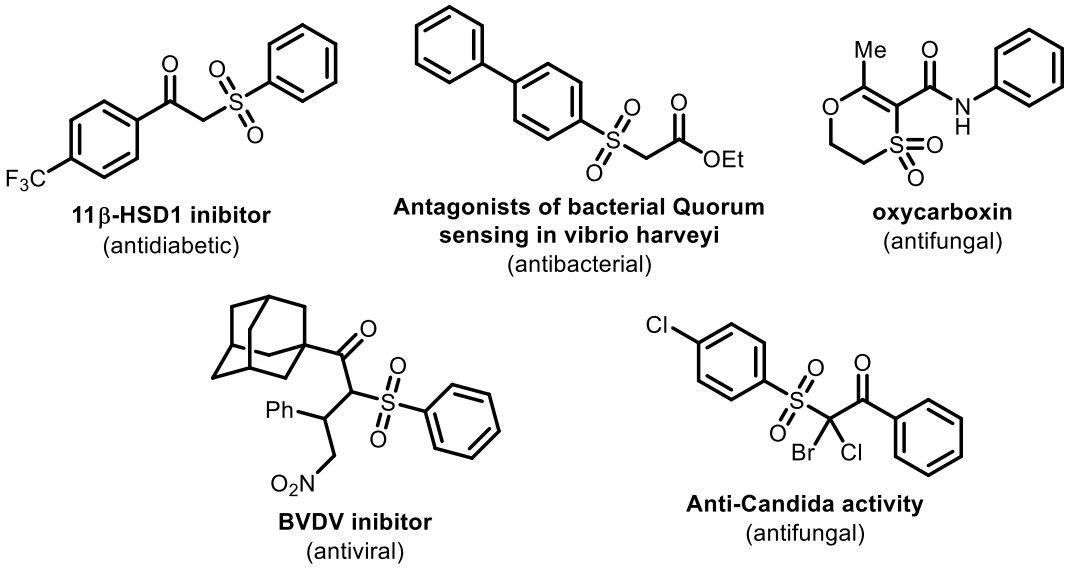
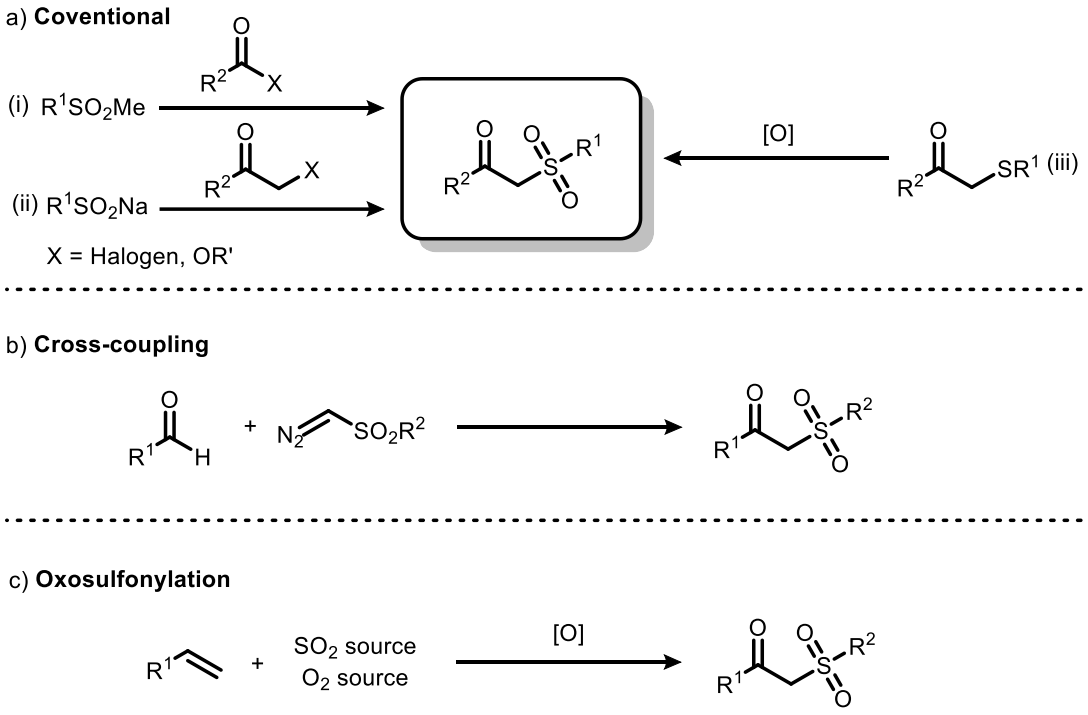


Figure 3.1 Biologically active compounds containing *β*-ketosulfone motifs

The most common conventional methods to prepare *β*-ketosulfones include: (i) acylation of alkyl sulfones; (ii) alkylation of sodium arene sulfinates with α-halo ketones; and (iii) oxidation of *β*-ketosulfides (Scheme 3.8a).[204] However, these strategies are stifled by the requirement of prefunctionalised starting materials as well as the generation of stoichiometric by-products, which diminish step- and atom-economy, respectively.[204]

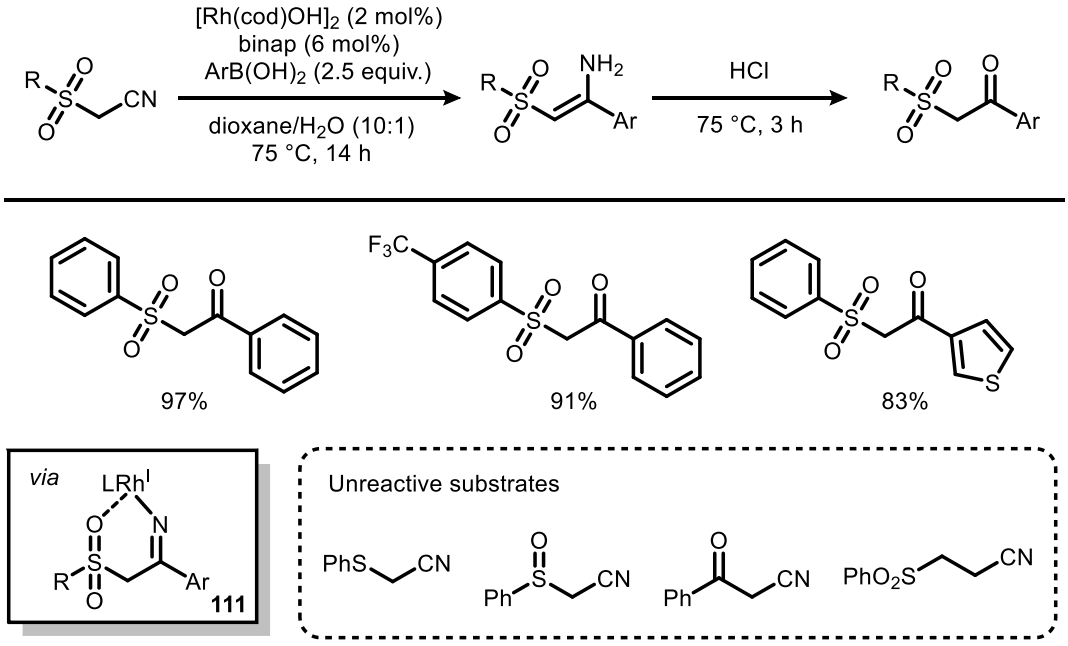
These drawbacks were initially abated by the development of cross-coupling reactions (Scheme 3.8b). [209]



Scheme 3.8 Strategies to prepare *β*-ketosulfones

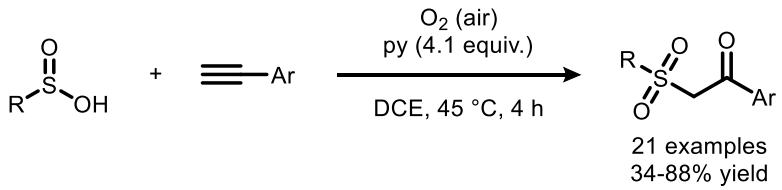
Some examples include the pairing of sulfonyl hydrazides[210] or arylsulfinates[211] with diazo compounds. In 2010, the Lautens group devised an efficient synthesis of *β*-ketosulfones through rhodium(I)-catalysed addition of arylboronic acids to arylsulfonyl acetonitriles (Scheme 3.9).[212] This one-pot, tandem protocol involved stereoselective formation of *β*-sulfonylvinylamines and subsequent hydrolysis, yielding a broad scope of aryl *β*-ketosulfones. The authors postulated that the sulfone group coordinated to rhodium, forming a stabilised six-membered rhodacycle (**111**). This hypothesis was supported by the unreactivity of different *β*-substituted acetonitriles. Numerous comparable coupling processes have been reviewed elsewhere.[204, 208] Importantly, cross-coupling procedures do not completely evade the generation of undesired by-products or multi-step synthesis of coupling partners.[209] Moreover, many of these methods need forcing reaction conditions.[203] To remedy this, there has been a shift towards oxosulfonylation protocols in

which oxo and sulfonyl groups are introduced in one step (Scheme 3.8c).[209] Compared to earlier approaches, direct oxosulfonylations are atom-efficient and use readily accessible keto and sulfone sources.[209]



Scheme 3.9 Lautens' route to *β*-ketosulfones *via* Rh(I)-catalysed addition of arylboronic acids

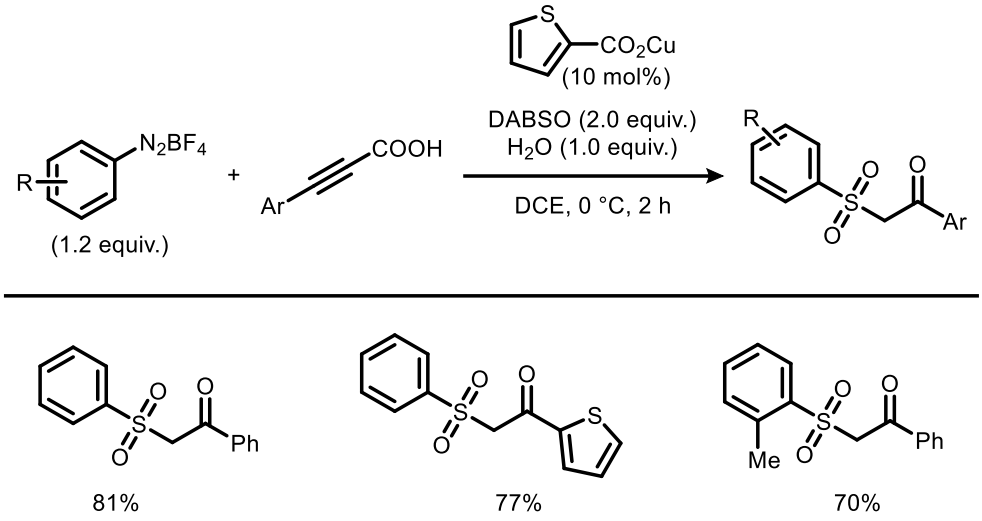
These practicalities were astutely showcased by the Lei group in their seminal synthesis of *β*-ketosulfones, using an oxygen-triggered radical process.[213] A wide range of arylacetylenes underwent aerobic difunctionalisation with sulfinic acids, under mild conditions, providing the target products in good to high yields (Scheme 3.10).



Scheme 3.10 The Lei group's direct aerobic difunctionalisation of terminal alkynes

This report later inspired a plethora of synthetic transformations that focused on achieving simple and sustainable syntheses of *β*-ketosulfones. For instance, in 2017, Wu *et al* published a copper(I)-catalysed multicomponent coupling of aryldiazonium

tetrafluoroborates; 3-arylpropiolic acids; DABSO; and water, delivering various *β*-ketosulfones (Scheme 3.11).[214] This reaction proceeded through a tandem radical decarboxylation–sulfonylation mechanism and tolerated a host of functional groups. Remarkably, the combination of aryldiazonium tetrafluoroborates with DABSO permitted the generation of key sulfonyl radical intermediates under mild conditions.



Scheme 3.11 Wu's synthesis of *β*-ketosulfones through sulfonylation and decarboxylation

Over the last decade, methods to access *β*-ketosulfones have become more efficient. Strategies that employ photoredox, electrochemical and sulfonyl radical manipulations have all been explored.[204] Despite this success, a number of limiting factors generally persist such as, high temperatures, preactivated substrates and low yields. What's more, the majority of reactions are incompatible with aliphatic precursors. Thus, there remains a demand for general, mild and convenient methods to access *β*-ketosulfones.

3.1.2.2 *β*-ketosulfonamides

The sulfonamide functional group is one of the most important pharmacophores in medicinal chemistry.[215] Drugs possessing sulfonamide moieties have multiple therapeutic applications due to their anti-inflammatory; antibacterial; antimalarial; and antitumor activities.[142] Aryl sulfonamides are routinely obtained from aryl sulfonyl chlorides, but their alkyl cognates are more challenging to prepare.[216] *β*-ketosulfonamides are especially attractive synthons for many bioactive molecules (Figure 3.2).[216]

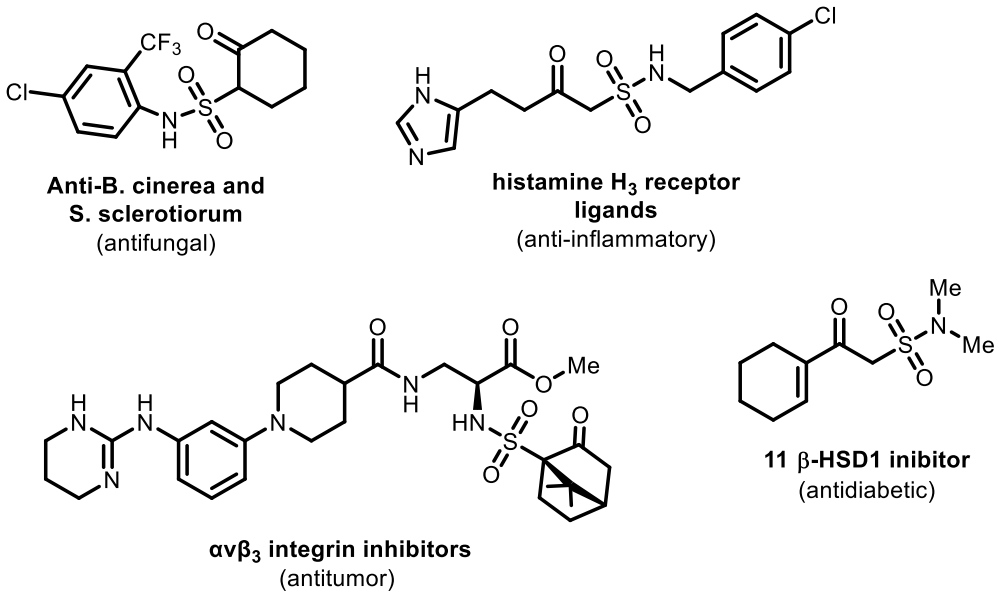
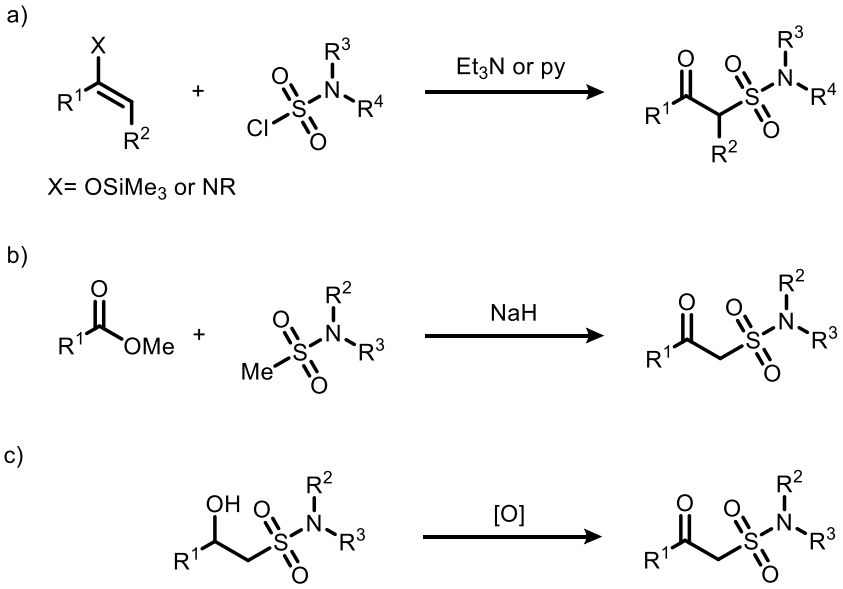


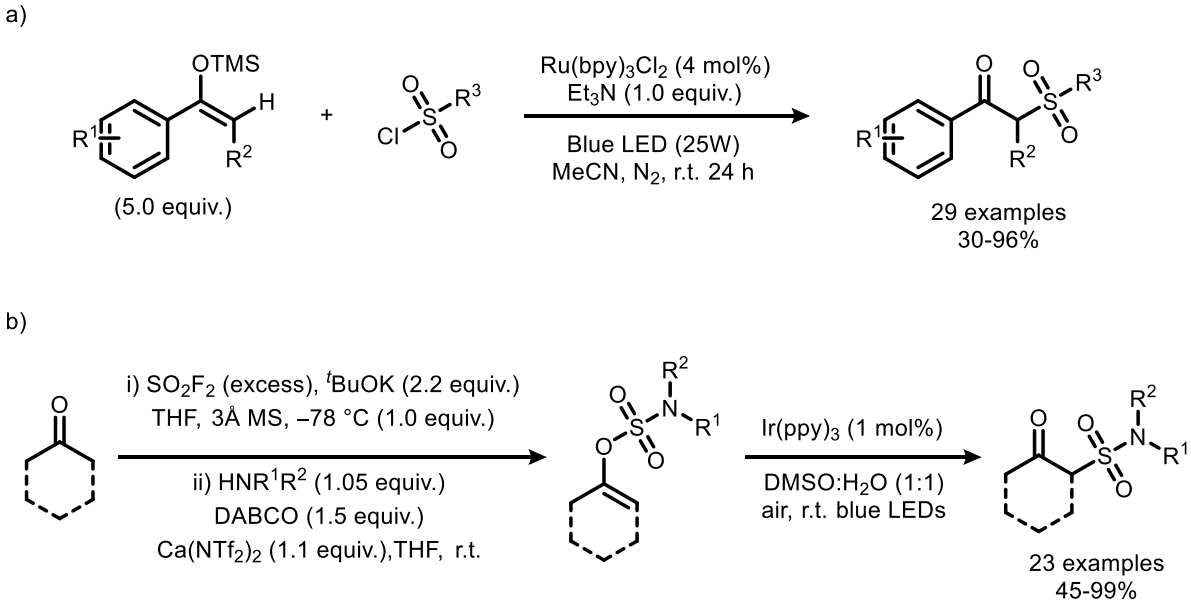
Figure 3.2 Examples of medicinally relevant compounds containing an *β*-ketosulfonamide moiety

Traditionally, *β*-ketosulfonamides have been synthesised *via* substitution of sulfamoyl chlorides with silyl enol ethers or enamines (Scheme 3.12a).[216] However, sulfamoyl chlorides require multistep syntheses and are notoriously hard to purify owing to their moisture sensitivity.[217] The reverse of the self-same polar disconnection is also a viable route to *β*-ketosulfonamides. This strategy entails Claisen condensation of deprotonated sulfonamides with esters; thus, requires strong base and or high temperatures (Scheme 3.12b).[218] A third approach relies on the oxidation of *β*-hydroxysulfonamides (Scheme 3.12c).[219]



Scheme 3.12 Traditional ways to access *β*-ketosulfonamides

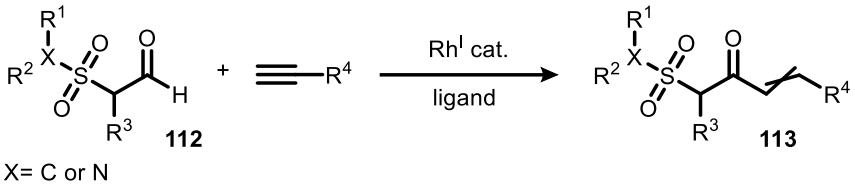
In recent years, there has been a departure from polar processes. For example, the Wang group communicated a novel photoredox-catalysed synthesis of highly functionalised *β*-ketosulfonamides (Scheme 3.13a).[220] A representative set of enol silyl ethers readily reacted with sulfamyl radicals generated from chlorosulfonamide. Subsequent radical sulfonamidation delivered the desired sulfonamides in modest to excellent yields. Although the transformation used mild conditions, large excesses of enol silyl ethers (5.0 equiv.) were requisite. In 2021, Michaudel and co-workers established a modular route to *β*-ketosulfonamides *via* photomediated 1,3-rearrangement of alkenyl sulfamates (Scheme 3.13b).[216] This two-step protocol first harnessed SO_2F_2 as a linchpin to couple feedstock ketones and amines by sulfur(VI) fluoride exchange. The resultant alkenyl sulfamates were then irradiated, with visible light, in the presence of photosensitizer, $Ir(ppy)_3$, affording a broad array of *β*-ketosulfonamide in high yields. In comparison to Wang's technique, this procedure obviated the use of excess amounts of coupling partners but increased the overall step count of the transformation. Taken together, despite the methodologies reviewed above, the synthesis of *β*-ketosulfonamides remains in its infancy.



Scheme 3.13 Modern methods to access *β*-ketosulfonamides a) Wang's photoredox-catalysed route b) Michaudel's photomediated procedure

3.1.3 Project aims

Recently, our laboratory successfully utilised versatile 1,3-dicarbonyls to assist intermolecular rhodium-catalysed hydroacylation.[127] Inspired by this, we sought to explore new synthetically useful coordinating groups with the aim of accessing valuable *β*-ketosulfonyl compounds. Given the aforementioned examples of sulfonyl-directed, rhodium-catalysed C-H activation, we envisioned that sulfonyl aldehydes **112** could promote intermolecular hydroacylation with terminal alkynes, giving rise to aliphatic or aromatic *β*-ketosulfonyl products (Scheme 3.14). The use of a Rh(I) catalyst offers the advantage of a reaction without external oxidants; predisposing (to some degree) milder conditions and functional group tolerance. Thus, this approach has the potential to serve as a novel and general route to *β*-keto- sulfones and sulfonamides.



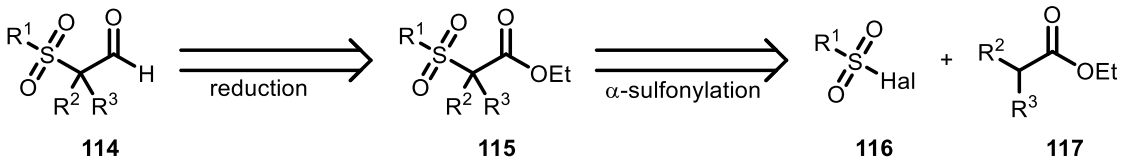
Scheme 3.14 Our proposed hydroacylation of *β*-sulfonyl aldehydes

3.2 Synthesis of sulfonyl aldehydes

In order to investigate the reactivity of sulfonyl aldehydes in hydroacylation, it was necessary to develop convenient ways to prepare gram quantities of the target substrates. Ideal sequences would also need to benefit from modularity to enable the assessment of reaction scope.

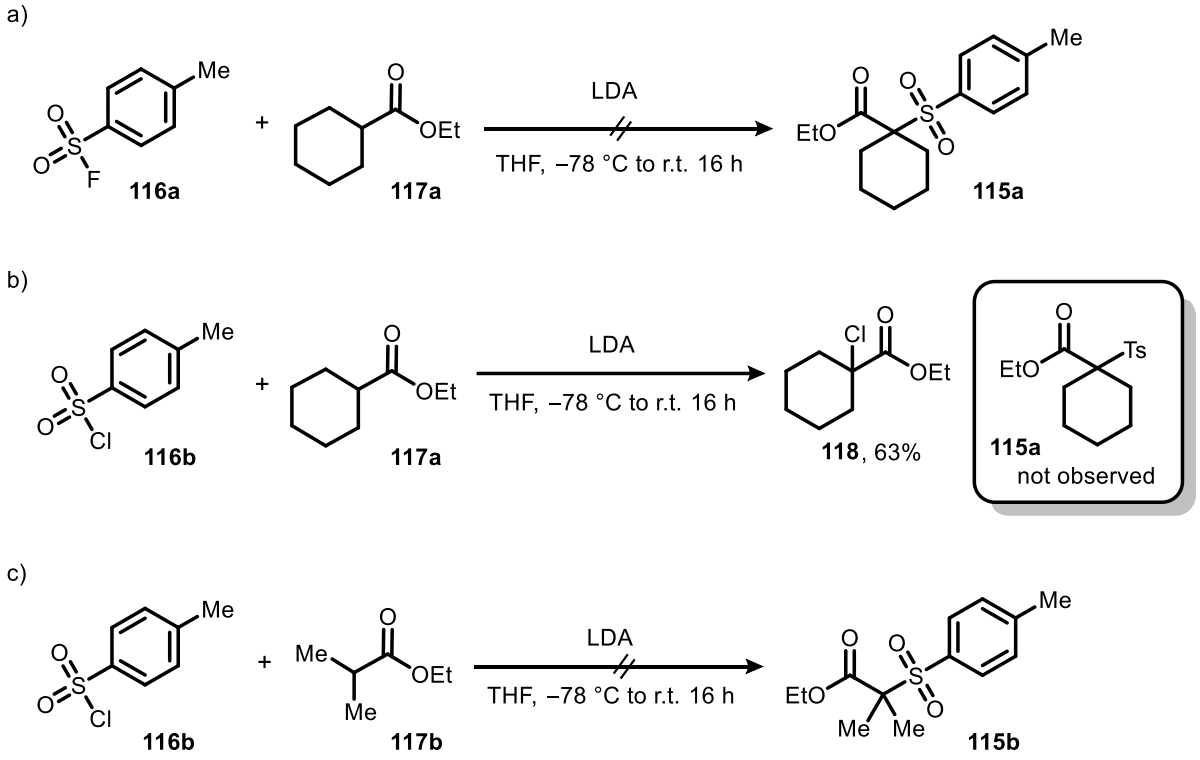
3.2.1 *β*-formyl sulfones

Initially, efforts were made to synthesis *α*-disubstituted *β*-sulfone aldehydes **114**. The proposed route involved coupling *α*-disubstituted esters with sulfonyl halides, followed by reduction to the appropriate aldehydes (Scheme 3.15).



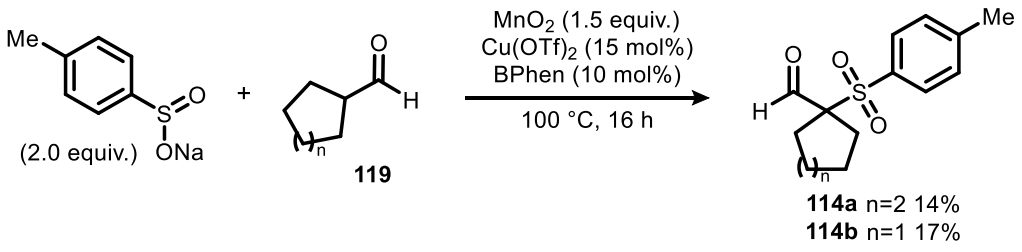
Scheme 3.15 Retrosynthetic approach to disubstituted *β*-sulfone aldehydes

Disappointingly, *α*-sulfonylation of ester **117a**, using LDA and *p*-toluenesulfonyl fluoride, failed to proceed (Scheme 3.16a). When the same reaction was conducted using an analogous sulfonyl chloride, *α*-halogenation occurred instead (Scheme 3.16b). Switching to a less bulky ester was also unsuccessful, returning a mixture of polymerisation products (Scheme 3.16c).



Scheme 3.16 Attempted synthesis of disubstituted *β*-sulfone aldehydes

Consequently, an alternative strategy was attempted; employing a copper-catalysed protocol developed by Bull and Higham.[221] This method presented the opportunity to access target *α*-sulfonyl aldehydes, in a single step, from readily available sulfinate salts and branched aldehydes (Scheme 3.17). Duly, conditions for this oxidative coupling were applied to carbaldehydes **119**, affording *β*-formyl sulfones **114a** and **114b**, respectively. The low isolated yields contrasted those reported in literature. It is plausible that product degradation was prevalent under the oxidising conditions.

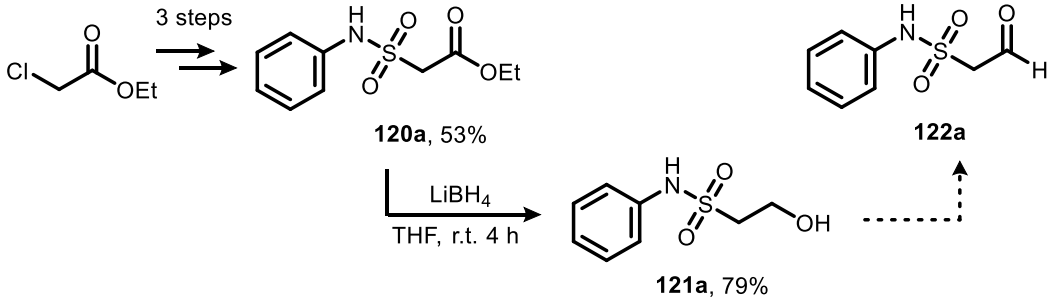


Scheme 3.17 Synthesis of disubstituted *β*-sulfone aldehydes *via* copper-catalysed oxidative *α* sulfonylation

Due to time constraints, no further endeavours were made to optimise the coupling reactions or explore alternate syntheses of the required substrates.

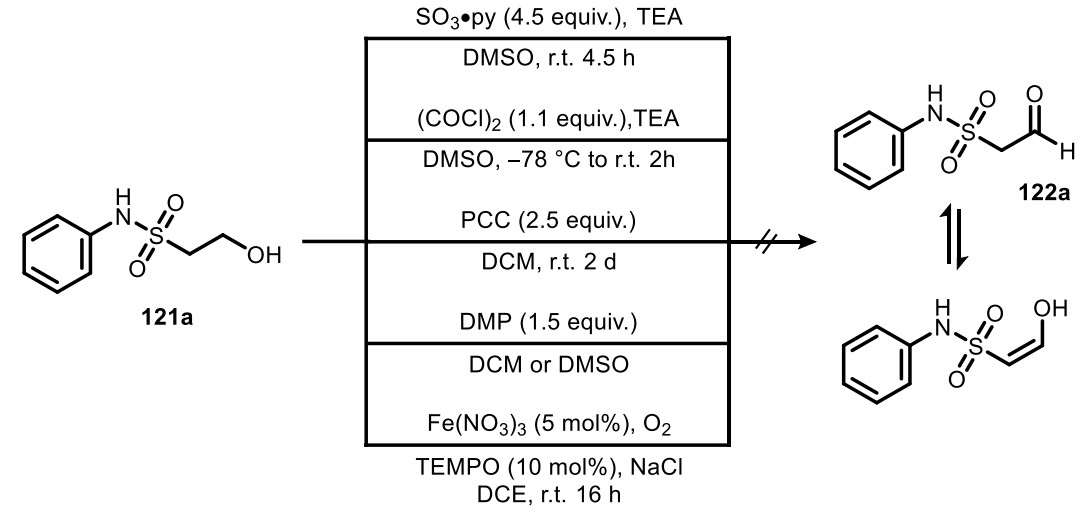
3.2.2 *β*-formyl sulfonamides

The synthesis of α-unsubstituted *β*-sulfonamide aldehydes is non-trivial since they readily tautomerize. Unsurprisingly, very few literature preparations of these compounds have been described. Nonetheless, we originally intended to access *β*-formyl sulfonamide **122a** *via* an ester precursor (Scheme 3.18). The latter could be made in three steps from ethyl chloroacetate without intermediate purification. Reduction of **120a** delivered alcohol **121a** in good yield.

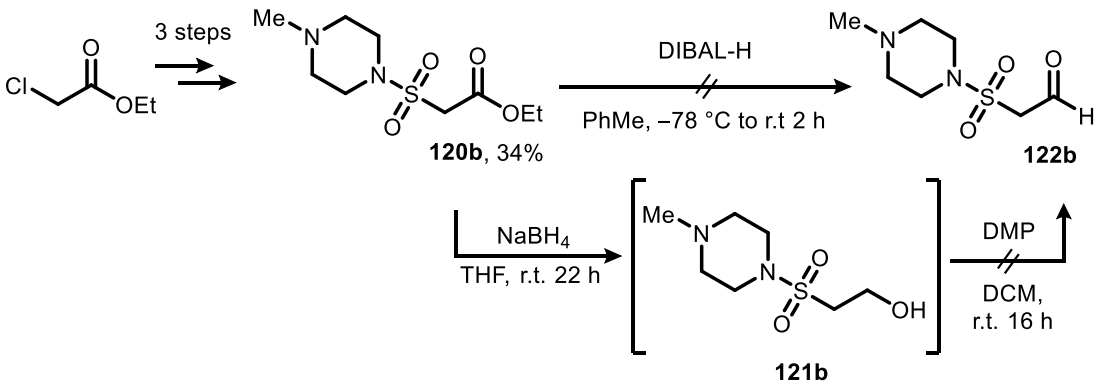


Scheme 3.18 Initial synthesis of *β*-formyl sulfonamide **122a**

Thereafter, a number of conditions were tried to elicit oxidation of **121a** to **122a** however, none were effective (Scheme 3.19). This was apparent from the recovery of starting material or detection of degradation products. The presence of the secondary amide was suspected to contribute to undesired reactivity. Accordingly, an analogous tertiary amide (**120b**) was synthesised using the aforesaid telescoped protocol (Scheme 3.20). Direct reduction of **120b**, using DIBAL-H, did not generate the expected aldehyde. A two-step approach *via* alcohol **121b** was also ineffectual.

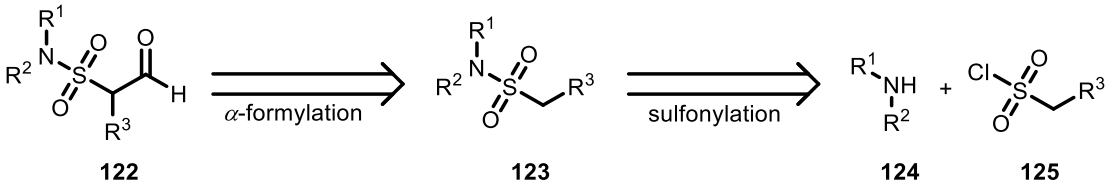


Scheme 3.19 Attempted synthesis of aldehyde **122a**



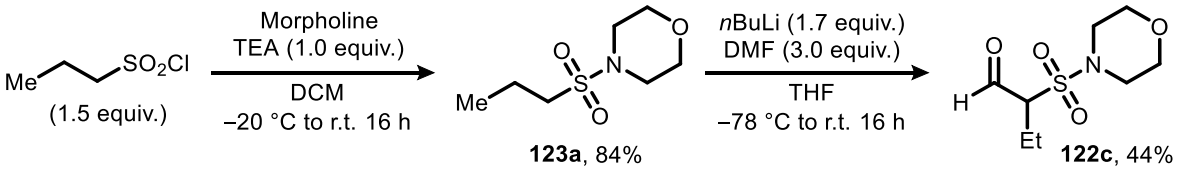
Scheme 3.20 Attempted synthesis of aldehyde **122b**

Given the difficulty of constructing α-unsubstituted substrates, our attention was redirected towards monosubstituted substrates. We envisaged that these compounds could be accessed by a simpler route, namely, α-formylation of sulfonamides (Scheme 3.21). These in turn could be prepared by pairing commercially available amines and sulfonyl chlorides.



Scheme 3.21 Retrosynthetic approach to monosubstituted β-formyl sulfonamides

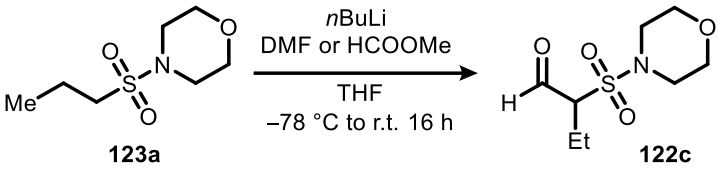
Pleasingly, this strategy was applied to the synthesis of aldehyde **122c** (Scheme 3.22). The S-N coupling step proved straightforward, although the ensuing formylation reaction with DMF did not go to completion. Therefore, only a modest yield of aldehyde **122c** could be isolated. Purification was also challenging as **122c** and **123a** have very similar R_f values.



Scheme 3.22 Synthesis of aldehyde **122c**

Following this, the stoichiometry of base and DMF were varied with the goal of driving the reaction to completion. This had a minimal effect on the ratio of product to starting material (Table 3.1, entries 1-4). Gratifyingly, employing a more activated electrophile, in the form of methyl formate, drastically improved the conversion to aldehyde **122c**, which could be isolated in 61% yield (Table 3.1, entry 5).

Table 3.1 Optimisation of α-formylation



123a **122c**

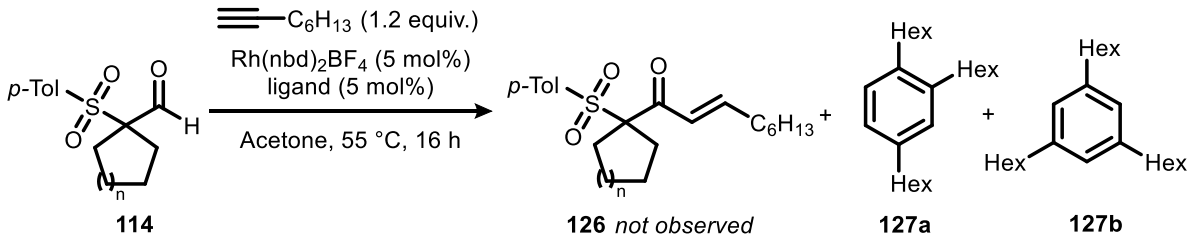
Entry	Equiv. of *n*BuLi	Equiv. of DMF or HCOOMe	123a:122c[a]
1	1.7	3.0[b]	1:2.5[d]
2	2.5	3.0[b]	2.3:1
3	2.5	3.5[b]	1:3.6
4	2.1	3.0[b]	1:3.8
5	2.1	3.0[c]	1:20[e]

[a]ratio determined by ^{1}H NMR spectra of the crude reaction mixtures. [b]DMF used. [c]Methyl formate used. [d]**122c** isolated in 44% yield. [e]**122c** isolated in 61% yield.

3.3 Reactivity of sulfonyl aldehydes in hydroacylation

With the target sulfonyl aldehydes in hand, we began to probe their reactivity with 1-octyne using Rh(I) catalysts. The experiments were conducted using the standard methodology formalised by the Willis group (See Section 2.2). Initial reactions with *β*-formyl sulfones, applying 5 mol% of catalyst featuring small bite-angle ligands, dppe or dcpm, did not produce the desired adduct. Instead, mixtures of starting material and trisubstituted hexylbenzenes were obtained (Table 3.2, entries 1 and 2). This is consistent with previous mechanistic studies on the hydroacylation of *β*-amido-aldehydes.[133] In this instance, a competitive cyclotrimerisation pathway was dominant when the concentration of (strongly binding) aldehyde was low (See Section 1.3.5).[133] Comparatively, it is conceivable that the binding of *β*-formyl sulfones **114** is inefficient. Utilising DPEPhos ligand did not promote the coupling but accelerated cyclotrimerisation (Table 3.2, entry 3). This effect may arise from the stabilising hemilabile Rh···O interaction.

Table 3.2 Hydroacylation of *β*-formyl sulfones with 1-octyne

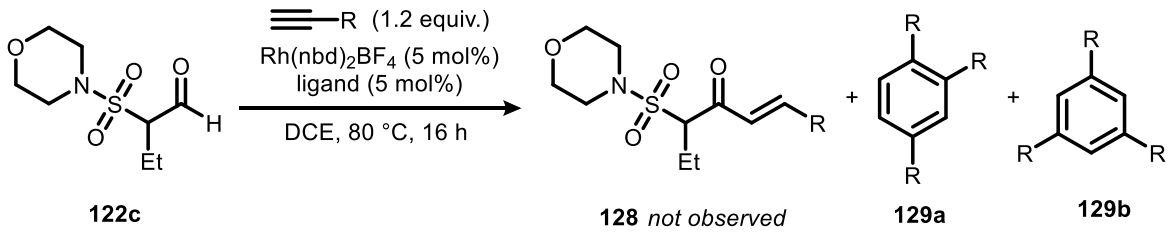


Entry	n	Ligand	114:127a:127b[a]
1	2	dppe	38.5:3.7:1
2	1	dcpm	75:4.5:1
3	1	DPEPhos	2.3:1.8:1

[a]ratio determined by ^{1}H NMR spectra of the crude reaction mixtures.

The reactivity of *β*-formyl sulfonamides was subsequently explored. Unfortunately, the sulfonamide moiety did not assist the coupling with 1-octyne, using a Rh-DPEPhos catalyst, in DCE, at 55 °C. Once more, a combination of starting material and arene by-products were observed (Table 3.3, entry 1). The decarbonylation product was also not detected. From this, we reasoned that the oxidative addition of aldehyde **122c** may be retarded, thus the reaction temperature was raised to 80 °C. In addition, a more sterically bulky alkyne partner was used to hinder the cyclotrimerisation pathway. Nonetheless, *β*-ketosulfonamide **128** did not form (Table 3.3, entry 2). Use of alternative diphosphine ligands also failed to produce the required enone (Table 3.3, entries 3 and 4). Unfortunately, no additional conditions were examined owing to time limits resulting from the Covid-19 pandemic.

Table 3.3 Hydroacylation of *β*-formyl sulfonamides with terminal alkynes



122c **128** *not observed* **129a** **129b**

Entry	R	Ligand	Temperature/ °C	122c:129a:129b[a]
1	C_6H_{13}	DPEPhos	55	6.5:2.2:1
2	Cy	DPEPhos	80	14.3:1.3:1
3	Cy	dcpe	80	60:10.2:1
4	Cy	BINAP	80	6.7:1:1.4

[a]ratio determined by ^{1}H NMR spectra of the crude reaction mixtures.

3.4 Summary

In conclusion, we have developed a route to novel monosubstituted *β*-formyl sulfonamides and tested their use, together with analogous sulfones, in Rh(I)-catalysed hydroacylation. Our preliminary experiments suggest the directing character of sulfone and sulfonamide groups in intermolecular hydroacylation is inferior to previously known tethers. This was evident from the detection of cyclotrimerisation by-products under the conditions examined. Further development of the catalyst system could promote sulfonyl-directed hydroacylation and yield *β*-keto- sulfones and sulfonamides.

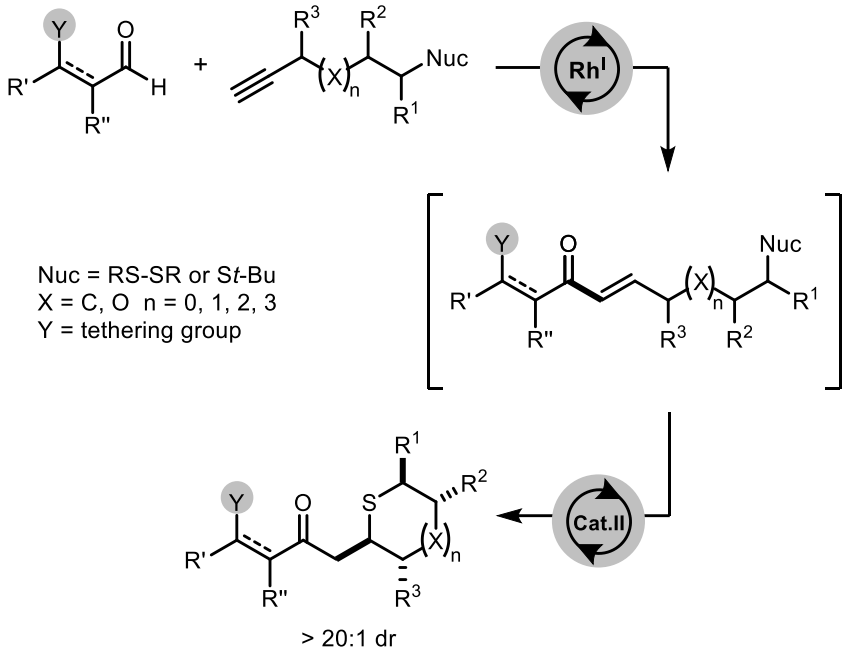
Chapter 4

Conclusions and future work

In recent times, hydroacylation has been established as a versatile C-C bond forming tool for the assembly of diverse ketones. This thesis has outlined two protocols that further endeavour to enhance the utility of chelate-controlled Rh-catalysed hydroacylation. The first procedure enables construction of fully saturated *S*-heterocycles. The second method exploits new synthetically desirable chelating groups. From the research conducted the following can be concluded:

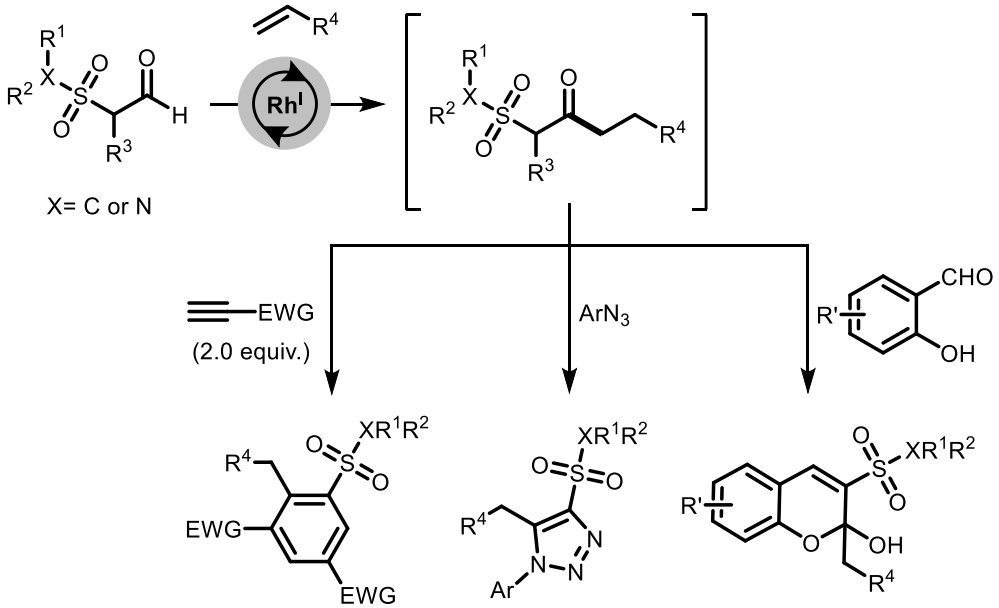
a) Synthesis of saturated *S*-heterocycles *via* hydroacylation

To the best of our knowledge, we have reported the first use of disulfide alkynes in Rh(I)-catalysed hydroacylation using a robust and highly selective rhodium(I)/dcpe catalyst. This catalyst was also employed in an efficient tandem hydroacylation/conjugate addition sequence that delivered a broad scope of substituted cyclic sulfides in good to excellent yields. Moderate diastereoselectivity was achieved and thietane products were inaccessible. Furthermore, a medicinally relevant *bis*-heterocyclic motif has been prepared by modular functionalisation of a thiane product. Future work includes the extension of this one-pot transformation to the synthesis of larger, 7- and 8-membered, sulfur rings. This would improve the generality of the methodology. It would also be beneficial to design a method to make diastereomically pure sulfur heterocycles. Such an approach may entail dual catalysis and would expand the efficiency of the reaction.



b) *β*-sulfonyl aldehydes as substrates for hydroacylation

Our initial investigations show *β*-sulfonyl aldehydes are not successful chelating groups in hydroacylation. Future work should explore further optimisation of this reaction. Particular attention should be paid to elucidating effective ligands, temperatures, and solvents. Moreover, the synthetic utility of this coupling should be broadened by inducing cyclisation of *β*-sulfonyl ketone products from alkene hydroacylation, to give various heterocycles.



Chapter 5

Experimental Data and Procedures

5.1 General considerations

All reactions were performed in oven-dried glassware, under argon or nitrogen, using standard Schlenk techniques. Heating was performed using DrySyns. Unless otherwise stated, solvents and reagents were supplied by Sigma Aldrich, FluoroChem, Alfa Aesar or Acros Organics. Petrol refers to the fractions of petroleum ether that boil between 40 – 60 °C. DCE and acetone were dried over Drierite™ overnight, distilled at atmospheric pressure, and degassed with argon before use. Anhydrous THF, CH_2Cl_2, DMF, Et_2O, MeCN and 1,4-dioxane were obtained by passing through anhydrous alumina columns, using an Innovative Technology Inc. PS-400-7 SPS. Potassium hydroxide, sodium hydroxide and sodium thiosulfate were ground to powders, using a pestle and mortar before use.

Reactions were monitored by analytical Thin Layer Chromatography (TLC), using Merck aluminium silica gel 60 F254 pre-coated plates. Spots were visualised under UV light (245 nm) or stained with vanillin, *p*-anisaldehyde or potassium permanganate solution. Normal phase flash chromatography was carried out with Fluorochem matrix 60 silica, under a positive pressure of nitrogen, using the specified eluent. All infrared data were run neat on a Bruker Tensor 27 FT-IR spectrometer, with adsorptions reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius on the Stuart Scientific Melting Point Apparatus SMP1 and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVIII400 (400 MHz) using the residual solvent signal as an internal standard ($CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm). ^{19}F spectra were recorded on 400 MHz spectrometers at 377 MHz. Chemical shifts (δ) are cited in ppm with multiplicities

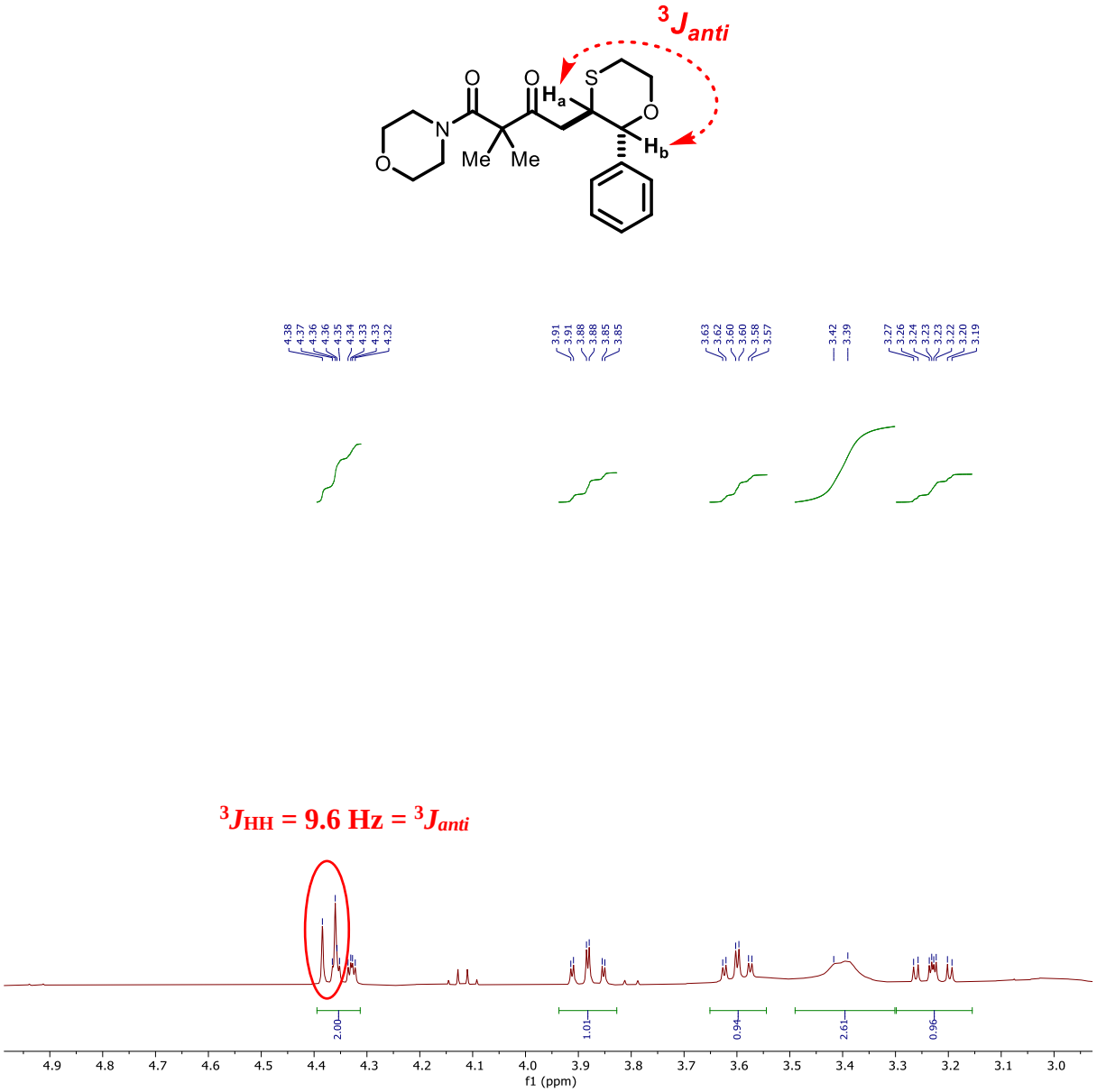
reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br, broad; bs, broad singlet etc. All coupling constants (*J* values) were reported in Hertz (Hz) rounded to the nearest 0.5 Hz. Spectra were assigned by use of chemical shifts, coupling constants, together with COSY, HSQC and HMBC experiments.

Low resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Thermo Scientific Exactive Mass Spectrometer (using a Waters Equity autosampler and pump) for electrospray ionisation (ESI). The m/z values are recorded in Daltons (Da) to one and five decimal place(s) for low and high resolution spectra respectively. For HR mass spectra the mass calculated from the monoisotopic molecular formula was compared to the mass found, and values are within an error of 5 ppm. Where diastereoisomeric products have been isolated as an inseparable mixture, the data for the ^{1}H and ^{13}C NMR major diastereoisomer is reported.

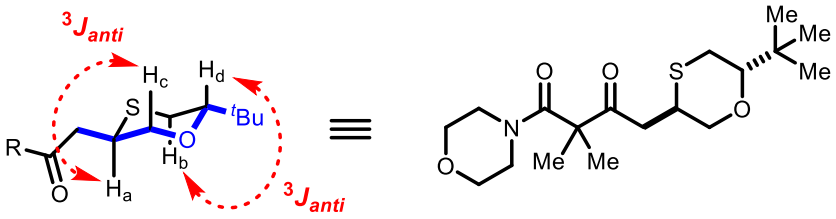
5.2 Chapter 2 Experimental

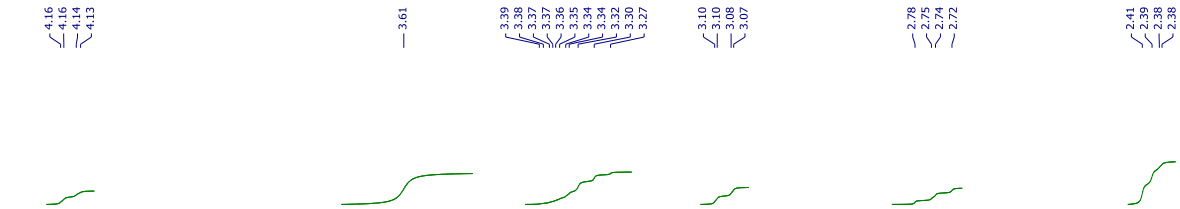
5.2.1 Assignment of Relative Configurations

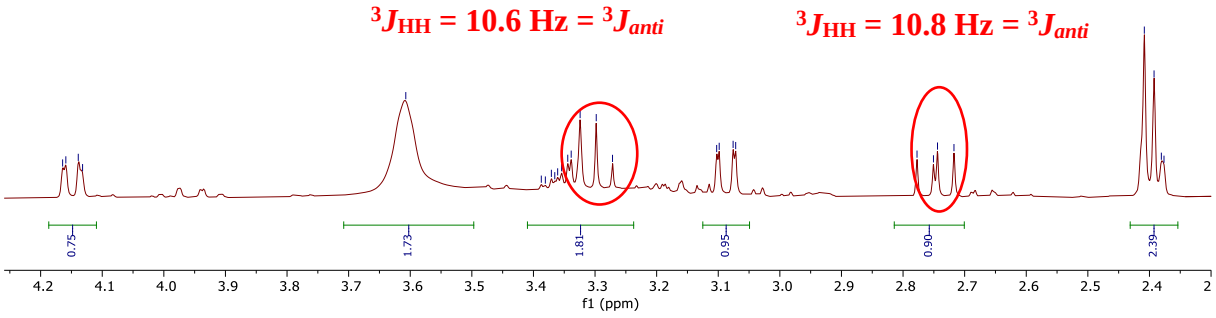
For the R^3 substituted sulfur heterocycles, the vicinal $^3J_{HH}$ couplings in product **83r** were used to confirm the relative configuration. The value of the coupling between protons H_a and H_b was measured as 9.6 Hz. This suggests that an *anti* relative configuration is adopted at this position.



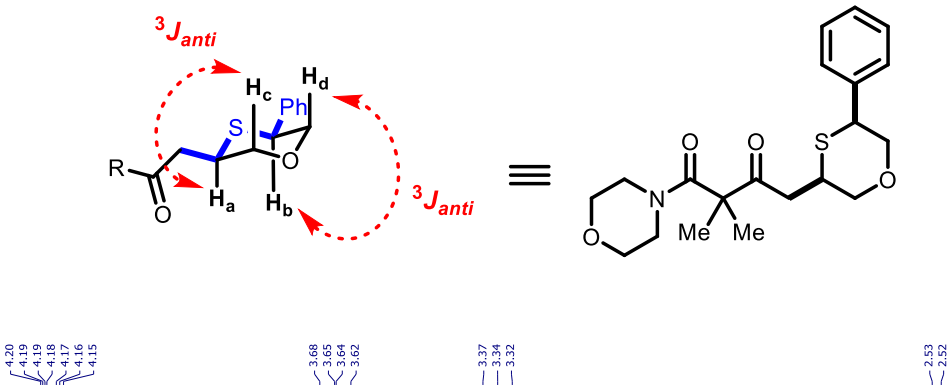
The relative configuration for R^2 substituted sulfur heterocycles was deduced by the vicinal $^3J_{HH}$ couplings in product **83s**. The coupling value between protons H_a and H_c is 10.6 Hz, and a coupling value of 10.8 Hz is present between protons H_b and H_d. Thus, we presume that an equatorial-equatorial relationship exists between the ring substituents in major diastereoisomer **83s**, leading to and *anti* relative configuration.

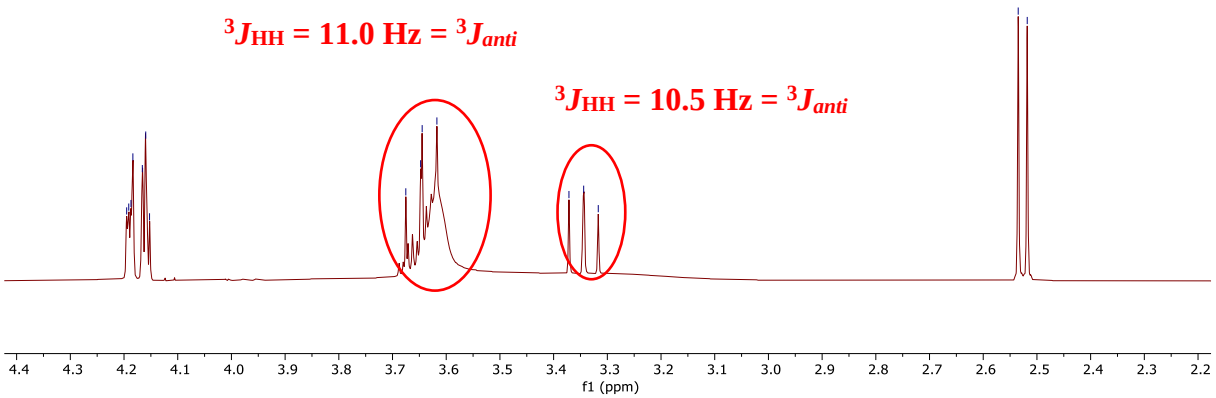






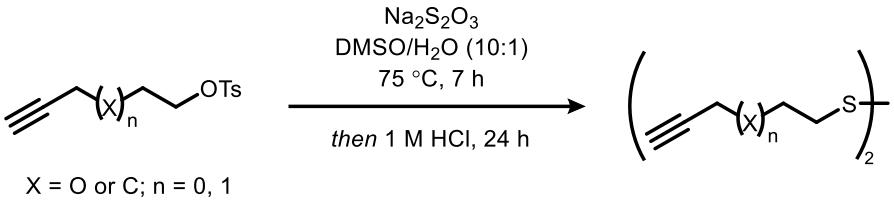
For the R^1 substituted *S*-heterocycle **83y**, the $^3J_{HH}$ coupling value between protons H_a and H_c is 11.0 Hz, and a coupling value of 10.5 Hz is present between protons H_b and H_d. The coupling values are similar in magnitude to those of R^2 substituted product **83s**. This suggests that methylene protons H_c and H_d are *anti* to methine protons H_a and H_b. Thus, an equatorial-equatorial relationship must exist between the ring substituents in the major diastereoisomer of **83y**, leading to a *syn* relative configuration.





5.2.2 Synthesis of Alkyne substrates

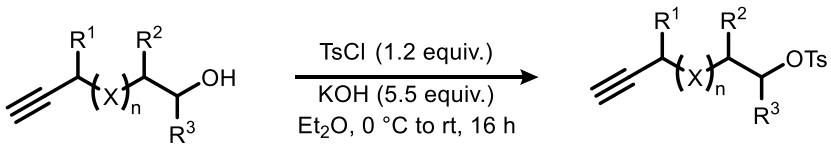
General procedure A: Synthesis of disulfides with DMSO oxidant



X = O or C; n = 0, 1

According to a modified procedure,[183] to a pre-dried flask was added a given tosylated alkynol (1.1 equiv.) and powdered $Na_2S_2O_3 \cdot 5H_2O$ (1.0 equiv.). Dry DMSO (10 mL) and water (1 mL) were introduced. The solution was stirred under nitrogen at 75 °C for 7 h. 1M HCl was added until pH 2 was reached (measured by litmus paper), and the solution heated overnight. Upon cooling to room temperature, H_2O (10 mL) was introduced. The mixture was then extracted with 1:1 hexane/EtOAc (5 × 20 mL). The combined organics were dried over anhydrous magnesium sulphate, and then concentrated *in vacuo*.

General procedure B: Tosylation of alkynols Method 1

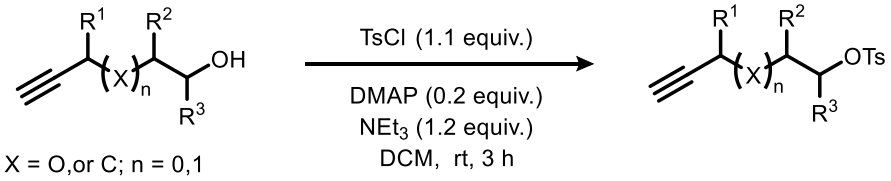


X = O,N or C; n = 0, 1

According to a modified literature procedure,[222] tosyl chloride (1.2 equiv.) was added to an oven dried flask followed by anhydrous diethyl ether. A given alkynol (1.0 equiv.) was introduced and the solution cooled to 0 °C. Powdered potassium hydroxide (5.5 equiv.) was then added in portions. The solution was allowed to warm to room temperature and stirred under a nitrogen atmosphere overnight. Upon completion, the suspension was added to ice

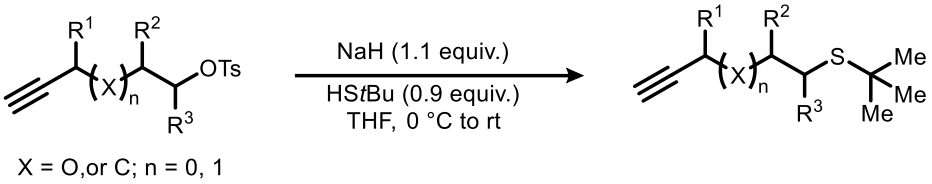
water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product.

General procedure C: Tosylation of alkynols Method 2



According to a modified literature procedure,[223] a given alkynol (1.0 equiv.), DMAP (0.2 equiv.), and TsCl (1.1 equiv.) were dissolved in CH_2Cl_2. Anhydrous NEt_3 (1.2 equiv.) was then introduced, and the solution stirred at room temperature for 3 h (unless otherwise stated). Sat. aq. NH_4Cl (10 mL) was then added, and the mixture extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product.

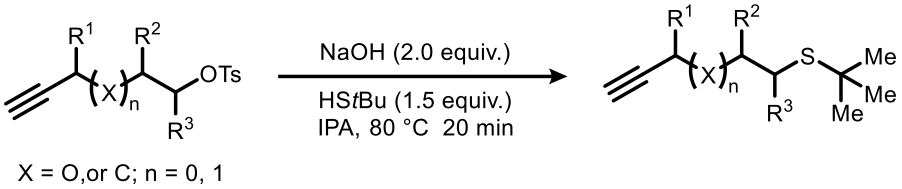
General procedure D: Thiolation of tosylated compounds Method 1



To a pre-dried flask was added NaH (60% dispersion in mineral oil, 1.1 equiv.) and THF. The suspension was then cooled to 0 °C. *Tert*-Butylthiol (0.9 equiv.) was then introduced, and the mixture stirred for 10 min. Next, a solution of a given tosylated alkynol (1.0 equiv.) in THF was added to the suspension. Upon completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure. The crude mixture was then dissolved in Et_2O (20 mL), then sequentially washed with water (2 × 20 mL) and sat. aq. $NaHCO_3$

(1 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product.

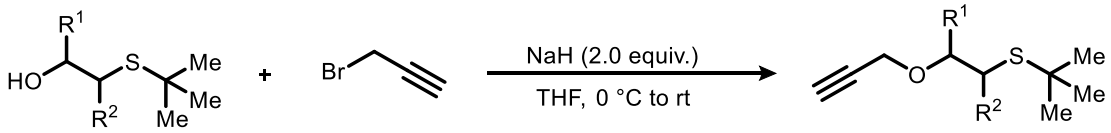
General procedure E: Thiolation of tosylated compounds Method 2



X = O,or C; n = 0, 1

According to a modified literature procedure,[224] powdered NaOH (2.0 equiv.), isopropanol and *tert*-butylthiol (1.5 equiv.) were added to a pre-dried flask. The suspension was stirred for 10 min, after which a solution of a given tosylated alkynol (1.00 equiv.) in isopropanol was added to the suspension. The mixture was then heated at 80 °C under an argon atmosphere for 20 min (unless otherwise stated). Upon cooling to room temperature, the mixture was diluted with ice water (20 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

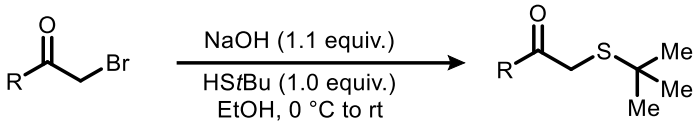
General procedure F: Propargylation of alcohols



To a pre-dried flask was added NaH (60% dispersion in mineral oil, 2.0 equiv) and THF. The suspension was then cooled to 0 °C. A given alcohol (1.0 equiv.) was then introduced and the mixture stirred for 5 min. Next, propargyl bromide (80 w/w in toluene, 1.5 equiv.) was added dropwise over 20 min. The mixture was then warmed to room temperature and stirred until completion as monitored by TLC analysis. The reaction was quenched with

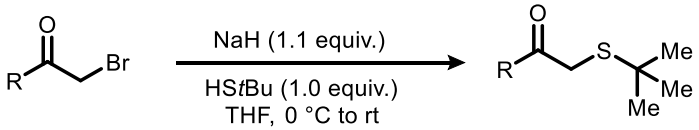
sat. aq. NH_4Cl (10 mL), diluted with water (10 mL) then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

General procedure G: Thiolation of *α*-bromo ketones



Powdered NaOH (1.1 equiv.) and ethanol were added to a pre-dried round-bottomed flask. The suspension was then cooled to 0 °C. *tert*-Butylthiol (1.0 equiv.) was then introduced dropwise and the mixture stirred for 10 min. Next, a solution of a given *α*-bromo ketone (1.00 equiv) in ethanol was added to the suspension. The reaction mixture was then stirred at room temperature. Upon completion of the reaction, as indicated by TLC, the solution was diluted with Et_2O (100 mL). The mixture was then washed with water (2 × 20 mL) and sat. aq. $NaHCO_3$ (1 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant crude residue was then carried on to the next step.

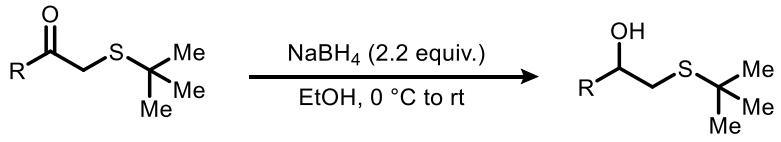
General procedure H: Thiolation of *α*-bromo ketones method 2



To a pre-dried flask was added NaH (60% dispersion in mineral oil, 1.1 equiv.) and THF. The suspension was then cooled to 0 °C. *Tert*-Butylthiol (1.0 equiv.) was then introduced, and the mixture stirred for 10 min. Next, a solution of a given *α*-bromo ketone (1.0 equiv.) in THF was added to the suspension. Upon completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure. The crude mixture was then dissolved in

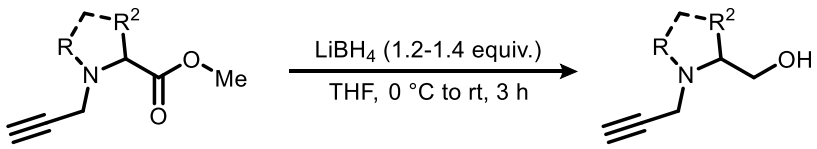
Et_2O (100 mL), then sequentially washed with water (2 × 20 mL) and sat. aq. $NaHCO_3$ (1 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product.

General Procedure I: $NaBH_4$ reduction of *α*-sulfido ketones



$NaBH_4$ (2.2 equiv.) and ethanol were added to a pre-dried round-bottomed flask. The suspension was then cooled to 0 °C. A solution of the crude ketone (1.0 equiv.) (from **general procedure G**) dissolved in ethanol was then introduced dropwise. The mixture was then warmed to room temperature and stirred under a nitrogen atmosphere. Upon completion of the reaction, as indicated by TLC, the reaction was quenched by dropwise addition of 1 M aq. HCl (10 mL) at 0 °C. The solution was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant crude residue was used, without further purification, in the next step.

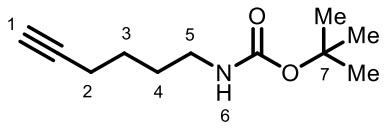
General Procedure J: Methyl Ester Reductions with $LiBH_4$



According to a literature procedure.[225] To solution of methyl ester (1.0 equiv.) in anhydrous THF under argon at 0 °C was added dropwise $LiBH_4$ solution (2 M in THF, 1.2-1.4 equiv.). The mixture was allowed to warm to room temperature and stirred for 3 h. Upon completion of the reaction, as indicated by TLC, the mixture was concentrated *in vacuo*. H_2O was added to the resulting residue, and the mixture was extracted with EtOAc (3 × 20 mL). The

combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product.

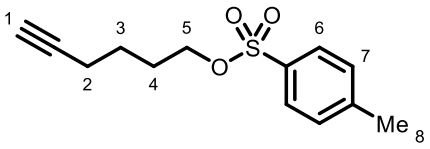
tert-Butyl hex-5-yn-1-ylcarbamate (80b)



According to a modified procedure,[226] *N*-(5-hexynyl)phthalimide (0.23 g, 1.0 mmol) was dissolved in THF (12 mL) and hydrazine hydrate (0.62 mL, 20 mmol) was introduced. The solution was refluxed for 3 h. The reaction was then cooled to 8 °C and filtered. The filtrate was concentrated *in vacuo*, yielding the crude amine as yellow liquid. The crude mixture was dissolved in THF (5 mL) and water (5 mL), then $NaHCO_3$ (0.11 g, 1.3 mmol) was added. The solution was cooled to 0 °C and Boc_2O (2 M in THF, 0.18 mL, 0.8 mmol) was introduced. The solution was stirred at 0 °C for 15 min then allowed to warm to r.t. After 2.5 h at r.t. the reaction was diluted with EtOAc (3 × 20 mL), then washed with water (20 mL), aq sat. $NaHCO_3$ (20 mL) and brine (20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (2:1 Petrol:EtOAc) yielded title compound **80b** (0.13 g, 0.66 mmol, 82%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 3.18-3.01 (2H, m, C(5)H_2), 2.19 (2H, td, J = 6.7, 2.6 Hz, C(2)H_2), 1.93 (1H, t, J = 2.6 Hz, C(1)H), 1.64-1.45 (4H, m, C(3 and 4)H_2), 1.41 (s, 9H C(7)H_3); **δ_C** (101 MHz, $CDCl_3$) 156.0, 84.1, 79.1, 68.7, 40.1, 29.2, 28.5, 25.7, 18.2 ; **ν_{max}**/ cm^{-1} 3343, 3307, 2976, 2933, 2866, 1687, 1514, 1454, 1391, 1365, 1272, 1248, 1166, 1099, 1040, 1004, 904. *Data is consistent with literature.*[226]

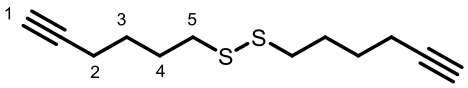
Hex-5-yn-1-yl 4-methylbenzenesulfonate (90a)



Synthesised according to **general procedure B**, using hex-5-ynol (1.7 mL, 15.4 mmol) and diethyl ether (32 mL). Purification by column chromatography (4:1 Hexane:EtOAc) yielded title compound **90a** (3.8 g, 15.1 mmol, 99%) as a viscous colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.3 Hz, *Ar*), 7.35 (2H, d, *J* = 7.9 Hz, *Ar*), 4.06 (2H, t, *J* = 6.3 Hz, C(5)H_2), 2.45 (3H, s, C(8)H_3), 2.16 (2H, td, *J* = 6.9, 2.7 Hz, C(2)H_2), 1.92 (1H, t, *J* = 2.6 Hz, C(1)*H*), 1.81-1.74 (2H, m, C(3)H_2), 1.59-1.52 (2H, m, C(4)*H*); **δ_C** (101 MHz, $CDCl_3$) 144.7, 133.1, 129.8, 127.9, 83.4, 69.9, 68.9, 27.7, 24.2, 21.6, 17.7; **ν_{max}**/ cm^{-1} (neat) 3290, 2955, 2117, 1734, 1598, 1495, 1454, 1434, 1354, 1307, 1291, 1244, 1211, 1188, 1172, 1119, 1097, 1043, 1017, 931; **m/z HRMS** (ESI^+) $C_{13}H_{17}O_3S^+$ $[M+H]^+$ calc. 253.0893 found 253.0865; *Data consistent with literature*[227]

1,2-Di(hex-5-yn-1-yl)disulfide (84a)

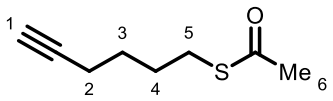


Synthesised according to **general procedure A**, using hex-5-yn-1-yl 4-methylbenzenesulfonate **90a** (2.7 g, 10.5 mmol). Purification by column chromatography (96:4 Hexane:EtOAc) yielded title compound **84a** (0.77 g, 71%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 2.71 (4H, t, *J* = 7.2 Hz, C(5)H_2), 2.23 (4H, td, *J* = 7.0, 2.7 Hz, C(2)H_2), 1.96 (2H, t, *J* = 2.7 Hz, C(1)*H*), 1.82 (4H, m, C(4)H_2), 1.70-1.58 (4H, m, C(3)H_2); **δ_C**

(101 MHz, $CDCl_3$) 83.9, 68.6, 38.5, 28.1, 27.1, 18.0 ; ν_{max}/ cm^{-1} (neat) 3293, 2936, 2861, 2116, 1455, 1432, 1413, 1350, 1326, 1293, 1256, 1236, 1202, 1036; **m/z HRMS** (ESI^+) $C_{12}H_{19}S_2$ $[M+H]^+$ calc. 227.0922 found 227.0926.

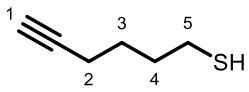
***S*-(Hex-5-yn-1-yl) ethanethioate (86)**



Prepared according to a modified procedure. 6-Chlorohex-1-yne (0.6 mL, 5.0 mmol) was dissolved in anhydrous DMF (5 mL) followed by addition of potassium thioacetate (900 mg, 6.0 mmol). The mixture was stirred at 50 °C under an atmosphere of nitrogen for 3.5 h. Upon cooling to room temperature, the solution was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (5 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (9:1 Petrol:Et_2O) afforded alkyne **86** (0.65 g, 4.16 mmol, 83%) as an orange/red oil.

δ_H (400 MHz, $CDCl_3$) 2.82 (2H, t, *J* = 7.1 Hz, C(5)H_2), 2.26 (3H, s, C(6)H_3), 2.15 (2H, td, *J* = 6.9, 2.7 Hz, C(2)H_2), 1.90 (1H, t, *J* = 2.6 Hz, C(1)*H*), 1.68-1.58 (2H, m, C(4)H_2), 1.58-1.48 (2H, m, C(3)H_2); δ_C (101 MHz, $CDCl_3$) 195.7, 83.8, 68.7, 30.6, 28.5, 28.5, 27.3, 17.9; ν_{max}/ cm^{-1} (neat) 3293, 2940, 2863, 2117, 1687, 1431, 1354, 1297, 1264, 1132, 1107, 954. *Data is consistent with literature*[228]

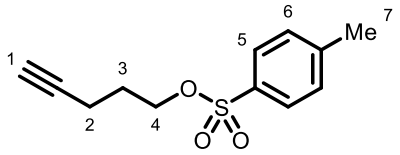
Hex-5-yne-1-thiol (87)



Prepared according to a modified literature procedure.[228] In a pre-dried flask, anhydrous THF (13 mL) was cooled to 0 °C and $LiAlH_4$ (19.9 mL, 1 M THF) introduced. The solution was stirred for 5 min then *S*-(hex-5-yn-1-yl) ethanethioate **86** (2.34 g, 15.0 mmol) was added dropwise. The mixture was gradually warmed to room temperature with stirring under an atmosphere of nitrogen. After 20 min, the reaction was cooled to 0 °C and quenched with slow addition of water (10 mL). Next, 20 mL of 1 M HCl was added. The solution was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (98:2 Petrol:EtOAc) yielded title compound **87** (300 mg, 12.3 mmol, 82%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 2.58-2.53 (1H, m, C(5)H_2S), 2.22 (2H, td, *J* = 6.9, 2.6 Hz, C(2)H_2), 1.96 (1H, t, *J* = 2.6 Hz, C≡C(1)*H*), 1.78-1.69 (2H, m, C(4)H_2), 1.68-1.60 (2H, m, C(3)H_2), 1.35 (1H, t, *J* = 7.8 Hz, S*H*); **δ_C** (101 MHz, $CDCl_3$) 83.9, 68.6, 32.9, 27.0, 24.1, 17.9; **ν_{max}**/ cm^{-1} (neat) 3293, 2933, 1433, 1264. *Data is consistent with literature.*[228]

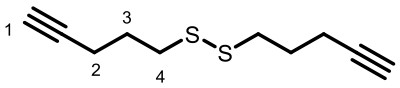
Pent-4-yn-1-yl 4-methylbenzenesulfonate (90b)



Synthesised according to **general procedure B**, using pent-4-ynol (1.9 mL, 20 mmol) and diethyl ether (20 mL). Purification by column chromatography (4:1 Hexane:EtOAc) yielded title compound **90b** (4.79 g, 20 mmol, >99%) as a pale brown oil.

δ_H (400 MHz, $CDCl_3$) 7.86-7.73 (2H, m, *Ar*), 7.40-7.31 (2H, m, *Ar*), 4.15 (2H, t, *J* = 6.1 Hz, C(4)H_2), 2.45 (3H, s, C(7)H_3), 2.26 (2H, td, *J* = 6.9, 2.6 Hz, C(2)H_2), 1.92-1.81 (3H, m, C(1)*H* and C(3)H_2); **δ_C** (101 MHz,$CDCl_3$) 144.7, 133.0, 129.8, 127.9, 82.1, 69.4, 68.7, 27.7, 21.6, 14.7; **ν_{max}**/ cm^{-1} (neat) 3289, 3065, 2925, 2119, 1598, 1495, 1435, 1355, 1307, 1291, 1210, 1188, 1173, 1120, 1096, 1011, 973, 934, 920; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{12}H_{14}O_3{}^{23}NaS^+$ calc. 261.0555, found 261.0556. *Data is consistent with literature*.[229]

1,2-Di(pent-4-yn-1-yl)disulfide (84b)

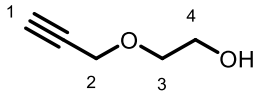


Synthesised according to **general procedure A**, using pent-4-yn-1-yl 4-methylbenzenesulfonate **90b** (2.40 g, 10 mmol). Purification by column chromatography (96:4 hexane:EtOAc) yielded title compound **84b** (0.28 g, 1.41 mmol, 28%) as a yellow/orange oil.

δ_H (400 MHz, $CDCl_3$) 2.78 (4H, m, C(4)H_2), 2.32 (4H, td, *J* = 6.9, 2.6 Hz, C(2)H_2), 1.96 (2H, t, *J* = 2.7 Hz, C(1)*H*), 1.91 (4H, p, *J* = 7.0 Hz, C(3)H_2); **δ_C** (101 MHz,$CDCl_3$) 83.2, 69.0, 37.4, 27.6, 17.1; **ν_{max}**/ cm^{-1} (neat) 3293, 2936, 2856, 2117, 1430, 1343, 1323, 1277,

1250, 1209, 1192, 1141, 1031, 1011; **m/z HRMS** (ESI^+) [M + H] for $C_{10}H_{15}S_2$ $[M+H]^+$ calc. 199.0610 found 199.0612. *Data is consistent with literature*.[230]

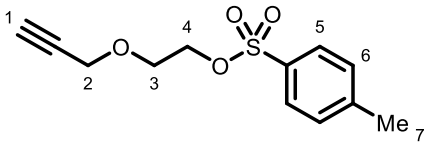
2-(Prop-2-yn-1-yloxy)ethan-1-ol (100d)



According to a modified procedure,[222] ethyleneglycol (1.1 mL, 20 mmol) was introduced into distilled water (0.7 mL). The suspension was cooled to 0 ◦C and KOH (0.46 g, 8.0 mmol) was added. Propargyl bromide (80 wt% in toluene, 0.3 mL, 4.0 mmol) was added dropwise and the mixture brought to room temperature and stirred for 24 h. Water (20 mL) was introduced, and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography (2:1 EtOAc:Petrol), afforded ether **100d** (0.14 g, 14 mmol, 28 %) as a colourless liquid.

δ_H (400 MHz, $CDCl_3$) 4.15 (2H, d, *J* = 2.4 Hz, C(2)H_2), 3.73-3.68 (2H, m, C(4)H_2), 3.60-3.57 (2H, m, C(3)H_2), 2.41 (1H, t, *J* = 2.4 Hz, C(1)*H*), 2.40-2.36 (1H, bs, O*H*); **δ_C** (101 MHz, $CDCl_3$) 79.4, 74.7, 71.2, 61.6, 58.4; **ν_{max}**/ cm^{-1} (neat) 3288, 2867, 2115, 1443, 1354, 1277, 1106, 1066, 1028, 952, 919; **m/z HRMS** (ESI^+) [M + H] for $C_5H_7O_2$ $[M–H]^-$ calc. 99.0448, found 99.0451. *Data is consistent with literature*.[222]

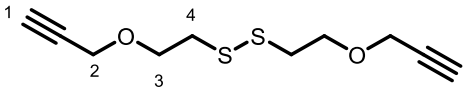
2-(Prop-2-yn-1-yloxy)ethyl 4-methylbenzenesulfonate (90c)



Synthesised according to **general procedure B**, using 2-(prop-2-yn-1-yloxy)ethan-1-ol **100d** (1.2 g, 12 mmol) and diethyl ether (19.5 mL). Purification by column chromatography (7:3 Petrol:EtOAc) yielded title compound **90c** (2.9 g, 11.4 mmol, 95%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.83-7.77 (2H, m, *Ar*), 7.38-7.31 (2H, m, *Ar*), 4.21-4.17 (2H, m, C(4)H_2), 4.12 (2H, d, *J* = 2.4 Hz, C(2)H_2), 3.75-3.70 (2H, m, C(3)H_2), 2.45 (3H, s, C(7)H_3), 2.42 (1H, t, *J* = 2.4 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 144.8, 132.9, 129.8, 128.0, 78.9, 75.0, 68.8, 67.1, 58.3, 21.6; **ν_{max}**/ cm^{-1} (neat) 3654, 3283, 2980, 2885, 2118, 1597, 1495, 1449, 1352, 1307, 1291, 1243, 1211, 1189, 1173, 1095, 1017, 992, 958, 916; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{12}H_{14}O_4{}^{23}NaS^+$ calc. 277.0505, found 277.0505. *Data is consistent with literature.*[222]

1,2-Bis(2-(prop-2-yn-1-yloxy)ethyl)disulfane (84c)

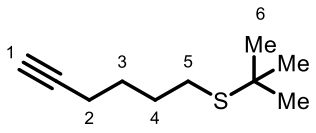


Synthesised according to **general procedure A**, using 2-(prop-2-yn-1-yloxy)ethyl 4-methylbenzenesulfonate **90c** (1.3 g, 5.0 mmol). Purification by column chromatography (4:1 hexane:EtOAc) yielded title compound **84c** (0.46 g, 1.99 mmol, 79%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.19 (4H, dd, *J* = 2.4, 0.8 Hz, C(2)H_2), 3.80 (t, *J* = 6.5 Hz, 4H, C(4)H_2), 2.92 (4H, t, *J* = 6.5 Hz, C(3)H_2), 2.46 (2H, t, *J* = 2.4 Hz, C(1)*H*); **δ_C** (101 MHz,

$CDCl_3$) 79.4, 74.8, 68.1, 58.2, 38.4; **ν_{max}**/ cm^{-1} (neat) 3287, 2856, 2115, 1732, 1468, 1441, 1387, 1353, 1270, 1192, 1087, 1043, 1013, 944; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{10}H_{14}O_2NaS_2$ calc. 253.0327 found 253.0327.

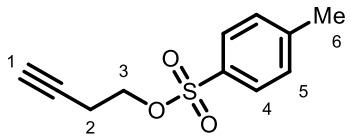
***tert*-Butyl(hex-5-yn-1-yl)sulfide (91a)**



Synthesised according to **general procedure E**, using hex-5-yn-1-yl 4-methylbenzenesulfonate **90a** (760 mg, 3.03 mmol) and IPA (7.5 mL). Purification by column chromatography (96:4 Hexane:EtOAc) yielded title compound **91a** (360 mg, 2.11 mmol, 71%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 2.55 (2H, t, *J* = 7.1 Hz, C(5)H_2), 2.22 (2H, td, *J* = 6.8, 2.6 Hz, C(2)H_2), 1.94 (1H, t, *J* = 2.7 Hz, C(1)*H*), 1.78-1.58 (4H, m, C(3)H_2 and C(4)H_2), 1.32 (9H, s, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 84.1, 68.5, 41.8, 30.9, 28.8, 27.8, 27.7, 18.0; **ν_{max}**/ cm^{-1} (neat) 3298, 2942, 2862, 2118, 1471, 1458, 1390, 1363, 1327, 1296, 1263, 1239, 1163, 1050, 933; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{19}S^+$ calc. 171.1202, found 171.1205. *Data is consistent with literature.*[224]

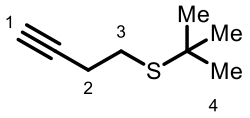
But-3-yn-1-yl 4-methylbenzenesulfonate(90d)



Synthesised according to **general procedure B**, using 3-butyn-1-ol (1.51 mL, 20 mmol) and diethyl ether (32 mL). Purification by column chromatography (100:0 to 90:10 Hexane:Et_2O) yielded title compound **90d** (4.27 g, 19 mmol, 95%) as a viscous colourless oil.

δ_H (400 MHz, $CDCl_3$)7.80 (2H, d, *J* = 8.3 Hz, *Ar*), 7.35 (2H, d, *J* = 8.1 Hz, *Ar*), 4.10 (2H, t, *J* = 7.1 Hz, C(3)H_2), 2.55 (2H, td, *J* = 7.1, 2.7 Hz, C(2)H_2), 2.45 (3H, s, C(6)H_3), 1.97 (1H, t, *J* = 2.7 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 145.1, 133.0, 130.0, 128.1, 78.5, 70.9, 67.5, 21.7, 19.6; **ν_{max}**/ cm^{-1} (neat) 3656, 3290, 2980, 2889, 1733, 1598, 1494, 1462, 1356,1307,1292, 1251,1221, 1188,1173, 1121, 1096, 1072, 1020, 974, 901; **m/z HRMS** (ESI^+) $C_{11}H_{12}O_3NaS$ $[M+Na]^+$ calc. 247.0399 found 247.0400. *Data consistent with literature.*[231]

But-3-yn-1-yl(tert-butyl)sulfane (91b)

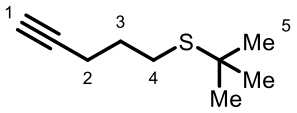


Synthesised according to **general procedure E**, using but-3-yn-1-yl 4-methylbenzenesulfonate **90d** (4.26 g, 18.9 mmol) and IPA (47 mL), with heating for 1 h. Purification by column chromatography (98:2 Hexane:EtOAc) yielded title compound **91b** (0.91 g, 6.37 mmol, 34%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 2.71 (2H, t, *J* = 7.6 Hz, C(3)H_2), 2.45 (2H, td, *J* = 7.7, 2.6 Hz, C(2)H_2, 2.03 (1H, td, *J* = 2.6, 0.6 Hz, C(1)*H*), 1.33 (s, 9H, C(4)H_3); **δ_C** (101 MHz, $CDCl_3$) 83.0, 69.3,

42.6, 31.1, 27.5, 20.2; **ν_{max}**/ cm^{-1} (neat) 3658, 3297, 2961, 2941, 2900, 2864, 2366, 2119, 1739, 1472, 1459, 1390, 1364, 1325, 1283, 1221, 1162, 1073, 1028, 960; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{15}S^+$ calc. 143.0889, found 143.0890.

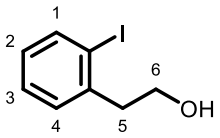
***tert*-Butyl(pent-4-yn-1-yl)sulfide (91c)**



Synthesised according to **general procedure E**, using pent-4-yn-1-yl 4-methylbenzenesulfonate **90b** (700 mg, 3.03 mmol) and IPA (7.5 mL), with heating for 30 min. Purification by column chromatography (100% Hexane) yielded title compound **91c** (240 mg, 1.51 mmol, 51%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 2.64 (2H, t, *J* = 7.3 Hz, C(4)H_2), 2.32 (2H, dd, *J* = 6.9, 2.7 Hz, C(2)H_2), 1.97 (1H, t, *J* = 2.7 Hz, C(1)*H*), 1.83-1.76 (2H, m, C(3)H_2), 1.33 (9H, s, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 83.7, 68.9, 42.2, 31.1, 28.8, 27.3, 17.9; **ν_{max}**/ cm^{-1} (neat) 3301, 2959, 2941, 2926, 2863, 2118, 1472, 1459, 1431, 1390,1364, 1346, 1326, 1281, 1258, 1163, 1024, 932; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{17}S^+$ calc.157.1045, found 157.1047.

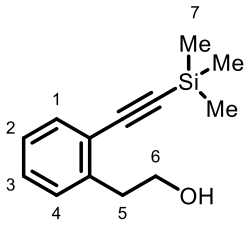
2-(2-Iodophenyl)ethan-1-ol (130)



According to a modified procedure,[232] 2-(2-iodophenyl)acetic acid (2.62 g, 10 mmol) was dissolved in THF (16 mL) and the solution cooled to 10 °C. $NaBH_4$ (757 mg , 20 mmol) was introduced followed by $BF_3{\cdot}OEt_2$ (2.5 mL, 20 mmol) and the solution stirred at 10 °C for 3 h. The reaction mixture was then allowed to warm to room temperature and left stirring overnight, unless otherwise stated. The reaction was then quenched by addition of water (20 mL) and MeOH (20 mL). The resulting mixture was extracted with Et_2O (4 × 30 mL) and washed with brine (20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (7:3 Pentane:EtOAc) yielded title compound **130** (2.36 g, 9.51 mmol, 95%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.90-7.70 (1H, m, *Ar*), 7.32-7.21 (2H, m, *Ar*), 6.95-6.86 (1H, m, *Ar*), 3.84 (2H, t, *J* = 6.8 Hz, C(6)H_2), 3.00 (2H, t, *J* = 6.8 Hz, C(5)H_2), 1.66 (bs, 1H, O*H*); **δ_C** (101 MHz, $CDCl_3$) 141.2, 139.8, 130.4, 128.4, 128.4, 100.9, 62.3, 43.8; **ν_{max}**/ cm^{-1} (neat) 3311, 2949, 2875, 1585, 1561, 1465, 1434, 1161, 1115, 1040, 1007; **m/z HRMS** (ESI^+) $[M + \text{radical ion}]^+$ $C_8H_9IO^+$ calc. 247.9693, found 247.9698. *Data is consistent with literature.*[232]

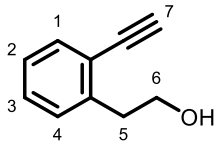
2-(2-((Trimethylsilyl)ethynyl)phenyl)ethan-1-ol (131)



According to a modified procedure,[233] compound **130** (2.31 g, 9.3 mmol) was dissolved in anhydrous NEt_3 (27 mL). Trimethylsilyl acetylene (1.7 mL, 12 mmol), $PdCl_2(PPh_3)_2$ (0.13 g, 0.19 mmol) and CuI (7.0 mg, 9.3 mmol) were added to the solution and the mixture heated at 30 °C for 3 h, under an atmosphere of argon. sat. aq. NH_4Cl (20 mL) was then added, and the mixture extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (3:2 Pentane:EtOAc) yielded title compound **131** (1.56 g, 7.1 mmol, 76%) as a brown oil.

δ_H (400 MHz, $CDCl_3$) 7.49 (1H, dd, *J* = 7.6, 0.8 Hz, *Ar*), 7.32-7.23 (2H, m, *Ar*), 7.20 (1H, td, *J* = 7.3, 1.9 Hz, *Ar*), 3.94 (2H, t, *J* = 6.5 Hz C(6)H_2), 3.08 (2H, t, *J* = 6.5 Hz, C(5)H_2), 1.63 (1H, bs, O*H*), 0.28 (s, 9H, SiC(7)H_3); **δ_C** (101 MHz, $CDCl_3$) 141.0, 132.8, 129.7, 128.8, 126.5, 123.0, 103.8, 98.5, 62.9, 38.2, 0.1; **ν_{max}**/ cm^{-1} (neat) 3333, 2958, 2154, 1482, 1447, 1249, 1189, 1103, 1042, 946; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{13}H_{18}OSi^+$ calc. 219.1200, found 219.1201. *Data is consistent with literature.*[233]

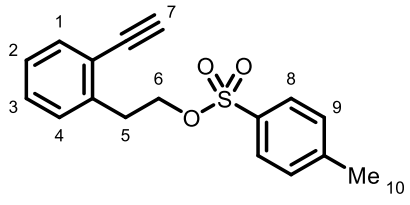
2-(2-Ethynylphenyl)ethan-1-ol (80c)



According to a modified procedure,[234] compound **131** (1.04 g, 4.76 mmol) was dissolved in THF (11 mL). TBAF (1 M in THF, 5.95 mL, 5.95 mmol) was then introduced and the solution stirred at room temperature for 1.5 h. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:1 Petrol:EtOAc) yielded title compound **80c** (482 mg, 3.29 mmol, 69%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* = 7.7, 1.4 Hz, *Ar*), 7.36-7.22 (2H, m, *Ar*), 7.20 (1H, td, *J* = 7.4, 1.7 Hz, *Ar*), 3.91 (2H, t, *J* = 6.7 Hz, C(6)*H_2*), 3.26 (1H, s, C(7)*H*), 3.08 (2H, t, *J* = 6.7 Hz, C(5)*H_2*); **δ_C** (101 MHz, $CDCl_3$) 141.1, 133.2, 129.8, 129.1, 126.6, 122.1, 82.3, 81.1, 63.0, 37.9; **ν_{max}**/ cm^{-1} (neat) 3289, 3065, 2933, 2879, 2102, 1599, 1483, 1446, 1244, 1161, 1101, 1040, 948; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{11}O^+$ calc. 147.0804, found 147.0805. *Data is consistent with literature.*[234]

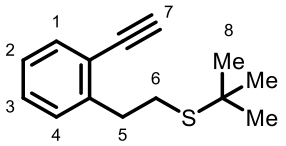
2-Ethynylphenethyl 4-methylbenzenesulfonate (90e)



Synthesised according to **general procedure C**, using alkynol **80c** (480 mg, 3.29 mmol) and CH_2Cl_2 (13.2 mL). Purification by column chromatography (9:1 Petrol:EtOAc) yielded title compound **90e** (562 mg, 1.87 mmol, 57%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.73-7.65 (2H, m, *Ar*), 7.41 (1H, dd, *J* = 7.5, 1.5 Hz, *Ar*), 7.30-7.21 (3H, m, *Ar*), 7.22-7.13 (2H, m, 2H, *Ar*), 4.28 (2H, t, *J* = 7.0 Hz, C(6)H_2), 3.17 (1H, s, C(7)*H*), 3.14 (2H, t, *J* = 7.0 Hz, C(5)H_2), 2.43 (3H, s, C(10)H_3); **δ_C** (101 MHz, $CDCl_3$) 144.6, 138.7, 133.1, 133.1, 130.0, 129.8, 129.1, 127.9, 127.0, 122.0, 81.6, 81.5, 69.6, 34.2, 21.7; **ν_{max}**/ cm^{-1} (neat) 3279, 2960, 1598, 1484, 1448, 1355, 1306, 1292, 1188, 1173, 1096, 1055, 1037, 1019, 963, 903; **m/z LRMS** (ESI^+) 323.0 $[M + Na]^+$.

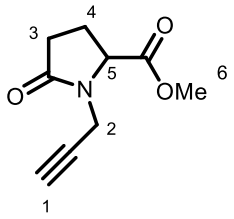
***tert*-Butyl(2-ethynylphenethyl)sulfane (91d)**



Synthesised according to **general procedure E**, using **90e** (542 mg, 3.7 mmol) and IPA (9.25 mL). Purification by column chromatography (9:1 Hexane:EtOAc) yielded title compound **91d** (464 mg, 2.12 mmol, 57%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.54-7.44 (1H, m, *Ar*), 7.33-7.22 (2H, m, *Ar*), 7.18 (1H, m, *Ar*), 3.27 (1H, s, C(7)*H*), 3.08-3.00 (m, 2H, C(5)H_2), 2.86-2.78 (2H, m, C(6)H_2), 1.34 (9H, s, C(8)H_3); **δ_C** (101 MHz, $CDCl_3$) 143.7, 133.1, 129.1, 129.1, 126.4, 121.6, 82.2, 81.1, 42.5, 35.6, 31.1, 29.0; **ν_{max}**/ cm^{-1} (neat) 3294, 2959, 2898, 2862, 2104, 1598, 1482, 1458, 1448, 1390, 1363, 1161, 1087, 1041, 947; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{19}S^+$ calc. 219.2020, found 219.1204.

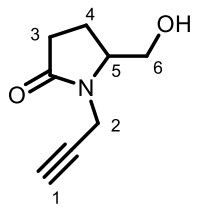
Methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (132)



Prepared according to a modified procedure.[235] To a suspension of solid KOH powder (1.85 g, 33 mmol, 1.1 equiv.) and tetrabutylammonium bromide (1.93 g, 6.0 mmol, 0.2 equiv.) in anhydrous THF (75 mL) was added dropwise a solution of propargyl bromide (80% w/w in toluene, 5.35 mL, 48 mmol, 1.6 equiv.) and methyl 5-oxopyrrolidine-2-carboxylate (3.5 mL, 30 mmol, 1.0 equiv.), in anhydrous THF (75 mL) at room temperature over 1 h. The mixture was then stirred overnight (18 h) before being concentrated *in vacuo*. The residue was diluted in Et_2O (100 mL) and then washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (1:1 to 2:8 Hex:EtOAc) yielded title compound **132** (1.07 g, 5.9 mmol, 20%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.61 (1H, dd, *J* = 17.7, 2.6 Hz, C(2)*H*H), 4.44-4.40 (1H, m, C(5)*H*), 3.78 (3H, s, C(6)H_3), 3.78 (1H, dd, *J* = 17.6, 2.7 Hz, C(2)H*H*), 2.56-2.33 (3H, m, C(3)H_2 and C(4)*H*H), 2.23 (1H, t, *J* = 2.6 Hz, C(1)*H*), 2.15-2.07 (1H, m, C(4)H*H*); **δ_C** (101 MHz, $CDCl_3$) 174.4, 172.0, 77.2, 73.0, 58.3, 52.5, 31.3, 29.3, 22.7; **ν_{max}**/ cm^{-1} (neat) 3271, 2956, 2120, 1737, 1687, 1437, 1412, 1349,1281, 1205, 1179,1152, 1042, 990; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{12}O_3N^+$ calc. 182.0812, found 182.0814.

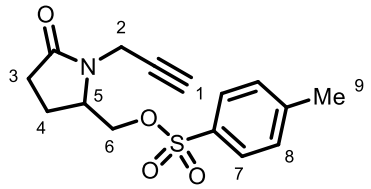
5-(Hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (80d)



Prepared according to **general procedure J**, using methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **132** (0.5 g, 2.76 mmol, 1.0 equiv.), THF (28 mL) and $LiBH_4$ (2 M in THF, 1.65 mL, 3.3 mmol, 1.2 equiv.). Purification by column chromatography (100:0 to 9:1 EtOAc:MeOH) yielded title compound **80d** (0.18 g, 1.17 mmol, 43%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.27-4.07 (2H, m, C(2)H_2), 3.98 (1H, dd, *J* = 12.0, 3.2 Hz, C(6)*H*H), 3.82 (1H, m, C(5)*H*), 3.67 (1H, dd, *J* = 12.0, 3.5 Hz, C(6)H*H*), 2.51 (1H, ddd, *J* = 16.9, 10.2, 6.5 Hz, C(3)*H*H), 2.36 (1H, ddd, *J* = 16.9, 10.2, 6.1 Hz, C(3)H*H*), 2.26 (t, *J* = 2.5 Hz, 1H, C(1)*H*), 2.22-2.06 (1H, m, C(4)*H*H), 2.08-1.90 (1H, m, C(4)H*H*); **δ_C** (101 MHz, $CDCl_3$) 175.6, 78.2, 72.1, 62.4, 59.2, 30.5, 30.4, 20.8; **ν_{max}**/ cm^{-1} (neat) 3387, 3282, 1660, 1420, 1348, 1254, 1185, 1058, 652; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_8H_{12}O_2NaN$ calc. 176.0682, found 176.0684.

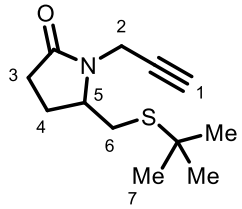
(5-Oxo-1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (90f)



Synthesised according to **general procedure B**, using alkynol **80d** (0.54 g, 3.5 mmol) and diethyl ether (6 mL), with stirring for 2 h. Purification by column chromatography (1:1 to 7:3 EtOAc:Petrol) yielded title compound **90f** (926 mg, 3.07 mmol, 86%) as white crystals.

m.p. 64–65 °C; **δ_H** (400 MHz, $CDCl_3$) 7.83-7.75 (2H, m, *Ar*), 7.40-7.34 (2H, m, *Ar*), 4.47 (1H, dd, *J* = 17.8, 2.6 Hz, C(2)*H*H), 4.21 (1H, dd, *J* = 10.7, 3.7 Hz, C(6)*H*H), 4.11 (1H, dd, *J* = 10.7, 3.6 Hz, C(6)H*H*), 4.05-3.99 (1H, m, C(5)*H*), 3.51 (1H, ddd, *J* = 17.9, 2.5, 1.1 Hz, C(2)H*H*), 2.50-2.39 (4H, m, C(9)H_3 and C(3)*H*H), 2.38-2.28 (1H, m, C(3)*H*H), 2.26-2.11 (2H, m, C(1)*H* and C(4)*H*H), 1.95-1.83 (1H, m, C(4)H*H*); **δ_C** (151 MHz, $CDCl_3$) 174.8, 145.5, 132.6, 130.2, 128.1, 72.9, 68.8, 55.8, 30.4, 29.8, 21.8, 21.1; **ν_{max}**/ cm^{-1} (neat) 3281, 2955, 2364, 2118, 1688, 1597, 1494, 1440, 1415, 1358, 1307, 1293, 1279, 1253, 1211, 1189, 1174, 1120, 1096, 1048, 1019, 991, 950; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{17}NO_4S^+$ calc. 308.0951, found 308.0952.

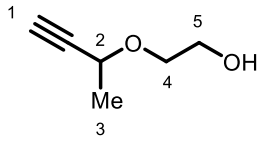
5-((*tert*-Butylthio)methyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (91e)



According to a modified procedure,[224] to a pre-dried flask was added powdered KOH (300 mg, 5.34 mmol, 2.0 equiv.), anhydrous acetonitrile (4.0 mL) and *tert*-butylthiol (0.45 mL, 4.0 mmol 1.5 equiv.). The suspension was stirred for 10 min, after which **90f** (820 mg, 2.67 mmol, 1.0 equiv.) dissolved in acetonitrile (8 mL) was added to the suspension. The mixture was then stirred at room temperature under a nitrogen atmosphere for 16 h. The mixture was next diluted with ice water (20 mL) and then extracted with EtOAc (3 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and then concentrated *in vacuo*. Purification by column chromatography (7:3 to 6:4 Petrol:EtOAc) yielded title compound **91e** (522 mg, 2.32 mmol, 87%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.59 (1H, dd, *J* = 17.7, 2.6 Hz, C(2)*H*H), 4.05-3.95 (1H, m, C(5)*H*), 3.74 (1H, ddd, *J* = 17.8, 2.5, 1.1 Hz, C(2)H*H*), 2.90 (1H, dd, *J* = 12.3, 3.4 Hz, C(6)*H*H), 2.66 (1H, dd, *J* = 12.3, 8.1 Hz, C(6)*H*H), 2.52-2.42 (1H, m, C(3)*H*H), 2.41-2.29 (1H, m, C(3)H*H*), 2.29-2.16 (2H, m, C(1)*H* and C(4)*H*H), 1.97-1.84 (1H, m, C(4)H*H*), 1.34 (9H, s, C(7)H_3); **δ_C** (101 MHz, $CDCl_3$) 174.7, 77.8, 72.4, 56.9, 42.4, 31.7, 31.0, 30.3, 30.0, 23.6; **ν_{max}**/ cm^{-1} (neat) 3310, 2960, 2926, 2901, 2865, 1748, 1696, 1459, 1393, 1364, 1338, 1287, 1229, 1163, 1021; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{12}H_{20}NOS^+$ calc. 226.1260, found 226.1262.

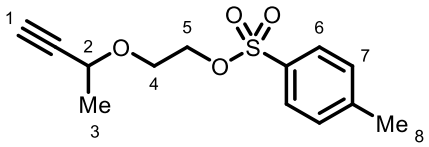
2-(But-3-yn-2-yloxy)ethan-1-ol (100a)



According to a modified procedure,[236] to a pre-dried flask was added but-3-yn-2-ol (1.57 mL, 20 mmol) and powdered KOH (1.35 g, 56.1 mmol). The mixture was cooled to 10 °C and stirred at this temperature for 5 min. 2-bromoethanol (0.71 mL, 10 mmol) was then introduced and the mixture heated at 70 °C for 3 h. The reaction mixture was then added to ice water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:1 Petrol:EtOAc) to yielded title compound **100a** (0.22 g, 1.95 mmol, 19%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.21 (1H, qd, *J* = 6.6, 2.0 Hz, C(2)*H*), 3.84(1H, ddd, *J* = 9.7, 5.4, 3.4 Hz, C(4)*H*H), 3.78-3.74 (2H, m, C(4)H*H*), 3.53 (1H, ddd, *J* = 9.5, 5.6, 3.7 Hz, C(5)H_2), 2.44 (1H, d, *J* = 2.1 Hz, C(1)*H*), 2.01 (1H, bs, O*H*), 1.47 (3H, d, *J* = 6.6 Hz, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 83.6, 73.3, 70.0, 65.7, 61.9, 22.1; **ν_{max}**/ cm^{-1} (neat) 3393, 3282, 2986, 2936, 2872, 2360, 2340, 2109, 1721, 1448, 1373, 1326, 1245, 1110, 1088, 1057, 949; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_6H_{10}O_2{}^{23}Na^+$ calc. 137.0573, found 137.0572.

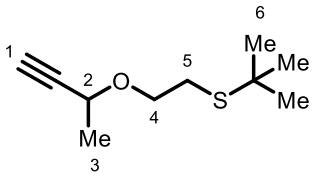
2-(But-3-yn-2-yloxy)ethyl 4-methylbenzenesulfonate (101a)



Synthesised according to **general procedure C**, using alkynol **100a** (200 mg, 1.75 mmol) and CH_2Cl_2 (7 mL), with stirring for 3.5 h. Purification by column chromatography (8:2 Petrol:EtOAc) yielded title compound **101a** (367 mg, 1.37 mmol, 78%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.84-7.77 (2H, m, *Ar*), 7.38-7.30 (2H, m, *Ar*), 4.26-4.07 (3H, m, C(5)H_2 and C(2)*H*), 3.91-3.83 (1H, m, C(4)*H*H), 3.66-3.53 (1H, m, C(4)H*H*), 2.44 (3H, s, C(8)H_3), 2.40 (1H, d, *J* = 2.0 Hz, C(1)*H*), 1.37 (3H, d, *J* = 6.6 Hz, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 144.9, 133.2, 129.9, 128.1, 83.0, 73.6, 69.2, 66.0, 65.6, 21.9, 21.7; **ν_{max}**/ cm^{-1} (neat) 3282, 2988, 2936, 2871, 2109, 1740, 1598,1495, 1450, 1400, 1354, 1291, 1241, 1211, 1189, 1174, 1146, 1118, 1096, 1016, 955, 917; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{13}H_{16}O_4{}^{23}NaS^+$ calc. 291.0662, found 291.0661.

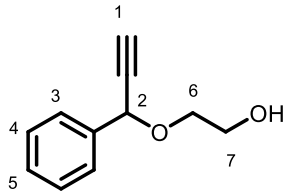
(2-(But-3-yn-2-yloxy)ethyl)(tert-butyl)sulfane (91f)



Synthesised according to **general procedure E**, using **101a** (360 mg, 1.34 mmol) and IPA (3.35 mL), with stirring for 1 h. Purification by column chromatography (98:2 Pentane:Et_2O) yielded title compound **91f** (181 mg, 0.97 mmol, 72%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.20 (1H, qd, *J* = 6.6, 2.0 Hz, C(2)*H*), 3.90-3.81 (1H, m, C(4)*H*H), 3.59-3.47 (1H, m, C(4)H*H*), 2.75 (2H, t, *J* = 7.4 Hz, C(5)H_2), 2.42 (1H, d, *J* = 2.0 Hz, C(1)*H*), 1.45 (3H, d, *J* = 6.6 Hz, C(3)H_3), 1.33 (9H, s, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 83.7, 73.1, 68.7, 65.3, 42.2, 31.1, 28.1, 22.1; **ν_{max}**/ cm^{-1} (neat) 3293, 2961, 2939, 2899, 2864, 2108, 1459, 1390, 1364, 1326, 1290, 1163, 1101, 1071, 1025, 926, 908; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{19}OS^+$ calc.187.1151, found 187.1154.

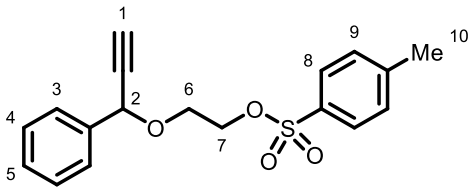
2-((1-Phenylprop-2-yn-1-yl)oxy)ethan-1-ol (100b)



According to a literature procedure,[222] to a round-bottomed flask was added 1-phenyl-2-propyn-1-ol (1.32 mL, 10 mmol, 1.0 equiv.), ethylene glycol (10 mL) and Amberlyst® 15 (3 g). The resulting suspension was heated to 80 °C and stirred for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (9:1 to 7:3 Petrol:EtOAc) yielded title compound **100b** (0.27 g, 1.56 mmol, 16%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.55-7.49 (m, 2H), 7.43-7.32 (3H, m, *Ar*), 5.24 (1H, d, *J* = 2.2 Hz, C(2)*H*), 3.88-3.55 (4H, m, C(6)H_2 and C(7)H_2), 2.67 (1H, d, J = 2.2 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 137.9, 128.8, 128.7, 127.5, 81.4, 76.2, 71.9, 69.7, 61.9; **ν_{max}**/ cm^{-1} (neat) 3419, 3286, 2931, 2869, 1453, 1059, 1025; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{11}H_{12}O_2{}^{23}Na^+$ calc. 199.0730, found 199.0731. *Data is consistent with literature[222]*

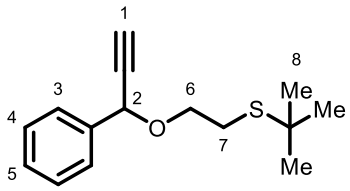
2-((1-Phenylprop-2-yn-1-yl)oxy)ethyl 4-methylbenzenesulfonate (101b)



Synthesised according to **general procedure B**, using **100b** (270 mg, 1.53 mmol) and 2.5 mL, with stirring over 3 h. Purification by column chromatography (9:1 to 8:2 Petrol:EtOAc) yielded title compound **101b** (306 mg, 0.93 mmol, 60%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.80-7.75 (2H, m, *Ar*), 7.46-7.42 (2H, m, *Ar*), 7.39-7.33 (3H, m, *Ar*), 7.32-7.24 (2H, m, *Ar*), 5.18 (1H, d, *J* = 2.2 Hz, C(2)*H*), 4.29-4.14 (2H, m, C(7)H_2), 3.87-3.79 (1H, m, C(6)*H*H), 3.78-3.67 (1H, m, C(6)H*H*), 2.64 (1H, d, *J* = 2.2 Hz, C(1)*H*), 2.42 (3H, s, C(10)H_3); **δ_C** (101 MHz, $CDCl_3$) 144.8, 137.5, 133.1, 129.9, 128.8, 128.6, 128.1, 127.4, 80.8, 76.4, 71.7, 69.1, 65.5, 21.7; **ν_{max}**/ cm^{-1} (neat) 3282, 3064, 2924, 2871, 2115, 1722, 1684, 1597, 1494, 1452, 1400, 1354, 1307, 1273, 1210, 1189, 1174, 1095, 1011, 959, 918; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{18}H_{18}O_4{}^{23}NaS^+$ calc. 353.0818, found 353.0817.

***tert*-Butyl(2-((1-phenylprop-2-yn-1-yl)oxy)ethyl)sulfane (91g)**

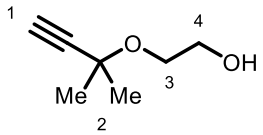


Synthesised according to **general procedure D**, using alkyne **101b** (300 mg, 0.9 mmol) and THF (3 mL). Purification by column chromatography (9:1 to 7:3 Hexane:EtOAc) yielded title compound **91g** (141 mg, 0.57 mmol, 63%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.55-7.49 (2H, m, *Ar*), 7.41-7.29 (3H, m, *Ar*), 5.23 (1H, d, *J* = 2.2 Hz, C(2)*H*), 3.84-3.75 (1H, m, C(6)*H*H), 3.70-3.59 (1H, m, C(6)*H*H), 2.82-2.74 (2H, m, C(7)H_2), 2.65 (1H, d, *J* = 2.2 Hz, C(1)*H*), 1.31 (9H, s, C(8)H_3); **δ_C** (101 MHz, $CDCl_3$) 138.0,

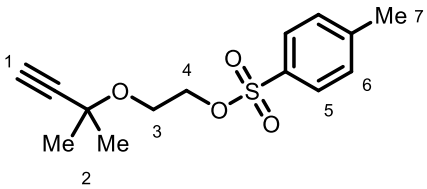
128.6, 127.5, 81.5, 75.9, 71.5, 68.2, 42.3, 31.1, 28.1; ν_{max}/ cm^{-1} (neat) 3289, 3063, 3032, 2960, 2925, 2898, 2863, 2113, 1719, 1602, 1493, 1454, 1390, 1364, 1272, 1189, 1162, 1086, 1070, 1029, 1006, 940, 916; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{20}O^{23}NaS^+$ calc. 271.1127, found 271.1127.

2-((2-Methylbut-3-yn-2-yl)oxy)ethan-1-ol (100c)



According to a modified procedure,[236] to a pre-dried flask was added 2-methylbut-3-yn-2-ol (4.24 mL, 20 mmol) and powdered KOH (1.35 g, 24 mmol). The mixture was cooled to 10 °C and stirred at this temperature for 5 min. 2-bromoethanol (0.71 mL, 10.0 mmol) was then introduced and the mixture heated at 70 °C for 3 h. The reaction mixture was then added to ice water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (1:1 Petrol:EtOAc) to yielded title compound **100c** (0.52 g, 4.03 mmol, 40%) as a colourless oil.

2-((2-Methylbut-3-yn-2-yl)oxy)ethyl 4-methylbenzenesulfonate (101c)

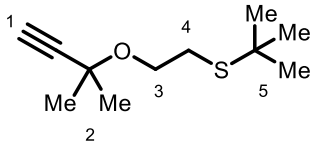


Synthesised according to **general procedure C**, using alkynol **100c** (0.52 g, 4.03 mmol) and CH_2Cl_2 (4.12 mL). Purification by column chromatography (9:1 to 3:2 Petrol:Et_2O) yielded title compound **101c** (1.05 g, 3.71 mmol, 92%) as a white solid.

m.p. 42-43 ºC; δ_H (400 MHz, $CDCl_3$) 7.84-7.77 (2H, m, *Ar*), 7.36-7.30 (2H, m, *Ar*), 4.20-4.13 (2H, m, C(4)H_2), 3.77-3.68 (2H, m, C(3)H_2), 2.44 (3H, s, C(7)H_3), 2.39 (1H, s, C(1)*H*), 1.39 (6H, s, C(2)H_3); δ_C (101 MHz, $CDCl_3$) 144.8, 133.3, 129.8, 128.1, 85.4, 72.6,

70.5, 69.6, 61.9, 28.5, 21.7; ν_{max}/ cm^{-1} (neat) 3252, 2930, 2362, 2339, 1596, 1449, 1367, 1353, 1280, 1223, 1192, 1175, 1157, 1095, 1026, 974; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{19}O_4{}^{23}S^+$ calc. 283.0999, found 283.0996. *Data is consistent with literature.*[237]

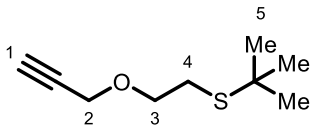
***tert*-Butyl(2-((2-methylbut-3-yn-2-yl)oxy)ethyl)sulfane (91h)**



Synthesised according to **general procedure E**, using **101c** (1.05 g, 3.7 mmol) and IPA (10 mL), with stirring for 1 h. Purification by column chromatography (98:2 Pentane:Et_2O) yielded title compound **91h** (0.38 g, 1.9 mmol, 51%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 3.72-3.63 (2H, m, C(3)H_2), 2.76-2.68 (2H, m, C(4)H_2), 2.41 (1H, s, C(1)*H*), 1.47 (6H, s, C(2)H_3), 1.33 (9H, s, C(5)H_3); δ_C (101 MHz, $CDCl_3$) 86.1, 72.1, 70.3, 64.4, 42.2, 31.2, 28.8, 28.7; ν_{max}/ cm^{-1} (neat) 3291, 2961, 2939, 2899, 2865, 1460, 1379, 1363, 1290, 1225, 1155, 1089, 1065, 1002, 942; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{11}H_{21}O^{23}S^+$ calc. 201.1308, found 201.1308.

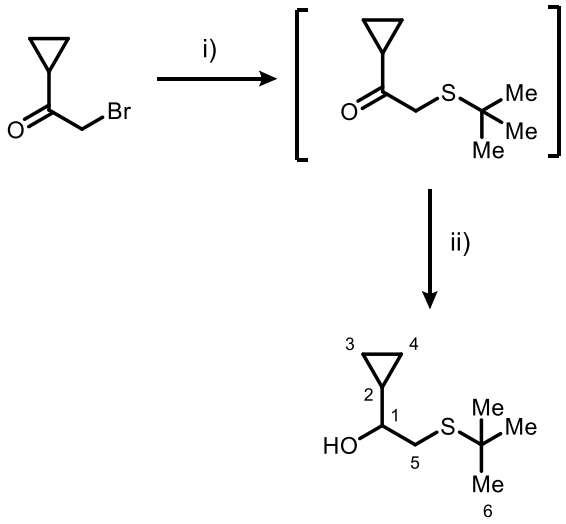
***tert*-Butyl(2-(prop-2-yn-1-yloxy)ethyl)sulfane (91i)**



Synthesised according to **general procedure E** using **90c** (2.54 g 10 mmol) and diethyl ether (25 mL), with stirring for 40 min. Purification by column chromatography (94:6 Hexane:EtOAc) yielded title compound **91i** (1.57 g, 9.11 mmol, 91%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.18 (2H, d, *J* = 2.4 Hz, C(2)H_2), 3.68 (2H, t, *J* = 7.1 Hz, C(3)H_2), 2.76 (2H, t, *J* = 7.1 Hz, C(4)H_2), 2.43 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.33 (9H, s, 9H, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 79.6, 74.7, 69.8, 58.2, 42.2, 31.1, 28.0; **ν_{max}**/ cm^{-1} (neat) 3291, 2960, 2898, 2863, 2116, 1607, 1459, 1390, 1364, 1290, 1270, 1162, 1090, 1045, 1011, 945, 908; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{17}OS^+$ calc. 173.0995, found 173.0997.

2-(*tert*-Butylthio)-1-cyclopropylethan-1-ol (133)

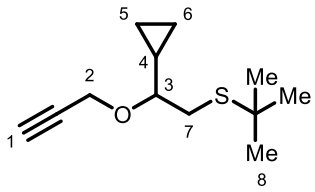


Steps i) and **ii)**: Synthesised according to **general procedures H** and **I**, using 2-bromo-1-cyclopropylethan-1-one (815 mg, 5.0 mmol), THF (12 mL) and ethanol (12 mL). Purification by column chromatography (9:1 Pentane:Et_2O) yielded title compound **133** (714 mg, 4.09 mmol, 82%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 2.99 (1H, td, *J* = 8.4, 3.6 Hz, C(1)*H*), 2.91 (1H, dd, *J* = 12.7, 3.6 Hz, 1H, C(5)*H*H), 2.68 (1H, dd, *J* = 12.7, 8.6 Hz, C(5)H*H*), 2.27 (1H, bs, O*H*), 1.33 (9H, s, C(6)H_3), 0.89-0.98 (1H, m, C(2)*H*), 0.59-0.49 (2H, m, C(3 and 4)H_2), 0.41-0.36 (1H, m, C(3 and 4)H_2), 0.27-0.22 (1H, m, C(3 and 4)H_2); **δ_C** (101 MHz, $CDCl_3$) 74.9, 42.5, 36.5, 31.2, 16.8, 3.0, 2.3; **ν_{max}**/ cm^{-1} (neat) 3419, 3080, 3004, 2960, 2924, 2899, 2863, 2361, 1652,

1459, 1429, 1391, 1364, 1320, 1261, 1162, 1117, 1044, 1021, 917; **m/z HRMS** (ESI^+) [M + radical ion]$^+$ $C_9H_{18}OS^+$ calc. 174.1078, found 174.1073.

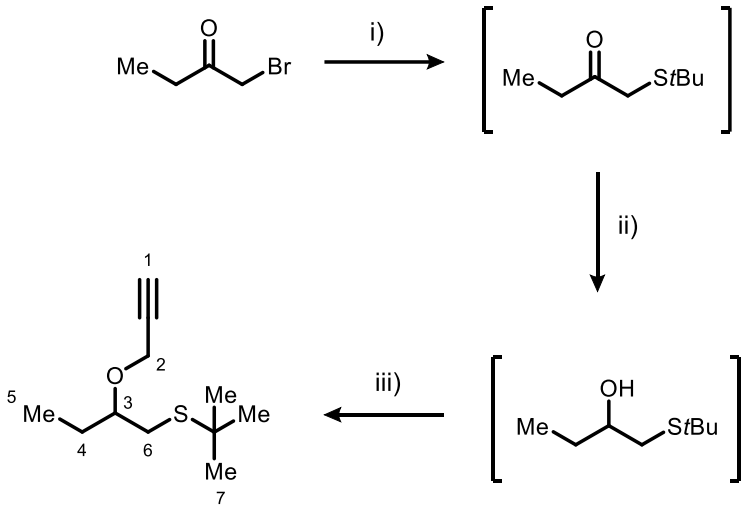
***tert*-Butyl(2-cyclopropyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91j)**



Step iii): synthesised according to **general procedure F**, using alcohol **133** (872 mg, 5.0 mmol) and THF (8 mL), with stirring for 16 h. Purification by column chromatography (98:2 to 94:6 Pentane:Et_2O) yielded title compound **91j** (771 mg, 3.63 mmol, 73%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.34 (2H, dd, *J* = 6.5, 2.4 Hz, C(2)H_2), 3.07 (1H, dt, *J* = 8.6, 5.8 Hz, C(3)*H*), 2.82 (2H, d, *J* = 5.8 Hz, C(7)H_2), 2.39 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.33 (9H, s, C(8)H_3), 0.97-0.88 (1H, m, C(4)*H*), 0.65-0.59 (1H, m, C(5 and 6)H_2), 0.56-0.47 (2H, m, C(5 and 6)H_2), 0.25-0.19 (1H, m, C(5 and 6)H_2); **δ_C** (101 MHz, $CDCl_3$) 81.7, 80.2, 74.3, 56.1, 41.9, 33.7, 31.0, 14.2, 4.4, 1.4; **ν_{max}**/ cm^{-1} (neat) 3309, 3081, 3005, 2972, 2959, 2923, 2898, 2862, 2114, 1473, 1459, 1443, 1392, 1364, 1326, 1295, 1267, 1211, 1162, 1122, 1095, 1075, 1023, 972, 931, 916; **m/z HRMS** (ESI^+) [M + Na]$^+$ $C_{12}H_{20}O^{23}NaS^+$ calc. 235.1127, found 235.1129.

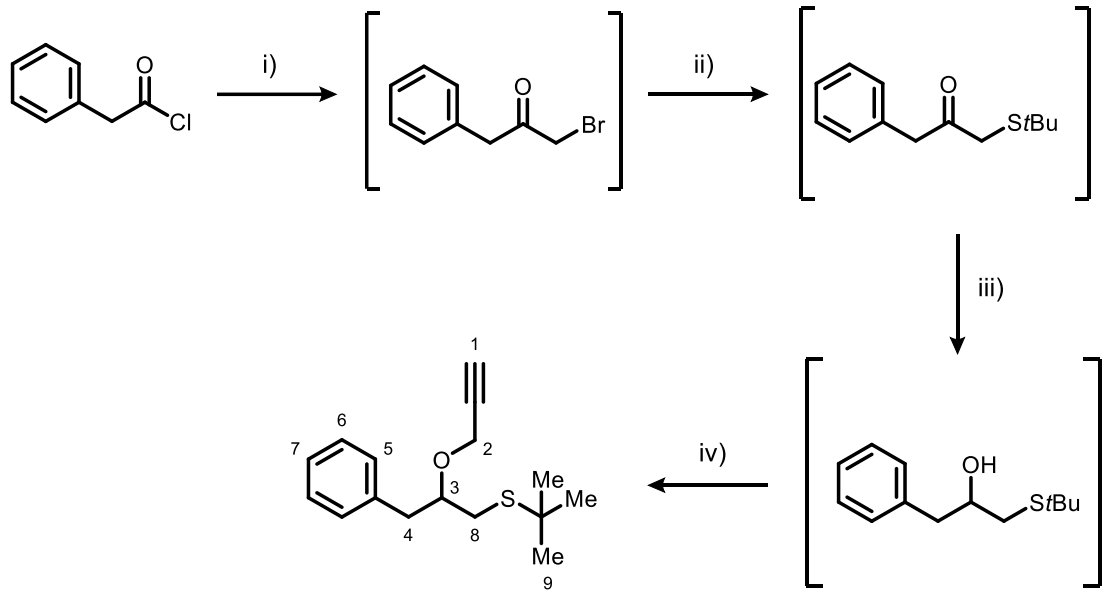
***tert*-Butyl(2-(prop-2-yn-1-yloxy)butyl)sulfane (91k)**



Steps i) and **ii):** synthesised according to **general procedures H** and **I**, using 1-bromobutan-2-one (0.51 mL, 5.0 mmol), THF (8 mL) and ethanol (12 mL), affording a colourless oil. **Step iii):** synthesised according to **general procedure F** using THF (6 mL), with stirring for 18 h. Purification by column chromatography (100:0 to 98:2 Petrol:Et_2O) yielded title compound **91k** (85 mg, 0.43 mmol, 8% over 3 steps) as a bright yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.24 (2H, d, *J* = 2.4 Hz, C(2)H_2), 3.62-3.56 (1H, m, C(3)*H*), 2.75 (1H, dd, *J* = 12.4, 5.2 Hz, C(6)*H*H), 2.63 (1H, dd, *J* = 12.4, 6.9 Hz, C(6)H*H*), 2.41 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.75-1.65 (1H, m, C(4)*H*H), 1.62-1.53 (1H, m, C(4)H*H*), 1.33 (9H, s, C(7)H_3), 0.95 (3H, t, *J* = 7.1 Hz, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 80.4, 79.6, 74.1, 56.8, 42.1, 31.6, 31.0, 26.4, 9.4; **ν_{max}**/ cm^{-1} (neat) 3310, 2960, 2924, 2860, 2116, 1459, 1364, 1342, 1259, 1234, 1163, 1082, 1012, 940, 917; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{11}H_{20}O^{23}NaS^+$ calc. 223.1127, found 223.1129.

***tert*-Butyl(3-phenyl-2-(prop-2-yn-1-yloxy)propyl)sulfane (91l)**

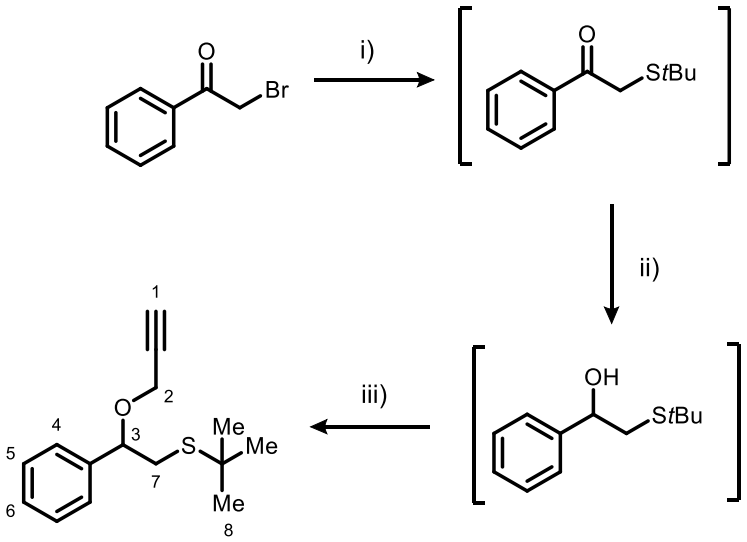


Step i) According to a modified procedure,[238] 2-phenylacetyl chloride (773 mg, 5.0 mmol) was dissolved in anhydrous acetonitrile (50 mL). The solution was then cooled to 0 °C and trimethylsilyl diazomethane (2 M in hexanes, 3.75 mL, 3.4 mmol) was added dropwise under an argon atmosphere. The mixture was then warmed to room temperature and stirred for 1 h, after which $HBr_{(aq)}$ (48% w/w, 3.2 mL) was added dropwise at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. The solution was next diluted with ice water (100 mL) and then extracted with EtOAc (3 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and then concentrated *in vacuo*. The crude residue was then used in the next step without further purification. **Steps ii) and iii)** Synthesised according to **general procedures G** and **H** using ethanol (8 mL) in both steps. **Step iv)** synthesised according to **general procedure F** using THF (8 mL), with stirring for 16 h. Purification by column chromatography (100:0 to 98:2 Pentane:Et_2O) yielded title compound **91l** (822 mg, 3.13 mmol, 63% over 4 steps) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.32-7.24 (4H, m, *Ar*), 7.24-7.18 (1H, m, *Ar*), 4.16 (2H, dd, *J* = 6.1, 2.4 Hz, C(2)H_2), 3.93-3.84 (1H, m, C(3)*H*), 2.97 (1H, dd, *J* = 13.8, 5.6 Hz, C(4)*H*H), 2.88

(1H, dd, *J* = 13.9, 6.6 Hz, C(4)H*H*), 2.72 (1H, dd, *J* = 12.5, 5.2 Hz, C(8)*H*H), 2.63 (1H, dd, *J* = 12.5, 6.6 Hz, C(8)H*H*), 2.38 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.30 (9H, s, C(9)H_3); **δC** (101 MHz, $CDCl_3$) 138.3, 129.7, 128.4, 126.4, 80.1, 79.7, 74.3, 57.1, 42.3, 40.0, 31.8, 31.0; **ν_{max}**/ cm^{-1} (neat) 3306, 3290, 3086, 3062, 3028, 2972, 2959, 2923, 2898, 2861, 2115, 1646, 1603,1495, 1456, 1391, 1364, 1341, 1295, 1268, 1213, 1162, 1091, 1077, 1065, 1029, 1009, 915; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{16}H_{22}{}^{23}NaOS^+$ calc. 285.1284, found 285.1285.

***tert*-Butyl(2-phenyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91m)**

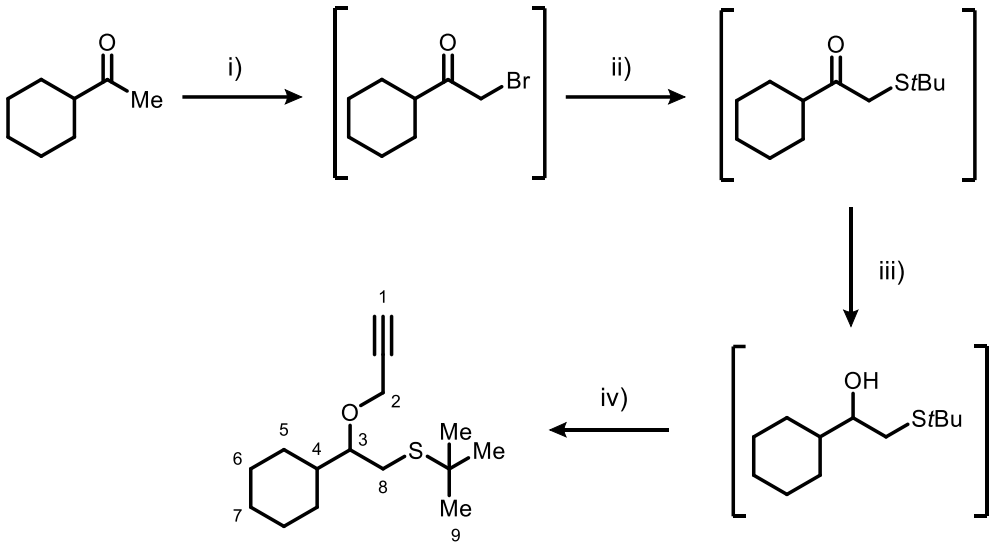


Steps i) and **ii)**: synthesised according to **general procedure H** and **I,** using 2-bromoacetophenone (990 mg, 5.0 mmol), THF (4 mL) and ethanol (4.5 mL). **Step iii)** synthesised according to **general procedure F** using THF (4 mL) with stirring for 16 h**.** Purification by column chromatography (100:0 to 98:2 Hexane:Et_2O) yielded title compound **91m** (611 mg, 2.46 mmol, 49% over three steps) as a bright yellow-orange oil.

δH (400 MHz, $CDCl_3$) 7.41-7.29 (5H, m, *Ar*), 4.66 (1H, dd, *J* = 7.7, 5.9 Hz, OC(3)*H*), 4.15 (dd, *J* = 15.8, 2.4 Hz, C(2)*H*H), 3.89 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)H*H*), 3.01 (1H, dd, *J* = 12.4, 7.7 Hz, C(7)*H*H), 2.80 (1H, dd, *J* = 12.4, 5.9 Hz, C(7)H*H*), 2.41 (1H, t, *J* = 2.4 Hz,

C(1)*H*), 1.30 (9H, s, C(8)H_3); **δC** (101 MHz, $CDCl_3$) 140.0, 128.7, 128.5, 127.2, 80.5, 79.7, 74.6, 55.9, 42.3, 35.8, 31.0; **ν_{max}**/ cm^{-1} (neat) 3307, 3287, 3062, 3030, 2972, 2958, 2923, 2898, 2860, 2115, 1602, 1492, 1473, 1456, 1389, 1364, 1286, 1267, 1236, 1209, 1161, 1087, 1068, 1025, 1007, 961, 949, 918; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{20}O^{23}NaS^+$ calc. 271.1127, found 271.1129.

***tert*-Butyl(2-cyclohexyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91n)**

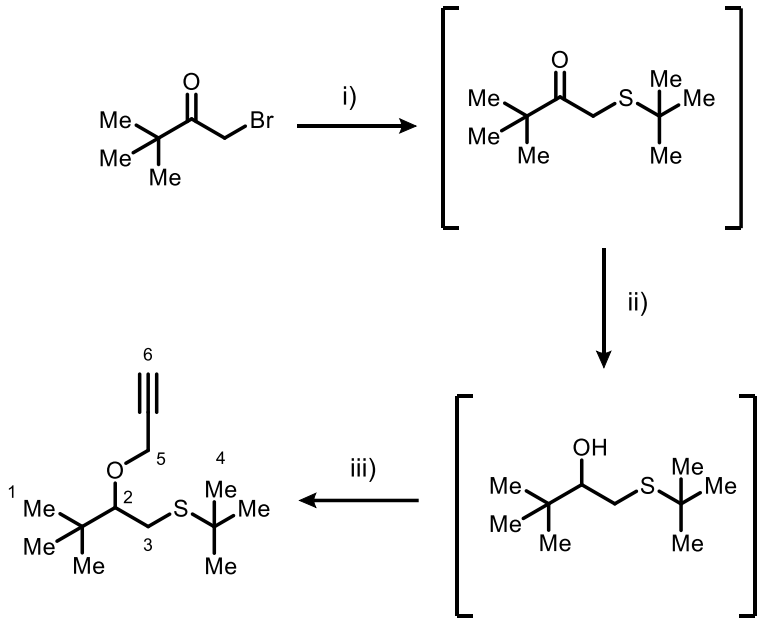


Step i) According to a modified procedure,[239] to a pre-dried flask was added, acetylcyclohexane (1.2 mL, 10 mmol) and MeOH (7.5 mL). The solution was then cooled to 0 °C and bromine (0.52 mL, 10 mmol) was added in one portion. The mixture was then stirred at the same temperature for 7 h, after which water was introduced (10 mL). The solution was then stirred overnight at room temperature under a nitrogen atmosphere. To the resulting mixture was added Et_2O (20 mL) and brine (10 mL). The organic layer was then separated and washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 ml). The organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, yielding a colourless oil. The crude intermediate was used in the next step without further purification. **Steps ii) and iii** synthesised according to **general procedures H** and **I** using THF (14 mL)

and ethanol (9 mL) respectively. **Step iv)** synthesised according to **general procedure F** using THF (8 mL), with stirring for 16 h. Purification by column chromatography (100:0 to 98:2 Pentane:Et_2O) yielded title compound **91n** (678 mg, 2.66 mmol, 27%, over 4 steps) as a bright yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.25 (2H, dd, *J* = 6.3, 2.4 Hz, C(2)H_2), 3.42 (1H, q, *J* = 5.6 Hz, C(3)*H*), 2.72 (2H, dd, *J* = 5.8, 0.9 Hz, C(8)H_2), 2.40 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.83-1.56 (5H, m, C(5 to 7)H_2 and C(4)*H*), 1.37-0.99 (15H, m, C(9)H_3 and C(5 to 7)H_2); **δ_C** (101 MHz, $CDCl_3$) 82.8, 80.6, 74.0, 57.7, 42.1, 40.9, 31.0, 29.5, 29.4, 27.8, 26.6, 26.4, 26.3; **ν_{max}**/ cm^{-1} (neat) 3310, 2972, 2959, 2924, 2852, 1448, 1391, 1363, 1339, 1265, 1162, 1071, 1035, 1016, 970, 936, 910; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{27}O^{23}NaS^+$ calc. 277.1597, found 277.1598.

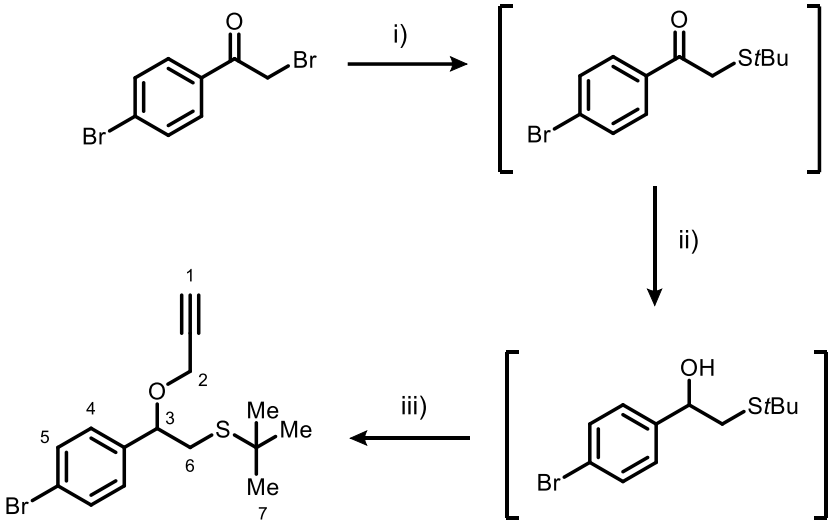
***tert*-Butyl(3,3-dimethyl-2-(prop-2-yn-1-yloxy)butyl)sulfane (91o)**



Steps i) and ii): synthesised according to **general procedures H** and **I**, using 1-bromo-3,3-dimethylbutan-2-one (895 mg, 5.0 mmol), THF (6 mL) and ethanol (12.5 mL), affording a colourless oil. **Step iii):** synthesised according to **general procedure F** using THF (8 mL) with stirring for 16 h. Purification by column chromatography (100:0 to 98:2 Pentane:Et_2O) yielded title compound **91o** (381 mg, 1.67 mmol, 33% over 3 steps) as a bright yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.45 (1H, dd, *J* = 15.4, 2.4 Hz, C(5)*H*H), 4.32 (1H, dd, *J* = 15.5, 2.4 Hz, C(5)H*H*), 3.17 (1H, dd, *J* = 8.0, 3.1 Hz, C(2)*H*), 2.78 (1H, dd, *J* = 12.8, 3.0 Hz, C(3)*H*H), 2.61 (1H, dd, *J* = 12.8, 8.0 Hz, C(3)*H*H), 2.40 (1H, t, *J* = 2.4 Hz, C(6)*H*), 1.32 (9H, s, C(1)H_3), 0.95 (9H, s, C(4)H_3); **δ_C** (101 MHz, $CDCl_3$) 87.3, 80.7, 73.9, 59.9, 42.5, 36.1, 30.9, 30.2, 26.4; **ν_{max}**/ cm^{-1} (neat) 3312, 2958, 2900, 2865, 1478, 1459, 1393, 1363, 1337, 1259, 1218, 1162, 1081, 1055, 1008, 982, 963, 933,903; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{13}H_{24}O^{23}NaS^+$ calc. 251.1451, found 251.1441.

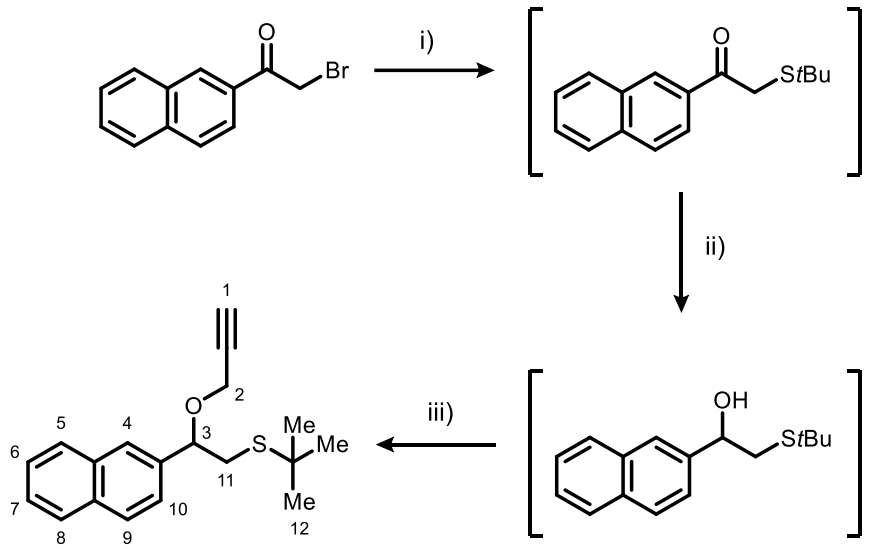
(2-(4-Bromophenyl)-2-(prop-2-yn-1-yloxy)ethyl)(*tert*-butyl)sulfane (91p)



Steps i) and **ii):** synthesised according to **general procedure H** and **I**, using 2-bromo-1-(4-bromophenyl)ethan-1-one (1.39 g, 5.0 mmol), THF (8.5 mL) and ethanol (10 mL). **Step iii):** synthesised according to **general procedure F** using THF (4 mL), with stirring for 3.5 h. Purification by column chromatography (9:1 to 1:1 Petrol:EtOAc) yielded title compound **91p** (487 mg, 1.49 mmol, 30%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.44-7.36 (2H, m, *Ar*), 7.20-7.08 (2H, m, *Ar*), 4.52 (1H, t, *J* = 6.8 Hz, C(3)*H*), 4.04 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)*H*H), 3.79 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)H*H*), 2.88 (1H, dd, *J* = 12.4, 7.2 Hz, C(6)*H*H), 2.66 (1H, dd, *J* = 12.4, 6.5 Hz, C(6)H*H*), 2.32 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.19 (9H, s, C(7)H_3); **δ_C** (101 MHz, $CDCl_3$) 139.1, 131.8, 129.0, 122.4, 79.9, 79.4, 74.9, 56.0, 42.4, 35.5, 31.0; **ν_{max}**/ cm^{-1} (neat) 3297, 2971, 2958, 2923, 2898, 2860, 2116, 1591, 1485, 1458, 1441, 1406, 1388, 1364, 1340, 1294, 1267, 1235, 1211, 1161, 1088, 1068, 1009, 956, 915; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{19}BrO^{23}NaS^+$ calc. 351.0211, found 351.0212.

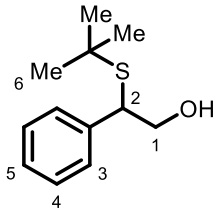
***tert*-Butyl(2-(naphthalen-2-yl)-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91q)**



Steps i) and **ii):** synthesised according to **general procedures H** and **I**, using 2-bromo-2′-acetonaphthone (1.25 g, 5.0 mmol), THF (12 mL) and ethanol (12 mL), affording a yellow oil. **Step iii):** synthesised according to **general procedure F** using THF (8 mL), with stirring for 16 h. Purification by column chromatography (100:0 to 96:4 Pentane:Et_2O) yielded title compound **91q** (722 mg, 2.42 mmol, 48%) as a bright-yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.88-7.80 (4H, m, *Ar*), 7.52-7.46 (3H, m, *Ar*), 4.83 (1H, dd, *J* = 7.5, 6.1 Hz, C(3)*H*), 4.18 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)*H*H), 3.92 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)H*H*), 3.10 (1H, dd, *J* = 12.4, 7.5 Hz, C(11)*H*H), 2.89 (1H, dd, *J* = 12.4, 6.1 Hz, C(11)H*H*), 2.43 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.31 (9H, s, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) 137.3, 133.5, 133.2, 128.7, 128.1, 127.9, 126.9, 126.4, 126.3, 124.4, 80.7, 79.6, 74.7, 56.0, 42.3, 35.7, 31.0; **ν_{max}**/ cm^{-1} (neat) 3291, 3055, 2959, 2924, 2897, 2861, 1601, 1508, 1458, 1442, 1364, 1317, 1270, 1162, 1123, 1072, 1016, 948, 916; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{19}H_{23}O^{23}NaS^+$ calc. 321.1284, found 321.1284.

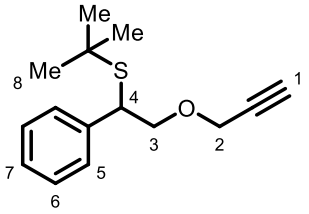
2-(*tert*-Butylthio)-2-phenylethan-1-ol (105)



According to a modified procedure,[240] to a pre-dried flask was added $InCl_3$ (221 mg, 1.0 mmol) was and CH_2Cl_2 (20 mL). The mixture was then cooled to 0 °C, after which styrene oxide (1.1 mL, 10.0 mmol) and *tert*-butylthiol (1.1 mL 10 mmol) were introduced. The solution was then stirred under a nitrogen atmosphere, at room temperature for 16 h. The mixture was then diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, and then concentrated *in vacuo*. Purification by column chromatography (9:1 Pentane:EtOAc) yielded title compound **105** (760 mg, 3.63 mmol, 36%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.37-7.30 (4H, m, *Ar*), 7.27-7.22 (1H, m, *Ar*), 3.98 (1H, dd, *J* = 8.6, 6.4 Hz, C(2)*H*), 3.77 (1H, dd, *J* = 11.3, 6.4 Hz, C(1)*H*H), 3.63 (1H, dd, *J* = 11.3, 8.5 Hz, C(1)*H*H), 2.04 (1H, bs, O*H*), 1.30 (9H, s, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 141.9, 128.8, 128.0, 127.4, 66.7, 51.1, 44.4, 31.6; **ν_{max}**/ cm^{-1} (neat) 3409, 3060, 3027, 2959, 2896, 2863, 1600, 1491, 1452, 1390, 1364, 1339, 1249, 1160, 1052, 1028, 977, 932, 908; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{12}H_{18}O^{23}NaS^+$ calc. 233.0971, found 233.0973.

***tert*-Butyl(1-phenyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91r)**

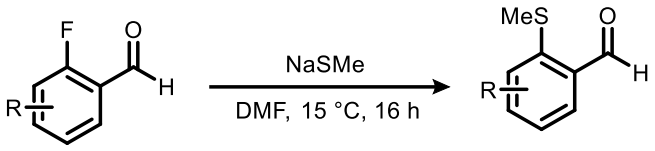


Synthesised according to **general procedure F**, using alcohol **105** (740 mg, 3.5 mmol), NaH (280 mg, 7.0 mmol), propargyl bromide (0.67 mL, 7.0 mmol) and THF (4 mL). Stirred for 16 h. Purification by column chromatography (100:0 to 98:2 Pentane:Et_2O) yielded title compound **91r** (630 mg 2.53 mmol, 72%) as a bright yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.37-7.29 (4H, m, *Ar*), 7.25-7.20 (1H, m, *Ar*), 4.11 (2H, t, *J* = 2.6 Hz, C(2)H_2), 4.05 (1H, dd, *J* = 8.4, 6.2 Hz, C(4)*H*), 3.88-3.78 (2H, m, C(3)H_2), 2.40 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.29 (9H, s, C(8)H_3); **δ_C** (101 MHz, $CDCl_3$) 142.4, 128.6, 128.0, 127.2, 79.6, 74.7, 74.3, 58.3, 47.0, 44.3, 31.5; **ν_{max}**/ cm^{-1} (neat) 3286, 3061, 3028, 2959, 2896, 2860, 2116, 1601, 1583, 1492, 1470, 1452, 1391, 1363, 1266, 1236, 1160, 1097, 1080, 1029, 1003, 985, 948, 908; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{20}O^{23}NaS^+$ calc. 271.1127, found 271.1127.

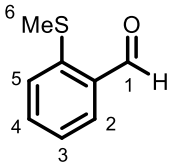
5.2.4 Synthesis of Aldehyde substrates

General Procedure K: Nucleophilic Substitution of 2-haloaldehydes with NaSMe



Prepared according to literature procedure.[241] A solution of NaSMe (1.14-1.2 equiv.) in DMF was cooled to 15 °C. To the resulting suspension, a solution of the corresponding 2-haloaldehyde (1.0 equiv.) was added and the reaction mixture stirred overnight. The resulting mixture was poured into H_2O and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product.

2-(Methylthio)benzaldehyde (57b)

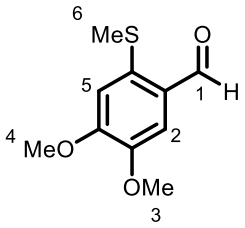


Prepared according to **general procedure K**, using NaSMe (1.50 g, 22 mmol) in DMF (22 mL), then 2-fluorobenzaldehyde (2.5 g, 20 mmol). Work-up using H_2O (25 mL), Et_2O (3 × 20 mL) and sat. LiCl (3 × 20 mL). Purification by column chromatography (9:1 Petrol:EtOAc) yielded title compound **57b** (2.57 g, 16.9 mmol, 84%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 10.28 (1H, s, C(1)*H*=O), 7.83 (1H, dd, *J* = 7.7, 1.6 Hz, *Ar*), 7.59-7.52 (1H, m, *Ar*), 7.36 (1H, d, J = 8.0 Hz, *Ar*), 7.33-7.28 (1H, m, *Ar*), 2.52 (3H, s, SC(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 191.4, 143.4, 133.9, 133.4, 132.7, 125.3, 124.3, 15.4; **ν_{max}**/ cm^{-1} (neat) 3059, 2983, 2919, 2826, 2739, 1674, 1586, 1558, 1461, 1435, 1397, 1321, 1303, 1287,

1257, 1195, 1127, 1076, 1046, 965; **m/z HRMS** (ESI^+) $C_8H_9O^{32}S^+$ $[M + H]^+$ calc. 153.0368, found 153.0371. *Data is consistent with literature.*[241]

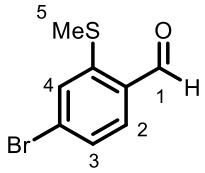
3,4-Dimethoxy-2-(methylthio)benzaldehyde (57c) (prepared by Daniel Moseley)



Prepared according to a modified procedure.[92] NaSMe (600 mg, 8.56 mmol, 1.2 equiv.) was added to a solution of 2-bromo-4,5-dimethoxybenzaldehyde (1.74 g, 7.13 mmol, 1.0 equiv.) in DMF (27 mL) at 0 °C, and the resulting solution stirred overnight (16 h) at 70 °C. After this time, H_2O (15 mL) was added and the mixture obtained extracted with Et_2O (3 × 15 mL), washed with brine (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:19 to 1:4 EtOAc:Petrol) yielded 3,4-dimethoxy-2-(methylthio)benzaldehyde **57c** (1.03 g, 4.85 mmol, 68%) as an off-white solid.

m.p. (CH_2Cl_2) 97–99 °C; **δ_H** (400 MHz, $CDCl_3$) 10.38 (1H, s, C(1)*H*=O), 7.38 (1H, s, *Ar*), 6.93 (1H, s, *Ar*), 4.01 (3H, s, C(3 or 4)H_3), 3.94 (3H, s, C(3 or 4)H_3), 2.53 (3H, s, SC(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 189.6, 154.0, 147.8, 136.6, 127.8, 111.7, 111.6, 56.1, 56.1, 18.2; **m/z HRMS** (ESI^+) $C_{10}H_{12}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 235.0399, found 235.0402. *Data is consistent with literature.*[92]

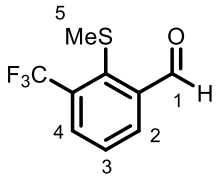
4-Bromo-2-(methylthio)benzaldehyde (57d) (prepared by Daniel Moseley)



Prepared according to a modified procedure. To a stirred solution of NaSMe (340 mg, 4.90 mmol, 1.13 equiv.), in DMF (25 mL) was added 4-bromo-2-fluorobenzaldehyde (1.0 g, 4.3 mmol, 1.0 equiv.) over 30 mins at –45 °C. The mixture was stirred at this temperature for 3 h before warming to room temperature overnight (16 h). The mixture was then quenched with H_2O (5 mL) and the resulting white precipitate was collected by Büchner filtration to yield 4-bromo-2-(methylthio)benzaldehyde **57d** (761 mg, 3.31 mmol, 78%) as a white solid.

m.p. (DMF) 80–83 °C; **δ_H** (400 MHz, $CDCl_3$) 10.17 (1H, s, C(1)*H*=O), 7.63 (1H, d, *J* = 8.1 Hz, C(2)*H*), 7.45-7.34 (2H, m, C(3 and 4)*H*), 2.49 (3H, s, SC(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 190.3, 145.6, 134.4, 131.6, 129.8, 128.1, 127.7, 15.6; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_8O^{79}Br^{32}S^+$ calc. 230.9474, found 230.9476, $C_8H_8O^{81}Br^{32}S^+$ calc. 232.9453, found 232.9456. *Data is consistent with literature.*[106]

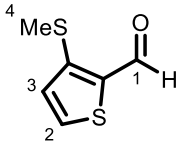
2-(Methylthio)-3-(trifluoromethyl)benzaldehyde (57e) (prepared by Daniel Moseley)



Prepared according to **general procedure K**, using NaSMe (290 mg, 4.14 mmol, 1.14 equiv.) in DMF (2.5 mL), then 2-fluoro-3-(trifluoromethyl)benzaldehyde (0.5 mL, 3.63 mmol, 1.0 equiv.) in DMF (7.5 mL). Work-up using H_2O (2 × 10 mL), EtOAc (3 × 10 mL) and brine (10 mL). Purification by column chromatography (3:97 EtOAc:Petrol) 3,4-dimethoxy-2-(methylthio)benzaldehyde **57e** (689 mg, 3.13 mmol, 86%) as an off-white solid.

m.p. (CH_2Cl_2) 34–36 °C; **δ_F** (377 MHz $CDCl_3$) -59.52; **δ_H** (400 MHz, $CDCl_3$) 10.77 (1H, d, *J* = 0.8 Hz, C(1)*H*=O), 8.04 (1H, ddd, *J* = 7.8, 1.0 Hz, *Ar*), 7.91 (1H, ddd, *J* = 7.8, 1.0 Hz, *Ar*), 7.56 (1H, app t, *J* = 7.7 Hz, *Ar*), 2.38 (3H, s, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 191.9, 139.9, 139.6, 135.4 (q, J_{CF} = 29.3 Hz), 132.2, 131.7 (q, J_{CF} = 5.6 Hz), 129.3, 123.4 (q, J_{CF} = 274.0 Hz), 23.0; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_8OF_3{}^{32}S^+$ calc. 221.0243, found 221.0245. *Data is consistent with literature.*[92]

3-(Methylthio)thiophene-2-carbaldehyde (57f) (prepared by Daniel Moseley)

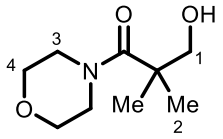


Prepared according to **general procedure K**, using NaSMe (650 mg, 9.34 mmol, 1.2 equiv.) in DMF (2.5 mL), then 3-bromothiophene-2-carbaldehyde (0.7 mL, 7.78 mmol, 1.0 equiv.) in DMF (7.5 mL). Work-up using H_2O (2 × 20 mL), EtOAc (3 × 20 mL) and brine (20 mL). Purification by column chromatography (1:49 to 1:9 EtOAc:Petrol) yielded

3-(methylthio)thiophene-2-carbaldehyde **57f** (693 mg, 4.39 mmol, 56%) as an off-white solid.

m.p. 34–37 °C; **δ_H** (400 MHz, $CDCl_3$) 10.01 (1H, d, *J* = 1.1 Hz, C(1)*H*=O), 7.71 (1H, dd, *J* = 5.1, 1.1 Hz, *Ar*), 7.08 (1H, d, *J* = 5.1 Hz, *Ar*), 2.57 (3H, s, SC(4)H_3); **δ_C** (101 MHz, $CDCl_3$) 181.6, 146.1, 135.2, 134.7, 128.2, 17.2; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_7O^{32}S_2^+$ calc. 158.9933, found 158.9933. *Data is consistent with literature.*[139]

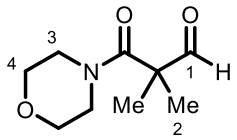
3-Hydroxy-2,2-dimethyl-1-morpholinopropan-1-one (134)



To a pre-dried flask was added 2-hydroxypivalic acid (3.0 g, 25.4 mmol, 1.0 equiv.) and CH_2Cl_2 (50 mL). Next, morpholine (2.4 mL, 28.0 mmol, 1.10 equiv.) and EDC•HCl (5.37 g, 28 mmol, 1.1 equiv.) were added. The mixture was stirred at room temperature for 4 h and then quenched sat. aq. $NaHCO_3$ (30 mL) and extracted with EtOAc. The combined organics were then washed with brine (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (9:1 to 100:0 EtOAc:Et_2O) yielded compound **134** (1.29 g, 6.87 mmol, 27%) as a white solid.

m.p. 45-48 °C; **δ_H** (400 MHz, $CDCl_3$) 3.71-3.61 (8H, m, C(3 and 4)H_2), 3.49 (2H, s, C(1)H_2), 1.27 (6H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 176.6, 72.8, 66.9, 45.4, 43.1, 22.0; **ν_{max}**/ cm^{-1} (neat) 3475, 2959, 2921, 2855, 1729, 1631, 1605, 1589, 1505, 1473,1459, 1432, 1403, 1357, 1301, 1275; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{18}O_3N^+$ calc. 188.1281, found 188.1282.

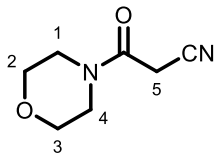
2,2-Dimethyl-3-morpholino-3-oxopropanal (57a)



Prepared according to a modified literature procedure.[133] A solution of oxalyl chloride (1.3 mL, 6.82 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL) was cooled to –78 °C. In a separate flask, dimethyl sulfoxide (0.88 mL, 12.4 mmol, 2.00 equiv.) was dissolved in CH_2Cl_2 (10 mL). This mixture was added dropwise to the oxalyl chloride solution, and the reaction mixture was stirred for 5 min. A solution of 3-hydroxy-2,2-dimethyl-1-morpholinopropan-1-one **134** (1.16 g, 6.2 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was then introduced dropwise. The reaction mixture was stirred for 30 min at –78 °C before Et_3N (2.3 mL, 31 mmol, 5.0 equiv.) was added. The mixture was then allowed to warm to room temperature over 30 min and then washed with 2 M $HCl_{(aq)}$ (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (6:4 Et_2O:Petane) yielded title compound **57a** (1.01 g, 5.46 mmol, 88%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 9.61 (1H, s, C(1)*H*=O), 3.71-3.21 (8H, m, C(3 and 4)H_2), 1.36 (6H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 199.8, 169.9, 66.8, 54.1, 20.6; **ν_{max}**/ cm^{-1} (neat) 2923, 2855, 2360, 2341, 1721, 1642, 1463, 1427, 1361, 1301, 1273, 1251, 1219, 1180, 1116, 1066, 1037, 995; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{16}O_3N^+$ calc. 186.1125, found 186.1124. *Data is consistent with literature.*[133]

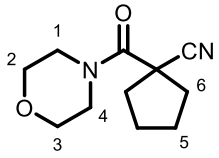
3-Morpholino-3-oxopropanenitrile (135)



Prepared according to a modified literature procedure,[242] methyl cyanoacetate (19.8 g, 200 mmol) and morpholine (17.5 mL, 200 mmol) were combined in a round-bottomed flask. The resulting solution was stirred at room temperature for 24 h under a nitrogen atmosphere. The solution was then concentrated under reduced pressure to give orange/red crystals. The crystals were washed with cold Et_2O (50 mL) and dried under vacuum, yielding title compound **135** (22.3 g, 145 mmol, 72%) as orange/red crystals.

δ_H (400 MHz, $CDCl_3$) 3.71-3.62 (4H, m, C(1 to 4)H_2), 3.61-3.55 (2H, m, C(1 to 4)H_2), 3.52 (2H, s, C(5)H_2), 3.45-3.38 (2H, m, C(1 to 4)H_2); **δ_C** (101 MHz, $CDCl_3$) 165.9, 122.3, 66.8 (bs), 66.1 (bs), 47.5 (bs), 45.0, 43.9 (bs), 37.5, 25.3; **ν_{max}**/ cm^{-1} (neat) 2972, 2928, 2872, 2264, 1662, 1650, 1615, 1532, 1466, 1449, 1430, 1390, 1364, 1318, 1278, 1242, 1217, 1194, 1105, 1067, 1032, 1012, 975, 928, 900; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{11}N_2O_2^+$ calc. 155.0815, found 155.0815. *Data is consistent with literature.*[242]

1-(Morpholine-4-carbonyl)cyclopentane-1-carbonitrile (136)

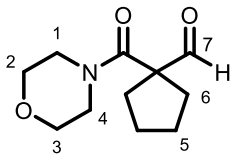


Prepared according to a modified literature procedure.[127] To a pre-dried flask was added 3-morpholino-3-oxopropanenitrile **135** (4.62 g, 30.0 mmol) and powdered K_2CO_3 (10.4 g, 75 mmol). DMF (60 mL) was added, followed by 1,4-dibromobutane (8.6 mL, 72 mmol) and 1-butyl-3-methylimidazolium tetrafluoroborate (1.1 mL, 6.0 mmol). The resulting mixture was stirred at room temperature overnight under a nitrogen atmosphere.

The reaction mixture was then filtered and washed with Et_2O (30 mL). The filtrate was diluted with water (200 mL) and extracted with Et_2O (4 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (7:3 then 3:2 Petrol:EtOAc) yielded title compound **136** (5.19 g, 24.9 mmol, 83%) as white crystals.

m.p 44–45 °C; **δ_H** (400 MHz, $CDCl_3$) 3.79-3.61 (8H, m, C(1 to 4)H_2), 2.45-2.35 (2H, m, C(5 and 6)H_2), 2.27-2.21 (2H, m, C(5 and 6)H_2), 1.92-1.74 (4H, m, C(5 and 6)H_2); **δ_C** (101 MHz, $CDCl_3$) 165.9, 122.3, 66.8, 66.1, 47.5, 45.0, 43.9, 37.5, 25.3; **ν_{max}**/ cm^{-1} (neat) 2966, 2946, 2922, 2866, 2851, 2229, 1738, 1695, 1643,1455, 1424, 1358, 1331, 1304, 1270, 1240, 1206, 1174, 1114, 1067, 1035, 1017, 994, 983, 953, 932, 912; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{11}H_{17}N_2O_2^+$ calc. 209.1285, found 209.1287. *Data is consistent with literature.*[127]

1-(Morpholine-4-carbonyl)cyclopentane-1-carbaldehyde (57g)

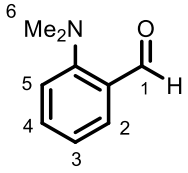


Prepared according to a modified procedure.[127] Nitrile **136** (1.25 g, 6.0 mmol) was dissolved in a mixture of water (15 mL) acetic acid (15 mL) and pyridine (30 mL). The solution was cooled to 0 ºC and Raney®-Nickel (50% w/w in water, 8.45 g, 72 mmol) was added followed by portion-wise addition of sodium hypophosphite monohydrate (4.45 g, 42 mmol). The reaction mixture was stirred at 90 ºC for 16 h. Upon cooling to room temperature, the mixture was filtered through a Celite® plug and the filtrate extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with 1M HCl (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue (676 mg) was purified according to a modified literature procedure, by first dissolving it in

a mixture of EtOAc (5 ml), EtOH (1 ml) and water (0.2 ml). Sodium bisulfite (286 mg, 2.75 mmol) was then introduced and the mixture stirred at 40 °C for 4 h. Upon cooling to room temperature, the mixture was filtered and washed with ethanol (10 mL). After drying, the bisulfite adduct (0.44 g) was obtained as a flaky white solid. This adduct was combined with TMS-Cl (0.49 mL, 3.88 mmol) and acetonitrile (4 mL). The mixture was then stirred at 40 °C for 2 h. Upon cooling to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with water (3 × 20 mL) and brine (3 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*, to give title compound **57g** (135 mg, 0.64 mmol, 46%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 9.48 (1H, s, C(7)*H*=O), 3.63 (6H, s, C(1 to 4)H_2), 3.25 (2H, s, C(1 to 4)H_2), 2.32-2.01 (4H, m, C(6)H_2), 1.77-1.51 (4H, m, C(5)H_2); **δ_C** (101 MHz, $CDCl_3$) 197.9, 169.3, 66.9 (bs), 66.6 (bs), 65.5, 46.6 (bs), 43.5 (bs), 34.7, 31.6, 26.0, 24.8; **ν_{max}**/ cm^{-1} (neat) 3294, 2959, 2863, 2722, 1716, 1637, 1426, 1361, 1300, 1272, 1238, 1216, 1177, 1114, 1066, 1017, 943, 909; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{11}H_{18}NO_3^+$ calc. 212.1281, found 212.1283. *Data is consistent with literature.*[127]

2-(Dimethylamino)benzaldehyde (57h) (prepared by Daniel Moseley)



Prepared according to a modified procedure.[243] To a mixture of 2-fluorobenzaldehyde (1.1 mL, 10 mmol, 1.0 equiv.) and K_2CO_3 (1.38 g, 10 mmol, 1.0 equiv.) in anhydrous DMF (20 mL) at room temperature was added Me_2NH solution (5.60 M in EtOH, 2.4 mL, 13.4 mmol, 1.34 equiv.) The resulting mixture was stirred and heated to 110 °C for 20 h. After this time, the reaction was cooled to room temperature and H_2O (40 mL) was added.

The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were then washed with a 5% w/w aq. LiCl solution (40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (97:3 to 19:1 Petrol:EtOAc) yielded title compound **57h** (1.26 g, 8.45 mmol, 85%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 10.22 (1H, s, C(1)*H*), 7.76 (1H, dd, *J* = 7.7, 1.8 Hz, *Ar*), 7.46 (1H, ddd, *J* = 8.3, 7.2, 1.8 Hz, *Ar*), 7.09-6.96 (2H, m, *Ar*), 2.92 (6H, s, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 191.3, 155.9, 134.7, 131.1, 127.1, 120.7, 117.7, 45.7; **ν_{max}**/ cm^{-1} (neat) 2981, 2868, 2839, 2794, 1680, 1658, 1596, 1487, 1455, 1433, 1386, 1326, 1279, 1187, 1151, 1137, 1051, 949, 845, 831, 762, 641; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{12}ON^+$ calc. 150.0913, found 150.0912. *Data is consistent with literature.*[243]

5.2.5 Synthesis of sulfur heterocycles

General procedure L: Rhodium-catalysed hydroacylation with disulfide alkynes

$Rh(nbd)_2]BF_4$ (3.7 mg, 0.01 mmol, 0.05 equiv.) was weighed into a tapered, 10 mL microwave vial. Next, dcpe (4.20 mg, 0.01 mmol, 0.05 equiv.) was introduced and the vial sealed with a subaseal and parafilmed. The vial was placed under vacuum and back-filled with argon. This cycle was repeated three times before 0.8 mL of distilled DCE was introduced, and the solution sonicated for 30 s. Hydrogen gas was bubbled through the solution for 2 min. The solvent was then removed using a stream of argon and the catalyst system re-dissolved in DCE (0.2 mL). A given disulfide (1.0 equiv.) and aldehyde (2.3 equiv.) were weighed into a separate concave, 10 mL microwave vial, sealed with a subaseal/microwave cap and parafilmed. This vial was then back-filled with argon three times. The catalyst solution was then added to the reactant mixture. The solution was stirred at 55 °C for 16-20 h, after which the solution was cooled to room temperature and concentrated *in vacuo*.

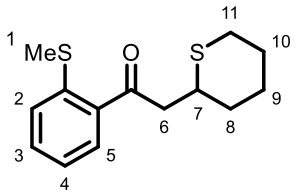
General procedure M: Rhodium-catalysed hydroacylation of *tert*-butyl sulfide alkynes

$Rh(nbd)_2]BF_4$ (3.7 mg, 0.01 mmol, 0.05 equiv.) was weighed into a tapered, 10 mL microwave vial. Next, dcpe (4.2 mg, 0.01 mmol, 0.05 equiv.) was introduced and the vial sealed with a subaseal and parafilmed. The vial was placed under vacuum and back-filled with argon. This cycle was repeated three times before 0.8 mL of distilled DCE was introduced, and the solution sonicated for 30 s. Hydrogen gas was bubbled through the solution for 2 min. The solvent was then removed using a stream of argon and the catalyst system re-dissolved in DCE (0.2 mL). A given alkyne (1.2-1.5 equiv.) and aldehyde (1.0 equiv.) were weighed into a separate concave, 10 mL microwave vial, sealed with a subaseal/microwave cap and parafilmed. This vial was then back-filled with argon three

times. The catalyst solution was then added to the reactant mixture. The solution was stirred at 55 °C for 16-20 h, after which the solution was cooled to room temperature. This step was followed by **general procedure N**.

General procedure N: The crude hydroacylation product was diluted with DCE (1.8 mL) (in the same microwave vial) and TFA (1.0-10 equiv.) was introduced. The mixture was then stirred at 40 °C for a given amount of time, after which the solution was filtered through a pad of silica with EtOAc. The filtrate was then concentrated under reduced pressure.

1-(2-(Methylthio)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83a)



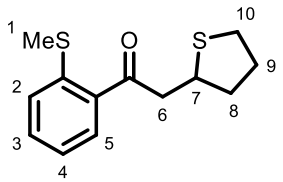
Synthesised according to **general procedures M** and **N**. **General procedure M** used 2-(methylthio)benzaldehyde **57b** (26 µL, 0.20 mmol, 1.0 equiv.) and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (41 mg, 0.24 mmol, 1.2 equiv.). **General procedure N** used TFA (40 µL, 0.40 mmol), with stirring for 4 h. Purification by column chromatography (9:1 Pentane:Et_2O) yielded title compound **83a** (43.9 mg, 0.17 mmol, 82%) as a yellow oil.

Gram-Scale Reaction: Following **general procedures M** and **N**. **General procedure M** used 2-(methylthio)benzaldehyde **57b** (0.13 mL, 1.0 mmol, 1.0 equiv.) and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (200 mg, 1.2 mmol, 1.2 equiv.), with $Rh(nbd)_2BF_4$ (18.7 mg, 0.05 mmol, 0.05 equiv.), dcpe (21.4 mg, 0.05 mmol, 0.05 equiv.) and DCE (1 mL) in a microwave vial. For **general procedure N**, a separate oven-dried round-bottom flask was backfilled under argon three times. The crude reaction mixture from **general procedure M** was diluted with DCE (19 mL) and transferred over to this flask *via* a syringe. TFA (0.2 mL, 2.0 mmol,

2.0 equiv.) was next introduced and the resulting solution was stirred for 6 h at 40 °C (before work-up according to **general procedure N**). Purification by column chromatography (column 92:8 Hexane:EtOAc then 9:1 Hexane:EtOAc), yielded title compound **83a** (130 mg, 0.50 mmol, 50%) as a yellow oil. This could be used in subsequent derivatisations (See Section 5.2.6.).

δ_H (400 MHz, $CDCl_3$) 7.80 (1H, dd, *J* = 7.8, 1.5 Hz, *Ar*), 7.49-7.45 (1H, m, *Ar*), 7.34-7.32 (1H, d, *J* = 8.0 Hz, *Ar*), 7.21-7.17 (1H, m, *Ar*), 3.44-3.37 (1H, m, C(7)*H*), 3.15-3.01 (2H, m, C(6)H_2), 2.79-2.72 (1H, m, C(11)*H*H), 2.63-2.57 (1H, m, C(11)H*H*), 2.43 (3H, s, C(1)H_3), 2.16-2.08 (1H, m, C(8)*H*H), 1.96-1.90 (1H, m, C(8)*H*H), 1.87-1.79 (1H, m, C(9)*H*H), 1.66-1.55 (m, 1H, C(10)H*H*), 1.50-1.41 (2H, m, C(8)H*H* and C(9)H*H*); **δ_C** (101 MHz, $CDCl_3$) 198.8, 142.6, 134.6, 132.4, 130.2, 125.3, 123.6, 46.0, 37.9, 34.4, 29.5, 27.0, 25.9, 16.1; **ν_{max}**/ cm^{-1} (neat) 2921, 2851, 2360, 1671, 1586, 1558, 1459, 1433, 1361, 1342, 1279, 1213, 1177, 1139, 1080, 1045, 1017, 984, 924; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{14}H_{18}O^{23}NaS_2^+$ calc. 289.0691, found 289.0692.

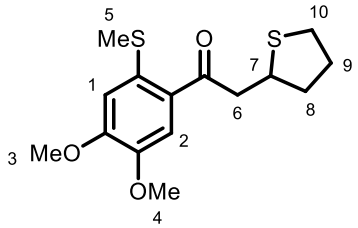
1-(2-(Methylthio)phenyl)-2-(tetrahydrothiophen-2-yl)ethan-1-one (83b)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57b** (26 µL, 0.20 mmol) and *tert*-butyl(pent-4-yn-1-yl)sulfide **91c** (38 mg, 0.24 mmol). **General procedure N** used TFA (20 µL, 0.20 mmol), with stirring for 2 h. Purification by column chromatography (8:2 Pentane:Et_2O) yielded title compound **83b** (22 mg, 0.09 mmol, 44%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.81 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.49-7.44 (1H, m, *Ar*), 7.34-7.32 (1H, m, *Ar*), 7.21-7.17 (1H, m, *Ar*), 3.92 (1H, p, *J* = 6.8 Hz, C(7)*H*), 3.31 (1H, dd, *J* = 17.1, 6.7 Hz, C(6)*H*H), 3.24 (1H, dd, *J* = 17.1, 6.7 Hz, C(6)H*H*), 2.96-2.83 (2H, m, C(10)H_2), 2.43 (3H, s, C(1)H_3), 2.30-2.22 (1H, m, C(8)*H*H), 2.12-2.04 (1H, m, C(9)*H*H), 2.01-1.91 (1H, m, C(9)H*H*), 1.68-1.60 (1H, m, C(8)H*H*); **δ_C** (101 MHz, $CDCl_3$) 199.5, 142.4, 134.3, 132.2, 130.1, 125.2, 123.5, 48.0, 43.4, 37.0, 32.4, 30.2, 16.0; **ν_{max}**/ cm^{-1} (neat) 2918, 2857, 1667, 1586, 1557, 1461, 1431, 1359, 1268, 1240, 1204, 1172, 1139, 1079, 1045, 1003, 977; **m/z** [**HRMS** (ESI^+) $[M + Na]^+$ $C_{13}H_{16}O^{23}NaS_2^+$ calc. 275.0535, found 275.0534.

1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-(tetrahydrothiophen-2-yl)ethan-1-one (83c)

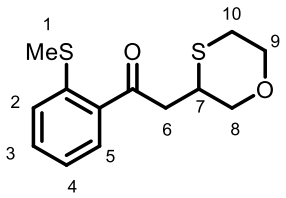


Synthesised according to **General procedure L**, using 1,2-di(pent-4-yn-1-yl)disulfide **84b** (40 mg, 0.20 mmol) and aldehyde **57c** (89 mg, 0.42 mmol). The crude hydroacylation product was dissolved in 1,4-dioxane (40 mL) and water (10 mL). TCEP·HCl (4.0 equiv.) was introduced followed by 4 N HCl in 1,4-dioxane (4.0 equiv.). The mixture was stirred at room temperature under nitrogen for 16 h. sat. $NaHCO_3$ (20 mL) was added and the solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried with anhydrous magnesium sulphate, and then concentrated. Purification by column chromatography (7:3 Pentane:Et_2O) yielded title compound **83c** (19 mg, 0.06 mmol, 15%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.29 (1H, s, *Ar*), 6.80 (1H, s, *Ar*), 4.00-3.85 (7H, m, C(2 and 3)H_3 and C(7)*H*), 3.34-3.17 (2H, m, C(6)H_2), 2.96-2.81 (2H, m, C(10)H_2), 2.43 (3H, s, C(5)H_3), 2.31-2.22 (1H, m, C(8)*H*H), 2.14-2.03 (1H, m, C(9)*H*H), 2.01-1.88 (1H, m, C(9)H*H*),

1.70-1.56 (m, 1H, C(8)H*H*); **δC** (101 MHz, $CDCl_3$)197.9, 152.6, 145.6, 136.2, 127.4, 113.4, 108.6, 56.5, 56.1, 47.9, 43.7, 37.2, 32.5, 30.3, 16.7; **νmax**/ cm^{-1} (neat) 2936, 2857, 2253, 1657, 1598, 1552, 1500, 1463, 1436,1402, 1376, 1357, 1336, 1264, 1221, 1199, 1165, 1066, 1030, 966; **m/z** [**HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{20}O_3{}^{23}NaS_2^+$ calc. 335.0746, found 335.0747.

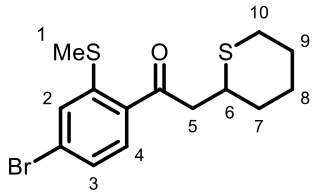
1-(2-(Methylthio)phenyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83d)



Synthesised according to **General procedure L**, using 1,2-bis(2-(prop-2-yn-1-yloxy)ethyl)disulfide **84c** (46 mg, 0.20 mmol) and aldehyde **57b** (60 µL, 0.42 mmol). The crude hydroacylation product was dissolved in 1,4-dioxane (45 mL) and water (5 mL). TCEP·HCl (4.00 equiv.) was introduced followed by 4 N HCl in 1,4-dioxane (4.0 equiv.). The mixture was stirred at 55 °C under nitrogen for 4 h. 1 M NaOH (20 mL) was added, and the solution extracted with CH_2Cl_2 (3 × 20 mL). Purification by column chromatography (1:1 Pentane:Et_2O) afforded compound **83d** (36 mg, 0.14 mmol, 34%) as a yellow solid.

m.p. 98−99 °C; **δH** (400 MHz, $CDCl_3$) 7.82 (1H, dd, J = 7.8, 1.5 Hz, *Ar*), 7.51-7.44 (1H, m, *Ar*), 7.33 (1H, dd, J = 8.2, 1.1 Hz, *Ar*), 7.23-7.16 (1H, m, *Ar*), 4.13 (1H, dd, J = 11.7, 2.8 Hz, C(8)*H*H), 4.00-3.93 (1H, m, C(10)*H*H), 3.90-3.81 (1H, m, C(10)H*H*), 3.67 (1H, dd, J = 11.6, 6.6 Hz, C(8)H*H*), 3.50-3.40 (1H, m, C(7)*H*), 3.35-3.19 (2H, m, C(6)H_2), 2.79-2.62 (2H, m, C(9)H_2), 2.43 (3H, s, C(1)H_3); **δC** (101 MHz, $CDCl_3$) 198.2, 142.8, 134.3, 132.5, 130.2, 125.4, 123.6, 73.2, 68.6, 42.2, 34.1, 26.1, 16.1; **νmax**/ cm^{-1} (neat) 2980, 2359, 2194, 2033, 2015, 2000, 1660, 1383, 1261, 1106, 971; **m/z** [**HRMS** (ESI^+) $[M + H]^+$ $C_{13}H_{17}O_2S_2^+$ calc. 269.0664, found 269.0665.

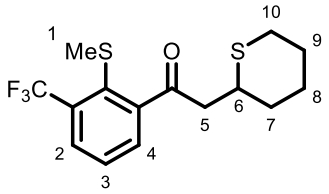
1-(4-Bromo-2-(methylthio)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83e)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57d** (46.0 mg, 0.20 mmol), and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (41 mg, 0.24 mmol). **General procedure N** used TFA (40 µL, 0.40 mmol), with stirring for 4 h. Purification by column chromatography (4:1 Hexane:Et_2O) yielded title compound **83e** (54 mg, 0.16 mmol, 79%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* = 8.3 Hz, *Ar*), 7.41 (1H, d, *J* = 1.9 Hz, *Ar*), 7.31 (1H, dd, J = 8.4, 1.8 Hz, *Ar*), 3.40-3.33 (1H, m, C(6)*H*), 3.11-2.96 (2H, m, C(5)H_2), 2.78-2.71 (1H, m, C(10)*H*H), 2.62-2.56 (1H, m, C(10)H*H*), 2.42 (3H, s, C(1)H_3), 2.13-2.07 (1H, m, C(7)*H*H), 1.96-1.89 (1H, m, C(9)*H*H), 1.87-1.79 (1H, m, C(8)*H*H), 1.65-1.54 (1H, m, C(9)H*H*), 1.49-1.37 (2H, m, C(7)H*H* and C(8)H*H*); **δ_C** (101 MHz, $CDCl_3$) 197.9, 145.4, 132.9, 131.5, 127.8, 126.6, 45.8, 37.8, 34.4, 29.5, 27.0, 25.9, 16.2; **ν_{max}**/ cm^{-1} (neat) 2921, 2851, 1672, 1572, 1536, 1458, 1436, 1364, 1342, 1312, 1275, 1210, 1177, 1148, 1095, 1041, 982, 925; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{18}O^{79}BrS_2^+$ calc. 346.9955, found 346.9956.

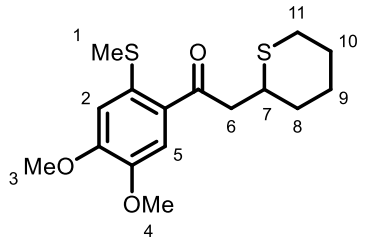
1-(2-(Methylthio)-3-(trifluoromethyl)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83f)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57e** (44.0 mg, 0.20 mmol), and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (41 mg, 0.24 mmol). **General procedure N** used TFA (40 µL, 0.40 mmol), with stirring for 4 h. Purification by column chromatography (9:1 Petane:Et_2O) yielded title compound **83f** (60.9 mg, 0.18 mmol, 91%) as an orange oil.

δ_F (377 MHz, $CDCl_3$) -59.73; **δ_H** (400 MHz, $CDCl_3$) 7.77-7.75 (1H, m, *Ar*), 7.54-7.46 (1H, m, *Ar*), 7.44-7.39 (1H, m, *Ar*), 3.41-3.39 (1H, br, C(6)*H*), 3.17-3.05 (2H, m, C(5)H_2), 2.78-2.68 (1H, m, C(10)*H*H), 2.65-2.56 (1H, m, C(10)*H*H), 2.32 (3H, s, C(1)H_3), 2.18-2.09 (1H, m, C(7)*H*H), 1.97-1.89 (1H, m, C(9)*H*H), 1.88-1.82 (1H, m, C(8)*H*H), 1.68-1.55 (1H, m, C(9)H*H*), 1.55-1.42 (2H, m, C(7)H*H* and C(8)H*H*); **δ_C** (101 MHz, $CDCl_3$) 203.4, 151.2, 135.2 (q, J_{CF} = 29.5 Hz), 130.9, 129.7, 129.3, 127.9 (q, J_{CF} = 5.6 Hz), 123.4 (q, J_{CF} = 274.0 Hz), 50.1, 37.1, 34.1, 29.2, 27.0, 25.7, 22.5; **ν_{max}**/ cm^{-1} (neat) 2924, 2853, 1706, 1578, 1422, 1317, 1281, 1137, 1100, 1014, 975; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{18}F_3OS_2^+$ calc. 335.0746, found 335.0746.

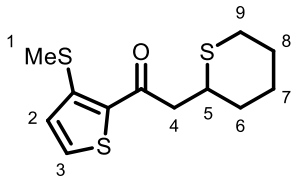
1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83g)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57c** (43 mg, 0.20 mmol) and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (41 mg, 0.24 mmol). **General procedure N** used TFA (40 µL, 0.40 mmol), with stirring for 4 h. Purification by column chromatography (1:1 Pentane:Et_2O) yielded title compound **83g** (24 mg, 0.07 mmol, 37%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.29 (1H, s, *Ar*), 6.81 (1H, s, *Ar*), 3.96 (3H, s, C(3 or 4)H_3), 3.92 (3H, s, C(3 or 4)H_3), 3.45-3.35 (1H, br, C(7)*H*), 3.12-2.97 (2H, m, C(6)H_2), 2.31-2.72 (1H, m, C(11)*H*H), 2.64-2.56 (1H, m, C(11)H*H*), 2.44 (3H, s, C(1)H_3), 2.17-2.09 (1H, m, C(8)*H*H), 1.98-1.90 (1H, m, C(10)*H*H), 1.87-1.80 (1H, m, C(9)*H*H), 1.65-1.54 (1H, m, C(10)H*H*), 1.47-1.38 (2H, m, C(8)H*H* and C(9)H*H*); **δ_C** (101 MHz, $CDCl_3$) 197.2, 152.7, 145.7, 136.4, 113.4, 108.7, 56.5, 56.1, 45.9, 38.1, 34.6, 27.1, 26.0, 16.8; **ν_{max}**/ cm^{-1} (neat) 2920, 2850, 1660, 1598, 1552, 1502, 1437, 1346, 1268, 1203, 1167, 1030; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{16}H_{22}O_3{}^{23}NaS_2{}^+$ calc. 349.0903, found 349.0903.

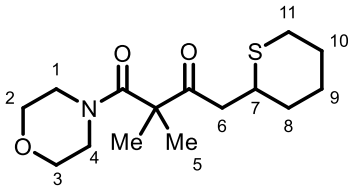
1-(3-(Methylthio)thiophen-2-yl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83h)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57f** (32 mg, 0.20 mmol) and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (41 mg, 0.24 mmol). **General procedure N** used TFA (40 µL, 0.400 mmol), with stirring for 4 h. Purification by column chromatography (85:15 Pentane:EtOAc) yielded title compound **83h** (44.7 mg, 0.16 mmol, 82%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.54 (1H, d, *J* = 5.2 Hz, *Ar*), 7.04 (1H, d, *J* = 5.2 Hz, *Ar*), 3.44-3.38 (1H, m, C(5)*H*), 3.00-2.88 (2H, m, C(4)H_2), 2.77-2.70 (1H, m, C(9)*H*H), 2.63-2.58 (1H, m, C(9)*H*H), 2.53 (3H, s, C(1)H_3), 2.14-2.09 (1H, m, C(6)*H*H), 1.96-1.89 (1H, m, C(8)*H*H), 1.86-1.81 (1H, m, C(7)*H*H), 1.68-1.56 (1H, m, C(8)H*H*), 1.52-1.40 (2H, m, C(6)H*H* and C(7)H*H*); **δ_C** (101 MHz, $CDCl_3$) 189.7, 146.4, 131.2, 126.4, 46.9, 38.1, 34.3, 29.4, 27.0, 25.8, 16.7; **ν_{max}**/ cm^{-1} (neat) 2850, 1641, 1478, 1397, 1355, 1173, 1004; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{12}H_{16}NOS_3^+$ calc. 273.0436, found 273.0436.

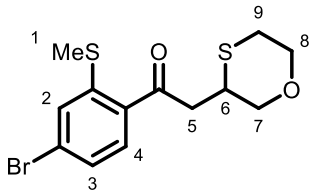
2,2-Dimethyl-1-morpholino-4-(tetrahydro-2*H*-thiopyran-2-yl)butane-1,3-dione (83i)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(hex-5-yn-1-yl)sulfide **91a** (41 mg, 0.24 mmol). **General procedure N** used TFA (40 µL, 0.40 mmol), with stirring for 4 h. Purification by column chromatography (1:1 Pentane:EtOAc) yielded title compound **83i** (40.8 mg, 0.17 mmol, 68%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 3.63 (8H, br, C(1 to 4)H_2), 3.32-3.22 (1H, m, C(7)*H*), 2.81-2.64 (1H, m, C(11)*H*H), 2.63-2.52 (3H, m, C(11)H*H* and C(6)H_2), 1.99-1.87 (2H, m, C(10)*H*H and C(8)*H*H), 1.87-1.76 (1H, m, C(9)*H*H), 1.72–1.48 (1H, m, C(10)H*H*), 1.49-1.39 (2H, m, C(8)H*H* and C(9)H*H*), 1.38 (6H, br, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 207.8, 170.9, 66.6 (bs, 2C), 55.8, 46.7 (bs), 44.0, 44.0 (bs), 36.4, 34.2, 29.1, 26.8, 25.7, 23.7, 23.2; **ν_{max}**/ cm^{-1} (neat) 2925, 2852, 1708, 1639, 1422, 1362, 1272, 1247, 1183, 1115, 1022; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{25}O_3N^{23}NaS^+$ calc. 322.1447, found 322.1448.

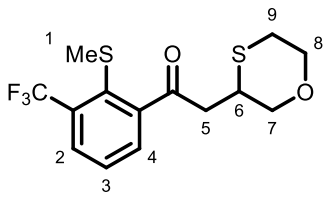
1-(4-Bromo-2-(methylthio)phenyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83j)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57d** (46 mg, 0.20 mmol) and *tert*-butyl(2-(prop-2-yn-1-yloxy)ethyl)sulfane **91i** (41 mg, 0.24 mmol). **General procedure N** used TFA (60 µL, 0.60 mmol), with stirring for 16 h. Purification by column chromatography (9:1 to 1:1 Pentane:Et_2O) yielded title compound **83j** (35 mg, 0.10 mmol, 51%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.69 (1H, d, *J* = 8.4 Hz, *Ar*), 7.42 (1H, d, *J* = 1.8 Hz, *Ar*), 7.32 (1H, dd, *J* = 8.3, 1.8 Hz, *Ar*), 4.11 (1H, dd, *J* = 11.7, 2.7 Hz, C(7)*H*H), 3.95 (1H, ddd, *J* = 11.7, 6.4, 3.2 Hz, C(8)*H*H), 3.86 (1H, ddd, *J* = 11.8, 6.8, 3.2 Hz, C(8)H*H*), 3.67 (1H, dd, *J* = 11.7, 6.4 Hz, C(7)H*H*), 3.41 (1H, qd, *J* = 6.6, 2.7 Hz, C(6)*H*), 3.30-3.18 (2H, m, C(5)H_2), 2.77-2.63 (2H, m, C(9)H_2), 2.43 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 197.2, 145.5, 132.5, 131.4, 128.1, 127.9, 126.6, 73.0, 68.6, 42.0, 34.0, 26.0, 16.2; **ν_{max}**/ cm^{-1} (neat) 2918, 2852, 1671, 1572, 1537, 1457, 1434, 1410, 1365, 1319, 1285, 1270, 1243, 1212, 1149, 1106, 1094, 1045, 1017, 987, 974, 924, 903; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{13}H_{15}BrO_2{}^{23}NaS_2{}^+$ calc. 370.9567, found 370.9567.

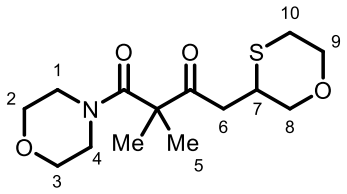
1-(2-(Methylthio)-3-(trifluoromethyl)phenyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83k)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57e** (44 mg, 0.20 mmol) and *tert*-butyl(2-(prop-2-yn-1-yloxy)ethyl)sulfane **91i** (41 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 16 h. Purification by column chromatography (9:1 to 7:3 Petrol:Et_2O) yielded title compound **83k** (23 mg, 0.07 mmol, 34%) as a yellow oil.

δ_F (377 MHz, $CDCl_3$) -59.76; **δ_H** (400 MHz, $CDCl_3$) 7.78 (1H, dd, *J* = 7.8, 1.5 Hz, *Ar*), 7.51 (1H, td, *J* = 7.7, 0.9 Hz, *Ar*), 7.41 (1H, dd, *J* = 7.7, 1.5 Hz, *Ar*), 4.15 (1H, dd, *J* = 11.7, 2.8 Hz, C(7)*H*H), 3.98 (1H, ddd, *J* = 11.8, 5.5, 3.7 Hz, C(8)*H*H), 3.84 (1H, ddd, *J* = 11.7, 6.4, 3.9 Hz, C(8)H*H*), 3.70 (1H, dd, *J* = 11.7, 6.8 Hz, C(7)H*H*), 3.42 (1H, qd, *J* = 6.9, 2.8 Hz, C(6)*H*), 3.31-3.28 (1H, dd, *J* = 17.9, 6.9 Hz, C(5)*H*H), 3.21 (1H, dd, *J* = 17.9, 6.9 Hz, C(5)H*H*), 2.75-2.66 (2H, m, C(9)H_2), 2.33 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 202.6, 150.8, 135.1 (q, J_{CF} = 29.7 Hz), 130.8, 129.4, 129.3, 127.9 (q, J_{CF} = 5.6 Hz), 123.3 (q, J_{CF} = 273.9 Hz), 72.9, 68.4, 46.1, 33.6, 26.0, 22.4; **ν_{max}**/ cm^{-1} (neat) 2926, 2854, 2348, 1706, 1578, 1422, 1318, 1161, 1130, 1101, 1053, 927; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{16}F_3O_2S_2^+$ calc. 353.0487, found 353.0487.

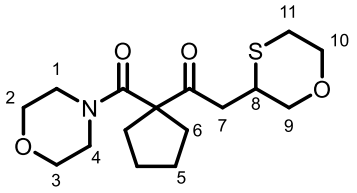
2,2-Dimethyl-1-morpholino-4-(1,4-oxathian-3-yl)butane-1,3-dione (83l)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(2-(prop-2-yn-1-yloxy)ethyl)sulfane **91i** (41 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 16 h. Purification by column chromatography (7:3 EtOAc:Pentane) yielded title compound **83l** (49.8 mg, 0.16 mmol, 83%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 3.99 (1H, dd, *J* = 11.7, 2.8 Hz, C(8)*H*H), 3.93-3.79 (2H, m, C(9)H_2), 3.67-3.51 (9H, m, C(1 to 4)H_2 and C(8)H*H*), 3.24 (1H, qd, *J* = 6.7, 2.7 Hz, C(7)*H*), 2.78 (2H, dd, *J* = 6.8, 2.1 Hz, C(6)H_2), 2.72-2.55 (2H, m, SC(10)H_2), 1.38 (6H, br, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 207.6, 170.8, 72.8, 68.6, 66.6 (bs, 2C), 55.8, 46.3 (bs), 43.4 (bs), 40.3, 33.1, 25.5, 23.6, 23.2; **ν_{max}**/ cm^{-1} (neat) 2921, 2853, 1708, 1637, 1456, 1421, 1385, 1363, 1272, 1249, 1183, 1112, 1095, 1063, 1021, 995, 980, 951, 926; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{23}NO_4S^+$ calc. 302.1421, found 302.1420.

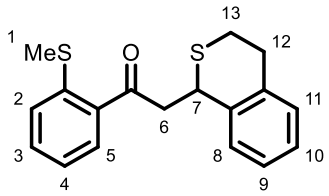
1-(1-(Morpholine-4-carbonyl)cyclopentyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83m)



Synthesised according to **general procedures M** and **N**. **General Procedure M** used aldehyde **57a** (42.3 mg, 0.20 mmol) and *tert*-butyl(2-(prop-2-yn-1-yloxy)ethyl)sulfane **91i** (41 mg, 0.24 mmol). **General procedure N** used TFA (0.16 mL, 2.0 mmol), with stirring for 22 h. Purification by column chromatography (7:3 Et_2O:Pentane) yielded title compound **83m** (18.4 mg, 0.06 mmol, 49%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 3.98 (1H, dd, *J* = 11.7, 2.7 Hz, C(8)*H*H), 3.95-3.79 (2H, m, C(10)H_2), 3.73-3.48 (9H, m, C(1 to 4)H_2 and C(9)H*H*), 3.30-3.17 (2H, m, C(7)*H*H and C(8)*H*), 2.83-2.66 (2H, m, C(7)H*H* and C(11)*H*H), 2.64-2.55 (1H, m, C(11)H*H*), 2.42-1.94 (4H, m, C(5 and 6)H_2), 1.73-1.50 (4H, m, C(5 and 6)H_2); **δ_C** (101 MHz, $CDCl_3$) 205.1, 170.6, 72.9, 68.6, 67.2, 66.9, 66.3, 46.3, 43.3, 40.8, 34.2, 33.4, 33.2, 26.3, 26.3, 25.5; **ν_{max}**/ cm^{-1} (neat) 3504, 3018, 2986, 2952, 2917, 2853, 2360, 1708, 1637, 1453, 1422, 1358, 1298, 1273, 1238, 1203, 1178, 1114, 1064, 1030, 993, 914; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{16}H_{25}NO_4{}^{23}NaS^+$ calc. 350.1397, found 350.1397.

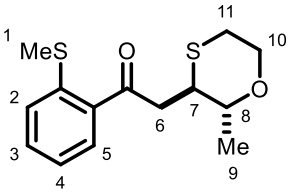
2-(Isothiochroman-1-yl)-1-(2-(methylthio)phenyl)ethan-1-one (83n)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57b** (26.0 µL, 0.20 mmol) and *tert*-butyl(2-ethynylphenethyl)sulfane **91d** (52.4 mg, 0.24 mmol). **General procedure N** used TFA (40 µL, 0.40 mmol), with stirring for 4 h. Purification by column chromatography (9:1 Pentane:Et_2O) yielded title compound **83n** (53 mg, 0.17 mmol, 84%) as yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.78 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.51-7.42 (1H, m, *Ar*), 7.38-7.31 (1H, m, *Ar*), 7.20-7.11 (5H, m, *Ar*), 4.67 (1H, dd, *J* = 8.8, 5.1 Hz, C(7)*H*), 3.70 (1H, dd, *J* = 17.1, 8.8 Hz, C(6)*H*H), 3.47 (1H, dd, *J* = 17.1, 5.1 Hz, C(6)*H*H), 3.11-3.05 (2H, m, C(12)H_2), 3.01-2.90 (1H, m, C(13)*H*H), 2.89-2.79 (1H, m, C(13)*H*H), 2.44 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 198.3, 142.7, 137.9, 136.7, 134.6, 132.4, 130.2, 129.7, 127.5, 127.0, 126.7, 125.4, 123.6, 48.7, 36.5, 31.0, 24.7, 16.2; **ν_{max}**/ cm^{-1} (neat) 3058, 3018, 2919, 2853, 2357, 1670, 1586, 1557, 1489, 1460, 1432, 1376, 1347, 1319, 1290,1273, 1233, 1205, 1171, 1141, 1107, 1079, 1045, 978, 903; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{18}H_{18}O^{23}NaS_2^+$ calc. 337.0691, found 337.0693.

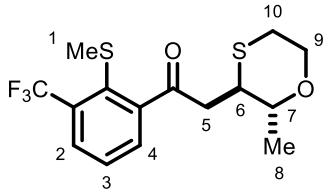
2-((2*R,3*R**)-2-Methyl-1,4-oxathian-3-yl)-1-(2-(methylthio)phenyl)ethan-1-one (83o)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57b** (26 µL, 0.20 mmol) and (2-(but-3-yn-2-yloxy)ethyl)(*tert*-butyl)sulfane **91f** (44.7 mg, 0.24 mmol). **General procedure N** used TFA (20 µL, 0.20 mmol), with stirring for 3 h. Purification of the crude residue (2:1 dr) by column chromatography (6:4 Pentane:Et_2O) yielded title compound as an inseparable mixture of diastereoisomers **83o** (12.7 mg, 0.045 mmol, 22%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.94-7.72 (1H, m, *Ar*), 7.51-7.43 (1H, m, *Ar*), 7.38-7.31 (1H, m, *Ar*), 7.24-7.17 (1H, m, *Ar*), 4.25-4.13 (1H, m, C(10)*H*H), 3.77-3.68 (1H, m, C(10)*H*H), 3.65-3.53 (1H, m, C(8)*H*), 3.43-3.29 (1H, m, C(7)*H*), 3.27-3.17 (1H, m, C(6)*H*H), 3.03-2.90 (2H, m, C(6)*H*H and C(11)*H*H), 2.44 (3H, s, C(1)H_3), 2.44-2.38 (1H, m, C(11)*H*H), 1.27 (3H, d, J = 6.3 Hz, C(9)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 198.1, 142.7, 132.5, 130.2, 125.56, 123.7, 78.2, 67.9, 42.7, 40.2, 29.8, 28.2, 19.8, 16.2; **ν_{max}**/ cm^{-1} (neat) 2979, 2917, 2853, 2363, 2342, 1672, 1586, 1558, 1461, 1433, 1376, 1352, 1296, 1273, 1246, 1221, 1174, 1140, 1107, 1089, 1047, 1017, 978; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{14}H_{18}O_2{}^{23}NaS_2{}^+$ calc. 351.0695, found 351.0697.

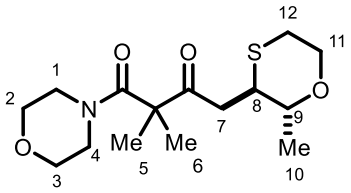
2-((2*R,3*R**)-2-Methyl-1,4-oxathian-3-yl)-1-(2-(methylthio)-3 (trifluoromethyl)phenyl)ethan-1-one (83p)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57e** (44 µL, 0.20 mmol) and (2-(but-3-yn-2-yloxy)ethyl)(*tert*-butyl)sulfane **91f** (44.7 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 22 h. Purification of the crude residue (2.4:1 dr) by column chromatography (94:6 to 8:2 Petrol:Et_2O) yielded title compound as an inseparable mixture of diastereoisomers **83p** (33.9 mg, 0.097 mmol, 48%) as a yellow oil.

δ_F (377 MHz, $CDCl_3$) (major signals only) -59.72; **δ_H** (400 MHz, $CDCl_3$) (major signals only) 7.79-7.77 (1H, m, *Ar*), 7.54-7.45 (3H, m, *Ar*), 4.20-4.15 (1H, m, C(9)*H*H), 3.75-3.69 (1H, m, C(9)H*H*), 3.63-3.56 (2H, m, C(5)*H*H and C(7)*H*), 3.38 (1H, dd, *J* = 17.9, 4.0 Hz, C(5)H*H*), 3.09-3.05 (1H, m, C(6)*H*), 3.03-2.91 (1H, m, C(10)*H*H), 2.42 (1H, dt, *J* = 13.6, 2.6 Hz, C(10)*H*H), 2.32 (3H, s, C(1)H_3), 1.31 (3H, d, *J* = 6.3 Hz, C(8)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only); 202.7, 150.9, 135.1 (q, J_{CF} = 29.5 Hz), 129.4, 129.3, 128.0 (q, J_{CF} = 5.6 Hz), 123.4 (q, J_{CF} = 273.8 Hz), 77.8, 68.0, 42.4, 36.4, 28.1, 22.5, 19.8; **ν_{max}**/ cm^{-1} (neat) 2979, 2927, 2854, 1707, 1577, 1421, 1377, 1316, 1298, 1277, 1162, 1133, 1101, 1052, 1019, 976; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{18}O_2F_3S_2^+$ calc. 351.0695, found 351.0697.

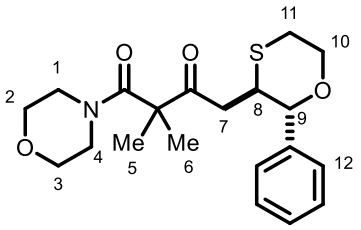
2,2-Dimethyl-4-((2*R,3*R**)-2-methyl-1,4-oxathian-3-yl)-1-morpholinobutane-1,3-dione (83q)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37.0 mg, 0.20 mmol) and (2-(but-3-yn-2-yloxy)ethyl)(*tert*-butyl)sulfane **91f** (44.7 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.8 mmol), with stirring for 16 h. Purification of the crude residue (3:1 dr) by column chromatography (7:3 EtOAc:Pentane) yielded title compound as an inseparable mixture of diastereoisomers **83q** (51 mg, 0.16 mmol, 81%) as a yellow-orange oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.21-4.08 (1H, m, C(11)*H*H), 3.81-3.50 (10H, m, C(1 to 4)H_2), C(9)*H* and C(11)H*H*), 3.19-3.10 (1H, m, SC(8)*H*), 2.96-12.86 (1H, m, C(12)*H*H), 2.78-2.68 (1H, m, C(7)*H*H), 2.63-2.54 (1H, m, C(7)*H*H), 2.45-2.37 (1H, m, C(12)*H*H), 1.39 (3H, s, C(5 or 6)H_3), 1.39 (3H, s, C(5 or 6)H_3), 1.22 (3H, d, J = 6.3 Hz, C(10)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 208.4, 170.8, 77.0, 67.5, 66.6 (bs, 2C), 55.9, 40.5, 38.9, 27.8, 23.8, 23.3, 19.5; **ν_{max}**/ cm^{-1} (neat) 2922, 2854, 1710, 1637, 1460, 1421, 1376, 1364, 1298, 1272, 1247, 1182, 1112, 1089, 1067, 1021, 954; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{26}NO_4{}^{23}NaS^+$ calc. 316.1577, found 316.1579.

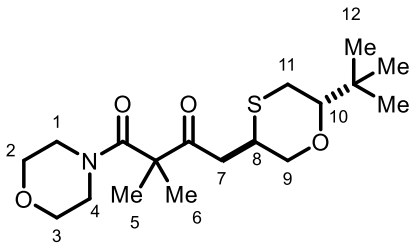
2,2-Dimethyl-1-morpholino-4-((2*R,3*R**)-2-phenyl-1,4-oxathian-3-yl)butane-1,3-dione (83r)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(2-((1-phenylprop-2-yn-1-yl)oxy)ethyl)sulfane **91g** (59.6 mg, 0.24 mmol). **General procedure N** used TFA (0.06 mL, 0.60 mmol), with stirring for 16 h. Purification of the crude residue (2:1 dr) by column chromatography (9:1 to 1:1 Petrol:EtOAc) yielded title compound as an inseparable mixture of diastereoisomers **83r** (32 mg, 0.86 mmol, 43%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.38-7.28 (5H, m, *Ar*), 4.39-4.31 (2H, m, C(9)*H* and C(10)*H*H), 3.88 (1H, td, *J* = 11.9, 2.0 Hz, C(10)*H*H), 3.60 (1H, td, *J* = 9.8, 2.5 Hz, C(8)*H*), 3.49-3.30 (4H, m, C(1 to 4)H_2), 3.30-3.15 (1H, m, C(11)*H*H), 3.14-2.89 (2H, m, C(1 to 4)H_2), 2.84-2.64 (2H, m, C(1 to 4)H_2), 2.53-2.39 (2H, m, C(11)*H*H and C(7)*H*H), 2.28-2.20 (1H, m, C(7)*H*H), 1.28 (3H, s, C(5 or 6)H_3), 1.18 (3H, s, C(5 or 6)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only); 206.4, 170.6, 139.2, 128.8, 128.8, 127.4, 85.3, 69.5, 66.5 (bs), 65.8 (bs), 55.4, 46.2 (bs), 43.0 (bs), 39.9, 38.7, 28.4, 23.7, 22.4; **ν_{max}**/ cm^{-1} (neat) 2918, 2855, 1714, 1639, 1421, 1361, 1298, 1272, 1248, 1183, 1115, 1023; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{20}H_{27}NO_4{}^{23}NaS^+$ calc. 400.1577, found 400.1557.

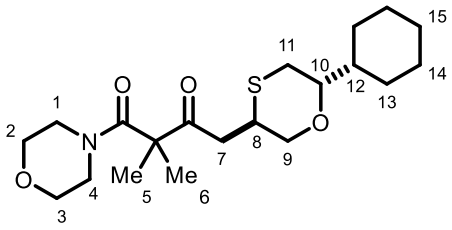
4-((3*R,6*S**)-6-(*tert*-Butyl)-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83s)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(3,3-dimethyl-2-(prop-2-yn-1-yloxy)butyl)sulfane **91o** (54.8 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 30 min. Purification of the crude residue (4:1 dr) by column chromatography (7:3 to 1:1 Petrol:EtOAc) yielded title compound as an inseparable mixture of diastereoisomers **83s** (53 mg, 0.15 mmol, 74%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.15 (1H, m, C(9)*H*H), 3.61 (8H, br, C(1 to 4)H_2), 3.38-3.25 (2H, m, C(9)H*H* and C(8)*H*), 3.08 (1H, dd, *J* = 10.7, 1.7 Hz, C(10)*H*), 2.74 (1H, dd, *J* = 13.3, 10.7 Hz, C(11)*H*H), 2.43-2.36 (3H, m, C(11)H*H* and C(7)H_2), 1.34 (3H, s, C(5 or 6)H_3), 1.34 (3H, s, C(5 or 6)H_3), 0.87 (9H, s, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.0, 170.7, 85.8, 74.7, 66.6 (bs, 2C), 55.8, 46.44 (bs), 43.44 (bs), 39.3, 34.9, 33.8, 27.8, 26.0, 23.7, 23.1; **ν_{max}**/ cm^{-1} (neat) 2957, 2855, 2363, 1710, 1639, 1466, 1421, 1363, 1301, 1272, 1248, 1182, 1150, 1114, 1091, 1065, 1022, 975, 950, 916; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{18}H_{32}NO_4S^+$ calc. 358.2047, found 358.2051.

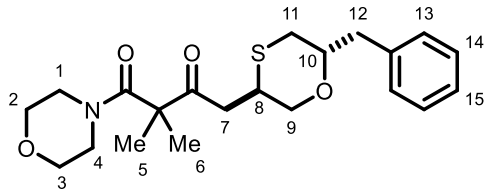
4-((3*R,6*S**)-6-Cyclohexyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83t)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(2-cyclohexyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane **91n** (61.1 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 1.5 h. Purification of the crude residue (3:1 dr) by column chromatography (8:1 to 1:1 Petrol:EtOAc) yielded title compound as an inseparable mixture of diastereoisomers **83t** (55 mg, 0.14 mmol, 72%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.16-4.10 (1H, m, C(9)*H*H), 3.73-3.46 (8H, br, C(1 to 4)H_2), 3.42-3.22 (2H, m, C(9)H*H* and C(8)*H*), 3.22-3.16 (1H, m, C(10)*H*), 2.77-2.60 (1H, m, C(11)*H*H), 2.45-2.37 (3H, m, C(11)H*H* and C(7)H_2), 1.88-1.80 (1H, m, Cy-*H*), 1.76-1.66 (2H, m, Cy-*H*), 1.67-1.58 (2H, m, Cy-*H*), 1.35 (3H, s, C(5 or 6)H_3), 1.35 (3H, s, C(5 or 6)H_3), 1.27-0.82 (6H, m, Cy-*H*); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.0, 170.7, 82.2, 74.2, 66.6 (bs, 2C), 55.8, 42.9, 39.4, 33.9, 29.9, 28.9, 28.7, 26.5, 26.2, 26.1, 23.7, 23.1; **ν_{max}**/ cm^{-1} (neat) 2922, 2851, 2246, 1709, 1638, 1447, 1420, 1385, 1362, 1300, 1272, 1247, 1183, 1150, 1113, 1089, 1020, 977, 950, 918; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{34}NO_4S^+$ calc. 384.2203, found 384.2200.

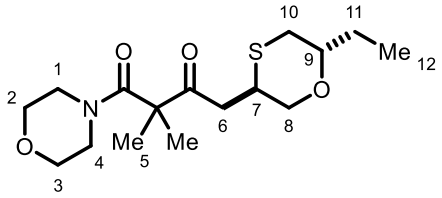
4-((3*R,6*S**)-6-Benzyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83u)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(3-phenyl-2-(prop-2-yn-1-yloxy)propyl)sulfane **91l** (63 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 2.5 h. Purification of the crude residue (2.6:1 dr) by column chromatography (7:3 to 1:1 Petrol:EtOAc) yielded title compound as an inseparable mixture of diastereoisomers **83u** (60 mg, 0.15 mmol, 77%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.27-7.08 (5H, m, *Ar*), 4.08 (1H, dd, *J* = 10.8, 2.4 Hz, C(9)*H*H), 3.67-3.59 (1H, m, C(10)*H*), 3.59-3.45 (8H, br, C(1 to 4)H_2), 3.38-3.23 (2H, m, C(9)H*H* and C(8)*H*), 2.89-2.81 (1H, m, C(11)*H*H), 2.69-2.53 (2H, m, C(11)H*H* and C(12)*H*H), 2.37 (1H, d, *J* = 6.3 Hz, C(7)H_2), 2.31 (1H, dd, *J* = 13.6, 1.9 Hz, C(12)*H*H), 1.29 (3H, s, C(5 or 6)H_3), 1.29 (3H, s, C(5 or 6)H_3); **δc** (101 MHz, $CDCl_3$) (major signals only) 206.9, 170.6, 137.5, 129.4, 128.5, 126.5, 78.4, 73.9, 66.6 (bs, 2C), 55.8, 46.4 (bs), 43.4 (bs), 42.3, 39.3, 33.7, 31.8, 23.7, 23.1; **ν_{max}**/ cm^{-1} (neat) 3499, 3026, 2919, 2854, 1734, 1708, 1636, 1495, 1453, 1421, 1385, 1361, 1300, 1271, 1246, 1183, 1144, 1113, 1092, 1020, 950, 911; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{21}H_{30}NO_4S^+$ calc. 392.1890, found 392.1886.

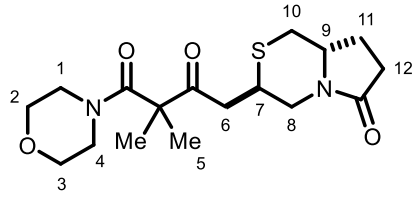
4-((3*R,6*S**)-6-Ethyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83v)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(2-(prop-2-yn-1-yloxy)butyl)sulfane **91k** (48.1 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 2.5 h. Purification of the crude residue (2.6:1 dr) by column chromatography (7:3 to 1:1 Petrol:EtOAc) yielded title compound as an inseparable mixture of diastereoisomers **83v** (26.8 mg, 0.099 mmol, 49%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.17-4.10 (1H, m, C(8)*H*H), 3.62 (8H, br, C(1 to 4)H_2), 3.50-3.20 (3H, m, C(8)H*H*, C(9)*H* and C(7)*H*), 2.67 (1H, dd, *J* = 13.5, 10.4 Hz, C(6)*H*H), 2.44 (2H, d, *J* = 6.4 Hz, C(10)H_2), 2.40 (1H, dd, *J* = 13.6, 1.9 Hz, C(6)H*H*), 1.62-1.41 (2H, m, C(11)H_2), 1.36-1.35 (6H, m, C(5)H_3), 0.92 (3H, t, *J* = 7.5 Hz, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.0, 170.7, 79.1, 73.9, 66.8 (bs, 2C), 55.8, 39.4, 33.9, 31.9, 28.8, 23.7, 23.1, 9.9; **ν_{max}**/ cm^{-1} (neat) 2962, 2920, 2853, 1709, 1638, 1464, 1421, 1363, 1302, 1272, 1248, 1184, 1115, 1082, 1020, 949, 903; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{16}H_{28}NO_4{}^{23}NaS^+$ calc. 330.1734, found 330.1729.

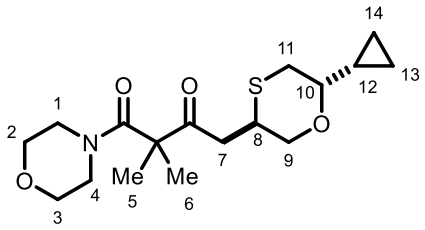
2,2-Dimethyl-1-morpholino-4-((3*R,8a*S**)-6-oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]thiazin-3-yl)butane-1,3-dione (83w)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and 5-((*tert*-butylthio)methyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one **91e** (54.1 mg, 0.24 mmol). **General procedure N** used TFA (0.1 mL, 2.00 mmol) with stirring for 22 h. Purification of the crude residue (3:1 dr) by column chromatography (100:0 to 9:1 EtOAc:MeOH) yielded title compound as an inseparable mixture of diastereoisomers **83w** (62 mg, 0.18 mmol, 88%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.46 (1H, dd, *J* = 13.0, 3.2 Hz, C(8)*H*H), 3.79-3.61 (9H, m, C(1 to 4)H_2 and C(9)*H*), 3.36-3.23 (1H, m, C(7)*H*), 2.75-2.65 (5H, m, C(6)H_2, C(8)H*H* and C(10)H_2), 2.54-2.46 (2H, m, C(12)H_2), 2.42-2.31 (1H, m, C(11)*H*H), 1.82-1.69 (1H, m, C(11)H*H*), 1.50-1.44 (6H, br, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 206.2, 174.1, 170.6, 66.6 (bs, 2C), 57.4, 55.8, 47.3, 46.6 (bs), 43.4 (bs), 40.5, 35.2, 34.9, 30.0, 24.7, 23.6, 23.2; **ν_{max}**/ cm^{-1} (neat) 3492, 2918, 2856, 1683, 1637, 1421, 1366, 1302, 1271, 1251, 1183, 1115, 1064, 1022, 922; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{17}H_{27}N_2O_4S^+$ calc. 355.1687, found 355.1686.

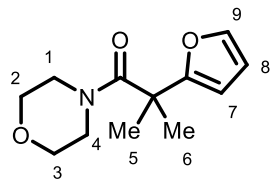
4-((3*R,6*S**)-6-Cyclopropyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83x)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(2-cyclopropyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane **91j** (56 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 2.5 h. Purification of the crude residue (2.7:1 dr) by column chromatography (1:1 Petrol:EtOAc) yielded title compound as an inseparable mixture of diastereoisomers **83x** (6.6 mg, 0.019 mmol, 10%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.16 (1H, dd, *J* = 11.1, 2.8 Hz, C(9)*H*H), 3.63 (8H, br, C(1 to 4)H_2), 3.45-3.36 (1H, m, C(8)*H*), 3.36-3.26 (1H, m, C(9)H*H*), 2.90-2.73 (2H, m, C(7)*H*H and C(10)*H*), 2.53 (1H, dd, *J* = 13.2, 1.6 Hz, C(7)H*H*), 2.44 (2H, dd, *J* = 6.6, 1.4 Hz, C(11)H_2), 1.37 (3H, s, C(5 or 6)H_3), 1.36 (3H, s, C(5 or 6)H_3), 0.95-0.85 (1H, m, C(12)*H*), 0.64-0.46 (2H, m, C(13 and 14)H_2), 0.44-0.33 (1H, m, C(13 and 14)H_2), 0.29-0.16 (1H, m, C(13 and 14)H_2); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.0, 170.7, 82.0, 74.0, 66.7 (bs, 2C), 55.9, 39.4, 33.8, 31.9, 23.8, 23.2, 15.8, 3.4, 2.0; **ν_{max}**/ cm^{-1} (neat) 3310, 2972, 2959, 2924, 2852, 1448, 1391, 1363, 1339, 1265, 1162, 1071, 1035, 1016, 970, 936, 910; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{17}H_{28}NO_4{}^{23}NaS^+$ calc. 342.1734, found 342.1732.

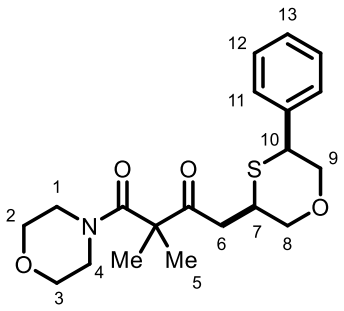
2-(Furan-2-yl)-2-methyl-1-morpholinopropan-1-one (94)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(2-cyclopropyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane **91j** (56 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol), with stirring for 2.5 h. Purification by column chromatography (1:1 Petrol:EtOAc) yielded title compound **94** (18.9 mg, 0.085 mmol, 42%) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.33 (1H, dd, *J* = 1.9, 0.8 Hz, C(9)*H*), 6.33 (1H, dd, *J* = 3.3, 1.9 Hz, C(8)*H*), 6.07 (1H, dd, *J* = 3.2, 0.8 Hz, C(7)*H*), 3.80-3.04 (10H, m, C(1 to 4)H_2), 1.53 (6H,s, C(5 or 6)H_3); **δ_C** (101 MHz, $CDCl_3$) 172.6, 159.3, 141.2, 110.7, 103.4, 66.8 (bs, 2C), 43.3, 26.6; **ν_{max}**/ cm^{-1} (neat) 2974, 2936, 2912, 2876, 2361, 2340, 1854, 1639, 1551, 1529, 1467, 1422, 1372, 1246, 1202, 1113, 1049, 1016; **HRMS** (ESI^+) $[M + H]^+$ $C_{12}H_{18}NO_3^+$ calc. 224.1281, found 224.1282.

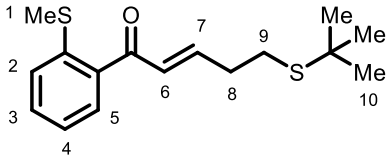
2,2-Dimethyl-1-morpholino-4-((3*R,5*S**)-5-phenyl-1,4-oxathian-3-yl)butane-1,3-dione (83y)**



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57a** (37 mg, 0.20 mmol) and *tert*-butyl(1-phenyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane **91r** (59.6 mg, 0.24 mmol). **General procedure N** used TFA (0.12 mL, 1.2 mmol), with stirring for 16 h. Purification of the crude residue (>20:1 dr) by column chromatography (7:3 to 8:2 Et_2O:Pentane) yielded title compound as a single diastereoisomer **83y** (43.7 mg, 0.12 mmol, 58%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.37-7.24 (5H, m, *Ar*), 4.24-4.14 (3H, m, C(8)H_2O and C(9)*H*H), 3.70-3.54 (10H, m, C(7)*H*, C(9)H*H* and C(1 to 4)H_2), 3.34 (1H, t, *J* = 10.9 Hz, C(10)*H*), 2.53 (2H, d, *J* = 6.7 Hz, C(6)H_2), 1.37 (6H, br, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 206.8, 199.8, 170.7, 137.5, 128.8, 128.1, 128.0, 73.7, 72.7, 66.6 (bs, 2C), 45.6, 39.4, 35.9, 23.7, 23.2; **ν_{max}**/ cm^{-1} (neat) 3505, 2987, 2922, 2852, 2247, 2063, 1709, 1636, 1491, 1451, 1422, 1386, 1361, 1298, 1272, 1248, 1182, 1152, 1111, 1092, 1065, 1036, 1018, 979, 948, 913; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{28}NO_4S^+$ calc. 378.1734, found 378.1729.

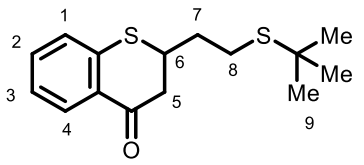
(*E*)-5-(*tert*-Butylthio)-1-(2-(methylthio)phenyl)pent-2-en-1-one (97a)



Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57b** (26 µL, 0.20 mmol) and but-3-yn-1-yl(tert-butyl)sulfane **91b** (34 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol) and $AlCl_3$ (2.7 mg, 0.02 mmol) with stirring for 16 h. Purification by column chromatography (8:2 Pentane:Et_2O) yielded title compound **97a** (13 mg, 0.044 mmol, 27%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.61 (1H, dd, *J* = 7.7, 1.5 Hz, *Ar*), 7.44 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz, *Ar*), 7.34 (1H, dd, *J* = 8.1, 1.2 Hz, *Ar*), 7.20 (1H, td, *J* = 7.5, 1.2 Hz, *Ar*), 6.86 (1H, dt, *J* = 15.6, 6.6 Hz, C(7)*H*), 6.70 (1H, dt, *J* = 15.6, 1.4 Hz, C(6)*H*), 2.72-2.63 (2H, m, C(9)H_2), 2.60-2.50 (2H, m, C(8)H_2), 2.44 (3H, s, C(1)H_3), 1.33 (9H, s, C(10)H_3); **δ_C** (101 MHz, $CDCl_3$) 193.1, 148.2, 140.6, 136.9, 131.5, 129.7, 129.4, 126.3, 124.1, 42.4, 33.1, 31.0, 26.8, 16.5; **ν_{max}**/ cm^{-1} (neat) 3059, 2958, 2921, 2858, 2361, 2341, 1741, 1698, 1661, 1616, 1586, 1433, 1363, 1342, 1142.13 1047, 1015, 922; **HRMS** (ESI^+) $[M + H]^+$ $C_{16}H_{23}OS_2^+$ calc. 298.1185, found 295.1183.

2-(2-(*tert*-Butylthio)ethyl)thiochroman-4-one (98)

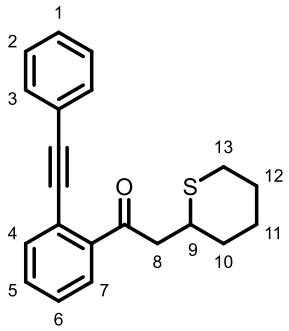


Synthesised according to **general procedures M** and **N**. **General procedure M** used aldehyde **57b** (26 µL, 0.20 mmol) and but-3-yn-1-yl(tert-butyl)sulfane **91b** (34 mg, 0.24 mmol). **General procedure N** used TFA (80 µL, 0.80 mmol) and $AlCl_3$ (2.70 mg, 0.02 mmol) with stirring for 16 h. Purification by column chromatography (8:2 Pentane:Et_2O) yielded title compound **98** (8.0 mg, 0.028 mmol, 14%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 8.08 (1H ddd, *J* = 8.0, 1.5, 0.5 Hz, *Ar*), 7.39 (1H, ddd, *J* = 7.9, 7.2, 1.6 Hz, *Ar*), 7.30-7.23 (1H, m, *Ar*), 7.17 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, *Ar*), 3.73-3.61 (1H, m, C(6)*H*), 3.09 (1H, dd, *J* = 16.3, 3.3 Hz, C(5)*H*H), 2.83 (1H, dd, *J* = 16.3, 9.9 Hz, C(5)H*H*), 2.75-2.60 (2H, m, C(8)H_2), 2.07-1.86 (2H, m, C(7)H_2), 1.32 (9H, s, C(9)H_3); **δ_C** (101 MHz, $CDCl_3$) 194.3, 141.0, 133.7, 130.8, 129.0, 127.9, 125.2, 46.0, 42.5, 40.6, 34.3, 31.1, 25.5; **ν_{max}**/ cm^{-1} (neat) 2958, 2924, 2861, 2360, 2341, 1680, 1590, 1459, 1436, 1364, 1328, 1287, 1235, 1162, 1116, 1092, 1073, 1028; **HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{21}OS_2^+$ calc. 281.1028, found 281.1028.

5.2.6 Product derivatisations

1-(2-(Phenylethynyl)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (106)

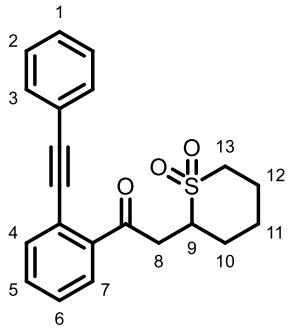


According to literature procedure,[106] $Rh(nbd)_2BF_4$ (6.0 mg, 0.016 mmol) and dcpe (7.0 mg, 0.016 mmol) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 min. The solution was purged with argon for 1 min. This was transferred *via* cannula to a mixture of cyclic sulfide **83a** (87 mg, 0.32 mmol), phenylacetylene (70 µL, 0.64 mmol), copper bromide (92 mg, 0.64 mmol) and silver carbonate (88 mg, 0.32 mmol). The reaction mixture was heated at 80 °C for 16 h. Upon cooling to room temperature, the mixture was concentrated under reduced pressure. Purification by column chromatography (100:0 to 9:1 Hexane:Et_2O) yielded title compound **106** (32 mg, 0.01 mmol, 31%) as a red-orange oil.

δ_H (400 MHz, $CDCl_3$) 7.72-7.68 (1H, m, *Ar*), 7.64-7.61 (1H, m, *Ar*), 7.59-7.54 (2H, m, *Ar*), 7.47 (1H, td, J = 7.5, 1.5 Hz, *Ar*), 7.41 (1H, dd, J = 7.6, 1.4 Hz, *Ar*), 7.39-7.34 (3H, m, *Ar*), 3.45-3.37 (1H, m, C(9)*H*), 3.36 (1H, s, C(8)*H*H), 3.34 (1H, d, J = 1.5 Hz, C(8)*H*H), 2.77-2.68 (1H, m, C(13)*H*H), 2.63-2.55 (1H, m, C(13)*H*H), 2.15-2.07 (1H, m, C(10)*H*H), 1.96-1.87 (1H, m, C(12)*H*H), 1.85-1.77 (1H, m, C(11)*H*H), 1.65-1.56 (1H, m, C(12)*H*H), 1.51-1.37 (2H, m, C(10)*H*H and C(11)*H*H); **δ_C** (101 MHz, $CDCl_3$) 200.8, 141.1, 133.9, 131.7, 131.2, 128.9, 128.6, 128.5, 122.9, 121.4, 95.0, 88.3, 48.2, 37.8, 34.3, 29.3, 27.0, 25.8;**ν_{max}**/ cm^{-1} (neat) 3980, 3902, 3855, 3820, 3746, 3690, 3676, 3648, 3567, 3484,3371, 3060, 2926, 2849, 2668, 2357, 2343, 2214, 2160, 2085, 2058, 2013, 1987, 1813, 1683, 1590, 1560, 1541, 1493,

1473, 1440, 1397, 1361, 1344, 1286, 1209, 1177, 1096, 1069, 1045, 1024, 990, 965, 925; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{21}H_{20}NO^{23}NaS^+$ calc. 343.1127, found 343.1128.

2-(1,1-Dioxidotetrahydro-2*H*-thiopyran-2-yl)-1-(2-(phenylethynyl)phenyl)ethan-1-one (107)

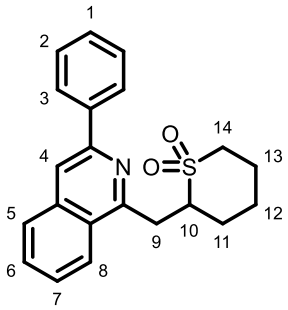


According to a modified procedure,[244] **106** (28.9 mg, 0.090 mmol) was dissolved in anhydrous CH_2Cl_2 (0.6 mL) in a microwave vial. *m*-CPBA (47 mg, 0.27 mmol) was introduced. The mixture was stirred under an argon atmosphere at r.t. for 3 h. The reaction was diluted with CH_2Cl_2 (2 mL) and washed with sat. aq. $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 2 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. Purification by column chromatography (6:4 Petrol:EtOAc) yielded title compound **107** (26.2 mg, 0.074 mmol, 83%) as a yellow-orange oil.

δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* = 8.0, 1.2 Hz, *Ar*), 7.69-7.57 (3H, m, *Ar*), 7.51 (1H, td, *J* = 7.6, 1.4 Hz, *Ar*), 7.43 (1H, dd, *J* = 7.7, 1.4 Hz, *Ar*), 7.43-7.33 (3H, m, *Ar*), 3.99-3.89 (1H, m, C(8)*H*H), 3.73-3.64 (1H, m, C(9)*H*), 3.54-3.44 (1H, m, C(8)H*H*), 3.17-3.09 (1H, m, C(13)*H*H), 3.05-2.94 (1H, m, C(13)H*H*), 2.32-2.22 (1H, m, C(10)*H*H), 2.14-2.02 (2H, m, C(12)H_2), 1.90-1.74 (2H, m, C(10)H*H* and C(11)*H*H), 1.66-1.51 (1H, m, C(11)H*H*); **δ_C** (101 MHz, $CDCl_3$) 197.9, 139.5, 134.4, 132.0, 131.9, 129.0, 128.8, 128.6, 128.5, 122.7, 122.0, 95.9, 88.1, 57.8, 52.1, 37.5, 30.4, 24.5, 24.2; **ν_{max}**/ cm^{-1} (neat) 3386, 3061, 2928, 2850, 2214, 1681, 1590, 1561, 1493, 1473, 1442, 1404, 1349, 1317, 1284, 1224, 1207, 1187, 1163,

1126, 1071, 1025, 1014, 991, 951, 927; **HRMS** (ESI^+) $[M + H]^+$ $C_{21}H_{20}O_3S^+$ calc. 353.1206, found 353.1201.

2-((3-Phenylisoquinolin-1-yl)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (108)



According to a modified procedure,[186] to a pre-dried flask was added ammonium acetate (27.4 mg, 0.36 mmol, 5.50 equiv.), $AgNO_3$ (9.0 mg, 0.053 mmol, 0.8 equiv.) and compound **107** (22.5 mg, 0.064 mmol, 1.0 equiv.). Following this, *t*-BuOH (0.53 mL) was introduced and the mixture stirred at 60 ^oC for 16 h, under nitrogen. Upon cooling, the reaction was quenched with sat. aq. $NaHCO_3$ and stirred for an additional 2 h. The mixture was next filtered through a cotton plug and washed with EtOAc (10-20 mL). The filtrate was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (7:3 then 6:4 Pentane:EtOAc) yielded title compound **108** (5.8 mg, 0.017 mmol, 27%) as a yellow oil.

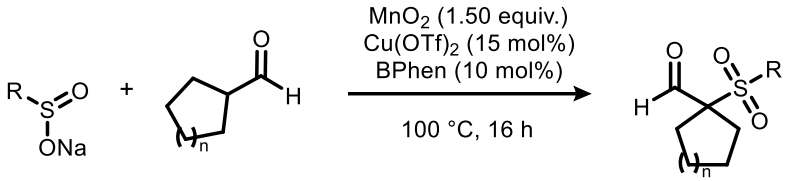
δ_H (400 MHz, $CDCl_3$) 8.22-8.13 (3H, m, *Ar*), 8.00 (1H, s, *Ar*), 7.89 (1H, d, *J* = 8.1 Hz, *Ar*), 7.74-7.65 (1H, m, *Ar*), 7.65-7.57 (1H, m, *Ar*), 7.55-7.48 (2H, m, *Ar*), 7.47-7.38 (1H, m, *Ar*), 4.17 (1H, dd, *J* = 15.6, 2.4 Hz, C(9)*H*), 4.05-3.93 (1H, m, C(10)*H*), 3.50 (1H, dd, *J* = 15.6, 10.7 Hz, C(9)*H*), 3.27-3.16 (1H, m, C(14)*H*), 3.13-3.01 (1H, m, C(14)*H*), 2.39-2.29 (1H, m, C(11)*H*), 2.21-2.12 (2H, m, C(13)*H*), 1.99-1.84 (2H, m, C(11)*H* and C(12)*H*), 1.62-1.45 (1H, m, C(12)*H*); **δ_C** (101 MHz, $CDCl_3$) 156.1, 137.2, 130.4, 128.9, 128.7, 128.0, 127.6, 126.8, 124.7, 60.5, 52.2, 30.0, 24.7, 24.2; **ν_{max}**/ cm^{-1} (neat) 2924, 2852, 2367, 1698, 1621,

1591, 1570, 1499, 1443, 1304, 1283, 1212, 1164, 1126, 1028, 927, 908; **HRMS** (ESI^+) $[M + H]^+$ $C_{21}H_{22}NO_2S^+$ calc. 352.1366, found 352.1364.

5.3 Chapter 3 Experimental

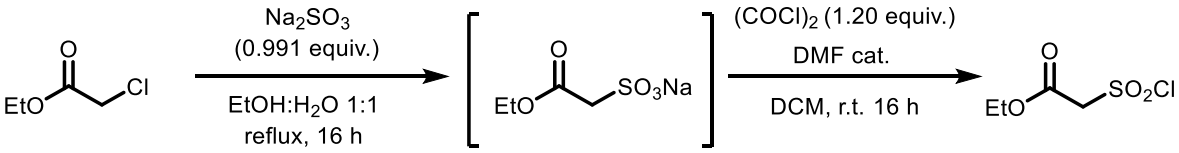
5.3.1 Synthesis of *β*-formyl sulfones

General procedure O: Synthesis of disubstituted *β*-sulfone aldehydes



According to a modified procedure,[221] manganese(IV) oxide (1.5 equiv.); copper(II) triflate (15 mol%); bathophenanthroline (10 mol%); sulfinic acid sodium salt (2.0 equiv.); aldehyde (1.0 equiv.); H_2O:EtOH:AcOH (1:1:1, 0.67 M); were added to a microwave vial, under air. The vial was sealed and stirred at 100 °C for 16 h. Upon cooling to room temperature, the mixture was filtered through silica using EtOAc (3 × 20 mL), and then concentrated *in vacuo*. Purification by column chromatography yielded the corresponding aldehyde.

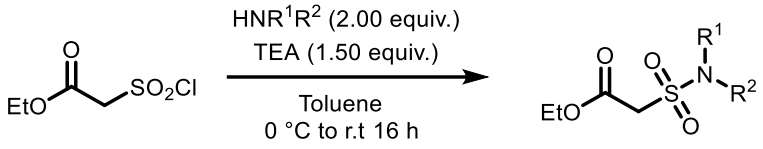
General procedure P: Synthesis of *β*-ester sulfonyl chlorides



According to a modified procedure,[245] Na_2SO_3 (0.99 equiv.) was dissolved in water. A solution of ethyl chloroacetate (1.0 equiv.) in EtOH was then introduced dropwise over 30 min with vigorous stirring. The reaction mixture was then refluxed overnight. The mixture was cooled to room temperature and most of the solvents were removed *in vacuo*. Then toluene was added, and the mixture concentrated *in vacuo*. The resulting white solid residue was added to a solution of DCM and DMF (9.8 mol%). Next, oxalyl chloride (1.2 equiv.) was added dropwise, and the suspension stirred for 16 h at room

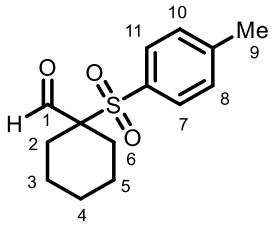
temperature. The mixture was then filtered through a pad of celite using DCM (100 mL). The filtrate was then concentrated *in vacuo*. The resultant crude residue was then carried on to the next step.

General procedure Q: Synthesis of *β*-ester sulfonamides



According to a modified procedure,[246] a solution ethyl 2-(chlorosulfonyl)acetate in toluene was cooled to 0 °C. In a separate flask, a given amine (2.0 equiv.) and triethylamine (1.5 equiv.) were dissolved in toluene. The reaction mixture was stirred at room temperature for 16 h and then sequentially washed with water (3 × 20 mL), 5% HCl (20 mL), saturated $NaHCO_3$ solution (20 mL), and brine (20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

1-Tosylcyclohexane-1-carbaldehyde (114a)

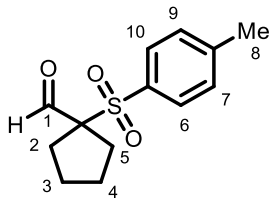


Synthesised according to **general procedure O**, using sodium 4-methylbenzenesulfinate (0.71 g, 4.0 mmol), cyclohexanecarbaldehyde (0.24 mL, 2.0 mmol). Purification by column chromatography (100:0 to 98:2 to 80:20 Pentane:Et_2O) yielded title compound **114a** (75 mg, 0.28 mmol, 14%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 9.65 (1H, s, C(1)*H*), 7.59 (2H, d, *J* = 8.5 Hz, *Ar*), 7.34 (2H, d, *J* = 8.0 Hz, *Ar*), 2.45 (3H, s, C(9)H_3), 2.26 (2H, m, C(2 or 6)H_2), 1.96-1.82 (2H, m, C(2 or 6)H_2), 1.81-1.49 (4H, m, C(3-5)H_2), 1.15 (2H, m, C(3-5)H_2); **δ_C** (101 MHz, $CDCl_3$) 197.9, 145.6,

132.2, 130.1, 129.8, 74.2, 25.3, 24.5, 22.1, 21.8; **ν_{max}**/ cm^{-1} 3064,3031, 2940, 2857, 1724, 1596,1493, 1303, 1291, 1206, 1088, 1048, 1018, 958; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{14}H_{18}O_3{}^{23}NaS^+$ calc. 289.0869, found 289.0868. *Data is consistent with literature.*[221]

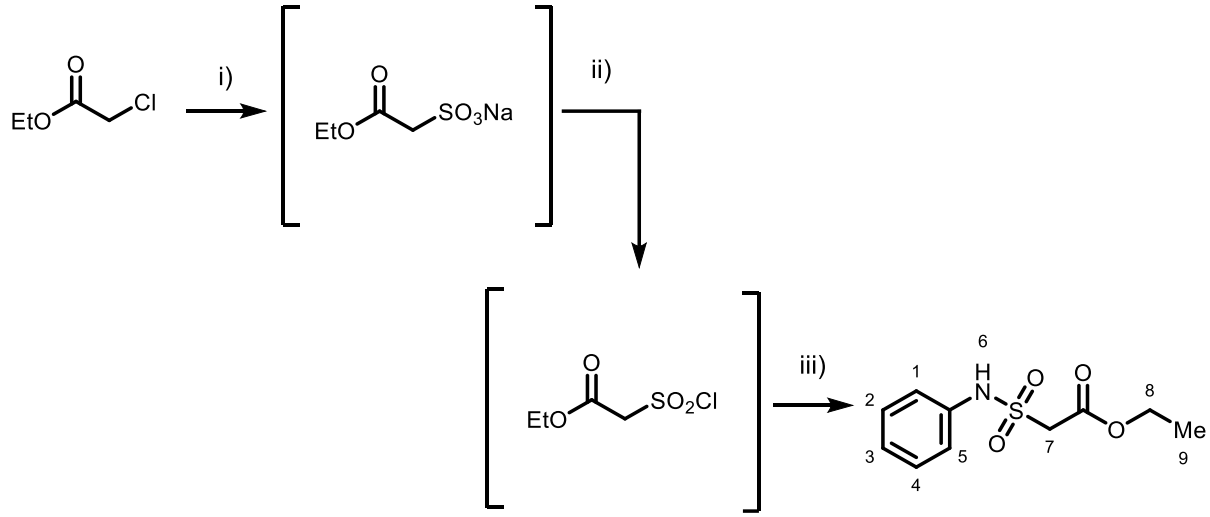
1-Tosylcyclopentane-1-carbaldehyde (114b)



Synthesised according to **general procedure O**, using sodium 4-methylbenzenesulfinate (0.71 g, 4.0 mmol), cyclopentanecarboxaldehyde (0.21 mL, 2.0 mmol). Purification by column chromatography (100:0 to 90:10 to 80:20 Pentane:Et_2O) yielded title compound **114b** (85.4 mg, 0.34 mmol, 17%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 9.77 (1H, s, C(1)*H*), 7.71-7.59 (2H, m, *Ar*), 7.34 (2H, m, *Ar*), 2.44 (3H, s, C(8)H_3), 2.36-2.23 (2H, m, C(2 or 5)H_2), 2.19-2.05 (2H, m, C(2 or 5)H_2), 1.87-1.73 (2H, m, C(3 or 4)H_2), 1.62-1.48 (2H, m, C(3 or 4)H_2); **δ_C** (101 MHz, $CDCl_3$) 194.8, 145.6, 134.08, 130.0, 129.3, 81.3, 28.9, 25.8, 21.8; **ν_{max}**/ cm^{-1}1710, 1496, 1402, 1123, 1033, 1007, 814, 683; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{13}H_{17}O_3S^+$ calc. 253.0893, found 253.0895. *Data is consistent with literature.*[221]

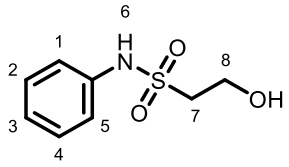
Ethyl 2-(*N*-phenylsulfamoyl)acetate (120a)



Steps i) and **ii)**: synthesised according to **general procedure P**, using ethyl chloroacetate (2.14 mL, 20 mmol), Na_2SO_3 (2.50 g, 19.8 mmol), EtOH (10 mL) and water (10 mL), affording a red-orange oil. Then, oxalyl chloride (2.03 mL, 24.0 mmol), DMF (0.15 mL, 1.96 mmol), and DCM (20 mL). **Step iii)** synthesised according to **general procedure Q**, using aniline (3.65 mL, 40 mmol), triethylamine (4.18 mL, 30 mmol), and toluene (69 mL). Purification by column chromatography (100:0 to 90:10 to 80:20 Pentane:EtOAc) yielded title compound **120a** (2.59 g, 10.7 mmol, 53% over 3 steps) as an orange oil.

δ_H (400 MHz, $CDCl_3$) 7.42-7.28 (4H, m, *Ar*), 7.27-7.20 (1H, m, *Ar*), 6.99 (1H, bs, N(6)*H*), 4.27 (2H, q, *J* = 7.1 Hz, C(8)H_2), 3.93 (2H, s, C(7)H_2), 1.31 (3H, t, *J* = 7.2 Hz, C(9)H_3); **δ_C** (101 MHz, $CDCl_3$) 164.1, 136.2, 129.7, 126.5, 122.7, 62.8, 53.0, 14.0; **ν_{max}**/ cm^{-1} 3271, 2987, 2940, 1734, 1598, 1494, 1413, 1349, 1303, 1208, 1158, 1026, 931; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{14}{}^{23}NO_4S^+$ calc. 244.0649, found 244.0637. *Data is consistent with literature.*[247]

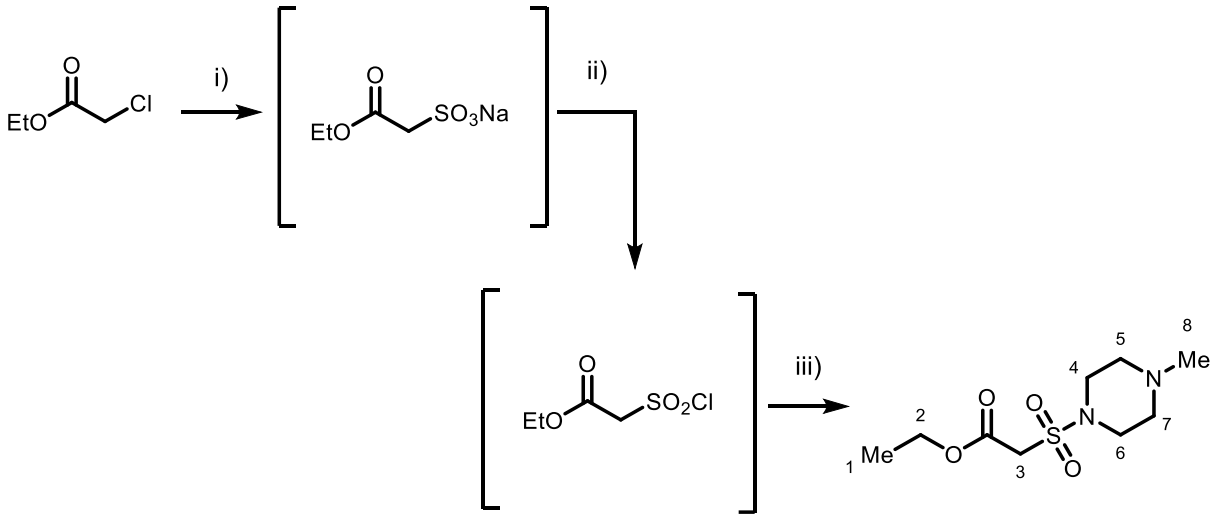
2-Hydroxy-*N*-phenylethane-1-sulfonamide (121a)



According to a modified procedure,[225] a solution of ethyl 2-(N-phenylsulfamoyl)acetate **120a** (2.11 g, 8.66 mmol) in anhydrous THF, under argon was cooled to 0 °C. Then, $LiBH_4$ solution (2 M in THF, 5.2 mL, 10.4 mmol) was added dropwise and the solution allowed to warm to room temperature, with stirring over 4 h. Upon completion of the reaction, as indicated by TLC, the mixture was concentrated *in vacuo*. To the resulting residue was added water (20 mL) and the mixture extracted with EtOAc (4 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:1 Petrol:EtOAc) yielded title compound **121a** (1.38 g, 6.88 mmol, 79%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.38-7.32 (2H, m, *Ar*), 7.30-7.24 (2H, m, *Ar*), 7.24-7.17 (1H, m, *Ar*), 6.71 (1H, bs, C(6)*H*), 4.18-4.06 (2H, m, C(7)H_2), 3.34-3.25 (2H, m, C(8)H_2), 2.48 (1H, bs, O*H*); **δ_C** (101 MHz, $CDCl_3$)136.6, 129.8, 125.8, 121.7, 57.3, 52.5; **ν_{max}**/ cm^{-1} 3505, 3262, 1598, 1494, 1415, 1331, 1299, 1220, 1140, 1059, 1031, 1012; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_8H_{11}{}^{23}NO_3NaS^+$ calc. 224.0352, found 224.0353. *Data is consistent with literature.*[248]

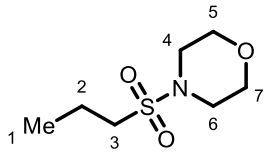
Ethyl 2-((4-methylpiperazin-1-yl)sulfonyl)acetate (120b)



Steps i) and ii): synthesised according to **general procedure P**, using ethyl chloroacetate (3.21 mL, 30 mmol), Na_2SO_3 (3.75 g, 29.7 mmol), EtOH (15 mL), water (15 mL), affording a red-orange oil. Then, oxalyl chloride (3.05 mL, 36 mmol), DMF (0.23 mL, 2.94 mmol), and DCM (30 mL). **Step iii):** synthesised according to **general procedure Q,** using toluene (106 mL) with stirring for 3.5 h. Purification by column chromatography (8:2 to 7:3 EtOAc:MeOH) yielded title compound **120b** (2.58 g, 10.3 mmol, 34% over 3 steps) as a red-orange oil.

δ_H (400 MHz, $CDCl_3$); 4.24 (2H, q, *J* = 7.1 Hz, C(2)H_2), 3.91 (2H, s, C(3)H_2), 3.41-3.34 (4H, m, C(4 and 6)H_2), 2.51-2.44 (4H, m, C(5 and 7)H_2), 2.31 (3H, s, C(8)H_3), 1.31 (3H, t, *J* = 7.1 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$);163.2, 62.4, 54.7 (2C), 46.0 (2C), 14.1; **ν_{max}**/ cm^{-1} 2941, 2800, 1738, 1455, 1350, 1331, 1288, 1224, 1169, 1144, 1095, 1066, 1026, 1003, 957; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{19}O_4{}^{23}N_2S^+$ calc. 251.1060, found 251.1054.

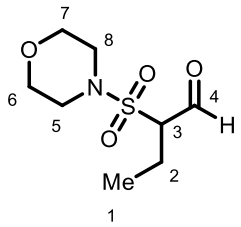
4-(Propylsulfonyl)morpholine (123a)



According to a modified procedure,[249] a solution of morpholine (1.75 mL, 20 mmol) in DCM (40 mL) was cooled to −20 °C. To this solution was added triethylamine (2.79 mL, 20 mmol). Then propane-1-sulfonyl chloride (3.38 mL, 30 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature with stirring over 16 h. Then aqueous sat. NH_4Cl solution (20 mL) was added. The solution was extracted with DCM (3 × 20 mL). The combined organics were washed with H_2O (3 × 20 mL) and brine (30 mL). Then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (9:1 to 7:3 to 1:1 Petrol:EtOAc) yielded title compound **123a** (3.23 g, 16.7 mmol, 84 %) as white solid.

m.p. 41-42 ºC; **δ_H** (400 MHz, $CDCl_3$) 3.78-3.71 (4H, m, C(4 and 5)H_2), 3.30-3.23 (4H, m, C(6 and 7)H_2), 2.93-2.83 (2H, m, C(3)H_2), 1.93-1.81 (2H, m, C(2)H_2), 1.11-1.02 (3H, m, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$); 66.7, 50.7, 45.9, 16.9, 13.3; **ν_{max}**/ cm^{-1} 2970, 2860, 2360, 1454, 1344, 1326, 1296, 1261, 1214, 1151, 1113, 1074, 1017; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_7H_{15}O_3{}^{23}NNaS^+$ calc. 216.0665, found 216.0666.

2-(Morpholinosulfonyl)butanal (122c)



To a round-bottom flask, under argon, was added 4-(propylsulfonyl)morpholine (**123a**) (0.58 g, 3.0 mmol) and THF (11.5 mL). The stirred solution was cooled to –78 °C and *n*-butyllithium (6.36 mL, 0.99 M in hexanes) was introduced dropwise over 10 minutes. The resulting solution was stirred at –78 °C for 30 min and then the ice bath was removed, and the solution allowed to warm to room temperature over 1 h. Then the solution was cooled back down to –78 °C and methyl formate (0.55 mL, 9.0 mmol) was added. The solution was stirred at –78 °C for 30 min, then allowed to warm to room temperature overnight. The reaction mixture was diluted with EtOAc (30 mL) and then washed with 1 M HCl (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (30 mL). Then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (6:4 to 1:1 Petrol:EtOAc) yielded title compound **122c** (0.4 g, 1.82 mmol, 61%) as yellow-orange oil.

δ_H (400 MHz, $CDCl_3$) 9.64 (1H, d, *J* = 3.6 Hz, C(4)*H*), 3.73-3.66 (5H, m, C(5 and 6)H_2 and C(3)*H*), 3.34-3.28 (4H, m, C(7 and 8)H_2), 2.27-2.03 (2H, m, C(2)H_2), 1.03 (3H, t, *J* = 7.5 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 194.4, 73.2, 66.8, 46.3, 18.6, 11.3; **ν_{max}**/ cm^{-1} 2863, 2360, 1723, 1665, 1455, 1344, 1326, 1262, 1205, 1154, 1114, 1072, 954; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{16}O_4{}^{23}NS^+$ calc. 222.0795, found 22.0796.

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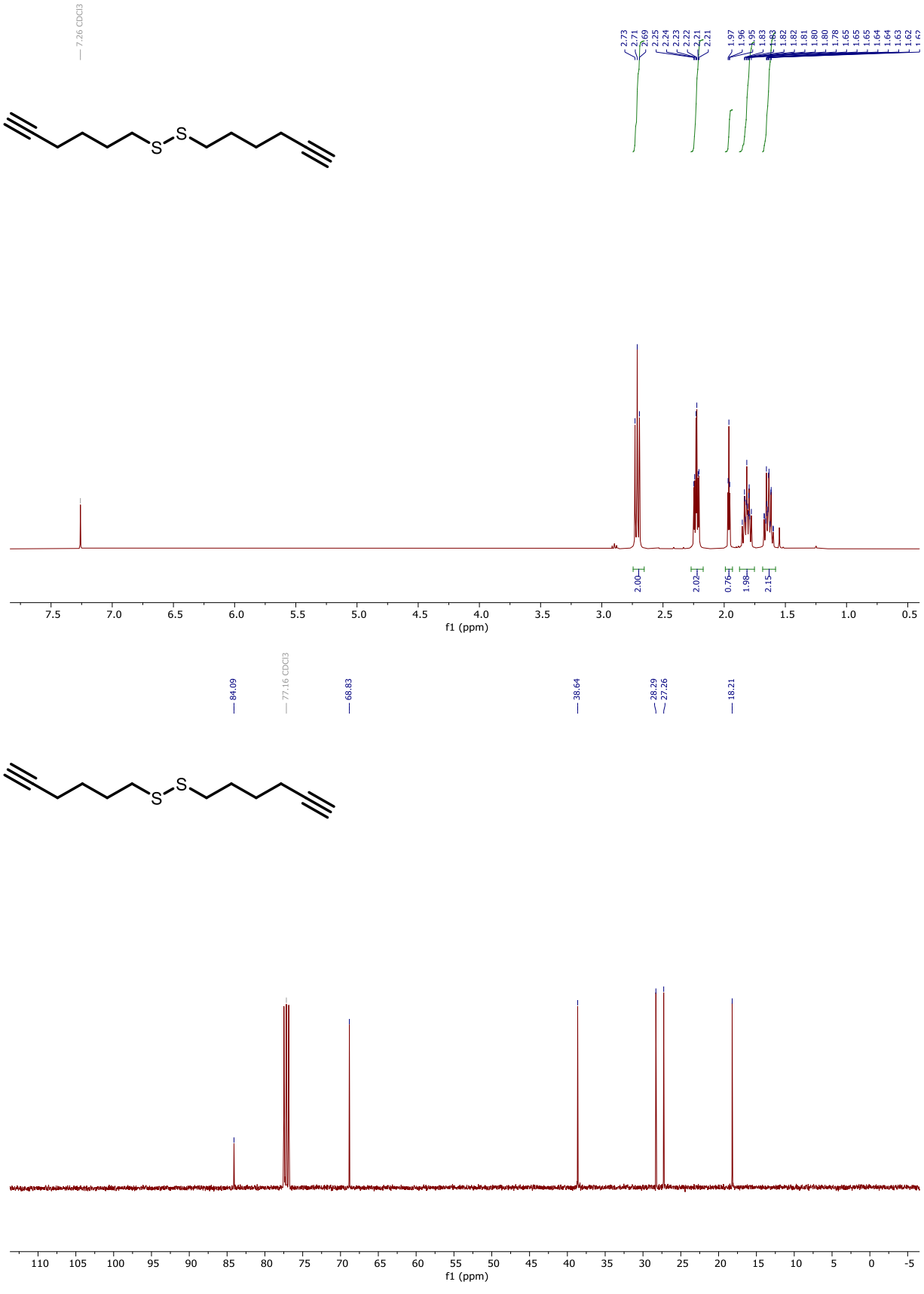
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Appendix: Spectra

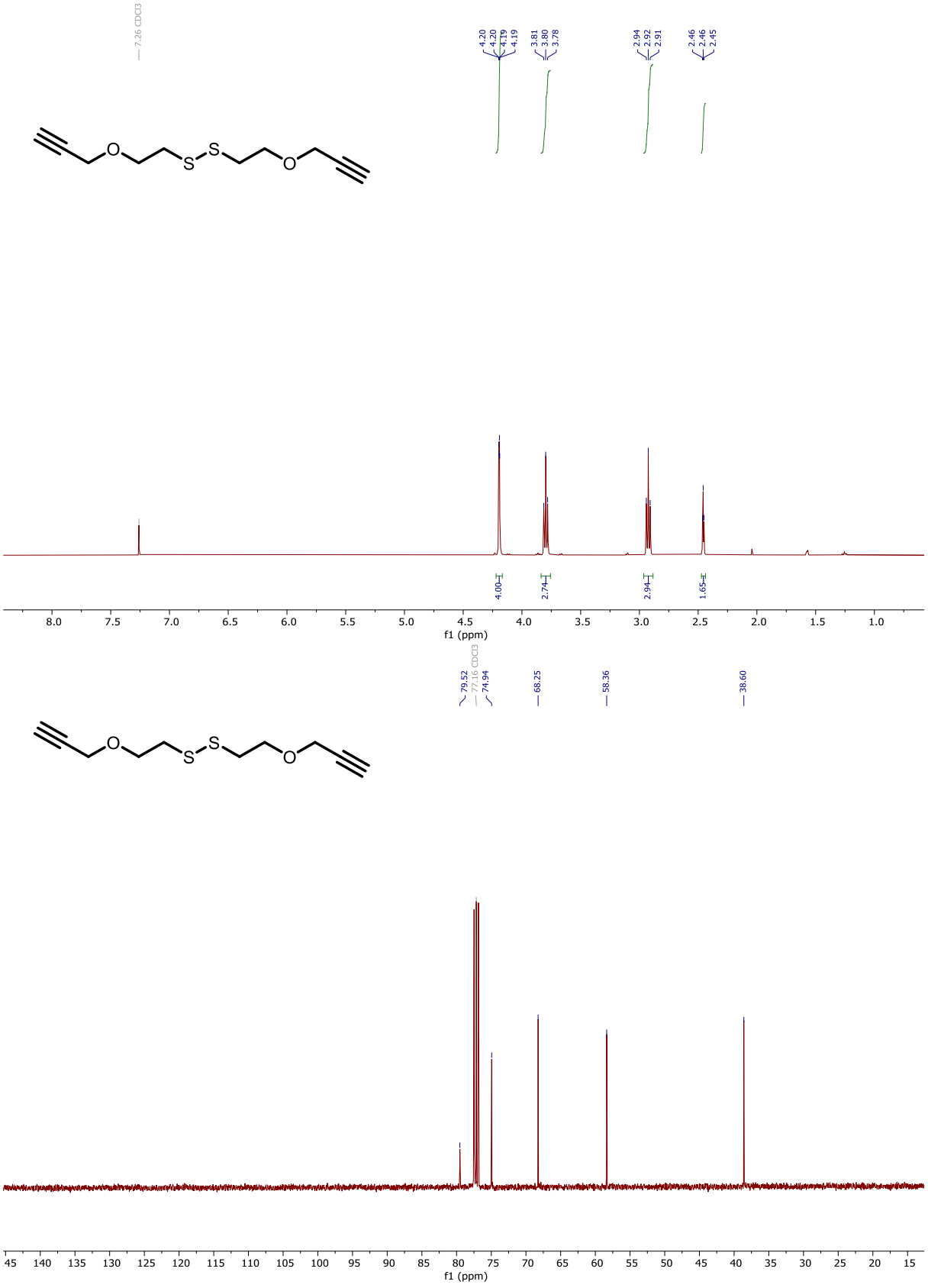
^{1}H and ^{13}C spectra of all novel compounds synthesised in Chapters 2 and 3

^{1}H and ^{13}C spectra of all novel compounds synthesised in Chapters 2

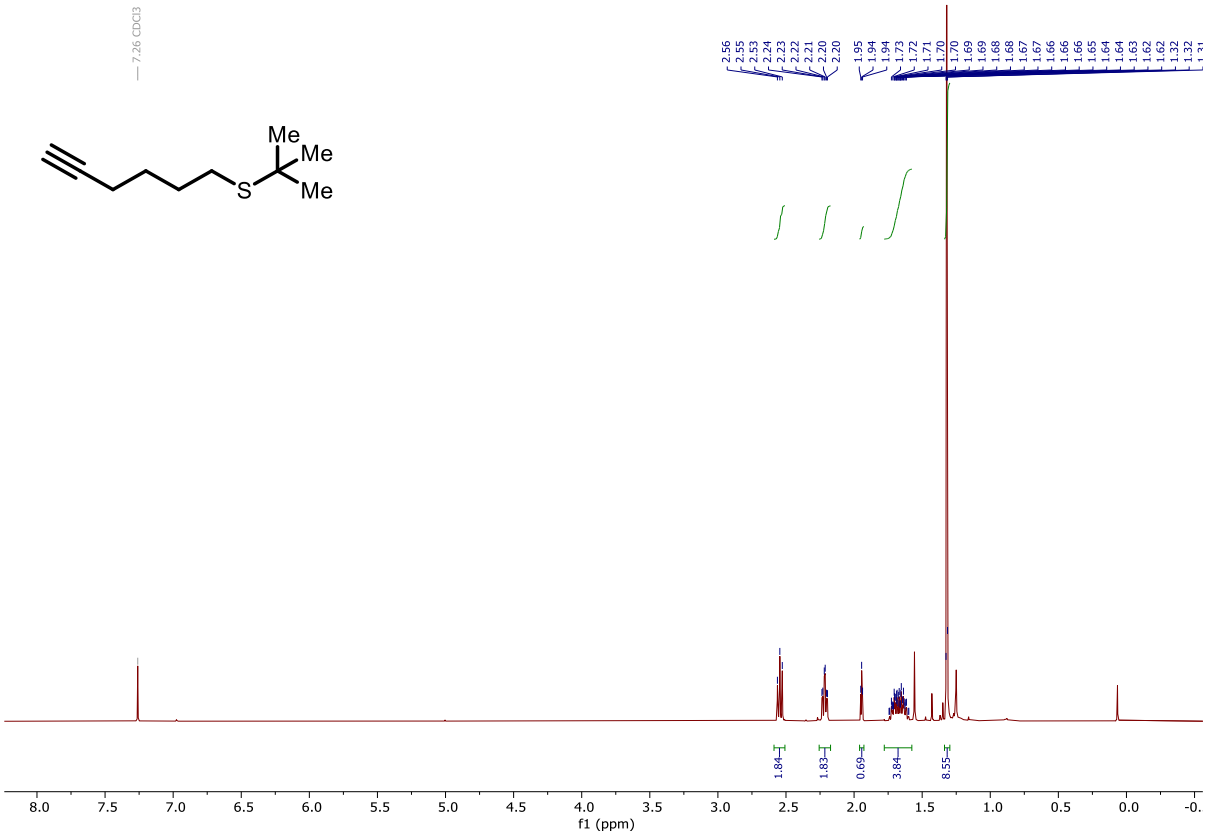
1,2-Di(hex-5-yn-1-yl)disulfide (84a)

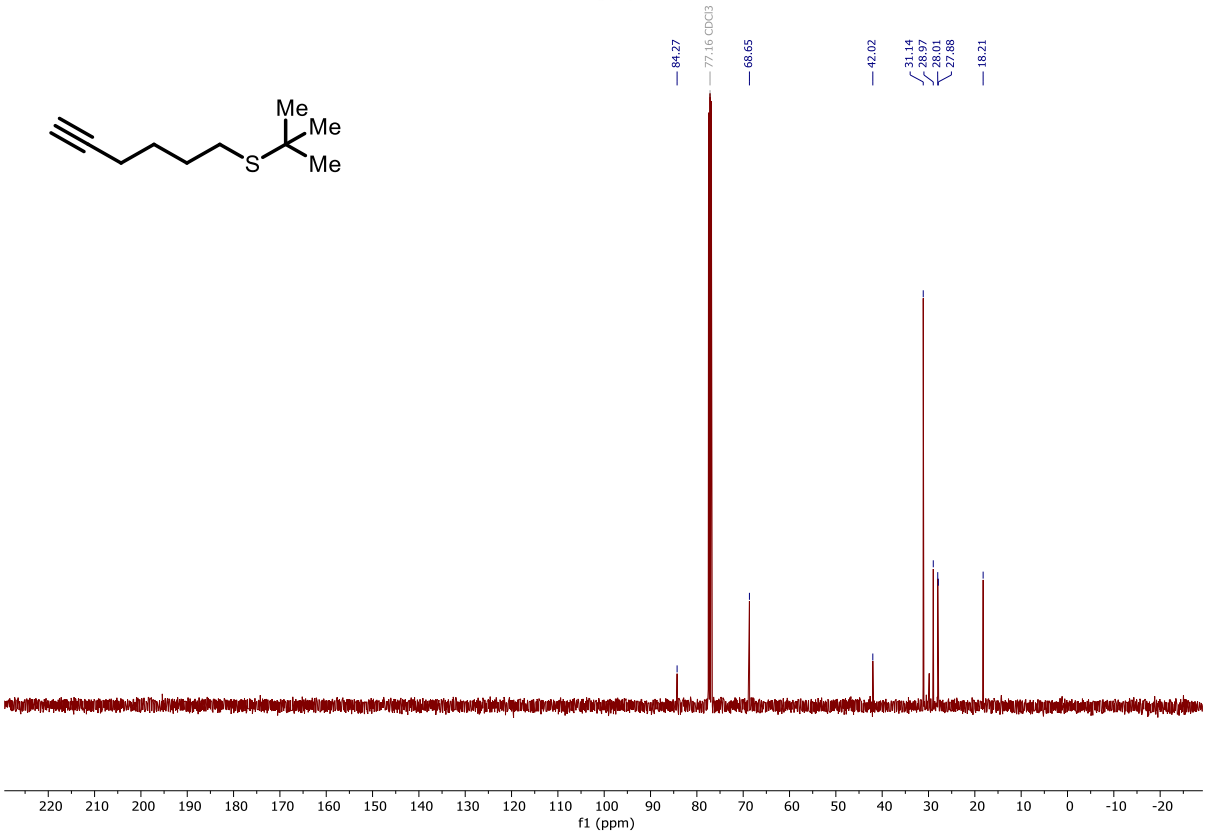


1,2-Bis(2-(prop-2-yn-1-yloxy)ethyl)disulfane (84c)

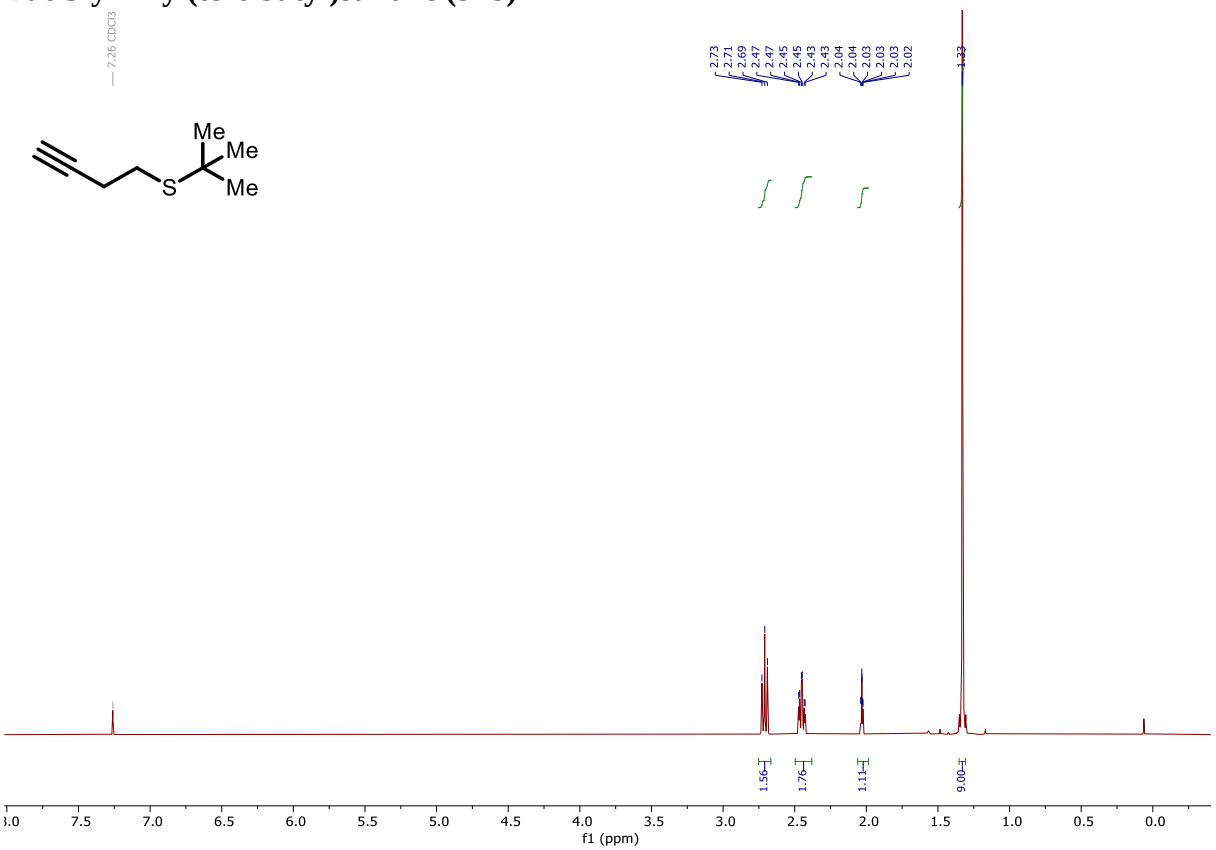


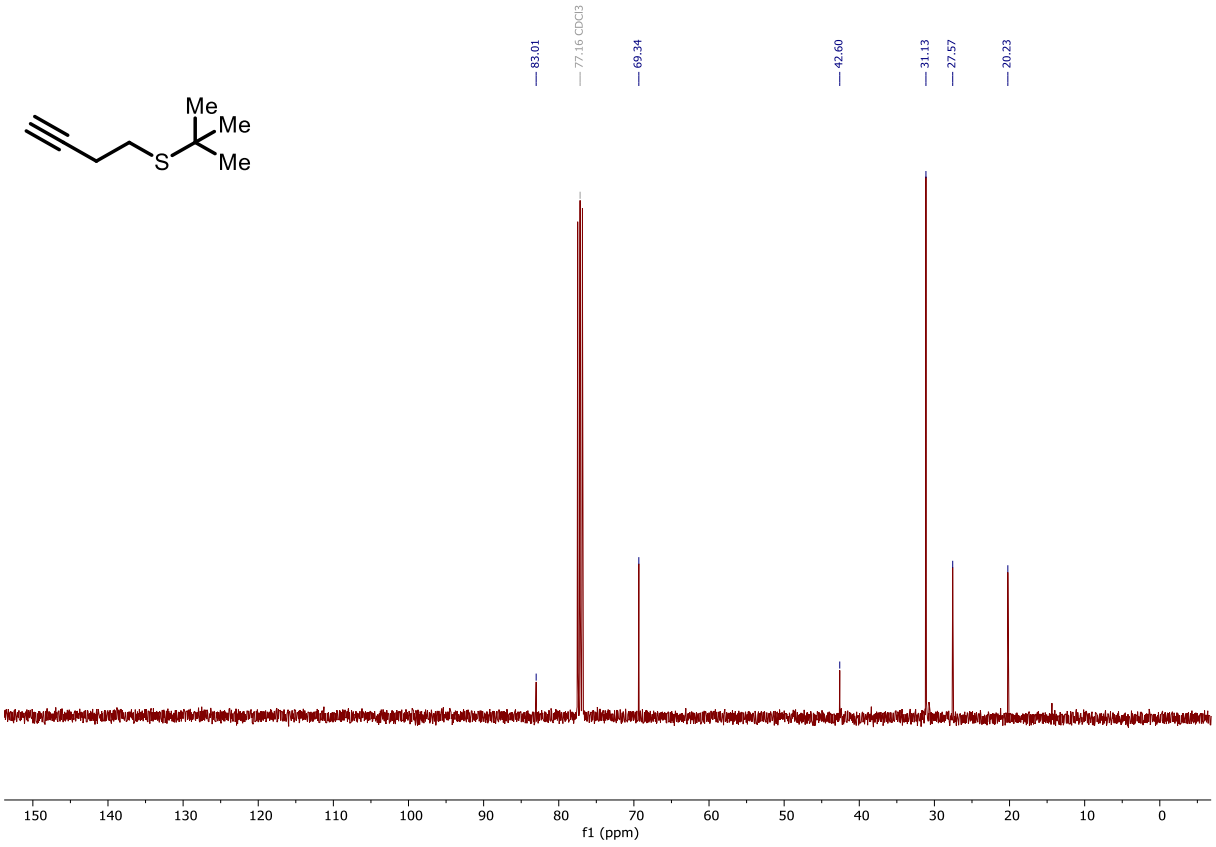
tert-Butyl(hex-5-yn-1-yl)sulfide (91a)



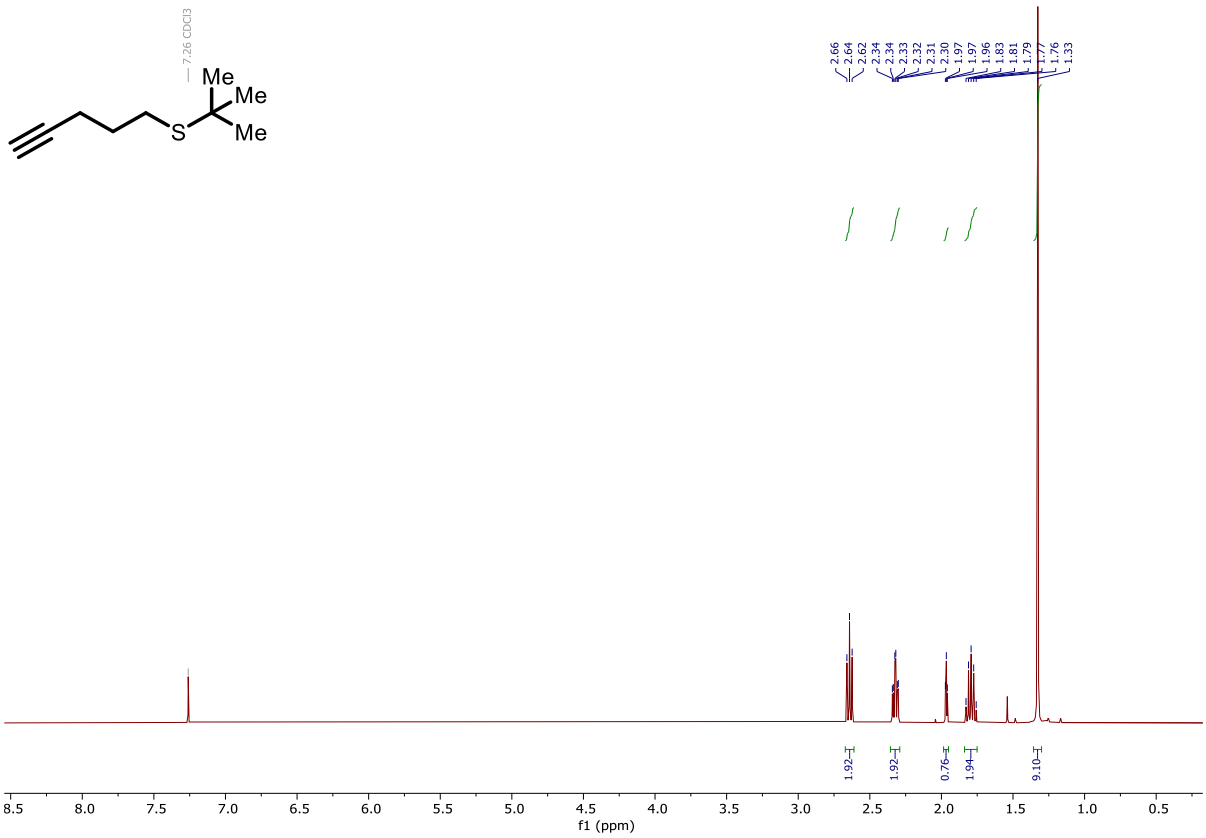


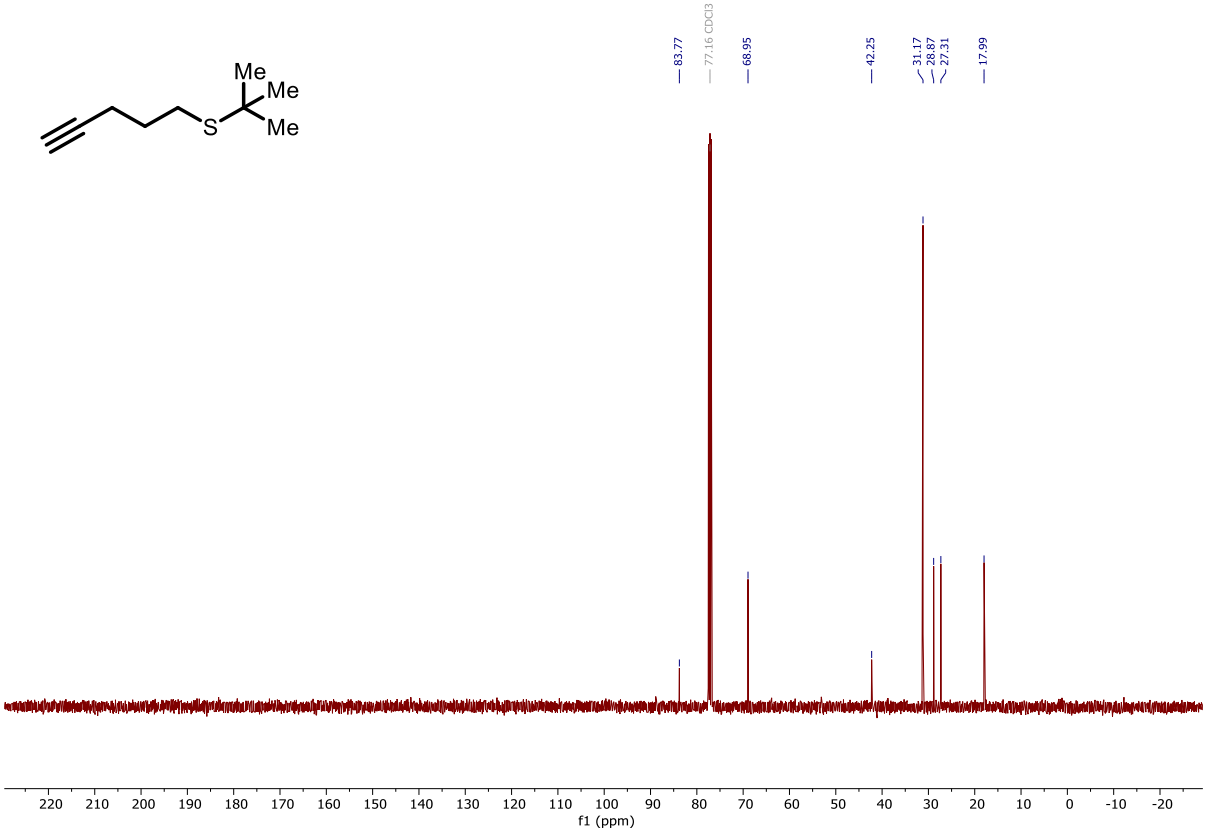
But-3-yn-1-yl(tert-butyl)sulfane (91b)



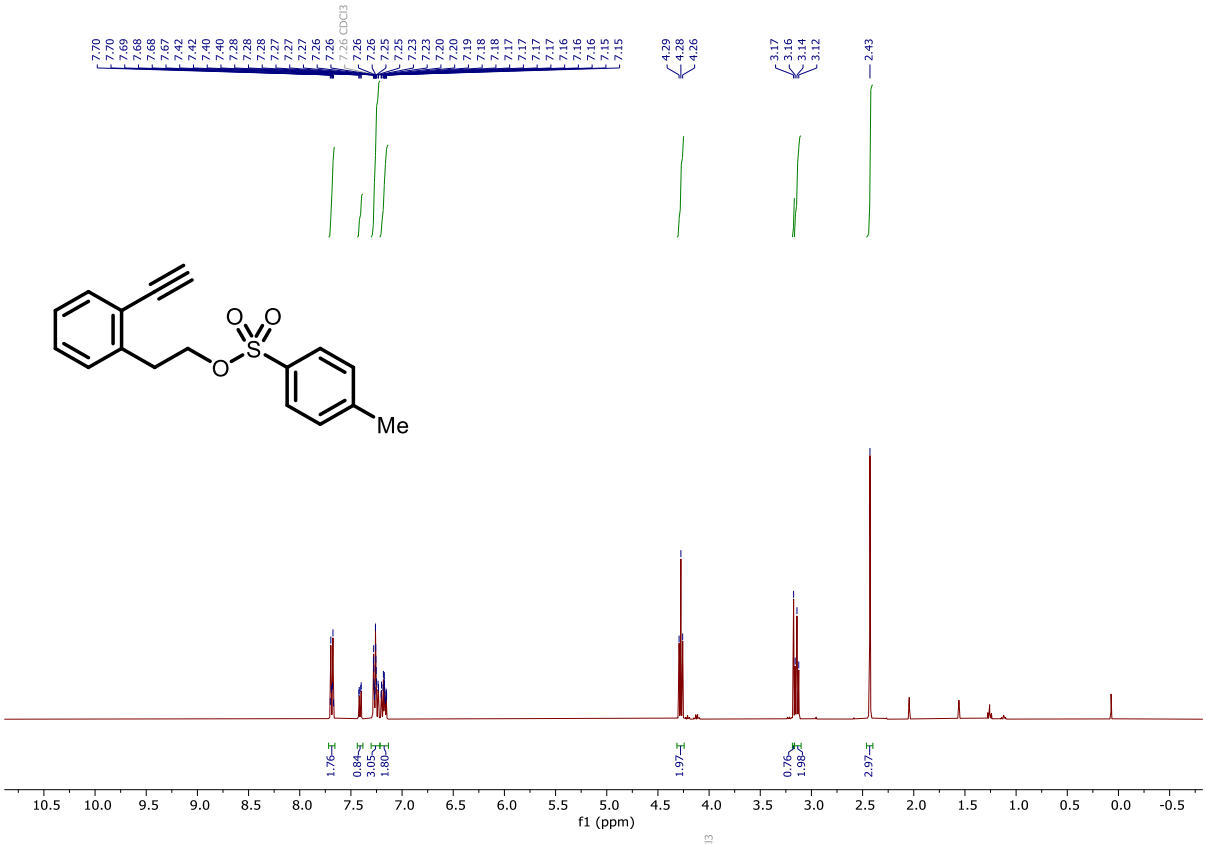


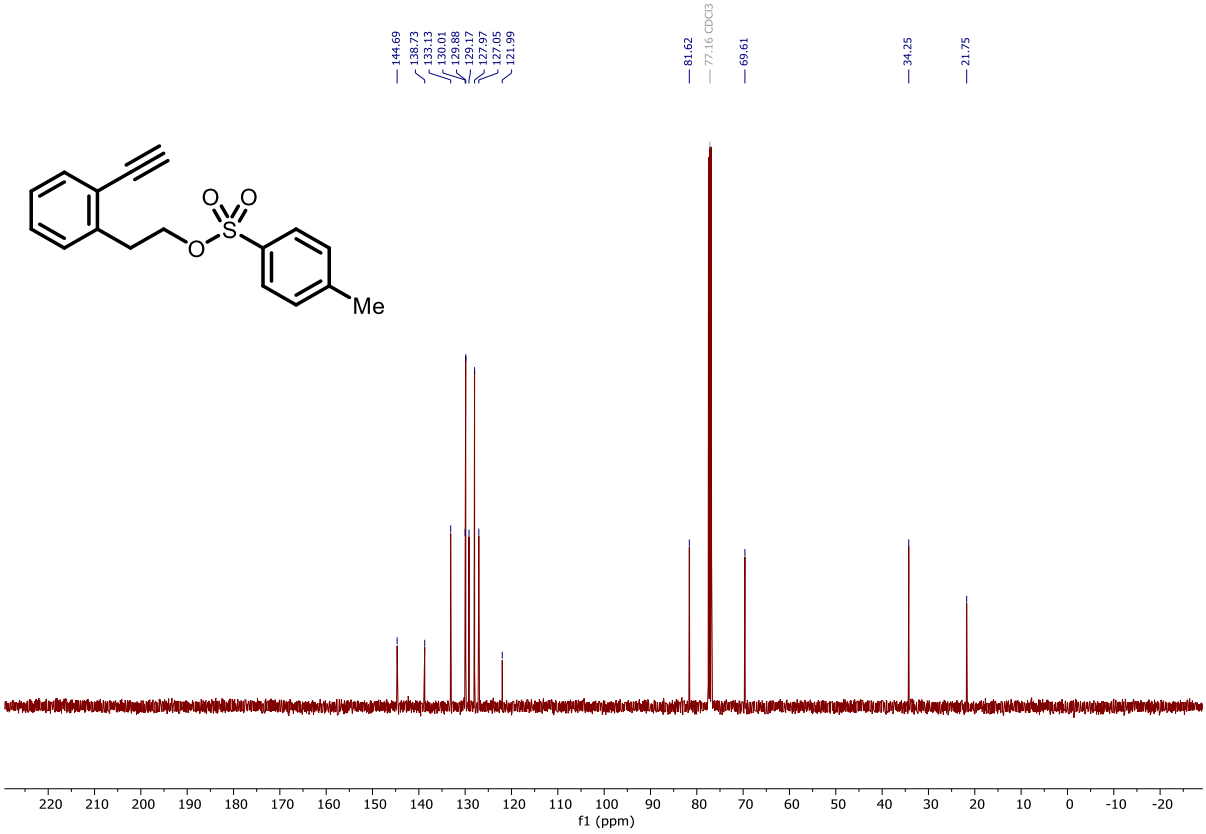
tert-Butyl(pent-4-yn-1-yl)sulfide (91c)



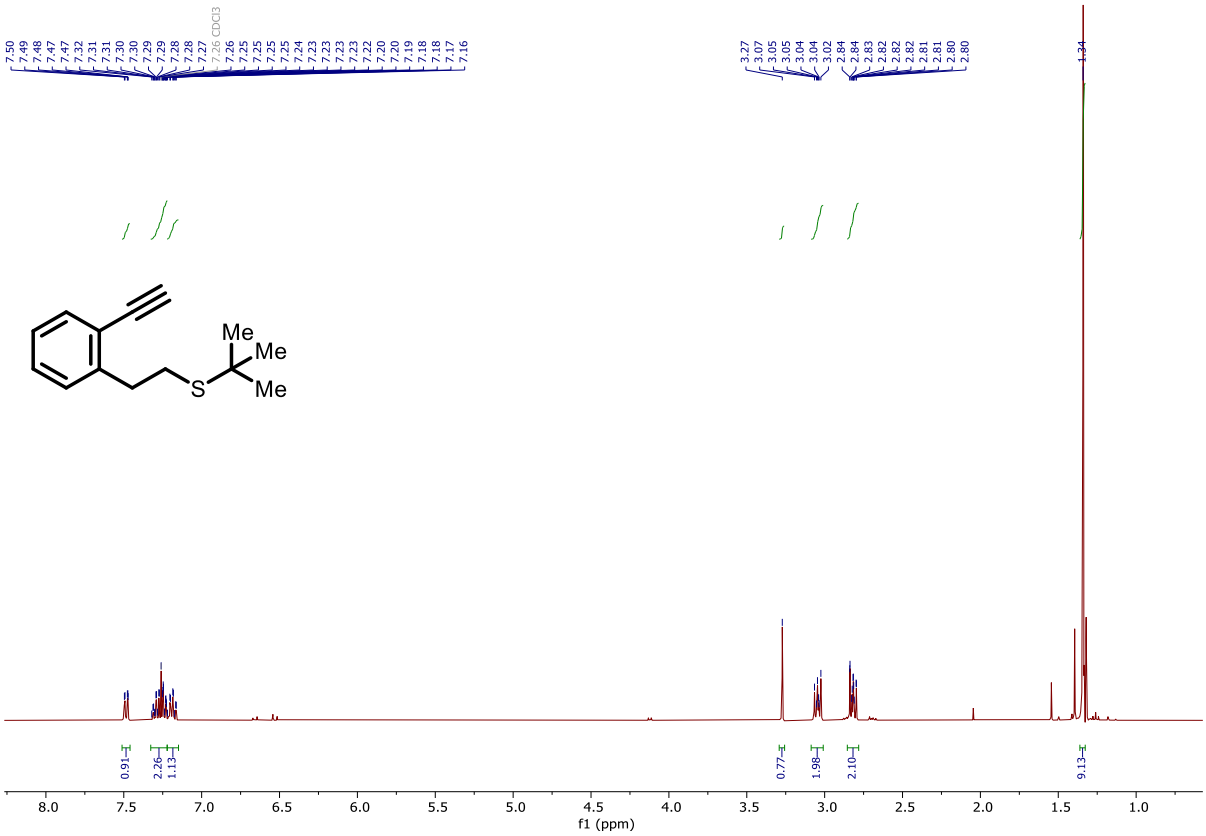


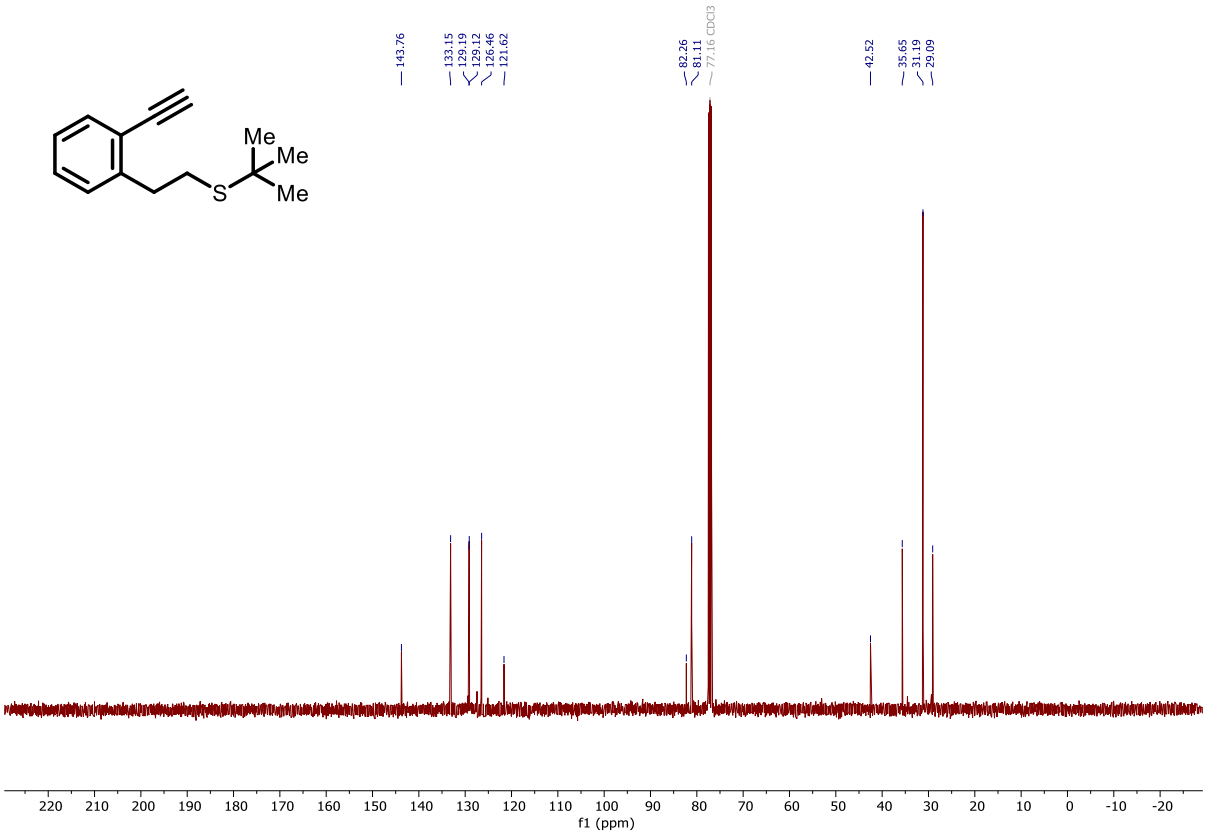
2-Ethynylphenethyl 4-methylbenzenesulfonate (90e)



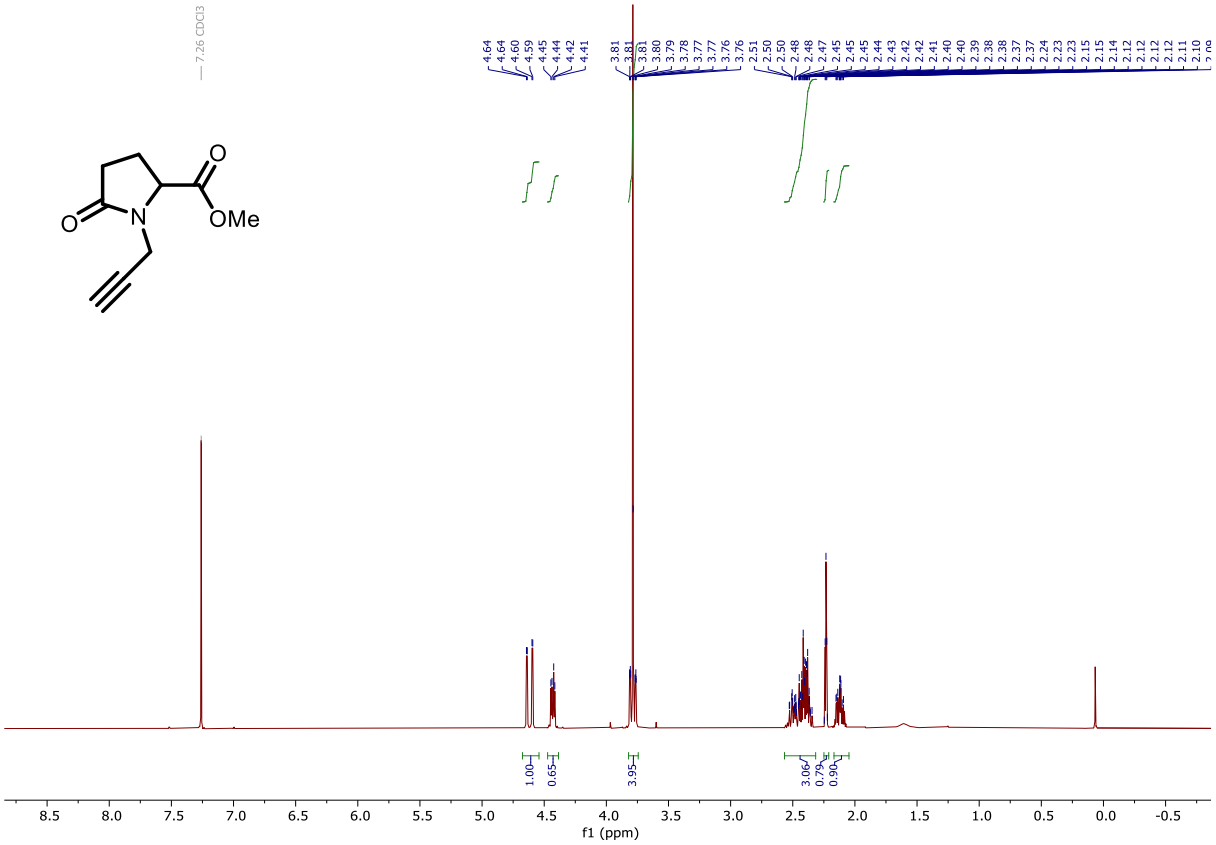


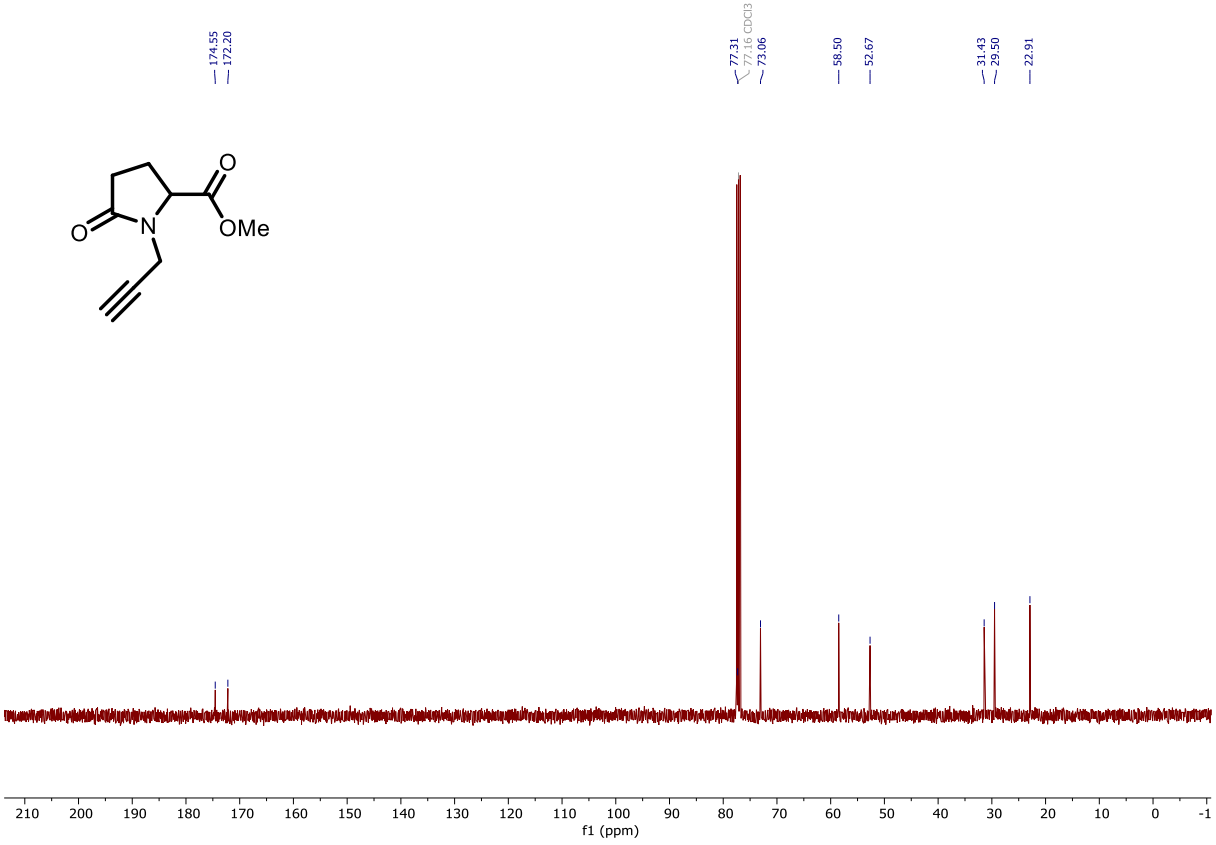
tert-Butyl(2-ethynylphenethyl)sulfane (91d)



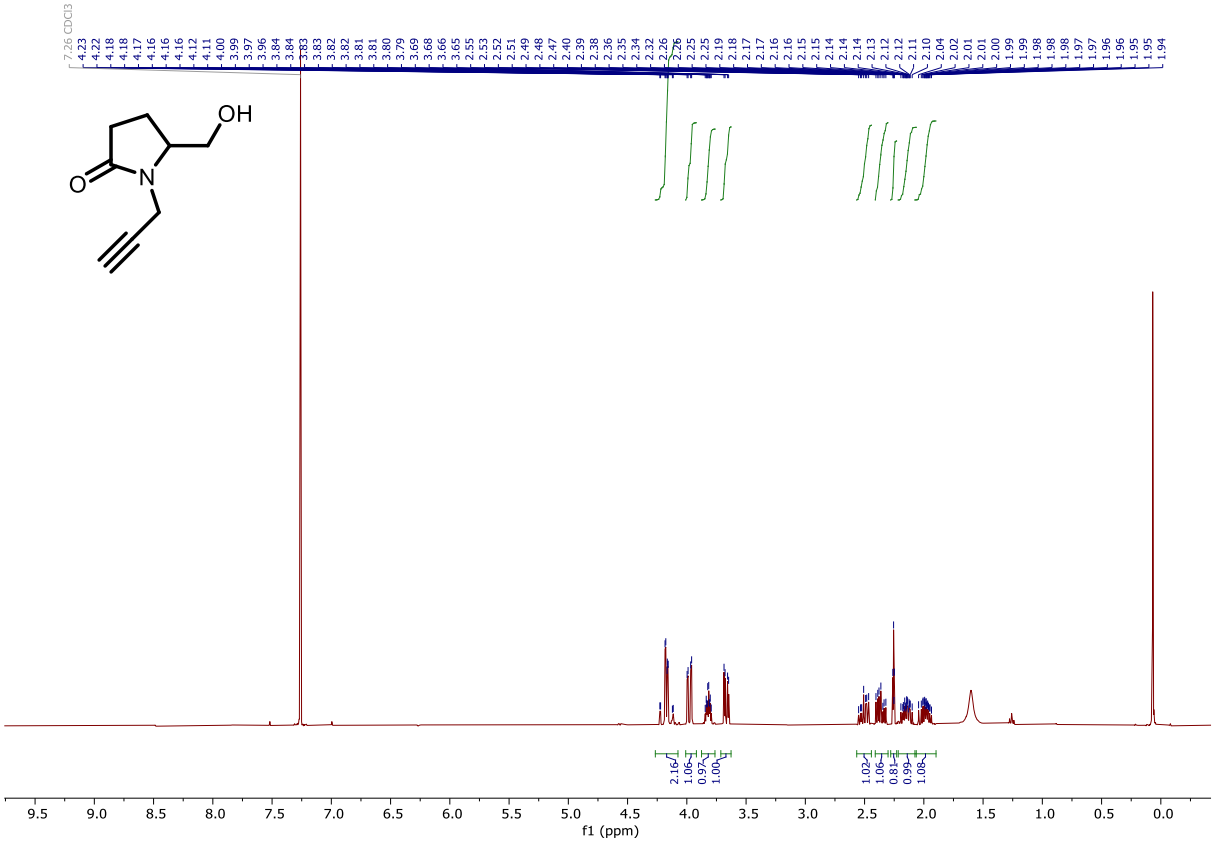


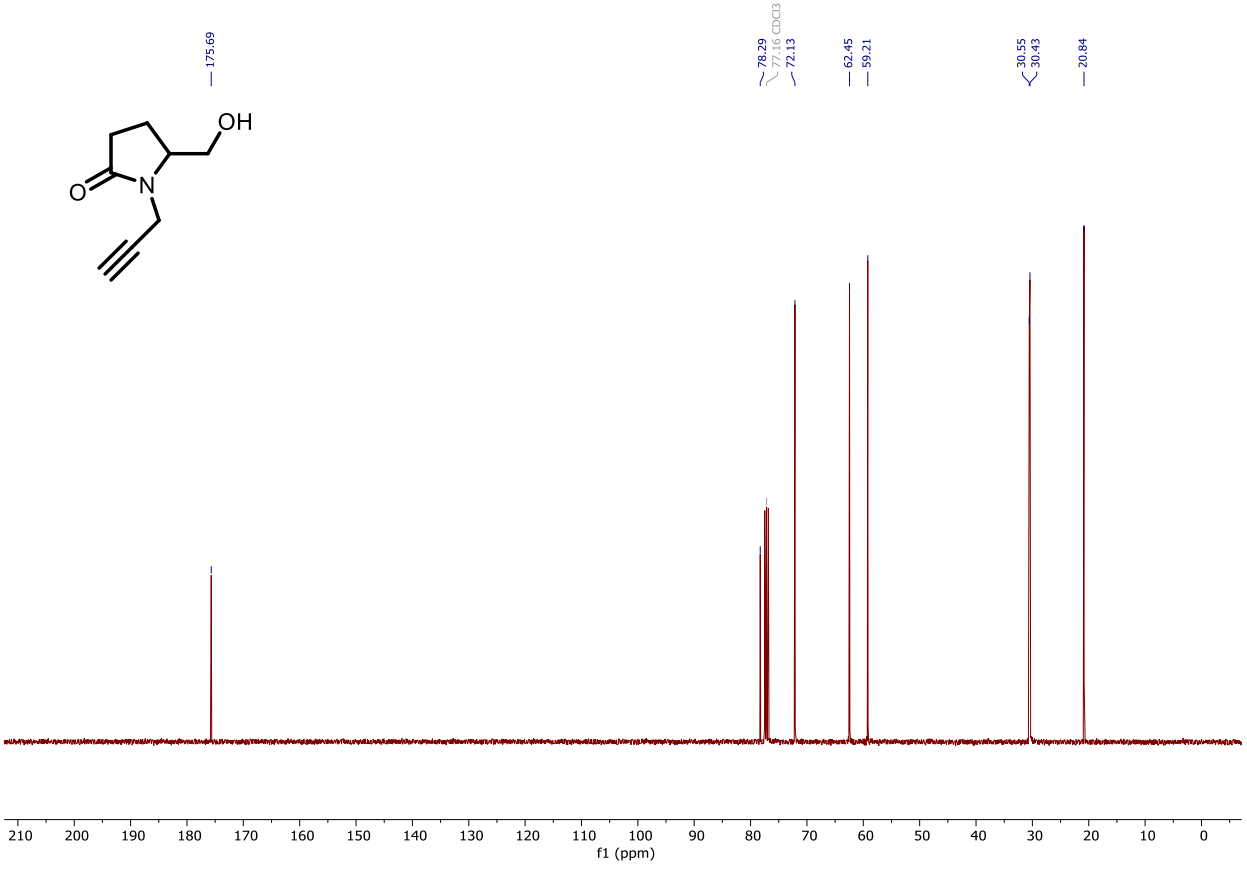
Methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (132)



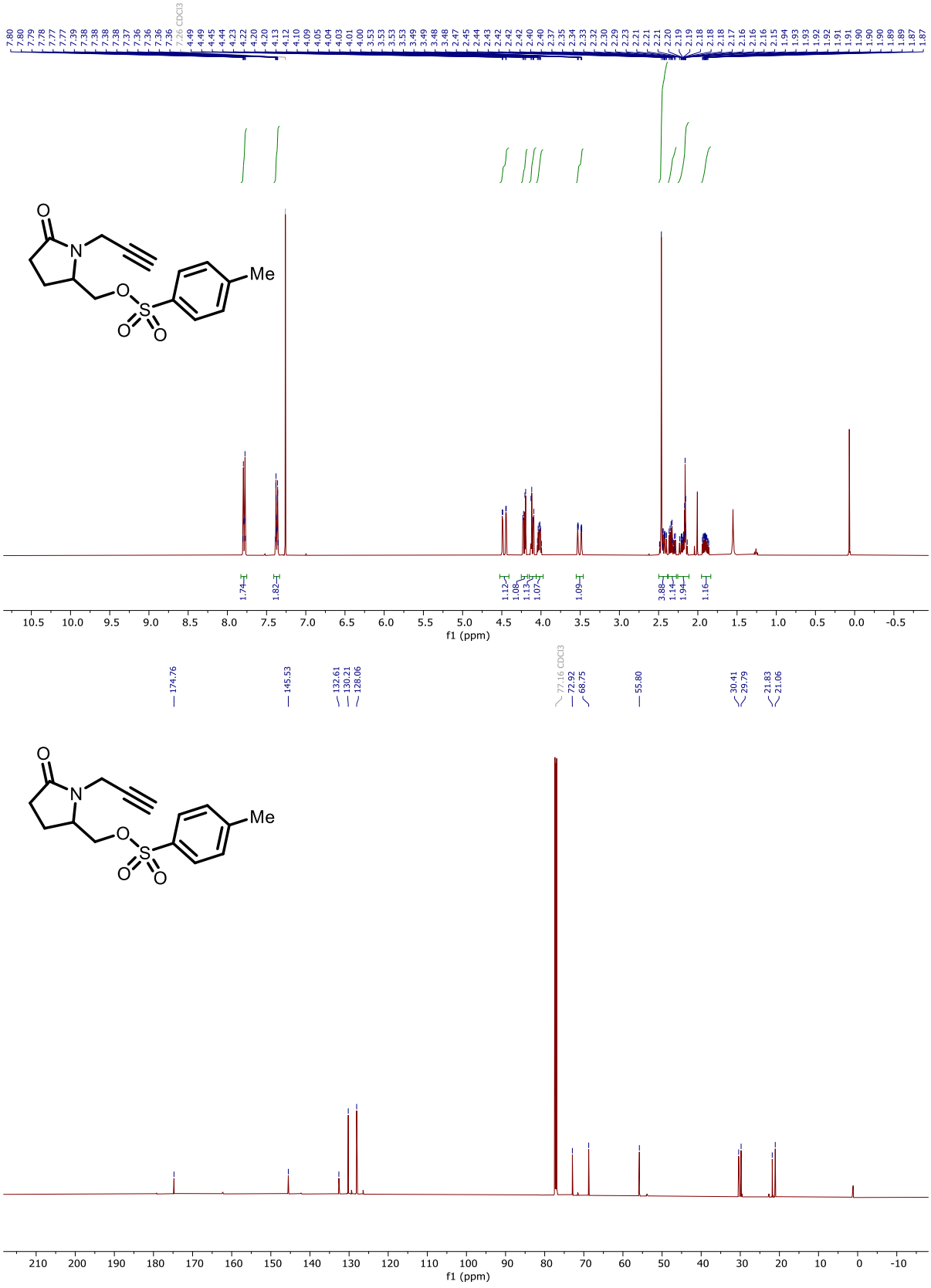


5-(Hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (80d)

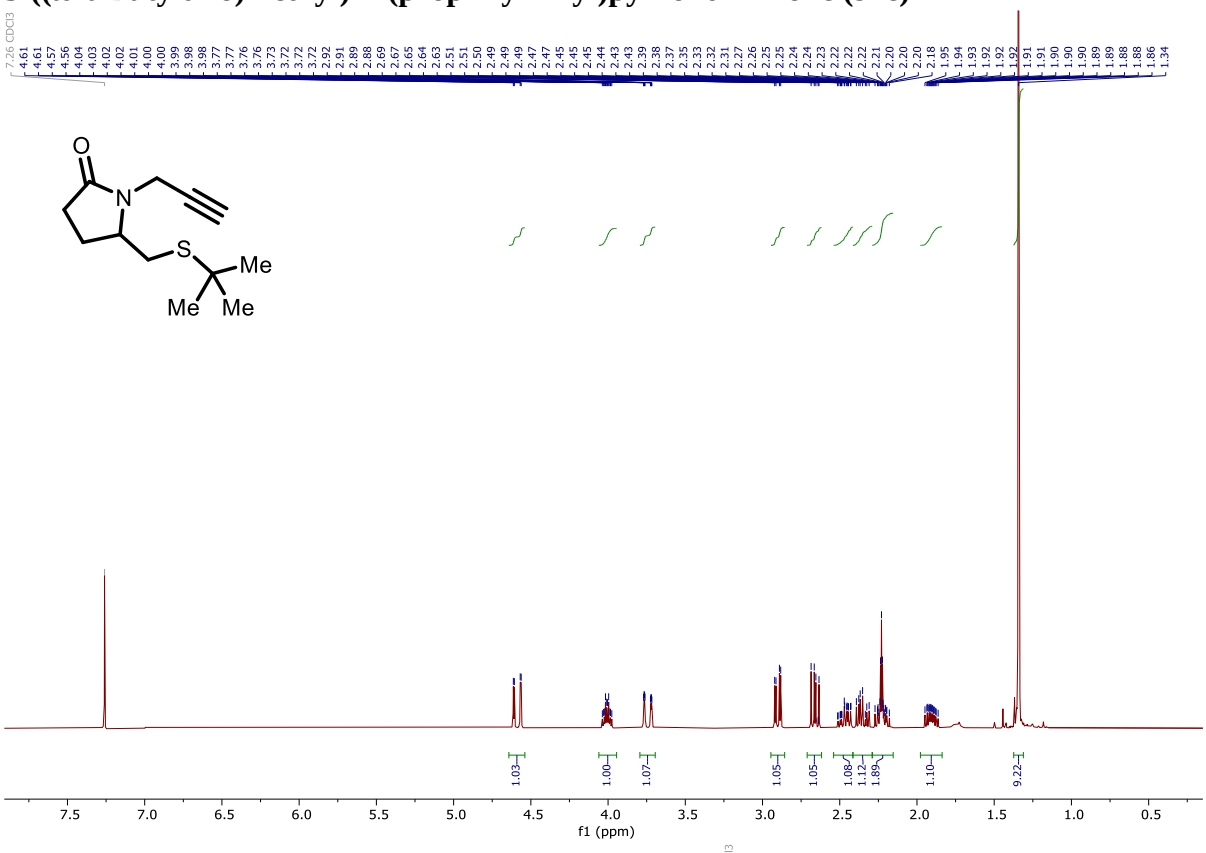


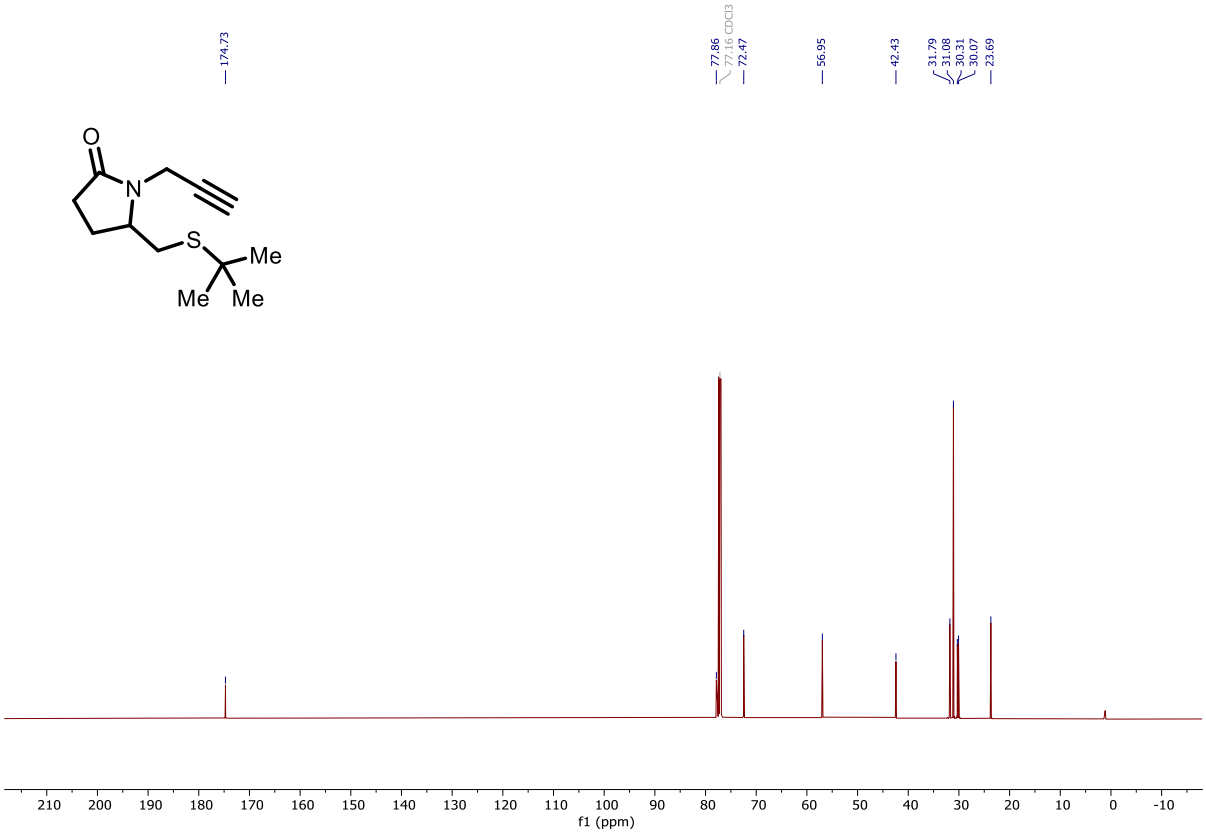


(5-Oxo-1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (90f)

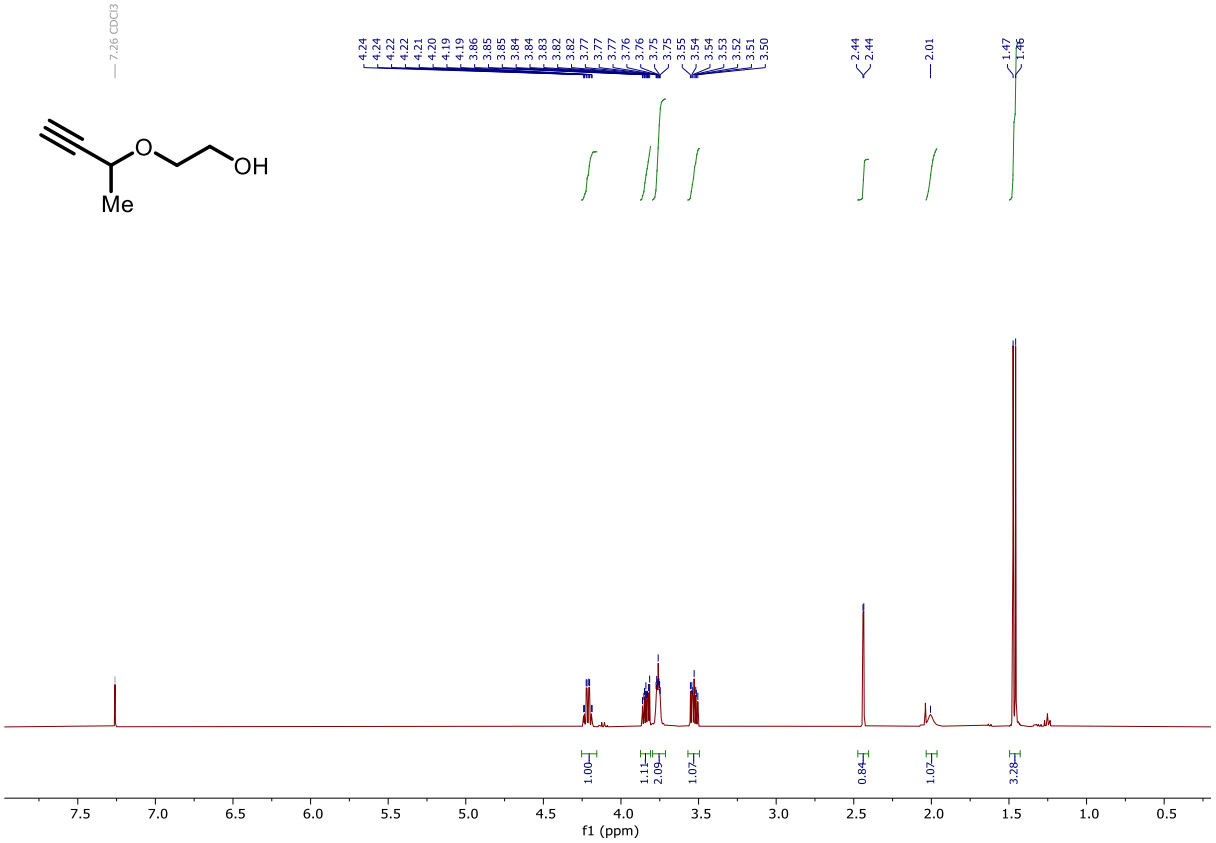


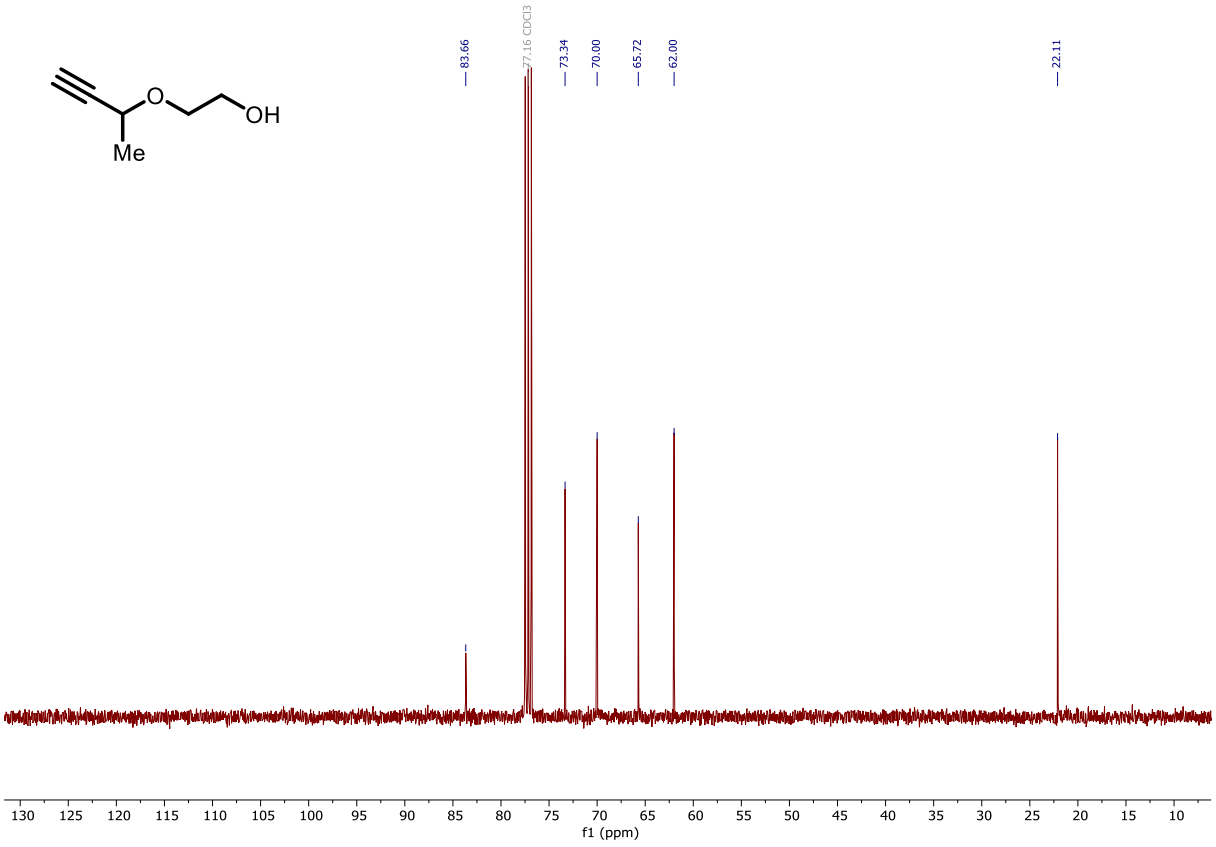
5-((*tert*-Butylthio)methyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (91e)



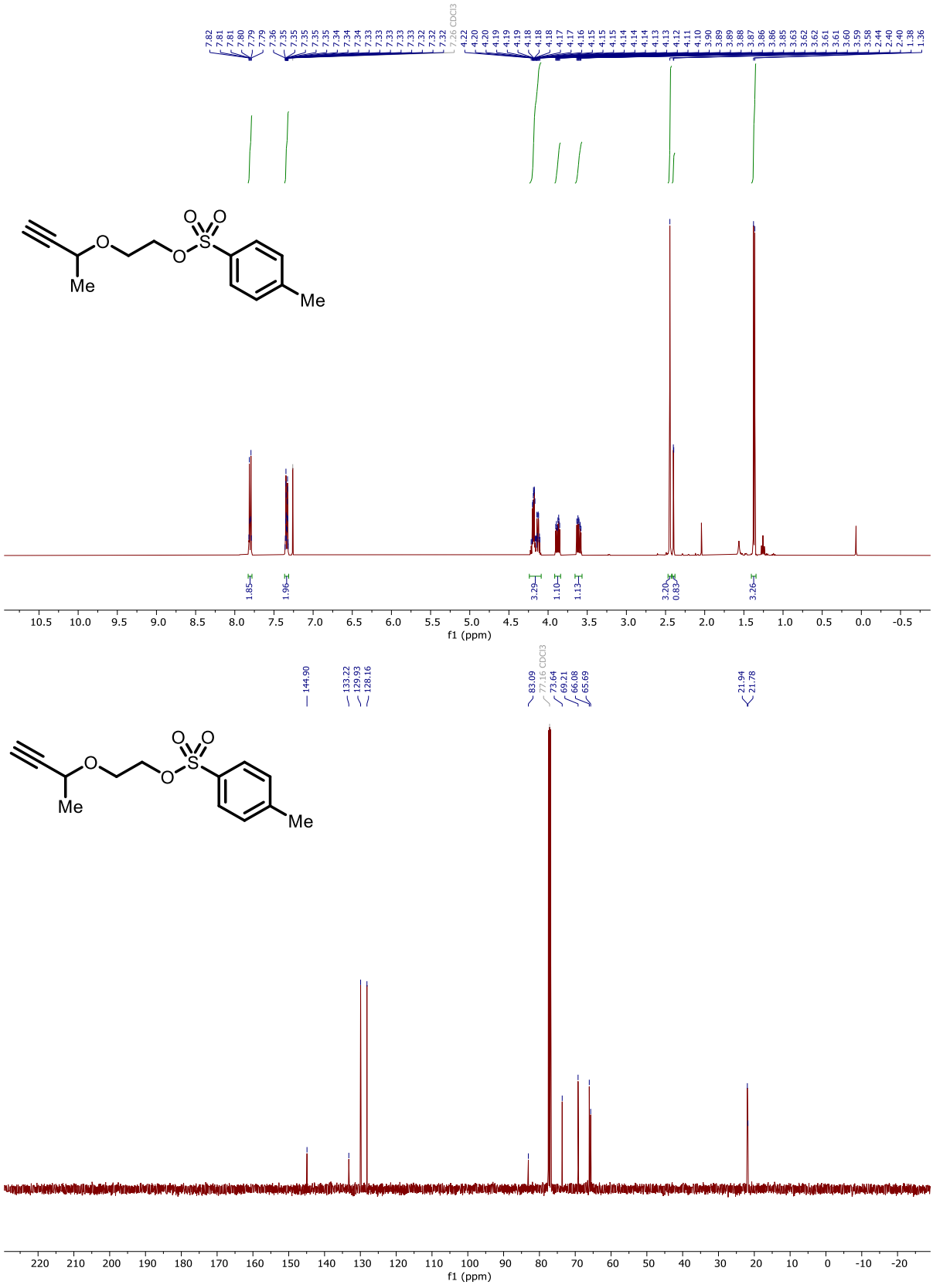


2-(But-3-yn-2-yloxy)ethan-1-ol (100a)

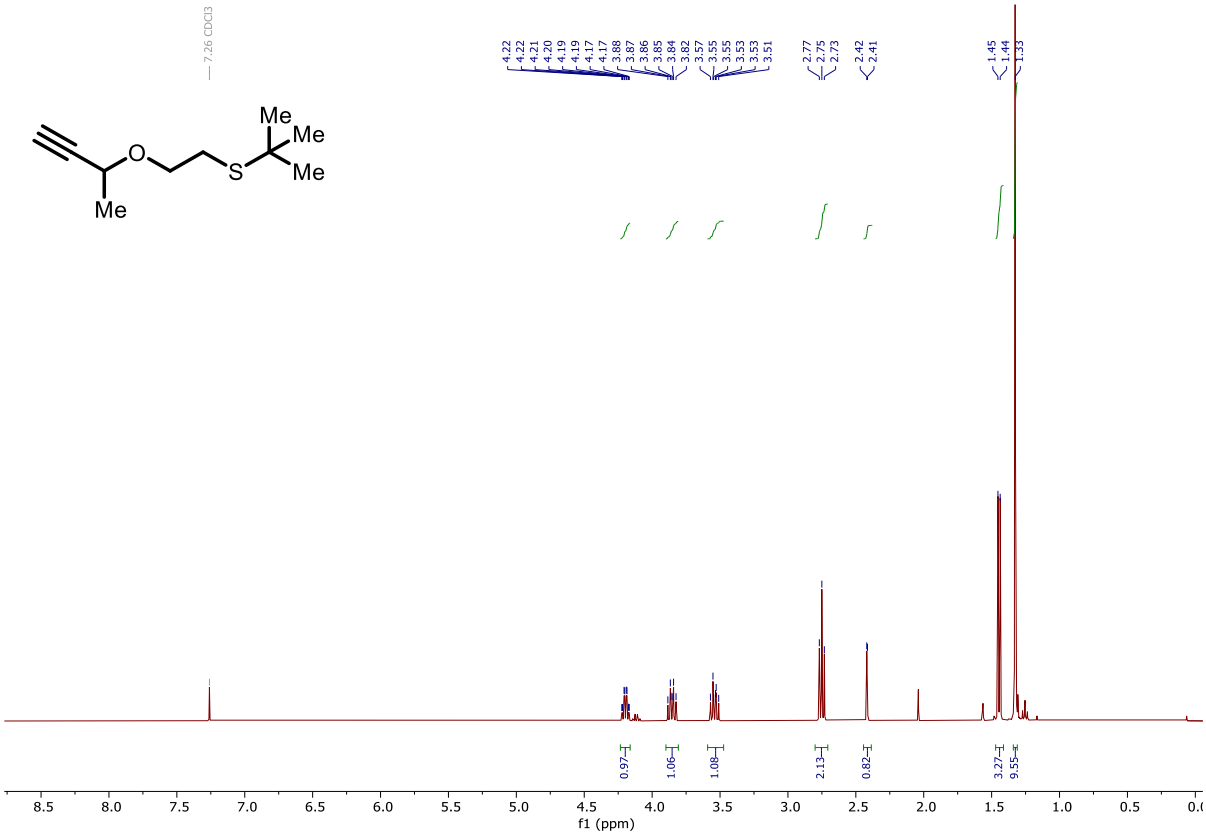


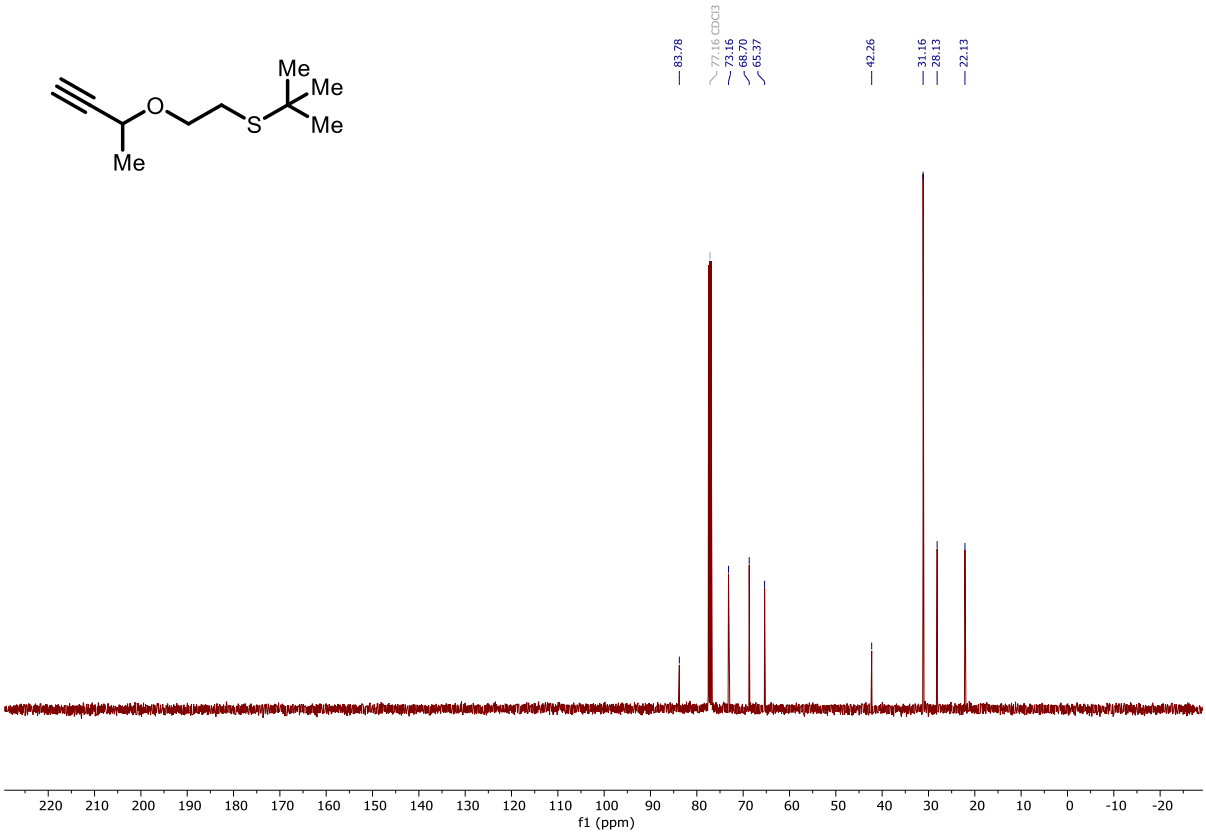


2-(But-3-yn-2-yloxy)ethyl 4-methylbenzenesulfonate (101a)

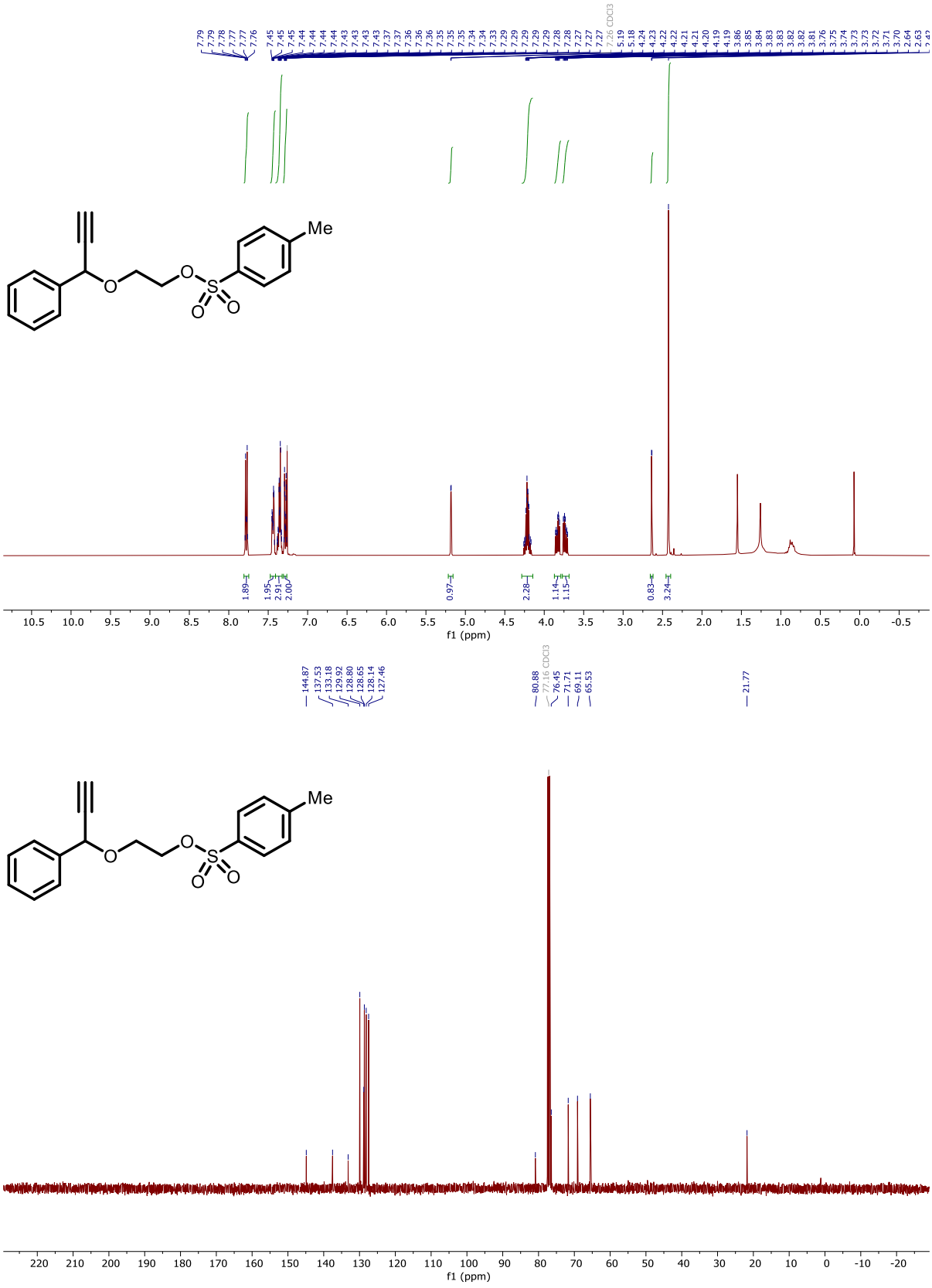


(2-(But-3-yn-2-yloxy)ethyl)(tert-butyl)sulfane (91f)

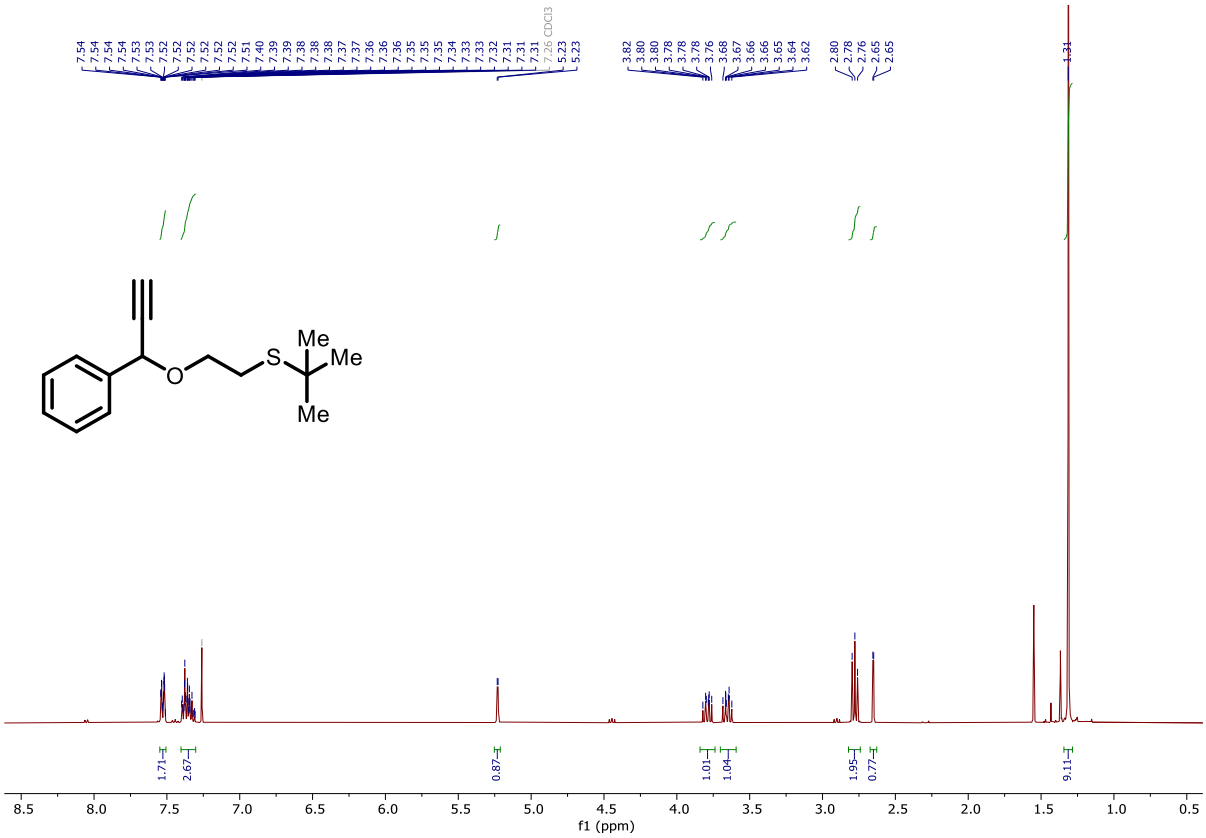


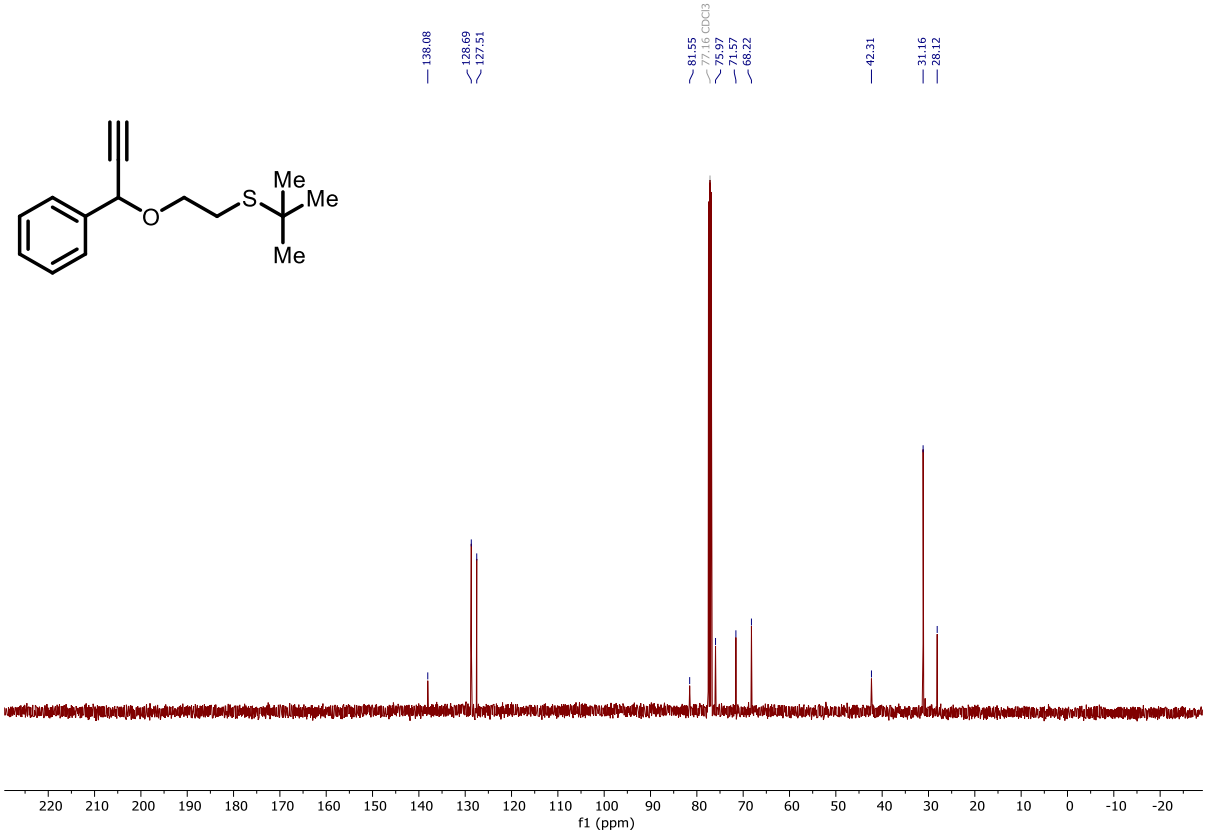


2-((1-Phenylprop-2-yn-1-yl)oxy)ethyl 4-methylbenzenesulfonate (101b)

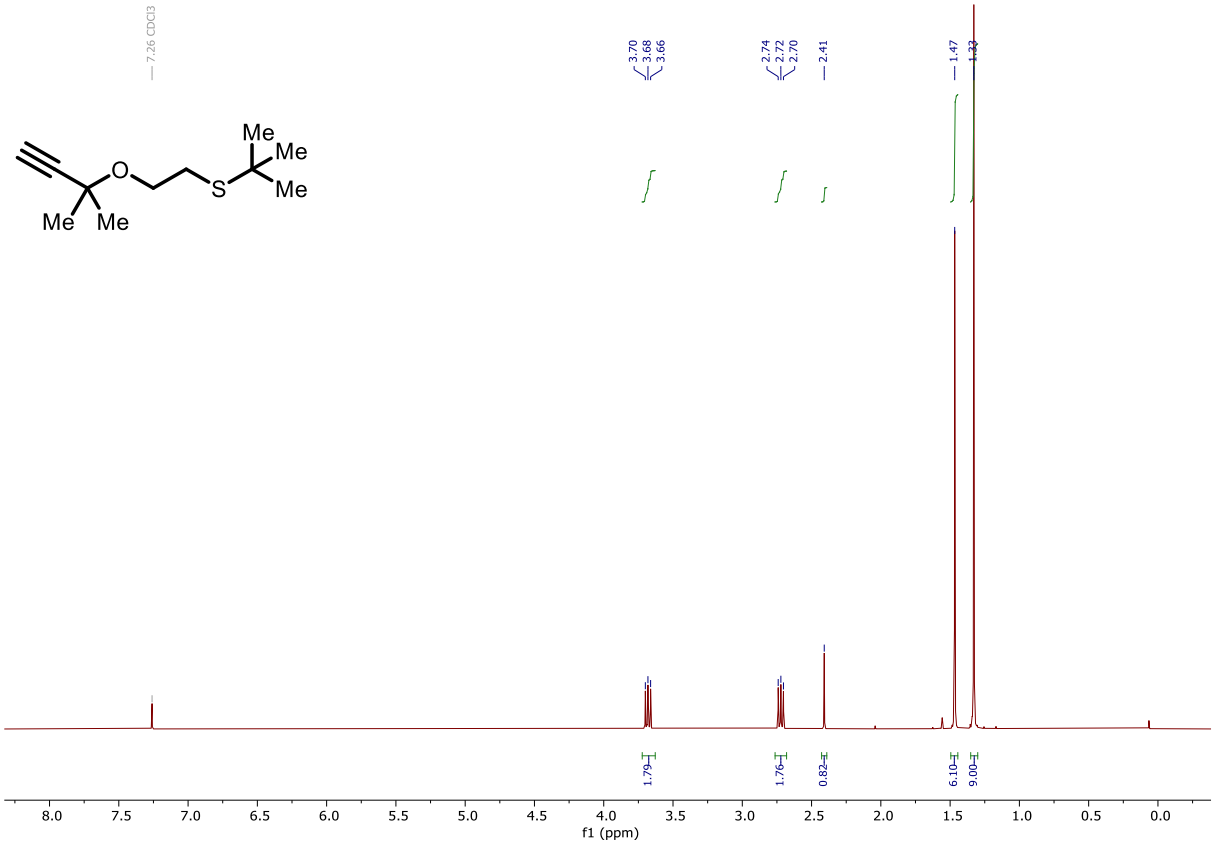


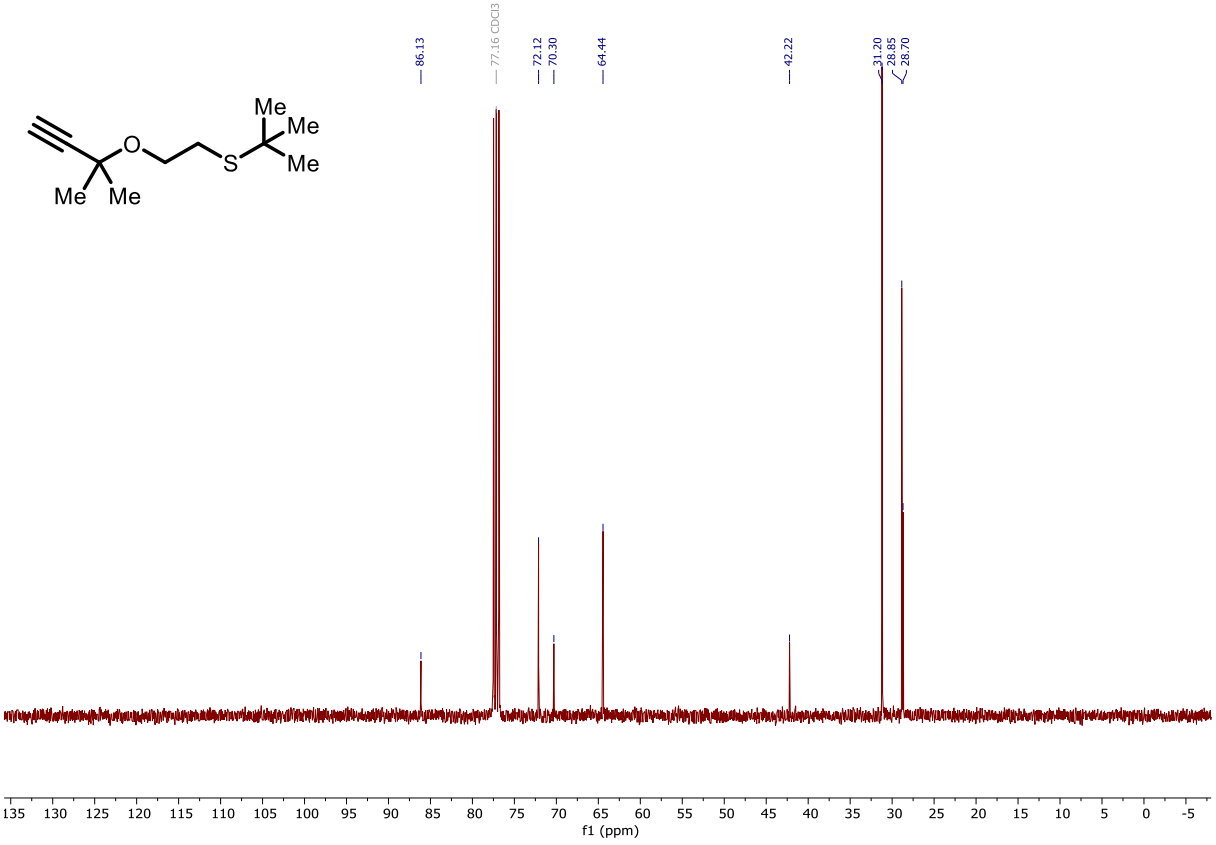
tert-Butyl(2-((1-phenylprop-2-yn-1-yl)oxy)ethyl)sulfane (91g)



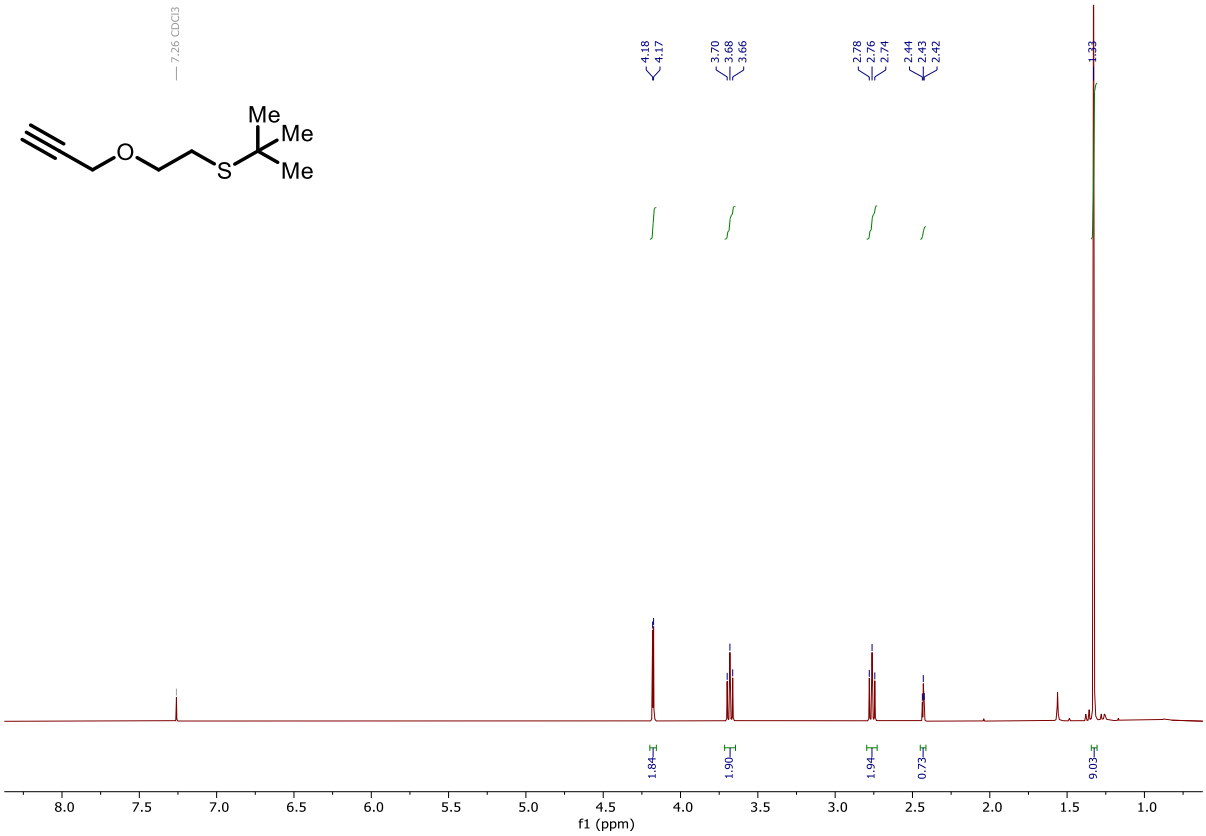


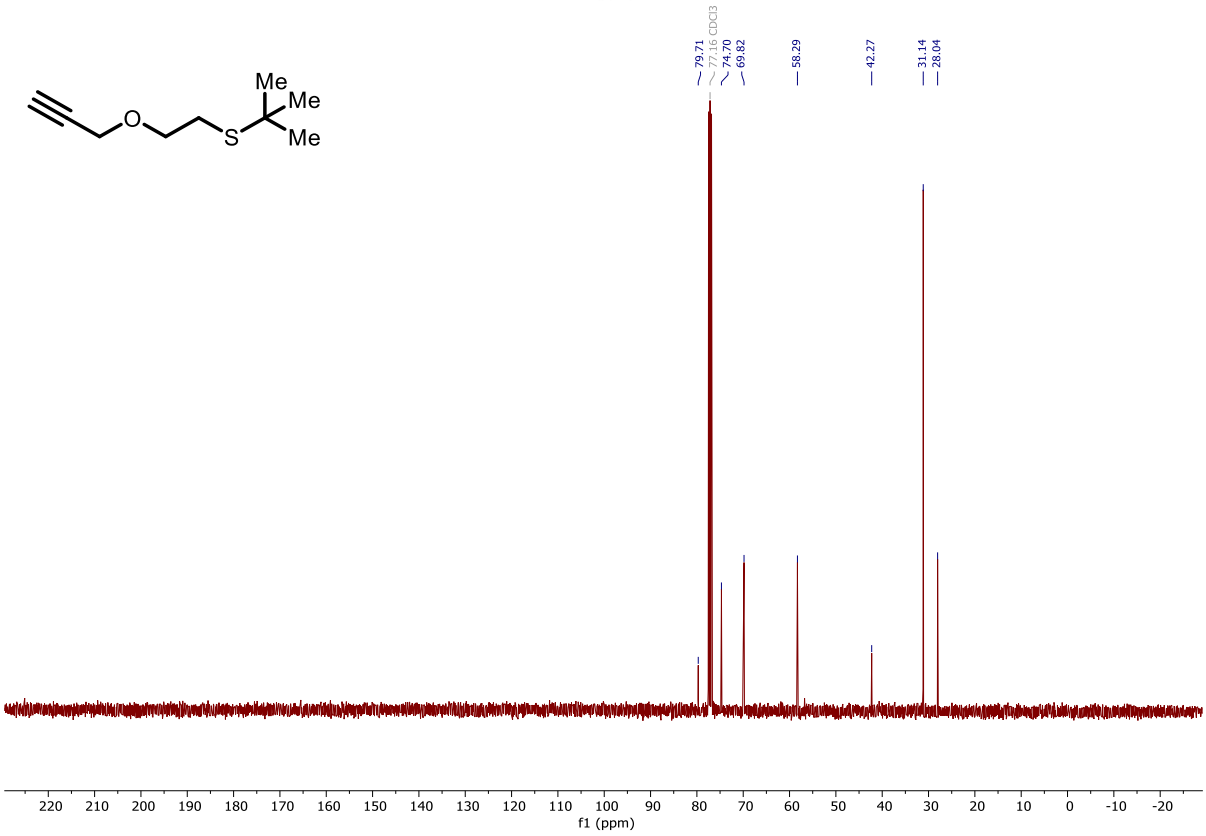
tert-Butyl(2-((2-methylbut-3-yn-2-yl)oxy)ethyl)sulfane (91h)



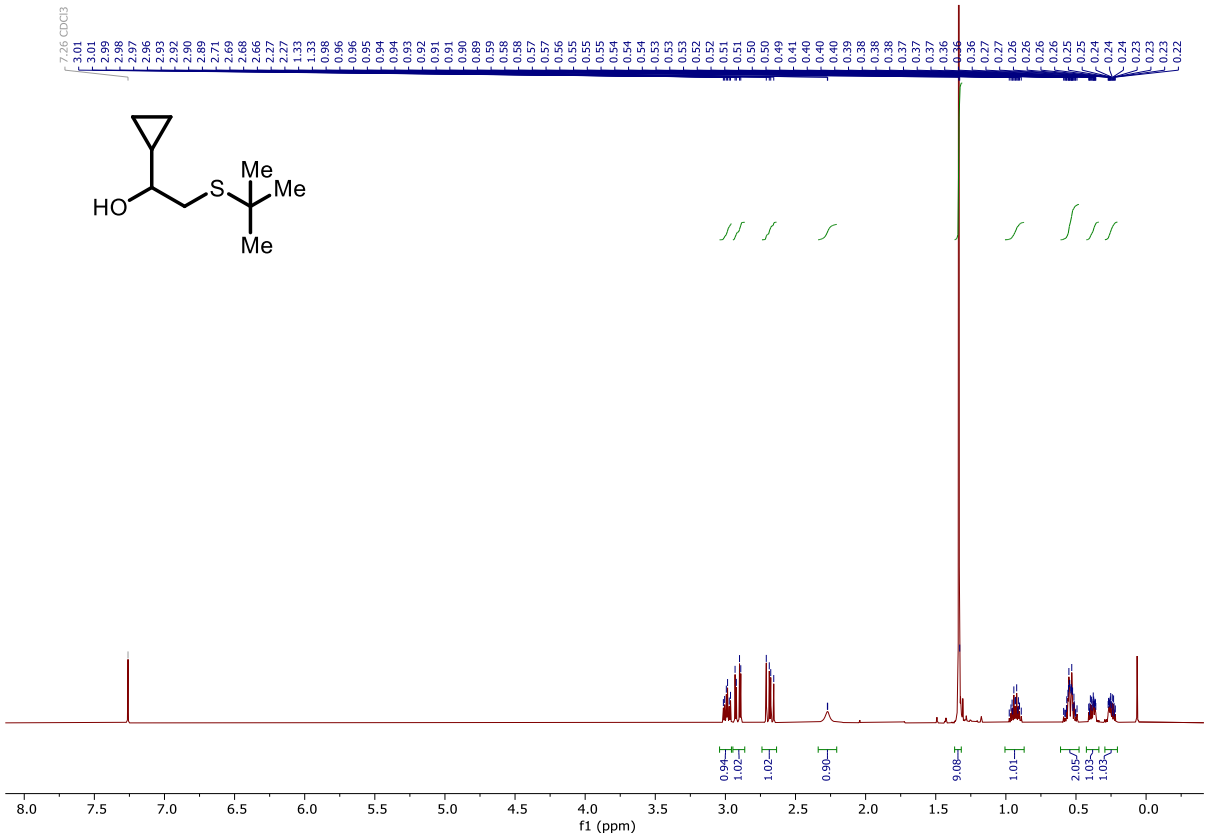


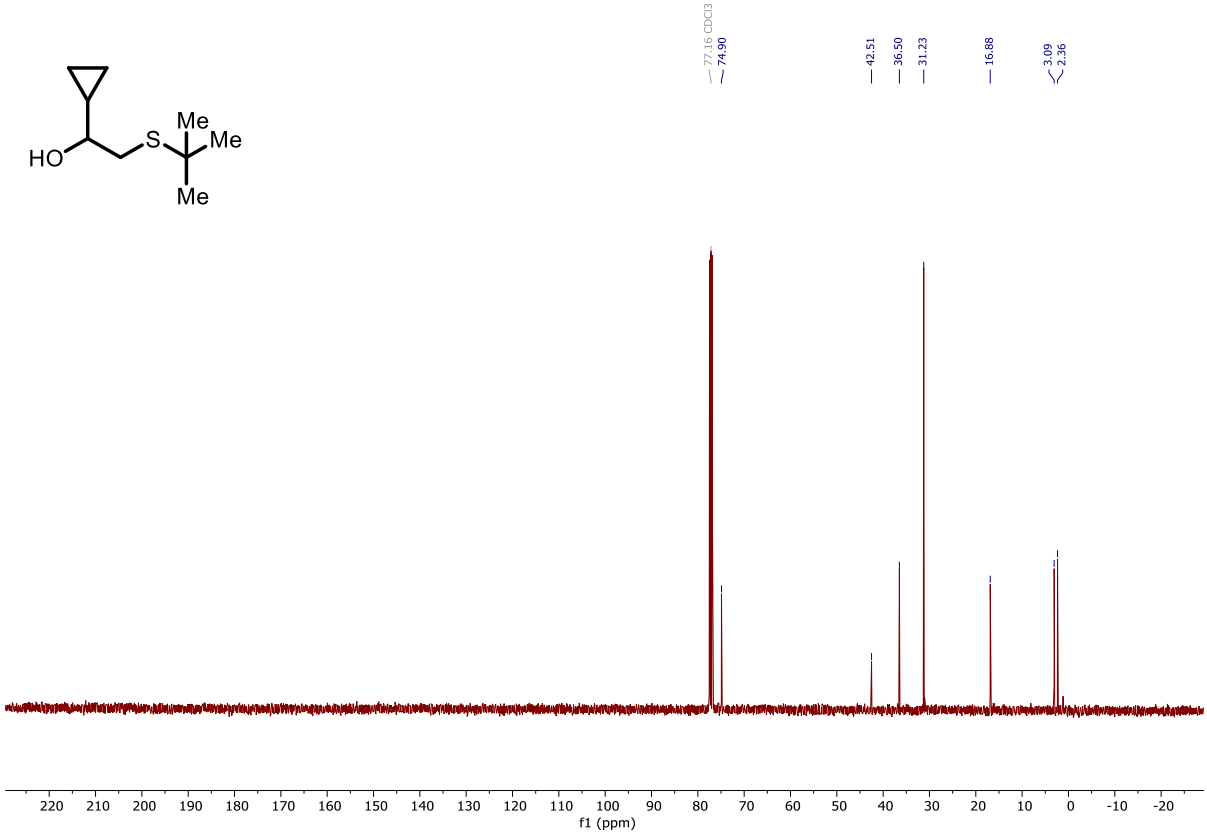
tert-Butyl(2-(prop-2-yn-1-yloxy)ethyl)sulfane (91i)



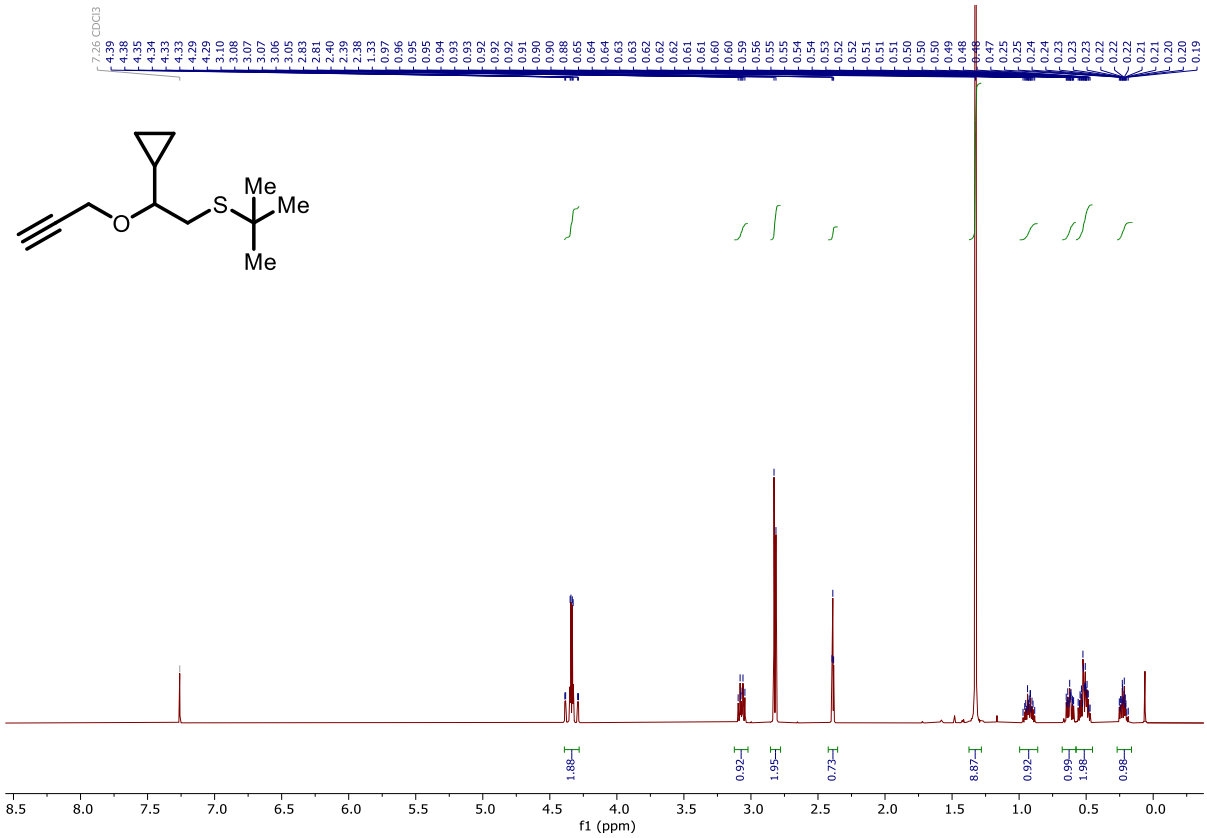


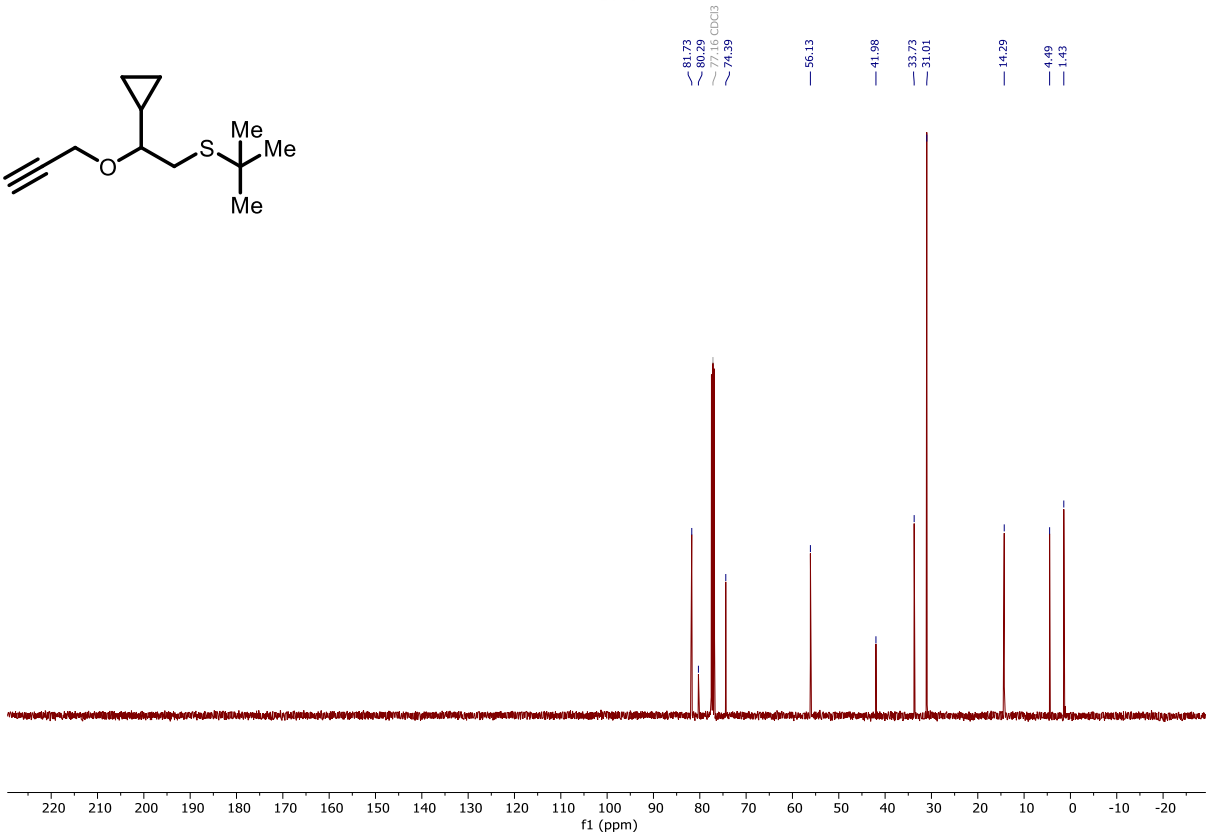
2-(*tert*-Butylthio)-1-cyclopropylethan-1-ol (133)



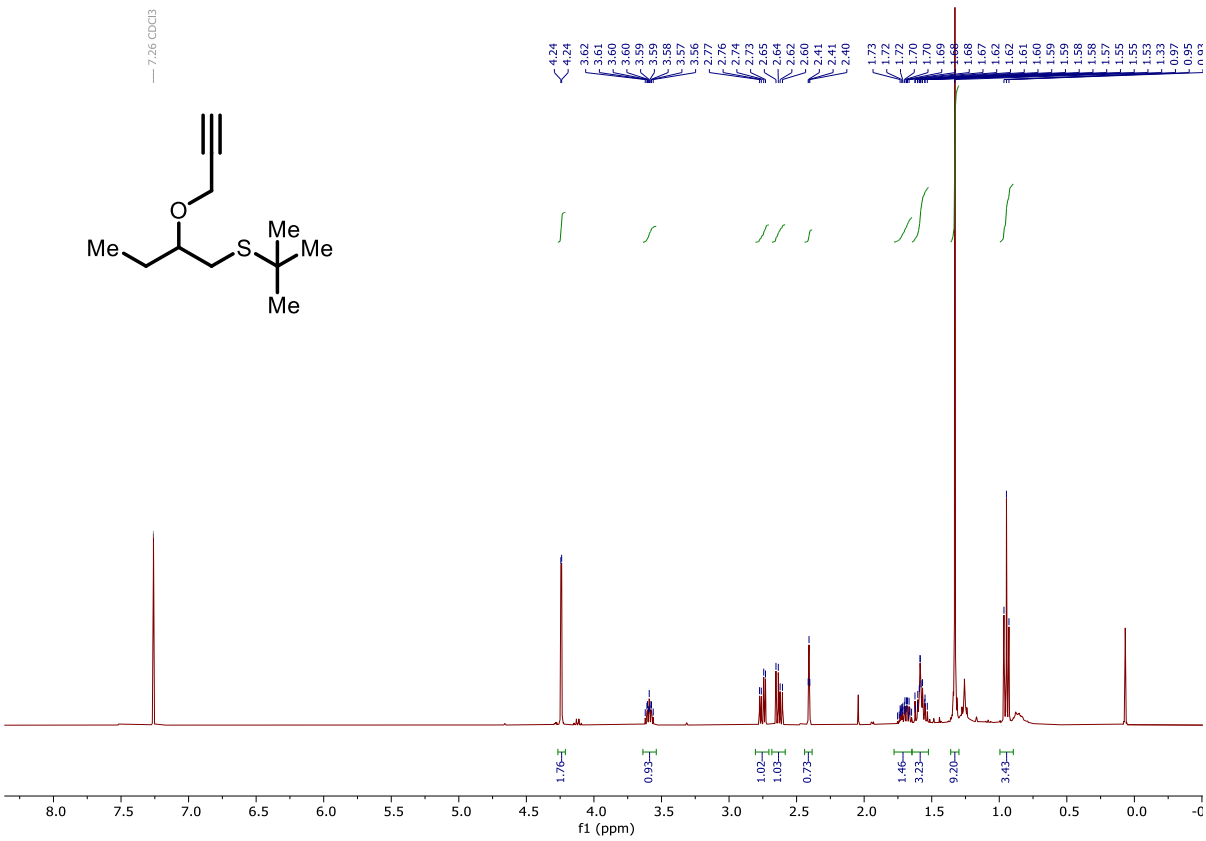


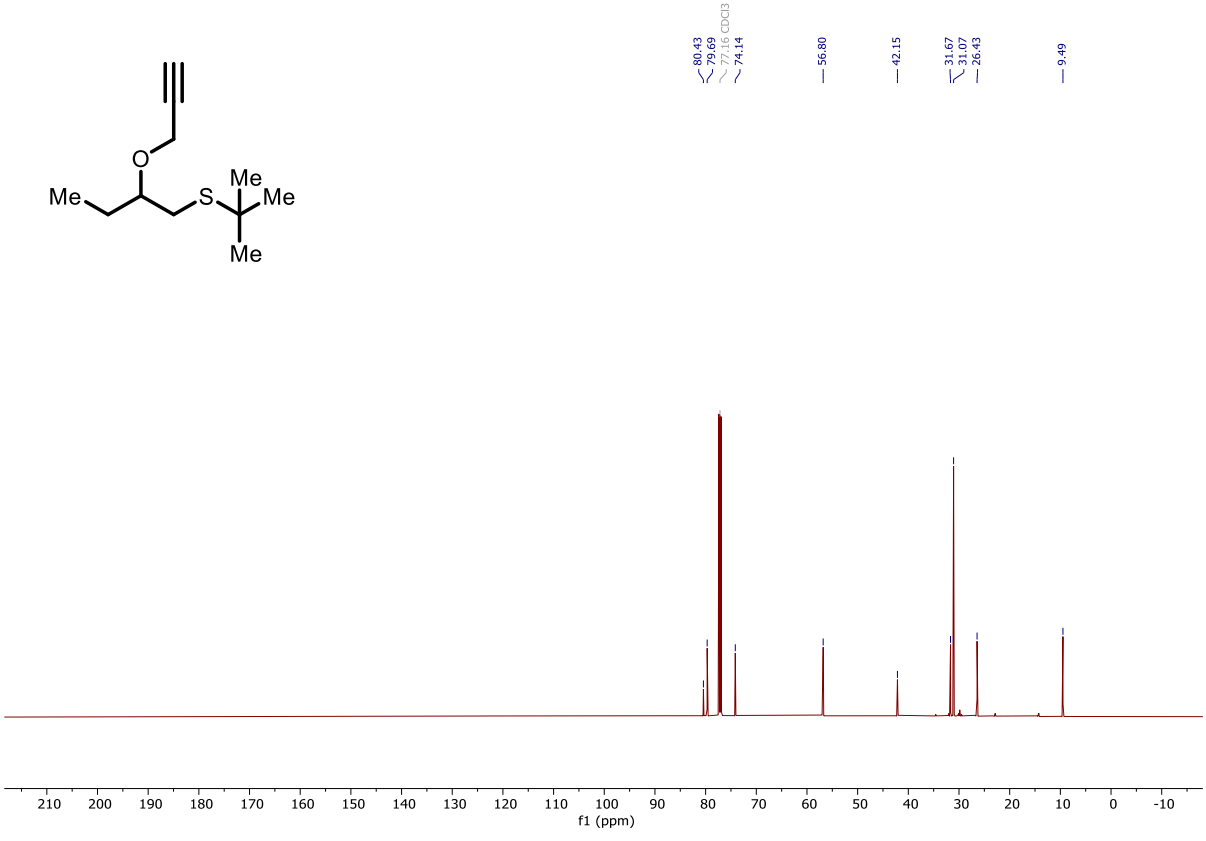
tert-Butyl(2-cyclopropyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91j)



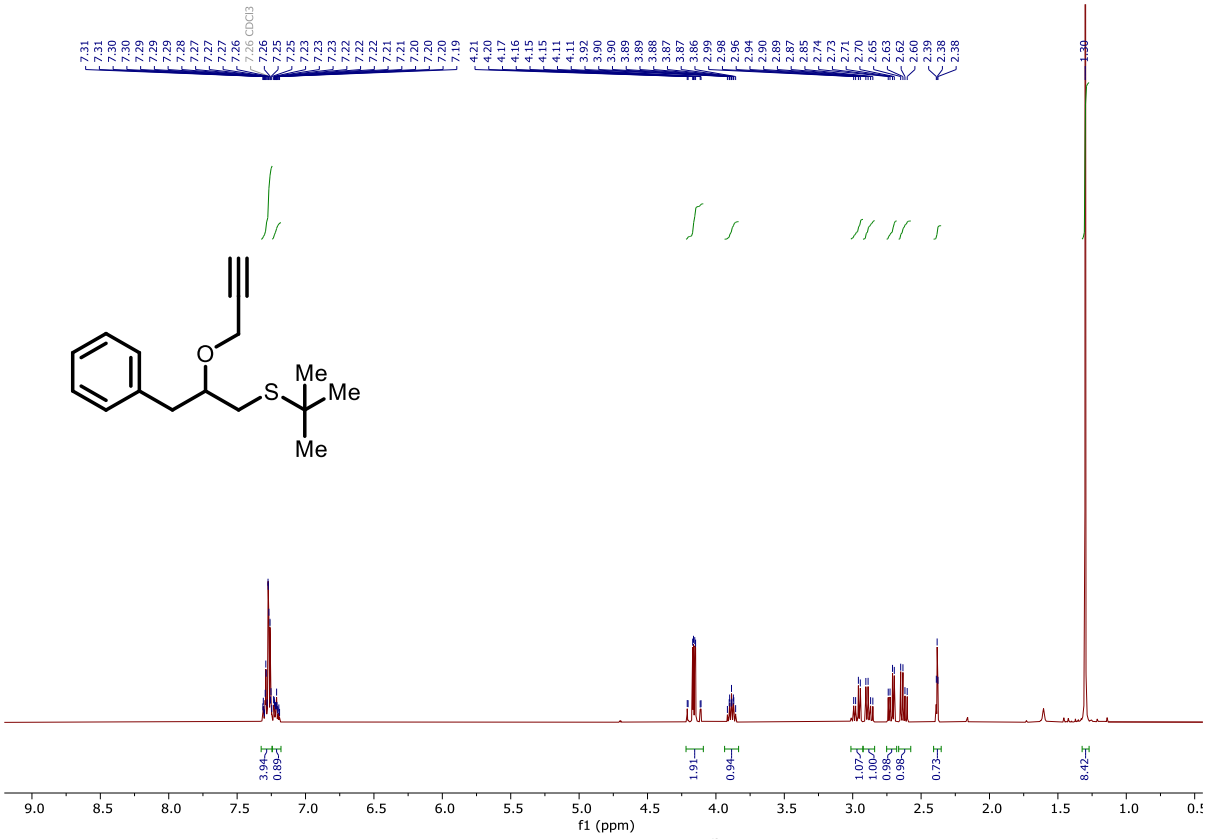


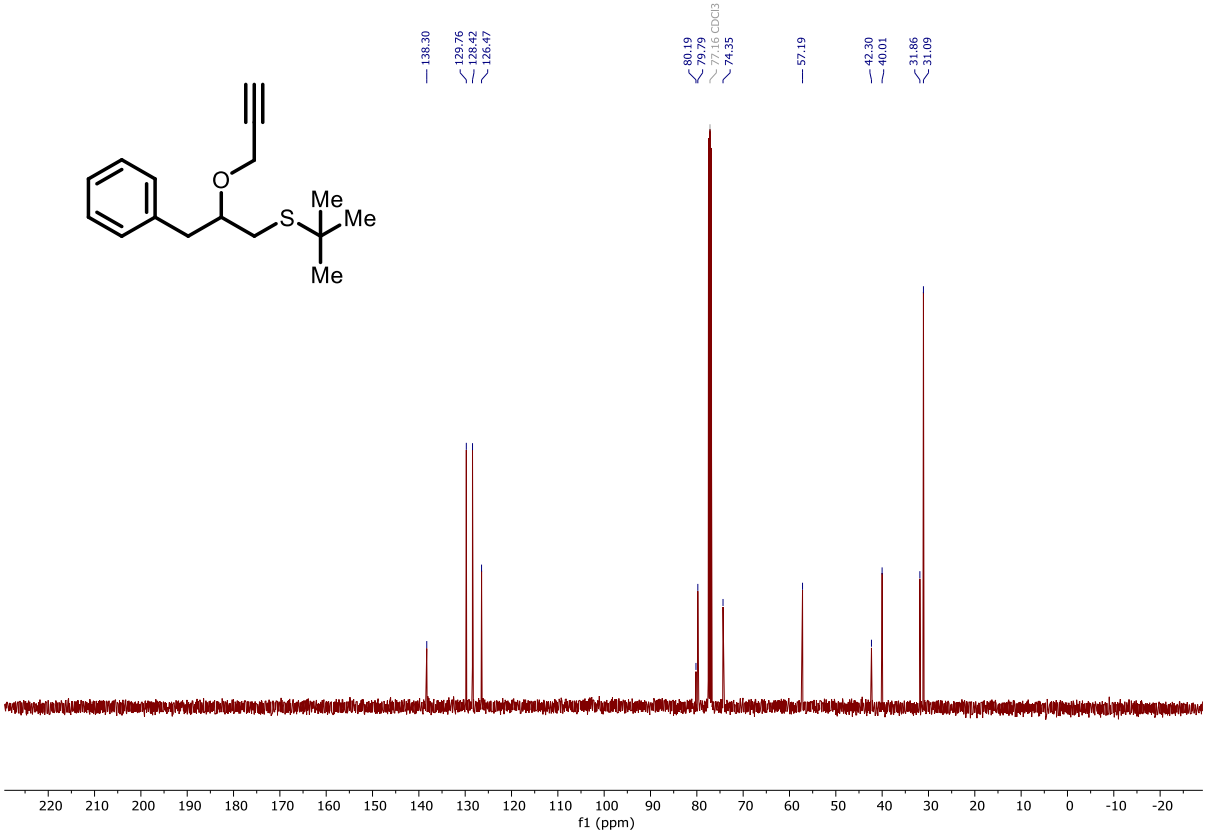
tert-Butyl(2-(prop-2-yn-1-yloxy)butyl)sulfane (91k)



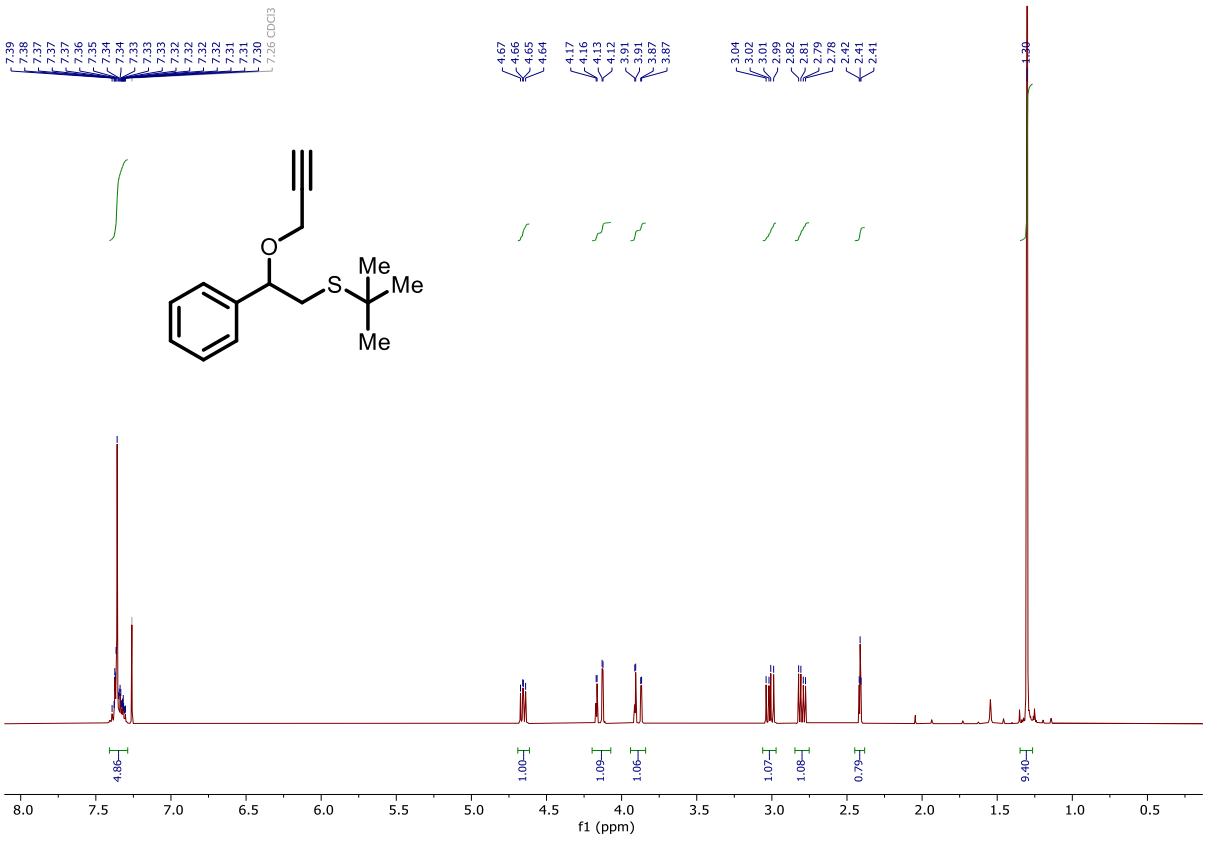


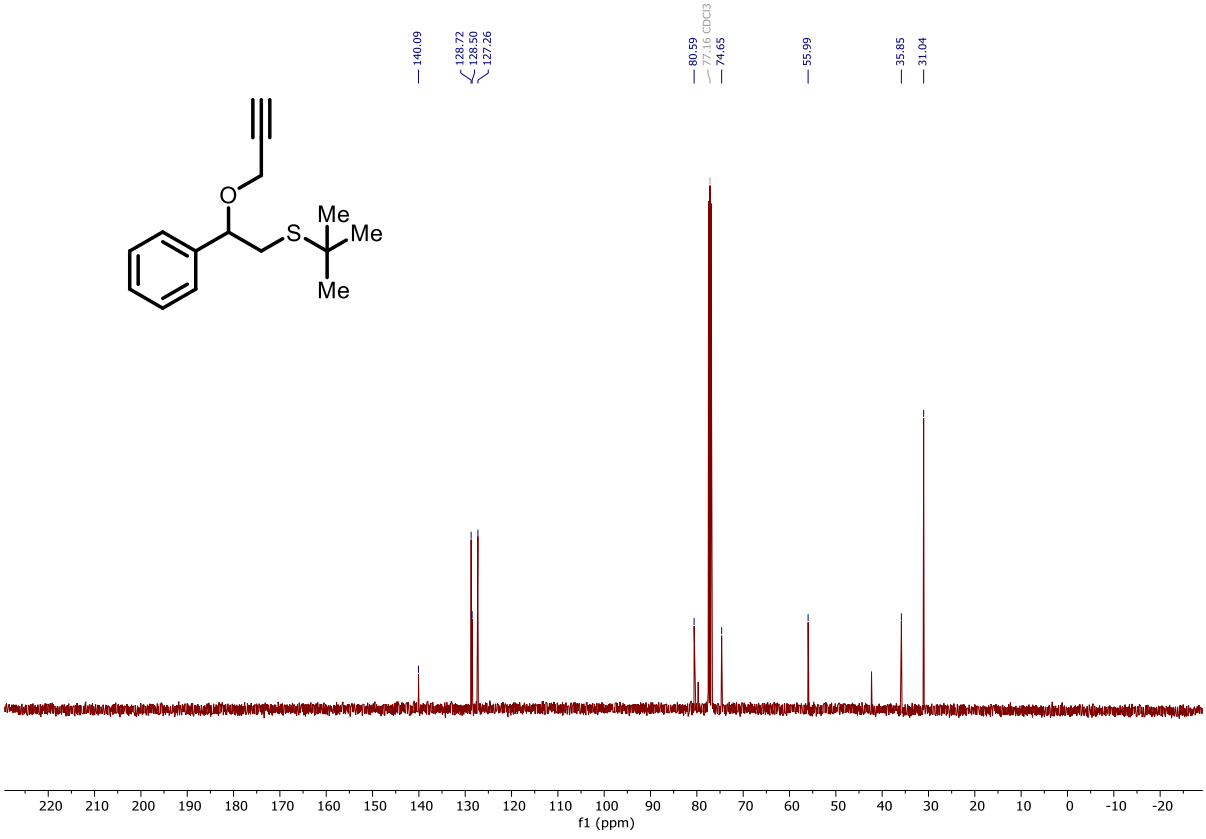
tert-Butyl(3-phenyl-2-(prop-2-yn-1-yloxy)propyl)sulfane (91l)



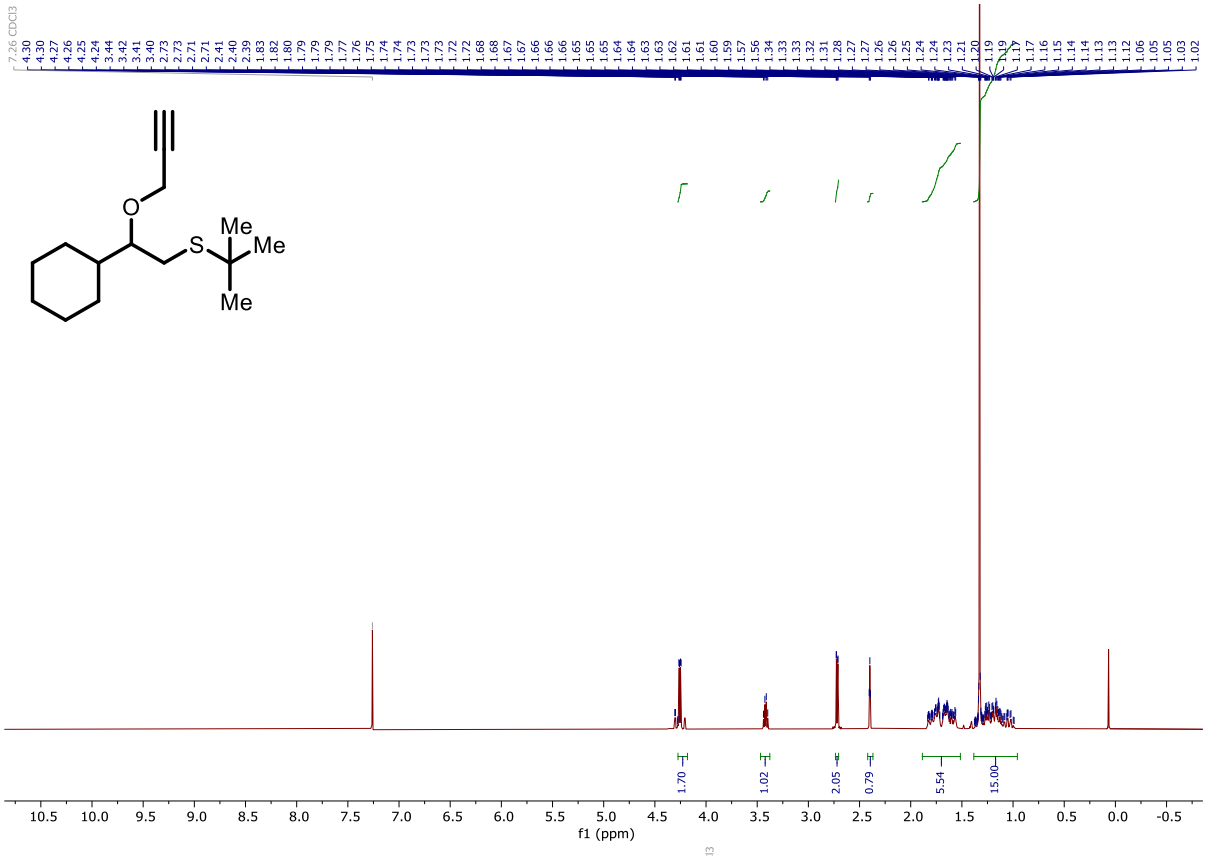


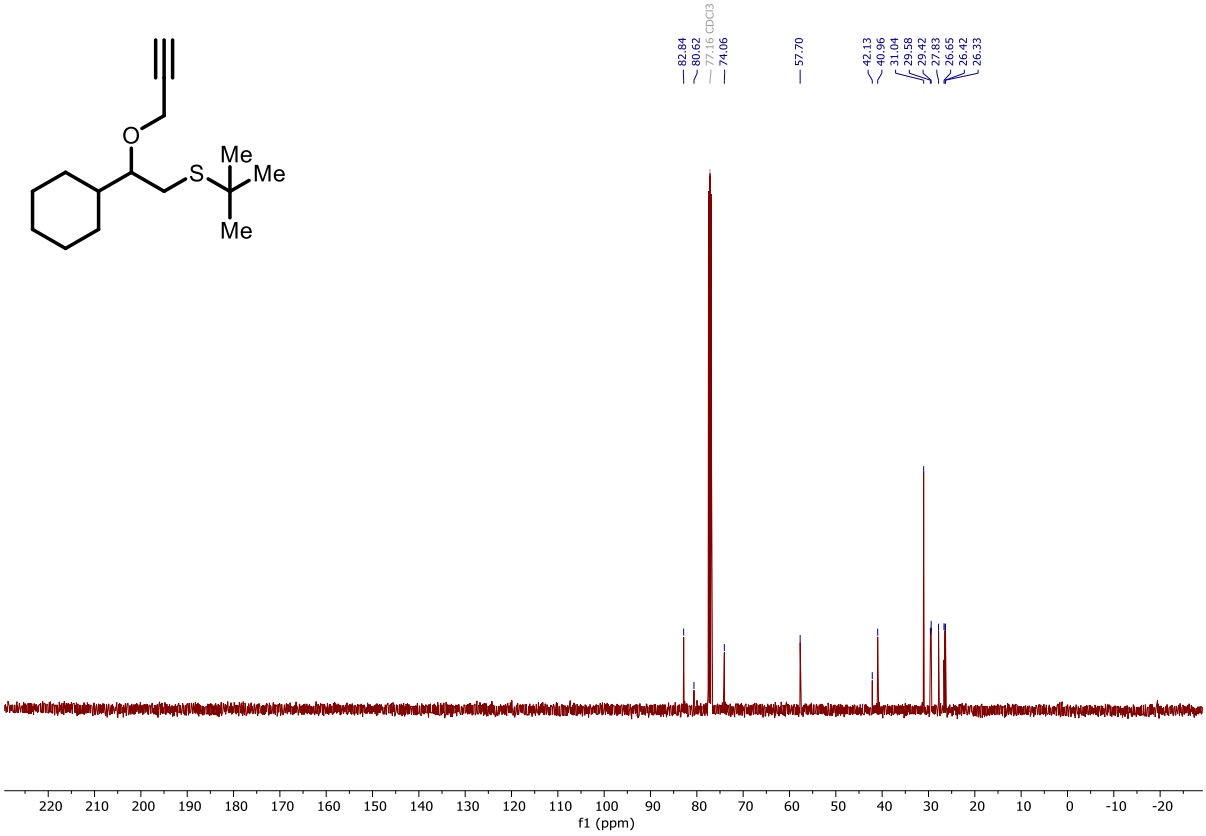
tert-Butyl(2-phenyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91m)



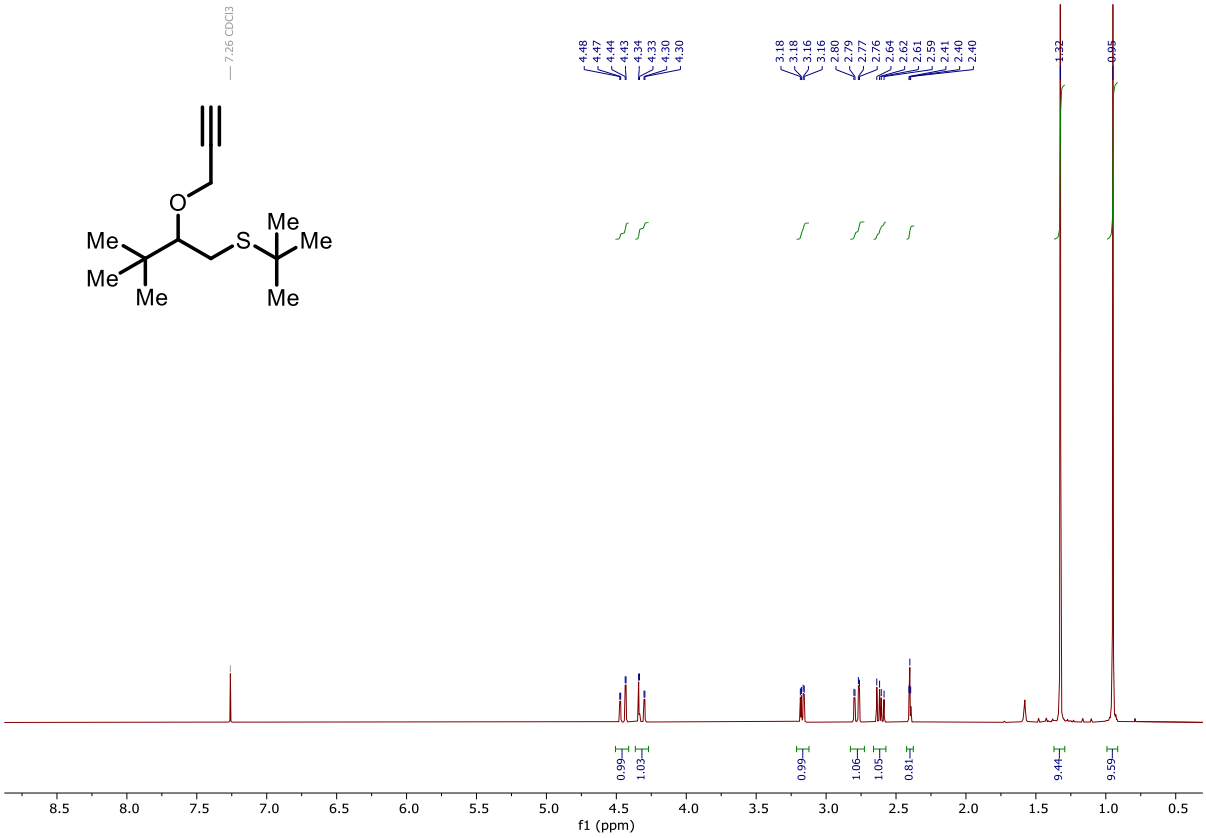


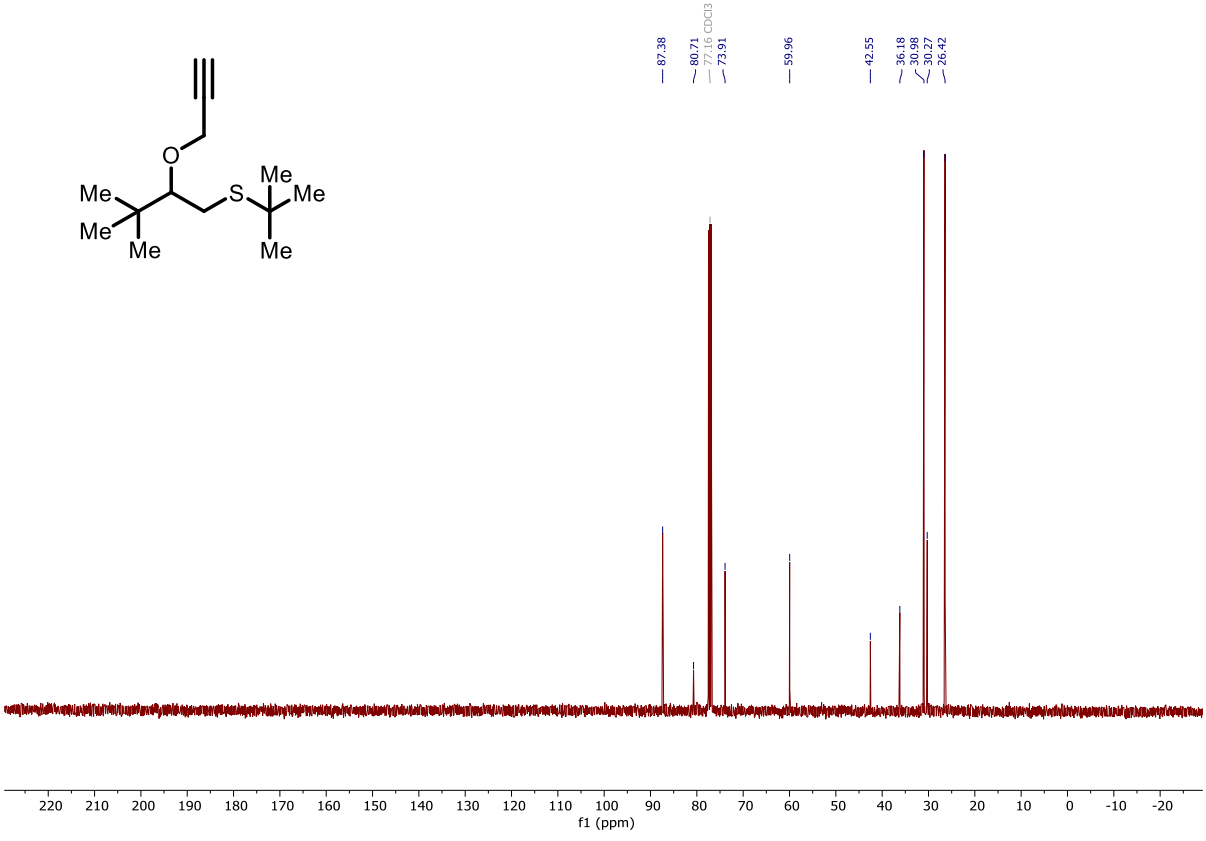
tert-Butyl(2-cyclohexyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91n)



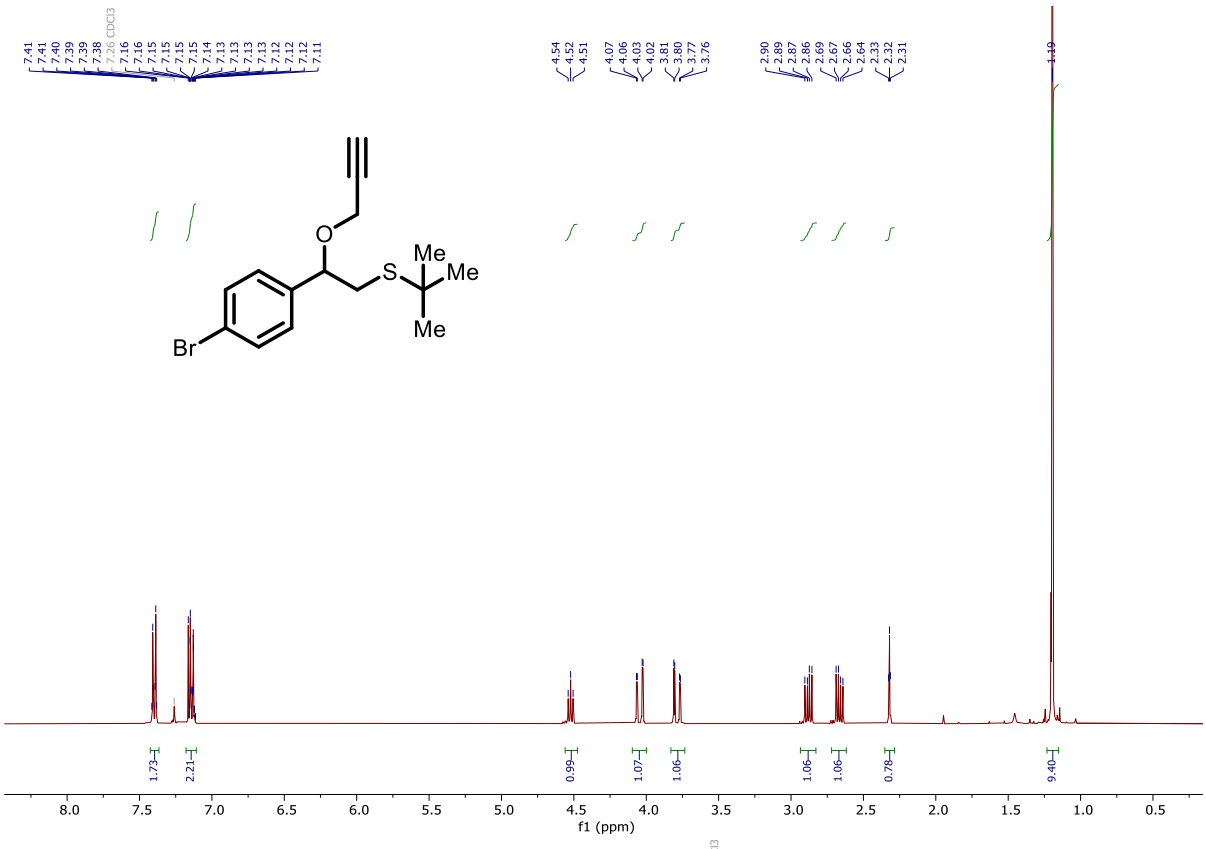


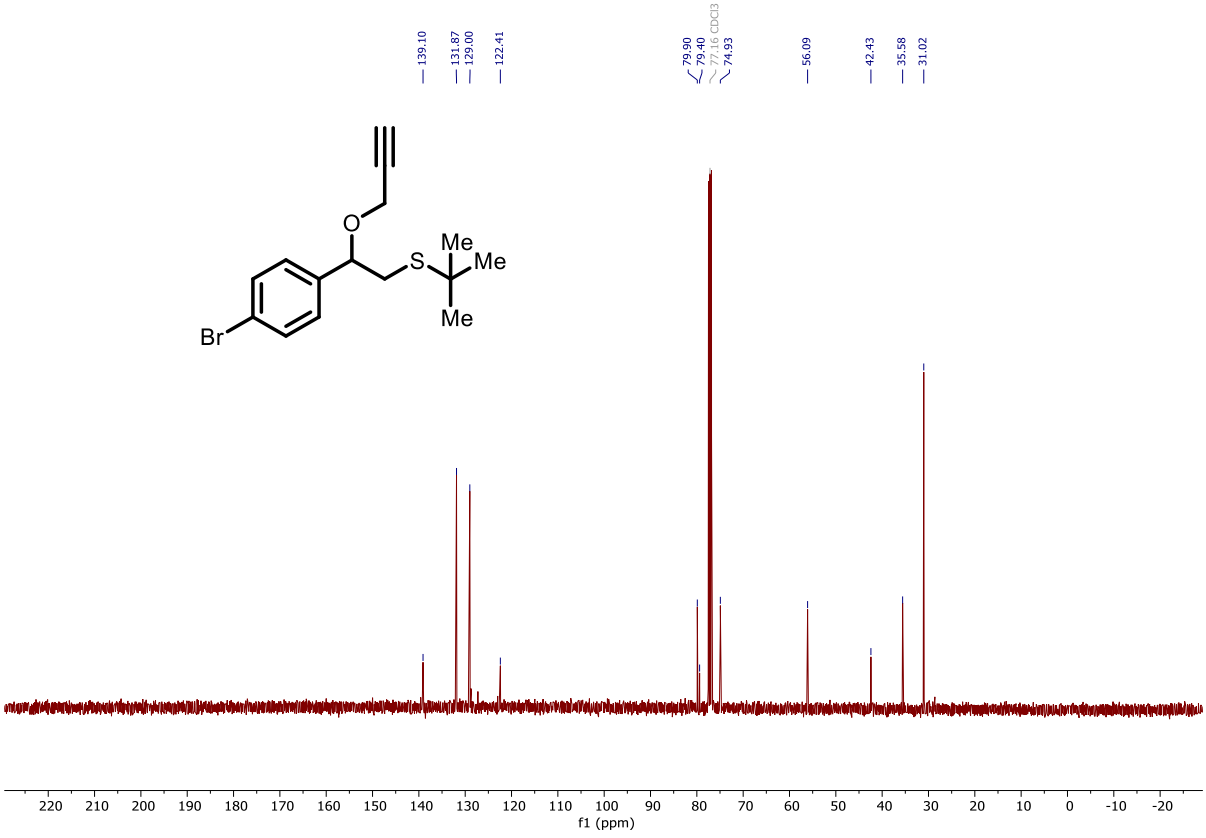
tert-Butyl(3,3-dimethyl-2-(prop-2-yn-1-yloxy)butyl)sulfane (91o)



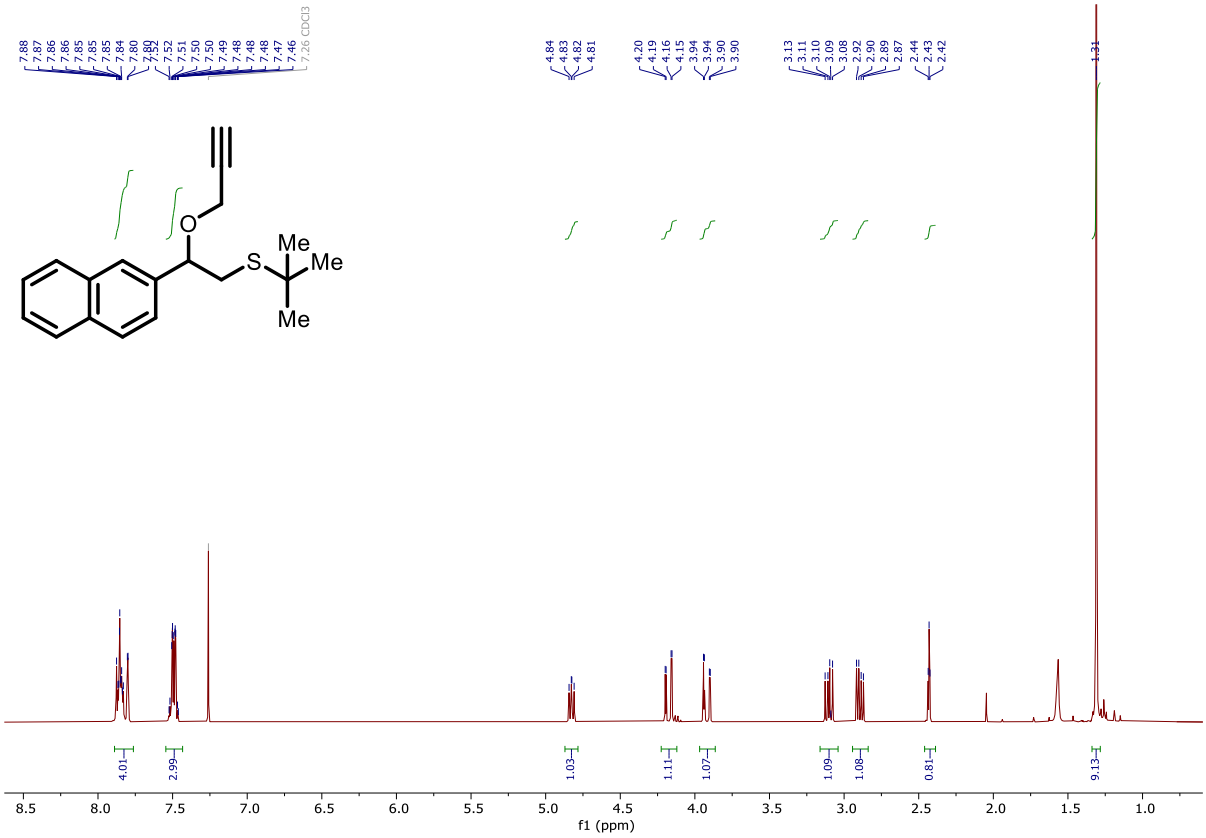


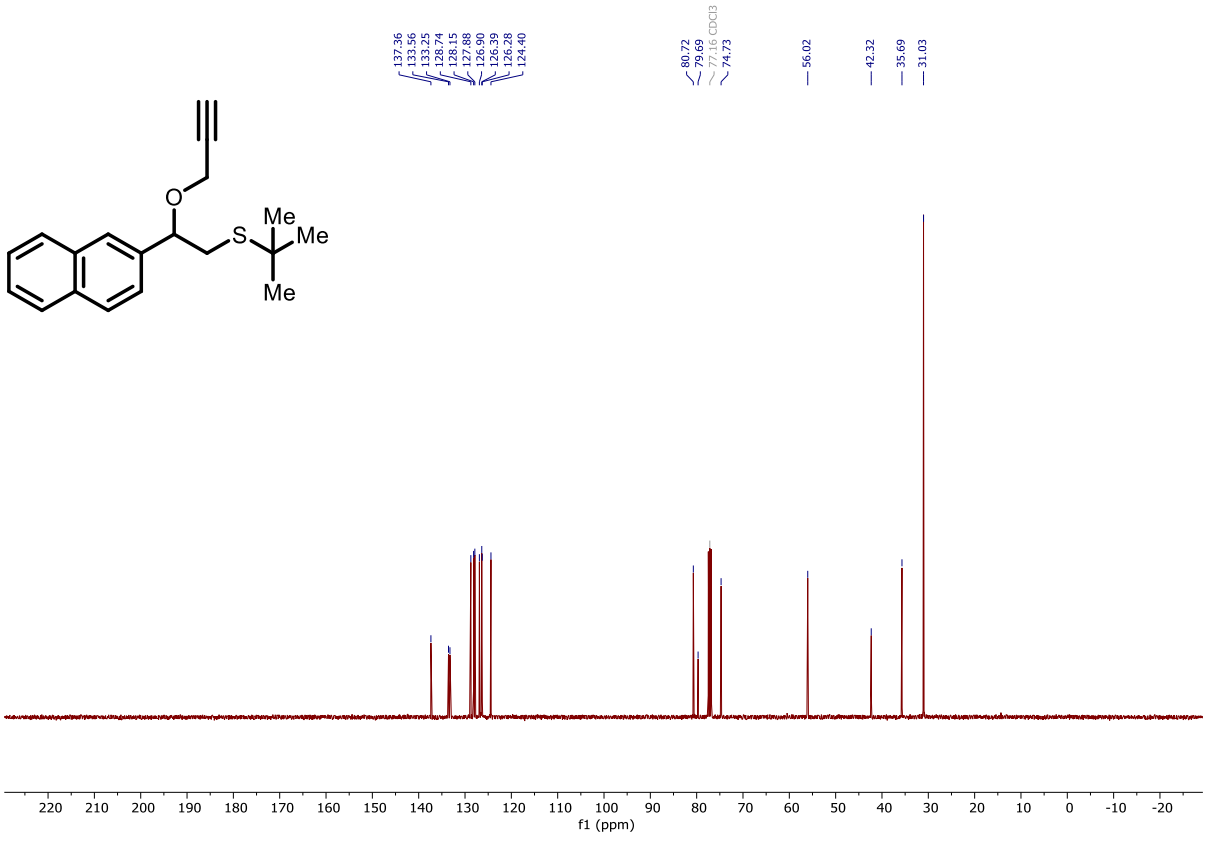
(2-(4-Bromophenyl)-2-(prop-2-yn-1-yloxy)ethyl)(*tert*-butyl)sulfane (91p)



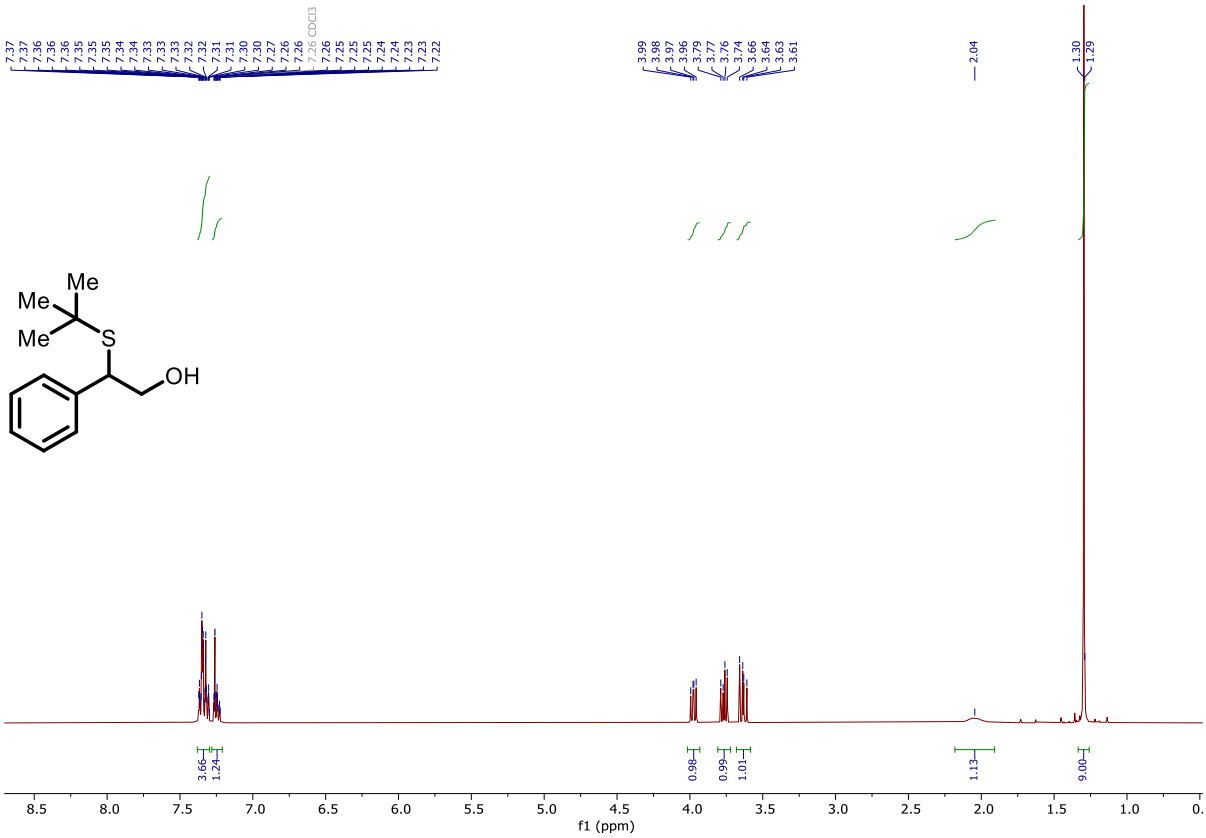


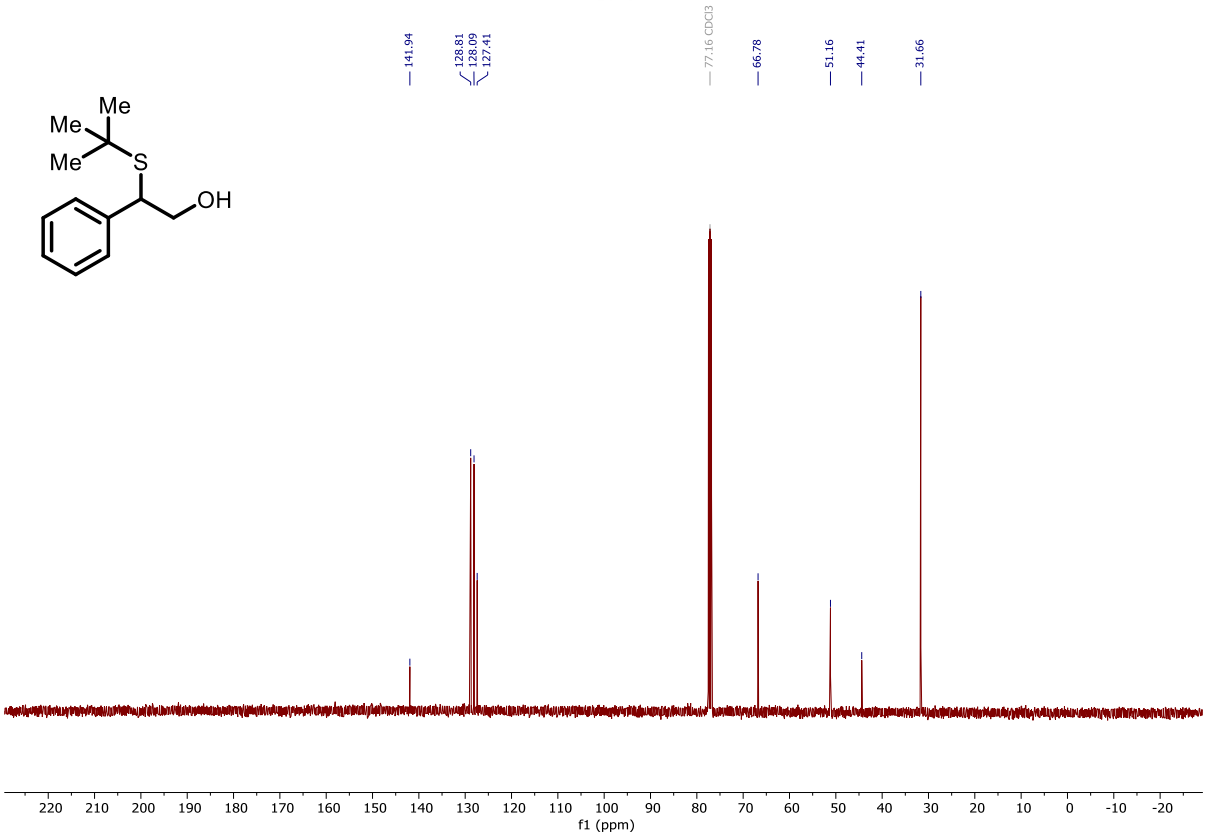
tert-Butyl(2-(naphthalen-2-yl)-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91q)



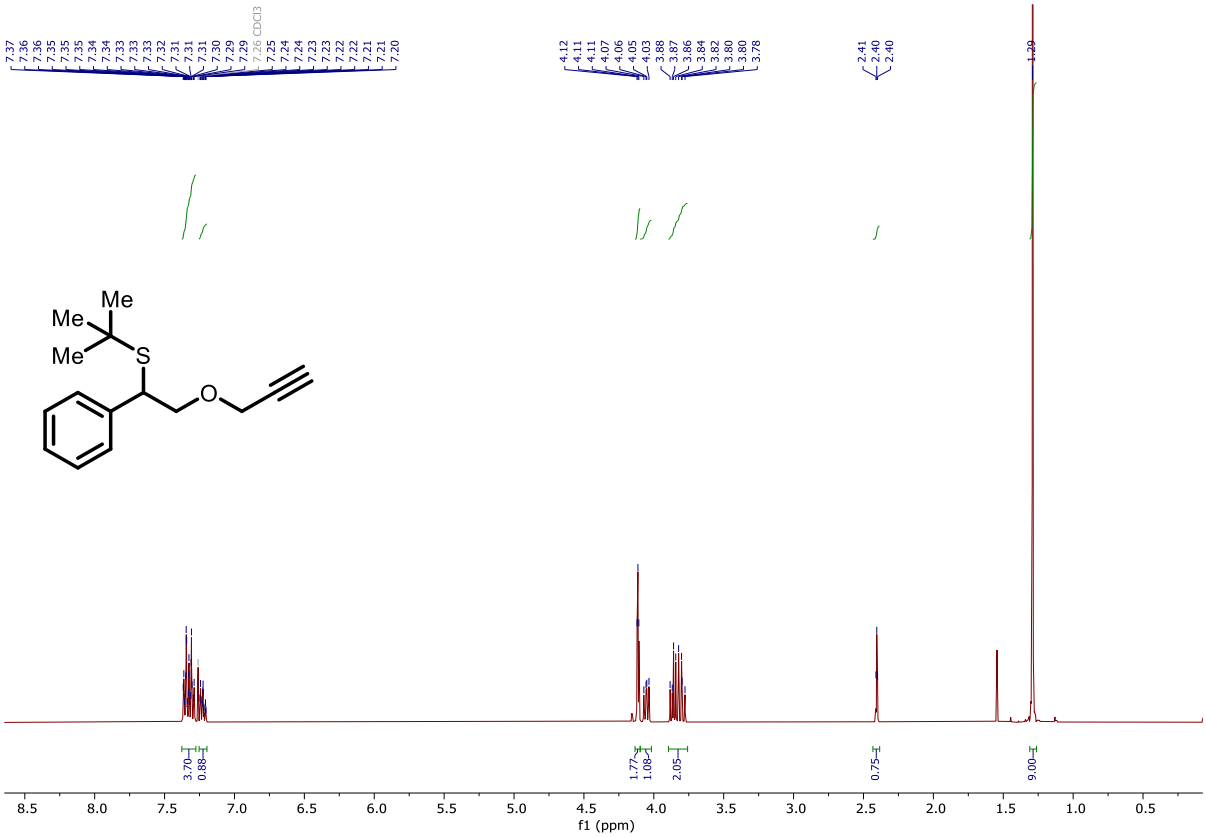


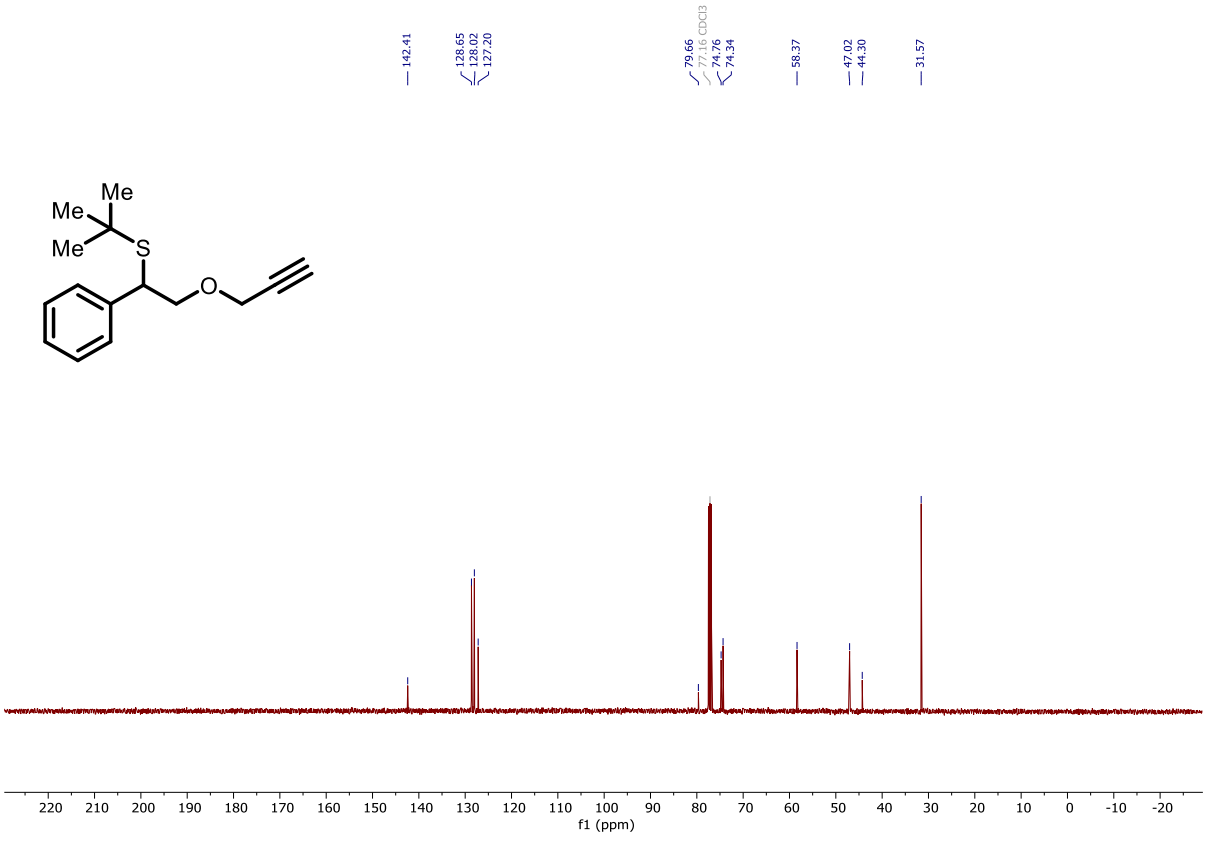
2-(*tert*-Butylthio)-2-phenylethan-1-ol (105)



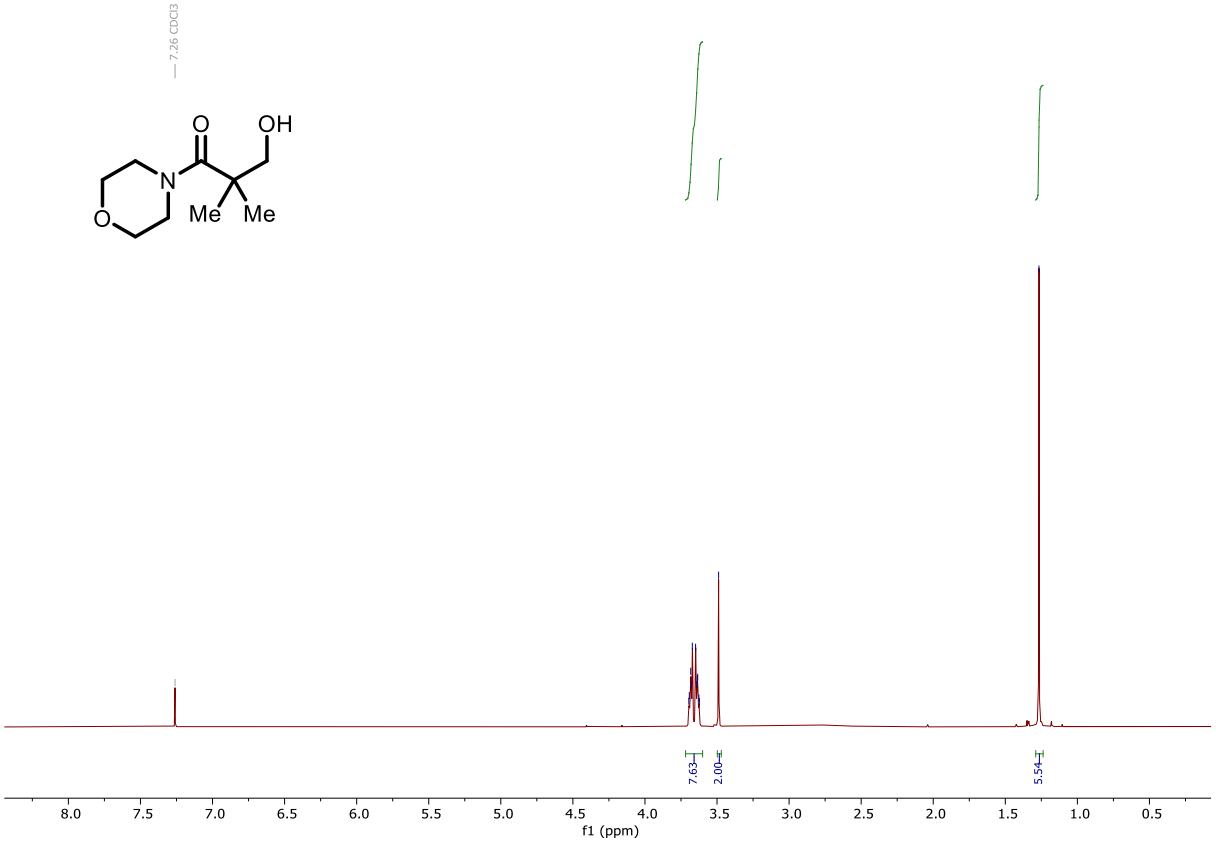


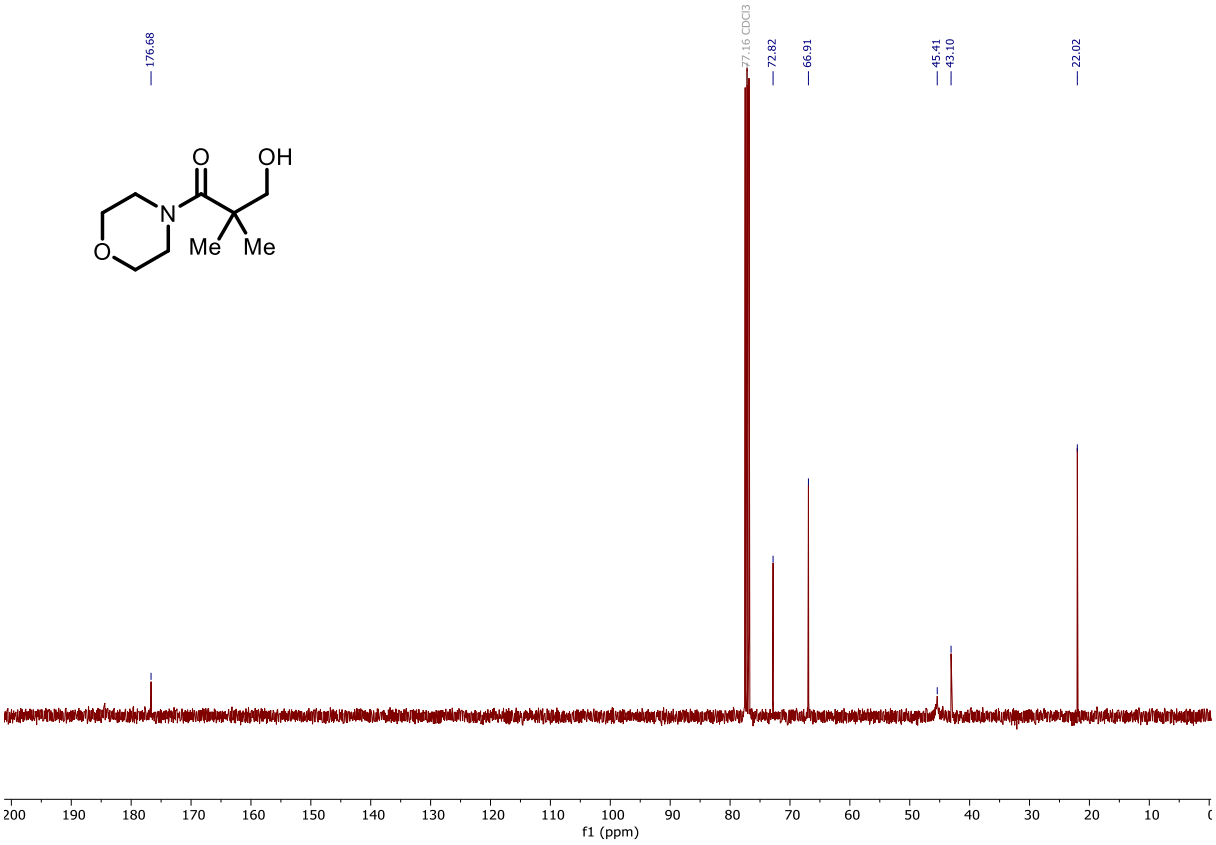
tert-Butyl(1-phenyl-2-(prop-2-yn-1-yloxy)ethyl)sulfane (91r)



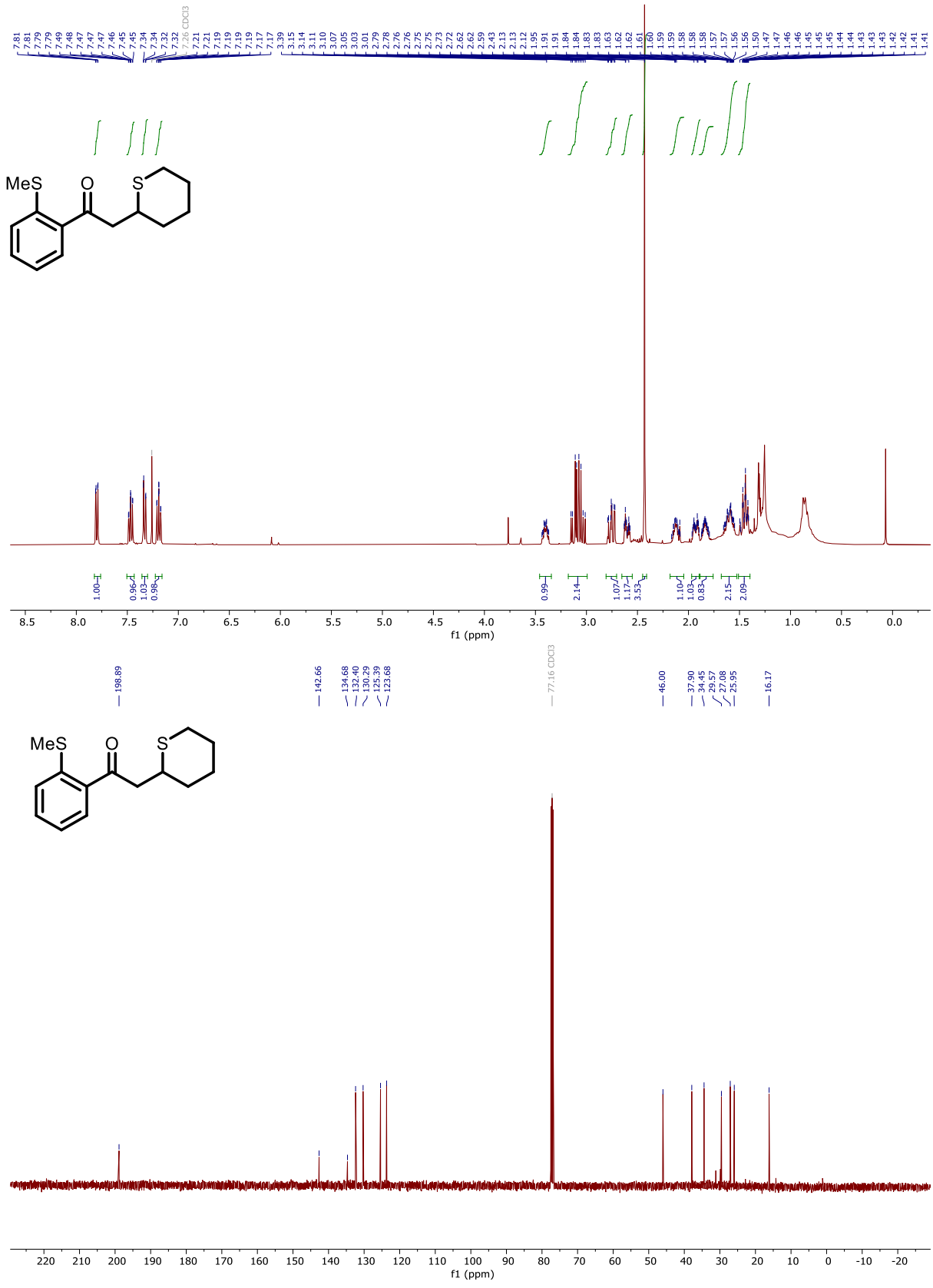


3-Hydroxy-2,2-dimethyl-1-morpholinopropan-1-one (134)

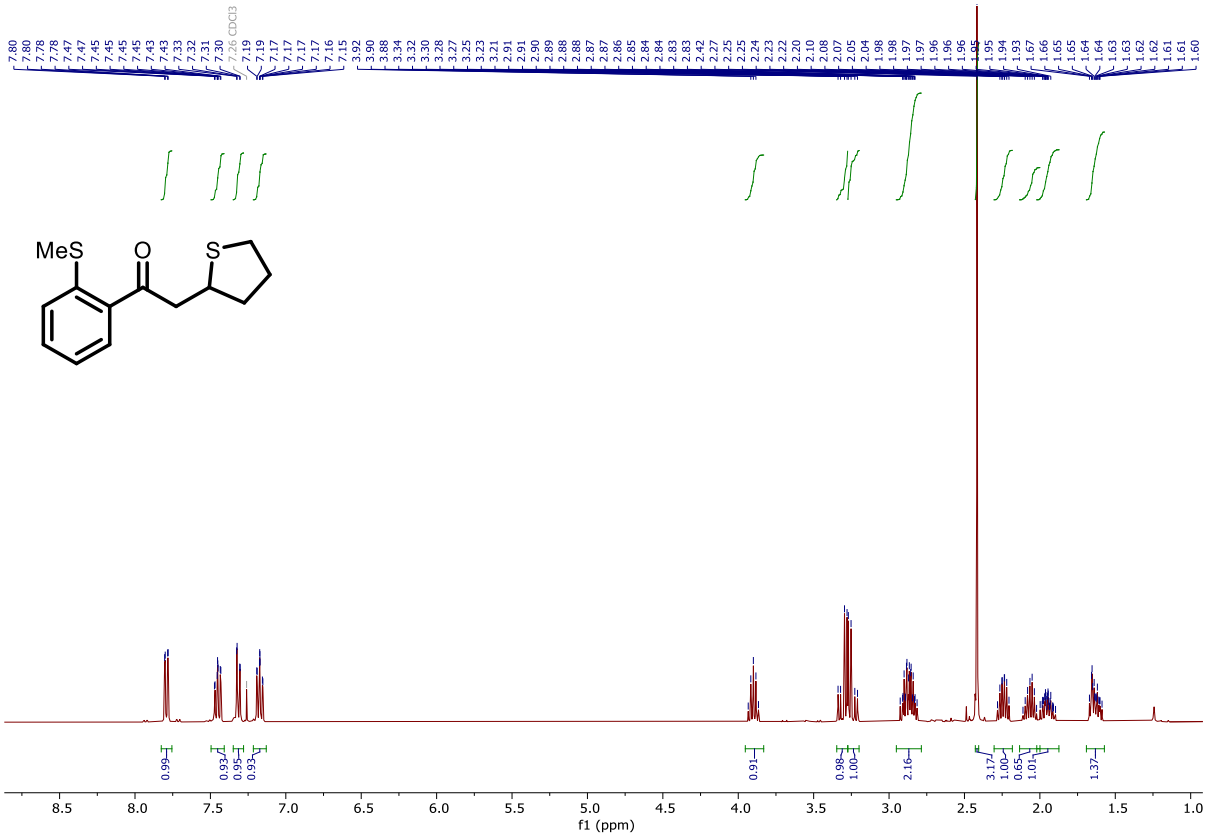


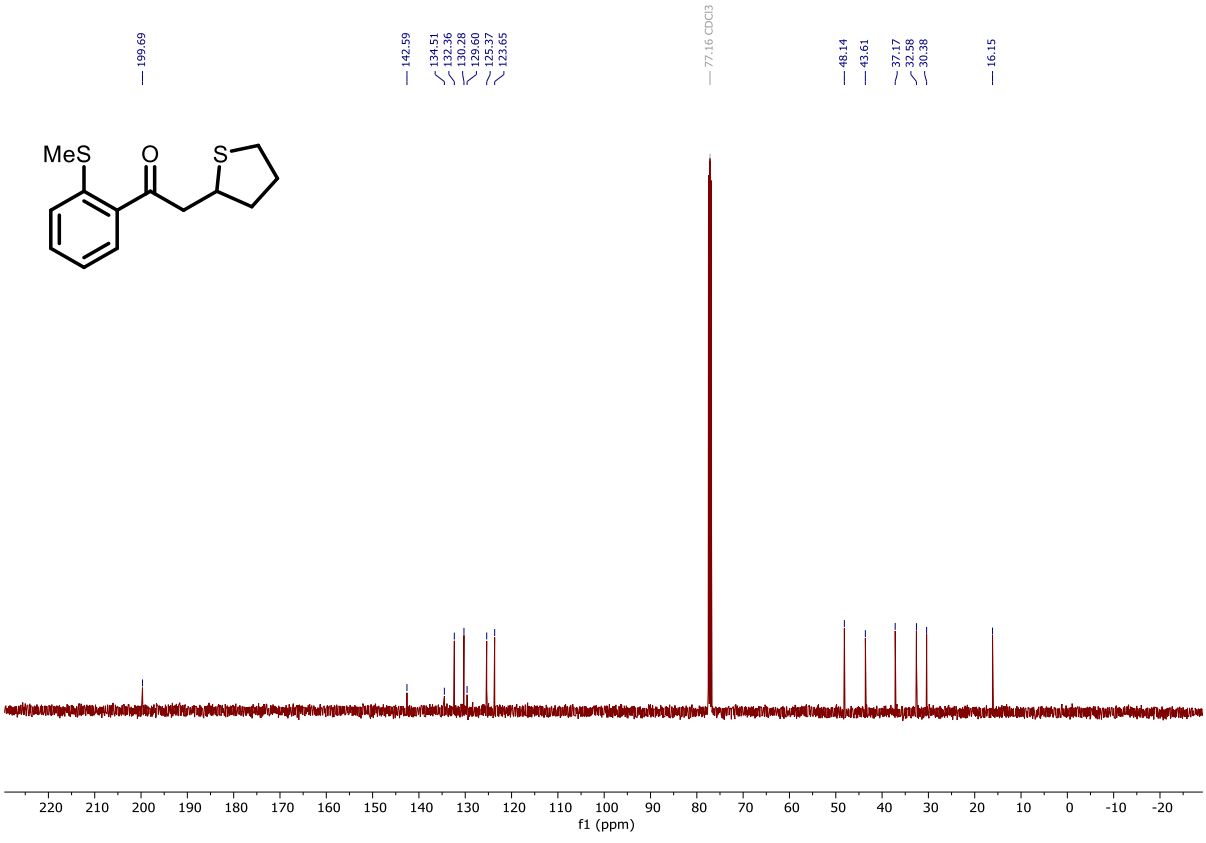


1-(2-(Methylthio)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83a)



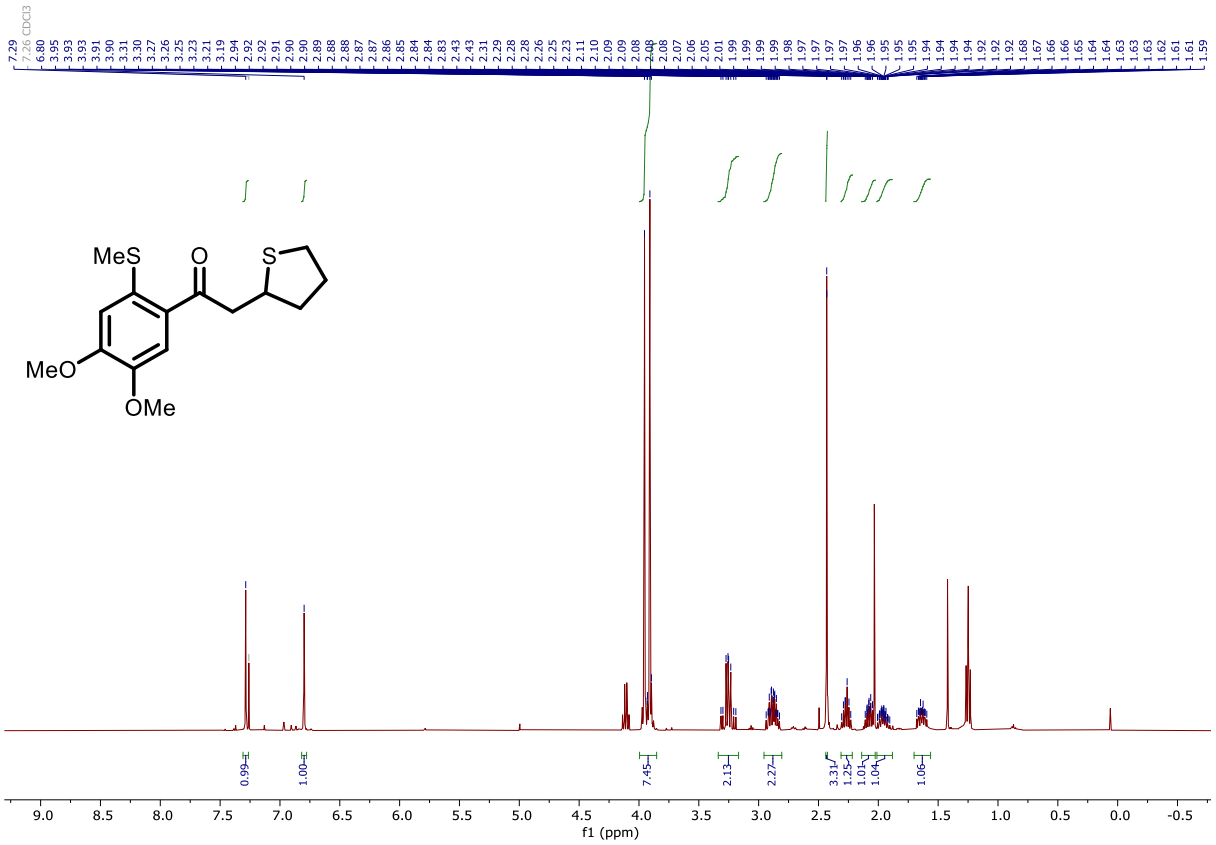
1-(2-(Methylthio)phenyl)-2-(tetrahydrothiophen-2-yl)ethan-1-one (83b)

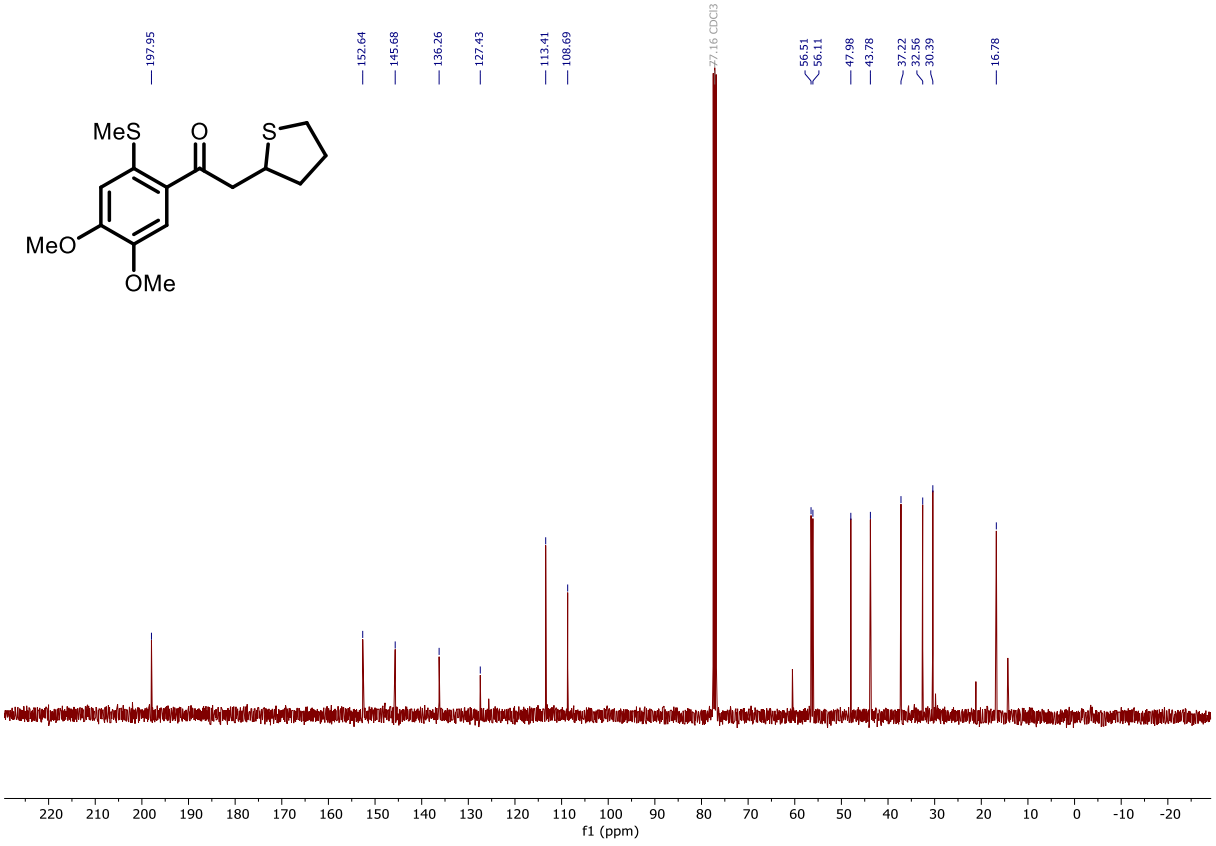




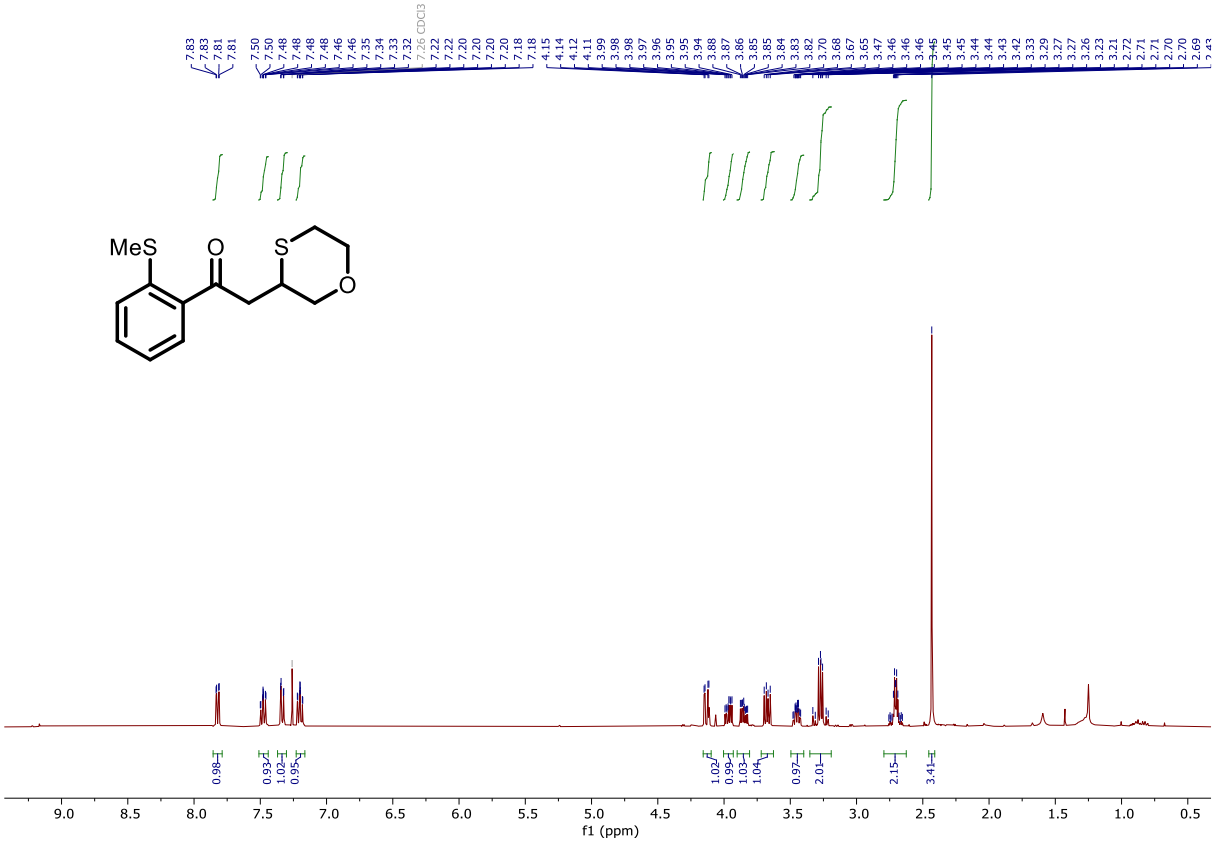
1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-(tetrahydrothiophen-2-yl)ethan-1-one

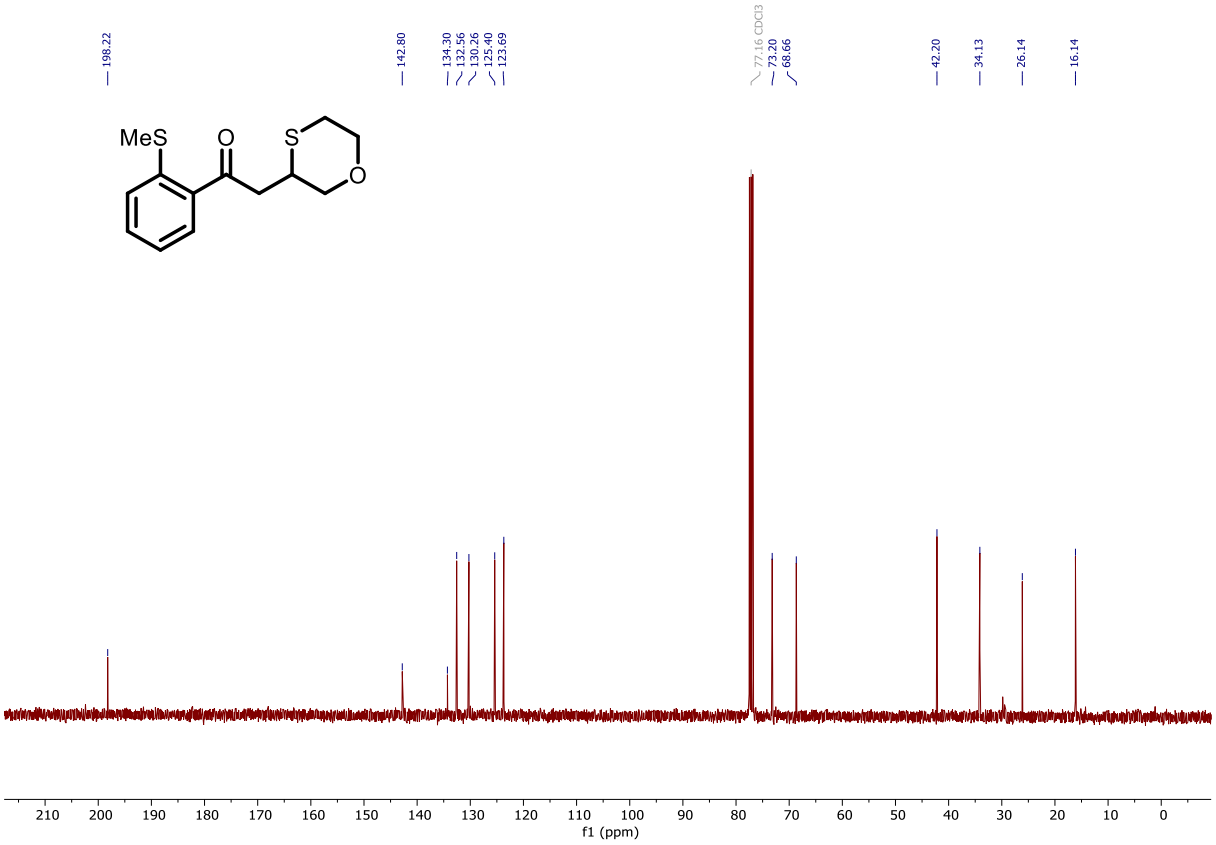
(83c)



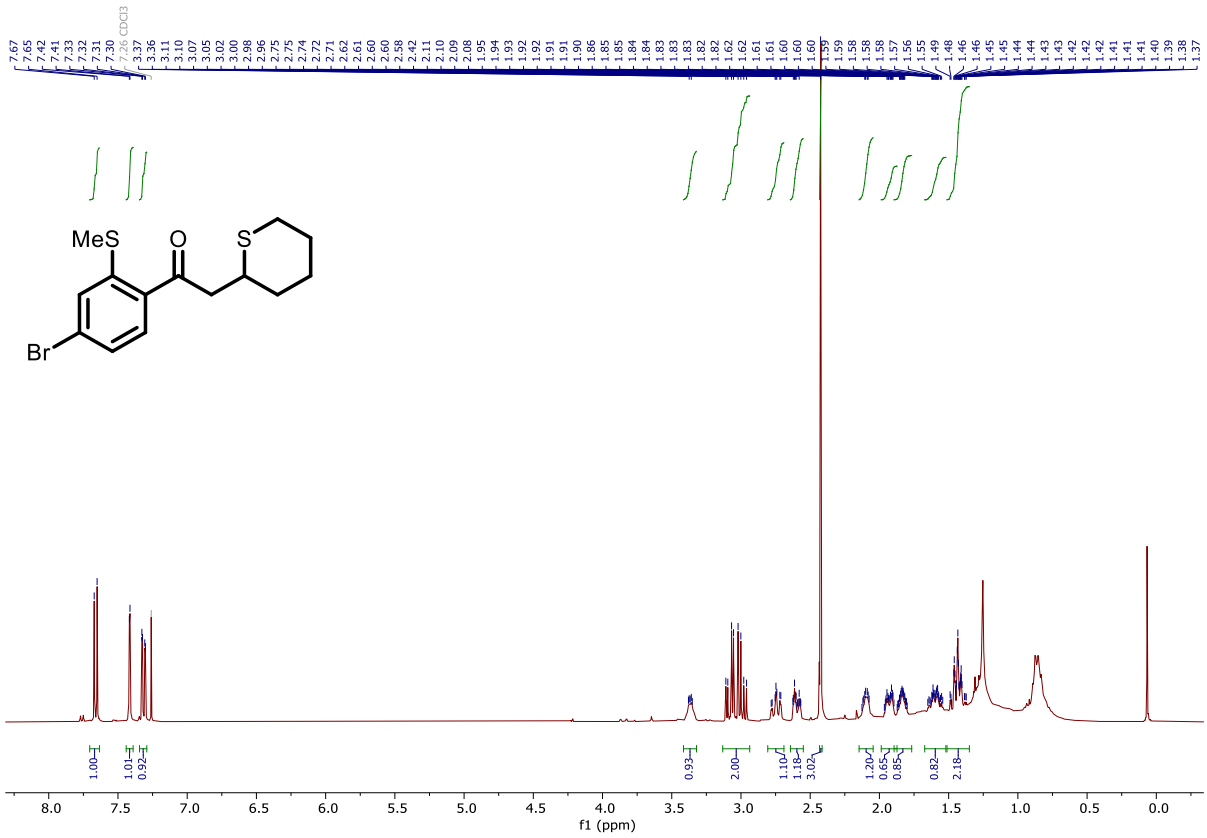


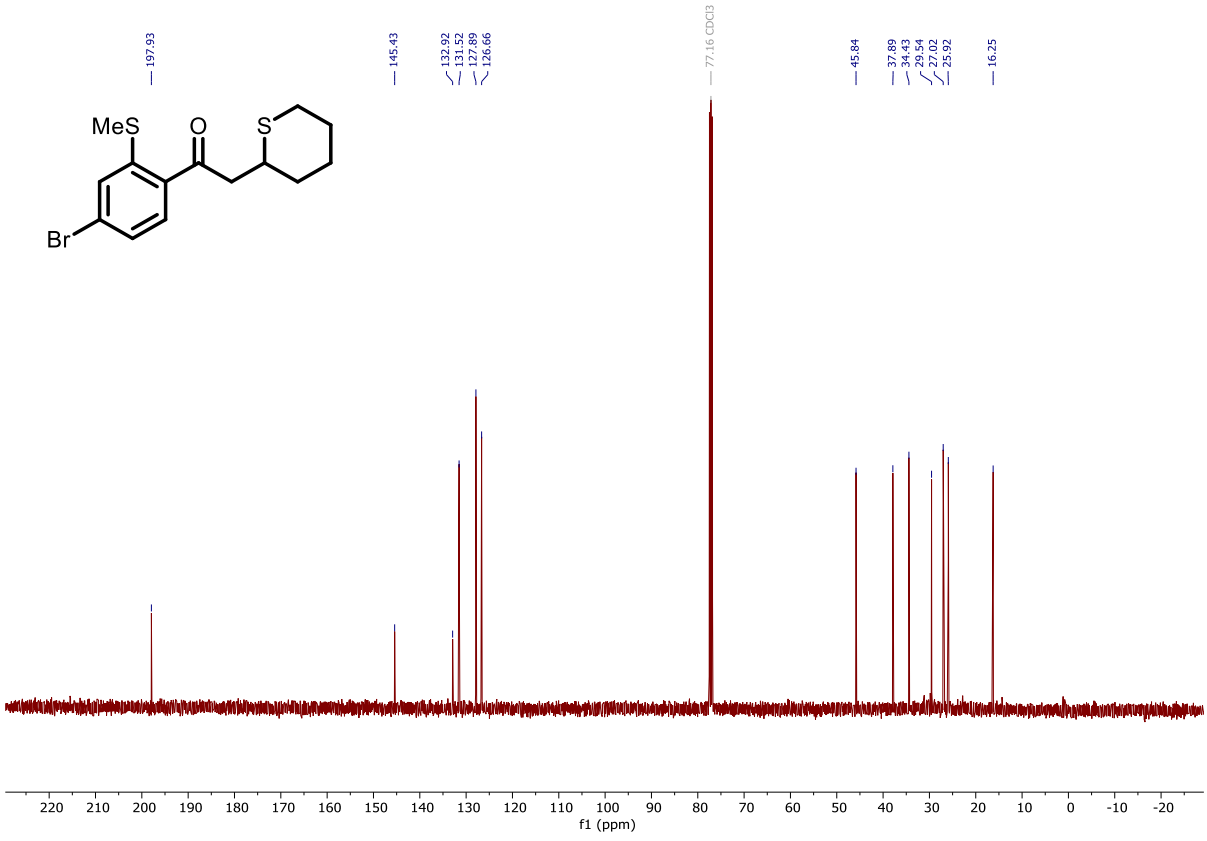
1-(2-(Methylthio)phenyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83d)



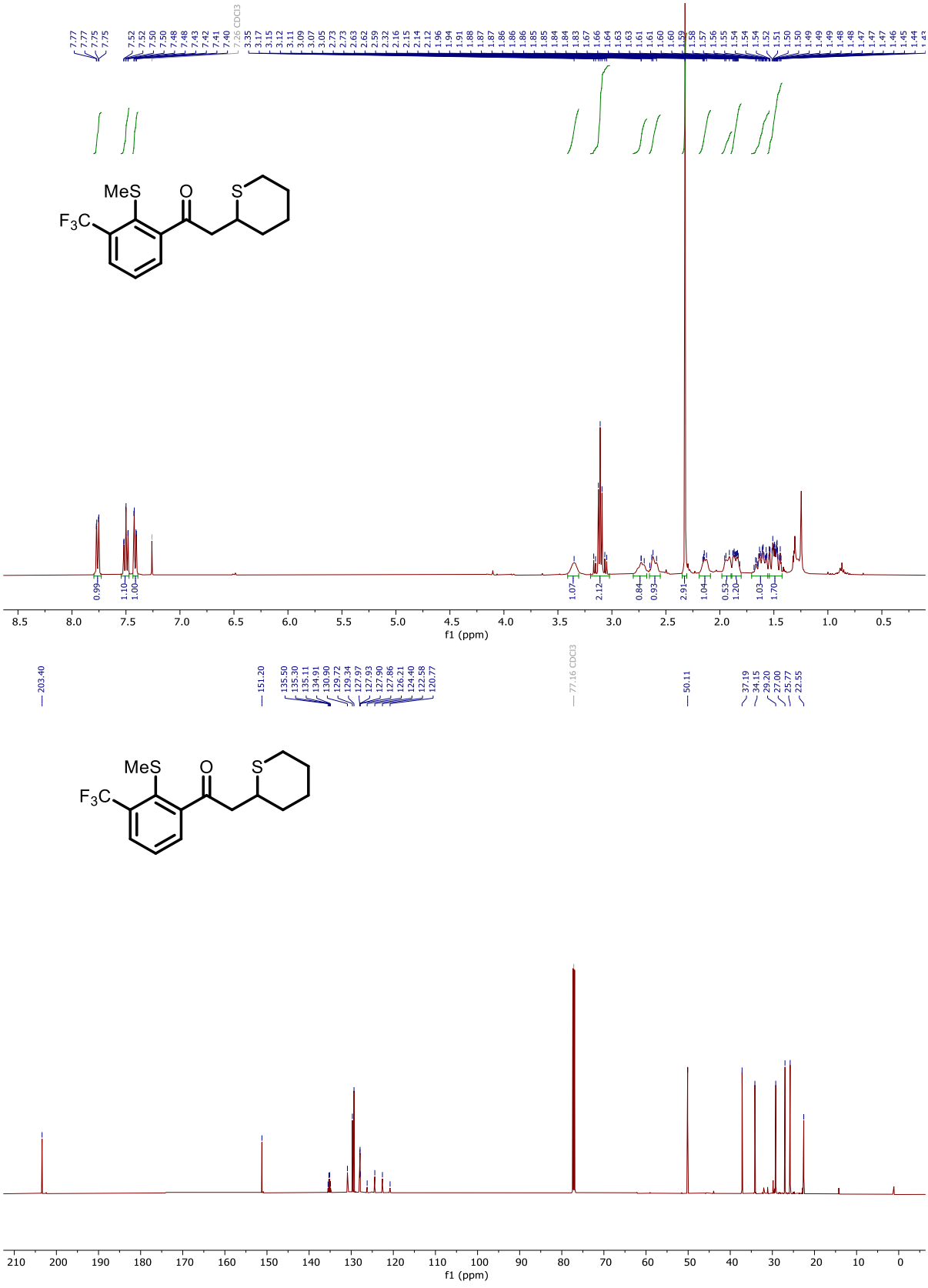


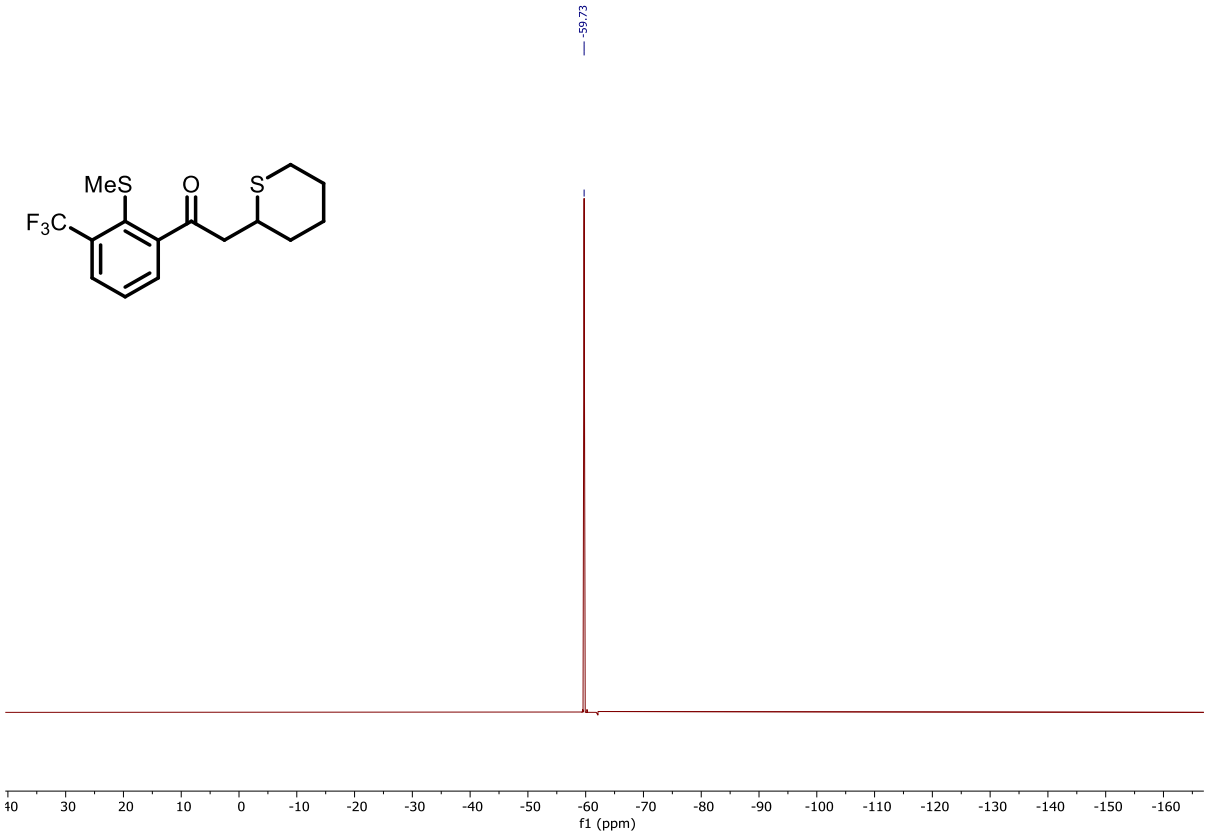
1-(4-Bromo-2-(methylthio)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83e)



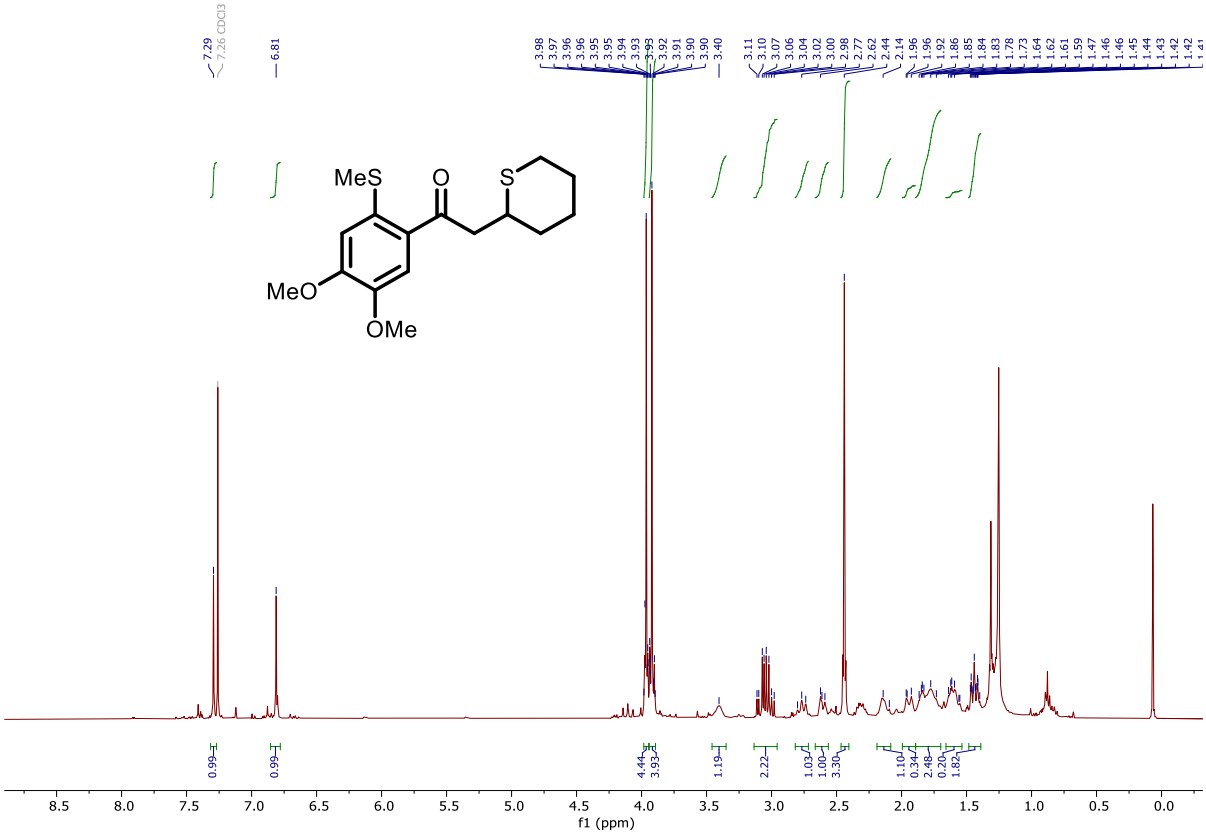


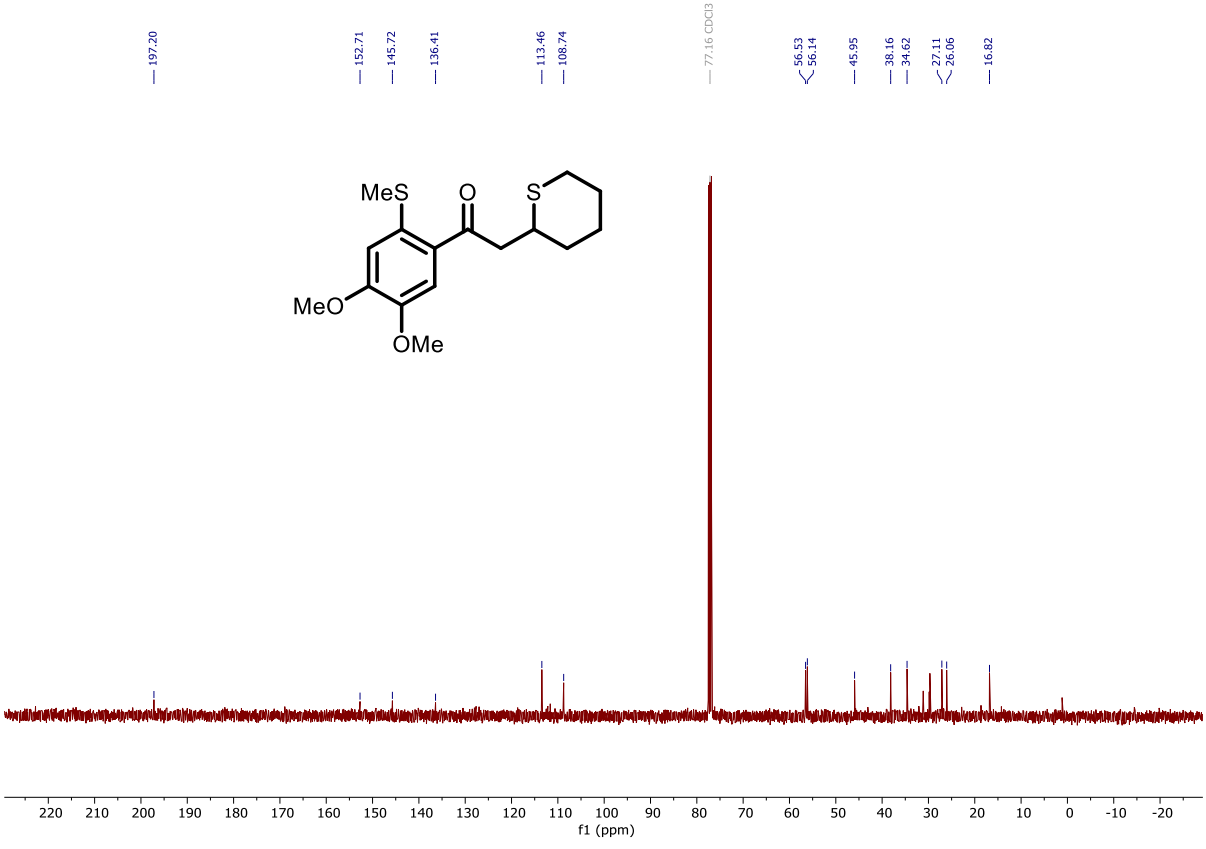
1-(2-(Methylthio)-3-(trifluoromethyl)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83f)



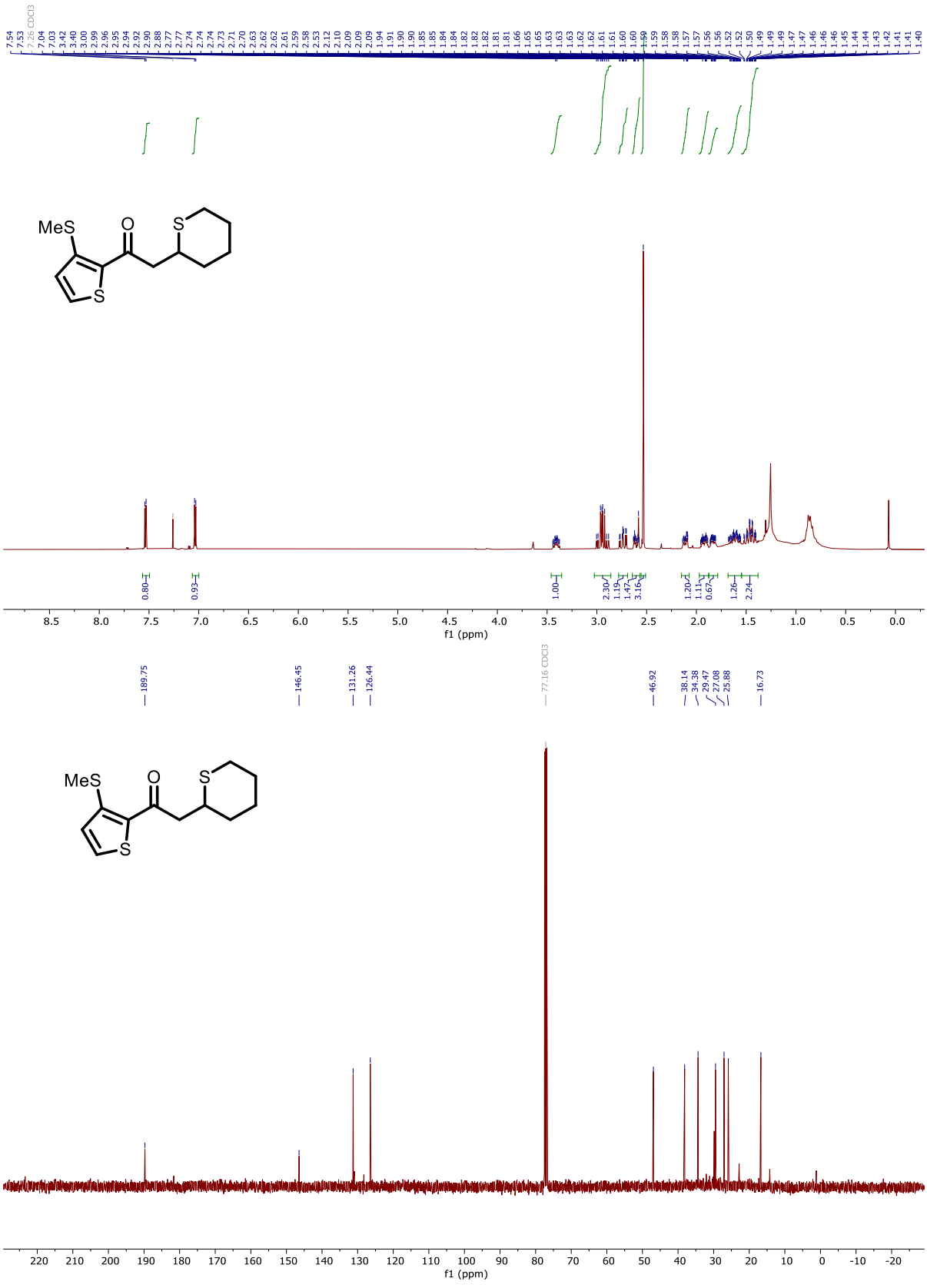

-59.73
MeS
O
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40
30
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-70
-80
-90
-100
-110
-120
-130
-140
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-160
f1 (ppm)

1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83g)

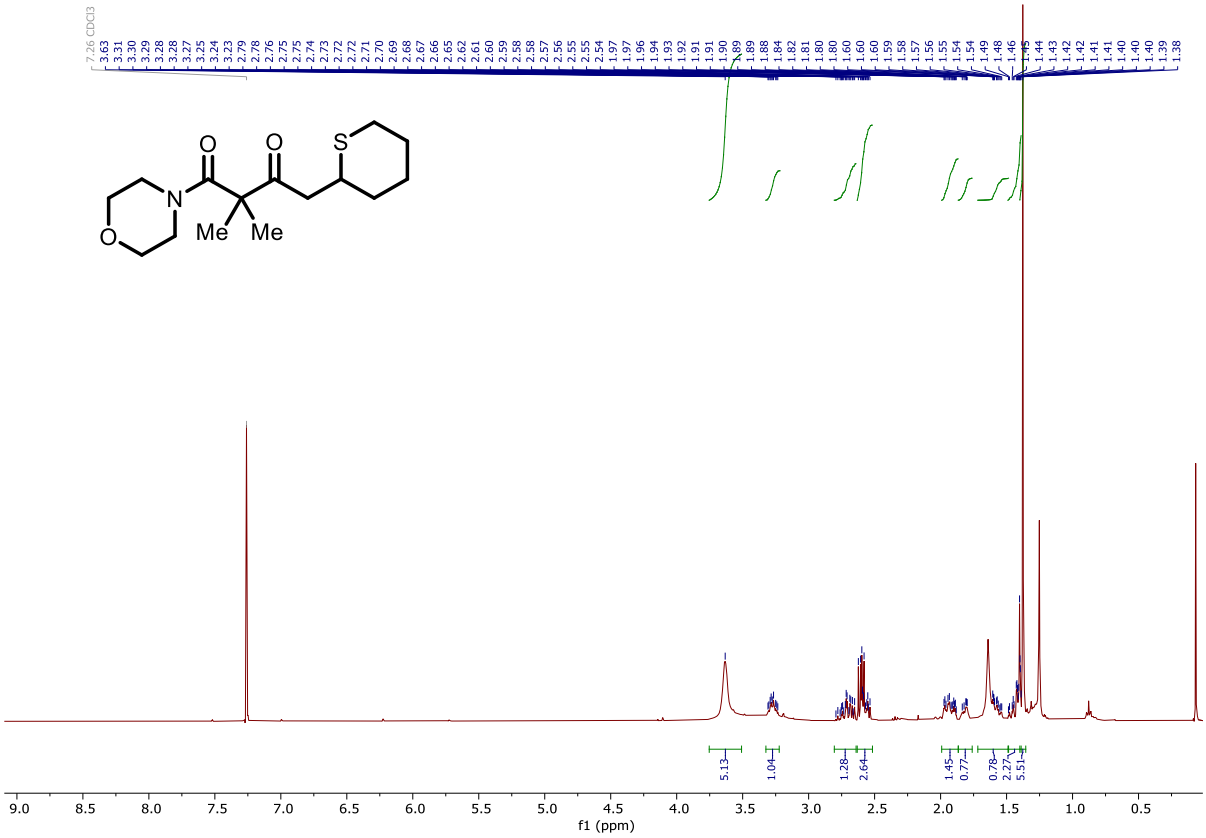


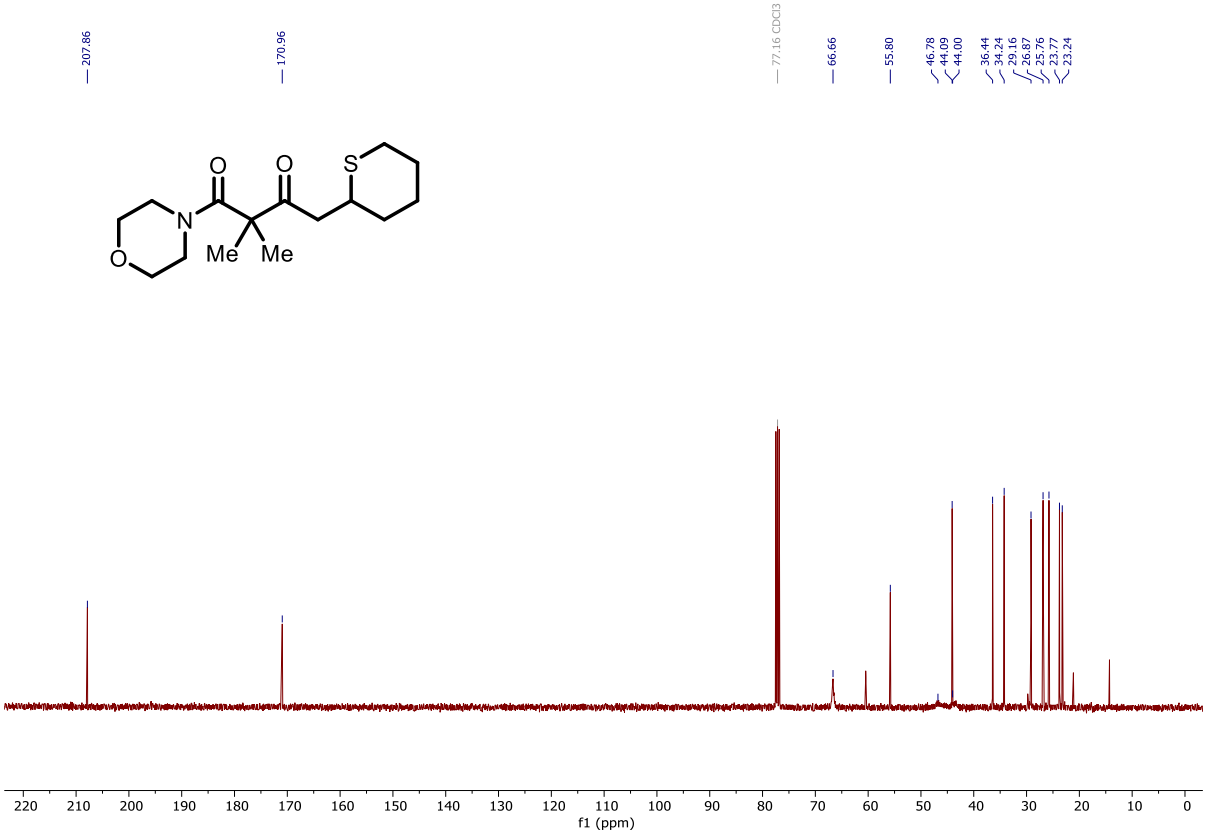


1-(3-(Methylthio)thiophen-2-yl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (83h)

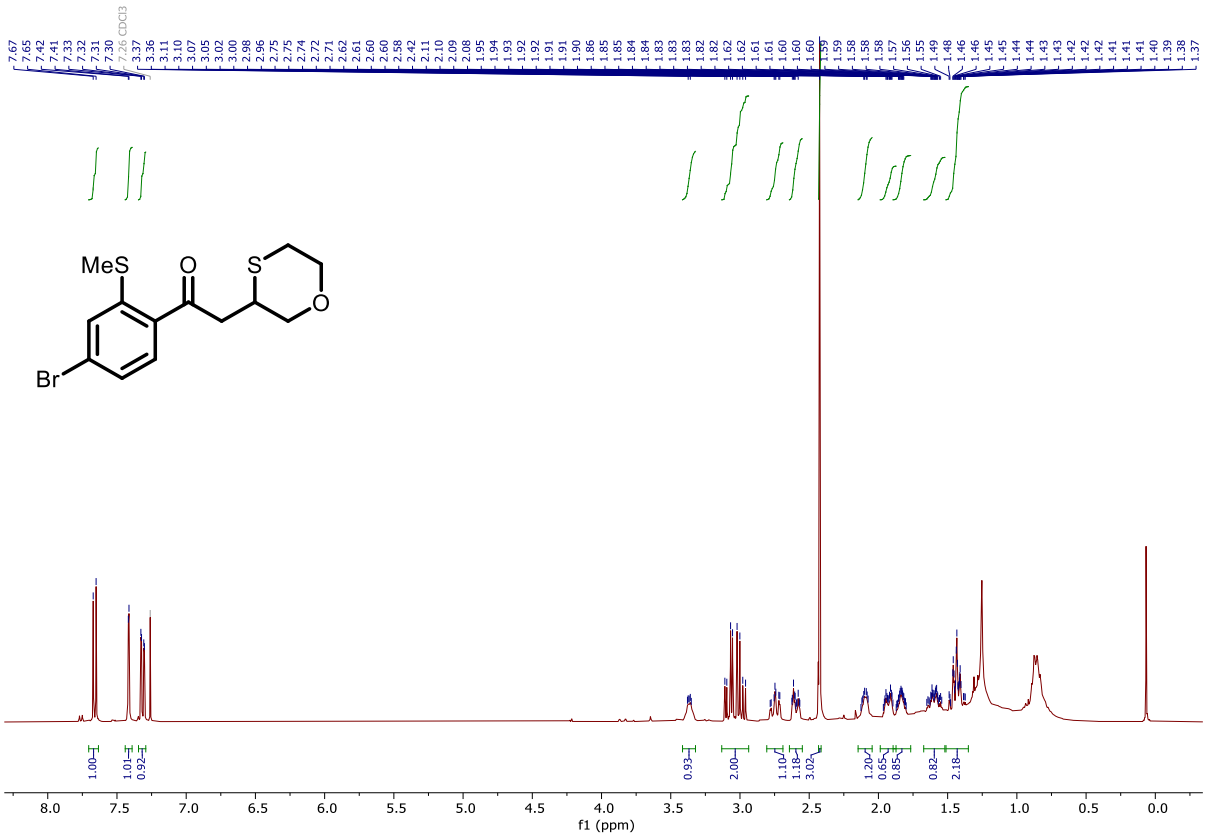


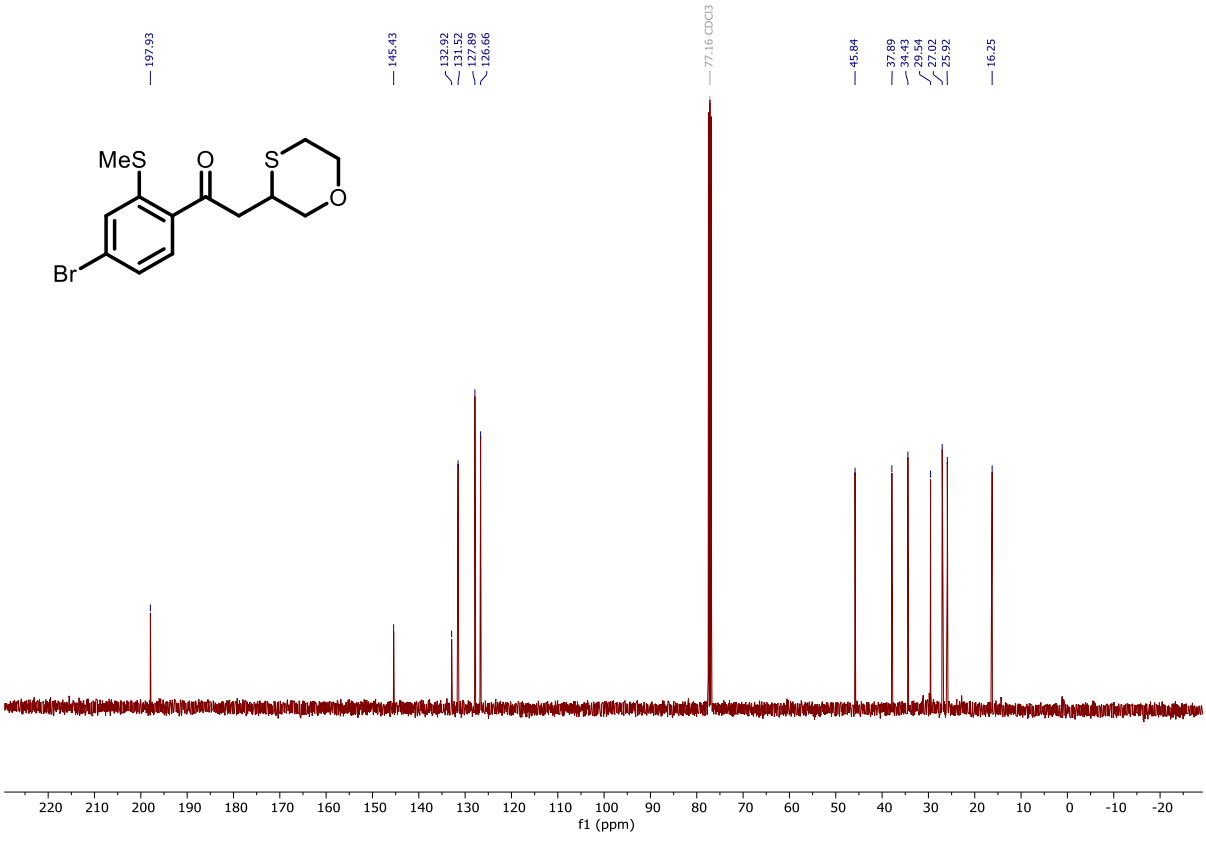
2,2-Dimethyl-1-morpholino-4-(tetrahydro-2*H*-thiopyran-2-yl)butane-1,3-dione (83i)



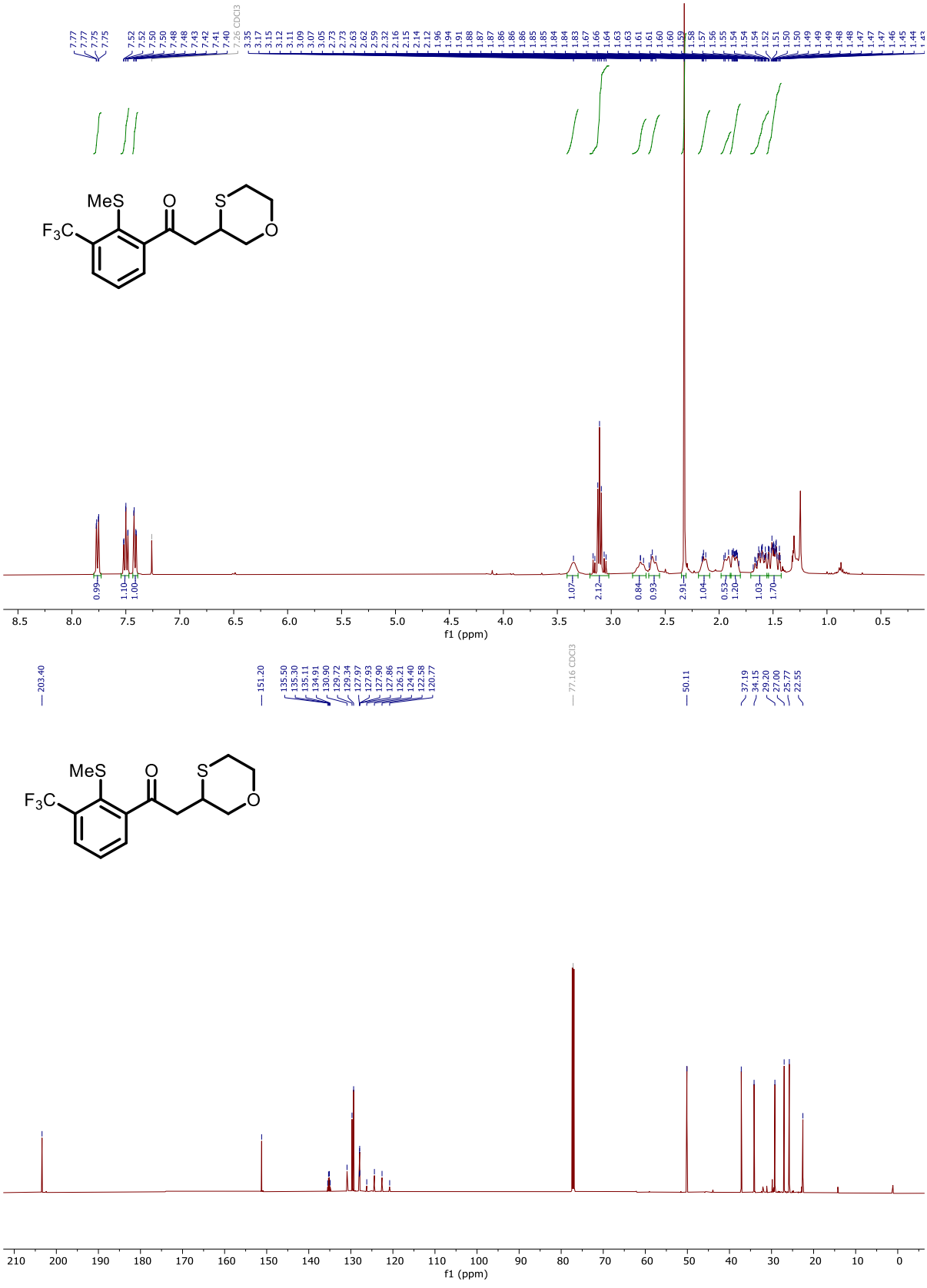


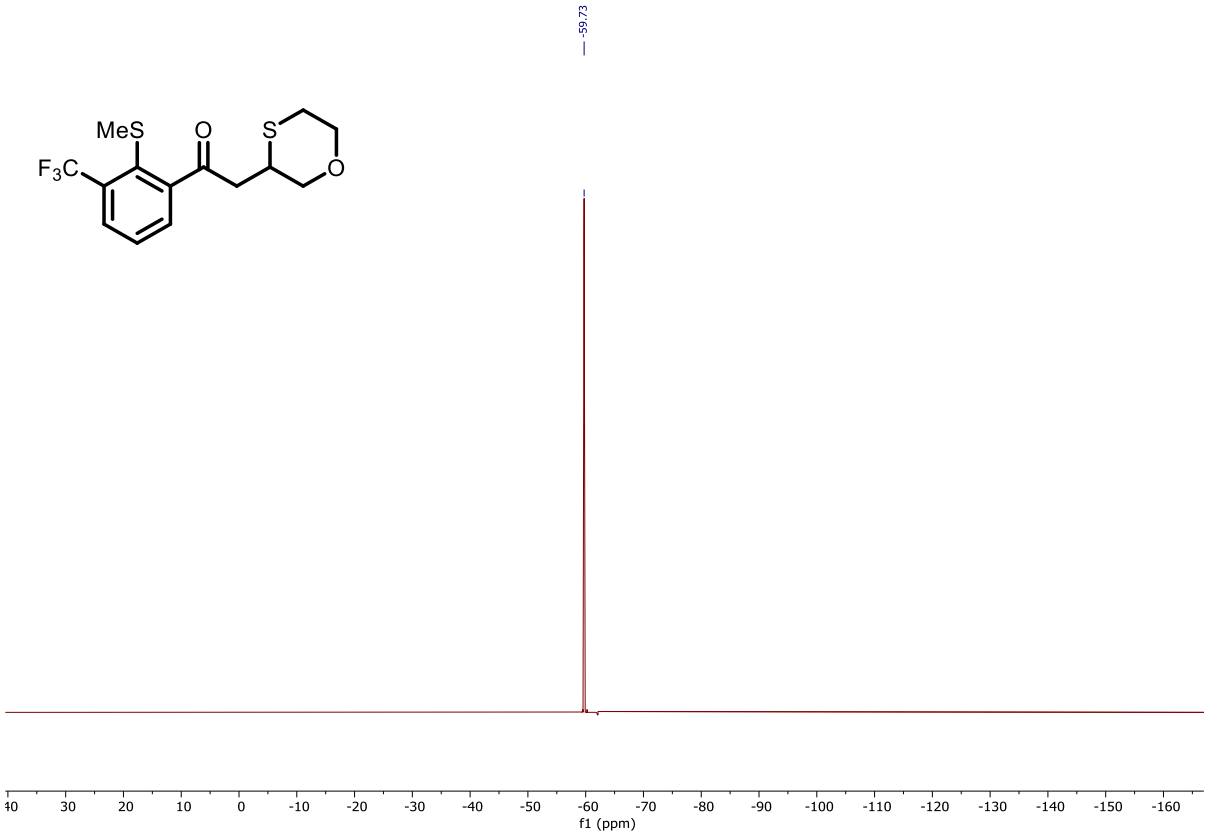
1-(4-Bromo-2-(methylthio)phenyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83j)



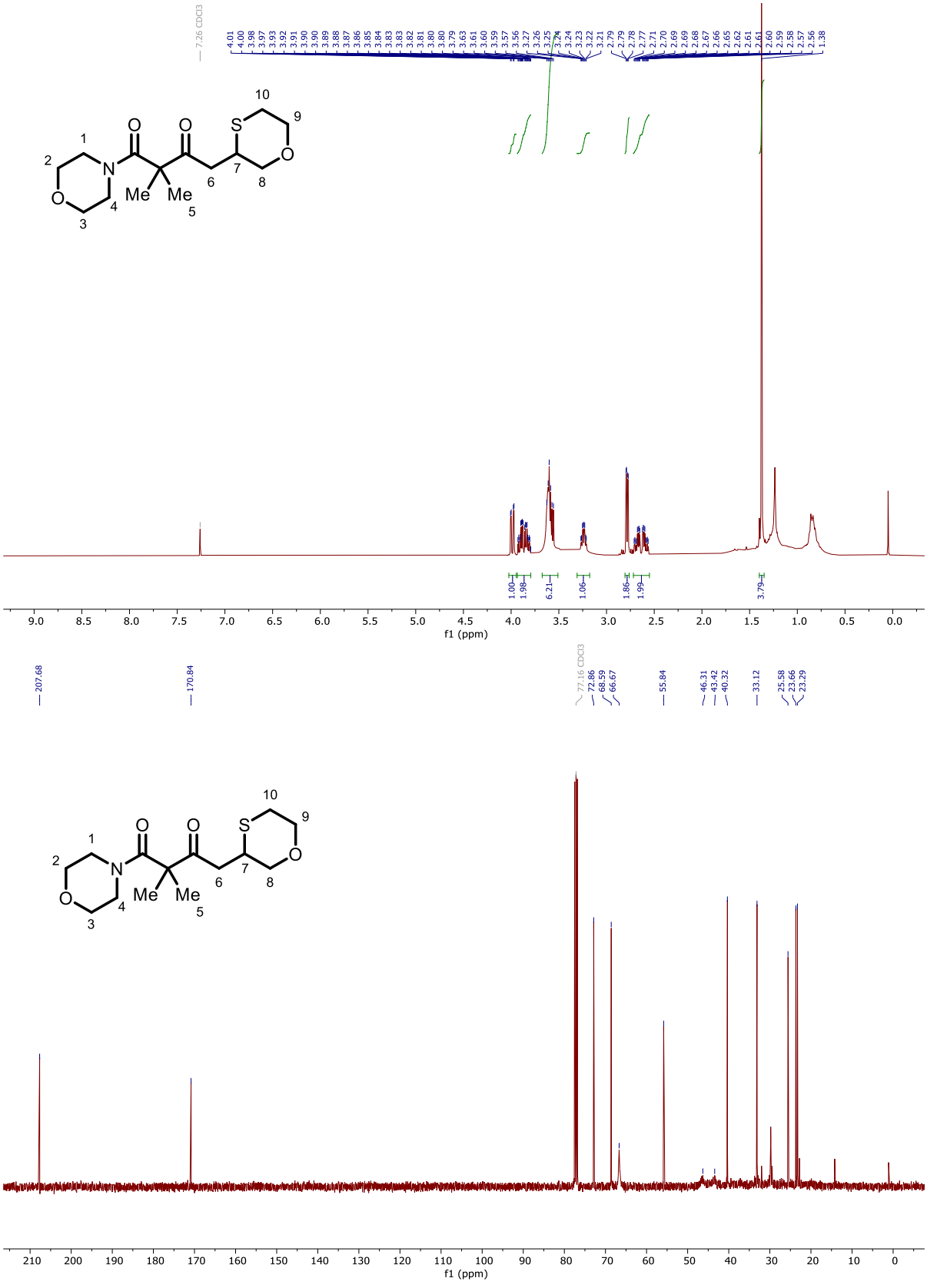


1-(2-(Methylthio)-3-(trifluoromethyl)phenyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83k)

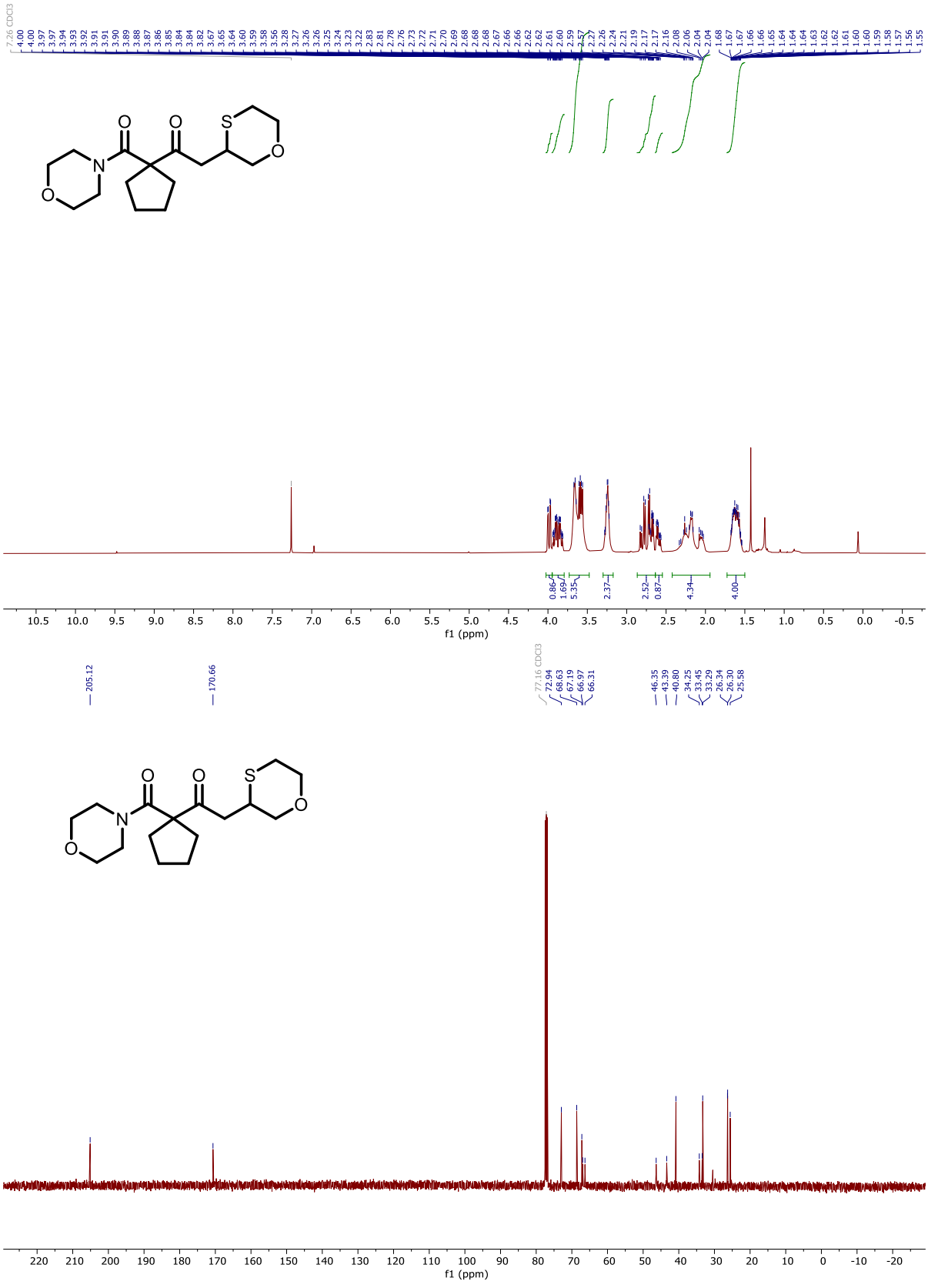



-59.73
MeS
O
S
F3C
O
40
30
20
10
0
-10
-20
-30
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-50
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-160
f1 (ppm)

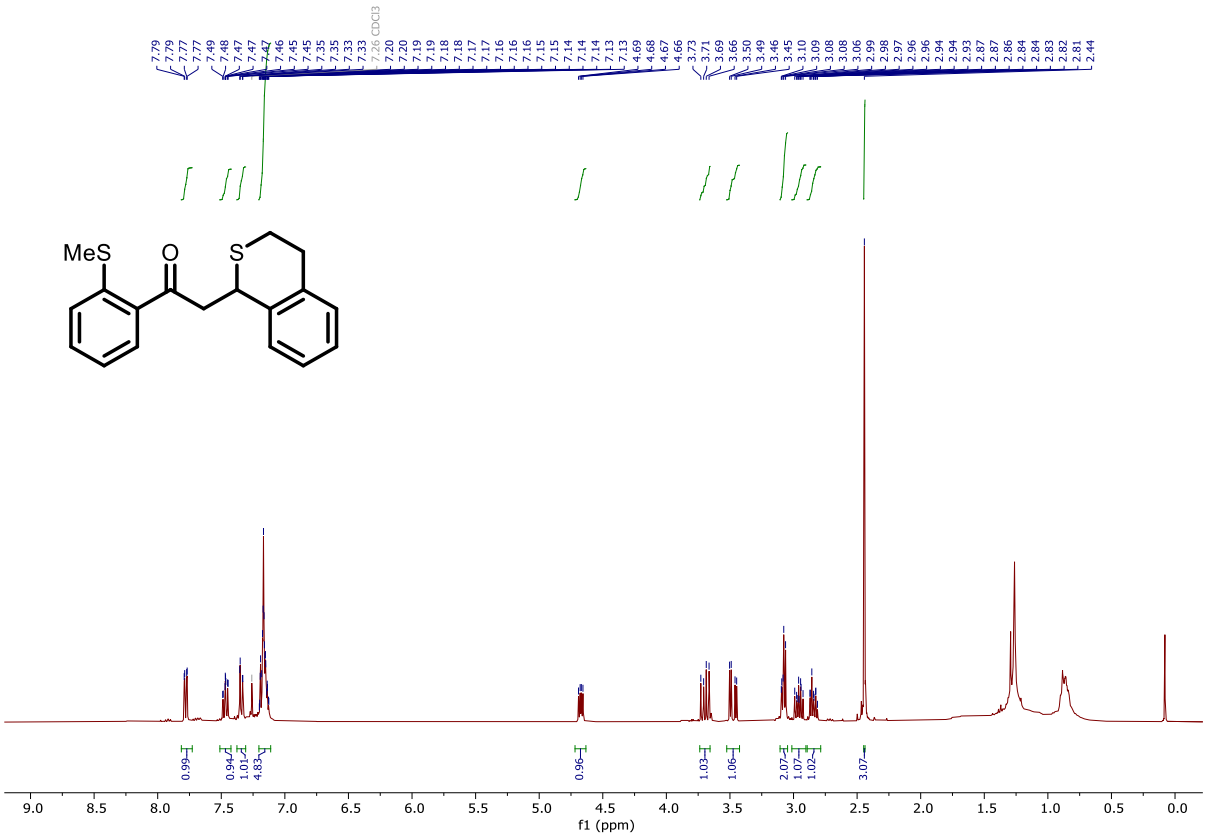
2,2-Dimethyl-1-morpholino-4-(1,4-oxathian-3-yl)butane-1,3-dione (83l)

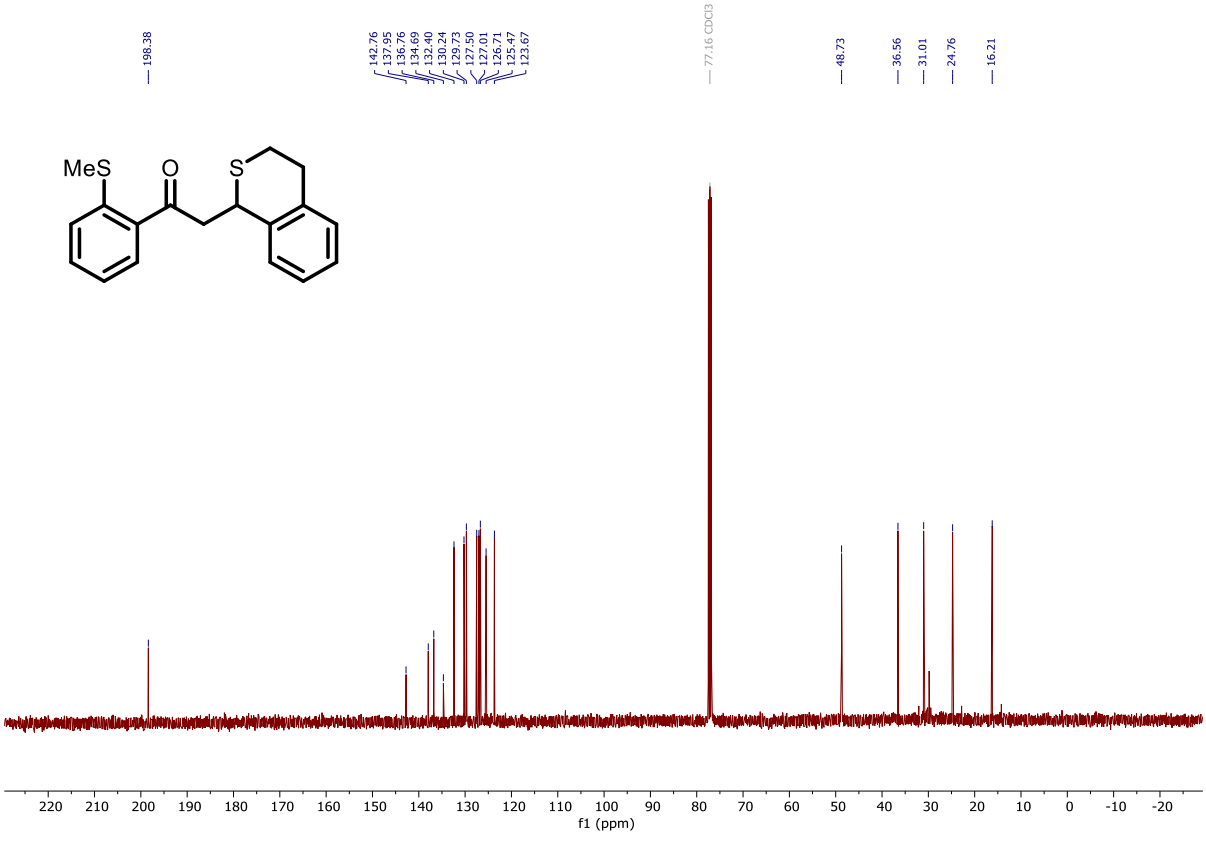


1-(1-(Morpholine-4-carbonyl)cyclopentyl)-2-(1,4-oxathian-3-yl)ethan-1-one (83m)

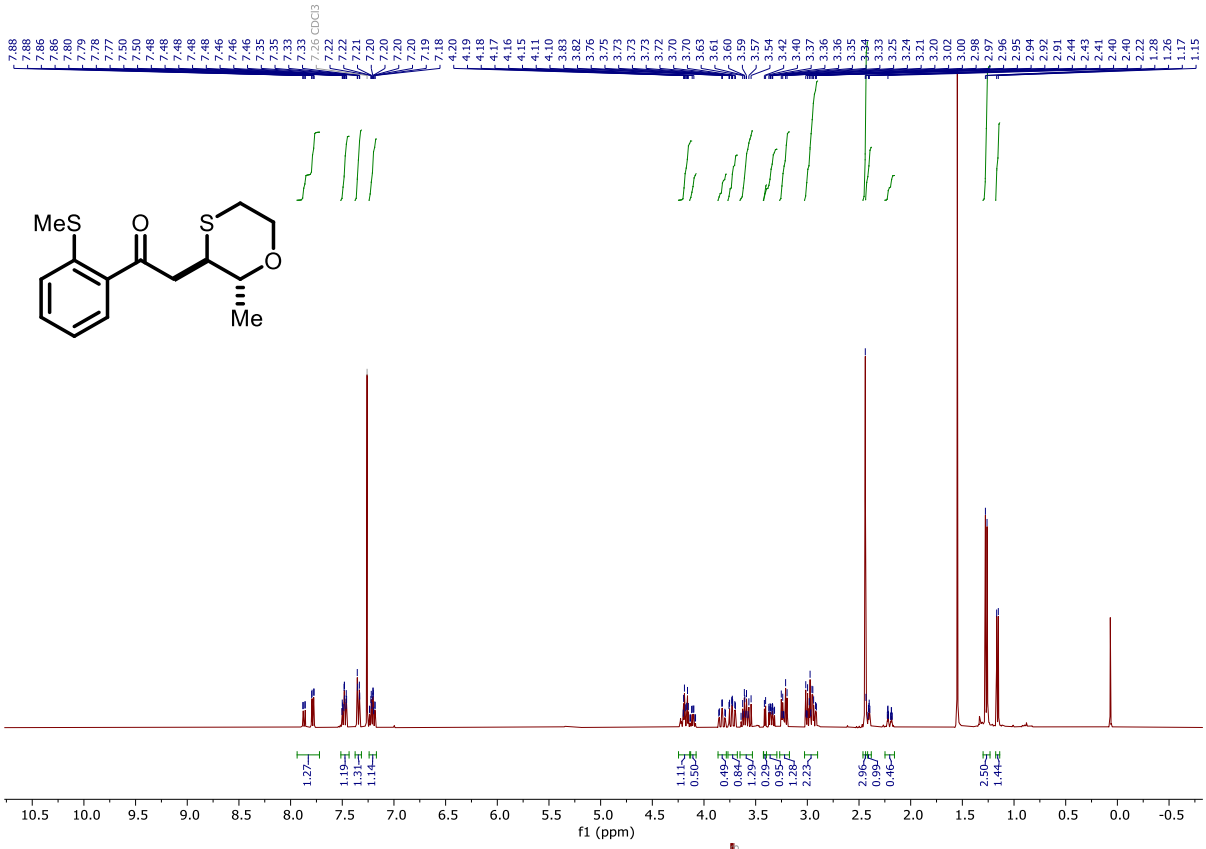


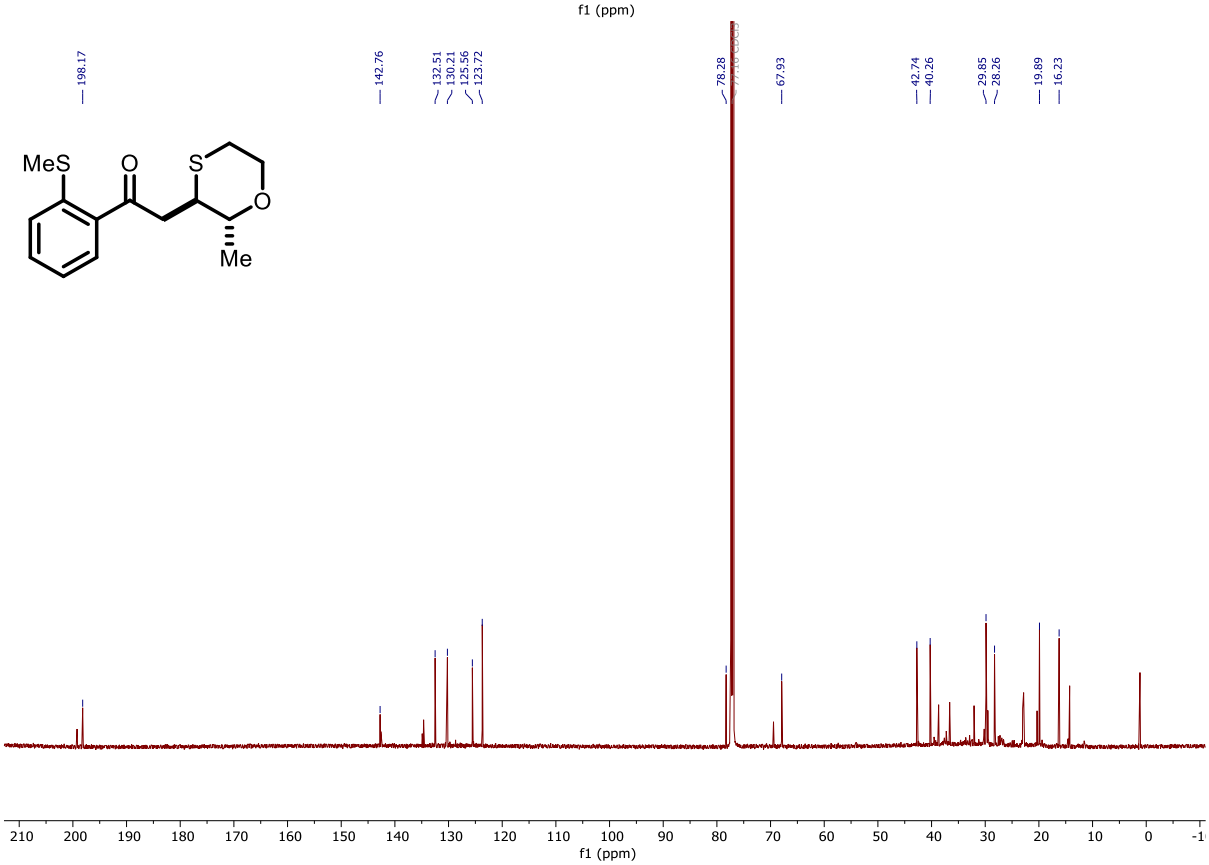
2-(Isothiochroman-1-yl)-1-(2-(methylthio)phenyl)ethan-1-one (83n)



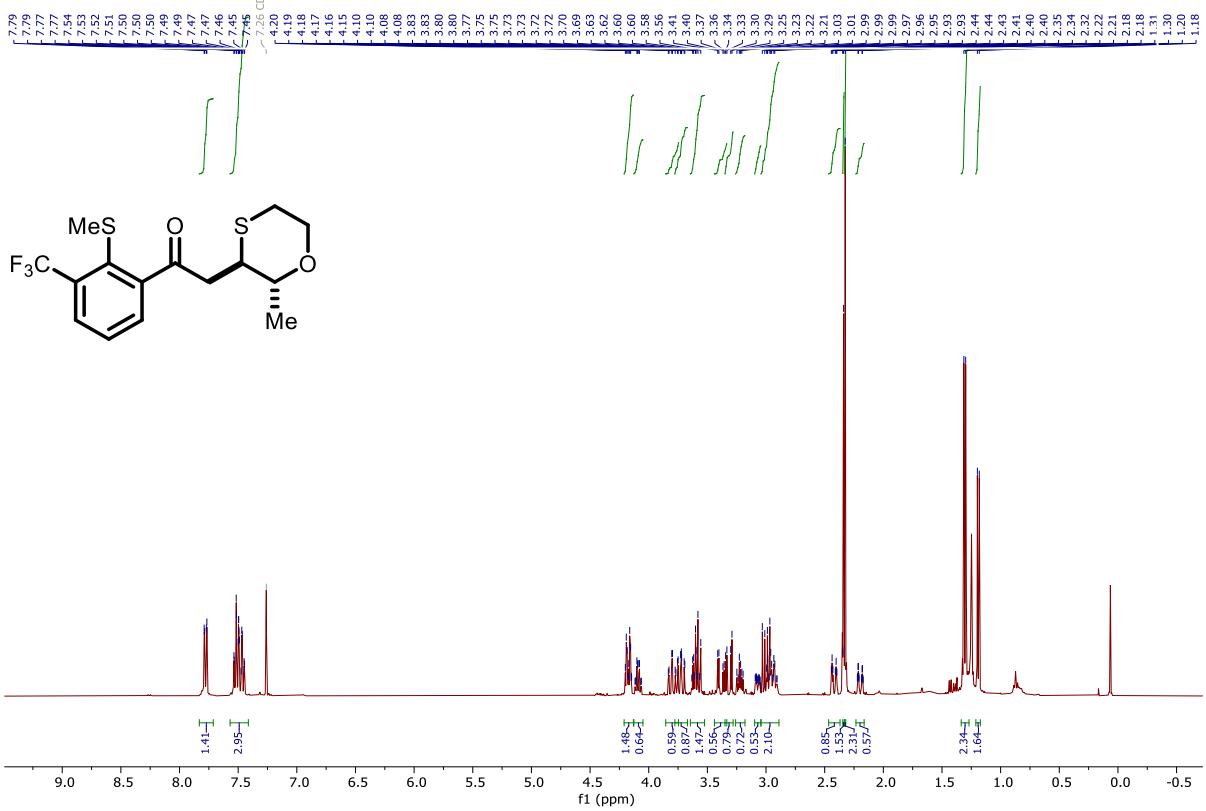


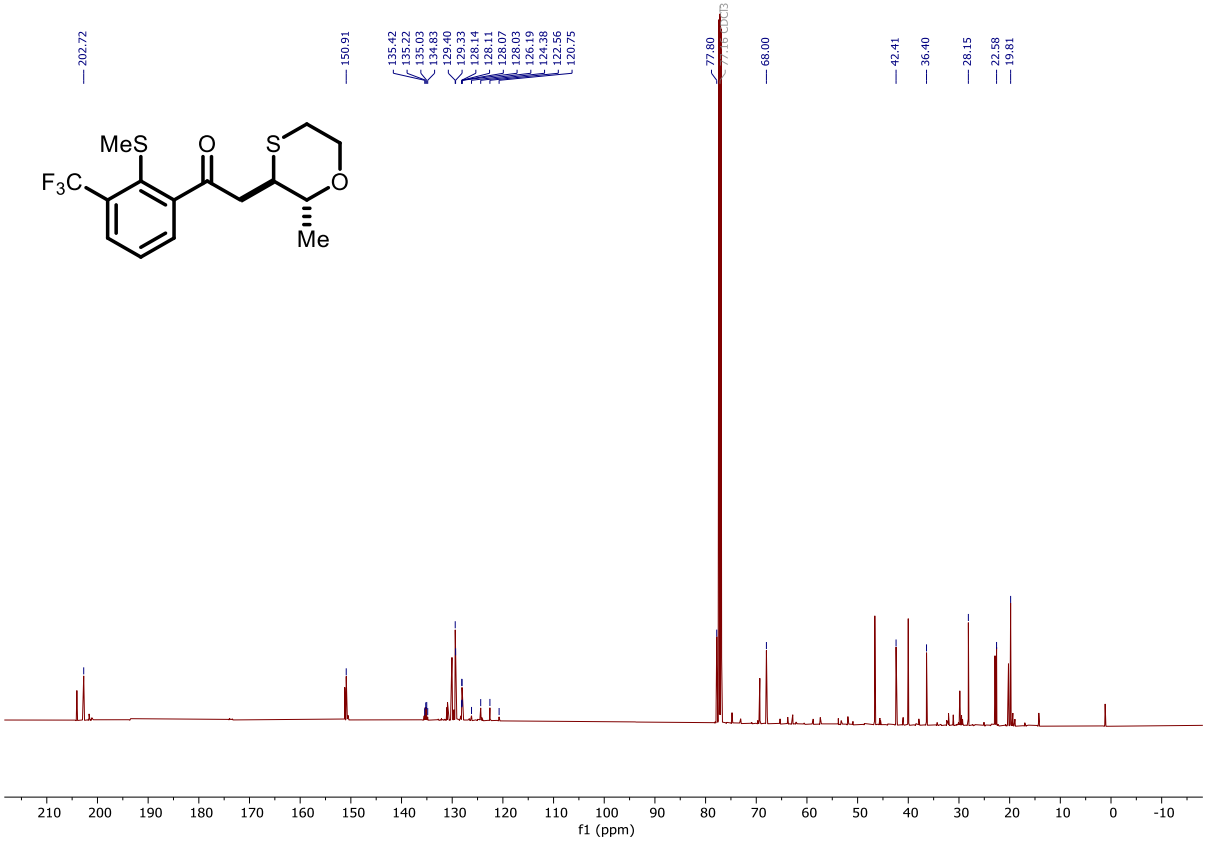
2-((2*R,3*R**)-2-Methyl-1,4-oxathian-3-yl)-1-(2-(methylthio)phenyl)ethan-1-one (83o)**



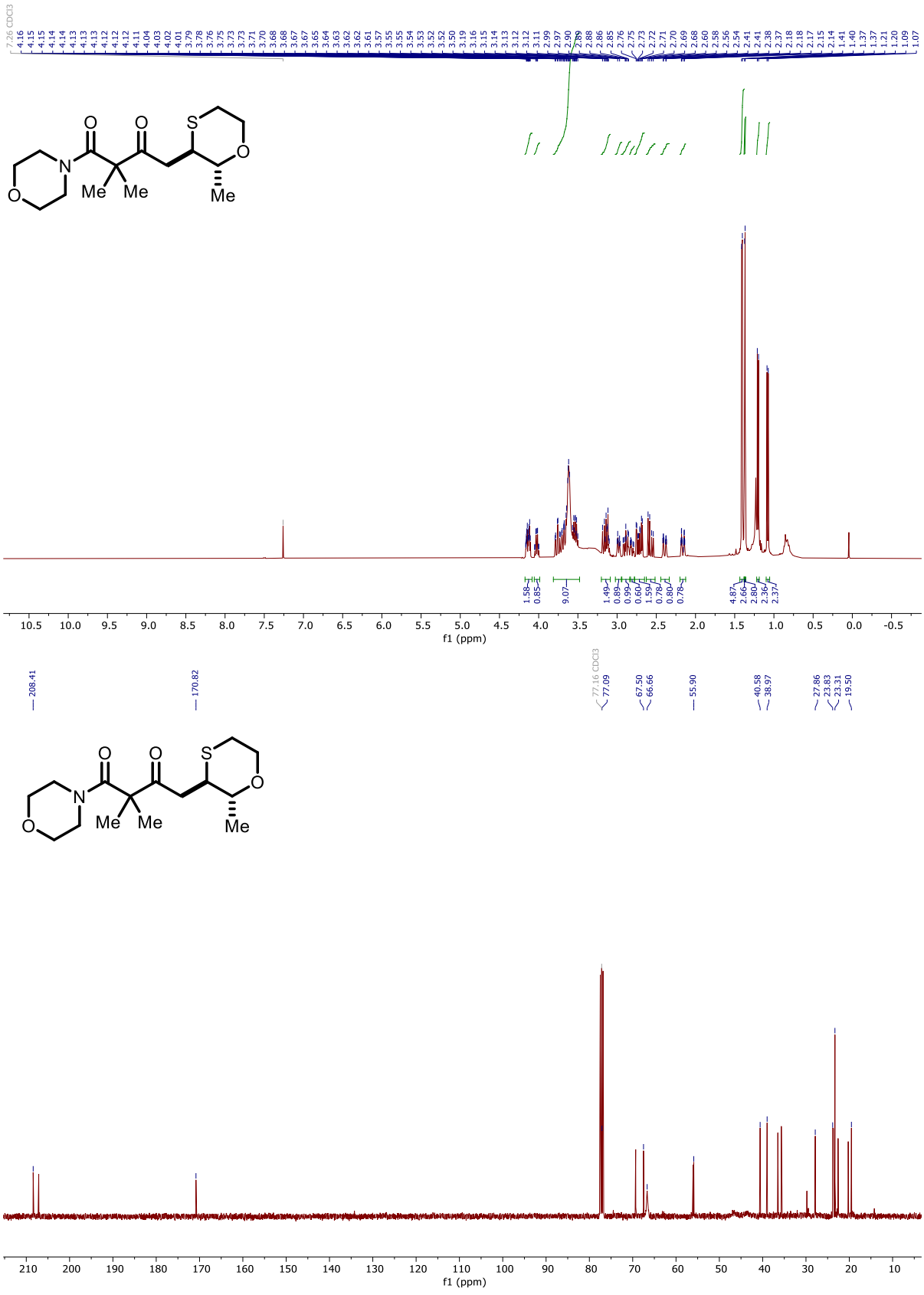


2-((2*R,3*R**)-2-Methyl-1,4-oxathian-3-yl)-1-(2-(methylthio)-3 (trifluoromethyl)phenyl)ethan-1-one (83p)**

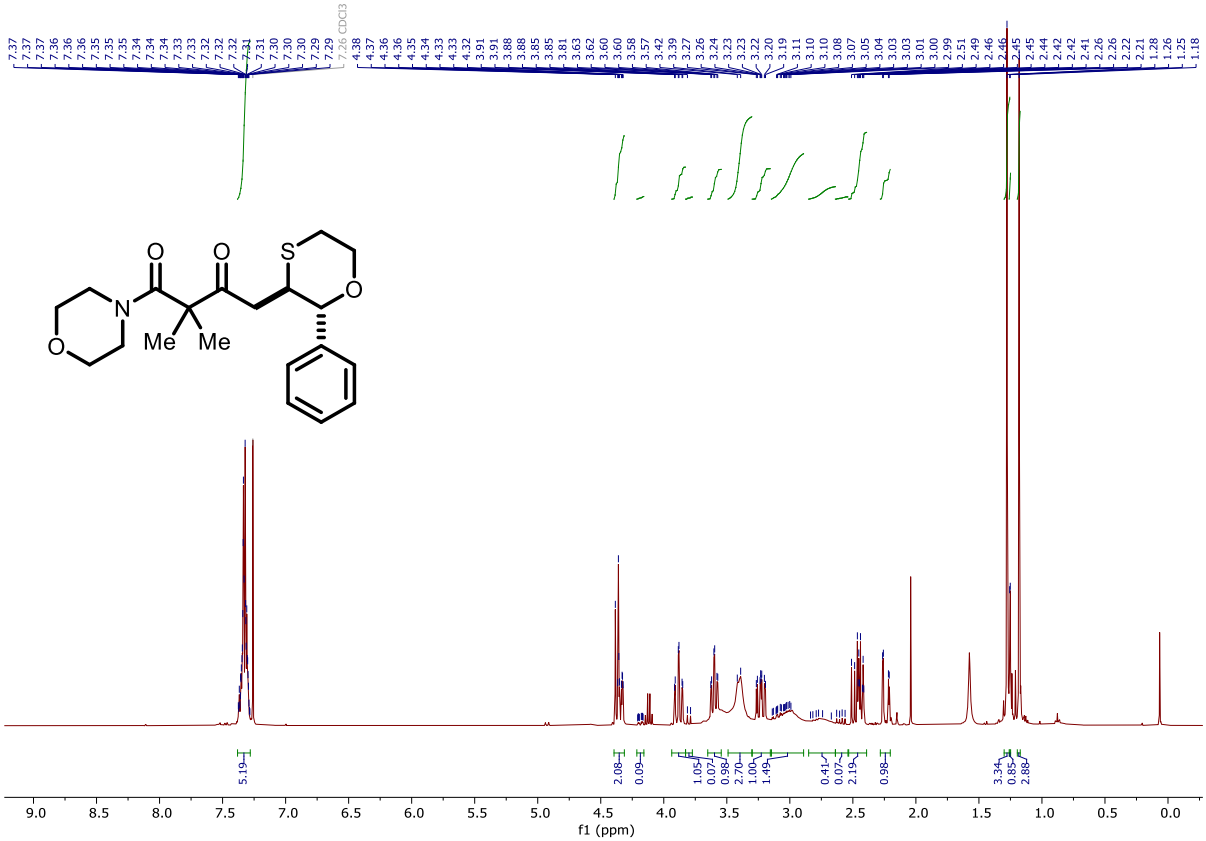


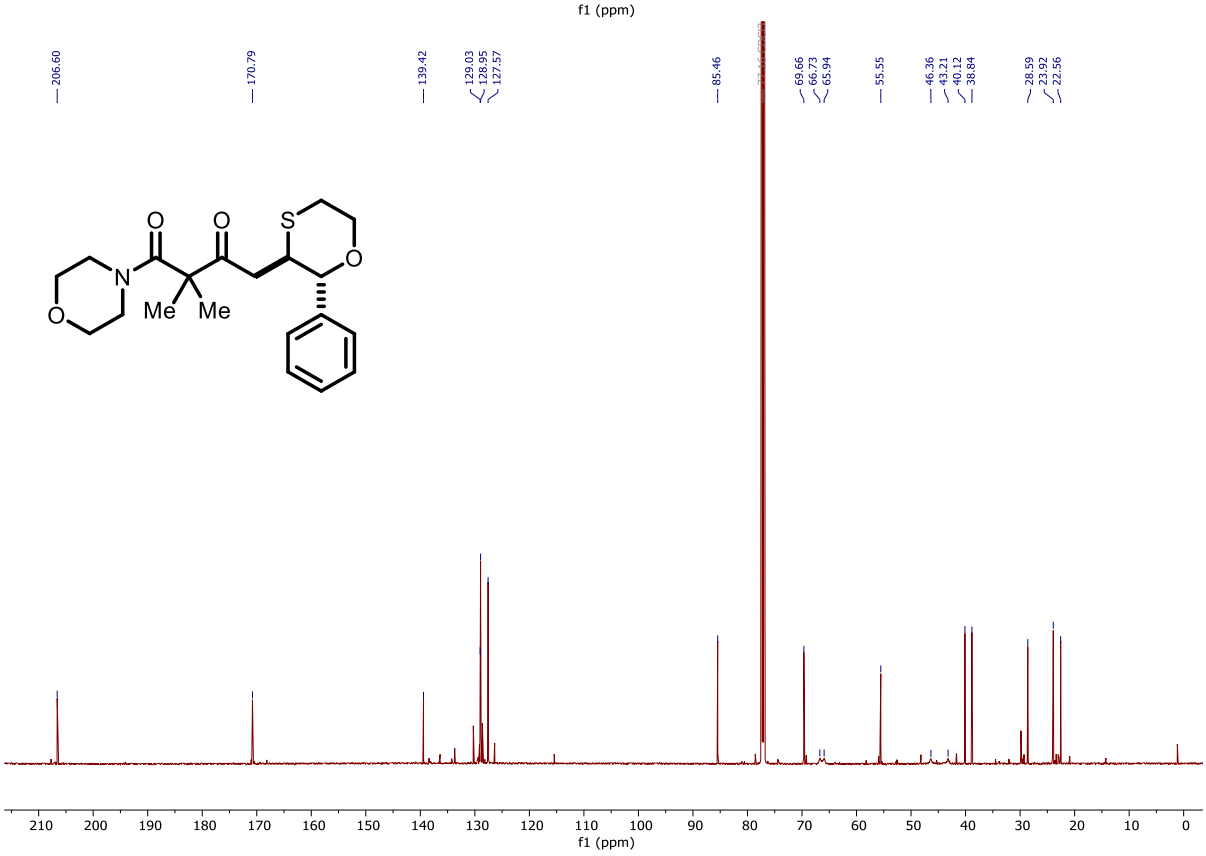


2,2-Dimethyl-4-((2*R,3*R**)-2-methyl-1,4-oxathian-3-yl)-1-morpholinobutane-1,3-dione (83q)**

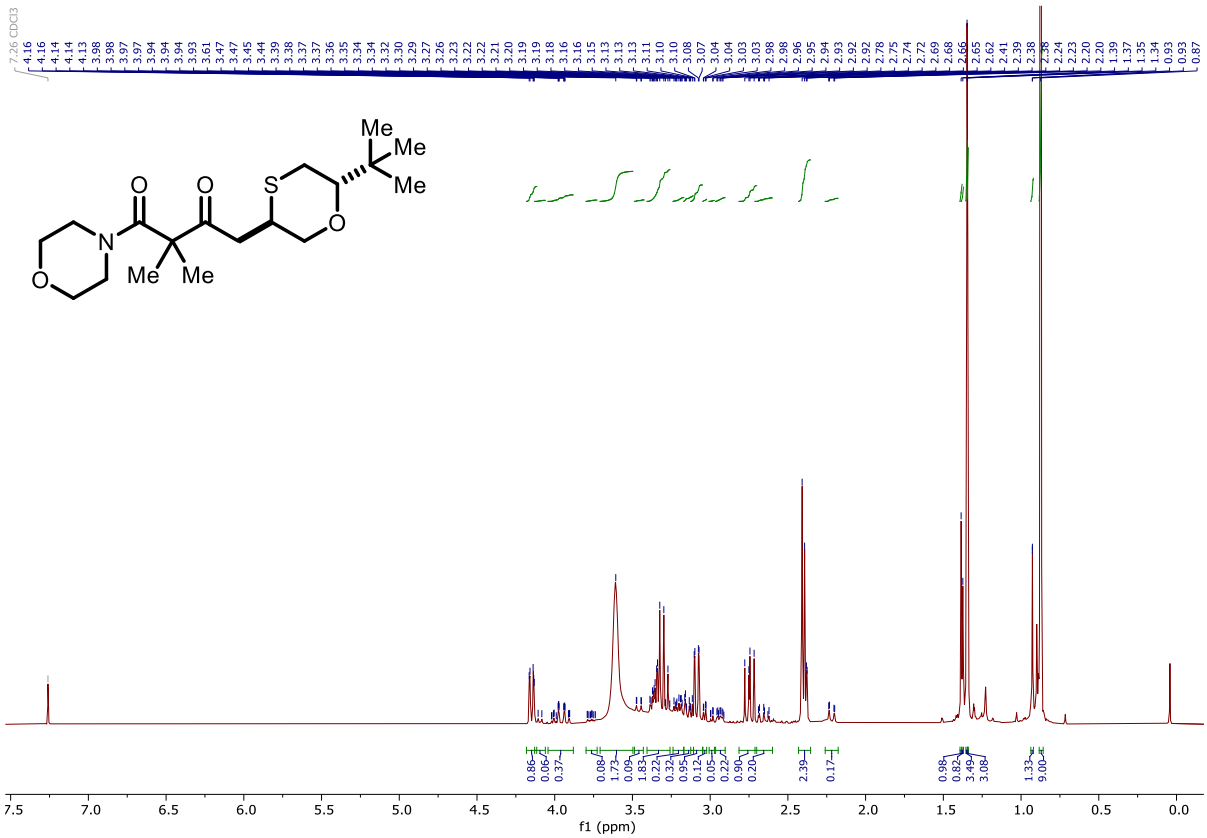


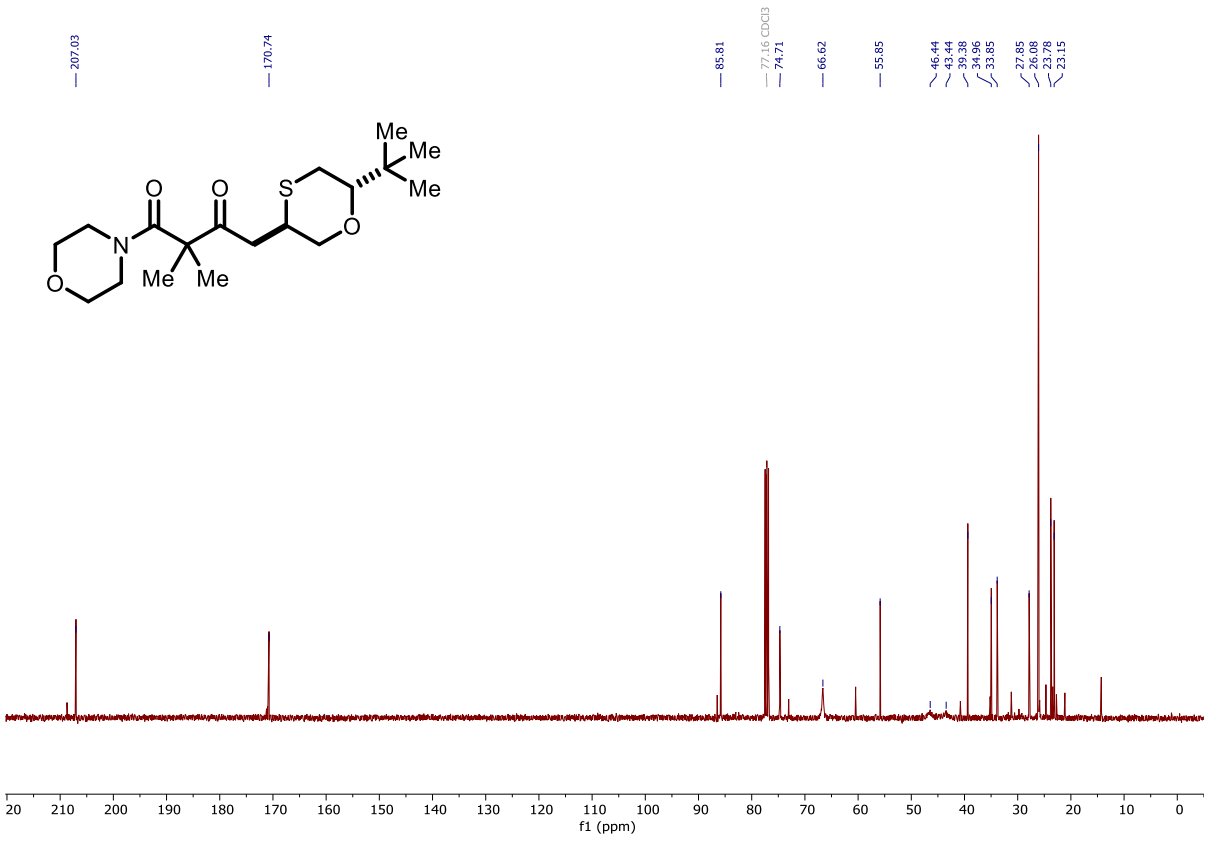
2,2-Dimethyl-1-morpholino-4-((2*R,3*R**)-2-phenyl-1,4-oxathian-3-yl)butane-1,3-dione (83r)**



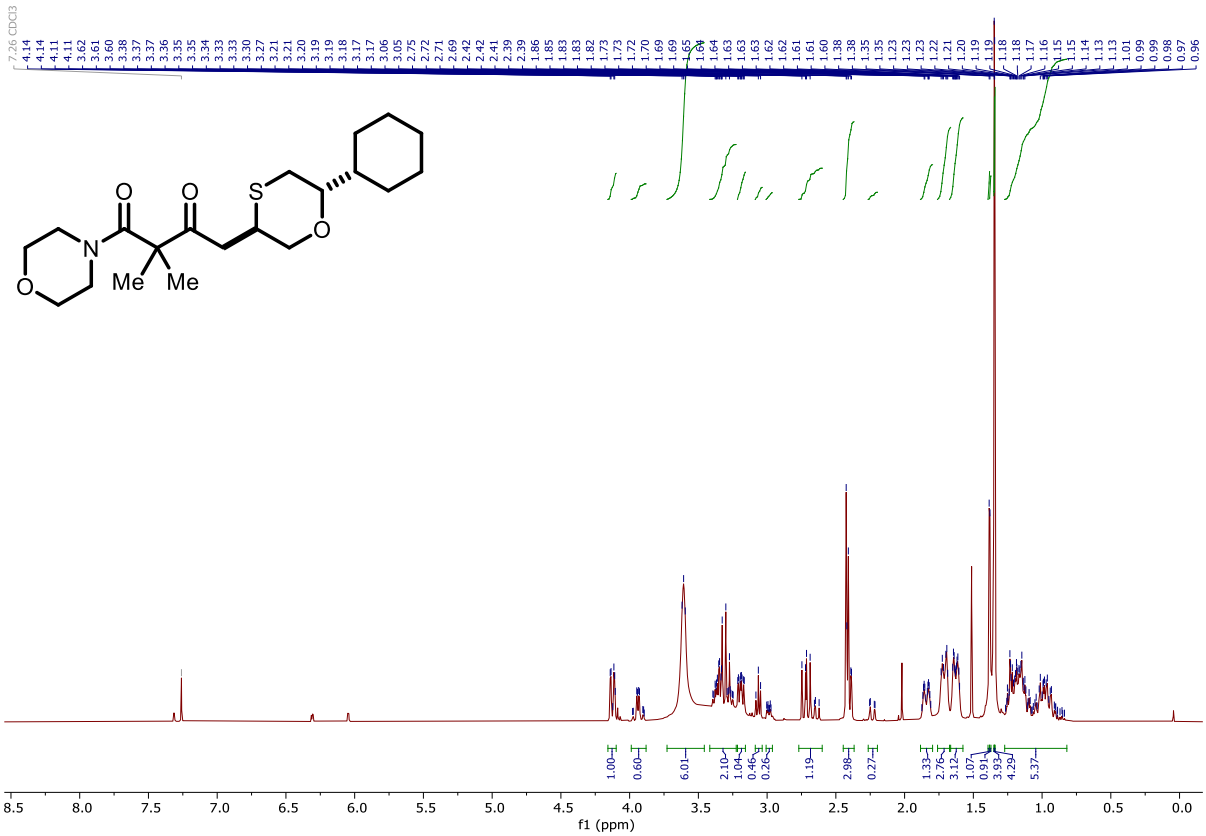


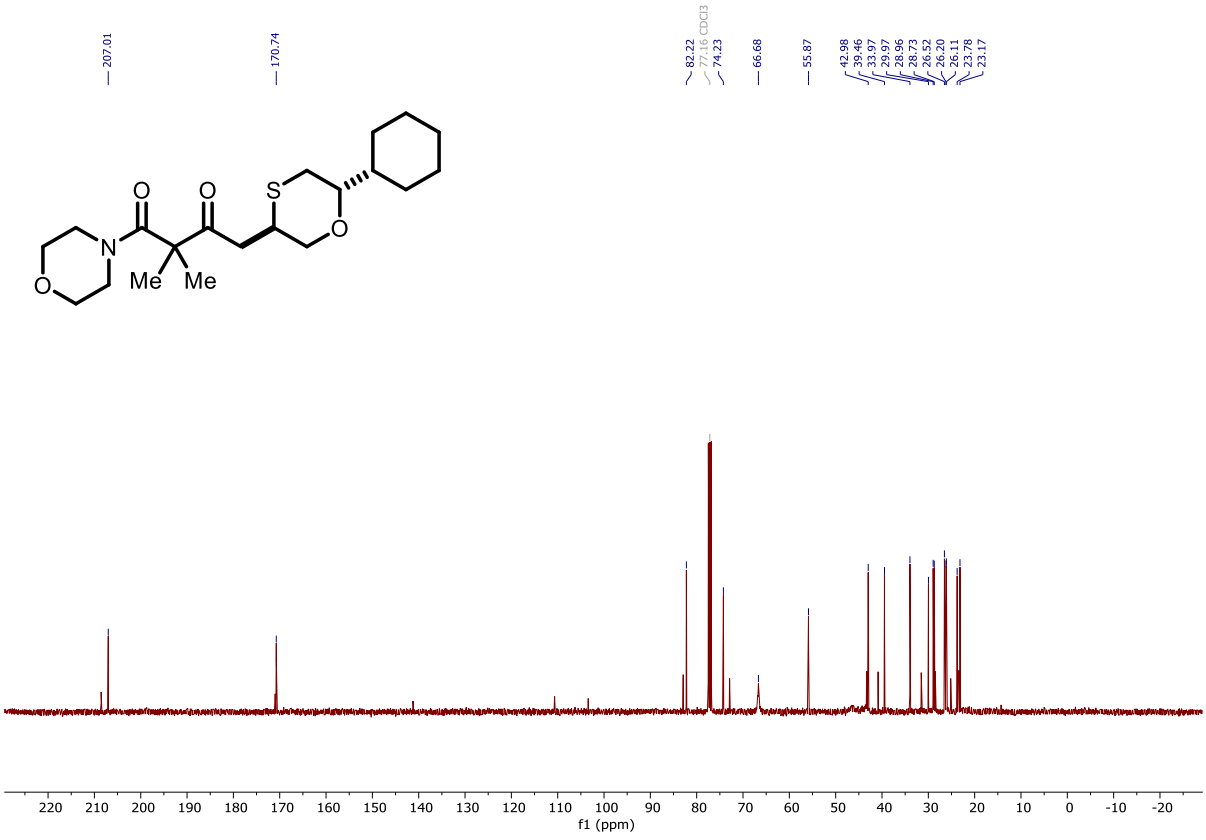
4-((3*R,6*S**)-6-(*tert*-Butyl)-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83s)**



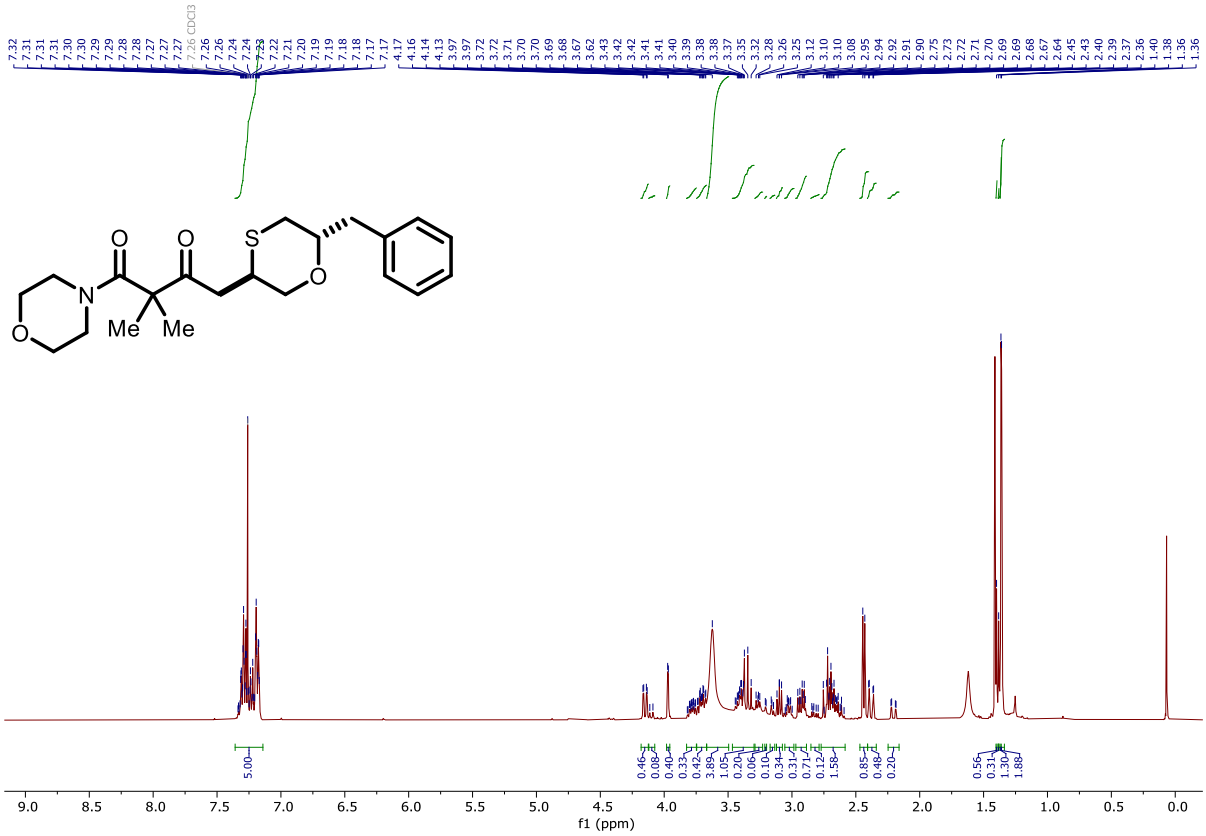


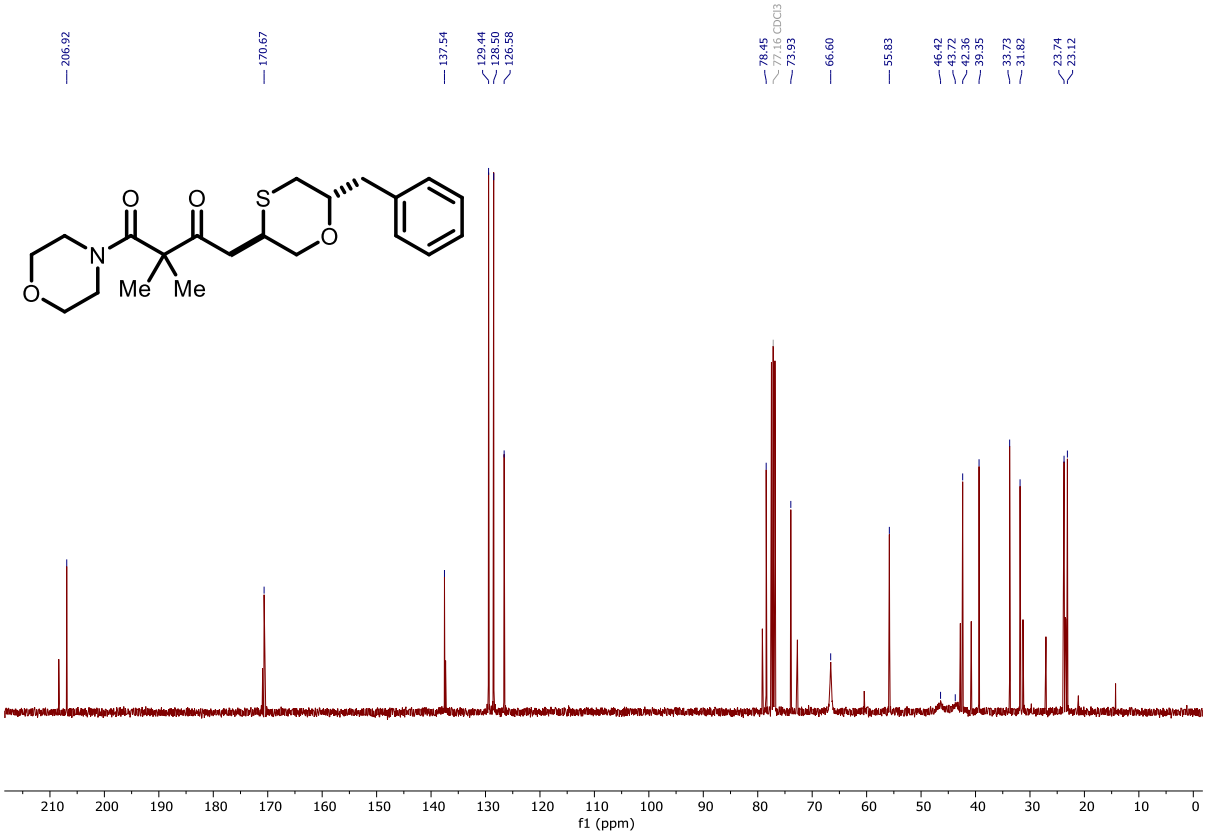
4-((3*R,6*S**)-6-Cyclohexyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83t)**



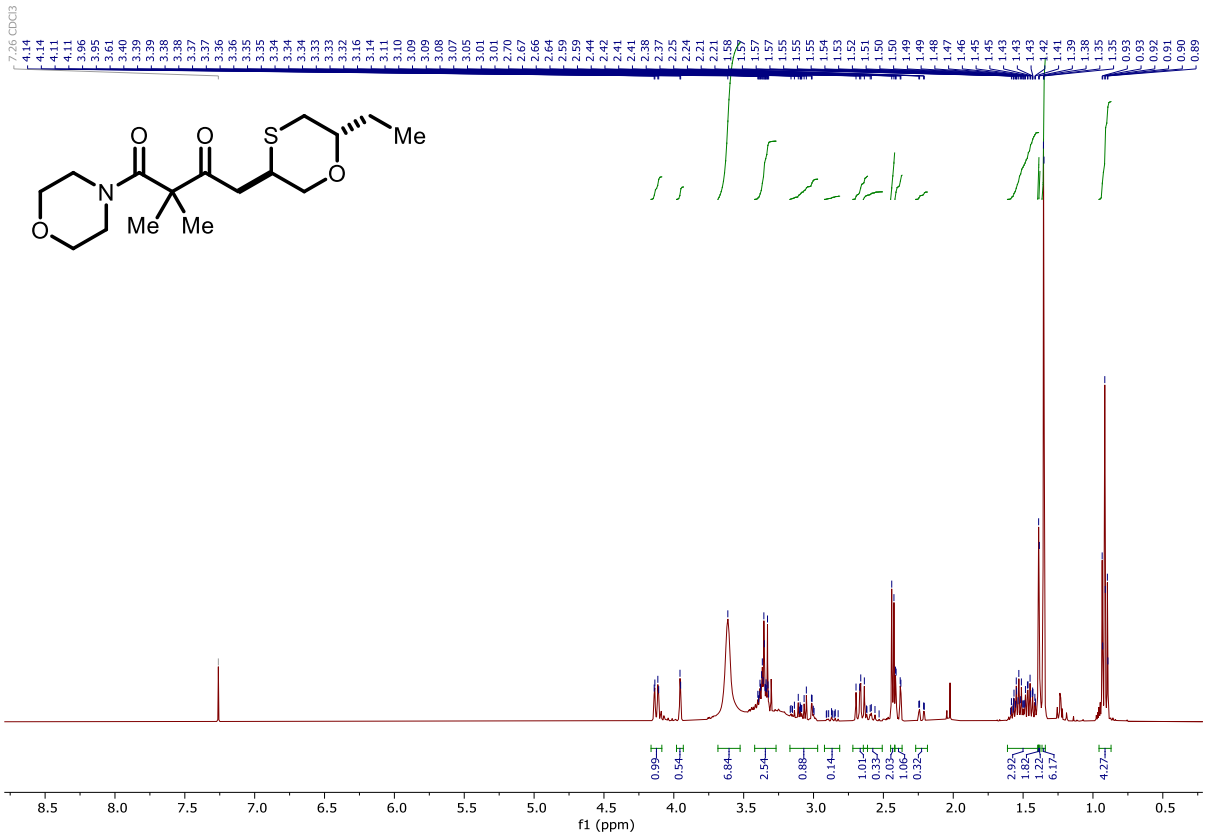


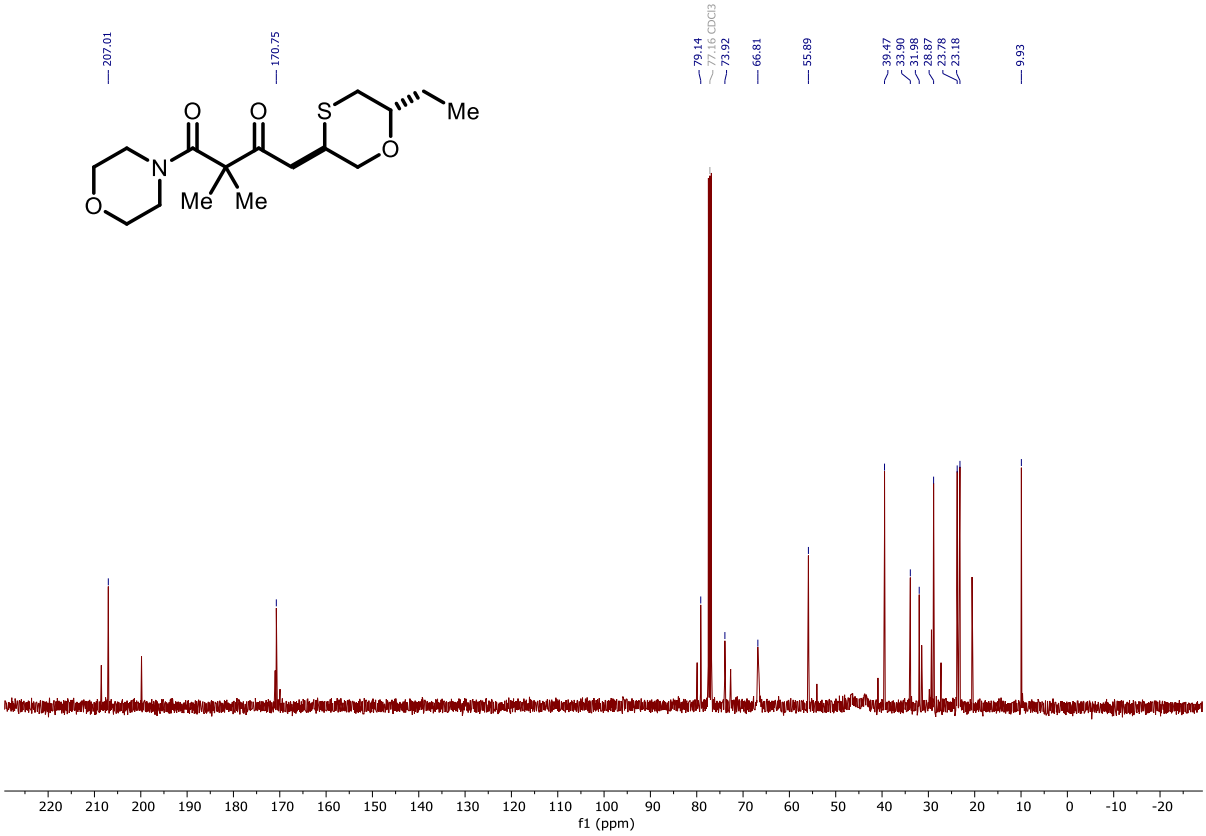
4-((3*R,6*S**)-6-Benzyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83u)**



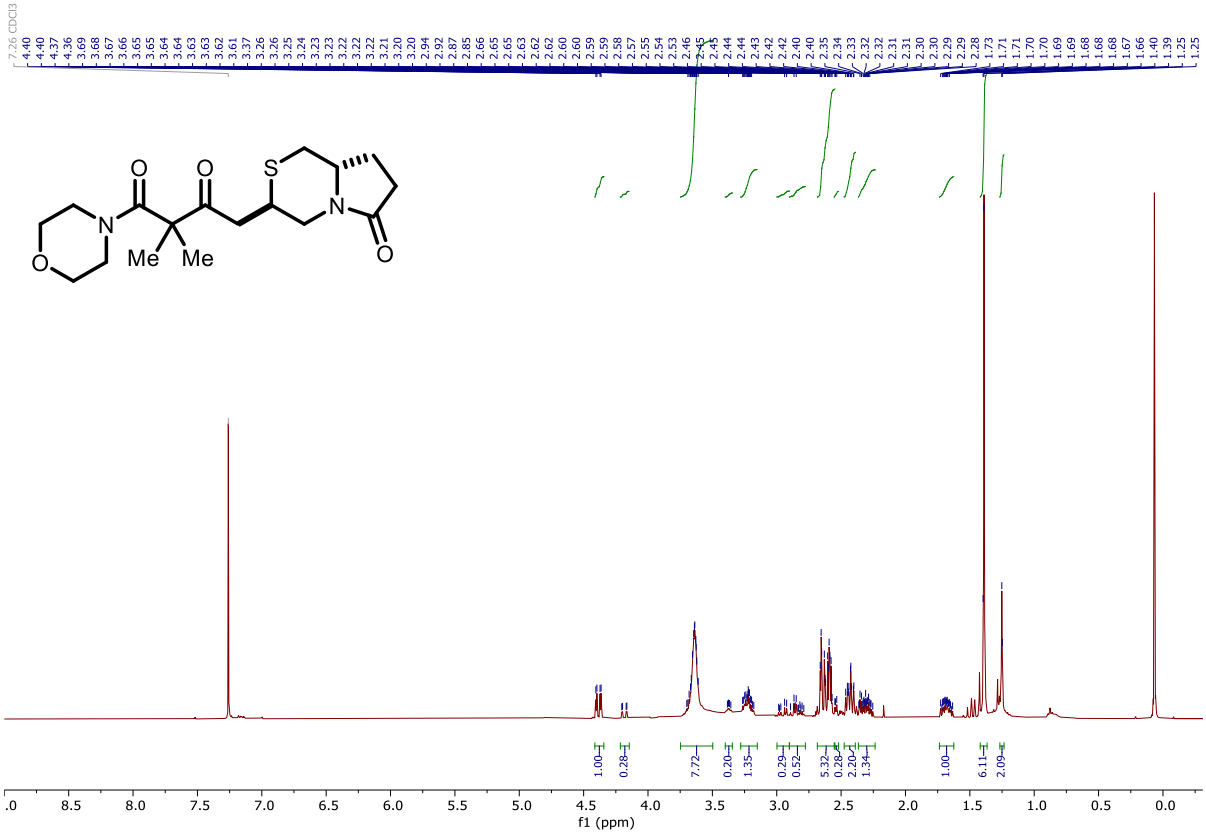


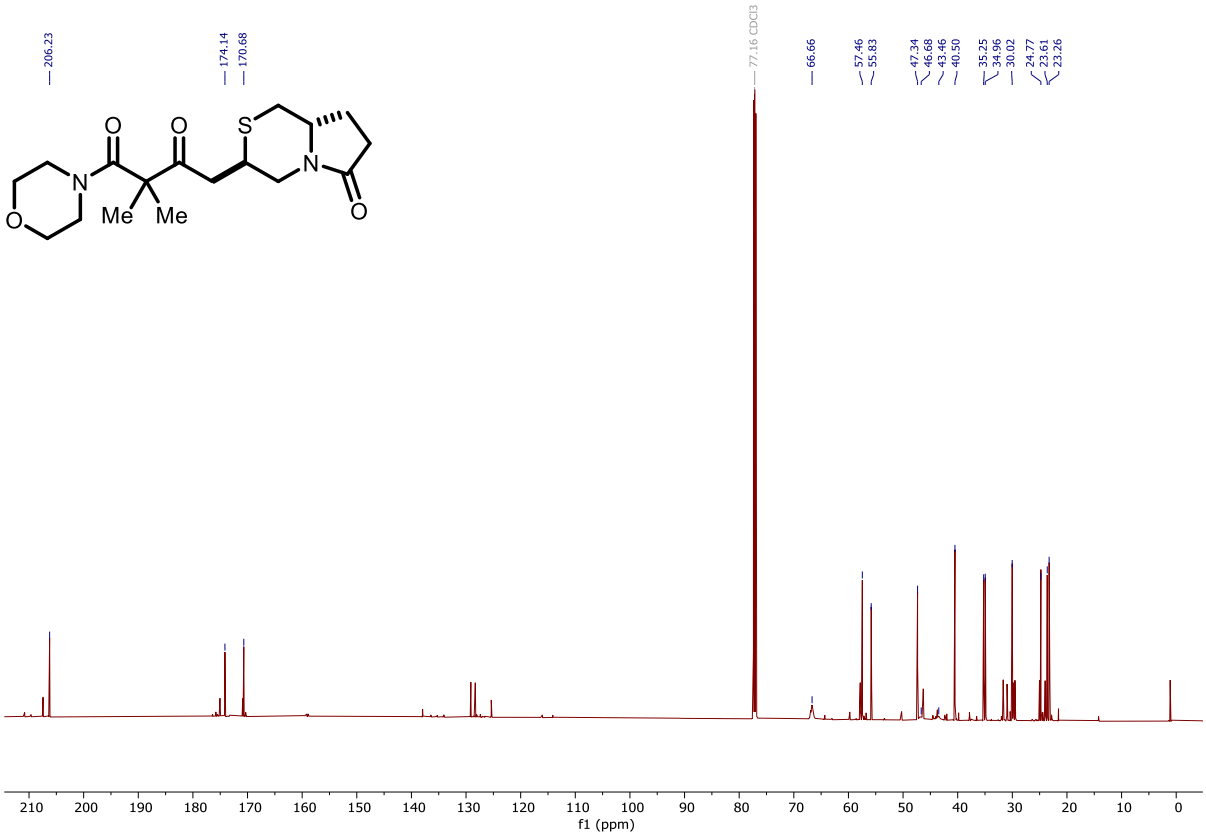
4-((3*R,6*S**)-6-Ethyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83v)**



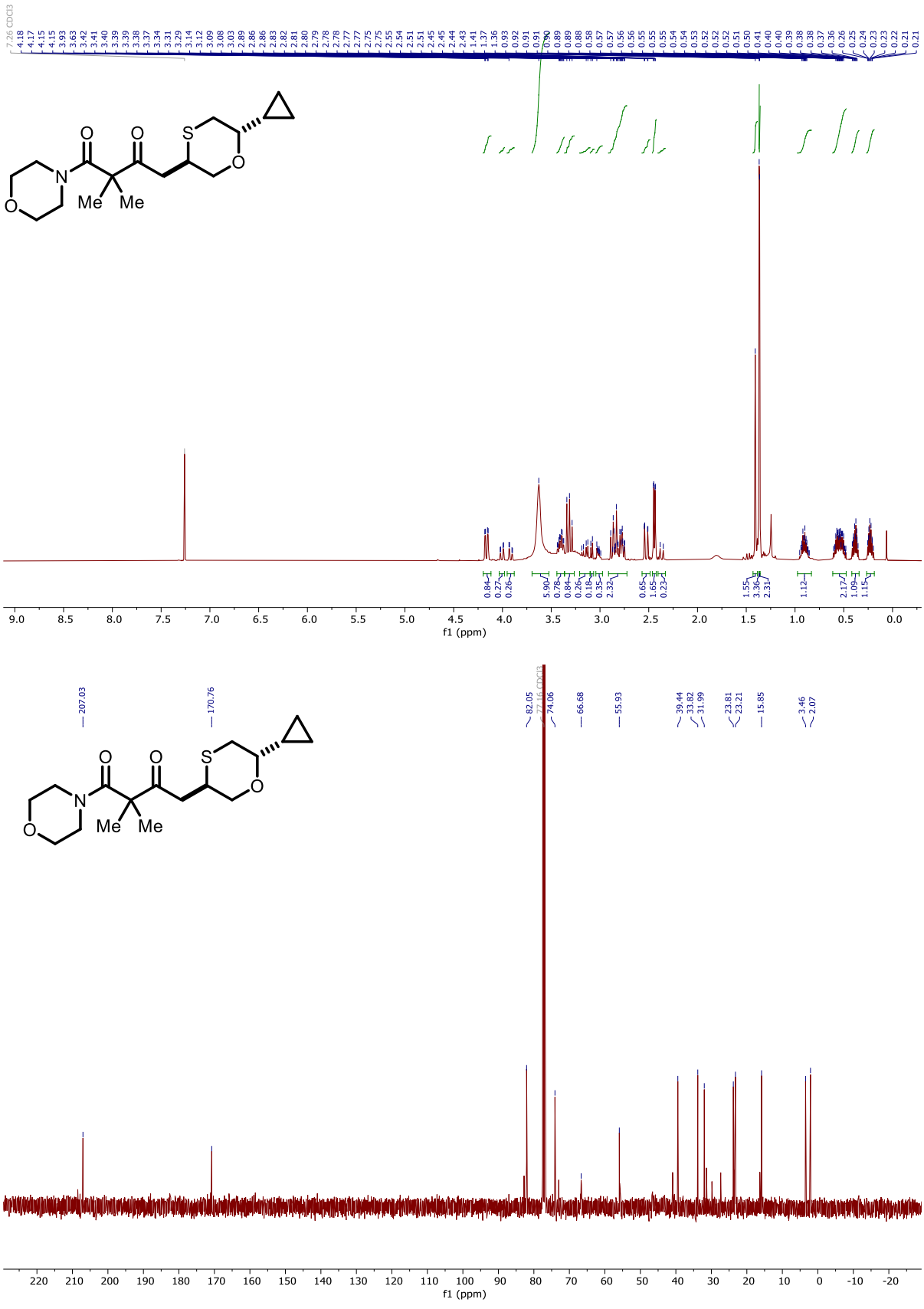


2,2-Dimethyl-1-morpholino-4-((3*R,8a*S**)-6-oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]thiazin-3-yl)butane-1,3-dione (83w)**

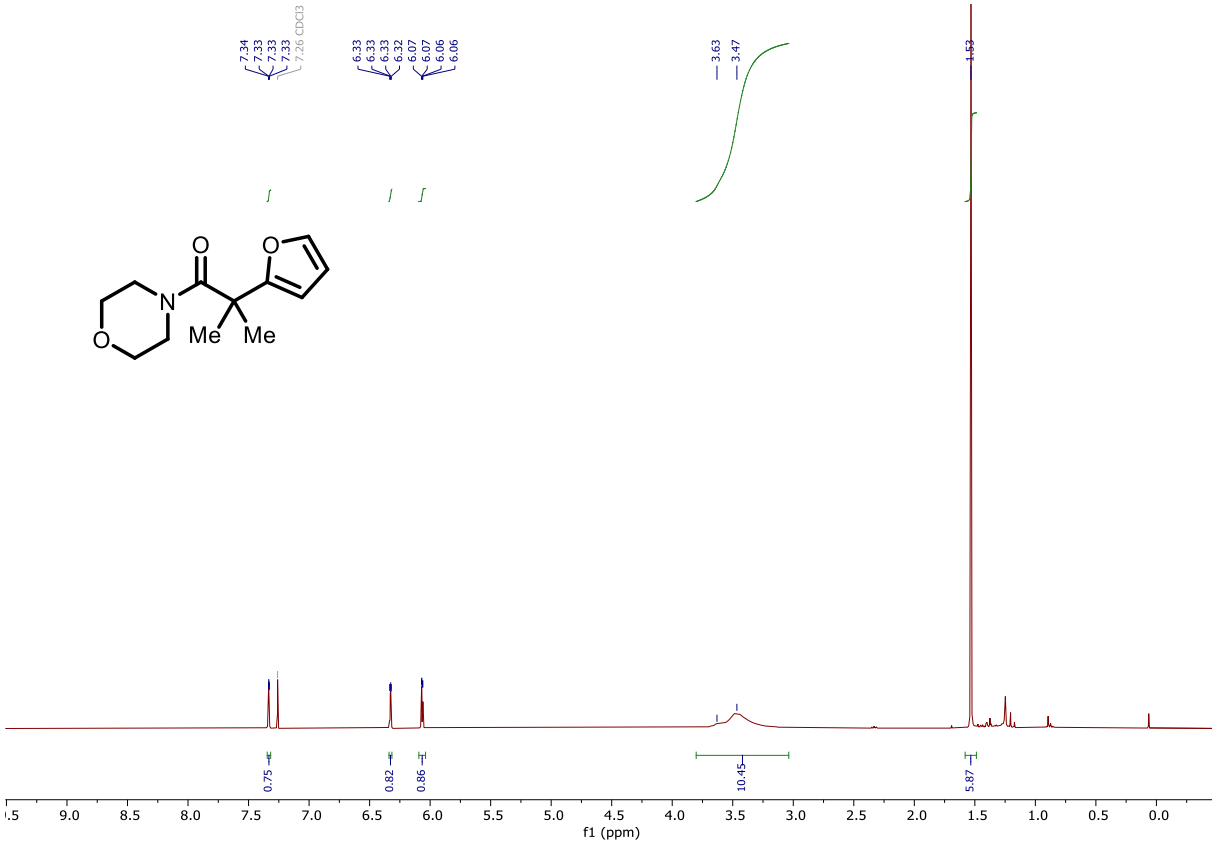


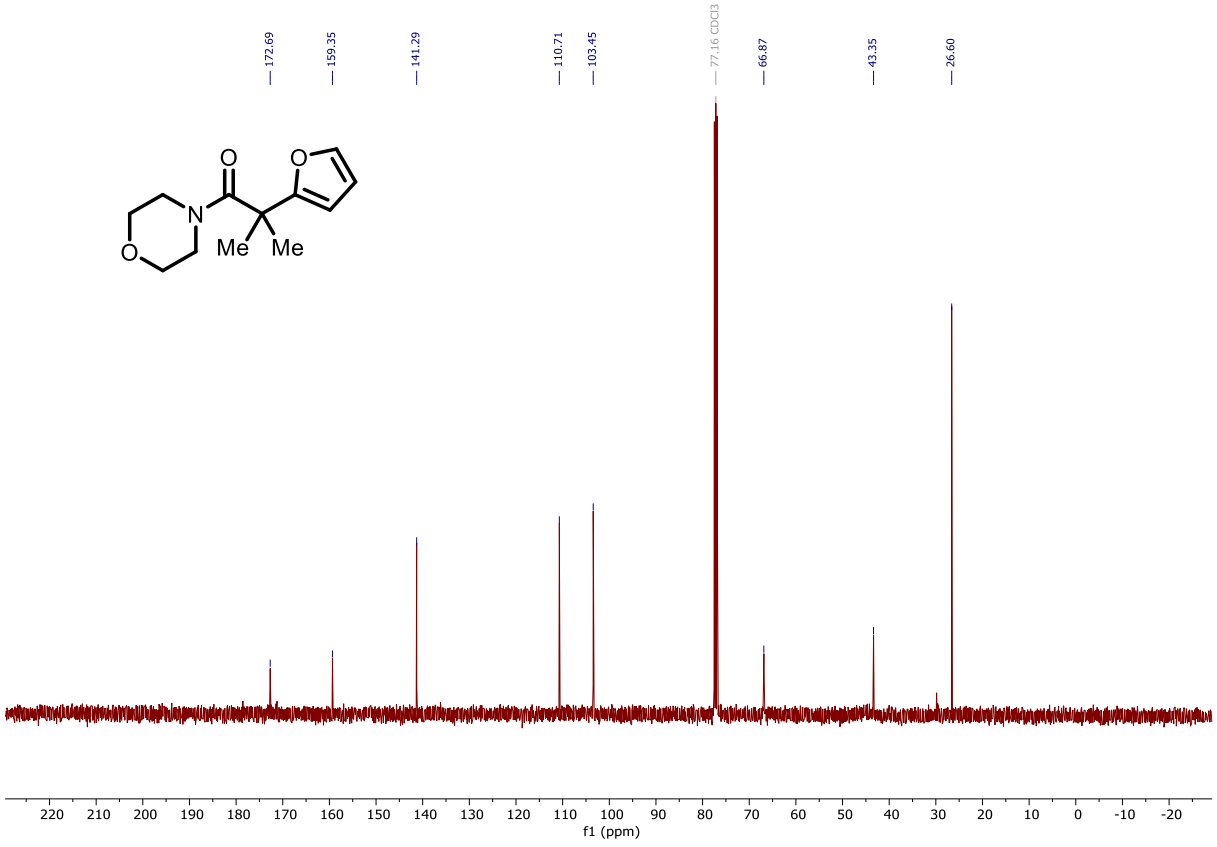


4-((3*R,6*S**)-6-Cyclopropyl-1,4-oxathian-3-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (83x)**

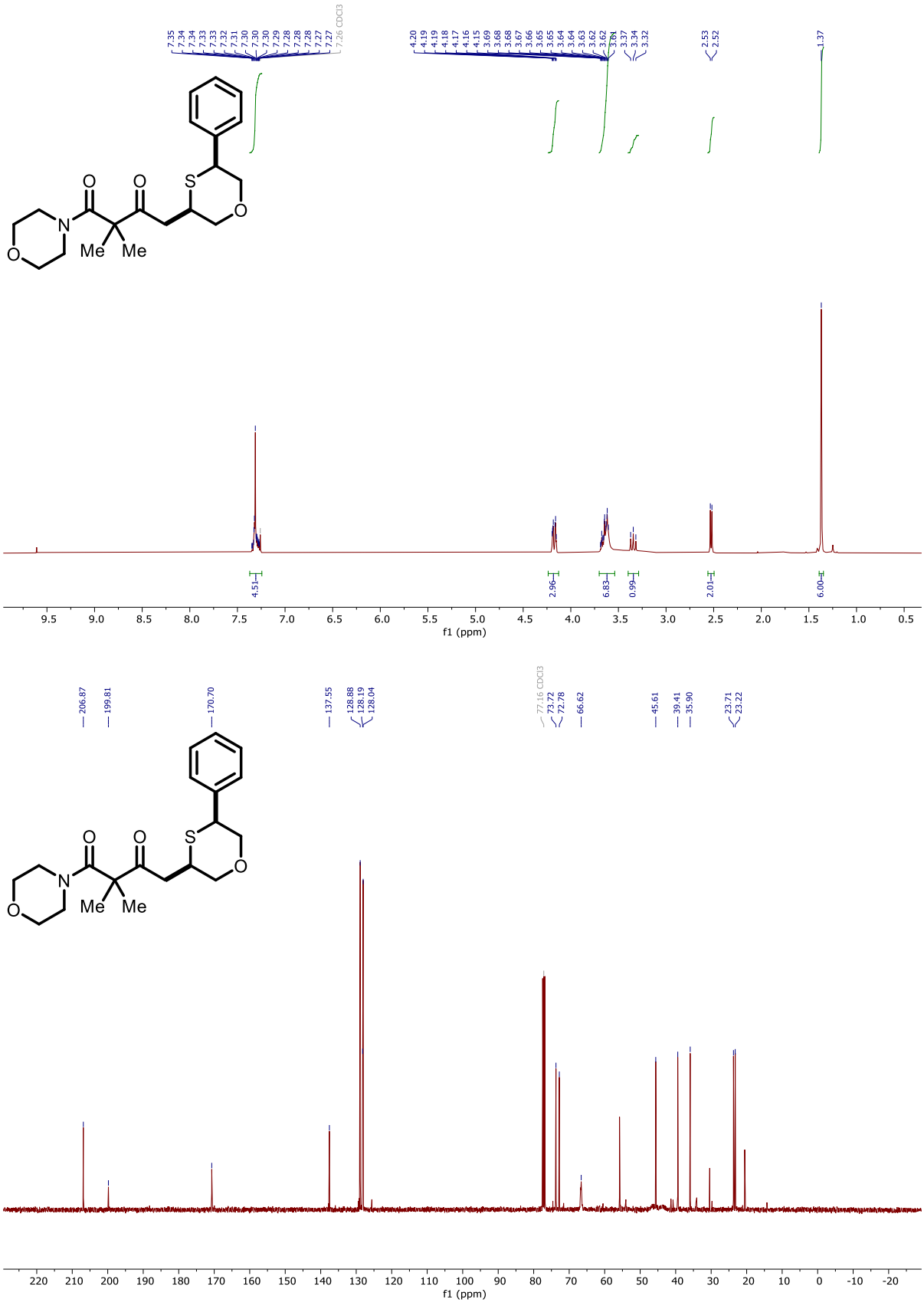


2-(Furan-2-yl)-2-methyl-1-morpholinopropan-1-one (94)

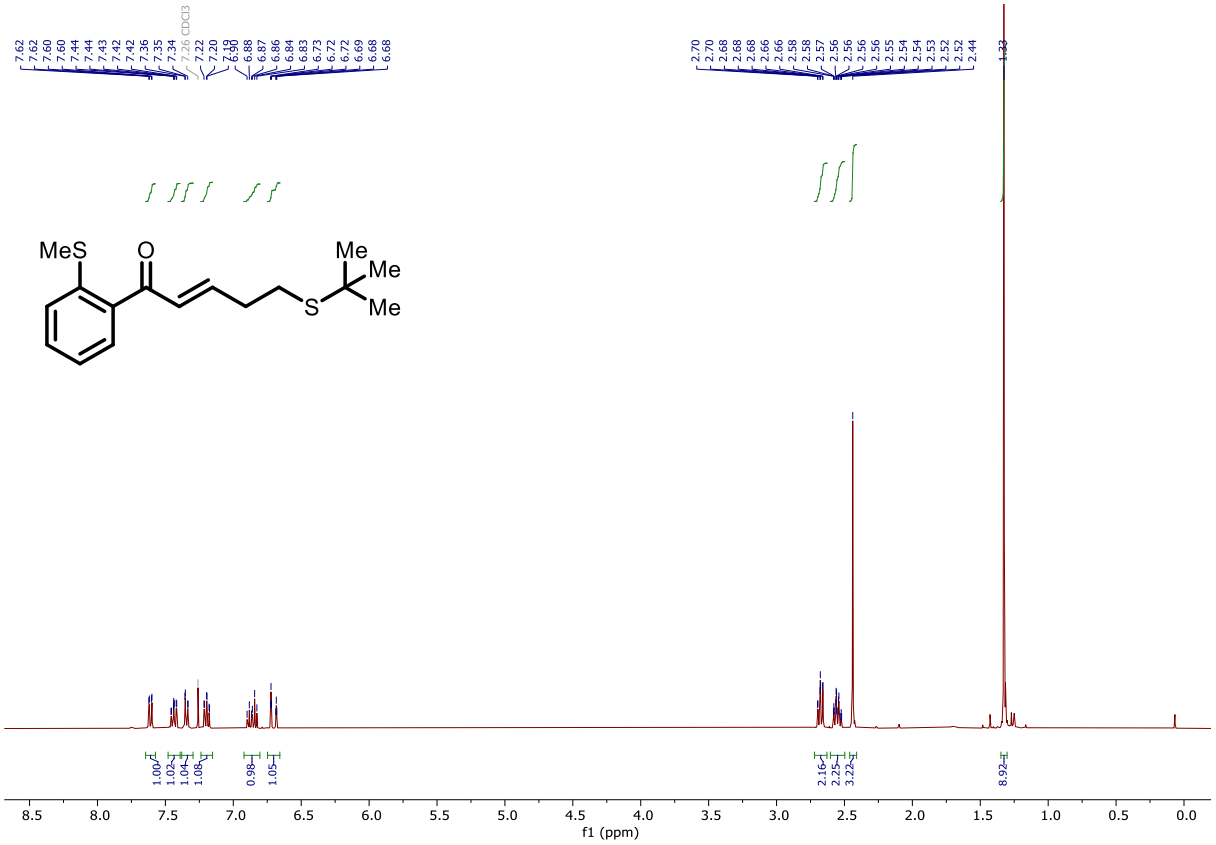


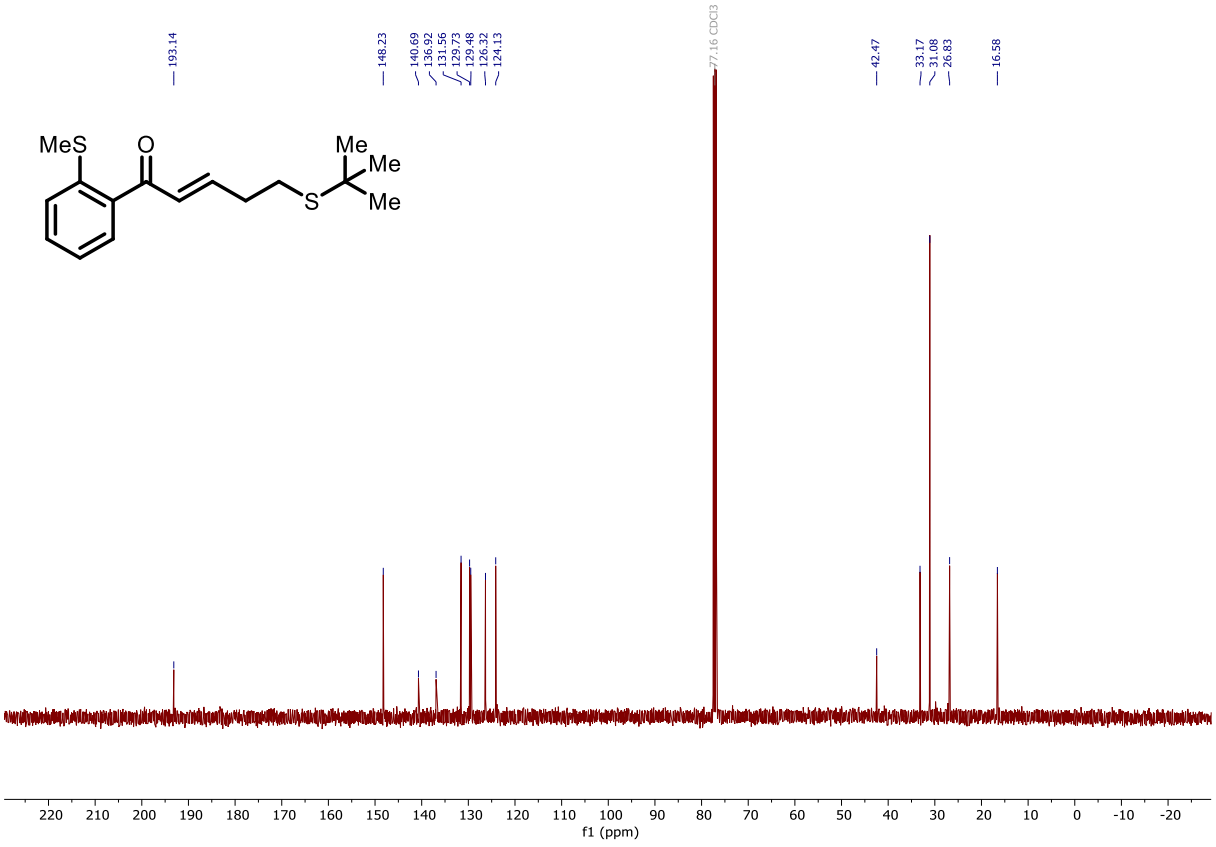


2,2-Dimethyl-1-morpholino-4-((3*R,5*S**)-5-phenyl-1,4-oxathian-3-yl)butane-1,3-dione (83y)**

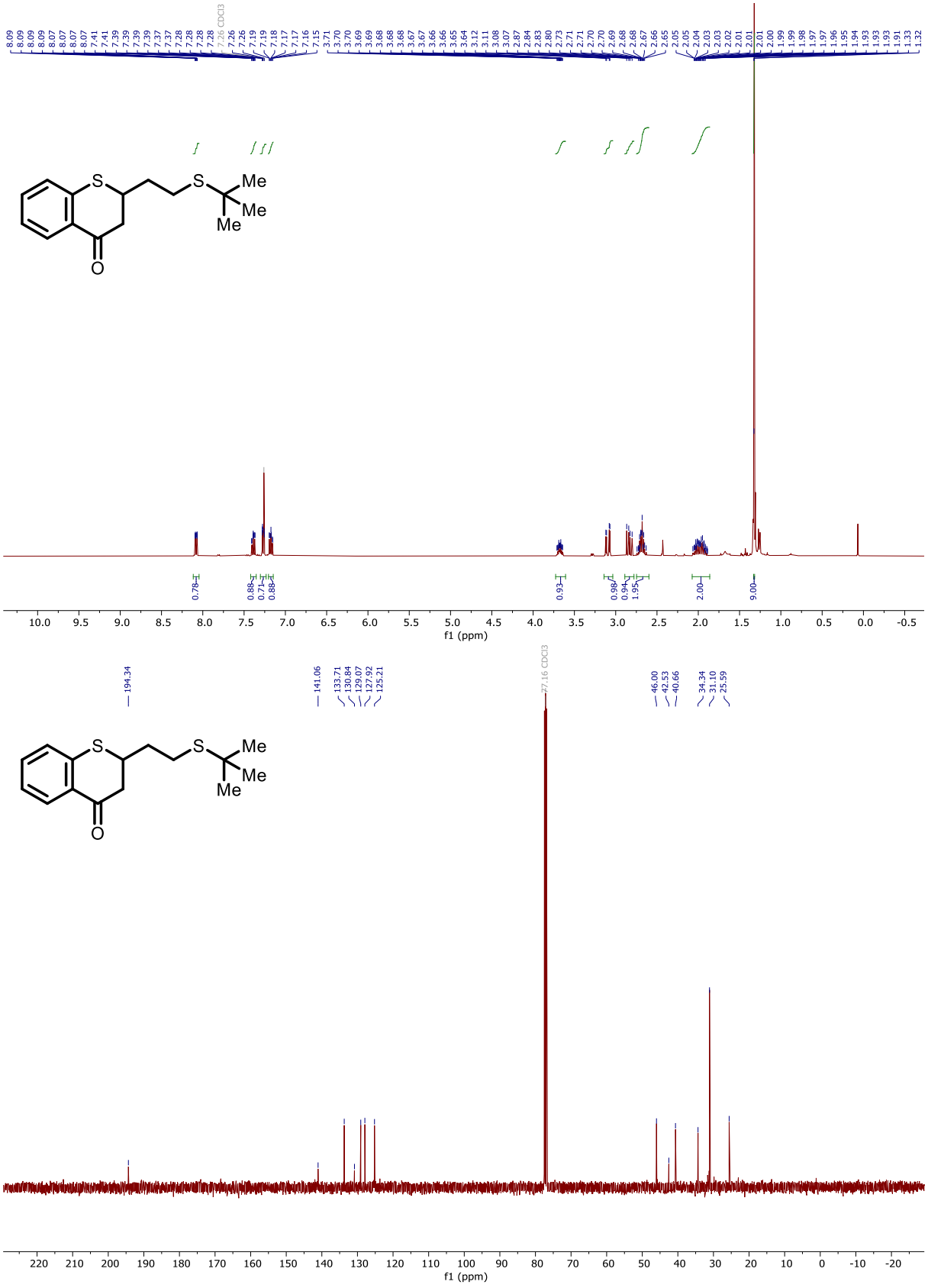


(*E*)-5-(*tert*-Butylthio)-1-(2-(methylthio)phenyl)pent-2-en-1-one (97a)

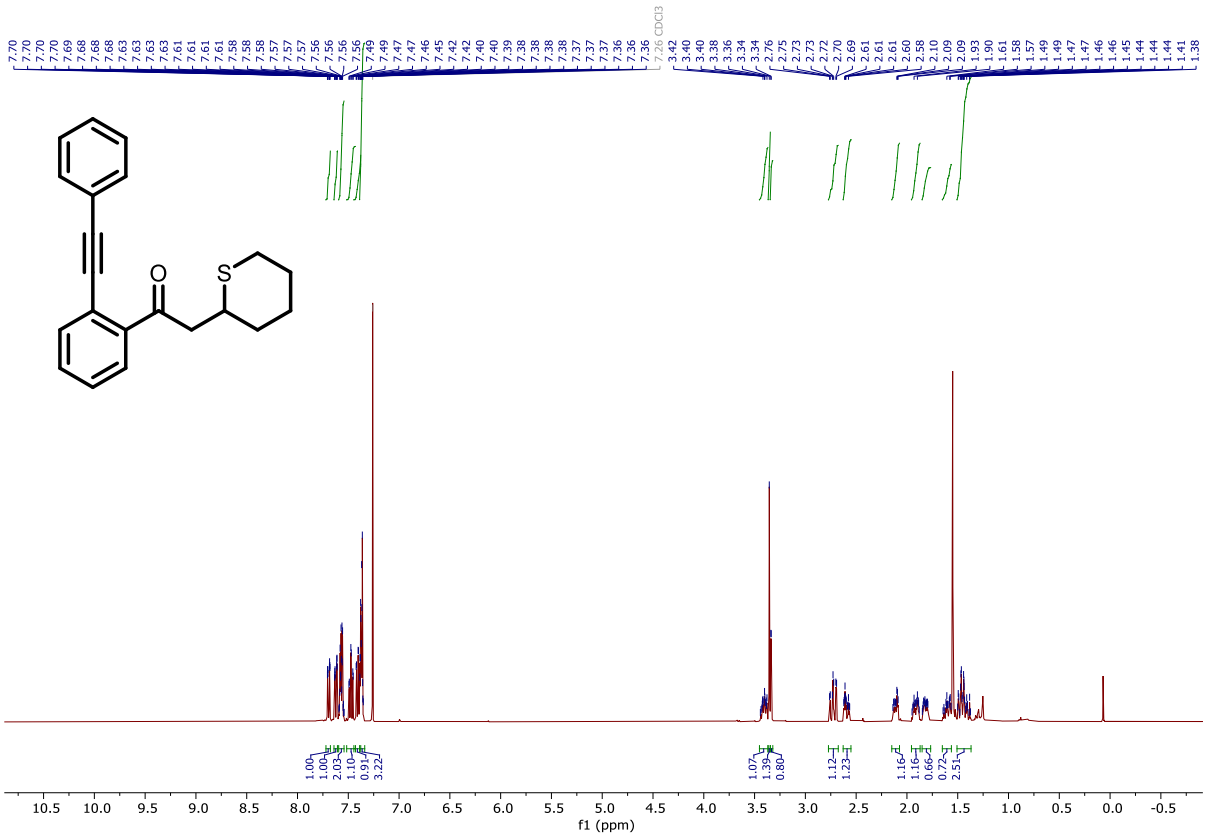


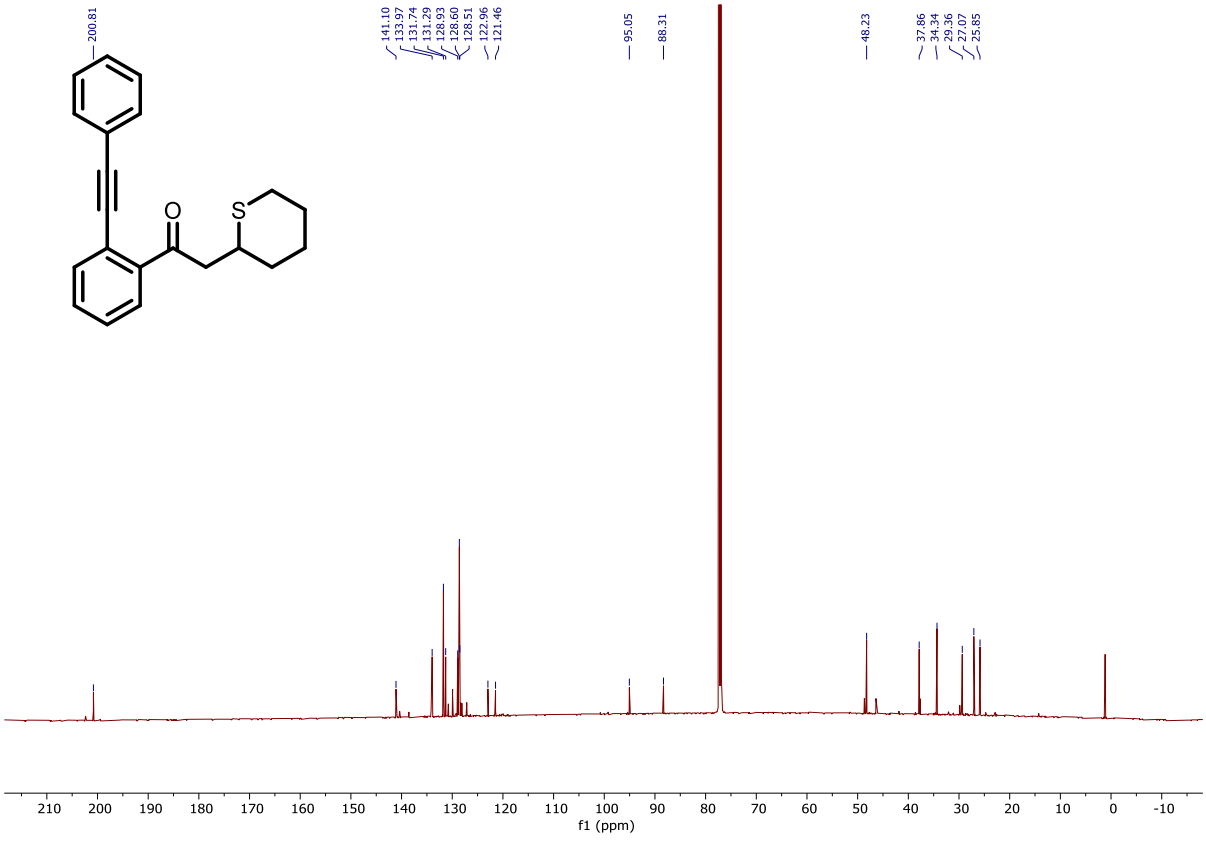


2-(2-(*tert*-Butylthio)ethyl)thiochroman-4-one (98)

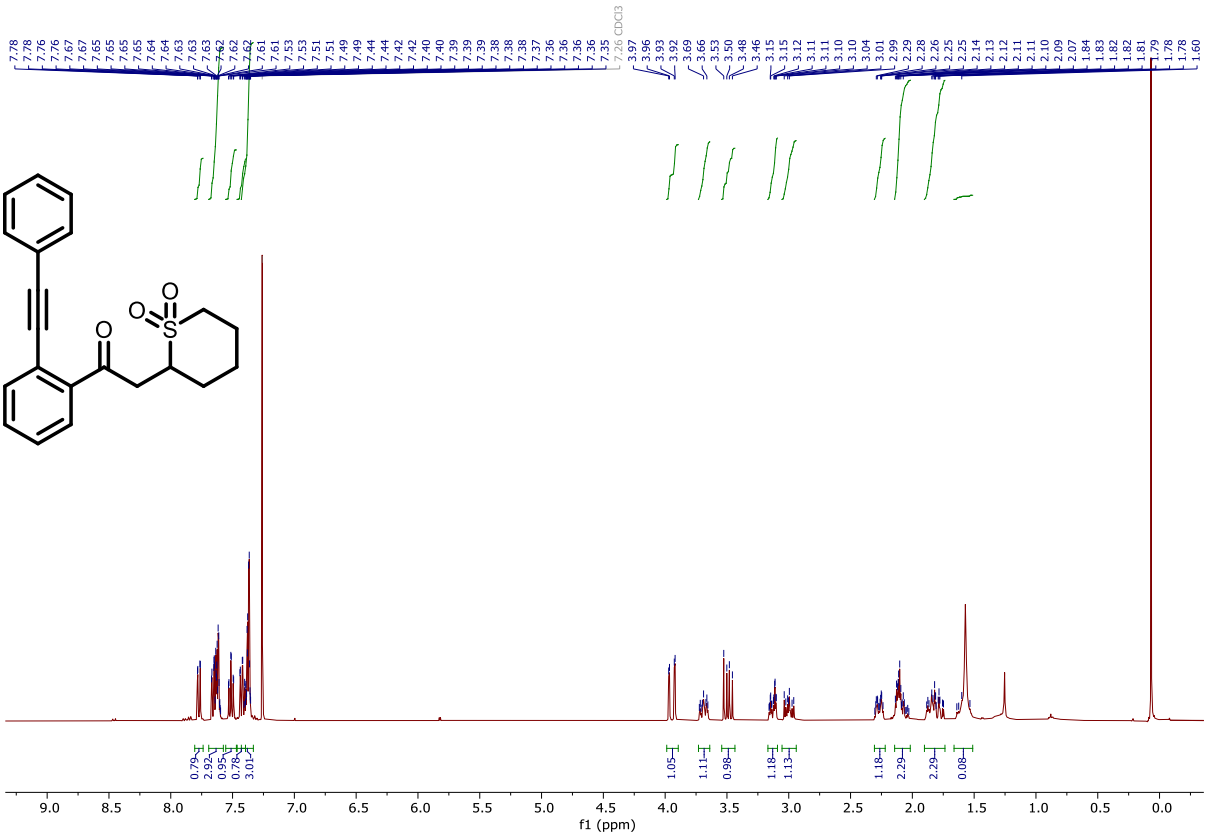


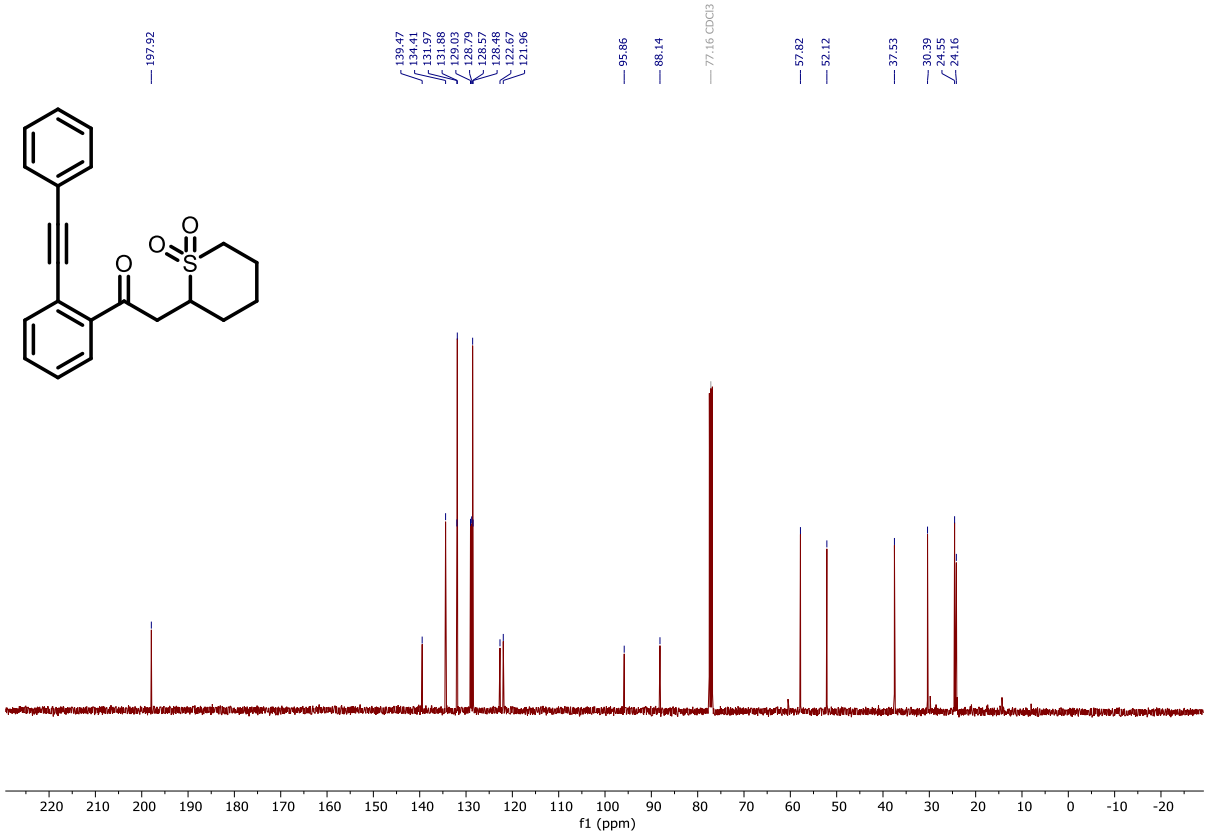
1-(2-(Phenylethynyl)phenyl)-2-(tetrahydro-2*H*-thiopyran-2-yl)ethan-1-one (106)



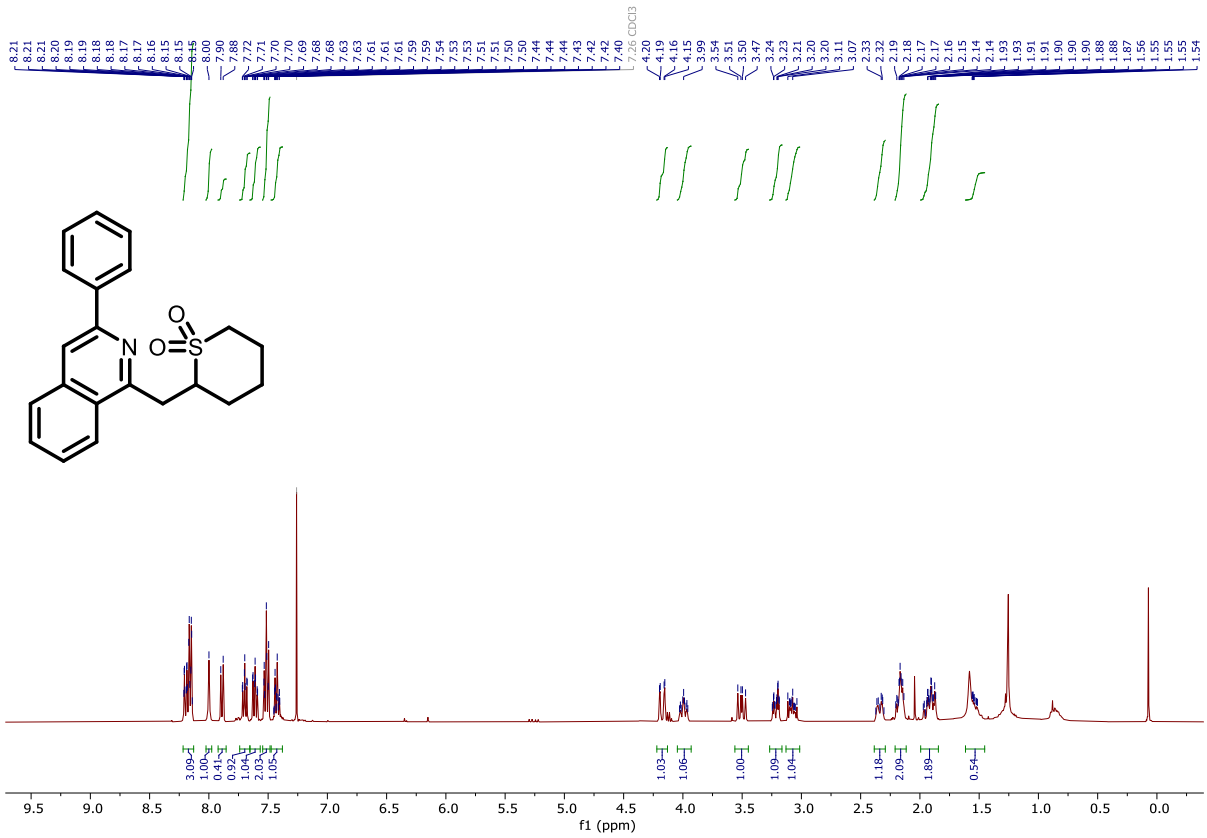


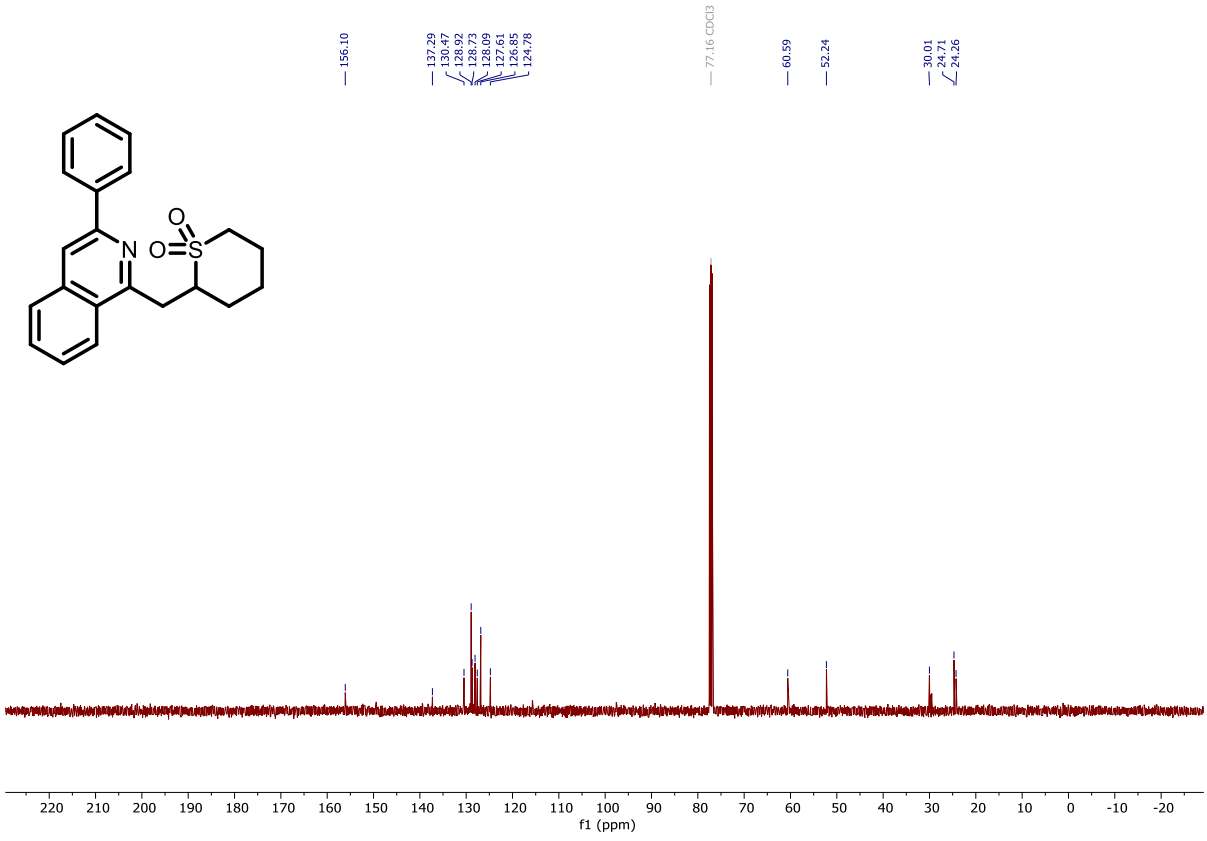
2-(1,1-Dioxidotetrahydro-2*H*-thiopyran-2-yl)-1-(2-(phenylethynyl)phenyl)ethan-1-one (107)





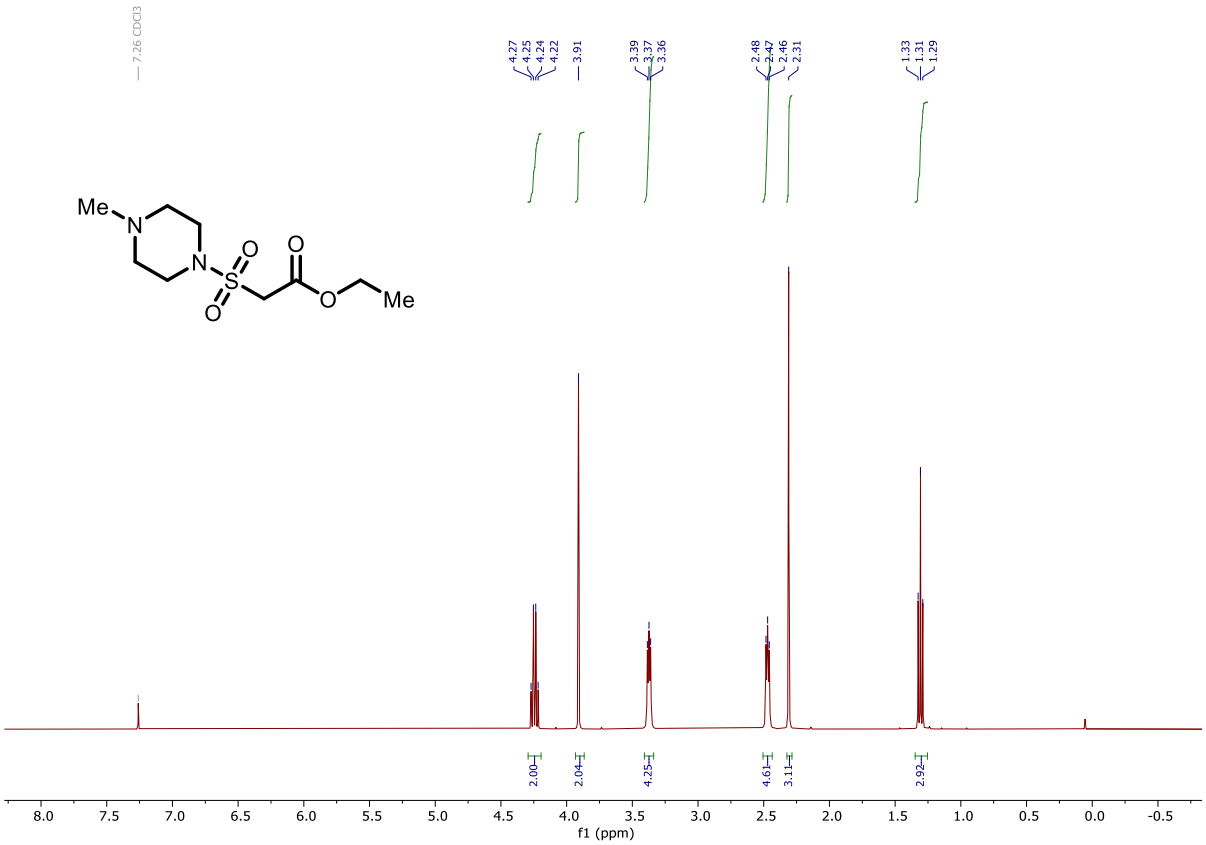
2-((3-Phenylisoquinolin-1-yl)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (108)

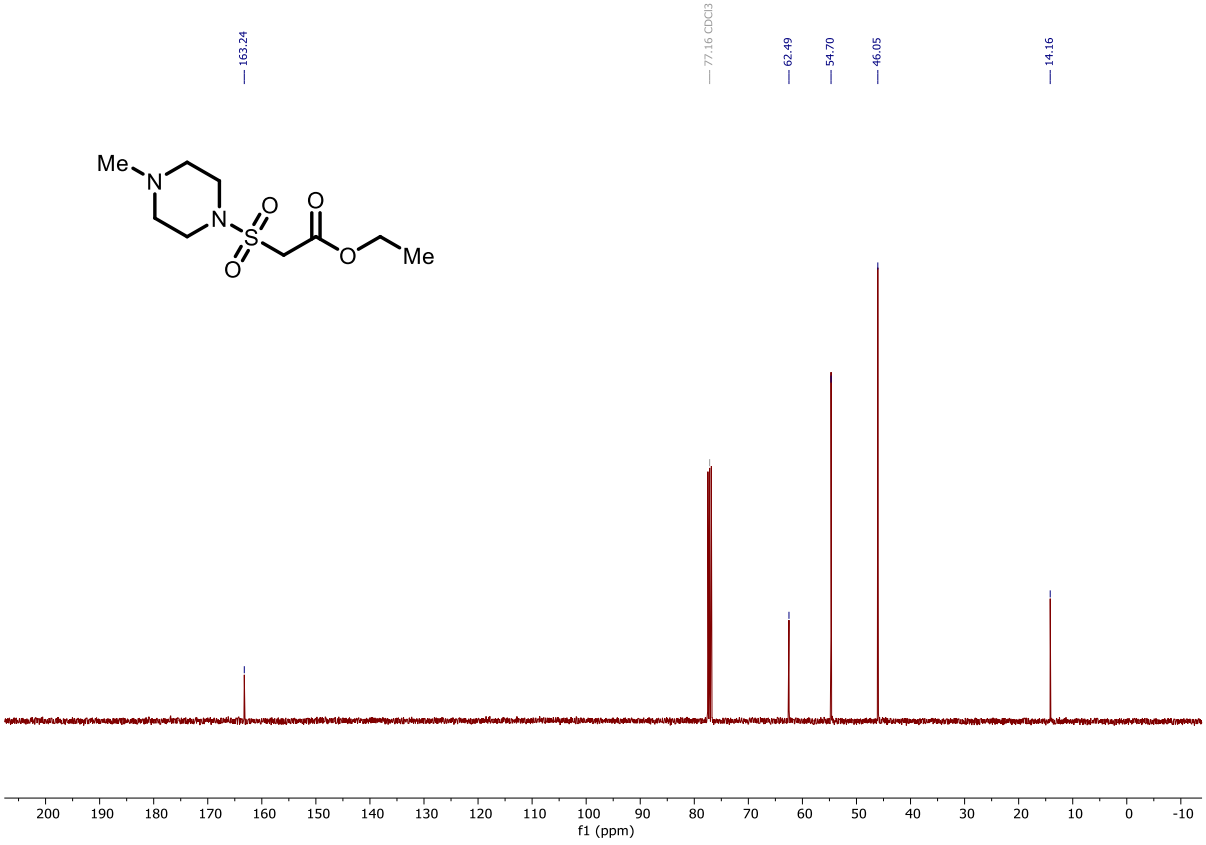




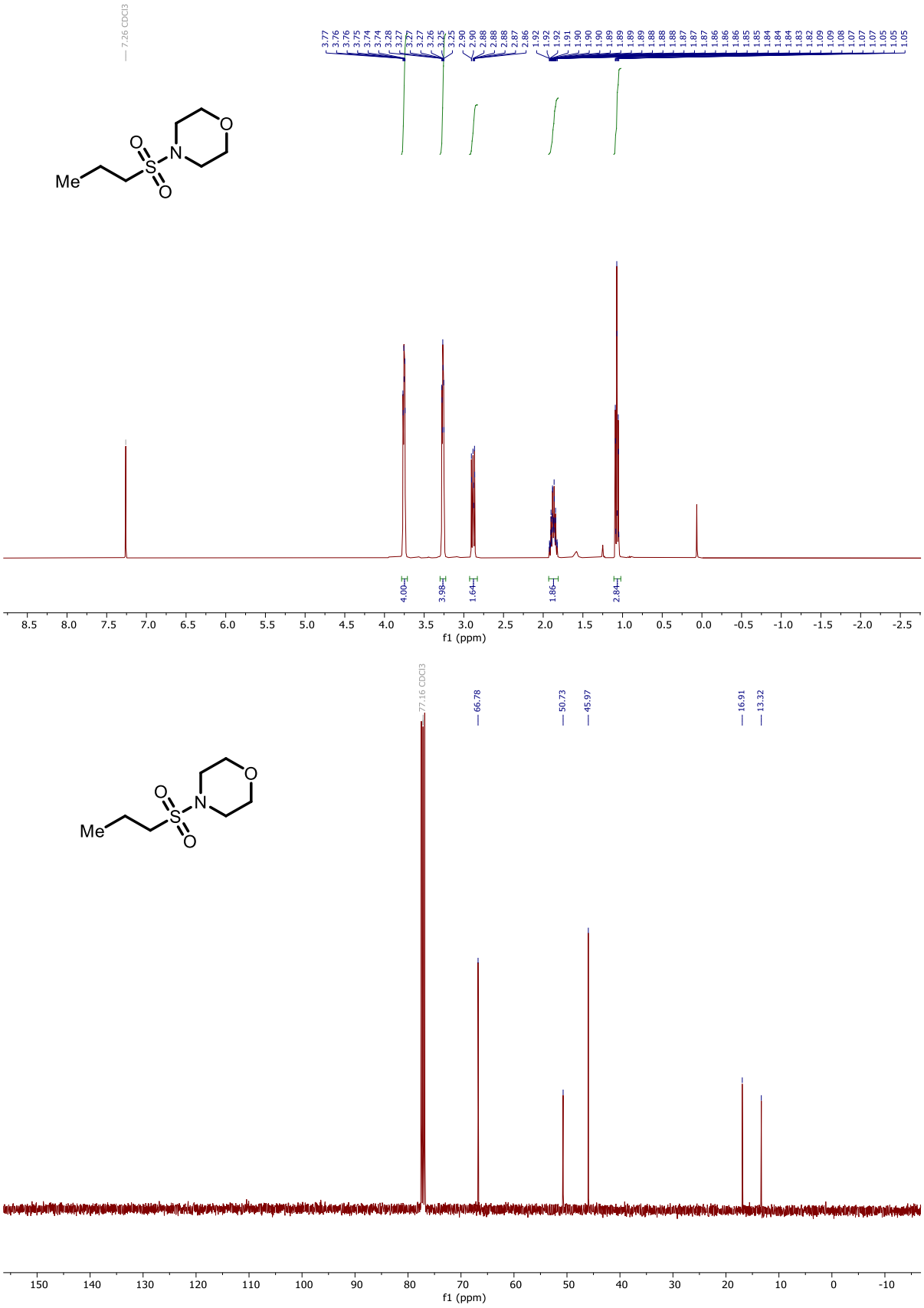
^{1}H and ^{13}C spectra of all novel compounds synthesised in Chapters 3

Ethyl 2-(*N*-phenylsulfamoyl)acetate (120b)





2-Hydroxy-*N*-phenylethane-1-sulfonamide (123a)



2-(Morpholinosulfonyl)butanal (122c)

