Rhodium(I) Catalysis for Intermolecular Alkyne Hydroacylation and Desymmetrisation

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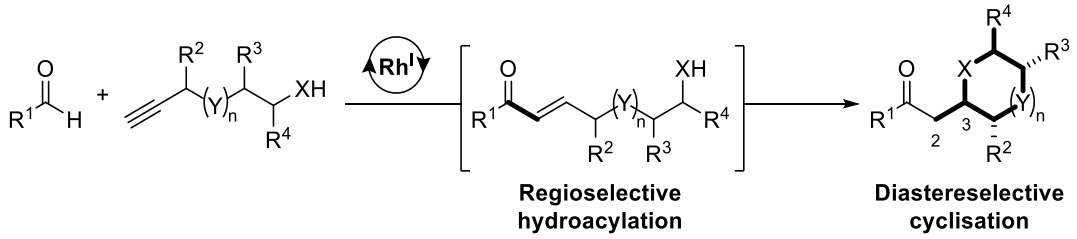
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

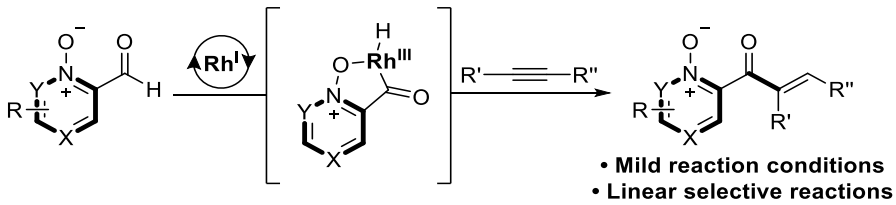
This thesis discloses the uses and development of rhodium(I) catalysis within intermolecular hydroacylation and asymmetric [2+2+2] cycloadditions.

Chapter 1 provides a general overview of the key methods and tethering strategies within the field rhodium(I) catalysed hydroacylation.

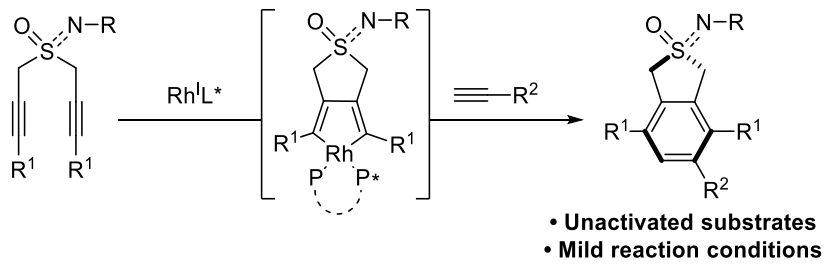
Chapter 2 describes the diverse synthesis of fully saturated *O*- and *N*-heterocycles through a hydroacylation/conjugate-addition sequence.



Chapter 3 uses azine *N*-oxides as novel directing groups for aldehyde C–H activation within intermolecular hydroacylation reactions.



Chapter 4 presents a short field overview of rhodium(I) catalysed [2+2+2] cycloaddition, before applying this reaction to sulfoximine desymmetrisation.



Declaration

I declare that the work in this thesis had not been previously submitted for a degree at the university of Oxford or any other higher education institution.

The work within Chapter 2 represents a section of a recent publication in *Chemical Science* (2022) which is co-first authored with Dr Ndidi U. Iwumene, a previous DPhil student in the Willis group. All characterisation data for this chapter is my own work, and the initial experimental work carried out by Dr Ndidi U. Iwumene is stated where appropriate. The X-ray crystallographic structures shown in this chapter were obtained by Dr Antoine de Gombert, another previous DPhil student in the Willis group.

The experimental work in Chapter 3 was carried out in collaboration with Dr Jagadeesh Kalepu, a former postdoctoral researcher in the Willis group. The work for this chapter has also been published in *Chemical Science* (2021). The experiments and procedures performed by Dr Jagadeesh Kalepu are clearly labelled within chapter 3 and the experimental section.

The experimental work in Chapter 4 was not carried out collaboratively. All results and characterisation data seen in this chapter are my own work.

Daniel F Moseley

2022

Acknowledgements

I cannot quite believe that I have made it the point where I am sat here writing my acknowledgements. It has been wild journey, one that I could not have done without the encouragement and support of others.

I would firstly like to thank Mike for being a consistently excellent supervisor; his wisdom, precision and most importantly patience has provided me with the best support that any DPhil student could possibly ask for. I like to think my Swern technique is strong now.

And then there are the many group members I have had the privilege of spending my time with. My first thanks go to Rob for daddying me through my first hydroacylations and always maintaining a chilled atmosphere in F1. I also thank Rita for sharing her rhodium knowledge and for a being a great OG sub-group buddy, good times! Also Qian-Wen, the boss of F1, for her brutal efficiency and good choice of music – columning to Ed Sheeran and John Mayer was always a pleasure. A special thanks to the legend, also known as (aka) Tilby, you always bought such an energetic vibe to the lab and knew how to have a good laugh even during the more stressful times. Antoine, what can I say… we had some brilliant times together, listening to Cake, Eminem and 'She's so heavy'. You were a great F1 pal and I wish you all the best mate. I also thank the good times spent with my permanent desk buddy, Janette. You always bought such a healthy balance to life in the lab and so I thank you for that. Also, see you at Truck! To the current F1 boys, the lads, the legends, the myths – Jonny, Ivan the beast, Ben, Charlie and Russell, thank you for some truly excellent times in and out of the labs, including horse-box coffee breaks and lunch trips to the 'holy trinity' (a delicious jacket potato meal with

a triple filling of hot baked beans, tuna and cheese topping). To the rest of the postdocs, Thomas, Loïc, Nick, Damien and Jagadeesh and Zexin, a huge thanks to all of you for maintaining the fun, yet hard-working atmosphere that makes the Willis group special. A particular thanks to Jagadeesh for being an excellent friend, and his highly motivating statements like, 'You can do it Daaaaaan'. Xinlan, Ndidi, Nicoleta and May, you all bought such a positive and levelled attitude to work and were always a great pleasure to chat to! Additional thanks to Charlie Bell for your encyclopedic chemistry knowledge, and your invaluable help with the chiral HPLC; I would have been lost without it! To the rest of F2; Mingyan, Mingkai and Di, you guys have always been a delight to chat with and I wish you all the very best with your DPhils.

A huge thanks also goes to Claudio, Reto and their colleagues at Novartis, alongside all the amazing people I met in Muttenz. You gave me such a fantastic placement experience that I will never forget.

Helena, it has been wonderful to share some great times with you over the last four years, and I thank you for providing me with a smile when times were tough.

To my parents and family, thank you so much for always supporting my decisions, and giving me the freedom to pursue the things that make me happy. Like running, you taught me that life can have many different avenues if you search hard enough for them.

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Abbreviations

Ac	acetyl
app.	apparent
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad
bs	broad singlet
Bu	*n*-butyl
°C	degrees Celcius
cat.	catalyst
COD	1,5-cyclooctadiene
conc.	concentrated
Cy	cyclohexyl
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dcpe	1,2-bis(dicyclohexylphosphino)ethane
dcpm	bis(dicyclohexylphosphino)methane

DIBAL	diisobutylaluminium
DM	dimethyl
DMF	dimethylformamide
DCEPhos	bis(dicyclohexylphosphinophenyl)ether
DPEPhos	bis((2-diphenylphosphino)phenyl) ether
dppb	1,4-butylenebis(diphenylphosphine)
dppbenz	*o*-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
et al.	et alii (Latin: and others)
FT	fourier transform
g	gram(s)
h	hour(s)

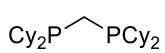
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
J	coupling constant (Hz)
L	ligand or litre
L*	chiral ligand
LRMS	low resolution mass spectrometry
m-	meta
m	multiplet
M	metal or molar concentration
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Me-Duphos	1,2-bis(2,5-dimethylphopholano)benzene
min	minute(s)
mol	mole(s)
m.p.	melting point
MS	mass spectroscopy
m/z	mass to charge ratio
nbd	norbornadiene
NBS	N-bromosuccinimide

NMR	nuclear magnetic resonance
o	ortho
Oct	*n*-octyl
p	Para
p-tolyl BINAP	2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
Pent	*n*-pentyl
PG	protecting group
Ph	phenyl
ppm	parts per million
Pr	*n*-propyl
q	quartet
R	generic group/substituent
rac	racemic
rt	room temperature
s	singlet
sat.	saturated
SEGPHOS	5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SynPhos	6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin
t	triplet

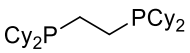
t-Bu	*tert*-butyl
TBAB	tetra-butyl ammonium bromide
TES	triethylsilane
Tf	trifluoromethanesulfonic/triflic
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilane
TPS	triphenylsilane
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
3,5-xyl-MeOBIPHEP	2,2′-bis[bis(3,5-dimethyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl
3,5-t-Bu-MeOBIPHEP	2,2′-bis[bis(3,5-di-tert-butyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl
δ	chemical shift (ppm)
ν_{max}	infrared absorption maximum

Ligands and Chemical Structures

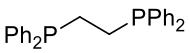
Achiral Ligands



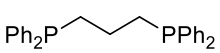
dcpm



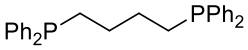
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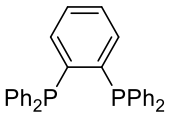
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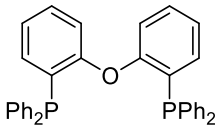
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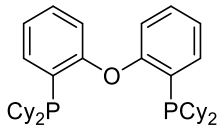
dppb



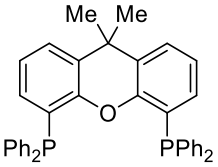
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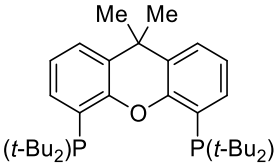
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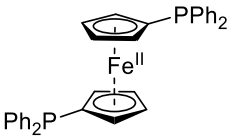
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XantPhos

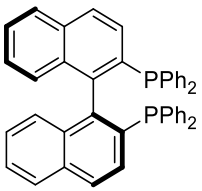


***t*-Bu-XantPhos**

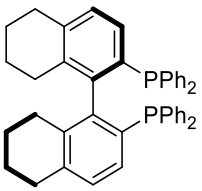


dppf

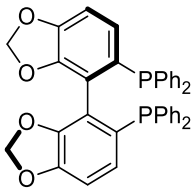
Chiral Ligands



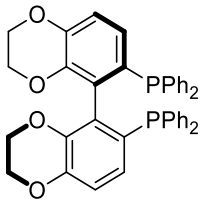
(*S*)-BINAP



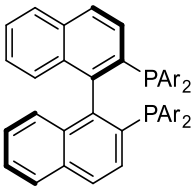
(*R*)-H$_8$-BINAP

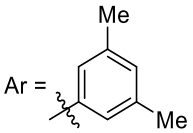


(*R*)-SEGPHOS

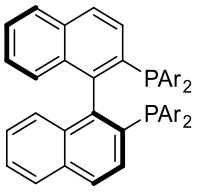


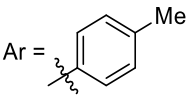
(*R*)-SynPhos



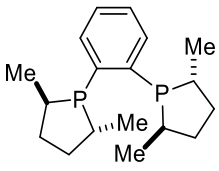


(*R*)-DM-BINAP

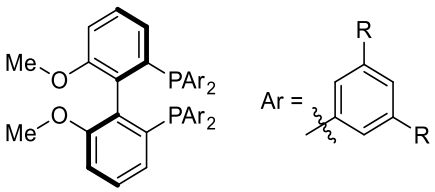




(*S*)-*p*-Tol-BINAP



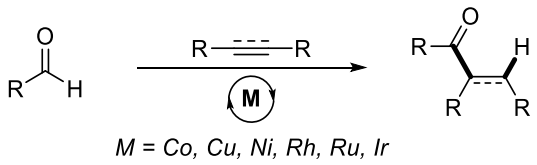
(*R*,*R*)-Me-DuPhos



(*R*)-3,5-Xyl-MeOBIPHEP, R = Me
(*R*)-3,5-*t*-Bu-MeOBIPHEP, R = *t*-Bu

Chapter 1 – An Introduction to Rhodium(I) – catalysed C–C π-bond Hydroacylation

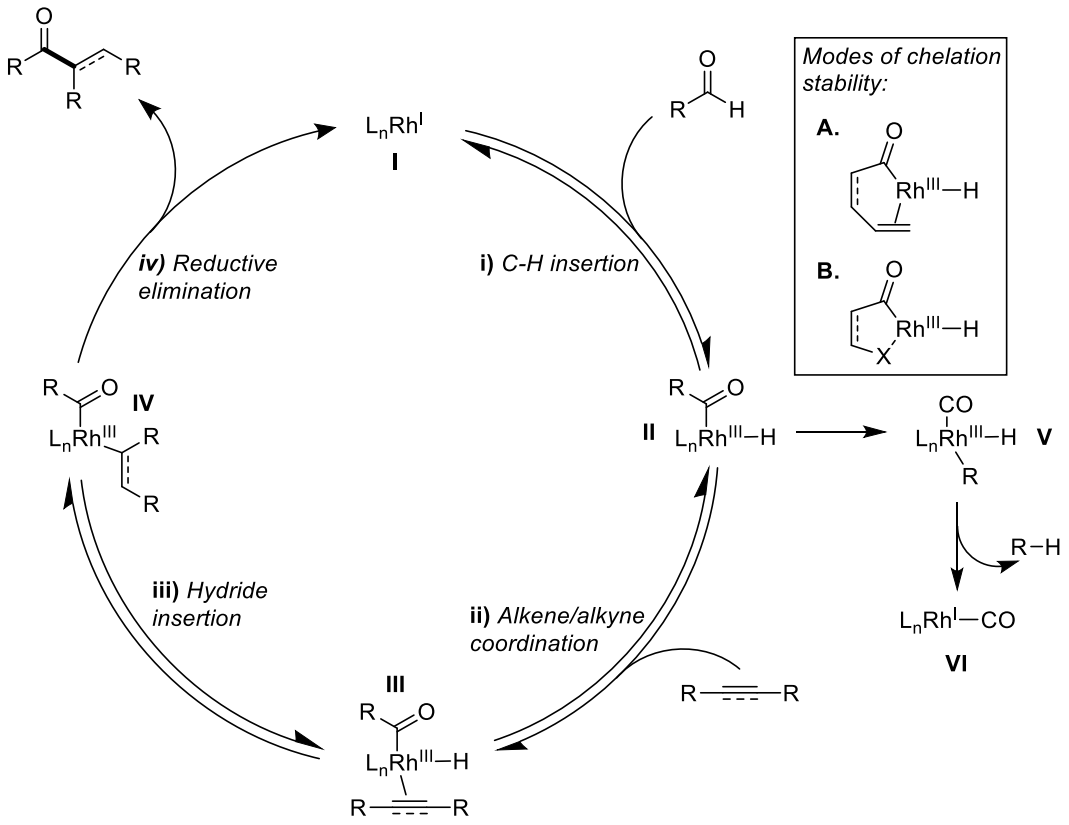
Transition metal-catalysed C–H activation chemistry has emerged as a comprehensive tool in modern synthesis.[1] The ability of these reactions to mitigate the requirement for more complex coupling agents has yielded a strong application to C–C bond forming processes.[2] One example is the hydroacylation of alkenes and alkynes; a highly atom-efficient method towards ketone and enone synthesis.[3] Where some methods show that substrates such as carboxylic acids,[4] anhydrides[5] and acid chlorides[6] can be used in hydroacylation, methods that involve C–H activation typically employ aldehyde substrates. Hydroacylation reactions using aldehydes are formally defined as the addition of a formyl C–H bond across a C–C π-bond, with initiation occurring by aldehyde oxidative C–H bond insertion (**Scheme 1.1**).



Scheme 1.1. A general reaction scheme for the transition metal-catalysed hydroacylation of C–C π-bonds.

Since its original discovery by Sakai, in 1972,[7] accelerating popularity has led to a greater knowledge of the catalyst and substrate properties necessary to circumvent the accompanying issues of regioselectivity and decarbonylation. A range of catalysts are known to successfully perform hydroacylation based on the following metals: Co,[8] Cu,[4, 5b] Ni,[9] Rh,[10] Ru[11] and Ir.[12] Out of these, rhodium catalysts have been studied most extensively.[3g, 13] Accordingly, this chapter will discuss current

and new hydroacylation methods associated with rhodium catalysis. To date, a series of key mechanistic findings have led to a greater understanding of this field. The first of these was the earliest known isolation of the acylrhodium(III) hydride intermediate from Wilkinson's catalyst by Suggs in 1978.[13d] Other key intermediates were unveiled in a collection of accounts by Milstein[13c, 14] that highlighted the formation of air-stable *cis*-acyl hydride complexes from pent-4-enone hydroacylation with $RhCl(PMe_3)_3$. Cationic Rh(I)-bisphosphines have also been studied mechanistically by Wills and Weller.[15] These accumulated findings have led to a general catalytic cycle (**Scheme 1.2**).

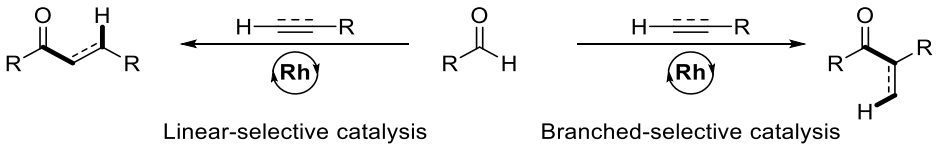


Scheme 1.2. The commonly accepted mechanism for rhodium-catalysed hydroacylation of alkenes and alkynes.

As illustrated, the reaction proceeds *via* an oxidative formyl C–H insertion by Rh(I)-bisphosphine complex **I**, generating Rh(III)-acyl hydride intermediate **II**.

Alkene/alkyne coordination then follows to give intermediate **III**. Subsequent 1,2-insertion leads to Rh(III)-acyl intermediate **IV**, and then reductive elimination is the C–C bond forming step that generates the desired ketone/enone whilst regenerating Rh(I) species **I**.

The absence of chelation within intermediate **II** can lead to a competing migratory elimination process, known as reductive decarbonylation.[3e, 15a, 15c, 16] Carbonyl deinsertion from species **II** will give intermediate **V** which rapidly undergoes reductive elimination to generate the inactive Rh(I)-CO species **VI**, prohibiting catalytic turnover. For an intramolecular process, chelation stability within intermediate **II** is gained through participating coordination from the alkene/alkyne contained within the substrate (**Scheme 1.2**, **A**). However, the intermolecular process normally requires a coordinating atom on the aldehyde to offer a similar degree of chelation stability (**Scheme 1.2**, **B**). Regioselectivity is also a factor to consider (**Scheme 1.3**).

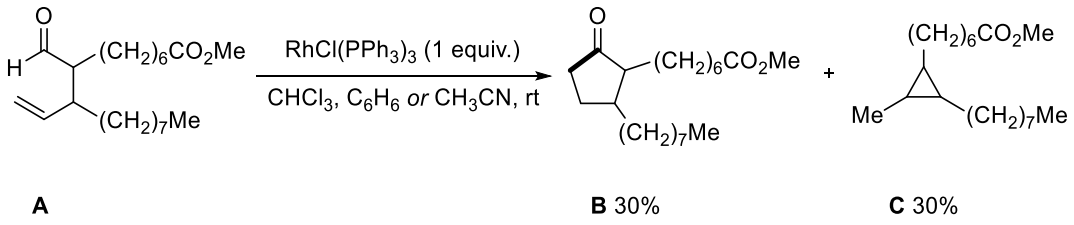


Scheme 1.3. Two possible regioisomers can be formed from the hydroacylation of unsymmetrical alkenes/alkynes.

If the unsaturated group that coordinates to the rhodium atom is unsymmetrical, then hydride insertion and reductive elimination will produce a set of regioisomers. Although good reaction selectivity can be harder to obtain with internal substrates, selectivity for the linear isomer is normally well-defined when terminal alkynes/alkenes are used. However, a switch in selectivity for the branched isomer can be engineered through ligand[3e, 17] or substrate design.[3f, 18]

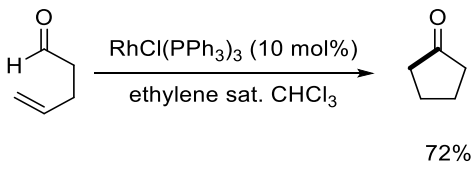
1.1 Intramolecular Rhodium-catalysed Hydroacylation Methods

The pioneering work in the field of hydroacylation was reported by Sakai in 1972,[7] as a novel strategy towards the formation of 9-oxoprostanoate, a natural substance belonging to a family of biologically active C_{20}-acid derivatives known as the prostaglandins.[19] Cyclisation of pent-4-ene-1-al **A** to 9-oxoprostanoate **B** was accomplished in presence of stoichiometric Wilkinson's catalyst at room temperature (**Scheme 1.4**). Despite their achievement, the authors observed an equimolar quantity of cyclopropane derivative **C**, a side product presumed to be the result of reductive decarbonylation.



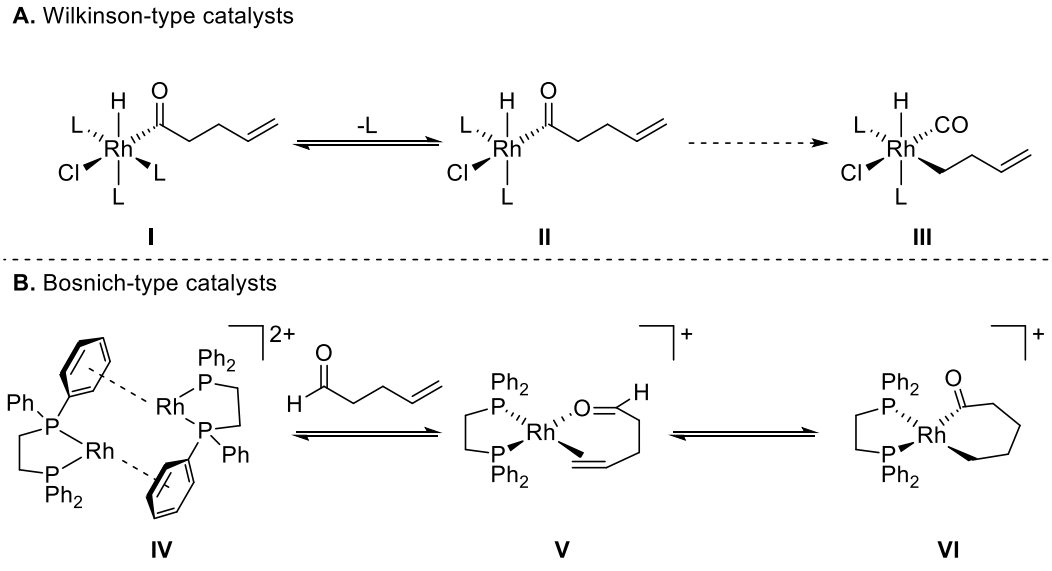
Scheme 1.4. Sakai's seminal report of alkene hydroacylation towards 9-oxoprostanoate.

Miller later proposed that the formation of this undesired side product was likely to be due to a vacant metal coordination site in a key catalytic intermediate.[20] The authors thus performed the same intramolecular cyclisation in presence of ethylene saturated $CHCl_3$ (**Scheme 1.5**). This resulted in a staggering reactivity increase towards the favoured hydroacylation product, which was obtained in 72% yield, using only a 10 mol% loading of Wilkinson's catalyst.



Scheme 1.5. Miller's use of ethylene saturation in cyclopentanone formation.

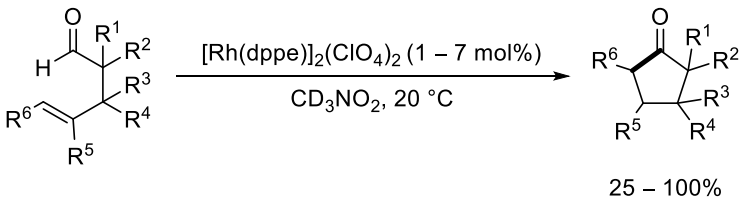
Larock later used this ethylene saturation technique to explore a range of *in situ* prepared Wilkinson-type catalysts constructed from $[Rh(COD)Cl]_2$ and a variety of monodentate phosphines.[21] Despite broadening the scope of cyclopentanones formed, the fundamental problem of decarbonylation consequentially led to low catalytic turnover. The issues that lied with these earlier catalysts could be rationalised by fundamental mechanistic details. Milstein had previously revealed that ligand exchange occurs after oxidative addition to permit olefin uptake (**Scheme 1.6A**).[14a] This process forms an acylrhodium(III)-hydride intermediate containing a vacant coordination site (**II**), which can readily undergo decarbonylation to intermediate **III**. The charge neutrality of these complexes also slows alkene coordination. In 1988, Bosnich designed a coordinatively unsaturated and cationic rhodium(I) phenyl-bridged dimer complex **IV** (**Scheme 1.6B**) that minimised decarbonylation issues.[22]



Scheme 1.6. A. and **B.** Mechanistic comparison between Wilkinson and Bosnich-type catalysts.

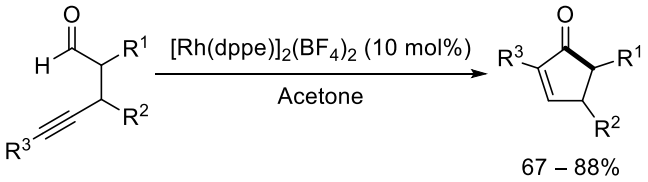
The coordinative unsaturation allows the alkene to rapidly coordinate to the metal, providing better chelation stability within the acylrhodium(III) intermediates. The

net positive charge of the complex increases the alkenes binding affinity. Alkenal addition to the dimer forms chelated complex **V**, where the proximal assistance of the rhodium-bound olefin accelerates the rate of C–H activation, and perfectly aligns the metal-hydride bond, for subsequent hydride insertion. The formed complex **VI** rapidly undergoes reductive elimination due to its coordinative unsaturation.[22a] These new catalysts permitted clean reactivity, providing yields of up to 100% for the cyclisation (**Scheme 1.7**). More importantly, even examples that showed low catalytic turnover did not lead to significant decarbonylation at 20 °C.



Scheme 1.7. Bosnich's reaction scope.

The synthesis of enantioenriched cyclopentanones was later explored by James[23] and Dong[13a, 24] through kinetic resolution[23,24] and desymmetrisation[13a] processes. The Bosnich catalysts have also been exploited in an intramolecular alkyne hydroacylation by Fu, in 2001,[3h] to synthesise a range of cyclopentenones (**Scheme 1.8**), where they served as a versatile alternative to Pauson-Khand methods.[25]

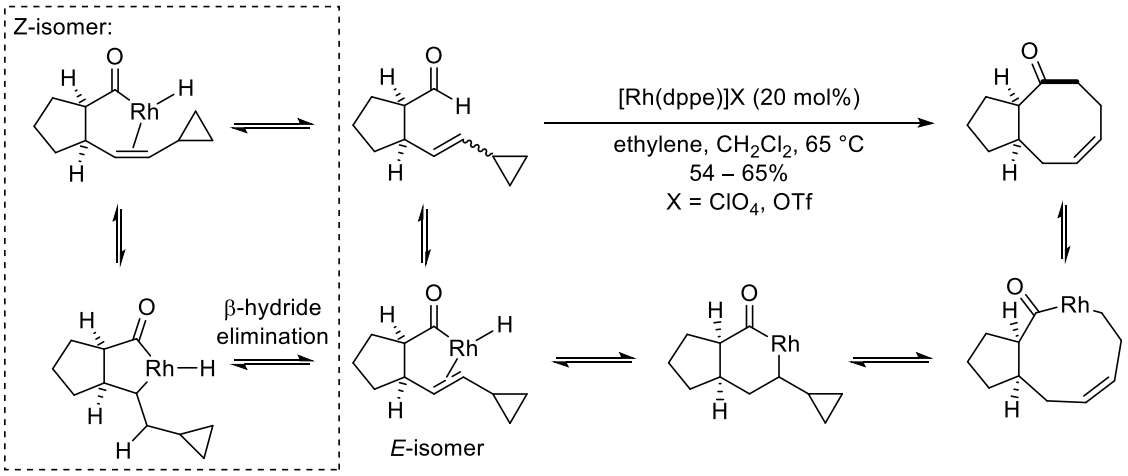


Scheme 1.8. Fu's hydroacylation cyclisation of alkynals.

The unusual *trans* addition of the Rh-hydride to the β-position of the cyclopentenone was confirmed to be an intramolecular process by deuterium labelling, where the hydride was transferred directly from the aldehyde C–H (C–D) bond. Fu later

extended this methodology to the asymmetric synthesis of chiral cyclopentenones through kinetic resolution processes.[26]

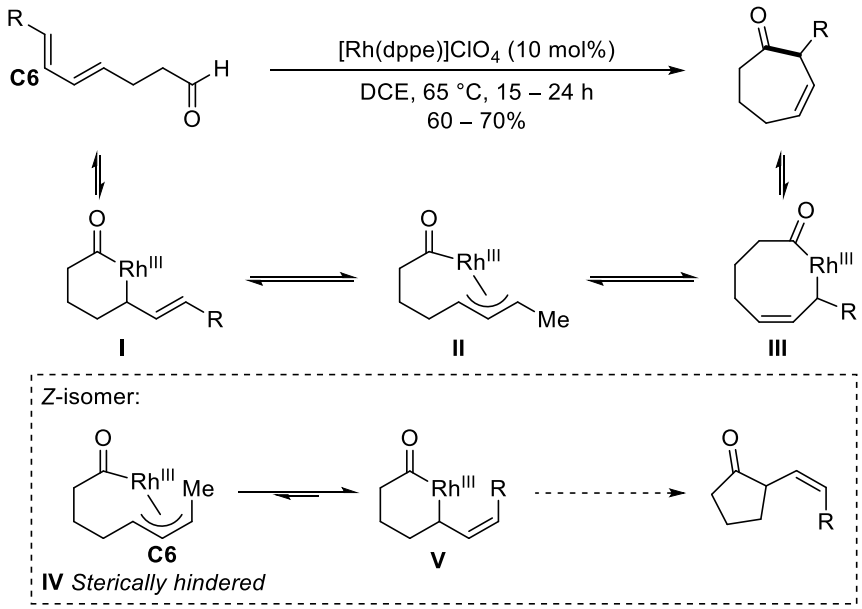
Desired intramolecular reactivity with longer chain alkenals, to generate medium-sized rings, is problematic as the catalytic intermediates are less well stabilised by chelation[27] leading to decarbonylation. In 2000, Shair reported the use of alkenals that contain a strained cyclopropane group to access 8-membered ketones (**Scheme 1.9**).[28]



Scheme 1.9. Shair's strain release methods to synthesise medium-sized cyclic ketones.

Their substrate model allowed oxidative addition and hydride insertion to form a 6-membered rhodacycle, analogous to traditional methods. Fragmentation of this intermediate then followed *via* a β-carbon elimination and reductive elimination to generate the product. Their deuterium labelling study concluded that the *E*-isomer was necessary for product formation, and the sterically compromised *Z*-isomer underwent isomerisation before proceeding in the cycle. Another fragmentation method was developed by Aissa[29] in 2010, where strain release from 4-membered ring systems was the driving force of the reaction to form 8 membered ring systems *via* hydroacylation.

Hydroacylation towards cycloheptanones from the intramolecular cyclisation of 4,6-dienals has additionally been reported by Mori in 2002 (**Scheme 1.10**).[30] The authors proposed that if the rhodium(III)-carbon bond in the forming 6-membered rhodacycle **I** is in conjugation with a proximal olefin, then ring expansion through a rhodium-π-allyl complex **II** should permit the formation of 8-membered rhodacycle **III**. Subsequent reductive elimination would lead to the formation of a 7-membered ketone product. A similar concept was later used as part of a hydroacylation/cycloisomerisation cascade, to form a 7,5-bicycle within the natural product (±)-epiglobulol.[31] Although the reasoning is not completely clear, the *E*-configuration at C6 (**Scheme 1.10**) was thought to be essential in driving the position of equilibrium from rhodium-π-allyl intermediate **II** to the cycloheptanone product. In contrast, when using the C6-*Z* isomer the disfavoured steric interaction within the rhodium-π-allyl intermediate **IV** alters the equilibrium position towards six-membered rhodacycle **V**, alternatively leading to a cyclopentanone product.

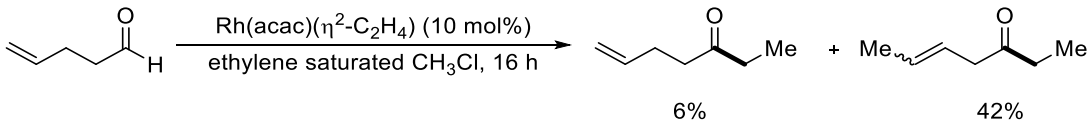


Scheme 1.10. Mori's dienal substrates in a hydroacylation/ring expansion sequence to generate medium-sized rings.

The intramolecular hydroacylation reaction has revolutionised rhodium(I) catalysis by showing that complex rings of varied size can be accessed with reasonable loadings of catalysts which are specifically tailored to prevent reductive decarbonylation. Nonetheless, the reactions normally require specific, complex substrate architectures, which limits the freedom to perform these reactions as part of a longer synthetic sequence. The inherent lack of modularity in these reactions also minimises product diversity. The next section delves into its intermolecular counterpart, showing specific attempts to simplify and diversify the hydroacylation reaction.

1.2 Intermolecular Rhodium-catalysed Hydroacylation Methods and Chelation-based Strategies

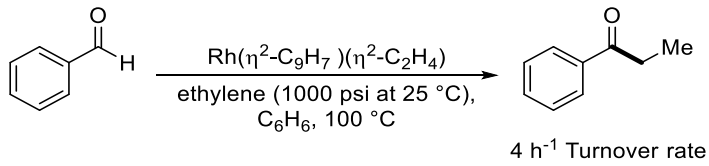
Intermolecular hydroacylation has emerged as a synthetically useful, highly modular strategy to construct a versatile range of ketone and enone building blocks. It was first observed during Miller's work with ethylene saturated $CHCl_3$ systems. Using 2,4-pentanedionatobis(ethylene)rhodium(I) as the catalyst afforded a hydroacylation product in 6% yield, alongside a double bond migration product in 42% yield (**Scheme 1.11**).



Scheme 1.11. Miller's seminal work on intermolecular ethylene hydroacylation.

Milstein made a further contribution to this finding, in 1988, by realising that the desired reactivity could be dramatically increased by using benzaldehydes with extreme partial pressures of ethylene (**Scheme 1.12**).[32] Despite the success of

Milstein's efforts, the method was limited to ethylene, which binds to metals more strongly that substituted olefins.[33]



Scheme 1.12. Milstein's approached to coordinative saturation in ethylene hydroacylation.

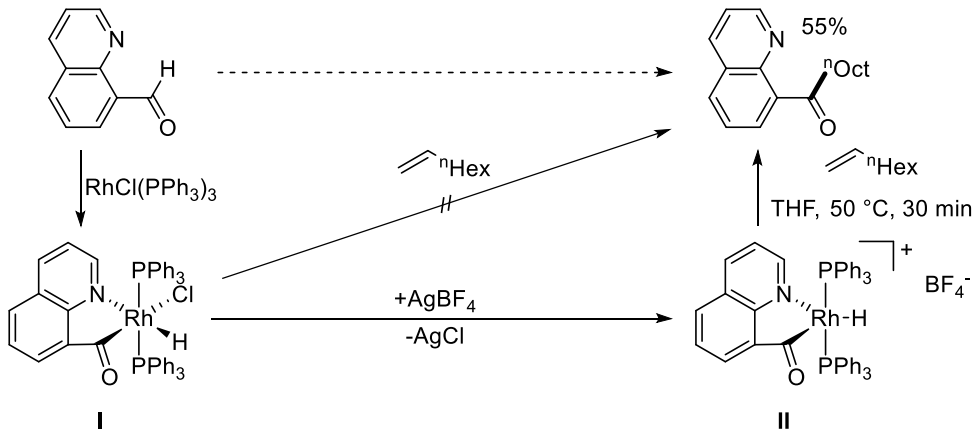
The harsh conditions described by Milstein can be rationalised by the inevitable entropic cost that arises from bringing the separate coupling partners together during an intermolecular process. This effect prohibits the hydroacylation of more intricate alkenes and alkynes that are less reactive due to sterics. The resulting desaturation at the metal centre can further lead to decarbonylation pathways. Another issue that develops in the intermolecular process is regioselectivity, as the orientation of the coordinating unsaturated bond is seldom restricted by a chelated intermediate.

The following sections report how chelation strategies that employ β-tethered aldehydes[15e, 34, 35, 3b, 13d, 36, 37] containing *N*-, *P*-, *O*- and *S*-coordinating groups, capable of forming stable 5- and 6-membered chelated acyl hydride intermediates,[34b, 37b] have revolutionised intermolecular reactions for simple, unactivated substrates by combatting challenges of reactivity, decarbonylation and regioselectivity.

1.2.1 *N*-coordinating Aldehydes

N-tethered aldehydes were initially used as substrates by Suggs, in 1978,[13d] during an attempt to find precedent for the existence of a rhodium(III)acyl hydride species. He postulated that quinoline-8-carboxaldehyde should provide a stable acyl hydride intermediate after formyl C–H activation, through the formation of a 5-membered

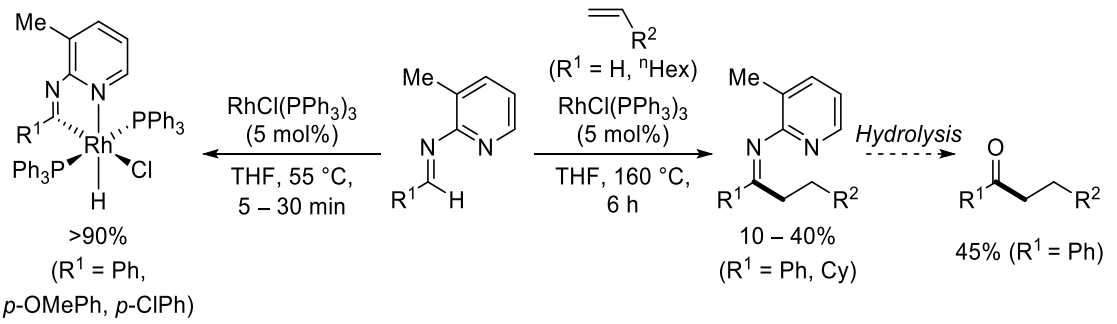
chelate. They were pleased to form a stable 6-coordinate species **I**, when subjecting the aldehyde to Wilkinson's catalyst (**Scheme 1.13**).



Scheme 1.13. Sugg's discovery of *N*-chelating groups for hydroacylation.

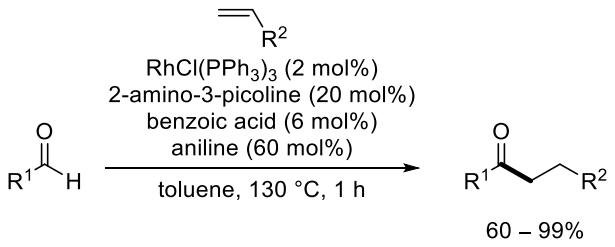
On its own, species **I** did not promote hydroacylation. However, chloride abstraction with $AgBF_4$ yielded a coordinatively unsaturated cationic complex **II**, where the vacant metal site enabled rapid alkene coordination. Accordingly, treatment of a THF solution of intermediate **II** with excess 1-octene at 50 °C gave 55% of the desired *n*-octanyl ketone. Although an excellent a proof of concept, the reaction was currently limited to aldehydes containing the specific architecture of Suggs' newly found 8-quinoline tether. To solve this issue, he utilised 3-methyl-2-amino-picolines to form traceless aldimine reagents, making the reaction applicable to a wider range of aldehyde precursors (**Scheme 1.14**).[38] The formation of air stable rhodacycle, from aldimine C–H scission, was favoured at 55 °C in THF. However, the full hydroacylation reaction required significantly elevated temperatures (of 160 °C). They additionally reported that the picoline group in the hydroacylation product could be removed *via* hydrolysis on moist silica gel to liberate the corresponding ketone. Although this method makes the reaction applicable to a wider range of

aldehydes, pre-forming the aldimine reagent prior to hydroacylation is still a limiting requirement.



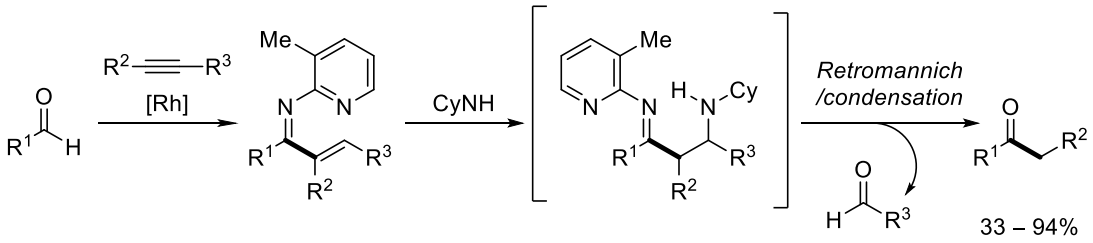
Scheme 1.14. Aldimine substrates that form chelated intermediates within intermolecular alkene hydroacylation.

In 1997, Jun and Lee opened this method to the direct consumption of commercial aldehydes, by demonstrating that the aldimine group could be generated and removed *in situ* to give the product as a ketone in one step from the aldehyde.[3c, 39] A similar catalytic process could also accommodate primary alcohols as substrates, whereby the aldehyde is formed *in situ* through transfer dehydrogentation.[40] They also realised, in a later study, that the rate of the aldimine formation could be increased when the condensation was catalysed by benzoic acid. From this, they deduced that the condensation step may be rate limiting; this prompted the utility of aniline as an additive (**Scheme 1.15**).[36a] This lowered the barrier of aldimine formation, through a transimination process.



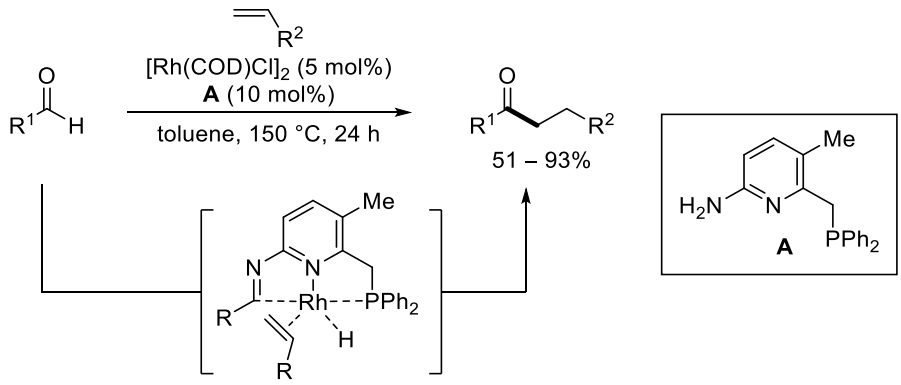
Scheme 1.15. Direct use of unactivated aldehydes within hydroacylation, through *in situ* aldimine formation.

They later demonstrated how microwave irradiation could facilitate this reversible aldimine process for alkene hydroacylation in absence of reaction solvent.[41] An alkyne hydroacylation could also be performed, in absence of aniline, on a variety of alkyl and aryl groups on aldehyde and alkene coupling components.[42] They later treated the formed enones from the alkyne hydroacylation as a synthetic handle for a retro-Mannich transformation, within a stepwise triple bond cleavage process (**Scheme 1.16**).[43]



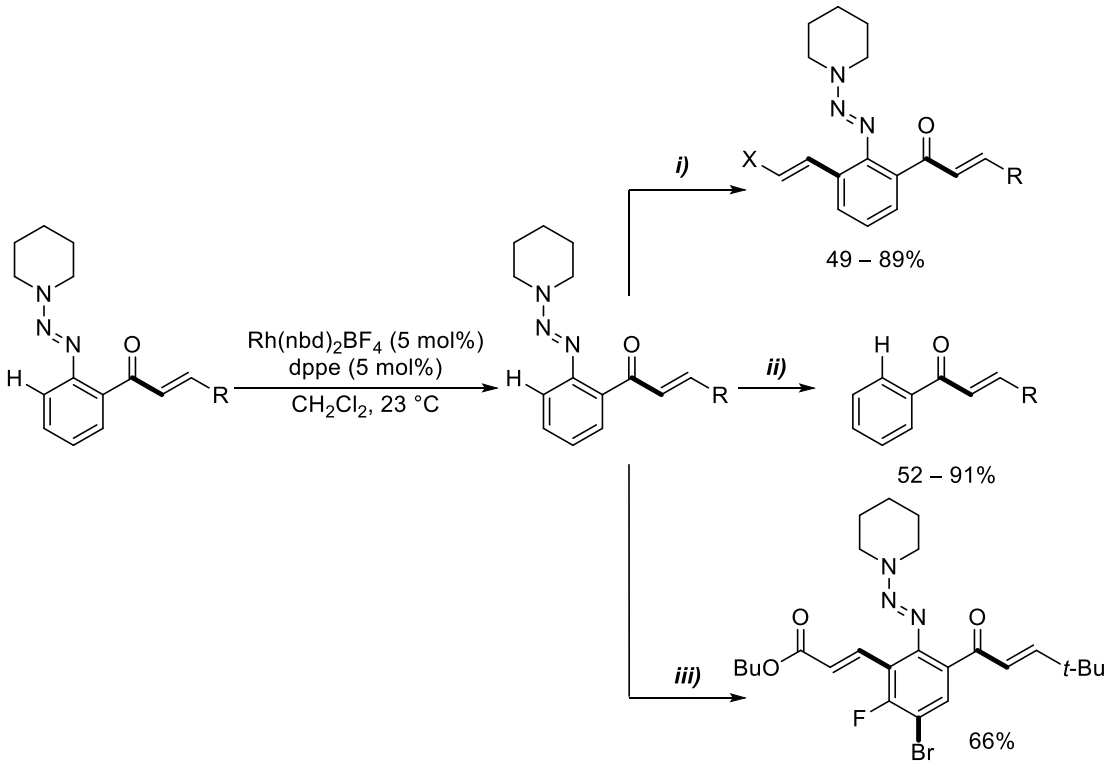
Scheme 1.16. *In situ* aldimine formation for the stepwise cleavage of alkynes, using hydroacylation and retro-Mannich transformations.

One drawback of the aminopicoline tethering strategy used by Jun and Lee is the requirement for a large amount of individual reaction components. To overcome this complexity, Breit developed a multifunctional *co*-catalyst (**A**), containing a pendant phosphine group (**Scheme 1.17**).[13b] His newly designed bifunctional catalyst not only accounted for the reversible directing properties of Jun and Lee's design, but also activated the rhodium catalyst through additional phosphine coordination, leading to a less demanding C–H activation step.



Scheme 1.17. Breit's aminopicoline-derived multi-functional *co*-catalyst for intermolecular alkene hydroacylation.

The main limitation with the aforementioned methods is the invariably high temperatures required for the desired reactivity. Several accounts by Willis demonstrate the use of new *N*-tethering groups that do not require the use of harsh conditions. The first employs aminobenzaldehydes, showing how such a medicinally relevant framework[44] could facilitate excellent hydroacylation reactivity.[3a] The second group is the enamine,[45] a key functional group abundant within many small molecules and natural products.[46] A third is the aryltriazene; not only are these multi-functional groups capable of activating C–H positions,[47] their electron-rich nature enables them to readily undergo electrophilic aromatic substitution. Other benefits include the ease of their removal,[48] and conversion to many functional groups.[49] Our laboratory decided to exploit 2-triazenyl benzaldehydes in a set of sequential catalytic methods that feature alkyne hydroacylation at the core (**Scheme 1.18**).[36b]



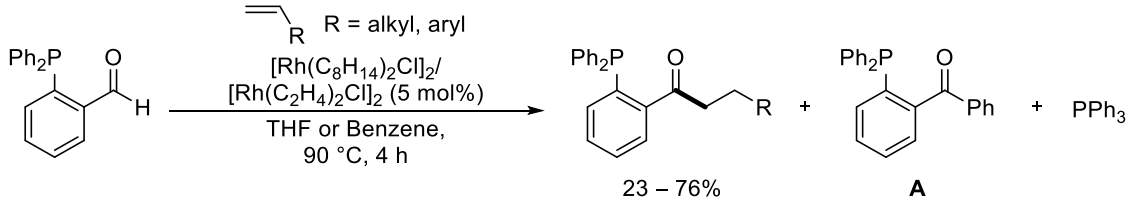
Scheme 1.18. Showing the sequential catalytic transformations performed by 2-triazenyl benzaldehydes; i) C–H alkenylation using $[Rh^{III}Cp^*Cl_2]_2$, $Cu(OAc)_2 \cdot H_2O$ and alkene; ii) reductive triazene removal using $BF_3 \cdot OEt_2$ or TfOH; iii) A hydroacylation/alkenylation/bromination sequence - bromination using NBS.

The hydroacylation was successful and could be carried out in tandem to Rh^{III}-catalysed *ortho*-C–H alkenylations and brominations. The hydroacylation reaction could also be followed by removal of the triazene tether, using $BF_3 \cdot OEt_2$ or TfOH.

1.2.2 *P*-coordinating Aldehydes

Jun and Lee developed phosphine tethered aldehydes as novel chelating groups for hydroacylation in 1995.[34c] The coupling of 2-(diphenylphosphino)-benzaldehyde with different vinyl derivatives, at 90 °C in THF or benzene, yielded a mixture of different results (**Scheme 1.19**). Alkyl substituted olefins provided clean conversion to the linear hydroacylation product, with no observable branched regioisomer. However, significant portions of accompanying products, triphenylphosphine and

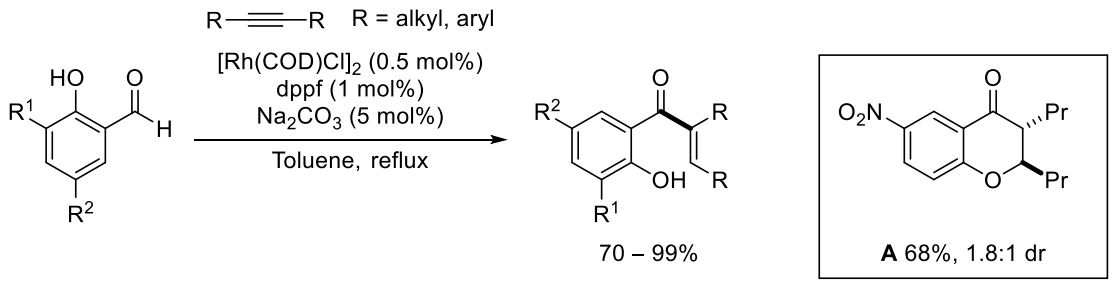
biaryl ketone **A**, were detected in reactions with aryl olefins. Whilst triphenylphosphine resulted from the basic decarbonylation process, biaryl ketone **A** formed from a P–C dissociative aryl migration, from phosphorus to the Rh-centre. This side reaction, alongside phosphine oxidation issues within starting materials and products, highlights the severe limitations on using phosphine tethered aldehydes in hydroacylation.



Scheme 1.19. Jun and Lee's alkene hydroacylation using 2-(diphenylphosphino)-benzaldehyde.

1.2.3 *O*-coordinating Aldehydes

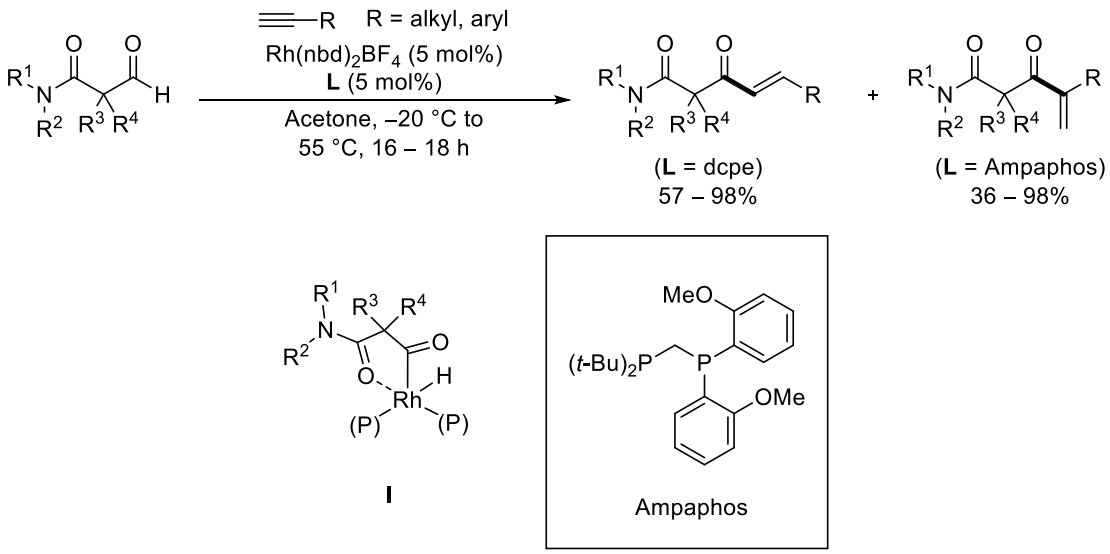
Of the *O*-coordinating substrates used in hydroacylation, salicaldehyde-derived aldehydes are the most widely used.[50, 18b, 18c, 35a, 51] The hydroxyl groups already contained within these aldehydes prevents the need for supplementary tether installation. Their clear potential as effective anchors in Pd-catalysed C–H activation[13e] lead to the earliest accounts of hydroacylation, by Miura, in 1997 and 1999.[35a, 51] Both cases used $[Rh(COD)Cl]_2$ and dppf as the catalytic system for the hydroacylation of alkynes (**Scheme 1.20**).



Scheme 1.20. Miura's seminal works on alkyne hydroacylation with salicaldehydes.

The addition of Na_2CO_3 was paramount in generating the phenolate anion required for O-Rh coordination. The methods tolerated a range of alkyl and aryl substituted alkynes, although they encountered poor regioselectivity for terminal substrates. The latter work showed that a subsequent intramolecular cyclisation of the phenolate tether onto the enone within the product enabled the formation of an *anti*-diastereoisomer **A** in 1.8:1 dr.

Carbonyl groups have been well established directing groups for various C–H activations.[52] Unlike many directing groups, carbonyls are ubiquitous in natural products and other biologically active compounds.[53] Recently, β-amido aldehydes have emerged as powerful chelating substrates in hydroacylation.[3e, 15a] In 2017, Willis described the formation of beta-keto amides from regioselective hydroacylation of terminal and internal alkynes (**Scheme 1.21**).[3e]



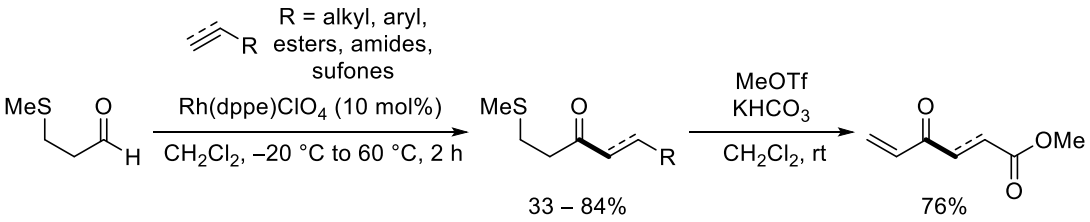
Scheme 1.21. Traceless β-amido aldehydes for intermolecular hydroacylation.

A broad scope could be achieved by combining mono- and disubstituted aldehydes containing collection of different amide groups with a wide variety of alkyne functional groups. A switch in the regioselectivity of the forming enone was

achieved through swapping the ligand from dcpe to ampaphos. Although Willis showed that this work could be extended in a highly regioselective reaction to internal amides, derivable from α-amino acids,[35b] further investigation is yet to be carried out for related amide directing groups in hydroacylation.

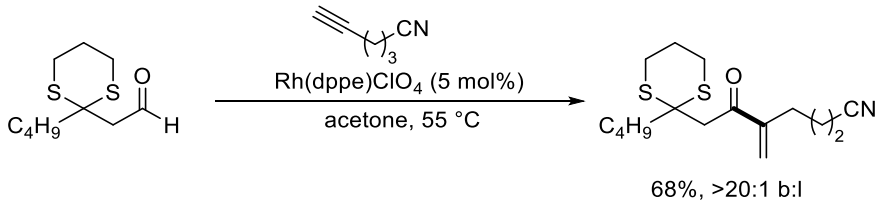
1.2.4 *S*-coordinating Aldehydes

β-*S*-tethered aldehydes have more recently been developed as a highly effective remedy to underlying decarbonylation issues. The initial discovery by Willis, in 2004, showed that simple feedstock sulfides exhibited good reactivity toward the hydroacylation of alkenes and alkynes, under mild conditions (**Scheme 1.22**). Elimination of the sulfide from the hydroacylation product using undemanding conditions could furnish the corresponding enone in 76% yield.



Scheme 1.22. A 1st generation Rh(I) catalyst for intermolecular hydroacylation with simple feedstock sulfides.

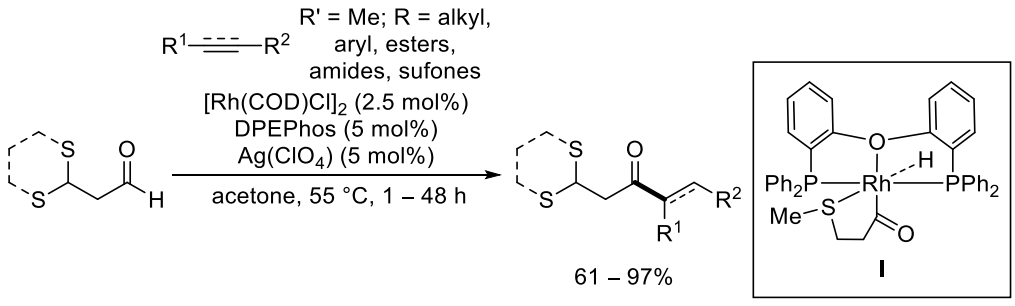
They reported that a 1st generation cationic Rh(I) catalyst, complexed with dppe ligand, was required to accelerate hydroacylation and minimise decarbonylation. They later expanded the aldehyde scope of this method to 1,3-dithianes.[18a] One particularly intriguing example was the coupling between a dithiane and a nitrile-tethered alkene, which exhibited branched regioselectivity (**Scheme 1.23**).[18a]



Scheme 1.23. A branched selective hydroacylation between a 1,3-dithiane-tethered aldehyde and a nitrile-tethered alkyne.

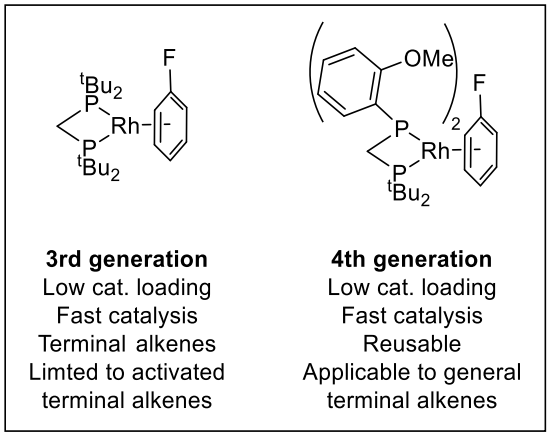
The alkene scope for these methods illustrated the tolerance of activated alkenes, including acrylate esters, arylamides, styrenes, vinyl sulfones and α-acrylate esters. Unactivated alkenes were also trialled; however low yields were observed. This outcome triggered an advent of new catalyst designs that complemented the hydroacylation of less reactive substrates.

A 2nd generation catalyst was developed by Willis and Weller to combat these issues.[37b] They reasoned that the lack of desired reactivity towards unactivated alkenes, present with the 1st generation catalyst, was due to the lability of its 5-coordinate rhodium(III)acyl hydride intermediate. They observed that complexes based on hemilabile P-O-P ligand DPEPhos permitted outstanding acyl hydride stability. This desired trait was accredited to the ligands ability to participate in a tertiary, O-Rh coordination mode (**Scheme 1.24**).



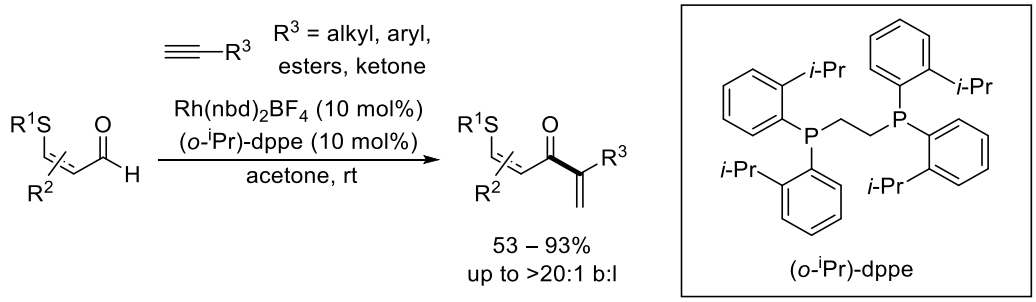
Scheme 1.24. A 2nd generation catalytic system, involving a hemilabile DPEPhos ligand, for more efficient hydroacylation reactions.

The ligand exhibited a *mer* arrangement (intermediate **I**) when stabilising the oxidative C–H insertion of a β-*S*-chelating aldehyde. Further advancements in Willis and Weller's catalytic system led to 3rd and 4th generation catalysts[16a, 54] both involving small bite-angle ligands, dtpm and ampaphos, to invoke fast reactivity towards unactivated alkenes and alkynes with β-*S*-chelating aldehydes (**Scheme 1.25**).



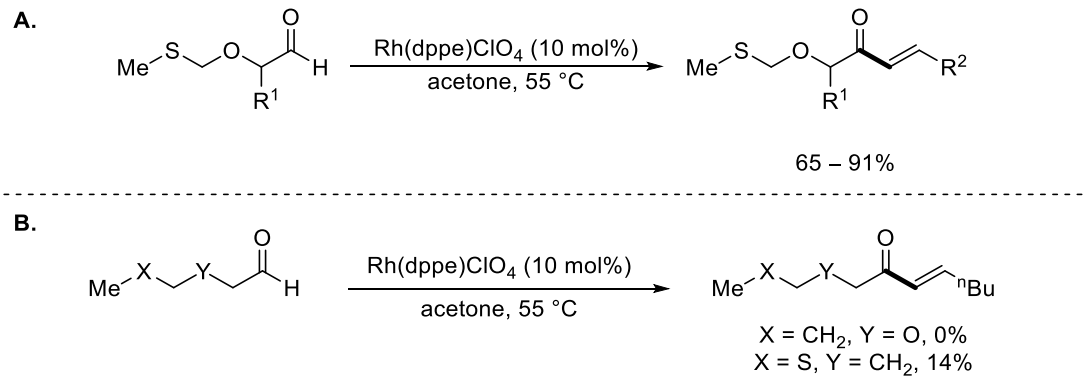
Scheme 1.25. 3rd and 4th generation Rh(I) catalysts for the hydroacylation of sterically compromised alkenes.

In 2011, Willis revealed that a structural modification within the 1st generation catalyst resulted in regioselective alkyne hydroacylation to form the branched isomer.[17] This was the first method to successfully favour branched selectivity solely from catalyst features, without additional substrate engineering. Using mild temperatures and (*o*-^{i}Pr)-dppe ligand in acetone, selectivity of up to >20:1 branched:linear could be obtained on substituted alkynes with a range of β-*S*-chelating aldehydes (**Scheme 1.26**).



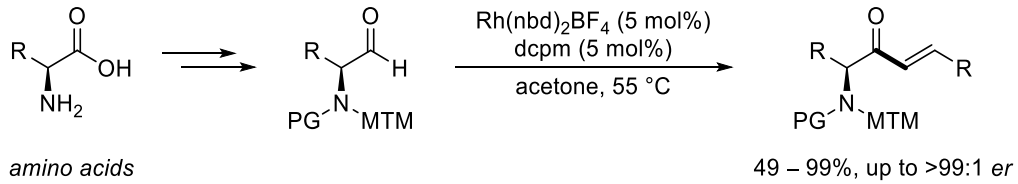
Scheme 1.26. A ligand-controlled branched regioselective alkyne hydroacylation, using β-*S*-tethered aldehydes.

Methylthiomethyl (MTM) protecting groups have proved to be effective for intermolecular hydroacylation reactions.[3d, 55] Alongside serving as excellent directing groups for aldehyde C–H activation, they can help to carry key chiral building blocks, such as amino acid and lactate derivatives, through the hydroacylation process. Upon deprotective MTM removal, these functionalities are liberated within the product. Willis described the seminal use of these groups in 2011,[55] where MTM-ether aldehydes were reacted with a variety of different alkyne substrates (**Scheme 1.27A**).



Scheme 1.27. A. Rh-coordinating methylthiomethyl (MTM) protecting groups, carrying lactate derived aldehydes through hydroacylation; **B.** control experiments to probe the directing properties of MTM-ether aldehydes.

Several control experiments were conducted to probe the role of the *O*- and *S*-heteroatomic groups on the aldehyde (**Scheme 1.27B**). Absence of the *S*-tethering atom provided no desired product when the new substrate was subjected to the reaction conditions. When only removing the ethereal *O*-heteoroatom, the desired reactivity could still be observed, although the yield dropped to 14%. These results suggest that not only is the sulfide linker is essential to promote baseline reactivity, but also that the ethereal linker is needed to produce an efficient reaction, most likely by inducing more favourable chelation within the 6-membered metallocycle intermediates. Their second paper showed MTM-protected α-amino aldehydes facilitated excellent reactivity in hydroacylation (**Scheme 1.28**).[3d] The authors illustrated the desired reactivity towards the linear hydroacylation products when using a small bite-angle ligand, dcpm. They additionally demonstrated that the enantiopurity of the chiral aldehyde building blocks was retained in the reaction process.

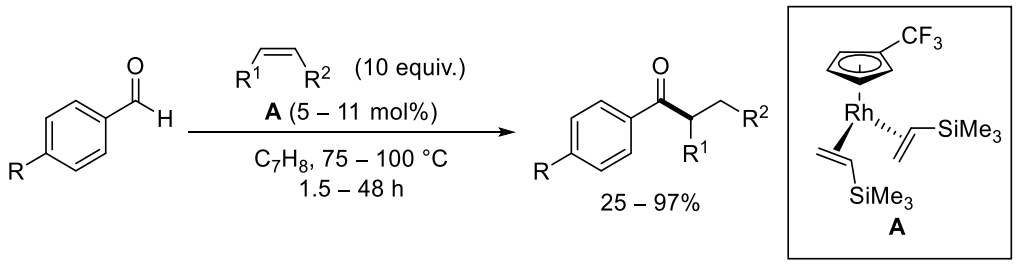


Scheme 1.28. MTM-protected α-amino-aldehydes for intermolecular alkyne hydroacylation.

1.3 Intermolecular Hydroacylation with Non-chelating Aldehydes

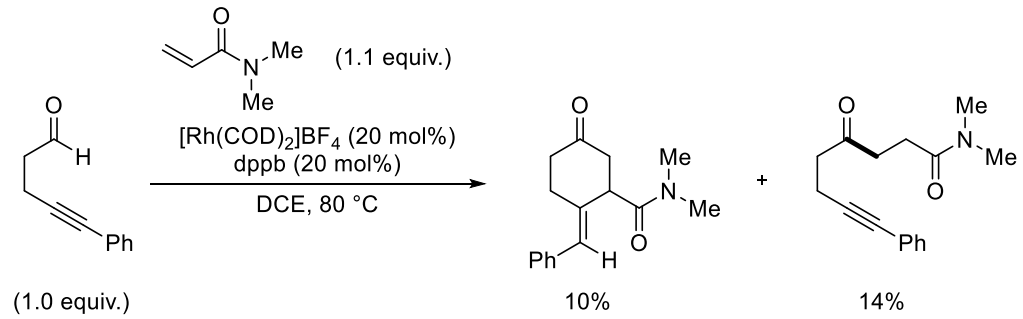
The aldehyde scope of most known intermolecular hydroacylation methods is usually restricted by the inherent requirement for pre-installed tethering groups. Nonetheless, several accounts present how catalyst or alkene substrate features have extended the application of this methodology to a wider variety of simple, non-chelating aldehydes.

Brookhart's highly electrophilic rhodium(I)-vinylsilane complex (**A**) was carefully tailored to enable a regioselective hydroacylation of substituted alkenes with simple benzaldehydes (**Scheme 1.29**).[56] The catalyst design was inspired by their previously studied cobalt catalyst[8a, 8b] and Maitlis' rhodium catalysts,[57] and exhibit the combined benefits of efficient C–H activation and rapid C–C bond formation. Nonetheless, the scope was limited to aryl aldehydes with a high C(sp^2)-CO σ-bond strength in order to suppress decarbonylation.[56] Other limitations also existed, such as the requirement of high temperatures and alkene loadings.



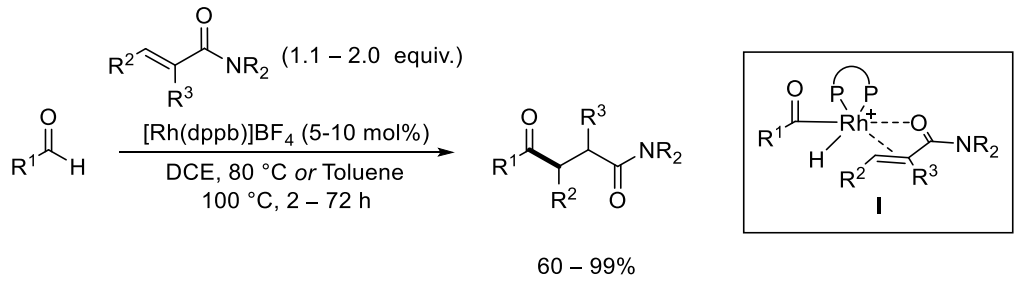
Scheme 1.29. Brookhart's highly electrophilic catalyst in olefin hydroacylation with non-chelating aldehydes.

Alkene-coordinating strategies are well-established within intermolecular hydroacylation.[3f, 3g, 58] Tanaka unexpectedly discovered an *N*,*N*-dialkylacrylamide directed hydroacylation in 2007,[3g] when using these substrates for an intermolecular [4+2] carbocyclisation with 5-substituted-4-alkynals (**Scheme 1.30**).[59] They observed a hydrocylation side-product in a low 14% yield from their initial reaction conditions. They rationalised this side-product to be a result of alternative chelation from the acrylamide.



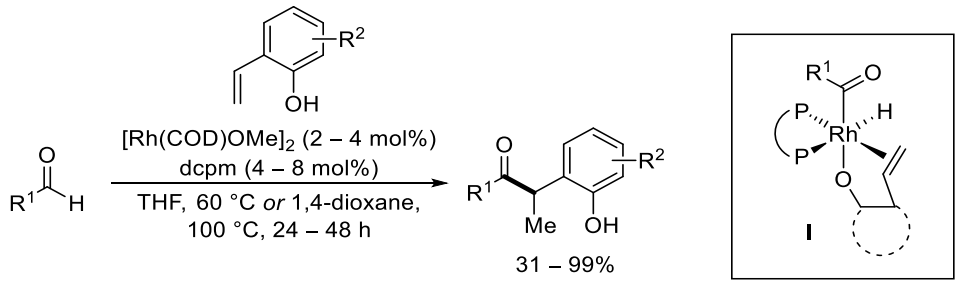
Scheme 1.30. The formation of an unexpected alkene hydroacylation product in Tanaka's [4+2] carbocyclisation.

When reacting different substituted *N*,*N*-dialkylacrylamides with different aliphatic and aryl aldehydes, they could achieve the desired hydroacylation products in excellent yields (**Scheme 1.31**).[3g]



Scheme 1.31. Tanaka's *N*,*N*-dialkylacrylamide-directed hydroacylation with non-chelating aldehydes.

Tanaka later developed an enantioselective variant of this reaction,[60] using Rh((*R*,*R*)-QuinoxP*)BF_4 as the catalyst. Dong later discovered that 2-vinylphenols could also provide sufficient directing properties, enabling a branched-selective hydroacylation with simple, non-chelating aldehydes (**Scheme 1.32**). The authors proposed that the selectivity resulted from the *in situ* production of intermediate **I**, formed from the chelation of the olefin-tethered phenolate to the acylrhodium(III) hydride intermediate.



Scheme 1.32. 2-Vinylphenols as directing groups that permit branched-selective hydroacylation with non-chelating aldehydes.

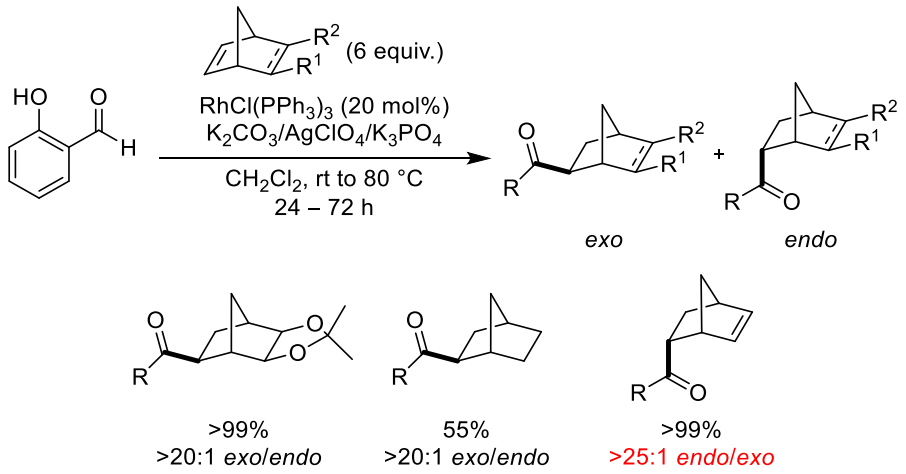
Unlike other phenolate-directed methods,[61, 18b, 18c, 50, 35a, 51] the authors discovered that base was no longer required when using $[Rh(COD)OMe]_2$. This is thought to be due to the formation of a hydrogen-bonded adduct between the OMe ligand and the phenol substrate, which is capable of undergoing preferential ligand exchange.[62] The authors then described how the branched adducts could be cyclised using TFA to generate benzofuran-based scaffolds found within eupomatenoid natural products.[63]

A similar mode of substrate chelation has been demonstrated in a method by Zhang,[58a] which uses the chelation of strained alkenols to stabilise key catalytic intermediates within a one-pot, rhodium-catalysed ring-opening/transfer hydrogenation/hydroacylation sequence.

1.4 Double-chelation Strategies within Intermolecular Hydroacylation

The final class of chelation strategies seen within intermolecular hydroacylation is one using chelation from both aldehyde and alkene components. This added chelation enables the possibility for a single catalytic system to demonstrate switchable regiocontrol.

One example, by Suemune,[61] demonstrates how different outcomes in reaction selectivity can be distinguished when double chelation is used over single chelation. The authors performed a hydroacylation reaction between salicaldehyde and different norbornenes, using Wilkinson's catalyst, to accomplish *exo* π-selectivity in the products (**Scheme 1.33**).

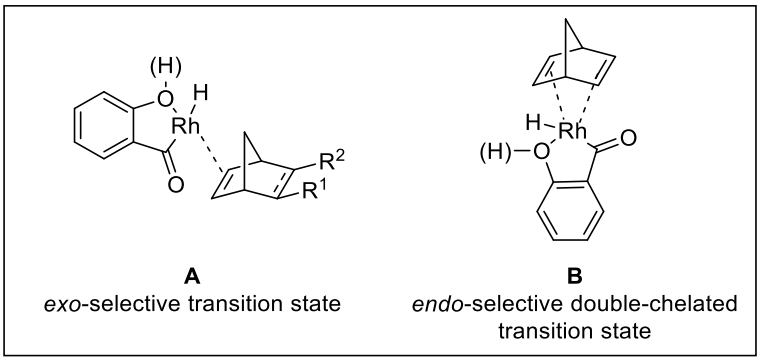


Scheme 1.33. Single chelation vs double chelation in Suemune's hydroacylation system, offering alternating facial selectivity.

To their surprise, the *endo* isomer formed when norbornadiene (NBD) was administered under the same conditions (**Scheme 1.33**). Their deuterium labelling study confirmed that the selectivity was governed by the presence of two possible transition states, arising from different levels of substrate coordination. Norbornene was unable to chelate to the Rh-centre, and so the acyl hydride is directed to the less sterically encumbered *exo* face (**Scheme 1.34**, **A**). Conversely in the double-chelated intermediate, where NBD and salicaldehyde are both chelated to the Rh centre, the metal-hydride bond is proximal to the NBD *endo* face, leading to selectivity for the opposing pathway (**Scheme 1.34**, **B**).

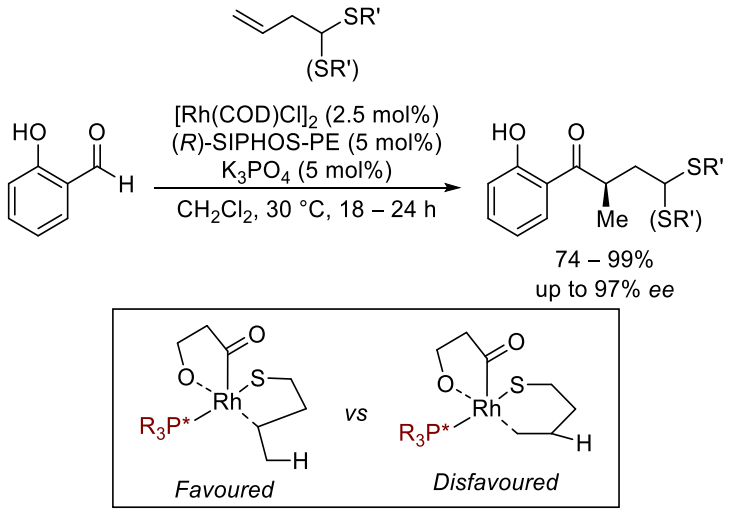
Double-chelation methods can also be used to control hydroacylation regioselectivity. Suemune has shown this to be the case when using acyclic diene

substrates in hydroacylation, whereby the regioselectivity is controlled by the diene chain length.[27b] However, the products accessible by this methodology are rather limited.



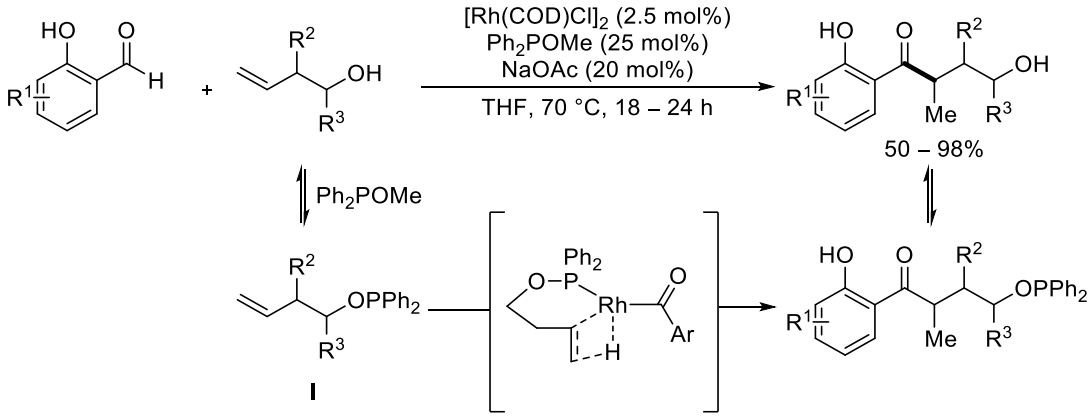
Scheme 1.34. Suemune's proposed *exo*- and *endo*-selective transition states.

Dong has shown that removable or functionalisable heteroatomic groups can also be used in double-chelation to provide regioselective transformations.[18b, 18c] Dong first described an enantioselective branched hydroacylation of homoallyl sulfides using $[Rh(COD)Cl]_2$ and (*R*)-SIPHOS (**Scheme 1.35**).[18b]



Scheme 1.35. Dong's sulfide directed double-chelation strategy for an asymmetric, branched alkene hydroacylation.

Here, the allyl-sulfide can chelate to the metal, and the hydride insertion favours the formation of the 5-membered metallocycle intermediate prior to reductive elimination. In 2010, Breit illustrated how a regioselective hydroformylation of bishomoallylic alcohols could be established through the reversible, *in situ* formation of a transient phosphinite directing group.[64] This strategy was later extended to a branched selective hydroacylation, by Dong, towards homoaldol products (**Scheme 1.36**).[18c]



Scheme 1.36. Transient phosphinite groups can be used to control a branched selective hydroacylation of homoallyl alcohols.

Initial reaction of the homoallyl alcohol with the ligand Ph_2POMe generates phosphinite **I**, which proceeds through a 6-membered rhodacycle leading to the desired product.

1.5 Thesis Aims

This introductory chapter has briefly summarised methods within rhodium(I)-catalysed alkyne hydroacylation, outlining issues with reaction regioselectivity and reductive decarbonylation in both intra- and intermolecular processes, and the catalysts and chelation types used to circumvent them.

The next two chapters will focus on different topics within rhodium(I)-catalysed hydroacylation of alkynes. Chapter 2 will delve into the application of this method towards the formation of fully saturated heterocycles, by using the enones generated in hydroacylation as electrophiles for a subsequent intramolecular cyclisation. Chapter 3 establishes the use of 2-formyl azine *N*-oxides as novel directing groups for intermolecular hydroacylation, to resolve challenges previously faced when using azine aldehydes within hydroacylation.

Rhodium(I)-catalysts used in alkyne hydroacylation have also played a significant role in the progress of [2+2+2] cycloaddition reactions. The work in chapter 4 employs these catalysts towards a bimolecular [2+2+2] cycloaddition, with the aim to achieve enantioenriched sulfur(IV and VI) compounds, through 1,6-diyne desymmetrisation. An introduction to the concepts within [2+2+2] cycloadditions, and chiral sulfur compounds, can also be found within chapter 4.

Chapter 2 − Diverse Saturated *O*- and *N*-Heterocycles from a Hydroacylation/Conjugate-Addition Cascade

2.1 Introduction

Increasing the amount of sp^3-character within therapeutics has been an emphasis of recent drug development.[65, 66] The resulting increased three-dimensionality often provides drug candidates with better drug target selectivity,[67] and improved aqueous solubility[65, 68] Saturated *N*- and *O*-heterocycles are prevalent in a plethora of biologically active molecules, including natural and pharmaceutical products (**Figure 2.1**).[69] Accordingly, the search for new and direct catalytic methods for the development of these fragments is highly important for medicinal chemistry.

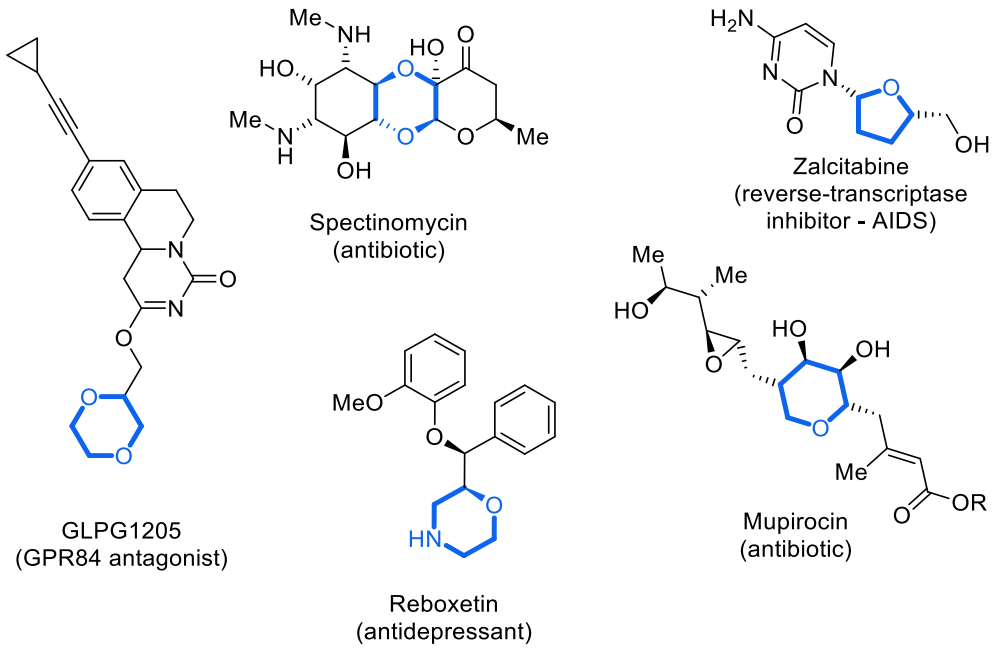
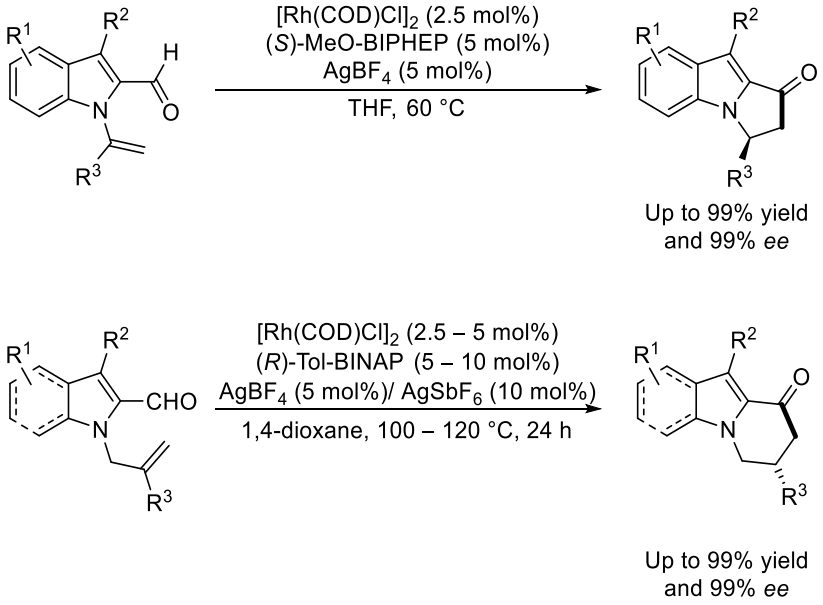


Figure 2.1. Examples of biologically active compounds containing saturated *N*-, *O*- and *S*-heterocycles.

2.1.1 Intramolecular Hydroacylation Methods for Heterocycle Formation

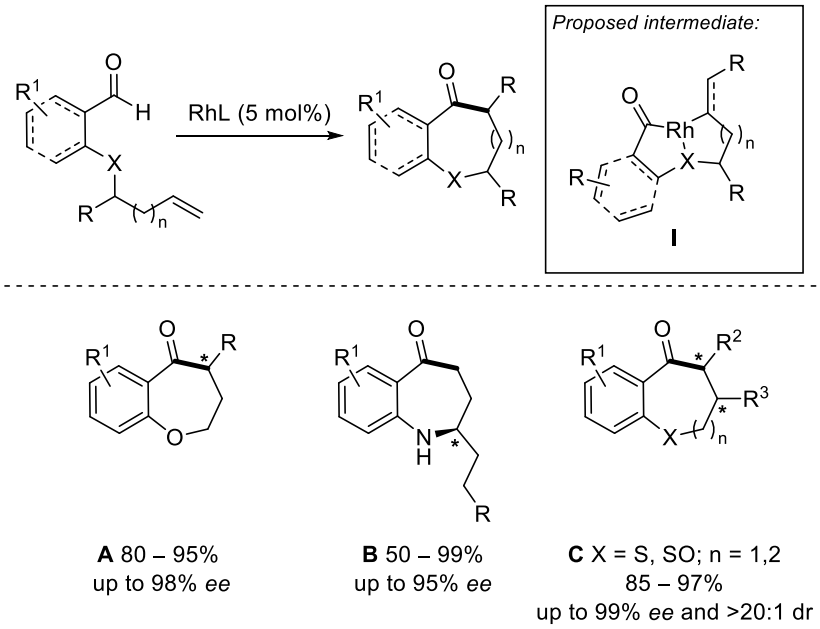
There have been numerous successful approaches to form small and medium-ring heterocycles of partial saturation through intermolecular hydroacylation cyclisations, from the corresponding enal precursors. [70, 71, 18d] Fused 5,5- and 5,6-nitrogen heterocycles have been prepared by Stanley and co-workers using substituted *N*-vinylindole- and *N*-allylindole-2-carboxaldehydes (**Scheme 2.1**).[70]



Scheme 2.1. Stanley's enantioselective intramolecular hydroacylation/cyclisation towards 5,5- and 5,6-nitrogen heterocycles.

The synthesis of partially saturated medium-sized 7- and 8-membered *N*-,[71] *S*- and *O*-heterocycles[18d] has been achieved *via* a similar cyclisation strategy. Dong[18d] and Nguyen[71] explored the use of *O*- and *N*-coordinating alkenals to form enantioenriched *O*- and *N*-saturated heterocycles (**Scheme 2.2**). Dong's *S*- and *O*-chelating strategy, to products **A** and **C** installed the chirality in the hydroacylation cyclisation step through employment of a chiral ligand (*R*,*R*)-Me-DuPhos. Conversely, the chirality in Nguyen's *N*-heterocyclic hydroacylation products (**B**) was installed in a dynamic kinetic asymmetric amination step prior to

hydroacylation, using a chiral catalytic system developed in their previous work on enantioselective amination.[72] Mechanistic studies have shown that heteroatoms embedded within these substrates coordinate to the rhodium centre, providing 5-membered chelation stability (**Scheme 2.2**, **I**) to prevent decarbonylation.[18d, 73]

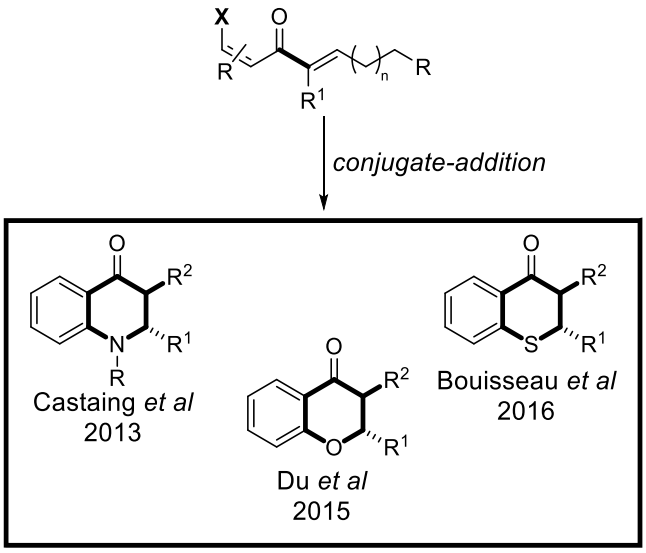


Scheme 2.2. Dong and Nguyen's asymmetric strategies towards medium-sized *O*- and *N*-saturated heterocycles, including a proposed metallobicyclic intermediate.

2.1.2 Intermolecular Methods for Heterocycle Formation

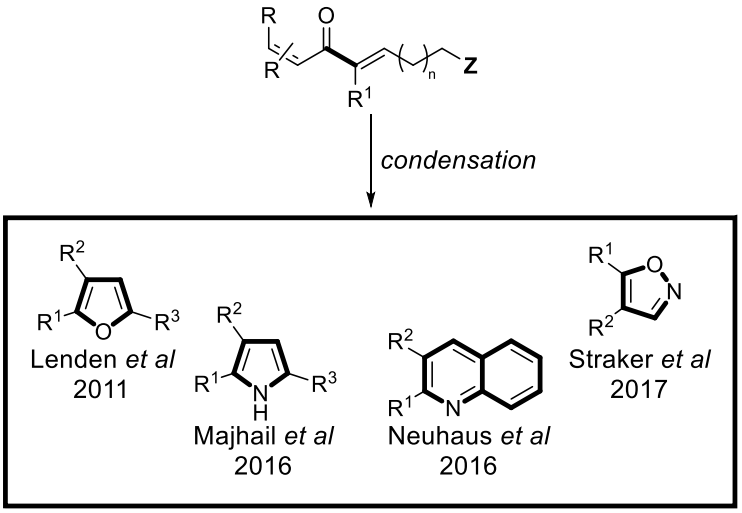
Various heterocyclic scaffolds exhibiting full or partial saturation can be constructed through tandem reactions that utilise intermolecular alkyne hydroacylation, using β-coordinating aldehydes as the foundation of the transformation. Not only does the intermolecular method offer a higher degree of modularity within the heterocycle synthesis, but it also allows access to more diverse heterocycle classes. Hydroacylation/conjugate-addition sequences[3a, 45, 74] exploit the reactivity of the α,β-unsaturated enone intermediates formed in hydroacylation (**Scheme 2.3**). The aldehyde heteroatomic coordinating group (X) is nucleophilic enough to perform an

intramolecular conjugate addition to produce different 6-membered *N*-heterocycles,[3a, 45, 75] thiochroman-4-ones,[74a] and chroman-4-ones.[76]



Scheme 2.3. Conjugate-addition methods, *via* α,β-unsaturated enones generated from intermolecular hydroacyation.

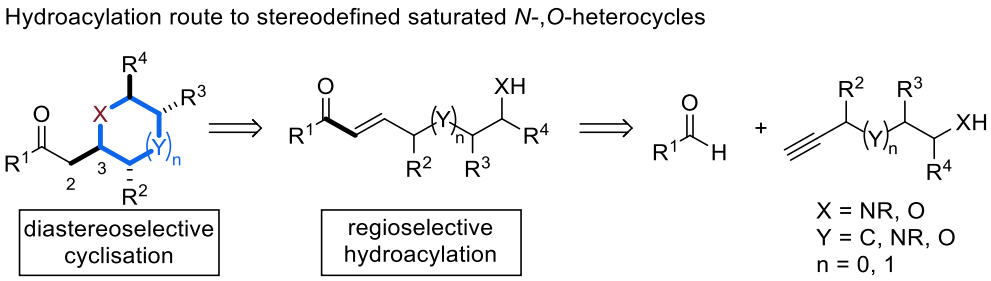
If the enone intermediate contains a pendant reactive group on the alkyne component (Z), this can undergo an intramolecular condensation with the existing carbonyl group, allowing access to a variety of substituted furans,[77] pyrroles,[74b] quinolines[74c] and isoxazoles (**Scheme 2.4**).[74d] Although these results are highly encouraging, they generally rely on the use of specific substrates, and the nucleophile used for the conjugate-addition reactions is limited to groups that make suitable tethers for the hydroacylation step. [74a 3a 76] Other limitations include the requirement of forcing conditions for cyclisation,[3a, 74a, 74d, 76, 78] and/or the absence of one-pot processes.[3a, 45, 74d]



Scheme 2.4. Condensation methods, via α,β-unsaturated enones, generated from intermolecular hydroacyation.

We envisaged a new retrosynthetic strategy, where heterocycles of varying ring-sizes could be accessed from *O*- and *N*-substituted enone intermediates, prepared *via* an intermolecular hydroacylation reaction between β-tethered aldehydes and nucleophile-substituted alkynes of varied substitution. The reactive nucleophile within the enone intermediate undergoes an intermolecular conjugate-addition, generating fully saturated structures that contain a newly formed stereocentre at position C3 (**Scheme 2.5**). It is possible that this new stereocentre could be generated in a stereo-controlled manner, provided appropriate cyclisation conditions are used.

This chapter describes the development of a one-pot hydroacylation/conjugate-addition sequence to access a range of saturated *O*- and *N*-heterocycles, from aldehydes and alkynes derived from simple precursors. We later demonstrate how the aryl sulfide-substituted products can be transformed into traceless derivatives.



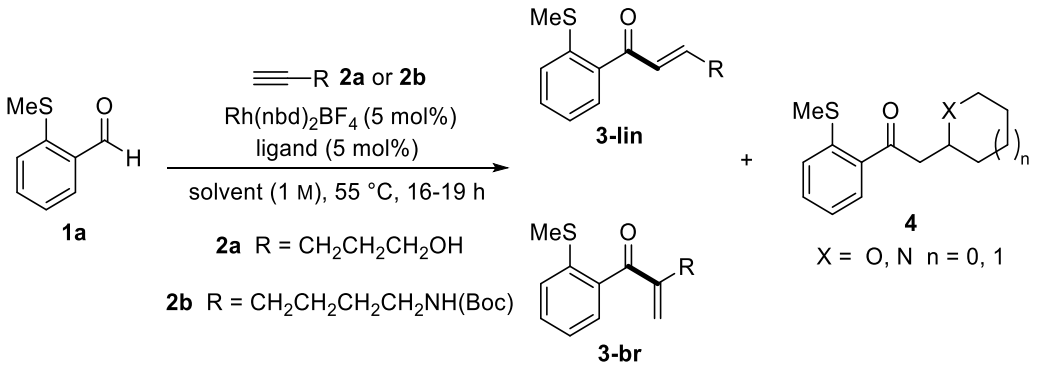
Scheme 2.5. A retrosynthetic route to stereo-defined saturated heterocycles.

2.2 Results and Discussion

2.2.1 Reaction Optimisation

Our optimisation began by investigating the tolerance of alkynol **2a** and alkynamine **2b** in a hydroacylation reaction with aryl sulfide-substituted aldehyde **1a**. Previous studies have used Rh^{I}-catalysts containing small bite-angle ligands to permit fast and regioselective transformations. When employing similar catalysts in our substrate system, conversion was initially low (**Table 2.1**, entry 1), but the selectivity for the linear isomer was high.[17, 42] Conversion could be improved by using 1,2-dichloroethane (DCE) as the solvent and 1,2 bis(dicyclohexylphosphino)ethane (dcpe) as the ligand (entries 2 and 3). With both alkyne substrates **2a** and **2b**, a notable yield of the corresponding tetrahydrofuran and *N*-Boc-piperidines would also form, suggesting that the *O*- and *N*-Boc-tethered enone substrate could readily cyclise at 55 °C, in agreement with a previous account from our laboratory.[3d]

Table 2.1. Showing the initial hydroacylation reactivity of aldehyde **1a** with alkynol **2a** and alkynamine **2b** (Experiments performed by Miss Ndidi U. Iwumene).[a]

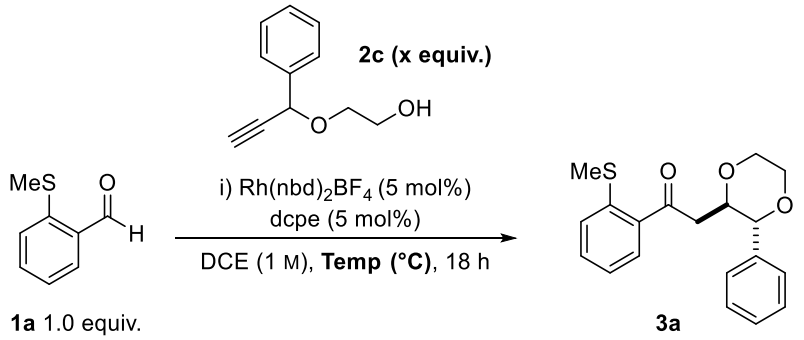


Entry	Alkyne	Solvent	Ligand	Conversion (%)[b]	Ratio (3l:3br:4)
1	**2a**	Acetone	dppe	50	10:2:5
2	**2a**	DCE	dppe	95	10:1:4
3	**2a**	DCE	dcpe	100	10:1:9
4	**2b**	DCE	dppe	85	10:1:2
5	**2b**	DCE	dcpe	100	13:1:2

[a] Reaction conditions: aldehyde (1.0 equiv.), alkyne (1.5 equiv.); nbd, norbornadiene; dppe, 1,2-bis(diphenylphosphino)ethane, dcpe, 1,2-bis(dicyclohexylphosphino)ethane; DCE,1,2-dichloroethane; [b] determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

The result obtained from alkynol **2a** prompted us to build substituted alkynols, capable of providing a diastereoselective cyclisation. The initial reactivity of phenyl-susbstituted alkynol **2c** was tested (**Table 2.2**). The enone that forms from this hydroacylation was observed to cyclise more readily than unsubstituted alkynol **2a**, giving 1,4-dioxane in a modest 4:1 dr and 86% yield total yield (entry 1). Running the reaction at lower temperatures had a negative impact on the diastereoselectivity (entries 2 and 3).

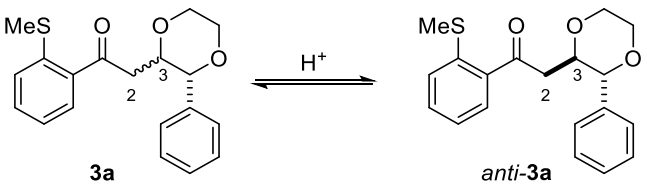
Table 2.2. Condition optimisation for the hydroacylation step with substituted alkynol **2c**.



Entry	Alkyne (equiv.)	Temp (°C)	3a (%)[a]	Crude dr[b]
1	1.2	55	86[c]	4:1
2	1.2	rt	64[d]	3:1
3	1.2	35	88[c]	3.3:1

[a] ^{1}H NMR yields based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [b] dr measured from ^{1}H NMR spectroscopy of the crude reaction mixture; [c] >20:1 l:b regioselectivity, and >20:1 **3a**:**1a** determined by ^{1}H NMR spectroscopy; [d] 13.9:1 l:b regioselectivity, and 6.2:1 **3a**:**1a** determined by ^{1}H NMR spectroscopy.

We realised that the forming stereocentre of **3a** (**Scheme 2.6**, C3) should be capable of epimerising through a second reversible ring-closure step, which could maximise the formation of the energetically favoured diastereoisomer (**Scheme 2.6**, *anti*-**3a**). Accordingly, we set out to induce epimerisation in product **3a** as part of a one-pot process with hydroacylation.

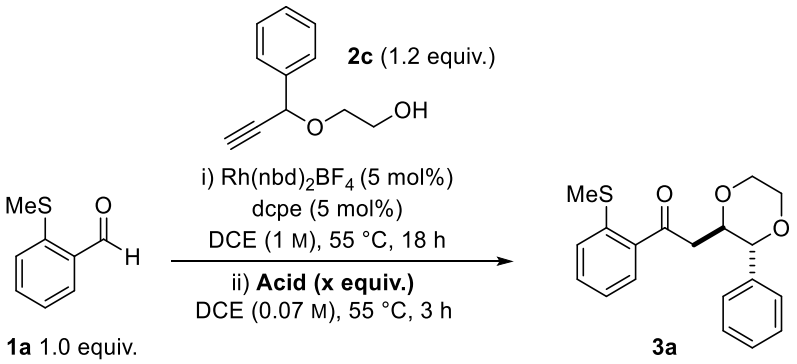


Scheme 2.6. Potential C3 epimerisation within 1,4-dioxane **3a**.

Adding stoichiometric quantities of the Brønsted acids, *p*-TsOH and MsOH into the same reaction pot after the hydroacylation step increased selectivity to 11:1 and >20:1 dr, respectively (**Table 2.3**, entries 1 and 2). However, this was accompanied by a significant reduction in the overall yield; it was therefore difficult to conclude

whether substrate epimerisation, or selective degradation, was occurring in these cases.

Table 2.3. Acid evaluation for the cyclisation/epimerisation step.



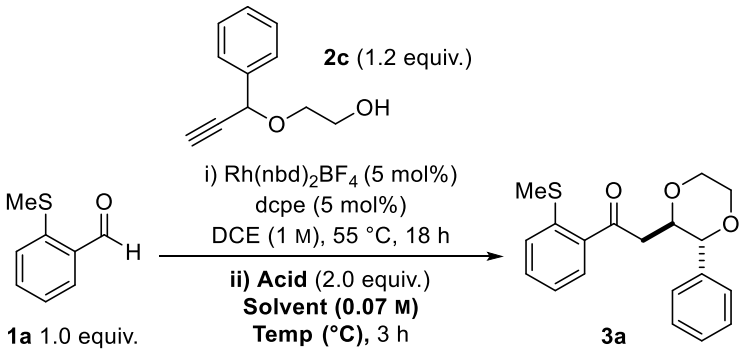
Entry	Acid	Loading (equiv.)	Total yield (%)[a]	Crude dr[b]
1	*p*-TsOH	2	62	11:1
2	MsOH	2	33	>20:1
3	*p*-TsOH	0.2	87	6.8:1
4	MsOH	0.2	98	4.4:1
5	$Sc(OTf)_3$	0.2	78	4.9:1
6	$Ti(^iPrO)_4$	0.2	96	4.2:1
7	BF_3OEt_2	0.2	76	4.4:1
8	$AlCl_3$	0.2	87	4.4:1
9	BCl_3	0.2	83	7.3:1
10[c]	SiO_2	-	83	4.3:1
11[d]	Amberlyst 15	-	78	5.3:1

[a] ^{1}H NMR yields based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [b] dr measured from ^{1}H NMR spectroscopy of the crude reaction mixture; [c] 0.5 g of SiO_2; [d] 200 mg of Amberlyst 15.

A sub-stoichiometric quantity of these acids (20 mol%) provided a smaller dr increase, but with no overall yield degeneration (entries 3 and 4). This was the first example that confirmed the presence of product epimerisation within our system. Most Lewis acids trialled had no overall effect on dr (entries 5 – 8). However, when BCl_3 was used (entry 9), a dr of 7.3:1 was observed, with no overall yield reduction. When the reaction mixture was subjected to silica (SiO_2) or acidic resin Amberlyst 15 (entries 10 and 11), no change in dr was observed. Stoichiometric quantities of

p-TsOH, MsOH and 2,4-DNSA were trialled in the cyclisation step at room temperature (**Table 2.4**, entries 1 – 3), however, the overall increase in dr was marginal.

Table 2.4. Room temperature reactions and DCE/THF solvent-switches for *p*-TsOH and 2,4-DNSA addition.



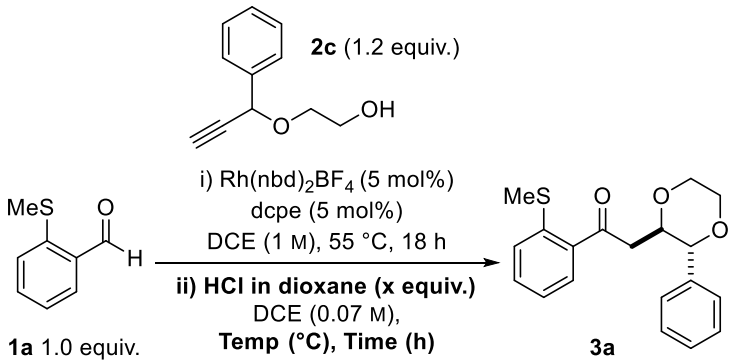
Entry	Acid	Solvent	Temp (°C)	Total yield (%)[a]	Crude dr[b]
1	*p*-TsOH	DCE	rt	78	4.5:1
2	MsOH	DCE	rt	69	5.2:1
3	2,4-DNSA	DCE	rt	93	3.8:1
4	*p*-TsOH	THF	rt	94	5.7:1
5	*p*-TsOH	THF	35	82	5.7:1
6	2,4-DNSA	THF	rt	94(80)[c]	5.2:1
7	2,4-DNSA	THF	35	81	4.8:1

[a] ^{1}H NMR yields based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [b] dr measured from ^{1}H NMR spectroscopy of the crude reaction mixture; [c] isolated yield of major diastereoisomer (>20:1 dr) in parentheses.

A lack of solubility at room temperature was observed for *p*-TsOH and 2,4-DNSA in DCE. As a result, a solvent-switch to THF for the second step was attempted to better solubilise the acids. A slight increase in dr for both acids was observed at room temperature and 35 °C (entries 4 – 7), however, the result was not significant enough to justify further optimisation in this area. In the initial acid evaluation (**Table 2.3**), of the generation of fuming HCl was noted when adding BCl_3 to the reaction vial; we considered whether the *in situ* degradation of this reagent

correlated to the high dr it could produce. Addition of a sub-stochiometric quantity (20 mol%) of HCl (**Table 2.5**, entry 1) only resulted in a marginal dr increase.

Table 2.5. Condition screening using 4 M HCl in dioxane for the cyclisation/epimerisation step.



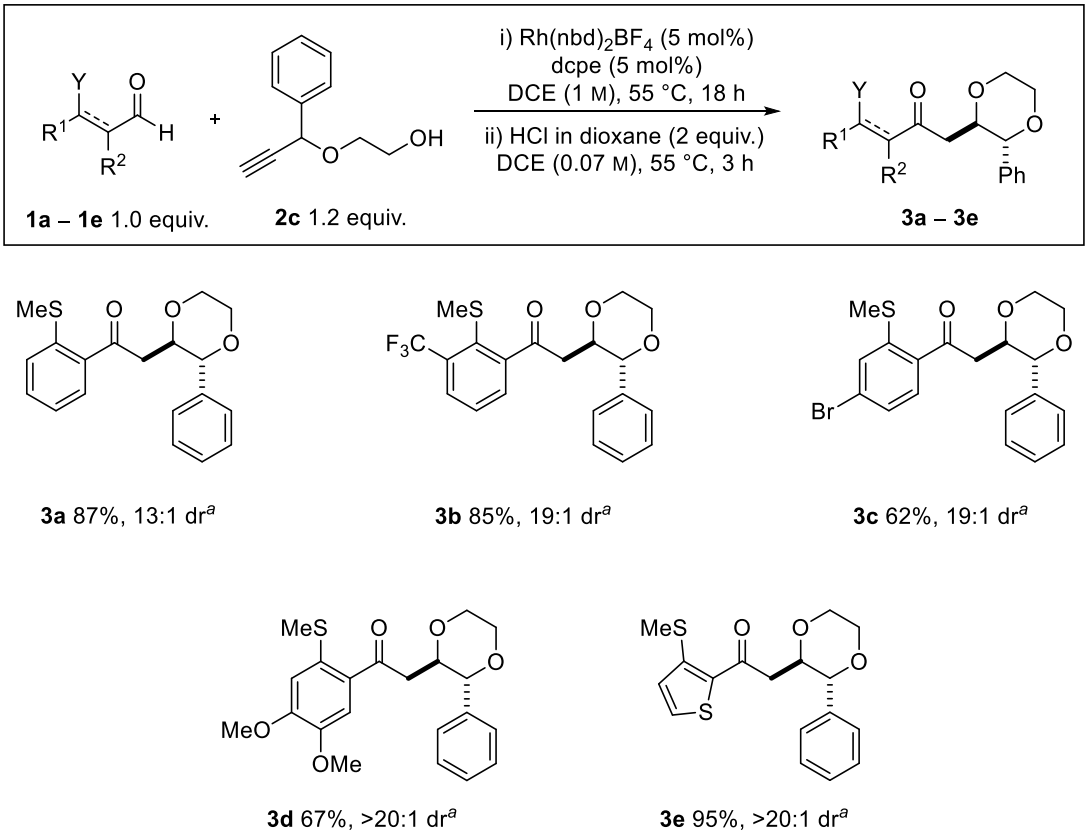
Entry	HCl in dioxane (equiv.)	Time (h)	Temp (°C)	Total yield (%)[a]	Crude dr[b]
1	0.2	3	55	87	5.2:1
2	0.2	3	rt	88	4.9:1
3	2.0	3	55	95(87)[c]	13:1
4	2.0	3	rt	94	5:1
5	2.0	5	55	93	13:1
6	2.0	7	"	95	12:1
7	2.0	24	"	91	11:1
8	3.0	3	55	94(82)[c]	15:1
9	4.0	3	"	95(84)[c]	14:1
10	5.0	3	"	85	12:1
11	10.0	3	"	80	11:1

[a] ^{1}H NMR yields based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [b] dr measured from ^{1}H NMR spectroscopy of the crude reaction mixture; [c] isolated yield of major diastereoisomer (>20:1 dr) shown in parentheses.

However, when a stoichiometric quantity (2.0 equiv.) was employed at 55 °C, a stark increase in selectivity to 13:1 dr, could be observed with no overall yield degradation, giving product **3a** in an 87% isolated yield (entry 3). Trying the quantities at lower temperatures (entries 2 and 4) had no large effect on dr. When increasing the time of epimerisation (entries 5 – 7) or the loading of HCl (entries 8 – 11), although a slight dr increase could be seen when adding 3.0 or 4.0 equivalents of HCl, the isolated yields in both cases were lower.

2.2.2 Aldehyde Scope

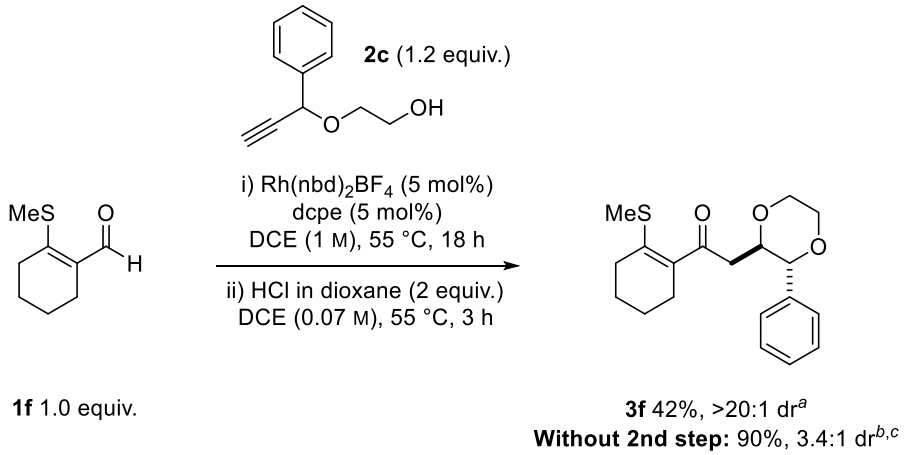
With the newly optimised conditions, we decided to explore the reaction substrate scope on other aryl sulfide-substituted aldehydes (**Scheme 2.7**). An electron-withdrawing CF_3-substituent (**3b**) and donating OMe-substituents (**3d**) provided good yields and diastereoselectivity. The reaction was also compatible with aryl bromides (**3c**). A thiophene-derived aldehyde, could cleanly form product **3e** in 95% yield and >20:1 dr.



Scheme 2.7. Aryl sulfide-substituted aldehyde scope; diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [a] isolated yield of a single major diastereoisomer.

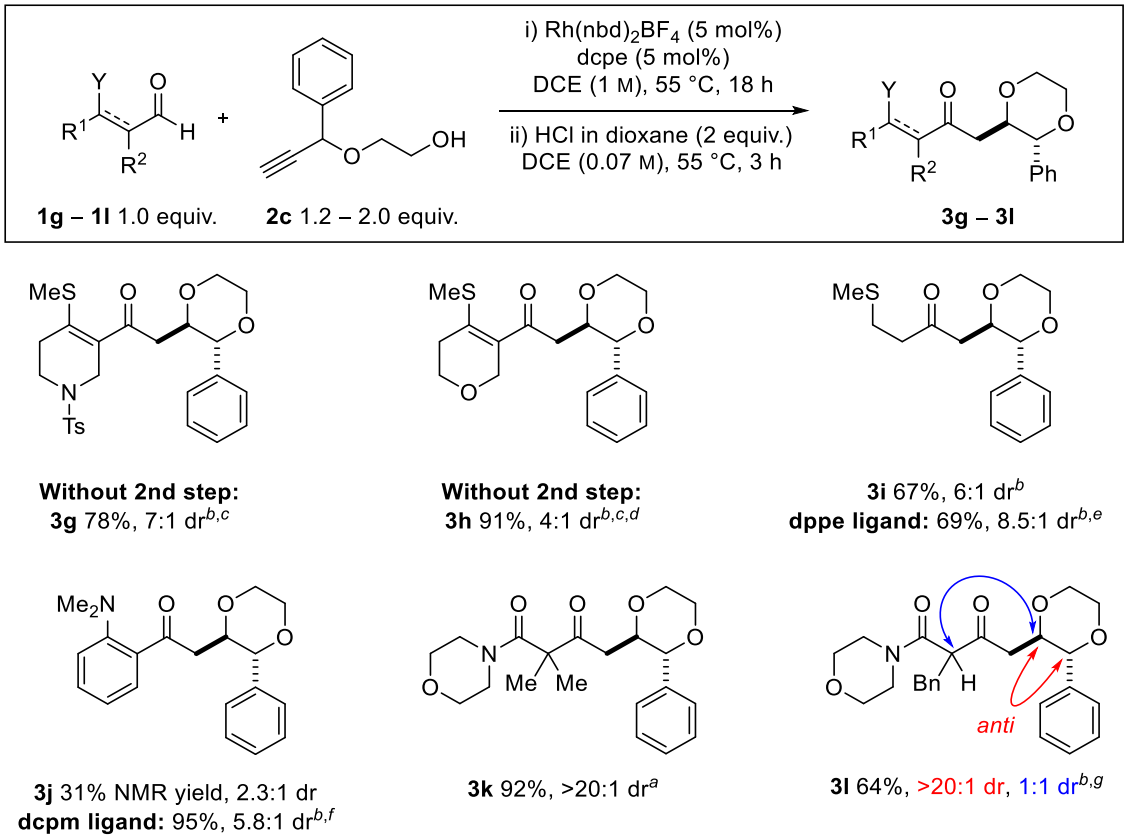
When probing the reactivity of vinyl sulfide substituted aldehyde **1f**, we observed a large amount of degradation upon addition of HCl, producing dioxane **3f** in 42%, >20:1 dr (**Scheme 2.8**). We proposed that this was due to instability of the vinyl

sulfide under these conditions. When avoiding the acidic epimerisation step, a greater isolated yield of 90% could be obtained, however, the dr was greatly reduced (3.4:1 dr).



Scheme 2.8. Aryl sulfide-tethered aldehyde scope; diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [a] isolated yield of a single major diastereoisomer; [b] total isolated yield of both diastereoisomers; [c] reactions with step i) only.

We decided to extend the scope of the reaction using a vinyl sulfide substituent to heterocyclic analogues **3g** and **3h**, which were produced in 78%, 7:1 dr, and 91%, 4:1 dr, both in absence of the epimerisation step (**Scheme 2.9**). The higher dr value obtained in product **3g** is likely due to steric effects provided by the *N*-Ts group. β-ketoamides could be also used as controlling groups without modification of reaction conditions, giving products **3k** and **3l** with high diastereoselectivity for ring closure (>20:1 dr). Other coordinating groups, such as alkyl sulfide **3i** and aminobenzaldehyde **3j**, worked well when using alternative Rh^{I}-catalysts.[3a, 18a]

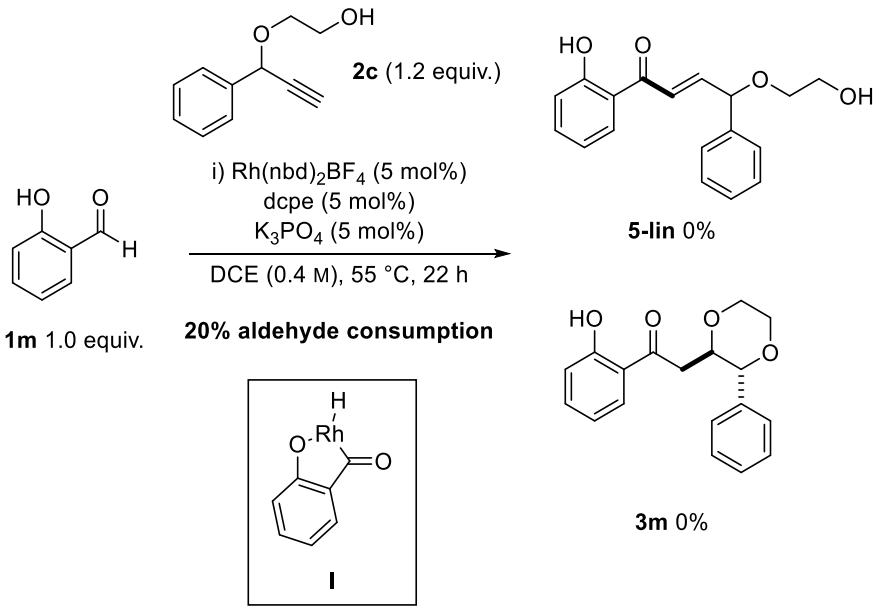


Scheme 2.9. Aryl sulfide-tethered aldehyde scope; diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [a] isolated yield of a single major diastereoisomer; [b] total isolated yield of both diastereoisomers; [c] reactions with step i) only; [d] reactions carried out on 0.2 mmol scale; [e] step i) conditions: alkyne (2.0 equiv.), $Rh(nbd)_2BF_4$ (5 mol%), dppe (5 mol%), acetone (0.15 M), 55 °C, 2 h; [f] step i) conditions: $Rh(nbd)_2BF_4$ (10 mol%), dcpm (10 mol%), acetone (0.15 M), 55 °C, 4 h; [g] >20:1 dr with respect to ring closure, 1:1 dr with respect to the aldehyde stereocentre.

2.2.3 Salicaldehyde-derived Products

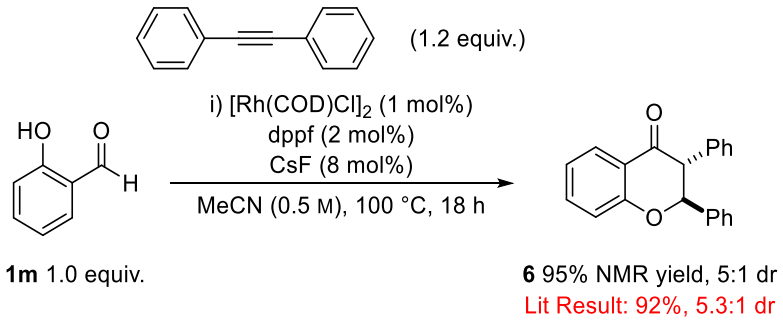
Another aim was to achieve heterocycle formation using phenolic-substituted aldehydes, such as salicaldehyde **1m**. We wanted to apply our standard Rh^{I}-dcpe catalytic system to this substrate, however, the corresponding phenolate anion is the active directing species due to the formation of a stable acylrhodium(III) hydride intermediate (**Scheme 2.10**, **I**), so base is generally required to permit

hydroacylation. We therefore incorporated K_3PO_4 base and an altered reaction concentration, using previous work by Dong as a starting point.[79]



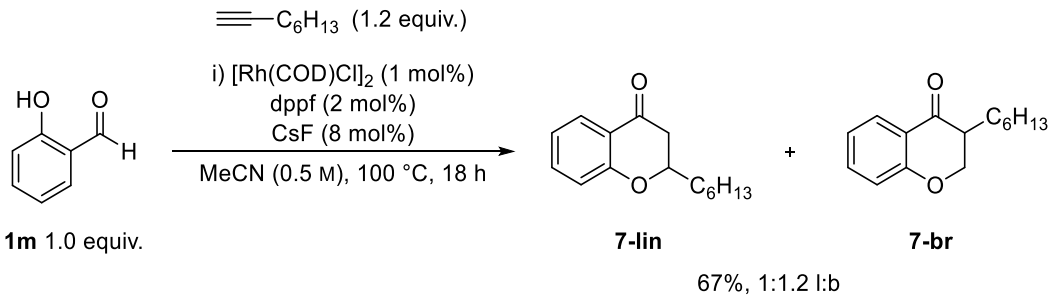
Scheme 2.10. An initial attempt to employ salicaldehyde **1m** in hydroacylation with alkynol **2c**.

Unfortunately, minimal consumption of salicaldehyde **1m** was observed (20%), with no detection of either of the desired products **3m** or **5-lin**. This poor result prompted us to delve into another set of conditions from Stanley.[76] With this method, salicaldehydes display excellent reactivity with symmetrical alkynes when using a dppf-derived catalytic system and CsF as the base (**Scheme 2.11**).



Scheme 2.11. Reproducing Levi Stanley's hydroacylation method, with 1,2-diphenyl acetylene.

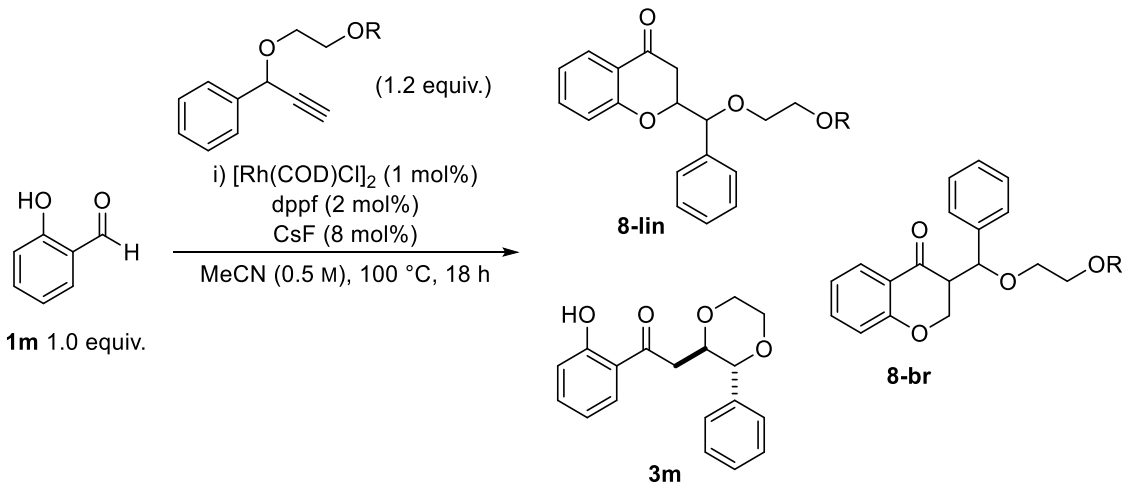
The reported reaction between aldehyde **1m** and 1,2-diphenylacetylene was successfully reproduced; we were able to obtain hydroacylation/oxo-Michael addition product **6** in 95% NMR yield and 5:1 dr. We additionally decided to use the same conditions on a terminal alkyne, such as 1-octyne, to see if this system was able to provide good linear regioselectivity. Unfortunately, regioisomers **7-lin** and **7-br** were obtained in 1:1.2 l:b regioselectivity, suggesting that Rh^{I}-dppf does not provide a selective reaction with terminal alkynes (**Scheme 2.12**).



Scheme 2.12. A lack of observed linear regioselectivity when using 1-octyne.

Despite this, the coupling was attempted using free alkynol **2c** (**Table 2.6**, entry 1). Unfortunately, a complex reaction mixture formed with no detectable products **8-lin** and **8-br**, or **3m**. The reason for this complex mixture could be the potentially poor regioselectivity, alongside the possibility for both free OH groups to cyclise and generate diastereoisomers. THP-protected alkynol **2d** was instead employed (**Table 2.6**, entry 2), with the aim to control cyclisation selectivity, and prevent any undesired coordination to the Rh^{I}-dppf catalyst. Unfortunately, a complex mixture also resulted from this reaction, and no identifiable hydroacylation products could be isolated following chromatographic purification.

Table 2.6. No desired products observed when applying Levi Stanley's alkyne hydroacylation conditions on free alkynol **2c** and THP-protected alkynol **2d**.

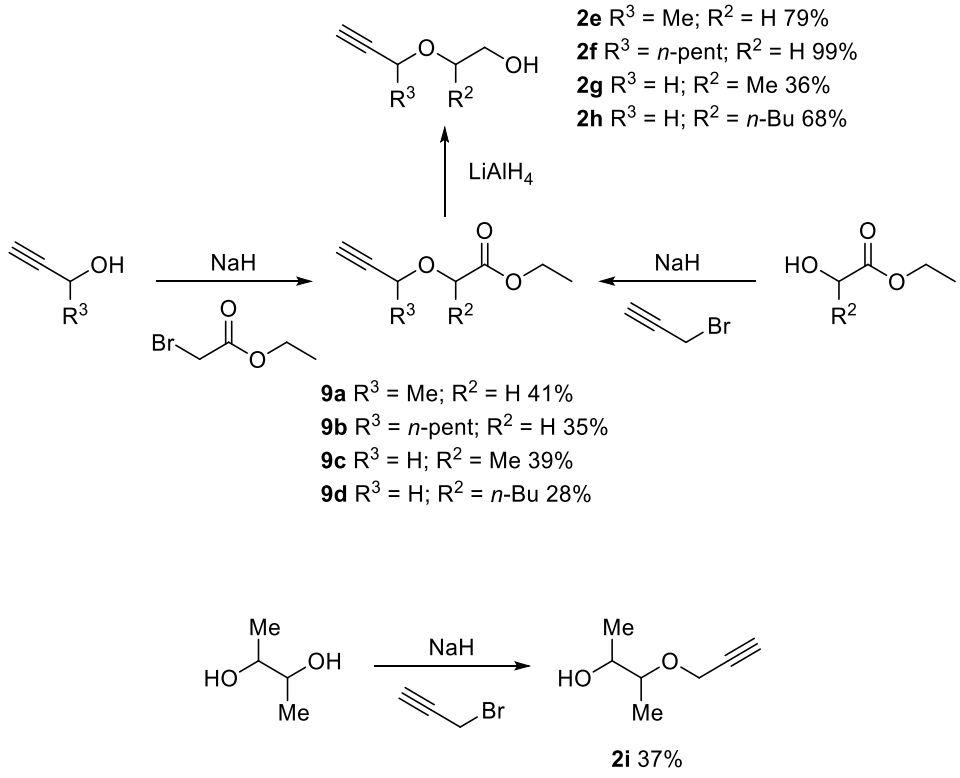


Entry	Alkyne R	Total yield (%)[a]	Crude dr[b]
1	H (**2c**)	0	-
2	THP (**2d**)	0	-

[a] ^{1}H NMR yields based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [b] dr measured from ^{1}H NMR spectroscopy of the crude reaction mixture.

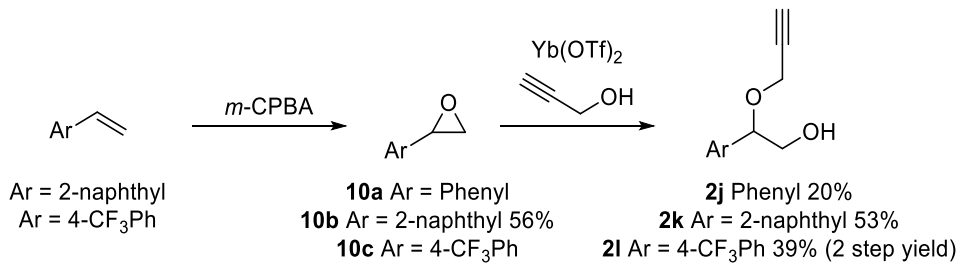
2.2.4 Alkyne Substrate Synthesis

We then set out to build a collection of different substituted nucleophile-tethered alkyne substrates. The first general method that we employed was to generate esters **9a** – **9d**, either through the addition of R^3-substituted propargyl alcohols into ethyl 2-bromoacetate, or *via* the propargylation of 2-hydroxy esters (**Scheme 2.13**). An ester reduction using $LiAlH_4$ followed, to generate different R^3 and R^2 alkyl-substituted alkynols **2e** – **2h**. Propargylation of butane-2,3-diol, could also produce dimethyl-substituted alkynol **2i** in 37% yield.



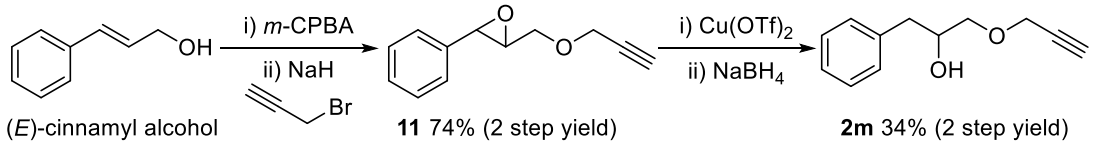
Scheme 2.13. Synthesis of different alkyl-substituted alkynols **2e – 2i**.

Another synthetic strategy used was a $Yb(OTf)_2$ catalysed ring opening of epoxides **10a** – **10c** with propargyl alcohol, to generate different R^2 aryl-substituted alkynols **2j** – **2l** in 20 – 53% yield (**Scheme 2.14**). Epoxide intermediates **10b** and **10c** were generated from the corresponding styrenes.



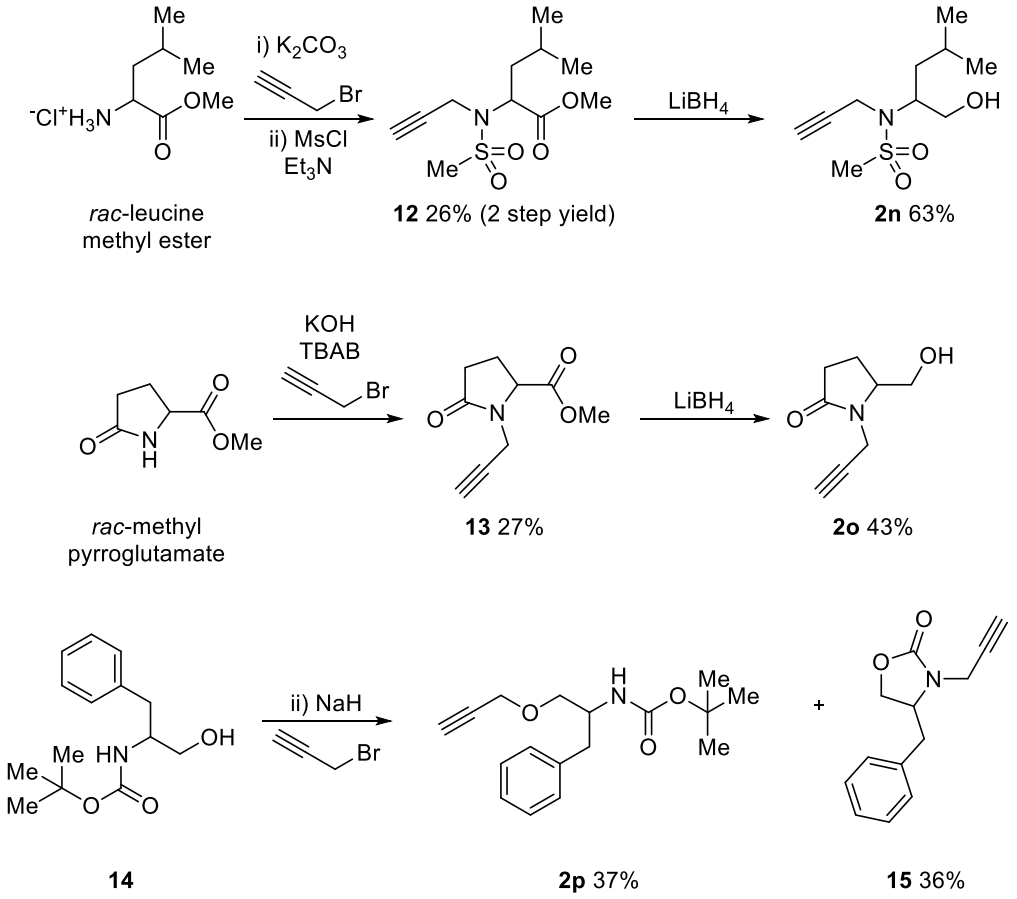
Scheme 2.14. Epoxide openings to generate different R^2-substituted alkynols **2j** – **2l**.

Epoxidation and propargylation of (*E*)-cinnamyl alcohol generated epoxide **11** (**Scheme 2.15**). Rearrangement using $Cu(OTf)_2$ followed by reduction using $NaBH_4$ led to R^1 benzyl-substituted alkynol **2m**.



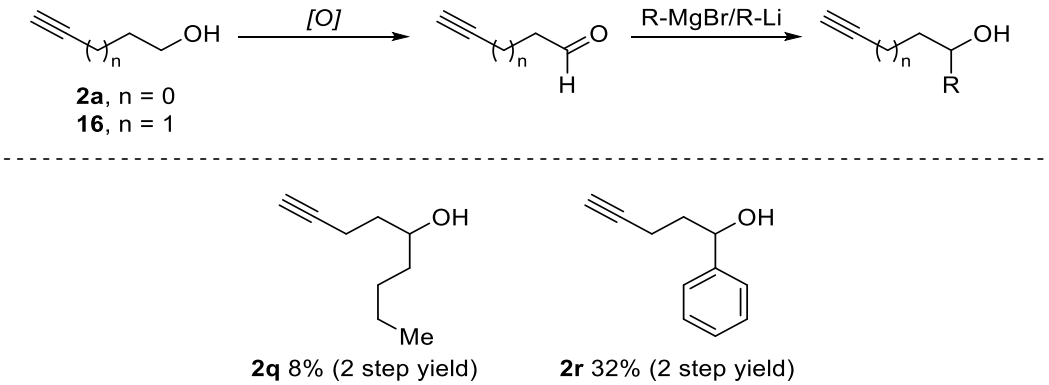
Scheme 2.15. Showing the synthesis of R^1-substituted alkynol **2m**, from (*E*)-cinnamyl alcohol.

We then decided to approach more intricate substrate designs, each derived from amino acids (**Scheme 2.16**). Propargylation and mesylation of *rac*-leucine could generate methyl ester **12**, which could then be reduced with $LiBH_4$ to generate alkynol **2n**. A similar propargylation/$LiBH_4$ reduction approach could be successfully applied to the synthesis of cyclic alkynol **2o**, from *rac*-methyl pyrroglutamate. An *N*-nucleophilic substrate **2p** could also be generated from *rac*-phenylalaninol through *N*-boc-protection and propargylation, however, an undesired cyclisation to carbamate **15** was found to be equally favoured reaction process, in 36% yield.



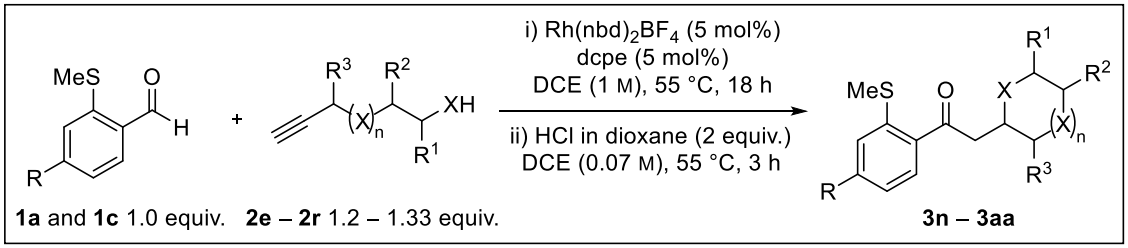
Scheme 2.16. Illustrating the preparation of α-amino acid-derived substrates.

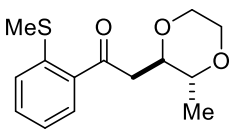
Tetrahydropyran and tetrahydrofuran substrates were synthesised according to two literature procedures,[80] that both proceed via an oxidation of the unsubstituted alkynols **2a** and **16** (**Scheme 2.17**). Grignard/R-Li addition into these intermediates generated substrates **2q** and **2r**.



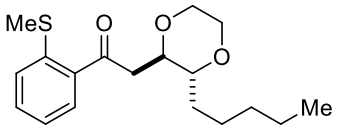
Scheme 2.17. Illustrating the preparation of substrates **2q** and **2r**.

2.2.5 Alkyne Scope

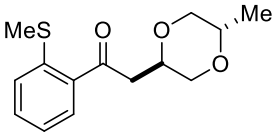




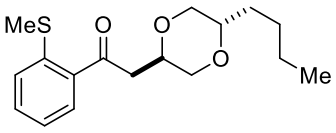
3n R = Me, 85%, 9:1 dr[a]



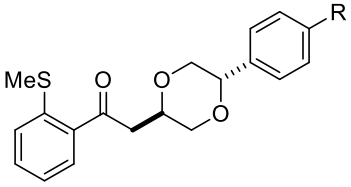
3o 75%, 8:1 dr[c]



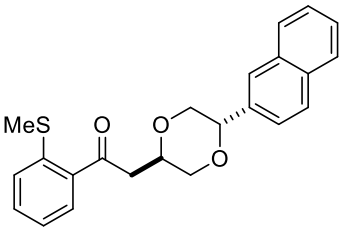
3p 81%, 8:1 dr[a]



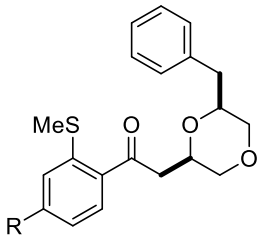
3q 85%, 10:1 dr[a,b]



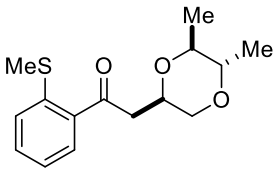
3r R = H, 85%, 11:1 dr[a]
3s R = CF_3, 77%, 7:1 dr[a]



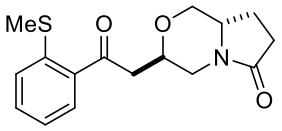
3t 75%, 6:1 dr[a]



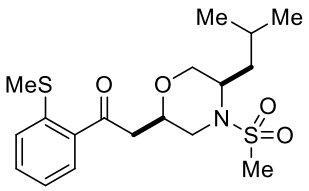
3u R = H, 78%, 11:1 dr[a]
3v R = Br, 71%, 3.5:1 dr[a]



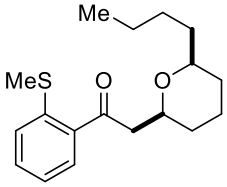
3w 79%, 16:1 dr[a]



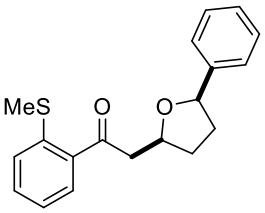
3x 63%, >20:1 dr[c]



3y 62%, 2.8:1 dr[a] **Syn-selective**



3z 62%, >20:1 dr[c]

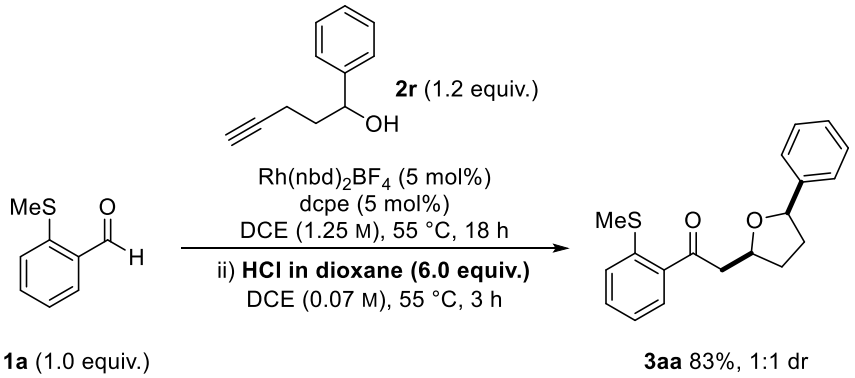


3aa 79%, 1:1 dr[a]

Scheme 2.18. Aldehyde and alkyne scope; diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [a] total isolated yield of both diastereoisomers; [b] 1.33 equiv. alkyne used; [c] isolated yield of a single major diastereoisomer.

With the tethered alkynes synthesised, we then explored the alkyne reaction scope, using aldehyde **1a** in the majority of examples (**Scheme 2.18**). Respectable yields

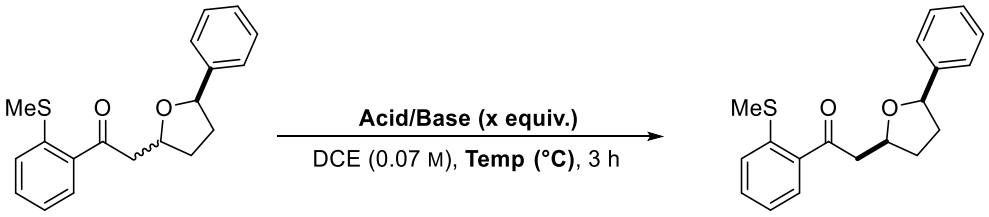
and selectivity were obtainable with substituents at all positions around the 1,4-dioxane ring (**3n** – **3w**). Morpholines **3x** and **3y** could also be successfully obtained in 63%, >20:1 dr and 62%, 2.8:1 dr, respectively. The scope was successfully extended to other *O*-heterocycles, tetrohydropyran (THP) **3z** and tetrahydrofuran (THF) **3aa**, which could be isolated in 62%, >20:1 dr, and 79%, 1:1 dr, respectively. Several attempts at improving the dr of the THF product **3aa** were made. We first decided to repeat the one-pot process, however, using three times the acid loading (6 equivalents) (**Scheme 2.19**).



Scheme 2.19. Higher acid loading in the cyclisation/epimerisation step towards the formation of diastereoisomeric mixture **3aa**.

Unfortunately, this did not yield a dr increase from 1:1. The isolated product **3aa** was then subjected to more forcing acid conditions (**Table 2.7**, entry 1), however, this additionally failed to improve the dr. Stoichiometric quantities of different bases were also applied to the 1:1 diastereoisomeric mixture **3aa**, however, the dr remained as 1:1 in all cases (entries 2 – 5).[81]

Table 2.7. Other attempts to improve the diastereoisomeric ratio in diastereoisomeric mixture **3aa**.



3aa 1:1 dr **3aa** 1:1 dr

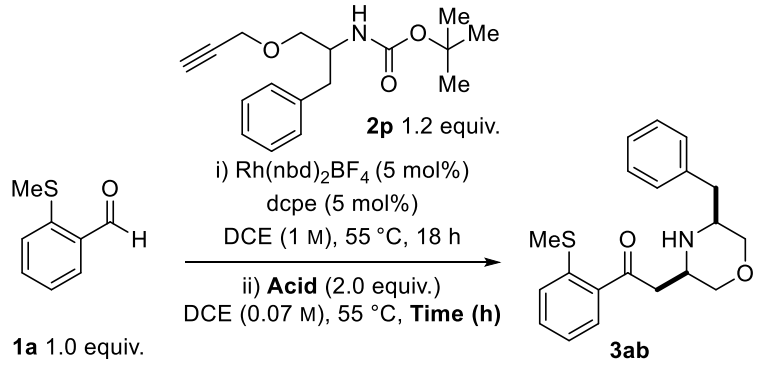
Entry	Acid/Base	Loading (equiv.)	Temp (°C)	Crude dr[a]
1	HCl in dioxane	6.0	100	1:1
2	*t*-BuOK	2.0	55	1:1
3	NaH	2.0	55	1:1
4	DBU	2.0	55	1:1
5	TEA	2.0	55	1:1

[a] dr measured from ^{1}H NMR spectroscopy of the crude reaction mixture.

2.2.6 *N*-nucleophiles, Enantioretention and Gram-scalability

The utility of *N*-nucleophiles for the cyclisation were also trialled. A hydroacylation reaction between aryl sulfide-tethered aldehyde **1a** and phenylalanine-derived substrate **2p** provided smooth hydroacylation reactivity. Unlike the reaction with *N*-Boc-alkylamine **2b** (**Table 2.8**), cyclisation with this substrate did not readily occur in step i). Accordingly, acid was required, not only to epimerise the morpholine product, but to also permit initial cyclisation (**Table 2.8**).

Table 2.8. Acid evaluation for the cyclisation to compound **3ab**.

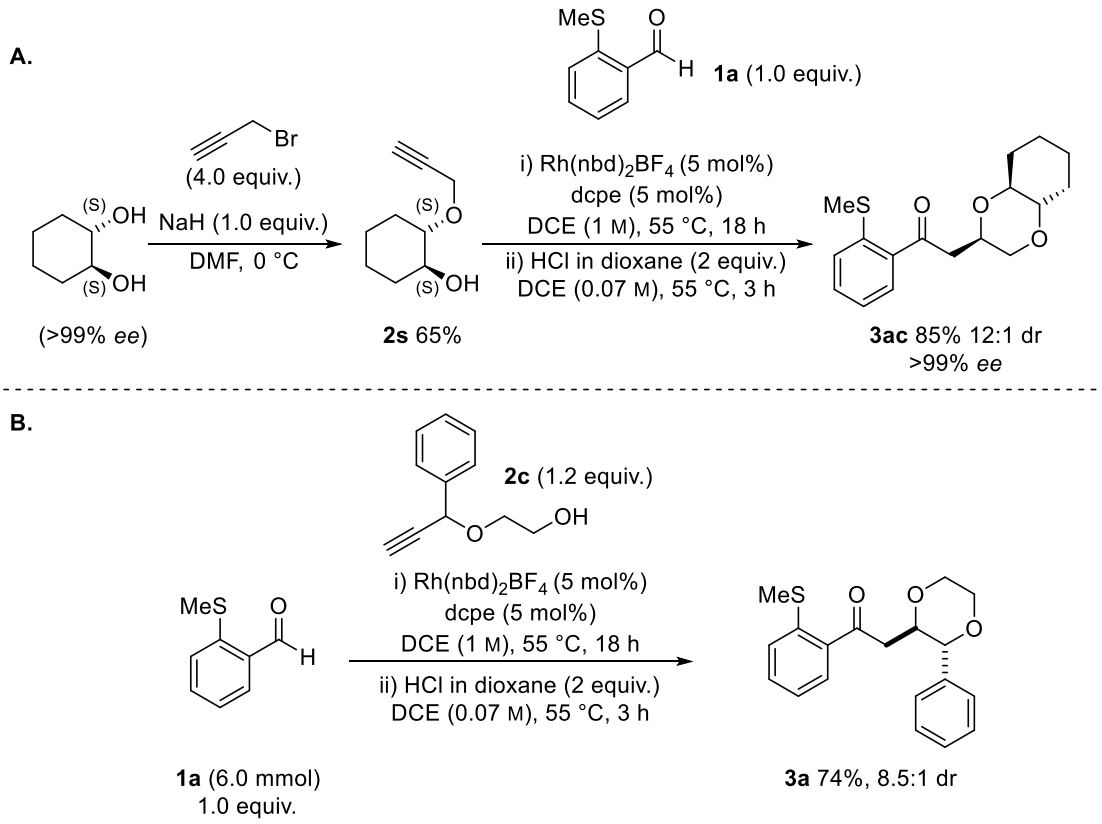


Entry	Acid	Time (h)	Total yield (%)[a]	dr[b]
1	HCl in dioxane	3	17	n/a[c]
2	TFA	36	42	n/a[c]
3	*p*-TSA	3	50	2.4:1

[a] Isolated yields; [b] dr was measured from ^{1}H NMR spectroscopy of the crude reaction mixture; [c] crude ^{1}H NMR was too complex to give a dr value.

Cyclisation was fast when using HCl in dioxane and *p*-TSA (entries 1 and 3), however, contrary to what we observed in the condition optimisation for the *O*-nucleophilic substrates, more degradation occurred upon subjection to HCl, yielding morpholine **3ab** in 17% total isolated yield. *p*-TSA provided cleaner cyclisation, yielding **3ab** in 50% total isolated yield, and a 2.4:1 dr could be observed. TFA delivered the slowest cyclisation to morpholine **3ab**, however, this gave a total isolated yield of 42% (entry 2). With all acids, *N*-Boc deprotection also occurred alongside cyclisation, to give the product as the free morpholine.

An enantiopure (*S*,*S*)-*trans*-1,2-diol could be successfully propargylated to give alkynol **2s**, which could then be coupled with aldehyde **1a**, yielding (*S*,*S*)-6,6-*trans*-bicycle **3ac**, in 85%, 12:1 dr (**Scheme 2.20A**). We showed that the reaction occurred with overall enantioretention (>99% *ee*), confirming that, as expected, the stereocentres within alkynol **2s** did not epimerise during the two-step process.

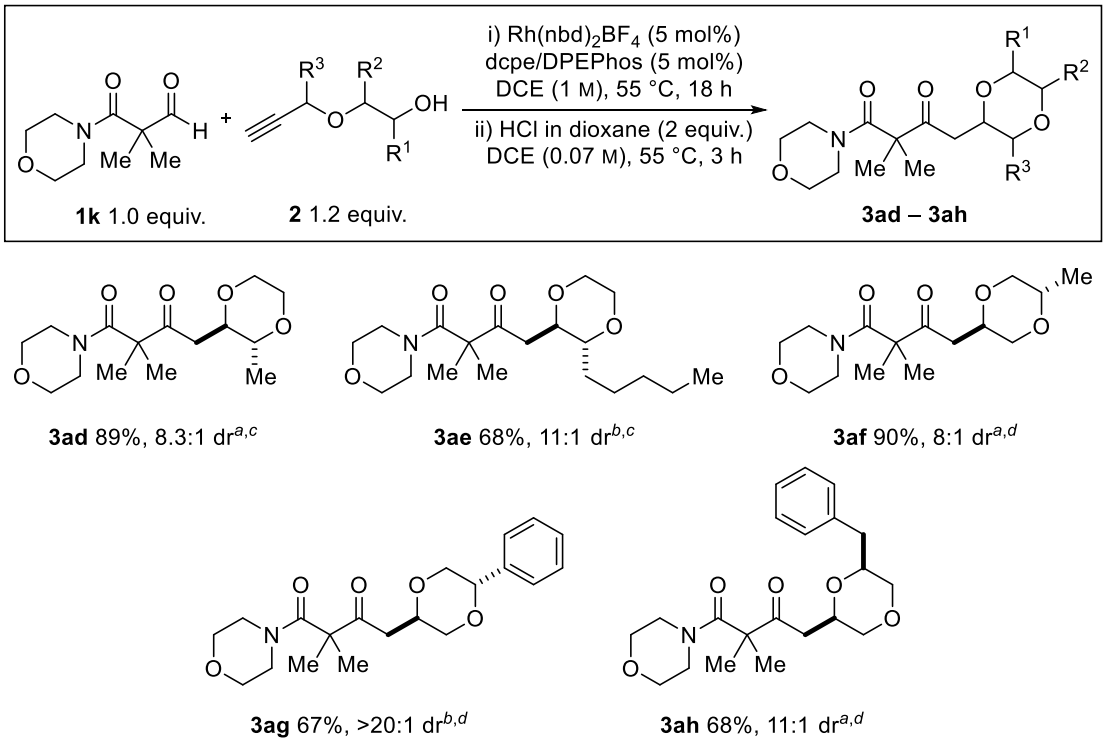


Scheme 2.20. A. Synthesis and hydroacylation of enantiopure alkynol **2s**, to generate 6,6-*trans*-bicycle **3ac** with retention of enantiopurity; **B.** 6.0 mmol scale reaction between aldehyde **1a** and alkynol **2c**.

The reaction between aldehyde **1a** and alkynol **2c**, could be performed on 6.0 mmol scale, giving dioxane **3a** in 74% total yield after recrystallisation (1.46 g) (**Scheme 2.20B**). 0.98 g of the major *anti* diastereoisomer could be isolated and used in further functionalisation reactions (section **2.2.9**). A respectable 8.5:1 dr was achievable on this scale, however, we expect that the reason for the selectivity being lower than that obtained on 0.3 mmol standard scale (13:1 dr), might be related to a differing reaction setup (see experimental, section **6.2.4**).

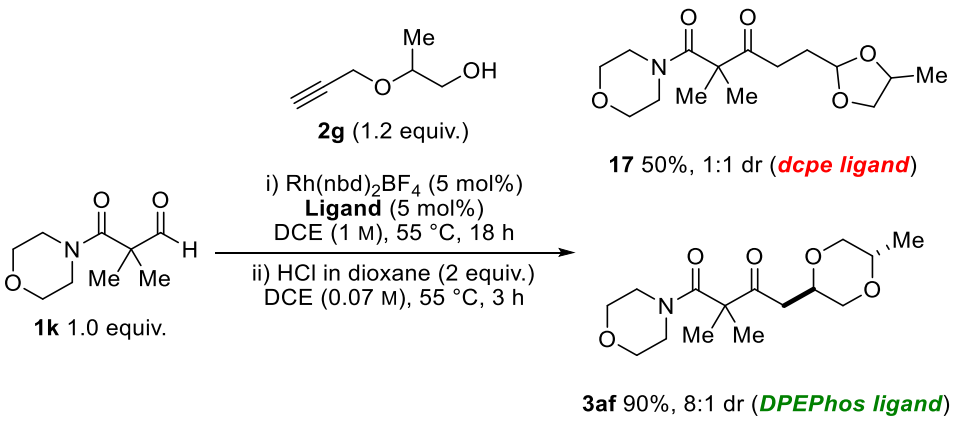
2.2.7 Expanding the Scope of *β*-amido Aldehydes

The β-keto-amido-directing aldehydes are traceless substrates for hydroacylation.[3e, 15a, 35b] It was therefore essential to show that this class of substrate was also compatible with a broader range of alkynes (**Scheme 2.21**).



Scheme 2.21. Aldehyde and alkyne scope with *β*-amido aldehyde **1k**; diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; [a] total isolated yield of both diastereoisomers; [b] isolated yield of a single major diastereoisomer; [c] reactions using dcpe; [d] reactions using DPEPhos.

Good yields and ring-closing diastereoselectivities were obtainable at all positions around the forming ring in cyclised products **3ad** – **3ah**. In terms of the catalytic system involved for these substrates, R^3-substituted alkynols were well tolerated using our standard Rh^I-dcpe catalyst. However, an alternative 1,3-dioxolane side-product **17** was formed as the major product, in 50% isolated yield, 1:1 dr, when using R^2-substiuted alkynol **2g** (**Scheme 2.22**).



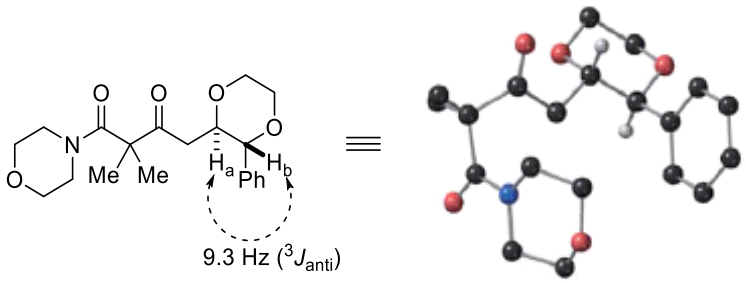
Scheme 2.22. Ligand control between the formation of 1,3-dioxolane side-product **17** and desired 1,4-dioxane **3af**.

Interestingly, the reactivity for undesired product **17** could be completely eradicated by using hemilabile DPEPhos as the ligand, regaining selectivity for the desired 1,4-dioxane product **3af** in 90% yield, 8:1 dr. Carrying on with the rest of the alkyne scope (**3ag** and **3ah**), we decided to use DPEPhos as the ligand to prevent the reoccurrence of this side-reaction. Previous experiments showed that side-product **17** forms under the Rh-dcpe-catalysed step (see experimental, section **6.2.4d**).

2.2.8 Determination of Product Relative Configuration

2.2.8a R^3 Substituents

The major diastereoisomers in all R^3-substituted products display a vicinal $^3J_{HH}$ constant 9 – 10 Hz between protons Ha and Hb. We confirm this to be an *anti*-coupling constant, where the smaller coupling constant observed within the minor diastereoisomers (3 – 4 Hz) suggests that a *syn*-configuration is present (see experimental, sections **6.2.3** and **6.2.4**). The relative stereochemistry at this position could also be determined unambiguously by X-ray crystal structure of **3k**, which had a correlating vicinal $^3J_{HH}$ constant of 9.3 Hz (**Scheme 2.23**).

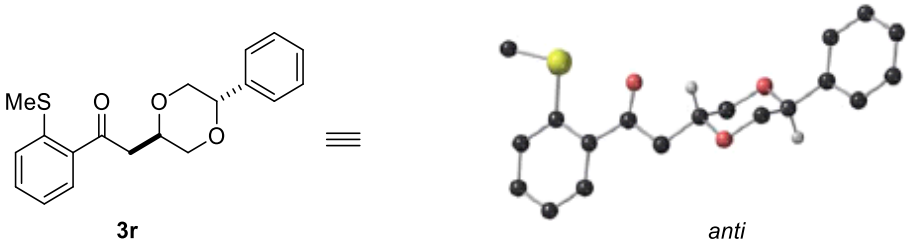


3k *anti*

Scheme 2.23. Vicinal *J*-values and X-ray crystallographic data for **3k**, as evidence for the *anti*-relative configuration in R^3-substituted products (X-ray crystallography performed by Dr Antoine de Gombert).

2.2.8b R^2 Substituents

The relative stereochemistry of most R^2-substituted products could be determined unambiguously through the X-ray crystallographic structure of phenyl-substituted product **3r** and morpholine **3x**, both of which show an *anti*-relative configuration (**Scheme 2.24**).



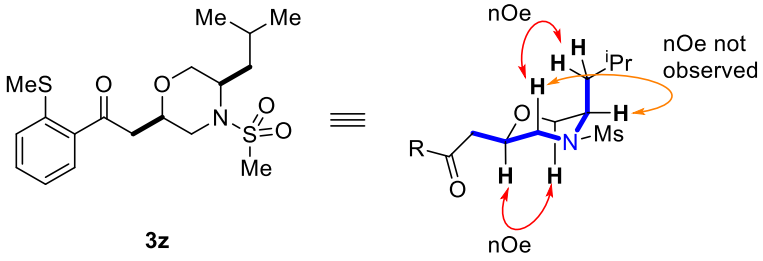
3r *anti*



3x *anti*

Scheme 2.24. X-ray structures of products **3r** and **3x** both showing an *anti*-relative configuration (X-ray crystallography performed by Dr Antoine de Gombert).

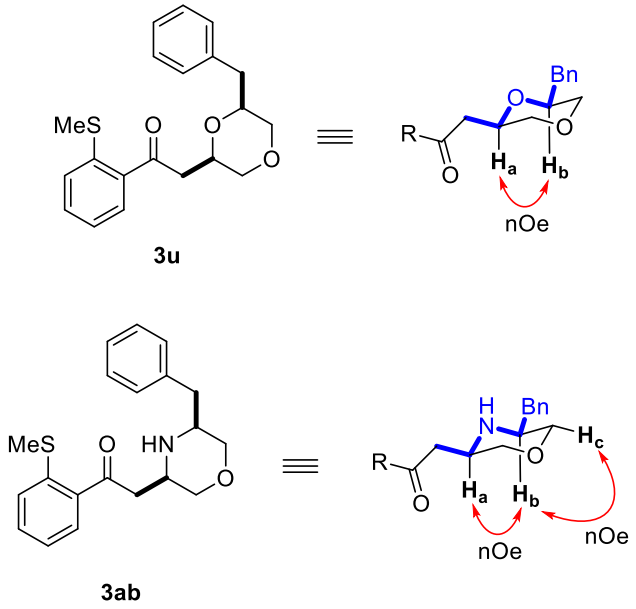
However, for the leucine-derived product **3z**, ^{1}H NOESY correlations detected a *syn*-relative configuration (**Scheme 2.25**). This is consistent with the diastereoselectivity observed in a previous method towards morpholines of similar ring substitution.[82]



Scheme 2.25. ^{1}H NOESY correlations within morpholine **3z**, revealing it's *syn*-relative configuration.

2.2.8c R^{1} Substituents

For R^{1}-substituted products, the major diastereoisomer relative configuration could be easily determined using ^{1}H NOESY correlations (**Scheme 2.26**).



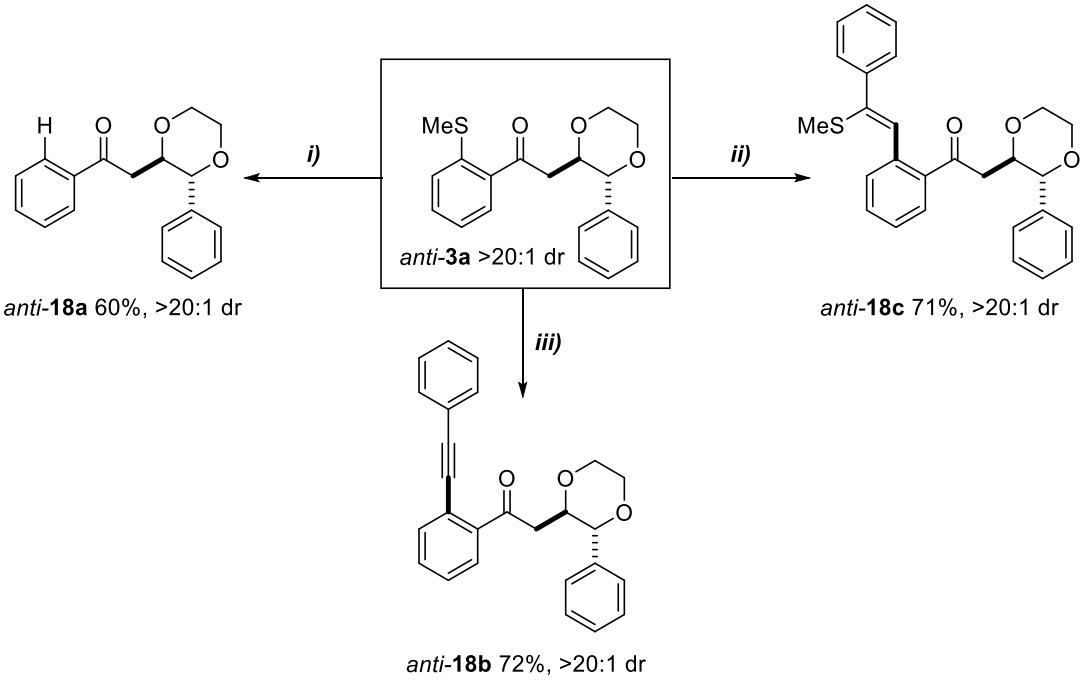
Scheme 2.26. NOESY analysis addressing the *syn*-relative configurations in R^{1}-substituted products **3u** and **3ab**.

For products **3u** and **3ab**, a key NOESY interaction between methine environments Ha and Hb could be detected. This suggests that the interacting environments are likely to have an axial-axial relationship to one another, suggesting that a *syn*-relative configuration exists.

All related NMR spectra that accompany these assignments, alongside conclusive data for minor diastereomer relative configurations, can be found in chapter 6 (see experimental, sections **6.2.3** and **6.2.4**).

2.2.9 Product Derivatisation

Unlike the β-ketoamide products, the aryl sulfide products contain a tether which needs to be removed/functionalised after hydroacylation, to generate traceless derivatives.[34b, 83] We initially wanted to demonstrate how the newly formed heterocycle products could tolerate C–S bond functionalisations, which have been previously studied within our laboratory (**Scheme 2.27**).

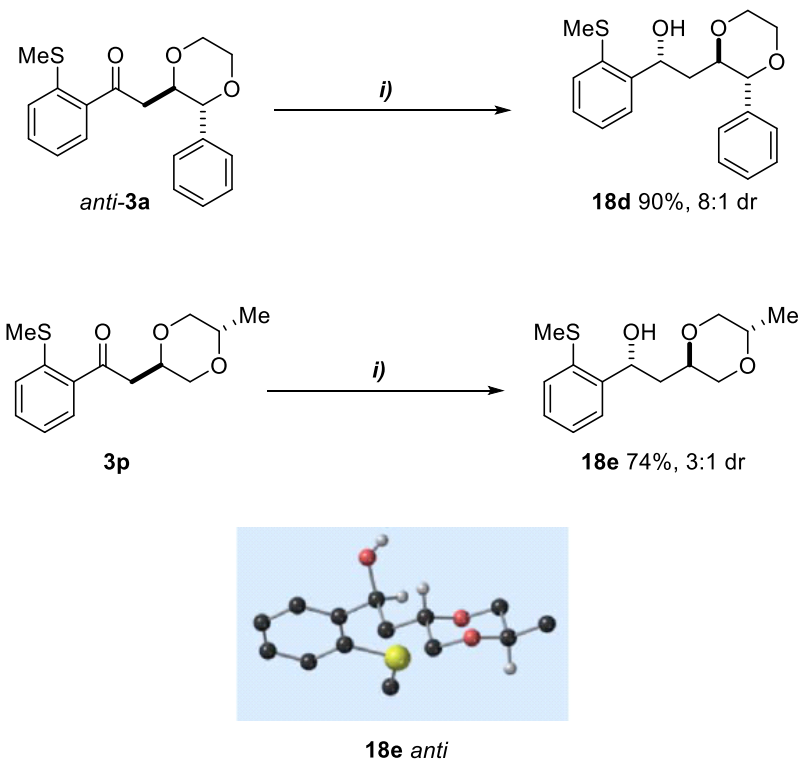


Scheme 2.27. C–S bond activations on saturated heterocycle hydroacylation adducts; i) $Rh(nbd)_2BF_4$ (5 mol%), dcpm (5 mol%), EtO_3SiH (10 equiv.), CH_2Cl_2 (0.15 M), r.t, 24 h; ii) $Rh(nbd)_2BF_4$ (5 mol%), Xantphos (5 mol%), phenylacetylene (2.0 equiv.), DCE (0.3 M), 100 – 120 °C, 21 h; iii) $Rh(nbd)_2BF_4$ (5 mol%), dcpe (5 mol%), CuBr (2.0 equiv.), Ag_2CO_3 (1.0 equiv.), phenylacetylene (2.0 equiv.), DCE (0.075 M), 80 °C.

We firstly showed how a rhodium-catalysed, silane-mediated, desulfurisation could yield phenyl ketone **18a** in 60% yield.[34b] We further demonstrated how the SMe tether could be recycled in a rhodium-catalysed carbothiolation process, generating

product **18c** in 71% yield.[83b] The SMe tether was successfully activated in a Sonogashira-type coupling to form coupled adduct **18b** in 72% yield.[83d]

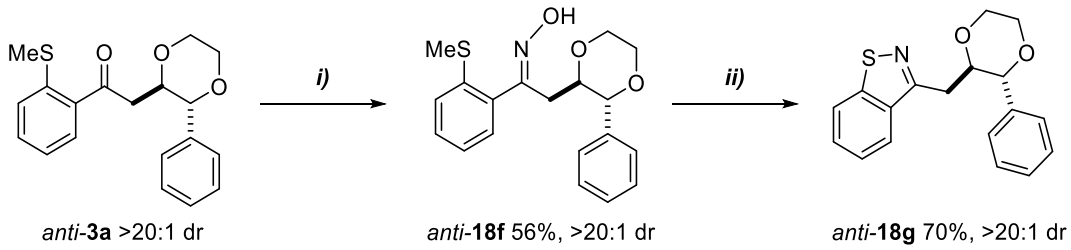
We next turned our focus to various ketone transformations, one of which being a diastereoselective reduction on product **3a**, using $Eu(OTf)_3$ and $LiBH_4$, to afford alcohol **18d** in 90% yield and 8:1 dr.[84] These exact conditions were also applied to dioxane **3p**, containing a distal methyl-substituent, giving moderate diastereoselectivity. An X-ray crystallographic structure of the major diastereoisomer of alcohol **18e** showed that the *anti*-diastereoisomer was preferentially formed from these reductions (**Scheme 2.28**).

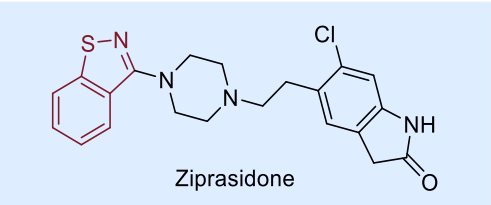


Scheme 2.28. Diastereoselective ketone reductions on saturated heterocycle products; i) $Eu(OTf)_3$, $LiBH_4$, −78 °C, Et_2O, 2 − 3 h.

We next employed a ketone transformation, *via* a two-step sequence from product *anti*-**3a**, to demonstrate how the sulfide tether could be incorporated into a medicinally relevant heterocycle within a tracless bis-heterocyclic scaffold (**Scheme**

2.29). Oxime **18f** could be initially formed from a condensation with hydroxylamine hydrochloride in 56% isolated yield.[85] Activation of the oxime using acetic anhydride and pyridine resulted in the formation of benzoisothiazole **18g**, in 70% yield.[86] Such a heterocycle features in FDA approved drug scaffolds,[87] with one example being ziprasidone.[88]





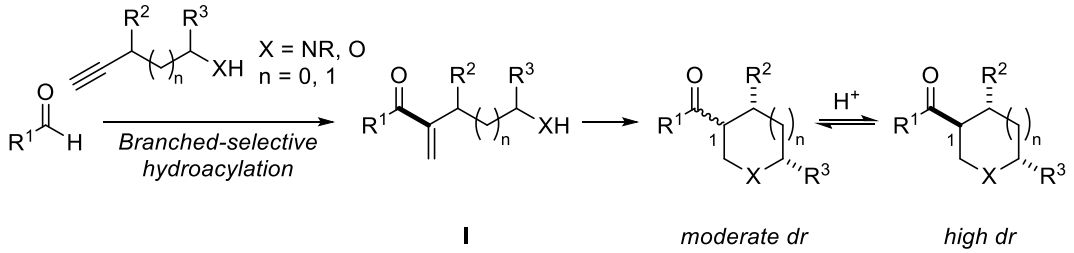
Scheme 2.29. Ketone condensation of dioxane *anti*-**3a**, towards benzoisothiazole formation; i) $NH_2OH{\cdot}HCl$ (4.0 equiv.), pyridine (4.0 equiv.), MeOH, 60 °C, 20 h; ii) Ac_2O (4.0 equiv.), pyridine, 120 °C, 20 h.

2.3 Conclusions and Future Work

To summarise, an efficient one-pot hydroacylation/conjugate-addition sequence has been developed to deliver a broad range of substituted *O*- and *N*-saturated heterocycles. The Rh^I-dcpe catalyst, employed for the hydroacylation step, offers a balance of exemplary conversion and excellent linear regioselectivity with various nucleophile-substituted alkynes. The diastereoselectivity of the second step can be enhanced by epimerising the forming enone, through ring-closing reversibility. We found that HCl can offer excellent dr for most substrates (up to >20:1 dr), providing clean epimerisation with minimal product degeneration, to access single

diastereoisomers in high yields. The heterocyclic products have also shown to tolerate a range of different C–S bond and ketone functionalisations, to yield traceless, and synthetically intriguing scaffolds.

Future work in this area could investigate the formation of fully saturated heterocycles derived from branched-selective alkyne hydroacylation (**Scheme 2.30**).



Scheme 2.30. Branched-selective alkyne hydroacylation to access fully saturated heterocycles.

Ligands that our laboratory have used to permit branched selective alkyne hydroacylation, such Ampaphos and (*o*-^{i}Pr)-dppe,[3e, 17] could be used to access branched enone intermediate **I**. The following *endo*-trig cyclisation would access heterocycles with a different substitution pattern to the ones synthesised in this chapter. The forming stereocentre at C1 could also epimerise; it would be interesting to observe whether the diastereoselectivity of these products could also be controlled through a similar two-step process.

Chapter 3 − Azine *N*-oxides as Effective Controlling Groups for Rhodium-Catalysed Intermolecular Alkyne Hydroacylation

3.1 Introduction

A wide variety of different pharmaceutical and agrochemical compounds contain C(2)-substituted azines cores[89] (**Figure 3.1**). Incorporation of these units within drugs can deliver a collection of benefits, such as target selectivity and potency, and other traits including enhanced lipophilicity and aqueous solubility.[67]

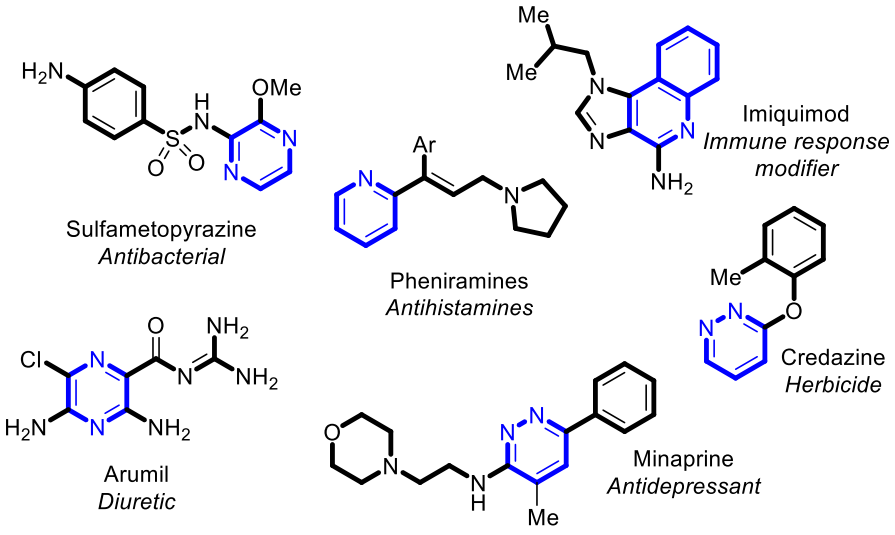


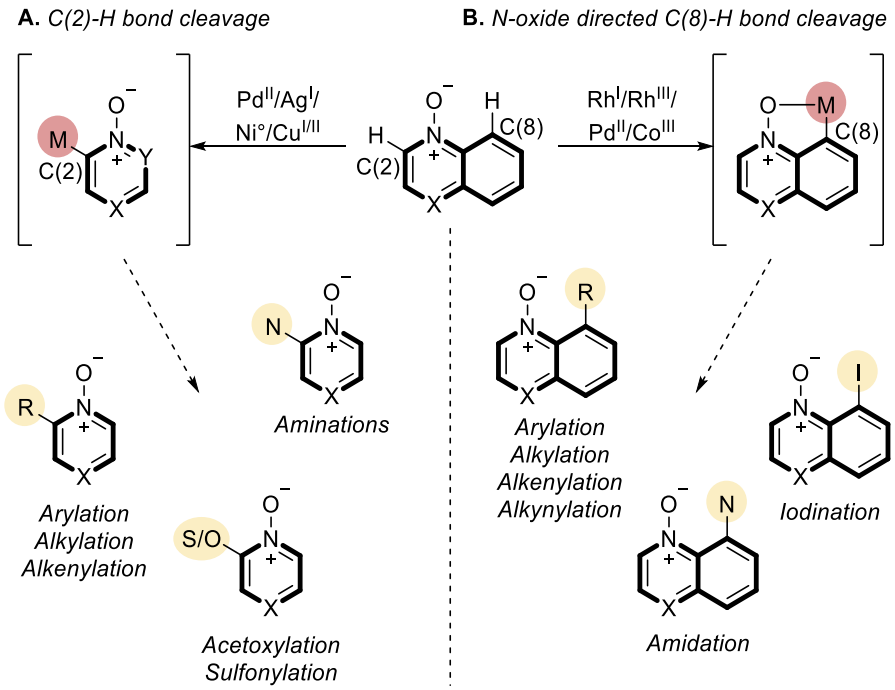
Figure 3.1. A selection of C(2)-substituted azines present in biologically important compounds.

Developing new methods for their production and functionalisation is highly important for drug development.

The *N*-oxide is a versatile directing group, proved to be effective for azine C–H functionalisation.[1, 90] The coordinating group consists of a single '*O*' atom which can be easily removed within a simple redox transformation.[91] This removal process

can sometimes be included in a reaction's catalytic cycle, usually through *O*-atom transfer[92] or direct deoxygenation.[93] These processes are significant, as they relinquish the need for external oxidants, and other *N*-oxide reduction steps.

N-oxide groups can be used to direct a series of azine C(2)-H and C(8)-H bond activations towards a range of functionalised products (**Scheme 3.1**). C(2)-H functionalisations have been successful with a variety of different catalytic systems. The C(2)-regioselectivity is said to be derived from the enhanced reactivity that the *N*-oxide provides to the C–H bond at this position.[94] This particular class of reactivity is seen in different $Pd^{II}/Ag^{I}/Ni^{0}/Cu^{I/II}$-catalysed functionalisations, towards C–C,[95,91b] C–O,[96] C–S[97] and C–N[98] coupled products (**Scheme 3.1A**).

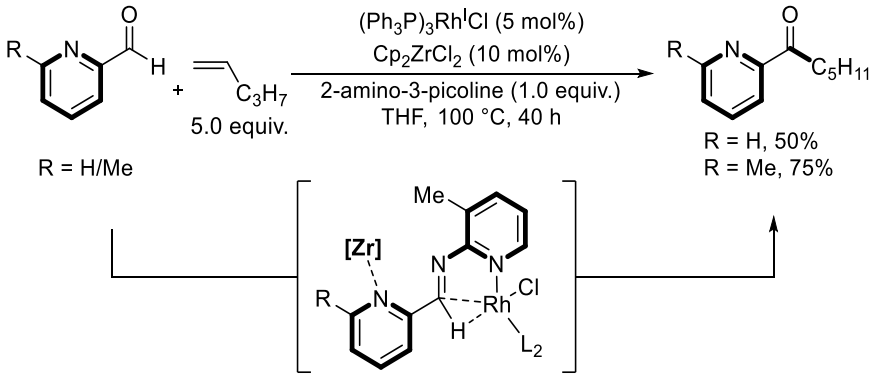


Scheme 3.1. Azine C(2)-H and C(8)-H functionalisation strategies using *N*-oxides.

A previous investigation on azine C(2)-H functionalisation by Chang,[91b] has shown that a metal-coordinated *N*-oxide species is likely to be inactive, lying outside of the desired catalytic cycle. Despite this observation, an alkenylation reaction by Shibata[99] was the first method to demonstrate how quinoline *N*-oxide could offer an

alternative C(8)-regioselectivity, with C–H activation proceeding through direct coordination of the *N*-oxide to a Rh^{I}-catalyst. Such a process has been expanded to a range of other systems, that employ Rh^{III}/Ir^{III}/Pd^{II} and Co^{III}-catalysts to generate C–C,[92a, 92c, 92d, 99-100] C–N[101] and C–I[101] functionalised products (**Scheme 3.1B**).

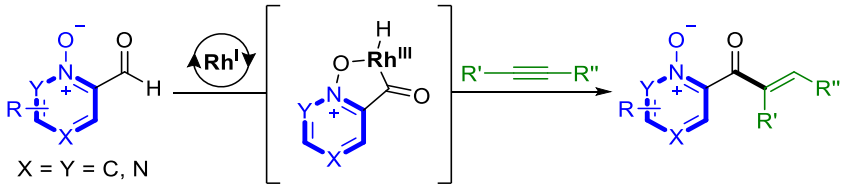
Shibata's alkenylation made us consider the use of azine *N*-oxide-directed C–H activation in the context of intermolecular hydroacylation.[3i-o] Despite their potential value, intermolecular hydroacylation reactions with 2-formyl azines are uncommon, because the free lone-pair on the azine substrate can prohibit the formation of key Rh^{III} intermediates, required for a successful transformation. Jun and Lee previously used 2-pyridyl aldehydes as part of an aldimine-tethered strategy for the intermolecular hydroacylation reaction with 1-pentene (**Scheme 3.2**). Moderate to high yields of the hydroacylation product could only be obtained when using a zirconium additive and a sterically obstructing C(6)-Me group, to block the disfavoured coordination of the *N*-lone pair on the aldehyde. A high loading of the alkene was also required (5.0 equiv.).[39]



Scheme 3.2. Challenges faced with pyridyl groups in intermolecular hydroacylation.

N-oxides have not previously been used to direct aldehyde C–H activations, however, we envisaged that they could produce a solution to the challenges that accompany the use of this substrate class within hydroacylation reactions. We

therefore disclose the use of azine *N*-oxides in their first known aldehyde C–H activation, to permit an intermolecular hydroacylation reaction (**Scheme 3.3**).[102]

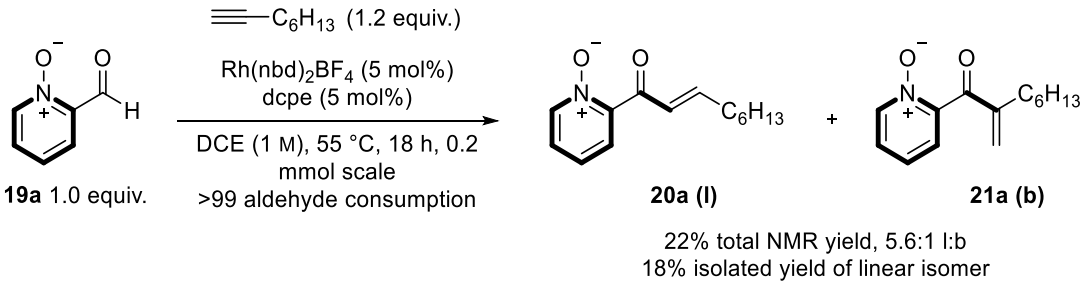


Scheme 3.3. Azine-*N*-oxides as a solution to the compromised reactivity of 2-formyl azines.

3.2 Results and Discussion

3.2.1 Reaction Optimisation

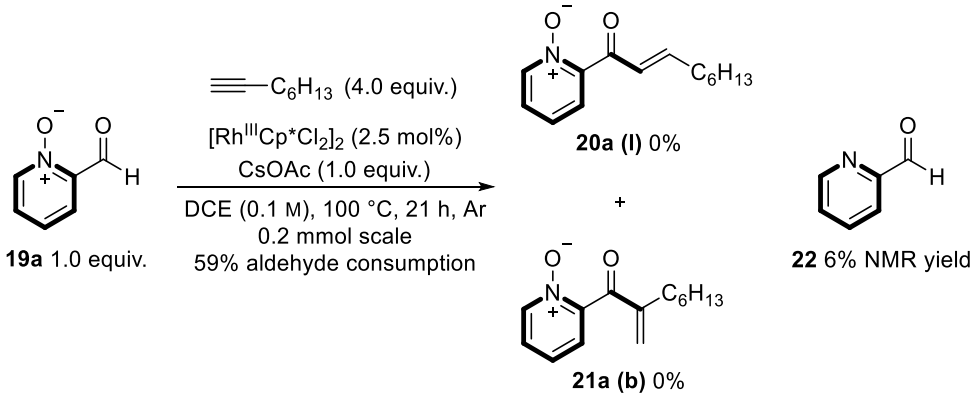
We began our investigation by studying the reaction between aldehyde **19a** and 1-octyne. When employing a Rh-dcpe catalyst, we were delighted to obtain both regioisomers **20a** and **21a**, in a 22% total NMR yield, and 5.6:1 crude l:b (linear:branched) selectivity (**Scheme 3.4**). The linear isomer **20a** could be isolated in 18% yield.



Scheme 3.4. Initial reactivity between aldehyde **19a** and 1-octyne.

Full consumption of aldehyde **19a** over the 18 h reaction duration was noted. With no other distinct side products observable by ^{1}H NMR spectroscopy of the crude reaction mixture, we presumed this to be a result of degradation. Rh^{I}-species have been previously reported to oxidatively cleave the N–O bond within azine *N*-oxides.[92] This prompted us to try a set of Rh^{III}-catalysed hydroacylation conditions

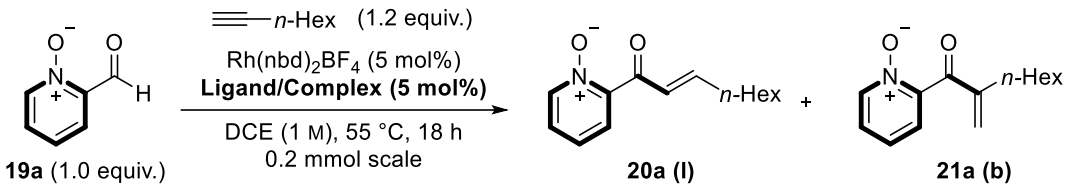
by Zhang *et al*, which delivers a redox-neutral catalytic cycle, avoiding the more reducing Rh^{I}-species.[10b] Unfortunately, no desired hydroacylation product was observed from these conditions (**Scheme 3.5**). Interestingly, the free 2-formyl pyridine **22** could be detected as a distinct side-product.



Scheme 3.5. A lack of desired reactivity when using a Rh^{III}-catalysed hydroacylation system.[10b]

Returning the Rh^{I}-catalytic system, we then evaluated several different phosphine ligands within the reaction (**Table 3.1**).

Table 3.1. Initial ligand evaluation.

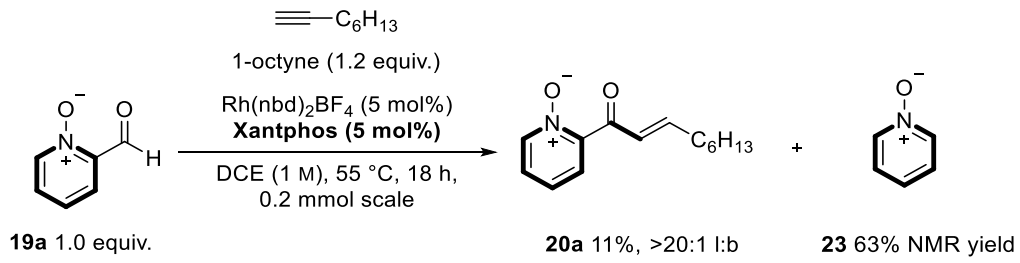


Entry	Ligand/ Complex	Aldehyde consumption (%)[c]	l:b	20a + 21a (%)[d,e]
1	dcpe	>99	5.6:1	22
2	dppe	>99	>20:1	25
3	dcpm	86	-	0
4[a]	PPh_3	64	-	0
5	DPEPhos	>99	2.8:1	53(54)
6	*rac*-BINAP	>99	1:1	40
7	dppbenz	>99	>20:1	17
8	dppf	>99	1.9:1	61(67)
9[b]	dppf	94	1.3:1	43
10	DCEPhos	33	5.1:1	2
11	*t*-Bu-Xantphos	35	-	0
12	dppb	82	14:1	15
13	dppp	>99	>20:1	17

[a] 10 mol% PPh_3 used; [b] 2.5 mol% $[Rh(COD)Cl]_2$ pre-catalyst was used instead of $Rh(nbd)_2BF_4$; [c] Aldehyde consumption was determined by ^1H NMR spectroscopy of the crude reaction mixture; [d] ^1H NMR yields were based on ^1H NMR standard (methyl-3,5-dinitrobenzoate); [e] Isolated yields in parentheses.

These results indicated that larger bite-angle bidentate ligands produced more promising reactivity, specifically DPEPhos, *rac*-BINAP and dppf (entries 5, 6 and 8). These three ligands contain phenyl-substituted phosphines, which exhibit a higher degree of π-acidity. Comparing this with the low yields exhibited by the alkyl-phosphine ligands (**Table 3.1**, entries 1, 3, 10 and 11), we concluded that using ligands that facilitate a more electron-deficient metal is better tolerated by these tethering groups. It was unsurprising that the Rh-BINAP catalyst provided good reactivity, as similar catalysts feature in Shibata's quinoline C(8)-H alkenylation chemistry.[99] The high yield produced by the dppf-derived catalyst is notable, as this ligand has a strong reputation for promoting hydroacylation directed by a salicaldehyde phenolate-anion,[76] a coordinating group that is *iso*-electronic to the

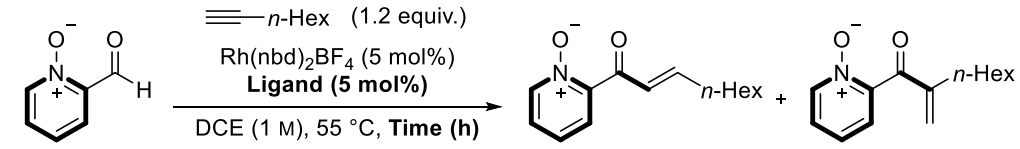
pyridine-*N*-oxide substrate **19a**. Of the three desired ligands, DPEPhos delivered the most promising linear regioselectivity (2.8:1, l:b). A wider bite-angle ligand, such as Xantphos, produced a very different result (**Scheme 3.6**). Although we could achieve >20:1 l:b selectivity, linear product **20a** could only be produced in 11% yield, with reductive decarbonylation to *N*-oxide **23** being the dominating transformation (63% NMR yield).



Scheme 3.6. A prevalent reductive decarbonylation side reaction with Rh^{I}-Xantphos.

Monitoring the reaction times with both dppf and DPEPhos derived catalysts showed that dppf permits a fast hydroacylation (**Table 3.2**, entry 1), whereas the DPEPhos reaction was incomplete after 6 h (**Table 3.2**, entry 2).

Table 3.2. Shorter reaction times for DPEPhos and dppf.



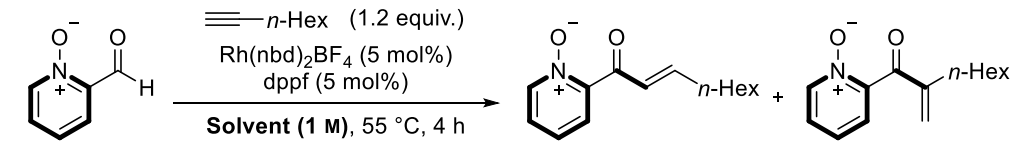
Entry	Ligand	Time (h)	l:b	20a + 21a (%)[a,b]
1[c]	dppf	4	2.1:1	74(66)
2[d]	DPEPhos	6	2.5:1	27

[a] ^{1}H NMR yields were based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [b] Isolated yields in parentheses; [c] >99% aldehyde consumption; [d] 55% aldehyde consumption.

Trialling the use of other solvents in the dppf system was briefly attempted to improve the regioselectivity. However, MeCN, CH_2Cl_2 and *t*-BuCN failed to alter the l:b ratio (**Table 3.3**, entries 1 to 3). We realised that the higher yield seen for the

Rh^{I}-dppf catalyst could be attributed to its fast hydroacylation reactivity, which might minimise the progression of decomposition pathways. Accordingly, promoting a faster hydroacylation reaction with DPEPhos would be a beneficial step towards a desirable balance of yield and selectivity.

Table 3.3. Solvent evaluation for the Rh-dppf catalytic system.



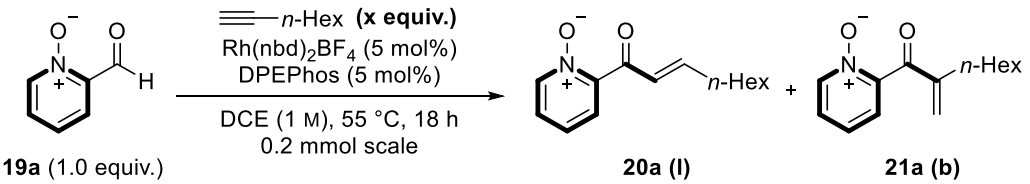
19a (1.0 equiv.) **20a (l)** **21a (b)**

Entry	Solvent	Aldehyde consumption (%)[a]	l:b	20a + 21a (%)[b,c]
1	MeCN	97	1.8:1	65
2	CH_2Cl_2	49	2:1	28
3	*t*-BuCN	73	1.8:1	40

[a] Aldehyde consumption was determined by crude ^{1}H NMR spectroscopy; [b] ^{1}H NMR yields were based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [c] Isolated yields in parentheses.

Pleasingly, increasing the loading of 1-octyne to 2.0 equivalents made a significant improvement in reactivity with DPEPhos, providing the desired products in 67% total yield, and 2.8:1 l:b (**Table 3.4**, entry 3). From this result, subsequent adjustments in reaction scale, concentration (M) and reaction time (h) led to an optimised result of 73% total isolated yield of **20a** and **21a**, with a regioselectivity of 2.9:1 l:b (entry 10).

Table 3.4. Condition optimisation with a Rh^{I}-DPEPhos catalytic system.



19a (1.0 equiv.) **20a (l)** **21a (b)**

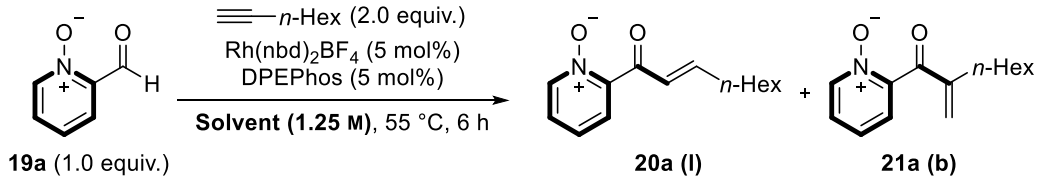
Entry	Alkyne (equiv.)	Scale (mmol)	Aldehyde conc. (M)	Time (h)	l:b	20a + 21a (%)[b,c]
1	1.2	0.2	1.0	18	2.8:1	53(54)
2	1.5	0.2	1.0	18	2.8:1	64
3	2.0	0.2	1.0	18	2.8:1	67
4	3.0	0.2	1.0	18	2.4:1	59
5	2.0	0.3	1.0	18	2.9:1	57
6	2.0	0.3	1.25	18	3.1:1	73
7	2.0	0.3	1.5	18	2.8:1	68
8[d]	2.0	0.3	1.25	4	2.9:1	66
9[e]	2.0	0.3	1.25	5	2.8:1	76
10	2.0	0.3	1.25	6	2.9:1	79(73)

[a] Aldehyde consumption was determined by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] ^{1}H NMR yields were based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [c] Isolated yields in parentheses; [d] 82% aldehyde conumption; [e] 98% aldehyde consumption.

Showing that the reaction could work in solvents, other than in DCE, was also important (**Table 3.5**). MeCN produced a yield that matched what could be achieved with DCE (entry 3), however, the crude regioselectivity was reduced to 1.8:1 l:b. The other solvents provided poorer levels of conversion.

Throughout the reaction optimisation, the regioselectivities gained with Rh-DPEPhos were generally poor. Although some additional experiments showed that the linear regioselectivity could be increased when using this catalyst at lower temperatures, the product yields and reaction conversions suffered (see experimental, section **6.3.3**). We expected that the linear regioselectivity would be highly substrate dependent. With this in mind, we decided to test other alkynes under our optimised conditions.

Table 3.5. Solvent Evaluation for the Rh-DPEPhos catalytic system.



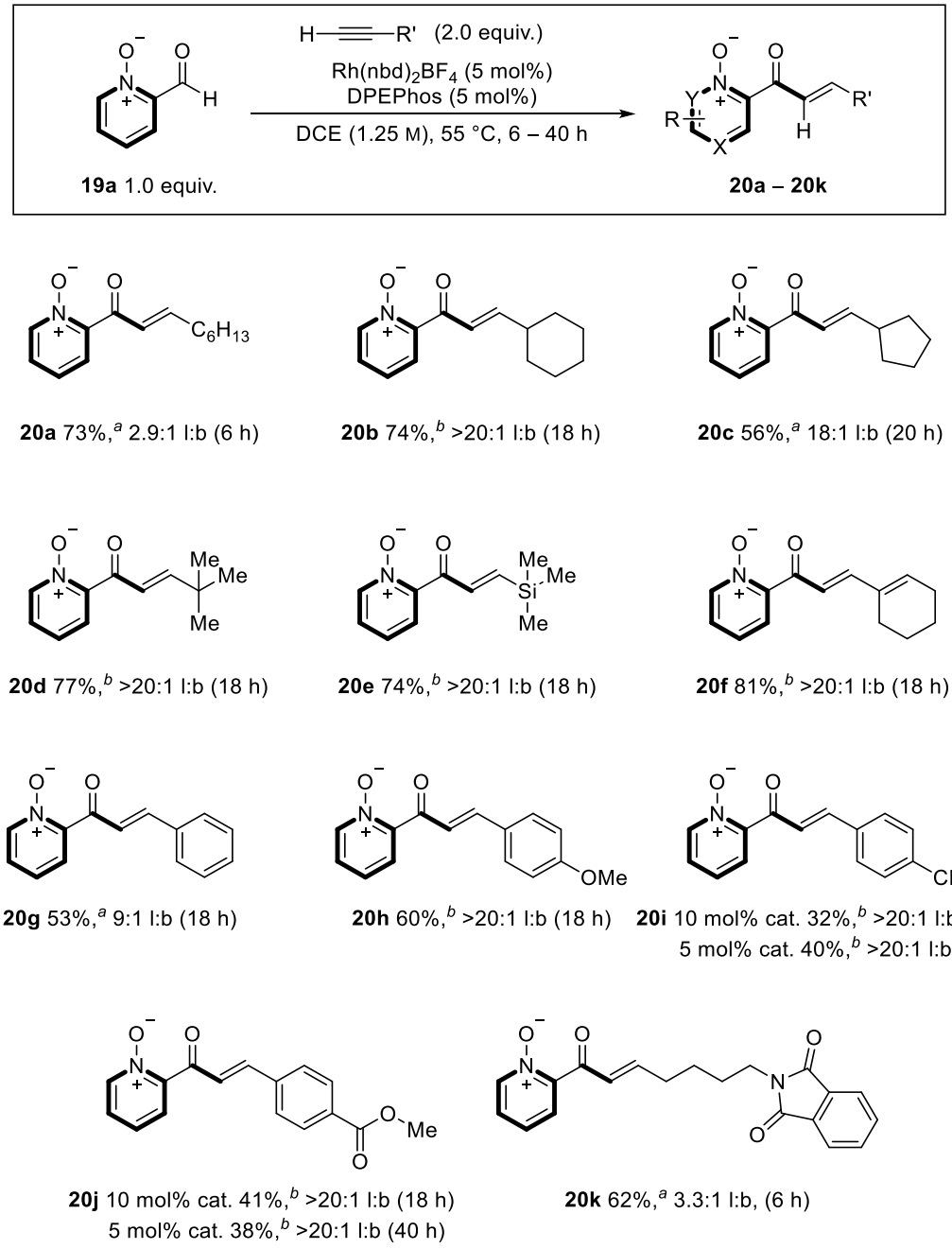
19a (1.0 equiv.) **20a (l)** **21a (b)**

Entry	Solvent	Aldehyde consumption (%)[a]	l:b	20a + 21a (%)[b,c]
1	Acetone	40	1.2:1	29
2	CH_2Cl_2	75	2.7:1	45
3	MeCN	>99	1.8:1	72
4	1:1 DCE:Dioxane	53	2.1:1	25
5	1:1 DCE:THF	54	2:1	25
6	1:1 DCE:Toluene	53	2.3:1	27
7	1:1 DCE:*o*-Xylene	65	2.3:1	27

[a] Reaction conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] ^{1}H NMR yields were based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [c] Isolated yields in parentheses.

3.2.2 Terminal Alkyne Reaction Scope

With the newly optimised conditions in hand, we decided to subject different terminal alkynes to the reaction (**Scheme 3.7**). Although a return to the longer reaction time (18 h) was required for the more sterically hindered aliphatic alkynes, they delivered a notable increase in linear selectivity, up to >20:1 l:b, in examples **20b** – **20d**. TMS-acetylene reacted similarly to *t*-Bu-acetylene, delivering linear hydroacylation product **20e** in 74% and >20:1 l:b selectivity. A cyclohexenyl-substituted alkyne, provided linear product **20f** in the highest yield of 81%, with >20:1 l:b selectivity.

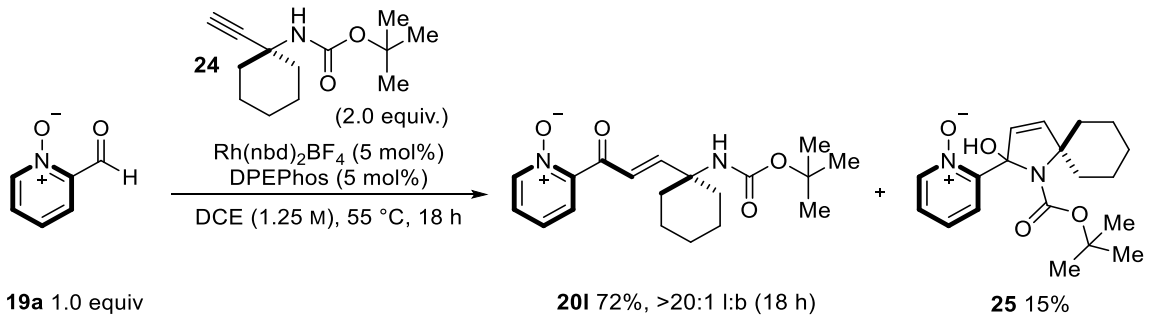


Scheme 3.7. Reaction scope of both alkyne and aldehyde components using 0.3 mmol of aldehyde; [a] yield corresponds to the total isolated yield of both regioisomers; [b] yield corresponds to the isolated yield of the single linear regioisomer.

The phenylacetylene derived alkynes were more challenging substrates, showing poorer reactivity (**20g – 20i**). However, >20:1 l:b selectivity could be easily obtained by incorporating CF_3 or CO_2Me as the *para*-substituent (**20i** and **20j**). Full

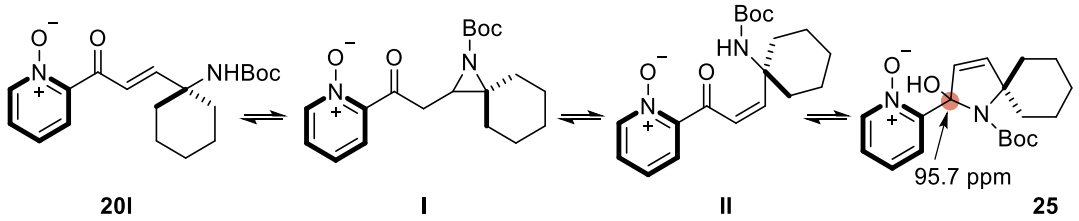
conversion with these two alkynes could only be achieved with a higher catalyst loading (10 mol%), or longer reaction duration (40 h).

We next evaluated the efficacy alkynes substituted with *N*-functionality. A phthalimide-tethered alkyne worked well (**Scheme 3.8**), providing product **20k** in 62% yield, with similar selectivity to that achieved with 1-octyne (3.3:1 l:b). When subjecting cyclohexyl-substituted propargylamine **24** to the standard conditions, the linear hydroacylation product **20l** could be obtained in 72%, >20:1 l:b, however, a spirocyclic side-product **25** was additionally isolated in 15% yield (**Scheme 3.8**).



Scheme 3.8. Showing the coupling of aldehyde **19a** with propargylamine **24**, to generate linear product **20l** and a spirocyclic side-product **25**; (This reaction was performed by Dr Jagadeesh Kalepu).

A possible mechanism for the formation of side-product **25** is shown in **Scheme 3.9**. A 3-*exo*-trig cyclisation of linear product **20l** could firstly generate aziridine intermediate **I**. Re-opening of the ring can now generate two possible stereoisomers, one being *cis*-intermediate **II**. Intramolecular nucleophilic attack of the *N*-Boc amine onto the carbonyl group would then generate the hemiaminal side-product **25**. A distinct quaternary carbon shift of 95.7 ppm, within the ^{13}C NMR spectrum of isolated side-product **25**, helped us to conclude its formation, as this shift is indicative of a hemiaminal quaternary environment.[103]

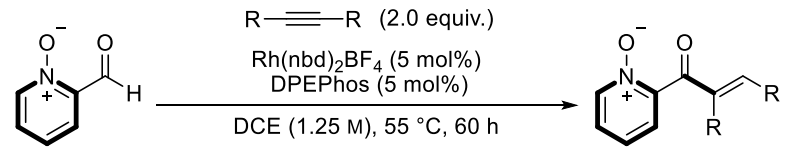


Scheme 3.9. A proposed mechanism for the formation of hemiaminal side-product **25**.

3.2.3 Reactions with Internal Alkynes

With a satisfactory scope of terminal alkynes demonstrated, focus was then turned to the use of internal alkyne substrates. We started by observing the reactivity of symmetrical internal alkynes (R = Ph and *n*-Pr respectively) under our standard conditions (**Table 3.6**). Unfortunately, low conversion to the desired product was observed in each case, and the phenyl derived hydroacylation product **20m** was isolated as an inseparable mixture with the remaining aldehyde **19a**.

Table 3.6. Initial reactivity with internal alkynes.

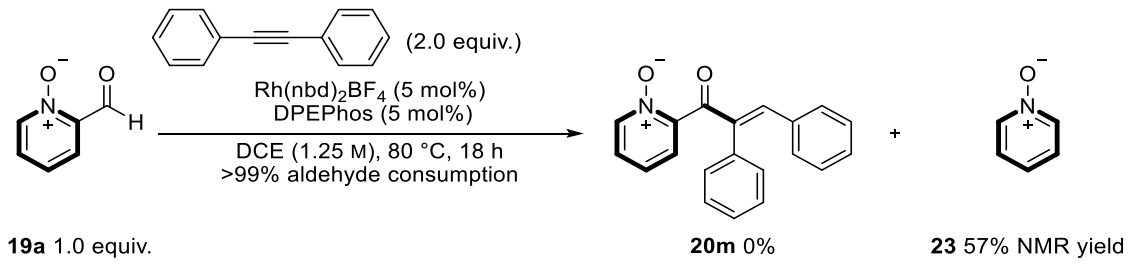


19a 1.0 equiv. **20m** and **20n**

Entry	Alkyne R	Yield/%
1	Ph	18[a](**20m**)
2	*n*-Pr	Trace(**20n**)

[a] Isolated as an inseparable 1:1.4 product : aldehyde mixture.

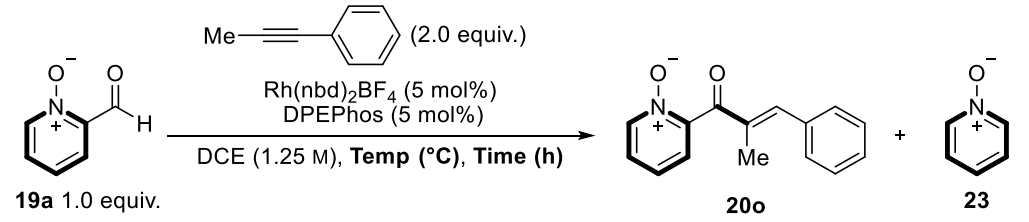
To circumvent the issues with poor conversion, 1,2-diphenylacetylene was submitted to a higher reaction temperature (80 °C), however, no desired product was observed (**Scheme 3.10**), and reductive decarbonylation to pyridine *N*-oxide **23** prevailed (57% NMR yield).



Scheme 3.10. Higher temperature reaction with 1,2-diphenylacetylene.

Attempting a less sterically hindered and unsymmetrical alkyne, 1-phenyl-1-propyne, under the previously optimum conditions at 55 °C, similarly yielded the hydroacylation product **20o** in a poor result of 18%, 3.2:1 rr (rr = relative regioselectivity), due to incomplete reaction conversion (**Table 3.7**, entry 1). However, reductive decarbonylation of aldehyde **19a** did not occur when increasing the temperature to 80 °C, and desired hydroacylation product **20o** could be obtained in 39% yield, 15:1 rr (entry 2).

Table 3.7. Reactivity with 1-phenyl-1-propyne.



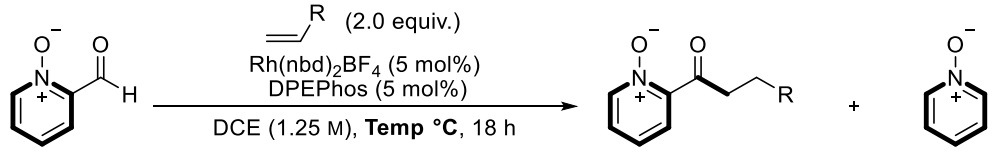
Entry	Alkyne R	Temp (°C)	Time (h)	20o (%)	23 (%)
1[a]	Me	55	72	18[c](3.2:1 rr)[e]	0
2[b]	Me	80	18	39[d](15:1 rr)[e]	0

[a] Incomplete conversion; [b] >99% consumption of aldehyde **19a**; [c] total ^{1}H NMR yield of both regioisomers, based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate); [d] isolated yield of a single regioisomer; [e] Relative regioselectivity determined by crude ^{1}H NMR spectroscopy.

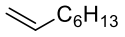
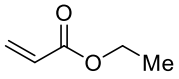
3.2.4 Reactions with Terminal Alkenes

Terminal alkenes proved to be highly challenging substrates that remained unreactive under our standard catalytic system (**Table 3.8**). 1-Octene and ethyl acrylate substrates were firstly examined at the standard reaction temperature (55 °C). Only moderate levels of aldehyde consumption were observed after 18 h, with no detectable hydroacylation products (entries 1 and 3). Subjecting 1-octene to a higher reaction temperature of 80 °C gave full consumption of aldehyde **19a**, however, a large quantity of the decarbonylation side-product **23** was again observed (entry 2).

Table 3.8. Reactivity with terminal alkenes.



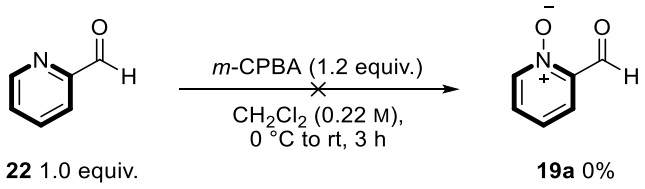
19a 1.0 equiv. **20p** and **20q** **23**

Entry	Alkene	Temp (°C)	Aldehyde Consumption (%)[a]	Yield (%)	23 (%)[a]
1		55	23	0	0
2		80	>99	0	59
3		55	33	0	0

[a] ^{1}H NMR yields and aldehyde consumption are based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate).

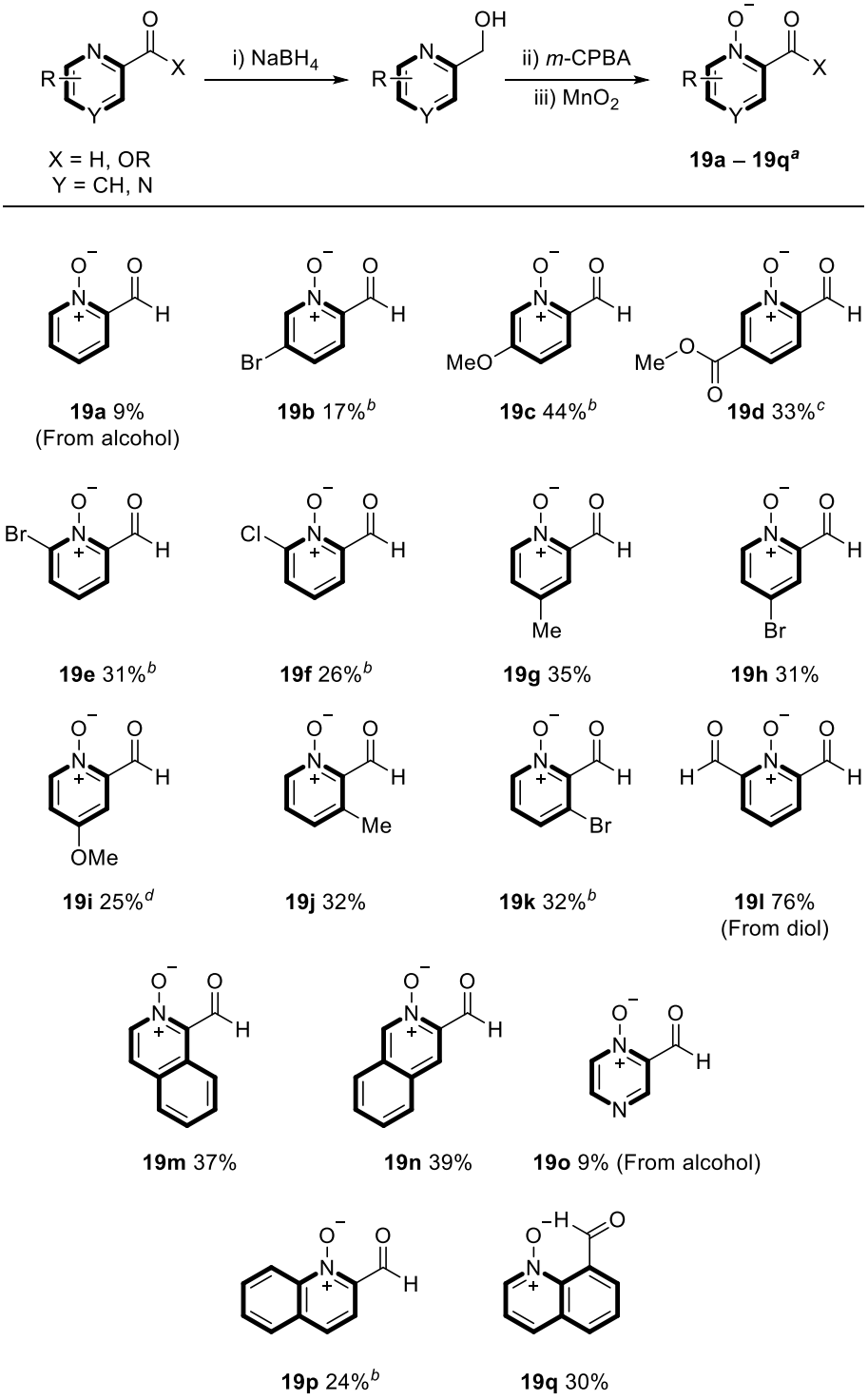
3.2.5 Aldehyde Substrate Synthesis

We then set out to synthesise other 2-formyl azine *N*-oxides that could be used with the hydroacylation reaction. Starting from a readily available precursor, such as a 2-formyl azine, appeared to be the most viable starting point. Subjecting 2-formyl pyridine **22** to our standard *m*-CPBA oxidations conditions did not yield the desired product **19a**, most likely a result of aldehyde instability (**Scheme 3.11**).



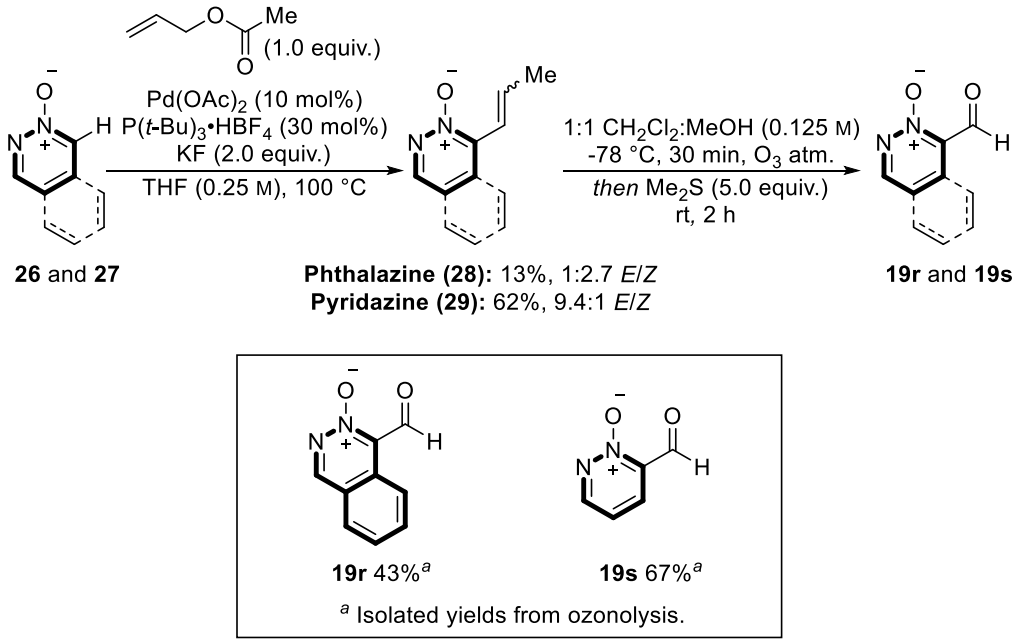
Scheme 3.11. A. An unsuccessful direct oxidation of free pyridyl aldehyde **22** to 2-formyl pyridine-*N*-oxide **19a**.

More nucleophilic oxidants, such as using H_2O_2, were disregarded for the direct oxidation, due to the presence of the aldehyde functionality in **22**. We instead decided to approach the substrate approach the aldehyde synthesis through a multi-step reduction/oxidation sequence, to successfully yield 17 different azine aldehydes in respectable yields, with minimal chromatographic purification (**Scheme 3.12**). Several of these aldehydes were prepared in collaboration with Dr Jagadeesh Kalepu.



Scheme 3.12. Showing the standard multi-step aldehyde synethsis, and all 2-formyl azine-*N*-oxides synthesised; [a] yields correspond to the total isolated yield over the multi-step sequence; [b] all steps perfomed by Dr Jagadeesh Kalepu; [c] steps ii) and iii) performed by Dr Jagadeesh Kalepu; [d] steps i) and ii) performed by Dr Jagadeesh Kalepu.

Several 2-formyl diazine *N*-oxides had to be prepared *via* an alternative strategy. Taking phthalazine *N*-oxide **26** and pyridazine *N*-oxide **27**, we performed a Pd^{II}-catalysed C(2)-H alkenylation, recently developed by Poli and Oble.[104] The coupling with allyl acetate formed 2-vinyl-phthalazine **28** and 2-vinyl-pyridazine **29** in 13%, 1:2.7 *E*/*Z* and 62%, 9.4:1 *E*/*Z*, respectively. Ozonolysis of these products gave aldehydes **19r** and **19s** in 67% and 43% yields, respectively (**Scheme 3.13**).

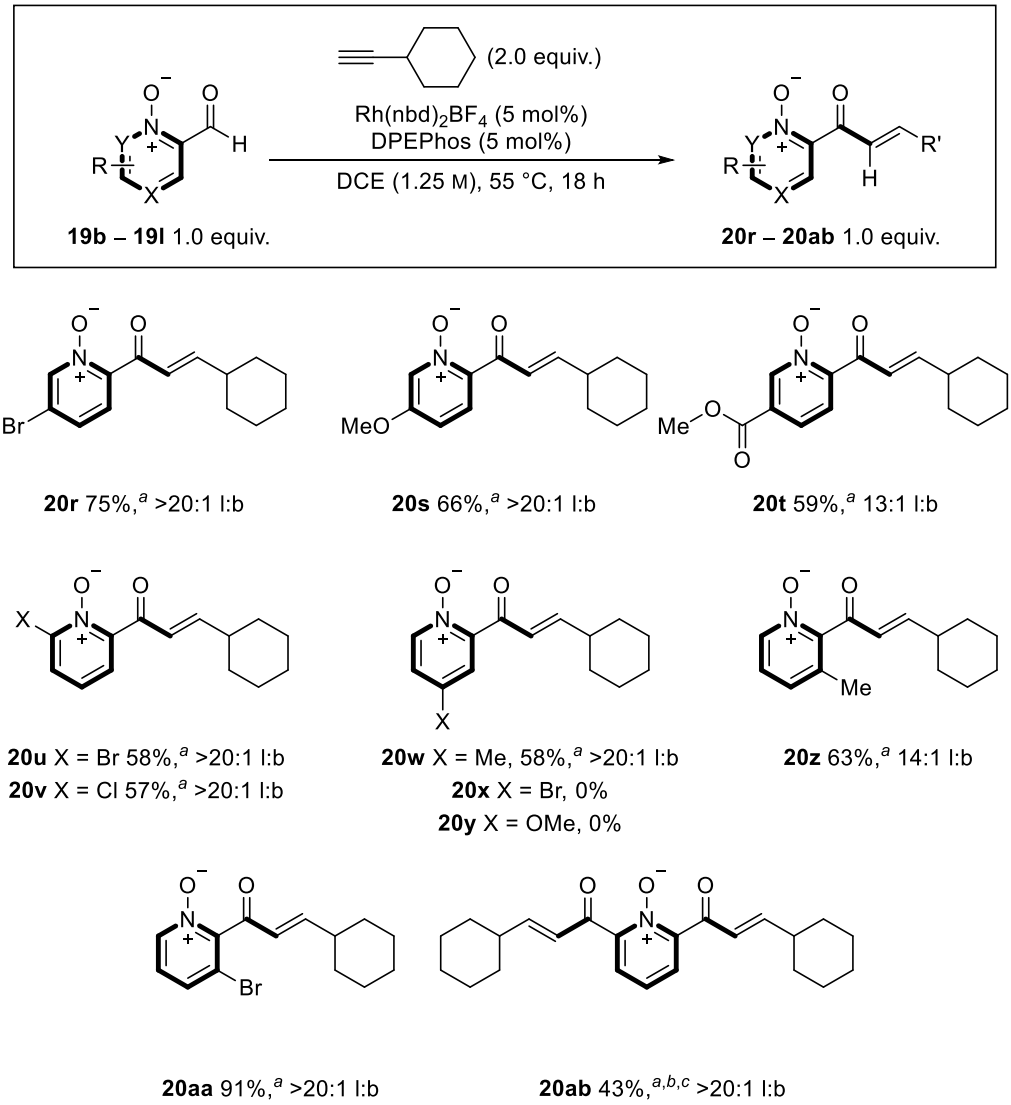


Scheme 3.13. A multi-step C–H allylation/ozonolysis sequence, from diazine-*N*-oxides **26** and **27**, to obtain pyridazine and phthalazine aldehydes **19r** and **19s**.

3.2.6 Aldehyde Reaction Scope

We then turned our focus towards the reaction scope of the aldehydes, using ethynylcyclohexane as the coupling partner (**Scheme 3.14**). Excellent reactivity was provided by C(5)-substituted aldehydes, giving 5-bromo (**20r**), 5-methoxy (**20s**), and nicotinate (**20t**) products in good yields and linear selectivity (up to >20:1 l:b). We initially thought that the more sterically encumbered 6-halo-substituted aldehydes might be too bulky for coordination to the Rh^{I} catalyst. Nevertheless, both

6-bromo and 6-chloro substrates delivered good reactivity, and high l:b selectivity. Mixed results were seen when C(4)-substituted aldehydes were employed. Firstly, 4-picoline aldehyde **20w** provided a similar result to the 5-substituted substrates, however, the alteration of the electronics at this position, by employing 4-Br and 4-OMe substituents, resulted in no desired hydroacylation product. This is likely due to the instability of these aldehydes. As for the C(3)-substituted aldehydes, good yields and selectivity were obtained for 3-Me and 3-Br products **20z** and **20aa**. A 2,6-*bis*-aldehyde could achieve a double hydroacylation, using 4.0 equivalents of alkyne, delivering 2,6-bis-functionalised product **20ab**, in 43%, with >20:1 l:b selectivity.

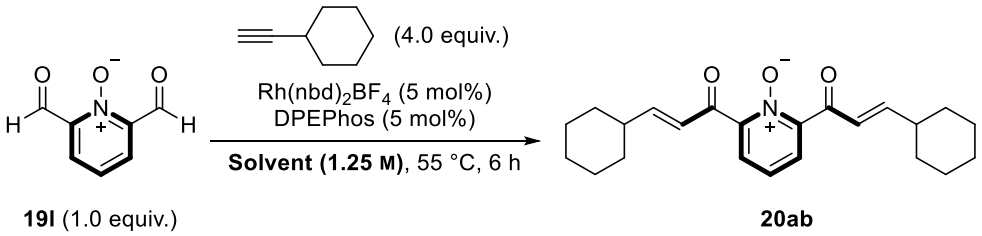


Scheme 3.14. Reaction scope of pyridine-derived aldehydes, using 0.3 mmol of aldehyde 1; [a] yield corresponds to the isolated yield of the single linear regioisomer; [b] using 4.0 equiv. alkyne; [c] reactions were performed on a 0.2 mmol scale.

The low reaction conversion to double hydroacylation product **20ab** was attributed to the poor solubility of the 2,6-bis-aldehyde precursor in DCE. We realised that this precursor could exhibit better solubility in MeCN; a solvent that provided efficient reactivity from the solvent evaluation (section **3.2.1**, **Table 3.5**). Despite the improved reaction solubility, a significant drop in reaction conversion and isolated

yields of product **20ab** were found with MeCN solvent systems (**Table 3.9**, entries 2 and 3).

Table 3.9. Reactions with 2,6-bis-aldehyde **19l** in MeCN solvent systems, to improve substrate solubility.

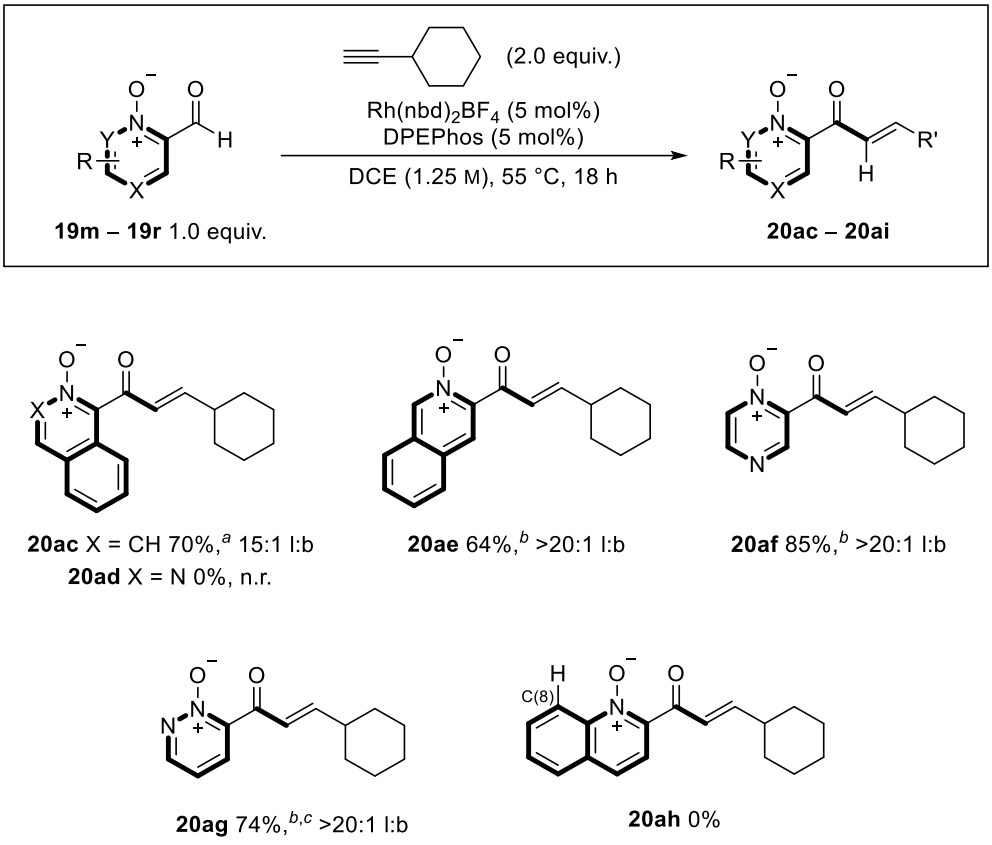


19l (1.0 equiv.) **20ab**

Entry	Solvent	Prod:SM[a]	l:b	Yield (%)[b]
1	DCE	3:1	>20:1	43
2	MeCN	1:3.3	>20:1	7
3	1:1 DCE:MeCN	1:8.5	19.5:1	10

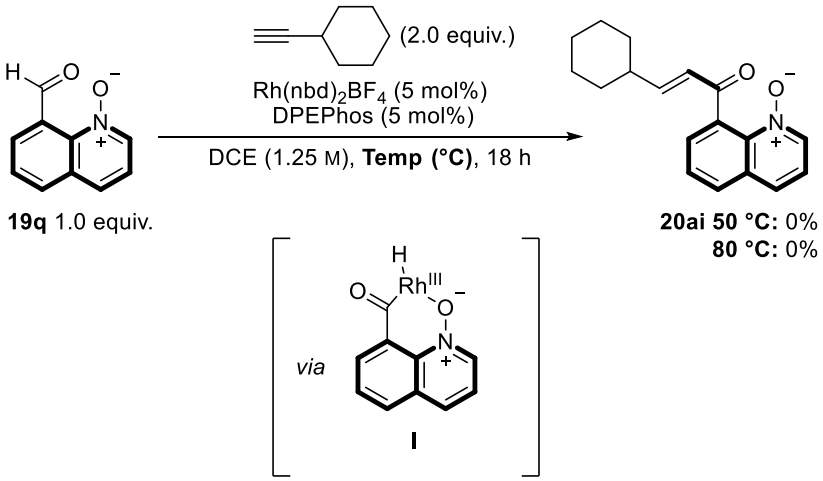
[a] Prod:SM ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] Isolated yields.

Other azine cores were also explored in the reaction (**Scheme 3.15**). 3-Formyl-2-isoquinoline-oxide and 4-formyl-4-isoquinoline-oxide respectively provided enones **20ac** and **20ae**, in good yields and linear selectivity. However, 1-formylphthalazine 2-oxide **19r** failed to yield any reactivity towards product **20ad** after 18 h. Despite this, monocyclic diazines worked well, with pyrazine (**20af**) and pyridazine (**20ag**) derived products being obtained in 85%, >20:1 l:b and 74%, >20:1 l:b, respectively. These two results are noteworthy, as we expected the free azine lone-pair to completely prohibit desired hydroacylation reactivity.[39]



Scheme 3.15. Reaction scope of both alkyne and aldehyde components using 0.3 mmol of aldehyde 1; [a] yield corresponds to the total isolated yield of both regioisomers; [b] yield corresponds to the isolated yield of the single linear regioisomer; [c] reactions were performed on a 0.2 mmol scale.

2-Formylquinoline *N*-oxide **19p** failed to yield desired hydroacylation product **20ah** after 18 h. The complex mixture that formed might result from possible oxidative cleavage of the co-existing C(8)-H bond, present within the quinoline aldehyde. 8-Formylquinoline *N*-oxide **19q** blocks the reactive C(8) position, however, a hydroacylation with this substrate would proceed *via* a less traditional 6-membered acylrhodium(III) hydride intermediate **I** (**Scheme 3.16**).[3d, 35b, 55] Unfortunately, this substrate failed to react at 55 °C and 80 °C.



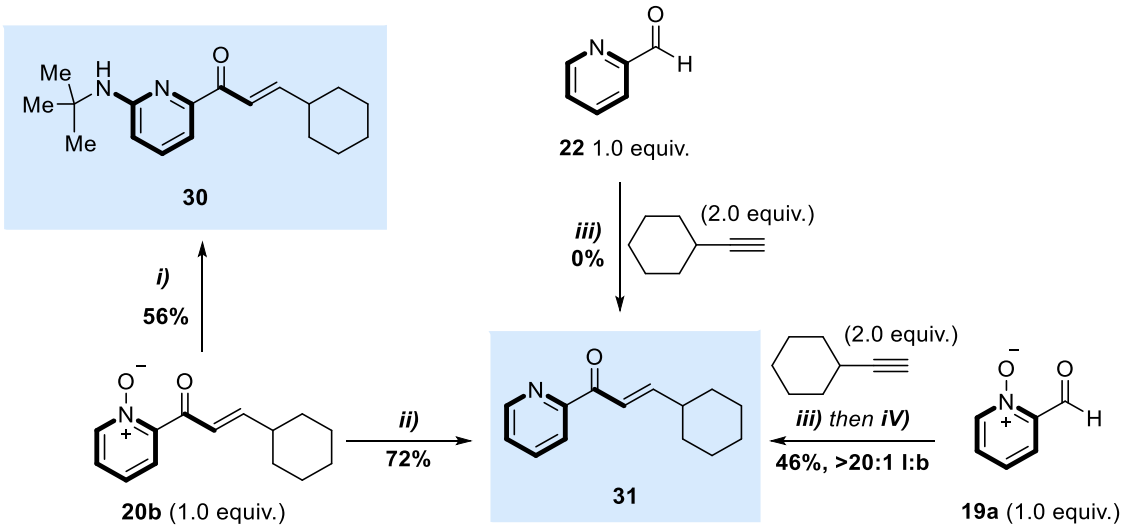
Scheme 3.16. Failing to generate 6-membered rhodacycle **I**, necessary to form product **20ai**, from aldehyde **19q**.

3.2.7 Access to Free 2-pyridyl Motifs

Despite its effectiveness in directing C–H activations, the *N*-oxide group will not normally be required within final molecular targets. Showing that free 2-pyridyl motifs can be simply acquired from the azine *N*-oxide products is therefore paramount to the generality of this method. We therefore set out to achieve reductive derivatisations that incorporate N–O bond cleavage (**Scheme 3.17**).

A myriad of published works demonstrate how the deoxygenation step can operate in tandem with a non-catalytic C(6)-H functionalisation.[105] We attempted a deoxyamination reaction on hydroacylation product **20b**, and successfully obtained 6-aminopyridylic enone **30**, in 56% yield. Direct N–O deoxygenation of hydroacylation product **20b** could be achieved using PCl_3, to give free pyridyl enone **31** in 72% yield.[91b] An *in situ* deoxygenation could also be performed, subsequent to the hydroacylation between aldehyde **19a** and cyclohexyl alkyne, in the same reaction pot to directly generate free pyridyl enone **31** in 46%, >20:1 l:b. This experiment prompted us to carry out a control reaction between 2-formylpyridine

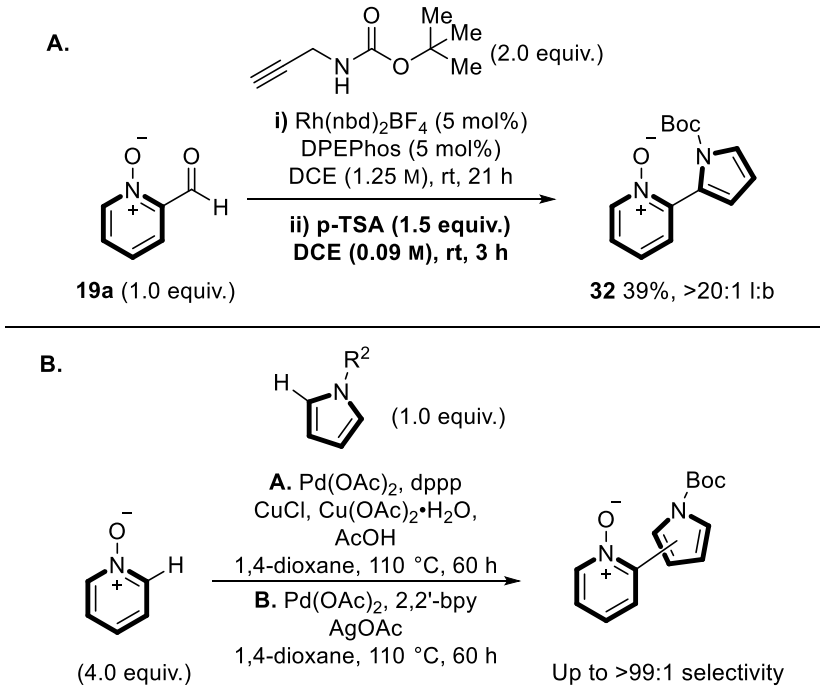
22 and cyclohexyl alkyne. The complete lack of reactivity reinforced the necessity for the *N*-oxide group to direct the desired reaction.



Scheme 3.17. Access of free 2-pyridylic enones **30** and **31** from *N*-oxide deoxygenations; conditions: **i)** Ts_2O (3.5 equiv.), *t*-$BuNH_2$ (8.0 equiv.), 2.5:1 $PhCF_3$:CH_2Cl_2, 30 °C, 18 h; **ii)** PCl_3 (1.2 equiv.), toluene (0.2 M), rt, 15 min; **iii)** $Rh(nbd)_2BF_4$ (5 mol%), DPEPhos (5 mol%), DCE (1.25 M), 55 °C, 18 h; **iv)** PCl_3 (1.2 equiv.), DCE (0.2 M), rt, 15 min.

3.2.8 One-pot Ligand Synthesis and Hydroacylation Scalability

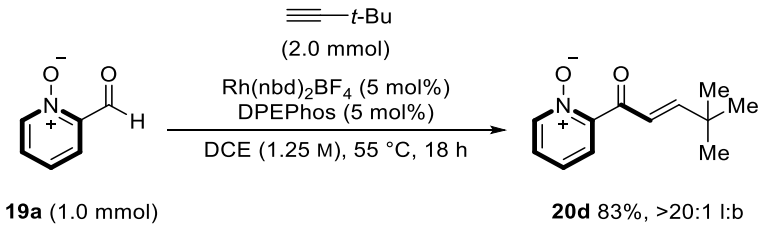
We also demonstrated how the coupling of aldehyde **19a** and *N*-Boc propargylamine could be tied into a one-pot two-step hydroacylation/cyclisation process, using previously established conditions for the cyclisation step,[74b] to generate pyridine-pyrrole **32**, a potential ligand for metals, in 39% yield and >20:1 l:b. (**Scheme 3.18 A**).



Scheme 3.18. A. A two-step one-pot hydroacylation/cyclisation towards pyrrolyl ligand **32**; **B.** Tzschucke's C(2)-H heteroarylation.

We found that a milder hydroacylation was required, as no reactivity could be observed in this step after 18 h at 55 °C, possibly due to product degradation. Tzschucke has previously shown that similar products can be synthesised through a pyridine-*N*-oxide-directed dehydrogenative C(2)-H heteroarylation; however, our strategy prevents 2-/3-pyrrolyl-coupled mixtures, observed by Tzschucke (**Scheme 3.18B**), and also does not require excess of the *N*-oxide substrate.[106]

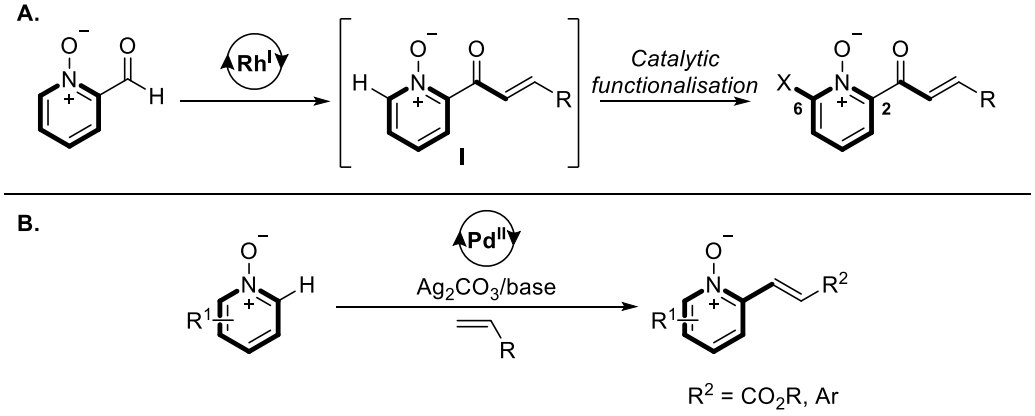
We additionally showed that the optimised hydroacylation conditions were scalable (**Scheme 3.19**). A 1.0 mmol scale hydroacylation reaction between aldehyde **19a** and *t*-Bu-acetylene gave linear product **20d** in good yield and high linear selectivity (170 mg, 83%, >20:1 l:b). The isolated product from this reaction was then used in a set of catalytic C(6)-H functionalisations, featured in the following section.



Scheme 3.19. Showing a successful 1.0 mmol scale reaction between aldehyde **19a** and *t*-Bu-acetylene.

3.2.9 Catalytic C(6)-H Functionalisations

We also wanted to see if it was possible to perform the C–H activation of aldehyde **19a**, in tandem with a catalytic C(6)-H transformation, to generate a 2,6-bis-functionalised azine motif (**Scheme 3.20A**). One particular transformation class that was of particular interest was the Pd^{II}-catalysed alkenylation chemistry[91b, 6] (**Scheme 3.20B**).

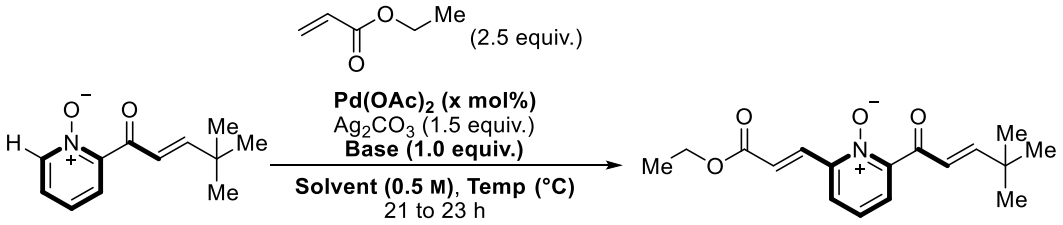


Scheme 3.20. A. *N*-oxide directed alkyne hydroacylation in tandem with catalytic C(6)-H functionalisation; **B.** Pd^{II}-catalysed alkenylations.

Although these methods display good general reactivity, a main limitation with Pd-catalysed *N*-oxide C–H functionalisations, is the common requirement for the *N*-oxide to be used as the excess reaction component.[91, 95e, 95h, 107] This requirement might limit the use of these catalytic methods in the tandem reactions we envisaged,

as ideally we would want hydroacylation intermediate **I** (**Scheme 3.20A**) to be fully consumed in the alkenylation step. We decided to run a collection of alkenylations on isolated hydroacylation product **20d**, using ethyl acrylate as the excess coupling reagent (**Table 3.10**).

Table 3.10. Condition evaluation for the Pd-catalysed C–H alkenylation of enone **20d**.



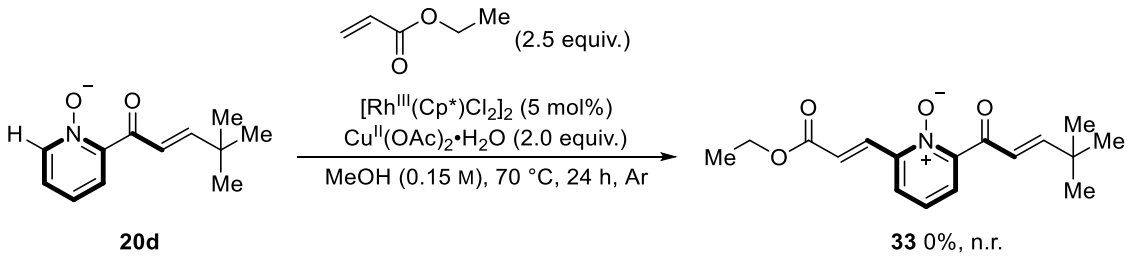
Entry	Cat. Loading (mol%)	Base	Solvent	Temp (°C)	Consumption of 20d (%)[a]	Yield (%)[b]
1	10	K_2CO_3	1,4-dioxane	100	-	0
2	10	Pyridine	1,4-dioxane	100	55	21(19)[c]
3	10	Pyridine	1,4-dioxane	120	>99	0
4	20	Pyridine	1,4-dioxane	100	60	22
5	10	Pyridine	DCE	100	57	0
6	10	Pyridine	DCE	120	>99	0

[a] Consumption of **20d** determined by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] NMR yields based on NMR standard (methyl-3,5-dinitrobenzoate); [c] Isolated yield in parenthesis.

We were initially able to isolate the alkenylated product in 19% yield, when using 10 mol% $Pd(OAc)_2$, in 1,4-dioxane at 100 °C, and pyridine as the base (entry 2). However, we were unable to obtain a significantly higher yield, even when forcing the temperature and catalyst loading (entries 3, 4 and 6).

A set of Rh^{III}-catalysed triazene-directed aryl alkenylation conditions were recently developed by Willis and co-workers, as part of a sequential catalytic route to 2,6-bisfunctionalised arenes.[36b] Our interest in this transformation was the inverted stoichiometry, using the alkene reagent as the excess reaction component, and making it suitable for a tandem process. However, when submitting enone **20d** to

the standard literature conditions, no conversion from the starting material was observed (**Scheme 3.21**).



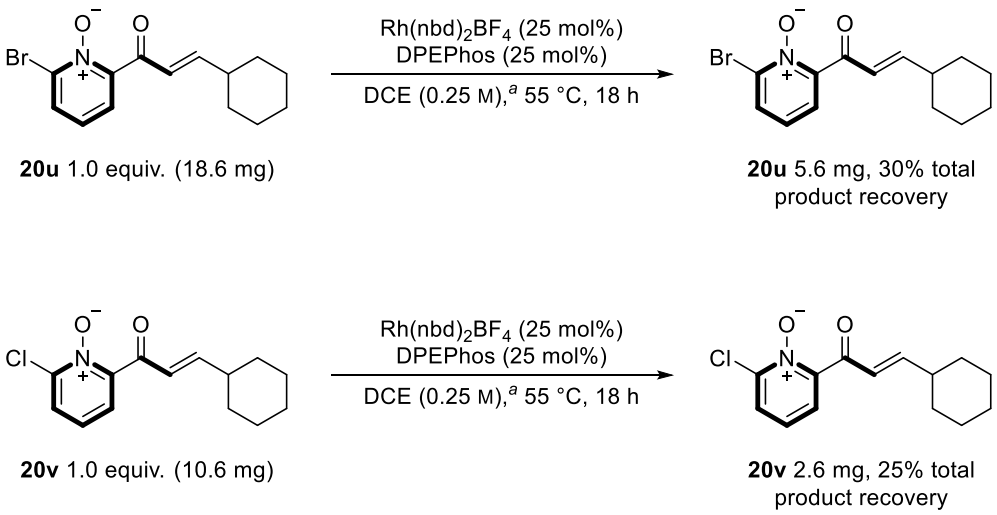
Scheme 3.21. Application the Rh^{III}-catalysed conditions developed by Seo *et al*.[36b]

It is likely that the formation of a rhodacycle, as seen in the triazene-directed method,[36b] is required for such a catalyst to undergo C–H activation, and it is unlikely that such an intermediate would form on *N*-oxide substrate **20d**.

3.2.10 Control Experiments Testing for Degradation *in situ*

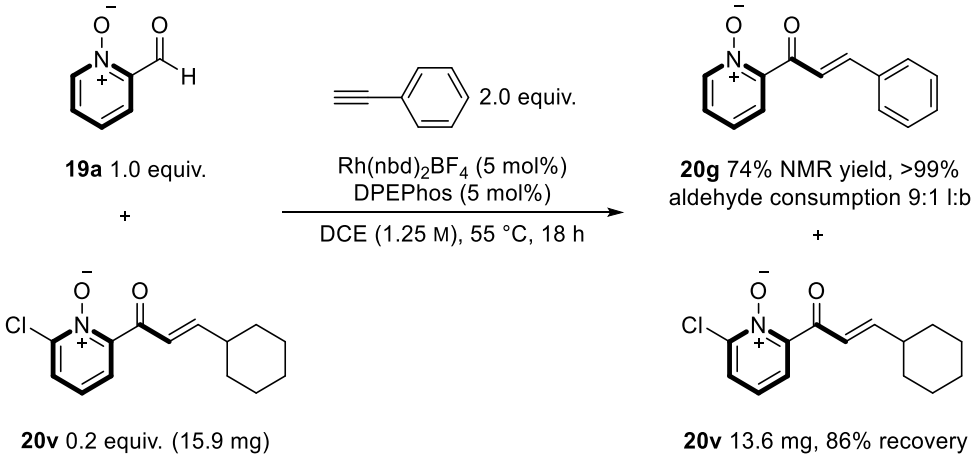
Many of the hydroacylation reactions, with the 2-formyl azine *N*-oxide substrates prepared in this chapter, exhibit a notable mismatch between product yield and aldehyde consumption. On occasions, such as the coupling with less reactive substrates (internal alkynes and alkenes), clear side-reactions can be observed. However, distinct side products are absent in many other cases. We therefore conducted a set of control reactions to probe possible degradation.

We started by testing for product degradation using freshly prepared hydroacylation products **20u** and **2v** (**Scheme 3.22**). Each were submitted to the Rh^{I}-DPEPhos catalyst at 55 °C, and after 18 h, products **20u** and **20v** were recovered in 30% and 25% respectively.



Scheme 3.22. Showing the direct degradation of hydroacylation products **20u** and **20v**, when directly subjected to Rh-DPEPhos at 55 °C; [a] substrate concentration.

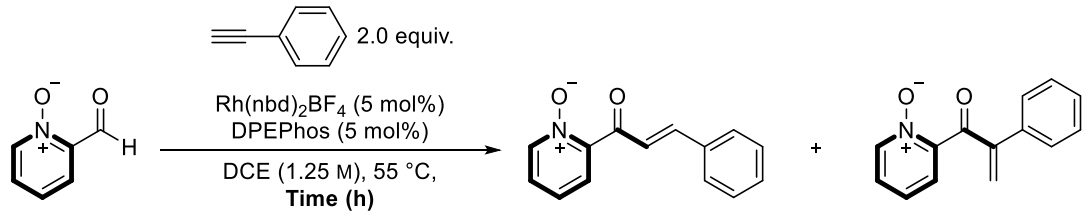
From this, we could deduce that catalytic degradation of the product was possible in direct presence of Rh^{I}-DPEPhos. A mixture of 6-chloro product **20v**, aldehyde **19a** and phenylacetylene was then subjected to the catalyst to test for the degradation of product **20v** in presence of a running hydroacylation reaction (**Scheme 3.23**). Even though more of 6-chloro product **20v** could be recovered (86% recovery), some degradation was still observed over the reaction period.



Scheme 3.23. Illustrating the degradation of hydroacylation product **20v**, in presence of a hydroacylation reaction between aldehyde **19a** and phenylacetylene.

Although both sets of experiments indicate that the products degrade under the reaction conditions, it does not conclude at which stage. Stopping a reaction between aldehyde **19a** and phenylacetylene at incomplete conversion (6 h) revealed a better match between total product NMR yield and aldehyde consumption, compared to the 18 h reaction (**Table 3.11**). This suggests that product degradation is more likely to occur after reaction progression, or towards the end of the reaction, when substrate concentration is low, and product concentration is high.

Table 3.11. A comparison of total product yield, selectivity and aldehyde consumption, for the hydroacylation reaction between aldehyde **19a** and phenylacetylene, at 6 h and 18 h**.**



Entry	Time (h)	Aldehyde consumption (%)[a]	l:b[b]	Total Yield (%)[a]
1	6	64	6:1	58
2	18	>99	9:1	69(53)[c]

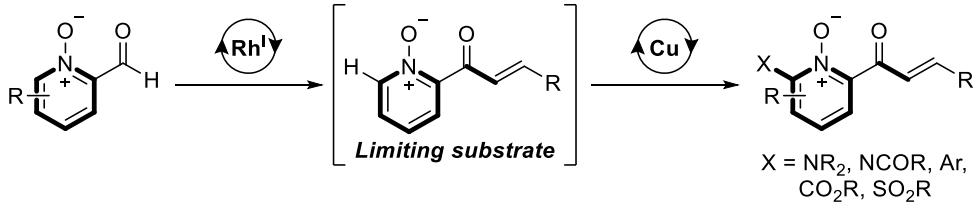
[a] Aldehyde consumption and total yield of both regioisomers calculated by ^{1}H NMR spectroscopy of the crude reaction mixture with respect to ^{1}H NMR standard methyl-3,5-dinitrobenoate; [b] l:b regioselectivity determined by crude ^{1}H NMR spectroscopy. [c] Isolated yield of the major linear isomer **20g** in the parenthesis.

However, degradation of the aldehyde starting material should not be ruled out. When looking at two of the earlier optimisation reactions with DPEPhos (**Table 3.1**, entry **5**, and table **3.2**, entry **2**), a similar degree of mismatch between yield and conversion is seen at a 6 h reaction time (**Table 3.2**, entry **2**), compared to the 18 h reaction time (**Table 3.1**, entry **5**). Observing a high degree of potential degradation earlier in the reaction (i.e. when the substrate concentration is still high) might suggest that aldehyde degradation can also occur.

3.3 Conclusions and Future Work

To conclude, we have shown that 2-formyl azine *N*-oxides can successfully direct rhodium-catalysed intermolecular alkyne hydroacylation reactions. The reactions featured in this chapter are generally performed at milder temperatures than $Rh^{I/III}$-catalysed quinoline-*N*-oxide C(8)-H functionalisations, allowing coupling with terminal alkynes, a less common class of substrate seen in C(8)-H alkenylations. Using the DPEPhos derived catalyst, coupling with terminal alkynes can be achieved in good to high linear regioselectivity (up to >20:1 l:b). The toleration of diazine aldehydes within this method, that contain a free azine *N*-lone pair, is an excellent feat for the hydroacylation reaction, and is a strong implication for the method's general synthetic application. Future work in this area of research could aim to improve the 2-formyl *N*-oxide's coupling reactivity to a more diverse range of unsaturated substrates, particularly alkenes. The unsuccessful couplings with alkenes suggest that a different ligand will be necessary to promote reactivity and minimise decarbonylative side reactions.

From a derivatisation perspective, being able to directly perform a C(6)-H functionalisation, on the enone product generated from hydroacyation, would be an efficient way to generate densely functionalised azine products. The main limitation that we encountered with Pd^{II}-catalysed alkenylation, was inefficient stoichiometry. However, this issue could be circumvented by using copper catalysis for the sequential C(6)-H activation step,[98b] as these methods generally use the *N*-oxide as the limiting substrate. Such catalysis could be used for tandem hydroacylation processes involving C(6)-H aminations/amidations,[98] arylations,[95f, 108] acetoxylations[96] and sulfonylations (**Scheme 3.24**).[97]

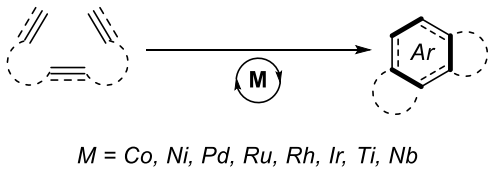


Scheme 3.24. Tandem catalytic processes using *N*-oxide directed hydroacylation and copper-catalysed C(6)-H heterofunctionalisation.

Chapter 4 – A Rhodium-catalysed [2+2+2] Cycloaddition for Sulfoximine Desymmetrisation

4.1 An Introduction to Transition-metal Catalysed [2+2+2] Cycloaddition

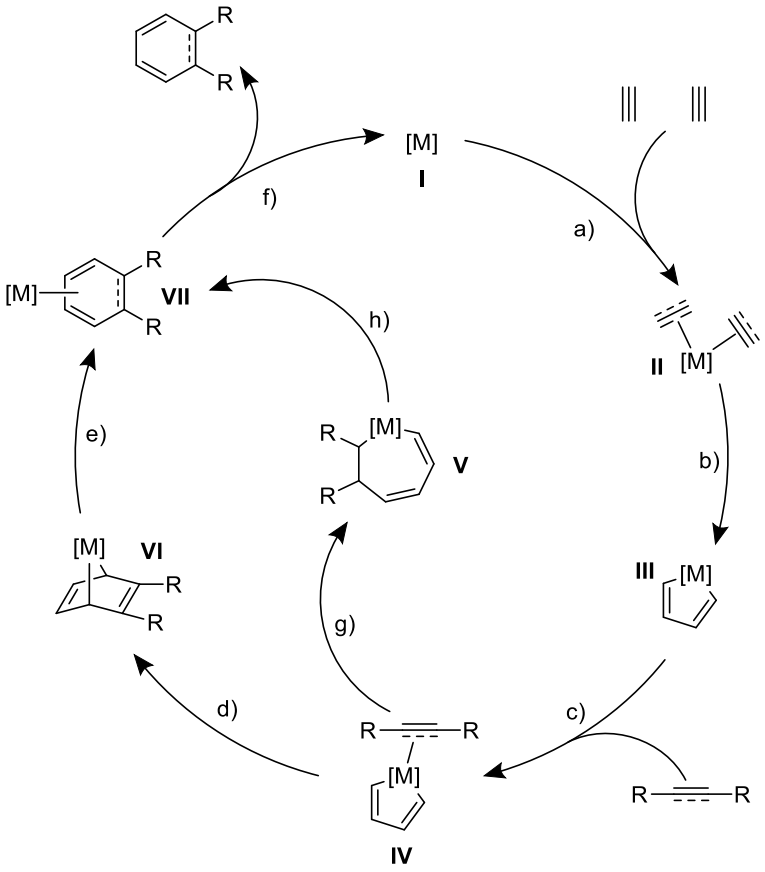
The transition-metal catalysed [2+2+2] cycloaddition of alkenes and alkynes is known as one of the most efficient ways to rapidly build densely functionalised carbocycles and heterocycles (**Scheme 4.1**).[109]



Scheme 4.1. Transition-metal catalysed [2+2+2] cycloaddition.

Since its initial discovery, by Reppe in 1948,[110] new catalytic reaction systems based on Co,[111] Ru,[112] Ni,[113] Pd,[114] Rh,[115] Ir,[116] Ti[117] and Nb,[118] have developed to tackle underlying challenges of chemo- and regioselectivity. These developments have made the transformation more attractive for general synthesis, as testified by its use in aqueous phase reactions[119] and inclusion in natural product synthesis.[120]

The mechanism of the transition-metal catalysed [2+2+2] cycloaddition is quite perplexing, as several pathways are thought to be co-existing.[121] Significant amounts of mechanistic work have been carried out by the groups of Aubert and Saá, on reactions involving alkyne trimerization,[121a] and cyclisation between two alkynes and one alkene.[121b, 121c] These findings have led to a generally accepted catalytic cycle for these types of cycloadditions (**Scheme 4.2**).



Scheme 4.2. Illustrating the commonly accepted catalytic cycle for the transition-metal catalysed [2+2+2] cycloaddition of alkynes and alkenes.

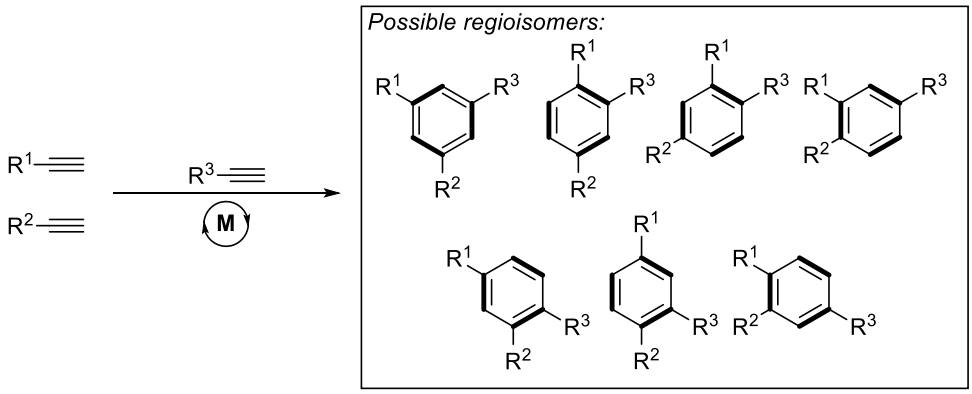
Generally, the cycle starts with initial alkyne/alkene coordination (step a) to metal catalyst **I**, to generate coordination complex **II**. Oxidative cyclisation (step b) then follows to generate metallacyclopentadiene complex **III**, with subsequent coordination of a third alkyne/alkene (step c) to generate species **IV**. Two possible pathways can occur from this intermediate. DFT studies by Aubert suggest that a third alkyne component will be incorporated through a [4+2] cycloaddition pathway (step d).[121a] This pathway would give bicyclic complex **VI**, which can then undergo reductive isomerisation (step e) to intermediate **VII**. However, if the coupling substrate is an alkene, both Aubert and Saá have concluded that migratory insertion (step g) to metallacycloheptatriene intermediate **V** is more likely. From this intermediate, reductive elimination will normally occur (step h) to give species **VII**.

Both of the possible pathways terminate through catalyst dissociation (step f) to restart the cycle.[121]

Although most [2+2+2] reactions typically proceed through one of the mechanistic pathways mentioned above, deviations have been observed, for example in work by Tong and co-workers which uses potassium (Z)-(2-bromovinyl)trifluoroborates as alkyne surrogates.[122]

4.1.1 Issues with Chemo- and Regioselectivity

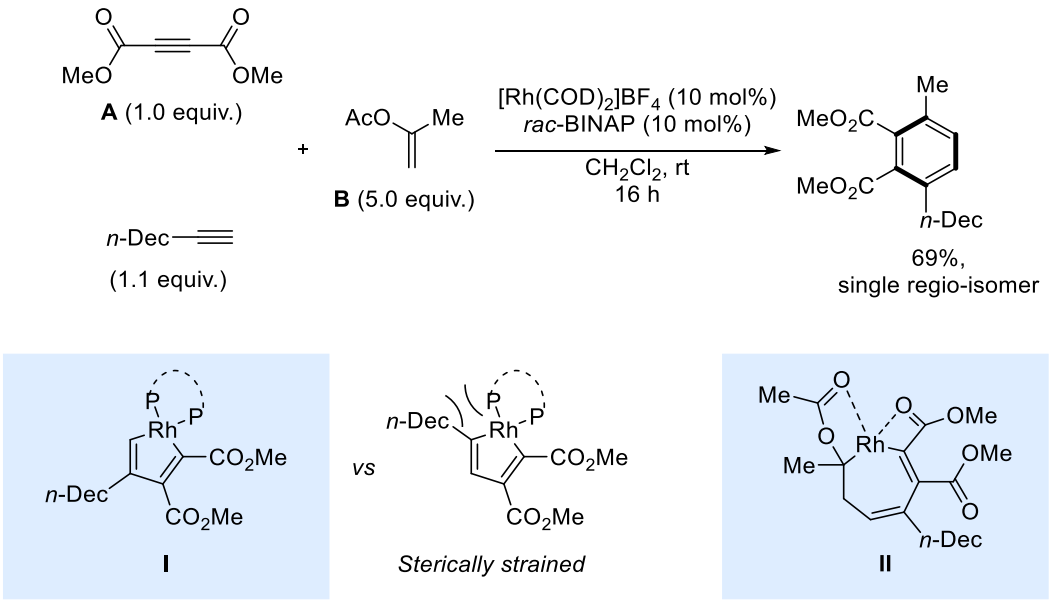
An aspect of the main mechanism which was not mentioned in the catalytic cycle in scheme **4.2**, is the underlying issues with chemo- and regioselectivity that inherently arise during a cycloaddition process. Scheme **4.3** shows how a simple alkyne cyclotrimerisation can lead to several different regioisomers.



Scheme 4.3. Illustrating the possible regioisomeric products from a simple alkyne cyclotrimerisation.

However, this model does not contemplate the formation of homo-coupled products. When this factor is also considered, a total of 38 different isomers can be generated.[109a] The substrates in a three-component coupling generally possess a large degree of orientational freedom, compared to those within intramolecular processes, making three-component reactions more liable to selectivity issues[115a,

[115b] This is unfortunate, as three-component reactions seem highly attractive at a first glimpse; they offer a high degree of modularity and would utilise simple starting materials. Tanaka and Louie have shown that vinylene carbonates/carbamates, and enol ethers/acetates can be used as simple alkyne surrogates within three-component cyclotrimerisation reactions.[123] These heterofunctionalised substrates could successfully tune the reaction chemo- and regioselectivity (**Scheme 4.4**).

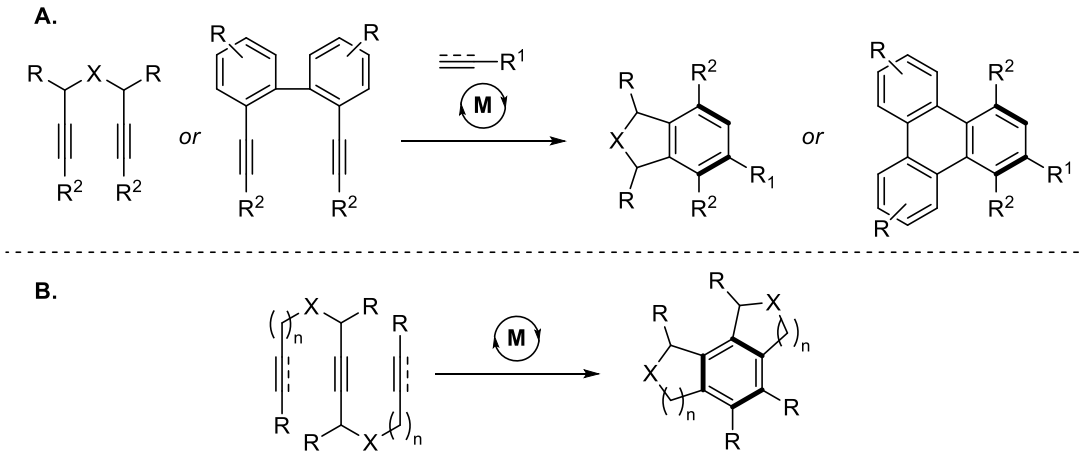


Scheme 4.4. Tanaka's regioselective three-component alkyne cyclotrimerisation.

The authors found that 1-dodecyne would preferably react with electron poor alkyne **A**, and the regioselectivity gained within intermediate **I** occurs because the alkyne substituent prefers to avoid a steric interaction with the BINAP ligand. The regioselectivity for the insertion of alkene **B** can be rationalised by a stabilising O-Rh interaction within the forming intermediate **II**. Although this method produces excellent selectivity, it does not easily lend itself to a general cycloaddition method, due to the requirement for specifically tailored substrates. Development of a chemo-

and regioselective three-component reaction which uses unactivated substrates therefore remains a challenge within this area of research.

The use of bimolecular reactions has emerged as a more popular coupling strategy, that minimises the aforementioned selectivity issues (**Scheme 4.5**).[124]



Scheme 4.5. A. Bimolecular [2+2+2] cycloadditions; **B.** fully intramolecular [2+2+2] cycloadditions.

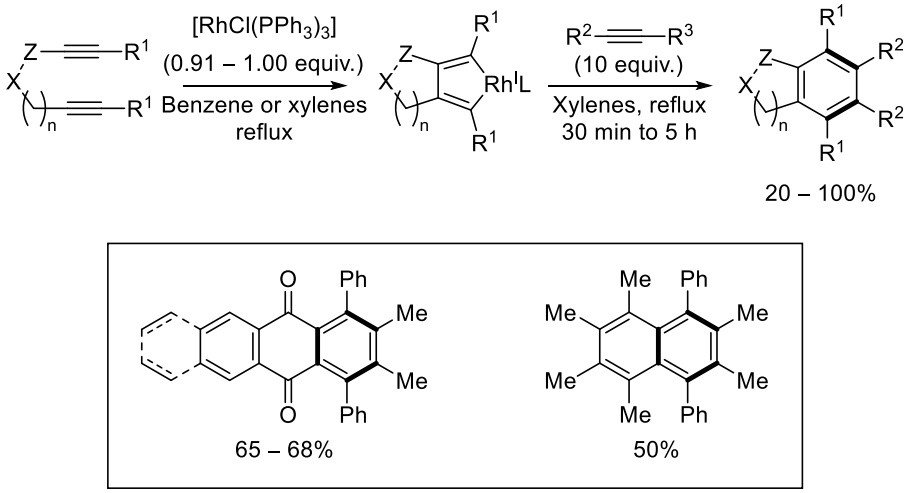
1,7- or 1,6-diynes are most commonly used in bimolecular reactions (**Scheme 4.5A**),[125] however larger linking chains are known.[126] Oxidative cyclisations on these substrates will be intramolecular, occurring more favourably than any competing intermolecular process, therefore relinquishing chemoselectivity issues.[127] The regioselectivity of oxidative cyclisation will also benefit from the locked orientation of the diyne substrate.[128]

Fully intramolecular reactions also exist (**Scheme 4.5B**),[129] whereby substrates containing all the required unsaturated groups will cyclise to generate complex scaffolds.[115e, 130] Although these reactions normally provide excellent reaction selectivity, the substrates required have highly engineered, intricate designs.[128b, 131] Bimolecular and fully intramolecular substrate systems have applied themselves to a plethora of different substrate types; ynamides,[120b, 132] alkynyl ethers/sulfides,[131b,

[133] α,β-unsaturated enones,[134] naphthosilines[124] and fullerenes,[135] generating a vast range of different multicyclic arenes and heterocycles. Within this array of reactions, many [2+2+2] transformations are asymmetric, catalysed by a variety of metals in conjunction with chiral ligands.[109b] Out of these, chiral rhodium(I) species have been used most regularly.[125b, 130, 136] The following sections will delve into the development of rhodium catalysis towards enantioselective [2+2+2] cycloadditions.

4.1.2 Rhodium Catalysis in [2+2+2] Cycloadditions

Out of the metals known to catalyse [2+2+2] reactions, rhodium catalysts have provided highly versatile reactions, that allow a broad range of functional group tolerance.[127a, 132a, 137] The first documented rhodium-catalysed [2+2+2] cycloaddition, is by Müller in 1974 (**Scheme 4.6**).[138]



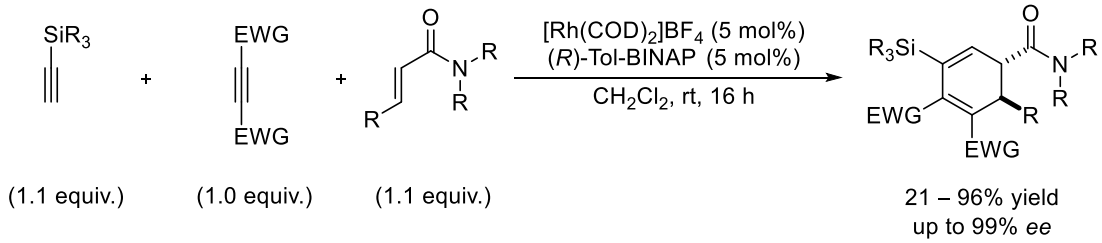
Scheme 4.6. The seminal report for Rh-catalysed [2+2+2] cycloaddition; L = PPh_3.

Müller was able to use Wilkinson's catalyst to isolate several rhodacyclopentadiene complexes and react them with various alkynes. Other types of rhodium catalysts have been reported, such as $RhCl_3 \cdot 3H_2O$/*i*-Pr_2NEt,[139] and more recently, the first use of a rhodium–NHC complex; [RhCl(COD)(NHC)].[140] Undoubtedly, however, cationic Bosnich-type Rh(I)-complexes have emerged as the most versatile class of

catalyst.[22] Their ability to complex with many different bis-phosphines, not only makes them electronically and sterically tuneable, but also makes them highly suited to asymmetric [2+2+2] reactions.[129-130, 141]

4.1.3 Enantioselective Three-component [2+2+2] Reactions

Enantioselective work on three-component reactions is sparse, and the first example was developed by Tanaka only recently (**Scheme 4.7**).[142]



Scheme 4.7. Tanaka's chemo-, regio- and enantioselective three-component [2+2+2] cycloadditions reaction.

Within these reactions the chemo- and regioselectivity issues were tackled through the concepts relating to their previous three-component coupling method,[123a] however acrylamides were used to generate the point chirality within the products. The method yielded a range of cyclic products in up to 96% yield and up to 99% *ee*. The substituted acrylamides also gave the cyclised products as single diastereoisomers.

4.1.4 Enantioselective Bimolecular and Fully Intramolecular [2+2+2] Reactions

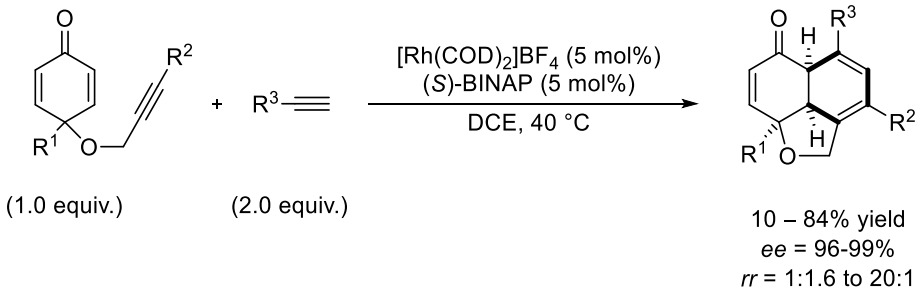
Most enantioselective rhodium-catalysed methods are either bimolecular or fully intramolecular reactions.[109b] A multitude of published works, predominantly by the groups of Tanaka and Shibata, show how chiral rhodium(I) catalysts can produce different types of chirality within the desired products.[115e, 143] This section will show

selected works that demonstrate how point, axial, helical, and planar chirality can be generated from a [2+2+2] reaction process.

4.1.4a Point Chirality

It is very common for biologically active molecules to exhibit point chirality.[144] The enantioselective production of compounds possessing one or more chiral centres is a speciality of rhodium-catalysed [2+2+2] cycloadditions.[109b] The methodology has shown that multiple stereocentres can be set in a single step, through desymmetrisation,[134a] kinetic resolution,[145] and other multi-bond forming procedures.[141e]

Xu and co-workers recently explored a desymmetrisation of cyclic ene-yne substrates, coupling with terminal alkynes and using a Rh^{I}/(*S*)-BINAP catalytic system (**Scheme 4.8**).[134a]

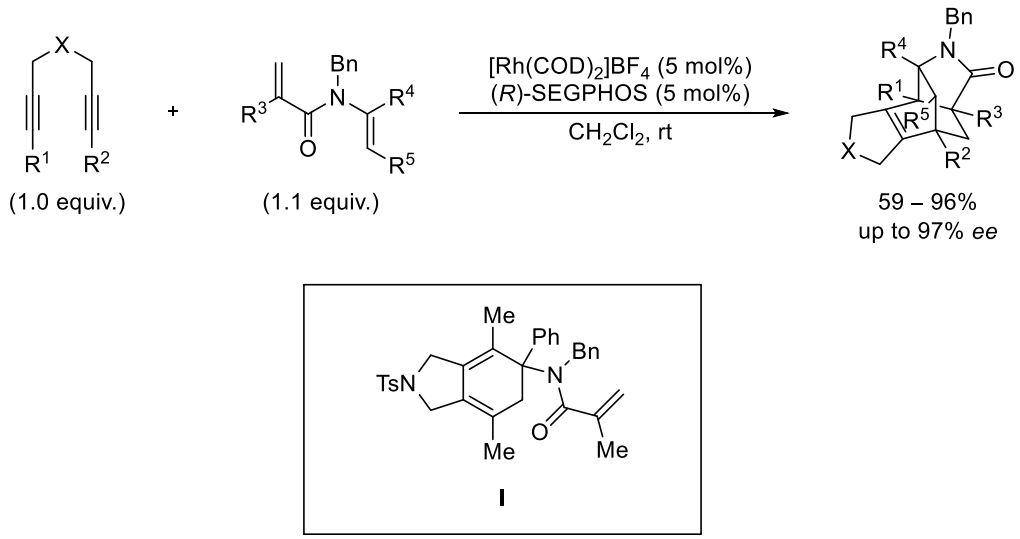


Scheme 4.8. Desymmetrisation of a cyclic ene-yne to access tricyclic hydronaphthofurans.

Three new stereocentres were simultaneously set during the reaction process, to generate fused tricyclic hydronaphthofurans in excellent enantioselectivity, and good regioselectivity (up to >20:1 rr).

Other complex motifs that utilise bimolecular [2+2+2] cycloaddition, as part of a cascade process, have been developed.[146] Tanaka disclosed a one-pot method towards bridged multicyclic frameworks (**Scheme 4.9**).[146] The diyne substrate did

initially undergo a [2+2+2] cycloaddition, generating intermediate **I**. This would spontaneously undergo an intramolecular Diels-Alder reaction, yielding the stereodefined products in highly respectable yields and selectivity.



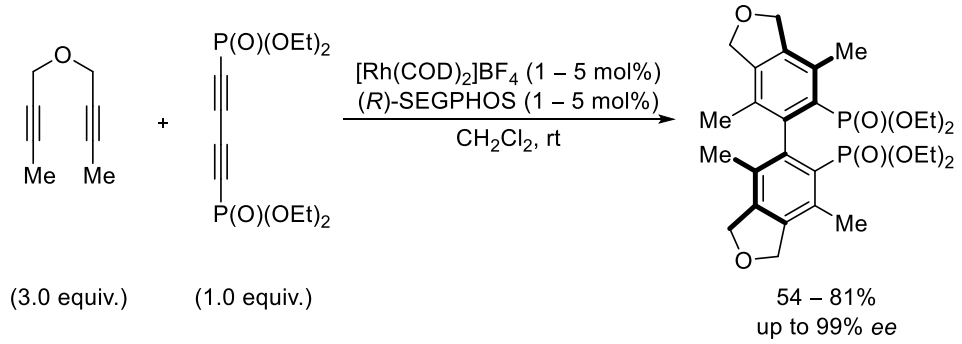
Scheme 4.9. Tanaka's [2+2+2]/intramolecular Diels-Alder cascade process.

Other multicyclic point chiral structures are accessible in a single step, from fully intramolecular cyclisations of diyne-enes[141e] and diene-ynes.[141d, 147]

4.1.4b Axial Chirality

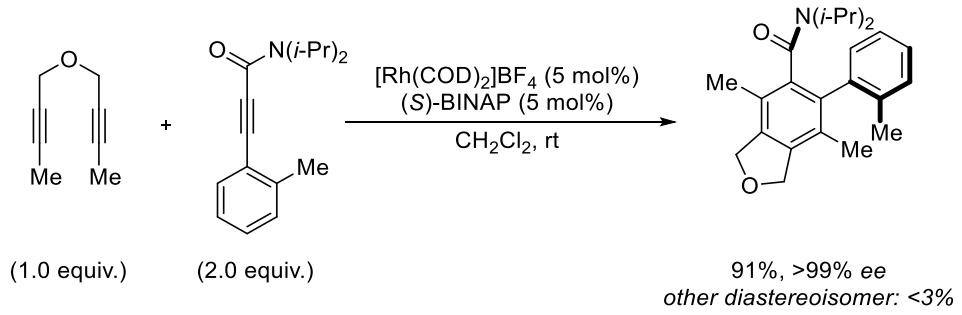
Axial chirality is an ubiquitous property contained within many biologically active molecules.[148] Moreover, atropisomerism finds itself at the heart of modern ligand development, for asymmetric catalysis.[149] Accordingly, the demand for new catalytic reaction designs that produce such chirality, is ever rising.

Previous works have shown that [2+2+2] cycloadditions between 1,6-diynes and phosphonate-substituted alkynes can generate axially chiral biaryl mono- and di-phosphonates.[150] Tanaka has shown that similar products can be obtained from a double [2+2+2] cycloaddition, using 1,6-diynes and phosphonate-substituted 1,3-diynes (**Scheme 4.10**).[127b]



Scheme 4.10. Tanaka's synthesis of axially chiral biaryl diphosphonates through a double [2+2+2] cycloaddition between 1,6- and 1,3-diynes.

Tanaka also showed that axially chiral *N*,*N*-dialkylbenzamides could be formed using Rh/(*S*)-BINAP.[128a] In one particular example, the authors could generate two modes of axial chirality from a single cycloaddition reaction. The desired product possessed aryl-carbonyl and aryl-aryl chirality and could be achieved in excellent selectivity (**Scheme 4.11**).[128a]

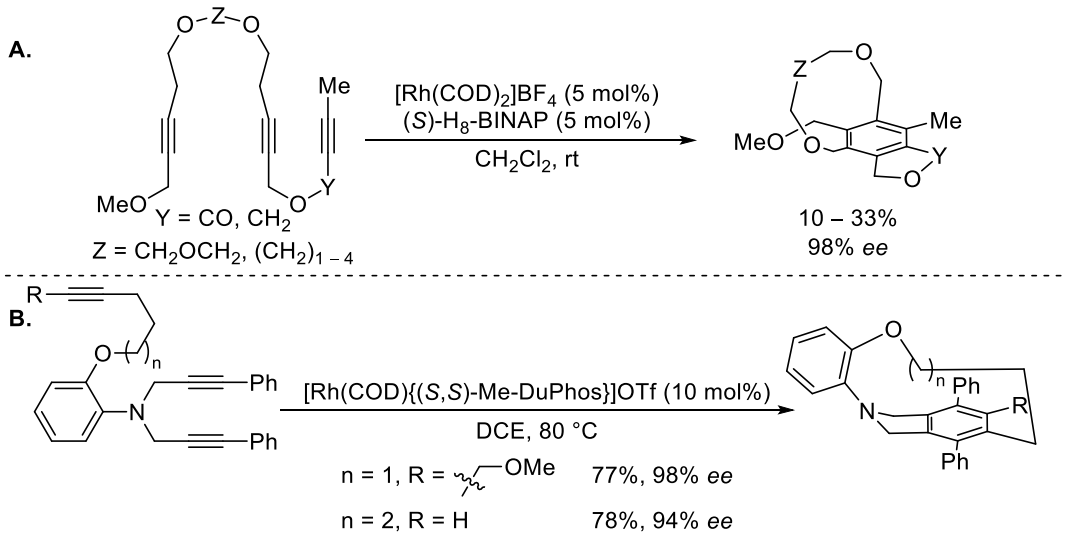


Scheme 4.11. Accessing products containing two separate modes of axial chirality.

4.1.4c Planar Chirality

Compounds containing this mode of chirality are generally less common and are normally cyclophane structures bearing a small aliphatic chain which is restricted to one face of an aromatic ring.[109b] One of the earlier known [2+2+2] methods to generate planar chiral products was by Tanaka, where ethereal linked triynes were cyclised to generate *meta*-cyclophanes, in good yield and enantioselectivity

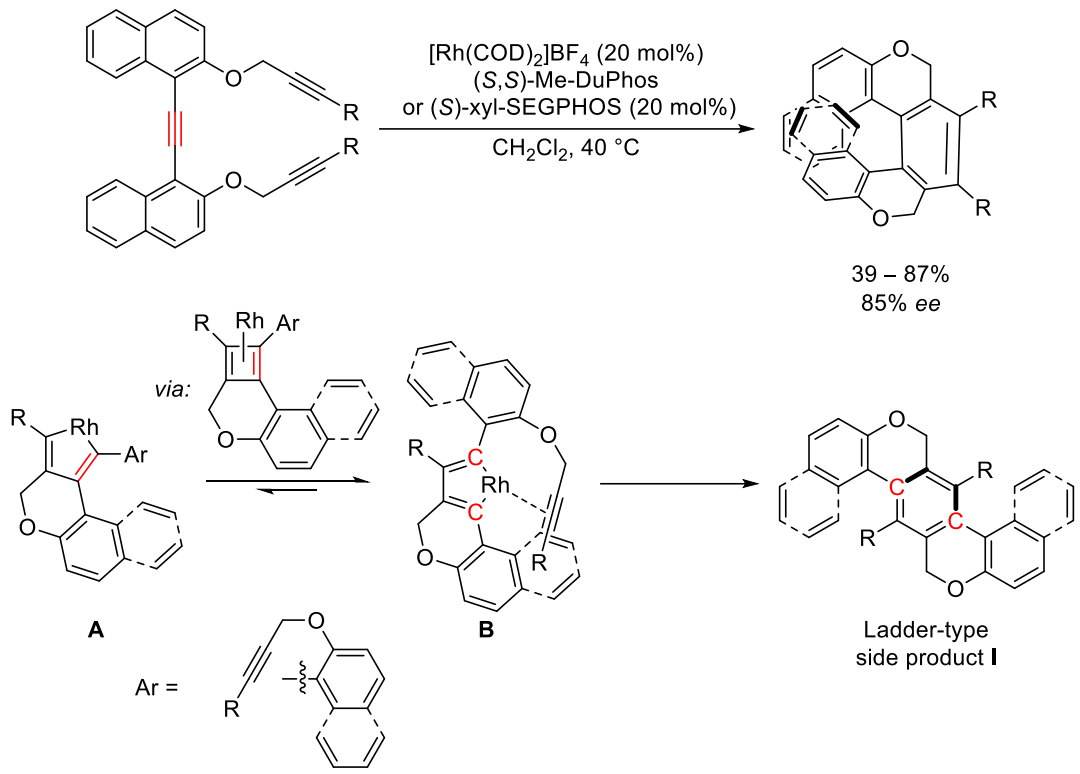
(**Scheme 4.12A**).[126] It was later revealed that the same class of cyclophanes were enantioselectively accessible from bimolecular reactions.[136] The asymmetric production of *para*-cyclophanes have also been obtained from [2+2+2] reactions (**Scheme 4.12B**).[151]



Scheme 4.12. [2+2+2] cycloadditions toward planar chiral products.

4.1.4d Helical Chirality

Compounds containing helical chirality yield a strong application for chiral ligand development and supramolecular chemistry.[152] Rhodium catalysed [2+2+2] cycloadditions are able to enantioselectively produce many different helicene structures.[130, 143b, 143d, 143e] A typical example is the cyclisation of a triyne substrate, using Rh^{I}/(*R*,*R*)-Me-DuPhos as the chiral catalyst, to generate a helicene (**Scheme 4.13**).[153]



Scheme 4.13. [2+2+2] cycloadditions towards helical chirality.

Although respectable yields and *ee*s were obtainable for such a complex transformation, the reoccurrence of a ladder-type side-product was a limitation (**Scheme 4.13**).[153] This intermediate was formed from a strain relieving pathway, whereby the standard helicene precursor rhodacyclopentadiene **A** rearranges to less sterically hindered complex **B** which is thought to proceed *via* the formation of a cyclobutadiene complex.[153]

This section has summarised the transition-metal catalysed [2+2+2] cycloaddition reaction for alkynes and alkenes, outlining mechanistic concepts and the associated challenges of reaction selectivity. The utility of chiral rhodium(I) catalysts for the access of chiral products has also been displayed, as it is a solid testament to the widespread application of these reactions. Despite this field's many achievements, perfecting the three-component reaction remains as an ongoing challenge. A

catalytic system, capable of selectively coupling three different unactivated alkyne or alkenes, would considerably advance this field.

4.2 An Introduction to Chiral Sulfoximines

Sulfoximines are becoming increasingly prevalent within pharmaceutically relevant scaffolds (**Figure 4.1**).[154] Sulfoximines are mono-aza-analogues of sulfones; introduction of a single nitrogen atom brings several advantageous characteristics to light.[155] They can accept and donate hydrogen bonding, thus making them more hydrophilic than their parent sulfone.[155]

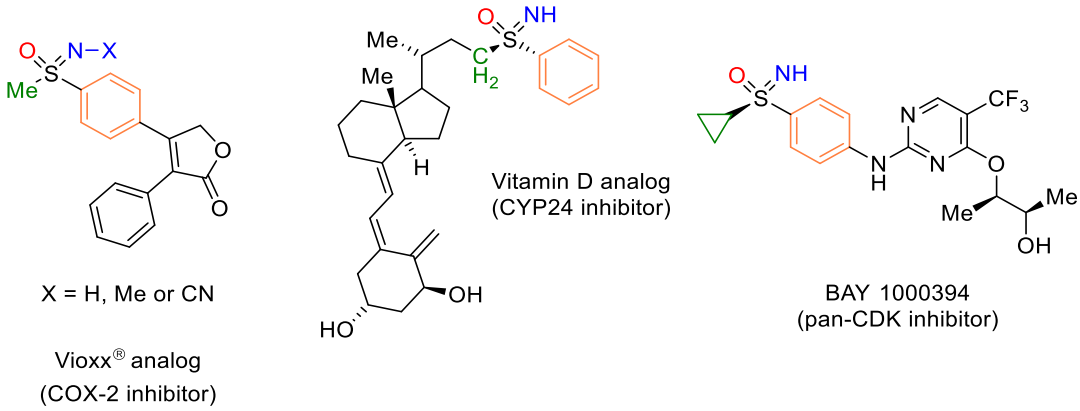


Figure 4.1. Illustrating a variety of different drugs containing sulfoximines.

Nitrogen incorporation adds an additional vector of complexity to the molecule in question; it is possible to generate an entirely new area of chemical space on a molecule by derivatising from the nitrogen position.[155] If the parent sulfone is unsymmetrical ($R^1 \neq R^2$), then the sulfoximine analogue will introduce a configurationally stable chiral centre into that molecule (**Figure 4.2**).[156]

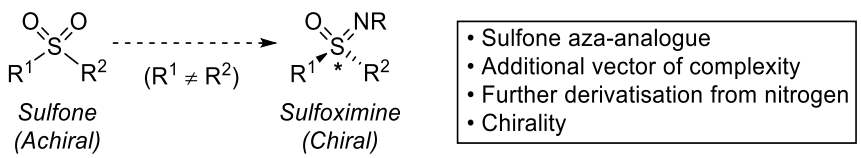
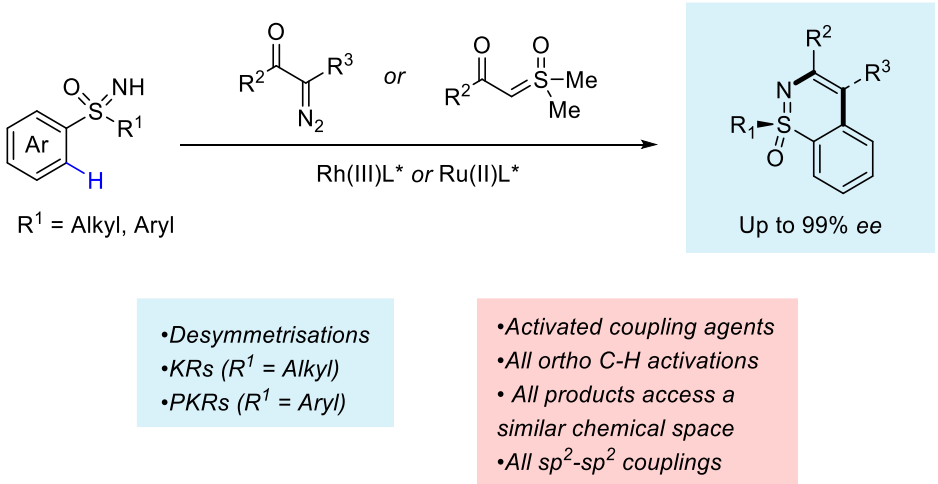


Figure 4.2. Outlining the relationship between sulfones and sulfoximines.

The first reported synthesis of a sulfoximine was described over 70 years ago.[157] Despite this early discovery, interest in sulfoximines and their potential medicinal applications did not grow until years later.[158] Although a perfect explanation for this phenomena is unclear, one might put this down to earlier methods of preparation involving harsh reagents, making them unattractive compounds to synthesise.[159] More recently however, an advent of modern methods has been unveiled,[156b, 160] advertising safer, scalable, cost effective methods of sulfoximine preparation, making them a more attainable substrates for drug testing.[161]

4.2.1 Enantioselecive Sulfoximine Synthesis using Transition-metals

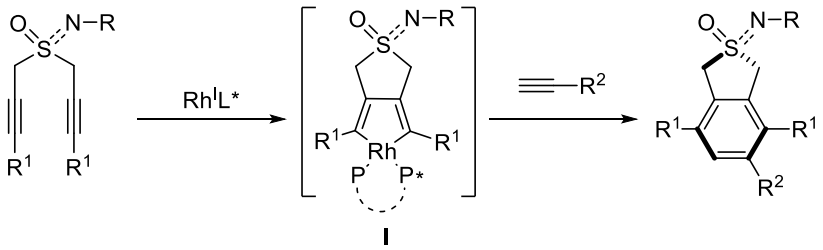
Although the chirality within sulfoximines can be indirectly installed through asymmetric sulfoxidations[162] and imidations[156c] of sulfides, many chiral methods perform a desymmetrisation or kinetic resolution on a pre-formed achiral or racemic sulfoximine.[163] Reactions of this class generally involve a transition metal-catalyst, which usually undergoes *ortho*-C–H activation on an aryl sulfoximine, to form stereodefined ring annulated products (**Scheme 4.14**).[164]



Scheme 4.14. Transition-metal catalysed methods toward enantioenriched sulfoximines.

The substrates that couple to the sulfoximine are normally carbene precursors, such as diazo compounds or α-carbonyl sulfoxonium ylides.[164] Although these methods provide good yields, enantioselectivity and functional group toleration, they possess some clear drawbacks.[164] The requirement for specific and activated substrates is the first of these; this limits the pool of readily available materials for these reactions. The methods are also limited to *ortho*-C–H activations, for sp^2–sp^2 coupling; this essentially limits the degree of chemical space that can be harnessed within the chiral sulfoximine products. To access chiral sulfoximines within a new degree of chemical space, a different transition-metal catalysed process would have to be considered.

The study of this thesis has been primarily centred on the uses of cationic Bosnich-type rhodium(I) catalysts.[22] When bearing in mind the extensive successes they have provided to the development of enantioselective [2+2+2] chemistry,[129-130, 141] we envisaged this as a new catalytic entry point towards enantioenriched sulfoximines (**Scheme 4.15**).



• *Unactivated substrates*
• *Mild conditions*
• *Relatively new chemical space for chiral sulfur groups*

Scheme 4.15. Our new catalytic proposal for sulfoximine desymmetrisation.

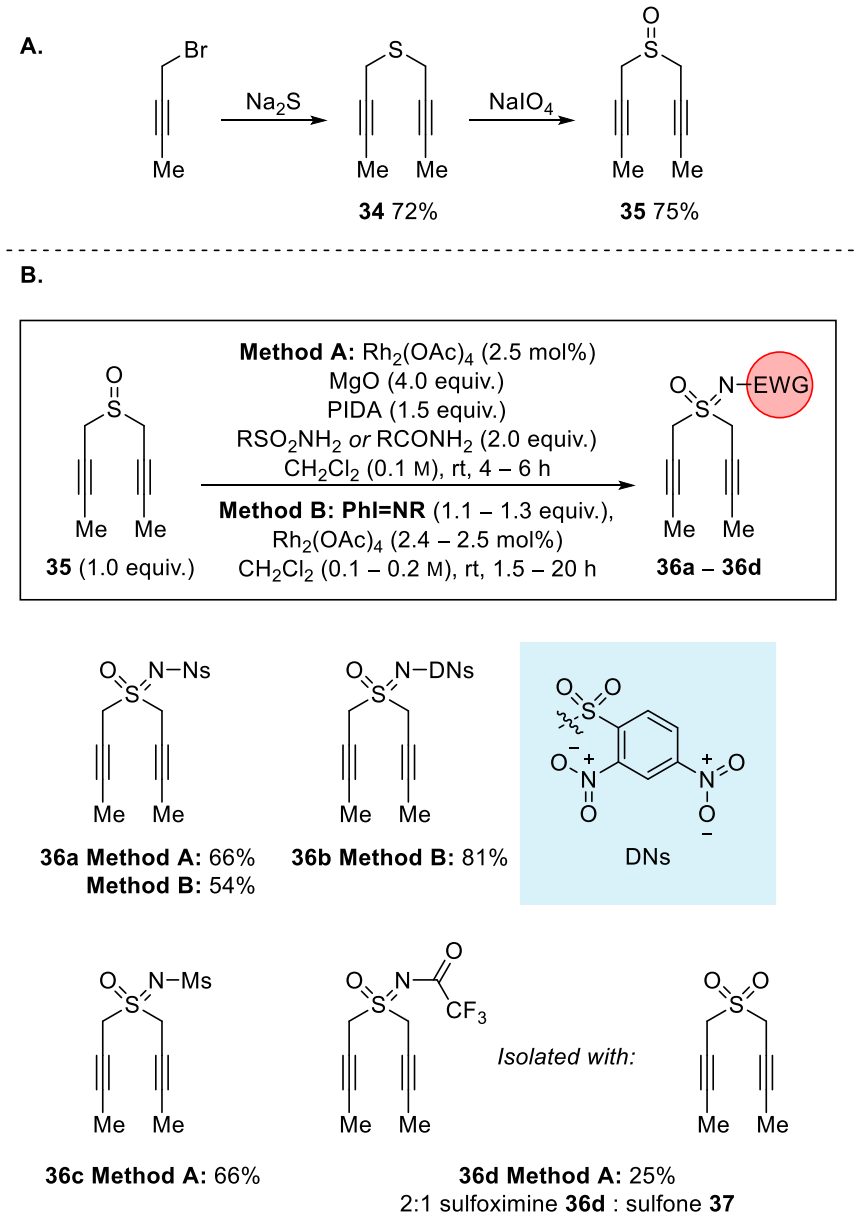
Our proposal was to form a prochiral 1,6-diyne substrate, bearing a sulfoximine in the central bridging atom. This could then undergo oxidative cyclisation to form

rhodacyclopentadiene complex **I**. This intermediate could be capable of controlling the positional and facial selectivity of subsequent monoyne addition, to ultimately access the enantioenriched sulfoximine product. The benefits that accompany this method include the use of unactivated alkyne substrates, alongside the absence of a C–H bond activation; this route could possibly lead to catalysis under mild reaction conditions. Most importantly, the area of chemical space that this product class can access is relatively new for chiral sulfur groups. The nitrogen group is no longer bound to a ring; this should lead to easier diversification of the enantioenriched product.

4.3 Results and Discussion

4.3.1 Initial Proof of Concept

We began our study by synthesising an *N*-protected protected sulfoximine diynes **36** (**Scheme 4.16**).

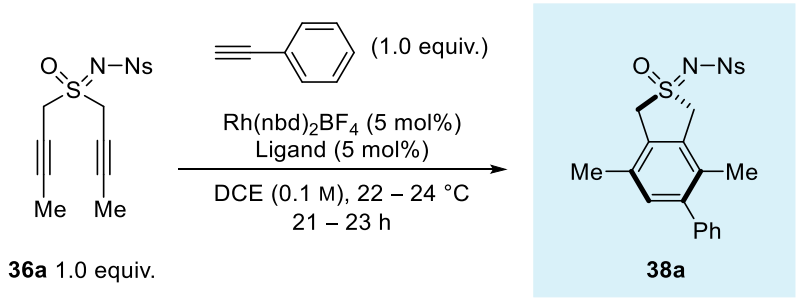


Scheme 4.16. A. Synthesis of sulfoxide diyne **35**; **B.** rhodium-catalysed sulfoxide imidations.

Initial attempts considered making sulfoxide diyne **35** in two steps from 1-bromo-2-butyne (**Scheme 4.16A**). Rhodium-catalysed sulfur imidations could then be

applied to sulfoxide diyne **35**, to generate sulfoximine diynes **36a** – **36d** (**Scheme 4.16B**). Despite several products being synthesised in moderate to excellent yields, a pure sample of the *N*-$COCF_3$ protected diyne **36d** could not be obtained from the imidation. The *N*-nosyl (*N*-Ns) substrate **36a** was then tested in a ligand evaluation for an asymmetric [2+2+2] reaction (**Table 4.1**). The design of our reaction system was based on previous literature accounts.[165] Phenylacetylene was used as the coupling substrate because it was previously used in a racemic [2+2+2] reaction with a sulfoxide diyne,[165a] whereas the reaction concentration and substrate stoichiometry were both taken from an account by Clayden and co-workers.[165b]

Table 4.1. Initial ligand evaluation for the [2+2+2] cycloaddition between sulfoximine diyne **36a** and phenylacetylene.



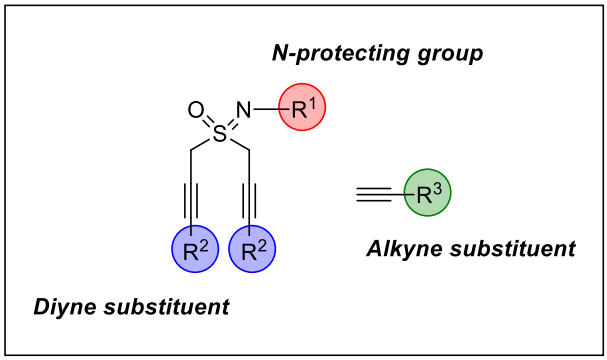
36a 1.0 equiv. **38a**

Entry	Ligand	Prod:SM	Isolated Yield (%)	*er*
1	*rac*-BINAP	>20:1	56	50:50
2	(*S*)-BINAP	15:1	61	37.5:62.5
3	(*R*)-DM-BINAP	1:2.7	43	56.5:43.5
4	(*R*)-3,5-Xyl-MeOBIPHEP	1:11.8	46	50:50
5	(*R*)-3,5-*t*-Bu-MeOBIPHEP	1:2.9	53	50:50
6	(*R,R*)-Me-DuPhos	-	0	-

We were pleased to obtain a 56% yield of the desired product from the racemic cycloaddition, when using *rac*-BINAP as the ligand (entry 1). When instead using (*S*)-BINAP as the ligand, a yield of 61% was obtained, with an *er* of 37.5:62.5, (entry 2). This was an excellent initial proof of concept, showing that chirality could

be induced within our system. However, we saw a decrease in *er* (56.5:43.5) when (*R*)-DM-BINAP was instead employed (entry 3), and racemic product when switching to BIPHEP-type ligands (entries 4 and 5). No reaction was observed after 21 h when (*R*,*R*)-Me-DuPhos was used as the chiral ligand (entry 6).

Despite these promising first results, they did not reveal to us what the key selectivity inducing factors were, and similar desymmetrisation models did not exist within the literature. For this reason, further ligand evaluation was not initially pursued, and we instead focussed on determining the substrate factors governing reaction selectivity. To do this, we considered where steric and electronic modifications could be made within our standard substrate model (**Scheme 4.17**).

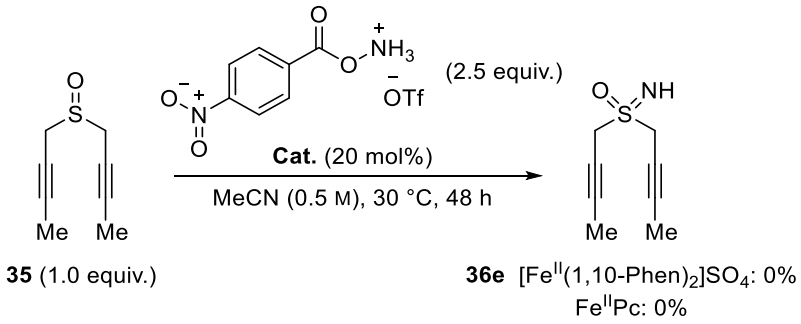


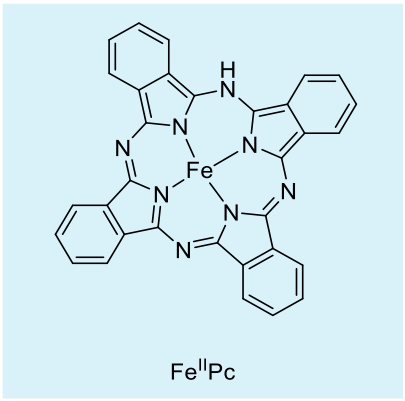
Scheme 4.17. Showing the groups capable of being modified in the current substrate system.

Making sufficient modifications on groups R^1, R^2 and R^3 seemed like an obvious starting point. Out of these, modifying the sulfoximine protecting group (R^1) initially seemed the most appropriate; such groups can easily be removed after the [2+2+2] step, and it should be possible to make a broad range of substrates, due to sulfoximine *N*-functionalisation chemistry being well developed.[166]

4.3.2 Synthesis of R^1 Protected Sulfoximine Diynes

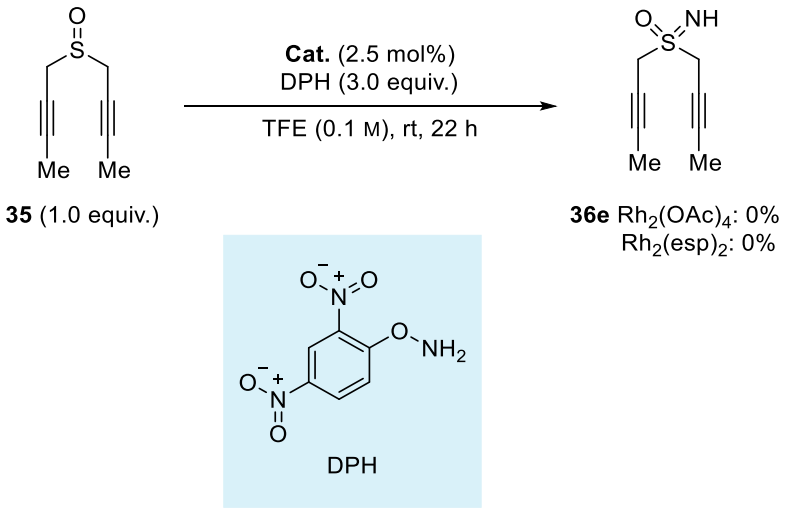
To make different *N*-protected sulfoximines, we had to consider a new synthetic route. The rhodium catalysed imidations are efficient reactions, however, they are limited to electron-withdrawing protecting groups.[167] Therefore, a new common intermediate had to be obtained – the free sulfoximine diyne. We initially attempted the synthesis of this intermediate through an iron-catalysed sulfoxide imination by Bolm.[168] However, both iron catalysts, $[Fe^{II}(1,10\text{-Phen})_2]SO_4$ and $Fe^{II}Pc$, failed to produce any detectable conversion to the desired product **36e** (**Scheme 4.18**).





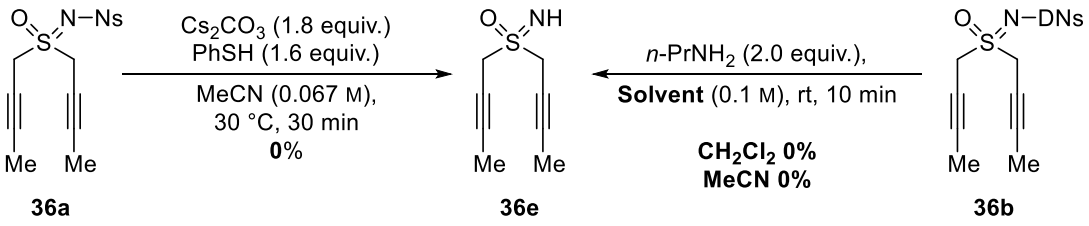
Scheme 4.18. Iron catalysed sulfoxide iminations.

A rhodium-catalysed sulfoxide imination[169] also failed to produce any desired product after a 22 h reaction time, when catalysts $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ were employed (**Scheme 4.19**).



Scheme 4.19. Rhodium catalysed sulfoxide iminations.

When trying to access the free sulfoximine from the deprotections of *N*-nosyl and *N*-DNs protected sulfoximine diynes,[170] rapid starting material consumption was observed in both cases, giving a complex mixture with no observable product **36e** (**Scheme 4.20**).

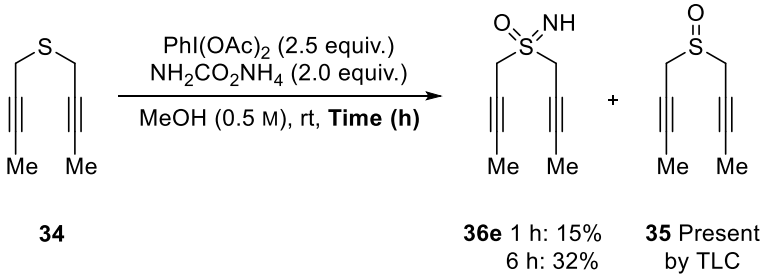


Scheme 4.20. *N*-Ns and *N*-DNs deprotections.

The complex mixtures that formed in these deprotections were a likely to be a result of degradation, as we expect that these substrates might be base labile.

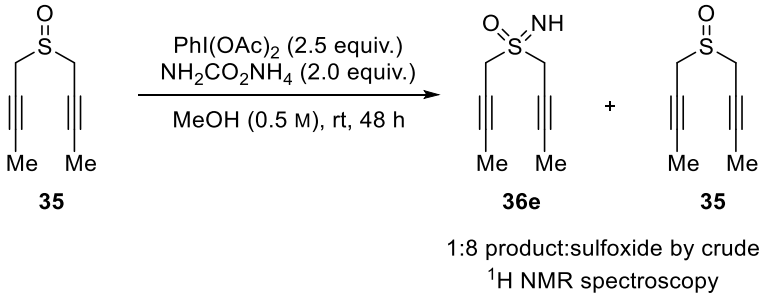
Because the free sulfoximine synthesis from higher oxidation state sulfur compounds was not looking encouraging, we turned our focus to direct sulfide oxidations. When submitting sulfide diyne to literature known conditions by Bull and co-workers,[171] we were pleased to find that desired product **36e** could be isolated

in 15% yield. When leaving the reaction for a longer duration (6 h), the yield could be improved to 32% (**Scheme 4.21**).



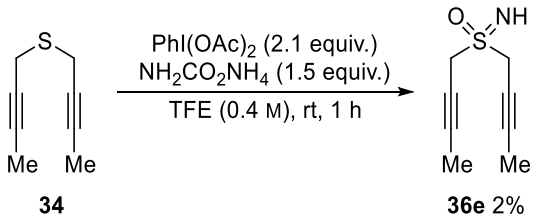
Scheme 4.21. Sulfoximine formation from a sulfide oxidation.

Despite this success, the isolated free sulfoximine was not pure, as it was very difficult to avoid co-elution during chromatography. The sulfoxide diyne **35** could also be detected within the crude TLCs of these experiments. When applying sulfoxide **35** to these conditions, a very low degree of reaction conversion was observed by ^{1}H NMR spectroscopy of the crude reaction mixture, after a 48 h reaction time (**Scheme 4.22**).



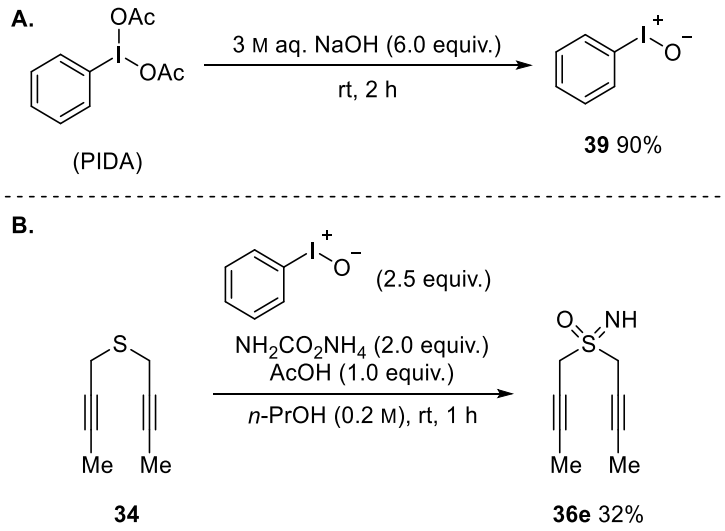
Scheme 4.22. Sulfoxide imination using Bull's conditions.

This suggested that when sulfoxide diyne **35** forms in the sulfide oxidation, further oxidation from this intermediate is slow. Alternative oxidation conditions by Magnier and Reboul,[172] which uses an adjusted stoichiometry and 2,2,2-trifluoroethanol (TFE) as the reaction solvent, could only produce a 2% isolated yield of the product (**Scheme 4.23**).



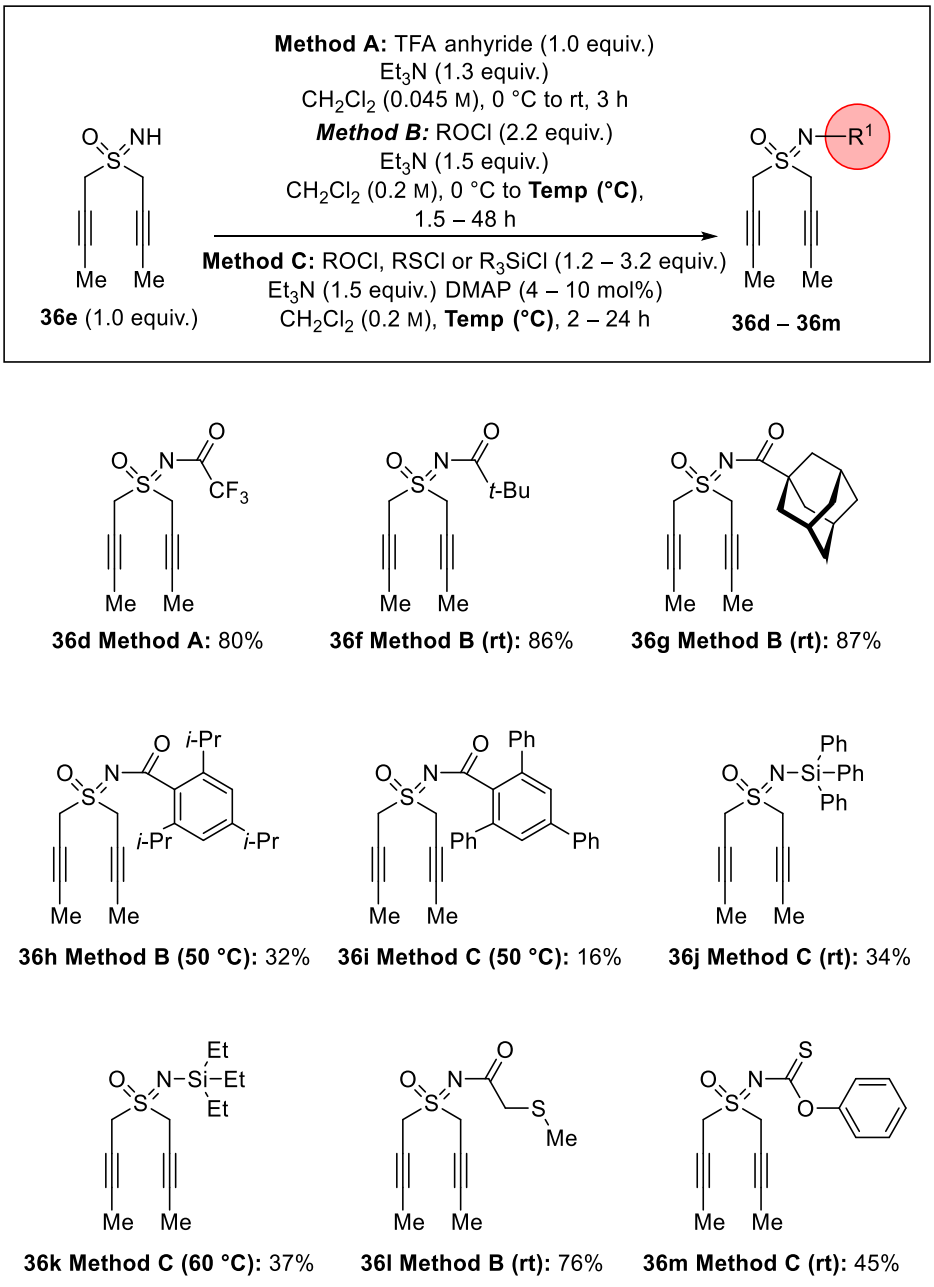
Scheme 4.23. Alternative sulfide oxidation conditions.

Bull and Luisi have recently shown that switching the oxidant, $PhI(OAc)_2$ (PIDA), to iodosylbenzene (PhIO) can provide highly efficient oxidations on sulfenamides.[173] Such a reagent could easily be prepared in a single step from PIDA, on a multi-gram scale (**Scheme 4.24A**). When submitting sulfide diyne **34** to these alternative conditions, we were delighted to observe much cleaner reaction, with no detectable sulfoxide by TLC. The product could be isolated as a pure solid, in 32% yield (**Scheme 4.24B**). This yield was no higher than that obtained from the PIDA conditions; we expect that this is probably due to some product degradation in the workup/purification steps. Despite this, the PhIO conditions seemed preferable, as a purer product could be consistently isolated.



Scheme 4.24. Using iodosylbenzene as an oxidant in sulfide oxidations.

With a reasonable strategy to make free sulfoximine substrate **36e** obtained, we set out to prepare different *N*-protected sulfoximines, containing sterically and electronically different groups (**Scheme 4.25**).

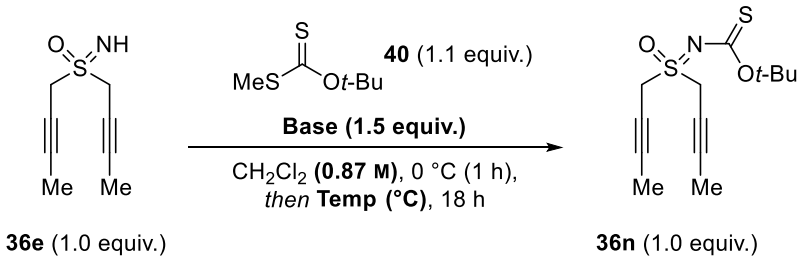


Scheme 4.25. Illustrating the synthesis of different *N*-protected sulfoximine diynes from free sulfoximine **36e**.

Pleasingly, a broad variety of different *N*-protected sulfoximine diynes could be prepared using similar synthetic methods. A family of electronic withdrawn

products of varying steric bulk (**36d** – **36i**) were obtained in yields between 16 – 87%. Electron rich diynes **36j** and **36k** were both prepared in moderate yields, and the *N*-TES protected substrate **36k** was prone to hydrolysis. We also synthesised sulfoximines bearing coordinating groups (**36l** and **36m**), as we envisaged that the presence of a directing group could positively influence cycloaddition selectivity. SMe tethered substrate **36l** and thiocarbamate protected substrate **36m** were produced in yields of 76% and 45%. Initial attempts towards a thiocarbamate substrate were made through a Botc protection method.[174] Free sulfoximine **36e** was reacted with xanthate ester **40**, under a set of different conditions (**Table 4.2**)

Table 4.2. Condition alteration for the Botc protection of free sulfoximine **36e**.



36e (1.0 equiv.) **36n** (1.0 equiv.)

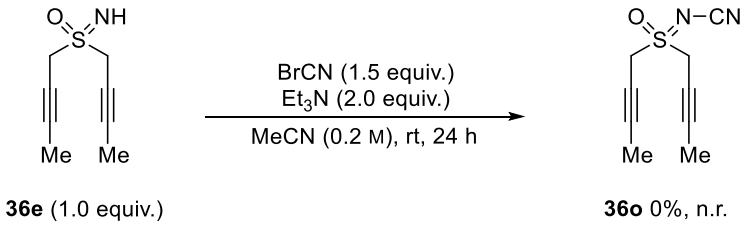
Entry	Temp (°C)	Base	Yield
1	rt	-	0[a]
2	rt	Et_3N	0[a,b]
3	50	-	0[c]
4	50	Et_3N	0[d,b]

[a] No reaction; [b] xanthate ester fully consumed; [c] both starting materials present, with undesired decomposition products; [d] complex crude mixture.

Although the literature reports these protections being performed in *n*-pentane, the reactions in this case had to be performed in CH_2Cl_2, due to free sulfoximine **36e** being poorly soluble in *n*-pentane. No desired reaction occurred after 18 h without base at room temperature and 50 °C (entries 1 and 3). Adding base at these

temperatures resulted in full consumption of xanthate ester **40**, with no desired product formation (entries 2 and 4).

We additionally wanted to generate an *N*-cyanated species **36o**, as this substrate might behave differently to other electron-poor substrates, within the [2+2+2] cycloaddition. A standard set of cyanation conditions, previously used in our laboratory,[175] was applied to substrate **36e** (**Scheme 4.26**).



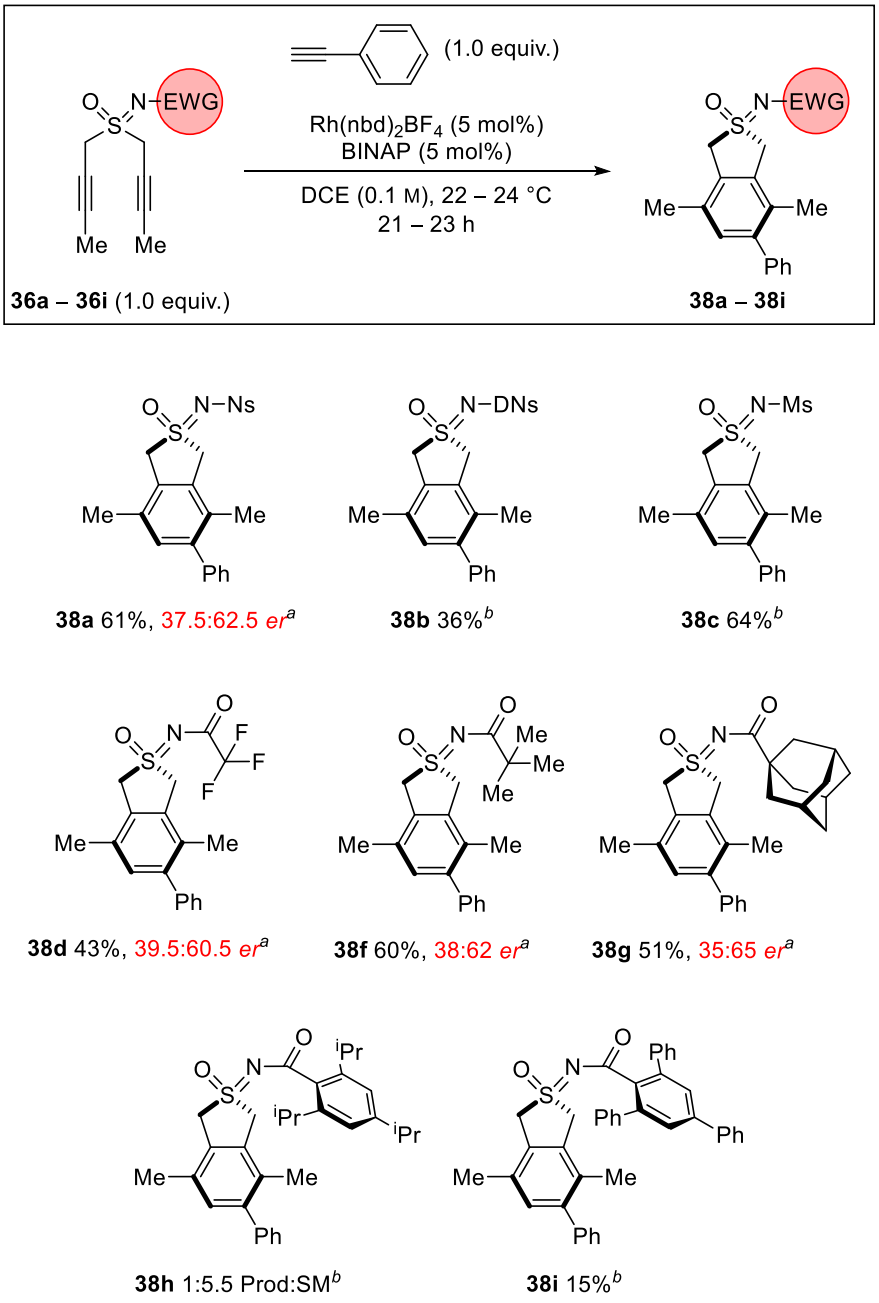
Scheme 4.26. An attempt to synthesise *N*-cyanated sulfoximine diyne **36o**.

Surprisingly, desired reactivity was absent under these conditions, and free sulfoximine diyne **36e** was still present after 24 h by ^{1}H NMR spectroscopy.

4.3.3 R^{1} Group Evaluation in [2+2+2] Cycloadditions

4.3.3a Electron-poor Substrates

The electron poor R^{1} substituted substrates were first tested under the standard [2+2+2] cycloaddition conditions, including substrates **36b** and **36c** made from the sulfoxide imidations (**Scheme 4.27**).



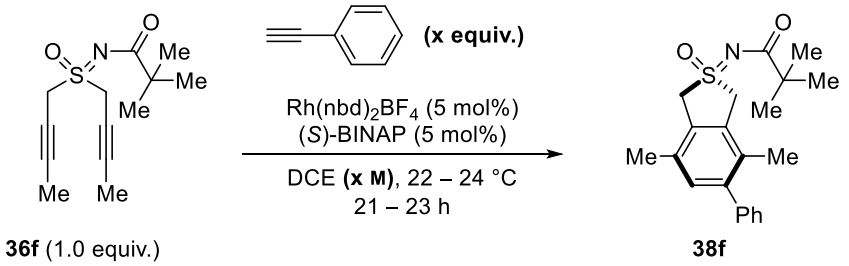
Scheme 4.27. Evaluating electron poor sulfoximine diynes within the [2+2+2] reaction; [a] results when using (*S*)-BINAP; [b] reactions using *rac*-BINAP.

For all the substrate examples in scheme **4.27**, racemic reactions were performed under the standard reaction conditions, using *rac*-BINAP as the ligand, with isolated yields ranging between 15 – 64%. Unfortunately, the *N*-Ms and *N*-DNs protected products experienced solubility issues under the chiral HPLC methods attempted, and so no *er* values were obtainable for these examples. The low yield exhibited by

the *N*-DNs protected product was a result of poor reaction conversion, most likely due to its partial insolubility in DCE. The amide protected substrates were slower to react and did not show full conversion after a 21 h reaction time. Despite some limitations, respectable yields could be obtained for examples **38d – 38g**. For these products, no significant change in product *er* was observed, even for the bulky adamantyl protected substrate (35:65 *er*). When looking at the even bulkier examples **38h** and **38i**, very poor conversion was experienced in both cases, and even though a small amount of product **38i** could be isolated from the racemic reaction (15%), chiral reactions were not pursued due to time constraints. Although we were unable to obtain *er* values for the bulkiest substrates, we still managed to obtain them for a collection of different electron-withdrawing groups (EWGs), of differing shape and size. The absence of any notable change in e*r* across these substrates suggests that protecting group sterics is unlikely to significantly contribute to cycloaddition selectivity.

A brief condition evaluation was also performed using *N*-pivaloyl sulfoximine diyne **36f**, to see whether the reaction *er* could be tweaked by simple alterations in alkyne loading and reaction concentration (**Table 4.3**).

Table 4.3. Condition evaluation for the [2+2+2] cycloaddition between diyne **36f** and phenylacetylene.



36f (1.0 equiv.) **38f**

Entry	Conc. (M)	Alkyne Loading (equiv.)	Prod:SM[a]	Isolated yield	*er*
1	0.1	1.0	3.2:1	60	38:62
2	0.1	2.0	2.1:1	48	38:62
3	0.25	1.0	3.3:1	51	39:61
4	0.5	1.0	1.5:1	39	38.5:61.5

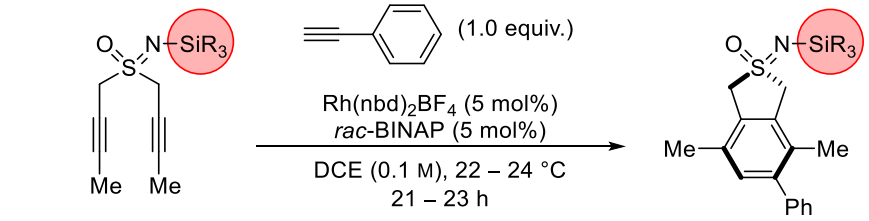
[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Increasing these two parameters did not seem to provide an increase in the reaction enantioselectivity (entries 2 to 4). In addition, lower conversion and isolated yields were obtained when either doubling the loading of phenylacetylene or using a 0.5 M reaction concentration (entries 2 and 4).

4.3.3b Reactions of Electron-rich Substrates and Free Sulfoximines

The *N*-silyl protected sulfoximines were then tested to see if electron rich substrate could induce a higher degree of reaction selectivity (**Table 4.4**).

Table 4.4. Submitting electron rich diynes **36j** and **36k** to the standard cycloaddition conditions.



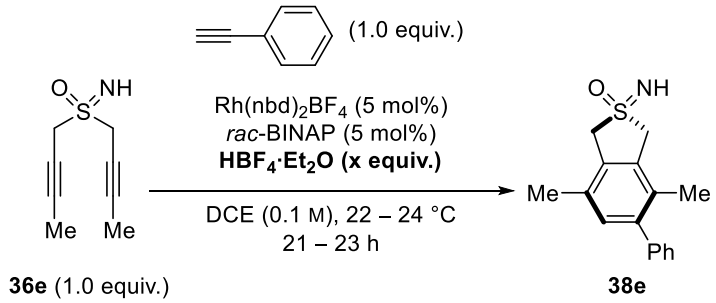
36j and **36 k** (1.0 equiv.) — **38j** and **38k**

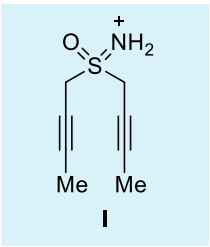
Entry	SiR_3	Prod:SM	Isolated Yield (%)
1	TPS(**36j**)	-	0
2	TES(**36k**)	-	0

Unfortunately, no conversion from the starting diyne could be observed after 21 h for both TPS and TES protected sulfoximines, and no product desired product could be isolated as a result. We also decided to try the free sulfoximine diyne **36e** as a substrate in the reaction (**Table 4.5**). Unfortunately, no reactivity towards desired product **38e** could be observed when running this substrate under the standard reaction conditions (entry 1). The nitrogen lone pair on free sulfoximine diyne **36e** will be highly Lewis basic and completely unhindered in the absence of a large protecting group. These two factors contribute to the ability of this lone pair to prohibit desired reactivity by coordinating to the rhodium catalyst. It was envisaged that the addition of a Brønsted acid, such as $HBF_4{\cdot}Et_2O$ might eradicate this basicity, through *in situ* generation of protonated species **I**. This acid was used, as it shared the same counter-ion as our standard rhodium catalyst. Having $HBF_4{\cdot}Et_2O$ present at differing loadings did not initiate any desired conversion to cycloaddition product

38e (entries 2 and 3). Experiments from this section suggest that an electron withdrawing protecting group is necessary to accomplish cycloaddition reactivity.

Table 4.5. Free sulfoximine diyne **36e** within the [2+2+2] cycloaddition.



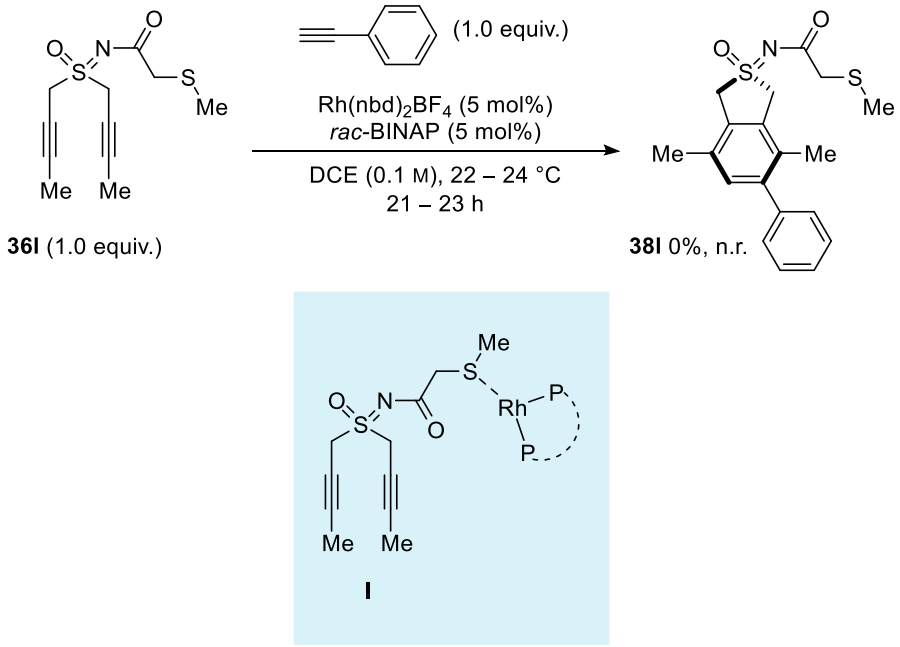


Entry	Acid loading (equiv.)	Isolated Yield (%)
1	0	0
2	1.0	0
3	2.0	0

4.3.3c Directed Substrates

When considering the reaction mechanism, the metal centre and bridging sulfoximine group are likely to be remote from each other, within any of the catalytic intermediates. This is a potential reason for the low enantioselectively observed within our reactions so far, as an interplay between the chiral catalyst and the sulfoximine group is likely to be important for gaining high selectivity. An interaction between these two components could be enhanced by using a directing group. We were therefore intrigued to see how sulfoximine diynes **36l** and **36m**, each bearing a coordinating sulfur atom, would affect the reaction selectivity. When employing SMe tethered diyne **36l** under the standard conditions, we were

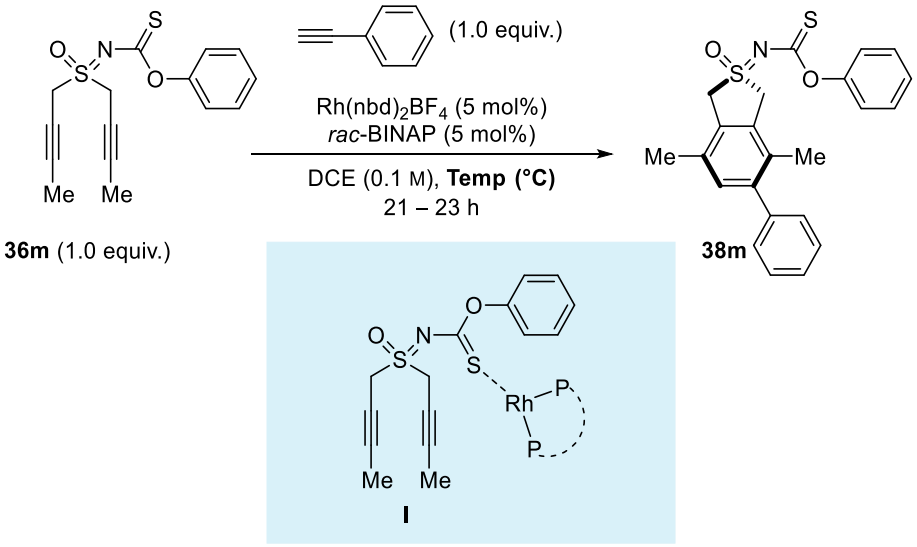
disappointed to observe no reactivity from the starting materials after 21 h; no desired product could be observed or isolated (**Scheme 4.28**).



Scheme 4.28. Showing a lack of reactivity of SMe tethered sulfoximine diyne **36l** under the standard [2+2+2] reaction conditions.

The lack of reactivity suggested that the SMe tether was coordinating to the catalyst (intermediate **I**), however it was likely that this coordination prevented the catalyst from facilitating the desired reaction. We next tried the thiocarbamate substrate **36m** under the standard [2+2+2] conditions (**Table 4.6**, entry 1).

Table 4.6. Showing a lack of reactivity when using thiocarbamate protected diyne **36m** under the standard [2+2+2] reaction conditions.



Entry	Temp (°C)	Yield (%)
1	rt	0[a]
2	50	0[a]
3	80	0[a]

[a] No conversion from starting material was observed by ^{1}H NMR spectroscopy of the crude reaction mixture.

The reaction did not proceed as room temperature, and we again concluded that the lack of observed reactivity was likely due to an undesired effect of substrate coordination (intermediate **I**). We decided to run the reaction at higher temperatures, to see whether this might initiate some reactivity towards product **38m**. However, the cycloaddition was still absent at 50 °C and 80 °C (entries 2 and 3).

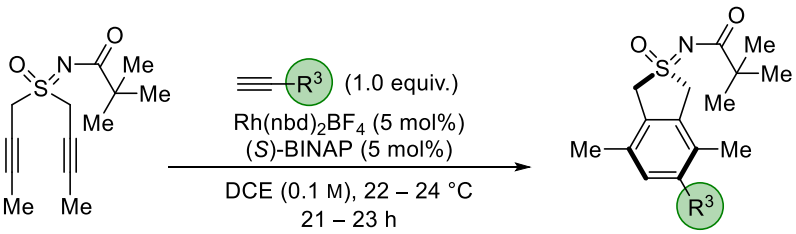
4.3.4 Modifications in R^2 and R^3 Groups

With the *N*-protecting group modifications proving generally unsuccessful, we set out to vary the R^2 and R^3 groups, from the standard substrate model (section **4.3.1**, **Scheme 4.17**).

4.3.4a R^3 Group Alteration

A bulkier alkyne, such as *t*-Bu acetylene, was trialled under the standard reaction conditions with the *N*-pivaloyl sulfoximine diyne **36f** (**Table 4.7**).

Table 4.7. A comparison of reactivity and enantioselectivity between *t*-Bu-acetylene and phenylacetylene.



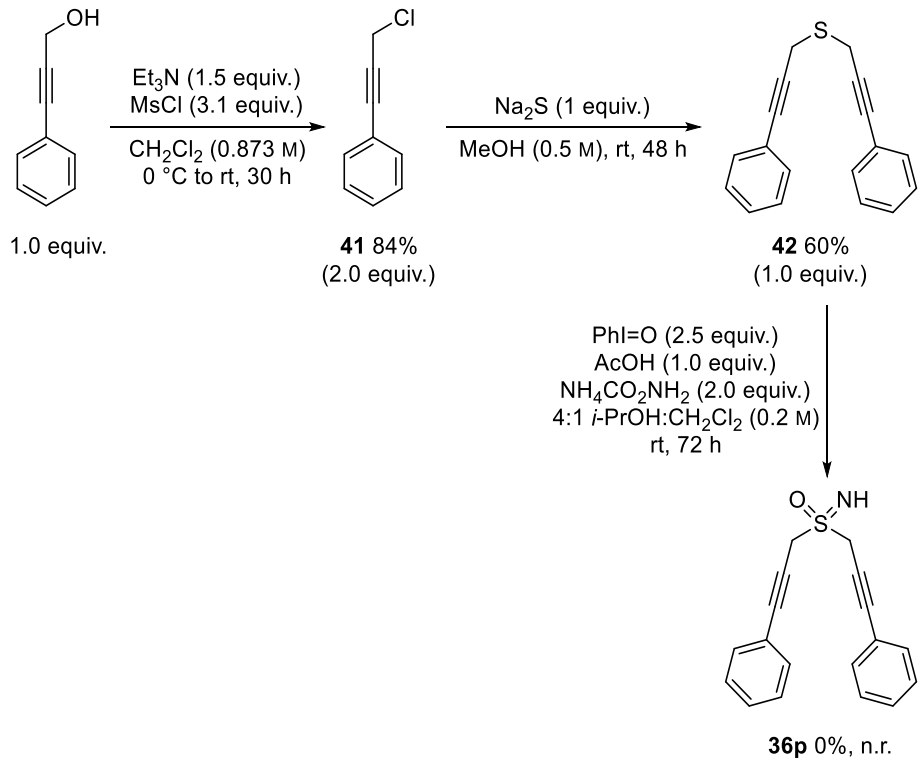
36f (1.0 equiv.) → **38f** and **38n**

Entry	Alkyne R	Prod:SM	Isolated Yield (%)	*er*
1	*t*-Bu	1:1.2	32(**38n**)	44.5:55.5
2	Ph	3.2:1	60(**38f**)	38:62

We expected *t*-Bu acetylene to positively influence the reaction selectivity due to its increased steric bulk, however a significant drop in reaction *er* was instead observed (entry 1) in comparison to the standard reaction using phenylacetylene (entry 2). Alongside this, the overall reaction conversion was lower with *t*-Bu acetylene, leading to a lower isolated yield of product **38n**. The racemic reaction with *t*-Bu acetylene was performed under the standard conditions, using *rac*-BINAP as the ligand, and achieved the desired product **38n** in 18% yield (1:2.74 Prod:SM).

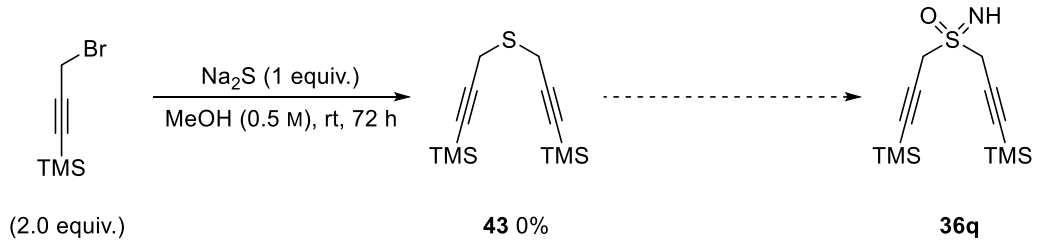
4.3.4b R^2 Group Alteration

The final substrate parameter we were interested in modifying was the diyne substitutent (R^2). A more sterically bulky substituent such as phenyl or TMS, might help to increase reaction selectivity. We firstly set out to prepare the phenyl substituted sulfoximine diyne **36p** (**Scheme 4.29**).



Scheme 4.29. Showing an attempt towards the synthesis of phenyl substituted free sulfoximine diyne **36p**.

Chlorination of 3-phenyl-2-propyn-1-ol, followed by treatment with Na_2S successfully yielded phenyl substituted sulfide diyne **42**. When subjecting this substrate to the oxidation conditions used on Me-substituted sulfide diyne **34**, we initially realised that sulfide **42** was not soluble in *i*-PrOH. To overcome this, a 4:1 *i*-PrOH:CH_2Cl_2 was used to improve sulfide solubility. Regardless, no desired formation of free sulfoximine **36p** could be observed after 72 h, and no reaction progression was detected. As disappointing as this was, we decided attempt to synthesis the TMS-substituted analogue (**Scheme 4.30**).



Scheme 4.30. An unsuccessful attempt toward TMS-substituted diyne **36q**.

Synthesis of sulfide under standard reaction conditions resulted in the formation of several unidentifiable products, as observed by ^{1}H NMR spectroscopy of the crude reaction mixture. Unfortunately, these products were inseparable during chromatography and the reaction was deemed unsuccessful.

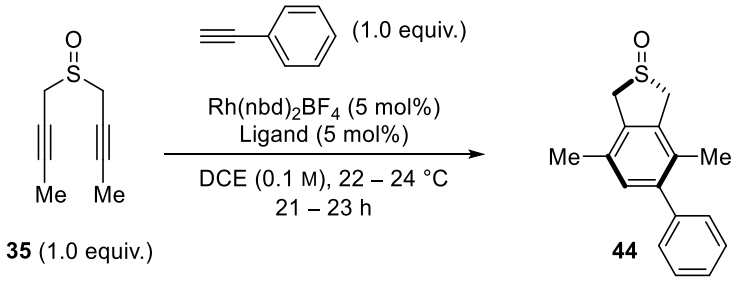
4.3.5 Desymmetrisation of Sulfur(IV) Diynes

4.3.5a Sulfoxide Diynes

Another synthetic route to this class of chiral sulfoximine would be to perform the [2+2+2] desymmetrisation on a prochiral sulfur(IV) precursor, such as sulfoxide diyne **35**. Electronically, this substrate is very different to the sulfoximine diynes because it bears a free sulfur lone pair. This could help to induce selectivity within the cycloaddition. We therefore applied sulfoxide diyne **35** to various BINAP derived ligands, to see if an enantioselective reaction could be achieved (**Table 4.8**). An initial racemic cycloaddition, again using *rac*-BINAP as the ligand, showed that the desired product **44** could be obtained in 39% yield (entry 1). Like the sulfoximines, moderate enantioselectivity could be achieved when using (*S*)-BINAP as the ligand (entry 2). However, when making structural changes to the ligand backbone, no significant changes to the reaction *er* could be observed (entries 3 to 6). As mentioned earlier, in the context of the *S*-directed substrates (section **4.3.3c**), it is possible that there is a large distance between the sulfoximine group and the

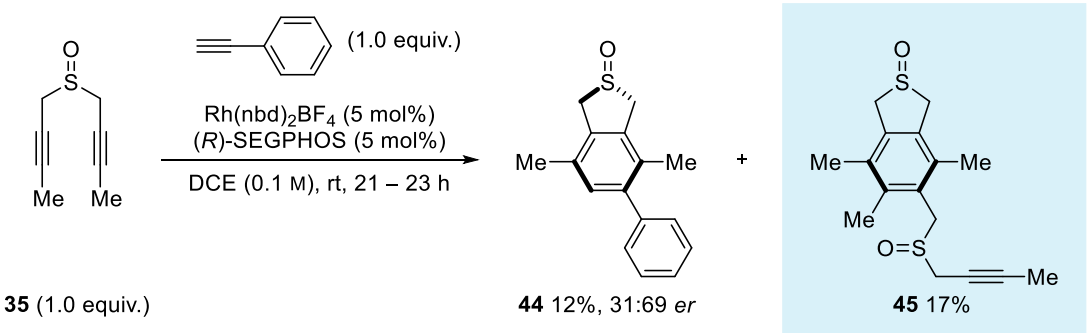
metal centre in any one of the catalytic intermediates. Therefore, it makes sense that modifications made on a remote group does not hugely influence reaction selectivity.

Table 4.8. An evaluation of BINAP derived ligands with sulfoxide **35**.



Entry	Ligand	Isolated Yield (%)	*er*
1	*rac*-BINAP	39	50:50
2	(*S*)-BINAP	43	67:33
3	(*S*)-*p*-Tol-BINAP	46	63:37
4	(*R*)-H_8-BINAP	53	34:66
5	(*R*)-SEGPHOS	12	31:69
6	(*R*)-SynPhos	53	37:63

A significant degree of diyne dimerization to side product **45** was observed in these reactions by TLC and could be isolated in 17% yield from the reaction catalysed by Rh^{I}-(*R*)-SEGPHOS (**Scheme 4.31**).

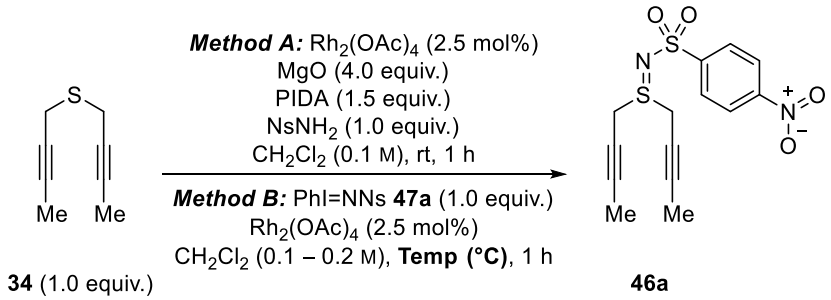


Scheme 4.31. Isolation of dimerized product **45**.

4.3.5b Sulfilimine Diynes

Another sulfur(IV) group deserving of consideration was the sulfilimine. A sulfilimine diyne should resemble the sulfoxide electronically, however these substrates should also be sterically influential, due to the presence of larger group bound to the sulfur (*N*–PG). This perfect balance of steric and electronic factors might be the key to achieving good enantioselectivity in these cycloadditions. The synthesis of *N*-nosyl sulfilimine diyne **46a** was initially attempted through a set of rhodium catalysed sulfide imidations (**Table 4.9**).

Table 4.9. Attempts at the formation of sulfilimine diyne **46a** *via* sulfide imidation.

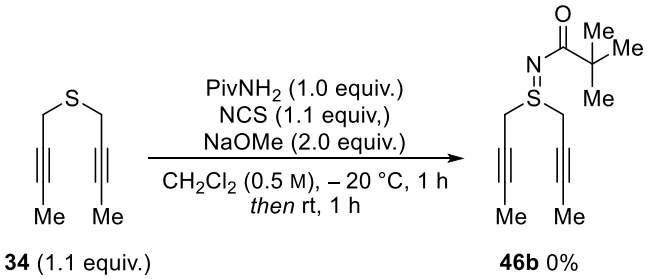


34 (1.0 equiv.) **46a**

Entry	Method	Temp (°C)	Yield (%)
1	**A**	rt	0
2	**B**	rt	0
3	**B**	0	0

When performing the imidation reaction by generating the active nitrene species *in situ* (method **A**), full consumption of sulfide diyne was observed after 1 h, however no desired sulfilimine diyne **46a** was present by ^{1}H NMR spectroscopy (entry 1). It was possible that a significant degree of alkyne oxidation was occurring instead. The imidation was also ran using the pre-formed nitrene reagent PhI=NNs (**47a**, method **B**), at room temperature and 0 °C (entries 2 and 3). Similarly, the desired sulfilimine was absent in the crude reaction mixtures of these reactions.

Sulfide diyne **34** was also employed within a chlorinative imidation procedure,[176] with the aim to produce *N*-pivaloyl sulfilimine diyne **46b** (**Scheme 4.32**). Unfortunately, a complex mixture resulted after 1 h, as observed by TLC and ^{1}H NMR spectroscopy, and no desired product could be clearly detected.

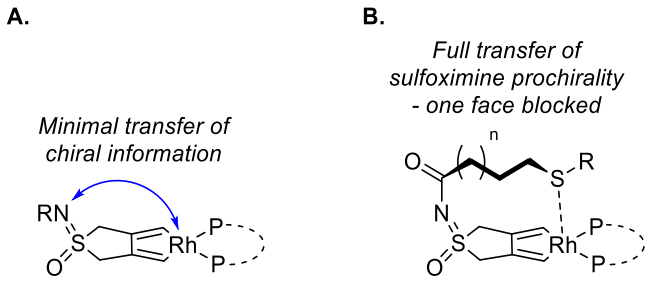


Scheme 4.32. An unsuccessful imidation of sulfide diyne **34**.

4.4 Conclusions and Future Work

To conclude this chapter, we have synthesised a novel class of sulfoximine substrates, capable of partaking within rhodium-catalysed [2+2+2] cycloadditions. Initial desired reactivity was observed from racemic conditions using *rac*-BINAP as the ligand. The racemic products obtained are novel to this field of research and so this was already an intriguing result. A reasonable degree of enantioselectivity could also be induced in the presence of a chiral catalyst. Although alterations in the ligand, substrate and conditions saw no significant change in cycloaddition enantioselectivity, further optimisation of these parameters, as well as gaining an understanding of the stereodeterming step, would be needed to reach a fully conclusive outcome for this reaction system. We suspect that the low selectivity observed from these cycloadditions might be due to the prochiral sulfoximine group being far away from the chiral metal centre within the standard [2+2+2] reaction model. Scheme **4.33A** uses the rhodacyclopentadiene complex as an example to illustrate this. The lack of reactivity seen for the substrates containing *S*-directing

groups suggests that coordination to the catalyst does occur to some degree. It might be possible to engineer such a substrate, so that a [2+2+2] reaction can happen alongside this coordination. Producing a substrate with a longer coordinating tether, would be a possible option (**Scheme 4.33B**).



Scheme 4.33. Using the standard rhodacyclopentadiene complex to illustrate how a longer tethering groups could fully transfer information to the chiral catalyst.

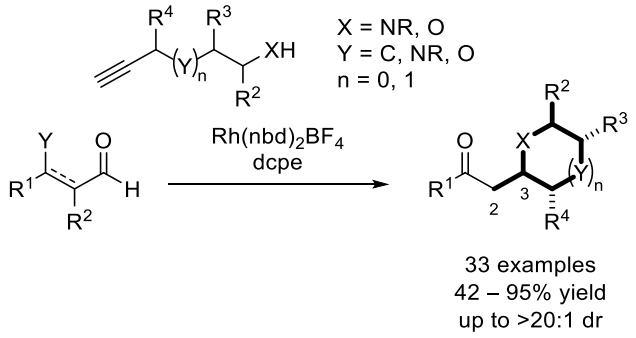
The results from the *N*-protecting group evaluation showed that steric factors alone are unlikely to significantly influence reaction enantioselectivity. Although electron rich sulfoximines, such as the silylated substrates should provide both, an electronic and steric bias, they were unreactive under the standard reaction conditions. Interestingly, the sulfoxide substrate could also produce a good initial *er*; we suspect this to be related to the presence of a free sulfur lone pair. Sulfilimine diynes would share these favourable electronics, in combination with steric effects provided by an electron withdrawing *N*-protecting group. However, our work on sulfilimines was rather limited; issues with the sulfide imidations meant that such substrates could not be prepared. Finding an alternative syntheic route to these sulfimine diynes would be highly valuable to future explorations of this method.

Chapter 5 – Conclusions and Future Work

5.1 Conclusions

Rhodium catalysis has made a significant contribution to modern C–C bond forming processes that utilise simple, unactivated precursors to rapidly produce complex molecular structures. By targeting traditionally unreactive C–H bonds, highly efficient reactions have been facilitated without the need for activated groups. Intermolecular hydroacylation has proved to be an excellent strategy for aldehyde C–H activation, to access a broad range of ketones and enones. High regio- and enantioselectivity can be produced in these reactions through suitable ligand and substrate design.

Chapter 2 demonstrated that sp^3 rich *O*- and *N*-heterocycles could be formed through a hydroacylation/conjugate-addition sequence, exploiting directed aldehydes and nucleophile tethered alkynes (**Scheme 5.1**).

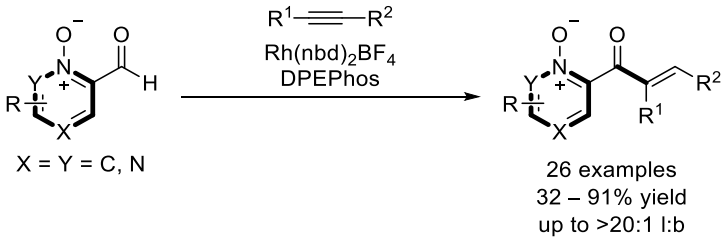


Scheme 5.1. A hydroacylation/conjugate-addition sequence towards diverse saturated *O*- and *N*-heterocycles.

A broad range of mono- and bi-cyclic scaffolds were produced from *O*- and *N*-nucleophilic alkynes. Efficient epimerisation of the newly formed C3 stereocentre, in presence of stoichiometric HCl, led to excellent diastereoselectivity within the

products through reversibility of ring closure. Reaction scalability was also demonstrated, and traceless scaffolds could be generated upon directing group functionalisation.

2-Formyl azines are highly challenging groups in hydroacylation reactions due to them bearing a free *N*-lone pair, which can coordinate to the rhodium centre and prohibit desired reactivity.[39] The *N*-oxide directed azine aldehydes, employed within chapter 3, proved to be simple and effective solution for this compromised reactivity (**Scheme 5.2**)

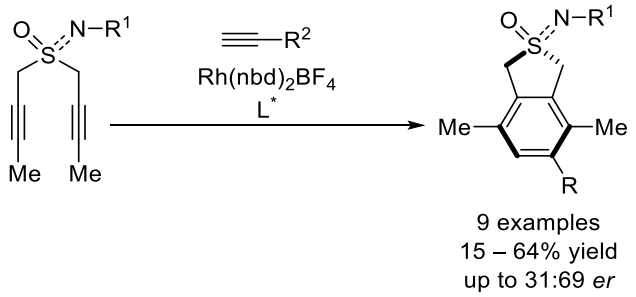


Scheme 5.2. Azine *N*-oxide directed hydroacylation.

DPEPhos was a successfully identified ligand to provide a good balance of high yield and linear regioselectivity. Sterically hindered alkynes provided a large increase in linear regioselectivity (up to >20:1 l:b). Attractive substrates such as internal alkynes and diazine aldehydes also showed good reactivity, and a one-pot processes to obtain free pyridyl products and bidentate ligands were demonstrated.

Transition-metal catalysed [2+2+2] cycloadditions are an effective strategy to rapidly build densely functionalised arenes. The absence of a C–H activation step means that these reactions can be performed at mild temperatures. Cationic Bosnich-type rhodium(I) bisphosphine catalysts have played a key role in the development of enantioselective cycloadditions in recent years, owed to their efficient reactivity, and the widespread commercial availability of chiral bisphosphine ligands. Chapter

4 used these catalysts to facilitate a [2+2+2] cycloaddition for the desymmetrisation of prochiral sulfoximines (**Scheme 5.3**).

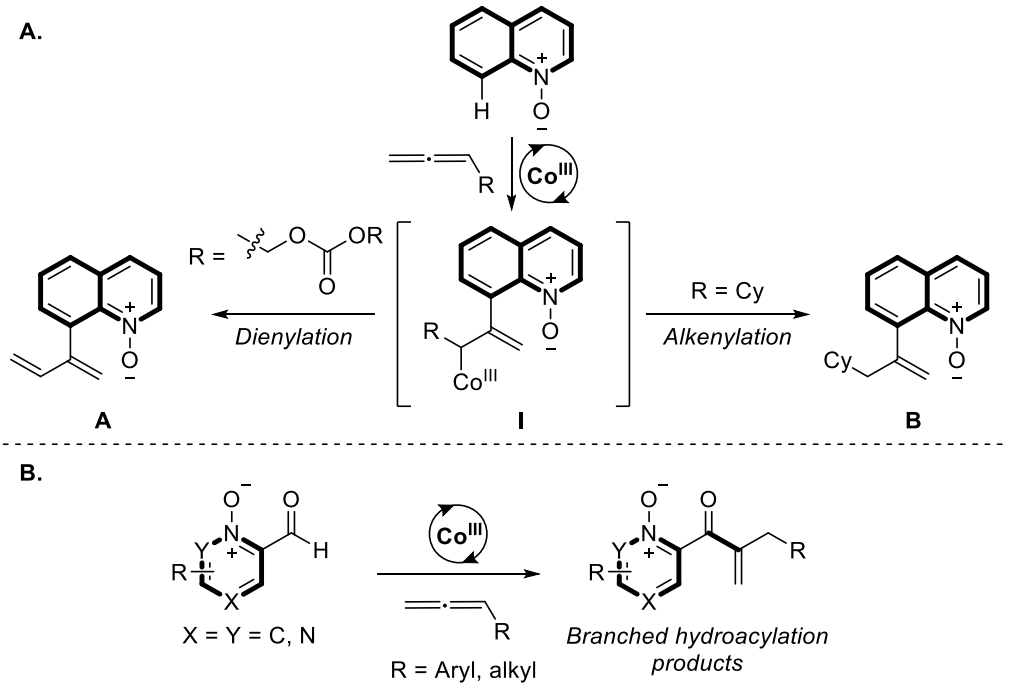


Scheme 5.3. A rhodium catalysed [2+2+2] cycloaddition for the desymmetrisation of sulfoximine diynes.

A range of novel *N*-protected 1,6-sulfoximine diynes were successfully prepared from a synthetically convenient sulfide diyne. These prochiral substrates underwent efficient [2+2+2] cycloaddition reactions and were capable of inducing enantioenriched products. However, initial modifications of the ligand, substrate sterics/electronics, and reaction conditions did not seem to have any significant affect on the enantioselectivity for this reaction. A more extensive condition and ligand evaluation will be required to gain a deeper understanding of the factors governing the selectivity for this process.

5.2 Future Work

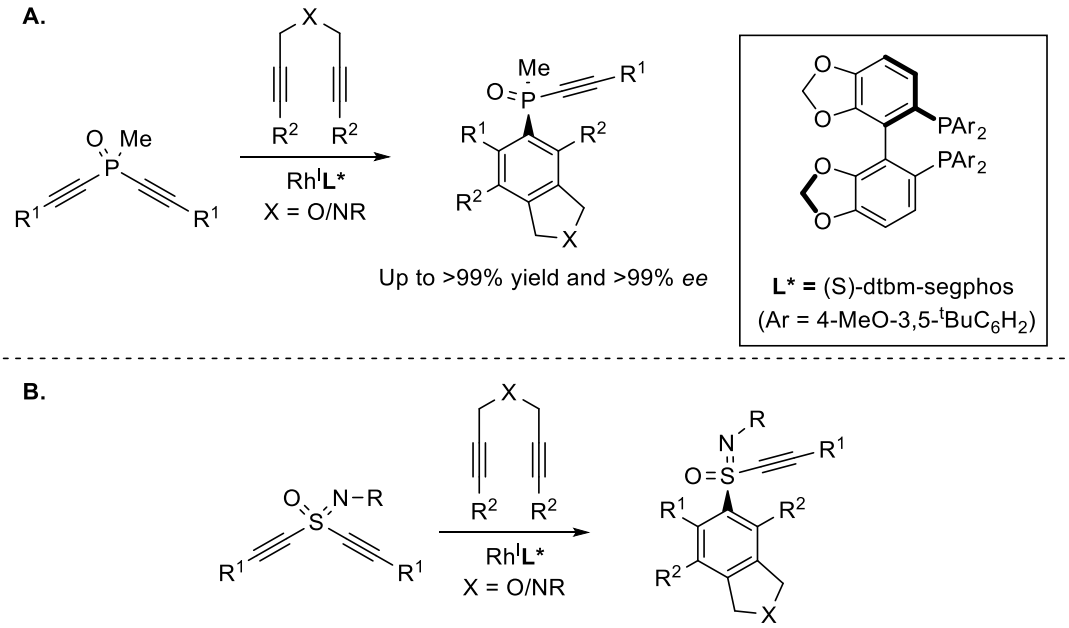
This thesis has shown that rhodium(I) bisphosphines are well adapted to achieving regio-, diastereo- and enantioselective transformations. However, their expense has prompted the use of other metals to deliver the same transformations. [4, 5b, 8-10, 12, 111, 112-113, 114] Different metals have been used in azine *N*-oxide directed C–H activations.[95g, 98b, 100b, 100c] One method of particular interest is a cobalt catalysed C(8)–H dienylation developed by Volla and co-workers.[100h] Quinoline C(8)–H activation, followed by a 2,3-migratory insertion onto an allene, forms Co-σ-allyl intermediate **I** (**Scheme 5.4A**).



Scheme 5.4. A. Volla's Co-catalysed quinoline C(8)–H dienylation/alkenylation; **B.** utility of Volla's method in *N*-oxide directed hydroacylation.

If the substrate is an allenyl carbonate, then β-oxy elimination generates the dienylated product **A**. However, in the absence of a suitable leaving group, protonation will occur to give alkenylated product **B**. We envisaged that the latter class of allene could be used on 2-formyl azine *N*-oxide substrates, in a cobalt-

catalysed branched-selective hydroacylation reaction to complement our previous linear selective methodology (**Scheme 5.4B**). It would be desirable to improve the moderate enantioselectivity seen from our [2+2+2] reaction. We hypothesise that the sulfoximine group and metal centre are too distal from each other, within catalytic intermediates. Other substrate models might be required to prevent this. Tanaka showed how alkynylphosphine oxides could be desymmetrised through [2+2+2] cycloadditions (**Scheme 5.5A**).[127a] Analogous sulfoximine diynes might also be capable of producing desired cycloaddition reactivity and would be an attractive avenue of investigation (**Scheme 5.5B**).



Scheme 5.5. A. Tanaka's enantioselective [2+2+2] cycloaddition towards chiral phosphine oxides; **B.** analogous sulfoximine diynes for [2+2+2] cycloaddition.

In this model, the alkynes are directly adjacent to the sulfoximine group; it is likely that this will lead to a higher degree of enantioenrichment within the cyclised products.

Chapter 6 – Experimental Section

6.1 General Information

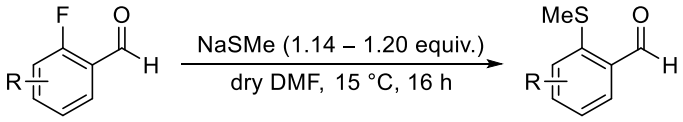
All reactions were performed in oven-dried glassware. All rhodium catalysed reactions were performed under argon, using standard Schlenk techniques. Reactions towards substrates used an inert atmosphere when indicated. Unless otherwise stated, solvents and reagents were supplied by Sigma Aldrich, FluoroChem, Alfa Aesar or Acros Organics. Acetone and 1,2-DCE were dried over Drierite™ for 16 hours, distilled at atmospheric pressure and degassed using freeze-pump-thawed method with argon before use. Anhydrous THF and DMF were obtained by filtration through anhydrous alumina columns, using an Innovative Technology Inc. PS-400-7 solvent purification system. "Petrol" refers to the fraction of petroleum ether that boils between 40 and 60 °C. "Brine" refers to a saturated aqueous solution of sodium choride. Reactions were monitored by analytical Thin Layer Chromatography (TLC), using silica gel F254 aluminium plates. Spots were visualised under UV light (254 nm) or stained with a vanillin or potassium permanganate solution. Flash column chromatography was carried out with matrix 60 silica supplied by Sigma Aldrich. All infrared data were run neat on a Bruker Tensor 27 FT-IR spectrometer, with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded on a Stuart Scientific Melting Point Apparatus SMP1. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AVIII spectrometers (400 – 600 MHz) using the signal of the residual deuterated solvent as an internal standard. Chemical shifts (δ) are quoted in ppm with multiplicities reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br, broad; bs, broad singlet. All coupling constants (*J* values) were reported in Hertz (Hz). High

and Low resolution ESI mass spectra were recorded on a Waters LCT Premier high resolution mass spectrometer. For chiral analysis, optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter at 589 nm, 25 °C. $[\alpha]_D^{25}$ is expressed in deg cm^3 g^{-1} dm^{-1} and c is expressed in g 100 cm^{-3}. The enantiomeric ratio (*er*) was determined by chiral stationary phase HPLC in a Dionex P680 chromatogram with a Dionex UVD170U detector (λ_{max} = 225 – 275 nm) using a flow rate of 1.0 mL min^{-1} with the Daicel Chiralpack column stated in the compound assignment. The eluent used and retention times ($\mathbf{T}_{major}$ and $\mathbf{T}_{minor}$) are described in the compound assignment. Where diastereoisomeric products have been isolated as an inseparable mixture, the data for the ^{1}H and ^{13}C NMR major diastereoisomer is reported, unless the isolated ratio is 1:1.

6.2 Experimental for Chapter 2

6.2.1 General Procedures

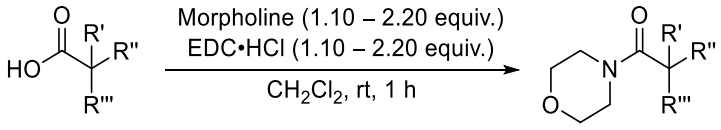
General Procedure A: Nucleophilic Substitution of 2-haloaldehydes with NaSMe



1.00 equiv.

Prepared according to literature procedure.[177] NaSMe (1.14 – 1.20 equiv.) was added to a round-bottom flask and sparged with argon gas for 15 min. Anhydrous DMF was added and a cooling bath (ca. 15 °C) was applied. To the resulting suspension, a solution of the corresponding 2-haloaldehyde (1.00 equiv.) in DMF was added and the mixture stirred overnight (16 h). Once the reaction was complete as monitored by TLC analysis, the resulting mixture was poured into H_2O and the organic layer was separated. The remaining aqueous layer was extracted with EtOAc (× 3) and the combined organic extracts were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography to yield the desired product(s).

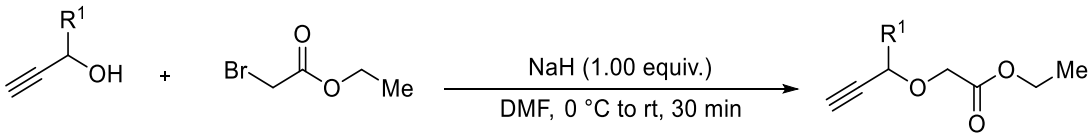
General Procedure B: Amide Couplings



1.00 equiv.

To a solution of the corresponding acid (1.00 equiv.) in CH_2Cl_2 was added morpholine (1.10 – 2.20 equiv.) and EDC·HCl (1.10 – 2.20 equiv.) and the mixture stirred for 1 h at room temperature. Once complete by TLC analysis, the mixture was quenched with sat. aq. $NaHCO_3$ and the layers were separated. The organic phase was then washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography yielded the corresponding amides.

General Procedure C: Alkylation of Propargyl Alcohols with ethyl 2-bromoacetate

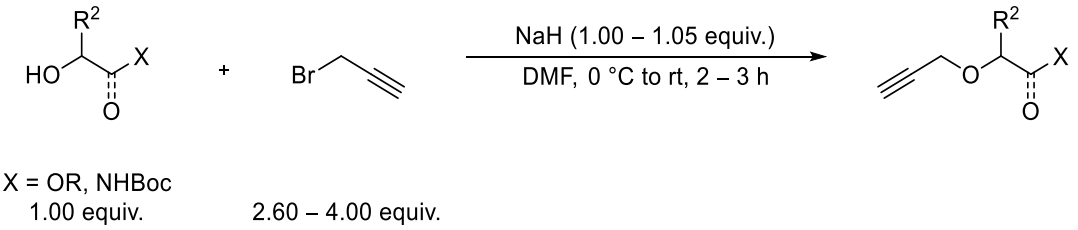


1.00 equiv. 1.20-2.00 equiv.

Prepared according to a modified literature procedure.[178] To a stirred suspension of NaH (60% in mineral oil, 1.00 equiv.) in DMF under N_2 at 0 °C was added a solution of the corresponding propargyl alcohol (80% w/w in toluene, 1.00 equiv.) in DMF. The resulting slurry was stirred at 0 °C for 30 min before a solution of ethyl-2-bromoacetate (1.20 – 2.00 equiv.) in DMF, was added dropwise at 0 °C. The mixture was then warmed to room temperature (unless otherwise stated) and stirred for a further 30 min (unless otherwise stated). After completion (as monitored by TLC analysis), the reaction mixture was quenched by addition of sat. aq. NH_4Cl at 0 °C.

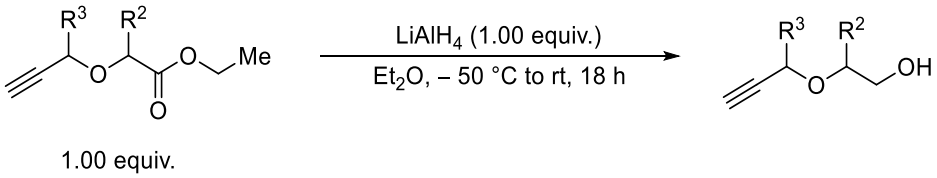
The mixture was then extracted with EtOAc (× 3) and the combined organic extracts were washed with 5% aq. LiCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the corresponding propargyl ether.

General Procedure D: Propargylation of alpha-hydroxyesters and *N*Boc phenylalaninol



Prepared according to a literature procedure.[179] The desired alpha-hydroxyester (1.00 equiv.) was dissolved in anhydrous DMF and cooled to 0 °C. NaH (60% in mineral oil, 1.00 – 1.05 equiv.) was then added portion wise and the resulting solution was stirred for 1 h at 0 °C. Propargyl bromide (80% in toluene, 2.60 – 4.00 equiv.) was added dropwise at this temperature before warming to room temperature and stirring for 2 – 3 h (unless otherwise stated). Once complete, the reaction was quenched with sat. aq. NH_4Cl and the resulting mixture was extracted with EtOAc (× 3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the corresponding propargyl ether.

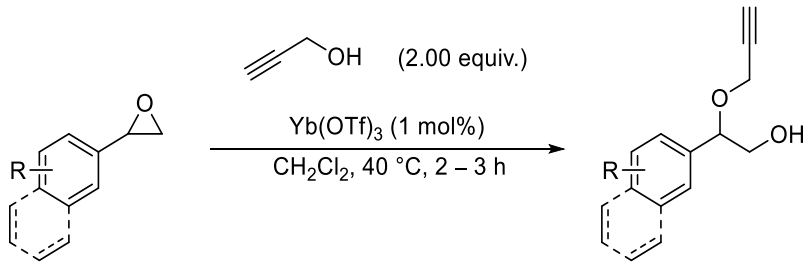
General Procedure E: Ethyl Ester Reductions with $LiAlH_4$



1.00 equiv.

Prepared according to a literature procedure.[180] A solution of $LiAlH_4$ (4 M in Et_2O, 1.00 equiv.) was added to a two-neck flask containing Et_2O, at –50 °C under N_2. A solution of ethyl 2-(but-3-yn-2-yloxy)acetate (1.00 equiv.) in Et_2O, was then added dropwise over 1 h at –50 °C with stirring. The resulting mixture was then stirred for 90 min at –30 °C before being warmed to room temperature and stirred overnight (16 h). The mixture was then quenched by addition of H_2O (1 mL), NaOH (3.80 M, 1 mL), and then H_2O (1 mL), followed by filtration through celite. The filter cake was washed with Et_2O (2 × 10 mL) and the combined filtrate was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography yielded the corresponding alcohol.

General Procedure F: $Yb(OTf)_3$ Catalysed Epoxide Ring Openings

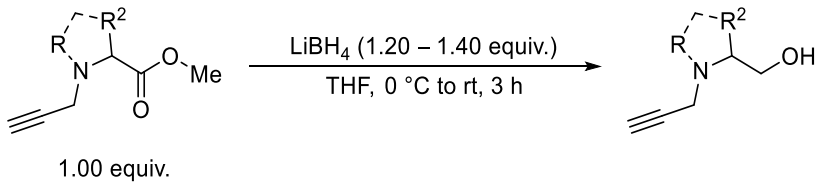


1.00 equiv.

Prepared according to a modified literature procedure.[181] A two-neck flask containing anhydrous Yb(III)OTf (0.010 equiv.) was evacuated and backfilled 3-times with N_2 before anhydrous CH_2Cl_2 and the corresponding epoxide (1.00 equiv.) and were added sequentially. Propargyl alcohol (2.00 equiv.) was then added and

the mixture was stirred at reflux (ca. 40 °C, unless otherwise stated) for 2 – 3 h. Once the reaction was complete by TLC analysis, the crude mixture was poured into H_2O and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (×3) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography to yield the corresponding ring-opened product.

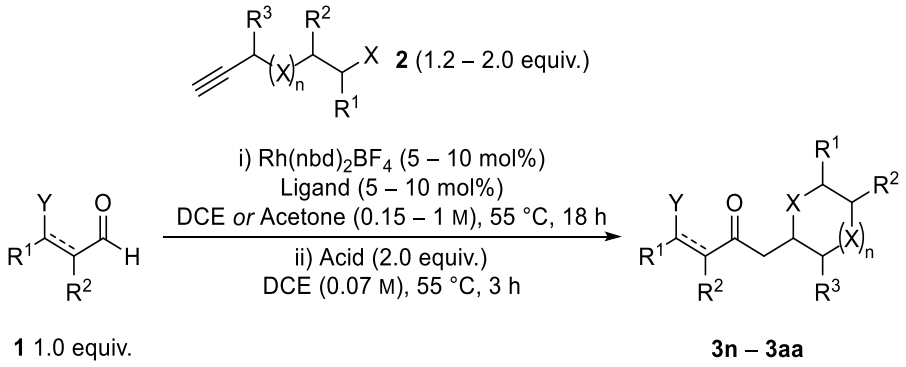
General Procedure G: Methyl Ester Reductions with $LiBH_4$



1.00 equiv.

Prepared according to a literature procedure.[182] To solution of methyl ester (1.00 equiv.) in anhydrous THF under argon at 0 °C was added dropwise $LiBH_4$ solution (2 M in THF, 1.20 – 1.40 equiv.). The mixture was allowed to warm to room temperature and stirred for 3 h ***(Unless stated otherwise)***. Once the reaction was complete by TLC analysis, the mixture was concentrated *in vacuo*. H_2O was added to the resulting residue, and the mixture was extracted with EtOAc (×3). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the corresponding alcohol.

General procedures for reaction scope:



The scope reactions within this project were ran using **general procedures H**, **I** and **J**, described below:

General procedure H: Rh-catalysed alkyne hydroacylation (step i)

$Rh(nbd)_2BF_4$ (2.5 – 10 mol%) was weighed into a tapered 10 mL microwave vial. Next, ligand (2.5 – 10 mol%) was introduced and the vial sealed with a suba-seal and parafilmed. The vial was placed under vacuum on a Schlenk line and back-filled with argon. After this, 1.0 mL of distilled solvent (acetone or DCE) was introduced, and the solution sonicated for 30 s. Hydrogen gas was then bubbled through the solution for 1 – 2 min. The solvent was then removed using a stream of argon and the catalyst system re-dissolved in solvent (0.150 M – 1.00 M). Alkyne (1.20 – 2.00 equiv.) was weighed into a separate concave 10 mL microwave vial along with aldehyde (1.00 equiv.) if a solid. The vial was sealed with a suba-seal/microwave cap and parafilmed (if suba-sealed). It was then placed under vacuum on a Schlenk line, evacuated and back-filled with argon three times. If the aldehyde was a liquid, it was then syringed into the vial post vac-cycle. The catalyst solution was then added to the reactant mixture, and the solution was stirred at 55 °C or rt for 18 h (unless otherwise stated).

General procedure I: step ii) using HCl in dioxane

A separate oven-dried flask was evacuated and backfilled with argon three-times before adding DCE (4.0 mL/0.3 mmol scale), followed by HCl (4 M in dioxane, 2.00 equiv.). This solution was then added dropwise into the microwave vial containing the crude hydroacylation reaction mixture. The resulting mixture was then stirred at 55 °C for 3 h. If a solvent-switch occurred between **general procedures H and I**, the hydroacylation reaction was cooled to room temperature and concentrated *in vacuo*. Then a solution of HCl (4 M in dioxane, 2.00 equiv.) in DCE (4.3 mL/0.3 mmol scale) was added to the residue and the mixture was stirred at 55 °C for 3 h. After this time, sat. aq. $NaHCO_3$ (6 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product.

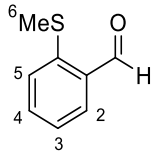
General procedure J: step ii) using *p*-$TsOH \cdot H_2O$

The crude reaction mixture was diluted with DCE (4.0 mL/0.3 mmol scale), and then *p*-$TsOH \cdot H_2O$ (2.00 equiv.) was added. The resulting mixture was then stirred at 55 °C for 3 h. After this time, sat. aq. $NaHCO_3$ (6 mL) was added. The aqueous layer was exactred with CH_2Cl_2 (3 × 10 mL), dried over anhydrouys $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product.

6.2.2 Substrate Synthesis

6.2.2a Aldehyde Substrates

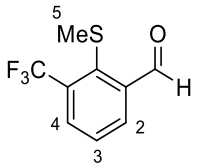
2-(Methylthio)benzaldehyde (1a)



Prepared according to **general procedure A**, using NaSMe (1.80 g, 25.7 mmol, 1.14 equiv.) in DMF (7.5 mL), then 2-fluorobenzaldehyde (2.4 mL, 22.5 mmol, 1.00 equiv.) in DMF (15 mL). Work-up using H_2O (2 × 50 mL), EtOAc (3 × 35 mL) and brine (50 mL). Purification by column chromatography (6:1 to 4:1 Petrol:EtOAc) yielded 2-(methylthio)benzaldehyde **1a** (3.24 g, 21.3 mmol, 95%) as a yellow oil.

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 10.27 (1H, s, C(1)*H*=O), 7.81 (1H, dd, *J* = 7.7, 1.6 Hz, *Ar*), 7.53 (1H, ddd, *J* = 8.1, 7.3, 1.6 Hz, *Ar*), 7.37 – 7.32 (1H, m, *Ar*), 7.28 (1H, dd, *J* = 8.2, 7.1 Hz, *Ar*), 2.50 (3H, s, SC(6)H_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 191.5, 143.5, 134.1, 133.4, 133.0, 125.6, 124.5, 15.6; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 2920, 2840, 2739, 1617, 1586, 1558, 1260, 1195, 843, 750. Data is consistent with literature.[177]

2-(Methylthio)-3-(trifluoromethyl)benzaldehyde (1b)

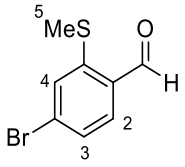


Prepared according to **general procedure A**, using NaSMe (290 mg, 4.14 mmol, 1.14 equiv.) in DMF (2.5 mL), then 2-fluoro-3-(trifluoromethyl)benzaldehyde (0.5 mL, 3.63 mmol, 1.00 equiv.) in DMF (7.5 mL). Work-up using H_2O (2 × 10 mL), EtOAc (3 × 10 mL) and brine (10 mL). Purification by column chromatography

(3:97 EtOAc:Petrol) 3,4-dimethoxy-2-(methylthio)benzaldehyde **1b** (689 mg, 3.13 mmol, 86%) as an off-white solid.

m.p. (CH_2Cl_2) 34 – 36 °C; (*Lit:* 36 – 38 °C);[17] **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.[17]

4-Bromo-2-(methylthio)benzaldehyde (1c)

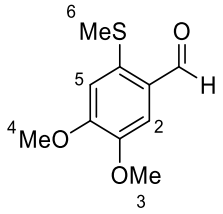


Prepared according to a modified procedure.[83d] To a stirred solution of NaSMe (340 mg, 4.90 mmol, 1.13 equiv.), in DMF (25 mL) was added 4-bromo-2-fluorobenzaldehyde (1.00 g, 4.30 mmol, 1.00 equiv.) over 30 mins at –45 °C. The mixture was stirred at this temperature for 3 h before warming to room temperature 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 **1c** (761 mg, 3.31 mmol, 78%) as a white solid.

m.p. (DMF) 80 – 83 °C; (*Lit:* 78 °C);[34b] **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.[83d]

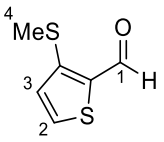
3,4-Dimethoxy-2-(methylthio)benzaldehyde (1d)



Prepared according to a modified procedure.[17] NaSMe (600 mg, 8.56 mmol, 1.20 equiv.) was added to a solution of 2-bromo-4,5-dimethoxybenzaldehyde (1.74 g, 7.13 mmol, 1.00 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 **1d** (1.03 g, 4.85 mmol, 68%) as an off-white solid.

m.p. (CH_2Cl_2) 97 – 99 °C; (*Lit:* 106 – 111 °C);[183] **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.[17]

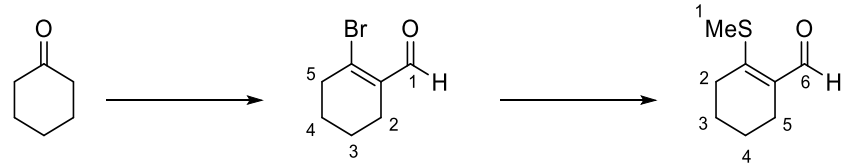
3-(Methylthio)thiophene-2-carbaldehyde (1e)



Prepared according to **general procedure A**, using NaSMe (650 mg, 9.34 mmol, 1.20 equiv.) in DMF (2.5 mL), then 3-bromothiophene-2-carbaldehyde (0.7 mL, 7.78 mmol, 1.00 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 **1e** (693 mg, 4.39 mmol, 56%) as an off-white solid.

m.p. (CH_2Cl_2) 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.[74b]

2-Bromocyclohex-1-ene-1-carbaldehyde (47b) and 2-(methylthio)cyclohex-1-ene-1-carbaldehyde (1f)



47b **1f**

2-Bromocyclohex-1-ene-1-carbaldehyde (47b): Prepared according to a modified procedure.[184] To a solution of DMF (4.6 mL, 60.0 mmol, 3.00 equiv.) in CH_2Cl_2 (25 mL) was added PBr_3 (5.1 mL, 54.0 mmol, 2.70 equiv.) dropwise at 0 °C. The mixture was then stirred at this temperature for 1 h before cyclohexanone (2.1 mL, 20.0 mmol, 1.00 equiv.) was added at 0 °C. The mixture was then warmed to room temperature and stirred overnight (16 h). Once completion was shown by TLC analysis, the reaction mixture was poured into H_2O (75 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (75 mL), brine (75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (3:97 to 1:9 EtOAc:Petrol) yielded 2-bromocyclohex-1-ene-1-carbaldehyde **47b** (1.40 g, 7.45 mmol, 37%) as a colourless oil.

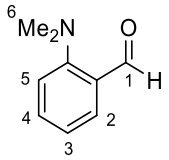
δ_H (400 MHz, $CDCl_3$) 9.95 (1H, s, C(1)*H*=O), 2.71 – 2.65 (2H, m, C(2 or 5)H_2), 2.24 – 2.18 (2H, m, C(2 or 5)H_2), 1.75 – 1.66 (2H, m, C(3 or 4)H_2), 1.66 – 1.57 (2H, m, C(3 or 4)H_2); **δ_C** (101 MHz, $CDCl_3$) 193.5, 143.5, 135.3, 38.8, 25.0, 24.3, 21.1; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{10}O^{79}Br^+$ calc. 188.9910, found 188.9911, $C_7H_{10}O^{81}Br^+$ calc. 190.9889, found 190.9891. Data is consistent with literature.[185]

2-(Methylthio)cyclohex-1-ene-1-carbaldehyde (1f): Prepared according to **general procedure A**, using NaSMe (320 mg, 4.48 mmol, 1.20 equiv.) in DMF (10 mL),

then 2-bromocyclohex-1-ene-1-carbaldehyde **47b** (700 mg, 3.71 mmol, 1.00 equiv.) in DMF (10 mL). Work-up using H_2O (2 × 10 mL), EtOAc (3 × 10 mL) and brine (10 mL). Purification by column chromatography (1:19 Et_2O:Petrol) yielded 2-(methylthio)cyclohex-1-ene-1-carbaldehyde **1f** (383 mg, 2.43 mmol, 46%) as a yellow solid.

m.p. (CH_2Cl_2) 48 – 50 °C; (*Lit:* 45 – 47 °C);[17] **δ_H** (400 MHz, $CDCl_3$) 10.26 (1H, s, C(6)*H*=O), 2.55 – 2.48 (2H, m, C(2 or 5)H_2), 2.33 (3H, s, C(1)H_3), 2.29 – 2.24 (2H, m, C(2 or 5)H_2), 1.77 – 1.69 (2H, m, C(3 or 4)H_2), 1.66 – 1.57 (2H, m, C(3 or 4)H_2); **δ_C** (101 MHz, $CDCl_3$) 189.8, 156.9, 135.1, 30.9, 24.1, 23.1, 21.4, 14.2; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{13}O^{32}S^+$ calc. 157.0682, found 157.0684. Data is consistent with literature.[17]

2-(Dimethylamino)benzaldehyde (1j)

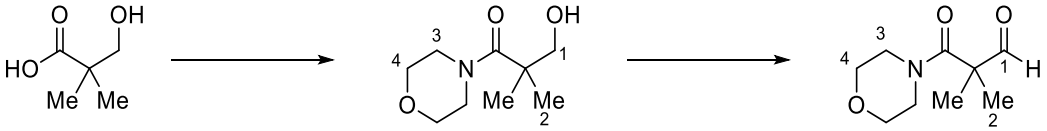


Prepared according to a modified procedure.[186] To a mixture of 2-fluorobenzaldehyde (1.1 mL, 10.0 mmol, 1.00 equiv.) and K_2CO_3 (1.38 g, 10.0 mmol, 1.00 equiv.) in anhydrous DMF (20 mL) at room temperature was added Me_2NH solution (5.60 M in EtOH, 2.4 mL, 13.4 mmol, 1.34 equiv.) The resulting mixture 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 2-(dimethylamino)benzaldehyde **1j** (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.[186]

3-Hydroxy-2,2-dimethyl-1-morpholinopropan-1-one (48) and 2,2-dimethyl-3-morpholino-3-oxopropanal (1k)



48 **1k**

3-Hydroxy-2,2-dimethyl-1-morpholinopropan-1-one (48): Prepared according to **general procedure B** using 2-hydroxypivalic acid (3.00 g, 25.4 mmol, 1.00 equiv.), CH_2Cl_2 (130 mL), morpholine (2.4 mL, 28.0 mmol, 1.10 equiv.) and EDC·HCl (5.37 g, 28.0 mmol, 1.10 equiv.). Quench using sat. aq. $NaHCO_3$ (70 mL). Work-up using brine (70 mL). Purification by column chromatography (EtOAc) yielded 3-hydroxy-2,2-dimethyl-1-morpholinopropan-1-one **48** (2.33 g, 12.5 mmol, 49%) as a white solid.

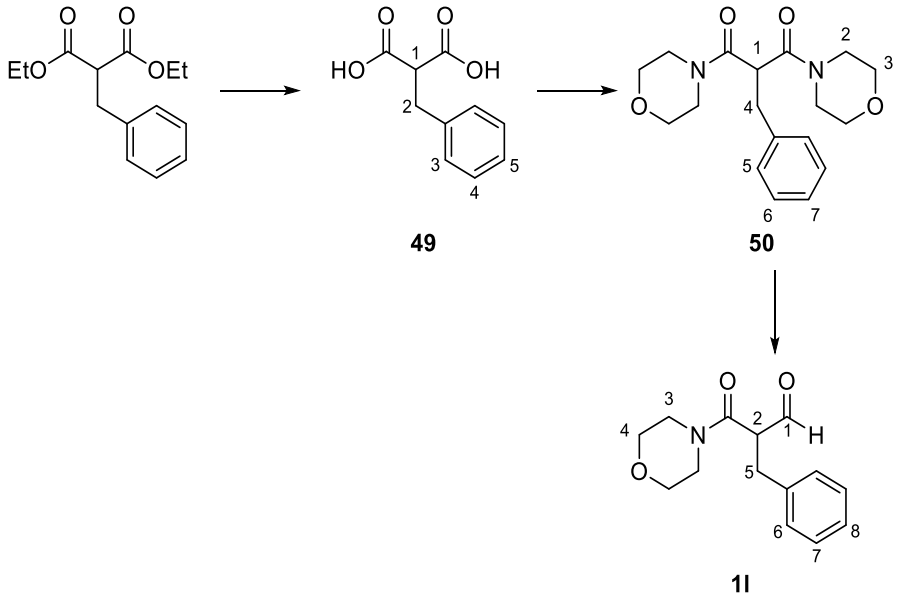
m.p. (CH_2Cl_2) 45 – 48 °C; **δ_H** (400 MHz, $CDCl_3$) 3.71 – 3.63 (8H, m, C(3 and 4)H_2), 3.61 – 3.56 (1H, m, O*H*), 3.51 – 3.49 (2H, m, C(1)H_2), 1.27 (6H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 176.1, 72.1, 66.5, 45.1, 42.8, 21.7; **ν_{max}**/ cm^{-1} (neat) 3458, 2863,

2358, 1608, 1425, 1268, 1159, 1115, 1031, 850; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{18}O_3N^+$ calc. 188.1281, found 188.1281.

2,2-Dimethyl-3-morpholino-3-oxopropanal (1k): Prepared according to a modified literature procedure.[15a] CH_2Cl_2 (10 mL) and oxalyl chloride (0.59 mL, 6.82 mmol, 1.10 equiv.) were added to an argon flushed three-neck flask fitted with a thermometer and cooled to –78 °C. In a separate flask under argon, 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, ensuring that the temperature did not exceed –65 °C. After addition was complete, the reaction mixture was stirred at this temperature for 5 min. In another flask under argon, 3-hydroxy-2,2-dimethyl-1-morpholinopropan-1-one **48** (1.16 g, 6.20 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL). This solution was then added dropwise to the first solution, and the mixture was stirred for 30 min at –78 °C before Et_3N (4.3 mL, 31.0 mmol, 5.00 equiv.) was added dropwise. The mixture was then allowed to warm to room temperature over 30 min before being washed with 2 M $HCl_{(aq)}$ (5.6 mL), sat. aq. $NaHCO_3$ (5.6 mL) and brine (5.6 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:1 EtOAc:Petrol) yielded 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (1.09 g, 5.89 mmol, 95%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 9.61 (1H, s, C(1)*H*=O), 3.71 – 3.25 (8H, m, C(3 and 4)H_2), 1.37 (6H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 199.9, 170.0, 66.8, 54.1, 45.0 (bs), 20.6; **ν_{max}**/ cm^{-1} (neat) 2859, 1722, 1638, 1429, 1263, 1115, 1034; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{16}O_3N^+$ calc. 186.1125, found 186.1126. Data is consistent with literature.[3e]

2-Benzylmalonic acid (49), 2-benzyl-1,3-dimorpholinopropane-1,3-dione (50) and 2-benzyl-3-morpholino-3-oxopropanal (1l)



2-Benzylmalonic acid (49): NaOH pellets (5.00 g, 125 mmol, 2.09 equiv.) was ground with a pestle and mortar and added to a solution of 2-benzyl diethyl malonate (14.1 mL, 59.9 mmol, 1.00 equiv.) in H_2O (300 mL) and stirred over 48 h. Once the reaction was complete by TLC analysis, the mixture was washed with EtOAc (100 mL) to remove any remaining ester. The aqueous layer was then acidified by dropwise addition of 37% w/w aq. HCl was then undertaken until the mixture turned litmus paper red (pH 3). The acidified aqueous layer was then extracted with EtOAc (3 × 100 mL) and the combined organic extracts concentrated *in vacuo* to yield 2-benzylmalonic acid **49** (11.6 g, 59.4 mmol, 99%) as a white powder.

m.p. (CH_2Cl_2) 108 – 111 °C; (*Lit:* 110 – 114 °C);[187] **δ_H** (400 MHz, $CDCl_3$) 7.35 – 7.20 (5H, m, *Ar*), 3.77 (1H, t, *J* = 7.5 Hz, C(1)*H*), 3.28 (2H, d, *J* = 7.5 Hz, C(2)H_2); **δ_C** (101 MHz, MeOD-d_4) 172.5, 139.5, 139.5, 129.7, 129.4, 127.5, 54.9, 35.7, 35.6; **ν_{max}**/ cm^{-1} (neat) 3263, 1760, 1661, 1230, 1082; **m/z HRMS** (ESI^-) $[M - H]^-$ $C_{10}H_9O_4^-$ calc. 193.0506, found 193.0504. Data is consistent with literature.[188]

2-Benzyl-1,3-dimorpholinopropane-1,3-dione (50): Prepared according to **general procedure B** using di-acid **49** (1.94 g, 10.0 mmol, 1.00 equiv.), CH_2Cl_2 (50 mL), morpholine (1.90 mL, 22.0 mmol, 2.20 equiv.) and EDC·HCl (4.22 g, 22.0 mmol, 2.20 equiv.). Quench using sat. aq. $NaHCO_3$ (30 mL). Work-up using brine (30 mL). Purification by column chromatography (100:0 to 99:1 EtOAc:Methanol) yielded 2-benzyl-1,3-dimorpholinopropane-1,3-dione **50** (2.11 g, 6.35 mmol, 64%) as a white solid.

m.p. (CH_2Cl_2) 144 – 146 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.33 – 7.20 (5H, m, *Ar*), 3.89 (1H, t, *J* = 7.3 Hz, C(1)*H*), 3.73 – 3.17 (18H, m, C(2 and 3)H_2 and C(4)H_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 167.8, 138.8, 129.3, 128.8, 127.0, 66.8, 66.3, 50.5, 46.0, 42.8, 35.9; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3517, 2857, 2362, 1643, 1434, 1237; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{18}H_{25}O_4N_2^+$ calc. 333.1809, found 333.1809.

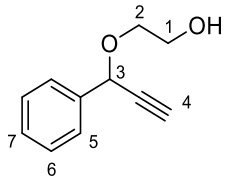
2-Benzyl-3-morpholino-3-oxopropanal (1l): A solution of DIBAL-H (1.00 M in CH_2Cl_2, 1.50 mL, 1.50 mmol, 1.00 equiv.) was added dropwise to a solution of bisamide **50** (500 mg, 1.50 mmol, 1.00 equiv.) in CH_2Cl_2 (20 mL) at –78 ˚C. The mixture was stirred for 2 h at –78 ˚C before being quenched by a sat. aqueous solution of Rochelle's Salt (20 mL). The resulting mixture was allowed to warm to room temperature with stirring for 2 h until a biphasic mixture could be distinguished. The layers were separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (1:1 EtOAc:Petrol) yielded 2-benzyl-3-morpholino-3-oxopropanal **1l** (320 mg, 1.29 mmol, 86%) as a viscous colourless oil.

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.71 (1H, s, C(1)*H*=O), 7.34 – 7.16 (5H, m, *Ar*), 3.77 – 2.86 (11H, m, C(2)*H* and C(3, 4 and 5)H_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 198.4, 167.2, 137.5,

129.1, 128.9, 127.2, 66.6, 66.2, 56.6, 46.3, 42.3, 34.5; **ν_{max}**/ cm^{-1} (neat) 3382, 2974, 2923, 2860, 1614, 1447, 1234, 1114, 753, 702; **m/z LRMS** (ESI^+) 270.0 $[M + Na]^+$. Data is consistent with literature.[3e]

6.2.2b Alkyne Substrates

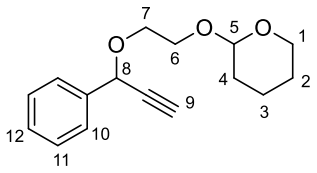
2-((1-Phenylprop-2-yn-1-yl)oxy)ethan-1-ol (2c)



Prepared according to a literature procedure.[189] To a round-bottomed flask was added 1-phenyl-2-propyn-1-ol (0.62 mL, 5.00 mmol, 1.00 equiv.), ethylene glycol (5 mL) and Amberlyst® 15 (1.50 g). The resulting suspension was heated to 80 °C and stirred for 2 h. Once the reaction was complete as monitored by TLC analysis, the suspension was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was then purified by column chromatography (20:1 to 5:1 Petrol:Et_2O) to afford 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (687 mg, 3.90 mmol, 78%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.55 – 7.49 (2H, m, *Ar*), 7.43 – 7.29 (3H, m, *Ar*), 5.23 (1H, d, *J* = 2.2 Hz, C(3)*H*), 3.86 – 3.56 (4H, m, C(1)H_2 and C(2)H_2), 2.68 (1H, d, *J* = 2.2 Hz, C(4)*H*), 1.91 (1H, bs, O*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, 754, 697, 650; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{11}H_{12}O_2{}^{23}Na^+$ calc. 199.0730, found 199.0732. Data is consistent with literature.[189]

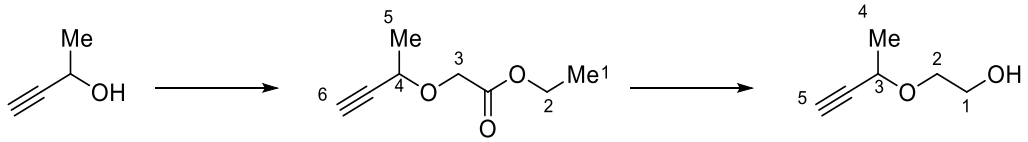
2-(2-((1-Phenylprop-2-yn-1-yl)oxy)ethoxy)tetrahydro-2H-pyran (2d)



Prepared according to a modified procedure.[190] To a solution of alcohol **2c** (150 mg, 0.850 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (1 mL) was added dihydropyran (159 µL, 1.74 mmol, 2.05 equiv.). The solution was then cooled to 0 °C before *p*-TsOH·H_2O (19.4 mg, 0.102 mmol, 0.120 equiv.) was added in one portion. The resulting solution was then warmed to room temperature and stirred for 18 h. Sat. aq $NaHCO_3$ (5 mL) was then added, and the layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue (18:1 dr) by column chromatography (1:19 to 1:5 Et_2O:Petrol) yielded single diastereoisomer **2d** as a rotameric mixture (122 mg, 0.469 mmol, 55%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.60 – 7.50 (2H, m, *Ar*), 7.41 – 7.29 (3H, m, *Ar*), 5.31 (1H, d, *J* = 2.2 Hz, C(8)*H*), 4.71 – 4.61 (1H, m, C(5)*H*), 3.97 – 3.60 (5H, m, C(6 and 7)H_2, C(1)*H*H), 3.53 – 3.45 (1H, m, C(1)H*H*), 2.65 (1H, d, *J* = 2.2 Hz, C(9)*H*), 1.93 – 1.45 (6H, m, C(2, 3 and 4)H_2); **δ_C** (101 MHz, $CDCl_3$) 138.3, 128.6, 128.6, 127.5, 99.0, 98.8, 81.7, 81.7, 75.8, 75.8, 71.6, 71.6, 67.5, 66.6, 66.5, 62.3, 62.1, 30.7, 30.7, 25.6, 19.5, 19.5 (Rotamer signals present in ^{13}C NMR); **ν_{max}**/ cm^{-1} (neat) 2942, 2870, 1720, 1493, 1454, 1276, 1123, 1074, 1034, 987; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{16}H_{20}O_3Na^+$ calc. 283.1305, found 283.1301.

Ethyl 2-(but-3-yn-2-yloxy)acetate (9a) and 2-(but-3-yn-2-yloxy)ethan-1-ol (2e)



9a **2e**

Ethyl 2-(but-3-yn-2-yloxy)acetate (9a): Prepared according to **general procedure C** using NaH (60% in mineral oil, 2.04 g, 51.0 mmol, 1.00 equiv.), but-3-yn-2-ol (4.0 mL, 51.0 mmol, 1.00 equiv.), ethyl-2-bromoacetate (6.8 mL, 61.2 mmol, 1.20 equiv.) and DMF (3 × 60 mL). Quench using sat. aq. NH_4Cl (140 mL). Work-up using EtOAc (3 × 100 mL) and 5% aq. LiCl (100 mL). Purification by column chromatography (1:30 to 1:15 Et_2O:Petrol) yielded ethyl 2-(but-3-yn-2-yloxy)acetate **9a** (3.30 g, 21.1 mmol, 41%) as colourless oil.

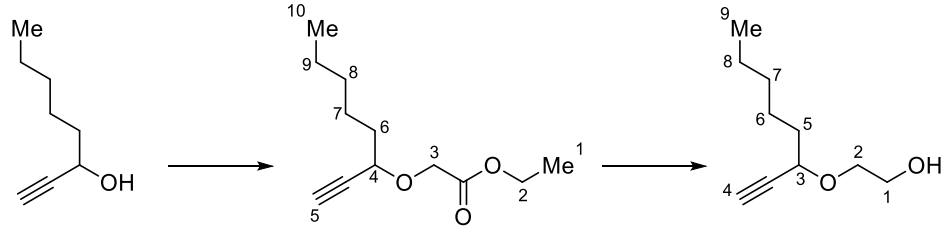
δ_H (400 MHz, $CDCl_3$) 4.34 (1H, qd, *J* = 6.8, 2.1 Hz, C(4)*H*), 4.25 – 4.08 (4H, m, C(2)H_2 and C(3)H_2), 2.43 (1H, d, *J* = 2.1 Hz, C(6)*H*), 1.45 (3H, d, *J* = 6.6 Hz, C(5)H_3), 1.24 (3H, t, *J* = 7.1 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 170.2, 82.6, 74.1, 65.5, 65.5, 60.9, 21.9, 14.2; **ν_{max}**/ cm^{-1} (neat) 3296, 1749, 1205, 1118, 1035; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{13}O_3^+$ calc. 157.0859, found 157.0864. Data is consistent with literature.[178]

2-(But-3-yn-2-yloxy)ethan-1-ol (2e): Prepared according to **general procedure E** using $LiAlH_4$ (4 M in Et_2O, 2.24 mL, 8.96 mmol, 1.00 equiv.) in Et_2O (10 mL), then 2-(but-3-yn-2-yloxy)acetate **9a** (1.40 g, 8.96 mmol, 1.00 equiv.) in Et_2O (31 mL). Purification by column chromatography (1:9 to 1:1 Et_2O:Petrol) yielded 2-(but-3-yn-2-yloxy)ethan-1-ol **2e** (809 mg, 7.09 mmol, 79%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.21 (1H, qd, *J* = 6.6, 2.0 Hz, C(3)*H*), 3.86 – 3.80 (1H, m, C(1 or 2)*H*), 3.78 – 3.73 (2H, m, C(1 or 2)H_2), 3.56 – 3.50 (1H, m, C(1 or 2)*H*), 2.44

(1H, d, *J* = 2.0 Hz, C(5)*H*), 2.03 (1H, t, *J* = 6.2 Hz, O*H*), 1.46 (3H, d, *J* = 6.7 Hz, C(4)H_3); **δC** (101 MHz, $CDCl_3$) 83.7, 73.3, 70.0, 65.7, 62.0, 22.1; **νmax**/ cm^{-1} (neat) 3379, 3294, 2981, 2361, 2341, 1637, 1460, 1374, 1326, 1252, 1110, 1091, 1058, 948, 890, 850, 802; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_6H_{10}O_2{}^{23}Na^+$ calc. 137.0573, found 137.0572.

Ethyl 2-(oct-1-yn-3-yloxy)acetate (9b) and 2-(oct-1-yn-3-yloxy)ethan-1-ol (2f)



9b **2f**

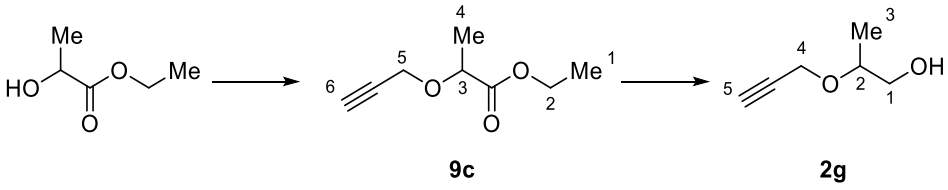
Ethyl 2-(oct-1-yn-3-yloxy)acetate (9b): Prepared according to **general procedure C** using NaH (60% in mineral oil, 820 mg, 20.6 mmol, 1.00 equiv.), oct-1-yn-3-ol (3.0 mL, 20.6 mmol, 1.00 equiv.), ethyl-2-bromoacetate (7.6 mL, 68.5 mmol, 2.00 equiv.) and DMF (3 × 50 mL) ***with stirring at 50 °C, overnight (18 h)***. Quench using sat. aq. NH_4Cl (100 mL). Work-up using EtOAc (3 × 50 mL) and 5% aq. LiCl (50 mL). Purification by column chromatography (1:99 to 1:19 Et_2O:Petrol) yielded ethyl 2-(oct-1-yn-3-yloxy)acetate **9b** (1.54 g, 7.26 mmol, 35%) as a colourless oil.

δH (400 MHz, $CDCl_3$) 4.29 – 4.12 (5H, m, C(2)H_2, C(3)H_2 and C(4)*H*), 2.44 (1H, d, *J* = 2.1 Hz, C(5)*H*), 1.84 – 1.66 (2H, m, C(6)H_2), 1.52 – 1.43 (2H, m, C(7)H_2), 1.36 – 1.26 (4H, m, C(8 and 9)H_2), 1.27 (3H, t, *J* = 7.2 Hz, C(1)H_3), 0.93 – 0.84 (3H, t, *J* = 7.0 Hz, C(10)H_3); **δC** (101 MHz, $CDCl_3$) 170.4, 82.0, 74.7, 69.9, 65.6, 60.9, 35.5, 31.6, 24.8, 22.6, 14.3, 14.1; **νmax**/ cm^{-1} (neat) 3272, 2957, 1752, 1204, 1120, 1029; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{12}H_{21}O_3{}^+$ calc. 213.1485, found 213.1490.

2-(Oct-1-yn-3-yloxy)ethan-1-ol (2f): Prepared according to **general procedure E** using $LiAlH_4$ (4 M in Et_2O, 0.90 mL, 3.63 mmol, 1.00 equiv.) in Et_2O (10 mL), then 2-(oct-1-yn-3-yloxy)acetate **9b** (770 mg, 3.63 mmol, 1.00 equiv.) in Et_2O (10 mL). Purification by column chromatography (1:9 to 1:1 Et_2O:Petrol) yielded 2-(oct-1-yn-3-yloxy)ethan-1-ol **2f** (611 mg, 3.59 mmol, 99%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 4.06 (1H, td, *J* = 6.6, 2.1 Hz, C(3)*H*), 3.87 – 3.81 (1H, m, C(2)*H*H), 3.79 – 3.71 (2H, m, C(1)H_2), 3.52 (1H, m, C(2)H*H*), 2.44 (1H, d, *J* = 2.0 Hz, C(4)*H*), 2.05 (1H, t, *J* = 5.8 Hz, O*H*), 1.82 – 1.64 (2H, m, C(5)H_2), 1.51 – 1.39 (2H, m, C(6)H_2), 1.37 – 1.24 (4H, m, C(7 and 8)H_2), 0.89 (3H, t, *J* = 6.8 Hz, C(9)H_3); **δ_C** (101 MHz, $CDCl_3$) 83.0, 74.0, 70.1, 70.1, 62.0, 35.7, 31.6, 25.0, 22.7, 14.1; **ν_{max}**/ cm^{-1} (neat) 3426, 3272, 2957, 2112, 1466, 1379, 1274, 1204, 1121, 1029, 944, 668; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{10}H_{18}O_2{}^{23}Na^+$ calc. 193.1199, found 193.1201.

Ethyl 2-(prop-2-yn-1-yloxy)propanoate (9c) and 2-(prop-2-yn-1-yloxy)propan-1-ol (2g)



9c **2g**

Ethyl 2-(prop-2-yn-1-yloxy)propanoate (9c): Prepared according to **general procedure D** using ethyl lactate (4.0 mL, 34.9 mmol, 1.00 equiv.), DMF (190 mL), NaH (60% in mineral oil, 1.46 g, 36.6 mmol, 1.05 equiv.) and propargyl bromide (80% w/w in toluene, 15.5 mL, 139 mmol, 4.00 equiv.) with stirring for 2.5 h. Quench using sat. aq. NH_4Cl (190 mL). Work-up using EtOAc (3 × 190 mL) and 5% aq. LiCl (190 mL). Purification by column chromatography (98:2 to 19:1

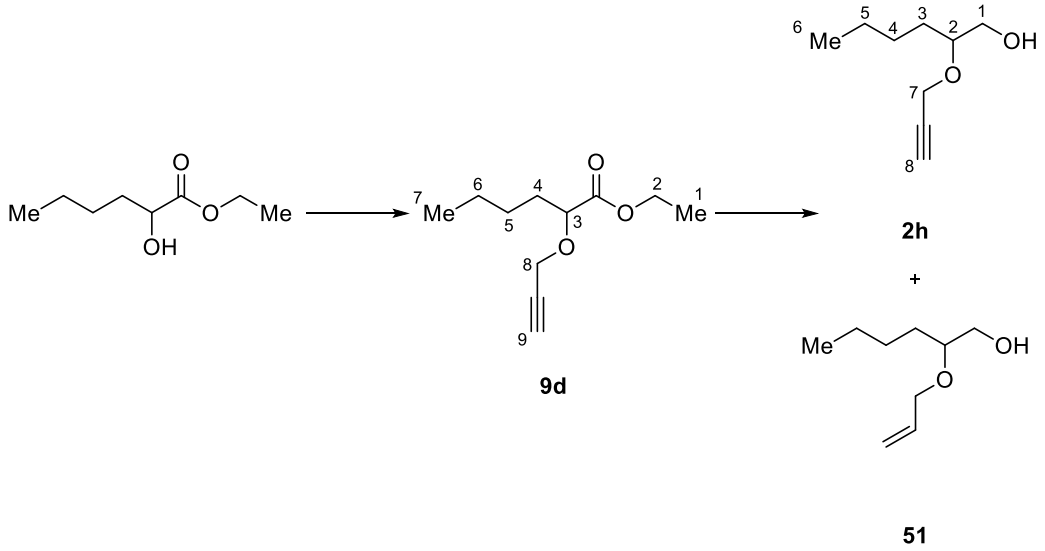
Petrol:EtOAc) yielded ethyl 2-(prop-2-yn-1-yloxy)propanoate **9c** (2.10 g, 13.45 mmol, 39%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.39 – 4.10 (5H, m, C(2)H_2, C(3)*H* and C(5)H_2), 2.44 (1H, app. t, *J* = 2.4 Hz, C(6)*H*), 1.43 (3H, d, *J* = 6.9 Hz, C(4)H_3), 1.29 (3H, t, *J* = 7.1 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 172.8, 79.2, 75.1, 73.3, 61.1, 57.2, 18.6, 14.3; **ν_{max}**/ cm^{-1} (neat) 2955, 2859, 1742, 1468, 1377, 1254, 1145, 1093, 1093, 1049, 981, 832, 775; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_8H_{12}O_3{}^{23}Na^+$ calc. 179.0679, found 179.0679. Data is consistent with literature.[191]

2-(Prop-2-yn-1-yloxy)propan-1-ol (2g): Prepared according to **general procedure E** using $LiAlH_4$ (4M in Et_2O, 1.6 mL, 6.40 mmol, 1.00 equiv.) in Et_2O (10 mL), then ethyl 2-(prop-2-yn-1-yloxy)propanoate **9c** (1.00 g, 6.40 mmol, 1.00 equiv.) in Et_2O (22 mL). Purification by column chromatography (9:1 to 1:1 Petrol:Et_2O) yielded 2-(prop-2-yn-1-yloxy)propan-1-ol **2g** (263 mg, 2.31 mmol, 36%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.22 (1H, dd, *J* = 15.9, 2.4 Hz, C(4)*H*H), 4.11 (1H, dd, *J* = 15.9, 2.4 Hz, C(4)H*H*), 3.78 – 3.64 (1H, m, C(2)*H*), 3.56 (1H, ddd, *J* = 11.3, 7.9, 3.2 Hz, C(1)*H*H), 3.43 (1H, ddd, *J* = 11.6, 7.1, 4.3 Hz, C(1)H*H*), 2.38 (1H, app. t, *J* = 2.4 Hz, C(5)*H*), 1.96 (1H, dd, *J* = 8.0, 4.6 Hz, O*H*), 1.09 (3H, d, *J* = 6.3 Hz, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 80.2, 75.7, 74.4, 66.4, 56.3, 15.7; **ν_{max}**/ cm^{-1} (neat) 3288, 2977, 2888, 1456, 1380, 1065, 664; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_6H_{10}O_2{}^{23}Na^+$ clac. 137.0573, found 137.0574. Data is consistent with literature.[192]

Ethyl 2-(prop-2-yn-1-yloxy)hexanoate (9d) and 2-(prop-2-yn-1-yloxy)hexan-1-ol (2h)



Ethyl 2-(prop-2-yn-1-yloxy)hexanoate (9d): Prepared according to **general procedure D** using ethyl 2-hydroxyhexanoate (2.1 mL, 12.5 mmol, 1.00 equiv.), DMF (70 mL), NaH (60% in mineral oil, 524 mg, 13.1 mmol, 1.05 equiv.) and propargyl bromide (80% w/w in toluene, 5.6 mL, 50.0 mmol, 4.00 equiv.) ***with stirring overnight (18 h)***. Quench using sat. aq. NH_4Cl (70 mL). Work-up using EtOAc (3 × 70 mL) and 5% aq. LiCl (70 mL). Purification by column chromatography (1:99 to 1:49 EtOAc:Petrol) yielded ethyl 2-(prop-2-yn-1-yloxy)hexanoate **9d** (700 mg, 3.53 mmol, 28%), as a pale-yellow oil.

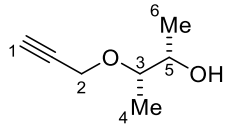
δ_H (400 MHz, $CDCl_3$) 4.32 (1H, dd, *J* = 16.0, 2.4 Hz, C(8)*H*H), 4.24 – 4.16 (2H, qd, *J* = 7.1, 3.5 Hz, C(2)H_2), 4.14 (1H, dd, *J* = 16.0, 2.3 Hz, C(8)H*H*) 4.10 (1H, dd, *J* = 6.5, 5.2 Hz, C(3)*H*), 2.42 (1H, app. t, *J* = 2.4 Hz, C(9)*H*), 1.79 – 1.68 (2H, m, C(4)H_2), 1.44 – 1.25 (4H, m, C(5 and 6)H_2), 1.28 (3H, t, *J* = 7.1 Hz, C(1)H_3), 0.88 (3H, t, *J* = 7.1 Hz, C(7)H_3); δ_C (101 MHz, $CDCl_3$) 172.6, 79.2, 77.2, 75.0, 61.0, 57.4, 32.6, 27.3, 22.5, 14.4, 14.0; ν_{max}/ cm^{-1} (neat) 3274, 2958, 2361, 1745, 1457,

1195, 1123, 1100, 1026; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{11}H_{19}O_3^+$ calc. 199.1329, found 199.1330.

2-(Prop-2-yn-1-yloxy)hexan-1-ol (2h): Prepared according to **general procedure E** using $LiAlH_4$ (4M in Et_2O, 0.88 mL, 3.53 mmol, 1.00 equiv.) in Et_2O (6 mL), then ethyl 2-(prop-2-yn-1-yloxy)hexanoate **9d** (700 mg, 3.53 mmol, 1.00 equiv.) in Et_2O (6 mL). Purification by column chromatography (7:3 Petrol:Et_2O) yielded 2-(prop-2-yn-1-yloxy)hexan-1-ol **2h** as a 9:1 inseparable mixture with 2-(allyloxy)hexan-1-ol side product **51** (374 mg, 2.40 mmol, 68%) as a pale-yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.26 (1H, dd, *J* = 15.9, 2.4 Hz, C(7)*H*H), 4.18 (1H, dd, *J* = 15.9, 2.4 Hz, C(7)H*H*), 3.70 – 3.63 (1H, m, C(1)*H*H), 3.66 – 3.42 (2H, m, C(1)H*H* and C(2)*H*), 2.43 (1H, app. t, *J* = 2.4 Hz, C(8)*H*), 2.19 (1H, dd, *J* = 7.0, 5.1 Hz, O*H*), 1.60 – 1.49 (1H, m, C(3)*H*H), 1.49 – 1.39 (1H, m, C(3)H*H*), 1.38 – 1.20 (4H, m, C(4 and 5)H_2), 0.95 – 0.81 (3H, m, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 80.4, 80.0, 74.3, 64.4, 57.0, 30.4, 27.6, 22.9, 14.0; **ν_{max}**/ cm^{-1} (neat) 3406, 3309, 2932, 2862, 2361, 1458, 1345, 1082, 919, 667; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_9H_{16}O_2{}^{23}Na^+$ calc. 179.1048, found 179.1044.

(2*S,3*S**)-3-(Prop-2-yn-1-yloxy)butan-2-ol (2i)**

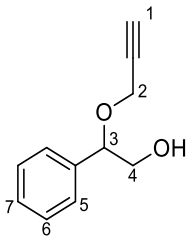


Prepared according to **general procedure D**, using (2*S**,3*S**)-butan-1,2-diol (0.40 mL, 4.45 mmol, 1.00 equiv.) in DMF (20 mL), NaH (60% dispersion in mineral oil, 178 mg, 4.45 mmol, 1.00 equiv.) and propargyl bromide (80% w/w in toluene 1.98 mL, 17.8 mmol, 4.00 equiv. with stirring at room temperature for 2 h. Quench using

sat. aq. NH_4Cl (20 mL) work-up using EtOAc (3 × 20 mL), 5% aq. LiCl (20 mL). Purification by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded (2*S**,3*S**)-3-(prop-2-yn-1-yloxy)butan-2-ol **2i** (209 mg, 1.63 mmol, 37%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.18 (1H, dd, *J* = 15.9, 2.4 Hz, C(2)*H*H), 4.06 (1H, dd, *J* = 15.9, 2.4 Hz, C(2)H*H*), 3.50 (1H, app p, *J* = 6.4 Hz, C(3 or 5)*H*), 3.38 – 3.24 (1H, app p, C(3 or 5)*H*), 2.82 (1H, bs, O*H*), 2.38 (1H, app. t, *J* = 2.4 Hz, C(1)*H*), 1.05 (3H, d, *J* = 6.4 Hz, C(4 or 6)H_3), 1.03 (3H, d, *J* = 6.3 Hz, C(4 or 6)H_3); **δ_C** (101 MHz, $CDCl_3$) 80.0, 79.6, 74.4, 70.7, 56.2, 18.40, 15.0; **ν_{max}**/ cm^{-1} (neat) 3418, 3291, 2980, 2889, 2200, 1741, 1522, 1381, 1346, 1263, 1084, 1019, 923, 697, 670, **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_7H_{12}O_2{}^{23}Na^+$ calc. 151.0730, found 151.0728.

2-Phenyl-2-(prop-2-yn-1-yloxy)ethan-1-ol (2j)

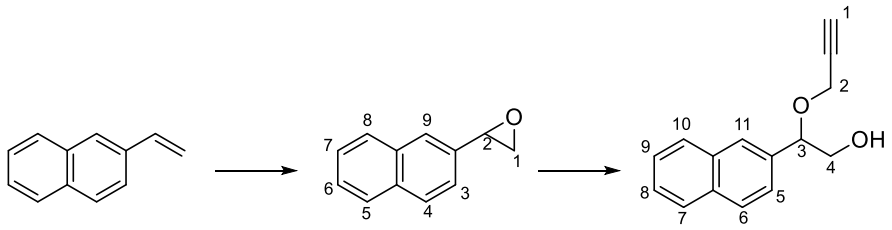


Prepared according to **general procedure F**, using styrene oxide **10a** (1.4 mL, 12.5 mmol, 1.00 equiv.), propargyl alcohol (1.4 mL, 25.0 mmol, 2.00 equiv.), $Yb(OTf)_3$ (78.0 mg, 0.130 mmol, 0.010 equiv.) and CH_2Cl_2 (87 mL). Workup with H_2O (100 mL) and CH_2Cl_2 (3 × 50 mL). Purification by column chromatography (1:49 to 1:5 EtOAc:Petrol) yielded 2-phenyl-2-(prop-2-yn-1-yloxy)ethan-1-ol **2j** (442 mg, 2.51 mmol, 20%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 7.35 – 7.28 (2H, m, *Ar*), 7.37 – 7.21 (3H, m, *Ar*), 4.68 (1H, dd, *J* = 8.4, 3.7 Hz, C(3)H), 4.20 (1H, dd, *J* = 15.7, 2.3 Hz, C(2)*H*H), 3.96 (1H, dd,

J = 15.7, 2.4 Hz, C(2)H*H*), 3.79 – 3.71 (1H, m, C(4)*H*H), 3.68 – 3.60 (1H, m, C(4)H*H*), 2.61 – 2.54 (1H, m, O*H*), 2.45 (1H, app. t, *J* = 2.4 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 137.4, 128.7, 128.5, 127.2, 81.8, 79.6, 74.8, 67.1, 56.1; **ν_{max}**/ cm^{-1} (neat) 3304, 1086, 1065, 1041, 906, 727, 701, 647, **m/z HRMS** (ESI^+) $[M + Na]^+$, $C_{11}H_{12}O_2{}^{23}Na^+$ calc. 199.0730, found 199.0732.

2-Vinylnapthalene oxide (10b) and 2-(naphthalen-2-yl)-2-(prop-2-yn-1-yloxy)ethan-1-ol (2k)



10b **2k**

2-Vinylnapthalene oxide (10b): Prepared according to a literature procedure.[193] 2-vinylnapthalene (2.00 g, 13.0 mmol, 1.00 equiv.), and $NaHCO_3$ (1.14 g, 13.6 mmol, 1.15 equiv.) were dissolved in CH_2Cl_2 (65 mL) at 0 °C, and *m*-CPBA (75% w/w, 3.45 g, 15.0 mmol, 1.15 equiv.) was added portion-wise. The resulting mixture was warmed to room temperature and stirred under N_2 for 48 h. The solution was then washed with 5% w/w aq. $NaHSO_3$ solution (2 × 50 mL) and sat. aq. $NaHCO_3$ (4 × 40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:19 EtOAc:Petrol) yielded 2-vinylnapthalene oxide **10b** (1.23 g, 7.28 mmol, 56%) as a white powdered solid.

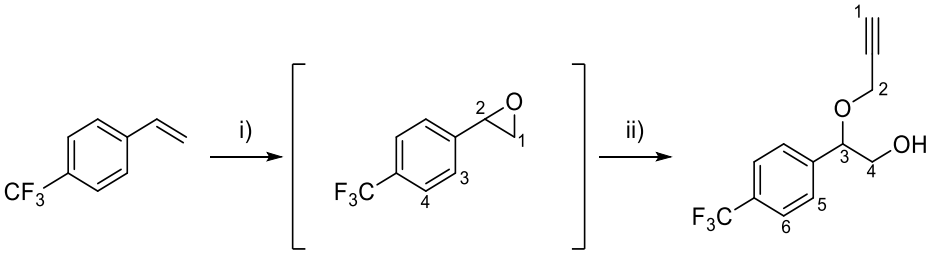
m.p. (CH_2Cl_2) 56 – 58 °C; (*Lit:* 57 – 58 °C);[194] **δ_H** (400 MHz, $CDCl_3$) 7.88 – 7.78 (4H, m, *Ar*), 7.54 – 7.44 (2H, m, *Ar*), 7.34 (1H, dd, *J* = 8.5, 1.8 Hz, *Ar*), 4.04 (1H, dd, *J* = 4.1, 2.5 Hz, C(2)*H*), 3.23 (1H, dd, *J* = 5.4, 4.1 Hz, C(1)*H*H), 2.92 (1H, dd, *J*

= 5.5, 2.6 Hz, C(1)H*H*); **δC** (101 MHz, $CDCl_3$) 135.2, 133.5, 133.3, 128.5, 127.9, 126.5, 126.2, 125.3, 122.8, 52.7, 51.4. Data is consistent with literature.[193]

2-(Naphthalen-2-yl)-2-(prop-2-yn-1-yloxy)ethan-1-ol (2k): Prepared according to **general procedure F**, using 2-vinylnapthalene oxide **10b** (750 mg, 4.40 mmol, 1.00 equiv.), propargyl alcohol (0.5 mL, 8.80 mmol, 2.00 equiv.), $Yb(OTf)_3$ (27.0 mg, 0.040 mmol, 0.010 equiv.) and CH_2Cl_2 (30 mL), ***with stirring at 30 °C***. Workup with H_2O (40 mL) and CH_2Cl_2 (3 × 20 mL). Purification by column chromatography (1:9 to 1:7 EtOAc:Petrol) yielded 2-(naphthalen-2-yl)-2-(prop-2-yn-1-yloxy)ethan-1-ol **2k** (530 mg, 2.35 mmol, 53%) as a white powdered solid.

m.p. (CH_2Cl_2) 58 – 60 °C; **δH** (400 MHz, $CDCl_3$) 7.94 – 7.77 (4H, m, *Ar*), 7.58 – 7.40 (3H, m, *Ar*), 4.85 (1H, dd, *J* = 8.2, 3.9 Hz, C(3)*H*), 4.26 (1H, dd, *J* = 15.7, 2.4 Hz, C(2)*H*H), 4.01 (1H, dd, *J* = 15.7, 2.4 Hz, C(2)H*H*), 3.94 – 3.65 (2H, m, C(4)H_2), 2.46 (1H, app. t, *J* = 2.4 Hz, C(1)*H*), 2.25 (1H, dd, *J* = 9.3, 3.9 Hz, O*H*); **δC** (101 MHz, $CDCl_3$) 134.9, 133.6, 133.3, 128.8, 128.1, 127.9, 126.8, 126.5, 126.4, 124.6, 82.0, 79.7, 74.9, 67.1, 56.3; **ν_{max}**/ cm^{-1} (neat) 3413, 3289, 3055, 2860, 2100, 1601, 1508, 1442, 1361, 1328, 1271, 1097, 1075, 1043, 859, 821, 748, 673; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{14}O_2{}^{23}Na^+$ calc. 249.0886, found 249.0887.

2-(Prop-2-yn-1-yloxy)-2-(4-(trifluoromethyl)phenyl)ethan-1-ol (2l)

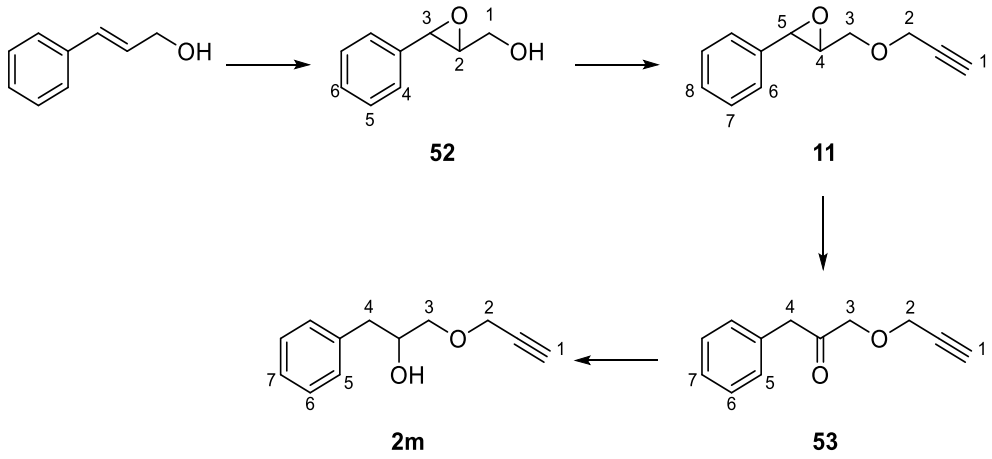


Step i): Prepared according to a literature procedure.[195] To a solution of trifluoromethyl styrene (0.7 mL, 4.74 mmol, 1.00 equiv.) in CH_2Cl_2 (21 mL), was added *m*-CPBA (75% w/w, 1.64 g, 7.11 mmol, 1.50 equiv.) at 0 °C. The reaction mixture was then warmed to room temperature and stirred under N_2 for 18 h. Once complete by TLC analysis, the reaction mixture was quenched with sat. aq. $NaHSO_3$ (20 mL) and the layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude 2-(4-(trifluoromethyl)phenyl)oxirane **10c** (874 mg) as a colourless oil. **Step ii):** Prepared according to **general procedure F**, using crude 2-(4-(trifluoromethyl)phenyl)oxirane **10c** (874 mg, 4.65 mmol, 1.00 equiv.), propargyl alcohol (0.57 mL, 9.30 mmol, 2.00 equiv.), $Yb(OTf)_3$ (29 mg, 0.050 mmol, 0.010 equiv.) and CH_2Cl_2 (30 mL). Workup with H_2O (40 mL) and CH_2Cl_2 (3 × 20 mL). Purification by column chromatography (1:49 to 1:9 EtOAc:Petrol) yielded 2-(prop-2-yn-1-yloxy)-2-(4-(trifluoromethyl)phenyl)ethan-1-ol **2l** (455 mg, 1.86 mmol, 39% over two steps) as a yellow oil.

δ_F (377 MHz, $CDCl_3$) –62.64; **δ_H** (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* = 8.0 Hz, C(6)*H*), 7.46 (2H, d, *J* = 8.0 Hz, C(5)*H*), 4.74 (1H, dd, *J* = 7.8, 3.9 Hz, C(3)*H*), 4.23 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)*H*H), 3.98 (1H, dd, *J* = 15.7, 2.4 Hz, C(2)H*H*), 3.78 – 3.60

(2H, m, C(4)H_2), 2.53 (1H, bs, O*H*), 2.46 (1H, app. t, *J* = 2.4 Hz, C(1)*H*); **δc** (101 MHz, $CDCl_3$) 141.8, 130.8 (q, J_{CF} = 32.5 Hz), 127.6, 125.8 (q, J_{CF} = 3.8 Hz), 124.1 (q, J_{CF} = 272.4 Hz), 81.3, 79.2, 75.3, 67.0, 56.6; **ν_{max}**/ cm^{-1} (neat) 3307, 2923, 2360, 1620, 1420, 1326, 1166, 1125, 1067, 1019, 841, 669; **m/z HRMS** (ESI^+) $[M + Na]^+$, $C_{12}H_{11}O_2F_3{}^{23}Na^+$ calc. 267.0603, found 267.0604.

(3-Phenyloxiran-2-yl)methanol (52), 2-phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane (11), 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-one (53), 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol (2m)



(3-Phenyloxiran-2-yl)methanol (52): Prepared according to a literature procedure.[196] *m*-CPBA (75% w/w, 20.0 g, 89.4 mmol, 1.50 equiv.) was added to a stirred solution of (*E*)-cinnamyl alcohol (7.7 mL, 59.6 mmol, 1.00 equiv.) in CH_2Cl_2 (300 mL) at 0 °C. The reaction was stirred at room temperature for 2 h. Once complete by TLC analysis, sat. aq. Na_2SO_3 (100 mL) was added to quench excess *m*-CPBA. Additional CH_2Cl_2 (100 mL) was added to the reaction mixture and the two layers were separated. The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:9 to 3:2

EtOAc:Petrol) yielded (3-phenyloxiran-2-yl)methanol **52** (6.71 g, 44.7 mmol, 75%), as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.43 – 7.25 (5H, m, *Ar*), 4.05 (1H, ddd, *J* = 12.8, 5.2, 2.4 Hz, C(1)*H*H), 3.93 (1H, d, *J* = 2.2 Hz, C(3)*H*), 3.81 (1H, ddd, *J* = 12.7, 7.7, 3.8 Hz, C(1)H*H*), 3.24 – 3.21 (1H, m, C(2)*H*), 1.94 (1H, bs, O*H*); **δ_C** (101 MHz, $CDCl_3$) 136.8, 128.6, 128.5, 125.9, 62.6, 61.3, 55.7; **ν_{max}**/ cm^{-1} (neat) 3400, 1459, 1074, 1025, 874, 759, 698; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_9H_{10}O_2{}^{23}Na^+$ calc. 173.0573, found 173.0576. Data is consistent with literature.[196]

2-Phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane (11): Prepared according to a literature procedure.[196] NaH (60% dispersion in mineral oil, 1.40 g, 35.0 mmol, 1.50 equiv) was added to a dry two-neck round bottomed flask under argon, followed by anhydrous THF (65 mL). The reaction flask was then cooled to 0 °C. To this, a solution of (3-phenyloxiran-2-yl)methanol **52** (3.50 g, 23.3 mmol, 1.00 equiv.) in THF (65 mL) was added dropwise. The reaction mixture was allowed to stir for 30 min at 0 °C, and then propargyl bromide (80% w/w in toluene, 3.1 mL, 28.0 mmol, 1.20 equiv.) in THF (6 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. Once the reaction was complete by TLC analysis, the excess NaH was quenched by adding EtOAc (10 mL). The solvent was removed from the reaction mixture, and the residue was dissolved in EtOAc (150 mL). The solution was washed with H_2O (150 mL) and brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (3:97 to 1:24 EtOAc:Petrol) yielded 2-phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane **11** (4.28 g, 22.9 mmol, 98%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.39 – 7.25 (5H, m, *Ar*), 4.26 (2H, d, *J* = 2.3 Hz, C(2)H_2), 3.92 (1H, dd, *J* = 11.4, 3.1 Hz, C(3)*H*H), 3.82 (1H, d, *J* = 2.0 Hz, C(5)*H*), 3.70 (1H, dd, *J* = 11.4, 5.3 Hz, C(3)H*H*), 3.24 (1H, ddd, *J* = 5.2, 3.1, 2.1 Hz, C(4)*H*), 2.48 (1H, t, *J* = 2.4 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 136.8, 128.6, 128.5, 125.8, 79.3, 75.1, 69.4, 60.8, 58.6, 56.0; **ν_{max}**/ cm^{-1} (neat) 3286, 2100, 1456, 1357, 1100, 876, 758, 692; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{12}H_{12}O_2{}^{23}Na^+$ calc. 211.0730, found 211.0730. Data is consistent with literature.[196]

1-Phenyl-3-(prop-2-yn-1-yloxy)propan-2-one (53): Prepared according to a modified procedure.[196] $Cu(OTf)_2$ (77.0 mg, 0.210 mmol, 0.020 equiv.) was added to a solution of 2-phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane **11** (2.00 g, 10.6 mmol, 1.00 equiv.) in CH_2Cl_2 (70 mL) and the reaction mixture was stirred for 2 h at room temperature. Once complete by TLC analysis, the solvent was removed *in vacuo*. Purification of the crude residue by column chromatography (1:9 EtOAc:Petrol) yielded 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-one **53** (1.06 g, 5.63 mmol, 53%), as a colourless oil.

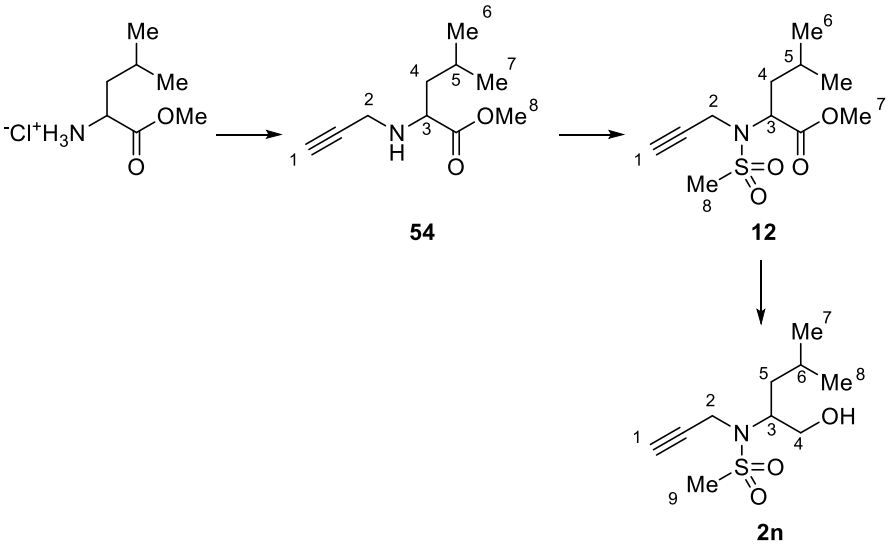
δ_H (400 MHz, $CDCl_3$) 7.37 – 7.20 (5H, m, *Ar*), 4.24 (2H, d, *J* = 2.4 Hz, C(2)H_2), 4.22 (2H, s, C(3 or 4)H_2), 3.78 (2H, s, C(3 or 4)H_2), 2.46 (1H, t, *J* = 2.4 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 205.4, 133.3, 129.6, 128.9, 127.3, 78.6, 75.8, 73.6, 58.5, 46.4; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{12}H_{12}O_2{}^{23}Na^+$ calc. 211.0730, found 211.0729. Data is consistent with literature.[196]

1-Phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol (2m): Prepared according to a modified procedure.[197] To a solution of 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-one **53** (400 mg, 2.13 mmol, 1.00 equiv.) in anhydrous THF (25 mL) was added $NaBH_4$ (240 mg, 6.40 mmol, 3.00 equiv.) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 2 h. Once complete by TLC analysis,

H_2O (25 mL) was added and the layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:19 EtOAc:Petrol) yielded 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol **2m** (262 mg, 1.38 mmol, 65%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.35 – 7.21 (5H, m, *Ar*), 4.19 (2H, d, *J* = 2.4 Hz, C(2)H_2), 4.10 – 4.00 (1H, m, C(4)*H*), 3.58 (1H, dd, *J* = 9.4, 3.4 Hz, C(3 or 5)*H*H), 3.45 (1H, dd, *J* = 9.4, 6.9 Hz, C(3 or 5)H*H*), 2.82 (2H, d, *J* = 6.7 Hz, C(3 or 5)H_2), 2.45 (1H, t, *J* = 2.4 Hz, C(1)*H*), 2.32 (1H, d, *J* = 4.0 Hz, O*H*); **δ_C** (101 MHz, $CDCl_3$) 137.9, 129.5, 128.6, 126.6, 79.6, 74.9, 73.4, 71.4, 58.7, 39.9; **ν_{max}**/ cm^{-1} (neat) 3423, 3288, 3288, 2916, 2100, 1092, 744, 695; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{12}H_{14}O_2{}^{23}Na^+$ calc. 213.0886, found 213.0885.

Methyl prop-2-yn-1-ylleucinate (54), Methyl *N*-(methylsulfonyl)-*N*-(prop-2-yn-1-yl)leucinate (12) and *N*-(1-hydroxy-4-methylpentan-2-yl)-*N*-(prop-2-yn-1-yl)methanesulfonamide (2n)



Methyl prop-2-yn-1-ylleucinate (54): Prepared according to a modified literature procedure.[198] Propargyl bromide (80% in toluene, 2.9 mL, 30.6 mmol, 1.23 equiv.) was added dropwise to a suspension of leucine hydrochloride methyl ester (4.50 g, 24.8 mmol, 1.00 equiv.) and K_2CO_3 (7.20 g, 52.1 mmol, 2.10 equiv.) in anhydrous DMF (60 mL) under N_2. The resulting mixture was left to stir at room temperature for 48 h before H_2O (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:9 EtOAc:Petrol) yielded methyl prop-2-yn-1-ylleucinate **54** (3.39 g, 18.5 mmol, 75%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, OC(8)H_3), 3.44 – 3.37 (2H, m, C(2)*H*H, C(3)*H*), 3.30 (1H, dd, *J* = 16.8, 2.3 Hz, C(2)H*H*), 2.16 (1H, app t, *J* = 2.5 Hz, C(1)*H*), 1.76 – 1.62 (2H, m, C(5)*H*, N*H*), 1.50 – 1.36 (2H, m, C(4)H_2), 0.88 (3H, d, *J* = 3.6 Hz, C(6 or 7)H_3), 0.87 (3H, d, *J* = 3.5 Hz, C(6 or 7)H_3); **δ_C** (101 MHz, $CDCl_3$) 175.9,

81.6, 71.6, 58.6, 51.7, 42.6, 37.0, 24.9, 22.8, 22.2; ν_{max}/ cm^{-1} (neat) 3293, 1733, 1435, 1198, 1117, 892, 767, 652; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{18}O_2N^+$ calc. 184.1332, found 184.1332. Data is consistent with literature.[199]

Methyl N-(methylsulfonyl)-N-(prop-2-yn-1-yl)leucinate (12): Prepared according to a literature procedure.[200] To a solution of methyl prop-2-yn-1-ylleucinate **54** (1.00 g, 5.46 mmol, 1.00 equiv.) and Et_3N (0.84 mL, 6.00 mmol, 1.10 equiv.) in CH_2Cl_2 (100 mL) at 20 °C was added methanesulfonyl chloride (0.51 mL, 6.55 mmol, 1.20 equiv.) dropwise. The mixture was then warmed to room temperature and stirred overnight (18 h). Once complete by TLC analysis, the reaction was quenched by addition of H_2O (20 mL) and the layers were separated. The organic phase was washed with H_2O (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded methyl *N*-(methylsulfonyl)-*N*-(prop-2-yn-1-yl)leucinate **12** (497 mg, 1.90 mmol, 35%) as a colourless oil.

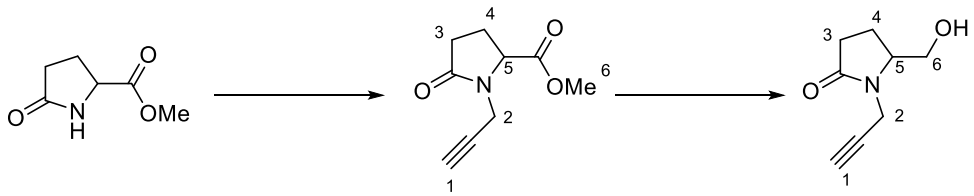
δ_H (400 MHz, $CDCl_3$) 4.61 – 4.55 (1H, m, C(3)*H*), 4.13 (1H, dd, *J* = 18.8, 2.4 Hz, C(2)*H*H), 4.06 (1H, dd, *J* = 18.8, 2.5 Hz, C(2)H*H*), 3.72 (3H, s, OC(7)H_3), 3.04 (3H, s, C(8)H_3), 2.30 (1H, app. t, *J* = 2.5 Hz, C(1)*H*), 1.86 – 1.64 (3H, m, C(4)H_2, C(5)*H*), 0.95 (6H, t, *J* = 6.2 Hz, C(6)H_3); δ_C (101 MHz, $CDCl_3$) 171.8, 78.9, 72.9, 57.8, 52.4, 40.7, 38.4, 33.6, 24.6, 23.0, 21.4; ν_{max}/ cm^{-1} (neat) 3275, 1737, 1331, 1149, 1056, 993, 970, 903, 871, 773, 664; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{11}H_{19}O_4N^{23}Na^{32}S^+$ calc. 284.0927, found 284.0925.

N-(1-hydroxy-4-methylpentan-2-yl)-N-(prop-2-yn-1-yl)methanesulfonamide (2n): Prepared according to **general procedure G**, using methyl *N*-(methylsulfonyl)-*N*-(prop-2-yn-1-yl)leucinate **12**, (0.450 g, 1.72 mmol, 1.00 equiv.), $LiBH_4$ (2 M in THF, 1.2 mL, 2.41 mmol, 1.40 equiv.) and THF (17 mL)

with stirring at 60 °C overnight. Purification by column chromatography (3:7 to 4:6 EtOAc:Petrol) yielded title compound **2n** (254 mg, 1.09 mmol, 63%) as a white powder.

m.p. (CH_2Cl_2) 62 – 64 °C; **δ_H** (400 MHz, $CDCl_3$) 4.18 (1H, dd, *J* = 18.8, 2.5 Hz, C(2)*H*H), 4.07 – 3.96 (1H, m, C(3)*H*), 3.91 (1H, dd, *J* = 18.8, 2.5 Hz, C(2)H*H*), 3.75 – 3.65 (1H, m, C(4)*H*H), 3.65 – 3.55 (1H, m, C(4)H*H*), 3.07 (3H, s, C(9)H_3), 2.38 (1H, app. t, *J* = 2.5 Hz, C(1)*H*), 2.30 (1H, bs, O*H*), 1.73 – 1.58 (1H, m, C(6)*H*), 1.44 (1H, ddd, *J* = 14.3, 9.1, 5.2 Hz, C(5)*H*H), 1.25 – 1.14 (1H, ddd, *J* = 14.3, 8.7, 6.5 Hz, C(5)H*H*), 0.93 (3H, d, *J* = 2.8 Hz, C(7)H_3), 0.91 (3H, d, *J* = 3.0 Hz, C(8)H_3); **δ_C** (101 MHz, $CDCl_3$) 80.0, 73.0, 63.4, 58.5, 41.3, 38.1, 31.6, 24.6, 23.1, 22.1; **ν_{max}**/ cm^{-1} (neat) 3516, 3275, 1322, 1145, 880, 775; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{10}H_{19}O_3N^{23}Na^{32}S^+$ calc. 256.0978, found 256.0978.

Methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (13) and 5-(hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (2o)



Methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (13): Prepared according to a modified procedure.[201] To a suspension of solid KOH powder (1.85 g, 33.0 mmol, 1.10 equiv.) and tetrabutylammonium bromide (0.480 g, 1.50 mmol, 0.200 equiv.) in anhydrous THF (75 mL) was added dropwise a solution of propargyl bromide (80% w/w in toluene, 5.4 mL, 48.0 mmol, 1.60 equiv.) and methyl 5-oxopyrrolidine-2-carboxylate (3.50 g, 30.0 mmol, 1.00 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 of the crude residue by column chromatography (1:3 to 1:1 EtOAc:Petrol) to yield methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **13** (1.44 g, 7.95 mmol, 27%) as a colourless oil.

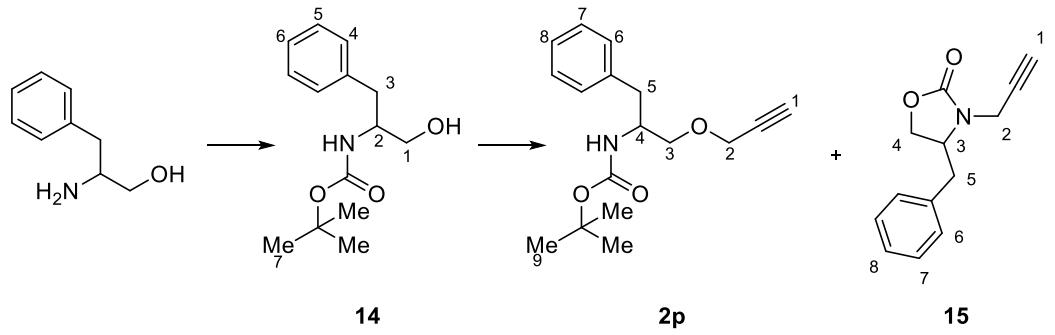
δ_H (400 MHz, $CDCl_3$) 4.61 (1H, dd, *J* = 17.7, 2.6 Hz, C(2)*H*H), 4.44 – 4.40 (1H, m, C(5)*H*), 3.78 (3H, s, C(6)H_3), 3.78 (1H, dd, *J* = 17.6, 2.7 Hz, C(2)H*H*), 2.56 – 2.33 (3H, m, C(3)H_2 and C(4)*H*H), 2.23 (1H, app. t, *J* = 2.6 Hz, C(1)*H*), 2.15 – 2.07 (1H, m, C(4)H*H*); **δ_C** (101 MHz, $CDCl_3$) 174.4, 172.0, 77.2, 73.0, 58.3, 52.5, 31.3, 29.3, 22.7; **ν_{max}**/ cm^{-1} (neat) 2150, 1739, 1689, 1438, 1410, 1348, 1179, 1043, 992, 695; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_{12}O_3N^+$ calc. 182.0812, found 182.0811.

5-(Hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one (2o): Prepared according to **general procedure G**, using methyl 5-oxo-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **13** (800 mg, 4.40 mmol, 1.00 equiv.), THF (44 mL) and $LiBH_4$ (2 M in THF, 3.10 mL, 6.30 mmol, 1.20 equiv.). Work-up using H_2O (20 mL) and EtOAc (3 × 20 mL). Purification by column chromatography (1:0 to 9:1 EtOAc:MeOH) yielded 5-(hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one **2o** (287 mg, 1.89 mmol, 43%) as a white powder.

m.p. (CH_2Cl_2) 43 – 45 °C; **δ_H** (400 MHz, $CDCl_3$) 4.34 (1H, dd, *J* = 17.6, 2.6 Hz, C(2)*H*H), 3.91 (1H, dd, *J* = 17.6, 2.6 Hz, C(2)H*H*), 3.93 – 3.86 (1H, m, C(6)*H*H), 3.85 – 3.78 (1H, m, C(5)*H*), 3.58 (1H, ddd, *J* = 12.1, 7.4, 3.2 Hz, C(6)H*H*), 3.30 (1H, dd, *J* = 7.4, 6.8 Hz, O*H*), 2.41 (1H, dddd, *J* = 17.1, 10.1, 7.0 Hz, C(3)*H*H), 2.26 (1H, ddd, 17.1, 10.1, 5.6 Hz, C(3)H*H*), 2.20 (1H, app. t, *J* = 2.5 Hz, C(1)*H*), 2.12 – 2.00 (1H, m, C(4)*H*H), 1.99 – 1.88 (1H, m, C(4)H*H*); **δ_C** (101 MHz, $CDCl_3$) 175.7, 78.3, 72.1, 62.5, 59.2, 30.6, 30.4, 20.9; **ν_{max}**/ cm^{-1} (neat) 3387, 3282, 1660, 1420,

1348, 1254, 1185, 1058, 652; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{12}O_2N^+$ calc. 154.0863, found 154.0863.

***tert*-Butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (14), *tert*-butyl (1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-yl)carbamate (2p) and *tert*-Butyl (1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-yl)carbamate (15)**



tert-Butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (14): Prepared according to a modified procedure.[202] In a round-bottomed flask under N_2, phenylalaninol (1.00 g, 6.60 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Then, Boc_2O (1.7 mL, 7.59 mmol, 1.15 mmol), was added and the mixture was stirred at 0 °C for 18 h. Once the reaction was complete by TLC analysis, the mixture was washed with 5% aqueous citric acid solution (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography (19:1 to 1:1 Petrol:EtOAc) to yield *tert*-butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate **14** (1.42 g, 5.65 mmol, 86%) as a white powder.

m.p. (CH_2Cl_2) 88 – 90 °C; (*Lit:* 89 – 91 °C);[203] $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.36 – 7.16 (5H, m, *Ar*), 4.72 (1H, bs, N*H*), 3.87 (1H, bs, C(2)*H*), 3.71 – 3.64 (1H, m, C(1)*H*H), 3.59 – 3.52 (1H, m, C(1)H*H*), 2.84 (2H, d, J = 7.2 Hz, C(3)H_2), 1.41 (9H, s, C(7)H_3);

δ_C (101 MHz, $CDCl_3$) 156.3, 137.9, 129.4, 128.7, 126.7, 79.9, 64.5, 53.9, 37.6, 28.5; **ν_{max}**/ cm^{-1} (neat) 3355, 2980, 2875, 1686, 1526, 1315, 1268, 1251, 1169, 1005, 700; **m/z LRMS** 274.1 $[M + Na]^+$. Data is consistent with literature.[202]

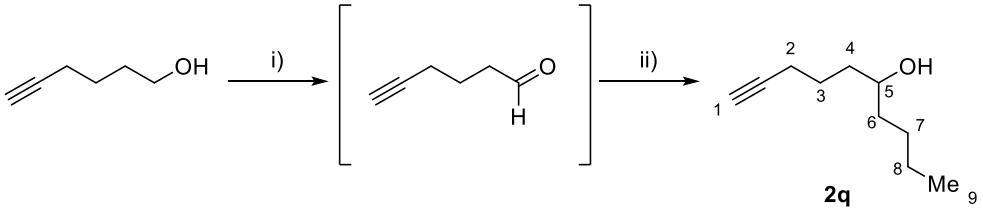
tert-Butyl (1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-yl)carbamate (2p): Prepared according to **general procedure D**, using *tert*-butyl (1-hydroxy-3-phenylpropan-2-yl)carbamate **14** (1.00 g, 3.99 mmol, 1.00 equiv.), NaH (60% in mineral oil, 167 mg, 4.18 mmol, 1.05 equiv.), propargyl bromide (80% in toluene, 1.2 mL, 10.36 mmol, 2.60 equiv.) and DMF (17.5 mL). Quench using sat. aq. NH_4Cl (20 mL). Work-up using EtOAc (3 × 20 mL), 5% aq. LiCl (20 mL). Purification by column chromatography (1:99 to 3:7 EtOAc:Petrol) yielded *tert*-butyl (1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-yl)carbamate **2p** (423 mg, 1.46 mmol, 37%) and cyclised side adduct 4-benzyl-3-(prop-2-yn-1-yl)oxazolidin-2-one **15** (307 mg, 1.42 mmol, 36%) as a white powder and pale-yellow oil respectively.

tert-Butyl (1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-yl)carbamate (2p): **m.p.** (CH_2Cl_2) 40 – 42 °C; **δ_H** (400 MHz, $CDCl_3$) 7.31 – 7.17 (5H, m, *Ar*), 4.85 (1H, bs, N*H*), 4.14 (2H, dd, *J* = 2.4, 1.1 Hz, C(3)H_2), 3.95 (1H, m, C(4)*H*), 3.43 (2H, dd, *J* = 3.9, 1.6 Hz, C(5)H_2), 2.85 (2H, app hept, *J* = 7.8 Hz, C(2)H_2), 2.42 (1H, t, *J* = 2.4 Hz, C(1)*H*), 1.41 (9H, s, C(9)H_3); **δ_C** (101 MHz, $CDCl_3$) 155.3, 138.1, 129.5, 128.4, 126.4, 79.5, 79.2, 74.8, 69.9, 58.4, 51.5, 37.8, 28.4; **ν_{max}**/ cm^{-1} (neat) 3294, 2976, 1700, 1498, 1453, 1391, 1364, 1246, 1168, 1059, 1029, 742, 701; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{17}H_{23}O_3N^{23}Na^+$ calc. 312.1570, found 312.1570.

4-benzyl-3-(prop-2-yn-1-yl)oxazolidin-2-one (15): **δ_H** (400 MHz, $CDCl_3$) 7.37 – 7.31 (2H, m, *Ar*), 7.31 – 7.27 (1H, m, *Ar*), 7.22 – 7.15 (2H, m, *Ar*), 4.43 (1H, dd, *J* = 17.9, 2.6 Hz, C(2)*H*H), 4.29 – 4.16 (2H, m, C(3)*H* and C(4)*H*H), 4.09 – 3.98 (1H, m, C(4)H*H*), 3.83 (1H, dd, *J* = 17.8, 2.5 Hz, C(2)H*H*), 3.24 (1H, dd, *J* = 13.6, 4.2

Hz, C(5)*H*H), 2.70 (1H, dd, *J* = 13.9, 8.6 Hz, C(5)H*H*), 2.34 (1H, app t, *J* = 2.5 Hz, C(1)*H*); **δC** (101 MHz, $CDCl_3$) 157.8, 135.4, 129.1, 129.1, 127.4, 77.0, 73.5, 67.3, 55.8, 38.4, 32.6; **ν_{max}**/ cm^{-1} (neat) 3283, 2980, 1750, 1250, 1091; **m/z LRMS** (ESI^+) 238.0 $[M + Na]^+$. Data is consistent with literature.[204]

Dec-9-yn-5-ol (2q)

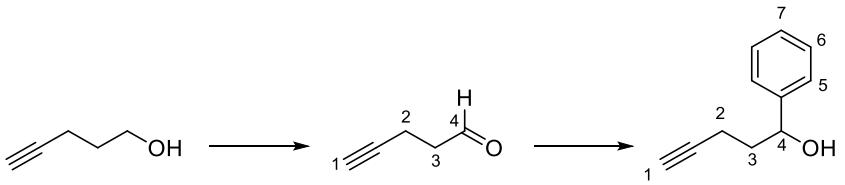


Prepared according to literature procedure.[80a] A anhydrous flask under argon was charged with CH_2Cl_2 (42 mL), Et_3N (4.2 mL, 30.2 mmol, 3.28 equiv.), dimethyl sulfoxide (2.1 mL, 29.6 mmol, 3.21 equiv.) and hex-5-yn-1-ol (1.0 mL, 9.22 mmol, 1.00 equiv.). The solution was cooled to 0 °C and stirred for 5 min before pyridine-sulfur trioxide complex (4.42 g, 27.8 mmol, 3.02 equiv.) was added. The mixture was then warmed to room temperature and stirred vigorously for 2 h before being quenched by sat. aq. NH_4Cl (20 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude aldehyde. *n*-Butyllithium (2.15 M in THF, 8.6 mL, 18.44 mmol 2.00 equiv.) was then added to a flask containing anhydrous THF (188 mL) and cooled to –78 °C. The crude aldehyde was then added dropwise to this solution and the resulting mixture was allowed to warm to room temperature over 2 h. After this time, the reaction was quenched with MeOH (5 mL) at 0 °C and concentrated *in vacuo*. The residue was then dissolved in 10% w/w aq. HCl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts

were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (0:1 to 1:19 Et_2O:Petrol) yielded to dec-9-yn-5-ol **2q** (118 mg, 0.766 mmol, 8% over two steps) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 3.66 – 3.57 (1H, m, C(5)*H*), 2.22 (2H, td, *J* = 6.7, 2.6 Hz C(2)H_2), 1.95 (1H, t, *J* = 2.7 Hz, C(1)*H*), 1.75 – 1.25 (10H, m, C(3, 4, 6, 7 and 8)H_2), 0.90 (3H, t, *J* = 7.0 Hz, C(9)H_3); **δ_C** (101 MHz, $CDCl_3$) 84.5, 71.6, 68.6, 37.4, 36.5, 27.9, 24.7, 22.7, 18.6, 14.2; **ν_{max}**/ cm^{-1} (neat) 3309, 2930, 2861, 1457, 1434, 1127, 1057, 1004, 630. Data is consistent with literature.[80a]

1-Phenylpent-4-yn-1-al (55) and 1-phenylpent-4-yn-1-ol (2r)



1-Phenylpent-4-yn-1-al (55): Prepared according to a literature procedure.[80b] Oxalyl chloride (2.8 mL, 33.0 mmol, 1.10 equiv.), was dissolved in anhydrous CH_2Cl_2 (63 mL) and cooled to –78 °C under N_2. A solution containing dimethyl sulfoxide (4.7 mL, 66.0 mmol, 2.20 equiv.) in CH_2Cl_2 (5 mL) was added dropwise over 30 min with stirring at –78 °C. A solution of pent-4-yn-1-ol (2.8 mL, 30.0 mmol, 1.00 equiv.) in CH_2Cl_2 (5 mL) was then added dropwise and the mixture was stirred for a further 60 min at –78 °C. Et_3N (21.3 mL, 153 mmol, 5.10 mmol) in CH_2Cl_2 (20 mL) was then added dropwise and the solution was allowed to warm to room temperature overnight. After this time, H_2O (100 mL) was then added and the layers were separated. The aqueous layer was acidified with 1 M aq. HCl (75 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with 1 M HCl (75 mL), sat. aq. $NaHCO_3$ (75 mL), dried over $MgSO_4$, filtered and

concentrated *in vacuo*. Purification of the crude residue by distillation (Lit bp: 127 – 129 °C at 1 atm)[80b] yielded 1-phenylpent-4-yn-1-al **55** (1.54 g, 18.8 mmol, 63%).

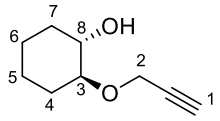
δ_H (400 MHz, $CDCl_3$) 9.80 (1H, t, *J* = 1.1 Hz C(4)*H*), 2.74 – 2.66 (2H, m, C(3)H_2), 2.54 – 2.48 (2H, m, C(2)H_2), 1.99 (1H, t, *J* = 2.7 Hz, C(1)*H*); **δ_C** (101 MHz, $CDCl_3$) 200.2, 82.4, 69.4, 42.4, 11.7; **ν_{max}**/ cm^{-1} (neat) 3292, 2980, 1723, 1134, 1066, 940, 629. Data is consistent with literature.[80b]

1-Phenylpent-4-yn-1-ol (2r): Prepared according to a modified procedure.[80b] To dry flask under argon containing magnesium turnings (280 mg, 11.6 mmol, 1.90 equiv.) was added dropwise anhydrous Et_2O (8 mL) and the mixture stirred vigorously for 30 min. A solution of bromobenzene (0.92 mL, 8.71 mmol, 1.43 equiv.) in Et_2O (8 mL) was added dropwise. The mixture was then stirred at room temperature for 1 h and heated to reflux for 30 min. The newly formed Grignard reagent was added dropwise to a solution of pent-4-yn-1-ol **55** (680 mg, 6.09 mmol, 1.00 equiv.) in Et_2O (8 mL) and the mixture was heated to reflux for 2 h. After cooling to room temperature, ice (3 g) was added, and the resulting suspension was dissolved in 1 M aq. HCl (20 mL). The layers were then separated and the organic layer was washed with sat. aq. $NaHSO_3$ (20 mL), sat. aq. $NaHCO_3$ (20 mL), H_2O (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:9 to 1:4 Et_2O:Petrol) yielded 1-phenylpent-4-yn-1-ol **2r** (488 mg, 3.05 mmol, 50%) as a white solid.

m.p. (CH_2Cl_2) 30 – 31 °C; **δ_H** (400 MHz, $CDCl_3$) 7.39 – 7.25 (5H, m, *Ar*), 4.86 (1H, ddd, *J* = 8.3, 5.0, 3.3 Hz, C(4)*H*), 2.42 – 2.31 (1H, bs, O*H*), 2.36 – 2.27 (1H, m, C(2)*H*H), 2.25 – 2.15 (1H, m, C(2)H*H*), 2.01 (1H, t, *J* = 2.7 Hz, C(1)*H*), 2.00 – 1.93 (1H, m, C(3)*H*H), 1.92 – 1.82 (1H, m, C(3)H*H*); **δ_C** (101 MHz, $CDCl_3$) 144.1, 128.5, 127.7, 125.9, 84.0, 73.0, 69.0, 37.4, 15.1; **ν_{max}**/ cm^{-1} (neat) 3295, 3030, 2980, 1493,

1452, 1431, 1395, 1061, 1025, 942, 915, 763, 700, 630. Data is consistent with literature.[80b]

(1*S*,2*S*)- 2-(Prop-2-yn-1-yloxy)cyclohexan-1-ol (2s)

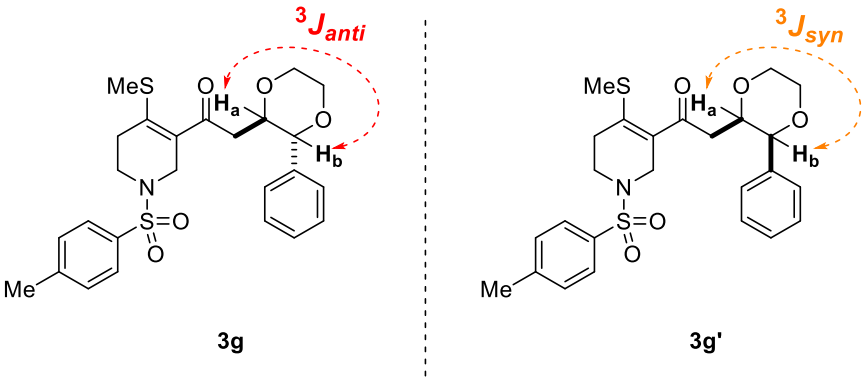


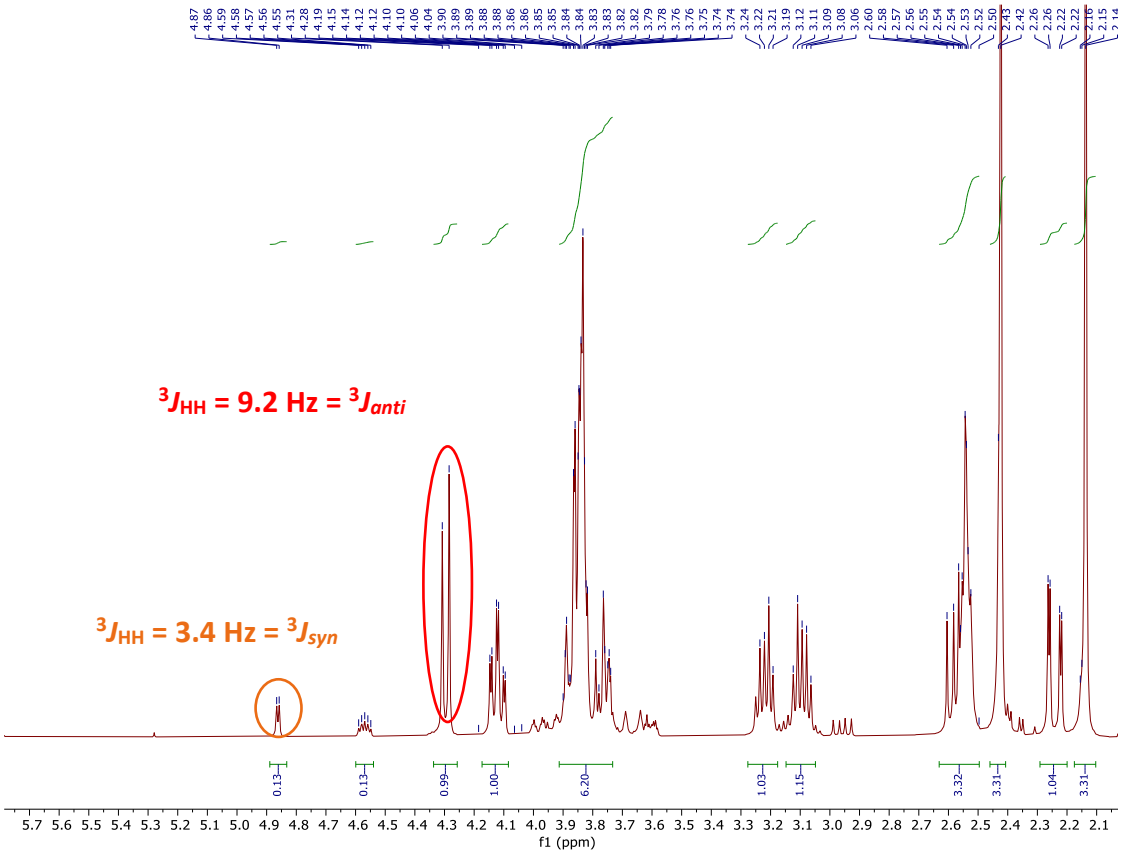
Prepared according to **general procedure D**, using (1*S*,2*S*) -cyclohexane-1,2-diol (300 mg, 2.58 mmol. 1.00 equiv.) in DMF (20 mL), NaH (60%, 103 mg, 2.58 mmol, 1.00 equiv.) and propargyl bromide (80% w/w in toluene, 1.2 mL, 10.3 mmol, 4.00 equiv.) with stirring at room temperature for 2 h. Quench using sat. aq. NH_4Cl (20 mL), and workup using EtOAc (3 × 20 mL), 5% aq. LiCl (20 mL). Purification of the crude residue by column chromatography (1:19 to 1:4 EtOAc:Petrol) yielded (1*S*,2*S*)- 2-(prop-2-yn-1-yloxy)cyclohexan-1-ol **2s** (167 mg, 1.08 mmol, 42%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$) 4.29 (1H, dd, *J* = 15.9, 2.4 Hz, C(2)*H*H), 4.18 (1H, dd, *J* = 15.8, 2.4 Hz, C(2)H*H*), 3.49 – 3.40 (1H, m, C(3 or 8)*H*), 3.29 – 3.21 (1H, m, C(3 or 8)*H*), 2.69 (1H, bs, O*H*), 2.44 (1H, t, *J* = 2.4 Hz, C(1)*H*), 2.12 – 2.05 (1H, m, C(4 or 7)*H*H), 2.04 – 1.98 (1H, m, C(4 or 7)*H*H), 1.77 – 1.64 (2H, m, C(5 or 6)H_2), 1.35 – 1.09 (4H, m, C(4 and 7)H*H* and C(5 or 6)H_2); **δc** (101 MHz, $CDCl_3$) 83.1, 80.4, 74.4, 73.7, 56.3, 32.3, 29.1, 24.3, 24.0; **ν_{max}**/ cm^{-1} (neat) 3295, 2934, 2862, 1451, 1082, 1015, 847, **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_9H_{14}O_2{}^{23}Na^+$ calc. 177.0886, found 177.0887; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +79.1 (*c* = 1.0, $CHCl_3$).

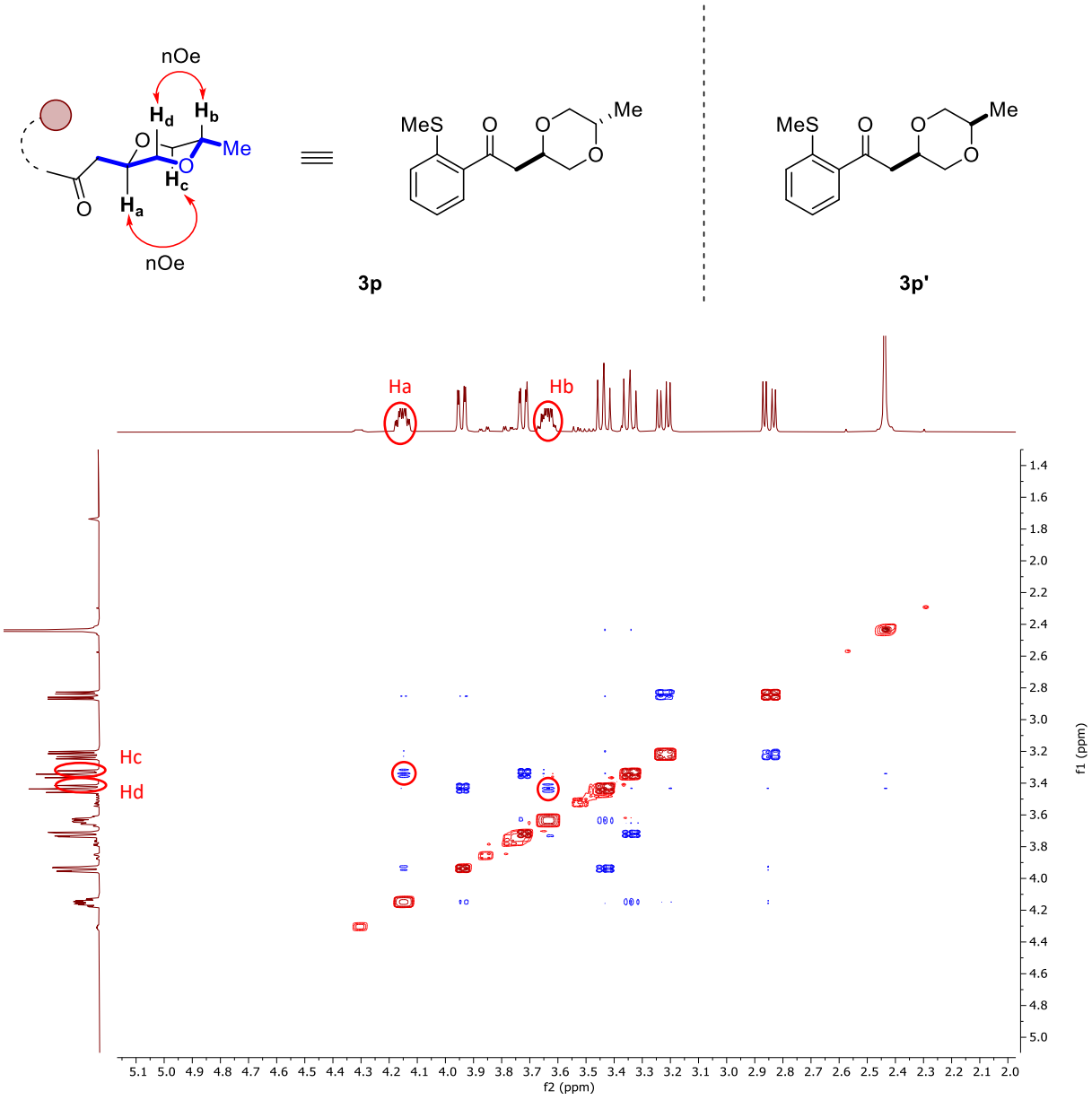
6.2.3 Assignment of Relative Configurations of Cyclised Products

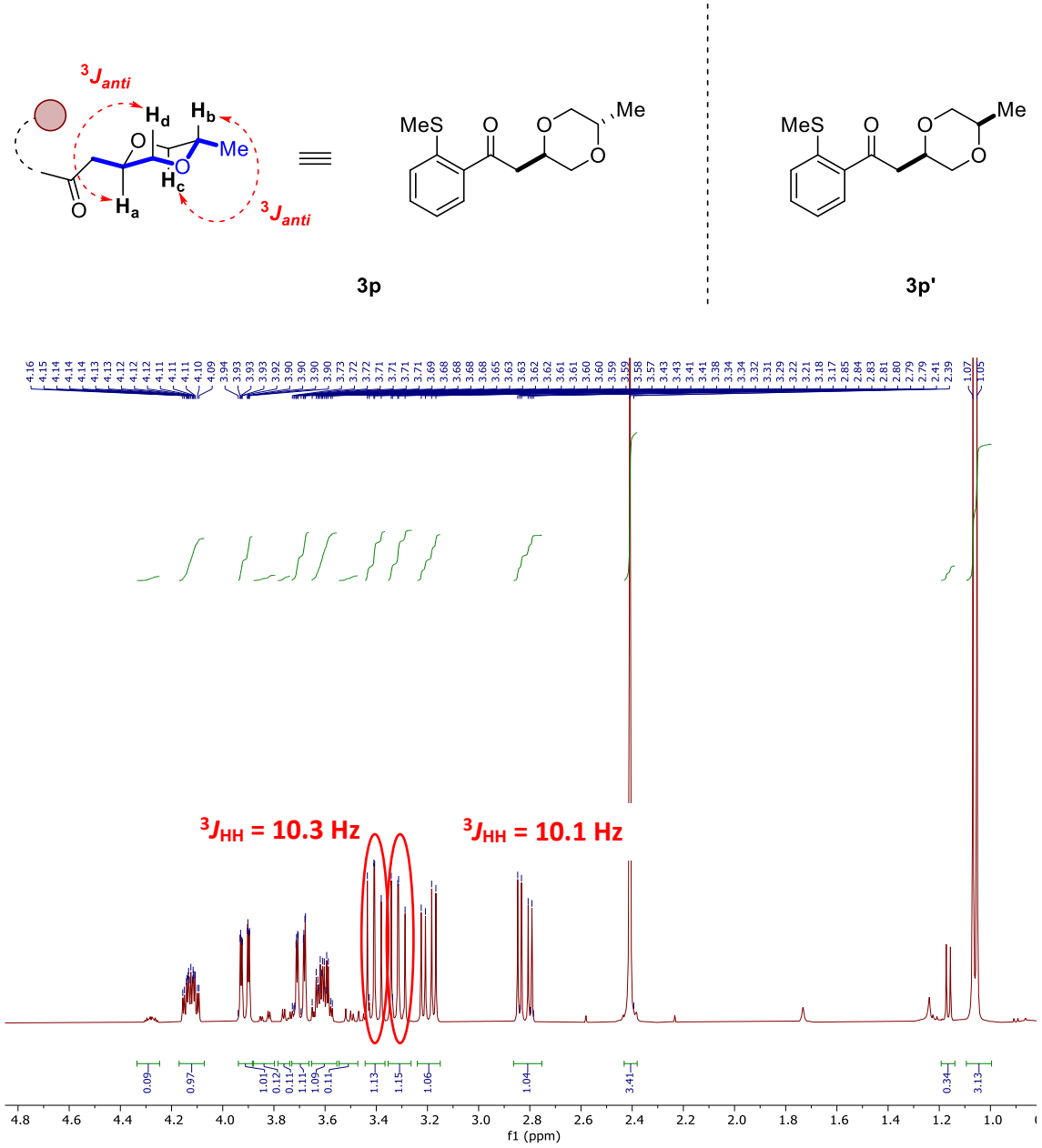
6.2.3a R^3 Substituents



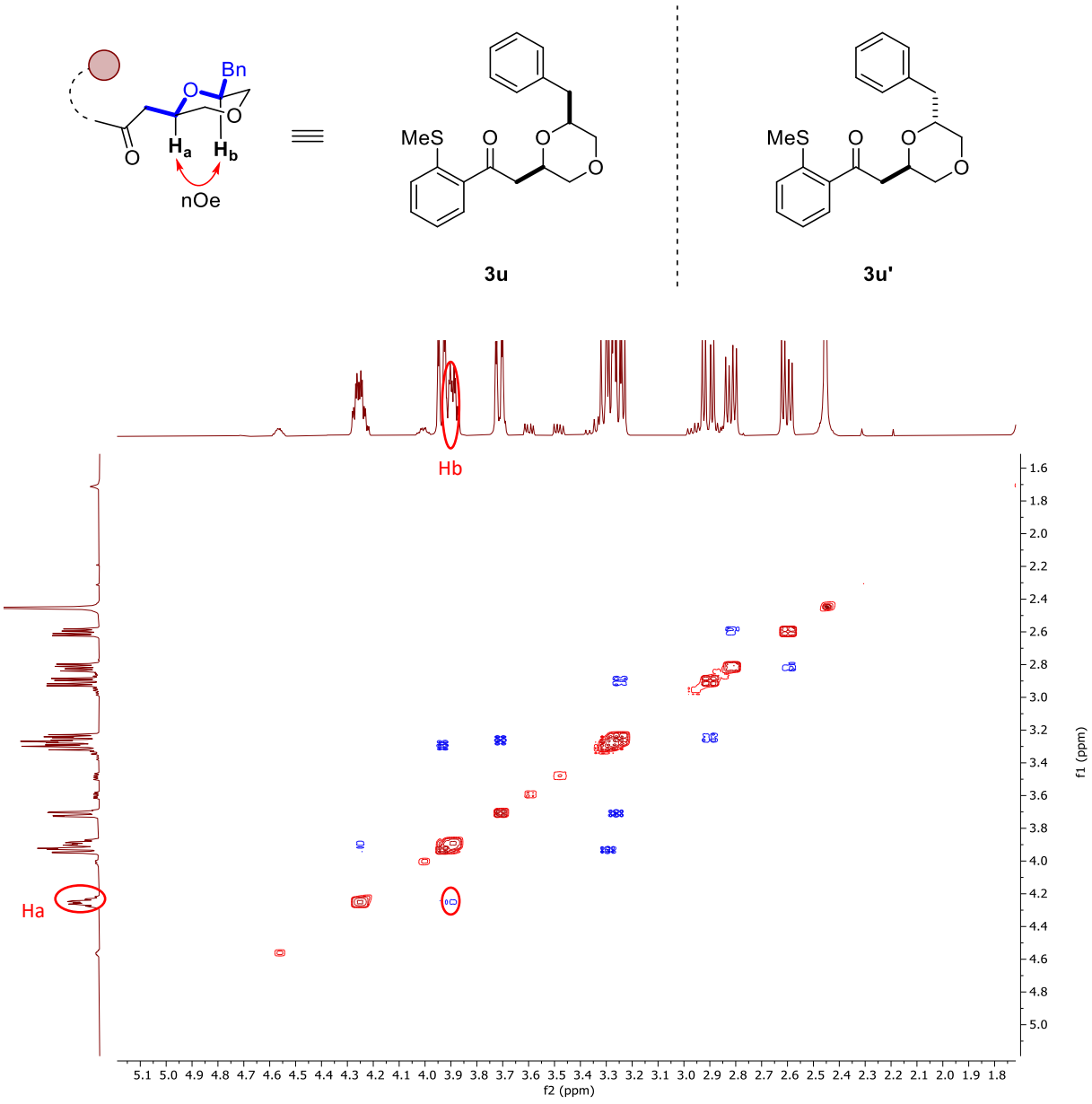


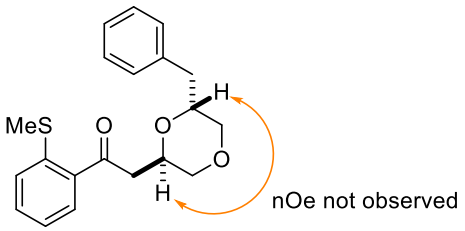
6.2.3b R^2 Substituents



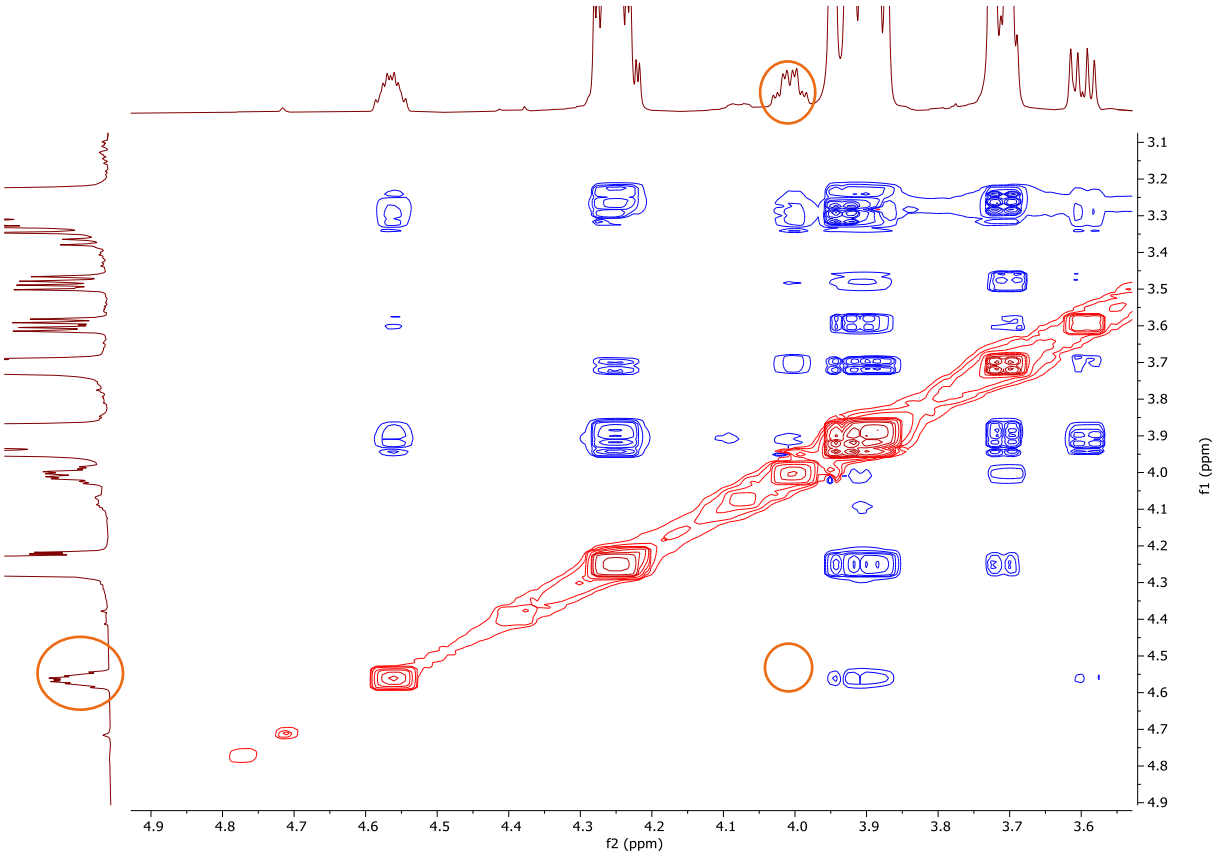

3J anti
Hd
Hb
Me
Hc
Ha
3J anti
MeS
O
Me
3p
3p'
3JHH = 10.3 Hz
3JHH = 10.1 Hz
f1 (ppm)

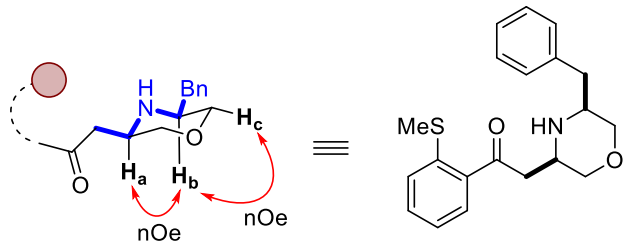
6.2.3c R^1 Substituents



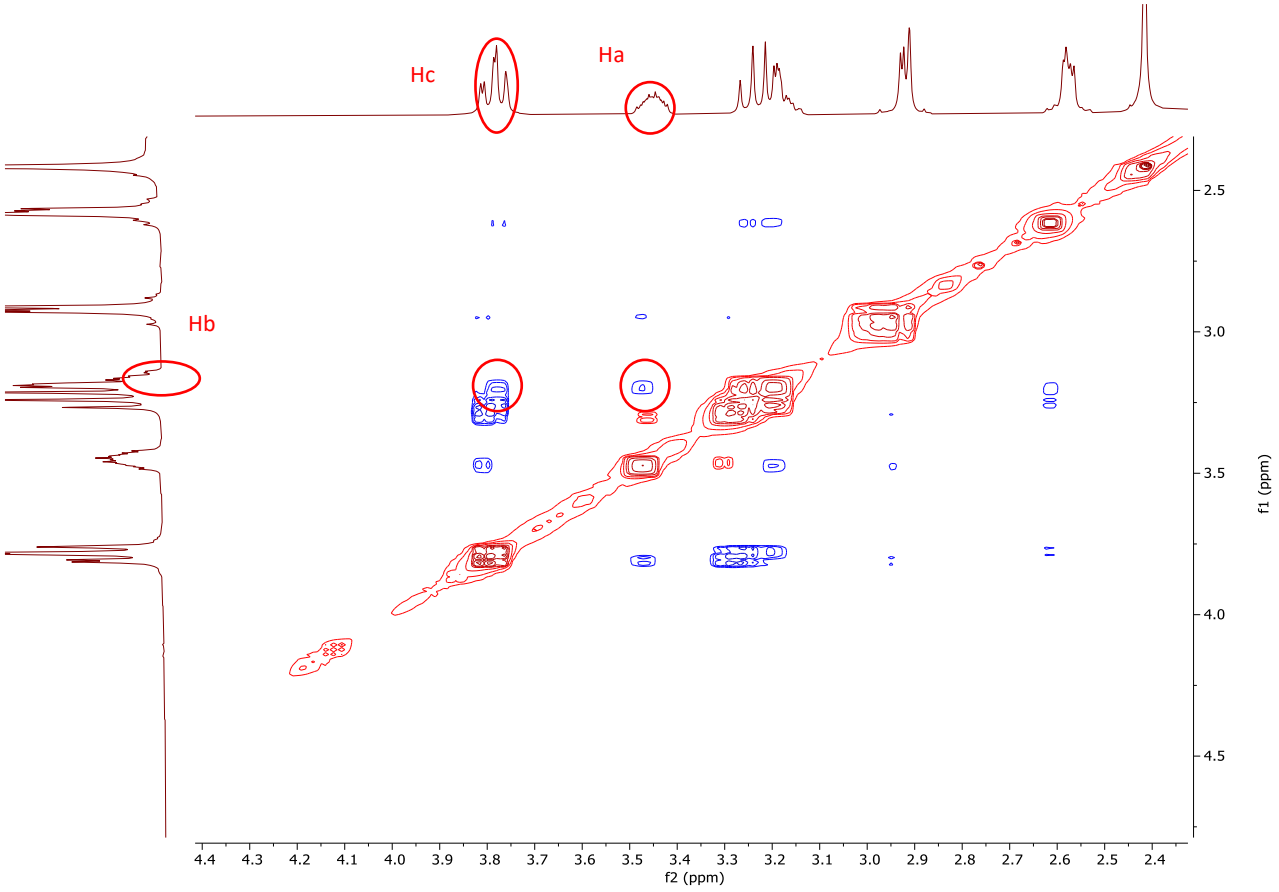


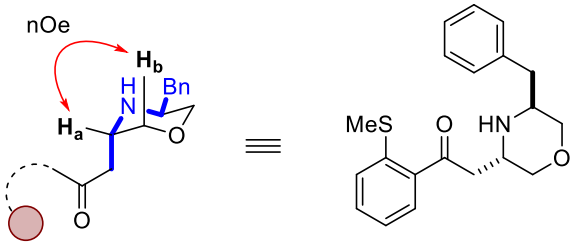
3u'



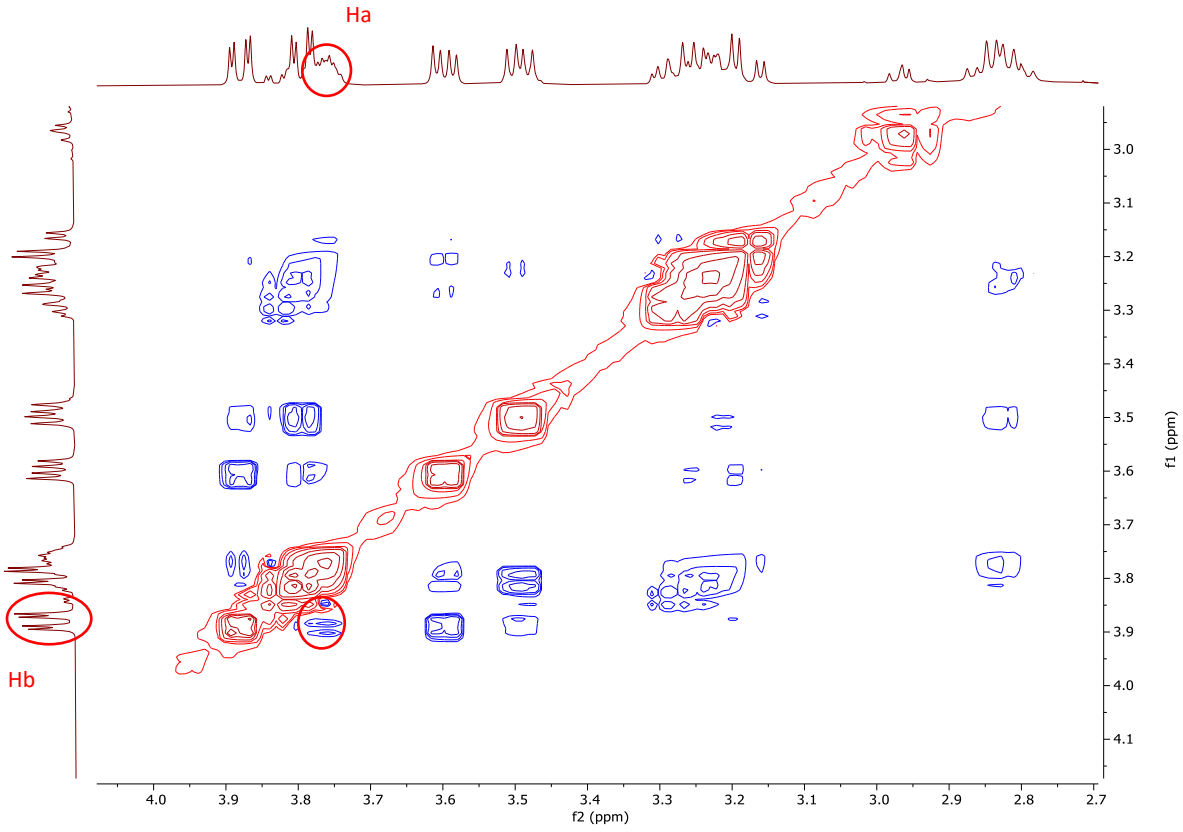

H
Bn
N
O
H_c
H_a
H_b
O
nOe
nOe
MeS
O
HN
O

3ab


Hc
Ha
Hb
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4
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3.5
4.0
4.5
f1 (ppm)



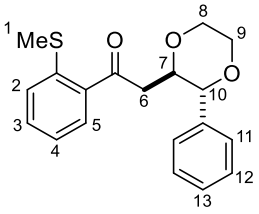
3ab'



6.2.4 *O*- and *N*-heterocycles Substrate Scope

6.2.4a Aldehyde Scope Compounds

1-(2-(Methylthio)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3a)**



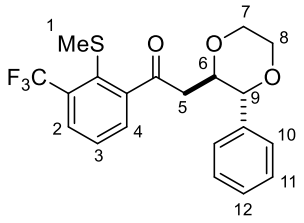
Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (13:1 dr) by column chromatography (1:9 to 1:5 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3a** (85.9 mg, 0.262 mmol, 87%) as an off-white solid.

m.p. (CH_2Cl_2) 69 – 71 °C; **δ_H** (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J* = 7.8, 1.5 Hz, *Ar*), 7.46 – 7.37 (3H, m, *Ar*), 7.38 – 7.31 (3H, m, *Ar*), 7.31 – 7.25 (1H, m, *Ar*), 7.12 (1H, td, *J* = 7.6, 1.2 Hz, *Ar*), 4.37 (1H, d, *J* = 9.2 Hz, C(10)*H*), 4.24 (1H, app td, *J* = 9.2, 2.4 Hz, C(7)*H*), 3.95 – 3.79 (4H, m, C(8 and 9)H_2), 3.11 (1H, dd, *J* = 15.9, 9.2 Hz, C(6)*H*H), 2.61 (1H, dd, *J* = 15.9, 2.4 Hz, C(6)H*H*), 2.38 (3H, s, SC(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 198.4, 142.4, 138.0, 134.9, 132.2, 130.5, 128.8 (2C), 127.9, 125.3, 123.5, 82.7, 77.5, 67.1, 67.1, 41.7, 16.1; **ν_{max}**/ cm^{-1} (neat) 1672, 1433, 1271, 1115,

990, 842, 756, **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{21}O_3{}^{32}S^+$ calc. 329.1206, found 329.1203.

Gram-Scale Reaction: Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (912 mg, 6.00 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (1.27 g, 7.20 mmol, 1.20 equiv.), with $Rh(nbd)_2BF_4$ (56 mg, 0.150 mmol, 0.025 equiv.), dcpe (63 mg, 0.150 mmol, 0.025 equiv.) and DCE (6.0 mL) in a normal microwave vial. For **general procedure I**, a separate oven-dried round-bottom flask was backfilled under argon three times. The crude reaction mixture from **general procedure H** was transferred over to this flask *via* a syringe. Then, in another oven-dried round-bottom flask, was prepared a degassed (argon) solution of HCl (4 M in dioxane, 3.0 mL, 12.0 mmol, 2.00 equiv.) in DCE (80 mL). This solution was slowly added to the round-bottom flask containing the crude reaction mixture, and the resulting solution was stirred for 3 h at 55 °C (before work-up according to **general procedure I**). Purification of the crude residue (8.5:1 dr) *via* column chromatography (3:17 EtOAc:Petrol), followed by recrystallisation in 1:19 EtOAc:Hexane, yielded title compound **3a** (1.46 g, 5.00 mmol, 74%) as a pale-brown solid. Out of the material obtained, 0.98 g was recrystallised as pure major diastereoisomer, which could be used in subsequent derivatisations (see SI, section **6.5**).

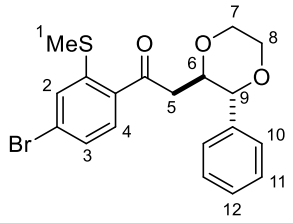
1-(2-(Methylthio)-3-(trifluoromethyl)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3b)**



Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)-3-(trifluoromethyl)benzaldehyde **1b** (66 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (19:1 dr) by column chromatography (1:9 to 1:5 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3b** (101 mg, 0.255 mmol, 85%) as a yellow viscous oil.

δ_F (377 MHz, $CDCl_3$) –59.74 (C*F*$_3$); **δ_H** (400 MHz, $CDCl_3$) 7.73 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.49 – 7.42 (1H, m, *Ar*), 7.38 – 7.30 (6H, m, *Ar*), 4.29 (1H, d, *J* = 9.1 Hz, C(9)*H*), 4.07 (1H, ddd, *J* = 9.3, 9.1, 2.9 Hz, C(6)*H*), 3.96 – 3.82 (4H, m, C(7 and 8)H_2), 3.02 (1H, dd, *J* = 16.0, 9.3 Hz, C(5)*H*H), 2.82 (1H, dd, *J* = 16.0, 2.9 Hz, C(5)H*H*), 2.15 (3H, s, SC(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 203.4, 150.9, 137.8, 134.8 (q, J_{CF} = 29.5 Hz), 130.9, 130.1, 129.1, 128.9, 128.8, 127.8 (q, J_{CF} = 5.5 Hz), 127.8, 123.5 (q, J_{CF} = 273.8 Hz), 82.7, 77.5, 67.0 (2C), 45.9, 22.1; **ν_{max}**/ cm^{-1} (neat) 2800, 1705, 1317, 1267, 1163, 1114, 910, 731, 700; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{20}O_3F_3{}^{32}S^+$ calc. 397.1080, found 397.1081.

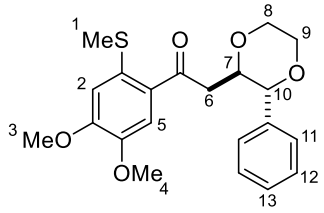
1-(4-Bromo-2-(methylthio)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3c)**



Following **general procedures H** and **I**. **General procedure H** used 4-bromo-2-(methylthio)benzaldehyde **1c** (69 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General rocedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (19:1 dr) by column chromatography (1:12 to 1:7 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3c** (75.9 mg, 0.187 mmol, 62%) as a pale-brown solid.

m.p. (CH_2Cl_2) 95 – 96 °C; **δ_H** (400 MHz, $CDCl_3$) 7.49 (1H, d, *J* = 8.4 Hz, *Ar*), 7.42 – 7.28 (6H, m, *Ar*), 7.24 (1H, dd, *J* = 8.4, 1.8 Hz, *Ar*), 4.35 (1H, d, *J* = 9.1 Hz, C(9)*H*), 4.19 (1H, app td, *J* = 9.1, 2.5 Hz, C(6)*H*), 3.95 – 3.76 (4H, m, C(7 and 8)H_2), 3.04 (1H, dd, *J* = 15.7, 9.1 Hz, C(5)*H*H), 2.57 (1H, dd, *J* = 15.7, 2.6 Hz, C(5)H*H*), 2.37 (3H, s, SC(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 197.6, 145.2, 138.0, 133.2, 131.8, 128.9, 128.8, 127.9, 127.7, 127.7, 126.5, 82.7, 77.5, 67.1, 67.1, 41.6, 16.2; **ν_{max}**/ cm^{-1} (neat) 1673, 1574, 1537, 1437, 1369, 1269, 1114, 990, 942, 799, 726, 648, 624; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{20}O_3{}^{79}Br^{32}S^+$ calc. 407.0311, found 407.0311, $C_{19}H_{20}O_3{}^{81}Br^{32}S^+$ calc. 409.0290, found 409.0290.

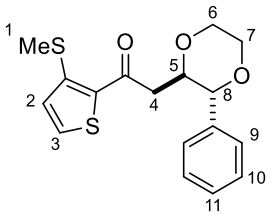
1-(4,5-Dimethoxy-2-(methylthio)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3d)**



Following **general procedures H** and **I**. **General procedure H** used 4,5-dimethoxy-2-(methylthio)benzaldehyde **1d** (64 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.05 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (>20:1 dr) by column chromatography (1:3 to 2:3 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3d** (80.0 mg, 0.206 mmol, 67%) as an off-white solid.

m.p. (CH_2Cl_2) 153 – 155 °C; **δ_H** (400 MHz, $CDCl_3$) 7.42 – 7.39 (2H, m, *Ar*), 7.36 – 7.29 (3H, m, *Ar*), 7.12 (1H, s, C(2 or 5)*H*), 6.75 (1H, s, C(2 or 5)*H*), 4.36 (1H, d, *J* = 9.1 Hz, C(10)*H*), 4.20 (1H, app td, *J* = 9.2, 2.5 Hz, C(7)*H*), 3.92 (3H, s, C(3 or 4)H_3), 3.91 – 3.78 (4H, m, C(8 and 9)H_2), 3.81 (3H, s, C(3 or 4)H_3), 3.02 (1H, dd, *J* = 15.5, 9.2 Hz, C(6)*H*H), 2.65 (1H, dd, *J* = 15.5, 2.5 Hz, C(6)H*H*), 2.36 (3H, s, SC(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 197.0, 152.4, 145.6, 138.1, 135.9, 128.7 (2C), 128.1, 127.9, 113.8, 108.9, 82.7, 77.6, 67.1, 67.1, 56.4, 56.0, 41.9, 16.9; **ν_{max}**/ cm^{-1} (neat) 2852, 2361, 1660, 1598, 1552, 1502, 1437, 1378, 1336, 1266, 1202, 1167, 1113, 914, 763, 729, 702; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{21}H_{25}O_5{}^{32}S^+$ calc. 389.1417, found 389.1417.

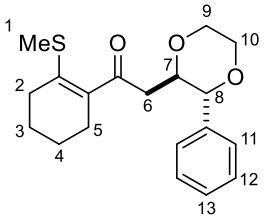
1-(3-(Methylthio)thiophen-2-yl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3e)**



Following **general procedures H** and **I**. **General procedure H** used 3-(methylthio)thiophene-2-carbaldehyde **1e** (48 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (>20:1 dr) by column chromatography (1:9 to 1:5 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3e** (95.3 mg, 0.285 mmol, 95%), as an orange/brown solid.

m.p. (CH_2Cl_2) 113 – 117 °C; **δ_H** (400 MHz, $CDCl_3$) 7.47 (1H, d, *J* = 5.2 Hz, C(3)H), 7.42 – 7.38 (2H, m, *Ar*), 7.37 – 7.25 (3H, m, *Ar*), 6.96 (1H, d, *J* = 5.2 Hz, C(2)H), 4.38 (1H, d, *J* = 9.2 Hz, C(8)*H*), 4.25 (1H, td, *J* = 9.0, 2.6 Hz, C(5)*H*), 3.98 – 3.74 (4H, m, C(6 and 7)H_2), 2.91 (1H, dd, *J* = 15.6, 8.9 Hz, C(4)*H*H), 2.53 (1H, dd, *J* = 15.6, 2.6 Hz, C(4)H*H*), 2.47 (3H, s, SC(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 188.9, 146.3, 137.9, 131.2, 130.9, 128.7, 128.7, 127.8, 126.2, 82.5, 77.2, 67.0 (2C), 42.6, 16.6; **ν_{max}**/ cm^{-1} (neat) 2981, 2856, 1682, 1594, 1490, 1454, 1433, 1378, 1326, 1284, 1269, 1115, 944, 757, 702, 647, 622; **m/z HRMS** (ESI^+) $C_{17}H_{18}O_3{}^{23}Na^{32}S_2{}^+$ $[M + Na]^+$ calc. 357.0590, found 357.0590.

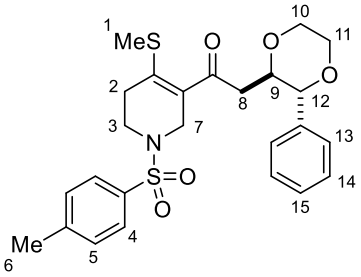
1-(2-(Methylthio)cyclohex-1-en-1-yl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3f)**



Following **general procedure H** ***(general procedure I was not pursued for this example)***, using 2-(methylthio)cyclohex-1-ene-1-carbaldehyde **1f** (47 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL), purification of the crude residue (3.4:1 dr) by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3f** (90.1 mg, 0.271 mmol, 90%) as a yellow viscous oil.

δ_H (400 MHz, Acetone-d_6) (major signals only) 7.46 – 7.37 (2H, m, *Ar*), 7.41 – 7.21 (3H, m, *Ar*), 4.30 (1H, d, J = 9.1 Hz, C(8)*H*), 4.01 (1H, td, J = 9.2, 2.5 Hz, C(7)*H*), 3.86 – 3.70 (4H, m, C(9 and 10)H_2), 2.70 (1H, dd, J = 15.8, 9.3 Hz, C(6)*H*H), 2.42 – 2.35 (2H, m, C(2 and 5)H_2), 2.34 – 2.14 (3H, m, C(2 and 5)H_2 and C(6)H*H*), 2.09 (3H, s, C(1)H_3), 1.69 – 1.51 (4H, m, C(3 or 4)H_2); **δ_C** (101 MHz, Acetone-d_6) (major signals only) 199.5, 145.4, 139.8, 132.8, 129.1, 129.0, 128.7, 83.2, 78.6, 67.5, 67.5, 42.8, 30.2, 28.5, 23.7, 22.6, 14.5; **ν_{max}**/ cm^{-1} (neat) 2925, 2855, 1700, 1651, 1518, 1449, 1417, 1268, 1246, 1136, 1113, 1011, 985, 943, 894, 760, 701, 650, 624; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{25}O_3{}^{32}S^+$ calc. 333.1519, found 333.1520.

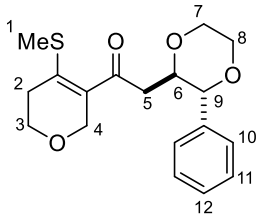
1-(4-(Methylthio)-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3g)**



Following **general procedure H** ***(general procedure I was not pursued for this example)***, using 4-(methylthio)-1-tosyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde **1g**[83h] (62 mg, 0.200 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (42 mg, 0.240 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (3.7 mg, 0.010 mmol, 0.050 equiv.), dcpe (4.2 mg, 0.010 mmol, 0.050 equiv.) and DCE (0.2 mL), purification of the crude residue (7:1 dr) by column chromatography (3:7 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3g** (76.3 mg, 0.157 mmol, 78%) as an off-white solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.73 – 7.68 (2H, m, *Ar*), 7.44 – 7.29 (7H, m, *Ar*), 4.34 (1H, d, *J* = 9.2 Hz, C(12)*H*), 4.16 (1H, app td, *J* = 9.2, 2.6 Hz, C(9)*H*), 3.96 – 3.75 (6H, m, C(10 and 11)H_2 and C(7)H_2), 3.32 – 3.22 (1H, m, C(3)*H*H), 3.18 – 3.09 (1H, m, C(3)H*H*), 2.61 (1H, dd, *J* = 15.9, 9.1 Hz, C(8)*H*H), 2.60 – 2.55 (2H, m, C(2)H_2), 2.46 (3H, s, C(6)H_3), 2.28 (1H, dd, *J* = 15.8, 2.5 Hz, C(8)H*H*), 2.18 (3H, s, C(1)H_3); **δ_C** (126 MHz, $CDCl_3$) (major signals only) 195.5, 148.7, 144.1, 137.9, 133.4, 129.9, 128.7, 127.8, 127.8 (2C), 125.7, 82.6, 77.4, 67.0, 67.0, 46.4, 42.6, 41.8, 29.8, 21.6, 14.6; **ν_{max}**/ cm^{-1} (neat) 3033, 2921, 1652, 1526, 1341, 1164, 1113, 939, 914, 758, 730, 703, 657; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{25}H_{30}O_5N^{32}S_2^+$ calc. 488.1560, found 488.1558.

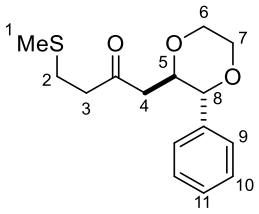
1-(4-(Methylthio)-5,6-dihydro-2*H*-pyran-3-yl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3h)**



Following **general procedure H** ***(general procedure I was not pursued for this example)***, 4-(methylthio)-5,6-dihydro-2*H*-pyran-3-carbaldehyde **1h**[83h] (47 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL), purification of the crude residue (4:1 dr) by column chromatography (1:4 to 1:1 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3h** (90.9 mg, 0.272 mmol, 91%) as an orange powdered solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.38 – 7.28 (5H, m, *Ar*), 4.42 (1H, app dt, *J* = 14.7, 2.2 Hz, C(4)*H*H), 4.33 – 4.26 (2H, m, C(4)H*H* and C(9)*H*), 4.16 (1H, app td, *J* = 9.0, 2.5 Hz, C(6)*H*), 4.01 – 3.68 (6H, m, C(3)H_2 and C(7 and 8)H_2), 2.53 – 2.44 (3H, m, C(2)H_2 and C(5)*H*H), 2.21 (3H, s, SC(1)H_3), 2.17 – 2.09 (1H, dd, *J* = 15.9, 2.5 Hz, C(5)H*H*); **δ_C** (126 MHz, $CDCl_3$) (major signals only) 194.3, 150.4, 138.0, 128.7, 127.8, 126.9, 126.3, 82.6, 77.0, 67.0, 66.9, 63.9, 41.1, 29.3, 29.2, 14.1; **ν_{max}**/ cm^{-1} (neat) 2855, 1650, 1528, 1453, 1412, 1351, 1270, 1145, 1112, 1013, 943, 914, 898, 762, 729, 701, 650; **m/z HRMS** (ESI^+) $C_{18}H_{22}O_4{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 357.1131, found 357.1132.

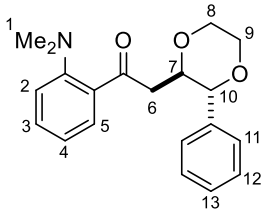
4-(Methylthio)-1-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)butan-2-one (3i)**



Following **general procedures H** and **I**. **General procedure H** used 3-(methylthio)propanal **1i** (30 μL, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (106 mg, 0.600 mmol, 2.00 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.) and dppe (6.0 mg, 0.015 mmol, 0.050 equiv.) ***in acetone (2.0 mL), with stirring for 2 h before addition of acid. It is important to note that a solvent-switch also occurred between procedures H and I for this example.*** **General procedure H** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.3 mL). Purification of the crude residue (8.5:1 dr) by column chromatography (1:19 to 1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3i** (58.2 mg, 0.208 mmol, 69%) as a viscous yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.37 – 7.29 (5H, m, *Ar*), 4.24 (1H, d, *J* = 9.1 Hz, C(8)*H*), 4.01 (1H, app td, *J* = 9.1, 3.1 Hz, C(5)*H*), 3.93 – 3.78 (4H, m, C(6 and 7)H_2), 2.65 – 2.59 (4H, m, C(2 and 3)H_2), 2.49 (1H, dd, *J* = 15.5, 9.1 Hz, C(4)*H*H), 2.15 (1H, dd, *J* = 15.5, 3.1 Hz, C(4)H*H*), 2.04 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 206.4, 137.8, 128.8, 128.7, 127.7, 82.7, 77.1, 67.0, 67.0, 44.7, 43.6, 27.6, 15.8; **ν_{max}**/ cm^{-1} (neat) 3657, 2980, 2913, 1715, 1494, 1380, 1268, 1114, 943, 758, 701, 649; **m/z HRMS** $C_{15}H_{20}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 303.1025, found 303.1025.

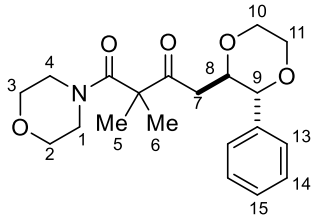
1-(2-(Dimethylamino)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (3j)**



Following **general procedures H** and **I**. **General procedure H** used 2-(dimethylamino)benzaldehyde **1j** (44.7 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (11.2 mg, 0.030 mmol, 0.100 equiv.) and dcpm (11.5 mg, 0.030 mmol, 0.100 equiv.) ***in acetone (2 mL), for 4 h before addition of acid. It is important to note that a solvent-switch (acetone to DCE) also occurred between procedures H and I for this example.*** **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.3 mL). Purification of the crude residue (5.8:1 dr) by column chromatography (1:19 to 1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3j** (92.3 mg, 0.284 mmol, 95%) as an orange/yellow solid.

δ_H (400 MHz, MeOD-*d*$_4$) (major signals only) 7.38 – 7.27 (6H, m, *Ar*), 7.16 (1H, dd, *J* = 5.9, 1.8 Hz, *Ar*), 6.99 (1H, dd, *J* = 8.3, 0.8 Hz, *Ar*), 6.90 (1H, app td, *J* = 7.4, 1.1 Hz, *Ar*), 4.26 (1H, d, *J* = 9.1 Hz, C(10)*H*), 3.97 – 3.59 (7H, m, C(7)*H*, C(8, 9 and 6)H_2), 2.46 (6H, s, NC(1)H_3); **δ_C** (126 MHz, MeOD-*d*$_4$) (major signals only) 206.1, 153.1, 139.7, 133.7, 133.1, 130.4, 129.6, 129.5, 129.4, 128.9, 121.8, 118.5, 83.8, 79.0, 68.0, 67.9, 44.7; **ν_{max}**/ cm^{-1} (neat) 2981, 2856, 1682, 1594, 1490, 1454, 1433, 1378, 1284, 1269, 1158, 1115, 970, 945, 757, 702; **m/z HRMS** (ESI^+) $C_{20}H_{24}O_3N^+$ $[M + H]^+$ calc. 326.1751, found 326.1749.

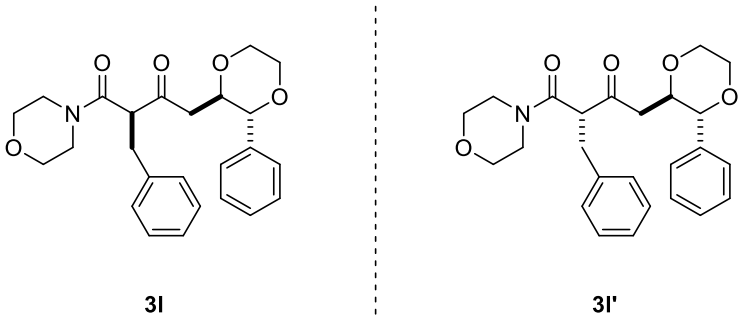
2,2-dimethyl-1-morpholino-4-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)butane-1,3-dione (3k)**



Following **general procedures H** and **I**. **General procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (>20:1 dr) by column chromatography (1:4 to 1:1 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3k** (100 mg, 0.277 mmol, 92%) as a colourless crystalline solid.

m.p. (CH_2Cl_2) 124 – 126 °C; **δ_H** (400 MHz, $CDCl_3$) 7.32 (5H, s, *Ar*), 4.23 (1H, d, *J* = 9.3 Hz, C(9)*H*), 4.10 (1H, app td, 9.3, 1.9 Hz, C(8)*H*), 3.92 – 3.73 (4H, m, C(10 and 11)H_2), 3.70 – 2.80 (8H, br., C(1, 2, 3 and 4)H_2), 2.63 (1H, dd, *J* = 17.4, 9.4 Hz, C(7)*H*H), 2.06 (1H, dd, *J* = 17.4, 1.9 Hz, C(7)H*H*), 1.28 (3H, s, C(5 or 6)H_3), 1.22 ((3H, s, C(5 or 6)H_3); **δ_C** (101 MHz, $CDCl_3$) 207.3, 170.9, 137.9, 129.0, 128.8, 127.8, 82.3, 76.1, 67.1, 66.9, 66.4 (bs, 2C), 55.9, 46.4 (bs), 43.3 (bs), 39.6, 23.3, 23.1; **ν_{max}**/ cm^{-1} (neat) 2856, 1713, 1637, 1423, 1271, 1250, 1115, 1025, 943, 761, 705; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{28}O_5N^+$ calc. 362.1962, found 362.1955.

(*R)-2-Benzyl-1-morpholino-4-((2*R**,3*R**)-3-phenyl-1,4-dioxan-2-yl)butane-1,3-dione (3l) and (*S**)-2-benzyl-1-morpholino-4-((2*R**,3*R**)-3-phenyl-1,4-dioxan-2-yl)butane-1,3-dione (3l')**



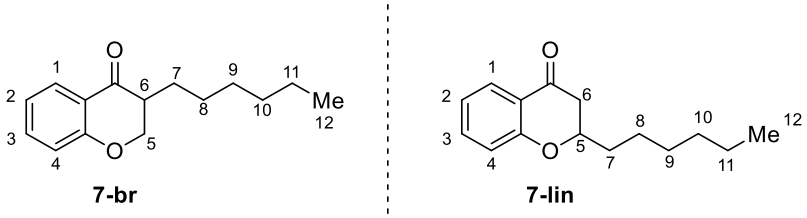
3l 3l'

Following **general procedures H** and **I**. **General procedure H** used 2-benzyl-1,3-dimorpholinopropane-1,3-dione **1l** (74 mg, 0.300 mmol, 1.00 equiv.) and 2-((1-phenylprop-2-yn-1-yl)oxy)ethan-1-ol **2c** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.) and dcpe (6.3 mg, 0.015 mmol). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (1:1 dr) by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3l** and **3l'** (81.1 mg, 0.191 mmol, 64%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) (1:1 mixture) 7.37 – 7.29 (9H, m, *Ar*), 7.27 – 7.16 (7H, m, *Ar*), 7.14 – 7.05 (4H, m, *Ar*), 4.26 (1H, d, *J* = 9.1 Hz), 4.21 (1H, d, *J* = 9.1 Hz), 4.04 – 3.72 (12H, m), 3.61 – 2.91 (20H, m), 2.61 (1H, dd, *J* = 15.6, 10.1 Hz), 2.58 (1H, dd, *J* = 15.9, 8.5 Hz), 2.19 (1H, dd, *J* = 15.8, 3.4 Hz), 2.10 (1H, dd, *J* = 15.4, 2.4 Hz); **δ_C** (101 MHz, $CDCl_3$) (1:1 mixture) 203.0, 202.8, 167.2, 167.2, 138.5, 138.4, 137.7, 137.6, 129.1, 129.0, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 127.7, 127.7, 126.8, 126.8, 82.6, 82.3, 77.6, 77.4, 77.0, 67.0, 67.0, 66.9, 66.9, 66.7, 66.6, 66.2, 59.6, 58.6, 46.5, 46.3, 42.6, 42.5, 41.7, 34.6, 34.4; (Proton and Carbon NMR data

too complex to fully assign); ν_{max}/ cm^{-1} (neat) 1720, 1635, 1441, 1110, 911, 730; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{25}H_{30}O_5N^+$ calc. 424.2119, found 424.2112.

3-Hexylchroman-4-one (7-br) and 2-hexylchromen-4-one (7-lin)



Prepared according to a modified procedure.[76] In an argon filled glovebox, $[Rh(COD)Cl]_2$ (1.5 mg, 0.003 mmol, 1 mol%), dppf (3.3 mg, 0.006 mmol, 2 mol%), CsF (3.6 mg, 0.024 mmol, 8 mol%), 1-octyne (53 µL, 0.360 mmol, 1.20 equiv.), salicaldehyde **1m** (31 µL, 0.300 mmol, 1.00 equiv.) and anhydrous MeCN (0.6 mL) were added to an oven-dried microwave vial. The resulting mixture was then stirred at 100 °C for 18 h. After this time, the reaction mixture (1:1.2 l:b isomer ratio) was filtered through a silica plug and washed with EtOAc (3 × 5 mL). The resulting solution was concentrated *in vacuo* and purified by column chromatography (1:99 to 1:49 Et_2O:Petrol) to yield major regioisomer **7-br** (27.5 mg, 0.118 mmol, 39%) and minor regioisomer **7-lin** (19.3 mg, 0.083 mmol, 28%) as colourless oils.

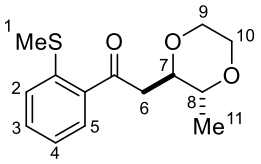
7b: δ_H (400 MHz, $CDCl_3$) 7.89 (1H, dd, *J* = 7.8, 1.8 Hz, *Ar*), 7.49 – 7.42 (1H, m, *Ar*), 7.03 – 6.98 (1H, m, *Ar*), 6.95 (1H, dd, *J* = 8.4, 1.0 Hz, *Ar*), 4.51 (1H, dd, *J* = 11.4, 4.5 Hz, C(5)*H*H), 4.27 (1H, dd, *J* = 11.4, 8.4 Hz, C(5)H*H*), 2.68 – 2.60 (1H, m, C(6)*H*), 1.94 – 1.80 (1H, m, C(7)*H*H), 1.59 – 1.15 (9H, m, C(7)H*H*, C(8 to 11)H_2), 0.95 – 0.83 (3H, m, C(12)H_3); δ_C (101 MHz, $CDCl_3$) 194.8, 161.6, 135.8, 127.6, 121.4, 120.8, 117.8, 70.6, 46.1, 31.7, 29.4, 27.1, 26.5, 22.7, 14.2; ν_{max}/ cm^{-1} (neat) 2954, 2925, 1689, 1606, 1580, 1465, 1456, 1381, 1324, 1296, 1215, 1148,

1130, 1035, 1013, 756; **m/z HRMS** (ESI$^+$) [M + Na]$^+$ $C_{15}H_{21}O_2^+$ calc. 233.1536, found 233.1537.

7l: **δ_H** (400 MHz, $CDCl_3$) 7.87 (1H, dd, *J* = 7.8, 1.8 Hz, *Ar*), 7.46 (1H, m, *Ar*), 7.04 – 6.94 (2H, m, *Ar*), 4.44 (1H, app. qd, *J* = 7.7, 5.2 Hz, C(5)*H*), 2.68 (2H, d, *J* = 7.7 Hz, C(6)H_2), 1.94 – 1.83 (1H, m, C(7)*H*H), 1.76 – 1.64 (1H, m, C(7)H*H*), 1.61 – 1.15 (8H, m, C(8, 9, 10 and 11)H_2), 0.94 – 0.87 (3H, m, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) 192.8, 161.9, 136.1, 127.1, 121.3, 121.2, 118.1, 78.1, 43.2, 35.1, 31.8, 29.2, 25.0, 22.7, 14.2; **ν_{max}**/ cm^{-1} (neat) 2928, 2858, 1693, 1608, 1464, 1380, 1306, 1230, 1149, 1123, 1065, 763; **m/z HRMS** (ESI$^+$) [M + H]$^+$ calc. 233.1538, found. 233.1536.

6.2.4b Alkyne Scope Compounds

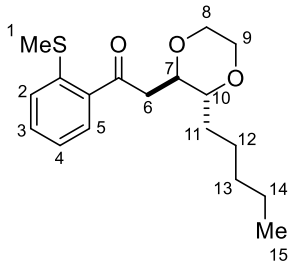
2-((2*R,3*R**)-3-Methyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3n)**



Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-(but-3-yn-2-yloxy)ethan-1-ol **2e** (41 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (9:1 dr) by column chromatography (1:12 to 1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3n** (67.5 mg, 0.254 mmol, 85%) as a viscous yellow oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.90 – 7.73 (1H, m, *Ar*), 7.50 – 7.40 (1H, m, *Ar*), 7.34 – 7.29 (1H, m, *Ar*), 7.24 – 7.09 (1H, m, *Ar*), 3.85 (1H, ddd, *J* = 8.9, 8.1, 3.6 Hz, C(7)*H*), 3.75 – 3.65 (4H, m, C(9 and 10)H_2), 3.46 (1H, dq, *J* = 8.9, 6.3 Hz, C(8)*H*), 3.13 (1H, dd, *J* = 15.8, 8.1 Hz, C(6)*H*H), 2.90 (1H, dd, *J* = 15.8, 3.6 Hz, C(6)H*H*), 2.42 (3H, s, SC(1)H_3), 1.15 (3H, d, *J* = 6.3 Hz, C(11)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 198.8, 142.4, 135.2, 132.3, 130.6, 125.4, 123.7, 77.9, 75.5, 67.0, 66.9, 42.6, 17.6, 16.2; **ν_{max}**/ cm^{-1} (neat) 2854, 1671, 1587, 1558, 1433, 1355, 1316, 1274, 1199, 1113, 1073, 1050, 1017, 987, 923, 902, 849, 754, 693, 628; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{14}H_{18}O_3{}^{23}Na^{32}S^+$ calc. 289.0869, found 289.0868.

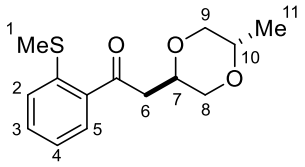
1-(2-(Methylthio)phenyl)-2-((2*R,3*R**)-3-pentyl-1,4-dioxan-2-yl)ethan-1-one (3o)**



Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-(oct-1-yn-3-yloxy)ethan-1-ol **2f** (61 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.60 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.30 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (8:1 dr) by column chromatography (1:12 to 1:5 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3o** (72.6 mg, 0.225 mmol, 75%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 7.81 (1H, dd, *J* = 7.8, 1.5 Hz, *Ar*), 7.45 (1H, ddd, *J* = 8.1, 7.3, 1.5 Hz, *Ar*), 7.31 (1H, dd, *J* = 8.2, 1.1 Hz, *Ar*), 7.18 (1H, ddd, *J* = 8.0, 7.4, 1.2 Hz, *Ar*), 3.92 (1H, ddd, *J* = 9.0, 8.1, 3.6 Hz, C(7)*H*), 3.76 – 3.63 (4H, m, C(8)H_2 and C(9)H_2), 3.35 – 3.25 (1H, ddd, 9.0, 6.7, 4.5 Hz, C(10)*H*), 3.12 (1H, dd, *J* = 15.7, 8.2 Hz, C(6)*H*H), 2.91 (1H, dd, *J* = 15.7, 3.5 Hz, C(6)H*H*), 2.42 (3H, s, SC(1)H_3), 1.61 – 1.14 (8H, m, C(11, 12, 13 and 14)H_2), 0.87 (3H, t, *J* = 6.9 Hz, C(15)H_3); **δ_C** (101 MHz, $CDCl_3$) 199.0, 142.3, 135.3, 132.2, 130.6, 125.4, 123.7, 79.3, 76.7, 66.9, 66.9, 42.6, 32.0, 31.5, 24.9, 22.7, 16.2, 14.2; **ν_{max}**/ cm^{-1} (neat) 2980, 2956, 2856, 2360, 1673, 1587, 1559, 1463, 1433, 1379, 1273, 1116, 929, 753, 631; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{18}H_{26}O_3{}^{23}Na^{32}S^+$ calc. 345.1495, found 345.1496.

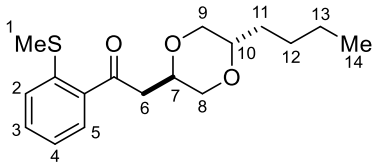
2-((2*R,5*S**)-5-Methyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3p)**



Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-(prop-2-yn-1-yloxy)propan-1-ol **2g** (41 mg. 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (8:1 dr) by column chromatography (1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3p** (64.4 mg, 0.242 mmol, 81%) as an off-white powdered solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.80 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.48 – 7.41 (1H, m, *Ar*), 7.34 – 7.28 (1H, m, *Ar*), 7.17 (1H, ddd, *J* = 7.8, 7.2, 1.2 Hz, *Ar*), 4.12 (1H, dddd, *J* = 10.3, 6.6, 5.9, 2.6 Hz, C(7)*H*), 3.91 (1H, dd, *J* = 11.3, 2.6 Hz, C(8)*H*H), 3.70 (1H, dd, *J* = 11.4, 2.6 Hz, C(9)*H*H), 3.66 – 3.56 (1H, m, C(10)*H*), 3.41 (1H, dd, *J* = 11.4, 10.3 Hz, C(8)H*H*), 3.31 (1H, dd, *J* = 11.5, 10.1 Hz, C(9)H*H*), 3.20 (1H, dd, *J* = 16.3, 6.6 Hz, C(6)*H*H), 2.82 (1H, dd, *J* = 16.3, 5.9 Hz, C(6)H*H*), 2.41 (3H, s, SC(1)H_3), 1.06 (3H, d, *J* = 6.3 Hz, C(11)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 198.2, 142.6, 134.5, 132.4, 130.5, 125.3, 123.6, 72.6, 71.5, 71.1, 71.0, 42.2, 16.8, 16.1; **ν_{max}**/ cm^{-1} (neat) 2972, 2898, 2361, 1671, 1434, 1276, 1100, 753, 645; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{19}O_3{}^{32}S^+$ calc. 267.1049, found 267.1049.

2-((2*R,5*S**)-5-Butyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3q)**

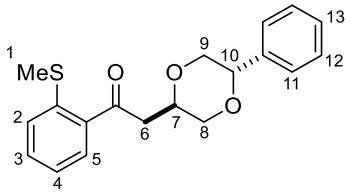


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and the 9:1 inseparable mixture of 2-(prop-2-yn-1-yloxy)hexan-1-ol **2h** and 2-(allyloxy)hexan-1-ol **51** (62 mg, 0.400 mmol, 1.33 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (10:1 dr) by column chromatography (1:13 to 1:9 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3q** (78.1 mg, 0.253 mmol, 85%) as an off-white powdered solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.81 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.50 – 7.42 (1H, m, *Ar*), 7.35 – 7.28 (1H, m, *Ar*), 7.19 (1H, ddd, *J* = 8.3, 7.3, 1.2 Hz, *Ar*), 4.14 (1H, dddd, *J* = 10.3, 6.6, 5.7, 2.6 Hz, C(7)*H*), 3.93 (1H, dd, *J* = 11.3, 2.6 Hz, C(8)*H*H), 3.73 (1H, dd, *J* = 11.3, 2.2 Hz, C(9)*H*H), 3.50 – 3.42 (1H, m, C(10)*H*), 3.37 (1H, dd, *J* = 11.2, 10.2 Hz, C(9)H*H*), 3.36 (1H, dd, *J* = 18.5, 11.3 Hz, C(8)H*H*), 3.20 (1H, dd, *J* = 16.2, 6.7 Hz, C(6)*H*H), 2.83 (1H, dd, *J* = 16.2, 5.8 Hz, C(6)H*H*), 2.43 (3H, s, SC(1)H_3), 1.46 – 1.21 (6H, m, C(11, 12 and 13)H_2), 0.98 – 0.78 (3H, m, C(14)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 198.3, 142.7, 134.7, 132.4, 130.6, 125.3, 123.7, 75.1, 71.9, 71.7, 71.1, 42.3, 31.3, 27.4, 22.9, 16.1, 14.1; **ν_{max}**/ cm^{-1} (neat) 3019, 2929, 2856, 2360, 1671, 1587, 1558, 1463, 1433, 1354, 1274,

1197, 1136, 1103, 1045, 982, 925, 850, 752, 697, 665, 648; **m/z HRMS** (ESI^+) [M + H]$^+$ $C_{17}H_{25}O_3{}^{32}S^+$ calc. 309.1524, found 309.1515.

1-(2-(Methylthio)phenyl)-2-((2*R,5*S**)-5-phenyl-1,4-dioxan-2-yl)ethan-1-one (3r)**

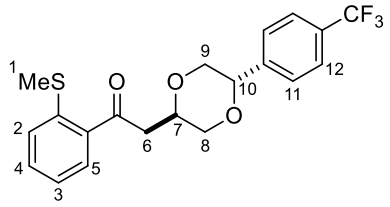


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-phenyl-2-(prop-2-yn-1-yloxy)ethan-1-ol **2j** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (11:1 dr) by column chromatography (1:19 to 1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3r** (83.5 mg, 0.255 mmol, 85%) as an off-white powdered solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.86 (1H, dd, *J* = 7.8, 1.5 Hz, *Ar*), 7.49 (1H, ddd, *J* = 8.5, 7.2, 1.5 Hz, *Ar*), 7.43 – 7.27 (6H, m, *Ar*), 7.21 (1H, ddd, *J* = 8.2, 7.6, 1.2 Hz, *Ar*), 4.58 (1H, dd, *J* = 10.4, 2.8 Hz, C(10)*H*), 4.32 (1H, m, C(7)*H*), 4.15 (1H, dd, *J* = 11.6, 2.6 Hz, C(8)*H*H), 3.88 (1H, dd, *J* = 11.7, 2.7 Hz, C(9)*H*H), 3.61 (1H, dd, *J* = 11.5, 10.4 Hz, C(8)H*H*), 3.57 (1H, dd, *J* = 11.7, 10.4 Hz, C(9)H*H*), 3.30 (1H, dd, *J* = 16.5, 6.4 Hz, C(6)*H*H), 2.93 (1H, dd, *J* = 16.4, 6.1 Hz, C(6)H*H*), 2.44 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 198.1, 142.8, 138.1, 134.5, 132.6, 130.6, 128.6, 128.3, 126.4, 125.4, 123.7, 77.7, 72.8, 71.8, 71.3, 42.2,

16.2; ν_{max}/ cm^{-1} (neat) 2958, 2898, 2860, 1671, 1433, 1104, 753, 699; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{21}O_3{}^{32}S^+$ calc. 329.1206, found 329.1204.

1-(2-(Methylthio)phenyl)-2-((2*R,5*S**)-5-(4-(trifluoromethyl)phenyl)-1,4-dioxan-2-yl)ethan-1-one (3s)**

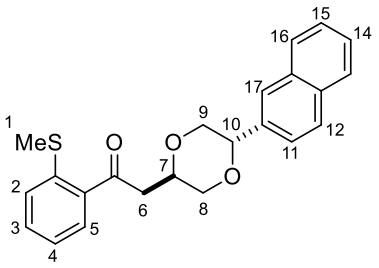


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-(prop-2-yn-1-yloxy)-2-(4-(trifluoromethyl)phenyl)ethan-1-ol **2l** (88 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (7:1 dr) by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3s** (91.9 mg, 0.232 mmol, 77%) as an off-white powdered solid.

δ_F (377 MHz, $CDCl_3$) (major signals only) –62.59 (C*F*$_3$); **δ_H** (400 MHz, $CDCl_3$) (major signals only) 7.88 – 7.82 (1H, m, *Ar*), 7.64 – 7.57 (2H, m, *Ar*), 7.55 – 7.44 (3H, m, *Ar*), 7.34 (1H, dd, *J* = 8.2, 1.1 Hz, *Ar*), 7.21 (1H, ddd, *J* = 7.8, 7.2 1.1 Hz, *Ar*), 4.63 (1H, dd, *J* = 10.4, 2.8 Hz, C(10)*H*), 4.35 – 4.26 (1H, m, C(7)*H*), 4.17 (1H, dd, *J* = 11.5, 2.6 Hz, C(8)*H*H), 3.89 (1H, dd, *J* = 11.8, 2.9 Hz, C(9)*H*H), 3.61 (1H, dd, *J* = 11.5, 10.3 Hz, C(8)H*H*), 3.50 (1H, dd, *J* = 11.7, 10.3 Hz, C(9)H*H*), 3.29 (1H, dd, *J* = 16.6, 6.3 Hz, C(6)*H*H), 2.94 (1H, dd, *J* = 16.5, 6.1 Hz, C(6)H*H*), 2.44 (3H, s, C(1)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 197.9, 142.8, 142.1, 134.4,

132.6, 130.6, 130.3 (q, J_{CF} = 32.2 Hz), 126.6, 125.5 (q, J_{CF} = 3.7 Hz), 125.3, 124.2 (q, J_{CF} = 272.0 Hz), 123.7, 76.8, 72.6, 71.8, 71.2, 42.1, 16.1; ν_{max}/ cm^{-1} (neat) 2891, 1670, 1621, 1588, 1558, 1463, 1434, 1323, 1271, 1163, 1109, 1067, 1018, 981, 926, 908, 839, 751, 697, 680, 652, 609; **m/z HRMS** (ESI^+) $[M + H]^+$, $C_{20}H_{20}O_3F_3{}^{32}S^+$ calc. 397.1091, found 397.1079.

1-(2-(Methylthio)phenyl)-2-((2*R,5*S**)-5-(naphthalen-2-yl)-1,4-dioxan-2-yl)ethan-1-one (3t)**

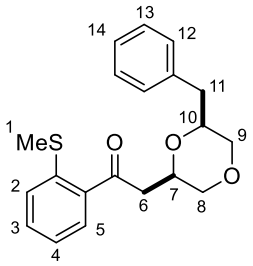


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 2-(naphthalen-2-yl)-2-(prop-2-yn-1-yloxy)ethan-1-ol **2k** (81 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.60 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.30 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (6:1 dr) by column chromatography (1:12 to 1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3t** (85.0 mg, 0.225 mmol, 75%) as an off-white powdered solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.90 – 7.79 (5H, m, *Ar*), 7.53 – 7.42 (4H, m, *Ar*), 7.38 – 7.32 (1H, m, *Ar*), 7.22 (1H, ddd, *J* = 7.8, 7.2, 1.2 Hz, *Ar*), 4.75 (1H, dd, *J* = 10.4, 2.8 Hz, C(10)*H*), 4.37 (1H, m, C(7)*H*), 4.21 (1H, dd, *J* = 11.5, 2.6 Hz, C(8)*H*H), 3.98 (1H, dd, *J* = 11.7, 2.8 Hz, C(9)*H*H), 3.68 (1H, dd, *J* = 11.2, 9.1 Hz,

C(8)H*H*), 3.65 (1H, dd, *J* = 11.7, 10.4 Hz, C(9)H*H*), 3.32 (1H, dd, *J* = 16.4, 6.4 Hz, C(6)*H*H), 2.96 (1H, dd, *J* = 16.4, 6.1 Hz, C(6)H*H*), 2.45 (3H, s, SC(1)H_3); **δc** (101 MHz, $CDCl_3$) (major signals only) 198.1, 142.8, 135.6, 134.5, 133.3, 133.2, 132.5, 130.6, 128.3, 128.1, 127.8, 126.3, 126.1, 125.4, 125.3, 124.2, 123.7, 77.7, 72.8, 71.8, 71.3, 42.2, 16.1; ν_{max}/ cm^{-1} (neat) 2851, 1669, 1587, 1556, 1463, 1433, 1357, 1341, 1274, 1198, 1102, 820, 748; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{23}H_{23}O_3{}^{32}S^+$ calc. 379.1362, found 379.1364.

2-((2*R,6*S**)-6-Benzyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3u)**

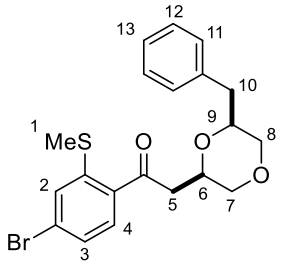


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol **2m** (69 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (11:1 dr) by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3u** (80.1 mg, 0.234 mmol, 78%) as a viscous yellow oil.

δH (400 MHz, $CDCl_3$) (major signals only) 7.81 – 7.76 (1H, m, *Ar*), 7.46 (1H, ddd, *J* = 8.5, 7.2, 1.5 Hz, *Ar*), 7.31 (1H, dd, *J* = 8.2, 1.1 Hz, *Ar*), 7.28 – 7.11 (6H, m, *Ar*),

4.26 – 4.18 (1H, m, C(7)*H*), 3.90 (1H, dd, *J* = 11.1, 2.5 Hz, C(8)*H*H), 3.88 – 3.82 (1H, m, C(10)*H*), 3.68 (1H, dd, *J* = 11.5, 2.6 Hz, C(9)*H*H), 3.26 (1H, dd, *J* = 11.3, 10.3 Hz, C(8)H*H*), 3.23 (1H, dd, *J* = 11.6, 10.7 Hz, C(9)H*H*), 3.22 (1H, dd, *J* = 16.2, 6.1 Hz, C(6)*H*H), 2.88 (1H, dd, *J* = 16.2, 6.3 Hz, C(6)H*H*), 2.78 (1H, dd, *J* = 14.0, 6.8 Hz, C(11)*H*H), 2.56 (1H, dd, *J* = 14.0, 6.5 Hz, C(11)H*H*), 2.42 (3H, s, SC(1)H_3); **δC** (101 MHz, $CDCl_3$) (major signals only) 198.4, 142.5, 137.4, 134.7, 132.4, 130.7, 129.3, 128.4, 126.5, 125.3, 123.6, 76.3, 72.5, 70.5, 70.4, 42.5, 38.4, 16.1; **ν_{max}**/ cm^{-1} (neat) 3028, 2917, 2851, 1670, 1433, 1119, 753, 701; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{23}O_3{}^{32}S^+$ calc. 343.1362, found 343.1358.

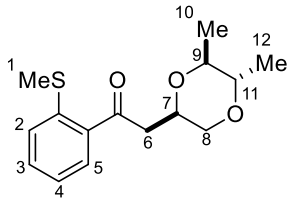
2-((2*R,6*S**)-6-Benzyl-1,4-dioxan-2-yl)-1-(4-bromo-2-(methylthio)phenyl)ethan-1-one (3v)**



Following **general procedures H** and **I**. **General procedure H** used 4-bromo-2-(methylthio)benzaldehyde **1c** (46 mg, 0.200 mmol, 1.00 equiv.) and 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol **2m** (46 mg, 0.240 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (3.7 mg, 0.010 mmol, 0.050 equiv.), dcpe (4.2 mg, 0.01 mmol, 0.050 equiv.) and DCE (0.2 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.100 mL, 0.400 mmol, 2.00 equiv.) and DCE (2.7 mL). Purification of the crude residue (3.5:1 dr) by column chromatography (1:9 to 1:5 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3v** (59.5 mg, 0.142 mmol, 71%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.64 (1H, d, *J* = 8.3 Hz, *Ar*), 7.41 (1H, d, *J* = 1.7 Hz, *Ar*), 7.31 – 7.16 (5H m, *Ar*), 7.13 (1H, app d, *J* = 7.6 Hz, *Ar*), 4.23 – 4.13 (1H, m, C(6)*H*), 3.83 – 3.74 (2H, m, C(7)*H*H and C(9)*H*), 3.61 (1H, dd, *J* = 11.5, 2.5 Hz, C(8)*H*H), 3.23 – 3.12 (2H, m, C(7)H*H* and C(8)H*H*), 3.16 (1H, dd, *J* = 16.1, 6.5 Hz, C(5)*H*H), 2.74 (1H, dd, *J* = 16.0, 6.1 Hz, C(5)H*H*), 2.76 (1H, dd, *J* = 14.0, 7.0 Hz, C(10)*H*H), 2.63 – 2.52 (1H, dd, *J* = 14.1, 6.2 Hz, C(10)H*H*), 2.42 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 197.7, 145.1, 137.3, 133.1, 132.0, 129.3, 128.4, 127.9, 127.8, 126.6, 126.5, 76.4, 72.5, 70.4, 70.4, 42.4, 38.4, 16.2; **ν_{max}**/ cm^{-1} (neat) 2981, 1723, 1670, 1609, 1521, 1347, 1237, 1091, 733, 670; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{22}O_3{}^{79}Br^{32}S^+$ calc. 421.0468, found 421.0468, $C_{20}H_{22}O_3{}^{81}Br^{32}S^+$ calc. 423.0447, found 423.0446.

2-((2*R,5*S**,6*S**)-5,6-Dimethyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3w)**

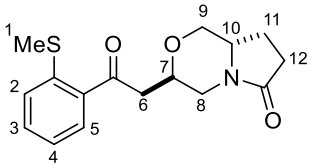


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and (2*S**,3*S**)-3-(prop-2-yn-1-yloxy)butan-2-ol **2i** (46 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (16:1 dr) by column chromatography (1:12 to 1:5 EtOAc:Petrol)

yielded the title compound as an inseparable mixture of diastereoisomers **3w** (66.2 mg, 0.236 mmol, 79%) as an off-white solid.

δ_H (400 MHz, $CDCl_3$) (major signals only) 7.81 (1H, ddd, *J* = 11.7, 7.9, 1.4 Hz, *Ar*), 7.49 – 7.41 (1H, m, *Ar*), 7.31 (1H, app d, *J* = 8.0 Hz, *Ar*), 7.17 (1H, app td, *J* = 7.9, 1.1 Hz, *Ar*), 4.21 (1H, app dtd, *J* = 10.2, 6.3, 2.6 Hz, C(7)*H*), 3.92 (1H, dd, *J* = 11.2, 2.6 Hz, C(8)*H*H), 3.42 – 3.28 (2H, m, C(8)H*H* and C(9)*H*), 3.22 (1H, dd, *J* = 16.3, 6.3 Hz, C(6)*H*H), 3.19 – 3.14 (1H, m, C(11)*H*), 2.83 (1H, dd, *J* = 16.3, 6.5 Hz, C(6)H*H*), 2.41 (3H, s, C(1)H_3), 1.09 (3H, d, *J* = 6.3 Hz, C(12)H_3), 1.07 (3H, d, *J* = 6.3 Hz, C(10)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 198.3, 142.5, 134.7, 132.4, 130.5, 125.3, 123.6, 77.4, 76.7, 72.0, 71.1, 42.6, 17.5, 17.3, 16.1; **ν_{max}**/ cm^{-1} (neat) 2975, 2851, 1670, 1587, 1558, 1433, 1381, 1360, 1278, 1201, 1108, 944, 753; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{21}O_3{}^{32}S^+$ calc. 281.1206, found 281.1207.

(3*R,8a*S**)-3-(2-(2-(Methylthio)phenyl)-2-oxoethyl)hexahydro-6H-pyrrolo[2,1-c][1,4]oxazin-6-one (3x)**

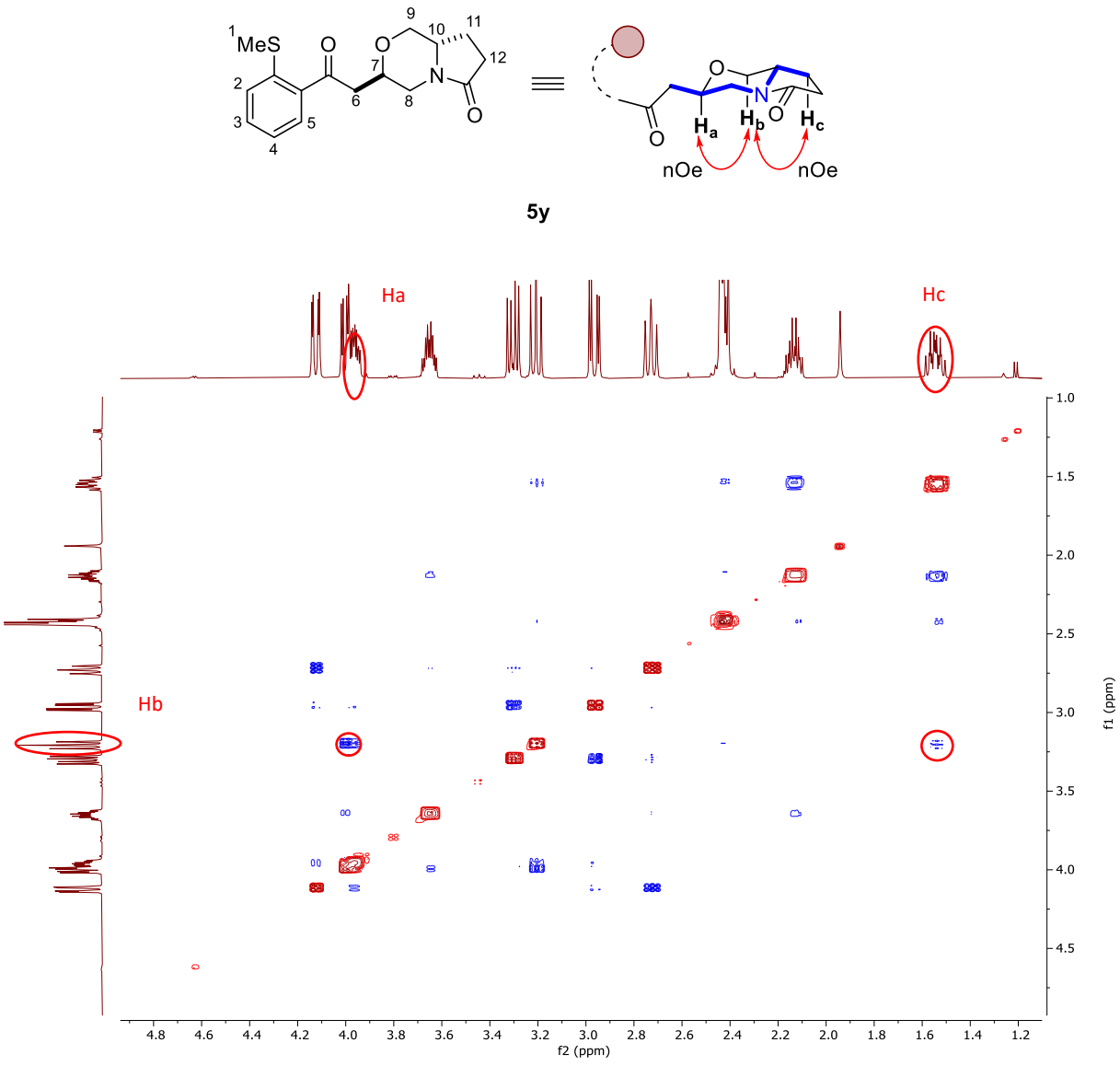


Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 5-(hydroxymethyl)-1-(prop-2-yn-1-yl)pyrrolidin-2-one **2o** (55 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (>20:1 dr) by column chromatography (1:0:99 to 1:5:94 IPA:MeOH:CH_2Cl_2) yielded the title compound as a single diastereoisomer **3x** (58.1 mg, 0.190 mmol, 63%) as an off-white solid.

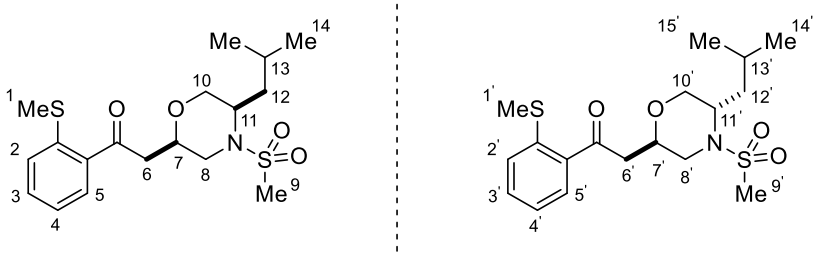
m.p. (CH_2Cl_2) 74 – 77 °C; **δ_H** (400 MHz, $CDCl_3$) 7.78 (1H, dd, *J* = 8.0, 1.5 Hz, *Ar*), 7.45 (1H, ddd, *J* = 8.2, 7.3, 1.5 Hz, *Ar*), 7.31 (1H, dd, *J* = 8.2, 1.1 Hz, *Ar*), 7.17 (1H, ddd, *J* = 8.2, 7.3, 1.2 Hz, *Ar*), 4.10 (1H, dd, *J* = 13.0, 2.9 Hz, C(8)*H*H), 4.00 – 3.95 (1H, dd, *J* = 11.1, 3.5 Hz, C(9)*H*H), 3.98 – 3.89 (1H, m, C(7)*H*), 3.68 – 3.53 (1H, m, C(10)*H*), 3.27 (1H, dd, *J* = 16.3, 7.5 Hz, C(6)*H*H), 3.22 – 3.12 (1H, app t, *J* = 11.0 Hz, C(9)H*H*), 2.93 (1H, dd, *J* = 16.3, 4.6 Hz, C(6)H*H*), 2.74 – 2.66 (1H, m, C(8)H*H*), 2.42 – 2.36 (2H, m, C(12)H_2), 2.41 (3H, s, SC(1)H_3), 2.15 – 2.05 (1H, m, C(11)*H*H), 1.57 – 1.46 (1H, m, C(11)H*H*); **δ_C** (101 MHz, $CDCl_3$) 197.5, 173.2, 142.7, 134.5, 132.4, 130.4, 125.4, 123.6, 72.8, 72.1, 54.5, 44.7, 43.3, 30.3, 20.6, 16.1; **ν_{max}**/ cm^{-1} (neat) 2917, 1668, 1587, 1558, 1433, 1353, 1302, 1267, 1190, 1102,

979, 915, 727, 650; **m/z HRMS** (ESI$^+$) $[M + H]^+$ $C_{16}H_{20}O_3N^{32}S^+$ calc. 306.1158, found 306.1158.

NOESY spectrum of 3x:



2-((2*R,5*R**)-5-Isobutyl-4-(methylsulfonyl)morpholin-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3y) and 2-((2*R**,5*S**)-5-isobutyl-4-(methylsulfonyl)morpholin-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3y')**



3y **3y'**

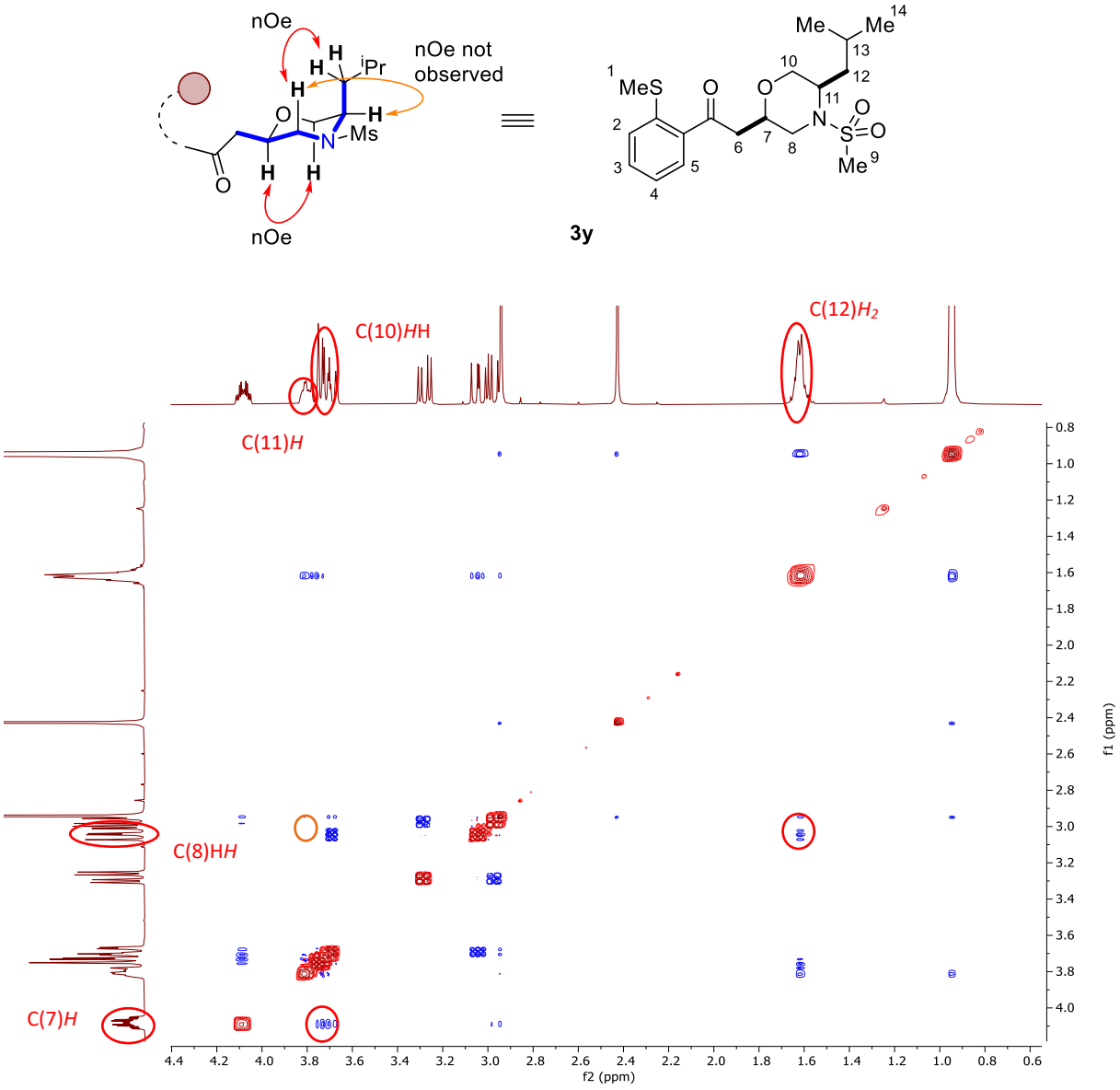
Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and *N*-(1-hydroxy-4-methylpentan-2-yl)-*N*-(prop-2-yn-1-yl)methanesulfonamide **2n** (84 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (2.8:1 dr) by column chromatography (CH_2Cl_2) yielded major diastereoisomer **3y** (55.9 mg, 0.145 mmol, 48%), and minor diastereoisomer **3y'** (15.7 mg, 0.041 mmol, 14%) as a colourless viscous oil and a white solid, respectively.

3y: δ_H (400 MHz, $CDCl_3$) 7.79 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.47 (1H, ddd, *J* = 8.6, 7.2, 1.5 Hz, *Ar*), 7.33 (1H, dd, *J* = 8.2, 1.1 Hz, *Ar*), 7.19 (1H, ddd, *J* = 8.3, 7.6, 1.1 Hz, *Ar*), 4.12 – 4.04 (1H, m, C(7)*H*), 3.84 – 3.77 (1H, m, C(11)*H*), 3.76 (1H, dd, *J* = 11.9, 1.1 Hz, C(10)*H*H), 3.71 (1H, dd, *J* = 11.7, 2.9 Hz, C(10)H*H*), 3.68 (1H, app dd, *J* = 13.6, 2.8 Hz, C(8)*H*H), 3.28 (1H, dd, *J* = 16.7, 6.2 Hz, C(6)*H*H), 3.04 (1H, dd, *J* = 13.7, 11.1 Hz, C(8)H*H*), 2.97 (1H, dd, *J* = 16.7, 6.0 Hz, C(6)H*H*), 2.94 (3H,

s, C(9)*H*$_3$), 2.43 (3H, s, C(1)*H*$_3$), 1.66 – 1.57 (3H, m, C(12)*H*$_2$ and C(13)*H*), 0.98 – 0.91 (6H, m, C(14)*H*$_3$); **δC** (101 MHz, $CDCl_3$) 197.6, 142.8, 134.4, 132.6, 130.5, 125.4, 123.7, 72.4, 69.7, 51.0, 44.9, 43.5, 40.9, 37.8, 25.0, 22.8, 22.5, 16.1; **ν_{max}**/ cm^{-1} (neat) 1669, 1587, 1558, 1464, 1433, 1327, 1278, 1205, 1149, 1100, 1073, 1045, 969, 912, 853, 776, 732, 694, 650; **m/z HRMS** (ESI^+) [M + Na]$^+$ $C_{18}H_{27}O_4N^{23}Na^{32}S_2^+$ calc. 408.1274, found 408.1275.

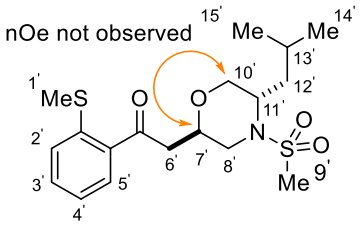
3y': **m.p.** (CH_2Cl_2) 115 – 118 °C; **δH** (400 MHz, $CDCl_3$) 7.87 (1H, app dd, *J* = 7.9, 1.5 Hz, *Ar*), 7.49 (1H, app ddd, *J* = 8.5, 7.3, 1.5 Hz, *Ar*), 7.34 (1H, dd, *J* = 7.7 Hz, 1H), 7.24 (1H, app td, *J* = 7.5, 1.2 Hz, *Ar*), 4.21 – 4.10 (2H, m, C(7')*H* and C(8')*H*), 4.09 – 4.00 (1H, m, C(11')*H*), 3.99 – 3.88 (2H, m, C(10' and 8')H*H*), 3.82 (1H, dd, *J* = 15.5, 3.8 Hz, C(6')*H*H), 3.61 – 3.52 (2H, m, C(6' and 10')H*H*), 2.96 (3H, s, C(14' or 15')*H*$_3$), 2.43 (3H, s, C(14' or 15')*H*$_3$), 1.64 – 1.50 (2H, m, C(12')*H*H and C(13')*H*), 1.43 – 1.35 (1H, m, C(12')H*H*), 0.99 – 0.92 (6H, m, C(14')*H*$_3$); **δC** (101 MHz, $CDCl_3$) 200.4, 143.0, 134.0, 132.8, 130.5, 125.7, 124.1, 76.8, 74.2, 56.0, 50.5, 43.2, 40.7, 39.7, 24.7, 22.8, 22.8, 16.3; **ν_{max}**/ cm^{-1} (neat) 2953, 2924, 1663, 1587, 1558, 1463, 1434, 1325, 1208, 1099, 1049, 972, 771, 742; **m/z HRMS** (ESI^+) [M + H]$^+$ $C_{18}H_{28}O_4N^{32}S_2^+$ calc. 386.1454, found 386.1456.

NOESY spectrum of 3y:

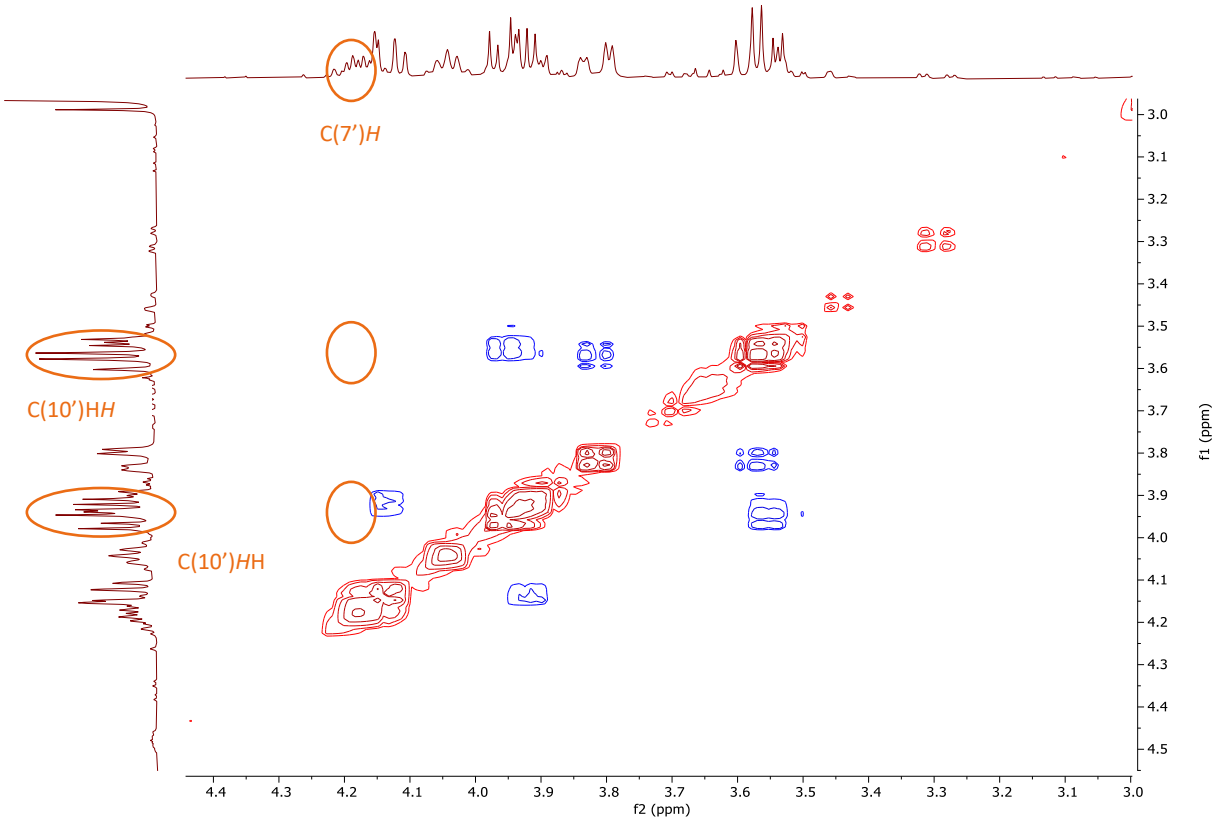


From the NOESY spectrum of **3y** (above), we believe that two key NOESY interactions occur, firstly between C(10)*H*H (3.76 ppm) and C(7)*H* (4.04 ppm) environments, and also between C(8)H*H* (3.04 ppm) and C(12)H_2 (1.66 – 1.57 ppm) environments. Alongside the absence of a NOESY interaction between C(8)*H*H and C(11)*H*, this suggests a *syn* relative configuration is present. For the NOESY spectrum of minor *anti* diastereomer **3y'**, neither of the C(7')*H* - C(10')*H*H or C(8')H*H* - C(12')H_2 interactions were clearly observable (shown below).

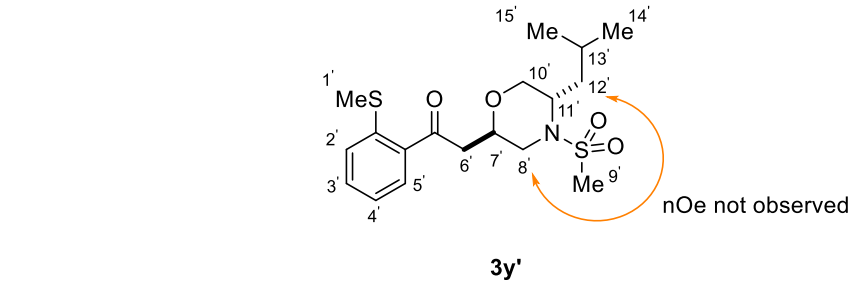
Absence of the C(7')*H* - C(10')*H*H interaction in 3y':



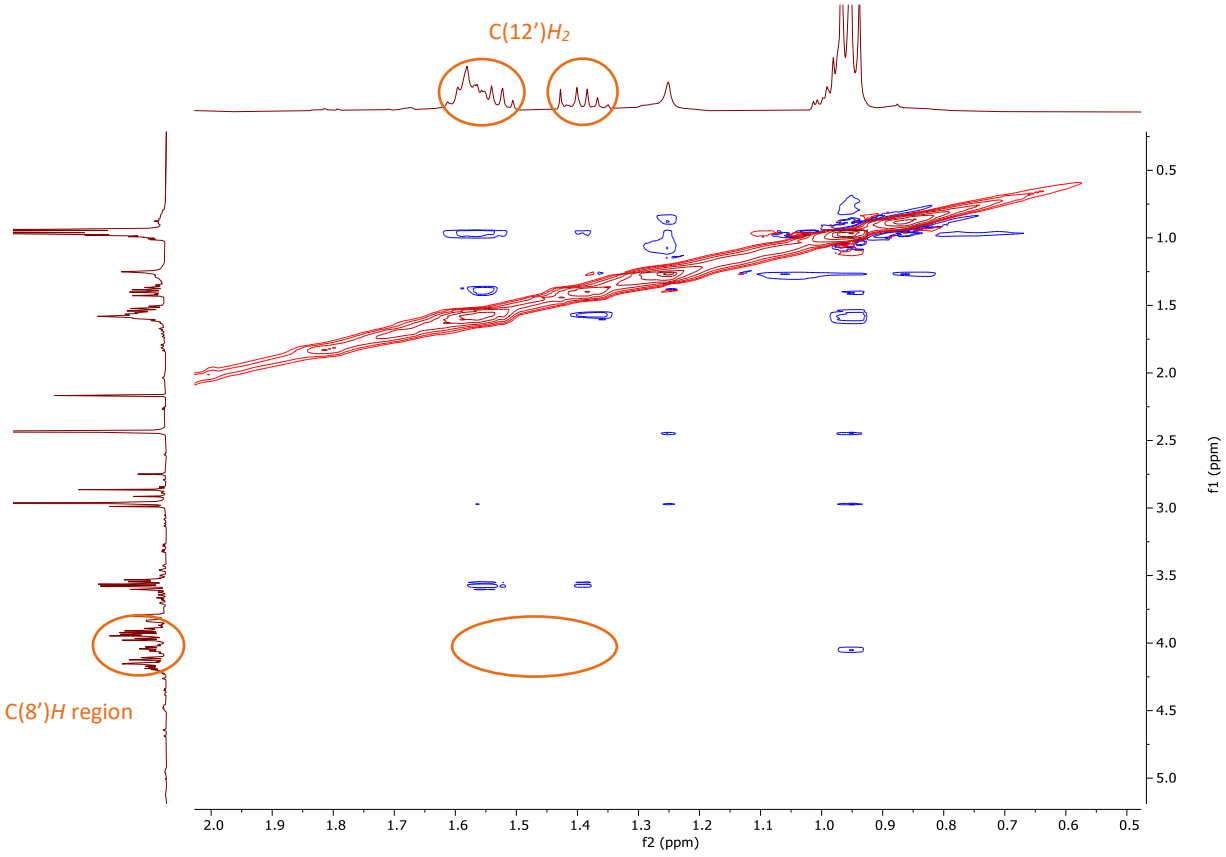
3y'



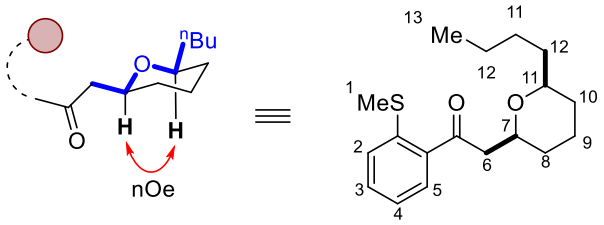
Absence of the C(8')*H*H - C(12')*H* interaction in 3y':



3y'



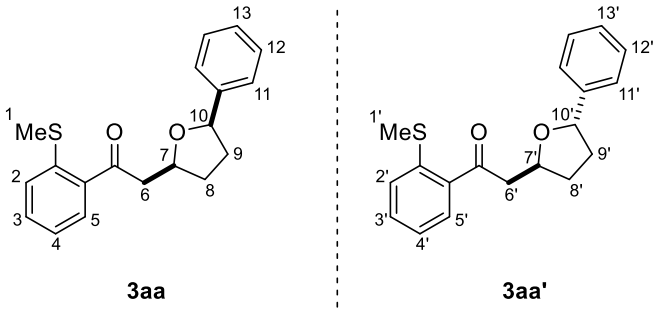
2-((2*S,6*S**)-6-Butyltetrahydro-2*H*-pyran-2-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3z)**



Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and dec-9-yn-5-ol **2q** (56 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.60 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.30 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (>20:1 dr) by column chromatography (1:49 to 1:24 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3z** (56.8 mg, 0.187 mmol, 62%) as an off-white solid.

m.p. (CH_2Cl_2) 73 – 76 °C; **δ_H** (400 MHz, $CDCl_3$) 7.86 (1H, dd, *J* = 7.8, 1.4 Hz, *Ar*), 7.43 (1H, ddd, *J* = 8.7, 7.3, 1.5 Hz, *Ar*), 7.30 (1H, m, *Ar*), 7.16 (1H, app td, *J* = 7.8, 1.1 Hz, *Ar*), 3.99 – 3.85 (1H, m, C(7)*H*), 3.34 – 3.16 (2H, m, C(11)*H* and C(6)*H*H), 2.91 (1H, dd, *J* = 15.7, 6.2 Hz, C(6)H*H*), 2.41 (3H, s, C(1)H_3), 1.85 – 1.77 (1H, m, C(9)*H*H), 1.77 – 1.68 (1H, m, C(8)*H*H), 1.62 – 1.10 (10H, m, C(8 and 9)H*H*, C(10, 12, 13 and 14)H_2), 0.85 (3H, m, C(15)H_3); **δ_C** (101 MHz, $CDCl_3$) 200.0, 142.2, 135.3, 132.1, 130.8, 125.1, 123.5, 78.2, 74.8, 47.2, 36.3, 31.9, 31.5, 27.8, 23.7, 22.8, 16.1, 14.2; **ν_{max}**/ cm^{-1} (neat) 2930, 2858, 1670, 1587, 1559, 1462, 1433, 1372, 1344, 1280, 1194, 1067, 1046, 986; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{18}H_{26}O_2{}^{23}Na{}^{32}S^+$ calc. 329.1546, found 329.1542.

1-(2-(methylthio)phenyl)-2-((2*R,5*S**)-5-phenyltetrahydrofuran-2-yl)ethan-1-one (3aa) and 1-(2-(methylthio)phenyl)-2-((2*R**,5*R**)-5-phenyltetrahydrofuran-2-yl)ethan-1-one (3aa')**

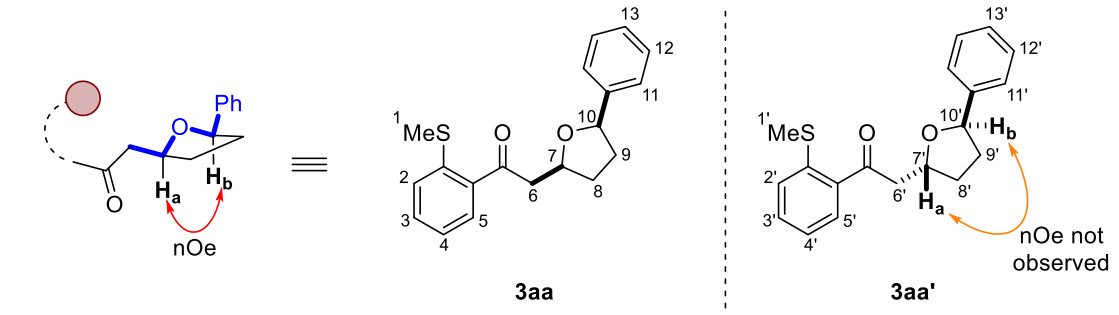


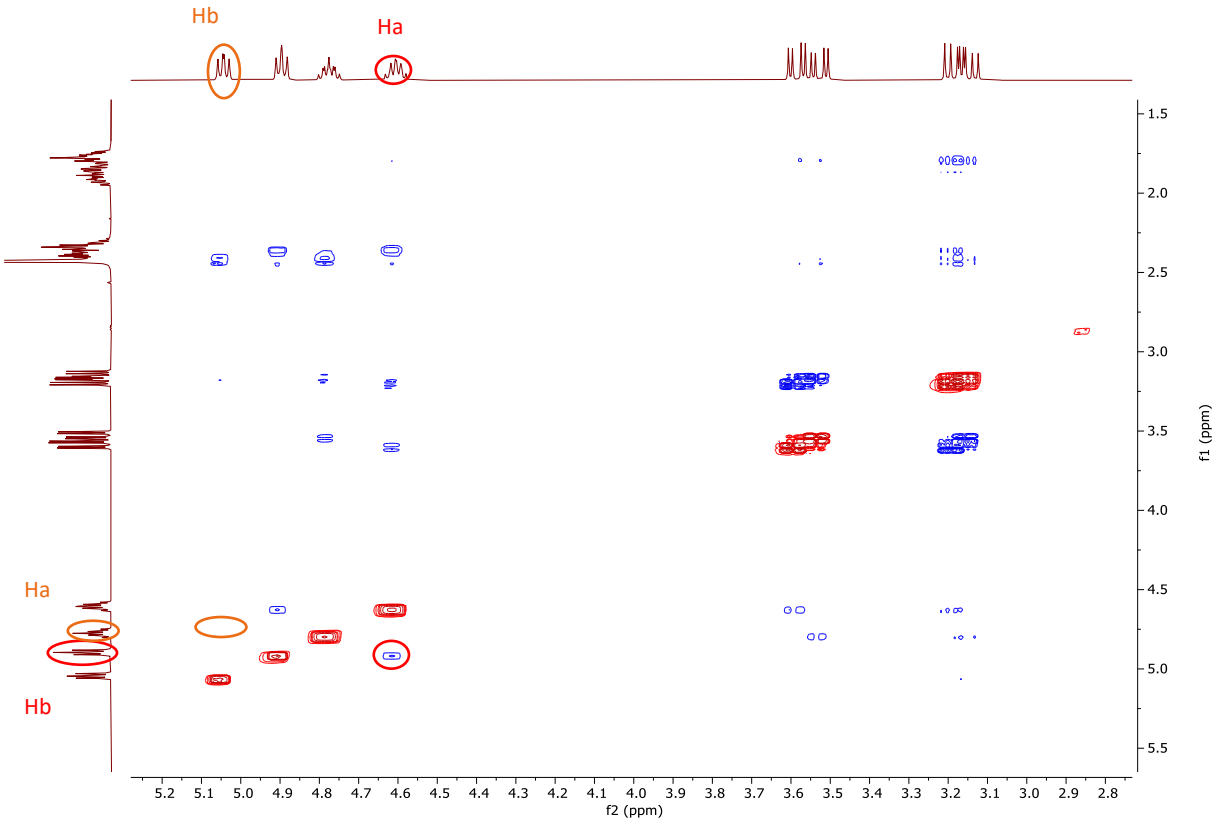
Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and 1-phenylpent-4-yn-1-ol **2r** (58 mg, 0.360 mmol, 1.20 equiv.), with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.30 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (1:1 dr) by column chromatography (1:19 to 1:9 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3aa** and **3aa'** (73.6 mg, 0.236 mmol, 79%) as an off white solid.

δ_H (400 MHz, $CDCl_3$) (1:1 mixture) 7.92 – 7.87 (2H, m, *Ar*), 7.50 – 7.44 (2H, m, *Ar*), 7.36 – 7.29 (10H, m, *Ar*), 7.28 – 7.17 (4H, m, *Ar*), 5.04 (1H, dd, *J* = 8.0, 6.1 Hz, C(10')*H*), 4.90 (1H, t, *J* = 7.0 Hz, C(10)*H*), 4.82 – 4.73 (1H, m, C(7')*H*), 4.66 – 4.55 (1H, m, C(7)*H*), 3.59 (1H, dd, *J* = 16.3, 5.3 Hz, C(6)*H*H), 3.53 (1H, dd, *J* = 16.2, 5.4 Hz, C(6')*H*H), 3.18 (1H, dd, *J* = 16.3, 7.7 Hz, C(6)H*H*), 3.15 (1H, dd, *J* = 16.2, 7.5 Hz, C(6')*H*), 2.43 (3H, s, C(1 or 1')H_3), 2.43 (3H, s, C(1 or 1')H_3), 2.42 – 2.28 (4H, m, C(8 and 9)*H*H, C(8' and 9')*H*H), 1.97 – 1.71 (4H, m, C(8 and 9)H*H*, C(8' and 9')H*H*); **δ_C** (101 MHz, $CDCl_3$) (1:1 mixture) 199.5, 199.4, 143.6, 143.0,

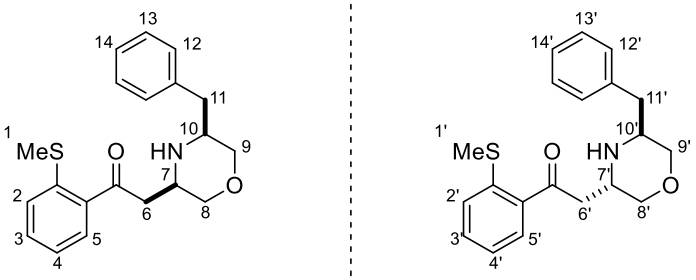
142.6, 142.5, 134.6, 134.5, 132.3, 132.3, 130.7, 130.6, 128.4, 128.3, 127.2, 127.2, 125.8, 125.6, 125.1 (2C), 123.6, 123.5, 80.8, 80.4, 76.4, 76.3, 46.4, 46.3, 35.3, 34.2, 32.7, 31.7, 16.0 (2C); ν_{max}/ cm^{-1} (neat) 3650, 2980, 1668, 1586, 1557, 1493, 1462, 1433, 1382, 1270, 1082, 1054, 985, 951, 752, 700; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{21}O_2{}^{32}S^+$ calc. 313.1258, found 313.1257.

NOESY spectrum of the 1:1 mixture 3aa and 3aa':





2-((3*R,6*S**)-5-Benzylmorpholin-3-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3ab) and 2-((3*R**,6*R**)-5-benzylmorpholin-3-yl)-1-(2-(methylthio)phenyl)ethan-1-one (3ab')**



3ab **3ab'**

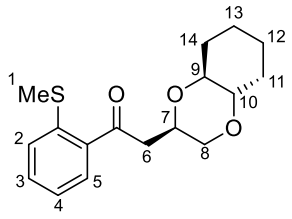
Following **general procedures H** and **J**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and *tert*-butyl (1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-yl)carbamate **2p** (104 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure J** used *p*-$TsOH{\cdot}H_2O$ (114 mg, 0.600 mmol, 2.00 equiv.) and DCE (4.0 ml). Purification of the crude residue (2.4:1 dr) by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded major diastereoisomer **3ab** (33.4 mg, 0.098 mmol, 33%) as an off-white solid and minor diastereoisomer **3ab'** (17.6 mg, 0.052 mmol, 17%, containing 15% **3ab** by ^{1}H NMR integration) as a yellow viscous oil.

3ab: **m.p.** (CH_2Cl_2) 58 – 60 °C; **δ_H** (400 MHz, $CDCl_3$) 7.79 – 7.72 (1H, m, *Ar*), 7.51 – 7.42 (1H, m, *Ar*), 7.34 – 7.25 (3H, m, *Ar*), 7.24 – 7.14 (4H, m, *Ar*), 3.84 – 3.74 (2H, m, C(8 and 9)*H*H), 3.50 – 3.41 (1H, m, C(7)*H*), 3.28 – 3.13 (3H, m, C(8 and 9)H*H*, C(10)*H*), 2.97 – 2.86 (2H, m, C(6)H_2), 2.63 – 2.53 (2H, m, C(11)H_2), 2.42 (3H, s, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 199.5, 142.6, 137.7, 134.4, 132.6, 130.2,

129.2, 128.7, 126.6, 125.3, 123.7, 72.2, 71.5, 56.2, 51.5, 42.3, 39.4, 16.1; ν_{max}/ cm^{-1} (neat) 3323, 2847, 1667, 1587, 1558, 1454, 1433, 1107, 751, 701, 627; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{24}O_2N_{32}S^+$ calc. 342.1522, found 342.1520.

3ab': δ_H (400 MHz, $CDCl_3$) 7.77 (1H, dd, *J* = 7.9, 1.5 Hz, *Ar*'), 7.46 (1H, ddd, *J* = 8.6, 7.3, 1.5 Hz, *Ar*'), 7.35 – 7.25 (3H, m, *Ar*'), 7.25 – 7.13 (4H, m, *Ar*'), 3.85 (1H, dd, *J* = 11.1, 3.1 Hz, C(8')*H*H), 3.77 (1H, dd, *J* = 11.2, 3.1 Hz, C(9')*H*H), 3.73 (1H, dq, *J* = 4.9, 2.4 Hz, C(7')*H*), 3.57 (1H, dd, *J* = 11.1, 5.1 Hz, C(8')H*H*), 3.46 (1H, dd, *J* = 11.2, 6.5 Hz, C(9')H*H*), 3.31 – 3.11 (3H, m, C(6')H_2, C(10')*H*), 2.86 – 2.73 (2H, m, C(11')H_2), 2.42 (3H, s, C(1')H_3); δ_C (101 MHz, $CDCl_3$) 200.1, 142.5, 138.2, 134.6, 132.5, 130.3, 129.3, 128.8, 126.6, 125.3, 123.7, 71.2, 71.1, 52.0, 47.7, 41.1, 38.3, 16.1; ν_{max}/ cm^{-1} (neat) 3327, 2917, 2851, 1667, 1455, 1433, 1107, 751, 701; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{24}O_2N_{32}S^+$ calc. 342.1522, found 342.1519.

1-(2-(Methylthio)phenyl)-2-((7*R*,9*S*,10*S*)-(octahydrobenzo[b][1,4]dioxin-2-yl)ethan-1-one (3ac)



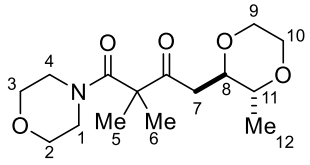
Following **general procedures H** and **I**. **General procedure H** used 2-(methylthio)benzaldehyde **1a** (40 μL, 0.300 mmol, 1.00 equiv.) and (1*S*,2*S*)-2-(prop-2-yn-1-yloxy)cyclohexan-1-ol **2s** (56 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (12:1 dr) by column chromatography (1:9 to 1:5 EtOAc:Petrol)

yielded the title compound as a single diastereoisomer **3ac** (78.4 mg, 0.256 mmol, 85%) as an off-white solid.

m.p. (CH_2Cl_2) 91 – 95 °C; **δ_H** (400 MHz, $CDCl_3$) 7.82 (1H, dd, *J* = 7.8, 1.5 Hz, *Ar*), 7.49 – 7.43 (1H, m, *Ar*), 7.32 (1H, dd, *J* = 8.2, 1.1 Hz, *Ar*), 7.18 (1H, ddd, *J* = 8.2, 7.3, 1.2 Hz, *Ar*), 4.29 (1H, dddd, *J* = 10.3, 6.6, 6.1 2.6 Hz, C(7)*H*), 3.97 (1H, dd, *J* = 11.3, 2.6 Hz, C(8)H*H*), 3.42 (1H, dd, *J* = 11.3, 10.3 Hz, C(8)H*H*), 3.26 (1H, dd, *J* = 16.6, 6.1 Hz, C(6)*H*H), 3.30 – 3.21 (1H, m, C(9)*H*), 3.14 – 3.05 (1H, m, C(10)*H*), 2.86 (1H, dd, *J* = 16.5, 6.6 Hz, C(6)H*H*), 2.42 (3H, s, SC(1)H_3), 1.94 – 1.79 (2H, m, C(11 and 14)*H*H), 1.76 – 1.64 (2H, m, C(12 and 13)*H*H), 1.38 – 1.18 (4H, m, C(11 and 14)H*H* and C(12 and 13)H*H*); **δ_C** (101 MHz, $CDCl_3$) 198.2, 142.7, 134.6, 132.4, 130.6, 125.3, 123.6, 80.1, 79.6, 72.3, 71.5, 42.6, 30.4, 30.2, 24.4, 24.3, 16.1; **ν_{max}**/ cm^{-1} (neat) 2935, 2862, 1671, 1587, 1558, 1433, 1355, 1272, 1211, 1099, 753, 644; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{17}H_{22}O_3{}^{23}Na^{32}S^+$ calc. 329.1182, found 329.1183; ***er*** was determined by HPLC using a Chiralpak OJ-H column (*n*-hexane:*i*-PrOH, 90:10, λ = 225 nm); $\mathbf{T}_{minor}$ = 18.99 min, $\mathbf{T}_{major}$ = 25.25 min (>99% *ee*); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +16.0° (c 0.25, $CHCl_3$).

6.2.4c Alkyne Scope with β-amido Aldehyde 1k

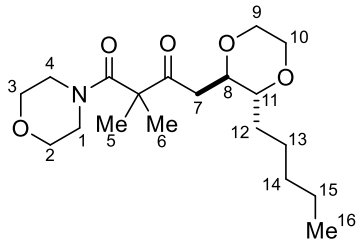
2,2-Dimethyl-4-((2*R,3*R**)-3-methyl-1,4-dioxan-2-yl)-1-morpholinobutane-1,3-dione (3ad)**



Following **general procedures H** and **I**. **Procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.300 mmol, 1.00 equiv.) and 2-(but-3-yn-2-yloxy)ethan-1-ol **2e** (41 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.05 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (8.3:1 dr) by column chromatography (1:2 to 1:1 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3ad** (80.1 mg, 0.268 mmol, 89%) as a pale-yellow viscous oil.

δ_H (500 MHz, $CDCl_3$) (major signals only) 3.81 – 3.07 (14H, m, C(1 to 4)H_2, C(9 and 10)H_2 and C(8 and 11)*H*), 2.61 (1H, dd, *J* = 16.9, 9.4 Hz, C(7)*H*H), 2.32 (1H, dd, *J* = 16.9, 2.4 Hz, C(7)*H*H), 1.33 (6H, d, *J* = 8.2 Hz, C(5 and 6)H_3), 1.04 (3H, d, *J* = 6.3 Hz, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.5, 170.9, 76.8, 74.8, 66.8, 66.7, 66.6 (bs, 2C), 56.2, 46.6 (bs), 43.4 (bs), 39.9, 23.8, 22.8, 17.5; **ν_{max}**/ cm^{-1} (neat) 2855, 1712, 1637, 1422, 1273, 1247, 1113, 923, 847; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{25}O_5N^{23}Na^+$ calc. 322.1625, found 322.1625.

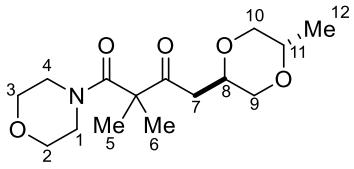
2,2-Dimethyl-1-morpholino-4-((2*R,3*R**)-3-pentyl-1,4-dioxan-2-yl)butane-1,3-dione (3ae)**



Following **general procedures H** and **I**. **General procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.300 mmol, 1.00 equiv.) and 2-(oct-1-yn-3-yloxy)ethan-1-ol **2f** (61 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (11:1 dr) by column chromatography (1:4 to 2:3 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3ae** (72.5 mg, 0.204 mmol, 68%) as an off-white solid.

m.p. (CH_2Cl_2) 59 – 62 °C; **δ_H** (400 MHz, $CDCl_3$) 3.84 – 3.77 (1H, m, C(8)*H*), 3.77 – 3.72 (1H, m, C(9)*H*H), 3.72 – 3.12 (11H, br., C(1 to 4)H_2, C(9)H*H* and C(10)H_2), 3.25 – 3.18 (1H, m, C(11)*H*), 2.64 (1H, dd, *J* = 16.8, 9.3 Hz, C(7)*H*H), 2.39 (1H, app d, *J* = 16.8 Hz, C(7)H*H*), 1.53 – 1.43 (1H, m, C(12 to 15)H_2), 1.38 (3H, s, C(5 or 6)H_3), 1.36 (3H, s, C(5 or 6)H_3), 1.41 - 1.15 (7H, m, C(12 to 15)H_{2f}), 0.88 (3H, app t, *J* = 7.3 Hz, C(16)H_3); **δ_C** (101 MHz, $CDCl_3$) 207.7, 171.0, 78.6, 75.5, 66.9, 66.7 (bs, 2C), 66.6, 56.3, 46.4 (bs), 43.3 (bs), 39.9, 32.0, 31.5, 24.8, 23.9, 22.9, 22.6, 14.1; **ν_{max}**/ cm^{-1} (neat) 2926, 2855, 1713, 1638, 1422, 1360, 1272, 1247, 1184, 1115, 1022, 927, 888, 847; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{34}O_5N^+$ calc. 356.2432, found 356.2434.

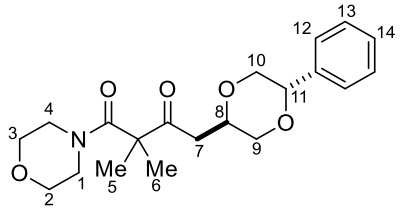
2,2-Dimethyl-4-((2*R,5*S**)-5-methyl-1,4-dioxan-2-yl)-1-morpholinobutane-1,3-dione (3af)**



Following **general procedures H** and **I**. **General procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.300 mmol, 1.00 equiv.) and 2-(prop-2-yn-1-yloxy)propan-1-ol **2g** (41 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (8:1 dr) by column chromatography (1:1 to 7:3 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3af** (80.3 mg, 0.269 mmol, 90%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) (major signals only) 4.00 (1H, m, C(8)*H*), 3.71 (1H, dd, *J* = 11.3, 2.5 Hz, C(9)*H*H), 3.66 – 3.05 (10H, m, C(1 to 4)H_2, C(10)*H*H and C(11)*H*), 3.30 (1H, dd, *J* = 11.3, 10.6 Hz, C(9)H*H*), 3.25 (1H, dd, *J* = 11.4, 10.3 Hz, C(10)H*H*), 2.62 (1H, dd, *J* = 17.1, 8.0 Hz, C(7)*H*H), 2.26 (1H, dd, *J* = 17.1, 4.1 Hz, C(7)H*H*), 1.33 (3H, s, C(5 or 6)H_3), 1.33 (3H, s, C(5 or 6)H_3), 1.03 (3H, d, *J* = 6.3 Hz, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.4, 170.9, 72.3, 71.1, 70.6, 70.5, 66.6 (bs, 2C), 56.1, 46.5 (bs), 43.3 (bs), 39.8, 23.7, 22.8, 16.7; **ν_{max}**/ cm^{-1} (neat) 2858, 1711, 1634, 1425, 1365, 1273, 1248, 1116, 1021, 908, 727, 648; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{15}H_{25}O_5N^{23}Na^+$ calc. 322.1625, found 322.1623.

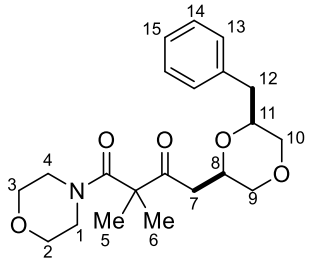
2,2-Dimethyl-1-morpholino-4-((2*R,5*S**)-5-phenyl-1,4-dioxan-2-yl)butane-1,3-dione (3ag)**



Following **general procedures H** and **I**. **General procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.300 mmol, 1.00 equiv.) and 2-phenyl-2-(prop-2-yn-1-yloxy)ethan-1-ol **2j** (63 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (>20:1 dr) by column chromatography (1:4 to 1:1 EtOAc:Petrol) yielded the title compound as a single diastereoisomer **3ag** (72.6 mg, 0.201 mmol, 67%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 7.39 – 7.24 (5H, m, *Ar*), 4.51 (1H, dd, *J* = 10.4, 2.8 Hz, C(11)*H*), 4.20 (1H, m, C(8)*H*), 3.94 (1H, dd, *J* = 11.5, 2.6 Hz, C(9)*H*H), 3.81 (1H, dd, *J* = 11.8, 2.8 Hz, C(10)*H*H), 3.75 – 3.09 (10H, br., C(1 to 4)H_2, C(9 and 10)H*H*), 2.72 (1H, dd, *J* = 17.2, 8.1 Hz, C(7)*H*H), 2.36 (1H, dd, *J* = 17.2, 4.1 Hz, C(7)H*H*), 1.39 (3H, s, C(5 or 6)H_3), 1.39 (3H, s, C(5 or 6)H_3); **δ_C** (101 MHz, $CDCl_3$) 207.3, 170.9, 137.9, 128.6, 128.3, 126.4, 77.6, 72.4, 70.8, 70.7, 66.6 (bs, 2C), 56.2, 46.7 (bs), 43.4 (bs), 39.8, 23.8, 22.9; **ν_{max}**/ cm^{-1} (neat) 2855, 1710, 1636, 1423, 1113, 1027, 701; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{28}O_5N^+$ calc. 362.1957, found 362.1957.

4-((2*R,6*S**)-6-Benzyl-1,4-dioxan-2-yl)-2,2-dimethyl-1-morpholinobutane-1,3-dione (3ah)**

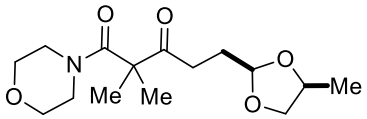


Following **general procedures H** and **I**. **General procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.300 mmol, 1.00 equiv.) and 1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol **2m** (69 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure H** used HCl in dioxane (4.0 M in dioxane, 0.15 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue (11:1 dr) by column chromatography (1:4 to 1:1 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **3ah** (76.0 mg, 0.203 mmol, 68%) as a yellow viscous oil.

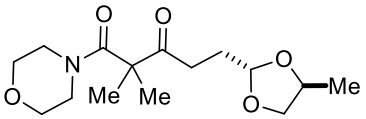
δ_H (400 MHz, $CDCl_3$) (major signals only) 7.33 – 7.16 (5H, m, *Ar*), 4.24 – 4.19 (1H, m, C(8)*H*), 3.99 – 3.87 (1H, m, C(11)*H*), 3.83 – 3.10 (8H, br., C(1 to 4)H_2), 3.75 (1H, dd, *J* = 11.2, 2.6 Hz, C(9)*H*H), 3.69 (1H, dd, *J* = 11.5, 2.5 Hz, C(10)*H*H), 3.23 (1H, dd, *J* = 11.2, 10.3 Hz, C(10)H*H*), 3.23 (1H, dd, *J* = 11.2, 10.4 Hz, C(9)H*H*), 2.79 (1H, dd, *J* = 14.0, 7.0 Hz, C(12)*H*H), 2.70 (1H, dd, *J* = 17.1, 7.8 Hz, C(7)*H*H), 2.61 (1H, dd, *J* = 14.2, 6.5 Hz, C(12)H*H*), 2.34 (1H, dd, *J* = 17.2, 4.4 Hz, C(7)H*H*), 1.38 (3H, s, C(5 or 6)H_3), 1.37 (3H, s, C(5 or 6)H_3); **δ_C** (101 MHz, $CDCl_3$) (major signals only) 207.3, 170.9, 137.1, 129.1, 128.5, 126.5, 75.9, 71.4, 70.3, 70.0, 66.6 (bs, 2C), 56.0, 46.3 (bs), 43.5 (bs), 40.1, 38.2, 23.6, 22.9; **ν_{max}**/ cm^{-1} (neat) 2853,

1711, 1637, 1496, 1454, 1423, 1360, 1272, 1248, 1183, 1115, 1022, 946, 915, 816, 731, 701, 640, **m/z HRMS** (ESI$^+$) $[M + Na]^+$ $C_{21}H_{29}O_5N^{23}Na^+$ calc. 398.1938, found 398.1939.

2,2-Dimethyl-5-((2*R,4*S**)-4-methyl-1,3-dioxolan-2-yl)-1-morpholinopentane-1,3-dione (17) and 2,2-dimethyl-5-((2*S**,4*S**)-4-methyl-1,3-dioxolan-2-yl)-1-morpholinopentane-1,3-dione (17')**



17



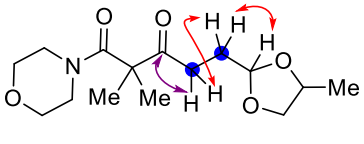
17'

Prepared following **general procedures H** and **I**. **General procedure H** used 2,2-dimethyl-3-morpholino-3-oxopropanal **1k** (55.5 mg, 0.30 mmol, 1.00 equiv.) and 2-(prop-2-yn-1-yloxy)propan-1-ol **2g** (41 mg, 0.360 mmol, 1.20 equiv.) with $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), dcpe (6.3 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.3 mL). **General procedure I** used HCl in dioxane (4 M in dioxane, 0.150 mL, 0.600 mmol, 2.00 equiv.) and DCE (4.0 mL). Purification of the crude residue by column chromatography (1:4 to 1:0 EtOAc:Petrol) yielded the title compound as an inseparable mixture of diastereoisomers **17** and **17'** (45.2 mg, 0.151 mmol, 50%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) (1:1 mixture) 5.03, (1H, app. t, *J* = 4.3 Hz), 4.93 (1H, app. t, *J* = 4.2 Hz), 4.21 – 4.05 (3H, m), 3.91 (1H, dd, *J* = 7.5, 6.5 Hz), 3.80 – 3.05 (18H, m), 2.65 – 2.54 (4H, m), 1.98 – 1.88 (4H, m), 1.36 (6H, s), 1.35 (6H, s), 1.25 (3H, d, *J* = 6.1 Hz), 1.21 (3H, d, *J* = 6.1 Hz); **δ_C** (101 MHz, $CDCl_3$) (1:1 mixture) 210.3 (2C), 171.3 (2C), 103.1, 102.2, 73.0, 72.2, 72.0, 71.1, 66.6 (br, 4C), 55.8, 55.8, 46.4 (2C), 46.2 (bs 2C), 43.4 (bs 2C), 31.9, 31.9, 28.0, 27.9, 23.6, 23.6, 18.7, 18.5 (Proton

and Carbon NMR data too complex to fully assign); **ν_{max}**/ cm^{-1} (neat) 2977, 2888, 1709, 1641, 1646, 1422, 1384, 1270, 1249, 952, **m/z LRMS** (ESI^+) 322.2 [M + Na]$^+$; **HRMS** (ESI^+) [M + H]$^+$ $C_{15}H_{26}O_5N^+$ calc. 300.1806, found 300.1806.

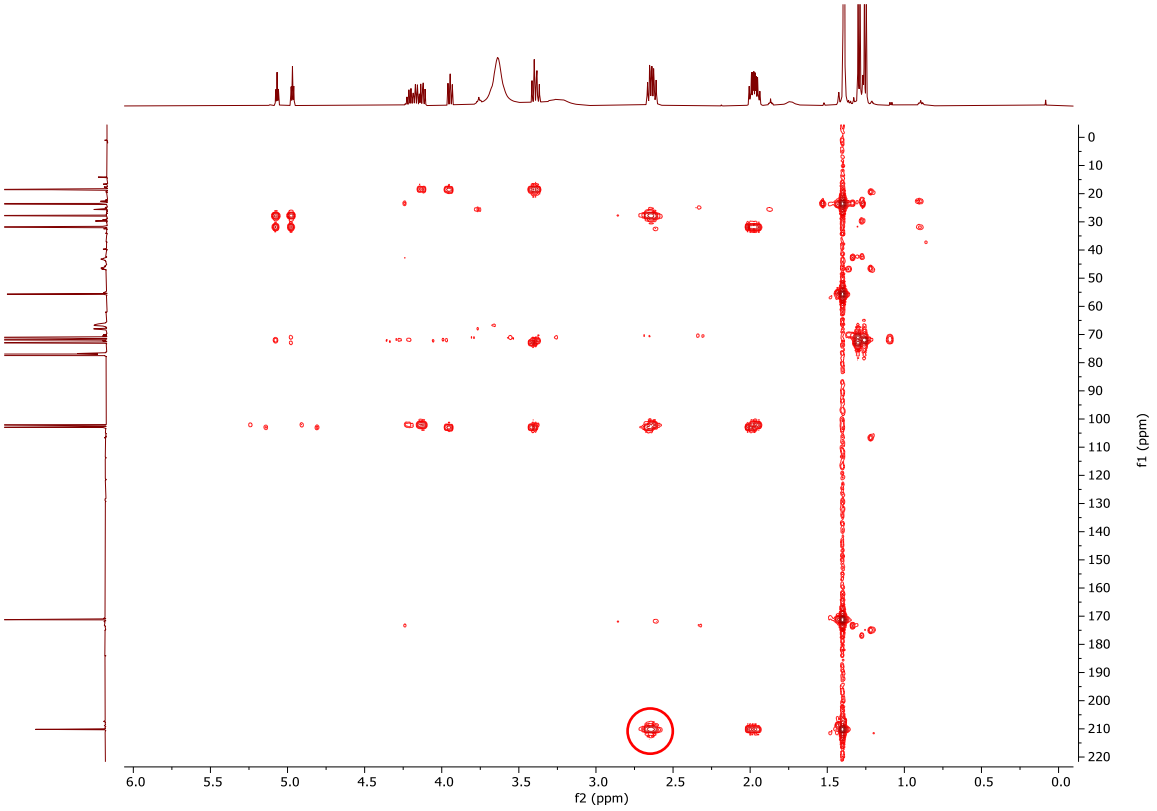
2D NMR correlations for 1:1 mixture 17 and 17':



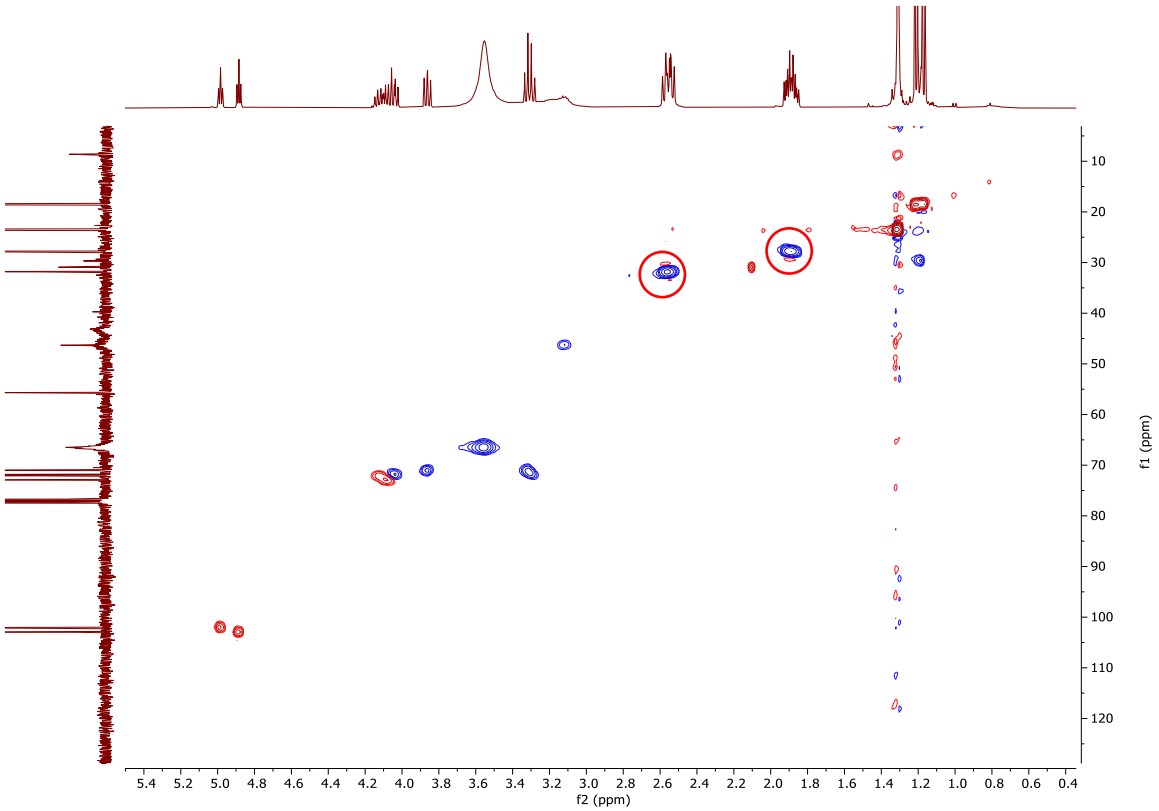
17

HMBC correlation
COSY correlations
● = CH_2 environments

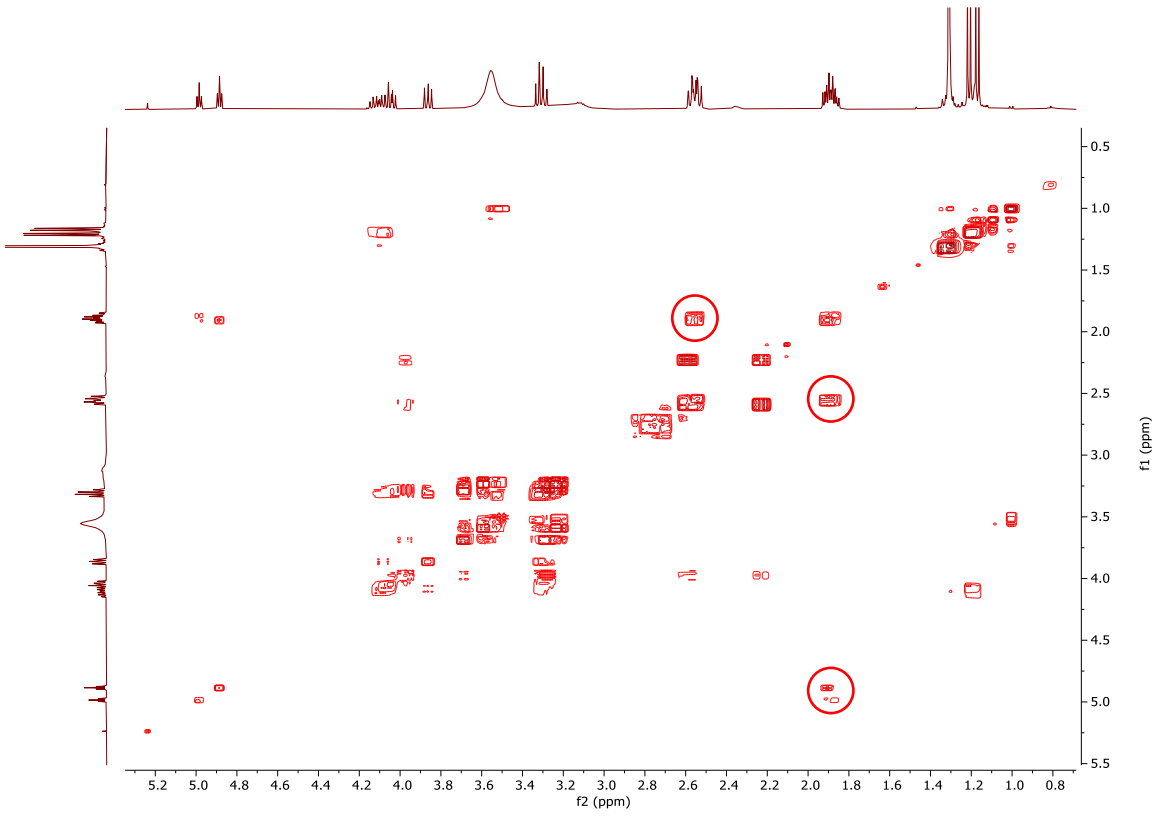
HMBC:



HSQC:

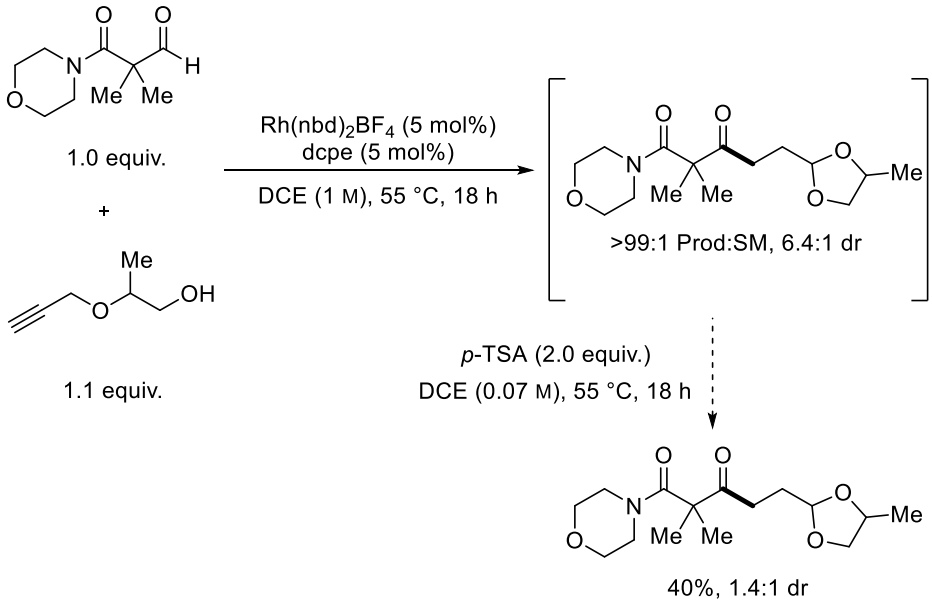


COSY:



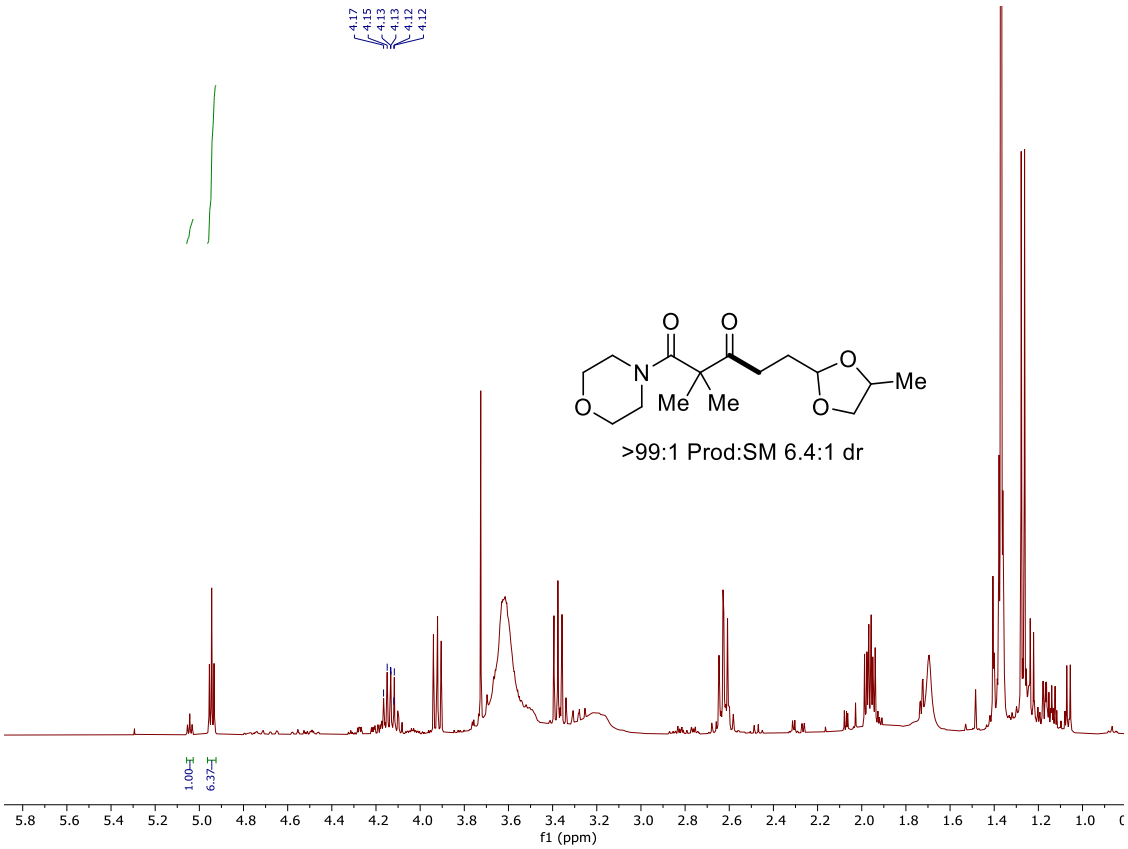
6.2.4d Probing the Formation of Dioxolane 17:

Side-product 17 formation from hydroacylation conditions:

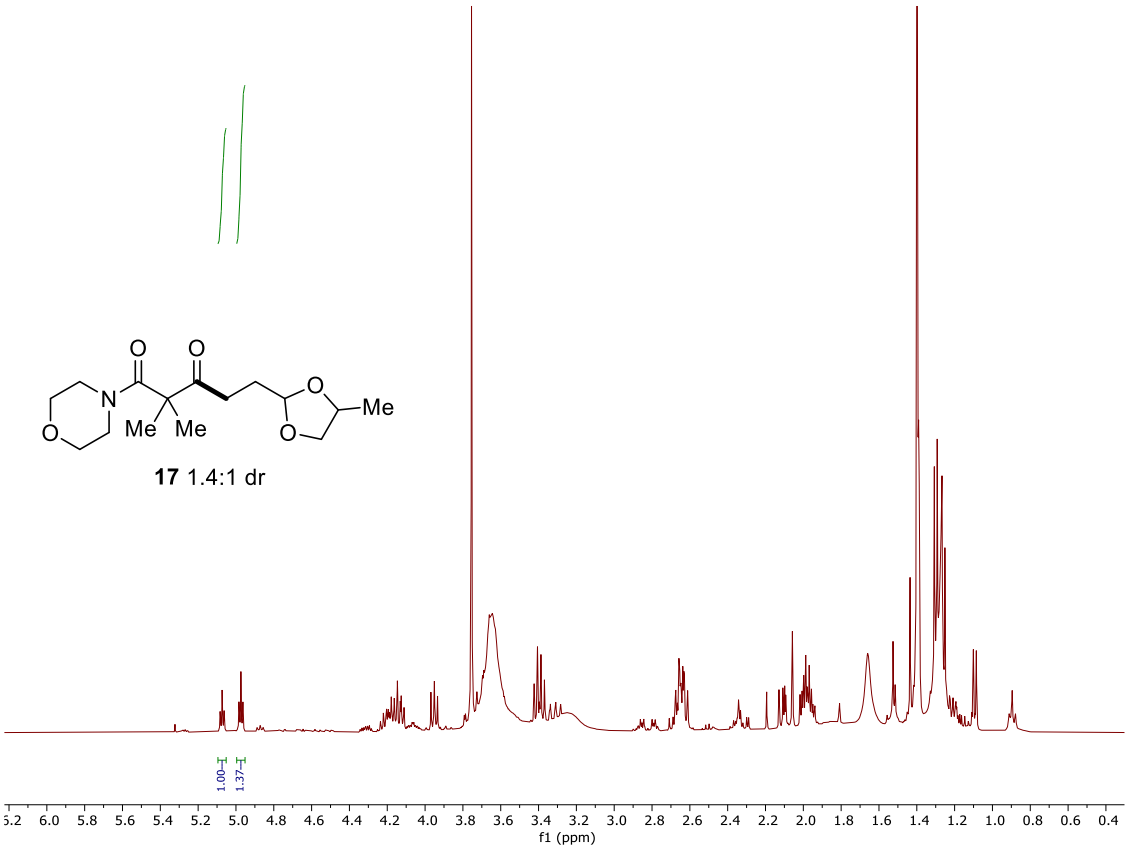


Scheme 6.1: Showing that the side-reaction to dioxolane is entirely driven by the step i) conditions and that a decrease in the dr of product **17** occurs during acid treatment in step ii)

^{1}H NMR spectrum after step i):

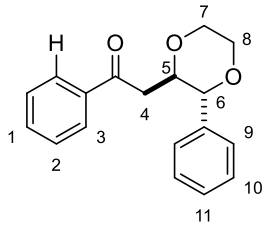


^{1}H NMR spectrum after step ii):



6.2.5 Production Derivatisations

1-Phenyl-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (18a)**

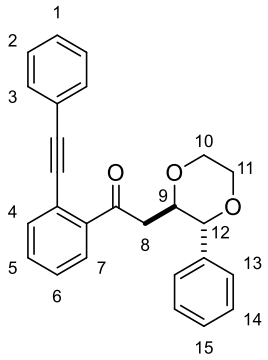


According to a modified literature procedure,[34b] **3a** (30 mg, 0.092 mmol, >20:1 dr, 1.00 equiv.) was added to an oven-dried vial and vacuated and backfilled times with argon. A separate vial containing $Rh(nbd)_2BF_4$ (1.80 mg, 0.005 mmol, 0.050 equiv.) and dcpm (2.0 mg, 0.005 mmol, 0.050 equiv.) was additionally vac-cycled three times under argon, before adding anhydrous, argon degassed CH_2Cl_2 (1.0 mL). This mixture was then sonicated and hydrogen gas was bubbled through the resulting solution for 2 – 3 mins. The solvent was removed by a steady stream of argon gas before the residue dissolved by a known volume of anhydrous, argon degassed CH_2Cl_2 (0.6 mL). This solution was transferred to the vial containing substrate **5a** and stirred before triethoxysilane (34 µL, 0.018 mmol, 2.00 equiv.) was added. The resulting mixture was stirred at room temperature for 2 h. After this time, TLC analysis still showed a significant amount of starting material, so more triethoxysilane (34 µL, 0.018 mmol, 2.00 equiv.) was added and the mixture was stirred at room temperature for another 18 h. Product formation could be seen after this time; however some starting material was still remaining, so more triethoxysilane (102 µL, 0.054 mmol, 6.00 equiv., a total of 10.0 equiv.) was added and the reaction was stirred for another 4 h. After this time, only trace starting material could be seen by TLC analysis, and so the resulting solution was concentrated *in vacuo*. Purification by column chromatography (1:19 to 1:9

EtOAc:Petrol) yielded the title compound **18a** (15.6 mg, 0.055 mmol, 60%) as an off-white solid.

m.p. (CH_2Cl_2) 104 – 105 °C; **δ_H** (400 MHz, $CDCl_3$) 7.82 – 7.75 (2H, m, *Ar*), 7.55 – 7.49 (1H, m, *Ar*), 7.46 – 7.29 (7H, m, *Ar*), 4.38 (1H, d, *J* = 9.1 Hz, C(6)*H*), 4.24 (1H, app td, *J* = 9.1, 2.7 Hz, C(5)*H*), 3.97 – 3.80 (4H, m, C(6 and 7)H_2), 3.10 (1H, dd, *J* = 15.9, 9.0 Hz, C(4)*H*H), 2.66 (1H, dd, *J* = 15.8, 2.7 Hz, C(4)H*H*); **δ_C** (101 MHz, $CDCl_3$) 197.4, 138.1, 137.3, 133.2, 128.9, 128.8, 128.6, 128.3, 127.9, 83.0, 77.3, 67.2, 67.2, 40.4; **ν_{max}**/ cm^{-1} (neat) 3651, 2981, 2889, 1685, 1382, 1252, 1153, 1115, 1074, 954, 755, 700; **m/z HRMS** (ESI^+) $C_{18}H_{18}O_3{}^{23}Na$ $[M + Na]^+$ calc. 305.1148, found 305.1148.

2-((2*R,3*R**)-3-Phenyl-1,4-dioxan-2-yl)-1-(2-(phenylethynyl)phenyl)ethan-1-one (18b)**

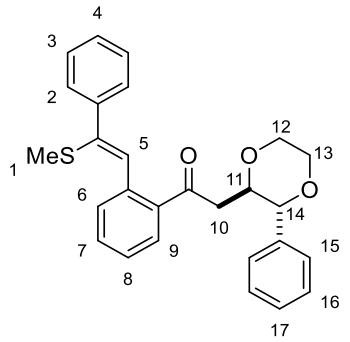


According to literature procedure,[83d] $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 0.050 equiv.) and dcpe (3.2 mg, 0.0075 mmol, 0.050 equiv.) were dissolved in DCE (2 mL). H_2 gas was bubbled through the solution for 2 min. The solution was purged with gas argon for 1 min. A separate vial containing aryl sulfide **3a** (49.0 mg, 0.150 mmol, >20:1 dr, 1.00 equiv.), phenylacetylene (33 µL, 0.300 mmol, 2.00 equiv.), copper bromide (43 mg, 0.300 mmol, 2.00 equiv.) and silver carbonate (41 mg, 0.150 mmol, 1.00 equiv.) was evacuated and backfilled with argon three times. The

catalyst solution was then added to this vial *via* a cannula. The resulting mixture was heated at 80 °C for 16 h. Upon cooling to room temperature the mixture was concentrated *in vacuo*. Purification by column chromatography (1:19 to 1:9 EtOAc:Petrol) yielded the title compound **18b** (40.8 mg, 0.107 mmol, 71%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 7.56 (1H, dd, *J* = 7.7, 1.4 Hz, *Ar*), 7.53 (1H, dd, *J* = 7.8, 1.4 Hz, *Ar*), 7.46 – 7.29 (9H, m, *Ar*), 7.25 – 7.21 (3H, m, *Ar*), 4.31 (1H, d, *J* = 9.1 Hz, C(12)*H*), 4.23 (1H, app td, *J* = 9.2, 2.9 Hz, C(9)*H*), 3.94 – 3.76 (4H, m, C(10 and 11)H_2), 3.37 (1H, dd, *J* = 16.1, 9.2 Hz, C(8)*H*H), 2.87 (1H, dd, *J* = 16.1, 2.9 Hz, C(8)H*H*); **δ_C** (101 MHz, $CDCl_3$) 200.7, 141.7, 137.9, 133.6, 131.7, 131.0, 128.8, 128.7, 128.5, 128.5, 128.4, 127.8, 122.9, 121.1, 94.9, 88.0, 83.0, 77.6, 67.2, 67.1, 44.2; **ν_{max}**/ cm^{-1} (neat) 3062, 2959, 2855, 1687, 1591, 1493, 1443, 1269, 1206, 1182, 1114, 995, 942, 914, 895, 756, 700, 691, 648, 614; **m/z HRMS** (ESI^+) $C_{26}H_{22}O_3{}^{23}Na^+$ $[M + Na]^+$ calc. 405.1461, found 405.1459

1-(2-((*Z*)-2-(Methylthio)-2-phenylvinyl)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one (18c)**

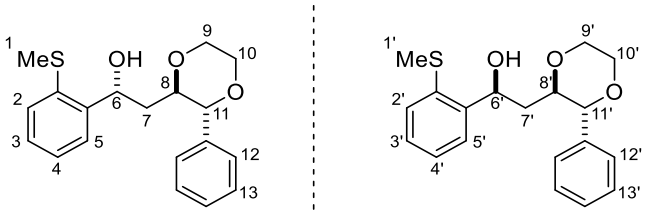


Prepared according to **general procedure H**, instead using **3a** (20.0 mg, 0.061 mmol, >20:1 dr, 1.00 equiv.), phenylacetylene (13 µL, 0.120 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (1.1 mg, 0.0031 mmol, 0.050 equiv.), Xantphos (1.8 mg, 0.0031

mmol, 0.050 equiv.) and DCE (0.2 mL, 0.3 M) under N_2, with reaction temperature at 100 °C.[83b] After 5 h at 100 °C, TLC analysis showed low reaction conversion. Consequently, the reaction temperature was raised to 120 °C and the reaction mixture was stirred overnight (16 h). After this time, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:19 to 1:9 EtOAc:Petrol) yielded the title compound **18c** (18.3 mg, 0.043 mmol, 70%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 7.69 – 7.52 (5H, m, *Ar*), 7.52 – 7.32 (9H, m, *Ar*), 7.03 (1H, s, C(5)*H*), 4.39 (1H, d, *J* = 9.1 Hz, C(14)*H*), 4.25 (1H, app td, *J* = 9.2, 2.9 Hz, C(11)*H*), 4.02 – 3.83 (4H, m, C(12 and 13)H_2), 3.17 (1H, dd, *J* = 15.8, 9.3 Hz, C(10)*H*H), 2.68 (1H, dd, *J* = 15.7, 2.8 Hz, (10)H*H*), 1.91 (3H, s, SC(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 201.1, 140.1, 139.4, 138.3, 138.0, 136.7, 131.2, 130.9, 130.5, 128.8, 128.8, 128.5, 128.5, 128.1, 127.8, 127.2, 83.0, 77.6, 67.2, 67.1, 43.6, 16.3; **ν_{max}**/ cm^{-1} (neat) 3735, 3059, 2959, 2951, 2855, 1685, 1490, 1473, 1269, 1100, 942, 758, 700, 648; **m/z HRMS** (ESI^+) $C_{27}H_{26}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 453.1495, found 453.1494.

(*R)-1-(2-(methylthio)phenyl)-2-((2*R**,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-ol (18d) and (*S**)-1-(2-(Methylthio)phenyl)-2-((2*R**,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-ol (18d')**



18d **18d'**

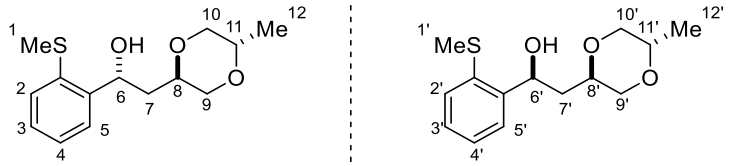
According to a modified literature procedure,[84] **3a** (30 mg, 0.091 mmol, >20:1 dr, 1.00 equiv.) and $Eu(OTf)_3$ (164 mg, 0.270 mmol, 3.00 equiv.) were added to a dry flask containing anhydrous Et_2O (1.6 mL). The flask was then purged with N_2 and cooled to –78 °C, with stirring. A solution of $LiBH_4$ (2 M in THF, 92 µL, 0.180 mmol, 2.00 equiv.) was then added dropwise and the resulting solution was stirred for 3 h at –78 °C. Once complete as monitored by TLC analysis, the mixture was quenched by addition of 1 M NaOH (1 mL) and the solution was warmed to room temperature. The mixture was then extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue (8:1 dr) by column chromatography (1:4 EtOAc:Petrol) yielded a mixture of diastereoisomers (27.4 mg, 0.083 mmol, 91%), where pure fractions of both major diastereoisomer **18d** (23.1 mg, 0.070 mmol, 77%) and minor diastereoisomer **18d'** (1.6 mg, 0.0048 mmol, 5%) could be partially isolated as an off-white solid and a colourless viscous oil respectively.

18d: **m.p.** (CH_2Cl_2) 139 – 140 °C; **δ_H** (400 MHz, $CDCl_3$) 7.43 – 7.38 (1H, m, *Ar*), 7.32 – 7.27 (5H, m, *Ar*), 7.25 – 7.12 (3H, m, *Ar*), 5.42 – 5.33 (1H, m, C(6)*H*), 4.32 (1H, d, *J* = 9.1 Hz, C(11)*H*), 4.00 – 3.87 (4H, m, C(9 and 10)H_2), 3.81 (1H, app td,

J = 9.2, 2.7 Hz, C(8)*H*), 3.15 – 3.07 (1H, m, O*H*), 2.34 (3H, s, SC(1)H_3), 1.77 (1H, ddd, *J* = 14.7, 9.3, 2.8 Hz, C(7)*H*H), 1.60 (1H, ddd, *J* = 14.6, 8.9, 2.8 Hz, C(7)H*H*); **δ_C** (101 MHz, $CDCl_3$) 142.8, 138.1, 135.1, 128.6, 128.6, 127.9, 127.9, 126.9, 125.9, 125.6, 83.0, 78.0, 67.7, 67.1, 67.1, 37.7, 16.7; **ν_{max}**/ cm^{-1} (neat) 3448, 2954, 2917, 2855, 1439, 1266, 1115, 1094, 1036, 977, 943; **m/z HRMS** (ESI^+) $C_{19}H_{22}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 353.1182, found 353.1181.

18d': **δ_H** (400 MHz, $CDCl_3$) 7.51 – 7.47 (1H, m, *Ar*'), 7.33 – 7.27 (5H, m, *Ar*'), 7.20 – 7.12 (3H, m, *Ar*'), 5.20 (1H, app dd, *J* = 9.0, 2.7 Hz, C(6')*H*), 4.21 (1H, d, *J* = 8.9 Hz, C(8')*H*), 4.05 – 3.86 (6H, m, O*H*, C(11')*H* and C(9' and 10')H_2), 2.23 (3H, s, SC(1')H_3), 1.70 – 1.58 (2H, m, C(7')H_2; **δ_C** (126 MHz, $CDCl_3$) 142.7, 137.9, 135.2, 128.7, 128.7, 127.8, 127.8, 127.1, 125.8, 125.7, 83.3, 82.0, 70.9, 67.1, 67.0, 39.0, 16.7; **ν_{max}**/ cm^{-1} (neat) 3427, 2979, 1380, 1141, 1109, 1083, 857; **m/z HRMS** (ESI^+) $C_{19}H_{22}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 353.1182, found 353.1182.

(*R)-2-((2*R**,5*S**)-5-Methyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-ol (18e) and (*S**)-2-((2*R**,5*S**)-5-methyl-1,4-dioxan-2-yl)-1-(2-(methylthio)phenyl)ethan-1-ol (18e')**



18e **18e'**

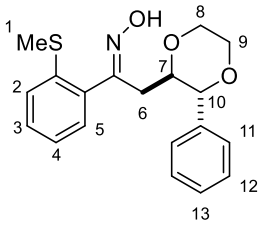
According to modified procedure,[84] **3p** (20.0 mg, 0.075 mmol, 1.00 equiv.) and $Eu(OTf)_3$ (135 mg, 0.225 mmol, 3.00 equiv.) were added to a dry flask containing anhydrous Et_2O (1.3 mL). The flask was then purged with N_2 and cooled to –78 °C, with stirring. A solution of $LiBH_4$ (2 M in THF, 75 µL, 0.150 mmol, 2.00 equiv.) was then added dropwise and the resulting solution was stirred for 2 h at –78 °C. Once complete as montiroed by TLC analysis, the mixture was quenched by addition of 1 M NaOH (1 mL) and the solution was warmed to room temperature. The mixture was then extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue (3:1 dr) by column chromatography (1:19 to 1:5 EtOAc:Petrol) yielded a mixture of diastereoisomers (14.8 mg, 0.055 mmol, 74%), where pure fractions of both major diastereoisomer **18e** (8.1 mg, 0.03 mmol, 41%) and minor diastereoisomer **18e'** (3.6 mg, 0.015 mmol, 20%) could be partially isolated as off-white solids.

18e: **m.p.** (CH_2Cl_2) 109 – 113 °C; **δ_H** (400 MHz, $CDCl_3$) 7.55 – 7.50 (1H, m, *Ar*), 7.28 – 7.18 (3H, m, *Ar*), 5.40 – 5.31 (1H, m, C(6)*H*), 3.80 (1H, dd, *J* = 11.5, 2.5 Hz, C(10)*H*H), 3.77 – 3.62 (3H, m, C(8 and 11)*H*, C(9)*H*H), 3.52 (1H, dd, *J* = 11.5, 10.4

Hz, C(9)H*H*), 3.34 (1H, app d, *J* = 4.7 Hz, O*H*), 3.30 (1H, dd, *J* = 11.4, 10.2 Hz, C(10)*H*H), 2.47 (3H, s, SC(1)H_3), 1.86 – 1.79 (2H, m, C(7)H_2), 1.07 (3H, d, *J* = 6.3 Hz, C(12)H_3); **δC** (101 MHz, $CDCl_3$) 142.5, 135.0, 127.9, 126.3, 125.8, 125.6, 73.0, 72.5, 71.2, 70.9, 68.1, 37.8, 16.8, 16.4; **ν_{max}**/ cm^{-1} (neat) 3421, 2972, 2853, 1440, 1378, 1350, 1280, 1150, 1119, 1097, 1051, 1023, 943, 886, 842, 822, 755, 735, 659, 618; **m/z HRMS** (ESI^+) $C_{14}H_{20}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 291.1025, found 291.1025.

18e': **m.p.** (CH_2Cl_2) 105 – 106 °C; **δ_H** (400 MHz, $CDCl_3$) 7.60 – 7.56 (1H, m, *Ar*'), 7.25 – 7.17 (3H, m, *Ar*'), 5.35 – 5.31 (1H, m, C(6')*H*), 3.90 (1H, app tt, *J* = 10.1, 2.8 Hz, C(8')*H*), 3.85 – 3.78 (2H, m, O*H* and C(9')*H*H), 3.73 (1H, dd, *J* = 11.6, 2.5 Hz, C(10')*H*H), 3.71 – 3.61 (1H, m, C(11')*H*), 3.39 (1H, dd, *J* = 11.4, 10.2 Hz, C(9')H*H*), 3.37 (1H, dd, *J* = 11.6, 10.3 Hz, C(10')H*H*), 2.47 (3H, s, C(1')H_3), 1.80 (1H, app dt, *J* = 14.6, 2.7 Hz, C(7')*H*H), 1.64 (1H, app dt, *J* = 14.6, 9.8 Hz, C(7')H*H*), 1.10 (3H, d, *J* = 6.3 Hz, C(12')H_3); **δC** (101 MHz, $CDCl_3$) 142.4, 135.0, 127.9, 126.1, 125.8, 125.7, 76.0, 72.4, 71.3, 71.0, 70.5, 39.1, 16.9, 16.4; **ν_{max}**/ cm^{-1} (neat) 3435, 2920, 2853, 1441, 1348, 1310, 1282, 1118, 1100, 824, 755, 659; **m/z HRMS** (ESI^+) $C_{14}H_{20}O_3{}^{23}Na^{32}S^+$ $[M + Na]^+$ calc. 291.1025, found 291.1025.

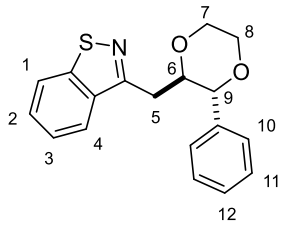
(*E*)-1-(2-(Methylthio)phenyl)-2-((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)ethan-1-one oxime (18f)**



According to a modified literature procedure,[85] product **3a** (120 mg, 0.366 mmol, >20:1 dr, 1.00 equiv.), hydroxylamine hydrochloride (100 mg, 1.44 mmol, 4.00 equiv.) and pyridine (116 µL, 1.44 mmol, 4.00 equiv.) in MeOH (1.6 mL) were stirred at 60 °C for 20 h. Once complete as determined by TLC analysis, the solvent was removed *in vacuo*. H_2O (5 mL) was added and the residue extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with 1 M HCl (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:4 to 7:3 EtOAc:Petrol) yielded the title compound **18f** (69.9 mg, 0.204 mmol, 56%) as an off-white solid.

m.p. (CH_2Cl_2) 125 – 127 °C; **δ_H** (400 MHz, $CDCl_3$) 7.86 – 7.66 (1H, br., O*H*), 7.36 – 7.27 (5H, m, *Ar*), 7.22 – 7.12 (2H, m, *Ar*), 4.22 (1H, d, *J* = 8.9 Hz, C(10)*H*), 3.91 – 3.78 (3H, m, C(8 and 9)H_2), 3.77 – 3.60 (2H, m, C(7)*H*, C(8 and 9)H_2), 3.02 (1H, dd, *J* = 14.6, 10.6 Hz, C(6)*H*H), 2.57 (1H, dd, *J* = 14.6, 2.6 Hz, C(6)H*H*), 2.28 (3H, s, SC(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 158.3, 138.1, 137.5, 136.0, 129.8, 129.2, 128.6, 128.6, 127.8, 127.2, 125.2, 83.3, 77.7, 67.0, 67.0, 30.6, 17.0; **ν_{max}**/ cm^{-1} (neat) 3340, 2856, 1699, 1585, 1522, 1473, 1434, 1354, 1271, 1115, 1046, 1008, 972, 942, 917, 756, 734, 700, 648; **m/z HRMS** (ESI^+) $C_{19}H_{21}O_3N^{23}Na^{32}S^+$ [M + Na]+ calc. 366.1134, found 366.1134.

3-(((2*R,3*R**)-3-phenyl-1,4-dioxan-2-yl)methyl)benzo[d]isothiazole (18g)**



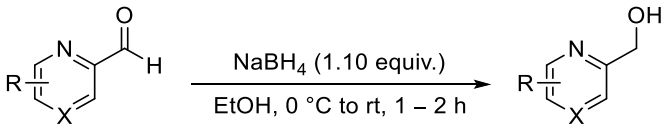
According to a modified literature procedure,[86] in an oven-dried microwave vial, oxime **18f** (69.9 mg, 0.204 mmol, >20:1 dr, 1.00 equiv.) was dissolved in pyridine (0.82 mL) and the vial was sealed under air. Acetic anhydride (78 µL, 0.816 mmol, 4.00 equiv.) was then added dropwise. This mixture was heated to 120 °C for 20 h. Once complete as determined by TLC analaysis, the reaction mixture was cooled to room temperature. Sat aq. NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:19 to 1:9 EtOAc:Petrol) yielded the title compound **18g** (44.3 mg, 0.142 mmol, 70%) as an off-white solid.

m.p. (CH_2Cl_2) 108 – 110 °C; **δ_H** (400 MHz, $CDCl_3$) 7.87 (1H, app dt, *J* = 8.2, 0.9 Hz, *Ar*), 7.69 (1H, app dt, *J* = 8.2, 1.0 Hz, *Ar*), 7.52 – 7.44 (3H, m, *Ar*), 7.42 – 7.30 (4H, m, *Ar*), 4.43 (1H, d, *J* = 9.0 Hz, C(9)*H*), 4.15 (1H, td, *J* = 9.1, 3.0 Hz, C(6)*H*), 3.95 – 3.86 (2H, m, C(7 and 8)*H*H), 3.85 – 3.76 (2H, m, C(7 and 8)H*H*), 3.17 (1H, dd, *J* = 14.6, 9.1 Hz, C(5)*H*H), 2.98 (1H, dd, *J* = 14.6, 3.0 Hz, C(5)H*H*); **δ_C** (101 MHz, $CDCl_3$) 163.0, 152.5, 138.3, 135.2, 128.8, 128.8, 128.0, 127.4, 124.4, 123.7, 119.9, 83.2, 79.4, 67.1, 67.0, 33.7; **ν_{max}**/ cm^{-1} (neat) 2958, 2854, 1593, 1491, 1453, 1371, 1350, 1324, 1272, 114, 1009, 974, 942, 914, 894, 757, 735, 701, 649, 622; **m/z HRMS** (ESI^+) $C_{18}H_{18}O_2N^{32}S^+$ $[M + H]^+$ calc. 312.1053, found 312.1054**.**

6.3 Experimental for Chapter 3

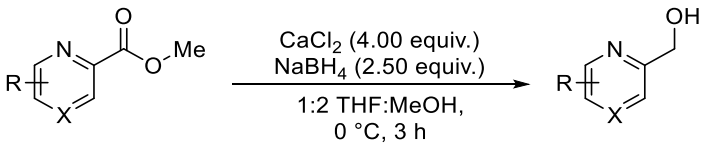
6.3.1 General Procedures

General Procedure K: 2-pyridyl Aldehyde Reductions using $NaBH_4$



A stirred solution of the corresponding 2-formyl pyridine (1.00 equiv.) in EtOH (1.60 mL/mmol) was cooled to 0 °C before $NaBH_4$ (1.10 equiv.) was added portion-wise. The resulting mixture was warmed to room temperature and stirred for 1 – 2 h, ***(unless stated otherwise)***. After completion was shown by TLC, the mixture was cooled to 0 °C, quenched with 1 M $HCl_{(aq)}$ (10 mL for 4 mmol scale) and neutralised with sat. aq. $NaHCO_3$. The resulting mixture was extracted using EtOAc (3 × 10 mL for 4 mmol scale) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude alcohol which was submitted directly into **general procedure M**.

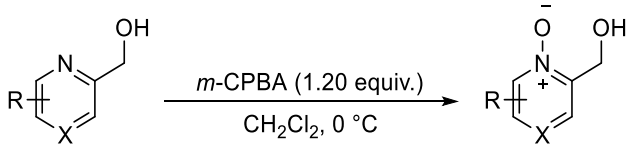
General Procedure L: Methyl Ester Reductions using $CaCl_2$ and $NaBH_4$



Prepared according to a modified literature procedure.[205] $NaBH_4$ (2.50 equiv.) was added in portions to a slurry of 2,5-pyridinedicarboxylic acid dimethyl ester (1.00 equiv.) and $CaCl_2$ (4.00 equiv.) in a mixture of dry THF (1.80 mL/mmol) and dry MeOH (3.60 mL/mmol) at 0 °C. The reaction was stirred at 0 °C for 3 h. After completion was shown by TLC, excess of $NaBH_4$ was then quenched at 0 °C by adding ice-cold water (30 mL for 7.70 mmol scale). After extraction with CH_2Cl_2

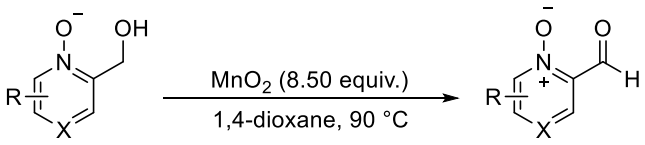
(3 × 20 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the crude alcohol which was submitted directly into **general procedure M**.

General Procedure M: *N*-oxidations of 2-Pyridylic Alcohols



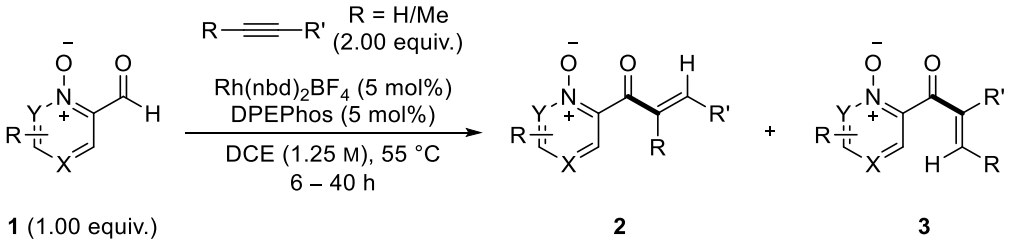
Prepared according to a modified literature procedure.[206] The crude alcohol from either **general procedure K** or **L** was re-dissolved in CH_2Cl_2 (4.50 mL/mmol) and the solution was cooled to 0 °C, with stirring. Then, *m*-CPBA (60% or 75% w/w, 1.20 equiv.) was added portion-wise and the mixture was warmed to room temperature with stirring overnight ***(12 – 20 h, unless stated otherwise)***. ***Note: For more the more sterically hindered 6-halopyridines, stirring at 80 °C in 1,2-DCE, instead of CH_2Cl_2, was required to achieve full conversion.*** After completion was shown by TLC, the solvent was removed *in vacuo*. Et_2O (4.50 mL/mmol) was then added and the solution was stirred vigorously at room temperature for 10 – 15 min. Büchner filtration then followed to yield the corresponding alcohol *N*-oxide, which was washed with Et_2O (3 × 10 mL for 4 mmol scale). If a solid precipitate did not form during stirring in Et_2O, the crude residue was concentrated *in vacuo* and purified by column chromatography.

General Procedure N: Pyridylic Alcohol Oxidations using MnO_2



Prepared according to a modified literature procedure.[206] To a solution of the corresponding pyridylic alcohol *N*-oxide (1.00 equiv.) in dry 1,4-dioxane (7.8 mL/mmol) was added MnO_2 (8.50 equiv.) and the mixture was stirred at 90 °C for 1 – 3 h, ***unless stated otherwise***. After completion was shown by TLC, the reaction mixture was cooled to room temperature before the addition of celite and solvent removal *in vacuo*. The celite-bound residue was then loaded directly onto a column and purified using either an EtOAc/Petrol or CH_2Cl_2:Acetone eluent system. ***Note: It is crucial that eluent mixtures containing EtOH or MeOH are not used during column chromatography, as this leads to product degradation***.

General procedure O: *N*-Oxide-Directed Intramolecular Alkyne Hydroacylation



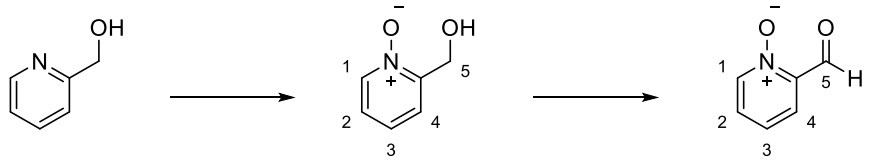
$Rh(nbd)_2BF_4$ (0.015 mmol, 5 mol%) was weighed into a tapered, 10 mL microwave vial. Next, DPEPhos (0.015 mmol, 5 mol%) was introduced and the vial sealed with a microwave cap. The vial was placed under vacuum on a Schlenck line and back-filled with argon three times. After this, 1.0 mL of distilled DCE was introduced, and the solution sonicated for 30 s. Hydrogen gas was bubbled through the solution for 1 – 3 min. The solvent was then removed using a stream of argon and the catalyst

system re-dissolved in DCE (1.25 M). Aldehyde (0.300 mmol, 1.00 equiv) was weighed into a separate concave, 10 mL microwave vial, alongside alkyne (0.600 mmol, 2.00 equiv), if a solid. The vial was sealed with a suba-seal/microwave cap and para-filmed (if suba-sealed). It was then placed under vacuum on a Schlenck line and back-filled with argon three times. ***If the alkyne was a liquid, it was then syringed into the vial post vac-cycle.*** The catalyst solution was then added to the reactant mixture. The resulting solution was then stirred at 55 °C for 6 – 40 h. Once complete by TLC, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography yielded the enone products.

6.3.2 Substrate Synthesis

6.3.2a Aldehyde Substrates

2-(Hydroxymethyl)pyridine 1-oxide (56) and 2-formylpyridine 1-oxide (19a):



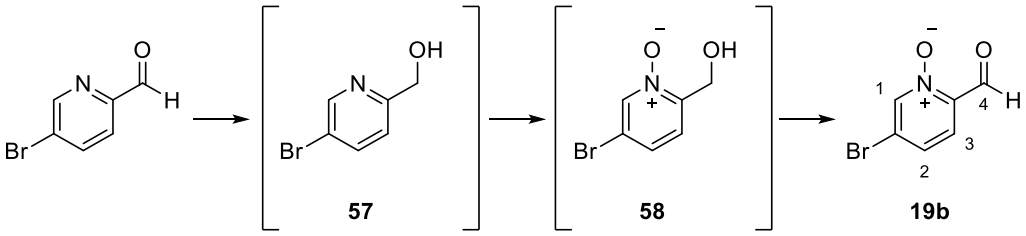
2-(Hydroxymethyl)pyridine 1-oxide (56): Prepared according to **general procedure M**, using 2-pyridinemethanol (2.65 mL, 27.5 mmol, 1.00 equiv.) and *m*-CPBA (75% w/w, 7.60 g, 33.0 mmol, 1.20 equiv.) stirring for 60 h. After completion, Et_2O trituration gave crude bromo-2-(Hydroxymethyl)pyridine 1-oxide **56** (2.65 g, 21.2 mmol, 77%) as an off-white powdered solid.

m.p. (Et_2O) 136 – 139 °C; (*Lit:* 130 – 132 °C);[207] **δ_H** (400 MHz, $CDCl_3$) 8.23 (1H, dd, *J* = 6.4, 1.2 Hz, *Ar*), 7.41 (1H, dd, *J* = 7.7, 2.1 Hz, *Ar*), 7.34 (1H, td, *J* = 7.7, 1.2 Hz, *Ar*), 7.26 (1H, td, *J* = 7.5, 7.0, 2.2 Hz, *Ar*), 4.95 – 4.84 (1H, bs, O*H*), 4.80 (2H, s, C(5)*H*); **m/z LRMS** (ESI^+) 148.0 $[M + Na]^+$. Data is consistent with literature.[206]

2-Formylpyridine 1-oxide (19a): Prepared according to a modified literature procedure,[206] using 2-(hydroxymethyl)pyridine 1-oxide **56** (700 mg, 5.57 mmol, 1.00 equiv.) and MnO_2 (85% w/w, 4.90 g, 47.9 mmol, 8.50 equiv.) with stirring for 5 h. After this time, the mixture was filtered hot, through celite and the filter cake was separately washed with hot dioxane and EtOH, and the filtrate was concentrated *in* vacuo. Purification by column chromatography (neat EtOAc) yielded 2-formyl-5-methoxypyridine 1-oxide **19a** (98 mg, 0.64 mmol, 66%) as a white powdered solid.

m.p. (CH_2Cl_2) 72 – 78 °C; **δ_H** (400 MHz, $CDCl_3$) 10.63 (1H, d, *J* = 0.8 Hz, C(5)*H*), 8.21 (1H, dt, *J* = 6.5, 0.8 Hz, *Ar*), 7.82 (1H, dd, *J* = 7.8, 2.2 Hz, *Ar*), 7.46 (1H, ddd, *J* = 7.5, 6.5, 2.2 Hz, *Ar*), 7.32 (1H, tt, *J* = 7.7, 1.0 Hz, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 185.8, 143.9, 140.5, 130.1, 125.7, 125.3; **m/z LRMS** (ESI^+) 124.0 $[M + H]^+$. Data is consistent with literature.[206]

5-Bromo-2-formylpyridine 1-oxide (19b)

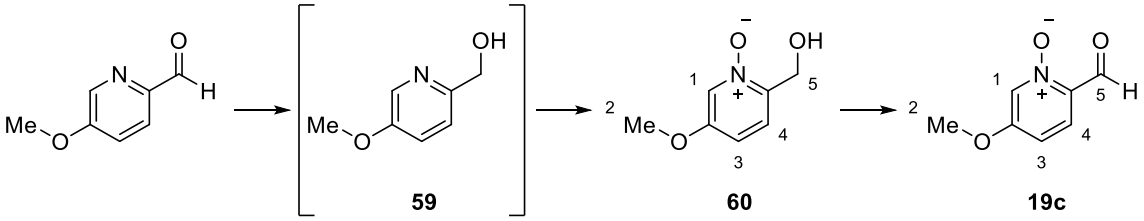


5-Bromo-2-formylpyridine 1-oxide (19b): Prepared according to **general procedures K** and **M**. **General procedure K** used 5-bromopicolinaldehyde (552 mg, 3.00 mmol, 1.00 equiv.) and $NaBH_4$ (125 mg, 3.30 mmol, 1.10 equiv.) with stirring for 1 h. **General procedure M** used crude alcohol **57** obtained from **general procedure K** and *m*-CPBA (60% w/w, 1.03 g, 3.60 mmol, 1.20 equiv.), with stirring for 12 h. After completion, Et_2O trituration gave crude bromo-2-(hydroxymethyl)pyridine-1-oxide **58** (300 mg, 0.980 mmol). This crude compound was subjected to general method **D** without any further purification, using MnO_2 (10.9 g, 12.5 mmol). Purification by column chromatography (1:1 EtOAc: Petrol to 3:1 EtOAc: Petrol) yielded title compound **19b** (100 mg, 0.500 mmol, 17% over three steps) as a white powdered solid (These reactions were performed by Dr Jagadeesh Kalepu).

m.p. (CH_2Cl_2) 134 – 135 °C; **δ_H** (400 MHz, $CDCl_3$) 10.54 (1H, d, *J* = 0.8 Hz, C(4)*H*), 8.36 (1H, dd, *J* = 1.7, 0.5 Hz, *Ar*), 7.69 (1H, d, *J* = 8.5 Hz, *Ar*), 7.45 (1H, ddd, *J* = 8.5, 1.7, 0.8 Hz, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 185.0, 142.9, 141.8, 128.5,

126.0, 125.7; ν_{max}/ cm^{-1} (neat) 2981, 1685, 1375, 1242, 1177, 1083, 955, 819; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_5O_2N^{79}Br^+$ calc. 201.9498, found 201.9500. Data is consistent with literature.[206]

2-(Hydroxymethyl)-5-methoxypyridine 1-oxide (60) and 2-formyl-5-methoxypyridine 1-oxide (19c)



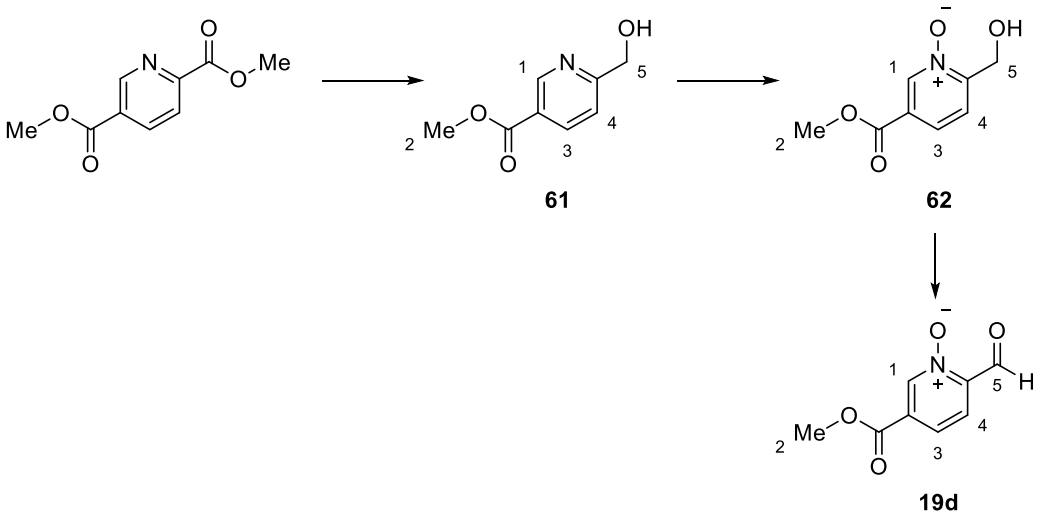
2-(Hydroxymethyl)-5-methoxypyridine 1-oxide (S5): Prepared according to **general procedures K** and **M**. **General procedure K** used 5-methoxypicolinaldehyde (200 mg, 1.45 mmol, 1.00 equiv.) and $NaBH_4$ (60.0 mg, 1.60 mmol, 1.10 equiv.) with stirring for 1 h. **General procedure M** used crude alcohol **59** obtained from **general procedure K** and *m*-CPBA (60% w/w, 499 mg, 1.74 mmol, 1.20 equiv.) stirring for 12 h. After completion, Et_2O trituration gave pure 2-(hydroxymethyl)-5-methoxypyridine 1-oxide **60** (150 mg, 0.97 mmol, 67% yield over two steps) as an off-white powdered solid (These reactions were performed by Dr Jagadeesh Kalepu).

m.p. (Et_2O) 40 – 42 °C; δ_H (400 MHz, $CDCl_3$) 7.96 (1H, d, *J* = 2.4 Hz, *Ar*), 7.23 (1H, d, *J* = 8.8 Hz, *Ar*), 6.90 (1H, dd, *J* = 8.8, 2.4 Hz, *Ar*), 5.05 – 4.86 (1H, bs, O*H*), 4.71 (2H, s, C(5)*H*), 3.81 (3H, s, OC(2)H_3); δ_C (101 MHz, $CDCl_3$) 157.2, 143.0, 127.6, 124.3, 114.3, 60.7, 56.3; ν_{max}/ cm^{-1} (neat) 3233, 2839, 1600, 1501, 1290, 1270, 1248, 1067, 1028, 830; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{10}O_3N^+$ calc. 156.0655, found 156.0655.

2-Formyl-5-methoxypyridine 1-oxide (19c): Prepared according to **general procedure N**, using 2-(hydroxymethyl)-5-methoxypyridine 1-oxide **60** (150 mg, 0.970 mmol, 1.00 equiv.) and MnO_2 (725 mg, 8.33 mmol, 8.50 equiv.), with stirring for 1 h. Purification by column chromatography (1:1 EtOAc: Petrol to 3:1 EtOAc: Petrol) yielded 2-formyl-5-methoxypyridine 1-oxide **19c** (98 mg, 0.64 mmol, 66%) as a white powdered solid.

m.p. (CH_2Cl_2) 149 – 151 °C; **δ_H** (400 MHz, $CDCl_3$) 10.49 (1H, d, *J* = 0.8 Hz, C(5)*H*), 7.91 (1H, d, *J* = 2.3 Hz, *Ar*), 7.74 (1H, d, *J* = 9.0 Hz, *Ar*), 6.88 (1H, ddd, *J* = 9.0, 2.3, 0.8 Hz, *Ar*), 3.90 (3H, s, OC(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 185.0, 161.5, 138.5, 127.9, 126.1, 112.5, 56.7; **ν_{max}**/ cm^{-1} (neat) 2981, 2886, 1683, 1592, 1406, 1375, 1316, 1275, 1195, 1176, 1151, 964, 832, 813, 662; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_7H_7O_3N^{23}Na^+$ calc. 176.0316, found 176.0320.

Methyl 6-(hydroxymethyl)nicotinate (61), 2-(hydroxymethyl)-5-(methoxycarbonyl)pyridine 1-oxide (62) and 2-bromo-6-formylpyridine 1-oxide (19d)



Methyl 6-(hydroxymethyl)nicotinate (61): Prepared according to **general procedure L**, using dimethyl pyridine-2,5-dicarboxylate (1.50 g, 7.70 mmol, 1.00

equiv.), $CaCl_2$ (3.42 g, 30.8 mmol, 4.00 equiv.) and $NaBH_4$ (726 mg, 19.2 mmol, 2.50 equiv.), with stirring for 3 h. Work-up yielded pure alcohol **61** (951 mg, 5.69 mmol, 74%) as an off-white solid.

m.p. (CH_2Cl_2) 64 – 68 °C; (*Lit:* 75 – 78 °C (Et_2O));[208] **δ_H** (400 MHz, $CDCl_3$) 9.16 – 9.11 (1H, m, *Ar*), 8.28 (1H, dd, *J* = 8.2, 2.1 Hz, *Ar*), 7.38 (1H, d, *J* = 8.1 Hz, *Ar*), 4.83 (2H, s, C(5)H_2), 3.94 (3H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 165.7, 163.8, 150.0, 138.0, 125.1, 120.2, 64.4, 52.5; **ν_{max}**/ cm^{-1} (neat) 3341, 2981, 1723, 1600, 1436, 1386, 1289, 1117, 1064, 1024, 955, 754; **m/z LRMS** (ESI^+) 168.0 $[M + H]^+$. Data is consistent with literature.[205]

2-(Hydroxymethyl)-5-(methoxycarbonyl)pyridine 1-oxide (62): Prepared according to **general procedure M**, using alcohol **61** (400 mg, 2.39 mmol, 1.00 equiv.) and *m*-CPBA (60% w/w, 823 g, 2.87 mmol, 1.20 equiv.), with stirring for 12 h. After completion, Et_2O trituration gave pure 2-(Hydroxymethyl)-5-(methoxycarbonyl)pyridine 1-oxide **62** (380 mg, 2.08 mmol, 87%) as an off-white solid (This reaction was performed by Dr Jagadeesh Kalepu).

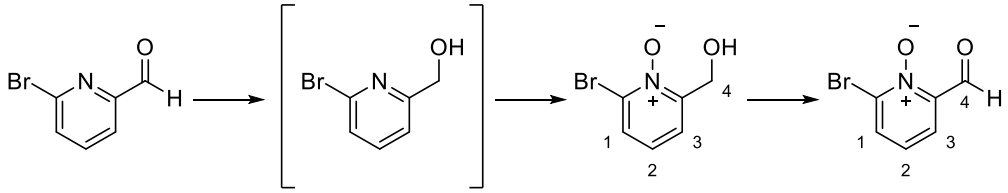
m.p. (Et_2O) 124 – 126 °C; **δ_H** (400 MHz, $CDCl_3$) 8.78 (1H, d, *J* = 1.6 Hz, *Ar*), 7.91 (1H, dd, *J* = 8.1, 1.5 Hz, *Ar*), 7.54 (1H, d, *J* = 8.1 Hz, *Ar*), 4.84 (2H, s, C(5)H_2), 3.95 (3H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 163.2, 154.2, 140.3, 128.3, 127.5, 124.2, 60.8, 53.1; **ν_{max}**/ cm^{-1} (neat) 3134, 3053, 2972, 1732, 1387, 1294, 1214, 1104, 1077, 988, 755; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{10}O_4N^+$ calc. 184.0604, found 184.0606.

2-Formyl-5-(methoxycarbonyl)pyridine 1-oxide (19d): Prepared according to **general procedure N**, using 2-bromo-6-(hydroxymethyl)pyridine 1-oxide **62** (350 mg, 1.91 mmol, 1.00 equiv.) and MnO_2 (1.66 g, 19.1 mmol, 10.0 equiv.), with stirring for 2 h. Purification by column chromatography (1:1 EtOAc:Petrol to 3:1

EtOAc:Petrol) yielded 2-formyl-5-(methoxycarbonyl)pyridine 1-oxide **19d** (180 mg, 0.990 mmol, 52%) as an off-white solid (This reaction was performed by Dr Jagadeesh Kalepu). ***Note: a higher loading of MnO_2 was used here, to achieve full conversion.***

m.p. (CH_2Cl_2) 158 – 160 °C; **δ_H** (400 MHz, $CDCl_3$) 10.60 (1H, d, *J* = 0.7 Hz, *Ar*), 8.77 – 8.74 (1H, m, *J* = 1.0 Hz, *Ar*), 7.90 – 7.81 (2H, m, *Ar*), 3.99 (3H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 185.3, 162.9, 145.8, 141.7, 132.8, 125.5, 125.4, 53.6; **ν_{max}**/ cm^{-1} (neat) 2981, 1718, 1695, 1302, 1178, 1089, 994, 754; **m/z HRMS** (ESI^+) [M + H]$^+$ $C_8H_8O_4N^+$ calc. 182.0448, found 182.0451.

2-Bromo-6-(hydroxymethyl)pyridine 1-oxide (64) and 2-bromo-6-formylpyridine 1-oxide (19e)



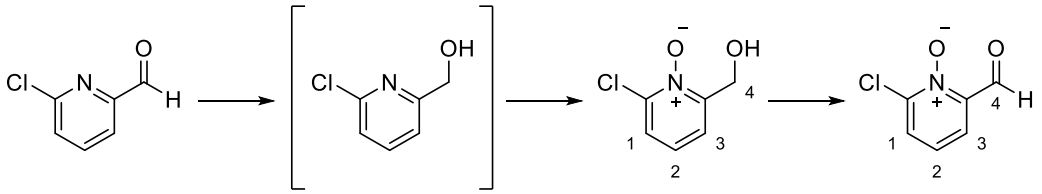
2-Bromo-6-(hydroxymethyl)pyridine 1-oxide (64): Prepared according to **general procedures K** and **M**. **General procedure K** used 6-bromopicolinealdehyde (1.00 g, 5.37 mmol, 1.00 equiv.) and $NaBH_4$ (224 mg, 5.91 mmol, 1.10 equiv.), with stirring for 1 h. **General procedure M** used crude alcohol **63** obtained from **general procedure K** and *m*-CPBA (60% w/w, 1.85 g, 6.44 mmol, 1.20 equiv.), ***and the reaction was instead stirred at 80 °C in 1,2-DCE for 18 h, in order to achieve full conversion***. After completion, Et_2O trituration gave pure 2-bromo-6-(hydroxymethyl)pyridine 1-oxide **64** (760 mg, 3.72 mmol, 69% yield over two steps) as an off-white powdered solid (These reactions were performed by Dr Jagadeesh Kalepu).

m.p. (Et_2O) 146 – 149 °C; **δ_H** (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J* = 8.1, 2.0 Hz, *Ar*), 7.36 (1H, dd, *J* = 7.7, 2.0 Hz, *Ar*), 7.17 (1H, app. t, *J* = 7.9 Hz, *Ar*), 4.82 (2H, s, C(4)H_2), 4.57 – 4.37 (1H, bs, O*H*); **δ_C** (101 MHz, $CDCl_3$) 151.8, 133.5, 129.7, 126.5, 123.5, 62.0; **ν_{max}**/ cm^{-1} (neat) 3217, 2981, 1471, 1386, 1235, 1083, 1067, 847, 791, 659; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_7O_2N^{79}Br^+$ calc. 203.9655, found 203.9657. Data is consistent with literature.[206]

2-Bromo-6-formylpyridine-1-oxide (19e): Prepared according to **general procedure N**, using 2-bromo-6-(hydroxymethyl)pyridine 1-oxide **64** (400 mg, 1.96 mmol) and MnO_2 (1.45 g, 16.7 mmol, 8.50 equiv.), with stirring for 2 h. Purification by column chromatography (1:1 EtOAc:Petrol to 3:1 EtOAc:Petrol) yielded 2-bromo-6-formylpyridine-1-oxide **19e** (180 mg, 0.89 mmol, 45% yield) as an off-white powdered solid (This reaction was performed by Dr Jagadeesh Kalepu).

m.p. (CH_2Cl_2) 110 – 112 °C; **δ_H** (400 MHz, $CDCl_3$) 10.58 (1H, d, *J* = 0.8 Hz, C(4)*H*), 7.86 (1H, dd, *J* = 8.1, 2.1 Hz, *Ar*), 7.79 (1H, dd, *J* = 7.8, 2.1 Hz, *Ar*), 7.18 (1H, app. td, *J* = 7.9, 0.8 Hz, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 185.7, 145.3, 134.7, 134.6, 124.9, 124.6; **ν_{max}**/ cm^{-1} (neat) 2981, 1689, 1592, 1383, 1357, 1234, 1128, 716; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_5O_2N^{79}Br^+$ calc. 201.9498, found 201.9501. Data is consistent with literature.[206]

2-Chloro-6-(hydroxymethyl)pyridine 1-oxide (66) and 2-Chloro-6-formylpyridine-1-oxide (19f)



65 **66** **19f**

2-Chloro-6-(hydroxymethyl)pyridine 1-oxide (66): Prepared according to **general procedures K** and **M**. **General procedure K** used 6-chloropicolinaldehyde (500 mg, 3.53 mmol, 1.00 equiv.) and $NaBH_4$ (148 mg, 3.89 mmol, 1.10 equiv.), with stirring for 1 h. **General procedure M** used crude alcohol **65** obtained from **general procedure K** and *m*-CPBA (60% w/w, 1.21 g, 4.24 mmol, 1.20 equiv.), ***and the reaction was instead stirred at 80 °C in 1,2-DCE for 18 h, in order to achieve full conversion***. After completion, Et_2O trituration gave pure 2-chloro-6-(hydroxymethyl)pyridine 1-oxide **66** (350 mg, 2.19 mmol, 62% yield over two steps) as an off-white powdered solid (These reactions were performed by Dr Jagadeesh Kalepu).

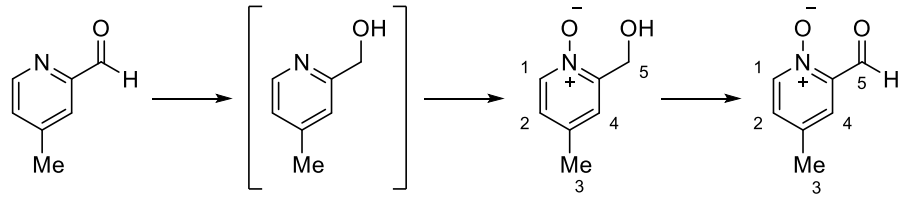
m.p. (Et_2O) 110 – 114 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.46 (1H, dd, *J* = 8.1, 2.0 Hz, *Ar*), 7.39 (1H, dd, *J* = 7.8, 2.0 Hz, *Ar*), 7.25 (1H, app. t, *J* = 7.9 Hz, *Ar*), 4.80 (2H, s, C(4)H_2), 4.78 – 4.60 (1H, bs, O*H*); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 152.4, 142.1, 126.6, 125.6, 122.4, 61.2; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3199, 1474, 1391, 1335, 1236, 1205, 1184, 1157, 1087, 1070, 867, 845, 795, 681; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_7O_2N^{35}Cl^+$ calc. 160.0160, found 160.0161.

2-Chloro-6-formylpyridine-1-oxide (19f): Prepared according to **general procedure N**, using 2-chloro-6-(hydroxymethyl)pyridine 1-oxide **66** (315 mg, 1.98 mmol, 1.00 equiv.) and a higher loading of MnO_2 (2.00 g, 23.0 mmol, 11.6 equiv.),

with stirring for 2 h. Purification by column chromatography (1:1 EtOAc:Petrol to 3:1 EtOAc:Petrol) yielded 2-chloro-6-formylpyridine-1-oxide **19f** (130 mg, 0.82 mmol, 42% yield) as an off-white powdered solid (This reaction was performed by Dr Jagadeesh Kalepu). ***Note: a higher loading of MnO_2 was used here, to achieve full conversion.***

m.p. (CH_2Cl_2) 101 – 105 °C; δ_H 10.58 (1H, d, *J* = 0.8 Hz, C(4)*H*), 7.75 (1H, dd, *J* = 7.8, 2.1 Hz, *Ar*), 7.69 (1H, dd, *J* = 8.1, 2.1 Hz, *Ar*), 7.26 (1H, dd, *J* = 15.9, 0.8 Hz, *Ar*); δ_C (101 MHz, $CDCl_3$) 185.4, 145.1, 143.1, 130.9, 124.8, 123.8; ν_{max}/ cm^{-1} (neat) 2976, 1695, 1612, 1387, 1367, 847, 784, 738; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_5O_2N^{35}Cl^+$ calc. 158.0003, found 158.0003.

2-(Hydroxymethyl)-4-methylpyridine 1-oxide (68) and 2-formyl-4-methylpyridine 1-oxide (19g)



67 **68** **19g**

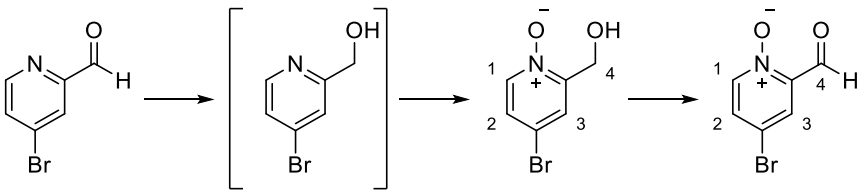
2-(Hydroxymethyl)-4-methylpyridine 1-oxide (68): Prepared according to **general procedures K** and **M**. **General procedure K** used 4-methylpicolinaldehyde (500 mg, 4.13 mmol, 1.00 equiv.) and $NaBH_4$ (172 mg, 4.54 mmol, 1.10 equiv.) with stirring for 1 h. **General procedure M** used crude alcohol **67** obtained from **general procedure K** and *m*-CPBA (60% w/w, 1.43 g, 4.96 mmol, 1.20 equiv.) with stirring for 12 h. Purification by column chromatography (EtOAc to 1:4 MeOH:EtOAc) yielded 2-(hydroxymethyl)-4-methylpyridine 1-oxide **68** (356 mg, 2.56 mmol, 62% over two steps) as an off-white solid.

m.p. (CH_2Cl_2) 109 – 112 °C; **δ_H** (400 MHz, $CDCl_3$) 8.11 (1H, d, *J* = 6.5 Hz, *Ar*), 7.19 (1H, d, *J* = 2.5 Hz, *Ar*), 7.04 (1H, dd, *J* = 6.6, 2.5 Hz, *Ar*), 5.28 (1H, bs, O*H*), 4.76 (2H, s, C(5)H_2), 2.35 (3H, s, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 149.7, 139.7, 138.8, 125.4, 125.3, 61.0, 20.6; **ν_{max}**/ cm^{-1} (neat) 3227, 1480, 1456, 1213, 1066, 820, 732; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{10}O_2N^+$ calc. 140.0706, found 140.0706.

2-Formyl-4-methylpyridine 1-oxide (19g): Prepared according to **general procedure N**, using 2-(hydroxymethyl)-4-methylpyridine 1-oxide **68** (356 mg, 2.56 mmol, 1.00 equiv.) and MnO_2 (1.89 g, 21.76 mmol, 8.50 equiv.), with stirring for 2 h. Purification by column chromatography (1:1 CH_2Cl_2:Acetone) yielded 2-formyl-4-methylpyridine 1-oxide **19g** (195 mg, 1.43 mmol, 56%) as a pale-yellow solid.

m.p. (CH_2Cl_2) 101 – 103 °C; **δ_H** (400 MHz, $CDCl_3$) 10.61 (1H, s, C(5)*H*), 8.09 (1H, d, *J* = 6.7 Hz, *Ar*), 7.60 (1H, d, *J* = 2.7 Hz, *Ar*), 7.28 – 7.21 (1H, m, *Ar*), 2.37 (3H, s, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 186.1, 142.9, 139.8, 137.1, 130.8, 125.9, 20.4; **ν_{max}**/ cm^{-1} (neat) 1695, 1475, 1200, 1066, 1037, 826; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_8O_2N^+$ calc. 138.0550, found 138.0548.

4-Bromo-2-(hydroxymethyl)pyridine 1-oxide (70) and 4-bromo-2-formylpyridine 1-oxide (19h)



69 **70** **19h**

For 4-bromo-2-(hydroxymethyl)pyridine 1-oxide (70): Prepared according to **general procedures K** and **M**. **General procedure K** used 4-bromopicolinaldehyde (500 mg, 2.69 mmol, 1.00 equiv.) and $NaBH_4$ (112 mg, 2.96

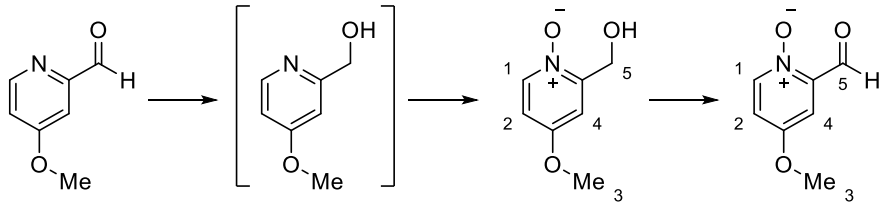
mmol, 1.10 equiv.), with stirring for 5 h. ***After this time, TLC showed incomplete conversion, and so more $NaBH_4$ (41.0 mg, 1.08 mmol, 0.400 equiv.) was added. After an additional 3 h, TLC showed completion.*** **General procedure M** used crude alcohol **69** obtained from **general procedure K** and *m*-CPBA (60% w/w, 930 mg, 3.23 mmol, 1.20 equiv.), with stirring for 12 h. After completion, Et_2O trituration gave pure 4-bromo-2-(hydroxymethyl)pyridine 1-oxide **70** (379 mg, 1.86 mmol, 69% yield over two steps) as a white powdered solid.

m.p. (Et_2O) Decomp. at 140 – 142 °C; $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 8.17 (1H, d, *J* = 6.9 Hz, *Ar*), 7.63 (1H, d, *J* = 2.9 Hz, *Ar*), 7.57 (1H, dd, *J* = 6.9, 3.0 Hz, *Ar*), 4.55 (2H, s, C(4)H_2); $\boldsymbol{\delta_C}$ (101 MHz, DMSO-d_6) 153.2, 140.0, 127.1, 125.7, 117.6, 57.9; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3256, 3105, 1466, 1432, 1408, 1254, 1209, 1086, 1060, 815, 650; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_7O_2N^{79}Br^+$ calc. 203.9655, found 203.9656.

4-Bromo-2-formylpyridine 1-oxide (19h): Prepared according to **general procedure N**, using 4-bromo-2-(hydroxymethyl)pyridine 1-oxide **70** (300 mg, 1.48 mmol, 1.00 equiv.) and MnO_2 (1.09 g, 12. 6 mmol, 8.50 equiv.), with stirring for 4 h. ***After this time, TLC showed incomplete conversion, and so more MnO_2 (192 mg, 2.22 mmol, 1.50 equiv.) was added and the temperature was increased to 100 °C. TLC showed completion after 1 h at this temperature.*** Purification by column chromatography (1:0 to 3:1 CH_2Cl_2:Acetone) yielded 4-Bromo-2-formylpyridine 1-oxide **19h** (132 mg, 0.66 mmol, 45%) as an off-white solid.

m.p. (CH_2Cl_2) 152 – 154 °C; $\boldsymbol{\delta_H}$ 10.52 (1H, d, *J* = 0.7 Hz, C(4)*H*), 8.05 (1H, dd, *J* = 6.9, 0.5 Hz, *Ar*), 7.90 (1H, d, *J* = 3.0 Hz, *Ar*), 7.55 (1H, dd, *J* = 6.9, 3.0 Hz, *Ar*); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 184.6, 144.2, 141.4, 133.0, 128.7, 118.6; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3085, 1680, 1594, 1455, 1415, 1369, 1264, 1242, 1213, 1174, 889, 845, 828, 650, 617; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_5O_2N^{79}Br^+$ calc. 201.9498, found 201.9500.

2-(Hydroxymethyl)-4-methoxypyridine 1-oxide (72) and 2-formyl-4-methoxypyridine 1-oxide (19i)



2-(Hydroxymethyl)-4-methoxypyridine 1-oxide (72): Prepared according to **general procedures K** and **M**. **General procedure K** used 5-methoxypicolinaldehyde (500 mg, 3.64 mmol, 1.00 equiv.) and $NaBH_4$ (152 mg, 4.00 mmol, 1.10 equiv.) with stirring for 1 h. **General procedure M** used crude alcohol **71** obtained from **general procedure K** and *m*-CPBA (60%, 1.25 mg, 4.37 mmol, 1.20 equiv.) and stirring for 12 h. After completion, Et_2O trituration gave pure 2-(hydroxymethyl)-4-methoxypyridine 1-oxide **72** (280 mg, 1.80 mmol, 49% yield over two steps) as an off-white solid.

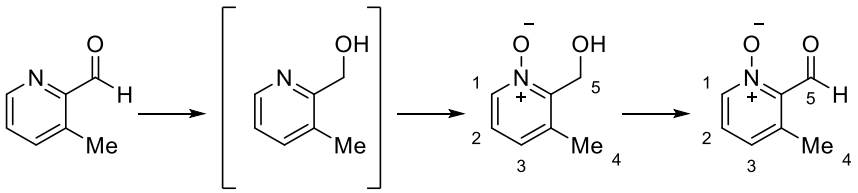
m.p. (Et_2O) 129 – 132 °C; (*Lit:* 135 – 137 °C);[209] $\boldsymbol{\delta_H}$ 8.09 (1H, d, *J* = 7.2 Hz, *Ar*), 6.99 (1H, d, *J* = 3.5 Hz, *Ar*), 6.75 (1H, dd, *J* = 7.2, 3.4 Hz, *Ar*), 5.58 (1H, bs, O*H*), 4.77 (2H, s, C(5)H_2), 3.85 (3H, s, C(3)H_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 159.3, 152.1, 140.2, 110.9, 109.2, 60.8, 56.3; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 2981, 1629, 1487, 1469, 1430, 1302, 1203, 1187, 1157, 1107, 1063, 1025, 820, 720; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{10}O_3N^+$ calc. 156.0655, found 156.0655. Data is consistent with literature.[208]

2-Formyl-4-methoxypyridine 1-oxide (19i): Prepared according to **general procedure N**, using 2-(hydroxymethyl)-4-methoxypyridine 1-oxide **72** (256 mg, 1.65 mmol, 1.00 equiv.) and MnO_2 (1.22 g, 14.0 mmol, 8.50 equiv.), with stirring for 1 h. Purification by column chromatography (1:1 EtOAc:Acetone) yielded 2-

formyl-4-methoxypyridine 1-oxide **19i** (127 mg, 0.83 mmol, 50%) as a yellow powdered solid.

m.p. (CH_2Cl_2) 106 – 110 °C; **δ_H** (400 MHz, $CDCl_3$) 10.62 (1H, s, C(5)*H*), 8.11 (1H, d, *J* = 7.3 Hz, *Ar*), 7.29 (1H, d, *J* = 3.6 Hz, *Ar*), 7.01 (1H, dd, *J* = 7.3, 3.7 Hz, *Ar*), 3.90 (3H, s, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 186.0, 157.3, 143.7, 141.4, 117.6, 108.8, 56.6; **ν_{max}**/ cm^{-1} (neat) 3073, 2981, 1631, 1450, 1430, 1303, 1206, 1187, 1159, 1069, 1023, 827, 759; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_8O_3N^+$ calc. 154.0499, found 154.0498.

2-(Hydroxymethyl)-3-methylpyridine 1-oxide (74) and 2-formyl-3-methylpyridine 1-oxide (19j)



73 **74** **19j**

2-(Hydroxymethyl)-3-methylpyridine 1-oxide (74): Prepared according to **general procedures K** and **M**. **General procedure K** used 3-methylpicolinaldehyde (463 mg, 4.13 mmol, 1.00 equiv.) and $NaBH_4$ (172 mg, 4.54 mmol, 1.10 equiv.), with stirring for 1.5 h. **General procedure M** used crude alcohol **73** obtained from **general procedure K** and *m*-CPBA (60% w/w, 1.43 g, 4.96 mmol, 1.20 equiv.), with stirring for 2 h. Purification by column chromatography (1:1 EtOAc:Petrol to 1:9 MeOH:EtOAc) yielded 2-(hydroxymethyl)-3-methylpyridine 1-oxide **74** (333 mg, 2.40 mmol, 58% over two steps) as an off-white solid.

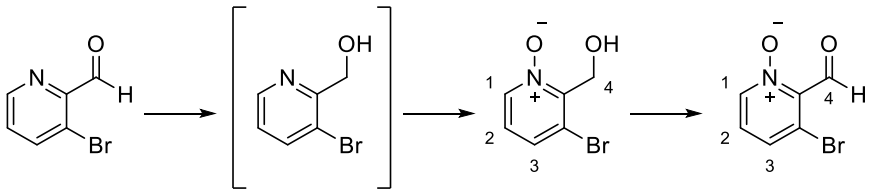
m.p. (CH_2Cl_2) 131 – 135 °C; **δ_H** (400 MHz, $CDCl_3$) 8.10 (1H, dd, *J* = 5.7, 2.0 Hz, *Ar*), 7.18 – 7.08 (2H, m, *Ar*), 5.74 (1H, bs, O*H*), 4.82 (2H, s, C(5)H_2), 2.37 (3H, s,

C(4)*H*$_3$); **δ**$_C$ (101 MHz, $CDCl_3$) 148.7, 137.5, 134.6, 129.4, 124.1, 58.0, 18.5; **ν$_{max}$**/ cm^{-1} (neat) 3144, 1251, 1224, 1182, 1093, 1058, 1042, 1026, 804; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{10}O_2N^+$ calc. 140.0706, found 140.0705.

2-Formyl-3-methylpyridine 1-oxide (19j): Prepared according to **general procedure N**, using 2-(hydroxymethyl)-3-methylpyridine 1-oxide **74** (270 mg, 1.94 mmol, 1.00 equiv.) and MnO_2 (1.43 g, 16.5 mmol, 8.50 equiv.), with stirring for 3 h. Purification by column chromatography (1:1 CH_2Cl_2:Acetone) yielded 2-formyl-3-methylpyridine 1-oxide **19j** (147 mg, 1.07 mmol, 55%) as an off-white solid.

m.p. (CH_2Cl_2) 105 – 108 °C; **δ$_H$** (400 MHz, $CDCl_3$) 10.63 (1H, d, *J* = 0.6 Hz, C(5)*H*), 8.10 (1H, d, *J* = 6.4 Hz, *Ar*), 7.30 (1H, dd, *J* = 7.9, 6.4 Hz, *Ar*), 7.11 (1H, dq, *J* = 8.0, 0.9 Hz, *Ar*), 2.53 (3H, s, C(4)*H*$_3$); **δ$_C$** (101 MHz, $CDCl_3$) 188.6, 142.7, 139.7, 137.9, 128.8, 128.4, 19.2; **ν$_{max}$**/ cm^{-1} (neat) 2981, 1699, 1587, 1476, 1445, 1418, 1382, 1265, 1207, 1177, 1092, 1070, 1042, 960, 834, 752; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_8O_2N^+$ calc. 138.0550, found 138.0548.

3-Bromo-2-(hydroxymethyl)pyridine 1-oxide (76) and 3-bromo-2-formylpyridine 1-oxide (19k)



75 **76** **19k**

3-Bromo-2-(hydroxymethyl)pyridine 1-oxide (76): Prepared according to the **general procedures K** and **M**. **General procedure K** used 3-bromopicolinaldehyde (1.00 g, 5.43 mmol, 1.00 equiv.) and $NaBH_4$ (227 mg, 5.98 mmol, 1.10 equiv.), with stirring for 1 h. **General procedure M** used crude alcohol

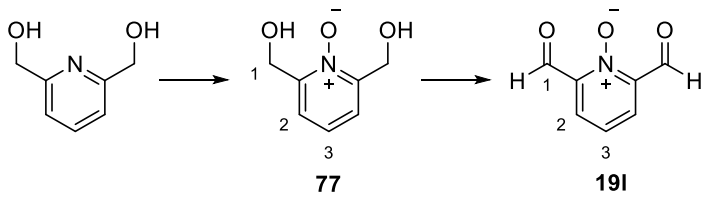
75 obtained from **general procedure K** and *m*-CPBA (60% w/w, 1.86 g, 6.52 mmol, 1.20 equiv.), with stirring for 12 h. After completion, Et_2O trituration gave pure 3-bromo-2-(hydroxymethyl)pyridine 1-oxide **76** (760 mg, 3.76 mmol, 69% yield over two steps) as an off-white solid (These reactions were performed by Dr Jagadeesh Kalepu).

m.p. (Et_2O) 136 – 140 °C; $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 8.31 (1H, dd, *J* = 6.5, 1.0 Hz, *Ar*), 7.64 (1H, dd, *J* = 8.3, 1.0 Hz, *Ar*), 7.31 (1H, dd, *J* = 8.3, 6.5 Hz, *Ar*), 5.41 (1H, s, O*H*), 4.79 (2H, s, C(4)H_2); $\boldsymbol{\delta_C}$ (101 MHz, DMSO-d_6) 149.2, 138.8, 129.5, 125.7, 121.5, 57.6; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3258, 3104, 3010, 2875, 1412, 1229, 1164, 1036, 969, 862; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_7O_2N^{79}Br^+$ calc. 203.9655, found 203.9657.

3-Bromo-2-formylpyridine 1-oxide (19k): Prepared according to **general procedure N**, using 3-bromo-2-(hydroxymethyl)pyridine 1-oxide **76** (400 mg, 1.96 mmol, 1.00 equiv.) and MnO_2 (2.56 g, 29.4 mmol, 15.0 equiv.). Purification by column chromatography (1:1 EtOAc:Petrol to 3:1 EtOAc: Petrol) yielded 3-bromo-2-formylpyridine 1-oxide **19k** (180 mg, 0.90 mmol, 46%) as an off-white solid (This reaction was performed by Dr Jagadeesh Kalepu). ***Note: a higher loading of MnO_2 was used here, to achieve full conversion.***

m.p. (CH_2Cl_2) 122 – 125 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 10.28 (1H, d, *J* = 0.7 Hz, C(4)*H*), 8.18 (1H, dd, *J* = 6.5, 1.0 Hz, *Ar*), 7.53 (1H, app. dt, *J* = 8.4, 0.8 Hz, *Ar*), 7.26 (1H, dd, *J* = 8.4, 6.4 Hz, *Ar*); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 184.3, 142.8, 139.3, 131.1, 128.2, 120.2; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3102, 1707, 1455, 1421, 1228, 1180, 1064, 1028, 987, 902, 792, 726; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_6H_5O_2N^{79}Br^+$ calc. 201.9498, found 201.9501.

2,6-Bis(hydroxymethyl)pyridine 1-oxide (77) and 2,6-Diformylpyridine 1-oxide (19l)



77 **19l**

For 2,6-Bis(hydroxymethyl)pyridine 1-oxide (77): Prepared according to **general procedure M**, using pyridine-2,6-diyldimethanol (2.00 g, 14.4 mmol, 1.00 equiv.), with *m*-CPBA (60% w/w, 4.96 g, 17.3 mmol, 1.20 equiv.) ***as a more diluted solution in $CHCl_3$ (0.075 M) instead of CH_2Cl_2***.[209] The reaction was stirred for 2 h. After completion, Et_2O trituration gave 2,6-bis(hydroxymethyl)pyridine 1-oxide **77** (2.17 g, 14.0 mmol, 97%) as a white powdered solid.

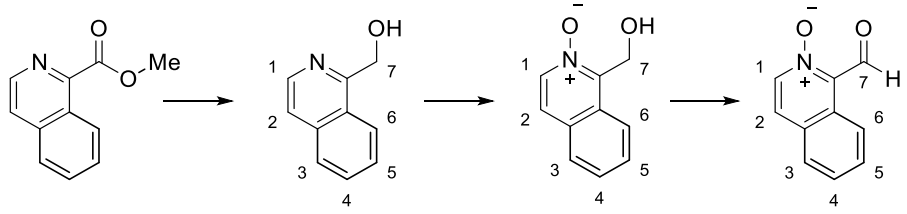
m.p. (Et_2O) 135 – 138 °C; **δ_H** (400 MHz, DMSO-*d_6*) 7.51 – 7.39 (3H, m, *Ar*), 5.57 (2H, t, *J* = 5.7 Hz, O*H*), 4.60 (4H, d, *J* = 5.7 Hz, C(1)*H_2*); **δ_C** (101 MHz, MeOD-*d_4*) 153.5, 130.2, 122.4, 59.6; **ν_{max}**/ cm^{-1} (neat) 3455, 3264, 2972, 2890, 1412, 1250, 1207, 1155, 1091, 954, 840, 776, 669; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_{10}O_3N^+$ calc. 156.0655, found 156.0654.

2,6-Diformylpyridine 1-oxide (19l): Prepared according to **general procedure N**, using 2,6-bis(hydroxymethyl)pyridine 1-oxide **77** (490 mg, 3.16 mmol, 1.00 equiv.) and MnO_2 (4.67 g, 53.72 mmol, 17.0 equiv.), with stirring for 6 h. Purification by column chromatography (1:1 to 3:1 EtOAc:Pentane) yielded 2,6-diformylpyridine 1-oxide **19l** (373 mg, 2.48 mmol, 78%) as an off-white powdered solid. ***Note: double the loading of MnO_2 was used here, to permit double alcohol oxidation.***

m.p. (CH_2Cl_2) 182 – 184 °C; **δ_H** (400 MHz, DMSO-*d_6*) 10.39 (2H, d, *J* = 0.8 Hz, C(1)*H*), 8.00 (2H, d, *J* = 7.8 Hz, *Ar*), 7.53 (1H, t, *J* = 7.8 Hz, *Ar*); **δ_C** (101 MHz,

DMSO-d_6) 185.3, 144.0, 129.1, 125.2; ν_{max}/ cm^{-1} (neat) 3046, 2981, 1702, 1677, 1549, 1399, 1379, 1269, 1249, 1205, 906, 850, 809, 708; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_7H_6O_3N^+$ calc. 152.0342, found 152.0342.

Isoquinolin-1-ylmethanol (78), 1-(Hydroxymethyl)isoquinoline 2-oxide (79) and 1-Formylisoquinoline 2-oxide (19m)



For Isoquinolin-1-ylmethanol (78): Prepared according to **general procedure L**, using methyl isoquinoline-1-carboxylate (1.46 g, 7.79 mmol, 1.00 equiv.), $CaCl_2$ (3.46 g, 31.2 mmol, 4.00 equiv.) and $NaBH_4$ (738 mg, 19.5 mmol, 2.50 equiv.) with stirring for 5 h. Work-up yielded isoquinolin-1-ylmethanol **78** (1.24 g, 7.78 mmol, >99%), as an off-white solid.

m.p. (CH_2Cl_2) 60 – 62 °C; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, d, *J* = 5.8 Hz, *Ar*), 7.95 – 7.87 (1H, m, *Ar*), 7.87 – 7.81 (1H, m, *J* = 9.2, 1.0 Hz, *Ar*), 7.70 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz, *Ar*), 7.65 – 7.54 (2H, m, *Ar*), 5.22 (2H, s, C(7)H_2), 4.71 (1H, s, O*H*); δ_C (101 MHz, $CDCl_3$) 157.6, 140.5, 136.0, 130.6, 127.6, 127.5, 125.1, 123.3, 120.4, 61.6; **m/z LRMS** (ESI^+) 160.0 $[M + H]^+$. Data is consistent with literature.[210]

***For 1-(Hydroxymethyl)isoquinoline 2-oxide (79)*:** Prepared according to **general procedure M**, using isoquinolin-1-ylmethanol **78** (500 mg, 3.14 mmol, 1.00 equiv.), with *m*-CPBA (60% w/w, 1.08 g, 3.77 mmol, 1.20 equiv.) and stirring for 36 h. Purification by column chromatography (3:1 to 1:3 CH_2Cl_2:Acetone) yielded

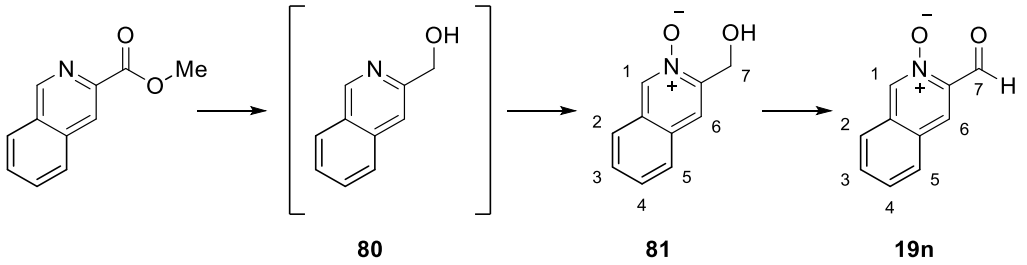
1-(hydroxymethyl)isoquinoline 2-oxide **79** (296 mg, 1.69 mmol, 54%) as an off-white solid.

m.p. (CH_2Cl_2) 124 – 126 °C; **δ_H** (400 MHz, $CDCl_3$) 8.16 (1H, d, *J* = 7.1 Hz, *Ar*), 8.06 – 7.99 (1H, m, *Ar*), 7.82 (1H, d, *J* = 7.2 Hz, *Ar*), 7.73 – 7.59 (3H, m, *Ar*), 6.04 – 5.41 (1H, bs, O*H*), 5.27 (2H, s, C(7)H_2); **δ_C** (101 MHz, $CDCl_3$) 146.2, 136.3, 129.8, 129.7, 129.3, 127.6, 127.4, 123.7, 123.2, 57.1; **ν_{max}**/ cm^{-1} (neat) 3221, 2981, 1333, 1278, 1215, 1179, 1143, 1066, 1012, 817, 750; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{10}O_2N^+$ calc. 176.0706, found 176.0706.

For 1-Formylisoquinoline 2-oxide (19m): Prepared according to **general procedure N**, using 1-(hydroxymethyl)isoquinoline 2-oxide **79** (270 mg, 1.54 mmol, 1.00 equiv.) and MnO_2 (1.14 g, 13.1 mmol, 8.50 equiv.), with stirring for 1 h. Purification by column chromatography (4:1 CH_2Cl_2:Acetone) yielded 1-formylisoquinoline 2-oxide **19m** (185 mg, 1.07 mmol, 69%) as a yellow powdered solid.

m.p. (CH_2Cl_2) 134 – 136 °C; **δ_H** (400 MHz, $CDCl_3$) 10.81 (1H, s, C(7)*H*), 8.90 (1H, d, *J* = 8.7 Hz, *Ar*), 8.11 (1H, d, *J* = 7.1 Hz, *Ar*), 7.82 (1H, d, *J* = 7.1 Hz, *Ar*), 7.78 (1H, d, *J* = 8.1 Hz, *Ar*), 7.76 – 7.68 (1H, m, *Ar*), 7.66 – 7.57 (1H, m, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 188.6, 138.8, 137.1, 131.9, 129.2, 128.7, 128.5, 127.9, 127.3, 123.8; **ν_{max}**/ cm^{-1} (neat) 1686, 1623, 1498, 1432, 1317, 1230, 1141, 823, 751; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_8O_2N^+$ calc. 174.0550, found 174.0550. Data is consistent with literature.[206]

3-(Hydroxymethyl)isoquinoline 2-oxide (81) and 3-Formylisoquinoline-2-oxide (19n)



For 3-(Hydroxymethyl)isoquinoline 2-oxide (81): Prepared according to **general procedures L** and **M**. **General procedure L** used methyl isoquinoline-3-carboxylate (500 mg, 2.67 mmol, 1.00 equiv.), $CaCl_2$ (1.19 g, 10.69 mmol, 4.00 equiv.) and $NaBH_4$ (253 mg, 6.68 mmol, 2.50 equiv.) with stirring for 1.5 h. **General procedure M** used crude alcohol **80** obtained from **general procedure L**, with *m*-CPBA (60% w/w, 920 mg, 3.20 mmol, 1.20 equiv.) and stirring for 20 h. After completion, Et_2O trituration gave 3-(hydroxymethyl)isoquinoline 2-oxide **81** (397 mg, 2.27 mmol, 85% over two steps) as an off-white solid.

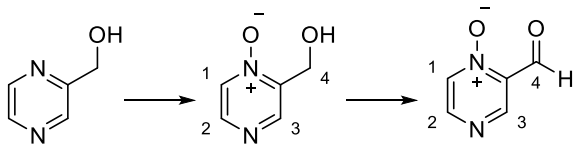
m.p. (Et_2O) 204 – 208 °C; $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 9.01 (1H, s, *Ar*), 8.02 – 7.96 (2H, m, *Ar*), 7.93 – 7.84 (1H, m, *Ar*), 7.66 – 7.55 (2H, m, *Ar*), 5.67 (1H, t, J = 5.7 Hz, O*H*), 4.71 (2H, dd, J = 5.6, 1.4 Hz, C(7)H_2); $\boldsymbol{\delta_C}$ (101 MHz, DMSO-d_6) 148.5, 135.3, 128.4, 128.1, 128.1, 126.5, 124.5, 120.1, 58.1; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3247, 2972, 1320, 1207, 1170, 1103, 751; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{10}O_2N^+$ calc. 176.0706, found 176.0707.

For 3-Formylisoquinoline 2-oxide (19n): Prepared according to **general procedure N**, using 3-(hydroxymethyl)isoquinoline 2-oxide **81** (300 mg, 1.71 mmol, 1.00 equiv.) and MnO_2 (1.27 g, 14.57 mmol, 8.50 equiv.), with stirring for 2.5 h. ***After this time, starting material could still be observed by TLC, and so more***

MnO_2 (374 mg, 4.23 mmol, 2.5 equiv.) was added and the temperature was increased to 100 °C. TLC showed completion after 1 h at this temperature. Purification by column chromatography (1:1 CH_2Cl_2:Acetone) yielded 3-formylisoquinoline 2-oxide **19n** (137 mg, 0.792 mmol, 46%) as a yellow solid.

m.p. (CH_2Cl_2) Decomp. at 220 – 224 °C; **δ_H** (400 MHz, $CDCl_3$) 10.80 (1H, s, C(7)*H*), 8.77 (1H, s, *Ar*), 8.30 (1H, s, *Ar*), 7.93 (1H, d, *J* = 8.1 Hz, *Ar*), 7.81 – 7.69 (2H, m, *Ar*), 7.69 – 7.61 (1H, m, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 186.4, 140.2, 137.2, 132.0, 131.6, 130.0, 129.2, 128.2, 125.9, 125.1; **ν_{max}**/ cm^{-1} (neat) 1692, 1623, 1599, 1317, 1179; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_8O_2N^+$ calc. 174.0550, found 174.0551. Data is consistent with literature.[206]

2-(Hydroxymethyl)pyrazine 1-oxide (82) and 2-Formylpyrazine 1-oxide (19o)



82 **19o**

For 2-(Hydroxymethyl)pyrazine 1-oxide (82): Prepared according to **general procedure M**, using 2-pyrazinylmethanol (404 mg, 3.67 mmol, 1.00 equiv.), with *m*-CPBA (60% w/w, 950 mg, 3.30 mmol, 0.900 equiv.) and stirring for 20 h. Purification by column chromatography (1:1 to 1:3 CH_2Cl_2:Acetone) yielded pure 2-(hydroxymethyl)pyrazine 1-oxide **82** (108 mg, 0.857 mmol, 23%) as an off-white solid.

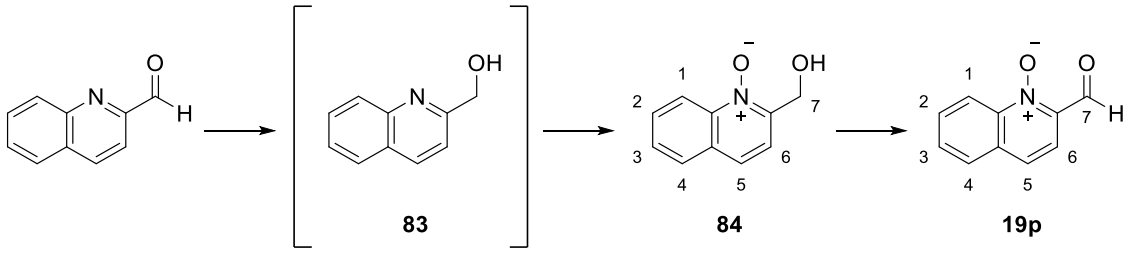
m.p. (Et_2O) 89 – 91 °C; **δ_H** (400 MHz, Acetone-d_6) 8.67 (1H, s, *Ar*), 8.46 (1H, d, *J* = 4.1 Hz, *Ar*), 8.21 (1H, dd, *J* = 4.1, 0.7 Hz, *Ar*), 4.78 (3H, app. s, C(4)H_2 and O*H*); **δ_C** (101 MHz, Acetone-d_6) 147.3, 146.9, 146.5, 134.2, 58.3; **ν_{max}**/ cm^{-1} (neat) 3252,

3108, 1592, 1456, 1437, 1402, 1248, 1197, 1174, 1072, 1049, 864, 847, 838, 694; **m/z HRMS** (ESI$^+$) $[M + H]^+$ $C_5H_7O_2N_2^+$ calc. 127.0502, found 127.0503.

2-Formylpyrazine 1-oxide (19o): Prepared according to **general procedure N**, using ***2***-(hydroxymethyl)pyrazine 1-oxide **82** (108 mg, 0.857 mmol, 1.00 equiv.) and MnO_2 (633 mg, 7.28 mmol, 8.50 equiv.), with stirring for 3 h. Purification by column chromatography (3:1 CH_2Cl_2:Acetone) yielded 2-formylpyrazine 1-oxide **19o** (42.3 mg, 0.341 mmol, 40%) as an off-white powdered solid.

m.p. (CH_2Cl_2) 116 – 118 °C; δ_H (400 MHz, Acetone-d_6) 10.44 (1H, s, C(4)*H*), 8.81 (1H, s, *Ar*), 8.69 (1H, d, *J* = 4.3 Hz, *Ar*), 8.32 (1H, dd, *J* = 4.2, 0.8 Hz, *Ar*); δ_C (101 MHz, Acetone-d_6) 185.8, 152.0, 148.0, 140.1, 135.9; ν_{max}/ cm^{-1} (neat) 2924, 1676, 1586, 1445, 1412, 1381, 1306, 1275, 1195, 1056, 871, 809, 661; **m/z HRMS** (ESI$^+$) $[M + H]^+$ $C_5H_5O_2N_2^+$ calc. 125.0346, found 125.0347.

2-(Hydroxymethyl)quinoline 1-oxide (84) and 2-Formylquinoline 1-oxide (19p)



For 2-(Hydroxymethyl)quinoline 1-oxide (84): Prepared according to **general procedures K** and **M**. **General procedure K** used quinoline carboxaldehyde (800 mg, 5.10 mmol, 1.00 equiv.) and $NaBH_4$ (213 mg, 5.61 mmol, 1.10 equiv.) with stirring for 1 h. **General procedure M** used crude alcohol **83** obtained from **general procedure K**, with *m*-CPBA (60% w/w, 1.75 g, 6.12 mmol, 1.20 equiv.) and stirring for 12 h. After completion, Et_2O trituration gave pure 2-(hydroxymethyl)quinoline

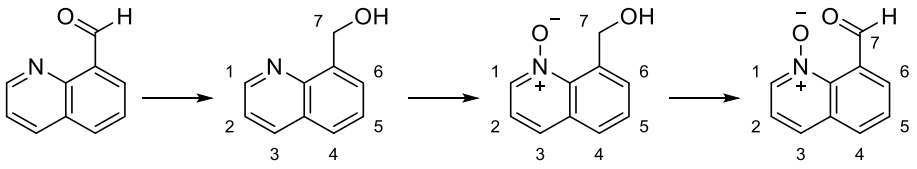
1-oxide **84** (420 mg, 2.40 mmol, 47% yield over two steps) as an off white solid (These reactions were performed by Dr Jagadeesh Kalepu).

m.p. (Et_2O) 109 – 113 °C; **δ_H** (400 MHz, $CDCl_3$) 8.70 (1H, d, *J* = 8.8 Hz, *Ar*), 7.88 – 7.82 (1H, m, *Ar*), 7.82 – 7.73 (2H, m, *Ar*), 7.67 – 7.59 (1H, m, *Ar*), 7.43 (1H, d, *J* = 8.5 Hz, *Ar*), 5.18 (1H, bs, O*H*), 5.01 (2H, s, C(7)H_2); **δ_C** (101 MHz, $CDCl_3$) 147.3, 141.3, 131.0, 129.6, 128.6, 128.3, 127.1, 120.5, 119.1, 62.0; **ν_{max}**/ cm^{-1} (neat) 3222, 2981, 2886, 1340, 1229, 1211, 1185, 1094, 1066, 813, 768, 736; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{10}O_2N^+$ calc. 176.0706, found 176.0707.

For 2-Formylquinoline 1-oxide (19p): Prepared according to **general procedure N**, using 2-(hydroxymethyl)quinoline 1-oxide **84** (400 mg, 2.28 mmol) and MnO_2 (1.69 g, 19.2 mmol, 8.50 equiv.) with stirring for 2 h. Purification by column chromatography (1:1 to 3:1 EtOAc: Petrol) yielded 2-formylquinoline 1-oxide **19p** (200 mg, 1.15 mmol, 50% yield) as a yellow/orange solid (This reaction was performed by Dr Jagadeesh Kalepu).

m.p. (CH_2Cl_2) 103 – 105 °C; **δ_H** (400 MHz, $CDCl_3$) 10.83 (1H, d, *J* = 0.8 Hz, C(7)*H*), 8.78 – 8.73 (1H, m, *Ar*), 7.88 (1H, dd, *J* = 8.0, 1.5 Hz, *Ar*), 7.82 – 7.68 (4H, m, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 186.5, 142.3, 140.4, 132.2, 131.1, 131.1, 128.6, 124.8, 120.1, 119.1; **ν_{max}**/ cm^{-1} (neat) 3104, 3060, 1696, 1676, 1448, 1371, 1227, 1208, 824, 770; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_8O_2N^+$ calc. 174.0550, found 174.0550. Data is consistent with literature.[206]

Quinolin-8-ylmethanol (85), 8-(Hydroxymethyl)quinoline 1-oxide (86) and 8-Formylquinoline 1-oxide (19q)



For Quinolin-8-ylmethanol (85): Prepared according to **general procedure K**, using quinoline-8-carbaldehyde (1.00 g, 6.37 mmol, 1.00 equiv.), $NaBH_4$ (265 mg, 7.00 mmol, 1.10 equiv.) with stirring for 1.5 h. Purification by column chromatography (1:9 to 1:1 EtOAc:Petrol) yielded quinolin-8-ylmethanol **85** (622 mg, 3.91 mmol, 61%), as an off-white solid.

m.p. ($CHCl_3$) 73 – 75 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.87 (1H, dd, *J* = 4.2, 1.8 Hz, *Ar*), 8.20 (1H, dd, *J* = 8.3, 1.8 Hz, *Ar*), 7.76 (1H, dd, *J* = 8.2, 1.5 Hz, *Ar*), 7.61 – 7.57 (1H, m, *Ar*), 7.49 (1H, dd, *J* = 8.2, 7.0 Hz, *Ar*), 7.44 (1H, dd, *J* = 8.3, 4.2 Hz, *Ar*), 5.21 (2H, s, C(7)H_2), 5.03 (1H, s, O*H*); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 149.1, 147.2, 138.3, 137.0, 128.6, 127.9, 127.6, 126.6, 121.3, 64.9.

For 8-(Hydroxymethyl)quinoline 1-oxide (86): Prepared according to **general procedure M**, using quinolin-8-ylmethanol **85** (622 mg, 3.91 mmol, 1.00 equiv.), with *m*-CPBA (60% w/w, 1.35 g, 4.69 mmol, 1.20 equiv.) and stirring for 20 h. Purification by column chromatography (1:1 EtOAc:Pentane to 9:1 EtOAc:Methanol) yielded 8-(hydroxymethyl)quinoline 1-oxide **86** (518 mg, 2.96 mmol, 76%) as an off-white solid.

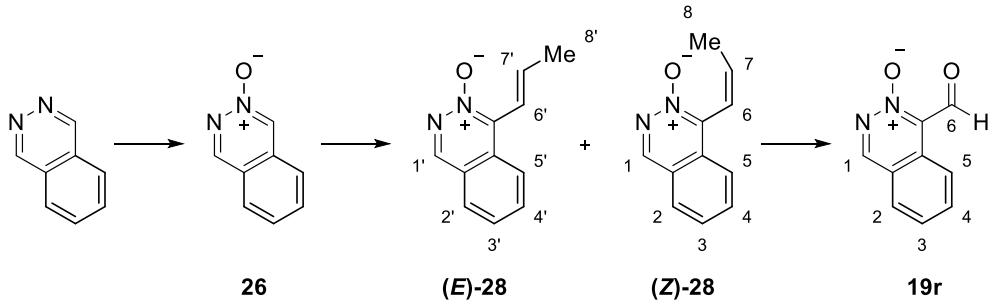
m.p. (CH_2Cl_2) Decomp. at 108 – 110 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.58 (1H, dd, *J* = 6.1, 1.2 Hz, *Ar*), 7.82 (1H, ddd, *J* = 7.5, 5.9, 1.4 Hz, *Ar*), 7.61 (1H, dd, *J* = 7.1, 1.6 Hz, *Ar*), 7.54 (1H, t, *J* = 7.6 Hz, *Ar*), 7.33 (1H, dd, *J* = 8.4, 6.1 Hz, *Ar*), 5.88 (1H,

bs, O*H*), 5.10 (2H, s, C(7)H_2); **δ_C** (101 MHz, $CDCl_3$) 141.0, 138.3, 135.1, 133.4, 132.7, 129.3, 128.9, 128.7, 121.0, 66.4; **ν_{max}**/ cm^{-1} (neat) 3364, 1577, 1422, 1387, 1301, 1206, 1162, 1006, 814, 757; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_{10}O_2N^+$ calc. 176.0706, found 176.0708.

For 8-Formylquinoline 1-oxide (19q): Prepared according to **general procedure N**, using 8-(Hydroxymethyl)quinoline 1-oxide **86** (300 mg, 1.71 mmol, 1.00 equiv.) and MnO_2 (1.27 g, 14.6 mmol, 8.50 equiv.), ***with initial stirring at 55 °C for 1.5 h. However, conversion was incomplete after this time, and so the temperature was increased to 90 °C for 1 h.*** Purification by column chromatography (9:1 to 7:3 CH_2Cl_2:Acetone) yielded 8-formylquinoline 1-oxide **19q** (191 mg, 1.10 mmol, 65%) as a yellow powdered solid.

m.p. (CH_2Cl_2) 140 – 142 °C; **δ_H** (400 MHz, $CDCl_3$) 11.21 (s, 1H), 8.51 (dd, *J* = 6.0, 1.1 Hz, 1H), 8.00 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.88 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.73 – 7.65 (m, 1H), 7.37 (dd, *J* = 8.4, 6.0 Hz, 1H); **δ_C** (101 MHz, $CDCl_3$) 191.2, 139.8, 136.5, 133.7, 131.8, 131.3, 131.1, 128.8, 126.7, 122.0; **ν_{max}**/ cm^{-1} (neat) 2885, 1679, 1311, 1226, 1159, 1124, 845, 812, 760; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{10}H_8O_2N^+$ calc. 174.0550, found 174.0552.

Phthalazine 2-oxide (26), 1-(prop-1-en-1-yl)phthalazine 2-oxide (28) and 1-formylphthalazine 2-oxide (19r)



For phthalazine 2-oxide (26): Synthesised according to a standard literature procedure[211]

For 1-(prop-1-en-1-yl)phthalazine 2-oxide (28): Prepared according to a modified procedure.[104] In an oven-dried microwave vial was added phthalazine 2-oxide **26** (438 mg, 3.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (33.7 mg, 0.150 mmol, 0.100 equiv.), $P(t\text{-Bu})_3 \cdot HBF_4$ (130.6 mg, 0.450 mmol, 0.300 equiv.) and KF (174 mg, 3.00 mmol, 2.00 equiv.). The vial was sealed with a microwave cap and vac-cycled under Ar (×3). Dry and degassed THF (6 mL, 0.25 M) was then added, followed by allyl acetate (162 μL, 1.50 mmol, 1.00 equiv.) and the resulting mixture was heated to 100 °C for 13 h. Once complete, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. Purification of the crude residue by column chromatography (0:50:50 to 5:95:0 MeOH:EtOAc:Petrol) yielded a 1:2.7 inseparable *E*/*Z* mixture of 1-(prop-1-en-1-yl)phthalazine 2-oxide **28** (36.5 mg, 0.196 mmol, 13%) as a brown oil.

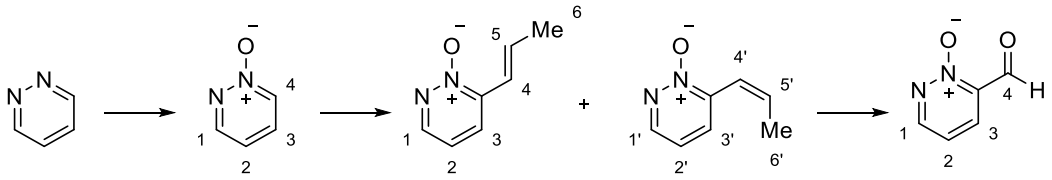
δ_H (400 MHz, $CDCl_3$) 9.01 (1H, s, C(1)*H*), 8.90 (1H, s, C(1')*H*), 8.04 (1H, dd, *J* = 8.6, 0.9 Hz, *Ar'*), 7.91 (1H, dd, *J* = 8.1, 1.0 Hz, *Ar*), 7.87 (1H, dt, *J* = 8.1, 1.1 Hz, *Ar'*), 7.82 – 7.75 (2H, m, *Ar* and *Ar'*), 7.70 (1H, dq, *J* = 8.5, 1.0 Hz, *Ar*), 7.67 – 7.60 (2H, m, *Ar* and *Ar'*), 7.07 (1H, dq, *J* = 15.9, 6.7 Hz, C(7')*H*), 6.82 (1H, dq, *J* = 15.9,

1.7 Hz, C(6')*H*), 6.55 – 6.48 (1H, m, C(6)*H*), 6.36 (1H, dq, *J* = 11.4, 7.0 Hz, C(7)*H*), 2.09 (3H, dd, *J* = 6.7, 1.7 Hz, C(8')H_3), 1.60 (3H, dd, *J* = 7.0, 1.7 Hz, C(8)H_3); **δ_C** (101 MHz, $CDCl_3$) 151.4, 150.2, 139.8, 135.7, 135.5, 135.1, 133.7, 133.6, 131.7, 131.4, 129.0, 128.8, 127.7, 127.6, 124.2, 123.3, 121.2, 120.9, 119.3, 119.1, 20.0, 16.5 (spectrum too complex to assign *E* and *Z* isomers); **ν_{max}**/ cm^{-1} (neat) 1748, 1644, 1614, 1550, 1346, 1321, 1202, 1125, 767; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{11}H_{11}ON_2^+$ calc. 187.0866, found 187.0868.

For 1-formylphthalazine 2-oxide (19r): Prepared according to a modified procedure.[104] In a dry two-neck flask, a 1:2.7 *E*/*Z* mixture of 1-(prop-1-en-1-yl)phthalazine 2-oxide **28** (36.5 mg, 0.196 mmol, 1.00 equiv.) was dissolved in a 1:1 CH_2Cl_2:MeOH solvent mixture (1.56 mL, 0.125 M). The solution was then cooled to – 78 °C and ozone was bubbled through for 30 min with stirring. After this time, dimethyl sulfide (72 μL, 0.980 mmol, 5.00 equiv.) was added and the solution was warmed to room temperature with stirring for 2 h. The resulting mixture was then concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:1 EtOAc:Petrol) yielded 1-formylphthalazine 2-oxide **19r** (14.5 mg, 0.083 mmol, 43%) as a white powdered solid.

m.p. ($CHCl_3$) 160 – 162 °C; **δ_H** (400 MHz, $CDCl_3$) 10.71 (1H, s, C(6)*H*), 9.17 (1H, s, *Ar*), 8.98 – 8.90 (1H, m, *Ar*), 8.00 – 7.90 (2H, m, *Ar*), 7.72 (1H, td, *J* = 7.3, 1.0 Hz, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 188.1, 155.7, 136.4, 131.0, 130.6, 129.9, 127.9, 122.9, 120.7; **ν_{max}**/ cm^{-1} (neat) 1685, 1552, 1448, 1432, 1322, 1198, 1133, 1051, 884, 764; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_9H_7O_2N_2^+$ calc. 175.0502, found 175.0504.

Pyridazine 1-oxide (27), 6-(Prop-1-en-1-yl)pyridazine 1-oxide (29) and 6-Formylpyridazine 1-oxide (19s)



For Pyridazine 1-oxide (27): According to a modified procedure,[104] a solution of pyridazine (0.72 mL, 10.0 mmol, 1.00 equiv.), in CH_2Cl_2 (50 mL) was cooled to 0 °C. *m*-CPBA (60% w/w, 2.88 g, 10.0 mmol, 1.00 equiv.) was added portion-wise before the resulting mixture was warmed to room temperature and stirred overnight. Once TLC showed completion (18 h), PPh_3 (1.31 g, 5.00 mmol, 0.500 equiv.) was added slowly, and the resulting mixture was stirred for a further 4 h. After this time, celite was added to the mixture and the solvent was removed *in vacuo*. The resulting celite-bound residue was loaded directly onto a flash column (1:0 to 9:1 EtOAc:MeOH) to yield pyridazine 1-oxide **27** (935 mg, 9.74 mmol, 97%) as a pink solid.

m.p. (CH_2Cl_2) 39 – 40 °C; (*Lit:* 39 – 40 °C);[212] **δ_H** (400 MHz, $CDCl_3$) 8.46 – 8.40 (1H, m, *Ar*), 8.13 (1H, d, *J* = 6.5 Hz, *Ar*), 7.66 – 7.57 (1H, m, *Ar*), 7.05 (1H, ddd, *J* = 7.7, 5.4, 0.9 Hz, *Ar*); **δ_C** (101 MHz, $CDCl_3$) 150.6, 134.4, 134.2, 116.0. Data is consistent with literature.[104]

For 6-(Prop-1-en-1-yl)pyridazine-1-oxide (29): According to a modified procedure,[104] in an oven-dried microwave vial was added pyridazine 1-oxide **27** (96.1 mg, 1.00 mmol, 2.00 equiv.), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol, 0.100 equiv.), P(*t*-Bu)$_3$·HBF_4 (43.5 mg, 0.150 mmol, 0.300 equiv.) and KF (58 mg, 1.00 mmol, 2.00 equiv.). The vial was sealed with a microwave cap and vac-cycled under Ar

(×3). Dry and degassed THF (2 mL, 0.25 M) was then added, followed by allyl acetate (54 μL, 0.500 mmol, 1.00 equiv.) and the resulting mixture was heated to 100 °C for 20 h. Once complete, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. Purification of the crude residue by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded a 9.4:1 inseparable *E*/*Z* mixture of 6-(prop-1-en-1-yl)pyridazine-1-oxide **29** (42.2 mg, 0.310 mmol, 62%) as a pale-red oil.

δ_H (400 MHz, $CDCl_3$) 8.40 – 8.35 (1H, m, *Ar'*), 8.31 (1H, dd, *J* = 5.2, 2.4 Hz, *Ar*), 7.71 (1H, dd, *J* = 8.1, 2.4 Hz, *Ar*), 7.65 (1H, dd, *J* = 7.9, 2.5 Hz, *Ar'*), 7.09 – 7.02 (1H, m, *Ar'*), 7.01 (1H, ddd, *J* = 8.1, 5.2, 0.6 Hz, *Ar*), 6.91 (1H, dq, *J* = 16.1, 1.5 Hz, C(4)*H*), 6.73 – 6.61 (1H, m, C(4')*H*), 6.69 (1H, dq, *J* = 16.1, 6.7 Hz, C(5)*H*), 6.22 (1H, dq, *J* = 11.8, 7.3 Hz, C(5')*H*), 2.00 (3H, dd, *J* = 6.7, 1.7 Hz, C(6)H_3), 1.90 (3H, dd, *J* = 7.3, 1.9 Hz, C(6')H_3); **δ_C** (101 MHz, $CDCl_3$) 148.4*, 148.0, 142.9 (*E* and *Z*), 136.0, 134.1*, 133.7*, 130.6, 121.6, 120.9*, 116.3, 115.6*, 19.2, 14.9* (* denotes the minor *Z* isomer ***Z*-S25**); **m/z LRMS** (ESI^+) 137.0 $[M + H]^+$. Data is consistent with literature.[104]

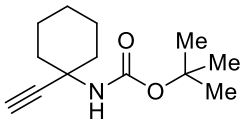
For 6-Formylpyridazine 1-oxide (19s): According to a modified procedure,[104] in a dry two-neck flask, a 9.4:1 E/*Z* mixture of 6-(prop-1-en-1-yl)pyridazine 1-oxide **29** (42.2 mg, 0.310 mmol, 1.00 equiv.) was dissolved in a 1:1 CH_2Cl_2:MeOH solvent mixture (2.50 mL, 0.125 M). The solution was then cooled to –78 °C and ozone was bubbled through for 30 min with stirring. After this time, dimethyl sulfide (114 μL, 1.55 mmol, 5.00 equiv.) was added and the solution was warmed to room temperature with stirring for 2 h. The resulting mixture was then concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:4 to 1:0

EtOAc:Pentane) yielded 6-formylpyridazine 1-oxide **19s** (25.9 mg, 0.208 mmol, 67%) as a white powdered solid.

m.p. (CH_2Cl_2) 126 – 129 °C; δ_H (400 MHz, $CDCl_3$) 10.42 (1H, d, *J* = 0.8 Hz, C(4)*H*), 8.61 (1H, dd, *J* = 5.6, 2.5 Hz, *Ar*), 8.08 (1H, dd, *J* = 7.9, 2.6 Hz, *Ar*), 7.17 (1H, ddd, *J* = 8.0, 5.3, 0.9 Hz, *Ar*); δ_C (101 MHz, $CDCl_3$) 184.8, 153.7, 138.8, 133.2, 116.2; ν_{max}/ cm^{-1} (neat) 2923, 1697, 1683, 1590, 1536, 1384, 1300, 1261, 1023, 1013, 881, 807, 742, 733, 645; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_5H_5O_2N_2^+$ calc. 125.0346, found 125.0347.

6.3.2b Alkyne Substrates

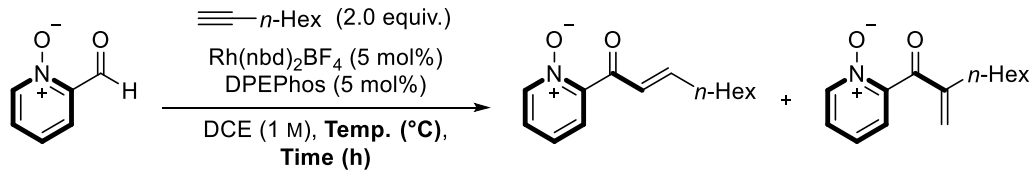
***Tert*-butyl (1-ethynylcyclohexyl)carbamate (24)**



Synthesised according to a standard literature procedure[213] (This reaction was performed by Dr Jagadeesh Kalepu).

6.3.3 Additional Reaction Optimisation

Table 6.1. Lower temperature reactions (0.2 mmol scale).

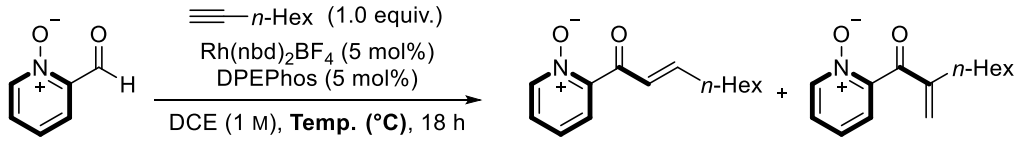


19a (1.0 equiv.) **20a (l)** **21a (b)**

Entry	Time (h)	Temp. (°C)	Aldehyde consumption (%)[a]	l:b	20a + 21a (%)[b]
1	18	35	57	3.7:1	34
2	18	rt	45	4.6:1	30
3	48	rt	47	6.7:1	34

[a] Aldehyde consumption determined by ^{1}H NMR spectroscopy of the crude reaction mixture; [b] ^{1}H NMR yields based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate).

Table 6.2. Stoichiometry-switch whilst maintaining a 1 M aldehyde concentratiom (0.2 mmol).



19a (2.0 equiv.) **20a (l)** **21a (b)**

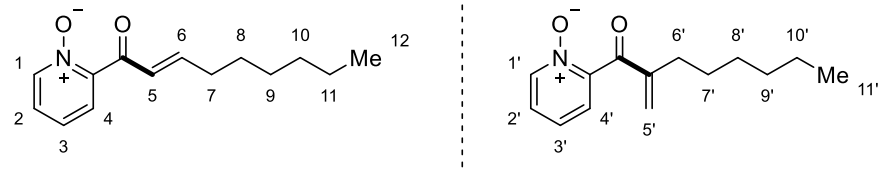
Entry	Temp (°C)	l:b	20a + 21a (%)[a]
1	55	2.1:1	26
2	rt	5.9:1	17

[a] ^{1}H NMR yields were based on ^{1}H NMR standard (methyl-3,5-dinitrobenzoate).

6.3.4 Substrate Scope

6.3.4a Alkyne Scope

(*E*)-2-(Non-2-enoyl)pyridine 1-oxide (20a) and 2-(2-Methyleneoctanoyl)pyridine 1-oxide (21a)



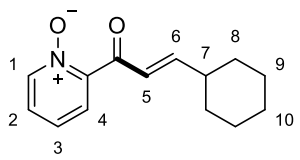
20a **21a**

Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 1-octyne (87 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 6 h. Purification of the crude residue (2.9:1 l:b) by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded (*E*)-2-(non-2-enoyl)pyridine 1-oxide **20a** (37.3 mg, 0.160 mmol, 53%) and 2-(2-methyleneoctanoyl)pyridine 1-oxide **21a** (14.0 mg, 0.06 mmol, 20%) both as yellow viscous oils.

***(E)-2-(Non-2-enoyl)pyridine 1-oxide (20a)*: δ_H** (400 MHz, $CDCl_3$) 8.22 – 8.15 (1H, m, *Ar*), 7.58 – 7.47 (1H, m, *Ar*), 7.38 – 7.27 (2H, m, *Ar*), 7.04 (1H, dt, *J* = 15.6, 6.6 Hz, C(6)*H*), 6.93 (1H, dt, *J* = 15.5, 1.2 Hz, C(5)*H*), 2.27 (2H, app. dtd, *J* = 7.8, 6.7, 1.3 Hz, C(7)H_2), 1.53 – 1.41 (2H, m, C(8)H_2), 1.41 – 1.14 (6H, m, C(9 to 11)H_2), 0.93 – 0.75 (3H, m, C(12)H_3); **δ_C** (101 MHz, $CDCl_3$) 187.0, 150.7, 147.4, 140.4, 128.1, 127.5, 126.9, 125.7, 32.8, 31.7, 29.0, 28.0, 22.6, 14.1; **ν_{max}**/ cm^{-1} (neat) 2955, 2926, 1667, 1619, 1426, 1297, 1247, 1197, 1031, 969, 859; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{20}O_2N^+$ calc. 234.1489, found 234.1490.

***2-(2-Methyleneoctanoyl)pyridine 1-oxide (21a)*: δ_H** (400 MHz, $CDCl_3$) 8.25 – 8.16 (1H, m, *Ar*'), 7.38 – 7.31 (2H, m, *Ar*'), 7.29 – 7.25 (1H, m, *Ar*'), 5.93 (1H, app. t, *J* = 1.4 Hz, C(5')*H*H), 5.66 (1H, s, C(5')H*H*), 2.49 – 2.41 (2H, m, C(6')H_2), 1.60 – 1.49 (2H, m, C(7')H_2), 1.41 – 1.26 (6H, m, C(8' to 10')H_2), 0.9 – 0.85 (3H, m, C(11')H_3); **δ_C** (101 MHz, $CDCl_3$) 191.4, 148.1, 147.4, 140.2, 127.8, 126.7, 125.5, 125.1, 31.8, 30.0, 29.1, 28.0, 22.7, 14.2; **ν_{max}**/ cm^{-1} (neat) 2954, 2927, 2856, 1627, 1426, 1247, 987, 847, 769; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{20}O_2N^+$ calc. 234.1489, found 234.1489.

(*E*)-2-(3-Cyclohexylacryloyl)pyridine 1-oxide (20b)

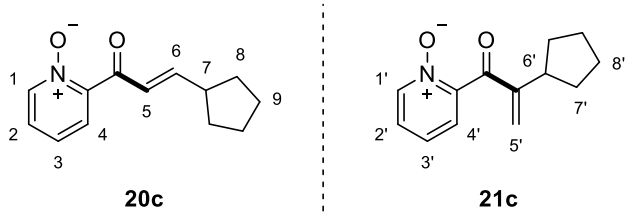


Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 4:1 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-cyclohexylacryloyl)pyridine 1-oxide **20b** (51.1 mg, 0.221 mmol, 74%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 8.16 (1H, dd, *J* = 6.1, 1.4 Hz, *Ar*), 7.51 (1H, dd, *J* = 7.5, 2.4 Hz, *Ar*), 7.36 – 7.26 (2H, m, *Ar*), 6.97 (1H, dd, *J* = 15.7, 6.2 Hz, C(6)*H*), 6.89 (1H, d, *J* = 15.9 Hz, C(5)*H*), 2.26 – 2.13 (1H, m, C(7)*H*), 1.84 – 1.67 (4H, m, C(8)H_2), 1.67 – 1.58 (1H, m, C(10)*H*H), 1.34 – 1.06 (5H, m, C(9)H_2 and C(10)H*H*); **δ_C** (101 MHz, $CDCl_3$) 187.3, 155.0, 147.4, 140.4, 127.5, 126.9, 125.8, 125.6, 40.9, 31.6, 26.0, 25.7; **ν_{max}**/ cm^{-1} (neat) 2925, 2851, 1668, 1618, 1427, 1332, 1317, 1297, 1248,

770; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{14}H_{19}O_2N^+$ calc. 232.1332, found 232.1332. Data is consistent with literature.[214]

(*E*)-2-(3-Cyclopentylacryloyl)pyridine 1-oxide (20c) and 2-(2-Cyclopentylacryloyl)-pyridine 1-oxide (21c)



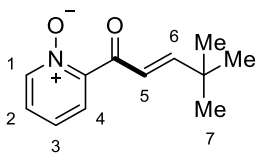
20c **21c**

Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclopentane (70 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 20 h. Purification of the crude residue (18:1 l:b) by column chromatography (1:1 to 7:3 EtOAc:Pentane) yielded (*E*)-2-(3-cyclopentylacryloyl)pyridine 1-oxide **20c** (33.6 mg, 0.155 mmol, 51%) and 2-(2-cyclopentylacryloyl)-pyridine 1-oxide **21c** (3.0 mg, 0.014 mmol, 5%) both as yellow viscous oils.

***(E)-2-(3-Cyclopentylacryloyl)pyridine 1-oxide (20c)*: δ_H** (400 MHz, $CDCl_3$) 8.20 – 8.13 (1H, m, *Ar*), 7.52 (1H, dd, *J* = 7.5, 2.4 Hz, *Ar*), 7.31 (2H, ddd, *J* = 9.0, 6.7, 1.8 Hz, *Ar*), 7.02 (1H, dd, *J* = 15.5, 7.6 Hz, C(6)*H*), 6.93 (1H, d, *J* = 15.6 Hz, C(5)*H*), 2.67 (1H, app. hex, *J* = 7.9 Hz, C(7)*H*), 1.92 – 1.77 (2H, m, C(8 and 9)H_2), 1.74 – 1.50 (4H, m, C(8 and 9)H_2), 1.50 – 1.35 (2H, m, C(8 and 9)H_2); **δ_C** (101 MHz, $CDCl_3$) 187.1, 154.6, 147.4, 140.4, 127.5, 126.9, 126.2, 125.6, 43.3, 32.5, 25.5; **ν_{max}**/ cm^{-1} (neat) 2951, 2867, 1665, 1615, 1426, 1314, 1294, 1247, 1029, 981, 771; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{13}H_{16}O_2N^+$ calc. 218.1176, found 218.1177.

***2-(2-Cyclopentylacryloyl)-pyridine 1-oxide (21c)*: δ_H** (500 MHz, $CDCl_3$) 8.18 (1H, dd, *J* = 4.9, 2.7 Hz, *Ar'*), 7.37 – 7.32 (2H, m, *Ar'*), 7.32 – 7.27 (1H, m, *Ar'*), 5.90 (1H, d, *J* = 1.5 Hz, C(5')*H*H), 5.61 (1H, app. s, C(5')H*H*), 3.14 – 3.04 (1H, m, C(6')*H*), 2.04 – 1.96 (2H, m, C(7' and 8')H_2), 1.77 – 1.70 (2H, m, C(7' and 8')H_2), 1.69 – 1.61 (2H, m, C(7' and 8')H_2), 1.59 – 1.46 (2H, m, C(7' and 8')H_2); **δ_C** (126 MHz, $CDCl_3$) 191.8, 151.8, 147.6, 140.2, 126.7, 125.5, 125.2, 125.1, 39.9, 31.8, 25.1; **ν_{max}**/ cm^{-1} (neat) 2953, 2924, 2868, 1674, 1427, 1248, 990, 850, 770; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{13}H_{16}O_2N^+$ calc. 218.1176, found 218.1176.

(*E*)-2-(4,4-Dimethylpent-2-enoyl)pyridine 1-oxide (20d)



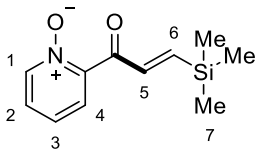
Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 3,3-dimethylbut-1-yne (74 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 4:1 EtOAc:Pentane) yielded single isomer (*E*)-2-(4,4-dimethylpent-2-enoyl)pyridine 1-oxide **20d** (47.1 mg, 0.230 mmol, 77%) as a pale-brown solid.

1.00 mmol scale reaction: Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (123 mg, 1.00 mmol, 1.00 equiv.), 3,3-dimethylbut-1-yne (246 μL, 2.00 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (18.7 mg, 0.05 mmol, 0.050 equiv.), DPEPhos (27 mg, 0.05 mmol, 0.050 equiv.) and DCE (0.8 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography

(1:1 to 1:0 EtOAc:Petrol) yielded single isomer (*E*)-2-(4,4-dimethylpent-2-enoyl)pyridine 1-oxide **20d** (170 mg, 0.828 mmol, 83%) as a pale-brown solid.

m.p. (CH_2Cl_2) 85 – 88 °C; (*Lit:* 85 – 88 °C);[215] **δ_H** (400 MHz, $CDCl_3$) 8.25 – 8.18 (1H, m, *Ar*), 7.61 – 7.54 (1H, m, *Ar*), 7.41 – 7.29 (2H, m, *Ar*), 7.07 (1H, d, *J* = 15.9 Hz, C(6)*H*), 6.93 (1H, d, *J* = 15.8 Hz, C(5)*H*), 1.13 (9H, s, C(7)H_3); **δ_C** (101 MHz, $CDCl_3$) 187.5, 159.6, 147.4, 140.4, 127.5, 126.9, 125.6, 123.5, 34.3, 28.7; **ν_{max}**/ cm^{-1} (neat) 2961, 1667, 1615, 1427, 1317, 1029, 863, 772, 654; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{12}H_{16}O_2N^+$ calc. 206.1176, found 206.1778. Data is consistent with literature.[215]

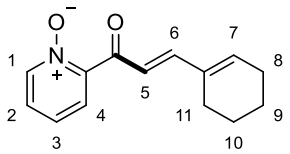
(*E*)-2-(3-(Trimethylsilyl)acryloyl)pyridine 1-oxide (20e)



Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), ethynyltrimethylsilane (83 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (7:3 EtOAc:Pentane) yielded single isomer (*E*)-2-(3-(trimethylsilyl)acryloyl)pyridine 1-oxide **20e** (49.0 mg, 0.222 mmol, 74%) as an off-white solid.

m.p. (CH_2Cl_2) 53 – 56 °C; **δ_H** (400 MHz, $CDCl_3$) 8.26 – 8.20 (1H, m, *Ar*), 7.60 – 7.53 (1H, m, *Ar*), 7.43 – 7.33 (2H, m, *Ar*), 7.31 (2H, app. s, C(5 and 6)*H*), 0.17 (9H, s, C(7)H_3); **δ_C** (101 MHz, $CDCl_3$) 186.5, 149.0, 147.1, 140.3, 139.4, 127.7, 127.0, 125.6, – 1.74; **ν_{max}**/ cm^{-1} (neat) 2957, 1669, 1427, 1295, 1248, 1020, 987, 875, 844, 756; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{11}H_{16}O_2NSi^+$ calc. 222.0946, found 222.0945.

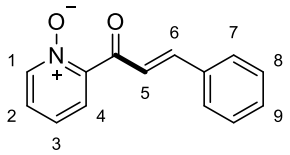
(*E*)-2-(3-(Cyclohex-1-en-1-yl)acryloyl)pyridine 1-oxide (20f)



Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 1-ethynylcyclohex-1-ene (71 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 9:1 EtOAc:Pentane) yielded single isomer (*E*)-2-(3-(cyclohex-1-en-1-yl)acryloyl)pyridine 1-oxide **20f** (55.6 mg, 0.243 mmol, 81%) as a pale-brown solid.

m.p. (CH_2Cl_2) 68 – 70 °C; **δ_H** (400 MHz, $CDCl_3$) 8.18 – 8.13 (1H, m, *Ar*), 7.56 – 7.50 (1H, m, *Ar*), 7.35 – 7.27 (3H, m, *Ar* and C(5 or 6)*H*), 6.92 (1H, d, *J* = 15.6 Hz, C(5 or 6)*H*), 6.25 (1H, bs, C(7)*H*), 2.22 – 2.14 (4H, m, C(8 to 11)H_2), 1.69 – 1.52 (4H, m, C(8 to 11)H_2); **δ_C** (101 MHz, $CDCl_3$) 187.1, 148.5, 147.6, 142.0, 140.4, 135.9, 127.4, 126.9, 125.6, 121.5, 26.9, 24.3, 22.0, 22.0; **ν_{max}**/ cm^{-1} (neat) 2929, 1657, 1577, 1426, 1322, 1244, 1190, 1031, 768; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{16}O_2N^+$ calc. 230.1176, found 230.1178.

2-Cinnamoylpyridine 1-oxide (20g)

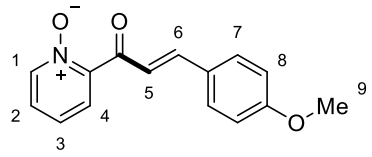


Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), phenylacetylene (66 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015

mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (9:1 l:b) by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded single isomer 2-cinnamoylpyridine 1-oxide **20g** (36.0 mg, 0.160 mmol, 53%) as a pale-brown solid. A pure fraction of the branched isomer could not be isolated.

m.p. (CH_2Cl_2) 100 – 104 °C; (*Lit:* 104 – 107 °C);[215] δ_H (400 MHz, $CDCl_3$) 8.26 – 8.22 (1H, m, *Ar*), 7.82 (1H, d, *J* = 15.9 Hz, C(5 or 6)*H*), 7.73 (1H, d, *J* = 15.9 Hz, C(5 or 6)*H*), 7.73 – 7.66 (1H, m, *Ar*), 7.67 – 7.61 (2H, m, *Ar*), 7.42 – 7.31 (5H, m, *Ar*); δ_C (101 MHz, $CDCl_3$) 186.5, 147.4, 144.4, 140.6, 134.8, 130.9, 129.0, 129.0, 127.8, 127.4, 125.8, 124.4; ν_{max}/ cm^{-1} (neat) 2919, 1666, 1610, 1428, 1336, 765; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{14}H_{11}O_2N^{23}Na^+$ calc. 248.0682, found 248.0682. Data is consistent with literature.[215]

(*E*)-2-(3-(4-Methoxyphenyl)acryloyl)pyridine 1-oxide (20h)

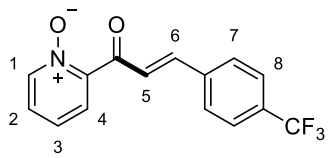


Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 1-ethynyl-4-methoxybenzene (79 mg, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-(4-methoxyphenyl)acryloyl)pyridine 1-oxide **20h** (45.6 mg, 0.180 mmol, 60%) as a pale-brown solid.

m.p. (CH_2Cl_2) 95 – 98 °C; (*Lit:* 113 – 116 °C);[215] δ_H (400 MHz, $CDCl_3$) 8.24 – 8.18 (1H, m, *Ar*), 7.74 (1H, d, *J* = 15.8 Hz, C(5 or 6)*H*), 7.63 (1H, dd, *J* = 7.4, 2.6 Hz, *Ar*), 7.61 – 7.54 (3H, m, C(5 or 6)*H* and *Ar*), 7.39 – 7.28 (2H, m, *Ar*), 6.92 – 6.84

(2H, m, *Ar*), 3.81 (3H, s, OC(9)H_3); **δC** (101 MHz, $CDCl_3$) 186.3, 162.1, 147.6, 144.6, 140.5, 130.8, 127.6, 127.4, 127.2, 125.7, 122.2, 114.5, 55.5; **νmax**/ cm^{-1} (neat) 2839, 1738, 1657, 1597, 1570, 1512, 1427, 1254, 1174, 1033; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{14}O_3N^+$ calc. 256.0968, found 256.0970. Data is consistent with literature.[215]

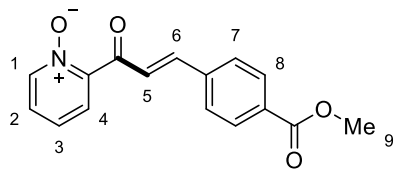
(*E*)-2-(3-(4-(Trifluoromethyl)phenyl)acryloyl)pyridine 1-oxide (20i)



Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 1-ethynyl-4-(trifluoromethyl)benzene (98 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 40 h. Purification of the crude residue (>20:1 l:b) by column chromatography (9:1 to 1:0 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-(4-(trifluoromethyl)phenyl)acryloyl)pyridine 1-oxide **20i** (35.2 mg, 0.120 mmol, 40%) as a pale-brown solid.

m.p. (CH_2Cl_2) 112 – 116 °C; (*Lit:* 123 – 126 °C);[216] **δF** (376 MHz, $CDCl_3$) –62.86 (CF_3); **δH** (400 MHz, $CDCl_3$) 8.27 – 8.21 (1H, m, *Ar*), 7.81 (2H, app. d, *J* = 1.5 Hz, C(5 and 6)*H*), 7.75 – 7.70 (3H, m, *Ar*), 7.63 (2H, d, *J* = 8.2 Hz, *Ar*), 7.46 – 7.34 (2H, m, *Ar*); **δC** (127 MHz, $CDCl_3$) 186.1, 147.0, 141.8, 140.6, 138.2, 132.1 (q, *J* = 32.6 Hz), 129.0, 128.2, 127.7, 126.6, 125.9, 125.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.3 Hz); **νmax**/ cm^{-1} (neat) 1668, 1612, 1430, 1322, 1167, 1068, 830, 769; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{11}O_2NF_3^+$ calc. 294.0736, found 294.0735. Data is consistent with literature.[216]

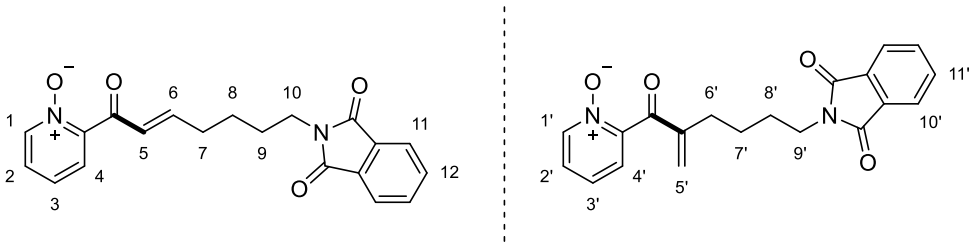
(*E*)-2-(3-(4-(Methoxycarbonyl)phenyl)acryloyl)pyridine 1-oxide (20j)



Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), methyl 4-ethynylbenzoate (96.1 mg, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 40 h. Purification of the crude residue (>20:1 l:b) by column chromatography (9:1 to 1:0 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-(4-(methoxycarbonyl)phenyl)acryloyl)pyridine 1-oxide **20j** (32.5 mg, 0.115 mmol, 38%) as a pale-brown solid.

m.p. (CH_2Cl_2) 148 – 150 °C; **δ_H** (400 MHz, $CDCl_3$) 8.28 – 8.22 (1H, m, *Ar*), 8.04 (2H, d, *J* = 8.5 Hz, *Ar*), 7.81 (2H, app. s, C(5 and 6)*H*), 7.77 – 7.65 (3H, m, *Ar*), 7.46 – 7.33 (2H, m, *Ar*), 3.93 (3H, s, C(9)H_3); **δ_C** 186.1, 166.6, 147.1, 142.5, 140.7, 139.0, 131.8, 130.2, 128.8, 128.2, 127.7, 126.4, 126.1, 52.4; **ν_{max}**/ cm^{-1} (neat) 1719, 1664, 1614, 1432, 1284, 1112, 764, 743; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{16}H_{14}O_4N^+$ calc. 284.0917, found 284.0918. Data is consistent with literature.[217]

(*E*)-2-(7-(1,3-Dioxoisoindolin-2-yl)hept-2-enoyl)pyridine 1-oxide (20k) and 2-(6-(1,3-Dioxoisoindolin-2-yl)-2-methylenehexanoyl)pyridine 1-oxide (21k)



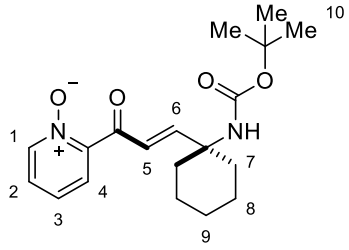
20k **21k**

Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 2-(hex-5-yn-1-yl)isoindoline-1,3-dione (136 mg, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 6 h. Purification of the crude residue (3.3:1 l:b) by column chromatography (99:1 CH_2Cl_2:MeOH to 97:3 CH_2Cl_2:MeOH) yielded (*E*)-2-(7-(1,3-dioxoisoindolin-2-yl)hept-2-enoyl)pyridine 1-oxide **20k** (45.9 mg, 0.131 mmol, 43%) and 2-(6-(1,3-dioxoisoindolin-2-yl)-2-methylenehexanoyl)pyridine 1-oxide **21k** (19.4 mg, 0.055 mmol, 18%) both as yellow viscous oils.

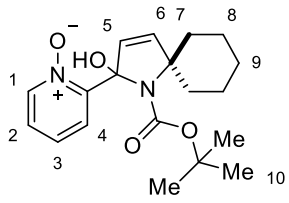
***(E)-2-(7-(1,3-Dioxoisoindolin-2-yl)hept-2-enoyl)pyridine 1-oxide (20k)*: δ_H** (400 MHz, $CDCl_3$) 8.16 (1H, dd, *J* = 6.2, 1.4 Hz, *Ar*), 7.80 (2H, dd, *J* = 5.4, 3.1 Hz, *Ar*), 7.68 (2H, dd, *J* = 5.4, 3.0 Hz, *Ar*), 7.52 (1H, dd, *J* = 7.5, 2.5 Hz, *Ar*), 7.37 – 7.27 (2H, m, *Ar*), 7.03 – 6.95 (1H, m, C(6)*H*), 6.93 (1H, d, *J* = 15.7 Hz, C(5)*H*), 3.67 (2H, app. t, *J* = 7.1 Hz, C(10)H_2), 2.38 – 2.27 (2H, m, C(7)H_2), 1.70 (2H, app. p, *J* = 7.7 Hz, C(9)H_2), 1.53 (2H, app. p, *J* = 7.6 Hz, C(8)H_2); **δ_C** (101 MHz, $CDCl_3$) 186.8, 168.5, 149.2, 147.2, 140.4, 134.0, 132.2, 128.5, 127.6, 126.9, 125.7, 123.3, 37.6, 32.2, 28.3, 25.3; **ν_{max}**/ cm^{-1} (neat) 2939, 1706, 1619, 1429, 1397, 721; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{19}O_4N_2^+$ calc. 351.1339, found 351.1340.

***2-(6-(1,3-Dioxoisoindolin-2-yl)-2-methylenehexanoyl)pyridine 1-oxide (21k)*: δ_H** (400 MHz, $CDCl_3$) 8.28 – 8.22 (1H, m, *Ar'*), 7.83 (2H, dd, *J* = 5.5, 3.0 Hz, *Ar'*), 7.70 (2H, dd, *J* = 5.5, 3.0 Hz, *Ar'*), 7.44 – 7.33 (2H, m, *Ar'*), 7.37 – 7.27 (1H, m, *Ar'*), 5.97 (1H, s, C(5')*H*H), 5.67 (1H, s, C(5')H*H*), 3.72 (2H, t, *J* = 7.2 Hz, C(9')H_2), 2.56 – 2.47 (2H, m, C(6')H_2), 1.83 – 1.71 (2H, m, C(8')H_2), 1.68 – 1.54 (2H, m, C(7')H_2); **δ_C** (151 MHz, $CDCl_3$) 190.8, 168.6, 147.3, 147.2, 140.2, 134.0, 132.3, 128.8, 126.9, 126.7, 125.3, 123.3, 37.8, 29.5, 28.2, 25.3; **ν_{max}**/ cm^{-1} (neat) 2940, 1704, 1672, 1427, 1397, 771, 721; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{20}H_{19}O_4N_2^+$ calc. 351.1339, found 351.1339.

(*E*)-2-(3-(1-((*Tert*-butoxycarbonyl)amino)cyclohexyl)acryloyl)pyridine 1-oxide (20l) and 2-(1-(tert-butoxycarbonyl)-2-hydroxy-1-azaspiro[4.5]dec-3-en-2-yl)pyridine 1-oxide (25)



20l



25 (*Z*-isomer derived)

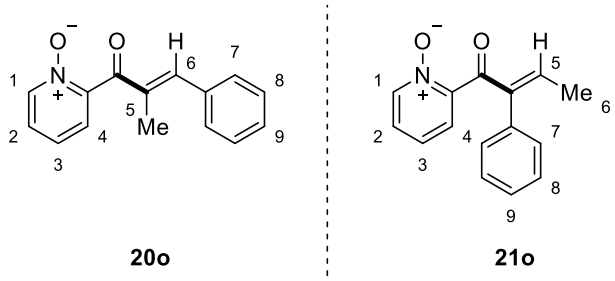
Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), *tert*-butyl (1-ethynylcyclohexyl)carbamate (223 mg, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (7:3 EtOAc:Pentane) yielded single regioisomer (*E*)-2-(3-(1-((*tert*-butoxycarbonyl)amino)cyclohexyl)acryloyl)pyridine 1-oxide **20l** (75.0 mg, 0.216 mmol, 72%) and 2-(1-(tert-butoxycarbonyl)-2-hydroxy-1-azaspiro[4.5]dec-3-en-2-

yl)pyridine 1-oxide **25** as a rotameric mixture (16.0 mg, 0.046 mmol, 15%). Both products were obtained as off-white solids (This reaction was performed by Dr Jagadeesh Kalepu).

(E)-2-(3-(1-((Tert-butoxycarbonyl)amino)cyclohexyl)acryloyl)pyridine 1-oxide (20l): **m.p.** (CH_2Cl_2) 50 – 55 °C; δ_H (400 MHz, $CDCl_3$) 8.20 – 8.11 (1H, m, *Ar*), 7.60 – 7.51 (1H, m, *Ar*), 7.37 – 7.26 (2H, m, *Ar*), 7.06 (1H, d, *J* = 15.7 Hz, C(5 or 6)*H*), 7.02 (1H, d, *J* = 15.7 Hz, C(5 or 6)*H*), 4.63 (1H, bs, N*H*), 2.07 – 1.94 (2H, m, C(7 to 9)H_2), 1.65 – 1.42 (7H, m, C(7 to 9)H_2), 1.39 (9H, s, C(10)H_3), 1.33 – 1.21 (1H, m, C(7 to 9)*H*); δ_C (101 MHz, $CDCl_3$) 187.1, 154.0 (2C), 147.3, 140.4, 127.6, 127.3, 125.5, 125.2, 79.6, 55.6, 34.8, 28.5, 25.4, 21.4; ν_{max}/ cm^{-1} (neat) 3247, 2978, 2931, 2859, 1699, 1619, 1520, 1428, 1356, 1317, 1249, 1167, 759; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{26}O_4N_2{}^{23}Na^+$ calc. 369.1785; found 369.1783.

2-(1-(Tert-butoxycarbonyl)-2-hydroxy-1-azaspiro[4.5]dec-3-en-2-yl)pyridine 1-oxide (25): **m.p.** (CH_2Cl_2) 160 – 165 °C; δ_H (500 MHz, $CDCl_3$) 8.15 (1H, app d, *J* = 6.4 Hz, *Ar*), 7.38 – 7.30 (2H, m, *Ar*), 7.28 – 7.20 (1H, m, *Ar*), 6.46 (1H, d, *J* = 6.3 Hz, C(5 or 6)*H*), 5.96 (1H, bs, C(5 or 6)*H*), 2.77 (1.5H, bs, O*H* and C(7 to 9)H_2), 2.57 (0.5H, bs, O*H*), 1.88 – 1.65 (4H, m, C(7 to 9)H_2), 1.60 – 1.13 (14H, m, C(7 to 9)H_2 and C(10)H_3); δ_C (126 MHz, $CDCl_3$) 152.2, 150.9, 140.2, 135.1, 128.9, 127.9, 124.6, 95.7, 81.0, 80.5, 71.2, 36.0, 35.2, 34.3, 33.4, 28.5, 28.4, 25.4, 25.3, 24.6, 24.4; ν_{max}/ cm^{-1} (neat) 2972, 2926, 2863, 2694, 1694, 1423, 1361, 1283, 1170, 772.0, 732; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{26}O_4N_2{}^{23}Na^+$ calc. 369.1785, found 369.1783.

(*E*)-2-(2-methyl-3-phenylacryloyl)pyridine 1-oxide (20o) and (*E*)-2-(2-phenylbut-2-enoyl)pyridine 1-oxide (21o)



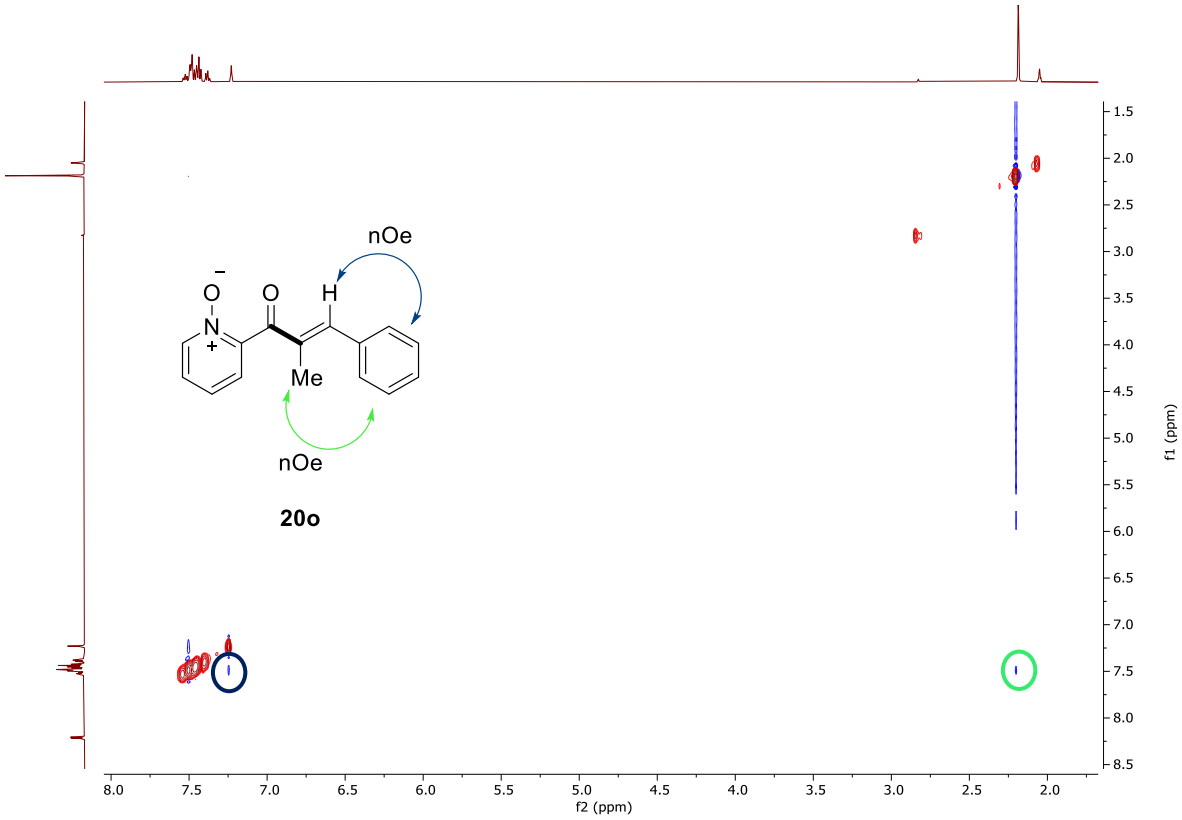
Prepared according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), 1-phenyl-1-propyne (75 µL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), ***with stirring for 18 h at 80 °C***. Purification of the crude residue (15:1 rr) by column chromatography (1:0 to 19:1 EtOAc:MeOH) yielded (*E*)-2-(2-methyl-3-phenylacryloyl)pyridine 1-oxide **20o** (27.7 mg, 0.116 mmol, 39%) and (*E*)-2-(2-phenylbut-2-enoyl)pyridine 1-oxide **21o** (1.0 mg, 0.004 mmol, 1%) as an off-white solid and a dark viscous oil respectively.

(E)-2-(2-methyl-3-phenylacryloyl)pyridine 1-oxide (20o): **m.p.** (CH_2Cl_2) 106 – 108 °C; δ_H (400 MHz, Acetone-d_6) 8.24 – 8.18 (1H, m, *Ar*), 7.56 – 7.35 (8H, m, *Ar*), 7.23 (1H, s, C(6)*H*), 2.19 (3H, d, *J* = 1.4 Hz, C(5)H_3); δ_C (101 MHz, Acetone-d_6) 192.9, 148.2, 143.1, 140.6, 136.8, 136.4, 130.9, 130.0, 129.4, 127.8, 126.1, 125.5, 12.8; ν_{max}/ cm^{-1} (neat) 3110, 3054, 2963, 1657, 1620, 1448, 1303, 1241, 1157, 1019, 927, 845, 770, 695; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{14}O_2N^+$ calc. 240.1019, found 240.1019.

(E)-2-(2-phenylbut-2-enoyl)pyridine 1-oxide (21o): δ_H (600 MHz, Acetone-d_6) 8.13 (1H, d, *J* = 6.3 Hz, *Ar*), 7.50 – 7.44 (2H, m, *Ar*), 7.43 – 7.35 (3H, m, *Ar*), 7.34 – 7.30 (1H, m, *Ar*), 7.31 – 7.26 (2H, m, *Ar*), 6.70 (1H, q, *J* = 7.1 Hz, C(5)*H*), 1.79

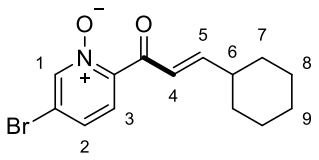
(3H, d, *J* = 7.1 Hz, C(6)H_3); **δc** (151 MHz, Acetone-d_6) 191.0, 148.5, 143.6, 142.9, 140.5, 135.4, 130.9, 128.7, 128.4, 127.8, 125.9, 125.2, 15.9; **ν_{max}**/ cm^{-1} (neat) 2974, 2920, 1665, 1628, 1428, 1298, 1230, 863, 770, 706, 700; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{14}O_2N^+$ calc. 240.1019, found 240.1020.

A NOESY spectrum of product 20o:



6.3.4b Aldehyde Scope

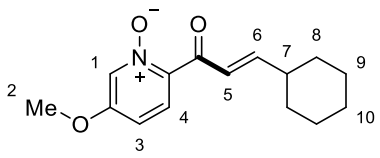
(*E*)-5-Bromo-2-(3-cyclohexylacryloyl)pyridine-1-oxide (20r)



Prepared according to **general procedure O**, using 5-bromo-2-formylpyridine 1-oxide **19b** (60 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:9 to 15:85 EtOAc:Petrol) yielded single isomer (*E*)-5-bromo-2-(3-cyclohexylacryloyl)pyridine-1-oxide **20r** (69.6 mg, 0.225 mmol, 75%) as an off-white solid.

m.p. (CH_2Cl_2) 70 – 74 °C; δ_H (400 MHz, $CDCl_3$) 8.34 (1H, dd, *J* = 1.5, 0.6 Hz, *Ar*), 7.48 (1H, dd, *J* = 8.6, 0.6 Hz, *Ar*), 7.44 (1H, dd, *J* = 8.5, 1.6 Hz, *Ar*), 7.04 (1H, dd, *J* = 15.7, 6.4 Hz, C(5)*H*), 6.94 (1H, dd, *J* = 15.7, 1.0 Hz, C(4)*H*), 2.30 – 2.17 (1H, m, C(6)*H*), 1.86 – 1.72 (4H, m, C(7 to 9)H_2), 1.72 – 1.61 (1H, m, C(7 to 9)H_2), 1.38 – 1.11 (5H, m, C(7 to 9)H_2); δ_C (101 MHz, $CDCl_3$) 186.2, 155.6, 146.3, 141.8, 128.7, 127.3, 125.5, 122.7, 41.0, 31.7, 26.0, 25.8; ν_{max}/ cm^{-1} (neat) 3106, 2932, 2855, 1717, 1699, 1376, 910; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{17}O_2N^{79}Br^+$ calc. 310.0437, found 310.0437, $C_{14}H_{17}O_2N^{81}Br^+$ calc. 312.0417, found 312.0416.

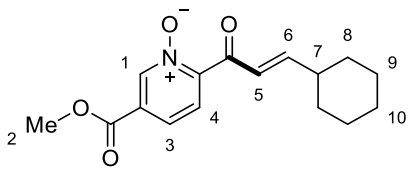
(*E*)-2-(3-Cyclohexylacryloyl)-5-methoxypyridine 1-oxide (20s)



Prepared according to **general procedure O**, using 2-formyl-5-methoxypyridine 1-oxide **19c** (46 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 7:3 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-cyclohexylacryloyl)-5-methoxypyridine 1-oxide **20s** (51.7 mg, 0.198 mmol, 66%) as a yellow/orange powdered solid.

m.p. (CH_2Cl_2) 80 – 84 °C; **δ_H** (400 MHz, $CDCl_3$) 7.91 (1H, d, *J* = 2.3 Hz, *Ar*), 7.60 (1H, d, *J* = 9.0 Hz, *Ar*), 7.11 (1H, dd, *J* = 15.7, 1.0 Hz, C(5)*H*), 7.02 (1H, dd, *J* = 15.7, 6.4 Hz, C(6)*H*), 6.90 (1H, dd, *J* = 9.0, 2.3 Hz, *Ar*), 3.88 (3H, s, C(2)H_3), 2.29 – 2.16 (1H, m, C(7)*H*), 1.87 – 1.78 (2H, m, C(8 to 10)H_2), 1.75 (2H, app dt, *J* = 11.7, 3.7 Hz, C(8 to 10)H_2), 1.71 – 1.61 (1H, m, C(8 to 10)H_2), 1.37 – 1.12 (5H, m, C(8 to 10)H_2); **δ_C** (101 MHz, $CDCl_3$) 186.2, 159.6, 154.2, 141.3, 128.2, 127.8, 126.1, 113.2, 56.5, 40.9, 31.8, 26.1, 25.9; **ν_{max}**/ cm^{-1} (neat) 2925, 2851, 1664, 1616, 1396, 1173, 1018, 971; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{20}O_3N^+$ calc. 262.1438, found 262.1437.

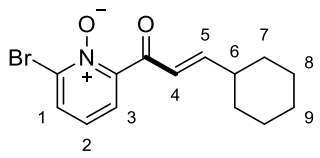
(*E*)-2-(3-Cyclohexylacryloyl)-5-(methoxycarbonyl)pyridine 1-oxide (20t)



Prepared according to **general procedure O**, using 2-formyl-5-(methoxycarbonyl)pyridine 1-oxide **19d** (54.3 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:4 to 1:1 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-cyclohexylacryloyl)-5-(methoxycarbonyl)pyridine 1-oxide **20t** (51.0 mg, 0.176 mmol, 59%) as an off-white solid.

m.p. (CH_2Cl_2) 66 – 70 °C; **δ_H** (400 MHz, $CDCl_3$) 8.75 (1H, d, *J* = 1.4 Hz, *Ar*), 7.86 (1H, dd, *J* = 8.2, 1.2 Hz, *Ar*), 7.59 (1H, d, *J* = 8.2 Hz, *Ar*), 7.01 (1H, dd, *J* = 15.8, 6.6 Hz, C(6)*H*), 6.87 (1H, dd, *J* = 15.7, 1.2 Hz, C(5)*H*), 3.98 (3H, s, C(2)H_3), 2.29 – 2.18 (1H, m, C(7)*H*), 1.86 – 1.71 (4H, m, C(8 to 10)H_2), 1.71 – 1.63 (1H, m, C(8 to 10)H_2), 1.37 – 1.11 (5H, m, C(8 to 10)H_2); **δ_C** (101 MHz, $CDCl_3$) 186.7, 163.1, 156.1, 150.0, 141.6, 130.8, 126.7, 125.9, 125.5, 53.4, 41.0, 31.7, 26.0, 25.8; **ν_{max}/** cm^{-1} (neat) 2926, 2852, 1733, 1618, 1438, 1387, 1301, 1233, 1113; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{16}H_{20}O_4N^+$ calc. 290.1387, found 290.1387.

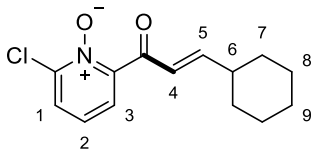
(*E*)-2-Bromo-6-(3-cyclohexylacryloyl)pyridine 1-oxide (20u)



Prepared according to **general procedure O**, using 2-bromo-6-formylpyridine-1-oxide **19e** (60 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded single isomer (*E*)-2-bromo-6-(3-cyclohexylacryloyl)pyridine 1-oxide **20u** (53.8 mg, 0.174 mmol, 58%) as a white solid.

m.p. (CH_2Cl_2) 101 – 102 °C; **δ_H** (400 MHz, Acetone-d_6) 7.98 (1H, dd, *J* = 8.1, 2.0 Hz, *Ar*), 7.54 (1H, dd, *J* = 7.8, 2.0 Hz, *Ar*), 7.34 (1H, t, *J* = 7.9 Hz, *Ar*), 6.87 (1H, dd, *J* = 15.8, 6.7 Hz, C(5)*H*), 6.70 (1H, dd, *J* = 15.8, 1.3 Hz, C(4)*H*), 2.31 – 2.17 (1H, m, C(7)*H*), 1.83 – 1.70 (4H, m, C(7 to 9)H_2), 1.71 – 1.61 (1H, m, C(7 to 9)H_2), 1.41 – 1.27 (2H, m, C(7 to 9)H_2), 1.27 – 1.12 (3H, m, C(7 to 9)H_2); **δ_C** (101 MHz, Acetone-d_6) 187.6, 154.6, 149.2, 133.9, 133.2, 126.7, 126.0, 126.0, 41.4, 32.3, 26.6, 26.3; **ν_{max}**/ cm^{-1} (neat) 2923, 2850, 1668, 1615, 1374; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{17}O_2N^{79}Br^+$ calc. 310.0437, found 310.0438.

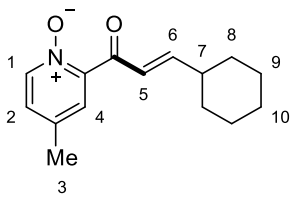
(*E*)-2-Chloro-6-(3-cyclohexylacryloyl)pyridine 1-oxide (20v)



Prepared according to **general procedure O**, using 2-chloro-6-formylpyridine-1-oxide **19f** (47 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:9 to 1:4 EtOAc:Petrol) yielded single isomer (*E*)-2-chloro-6-(3-cyclohexylacryloyl)pyridine 1-oxide **20v** (45.3 mg, 0.171 mmol, 57%) as an off-white solid.

m.p. (CH_2Cl_2) 84 – 86 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.59 (1H, dd, *J* = 8.1, 2.1 Hz, *Ar*), 7.49 (1H, dd, *J* = 7.9, 2.1 Hz, *Ar*), 7.24 (1H, app t, *J* = 7.9 Hz, *Ar*), 7.02 (1H, dd, *J* = 15.7, 6.6 Hz, C(5)*H*), 6.90 (1H, dd, *J* = 15.7, 1.2 Hz, C(4)*H*), 2.29 – 2.16 (1H, m, C(6)*H*), 1.85 – 1.71 (3H, m, C(7 to 9)H_2), 1.71 – 1.62 (1H, m, C(7 to 9)H_2), 1.36 – 1.11 (6H, m, C(7 to 9)H_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 186.4, 155.4, 148.8, 143.0, 128.5, 125.5, 125.3, 125.0, 41.0, 31.7, 26.0, 25.8; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 2924, 2851, 1670, 1616, 1380; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{17}O_2N^{35}Cl^+$ calc. 266.0942, found 266.0941.

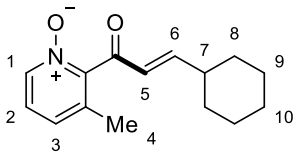
(*E*)-2-(3-Cyclohexylacryloyl)-4-methylpyridine 1-oxide (20w)



Prepared according to **general procedure O**, using 2-formyl-4-methylpyridine 1-oxide **19g** (41.1 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 EtOAc:Petrol to 3:97 MeOH:EtOAc) yielded single isomer (*E*)-2-(3-cyclohexylacryloyl)-4-methylpyridine 1-oxide **20w** (42.6 mg, 0.174 mmol, 58%) as a pale-brown viscous oil.

δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* = 6.6 Hz, *Ar*), 7.31 (1H, d, *J* = 2.6 Hz, *Ar*), 7.12 (1H, dd, *J* = 6.7, 2.7 Hz, *Ar*), 6.97 (1H, dd, *J* = 15.8, 5.6 Hz, C(6)*H*), 6.91 (1H, d, *J* = 15.8 Hz, C(5)*H*), 2.33 (3H, s, C(3)H_3), 2.25 – 2.14 (1H, m, C(7)*H*), 1.83 – 1.67 (4H, m, C(8 to 10)H_2), 1.68 – 1.58 (1H, m, C(8 to 10)H_2), 1.33 – 1.08 (5H, m, C(8 to 10)H_2); **δ_C** (101 MHz, $CDCl_3$) 187.5, 154.9, 146.6, 139.7, 137.4, 128.3, 127.2, 125.9, 40.9, 31.7, 26.0, 25.8, 20.4; **ν_{max}**/ cm^{-1} (neat) 2924, 2851, 1668, 1624, 1608, 1449, 1421, 1241, 1200, 848, 826; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{20}O_2N^+$ calc. 246.1489, found 246.1488.

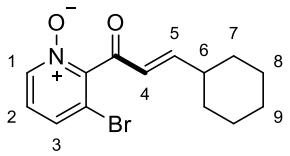
(*E*)-2-(3-Cyclohexylacryloyl)-3-methylpyridine 1-oxide (20z)



Prepared according to **general procedure O**, using 2-formyl-3-methylpyridine 1-oxide **19j** (41.1 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (14:1 l:b) by column chromatography (1:1 EtOAc:Petrol to 19:1 EtOAc:MeOH) yielded single isomer (*E*)-2-(3-cyclohexylacryloyl)-3-methylpyridine 1-oxide **20z** (46.3 mg, 0.189 mmol, 63%) as an off-white solid.

m.p. (CH_2Cl_2) 99 – 102 °C; **δ_H** (400 MHz, $CDCl_3$) 8.09 (1H, d, *J* = 6.2 Hz, *Ar*), 7.24 – 7.14 (2H, m, *Ar*), 6.71 (1H, dd, *J* = 16.1, 6.4 Hz, C(6)*H*), 6.38 (1H, dd, *J* = 16.0, 1.4 Hz, C(5)*H*), 2.27 – 2.16 (1H, m, C(7)*H*), 1.84 – 1.69 (4H, m, C(8 to 10)H_2), 1.70 – 1.61 (1H, m, C(8 to 10)H_2), 1.35 – 1.20 (2H, m, C(8 to 10)H_2), 1.21 – 1.08 (3H, m, C(8 to 10)H_2); **δ_C** (101 MHz, $CDCl_3$) 189.6, 156.6, 146.5, 137.3, 134.8, 128.3, 127.1, 125.4, 40.8, 31.5, 26.0, 25.8, 17.6; **ν_{max}**/ cm^{-1} (neat) 2925, 2851, 1664, 1619, 1448, 1419, 1289, 1241, 966, 789; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{15}H_{20}O_2N^+$ calc. 246.1489, found 246.1486.

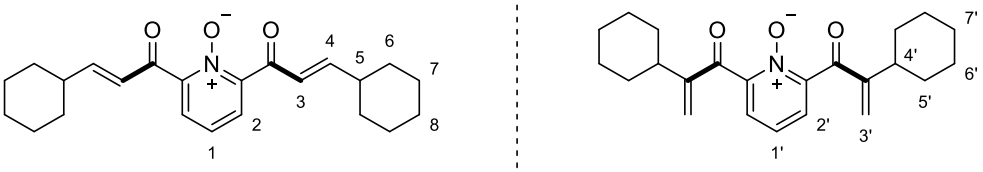
(*E*)-3-Bromo-2-(3-cyclohexylacryloyl)pyridine 1-oxide (20aa)



Prepared according to **general procedure O**, using 3-bromo-2-formylpyridine 1-oxide **19k** (60 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 1:0 EtOAc:Petrol) yielded single isomer (*E*)-3-bromo-2-(3-cyclohexylacryloyl)pyridine 1-oxide **20aa** (84.6 mg, 0.274 mmol, 91%) as an off-white solid.

m.p. (CH_2Cl_2) 80 – 82 °C; **δ_H** (400 MHz, $CDCl_3$) 8.15 (1H, dd, *J* = 6.5, 0.9 Hz, *Ar*), 7.49 (1H, dd, *J* = 8.3, 0.9 Hz, *Ar*), 7.18 (1H, dd, *J* = 8.3, 6.5 Hz, *Ar*), 6.69 (1H, dd, *J* = 16.2, 6.4 Hz, C(5)*H*), 6.31 (1H, dd, *J* = 16.2, 1.5 Hz, C(4)*H*), 2.29 – 2.15 (1H, m, C(6)*H*), 1.85 – 1.73 (4H, m, C(7 to 9)H_2), 1.70 – 1.59 (1H, m, C(7 to 9)H_2), 1.35 – 1.22 (2H, m, C(7 to 9)H_2), 1.22 – 1.08 (3H, m, C(7 to 9)H_2); **δ_C** (101 MHz, $CDCl_3$) 187.5, 158.2, 146.9, 138.8, 129.6, 126.2, 125.9, 118.1, 40.9, 31.4, 25.9, 25.7; **ν_{max}**/ cm^{-1} (neat) 2924, 2851, 1692, 1411, 1283, 1249, 907; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{17}O_2N^{79}Br^+$ calc. 310.0437, found 310.0438.

2,6-Bis((*E*)-3-cyclohexylacryloyl)pyridine 1-oxide (20ab), 2,6-bis(2-cyclohexylacryloyl)pyridine 1-oxide (21ab)

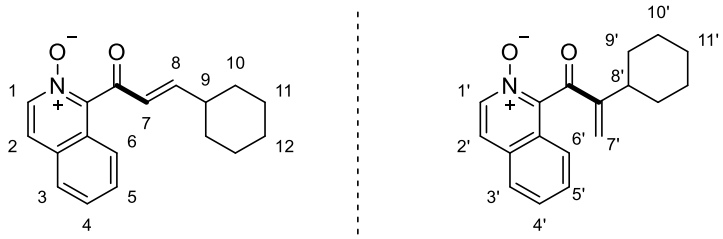


20ab **21ab**

Prepared according to **general procedure O**, using 2,6-diformylpyridine 1-oxide **19l** (30 mg, 0.200 mmol, 1.00 equiv.), ethynylcyclohexane (105 μL, 0.800 mmol, 4.00 equiv.), $Rh(nbd)_2BF_4$ (3.7 mg, 0.010 mmol, 0.050 equiv.), DPEPhos (5.4 mg, 0.010 mmol, 0.050 equiv.) and DCE (0.16 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:19 to 1:4 EtOAc:Petrol) yielded a >20:1 total inseparable mixture of regioisomers **20ab**/**21ab** (31.6 mg, 0.086 mmol, 43%) as an off-white solid.

δ_H (400 MHz, $CDCl_3$) 7.59 (2H, d, *J* = 7.8 Hz, *Ar*), 7.35 (1H, dd, *J* = 8.1, 7.5 Hz, *Ar*), 6.99 (2H, dd, *J* = 15.7, 6.7 Hz, C(4)*H*), 6.83 (2H, dd, *J* = 15.7, 1.3 Hz, C(3)*H*), 5.89 (2H, d, *J* = 1.3 Hz, C(3')*H*H), 5.63 (2H, app s, C(3')H*H*), 2.29 – 2.15 (2H, m, C(5)*H*), 1.85 – 1.70 (8H, m, C(6 to 8)H_2), 1.70 – 1.56 (2H, m, C(6 to 8)H_2), 1.36 – 1.09 (10H, m, C(6 to 8)H_2); **δ_C** (101 MHz, $CDCl_3$) 187.1, 155.5, 148.1, 128.2, 125.7, 125.5, 41.0, 32.5*, 31.7, 26.7*, 26.0, 25.8 (* denotes the minor branched regioisomer **21ab**); **ν_{max}**/ cm^{-1} (neat) 2924, 2851, 1674, 1621, 1448, 1386, 978, 968, 754; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{23}H_{30}O_3N^+$ calc. 368.2220, found 368.2221.

(*E*)-1-(3-Cyclohexylacryloyl)isoquinoline 2-oxide (20ac) and 1-(2-cyclohexylacryloyl)iso -quinoline 2-oxide (21ac)

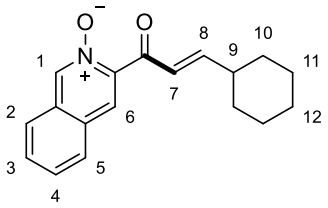


Prepared according to **general procedure O**, using 1-formylisoquinoline 2-oxide **19m** (52 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (15:1 l:b) by column chromatography (1:1 to 19:1 EtOAc:Petrol) yielded a 15:1 total inseparable mixture of regioisomers **20ac**/**21ac** (59.4 mg, 0.211 mmol, 70%) as a pale-brown solid.

δ_H (400 MHz, $CDCl_3$) 8.07 (1H, d, *J* = 7.1 Hz, *Ar*), 7.84 – 7.75 (1H, m, *Ar*), 7.69 (1H, d, *J* = 7.1 Hz, *Ar*), 7.61 – 7.51 (3H, m, *Ar*), 6.74 (1H, dd, *J* = 16.0, 6.3 Hz, C(8)*H*), 6.52 (1H, dd, *J* = 16.0, 1.4 Hz, C(7)*H*), 5.89 (1H, d, *J* = 1.2 Hz, C(7')*H*H), 5.54 (1H, app s, C(7')H*H*), 2.89 – 2.80 (1H, m, C(8')*H*), 2.25 – 2.11 (1H, m, C(9)*H*), 1.99 (2H, d, *J* = 9.6 Hz, C(10' to 12')H_2), 1.81 – 1.65 (4H, m, C(10 to 12)H_2), 1.66 – 1.56 (1H, m, C(10 to 12)H_2), 1.49 – 1.35 (4H, m, C(10' to 12')H_2), 1.33 – 1.04 (5H, m, C(10 to 12)H_2); **δ_C** (101 MHz, $CDCl_3$) 191.6*, 189.3, 157.2, 153.5*, 142.9, 136.8, 130.1, 129.0, 128.8, 127.3, 127.2, 127.1*, 124.8, 124.6, 123.5, 123.2*, 40.8, 37.3*, 32.4*, 31.4, 26.6*, 26.3*, 25.9, 25.7 (* denotes the minor branched regioisomer **21ac**); **ν_{max}**/ cm^{-1} (neat) 2926, 2852, 1664, 1618, 1426, 1331, 1229,

1146, 979, 965, 819, 750; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{18}H_{20}O_2N^+$ calc. 282.1489, found 282.1484.

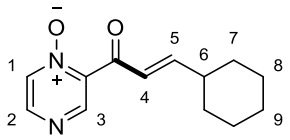
(*E*)-3-(3-Cyclohexylacryloyl)isoquinoline 2-oxide (20ae)



Prepared according to **general procedure O**, using 3-formylisoquinoline 2-oxide **19n** (52 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:1 to 7:3 EtOAc:Petrol) yielded single isomer (*E*)-3-(3-cyclohexylacryloyl)isoquinoline 2-oxide **20ae** (53.8 mg, 0.191 mmol, 64%) as an yellow viscous oil.

δ_H (600 MHz, Acetone-d_6) 8.86 (1H, s, *Ar*), 8.04 (1H, s, *Ar*), 8.03 (1H, d, *J* = 8.3 Hz, *Ar*), 7.92 (1H, d, *J* = 1.1 Hz, *Ar*), 7.73 (1H, ddd, *J* = 8.3, 6.9, 1.2 Hz, *Ar*), 7.66 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, *Ar*), 6.87 (1H, dd, *J* = 15.8, 6.4 Hz, C(8)*H*), 6.81 (1H, dd, *J* = 15.8, 1.0 Hz, C(7)*H*), 2.28 – 2.21 (1H, m, C(9)*H*), 1.82 – 1.78 (2H, m, C(10 to 12)H_2), 1.75 (2H, ddd, *J* = 12.5, 5.5, 2.4 Hz, C(10 to 12)H_2), 1.70 – 1.62 (1H, m, C(10 to 12)H_2), 1.38 – 1.28 (2H, m, C(10 to 12)H_2), 1.25 – 1.16 (3H, m, C(10 to 12)H_2); **δ_C** (151 MHz, Acetone-d_6) 188.3, 153.7, 146.1, 137.1, 131.6, 131.2, 129.6, 128.9, 128.6, 127.6, 125.5, 125.4, 41.4, 32.4, 26.6, 26.4; **ν_{max}**/ cm^{-1} (neat) 2925, 2851, 1669, 1625, 1438, 1317, 1210, 1179, 1125; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{18}H_{20}O_2N^+$ calc. 282.1489, found 282.1489.

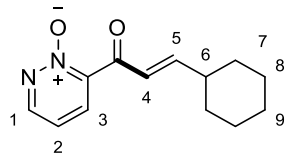
(*E*)-2-(3-Cyclohexylacryloyl)pyrazine 1-oxide (20af)



Prepared according to **general procedure O**, using 2-formylpyrazine 1-oxide **19o** (37 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:4 to 1:1 EtOAc:Petrol) yielded single isomer (*E*)-2-(3-cyclohexylacryloyl)pyrazine 1-oxide **20af** (58.6 mg, 0.254 mmol, 85%) as a pale-yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 8.72 (1H, s, *Ar*), 8.48 (1H, d, *J* = 4.2 Hz, *Ar*), 8.06 (1H, d, *J* = 4.1 Hz, *Ar*), 7.05 (1H, dd, *J* = 15.7, 6.7 Hz, C(5)*H*), 6.87 (1H, dd, *J* = 15.7, 1.3 Hz, C(4)*H*), 2.29 – 2.16 (1H, m, C(6)*H*), 1.85 – 1.69 (3H, m, C(7 to 9)H_2), 1.69 – 1.60 (1H, m, C(7 to 9)H_2), 1.37 – 1.11 (6H, m, C(7 to 9)H_2); **δ_C** (101 MHz, $CDCl_3$) 185.2, 156.6, 149.3, 148.5, 142.3, 134.7, 125.5, 41.1, 31.6, 26.0, 25.8; **ν_{max}**/ cm^{-1} (neat) 3098, 2924, 2851, 1665, 1613, 1583, 1507, 1446, 1410, 1324, 1019, 979, 967; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{13}H_{17}O_2N_2^+$ calc. 233.1285, found 233.1284.

(*E*)-6-(3-Cyclohexylacryloyl)pyridazine 1-oxide (20ag)

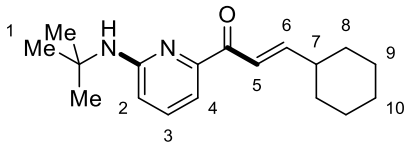


Prepared according to **general procedure O**, using 6-formylpyridazine 1-oxide **19s** (24.8 mg, 0.200 mmol, 1.00 equiv.), ethynylcyclohexane (52 μL, 0.400 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (3.7 mg, 0.010 mmol, 0.050 equiv.), DPEPhos (5.4 mg, 0.010 mmol, 0.050 equiv.) and DCE (0.16 mL), with stirring for 18 h. Purification of the crude residue (>20:1 l:b) by column chromatography (1:4 to 2:3 EtOAc:Petrol) yielded single isomer (*E*)-6-(3-cyclohexylacryloyl)pyridazine 1-oxide **20ag** (34.5 mg, 0.149 mmol, 75%) as a beige powdered solid.

m.p. (CH_2Cl_2) 82 – 83 °C; **δ_H** (400 MHz, $CDCl_3$) 8.52 (1H, dd, *J* = 5.3, 2.6 Hz, *Ar*), 7.94 (1H, dd, *J* = 7.9, 2.5 Hz, *Ar*), 7.13 (1H, dd, *J* = 7.9, 5.3 Hz, *Ar*), 7.07 (1H, dd, *J* = 15.6, 6.6 Hz, C(5)*H*), 6.94 (1H, dd, *J* = 15.7, 1.3 Hz, C(6)*H*), 2.28 – 2.18 (1H, m, C(6)*H*), 1.85 – 1.70 (4H, m, C(7 to 9)H_2), 1.71 – 1.61 (1H, m, C(7 to 9)H_2), 1.37 – 1.10 (5H, m, C(7 to 9)H_2); **δ_C** (101 MHz, $CDCl_3$) 185.6, 156.3, 151.9, 142.1, 135.4, 124.7, 116.3, 41.0, 31.6, 26.0, 25.7; **ν_{max}**/ cm^{-1} (neat) 2974, 2923, 2851, 1666, 1614, 1538, 1449, 1381; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{13}H_{16}O_2N_2{}^{23}Na^+$ calc. 255.1104, found 255.1105.

6.3.5 Deoxygenations and Other Derivatisations

(*E*)-1-(6-(*Tert*-butylamino)pyridin-2-yl)-3-cyclohexylprop-2-en-1-one (30)

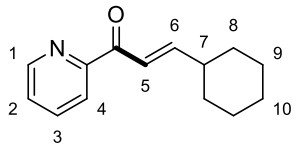


Reaction setup according to a modified literature procedure.[218] To a stirred solution of (*E*)-2-(3-cyclohexylacryloyl)pyridine 1-oxide **20b** (23 mg, 0.100 mmol, 1.00 equiv.) and *t*-butylamine (74 μL, 0.700 mmol, 7.00 equiv.) in 2.5:1 $PhCF_3$:CH_2Cl_2 (0.7 mL) was added Ts_2O (82 mg, 0.250 mmol, 2.50 equiv.) portion-wise, and the mixture was heated to 30 °C with stirring. After 30 min, starting material could still be observed by TLC, so more *t*-butylamine (11 μL, 0.100 mmol, 1.00 equiv.) and Ts_2O (32.8 mg, 0.100 mmol, 1.00 equiv.) were added and the reaction was stirred overnight (18 h). After this time, the mixture was cooled to room temperature and quenched with H_2O (1 mL) and the mixture was concentrated *in vacuo*. Purification by column chromatography (1:19 EtOAc:Petrol) yielded (*E*)-1-(6-(tert-butylamino)pyridin-2-yl)-3-cyclohexylprop-2-en-1-one **30** (16.0 mg, 0.056 mmol, 56%) as a yellow powdered solid.

m.p. (CH_2Cl_2) 84 – 87 °C; **δ_H** (400 MHz, $CDCl_3$) 7.55 – 7.42 (2H, m, *Ar* and C(5)*H*), 7.36 (1H, dd, *J* = 7.4, 0.9 Hz, *Ar*), 7.11 (1H, dd, *J* = 15.9, 6.4 Hz, C(6)*H*), 6.51 (1H, d, *J* = 8.3 Hz, *Ar*), 4.47 (1H, bs, N*H*), 2.31 – 2.19 (1H, m, C(7)*H*), 1.91 – 1.80 (2H, m, C(8 to 10)H_2), 1.78 (2H, app dt, *J* = 12.1, 3.4 Hz, C(8 to 10)H_2), 1.72 – 1.65 (1H, m, C(8 to 10)H_2), 1.50 (9H, s, C(1)H_3), 1.41 – 1.15 (5H, m, C(8 to 10)H_2); **δ_C** (101 MHz, $CDCl_3$) 190.9, 157.5, 153.8, 152.5, 137.5, 122.8, 113.0, 111.7, 51.3, 41.0, 31.9, 29.4, 26.2, 26.0; **ν_{max}**/ cm^{-1} (neat) 3386, 2980, 2926, 2853, 1671, 1617, 1593,

1517, 1506, 1453, 1388, 1360, 1226, 989, 964, 804; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{18}H_{27}ON_2^+$ calc. 287.2118, found 287.2118.

(*E*)-3-Cyclohexyl-1-(pyridin-2-yl)prop-2-en-1-one (31)



Prepared according to a modified literature procedure.[91b] To a stirred solution of (*E*)-2-(3-cyclohexylacryloyl)pyridine 1-oxide **20b** (23 mg, 0.100 mmol, 1.00 equiv.) in dry toluene (0.5 mL, 0.2 M) was added PCl_3 (10.5 μL, 0.120 mmol, 1.20 equiv.) dropwise at room temperature and the resulting mixture was stirred for 15 min. Once complete by TLC, the mixture was quenched with sat. aq. $NaHCO_3$ (2.5 mL) and the mixture was stirred for an additional 5 min. The mixture was then extracted in CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (9:1 to 4:1 Petrol:Et_2O) yielded (*E*)-3-cyclohexyl-1-(pyridin-2-yl)prop-2-en-1-one **31** (15.4 mg, 0.072 mmol, 72%) as a colourless oil.

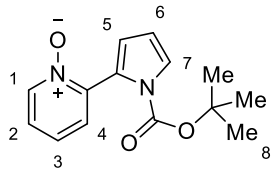
Or alternatively prepared via the following two-step one-pot method:

The first hydroacylation step was according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), ethynylcyclohexane (78 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), with stirring for 18 h. After this time, the reaction mixture was cooled to room temperature and diluted with dry DCE (1.26 mL, 0.2 M total conc.). PCl_3 (31.4 μL, 0.360 mmol, 1.20 equiv.) was then added dropwise to this solution, and the resulting mixture was stirred for 15 min. Once complete by TLC, the mixture was quenched with sat. aq.

$NaHCO_3$ (2.5 mL) and the mixture was stirred for an additional 5 min. The mixture was then extracted in CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue (>20:1 l:b) by column chromatography (9:1 to 4:1 Petrol:Et_2O) yielded single isomer (*E*)-3-cyclohexyl-1-(pyridin-2-yl)prop-2-en-1-one **31** (29.7 mg, 0.138 mmol, 46%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.69 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, *Ar*), 8.11 (1H, app dt, *J* = 7.9, 1.2 Hz, *Ar*), 7.83 (1H, app td, *J* = 7.7, 1.7 Hz, *Ar*), 7.56 (1H, dd, *J* = 15.8, 1.4 Hz, C(5)*H*), 7.45 (1H, ddd, *J* = 7.6, 4.8, 1.3 Hz, *Ar*), 7.18 (1H, dd, *J* = 15.8, 6.9 Hz, C(6)*H*), 2.36 – 2.22 (1H, m, C(7)*H*), 1.90 – 1.82 (2H, m, C(8 to 10)H_2), 1.82 – 1.74 (2H, m, C(8 to 10)H_2), 1.73 – 1.64 (1H, m, C(8 to 10)H_2), 1.39 – 1.17 (5H, m, C(8 to 10)H_2); **δ_C** (101 MHz, $CDCl_3$) 190.0, 155.4, 154.4, 148.9, 137.1, 126.8, 123.0, 122.1, 41.4, 32.0, 26.1, 25.9; **ν_{max}**/ cm^{-1} (neat) 2925, 2852, 1677, 1620, 1583, 1333, 1320, 1020, 993, 964, 743; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{18}ON^+$ calc. 216.1383, found 216.1384. Data is consistent with literature.[219]

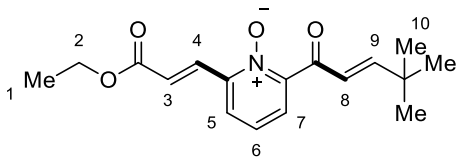
2-(1-(*Tert*-butoxycarbonyl)-1H-pyrrol-2-yl)pyridine 1-oxide (32)



First step undertaken according to **general procedure O**, using 2-formylpyridine 1-oxide **19a** (37 mg, 0.300 mmol, 1.00 equiv.), *t*-butyl prop-2-yn-1-ylcarbamate (93.1 μL, 0.600 mmol, 2.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 0.050 equiv.), DPEPhos (8.1 mg, 0.015 mmol, 0.050 equiv.) and DCE (0.24 mL), ***with stirring at room temperature for 21 h***. After this time, the reaction mixture was diluted with DCE (3 mL, 0.09 M total conc.) and *p*-toluene sulfonic acid monohydrate (86 mg, 0.450 mmol, 1.50 equiv.) was added. The mixture was then stirred at room temperature for a further 3 h before addition of sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted in CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (4:1 CH_2Cl_2:Acetone) yielded 2-(1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl)pyridine 1-oxide **32** (30.5 mg, 0.117 mmol, 39%) as a yellow/orange solid. (The second step conditions were modified from a literature procedure)[74b]

m.p. (CH_2Cl_2) 109 – 111 °C; **δ_H** (400 MHz, $CDCl_3$) 8.33 (1H, dd, *J* = 6.2, 1.6 Hz, *Ar*), 7.45 (1H, dd, *J* = 3.3, 1.7 Hz, *Ar*), 7.42 – 7.38 (1H, m, *Ar*), 7.35 – 7.22 (2H, m, *Ar*), 6.36 (1H, dd, *J* = 3.4, 1.8 Hz, *Ar*), 6.28 (1H, t, *J* = 3.3 Hz, *Ar*), 1.40 (9H, s, C(8)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 148.7, 144.5, 139.6, 127.4, 125.0, 125.0, 124.8, 123.7, 116.6, 110.7, 83.9, 27.7; **ν_{max}**/ cm^{-1} (neat) 2979, 2932, 1744, 1321, 1257, 1151, 849, 768; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{14}H_{17}O_3N_2^+$ calc. 261.1234, found 261.1235.

2-((*E*)-4,4-Dimethylpent-2-enoyl)-6-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)pyridine 1-oxide (33)



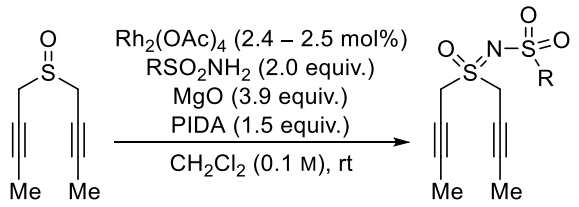
Prepared according to a modified literature procedure.[218] To an oven-dried microwave vial was added (*E*)-2-(4,4-dimethylpent-2-enoyl)pyridine 1-oxide **20d** (20.5 mg, 0.100 mmol, 1.00 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.100 equiv.) and Ag_2CO_3 (41.1 mg, 0.150 mmol, 1.50 equiv.). The vial was sealed and backfilled with argon three times. Dry and degassed 1,4-dioxane (0.2 mL) was then added to the vial, followed by pyridine (8 μL, 0.100 mmol, 1.00 equiv.) and ethyl acrylate (27.2 μL, 0.250 mmol, 2.50 equiv.). the mixture was then heated to 100 °C with stirring for 21 h. After this time, the mixture was cooled to room temperature and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:9 to 3:7 EtOAc:Petrol) yielded 2-((*E*)-4,4-dimethylpent-2-enoyl)-6-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)pyridine 1-oxide **33** (5.8 mg, 0.019 mmol, 19%) as a yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 8.06 (1H, d, *J* = 16.3 Hz, C(3 or 4)*H*), 7.62 (1H, dd, *J* = 7.9, 2.1 Hz, *Ar*), 7.49 (1H, dd, *J* = 7.8, 2.1 Hz, *Ar*), 7.29 (1H, app t, *J* = 7.8 Hz, *Ar*), 7.06 (1H, d, *J* = 15.9 Hz, C(8 or 9)*H*), 6.96 (1H, d, *J* = 16.3 Hz, C(3 or 4)*H*), 6.81 (1H, d, *J* = 15.8 Hz, C(8 or 9)*H*), 4.29 (2H, q, *J* = 7.1 Hz, C(2)H_2), 1.34 (3H, t, *J* = 7.1 Hz, C(1)H_3), 1.13 (9H, s, C(10)H_3); **δ_C** (101 MHz, $CDCl_3$) 187.6, 166.2, 159.7, 148.5, 146.2, 133.6, 127.2, 126.6, 125.6, 124.8, 123.5, 61.2, 34.4, 28.8, 14.4; **ν_{max}**/ cm^{-1} (neat) 2962, 1715, 1671, 1618, 1391, 1325, 1271, 1191; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{17}H_{22}O_4N^+$ calc. 304.1543, found 304.1543.

6.4 Experimental for Chapter 4

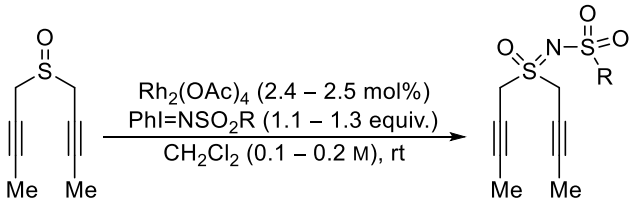
6.4.1 General Procedures

General Procedure P – Imidation of sulfoxide diyne 35 using $PhI(OAc)_2$ (PIDA) and sulfonamides



Following a modified literature procedure[220] $PhI(OAc)_2$ (1.50 equiv.) was added to a solution of MgO (3.90 equiv.), 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (1.00 equiv.), the respective sulfonamide (2.00 equiv.), $Rh_2(OAc)_4$ (2.4 – 2.5 mol%) in anhydrous CH_2Cl_2 (0.1 M) at room temperature. This mixture was stirred at room temperature for 4 – 36 h. After this time, the solvent was removed *in vacuo*. Purification of the crude residue by column chromatography yielded the desired sulfoximine diynes.

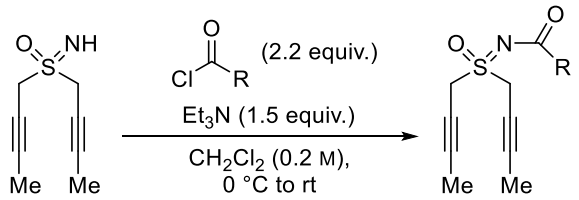
General Procedure Q – Imidation of sulfoxide diyne 35 using pre-formed iminoiodinanes



The respective iminoiodinane (1.10 – 1.30 equiv.) was added to a solution containing 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (1.00 equiv.) and $Rh_2(OAc)_4$ (2.4 – 2.5 mol%) in anhydrous CH_2Cl_2 (0.1 – 0.2 M) at room temperature. This mixture was stirred at room temperature for 20 h. After this time, the solvent was removed

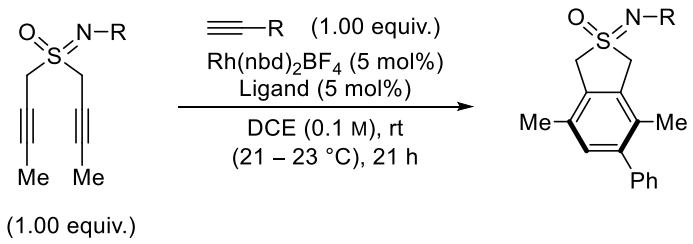
in vacuo. Purification of the crude residue by column chromatography yielded the desired sulfoximine diyne.

General Procedure R – Addition of *NH*-sulfoximine diyne 36e into electrophiles



Following a modified literature procedure,[221] Et_3N (1.50 equiv.) was added to a solution of di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (1.00 equiv.) in anhydrous CH_2Cl_2 (0.2 M) at 0 °C with stirring. The resulting mixture was then stirred at room temperature for 15 min before the respective acyl chloride (2.2 equiv.) was added at 0 °C. The headspace of the vial was purged with argon before being warmed to room temperature ***(if higher temperatures were required, it is stated in the individual procedure)***. The mixture was then stirred for 1.5 – 24 h before being quenched with sat. aq. NH_4Cl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

General procedure S – Standard Conditions for Rhodium-catalysed [2+2+2] Cycloaddition



The respective diyne (1.00 equiv.) and terminal alkyne (if it is a solid) (1.00 equiv.) were both added to an oven-dried 10 mL reaction vial, which was then evacuated and backfilled with argon three times. If the alkyne is a volatile liquid, it is added

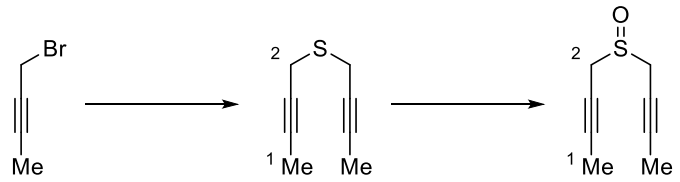
into the vial post-vac-cycle. $Rh(nbd)_2BF_4$ (5 mol%) and respective ligand (5 mol%) were both weighed into a separate tapered, 10 mL microwave vial, which was then sealed with a microwave cap. The vial was then evacuated and back-filled with argon three times. After this, DCE (0.6 mL) was introduced, and the solution sonicated for 30 s. Hydrogen gas was bubbled through the solution for 1 – 3 min. Argon was then bubbled through the resulting solution for 10 – 15 min which was then added to the vial containing diyne and terminal alkyne. Additional DCE was added to the reaction vial to make the concentration to 0.1 M. The resulting solution was then stirred at room temperature for 21 h. After this time, the reaction was concentrated *in vacuo*. Purification by column chromatography yielded the arene products.

General procedure towards racemic cycloaddition products

The racemic products used for chiral-phase HPLC analysis were obtained through **general procedure S** mentioned above, using *rac*-BINAP as the ligand.

6.4.2 Substrate Synthesis

Di(but-2-yn-1-yl)sulfane (34) and 1-(but-2-yn-1-ylsulfinyl)but-2-yne (35)



34 **35**

Di(but-2-yn-1-yl)sulfane (34): Following a modified literature procedure,[222] 1-bromobut-2-yne (5.88 mL, 66.3 mmol, 2.00 equiv.), was added to a solution of Na_2S (2.59 g, 33.2 mmol, 1.00 equiv.) in MeOH (66 mL). The resulting mixture was stirred at room temperature for 6 h, then poured onto H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. **CAUTION: The sulfide product has an extremely potent smell, and so bleaching glassware after workup is highly recommended.** Purification of the crude residue by column chromatography (1:0 to 9:1 Petrol:Et_2O), di(but-2-yn-1-yl)sulfane **34** (3.31 g, 24.0 mmol, 72%) as a yellow volatile oil.

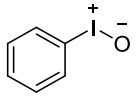
$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.37 (4H, q, *J* = 2.5 Hz, C(2)H_2), 1.83 (6H, app. t, *J* = 2.5 Hz, C(1)H_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 79.0, 74.4, 19.7, 3.7; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 2981, 2889, 2230, 1382, 1250, 1233, 1151, 1073, 955. Data is consistent with literature.[223]

1-(But-2-yn-1-ylsulfinyl)but-2-yne (35): Following a modified literature procedure,[224] a solution of di(but-2-yn-1-yl)sulfane **34** (621 mg, 4.50 mmol, 1.00 equiv.) in MeOH (24 mL) was added to a flask containing a solution of $NaIO_4$ (963 mg, 4.50 mmol, 1.00 equiv.) in H_2O (24 mL) at 0 °C, with stirring. The mixture was slowly warmed to room temperature and stirred for 18 h. After this time, $CHCl_3$

(30 mL) was added and the layers were separated. The aqueous phase was then extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the crude residue by column chromatography (1:0 to 1:1 Pentane:EtOAc) yielded the title compound 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (521 mg, 3.38 mmol, 75%) as a pale-yellow viscous oil.

δ_H (400 MHz, $CDCl_3$) 3.77 (2H, dq, *J* = 15.8, 2.6 Hz, C(2)*H*H), 3.59 (2H, dq, *J* = 15.7, 2.6 Hz, C(2)H*H*), 1.89 (6H, t, *J* = 2.6 Hz, C(1)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 84.8, 67.2, 41.5, 4.0; **ν_{max}**/ cm^{-1} (neat) 2981, 2235, 1395, 1250, 1240, 1164, 1151, 1059, 955; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_8H_{11}O^{32}S^+$ calc. 155.0525, found 155.0524.

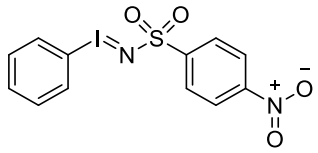
Iodosylbenzene (39)



Following a modified literature procedure,[173] $PhI(OAc)_2$ (30.0 g, 93.1 mmol, 1.00 equiv.) was added portion-wise to a stirred solution of 3 M $NaOH_{(aq)}$ (186 mL, 6.00 equiv.) at room temperature. After 1 h, H_2O (100 mL) was added, and the resulting mixture was stirred for 1 h at room temperature. After this time, the mixture was poured onto a Büchner filter, and the filter cake was washed with H_2O (100 mL) and $CHCl_3$ (100 mL) under suction. The resulting solid was dried under high-vacuum to yield the title compound iodosylbenzene **39** (18.4 g, 83.5 mmol, 90%) as an off-white solid.

δ_H (400 MHz, MeOD-d_4) 8.15 – 7.92 (2H, m, *Ar*), 7.57 (3H, dt, *J* = 5.4, 2.0 Hz, *Ar*); **δ_C** (101 MHz, MeOD -d_4) 133.3, 132.2, 132.0, 122.6; **ν_{max}**/ cm^{-1} (neat) 2981, 2889, 1382, 1153, 1068, 955, 737, 689. Data is consistent with literature.[173]

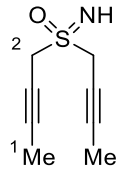
4-Nitro-*N*-(phenyl-λ^3-iodaneylidene)benzenesulfonamide (47a)



Following a modified literature procedure,[225] using a 3-neck flask, $PhI(OAc)_2$ (3.00 g, 9.30 mmol, 1.20 equiv.) was added portion-wise to a stirred solution of KOH (1.09 g, 19.4 mmol, 2.50 equiv.) and 4-Nitrobenzenesulfonamide (1.57 g, 7.75 mmol, 1.00 equiv.) in MeOH (35 mL) at 0 °C. The headspace of the flask was then purged with N_2 and then the mixture was warmed to room temperature. The mixture was stirred for 3 h at room temperature, before the stirring was stopped and the mixture left to stand overnight, in the absence of light. After this time, the pale-yellow precipitate was collected by Büchner filtration and washed with ice-cold MeOH (3 × 15 mL). A further 30 min of drying under high-vacuum yielded the title compound 4-nitro-*N*-(phenyl-λ^3-iodaneylidene)benzenesulfonamide **47a** (2.74 g, 6.78 mmol, 87%) as a pale-yellow powdered solid.

δ_H (400 MHz, DMSO-d_6) 8.08 – 7.98 (2H, m, *Ar*), 7.78 – 7.66 (4H, m, *Ar*), 7.45 – 7.35 (1H, m, *Ar*), 7.25 (2H, dd, J = 8.3, 7.1 Hz, *Ar*); **δ_C** (101 MHz, DMSO-d_6) 151.0, 147.9, 133.7, 130.6, 130.2, 127.5, 123.6, 117.2; **ν_{max}**/ cm^{-1} (neat) 1523, 1273, 1123, 1079, 877, 852, 734, 682, 619. Data is consistent with literature.[225-226]

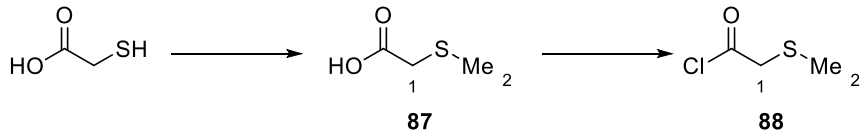
Di(but-2-yn-1-yl)(imino)-λ^6-sulfanone (36e)



Following a modified literature procedure,[173] iodosylbenzene (798 mg, 3.63 mmol, 2.50 equiv.), was added portion-wise to a solution of di(but-2-yn-1-yl)sulfane **34** (200 mg, 1.45 mmol, 1.00 equiv.), and finely ground $NH_4CO_2NH_2$ (226 mg, 2.90 mmol, 2.00 equiv.) in *i*-PrOH (7.3 mL) at room temperature. Acetic acid (83 μL, 1.45 mmol, 1.00 equiv.), was then added dropwise and the solution was stirred at room temperature for 1 h. After this time, sat. aq. $NaHCO_3$ (40 mL) was added and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:1 to 7:3 EtOAc:Hexane) yielded the title compound di(but-2-yn-1-yl)(imino)- λ^6-sulfanone **36e** (78.2 mg, 0.463 mmol, 32%) as an orange powdered solid.

m.p. (CH_2Cl_2) 55 – 57 °C; **δ_H** (400 MHz, $CDCl_3$) 4.04 (4H, app. P, *J* = 2.6 Hz, C(2)*H*$_2$), 2.73 (1H, bs, N*H*), 1.91 (6H, app. t, *J* = 2.6 Hz, C(1)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 84.9, 67.0, 46.5, 4.1; **ν_{max}**/ cm^{-1} (neat) 3291, 2957, 2918, 2241, 1441, 1398, 1255, 1224, 1098, 996; **m/z HRMS** (ESI$^+$) $[M + H]^+$ $C_8H_{12}ON^{32}S^+$ calc. 170.0634, found 170.0634.

2-(Methylthio)acetic acid (87) and 2-(methylthio)acetyl chloride (88)



87 **88**

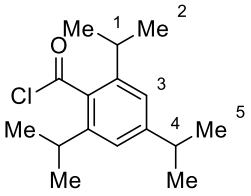
2-(Methylthio)acetic acid (87): Following a modified literature procedure,[227] 2 M $NaOH_{(aq)}$ (40 mL, 80.0 mmol, 4.00 equiv.) was added to a suspension of 2-mercaptoactetic acid (1.39 mL, 20.0 mmol, 1.00 equiv.) in EtOH (8 mL) at 0 °C. After stirring at this temperature for 15 min, methyl iodide (1.49 mL, 24.0 mmol, 1.20 equiv.) was added and then stirring was continued at 0 °C for 1 h. After this time, the mixture was acidified with 2 M $HCl_{(aq)}$ until pH 1 – 2. The resulting mixture was then extracted with EtOAc (3 × 30 mL), then the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to yield the crude title compound 2-(methylthio)acetic acid **87** (2.01 g, 19.0 mmol, 95%), which was used without further purification.

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 11.40 (1H, bs, O*H*), 3.22 (2H, s, C(1)H_2), 2.23 (3H, s, C(2)H_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 176.9, 35.7, 16.5; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3077, 2922, 1705, 1425, 1295, 1140, 666. Data is consistent with literature.[227]

2-(Methylthio)acetyl chloride (88): Following a modified literature procedure,[228] oxalyl chloride (3.43 mL, 40.0 mmol, 4.00 equiv.) was added to a solution of 2-(methylthio)acetic acid **87** (1.06 g, 10.0 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (20 mL) at room temperature, followed by 2 drops of anhydrous DMF. The mixture was then stirred at room temperature for 5 h, before the solvent was removed *in vacuo* to yield the crude title compound 2-(methylthio)acetyl chloride **88** (1.07 g, 8.59 mmol, 86%) as a dark-red oil, which was used without further purification.

δ_H (400 MHz, $CDCl_3$) 3.65 (2H, s, C(1)H_2), 2.21 (3H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 169.9, 47.3, 16.3; **ν_{max}**/ cm^{-1} (neat) 2981, 2972, 2889, 1782, 1696, 1624, 1390, 1243, 1156, 1083, 968. Data is consistent with literature.[228]

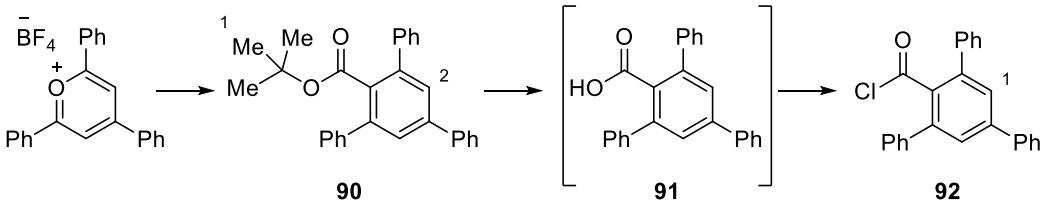
2,4,6-Triisopropylbenzoyl chloride (89)



According to an exact literature procedure,[229] 2,4,6-triisopropylbenzoic acid (1.25 g, 5.00 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (15 mL). One drop of DMF and $SOCl_2$ (0.44 mL, 6.05 mmol, 1.2 equiv.) was added and the reaction mixture was stirred for 16 h at 30 °C under N_2. After this time, all volatiles were removed *in vacuo* without further purification to yield the title compound 2,4,6-triisopropylbenzoyl chloride **89** (1.31 g, 4.93 mmol, 99%) as a white powdered solid.

m.p. (CH_2Cl_2) 65 – 67 °C; **δ_H** (400 MHz, $CDCl_3$) 7.03 (2H, s, C(3)*H*), 3.05 (2H, hept, *J* = 6.7 Hz, C(1)*H*), 2.90 (1H, hept, *J* = 6.7 Hz, C(4)*H*), 1.28 (12H, d, *J* = 6.8 Hz, C(2)H_3), 1.26 (6H, d, *J* = 7.0 Hz, C(5)H_3); **δ_C** (101 MHz, $CDCl_3$) 171.3, 151.7, 143.2, 135.4, 121.5, 34.6, 31.6, 24.1, 24.0; **ν_{max}**/ cm^{-1} (neat) 2981, 2905, 2244, 1631, 1271, 1235, 1109, 1089, 961, 755.

***tert*-Butyl 5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxylate (90) and 5'-phenyl-[1,1':3',1''-terphenyl]-2'-carbonyl chloride (92)**



tert-Butyl 5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxylate (90): Following a modified literature procedure,[230] a suspension of NaH (60% w/w in mineral oil, 400 mg, 10.0 mmol, 1.98 equiv.) in DMSO (20 mL) containing 1% H_2O (0.2 mL) was heated to 60 °C and stirred under argon until a clear solution resulted (approx. 1 h). The mixture was then cooled to room temperature and *tert*-butyl acetoacetate (0.82 mL, 5.02 mmol, 0.99 equiv.) was added, followed by the addition of 2,4,6-triphenylpyrylium tetrafluoroborate (2.00 g, 5.05 mmol, 1.00 equiv.). The mixture immediately turned deep purple, before slowly becoming discoloured. After 30 min of stirring at room temperature, the mixture was diluted with toluene (50 mL) and washed with H_2O (3 × 20 mL). The aqueous phase was then extracted with toluene (3 × 20 mL) and the combined organic layers were washed again with H_2O (7 × 20mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography (1:19 to 1:9 EtOAc:Petrol) to yield the title compound *tert*-butyl 5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxylate **90** (757 mg, 1.86 mmol, 37%) as a pale-yellow solid.

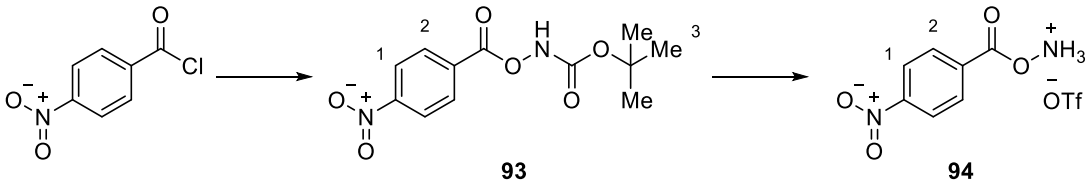
m.p. (CH_2Cl_2) 81 – 83 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.69 – 7.61 (2H, m, *Ar*), 7.59 (2H, s, C(2)*H*), 7.53 – 7.48 (4H, m, *Ar*), 7.48 – 7.35 (9H, m, *Ar*), 1.11 (9H, s, C(1)H_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 168.0, 141.7, 140.8, 140.2, 133.3, 129.0, 129.0, 128.2, 127.9, 127.7, 127.6, 127.4, 81.9, 27.6 (one aromatic carbon environment not observed due

to signal overlap); ν_{max}/ cm^{-1} (neat) 1721, 1288, 1171, 1119, 757, 699; an accurate mass could not be obtained for this compound.

5'-Phenyl-[1,1':3',1''-terphenyl]-2'-carbonyl chloride (92): Following a modified literature procedure,[230] *tert*-butyl 5'-phenyl-[1,1':3',1"-terphenyl]-2'-carboxylate **90** (613 mg, 1.51 mmol, 1.00 equiv.), was dissolved in CH_2Cl_2 (3 mL) and stirred at room temperature. TFA (3 mL) was then added at this temperature and the resulting solution was stirred overnight (18 h). After this time, TLC indicated completion and the CH_2Cl_2 and TFA were removed *in vacuo* to yield the crude carboxylic acid **91** as a pale-yellow solid. Then, according to a literature procedure,[229] the product **91** was re-dissolved in anhydrous CH_2Cl_2 (4.6 mL). One drop of DMF and $SOCl_2$ (0.13 mL, 1.81 mmol, 1.2 equiv.) was added and the reaction mixture was stirred for 16 h at 30 °C under N_2. After this time, all volatiles were removed *in vacuo* without further purification to yield the title compound 5'-phenyl-[1,1':3',1"-terphenyl]-2'-carbonyl chloride **92** (387 mg, 1.05 mmol, 70% over two steps) as a brown powdered solid.

m.p. (CH_2Cl_2) 93 – 95 °C; δ_H (400 MHz, $CDCl_3$) 7.70 – 7.66 (2H, m, *Ar*), 7.65 (2H, s, C(1)*H*), 7.54 – 7.39 (13H, m, *Ar*); δ_C (101 MHz, $CDCl_3$) 170.1, 143.5, 140.0, 139.5, 139.3, 136.2, 129.2, 129.1, 128.8, 128.5, 128.4, 128.1, 127.5; ν_{max}/ cm^{-1} (neat) 1787, 1594, 1496, 1188, 873, 806, 756, 699; an accurate mass could not be obtained for this compound.

***tert*-Butyl ((4-nitrobenzoyl)oxy)carbamate (93) and *O*-(4-nitrobenzoyl)hydroxylammonium trifluoromethanesulfonate (94)**



93 94

***tert*-Butyl ((4-nitrobenzoyl)oxy)carbamate (93):** Following a modified literature procedure,[231] 4-nitrobenzoyl chloride (4.08 g, 22.0 mmol, 1.1 equiv.) was added to a stirred solution of *tert*-butyl-*N*-hydroxycarbamate (2.66 g, 20.0 mmol, 1.00 equiv.) and Et_3N (3.06 mL, 22.0 mmol, 1.1 equiv.) in Et_2O (110 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 18 h. After this time, sat. aq. $NaHCO_3$ (100 mL), was added and the layers were separated. The organic layer was then washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentred *in vacuo* to yield the title compound *tert*-butyl ((4-nitrobenzoyl)oxy)carbamate **93** (3.84 g, 13.5 mmol, 67%) as a white solid

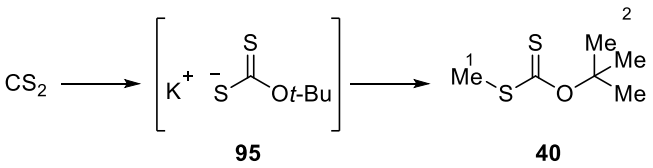
m.p. (CH_2Cl_2) 94 – 96 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.35 – 8.31 (2H, m, *Ar*), 8.29 – 8.25 (2H, m, *Ar*), 8.22 (1H, s, N*H*), 1.52 (9H, s, C(3)H_3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 164.4, 155.3, 151.3, 132.5, 131.3, 124.0, 84.1, 28.2; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 3657, 3244, 2981, 2888, 1764, 1721, 1607, 1538, 1479, 1395, 1371, 1348, 1248, 1153, 1099, 870, 714. Data is consistent with literature.[231]

***O*-(4-nitrobenzoyl)hydroxylammonium trifluoromethanesulfonate (94):** Following a literature procedure,[231] triflic acid (0.32 mL, 3.33 mmol, 1.1 equiv.) was added dropwise to a solution of *tert*-butyl ((4-nitrobenzoyl)oxy)carbamate **93** (850 mg, 3.01 mmol, 1.00 equiv.) in Et_2O (15 mL) with stirring at 0 °C. The solution was then stirred at room temperature for 2 h. The resulting precipitate was isolated

by Büchner filtration and washed with Et_2O (3 × 20 mL) to yield the title compound *O*-(4-nitrobenzoyl)hydroxylammonium trifluoromethanesulfonate **94** (347 mg, 0.850 mmol, 28%) as a white powdered solid.

δ_F (377 MHz, Acetonitrile-d_3) –79.42; **δ_H** (400 MHz, Acetonitrile-d_3) 8.44 (3H, bs, NH_3), 8.38 (2H, d, *J* = 9.0 Hz, *Ar*), 8.24 (2H, d, *J* = 9.1 Hz, *Ar*); **ν_{max}**/ cm^{-1} (neat) 3503, 2981, 1785, 1530, 1237, 1174, 1061, 1028, 713, 639. Data is consistent with literature.[231]

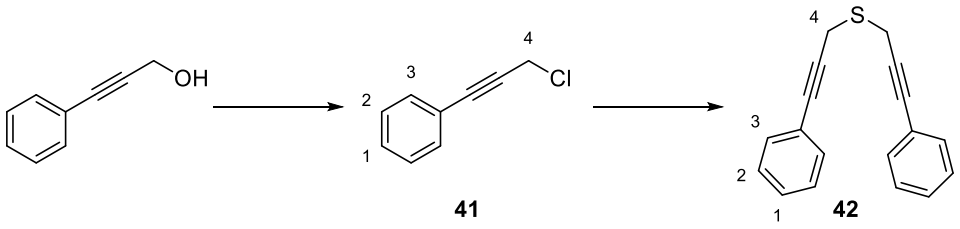
O-(*tert*-butyl) *S*-methyl carbonodithioate (40)



According to an modified literature procedure,[174a] CS_2 (1.41 mL, 23.5 mmol, 1.04 equiv.), was added dropwise over 5 min, to a solution of KO*t*-Bu (2.53 g, 22.6 mmol, 1.00 equiv.) in anhydrous toluene (52 mL), at 75 °C. The reaction mixture was stirred at 75 °C for a further 10 min. The resulting pale-yellow solid **95** was collected by filtration, washed with benzene (3 × 20 mL), dried (on a high-vacuum overnight). This solid was then suspended in anhydrous Et_2O (32 mL). methyl iodide (1.92 mL, 30.8 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was then filtered and concentrated *in vacuo* to give the title compound *O*-(*tert*-butyl) *S*-methyl carbonodithioate **40** (2.16 g, 13.2 mmol, 58% over two steps) as a yellow, odorous liquid. [Note: reaction mixture concentrated in a water bath set no higher than 25 °C]

δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, C(1)H_3), 1.69 (9H, s, C(2)H_3); **δ_C** (101 MHz, $CDCl_3$) 213.4, 90.9, 28.1, 19.3; **ν_{max}**/ cm^{-1} (neat) 1262, 1138, 1039, 1025. Data is consistent with literature.[174a]

(3-Chloroprop-1-yn-1-yl)benzene (41) and bis(3-phenylprop-2-yn-1-yl)sulfane (42)



(3-Chloroprop-1-yn-1-yl)benzene (41): Following a modified literature procedure,[232] Et_3N (7.67 mL, 55.0 mmol, 1.10 equiv.), and methanesulfonyl chloride (4.26 mL, 55.0 mmol, 1.10 equiv.) were added dropwise to a stirred solution of 3-phenylprop-2-yn-1-ol (6.23 mL, 50.0 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (57 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 4 h. After this time, additional equivalents of methanesulfonyl chloride (3.87 mL, 50.0 mmol, 1.00 equiv.) was added and the mixture was stirred for another 20 h. After this time, TLC analysis still showed incomplete consumption of the alcohol, and so more methanesulfonyl chloride (3.87 mL, 50.0 mmol, 1.00 equiv.) was added and the mixture was stirred for another 6 h (30 h total reaction time). After this time, the reaction mixture was washed with H_2O (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:0 to 19:1 Petrol:EtOAc) yielded the title compound (3-chloroprop-1-yn-1-yl)benzene **41** (6.31 g, 42.0 mmol, 84%) as a colourless oil.

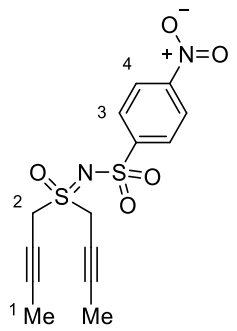
δ_H (400 MHz, $CDCl_3$) 7.49 – 7.45 (2H, m, *Ar*), 7.38 – 7.30 (3H, m, *Ar*), 4.39 (2H, s, C(4)H_2); δ_C (101 MHz, $CDCl_3$) 132.0, 129.0, 128.5, 122.2, 86.4, 83.9, 31.3; ν_{max}/ cm^{-1} (neat) 2981, 1491, 1274, 1251, 756, 689. Data is consistent with literature.[233]

Bis(3-phenylprop-2-yn-1-yl)sulfane (42): Following a modified literature procedure,[222] 3-chloroprop-1-yn-1-yl)benzene **41** (3.15 g, 21.0 mmol, 2.00 equiv.),

was added to a solution of Na_2S (820 mg, 10.5 mmol, 1.00 equiv.) in MeOH (42 mL). The resulting mixture was stirred at room temperature for 48 h, then poured onto H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (1:0 to 9:1 Petrol:Et_2O), yielded the title compound **42** (3.31 g, 24.0 mmol, 72%) as a yellow volatile oil.

δ_H (400 MHz, $CDCl_3$) 7.48 – 7.43 (4H, m, *Ar*), 7.33 – 7.28 (6H, m, *Ar*), 3.73 (4H, s, C(4)*H*$_2$); **δ_C** (101 MHz, $CDCl_3$) 131.9, 128.4, 128.4, 123.1, 84.8, 83.6, 20.3; **ν_{max}**/ cm^{-1} (neat) 2981, 1490, 1274, 1251, 756, 689. Data is consistent with literature.[222]

***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-4-nitrobenzenesulfonamide (36a)**

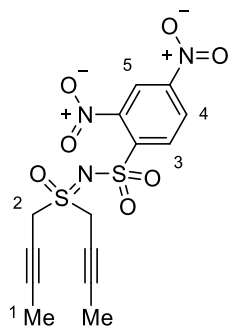


Following **general procedure P** using MgO (141 mg, 3.51 mmol, 3.90 equiv.), $PhI(OAc)_2$ (435 mg, 1.35 mmol, 1.50 equiv.), 4-nitrobenzenesulfonamide (364 mg, 1.80 mmol, 2.00 equiv.), $Rh_2(OAc)_4$ (9.5 mg, 0.022 mmol, 2.4 mol%), 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (139 mg, 0.900 mmol, 1.00 equiv.) and CH_2Cl_2 (9 mL). TLC analysis showed reaction completion after 36 h. Purification by column chromatography (1:0 to 9:1 CH_2Cl_2:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-4-nitrobenzenesulfonamide **36a** (146 mg, 0.412 mmol, 46%) as an off-white solid.

Alternative preparation following **general procedure Q** using 4-nitro-*N*-(phenyl-l3-iodaneylidene)benzenesulfonamide **47** (144 mg, 0.358 mmol, 1.10 equiv.), 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (50.0 mg, 0.325 mmol, 1.00 equiv.) and $Rh_2(OAc)_4$ (3.4 mg, 0.0075 mmol, 2.4 mol%) and CH_2Cl_2 (3.25 mL). TLC showed reaction completion after 20 h. Purification by column chromatography (1:0 to 9:1 CH_2Cl_2:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-4-nitrobenzenesulfonamide **36a** (62.5 mg, 0.177 mmol, 54%) as an off-white solid.

m.p. (Et_2O) 119 – 121 °C; **δ_H** (400 MHz, $CDCl_3$) 8.32 (2H, d, *J* = 9.0 Hz, *Ar*), 8.15 (2H, d, *J* = 8.9 Hz, *Ar*), 4.54 (2H, dqd, *J* = 16.8, 2.6, 1.1 Hz, C(2)*H*H), 4.33 (2H, dqd, *J* = 16.8, 2.6, 1.0 Hz, C(2)H*H*), 1.92 (6H, app. t, *J* = 2.6 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 150.0, 148.7, 128.3, 124.1, 87.4, 64.6, 45.2, 4.1; **ν_{max}**/ cm^{-1} (neat) 2981, 2244, 1530, 1351, 1326, 1306, 1227, 1155, 1089, 1069, 856, 744; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{14}H_{14}O_5N_2{}^{32}S_2{}^{23}Na^+$ calc. 377.0236, found 377.0237.

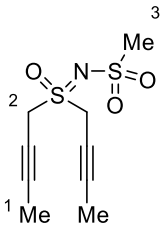
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,4-dinitrobenzenesulfonamide (36b)**



Following **general procedure Q** using 2,4-dinitro-*N*-(phenyl-l3-iodaneylidene)benzenesulfonamide[234] (379 mg, 0.845 mmol, 1.30 equiv.), 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (100 mg, 0.650 mmol, 1.00 equiv.) and $Rh_2(OAc)_4$ (7.2 mg, 0.0163 mmol, 2.5 mol%) and CH_2Cl_2 (3.25 mL). TLC showed reaction completion after 1.5 h. Purification by column chromatography (1:0 to 9:1 CH_2Cl_2:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,4-dinitrobenzenesulfonamide **36b** (210 mg, 0.526 mmol, 81%) as an off-white solid.

m.p. (Et_2O) 166 – 168 °C; **δ_H** (400 MHz, $CDCl_3$) 8.51 – 8.45 (2H, m, *Ar*), 8.40 – 8.35 (1H, m, *Ar*), 4.55 (2H, dqd, *J* = 16.8, 2.6, 1.0 Hz, C(2)*H*H), 4.35 (2H, dqd, *J* = 16.8, 2.6, 1.0 Hz, C(2)H*H*), 1.92 (6H, app. t, *J* = 2.6 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 149.7, 148.2, 141.4, 131.8, 126.3, 119.6, 87.9, 64.0, 45.4, 4.1; **ν_{max}**/ cm^{-1} (neat) 3104, 2980, 2971, 2244, 1540, 1352, 1327, 1227, 1161, 1105, 1065, 909, 753, 737; **m/z HRMS** (ESI$^+$) $[M + H]^+$ $C_{14}H_{14}O_7N_3{}^{32}S_2{}^+$ calc. 377.0236, found 377.0237.

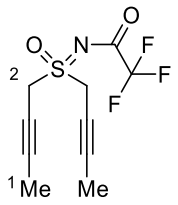
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)methanesulfonamide (36c)**



Following **general procedure P** using MgO (210 mg, 5.21 mmol, 3.90 equiv.), $PhI(OAc)_2$ (628 mg, 1.95 mmol, 1.50 equiv.), methanesulfonamide (247 mg, 2.60 mmol, 2.00 equiv.), $Rh_2(OAc)_4$ (14.4 mg, 0.033 mmol, 2.5 mol%), 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (200 mg, 1.30 mmol, 1.00 equiv.) and CH_2Cl_2 (13 mL). TLC showed reaction completion after 4 h. Purification by column chromatography (3:1 to 3:7 Petrol:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)methanesulfonamide **36c** (163 mg, 0.660 mmol, 51%) as an off-white solid.

m.p. (Et_2O) 121 – 123 °C; **δ_H** (400 MHz, $CDCl_3$) 4.55 – 4.40 (2H, m, C(2)*H*H), 4.36 – 4.19 (2H, m, C(2)H*H*), 3.11 (3H, s, C(3)H_3), 1.91 (6H, app. t, J = 2.6 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 86.8, 64.9, 45.0, 44.7, 4.1; **ν_{max}**/ cm^{-1} (neat) 2980, 2918, 2244, 1307, 1224, 1137, 1069, 967; **m/z HRMS** (ESI$^+$) $[M + Na]^+$ $C_9H_{13}O_3N^{23}Na^{32}S_2^+$ calc. 270.0229, found 270.0230.

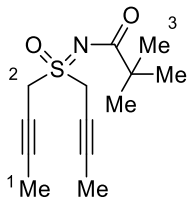
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,2,2-trifluoroacetamide (36d)**



Following a modified literature procedure,[235] Et_3N (91 μL, 0.650 mmol, 1.30 equiv.) was added to a solution of di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (84.5 mg, 0.500 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (11.1 mL) at 0 °C. Trifluoroacetic anhydride (70 μL, 0.500 mmol, 1.00 equiv.) was added dropwise and the resulting mixture was stirred at 0 °C for 20 min before being warmed to room temperature. After stirring for 3 h, the mixture was poured onto ice-water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (5:1 to 3:1 Petrol:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,2,2-trifluoroacetamide **36d** (106 mg, 0.399 mmol, 80%) as an off-white solid.

m.p. (Et_2O) 65 – 67 °C; **δ_F** (377 MHz, $CDCl_3$) –75.96; **δ_H** (400 MHz, $CDCl_3$) 4.56 (2H, dqd, *J* = 16.9, 2.6, 1.0 Hz, C(2)H*H*), 4.36 (2H, dqd, *J* = 16.9, 2.6, 1.0 Hz, C(2)*H*H), 1.92 (6H, app. t, *J* = 2.6 Hz, C(1)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 164.4 (q, *J* = 38.6 Hz), 115.9 (q, *J* = 287.8 Hz), 87.2, 64.1, 43.3, 3.9; **ν_{max}**/ cm^{-1} (neat) 2981, 2246, 1676, 1381, 1271, 1252, 1207, 1177, 1149, 1058, 953, 832, 729; **m/z HRMS** (ESI$^+$) $[M + Na]^+$ $C_{10}H_{10}O_2NF_3{}^{32}S^{23}Na^+$ calc. 288.0277, found 288.0274.

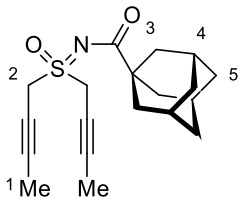
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)pivalamide (36f)**



Following **general procedure R** using di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (152 mg, 0.900 mmol, 1.00 equiv.), Et_3N (188 μL, 1.35 mmol, 1.50 equiv.), pivaloyl chloride (242 μL, 1.98 mmol, 2.20 equiv.) and anhydrous CH_2Cl_2 (4.5 mL). TLC showed reaction completion after 3 h. Purification by column chromatography (4:1 Petrol:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)pivalamide **36f** (195 mg, 0.770 mmol, 86%) as an off-white solid.

m.p. (Et_2O) 63 – 65 °C; **δ_H** (400 MHz, $CDCl_3$) 4.46 (2H, dqd, *J* = 16.6, 2.6, 1.0 Hz, C(2)*H*H), 4.22 (2H, dqd, *J* = 16.7, 2.6, 0.9 Hz, C(2)H*H*), 1.88 (6H, app. t, *J* = 2.6 Hz, C(1)H_3), 1.19 (9H, s, C(3)H_3); **δ_C** (101 MHz, $CDCl_3$) 188.8, 85.4, 65.8, 42.8, 41.5, 27.7, 4.0; **ν_{max}**/ cm^{-1} (neat) 2981, 2243, 1635, 1477, 1461, 1392, 1293, 1262, 1218, 1176, 1150, 1058, 1033, 955; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{13}H_{20}O_2N^{32}S^+$ calc. 254.1209, found 254.1207.

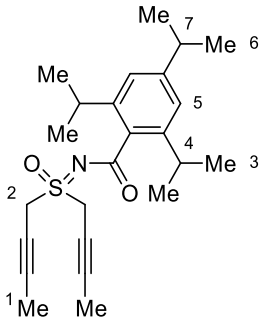
(1s,3s)-*N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)adamantane-1-carboxamide (36g)



Following **general procedure R**, using di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (100 mg, 0.592 mmol, 1.00 equiv.), Et_3N (124 μL, 0.888 mmol, 1.50 equiv.), (3r,5r,7r)-adamantane-1-carbonyl chloride (259 mg, 1.30 mmol, 2.20 equiv.) and anhydrous CH_2Cl_2 (3 mL). TLC showed reaction completion at 5 h. Purification by column chromatography (9:1 to 7:3 Petrol:EtOAc) yielded the title compound (1s,3s)-*N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)adamantane-1-carboxamide **36g** (171 mg, 0.516 mmol, 87%) as an off-white solid.

m.p. (Et_2O) 96 – 98 °C; **δ_H** (400 MHz, $CDCl_3$) 4.45 (2H, app. dq, *J* = 16.7, 2.7 Hz, C(2)*H*H), 4.21 (2H, app. dq, *J* = 16.5, 2.6 Hz, C(2)H*H*), 2.02 – 1.96 (3H, m, C(4)*H*), 1.91 – 1.81 (12H, m, C(1)H_3 and C(3)H_2), 1.76 – 1.62 (6H, m, C(5)H_2); **δ_C** (101 MHz, $CDCl_3$) 187.9, 85.4, 65.9, 43.4, 42.9, 39.4, 36.8, 28.4, 4.0; **ν_{max}**/ cm^{-1} (neat) 2981, 2905, 2851, 2244, 1631, 1271, 1235, 1109, 1089; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{26}O_2N^{32}S^+$ calc. 332.1679, found 332.1677.

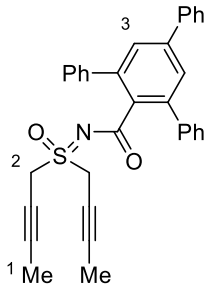
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,4,6-triisopropylbenzamide (36h)**



Following **general procedure R**, using di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (200 mg, 1.18 mmol, 1.00 equiv.), Et_3N (247 μL, 1.77 mmol, 1.50 equiv.), 2,4,6-triisopropylbenzoyl chloride **89** (692 mg, 2.60 mmol, 2.20 equiv.) and anhydrous CH_2Cl_2 (5.9 mL) ***with heating at 50 °C*** for 24 h. Purification by column chromatography (1:1 to 100:0 CH_2Cl_2:Petrol) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,4,6-triisopropylbenzamide **36h** (149 mg, 0.373 mmol, 32%) as an off-white solid.

m.p. (Et_2O) 120 – 122 °C; **δ_H** (400 MHz, $CDCl_3$) 6.98 (2H, s, C(5)*H*), 4.71 – 4.60 (2H, m, C(2)*H*H), 4.39 – 4.28 (2H, m, C(2)H*H*), 3.18 (2H, hept, *J* = 6.9 Hz, C(4)*H*), 2.86 (1H, hept, *J* = 6.9 Hz, C(7)*H*), 1.92 (6H, app. t, *J* = 2.6 Hz, C(1)H_3), 1.27 (12H, d, *J* = 6.8 Hz, C(3)H_3), 1.23 (6H, d, *J* = 6.9 Hz, C(6)H_3); **δ_C** (101 MHz, $CDCl_3$) 180.1, 149.1, 144.0, 135.5, 120.9, 85.8, 65.5, 43.1, 34.6, 31.0, 24.5, 24.2, 4.0; **ν_{max}**/ cm^{-1} (neat) 2961, 2924, 2870, 2244, 1630, 1291, 1251, 1215, 1142, 1107, 1087, 757; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{24}H_{34}O_2N^{32}S^+$ calc. 400.2305, found 400.2300.

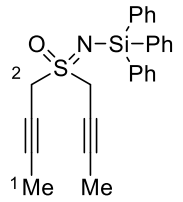
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxamide (36i)**



Following a modified literature procedure,[236] Et_3N (163 μL, 1.17 mmol, 1.50 equiv.) was added to a solution of di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (131.8 mg, 0.780 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (3.9 mL) at 0 °C. The mixture was left to stir for 15 mins at the same temperature, before adding 5'-phenyl-[1,1':3',1''-terphenyl]-2'-carbonyl chloride **92** (345 mg, 0.936 mmol, 1.20 equiv.) and DMAP (3.8 mg, 0.0312 mmol, 4 mol%). After stirring for 24 h at room temperature, only trace product could be observed by TLC, and so the temperature was raised to 50 °C and the mixture was stirred for another 48 h. After this time, a workup according to **general procedure R** was applied. Purification of the crude residue by column chromatography (9:1 to 7:3 Petrol:EtOAc) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxamide **36i** (61.0 mg, 0.122 mmol, 16%) as a white solid.

m.p. (Et_2O) 74 – 76 °C; **δ_H** (400 MHz, $CDCl_3$) 7.67 – 7.60 (6H, m, *Ar*), 7.59 (2H, s, C(3)*H*), 7.48 – 7.34 (9H, m, *Ar*), 4.17 – 4.07 (2H, m, C(2)*H*H), 3.99 – 3.88 (2H, m, C(2)H*H*), 1.86 (6H, app. t, J = 2.6 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 178.1, 141.5, 141.1, 140.5, 140.2, 136.7, 129.2, 129.0, 128.2, 127.9, 127.8, 127.5, 127.4, 85.9, 65.2, 42.8, 4.1; **ν_{max}**/ cm^{-1} (neat) 2244, 1631, 1292, 1270, 1219, 1128, 758, 701; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{33}H_{28}O_2N^{32}S^+$ calc. 502.1835, found 502.1832.

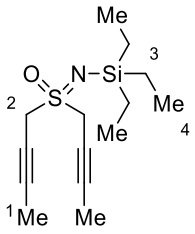
Di(but-2-yn-1-yl)((triphenylsilyl)imino)-λ^6-sulfanone (36j)



Following a modified literature procedure,[236] Et_3N (97 μL, 0.695 mmol, 1.50 equiv.) was added to a solution of di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (78.3 mg, 0.463 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (2.3 mL) at room temperature. The mixture was left to stir for 15 mins, before adding chlorotriphenylsilane (300 mg, 1.02 mmol, 2.20 equiv.) and DMAP (2.3 mg, 0.019 mmol, 4 mol%). After stirring for 2 h at room temperature, the mixture was purified directly by column chromatography (19:1 to 9:1 Petrol:EtOAc) to yield the title compound, di(but-2-yn-1-yl)((triphenylsilyl)imino)-λ^6-sulfanone **36j** (66.4 mg, 0.155 mmol, 34%) as an off-white solid.

m.p. (Et_2O) 58 – 60 °C; **δ_H** (400 MHz, $CDCl_3$) 7.75 – 7.67 (6H, m, *Ar*), 7.46 – 7.30 (9H, m, *Ar*), 3.84 (2H, dqd, *J* = 16.6, 2.6, 1.0 Hz, C(2)*H*H), 3.72 (2H, dqd, *J* = 16.5, 2.6, 1.0 Hz, C(2)H*H*), 1.81 (6H, app. t, *J* = 2.6 Hz, C(1)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 136.4, 135.5, 129.7, 127.8, 84.2, 68.5, 47.1, 3.9; **ν_{max}**/ cm^{-1} (neat) 2981, 2889, 2241, 1382, 1330, 1260, 1175, 1137, 1113, 1059, 966, 955, 744, 707; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{26}H_{26}ON^{32}S_2Si^+$ calc. 428.1499, found 428.1494.

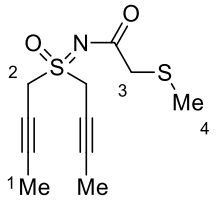
Di(but-2-yn-1-yl)((triethylsilyl)imino)-λ^6-sulfanone (36k)



Following a modified literature procedure,[236] Et_3N (247 μL, 1.78 mmol, 1.50 equiv.) was added to a solution of di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (200 mg, 1.18 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (5.9 mL) at room temperature. The mixture was left to stir for 15 mins, before adding chlorotriethylsilane (315 μL, 2.60 mmol, 2.20 equiv.) and DMAP (5.7 mg, 0.047 mmol, 4 mol%). After stirring for 5 h at room temperature, di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** was still detectable by TLC analysis, so more chlorotriethylsilane (143 μL, 1.18 mmol, 1.00 equiv.) was added and the reaction mixture was stirred for a further 18 h. After this time, starting material remained, so a reflux condenser was attached and the mixture heated to 60 °C and stirred for 4 h. After this time, a workup was performed according a modified literature procedure.[237] Brine (20 mL) was added to the mixture, and the layers were separated. The aqueous phase was then extracted with EtOAc (3 × 20mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (19:1 to 9:1 Petrol:EtOAc) yielded the title compound di(but-2-yn-1-yl)((triethylsilyl)imino)-λ^6-sulfanone **36k** (123 mg, 0.434 mmol, 37%) as a colourless oil. **NOTE: This product is very unstable to hydrolysis, and partial degradation could be observed during chromatographic purification.**

δ_H (400 MHz, C_6D_6) 3.81 – 3.71 (2H, m, C(2)*H*H), 3.72 – 3.61 (2H, m, C(2)H*H*), 1.39 (6H, app. t, *J* = 2.6 Hz, C(1)H_3), 1.16 (9H, t, *J* = 7.9 Hz, C(4)H_3), 0.77 (6H, q, *J* = 7.8 Hz, C(3)H_2); **δ_C** (101 MHz, C_6D_6) 83.4, 69.6, 48.0, 7.6, 7.2, 3.3; **ν_{max}**/ cm^{-1} (neat) 2954, 2913, 2876, 2242, 1224, 1097, 1013, 1007, 847, 736; an accurate mass could not be obtained for this compound.

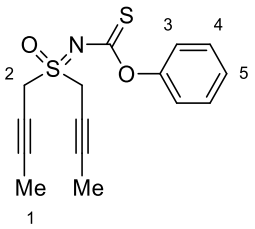
***N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2-(methylthio)acetamide (36l)**



Following **general procedure R**, using di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (120 mg, 0.710 mmol, 1.00 equiv.), Et_3N (148 μL, 1.07 mmol, 1.50 equiv.), 2-(methylthio)acetyl chloride **88** (157 μL, 1.56 mmol, 2.20 equiv.) and anhydrous CH_2Cl_2 (3.6 mL). TLC showed reaction completion after 1.5 h. Purification by column chromatography (1:39 to 1:19 EtOAc:CH_2Cl_2) yielded the title compound *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2-(methylthio)acetamide **36l** (138 mg, 0.537 mmol, 76%) as a pale-yellow solid.

m.p. (Et_2O) 61 – 63 °C; **δ_H** (400 MHz, $CDCl_3$) 4.49 (2H, dqd, *J* = 16.7, 2.6, 1.0 Hz, C(2)*H*H), 4.27 (2H, dqd, *J* = 16.7, 2.6, 0.9 Hz, C(2)H*H*), 3.22 (2H, s, C(3)H_2), 2.19 (3H, s, C(4)H_3), 1.88 (6H, app. t, *J* = 2.6 Hz, C(1)H_3); **δ_C** (101 MHz, $CDCl_3$) 178.8, 86.0, 65.3, 43.0, 40.6, 16.1, 4.0; **ν_{max}**/ cm^{-1} (neat) 2974, 2243, 1637, 1292, 1214, 1131, 1024, 986, 895; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{11}H_{15}O_2N^{32}S_2{}^{23}Na^+$ calc. 280.0436, found 280.0435.

***O*-phenyl (di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)carbamothioate (36m)**

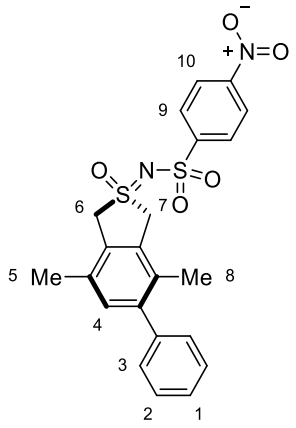


Following a modified literature procedure,[238] di(but-2-yn-1-yl)(imino)-λ^6-sulfanone **36e** (250 mg, 1.48 mmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (7.4 mL) before adding Et_3N (0.31 mL, 2.22 mmol, 1.50 equiv.) with stirring. The mixture was then cooled to 0 °C and *O*-phenyl carbonochloridothioate (0.45 mL, 3.25 mmol, 2.2 equiv.) was added dropwise, followed by the addition of DMAP (18.1 mg, 0.148 mmol, 10 mol%). The mixture was then warmed to room temperature and stirred for 24 h. After this time, H_2O (20 mL) was added and the layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude residue by column chromatography (19:1 to 6:4 Petrol:EtOAc) yielded the title compound **36m** (204 mg, 0.668 mmol, 45%) as a pale-orange solid.

m.p. (Et_2O) 104 – 106 °C; **δ_H** (400 MHz, $CDCl_3$) 7.43 – 7.36 (2H, m, *Ar*), 7.29 – 7.20 (1H, m, *Ar*), 7.15 – 7.07 (2H, m, *Ar*), 4.86 (2H, dqd, *J* = 16.8, 2.6, 1.0 Hz, C(2)*H*H), 4.47 (2H, dqd, *J* = 16.8, 2.6, 1.1 Hz, C(2)H*H*), 1.94 (6H, app. t, *J* = 2.6 Hz, C(1)*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 196.8, 153.9, 129.3, 126.2, 122.5, 86.6, 64.9, 42.4, 4.1; **ν_{max}**/ cm^{-1} (neat) 2981, 2907, 2243, 1326, 1264, 1202, 1137, 1032, 1016; **m/z HRMS** (ESI$^+$) $[M + H]^+$ $C_{15}H_{16}O_2N^{32}S_2^+$ calc. 306.0617, found 306.0618.

6.4.3 Final Compounds from the [2+2+2] Cycloaddition

_N_-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)-4-nitrobenzenesulfonamide (38a)

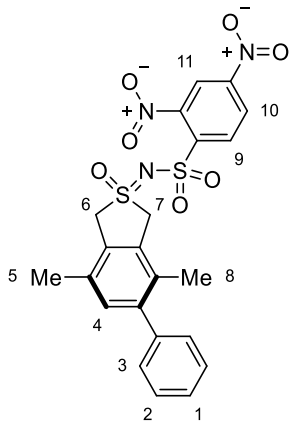


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-4-nitrobenzenesulfonamide **36a** (53.1 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (16.5 μL, 0.150 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 5 mol%), (*S*)-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (4:1 to 3:1 Pentane:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)-4-nitrobenzenesulfonamide **38a** (41.8 mg, 0.092 mmol, 61%) as a tanned powdered solid.

m.p. (Et_2O) 172 – 174 °C; **δ_H** (400 MHz, Acetonitrile-d_3) 8.35 – 8.27 (2H, m, *Ar*), 8.13 – 8.05 (2H, m, *Ar*), 7.49 – 7.34 (3H, m, *Ar*), 7.33 – 7.24 (2H, m, *Ar*), 7.12 (1H, s, C(4)*H*), 5.03 (2H, app. d, *J* = 16.3 Hz, C(6 and 7)*H*H), 4.78 (2H, app. d, *J* = 16.3 Hz, C(6 and 7)H*H*), 2.26 (3H, s, C(5)H_3), 2.09 (3H, s, C(8)H_3); **δ_C** (101 MHz, Acetonitrile-d_3) 151.0, 149.9, 143.9, 141.6, 133.6, 132.6, 131.4, 131.0, 130.1, 129.7, 129.3, 128.7, 128.4, 125.3, 59.6, 59.3, 19.3, 17.6; **ν_{max}**/ cm^{-1} (neat) 2981, 2889, 1529, 1473, 1462, 1383, 1350, 1252, 1154, 1088, 1072, 966, 955; **m/z HRMS**

(ESI$^+$) [M + Na]$^+$ $C_{22}H_{20}O_5N_2{}^{32}S_2{}^{23}Na^+$ calc. 479.0706, found 479.0708; ***er*** was determined by HPLC using a Chiralpak IC column (*n*-hexane:EtOAc, 80:20, λ = 275 nm); $\mathbf{T}_{minor}$ = 73.54 min, $\mathbf{T}_{major}$ = 79.73 min (37.5:62.5 *er*); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +1.84 (*c* = 0.5, MeCN).

_N_-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)-2,4-dinitrobenzenesulfonamide (38b)

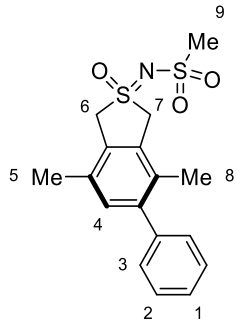


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,4-dinitrobenzenesulfonamide **36b** (59.9 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (16.5 μL, 0.150 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 5 mol%), *rac*-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (3:1 to 7:3 Petrol:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)-2,4-dinitrobenzenesulfonamide **38b** (27.3 mg, 0.054 mmol, 36%) as an off-white solid.

m.p. (Et_2O) 166 – 168 °C; $\boldsymbol{\delta_H}$ (400 MHz, Acetonitrile-d_3) 8.55 (1H, d, *J* = 2.2 Hz, *Ar*), 8.48 (1H, dd, *J* = 8.7, 2.3 Hz, *Ar*), 8.35 (1H, d, *J* = 8.7 Hz, *Ar*), 7.50 – 7.34 (3H, m, *Ar*), 7.33 – 7.26 (2H, m, *Ar*), 7.13 (1H, s, C(4)*H*), 5.05 (1H, d, *J* = 17.0 Hz, C(6 or 7)*H*H), 5.04 (1H, d, *J* = 16.9 Hz, C(6 or 7)*H*H), 4.83 (2H, app. d, *J* = 16.4 Hz,

C(6 and 7)H*H*), 2.26 (3H, s, C(5)*H*$_3$), 2.10 (3H, s, C(8)*H*$_3$); **δC** (151 MHz, Acetonitrile-*d*$_3$) 151.0, 148.6, 144.0, 141.5, 141.3, 133.7, 132.8, 132.4, 131.1, 131.0, 130.1, 129.3, 128.4, 127.7, 120.7, 59.6, 59.2, 19.3, 17.7 (one aromatic carbon environment not observed due to signal overlap); **ν$_{max}$**/ cm^{-1} (neat) 3102, 2981, 1552, 1539, 1351, 1333, 1254, 1212, 1158, 1106, 1073, 1036, 781, 744, 706; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{27}H_{14}O_7N_3{}^{32}S^+$ calc. 524.0547, found 524.0558.

***N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)methanesulfonamide (38c)**

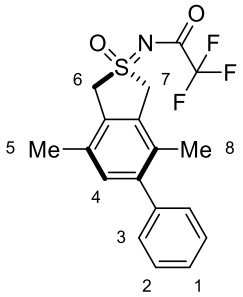


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)methanesulfonamide **36c** (37.0 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (16.5 μL, 0.150 mmol, 1.00 equiv.), Rh(nbd)$_2$BF$_4$ (2.8 mg, 0.0075 mmol, 5 mol%), *rac*-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (3:1 Petrol:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)methanesulfonamide **38c** (33.4 mg, 0.096 mmol, 64%) as an off-white solid.

m.p. (Et$_2$O) 92 – 94 °C; **δH** (400 MHz, Acetonitrile-*d*$_3$) 7.48 – 7.42 (2H, m, *Ar*), 7.42 – 7.35 (1H, m, *Ar*), 7.35 – 7.29 (2H, m, *Ar*), 7.15 (1H, s, C(4)*H*), 4.97 (2H, app. d, *J* = 16.3 Hz, C(6 and 7)*H*H), 4.74 (2H, app. d, *J* = 16.1 Hz, C(6 and 7)H*H*), 3.08

(1H, s, C(9)*H*$_3$), 2.29 (3H, s, C(5)*H*$_3$), 2.13 (3H, s, C(8)*H*$_3$); **δC** (101 MHz, Acetonitrile-*d*$_3$) 143.8, 141.7, 133.6, 132.5, 131.8, 130.9, 130.7, 130.2, 129.3, 128.3, 59.6, 59.2, 45.4, 19.3, 17.6; **ν$_{max}$**/ cm^{-1} (neat) 2952, 2854, 1308, 1140, 1074, 1042, 763; **m/z HRMS** (ESI$^+$) [M + H]$^+$ $C_{17}H_{20}O_3N^{32}S_2^+$ calc. 350.0879, found 350.0879.

_N_-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)-2,2,2-trifluoroacetamide (38d)

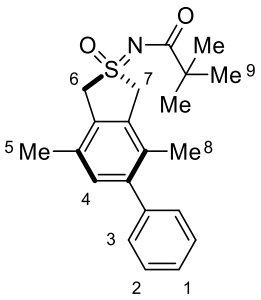


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)-2,2,2-trifluoroacetamide **36d** (39.8 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (16.5 μL, 0.150 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 5 mol%), (*S*)-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (6:1 Petrol:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)-2,2,2-trifluoroacetamide **38d** (23.7 mg, 0.065 mmol, 43%) as an off-white solid.

m.p. (Et_2O) 154 – 156 °C; **δF** (377 MHz, Acetonitrile-*d*$_3$) –76.41; **δH** (400 MHz, Acetonitrile-*d*$_3$) 7.49 – 7.43 (2H, m, *Ar*), 7.42 – 7.37 (1H, m, *Ar*), 7.34 – 7.29 (2H, m, *Ar*), 7.17 (1H, s, C(4)*H*), 5.02 (2H, app. d, *J* = 16.7 Hz, C(6 and 7)*H*H), 4.86 (2H, app. d, *J* = 16.5 Hz, C(6 and 7)H*H*), 2.29 (3H, s, C(5)*H*$_3$), 2.13 (3H, s, C(8)*H*$_3$); **δC** (151 MHz, Acetonitrile-*d*$_3$) 165.3 (q, *J* = 37.6 Hz), 144.0, 141.6, 133.7, 132.7, 131.3, 131.1, 130.2, 129.6, 129.3, 128.4, 117.2 (q, *J* = 287.1 Hz), 58.6, 58.1, 19.3, 17.6;

ν_{max}/ cm^{-1} (neat) 2925, 1672, 1474, 1379, 1258, 1205, 1173, 934, 847, 778, 763, 705; **m/z HRMS** (ESI^+) $[M + Na]^+$ $C_{18}H_{16}O_2NF_3{}^{32}S^{23}Na^+$ calc. 390.0746, found 390.0745; ***er*** was determined by HPLC using a Chiralpak IC column (*n*-hexane:EtOAc, 90:10, λ = 250 nm); $\mathbf{T}_{minor}$ = 11.47 min, $\mathbf{T}_{major}$ = 13.21 min (39.5:60.5 *er*); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +8.84 (*c* = 0.25, MeCN).

_N_-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)pivalamide (38f)

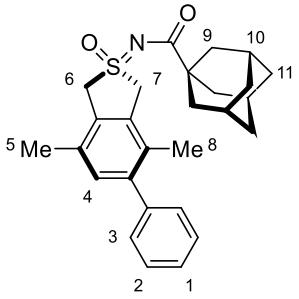


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)- λ^6-sulfaneylidene)pivalamide **36f** (38.0 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (16.5 μL, 0.150 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 5 mol%), (*S*)-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (6:1 Petrol:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)pivalamide **38f** (32.1 mg, 0.090 mmol, 60%) as an off-white solid.

m.p. (Et_2O) 94 – 96 °C; $\boldsymbol{\delta}_{\mathbf{H}}$ (400 MHz, Acetonitrile-d_3) 7.49 – 7.42 (2H, m, *Ar*), 7.42 – 7.36 (1H, m, *Ar*), 7.34 – 7.28 (2H, m, *Ar*), 7.12 (1H, s, C(4)*H*), 4.80 (2H, app. d, *J* = 16.5 Hz, C(6 and 7)*H*H), 4.64 (1H, d, *J* = 16.5 Hz, C(6 or 7)H*H*), 4.63 (1H, d, *J* = 16.4 Hz, C(6 or 7)H*H*), 2.28 (3H, s, C(5)H_3), 2.12 (3H, s, C(8)H_3), 1.16 (9H, s, C(9)H_3); $\boldsymbol{\delta}_{\mathbf{C}}$ (101 MHz, Acetonitrile-d_3) 189.5, 143.4, 141.9, 133.5, 132.3, 132.2, 130.8, 130.7, 130.2, 129.3, 128.2, 58.7, 58.2, 41.5, 28.0, 19.3, 17.6; ν_{max}/ cm^{-1} (neat)

2971, 1625, 1476, 1392, 1295, 1240, 1208, 1173, 861, 752, 704; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{21}H_{26}O_2N^{32}S^+$ calc. 356.1679, found 356.1681; ***er*** was determined by HPLC using a Chiralpak IC column (*n*-hexane:EtOAc, 80:20, λ = 250 nm); $\mathbf{T}_{minor}$ = 8.86 min, $\mathbf{T}_{major}$ = 9.78 min (38:62 *er*); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +10.84 (*c* = 0.25, MeCN).

(1*S*,3*S*)-*N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)adamantane-1-carboxamide (38g)

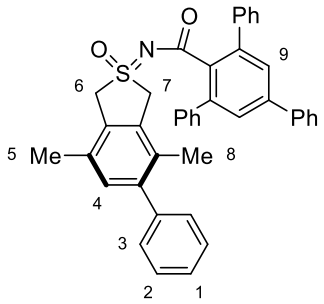


Following **general procedure S**, using (1*S*,3*S*)-*N*-(di(but-2-yn-1-yl)(oxo)-λ^6-sulfaneylidene)adamantane-1-carboxamide **36g** (49.7 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (16.5 μL, 0.150 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 5 mol%), (*S*)-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (19:1 to 9:1 Petrol:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)pivalamide **38g** (33.0 mg, 0.076 mmol, 51%) as an off-white solid.

m.p. (Et_2O) 113 – 115 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.45 – 7.39 (2H, m, *Ar*), 7.39 – 7.33 (1H, m, *Ar*), 7.26 – 7.23 (2H, m, *Ar*), 7.10 (1H, s, C(4)*H*), 4.81 (2H, app. d, *J* = 16.4 Hz, C(6 and 7)*H*H), 4.59 (2H, app. d, *J* = 16.4 Hz, C(6 and 7)H*H*), 2.27 (3H, s, C(5)H_3), 2.13 (3H, s, C(8)H_3), 2.05 – 199 (3H, m, C(10)*H*), 1.92 (6H, d, *J* = 3.0 Hz, C(9)H_2), 1.78 – 1.65 (6H, m, C(11)H_2); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 189.0, 143.1, 140.8, 132.2, 131.7, 130.9, 130.0, 129.2, 129.2, 128.4, 127.4, 58.5, 58.0, 43.1, 39.5,

36.8, 28.4, 19.5, 17.6; ν_{max}/ cm^{-1} (neat) 2905, 2850, 1620, 1272, 1235, 1108, 1089, 756, 704; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{27}H_{32}O_2N^{32}S^+$ calc. 434.2148, found 434.2147; ***er*** was determined by HPLC using a Chiralpak IC column (*n*-hexane:*i*-propanol, 70:30, λ = 250 nm); T_{minor} = 24.14 min, T_{major} = 26.84 min (35.5:64.5 *er*); $[\alpha]_D^{25}$ +10.0 (*c* = 0.5, $CHCl_3$).

_N_-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ⁴-benzo[c]thiophen-2-ylidene)-5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxamide (38i)

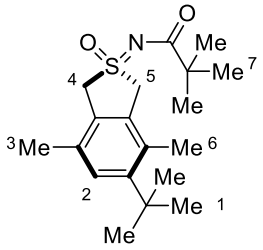


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)-λ⁶-sulfaneylidene)-5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxamide **36i** (37.6 mg, 0.075 mmol, 1.00 equiv.), phenylacetylene (8.2 μL, 0.075 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (1.4 mg, 0.0038 mmol, 5 mol%), *rac*-BINAP (2.4 mg, 0.0038 mmol, 5 mol%) and DCE (0.75 mL). Purification by column chromatography (4:1 Petrol:EtOAc) yielded the title compound *N*-(4,7-dimethyl-2-oxido-5-phenyl-1,3-dihydro-2λ⁴-benzo[c]thiophen-2-ylidene)-5'-phenyl-[1,1':3',1''-terphenyl]-2'-carboxamide **38i** (6.7 mg, 0.011 mmol, 15%) as an off-white solid.

m.p. (Et_2O) 97 – 99 °C; δ_H (400 MHz, $CDCl_3$) 7.68 – 7.62 (2H, m, *Ar*), 7.59 (2H, s, *Ar*), 7.59 – 7.53 (4H, m, *Ar*), 7.49 – 7.40 (4H, m, *Ar*), 7.41 – 7.35 (2H, m, *Ar*), 7.35 – 7.22 (8H, m, *Ar*), 7.09 (1H, s, C(4)*H*), 4.44 (1H, d, *J* = 16.5 Hz, C(6 or 7)*H*H), 4.43 (1H, d, *J* = 16.5 Hz, C(6 or 7)*H*H), 4.27 (2H, app. d, *J* = 16.4 Hz, C(6 and 7)H*H*), 2.19 (3H, s, C(5)*H₃*), 2.04 (3H, s, C(8)*H₃*); δ_C (151 MHz, $CDCl_3$) 178.6,

143.0, 141.5, 141.2, 140.8, 140.5, 140.3, 136.6, 132.0, 131.7, 130.5, 129.7, 129.3, 129.1, 129.0, 128.7, 128.5, 128.1, 127.9, 127.8, 127.5, 127.4, 127.4, 57.5, 57.0, 19.4, 17.5; ν_{max}/ cm^{-1} (neat) 2971, 2920, 1621, 1296, 1244, 1137, 760, 700; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{41}H_{34}O_2N^{32}S^+$ calc. 604.2305, found 604.2302.

***N*-(5-(*tert*-butyl)-4,7-dimethyl-2-oxido-1,3-dihydro-2λ^4-benzo[c]thiophen-2-ylidene)pivalamide (38n)**

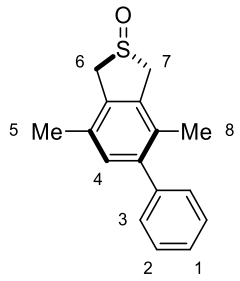


Following **general procedure S**, using *N*-(di(but-2-yn-1-yl)(oxo)- λ^6-sulfaneylidene)pivalamide **36f** (38.0 mg, 0.150 mmol, 1.00 equiv.), phenylacetylene (18.5 μL, 0.150 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (2.8 mg, 0.0075 mmol, 5 mol%), (*S*)-BINAP (4.7 mg, 0.0075 mmol, 5 mol%) and DCE (1.5 mL). Purification by column chromatography (9:1 to 6:1 Petrol:EtOAc) yielded the title compound **38n** (16.0 mg, 0.048 mmol, 32%) as an off-white solid.

m.p. (Et_2O) 146 – 148 °C; δ_H (400 MHz, $CDCl_3$) 7.22 (1H, s, C(2)*H*), 4.74 (1H, d, *J* = 16.5 Hz, C(4 or 5)*H*H), 4.73 (1H, d, *J* = 16.4 Hz, C(4 or 5)*H*H), 4.55 (1H, d, *J* = 16.5 Hz, C(4 or 5)H*H*), 4.54 (1H, d, *J* = 16.4 Hz, C(4 or 5)H*H*), 2.38 (3H, s, C(6)H_3), 2.24 (3H, s, C(3)H_3), 1.41 (9H, s, C(7)H_3), 1.21 (9H, s, C(1)H_3); δ_C (101 MHz, $CDCl_3$) 189.9, 149.1, 132.2, 131.8, 131.0, 128.1, 127.6, 59.0, 57.9, 41.1, 35.8, 31.2, 27.8, 19.8, 19.7; ν_{max}/ cm^{-1} (neat) 2966, 2925, 2870, 1626, 1477, 1295, 1244, 1208, 1177, 864, 758; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{19}H_{30}O_2N^{32}S^+$ calc. 336.1992, found 336.1990; ***er*** was determined by HPLC using a Chiralpak IC column (*n*-

hexane:*i*-propanol, 95:5, λ = 225 nm); $\mathbf{T}_{minor}$ = 73.08 min, $\mathbf{T}_{major}$ = 78.45 min (44.5:55.5 *er*); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +1.25 (*c* = 0.25, $CHCl_3$).

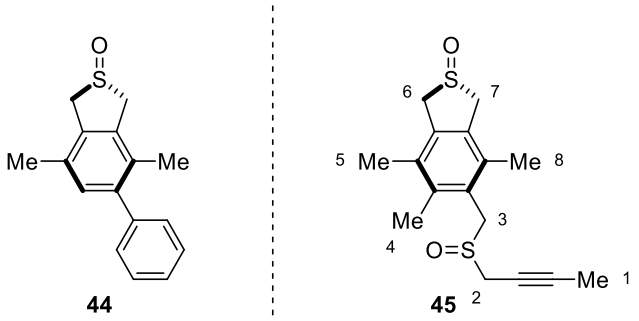
4,7-Dimethyl-5-phenyl-1,3-dihydrobenzo[c]thiophene 2-oxide (44)



Following **general procedure S**, using 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (46.2 mg, 0.300 mmol, 1.00 equiv.), phenylacetylene (33 μL, 0.300 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 5 mol%), (*S*)-BINAP (9.3 mg, 0.015 mmol, 5 mol%) and DCE (3 mL). Purification by column chromatography (50:50:0 to 0:95:5 Hexane:EtOAc:MeOH) yielded the title compound 4,7-dimethyl-5-phenyl-1,3-dihydrobenzo[c]thiophene 2-oxide **44** (33.4 mg, 0.130 mmol, 43%) as a tanned powdered solid.

m.p. (Et_2O) 88 – 90 °C; $\boldsymbol{\delta_H}$ (400 MHz, Acetonitrile-d_3) 7.47 – 7.41 (2H, m, *Ar*), 7.40 – 7.34 (1H, m, *Ar*), 7.34 – 7.30 (2H, m, *Ar*), 7.05 (1H, s, C(4)*H*), 4.30 (1H, d, *J* = 16.8 Hz, C(6 or 7)*H*H), 4.29 (1H, d, *J* = 16.8 Hz, C(6 or 7)*H*H), 4.04 (1H, d, *J* = 16.8 Hz, C(6 or 7)H*H*), 4.03 (1H, d, *J* = 16.8 Hz, C(6 or 7)H*H*), 2.31 (3H, s, C(5)H_3), 2.16 (3H, s, C(8)H_3); $\boldsymbol{\delta_C}$ (101 MHz, Acetonitrile-d_3) 143.0, 142.4, 137.2, 135.3, 133.9, 131.8, 131.3, 130.3, 129.2, 128.0, 60.0, 59.3, 19.4, 17.6; $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 2920, 1471, 1440, 1395, 1130, 1059, 1030, 875, 771, 705; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{16}H_{17}O^{32}S^+$ calc. 257.0995, found 257.0995; ***er*** was determined by HPLC using a Chiralpak OJ-H column (*n*-hexane:*i*-PrOH, 95:5, λ = 225 nm); $\mathbf{T}_{major}$ = 38.64 min, $\mathbf{T}_{minor}$ = 50.33 min (67:33 *er*); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +9.32 (*c* = 0.25, MeCN).

4,7-Dimethyl-5-phenyl-1,3-dihydrobenzo[c]thiophene 2-oxide (44) and 5-((but-2-yn-1-ylsulfinyl)methyl)-4,6,7-trimethyl-1,3-dihydrobenzo[c]thiophene 2-oxide (45)



Following **general procedure S**, using 1-(but-2-yn-1-ylsulfinyl)but-2-yne **35** (46.2 mg, 0.300 mmol, 1.00 equiv.), phenylacetylene (33 μL, 0.300 mmol, 1.00 equiv.), $Rh(nbd)_2BF_4$ (5.6 mg, 0.015 mmol, 5 mol%), (*R*)-SEGPHOS (9.2 mg, 0.015 mmol, 5 mol%) and DCE (3 mL). Purification by column chromatography (7:3 EtOAc:MeOH) yielded title compound 4,7-dimethyl-5-phenyl-1,3-dihydrobenzo[c]thiophene 2-oxide **44** (9.6 mg, 0.037 mmol, 12%, 31:69 *er*) as a tanned solid, and title compound 5-((but-2-yn-1-ylsulfinyl)methyl)-4,6,7-trimethyl-1,3-dihydrobenzo[c]thiophene 2-oxide **45** as an inseparable mixture of diastereoisomers (15.7 mg, 0.051 mmol, 17%), and as a tanned powdered solid.

Dimer side-product (45): **δ_H** (400 MHz, Acetonitrile-d_3) 4.46 (1H, dd, *J* = 13.6, 4.4 Hz, C(3)*H*H), 4.29 (2H, app. d, J = 16.7 Hz, C(6 and 7)HH), 4.18 (1H, dd, *J* = 13.6, 1.9 Hz, C(3)H*H*), 4.09 – 3.98 (2H, m, C(6 and 7)H*H*), 3.77 (1H, dq, *J* = 15.9, 2.6 Hz, C(2)*H*H), 3.63 (1H, app. dqd, *J* = 15.9, 2.6, 0.8 Hz, C(2)H*H*), 2.35 – 2.29 (6H, m, C(5 and 8)H_3), 2.25 (3H, s, C(4)H_3), 1.90 (3H, app. t, *J* = 2.6 Hz, C(1)H_3); **δ_C** (101 MHz, Acetonitrile-d_3) 138.3, 138.1, 136.4, 136.3, 134.6, 134.5, 134.3, 134.3, 133.3, 130.2, 130.2, 85.0, 69.7, 60.3, 60.3, 60.2, 60.1, 52.9, 44.1, 44.0, 18.1, 18.0, 17.6, 17.6, 17.1, 17.0, 3.7 (one aromatic carbon environment not observed due to

signal overlap or high sample dilution); $\boldsymbol{\nu_{max}}$/ cm^{-1} (neat) 2919, 1440, 1387, 1050, 1031, 755; **m/z HRMS** (ESI^+) $[M + H]^+$ $C_{16}H_{21}O_2{}^{32}S_2{}^+$ calc. 309.0977, found 309.0978; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +54.3 (*c* = 0.25, MeCN).

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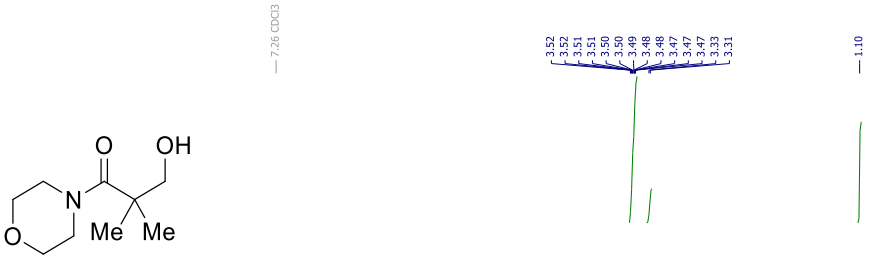
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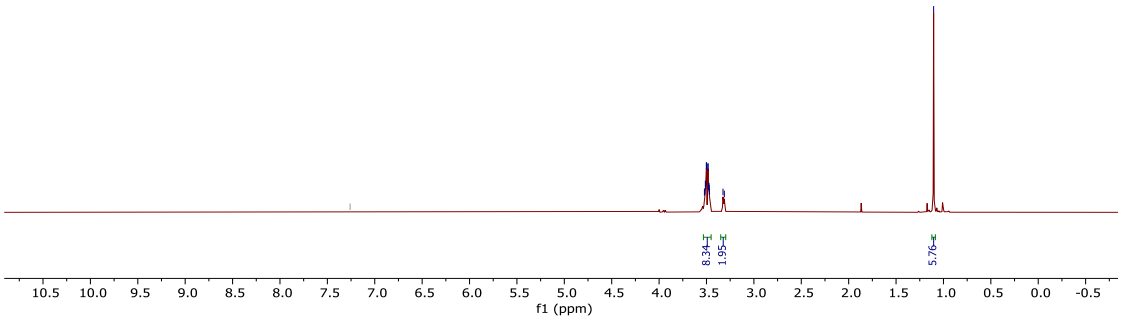
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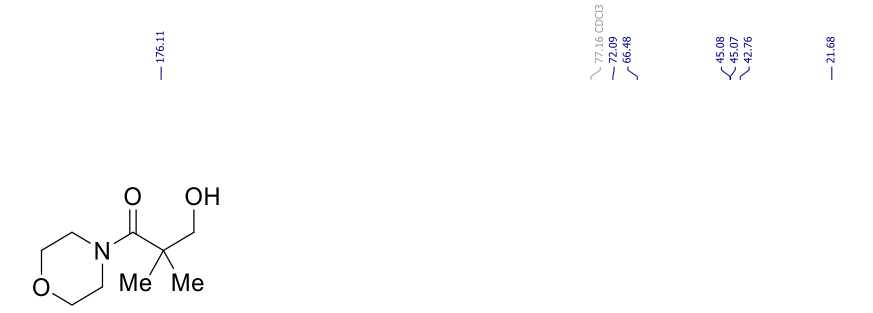
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NMR Spectra of Novel and Final Compounds

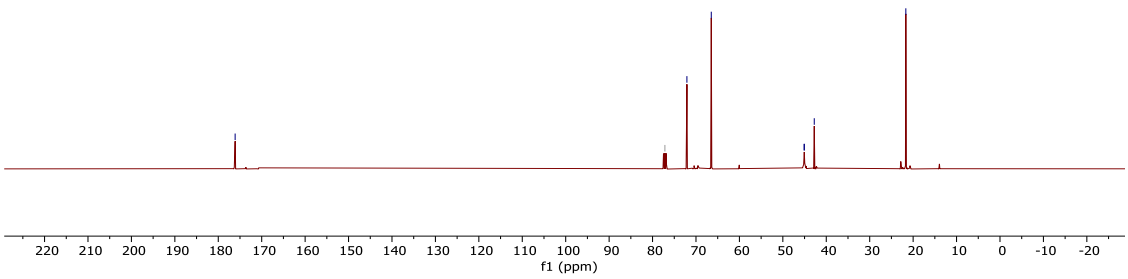


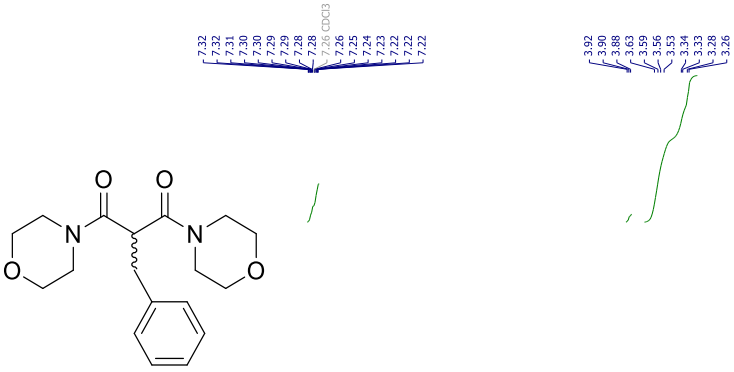
48 ^{1}H NMR ($CDCl_3$ 400 MHz)



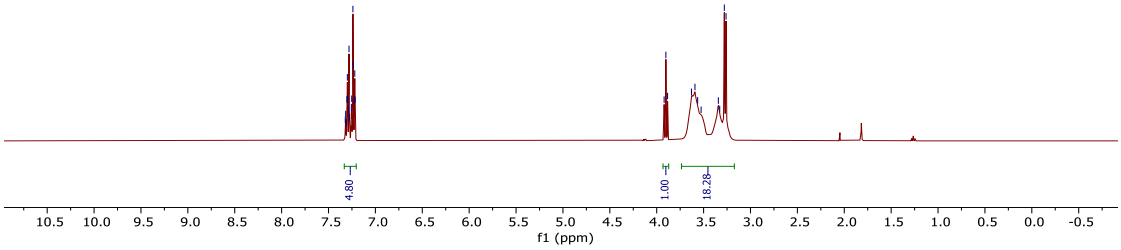


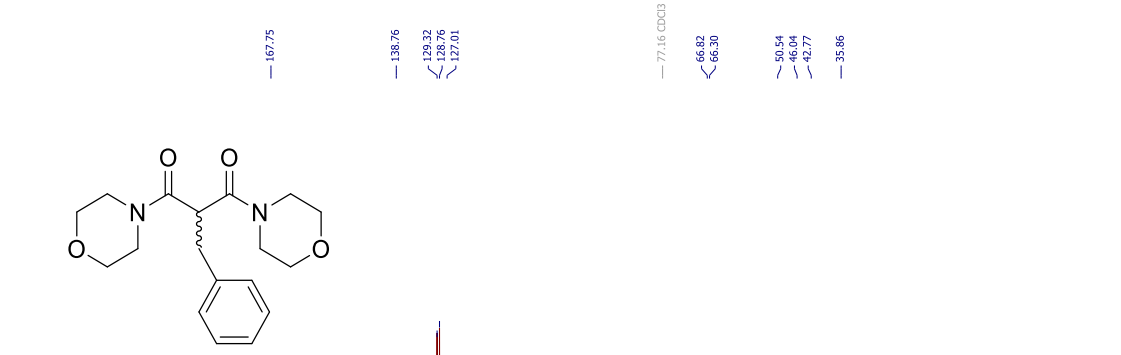
48 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



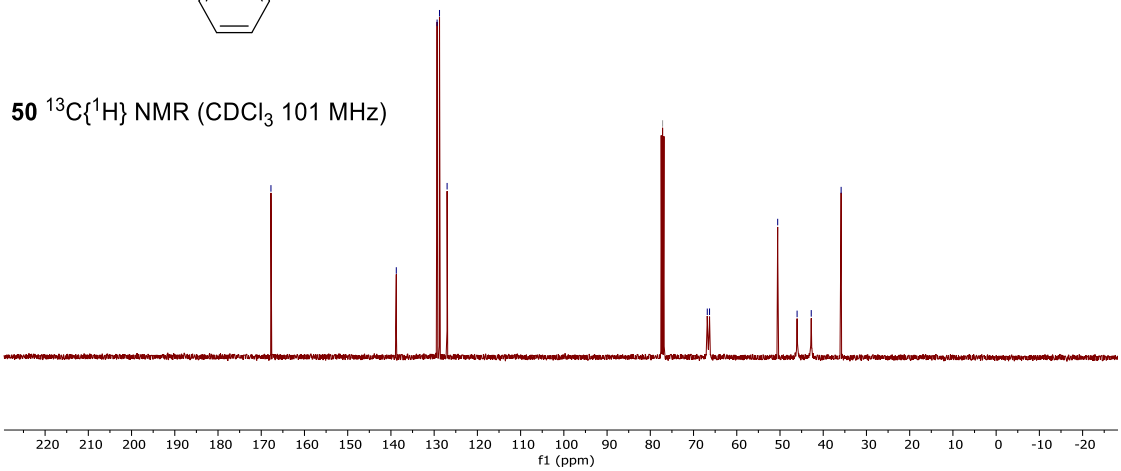


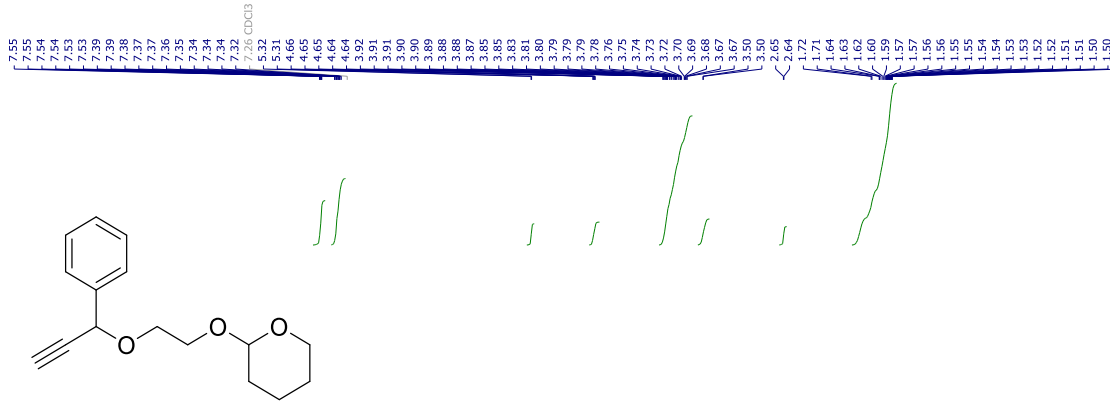
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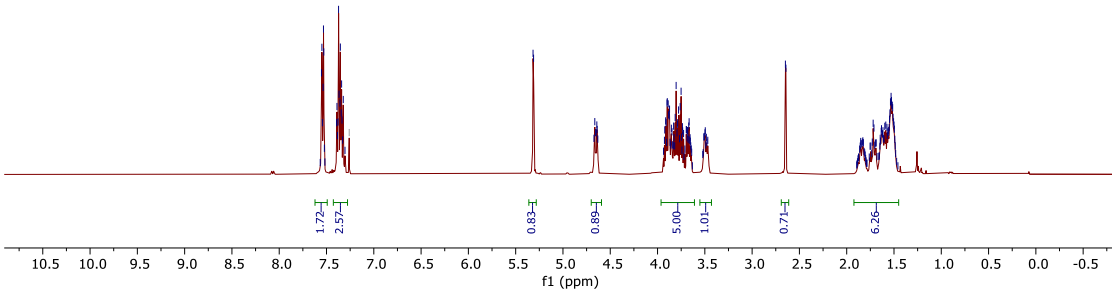


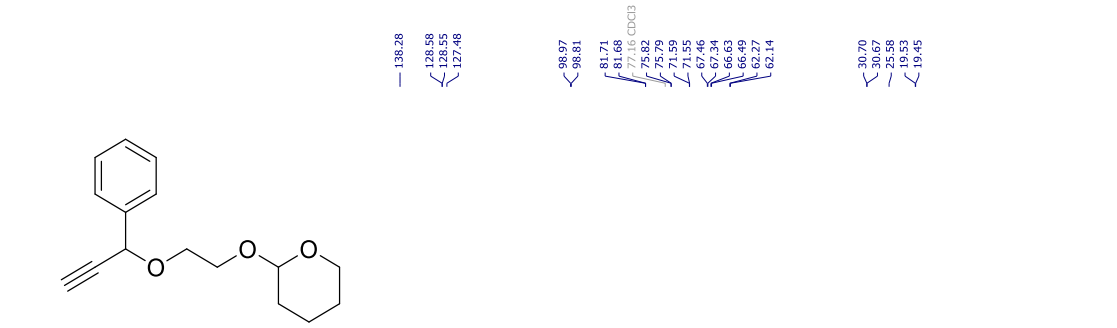
50 ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



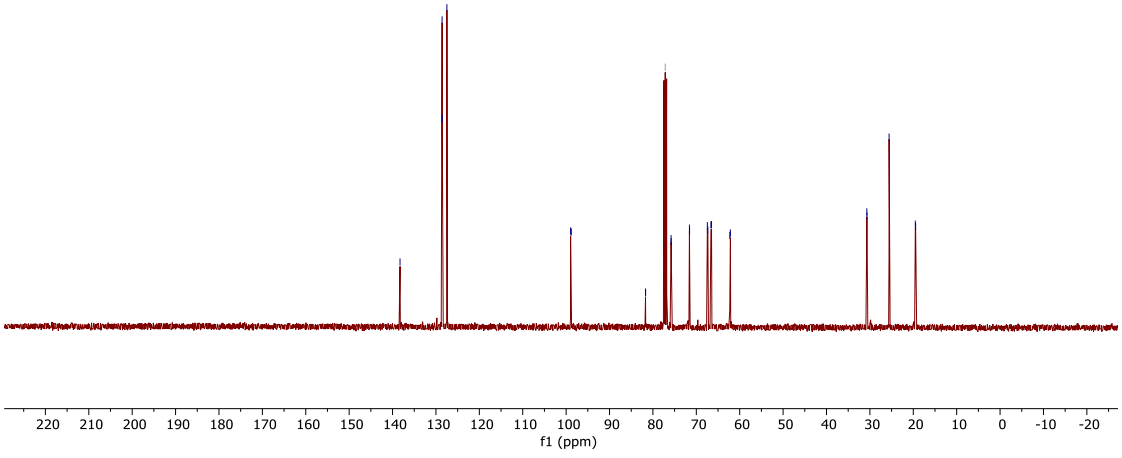


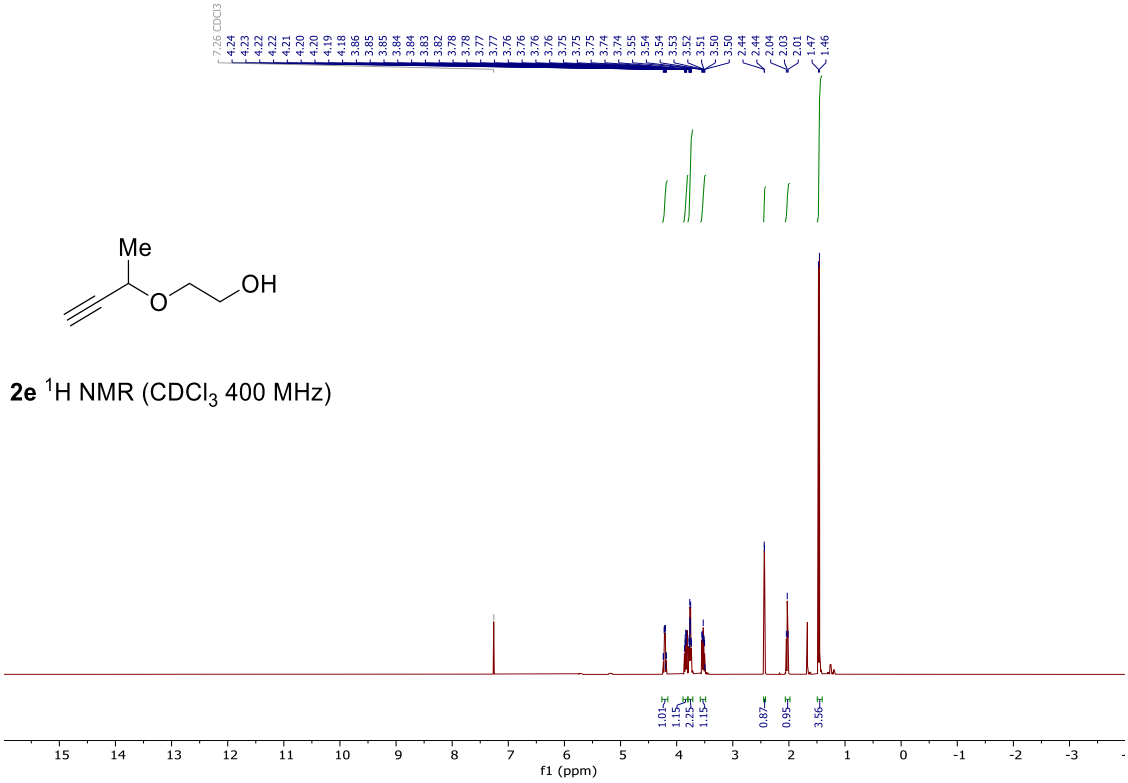
2d ^{1}H NMR ($CDCl_3$ 400 MHz)



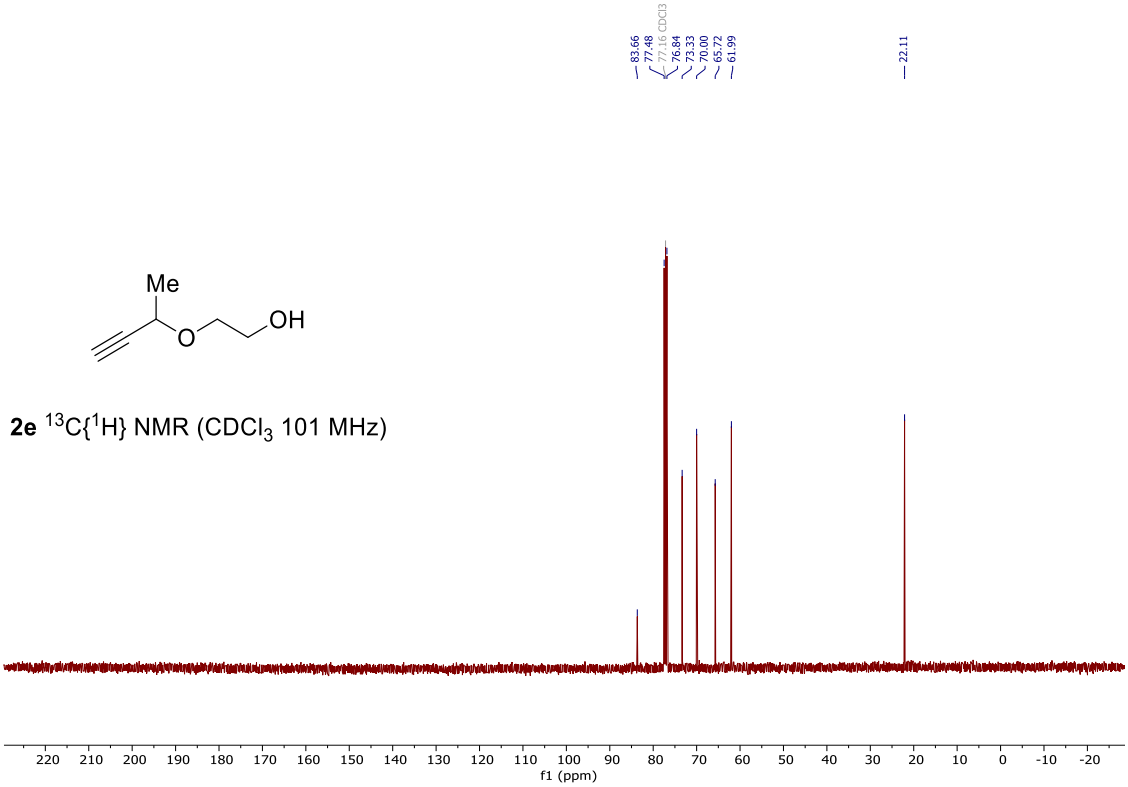


2d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

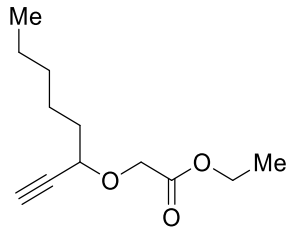


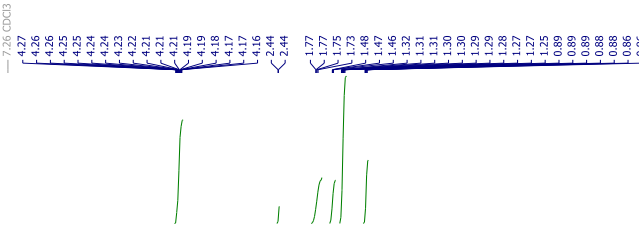


2e ^{1}H NMR ($CDCl_3$ 400 MHz)

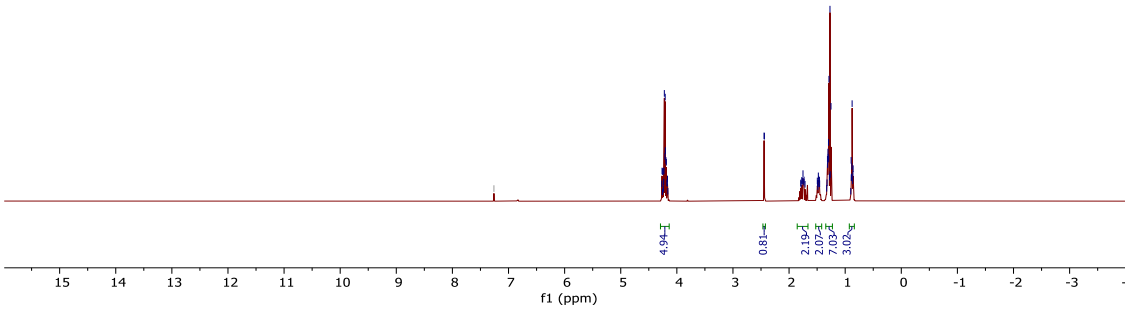


2e $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

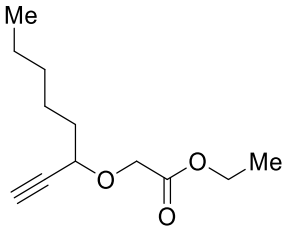




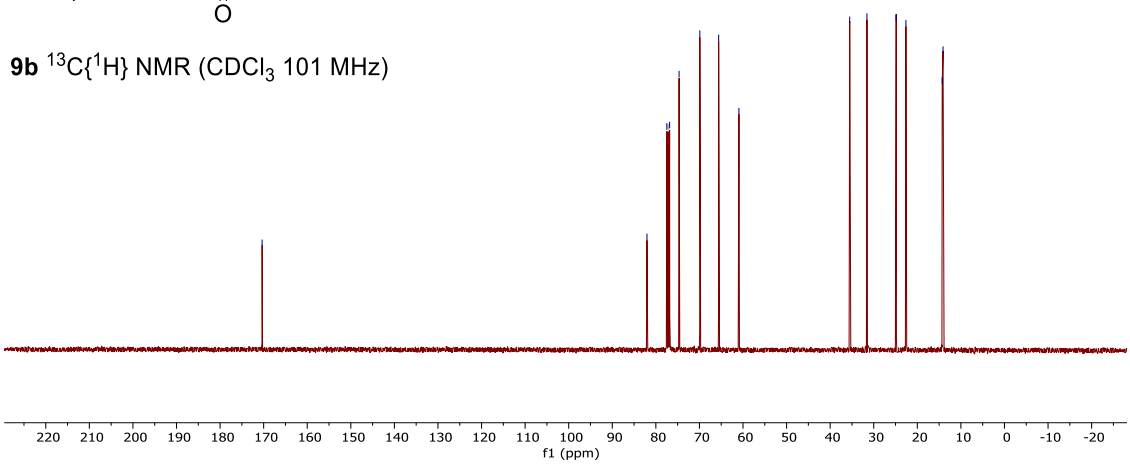
9b ^{1}H NMR ($CDCl_3$ 400 MHz)

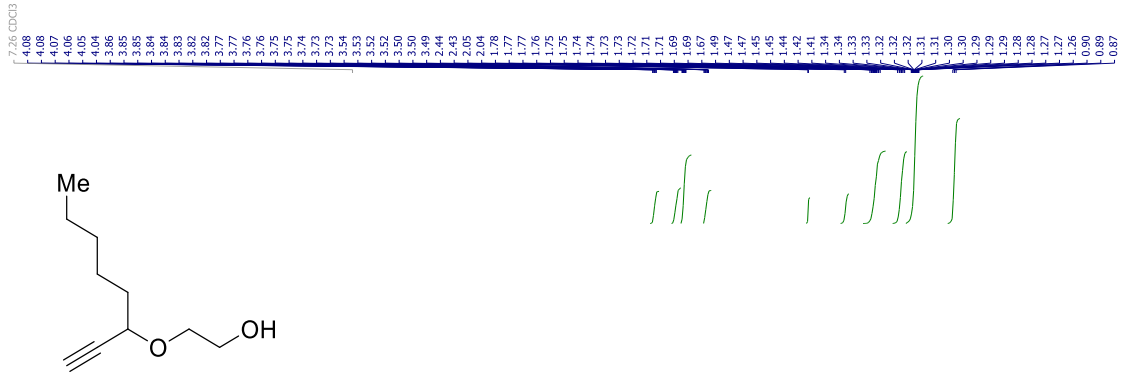




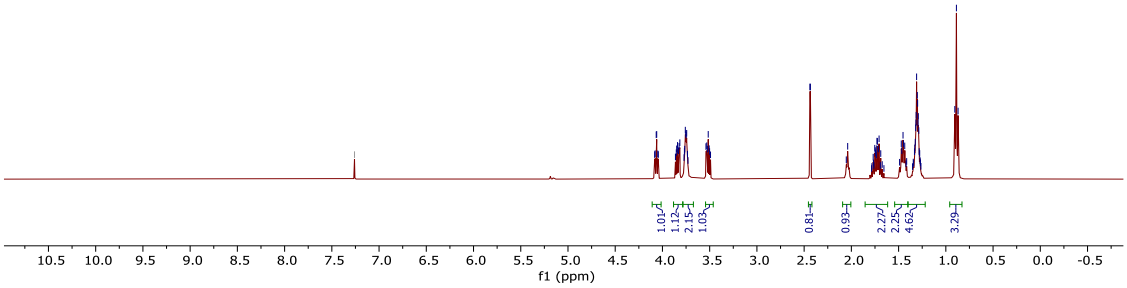


9b $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



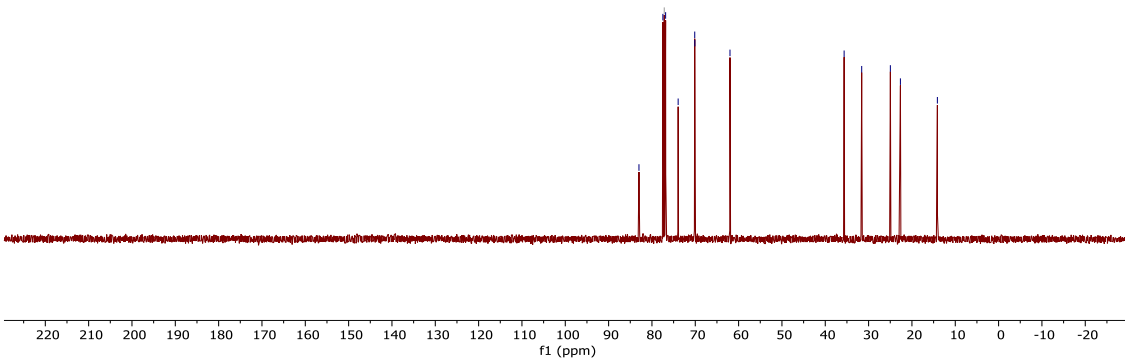


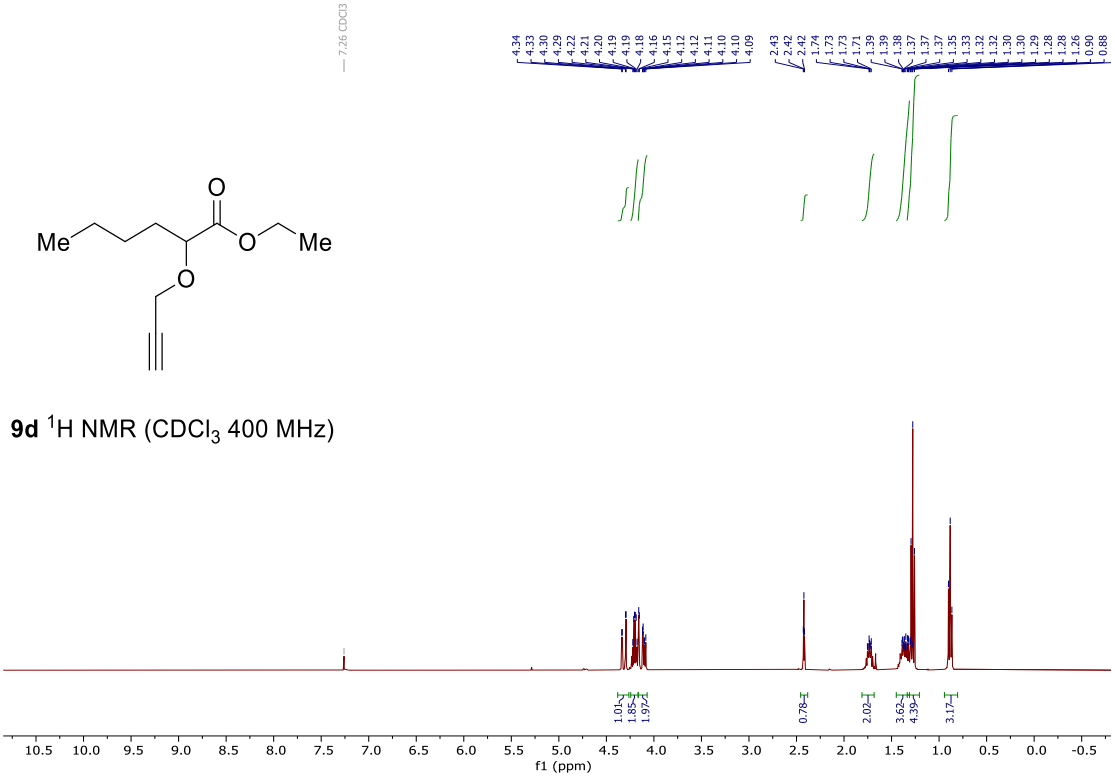
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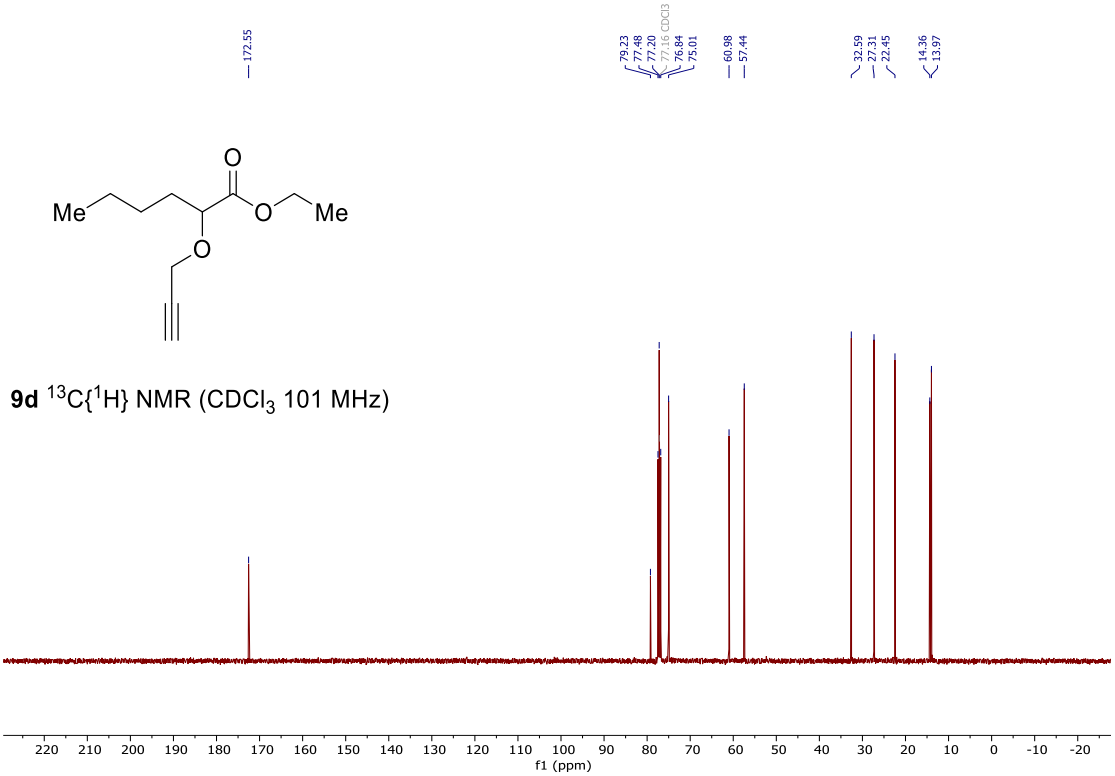


2f ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

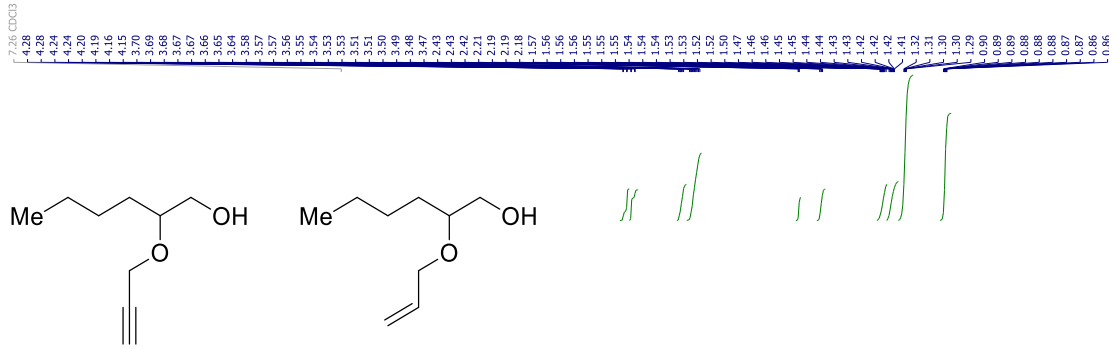




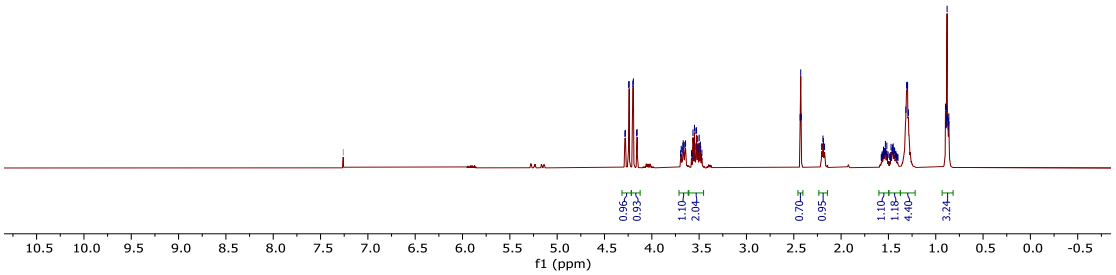
9d ^{1}H NMR ($CDCl_3$ 400 MHz)



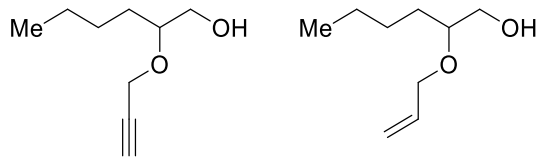
9d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



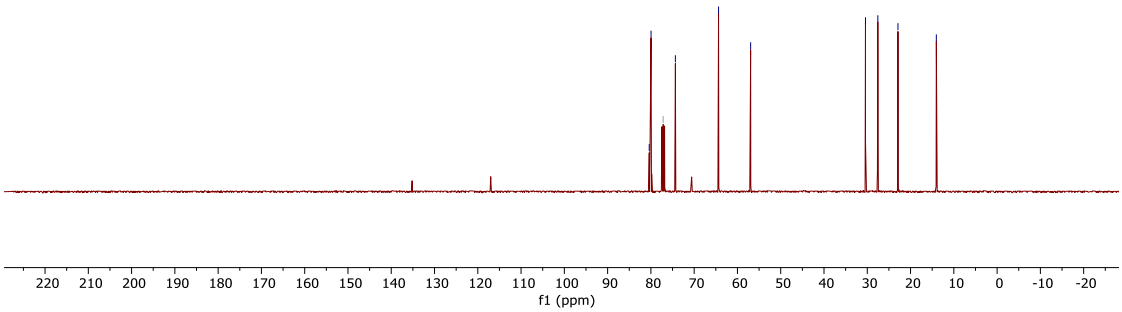
2h and **51** ^{1}H NMR ($CDCl_3$ 400 MHz)

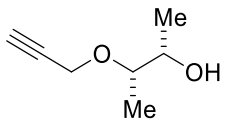




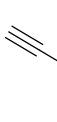


2h and **51** $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

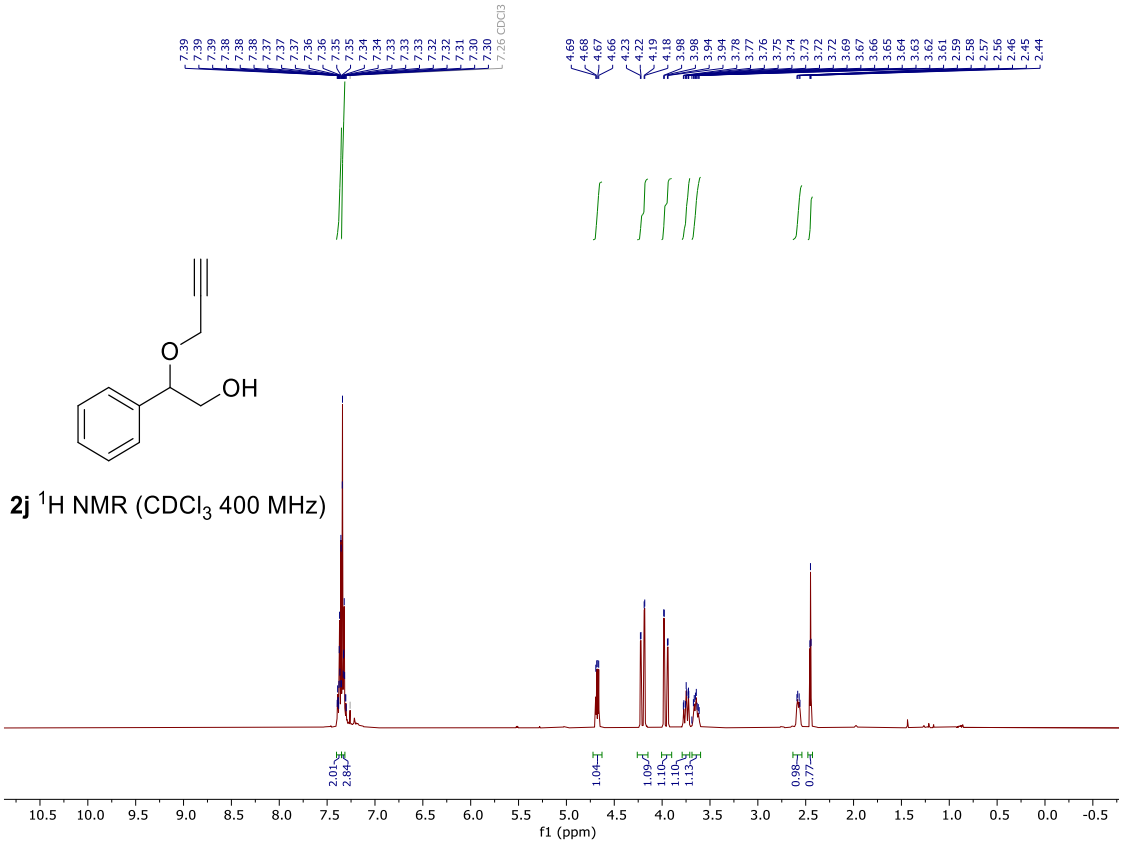


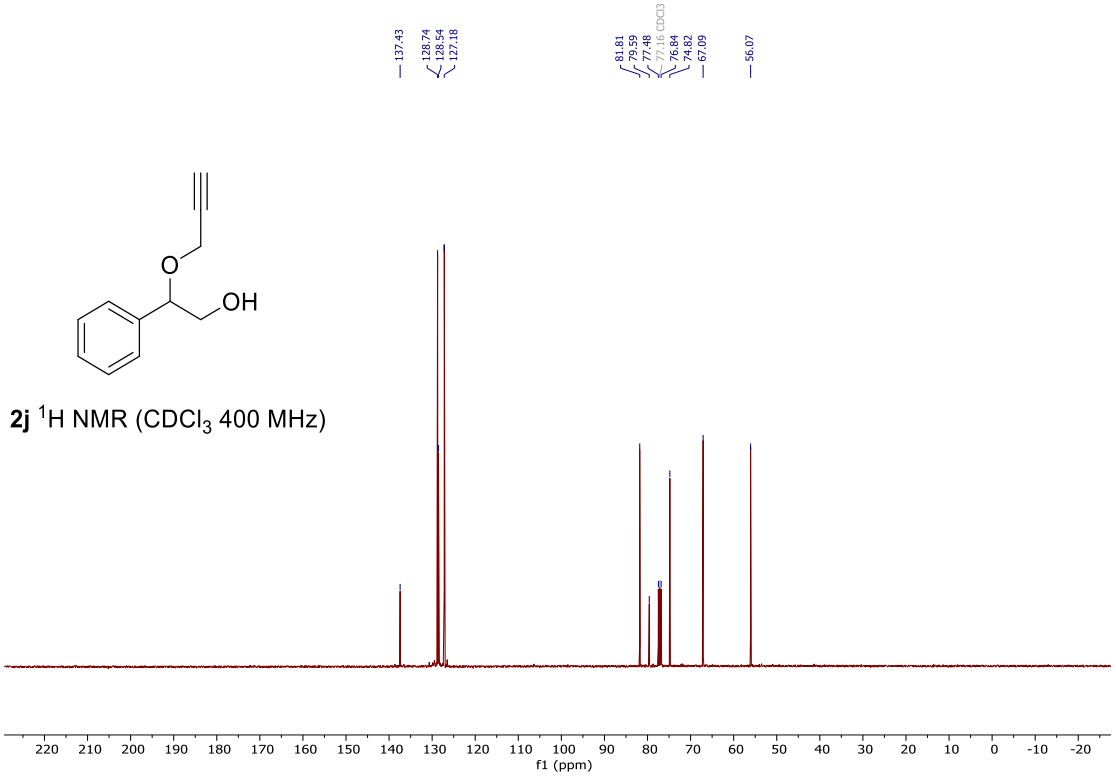


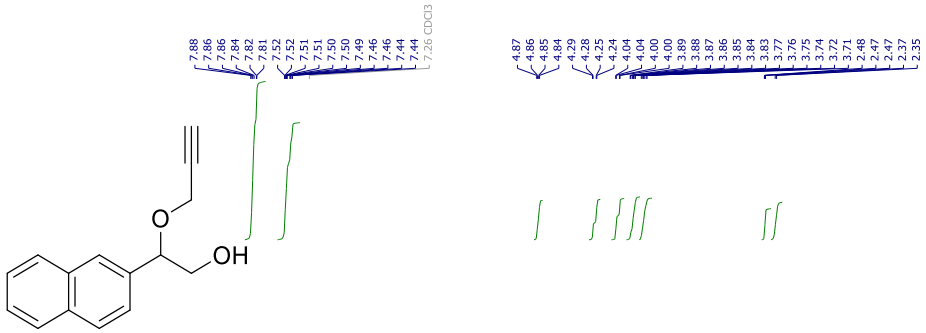
2i ^{1}H NMR ($CDCl_3$ 400 MHz)



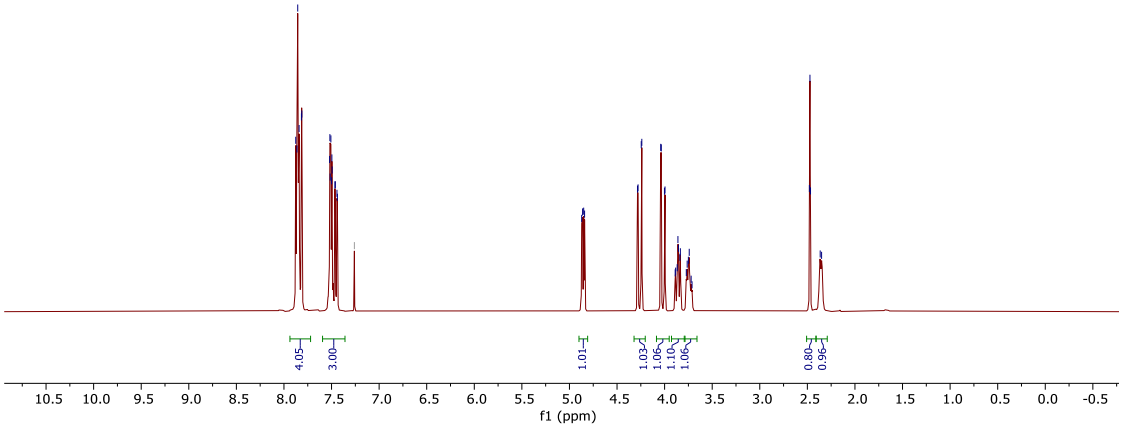
2i $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

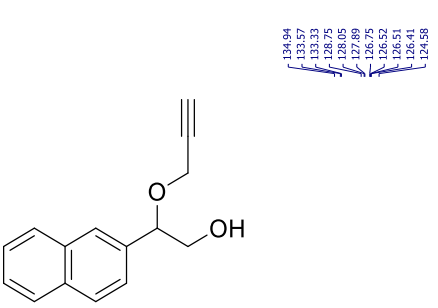

O
OH
2j ^{1}H NMR ($CDCl_3$ 400 MHz)
f1 (ppm)


O
OH
2j ^{1}H NMR ($CDCl_3$ 400 MHz)
f1 (ppm)

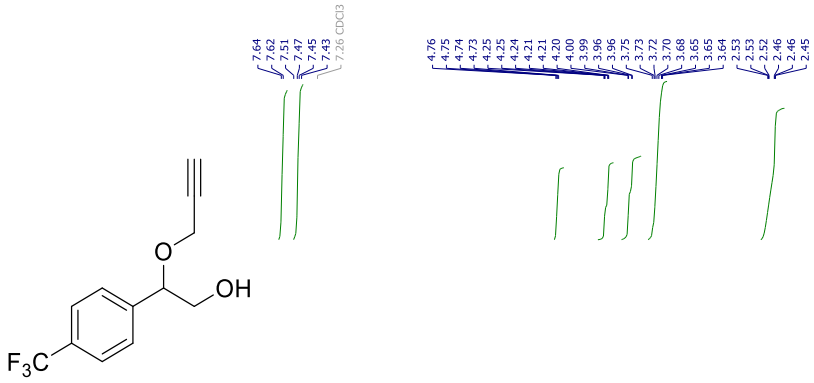


2k ^{1}H NMR ($CDCl_3$ 400 MHz)

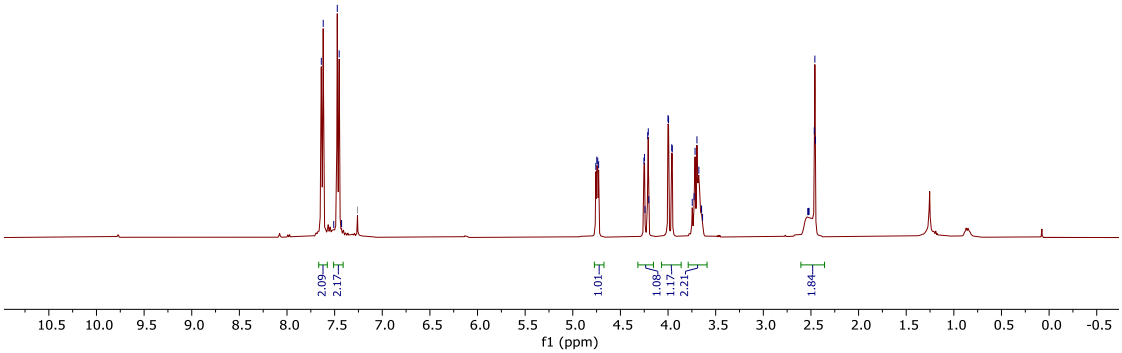


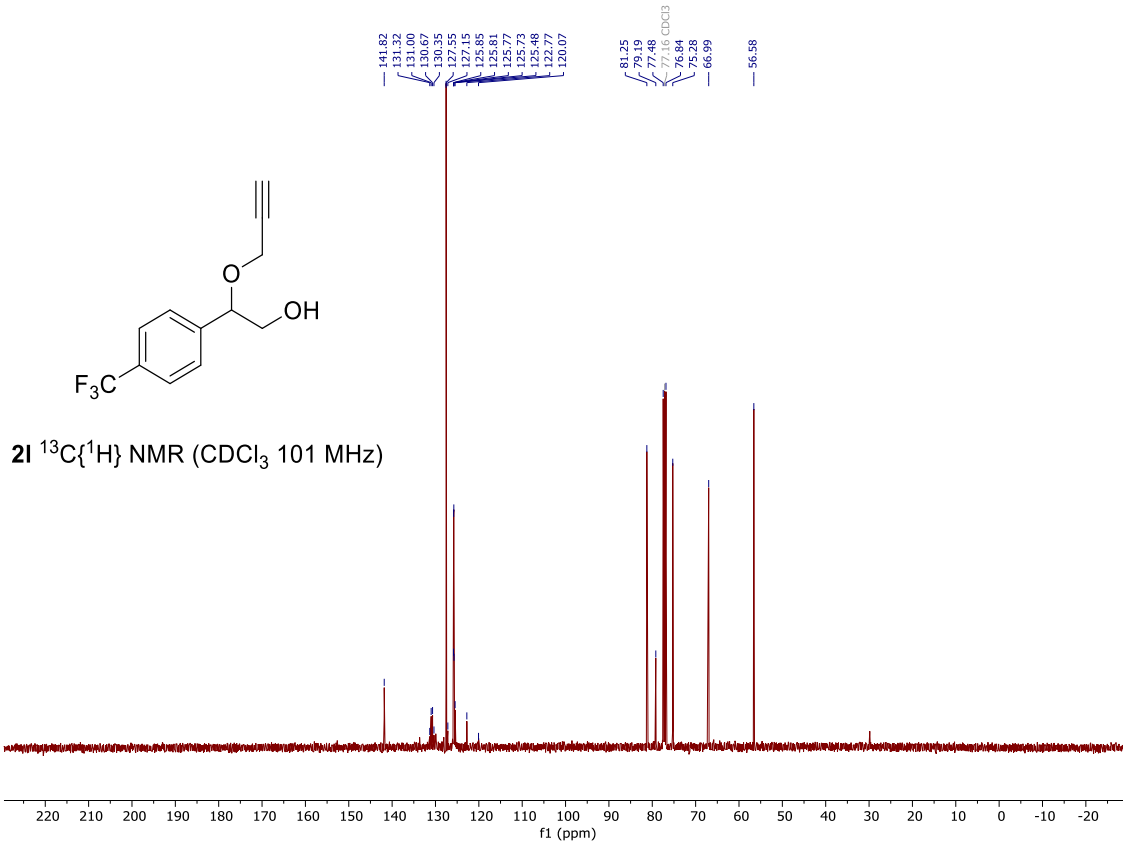


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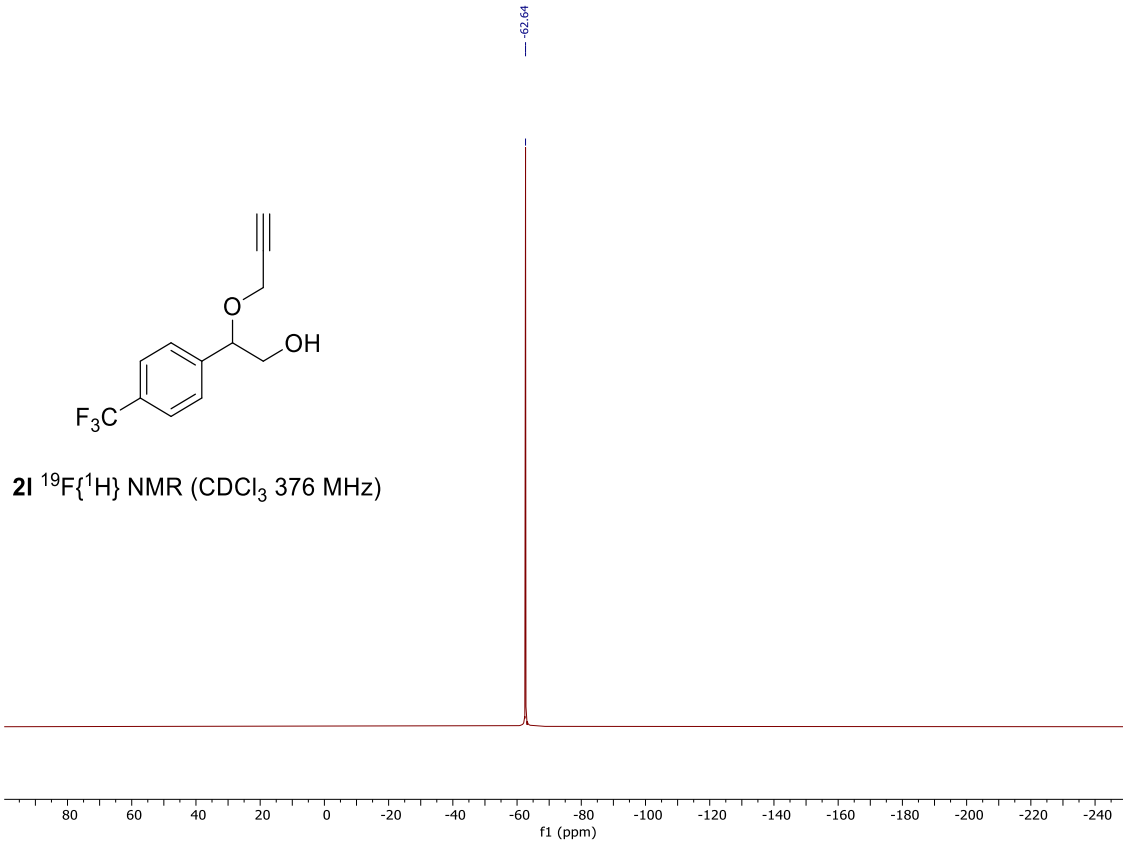


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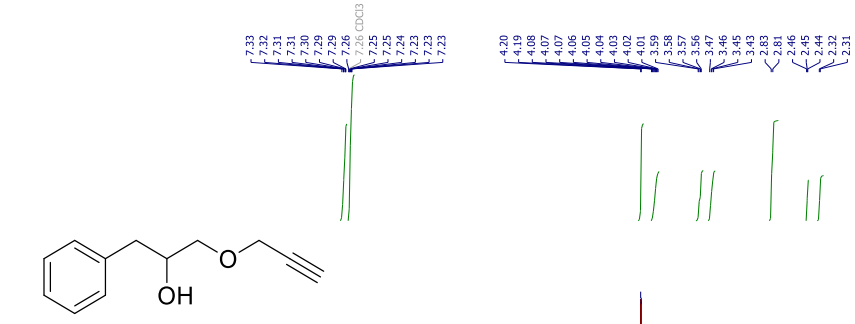




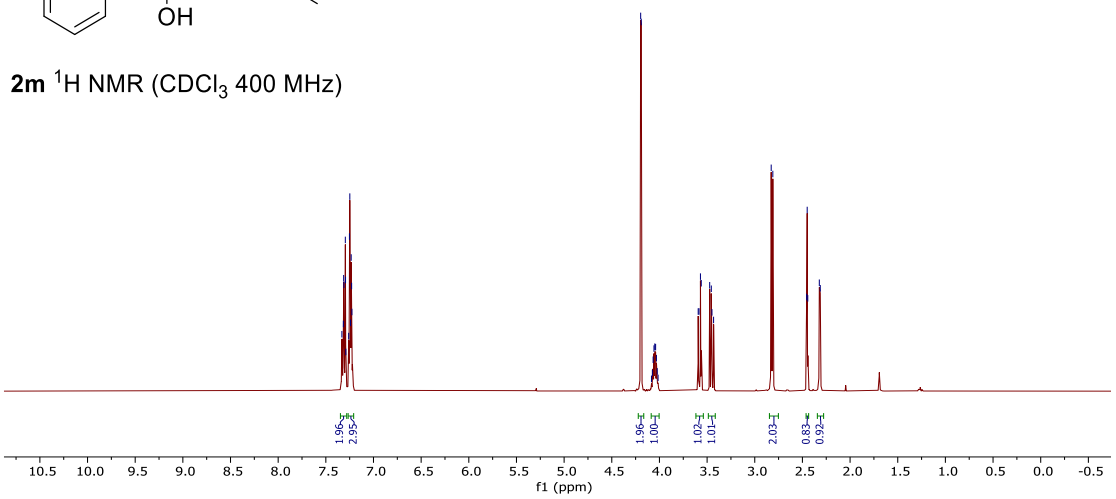
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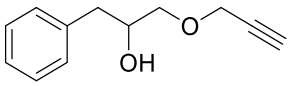
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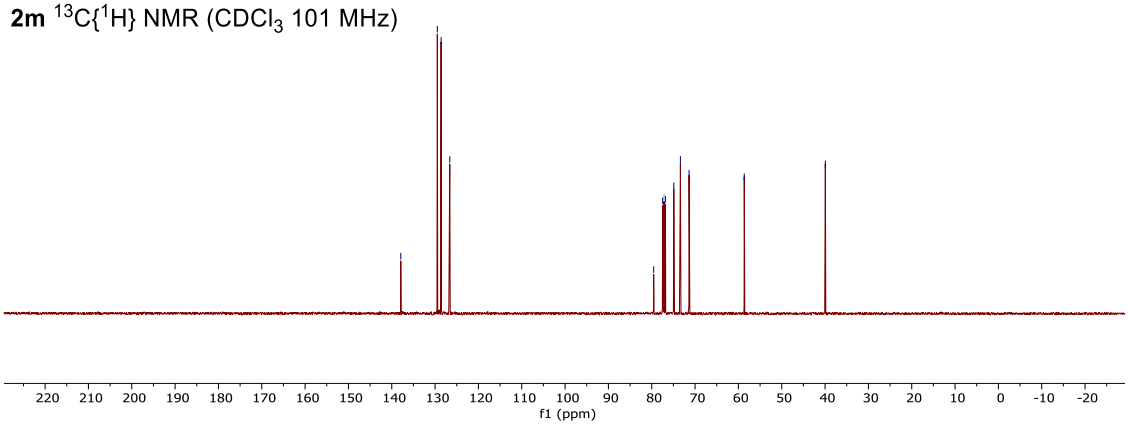
2m ^{1}H NMR ($CDCl_3$ 400 MHz)

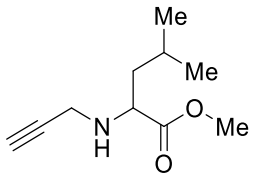




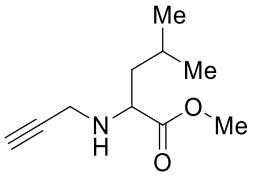


2m ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

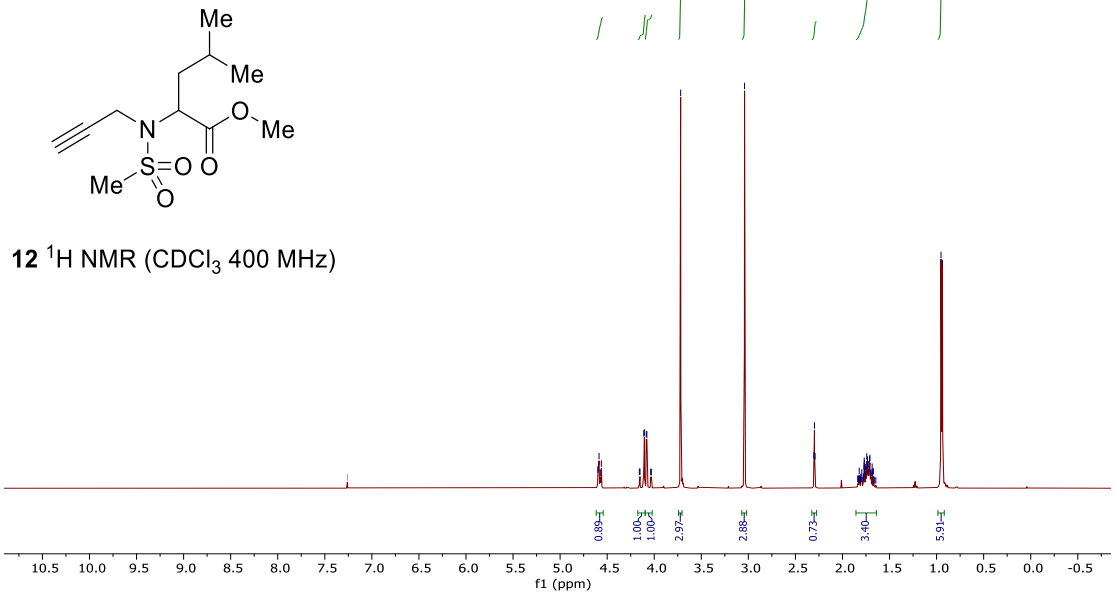




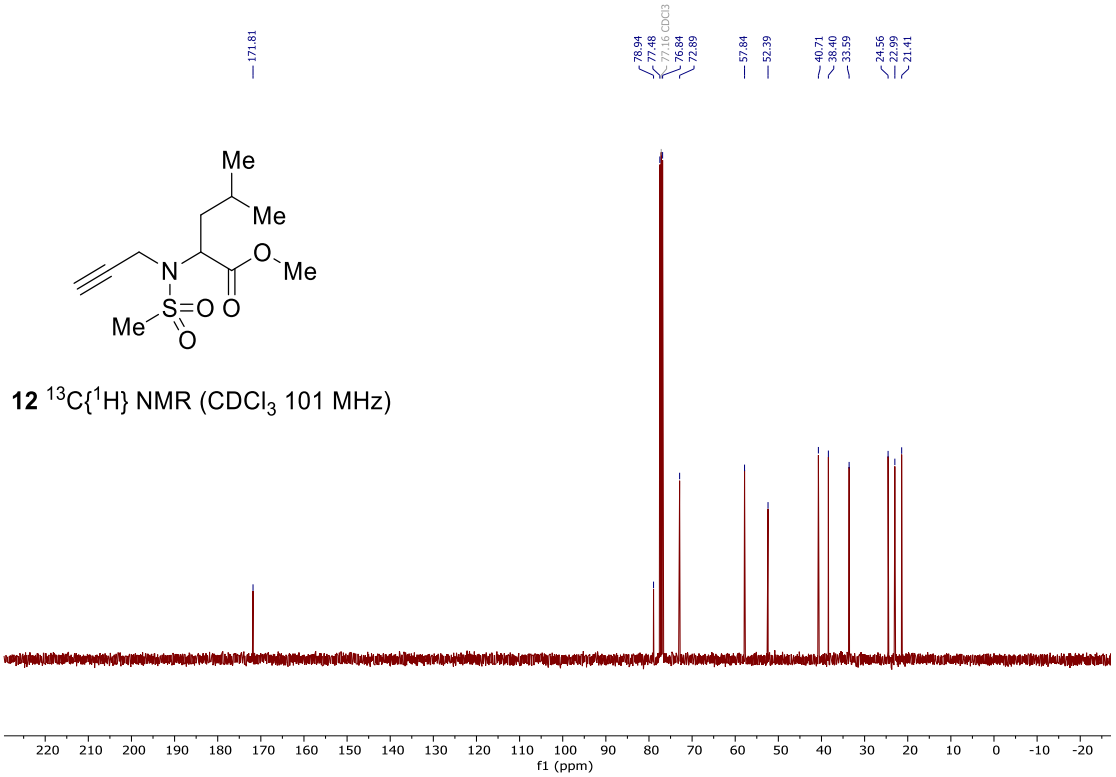
54 ^{1}H NMR ($CDCl_3$ 400 MHz)



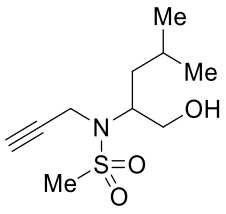
54 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



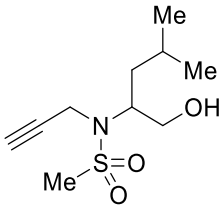
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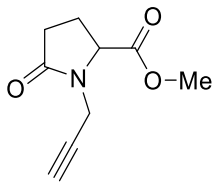
12 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



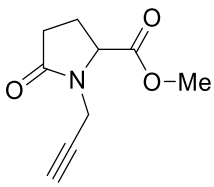
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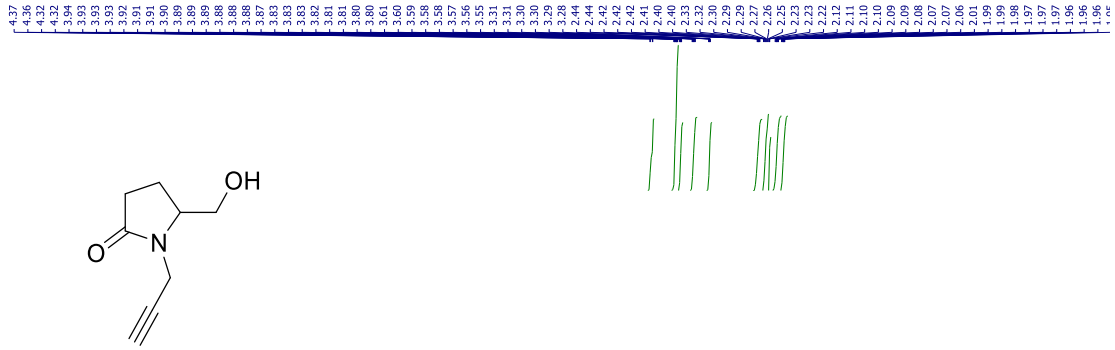
2n $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



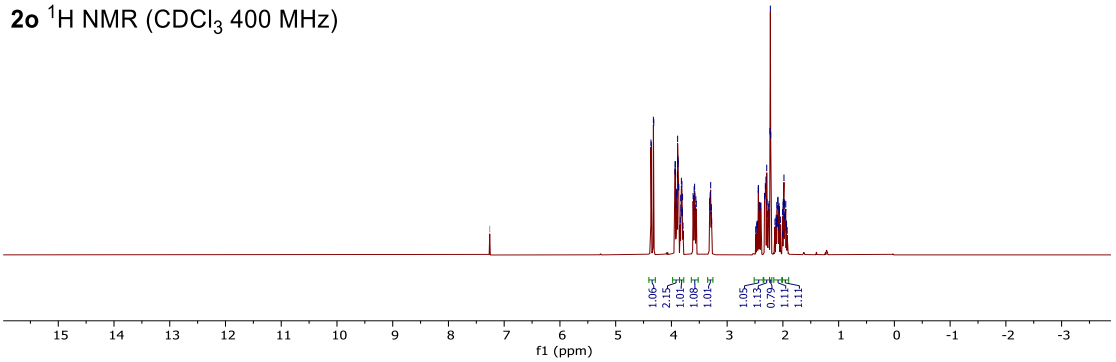
13 ^{1}H NMR ($CDCl_3$ 400 MHz)



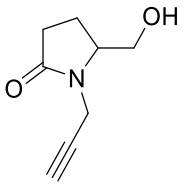
13 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



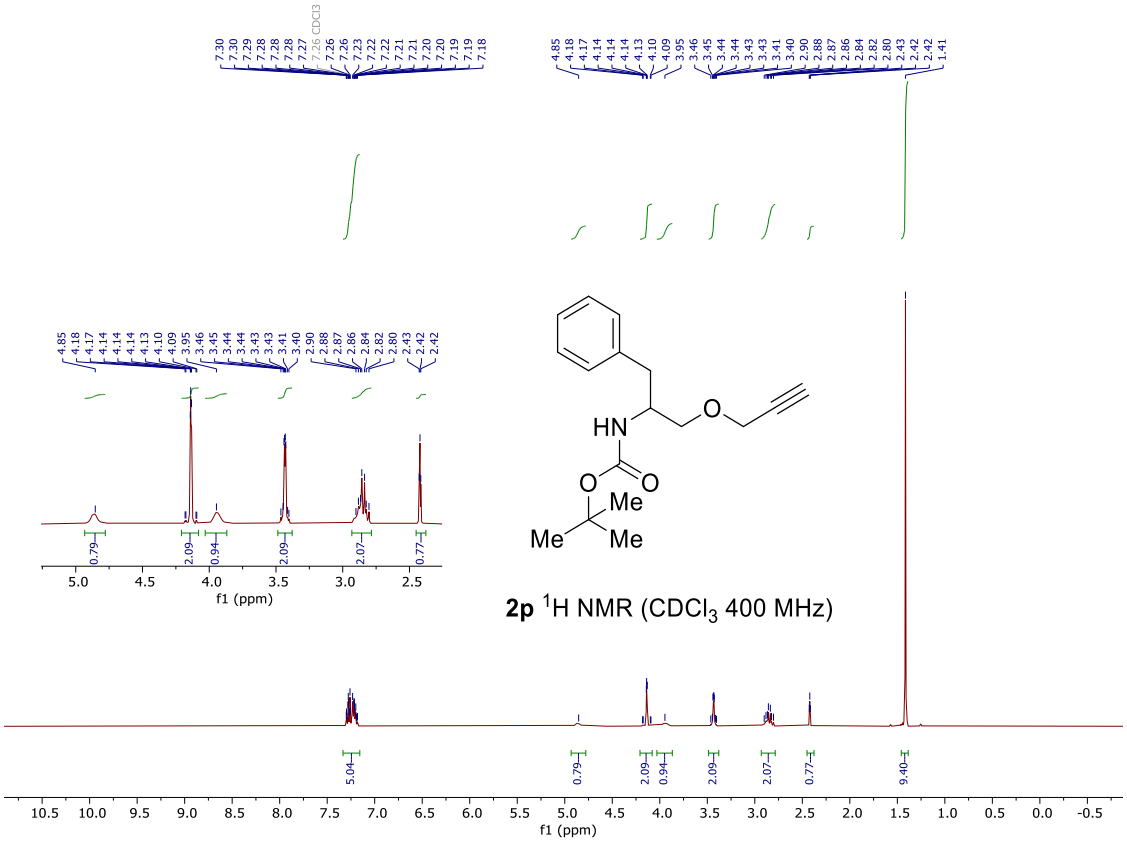
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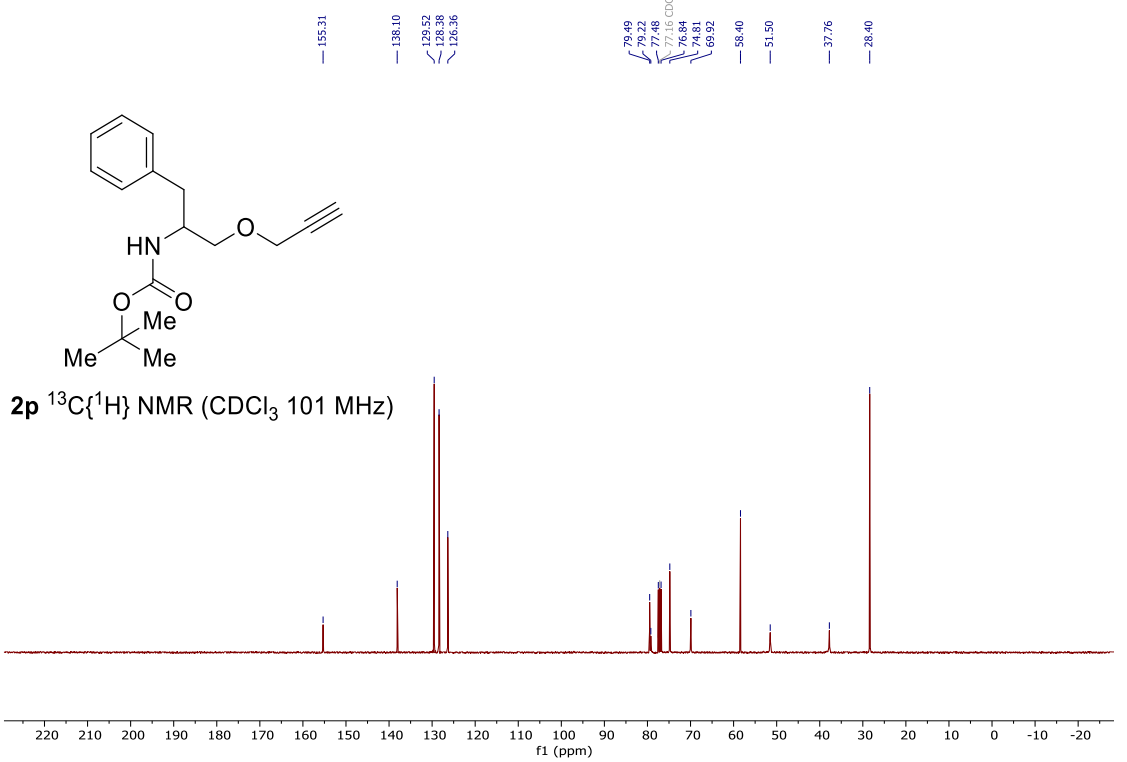




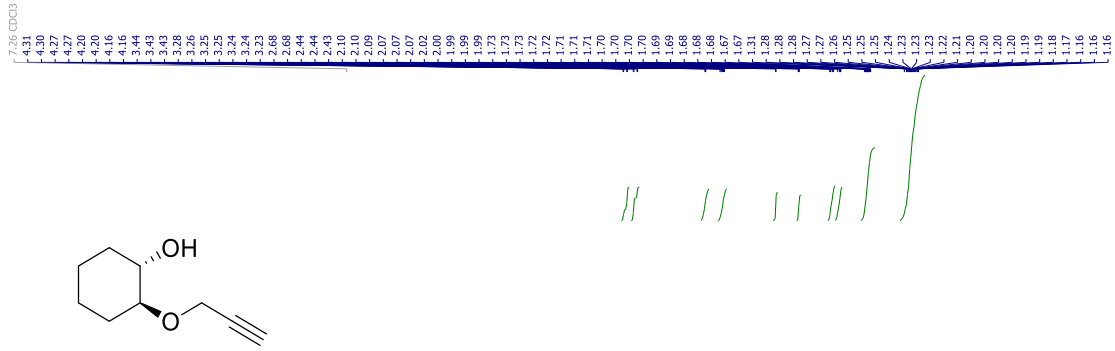
2o $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



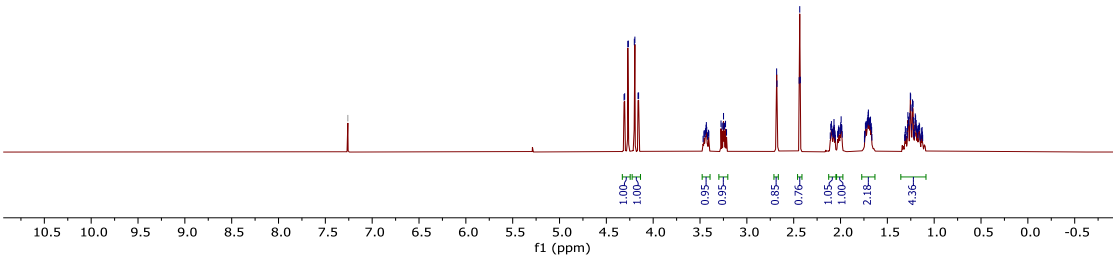
2p ^{1}H NMR ($CDCl_3$ 400 MHz)

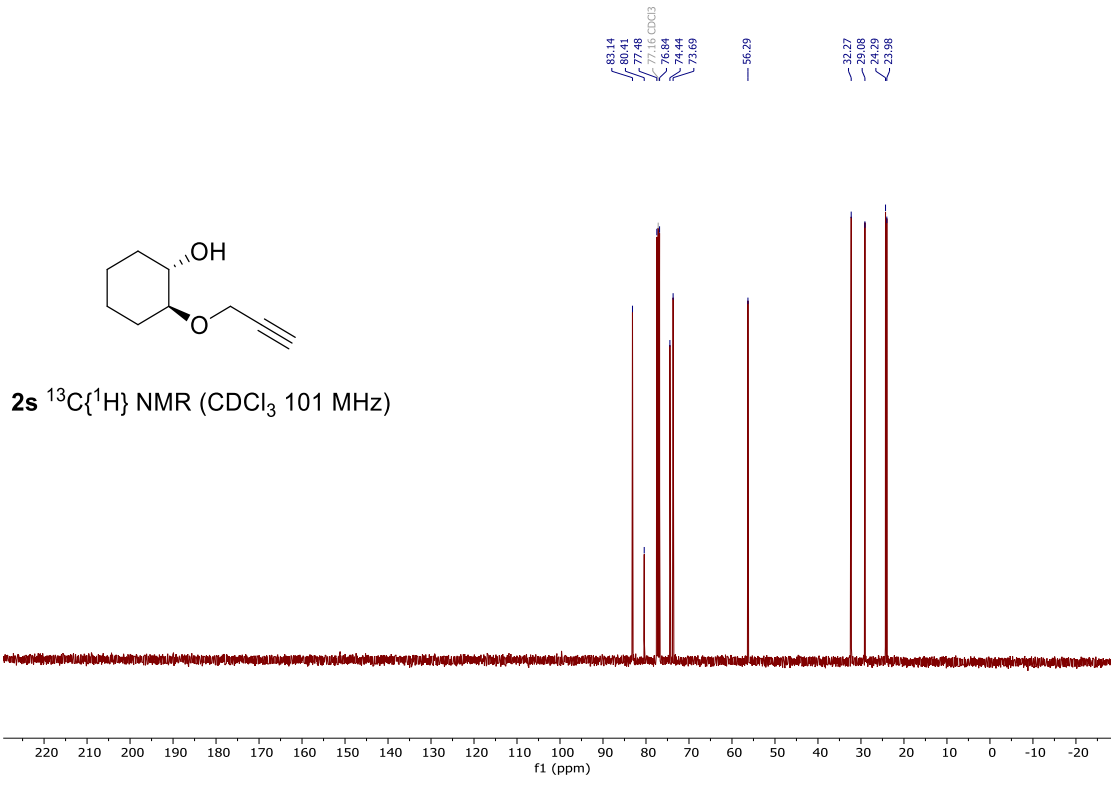


2p $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

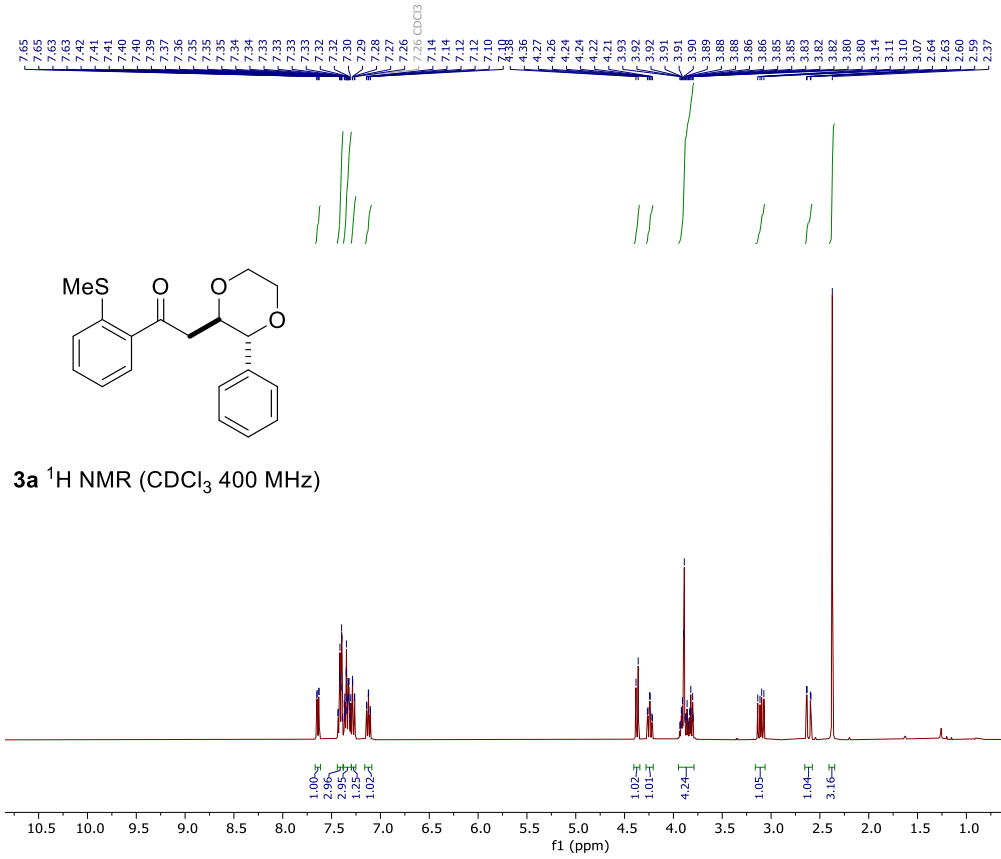


2s ^{1}H NMR ($CDCl_3$ 400 MHz)

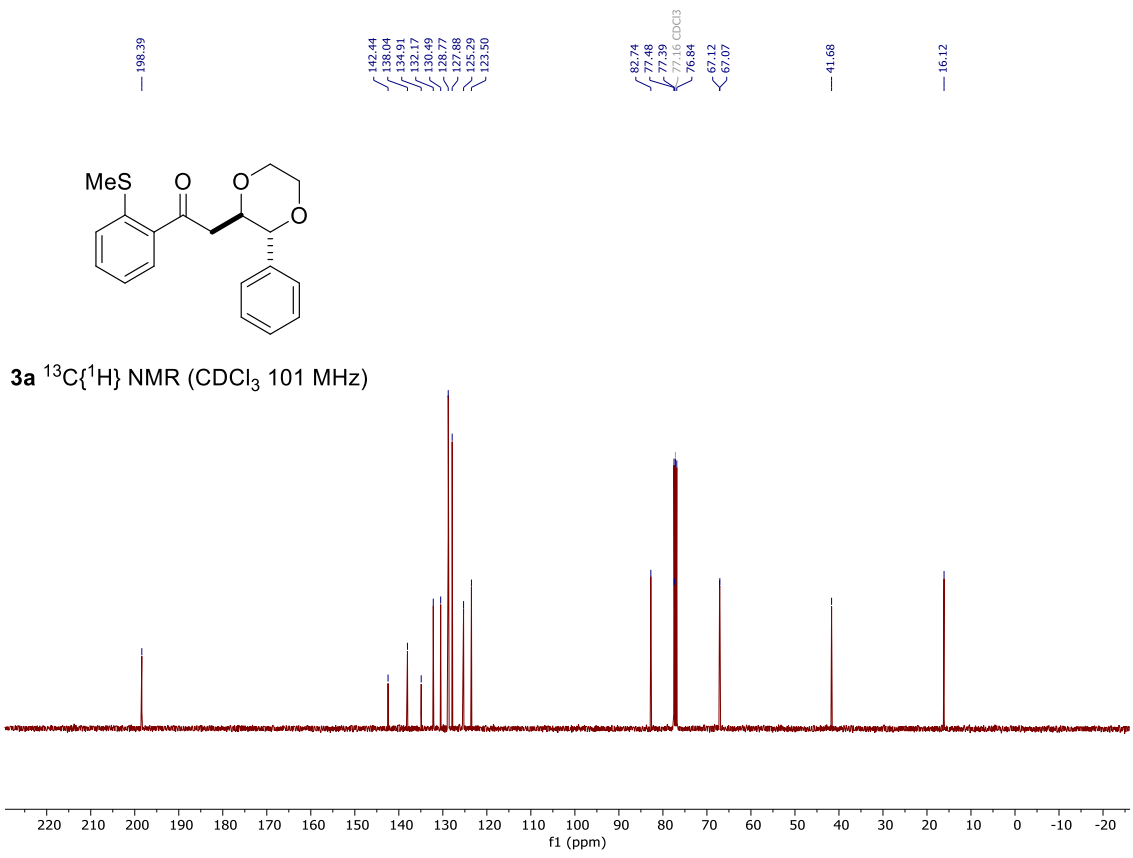




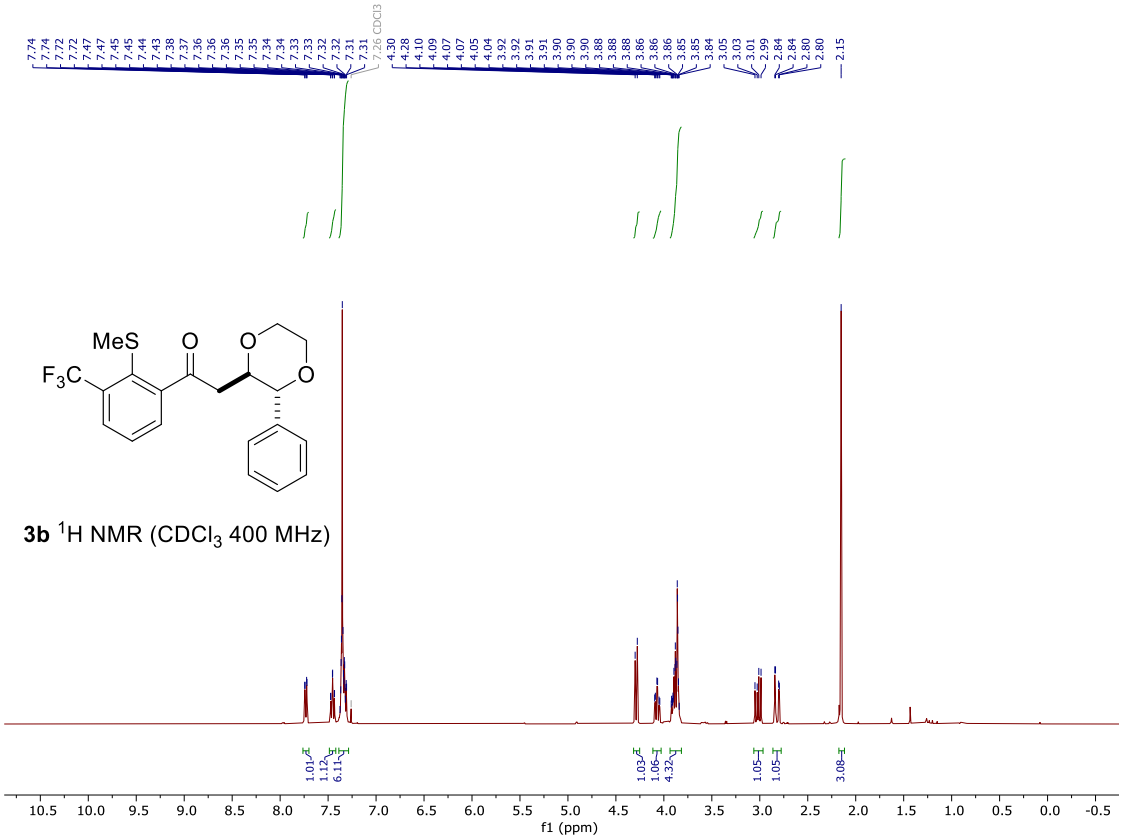
2s $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



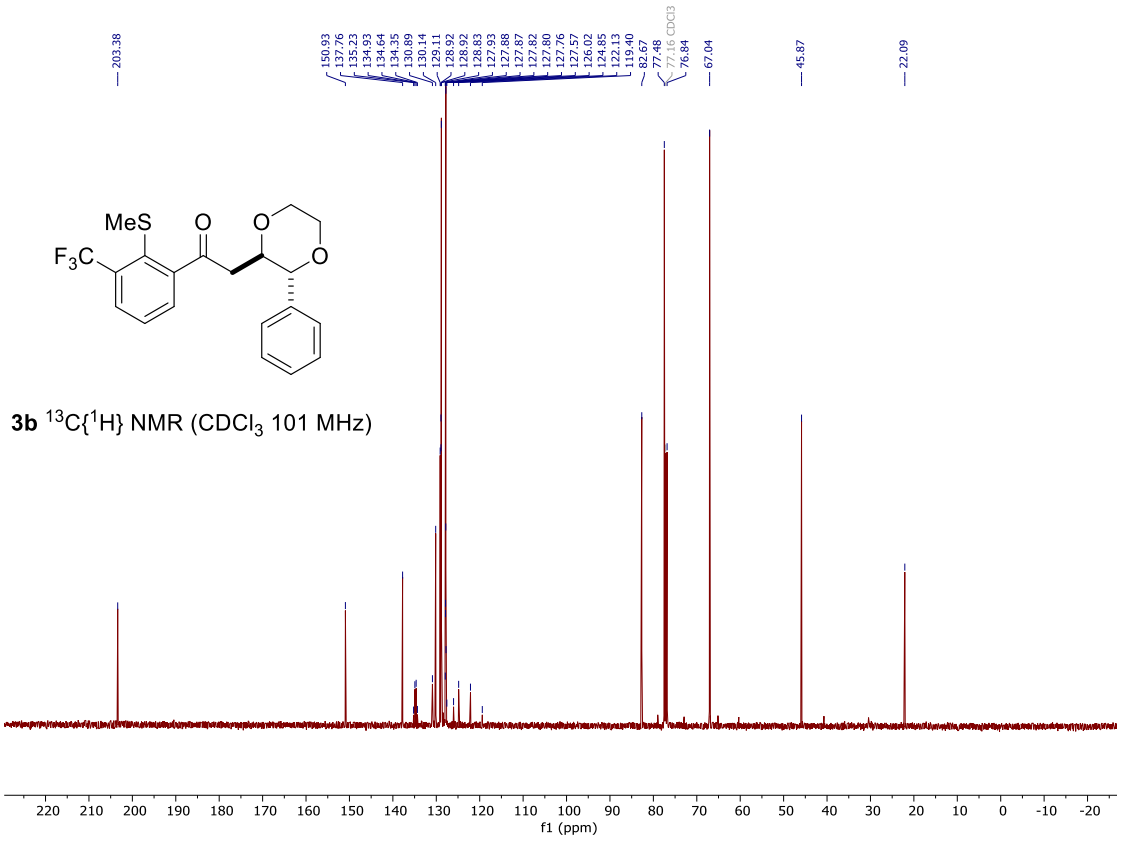
3a ^{1}H NMR ($CDCl_3$ 400 MHz)



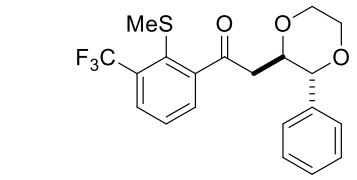
3a $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



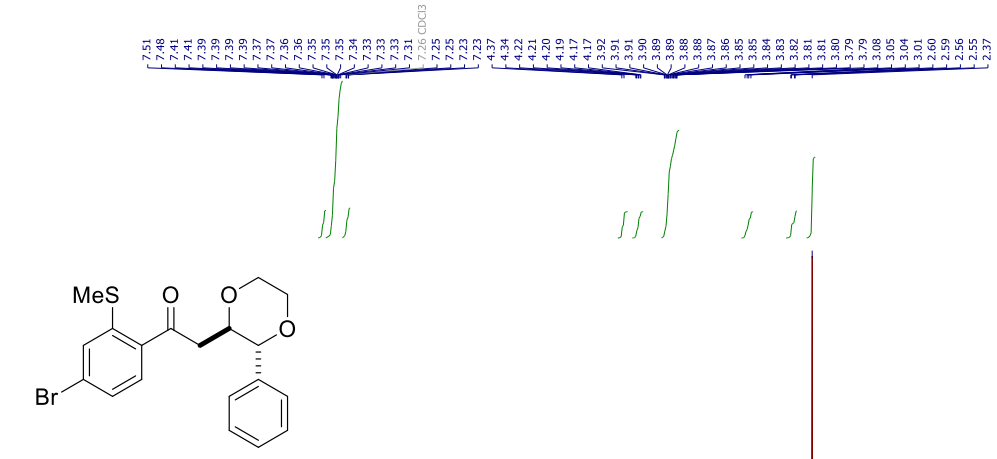
3b ^{1}H NMR ($CDCl_3$ 400 MHz)



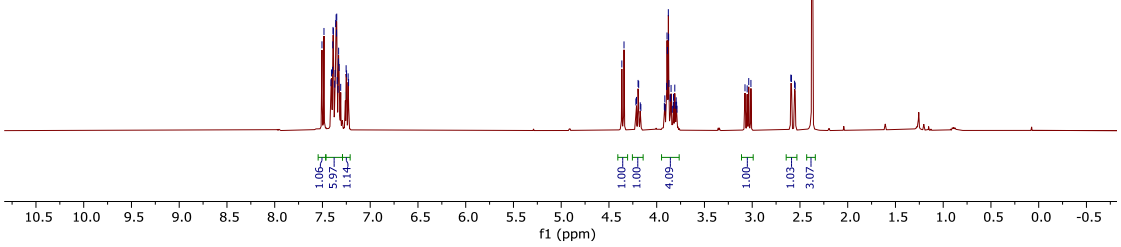
3b $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

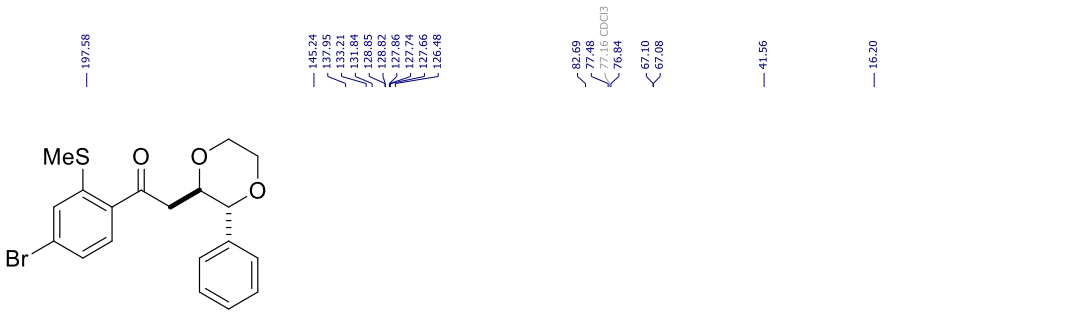


3b $^{19}F\{^{1}H\}$ NMR ($CDCl_3$ 376 MHz)

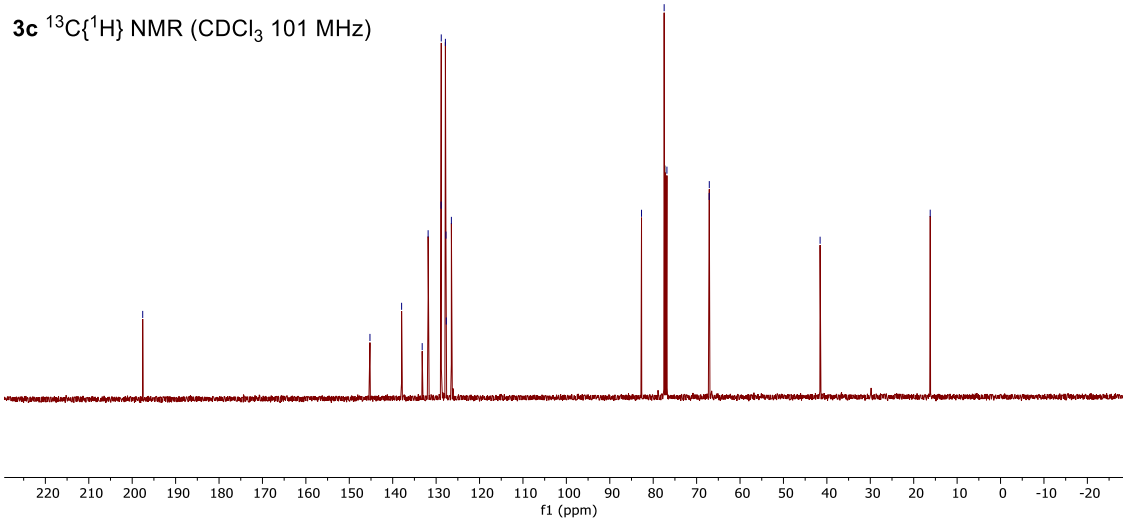


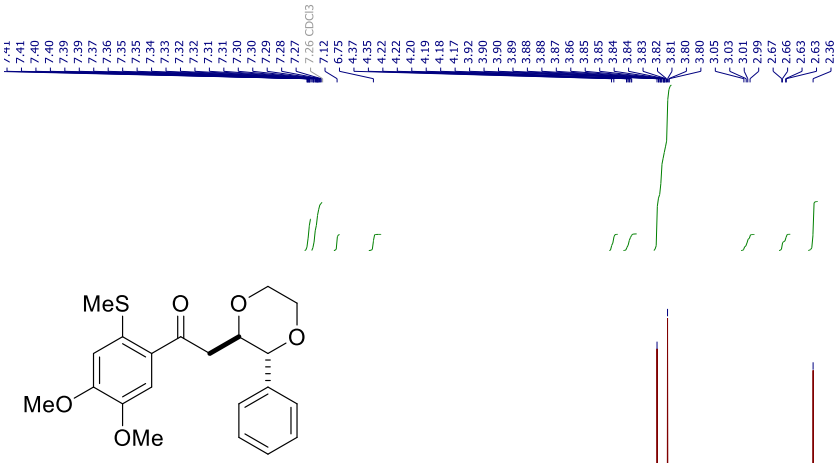
3c ^{1}H NMR ($CDCl_3$ 400 MHz)



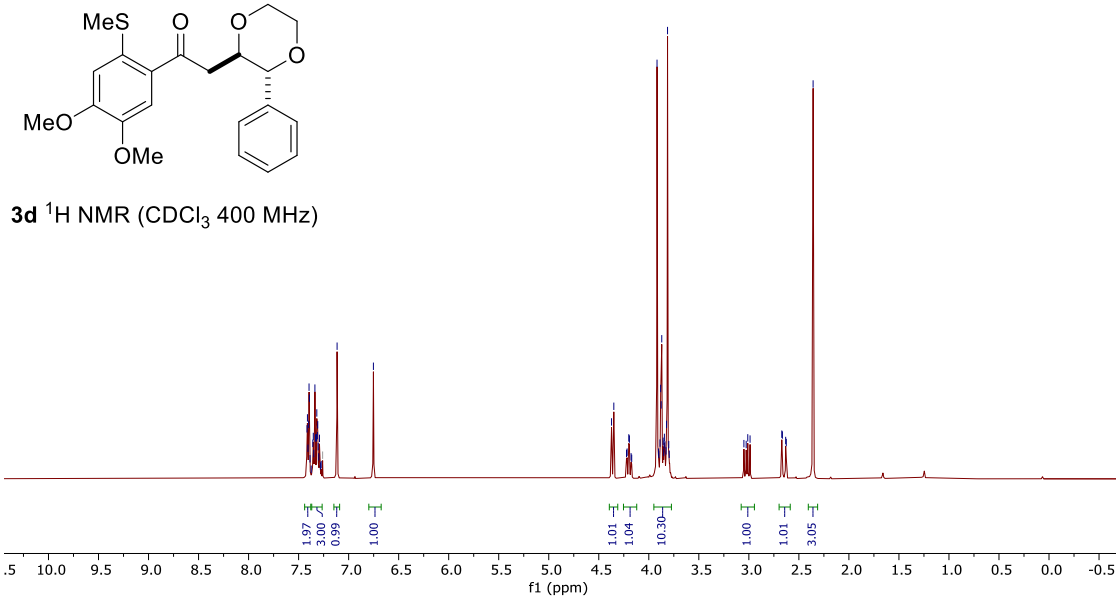


3c $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

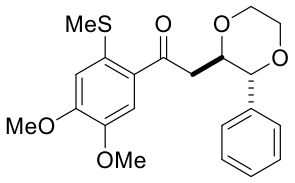




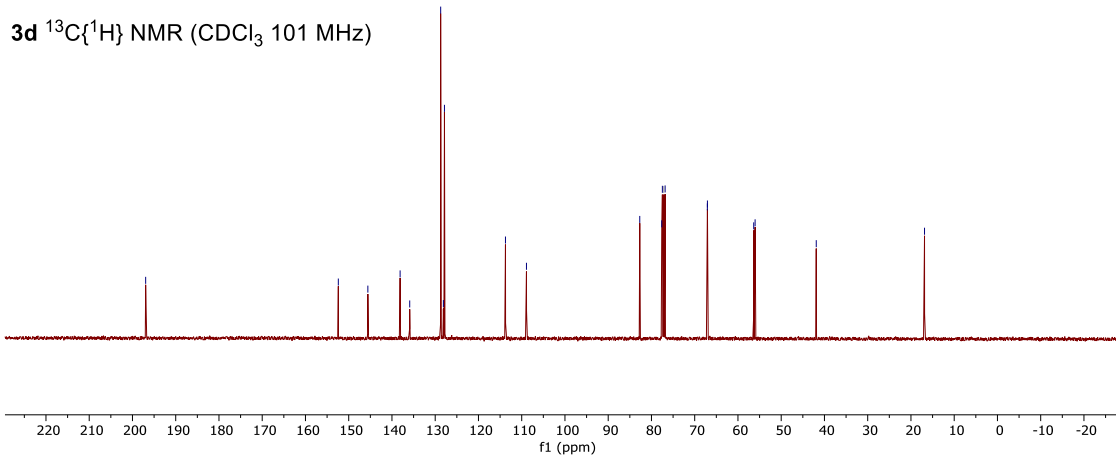
3d ^{1}H NMR ($CDCl_3$ 400 MHz)

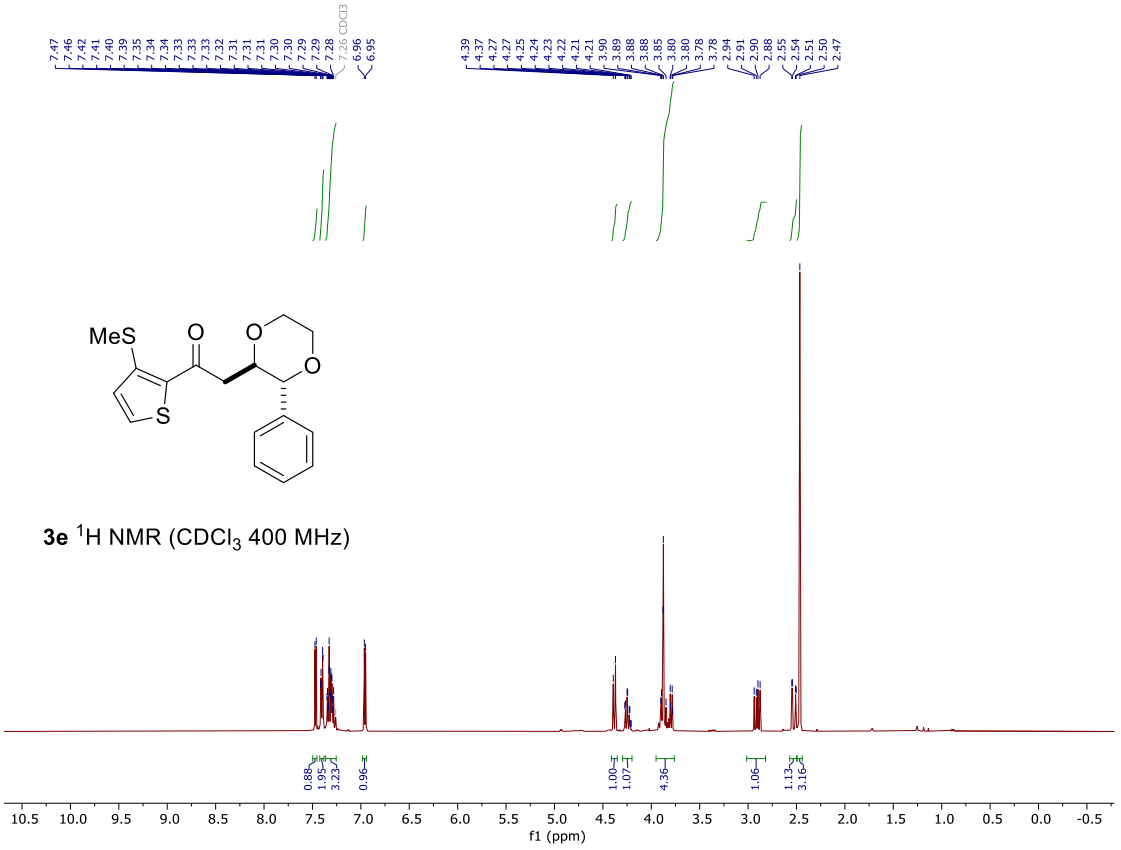




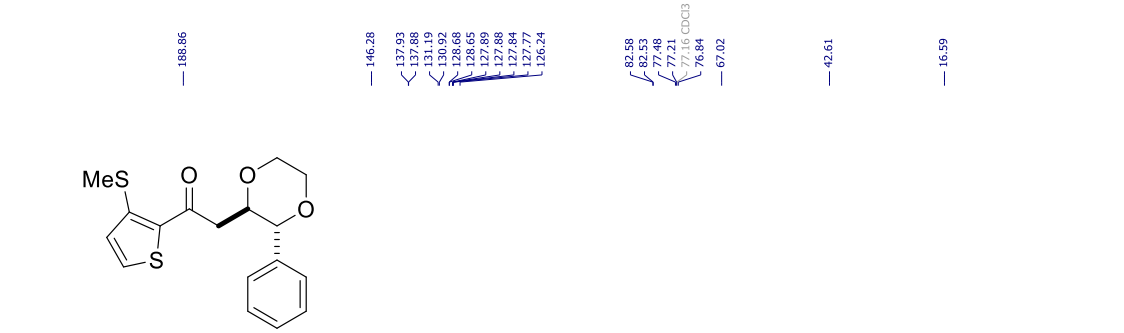


3d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

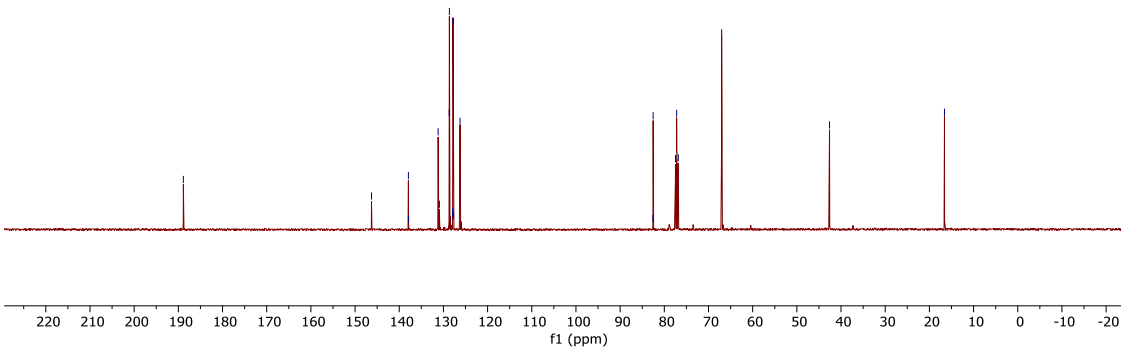


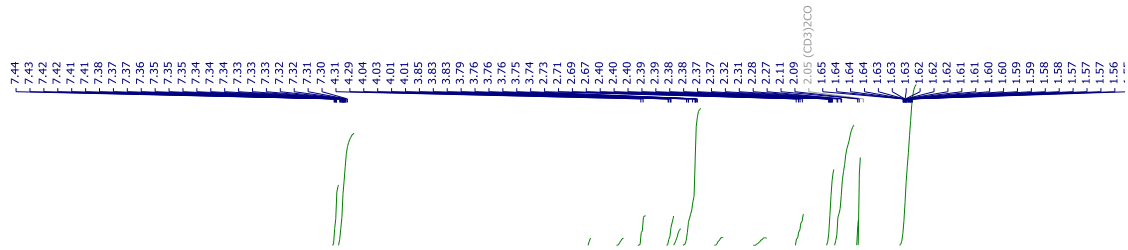


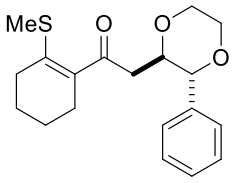
3e ^{1}H NMR ($CDCl_3$ 400 MHz)



3e $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

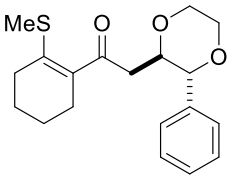




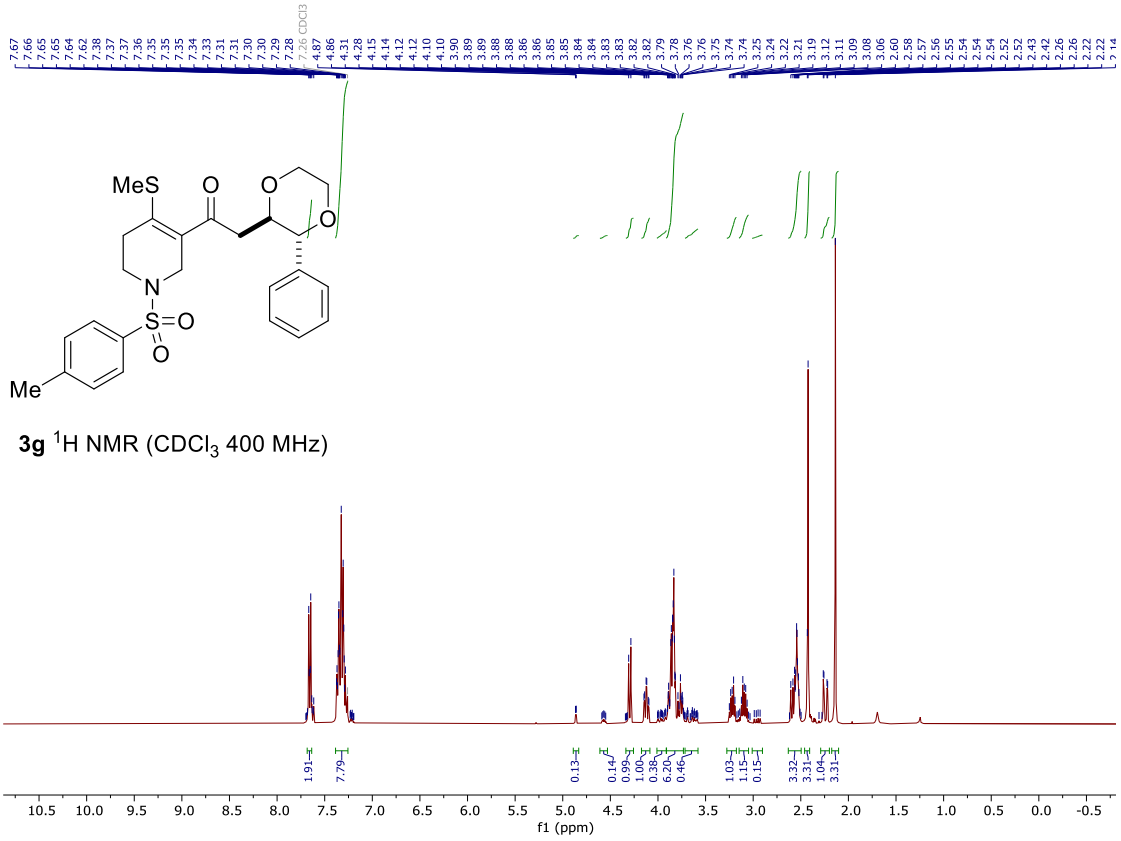


3f ^{1}H NMR (Acetone-d_6 400 MHz)

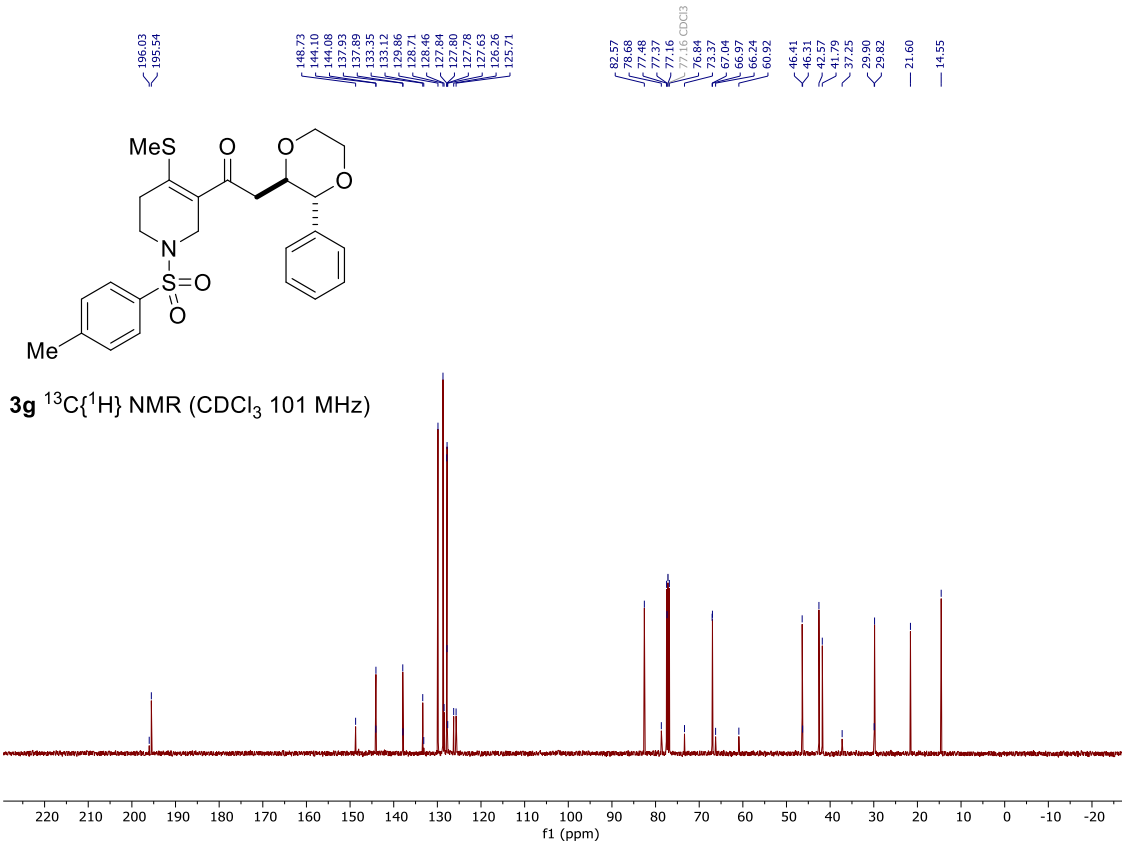




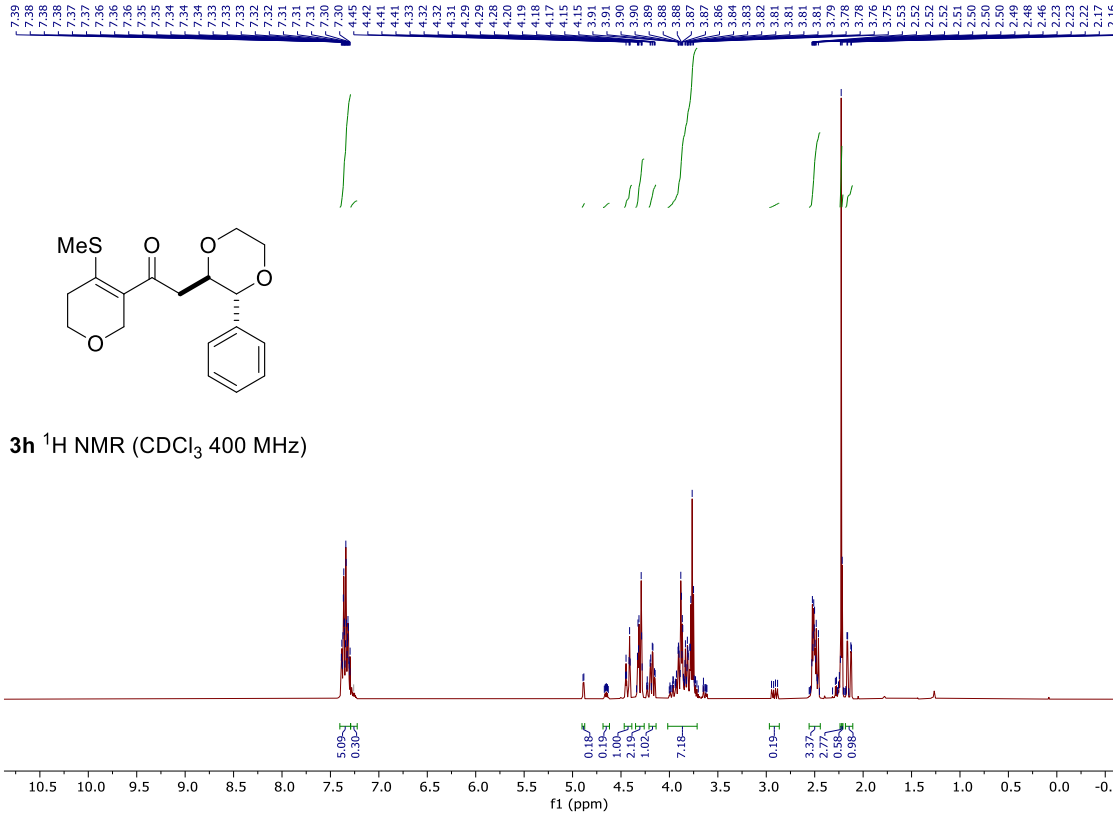
3f ^{13}C{^{1}H} NMR (Acetone-d_6 101 MHz)



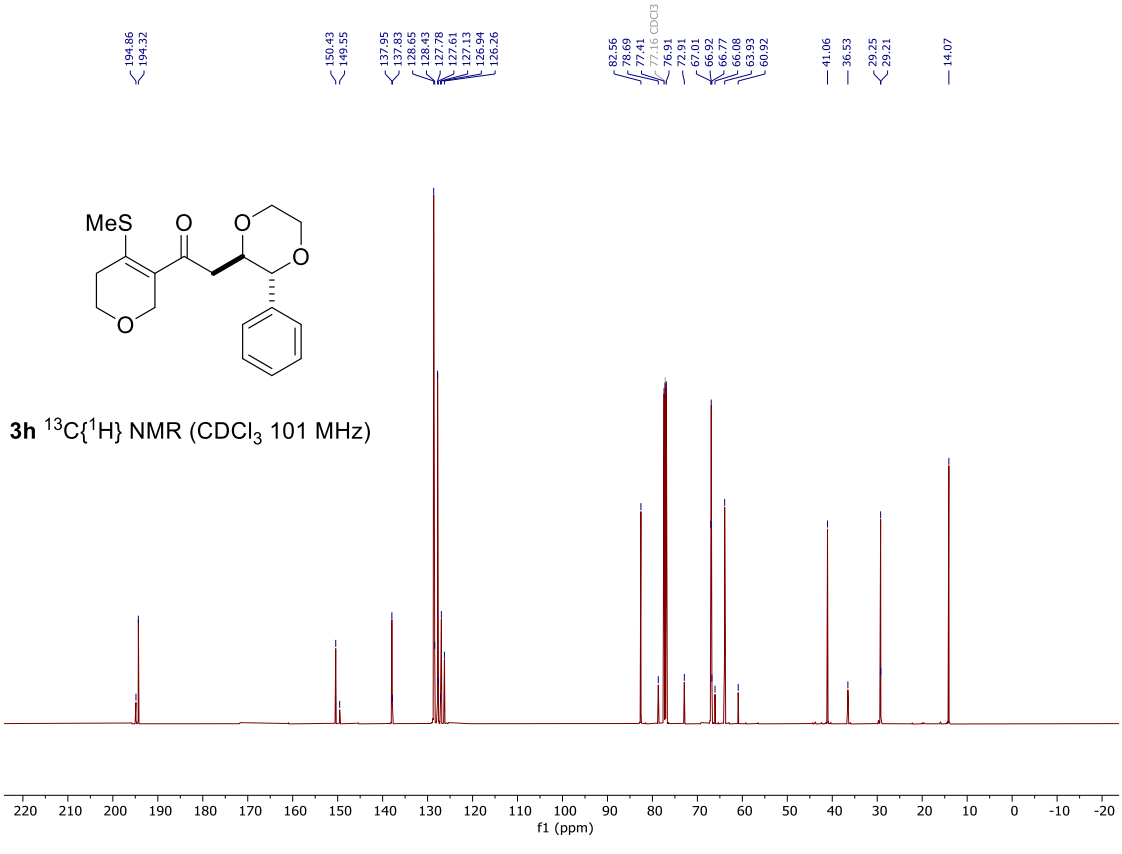
3g ^{1}H NMR ($CDCl_3$ 400 MHz)



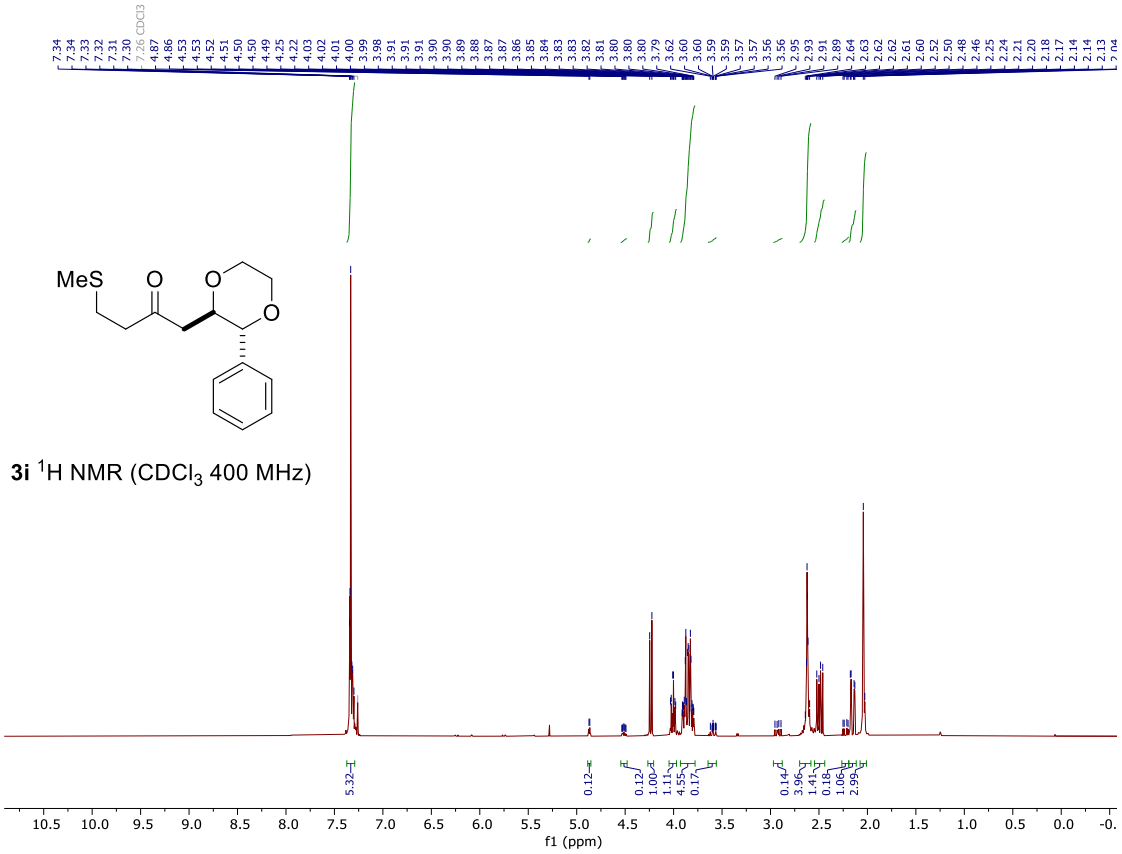
3g $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



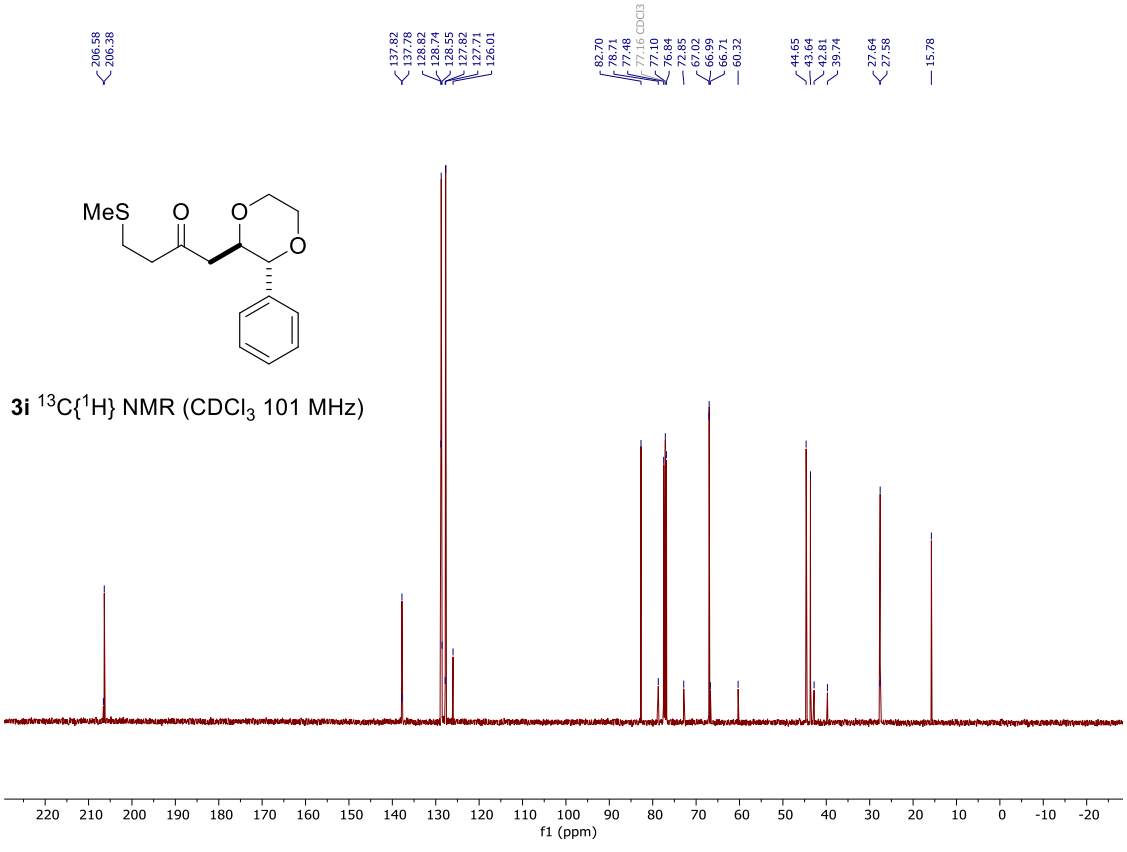
3h ^{1}H NMR ($CDCl_3$ 400 MHz)



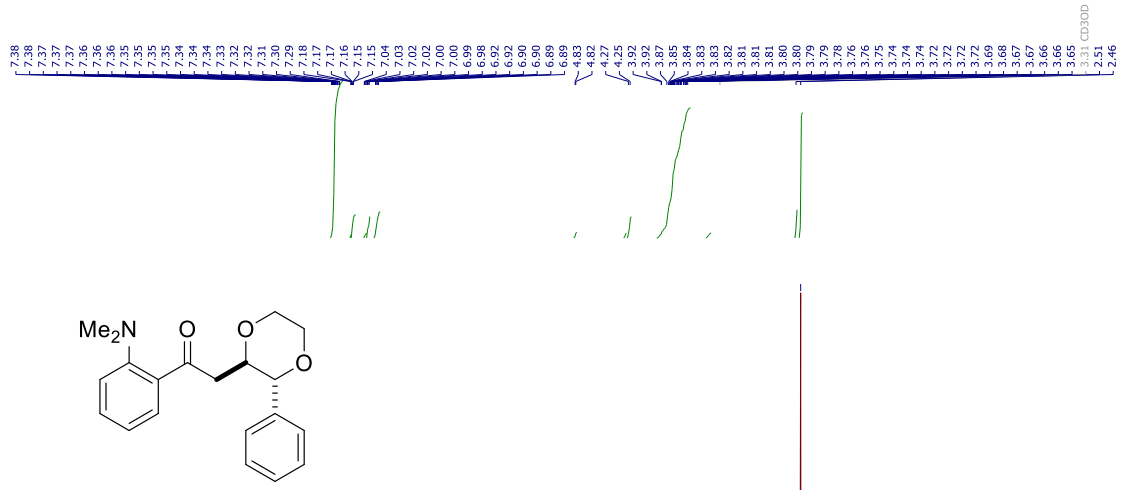
3h $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



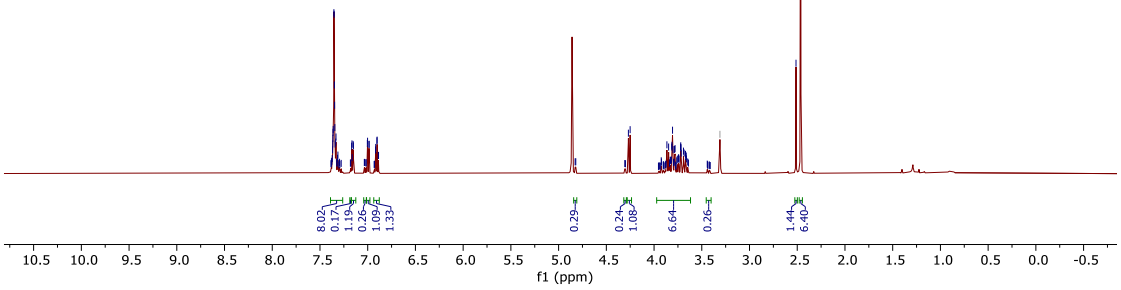
3i ^{1}H NMR ($CDCl_3$ 400 MHz)

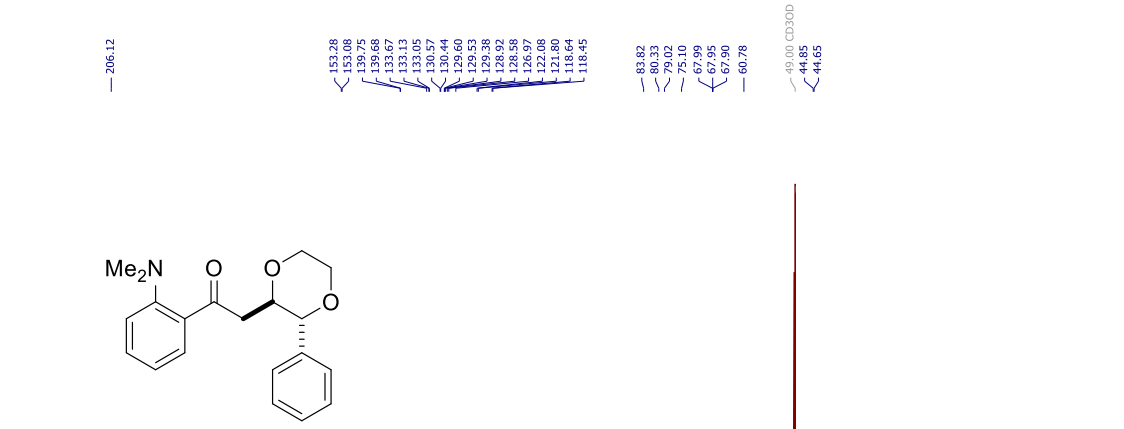


3i $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

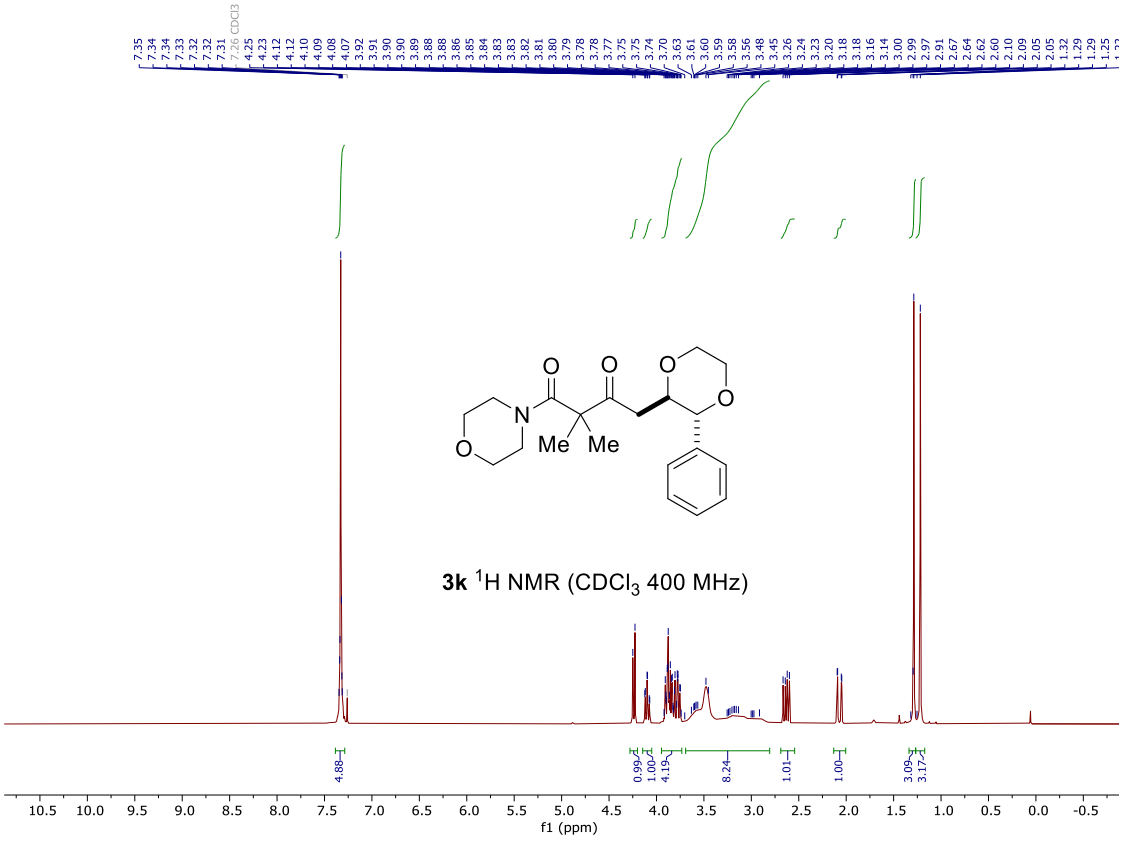


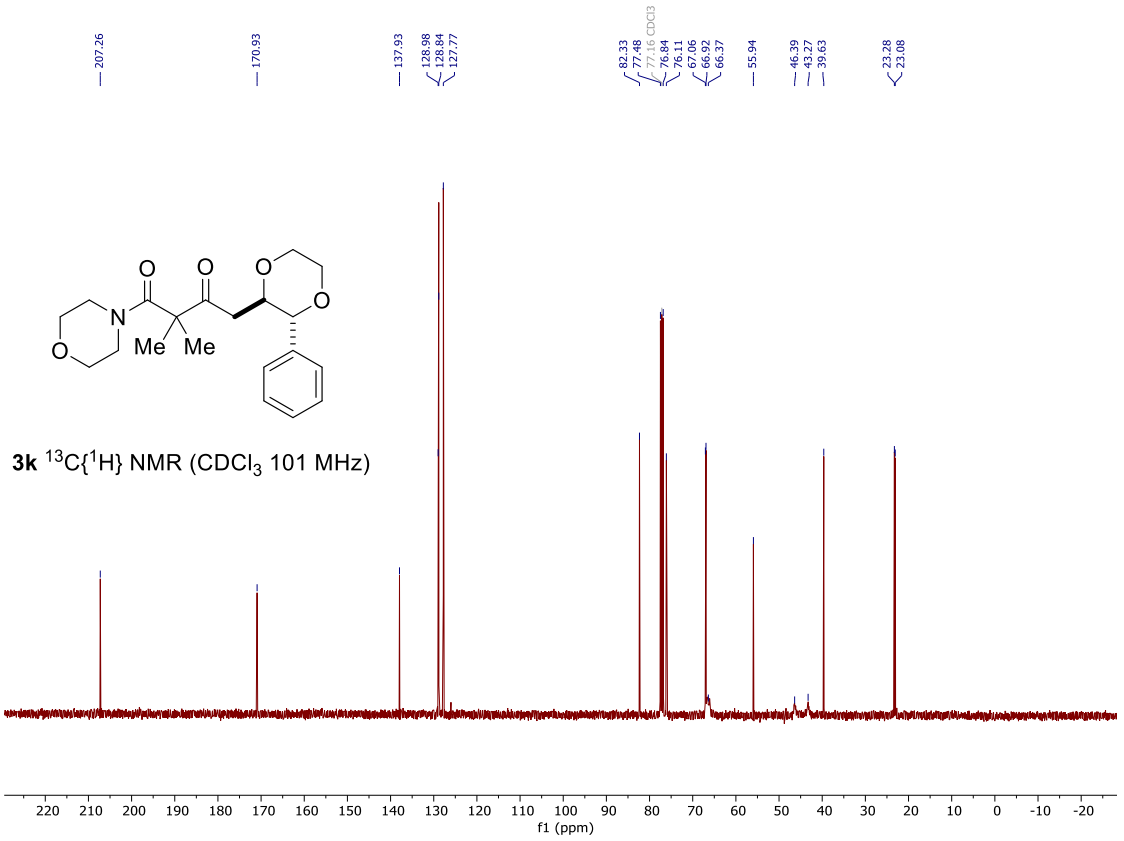
3j ^{1}H NMR (Methanol-d_4 500 MHz)

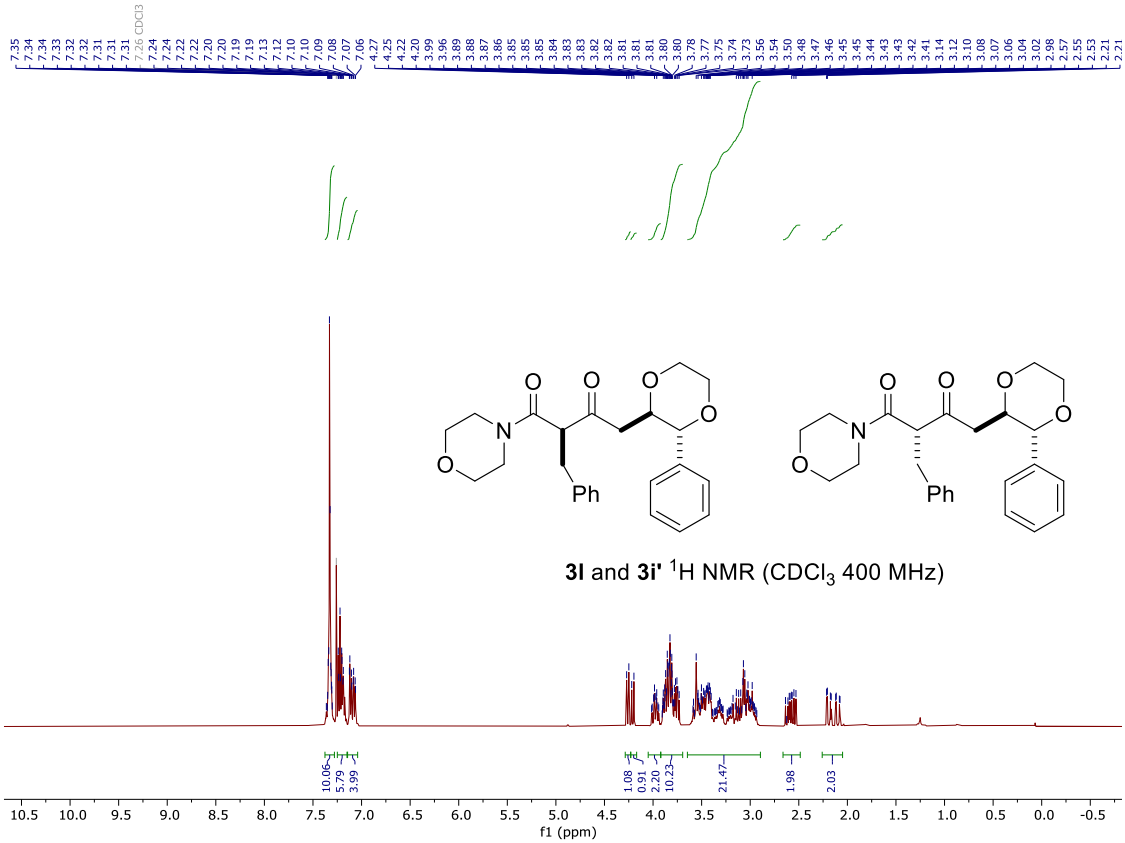




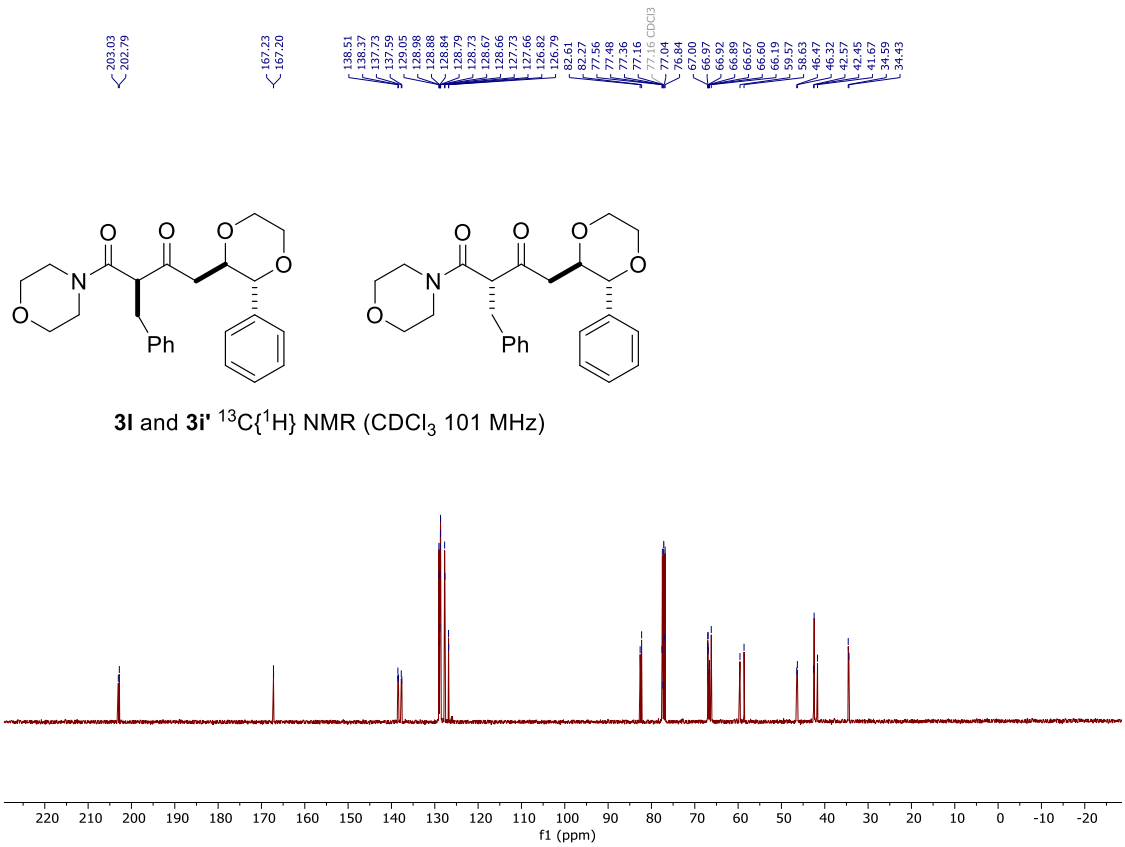
3j ^{13}C{^{1}H} NMR (Methanol-d_4 126 MHz)


Me Me
3k 1H NMR (CDCl3 400 MHz)
f1 (ppm)

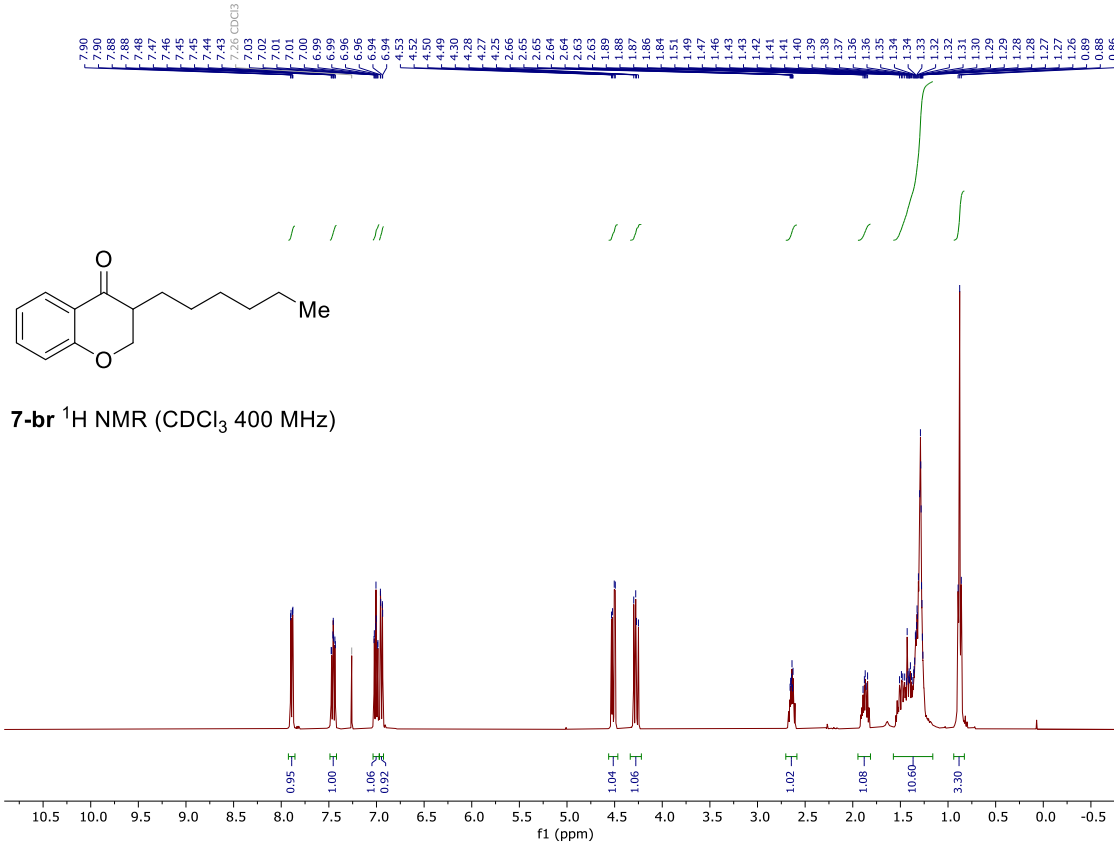

Me Me
3k 13C{1H} NMR (CDCl3 101 MHz)
f1 (ppm)



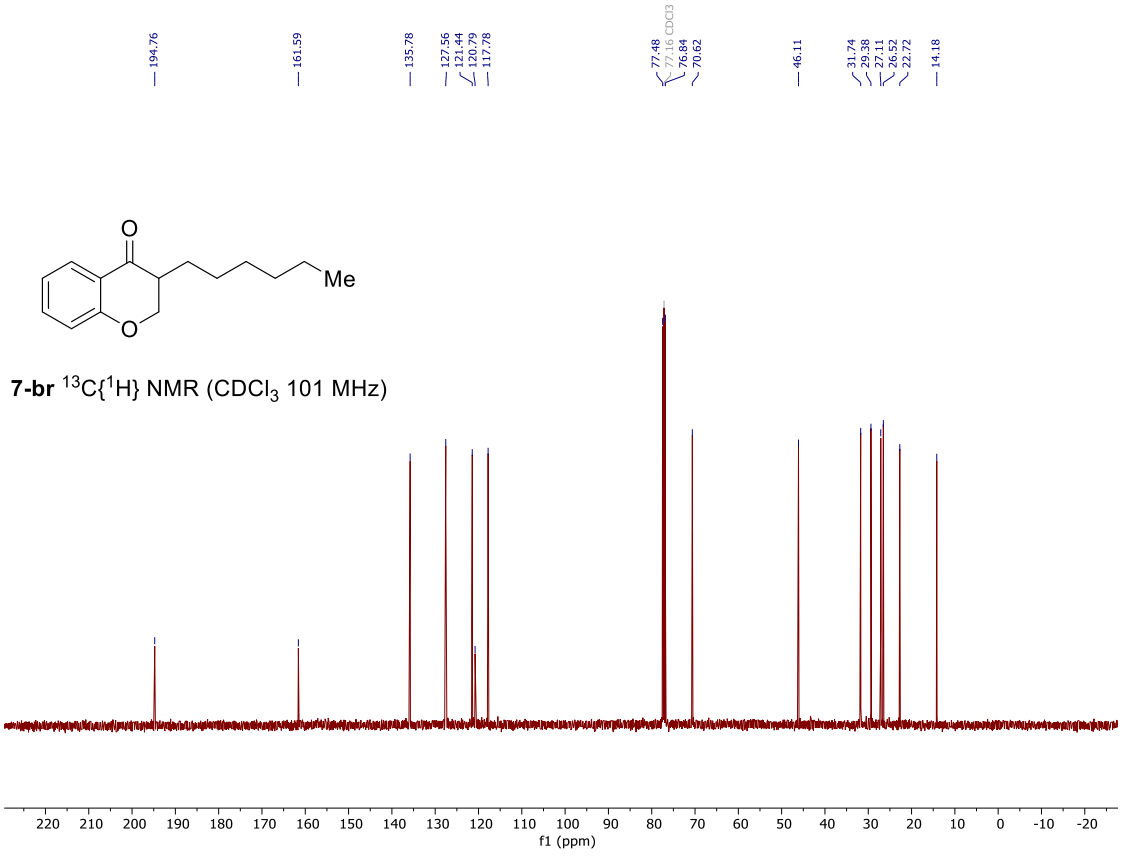
3l and **3i'** ^{1}H NMR ($CDCl_3$ 400 MHz)



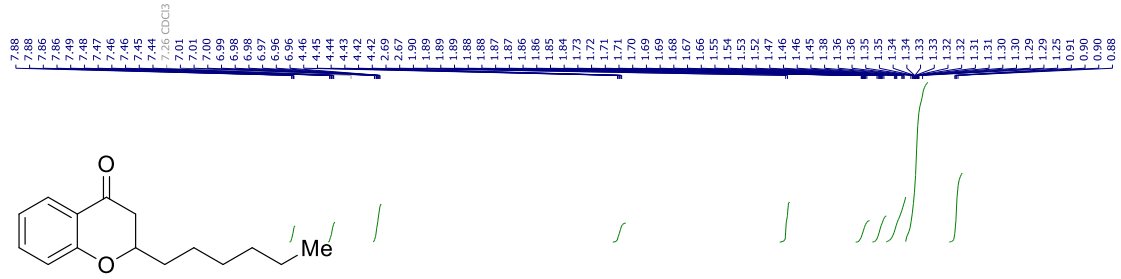
3l and **3i'** $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



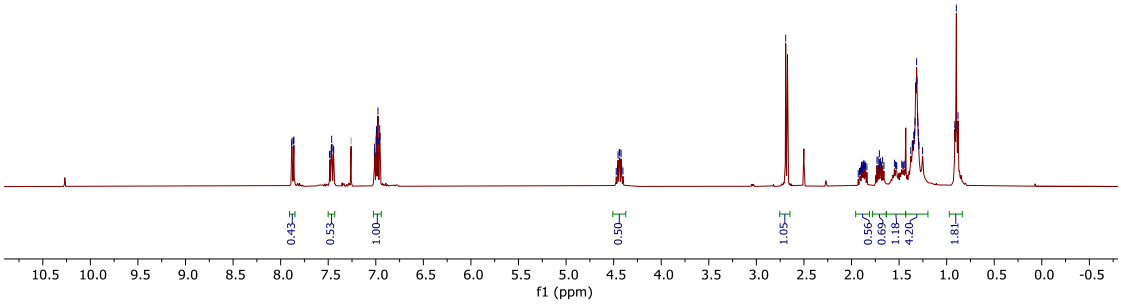
7-br ^{1}H NMR ($CDCl_3$ 400 MHz)

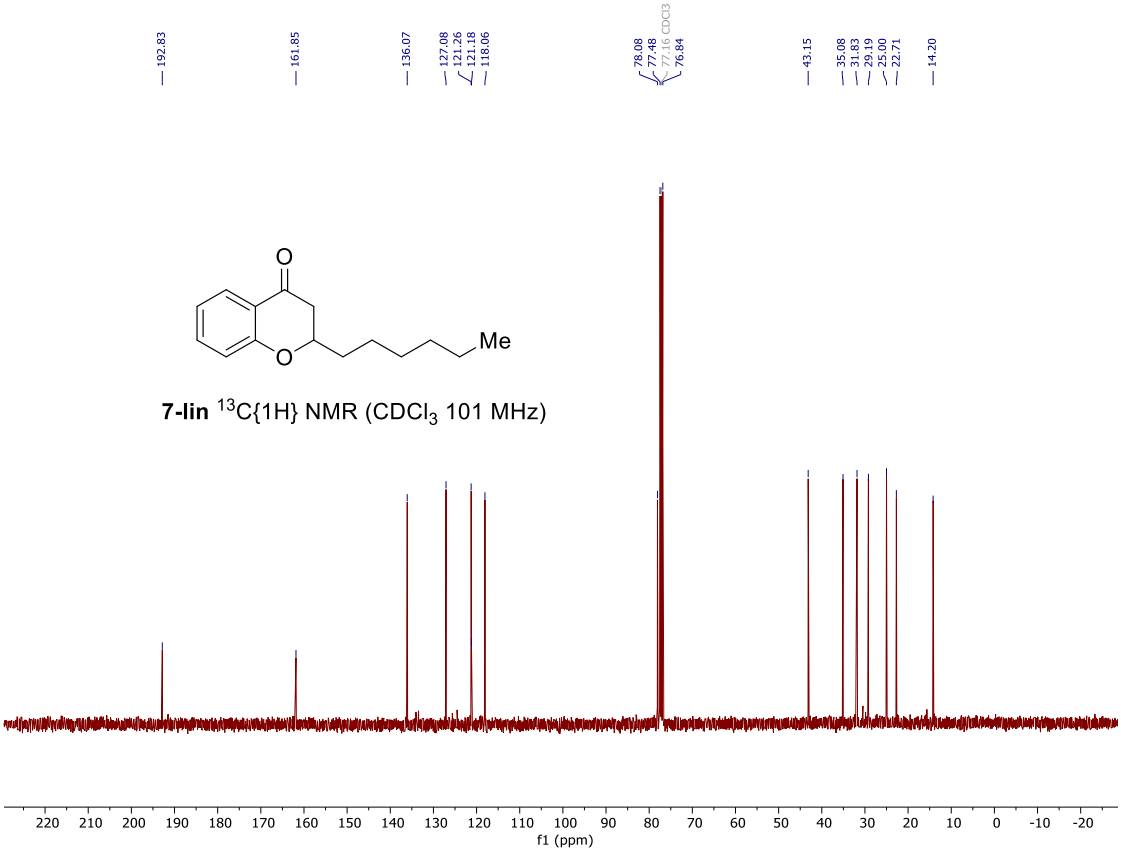


7-br $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

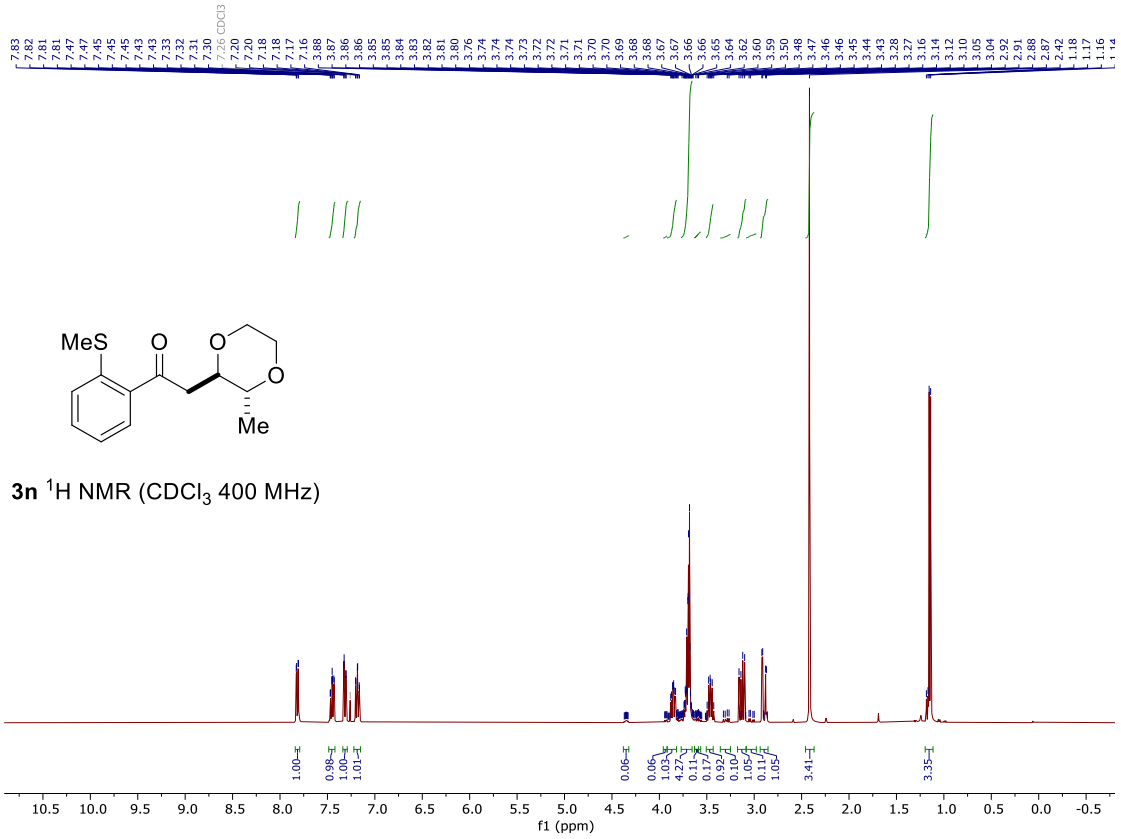


7-lin ^{1}H NMR ($CDCl_3$ 400 MHz)

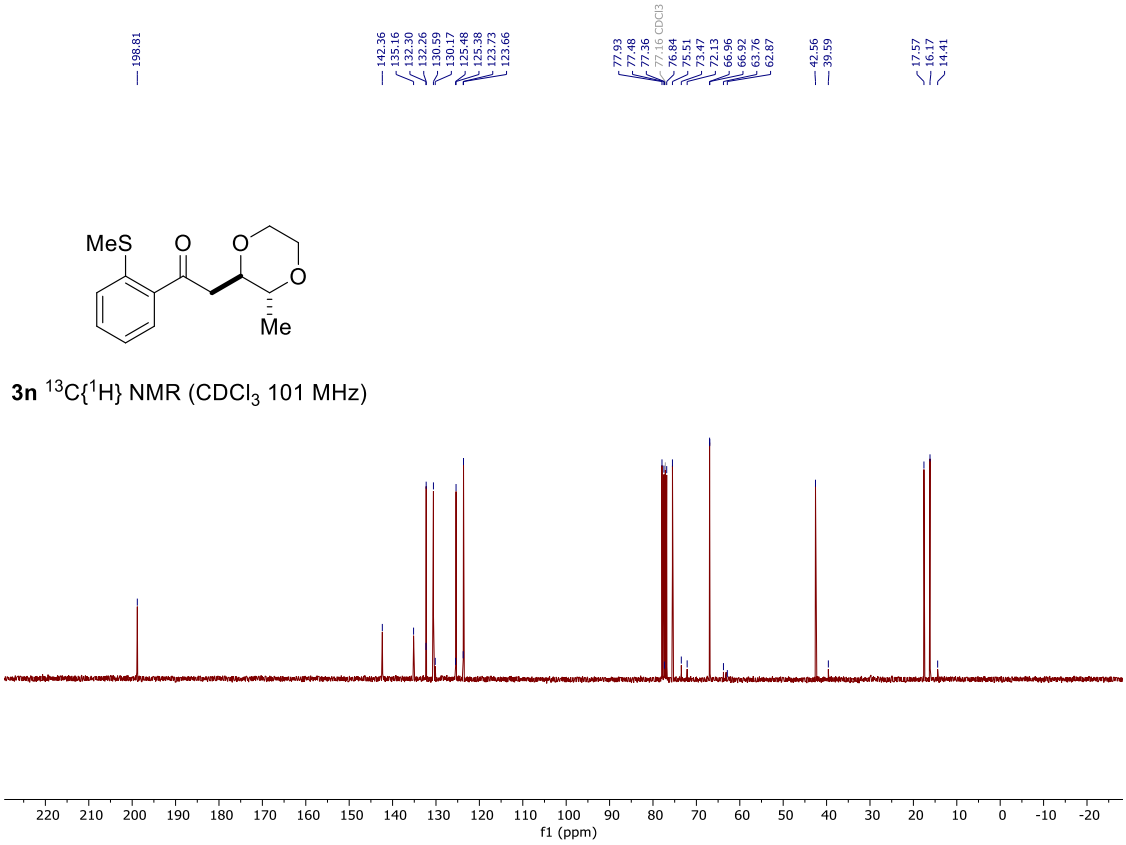




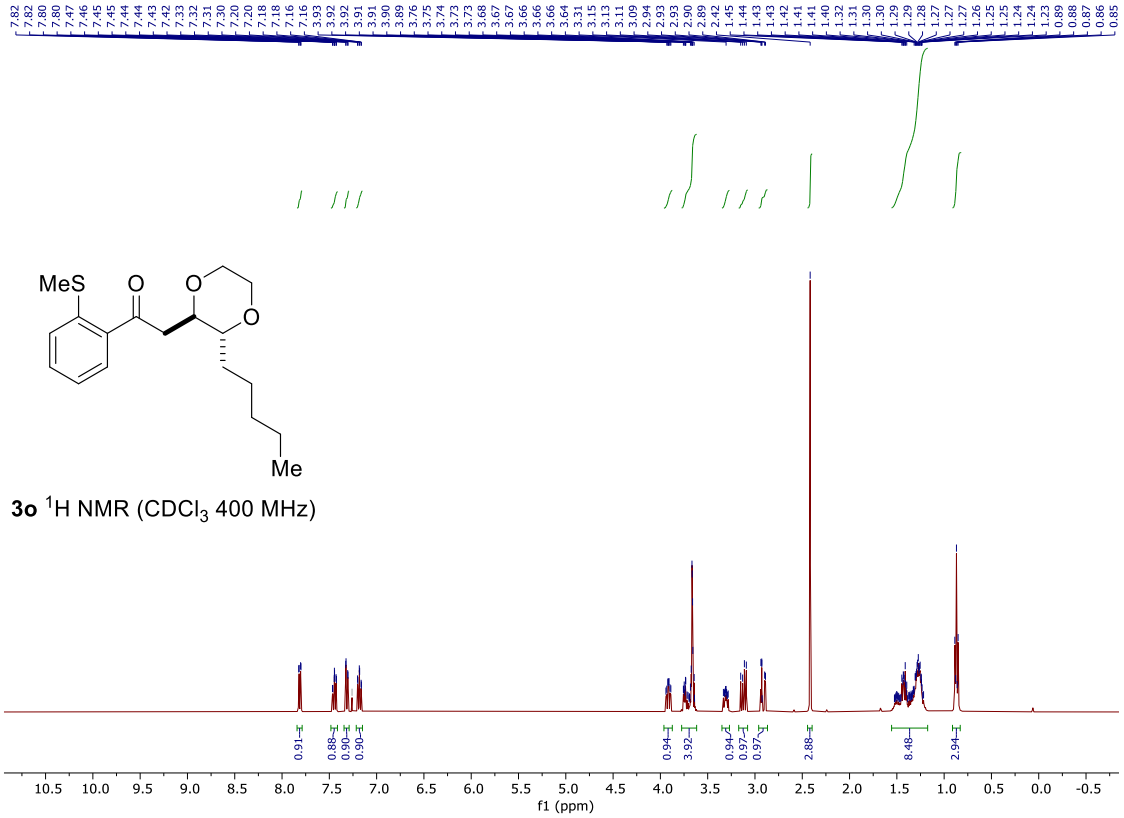
7-lin ^{13}C{1H} NMR ($CDCl_3$ 101 MHz)



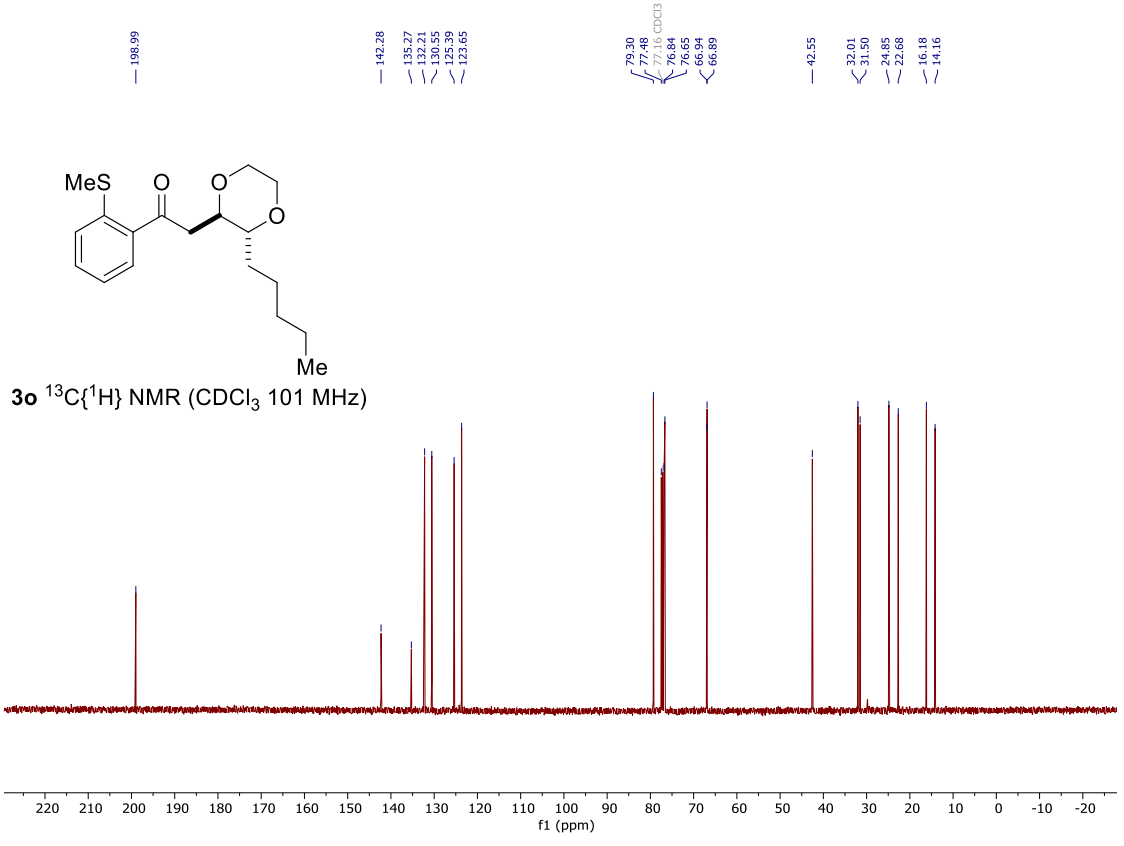
3n ^{1}H NMR ($CDCl_3$ 400 MHz)



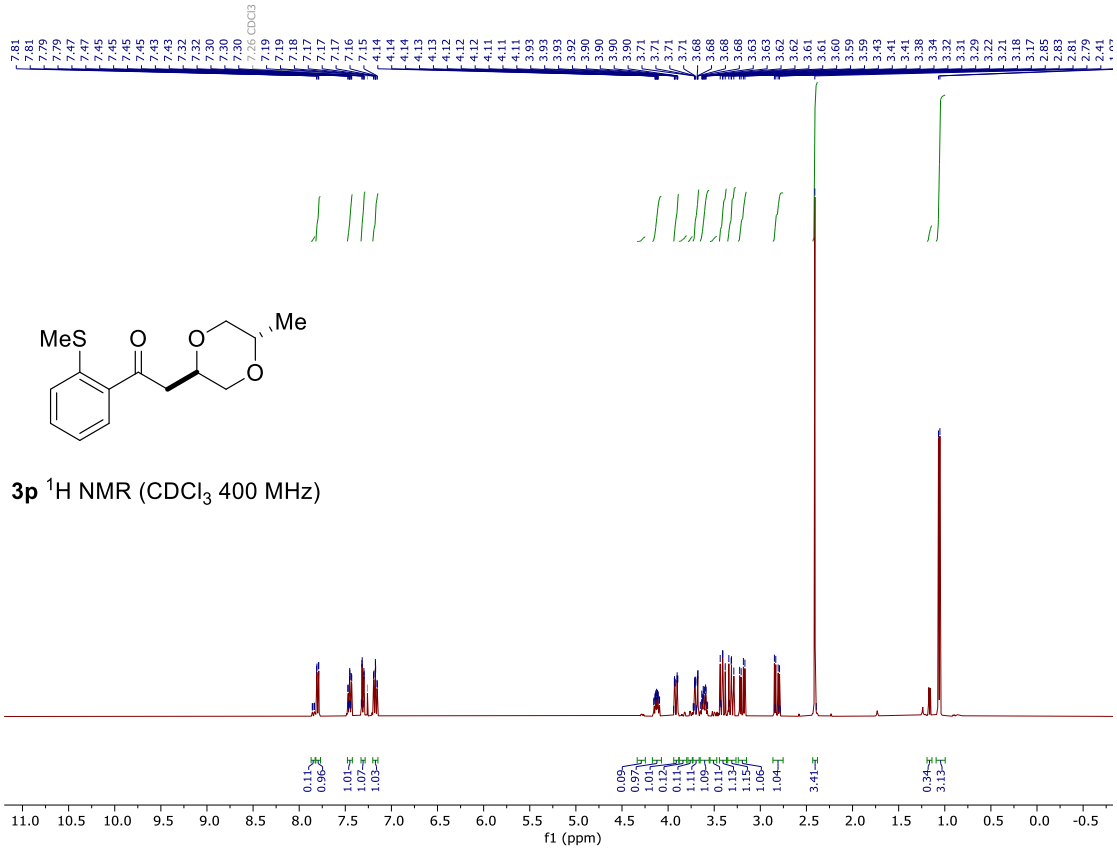
3n $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



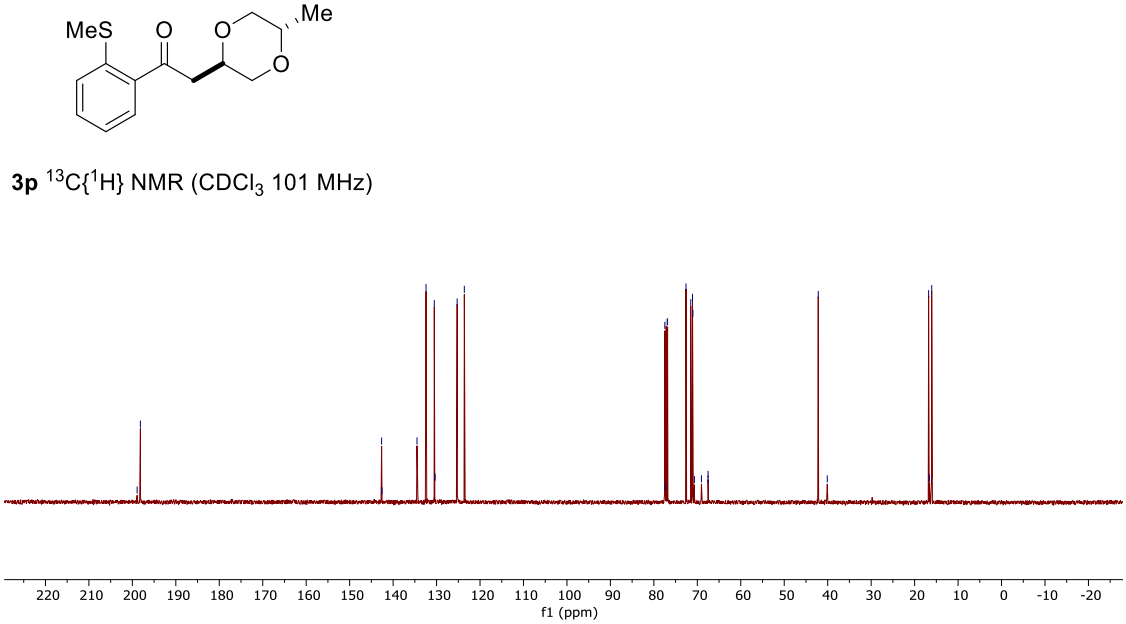
3o ^{1}H NMR ($CDCl_3$ 400 MHz)



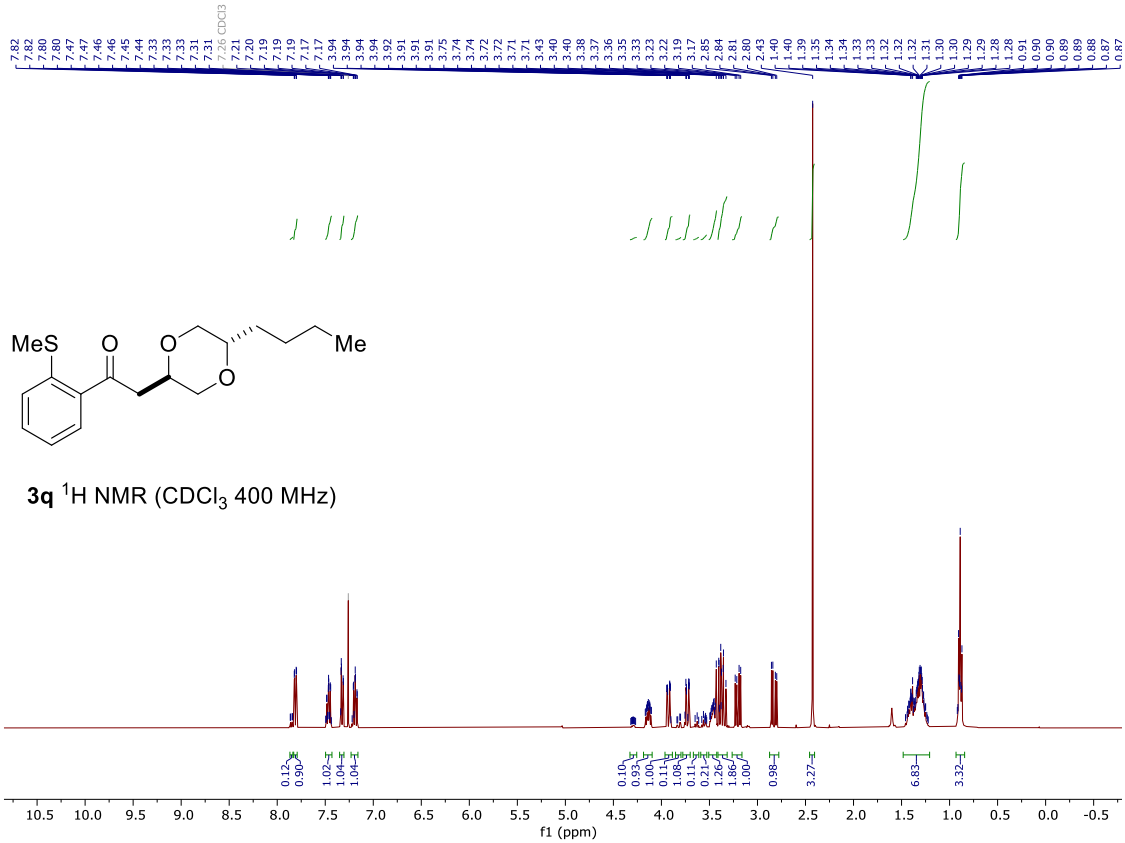
3o $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



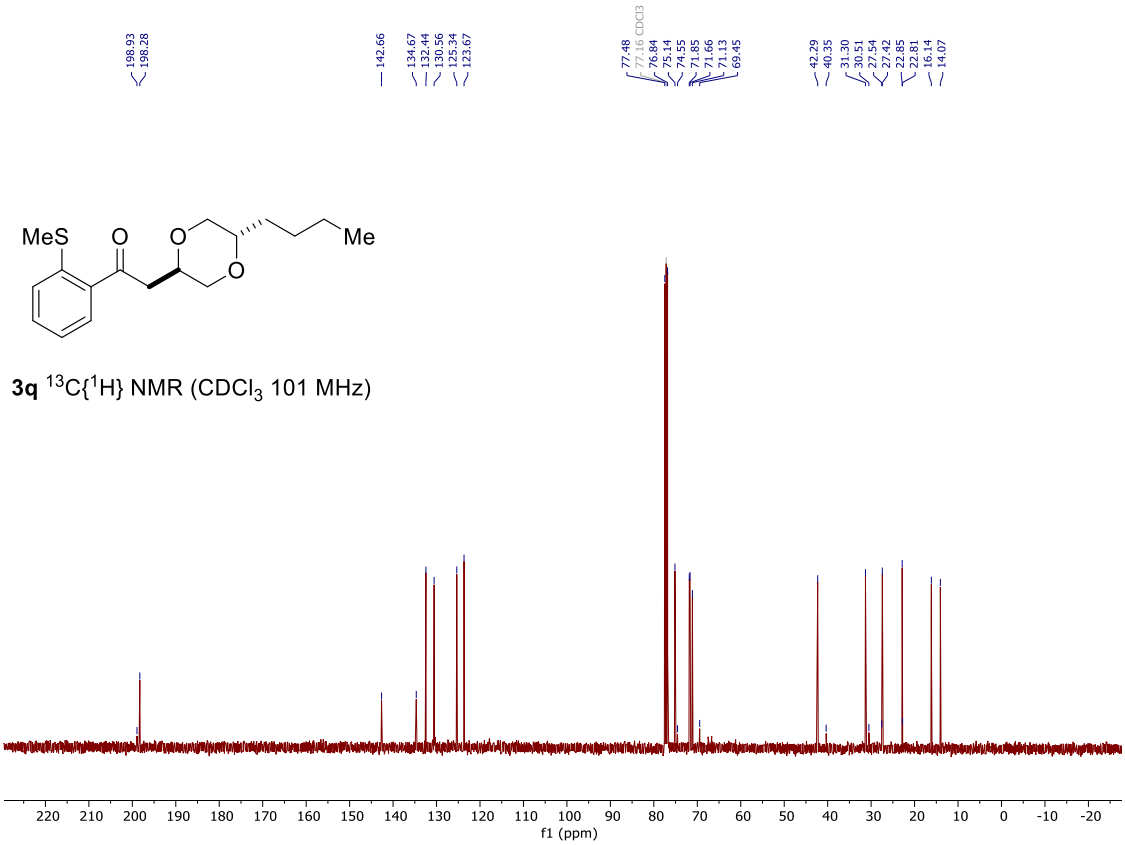
3p ^{1}H NMR ($CDCl_3$ 400 MHz)



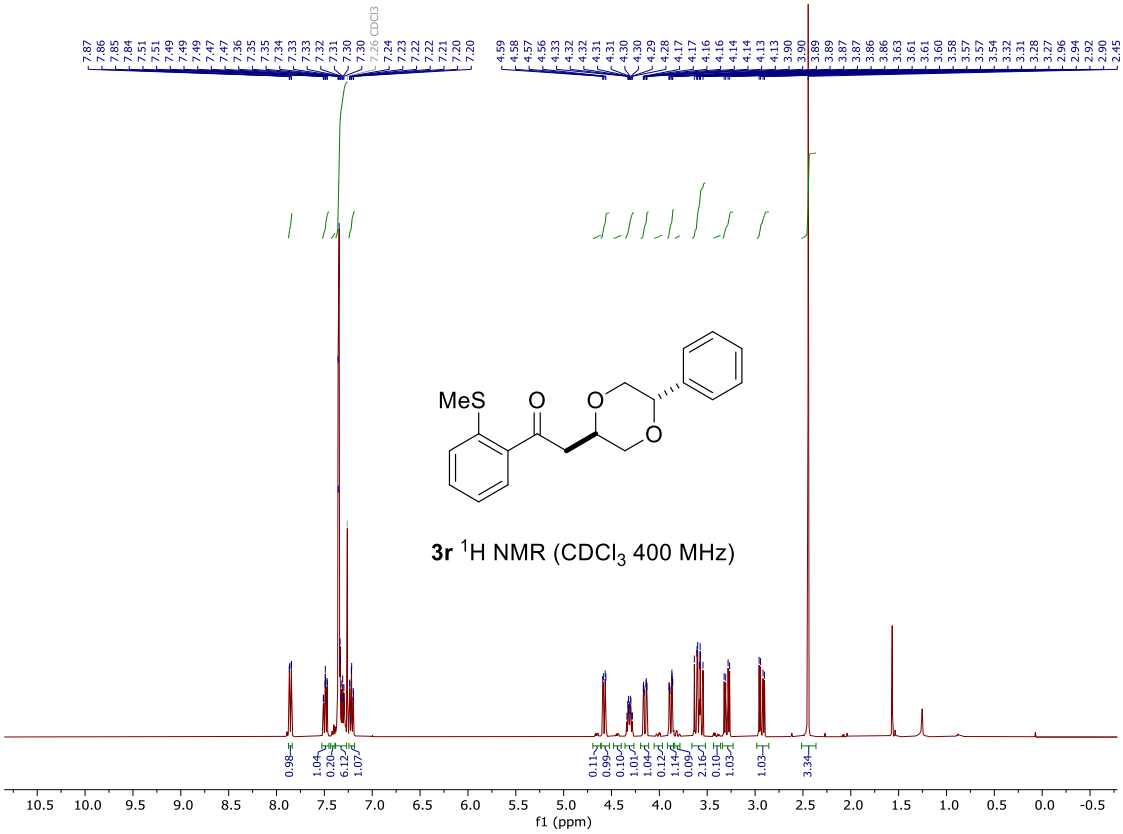
3p $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



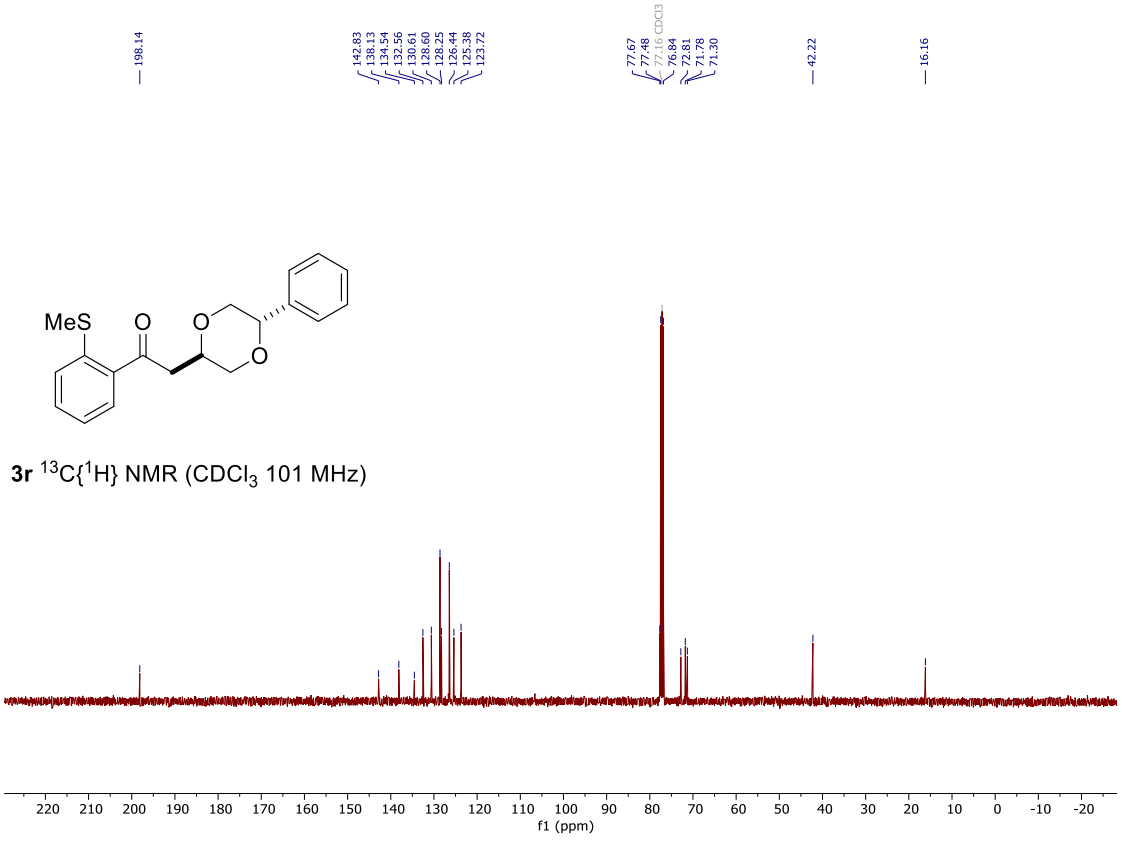
3q ^{1}H NMR ($CDCl_3$ 400 MHz)



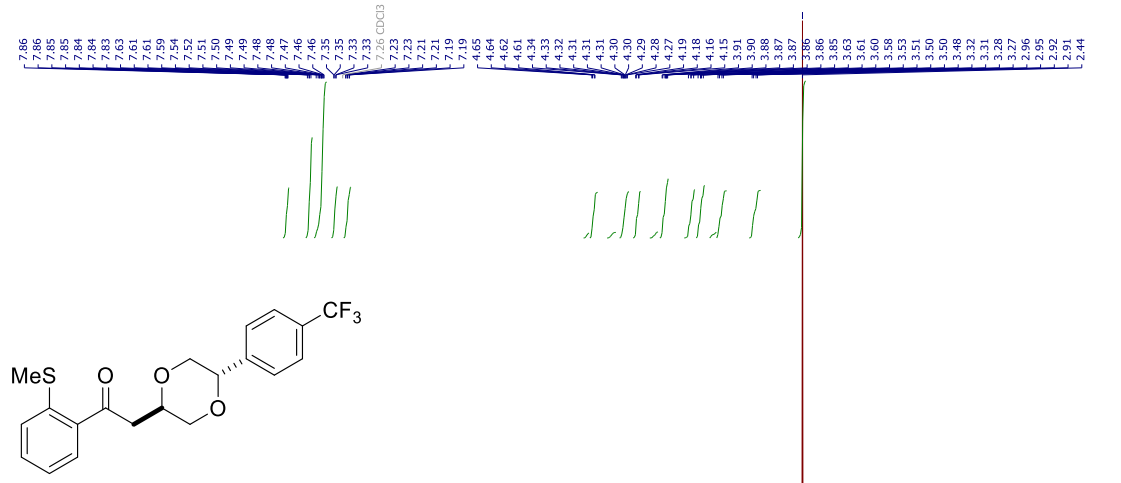
3q $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



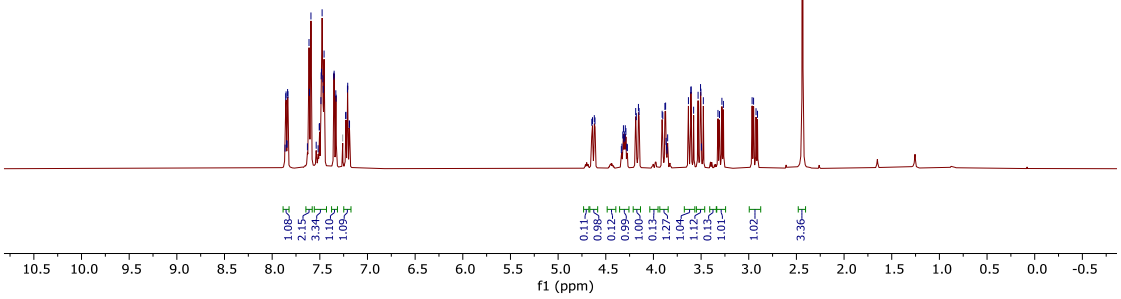
3r ^{1}H NMR ($CDCl_3$ 400 MHz)

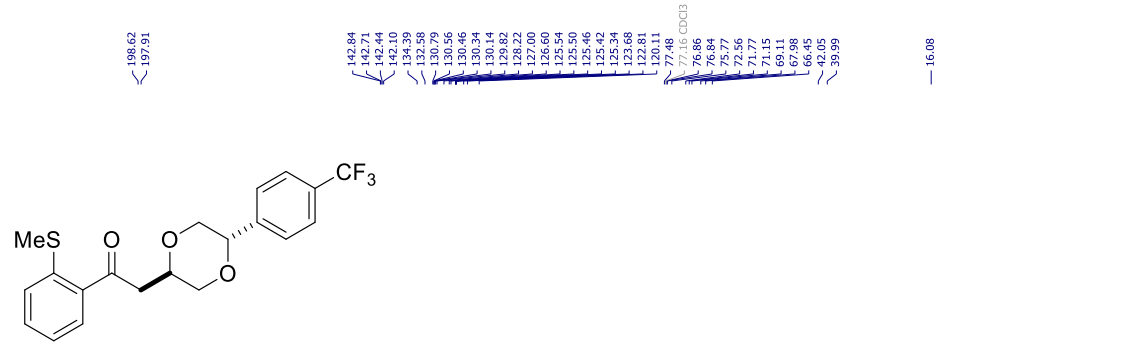


3r $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

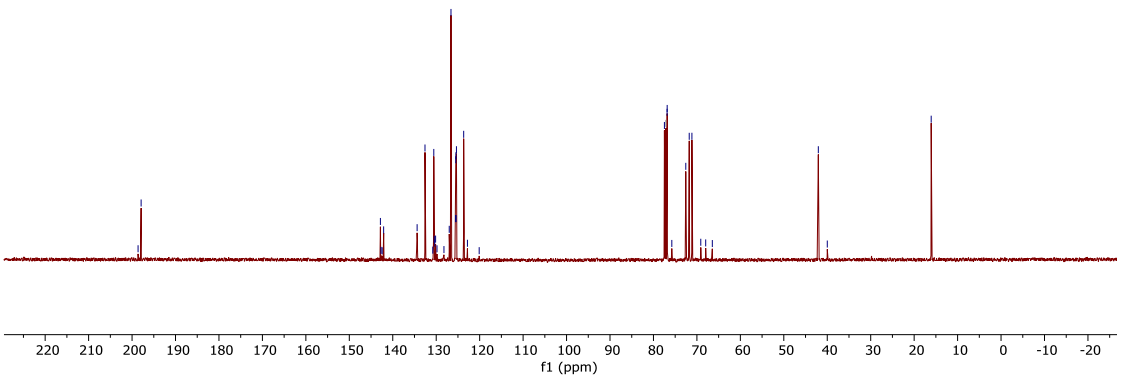


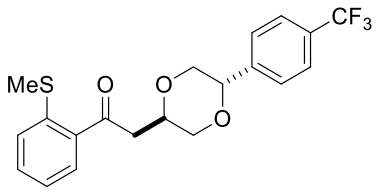
3s ^{1}H NMR ($CDCl_3$ 400 MHz)



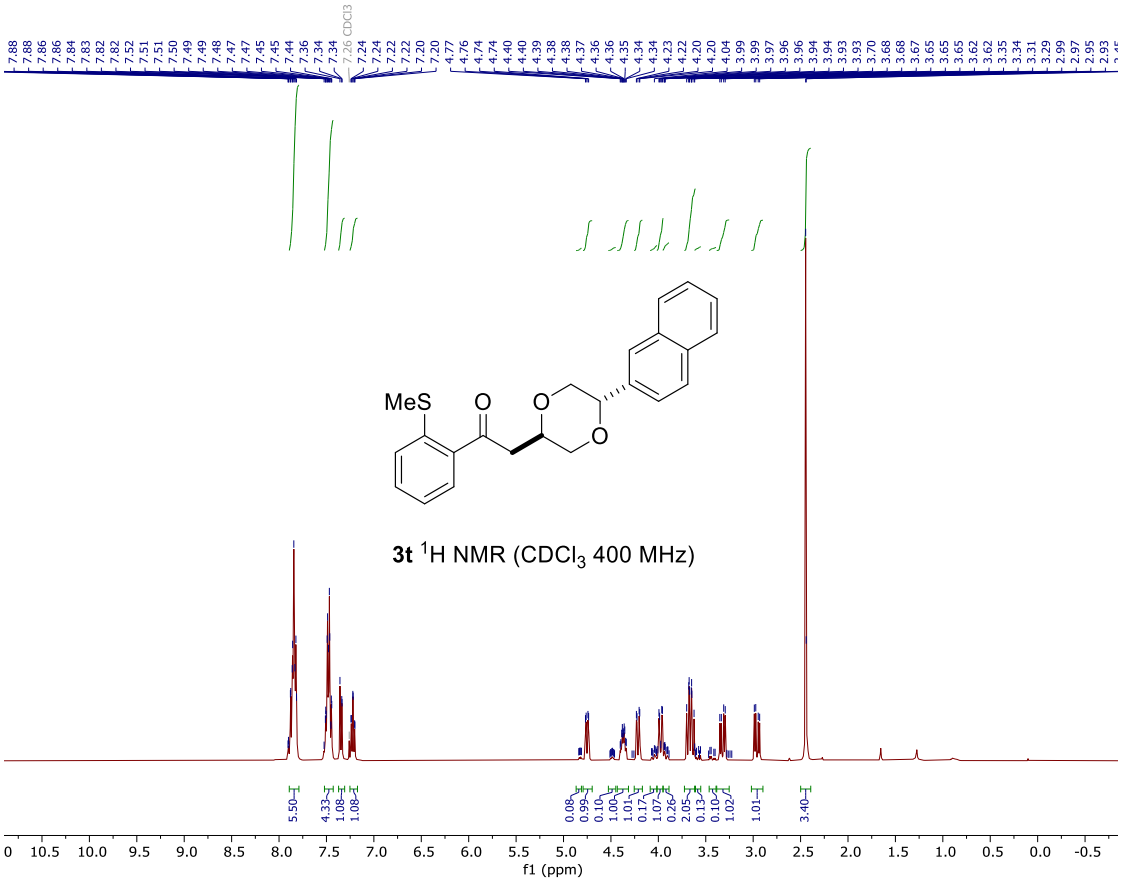


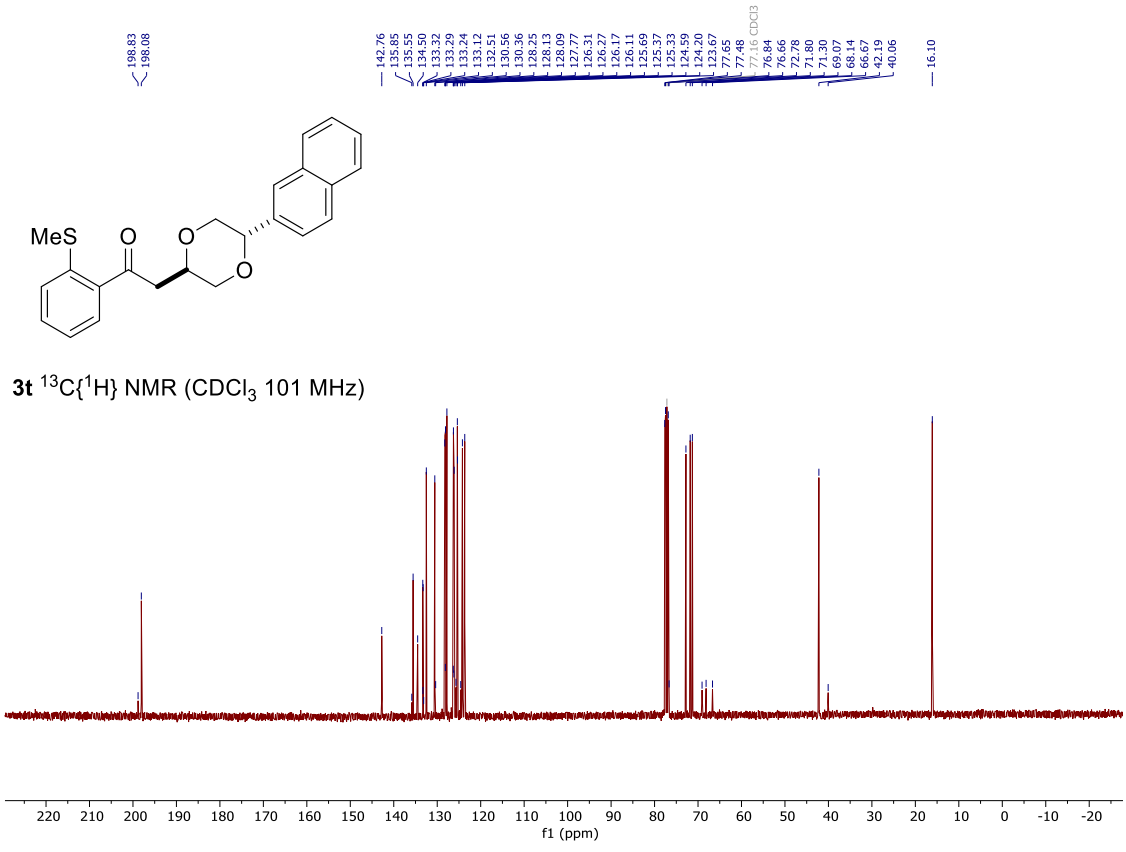
3s $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

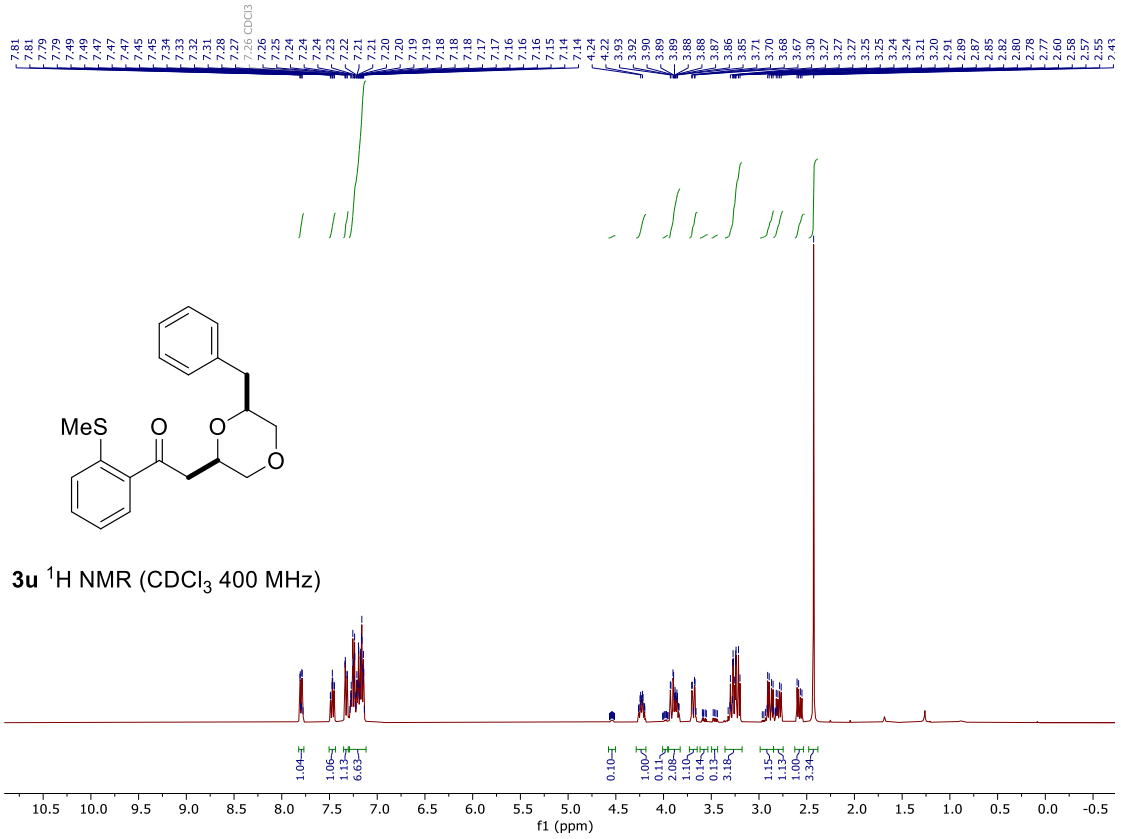




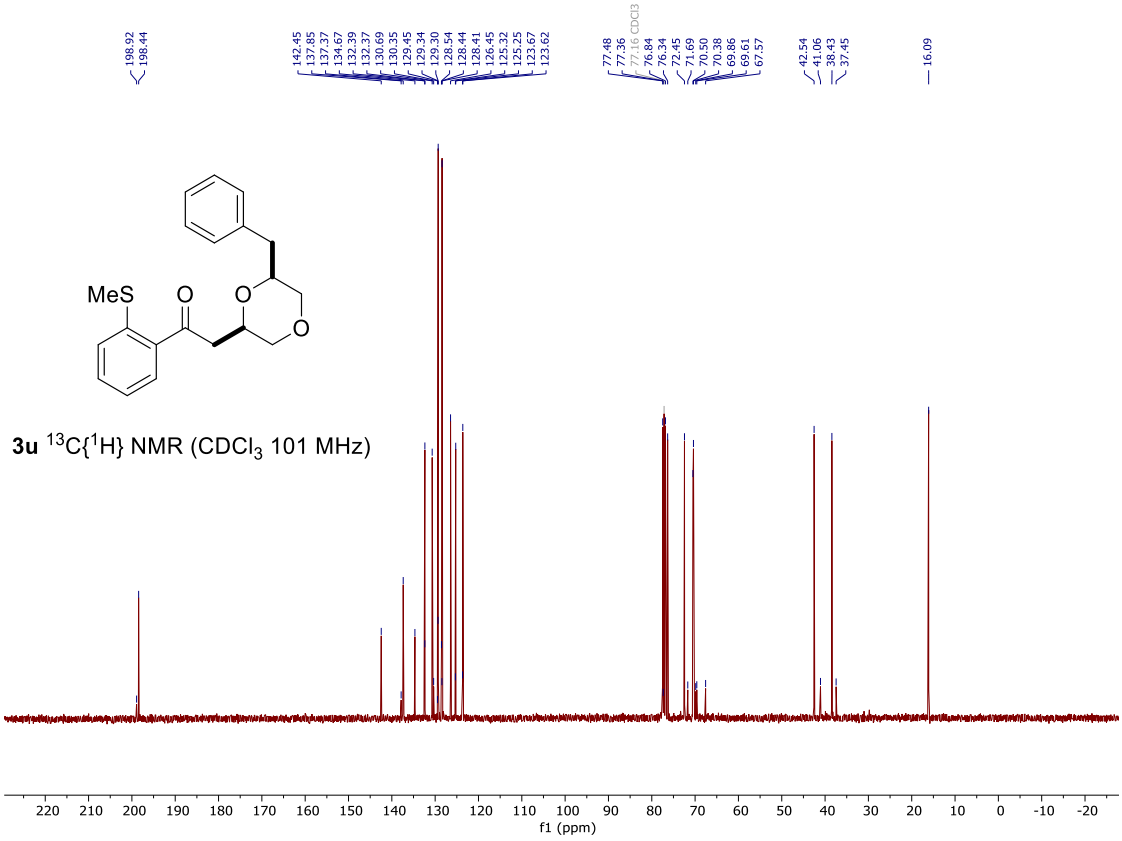
3s $^{19}F\{^{1}H\}$ NMR ($CDCl_3$ 377 MHz)


MeS
O
O
O
3t ^{1}H NMR ($CDCl_3$ 400 MHz)
f1 (ppm)

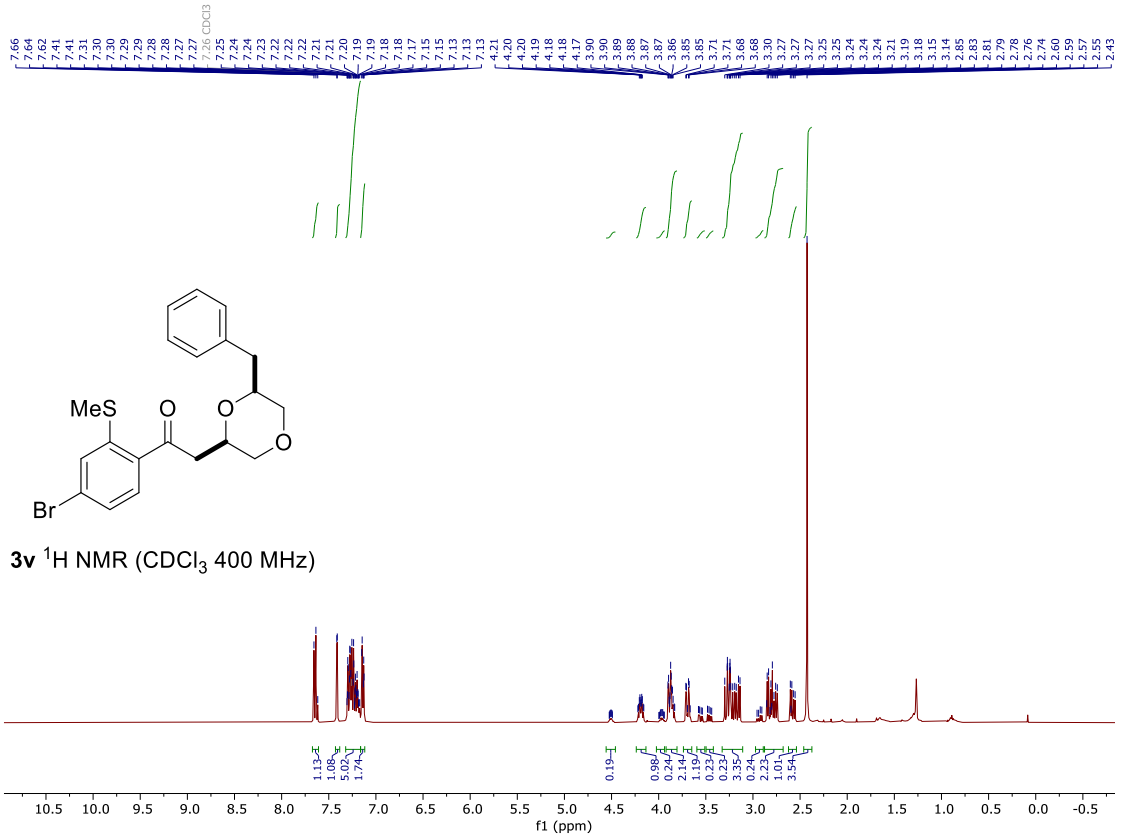

MeS
O
O
O
3t ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)
f1 (ppm)



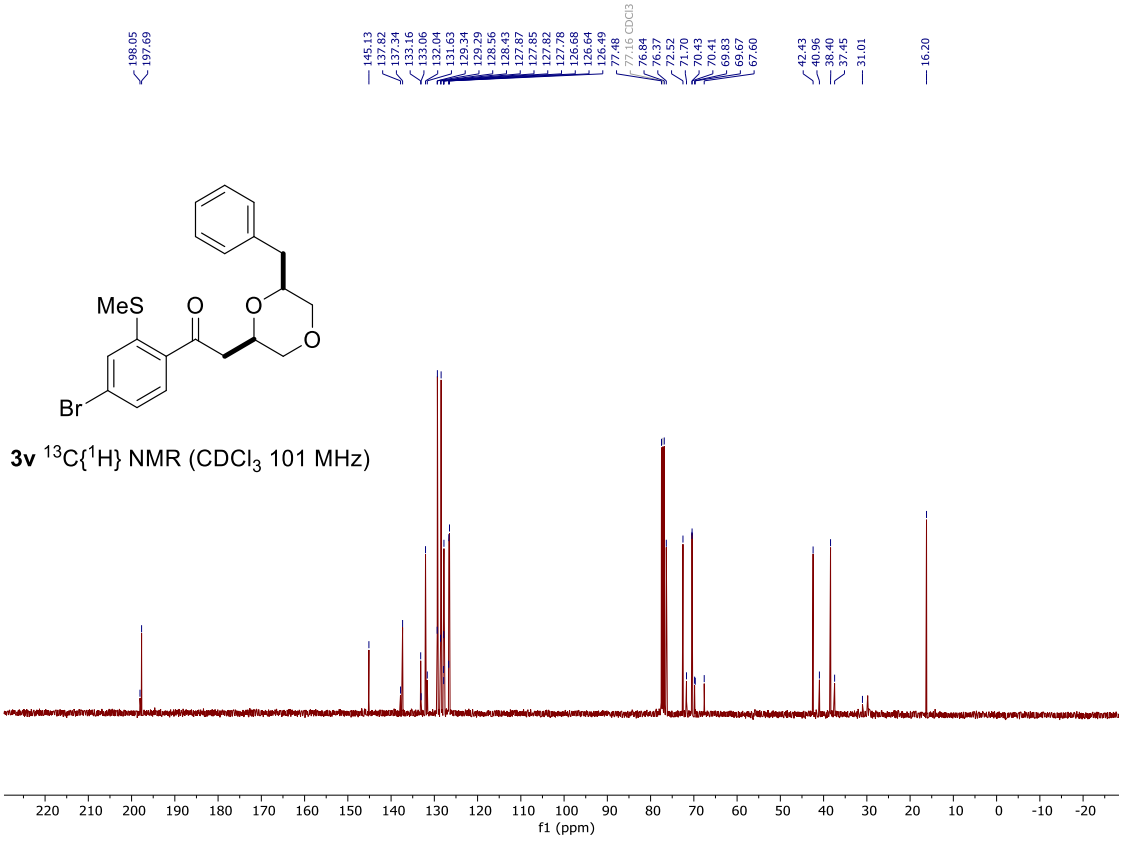
3u ^{1}H NMR ($CDCl_3$ 400 MHz)



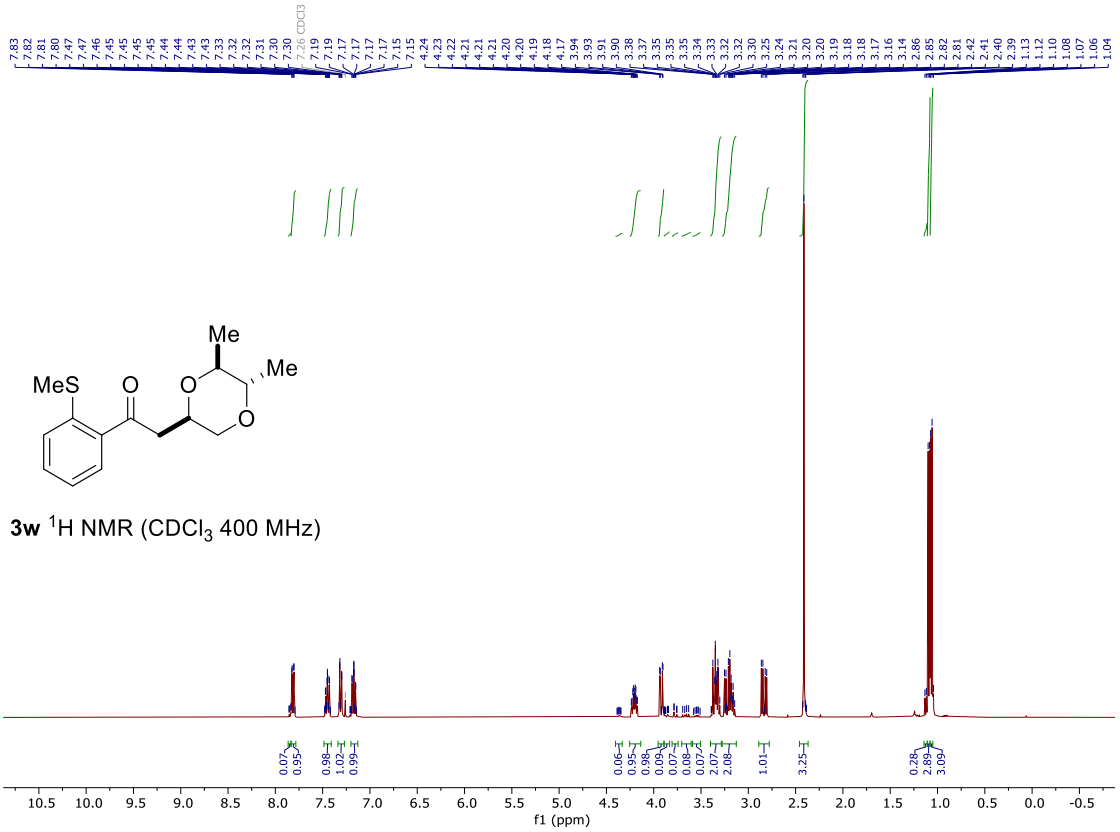
3u $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



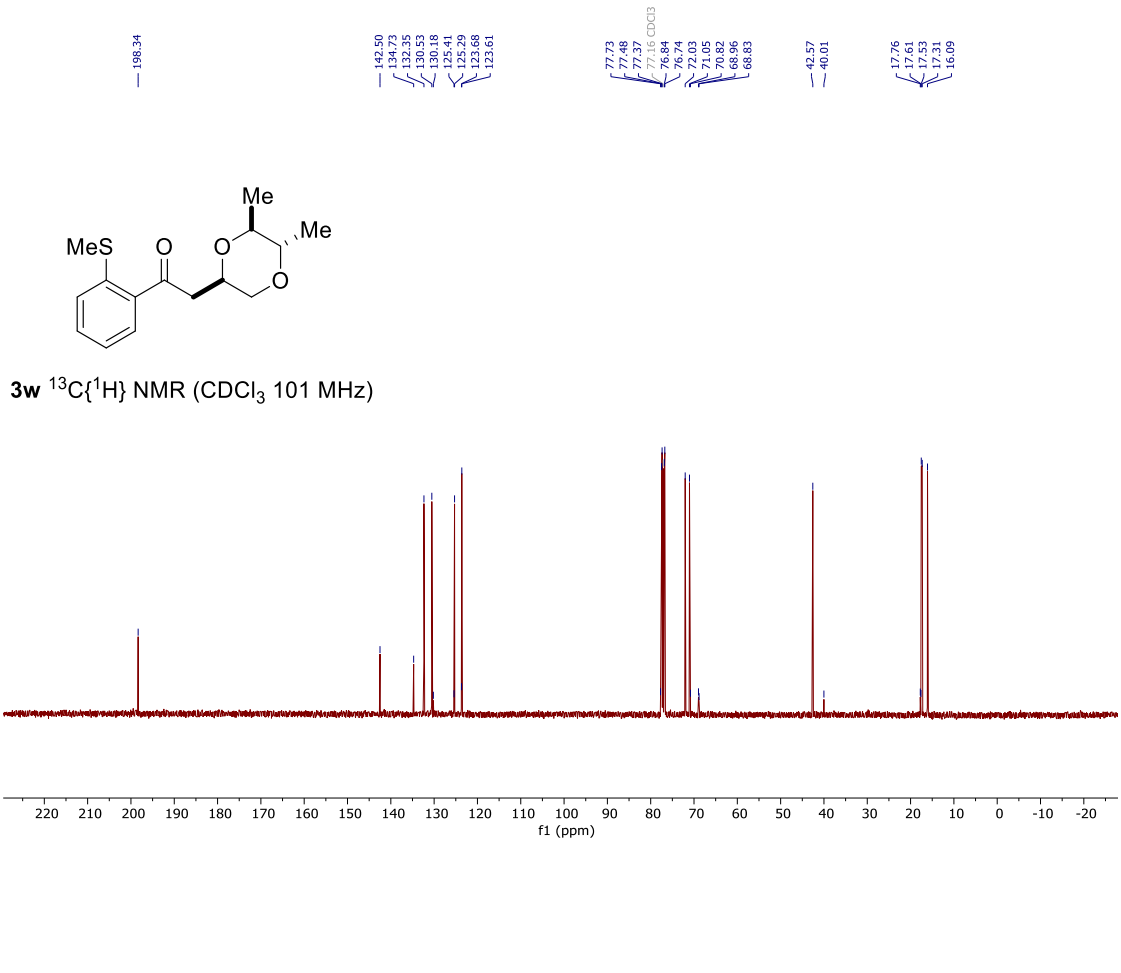
3v ^{1}H NMR ($CDCl_3$ 400 MHz)



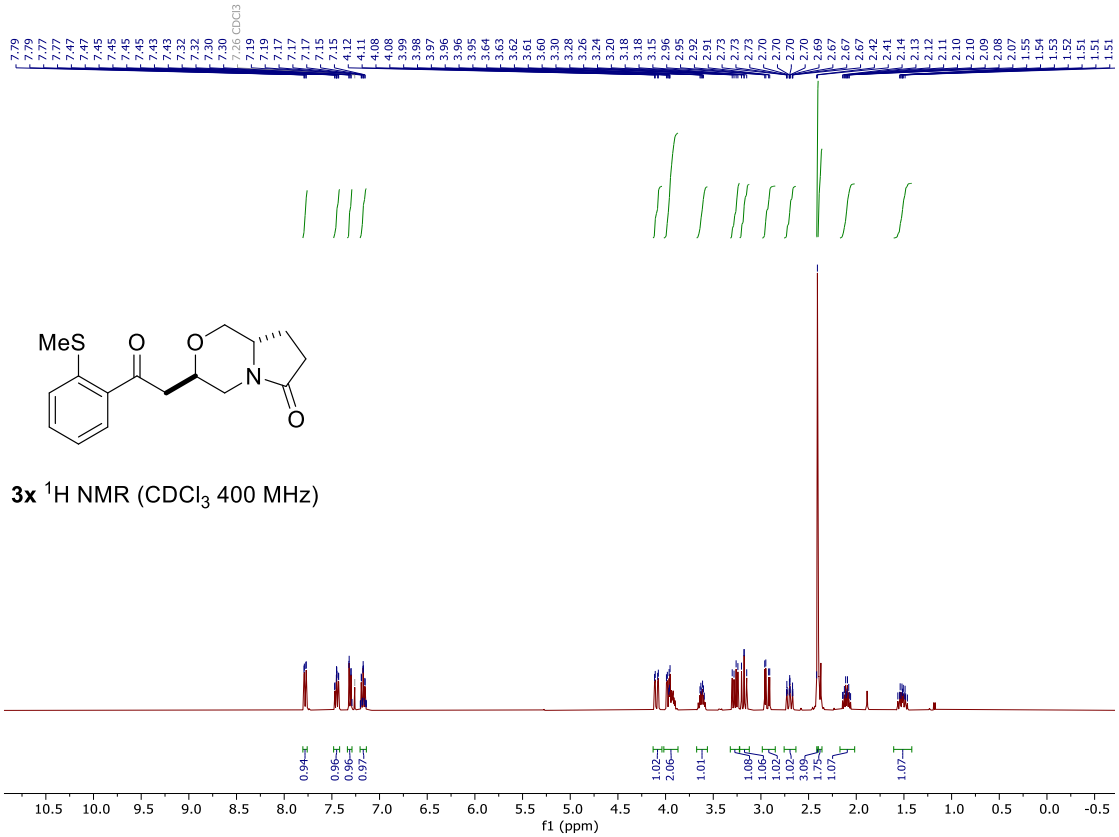
3v $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



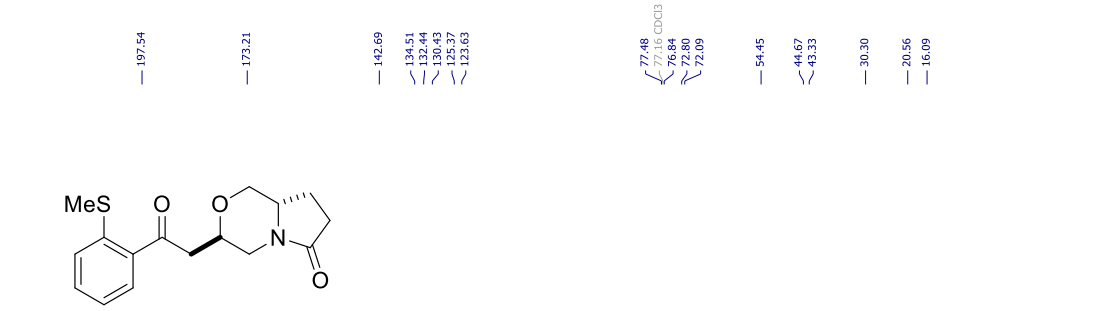
3w ^{1}H NMR ($CDCl_3$ 400 MHz)



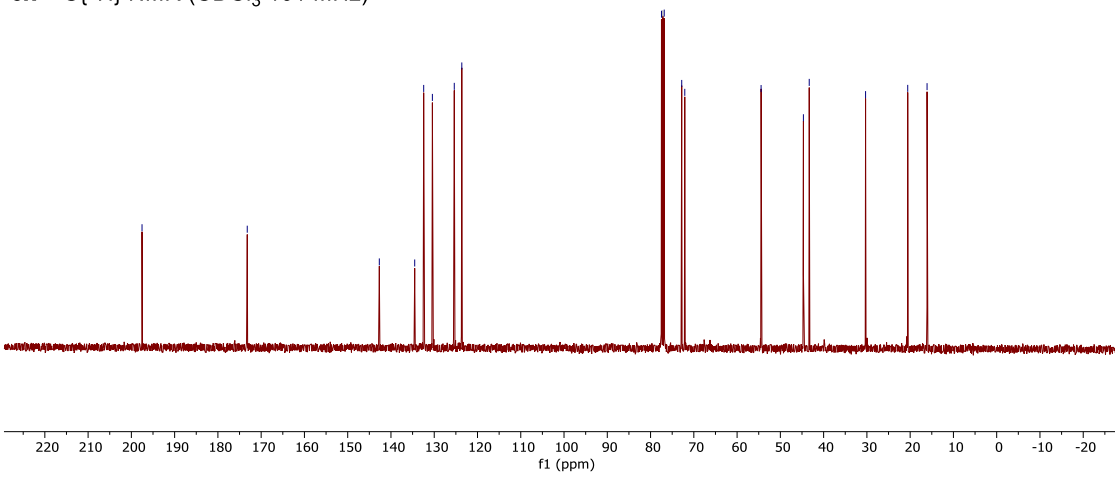
3w $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

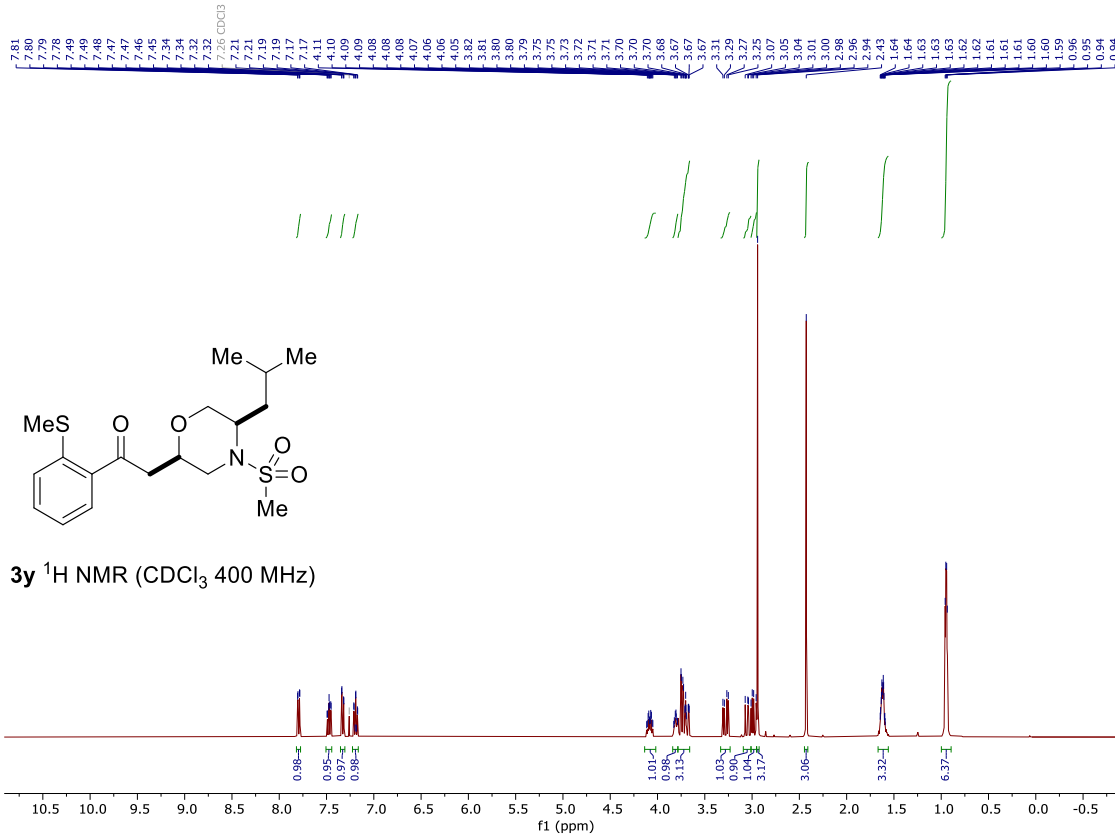


3x ^{1}H NMR ($CDCl_3$ 400 MHz)

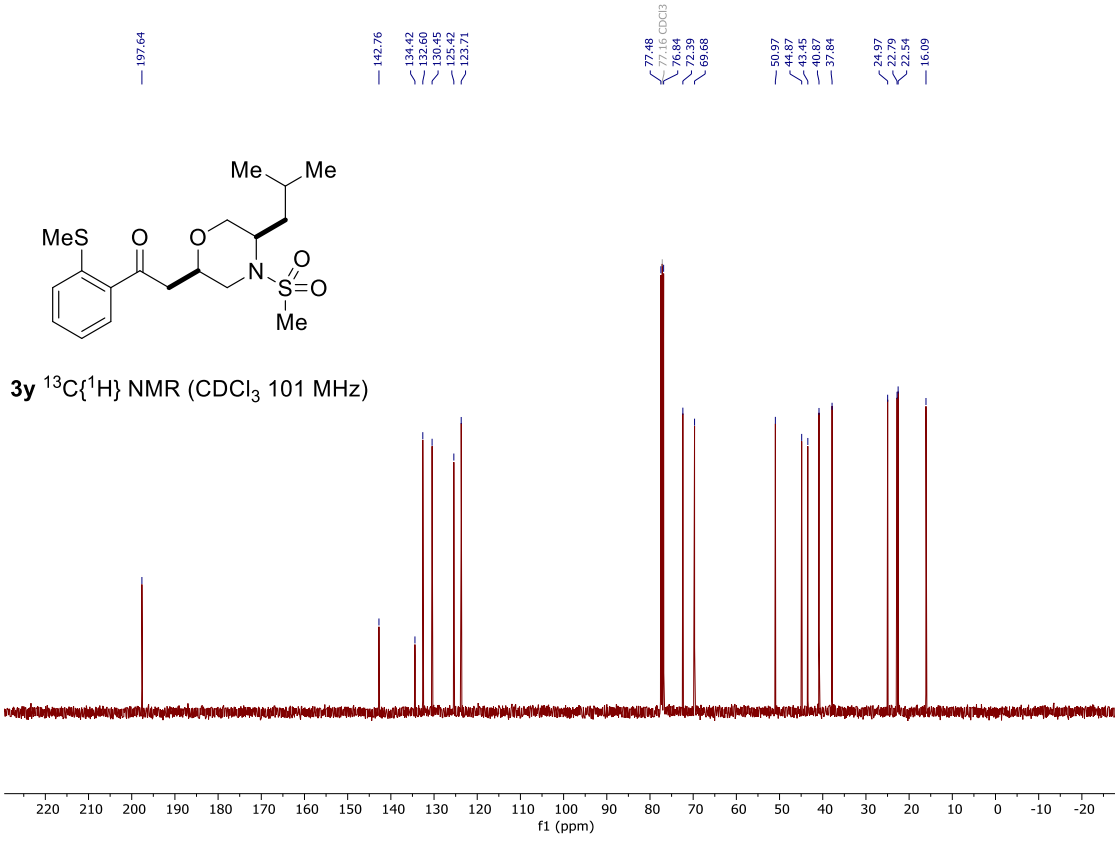


3x $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

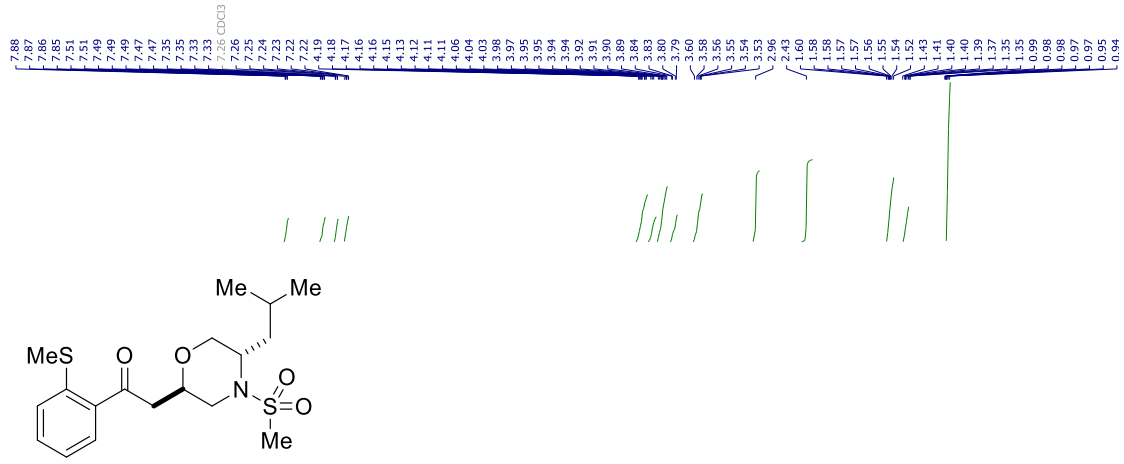




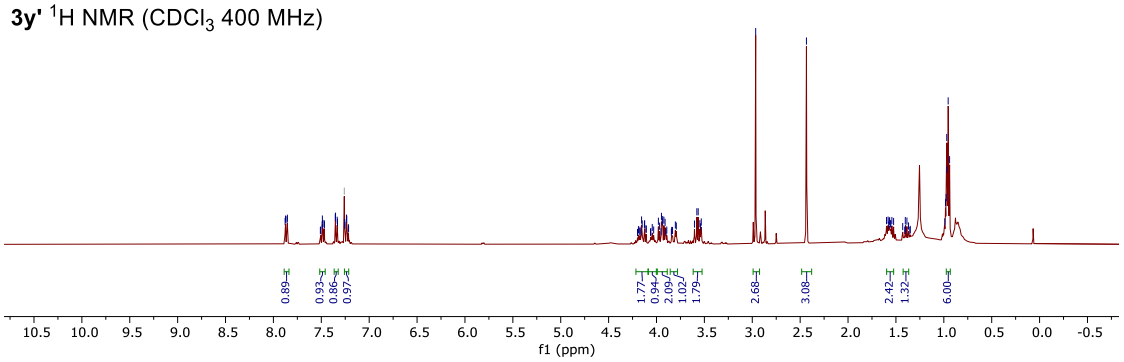
3y ^{1}H NMR ($CDCl_3$ 400 MHz)

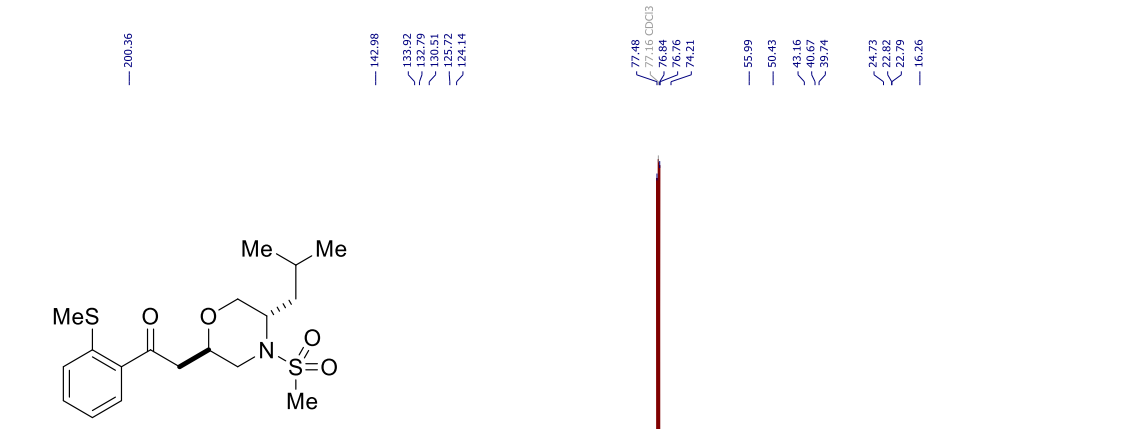


3y $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

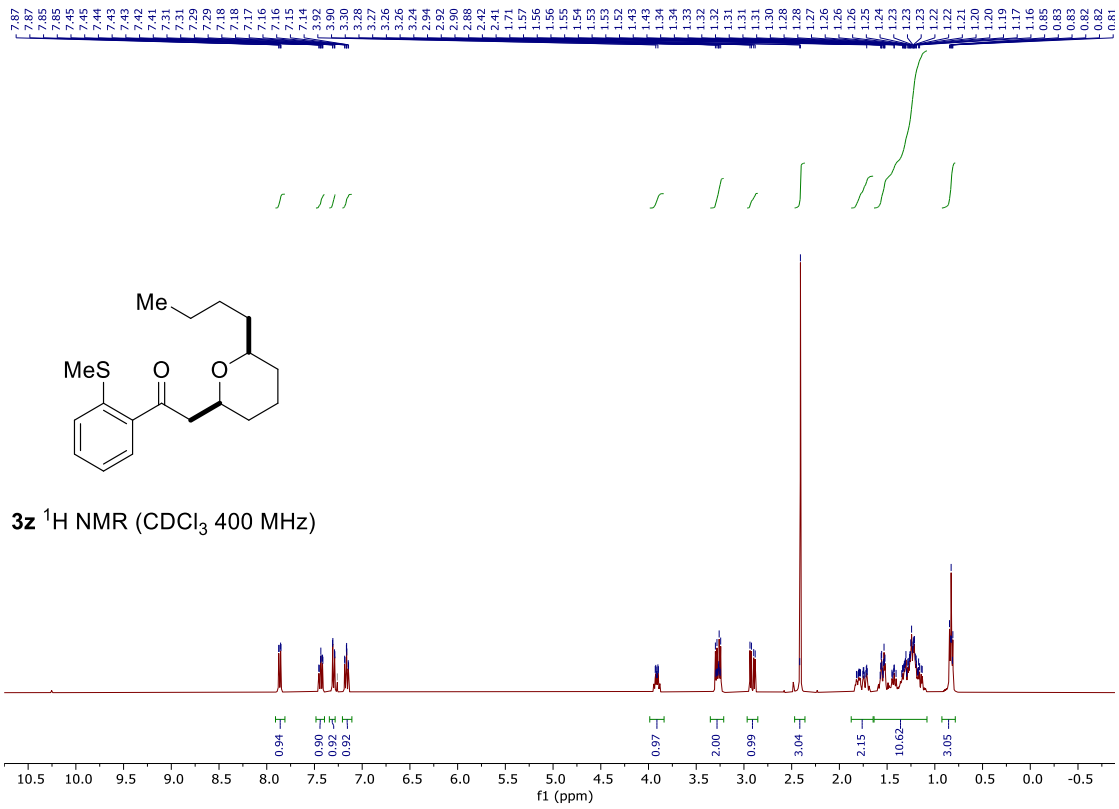


3y' ^{1}H NMR ($CDCl_3$ 400 MHz)

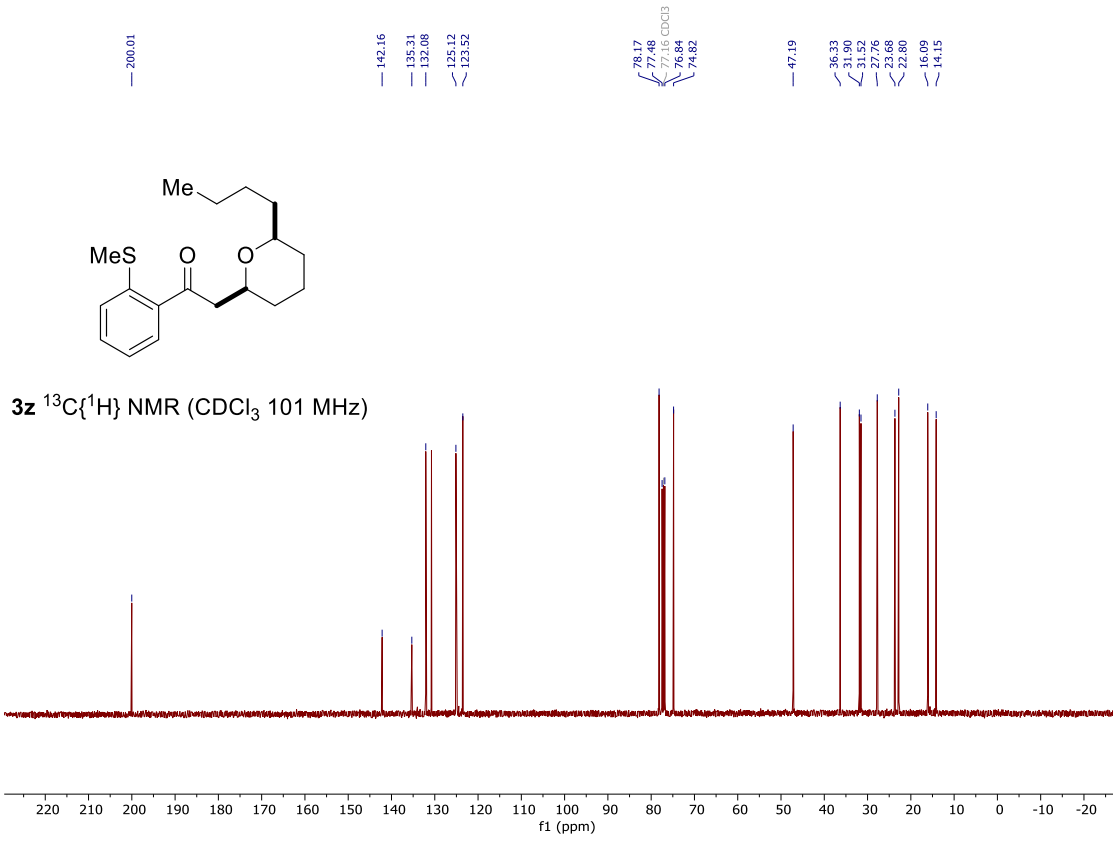




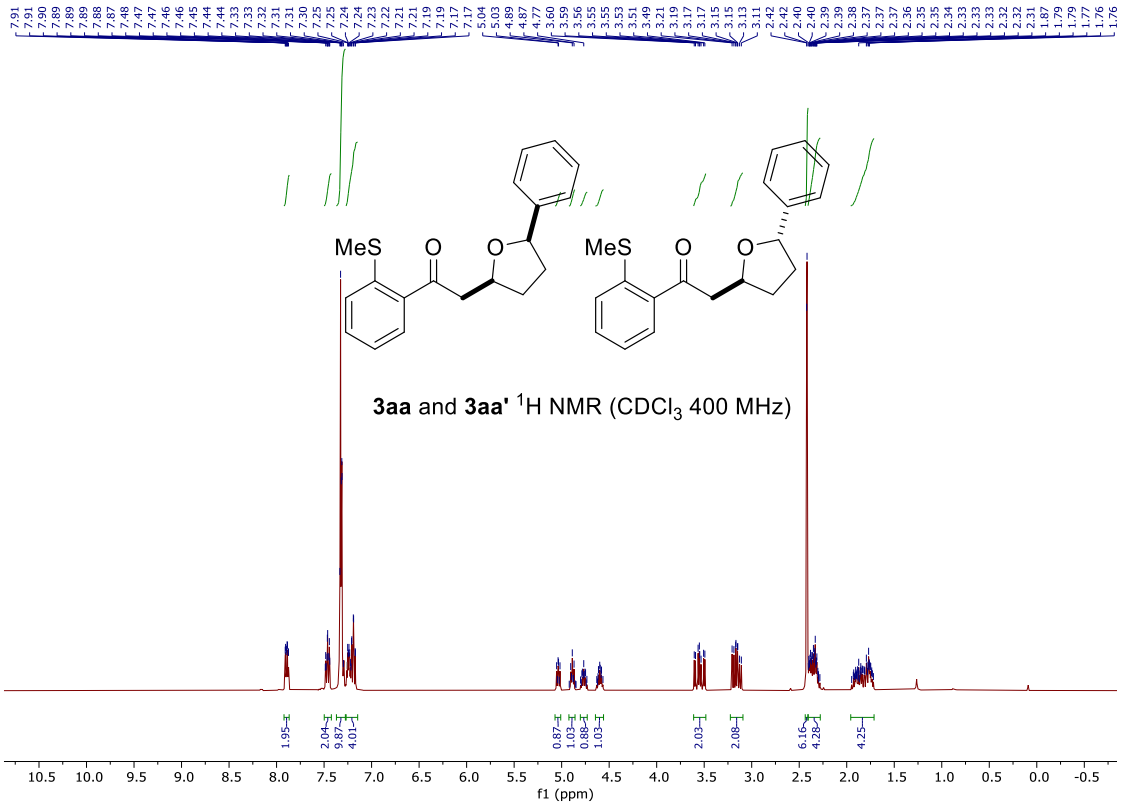
3y' $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



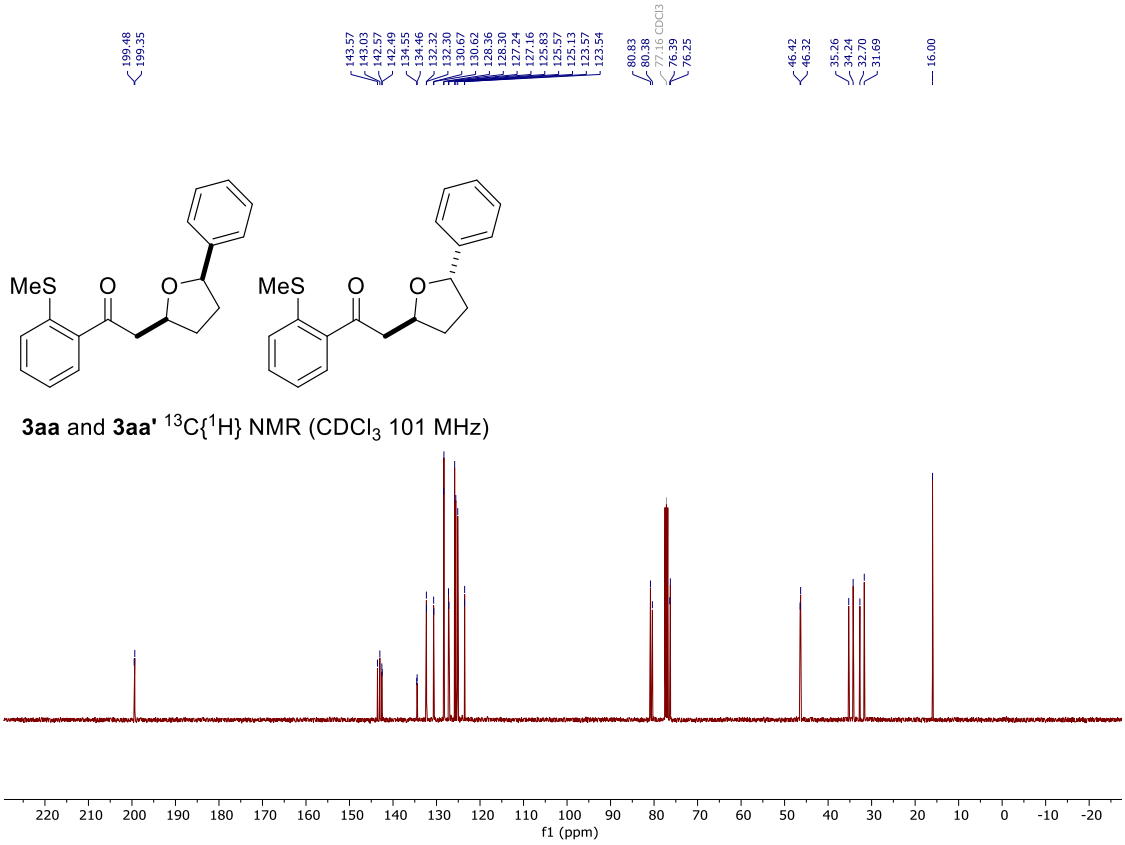
3z ^{1}H NMR ($CDCl_3$ 400 MHz)



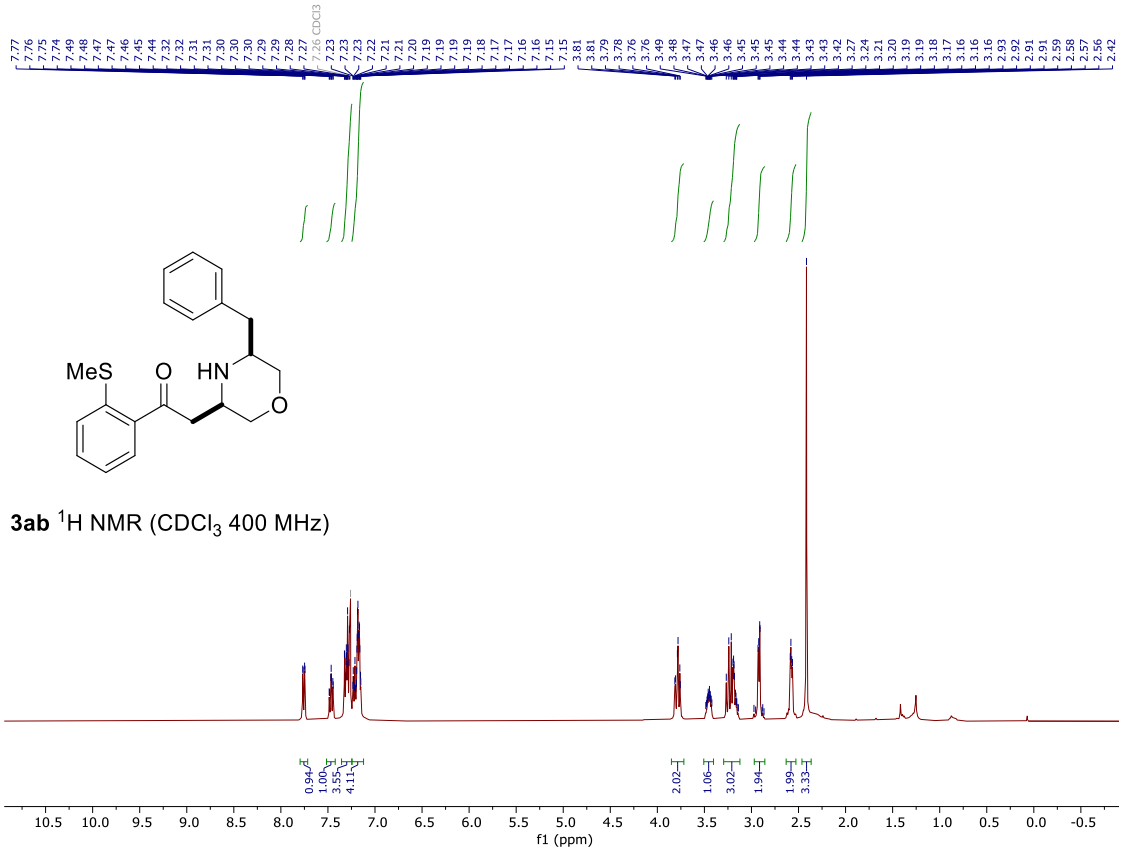
3z $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



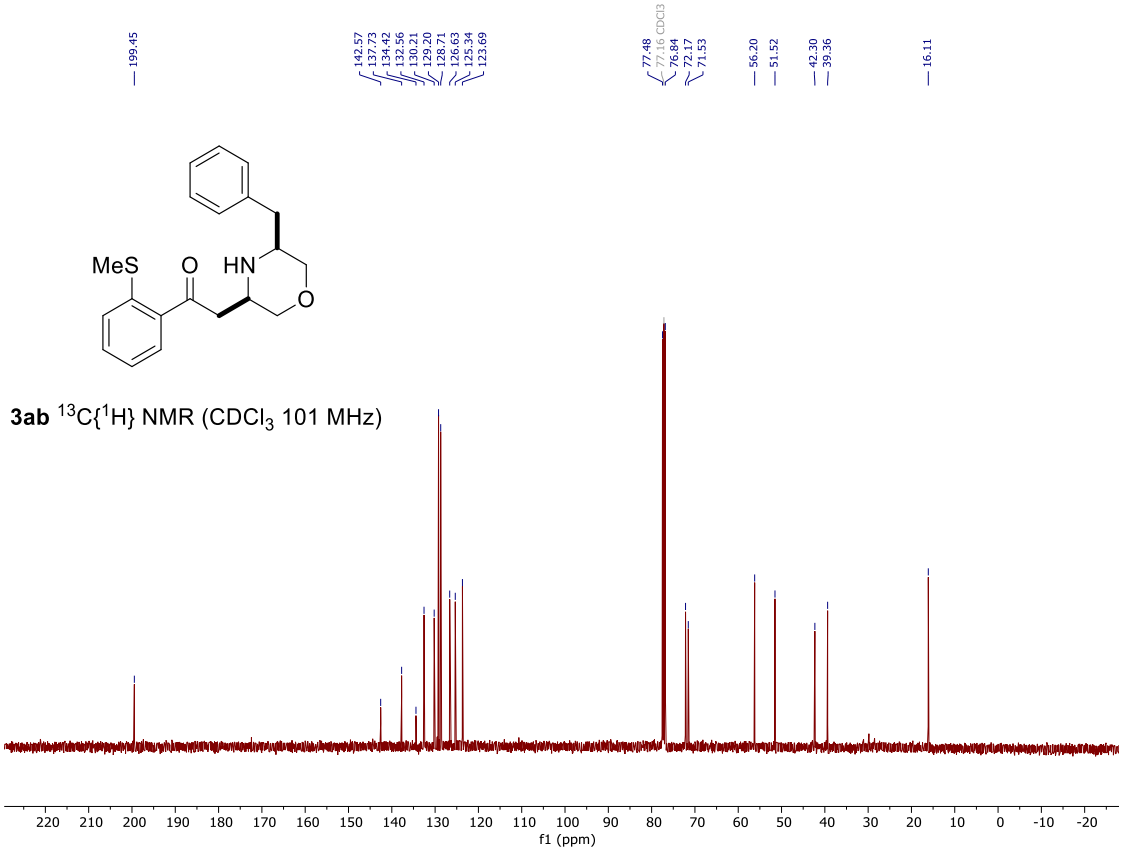
3aa and **3aa'** ^{1}H NMR ($CDCl_3$ 400 MHz)



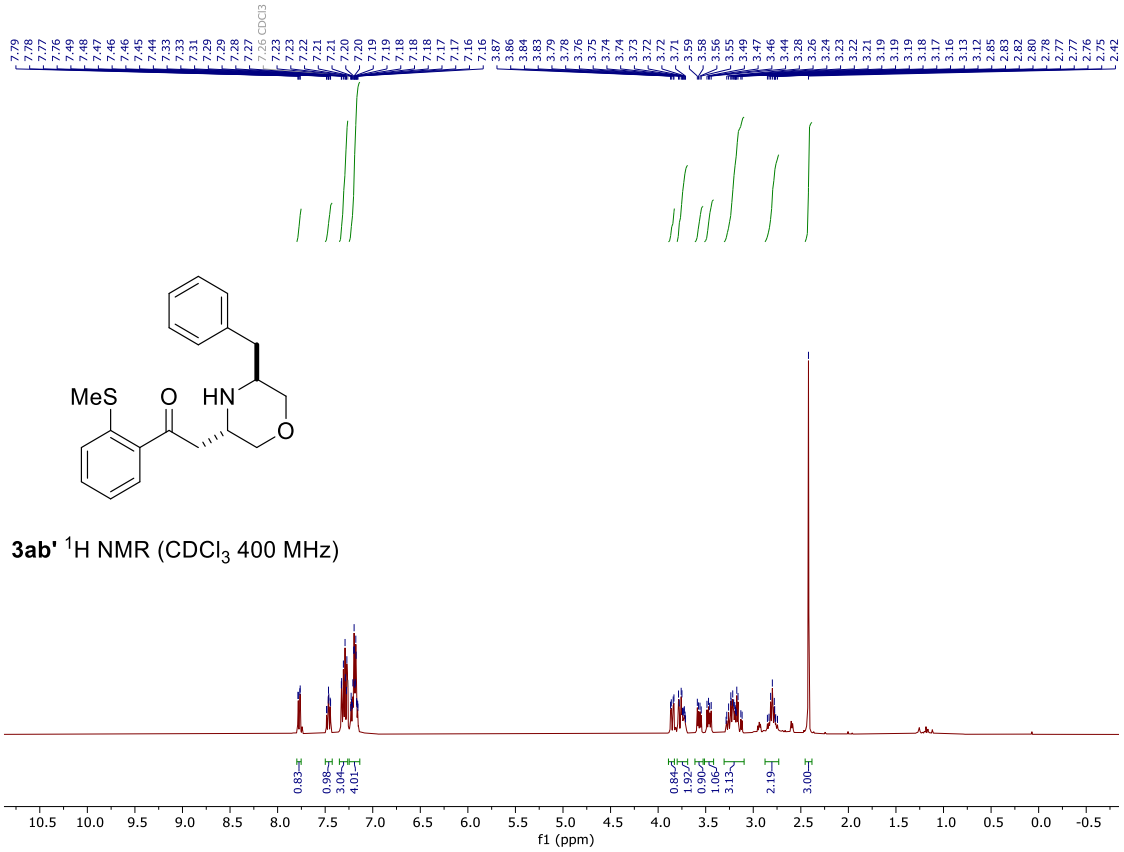
3aa and **3aa'** $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



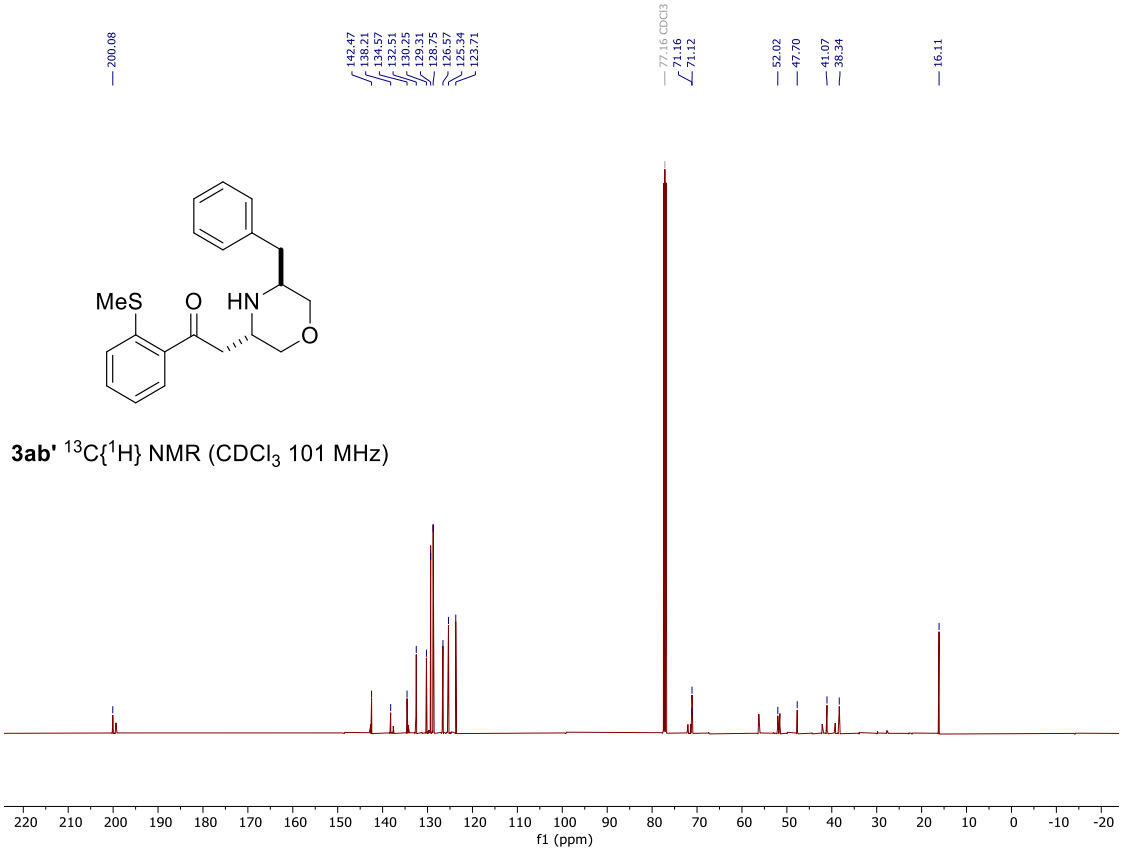
3ab ^{1}H NMR ($CDCl_3$ 400 MHz)



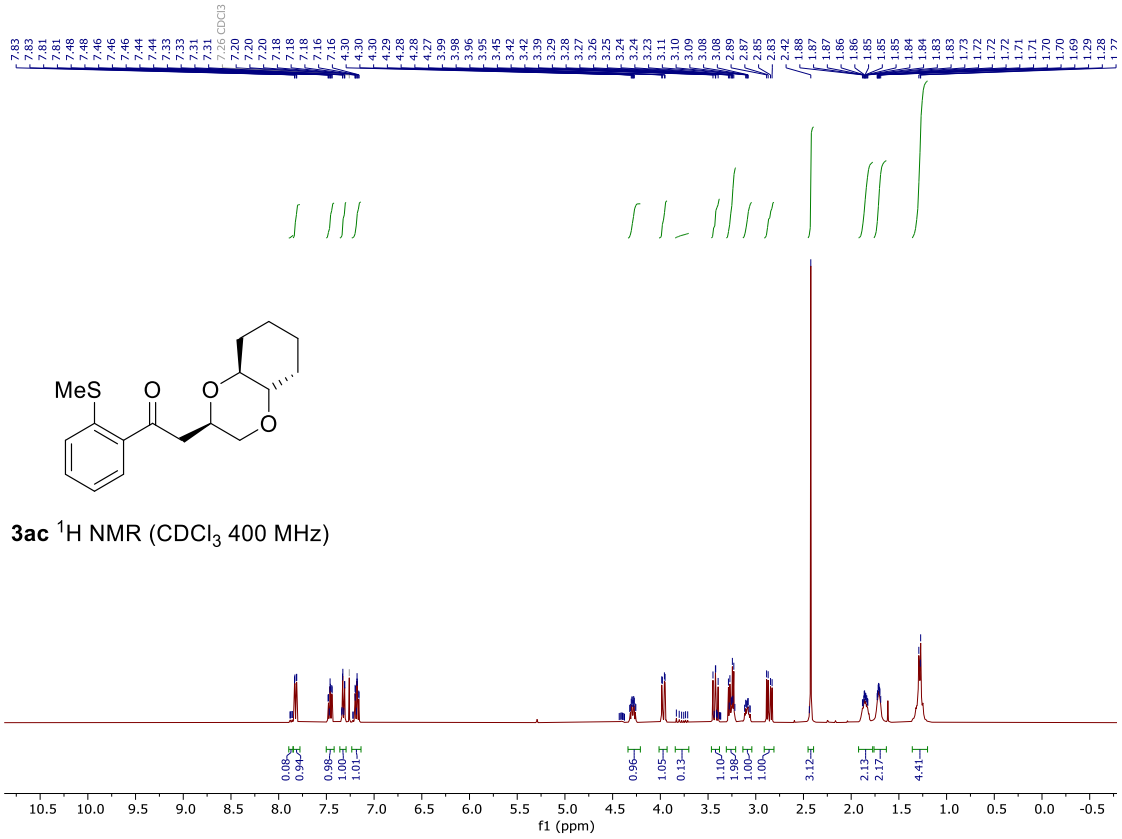
3ab $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



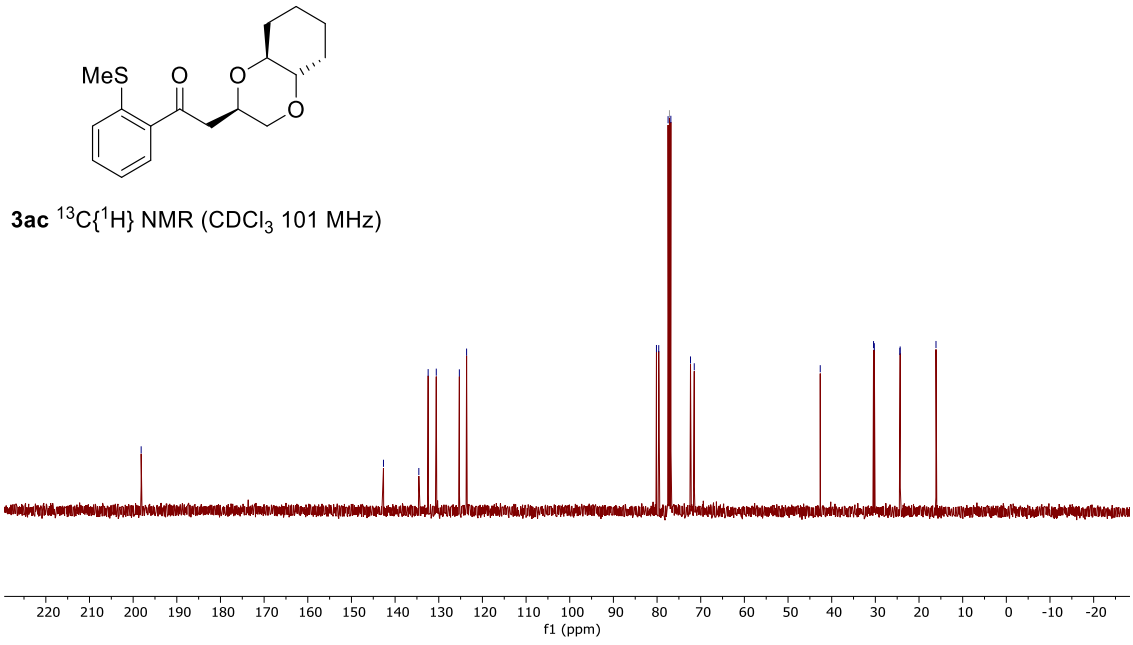
3ab' ^{1}H NMR ($CDCl_3$ 400 MHz)



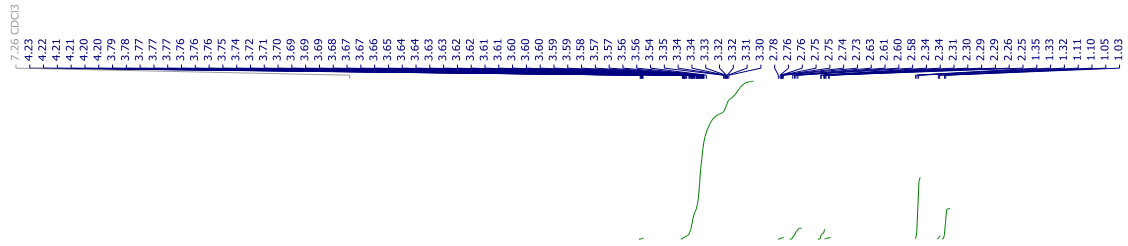
3ab' $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

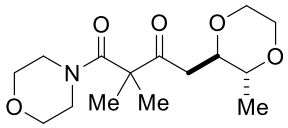


3ac ^{1}H NMR ($CDCl_3$ 400 MHz)

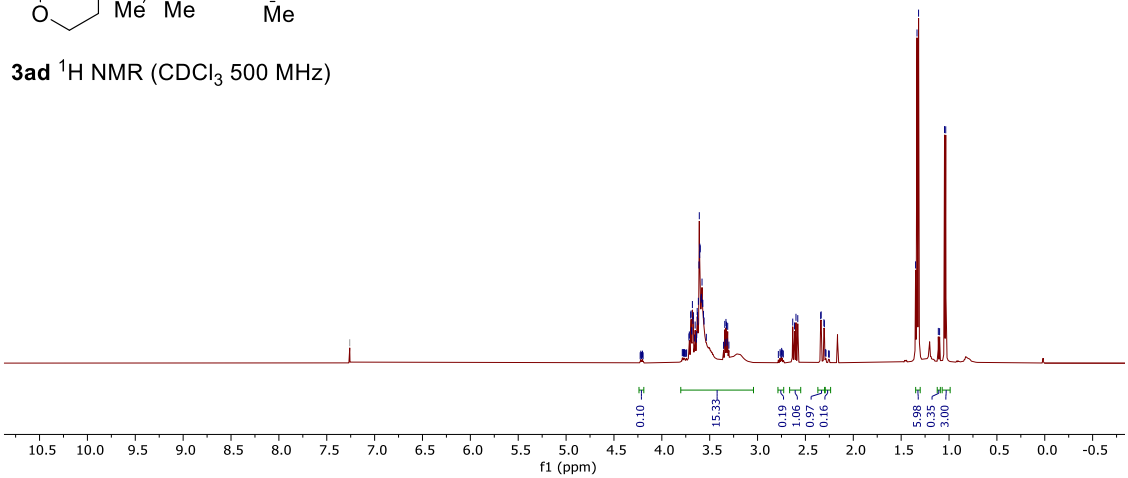


3ac $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

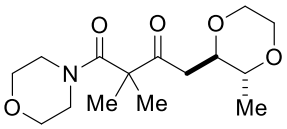




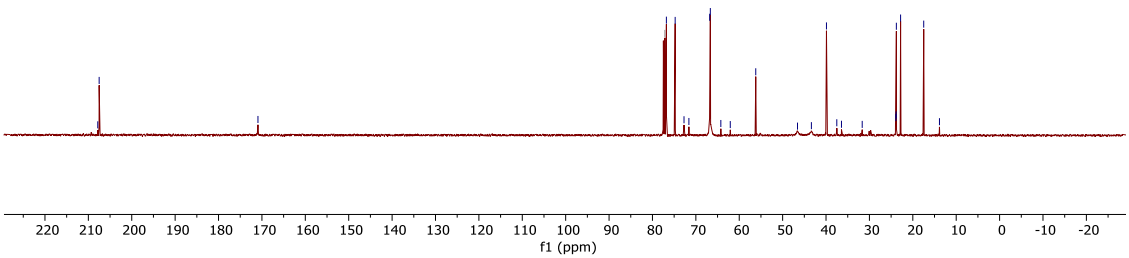
3ad ^{1}H NMR ($CDCl_3$ 500 MHz)

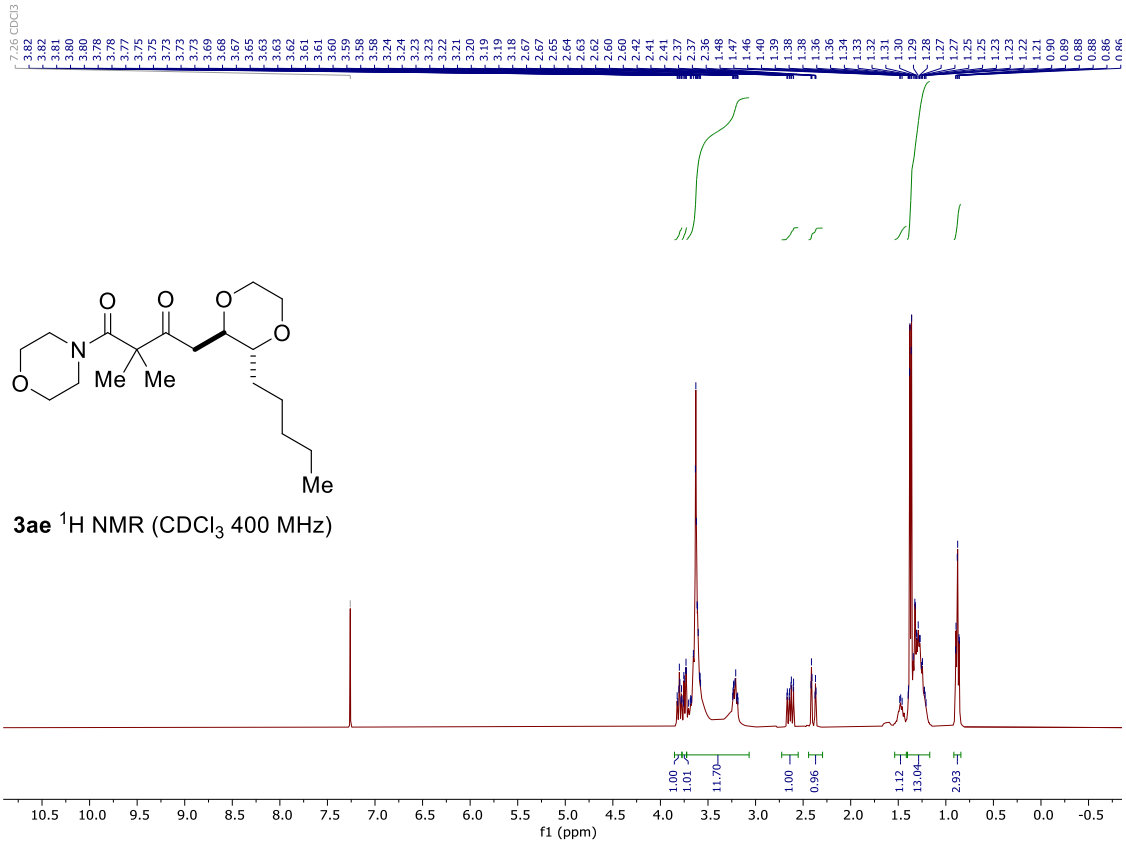




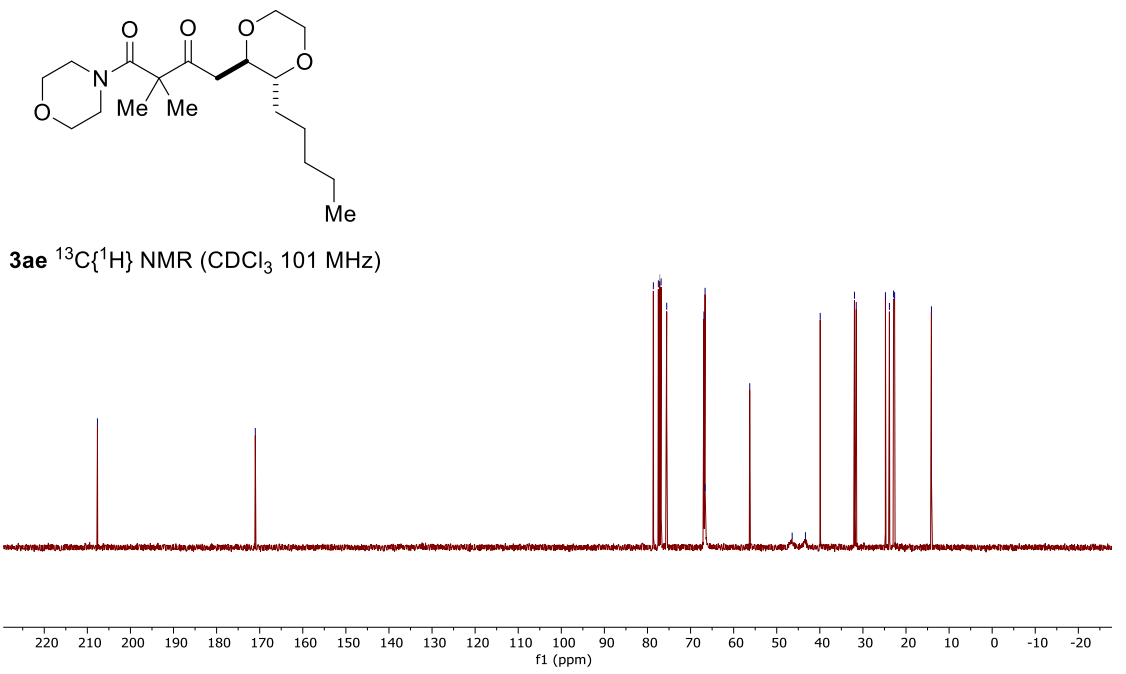


3ad $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

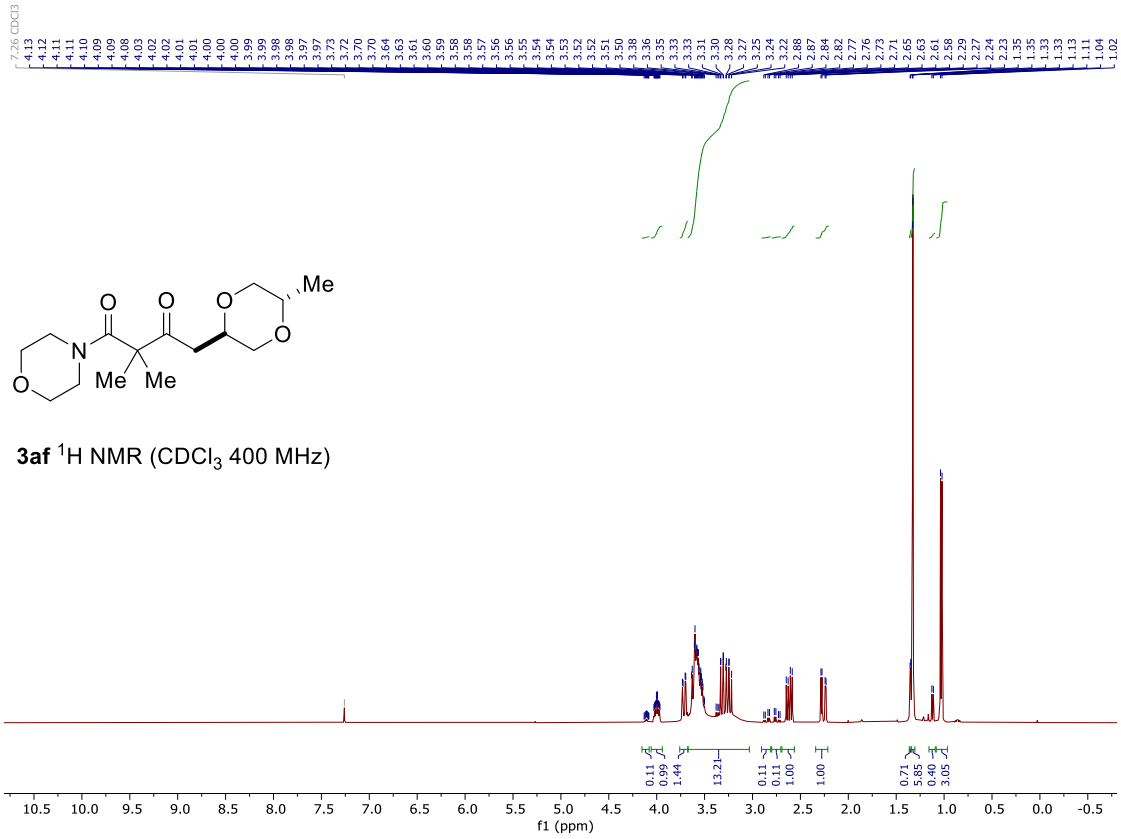




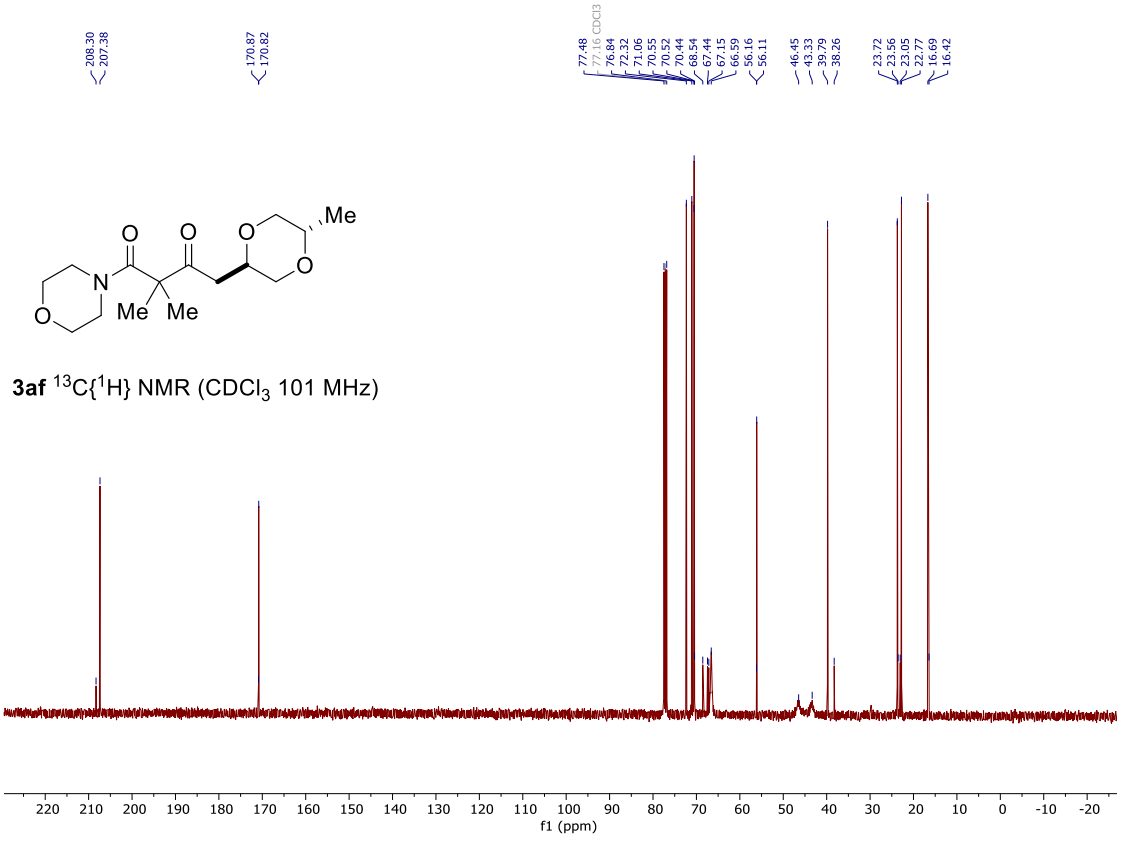
3ae ^{1}H NMR ($CDCl_3$ 400 MHz)



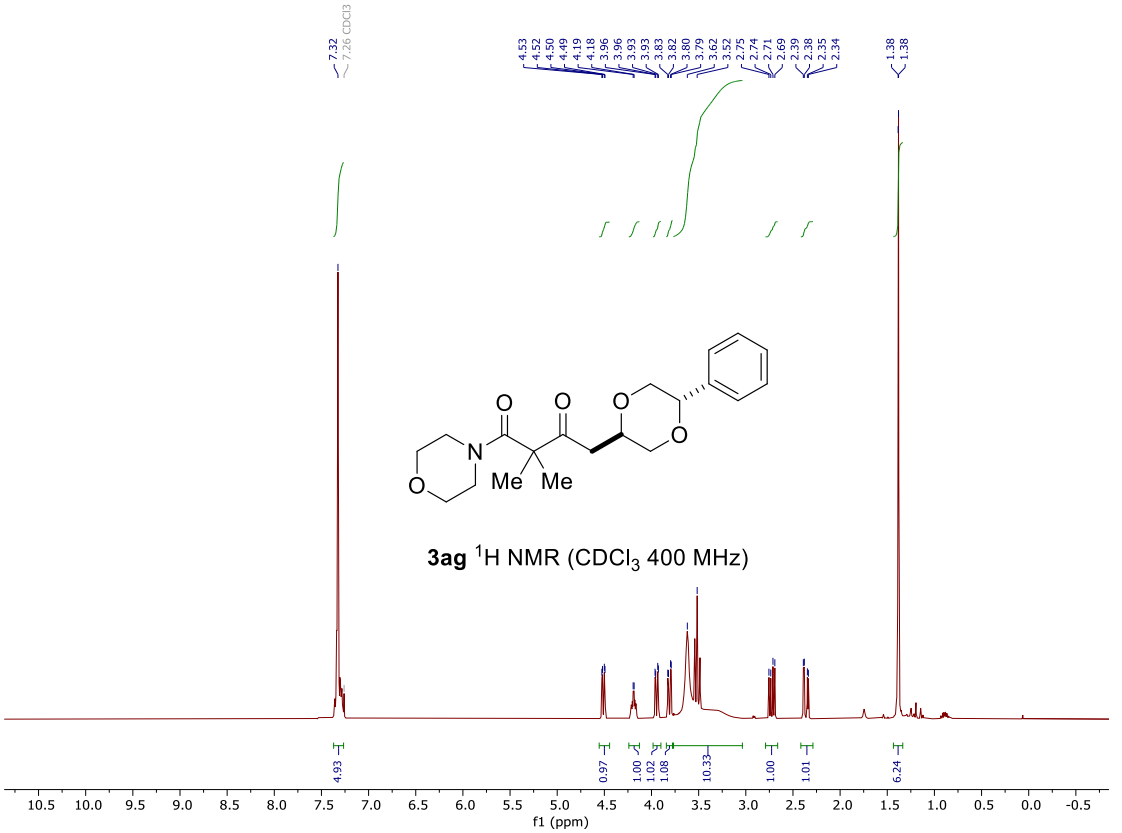
3ae $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



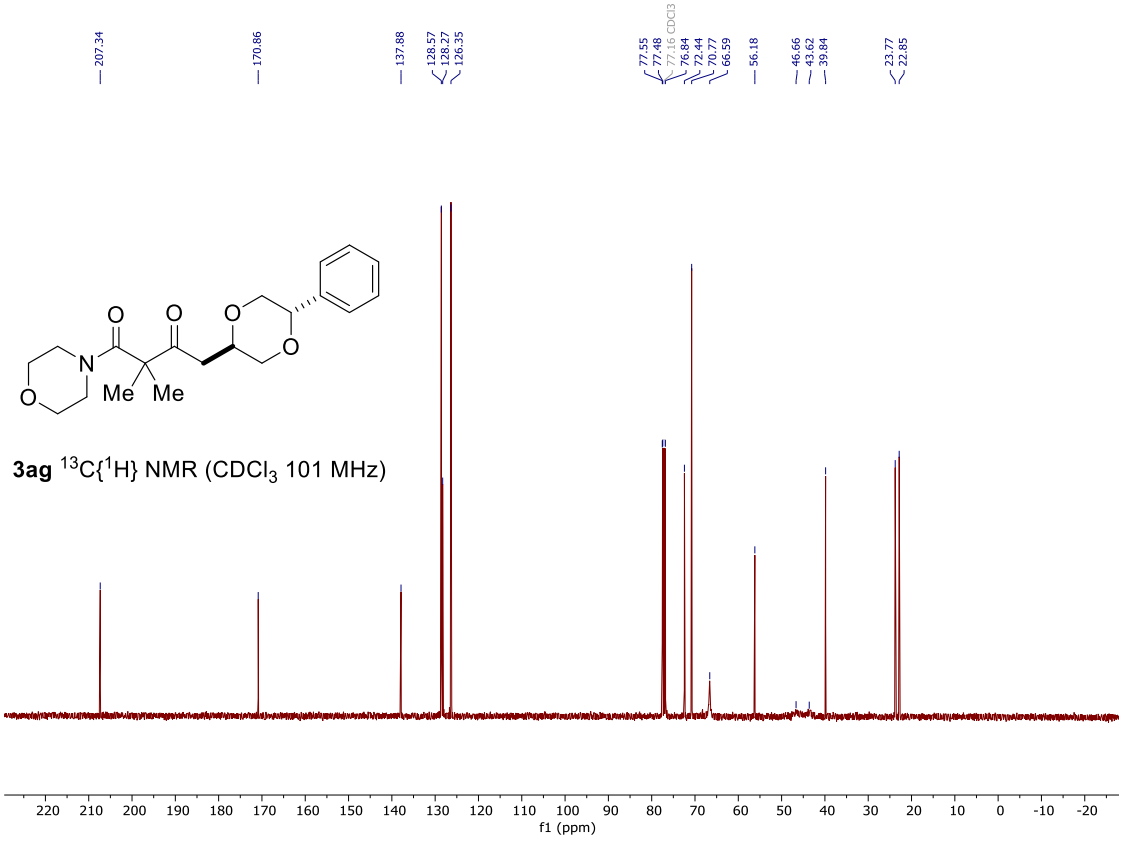
3af ^{1}H NMR ($CDCl_3$ 400 MHz)



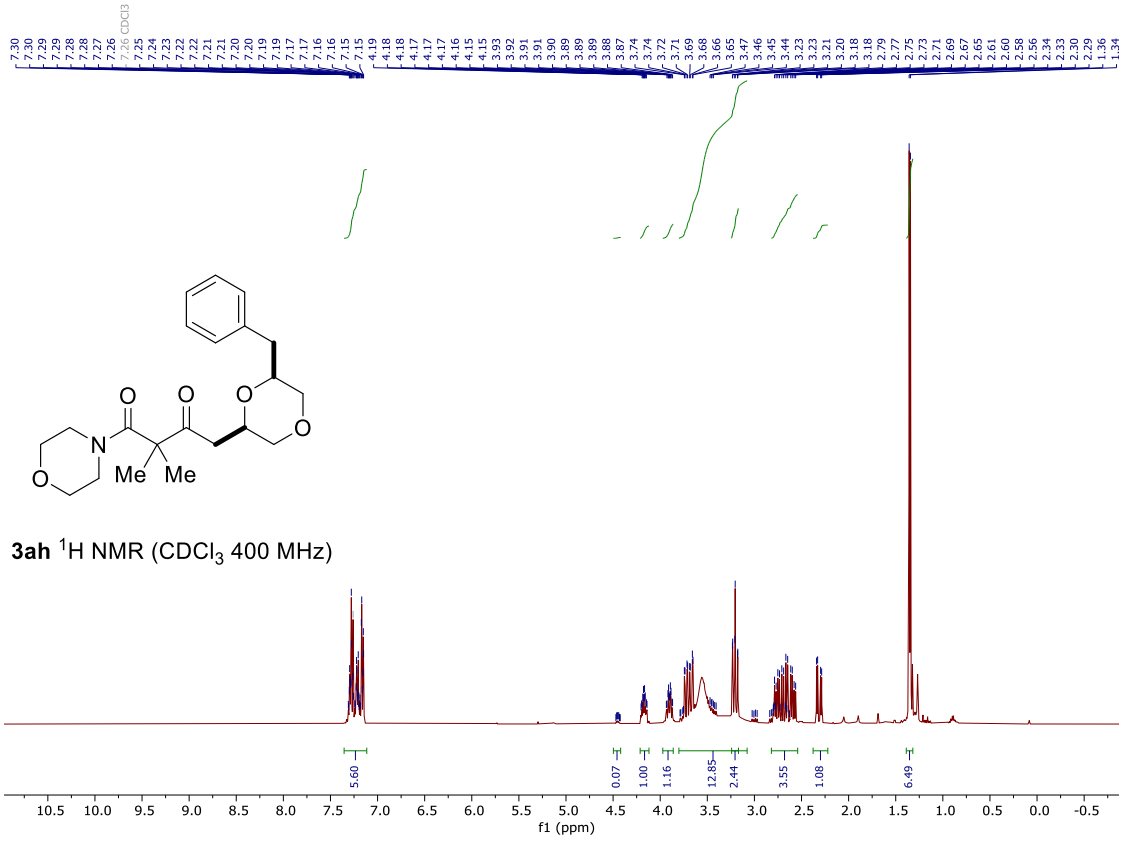
3af $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



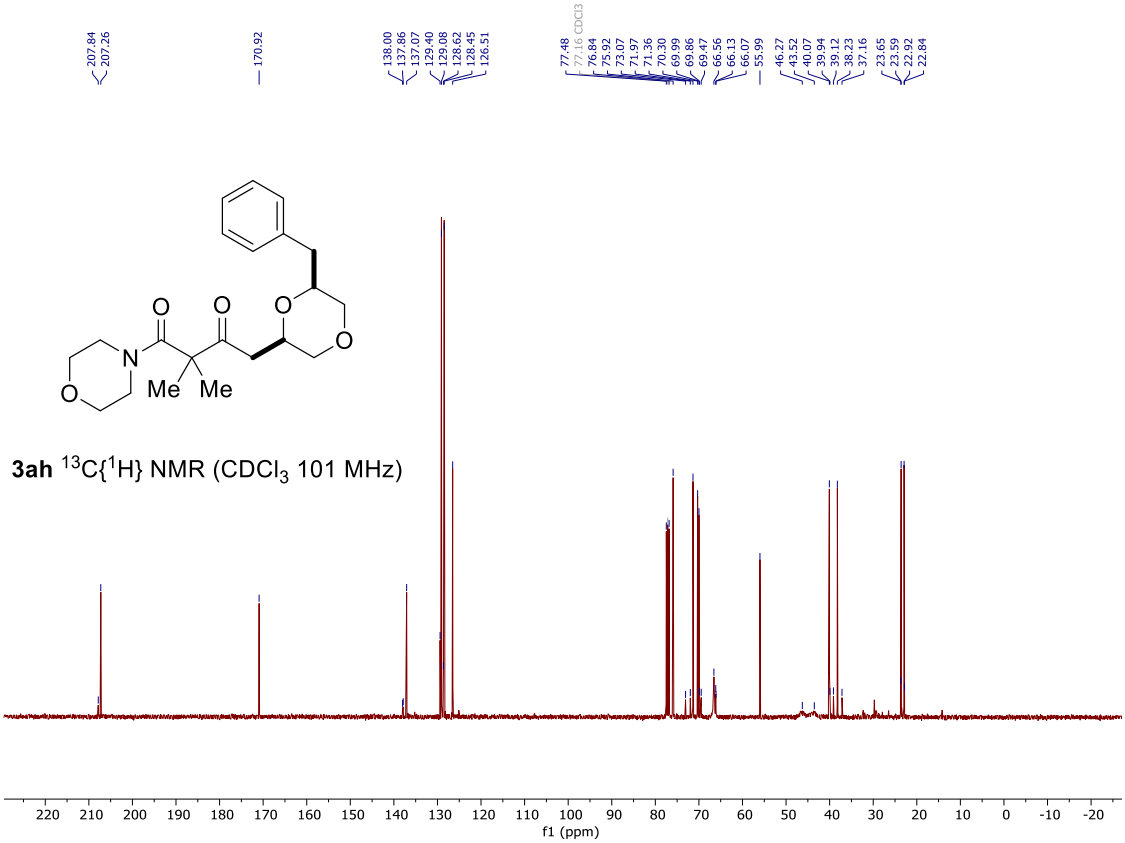
3ag ^{1}H NMR ($CDCl_3$ 400 MHz)



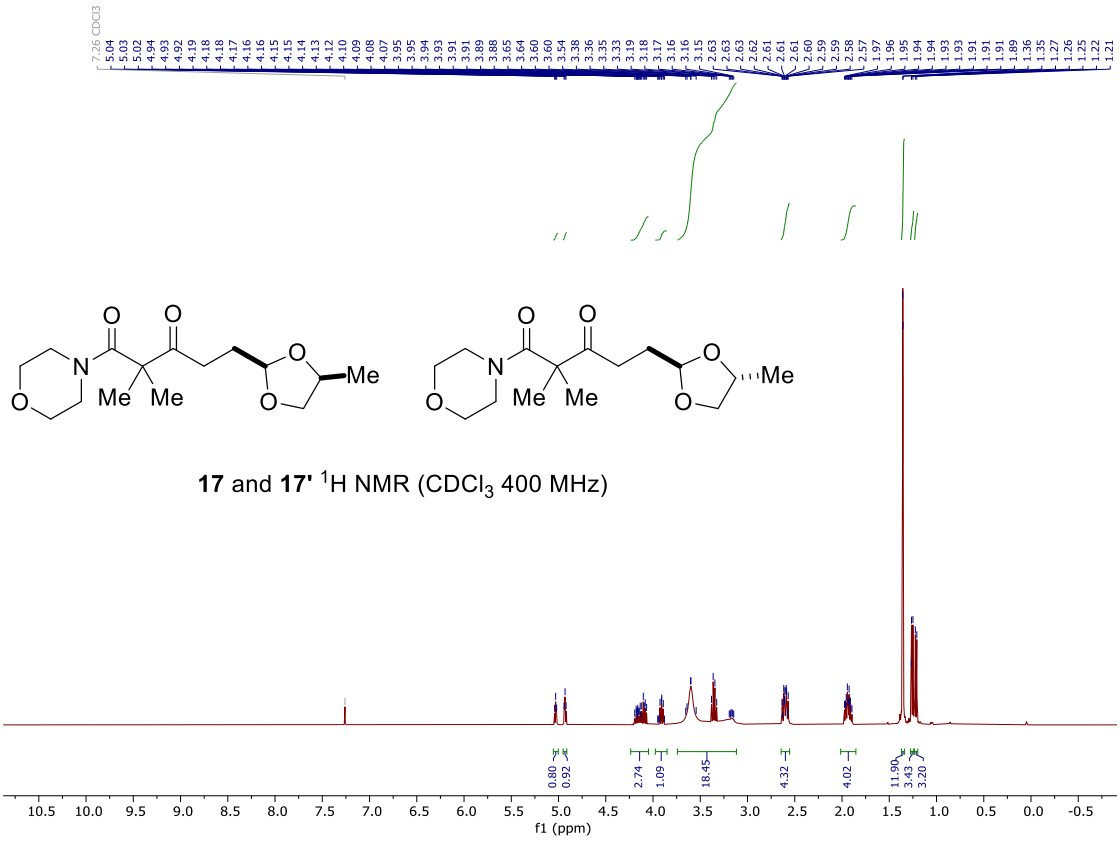
3ag $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



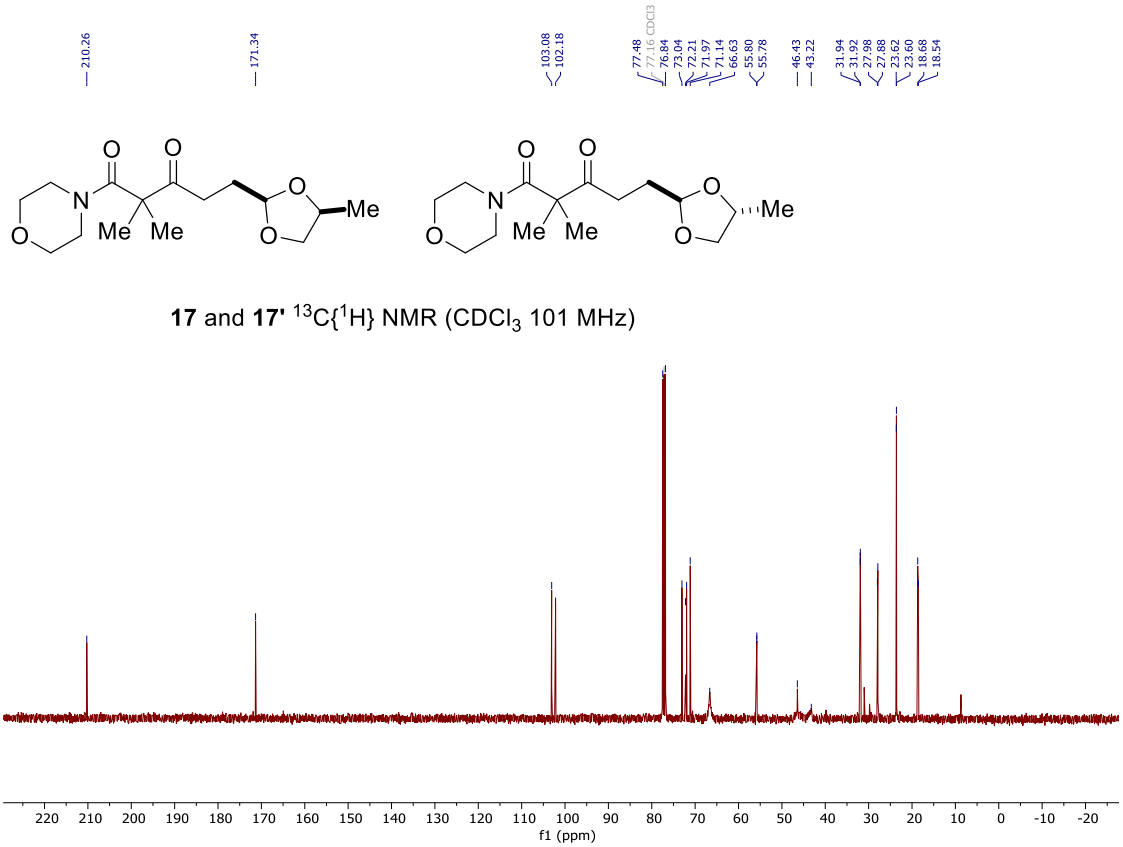
3ah ^{1}H NMR ($CDCl_3$ 400 MHz)



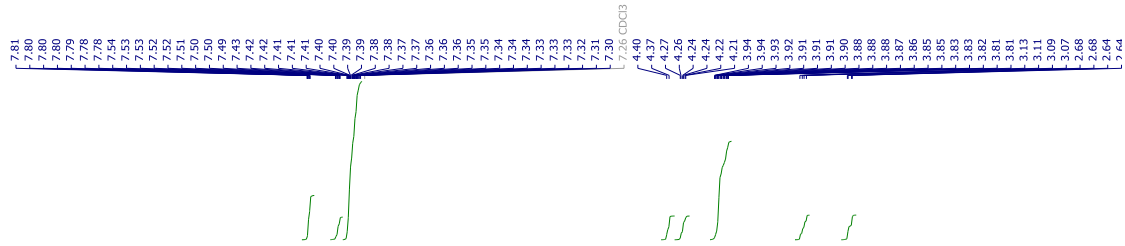
3ah $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

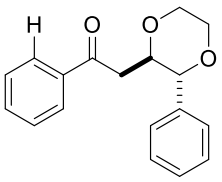


17 and **17'** ^{1}H NMR ($CDCl_3$ 400 MHz)

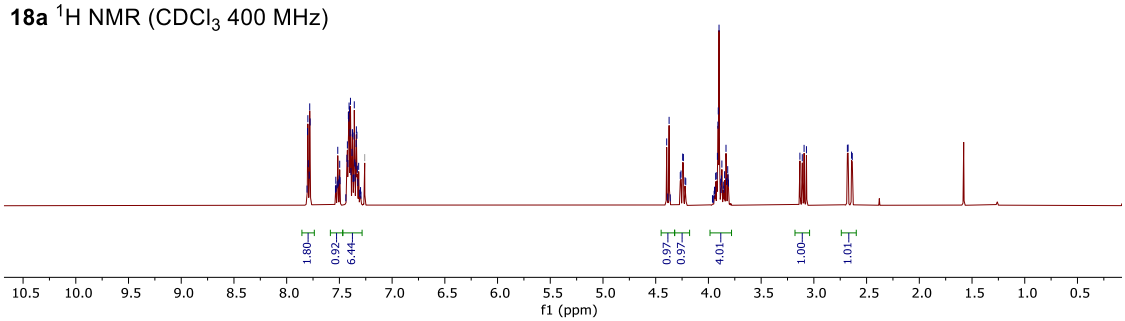


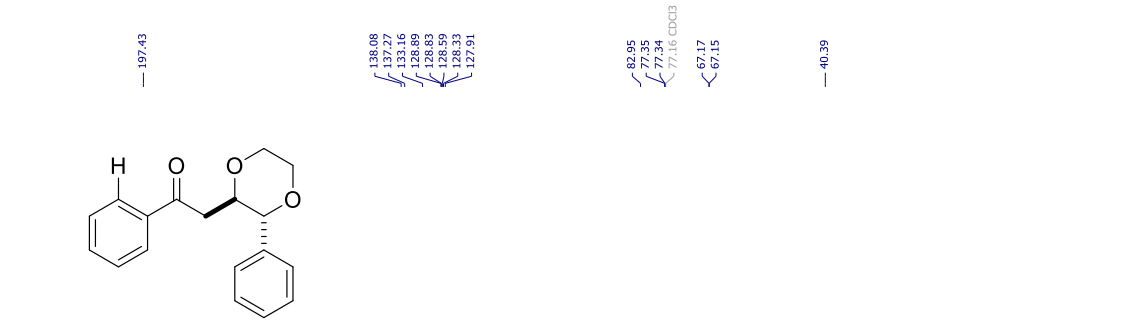
17 and **17'** $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



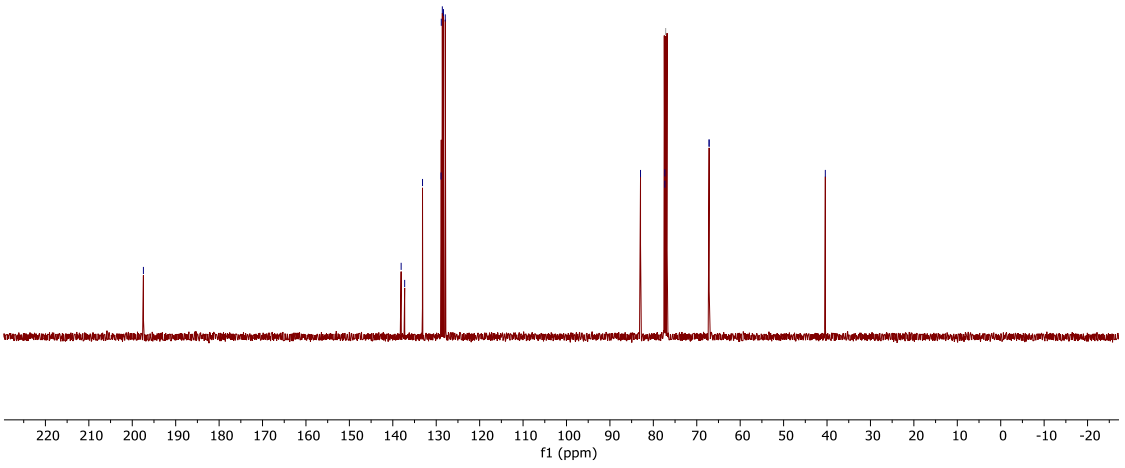


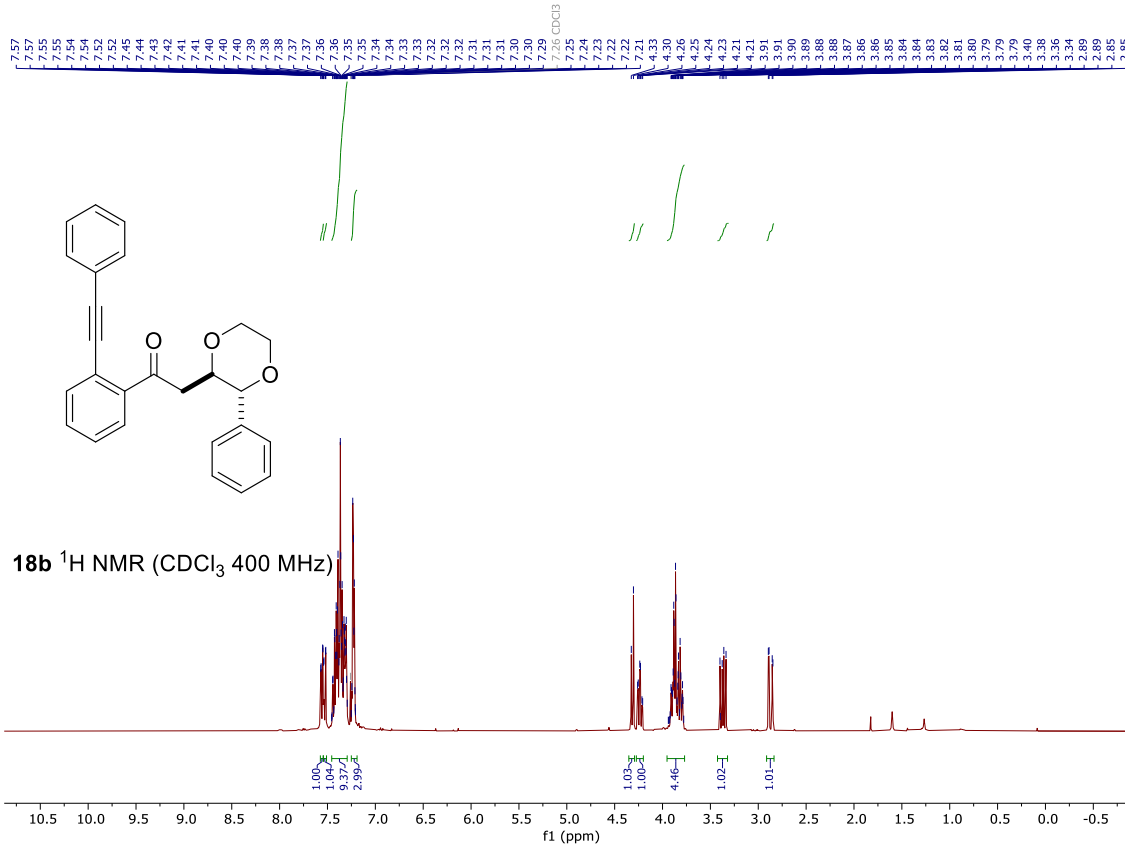
18a ^{1}H NMR ($CDCl_3$ 400 MHz)



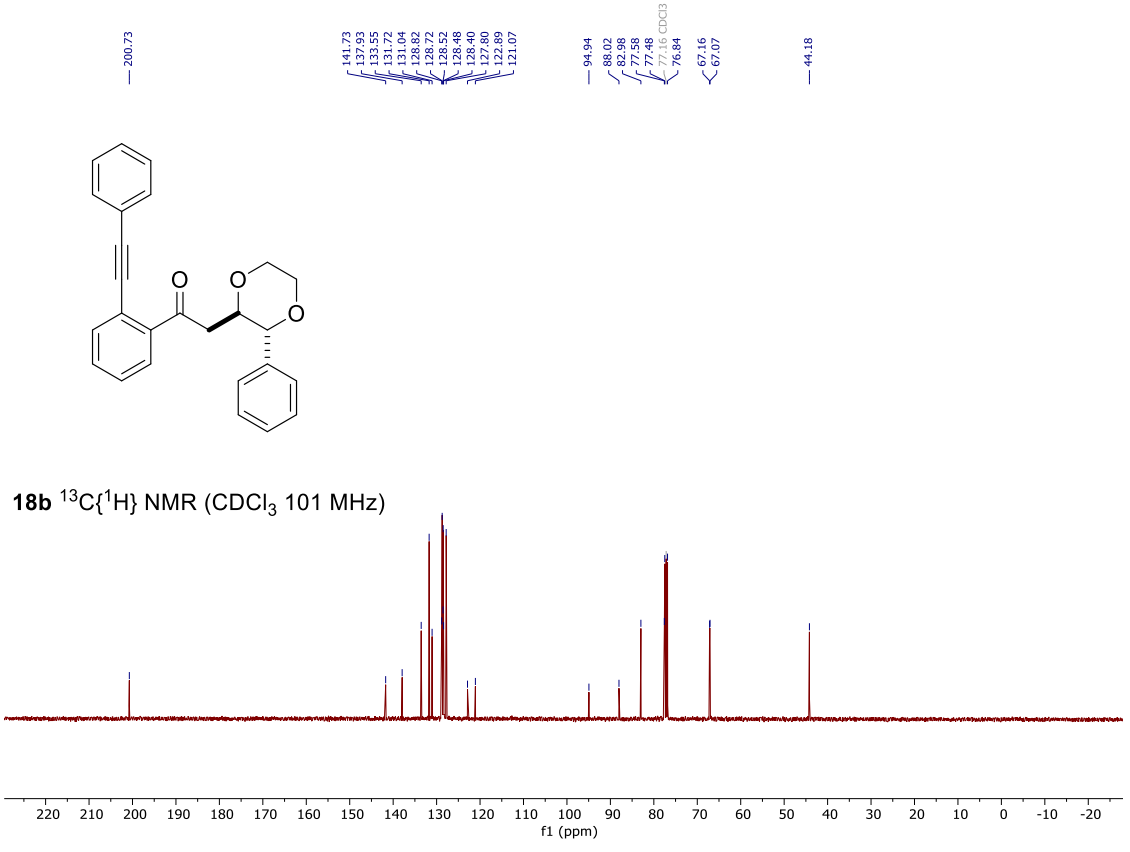


18a ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

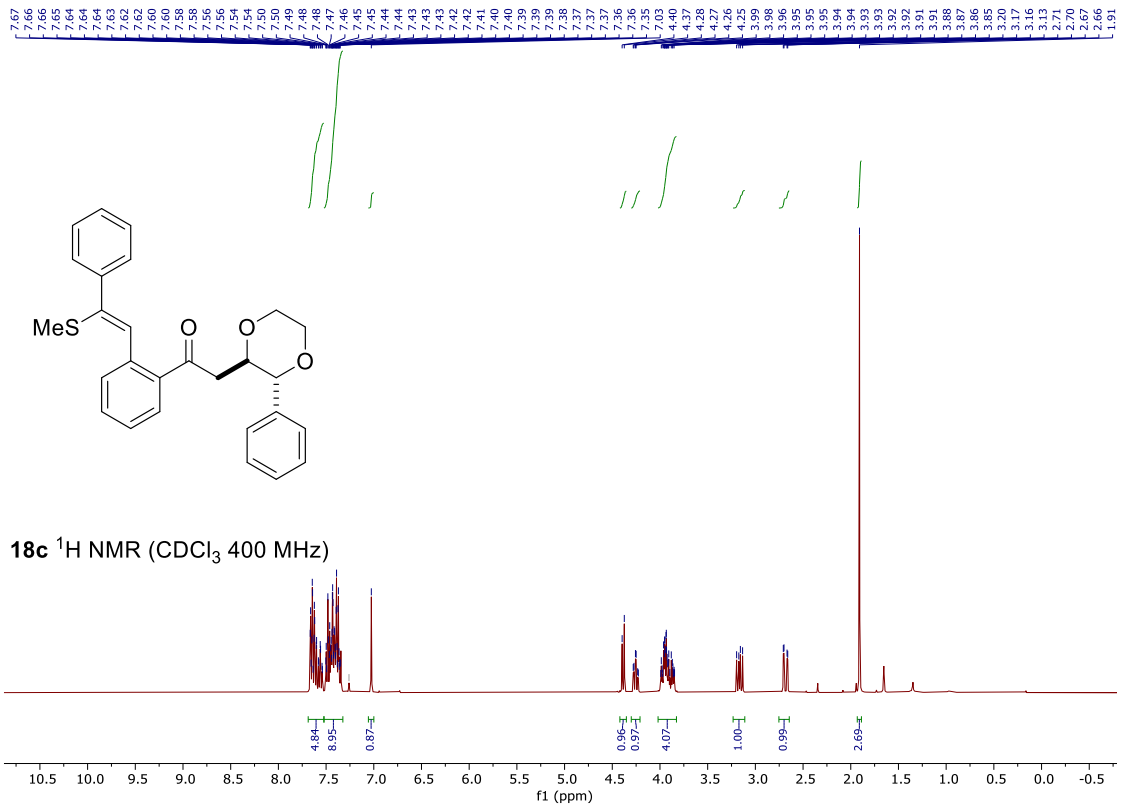




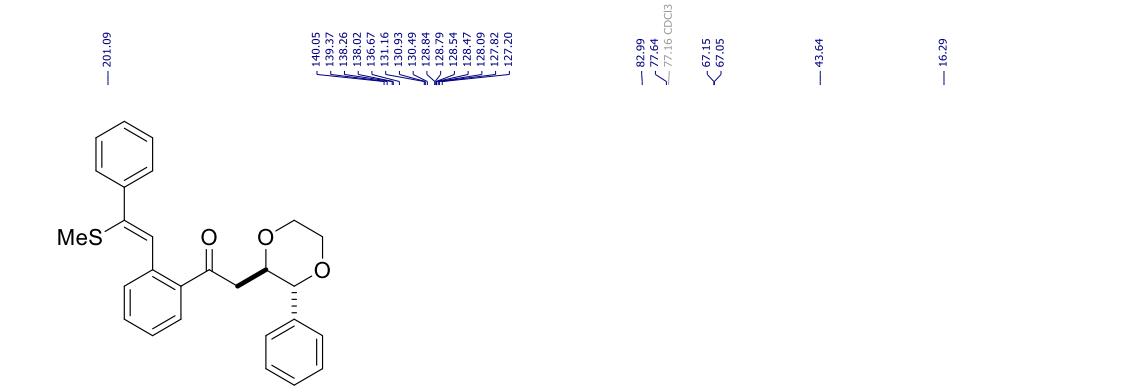
18b ^{1}H NMR ($CDCl_3$ 400 MHz)



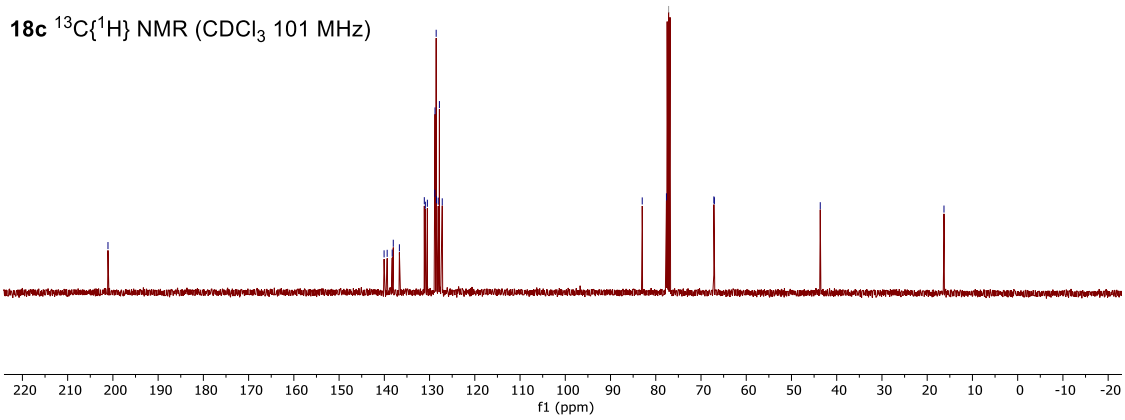
18b ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

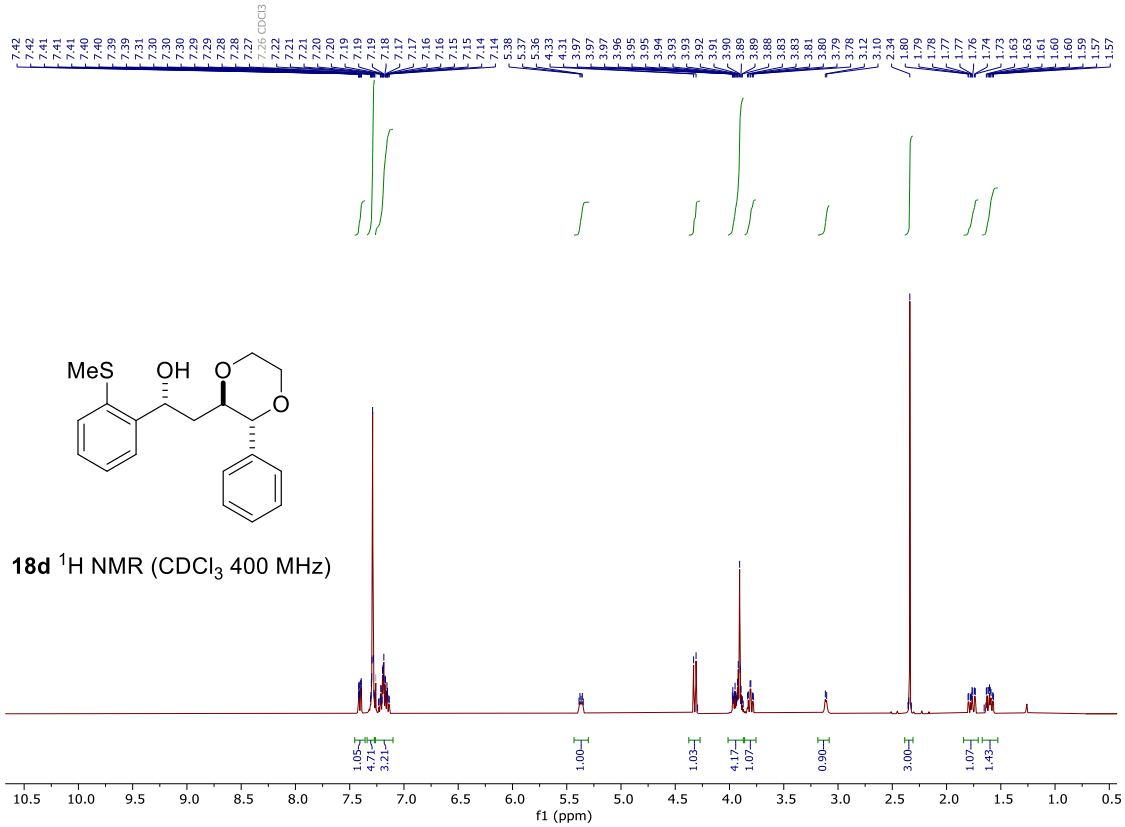


18c ^{1}H NMR ($CDCl_3$ 400 MHz)

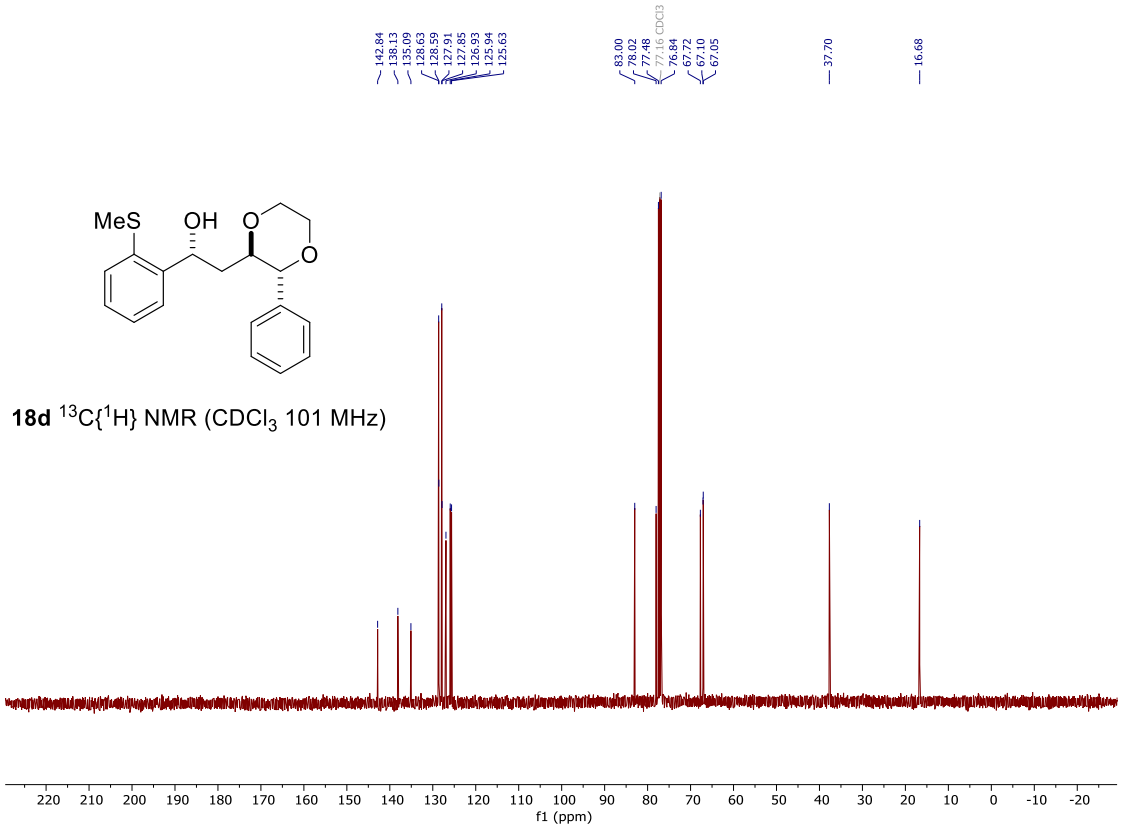


18c ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

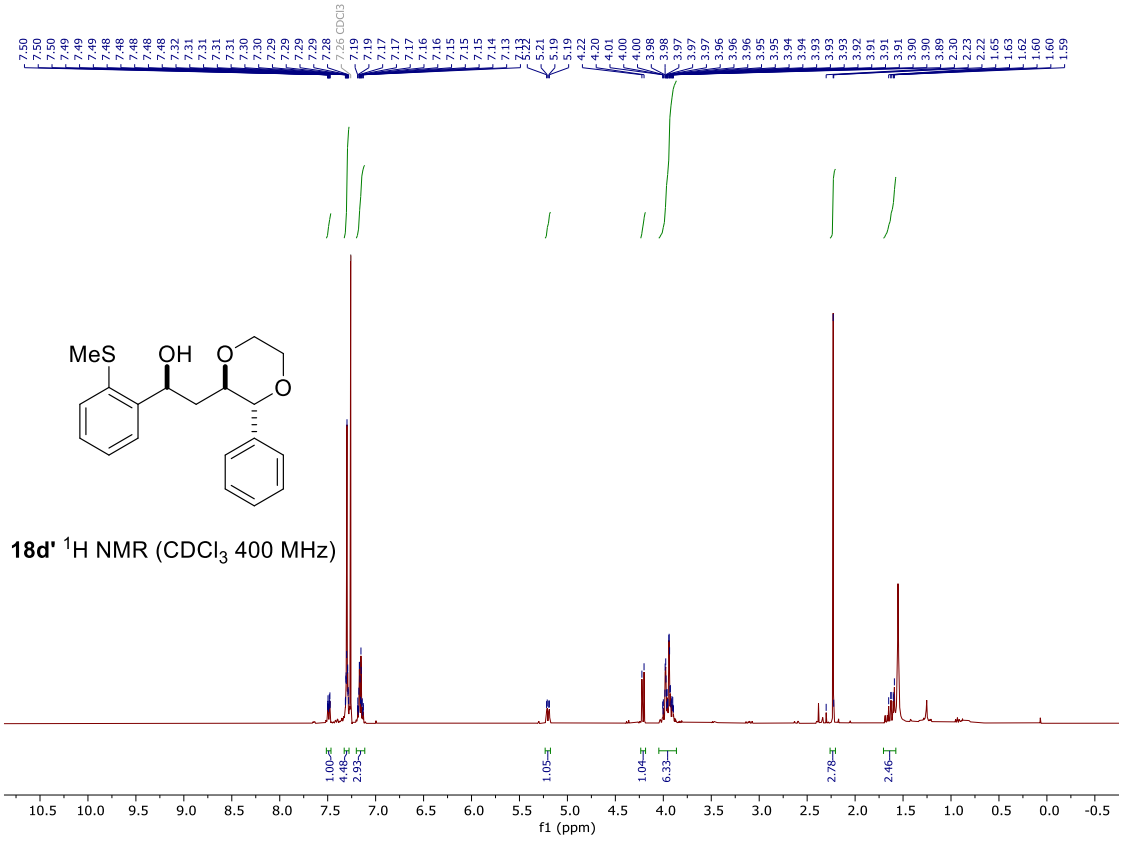




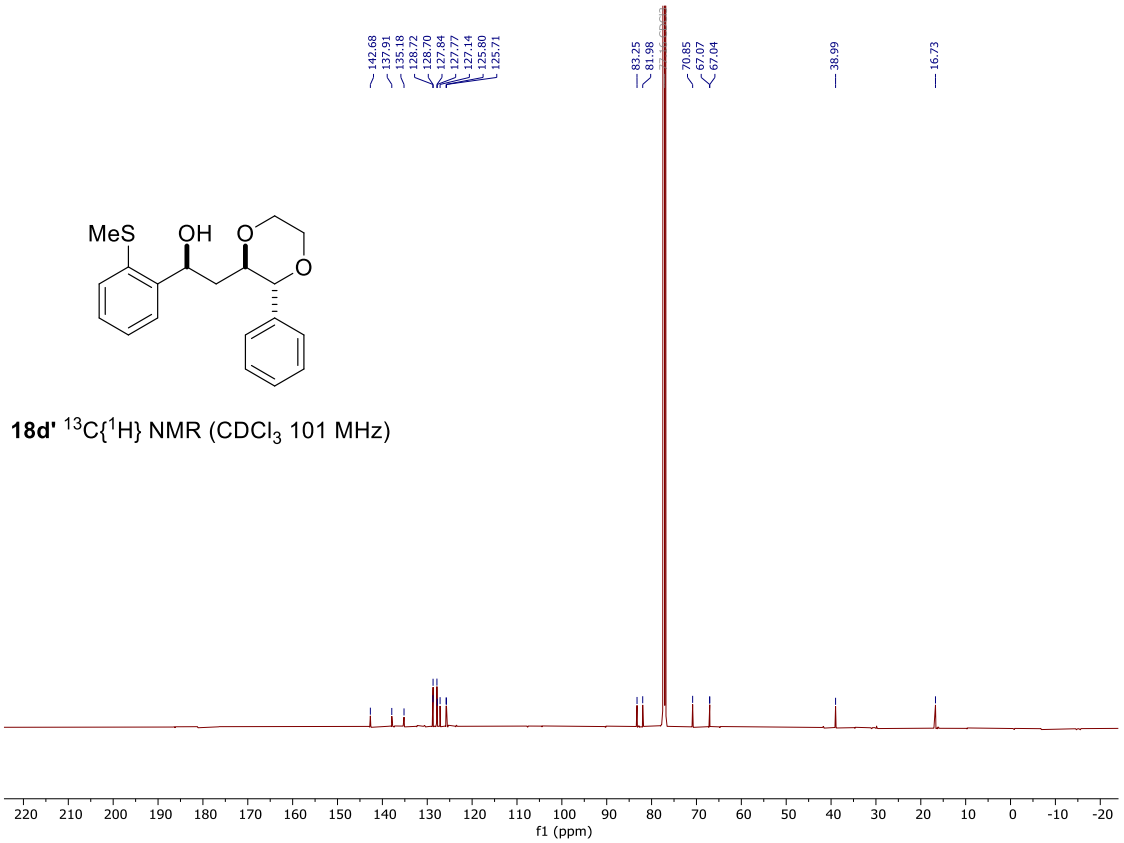
18d ^{1}H NMR ($CDCl_3$ 400 MHz)



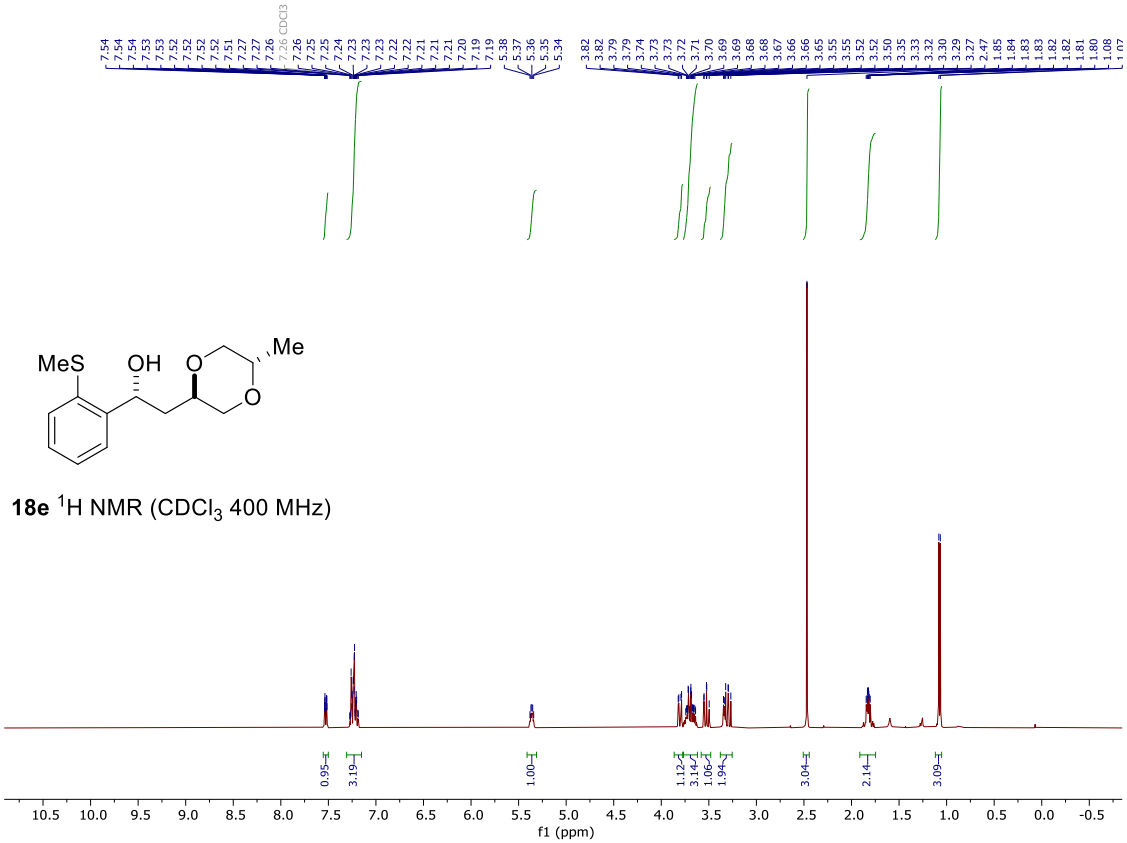
18d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



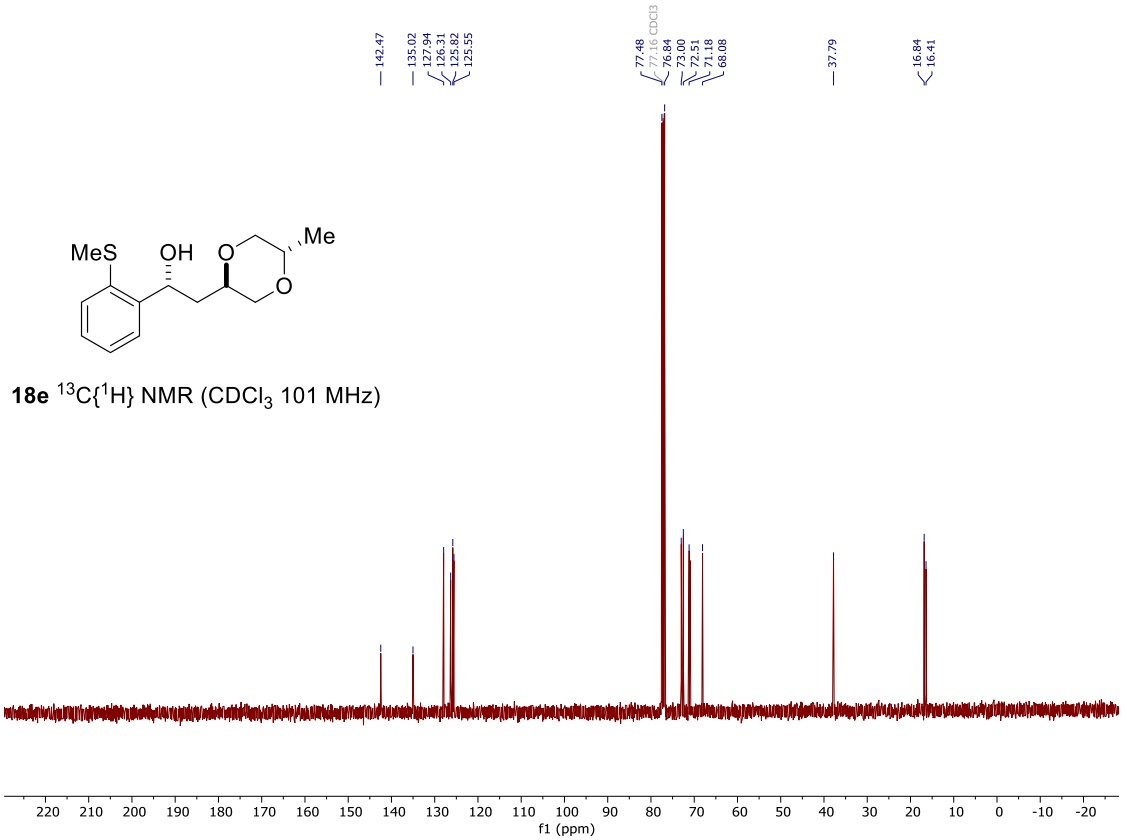
18d' ^{1}H NMR ($CDCl_3$ 400 MHz)



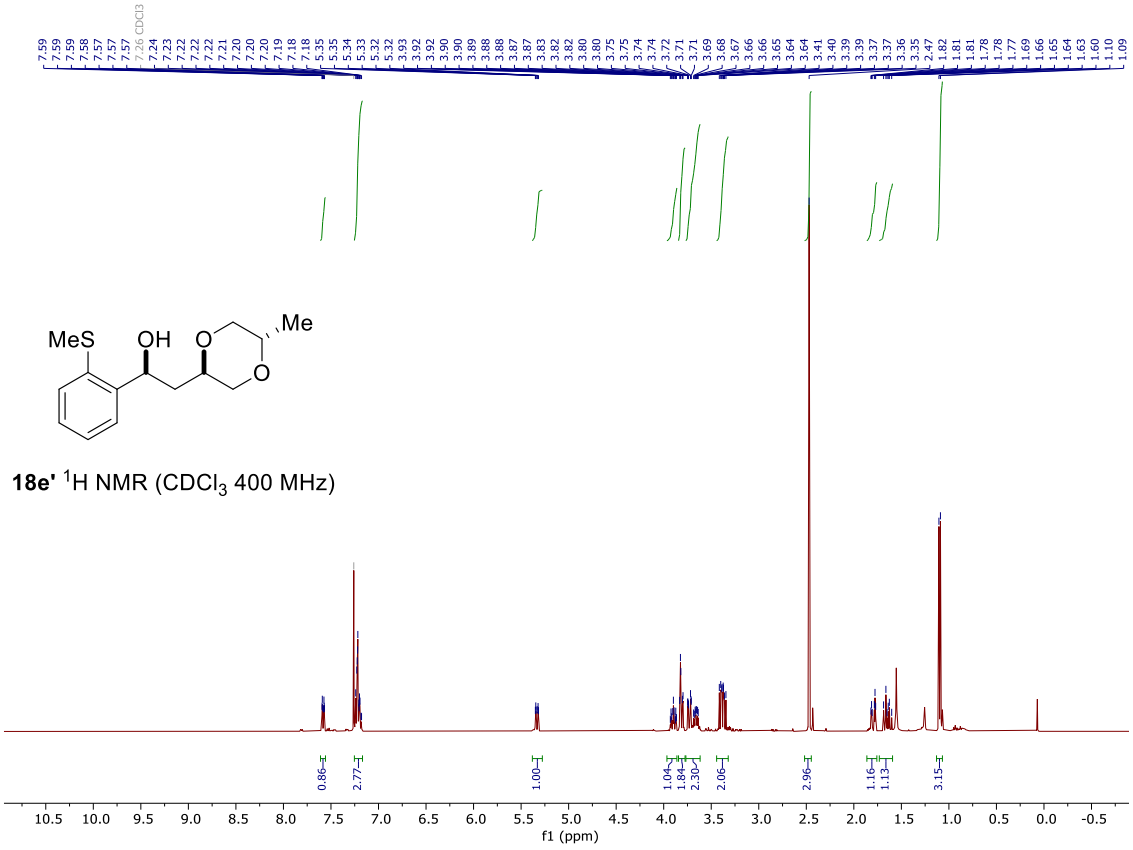
18d' $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



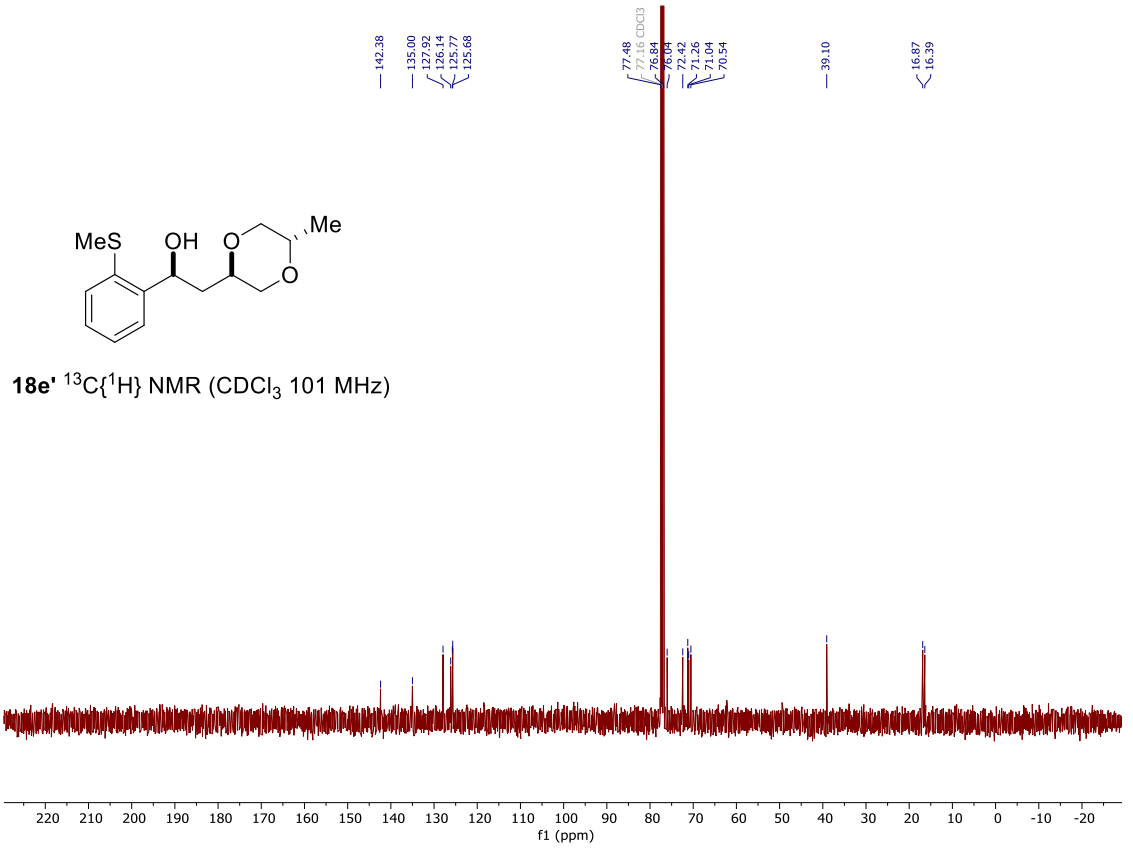
18e ^{1}H NMR ($CDCl_3$ 400 MHz)



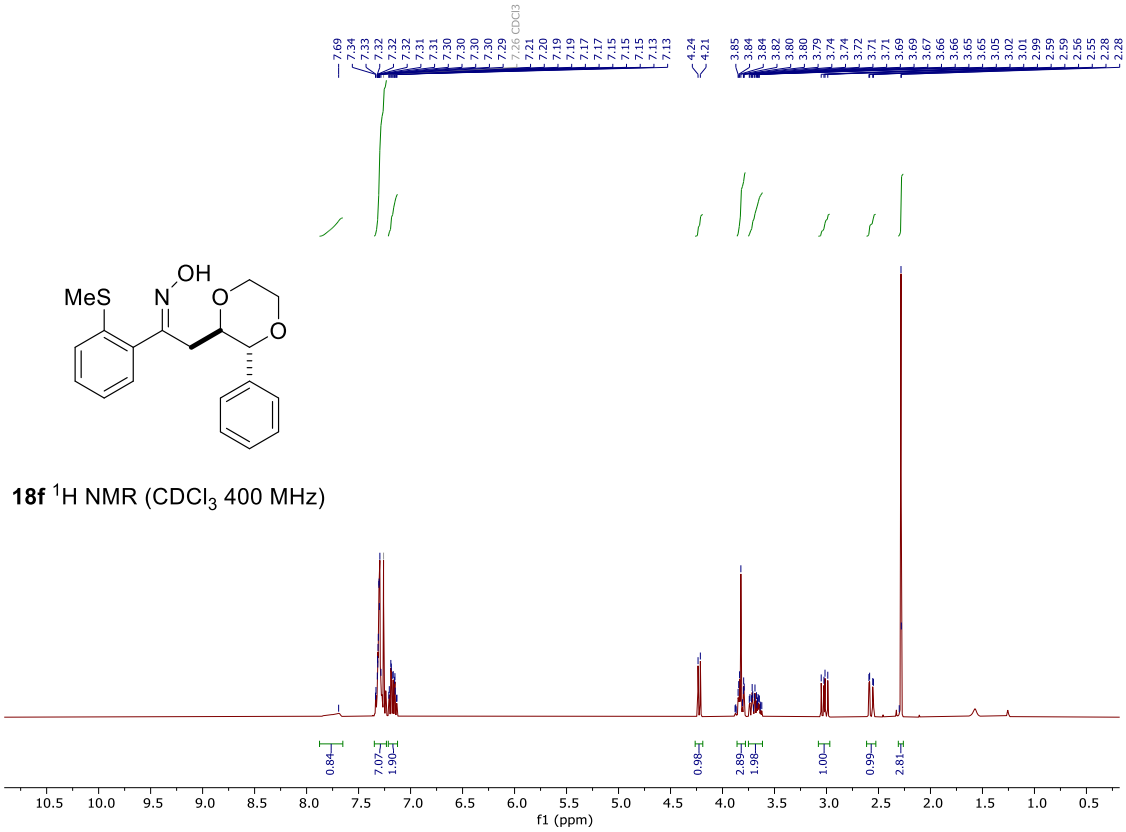
18e $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



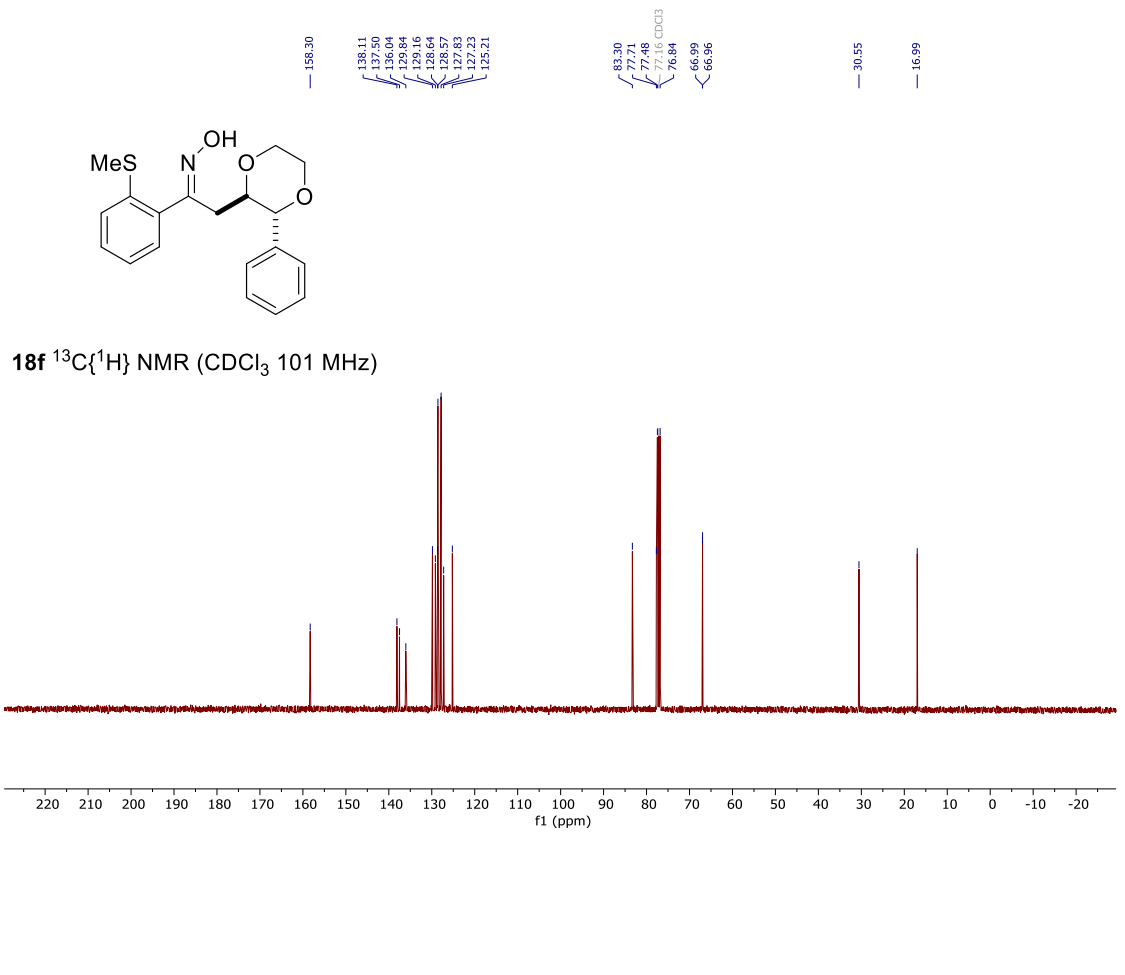
18e' ^{1}H NMR ($CDCl_3$ 400 MHz)



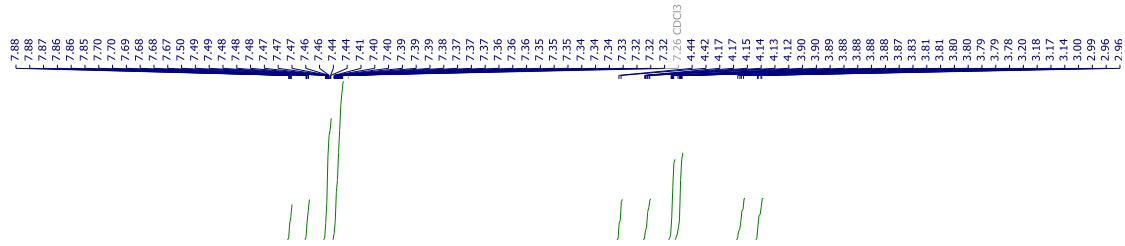
18e' $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

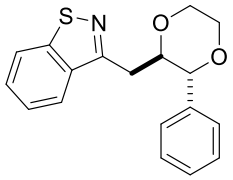


18f ^{1}H NMR ($CDCl_3$ 400 MHz)

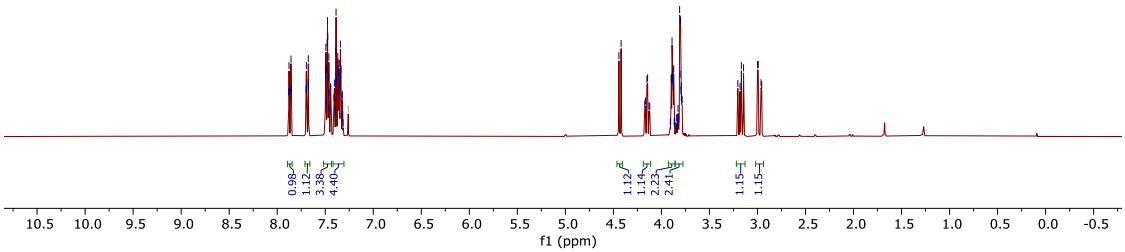


18f $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

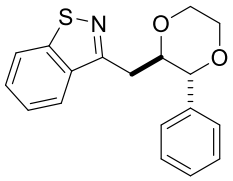




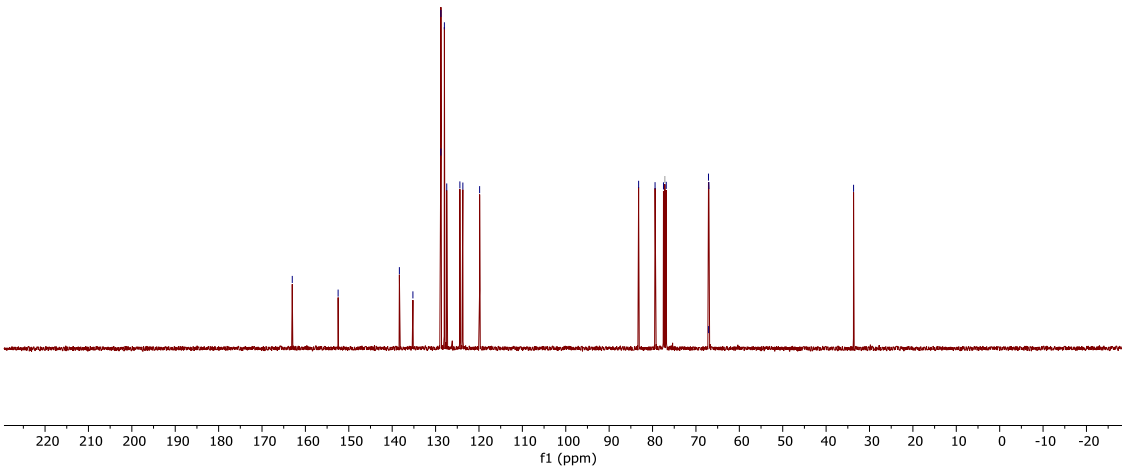
18g ^{1}H NMR ($CDCl_3$ 400 MHz)

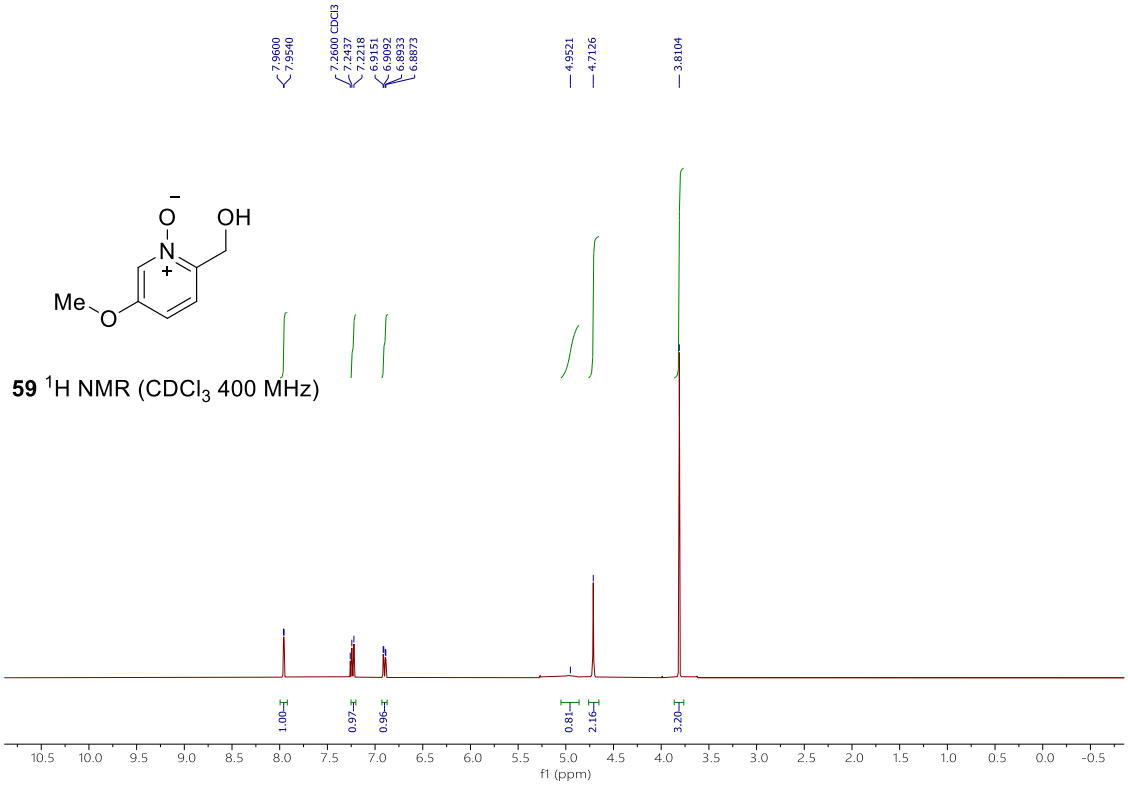




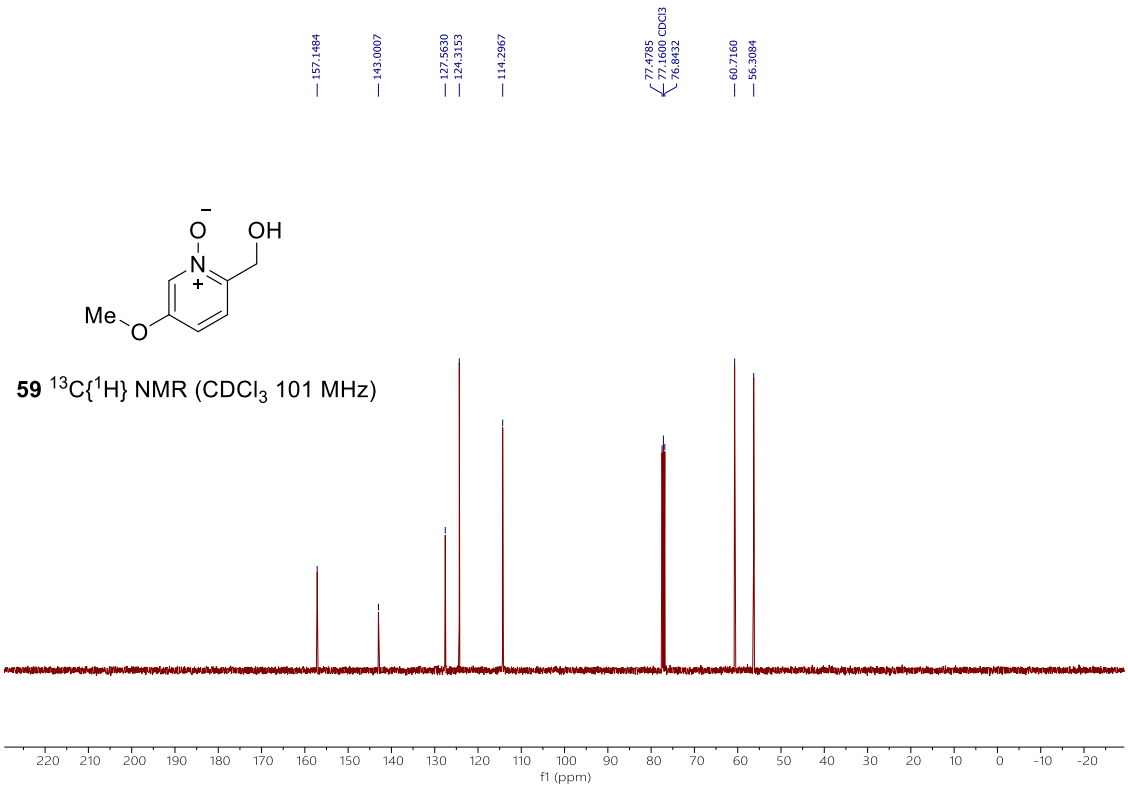


18g ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

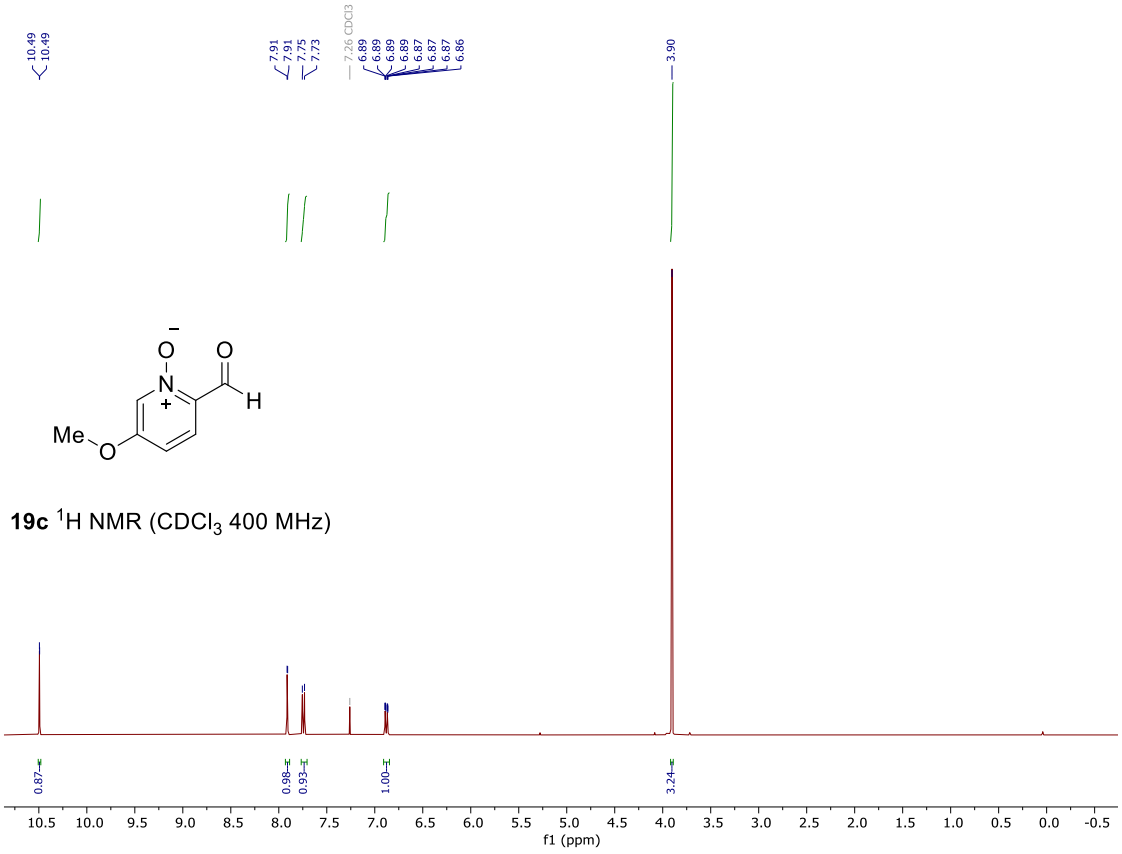




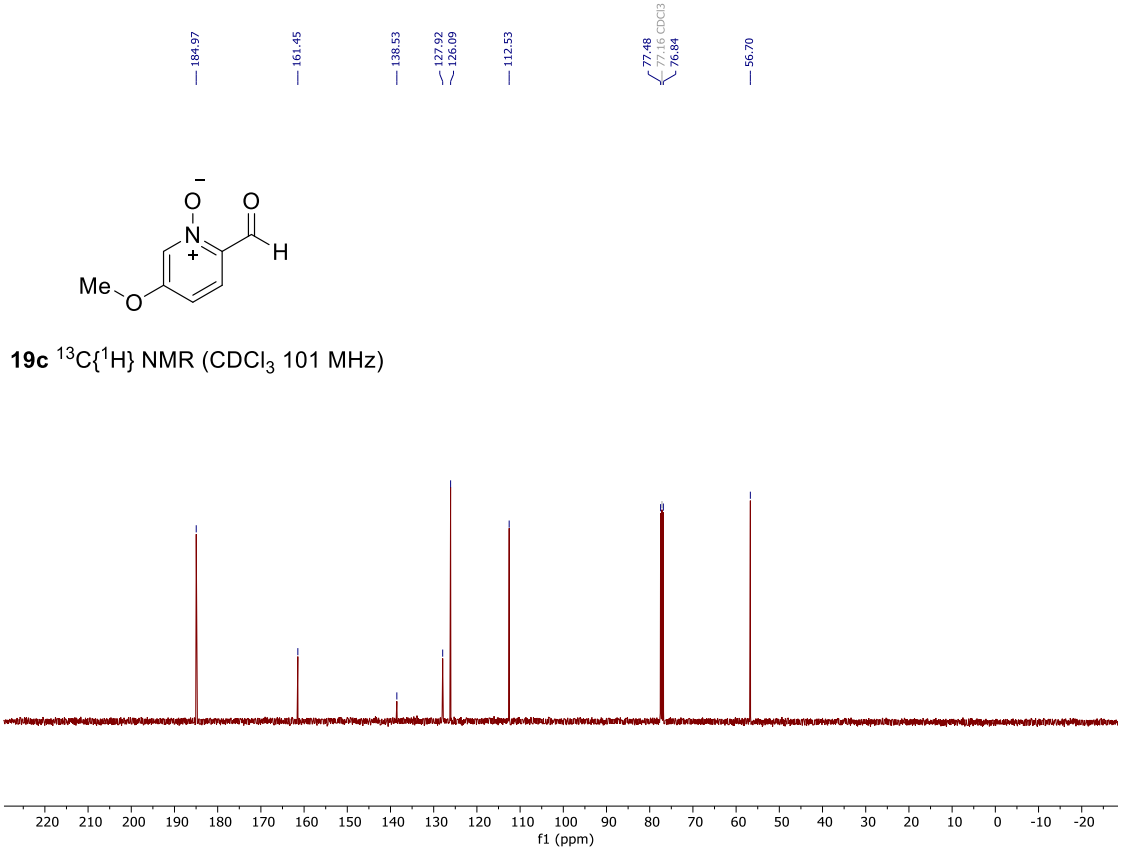
59 ^{1}H NMR ($CDCl_3$ 400 MHz)



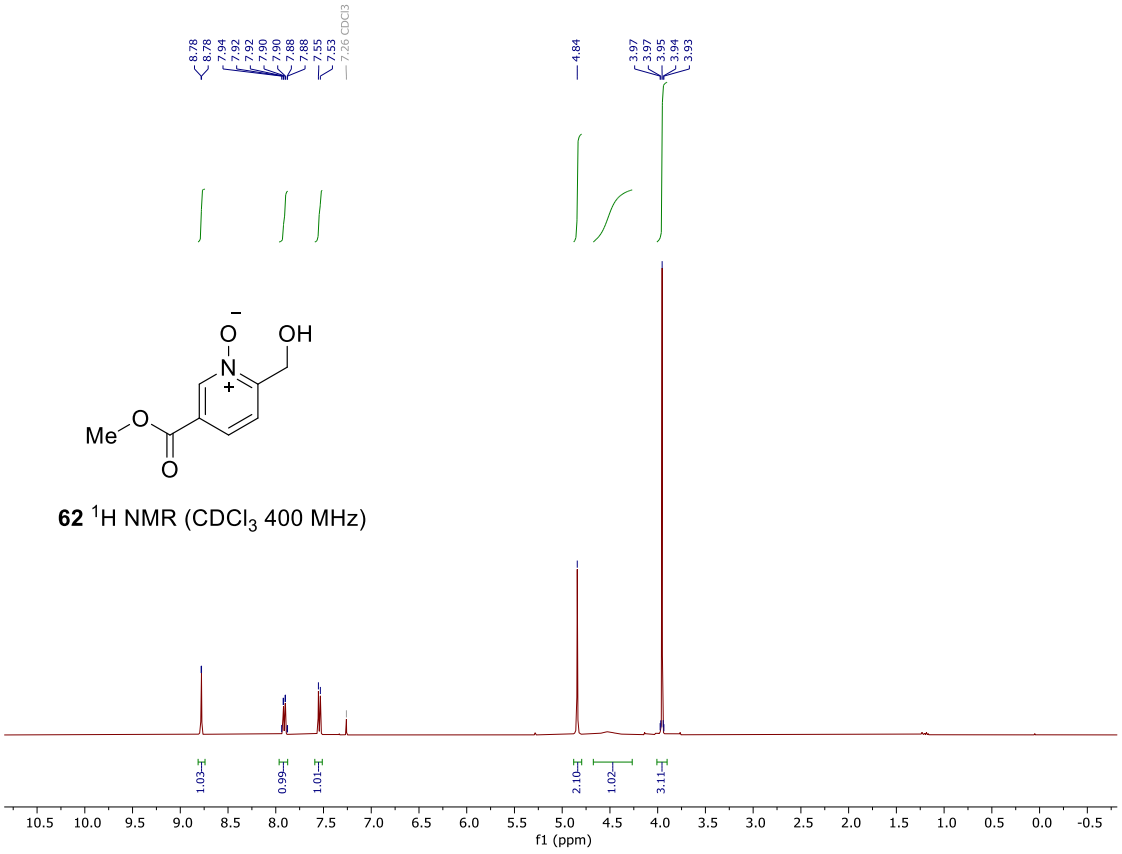
59 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



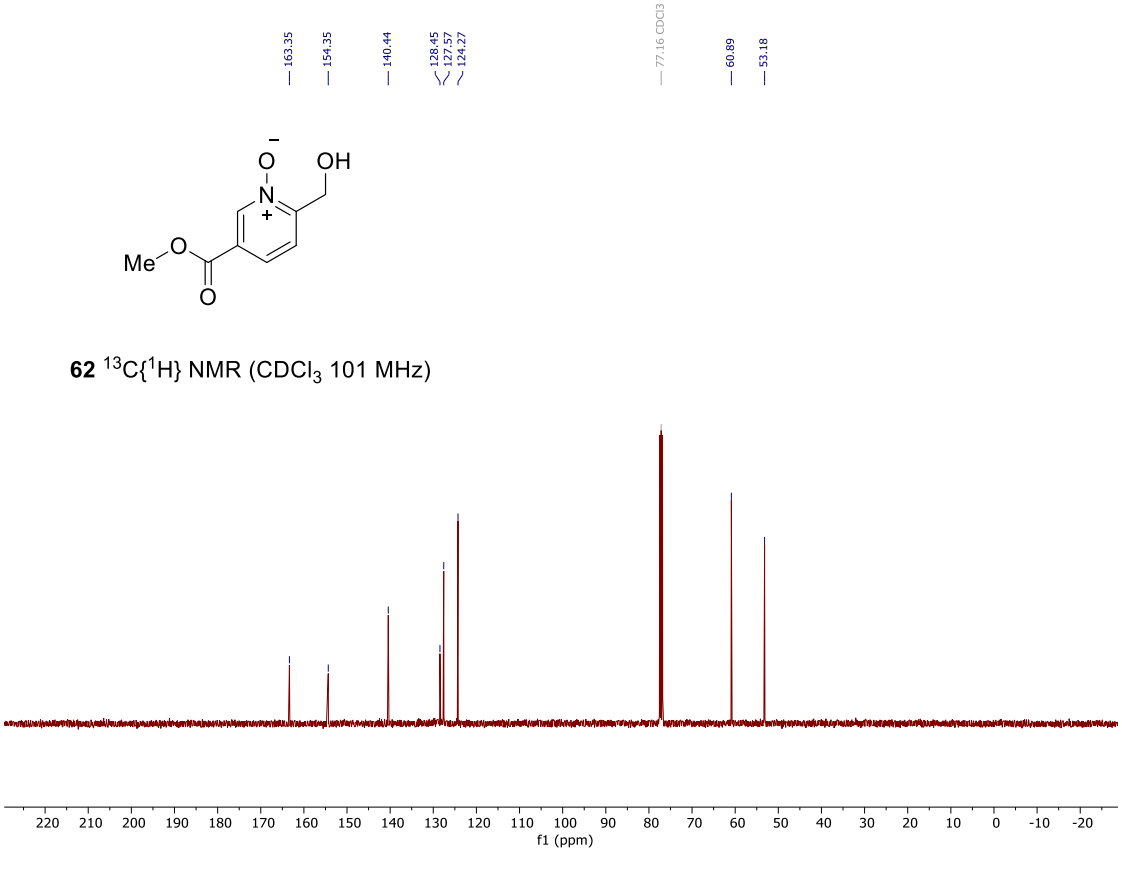
19c ^{1}H NMR ($CDCl_3$ 400 MHz)



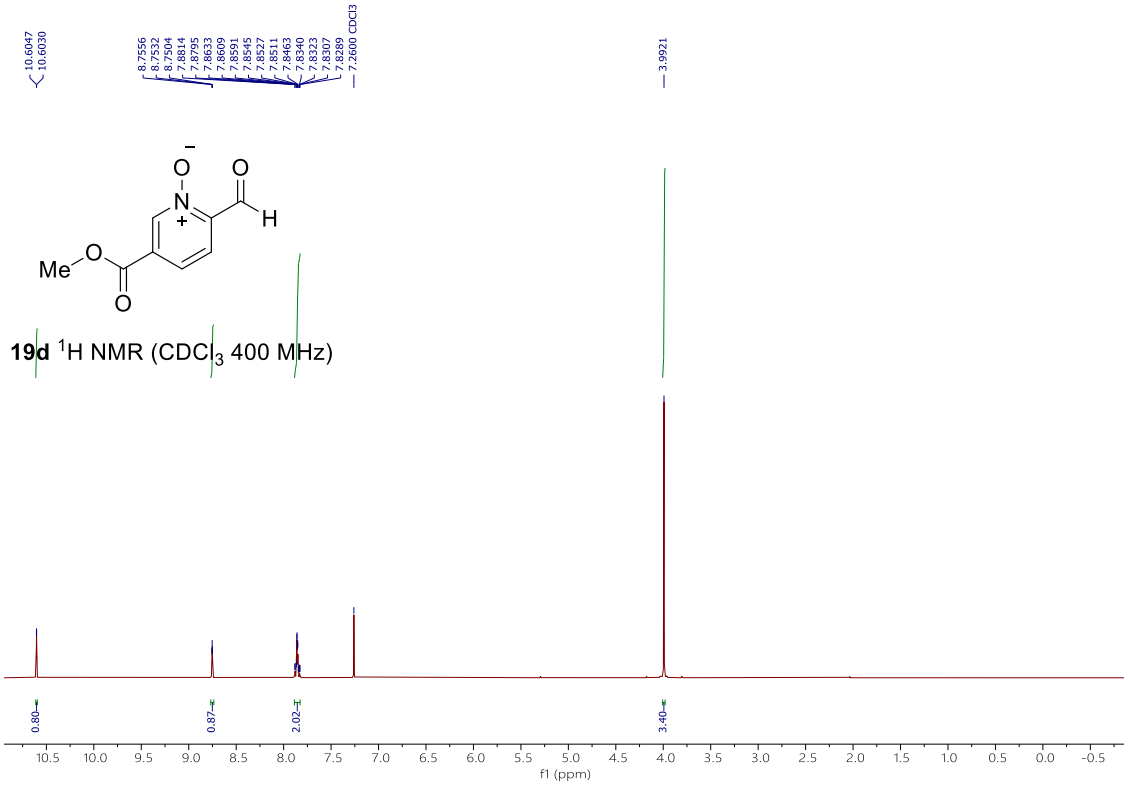
19c $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



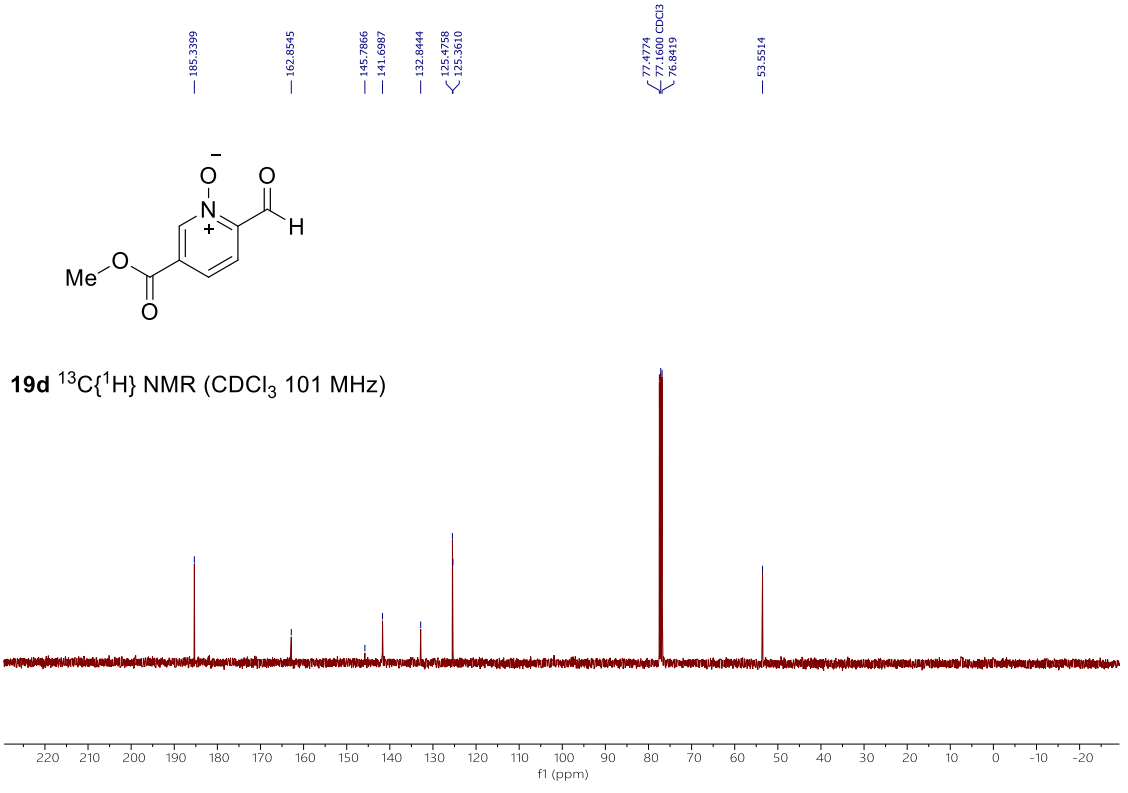
62 ^{1}H NMR ($CDCl_3$ 400 MHz)



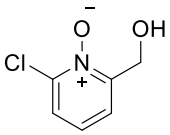
62 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



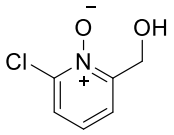
19d ^{1}H NMR ($CDCl_3$ 400 MHz)



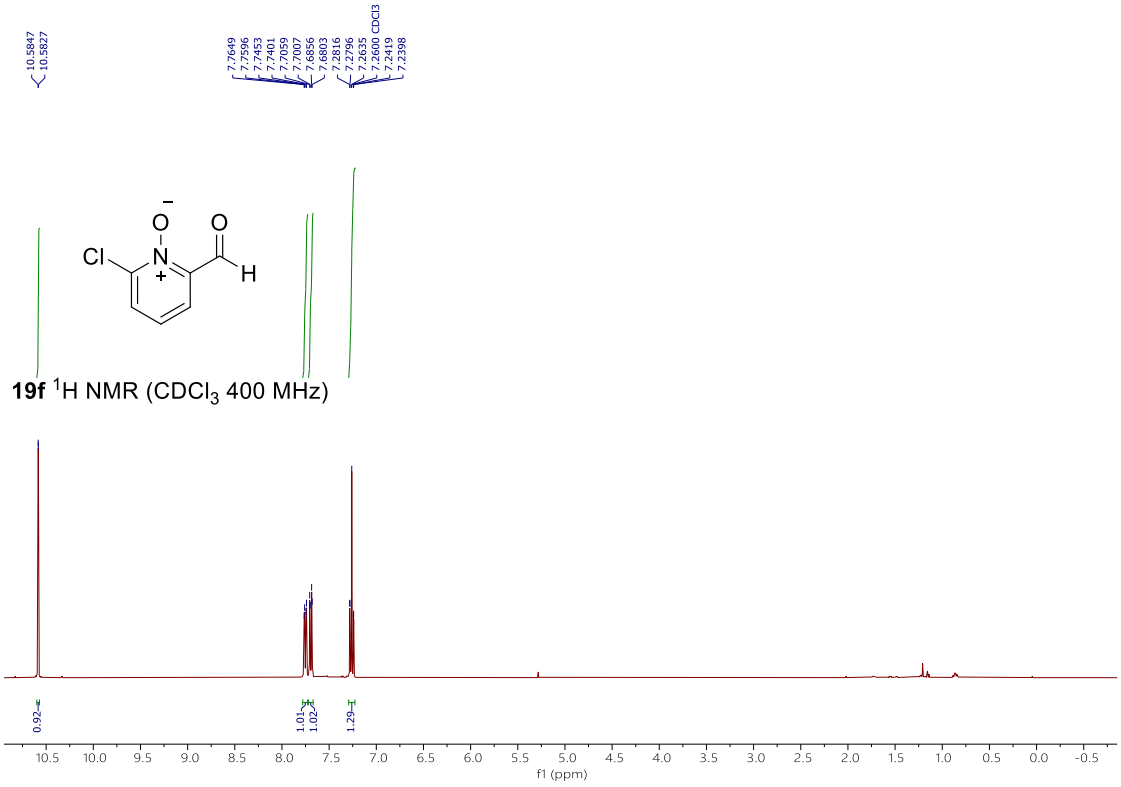
19d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



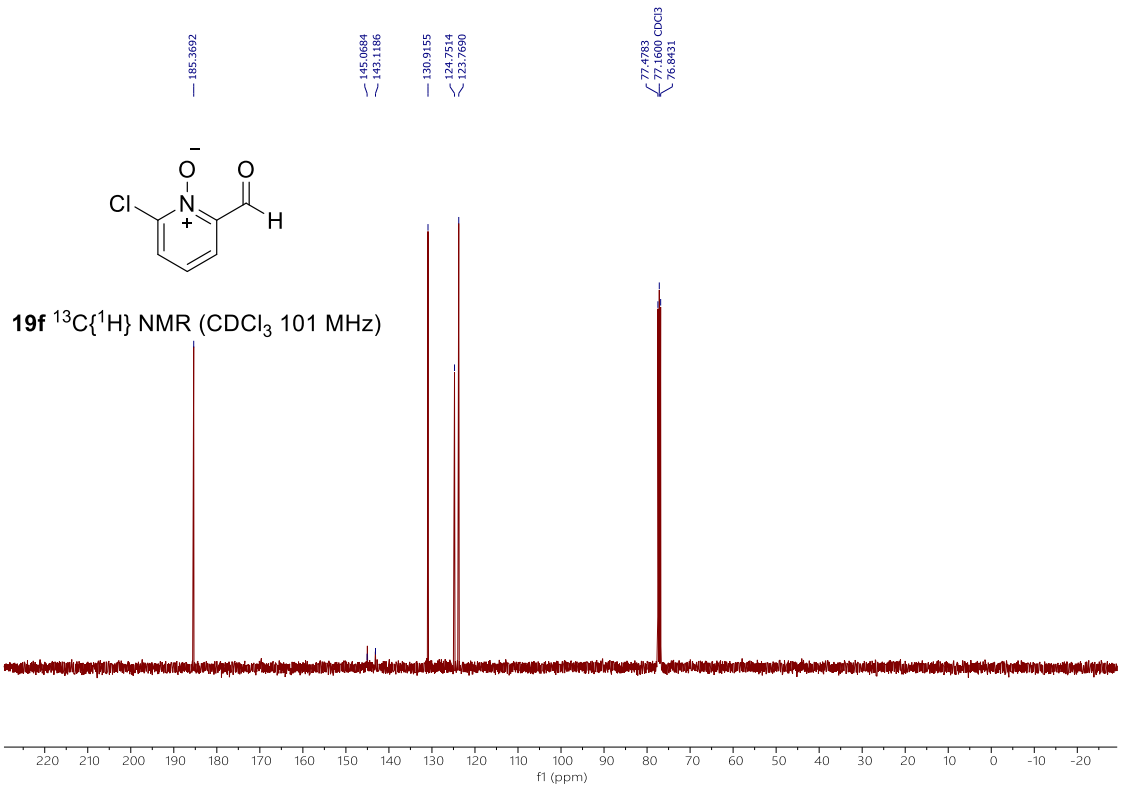
66 ^{1}H NMR ($CDCl_3$ 400 MHz)



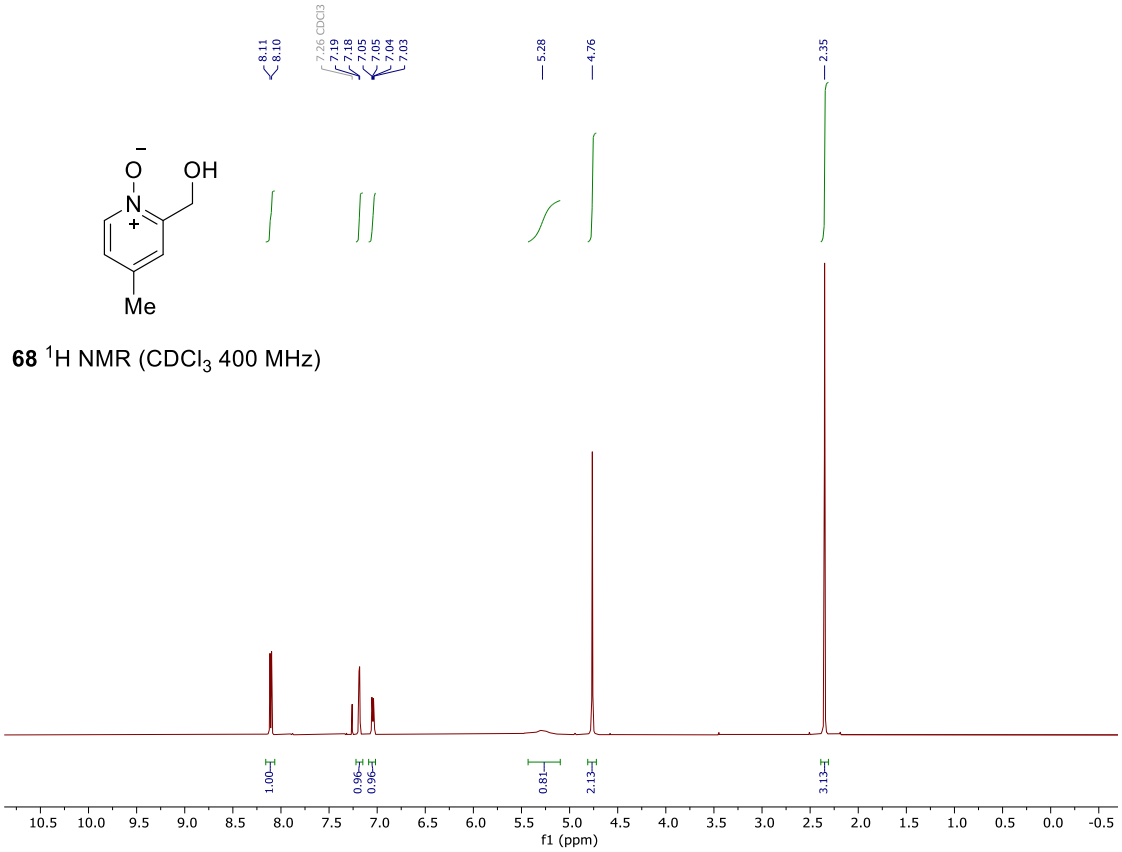
66 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



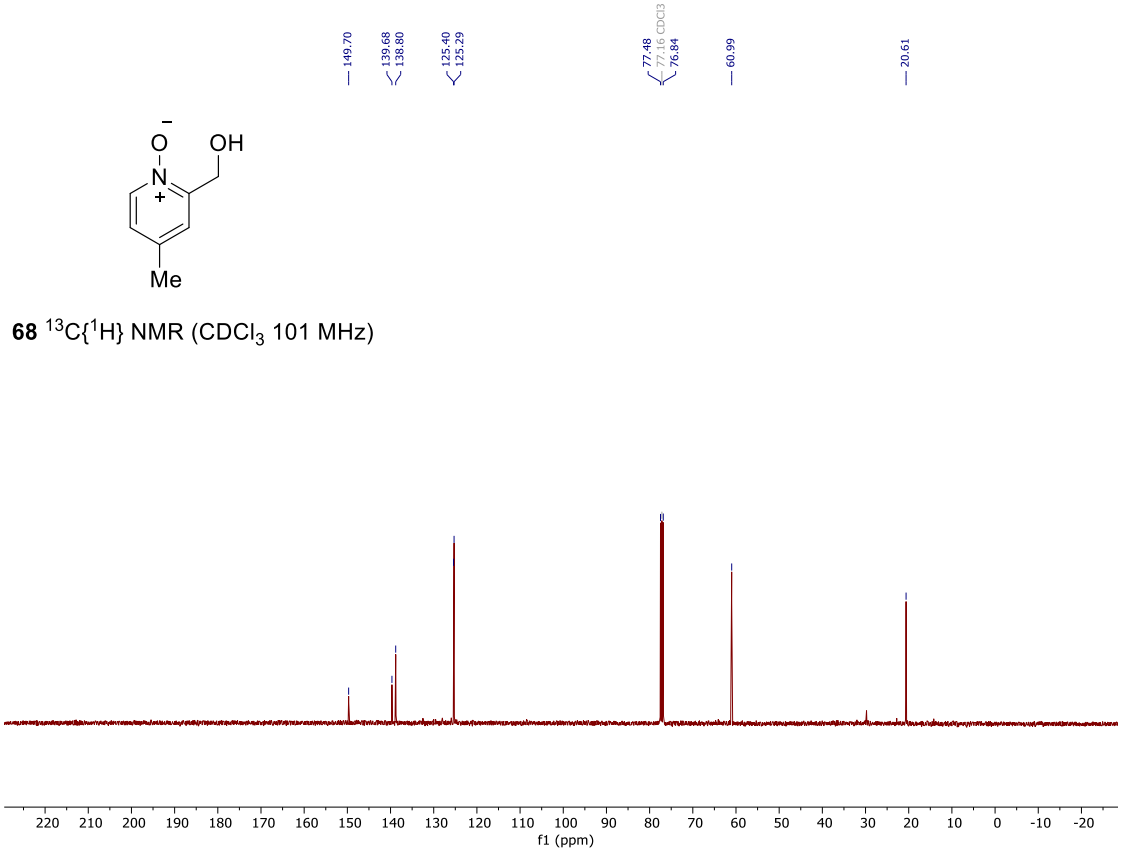
19f ^{1}H NMR ($CDCl_3$ 400 MHz)



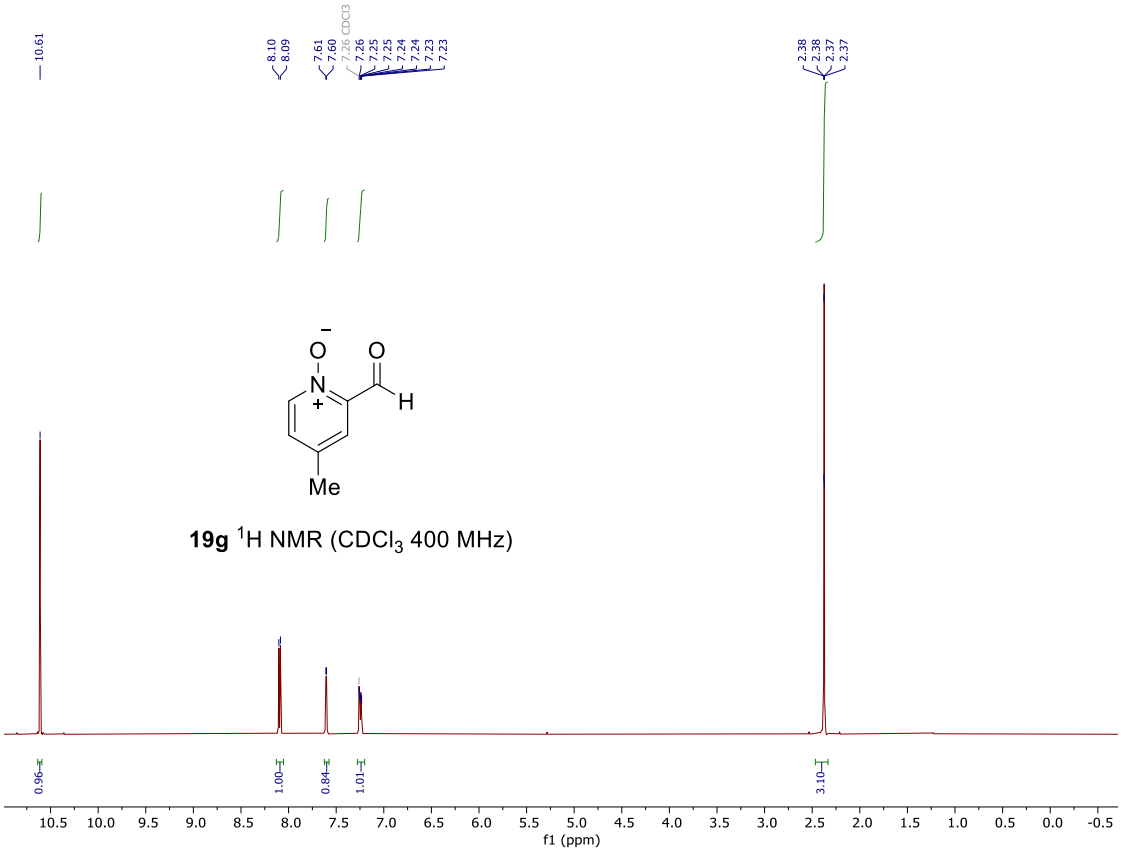
19f $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



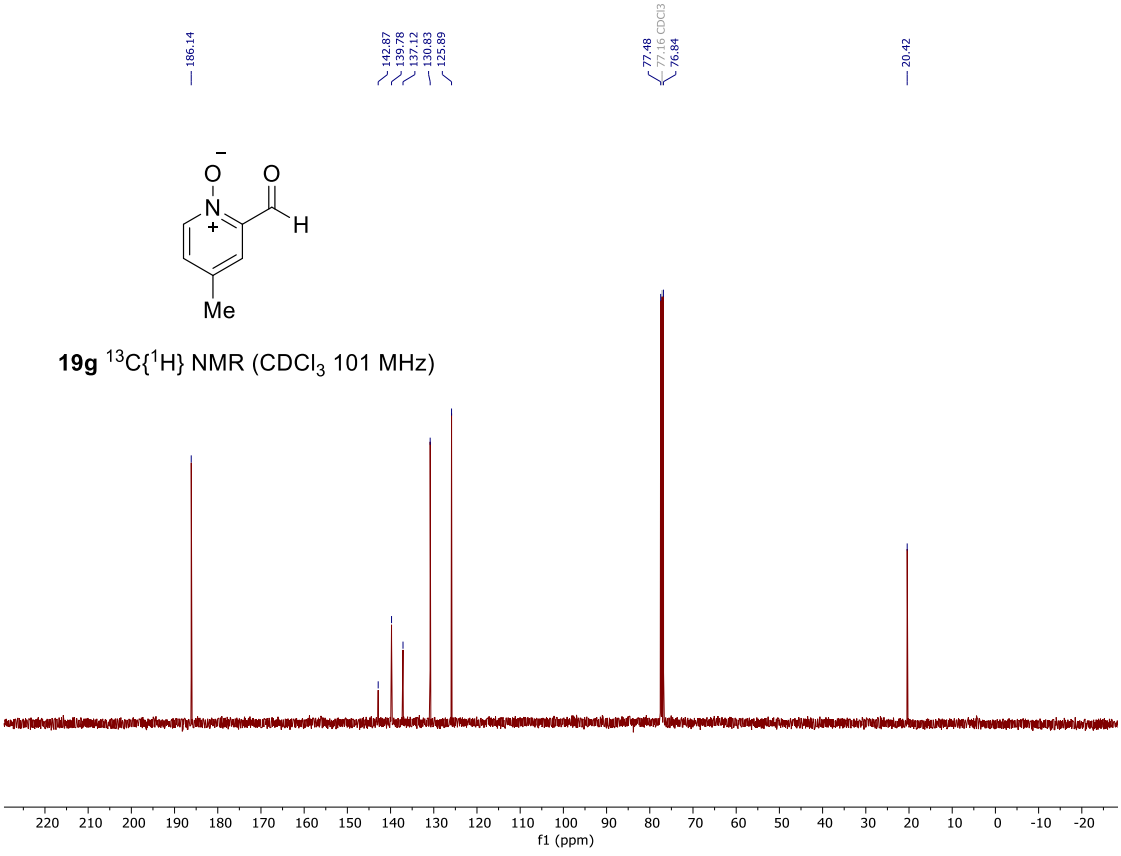
68 ^{1}H NMR ($CDCl_3$ 400 MHz)



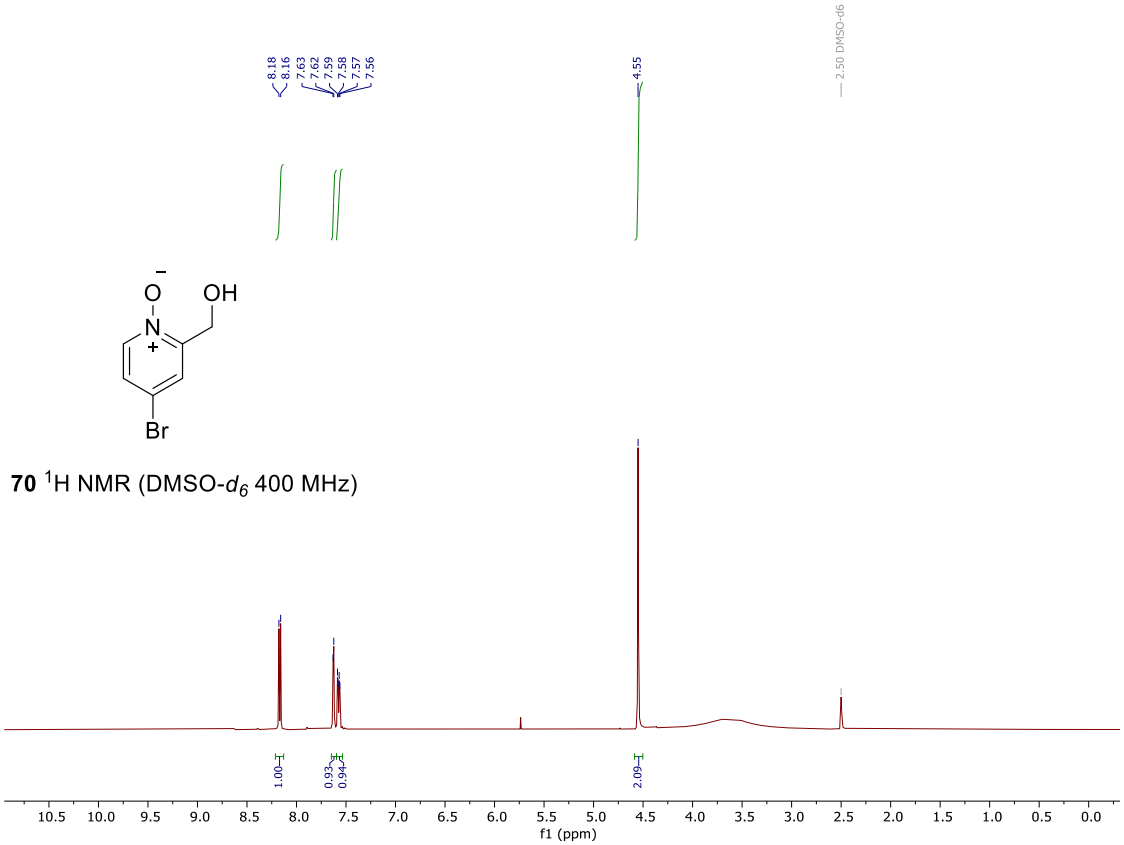
68 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



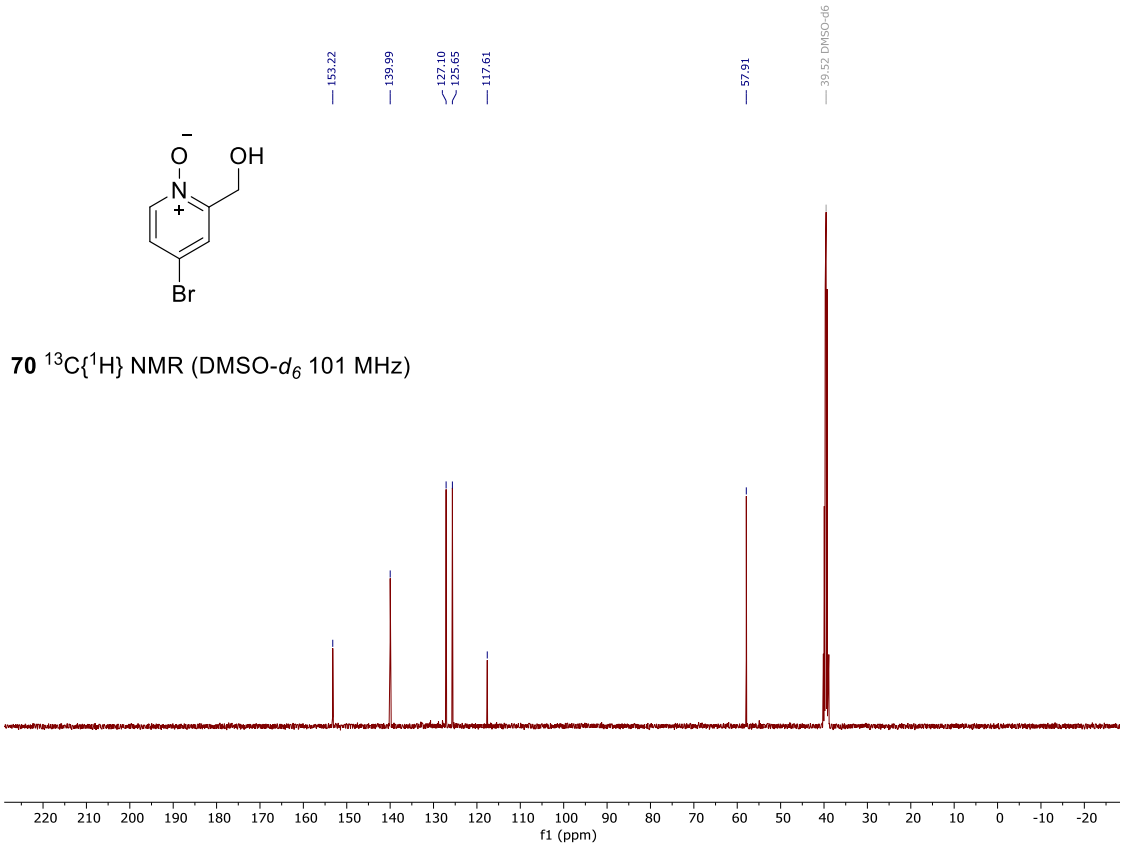
19g ^{1}H NMR ($CDCl_3$ 400 MHz)



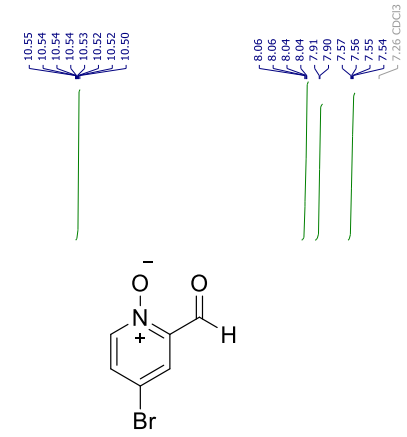
19g $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



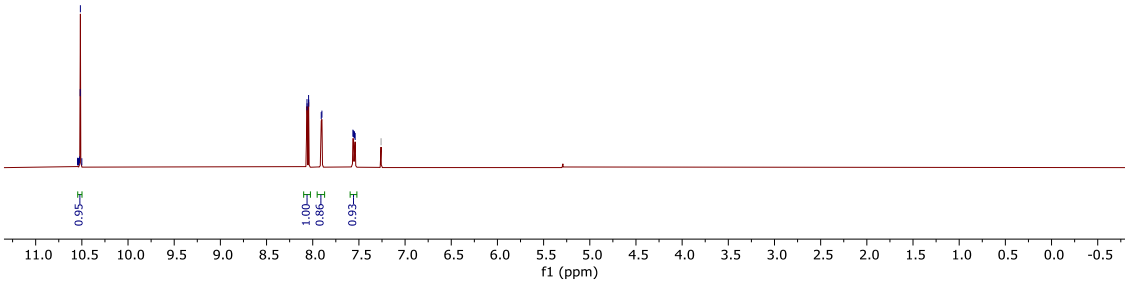
70 ^{1}H NMR (DMSO-d_6 400 MHz)

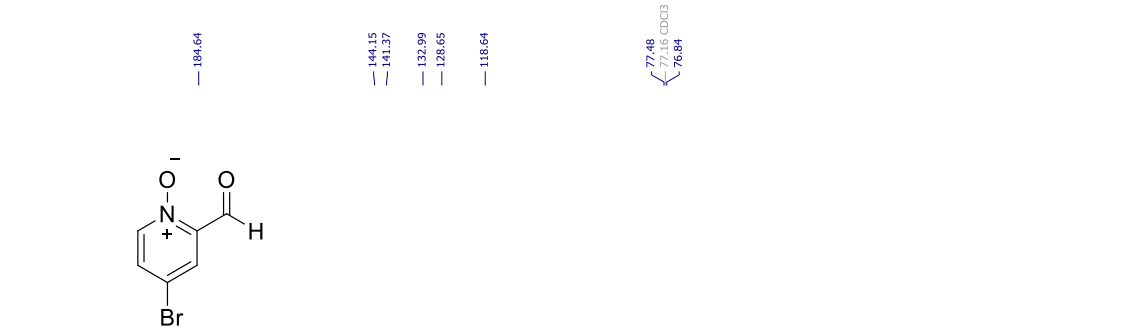


70 ^{13}C{^{1}H} NMR (DMSO-d_6 101 MHz)

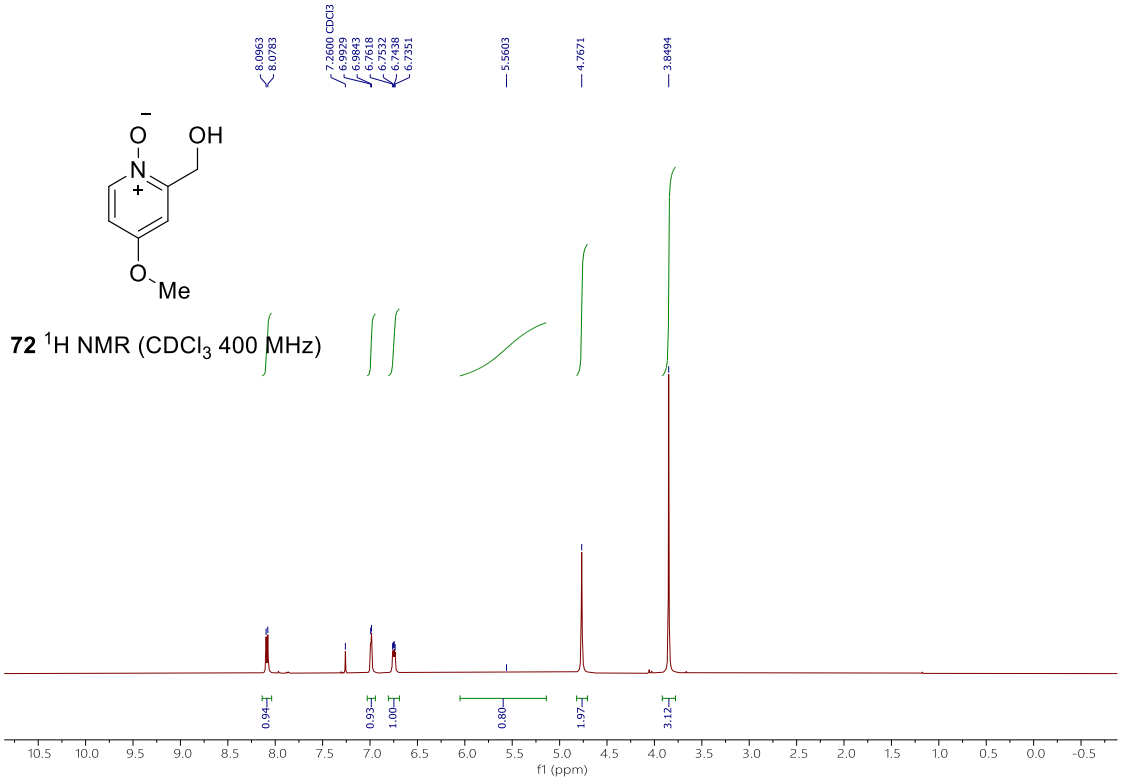


19h ^{1}H NMR ($CDCl_3$ 400 MHz)

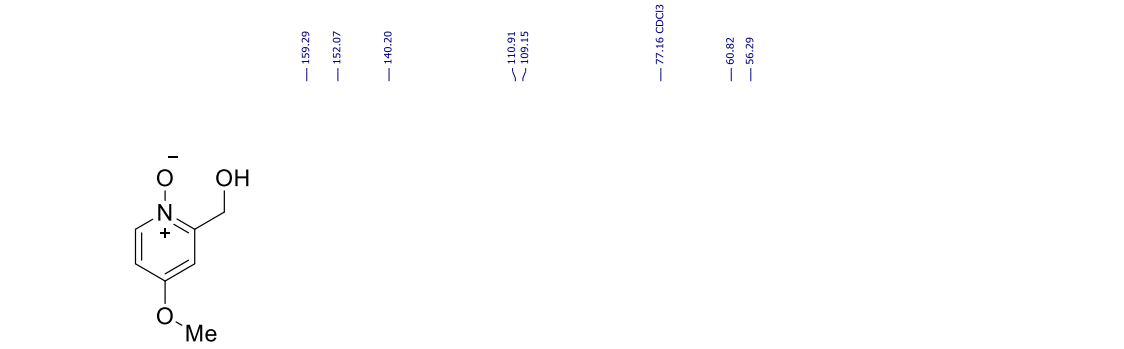




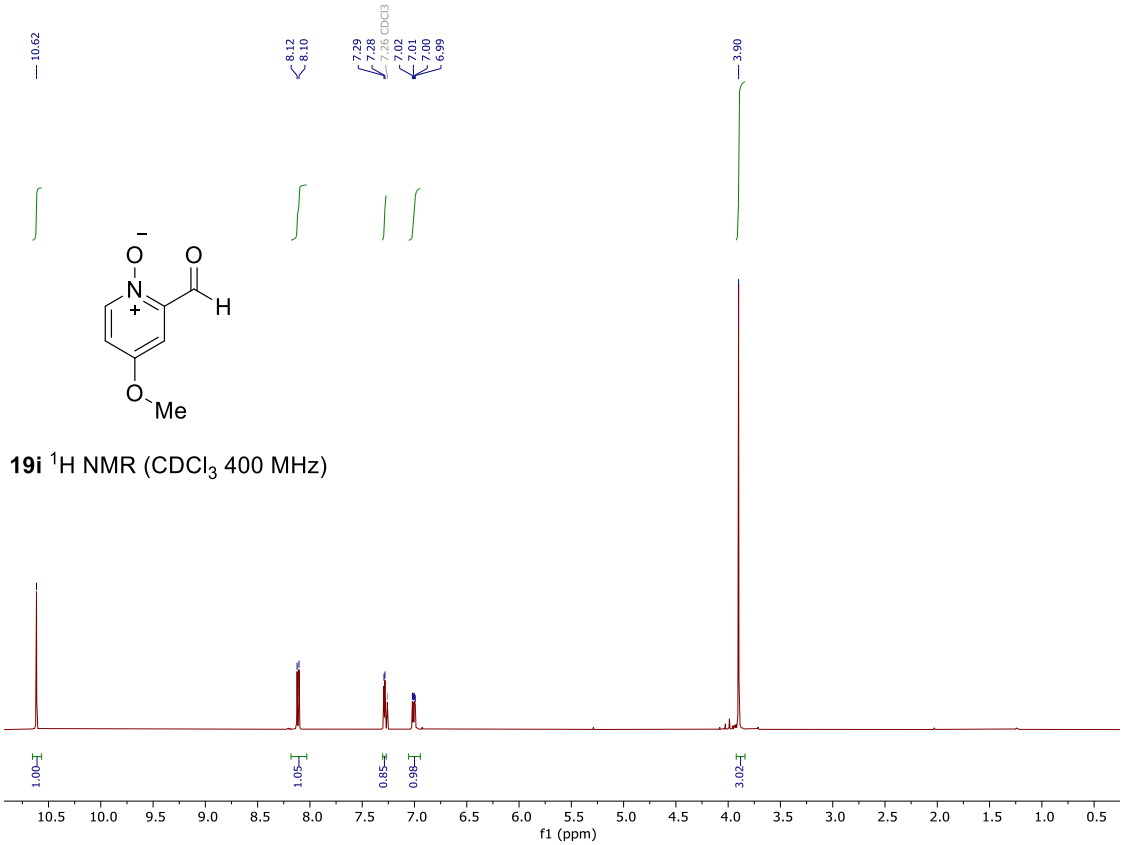
19h $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



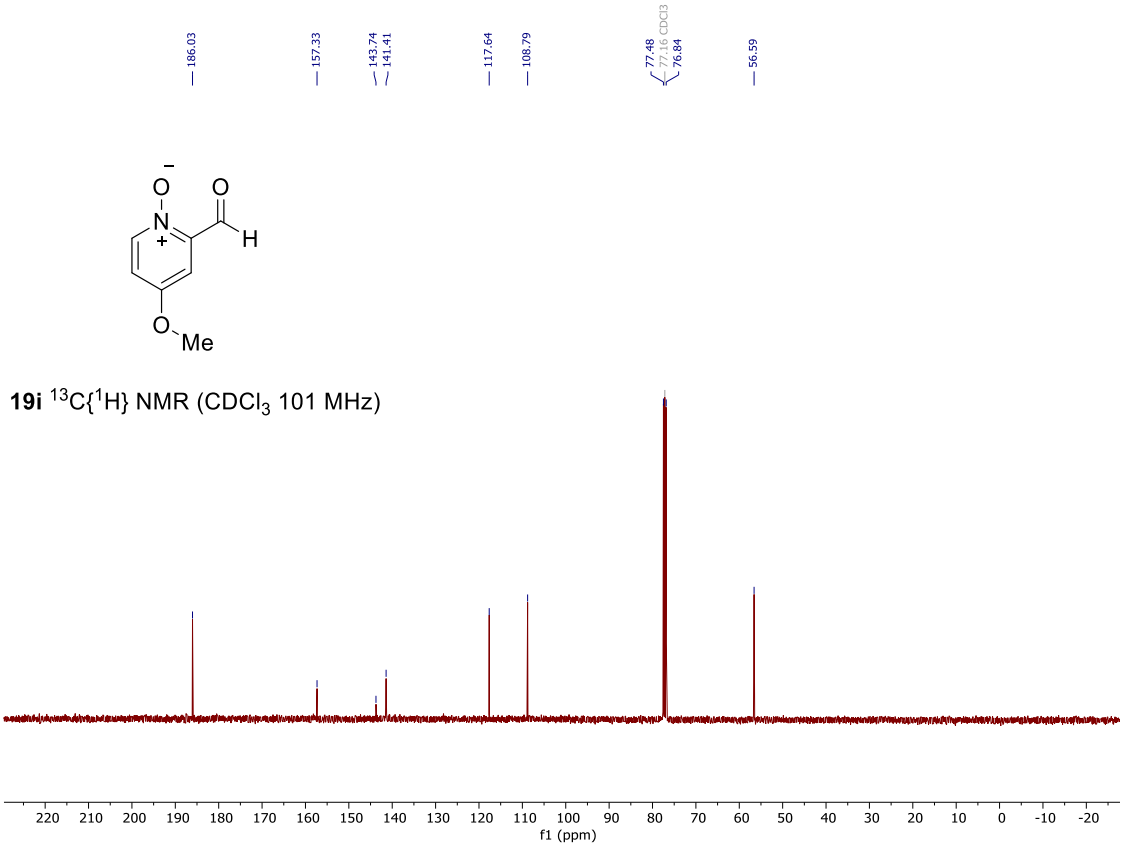
72 ^{1}H NMR ($CDCl_3$ 400 MHz)



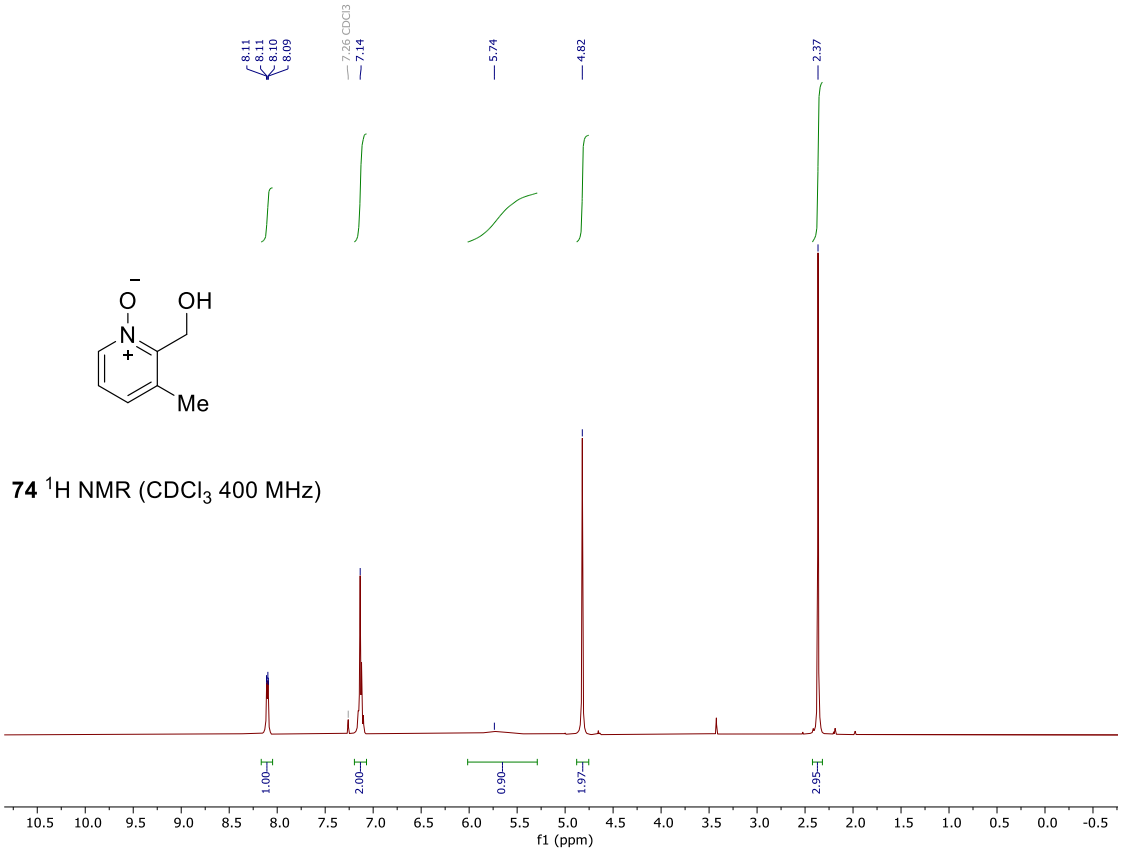
72 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



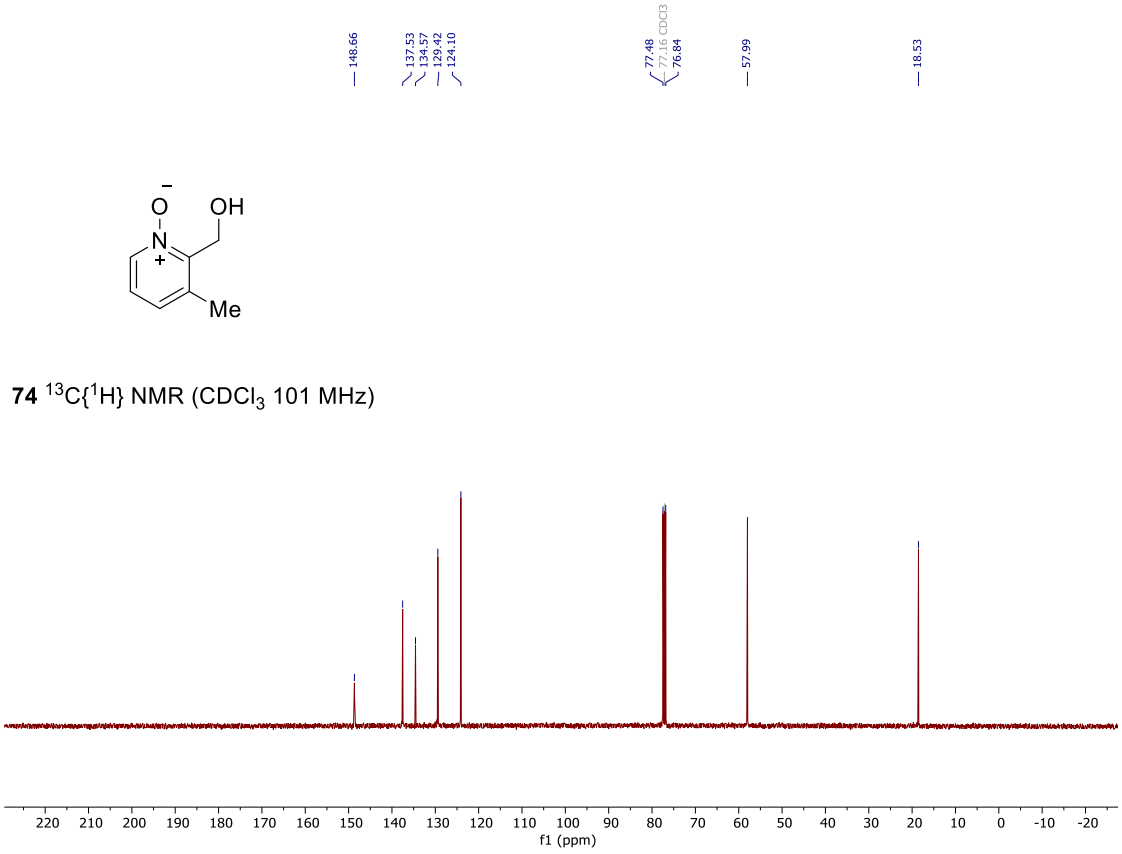
19i ^{1}H NMR ($CDCl_3$ 400 MHz)



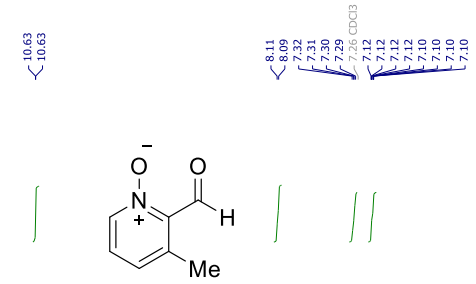
19i $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



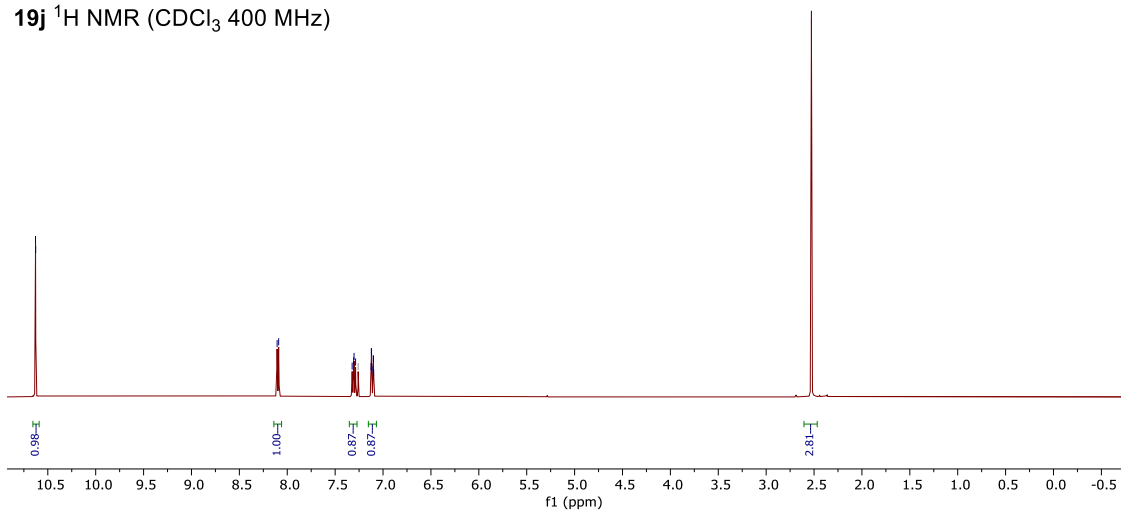
74 ^{1}H NMR ($CDCl_3$ 400 MHz)

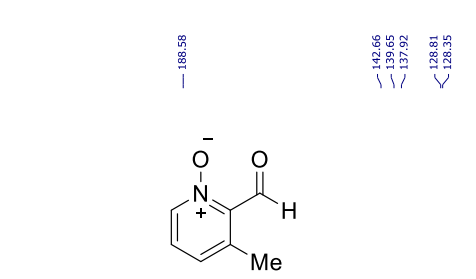


74 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

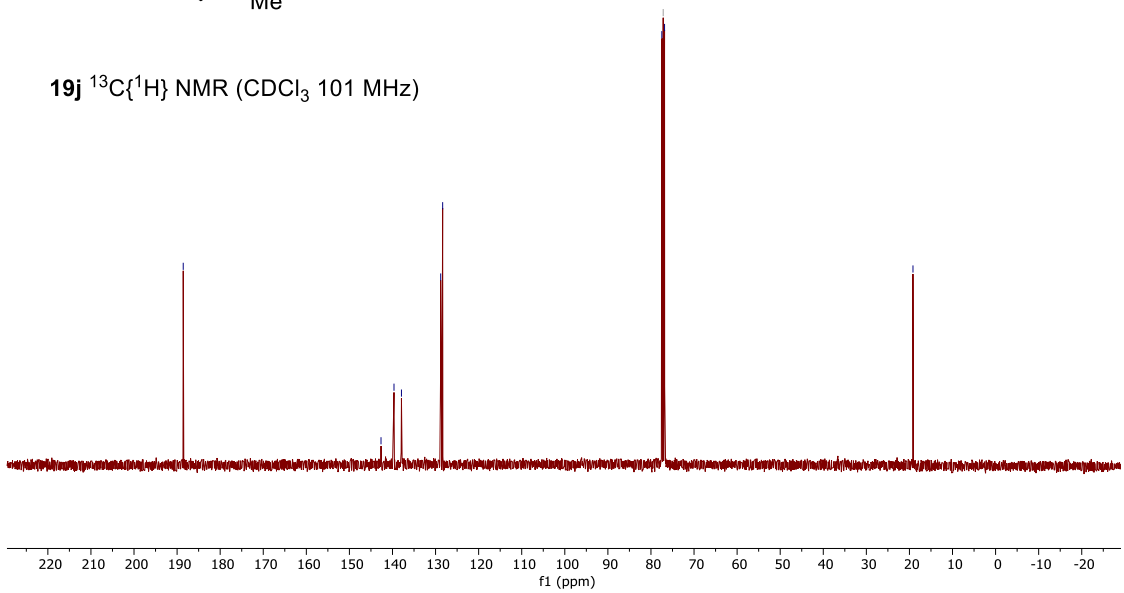


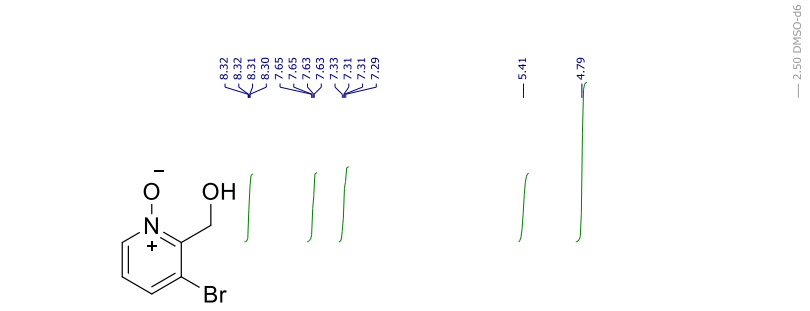
19j ^{1}H NMR ($CDCl_3$ 400 MHz)



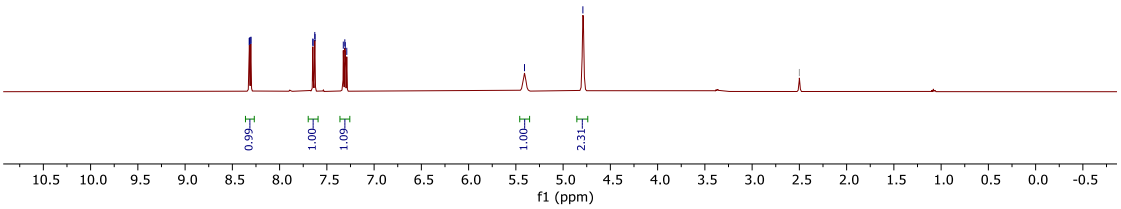


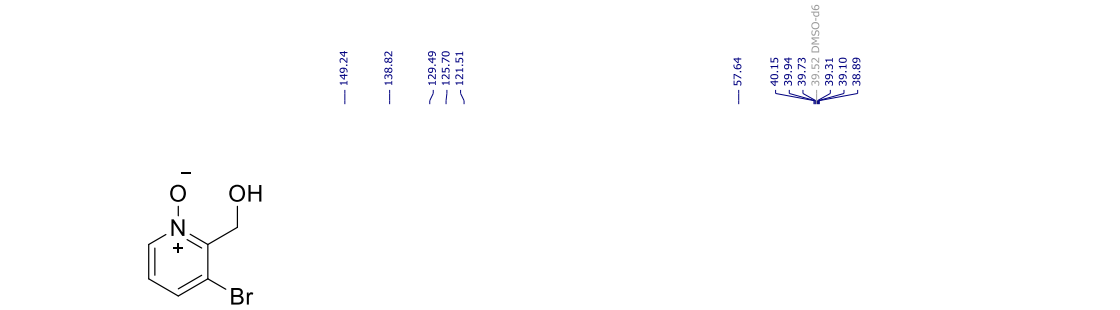
19j ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



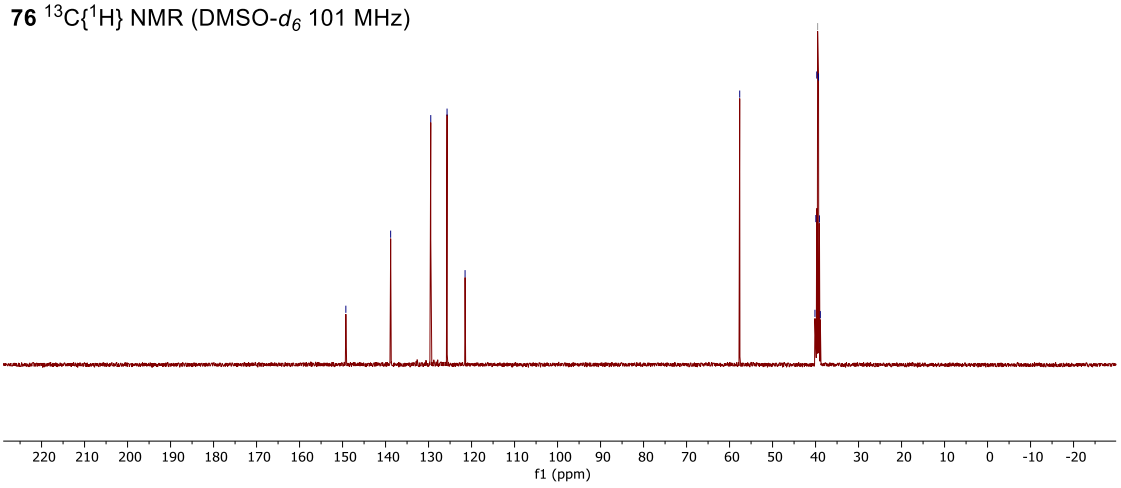


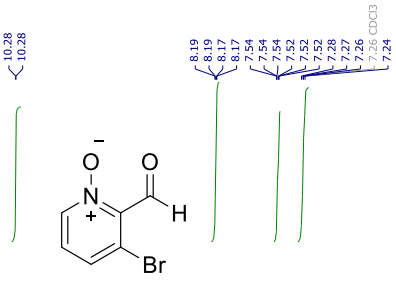
76 ^{1}H NMR (DMSO-d_6 400 MHz)



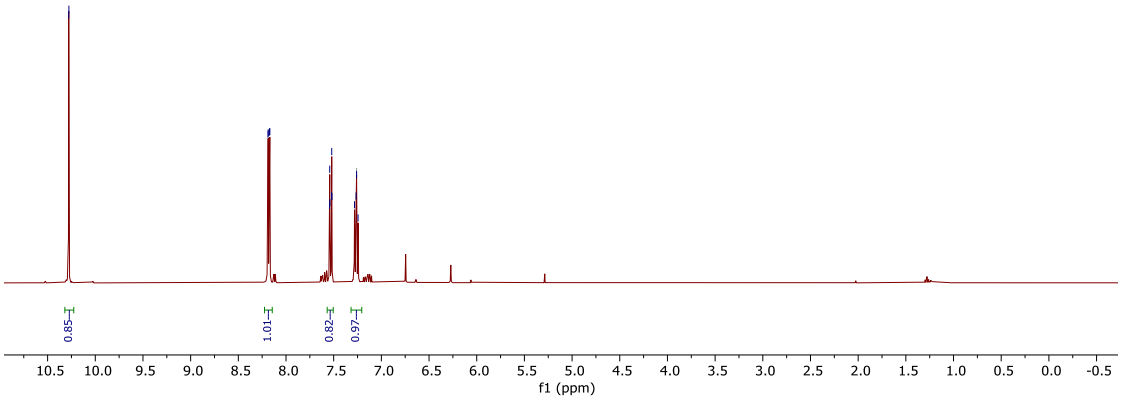


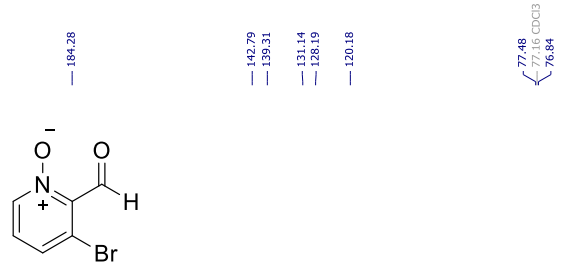
76 ^{13}C{^{1}H} NMR (DMSO-d_6 101 MHz)



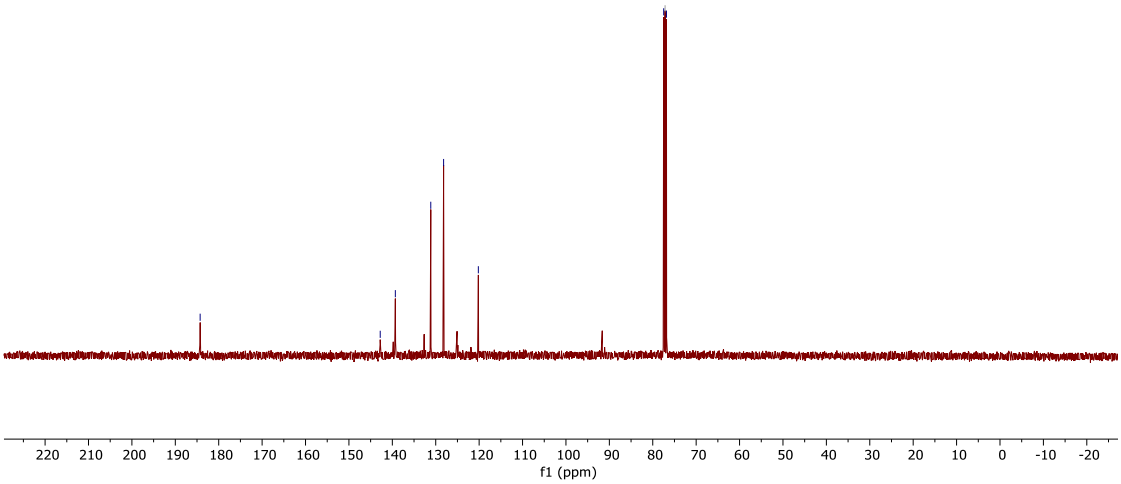


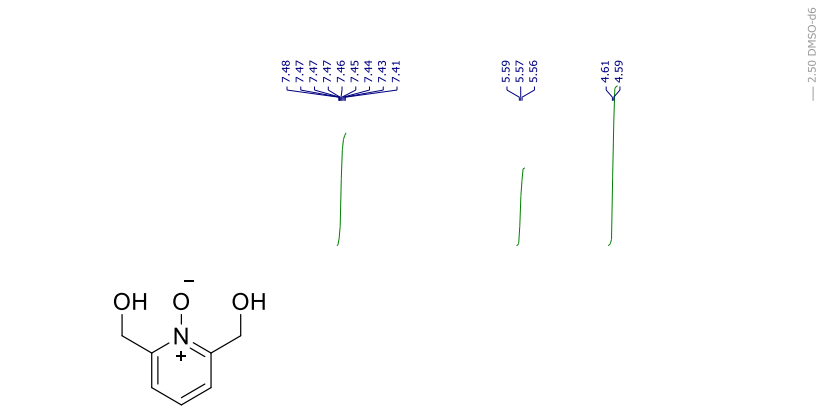
19k ^{1}H NMR ($CDCl_3$ 400 MHz)



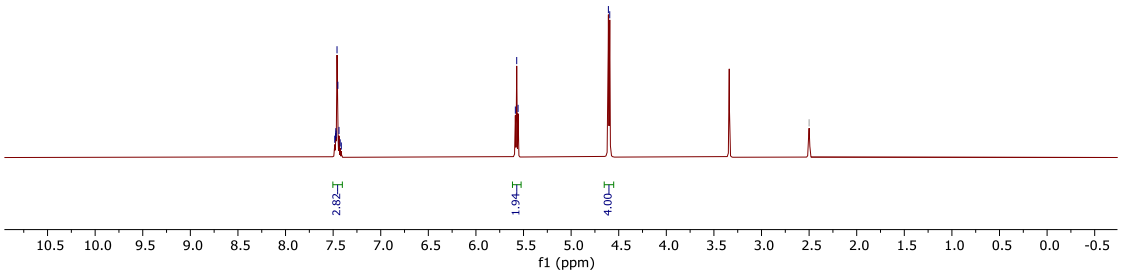


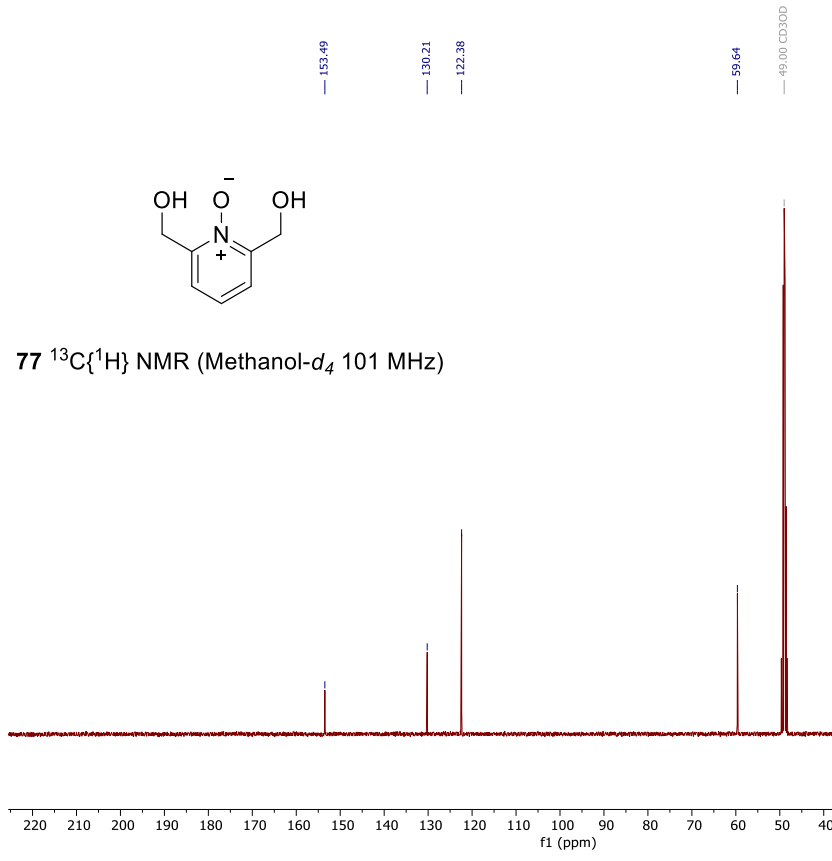
19k $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



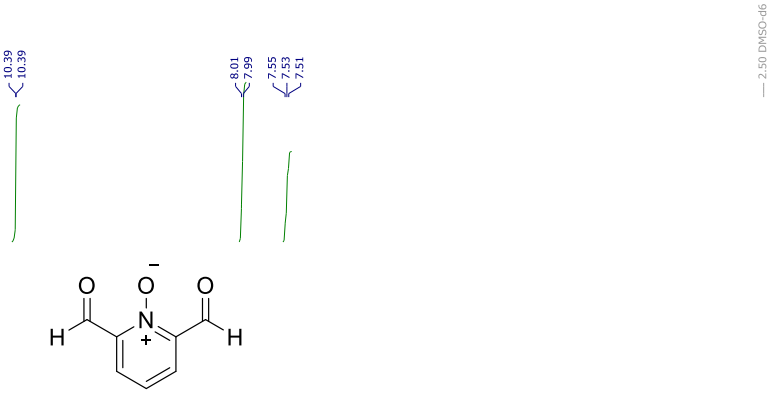


77 ^{1}H NMR (DMSO-d_6 400 MHz)

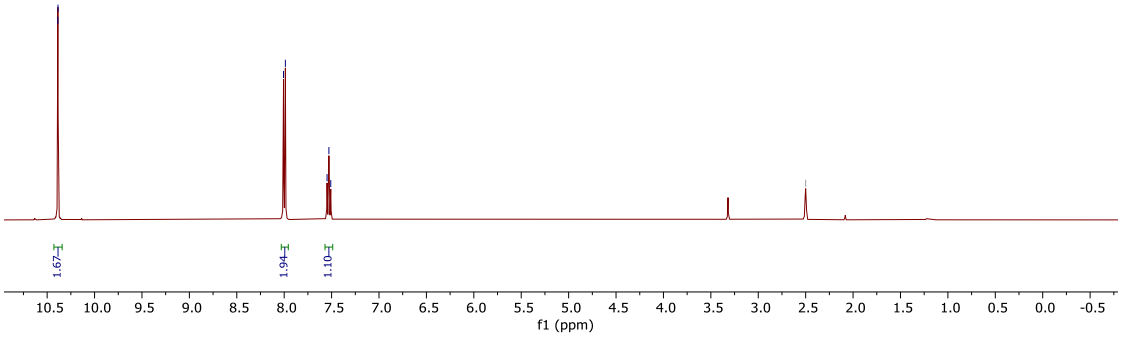


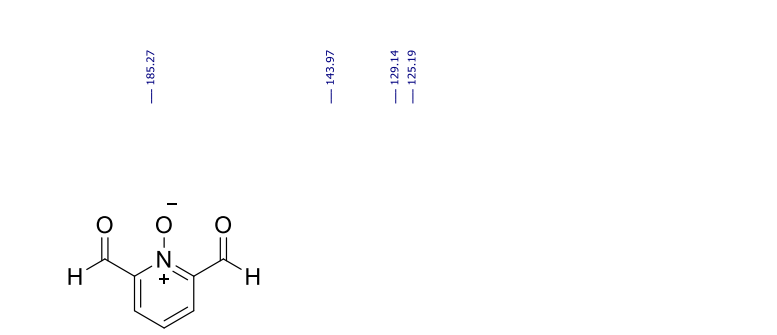


77 ^{13}C{^{1}H} NMR (Methanol-d_4 101 MHz)

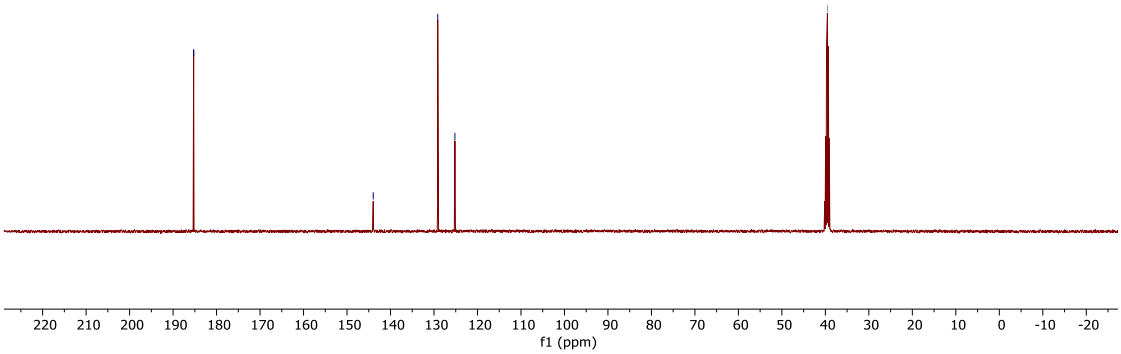


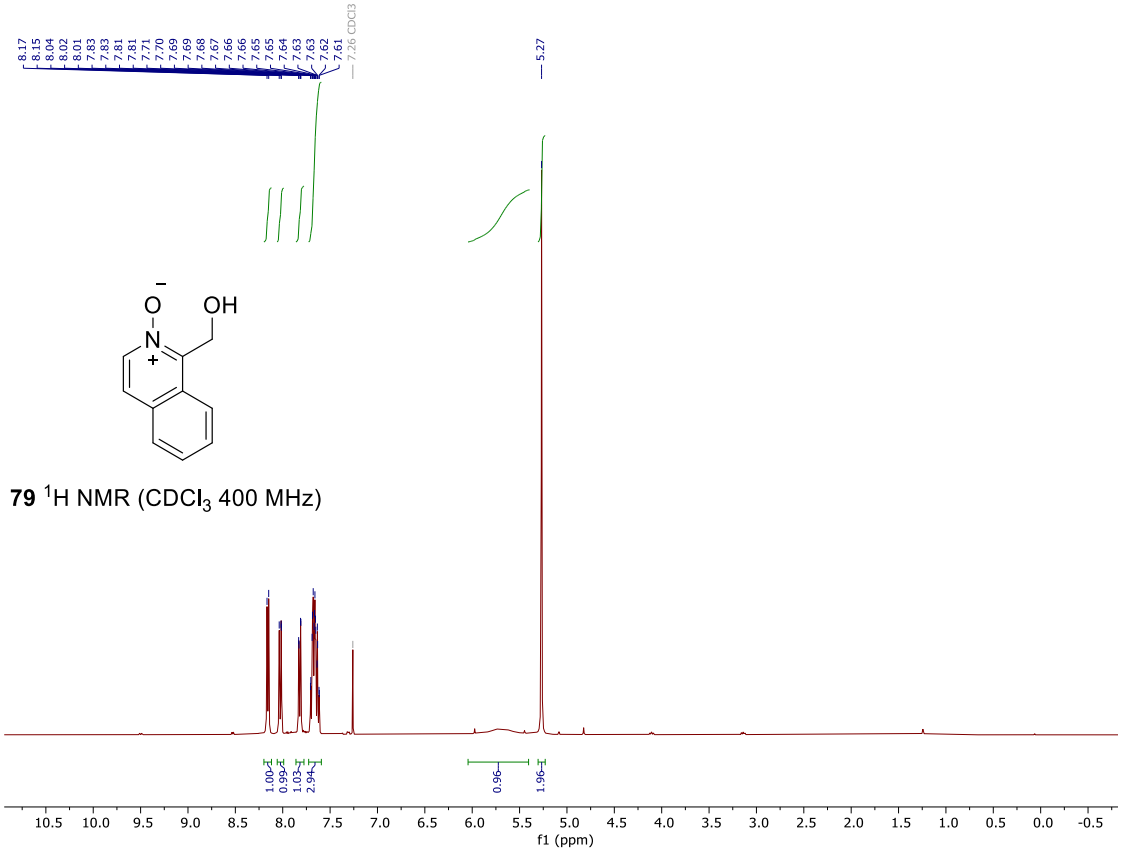
19l ^{1}H NMR (DMSO-d_6 400 MHz)



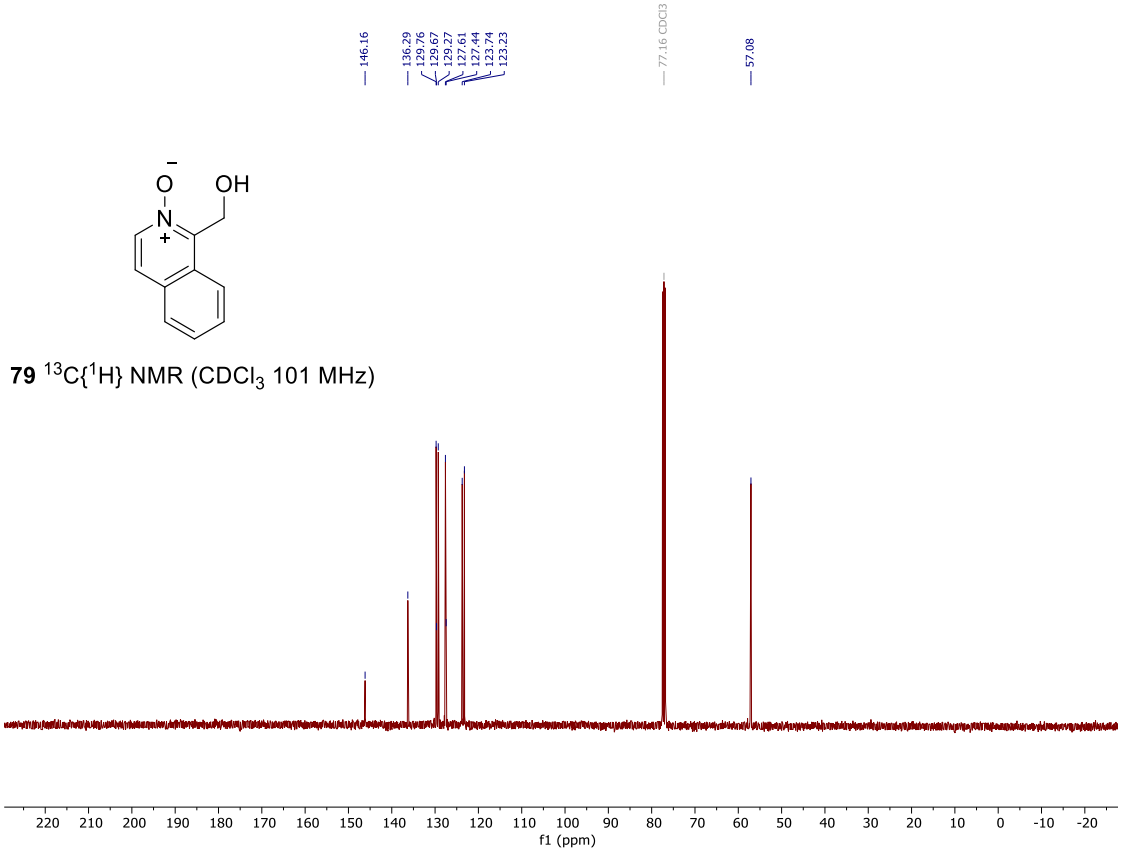


19l ^{13}C{^{1}H} NMR (DMSO-d_6 101 MHz)





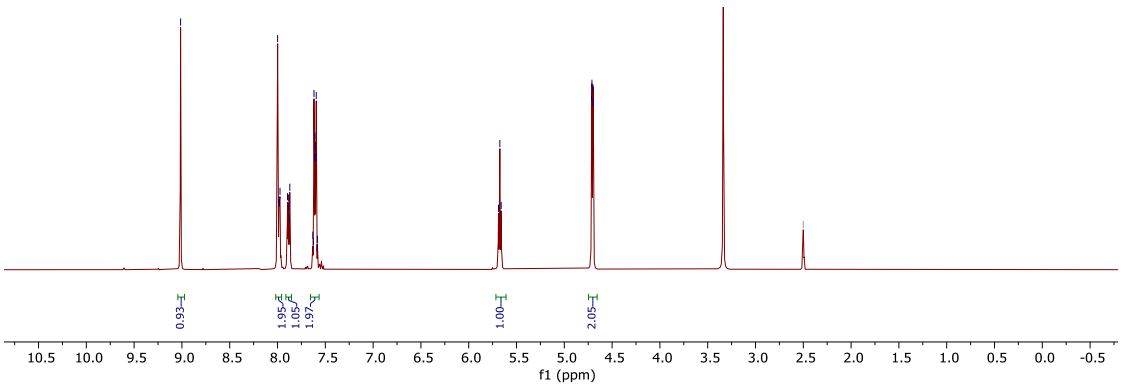
79 ^{1}H NMR ($CDCl_3$ 400 MHz)



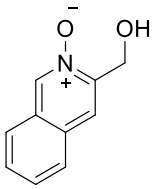
79 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



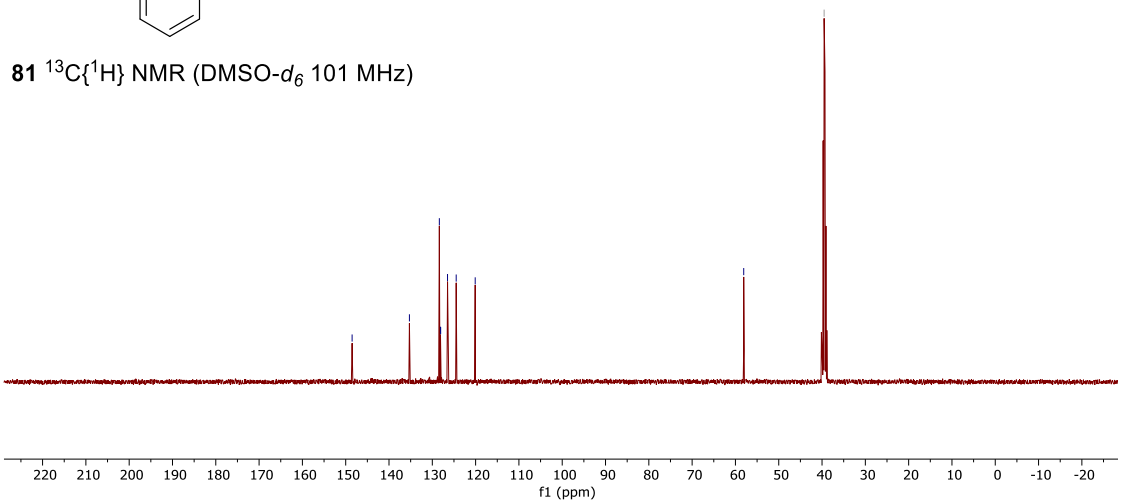
81 ^{1}H NMR (DMSO-d_6 400 MHz)

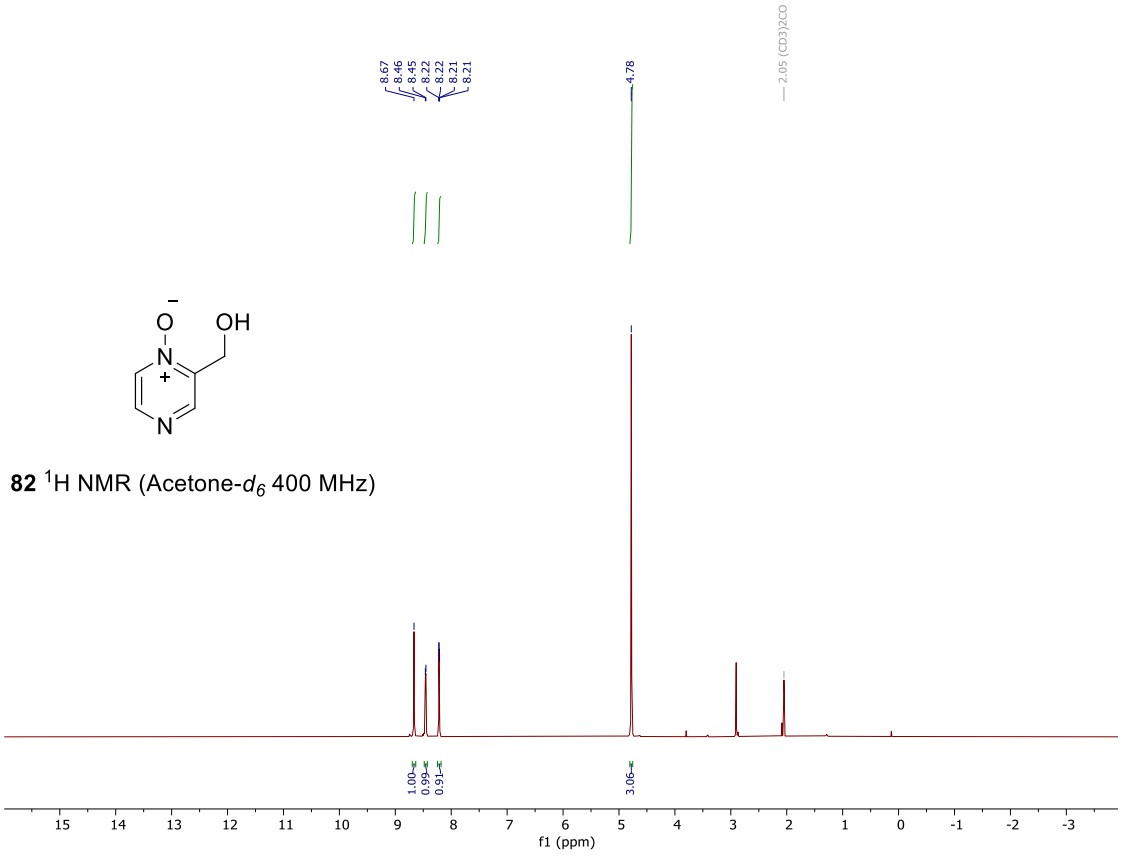




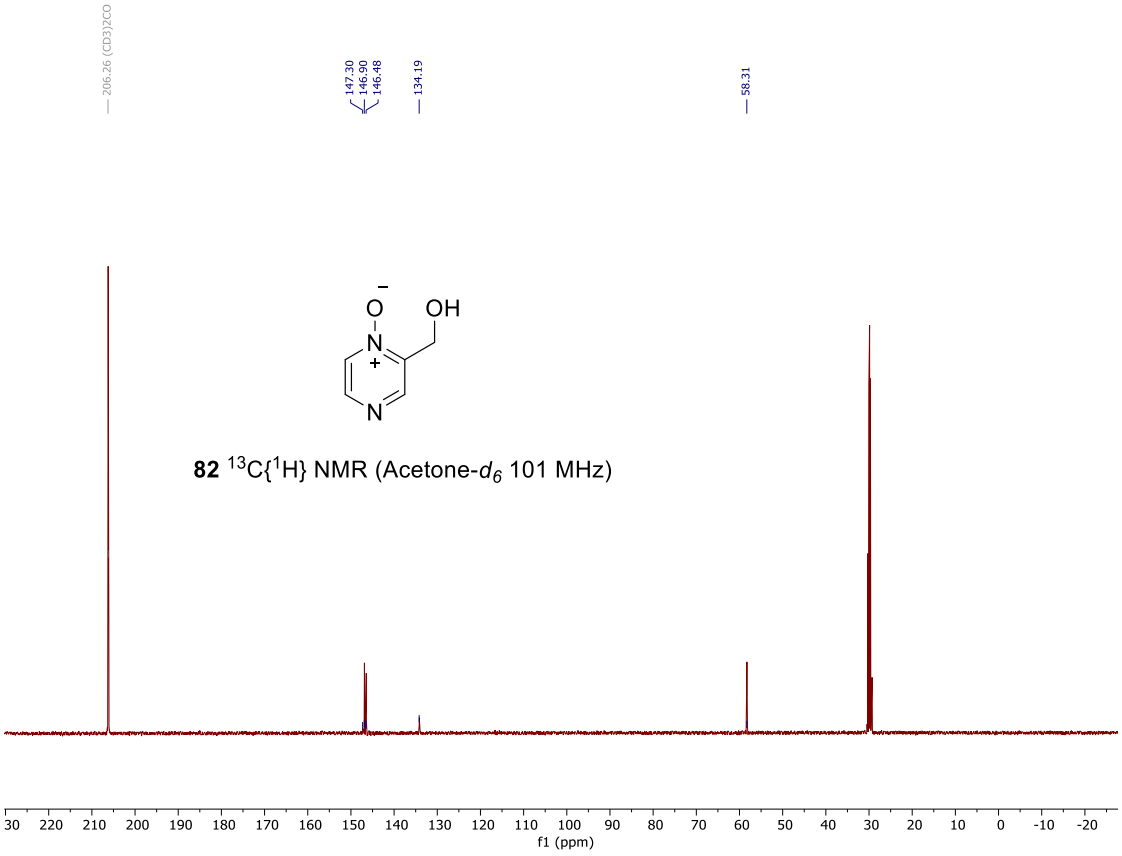


81 ^{13}C{^{1}H} NMR (DMSO-d_6 101 MHz)

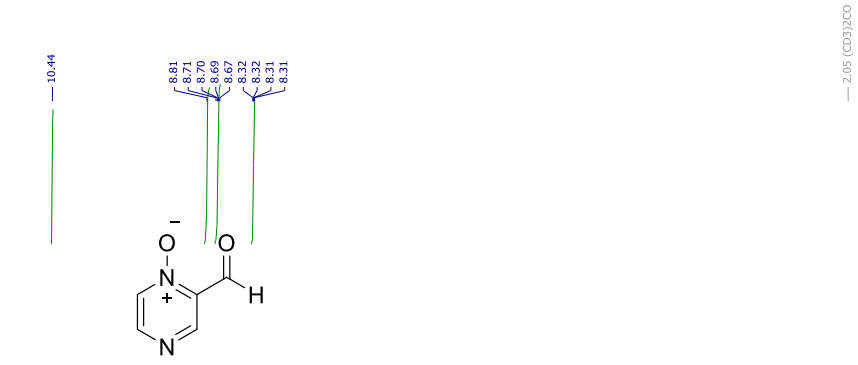




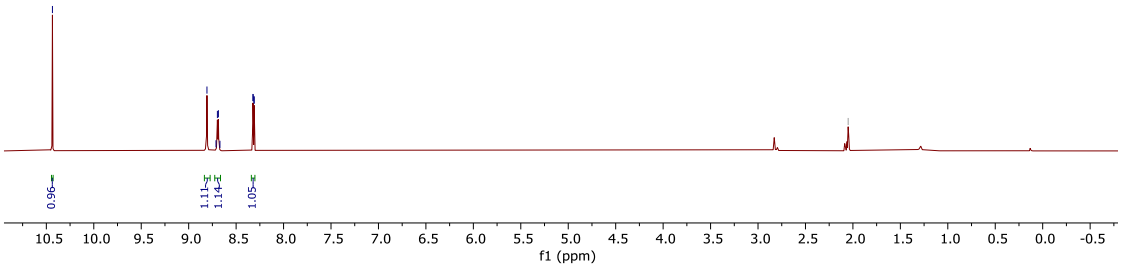
82 ^{1}H NMR (Acetone-d_6 400 MHz)

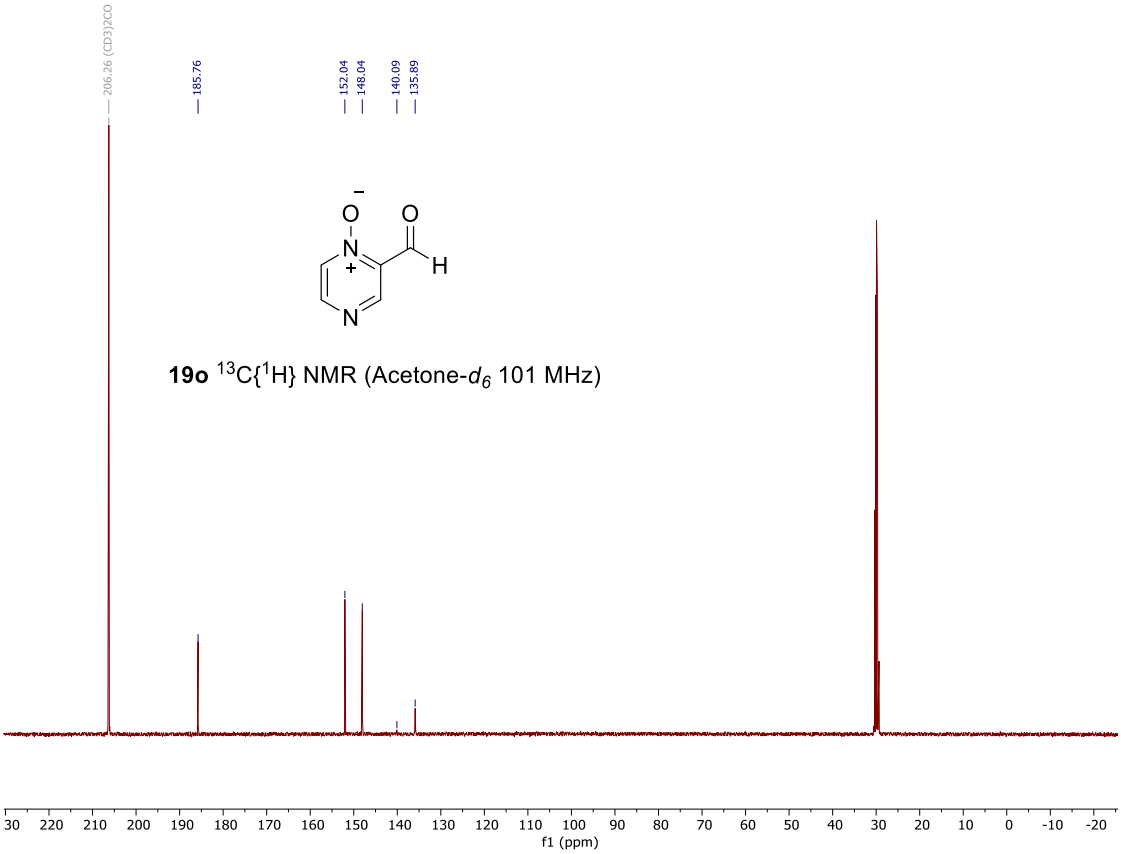


82 ^{13}C{^{1}H} NMR (Acetone-d_6 101 MHz)

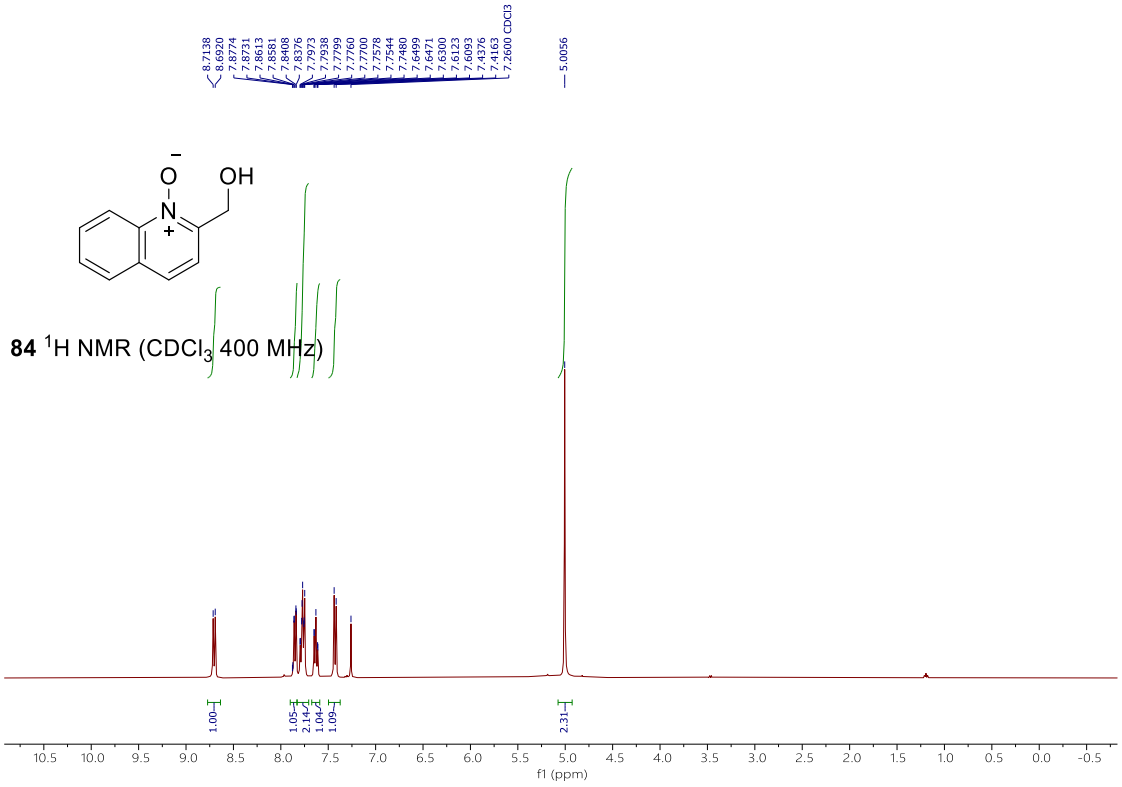


19o ^{1}H NMR (Acetone-d_6 400 MHz)

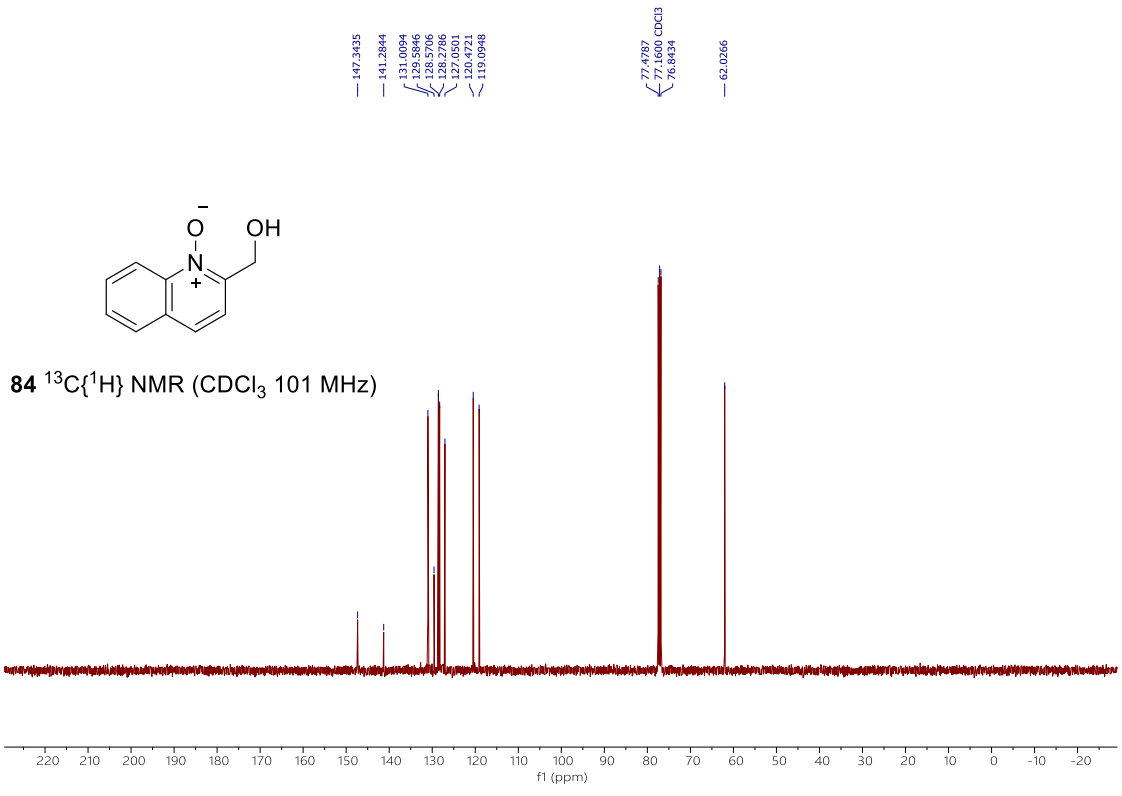




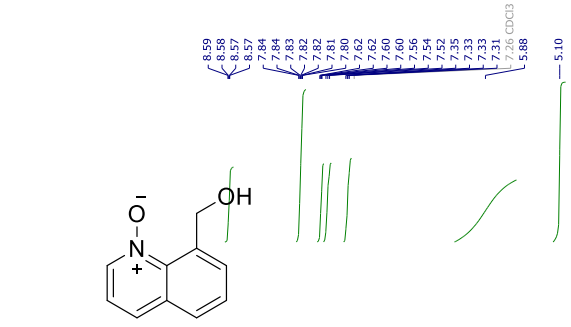
19o ^{13}C{^{1}H} NMR (Acetone-d_6 101 MHz)



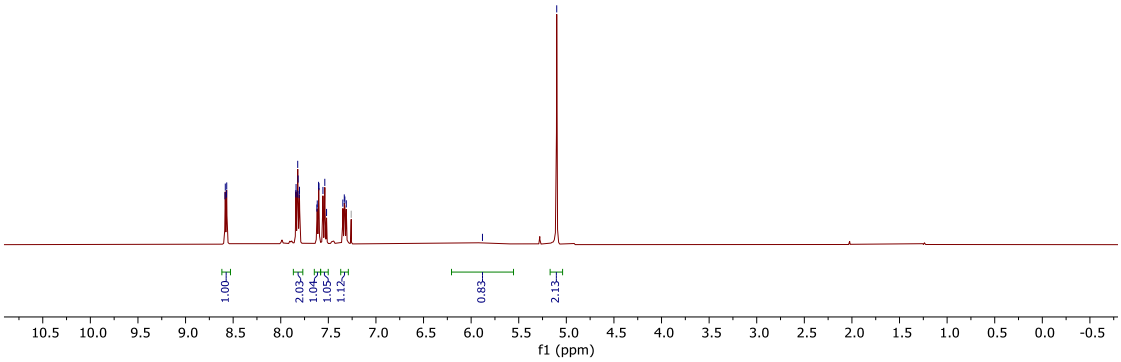
84 ^{1}H NMR ($CDCl_3$ 400 MHz)



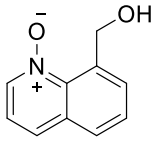
84 ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



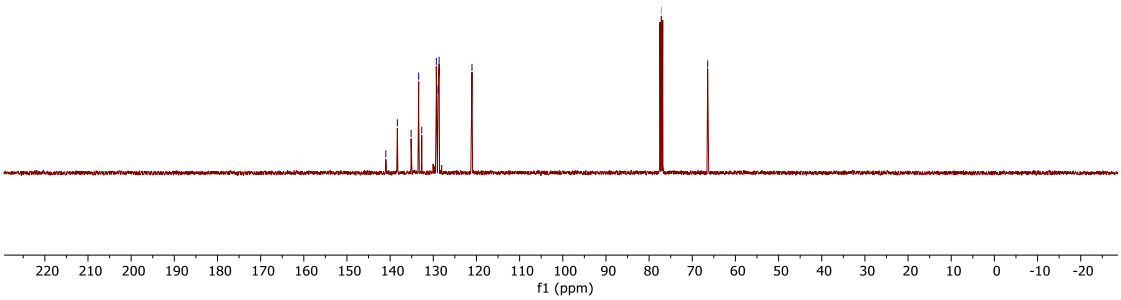
86 ^{1}H NMR ($CDCl_3$ 400 MHz)

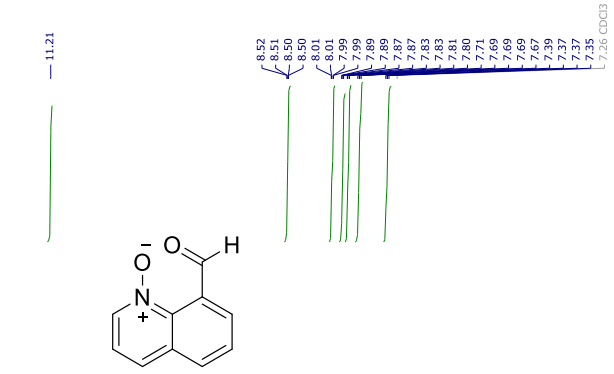




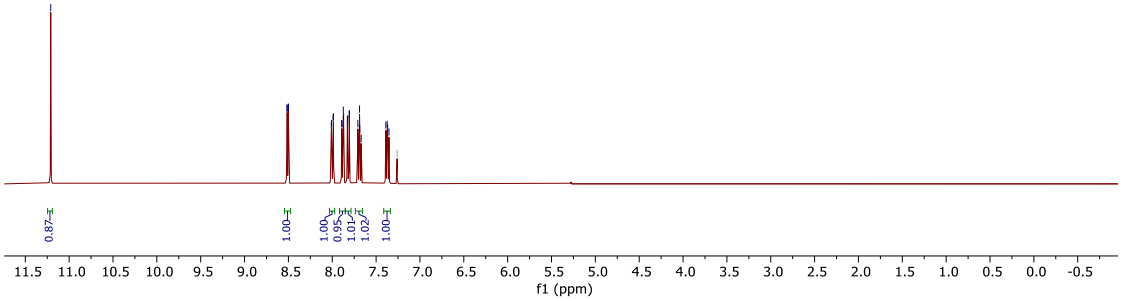


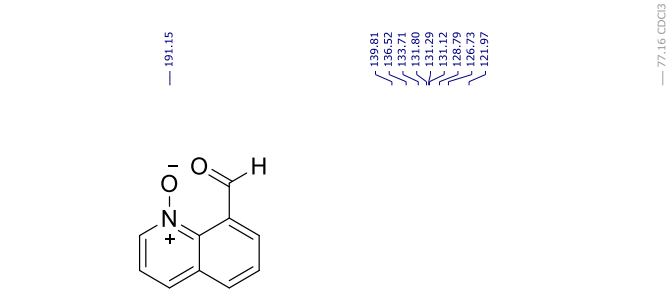
86 ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



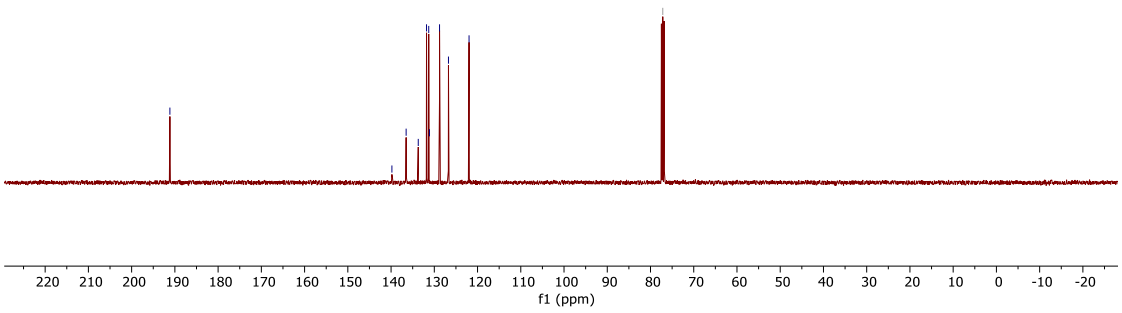


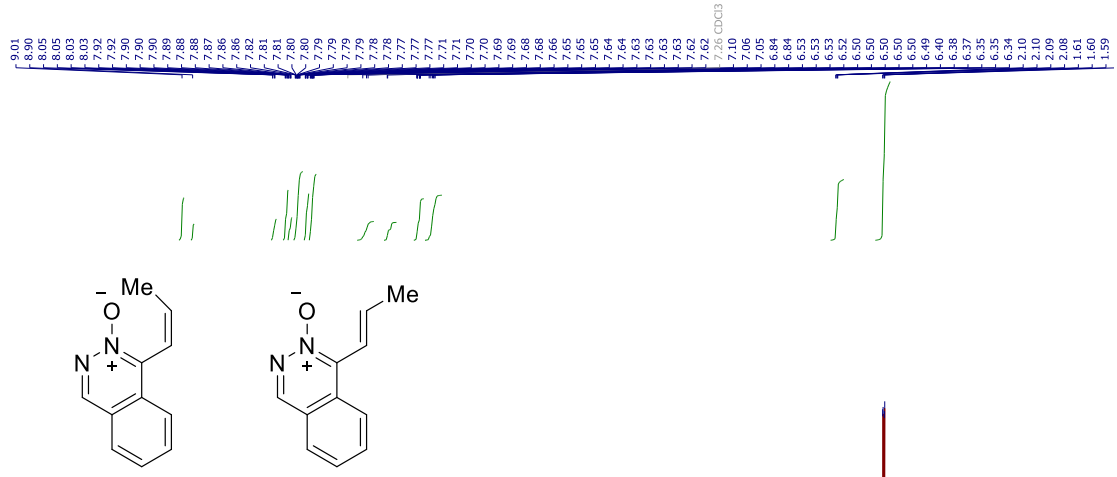
19q ^{1}H NMR ($CDCl_3$ 400 MHz)



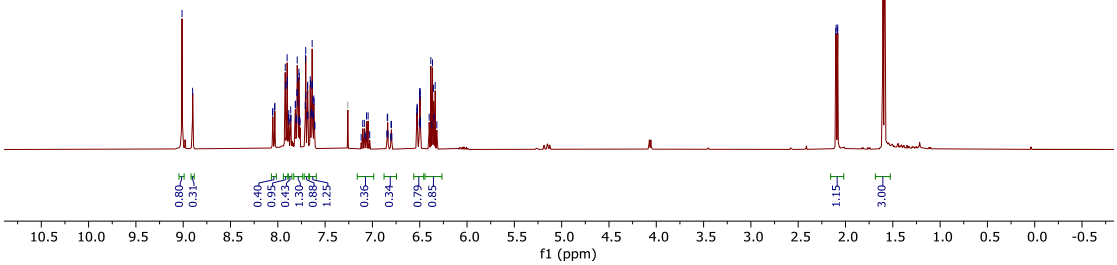


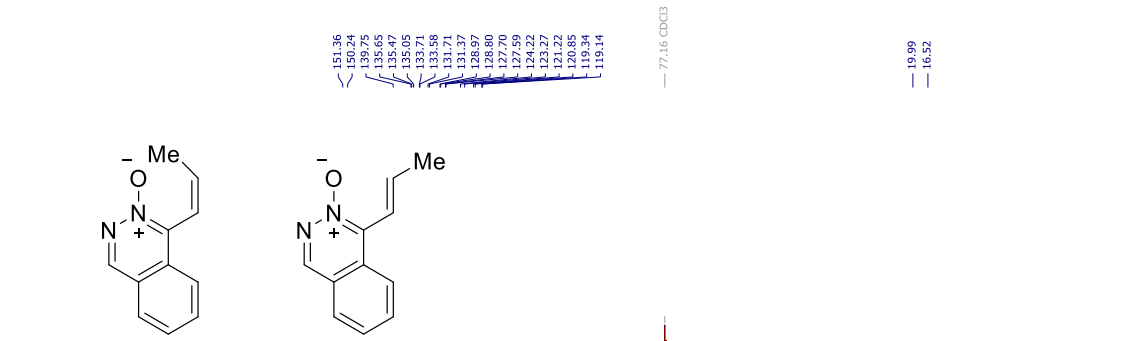
19q $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



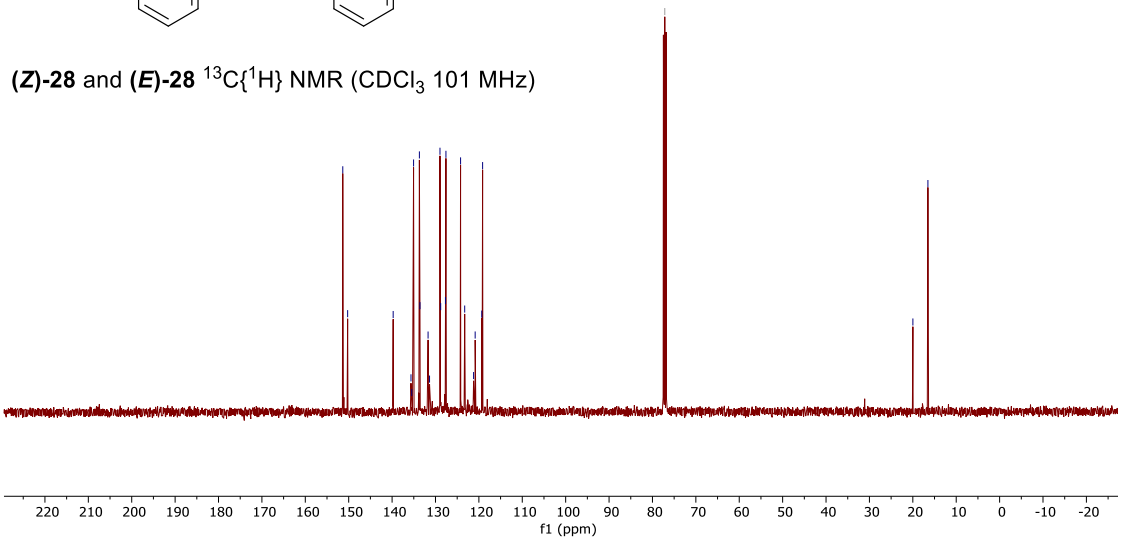


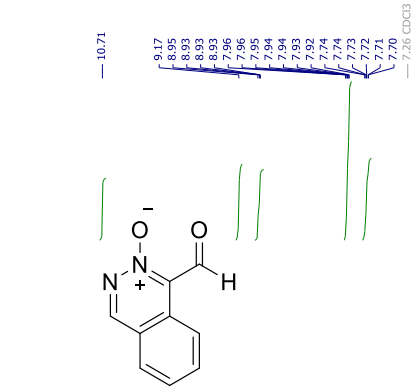
(*Z*)-28 and **(*E*)-28** ^{1}H NMR ($CDCl_3$ 400 MHz)



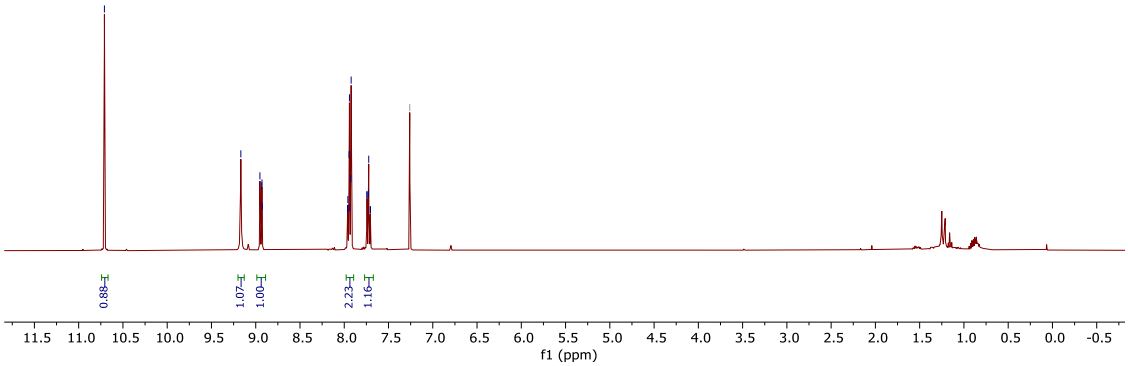


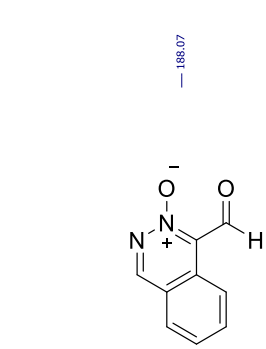
(*Z*)-28 and **(*E*)-28** $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



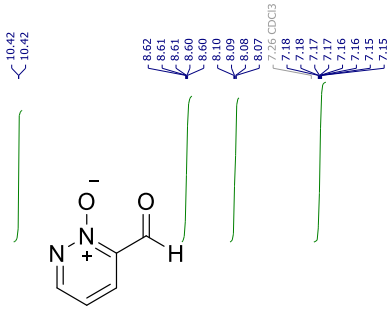


19r ^{1}H NMR ($CDCl_3$ 400 MHz)

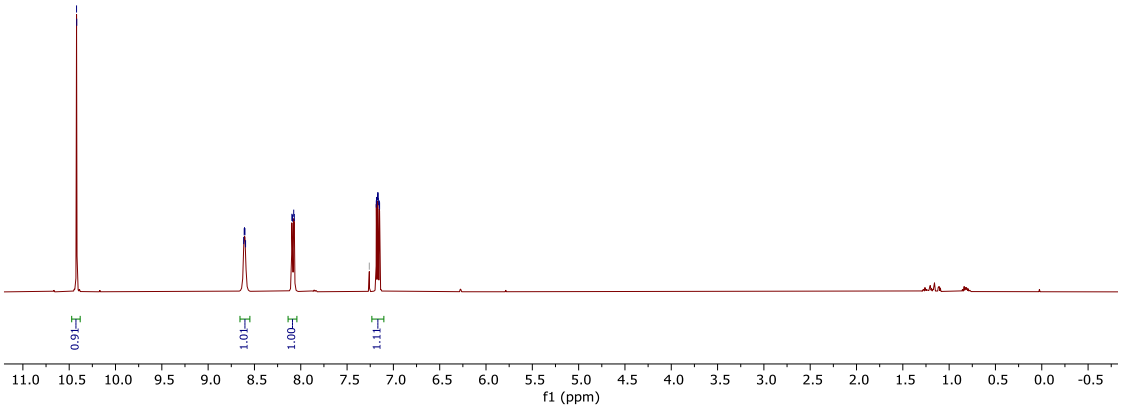




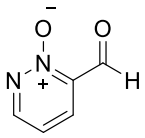
19r $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



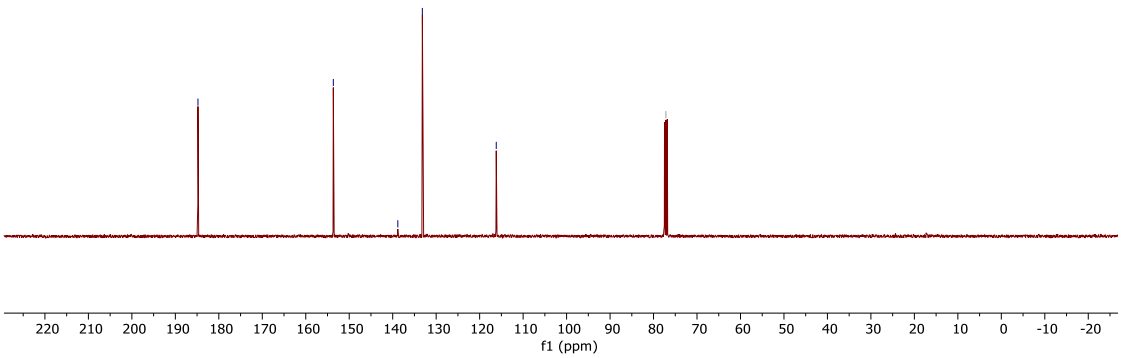
19s ^{1}H NMR ($CDCl_3$ 400 MHz)

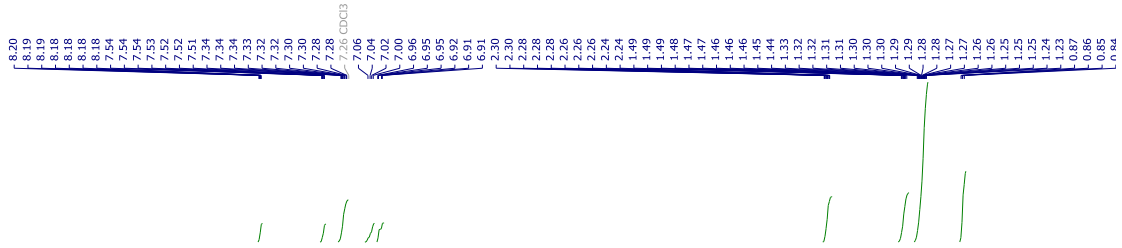


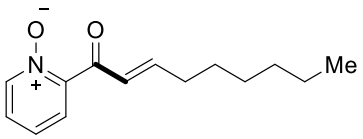




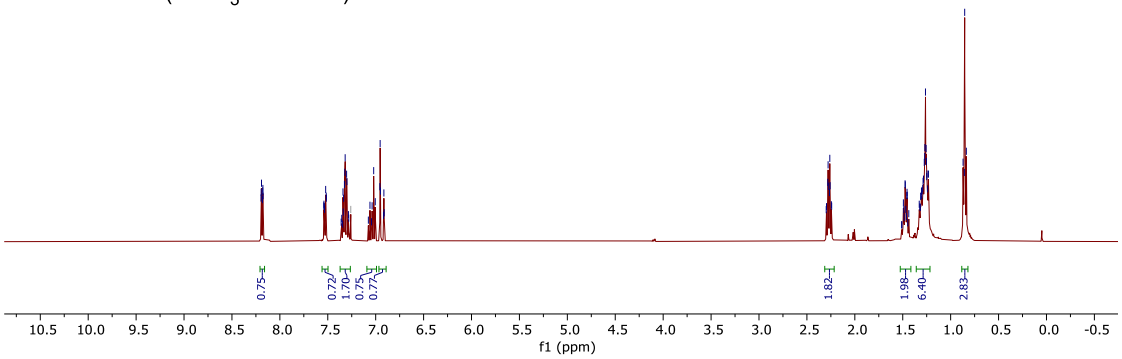
19s $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



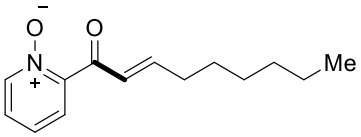




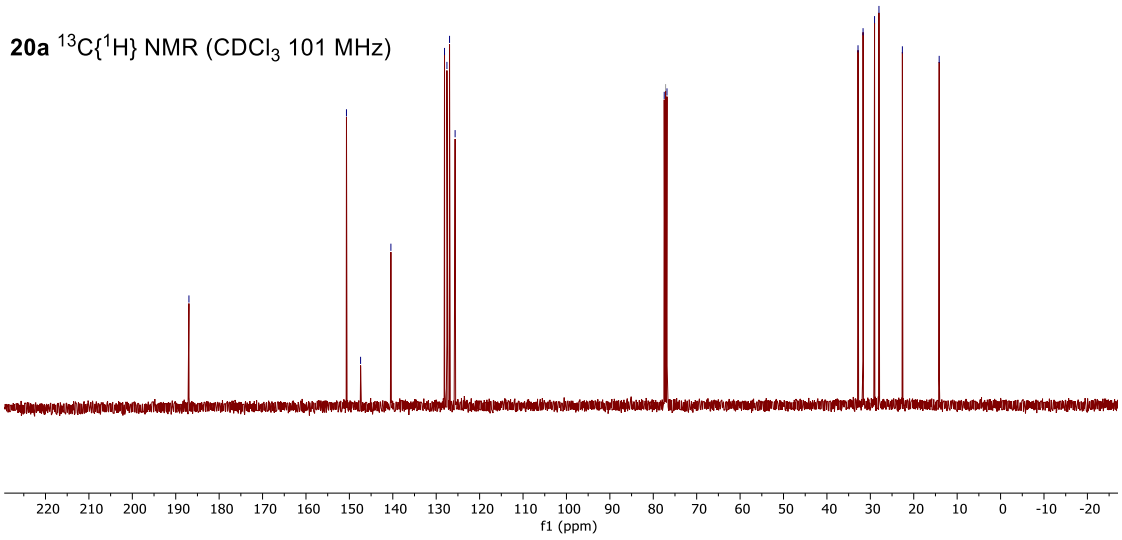
20a ^{1}H NMR ($CDCl_3$ 400 MHz)

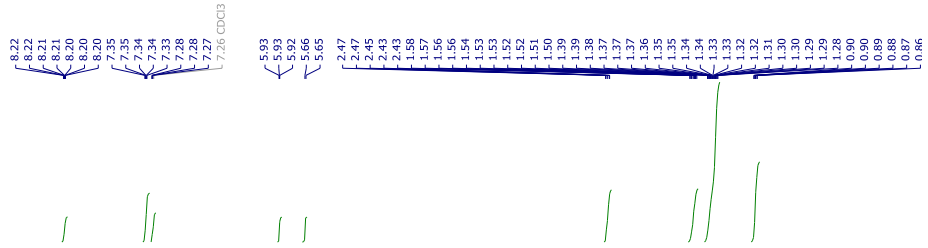


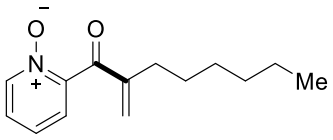




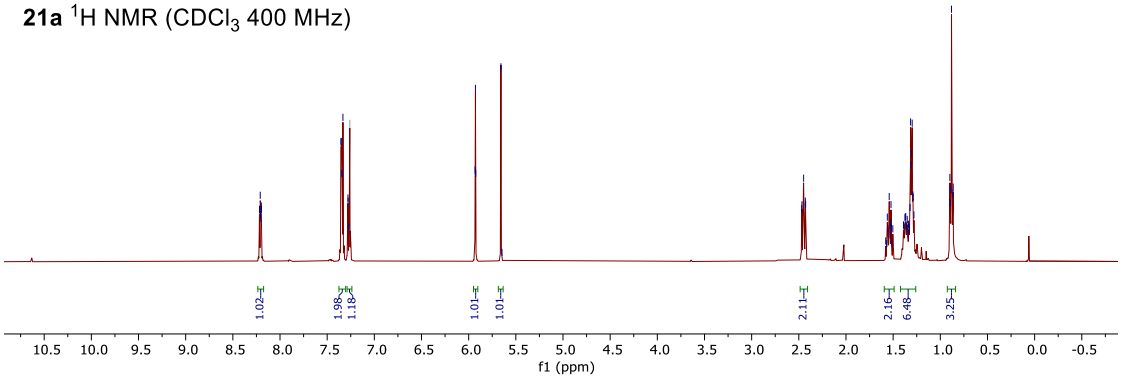
20a ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



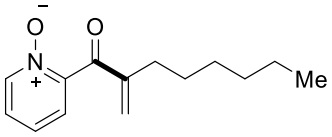




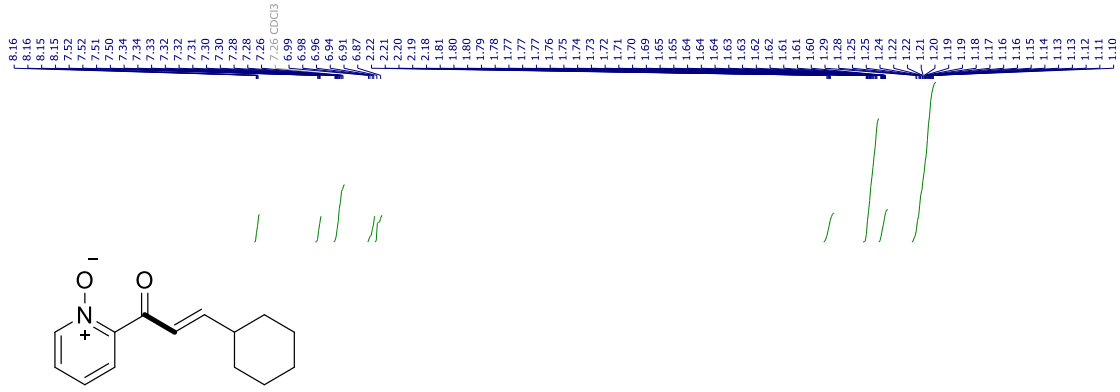
21a ^{1}H NMR ($CDCl_3$ 400 MHz)



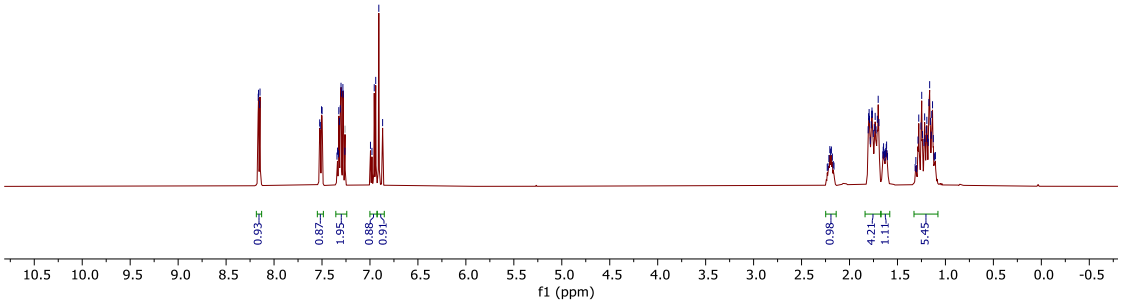


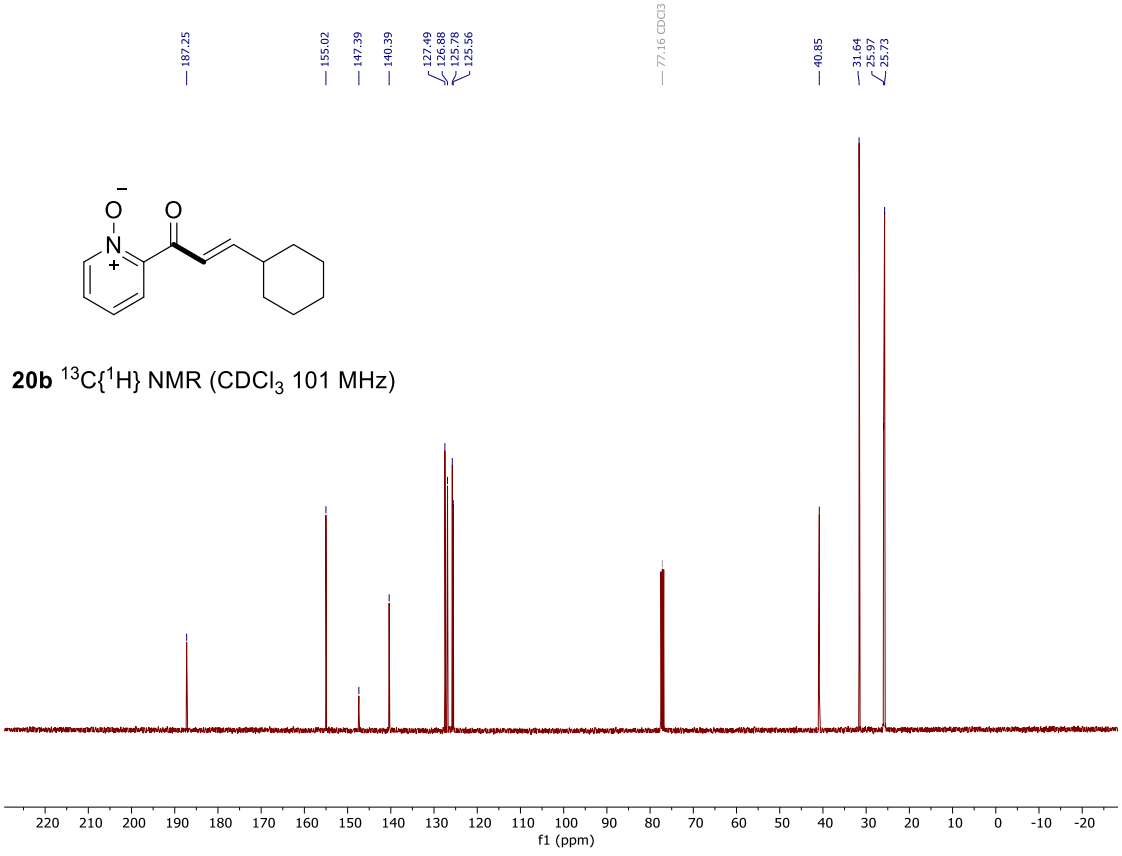


21a $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

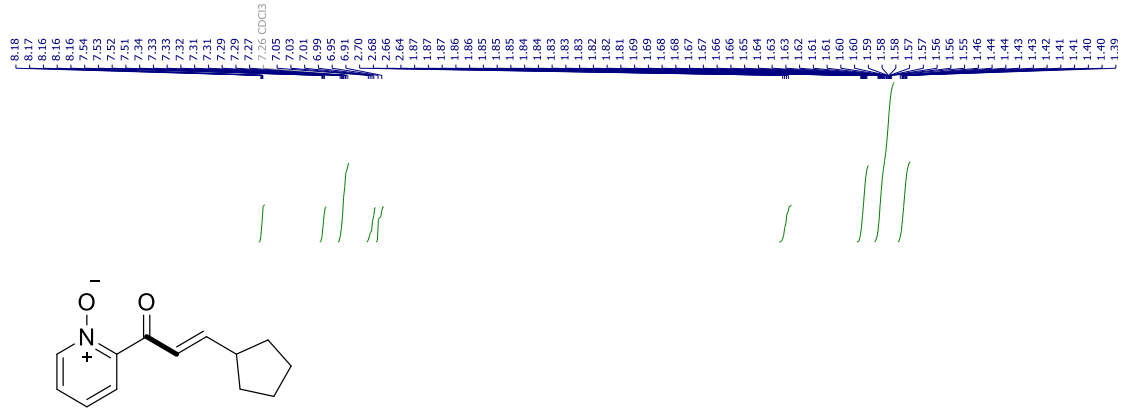


20b ^{1}H NMR ($CDCl_3$ 400 MHz)

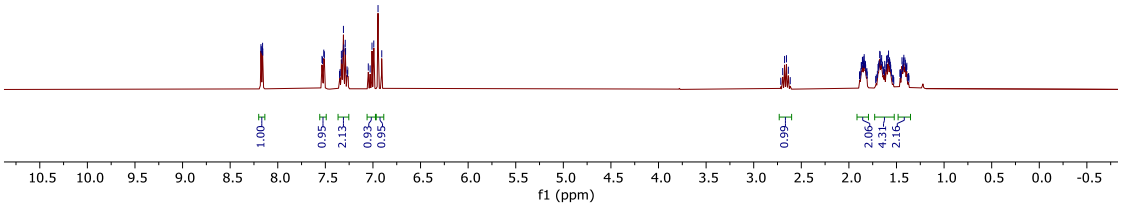




20b $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

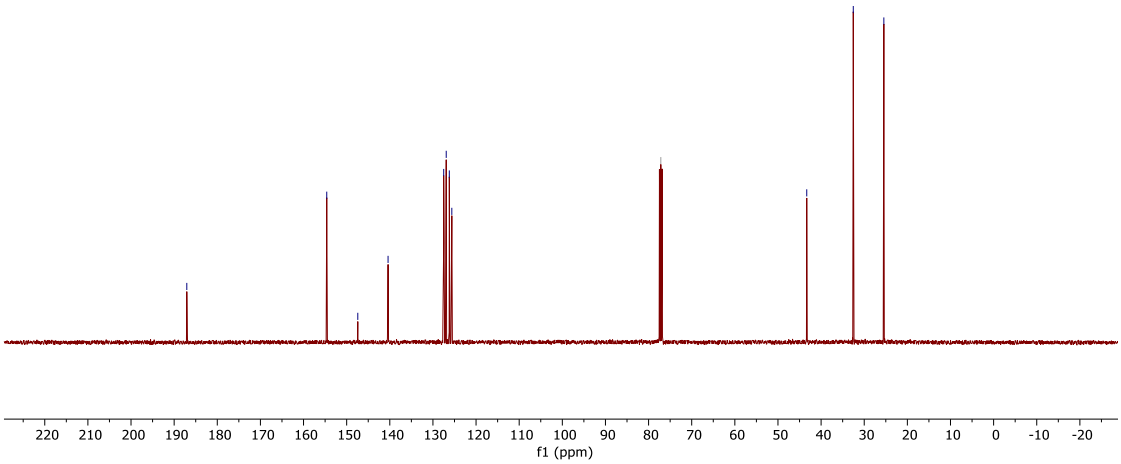


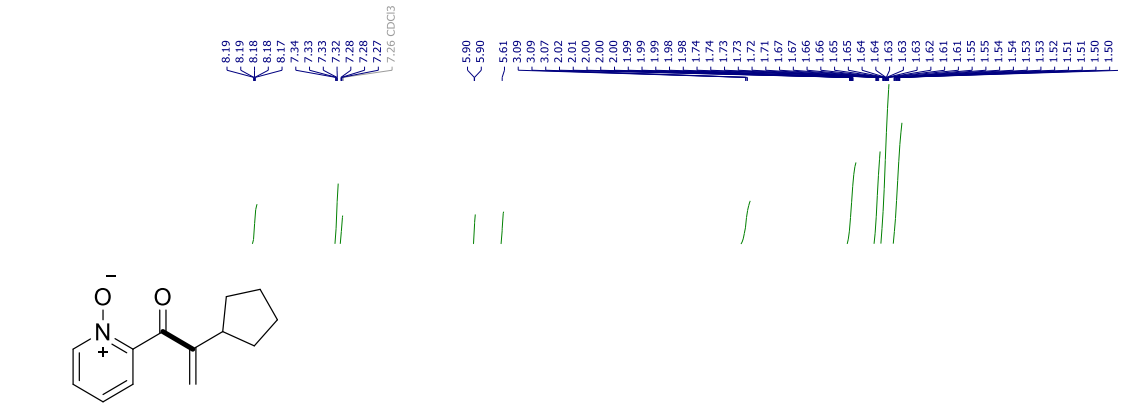
20c ^{1}H NMR ($CDCl_3$ 400 MHz)



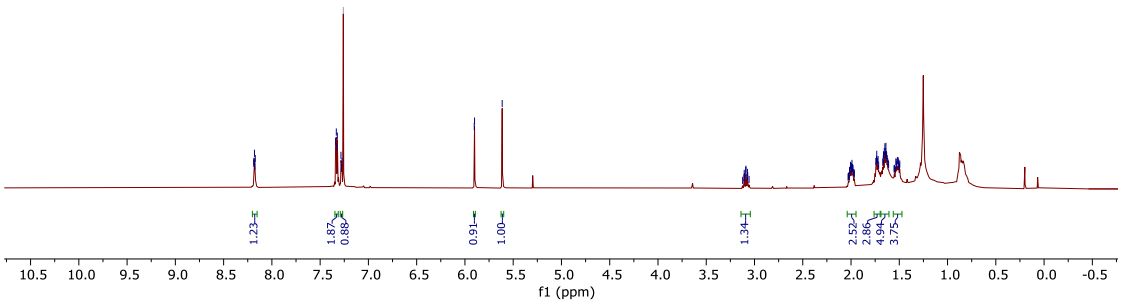


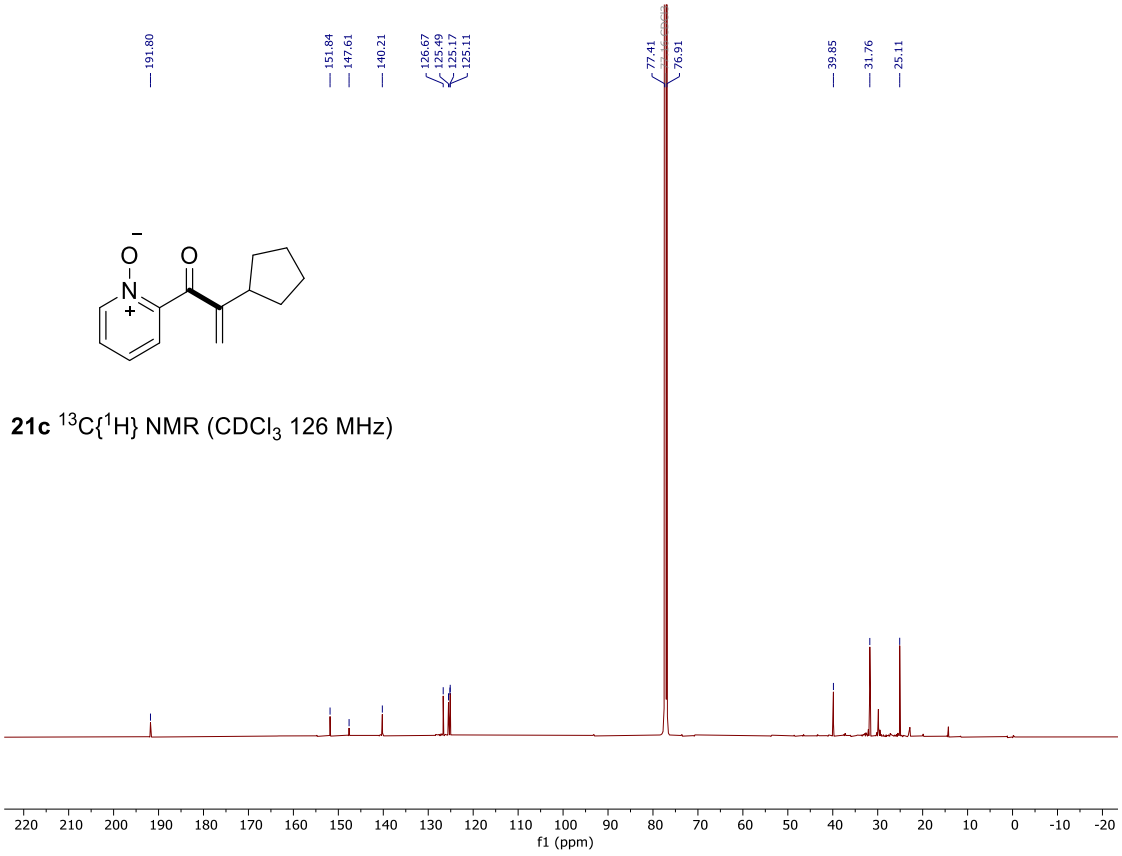
20c $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



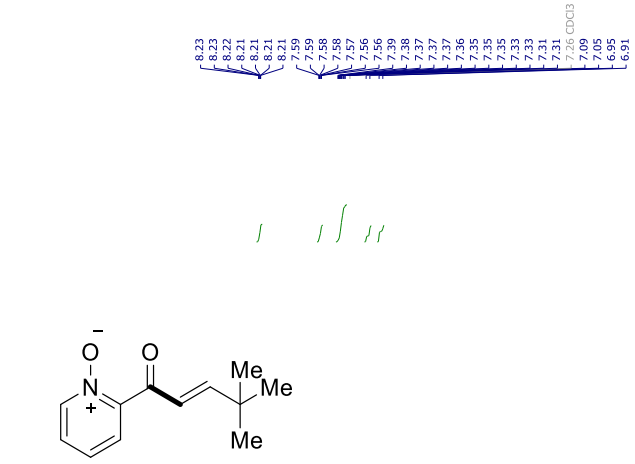


21c ^{1}H NMR ($CDCl_3$ 500 MHz)

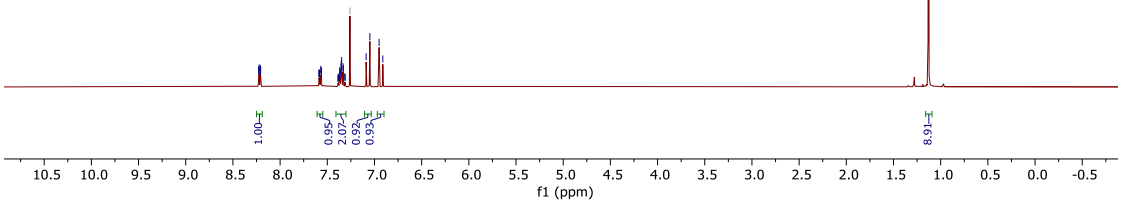


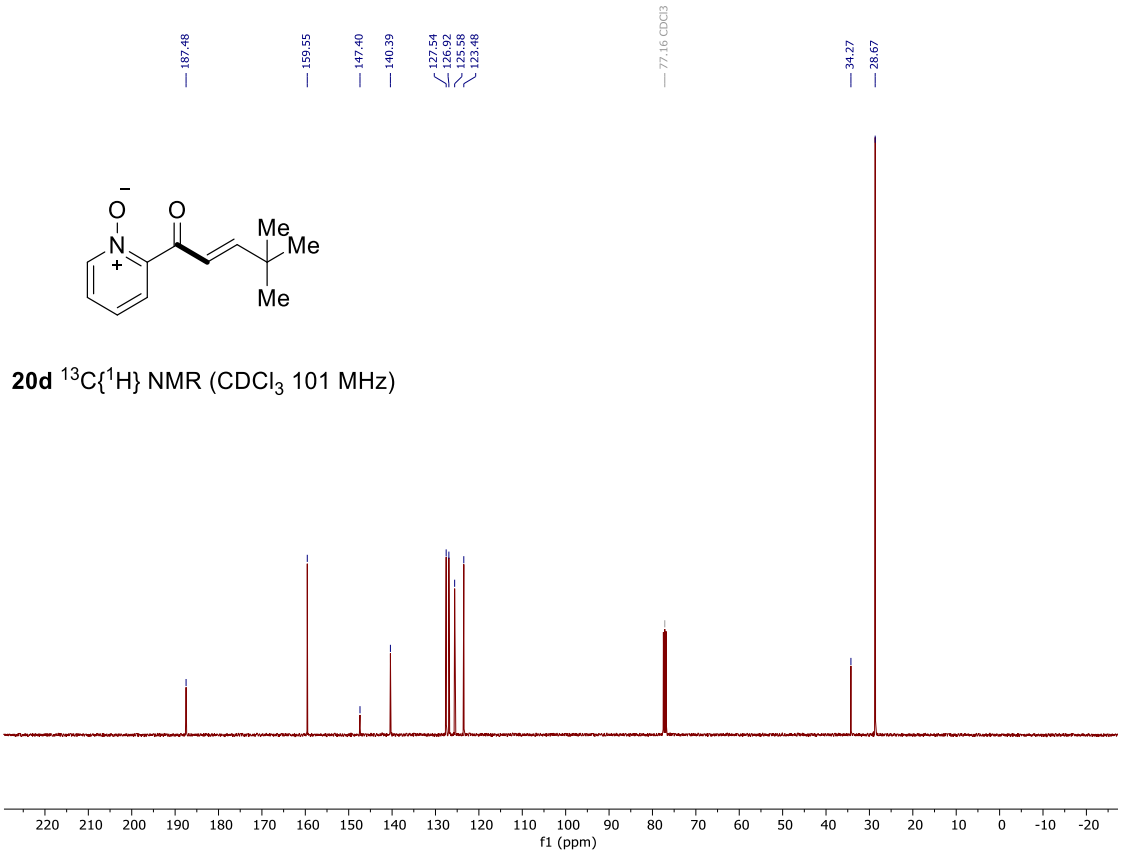


21c $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 126 MHz)

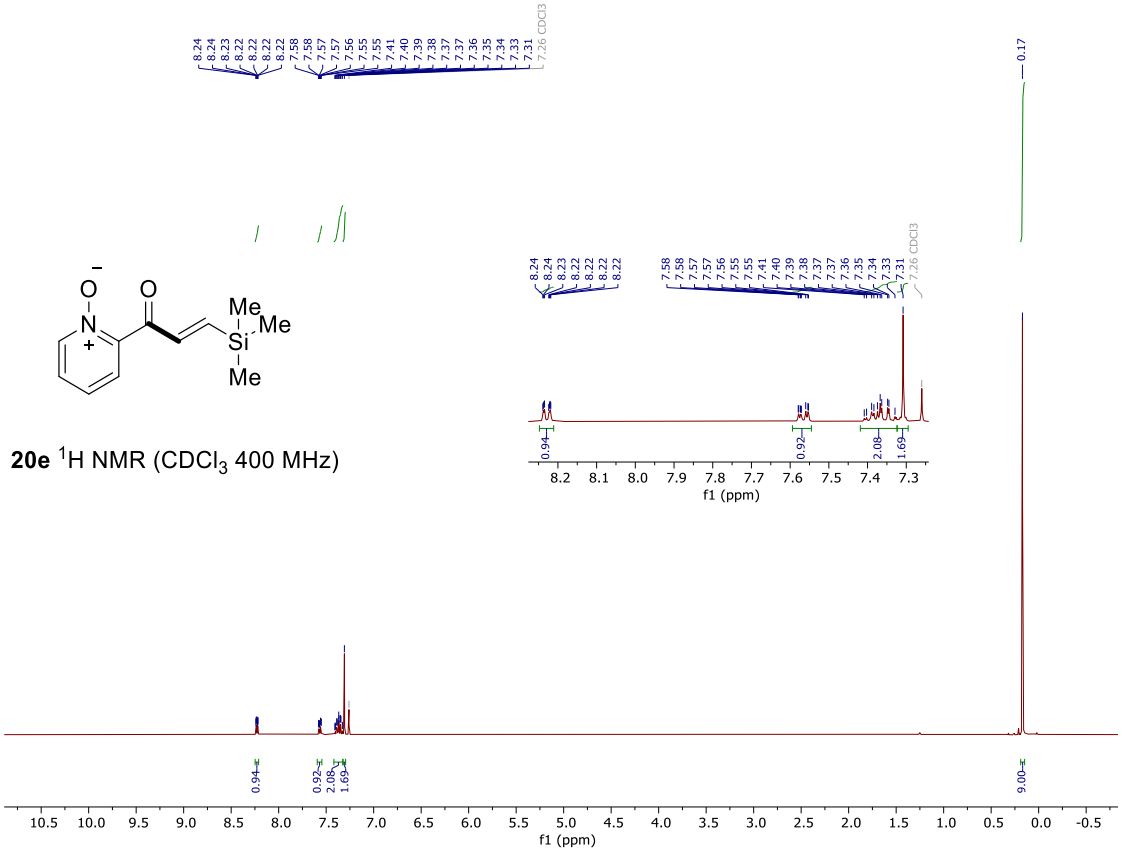


20d ^{1}H NMR ($CDCl_3$ 400 MHz)

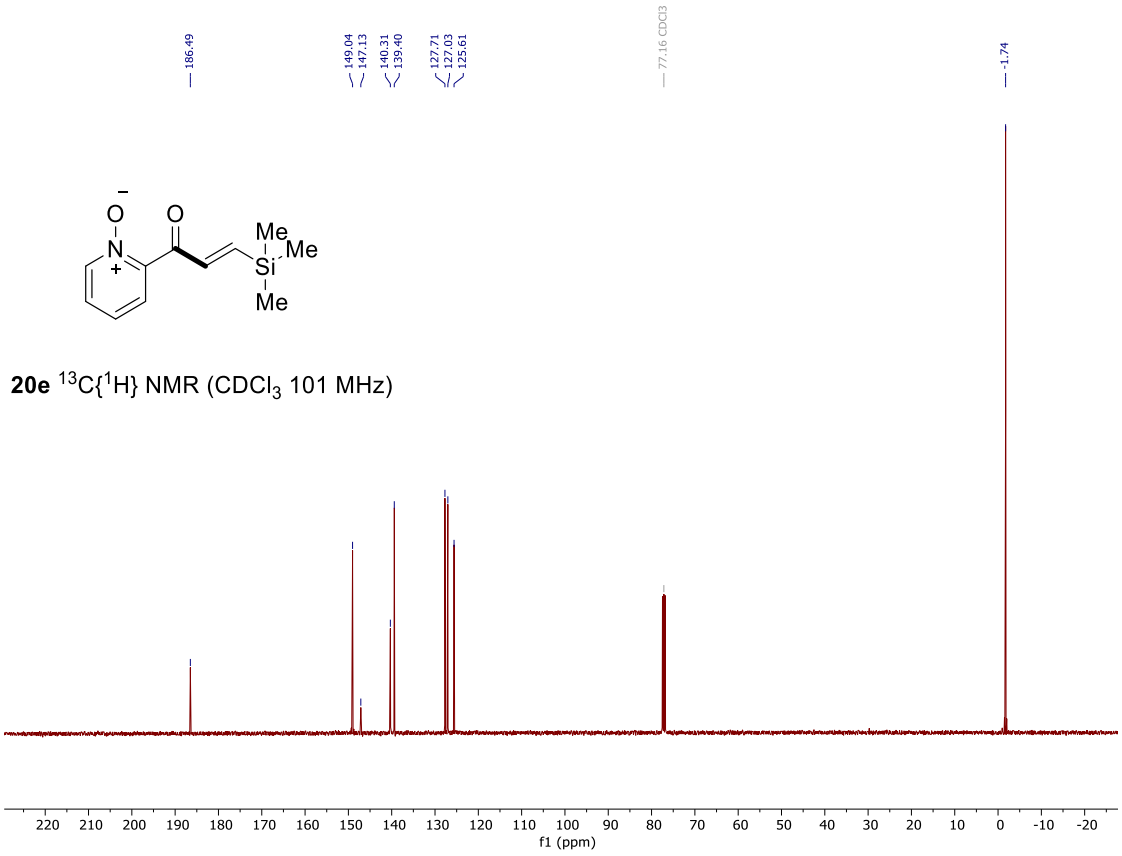




20d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

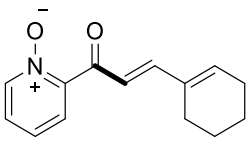


20e ^{1}H NMR ($CDCl_3$ 400 MHz)

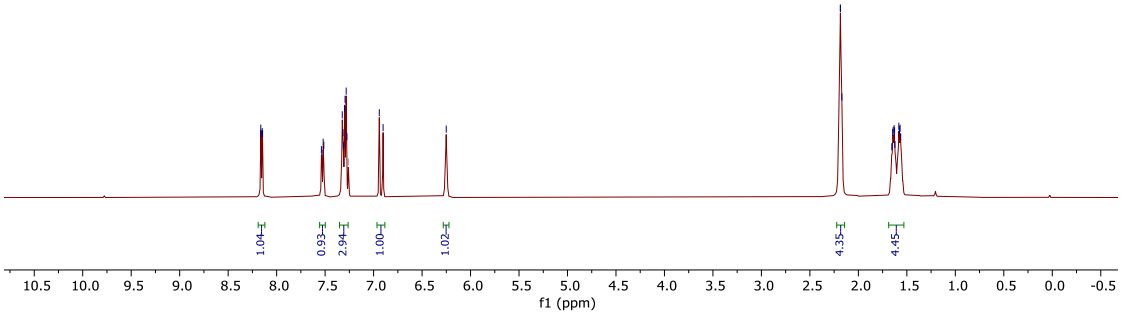


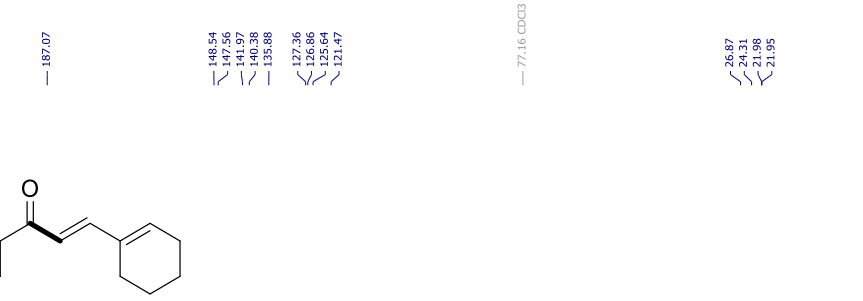
20e $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



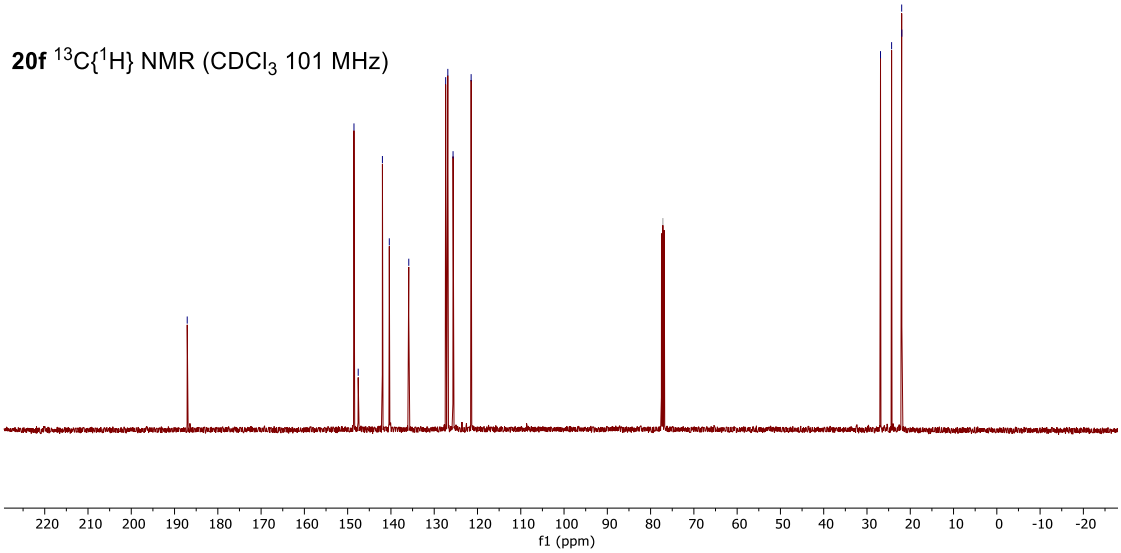


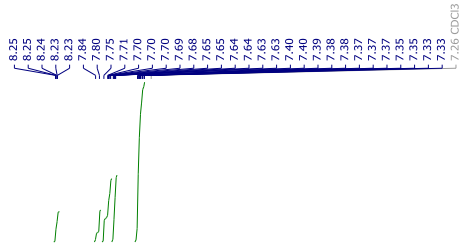
20f ^{1}H NMR ($CDCl_3$ 400 MHz)

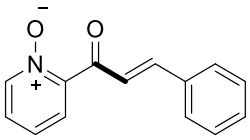




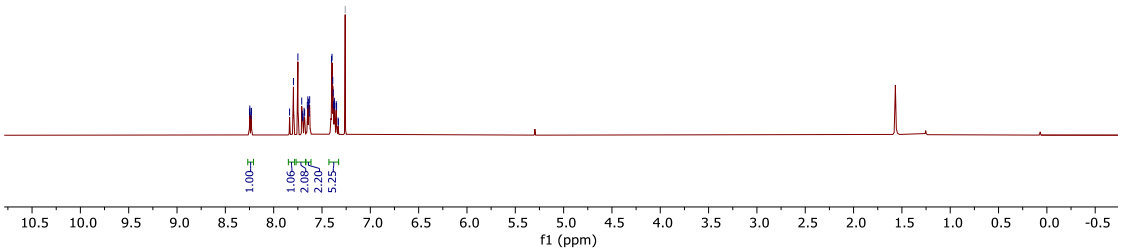
20f ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



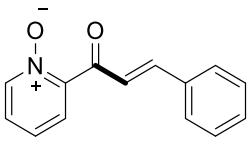




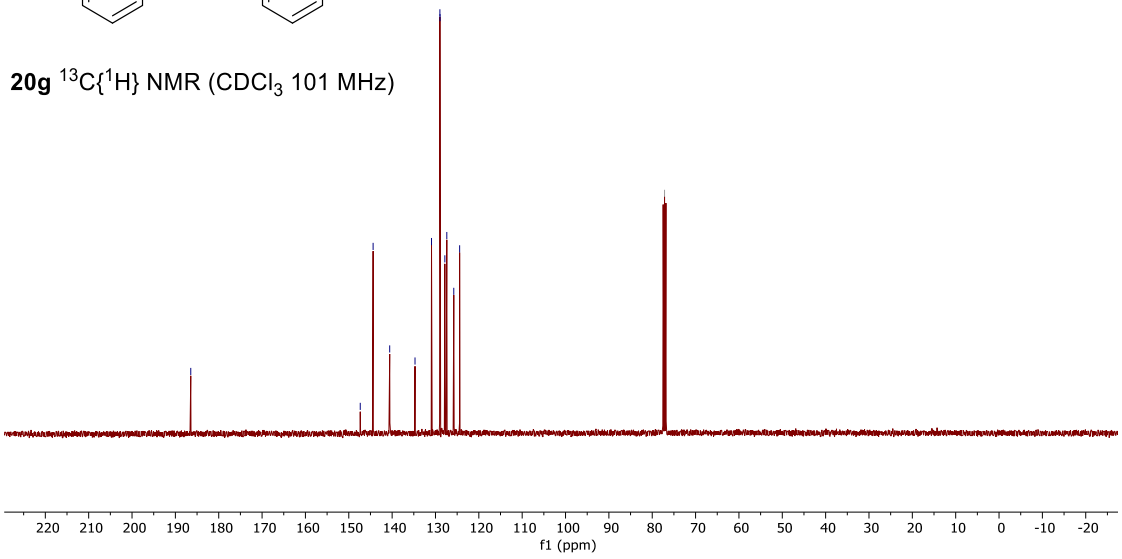
20g ^{1}H NMR ($CDCl_3$ 400 MHz)

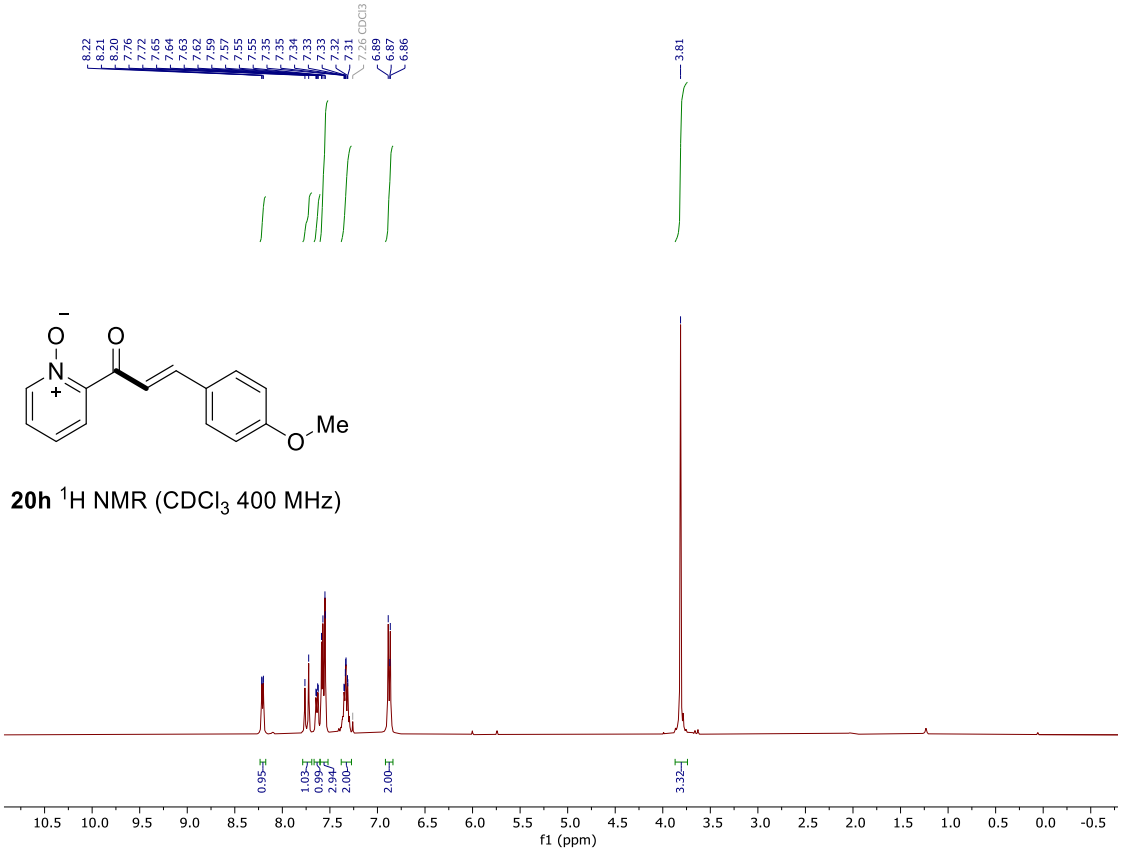




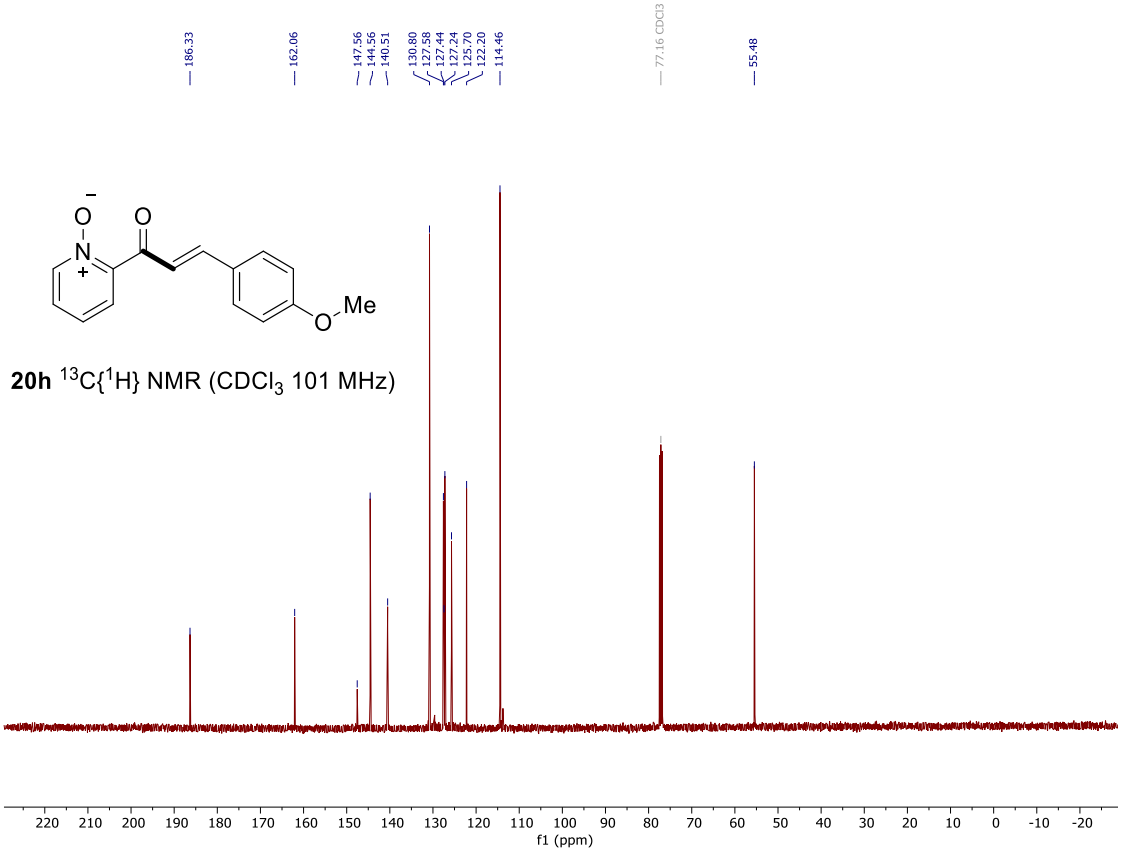


20g $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

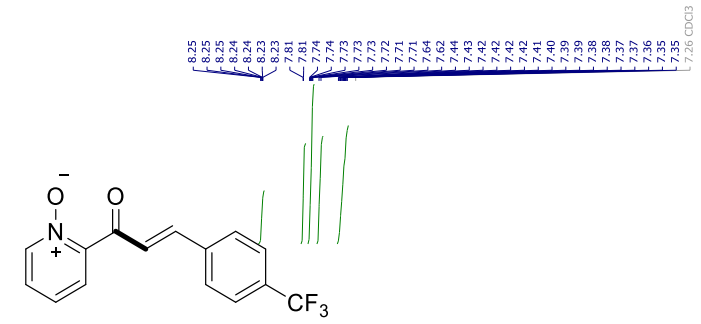




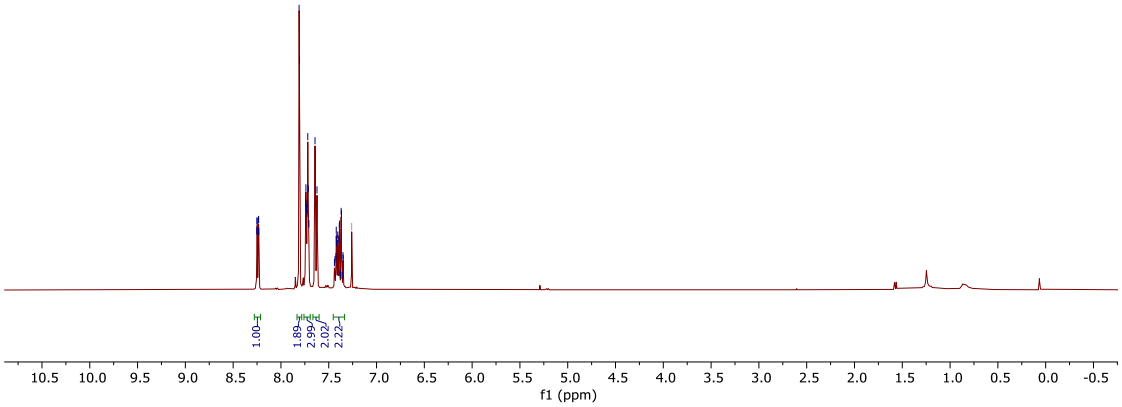
20h ^{1}H NMR ($CDCl_3$ 400 MHz)



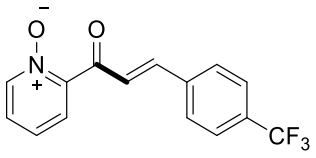
20h $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



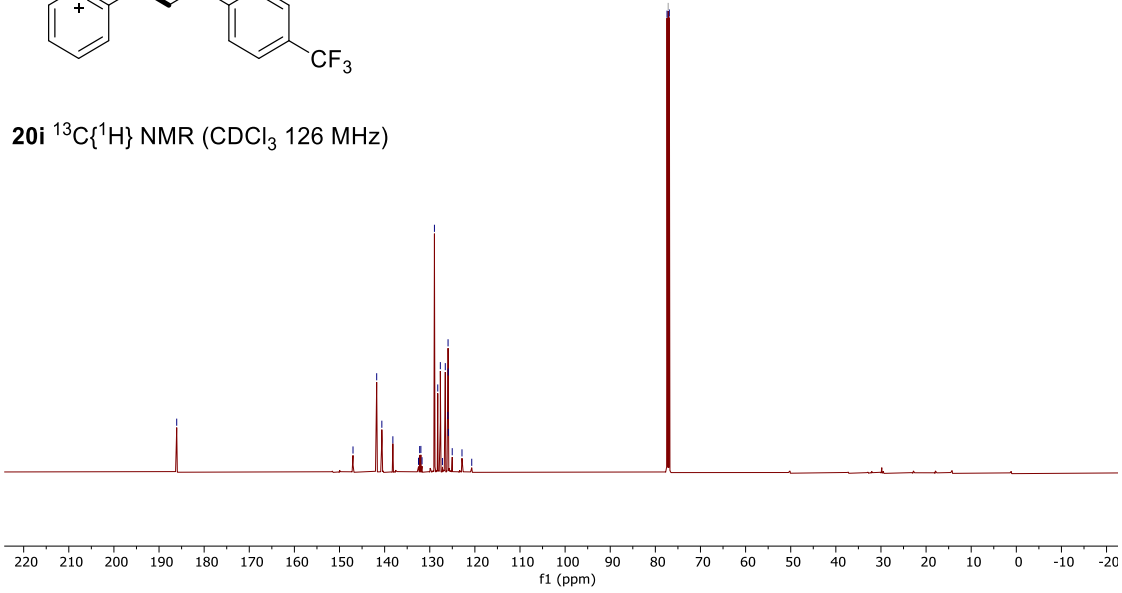
20i ^{1}H NMR ($CDCl_3$ 400 MHz)

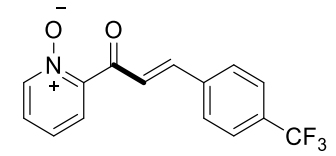




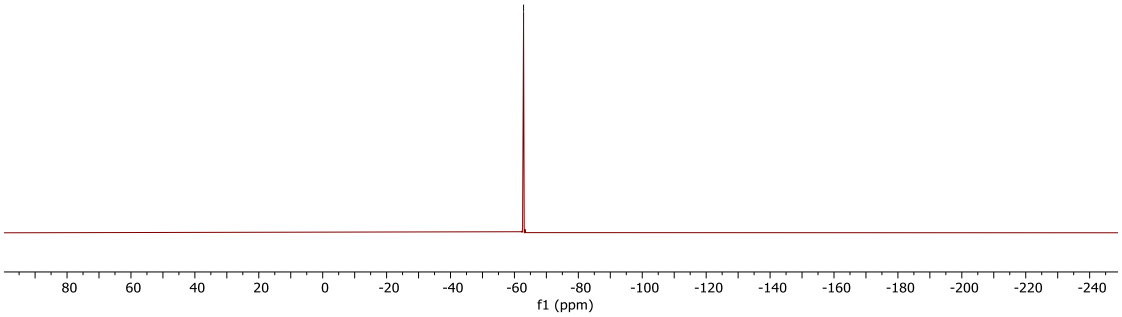


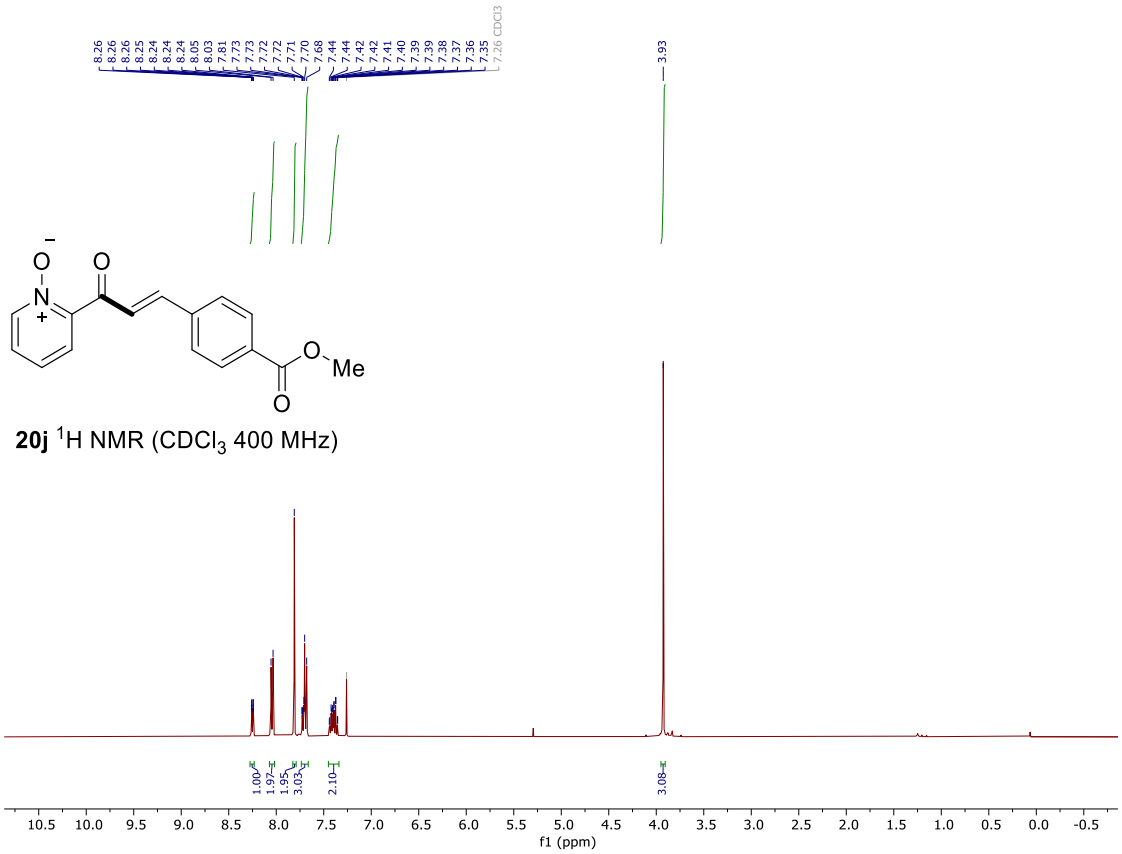
20i $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 126 MHz)



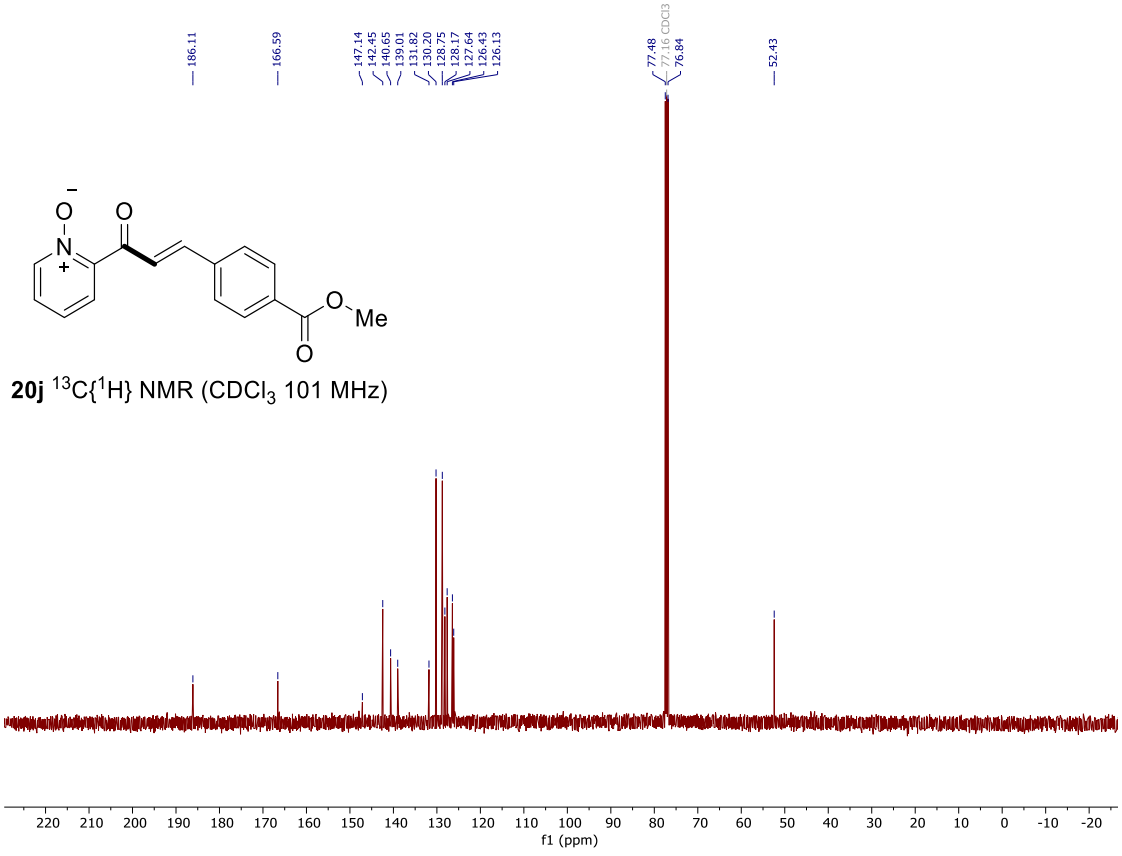


20i ^{19}F NMR ($CDCl_3$ 376 MHz)

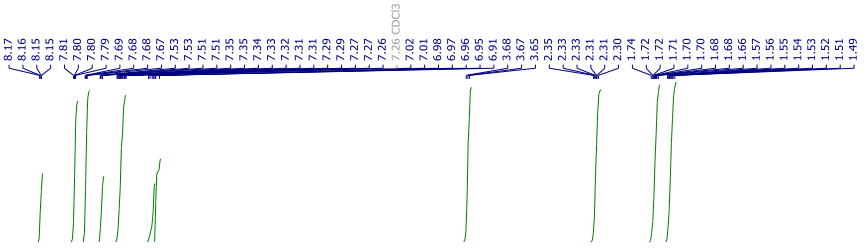


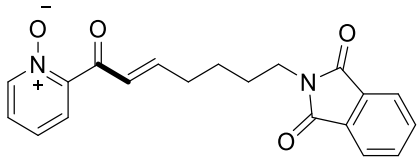


20j ^{1}H NMR ($CDCl_3$ 400 MHz)

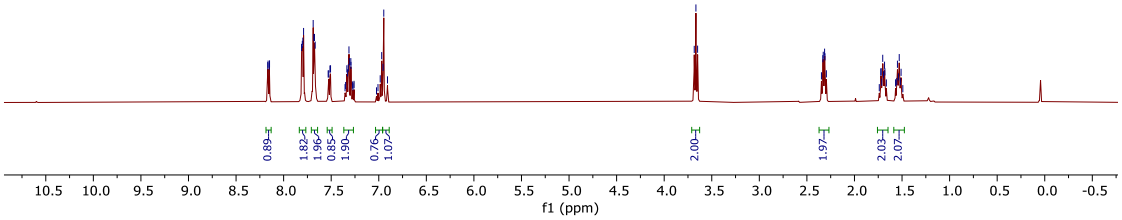


20j ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

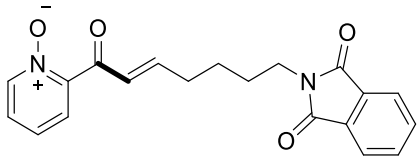




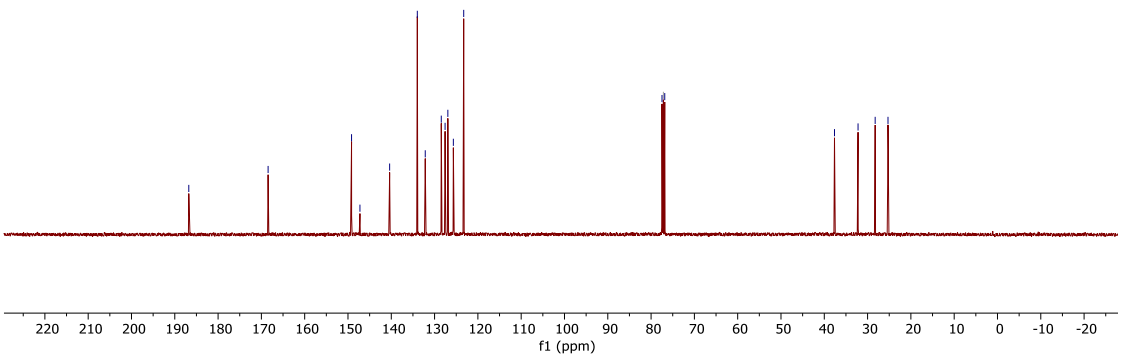
20k ^{1}H NMR ($CDCl_3$ 400 MHz)

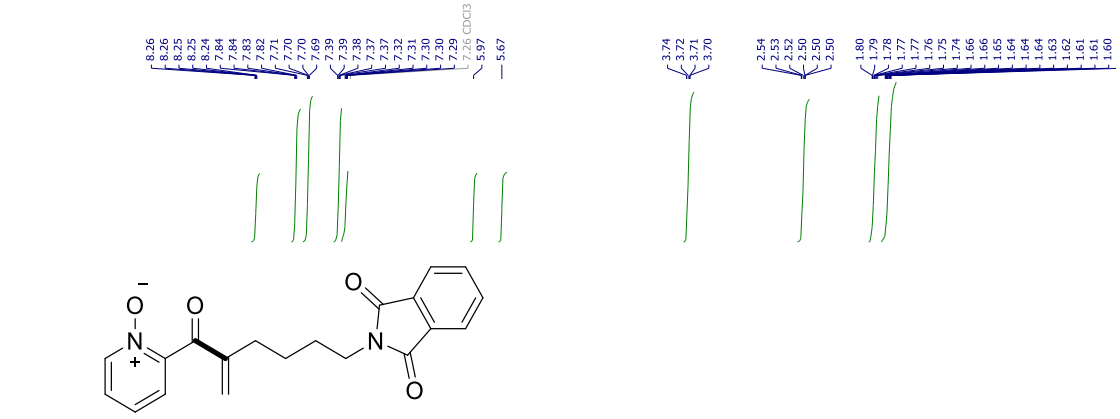




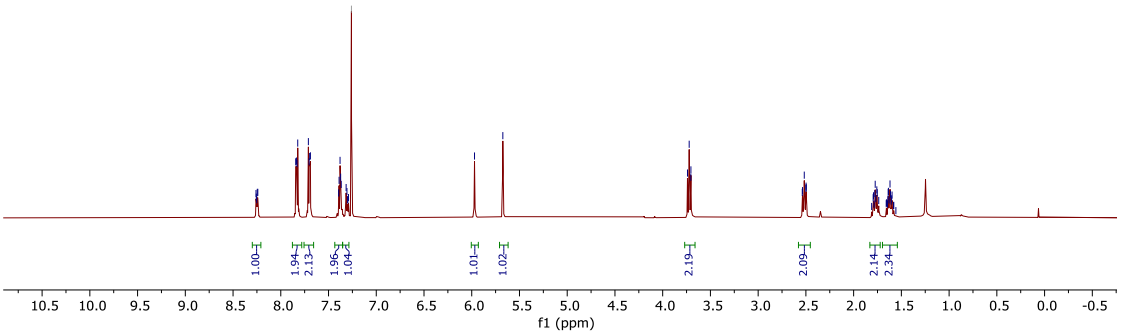


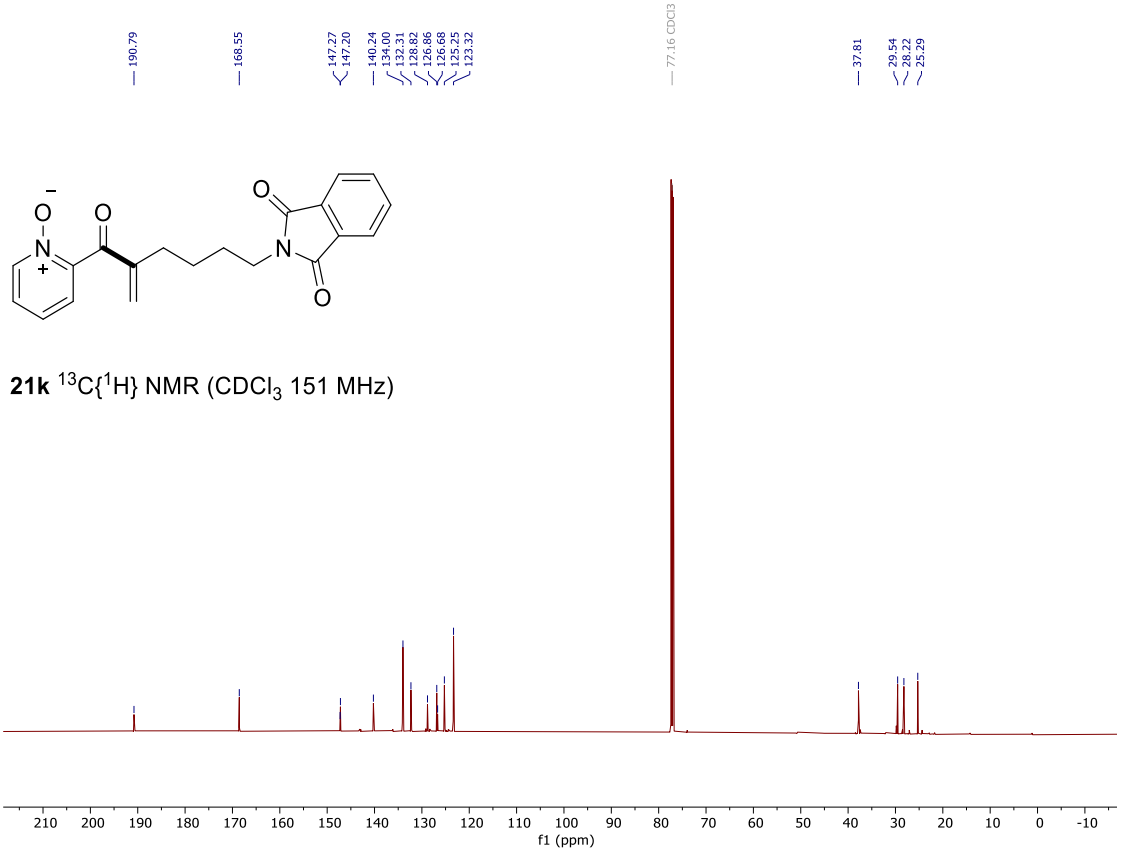
20k $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



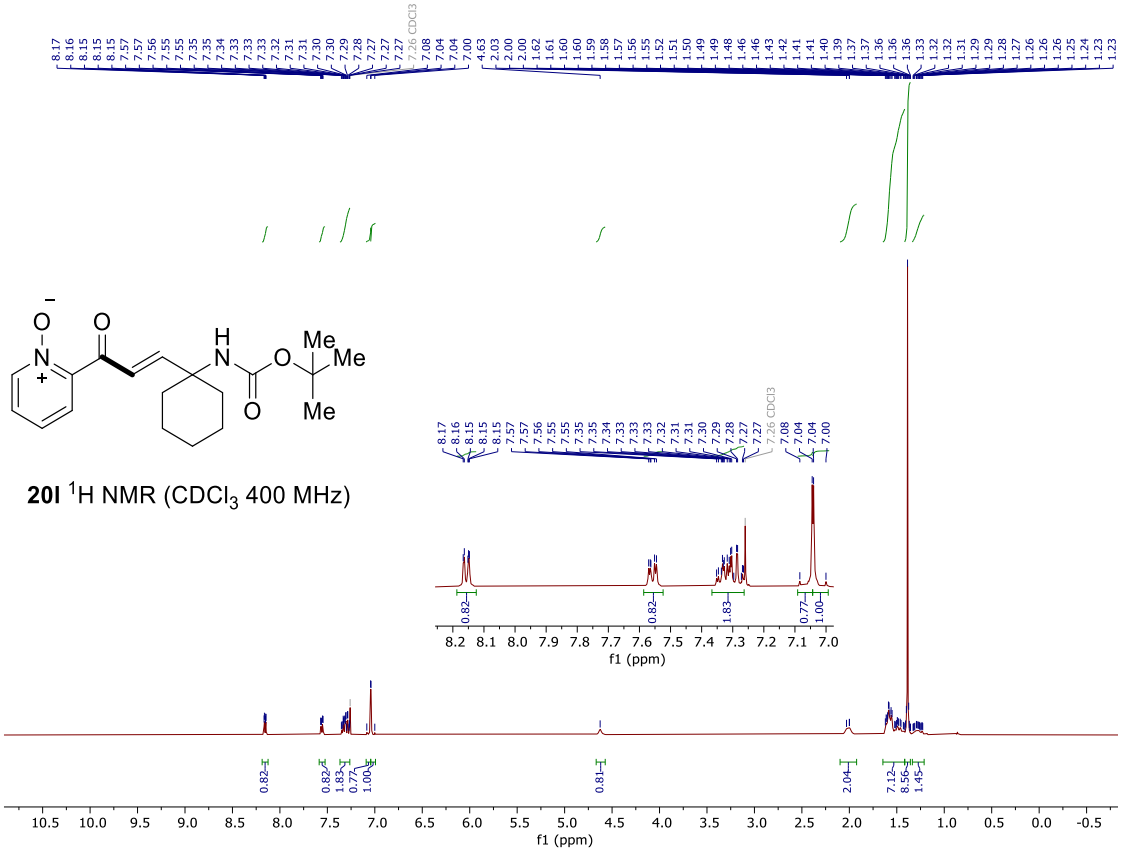


21k ^{1}H NMR ($CDCl_3$ 400 MHz)

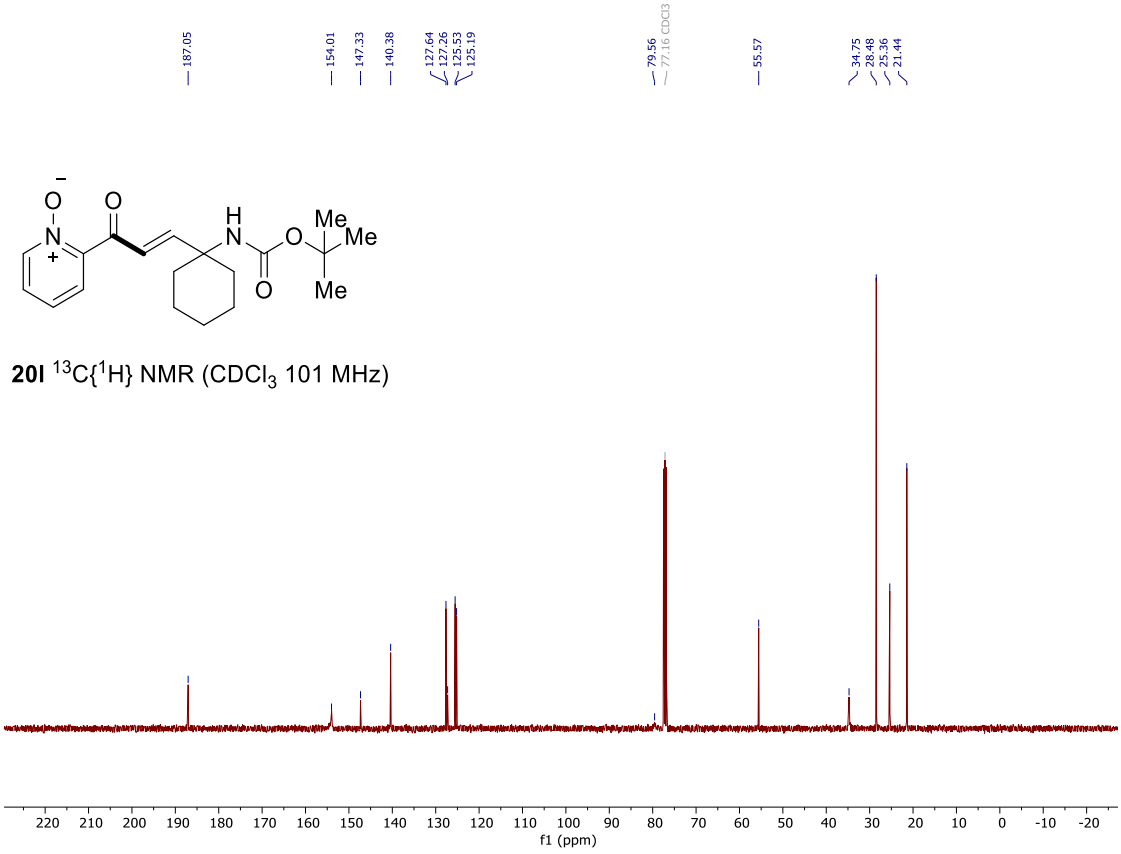




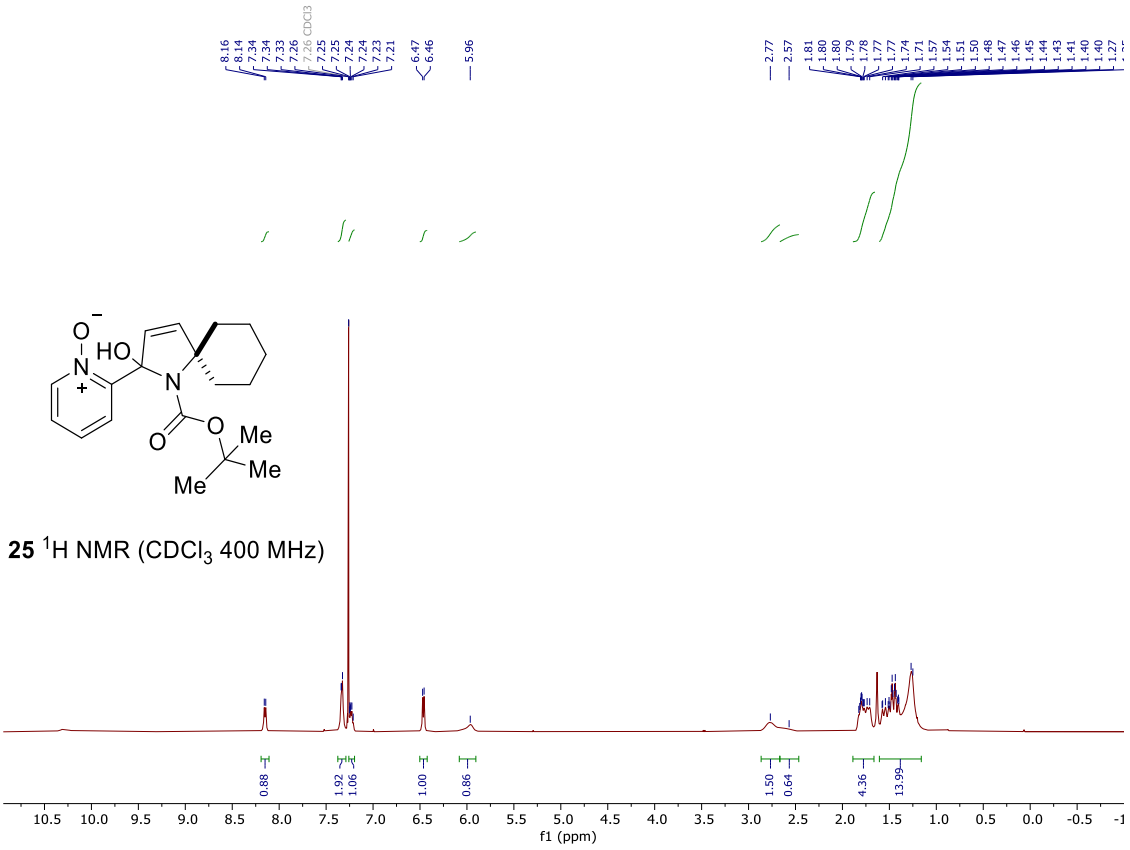
21k $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 151 MHz)



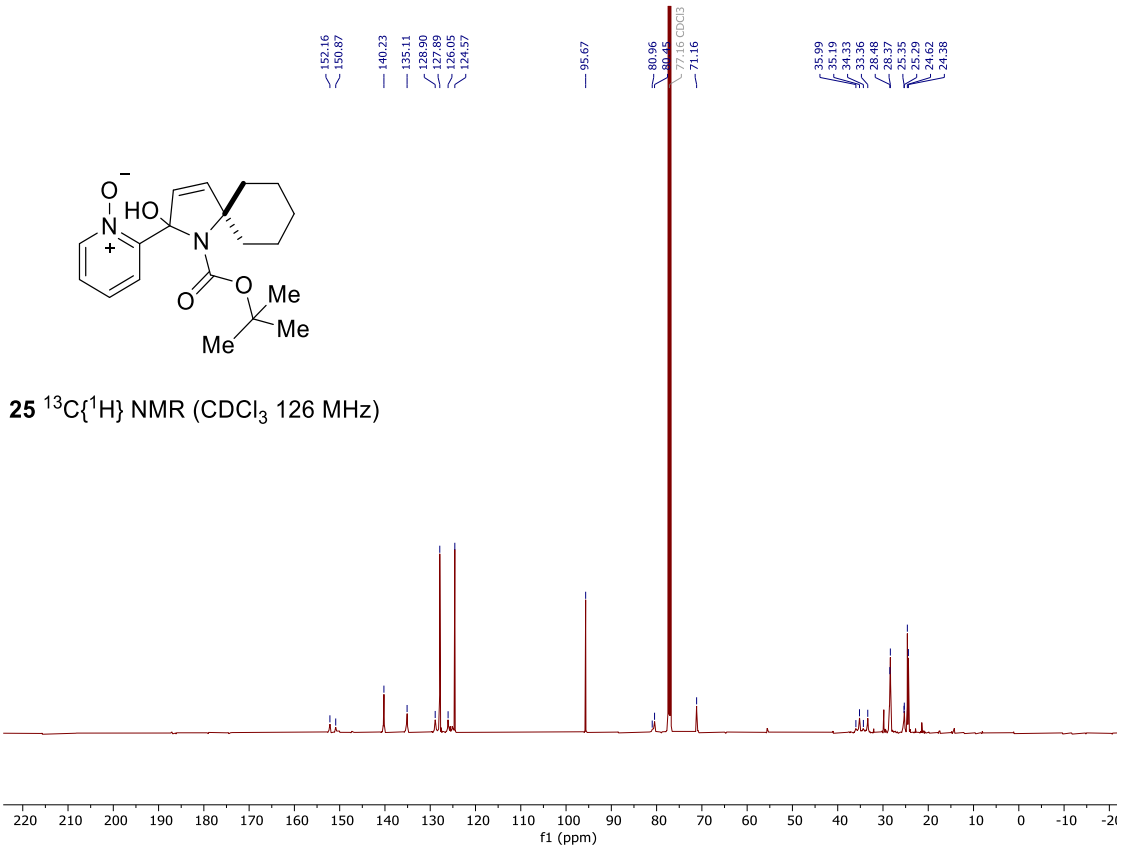
20l ^{1}H NMR ($CDCl_3$ 400 MHz)



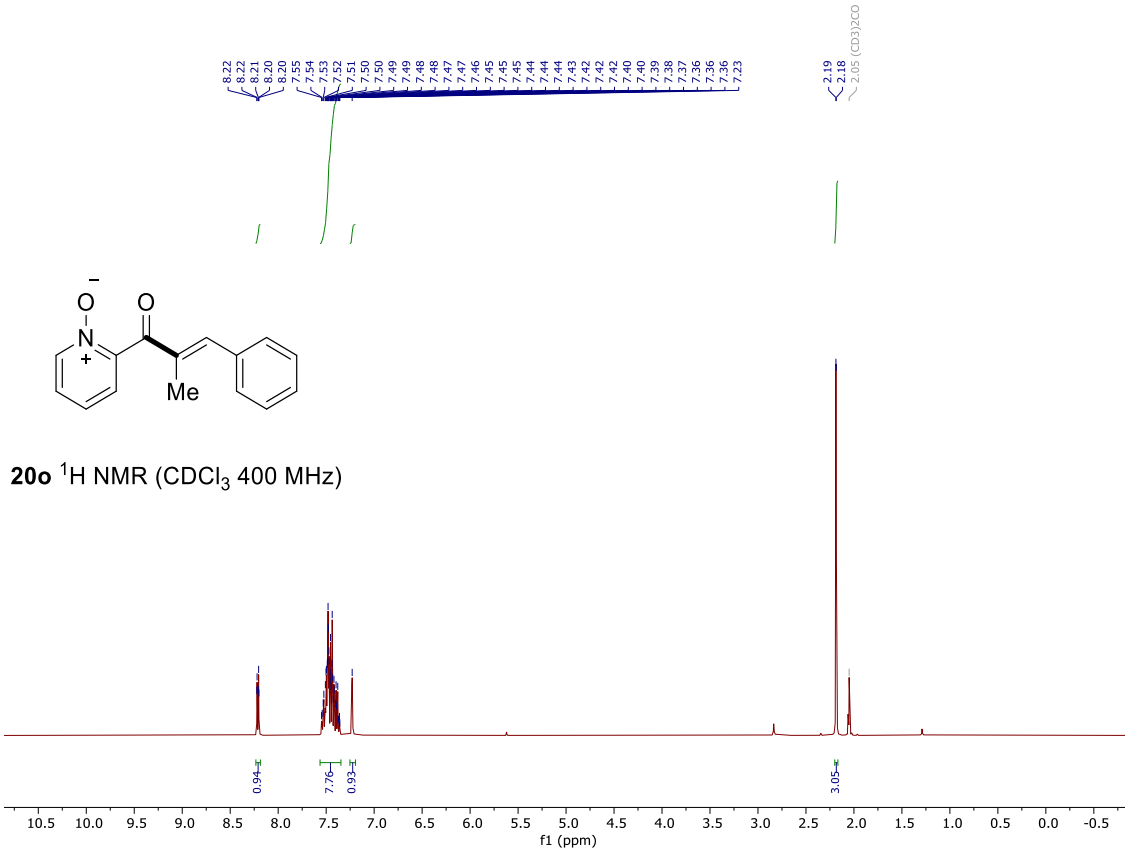
20l ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



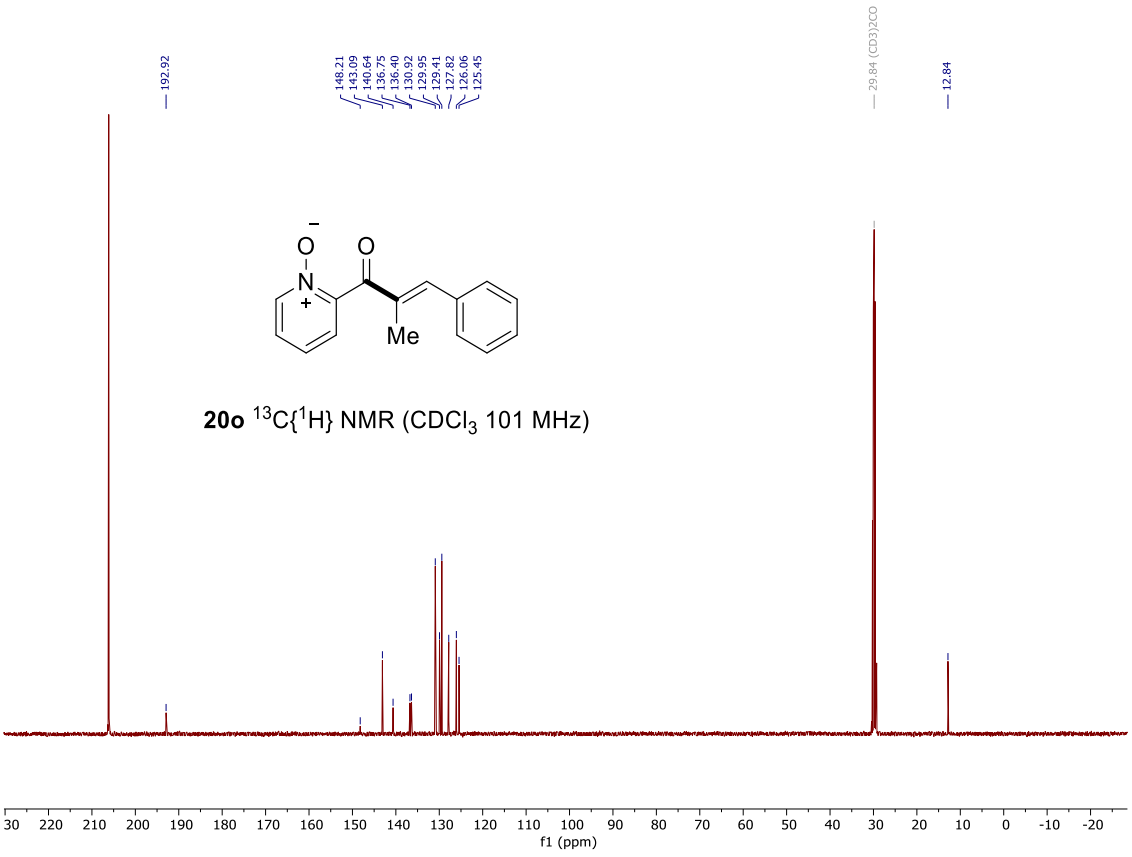
25 ^{1}H NMR ($CDCl_3$ 400 MHz)



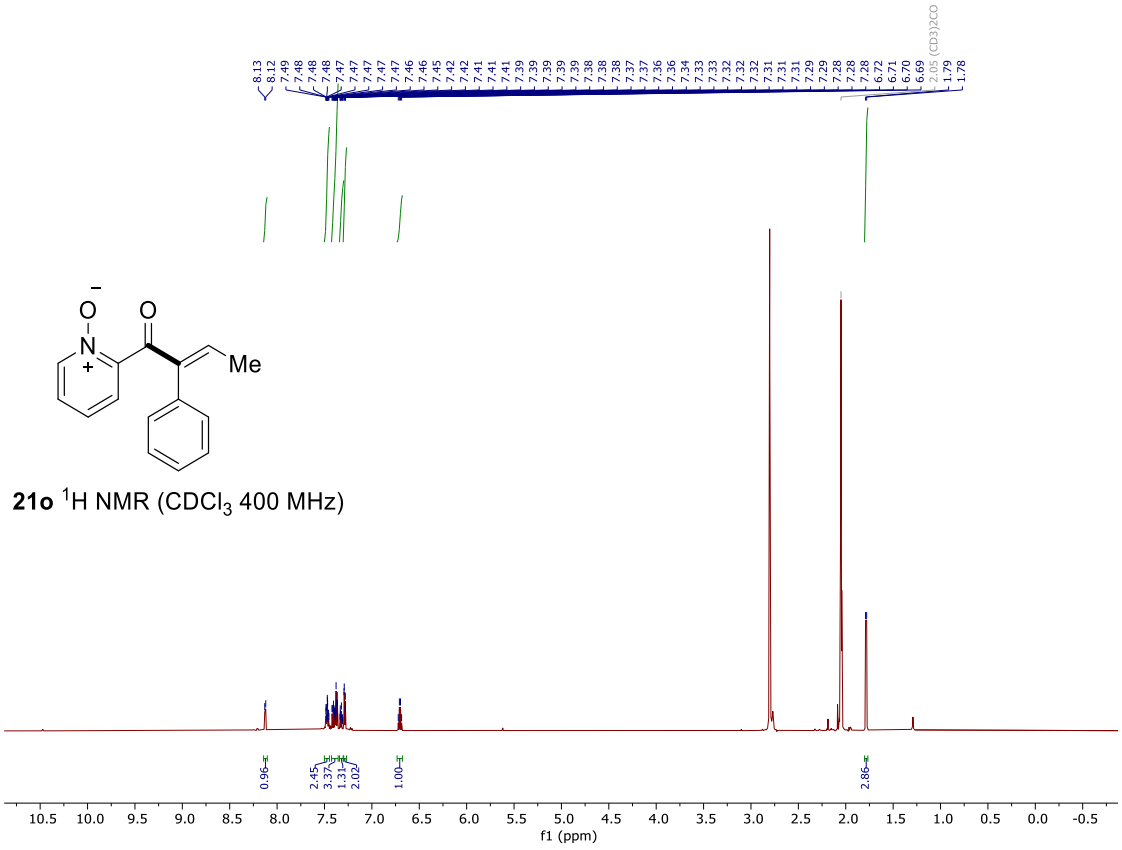
25 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 126 MHz)



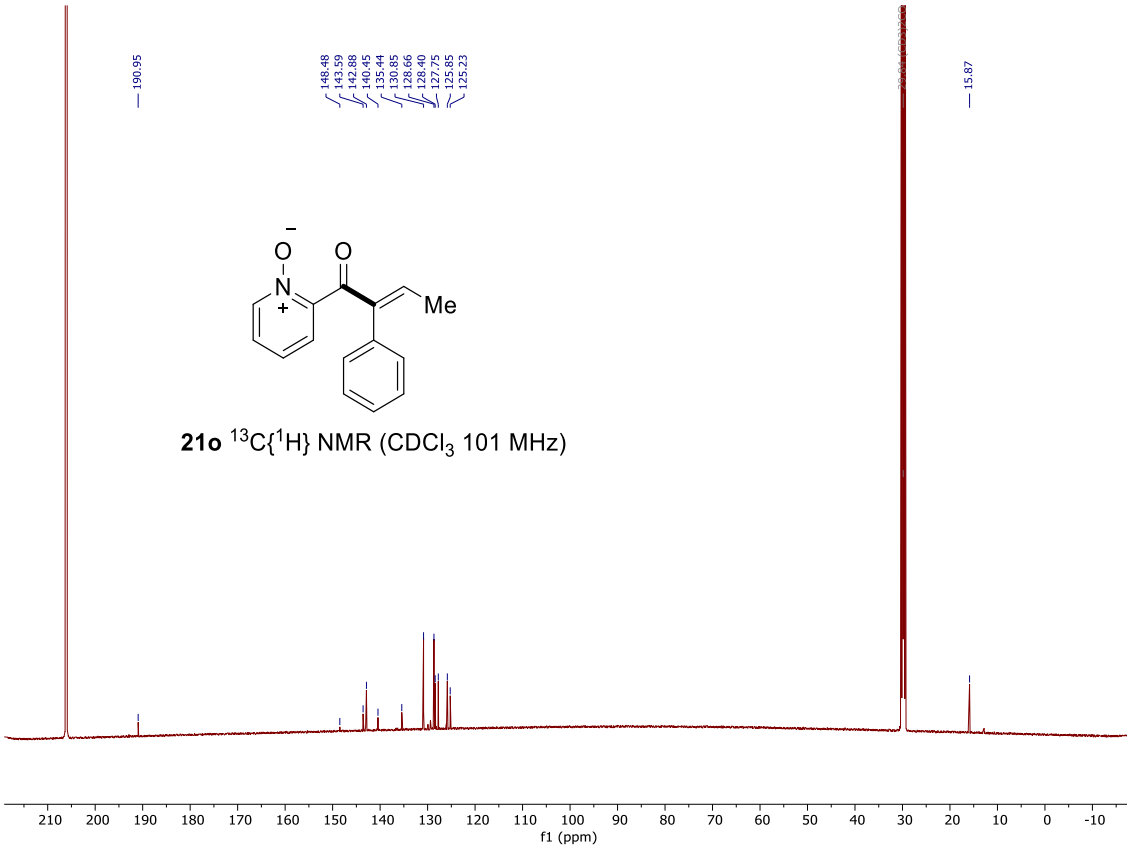
20o ^{1}H NMR ($CDCl_3$ 400 MHz)



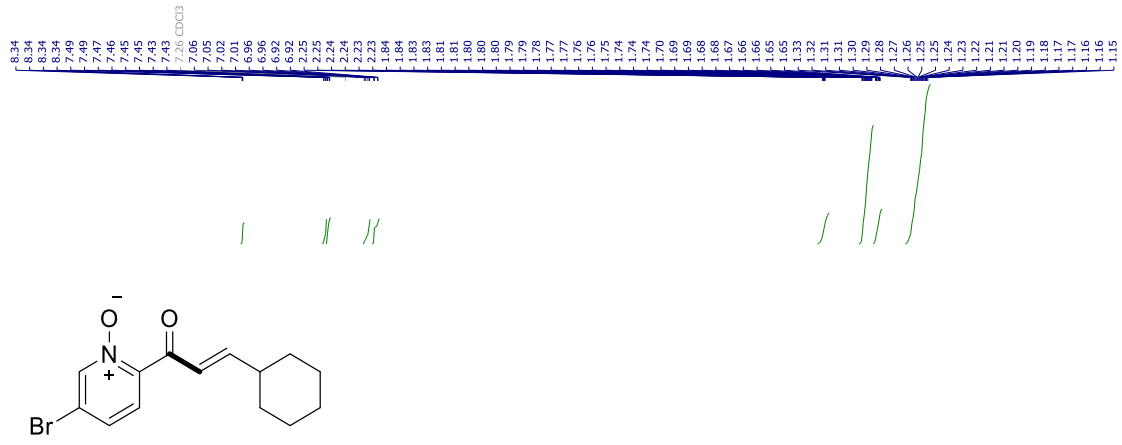
20o ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



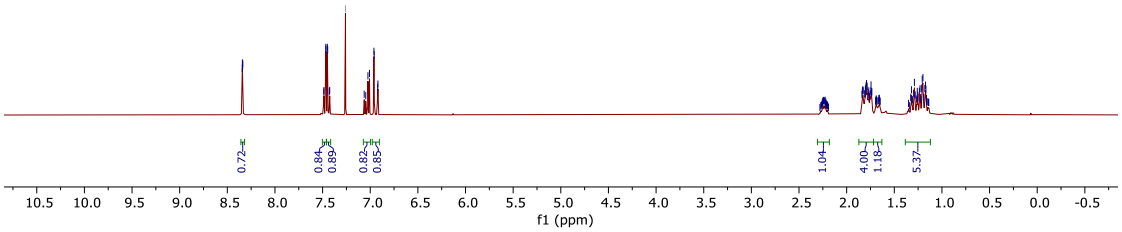
21o ^{1}H NMR ($CDCl_3$ 400 MHz)



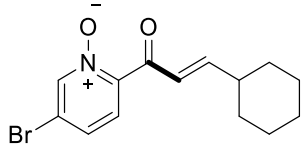
21o $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



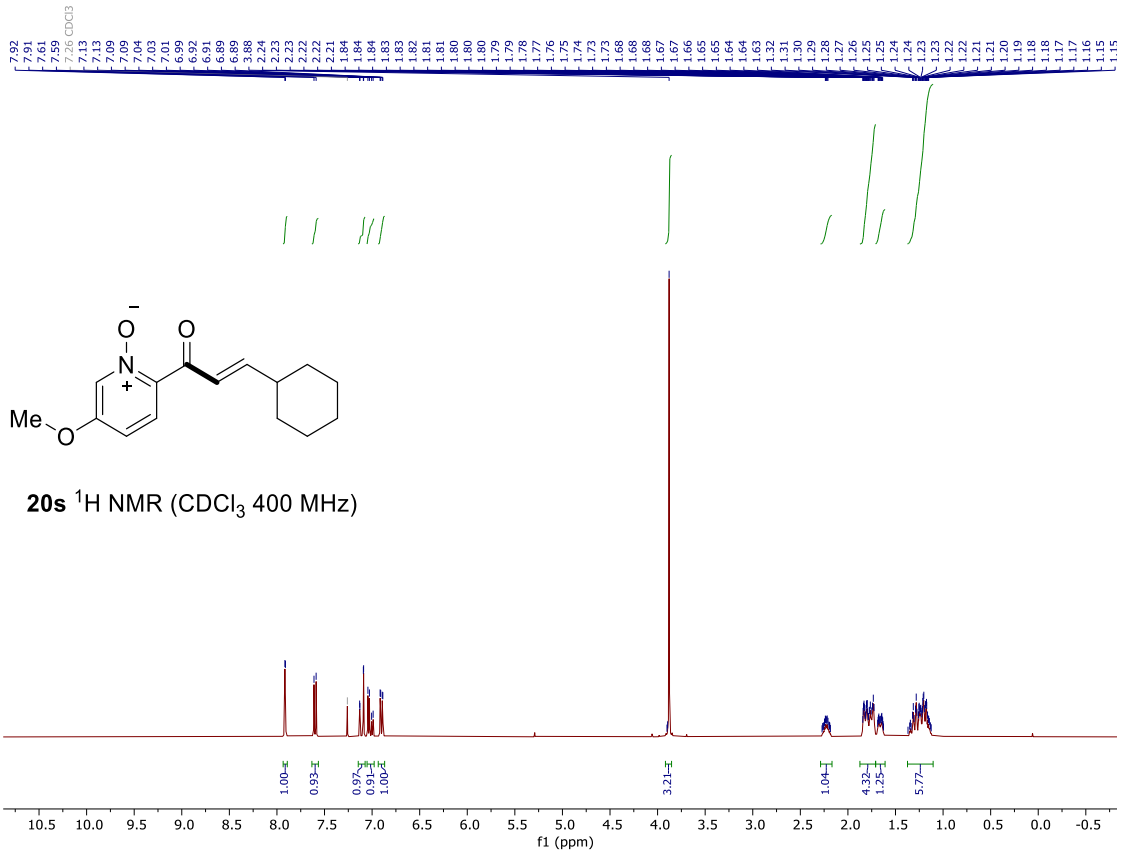
20r ^{1}H NMR ($CDCl_3$ 400 MHz)



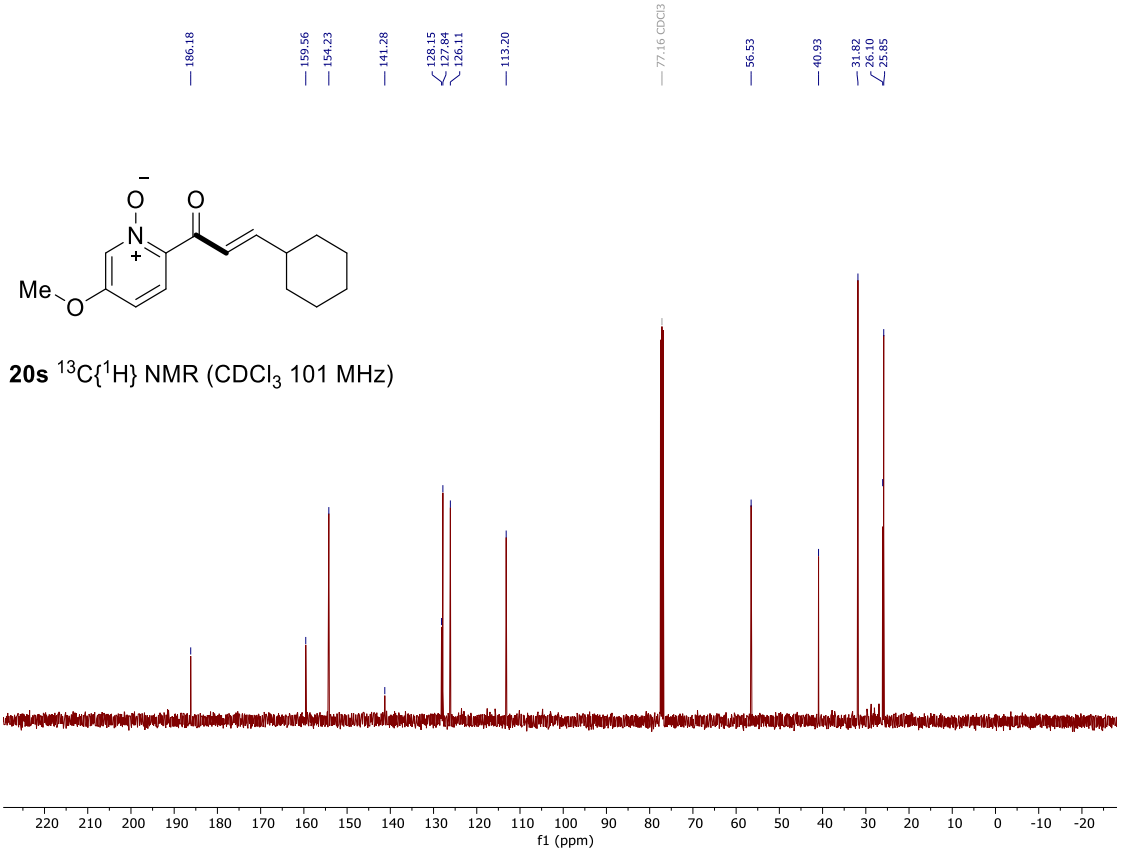




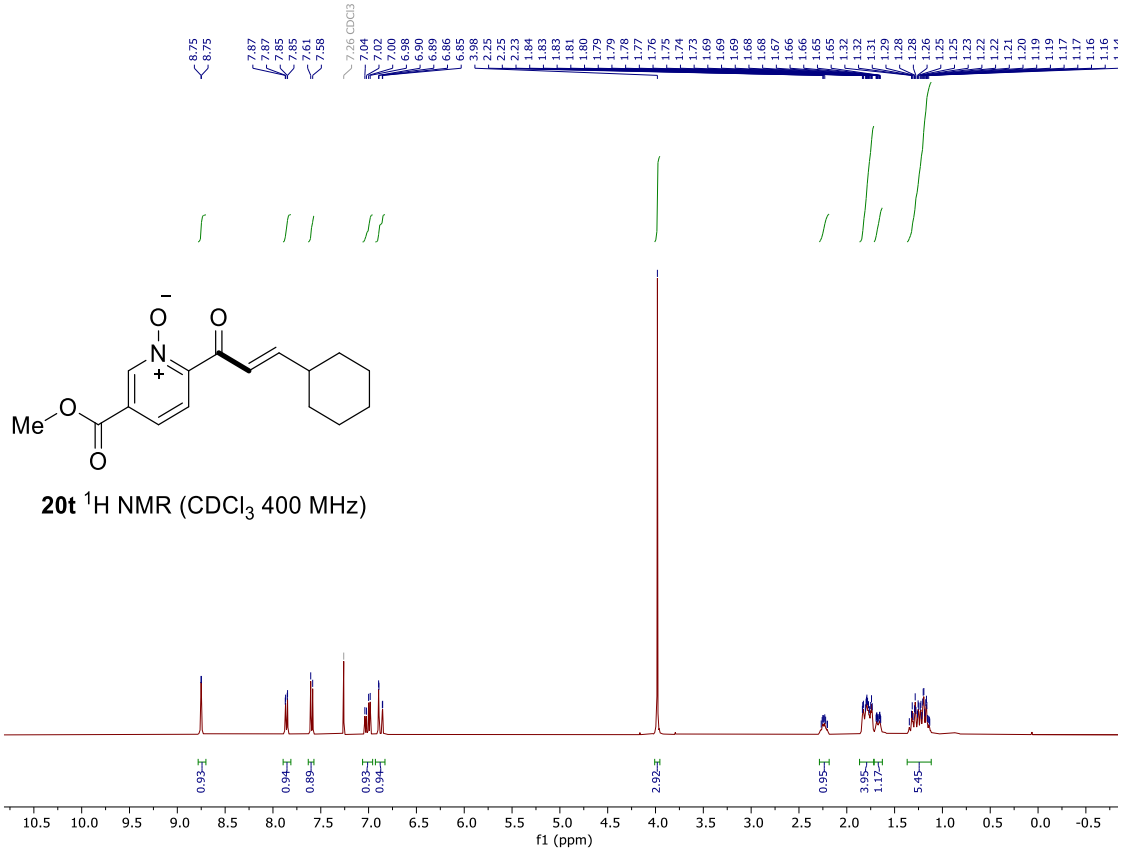
20r $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



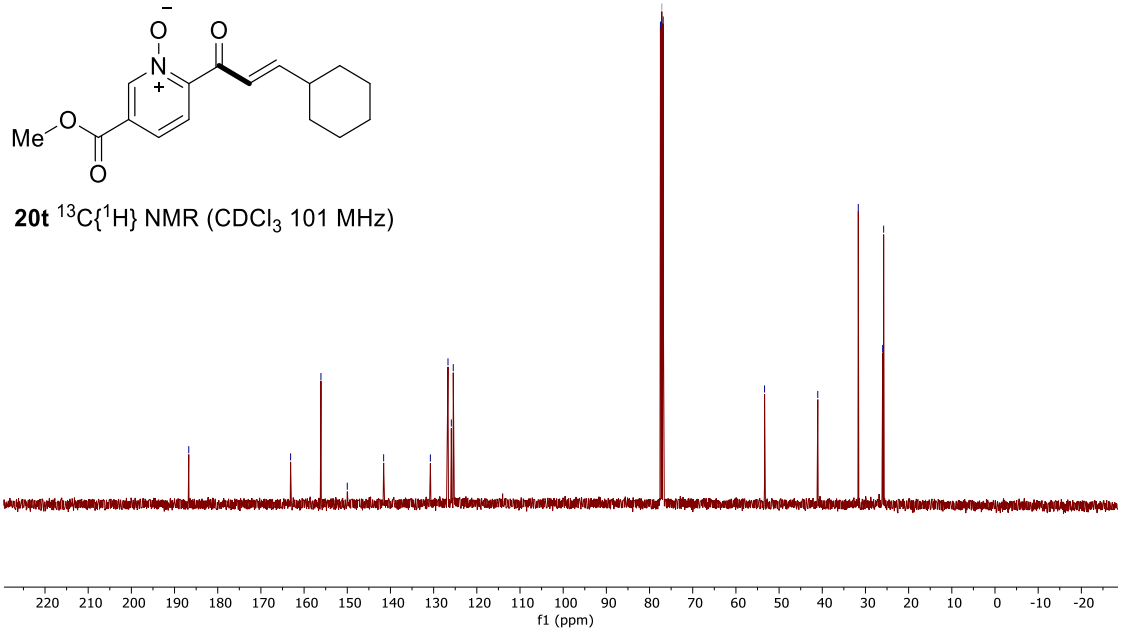
20s ^{1}H NMR ($CDCl_3$ 400 MHz)



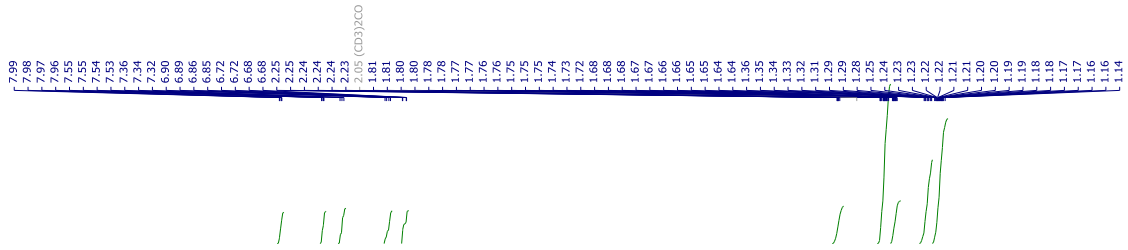
20s $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

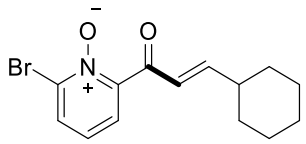


20t ^{1}H NMR ($CDCl_3$ 400 MHz)

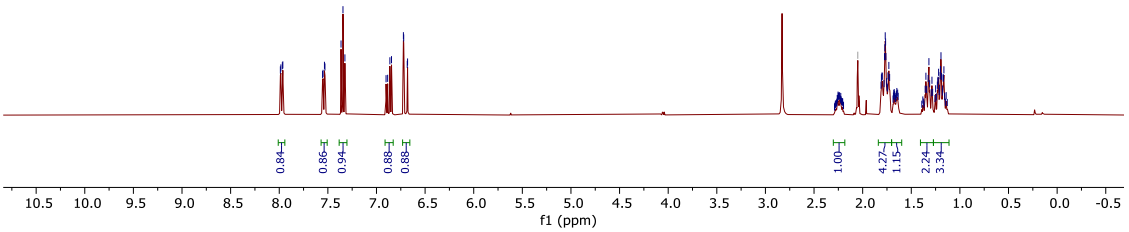


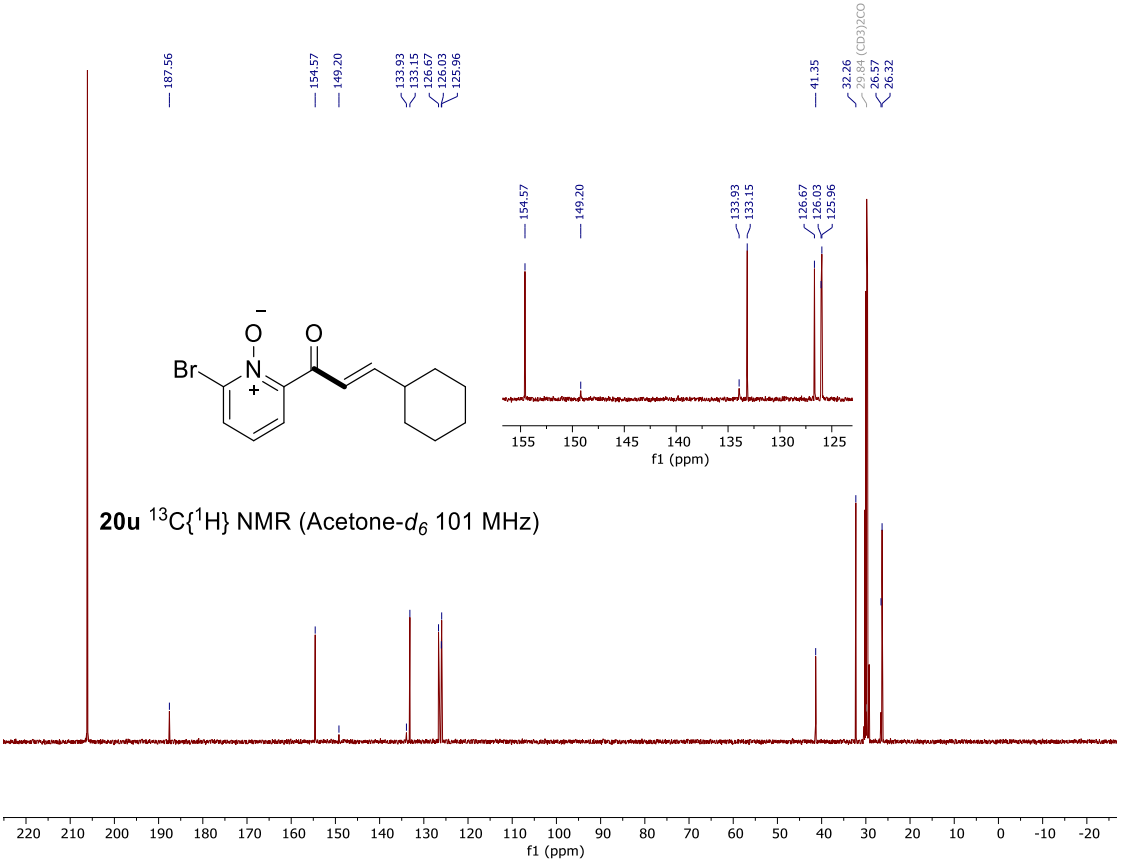
20t $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



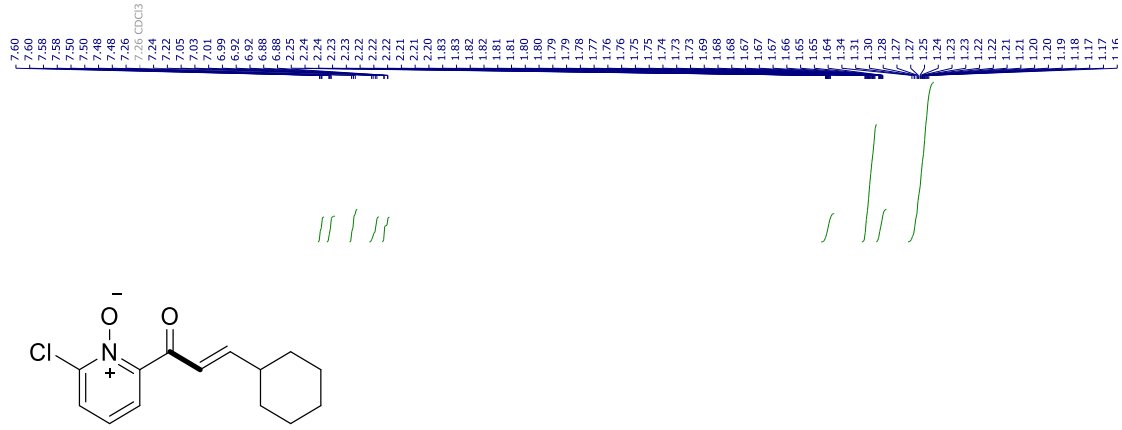


20u ^{1}H NMR (Acetone-d_6 400 MHz)

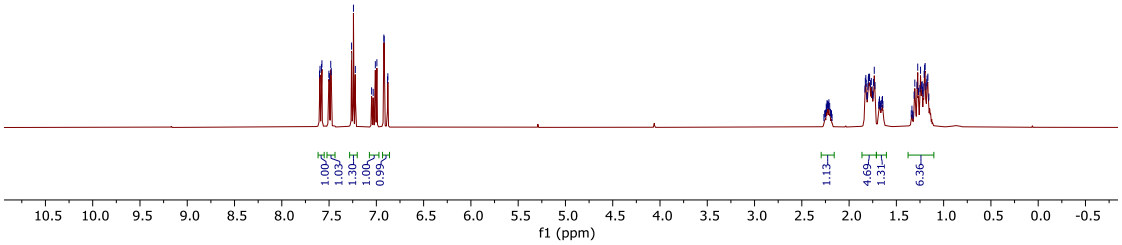




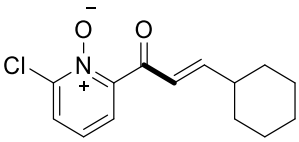
20u ^{13}C{^{1}H} NMR (Acetone-d_6 101 MHz)



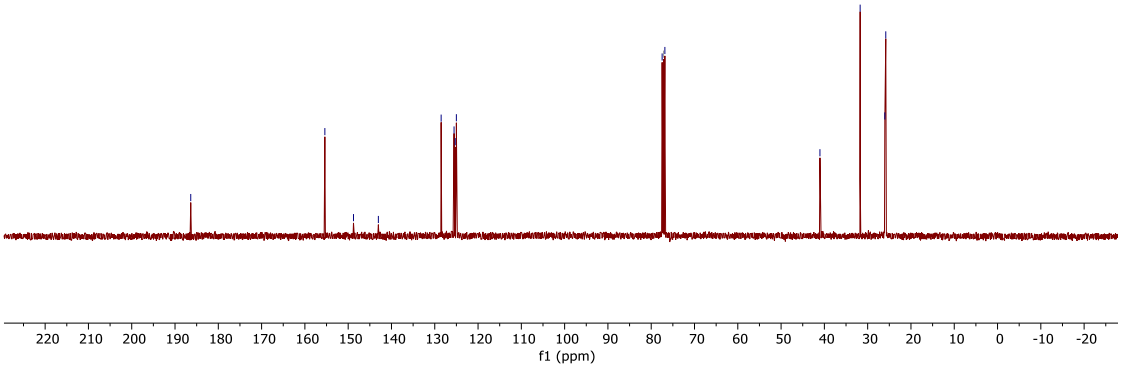
20v ^{1}H NMR ($CDCl_3$ 400 MHz)

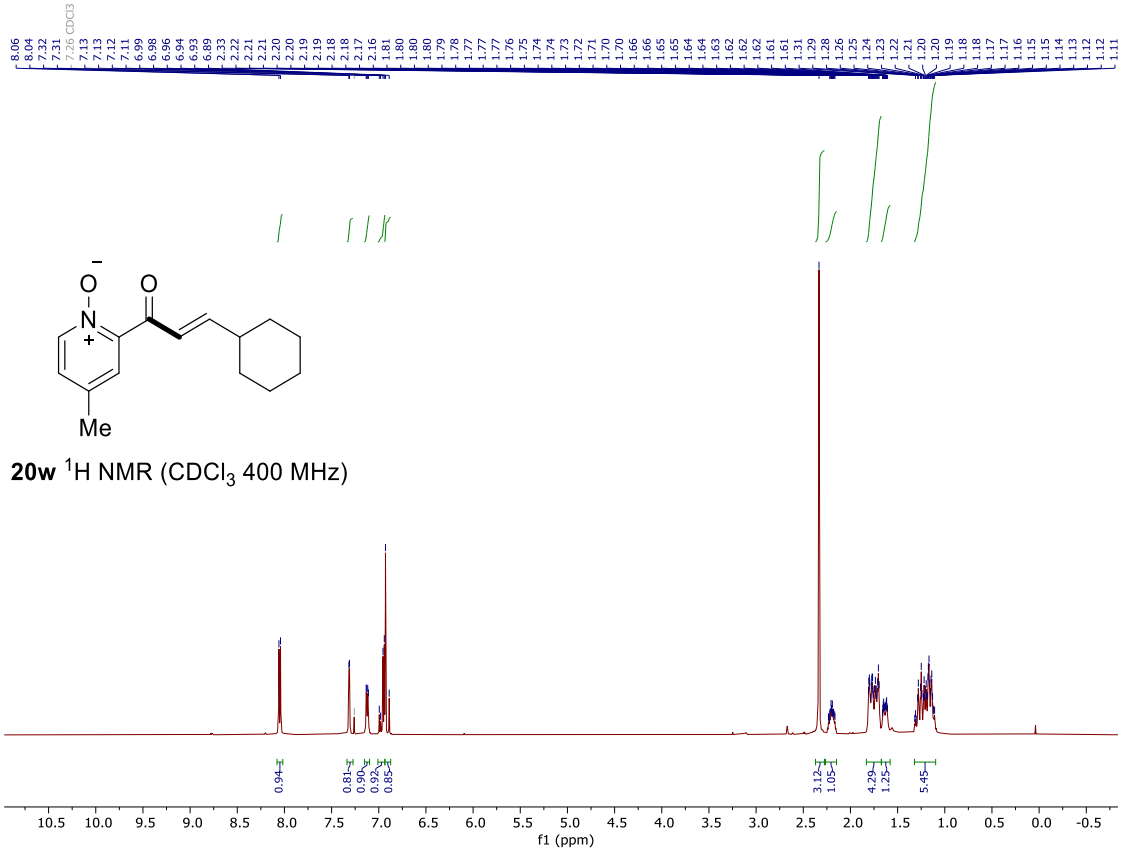




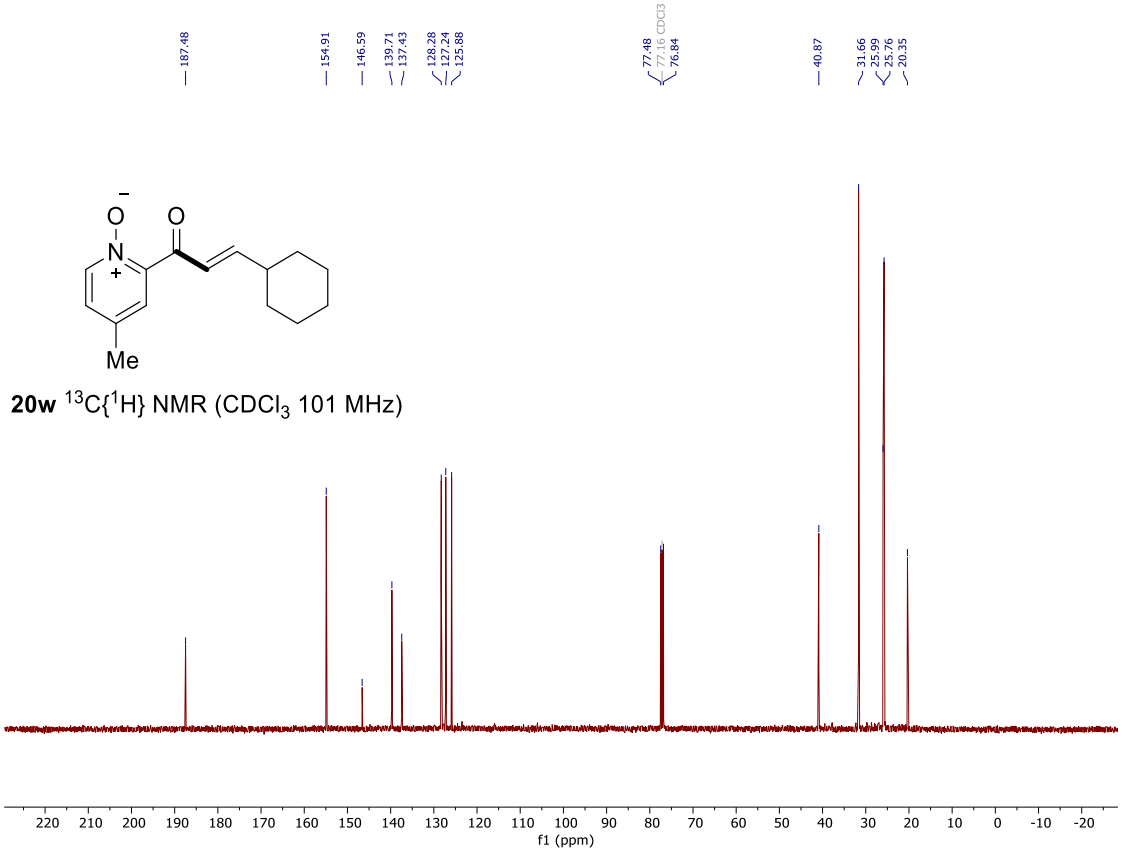


20v $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

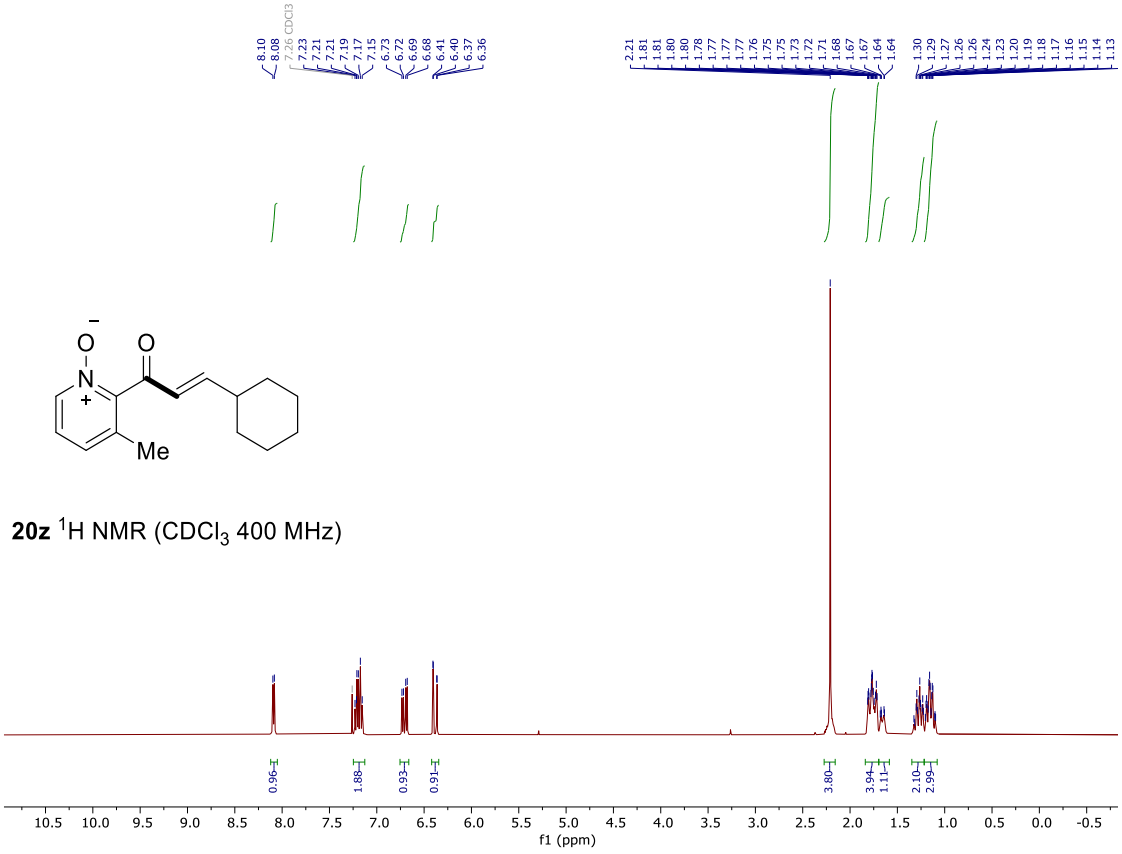




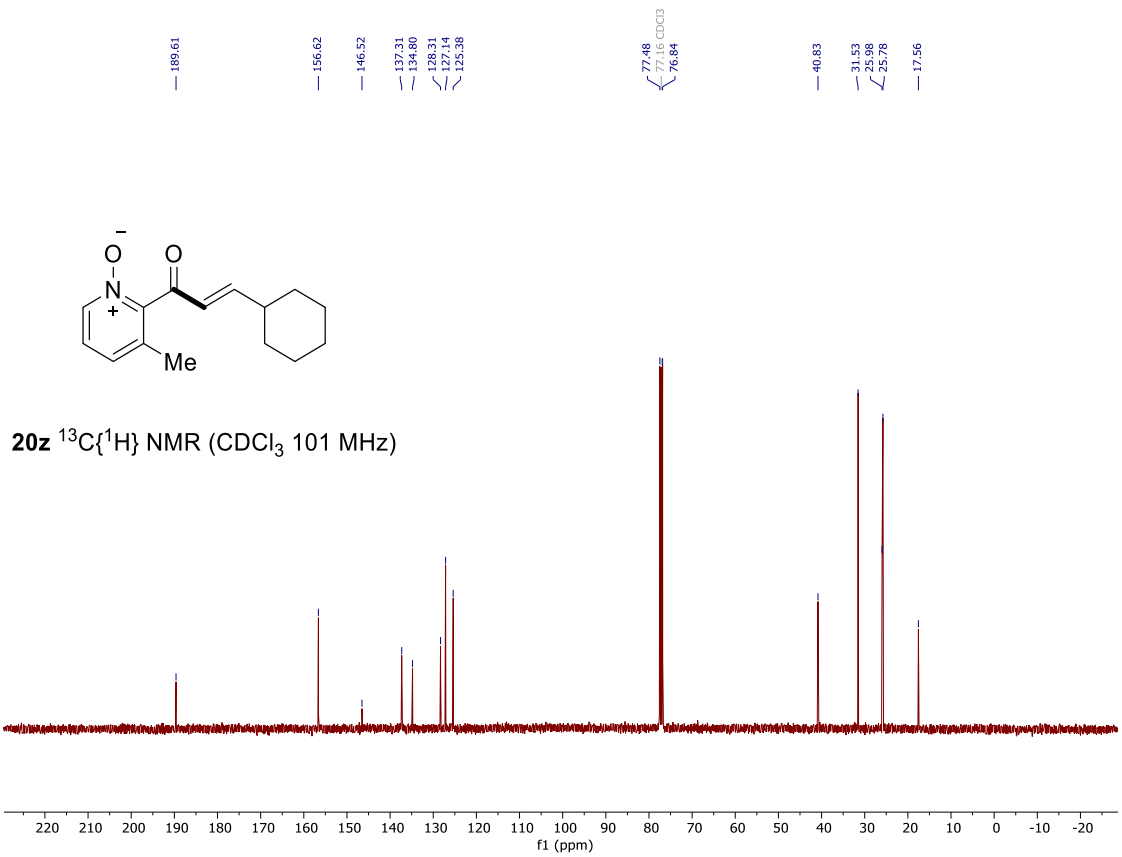
20w ^{1}H NMR ($CDCl_3$ 400 MHz)



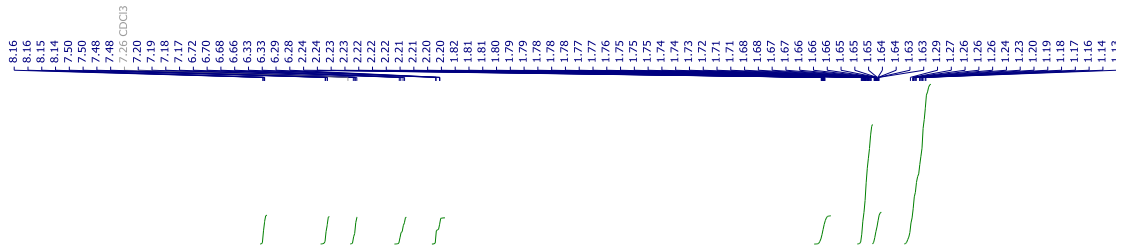
20w $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

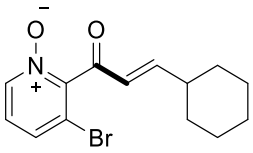


20z ^{1}H NMR ($CDCl_3$ 400 MHz)

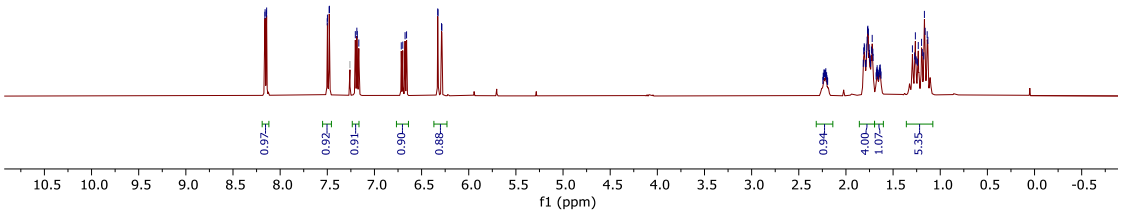


20z ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

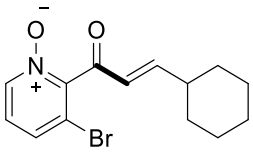




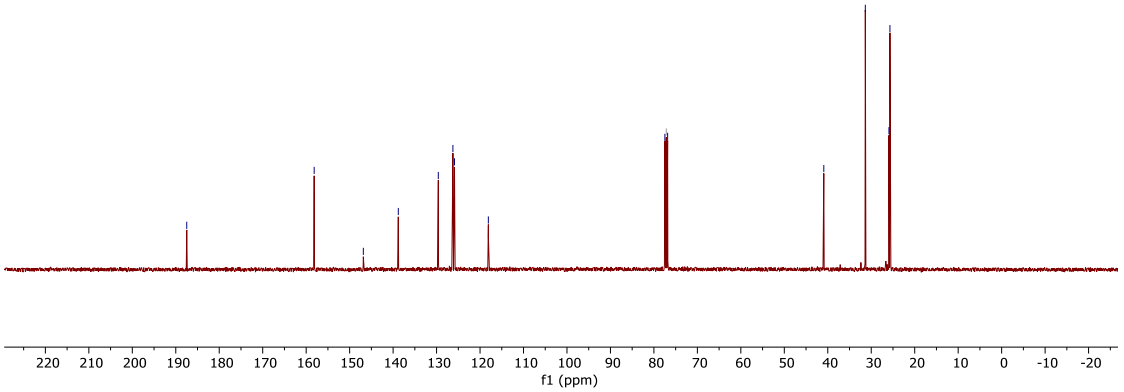
20aa ^{1}H NMR ($CDCl_3$ 400 MHz)

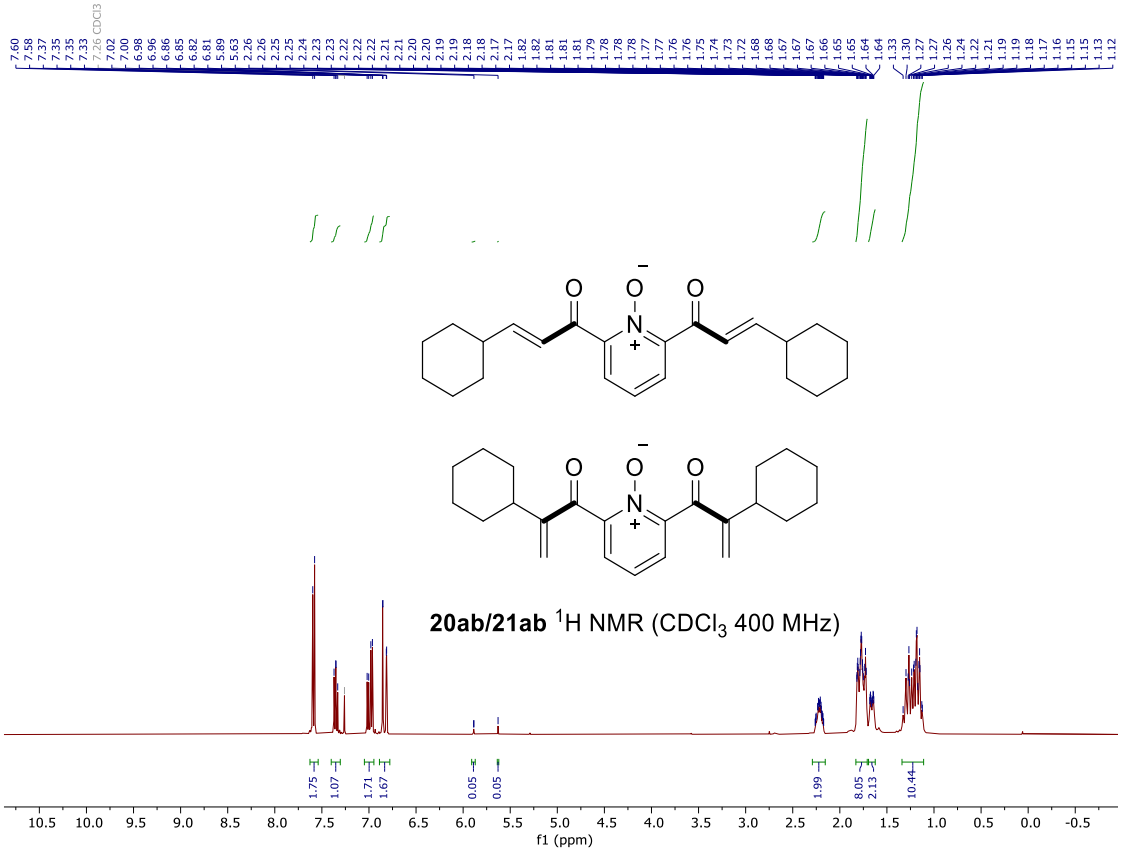




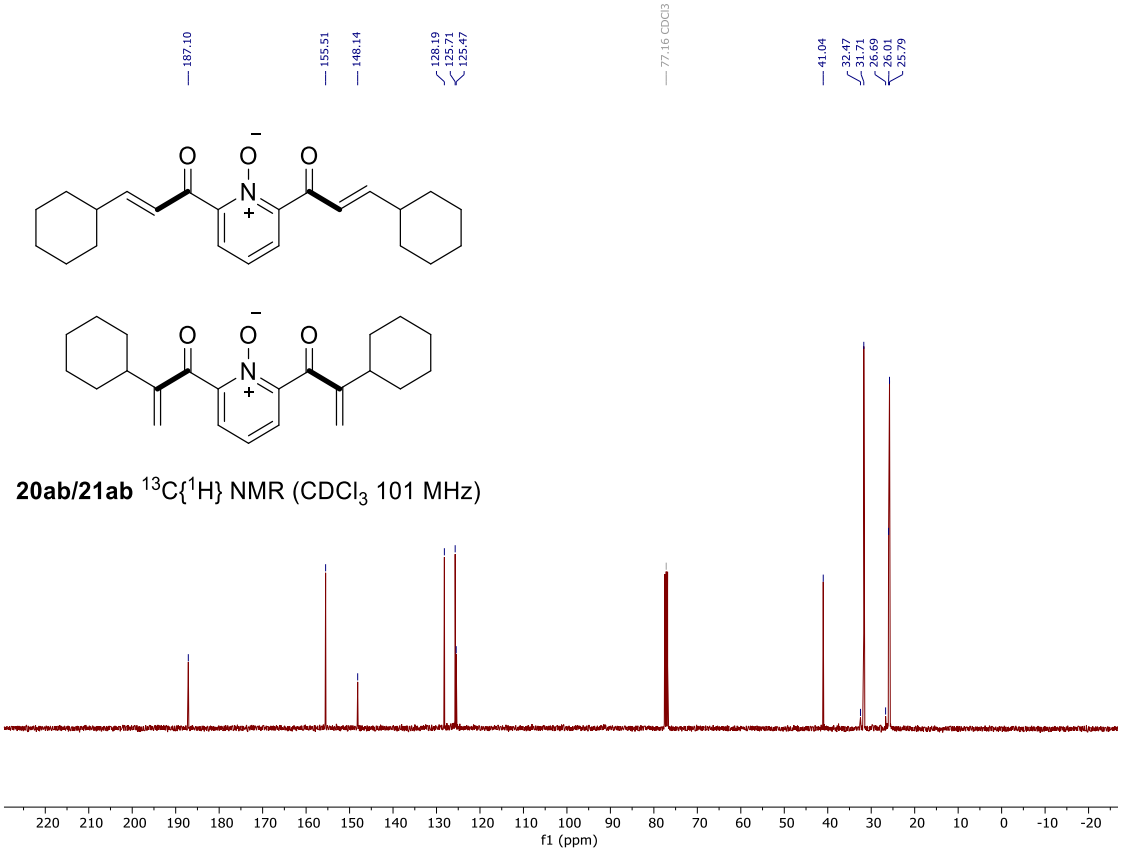


20aa ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

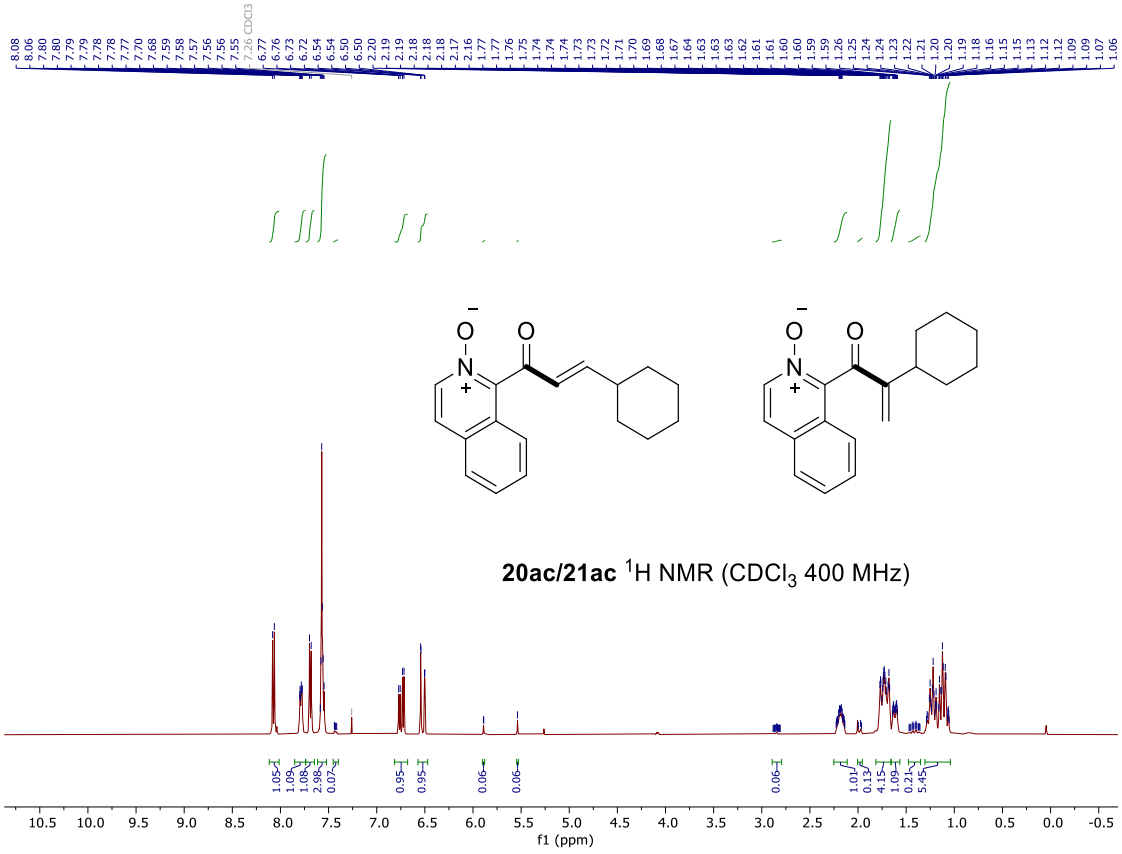




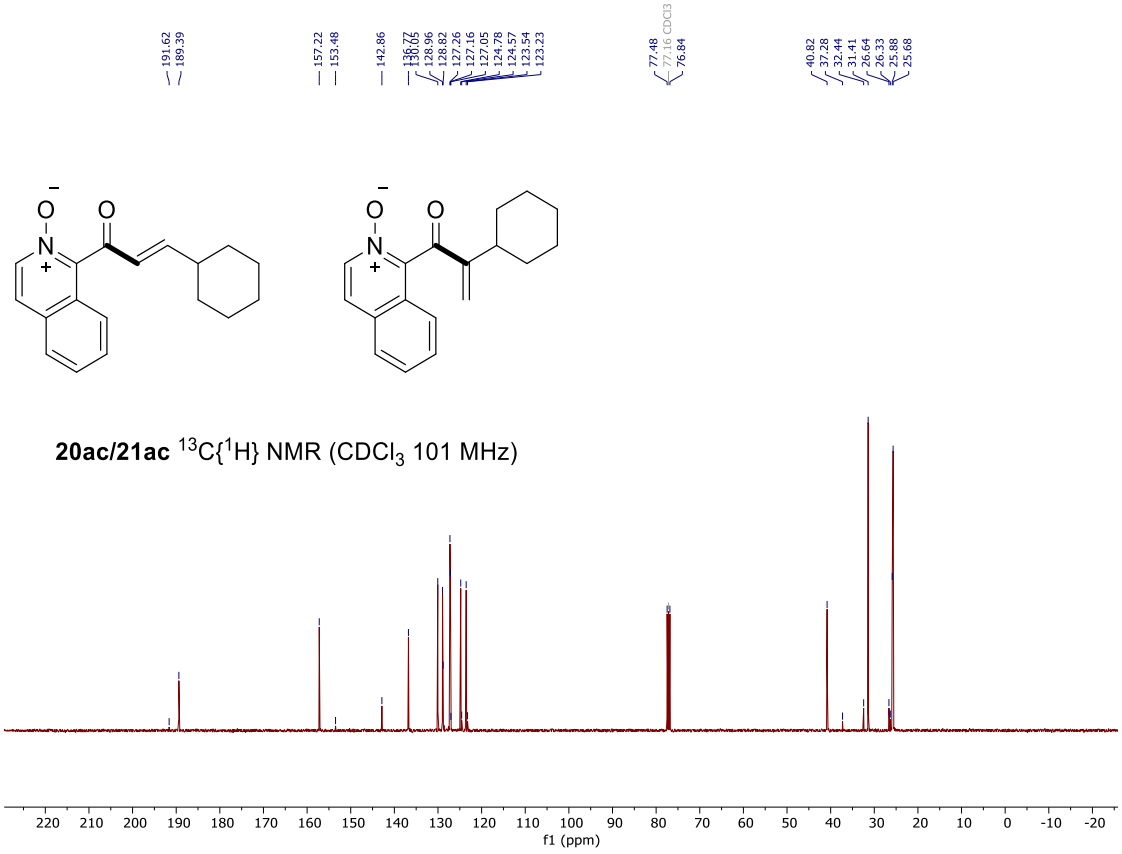
20ab/21ab ^{1}H NMR ($CDCl_3$ 400 MHz)



20ab/21ab $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



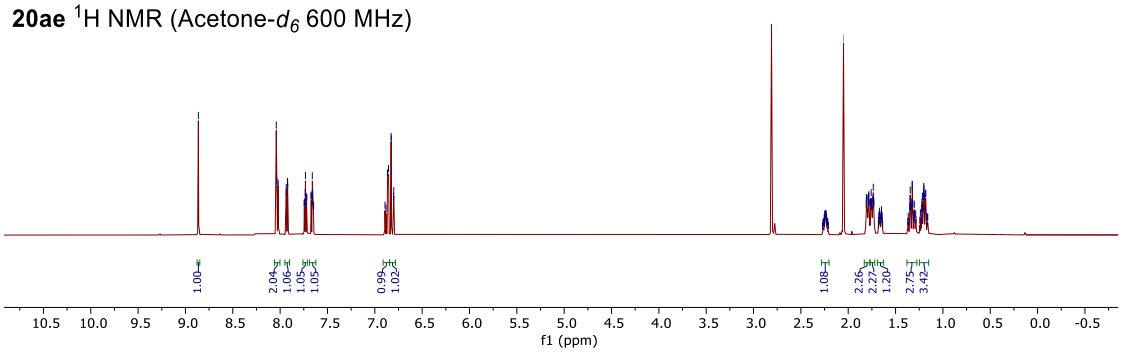
20ac/21ac ^{1}H NMR ($CDCl_3$ 400 MHz)

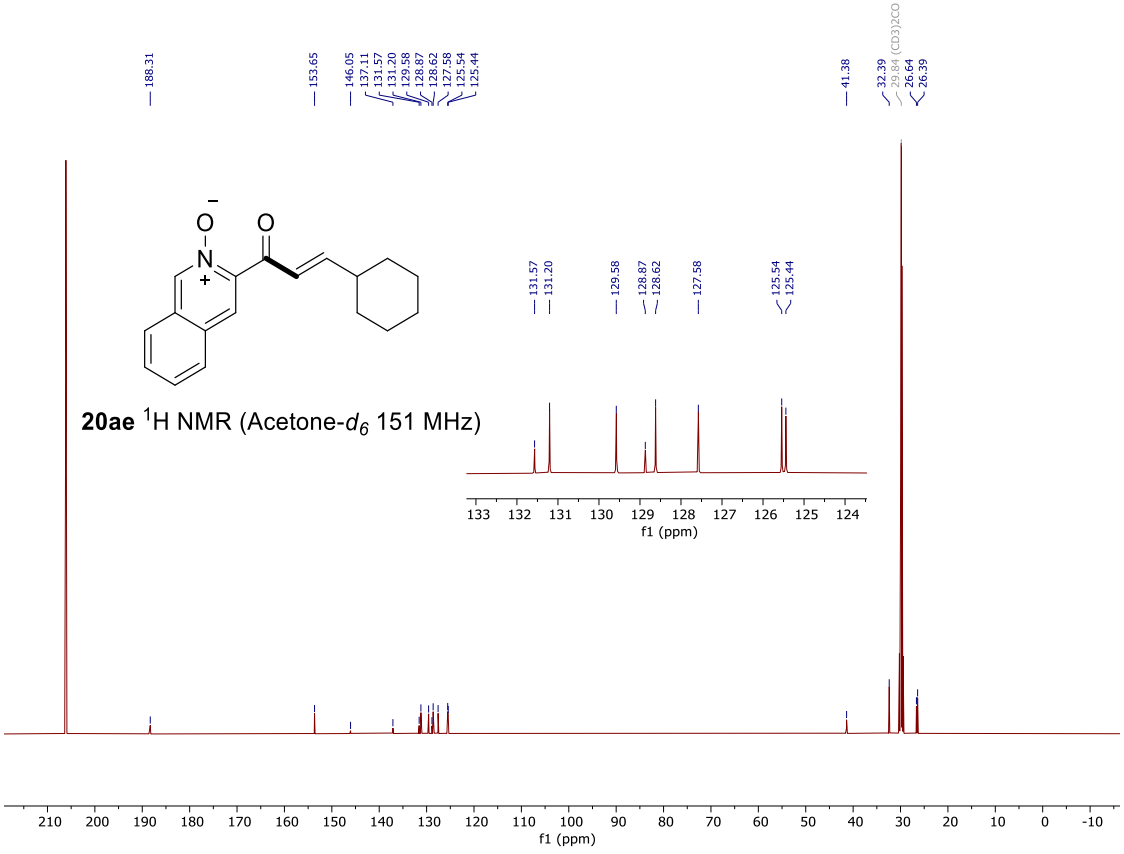


20ac/21ac $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

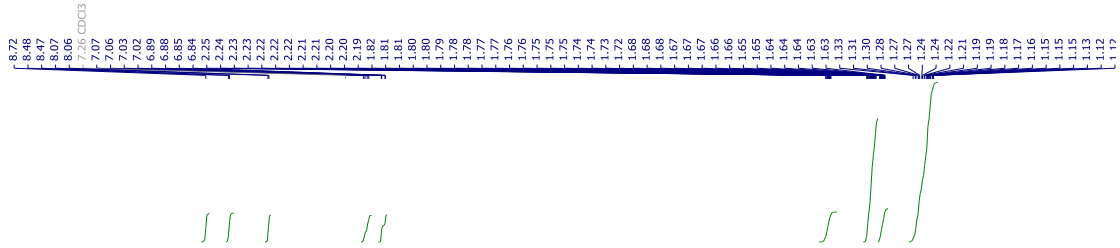


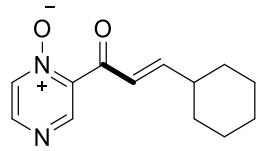
20ae ^{1}H NMR (Acetone-d_6 600 MHz)



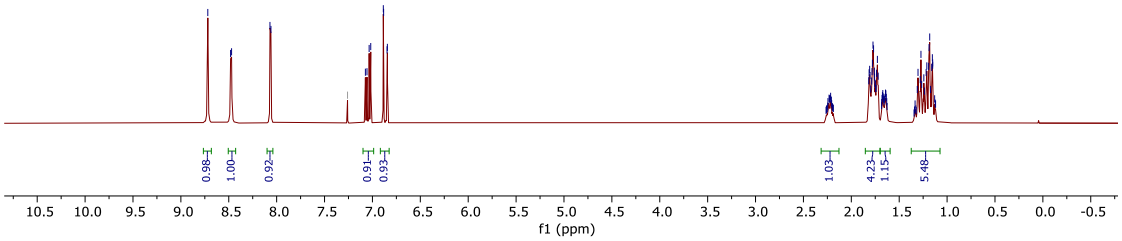


20ae ^{1}H NMR (Acetone-d_6 151 MHz)

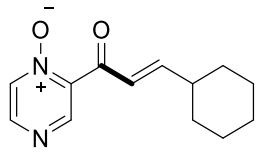




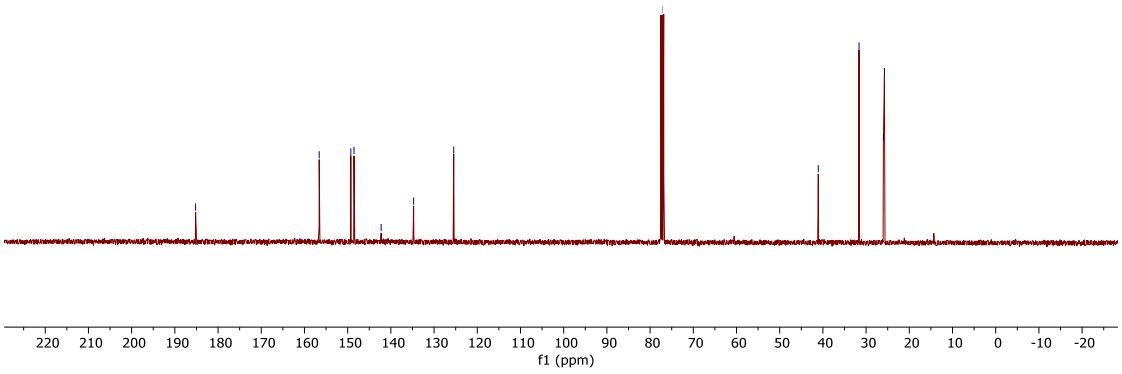
20af ^{1}H NMR ($CDCl_3$ 400 MHz)

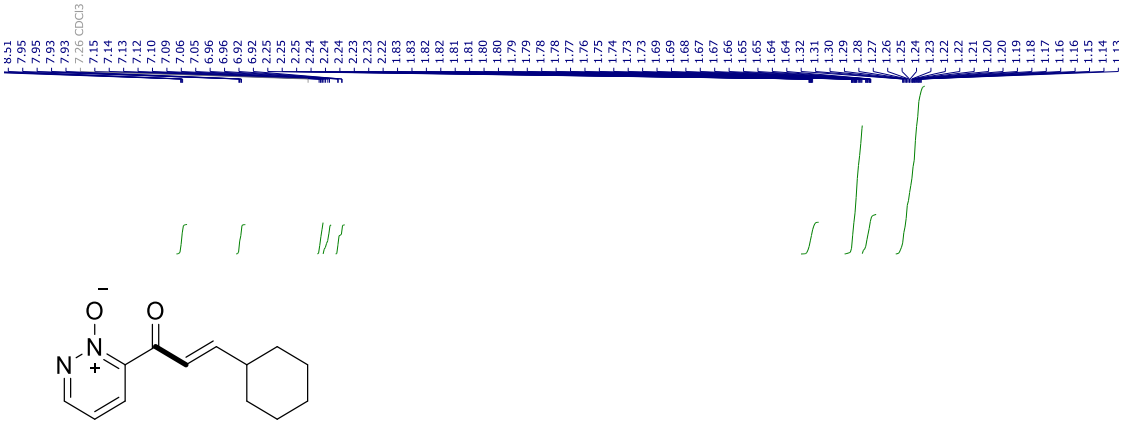




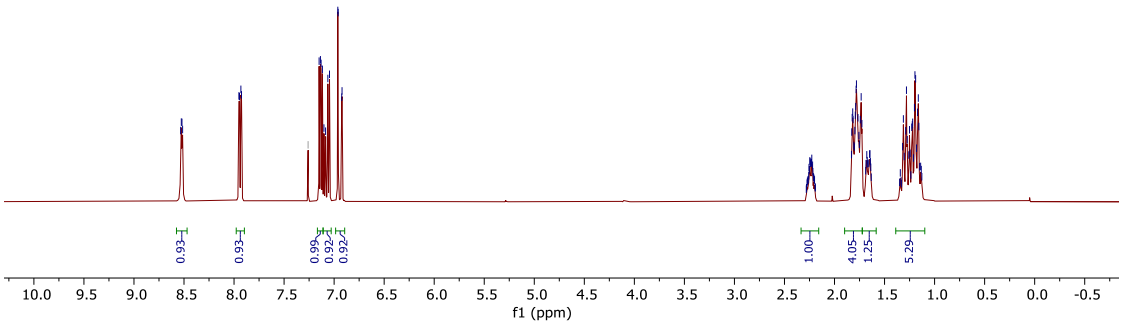


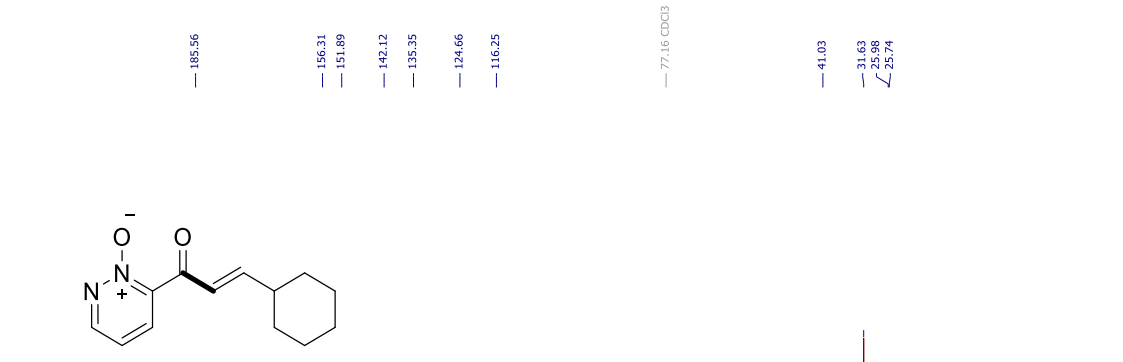
20af $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



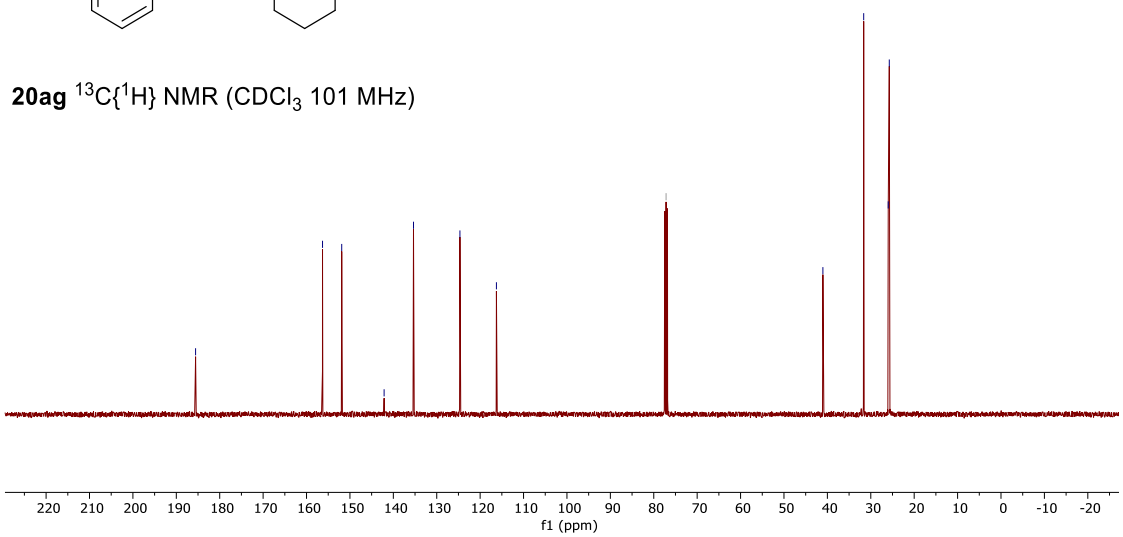


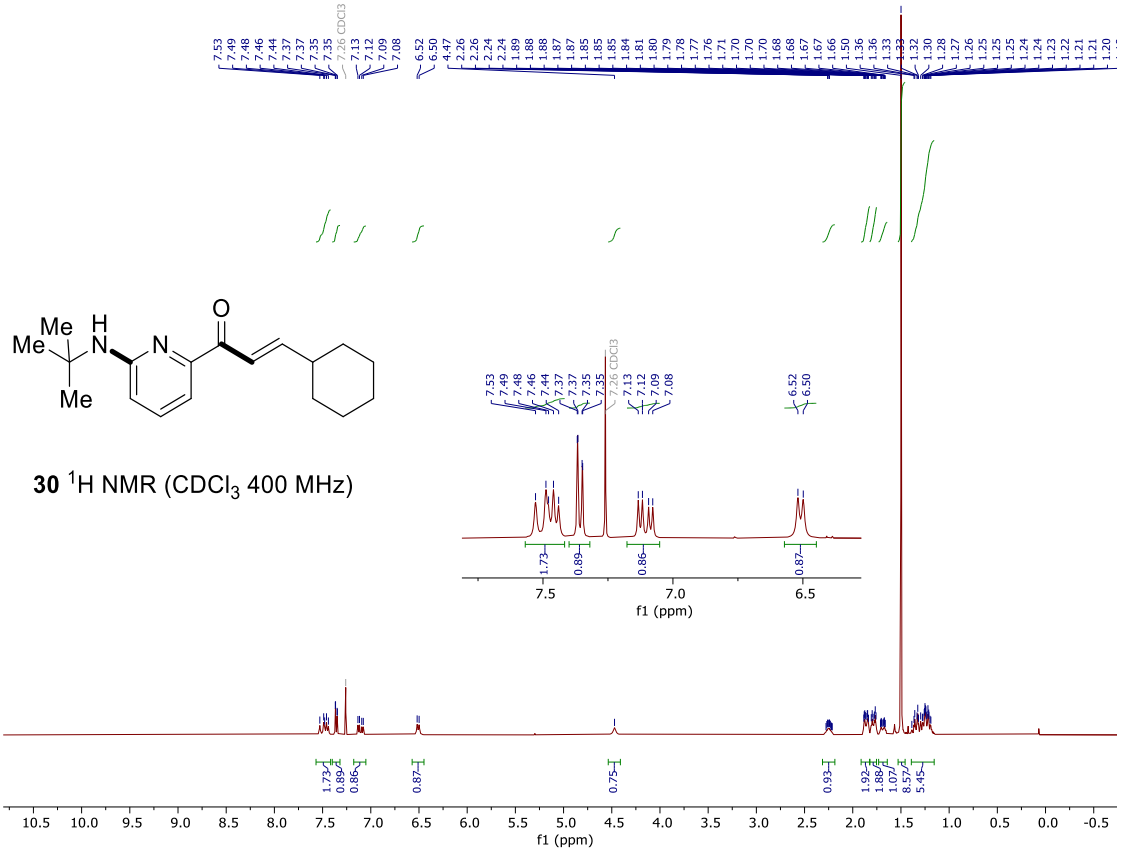
20ag ^{1}H NMR ($CDCl_3$ 400 MHz)



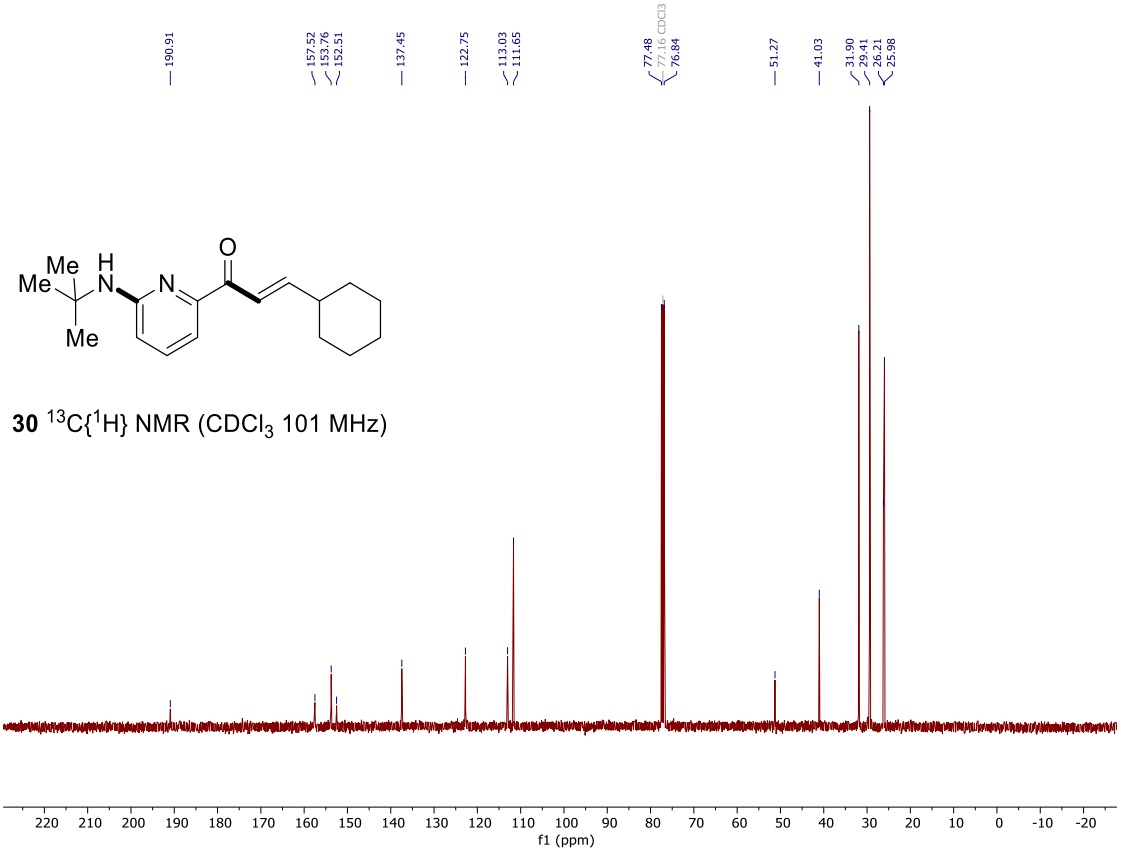


20ag $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

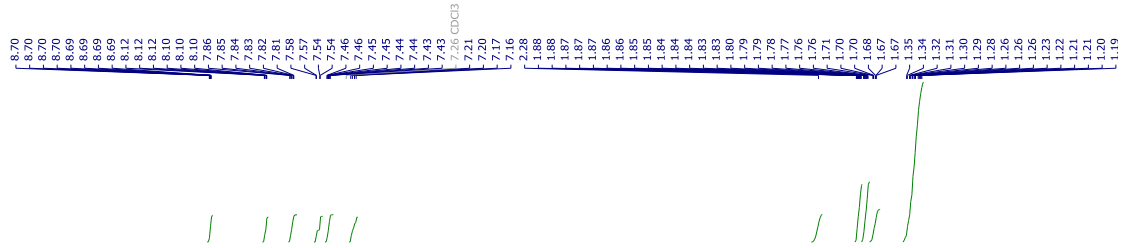


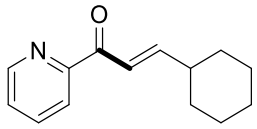


30 ^{1}H NMR ($CDCl_3$ 400 MHz)

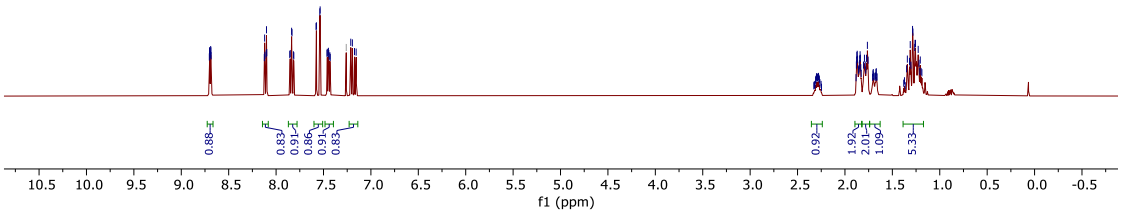


30 ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

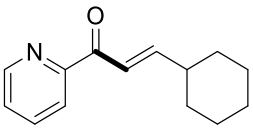




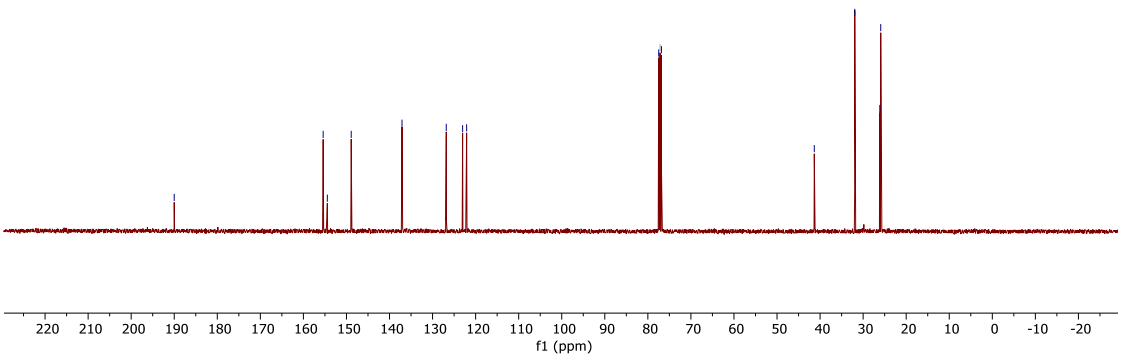
31 ^{1}H NMR ($CDCl_3$ 400 MHz)

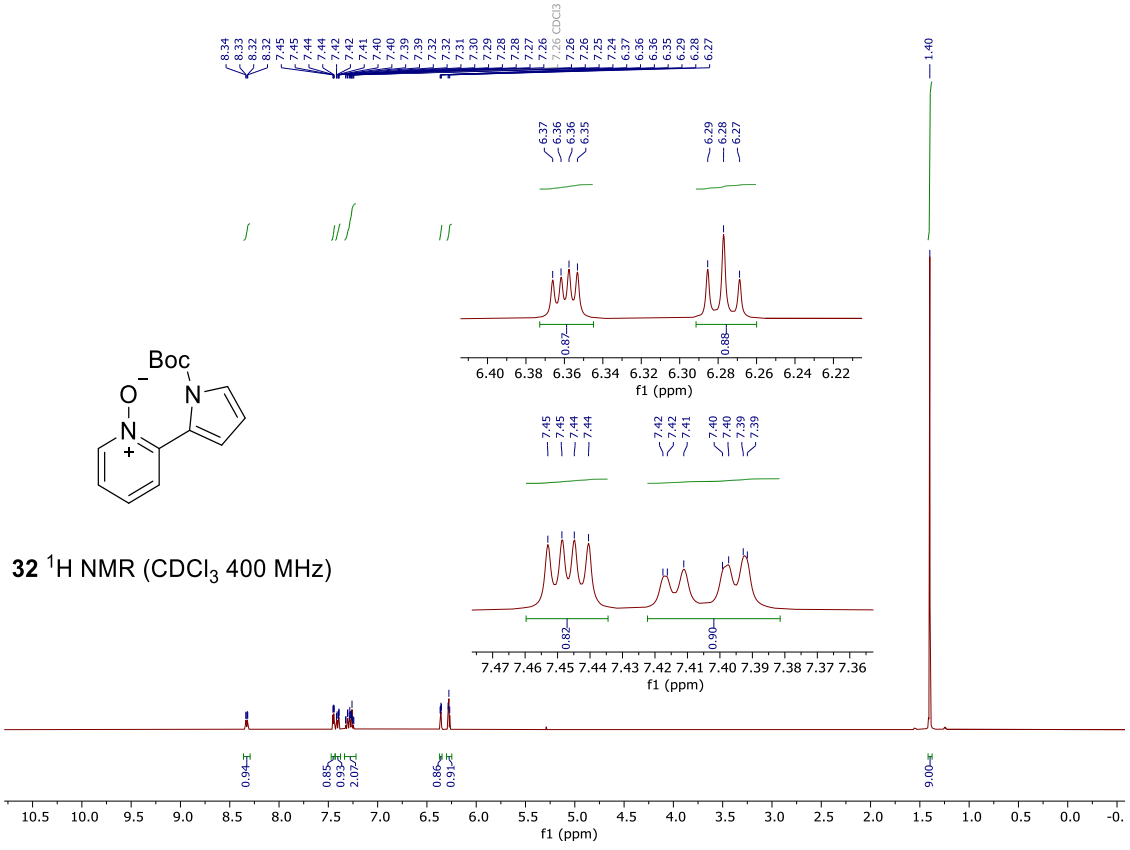




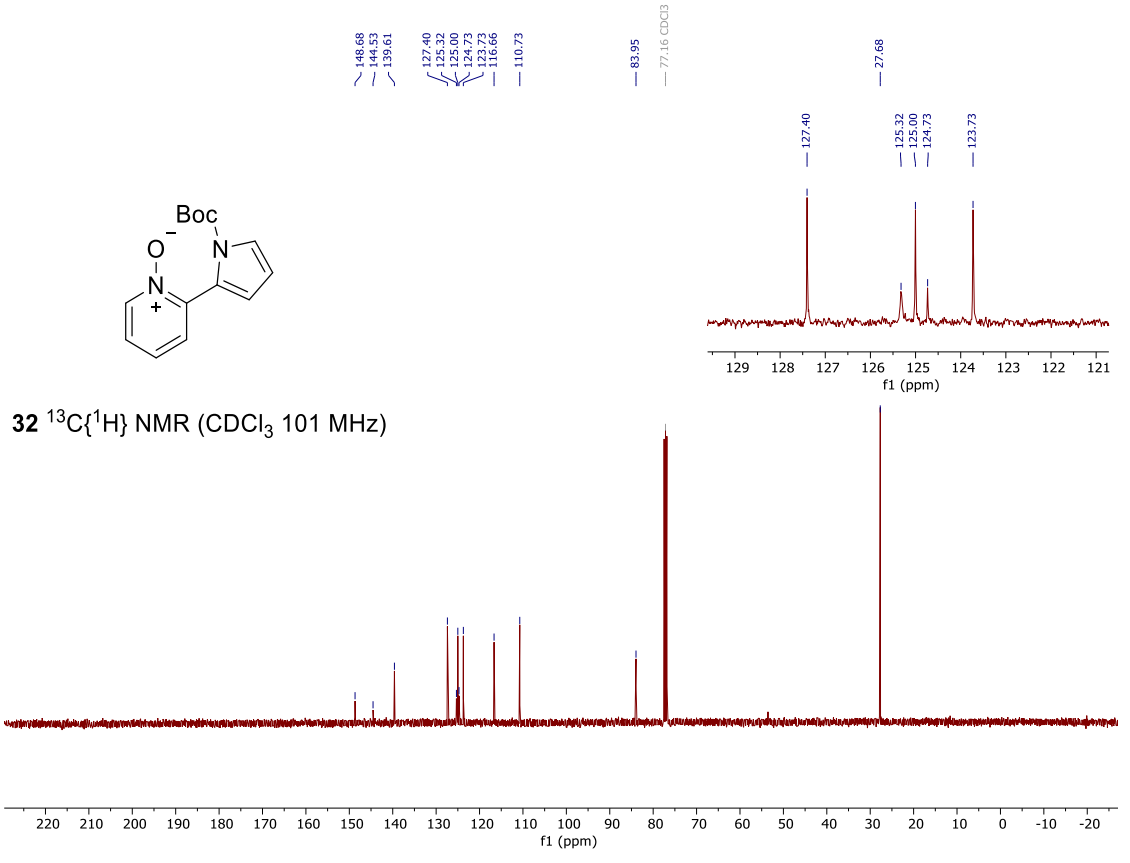


31 ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)

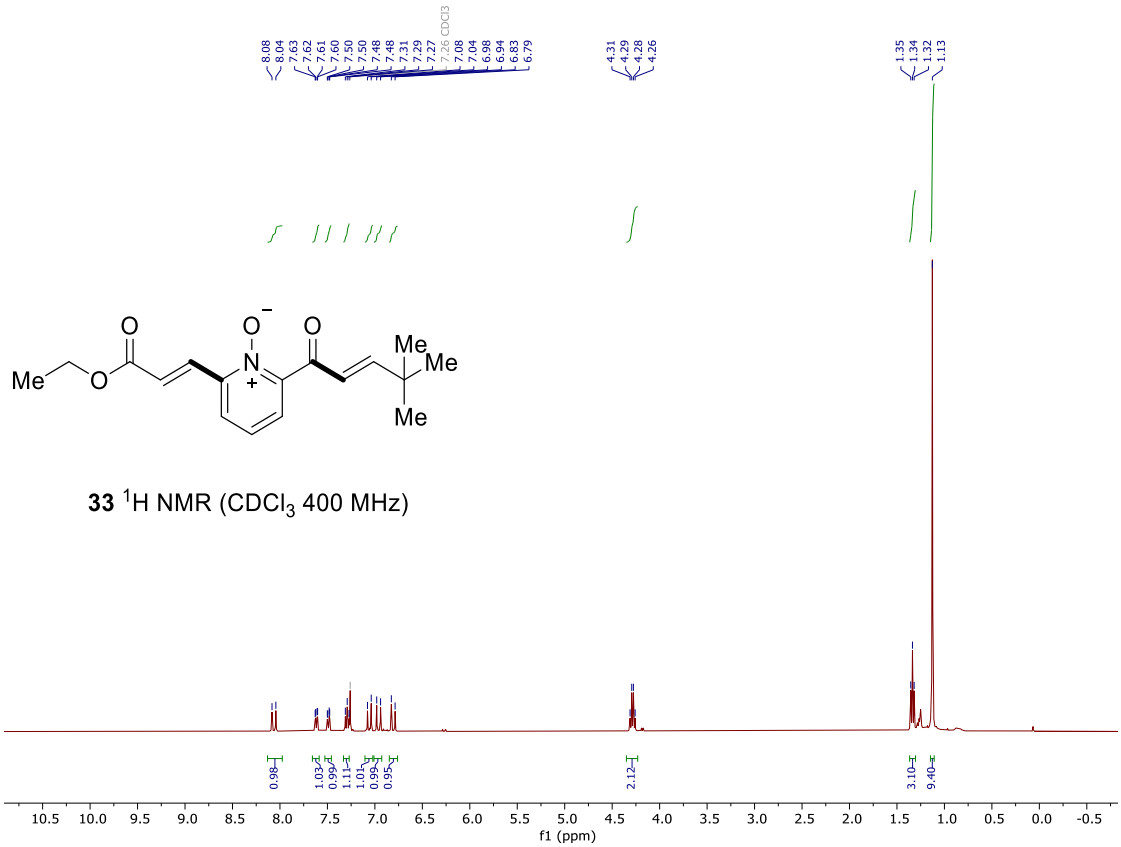




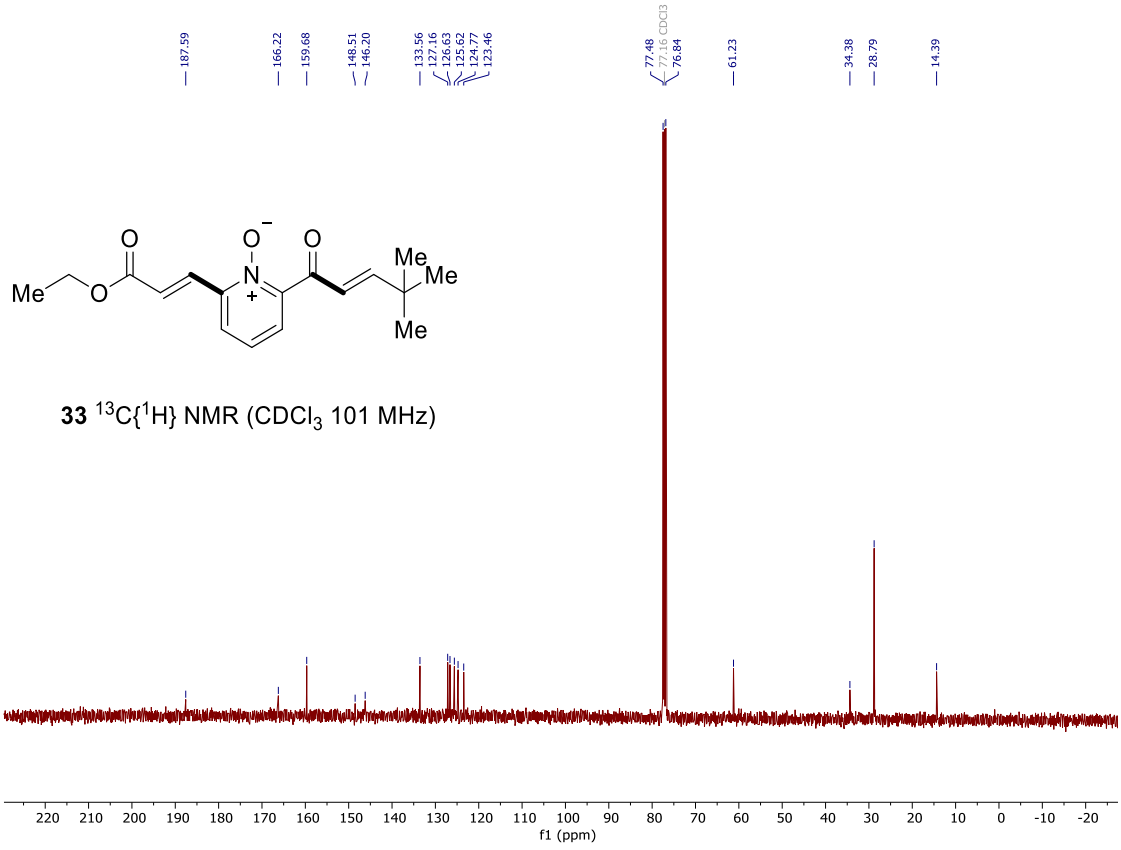
32 ^{1}H NMR ($CDCl_3$ 400 MHz)



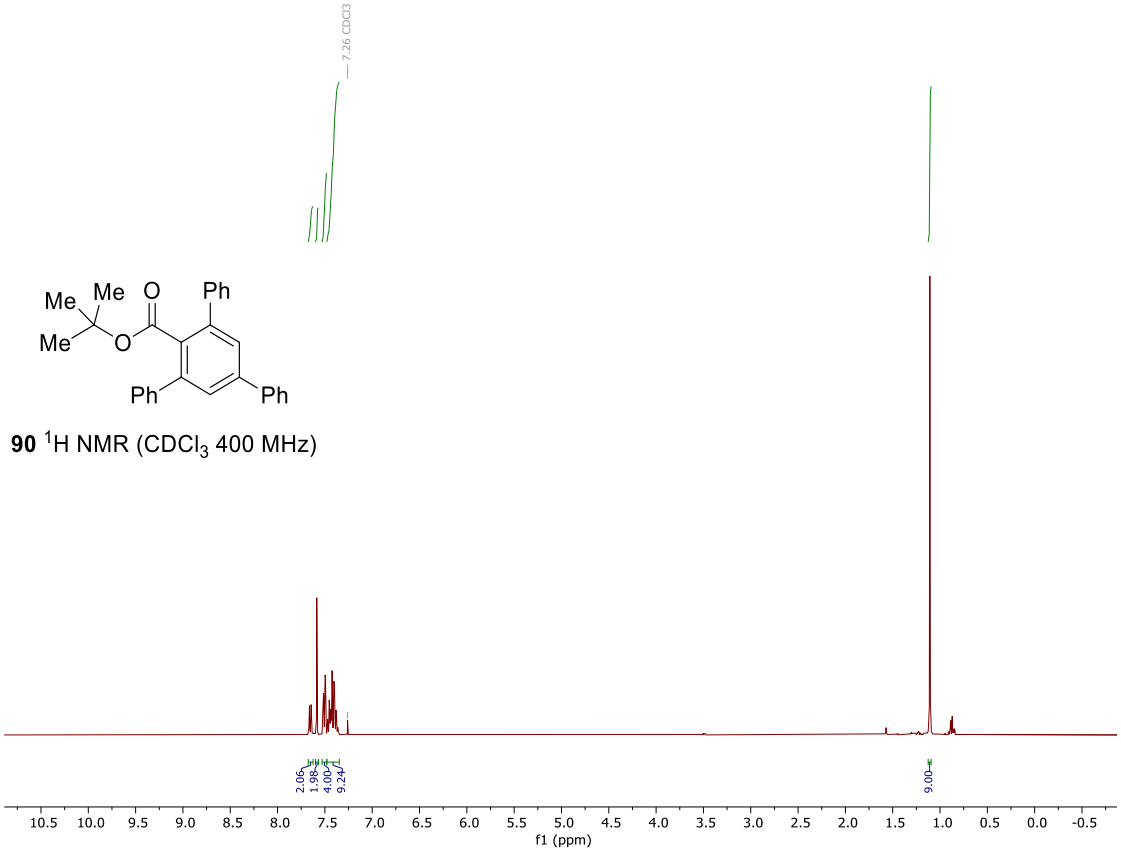
32 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



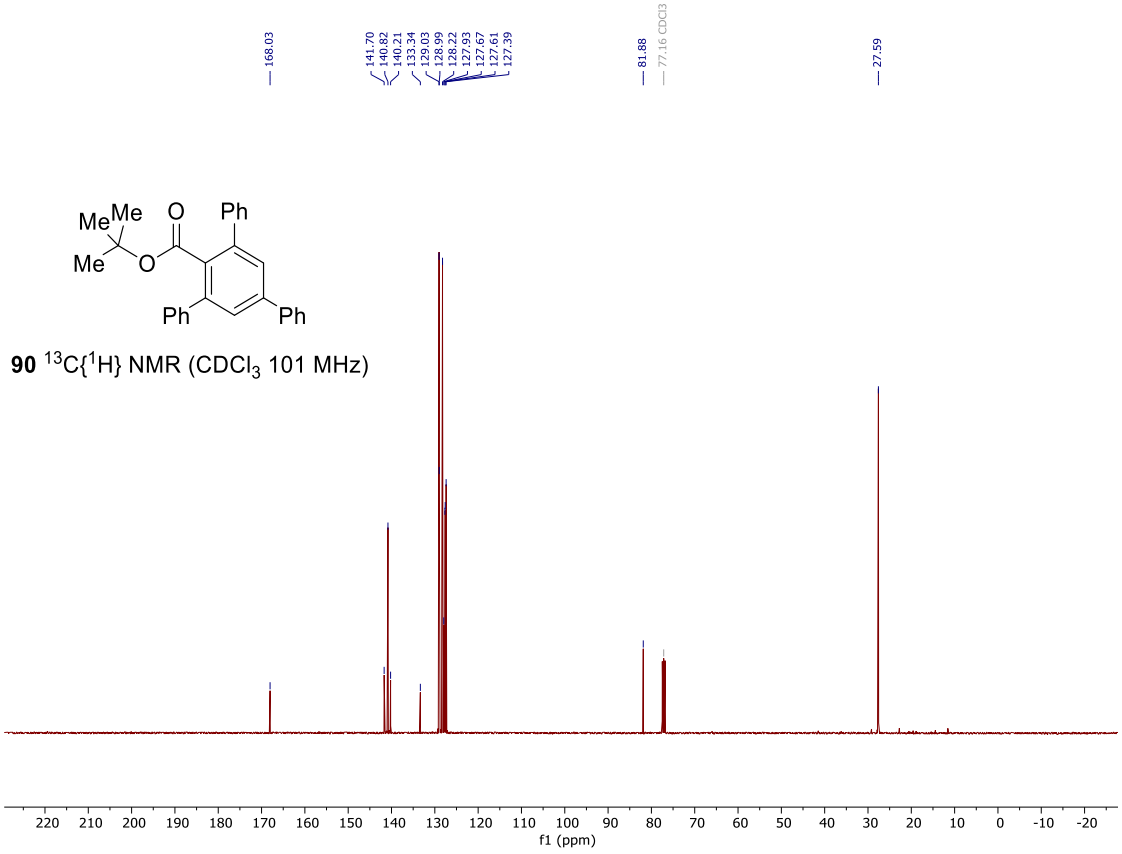
33 ^{1}H NMR ($CDCl_3$ 400 MHz)



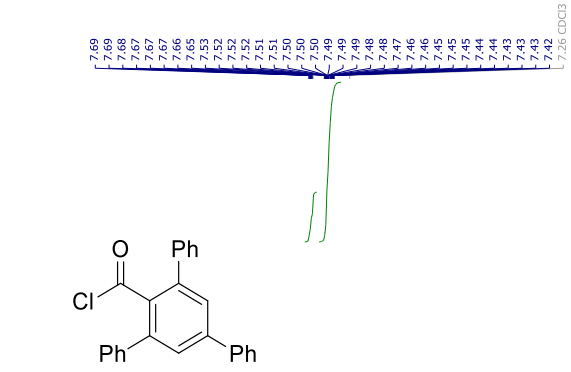
33 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



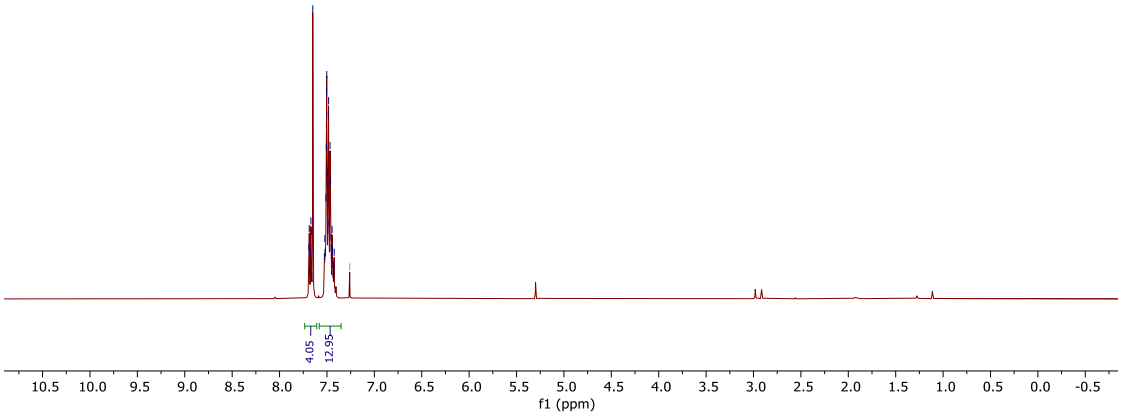
90 ^{1}H NMR ($CDCl_3$ 400 MHz)

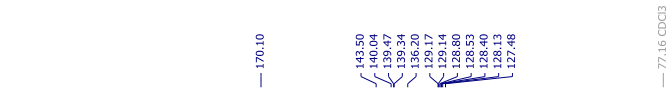


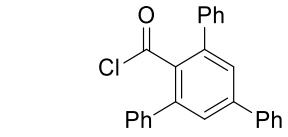
90 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



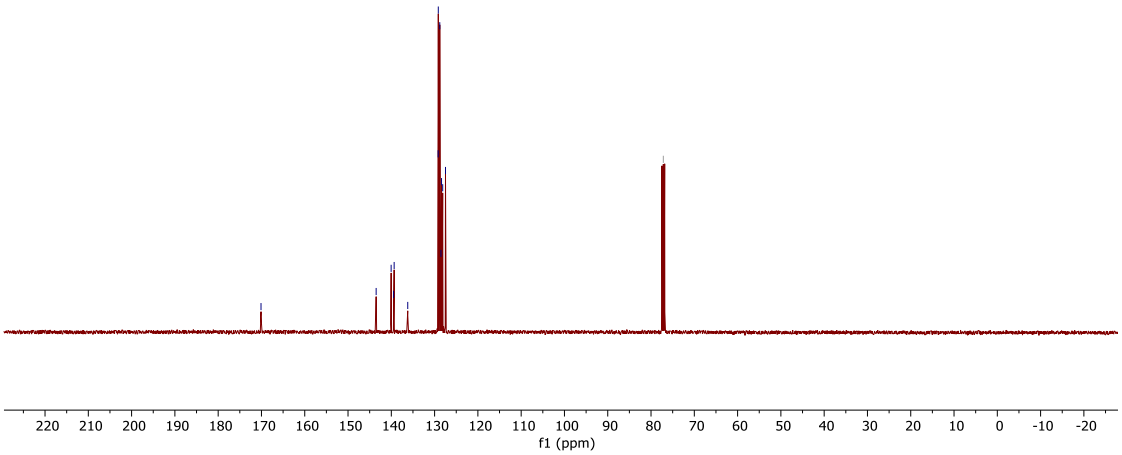
92 ^{1}H NMR ($CDCl_3$ 400 MHz)

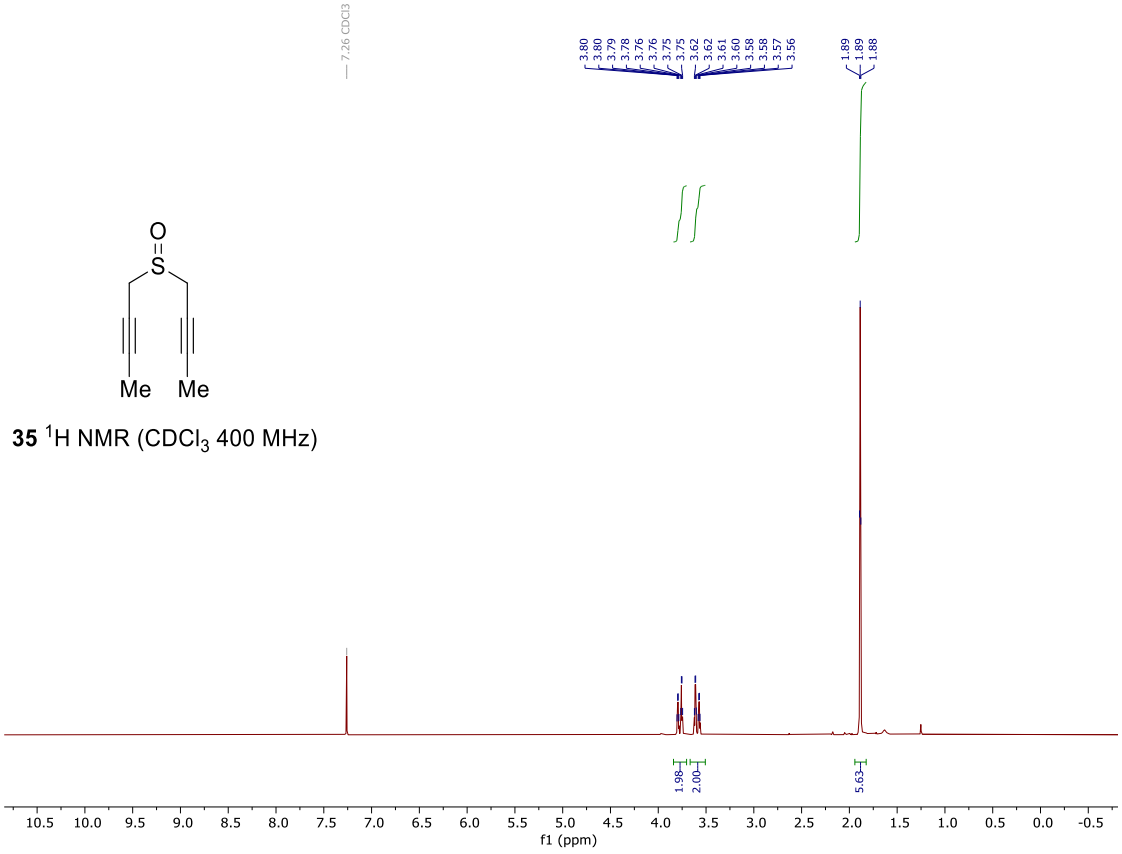




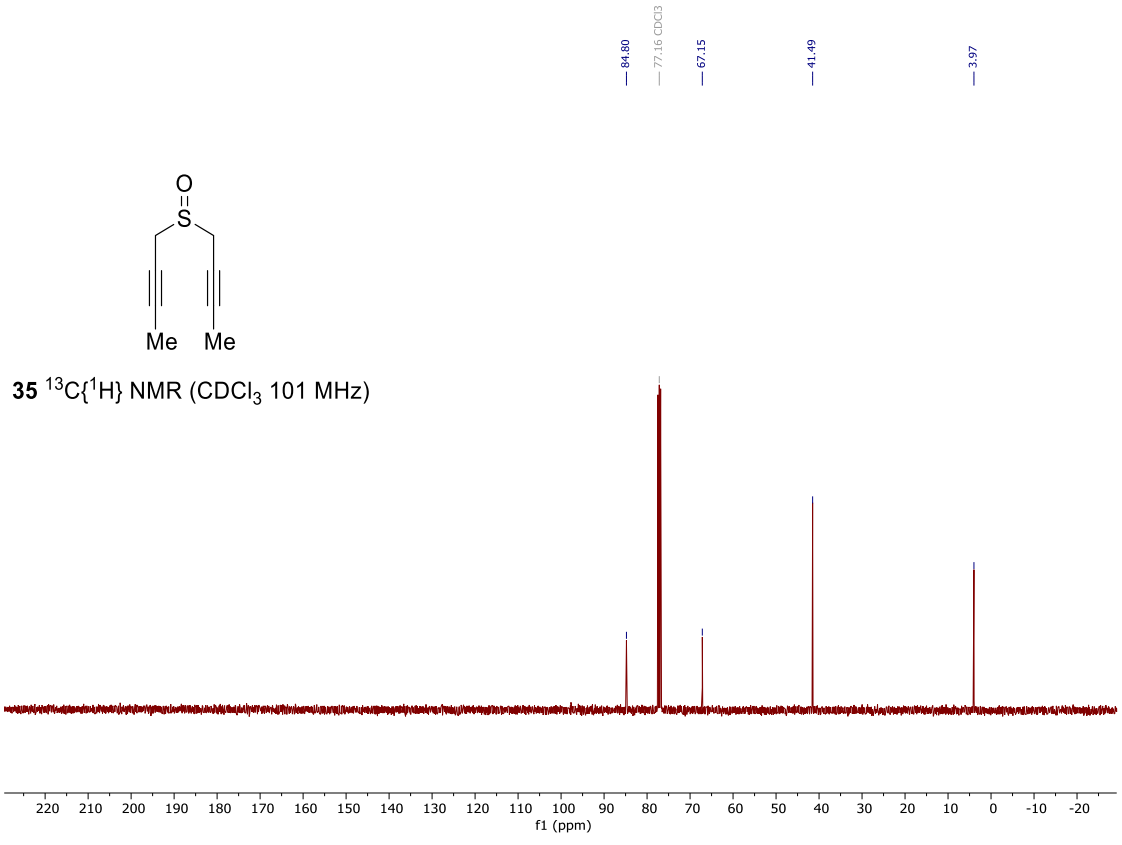


92 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

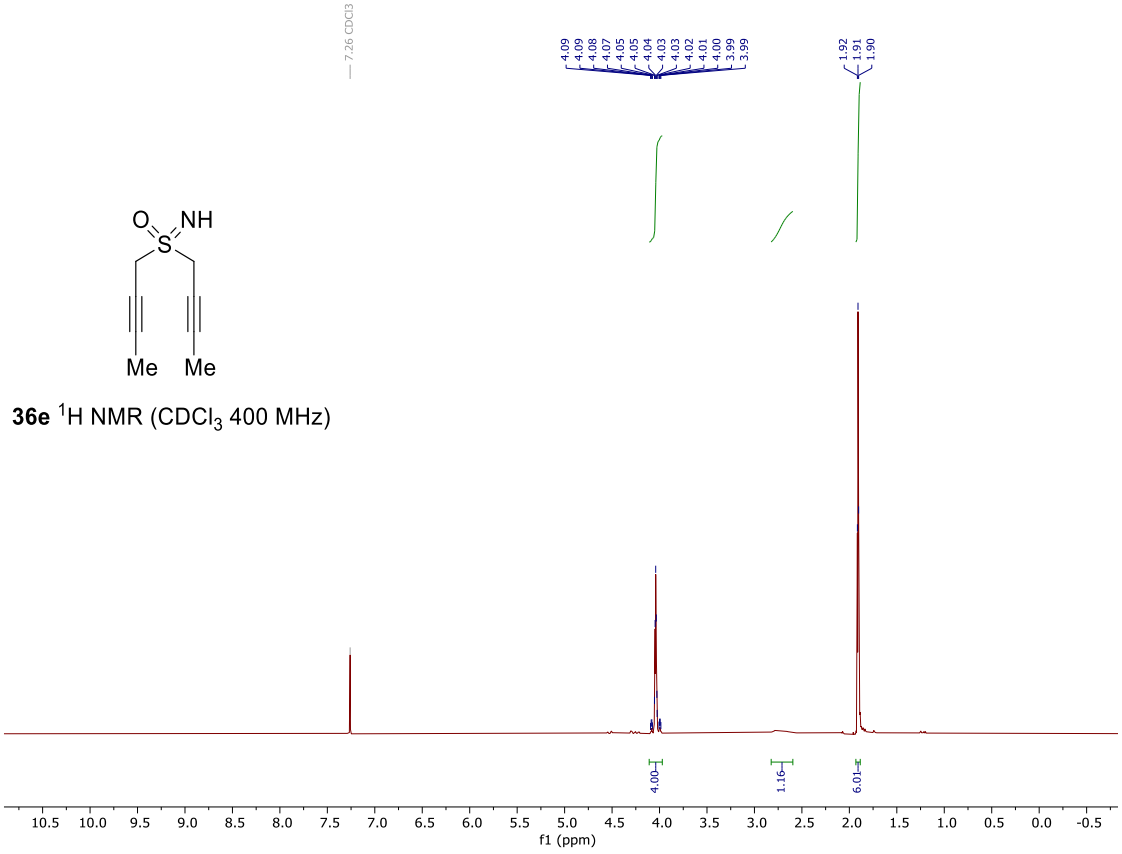




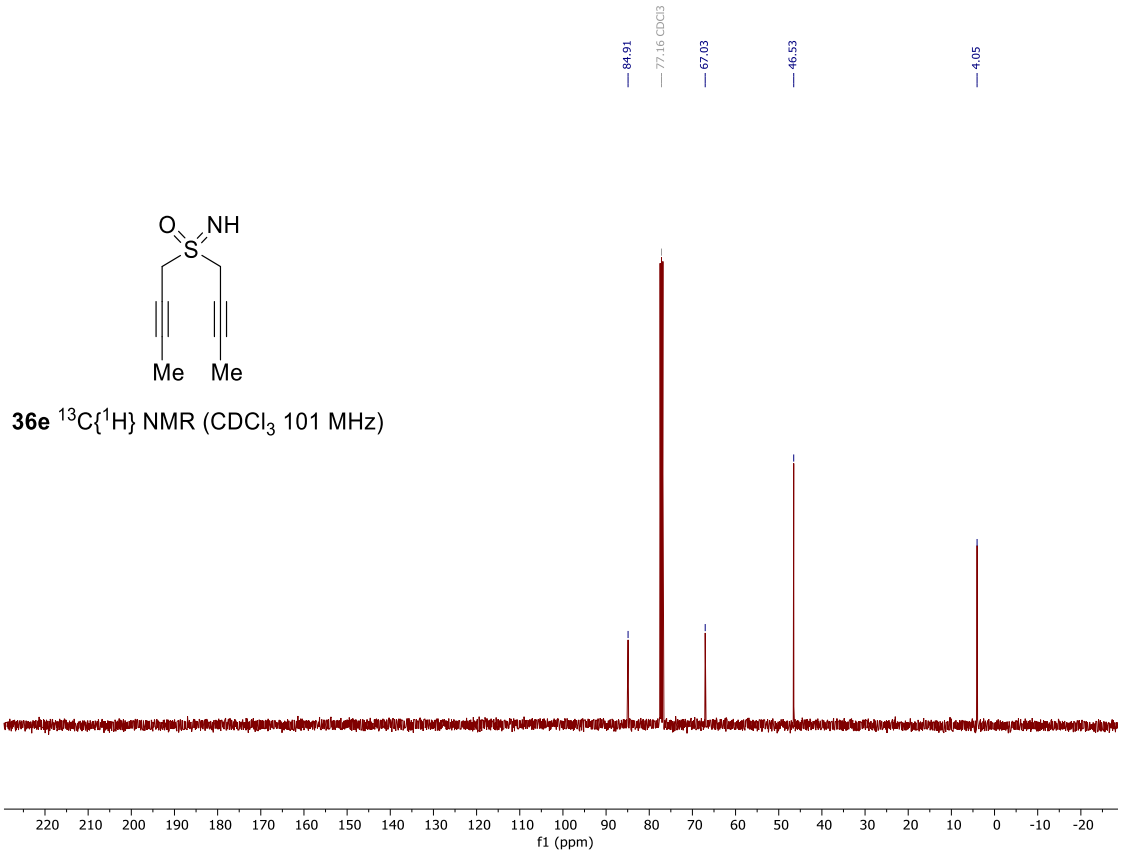
35 ^{1}H NMR ($CDCl_3$ 400 MHz)



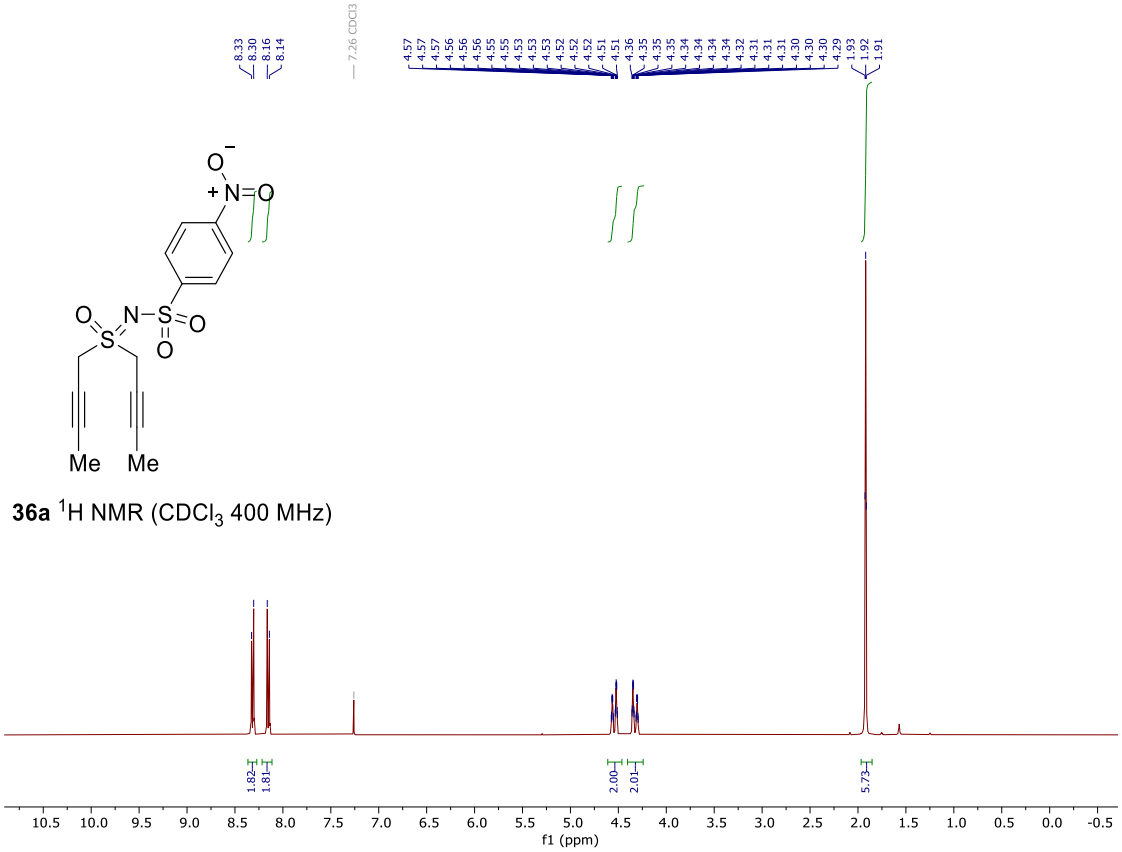
35 $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



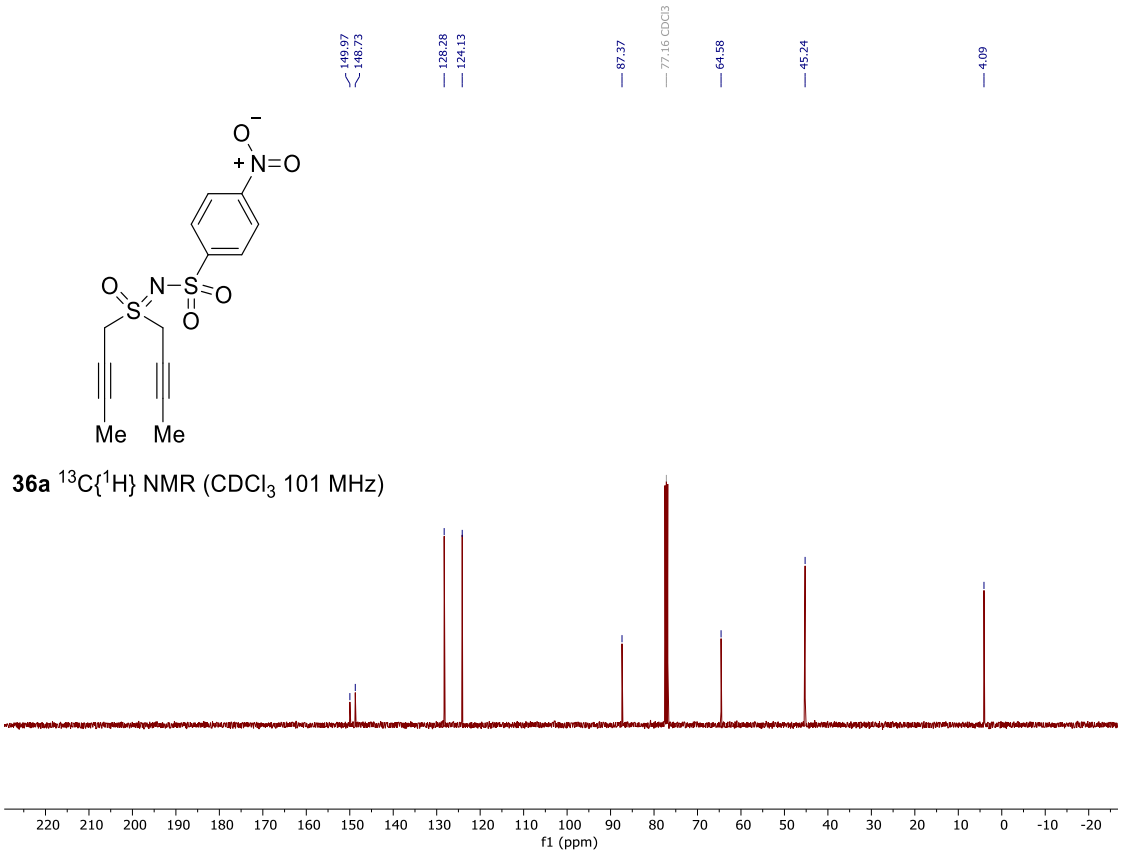
36e ^{1}H NMR ($CDCl_3$ 400 MHz)



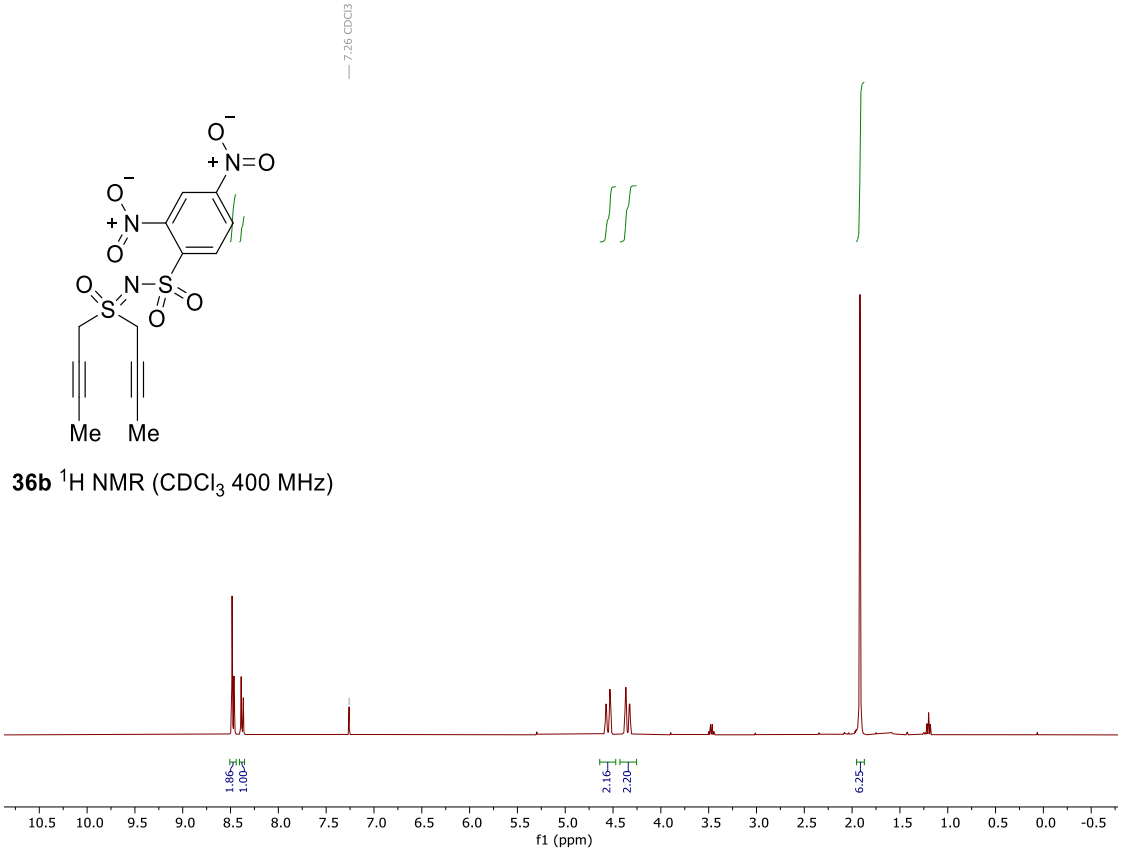
36e $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



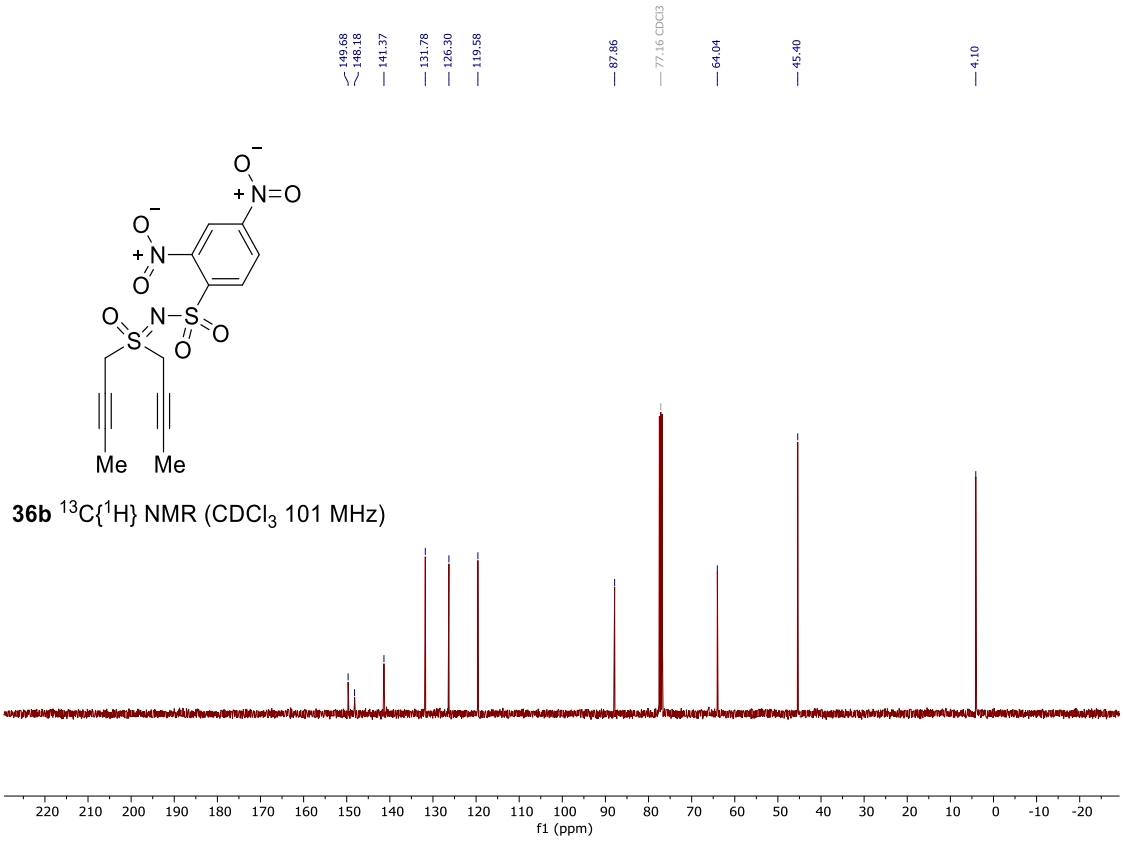
36a ^{1}H NMR ($CDCl_3$ 400 MHz)



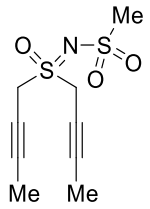
36a ^{13}C{^{1}H} NMR ($CDCl_3$ 101 MHz)



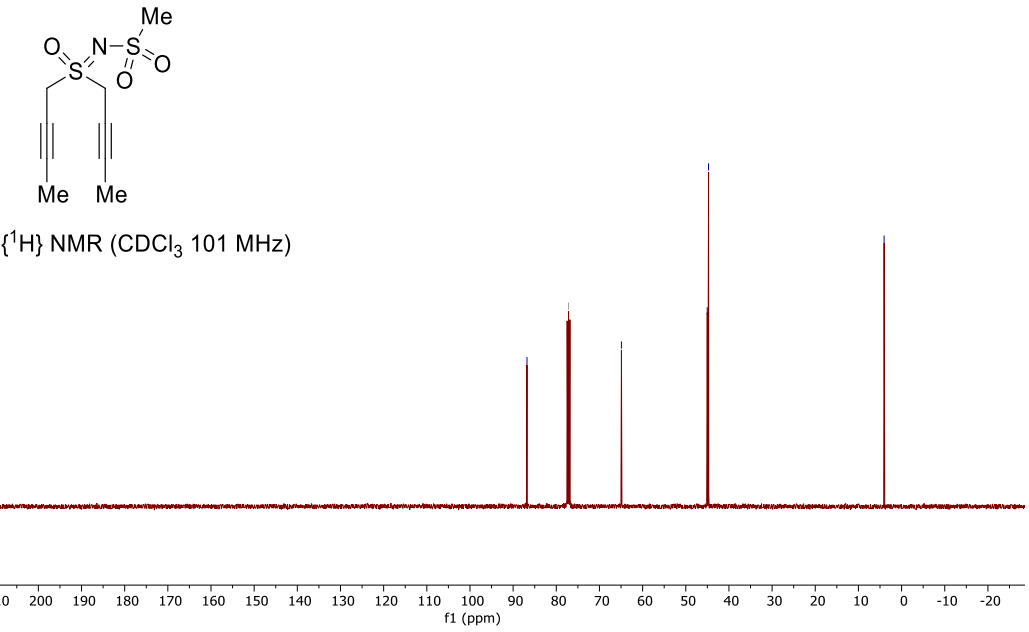
36b ^{1}H NMR ($CDCl_3$ 400 MHz)



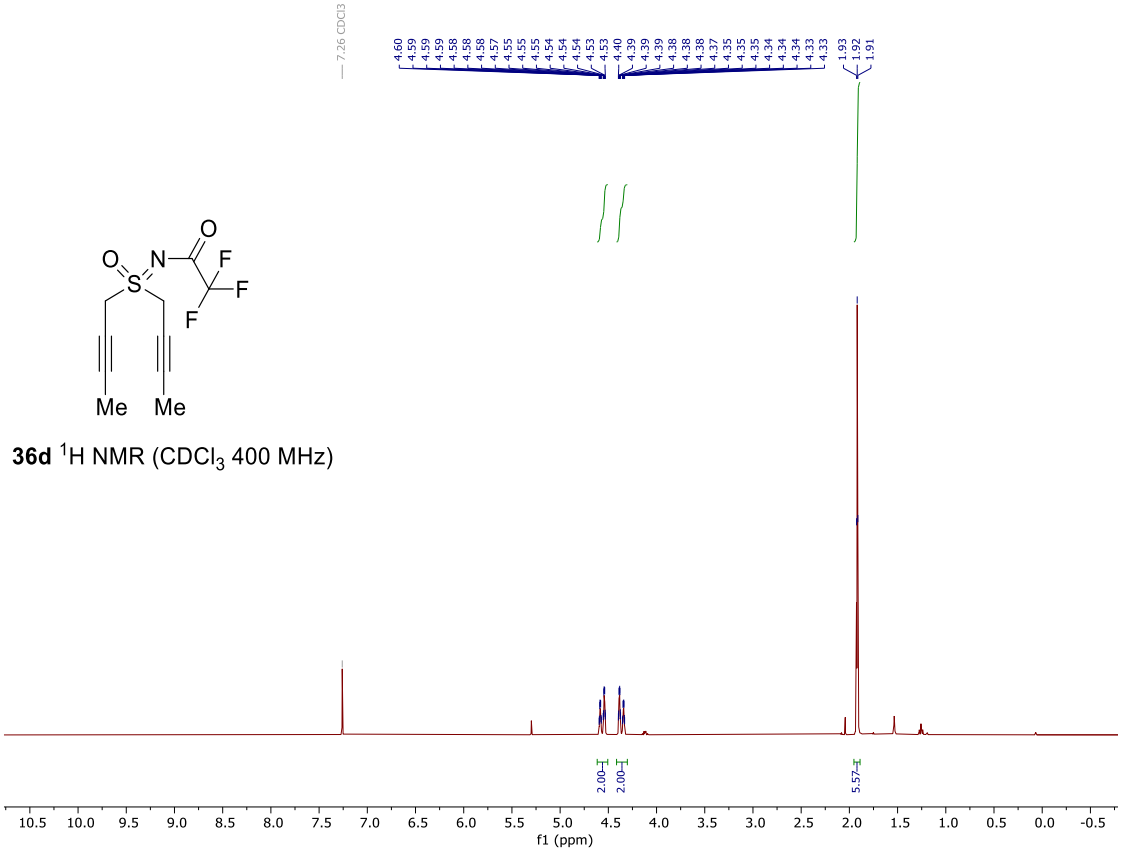
36b $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



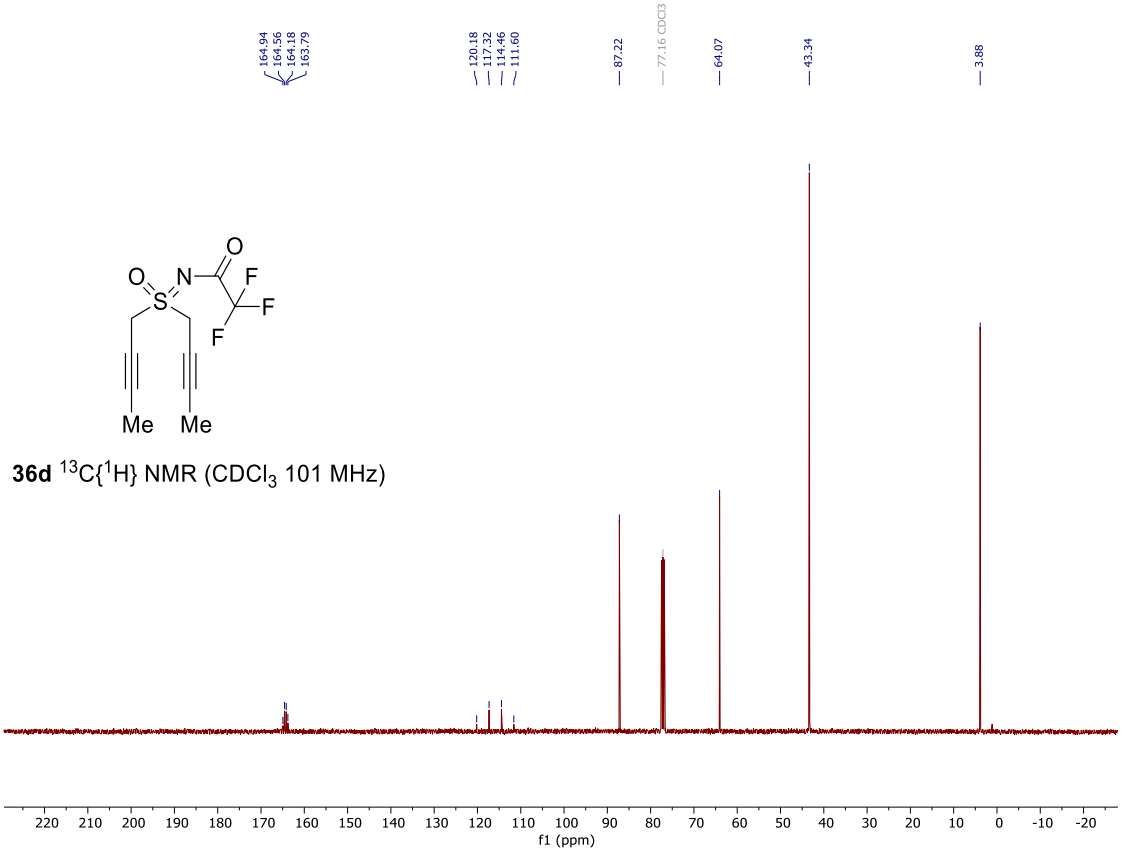
36c ^{1}H NMR ($CDCl_3$ 400 MHz)



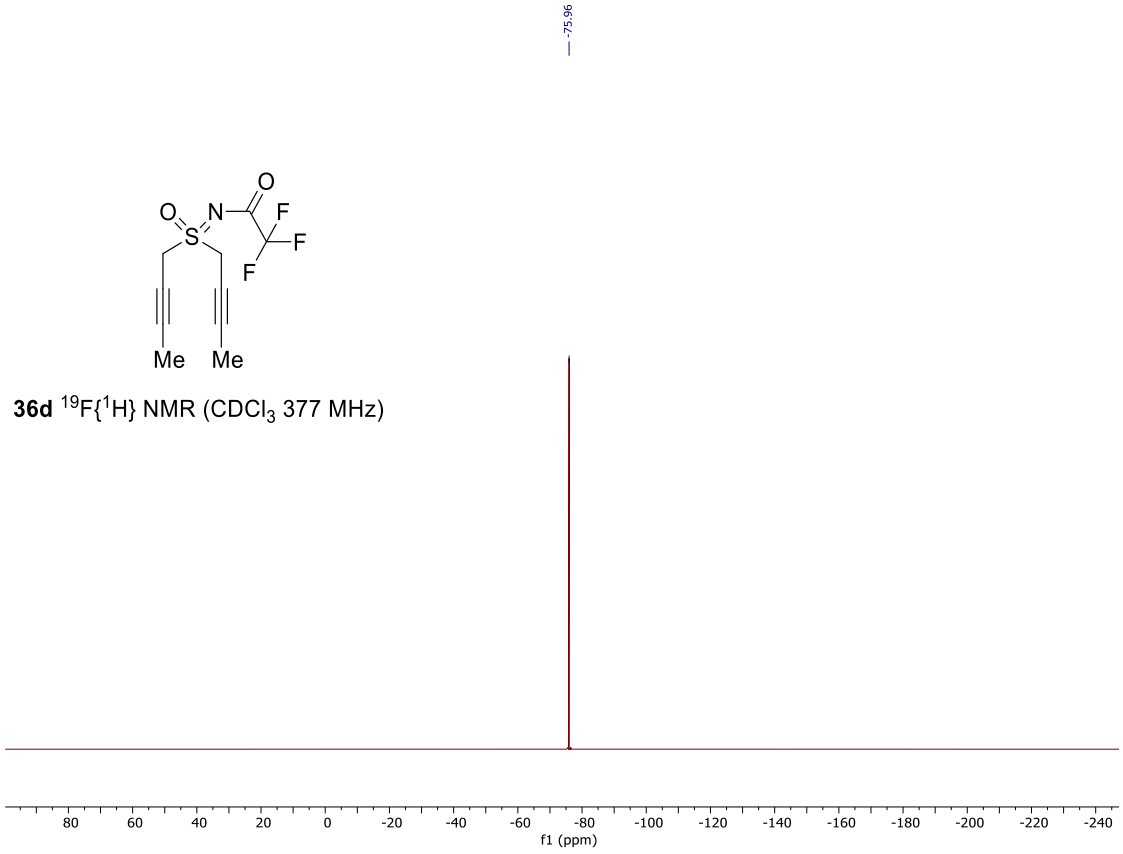
36c $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



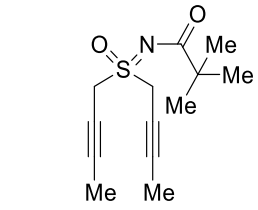
36d ^{1}H NMR ($CDCl_3$ 400 MHz)



36d $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



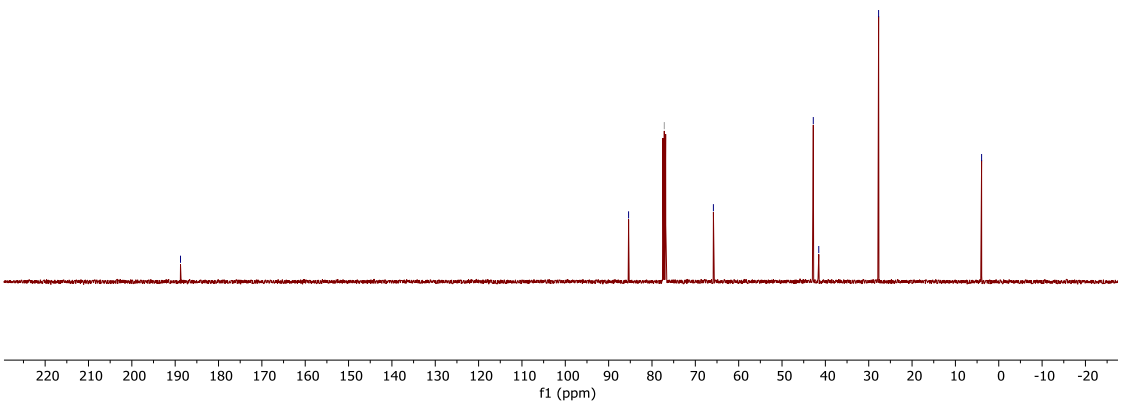
36d $^{19}F\{^{1}H\}$ NMR ($CDCl_3$ 377 MHz)

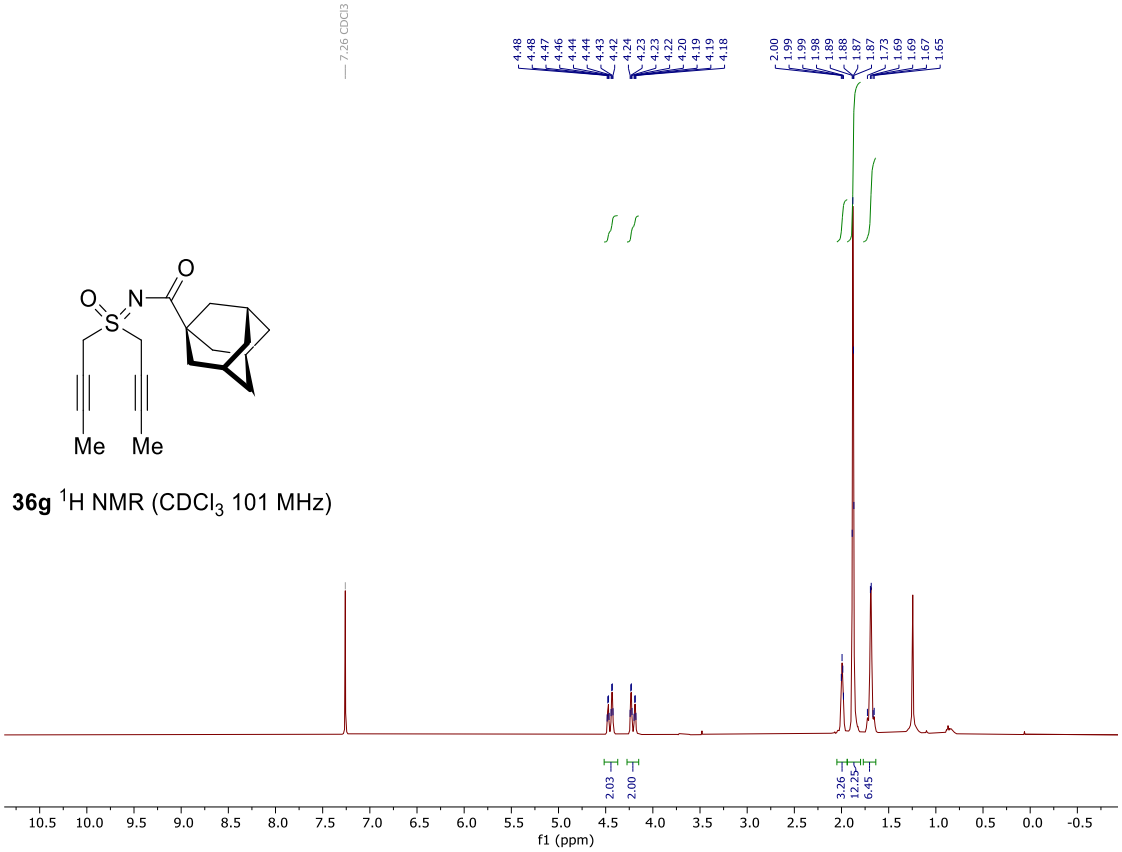


36f ^{1}H NMR ($CDCl_3$ 400 MHz)

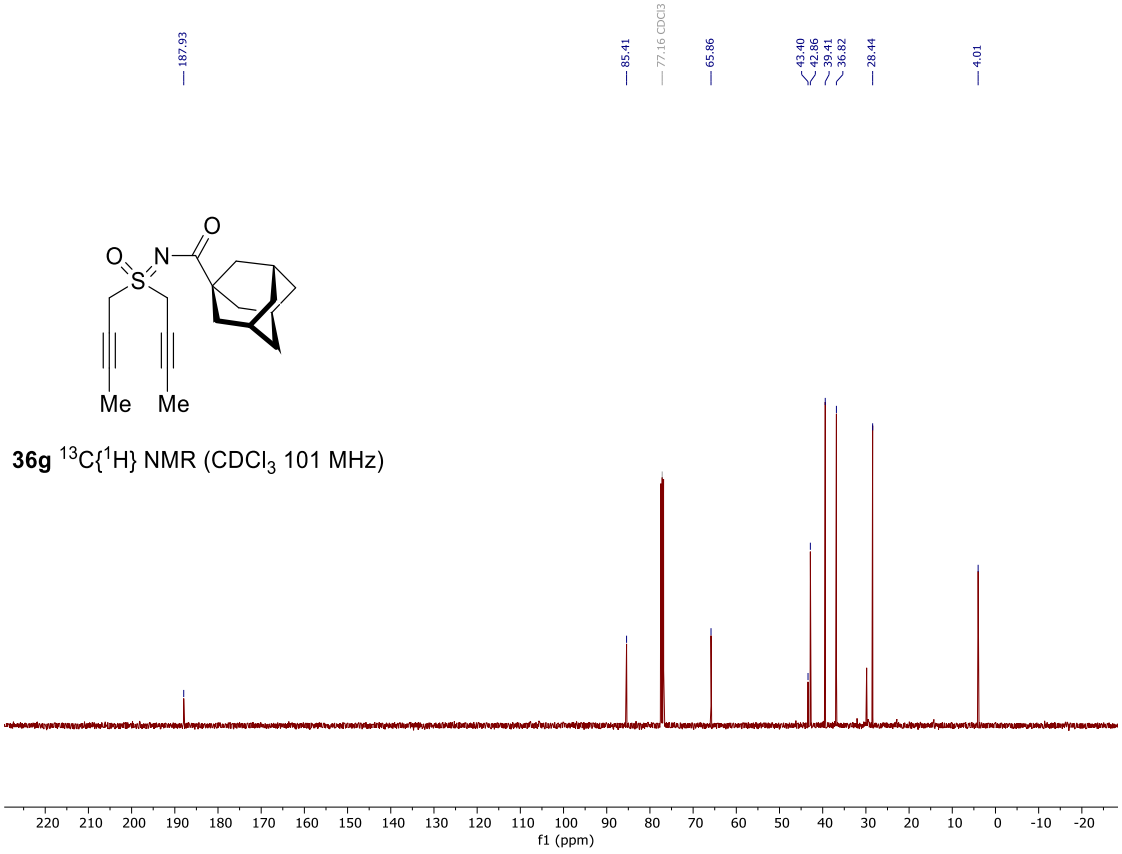


36f $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

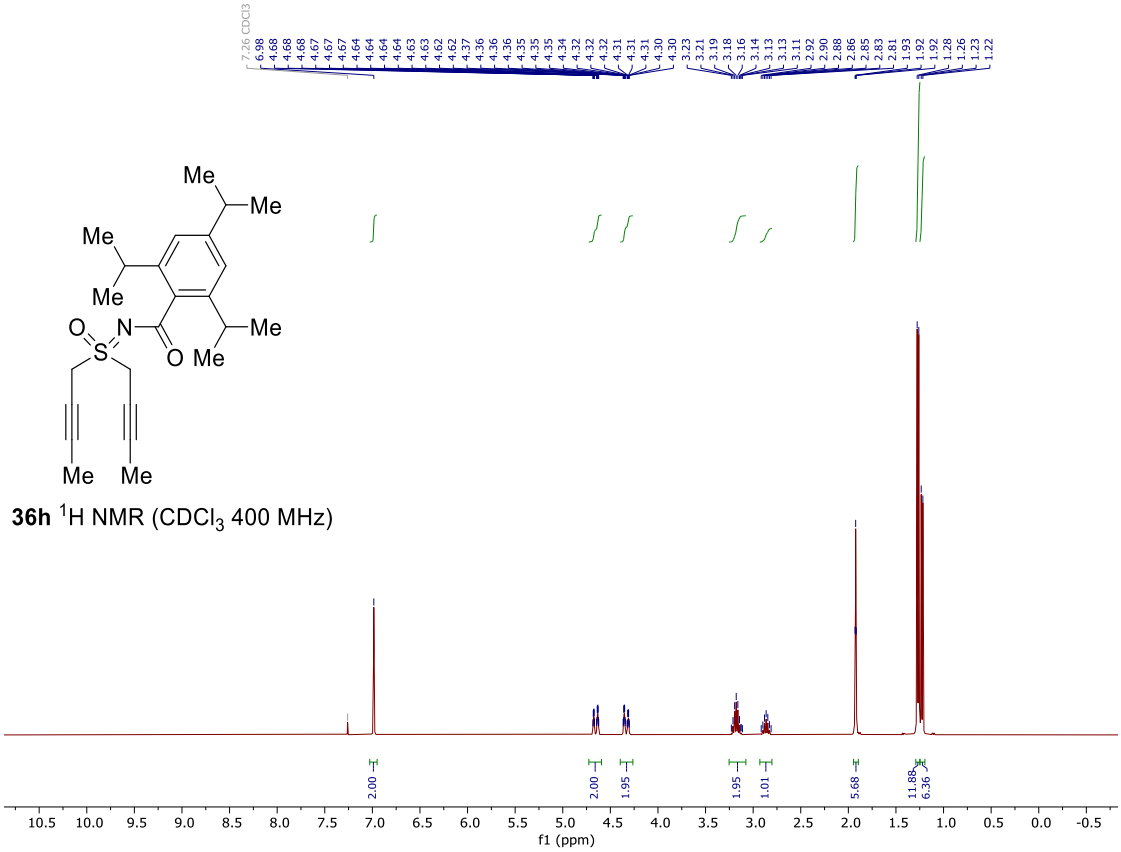




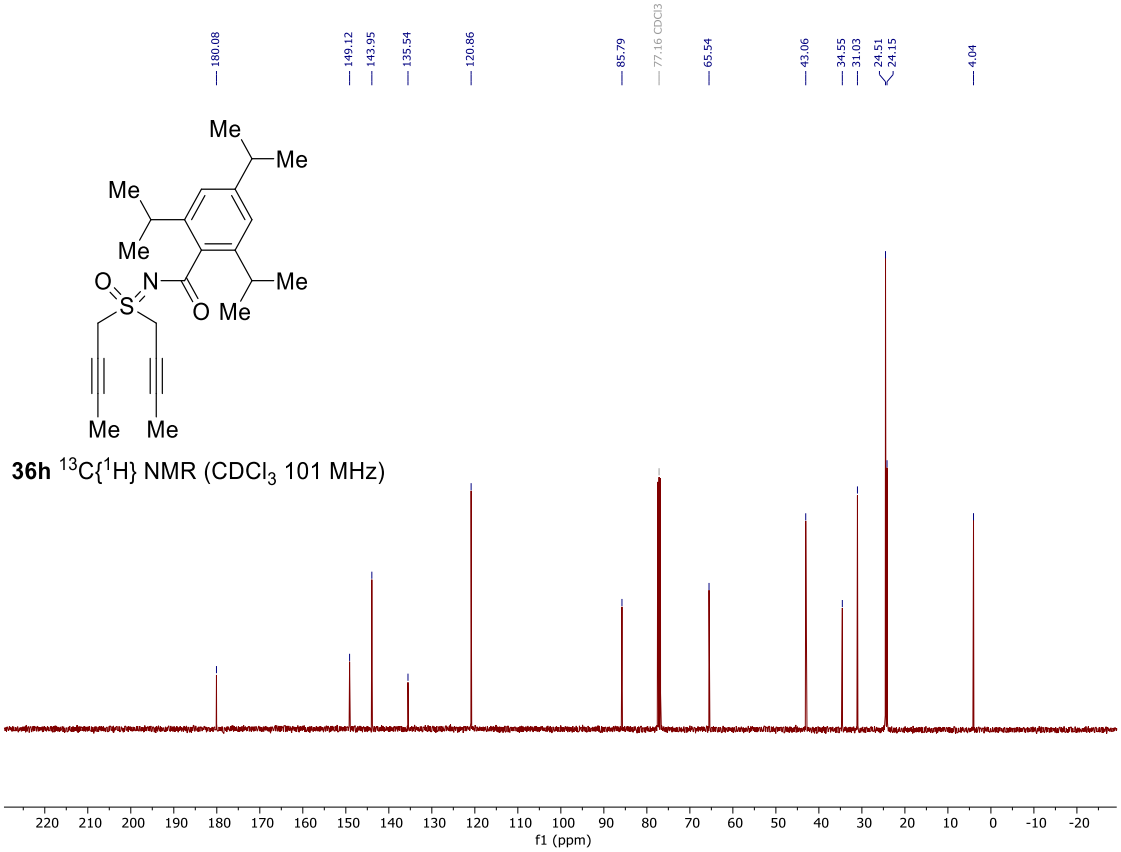
36g ^{1}H NMR ($CDCl_3$ 101 MHz)



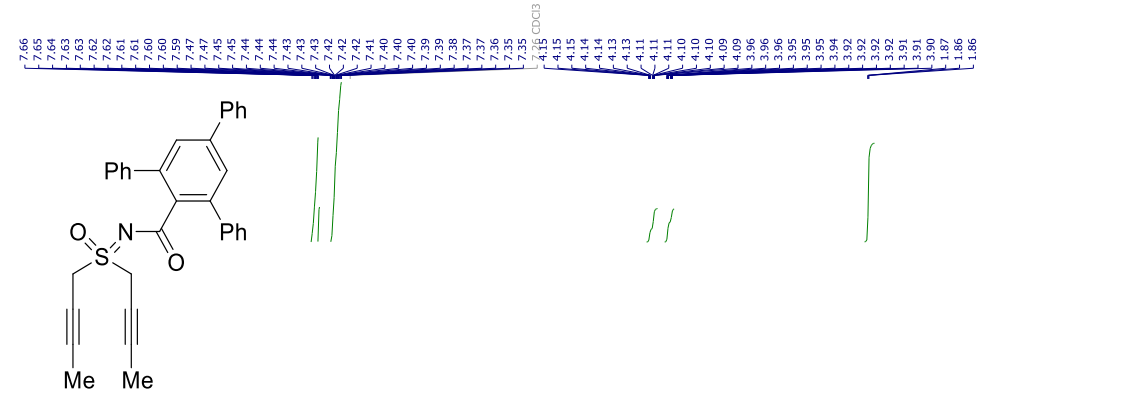
36g $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



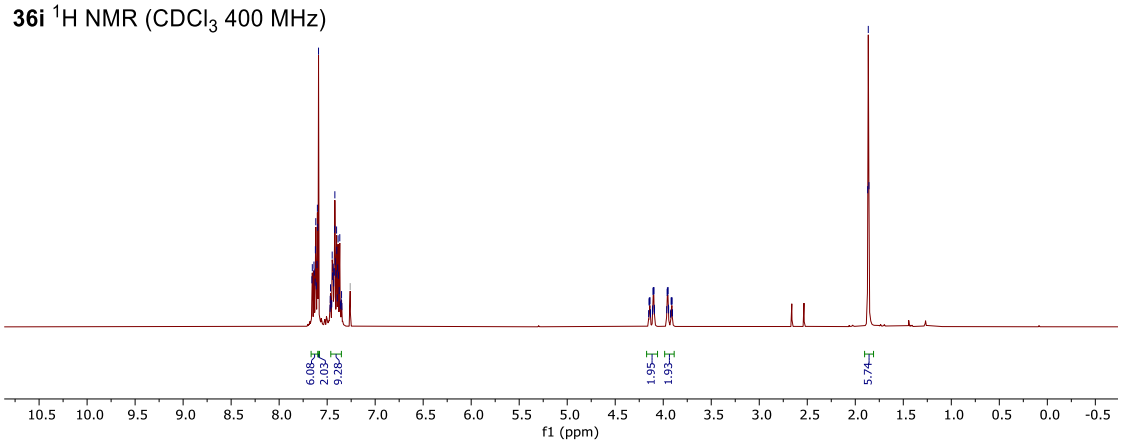
36h ^{1}H NMR ($CDCl_3$ 400 MHz)

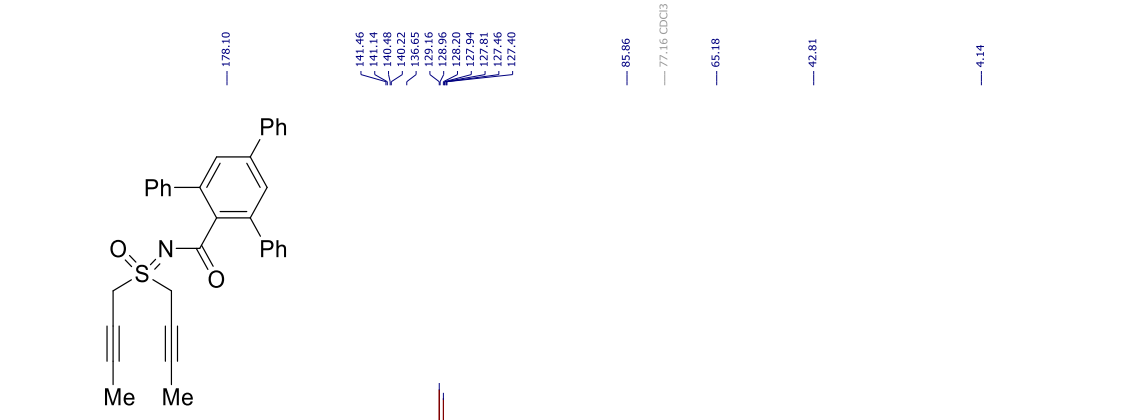


36h $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

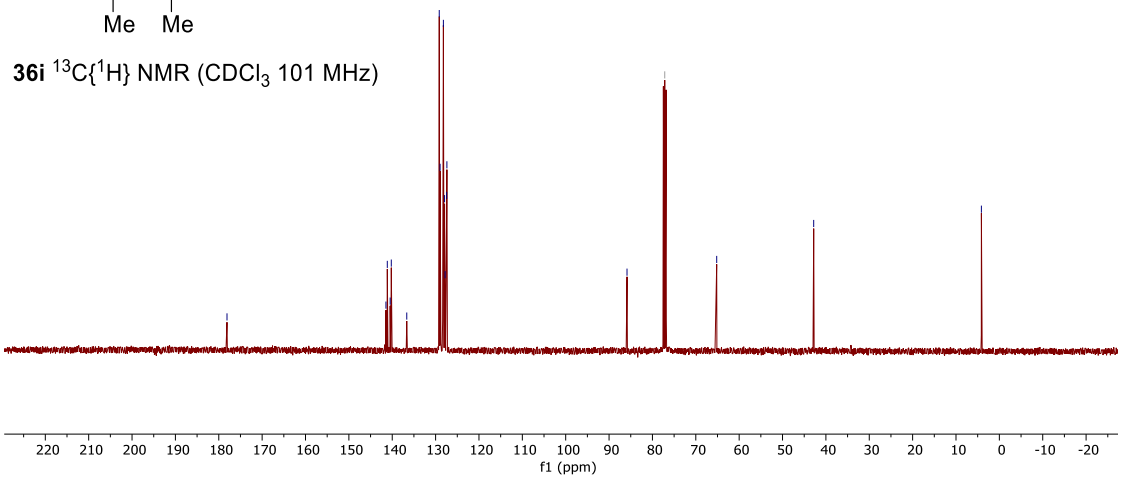


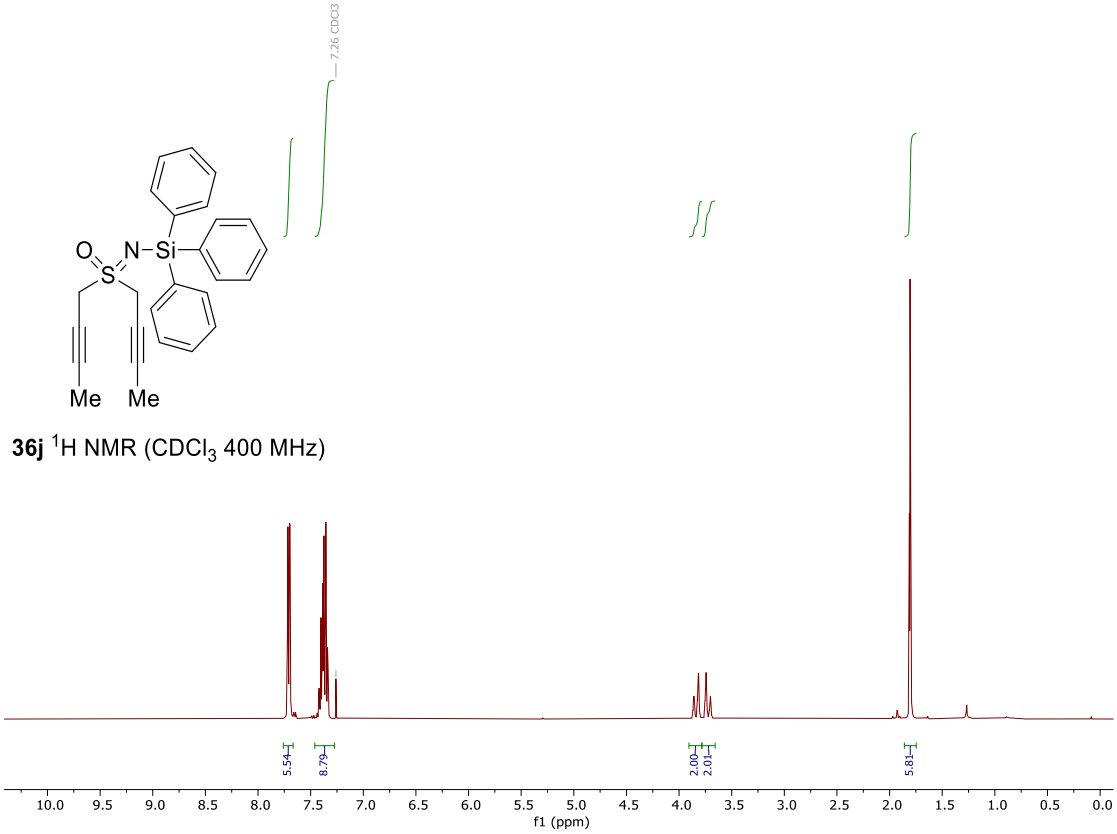
36i ^{1}H NMR ($CDCl_3$ 400 MHz)



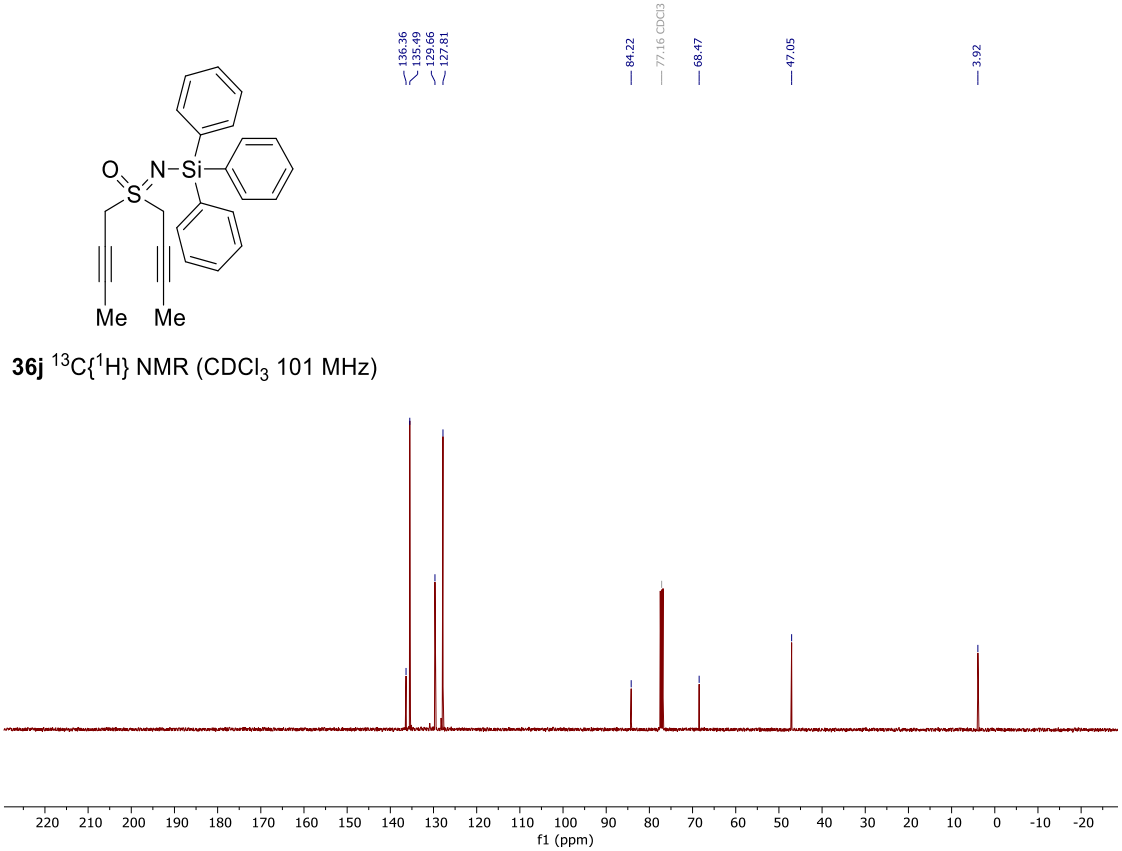


36i $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

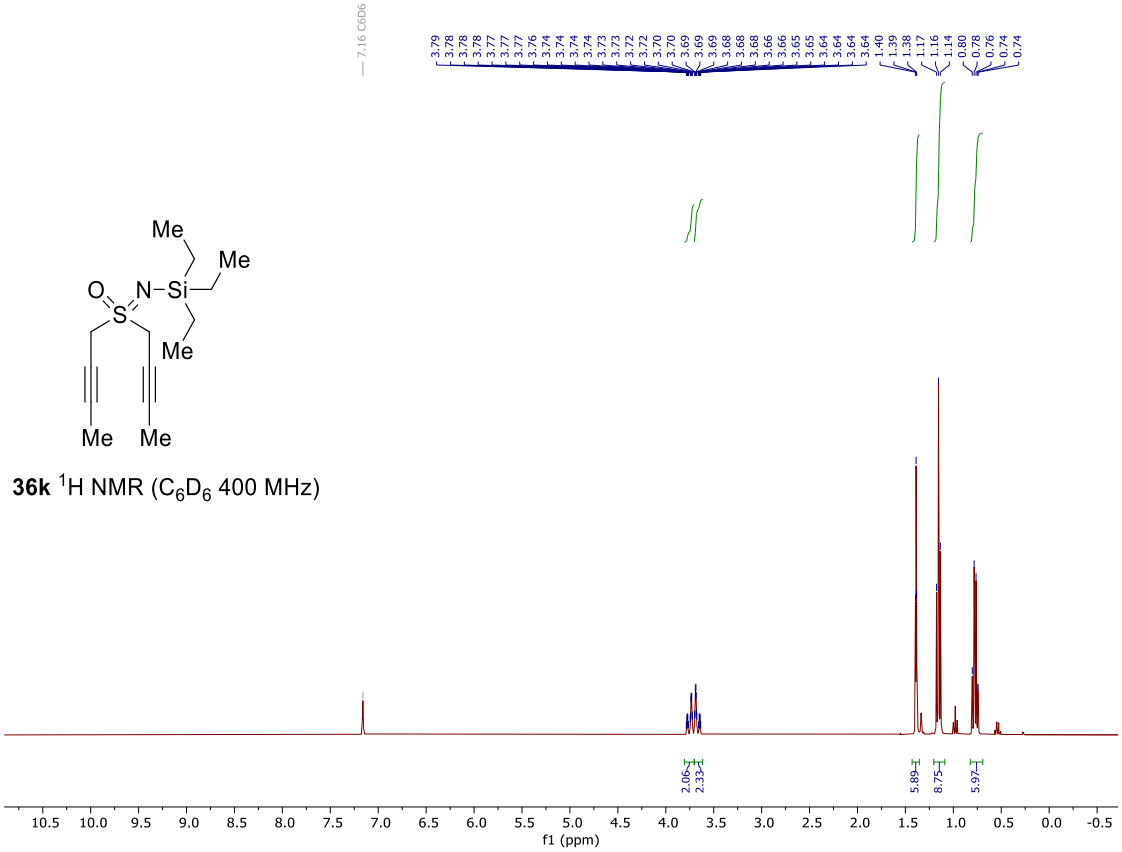




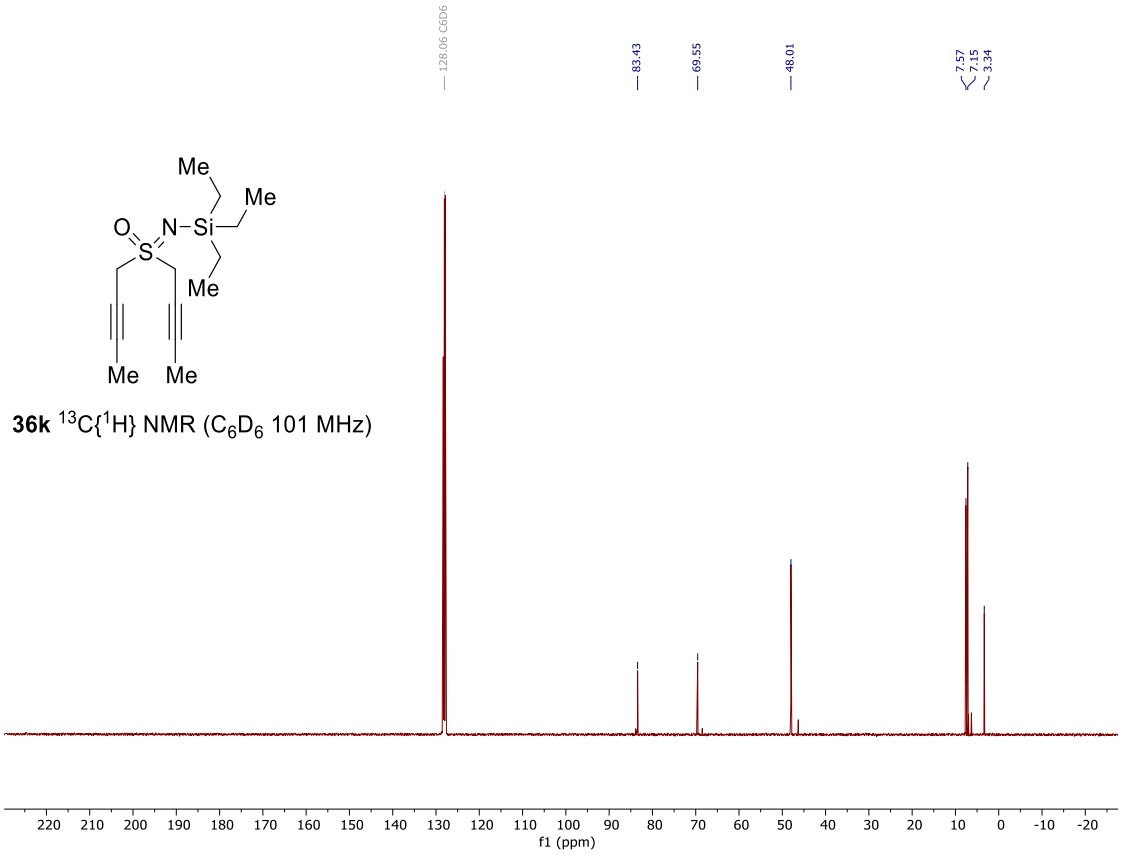
36j ^{1}H NMR ($CDCl_3$ 400 MHz)



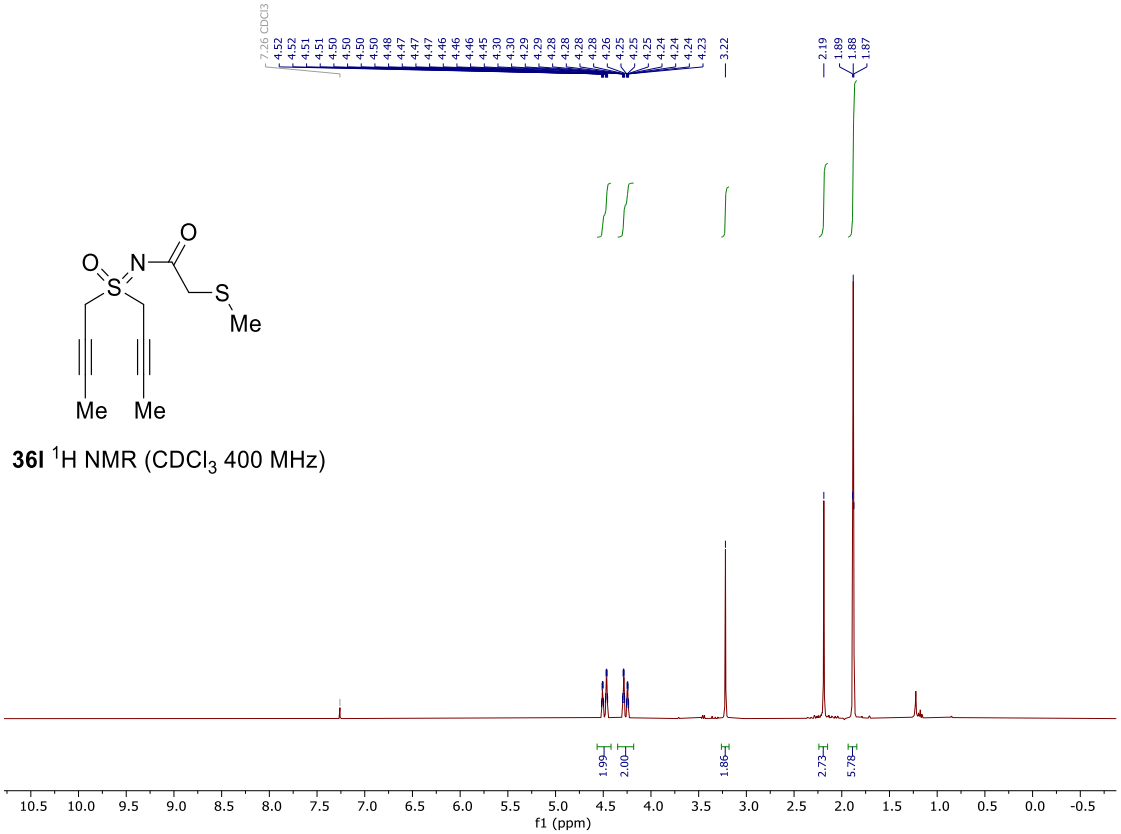
36j $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



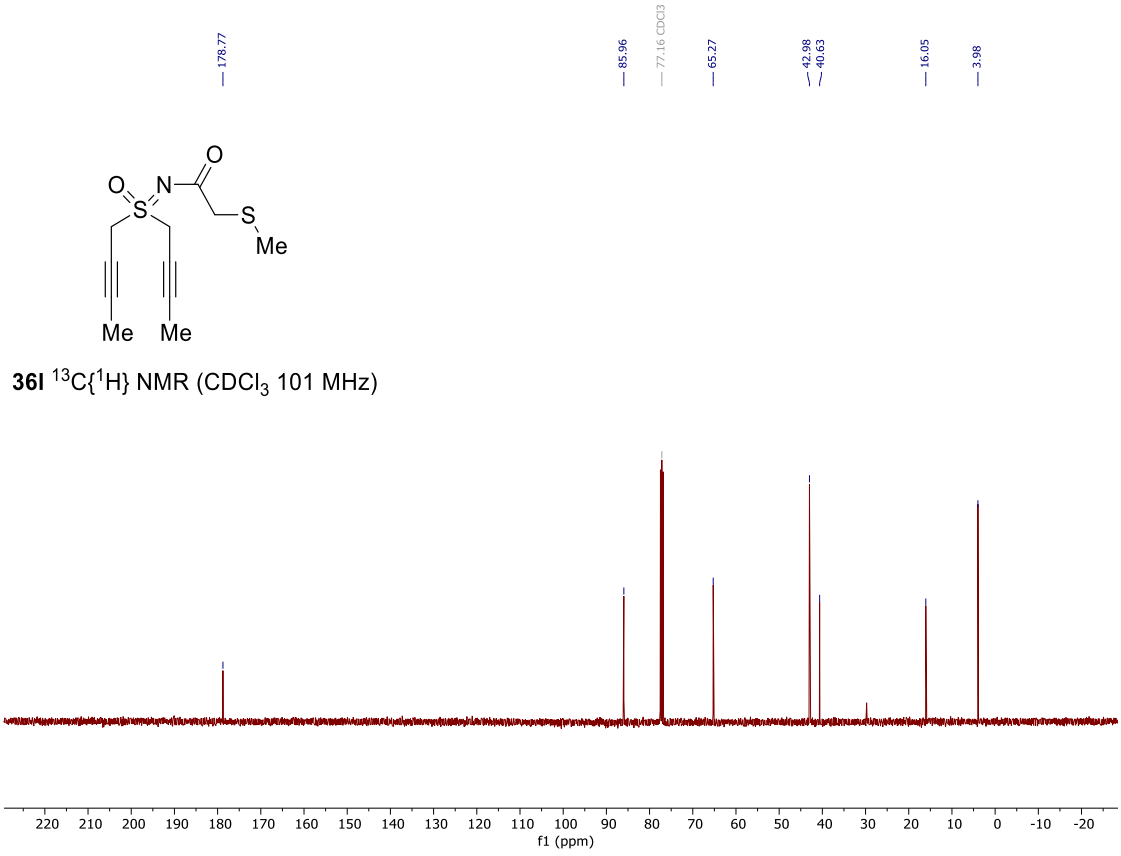
36k ^{1}H NMR (C_6D_6 400 MHz)



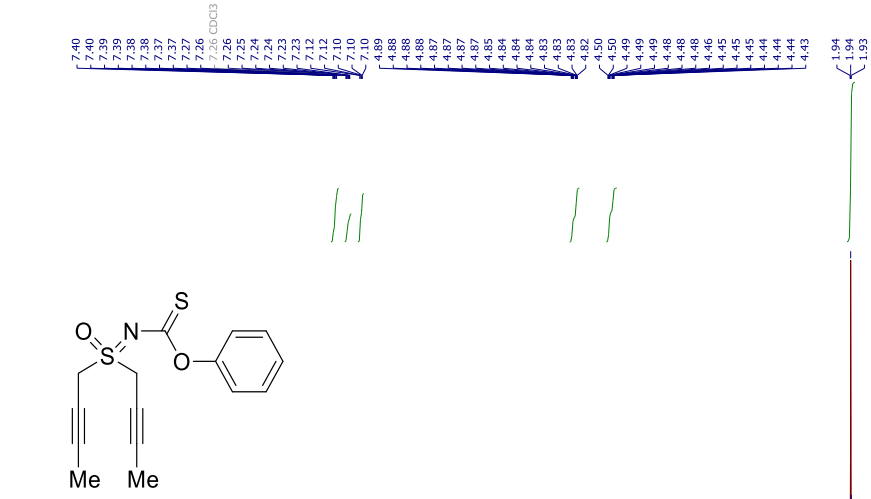
36k ^{13}C{^{1}H} NMR (C_6D_6 101 MHz)



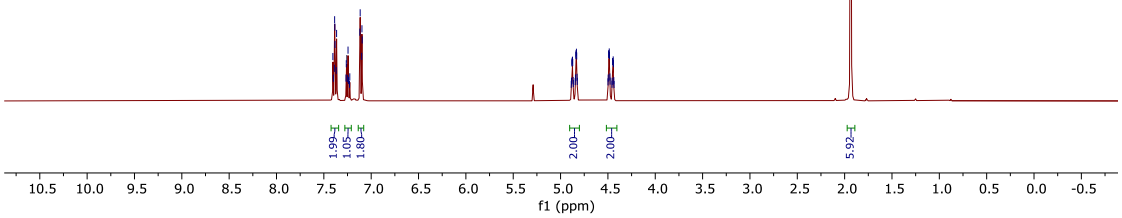
36l ^{1}H NMR ($CDCl_3$ 400 MHz)

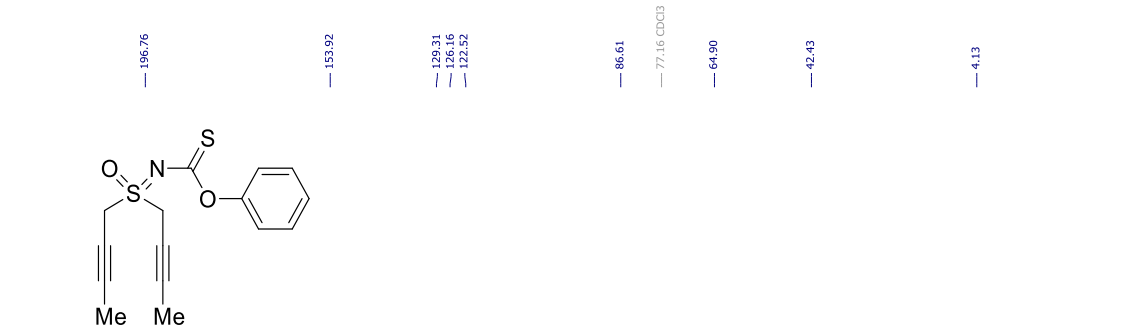


36l $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

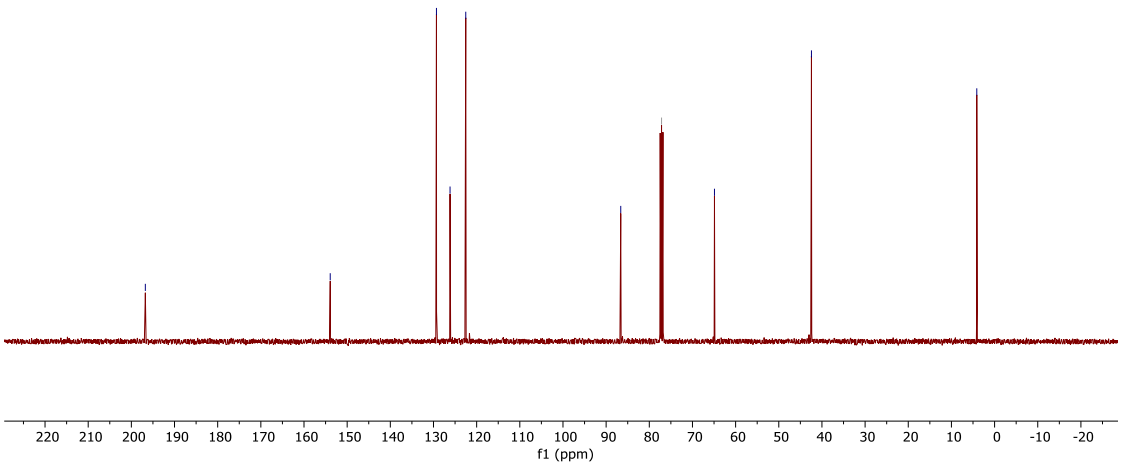


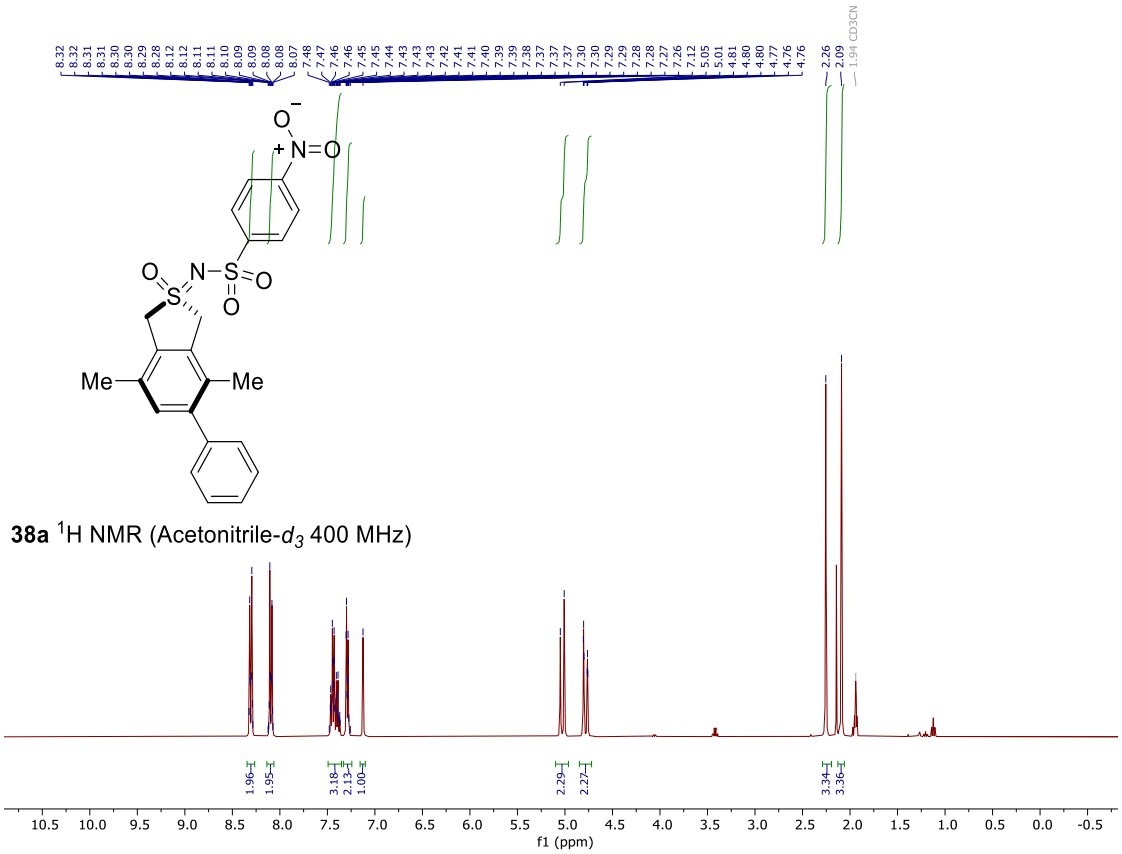
36m ^{1}H NMR ($CDCl_3$ 400 MHz)



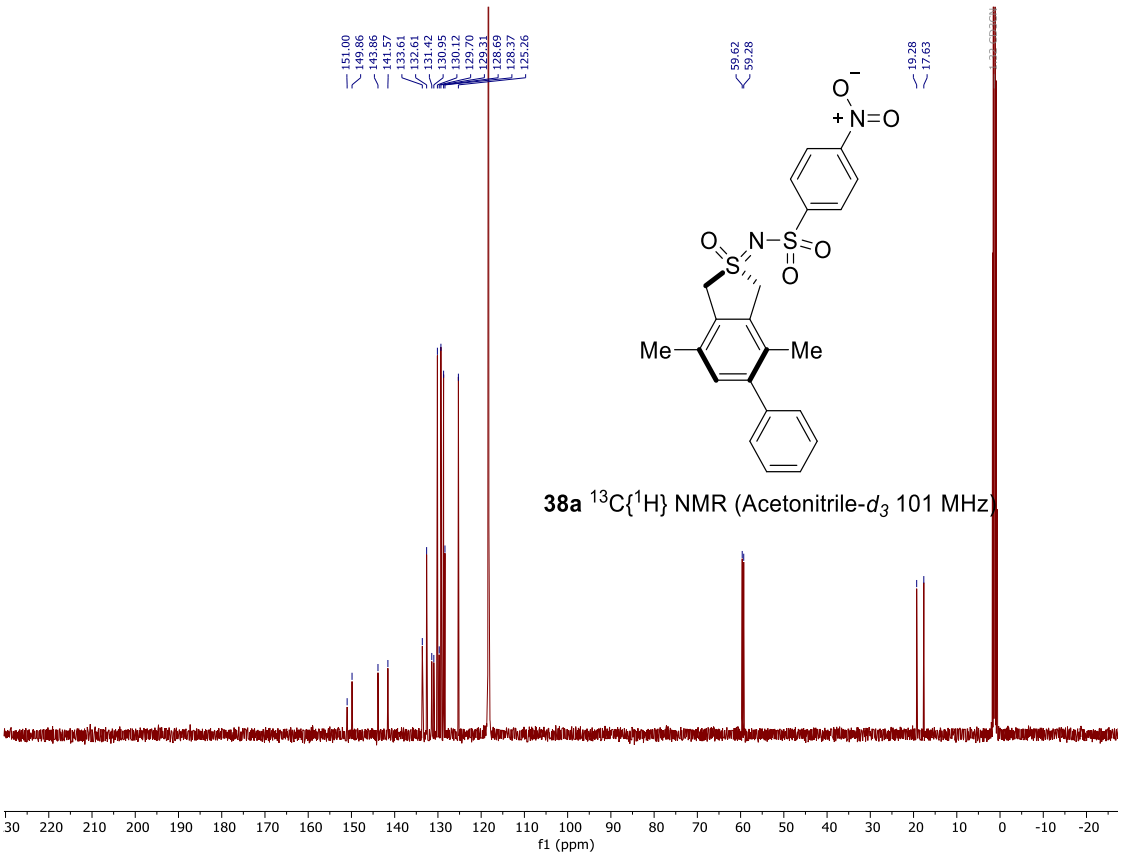


36m $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)

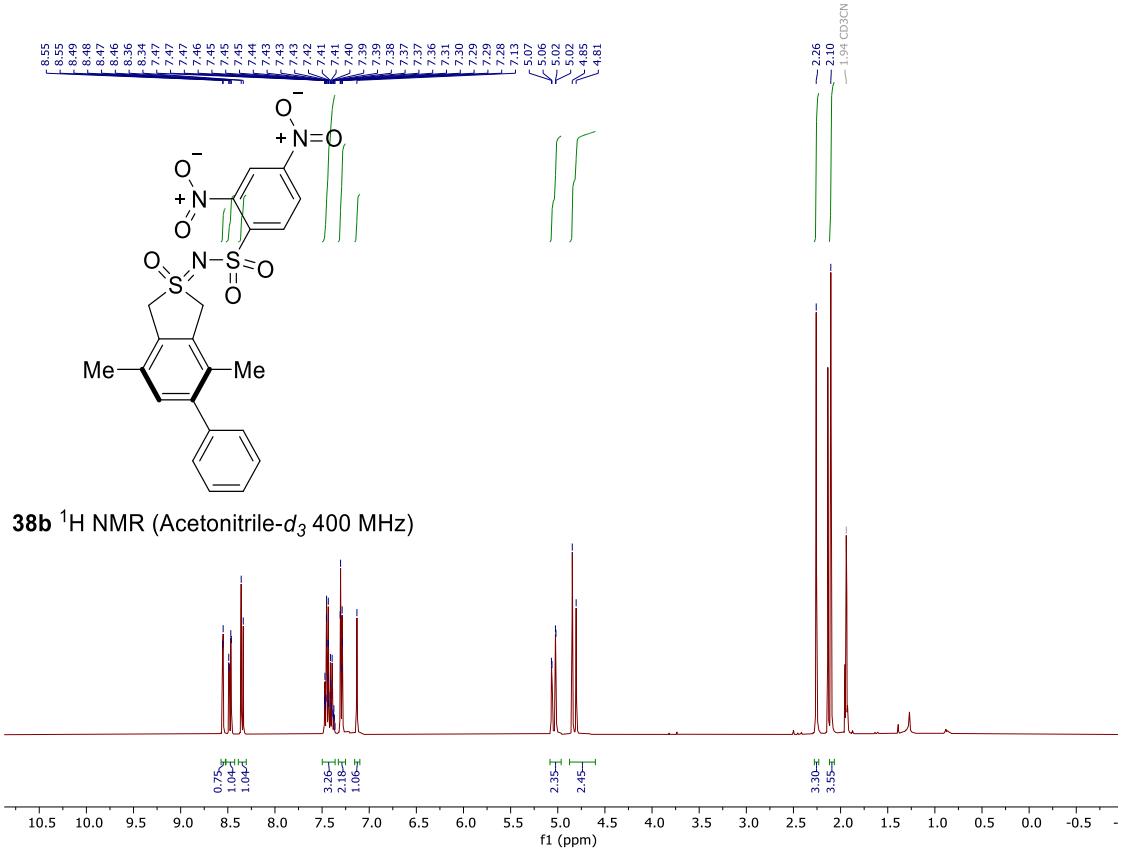




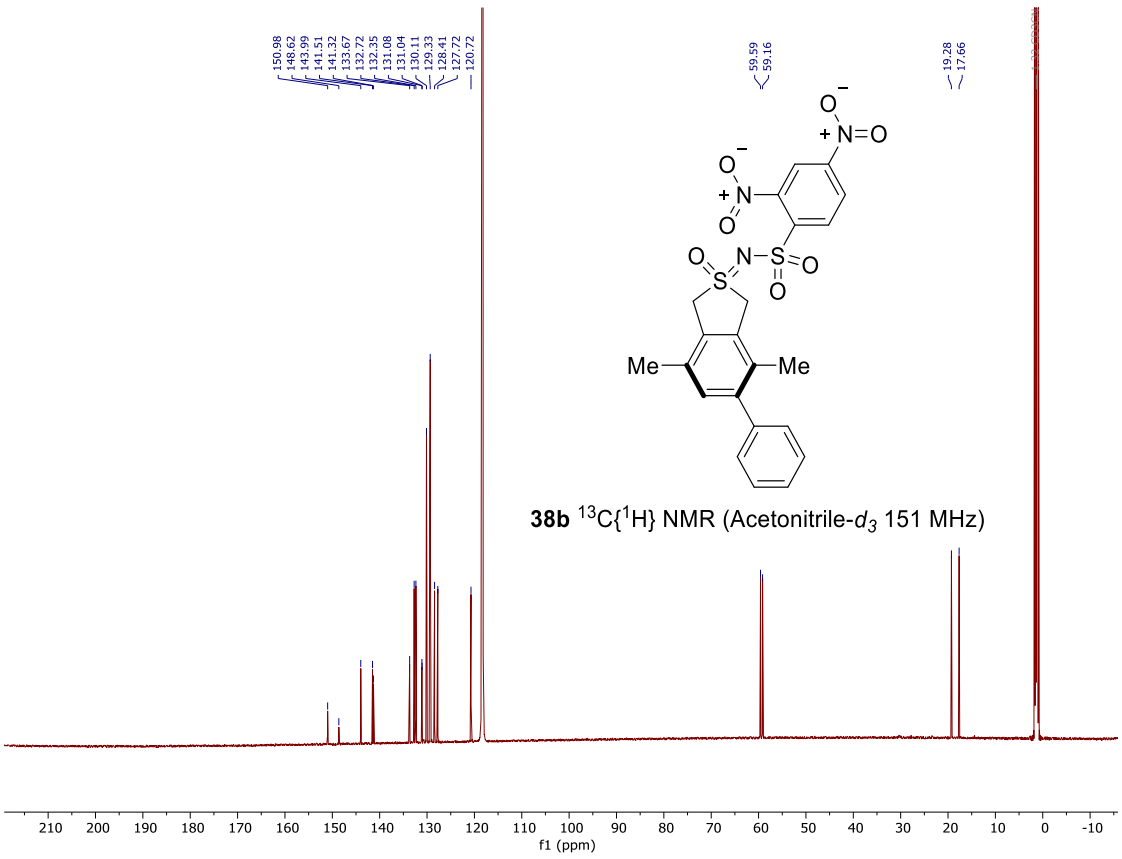
38a ^{1}H NMR (Acetonitrile-d_3 400 MHz)



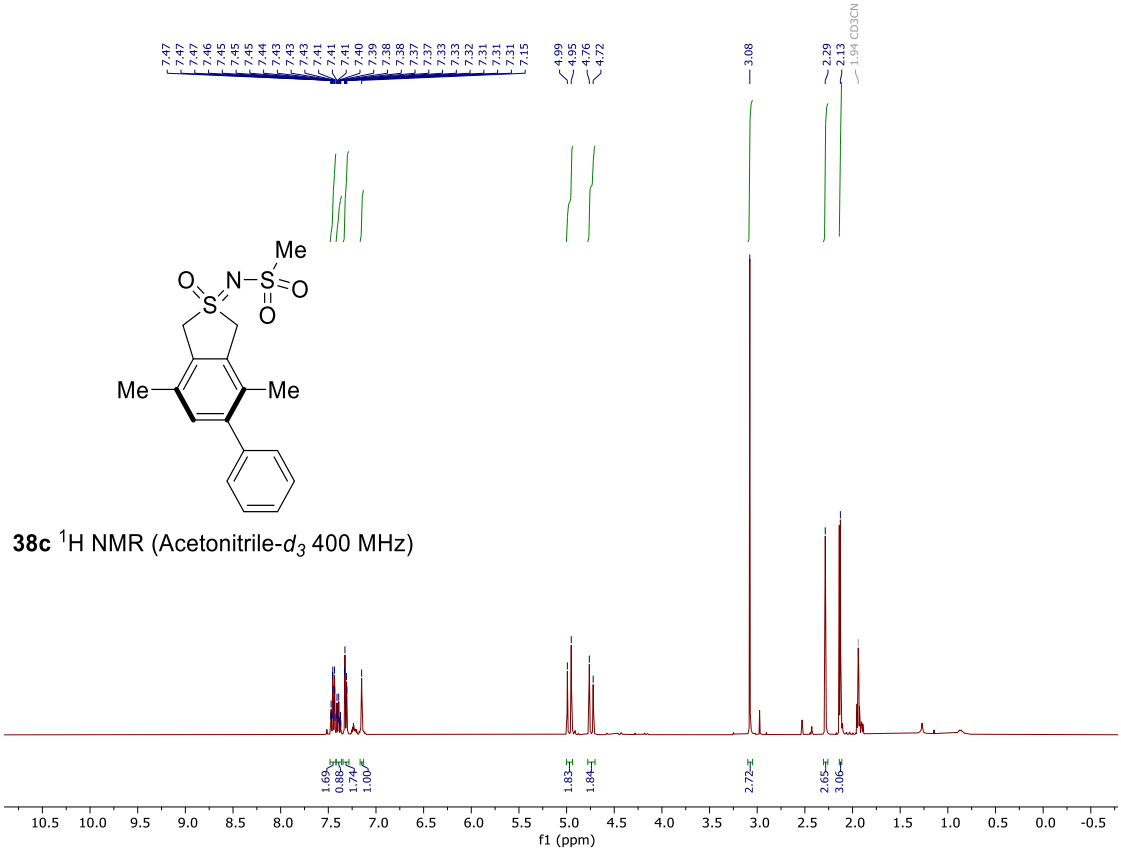
38a ^{13}C{^{1}H} NMR (Acetonitrile-d_3 101 MHz)



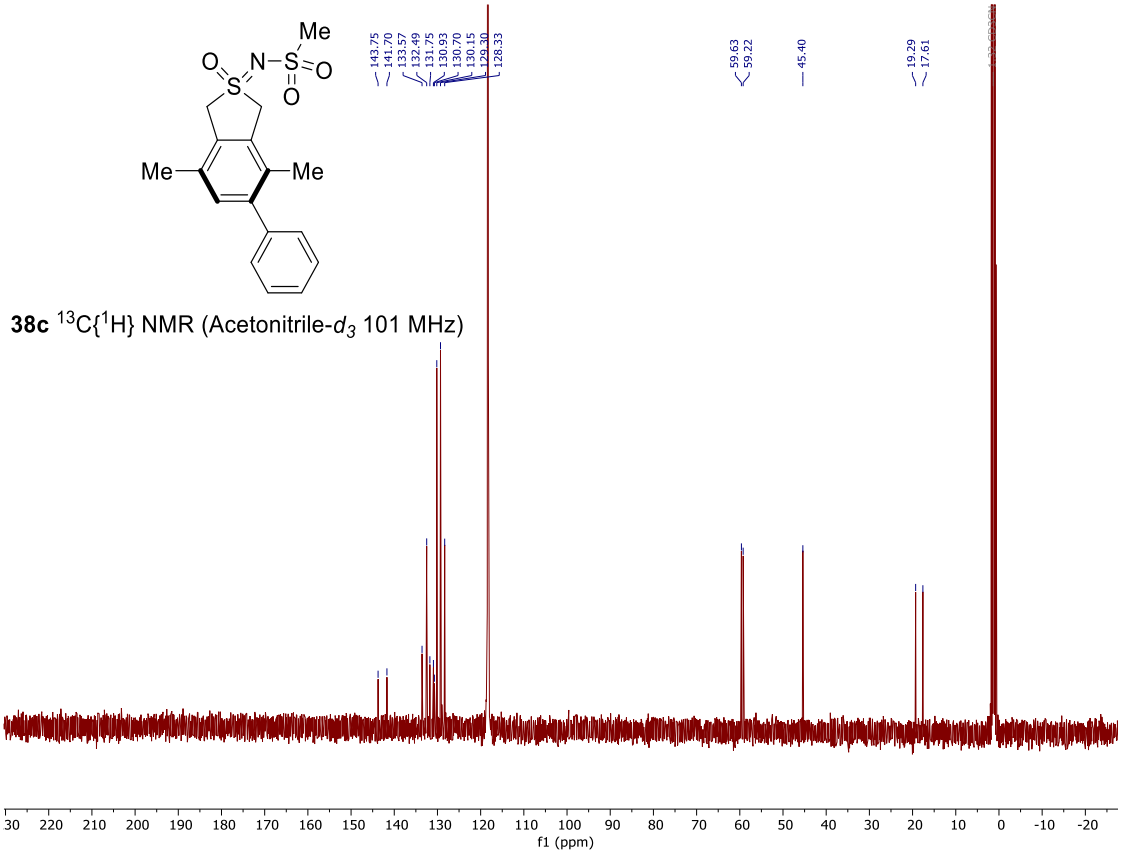
38b ^{1}H NMR (Acetonitrile-d_3 400 MHz)



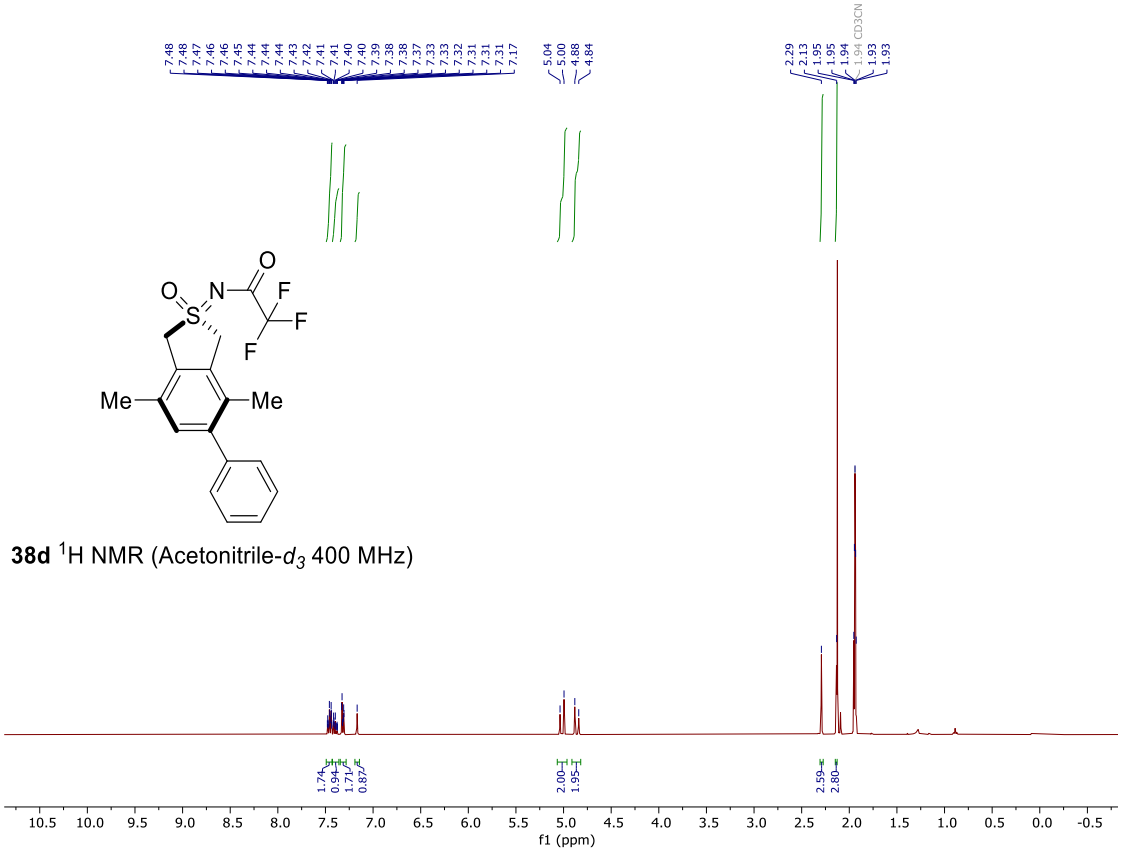
38b ^{13}C{^{1}H} NMR (Acetonitrile-d_3 151 MHz)



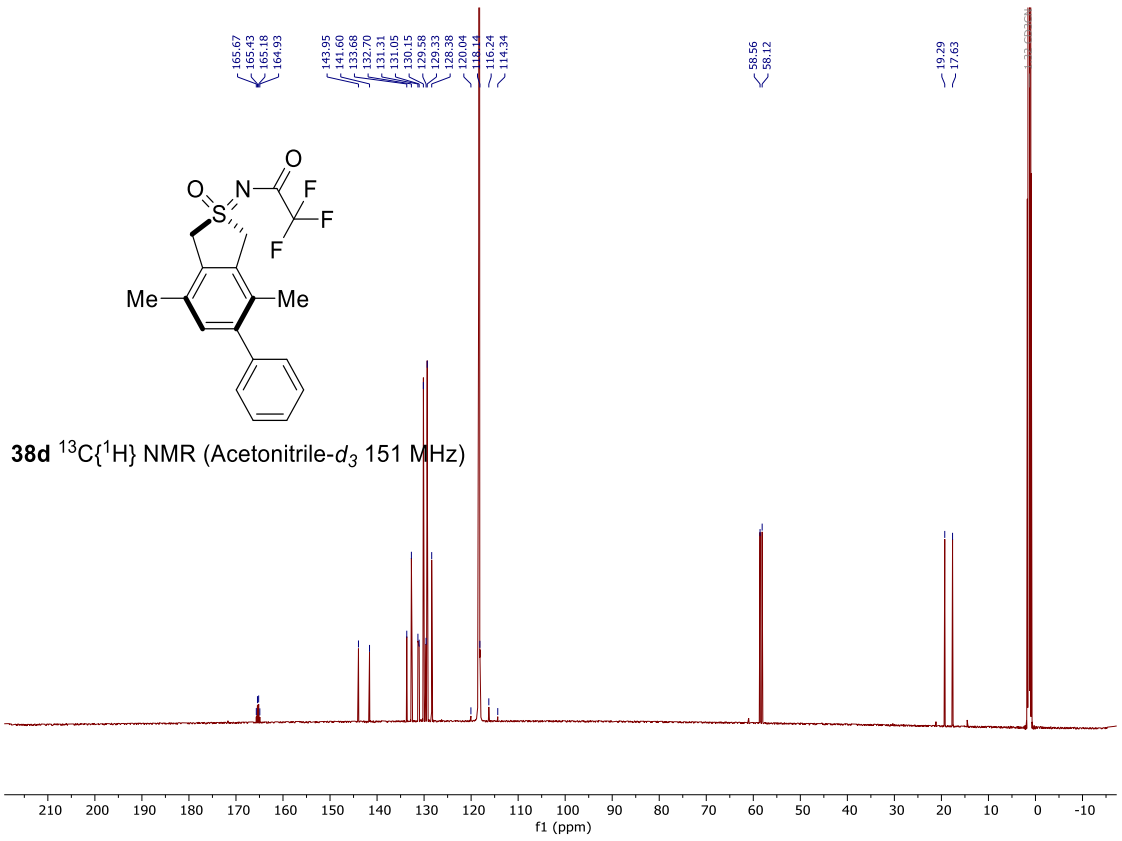
38c ^{1}H NMR (Acetonitrile-d_3 400 MHz)



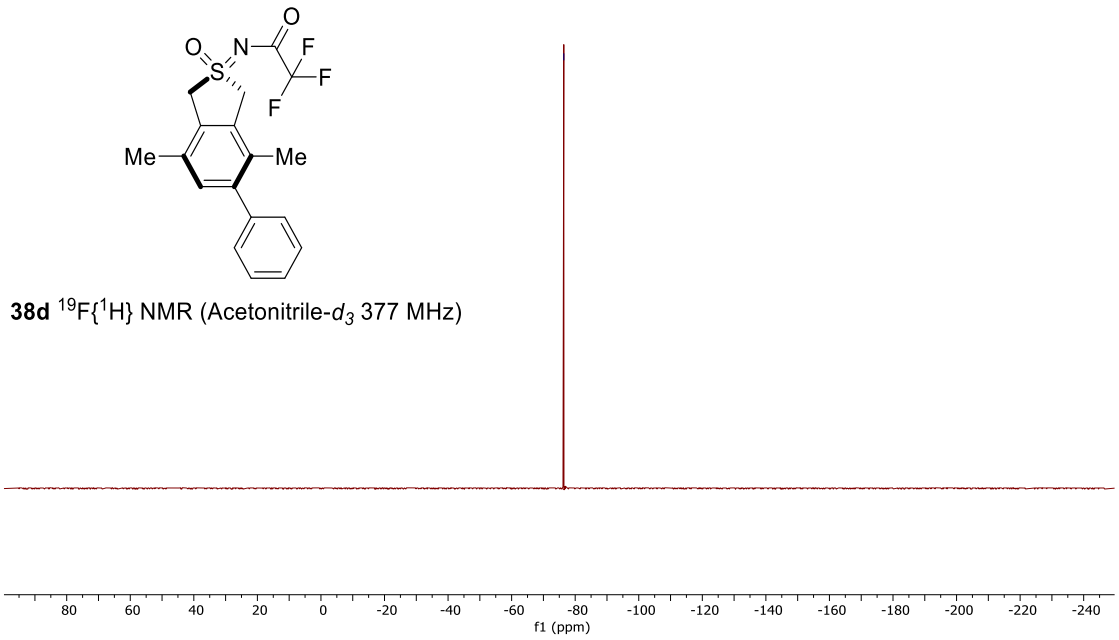
38c ^{13}C{^{1}H} NMR (Acetonitrile-d_3 101 MHz)



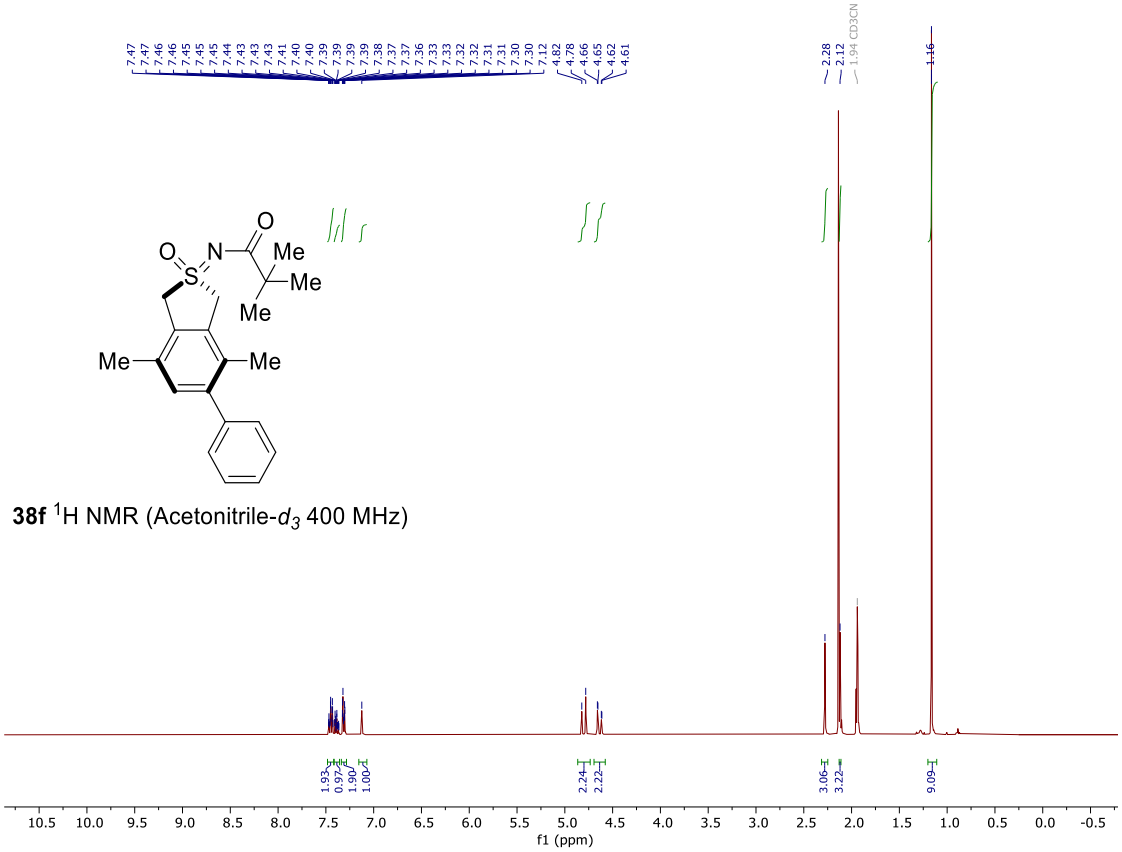
38d ^{1}H NMR (Acetonitrile-d_3 400 MHz)



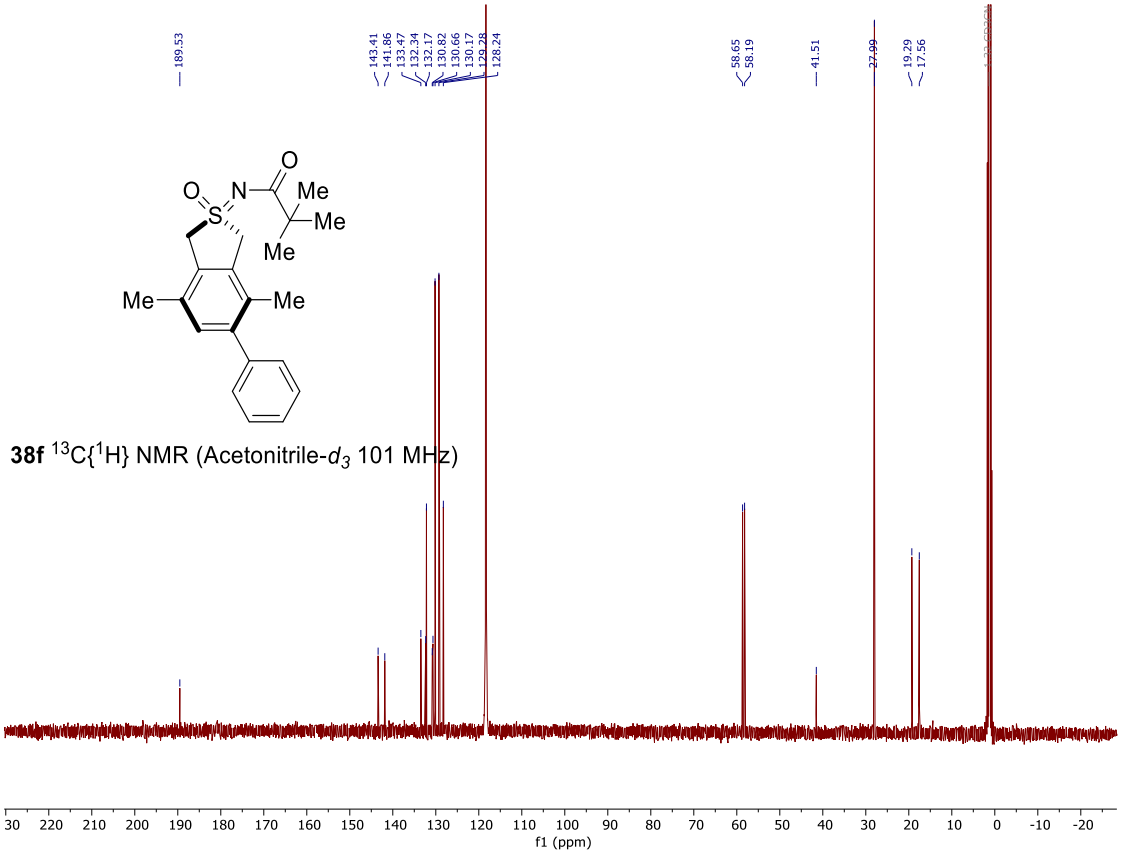
38d ^{13}C{^{1}H} NMR (Acetonitrile-d_3 151 MHz)



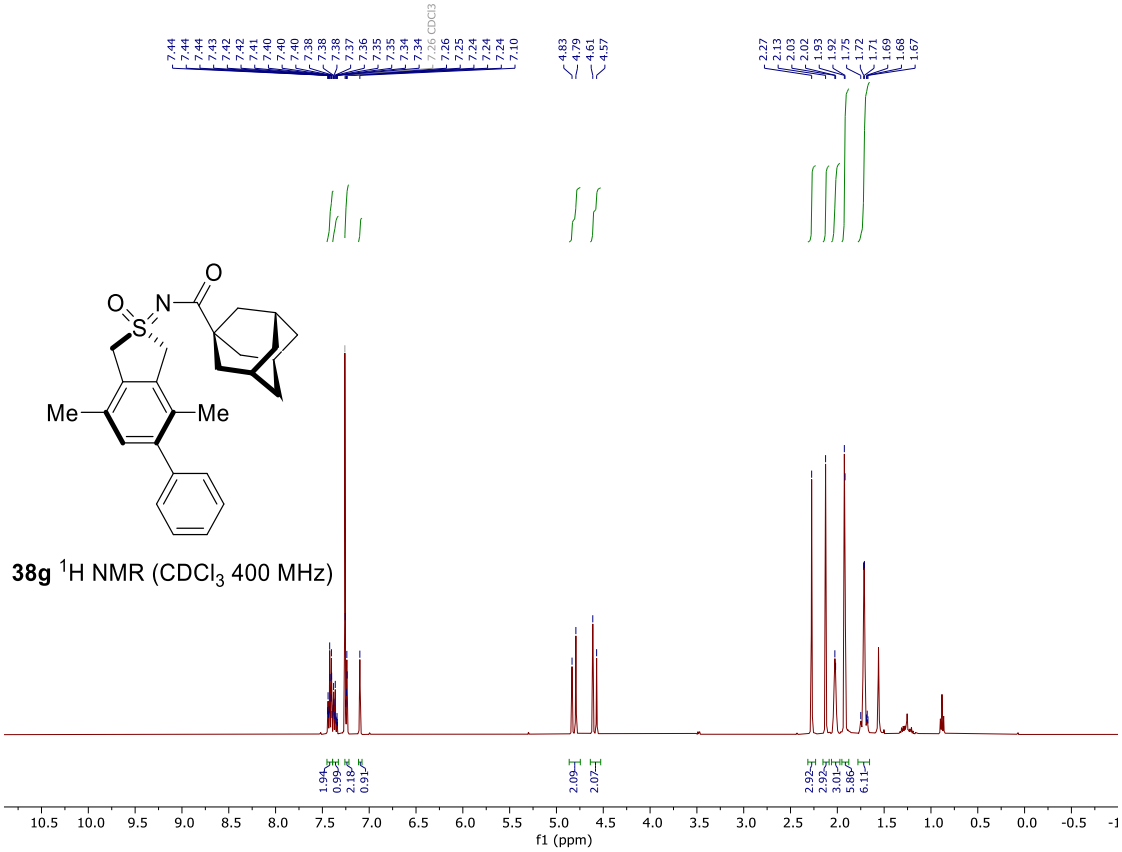
38d $^{19}F\{^{1}H\}$ NMR (Acetonitrile-d_3 377 MHz)



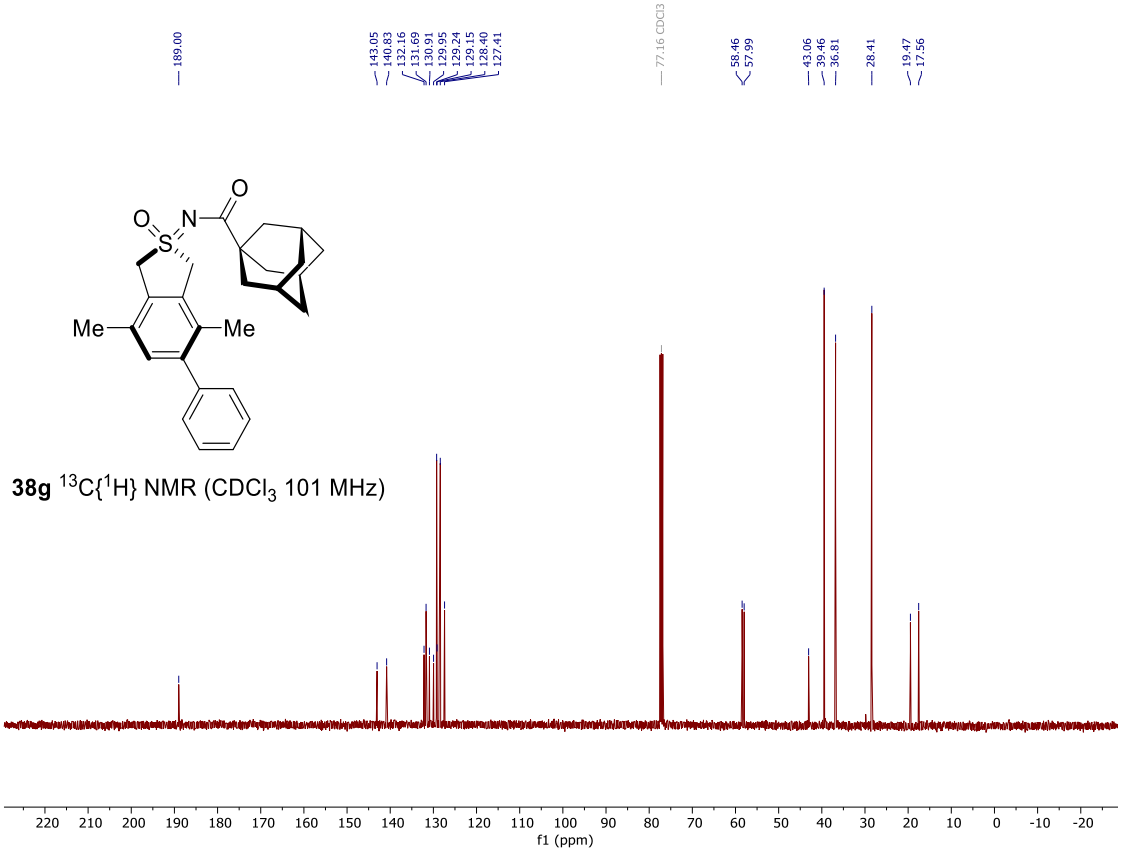
38f ^{1}H NMR (Acetonitrile-d_3 400 MHz)



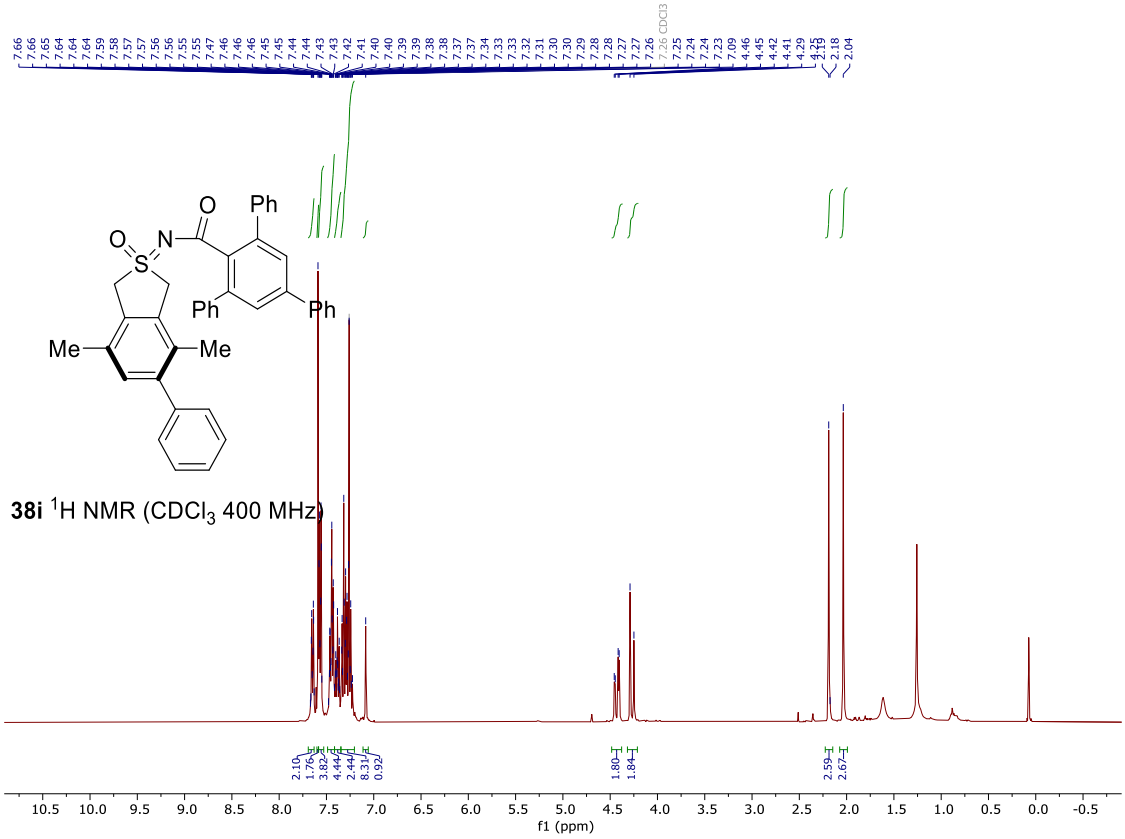
38f ^{13}C{^{1}H} NMR (Acetonitrile-d_3 101 MHz)



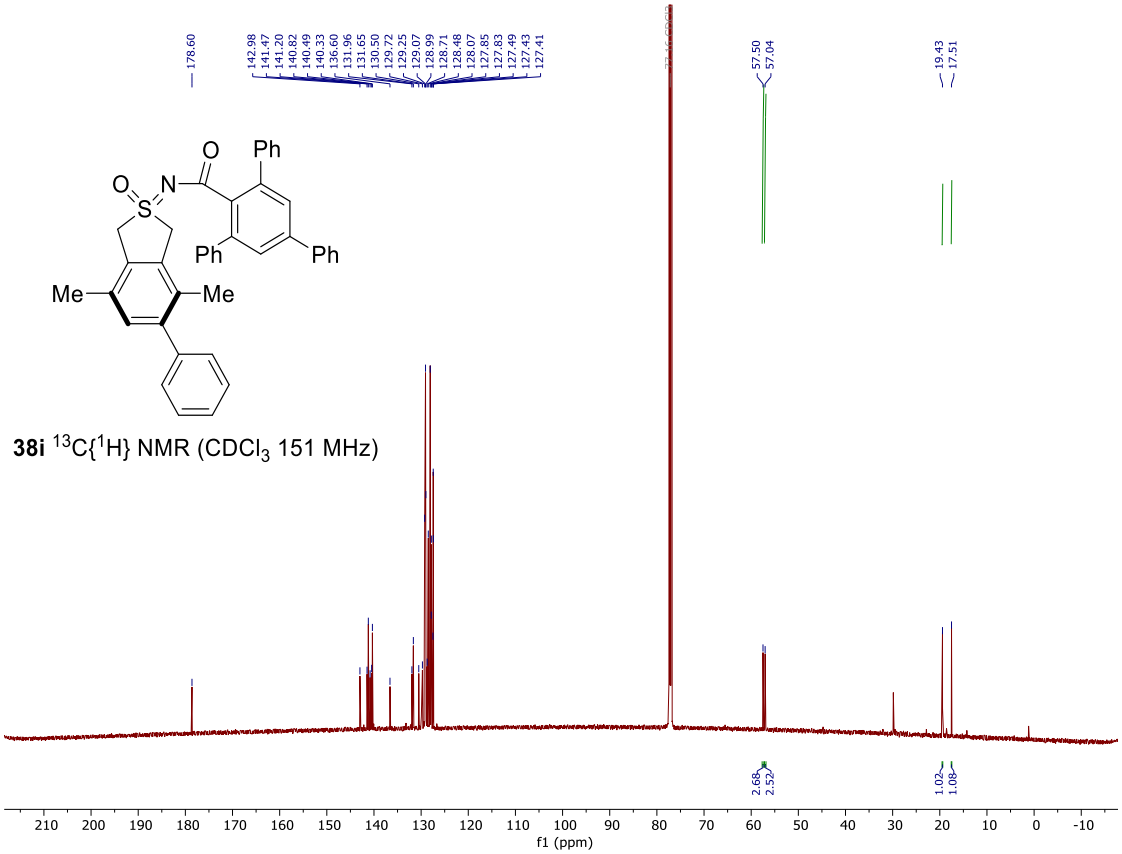
38g ^{1}H NMR ($CDCl_3$ 400 MHz)



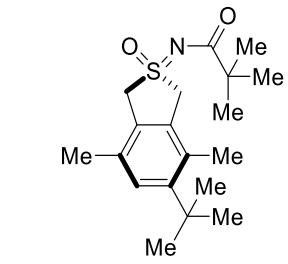
38g $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



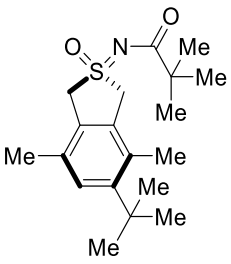
38i ^{1}H NMR ($CDCl_3$ 400 MHz)



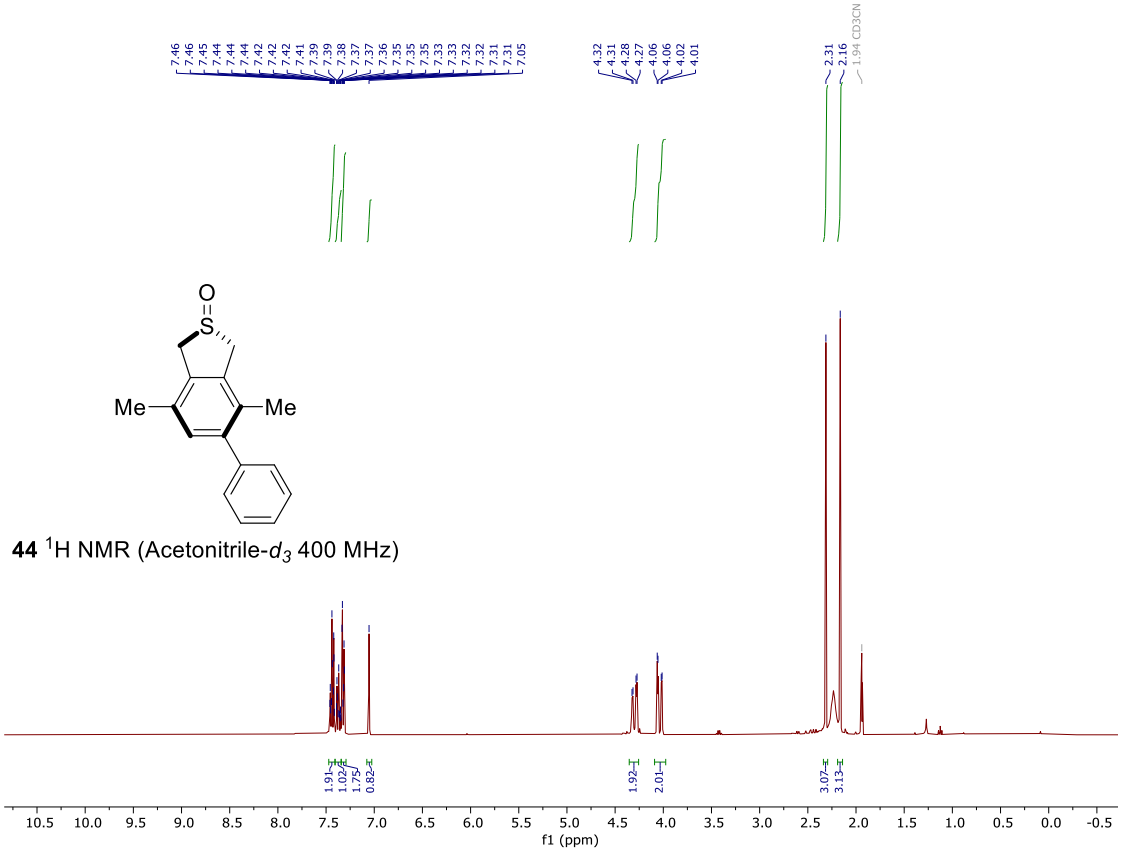
38i $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 151 MHz)



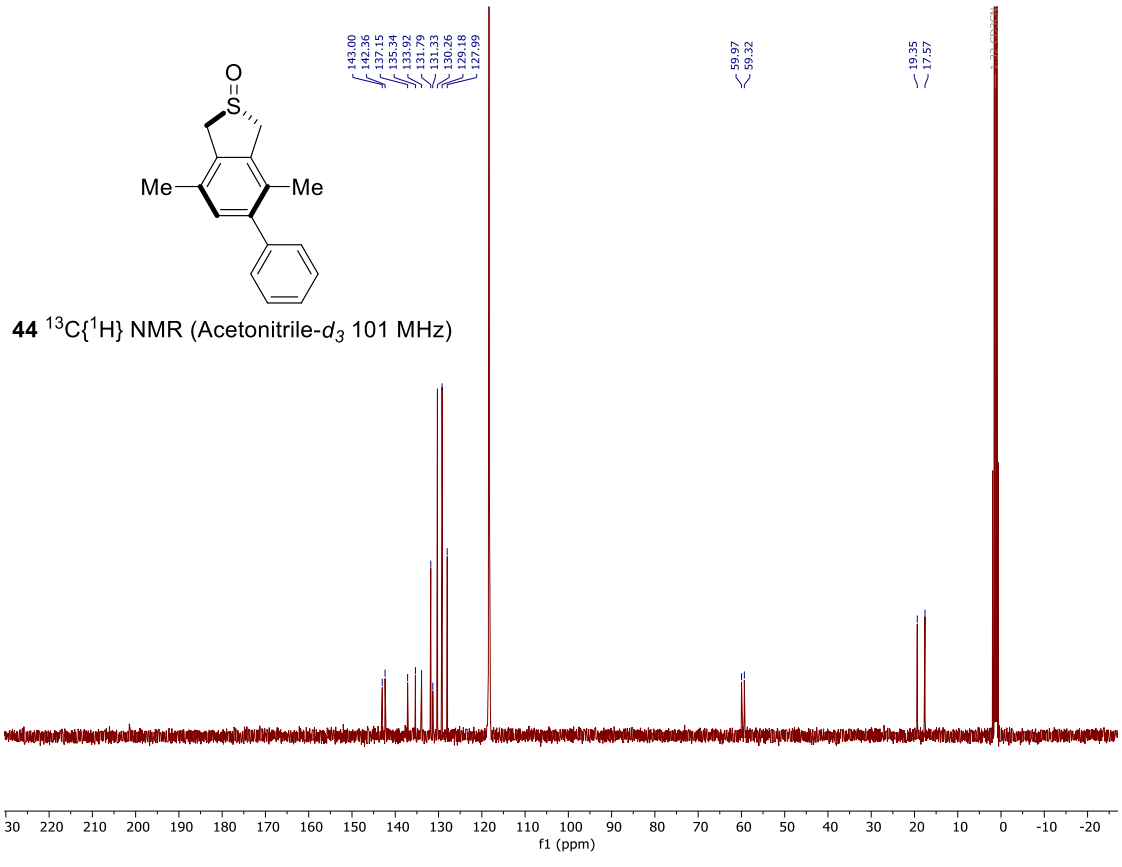
38n ^{1}H NMR ($CDCl_3$ 400 MHz)



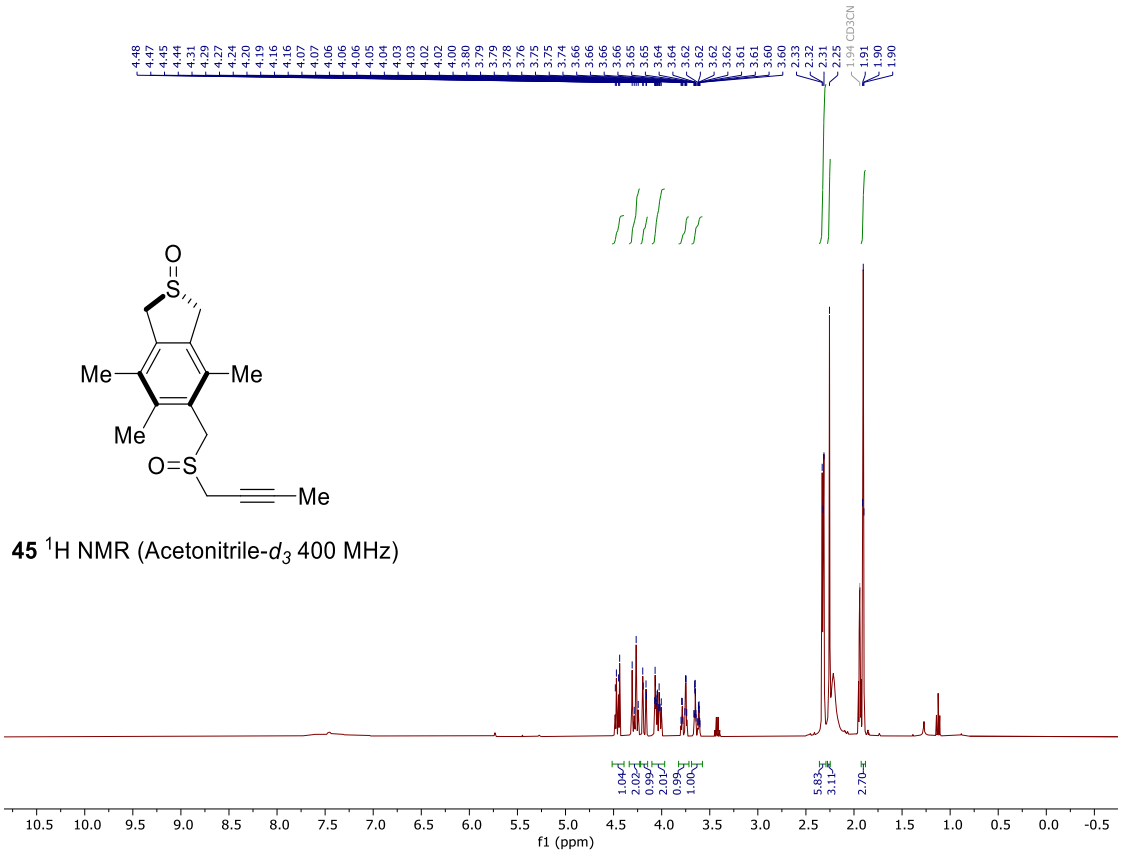
38n $^{13}C\{^{1}H\}$ NMR ($CDCl_3$ 101 MHz)



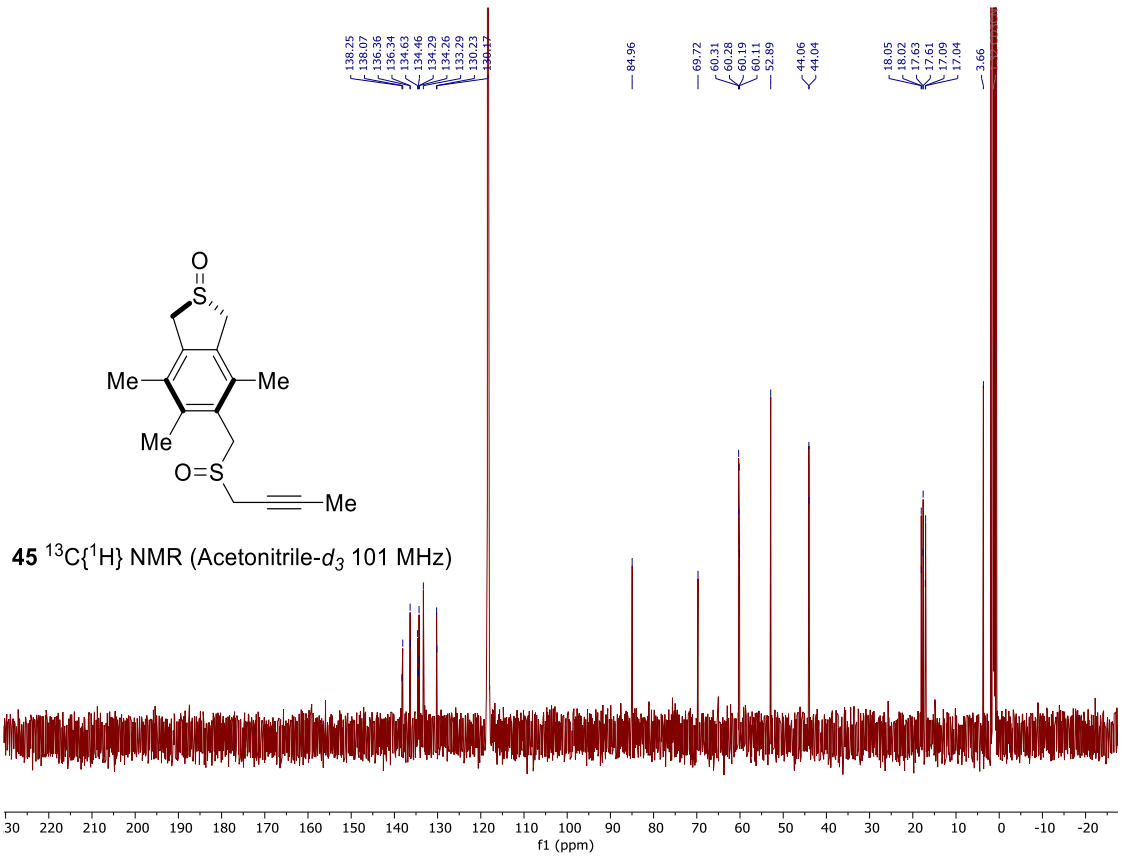
44 ^{1}H NMR (Acetonitrile-d_3 400 MHz)



44 ^{13}C{^{1}H} NMR (Acetonitrile-d_3 101 MHz)

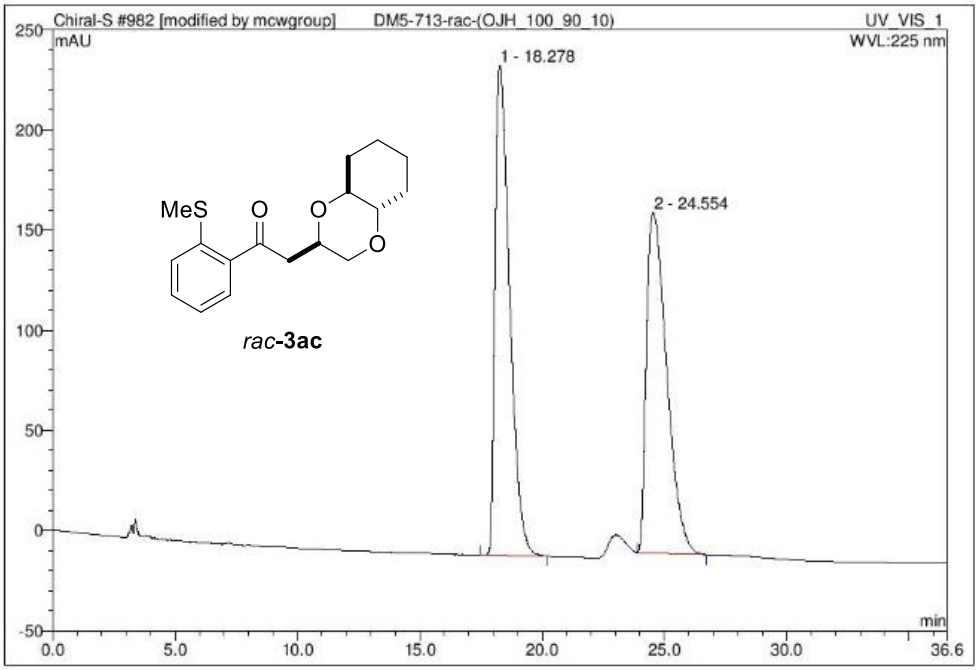


45 ^{1}H NMR (Acetonitrile-d_3 400 MHz)

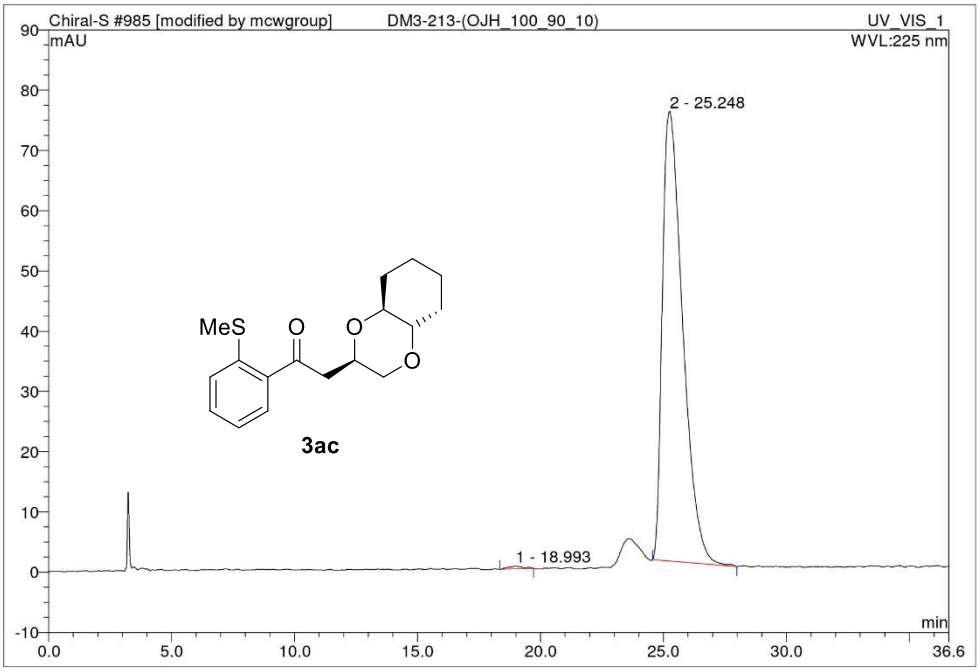


45 ^{13}C{^{1}H} NMR (Acetonitrile-d_3 101 MHz)

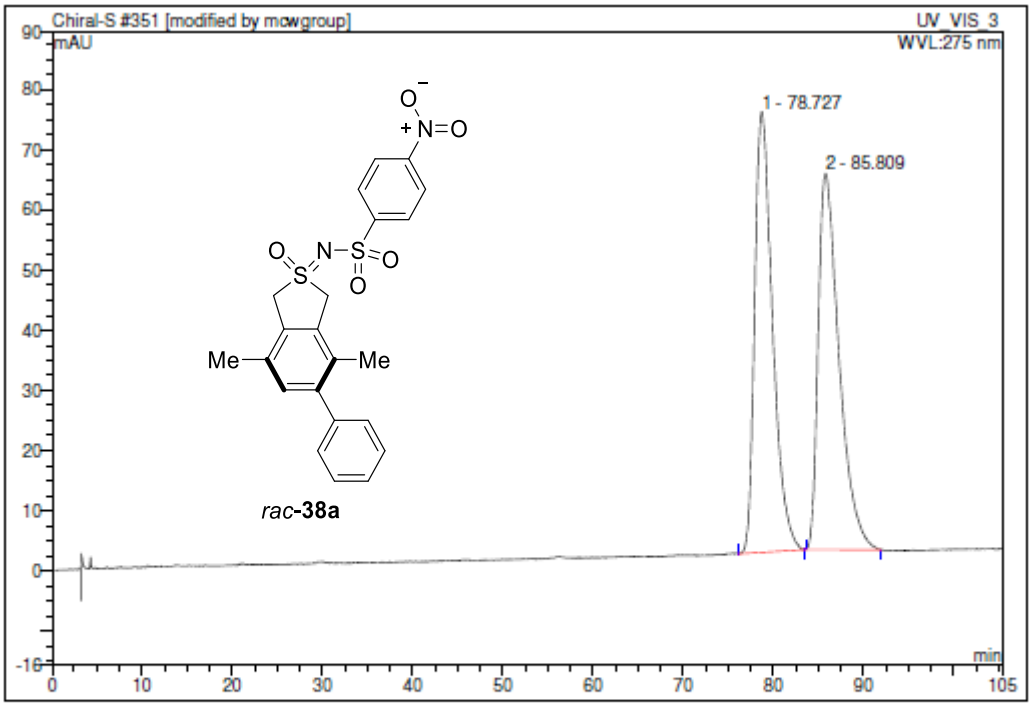
Chiral HPLC Traces for Final Compounds



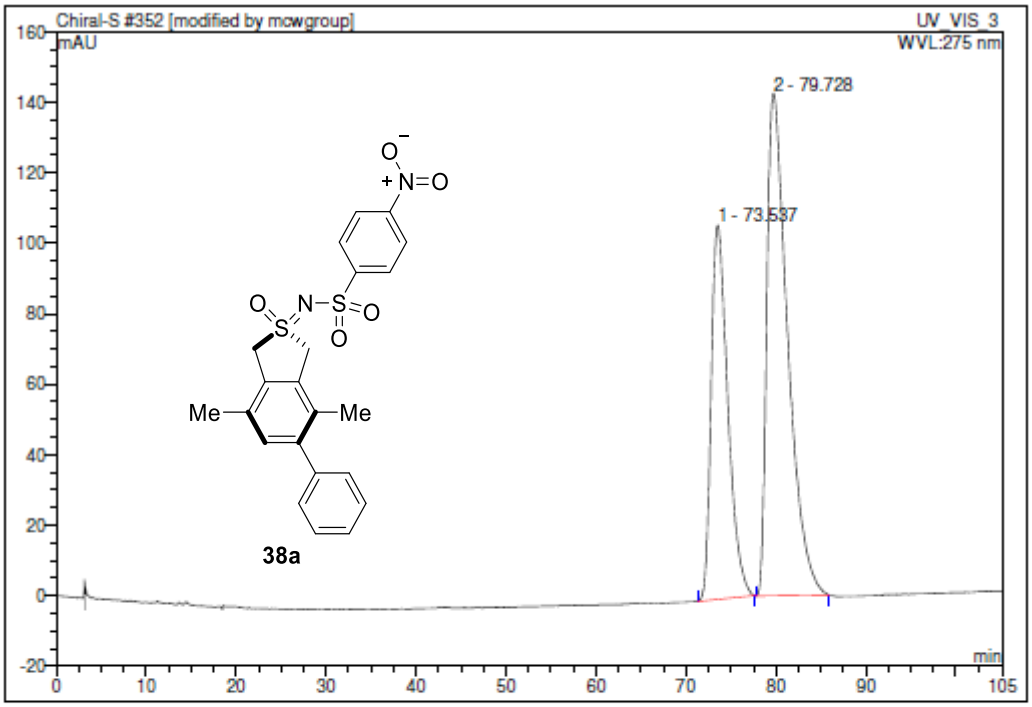
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.28	n.a.	244.810	169.776	50.96	n.a.	BMB*
2	24.55	n.a.	170.374	163.367	49.04	n.a.	BMB*
Total:			415.184	333.143	100.00	0.000	



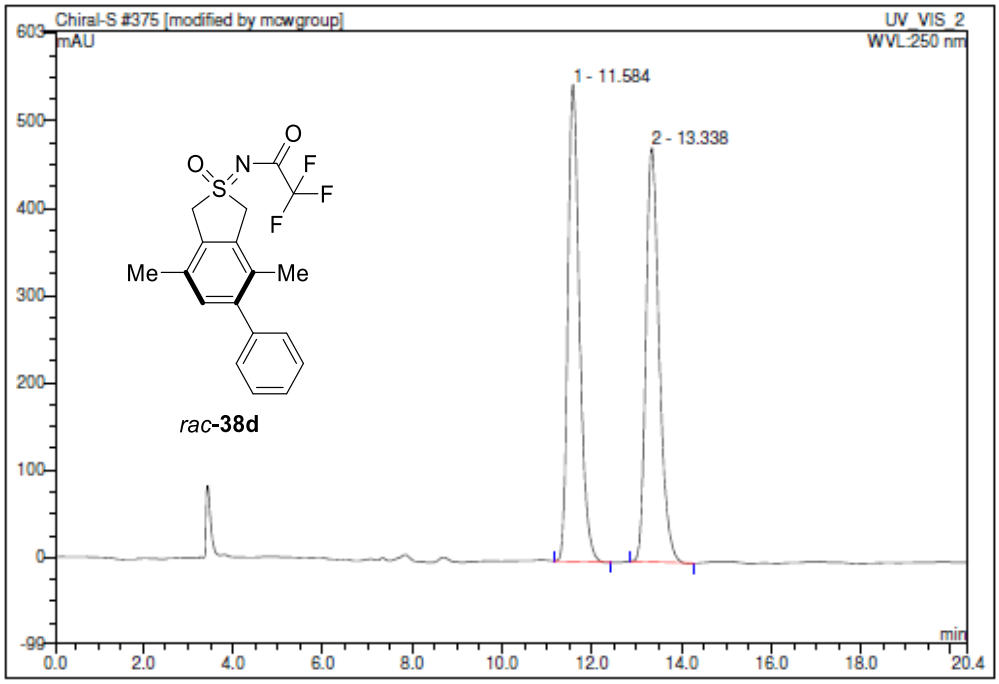
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.99	n.a.	0.442	0.325	0.45	n.a.	BMB*
2	25.25	n.a.	74.641	71.578	99.55	n.a.	BMB*
Total:			75.083	71.904	100.00	0.000	



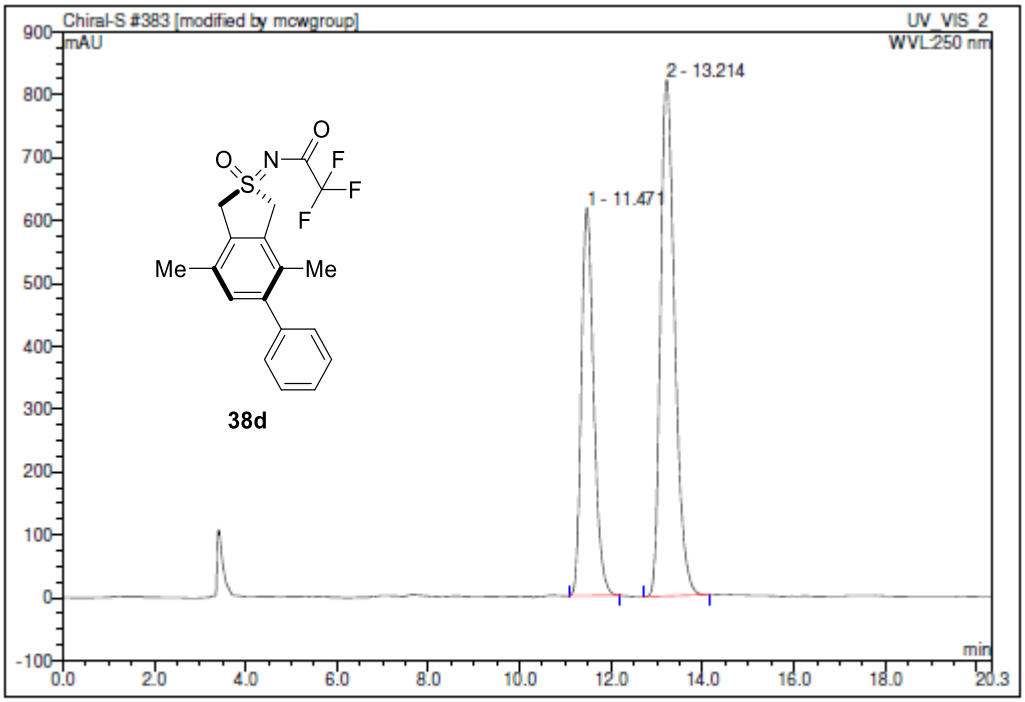
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	78.73	n.a.	73.218	168.342	50.06	n.a.	BMB*
2	85.81	n.a.	62.529	167.919	49.94	n.a.	BMB*
Total:			135.747	336.261	100.00	0.000	



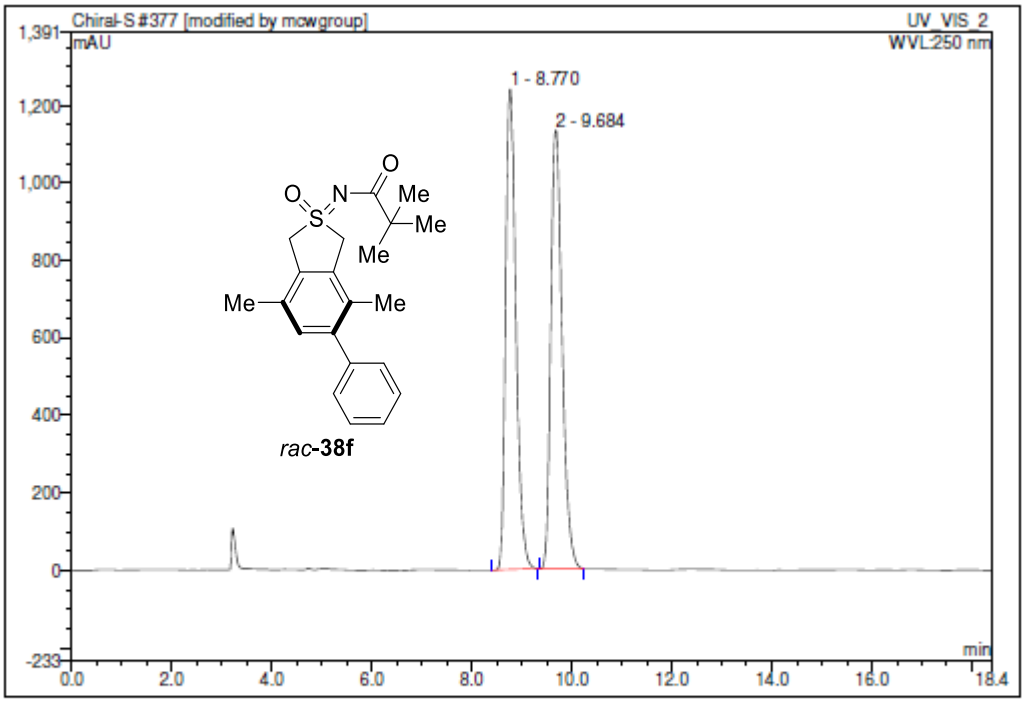
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	73.54	n.a.	106.207	227.773	37.34	n.a.	BMB*
2	79.73	n.a.	142.575	382.281	62.66	n.a.	BMB*
Total:			248.782	610.054	100.00	0.000	



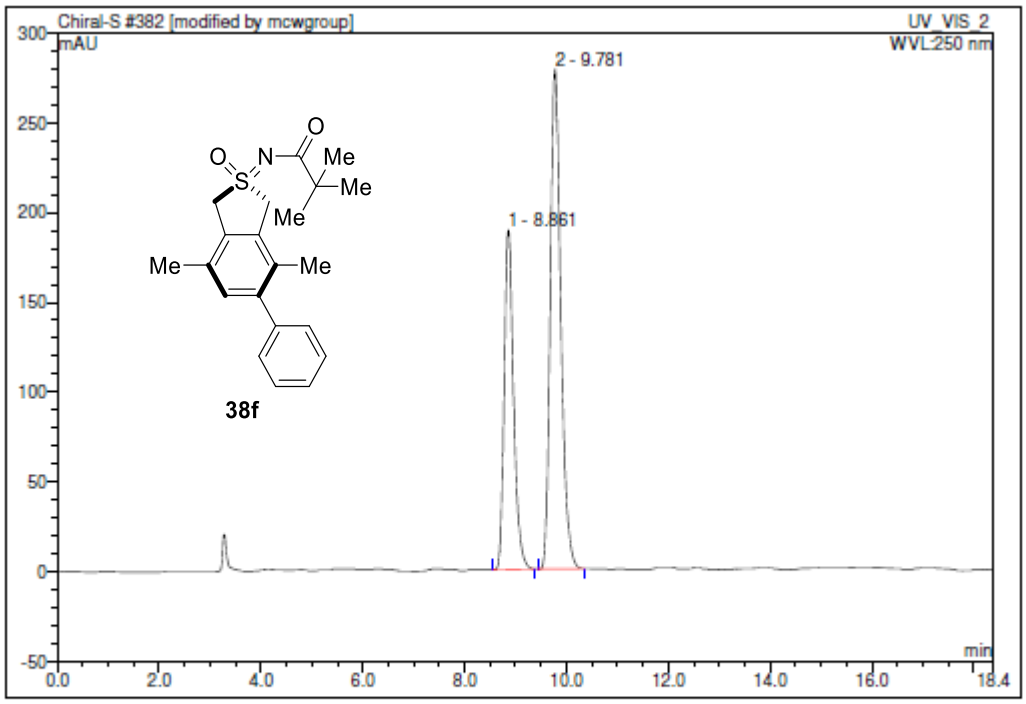
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.58	n.a.	546.188	163.351	50.16	n.a.	BMB*
2	13.34	n.a.	474.291	162.302	49.84	n.a.	BMB*
Total:			1020.479	325.652	100.00	0.000	



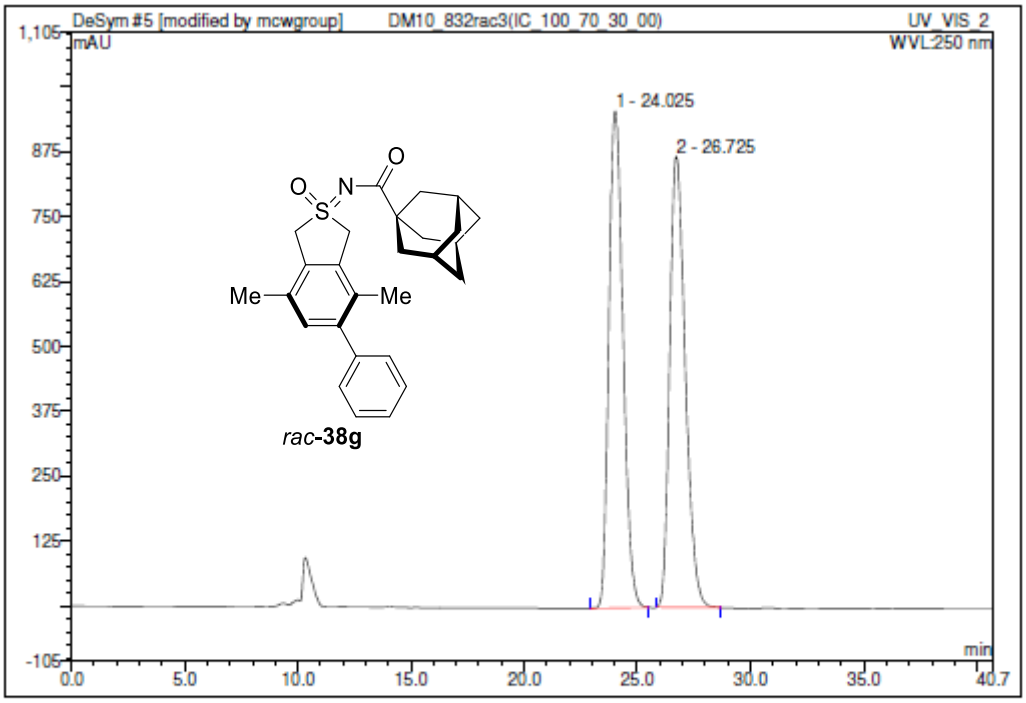
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.47	n.a.	617.076	193.637	39.48	n.a.	BMB*
2	13.21	n.a.	820.806	296.883	60.52	n.a.	BMB*
Total:			1437.882	490.520	100.00	0.000	



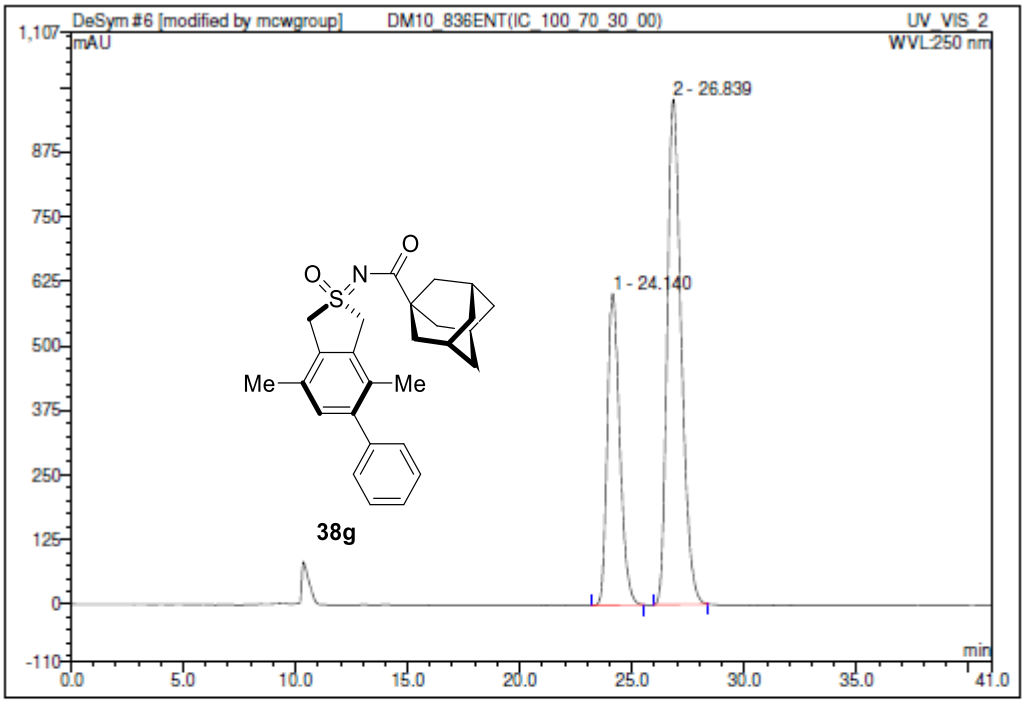
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.77	n.a.	1240.041	295.428	49.82	n.a.	BMB*
2	9.68	n.a.	1131.766	297.545	50.18	n.a.	BMB*
Total:			2371.807	592.973	100.00	0.000	



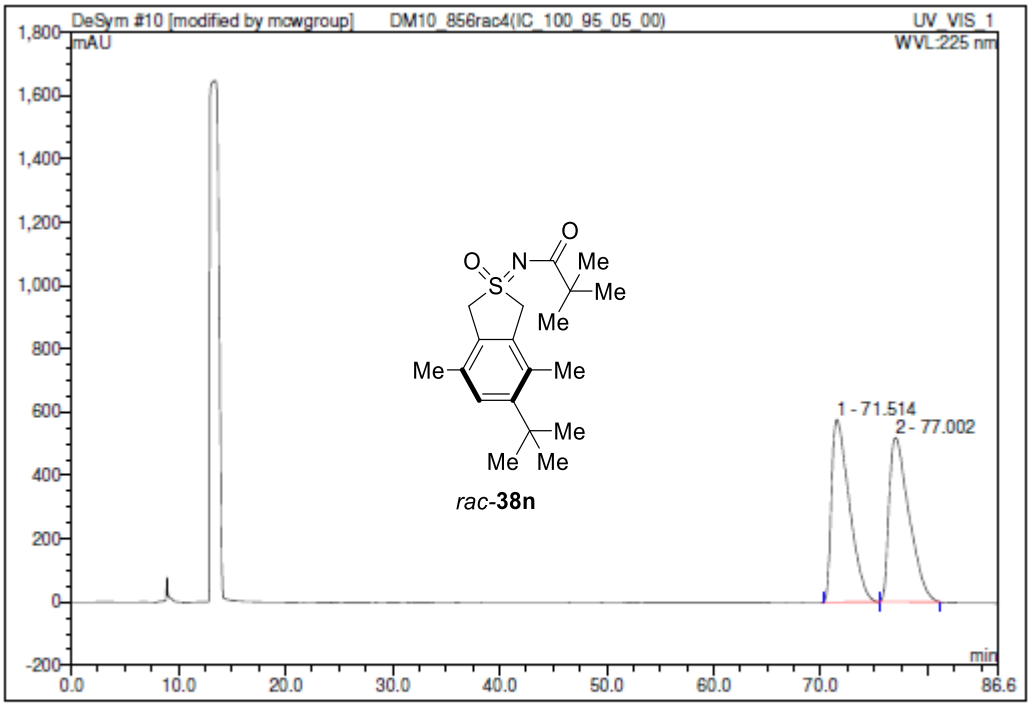
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.86	n.a.	189.022	40.421	37.76	n.a.	BMB*
2	9.78	n.a.	278.130	66.639	62.24	n.a.	BMB*
Total:			467.152	107.060	100.00	0.000	



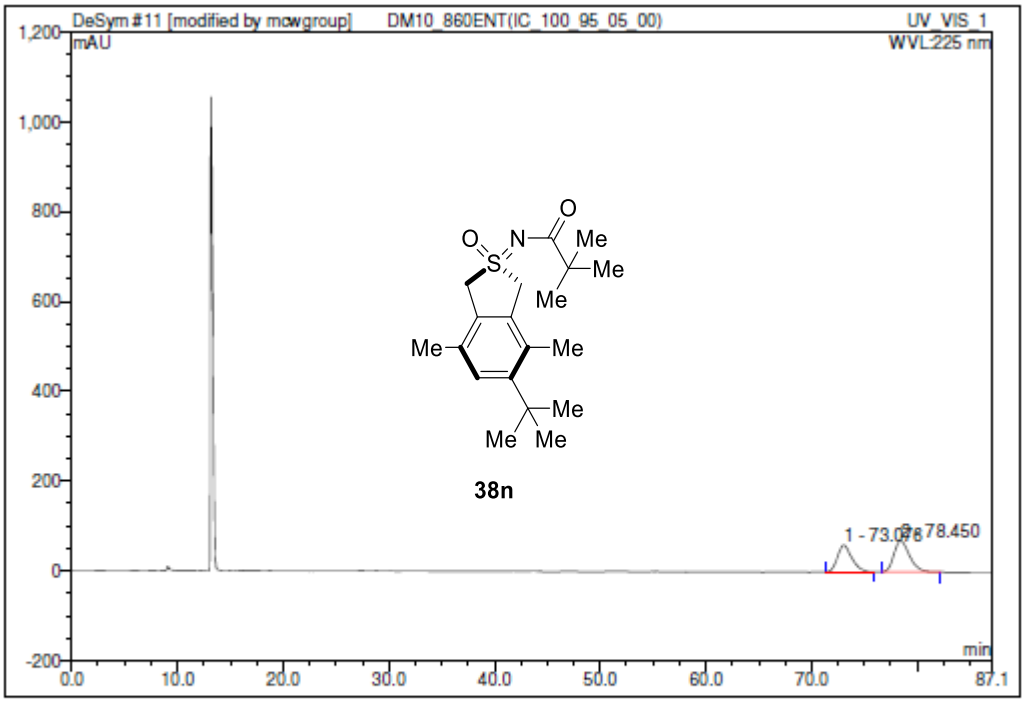
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.03	n.a.	956.566	694.386	50.10	n.a.	BMB*
2	26.72	n.a.	868.193	691.624	49.90	n.a.	BMB*
Total:			1824.760	1386.011	100.00	0.000	



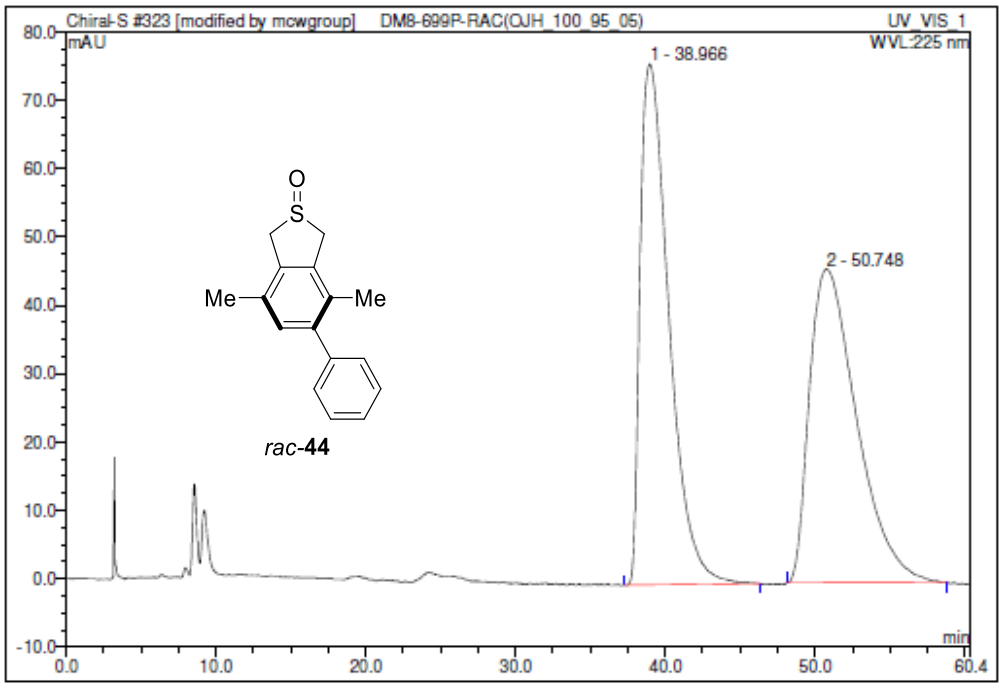
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.14	n.a.	602.743	388.076	35.33	n.a.	BMB*
2	26.84	n.a.	977.007	710.354	64.67	n.a.	BMB*
Total:			1579.750	1098.430	100.00	0.000	



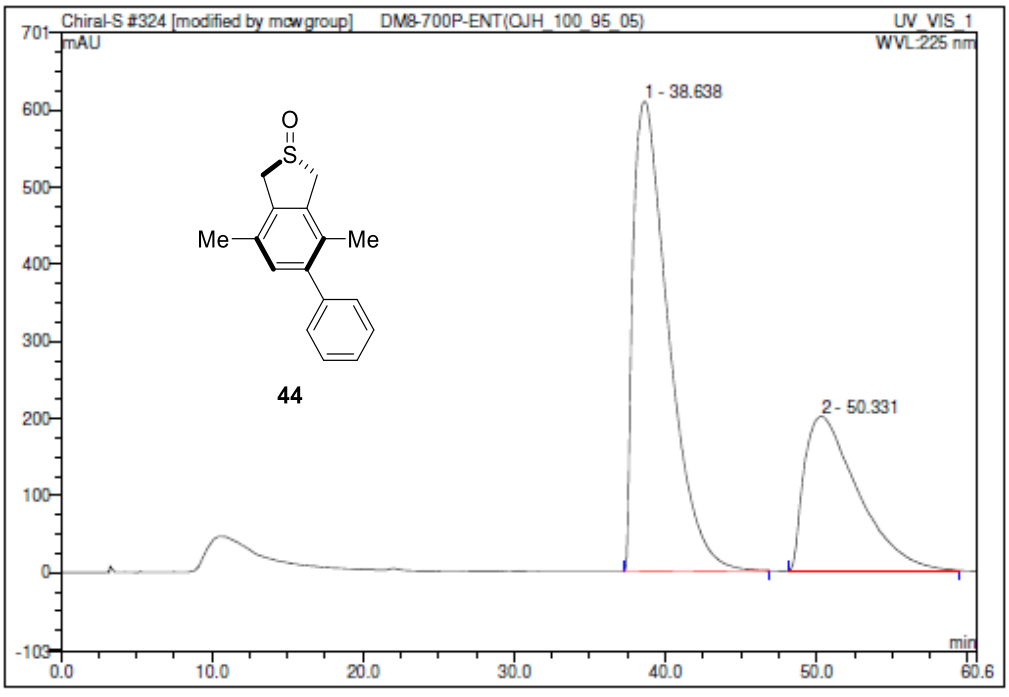
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	71.51	n.a.	575.821	1115.526	50.03	n.a.	BMB*
2	77.00	n.a.	517.647	1113.974	49.97	n.a.	BMB*
Total:			1093.468	2229.500	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	73.08	n.a.	59.828	93.955	44.33	n.a.	BMB*
2	78.45	n.a.	69.119	117.971	55.67	n.a.	BMB*
Total:			128.947	211.926	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38.97	n.a.	76.225	169.572	50.33	n.a.	BMB*
2	50.75	n.a.	45.888	167.369	49.67	n.a.	BMB*
Total:			122.113	336.942	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38.64	n.a.	610.379	1650.807	66.77	n.a.	BMB*
2	50.33	n.a.	200.089	821.701	33.23	n.a.	BMB*
Total:			810.468	2472.509	100.00	0.000	