Palladium-Catalysed Functionalisation of Csp^3–H Bonds Directed by Aliphatic Amines

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This dissertation is submitted for the Degree of Doctor of Philosophy

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Declaration

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy. It describes work carried out in the Department of Chemistry from October 2016 to March 2020. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

Cornelia S. Buettner

18th August 2020

Statement of length

This dissertation does not exceed the word limit of 60 000 as set by the Degree Committee for the faculty of Physics and Chemistry.

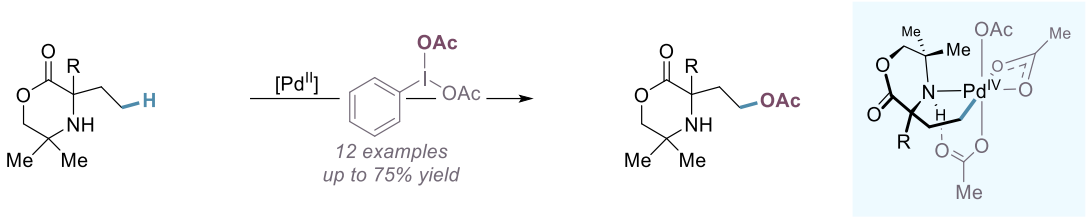
Cornelia S. Buettner

18th August 2020

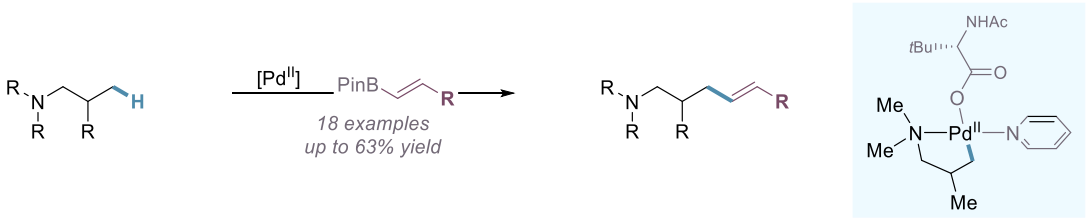
Abstract – Palladium-Catalysed Functionalisation of Csp^3–H Bonds Directed by Aliphatic Amines

Synthetic transformations on medicinally-relevant aliphatic amines are valuable in the diversification of molecules designed as pharmaceutical agents. This thesis describes two Csp^3–H functionalisation reactions, using native amines (secondary and tertiary) to direct C–H activation.

Chapter 2 describes a palladium-catalysed Csp^3–H acetoxylation directed by native secondary amines. A range of cyclic amines could be acetoxylated with excellent functional group tolerance to form the desired functionalised products. Kinetic experiments and DFT calculations elucidated the mechanism of the transformation, which features C–O bond formation *via* an external acetate attack onto the electrophilic C–Pd bond.



Chapter 3 describes a palladium-catalysed Csp^3–H alkenylation directed by tertiary aliphatic amines. A diverse set of amines were functionalised using alkenyl boronic ester coupling partners to give the desired olefinated products. The work includes enantioselective functionalisation using a chiral ligand and a preliminary study of stoichiometric aminoalkyl palladium(II) complexes.



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Abbreviations

Å	angstrom
Ac	acetate
Ad	adamantyl
AMLA	ambiphilic metal ligand activation
aq.	aqueous
Ar	aryl
ATR	attenuated total reflectance
bp	boiling point
BINPHAT	bis(tetrachlorobenzenediolato)mono(-1,1’-dinaphthyl-2,2’-diolato)phosphate
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	1,4-benzoquinone
Bu	butyl
Bz	benzoyl
c	centi
C	celcius
cal	calorie
CAN	ceric ammonium nitrate
cm^{-1}	wavenumbers
CMD	concerted metallation-deprotonation
CNS	central nervous system
COSY	correlation spectroscopy
Cy	cyclohexyl
DCE	dichloroethane
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DG	directing group
DMA	dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dmpe	1,2-bis(dimethylphosphino)ethane
e^-	electron
ee	enantiomeric excess
equiv	equivalents
ESI	electrospray ionisation

Et	ethyl
EWG	electron withdrawing group
FG	functional group
FID	flame ionisation detector
g	gram
GC	gas chromatography
Gly	glycine
h	hour
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i	iso
Int	intermediate
IR	infrared
J	coupling constant
K	kelvin
k	kilo
KIE	kinetic isotope effect
L	neutral ligand *or* litre
Leu	Leucine
LUMO	lowest unoccupied molecular orbital
M	metal *or* molar
m	milli *or* metre
Me	methyl
min	minutes
mol	mole
Mp	melting point
MPAA	monoprotected amino acid
MS	mass spectrometry
n	normal
n	nano
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ø	diameter

Ph	phenyl
Phth	phthalimido
Pin	pinacolato
Piv	pivaloyl
ppm	parts per million
Pr	propyl
quant	quantitative
R	undefined group
R_F	retention factor
rt	room temperature
SAR	structure activity relationship
sat.	saturated
SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
t	tert
TBHP	tert-butyl hydroperoxide
TCE	tetrachloroethane
TDG	transient directing group
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TOF	time of flight
Tol	tolyl
TRIP	3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
TS	transition state
Ts	tosyl
X	anionic ligand *or* halogen
δ	chemical shift
Δ	change
λ	wavelength
μ	micro
ν	frequency
ρ	Hammett reaction constant

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1. Introduction

1.1 Palladium-catalysed C–H activation

1.1.1 Introduction to C–H activation and early work

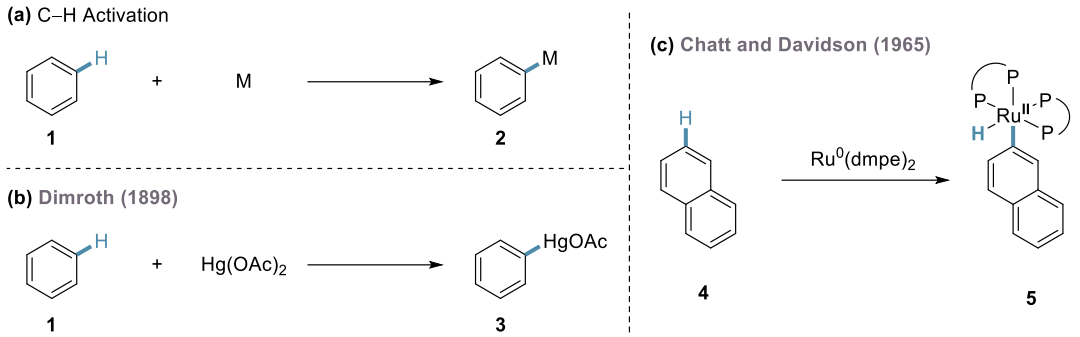
Transition metal-catalysed transformations have become some of the most valuable tools for synthetic chemists. Palladium, the stable and relatively non-toxic metal, is most commonly used as a hydrogenation catalyst and for cross-coupling reactions, such as the Heck, Suzuki, Buchwald-Hartwig, Stille and Negishi reactions.[1-2] Palladium-catalysed cross-coupling reactions are routinely used by medicinal chemists, with the Suzuki reaction being most popular and accounting for around 40% of all C–C bond forming processes.[3-5] The utility of palladium as a cross-coupling catalyst has been highlighted by the award of the Nobel prize to Richard Heck, Ei-ichi Negishi and Akira Suzuki in 2010 for their contribution to the field.[6]

Traditionally, palladium-catalysed transformations are dedicated to pre-functionalised substrates to form intermediate C–M (M = metal) bonds. Although processes of oxidative addition or transmetallation occur very efficiently and selectively to form key C–M intermediates, it always necessitates pre-functionalisation of the substrate. Therefore, directly utilising C–H bonds in the formation of intermediary C–M bonds offers an alternative and more direct approach in the construction of complex molecules.[7] This brings its own unique challenges with it.

C–H bonds are ubiquitous in organic structures. A large proportion of C–H bonds are remote from functionality making them unreactive using classical synthetic means.[8] These traditionally unreactive bonds tend to have low polarity and high dissociation energies (Et–H 101 $kcalmol^{-1}$)[9] making their activation challenging.[10] The now antiquated term ‘paraffin’ (*parum* barely + *affinis* affinity), describes accurately this observed lack of reactivity of unactivated C–H bonds and thus, the derivatisation of such bonds has long enticed the chemistry community.[11-13] The development of C–H activation processes by palladium-catalysis offers a more atom economic route for the synthesis of organic molecules, eliminating the need for pre-functionalisation.

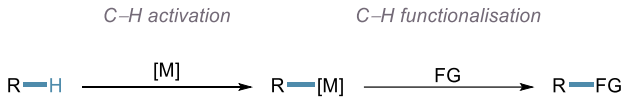
The term *C–H activation* describes the process by which traditionally unreactive C–H bonds are activated by a transition metal, to form an intermediate C–M bond (complex **2**, Scheme **1a**). The field of C–H activation has gained growing attention from the synthesis community since the initial report of aromatic electrophilic mercuration of benzene **1**, forming the aryl-mercury complex **3** (Scheme **1b**).[14-16] Mechanistically, the formation of the formal C–H activation complex **3** is preceded by the formation of a Wheland-intermediate, which is deprotonated to restore aromaticity.[17] However, the term C–H activation has since acquired mechanistic connotations, requiring the insertion of the transition metal into a C–H bond, in a manner analogous to H_2 activation.[18-19] Thus the first ‘true’ C–H activation was

reported by Chatt and Davison in 1965.[20-21] They observed the formation of C–H activation complex **5** by insertion of low valent ruthenium into various arenes, such as naphthalene **4** (Scheme **1c**).



Scheme 1 | **(a)** C–H Activation giving metallated (C–M) bond; **(b)** Report by Dimroth on the C–H activation of benzene using mercury(II) acetate;[16] **(c)** Seminal example of C–H activation by insertion of a ruthenium(0) catalyst[20]

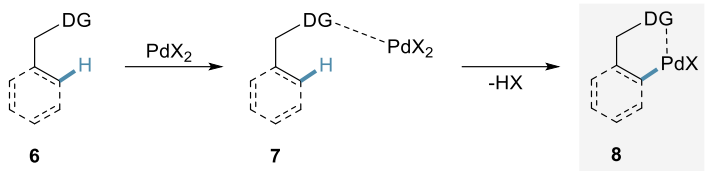
The functionalisation of C–H bonds can be divided into two steps (Scheme **2**). Initial C–H activation by cleavage of a C–H bond by a metal to form an intermediate C–M bond, followed by derivatisation of the C–M intermediate.[22] Although the term *C–H activation* is sometimes used in scientific literature to include the subsequent transformation of C–M bonds into C–C/X bonds (X = N, O, S, halogen), this process is more commonly termed *C–H functionalisation* (and is discussed further in *section 1.2*).[23] Finally, as this thesis will focus solely on palladium as a catalyst for C–H functionalisation, all further discussion will be exclusively focused on, and in the context of, palladium catalysis.



Scheme 2 | General C–H activation and C–H functionalisation

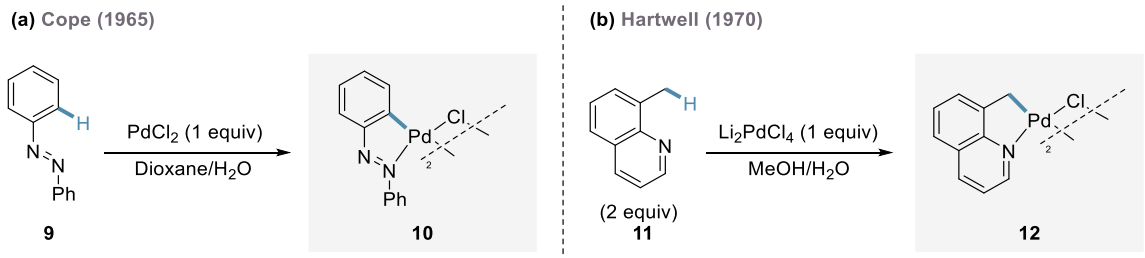
1.1.2 Selectivity of C–H activation

Aside from low reactivity, another significant challenge in C–H activation is controlling the selectivity of activation. Commonly, Lewis-basic moieties have been employed in directing the activation of specific C–H bonds (Scheme **3**). These groups facilitate selective C–H activation by directing the metal towards a specific site for activation (**7**). The ligation of Lewis-basic groups to the metal expedites the C–H activation process by lowering the entropic cost and facilitating *cyclometallation*, the C–H activation event, to form the palladacycle **8**.[24]



Scheme 3 | Cyclometallation with a directing group (DG) for a generic sp^2/sp^3 system

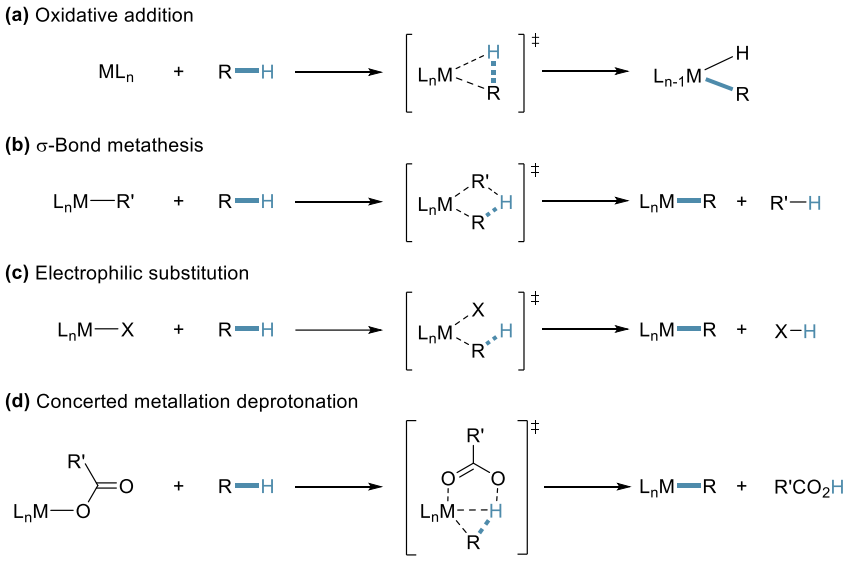
Stoichiometric studies featuring palladium have given rise to the isolation of palladacycles, where substrates bind to palladium in a bidentate fashion. These are characterised by forming five or six membered chelates containing a stable C–Pd bond.[25] In 1965, Cope reported the first isolated palladacycle **10** (Scheme **4a**).[26] The nitrogen present in the diazo moiety allows ligation to the palladium centre, enabling *ortho*-palladation using $PdCl_2$, which proceeded at room temperature. In 1970, Hartwell reported the first palladacycle formed from the C–H activation of an aliphatic C–H bond (**12**, Scheme **4b**).[27] Previously, it had been suggested that palladacycle formation was precluded by a π-arene complex, whereby the palladium bound to the directing nitrogen associates with the arene prior to the C–H activation event. However, the formation such a complex with planar 8-methylquinoline **11** is geometrically unlikely, suggesting that this species is not required for palladacycle formation as previously thought.[28]



Scheme 4 | **(a)** First isolation of palladacycle **10** by Cope;[26] **(b)** First example of aliphatic C–H activation complex **12**[27]

1.1.3 Mechanism of C–H activation

The seminal discoveries of palladacycle formation as described above (*section 1.1.2*), rapidly prompted the investigation into the mechanism of formation of such complexes. In general, four mechanistic possibilities are widely understood to give organometallic complexes using transition metals (Scheme **5**).[11, 29-30] There are alternate possibilities, where metals promote the reaction of a specific C–H bond without direct formation of a C–M intermediate (*vide infra*), however, whilst these are metal facilitated transformations they are not classed as 'true' C–H activation.[31]

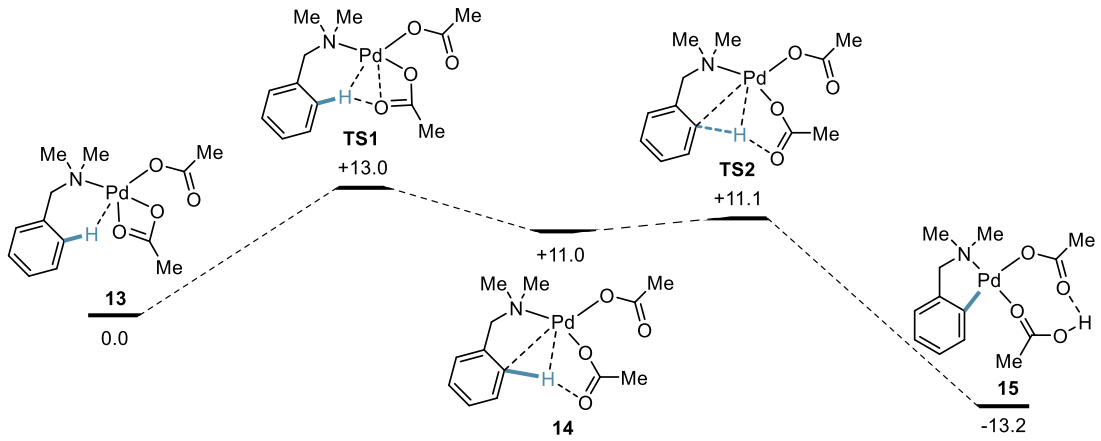


Scheme 5 | Common mechanisms for C–H activation

Oxidative addition of C–H bonds (Scheme **5a**) occurs for low valent and late transition metals, such as Re, Fe, Ru, Os, Rh, Ir and Pt.[11, 32] The coordinatively unsaturated metal centre will insert into C–H bonds forming the intermediate organometallic complex. Early transition metals with a d^0 electronic configuration (most commonly Sc, lanthanides and actinides) may undergo reversible σ-bond metathesis with external C–H bonds *via* a concerted four membered transition state (Scheme **5b**).[33-34] Late transition metals (Ir and Ru) undergo a two-step σ-bond metathesis process.[35] However, this process often consists of exchange of alkyl groups thus not giving net C–H activation. Electrophilic substitution of aromatic C–H bonds is common for electron deficient metal centres, such as Pd(II), Pt(II), Pt(IV), Hg(II) and Tl(III) which will undergo addition of an electron-rich π-system (Scheme **5c**).[36] This forms a formal positive charge on the π-system which is followed by re-aromatisation *via* deprotonation to return the M–C bond. Finally, concerted metalation deprotonation (CMD, sometimes termed ambiphilic metal ligand activation, AMLA) involves the carboxylate mediated C–H abstraction *via* a six membered transition state (Scheme **5d**).[37-38]

In 1985, Ryabov reported seminal studies on the mechanism of palladium-catalysed C–H activation with *N*,*N*-dimethylbenzylamine.[39-40] Ryabov showed that the Csp^2–H cyclopalladation of the amine with palladium acetate undergoes CMD to form a five membered palladacycle **15**. It was reported that dissociation of an amine ligand was necessary for the formation of a pseudo three coordinate palladium species **13** in which an acetate can bind in a bidentate fashion (κ^2) to saturate the binding sites of the square planar metal. In acetic acid, the rate determining step was hypothesised to be dissociation of multimeric palladium species to form complex **13**. Later, computational studies by Davies and co-workers showed that the key three coordinate complex **13** underwent a rate limiting rearrangement to the intermediate agostic complex **14** (Scheme **6**).[41-42] The formation of the agostic complex is associated

with a carbonyl oxygen de-ligation of the κ^2-acetate, which stabilises the polarised hydrogen (**TS1**) and allows coordination of the *ortho*-C–H bond.



Scheme 6 | Computed reaction profile for the C–H activation of *N*,*N*-dimethylbenzylamine with palladium(II) acetate[41]

Once the palladium intermediate **14** is stabilised by the agostic interaction, C–H activation is thought to proceed *via* a CMD mechanism.[37] The polarised C–H bond can form a hydrogen bond to the carbonyl oxygen atom of the ligated acetate, promoting CMD. Cyclopalladation occurs from the agostic complex **14** by a six membered transition state **TS2**, as Ryabov had suggested, with simultaneous deprotonation of the aryl group by the bound acetate and ligation of the deprotonated carbon to palladium. In chloroform, the Hammett slope of –1.6, as well as the primary kinetic isotope effect (KIE = 2.2), suggests that the *ortho*-palladation with an early transition state is the rate limiting step.[40] In order for the CMD mechanism to proceed, cyclopalladation has to occur in the same plane as the ligands, thus requiring the dissociation of the bidentate acetate (Figure **1**).[43] The free coordination site is occupied first by the C–H bond (agostic complex **14**, Scheme **6**) and finally by the activated carbon (complex **15**). Other computed mechanisms such as H^+ transfer to the adjacent acetate or oxidative addition of Pd(II) were found to be at significantly higher energies.[44]

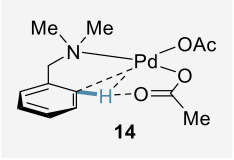
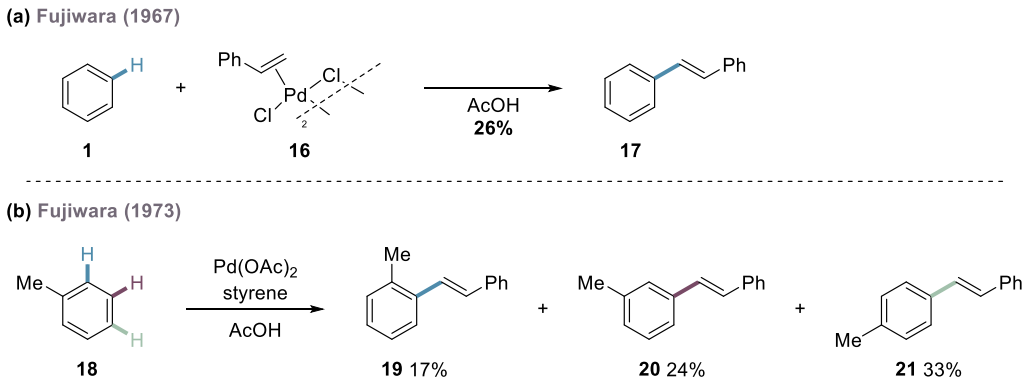


Figure 1 | Planar geometry of ligands around palladium centre

1.2 Palladium-catalysed Csp^3–H functionalisation

1.2.1 Early work

Following C–H activation, *C–H functionalisation* describes the transformation of the intermediate C–M bond to C–C/X bonds (X = N, O, S, halogen), to afford the functionalised product (Scheme **2**). In 1967, Fujiwara described the olefination of benzene, using stoichiometric palladium (Scheme **7a**).[45] Expecting acetoxylation of the olefin, Fujiwara and co-workers instead observed the C–H olefination product **17** when treating benzene **1** with styrene palladium complex **16**.[46] At the same time, and prior to the first report of the Mizoroki-Heck reaction, Heck reported the olefination of aryl mercurial salts.[47-48]



Scheme 7 | Early examples of C–H functionalisation by Fujiwara[45, 49]

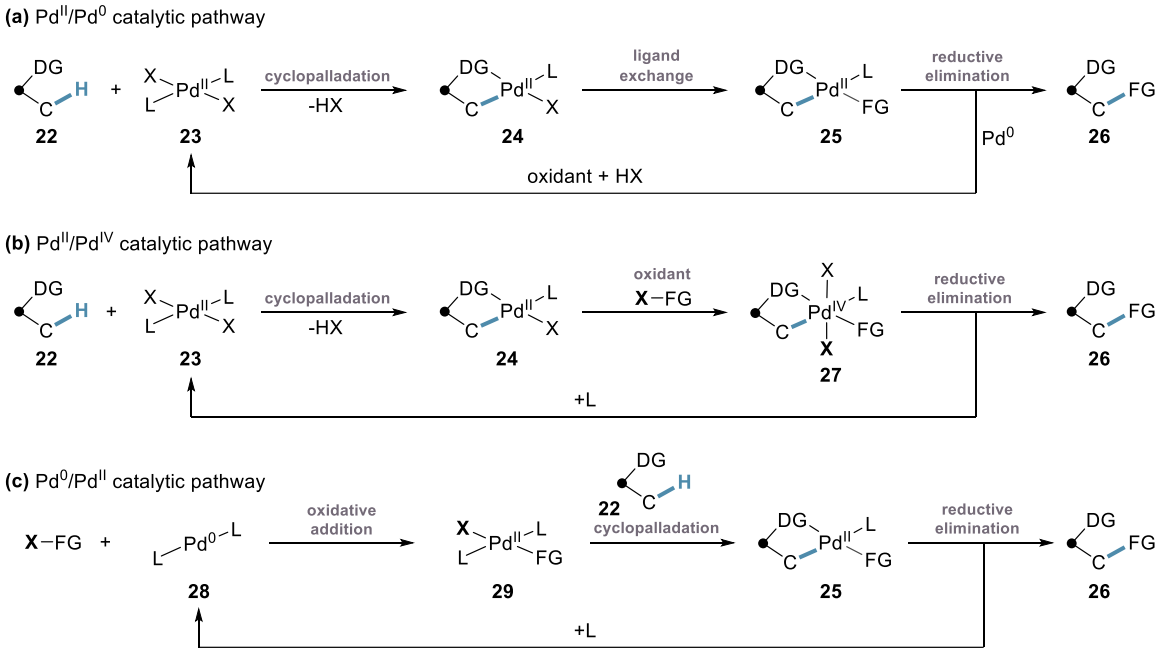
The unexpected olefination of benzene **1** prompted further studies on this unprecedented C–H functionalisation.[50] The observation that metallic palladium(0) formed during the reaction indicated a reductive elimination, which Fujiwara suggested occurred from a complex containing two σ-bound species resulting from C–H activation of both the arene and the olefin.[51] Subsequent studies showed that the C–C bond was furnished by carbopalladation of the olefin with an arene palladium complex.[52] Work by Davidson similarly demonstrated the association of palladium salts to benzene in polar solvents, to form complexes that underwent acetoxylation and biphenyl formation.[53-55] Addition of an external oxidant such as AgOAc or $Cu(OAc)_2$ rendered the reaction catalytic through oxidation of the resulting palladium(0) to palladium(II).[56] Additionally, transmetallation of pre-functionalised aryl mercurial salts (instead of the C–H activation of unfunctionalised arenes) could be used for olefination suggesting a mechanism similar to that of the Mizoroki-Heck reaction.[49]

Although the C–H olefination initially showed novel reactivity of palladium towards C–H bonds, reactions on substituted benzenes (such as toluene **18**) gave a mixture of regioisomers. The palladium catalyst employed was unable to control regioselectivity of C–H functionalisation resulting in an almost statistical mixture of olefinated products (**19**, **20** and **21**, Scheme **7b**).[57] Fundamentally, the undirected or non-chelate-assisted C–H functionalisation of arenes tend to be controlled by steric and electronic factors which are intrinsic to a specific substrate, making it difficult to overcome inherent selectivity.[58]

1.2.2 Mechanism of Csp^3–H functionalisation

After the preliminary reports of C–H functionalisation and early work on the mechanism of C–H activation, the synthetic chemistry community turned their attention towards understanding the mechanism of functionalisation. Early work highlighted that the selectivity of aliphatic C–H activation was largely dominated by sterics and followed the trend primary>secondary>>tertiary Csp^3–H bonds, offering distinctly different reactivity to other Csp^3–H functionalisations such as those involving metallocarbenoids.[59-60]

During C–H functionalisation reactions, palladium is known to undergo three distinct catalytic pathways between its most stable oxidation states (0, II and IV).[7, 61] The three pathways have characteristic redox states that interconvert by 2 e^- oxidation/reduction (Scheme **8**). In all three pathways, the C–H activation event takes place at the most stable oxidation state of 2+.[1] While there are some instances where Pd(I) and Pd(III) complexes have been observed, it is yet to be determined how fundamental they are for catalysis.[62]



Scheme 8 | Possible pathways for C–H bond functionalisation

The Pd(II)/Pd(0) pathway commences with C–H activation at the Pd(II) oxidation state, to form a cyclopalladated Pd(II) complex **24**. Subsequent ligand exchange (complex **25**) and reductive elimination yields the functionalised product **26** and returns Pd(0), which is oxidised to render this process catalytic (Scheme **8a**). Stahl has demonstrated the mild re-oxidation of Pd(0) to Pd(II) utilising molecular oxygen.[63] The Pd(II)/Pd(IV) pathway also begins with the C–H activation by Pd(II) salt **23**, which results in the formation of palladacycle **24** analogous to Scheme **8a**. An oxidant then delivers the functional group (FG) to the palladium centre, oxidising it to the palladium(IV) complex **27** in the process. Reductive elimination from the high valent palladium complex **27** yields the functionalised

product **26** and the initial Pd(II) salt **23** (Scheme **8b**). The formation of Pd(IV) is analogous to the Pt(IV) intermediate observed in Shilov chemistry, shown to be competent for catalytic C–H functionalisation.[64-66] Finally, the Pd(0)/Pd(II) redox pathway starts with oxidative addition of an appropriate substrate to a Pd(0) complex **28**, forming a Pd(II) complex **29** containing the desired FG. This complex undergoes a ligand exchange with the substrate and, after cyclopalladation, affords the Pd(II) complex **25** from which reductive elimination takes place to regenerate the catalytically active Pd(0) (Scheme **8c**). This pathway is analogous to traditional cross-coupling chemistry where palladium enters the catalytic cycle *via* oxidative addition.[67]

1.2.3 Amine directed Csp^3–H functionalisation

As discussed in *section 1.1.2*, for substrates where several bonds can undergo C–H bond cleavage, the selectivity of functionalisation is a key issue to overcome. More recent literature examples rely on directing groups to control the selectivity of the C–H activation processes as they often pre-arrange substrates favourably for activation.[68-69] Ligation of a directing group to the palladium centre controls selectivity by increasing the effective concentration of the appropriately placed C–H bond at the metal. Similarly, the directing group can stabilise the palladium metal by chelation. Better understanding of these kinetic and thermodynamic effects, can overcome the limitations faced with cyclometallation, to enable more challenging C–H activation events.[25, 70]

The success of alkaloids (natural products containing a basic nitrogen) and their derivatives as drugs, is often attributed to their ability to engage with biological targets.[71] Consequently, aliphatic amine moieties (nitrogen bearing only *H* or *alkyl* groups) are some of the most common functional groups found in drugs or pre-clinical candidates. Around 40% of FDA approved small molecule-drugs or drug candidates contain an aliphatic amine (Figure **2**).[5, 72] Favourable pharmacokinetic characteristics, as well as their contribution to efficacy through specific target interactions, make amines extremely powerful in drug discovery.[73] Their ability to cross the blood-brain barrier has also popularised amine moieties in molecules aimed to treat central nervous system (CNS) disorders.[74] Although there are numerous robust methods for C–N bond formation, the need for complex amines means the development of new catalytic methods for their synthesis is of substantial value.[75] The C–H activation of aliphatic amines thus offers a powerful technique for the diversification and synthesis of complex amine scaffolds.[76]

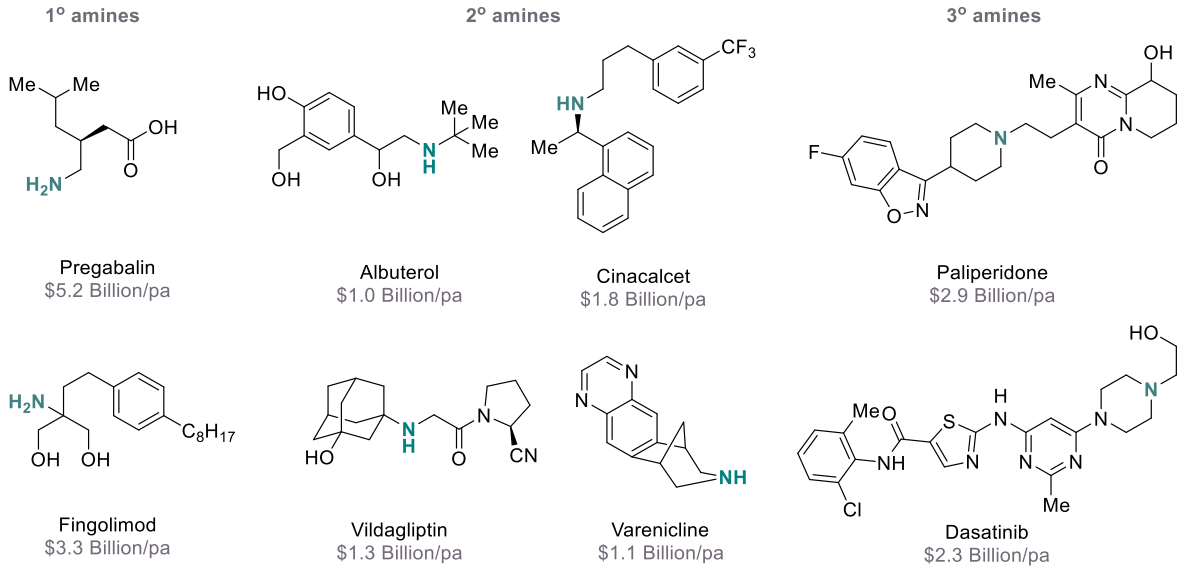
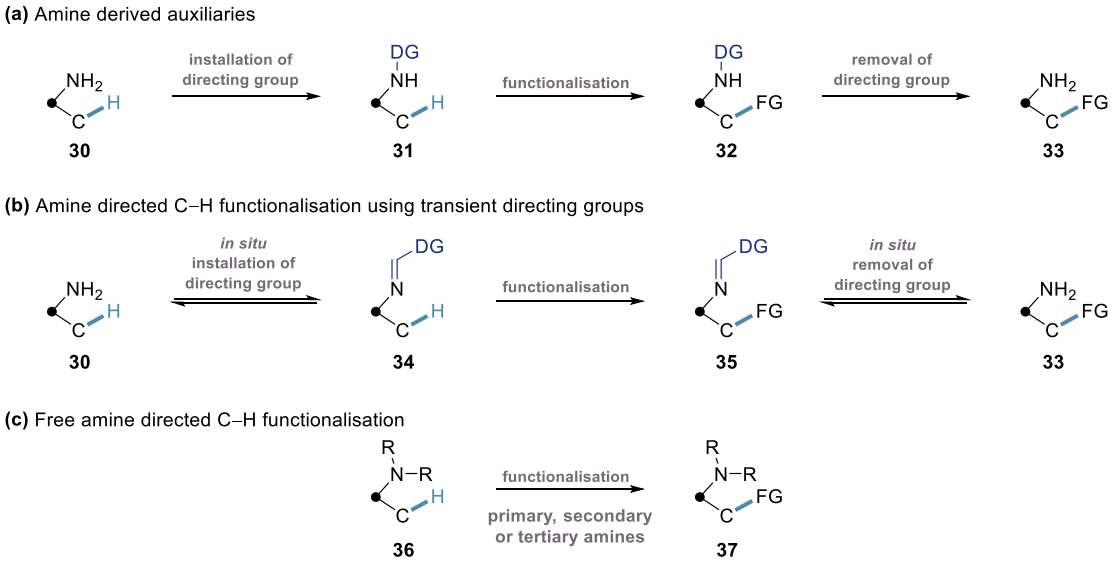


Figure 2 | Select drugs bearing aliphatic amine moieties, sales per annum (2018)[72]

To date, there are three common directing strategies to control the selectivity of functionalisation for aliphatic amines. These include the use of auxiliaries (Scheme **9a**), installed especially to facilitate C–H activation, transient directing groups (Scheme **9b**) that form directing groups *in situ* and native directing groups (Scheme **9c**) where pre-existing functionality is utilised for directing the C–H activation process. As this thesis will focus on results for amine directed Csp^3–H functionalisation, any further discussion of the literature will be limited to examples of amine-based auxiliaries, transient directing groups and native amines as directing groups.

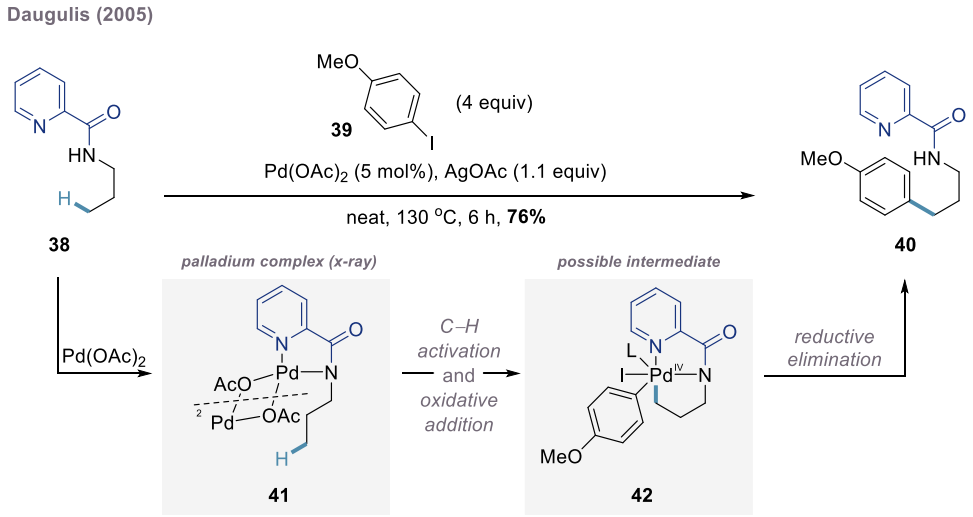


Scheme 9 | General C–H functionalisation processes for: **(a)** an amine derived auxiliary; **(b)** a transient directing group; **(c)** a native amine directed functionalisation

1.2.3.1 Amine derived auxiliaries

Auxiliary-based directing groups are installed specifically to facilitate C–H activation and functionalisation by ligating a palladium centre. Auxiliaries aim to stabilise the complex during C–H activation; they remain intact during the functionalisation and allow reversible coordination to the metal.[68] Auxiliaries tend to have very specific structures often allowing multidentate ligation but are not desired in the final product, therefore additional step(s) for the removal of the directing group are often required for these C–H functionalisation strategies (Scheme **9a**).

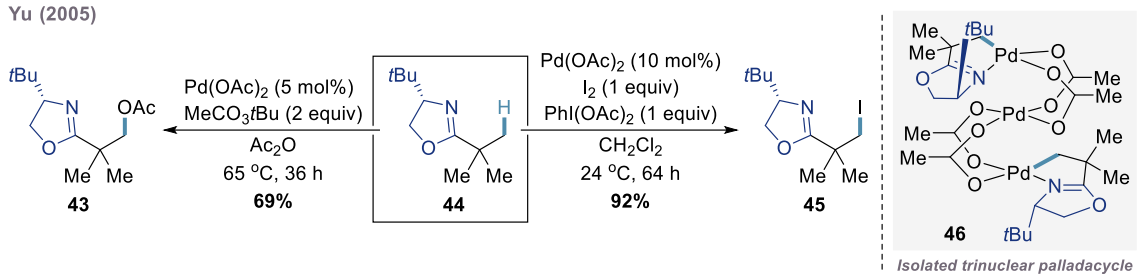
The seminal work concerning palladium-catalysed aliphatic C–H functionalisation was reported by Daugulis in 2005 (Scheme **10**).[77] Installation of a picolinamide group on the primary amine substrate (**38**) formed a bidentate auxiliary, permitting ligation of the metal centre by a neutral (pyridine) and charged (amido) group. High yields of arylation products (54-92%) were achieved for both the 8-aminoquinoline and picolinamide directing groups. The arylation of aliphatic C–H bonds proceeded efficiently and tolerated bromide, formyl and methoxy-arenes. The initial palladium complex **41** comprised of substrate **38** and palladium(II) acetate was characterised by X-ray crystallography. Cautious discussion of mechanism and invoking of intermediate **42** is based on the prior work of Canty, in which expeditious reductive elimination from Pd(IV) complexes was observed.[78] Further studies by Daugulis confirmed the proposed Pd(II)/Pd(IV) mechanistic pathway for this picolinamide directed Csp^3–H arylation.[79]



Scheme 10 | Daugulis' palladium-catalysed, picolinamide directed arylation of aliphatic C–H bonds[77]

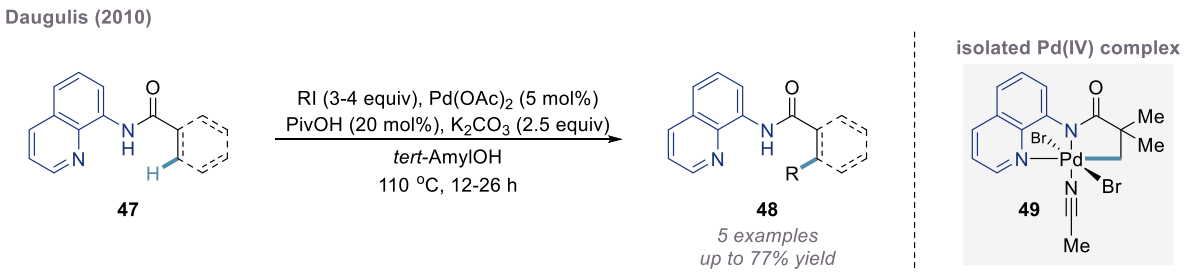
Subsequently, Yu and co-workers reported the elegant iodination and acetoxylation in back-to-back publications using an oxazoline directing group (Scheme **11**).[80-81] Although not an amine, this nitrogen based directing group was another very early example of directed Csp^3–H functionalisation. The iodination of oxazoline **44** proceeded in very high yields to give γ-iodinated product **45**. Secondary C–H bonds on cyclopropanes have likewise been shown to undergo this functionalisation. During the reaction, PdI_2 precipitation was observed and this species was found to be catalytically inactive. The

$PhI(OAc)_2$ oxidant was found to convert PdI_2 back to its active acetate form. Trinuclear palladacycle **46** was isolated exclusively in the *anti*-configuration (with *tert*-butyl groups on the convex face) and was shown to rapidly iodinate to form alkyl iodide **45** upon addition of iodine. The acetoxylation reaction afforded acetoxylation products such as **43**, using a mild peroxide oxidant in order to achieve C–H oxidation. The transformation tolerated esters, chloride and protected alcohols, and utilised a readily available oxidant in $MeCO_3tBu$. Prior studies using TBHP and benzoyl peroxide oxidants had demonstrated the facile oxygenation of Pd–C bonds, and the oxidation of palladium(II) complexes to palladium(IV).[82-83] Acetic anhydride was found to be crucial for the catalytic reaction, as no oxidative addition was found to occur without it. The rapid acetate exchange observed with the trinuclear complex **46** suggested the anhydride drives the fragmentation to a monomeric complex, believed to undergo the required oxidation. Further computational studies by Houk and Yu showed the iodination to be diastereoselective, which proved consistent with experimental results.[84]



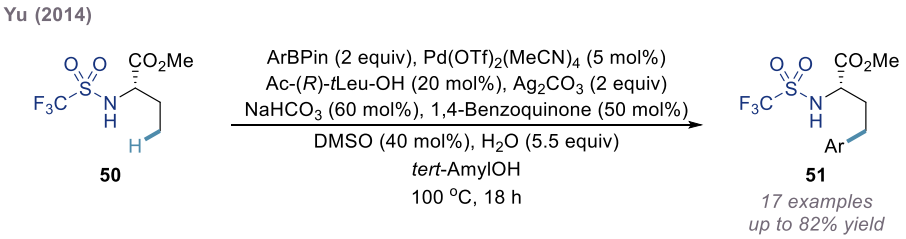
Scheme 11 | Oxazoline directed functionalisation of aliphatic C–H bonds by Yu[80-81]

In 2010, Daugulis reported the alkylation of aliphatic C–H bonds using the 8-aminoquinoline directing group (Scheme **12**).[79] This directing group is closely related to the picolinamides reported by Daugulis in 2005 (Scheme **10**).[77] The dual anionic and neutral binding mode of the bidentate directing group (**47**) stabilises the intermediate palladacycle complex through σ-donation. Remarkably, treatment of the intermediate palladacycle(II) with elemental bromine resulted in the formation of alkylpalladium(IV) complex **49**, which is the first example of a crystallographic characterisation of an alkylpalladium(IV) dibromide. The ligand stabilises the Pd(IV) oxidation state, allowing isolation of the complex as well as efficient catalysis through a Pd(II)/Pd(IV) mechanism. Kinetic studies on the isolated palladacycles demonstrated that these were able to turn over, showing that these are competent catalytic intermediates.



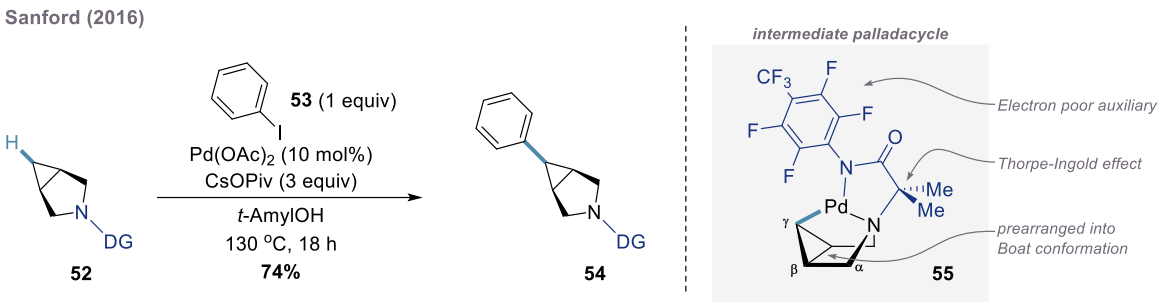
Scheme 12 | 8-Aminoquinoline directed alkylation of Csp^2/sp^3 bonds using alkyl iodides[79]

In 2014, Yu reported the arylation of Csp^3–H bonds using a triflimide directing group (Scheme **13**).[85] The amino acid-derived ligand is crucial to the success of the reaction and no background reaction is observed without it. It was found that the (*R*)-enantiomer of the amino acid ligand performed better than the (*S*)-enantiomer (65% vs 46%) for the arylation of protected (*S*)-amino acid **50**, supporting matching and mismatching of chiral substrate and ligand. Overall, electron rich aryl boronic ester coupling partners gave slightly lower yields, while esters, halides and ethers were well tolerated, giving good to excellent yields of arylation product **51**.



Scheme 13 | Triflimide directed arylation of amino acid derivatives by Yu[85]

In 2016, Sanford reported a transannular C–H arylation on aliphatic amines with aryl iodides, employing bridged nitrogen heterocycles such as alicyclic amine **52** (Scheme **14**).[86] The auxiliary bearing the fluorinated heterocycle used by Sanford, was easily installed by simple alkylation and subsequently removed by samarium iodide-mediated reductive cleavage. The g*em*-dimethyl groups on the auxiliary force palladium into close proximity to the γ-C–H bond *via* the Thorpe-Ingold effect (**55**).[87-88] With careful selection of amine substrates, the prearrangement of the scaffolds into the required boat formation was ensured, promoting activation of the methylene γ-C–H bonds. The increased *s*-character of cyclopropane C–H bonds (making them more olefin-like), ensure that these are more easily activated to form arylation product **54**.[80] Sanford and co-workers also demonstrated the use of bromobenzene (20 equiv) as an oxidant to give the desired arylated alicyclic amine in 14% yield. In the presence of silver salt a significant proportion of an aminal side product was recovered, presumably *via* α-oxidation of the tertiary amine and intramolecular trapping of resultant iminium by the pendant amide nitrogen. Fortuitously, replacement of the silver salt with a non-oxidising metal carboxylate (CsOPiv) suppressed the formation of the aminal side product. DFT studies by Zimmerman, showed the presence of caesium pivalate to play a critical role in enabling oxidative addition (by sequestering previously ligated acetic acid) as well as iodide abstraction (for catalyst regeneration).[89] Through the study of model complexes, it was observed that Csp^3–H activation occurred reversibly and at temperatures as low as 40 °C.[90] Follow up work by Sanford disclosed a second generation catalyst which allowed the arylation of the previously incompatible tropane core. Improved catalytic turnover was observed by employing pyridine and quinoline carboxylate ligands.[91] Kinetic studies showed that the addition of these ligands limited product inhibition and slowed catalyst decomposition.

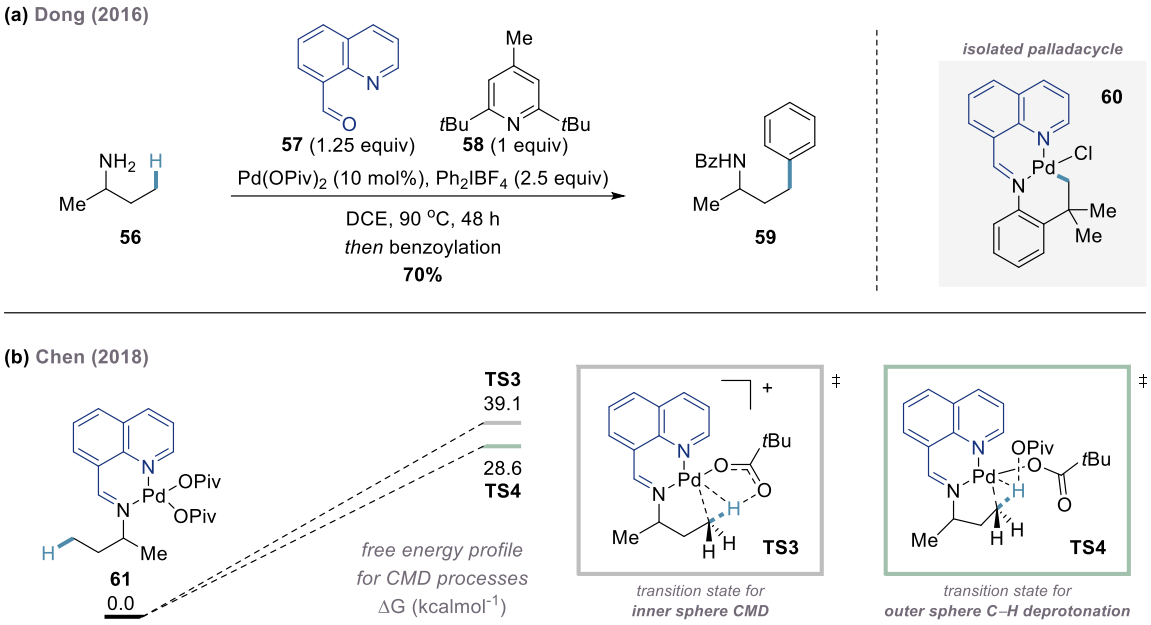


Scheme 14 | Sanford's transannular arylation of alicyclic amines using a fluorinated directing group;[86] DG = $C(Me)_2CONC_7F_7$

1.2.3.2 Free amine directed functionalisation using transient directing groups

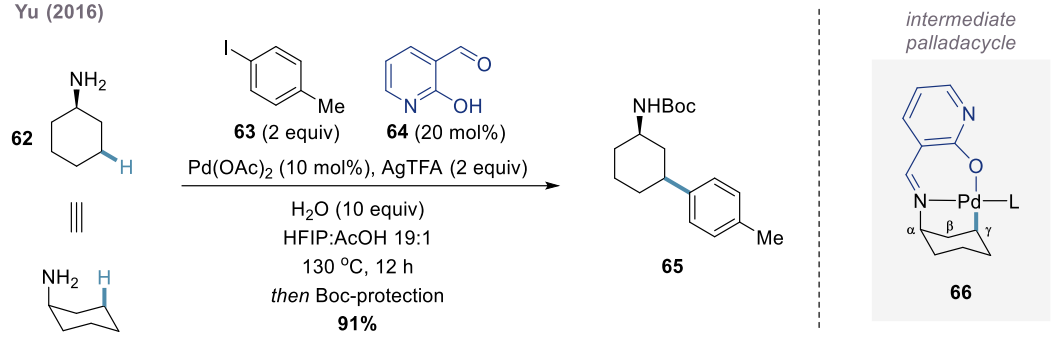
Transient directing groups direct and enable C–H functionalisation but are formed *in situ*. For amines, transient directing groups are generated by reversible reaction of the amine moiety on the reacting molecule and an external, organic catalyst. The functionality formed may then interact with the palladium centre to direct C–H activation. The benefit of this approach is that the directing group is sufficiently labile, therefore not requiring formal preinstallation or removal. Concomitantly, transient directing groups may even be used in sub-stoichiometric quantities.

In 1997, Jun reported the first C–H activation using a transient directing group in the rhodium catalysed functionalisation of aldehydes with terminal alkenes.[92-93] However, the use of palladium in such C–H functionalisations was only reported in 2016, when Dong demonstrated the functionalisation of primary aliphatic amines enabled by 8-formylquinoline **57** (Scheme **15a**).[94] In this work, the super stoichiometric amount of transient directing group **57** condenses with the primary amine substrate **56** furnishing an aromatic imine. This neutral bidentate directing group facilitates ligation to the palladium centre, providing the required proximity for C–H activation. The mechanism was studied using DFT calculations, which showed that the C–H activation occurred *via* an outer sphere C–H deprotonation (**TS4**, Scheme **15b**) rather than the inner sphere CMD (**TS3**) which would be required to occur from a cationic palladium complex.[95] Although this reaction requires a glovebox and activated iodonium salts for the oxidation, it afforded good yields for the arylation of aliphatic γ-C–H bonds on a range of substrates.



Scheme 15 | **(a)** Dong's arylation of primary amines using an 8-formyl quinoline directing group **57**;[94] **(b)** Chen's computational mechanistic analysis of the arylation of aliphatic primary amines[95]

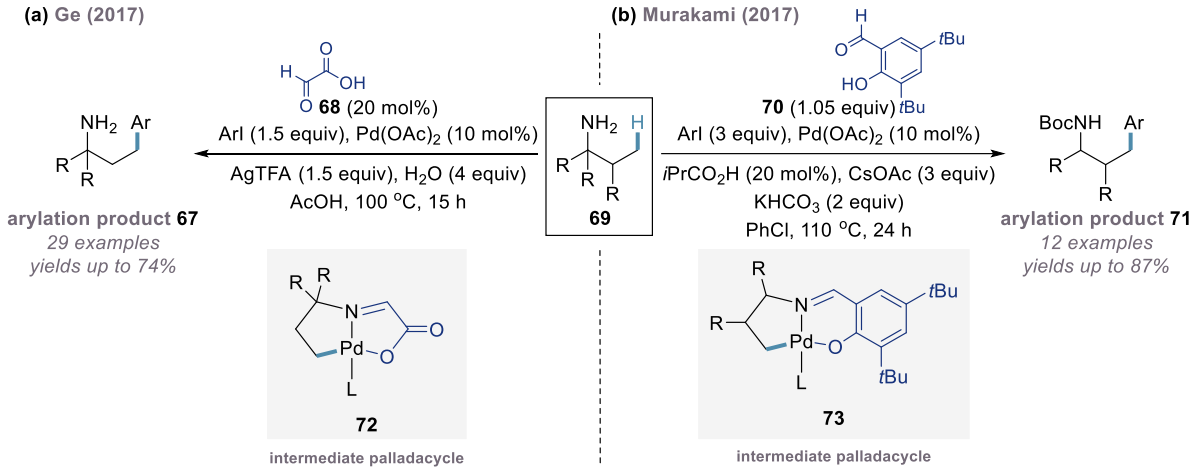
Similarly, Yu presented the arylation of aliphatic primary amines in 2016 (Scheme **16**).[96] Using 3-formyl-2-hydroxypyridine **64** as a directing group, Yu postulated that the condensation with the primary amine **62** would form an intermediary imine which undergoes selective γ-C–H activation to form the arylated product **65**. During the reaction, the hydroxy group was deprotonated to afford a bidentate chelate, which formed intermediary [5,6]-palladacycle complex **66**. Favourable imine equilibrium conditions meant that catalytic quantities of the transient directing group **64** could be employed for the arylation. The condensation of the directing group with the primary amine inhibited strong, monodentate binding to the palladium catalyst, which would forego any possible catalytic turnover. Moreover, the reaction is able to perform arylation of both primary and more hindered methylene C–H bonds.



Scheme 16 | Yu's arylation of primary amines using transient directing group **64**[96]

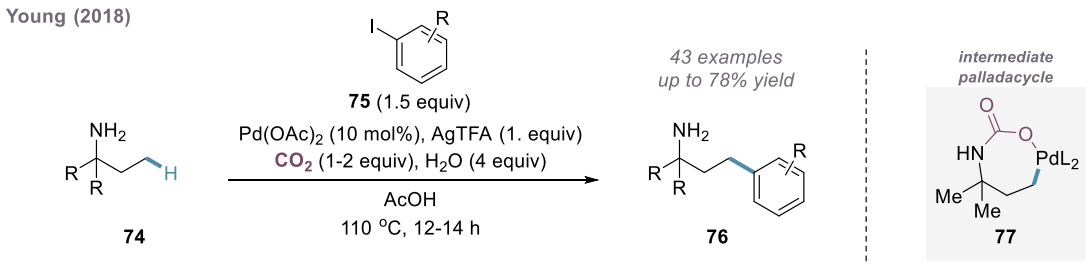
In 2017, Ge and Murakami independently reported examples of transient directing groups to facilitate the arylation of primary aliphatic amines **69** and furnish arylated amine products **67** and **71** (Scheme **17**).[97-98] In both examples, the process is proposed to go *via* a Pd(II)/Pd(IV) mechanism where the aryl iodide coupling partner acts as the oxidant, oxidising the respective palladacycles **72** and **73** to

palladium(IV). Although Ge presents significantly more examples of arylation, an α-tertiary amine centre is required for the transformation, and only minor amounts of product are observed with α-hydrogen substitution. On the other hand, Murakami's procedure tolerates α-hydrogens presumably because super stoichiometric amounts of the transient directing group **70** are pre-mixed with the amine starting material, therefore making it less prone to deleterious α-oxidation.



Scheme 17 | Arylation of primary amines by **(a)** Ge using glyoxylic acid **68**; **(b)** Murakami using aryl aldehyde **70**[96, 98]

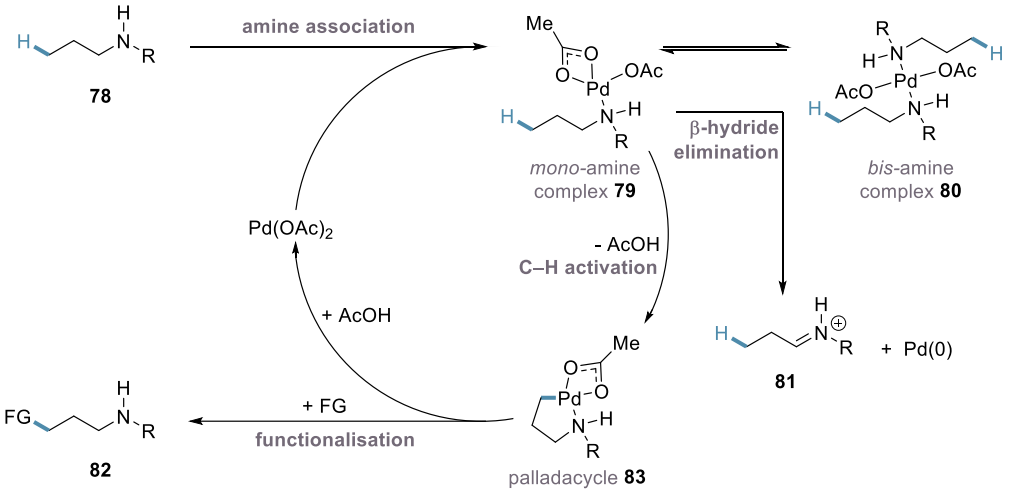
An innovative approach was taken by Young in the arylation of primary amines (Scheme **18**).[99] Inspired by the work of Larrosa, utilising carbon dioxide as a traceless directing group in the functionalisation of phenols, the authors reasoned that this approach would be amenable to primary aliphatic amines.[100] Solid carbon dioxide was added to the reaction in order to mediate the functionalisation of amines **74** to their γ-arylated products **76**; They observed very good yields and were able to tolerate secondary amine substrates, as well as substrates with α-hydrogen atoms, which are known to undergo decomposition through competing α-oxidation processes. It was reasoned that carbon dioxide formed a transient carbamate (**77**) with amine **74**, acting not only as a directing group, but also as a protecting moiety. Control reactions showed that the treatment of primary amine **74** (R = Me) with carbon dioxide gave isolatable salts (mixture of protonated amine and carbamate anion), which resulted in good yields for the arylation product in the absence of additional carbon dioxide.



Scheme 18 | Primary amine arylation using a CO_2 mediated transient directing group strategy[99]

1.2.3.3 Free amine directed C–H functionalisation

The use of native functionality to direct palladium-catalysed C–H activation requires no pre-installation of directing groups. Rather it utilises pre-existing functionality within a molecule to achieve C–H functionalisation. This is especially challenging with amines, however, as they are very strong binders to palladium and therefore do not always make the best substrates for catalytic transformations.[101]

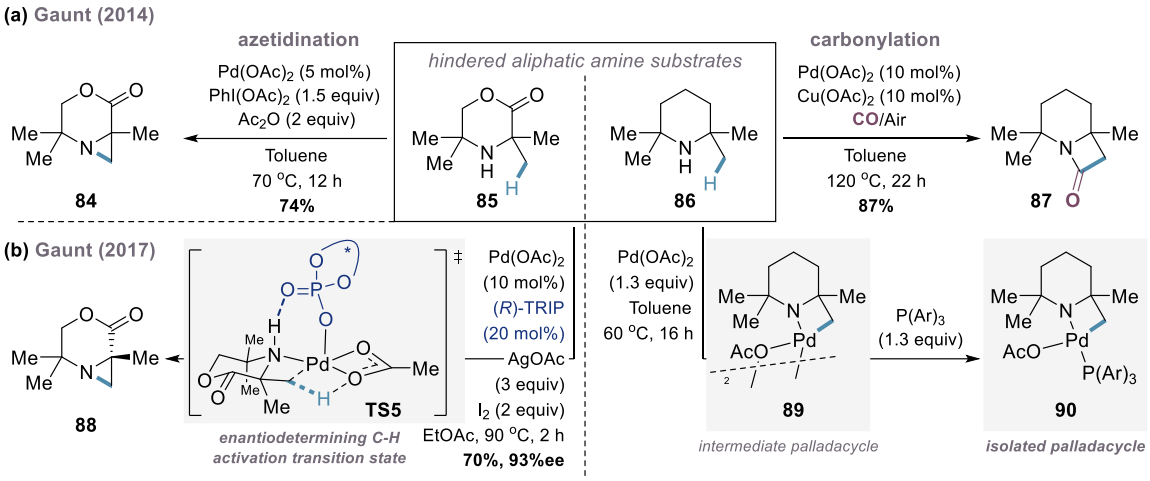


Scheme 19 | General process for free amine directed Csp^3–H functionalisation

In general, association of the amine **78** to the palladium(II) acetate catalyst forms a *mono*-amine complex **79** (Scheme **19**). This species can undergo C–H activation by CMD to form the palladacycle **83**, and further functionalisation furnishes the derivatised product **82**. There are two issues associated with amine directed C–H activation. Firstly, the ligation of amines to the palladium centre is facile. The amine functionality has high affinity for palladium, therefore two amine containing molecules can ligate the palladium centre. The resultant species, *bis*-amine complex **80**, is an off-cycle complex with the palladium centre coordinatively saturated and therefore unable to perform the C–H activation. The formation of such complexes precludes C–H activation by occupation of the binding site on the metal required for C–H bond association. The second issue is that β-hydride elimination from *mono*-amine complex **79** is irreversible and leads to amine decomposition (forming iminium **81**).

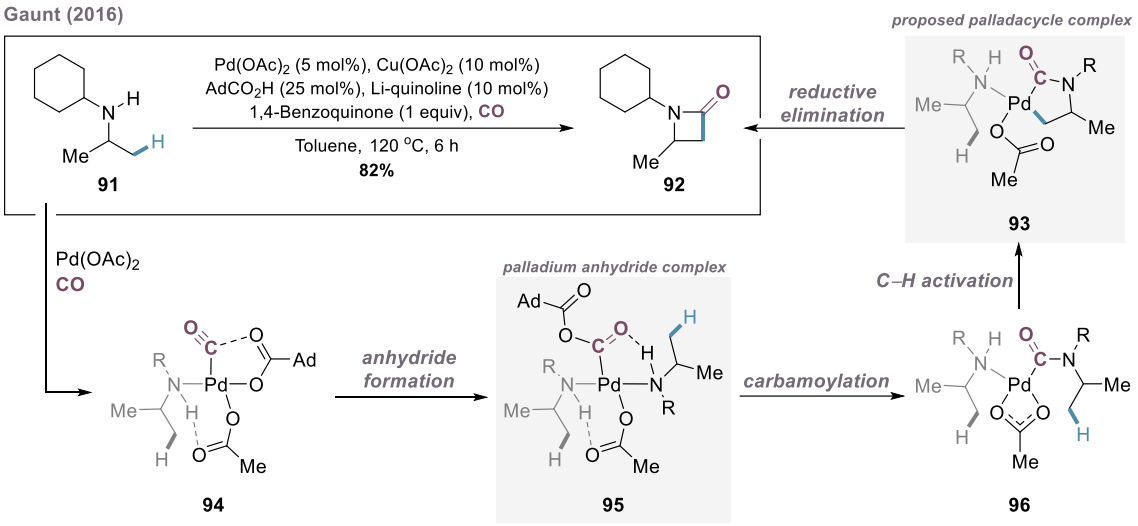
Steric factors can be used to both destabilise the *bis*-amine complex and entirely remove the problem of β-hydride elimination. In 2014, Gaunt and co-workers presented the first publication on native amine-directed, aliphatic C–H functionalisation (Scheme **20a**).[102] Here, they demonstrated the functionalisation of a fully α-substituted cyclic amine substrate, disclosing not only C–H amination of morpholinone **85** to give a variety of aziridine products such as **84**, but also the carbonylation of TMP **86** forming β-lactam motifs such as **87**. Notably, for the aziridination of morpholinone **85**, this occurred solely on the side of the ester presumably due to subtle stereo-electronic effects, with no activation of the distal *gem*-dimethyl being observed. Further investigation of the mechanism identified a key hydrogen bond between the palladium bound acetate and ligated amine (N–H) proton.[103-104] Exploiting

this interaction allowed the development of an enantioselective aziridination reaction by replacement of an achiral acetate with a chiral phosphoric acid (**TS5**, Scheme **20b**).[105] The DFT analysis of the rate limiting C–H activation transition state **TS5**, showed the enantioenriched ligand imparting a chiral environment on the complex due to the formation of the aforementioned key hydrogen bond.[106-107]



Scheme 20 | Seminal work by Gaunt on the functionalisation of aliphatic amines;[103] (*R*)-TRIP = 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate; Ar = tris(3,5-bis(trifluoromethyl)phenyl)phosphine

The carbonylation of secondary amine substrates was reported by Gaunt in 2016 (Scheme **21**).[108] Simple aliphatic amines were carbonylated in very good yields to furnish β-lactams. Failure to isolate a four membered palladacycle, observed in the functionalisation of hindered amines (**90**, Scheme **20a**), suggested that this reaction proceeded with an alternative mechanism.[102] In 1983, Moiseev observed the reduction of palladium(II) acetate with carbon monoxide to give elemental palladium and acetic anhydride.[109] To confirm the Pd(II)/Pd(0) catalytic cycle, a series of stoichiometric and DFT studies were conducted. Ligation of the amine and carbon monoxide yielded complex **94**, which by DFT showed a non-trivial interaction between the carbonyl and the carbon monoxide. This eventually resulted in the formation of anhydride complex **95**, from which attack of the amine at the proximal carbonyl (the bulky adamantyl disfavouring distal attack) forms a palladium carbamoyl complex **96**. Reversible Csp^3–H activation of **96** furnishes the non-traditional palladacycle **93**, from which benzoquinone driven reductive elimination occurs. The authors present the compatibility of the reaction conditions with 44 substrates bearing a range of functionality with yields of up to 89%. In follow up work, the group also disclosed the carbonylation of methylene C–H bonds in good yields.[110-111]



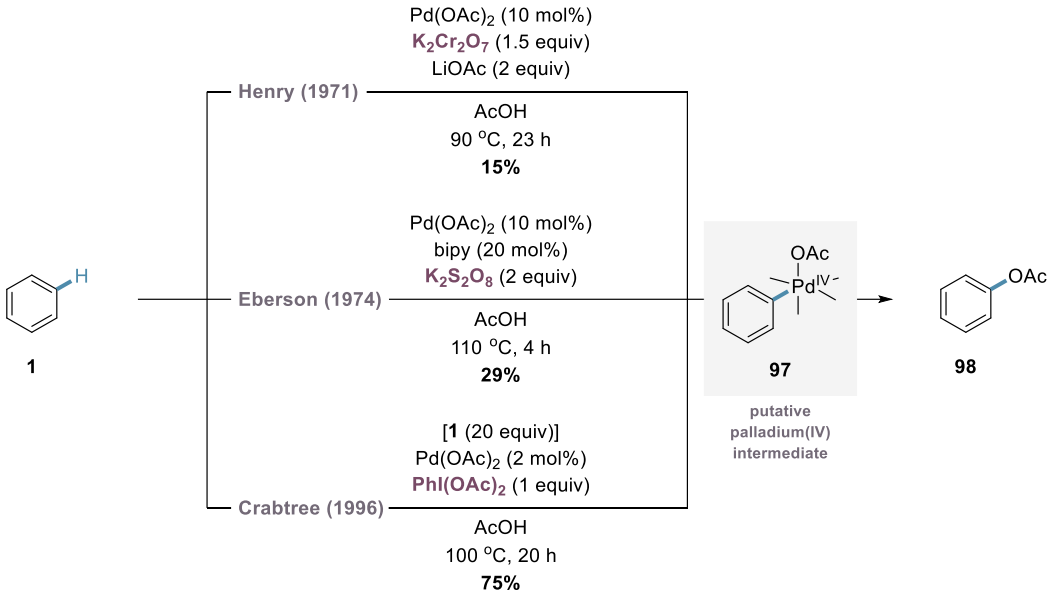
Scheme 21 | Carbonylation of secondary amines using carbon monoxide[108]

1.3 Palladium-catalysed Csp^3–O bond formation

The formation of Csp^3–O bonds from unactivated Csp^3–H bonds allows the construction of densely functionalised molecules that would usually be difficult to synthesise using any other methodology. The selective oxidation of remote C–H bonds is especially powerful for the exploration of SAR during the late stage functionalisation of drug-like molecules, or for the synthesis of drug metabolites formed by P450 enzymes.[112] The following section will present an overview of Csp^3–O bond formation; from early examples, to studies of mechanism and examples of native aliphatic amine directed acetoxylation. Although the C–O bond formation can occur from a range of oxygen sources the most commonly used moiety is acetate, therefore the term *acetoxylation* is often used to describe the C–O*Ac* bond formation.

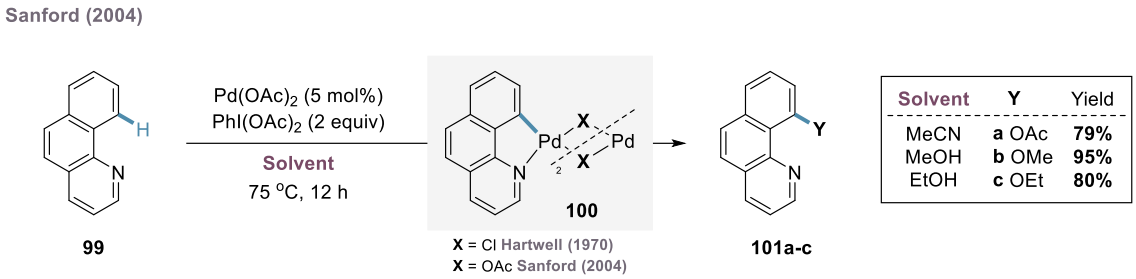
1.3.1 Early work

The earliest work on the palladium-catalysed acetoxylation of C–H bonds was reported in the 1970's by Henry and Eberson.[113-114] These reactions demonstrate the acetoxylation of benzene **1** to form phenyl acetate **98** (Scheme **22**). The report by Henry suggests that the oxidant is involved in the conversion of the palladium(II) species to the, at that time, elusive palladium(IV) complex **97** (the first report of an isolated palladium(IV) complex was in 1986).[113, 115] Furthermore, Eberson used a 2,2-bipyridine ligand and persulfate oxidant to give exceptionally clean acetoxylation reactions, yet only low yields of product **98** (29%) were observed.[114] In 1996, Crabtree employed a non-metal oxidant ($PhI(OAc)_2$) in combination with excess benzene, to observe significant increase in yield.[116] Kinetic analysis showed C–H activation to be rate limiting (KIE = 4.1), and zero-order with respect to the $PhI(OAc)_2$ oxidant. These studies laid the foundation for subsequent work that focused on developing reactions for more complex substrates.



Scheme 22 | Early examples on undirected benzene acetoxylation by Henry, Eberson and Crabtree[113-114, 116]

Building on the directing group free acetoxylation (Scheme **22**), as well as the studies on the formation of palladacycles, Sanford developed a catalytic directed acetoxylation reaction, in which heterocycle **99** was selected due to its propensity to form 5-membered palladacycle **100** under mild conditions (Scheme **23**).[27, 117] Remarkably, the acetoxylation of **99** to form heterocycle **101a** is reported alongside the formation of other C–O bond products (**101b-c**) that are exclusively formed through switching to the appropriate protic solvent. Sanford and co-workers proposed an intermediary palladium(IV) complex, from which the authors propose that C–O bond forming reductive elimination can occur *via* two pathways: a S_N2 process or intramolecular reductive elimination. Although there is precedent for C–O bond formation *via* a S_N2 process, these examples are reported on aliphatic or allylic carbon atoms and are geometrically unlikely for substrate **99**.[118-119] On the other hand, intramolecular reductive elimination to form C–O bonds has been observed Hartwig for the palladium(II) catalysed, and by Hillhouse for the nickel(III) catalysed, etherification of arenes.[120-121] In a further publication, Sanford also showed the acetoxylation of Csp^3–H bonds by employing oximes as directing groups.[122]



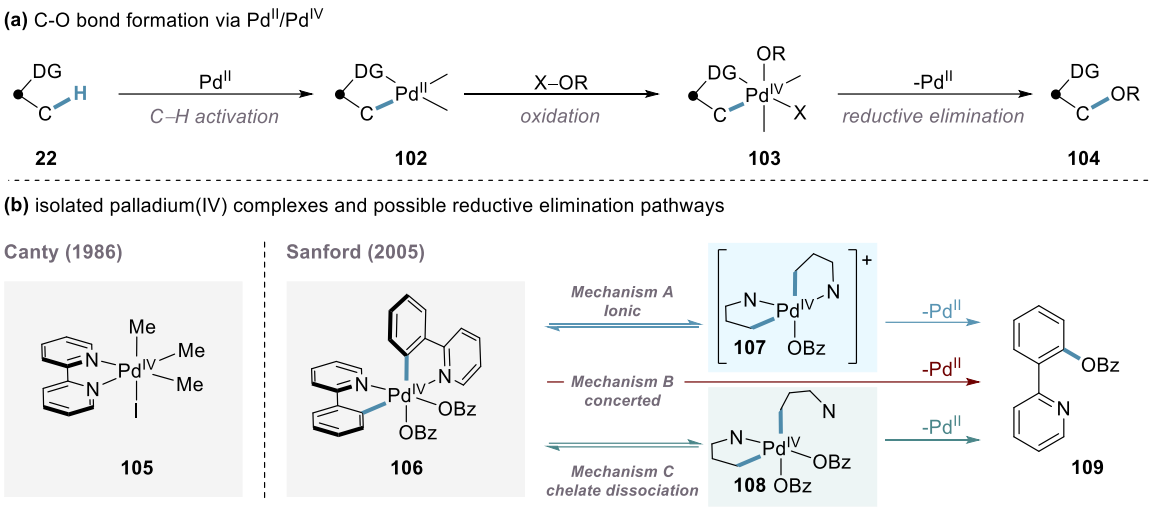
Scheme 23 | Nitrogen directed C–O bond formation as described by Sanford[117]

Generally, it was believed that the reaction proceeded through the following elementary steps (Scheme **24a**): directed C–H activation of the substrate **22**; oxidation of the cyclometallated palladium(II) complex **102** to the palladium(IV) complex **103**; and reductive elimination to give the C–O bond product **104**. More detailed mechanistic studies were subsequently completed by Sanford (*vide infra*).

1.3.2 Mechanism of reductive elimination in the formation of C–O bonds

Pioneering organometallic work on palladium complexes by Canty, revealed the first organometallic palladium(IV) complex **105** by oxidative addition of methyl iodide to a palladium(II) complex (Scheme **24b**).[115] Although this species was not stable at room temperature (rapidly eliminating ethane when warmed), it offered the first chance for the study of individual parts of the mechanism.[123] Previous studies by Canty on complex **105**, evoked the intermediacy of a cationic palladium(IV) intermediate in both oxidative addition and reductive elimination for C–C products, suggesting that both might be stepwise processes.[124-125] Despite the abundance of reports of palladium-catalysed C–O bond formation reactions, it was not until 2005 that the mechanism for this transformation was studied in detail.[126]

Sanford and co-workers reported the synthesis of surprisingly stable palladium(IV) complex **106** in 2005 (Scheme **24b**).[126] Selection of 2-phenylpyridine ligands ensured rigid, bidentate binding with strong σ-donating aryl groups to stabilise the high valent metal. The isolation and stability of this complex allowed the first thorough mechanistic study of C–O reductive elimination processes from high valent palladium. Sanford proposed three possible reductive elimination mechanisms from high valent complex **106**, which were investigated through DFT calculations and kinetic studies.[127-128]



Scheme 24 | **(a)** Generic C–H acetoxylation mechanism; **(b)** Seminal studies on the isolation of palladium(IV) complexes and possible reductive elimination pathways[7, 115, 126]

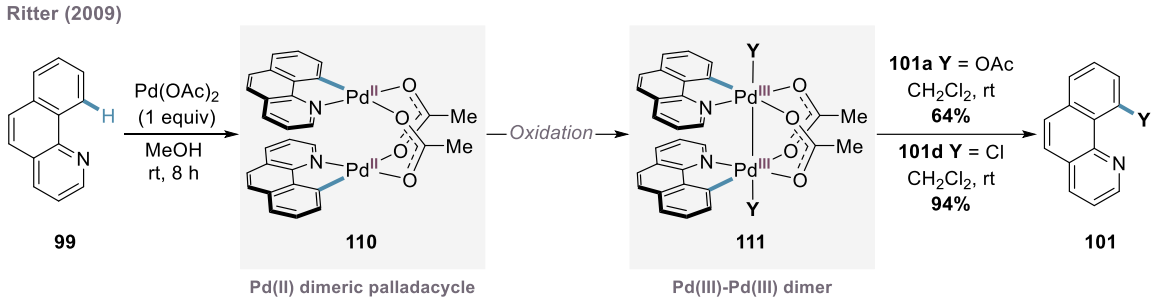
The three general mechanisms for reductive elimination from neutral high valent palladium complexes are shown in Scheme **24b**. There are two additional, highly unlikely possibilities, one being the homolytic cleavage of the C–Pd bond suggesting a radical mechanism and the other a heterolytic cleavage to form a carbocation.[129]

Mechanism A (*ionic* or *dissociative ionic*) exhibits dissociation of an anionic ligand to give an intermediary cationic palladium complex **107**, from which the C–O bond forming reductive elimination occurs. This process is analogous to the C–O reductive elimination seen in platinum(IV) complexes in stoichiometric studies reported by Goldberg.[118, 130] Mechanism B shows the direct concerted reductive elimination from the coordinatively saturated octahedral complex **106**, however, direct reductive elimination is very rare for high valent, octahedral complexes such as Pd(IV) or Pt(IV).[127] Mechanism C (*chelate dissociation* or *dissociative neutral*) proceeds through dissociation of a neutral ligand before reductive elimination from the coordinatively unsaturated palladium(IV) complex **108**.

Thorough mechanistic analysis showed that mechanism A was operative.[128-129] Firstly, the palladium(IV) complex **106** underwent rapid carboxylate exchange without C–O reductive elimination, indicating a fast and reversible carboxylate dissociation. Secondly, upon addition of Brønsted and Lewis acids (AcOH and AgOTf) the rates for carboxylate exchange and C–O reductive elimination were enhanced, indicating that the processes are linked. Finally, the ρ value obtained for *para*-substituted

phenoxide ligands on complex **106** was determined as –1.36, corroborating that the carboxylates act as a nucleophilic partner.

Work by Ritter and co-workers has shown that for some processes a palladium(III) dimer may be involved in catalysis (Scheme **25**). Initial reports of an isolated dimer with a Pd–Pd bond were reported in 2009 and featured the isolation of the dimeric palladacycle **110** (previously reported by Hartwell) and oxidised dimer **111**.[27, 131] The initial studies focused on the halogenation of nitrogen heterocycle **99**, forming aryl chloride **101d**, then turning their attention to C–O bond formation, to form acetoxylation product **101a**.[117, 132-134]



Scheme 25 | Isolation and reactivity of a Pd(III)–Pd(III) dimer by Ritter[131]

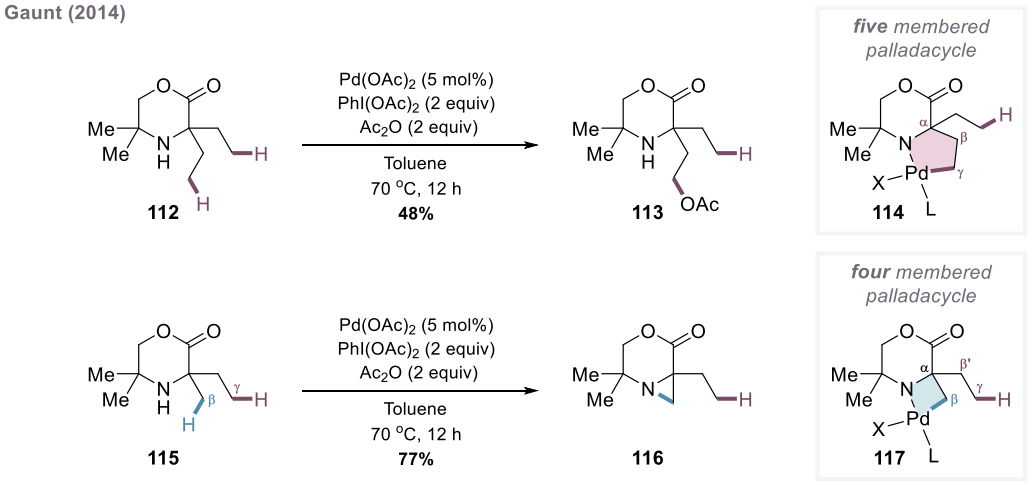
This novel complex was synthesised by precedented cyclometallation of heterocycle **99**, whereby the dimeric palladacycle complex **110** was oxidised with hypervalent iodine oxidants to form the palladium(III) dimer **111**.[131] The compound was stable below -30 °C, but decomposed rapidly at room temperature to form the functionalised product **101**. Evidence of a Pd–Pd bond is drawn from a 2.6 Å distance between the palladium atoms by X-ray diffraction of a single crystal and DFT studies of the HOMO-LUMO on dimer **111**. Kinetic studies for the determination of palladium nuclearity were unsuccessful as the rate limiting C–H activation step inhibited study of the subsequent catalytic intermediates.[135]

In 2012, Sanford and Ritter performed stoichiometric studies and showed the oxidation of palladium(II) dimers to yield either palladium(III) dimeric complexes or monomeric Pd(IV) species.[136] Combined kinetic studies indicated that oxidation of the palladacycle favoured the formation of bimetallic Pd(III) complex **111** with the caveat that this dimer undergoes cleavage of the Pd–Pd bond to give a monomeric palladium(IV) complex. These results were further supported by independent DFT studies performed by Canty and Yates, who showed that these Pd(III) dimers are typically mixed-valence rather than valence symmetric, indicating that they are a precursor to palladium(IV) complexes.[137-139]

1.3.3 Amine-directed acetoxylation of aliphatic C–H bonds

The use of amines in palladium-catalysed C–H acetoxylation poses numerous challenges. Aside from degradation by the catalyst, the amine substrates may also undergo oxidation by the presence of reagents required to access Pd(IV) intermediates. However, to date there have been three reports of aliphatic amine directed acetoxylation.

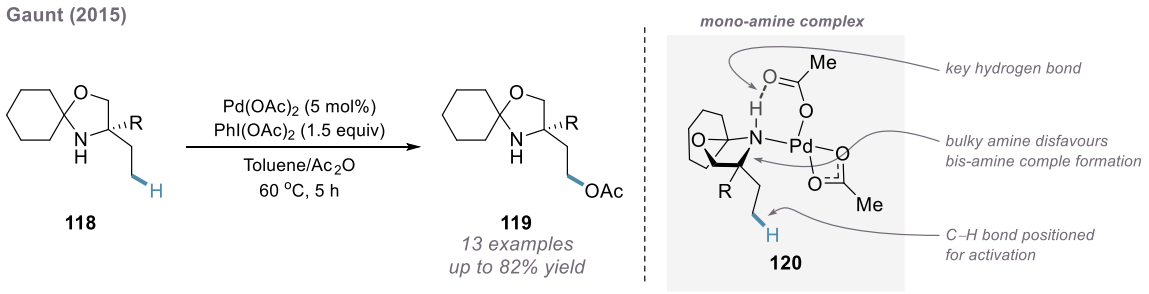
The first example of aliphatic amine directed C–H acetoxylation was described by Gaunt in 2014 (Scheme **26**).[102] Although this publication primarily reported the functionalisation of the observed four membered palladacycle to give C–H amination to azetidines and carbonylation products (Scheme **20**), it was reported that for substrate **112** bearing a *gem*-diethyl substitution, the acetoxylation product **113** was observed. While five membered palladacycle **114** was observed for morpholinone substrates bearing *di*-ethyl groups such as amine **112**, a four membered palladacycle was formed from amine **115**. The unusual four membered palladacycle **117** was formed preferentially to the five membered one in a ratio of 7:1, and furnished aziridine **116** when treated with $PhI(OAc)_2$ oxidant. The experimental results in the formation of palladacycle **117** were supported by DFT studies, showing that the transition state energy barrier of C–H activation to form the four membered palladacycle **117** was lower than that forming the five membered analogue (by 8.2 kcal mol^{-1}).[104]



Scheme 26 | Seminal work on the acetoxylation of aliphatic amines by Gaunt[102]

Further work on the functionalisation of protected amino alcohols by Gaunt in 2015, developed not only an acetoxylation reaction with excellent yields (Scheme **27**), but also arylation, carbonylation and alkenylation.[140] The amino alcohol substrates **118** were acetoxylated to give the corresponding γ-C–O bond products **119**, tolerating ethers, esters, protected alcohols and sulfonamide functionality. Interestingly the success of this transformation is attributed to the favourable *mono*-amine complex **120**. The hydrogen bond between the palladium bound acetate and the free amine (N–H) is thought to lock the conformation of the amine substrate, ensuring close positioning of the γ-C–H bond and not allowing for orientational flexibility to accommodate the bulky substrate in the off-cycle *bis*-amine complex.

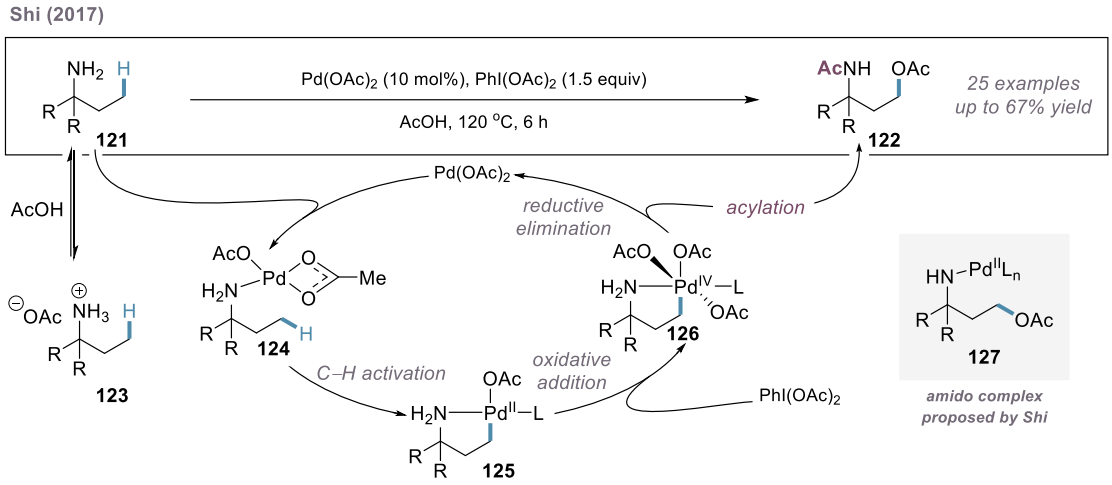
Selection of a hindered secondary amine further stabilises *mono*-amine complex **120** over the *bis*-amine, by hindering binding of an additional amine due to steric congestion around palladium. This claim is substantiated by the isolation of a trinuclear cyclopalladation complex instead of the expected *bis*-amine complex.



Scheme 27 | Development of an amine directed acetoxylation of protected amino alcohols by Gaunt[140]

In 2017, Shi demonstrated the acetoxylation of primary aliphatic amines in good yields (Scheme **28**).[141] Primary amine **121** (in equilibrium with its protonated form **123**) ligates to the palladium catalyst forming an intermediary *mono*-amine complex **124**. Upon the C–H activation event, the palladacycle(II) **125** may be oxidised by $PhI(OAc)_2$ to the octahedral palladium(IV) complex **126**. Reductive elimination and acylation give the functionalised product **122**. In the original publication by Shi, the formation of an amido–palladium complex **127** is invoked which undergoes acylation, however, scrutiny by Muzart highlights a control experiment indicating that the acetoxylated primary amine undergoes acylation without palladium.[142]

Interestingly, the authors discuss several of the potential obstacles in the development of an aliphatic acetoxylation reaction for primary amines. As primary amines are less sterically encumbered, they are predisposed to form the off-cycle *bis*-amine complex more easily, thus precluding the C–H activation event. Shi and co-workers concede that much of amine reactivity reported in literature is focused on the reactivity of the α-C–H bonds which readily undergo oxidation or hydrogen atom transfer.[143-144] Similarly, highly oxidising conditions, such as those required to access palladium(IV), may be incompatible with primary amines.[145]



Scheme 28 | Acetoxylation of primary aliphatic amines by Shi[141]

In an attempt to prevent deleterious reactivity, the choice of acetic acid as solvent results in protonation of the amine **121** at which point it can no longer act as a directing group. Overall, this has the effect of significantly lowering the concentration of free amine, favouring the formation of the catalytically active *mono*-amine complex **124**.[146] Furthermore, use of an α-tertiary primary amine **121** inhibited deleterious reactivity through α-oxidation. However, the authors disclose that they still observe some decomposition during the reaction.

1.4 Alkenylation of Csp^3–H bonds with amine derived directing groups

Arguably, traditional C–C cross-coupling reactions are some of the most valuable tools for the construction of organic molecules.[147] While the triad of palladium, copper and nickel were thought to be uniquely important to cross-coupling chemistry, the versatility of palladium soon proved superior by striking the delicate balance between selectivity and reactivity.[148]

These palladium-catalysed reactions have been used in *milli*-molar scale syntheses of clinical candidates, as well as ton-scale production of medicines, fine chemicals and agrochemicals.[2-3, 5, 67, 76] Traditionally, cross-coupling involves the linking of at least one pre-functionalised moiety using homogeneous palladium catalysis.[149] Substrates undergoing C–H activation require no pre-functionalisation, thus overall improving atom economy.

Alkenes are some of the most versatile functional groups, they are amenable to oxidations, reductions, nucleophilic additions, transition metal catalysis and radical reactions.[8, 75] Thus, the diverse reactivity profile of alkenes enables their use as a versatile synthetic handle when installed in organic molecules. For drug discovery, late stage modifications are especially useful in fine-tuning of efficacy, pharmacokinetics and pharmacodynamics.[150]

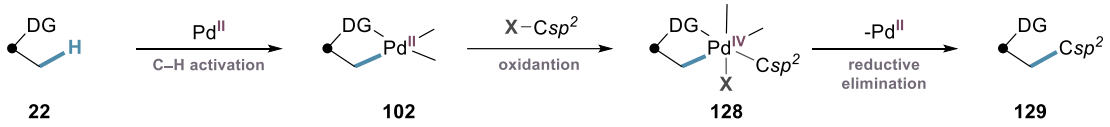
As discussed in *section 1.2.2* there are three general mechanisms for C–H functionalisation.[7] C–C Bond formation can occur *via* all of the possible functionalisation pathways (Pd(II)/Pd(0), Pd(II)/Pd(IV) and Pd(0)/Pd(II), Scheme **8**), however, the processes are often decided by olefination partner.[151-152] For example, high valent palladium is exclusively accessed by reaction partners that are able to oxidatively add to the palladium(II) metal once it has undergone C–H activation. The low valent pathway is preferred for substrates that will undergo migratory insertion or transmetallation, as observed in traditional C–C coupling reactions.[153]

This section will focus exclusively on the alkenylation of Csp^3–H bonds directed by amines and their derivatives. As there are only limited examples of native amine directing groups for palladium-catalysed, aliphatic C–H olefination, this section will cast a wider net of literature examples to include work covering amine derivatives such as amides, sulfonamides, or nitrogen heterocycles. Both the high valent and low valent alkenylation mechanisms will be described to give an overview of the contributions in this field.

1.4.1 High valent palladium – Pd(II)/Pd(IV) pathway

A very powerful method employed for the functionalisation of Csp^3–H bonds, uses the transiently generated palladium(IV) complex **128** to facilitate both Csp^3–C and Csp^3–X (X = heteroatom) bond forming processes (Scheme **29**).[7] Palladium(II) enters the catalytic cycle and facilitates C–H activation to form intermediary palladacycle **102**. This species may then be oxidised to the octahedral

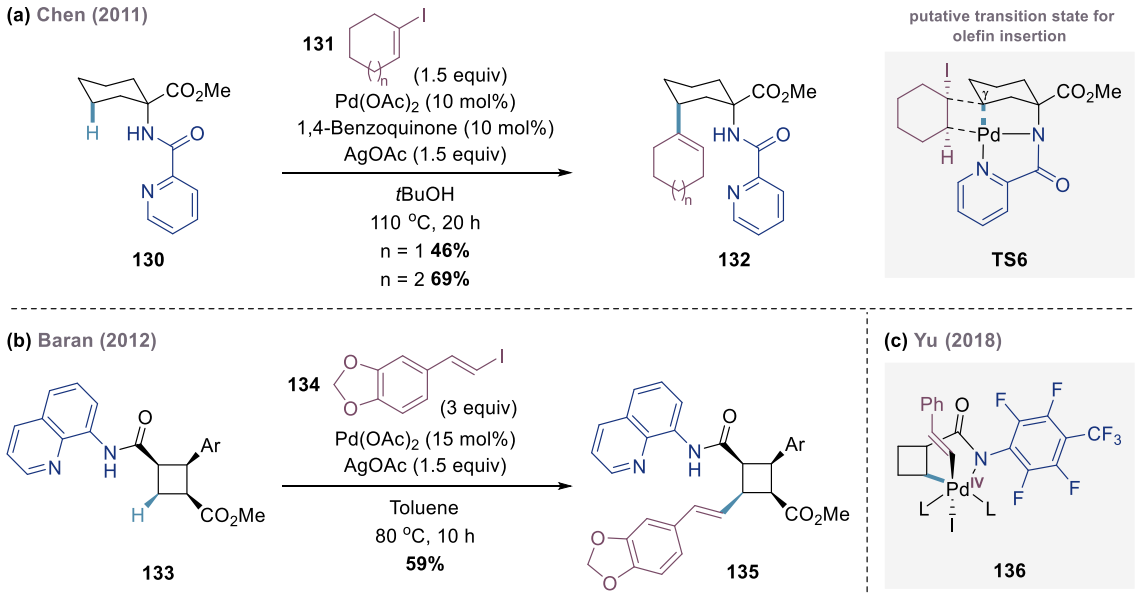
palladium(IV) complex **128** which rapidly undergoes reductive elimination, affording functionalised product **129**.



Scheme 29 | High valent Pd(II)/Pd(IV) pathway in the functionalisation of aliphatic C–H bonds[7]

As discussed extensively in *section 1.3* the formation of carbon–heteroatom bonds occurs almost exclusively using palladium(IV) intermediates.[129] However, using the appropriate reaction partners a high valent, octahedral palladium complex can also be accessed in the formation of C–Csp^2 bonds. It has been shown that cyclopalladated complexes can undergo oxidative addition into carbon–heteroatom bonds to give a variety of C–C bond products.[154]

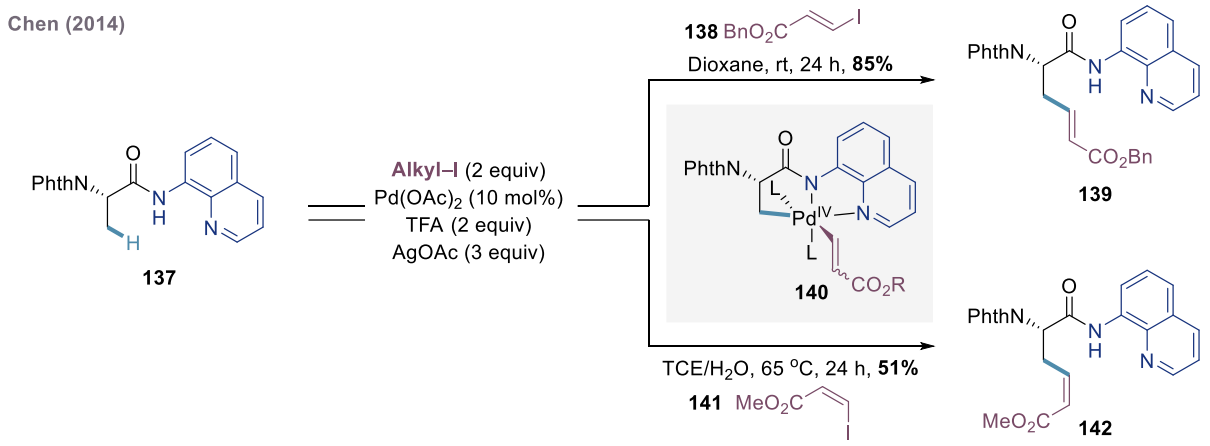
In 2011, Chen reported the first aliphatic C–H olefination reaction using alkenyl iodides (Scheme **30a**).[155] Cyclic iodides **131** were used in the methylene functionalisation of cyclic amide **130** to afford the alkenylated products **132** in good yields. The authors proposed that the functionalisation could proceed either through a palladium(IV) complex or through an olefin insertion *via* transition state **TS6**. The insertion of alkenyl and alkynyl bromides on arene substrates had previously been observed by Daugulis and Chatani.[156-157] Further studies by Chen indicated that the alkenylation proceeded through a high valent palladium(IV) species, with the alkenyl iodide facilitating oxidation of the intermediate palladacycle(II) complex.[158]



Scheme 30 | Early examples of alkenylation *via* palladium(IV);[155, 159-160] Ar = 1,3-Benzodioxole; L = bidentate coordination of *N*-((1*S*,2*S*)-1-((*R*)-4-isopropyl-4,5-dihydrooxazol-2-yl)-2-methylbutyl)acetamide ligand

In 2012, Baran reported a single example of an olefination using the common 8-aminoquinoline moiety as a directing group (Scheme **30b**).[159, 161] The natural product *pipercyclobutanamide A* contains a cyclopropane core bearing four different substituents. Based on the report by Chen a year earlier, Baran and co-workers were able to derivatise the densely functionalised cyclopropane core **133** with alkenyl iodide **134** to furnish the alkenylated product **135** in good yield. In 2018, studies on a very similar cyclopropane system by Yu indicated that this reaction proceeded via a palladium(IV) intermediate **136** (Scheme **30c**).[160]

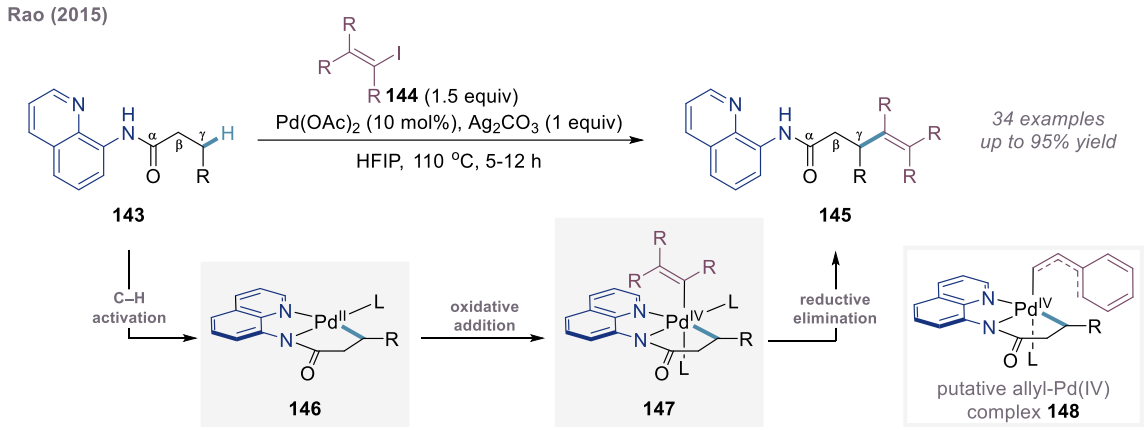
In 2014, the Chen group presented the olefination of aliphatic C–H bonds using alkenyl iodides to furnish olefinated products (Scheme **31**).[158] Protected amino acid **137** undergoes olefination to *trans*- and *cis*-products **139** and **142** respectively, with excellent stereo-retention of the reacting olefin. Mechanistically, the reaction is assumed to operate in a manner analogous to arylation using aryl iodides, presumably *via* a high valent palladium complex **140** from which reductive elimination takes place. The authors highlight the reactivity of the alkenes which, unlike arenes and alkanes, may ligate to the palladium centre and undergo unfavourable side-reactions. However, the ability to further functionalise alkenes also make their installation more attractive. Moreover, the reaction is performed at room temperature, tolerating moisture and air, as well as retaining the α-stereocentre of the amino acid derivative **137**.



Scheme 31 | Alkenylation of aliphatic C–H bonds *via* a palladium(IV) pathway;[158] L = undefined neutral ligand

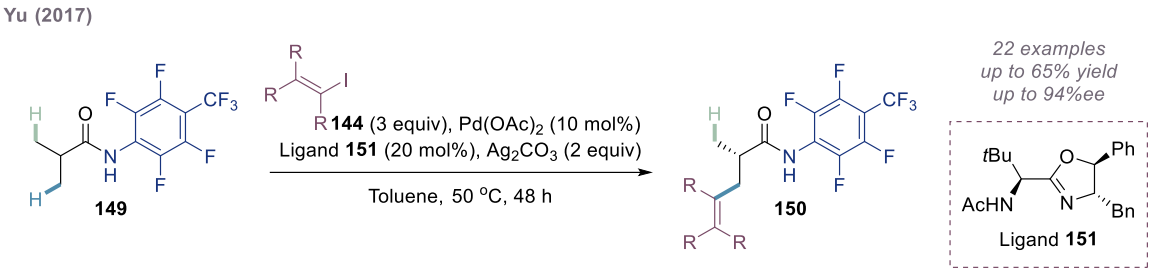
In 2015, Rao reported the methylene alkenylation using alkenyl iodides (Scheme **32**).[162] Amide **143** underwent alkenylation of the γ-methylene C–H bond to afford the olefinated product **145**. The transformation tolerated limited functionality on the substrates such as alkyl/aryl groups and protected nitrogen. Both electron poor (3-iodo-α,β-unsaturated ketones) and electron rich coupling partners (aryl substituted) generated the corresponding alkenylated products **145** in good yields. Remarkably, the use of an alkenyl bromide also affords the desired functionalised product, albeit in lower yield; Vinyl chlorides were shown to be inert in this reaction. The 8-aminoquinoline directing group facilitates C–H activation to give palladacycle **146** which upon oxidative addition with the alkenyl iodide **144** is oxidised

to the octahedral palladium(IV) complex **147**. Interestingly, the authors observed a degree of isomerisation when *Z*-alkenyl iodides were employed (2:1, *Z*:*E*). Since control reactions showed that neither the starting material **143**, nor the product **145** underwent isomerisation, it was proposed that the bulky directing group promotes isomerisation of *Z*-bound alkenes at complex **147** *via* a transient palladium-allyl species **148**.



Scheme 32 | Methylene alkenylation of aliphatic C–H bonds as reported by Rao;[162] L = undefined neutral ligand

Subsequent work by Yu and co-workers was able to establish a protocol for the desymmetrisation of aliphatic amide substrates using a chiral ligand.[163] The enantioselective alkenylation of amides **149** provided the α-chiral alkenylated products **150** in good yields and with excellent enantioselectivity (Scheme **33**). Chiral differentiation in amide **149** proved to be challenging, due to the requirement for the ligand to be able to differentiate between an α-methyl or α-hydrogen. Fortunately, bidentate oxazoline ligand **151** showed excellent enantioselectivity, with three stereocentres required for efficient asymmetric induction.

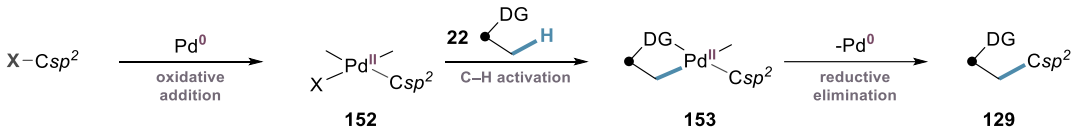


Scheme 33 | Enantioselective olefination of prochiral amides using alkenyl iodides as reported by Yu[163]

The alkenylation of aliphatic C−H bonds by alkenyl iodides is relatively well precedented as shown by the examples above. There are several examples of high valent C–C bond formations, including examples using native amine groups as the directing moiety, with much of this work focused on arylation.[152] In 2019, Yao published the first example of a primary amine directed arylation of Csp^3−H bonds proceeding *via* a high valent palladium pathway.[164-165] To date there are no examples of native amine directed alkenylation of aliphatic C−H bonds *via* palladium(IV).

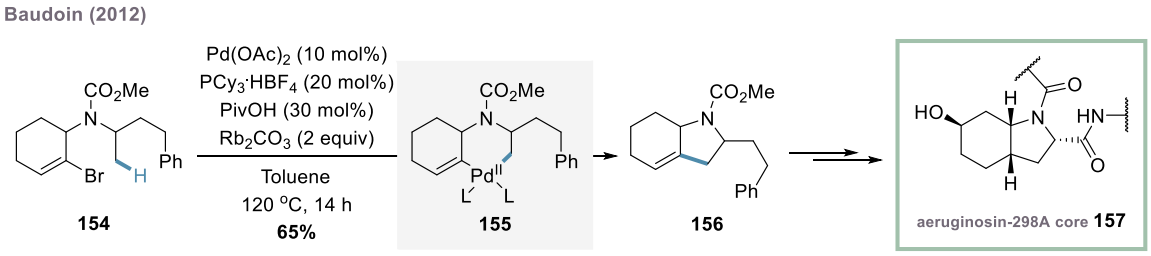
1.4.2 Low valent palladium – Pd(0)/Pd(II) pathway

There are limited examples employing a Csp^3–H alkenylation using a Pd(0)/Pd(II) redox pathway process.[152] Conventionally, this involves oxidative addition of an alkenyl halide or triflate to a palladium(0) catalyst forming palladium(II) complex **152**, followed by C–H activation of the substrate **22** and subsequent reductive elimination to return both palladium(0) catalyst and functionalised product **129** (Scheme **34**).



Scheme 34 | Low valent Pd(0)/Pd(II) pathway in the functionalisation of aliphatic C–H bonds[7]

In 2012, Baudoin and co-workers developed an intramolecular cyclisation to access the core of the natural product *aeruginosin 298A* **157** (Scheme **35**).[166] The total synthesis of *aeruginosin 298A* was later completed in 2015 using the Csp^3–H alkenylation methodology.[167] Vinyl bromide **154** is cyclised to bicycle **156** through the oxidative addition of the palladium(0) catalyst (presumably formed through reduction by the ligand) into the carbon-bromine bond on substrate **154**.[168] Subsequent intramolecular C–H activation yielded the intermediate palladium(II) complex **155** which is able to undergo reductive elimination, to return palladium(0). The oxidation of the palladium catalyst by the substrate negated the need for addition of oxidants which would be incompatible with the phosphine ligands typically used to promote transmetallation and reductive elimination.[151]



Scheme 35 | Baudoin's intramolecular cyclisation utilising a Pd(0)/P(II) mechanistic pathway[166]

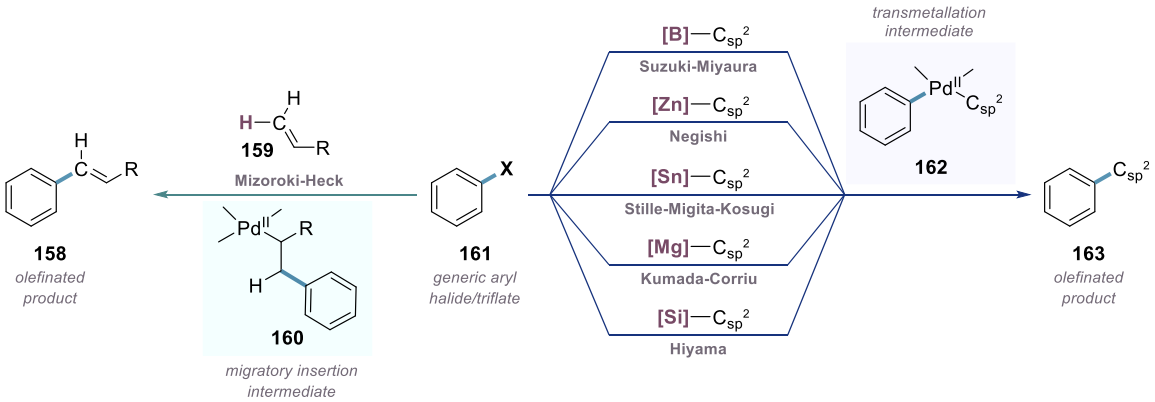
This is a rare example of a Pd(0)/Pd(II) redox mechanism in Csp^3–H alkenylation. To date, all examples of aliphatic alkenylation utilising this mechanism have been intramolecular.[151-152, 169] The challenging, rate-limiting, activation of aliphatic C–H bonds, is therefore in competition with the alkenyl halide, which can undergo further oxidative addition to yield a palladium(IV) complex.[23] At high valent palladium, C–H activation of aliphatic bonds is unlikely.[170] The dominance of intramolecular processes therefore suggests the requirement to bring the C–H bond into proximity of the palladium(II) centre imminently to prevent undesired reactivity.

1.4.3 Low valent palladium – Pd(II)/Pd(0) pathway

The third redox pathway for C–H functionalisation occurs through a Pd(II)/Pd(0) system (Scheme **36**). Here, the catalyst enters the catalytic cycle in its palladium(II) oxidation state and undergoes C–H activation with substrate **22** to form palladacycle **102**. The cyclopalladated complex undergoes a ligand substitution to bring the reacting moiety onto the metal centre; Reductive elimination from complex **153** yields the functionalised product **129**.

Scheme 36 | Low valent Pd(II)/Pd(0) pathway in the functionalisation of aliphatic C–H bonds[7]

However, in the case of alkenylation, the functionalisation step can occur with subtle differences depending on the olefin reaction partner.[149] In classical cross-coupling and C–H functionalisation reactions employing olefin coupling partners, there are two reaction pathways that can be followed depending on the olefin source (Scheme **37**).[149, 153] For the generic aryl halide/triflate **161**, alkenylation with an olefin bearing boron, zinc, tin, magnesium or silicon may undergo transmetallation. This process furnishes the intermediate palladium(II) complex **162** (with a σ-bound alkene) which undergoes reductive elimination to yield the alkenylated product **163**. Alkenes without a metal/metalloid functionality, undergo C–C bond formation *via* an alternative pathway. The alkene **159** associates with the palladium complex (π-bound alkene) and then undergoes migratory insertion to form the carbopalladated complex **160**, from which successive β-hydride elimination provides the alkenylation product **158**.



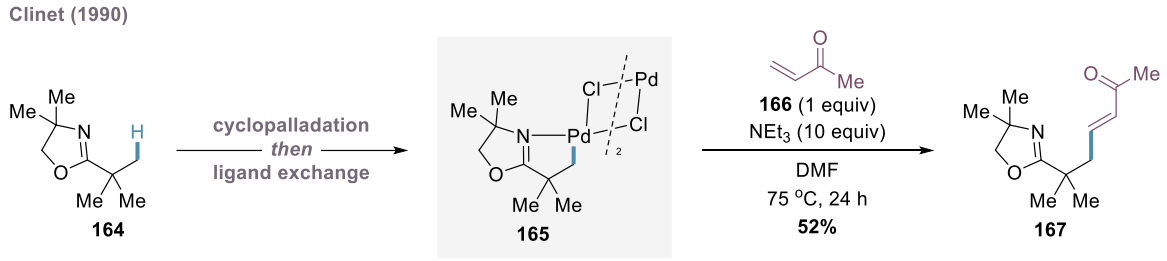
Scheme 37 | Overview of Csp^2–H alkenylation using various alkene sources; X = halide, triflate

The section below aims to introduce the seminal work of Csp^3–H alkenylation reactions, proceeding either *via* the migratory insertion or transmetallation pathway, and enabled by amine-based directing groups.

1.4.3.1 Csp^3–H Alkenylation via migratory insertion

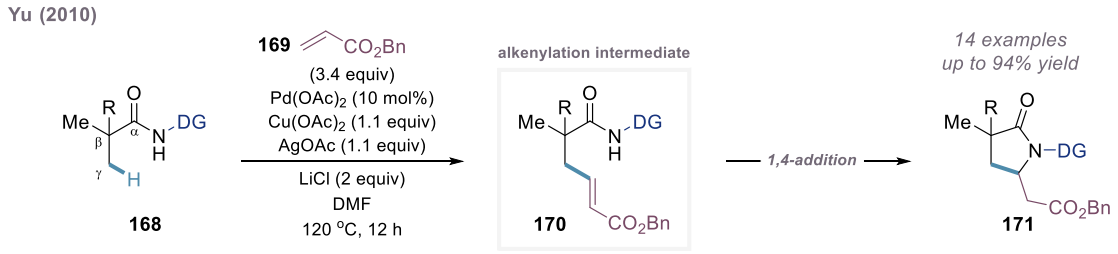
The palladium-catalysed olefination of aryl/alkenyl halides, also commonly known as the Mizoroki-Heck reaction, is used routinely in organic synthesis.[47-48, 171] Firstly, the alkene associates to the metal centre, acting as a π-donor and undergoes migratory insertion.[172] Secondly, the C–C bond product is released by β-hydride elimination. Commonly, the Mizoroki-Heck reaction employs non-activated terminal alkenes often conjugated to an electron withdrawing group.[173] The robust reaction has been widely studied, enabling the cross-coupling of electron rich olefins and control of alkene regioselectivity.[174-175] Using C–H activation to access a palladium(II) complex that can undergo this type of olefination reaction therefore piqued the interest of several research groups.

Early stoichiometric work by Clinet showed the first reported example of aliphatic C–H alkenylation mediated by palladium to form palladacycle **165** from oxazoline starting material **164** (Scheme **38**).[176] The cyclopalladation yielded the dimeric complex **165**, although the authors observed a small quantity of the trinuclear complex which was also observed later by Yu (**46**, Scheme **11**).[80-81] Stoichiometric studies which aimed to functionalise the C–Pd bond, showed that the alkenylation of the palladacycle **165** with methyl vinyl ketone **166** gave rise to enone **167** in 52% yield. This process is likely to undergo functionalisation through a classical Mizoroki-Heck-pathway involving carbopalladation of the terminal olefin.[47-48]



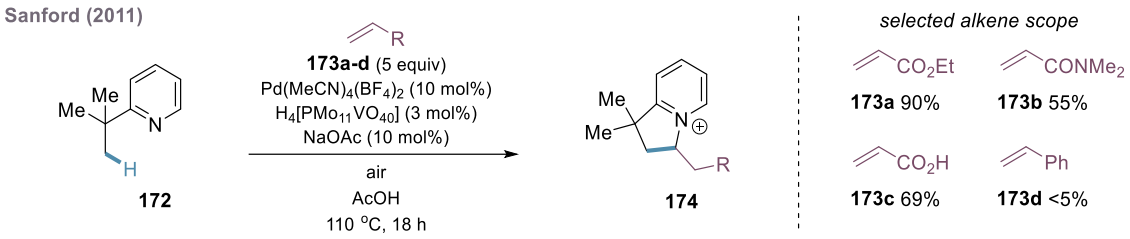
Scheme 38 | Stoichiometric alkenylation of palladacycle complex **165** by Clinet[176]

The first report of catalytic, aliphatic olefination using perfluorinated directing groups was described in 2010 by Yu (Scheme **39**).[177] Aliphatic amides **168** bearing an electron withdrawing directing group, were alkenylated with benzyl acrylate **169** under palladium-catalysis to furnish the intermediary alkenyl product **170**. Rapid intramolecular 1,4-addition yielded the cyclic functionalised product **171**. The authors propose the transformation to occur *via* a Pd(II)/Pd(0) redox mechanism with carbopalladation forming the C–Csp^2 bond, analogous to the transformation described by Clinet (Scheme **38**).[176] Silver and copper additives proved crucial for palladium(0) oxidation, while the addition of lithium chloride was suggested to inhibit the formation of palladium black. Overall, ester and ether functionality as well as β-hydrogen atoms were tolerated. Furthermore, the alkenylation of methylene C–H bonds was demonstrated on cyclopropyl substrates. In 2014, Yu demonstrated the alkenylation of protected alanine to give β-olefinated α-amino acids in excellent yield.[178]



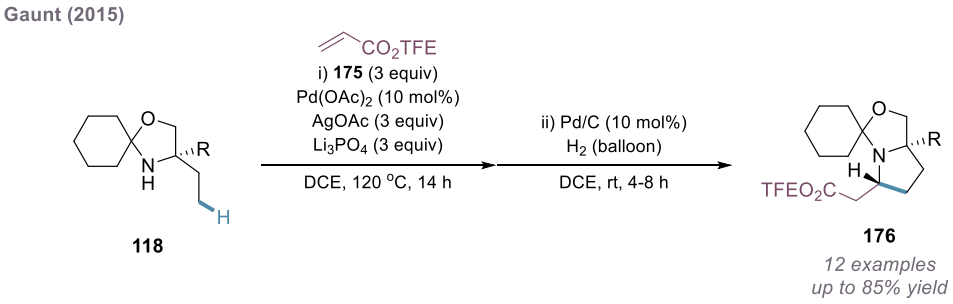
Scheme 39 | Olefination of unactivated aliphatic C–H bonds by Yu;[177] DG = C_7F_7 or $C_6F_5CF_3$

In 2011, Sanford published the alkenylation of Csp^3–H bonds using a pyridine directing group (Scheme **40**).[179] Pyridine directed aliphatic C–H activation of substrate **172** afforded the Michael addition product, cyclic pyridinium **174**. The alkene scope (**173a-d**) showed the requirement for electron poor alkenes, a trend mirrored by the analogous arene olefination.[180] Precedent for the unusual oxidation catalyst ($H_4[PMo_{11}VO_{40}]$) was based on previous work by Ishii, demonstrating efficient catalytic turnover using the $Pd(OAc)_2$/molybdovanadophosphoric acid system with O_2 as a terminal oxidant.[181] This non-traditional oxidant system proved more efficient than the commonly used copper or silver salts.



Scheme 40 | Olefination of unactivated aliphatic C–H bonds by Sanford[179]

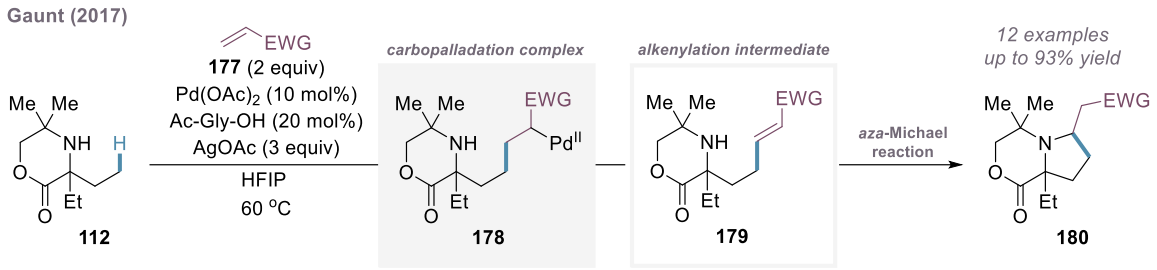
The first example of native amine directed alkenylation of electron poor alkenes was reported in 2015 by Gaunt and co-workers (Scheme **41**).[140] Protected chiral amino alcohols **118** underwent alkenylation with electron poor olefin **175** to furnish tricyclic pyrrolidine **176** in excellent diastereoselectivity. Small amounts of allylic amine were observed after the initial alkenylation step, prompting the subsequent hydrogenation step. The alkenylation tolerated protected heteroatoms such as nitrogen (Phth, Ts) and oxygen (TBS), esters and acetals all in good yield.



Scheme 41 | Native amine directed olefination of protected amino alcohols **118**[140]

A further report of alkenylation on native amine substrates was published by Gaunt in 2017 (Scheme **42**).[182] In this study, Gaunt and co-workers demonstrated the facile alkenylation of morpholinone **112**

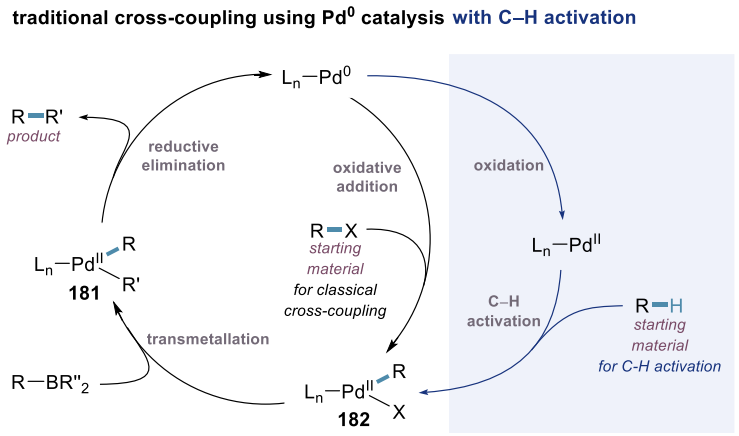
to furnish the bicyclic product **180**. As for traditional Mizoroki-Heck cross-coupling, this process featured a migratory insertion of the olefin **177** to form the carbopalladated complex **178**. Kinetic studies indicated the importance of the amino acid ligand in this transformation, facilitating C–H activation by participating in the CMD event. Kinetic isotope studies showed that exclusion of the ligand lead to irreversible C–H activation. Likely this is due to the presence of the acetyl-glycine ligand ensuring proximity of the protonated amide on the ligand, thus facilitating reprotonation.



Scheme 42 | Native amine directed olefination of morpholinones[182]

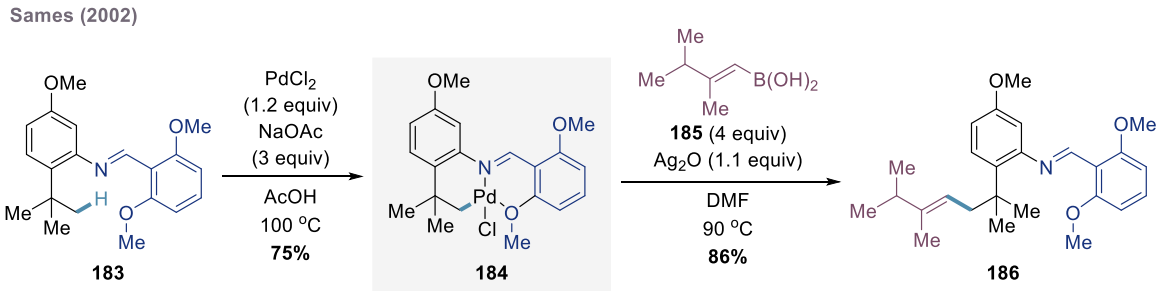
1.4.3.2 Csp³–H Alkenylation via transmetallation

The alkenylation of C*sp*^{3}–H bonds can proceed through transmetallation when using alkenyl metals/metalloids.[148] Instead of palladium(0) entering the catalytic cycle by oxidative addition, palladium(II) catalyses the C–H activation of the substrate to generate complex **182** (Scheme **43**).[11, 152] The resulting palladium(II) complex then undergoes a sequence of transmetallation (**181**) and reductive elimination processes to return palladium(0). Palladium(0) is oxidized back to a palladium(II) complex by an external oxidant. There are, however, subtle challenges in the combination of these two processes; the ligands used for cross-coupling are not usually stable to oxidants, neither are they known to facilitate C–H activation processes by CMD.[151] The following examples will discuss the recent advances in the alkenylation of aliphatic C–H bonds by transmetallation, which attempt to overcome these challenges. Emphasis will be placed on alkenyl boron reagents as the Suzuki-Miyaura reaction is the most popular of the cross-coupling methodologies and therefore these coupling partners are most readily available.[3, 183]



Scheme 43 | Combined catalytic cycle for the palladium-catalysed cross coupling by oxidative addition or C–H activation

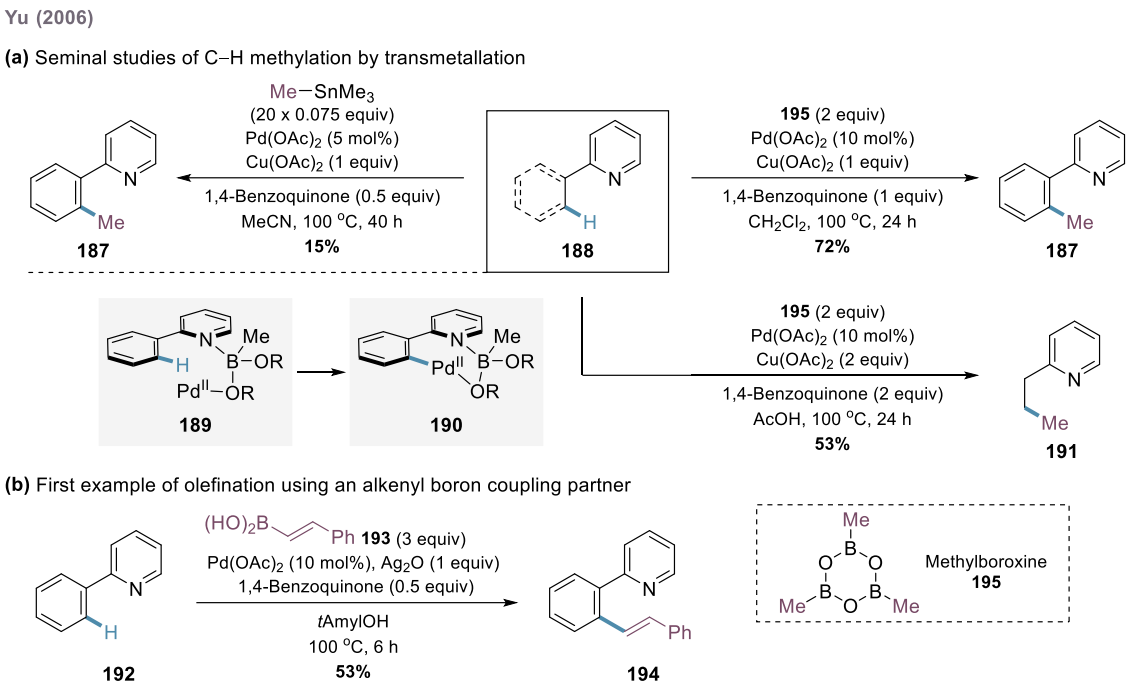
In 2002, Sames had demonstrated the elegant aliphatic alkenylation using an alkenyl boronic acid coupling partner (Scheme **44**).[184] This stoichiometric, palladium-catalysed alkenylation was utilised in the synthesis of the core of natural product *teleocidin B4*. Installation of the directing group ensured facile cyclopalladation of imine **183** to form complex **184**. Interestingly, while the *ortho*-methoxide moieties were originally installed to prevent Csp^2–H activation, unexpectedly they also stabilised the formed palladacycle **184**. Addition of the vinyl boronic acid **185** afforded the Csp^3–H alkenylation product **186** in excellent yield.



Scheme 44 | Stoichiometric aliphatic alkenylation in the synthesis of the core of *teleocidin B4* by Sames[184]

In 1996, Hartwig reported the stoichiometric functionalisation of a palladacycle using Me_3SnPh in a Stille-type transmetallation.[185] Inspired by this result, Yu and co-workers developed a catalytic C–C cross-coupling reaction by employing organotin reagents. In 2006, Yu reported the methylation of 2-phenyl pyridine to form the Csp^2–Csp^3 product **187** (Scheme **45a**).[186] Without the use of bulky phosphine ligands, it was found that addition of benzoquinone favoured reductive elimination, while copper(II) acetate ensured the oxidation of palladium(0). However, the organotin reagent had to be added portion-wise due to the high proportion of *homo*-coupling observed. To circumvent the requirement for toxic organotin coupling partners, Yu rationalised that less reactive boronic acid derivatives could be used instead. The non-toxic coupling partner methylboroxine **195** proved to give higher conversions to aryl **187** and moreover, no *homo*-coupling was observed.[187] In this report, the

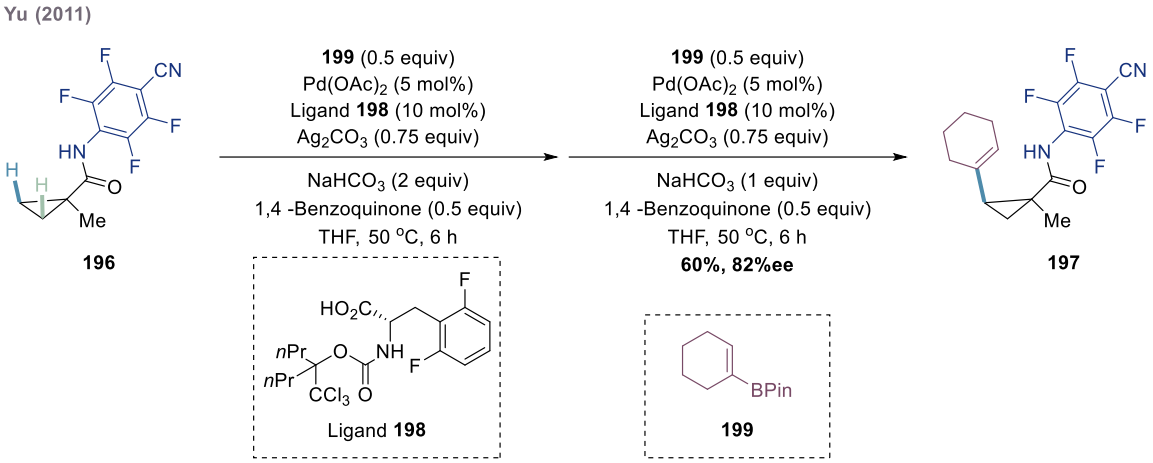
authors were also able to demonstrate methylation of aliphatic C–H bonds, forming homologation product **191**.



Scheme 45 | Yu's studies towards an efficient functionalisation of aromatic and aliphatic C–H bonds through transmetallation[186-187]

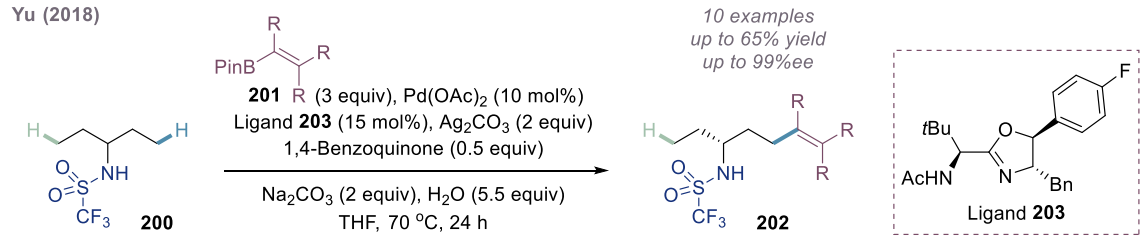
A single example in another 2006 publication by Yu featured the first catalytic alkenylation (albeit of Csp^2–H bonds) using alkenyl boronic acids (Scheme **45b**).[187] 2-Phenylpyridine **192** was alkenylated in good yield to furnish aryl **194**, by Pd(II)/Pd(0) catalysis. It was proposed that the cyclometallation proceeded from complex **189**, where the substrate had pre-associated with the methylboroxine **195**, present in two-fold excess. Ligation of the palladium centre facilitates proximity driven cyclopalladation to form the C–H activation complex **190**. In 2008, Yu reported on the asymmetric alkylation of prochiral arenes using alkyl boronic esters, and utilising protected amino acid ligands to induce a chiral environment for C–H activation.[188]

In 2011, Yu presented the first example of a catalytic alkenylation reaction using vinyl boron reagents (Scheme **46**).[189] Although this work primarily focused on the asymmetric arylation of cyclopropyl substrate **196**, the authors presented an example of asymmetric alkenylation. Amide **196** was olefinated using 1-cyclohexyl boronic ester **199** to give the functionalised cyclopropane **197**. Interestingly, the authors observed better conversions and more consistent yields by sequential addition of the reagents. The amino acid derived ligand **198** was previously used to facilitate enantioselective Csp^2–Csp^2 and Csp^2–Csp^3 coupling.[188, 190] Collaborative efforts between Yu, Houk, Blackmond, Musaev and Sigman have since demonstrated that mono-protected amino acid ligands not only impose a chiral environment, but are also directly involved in the C–H bond abstraction during CMD (see *section 3.1.1*).[191-194]



Scheme 46 | First example of a catalytic, aliphatic alkenylation reaction using a vinyl boron reagent[189]

In 2018, Yu reported another example of enantioselective alkenylation using a Pd(II)/Pd(0) redox mechanism. (Scheme **47**).[195] The desymmetrisation of sulfonamide **200** was demonstrated using alkenyl boronic ester coupling partners. The olefin products **202** were isolated in excellent enantiomeric excess, albeit in moderate yields. Alkyl and aryl substitution on the boronic ester coupling partner was tolerated, even with *tri*-substituted alkenyl boronic esters giving good yields. However, the presence of Boc-protected amine and ether moieties resulted in an appreciable loss in conversion. The particularly bulky oxazoline ligand **203** gave higher enantiomeric excess than the ligand used for the analogous arylation reaction of substrate **200**.



Scheme 47 | Enantioselective olefination of sulphonamide substrates using a Pd(II)/Pd(0) redox mechanism[195]

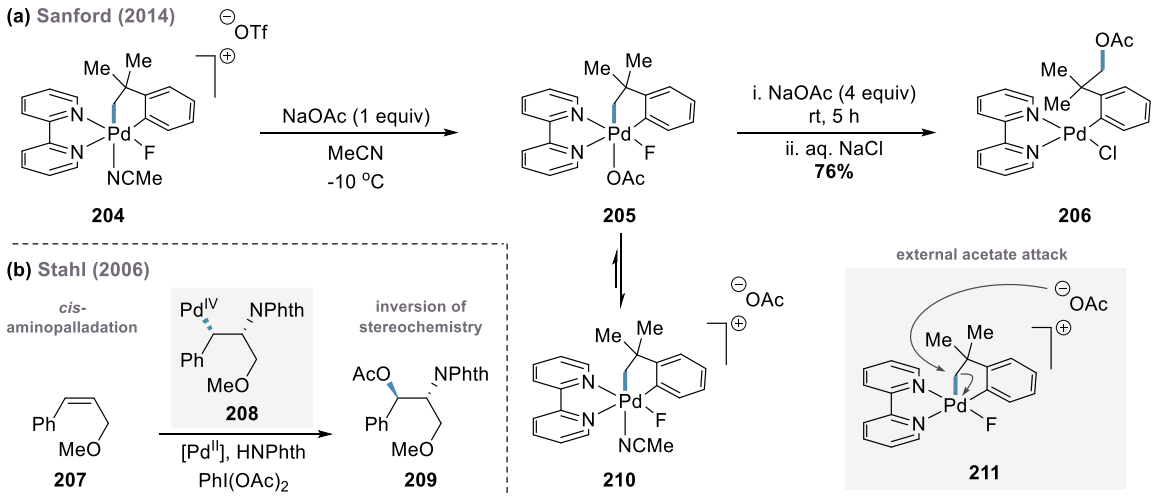
To date there are no known reports that show native amines as directing groups for the alkenylation of C*sp*^{3}–H bonds by alkenyl boronic esters/acids. Therefore, there is an opportunity to develop more atom economic processes that use alkenyl boron reagents as coupling partners in aliphatic C–H functionalisation reactions. The direct installation of alkenes as a functional handle would be a powerful tool to enable the modification of drug-like molecules.[150] Chapter 3 in this thesis will present an aliphatic alkenylation using boronic ester coupling partners directed by tertiary amines.

2. Acetoxylation of morpholinones

2.1 Introduction

2.1.1 Previous work

In 2014, Sanford published a stoichiometric study on Csp^3–H bond acetoxylation from pre-formed palladium complexes (Scheme **48a**).[196] Although the stoichiometric study of Csp^2–O bond formation from high valent palladium had earlier been reported for similar palladium complexes, this was the first study on an aliphatic system.[83, 197] The authors employed a similar complex to the one previously used for C–N reductive elimination studies.[198] Treatment of palladium(IV) complex **204** with an equivalent of sodium acetate gave acetoxy-ligated complex **205** in equilibrium with cationic solvato complex **210**. It was observed that less coordinating anions formed higher proportions of the cationic complex. Addition of excess sodium acetate furnished complex **206** where the Csp^3–O bond product remained bound to the palladium(II) centre. Mechanistic studies to investigate the formal reductive elimination processes showed a zero-order dependence on the acetate in the functionalisation of complex **204** to complex **206**.



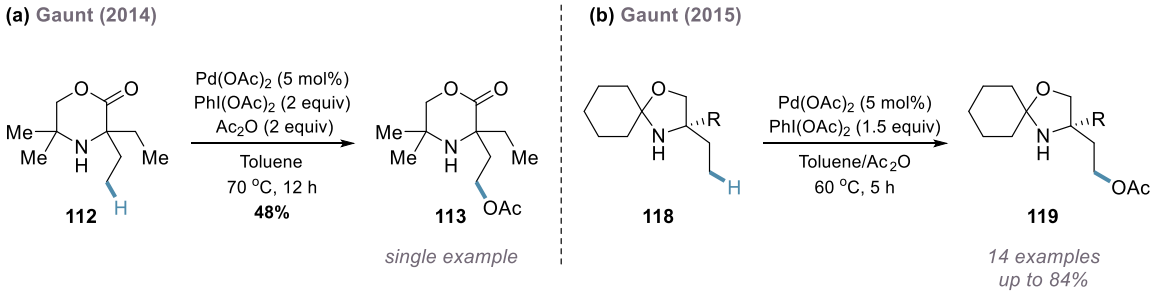
Scheme 48 | **(a)** Stoichiometric study of aliphatic C–O bond formation by Sanford;[196] **(b)** amino acetoxylation of alkenes by Stahl and observation of inversion for acetoxylation[199]

Sanford and co-workers observed that the rate was independent of the pKa of the nucleophile, an observation also documented by Hartwig for the Csp^3–O bond formation from palladium(II) complexes.[200] This result suggested two sequential steps with *opposing electronic requirements*. Sanford and co-workers therefore proposed an initial dissociation of an acetate ligand to form a cationic palladium(IV) complex, and subsequently a nucleophilic addition in a S_N2 fashion (**211**). This report of outer sphere Csp^3–O bond formation is consistent with the work on high valent platinum by Goldberg.[118, 130] Additionally, the work evidenced by Stahl in 2006 (Scheme **48b**) on the amino acetoxylation of alkenes equally indicated an inversion of stereochemistry (**208**, **209**).[199, 201] DFT

calculations published in 2017 on the Sanford system (**211**) have also suggested this pathway to be operative.[202]

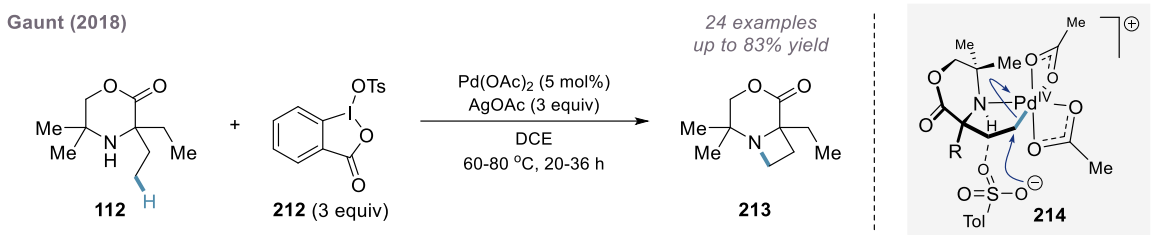
In 2014, Gaunt reported the palladium-catalysed acetoxylation of Csp^3–H bonds directed by aliphatic amines (Scheme **49a**).[102] In this first example of a native amine directed aliphatic acetoxylation, amine **112** is converted to the acetoxylated product **113** in 48% yield. It was observed that treatment of a five membered palladacycle formed by γ-C–H activation of amine **112** with $PhI(OAc)_2$ yielded the oxygenated product **113** while the analogous four membered palladacycle formed the aziridine product (Scheme **26**).

Following this work, Gaunt reported a comprehensive acetoxylation reaction on protected amino alcohols **118** in 2015 (Scheme **49b**).[140] Again, the iodonium salt $PhI(OAc)_2$ was employed due to its low-toxicity and clean reaction profiles, rendering it popular in C–O bond forming reactions.[203] Optimisation studies on amine **118** achieved excellent yields of up to 84% (R = *i*Bu), and showed that this reaction is able to tolerate a range of functional groups such as esters, ethers, ketones, tosyl protected nitrogen and silyl protected oxygen. However, only trace amounts of acetoxylated product **119** were observed for the α-amino ester (R = CO_2Me), presumably through bidentate binding of the substrate to the palladium catalyst.



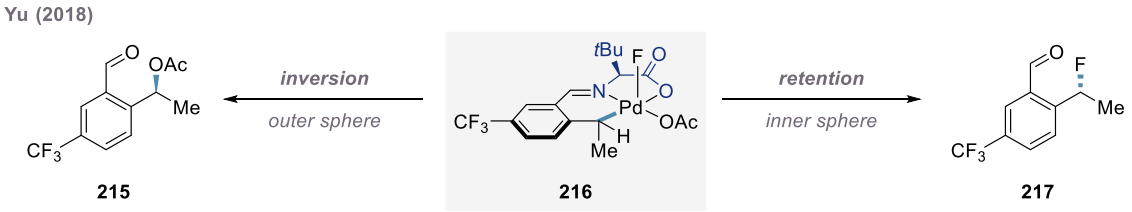
Scheme 49 | **(a)** Acetoxylation of morpholinone **112**;[102] **(b)** Acetoxylation of protected amino alcohols **118**[140]

In 2018, Gaunt also reported the azetidination of the morpholinones using $Pd(OAc)_2$, where a cyclic tosylate oxidant **212** was shown to afford azetidination products (**213**, Scheme **50**).[204] Here, it was demonstrated that the C–N bond formation did not occur by direct reductive elimination, and instead the oxidant **212** employed in the azetidination reaction ensured primary C–OTs bond formation *via* complex **214**, by external attack of the tosylate onto the C–Pd bond. Azetidine formation then followed through nucleophilic displacement of the tosylate. In contrast to this, the mechanism of aziridination *via* a four membered palladacycle was investigated by DFT calculations and was shown to proceed through deprotonation of the amine and C–N reductive elimination from an amido-palladium(IV) complex.[103]



Scheme 50 | Aziridination of morpholinones using cyclic tosylate oxidant **212**[204]

While conducting our study on the acetoxylation of morpholinones, Yu published the enantioselective acetoxylation and fluorination of benzylic C–H bonds in 2018.[205] This work built on the reports of platinum(IV) reductive elimination processes, which were investigated by enantioselective methylene activation to form a stereocentre upon C–H activation.[206] The square pyramidal palladium(IV) complex **216** was accessed by employing an transient amino acid directing group (Scheme **51**). As expected, the degree of enantioselectivity correlated to the size of the side chain on the chiral directing group. Interestingly, Yu observed inner sphere reductive elimination to give fluorinated products **217**; the acetoxylation products (**215**) were formed by inversion of stereochemistry with respect to the originally formed C–Pd bond in complex **216**.

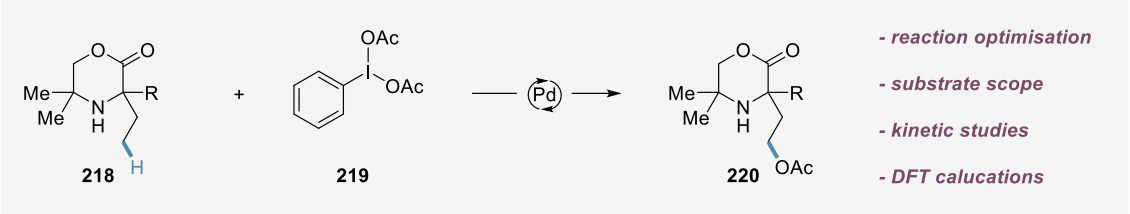


Scheme 51 | Controlling reductive elimination from palladium(IV) complexes by Yu[205]

2.1.2 Project aims

Following the preliminary studies of stoichiometric C–O bond forming processes (Sanford *et al.*) and the initial work that our group contributed to the facile C–H activation of morpholinone substrates, the aim of this project was to optimise the acetoxylation reaction on the morpholinone scaffold.[102-103, 140, 196, 204] Furthermore, the goal of this project was to demonstrate that the acetoxylation reaction could tolerate a range of functionality and therefore establish its utility for synthetic chemists. The catalytic reaction was to be investigated using kinetic studies; to determine the order of key reagents, as well as kinetic isotope studies. Finally, the C–H functionalisation of the morpholinone amines would be examined using DFT studies to give computational insight into the reaction mechanism. This work is

the first example of a mechanistic study of Csp^3–O bond formation for a native amine-directed, catalytic reaction (Scheme **52**).



Scheme 52 | Acetoxylation of morpholinones **218** with hypervalent iodine oxidant **219** to give acetoxylated products **220**

2.2 Results and discussion

2.2.1 Reaction optimisation

Optimisation of the morpholinone acetoxylation result, initially reported by our group in 2014, was the starting point for the investigation.[102] Amine **221** was chosen as a model substrate, bearing an ethyl and *n*-propyl chain on the *activating side* proximal to the *endo*-cyclic ester (significant activation at the distal *gem*-dimethyl group has not been observed). This amine was specifically selected to ensure C–H activation to form a five-membered palladacycle, as previous work on C–H amination had elucidated that the four-membered palladacycle would be favoured over the five membered palladacycle (Scheme **26**).[102] Extending the alkyl chain to bear an *n*-propyl would, if terminal C–H_B activation were to occur, yield a six-membered palladacycle (Figure **3**). This would be kinetically unfavourable compared to terminal activation of the ethyl (C–H_A) chain and has never been observed for our aliphatic amine directed palladacycles. Similarly, methylene activation (C–H_C) is unlikely to occur in competition with terminal C–H_A activation, as methylene activation is significantly more difficult.[59]

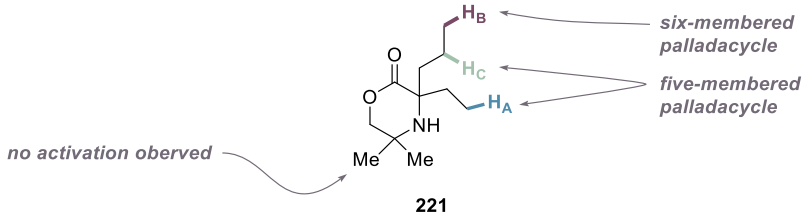
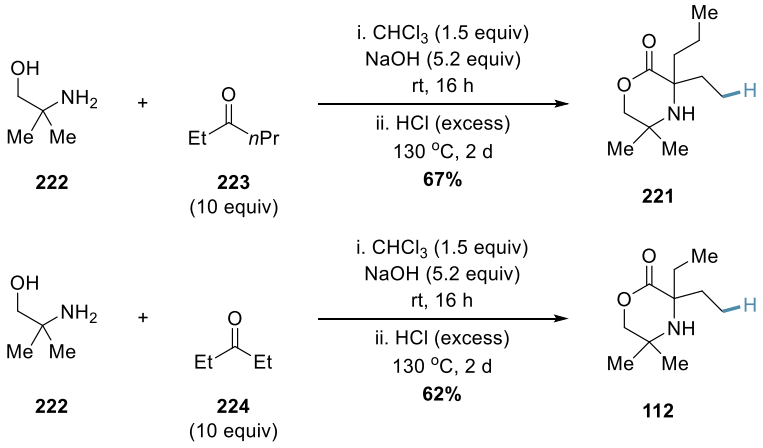


Figure 3 | Model substrate for optimisation of amine directed acetoxylation reaction, **221**

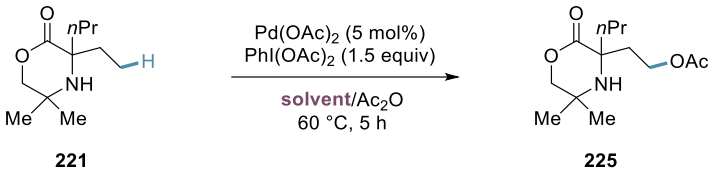
The model substrate **221** and the *di*-ethyl morpholinone **112** were synthesised from amino alcohol **222** and ketones **223** and **224** (Scheme **53**). The Bargellini reaction enables the synthesis of these alkyl morpholinone scaffolds **221** and **112** in a one-pot reaction, in 67% and 62% yield respectively.[207]



Scheme 53 | Bargellini reactions to furnish morpholinones **221** and **112**

Firstly, the acetoxylation of **221** was performed using the reported conditions for amine **118** (1 equivalent of amine, 5 mol% $Pd(OAc)_2$, 1.5 equivalents of $PhI(OAc)_2$, in toluene/acetic anhydride at

60 °C for 5 hours) to give an initial yield of 32% of desired product **225**.[140] Preliminary modifications to the initial conditions showed that recrystallisation of the oxidant, as well as distillation of both amine and acetic anhydride proved to be important for the reaction, leading to an increase in yield. Similarly, it was observed that conversions were significantly higher upon addition of acetic anhydride, which was postulated to act as a water scavenger in the reaction.



221 **225**

Entry	Solvent	Yield[a]
1	Dioxane	0%
2	THF	24%
3	Hexane	40%
4	DCE	41% (36% isol.)[b]
5	MeCN	41%
6	EtOAc	46%
7	PhMe	52%
8	Cyclohexane	52%
9	$CHCl_3$	52%
10	C_6H_6	57%
11	CH_2Cl_2	61%
12	$MeNO_2$	67%

Table 1 | Solvent screen for C–H acetoxylation of **221**. 0.1 mmol reactions; [a] Yields determined by ^{1}H-NMR using 1,1,2,2,-tetrachloroethane as an internal standard, [b] 0.25 mmol scale.

Since undirected oxidation of benzylic C–H bonds by palladium catalysts is known, the initial optimisation studies aimed to replace toluene to circumvent the possibility of undesired oxidation of the solvent.[46, 208] An extensive solvent screen showed that very polar solvents such as DMF, DMSO and DMA did not give any acetoxylated product **225**. Ethereal solvents such as dioxane (Table **1**, entry 1) and THF (entry 2) gave no or low yields of the C–O bond product, while hydrocarbon solvents such as hexane (entry 3), cyclohexane (entry 8) and benzene (entry 10) gave good yields of the desired product **225**. Interestingly, acetonitrile (entry 5) and ethyl acetate (entry 6) provided yields comparable to dichloroethane (entry 4) which had been used for the azetidination of morpholinones.[204] Reactions in chloroform (entry 9), dichloromethane (entry 11), cyclohexane (entry 8) and benzene (entry 10) were superior to those in toluene (entry 7). Nitromethane (entry 12) proved to be the solvent that gave the highest yield for the acetoxylation of morpholinone **221.** It has been reported that nitromethane is an

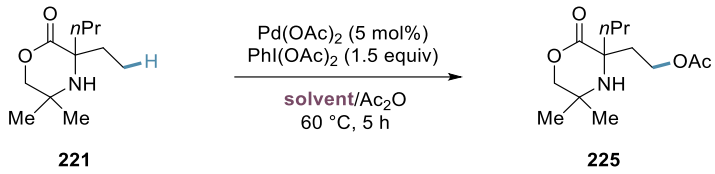
effective solvent for oxidations using hypervalent iodine reagents, although the reason for this has not been elucidated.[209-210]

221 **225**

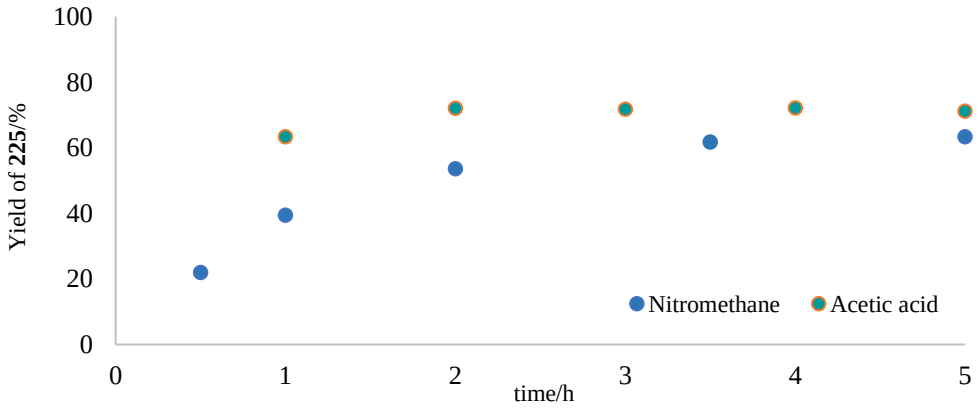
Entry	Solvent	Additive	Yield[a]
1	$MeNO_2$	AcOH 0.5 equiv	52%
2	$MeNO_2$	AcOH 1.0 equiv	52%
3	$MeNO_2$	AcOH 2.0 equiv	59%
4	AcOH	-	68%

Table 2 | Additive screen for C–H acetoxylation of **221**. 0.1 mmol reactions; [a] Yields determined by ^{1}H-NMR using 1,1,2,2,-tetrachloroethane as an internal standard

Next, an additive screen showed that the addition of acetic acid proved beneficial for the acetoxylation reaction. The increase in equivalents of acetic acid proved to be advantageous for the formation of product **225** (Table **2**, entries 1-3). Interestingly, when nitromethane was replaced with acetic acid as a solvent, the most significant improvement in yield was observed (entry 4). Acetic acid had previously been used in the seminal work on the alkenylation and acetoxylation of benzene by Fujiwara and Henry respectively.[45, 113-114, 116]



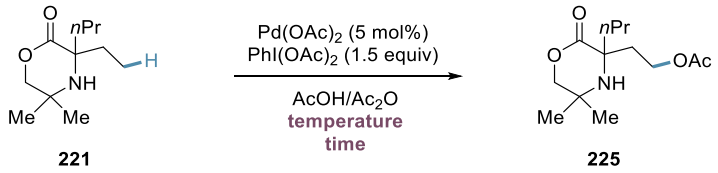
221 **225**



Graph 1 | GC-FID time study for the acetoxylation of model substrate **221**, performed in nitromethane and acetic acid

Subsequently, a time study was carried out to investigate the rates of conversion for the similarly performing solvents, nitromethane and acetic acid. Calibration of the product **225** on the GC-FID allowed the sampling of the reaction at specific time points, and to determine quantitatively the amount of product present. The yield of product **225** in nitromethane plateaued after five hours, while the reaction in acetic acid proceeded much faster, achieving yields above 60% within an hour (Graph **1**). Encouraged by the more rapid reaction rate, acetic acid was selected as the solvent for the acetoxylation and gave good conversions to product **225** while minimising decomposition of the starting material.

Further optimisation studies were conducted in order to fine-tune the reaction conditions and minimise decomposition of starting material (Table **3**). The increase of temperature to 70 °C (entry 2) gave a slight reduction in yield, however, by shortening the reaction time from five to three hours (entry 3), the product was obtained in an excellent isolated yield (72%). Increasing catalyst loading to 10 mol% (entry 4) also led to an increase in yield, affording 82% of the acetoxylated amine **225**. Shortening the reaction time to an hour still gave an excellent yield of isolated product (75%, entry 5). Further manipulation of oxidant equivalences indicated little effect on the conversion (entry 6 and 7). With the optimised conditions in hand (Table **3**, entry 5), we next aimed to demonstrate the tolerance of the reaction to a diverse range of functional groups.



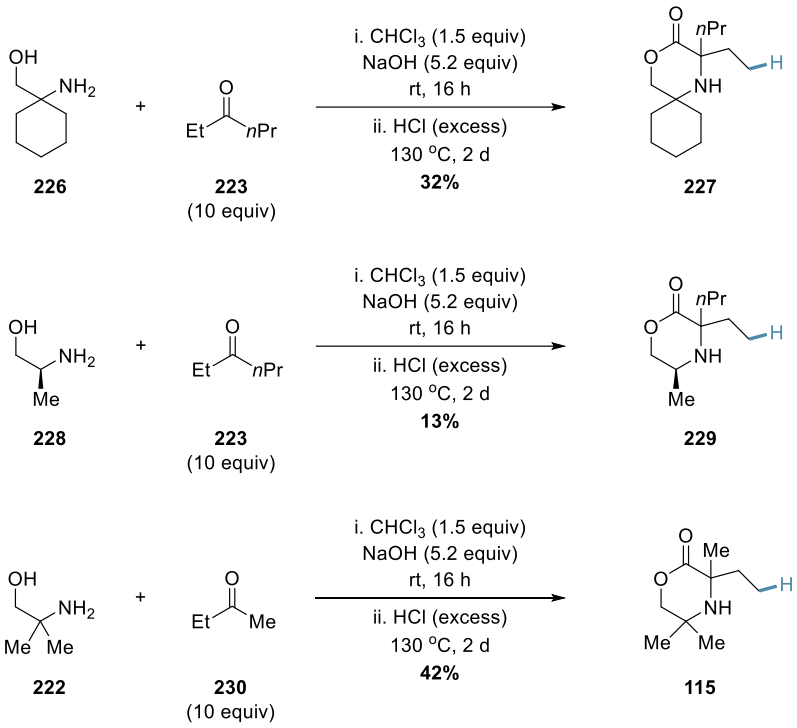
221 **225**

Entry	Δ	Reaction time / h	Temperature / °C	Yield[a]
1	-	5	60	68%
2	-	5	70	66%
3	-	3	70	72%[b]
4	10 mol% $Pd(OAc)_2$	3	70	82%
5	10 mol% $Pd(OAc)_2$	1	70	75%[b]
6	10 mol% $Pd(OAc)_2$ 2 equiv $PhI(OAc)_2$	1	70	72%
7	10 mol% $Pd(OAc)_2$ 1 equiv $PhI(OAc)_2$	1	70	69%

Table 3 | Optimisation studies for C–H acetoxylation of **221**, 0.1 mmol reactions; [a] Yields determined by ^{1}H-NMR using 1,1,2,2,-tetrachloroethane as an internal standard, [b] isolated yield, 0.3 mmol reaction

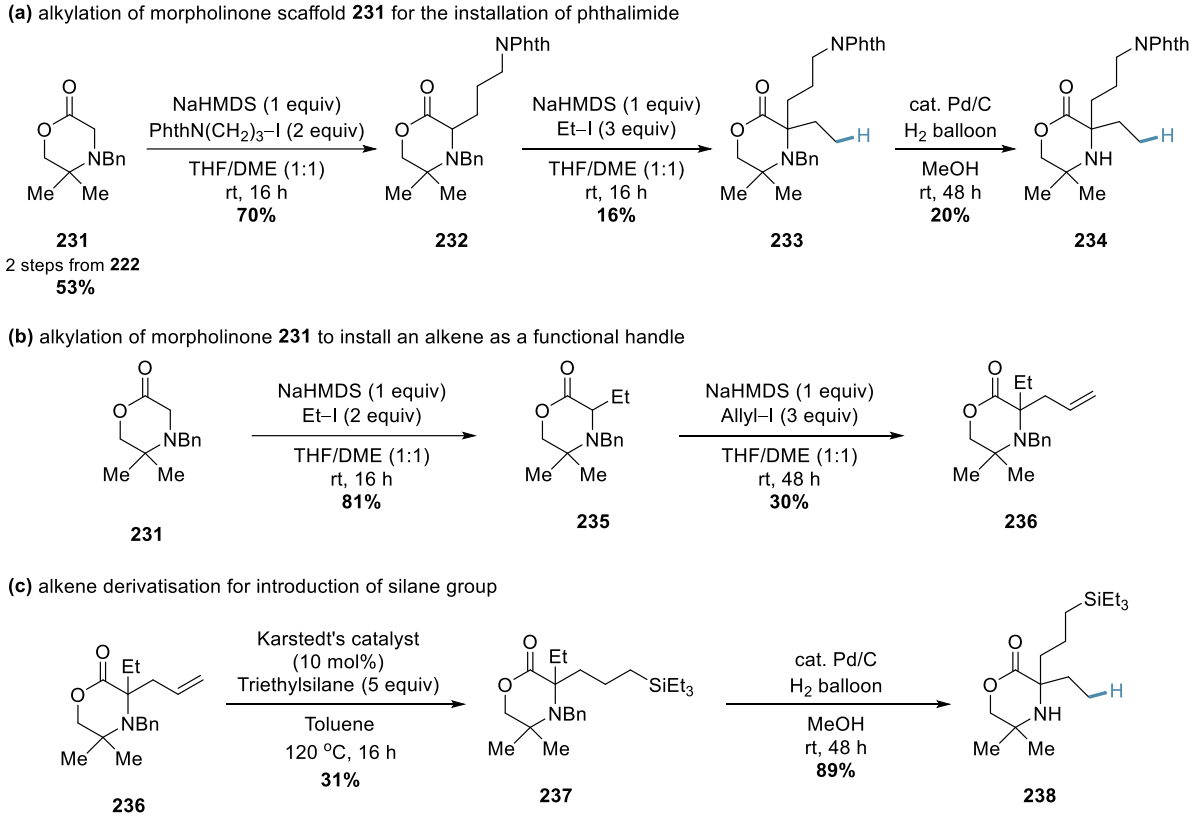
2.2.2 Substrate scope

Morpholinones bearing aliphatic substituents were synthesised *via* the Bargellini reaction.[211] Cyclohexyl substituted morpholinone **227** and *tri*-methyl substituted morpholinone **115** were isolated in modest yields while the less hindered morpholinone **229** was isolated in low yield (Scheme **54**). The variety of isolated yields for amines **227**, **229** and **115** was likely a result of the products requiring both column chromatography and subsequent distillation to achieve the purity required for the acetoxylation reaction.



Scheme 54 | Bargellini reaction for the synthesis of morpholinone substrates **227**, **229** and **115**

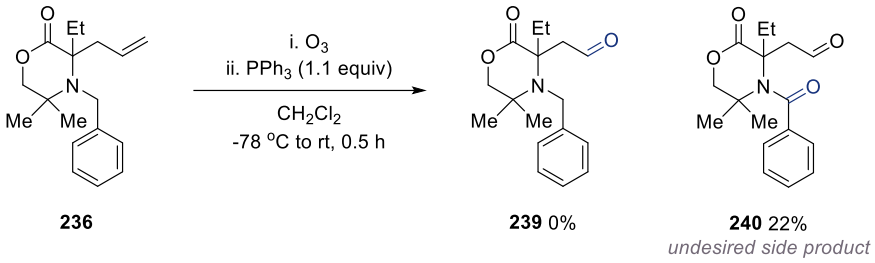
More complex morpholinones, in particular those bearing heteroatoms, could not be synthesised *via* the Bargellini reaction. In these cases, the morpholinone skeleton **231** was alkylated to install the desired substituents. The precursor morpholinone scaffold **231** could be accessed in two steps from amino alcohol **222** in good yield. Introduction of the phthalimide group was achieved through initial alkylation of ester **231** and subsequent alkylation of morpholinone **232** with ethyl iodide, to form the quaternary centre of amine **233** (Scheme **55a**). Finally, benzylamine hydrogenolysis afforded the desired acetoxylation substrate **234**.



Scheme 55 | **(a)** alkylation strategy to access phthalimide **234**; **(b)** synthesis of building block allyl morpholinone **236**; **(c)** hydrosilation strategy in the synthesis of substrate **238**

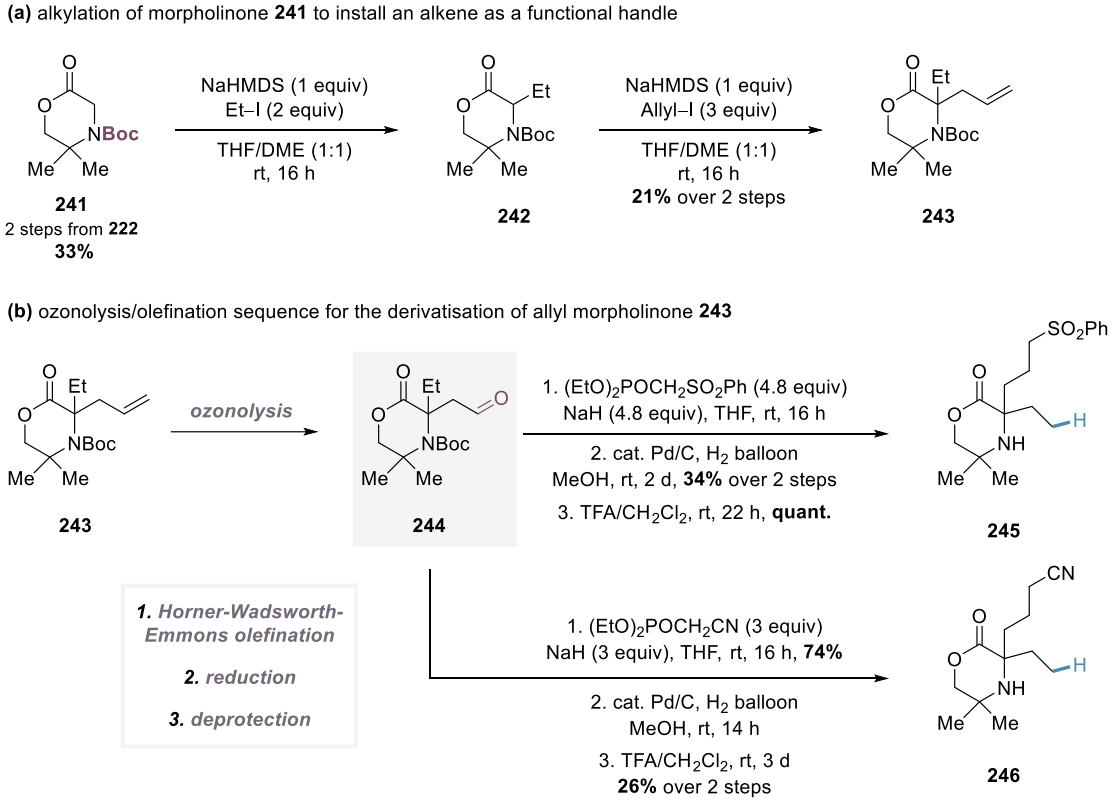
As an alternative, the synthesis of building block **236** containing the quaternary centre and a functional handle in form of a terminal alkene was rationalised (Scheme **55b**). The alkene would allow diverse functionalisation and negate the need for alkylation with various functional groups. Initial alkylation of morpholinone **231** with ethyl iodide afforded compound **235**. The allyl group was installed using NaHMDS and allyl iodide to give the desired allyl morpholinone **236** in 30% yield. From intermediate **236**, hydrosilylation provided the protected silyl-substituted morpholinone **237** in 31%, which could be deprotected in excellent yield to give the silyl-morpholinone **238** (Scheme **55c**). Attempts at cross-metathesis and Heck reaction with the terminal alkene of morpholinone **236**, were unsuccessful and therefore, alternative methods of exploiting the installed functional handle were sought.

Allyl morpholinone **236** was treated, sequentially, with ozone and triphenylphosphine. However, the desired aldehyde product **239** was not observed, instead, only compound **240** was isolated from the reaction in 22% yield (Scheme **56**). This reactivity had previously been reported for benzyl ethers, forming esters under ozonolysis conditions.[212] The observed oxidation compromised the directing group strategy and therefore an alternative amine protecting group was installed for the synthesis of the remaining substrates.[213]



Scheme 56 | Undesired oxidation of benzyl protecting group of allyl morpholinone **236** during ozonolysis

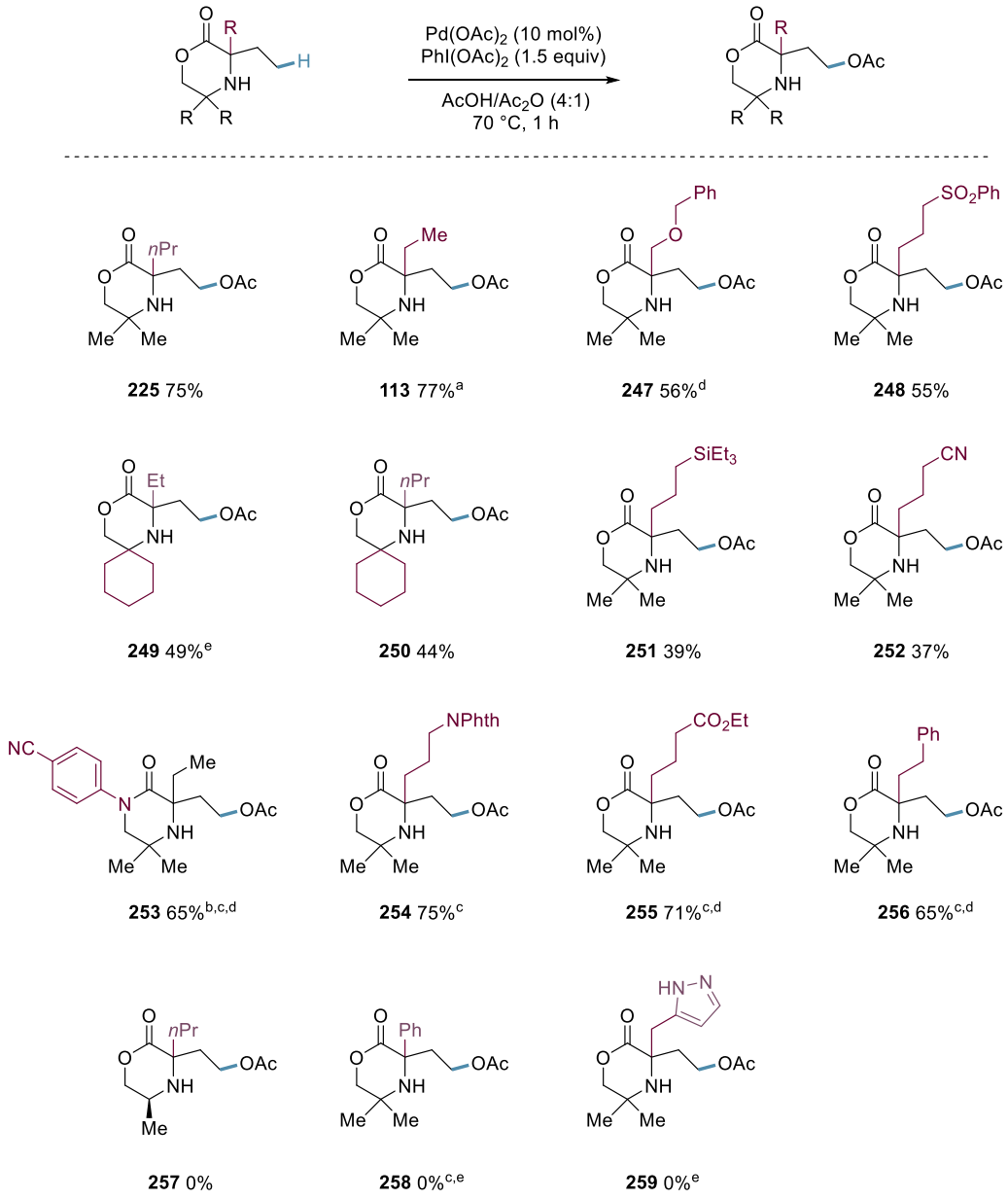
Boc-protected morpholinone **241** was synthesised and sequentially alkylated to give the analogous allyl morpholinone **243** (Scheme **57a**). Ozonolysis of olefin **243** afforded crude aldehyde **244**, which was derivatised by Horner-Wadsworth-Emmons olefination, reduction and deprotection to afford the desired sulfone and cyano amines **245** and **246** (Scheme **57b**).



Scheme 57 | **(a)** synthesis of Boc-protected morpholinone **243**; **(b)** derivatisation of allyl morpholinone **243** to afford sulfone **245** and cyano **246** substituted morpholinone substrates

The acetoxylation reaction scope proved relatively robust, with yields ranging from moderate (37%) to excellent (75%, Scheme **58**). High yields were achieved for the model substrate **225** and the diethyl substituted morpholinone **113** affording a mixture of *mono*- and *di*-substituted products. Protected oxygen **247** (substrate synthesised from **115** *via* the aziridine) and sulfones **248** were similarly tolerated giving good yields of 56% and 55% respectively, while the bulky cyclohexyl substitution gave moderate yields of 49% for **249** and 44% for **250**, presumably due to a more sterically encumbered directing amine. Silane groups were tolerated in modest yields of the acetoxylated product **251**, and morpholinone

252 bearing a cyano group gave the lowest conversions, likely due to competition for ligation to palladium. Finally, morpholinone related heterocycle **253** gave a good acetoxylation yield of 65%, while phthalimide **254** (75%), ester **255** (71%) and phenyl **256** (65%) substitutions gave very good conversion to their respective acetoxylated products.



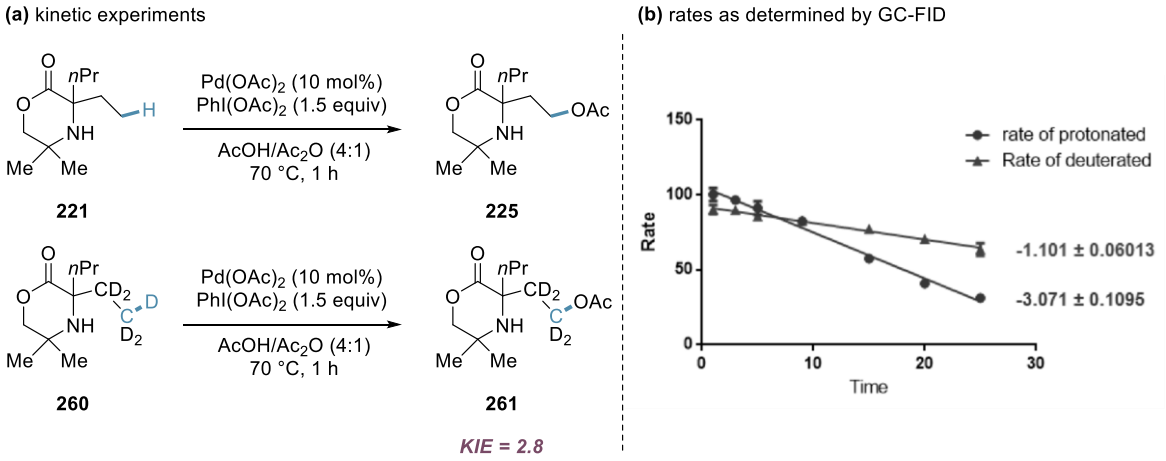
Scheme 58 | Substrate scope for the acetoxylation of morpholinones; [a] mixture of *mono*- and *di*-acetoxylated products; [b] 15 mol% $Pd(OAc)_2$, 30% yield with 10 mol% $Pd(OAc)_2$; [c] acetoxylation reactions performed by Dr Darren Willcox; [d] synthesised by Dr Darren Willcox; [e] synthesised by Dr Chuan He

Tertiary α-centres such as on morpholinone **257** were not tolerated and resulted in decomposition of the amine substrate, presumably through α-oxidation; While very sterically encumbered substrates such as α-phenyl morpholinone **258** also gave no conversion to product. Finally, the presence of a coordinating heterocycle present in morpholinone **259** precluded Csp^3–H activation. This was likely due to the

formation of a stable five membered chelate, being formed between the substrate and the palladium catalyst.

2.2.3 Kinetic studies

To elucidate the mechanism of amine directed acetoxylation, the kinetics of the reaction and the order of reaction components (amine, palladium acetate and $PhI(OAc)_2$) through initial rates was examined by Dr Darren Willcox. For the amine, a reaction order of –1 was determined from a rate *vs.* 1/[**221**] plot (see *Appendix I ii*), which is consistent with the formation of an off-cycle *bis*-amine complex at higher amine concentrations. At lower amine concentrations the equilibrium favours the *mono*-amine complex, which can undergo C–H activation. The order of the palladium catalyst was determined to be 0.33, consistent with the presence of trimeric palladium acetate in the reaction mixture which is well supported by the literature.[214-216] This indicated that the dissociation of this trimer into monomeric palladium acetate is required for catalysis to occur. Finally, the reaction exhibited zero-order kinetics with respect to the $PhI(OAc)_2$ oxidant, which indicated that the oxidation of the palladacycle occurred after the rate limiting step.



Scheme 59 | Kinetic isotope studies, reactions performed by Dr Darren Willcox **(a)** KIE experiments run; **(b)** Rate differences between protonated and deuterated morpholinone substrate in the determination of KIE

Kinetic isotope studies were carried out to determine whether the Csp^3–H bond breaking step would be rate limiting. The reactions of morpholinone **221** and its deuterated counterpart morpholinone **260** (Scheme **59a**) were monitored by GC-FID and the initial rates compared (Scheme **59b**). This revealed a primary kinetic isotope effect of 2.8, indicating a rate limiting C–H activation.[217] As the kinetic studies only gave insight into the reaction mixture before the rate determining step, DFT calculations were carried out to further elucidate the mechanism of aliphatic acetoxylation.

2.2.4 Computational studies

Computational studies were performed by Dr Ben Chappell using Amsterdam Density Functional (ADF) software, using ZORA-BLYP-D3 (TZ2P(Pd), DZP(other)) with solvent effects considered using an implicit conductor like solvation model (COSMO) in dichloroethane at 333.15 K. They are included here to provide further understanding of the C*sp*^{3}–H acetoxylation reaction. This level of calculation had previously been used for our work on the functionalisation of amines.[103, 108, 204, 218-219]

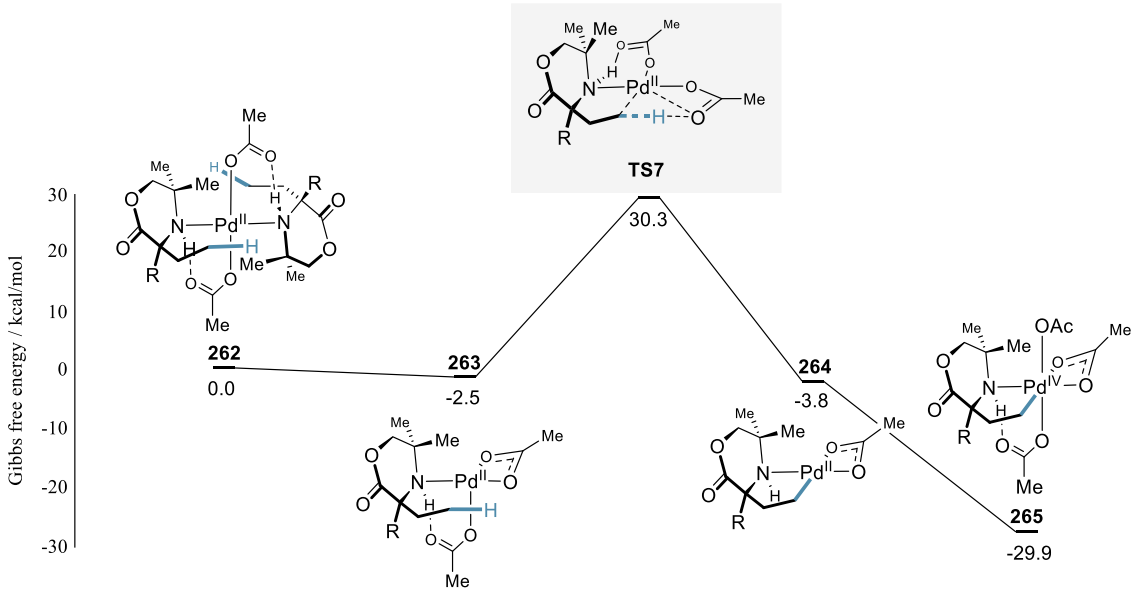


Figure 4 | DFT calculations for morpholinone C–H activation, calculations performed Dr Ben Chappell

Firstly, the calculation focused on C–H activation of the morpholinone, bound to the palladium acetate catalyst in a *bis*-amine complex **262** (Figure **4**). Initial dissociation formed the *mono*-amine palladium(II) complex **263**, which underwent C–H activation by CMD through six-membered transition state **TS7**. The barrier for C–H activation (between **263** and **TS7**) was calculated to be 32.8 kcal/mol and was the highest energy barrier calculated for the complete acetoxylation reaction, which indicated that this step was rate limiting. Palladacycle **264** subsequently underwent oxidation by $PhI(OAc)_2$, furnishing the palladium(IV) complex **265**. These results were consistent with the kinetic studies completed for this reaction (see *section 2.2.3*).

The mechanism of C–O bond formation from high valent palladium complex **265**, was explored (Figure **5**). The lowest energy pathway to the catalyst-bound acetoxylated product **267** was demonstrated to proceed *via* initial dissociation of an acetate (**TS8**), to form the key cationic palladium(IV) intermediate **266**. Subsequently, C–O bond formation took place *via* an external, nucleophilic addition of an acetate onto the highly electrophilic C–Pd bond (**TS9**).

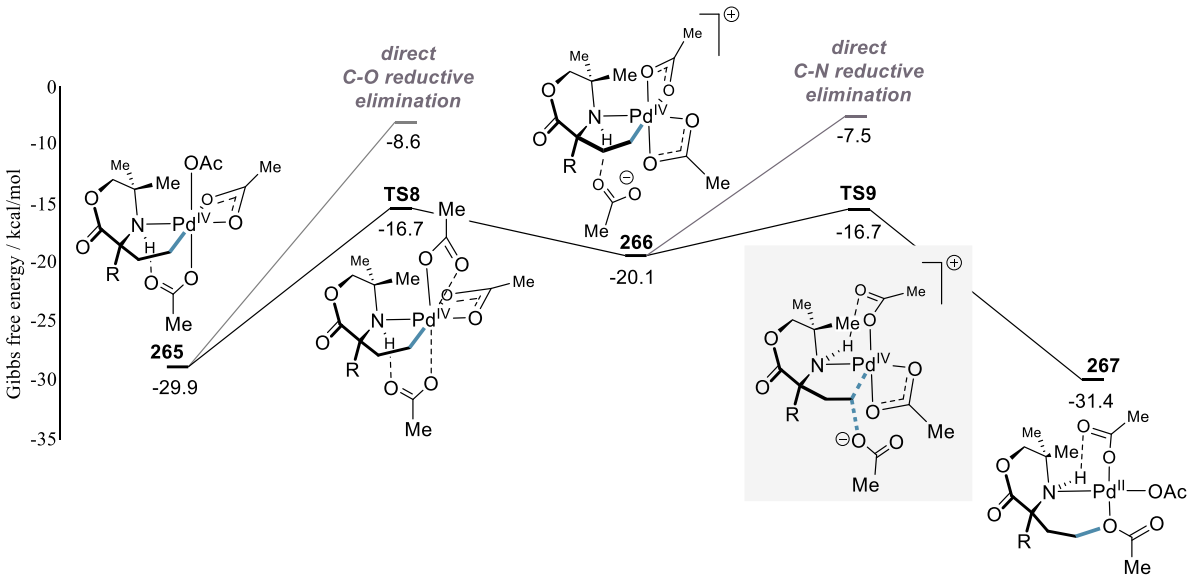
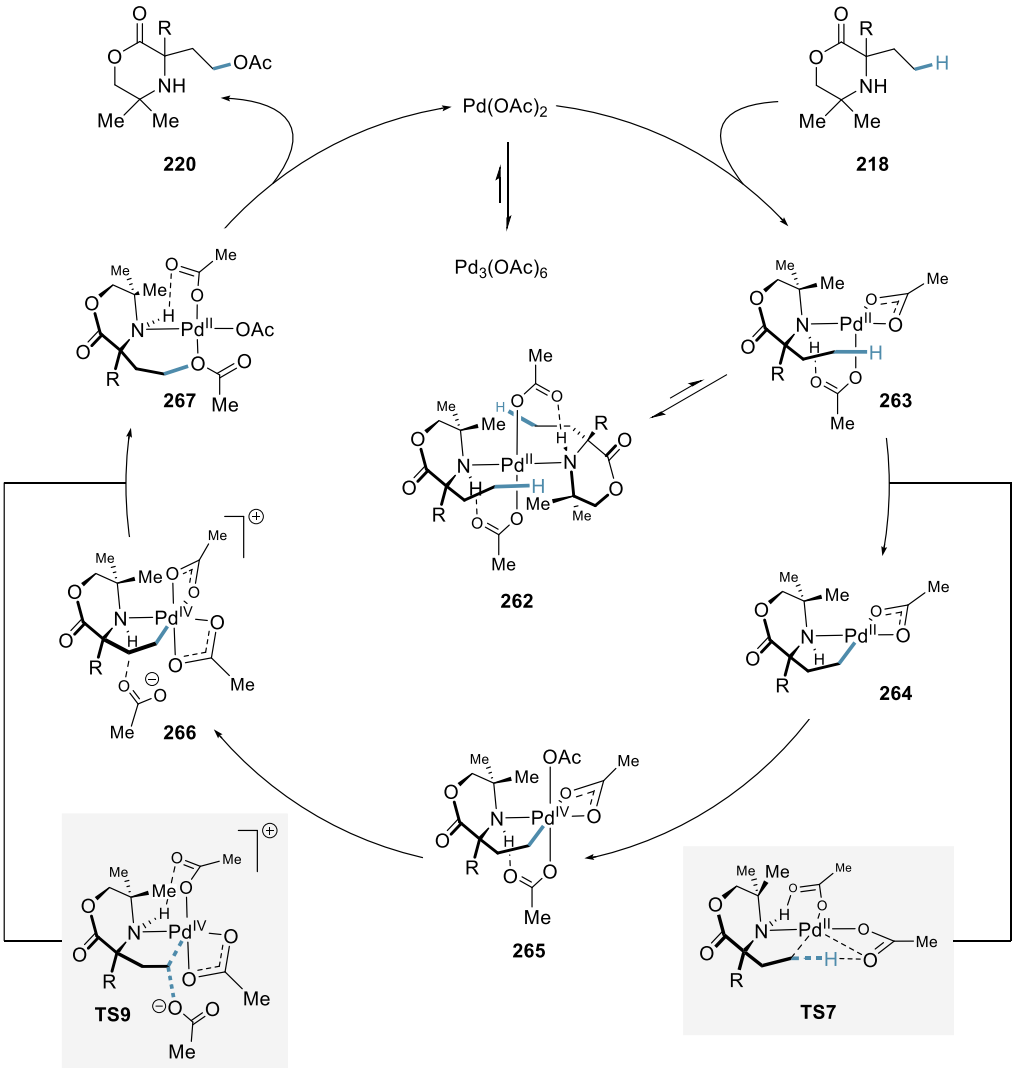


Figure 5 | DFT calculations for morpholinone C–H functionalisation, calculations performed by Dr Ben Chappell

Alternative acetoxylation pathways such as the direct C–O reductive elimination from oxidised palladium complex **265** proved to be significantly higher in energy. Similarly, the direct C–N reductive elimination product (which was never observed experimentally) was shown to proceed *via* a high energy pathway, including the deprotonation of the morpholinone to form an amido-palladium(IV) complex.

2.2.5 Proposed mechanism

The proposed mechanism was formulated based on the kinetic studies and DFT calculations (Scheme **60**) and is consistent with the related stoichiometric studies by Sanford, suggesting a S_N2 process for the Csp^3–O bond formation.[196] Trimeric palladium(II) acetate dissociates to form the monomeric palladium(II) acetate catalyst able to bind aliphatic amine **218**. The *mono*-amine complex **263** is in equilibrium with the off-cycle *bis*-amine complex **262**, in which the saturation of binding sites prohibits a C–H activation event from occurring. The rate limiting Csp^3–H activation (shown by both a primary KIE and highest calculated energetic barrier), arises from the *mono*-amine complex **263** which undergoes CMD *via* a six-membered transition state **TS7** to form palladacycle **264**. The palladium(II) complex **264** is oxidised by the hypervalent iodine reagent ($PhI(OAc)_2$) to furnish the octahedral complex **265**. This high valent palladium complex then undergoes an acetate dissociation to afford a cationic palladium(IV) intermediate **266**, which, in turn, undergoes the key Csp^3–O bond formation by attack of an external acetate onto the highly electrophilic C–Pd bond in a S_N2 fashion (**TS9**). The catalyst bound product, complex **267**, finally undergoes dissociation to return the palladium(II) catalyst and the acetoxylated product **220**.



Scheme 60 | Elucidated mechanism for the aliphatic acetoxylation for the functionalisation of morpholinone substrates **218** to give their C*sp*^{3}–O bond products **220**

2.3 Summary

This chapter has demonstrated a mild and efficient acetoxylation reaction directed by hindered secondary amines. This methodology allows the facile oxidation of aliphatic γ-C–H bonds, difficult to functionalise using traditional synthetic methods. Moreover, this chapter presents a mechanistic study of the developed reaction through kinetic studies and DFT calculation, to elucidate the mechanism of C*sp*^{3}–O bond formation for this catalytic, amine-directed transformation.

This work includes initial optimisation studies, developing conditions that allow for excellent acetoxylation of the model substrate in short reaction times. Subsequently, a substrate scope demonstrating the tolerance of several functional groups in this catalytic reaction was presented. Computational modelling (conducted by Dr Ben Chappell) and kinetic studies (conducted by Dr Darren

Willcox) were used to provide support for rate limiting Csp^3–H activation and C–O bond formation *via* a dissociative ionisation mechanism followed by a S_N2 process involving an external acetate attack.

The work described in this chapter was published in Chemical Science.[220]

3. Alkenylation of tertiary aliphatic amines

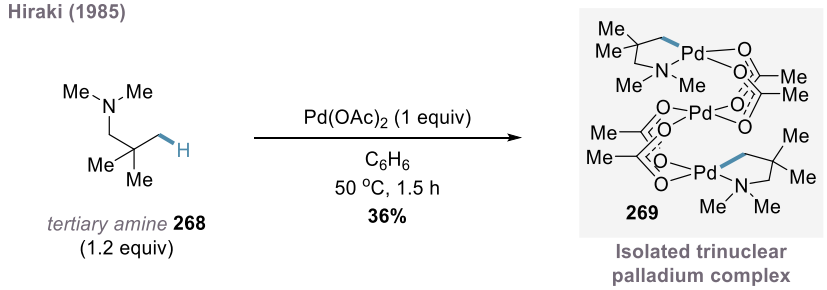
3.1 Introduction

3.1.1 Tertiary amines in C–H functionalisation

Tertiary amines have rarely been used to direct Csp^3–H functionalisation as they are monodentate, neutral directing groups and significantly more sterically encumbered than the secondary or primary amines often used as chelating moieties. Thus, tertiary amines can be classified as weak directing groups due to increased flexibility and conformational degrees of freedom. Yu suggests that weakly chelating groups result in cyclometallated intermediates that are thermodynamically less stable and therefore more reactive in the following C–Pd functionalisation step.[221] The electron rich nitrogen atom present also means this class of compounds is less stable to Csp^3–H functionalisation conditions, particularly to deleterious oxidative degradation processes associated by the presence of metal salts and commonly used oxidants.

Tertiary amines have been employed sporadically in the functionalisation of Csp^2–H bonds, which is facilitated by a more rigid system and initial π-orbital interactions between the metal and the Csp^2–H bond.[221] During the seminal studies on the mechanisms of C–H functionalisation, Ryabov utilised *N*,*N*-dimethylbenzylamine to study the kinetics of C–H activation.[40] To date, much of the work on the functionalisation of tertiary amines has focused on the *ortho*-derivatisation of benzyl amine scaffolds, notably alkenylation and arylation by Shi and Dixon respectively.[146, 222]

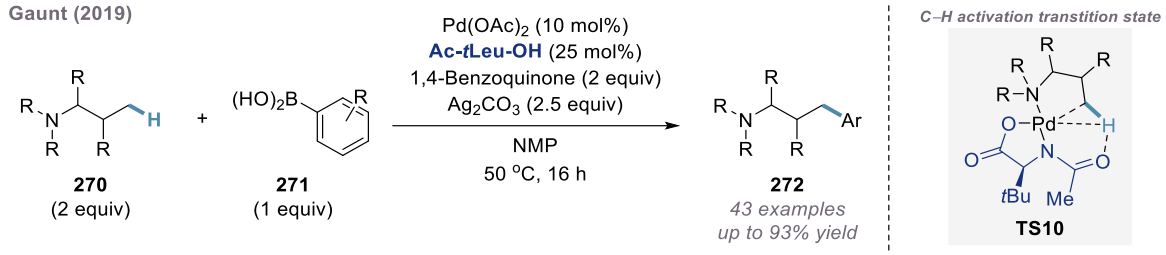
In 1985, Hiraki reported the first tertiary aliphatic amine-directed palladacycle **269** (Scheme **61**).[223] Formation of this complex was achieved by stirring amine **268** with palladium acetate in benzene, however, this complex was not observed when the reaction was conducted in polar solvents such as methanol or acetic acid. The amino-palladium complex **269** was isolated as a trinuclear cyclopalladated species, which was consistent with the observations of Ukhin that treatment of trimeric palladium acetate with an allyl ligand affords a similar trinuclear palladium complex to **269**.[224]



Scheme 61 | Synthesis of all alkyl, trinuclear palladacycle complex **269** by Hiraki[223]

In 2019, the Gaunt group reported the first example of an arylation reaction on tertiary aliphatic amines (Scheme **62**).[225] In this palladium-mediated arylation, a variety of amines **270** were coupled to aryl

boronic acids **271** in excellent yields, tolerating a range of functionality. An excess of amine was required for the reaction to afford excellent yields, especially because boronic acids often suffer from deleterious protodeboronation, oxidation, homocoupling and dehydration processes.[226] The ligand proved crucial in facilitating C–H activation by CMD, which was found to be of lower energy relative to the deleterious β-hydride elimination pathway. Importantly, the ligand was shown to be directly involved in deprotonation of the C–H bond (**TS10**).

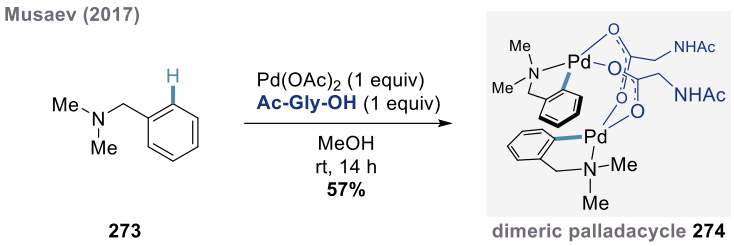


Scheme 62 | Arylation of tertiary aliphatic amines as reported by Gaunt[225]

In the development of the Csp^3–H arylation of tertiary amines, the addition of several reaction components proved critical for efficient catalysis. Silver salts have been routinely added to C–H functionalisation reactions as they oxidise palladium(0) back to palladium(II). However, it has been shown that the addition of silver can also assist Csp^2–H cleavage either as a monomeric, or heterodimeric species with palladium.[227-228] Kinetic and DFT studies have established the involvement of 1,4-benzoquinone in reductive elimination steps from palladium(II); 1,4-benzoquinone can also act as an oxidant.[229-230]

In 2008, Yu pioneered the use of mono-protected amino acid ligands (MPAA) for the pyridine directed Csp^2–H functionalisation of prochiral substrates.[188] These privileged scaffolds have since facilitated a range of C–H functionalisation reactions, including enantioselective induction by relaying chirality from the ligand to the prochiral substrate in the C−H activation transition state.[190, 231-234] Various mechanistic studies conducted by Yu and Houk,[191] Musaev[193] and Sigman[235] showed that C–H activation proceeded *via* an inner-sphere mechanism whereby the acetylated amine abstracted the proton during CMD (**TS10**).

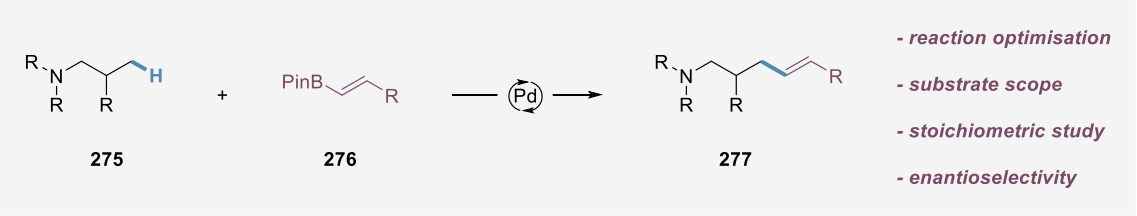
Kinetic studies by Yu and Blackmond showed a significant increase in rate of palladium-catalysed C–H olefination with MPAA ligands.[236] Computational work on the arylation of alkyl amines **270** (Scheme **62**), indicated that the ligand facilitated the Csp^3–H activation, whilst simultaneously disfavouring the deleterious β-hydride elimination.[225] In 2017, Musaev and Lewis reported the first example of a cyclopalladated palladium(II)-MPAA complex **274** (Scheme **63**).[237] The dimer afforded from cyclopalladation of tertiary amine **273** was shown by DFT calculation to be more stable than the monomeric palladium complex or the corresponding acetate bridged dimers studied previously.[238] To date there have been no reports of isolated aliphatic amine palladacycles bearing MPAA ligands.



Scheme 63 | Isolated dimeric cyclopalladated palladium(II)-MPAA complex isolated by Musaev and Lewis[237]

3.1.2 Project aims

Following the work by our group on the arylation of tertiary aliphatic amines, the aim of this project was to develop a C*sp*^{3}–H functionalisation reaction that would enable the installation of an alkene as a functional handle.[225] Olefins can be manipulated using a number of reagents, allowing specific fine-tuning, thus making this functionality ideal for late stage derivatisation. The goal of this project was to develop a palladium-catalysed alkenylation reaction on tertiary aliphatic amines mediated by MPAA ligands. We aimed to present a substrate scope that would demonstrate functional group tolerance and a variety of alkenylation products. Furthermore, isolation of an intermediate tertiary amine palladacycle would allow insight into reaction intermediates as well as stoichiometric studies. Finally, the use of chiral amino acid ligands would allow the evaluation of possible enantioinduction during the C*sp*^{3}–H alkenylation for prochiral substrates.



Scheme 64 | Alkenylation of tertiary aliphatic amines

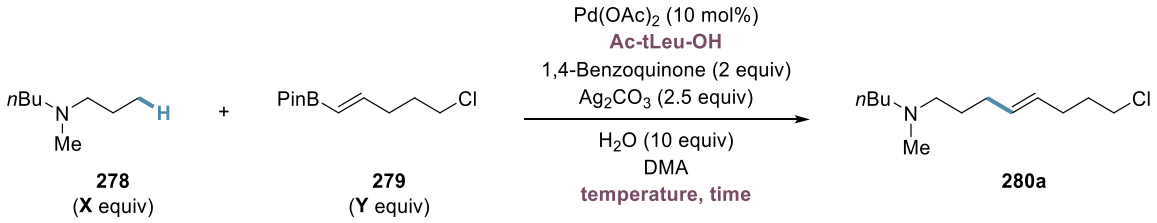
3.2 Results and discussion

3.2.1 Reaction discovery and optimisation

Starting point for the development of a tertiary amine olefination was the seminal study done by our group on the C–H arylation of tertiary aliphatic amines.[225] However, boronic acids in particular tend to be more reactive than their ester counterparts, undergo facile protodeboronation and can exist as boroxines where the extent of dehydration is often difficult to determine.[183, 239] Thus, the palladium-catalysed C–H alkenylation was developed using the more commercially available alkenyl boronic esters, in order to attenuate the reactivity of the alkenyl coupling partners.

Preliminary studies began with the reaction components believed to be crucial for catalysis: palladium acetate, a MPAA ligand, an oxidant and 1,4-benzoquinone. Water was added because, although exact transmetallation processes remain unknown, hydroxy-palladium(II) complexes have been reported as intermediate catalytic species.[240-243] Initial optimisation studies for the Csp^3–H alkenylation reaction in *tert*-amyl alcohol (which proved efficient for aryl boronic esters) afforded only trace amounts of product (see *Appendix I iii*).

Aliphatic amine **278** was selected for optimisation due to its volatility allowing its removal from the reaction on work up, which was envisaged to provide cleaner crude reaction profiles. A solvent screen found DMA to be the most effective solvent for the alkenylation of aliphatic amine **278**. Addition of ten equivalents of water similarly proved effective (more so than addition of hydroxide), while the bulky, acetyl-protected *tert*-leucine ligand performed significantly better than less bulky ligands.



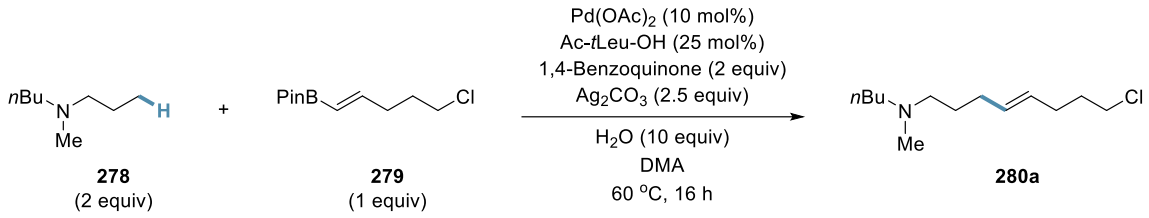
278 (**X** equiv) + **279** (**Y** equiv) → **280a**

Entry	X:Y equiv	Ligand	Temperature / ºC	Time / h	Yield[a]
1	1:1	15 mol%	80	4	18%
2	1:1	15 mol%	60	16	46%
3	1:1	15 mol%	60	40	38%
4	1:10	15 mol%	60	16	19%
5	1:5	15 mol%	60	16	27%
6	1:3	15 mol%	60	16	35%
7	2:1	25 mol%	60	16	53%

Table 4 | Reaction optimisation, all reactions performed at 0.1 mmol scale; [a] Yield determined by ^{1}H-NMR spectroscopy using 1,1,2,2,-tetrachloroethane as an internal standard

After preliminary screening, the formation of alkenyl amine **280a** was observed in moderate 18% yield (Table **4**, entry 1). Higher yields could be achieved by lowering reaction temperature but required longer reaction times (entry 2). However, it was evident that extending the reaction time to 40 hours (entry 3) gave lower yields, suggesting decomposition of amine **280a**. Increasing the amount of boronic ester **279** (entries 4-6) proved detrimental to conversion of the alkyl amine substrate **278**. The highest yields for initial screening of conditions indicated that an excess of amine was necessary to furnish olefin **280a** in synthetically useful yield.

Throughout the optimisation, issues with reproducibility were observed, which required repetition of multiple reactions in order to get reliable outcomes. It was proposed that this issue stemmed primarily from the insolubility of silver carbonate in the reaction solvent, DMA. As alternative oxidants (silver or copper salts) proved inferior, it was decided to investigate methods to enable a consistent dispersion of silver carbonate in the reaction mixture.



278 (2 equiv) | **279** (1 equiv) | **280a**

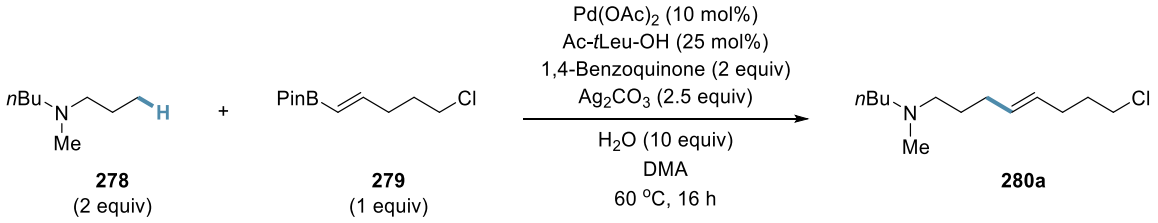
Entry	Δ	Yield[a]
1	2 h sonication	trace
2	cylindrical stirrer bar	31%
3	oval stirrer bar	38%
4	sand	49%
5	-[c]	60%[b]

Table 5 | Optimisation of reaction conditions for homogenisation of insoluble silver carbonate, 0.3 mmol scale; [a] Yield determined by ^{1}H-NMR spectroscopy using 1,1,2,2,-tetrachloroethane as an internal standard. [b] Average ^{1}H-NMR yield of reactions performed in duplicate (yields within 5%). [c] solids ground by pestle and mortar ("CB-mix").

Attempts at sonication of the reaction mixture for two hours prior to stirring at 60 °C for 16 hours, gave only trace amount of alkenylated product **280a** (Table **5**, entry 1). A slight increase in yield (from 31% to 38%) was observed when employing an oval stirrer bar (entry 3) over a cylindrical stirrer bar (entry 2). Presumably, this effect could be attributed to the ability of the oval stirrer bar to agitate the solids aggregating at the bottom of the reaction vessel. Furthermore, addition of sand (entry 4), which was postulated to increase the dispersion of the silver carbonate throughout the reaction mixture, did give a slight improvement in yield. Finally, the grinding of all solid components (palladium acetate, ligand, benzoquinone and most importantly silver carbonate) gave the highest yield of alkenylation product **280a**. The ground solids performed just as well as ground silver carbonate being added to the reaction.

This amended reaction protocol for addition of the insoluble oxidant ensured reproducible reaction yields.

Finally, after optimisation screening, some control studies were conducted to ensure the reaction parameters for best possible conversion had been reliably determined (Table **6**). The addition of only one equivalent of oxidant (entry 2) demonstrated a loss in conversion, to give amine **280a** in 53% yield. A decrease in yield was also observed upon removal of water (entry 3) demonstrating an inferior yield of 50%. Furthermore, both increasing (entry 4) and decreasing (entry 5) catalyst/ligand loading gave lower conversions, which indicates how sensitive this transformation is. Finally, the addition of equimolar amounts of amine **278** and boronic ester **279** afforded a significant loss in yield to 39%, which was observed in the analogous arylation reaction.[225]



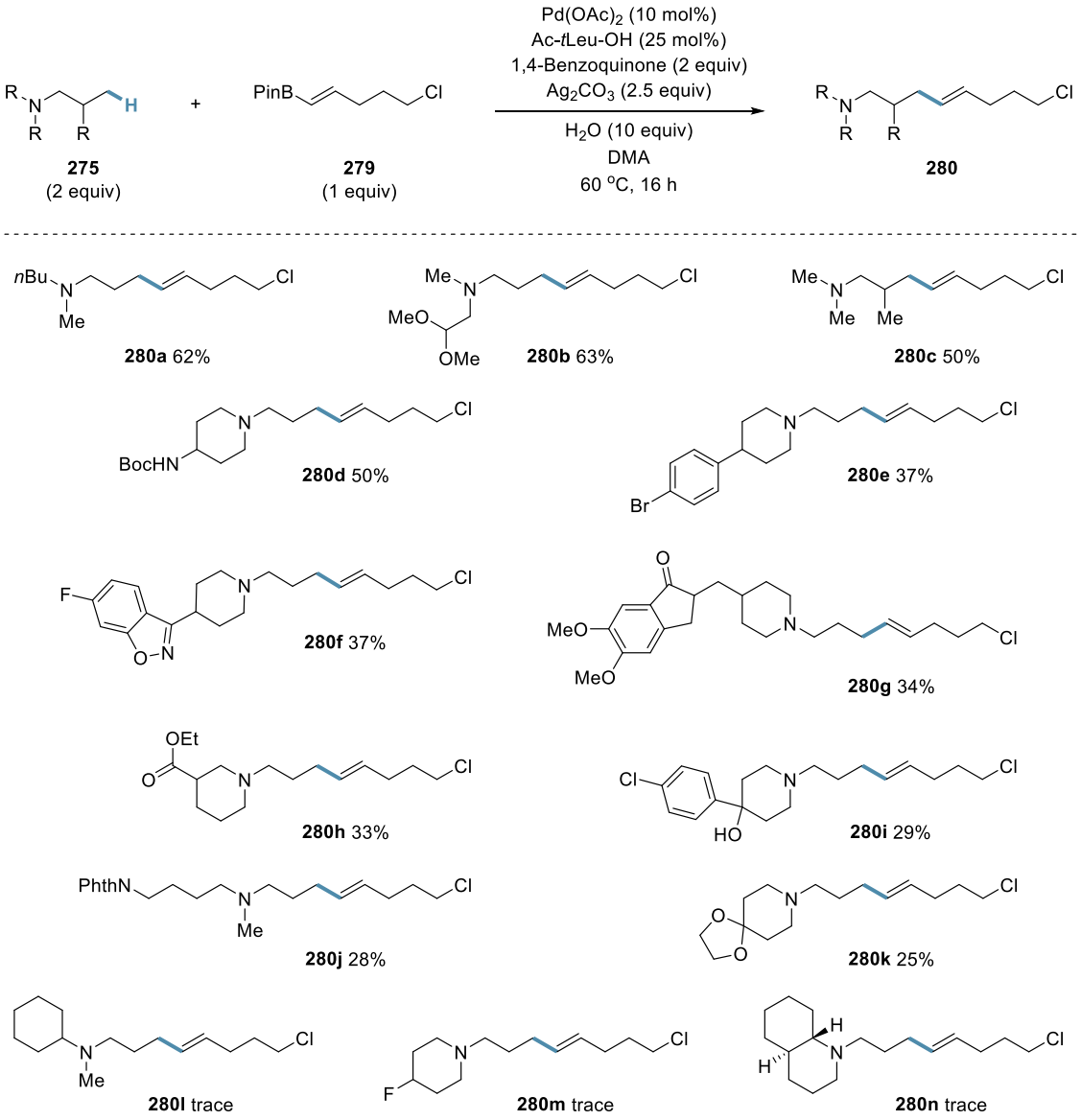
Entry	Δ	Yield[a]
1	-[b]	60% (43% isol.)
2	Ag_2CO_3 (1 equiv)	53%
3	No H_2O	50%
4	$Pd(OAc)_2$ (20 mol%), Ac-*t*Leu-OH (50 mol%)	44%
5	$Pd(OAc)_2$ (5 mol%), Ac-*t*Leu-OH (12.5 mol%)	28%
6	1 equiv amine **278**	39%

Table 6 | Reaction optimisation, performed at 0.3 mmol scale; [a] Yield determined by ^{1}H-NMR spectroscopy using 1,1,2,2,-tetrachloroethane as an internal standard; [b] solids ground by pestle and mortar ("CB-mix")

We noted that the protocol for the workup and purification required reviewing due to the discrepancy we observed between the ^{1}H-NMR assay and isolated yields (Table **6**, entry 1). This was attributed to two problems in the workup and purification procedure. Firstly, remaining DMA in the crude reaction mixture hindered purification by SCX column and adequate separation of reaction components by silica gel chromatography. Secondly, difficult separation of the crude reaction mixture, especially starting material and alkenylation products by column chromatography, which resulted in mixed fractions and ultimately lower isolated yields. To resolve these issues we implemented an additional brine wash in the workup procedure to ensure extraction of the polar aprotic solvent into the aqueous layer.[244] Additionally, we adjusted the conditions for column chromatography by using a very flat gradient, typically eluting with 1% methanol/ethyl acetate. Ultimately this allowed the isolation of clean alkenylation products for the examples highlighted in the substrate scope (*vide infra*).

3.2.2 Substrate scope

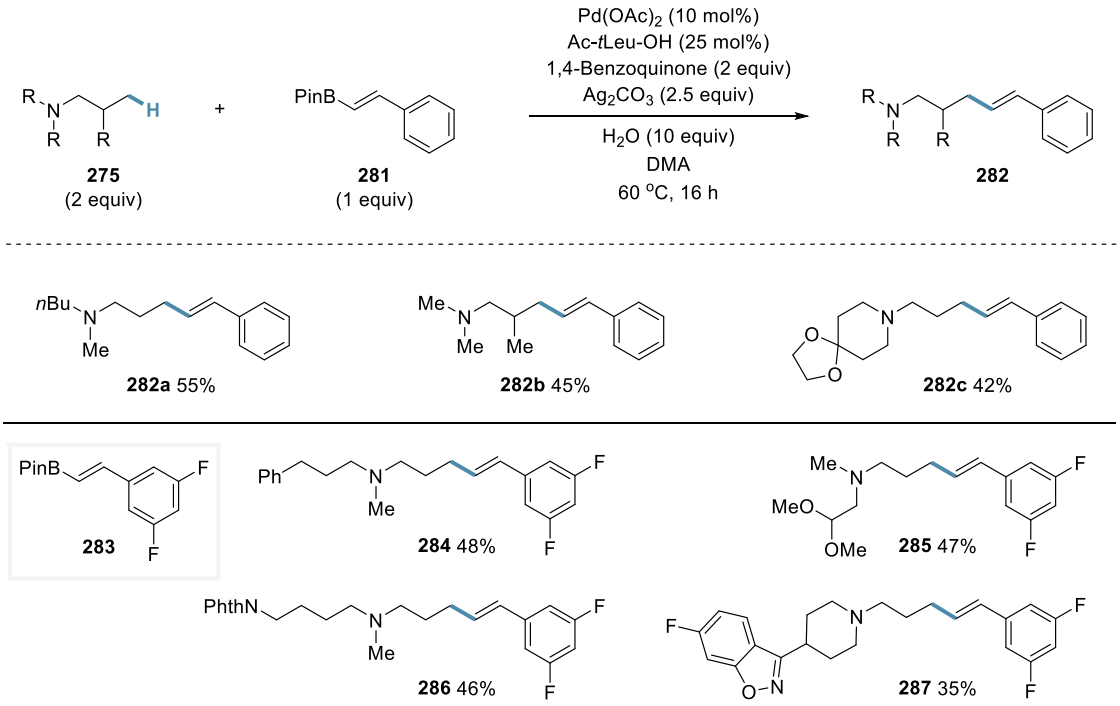
The alkenylation of tertiary amines with alkenyl boronic ester **279** proved to be tolerant and of a variety of functionality, albeit in moderate yields (Scheme **65**). Simple alkyl amines afforded the corresponding olefinated products **280a** and **280c** in 62% and 50% yield respectively, while acetal amine gave a 63% yield of the alkenylated product **280b**. Protected amine functionality was tolerant to the olefination reaction conditions and furnished compounds bearing two different aliphatic amines **280d** and **280j**, giving yields of 50% and 28% respectively. Moreover, the alkenylation of substrates containing aryl bromides were obtained in moderate yields to give the corresponding alkenylation product **280e** in 37% yield.



Scheme 65 | Substrate scope for the alkenylation of tertiary aliphatic amines with alkenyl boronic ester **279**

Derivatives of small molecule drug fragments such as *iloperidone* and *donepezil*, were alkenylated to give products **280f** and **280g**, which would be challenging to access from the parent amines when using traditional synthetic methods. Furthermore, esters **280h** (33%) and free alcohols **280i** (29%) could be tolerated, as well as substrates containing ketals **280k** (25%). Trace amounts of alkenylation products **280l**, **280m** and **280n** were observed by crude ^{1}H-NMR, however, not in sufficient quantities for isolation.

Moreover, the alkenylation of aliphatic amines utilising styryl boronic acids **281** and **283** was demonstrated (Scheme **66**). All-alkyl amines provided good yields of the alkenylation products **282a** (55%) and **282b** (45%), while aliphatic amine bearing a ketal functionality was shown to undergo good conversion to the corresponding olefin product **282c** in 42% yield. Furthermore, amines bearing γ-phenyl groups underwent exclusive alkenylation, in 48% yield, at the terminus of the propyl chain to give functionalised amine **284**. Again, acetals and protected nitrogen groups were tolerated giving the corresponding alkenylation products **285** and **286**, affording yields of 47% and 46% respectively. Finally, the installation of a fluorinated styrene appendage on the *iloperidone* fragment **287** was observed, albeit in a modest 35% yield. The use of an electron rich styryl boronic ester (R = 3,5-*di*-MeO) was unsuccessful; no alkenylated products could ever be recovered from those reactions.



Scheme 66 | Substrate scope for the alkenylation of tertiary aliphatic amines with styryl boronic esters **281** and **283**

For a significant proportion of substrates, no alkenylation products could be observed from the developed C–H functionalisation reaction. In the case of these unsuccessful substrates, reaction profiles showed a complex mixture of products, indicating undesired reactivity and starting material decomposition (Figure **6**). For reactions with the boronic ester **279**, eight amines afforded no isolatable

olefination products. In the case of amine **292** the steric environment around the native directing group likely precluded efficient ligation to the catalyst, while cyclic amine **290** gave an inseparable mixture of olefination products. Substrates **288**, **293**, **294** and **295** are able to form chelates with the palladium catalyst, which seem to preclude the association of the γ-C–H bond for activation; Whereas ketone containing amine **289** likely suffers from facile deprotonation of the moderately acidic α-carbonyl protons thus precluding the desired ligation to palladium. For vinyl boronic ester **296** the olefination proved unsuccessful for both amines **297** and **298** yielding complex mixtures. It has been reported that vinyl boronic esters can react not only *via* the traditional transmetallation, but also undergo a Mizoroki-Heck type reaction with aryl iodides.[245]

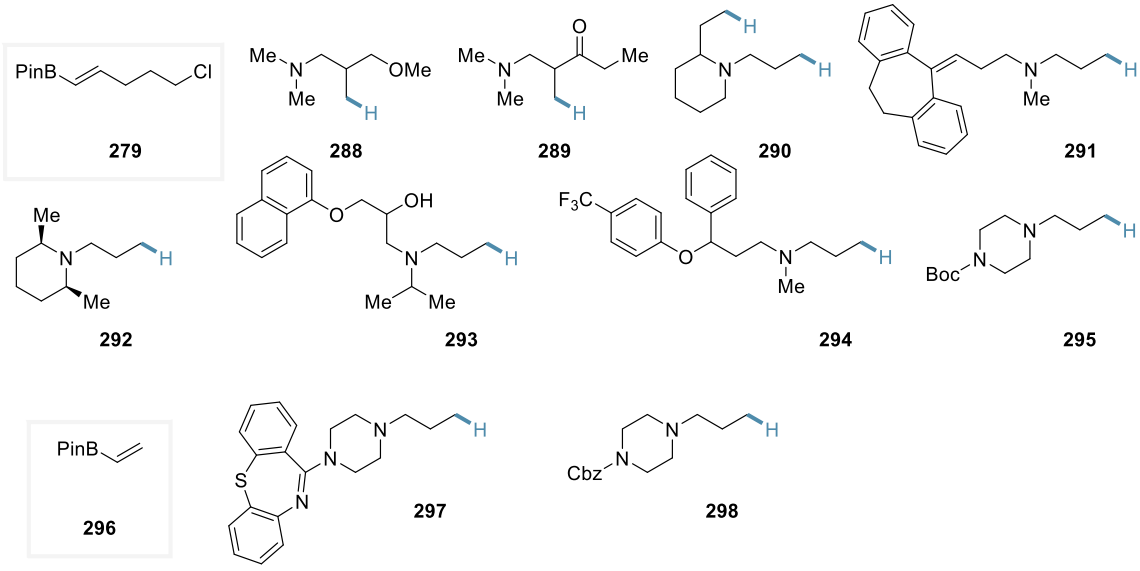
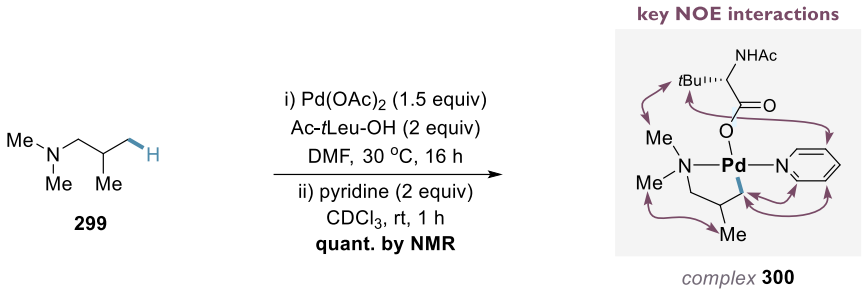


Figure 6 | Unsuccessful alkenylation substrates

Unfortunately, the yields for this Csp^3–H functionalisation were considerably lower than the corresponding arylation.[225] However, similarly modest yields for installation of alkenes from alkenyl boronic esters have been observed before by Yu in 2018 (Scheme **47**).[195] This can be attributed to the known reactivity of alkenes in the presence of palladium salts which have been shown to undergo Wacker-oxidation and intramolecular Mizoroki-Heck reaction, especially in the absence of phosphine ligands.[47-48, 172] Work by Engle has also shown the hydroarylation of unactivated alkenes using aryl boronic acids in the presence of palladium, although these use strong bidentate directing groups.[246-248] There is also precedent for Csp^2–H activation at the installed alkene to form an undesired palladacycle which can contribute to the consumption of product.[249] Ultimately, the alkenylation reactions suffer from poor mass balance indicative of deleterious processes that consume both starting materials and products (Table **4**, entries 2-3). While this may be controlled through close reaction monitoring, the installation of an alkene in this manner can be associated with deleterious side-reactivity which, fundamentally and paradoxically is what makes its installation so interesting.

3.2.3 Stoichiometric studies

To study the reaction intermediates, we explored the isolation of an aminoalkyl palladacycle facilitated by MPAA ligands. Isolation of a palladacycle proved difficult with the tertiary amine substrates. This could likely be attributed to the relatively facile dissociation of the directing amine and resulting palladacycle decomposition. However, previous organometallic study of palladium complexes within our group enabled the isolation of complex **300** from aliphatic amine **299**, which was shown to be sufficiently stable to be characterised by NMR (Scheme **67**).[250-251]



Scheme 67 | Synthesis of palladacycle complex **300**

Stirring of amine **299** with palladium acetate and MPAA ligand, in DMF at 30 °C overnight furnished a brown reaction mixture. The high boiling solvent was removed under a stream of air and the resultant amorphous solid dissolved in deuterated chloroform and filtered. After addition of excess pyridine, the solution turned light yellow, which indicated formation of monomeric palladium complex **300**. The colour change, as the monomeric palladium complex **300** was formed, had been observed by Hiraki after addition of a phosphine ligand to the trinuclear complex **269** (Scheme **61**). Interestingly, upon the addition of excess amine instead of pyridine, no monomeric complexes were observed by ^{1}H-NMR.

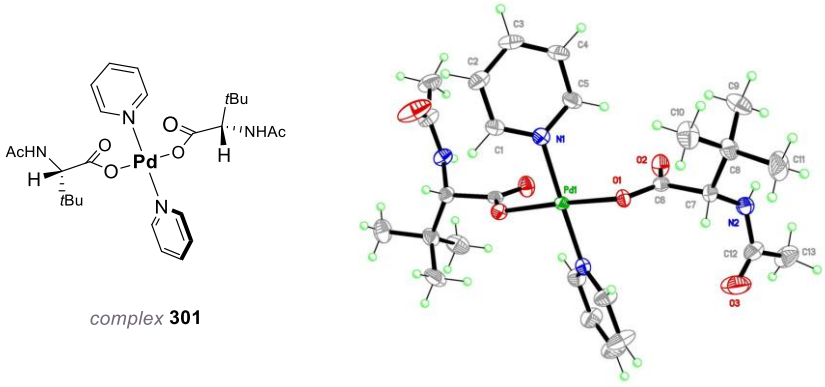


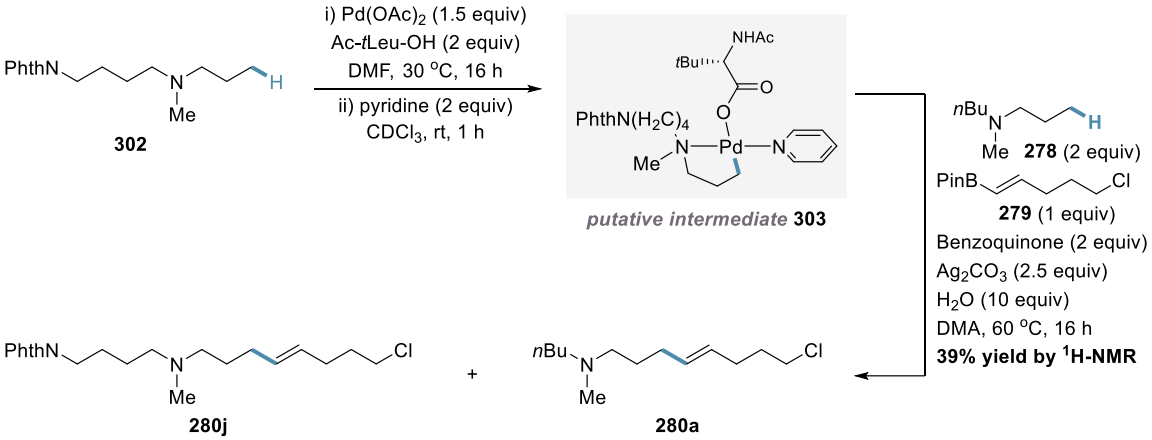
Figure 7 | Structure of the observed decomposition complex **301** during crystallisation attempts of palladacycle **300**

Attempts to crystallise complex **300** were unsuccessful, even when utilising phosphine ligands. Hiraki had previously reported the trinuclear aliphatic amine palladacycles, however isolation of the monomeric species similarly proved difficult when triphenyl phosphine was added to the trinuclear complex **269**.[223] It had also been reported that the addition of the phosphine ligand formed the desired

monomer as an oil. In this work, complex **300** was observed as a light yellow oil, while any crystalline solids proved to be the decomposition product, complex **301** (Figure **7**).

The synthesis of aminoalkyl palladacycles prompted the study of stoichiometric alkenylation utilising the intermediate palladacycle as the catalyst (Scheme **68**). To this end, amine **302** was cyclometallated and the crude monomeric palladacycle complex **303** formed. To investigate the catalytic viability of the palladacycle, the remaining reaction components (olefin **279**, benzoquinone, silver carbonate and water) as well as two equivalents of amine **278** were added to the crude palladacycle mixture. Addition of amine **278** allowed investigation into the catalytic viability of alkylamino palladacycle **303** through monitoring if olefination products were limited to the olefination of the bound amine **302** or a mixture of both (indicating catalytic viability). Early stoichiometric studies showed that the addition of a single equivalent of amine yielded no desired olefination product.

After work up, analysis of the reaction mixture by ^{1}H-NMR showed the formation of 39% alkenylated amine containing both olefinated products **280j** and **280a** (25% and 14% respectively, see *Appendix I vii*). The presence of alkenylated product **280a** indicated that complex **303** was capable of catalytic turnover, by showing that amine **278** underwent C–H functionalisation.



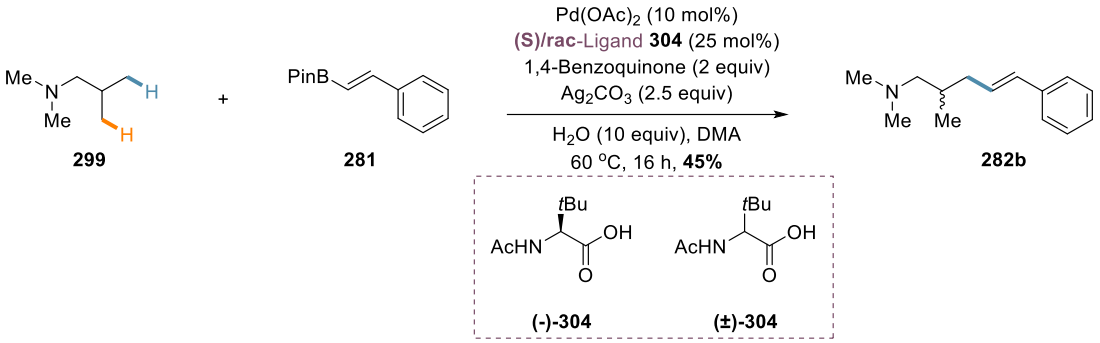
Scheme 68 | Stoichiometric studies of intermediate palladacycles with amines **302** and **278**

This stoichiometric study indicates the catalytic viability of the cyclometallated intermediate **303**. The formation of products **280j** and **280a** demonstrates catalytic turnover and therefore that palladacycle complexes are significant intermediates in this palladium-catalysed alkenylation reaction.

3.2.4 Enantioselective alkenylation

Furthermore, we wanted to investigate the possibility of enantioinductive alkenylation through the amino acid-based ligand. Recent work by Gong demonstrated the enantioselective arylation of Csp^3–H bonds by employing catalytic quantities of chiral phosphoric acid ligands.[252] Similarly, enantioinduction using MPAA ligands has been shown by our group, affording the arylated amines in

very good enantiomeric ratios.[225] For this purpose, alkyl amine **299** was selected as the prochiral substrate which upon C*sp*^{3}–H alkenylation would furnish a β-stereogenic centre on styryl product **282b** (Scheme **69**).



Scheme 69 | Alkenylation of prochiral aliphatic amine **299** with boronic ester **281** to afford enantioenriched amine **282b**

Alkyl amine **299** was subjected the optimised alkenylation reaction conditions, with the addition of either racemic **(±)-304** or chiral amino acid **(-)-304** ligand and the resultant olefinated products **282b** were isolated from the reaction mixture. Unfortunately, the ratio of enantiomers could not be determined by chiral chromatography on either chiral GC-MS or chiral SFC. Thus, to determine the ratio of enantiomers we therefore turned our attention to NMR in order to ascertain the enantiomeric excess (if any) for the alkenylation reaction. Derivatisation of the olefination product **282b**, as originally reported by Lacour, to the quaternary amine salt and introduction of the chiral BINPHAT anion, allowed the determination of the enantiomeric excess for the reaction (see *Appendix I viii*).[253] Resultant analysis by ^{1}H-NMR showed that the use of chiral ligand **(-)-304** had afforded a very good enantiomeric ratio of 92:8 (84% ee).

3.3 Summary

This chapter reports the development of a challenging alkenylation reaction of tertiary amines substrates. After extensive optimisation studies reaction conditions that achieved satisfactory yields of the alkenylation product were found, which demonstrated good functional group tolerance. We also report the isolation of a MPAA ligand-bound palladacycle which could be subjected to stoichiometric studies, demonstrating the catalytic capability of intermediary palladacycle complexes. Finally, the use of an amino acid derived ligand enabled the enantioselective alkenylation of a prochiral amine in very good enantiomeric excess. The developed reaction allows γ-C*sp*^{3}–H olefination remote from the directing amine utilising alkenyl boronic esters, which would be challenging to install using traditional synthetic methods.

4. Conclusions and outlook

Aliphatic amines are a privileged moiety featured heavily in molecules found to be pharmaceutically active. Traditionally, protecting groups have been utilised to attenuate the nucleophilicity of amines during derivatisation, especially for C–H activation. This thesis has presented two C–H functionalisation reactions that use native amines as directing groups.

The acetoxylation of cyclic amines was demonstrated with very good functional group tolerance in Chapter 2. Optimisation studies ensured fast reaction times to yield the desired acetoxylated products in synthetically useful yields. Kinetic studies and DFT calculations were employed to elucidate the mechanism of the transformation. These studies revealed mechanistic detail such as rate limiting Csp^3–H activation and C–O bond formation through external acetate attack onto a cationic palladium(IV) complex.

The facile C–H activation and acetoxylation of morpholinones offers the opportunity for the discovery of novel oxidants that can be utilised for Csp^3–O bond formations. In particular, this may be expanded to oxidants that can achieve selective oxidation to palladium(IV) species in the presence of α-hydrogen atoms. Also, the acetoxylation of less hindered aliphatic amines would allow for more diverse amine substrates. Additionally, this may be expanded to oxidants bearing other heteroatoms such as nitrogen to provide more versatile functionalisation opportunities.

The alkenylation of tertiary amines using alkenyl boronic ester reagents was described in Chapter 3. After initial optimisation of the heterogeneous reaction, the optimised conditions allowed the olefination of a range of aliphatic amines which proved tolerant of a diverse range of functionality. An enantioenriched MPAA ligand was able to relay chirality for the alkenylation of a prochiral amine substrate, providing very good enantiomeric excess (84% ee). Furthermore, isolation of the intermediate alkylamine palladacycle was demonstrated and could be used in stoichiometric reactions, albeit in modest yields.

The development of tertiary aliphatic amine directed C–H olefination has expanded the possibilities of developing more diverse functionalisations of such substrates by utilising other redox mechanisms. Enantioselective C–H activation of prochiral substrates is a powerful methodology which can benefit from future studies, especially through ligand tuning, to achieve excellent enantiomeric ratios. Additionally, the isolation of aliphatic amine palladacycles offers the expansion of possible C–Pd functionalisation reactions through stoichiometric studies. Development of an organometallic platform resulting from isolation of the intermediary palladacycles will also give insight into the behaviour of such species.

The work described in this thesis has demonstrated the ability of secondary and tertiary amine substrates to act as competent directing groups for C–O and C–C bond forming processes. Future research should be focused on trapping of high valent palladium(IV) complexes with external nucleophiles to give catalytic reactions affording a range of functionalised products, independent of the oxidant. In addition to this, accessing high valent palladium pathways for amine substrates bearing α-hydrogen atoms would be a powerful methodology. The realisation of this would dramatically increasing the scope of amines amenable to C–H functionalisations *via* a palladium(II)/palladium(IV) pathway.

Furthermore, the research in this thesis presents opportunities for the development of further Csp^3–H functionalisation methodologies, allowing the construction of high value molecules from feedstock chemicals. Related functionalisation processes such as C–N bond formation *via* palladium(II)/palladium(IV) could be developed using nitrogen-based oxidants to expand the toolbox of C–H activation for synthetic chemists. Fundamentally, the study of individual reactions feeds into a holistic understanding of C–H functionalisation using palladium-catalysts, and ultimately can enable a robust and general C–H activation platform.

5. Experimental procedures

5.1 General experimental

All reactions were run under an inert atmosphere (N_2) unless otherwise stated, with oven-dried glassware, using standard techniques. Anhydrous solvents were obtained from solvent stills (diethyl ether was distilled from sodium triphenylmethane ketyl; tetrahydrofuran from lithium aluminium hydride; acetonitrile, dichloromethane, hexane and toluene from calcium hydride). Petroleum ether is 40-60 bp unless stated otherwise. Reagents were used as supplied. Palladium(II) acetate was purchased from Alfa Aesar. Amines were used as supplied if sufficiently pure, otherwise they were purified by distillation. [Me_2NH_2] [(Δ,*S*)-BINPHAT] was prepared by Dr Dominik Reich.

Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 0.20 mm precoated, glass backed silica gel plates. Visualisation was performed by UV absorbance (λ_{max} = 254 nm), by aq. $KMnO_4$ or by ceric ammonium nitrate (CAN) solution. Flash column chromatography was performed using silica gel (Merck Geduran Si 60, 40-63 μm) with the specified solvent system.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 or DPX 500 spectrometer with cryoprobe. Chemical shifts (δ) for ^{1}H NMR spectra are recorded in ppm from Me_4Si with the solvent resonance as the internal standard ($CDCl_3$ = 7.26 ppm, MeOD-d^4 = 3.31 ppm, AcOD-d^4 = 11.65 ppm). Data is reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = sextet, hept = heptet, oct = octane, non = nonane, m = multiplet, br. = broad), coupling constant, integration and molecular assignment). ^{13}C NMR spectra are reported in ppm from Me_4Si with the solvent resonance as the internal standard ($CDCl_3$ = 77.16 ppm, MeOH-d^4 = 49.00 ppm). ^{19}F NMR spectra are reported in ppm from $CFCl_3$ and are uncorrected. ^{1}H NMR yields were determined with 1,1,2,2-tetrachloroethane. 2D experiments (COSY, HSQC, HMBC, NOESY) were used to assign spectra but are not included. Coupling constants are quoted to the nearest 0.1 Hz.

High resolution mass spectrometry (HRMS) was carried out by the EPSRC Mass Spectrometry Service at the University of Swansea using a LTQ Orbitrap XL spectrometer, the Mass Spectrometry Service at the University of Cambridge using a Waters Vion IMS Q-TOF and Shimadzu Q-TOF LCMS-9030 with positive ion nanoelectrospray. Infrared (IR) spectra were collected using a Perkin-Elmer Paragon 1000 Fourier transform Spectrometer equipped with ATR and a Thermo Fisher Scientific Nicolet Summit Pro equipped with an Everest ATR, with absorption maxima (ν_{max}) quoted in wavenumbers (cm^{-1}). Melting points (Mp) were recorded using a Gallenkamp melting point apparatus and are uncorrected. Optical rotation ($[\alpha]_D^{20}$) values were measured on an Anton Paar MCP 100 polarimeter using a sodium lamp (589 nm) and are reported in 10^{-1} deg cm^2 g^{-1} with concentration in mg mL^{-1}.

General Procedure A: Synthesis of morpholinones

Amino alcohol (1 equiv), ketone (10 equiv) and $CHCl_3$ (1.5 equiv) were added to a flask, cooled to 0 °C and powdered NaOH (5.2 equiv) was added slowly. The ice bath was removed after 1 h and the reaction mixture stirred at rt for 16 h. The reaction was filtered, and the white gum washed generously with MeOH. The filtrate was concentrated *in vacuo*, acidified with conc. HCl and then refluxed at 130 °C for 2 days. The reaction was cooled and neutralized by slow addition of $NaHCO_3$. The neutralised phase was extracted with CH_2Cl_2 (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was then purified as specified.

General Procedure B: Alkylation of morpholinones

Morpholinone (1 equiv) was dissolved in THF/DME (1:1, 2 mL/mmol) and cooled to -78 °C. NaHMDS (1 equiv) was added dropwise and the mixture stirred for 10 minutes. Alkyl iodide (2–3 equiv) was added to the reaction mixture which was stirred o/n, while warming to rt. The reaction was quenched by the addition of sat. aq. NH_4Cl and extracted with diethyl ether (3x). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography as specified.

General Procedure C: Acetoxylation of morpholinones

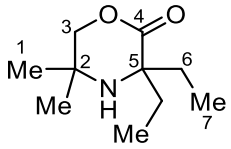
The morpholinone (1 equiv) was dissolved in acetic acid/acetic anhydride (4:1, 0.1 M). Palladium(II) acetate (10 mol%) and $PhI(OAc)_2$ (1.5 equiv) were added and stirred for a specified time at 70 °C. The reaction was cooled to rt, quenched by the addition of sat. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography as specified.

General Procedure D: Alkenylation of tertiary amines

A flask was charged with tertiary amine (2 equiv), alkenyl boronic ester (1 equiv), palladium(II) acetate (10 mol%), Ac-L-*t*Leu-OH ligand (25 mol%), 1,4-benzoquinone (2 equiv), Ag_2CO_3 (2.5 equiv, finely ground by pestle and mortar), water (10 equiv), DMA (0.4 M), sealed and stirred at 60 °C for 16 h. After completion, the reaction was cooled to rt. Et_2O was added to the reaction mixture which was subsequently filtered through a Celite plug. The organic layer was washed with 1% NaOH (3x) and brine, and dried over $MgSO_4$. The crude material was purified by flash chromatography as specified.

5.2 Experimental procedures for the acetoxylation of morpholinones

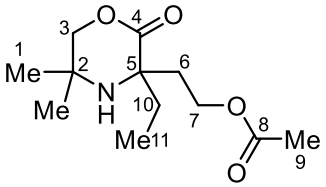
3,3-Diethyl-5,5-dimethylmorpholin-2-one **112**



Prepared according to general procedure **A**. The crude material was purified by flash chromatography (silica gel, 15 cm, 3 cm Ø), eluting with 0-30% EtOAc/petroleum ether, to give the title compound **112** as a light yellow oil (1.3 g, 7.0 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (s, 2H, H_3), 1.72 (dq, *J* = 14.0, 7.4 Hz, 2H, H_{6a}), 1.61 (dq, *J* = 14.0, 7.4 Hz, 2H, H_{6b}), 1.16 (s, 6H, H_1), 0.90 (t, *J* = 7.4 Hz, 6H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.2 (C_4), 77.5 (C_3), 61.4 (C_5), 48.6 (C_2), 32.9 (C_6), 26.8 (C_1), 8.3 (C_7). **IR** ν_{max}/cm^{-1} (film): 2970, 2950, 2880, 1709, 1459, 1379, 1285, 1222, 1183, 1131, 1104, 1050. **HRMS** (ESI) calculated for $[C_{10}H_{19}NO_2+H]^+$: 186.1489, found: 186.1485. $\mathbf{R_F}$ = 0.20 (20% EtOAc/petroleum ether). Data consistent with literature.[102]

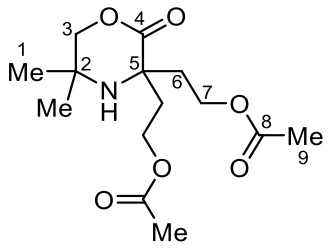
2-(3-Ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)ethyl acetate **113**



Prepared according to general procedure **C** using 3,3-diethyl-5,5-dimethylmorpholin-2-one **112** (56 mg, 0.30 mmol), the reaction was stirred at 70 °C for 1 h. The crude material was purified by flash chromatography (silica gel, 11 cm, 2 cm Ø), eluting with 0-20% EtOAc/CH_2Cl_2, to give the title compound **113** as a yellow oil (34 mg, 0.14 mmol, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, *J* = 6.7 Hz, 2H, H_7), 4.11 (s, 2H, H_3), 2.10 (dt, *J* = 14.4, 7.2 Hz, 1H, H_{6a}), 2.03 (s, 3H, H_9), 1.92 (dt, *J* = 14.2, 6.4 Hz, 1H, H_{6b}), 1.83 – 1.63 (m, 2H, H_{10}), 1.20 (s, 3H, H_{1a}), 1.19 (s, 3H, H_{1b}), 0.95 (t, *J* = 7.4 Hz, 3H, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5 (C_4), 171.0 (C_8), 77.7 (C_3), 60.9 (C_7), 59.9 (C_5), 48.6 (C_2), 38.3 (C_6), 33.9 (C_{10}), 26.9 (C_{1a}), 26.5 (C_{1b}), 21.1 (C_9), 8.4 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2970, 1728, 1460, 1379, 1366, 1232, 1051, 915, 731. **HRMS** (ESI) calculated for $[C_{12}H_{21}NO_4+H]^+$: 244.1543, found: 244.1545. $\mathbf{R_F}$ = 0.55 (20% EtOAc/CH_2Cl_2). Data consistent with literature.[102]

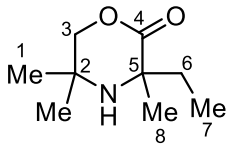
(5,5-Dimethyl-2-oxomorpholine-3,3-diyl)bis(ethane-2,1-diyl) diacetate **113b**



Isolated from the same reaction as the previous compound (2-(3-ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)ethyl acetate **113**) to give the title compound **113b** as a yellow oil (27 mg, 0.090 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (t, *J* = 6.5 Hz, 4H, H_7), 4.12 (s, 2H, H_3), 2.13 (dt, *J* = 14.2, 6.5 Hz, 2H, H_{6a}), 2.04 (s, 6H, H_9), 1.98 (dt, *J* = 14.2, 6.5 Hz, 2H, H_{6b}), 1.20 (s, 6H, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8 (C_4), 170.9 (C_8), 77.7 (C_3), 60.6 (C_7), 58.6 (C_5), 48.6 (C_2), 39.2 (C_6), 26.7 (C_1), 21.1 (C_9). **IR** ν_{max}/cm^{-1} (film): 2971, 1729, 1366, 1229, 1036, 915, 730. **HRMS** (ESI) calculated for $[C_{14}H_{23}NO_6+H]^+$: 302.1598, found: 302.1600. $\mathbf{R_F}$ = 0.29 (20% EtOAc/petroleum ether).

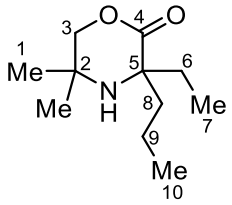
3-Ethyl-3,5,5-trimethylmorpholin-2-one **115**



Prepared according to general procedure **A**. The crude material was purified by flash chromatography (silica gel, 9 cm, 5.5 cm Ø), eluting with 0-50% EtOAc/petroleum ether. This material was repurified by Kugelrohr distillation (155 °C, 25 mBar) giving the title compound **115** as a colourless oil (1.9 g, 11 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (d, *J* = 16.4 Hz, 1H, H_{3a}), 4.10 (d, *J* = 16.4 Hz, 1H, H_{3b}), 1.80 (dq, *J* = 14.7, 7.4 Hz, 1H, H_{6a}), 1.57 (dq, *J* = 14.7, 7.4 Hz, 1H, H_{6b}), 1.39 (s, 3H, H_8), 1.24 (s, 3H, H_{1a}), 1.14 (s, 3H, H_{1b}), 0.95 (t, *J* = 7.4 Hz, 3H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (C_4), 78.0 (C_3), 58.3 (C_5), 48.9 (C_2), 35.8 (C_6), 29.3 (C_8), 27.0 (C_{1a}), 26.1 (C_{1b}), 8.6 (C_7). **IR** ν_{max}/cm^{-1} (film): 2970, 1727, 1378, 1284, 1223, 1118, 1054, 915, 732. **HRMS** (ESI) calculated for $[C_9H_{17}NO_2+H]^+$: 172.1332, found: 172.1330. $\mathbf{R_F}$ = 0.12 (20% EtOAc/petroleum ether). Data consistent with literature.[102]

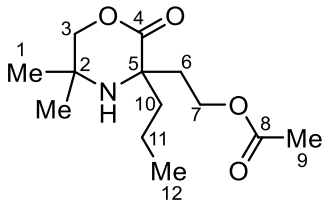
3-Ethyl-5,5-dimethyl-3-propylmorpholin-2-one **221**



Prepared according to general procedure **A**. The crude material was purified by flash chromatography (silica gel, 13 cm, 5 cm Ø), eluting with 0-20% EtOAc/petroleum ether. This material was repurified by Kugelrohr distillation (160 °C, 20 mBar) to give the title compound **221** as a light-yellow oil (6.8 g, 34 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 2H, H_3), 1.82 – 1.50 (m, 4H, H_6 and H_8), 1.44 – 1.30 (m, 2H, H_9), 1.18 (s, 6H, H_1), 0.92 (app. td, *J* = 7.3, 3.0 Hz, 6H, H_7 and H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3 (C_4), 77.5 (C_3), 61.2 (C_5), 48.6 (C_2), 42.7 (C_8), 33.5 (C_6), 26.9 (C_1), 17.2 (C_9), 14.5 (C_{10}), 8.3 (C_7). **IR** ν_{max}/cm^{-1} (film): 3676, 3347, 2965, 2875, 1728, 1463, 1379, 1284, 1130, 1055. **HRMS** (ESI) calculated for $[C_{11}H_{21}NO_2+H]^+$: 200.1645, found: 200.1642. $\mathbf{R_F}$ = 0.26 (20% EtOAc/petroleum ether). Data consistent with literature.[182]

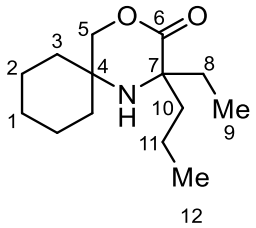
2-(5,5-Dimethyl-2-oxo-3-propylmorpholin-3-yl)ethyl acetate **225**



Prepared according to general procedure **C** using 3-Ethyl-5,5-dimethyl-3-propylmorpholin-2-one **221** (60 mg, 0.30 mmol), the reaction was stirred at 70 °C for 1 h. The crude material was purified by flash chromatography (silica gel, 21 cm, 2 cm Ø), eluting with 0-20% EtOAc/CH_2Cl_2, to give the title compound **225** as a yellow oil (58 mg, 0.23 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, *J* = 6.7 Hz, 2H, H_7), 4.10 (s, 2H, H_3), 2.10 (dt, *J* = 14.2, 6.7 Hz, 1H, H_{6a}), 2.03 (s, 3H, H_9), 1.95 (dt, *J* = 14.2, 6.7 Hz, 1H, H_{6b}), 1.73 – 1.58 (m, 2H, H_{10}), 1.44 – 1.31 (m, 2H, H_{11}), 1.19 (s, 3H, H_{1a}), 1.18 (s, 3H, H_{1b}), 0.92 (t, *J* = 7.3 Hz, 3H, H_{12}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4 (C_4), 170.9 (C_8), 77.6 (C_3), 60.8 (C_7), 59.5 (C_5), 48.4 (C_2), 43.3 (C_{10}), 38.6 (C_6), 26.7 (C_{1a}), 26.2 (C_{1b}), 21.0 (C_9), 17.2 (C_{11}), 14.2 (C_{12}). **IR** ν_{max}/cm^{-1} (film): 2966, 2876, 17.29, 1465, 1380, 1367, 1284, 1232, 1182, 1126, 1047. **HRMS** (ESI) calculated for $[C_{13}H_{23}NO_4+H]^+$: 258.1700, found: 258.1701. $\mathbf{R_F}$ = 0.56 (20% EtOAc/CH_2Cl_2).

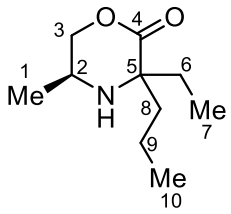
2-Ethyl-2-propyl-4-oxa-1-azaspiro[5.5]undecan-3-one **227**



Prepared according to general procedure **A**. The crude material was purified by flash chromatography (silica gel, 15 cm, 3 cm Ø), eluting with 0-30% EtOAc/petroleum ether, giving the title compound **227** as a light-yellow oil (0.40 g, 1.7 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (s, 2H, H_5), 1.77 – 1.33 (m, 16H, H_1, H_2, H_3, H_8, H_{10} and H_{11}), 0.95 (t, *J* = 7.3 Hz, 3H, H_{12}), 0.91 (t, *J* = 7.1 Hz, 3H, H_9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (C_6), 76.4 (C_5), 61.1 (C_7), 50.0 (C_4), 42.6 (C_{10}), 35.3 (C_{3a}), 35.2 (C_{3b}), 33.4 (C_8), 26.0 ($C_{1/2}$), 21.9 ($C_{1/2}$), 17.1 (C_{11}), 14.5 (C_{12}), 8.3 (C_9). **IR** ν_{max}/cm^{-1} (film): 2964, 1727, 1455, 1191, 1048, 910, 729. **HRMS** (ESI) calculated for $[C_{14}H_{25}NO_2+H]^+$: 240.1958, found: 240.1957. $\mathbf{R_F}$ = 0.40 (20% EtOAc/petroleum ether).

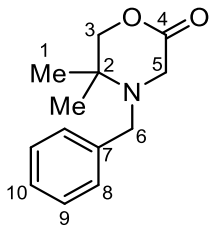
3-Ethyl-5-methyl-3-propylmorpholin-2-one **229**



Prepared according to general procedure **A**. The crude material was purified by flash chromatography (silica gel, 10 cm, 3.5 cm Ø), eluting with 0-25% EtOAc/petroleum ether. This material was repurified by Kugelrohr distillation (160 °C, 20 mBar) to give the title compound **229** as a colourless oil (0.30 g, 1.6 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (dd, *J* = 10.5, 3.1 Hz, 1H, H_{3a}), 3.92 (t, *J* = 10.5 Hz, 1H, H_{3b}), 3.33 (dqd, *J* = 10.5, 6.3, 3.1 Hz, 1H, H_2), 2.01 – 1.23 (m, 6H, H_6, H_8 and H_9), 1.07 (d, *J* = 6.3 Hz, 3H, H_1), 0.94 (tt, *J* = 7.0, 6.2 Hz, 6H, H_7 and H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6 (C_4), 173.5 (C_4), 76.2 (C_3), 76.2 (C_3), 63.6 (C_5), 63.3 (C_5), 44.3 (C_2), 44.1 (C_2), 42.4 (C_8), 41.7 (C_8), 33.1 (C_6), 32.5 (C_6), 17.7 (C_9), 17.3 (C_1), 17.3 (C_1), 17.3 (C_9), 14.6 (C_{10}), 14.4 (C_{10}), 8.8 (C_7), 8.1, (C_7). **IR** ν_{max}/cm^{-1} (film): 3677, 3338, 2964, 2876, 1725, 1461, 1214, 1181, 1146, 1047. **HRMS** (ESI) calculated for $[C_{10}H_{19}NO_2+H]^+$: 186.1489, found: 186.1485. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.3° (*c* = 1.0, $CHCl_3$). $\mathbf{R_F}$ = 0.10 (20% EtOAc/petroleum ether).

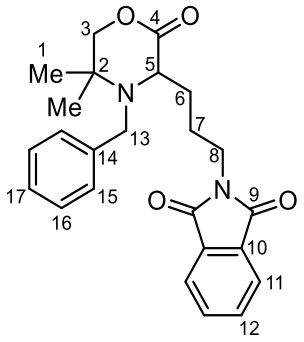
4-Benzyl-5,5-dimethylmorpholin-2-one **231**



A reaction mixture of 2-amino-2-methylpropan-1-ol (5.0 mL, 50 mmol) and benzaldehyde (6.9 mL, 68 mmol) in toluene (100 mL) was refluxed under Dean-Stark conditions for 1.5 h. The reaction mixture was then concentrated *in vacuo*, dissolved in EtOH (150 mL). Sodium borohydride (6.6 g, 180 mmol) was added portion-wise at 0 °C and the mixture left to stir at rt o/n. The reaction was quenched with 3 M HCl, concentrated *in vacuo* and extracted with CH_2Cl_2 (2 x 100 mL). The aqueous layer was then basified with solid NaOH and extracted with CH_2Cl_2 (2 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude amine was dissolved in toluene (100 mL), *N*,*N*-diisopropylethylamine (12 mL, 70 mmol) and 2-bromomethyl acetate (5.2 mL, 55 mmol) added to the reaction mixture which was stirred at 50 °C o/n. The reaction mixture was diluted with water (100 mL), extracted with CH_2Cl_2 (3 x 100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 14 cm, 5.5 cm Ø), eluting with 0-20% EtOAc/petroleum ether, to yield the title compound **231** as a white crystalline solid (5.8 g, 27 mmol, 53%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H, H_8, H_9 and H_{10}), 4.11 (s, 2H, H_3), 3.57 (s, 2H, H_6), 3.26 (s, 2H, H_5), 1.22 (s, 6H, H_1). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.6 (C_4), 137.8 (C_7), 128.7 (C_8 and C_9), 127.6 (C_{10}), 78.7 (C_3), 53.7 (C_6), 51.5 (C_2), 50.5 (C_5), 19.2 (C_1). **IR** ν_{max}/cm^{-1} (film): 2980, 2954, 2933, 1744, 1382, 1292, 1231, 1054, 863. **HRMS** (ESI) calculated for $[C_{13}H_{17}NO_2+H]^+$: 220.1332, found: 220.1332. **Mp** = 69-72 °C (lit. 66-68 °C). $\mathbf{R_F}$ = 0.27 (20% EtOAc/petroleum ether). Data consistent with literature.[204]

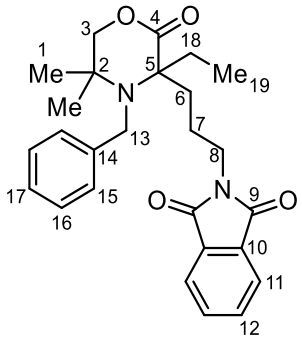
2-(3-(4-Benzyl-5,5-dimethyl-2-oxomorpholin-3-yl)propyl)isoindoline-1,3-dione **232**



Prepared according to general procedure **B**, using 2-(3-iodopropyl)isoindoline-1,3-dione prepared from a literature procedure.[254] The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 0-30% EtOAc/petroleum ether, to give the title compound **232** as a yellow oil (0.43 g, 1.0 mmol, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.4, 3.0 Hz, 2H, H_{11}), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H, H_{12}), 7.26 – 7.23 (m, 2H, H_{15}), 7.15 – 7.09 (m, 2H, H_{16}), 6.91 – 6.84 (m, 1H, H_{17}), 4.23 (d, *J* = 10.8 Hz, 1H, H_{3a}), 4.10 (d, *J* = 15.2 Hz, 1H, H_{13a}), 3.93 (d, *J* = 10.8 Hz, 1H, H_{3b}), 3.47 (dd, *J* = 6.1, 3.5 Hz, 1H, H_5), 3.44 (dt, *J* = 13.6, 6.8 Hz, 1H, H_{8a}), 3.38 (dt, *J* = 13.6, 6.8 Hz, 1H, H_{8b}), 3.19 (d, *J* = 15.2 Hz, 1H, H_{13b}), 1.86 (ttd, *J* = 12.7, 6.7, 4.4 Hz, 1H, H_{7a}), 1.65 (dtd, *J* = 12.1, 4.4, 3.5 Hz, 1H, H_{6a}), 1.44 (ttd, *J* = 12.7, 6.7, 4.4 Hz, 1H, H_{7b}), 1.31 (ddt, *J* = 12.1, 6.1, 4.4 Hz, 1H, H_{6b}), 1.17 (s, 3H, H_{1a}), 1.15 (s, 3H, H_{1b}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.7 (C_4), 168.3 (C_9), 140.8 (C_{14}), 133.9 (C_{12}), 132.3 (C_{10}), 128.4 (C_{16}), 127.6 (C_{15}), 127.0 (C_{17}), 123.3 (C_{11}), 77.2 (C_3), 64.1 (C_5), 55.4 (C_{13}), 53.0 (C_3), 37.7 (C_8), 31.7 (C_6), 24.9 (C_{1a}), 24.2 (C_7), 16.5 (C_{1b}). **IR** ν_{max}/cm^{-1} (film): 1771, 1735, 1708, 1467, 1396, 1066, 1037, 719. **HRMS** (ESI) calculated for $[C_{24}H_{26}N_2O_4+H]^+$: 407.1965, found: 407.1964. $\mathbf{R_F}$ = 0.10 (20% EtOAc/petroleum ether).

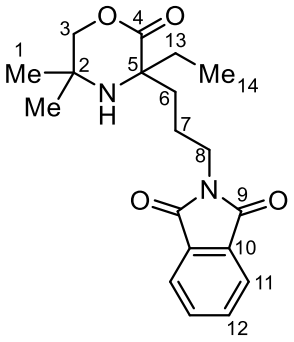
2-(3-(4-Benzyl-3-ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)propyl)isoindoline-1,3-dione **233**



Prepared according to general procedure **B** from 2-(3-(4-benzyl-5,5-dimethyl-2-oxomorpholin-3-yl)propyl)isoindoline-1,3-dione **232** and ethyl iodide. The crude material was purified by flash chromatography (silica gel, 13 cm, 3 cm Ø), eluting with 0-20% EtOAc/petroleum ether, to give the title compound **233** as a yellow oil (0.17 g, 0.38 mmol, 16%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H, H_{11}), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H, H_{12}), 7.33 – 7.25 (m, 2H, H_{15}), 7.26 – 7.17 (m, 2H, H_{16}), 7.10 – 7.01 (m, 1H, H_{17}), 4.11 (d, *J* = 10.9 Hz, 1H, H_{3a}), 4.05 (d, *J* = 10.9 Hz, 1H, H_{3b}), 3.92 (d, *J* = 16.5 Hz, 1H, H_{13a}), 3.86 (d, *J* = 16.5 Hz, 1H, H_{13b}), 3.60 (ddd, *J* = 13.6, 7.7, 6.0 Hz, 1H, H_{8a}), 3.50 (dt, *J* = 13.7, 7.0 Hz, 1H, H_{8b}), 2.06 – 1.90 (m, 1H, H_{7a}), 1.86 (dq, *J* = 14.8, 7.4 Hz, 1H, H_{18a}), 1.75 (td, *J* = 13.3, 3.9 Hz, 1H, H_{6a}), 1.71 – 1.59 (m, 2H, H_{7b} and H_{18b}), 1.40 (td, *J* = 13.3, 3.9 Hz, 1H, H_{6b}), 1.19 (s, 3H, H_{1a}), 1.17 (s, 3H, H_{1b}), 0.96 (t, *J* = 7.4 Hz, 3H, H_{19}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.1 (C_4), 168.3 (C_9), 142.6 (C_{14}), 133.9 (C_{12}), 132.2 (C_{10}), 128.3 (C_{16}), 127.2 (C_{15}), 126.6 (C_{17}), 123.2 (C_{11}), 76.3 (C_3), 68.3 (C_5), 52.1 (C_2), 47.6 (C_{13}), 37.9 (C_6), 37.8 (C_8), 32.4 (C_{18}), 24.9 (C_7), 23.6 (C_1), 10.7 (C_{19}). **IR** ν_{max}/cm^{-1} (film): 2971, 2901, 1707, 1730, 1396, 1065, 908, 714. **HRMS** (ESI) calculated for $[C_{26}H_{30}N_2O_4+H]^+$: 435.2278, found: 435.2276. $\mathbf{R_F}$ = 0.11 (20% EtOAc/petroleum ether).

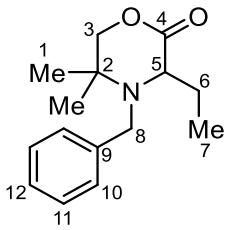
2-(3-(3-Ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)propyl)isoindoline-1,3-dione **234**



2-(3-(4-Benzyl-3-ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)propyl)isoindoline-1,3-dione **233** (0.38 g, 0.87 mmol) was dissolved in MeOH (14 mL) and Pd/C (10% Pd, 0.38 g) added. The reaction mixture was evacuated and backfilled with N_2 (3x), before being backfilled with H_2. The reaction mixture was stirred under a H_2 atmosphere o/n. Once completed, the reaction was filtered through Celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 9 cm, 3 cm Ø), eluting with 50% EtOAc/petroleum ether, to yield the title compound **234** as a colourless oil (60 mg, 0.17 mmol, 20%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{11}), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H, H_{12}), 4.12 (d, *J* = 10.8 Hz, 1H, H_{3a}), 4.07 (d, *J* = 10.8 Hz, 1H, H_{3b}), 3.70 (td, *J* = 7.0, 1.9 Hz, 2H, H_8), 1.83 – 1.59 (m, 6H, H_6, H_7 and H_{13}), 1.17 (s, 3H, H_{1a}), 1.16 (s, 3H, H_{1b}), 0.91 (t, *J* = 7.4 Hz, 3H, H_{14}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.8 (C_4), 168.5 (C_9), 134.1 (C_{12}), 132.3 (C_{10}), 123.4 (C_{11}), 77.7 (C_3), 60.9 (C_5), 48.7 (C_2), 38.3 (C_8), 37.4 (C_6), 33.2 (C_{13}), 26.9 (C_{1a}), 26.7 (C_{1b}), 23.2 (C_7), 8.4 (C_{14}). **IR** ν_{max}/cm^{-1} (film): 2972, 1709, 1396, 1286, 1047, 719. **HRMS** (ESI) calculated for $[C_{19}H_{24}N_2O_4+H]^+$: 345.1809, found: 345.1813. $\mathbf{R}_F$ = 0.30 (50% EtOAc/petroleum ether). Data consistent with literature.[182]

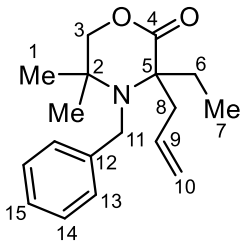
4-Benzyl-3-ethyl-5,5-dimethylmorpholin-2-one **235**



Prepared according to general procedure **B**. The crude material was purified by flash chromatography (silica gel, 18 cm, 3 cm Ø), eluting with 0-10% EtOAc/petroleum ether, to yield the title compound **235** as a white crystalline solid (3.5 g, 14 mmol, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H, H_{10} and H_{11}), 7.25 – 7.21 (m, 1H, H_{12}), 4.25 (d, *J* = 10.8 Hz, 1H, H_{3a}), 4.10 (d, *J* = 15.4 Hz, 1H, H_{8a}), 3.93 (d, *J* = 10.8 Hz, 1H, H_{3b}), 3.45 (dd, *J* = 6.0, 3.6 Hz, 1H, H_5), 3.29 (d, *J* = 15.4 Hz, 1H, H_{8b}), 1.69 (dqd, *J* = 14.5, 7.3, 3.6 Hz, 1H, H_{6a}), 1.38 (dqd, *J* = 14.5, 7.3, 6.0 Hz, 1H, H_{6b}), 1.20 (s, 3H, H_{1a}), 1.11 (s, 3H, H_{1b}), 0.83 (t, *J* = 7.4 Hz, 3H, H_7). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.2 (C_4), 141.3 (C_9), 128.4 (C_{11}), 127.7 (C_{10}), 127.1 (C_{12}), 77.3 (C_3), 65.2 (C_5), 55.1 (C_2), 53.0 (C_8), 27.2 (C_6), 25.0 (C_{1a}), 16.6 (C_{1b}), 9.2 (C_7). **IR** ν_{max}/cm^{-1} (film): 2966, 2935, 2901, 1726, 1452, 1387, 1222, 1063, 874, 718, 696. **HRMS** (ESI) calculated for $[C_{15}H_{21}NO_2+H]^+$: 248.1645, found: 248.1646. **Mp =** 78-80 °C. $\mathbf{R_F}$ = 0.43 (20% EtOAc/petroleum ether).

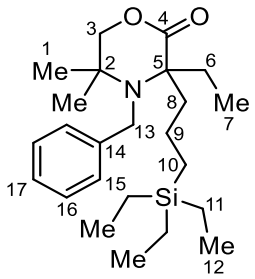
3-Allyl-4-benzyl-3-ethyl-5,5-dimethylmorpholin-2-one **236**



Prepared according to general procedure **B**. The crude material was purified by flash chromatography (silica gel, 20 cm, 5 cm Ø), eluting with 0-10% EtOAc/petroleum ether, to yield the title compound **236** as a light yellow oil (1.2 g, 4.3 mmol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 2H, H_{13}), 7.35 – 7.26 (m, 2H, H_{14}), 7.27 – 7.18 (m, 1H, H_{15}), 5.90 (ddt, *J* = 16.6, 10.6, 7.3 Hz, 1H, H_9), 5.16 – 5.05 (m, 2H, H_{10}), 4.10 (s, 2H, H_3), 4.06 (d, *J* = 16.6 Hz, 1H, H_{11a}), 3.92 (d, *J* = 16.6 Hz, 1H, H_{11b}), 2.53 (ddt, *J* = 14.3, 7.3, 1.3 Hz, 1H, H_{8a}), 2.42 (ddt, *J* = 14.3, 7.3, 1.2 Hz, 1H, H_{8b}), 1.85 (dq, *J* = 14.6, 7.4 Hz, 1H, H_{6a}), 1.60 (dq, *J* = 16.4, 7.4 Hz, 1H, H_{6b}), 1.20 (s, 3H, H_{1a}), 1.13 (s, 3H, H_{1b}), 1.00 (t, *J* = 7.4 Hz, 3H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2 (C_4), 143.1 (C_{12}), 135.0 (C_9), 128.4 (C_{14}), 127.5 (C_{13}), 126.9 (C_{15}), 118.5 (C_{10}), 76.6 (C_3), 69.5 (C_5), 52.3 (C_2), 48.0 (C_{11}), 44.7 (C_8), 32.8 (C_6), 24.7 (C_{1a}), 23.7 (C_{1b}), 10.4 (C_7). **IR** ν_{max}/cm^{-1} (film): 2975, 1731, 145, 1382, 1285, 1176, 1137, 1066. **HRMS** (ESI) calculated for $[C_{18}H_{25}NO_2+H]^+$: 288.1958, found: 288.1961. $\mathbf{R_F}$ = 0.46 (20% EtOAc/petroleum ether).

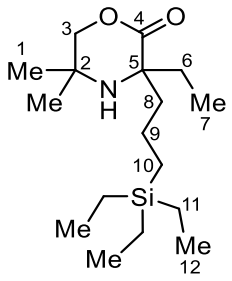
4-Benzyl-3-ethyl-5,5-dimethyl-3-(3-(triethylsilyl)propyl)morpholin-2-one **237**



3-Allyl-4-benzyl-3-ethyl-5,5-dimethylmorpholin-2-one **236** (0.17 g, 0.60 mmol) was dissolved in toluene (2.0 mL). Triethylsilane (0.48 mL, 3.0 mmol) and Karstedt's catalyst (~2% Pt in xylene, 72 μL, 0.060 mmol) were added to the reaction mixture and refluxed at 120 °C o/n. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (silica gel, 14 cm, 2 cm Ø), eluting with 0-5% EtOAc/petroleum ether, to yield the title product **237** as a light brown oil (76 mg, 0.19 mmol, 31%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H, H_{15}), 7.33 – 7.26 (m, 2H, H_{16}), 7.24 – 7.20 (m, 1H, H_{17}), 4.09 (s, 2H, H_3), 3.92 (s, 2H, H_{13}), 1.88 – 1.75 (m, 2H, H_{6a} and H_{8a}), 1.64 – 1.51 (m, 2H, H_{6b} and H_{9a}), 1.44 (ddd, *J* = 13.9, 12.4, 3.5 Hz, 1H, H_{8b}), 1.27 (tt, *J* = 12.3, 4.7 Hz, 1H, H_{9b}), 1.18 (s, 3H, H_{1a}), 1.17 (s, 3H, H_{1b}), 0.97 (t, *J* = 7.4 Hz, 3H, H_7), 0.94 (t, *J* = 7.9 Hz, 9H, H_{12}), 0.51 (q, *J* = 7.9 Hz, 6H, H_{11}), 0.47 – 0.39 (m, 1H, H_{10a}), 0.32 (ddd, *J* = 14.5, 12.2, 4.4 Hz, 1H, H_{10b}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.8 (C_4), 143.3 (C_{14}), 128.4 (C_{16}), 127.4 (C_{15}), 126.8 (C_{17}), 76.5 (C_3), 68.9 (C_5), 52.2 (C_2), 47.9 (C_{13}), 44.8 (C_6), 33.1 (C_8), 24.4 (C_{1a}), 24.2 (C_{1b}), 20.3 (C_9), 12.0 (C_{10}), 10.7 (C_7), 7.7 (C_{12}), 3.5 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2943, 2873, 1736, 1455, 1380, 1136, 1069, 714. **HRMS** (ESI) calculated for $[C_{24}H_{41}NO_2Si+H]^+$: 404.2979, found: 404.2974. $\mathbf{R}_F$ = 0.21 (5% EtOAc/petroleum ether).

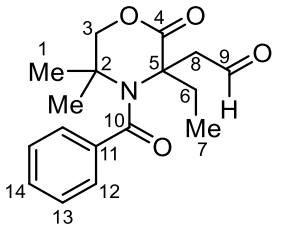
3-Ethyl-5,5-dimethyl-3-(3-(triethylsilyl)propyl)morpholin-2-one **238**



4-Benzyl-3-ethyl-5,5-dimethyl-3-(3-(triethylsilyl)propyl)morpholin-2-one **237** (76 mg, 0.11 mmol) was dissolved in MeOH (10 mL) and Pd/C (10% Pd, 50 mg) was added. The reaction mixture was evacuated and backfilled with N_2 (3x), before being backfilled with H_2. The reaction mixture was stirred under a H_2 atmosphere o/n. Once completed the reaction was filtered through Celite and concentrated *in vacuo*. The title compound **238** was isolated as a colourless oil (50 mg, 0.16 mmol, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (s, 2H, H_3), 1.80 – 1.69 (m, 2H, H_{6a} and H_{8a}), 1.68 – 1.59 (m, 2H, H_{6b} and H_{8b}), 1.40 – 1.30 (m, 2H, H_9), 1.18 (s, 6H, H_1), 0.92 (t, J = 7.4 Hz, 3H, H_7), 0.92 (t, J = 7.9 Hz, 9H, H_{12}), 0.50 (app. q, J = 7.9 Hz, 8H, H_{10} and H_{11}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.2 (C_4), 77.5 (C_3), 61.2 (C_5), 48.7 (C_2), 44.9 (C_6), 33.5 (C_8), 27.0 (C_{1a}), 26.9 (C_{1b}), 18.3 (C_9), 12.0 (C_{10}), 8.4 (C_7), 7.6 (C_{12}), 3.5 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2953, 2911, 2875, 1733, 1457, 1377, 1284, 1133, 1056, 1015. **HRMS** (ESI) calculated for $[C_{17}H_{35}NO_2Si+H]^+$: 314.2510, found: 314.2511.

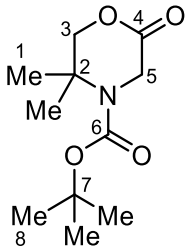
2-(4-Benzoyl-3-ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)acetaldehyde **240**



3-Allyl-4-benzyl-3-ethyl-5,5-dimethylmorpholin-2-one **236** (0.29 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. Ozone was bubbled through the reaction mixture for 0.5 h before triphenylphosphine (0.28 g, 1.1 mmol) was added and the reaction mixture warmed to rt. The reaction was quenched with the addition of water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 14 cm, 3.5 cm Ø), eluting with 0-100% EtOAc/petroleum ether, to yield the title compound **240** as a white crystalline solid (64 mg, 0.22 mmol, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 1.4 Hz, 1H, H_9), 7.48 – 7.30 (m, 5H, H_{12}, H_{13} and H_{14}), 4.47 (d, *J* = 11.9 Hz, 1H, H_{3a}), 3.98 (d, *J* = 11.9 Hz, 1H, H_{3b}), 3.80 (dd, *J* = 17.9, 1.6 Hz, 1H, H_{8a}), 3.46 (d, *J* = 17.9 Hz, 1H, H_{8b}), 2.92 (dq, *J* = 15.1, 7.6 Hz, 1H, H_{6a}), 2.14 (dq, *J* = 15.1, 7.6 Hz, 1H, H_{6b}), 1.55 (s, 3H, H_{1a}), 1.02 (s, 3H, H_{1b}), 0.98 (t, *J* = 7.6 Hz, 3H, H_7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.0 (C_9), 173.8 (C_{10}), 169.2 (C_4), 140.5 (C_{11}), 130.2 (C_{14}), 128.4 (C_{13}), 127.5 (C_{12}), 75.6 (C_3), 65.7 (C_5), 55.9 (C_2), 46.9 (C_8), 30.8 (C_6), 27.4 (C_{1a}), 26.0 (C_{1b}), 9.9 (C_7). **IR** ν_{max}/cm^{-1} (film): 1743, 1725, 1622, 1351, 1289, 1155, 1068, 910. **HRMS** (ESI) calculated for $[C_{17}H_{21}NO_4+H]^+$: 304.1543, found: 304.1549. **Mp** = 148-150 °C. $\mathbf{R_F}$ = 0.09 (20% EtOAc/petroleum ether).

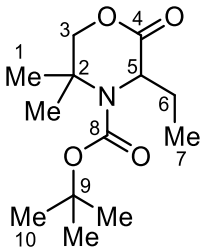
tert-Butyl 5,5-dimethyl-2-oxomorpholine-4-carboxylate **241**



2-Amino-2-methylpropan-1-ol (4.8 mL, 50 mmol) was dissolved in THF (100 mL), triethylamine (12 mL, 85 mmol) and ethyl bromoacetate (7.1 mL, 75 mmol) were added and the reaction mixture was stirred at 50 °C for 4 h. The reaction mixture was cooled to 0 °C, filtered and washed with THF (100 mL). The filtrate was concentrated to approx. 100 mL, di-*tert*-butyl dicarbonate (15 g, 70 mmol) was added to the reaction and stirred at rt o/n. The reaction was concentrated *in vacuo*, re-dissolved in toluene (150 mL) and washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated to approx. 100 mL. *p*-Toluenesulfonic acid (0.95 g, 5.0 mmol) was added and the reaction mixture refluxed under Dean-Stark conditions for 4 h. The reaction was cooled to rt, washed with water (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 10 cm, 7 cm Ø), eluting with 0-10% EtOAc/petroleum ether, to yield the title compound **241** as a white crystalline solid (3.7 g, 16 mmol, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (s, 2H, H_5), 4.06 (s, 2H, H_3), 1.48 (s, 9H, H_8), 1.46 (s, 6H, H_1). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.2 (C_4), 153.6 (C_6), 81.3 (C_7), 75.5 (C_3), 53.7 (C_2), 44.6 (C_5), 28.6 (C_8), 23.0 (C_1). **IR** ν_{max}/cm^{-1} (film): 2973, 1760, 1683, 1362, 1302, 1255, 1148, 100, 1051. **HRMS** (ESI) calculated for $[C_{11}H_{19}NO_4$-^{t}Butyl+H$]^+$: 173.0688, found: 173.0683. **Mp** = 98-100 °C. $\mathbf{R_F}$ = 0.22 (20% EtOAc/petroleum ether).

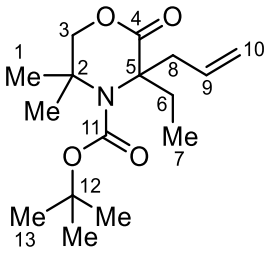
tert-Butyl 3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **242**



Title compound isolated as intermediate (from the synthesis of *tert*-butyl 3-allyl-3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **243**) by flash chromatography (silica gel, 13 cm, 7 cm Ø), eluting with 5% EtOAc/petroleum ether, to yield the title compound **242** as a light yellow crystalline solid (2.1 g, 8.2 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, *J* = 9.3, 6.6 Hz, 1H, H_5), 4.31 (d, *J* = 12.1 Hz, 1H, H_{3a}), 3.90 (d, *J* = 12.1 Hz, 1H, H_{3b}), 1.80 (m, 2H, H_6), 1.48 (s, 9H, H_{10}), 1.47 (s, 3H, H_{1a}), 1.45 (s, 3H, H_{1b}), 1.04 (t, *J* = 7.5 Hz, 3H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0 (C_4), 81.1 (C_9), 74.5 (C_3), 57.9 (C_5), 53.3 (C_2), 28.6 (C_{10}), 28.2 (C_6), 24.6 (C_{1a}), 22.9 (C_{1b}), 10.8 (C_7). **IR** ν_{max}/cm^{-1} (film): 2973, 2934, 1753, 1688, 1367, 1291, 1170, 1062, 731. **HRMS** (ESI) calculated for $[C_{13}H_{23}NO_4+H]^+$: 258.1700, found: 258.1698. **Mp =** 66-68 °C. $\mathbf{R_F}$ = 0.16 (10% EtOAc/petroleum ether).

tert-Butyl 3-allyl-3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **243**

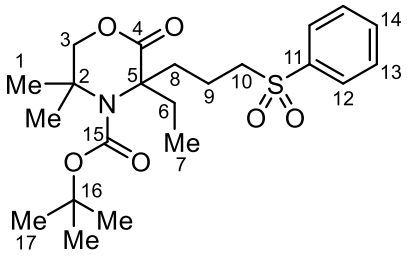


Prepared by sequential alkylation according to general procedure **B** from *tert*-butyl 5,5-dimethyl-2-oxomorpholine-4-carboxylate **241** using ethyl iodide (2 equiv) to give crude *tert*-butyl 3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **242** which was alkylated with allyl iodide (3 equiv) using general procedure **B**. The crude material was purified by flash chromatography (silica gel, 13 cm, 7 cm Ø), eluting with 5% EtOAc/petroleum ether, to yield the title compound **243** as a light yellow oil (1.0 g, 3.4 mmol, 21%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddt, *J* = 17.6, 10.1, 7.6 Hz, 1H, H_9), 5.19 – 5.08 (m, 2H, H_{10}), 4.12 (d, *J* = 11.7 Hz, 1H, H_3), 3.95 (d, *J* = 11.7 Hz, 1H, H_1), 3.10 (dd, *J* = 13.9, 7.8 Hz, 1H, H_{8a}), 2.83 (dd, *J* = 13.9, 7.3 Hz, 1H, H_{8b}), 2.34 (dq, *J* = 14.8, 7.5 Hz, 1H, H_{6a}), 2.27 (dq, *J* = 14.8, 7.5 Hz, 1H, H_{6b}), 1.50

(s, 9H, H_{13}), 1.41 (s, 3H, H_{1a}), 1.39 (s, 3H, H_{1b}), 0.84 (t, *J* = 7.5 Hz, 3H, H_7). **^{13}C NMR** (126 MHz, CDCl3) δ 171.2 (C_4), 154.0 (C_{11}), 133.6 (C_9), 119.5 (C_{10}), 80.9 (C_{12}), 74.3 (C_3), 68.8 (C_5), 52.7 (C_2), 42.5 (C_8), 30.9 (C_6), 28.6 (C_{13}), 24.7 (C_1), 9.9 (C_7). **IR** ν_{max}/cm^{-1} (film): 2973, 2934, 1744, 1693, 1367, 1344, 1298, 1157, 1074. **HRMS** (ESI) calculated for $[C_{16}H_{27}NO_4+H]^+$: 298.2013, found: 298.2009. $\mathbf{R_F}$ = 0.21 (10% EtOAc/petroleum ether).

tert-Butyl 3-ethyl-5,5-dimethyl-2-oxo-3-(3-(phenylsulfonyl)propyl)morpholine-4-carboxylate **245b**

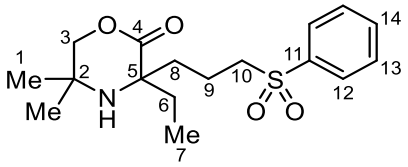


tert-Butyl 3-allyl-3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **243** (0.30 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL), cooled to -78 °C and ozone was bubbled through the reaction mixture for 0.5 h. Triphenylphosphine (0.28 g, 1.1 mmol) was added to the reaction mixture, which was allowed to warm to rt, stirring for 1 h and then concentrated *in vacuo*. In a separate oven-dried flask, diethyl ((phenylsulfonyl)methyl)phosphonate (1.4 g, 4.8 mmol) was dissolved in THF (15 mL), cooled to 0 °C, NaH (60%, 0.19 g, 4.8 mmol) was added and stirred for 0.5 h. The crude ozonolysis product was added to the ylide in THF (5 mL) and stirred at rt for 16 h. Water (50 mL) was added to the reaction, extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 14 cm, 2 cm Ø), eluting with 5-10% EtOAc/CH_2Cl_2, to yield the olefinated intermediate as a colourless oil which was dissolved in MeOH (20 mL) and Pd/C (10% Pd, 0.10 g) added. The reaction mixture was evacuated and backfilled with N_2 (3x), before being backfilled with H_2. The reaction mixture was stirred under a H_2 atmosphere for 2 d. Once completed the reaction was filtered through Celite and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 14 cm, 2 cm Ø), eluting with 20-50% EtOAc/petroleum ether, to afford the title compound **245b** as a colourless oil (0.15 g, 0.34 mmol, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H, H_{13}), 7.68 – 7.62 (m, 1H, H_{14}), 7.59 – 7.52 (m, 2H, H_{12}), 4.11 (d, *J* = 11.8 Hz, 1H, H_{3a}), 3.96 (d, *J* = 11.8 Hz, 1H, H_{3b}), 3.11 (ddd, *J* = 14.0, 9.9, 6.3 Hz, 1H, H_{10a}), 2.98 (ddd, *J* = 14.0, 9.8, 6.0 Hz, 1H, H_{10b}), 2.40 – 2.12 (m, 3H, H_{6a} and H_8), 1.64 – 1.50 (m, 1H, H_{6b}), 1.61 – 1.55 (m, 2H, H_9), 1.45 (s, 9H, H_{17}), 1.41 (s, 3H, H_{1a}), 1.36 (s, 3H, H_{1b}), 0.82 (t, *J* = 7.5 Hz, 3H, H_7). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.3 (C_4), 153.9 (C_{15}), 139.1 (C_{11}), 133.9 (C_{14}), 129.4 (C_{12}), 128.3 (C_{13}), 81.3 (C_{16}), 74.4 (C_3), 67.9 (C_5), 56.3 (C_{10}), 53.0 (C_2), 34.9 (C_8), 30.9 (C_6), 28.5 (C_{17}), 25.0

(C_{1a}), 24.2 (C_{1b}), 19.2 (C_9), 9.7 (C_7). **IR** ν_{max}/cm^{-1} (film): 2972, 1740, 1689, 1447, 1367, 1323, 1294, 1146, 1070. **HRMS** (ESI) calculated for $[C_{22}H_{33}NO_6S+NH_4]^+$: 457.2367, found: 457.2365. $\mathbf{R_F}$ = 0.38 (50% EtOAc/petroleum ether).

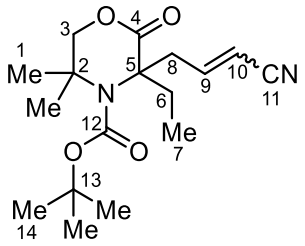
3-Ethyl-5,5-dimethyl-3-(3-(phenylsulfonyl)propyl)morpholin-2-one **245**



tert-Butyl 3-ethyl-5,5-dimethyl-2-oxo-3-(3-(phenylsulfonyl)propyl)morpholine-4-carboxylate **245b** (0.15 g, 0.34 mmol) was dissolved in CH_2Cl_2 (10 mL), trifluoroacetic acid (1 mL) was added and the reaction mixture stirred at rt for 22 h. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **245** as a colourless oil (0.11 g, 0.34 mmol, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.88 (m, 2H, H_{13}), 7.70 – 7.63 (m, 1H, H_{14}), 7.61 – 7.53 (m, 2H, H_{12}), 4.08 (s, 2H, H_3), 3.20 – 3.01 (m, 2H, H_{10}), 1.90 – 1.57 (m, 6H, H_6, H_8 and H_9), 1.16 (s, 3H, H_{1a}), 1.14 (s, 3H, H_{1b}), 0.91 (t, J = 7.4 Hz, 3H, H_7). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.4 (C_4), 139.3 (C_{11}), 133.9 (C_{14}), 129.5 (C_{12}), 128.2 (C_{13}), 77.9 (C_3), 60.9 (C_5), 56.5 (C_{10}), 48.7 (C_2), 38.5 (C_8), 33.5 (C_6), 26.8 (C_{1a}), 26.5 (C_{1b}), 17.6 (C_9), 8.4 (C_7). **IR** ν_{max}/cm^{-1} (film): 2968, 1726, 1446, 1303, 1286, 1146, 1086. **HRMS** (ESI) calculated for $[C_{17}H_{25}NO_4S+H]^+$: 340.1577, found: 340.1575.

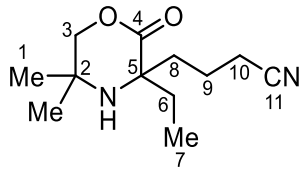
tert-Butyl 3-(3-cyanoallyl)-3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **246b**



tert-Butyl 3-allyl-3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **243** (0.45 g, 1.5 mmol) was dissolved in CH_2Cl_2 (15 mL), cooled to -78 °C and ozone was bubbled through the reaction mixture for 0.5 h. Dimethylsulfide (0.22 mL, 3.0 mmol) was added to the reaction mixture which was allowed to warm to rt, stirring for 1 h and then concentrated *in vacuo*. In a separate oven-dried flask, diethyl (cyanomethyl)phosphonate (0.73 mL, 4.5 mmol) was dissolved in THF (20 mL), cooled to 0 °C, NaH (60%, 0.18 g, 4.5 mmol) added and stirred for 0.5 h. The crude ozonolysis product was added to the ylide in THF (5 mL) and stirred at rt for 16 h. Water (50 mL) was added to the reaction and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 16 cm, 3 cm Ø), eluting with 10-30% EtOAc/petroleum ether, to yield the title compound **246b** as an inseparable, isomeric mixture of E/Z-isomers (1:1.5), as a colourless oil (0.36 g, 1.1 mmol, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (ddd, *J* = 15.8, 8.6, 6.9 Hz, 0.4H, $H_{9\text{-}E}$), 6.37 (ddd, *J* = 10.9, 8.6, 6.5 Hz, 0.6H, $H_{9\text{-}Z}$), 5.47 – 5.37 (m, 1H, $H_{10\text{-}E/Z}$), 4.19 (d, *J* = 11.9 Hz, 0.4H, $H_{3a\text{-}E}$), 4.17 (d, *J* = 11.9 Hz, 0.6H, $H_{3a\text{-}Z}$), 4.07 (d, *J* = 11.9 Hz, 0.6H $H_{3b\text{-}Z}$), 3.93 (d, *J* = 11.9 Hz, 0.4H, $H_{3b\text{-}E}$), 3.42 (ddd, *J* = 15.1, 6.5, 1.7 Hz, 0.6H, $H_{8\text{-}Z}$), 3.38 – 3.27 (m, 1H, $H_{8\text{-}E/Z}$), 3.13 (ddd, *J* = 14.0, 7.0, 1.6 Hz, 0.4H, $H_{8\text{-}E}$), 2.42 – 2.31 (m, 1.6H, $H_{6\text{-}E/Z}$), 2.20 (dq, *J* = 14.8, 7.5 Hz, 0.4H, $H_{6\text{-}E}$), 1.51 (app. d, *J* = 4.1 Hz, 9H, $H_{14\text{-}E/Z}$), 1.43 (app. d, *J* = 2.8 Hz, 4.8H, $H_{1a\text{-}E/Z}$), 1.37 (s, 1.2H, $H_{1b\text{-}E/Z}$), 0.89 (t, *J* = 7.5 Hz, 1.2H, $H_{7\text{-}E}$), 0.85 (t, *J* = 7.4 Hz, 1.8H, $H_{7\text{-}Z}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.8 ($C_{4\text{-}E}$), 169.6 ($C_{4\text{-}Z}$), 153.9 ($C_{12\text{-}E}$), 153.8 ($C_{12\text{-}Z}$), 150.7 ($C_{9\text{-}E}$), 149.3 ($C_{9\text{-}Z}$), 117.1 ($C_{11\text{-}E}$), 115.7 ($C_{11\text{-}Z}$), 103.8 ($C_{10\text{-}E}$), 102.5 ($C_{10\text{-}Z}$), 81.7 ($C_{13\text{-}E/Z}$), 81.6 ($C_{13\text{-}E/Z}$), 74.4 ($C_{3\text{-}E}$), 74.3 ($C_{3\text{-}Z}$), 67.7 ($C_{5\text{-}E}$), 67.3 ($C_{5\text{-}Z}$), 53.5 ($C_{2\text{-}Z}$), 53.3 ($C_{2\text{-}E}$), 40.0 ($C_{8\text{-}Z}$), 39.6 ($C_{8\text{-}E}$), 31.4 ($C_{6\text{-}E}$), 29.8 ($C_{6\text{-}Z}$), 28.5 ($C_{14\text{-}E/Z}$), 25.5 ($C_{1\text{-}E/Z}$), 25.0 ($C_{1\text{-}E/Z}$), 24.1 ($C_{1\text{-}E/Z}$), 9.7 ($C_{7\text{-}E}$), 9.6 ($C_{7\text{-}Z}$). **IR** ν_{max}/cm^{-1} (film): 2972, 1743, 1690, 1337, 1295, 1246, 1163, 1137, 1071. **HRMS** (ESI) calculated for $[C_{17}H_{26}N_2O_4+H]^+$: 323.1965, found: 323.1966. $\mathbf{R}_F$ = 0.19 (20% EtOAc/petroleum ether).

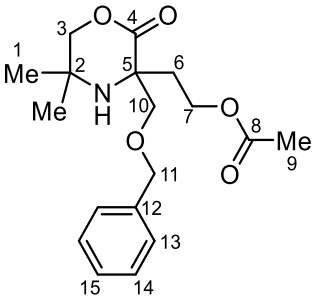
4-(3-Ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)butanenitrile **246**



tert-Butyl 3-(3-cyanoallyl)-3-ethyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate **246b** (0.35 mg, 0.11 mmol) was dissolved in MeOH (20 mL) and Pd/C (10% Pd, 0.15 g) was added. The reaction mixture was evacuated and backfilled with N_2 (3x), before being backfilled with H_2. The reaction mixture was stirred under a H_2 atmosphere for 14 h. Once completed the reaction was filtered through Celite and concentrated *in vacuo*. The crude amine was dissolved in CH_2Cl_2 (10 mL), trifluoroacetic acid (2 mL) was added and stirred at rt for 3 d. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (10 mL) extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 0-20% EtOAc/petroleum ether, to yield the title compound **246** as a colourless oil (64 mg, 0.29 mmol, 26%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 2H, H_3), 2.37 (td, *J* = 6.8, 2.1 Hz, 2H, H_{10}), 1.88 – 1.61 (m, 6H, H_6, H_8 and H_9), 1.20 (s, 3H, H_{1a}), 1.19 (s, 3H, H_{1b}), 0.95 (t, *J* = 7.4 Hz, 3H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4 (C_4), 119.6 (C_{11}), 77.9 (C_3), 60.8 (C_5), 48.7 (C_2), 39.2 (C_8), 33.5 (C_6), 26.9 (C_{1a}), 26.6 (C_{1b}), 20.3 (C_9), 17.6 (C_{10}), 8.4 (C_7). **IR** ν_{max}/cm^{-1} (film): 2968, 1726, 1458, 1379, 1284, 1219, 1155, 1117. **HRMS** (ESI) calculated for $[C_{12}H_{20}N_2O_2+H]^+$: 225.1598, found: 225.1600. $\mathbf{R_F}$ = 0.40 (20% EtOAc/CH_2Cl_2).

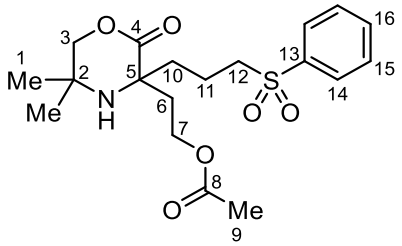
2-(3-((Benzyloxy)methyl)-5,5-dimethyl-2-oxomorpholin-3-yl)ethyl acetate **247**



Prepared according to general procedure **C** using 3-((benzyloxy)methyl)-3-ethyl-5,5-dimethylmorpholin-2-one (83 mg, 0.28 mmol), the reaction was stirred at 70 °C for 2.5 h. The crude material was purified by flash chromatography (silica gel, 11 cm, 2 cm Ø), eluting with 0-10% EtOAc/CH_2Cl_2, to give the title compound **247** as a yellow oil (52 mg, 0.16 mmol, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H, H_{13}, H_{14} and H_{15}), 4.56 (d, *J* = 12.0 Hz, 1H, H_{11a}), 4.52 (d, *J* = 12.0 Hz, 1H, H_{11b}), 4.26 (t, *J* = 6.3 Hz, 2H, H_7), 4.11 (d, *J* = 10.5 Hz, 1H, H_{3a}), 4.06 (d, *J* = 10.5 Hz, 1H, H_{3b}), 3.67 (d, *J* = 9.0 Hz, 1H, H_{10a}), 3.49 (d, *J* = 9.0 Hz, 1H, H_{10b}), 2.14 – 1.97 (m, 5H, H_6 and H_9), 1.81 (br. s, 1H, N–H),1.17 (s, 3H, H_{1a}), 1.14 (s, 3H, H_{1b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.5 (C_4), 171.0 (C_8), 137.6 (C_{12}), 128.7 (C_{14}), 128.1 (C_{15}), 127.9 (C_{13}), 77.8 (C_3), 75.6 (C_{10}), 73.6 (C_{11}), 60.7 (C_7), 60.0 (C_5), 48.3 (C_2), 37.5 (C_6), 26.2 (C_{1a}), 26.1 (C_{1b}), 21.0 (C_9). **IR** ν_{max}/cm^{-1} (film): 2967, 2916, 1732, 1365, 1232, 1097, 1045, 731. **HRMS** (ESI) calculated for $[C_{18}H_{25}NO_5+H]^+$: 336.1805, found: 336.1809. $\mathbf{R}_F$ = 0.33 (20% EtOAc/CH_2Cl_2).

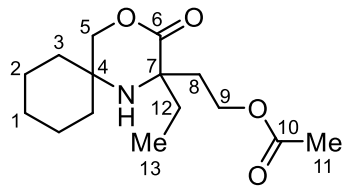
2-(5,5-Dimethyl-2-oxo-3-(3-(phenylsulfonyl)propyl)morpholin-3-yl)ethyl acetate **248**



Prepared according to general procedure **C** using 3-ethyl-5,5-dimethyl-3-(3-(phenylsulfonyl)propyl)morpholin-2-one **245** (97 mg, 0.30 mmol), the reaction was stirred at 70 °C for 2 h. The crude material was purified by flash chromatography (silica gel, 11 cm, 2 cm Ø), eluting with 0-20% EtOAc/CH_2Cl_2, to give the title compound **248** as a light yellow oil (63 mg, 0.16 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 2H, H_{15}), 7.67 – 7.61 (m, 1H, H_{16}), 7.55 (m, 2H, H_{14}), 4.17 (t, *J* = 6.5 Hz, 2H, H_7), 4.06 (s, 2H, H_3), 3.11 – 3.03 (m, 2H, H_{12}), 2.10 – 1.97 (m, 4H, H_{6a} and H_9), 1.91 – 1.69 (m, 5H, H_{6b}, H_{10} and H_{11}), 1.15 (s, 3H, H_{1a}), 1.12 (s, 3H, H_{1b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8 (C_4), 170.8 (C_8), 139.1 (C_{13}), 133.9 (C_{16}), 129.4 (C_{14}), 128.0 (C_{15}), 77.7 (C_3), 60.5 (C_7), 59.3 (C_5), 56.1 (C_{12}), 48.5 (C_2), 39.4 (C_{10}), 38.5 (C_6), 26.6 (C_{1a}), 26.5 (C_{1b}), 21.0 (C_9), 17.5 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2972, 1732, 1447, 1367, 1287, 1255, 1147, 1086. **HRMS** (ESI) calculated for $[C_{19}H_{27}NO_6S+H]^+$: 398.1632, found: 398.1629. $\mathbf{R}_F$ = 0.24 (20% EtOAc/CH_2Cl_2).

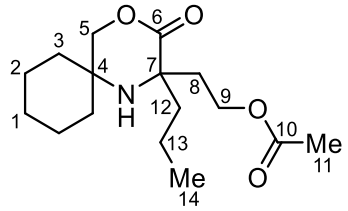
2-(2-Ethyl-3-oxo-4-oxa-1-azaspiro[5.5]undecan-2-yl)ethyl acetate **249**



Prepared according to general procedure **C** using 2,2-diethyl-4-oxa-1-azaspiro[5.5]undecan-3-one (68 mg, 0.30 mmol), the reaction was stirred at 70 °C for 1.5 h. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 0-10% EtOAc/CH_2Cl_2, to give the title compound **249** as a yellow oil (42 mg, 0.15 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (t, *J* = 6.8 Hz, 2H, H_9), 4.18 (d, *J* = 10.9 Hz, 1H, H_{5a}), 4.12 (d, *J* = 10.9 Hz, 1H, H_{5b}), 2.10 – 1.94 (m, 5H, H_{11} and H_{12}), 1.81 – 1.33 (m, 12H, H_1, H_2, H_3 and H_8), 1.24 (br. s, 1H, N–H), 0.96 (t, *J* = 7.4 Hz, 3H, H_{13}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.8 (C_6), 171.1 (C_{10}), 76.4 (C_5), 61.0 (C_9), 59.9 (C_7), 50.0 (C_4), 38.2 (C_8), 35.5 (C_{3a}), 34.8 (C_{3b}), 33.8 (C_{12}), 25.9 (C_1), 21.8 (C_{2a}), 21.7 (C_{2b}), 21.1 (C_{11}), 8.4 (C_{13}). **IR** ν_{max}/cm^{-1} (film): 2970, 1729, 1227, 1045, 915, 730. **HRMS** (ESI) calculated for $[C_{15}H_{25}NO_4+H]^+$: 284.1856, found: 284.1858. $\mathbf{R_F}$ = 0.71 (20% EtOAc/CH_2Cl_2).

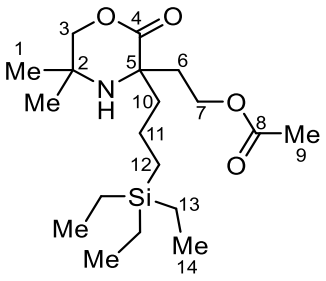
2-(3-Oxo-2-propyl-4-oxa-1-azaspiro[5.5]undecan-2-yl)ethyl acetate **250**



Prepared according to general procedure **C** using 2-ethyl-2-propyl-4-oxa-1-azaspiro[5.5]undecan-3-one **227** (72 mg, 0.30 mmol), the reaction was stirred at 70 °C for 2 h. The crude material was purified by flash chromatography (silica gel, 10 cm, 2 cm Ø), eluting with 0-20% EtOAc/CH_2Cl_2, to give the title compound **250** as a yellow oil (39 mg, 0.13 mmol, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (t, *J* = 6.8 Hz, 2H, H_9), 4.19 (d, *J* = 11.0 Hz, 1H, H_{5a}), 4.13 (d, *J* = 11.0 Hz, 1H, H_{5b}), 2.11 – 1.97 (m, 5H, H_8 and H_{11}), 1.75 – 1.34 (m, 14H, H_1, H_2, H_3, H_{12} and H_{13}), 1.25 (br. s, 1H, N–H), 0.93 (t, *J* = 7.2 Hz, 3H, H_{14}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.9 (C_6), 171.1 (C_{10}), 76.6 (C_5), 61.0 (C_9), 59.6 (C_7), 50.1 (C_4), 43.4 (C_{12}), 38.7 (C_8), 35.5 (C_{3a}), 34.6 (C_{3b}), 25.9 (C_1), 21.8 (C_{2a}), 21.8 (C_{2b}), 21.2 (C_{11}), 17.4 (C_{13}), 14.4 (C_{14}). **IR** ν_{max}/cm^{-1} (film): 2964, 1736, 1365, 1241, 1046, 683. **HRMS** (ESI) calculated for $[C_{16}H_{27}NO_4+H]^+$: 298.2013, found: 298.2015. $\mathbf{R_F}$ = 0.22 (20% EtOAc/CH_2Cl_2).

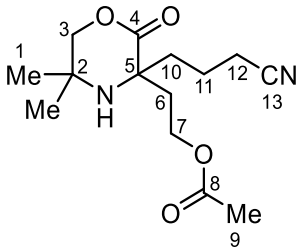
2-(5,5-Dimethyl-2-oxo-3-(3-(triethylsilyl)propyl)morpholin-3-yl)ethyl acetate **251**



Prepared according to general procedure **C** using 3-ethyl-5,5-dimethyl-3-(3-(triethylsilyl)propyl)morpholin-2-one **238** (50 mg, 0.16 mmol), the reaction was stirred at 70 °C for 1.5 h. The crude material was purified by flash chromatography (silica gel, 19 cm, 1 cm Ø), eluting with 0-5% EtOAc/CH_2Cl_2, to give the title compound **251** as a yellow oil (22 mg, 0.060 mmol, 39%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (t, *J* = 6.9 Hz, 2H, H_7), 4.12 (d, *J* = 10.8 Hz, 1H, H_{3a}), 4.09 (d, *J* = 10.8 Hz, 1H, H_{3b}), 2.11 (dt, *J* = 14.2, 6.9 Hz, 1H, H_{6a}), 2.04 (s, 3H, H_9), 1.93 (dt, *J* = 14.2, 6.9 Hz, 1H, H_{6b}), 1.77 (ddd, *J* = 13.8, 11.1, 5.8 Hz, 1H, H_{10a}), 1.66 (ddd, *J* = 13.7, 11.2, 5.5 Hz, 1H, H_{10b}), 1.40 – 1.31 (m, 2H, H_{11}), 1.20 (s, 3H, H_{1a}), 1.18 (s, 3H, H_{1b}), 0.92 (t, *J* = 7.9 Hz, 9H, H_{14}), 0.55 – 0.46 (m, 8H, H_{12} and H_{13}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.4 (C_4), 171.1 (C_8), 77.7 (C_3), 61.0 (C_7), 59.7 (C_5), 48.6 (C_2), 45.7 (C_{10}), 38.8 (C_6), 27.0 (C_{1a}), 26.5 (C_{1b}), 21.1 (C_9), 18.4 (C_{11}), 11.9 (C_{12}), 7.6 (C_{14}), 3.5 (C_{13}). **IR** ν_{max}/cm^{-1} (film): 2954, 2875, 1732, 1235, 908, 728, 647. **HRMS** (ESI) calculated for $[C_{19}H_{37}NO_4Si+H]^+$: 372.2565, found: 372.2565. $\mathbf{R_F}$ = 0.53 (10% EtOAc/CH_2Cl_2).

2-(3-(3-Cyanopropyl)-5,5-dimethyl-2-oxomorpholin-3-yl)ethyl acetate **252**

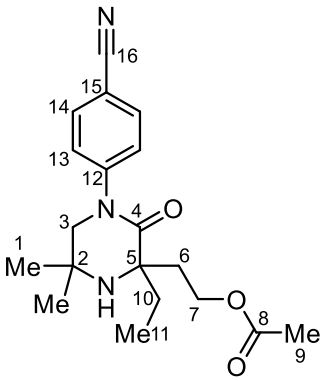


Prepared according to general procedure **C** using 4-(3-ethyl-5,5-dimethyl-2-oxomorpholin-3-yl)butanenitrile **246** (60 mg, 0.27 mmol), the reaction was stirred at 70 °C for 2.5 h. The crude material was purified by flash chromatography (silica gel, 14 cm, 2 cm Ø), eluting with 0-20% EtOAc/CH_2Cl_2, to give the title compound **252** as a yellow oil (28 mg, 0.99 mmol, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (t, *J* = 6.5 Hz, 2H, H_7), 4.12 (s, 2H, H_3), 2.41 – 2.33 (m, 2H, H_{12}), 2.10 (dt, *J* = 14.2, 6.5 Hz, 1H, H_{6a}), 2.04 (s, 3H, H_9), 1.92 (dt, *J* = 14.2, 6.5 Hz, 1H, H_{6b}), 1.87 – 1.71 (m, 4H, H_{10} and H_{11}), 1.30 (br. s, 1H, N–H), 1.19 (s, 6H, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8

(C_4), 170.8 (C_8), 119.3 (C_{13}), 77.8 (C_3), 60.5 (C_7), 59.2 (C_5), 48.7 (C_2), 40.1 (C_{10}), 38.5 (C_6), 26.7 (C_{1a}), 26.6 (C_{1b}), 21.0 (C_9), 20.2 (C_{11}), 17.4 (C_{12}). **IR** ν_{max}/cm^{-1} (film): 2968, 1729, 1460, 1479, 1367, 1285, 1234, 1177, 1048. **HRMS** (ESI) calculated for $[C_{14}H_{22}N_2O_4+H]^+$: 283.1652, found: 283.1655. $\mathbf{R_F}$ = 0.26 (20% EtOAc/CH_2Cl_2).

2-(4-(4-Cyanophenyl)-2-ethyl-6,6-dimethyl-3-oxopiperazin-2-yl)ethyl acetate **253**

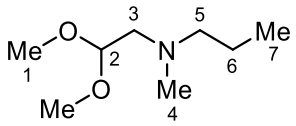


Prepared according to general procedure **C** using 4-(3,3-diethyl-5,5-dimethyl-2-oxopiperazin-1-yl)benzonitrile (86 mg, 0.30 mmol), the reaction was stirred at 70 °C for 2 h. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 0-20% EtOAc/CH_2Cl_2, to give the title compound **253** as a yellow oil (31 mg, 0.090 mmol, 30%). *This experiment was repeated by Dr Darren Willcox using 15 mol% $Pd(OAc)_2$ to afford acetoxylated product* **253** *in 65% yield*.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2H, H_{13}), 7.48 – 7.41 (m, 2H, H_{14}), 4.29 (td, *J* = 6.8, 2.9 Hz, 2H, H_7), 3.57 (app. d, *J* = 1.4 Hz, 2H, H_3), 2.16 – 2.06 (m, 1H, H_{6a}), 2.04 – 1.97 (m, 4H, H_{6b} and H_9), 1.86 (dq, *J* = 14.5, 7.4 Hz, 1H, H_{10a}), 1.72 (dq, *J* = 14.5, 7.4 Hz, 1H, H_{10b}), 1.30 (s, 3H, H_{1a}), 1.28 (s, 3H, H_{1b}), 0.98 (t, *J* = 7.4 Hz, 3H, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7 (C_4), 171.1 (C_8), 147.2 (C_{12}), 133.0 (C_{13}), 125.9 (C_{14}), 118.6 (C_{15}), 109.8 (C_{16}), 61.5 (C_7), 61.3 (C_3), 61.1 (C_5), 49.2 (C_2), 38.4 (C_6), 33.7 (C_{10}), 28.3 (C_{1a}), 27.8 (C_{1b}), 21.2 (C_9), 8.4 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2970, 1733, 1656, 1600, 1505, 1313, 1235, 1177, 1033, 845, 731. **HRMS** (ESI) calculated for $[C_{19}H_{25}N_3O_3+H]^+$: 344.1969, found: 344.1970. $\mathbf{R_F}$ = 0.26 (20% EtOAc/CH_2Cl_2).

5.3 Experimental procedures for the alkenylation of tertiary amines

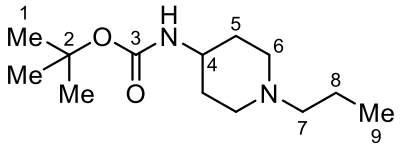
N-(2,2-Dimethoxyethyl)-N-methylpropan-1-amine **275a**



2,2-Dimethoxy-*N*-methylethan-1-amine (1.3 mL, 10 mmol), triethylamine (1.7 mL, 12 mmol) and CH_2Cl_2 (10 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (1.1 mL, 12 mmol) was added to the reaction mixture dropwise, which was stirred for 24 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 10 g column), eluting with 10-50% EtOAc/petroleum ether, to give the intermediate *N*-(2,2-dimethoxyethyl)-*N*-methylpropionamide as a colourless liquid. *N*-(2,2-Dimethoxyethyl)-*N*-methylpropionamide was dissolved in Et_2O (20 mL) at 0 °C and $LiAlH_4$ (0.38 g, 10 mmol) added portion-wise. The reaction was stirred for 20 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification of the crude material by Kugelrohr distillation (50 mBar, 100 °C) gave the title compound **275a** (0.59 g, 3.7 mmol, 37%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (t, *J* = 5.3 Hz, 1H, H_2), 3.36 (s, 6H, H_1), 2.50 (d, *J* = 5.3 Hz, 2H, H_3), 2.40 – 2.30 (m, 2H, H_5), 2.29 (s, 3H, H_4), 1.48 (h, *J* = 7.4 Hz, 2H, H_6), 0.88 (t, *J* = 7.4 Hz, 3H, H_7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 103.0 (C_2), 60.8 (C_5), 59.0 (C_3), 53.4 (C_1), 43.4 (C_4), 20.4 (C_6), 12.0 (C_7). **IR** ν_{max}/cm^{-1} (film): 2957, 2934, 2904, 2829, 1458, 1193, 1127, 1065, 967, 853. **HRMS** (ESI) calculated for $[C_8H_{19}O_2N+H]^+$: 162.1489, found: 162.1485. $\mathbf{R_F}$ = 0.28 (10% MeOH/EtOAc).

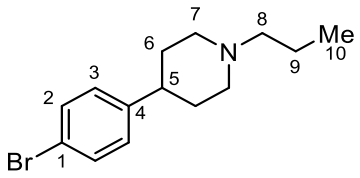
tert-Butyl (1-propylpiperidin-4-yl)carbamate **275b**



tert-Butyl piperidin-4-ylcarbamate (0.37 g, 1.9 mmol) was dissolved in CH_2Cl_2 (30 mL) and the reaction cooled to 0 °C. Propanal (0.20 mL, 2.77 mmol) and $NaBH(OAc)_3$ (0.59 g, 2.8 mmol) were added to the reaction mixture and stirred for 22 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (70 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 12 g column), eluting with EtOAc, to give *tert*-butyl (1-propylpiperidin-4-yl)carbamate **275b** (0.19 g, 0.78 mmol, 42%) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (br. s, 1H, N–H), 3.45 (br. s, 1H, H_4), 2.83 (d, *J* = 11.2 Hz, 2H, H_{6a}), 2.27 (t, *J* = 7.7 Hz, 2H, H_7), 2.03 (t, *J* = 11.4 Hz, 2H, H_{6b}), 1.92 (d, *J* = 12.1 Hz, 2H, H_{5a}), 1.55 – 1.36 (m, 13H, H_1, H_{5b} and H_8), 0.88 (t, *J* = 7.4 Hz, 3H, H_9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.2 (C_3), 79.1 (C_2), 60.7 (C_7), 52.5 (C_6), 47.9 (C_4), 32.7 (C_5), 28.4 (C_1), 20.3 (C_8), 12.0 (C_9). **IR** ν_{max}/cm^{-1} (film): 3184, 2977, 2939, 2818, 1700, 1537, 1278, 1168, 1145, 1043, 1006, 787. **HRMS** (ASAP) calculated for $[C_{13}H_{26}N_2O_2+H]^+$: 243.2073, found: 243.2071. $\mathbf{R_F}$ = 0.22 (10% MeOH/EtOAc).

4-(4-Bromophenyl)-1-propylpiperidine **275c**

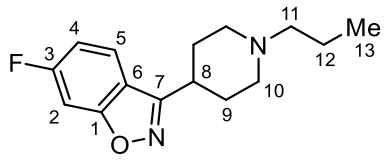


4-(4-Bromophenyl)piperidine (0.30 g, 1.3 mmol), triethylamine (0.21 mL, 1.5 mmol) and CH_2Cl_2 (10 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (0.13 mL, 1.5 mmol) was added to the reaction mixture dropwise, which was stirred for 2 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 7 cm, 2 cm Ø), eluting with 10-50% EtOAc/petroleum ether, to give the intermediate 1-(4-(4-bromophenyl)piperidin-1-yl)propan-

1-one as a colourless oil. 1-(4-(4-Bromophenyl)piperidin-1-yl)propan-1-one was dissolved in Et_2O (10 mL) at 0 °C and $LiAlH_4$ (50 mg, 1.25 mmol) added portion-wise. The reaction was stirred for 1 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification by flash chromatography (combiflash, silica gel, 5 g column), eluting with 5-40% MeOH/EtOAc, gave the title compound 4-(4-bromophenyl)-1-propylpiperidine **275c** (0.30 g, 1.1 mmol, 85%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 2H, H_2), 7.10 (d, *J* = 8.1 Hz, 2H, H_3), 3.05 (d, *J* = 11.7 Hz, 2H, H_{7a}), 2.45 (ddd, *J* = 16.1, 11.2, 4.6 Hz, 1H, H_5), 2.37 – 2.28 (m, 2H, H_8), 2.01 (td, *J* = 11.4, 3.2 Hz, 2H, H_{7b}), 1.78 (qd, *J* = 12.2, 3.4 Hz, 4H, H_6), 1.54 (h, *J* = 7.4 Hz, 2H, H_9), 0.92 (t, *J* = 7.4 Hz, 3H, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.6 (C_1), 131.6 (C_2), 128.8 (C_3), 119.8 (C_4), 61.3 (C_8), 54.4 (C_7), 42.5 (C_5), 33.6 (C_6), 20.4 (C_9), 12.2 (C_{10}). **IR** ν_{max}/cm^{-1} (film): 2957, 2932, 2873, 2803, 2766, 1489, 1376, 1075, 1010, 995, 820. **HRMS** (ESI) calculated for $[C_{14}H_{20}NBr+H]^+$: 282.0841, found: 282.0852. $\mathbf{R}_F$ = 0.15 (10% MeOH/EtOAc).

6-Fluoro-3-(1-propylpiperidin-4-yl)benzo[δ]isoxazole **275d**

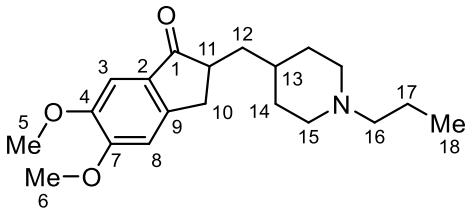


6-Fluoro-3-(piperidin-4-yl)benzo[δ]isoxazole·HCl (1.2 g, 4.6 mmol) was dissolved in CH_2Cl_2 (10 mL) and triethylamine (0.64 mL, 4.6 mmol) was added to the reaction at 0 °C. After stirring for 10 min at 0 °C, propanal (0.50 mL, 6.94 mmol) and $NaBH(OAc)_3$ (1.5 g, 6.9 mmol) were added to the reaction mixture and stirred for 17 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 5-10% MeOH/EtOAc, to give 6-fluoro-3-(1-propylpiperidin-4-yl)benzo[d]isoxazole **275d** (1.0 g, 3.9 mmol, 85%) as a light yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.7, 5.1 Hz, 1H, H_5), 7.23 (dd, *J* = 8.5, 2.1 Hz, 1H, H_4), 7.04 (td, *J* = 8.9, 2.1 Hz, 1H, H_2), 3.08 (m, 3H, H_8 and H_{10a}), 2.42 – 2.29 (m, 2H, H_{11}), 2.18 – 1.99 (m, 6H, H_9 and H_{10b}), 1.55 (h, *J* = 7.4 Hz, 2H, H_{12}), 0.92 (t, *J* = 7.3 Hz, 3H, H_{13}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{C\text{-}F}$ = 250.5 Hz, C_3), 164.0 (d, $^3J_{C\text{-}F}$ = 13.6 Hz, C_1), 161.3

(C_7), 122.8 (d, $^3J_{C\text{-}F}$ = 11.1 Hz, C_5), 117.5 (d, $^4J_{C\text{-}F}$ = 1.3 Hz, C_6), 112.4 (d, $^2J_{C\text{-}F}$ = 25.3 Hz, C_2), 97.6 (d, $^2J_{C\text{-}F}$ = 26.7 Hz, C_4), 61.1 (C_{11}), 53.7 (C_{10}), 34.9 (C_8), 30.7 (C_9), 20.3 (C_{12}), 12.2 (C_{13}). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -109.8. **IR** ν_{max}/cm^{-1} (film): 2957, 2769, 1615, 1495, 1416, 1273, 1138, 1121, 957, 839, 815. **HRMS** (ESI) calculated for $[C_{15}H_{19}N_2OF+H]^+$: 263.1554, found: 263.1550. $\mathbf{R_F}$ = 0.20 (10% MeOH/EtOAc).

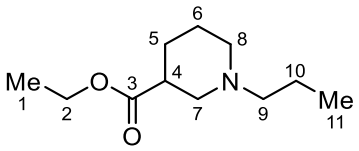
5,6-Dimethoxy-2-((1-propylpiperidin-4-yl)methyl)-2,3-dihydro-1H-inden-1-one **275e**



5,6-Dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one·HCl (1.0 g, 3.1 mmol) was dissolved in CH_2Cl_2 (10 mL) and triethylamine (0.43 mL, 3.1 mmol) was added to the reaction at 0 °C. After stirring for 10 min at 0 °C, propanal (0.33 mL, 4.6 mmol) and $NaBH(OAc)_3$ (0.98 g, 4.6 mmol) were added to the reaction mixture and stirred for 17 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 17 cm, 2 cm Ø), eluting with 10-50% MeOH/EtOAc, to give 5,6-dimethoxy-2-((1-propylpiperidin-4-yl)methyl)-2,3-dihydro-1H-inden-1-one **275e** (0.67 g, 2.0 mmol, 66%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H, H_3), 6.85 (s, 1H, H_8), 3.96 (s, 3H, H_6), 3.90 (s, 3H, H_5), 3.24 (dd, *J* = 17.5, 8.1 Hz, 1H, H_{10a}), 2.97 (dd, *J* = 11.3, 5.4 Hz, 2H, H_{15a}), 2.70 (m, 2H, H_{10b} and H_{11}), 2.36 – 2.26 (m, 2H, H_{16}), 2.04 – 1.85 (m, 3H, H_{12a} and H_{15b}), 1.74 (app. t, *J* = 15.1 Hz, 2H, H_{14a}), 1.54 (h, *J* = 7.2 Hz, 3H, H_{13} and H_{17}), 1.46 – 1.26 (m, 3H, H_{12b} and H_{14b}), 0.90 (t, *J* = 7.2 Hz, 3H, H_{18}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.9 (C_1), 155.6 (C_7), 149.6 (C_4), 148.9 (C_2), 129.5 (C_9), 107.5 (C_8), 104.5 (C_3), 61.2 (C_{16}), 56.4 (C_6), 56.3 (C_5), 54.0 (C_{12a}), 53.9 (C_{12b}), 45.5 (C_{11}), 38.9 (C_{12}), 34.6 (C_{13}), 33.6 (C_{10}), 32.9 (C_{14a}), 31.8 (C_{14b}), 20.2 (C_{17}), 12.2 (C_{18}). **IR** ν_{max}/cm^{-1} (film): 2926, 1695, 1606, 1591, 1501, 1466, 1313, 1265, 1222, 1122, 1038. **HRMS** (ESI) calculated for $[C_{20}H_{29}NO_3+H]^+$: 332.2220, found: 332.2210. $\mathbf{R_F}$ = 0.08 (20% MeOH/EtOAc). Data consistent with literature.[225]

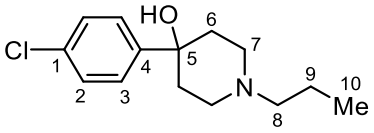
Ethyl 1-propylpiperidine-3-carboxylate **275f**



Ethyl piperidine-3-carboxylate (0.29 mL, 1.9 mmol) was dissolved in CH_2Cl_2 (30 mL) and the reaction cooled to 0 °C. Propanal (0.20 mL, 2.8 mol) and $NaBH(OAc)_3$ (0.59 g, 2.8 mmol) were added to the reaction mixture and stirred for 24 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 2-4% MeOH/EtOAc, to give ethyl 1-propylpiperidine-3-carboxylate **275f** (0.13 g, 0.65 mmol, 35%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, *J* = 7.1 Hz, 2H, H_2), 2.99 (app. d, *J* = 10.4 Hz, 1H, H_{7a}), 2.82 – 2.74 (m, 1H, H_{8a}), 2.55 (tt, *J* = 10.6, 3.8 Hz, 2H, H_4), 2.33 – 2.26 (m, 2H, H_9), 2.10 (t, *J* = 10.8 Hz, 1H, H_{7b}), 1.99 – 1.90 (m, 2H, H_{5a} and H_{8b}), 1.72 (dp, *J* = 14.9, 3.8 Hz, 1H, H_{6a}), 1.63 – 1.37 (m, 4H, H_{5b}, H_{6b} and H_{10}), 1.25 (t, *J* = 7.1 Hz, 3H, H_1), 0.88 (t, *J* = 7.4 Hz, 3H, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.5 (C_3), 61.1 (C_9), 60.4 (C_2), 55.6 (C_7), 54.0 (C_8), 42.0 (C_4), 27.2 (C_5), 24.8 (C_6), 20.1 (C_{10}), 14.4 (C_1), 12.1 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2957, 2936, 1730, 1304, 1226, 1175, 1145, 1090, 1036. **HRMS** (ESI) calculated for $[C_{11}H_{21}NO_2+H]^+$: 200.1645, found: 200.1650. $\mathbf{R_F}$ = 0.19 (10% MeOH/EtOAc).

4-(4-Chlorophenyl)-1-propylpiperidin-4-ol **275g**

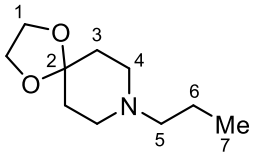


4-(4-Chlorophenyl)piperidin-4-ol (0.39 mL, 1.9 mmol) was dissolved in CH_2Cl_2 (10 mL) and the reaction cooled to 0 °C. Propanal (0.20 mL, 2.8 mmol) and $NaBH(OAc)_3$ (0.59 g, 2.8 mmol) were added to the reaction mixture and stirred for 24 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 5-15% MeOH/EtOAc, to give 4-(4-chlorophenyl)-1-propylpiperidin-4-ol **275g** (0.40 g, 1.6 mmol, 85%) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.33 – 7.29 (m, 2H), 2.85 (d, *J* = 11.3 Hz, 2H, H_{7a}), 2.49 – 2.37 (m, 4H, H_{7b} and H_8), 2.16 (td, *J* = 13.3, 4.3 Hz, 2H, H_{6a}), 1.73 (ddd, J = 14.3, 4.3, 2.3 Hz,

2H, H_{6b}), 1.57 (h, *J* = 7.4 Hz, 2H, H_9), 0.93 (t, *J* = 7.4 Hz, 3H, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0 (C_1), 132.9 (C_4), 128.6 (C_2), 126.3 (C_3), 71.3 (C_5), 60.9 (C_8), 49.6 (C_7), 38.5 (C_6), 20.3 (C_9), 12.2 (C_{10}). **IR** ν_{max}/cm^{-1} (film): 3288 (br), 2962, 2934, 1638, 1594, 1490, 1396, 1379, 1049, 1012, 989, 969, 827, 731, 543. **HRMS** (ESI) calculated for $[C_{14}H_{20}NOCl+H]^+$: 254.1306, found: 254.1300. $\mathbf{R_F}$ = 0.08 (10% MeOH/EtOAc).

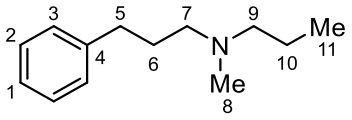
8-Propyl-1,4-dioxa-8-azaspiro[4.5]decane **275h**



1,4-Dioxa-8-azaspiro[4.5]decane (0.51 mL, 4.0 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Propanal (0.43 mL, 6.0 mmol) was added and the reaction mixture stirred for 15 min. $NaBH(OAc)_3$ (1.3 g, 6.0 mmol) was added to the reaction which was stirred at rt for 16 h. The reaction was quenched with sat. aq. K_2CO_3 (50 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 12 g column), eluting with 0-100% MeOH/EtOAc, to give 8-propyl-1,4-dioxa-8-azaspiro[4.5]decane **275h** (0.63 g, 3.4 mmol, 85%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 4H, H_1), 2.52 (br. s, 4H, H_4), 2.36 – 2.26 (m, 2H, H_5), 1.75 (t, *J* = 5.7 Hz, 4H, H_3), 1.50 (h, *J* = 7.4 Hz, 2H, H_6), 0.89 (t, *J* = 7.4 Hz, 3H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 107.5 (C_2), 64.3 (C_1), 60.5 (C_5), 51.5 (C_4), 35.0 (C_3), 20.6 (C_6), 12.2 (C_7). **IR** ν_{max}/cm^{-1} (film): 2957, 2932, 2876, 2811, 1364, 1220, 1155, 1090, 1038, 1006, 963, 945, 918, 491, 452. **HRMS** (ESI) calculated for $[C_{10}H_{19}NO_2+H]^+$: 186.1484, found: 186.1489. $\mathbf{R_F}$ = 0.14 (10% MeOH/EtOAc).

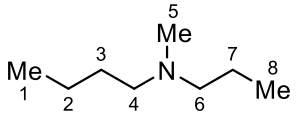
N-Methyl-3-phenyl-N-propylpropan-1-amine **275i**



3-Phenylpropan-1-amine (0.50 mL, 3.5 mmol), triethylamine (0.59 mL, 4.2 mmol) and CH_2Cl_2 (10 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (0.37 mL, 4.2 mmol) was added to the reaction mixture dropwise, which was stirred for 2 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude *N*-(3-phenylpropyl)propionamide was used directly in the next step. *N*-(3-Phenylpropyl)propionamide from was dissolved in THF (15 mL), cooled to 0 °C and NaH (60%, 0.17 g, 4.2 mmol) added portion-wise. The reaction mixture was stirred for 15 min, then MeI (0.27 mL, 4.2 mmol) was added and the reaction stirred for 17 h, warming to rt. The reaction was quenched by addition of H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 15 cm, 2 cm Ø), eluting with 10-100% Et_2O/petroleum ether, to give the intermediate *N*-methyl-*N*-(3-phenylpropyl)propionamide (0.41 g, 2.0 mmol, 47%) as a colourless oil. *N*-Methyl-*N*-(3-phenylpropyl)propionamide (0.70 g, 3.3 mmol) was dissolved in Et_2O (20 mL) at 0 °C and $LiAlH_4$ (2.4 M in THF, 2.8 mL, 6.8 mmol) added dropwise. The reaction was stirred for 2 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification by Kugelrohr distillation (30 mBar, 48 °C) gave the title compound *N*-methyl-3-phenyl-*N*-propylpropan-1-amine **275i** (0.40 g, 2.1 mmol, 63%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H, H_2), 7.23 – 7.13 (m, 3H, H_1 and H_3), 2.63 (t, *J* = 7.9 Hz, 2H, H_5), 2.41 – 2.32 (m, 2H, H_7), 2.33 – 2.24 (m, 2H, H_9), 2.21 (s, 3H, H_8), 1.86 – 1.73 (m, 2H, H_6), 1.55 – 1.40 (m, 2H, H_{10}), 0.89 (t, *J* = 7.4 Hz, 3H, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.6 (C_4), 128.5 (C_3), 128.4 (C_2), 125.8 (C_1), 60.0 (C_9), 57.5 (C_7), 42.4 (C_8), 33.9 (C_5), 29.3 (C_6), 20.6 (C_{10}), 12.1 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2956, 2935,2787, 1453, 1030, 744, 697. **HRMS** (ESI) calculated for $[C_{13}H_{21}N+H]^+$: 192.1747, found: 192.1744. $\mathbf{R}_F$ = 0.18 (10% MeOH/EtOAc). Data consistent with literature.[256]

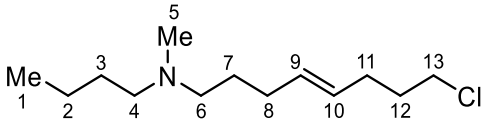
N-Methyl-N-propylbutan-1-amine **278**



N-Methylbutan-1-amine (5.9 mL, 50 mmol), triethylamine (8.4 mL, 60 mmol) and CH_2Cl_2 (60 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (5.2 mL, 60 mmol) was added to the reaction mixture dropwise, which was stirred for 2 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (100 mL), extracted with CH_2Cl_2 (2 x 100 mL), the combined organics washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude *N*-butyl-*N*-methylpropionamide was used directly in the next step. *N*-Butyl-*N*-methylpropionamide was dissolved in Et_2O (50 mL) at 0 °C and $LiAlH_4$ (2.4 M in THF, 20 mL, 50 mmol) added dropwise. The reaction was stirred at reflux for 3 h and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification by Kugelrohr distillation (220 mBar, 85 °C) gave the title compound *N*-methyl-*N*-propylbutan-1-amine **278** (4.1 g, 31 mmol, 63%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 – 2.22 (m, 4H, H_4 and H_6), 2.20 (s, 3H, H_5), 1.55 – 1.39 (m, 4H, H_3 and H_7), 1.30 (h, *J* = 7.3 Hz, 2H, H_2), 0.91 (t, *J* = 7.3 Hz, 3H, H_1), 0.88 (t, *J* = 7.4 Hz, 3H, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 60.1 (C_6), 57.8 (C_4), 42.5 (C_5), 29.7 (C_3), 20.9 (C_2), 20.6 (C_7), 14.2 (C_1), 12.1 (C_8). **IR** ν_{max}/cm^{-1} (film): 3346, 2961, 2931, 2875, 1459, 1378, 1139, 1086, 1035, 973. **HRMS** (ESI) calculated for $[C_8H_{19}N+H]^+$: 130.1590, found: 130.1588. $\mathbf{R_F}$ = 0.16 (10% MeOH/EtOAc). Data consistent with literature.[225]

(E)-N-Butyl-8-chloro-N-methyloct-4-en-1-amine **280a**

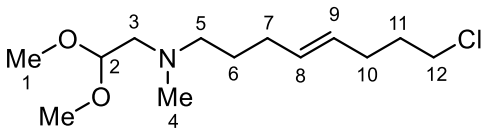


Prepared according to general procedure **D** using *N*-methyl-*N*-propylbutan-1-amine **278** (0.11 mL, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 15 cm, 2 cm Ø), eluting with 1-5% MeOH/EtOAc, to yield the title compound **280a** as a brown oil (43 mg, 0.19 mmol, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.2, 6.6 Hz, 1H, H_9), 5.37 (dt, *J* = 15.2, 6.5 Hz, 1H, H_{10}), 3.52 (t, *J* = 6.7 Hz, 2H, H_{13}), 2.39 – 2.32 (m, 4H, H_4 and H_6), 2.24 (s, 3H, H_5), 2.14 (q, *J* = 7.0 Hz, 2H, H_{11}), 2.00 (q, *J* = 6.4 Hz, 2H, H_8), 1.82 (p, *J* = 6.8 Hz, 2H, H_{12}), 1.55 (p, *J* = 7.5 Hz, 2H, H_7), 1.53 – 1.40 (m, 2H, H_3), 1.31 (dq, *J* = 14.5, 7.3 Hz, 2H, H_2), 0.92 (t, *J* = 7.3 Hz, 3H, H_1). **^{13}C NMR** (100 MHz,

$CDCl_3$) δ 131.8 (C_9), 128.6 (C_{10}), 57.8 (C_4 or C_6), 57.5 (C_4 or C_6), 44.6 (C_{13}), 42.5 (C_5), 32.4 (C_{12}), 30.6 (C_8), 29.8 (C_{11}), 29.7 (C_3), 27.3 (C_7), 20.9 (C_2), 14.2 (C_1). **IR** ν_{max}/cm^{-1} (film): 2955, 2932, 2862, 1457, 1308, 1261, 1054, 1033, 968, 655. **HRMS** (ESI) calculated for $[C_{13}H_{26}NCl+H]^+$: 232.1827, found: 232.1829. $\mathbf{R_F}$ = 0.18 (20% MeOH/EtOAc).

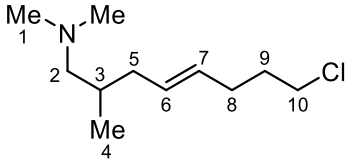
(E)-8-Chloro-N-(2,2-dimethoxyethyl)-N-methyloct-4-en-1-amine **280b**



Prepared according to general procedure **D** using *N*-(2,2-dimethoxyethyl)-*N*-methylpropan-1-amine **275a** (97 mg, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 8 cm, 2 cm Ø), eluting with 5-10% MeOH/EtOAc, to yield (*E*)-8-chloro-*N*-(2,2-dimethoxyethyl)-*N*-methyloct-4-en-1-amine **280b** as a brown oil (50 mg, 0.20 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dt, *J* = 15.3, 6.6 Hz, 1H, H_8), 5.36 (dt, *J* = 15.3, 6.6 Hz, 1H, H_9), 4.48 (t, *J* = 5.3 Hz, 1H, H_2), 3.52 (t, *J* = 6.7 Hz, 2H, H_{12}), 3.36 (s, 6H, H_1), 2.51 (d, *J* = 5.3 Hz, 2H, H_3), 2.42 – 2.36 (m, 2H, H_5), 2.29 (s, 3H, H_4), 2.13 (q, *J* = 7.0 Hz, 2H, H_{10}), 2.00 (q, *J* = 7.0 Hz, 2H, H_7), 1.82 (p, *J* = 6.8 Hz, 2H, H_{11}), 1.53 (p, *J* = 7.5 Hz, 2H, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.6 (C_8), 128.7 (C_9), 102.9 (C_2), 59.0 (C_3), 58.2 (C_5), 53.5 (C_1), 44.6 (C_{12}), 43.4 (C_4), 32.4 (C_{11}), 30.5 (C_7), 29.7 (C_{10}), 27.0 (C_6). **IR** ν_{max}/cm^{-1} (film): 2934, 2831, 1444, 1193, 1125, 1072, 967, 852, 652. **HRMS** (ASAP) calculated for $[C_{13}H_{26}NO_2Cl+H]^+$: 264.1725, found: 264.1721. $\mathbf{R_F}$ = 0.36 (20% MeOH/EtOAc).

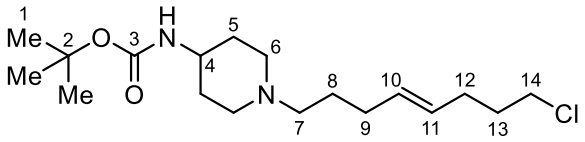
(E)-8-Chloro-N,N,2-trimethyloct-4-en-1-amine **280c**



Prepared according to general procedure **D** from *N*,*N*,2-trimethylpropan-1-amine **299** (0.17 mL, 1.2 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (0.14 mL, 0.60 mmol). The crude material was purified by flash chromatography (silica gel, 23 cm, 2 cm Ø), eluting with 1-10% MeOH/EtOAc, to yield the title compound **280c** as a brown oil (61 mg, 0.30 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (dt, *J* = 14.9, 6.8 Hz, 1H, H_7), 5.36 (dt, *J* = 14.9, 6.8 Hz, 1H, H_6), 3.53 (t, *J* = 6.7 Hz, 2H, H_{10}), 2.19 (s, 6H, H_1), 2.18 – 2.07 (m, 4H, H_{2a}, H_{5a} and H_8), 2.02 (dd, *J* = 11.9, 7.7 Hz, 1H, H_{2b}), 1.89 – 1.73 (m, 3H, H_{5b} and H_9), 1.64 (dddd, *J* = 14.6, 7.9, 6.6, 4.9 Hz, 1H, H_3), 0.87 (d, *J* = 6.6 Hz, 3H, H_4). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 130.2 (C_7), 129.9 (C_6), 66.6 (C_2), 46.0 (C_1), 44.6 (C_{10}), 38.2 (C_5), 32.5 (C_9), 31.5 (C_3), 29.8 (C_8), 18.1 (C_4). **IR** ν_{max}/cm^{-1} (film): 2952, 2763, 1459, 1443, 1379, 1263, 1034, 969, 842, 655. **HRMS** (ESI) calculated for $[C_{11}H_{22}NCl+H]^+$: 204.1514, found: 204.1508. $\mathbf{R_F}$ = 0.09 (10% MeOH/EtOAc).

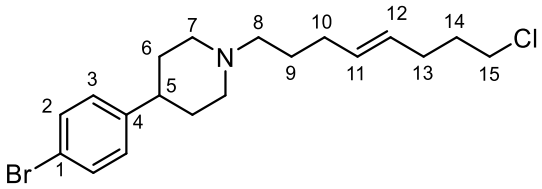
tert-Butyl (E)-(1-(8-chlorooct-4-en-1-yl)piperidin-4-yl)carbamate **280d**



Prepared according to general procedure **D** using *tert*-butyl-(1-propylpiperidin-4-yl)carbamate **275b** (73 mg, 0.30 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (35 μL, 0.15 mmol). The crude material was purified by flash chromatography (silica gel, 15 cm, 2 cm Ø), eluting with 2-5% MeOH/EtOAc, to yield the title compound **280d** as a brown oil (26 mg, 0.080 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (dt, *J* = 15.2, 6.4 Hz, 1H, H_{10}), 5.35 (dt, *J* = 15.2, 6.4 Hz, 1H, H_{11}), 4.45 (br. s, 1H, N–H), 3.51 (t, *J* = 6.7 Hz, 2H, H_{14}), 3.46 (br. s, 1H, H_4), 2.85 (br. d, *J* = 10.6 Hz, 2H, H_{6a}), 2.34 – 2.27 (m, 2H, H_7), 2.13 (q, *J* = 7.0 Hz, 2H, H_{12}), 2.05 (t, *J* = 12.0 Hz, 2H, H_{6b}), 1.99 (q, *J* = 7.2 Hz, 2H, H_9), 1.92 (d, *J* = 11.8 Hz, 2H, H_{5a}), 1.81 (p, *J* = 6.8 Hz, 2H, H_{13}), 1.54 (q, *J* = 7.8 Hz, 2H, H_8), 1.43 (s, 11H, H_1 and H_{5b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3 (C_3), 131.4 (C_{10}), 128.8 (C_{11}), 79.4 (C_2), 58.2 (C_7), 52.6 (C_6), 47.9 (C_4), 44.5 (C_{14}), 32.6 (C_5), 32.4 (C_{13}), 30.6 (C_9), 29.7 (C_{12}), 28.6 (C_1), 26.9 (C_8). **IR** ν_{max}/cm^{-1} (film): 2937, 1704, 1522, 1365, 1240, 1173, 1046, 1033, 1011. **HRMS** (ESI) calculated for $[C_{18}H_{33}N_2O_2Cl+H]^+$: 345.2303, found: 345.2302. $\mathbf{R_F}$ = 0.28 (10% MeOH/EtOAc).

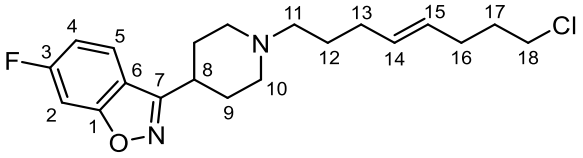
(E)-4-(4-Bromophenyl)-1-(8-chlorooct-4-en-1-yl)piperidine **280e**



Prepared according to general procedure **D** using 4-(4-bromophenyl)-1-propylpiperidine **275c** (0.17 g, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (combiflash, silica gel, 5 g column), eluting with 2-30% MeOH/EtOAc, to yield the title compound **280e** as a brown oil (42 mg, 0.11 mmol, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.1 Hz, 2H, H_2), 7.10 (d, *J* = 8.1 Hz, 2H, H_3), 5.48 (dt, *J* = 15.3, 6.3 Hz, 1H, H_{11}), 5.39 (dt, *J* = 15.3, 6.3 Hz, 1H, H_{12}), 3.53 (t, *J* = 6.6 Hz, 2H, H_{15}), 3.11 (d, *J* = 11.5 Hz, 2H, H_{7a}), 2.45 (m, 3H, H_5 and H_8), 2.19 – 2.09 (m, 4H, H_{7b} and H_{13}), 2.03 (q, *J* = 7.1 Hz, 2H, H_{10}), 1.83 (m, 6H, H_6 and H_{14}), 1.64 (p, *J* = 7.6 Hz, 2H, H_9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1 (C_4), 131.6 (C_2), 131.2 (C_{11}), 129.0 (C_{12}), 128.8 (C_3), 120.0 (C_1), 58.5 (C_8), 54.2 (C_7), 44.6 (C_{15}), 42.1 (C_5), 33.1 (C_6), 32.4 (C_{14}), 30.6 (C_{10}), 29.7 (C_{13}), 26.5 (C_9). **IR** ν_{max}/cm^{-1} (film): 2931, 2850, 2765, 1490, 1443, 1376, 1306, 1270, 1129, 1075, 1009, 969, 822, 531. **HRMS** (ESI) calculated for $[C_{19}H_{27}NBrCl+H]^+$: 384.1088, found: 384.1075. $\mathbf{R}_F$ = 0.11 (10% MeOH/EtOAc).

(E)-3-(1-(8-Chlorooct-4-en-1-yl)piperidin-4-yl)-6-fluorobenzo[δ]isoxazole **280f**

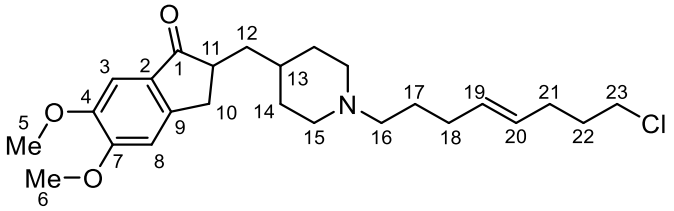


Prepared according to general procedure **D** using 6-fluoro-3-(1-propylpiperidin-4-yl)benzo[δ]isoxazole **275d** (0.16 g, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 2-10% MeOH/EtOAc, to yield the title compound **280f** as a brown oil (41 mg, 0.11 mmol, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.7, 5.1 Hz, 1H, H_5), 7.23 (dd, *J* = 8.5, 2.0 Hz, 1H, H_4), 7.05 (td, *J* = 8.8, 2.1 Hz, 1H, H_2), 5.49 (dt, *J* = 15.1, 6.4 Hz, 1H, H_{14}), 5.39 (dt, *J* = 15.1, 6.5 Hz, 1H, H_{15}), 3.53 (t, *J* = 6.7 Hz, 2H, H_{18}), 3.12 – 3.04 (m, 3H, H_8 and H_{10a}), 2.45 – 2.35 (m, 2H, H_{11}), 2.22 – 2.00 (m, 10H, H_9, H_{10b}, H_{13} and H_{16}), 1.83 (p, *J* = 6.9 Hz, 2H, H_{17}), 1.61 (p, *J* = 7.5 Hz, 2H, H_{12}). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.2 (d, $^{1}J_{C-F}$ = 250.6 Hz, C_3), 164.03 (d, $^{3}J_{C-F}$ = 13.7 Hz, C_1), 161.2 (C_7), 131.4 (C_{14}), 128.9 (C_{15}), 122.79 (d, $^{3}J_{C-F}$ = 11.0 Hz, C_5),

117.4 (C_6), 112.47 (d, $^2J_{C\text{-}F}$ = 25.4 Hz, C_2), 97.57 (d, $^2J_{C\text{-}F}$ = 26.9 Hz, C_4), 58.5 (C_{11}), 53.6 (C_{10}), 44.6 (C_{18}), 34.7 (C_8), 32.4 (C_{17}), 30.6 (C_9), 30.5 (C_{13}), 29.8 (C_{16}), 26.8 (C_{12}). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -110.6. **IR** ν_{max}/cm^{-1} (film): 2930, 2849, 2806, 2767, 1613, 1446, 1416, 1272, 1121, 969, 956, 838, 814, 732, 651. **HRMS** (ESI) calculated for $[C_{20}H_{26}N_2OFCl+H]^+$: 365.1791, found: 365.1795. **R_F** = 0.10 (10% MeOH/EtOAc).

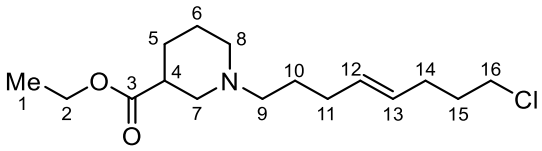
(E)-2-((1-(8-Chlorooct-4-en-1-yl)piperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one **280g**



Prepared according to general procedure **D** using 5,6-dimethoxy-2-((1-propylpiperidin-4-yl)methyl)-2,3-dihydro-1H-inden-1-one **275e** (0.20 g, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 13 cm, 2 cm Ø), eluting with 10-20% MeOH/EtOAc, to yield the title compound **280g** as a brown oil (44 mg, 0.10 mmol, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H, H_3), 6.85 (s, 1H, H_8), 5.46 (dt, *J* = 14.3, 6.5 Hz, 1H, H_{19}), 5.35 (dt, *J* = 15.2, 6.6 Hz, 1H, H_{20}), 3.95 (s, 3H, H_6), 3.89 (s, 3H, H_5), 3.51 (t, *J* = 6.7 Hz, 2H, H_{23}), 3.23 (dd, *J* = 17.6, 8.1 Hz, 1H, H_{10a}), 2.94 (dd, *J* = 9.8, 6.7 Hz, 2H, H_{15a}), 2.73 – 2.65 (m, 2H, H_{10b} and H_{11}), 2.30 (t, *J* = 7.8 Hz, 2H, H_{16}), 2.12 (q, *J* = 7.0 Hz, 2H, H_{21}), 1.99 (q, *J* = 6.6 Hz, 2H, H_{18}), 1.90 (m, 3H, H_{12a} and H_{15b}), 1.80 (p, *J* = 6.8 Hz, 2H, H_{22}), 1.79 – 1.64 (m, 2H, H_{14a}), 1.56 (p, *J* = 7.6 Hz, 2H, H_{17}), 1.51 – 1.44 (m, 1H, H_{13}), 1.41 – 1.21 (m, 3H, H_{12b} and H_{14b}). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.9 (C_1), 155.5 (C_7), 149.5 (C_4), 148.9 (C_2), 131.6 (C_{19}), 129.4 (C_9), 128.6 (C_{20}), 107.4 (C_8), 104.5 (C_3), 58.7 (C_{16}), 56.3 (C_6), 56.2 (C_5), 54.1 (C_{15a}), 54.0 (C_{15b}), 45.5 (C_{11}), 44.6 (C_{23}), 38.8 (C_{12}), 34.6 (C_{13}), 33.5 (C_{10}), 33.0 (C_{14a}), 32.4 (C_{22}), 31.9 (C_{14b}), 30.7 (C_{18}), 29.7 (C_{21}), 26.9 (C_{17}). **IR** ν_{max}/cm^{-1} (film): 2925, 1692, 1591, 1500, 1465, 1312, 1264, 1122, 1036, 729. **HRMS** (ESI) calculated for $[C_{25}H_{36}NO_3Cl+H]^+$: 434.2457, found: 434.2459. **R_F** = 0.17 (20% MeOH/EtOAc).

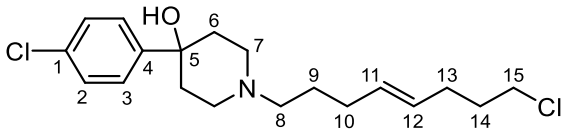
Ethyl (E)-1-(8-chlorooct-4-en-1-yl)piperidine-3-carboxylate **280h**



Prepared according to general procedure **D** using ethyl 1-propylpiperidine-3-carboxylate **275f** (60 mg, 0.30 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (35 μL, 0.15 mmol). The crude material was purified by flash chromatography (silica gel, 11 cm, 2 cm Ø), eluting with 5% MeOH/EtOAc, to yield the title compound **280h** as a brown oil (15 mg, 0.050 mmol, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dt, *J* = 14.7, 6.4 Hz, 1H, H_{12}), 5.37 (dt, *J* = 14.7, 6.5 Hz, 1H, H_{13}), 4.13 (q, *J* = 7.1 Hz, 2H, H_2), 3.52 (t, *J* = 6.6 Hz, 2H, H_{16}), 3.06 – 2.99 (m, 1H, H_{7a}), 2.81 (br. d, J = 11.2 Hz, 1H, H_{8a}), 2.59 (m, 1H, H_4), 2.40 – 2.33 (m, 2H, H_9), 2.13 (q, *J* = 6.7 Hz, 3H, H_{7b} and H_{14}), 1.98 (m, 4H, H_{5a}, H_{8b} and H_{11}), 1.82 (p, *J* = 6.9 Hz, 2H, H_{15}), 1.73 (dt, *J* = 13.0, 3.7 Hz, 1H, H_{6a}), 1.58 (m, 3H, H_{6b} and H_{10}), 1.43 (qd, *J* = 12.0, 4.4 Hz, 1H, H_{5b}), 1.25 (t, *J* = 7.1 Hz, 3H, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3 (C_3), 131.4 (C_{12}), 128.8 (C_{13}), 60.5 (C_2), 58.5 (C_9), 55.5 (C_7), 53.9 (C_8), 44.6 (C_4), 41.9 (C_{16}), 32.4 (C_{15}), 30.6 (C_{11}), 29.7 (C_{14}), 27.1 (C_5), 26.6 (C_{10}), 24.6 (C_6), 14.4 (C_1). **IR** ν_{max}/cm^{-1} (film): 2937, 2865, 1731, 1309, 1179, 1153, 1053, 1033. **HRMS** (ESI) calculated for $[C_{16}H_{28}NO_2Cl+H]^+$: 302.1881, found: 302.1880. $\mathbf{R}_F$ = 0.69 (10% MeOH/EtOAc).

(E)-1-(8-Chlorooct-4-en-1-yl)-4-(4-chlorophenyl)piperidin-4-ol **280i**

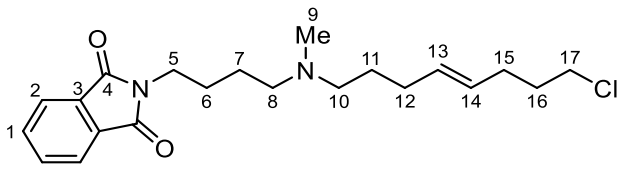


Prepared according to general procedure **D** using 4-(4-chlorophenyl)-1-propylpiperidin-4-ol **275g** (0.15 g, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 13 cm, 2 cm Ø), eluting with 2-10% MeOH/EtOAc, to yield the title compound **280i** as a brown oil (31 mg, 0.090 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H, H_3), 7.30 (d, *J* = 8.6 Hz, 2H, H_2), 5.47 (dt, *J* = 15.3, 6.4 Hz, 1H, H_{11}), 5.38 (dt, *J* = 15.3, 6.4 Hz, 1H, H_{12}), 3.52 (t, *J* = 6.6 Hz, 2H, H_{15}), 2.85 (d, *J* = 11.0 Hz, 2H, H_{7a}), 2.50 – 2.38 (m, 4H, H_{7b} and H_8), 2.21 – 2.09 (m, 4H, H_{6a} and H_{13}), 2.02 (q, *J* = 7.0 Hz, 2H, H_{10}), 1.82 (p, *J* = 6.8 Hz, 2H, H_{14}), 1.72 (d, *J* = 12.8 Hz, 2H, H_{6b}), 1.61 (p, *J* = 7.5 Hz, 2H, H_9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.9 (C_1), 132.9 (C_4), 131.3 (C_{11}), 128.9 (C_{12}), 128.5 (C_2), 126.3 (C_3), 71.1 (C_5), 58.3 (C_8), 49.5 (C_7), 44.5 (C_{15}), 38.4 (C_6), 32.4 (C_{14}), 30.6 (C_{10}), 29.7 (C_{13}), 26.7 (C_9). **IR**

ν_{max}/cm^{-1} (film): 2938, 2865, 2844, 1054, 1033, 1013. **HRMS** (ESI) calculated for $[C_{19}H_{27}NOCl_2+H]^+$: 356.1543, found: 356.1537. $\mathbf{R_F}$ = 0.41 (10% MeOH/EtOAc).

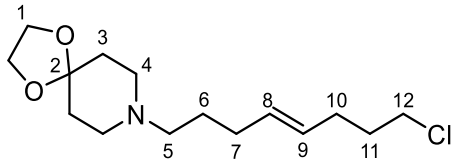
(E)-2-(4-((8-Chlorooct-4-en-1-yl)(methyl)amino)butyl)isoindoline-1,3-dione **280j**



Prepared according to general procedure **D** using 2-(4-(methyl(propyl)amino)butyl)isoindoline-1,3-dione **302** (0.16 g, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 17 cm, 2 cm Ø), eluting with 1-2% MeOH/EtOAc, to yield the title compound **280j** as a brown oil (32 mg, 0.080 mmol, 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H, H_1), 5.46 (dt, *J* = 15.2, 6.4 Hz, 1H, H_{13}), 5.36 (dt, *J* = 15.2, 6.5 Hz, 1H, H_{14}), 3.70 (t, *J* = 7.2 Hz, 2H, H_5), 3.52 (t, *J* = 6.7 Hz, 2H, H_{17}), 2.39 (t, *J* = 7.5 Hz, 2H, H_8), 2.33 (t, *J* = 7.7 Hz, 2H, H_{10}), 2.22 (s, 3H, H_9), 2.16 – 2.10 (m, 2H, H_{15}), 1.99 (q, *J* = 6.9 Hz, 2H, H_{12}), 1.82 (p, *J* = 6.7 Hz, 2H, H_{16}), 1.70 (p, *J* = 7.6 Hz, 2H, H_6), 1.52 (p, *J* = 7.5 Hz, 4H, H_7 and H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C_4), 134.0 (C_1), 132.3 (C_3), 131.6 (C_{13}), 128.7 (C_{14}), 123.3 (C_2), 57.4 (C_{10}), 57.2 (C_8), 44.6 (C_{17}), 42.2 (C_9), 38.0 (C_5), 32.4 (C_{16}), 30.5 (C_{12}), 29.8 (C_{15}), 27.1 (C_{11}), 26.7 (C_6), 24.6 (C_7). **IR** ν_{max}/cm^{-1} (film): 2935, 1710, 1438, 1396, 1368, 1043, 719. **HRMS** (ESI) calculated for $[C_{21}H_{30}N_2O_2Cl+H]^+$: 377.1996, found: 377.1984. $\mathbf{R_F}$ = 0.11 (10% MeOH/EtOAc).

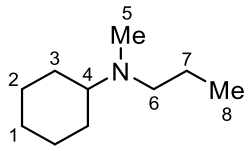
(E)-8-(8-Chlorooct-4-en-1-yl)-1,4-dioxa-8-azaspiro[4.5]decane **280k**



Prepared according to general procedure **D** using 8-propyl-1,4-dioxa-8-azaspiro[4.5]decane **275h** (0.11 g, 0.60 mmol) and *trans*-5-chloro-1-penten-1-ylboronic acid pinacol ester **279** (69 μL, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 17 cm, 2 cm Ø), eluting with 1-2% MeOH/EtOAc, to yield the title compound **280k** as a brown oil (22 mg, 0.080 mmol, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dt, *J* = 15.2, 6.5 Hz, 1H, H_8), 5.37 (dt, *J* = 15.2, 6.5 Hz, 1H, H_9), 3.95 (s, 4H, H_1), 3.52 (t, *J* = 6.6 Hz, 2H, H_{12}), 2.57 (br. s, 4H, H_4), 2.43 – 2.33 (m, 2H, H_5), 2.13 (q, *J* = 6.8 Hz, 2H, H_{10}), 2.00 (q, *J* = 7.1 Hz, 2H, H_7), 1.87 – 1.73 (m, 6H, H_3 and H_{11}), 1.57 (p, *J* = 7.6 Hz, 2H, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.4 (C_8), 128.8 (C_9), 107.2 (C_2), 64.4 (C_1), 57.7 (C_5), 51.4 (C_4), 44.6 (C_{12}), 34.7 (C_3), 32.4 (C_{11}), 30.6 (C_7), 29.7 (C_{10}), 26.9 (C_6). **IR** ν_{max}/cm^{-1} (film): 2931, 2813, 1365, 1310, 1142, 1093, 1040, 965, 946. **HRMS** (ESI) calculated for $[C_{15}H_{26}NO_2+H]^+$: 288.1730, found: 288.1720. $\mathbf{R}_F$ = 0.24 (10% MeOH/EtOAc).

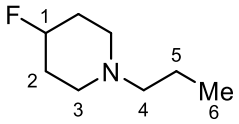
N-Methyl-N-propylcyclohexanamine **280l**



Cyclohexylamine (2.0 mL, 18 mmol), triethylamine (2.9 mL, 21 mmol) and CH_2Cl_2 (15 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (1.8 mL, 21 mmol) was added to the reaction mixture dropwise, which was stirred for 14 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 15 cm, 3.5 cm Ø), eluting with 20-100% EtOAc/petroleum ether, to give the intermediate *N*-cyclohexylpropionamide as an amorphous white solid. *N*-Cyclohexylpropionamide was dissolved in THF (150 mL), cooled to 0 °C and NaH (60%, 0.62 g, 16 mmol) added portion-wise. The reaction mixture was stirred for 20 min, then MeI (0.96 mL, 16 mmol) was added and the reaction stirred for 14 h, warming to rt. The reaction was quenched by addition of H_2O (100 mL) and extracted with CH_2Cl_2 (150 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 16 cm, 3 cm Ø), eluting with 0-30% EtOAc/petroleum ether, to give the intermediate *N*-cyclohexyl-*N*-methylpropionamide as a yellow oil. *N*-Cyclohexyl-*N*-methylpropionamide was dissolved in Et_2O (15 mL) at 0 °C and $LiAlH_4$ (2.4 M in THF, 5.8 mL, 14 mmol) added dropwise. The reaction was stirred for 5 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material was concentrated *in vacuo*. Purification by Kugelrohr distillation (50 mBar, 115 °C) gave the title compound *N*-methyl-*N*-propylcyclohexanamine **280l** (0.71 g, 4.6 mmol, 26%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 – 2.29 (m, 3H, H_4 and H_6), 2.24 (s, 3H, H_5), 1.83 – 1.71 (m, 4H, H_3), 1.66 – 1.55 (m, 1H, H_{1a}), 1.45 (h, J = 7.4 Hz, 2H, H_7), 1.30 – 1.00 (m, 5H, H_{1b} and H_2), 0.87 (t, J = 7.4 Hz, 3H, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 62.7 (C_4), 55.9 (C_6), 38.1 (C_5), 28.7 (C_2), 26.6 (C_1), 26.2 (C_3), 21.3 (C_7), 12.2 (C_8). **IR** ν_{max}/cm^{-1} (film): 2926, 2853, 2789, 1449, 1071, 1058, 1050, 976, 890. **HRMS** (ESI) calculated for $[C_{10}H_{21}N+H]^+$: 156.1747, found: 156.1743. $\mathbf{R_F}$ = 0.43 (10% MeOH/EtOAc). Data consistent with literature.[257]

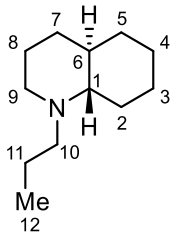
4-Fluoro-1-propylpiperidine **280m**



4-Fluoropiperidine (0.90 g, 8.7 mmol), triethylamine (1.5 mL, 11 mmol) and CH_2Cl_2 (50 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (0.92 mL, 11 mmol) was added to the reaction mixture dropwise, which was stirred for 1 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 24 g column), eluting with 0-40% EtOAc/heptane, to give the intermediate 1-(4-fluoropiperidin-1-yl)propan-1-one as a colourless oil. 1-(4-fluoropiperidin-1-yl)propan-1-one was dissolved in Et_2O (50 mL) at 0 °C and $LiAlH_4$ (1 M in THF, 12 mL, 12 mmol) added dropwise. The reaction was stirred for 1 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification by Hickman distillation gave the title compound 4-fluoro-1-propylpiperidine **280m** (0.43 g, 3.0 mmol, 34%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (dddd, J = 48.9, 10.6, 6.6, 3.9 Hz, 1H, H_1), 2.64 – 2.50 (m, 2H, H_{3a}), 2.39 – 2.32 (m, 2H, H_{3b}), 2.31 – 2.25 (m, 2H, H_4), 1.99 – 1.78 (m, 4H, H_2), 1.49 (h, J = 7.4 Hz, 2H, H_5), 0.89 (t, J = 7.4 Hz, 3H, H_6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 88.9 (d, $^1J_{C–F}$ = 170.5 Hz, C_1), 60.8 (d, $^5J_{C–F}$ = 1.3 Hz, C_4), 49.8 (d, $^3J_{C–F}$ = 6.1 Hz, C_3), 31.7 (d, $^2J_{C–F}$ = 19.4 Hz, C_2), 20.4 (C_5), 12.1 (C_6). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -181.1. **IR** ν_{max}/cm^{-1} (film): 2953, 2812, 1366, 1411, 1096, 1042, 1034, 994, 788. **HRMS** (ESI) calculated for $[C_8H_{16}NF+H]^+$: 146.1340, found: 146.1341. $\mathbf{R_F}$ = 0.47 (10% MeOH/EtOAc).

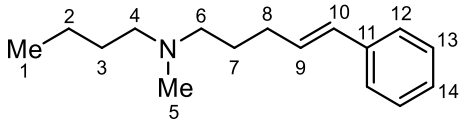
trans-1-Propyldecahydroquinoline **280n**



trans-Decahydroquinoline (0.50 g, 3.60 mmol), triethylamine (0.60 mL, 4.3 mmol) and CH_2Cl_2 (10 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (0.38 mL, 4.3 mmol) was added to the reaction mixture dropwise, which was stirred for 2 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (75 mL) and extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 5 g column), eluting with 10-100% EtOAc/petroleum ether, to give the intermediate 1-(*trans*-octahydroquinolin-1(2H)-yl)propan-1-one as a yellow oil. 1-(*trans*-Octahydroquinolin-1(2H)-yl)propan-1-one was dissolved in Et_2O (15 mL) at 0 °C and $LiAlH_4$ (0.14 g, 3.7 mmol) added portion-wise. The reaction was stirred for 20 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material was concentrated *in vacuo*. Purification of the crude material by Kugelrohr distillation (40 mBar, 145 °C) gave the title compound *trans*-1-propyldecahydroquinoline **280n** (0.37 g, 2.1 mmol, 60%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (dq, *J* = 11.1, 3.0 Hz, 1H, H_{9a}), 2.61 (ddd, *J* = 13.3, 9.4, 6.9 Hz, 1H, H_{10a}), 2.41 (ddd, *J* = 13.3, 9.3, 6.6 Hz, 1H, H_{10b}), 2.25 – 2.14 (m, 1H, H_{9b}), 2.05 (dt, *J* = 13.0, 3.0 Hz, 1H, H_{8a}), 1.83 – 1.68 (m, 2H, H_{7a} and H_1), 1.66 – 1.51 (m, 5H, H_2, H_6 and H_{7b}), 1.43 (h, *J* = 7.5 Hz, 2H, H_{11}), 1.29 – 1.14 (m, 3H, H_3 and H_4), 1.12 – 1.04 (m, 1H, H_{8b}), 1.04 – 0.90 (m, 2H, H_5), 0.83 (t, *J* = 7.5 Hz, 3H, H_{12}). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 65.8 (C_1), 55.2 (C_{10}), 53.6 (C_9), 42.1 (C_6), 33.2 (C_5), 32.7 (C_4), 30.2 (C_2), 26.0(4) (C_7), 26.0 (C_8), 25.9 (C_3), 17.4 (C_{11}), 12.1 (C_{12}). **IR** ν_{max}/cm^{-1} (film): 2920, 2853, 2786, 1447, 1265, 1239, 1171, 1113, 1083, 903, 816. **HRMS** (ESI) calculated for $[C_{12}H_{23}N+H]^+$: 182.1903, found: 182.1897. $\mathbf{R_F}$ = 0.61 (20% MeOH/EtOAc).

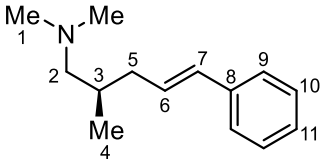
(E)-N-Butyl-N-methyl-5-phenylpent-4-en-1-amine **282a**



Prepared according to general procedure **D** using N-methyl-3-phenyl-N-propylpropan-1-amine **278** (0.10 mL 0.30 mmol) and *trans*-2-phenylvinylboronic acid pinacol ester **281** (22 mg, 0.15 mmol). The crude material was purified by flash chromatography (silica gel, 14 cm, 3 cm Ø), eluting with 2-15% MeOH/EtOAc, to yield the title compound **282a** as a brown oil (19 mg, 0.080 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H, H_{12} and H_{13}), 7.19 (tt, *J* = 7.1, 1.4 Hz, 1H, H_{14}), 6.39 (dt, *J* = 15.8, 1.4 Hz, 1H, H_{10}), 6.22 (dt, *J* = 15.8, 6.9 Hz, 1H, H_9), 2.41 – 2.31 (m, 4H, H_4 and H_6), 2.27 – 2.19 (m, 5H, H_5 and H_8), 1.66 (p, *J* = 7.5 Hz, 2H, H_7), 1.50 – 1.41 (m, 2H, H_3), 1.32 (h, *J* = 7.3 Hz, 2H, H_2), 0.92 (t, *J* = 7.3 Hz, 3H, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0 (C_{11}), 130.7 (C_9), 130.2 (C_{10}), 128.6 (C_{13}), 127.0 (C_{14}), 126.1 (C_{12}), 57.8 (C_4), 57.4 (C_6), 42.4 (C_5), 31.1 (C_8), 29.6 (C_3), 27.1 (C_7), 20.9 (C_2), 14.2 (C_1). **IR** ν_{max}/cm^{-1} (film): 2954, 2930, 2861, 2787, 1457, 963, 740, 692. **HRMS** (ESI) calculated for $[C_{16}H_{25}N+H]^+$: 232.2060, found: 232.2067. $\mathbf{R_F}$ = 0.17 (10% MeOH/EtOAc).

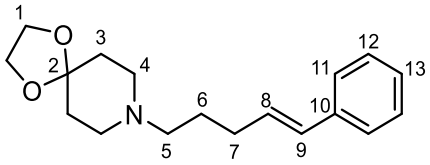
(E)-N,N,2-Trimethyl-5-phenylpent-4-en-1-amine **282b**



Prepared according to general procedure **D** using *N*,*N*,2-trimethylpropan-1-amine **299** (0.17 mL, 1.20 mmol) and *trans*-2-phenylvinylboronic acid pinacol ester **281** (0.14 g, 0.60 mmol). The crude material was purified by flash chromatography (silica gel, 9 cm, 4 cm Ø), eluting with 1-10% MeOH/EtOAc, to yield the title compound **282b** as a brown oil (55 mg, 0.27 mmol, 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H, H_9 and H_{10}), 7.23 – 7.17 (m, 1H, H_{11}), 6.40 (d, *J* = 15.7 Hz, 1H, H_7), 6.20 (dt, *J* = 15.7, 7.3 Hz, 1H, H_6), 2.38 – 2.25 (m, 8H, H_1, H_{2a} and H_{5a}), 2.24 – 2.15 (m, 1H, H_{2b}), 2.05 (dtd, *J* = 13.4, 7.4, 1.6 Hz, 1H, H_{5b}), 1.83 (h, *J* = 7.1 Hz, 1H, H_3), 0.98 (d, *J* = 6.6 Hz, 3H, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0 (C_8), 131.3 (C_7), 129.3 (C_6), 128.6 (C_{10}), 127.0 (C_{11}), 126.1 (C_9), 66.7 (C_2), 46.1 (C_1), 38.7 (C_5), 31.7 (C_3), 18.2 (C_4). **IR** ν_{max}/cm^{-1} (film): 2949, 2815, 2763, 1459, 1033, 964, 742, 692. **HRMS** (ESI) calculated for $[C_{14}H_{21}N+H]^+$: 204.1752, found: 204.1746. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –1.4° (*c* = 1.5, $CHCl_3$). $\mathbf{R_F}$ = 0.12 (10% MeOH/EtOAc).

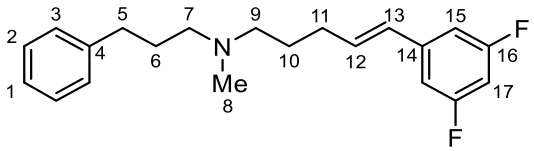
(E)-8-(5-Phenylpent-4-en-1-yl)-1,4-dioxa-8-azaspiro[4.5]decane **282c**



Prepared according to general procedure **D** using 8-propyl-1,4-dioxa-8-azaspiro[4.5]decane **275h** (0.11 g, 0.60 mmol) and *trans*-2-phenylvinylboronic acid pinacol ester **281** (69 mg, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 15 cm, 2 cm Ø), eluting with 1% MeOH/EtOAc, to yield the title compound **282c** as a brown oil (36 mg, 0.13 mmol, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 4H, H_{11} and H_{12}), 7.19 (tt, *J* = 7.2, 1.3 Hz, 1H, H_{13}), 6.39 (d, *J* = 15.8 Hz, 1H, H_9), 6.21 (dt, *J* = 15.8, 6.8 Hz, 1H, H_8), 3.95 (s, 4H, H_1), 2.54 (br. s, 4H, H_4), 2.44 – 2.38 (m, 2H, H_5), 2.26 – 2.20 (m, 2H, H_7), 1.76 (t, *J* = 5.7 Hz, 4H, H_3), 1.68 (p, *J* = 7.9 Hz, 2H, H_6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.9 (C_{10}), 130.5 (C_8), 130.2 (C_9), 128.6 (C_{12}), 127.0 (C_{13}), 126.1 (C_{11}), 107.4 (C_2), 64.4 (C_1), 57.9 (C_5), 51.5 (C_4), 35.0 (C_3), 31.1 (C_7), 27.0 (C_6). **IR** ν_{max}/cm^{-1} (film): 2928, 2880, 1364, 1310, 1142, 1092, 1040, 964, 946, 914, 744, 693. **HRMS** (ESI) calculated for $[C_{18}H_{25}NO_2+H]^+$: 288.1964, found: 288.1952. $\mathbf{R_F}$ = 0.23 (10% MeOH/EtOAc).

(E)-5-(3,5-Difluorophenyl)-N-methyl-N-(3-phenylpropyl)pent-4-en-1-amine **284**

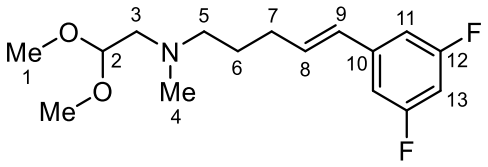


Prepared according to general procedure **D** using *N*-methyl-3-phenyl-*N*-propylpropan-1-amine **275i** (0.12 g, 0.60 mmol) and *trans*-2-(3,5-difluorophenyl)vinyl boronic acid pinacol ester **283** (68 mg, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 10 cm, 3 cm Ø), eluting with 5-20% MeOH/EtOAc, to yield the title compound **284** as a brown oil (47 mg, 0.14 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H, H_3), 7.21 – 7.15 (m, 3H, H_1 and H_2), 6.86 – 6.78 (m, 2H, H_{15}), 6.63 (tt, *J* = 8.9, 2.3 Hz, 1H, H_{17}), 6.34 – 6.20 (m, 2H, H_{12} and H_{13}), 2.64 (t, *J* = 7.8 Hz, 2H, H_5), 2.44 – 2.34 (m, 4H, H_7 and H_9), 2.27 – 2.18 (m, 5H, H_8 and H_{11}), 1.81 (p, *J* = 7.6 Hz, 2H, H_6), 1.64 (p, *J* = 7.5 Hz, 2H, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{C\text{-}F}$ = 247.1 Hz, C_{16a}), 163.3 (d, $^1J_{C\text{-}F}$ = 247.1 Hz, C_{16b}), 142.4 (C_4), 141.4 (t, $^3J_{C\text{-}F}$ = 9.6 Hz, C_{14}), 133.6 (C_{12}), 128.5 (C_2), 128.5 (C_{13}), 128.5 (C_3), 125.9 (C_1), 108.7 (d, $^2J_{C\text{-}F}$ = 18.4 Hz,

C_{15a}), 108.6 (d, $^2J_{C\text{-}F}$ = 18.6 Hz, C_{15b}), 102.1 (t, $^2J_{C\text{-}F}$ = 25.6 Hz, C_{17}), 57.4 (C_7), 57.2 (C_9), 42.3 (C_8), 33.8 (C_5), 30.9 (C_{11}), 29.1 (C_6), 26.8 (C_{10}). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -111.7. **IR** ν_{max}/cm^{-1} (film): 2941, 1619, 1588, 1453, 1317, 1116, 991, 964, 835, 747, 699. **HRMS** (ESI) calculated for $[C_{21}H_{25}NF_2+H]^+$: 330.2028, found: 330.2042. **R_F** = 0.18 (10% MeOH/EtOAc).

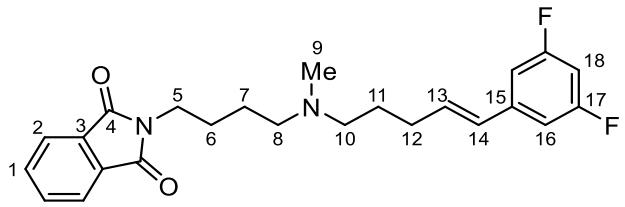
(E)-5-(3,5-Difluorophenyl)-N-(2,2-dimethoxyethyl)-N-methylpent-4-en-1-amine **285**



Prepared according to general procedure **D** using *N*-(2,2-dimethoxyethyl)-*N*-methylpropan-1-amine **275a** (97 mg, 0.60 mmol) and *trans*-2-(3,5-difluorophenyl)vinyl boronic acid pinacol ester **283** (68 mg, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 13 cm, 2 cm Ø), eluting with 1% MeOH/EtOAc, to yield the title compound **285** as a brown oil (42 mg, 0.14 mmol, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.78 (m, 2H, H_{11}), 6.63 (tt, *J* = 9.0, 2.4 Hz, 1H, H_{13}), 6.35 – 6.19 (m, 2H, H_8 and H_9), 4.48 (t, *J* = 5.3 Hz, 1H, H_2), 3.36 (s, 6H, H_1), 2.52 (d, *J* = 5.3 Hz, 2H, H_3), 2.47 – 2.40 (m, 2H, H_5), 2.30 (s, 3H, H_4), 2.23 (q, *J* = 7.0 Hz, 2H, H_7), 1.65 (p, *J* = 7.5 Hz, 2H, H_6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{C\text{-}F}$ = 247.2 Hz, C_{12a}), 163.3 (d, $^1J_{C\text{-}F}$ = 247.1 Hz, C_{12b}), , 141.4 (t, $^3J_{C\text{-}F}$ = 9.4 Hz, C_{10}), 133.6 (C_8), 128.5 (C_9), 108.69 (d, $^2J_{C\text{-}F}$ = 18.6 Hz, C_{11a}), 108.63 (d, $^2J_{C\text{-}F}$ = 18.6 Hz, C_{11b}), 103.0 (C_2), 102.1 (t, $^2J_{C\text{-}F}$ = 25.7 Hz, C_{13}), 59.1 (C_3), 58.1 (C_5), 53.5 (C_1), 43.4 (C_4), 30.8 (C_7), 26.8 (C_6). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -111.7. **IR** ν_{max}/cm^{-1} (film): 2938, 2830, 1618, 1587, 1444, 1317, 1116, 1061, 1033, 991, 963, 855, 833, 671, 509. **HRMS** (ESI) calculated for $[C_{16}H_{23}NO_2F_2+H]^+$: 300.1770, found: 300.1785. **R_F** = 0.32 (10% MeOH/EtOAc).

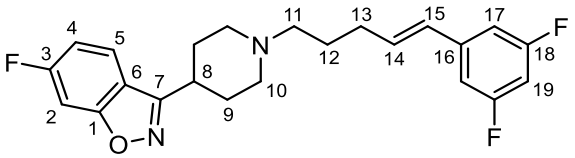
(E)-2-(4-((5-(3,5-Difluorophenyl)pent-4-en-1-yl)(methyl)amino)butyl)isoindoline-1,3-dione **286**



Prepared according to general procedure **D** using 2-(4-(methyl(propyl)amino)butyl)isoindoline-1,3-dione **302** (0.16 g, 0.60 mmol) and *trans*-2-(3,5-difluorophenyl)vinyl boronic acid pinacol ester **283** (68 mg, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 17 cm, 2 cm Ø), eluting with 5-10% MeOH/EtOAc, to yield the title compound **286** as a brown oil (55 mg, 0.14 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H, H_2), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H, H_1), 6.82 (dd, *J* = 7.3, 1.9 Hz, 2H, H_{16}), 6.61 (tt, *J* = 9.0, 2.1 Hz, 1H, H_{18}), 6.33 – 6.19 (m, 2H, H_{13} and H_{14}), 3.70 (t, *J* = 7.2 Hz, 2H, H_5), 2.37 (app. q, *J* = 7.2 Hz, 4H, H_8 and H_{10}), 2.21 (m, 5H, H_9 and H_{12}), 1.70 (p, *J* = 7.6 Hz, 2H, H_6), 1.62 (p, *J* = 7.4 Hz, 2H, H_{11}), 1.51 (p, *J* = 7.6 Hz, 2H, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5 (C_4), 163.4 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz, C_{17a}), 163.2 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz, C_{17b}), 141.4 (t, $^{3}J_{C\text{-}F}$ = 9.5 Hz, C_{15}), 134.0 (C_1), 133.6 (C_{13}), 132.3 (C_3), 128.4 (t, $^{4}J_{C\text{-}F}$ = 2.8 Hz, C_{14}), 123.3 (C_2), 108.7 (d, $^{2}J_{C\text{-}F}$ = 18.5 Hz, C_{16a}), 108.6 (d, $^{2}J_{C\text{-}F}$ = 18.5 Hz, C_{16b}), 102.1 (t, $^{2}J_{C\text{-}F}$ = 25.7 Hz, C_{18}), 57.3 (C_{10}), 57.2 (C_8), 42.2 (C_9), 38.0 (C_5), 30.8 (C_{12}), 26.8 (C_{11}), 26.7 (C_6), 24.6 (C_7). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -111.7. **IR** ν_{max}/cm^{-1} (film): 2940, 1709, 1619, 1588, 1396, 1369, 1116, 716. **HRMS** (ESI) calculated for $[C_{24}H_{26}N_2O_2F_2+H]^+$: 413.2035, found: 413.2032. $\mathbf{R_F}$ = 0.19 (10% MeOH/EtOAc).

(E)-3-(1-(5-(3,5-Difluorophenyl)pent-4-en-1-yl)piperidin-4-yl)-6-fluorobenzo[δ]isoxazole **287**

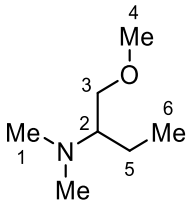


Prepared according to general procedure **D** using 6-fluoro-3-(1-propylpiperidin-4-yl)benzo[δ]isoxazole **275d** (0.16 g, 0.60 mmol) and *trans*-2-(3,5-difluorophenyl)vinyl boronic acid pinacol ester **283** (68 mg, 0.30 mmol). The crude material was purified by flash chromatography (silica gel, 18 cm, 2 cm Ø), eluting with 1-2% MeOH/EtOAc, to yield the title compound **287** as a brown oil (42 mg, 0.10 mmol, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.8, 5.1 Hz, 1H, H_5), 7.24 (dd, *J* = 8.6, 2.1 Hz, 1H, H_2), 7.05 (td, *J* = 8.9, 2.1 Hz, 1H, H_4), 6.89 – 6.78 (m, 2H, H_{17}), 6.64 (td, *J* = 8.9, 2.2 Hz, 1H,

H_{19}), 6.37 – 6.22 (m, 2H, H_{14} and H_{15}), 3.08 (m, 3H, H_8 and H_{10a}), 2.44 (t, J = 7.3 Hz, 2H, H_{11}), 2.27 (q, J = 7.0 Hz, 2H, H_{13}), 2.21 – 2.02 (m, 6H, H_9 and H_{10b}), 1.72 (p, J = 7.6 Hz, 2H, H_{12}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{C\text{-}F}$ = 250.5 Hz, C_3), 164.0 (d, $^3J_{C\text{-}F}$ = 13.6 Hz, C_1), 163.3 (dd, $^1J_{C\text{-}F}$ = 247.2, $^3J_{C\text{-}F}$ = 13.2 Hz, C_{18}), 161.2 (C_7), 141.3 (t, $^3J_{C\text{-}F}$ = 9.5 Hz, C_{16}), 133.5 (C_{14}), 128.6 (t, $^3J_{C\text{-}F}$ = 2.8 Hz, C_{15}), 122.7 (d, $^3J_{C\text{-}F}$ = 11.1 Hz, C_5), 117.4 (d, $^4J_{C\text{-}F}$ = 1.3 Hz, C_6), 112.5 (d, $^2J_{C\text{-}F}$ = 25.3 Hz, C_4), 108.8 (d, $^2J_{C\text{-}F}$ = 5.8 Hz, C_{17a}), 108.6 (d, $^2J_{C\text{-}F}$ = 5.7 Hz, C_{17b}), 102.2 (t, $^2J_{C\text{-}F}$ = 25.7 Hz, C_{19}), 97.6 (d, $^2J_{C\text{-}F}$ = 26.6 Hz, C_2), 58.4 (C_{11}), 53.7 (C_{10}), 34.8 (C_8), 31.0 (C_{13}), 30.9 (C_9), 26.6 (C_{12}). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -110.7, -111.6. **IR** ν_{max}/cm^{-1} (film): 2943, 1618, 1589, 1495, 1447, 1417, 1273, 1117, 992, 957, 839. **HRMS** (ESI) calculated for $[C_{23}H_{23}N_2OF_3+H]^+$: 401.1835, found: 401.1830. **R_F** = 0.46 (10% MeOH/EtOAc).

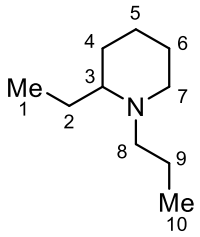
1-Methoxy-N,N-dimethylbutan-2-amine **288**



1-Methoxybutan-2-amine (5.8 mL, 0.050 mol) was dissolved in formic acid (25 mL) and formaldehyde (37%, 23 mL, 0.30 mol) added. The reaction mixture was refluxed at 100 °C for 16 h, then cooled to 0 °C and 10% aq. NaOH added until the mixture was basic. The resultant top layer was decanted and purified by Kugelrohr distillation (150 mBar, 85 °C) to give 1-methoxy-*N*,*N*-dimethylbutan-2-amine **288** as a colourless liquid (0.90 g, 4.5 mmol, 9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (dd, J = 10.0, 6.6 Hz, 1H, H_{3a}), 3.33 (s, 4H, H_{3b} and H_4), 2.45 (tt, J = 6.3, 4.7 Hz, 1H, H_2), 2.30 (s, 6H, H_1), 1.52 (dtd, J = 20.8, 7.5, 5.2 Hz, 1H, H_{5a}), 1.32 (dp, J = 13.8, 7.5 Hz, 1H, H_{5b}), 0.92 (t, J = 7.4 Hz, 3H, H_6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 72.4 (C_3), 65.3 (C_2), 59.0 (C_4), 41.4 (C_1), 20.1 (C_5), 11.8 (C_6). **IR** ν_{max}/cm^{-1} (film): 3394 (br), 2884, 2691, 1660, 1466, 1201, 1094. **HRMS** (ESI) calculated for $[C_7H_{17}NO+H]^+$: 132.1383, found: 132.1383. **R_F** = 0.15 (10% MeOH/EtOAc). Data consistent with literature.[225]

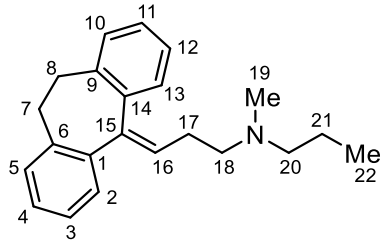
2-Ethyl-1-propylpiperidine **290**



2-Ethylpiperidine (1.2 mL, 9.2 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Propanal (1.0 mL, 14 mmol) and $NaBH(OAc)_3$ (2.9 g, 14 mmol) were added to the reaction mixture and stirred for 18 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by Kugelrohr distillation (30 mBar, 80 °C) to give 2-ethyl-1-propylpiperidine **290** (90 mg, 0.70 mmol, 6%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (dtd, *J* = 11.6, 4.1, 1.2 Hz, 1H, H_{7a}), 2.58 (ddd, *J* = 12.9, 9.4, 6.7 Hz, 1H, H_{8a}), 2.32 (ddd, *J* = 12.9, 9.4, 6.4 Hz, 1H, H_{8b}), 2.20 (ddd, *J* = 11.6, 10.0, 3.7 Hz, 1H, H_{7b}), 2.13 (tt, *J* = 8.9, 3.1 Hz, 1H, H_3), 1.73 – 1.17 (m, 10H, H_2, H_4, H_5, H_6 and H_9), 0.86 (td, *J* = 7.4, 3.1 Hz, 6H, H_1 and H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 61.5 (C_3), 55.7 (C_8), 52.4 (C_7), 30.0 (C_5), 25.9 (C_6), 24.2 (C_4), 24.0 (C_2), 18.8 (C_9), 12.3 (C_{12}), 10.2 (C_1). **IR** ν_{max}/cm^{-1} (film): 2965, 2939, 2877, 1647, 1460, 1382, 1051, 1033, 964. **HRMS** (ESI) calculated for $[C_{10}H_{21}N+H]^+$: 156.1747, found: 156.1742. $\mathbf{R_F}$ = 0.16 (10% MeOH/EtOAc).

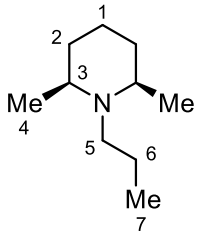
3-(10,11-Dihydro-5H-dibenzo[α,δ][7]annulen-5-ylidene)-N-methyl-N-propylpropan-1-amine **291**



3-(10,11-Dihydro-5H-dibenzo[α,δ][7]annulen-5-ylidene)-*N*-methylpropan-1-amine (0.99 g, 3.8 mmol), triethylamine (0.63 mL, 4.5 mmol) and CH_2Cl_2 (10 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (0.40 mL, 4.50 mmol) was added to the reaction mixture dropwise, which was stirred for 24 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 10 g column), eluting with 10-50% EtOAc/petroleum ether, to give the intermediate N-(3-(10,11-dihydro-5H-dibenzo[α,δ][7]annulen-5-ylidene)propyl)-N-methylpropionamide as a colourless oil. *N*-(3-(10,11-Dihydro-5H-dibenzo[α,δ][7]annulen-5-ylidene)propyl)-*N*-methylpropionamide was dissolved in Et_2O (10 mL) at 0 °C and $LiAlH_4$ (0.15 g, 3.9 mmol) added portion-wise. The reaction was stirred for 19 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification of the crude material by Kugelrohr distillation (25 mBar, 220 °C) gave the title compound **291** (0.74 g, 2.4 mmol, 65%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H, H_2), 7.23 – 7.09 (m, 6H, H_3, H_4, $H_{5/10}$, H_{11}, H_{12}, H_{13}), 7.06 – 7.00 (m, 1H, $H_{5/10}$), 5.86 (t, *J* = 7.3 Hz, 1H, H_{16}), 3.41 (br. s, 1H, $H_{7a/8a}$), 3.30 (br. s, 1H, $H_{7a/8a}$), 2.97 (br. s, 1H, $H_{7b/8b}$), 2.77 (br. s, 1H, $H_{7b/8b}$), 2.44 (t, *J* = 7.6 Hz, 2H, H_{18}), 2.28 (t, *J* = 7.4 Hz, 2H, H_{17}), 2.23 (t, *J* = 7.7 Hz, 2H, H_{20}), 2.15 (s, 3H, H_{19}), 1.43 (h, *J* = 7.4 Hz, 2H, H_{21}), 0.85 (t, *J* = 7.4 Hz, 3H, H_{22}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5 (C_{15}), 141.5 ($C_{1/14}$), 140.3 ($C_{1/14}$), 139.5 ($C_{6/9}$), 137.2 ($C_{6/9}$), 130.1 ($C_{5/10}$), 129.7 (C_{16}), 128.7 (C_2), 128.4, 128.1, 127.5, 127.1, 126.1, 125.9, 59.7 (C_{20}), 57.5 (C_{18}), 42.3 (C_{19}), 33.9 ($C_{7/8}$), 32.2 ($C_{7/8}$), 27.5 (C_{17}), 20.6 (C_{21}), 12.1 (C_{22}). **IR** ν_{max}/cm^{-1} (film): 2957, 2931, 2786, 1485, 1442, 1053, 767, 752, 741, 718, 599, 405. **HRMS** (ESI) calculated for $[C_{22}H_{27}N+H]^+$: 306.2216, found: 306.2208. $\mathbf{R_F}$ = 0.24 (10% MeOH/EtOAc).

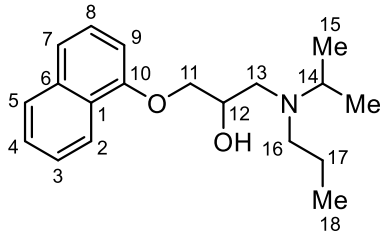
(2S,6R)-2,6-Dimethyl-1-propylpiperidine **292**



(2*S*,6*R*)-2,6-Dimethylpiperidine (1.34 mL, 10.0 mmol), triethylamine (1.7 mL, 12 mmol) and CH_2Cl_2 (10 mL) were added to an oven-dried reaction flask and cooled to 0 °C. Propionyl chloride (1.1 mL, 12.0 mmol) was added to the reaction mixture dropwise, which was stirred for 3 h while warming to rt. The reaction was quenched by addition of sat. aq. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 10 g column), eluting with 10-30% EtOAc/petroleum ether, to give the intermediate 1-((2*S*,6*R*)-2,6-dimethylpiperidin-1-yl)propan-1-one as a colourless oil. 1-((2*S*,6*R*)-2,6-dimethylpiperidin-1-yl)propan-1-one was dissolved in Et_2O (15 mL) at 0 °C and $LiAlH_4$ (0.42 g, 11 mmol) added portion-wise. The reaction was stirred for 20 h while warming to rt and subsequently quenched by the Fieser workup.[255] The solids were removed by filtration and the crude material concentrated *in vacuo*. Purification of the crude material by Kugelrohr distillation (50 mBar, 105 °C) gave the title compound (2*S*,6*R*)-2,6-dimethyl-1-propylpiperidine **292** (0.66 g, 4.3 mmol, 43%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 – 2.65 (m, 2H, H_5), 2.47 – 2.38 (m, 2H, H_3), 1.68 – 1.61 (m, 1H, H_{1a}), 1.59 – 1.51 (m, 2H, H_{2a}), 1.47 – 1.33 (m, 2H, H_6), 1.34 – 1.18 (m, 3H, H_{1b} and H_{2b}), 1.10 (d, J = 6.3 Hz, 6H, H_4), 0.80 (t, J = 7.4 Hz, 3H, H_7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.5 (C_3), 50.1 (C_5), 35.3 (C_2), 25.0 (C_1), 21.3 (C_4), 15.7 (C_6), 11.9 (C_7). **IR** ν_{max}/cm^{-1} (film): 2957, 2925, 2871, 1463, 1443, 1371, 1312, 1207, 1155, 1089, 1062, 1032, 1015, 944, 734. **HRMS** (ESI) calculated for $[C_{10}H_{21}N+H]^+$: 156.1747, found: 156.1747. $\mathbf{R_F}$ = 0.66 (20% MeOH/EtOAc).

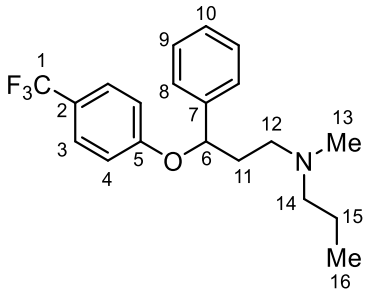
1-(Isopropyl(propyl)amino)-3-(naphthalen-1-yloxy)propan-2-ol **293**



Propanolol·HCl (0.27 g, 0.91 mmol) was dissolved in CH_2Cl_2 (40 mL) and triethylamine (0.13 mL, 0.91 mmol) was added to the reaction at 0 °C. After stirring for 10 min at 0 °C, propanal (0.10 mL, 1.4 mmol) and $NaBH(OAc)_3$ (0.29 g, 1.4 mmol) were added to the reaction mixture and stirred for 21 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 1-2% 1:9 NH_3/MeOH in CH_2Cl_2, to give 1-(isopropyl(propyl)amino)-3-(naphthalen-1-yloxy)propan-2-ol **293** (0.15 g, 0.50 mmol, 53%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.23 (m, 1H, H_2), 7.84 – 7.75 (m, 1H, H_5), 7.53 – 7.40 (m, 3H, H_3, H_4 and H_7), 7.37 (t, *J* = 7.9 Hz, 1H, H_8), 6.84 (dd, *J* = 7.5, 1.0 Hz, 1H, H_9), 4.28 – 4.18 (m, 1H, H_{12}), 4.17 – 4.06 (m, 2H, H_{11}), 3.06 (hept, *J* = 6.3 Hz, 1H, H_{14}), 2.68 (qd, *J* = 12.9, 6.6 Hz, 2H, H_{13}), 2.49 (t, *J* = 7.4 Hz, 2H, H_{16}), 1.53 (ddt, *J* = 15.9, 13.4, 6.7 Hz, 2H, H_{17}), 1.11 (d, *J* = 6.6 Hz, 3H, H_{15a}), 1.01 (d, *J* = 6.6 Hz, 3H, H_{15b}), 0.93 (t, *J* = 7.3 Hz, 3H, H_{18}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.6 (C_{10}), 134.6 (C_1), 127.6 (C_5), 126.5 (C_4/C_7), 126.0 (C_8), 125.8 (C_6), 125.3 (C_4/C_7), 122.1 (C_2), 120.6 (C_3), 104.9 (C_9), 70.8 (C_{12}), 65.9 (C_{11}), 53.0 (C_{13}), 52.7 (C_{16}), 50.9 (C_{14}), 22.3 (C_{17}), 20.3 (C_{15a}), 16.3 (C_{15b}), 11.9 (C_{18}). **IR** ν_{max}/cm^{-1} (film): 2962, 2871, 1580, 1401, 1268, 1100, 790, 736, 571, 419. **HRMS** (ESI) calculated for $[C_{19}H_{27}NO_2+H]^+$: 302.2115, found: 302.2118. $\mathbf{R_F}$ = 0.28 (10% 1:9 NH_3/MeOH in CH_2Cl_2).

N-Methyl-3-phenyl-N-propyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **294**

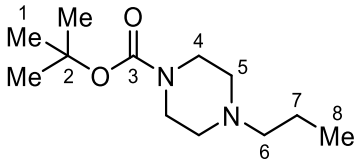


Fluoxetine·HCl (0.19 g, 0.55 mmol) was dissolved in CH_2Cl_2 (25 mL) and triethylamine (0.080 mL, 0.55 mmol) was added to the reaction at 0 °C. After stirring for 10 min at 0 °C, propanal (0.060 mL,

0.82 mmol) and $NaBH(OAc)_3$ (0.17 g, 0.84 mmol) were added to the reaction mixture and stirred for 22 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 10 cm, 2 cm Ø), eluting with 1-2% 1:9 NH_3/MeOH in CH_2Cl_2, to give *N*-methyl-3-phenyl-*N*-propyl-3-(4-(trifluoromethyl)phenoxy)propan-1-amine **294** (0.17 g, 0.48 mmol, 89%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H, H_3), 7.38 – 7.29 (m, 4H, H_8 and H_9), 7.32 – 7.21 (m, 1H, H_{10}), 6.91 (d, *J* = 8.5 Hz, 2H, H_4), 5.30 (dd, *J* = 8.3, 4.8 Hz, 1H, H_6), 2.60 – 2.48 (m, 1H, H_{12a}), 2.45 (ddd, *J* = 12.7, 8.0, 5.4 Hz, 1H, H_{12b}), 2.29 (t, *J* = 7.3 Hz, 2H, H_{14}), 2.22 (s, 3H, H_{13}), 2.21 – 2.13 (m, 1H, H_{11a}), 1.98 (dddd, *J* = 14.2, 8.2, 6.8, 4.8 Hz, 1H, H_{11b}), 1.45 (h, *J* = 7.3 Hz, 2H, H_{15}), 0.86 (t, *J* = 7.3 Hz, 3H, H_{16}). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9 (C_5), 141.4 (C_7), 128.9 (C_9), 127.9 (C_{10}), 126.8 (q, $^3J_{C\text{-}F}$ = 3.9 Hz, C_3), 126.0 (C_8), 123.0 (C_1), 122.6 (C_2), 115.9 (C_4), 78.7 (C_6), 60.0 (C_{14}), 53.9 (C_{12}), 42.3 (C_{13}), 36.7 (C_{11}), 20.6 (C_{15}), 12.0 (C_{16}). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ -61.5. **IR** ν_{max}/cm^{-1} (film): 2958, 1614, 1517, 1323, 1249, 1159, 1108, 1067, 1009, 833, 699. **HRMS** (ESI) calculated for $[C_{20}H_{24}NOF_3+H]^+$: 352.1883, found: 352.1887. $\mathbf{R_F}$ = 0.21 (10% 1:9 NH_3/MeOH in CH_2Cl_2). Data consistent with literature.[225]

tert-Butyl 4-propylpiperazine-1-carboxylate **295**

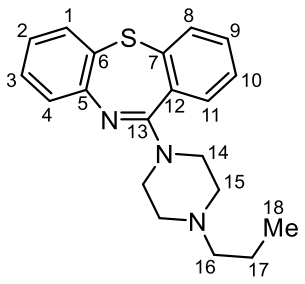


tert-Butyl piperazine-1-carboxylate·2HBr (0.73 g, 2.5 mmol) was suspended in THF (20 mL), K_2CO_3 (0.69 g, 5.0 mmol) and di-*tert*-butyl dicarbonate (0.65 g, 3.0 mmol) were added to the reaction mixture and refluxed for 4 h. The reaction was cooled to rt and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 13 cm, 2 cm Ø), eluting with 10% MeOH/EtOAc, to give *tert*-butyl 4-propylpiperazine-1-carboxylate **295** (0.57 g, 2.5 mmol, quant.) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (t, *J* = 5.1 Hz, 4H, H_4), 2.36 (t, *J* = 5.1 Hz, 4H, H_5), 2.33 – 2.25 (m, 2H, H_6), 1.57 – 1.41 (m, 11H, H_1 and H_7), 0.89 (t, *J* = 7.4 Hz, 3H, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.9 (C_3), 79.7 (C_2), 60.8 (C_6), 53.2 (C_5), 43.8 (C_4), 28.6 (C_1), 20.1 (C_7), 12.1 (C_8). **IR** ν_{max}/cm^{-1} (film): 2966, 2936, 1696, 1418, 1365, 1243, 1169, 1135, 1055, 1033, 1004. **HRMS** (ESI) calculated for

$[C_{12}H_{24}N_2O_2+H]^+$: 229.1911, found: 229.1911. $\mathbf{R_F}$ = 0.46 (10% MeOH/EtOAc). Data consistent with literature.[225]

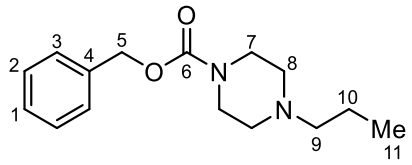
11-(4-Propylpiperazin-1-yl)dibenzo[β,ϕ][1,4]thiazepine **297**



11-(Piperazin-1-yl)dibenzo[β,ϕ][1,4]thiazepine·2HCl (0.67 g, 1.8 mmol), triethylamine (0.51 mL, 3.64 mmol), propanal (0.20 mL, 2.73 mmol) and CH_2Cl_2 (15 mL) were added to a reaction vessel and stirred at 0 ºC for 15 min. Then $NaBH(OAc)_3$ (0.58 g, 2.7 mmol) was added to the reaction mixture at 0 ºC and the mixture stirred for 24 h while warming to rt. The reaction was quenched with sat. aq. K_2CO_3 (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, 12 cm, 2 cm Ø), eluting with 1-2% 1:9 NH_3/MeOH in CH_2Cl_2, to give 11-(4-propylpiperazin-1-yl)dibenzo[β,ϕ][1,4]thiazepine **297** (0.55g, 1.6 mmol, 89%) as a light yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.8, 1.7 Hz, 1H, H_8), 7.39 (dd, *J* = 7.7, 1.5 Hz, 1H, H_1), 7.36 – 7.27 (m, 3H, H_9, H_{10} and H_{11}), 7.17 (td, *J* = 7.6, 1.5 Hz, 1H, H_3), 7.07 (dd, *J* = 8.0, 1.5 Hz, 1H, H_4), 6.88 (td, *J* = 7.5, 1.5 Hz, 1H, H_2), 3.56 (br. s, 4H, H_{14}), 2.57 (br. s, 2H, H_{15a}), 2.53 – 2.43 (m, 2H, H_{15b}), 2.36 (t, *J* = 7.4 Hz, 2H, H_{16}), 1.54 (h, *J* = 7.4 Hz, 2H, H_{17}), 0.92 (t, *J* = 7.4 Hz, 3H, H_{18}). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9 (C_{13}), 149.1 (C_6), 140.1 (C_{12}), 134.3 (C_7), 132.3 (C_1), 132.2(8) (C_8), 130.9 ($C_{9/10/11}$), 129.2 (C_3), 129.1(6) ($C_{9/10/11}$), 128.4 ($C_{9/10/11}$), 128.1 (C_5), 125.5 (C_4), 122.9 (C_2), 60.8 (C_{16}), 53.2 (C_{14} and C_{15}), 20.1 (C_{17}), 12.1 (C_{18}). **IR** ν_{max}/cm^{-1} (film): 2957, 2808, 1598, 1575, 1455, 1404, 1304, 1244, 761, 742. **HRMS** (ESI) calculated for $[C_{20}H_{23}N_3S+H]^+$: 338.1686, found: 338.1692. $\mathbf{R_F}$ = 0.46 (10% MeOH/EtOAc).

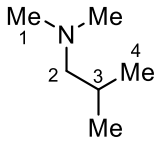
Benzyl 4-propylpiperazine-1-carboxylate **298**



Benzyl piperazine-1-carboxylate (0.73 g, 2.5 mmol) was dissolved in THF (20 mL), K_2CO_3 (0.69 g, 5.00 mmol) and CbzCl (0.39 mL, 2.8 mmol) were added to the reaction mixture and stirred for 14 h at rt. The reaction was concentrated *in vacuo*, H_2O (50 mL) added and extracted from with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 12 g column), eluting with 50-100% EtOAc/petroleum ether, to give benzyl 4-propylpiperazine-1-carboxylate **298** (0.44 g, 1.7 mmol, 66%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H, H_1, H_2 and H_3), 5.13 (s, 2H, H_5), 3.52 (app. t, *J* = 5.1 Hz, 4H, H_7), 2.39 (br. s, 4H, H_8), 2.30 (t, *J* = 7.7 Hz, 2H, H_9), 1.50 (h, *J* = 7.4 Hz, 2H, H_{10}), 0.90 (t, *J* = 7.4 Hz, 3H, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.4 (C_6), 136.9 (C_4), 128.6 (C_2), 128.1 (C_1), 128.0 (C_3), 67.2 (C_5), 60.8 (C_9), 53.0 (C_8), 43.9 (C_7), 20.1 (C_{10}), 12.0 (C_{11}). **IR** ν_{max}/cm^{-1} (film): 2958, 2934, 1700, 1428, 1288, 1237, 1219, 1134. **HRMS** (ESI) calculated for $[C_{15}H_{22}N_2O_2+H]^+$: 263.1754, found: 263.1756. $\mathbf{R_F}$ = 0.13 (EtOAc).

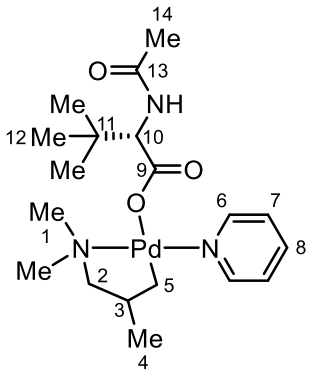
N,N,2-Trimethylpropan-1-amine **299**



2-Methylpropan-1-amine (5.0 mL, 50 mmol) was dissolved in formic acid (25 mL) and formaldehyde (37%, 23 mL, 300 mmol) added. The reaction mixture was refluxed at 100 °C for 17 h, then cooled to 0 °C and 10% aq. NaOH added until the mixture was basic. The resultant top layer was decanted and purified by Kugelrohr distillation (220 mBar, 45 °C) to give *N,N*,2-trimethylpropan-1 amine **299** as a colourless oil (0.65 g, 6.4 mmol, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 6H, H_1), 2.01 (d, *J* = 7.4 Hz, 2H, H_2), 1.72 (non, *J* = 6.6 Hz, 1H, H_3), 0.89 (d, *J* = 6.6 Hz, 6H, H_4). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.7 (C_2), 46.0 (C_1), 26.3 (C_3), 21.0 (C_4). **IR** ν_{max}/cm^{-1} (film): 2964, 2920, 1668, 1584, 1409, 1361, 1053, 1033, 1017, 800. **HRMS** (ESI) calculated for $[C_6H_{15}N+H]^+$: 102.1277, found: 102.1280. $\mathbf{R_F}$ = 0.17 (10% MeOH/EtOAc). Data consistent with literature.[258]

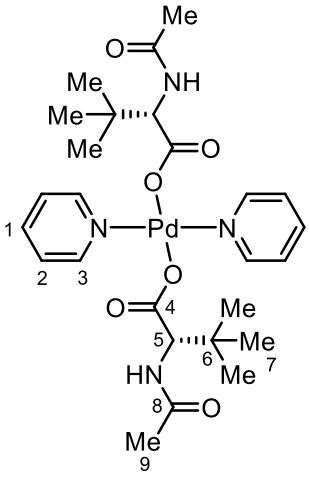
Alkylamine palladium(II) complex **300**



N,*N*,2-Trimethylpropan-1-amine **299** (14. uL, 0.10 mmol), palladium(II) acetate (34 mg, 0.15 mmol) and (*S*)-2-acetamido-3,3-dimethylbutanoic acid **(-)-304** (35 mg, 0.20 mmol) were dissolved in DMF (1 mL) and stirred at 30 °C for 16 h. The reaction solvent was subsequently blown off under air. The resultant material was dissolved in chloroform (5 mL), filtered through Celite and concentrated *in vacuo* to afford complex **300** as a yellow oil (quant. by ^{1}H-NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (dt, *J* = 5.0, 1.6 Hz, 2H, H_6), 7.69 (tt, *J* = 7.6, 1.6 Hz, 1H, H_8), 7.26 – 7.22 (m, 2H, H_7), 6.57 (br. d, *J* = 9.3 Hz, 1H, N–H), 4.24 (d, *J* = 9.3 Hz, 1H, H_{10}), 2.80 (d, *J* = 12.8 Hz, 3H, H_{1a}), 2.58 (d, *J* = 12.8 Hz, 3H, H_{1b}), 2.42 – 2.34 (m, 2H, H_2), 2.16 (tq, *J* = 11.7, 5.9 Hz, 1H, H_3), 1.96 (s, 3H, H_{14}), 1.67 (ddd, *J* = 8.9, 5.2, 2.4 Hz, 1H, H_{5a}), 1.57 (dd, *J* = 11.3, 8.8 Hz, 1H, H_{5b}), 0.92 – 0.86 (m, 12H, H_4 and H_{12}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.9 (C_9), 169.8 (C_{13}), 152.6 (C_6), 137.3 (C_8), 124.8 (C_7), 74.8 (C_2), 62.6 (C_{10}), 52.8 (C_{1a}), 49.2 (C_{1b}), 37.0 (C_3), 34.6 (C_{11}), 30.4 (C_5), 27.1 (C_{12}), 23.6 (C_{14}), 16.6 (C_4). **IR** ν_{max}/cm^{-1} (film): 2961, 2927, 1574, 1350, 1276, 1127, 894, 703, 682. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = – 1.3° (*c* = 1.3, $CHCl_3$).

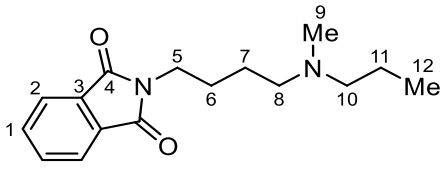
Decomposition complex **301**



N,*N*,2-Trimethylpropan-1-amine **299** (14. uL, 0.10 mmol), palladium(II) acetate (34 mg, 0.15 mmol) and (*S*)-2-acetamido-3,3-dimethylbutanoic acid **(-)-304** (35 mg, 0.20 mmol) were dissolved in DMF (1 mL) and stirred at 30 °C for 16 h. The reaction solvent was subsequently blown off under air. The resultant material was dissolved in chloroform (5 mL), filtered through Celite and concentrated *in vacuo* to afford **300** as a yellow oil. Vapour diffusion using CH_2Cl_2 (solvent)/Et_2O (precipitant) afforded the title complex **301** as colourless needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.65 (m, 4H, H_3), 7.84 – 7.69 (m, 2H, H_1), 7.42 – 7.30 (m, 4H, H_2), 6.01 (d, *J* = 9.3 Hz, 2H, N–H), 4.22 (d, *J* = 9.3 Hz, 2H, H_5), 1.89 (s, 6H, H_9), 0.66 (s, 18H, H_7). **IR** ν_{max}/cm^{-1} (film): 3346, 2961, 1655, 1611, 1528,1451, 1324, 729. **Mp** = 202-204 °C. $[\alpha]_D^{20}$ = –1.7° (*c* = 2.3, $CHCl_3$). **X-Ray structure** in *Appendix II iv.*

2-(4-(Methyl(propyl)amino)butyl)isoindoline-1,3-dione **302**

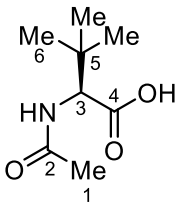


2-(4-Bromobutyl)isoindoline-1,3-dione (4.2 g, 15 mmol) was dissolved in MeCN (50 mL), K_2CO_3 (2.76 g, 20.0 mmol) then N-methylpropan-1-amine (2.1 mL, 20 mmol) were added to the reaction mixture which was stirred for 16 h at reflux. After cooling to rt, volatiles were removed *in vacuo* and the remaining material filtered with CH_2Cl_2 (100 mL). The organic layer was then washed with aq. NaOH (10%, 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (combiflash, silica gel, 12 g column), eluting with 2-30% EtOAc/petroleum ether, to

give 2-(4-(methyl(propyl)amino)butyl)isoindoline-1,3-dione **302** (2.7 g, 10 mmol, 68%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H, H_2), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H, H_1), 3.70 (t, *J* = 7.2 Hz, 2H, H_5), 2.34 (t, *J* = 7.3 Hz, 2H, H_8), 2.26 (t, *J* = 7.5 Hz, 2H, H_{10}), 2.18 (s, 3H, H_9), 1.69 (p, *J* = 7.5 Hz, 2H, H_6), 1.58 – 1.38 (m, 4H, H_7 and H_{11}), 0.87 (t, *J* = 7.4 Hz, 3H, H_{12}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C_4), 134.0 (C_1), 132.3 (C_3), 123.3 (C_2), 60.0 (C_{10}), 57.3 (C_8), 42.4 (C_9), 38.1 (C_5), 26.7 (C_6), 24.8 (C_7), 20.6 (C_{11}), 12.1 (C_{12}). **IR** ν_{max}/cm^{-1} (film): 2936, 2871, 2788, 1771, 1706, 1466, 1394, 1366, 1335, 1087, 1043, 717, 529. **HRMS** (ASAP) calculated for $[C_{16}H_{22}N_2O_2+H]^+$: 275.1754, found: 275.1750. $\mathbf{R}_F$ = 0.13 (20% MeOH/EtOAc).

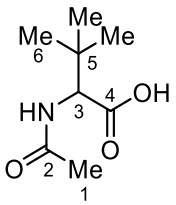
(S)-2-Acetamido-3,3-dimethylbutanoic acid **(-)-304**



L-*tert*-Leucine (3.0 g, 23 mmol) was dissolved in AcOH (30 mL) and Ac_2O (2.40 mL, 25 mmol) was added. The reaction was stirred at rt for 14 h after which it was concentrated *in vacuo*. The crude material was suspended in Et_2O, filtered and the collected solids recrystallised from MeCN/MeOH to give (*S*)-2-acetamido-3,3-dimethylbutanoic acid **(-)-304** (3.1 g, 18 mmol, 77%) as colourless needles.

^{1}H NMR (400 MHz, MeOD-d^4) δ 4.28 (s, 1H, H_3), 2.01 (s, 3H, H_1), 1.03 (s, 9H, H_6). **^{13}C NMR** (101 MHz, MeOD-d^4) δ 174.3 (C_4), 173.3 (C_2), 62.2 (C_3), 34.7 (C_5), 27.1 (C_6), 22.3 (C_1). **IR** ν_{max}/cm^{-1} (solid) 3353, 2968, 1701, 1611, 1474, 1126, 963, 722, 476. **HRMS** (ESI) calculated for $[C_8H_{15}NO_3+H]^+$: 174.1125, found: 174.1123. **Mp** = 224-226 °C (lit. 228-229 °C). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = –3.4° (*c* = 1.0, MeOH). Data consistent with literature.[182]

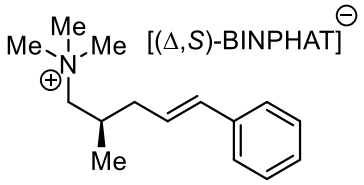
2-Acetamido-3,3-dimethylbutanoic acid **(±)-304**



tert-Leucine (1.0 g, 7.6 mmol) was dissolved in AcOH (10 mL) and Ac_2O (0.80 mL, 8.4 mmol) was added. The reaction was stirred at 30 ºC for 5 h after which it was cooled and concentrated *in vacuo*. The crude material was suspended in Et_2O, filtered and the collected solids recrystallised from MeCN/MeOH to give 2-acetamido-3,3-dimethylbutanoic acid **(±)-304** (0.68 g, 3.9 mmol, 51%) as colourless needles.

^{1}H NMR (400 MHz, MeOD-d^4) δ 4.29 (s, 1H, H_3), 2.02 (s, 3H, H_1), 1.03 (s, 9H, H_6). **^{13}C NMR** (101 MHz, MeOD-d^4) δ 174.2 (C_4), 173.3 (C_2), 62.2 (C_3), 34.7 (C_5), 27.1 (C_6), 22.3 (C_1). **IR** ν_{max}/cm^{-1} (solid) 3358, 2964, 1702, 1616, 1544, 1220, 651, 588. **HRMS** (ESI) calculated for $[C_8H_{15}NO_3+H]^+$: 174.1125, found: 174.1123. **Mp** = 224-226 °C (lit. 229-231 °C). Data consistent with literature.[259] **X-Ray structure** in *Appendix I v.*

[(E)-N,N,N,2-Tetramethyl-5-phenylpent-4-en-1-aminium][(Δ,S)-BINPHAT] **282bb**



282bb

(*E*)-*N*,*N*,2-Trimethyl-5-phenylpent-4-en-1-amine **282b** (24 mg, 0.12 mmol) was added to an oven-dried microwave vial and dissolved in anhydrous MeOH (0.20 mL). Methyl iodide (45 uL, 0.72 mmol) and $NaHCO_3$ (40 mg, 0.48 mmol) was added to the solution of amine, which was sealed and stirred at 60 °C for 14 h. Thereafter the reaction was cooled to rt and the reaction mixture concentrated under a stream of N_2. CH_2Cl_2 (5 mL) was added and the mixture stirred for 1 h at rt. This mixture was then filtered through a plug of cotton wool and concentrated *in vacuo* and used directly in the next step. $[Me_2NH_2][(\Delta,S)$-BINPHAT] (11.6 mg, 0.14 mmol) was added to the solution of the crude amine salt in anhydrous acetone (1.0 mL) and stirred vigorously at rt for 5 min. The reaction mixture was then filtered through alumina washing generously with CH_2Cl_2 (15 mL) and concentrated *in vacuo*. The resultant solid **282bb** was analysed rapidly by NMR to determine 84% ee.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H, H_{10} and H_{11}), 7.24 – 7.15 (m, 2H, H_9), 6.39 (dd, *J* = 15.7, 11.8 Hz, 1H, H_7), 6.12 (dtd, *J* = 15.7, 7.0, 1.7 Hz, 1H, H_6), 3.56 (q, J = 7.3 Hz, 2H, H_3), 3.42 (ddd, *J* = 13.4, 5.8, 2.2 Hz, 1H, H_{5a}), 3.31 (ddd, *J* = 13.5, 5.7, 2.5 Hz, 1H, H_{5b}), 2.33 – 2.15 (m, 4H, H_3 and H_4), 1.28 – 1.21 (m, 3H, H_{1a}), 1.15 (t, *J* = 6.5 Hz, 3H, H_{1b}). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.7 (C_8), 133.8 (C_7), 128.7 (C_9), 127.6 (C_{11}), 126.3 (C_9), 126.0 (C_6), 69.8 (C_5), 60.7 (C_2), 40.0 (C_3), 28.7 (C_4), 21.1 (C_{1a}), 8.8 (C_{1b}). **IR** ν_{max}/cm^{-1} (film): 2966, 2925, 2197, 1451, 907, 821, 723, 694, 672, 642, 616, 490. **HRMS** (ESI) calculated for $[C_{15}H_{25}N]^+$: 218.1903, found: 218.1905. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = –1.9° (*c* = 1.5, $CHCl_3$).

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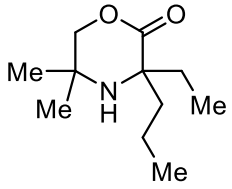
Appendix I. Supplementary data

*i) Variable temperature experiment of amine **221** (d^4-AcOH, 70 °C)*



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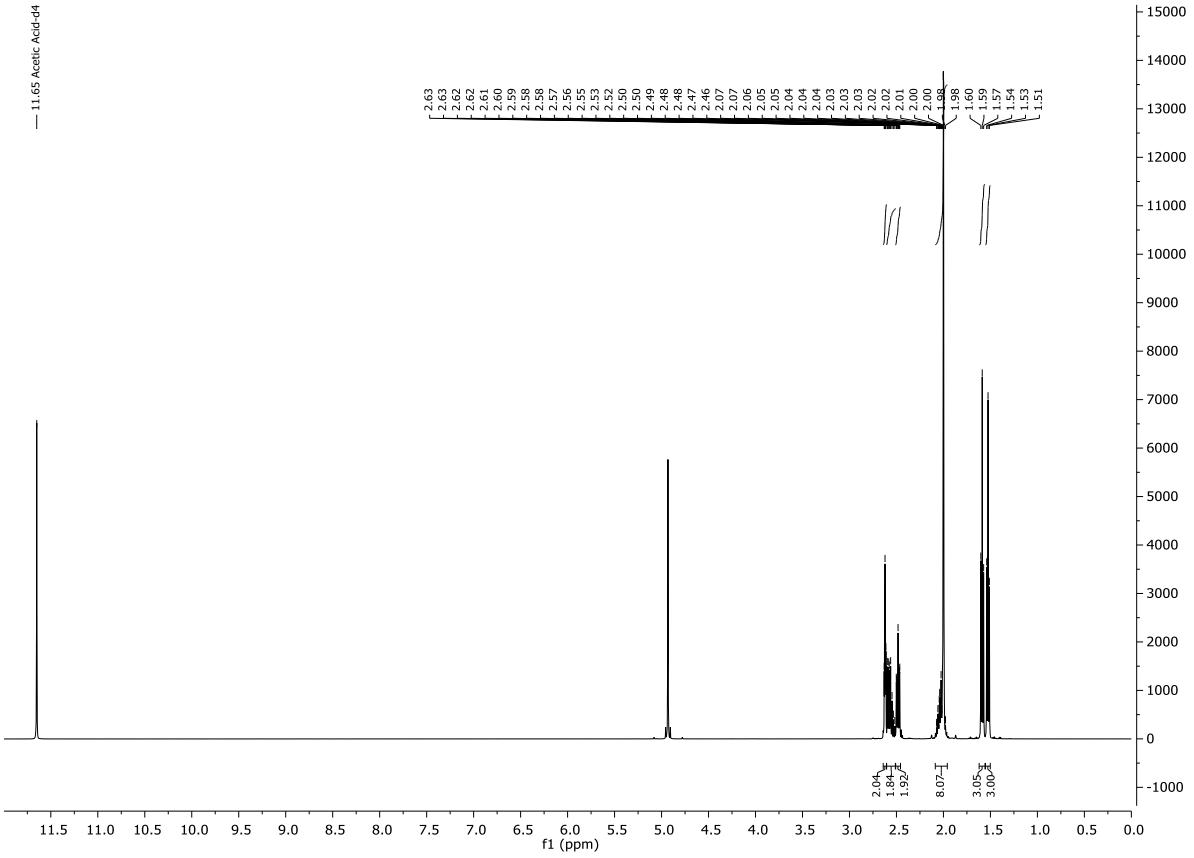
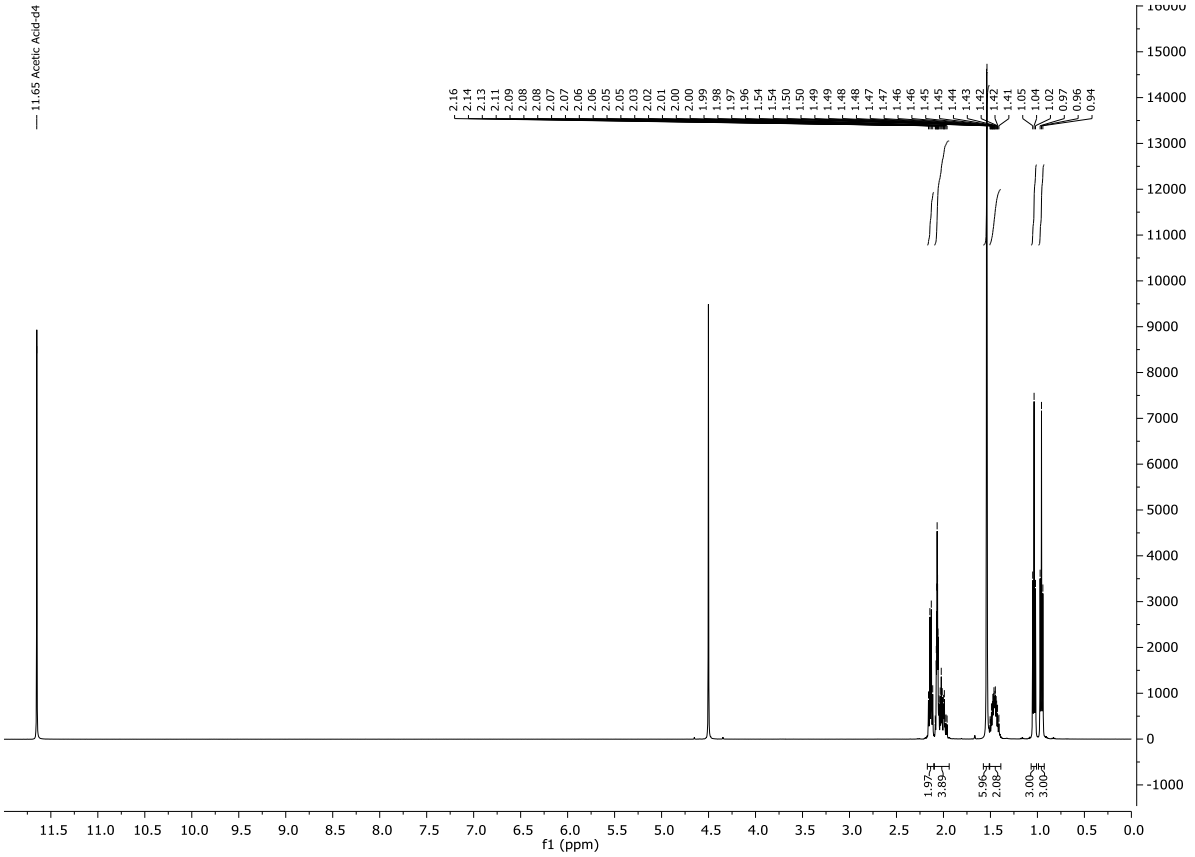
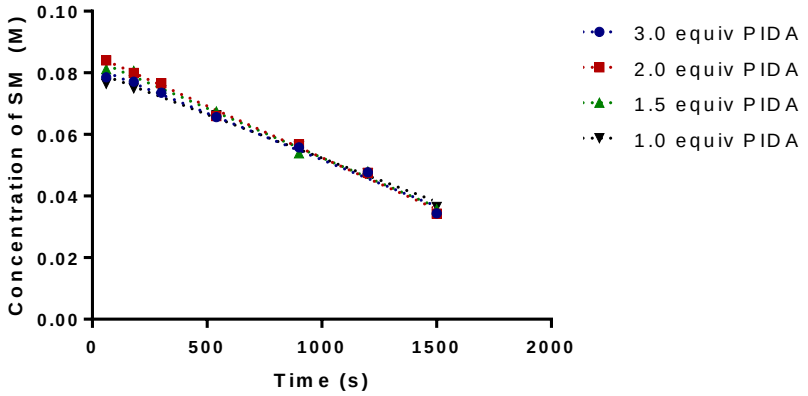



11.65 Acetic Acid-d4
2.16
2.14
2.13
2.11
2.09
2.08
2.08
2.07
2.07
2.06
2.06
2.05
2.05
2.03
2.02
2.01
2.00
2.00
1.99
1.98
1.97
1.96
1.54
1.54
1.50
1.50
1.49
1.49
1.48
1.48
1.47
1.47
1.46
1.46
1.45
1.45
1.44
1.43
1.42
1.42
1.41
1.05
1.04
1.02
0.97
0.96
0.94
1.97
3.89
5.96
2.08
3.00
3.00
f1 (ppm)

ii) Kinetic studies on the acetoxylation of morpholinones, carried out by Dr. Darren Willcox, included here for completeness

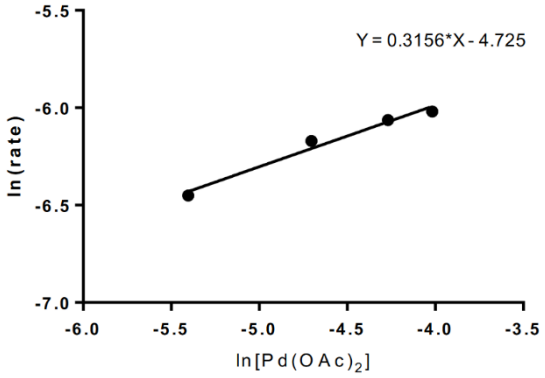
a. Order in PIDA

Entry	Equivalents of PIDA	Rate ($M\ s^{-1}$)
1	3.0	1.8×10^{-3}
2	2.0	2.0×10^{-3}
3	1.5	1.9×10^{-3}
4	1.0	1.7×10^{-3}



b. Order in Palladium acetate

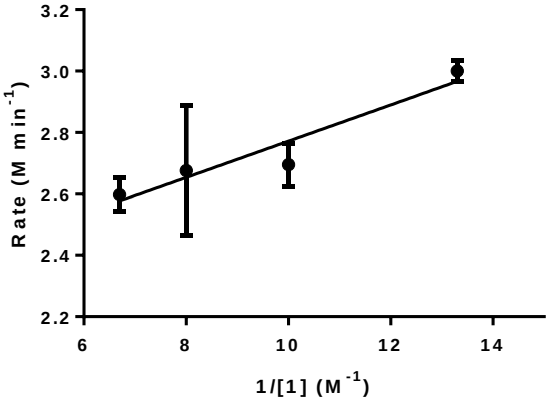
Concentration of $Pd(OAc)_2$ /M	Rate 1	Rate 2	Rate 3	Average rate	Standard deviation
0.0045	1.646	1.712	1.3787	1.579	0.176491
0.00907	2.1497	2.2835	1.834	2.089	0.230803
0.014	2.024	2.4932	2.4662	2.328	0.263445
0.018	2.5604	2.4311	2.2997	2.430	0.130351



The plot of *ln[Pd(OAc)₂]* vs *ln(rate*) indicating an order of 0.3 in palladium.

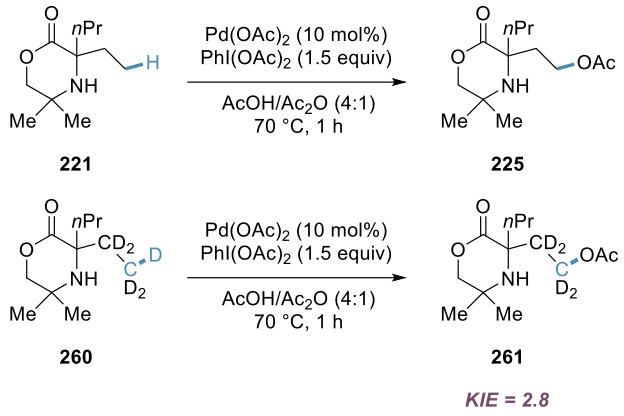
c. Order in Amine

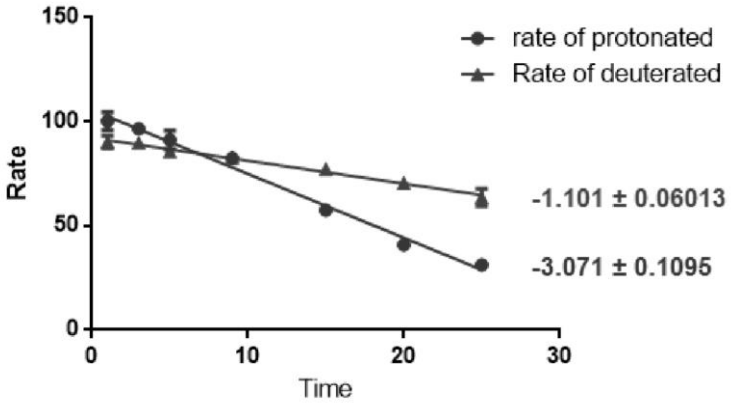
[1] / M	1/[1] M^{-1}	Rate 1	Rate 2	Rate 3	Average rate	Standard deviation
0.075	13.3	2.998	3.0366	2.9663	3.0003	0.035206
0.1	10	2.7185	2.6163	2.7511	2.6953	0.070331
0.125	8	2.4427	2.859	2.7267	2.676133	0.212707
0.15	6.7	2.5356	2.618	2.6392	2.5976	0.05473



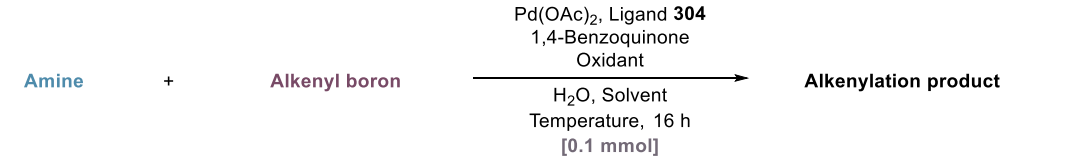
The straight line of the graph confirms the initial order of substrate to be -1

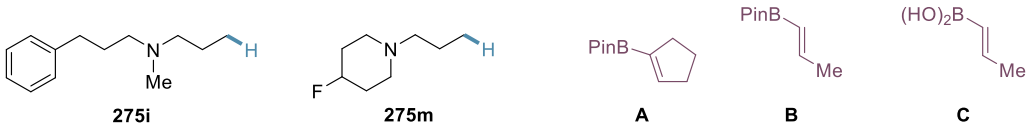
d. Kinetic isotope effect study





iii) Initial optimisation studies for the alkenylation of tertiary amines

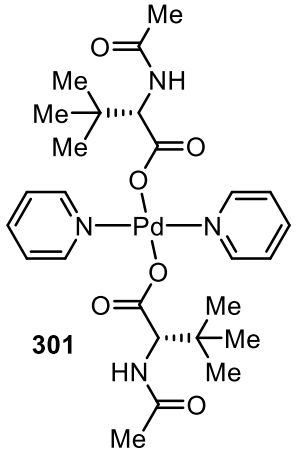




275i **275m** **A** **B** **C**

Entry	Amine (equiv)	Alkene (equiv)	$Pd(OAc)_2$ / mol%	L / mol%	Oxidant (equiv)	BQ /equiv	Water /equiv	Solvent	solvent / mL	T / °C	NMR Yield / %
1	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	60	**0**
2	**275i** (1)	**A** (1)	10	25	AgOAc (2.5)	2	0	*t*AmylOH	2.5	60	**0**
3	**275i** (1)	**A** (1)	10	25	AgTFA (2.5)	2	0	*t*AmylOH	2.5	60	**0**
4	**275i** (1)	**A** (1)	10	25	$AgBF_4$ (2.5)	2	0	*t*AmylOH	2.5	60	**0**
5	**275i** (1)	**A** (1)	10	25	AgF (2.5)	2	0	*t*AmylOH	2.5	60	**0**
6	**275i** (1)	**A** (1)	10	25	$Cu(OAc)_2$ (2.5)	2	0	*t*AmylOH	2.5	60	**0**
7	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	5	*t*AmylOH	2.5	60	**0**
8	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	10	*t*AmylOH	2.5	60	**0**
9	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	20	*t*AmylOH	2.5	60	**0**
10	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	5	DMF	2.5	60	**0**
11	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	10	DMF	2.5	60	**0**
12	**275i** (1)	**A** (1)	10	25	Ag_2CO_3 (2.5)	2	20	DMF	2.5	60	**0**
13	**275i** (1)	**B** (1)	10	25	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	60	**0**
14	**275i** (1)	**C** (1)	10	25	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	60	**0**
15	**275i** (1)	**B** (1)	20	50	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	60	**0**
16	**275i** (1)	**C** (1)	20	50	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	60	**Trace**
17	**275i** (2.5)	**B** (1)	10	25	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	50	**0**
18	**275m** (2.5)	**C** (1)	10	25	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	50	**0**
19	**275m** (2.5)	**B** (1)	10	25	Ag_2CO_3 (2.5)	2	0	*t*AmylOH	2.5	50	**0**

iv) Crystal structure of palladacycle decomposition complex **301**



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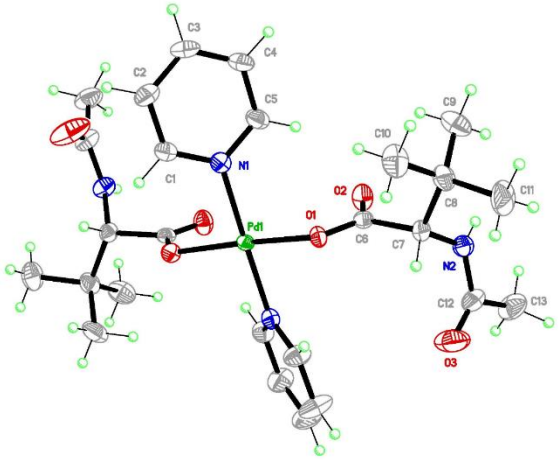
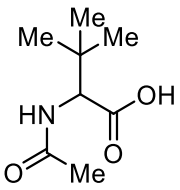
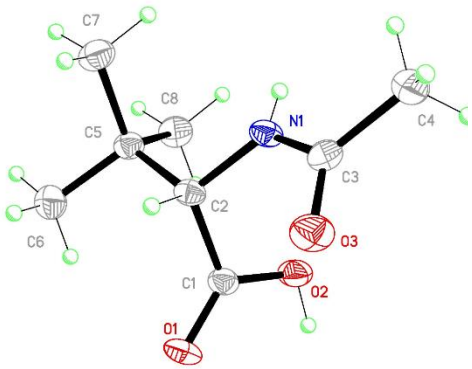


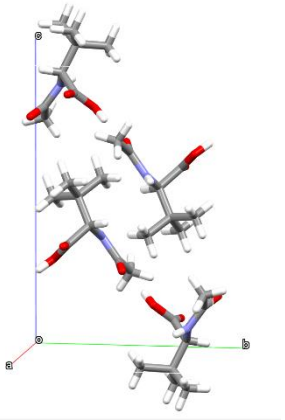
Empirical formula	$C_{26}H_{38}N_4O_6Pd$	
Formula weight	609.00	
Temperature	180(2) K	
Wavelength	1.54178 Å	
Crystal system	orthorhombic	
Space group	F 2 2 2	
Unit cell dimensions	a = 14.7978(8) Å	α = 90°
	b = 19.6106(10) Å	β = 90°
	c = 20.2921(11) Å	γ = 90°
Volume	5888.6(5) $Å^3$	
Z	8	
Density (calculated)	1.374 Mg/m^3	
Absorption coefficient (μ)	5.445 mm^{-1}	
F(000)	2528	
Crystal size	0.100 x 0.100 x 0.020 mm^3	
θ range for data collection	4.331 to 66.832°	
Index ranges	$-17 \leq h \leq 17$, $-19 \leq k \leq 23$, $-24 \leq l \leq 23$	
Reflections collected	7548	
Independent reflections	2567 [R(int) = 0.0471]	
Completeness to θ = 66.832°	99.5%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.6240	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2567 / 0 / 176	
Goodness-of-fit on F2	1.120	
Final R indices [I > 2σ(I)]	R1 = 0.0277, wR2 = 0.0577	
R indices (all data)	R1 = 0.0329, wR2 = 0.0592	
Absolute structure parameter	-0.016(9)	
Largest diff. peak and hole	0.488 and -0.540 $e.Å^{-3}$	

v) *Crystal structure of racemic Ac-tLeu-OH ligand* **(±)-304**



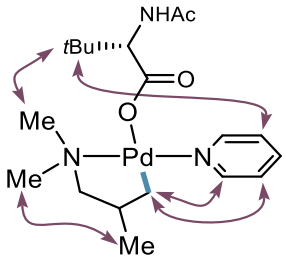
305



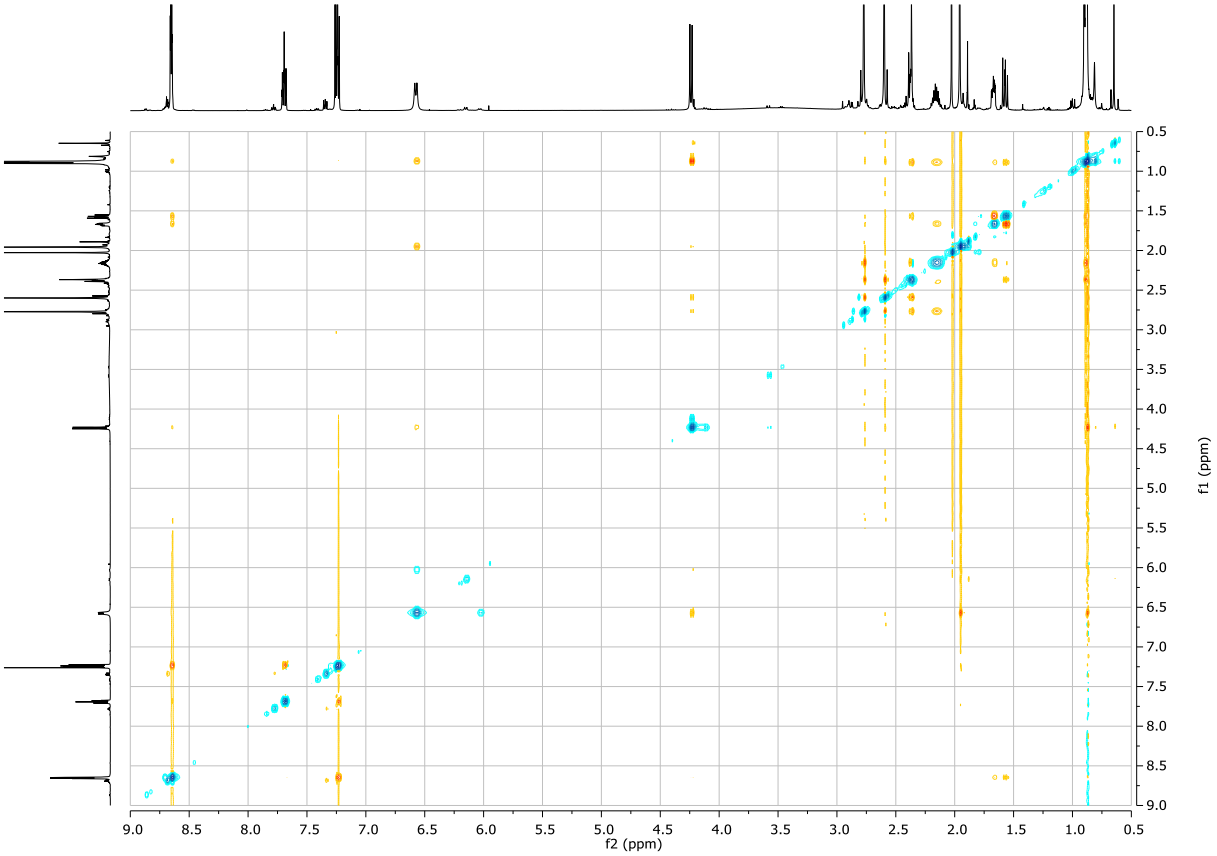


Empirical formula	$C_8H_{15}NO_3$	
Formula weight	173.21	
Temperature	180(2) K	
Wavelength	1.54178 Å	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 6.0621(4) Å b = 10.1950(7) Å c = 14.7141(10) Å	α = 90° β = 95.648(4)° γ = 90°
Volume	904.96(11) $Å^3$	
Z	4	
Density (calculated)	1.271 Mg/m^3	
Absorption coefficient (μ)	0.802 mm^{-1}	
F(000)	376	
Crystal size	0.180 x 0.140 x 0.080 mm^3	
θ range for data collection	5.287 to 66.716°	
Index ranges	$-7 \leq h \leq 7$, $-12 \leq k \leq 12$, $-16 \leq l \leq 17$	
Reflections collected	10092	
Independent reflections	1592 [R(int) = 0.0658]	
Completeness to θ = 66.832°	99.5%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7528 and 0.5413	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1592 / 0 / 121	
Goodness-of-fit on F2	1.040	
Final R indices [I > 2σ(I)]	R1 = 0.0536, wR2 = 0.1431	
R indices (all data)	R1 = 0.0636, wR2 = 0.1523	
Absolute structure parameter	-0.016(9)	
Largest diff. peak and hole	0.377 and -0.301 e.$Å^{-3}$	

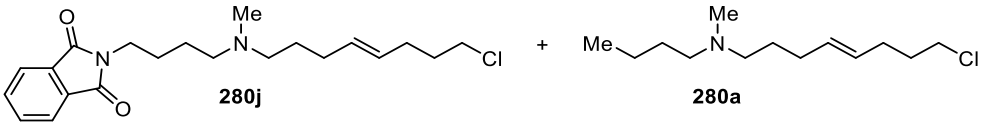
vi) *NOE spectrum of palladacycle* **300**

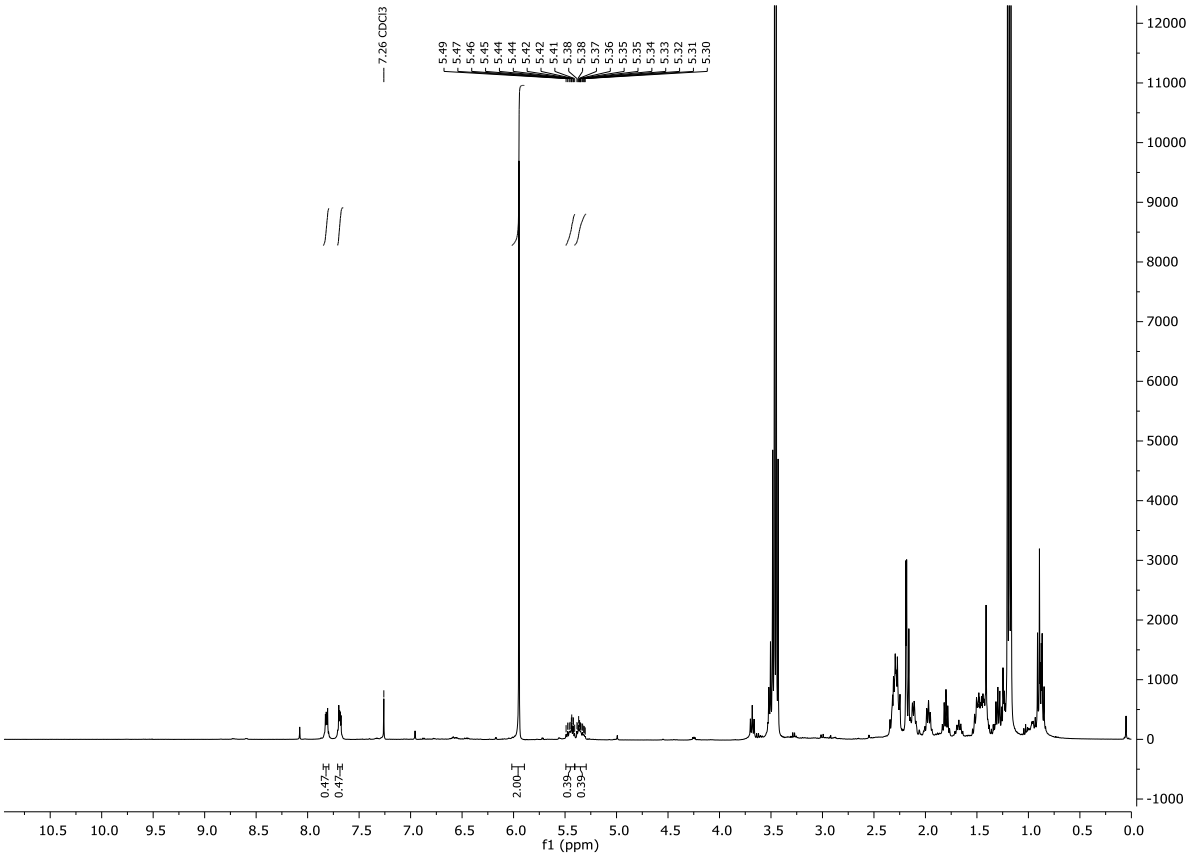


complex **X**

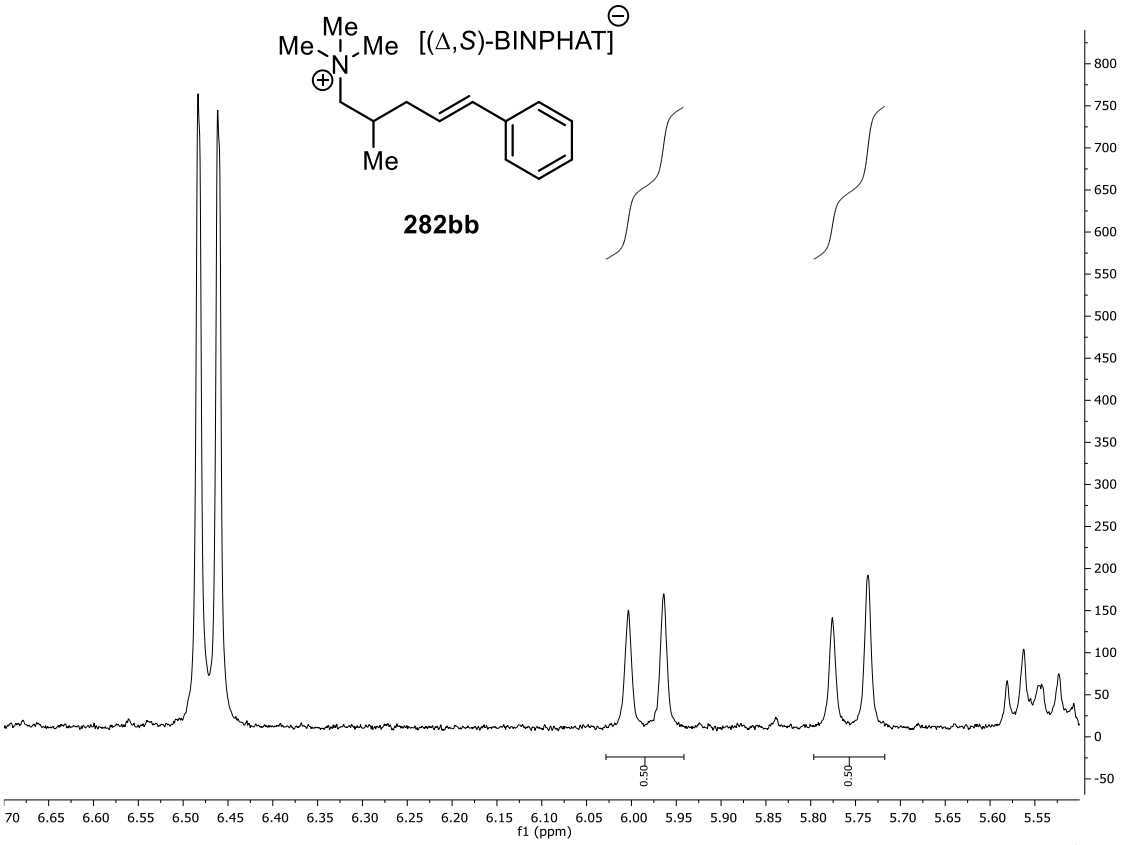


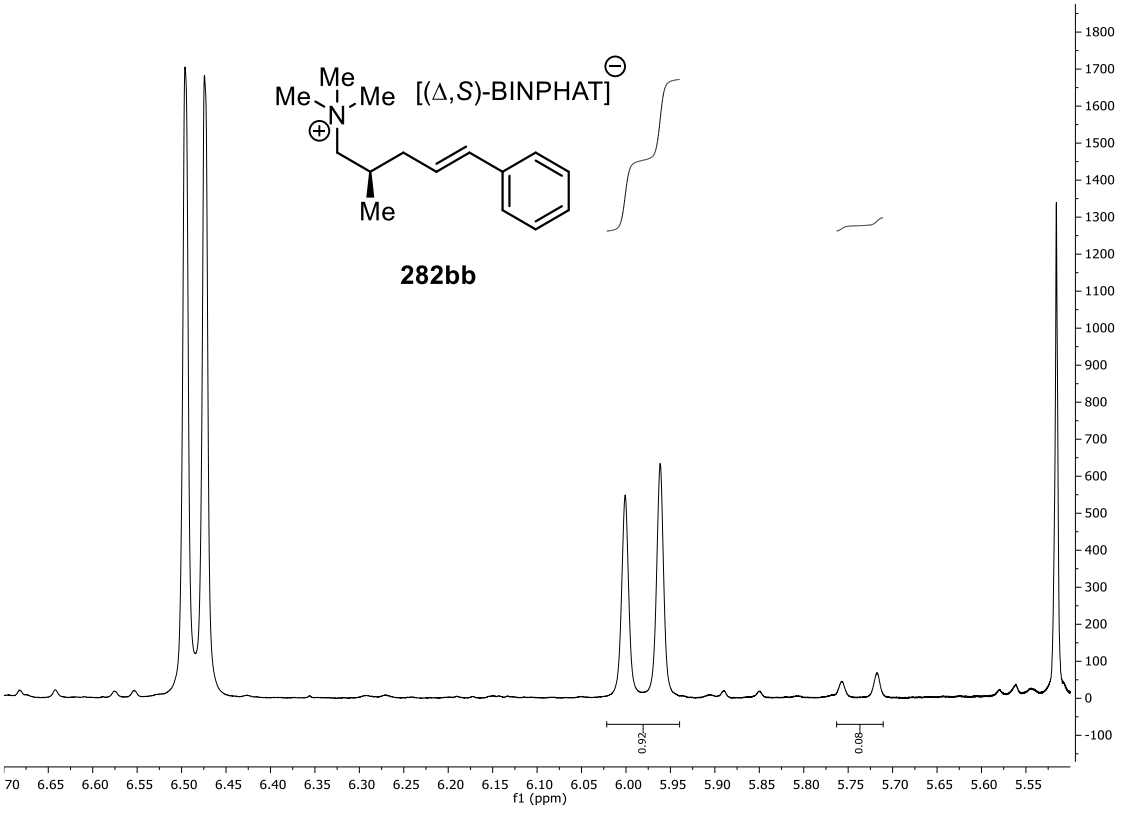
vii) *Stoichiometric alkenylation study*





viii) Determination of enantiomeric excess





(92:8 = 84% ee)

Appendix II. Published work

Chemical Science

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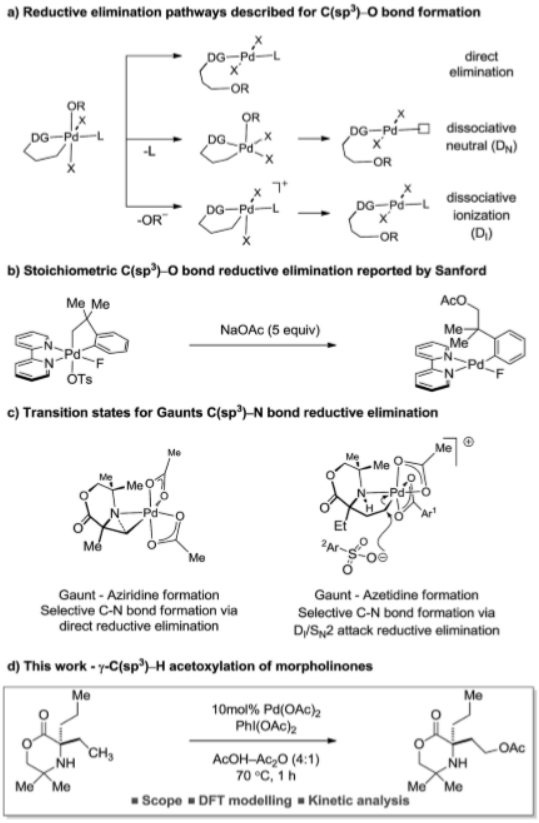
Mechanistic investigation into the C(sp^3)–H acetoxylation of morpholinones†

Cornelia S. Buettner,‡ Darren Willcox, ‡ Ben. G. N. Chappell‡ and Matthew J. Gaunt *

The study of a selective palladium(II)-catalyzed C(sp^3)–H acetoxylation reaction on a class of cyclic alkyl amines is reported. Computational modelling and kinetic studies were used to provide support for a mechanism involving selective C–O bond formation from a γ-aminoalkyl-Pd(IV) intermediate. The C–O bond forming step was computed to occur by a dissociative ionization mechanism followed by an S_N2 process involving external acetate attack at the C–Pd(IV) bond. This pathway was computed to be of lowest energy with no competing C–N products observed. Additionally, with a few modifications to reaction conditions, preliminary studies showed that this process could be rendered enantioselective in the presence of a non-racemic BINOL-phosphoric acid.

The reductive elimination from transient palladium(IV) species has enabled a range of carbon–heteroatom bond forming processes,[1] particularly in the area of C(sp^3)–H bond functionalization. Of these transformations, palladium catalyzed C(sp^3)–H acetoxylation has been the focus of significant study.[2] However, despite the report of an increasing number of catalytic processes, mechanistic understanding of the reductive elimination from the transient alkyl-palladium(IV) species has remained obscure. Important stoichiometric studies, by Sanford and co-workers, on C–H acetoxylation has led to three distinct mechanistic rationales being proposed for the reductive elimination pathway: (1) direct reductive elimination from palladium(IV) without loss of a ligand; (2) dissociative neutral (D_N) where a L-type ligand dissociates to form a neutral five-coordinate palladium(IV) intermediate followed by reductive elimination and (3) dissociative ionization (D_I), where a X-type ligand dissociates forming a five-coordinate cationic palladium(IV) species prior to reductive elimination (Scheme 1a).[3] Further investigations and DFT modelling studies into C(sp^3)–H acetoxylation reactions, using model palladium(IV) intermediates, indicated that a dissociative ionization mechanism is the major pathway for carbon–oxygen reductive elimination (Scheme 1b).[4]

Our group has a long standing interest in the development of processes founded on palladium(II)-catalyzed free(NH) alkylamine-directed C(sp^3)–H activation. One aspect of this work has involved the deployment of oxidants to access



Scheme 1 Mechanistic studies conducted for carbon–heteroatom bond formation.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and kinetic details. See DOI: 10.1039/c8sc03434f

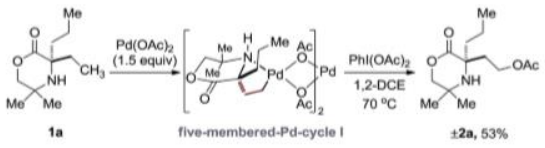
‡ Authors contributed equally to the work.

aminoalkyl-Pd(IV) intermediates, from which reductive elimination can take place to form carbon–heteroatom bonds. While we have reported a number of selective carbon–nitrogen bond formation reactions for the synthesis of both aziridines and azetidines,[5] the development of carbon–oxygen bond forming processes has been hindered by poor selectivity in the (product forming) reductive elimination step. Mechanistic studies into the β-C(sp^3)–H amination of alkylamines to form aziridines, facilitated by iodosobenzene diacetate as oxidant, identified that the process proceeded *via* a direct C–N bond forming reductive elimination from the aminoalkyl-palladium(IV) intermediate that was triggered by deprotonation of the amine by an internal acetate.[6] In contrast, we found that the corresponding γ-C(sp^3)–H amination to generate the azetidine product required the use of a benziodoxole tosylate oxidant. Interestingly, DFT studies identified that carbon–nitrogen bond formation occurred *via* a two-step dissociative ionization pathway involving loss of a sulfonate group from a palladium(IV) species followed by its S_N2 attack at the carbon–palladium(IV) bond to form a γ-C–OTs bond and finally internal displacement of the tosylate to form the 4-membered ring amine (Scheme 1c). Here, we report that controlling the mechanism of the reductive elimination process has enabled the development of a palladium(II)-catalyzed γ-C(sp^3)–H acetoxylation process on a class of cyclic amines (that we call morpholinones). We detail our preliminary mechanistic and computational studies that support the putative two-step dissociative pathway for C–O bond formation, optimize and explore the scope of the reaction, and, finally, identify that the γ-C(sp^3)–H acetoxylation reaction can be rendered enantioselective using chiral anionic ligands.

Results and discussion

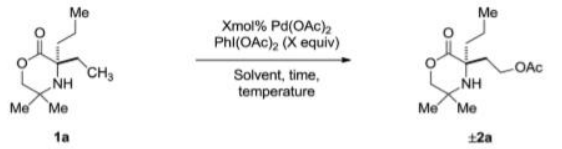
At the outset of our studies, we had observed that the treatment of amine **1a** with $Pd(OAc)_2$ and $PhI(OAc)_2$ produced no trace of azetidine product, instead undergoing exclusive γ-C(sp^3)–H acetoxylation to form **2b** in 48%.[5a] Based on this initial result, we confirmed the fundamental features of the mechanism by conducting a stoichiometric reaction with morpholinone **1a** and $Pd(OAc)_2$; stirring amine **1a** in the presence of 1.5 equivalents of $PdI(OAc)_2$ at 60 °C in a chloroform solution gave the anticipated γ-aminoalkyl-palladacycle and treatment with $PhI(OAc)_2$ in 1,2-DCE afforded the expected C–H acetoxylation product in 53% yield (Scheme 2).

Next, we assessed the reaction conditions required for a catalytic process. First, a simple survey of reaction parameters (Table 1) revealed that acetic acid in the presence of Ac_2O was the optimal media for the process, producing **2a** in 68% yield



Scheme 2 Stoichiometric acetoxylation of morpholinone **1a**.

Table 1 Standard reaction conditions: 5 mol% $Pd(OAc)_2$, 1.5 equiv. $PhI(OAc)_2$, solvent/Ac_2O (4 : 1, 0.1 M)



Entry	Solvent	Reaction time	Temperature	Yield[a]
1	PhMe	5 h	60 °C	52%
2	DCE	5 h	60 °C	41%
3	AcOH	5 h	60 °C	68%
4	AcOH	5 h	70 °C	66%
5	AcOH	3 h	70 °C	72%[b]
6	AcOH[c]	3 h	70 °C	82%
7	AcOH[c]	1 h	70 °C	75%[b]
8	AcOH[c,d]	1 h	70 °C	69%
9	AcOH[c,e]	1 h	70 °C	72%

[a] Yield determined by ^{1}H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [b] Yield of isolated product. [c] 10 mol% $Pd(OAc)_2$ loading. [d] 1.0 equiv. $PhI(OAc)_2$. [e] 2.0 equiv. $PhI(OAc)_2$.

(entries 1–3). The Ac_2O sequestered any water in the reaction mixture. Varying the temperature afforded no significant change in yield (entry 4). However, decreasing the reaction time from 5 h to 3 h allowed formation of **2a** in 72% yield (entry 5), suggesting that the acetoxylated amine **2a** was not indefinitely stable under the reaction conditions. Increasing the catalyst loading from 5 mol% to 10 mol% led to a further increase in yield to 82% (entry 6). Time course experiments indicated that the reaction was completed within 1 h with 10 mol% catalyst (entry 7). Adjusting the equivalents of $PhI(OAc)_2$ had no effect on the outcome of the reaction (entries 8 and 9). In conclusion, optimal conditions for the γ-C(sp^3)–H acetoxylation were found to involve treatment of **1a** with 10 mol% $Pd(OAc)_2$ as catalyst and 1.5 equivalents of $PhI(OAc)_2$ in a 0.1 M solution of AcOH/Ac_2O (4 : 1) at 70 °C for one hour, which afforded a 75% yield of isolated amine product after chromatography.

With optimized conditions in hand, we turned our attention to investigating the mechanism of this (Csp^3)–H acetoxylation process. Based on previous investigations of C–H activation reactions on morpholinone scaffolds, we envisaged a similar pathway for the C–H activation step *via* a mono-amino palladium(II) complex that proceeds through a CMD-type mechanism. Oxidation of the resulting γ-aminoalkyl-palladacycle, with $PhI(OAc)_2$, to generate the corresponding palladium(IV) intermediate primes the complex for the C–O bond forming step to furnish the desired acetoxylated amine product. The nature of the reductive elimination step could be in line with that observed in the C–H amination to aziridines (direct C–O bond reductive elimination) or *via* the two-step dissociative ionization/S_N2 pathway indentified in our azetidine forming reaction. To this end, both *in vitro* and *in silico* mechanistic studies were investigated to help to enlighten the mechanism of this process.

Our procedure to explore the kinetics of this reaction featured experiments to probe the reagent concentration dependencies and isotopic labelling studies to interrogate the mechanism of the stoichiometric reactions in Scheme 2. The process was monitored by taking aliquots from the reaction mixture at specific time intervals and measuring the concentration with 1,1,2,2-tetrachloroethane as internal standard by Flame ionization detector-gas chromatography (FID-GC). The reaction conditions involved the treatment of morpholinone **1a** with 10 mol% $Pd(OAc)_2$ formula, 1.5 equivalents of $PhI(OAc)_2$ in $AcOH/Ac_2O$ (4 : 1) solvent mixture at 70 °C. These conditions led to a rate profile which enabled us to follow the whole reaction over a 1 hour time scale (Fig. 1).

Due to the linear nature of the kinetic profile at the beginning of the reaction, the initial rates may be determined from the gradient of the concentration profile during this period and used to obtain the order in reagents. We first began by determining the order with respect to $PhI(OAc)_2$. Based on the rates obtained from reactions containing between one and three equivalents of $PhI(OAc)_2$ (Table S1, ESI†), the reaction exhibited zero-order kinetics with respect to the oxidant, indicating that the oxidation of the palladacycle occurs after the turnover limiting step (TOLS). By comparing the initial rates, we were also able to determine, from a concentration *vs.* 1/[**1a**] plot, a reaction order of −1 for the amine component (Table S3, ESI†). We propose that negative order in amine arises from the formation of an off-cycle bisamine complex at higher amine concentration. At lower amine concentrations, the mono/bisamine equilibrium lies towards the mono coordinated amine complex, thus enabling C–H activation to proceed, analogous to that observed in our previous work.[6] Determination of the order with respect to $Pd(OAc)_2$ under first-order conditions showed saturation type kinetics, however a plot of $\ln[Pd(OAc)_2]$ *vs.* ln(rate) reveals an order in $Pd(OAc)_2$ of 0.31 (Table S2, ESI†). This can be explained due to (1) $Pd(OAc)_2$ existing in a trimeric form in AcOH, (2) the slow dissociation of this trimer into the reactive monomer, even at elevated temperatures and (3) there being insufficient free amine to efficiently break down this trimer due to the amine being fully protonated under the reaction conditions. The combination of these factors should lead to the observed order of 0.33.[7] The dissociation of this palladium acetate-trimer to the monomeric species could also account for the induction period for starting material consumption observed in Fig. 1.

Further kinetic information was obtained by measurement of the kinetic isotope effect (KIE). A KIE was determined from initial rate measurements of substrate **1a** and d_5-**1a** (Scheme 3). A primary kinetic isotope effect of 2.8 was obtained, suggesting the C–H bond cleavage occurs as part of the TOLS.[8]

To test whether the acetoxylated product **2a** was inhibiting the reaction or leading to catalyst degradation, same "excess" experiments were performed.[9,10] Starting at 20% completion, time adjusting these results and overlaying onto the 0% completion plot (equivalent initial amine concentrations), indicated no product inhibition or catalyst deactivation (Table S4, ESI†). The kinetic data obtained in this study agrees with our previously reported mechanistic work on C–H activation of morpholinones[6] and so we envisage that the exclusive formation for the acetoxylated product must result from a difference in reductive elimination mechanism being in operation. As the reductive elimination step appears to take place after the rate-limiting C–H bond activation and the high reactivity of the γ-aminoalkyl-palladium(IV) intermediate, elucidation of the mechanism in this part of the catalytic cycle is challenging through experimental means.

Accordingly, DFT studies were conducted to interrogate the energetically favoured pathway for the γ-C(sp^3)–H acetoxylation reaction using **1b** as a model substrate. The calculations were performed on Amsterdam Density Functional (ADF) software, using ZORA-BLYP-D3 which has been used previously for palladium catalysed reactions and more specifically for the palladium catalysed C–H activation of amines within our group.[5d,6,11,12] The solvent effects were considered using an implicit conductor like solvation model (COSMO) in dichloroethane.

Initially, the C–H activation/oxidation sequence of to generate **Int-5** from the mono-coordinate amino-complex was

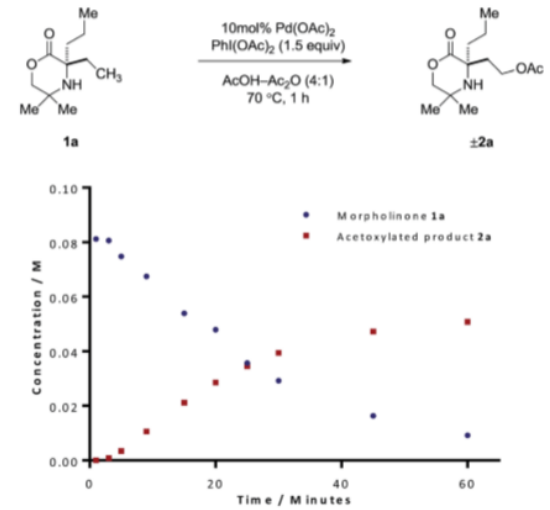
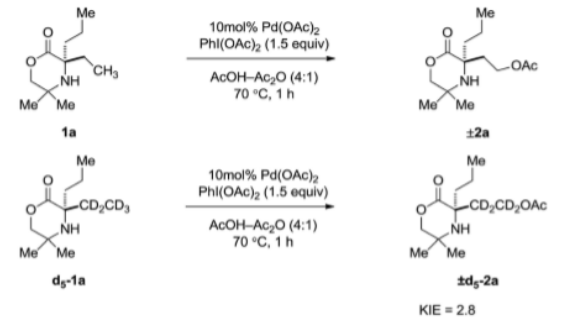


Fig. 1 Reaction profile for the acetoxylation of morpholinone **1a**.



Scheme 3 KIE measured from initial rate comparisons of **1a** and d_5-**1a**.

explored to enable a comparison with the kinetics results presented previously (Fig. 2). Initial dissociation of a single molecule of **1b** from **Int-1** led to the formation energetically favourable mono-amine complex **Int-2** (-2.45 kcal mol^{-1} lower than **Int-1**). From mono-amine complex **Int-2**, C–H activation proceeds through the expected six membered CMD transition state **TS1**, which was found to be +27.89 kcal mol^{-1} above **Int-2**. The palladium(II) complex **Int-3** then underwent dissociation of an acetate ligand to form the γ-aminoalkyl-palladacycle with a κ^2-bound acetate group (-13.31 kcal mol^{-1}, **Int-4**). Oxidation of **Int-4** with $PhI(OAc)_2$ yields the key γ-aminoalkyl-palladium(IV) complex **Int-5**.

From γ-aminoalkyl-palladium(IV) complex **Int-5**, the chemoselectivity of the reductive elimination process towards the formation of the C–O (acetoxylation) or C–N (azetidine) products was explored (Fig. 3). For the C–O bond formation product **2b**, the lowest energy pathway involves the full dissociation of the hydrogen bonded acetate leading to **Int-6**, *via* transition state **TS2**, which was found to be +13.08 kcal mol^{-1} above **Int-5**. Intermediate **Int-6** then undergoes attack by an external acetate at the electrophilic C–Pd(IV) bond to form the key C–O bond (+3.37 kcal mol^{-1} above **Int-6**). After the S_N2-type process, the amine remains bound to the reduced palladium(II) complex and upon de-ligation yields the acetoxylated product **2b**.

For azetidine formation to occur, **Int-6**, containing two κ^2-bound acetate groups, would be required to undergo deprotonation by an external acetate (**TS4**) resulting in the amido-Pd(IV) complex **Int-8**. From this complex, C–N bond forming reductive elimination can occur *via* **TS5** to give the azetidine product. We computed **TS5** to be +13.83 kcal mol^{-1} above **Int-8**. Therefore, we rationalise the exclusive C–O bond formation due to the significant energy barrier of C–N reductive elimination from complex **Int-8**.

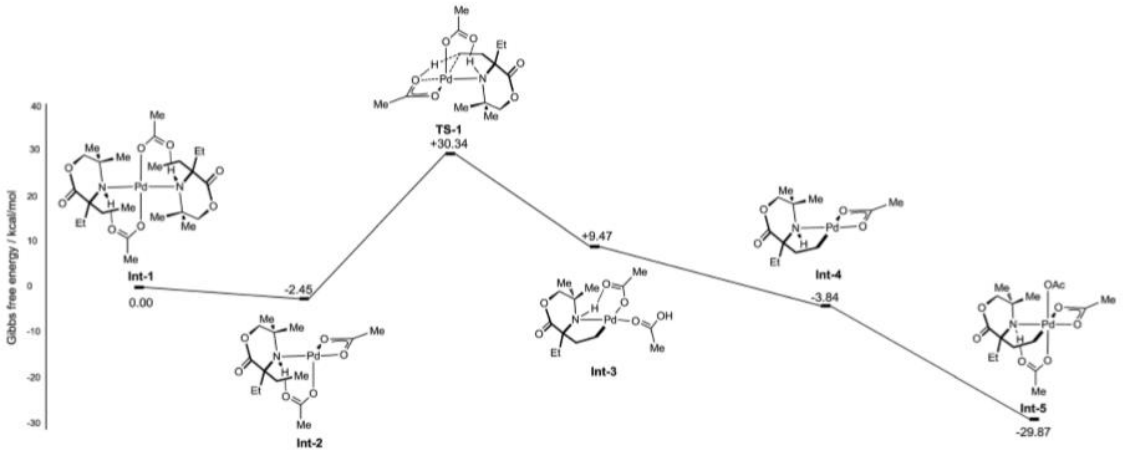


Fig. 2 Computed CMD C–H activation mechanism of morpholinones.

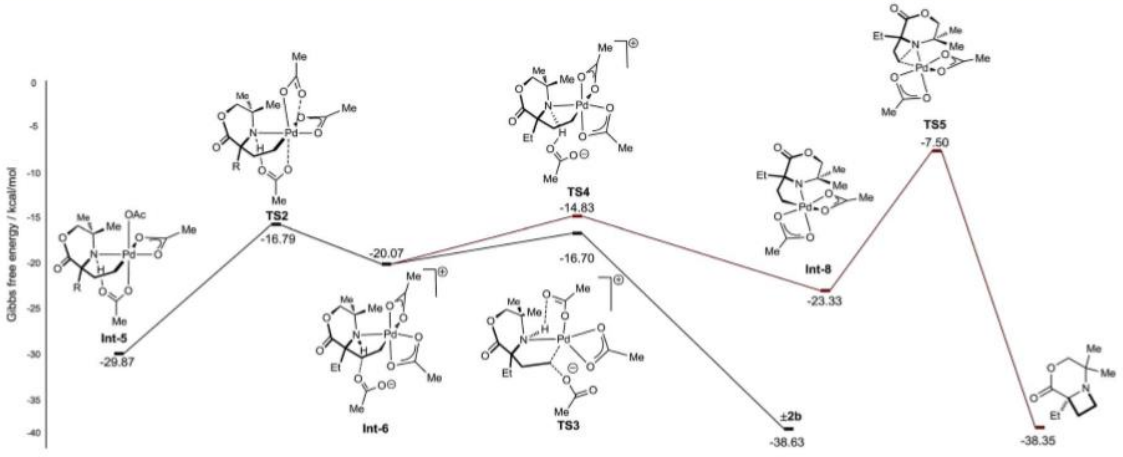


Fig. 3 Calculated energy barriers of C–N and C–O reductive elimination.

With a rationale in hand for the chemoselectivity of C–O bond formation, we explored other potential pathways of classical reductive elimination from the γ-aminoalkyl-palladium(IV) intermediate **Int-5**. Aside from external attack at the C–Pd(IV) bond, direct reductive elimination (transition state **TS6**) from the γ-aminoalkyl-palladium(IV) complex was computed to have a significantly greater energy barrier of +21.47 kcal mol^{-1}. The C–O reductive elimination processes from **Int-5** involving both the κ^2-bound, as well as the hydrogen bonded, acetate ligand was examined. However, these proved to be even higher in energy (see ESI† for details) (Fig. 4).

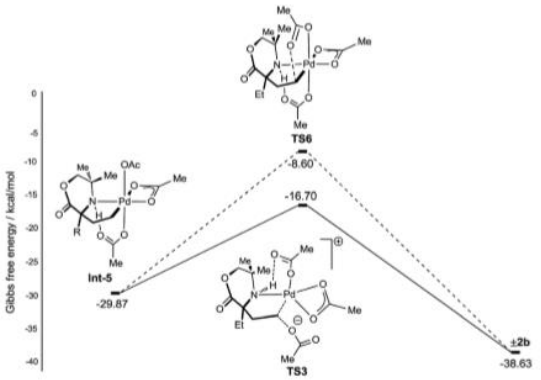
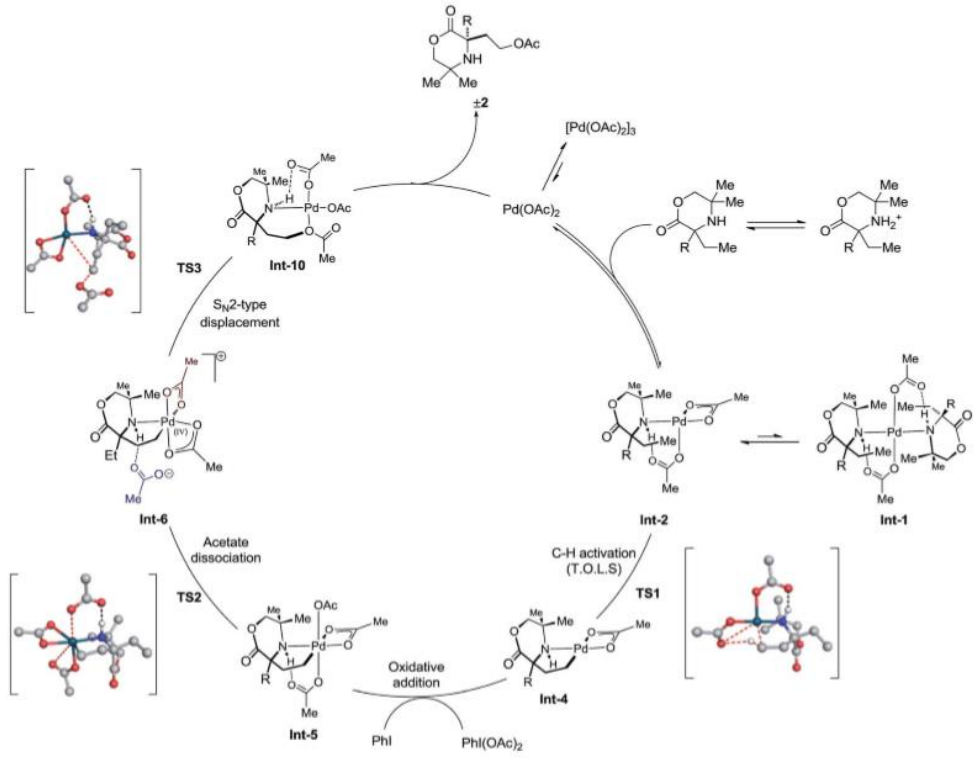


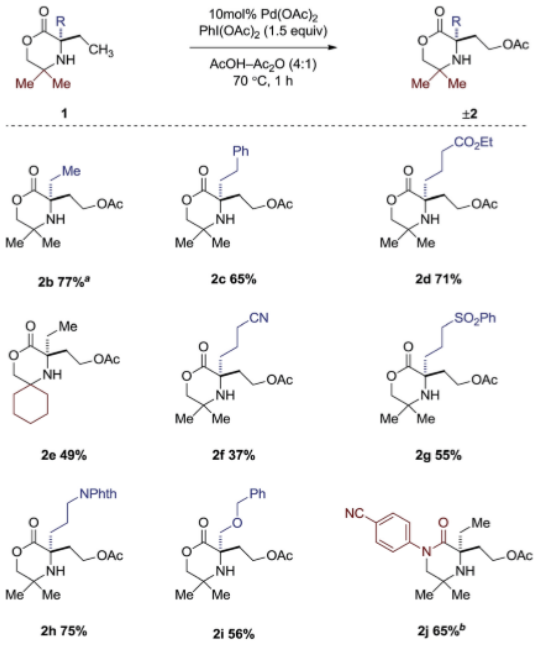
Fig. 4 Reductive elimination sequences for the C–O bond formation from Int-5.

Consolidation of the kinetic data with the DFT modeling allows a more complete mechanism to be proposed for the C(sp^3)–H acetoxylation (Scheme 4). The amine first coordinates to $Pd(OAc)_2$ formula to afford the mono-amine complex **Int-2**. This species is then capable of coordinating a further amine, to form the off-cycle bis-amine complex **Int-1**, or can undergo intramolecular γ-C–H activation to form the 5-membered cyclopalladated species **Int-4**, *via* **TS1**. This intermediate then undergoes oxidation by $PhI(OAc)_2$ to form γ-aminoalkyl-palladium(IV) species **Int-5**. Dissociation of an acetate ligand (**TS2**) precedes an S_N2-type displacement (**TS3**) from palladium(IV) species **Int-6** by the hydrogen-bonded acetate anion to generate the product ligated to $Pd(OAc)_2$, which upon decomplexation delivers the desired product **2** and regenerates $Pd(OAc)_2$ to renter the catalytic cycle.

Having gained a clearer understanding of the mechanism of the γ-C–H acetoxylation process, we briefly explored the scope of the new reaction. We found that simple alkyl substituents on the reacting side of the morpholinone scaffold were tolerated affording the corresponding acetoxylated products **2b–j** in good yield (Scheme 5). When di-ethylated compound **1b** was used,



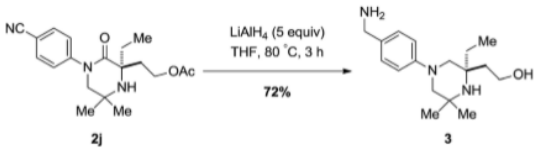
Scheme 4 Final elucidated catalytic cycle.



Scheme 5 Scope of acetoxylated morpholinones. [a] Isolated as a mixture of mono- and diacetoxylated products (1.6 : 1). [b] 15 mol% $Pd(OAc)_2$ in CH_2Cl_2–Ac_2O (4 : 1).

77% product as a 1.6 : 1 ratio of mono- to di-acetoxylated was observed. A range of functional groups were also tolerated in moderate to good yields such as esters (**2d**), sulfones (**2g**) and nitriles (**2f**), as well as protected alcohols (**2h**) and amines (**2i**). It is interesting to note that changing the *gem*-dimethyl groups on the non-reacting side for the spirocyclic cyclohexyl group affords only the mono-acetoxylated product (**2e**), albeit in 49% yield. Switching from the morpholinone scaffold to the piperazidinone scaffold (**1j**) required a slight modification of reaction conditions. It was found that when AcOH was used, a 1 : 1 mixture of mono- and di-acetoxylation was observed in 43% yield. However, a slight increase in catalyst loading, coupled with using dichloromethane as solvent, afforded the desired mono-acetoxylated product in 65% yield.

To highlight a simple application, piperazidinone **2j** could be reduced with lithium aluminium hydride afforded the corresponding piperazine bearing both a primary amine moiety and alcohol in 72% yield; heavily substituted piperazine scaffolds are difficult to form by other means (Scheme 6).[13]

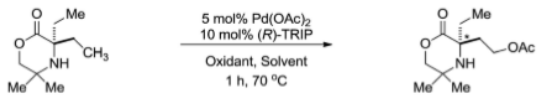


Scheme 6 Reduction of piperazidinone ±**2j**.

Finally, in light of the mechanistic studies conducted above, we investigated the potential for an asymmetric C–H acetoxylation process. We reasoned that with the C–H activation step being a part of the TOLS, that this should also be enantio-determining. From Int-2 in the catalytic cycle, we envisage that a chiral hydrogen bond acceptor ligand could induce asymmetry in the C–H activation step. Based on our work on asymmetric C–H amination to aziridines, we assessed a selection of chiral phosphoric acid ligands[14] under various reaction conditions (Table 2). We found that using the optimized $AcOH/Ac_2O$ solvent mixture lead to high yields, but racemic, product formation (entry 1). A solvent screen (entries 2–5) indicated that dichloromethane could be a suitable solvent for an enantioselective acetoxylation returning the product in 56% with 53 : 47 enantiomeric ratio (e.r.). Encouraged by this initial finding, we switched oxidant system to the I_2/AgOAc oxidant system[13] and found the desired product was obtained in 39% yield with 85 : 15 e.r. (entry 6). Using (*R*)-H_8-TRIP **2b** could be obtained in 33% yield, but with a decreased e.r. of 75 : 25. The results presented herein represent a rare example of catalytic enantioselective C(sp^3)–H acetoxylation and provide an exciting starting point for further development.

In summary, we have developed a palladium-catalyzed C–H acetoxylation of aliphatic amines using $PhI(OAc)_2$ as oxidant in $AcOH/Ac_2O$ solvent system. This process transforms readily available amine motifs into highly functionalized amino-alcohol derivatives. The mechanism of this C(sp^3)–H acetoxylation has been elucidated by detailed DFT and kinetic studies. These studies reveal the reaction proceeds *via* rate limiting C–H activation from the mono-amine complex. After oxidation of the 5-membered ring cyclopalladation complex, a dissociative ionization/S_N2-type reductive elimination sequence is responsible for the exclusive C(sp^3)–O bond formation product. Finally, nonracemic binol-phosphoric acid ligands were assessed for the induction of enantioselectivity in this transformation and an 85 : 15 e.r. was observed using (*R*)-TRIP and a modified oxidant system. We envisage this as a viable starting point for further development.

Table 2 Initial results towards an enantioselective C–H acetoxylation of morpholinones



Entry	Oxidant	Solvent	Yield (%)	e.r.
1	$PhI(OAc)_2$	$AcOH/Ac_2O$	70	50 : 50
2	$PhI(OAc)_2$	$MeNO_2$	42	50 : 50
3	$PhI(OAc)_2$	EtOAc	—	—
4	$PhI(OAc)_2$	1,2-DCE	—	—
5	$PhI(OAc)_2$	CH_2Cl_2	56	53 : 47
6	I_2/AgOAc	CH_2Cl_2	39	85 : 15
7	I_2/AgOAc	CH_2Cl_2	33	75 : 25

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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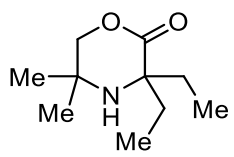
Appendix III. ^{1}H and ^{13}C NMR spectra



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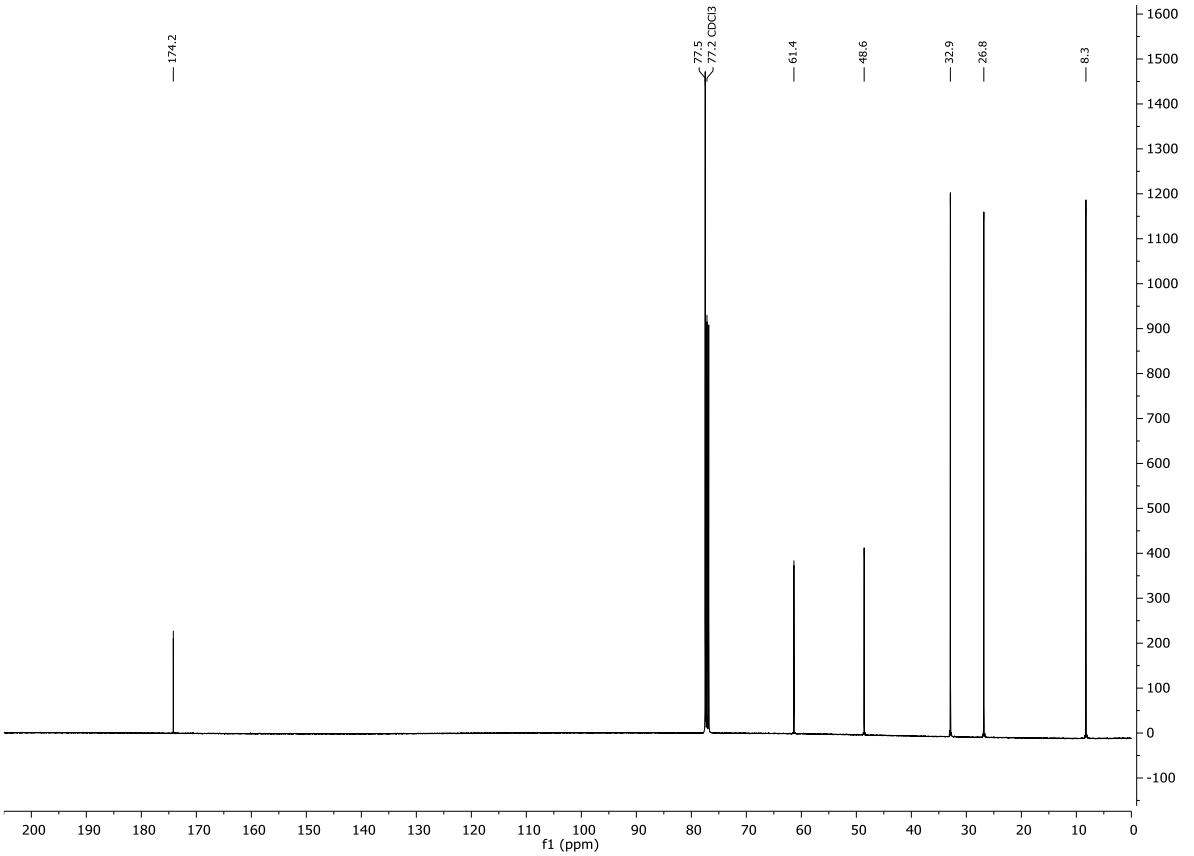

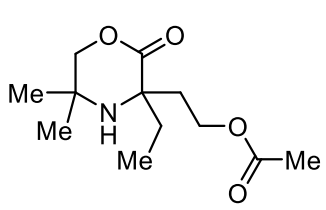
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7.26 CDCl3
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2.12
2.10
2.08
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1.70
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1.19
1.18
0.97
0.95
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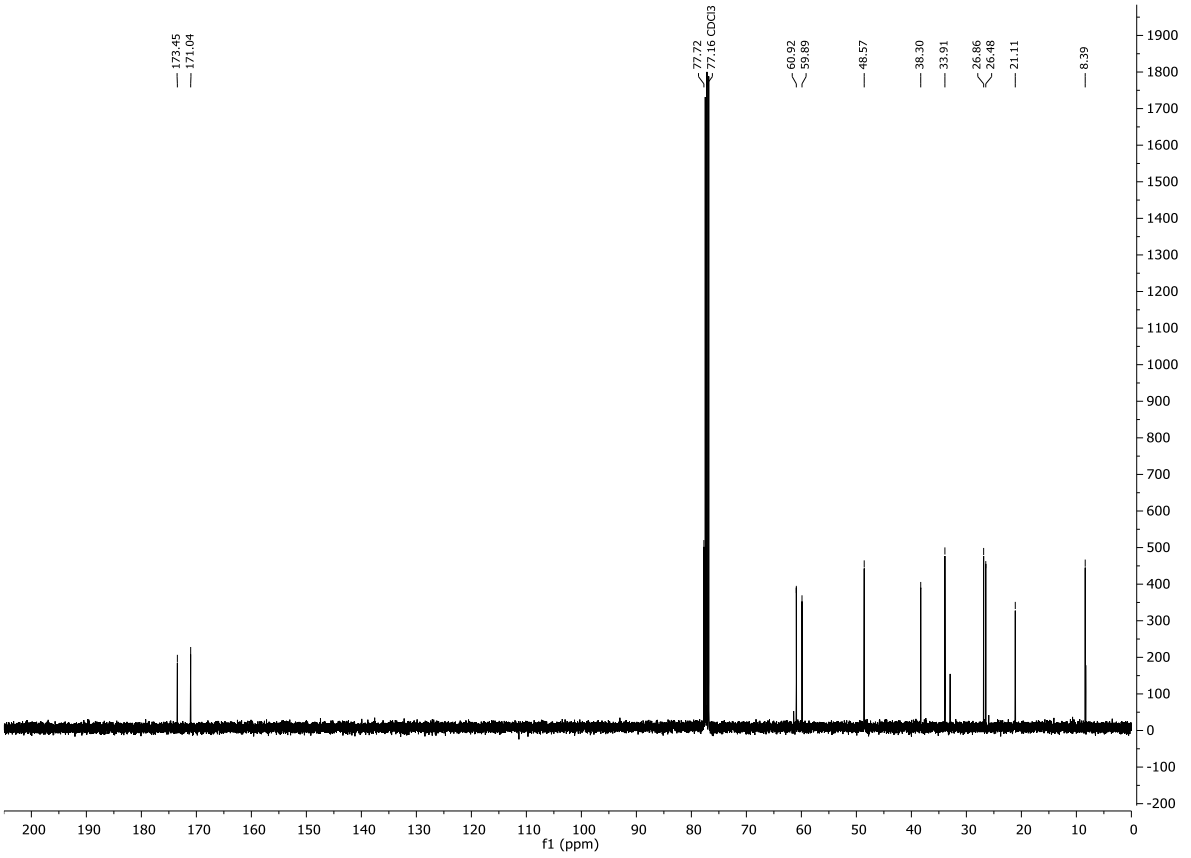
f1 (ppm)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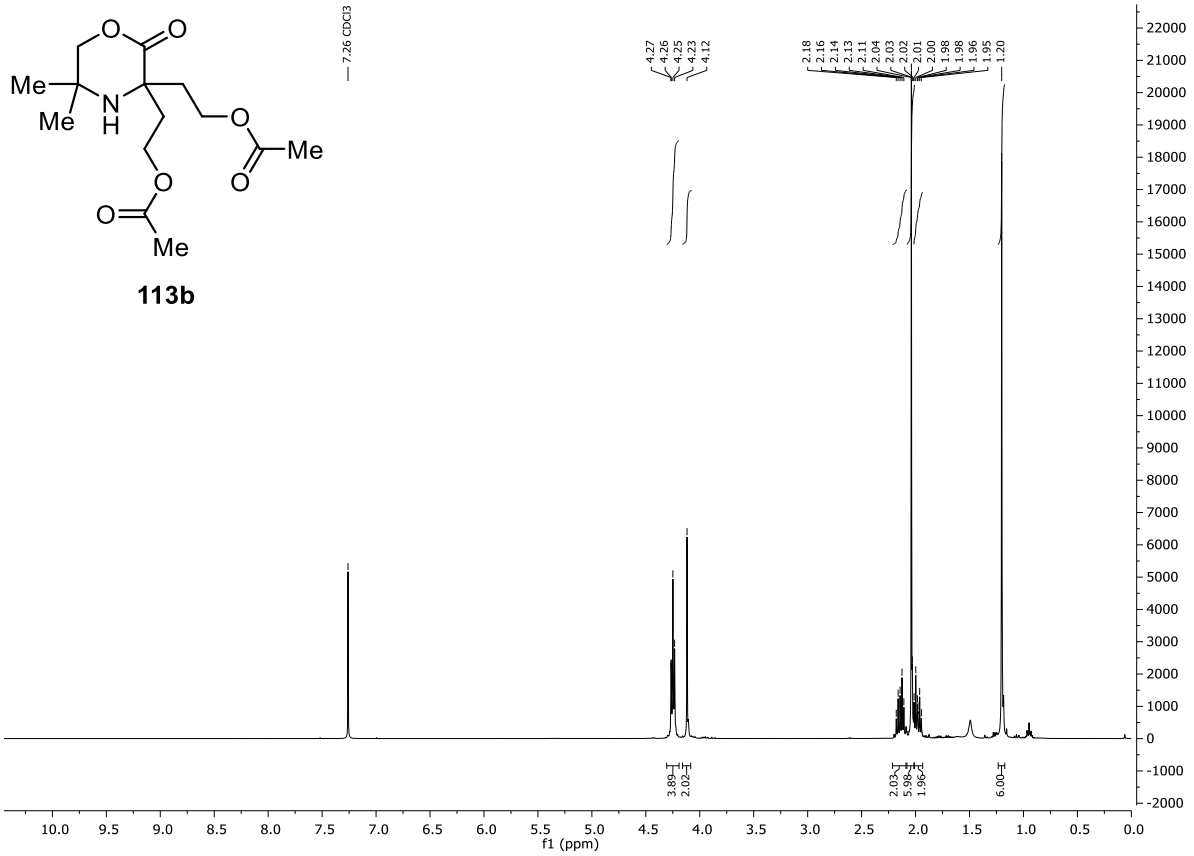
f1 (ppm)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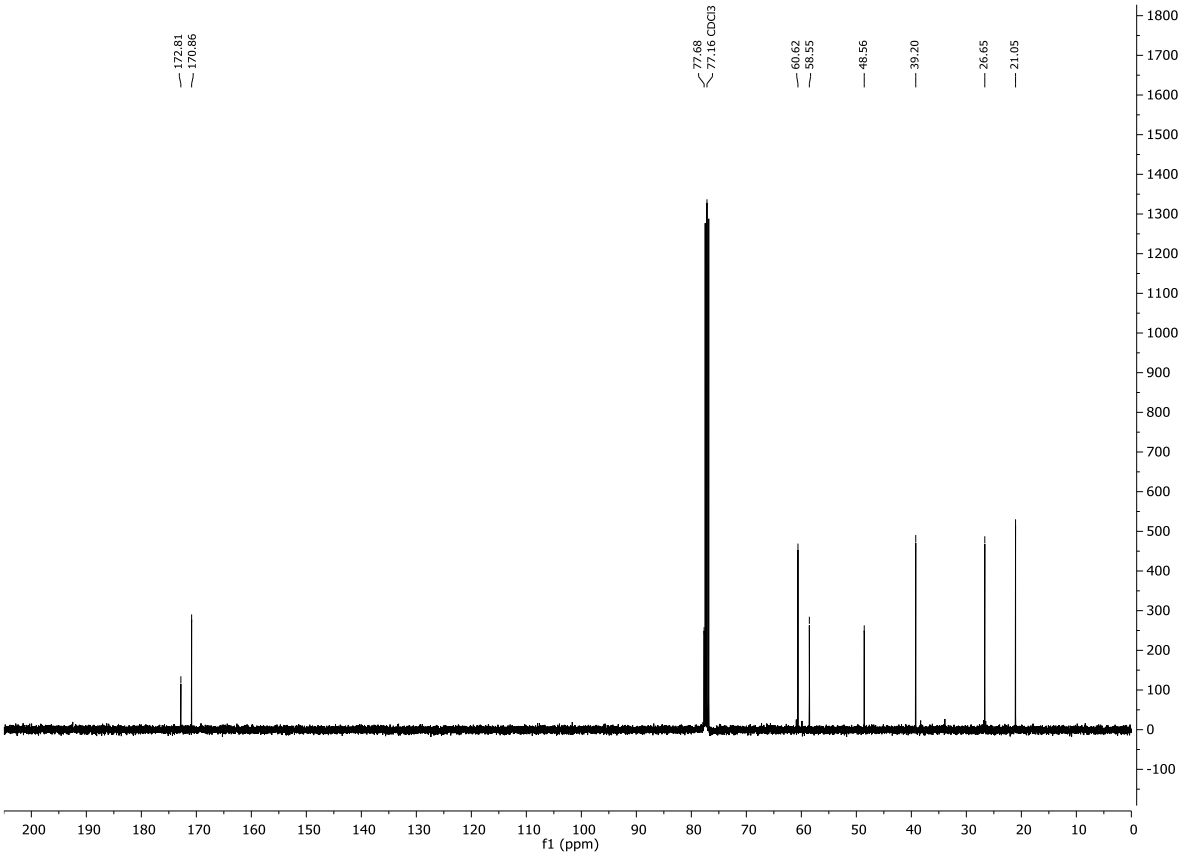
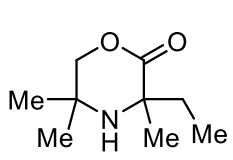
2.01
2.00
1.98
1.98
1.96
1.95
1.20
3.89
2.02
2.03
5.98
1.96
6.00
f1 (ppm)

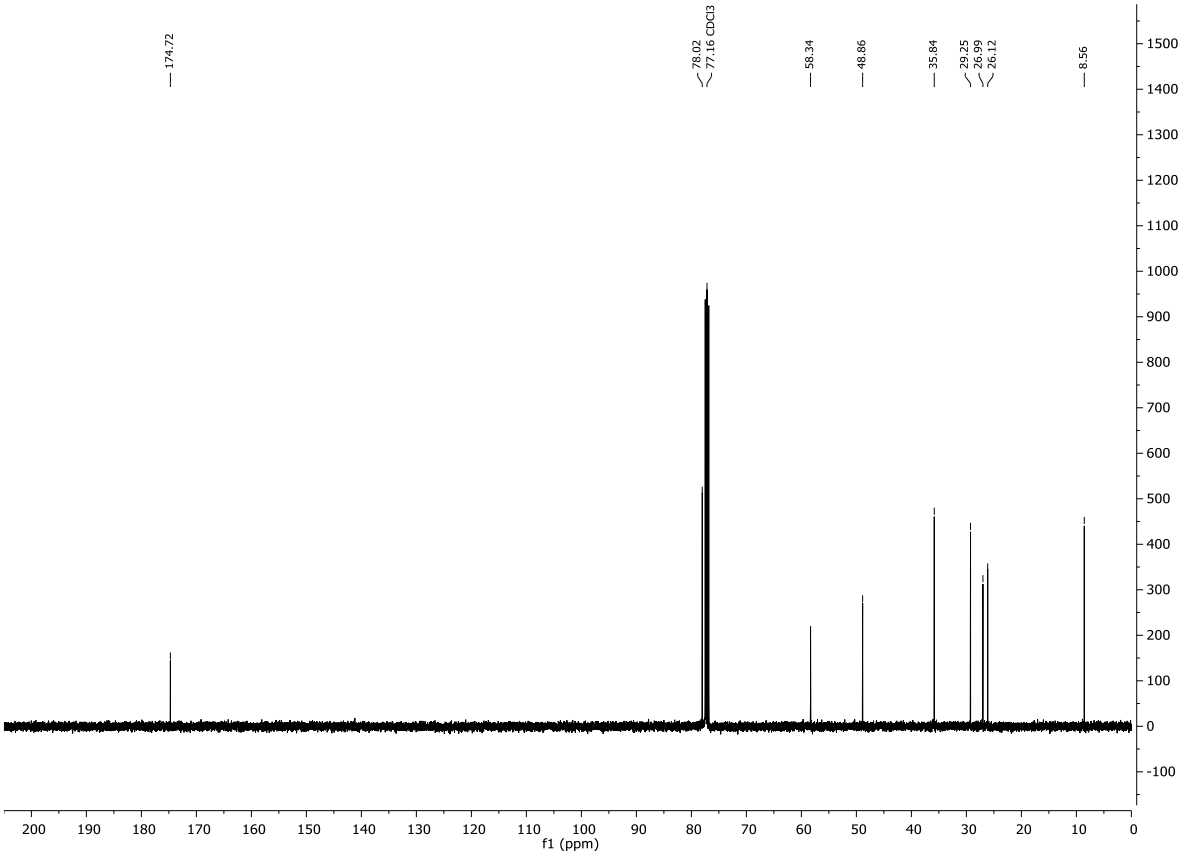
113b

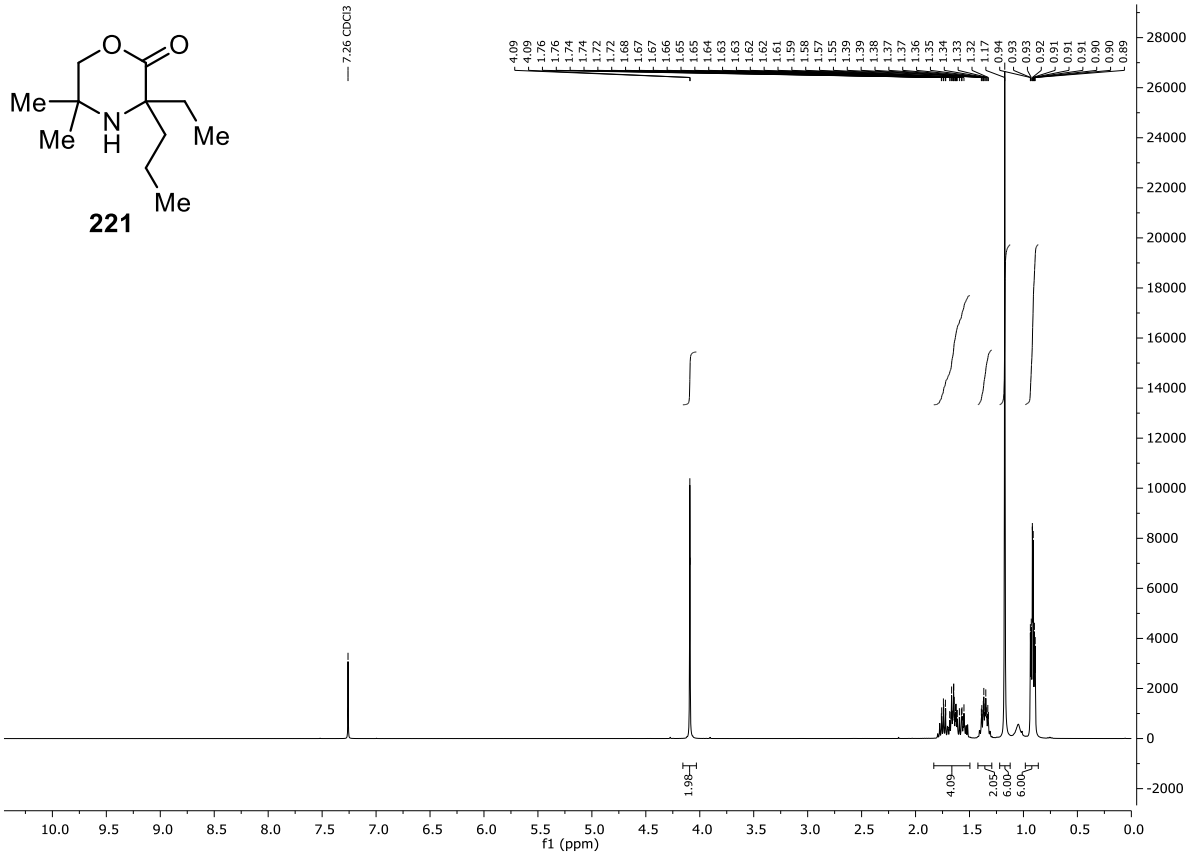

172.81
170.86
77.68
77.16 CDCl3
60.62
58.55
48.56
39.20
26.65
21.05
f1 (ppm)

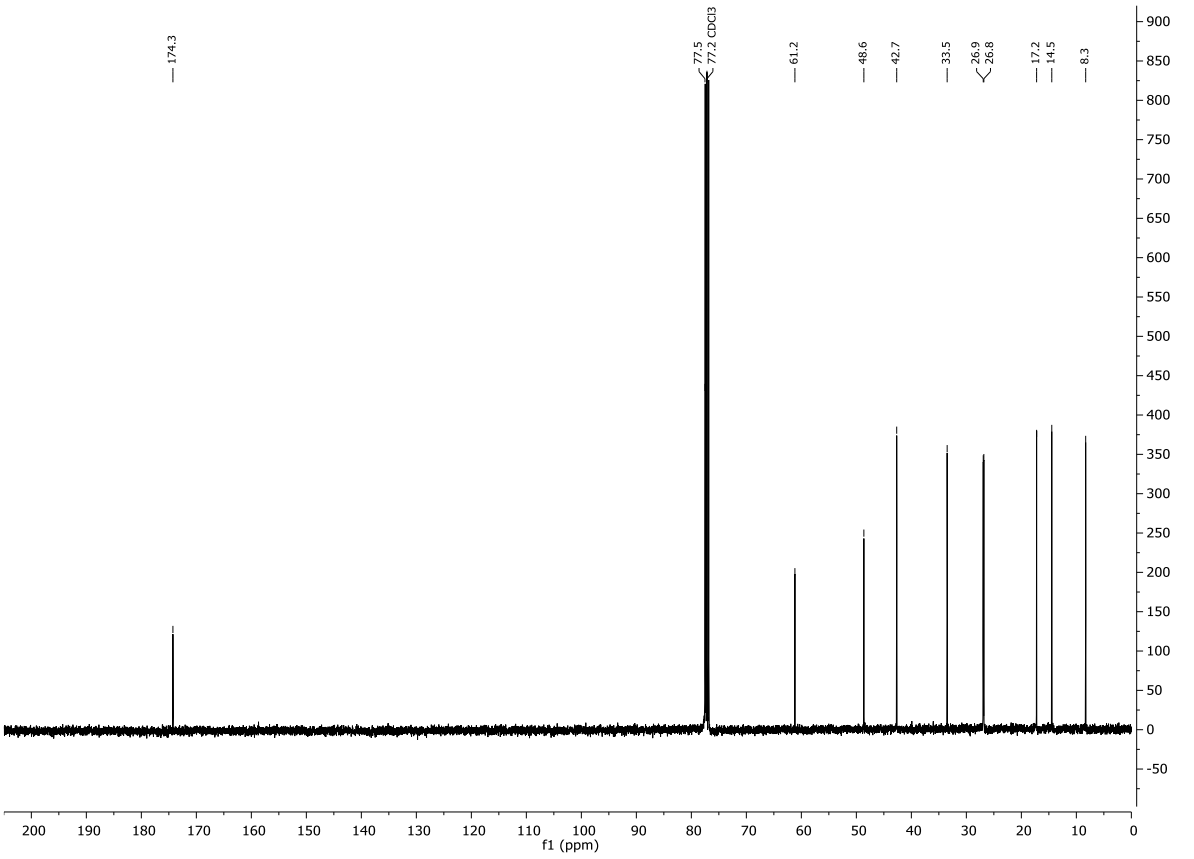

O
O
Me
N
H
Me
Me
Me

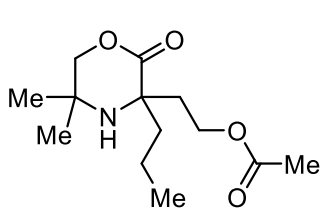
115

7.26 CDCl3
4.15
4.12
4.11
4.11
4.08
4.08
1.84
1.83
1.82
1.81
1.81
1.81
1.80
1.79
1.79
1.77
1.77
1.75
1.75
1.61
1.59
1.58
1.57
1.56
1.56
1.54
1.52
1.39
1.39
1.24
1.14
0.97
0.97
0.95
0.95
0.93
0.93
2.00
1.02
1.07
3.08
3.05
3.25
3.04
f1 (ppm)


174.72
78.02
77.16 CDCl3
58.34
48.86
35.84
29.25
26.99
26.12
8.56
f1 (ppm)

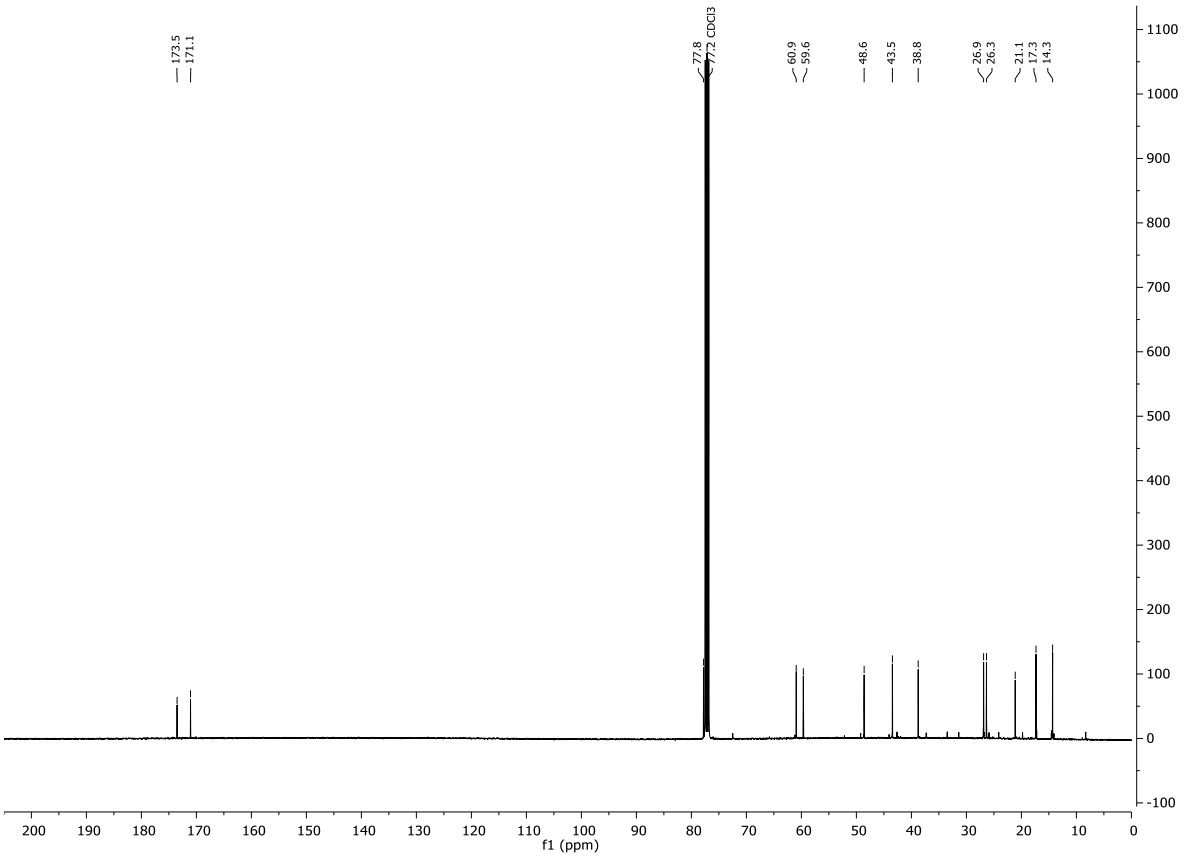

7.26 CDCl3
4.09
4.09
1.76
1.76
1.74
1.74
1.72
1.72
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.63
1.63
1.62
1.62
1.61
1.59
1.58
1.57
1.55
1.39
1.39
1.38
1.37
1.37
1.36
1.35
1.34
1.33
1.32
1.17
0.94
0.93
0.93
0.92
0.91
0.91
0.91
0.90
0.90
0.90
0.89
1.98
4.09
2.05
6.00
6.00
f1 (ppm)

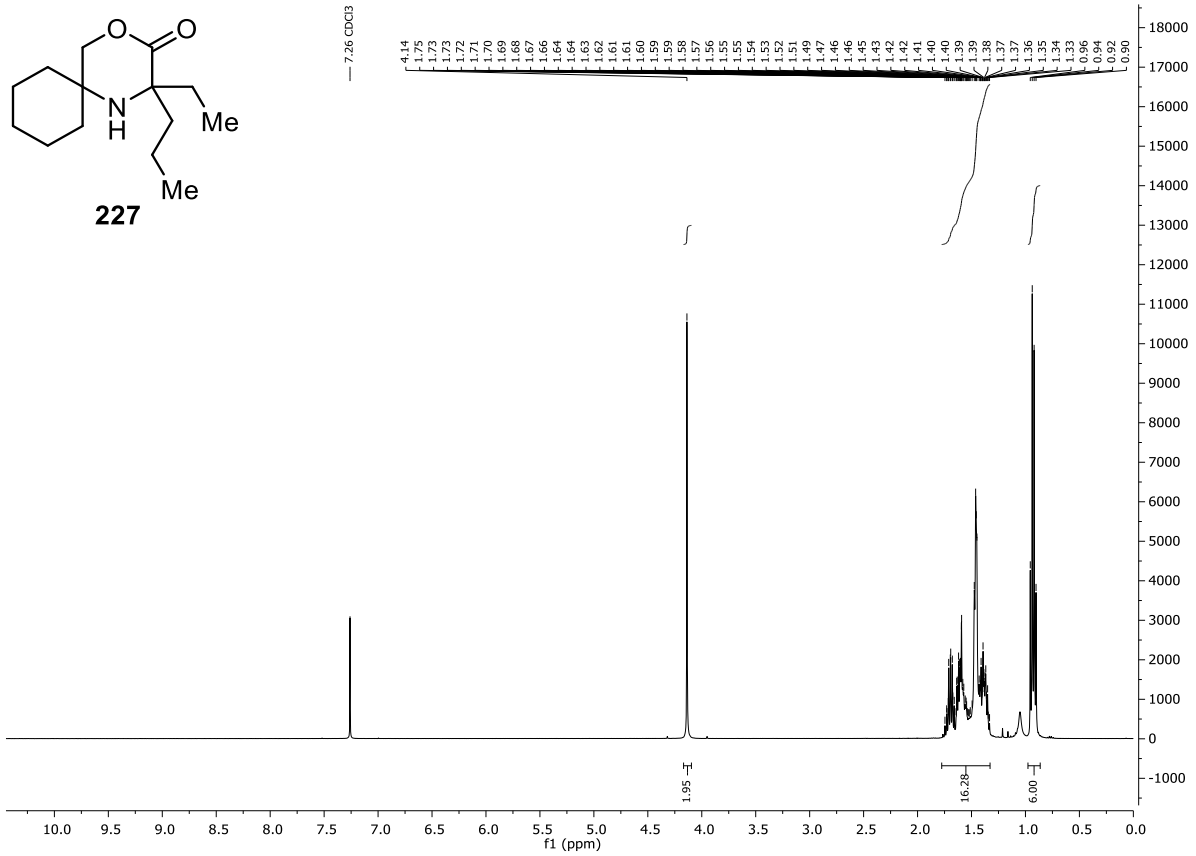

174.3
77.5
77.2 CDCl3
61.2
48.6
42.7
33.5
26.9
26.8
17.2
14.5
8.3
f1 (ppm)

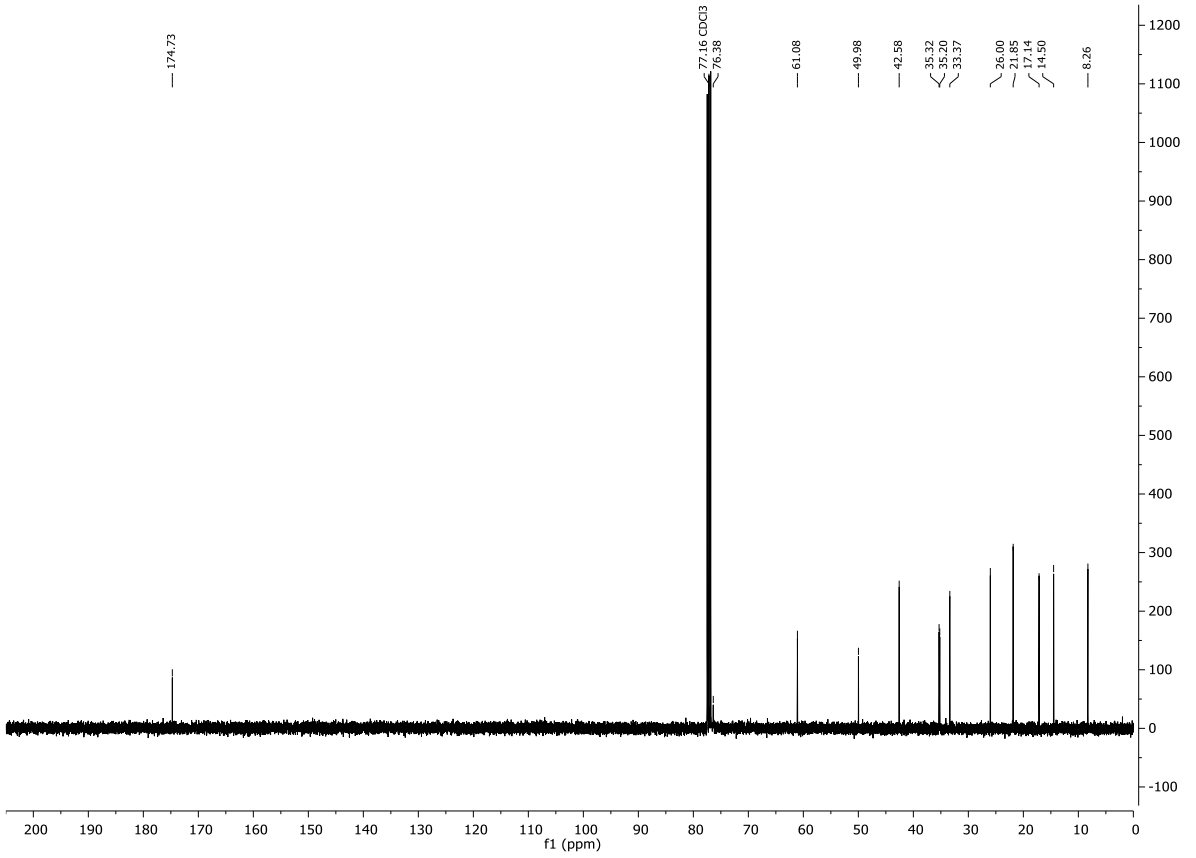

O
O
Me
Me
N
H
O
Me
O
Me

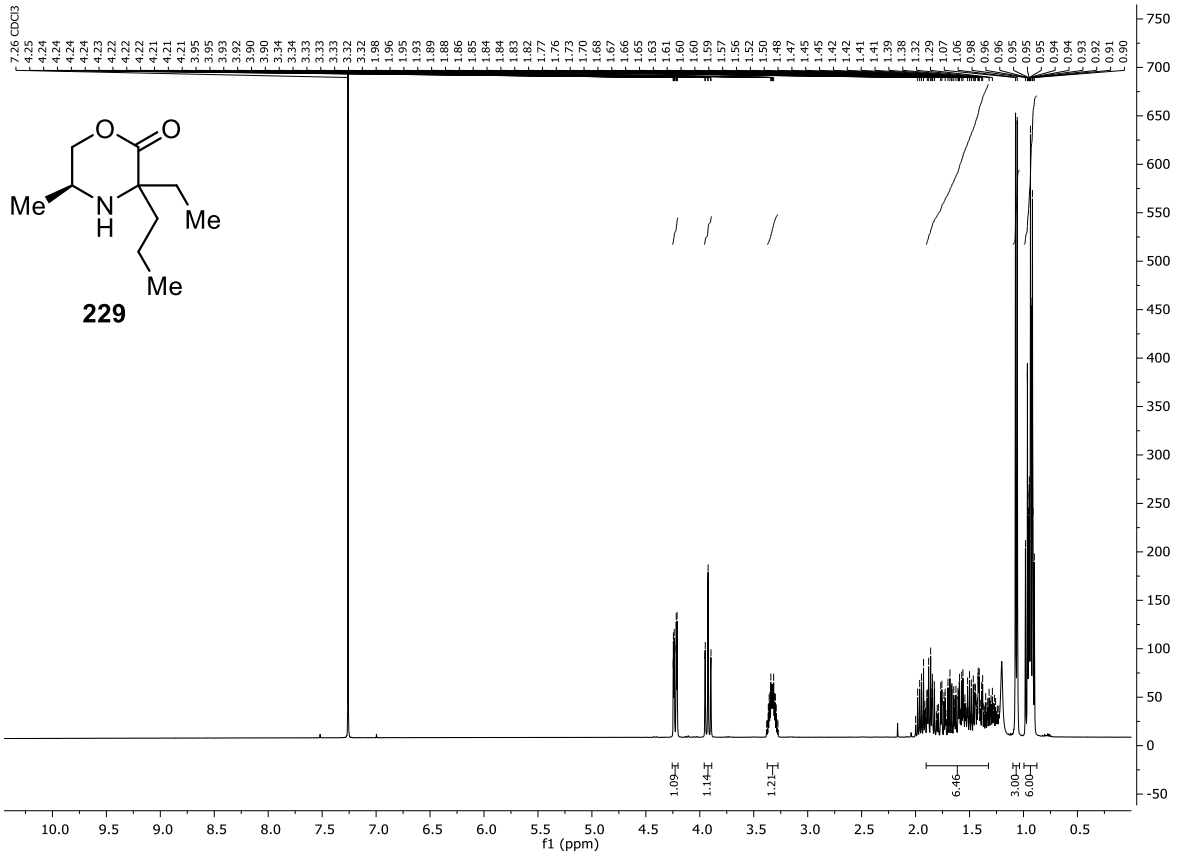
225

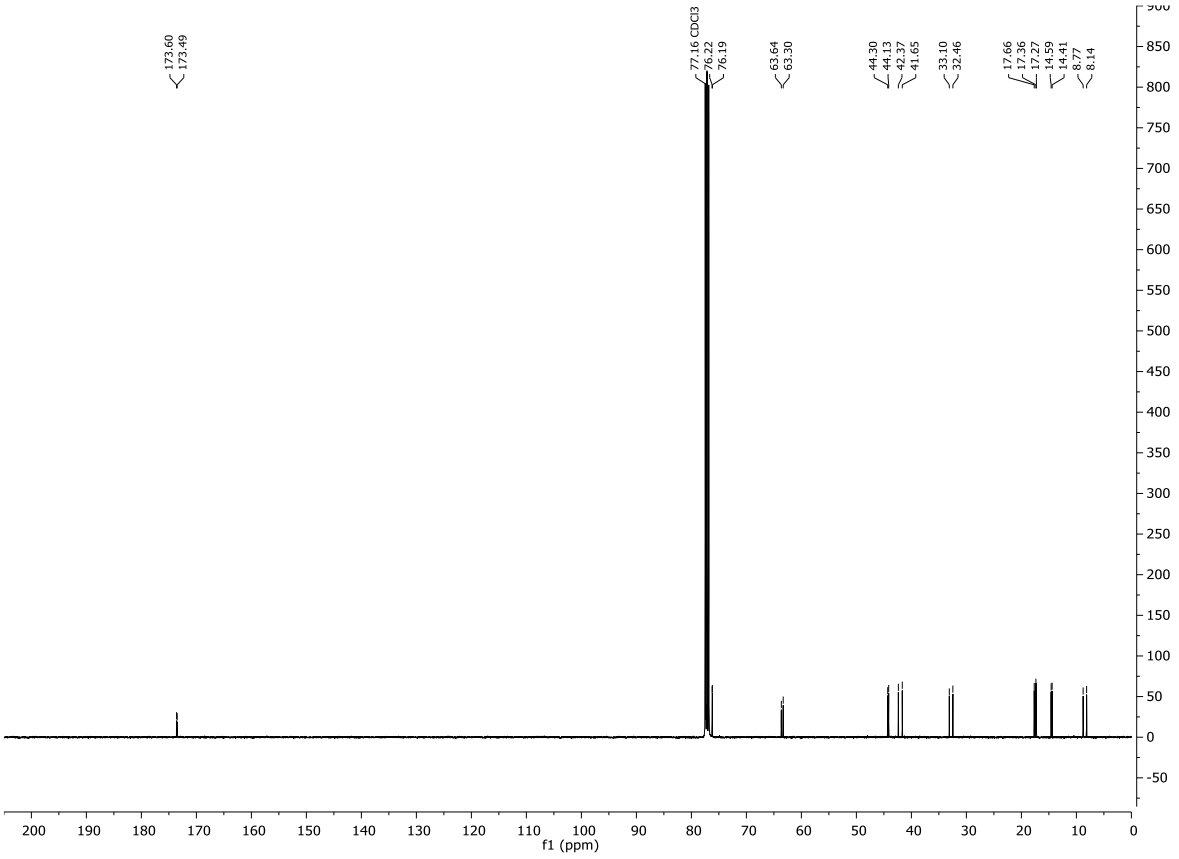
7.26 CDCl3
4.26
4.24
4.22
4.11
4.10
2.12
2.10
2.08
2.08
2.08
2.07
2.03
1.98
1.96
1.95
1.94
1.93
1.75
1.74
1.72
1.72
1.71
1.70
1.69
1.67
1.65
1.64
1.62
1.62
1.61
1.60
1.59
1.58
1.41
1.40
1.40
1.39
1.39
1.39
1.38
1.38
1.37
1.37
1.36
1.36
1.35
1.34
1.34
1.33
1.33
1.31
1.19
1.18
0.94
0.92
0.90
1.92
2.00
1.05
3.04
1.02
2.20
2.11
6.05
3.35
f1 (ppm)

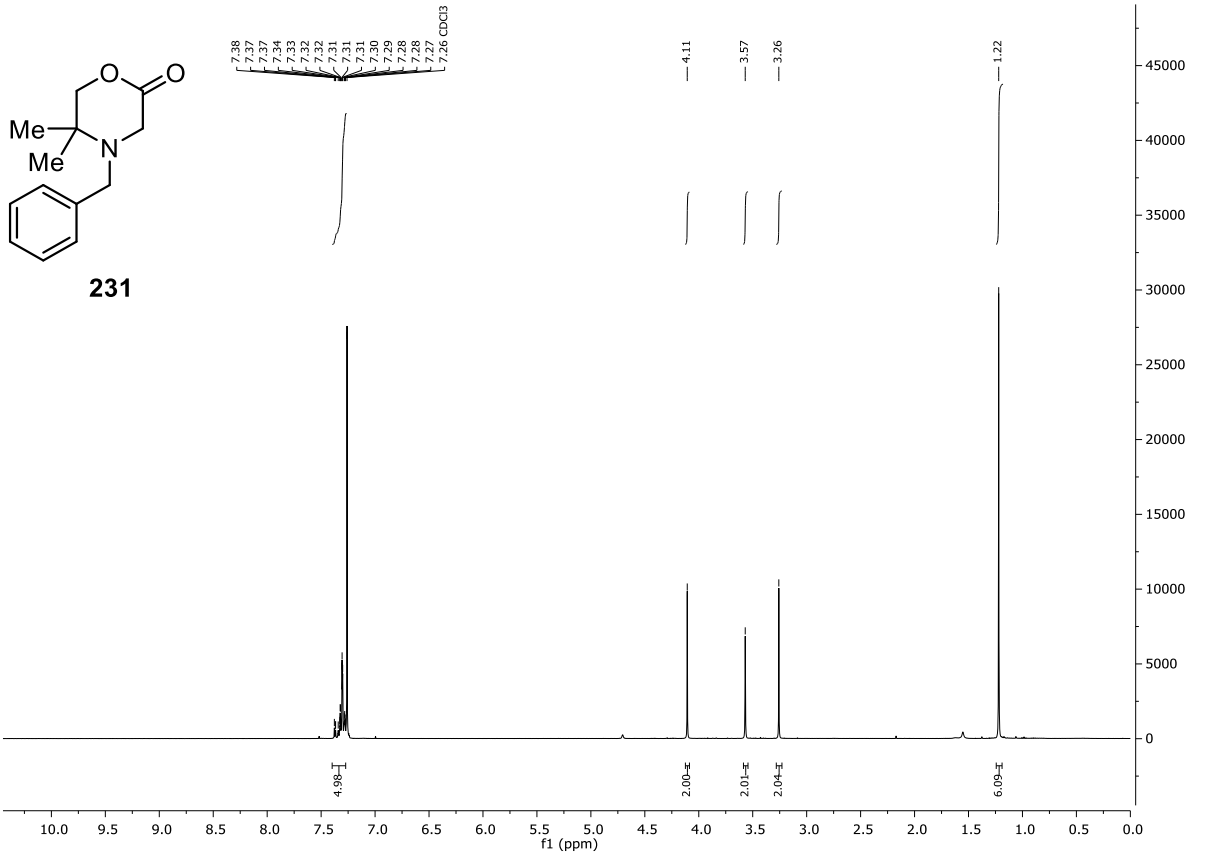

173.5
171.1
77.8
77.2 CDCl3
60.9
59.6
48.6
43.5
38.8
26.9
26.3
21.1
17.3
14.3
f1 (ppm)

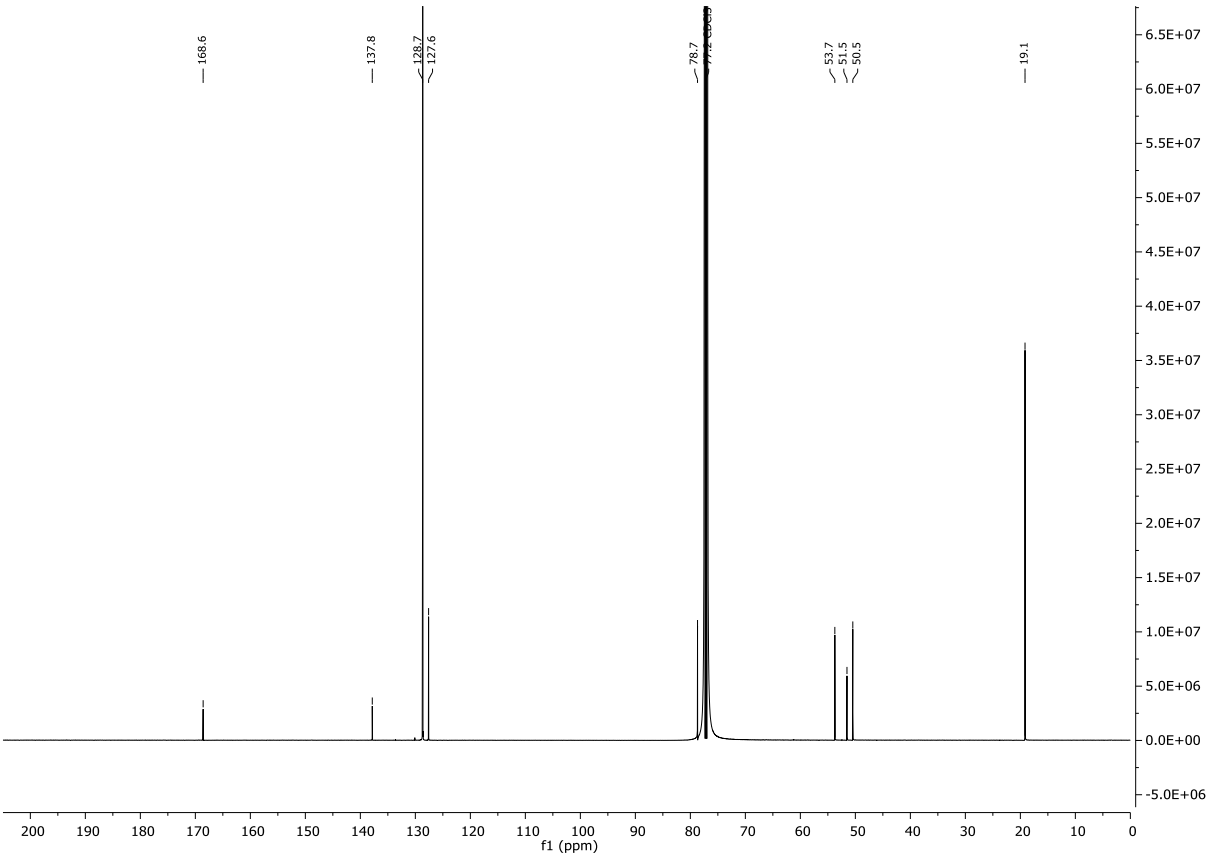

O
O
N
H
Me
Me
227
7.26 CDCl3
1.95
16.28
6.00
f1 (ppm)

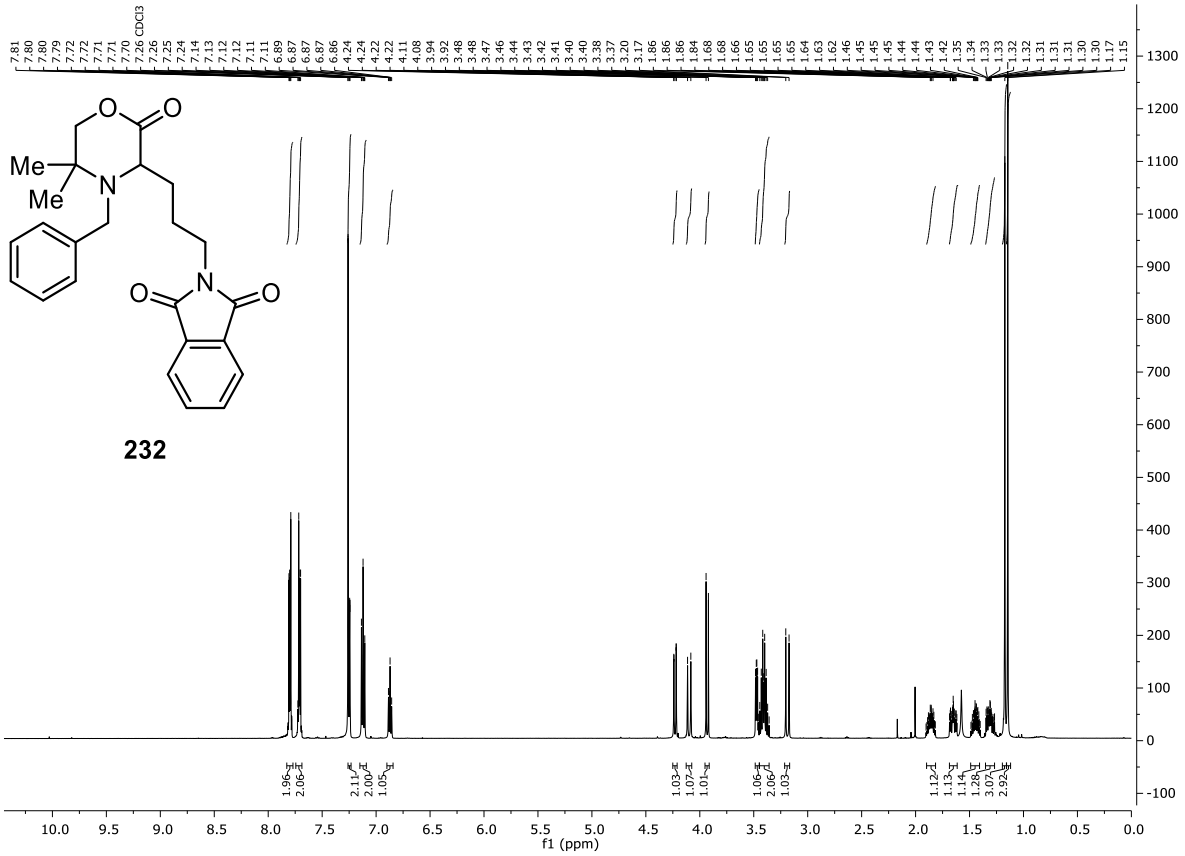

174.73
77.16 CDCl3
76.38
61.08
49.98
42.58
35.32
35.20
33.37
26.00
21.85
17.14
14.50
8.26
f1 (ppm)

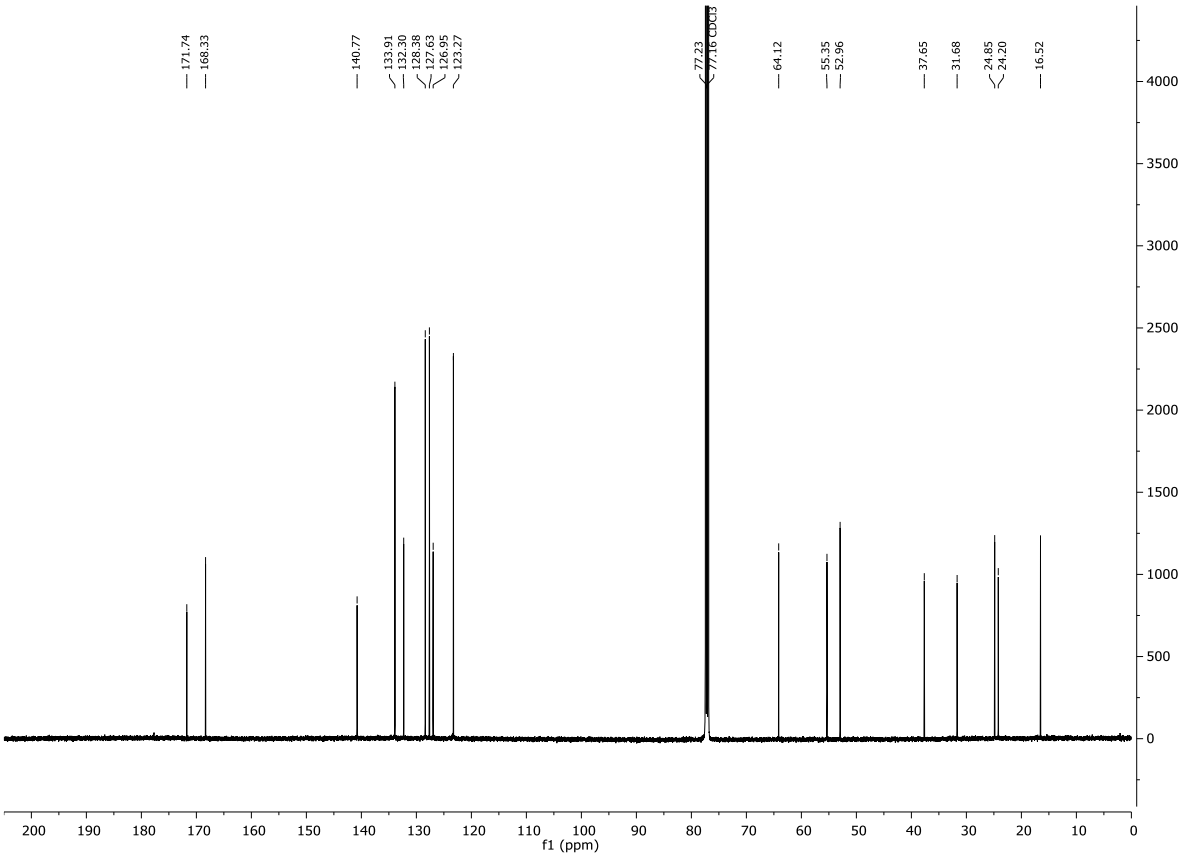

7.26 CDCl3
O
O
Me
N
H
Me
Me
229
1.09
1.14
1.21
6.46
3.00
6.00
f1 (ppm)

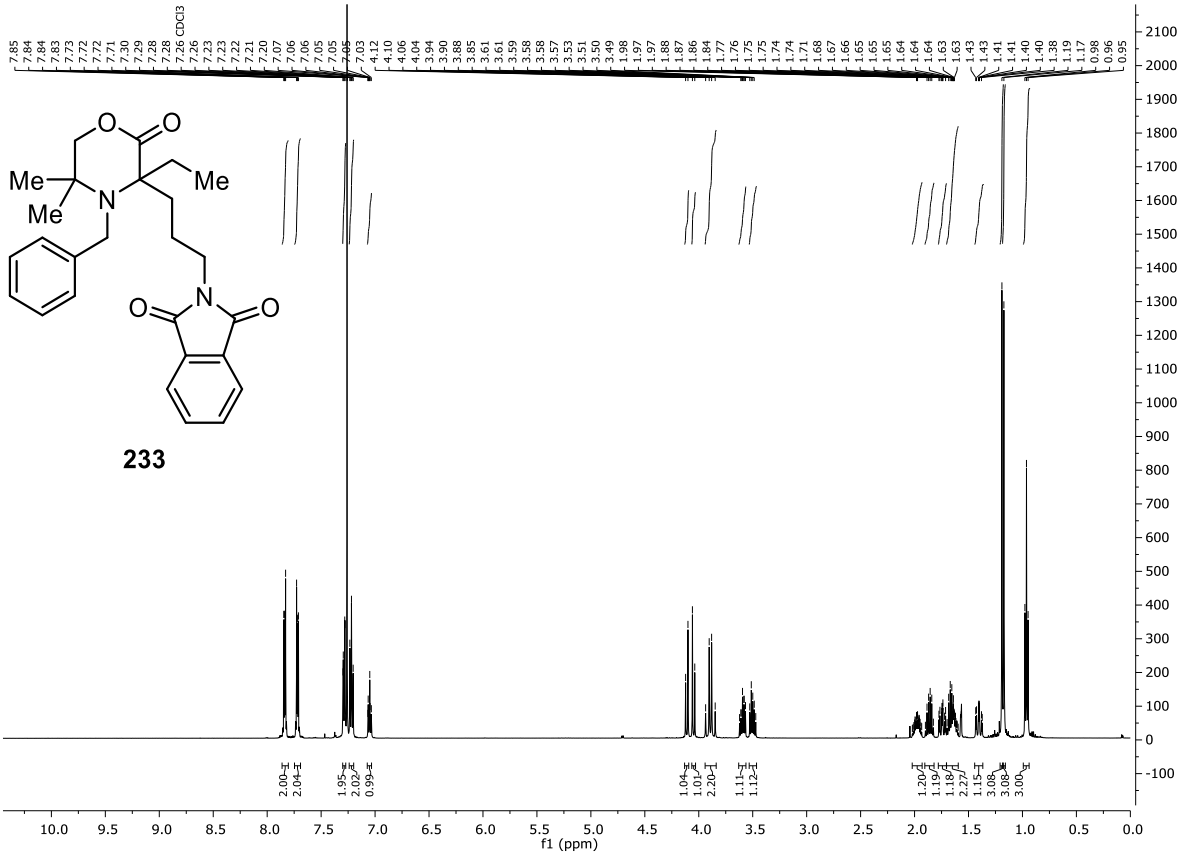

173.60
173.49
77.16 CDCl3
76.22
76.19
63.64
63.30
44.30
44.13
42.37
41.65
33.10
32.46
17.66
17.36
17.27
14.59
14.41
8.77
8.14
f1 (ppm)

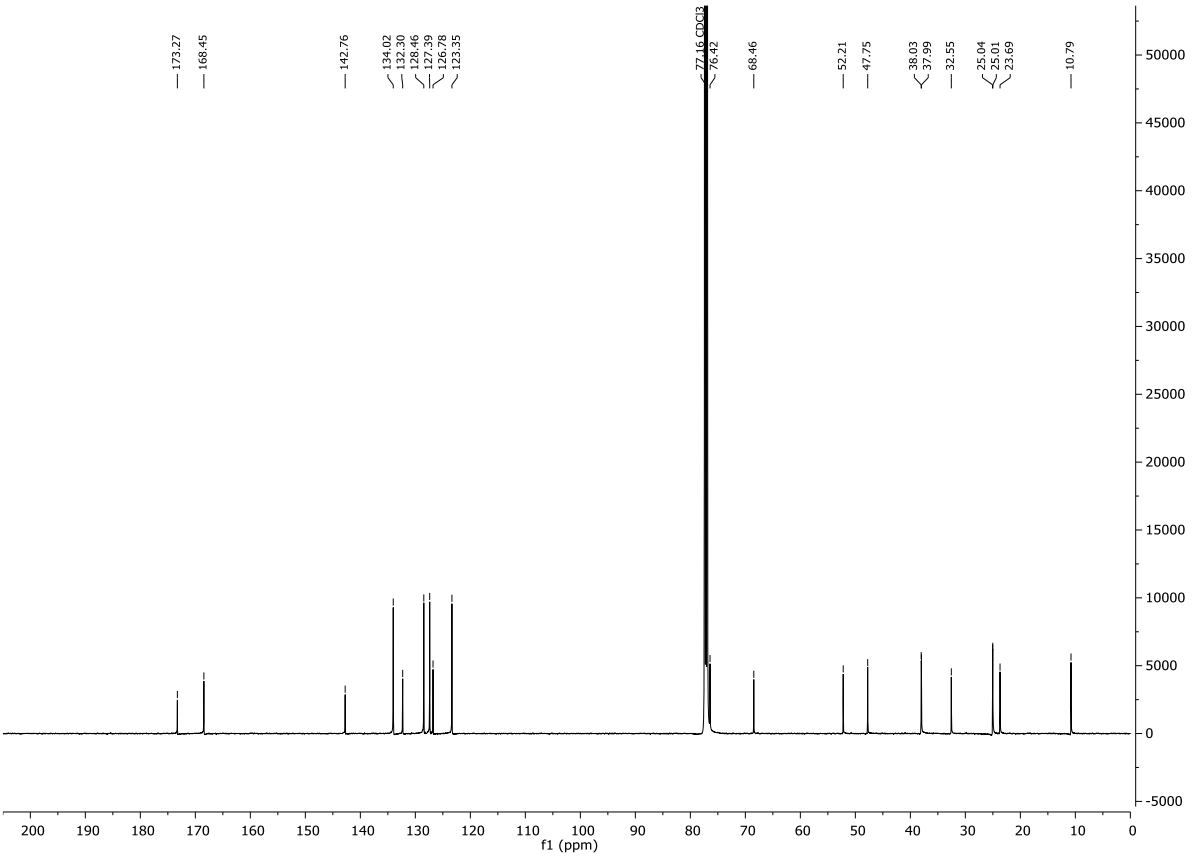

Me
Me
N
O
O
231
7.38
7.37
7.37
7.34
7.33
7.32
7.32
7.31
7.31
7.31
7.30
7.29
7.28
7.28
7.27
7.26 CDCl3
4.11
3.57
3.26
1.22
4.98
2.00
2.01
2.04
6.09
f1 (ppm)

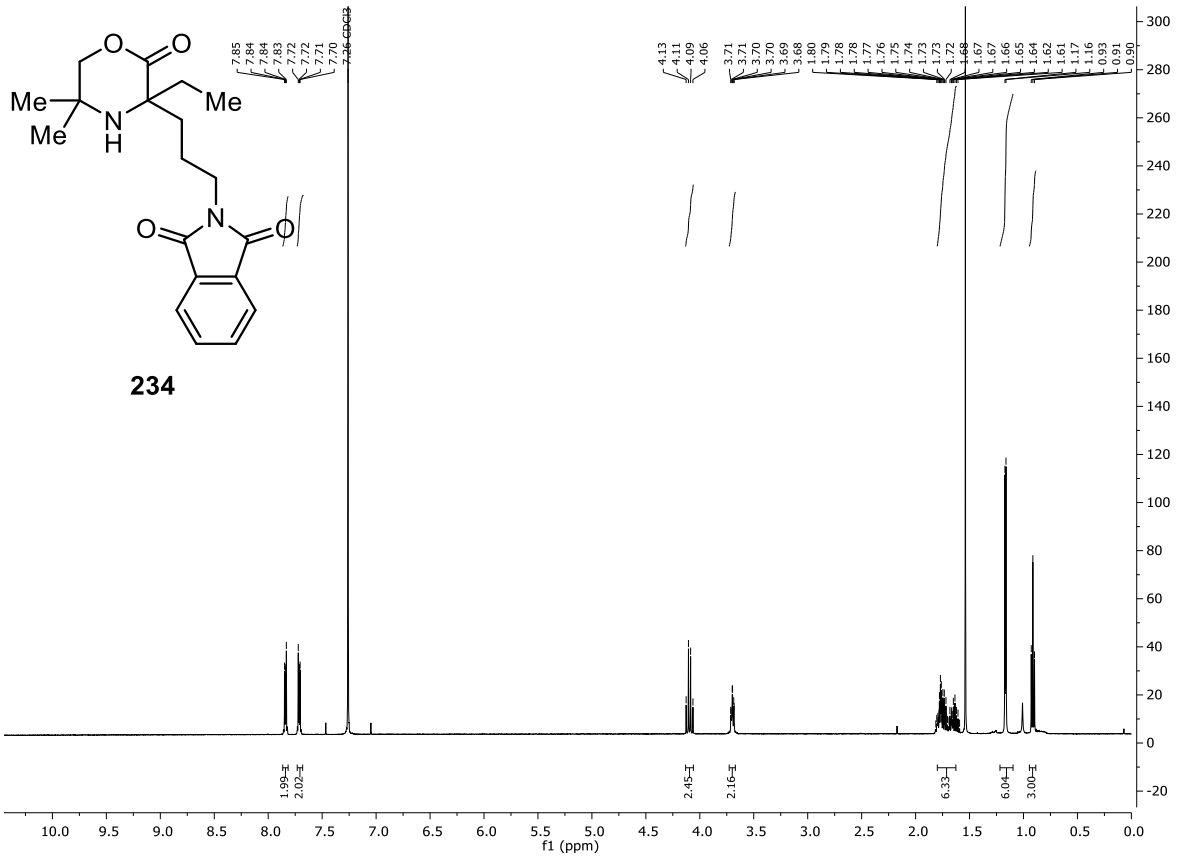

168.6
137.8
128.7
127.6
78.7
77.2 CDCl3
53.7
51.5
50.5
19.1
f1 (ppm)


CDCl3
Me
Me
N
O
O
N
O
O
232
f1 (ppm)

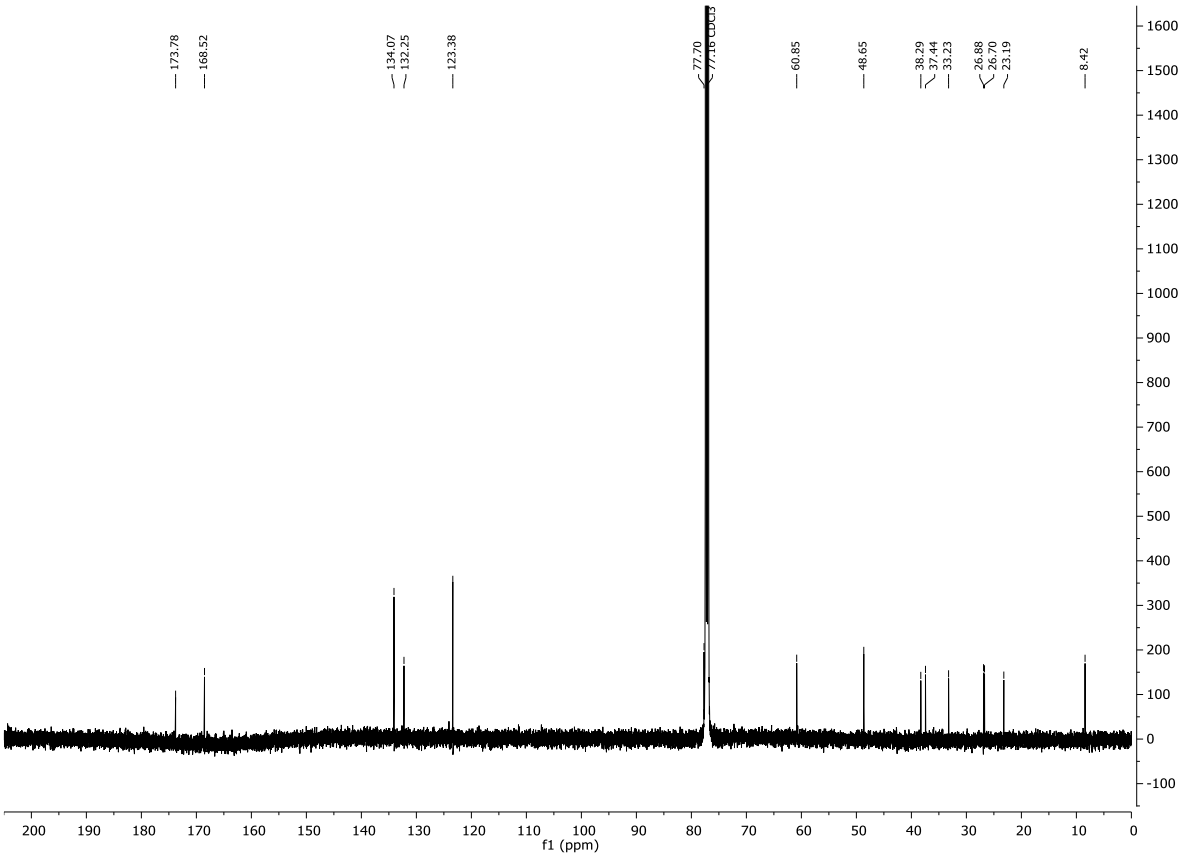

171.74
168.33
140.77
133.91
132.30
128.38
127.63
126.95
123.27
77.23
77.16 CDCl3
64.12
55.35
52.96
37.65
31.68
24.85
24.20
16.52
f1 (ppm)

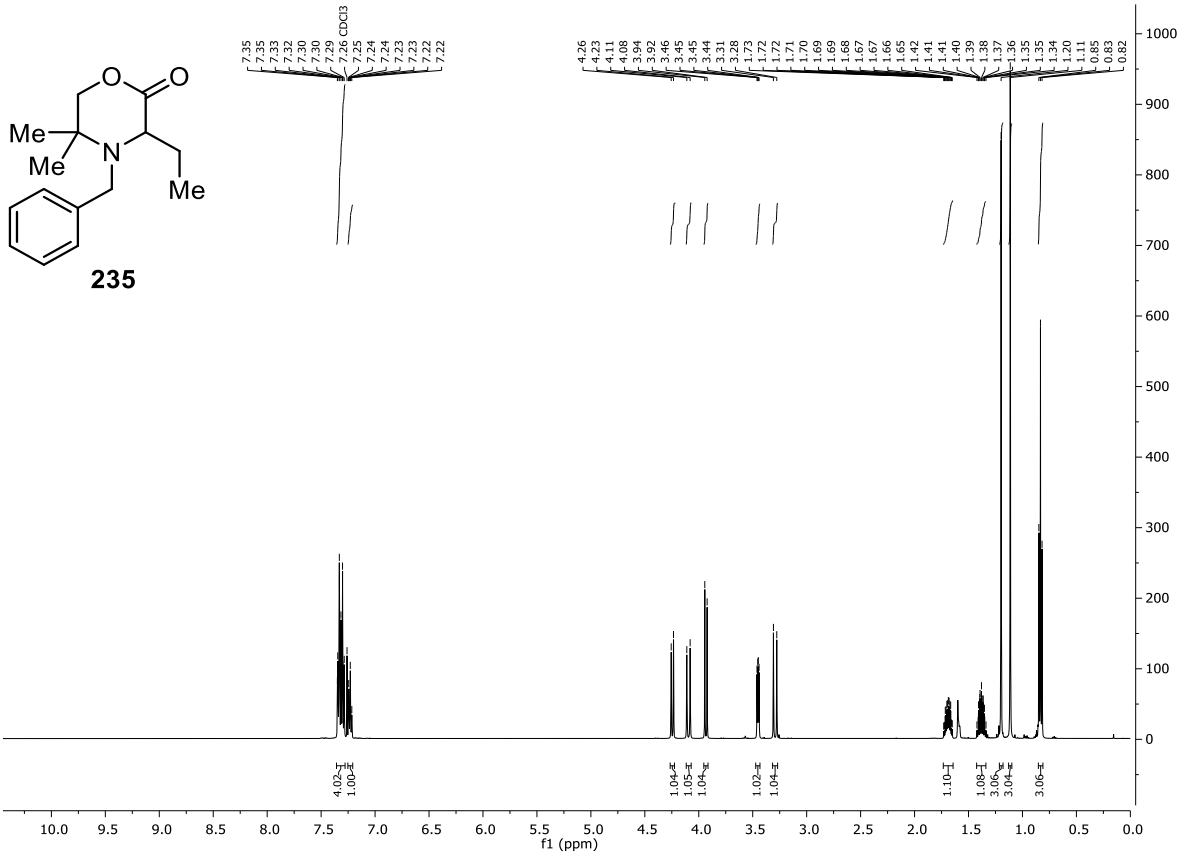

Me
Me
Me
N
O
O
N
O
O
233
f1 (ppm)

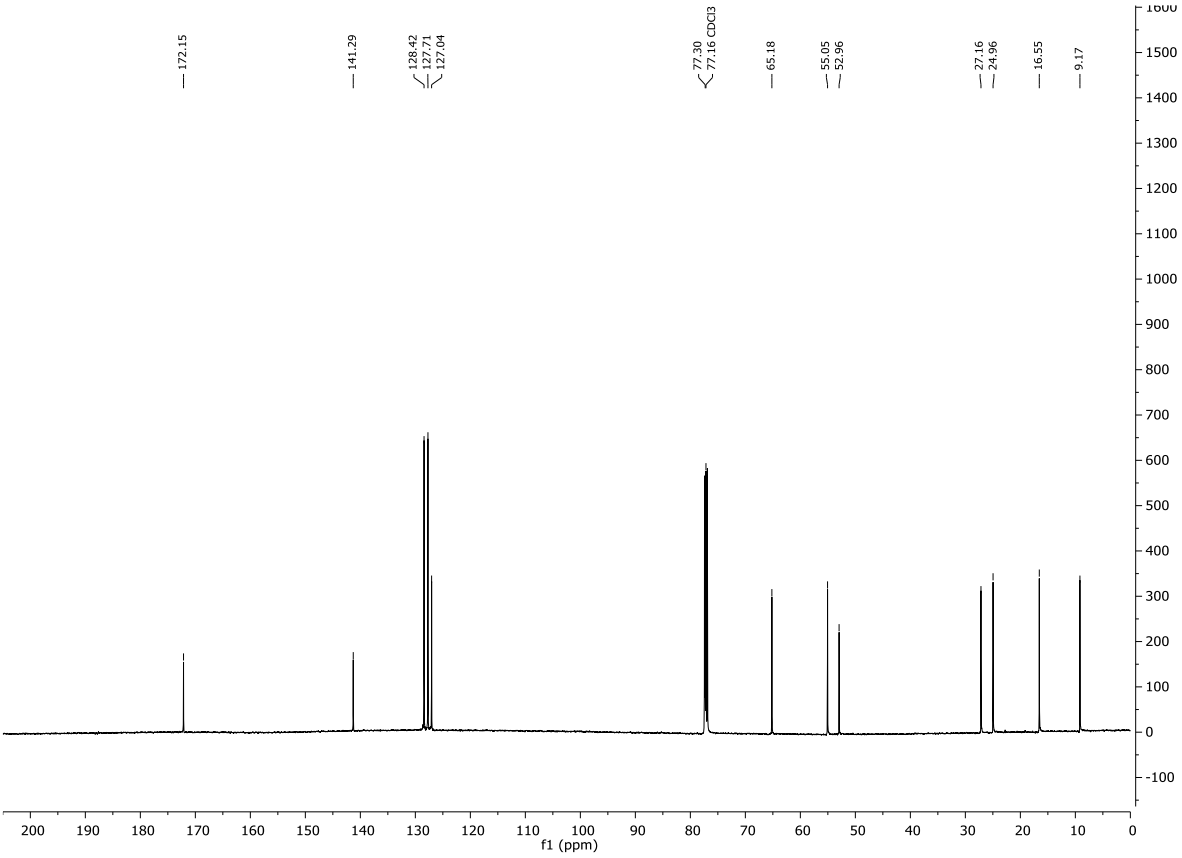

173.27
168.45
142.76
134.02
132.30
128.46
127.39
126.78
123.35
77.16 CDCl3
76.42
68.46
52.21
47.75
38.03
37.99
32.55
25.04
25.01
23.69
10.79
f1 (ppm)

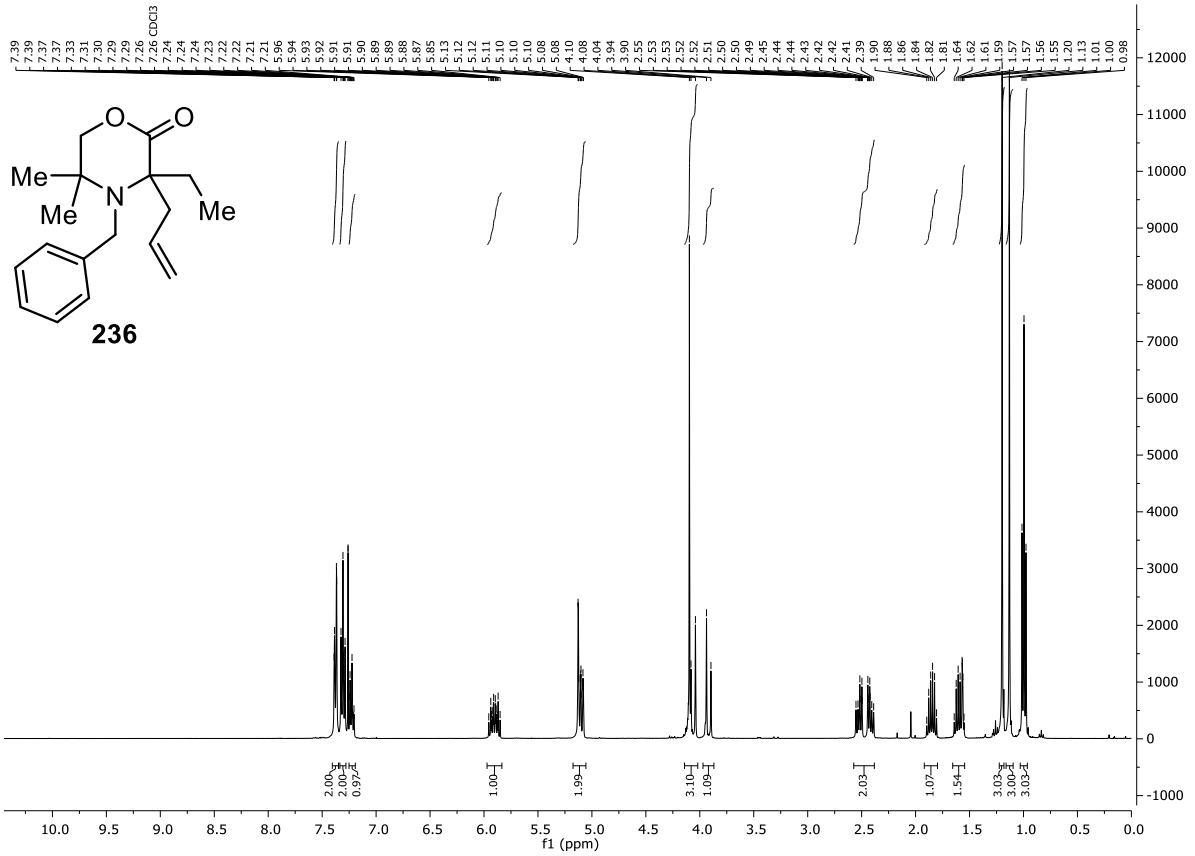

7.85
7.84
7.84
7.83
7.72
7.72
7.71
7.70
7.26 CDCl3
4.13
4.11
4.09
4.06
3.71
3.71
3.70
3.70
3.69
3.68
1.80
1.79
1.78
1.78
1.77
1.76
1.75
1.74
1.73
1.73
1.72
1.68
1.67
1.67
1.66
1.65
1.64
1.62
1.61
1.17
1.16
0.93
0.91
0.90
1.99
2.02
2.45
2.16
6.33
6.04
3.00
f1 (ppm)

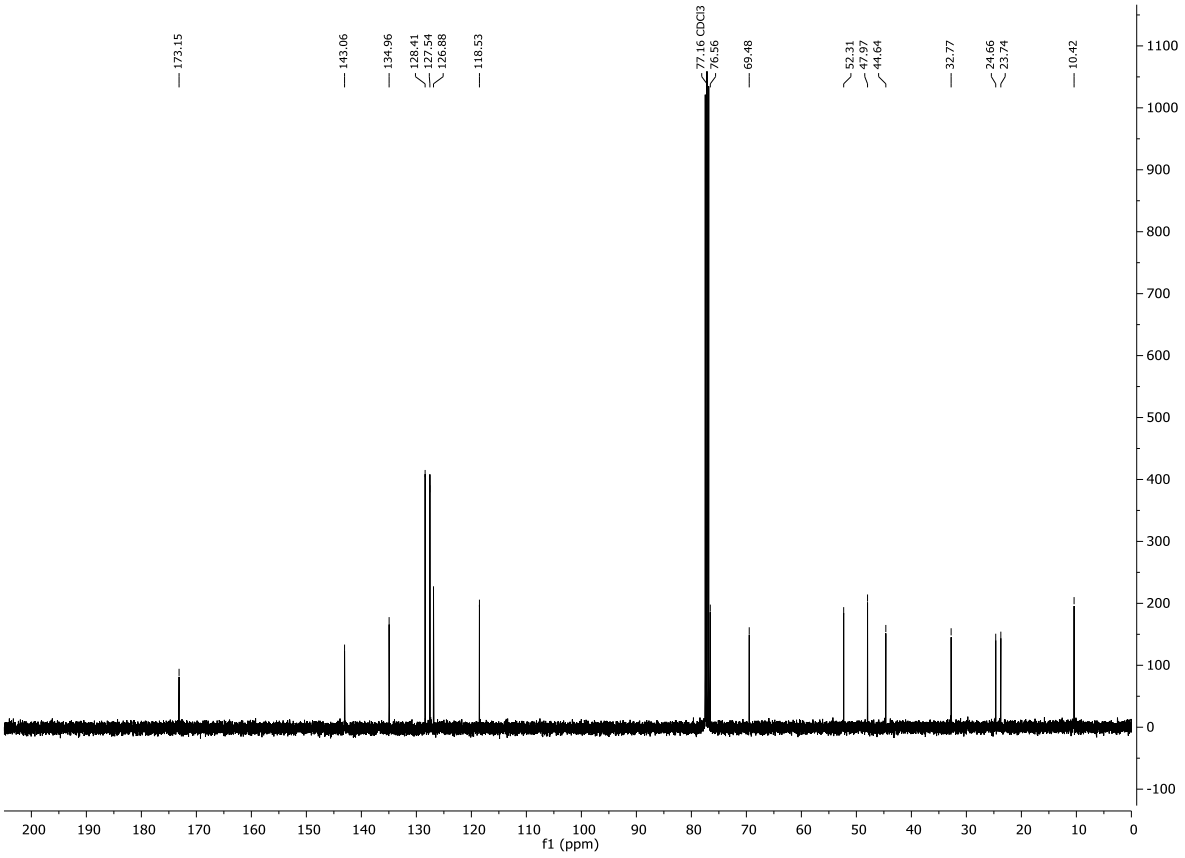
234

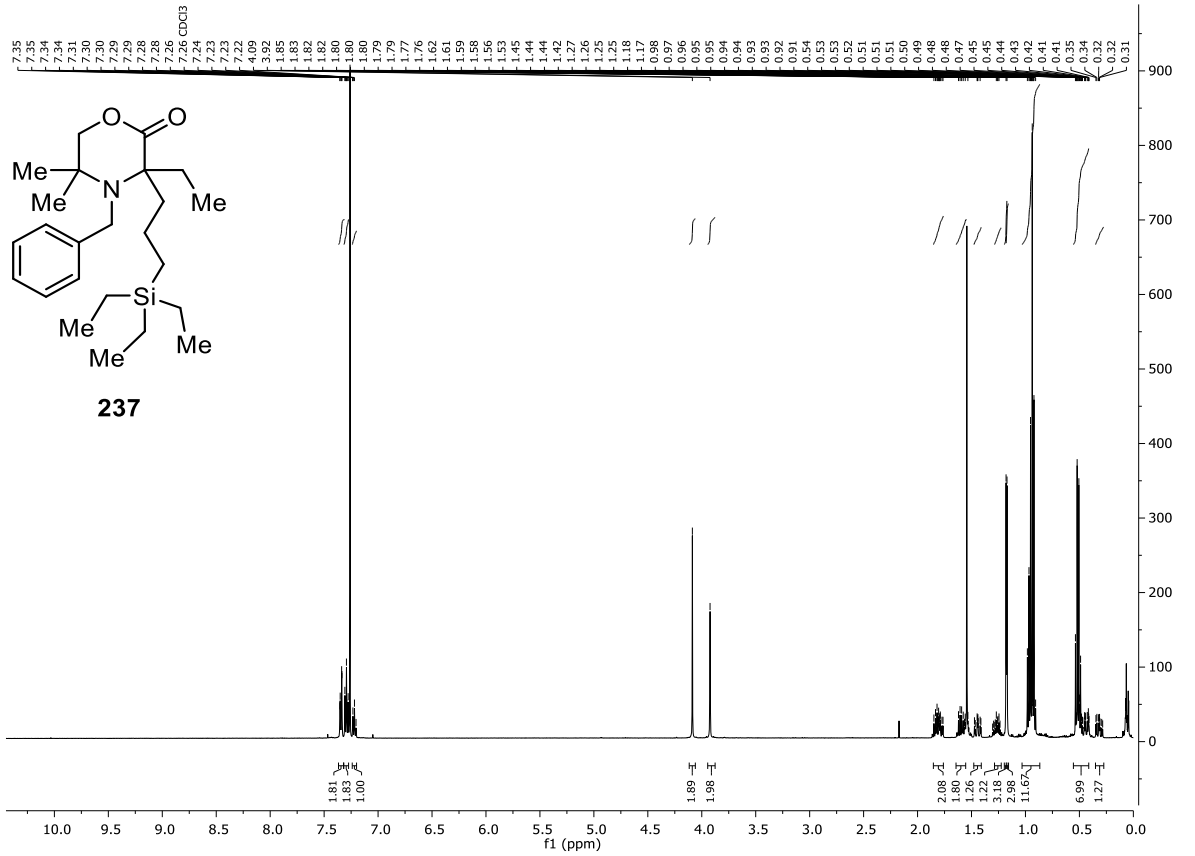

173.78
168.52
134.07
132.25
123.38
77.70
77.16 CDCl3
60.85
48.65
38.29
37.44
33.23
26.88
26.70
23.19
8.42
f1 (ppm)


Me
Me
N
O
O
Me
235
CDCl3
f1 (ppm)

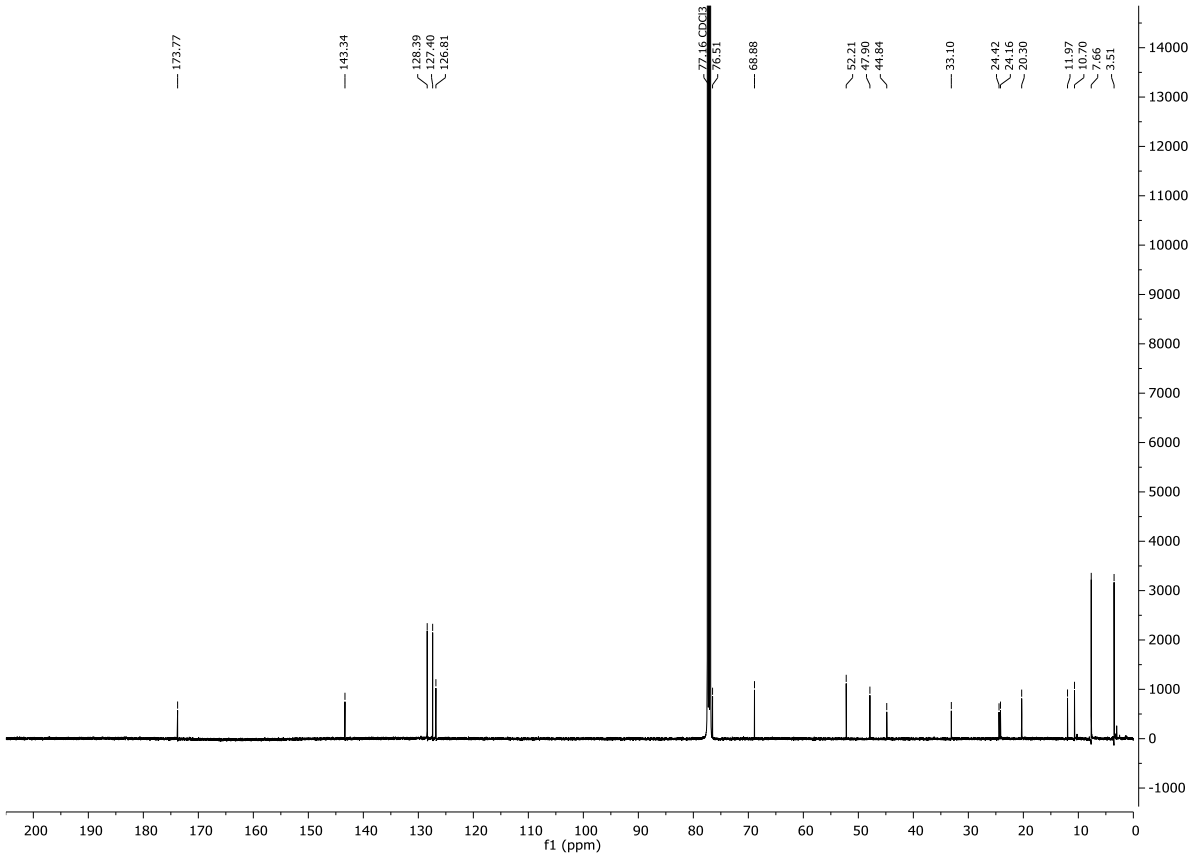

172.15
141.29
128.42
127.71
127.04
77.30
77.16 CDCl3
65.18
55.05
52.96
27.16
24.96
16.55
9.17
f1 (ppm)

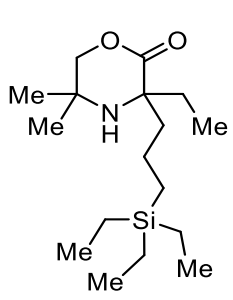

Me
Me
N
O
O
Me
236
f1 (ppm)


173.15
143.06
134.96
128.41
127.54
126.88
118.53
77.16 CDCl3
76.56
69.48
52.31
47.97
44.64
32.77
24.66
23.74
10.42
f1 (ppm)


CDCl3
f1 (ppm)

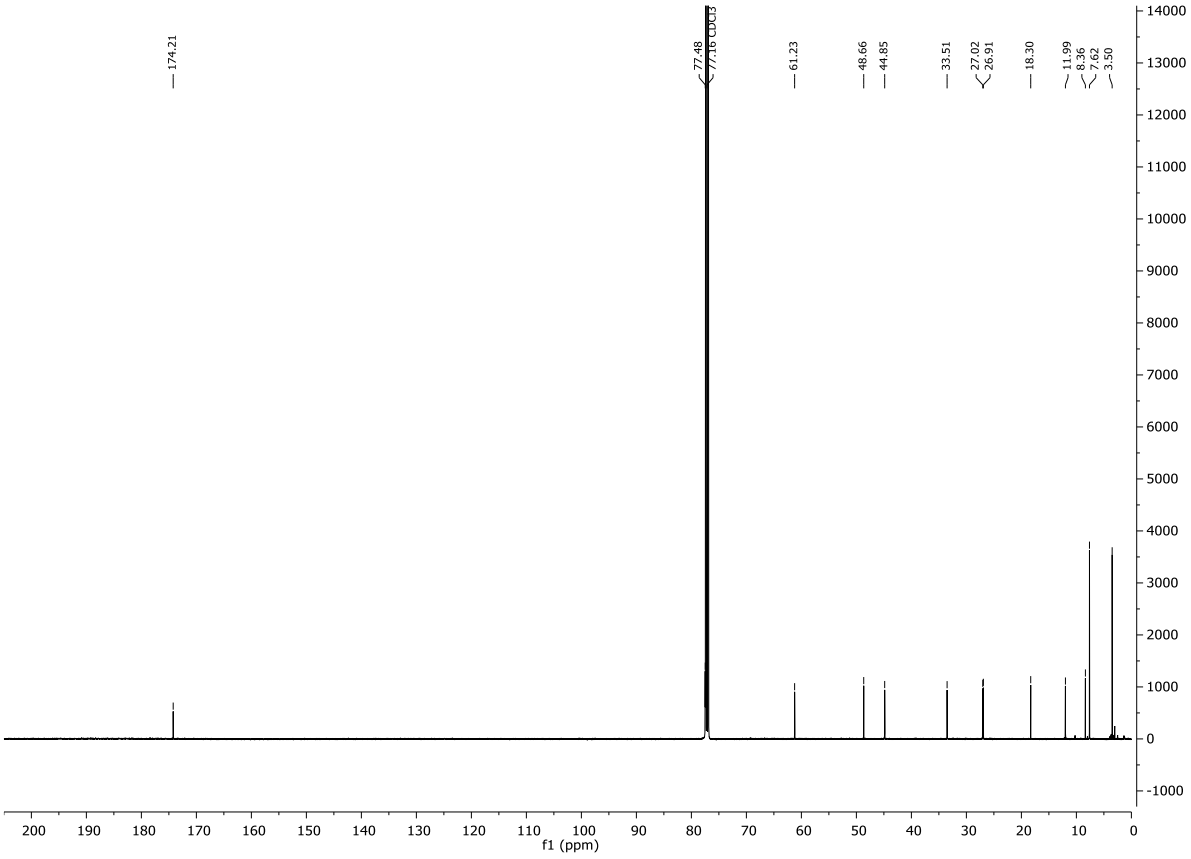
237

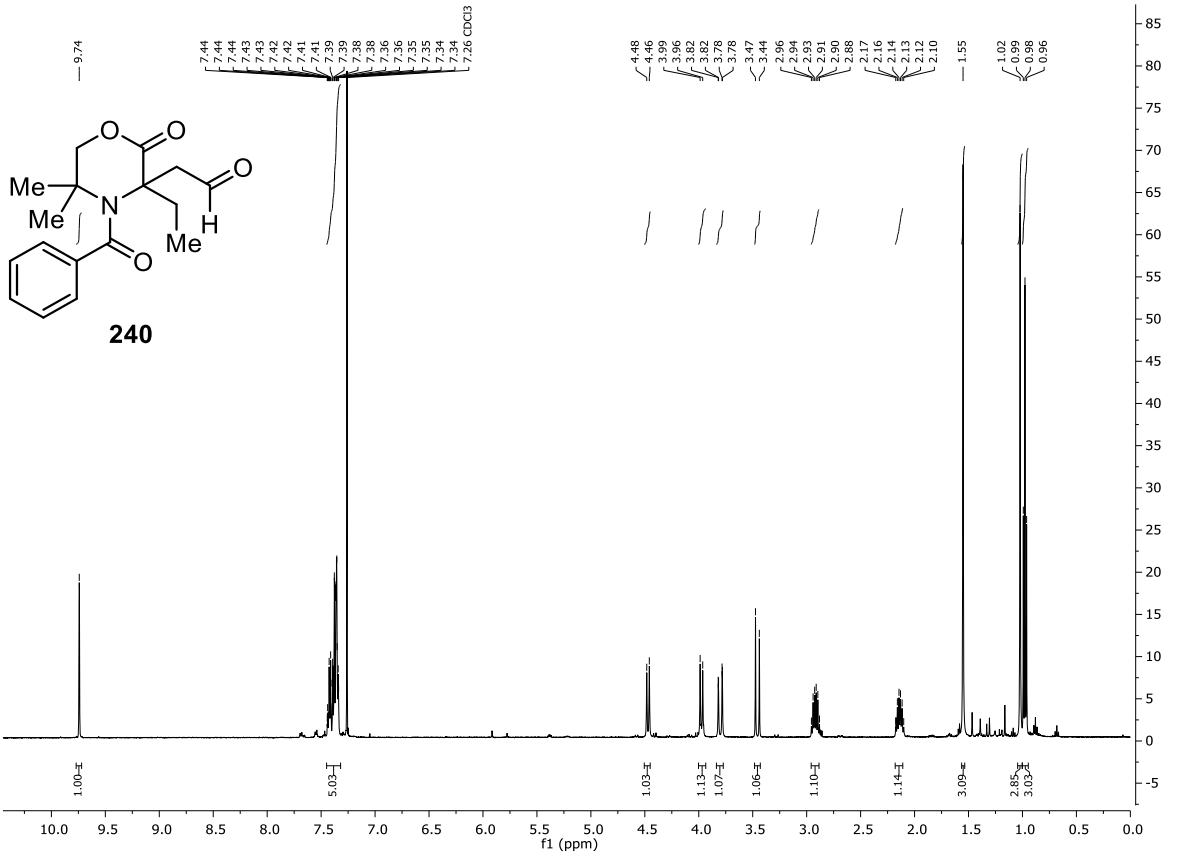

173.77
143.34
128.39
127.40
126.81
77.16 CDCl3
76.51
68.88
52.21
47.90
44.84
33.10
24.42
24.16
20.30
11.97
10.70
7.66
3.51
f1 (ppm)


O
O
Me
Me
N
H
Me
Si
Me
Me
Me

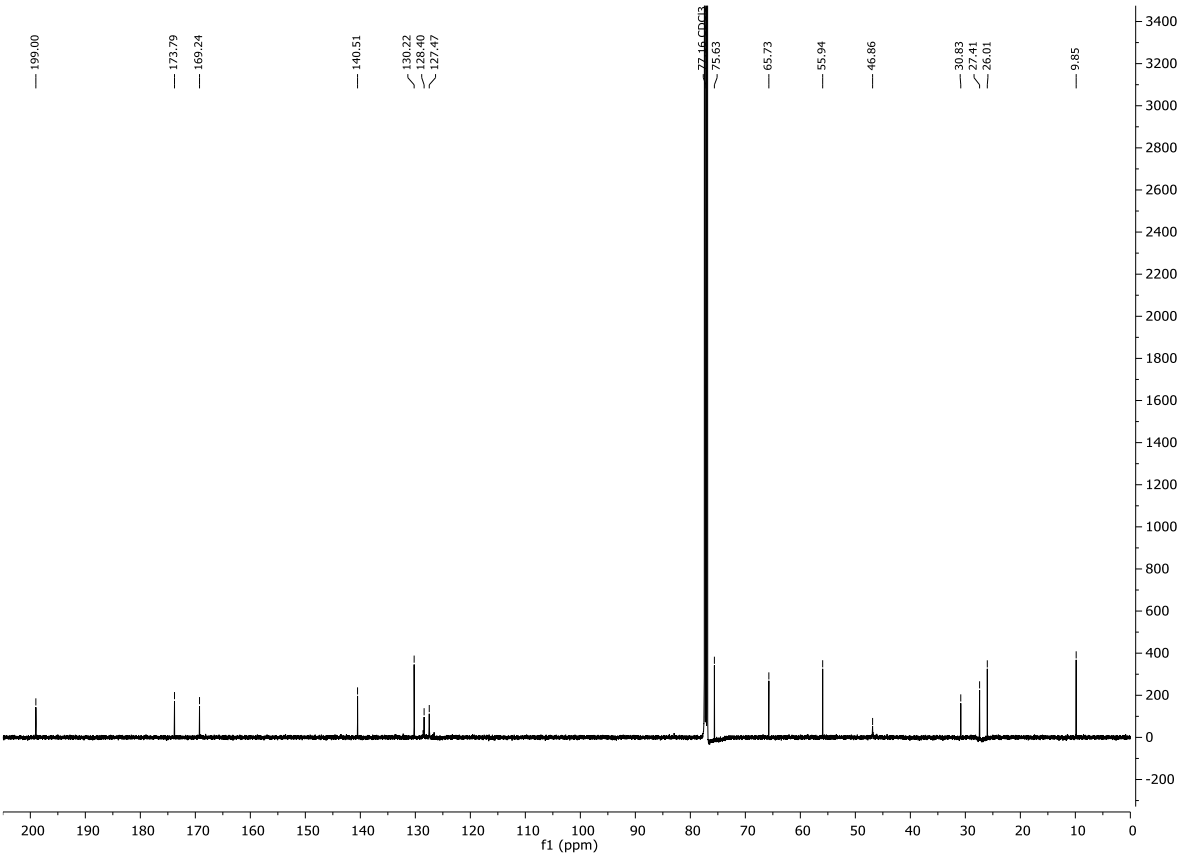
238

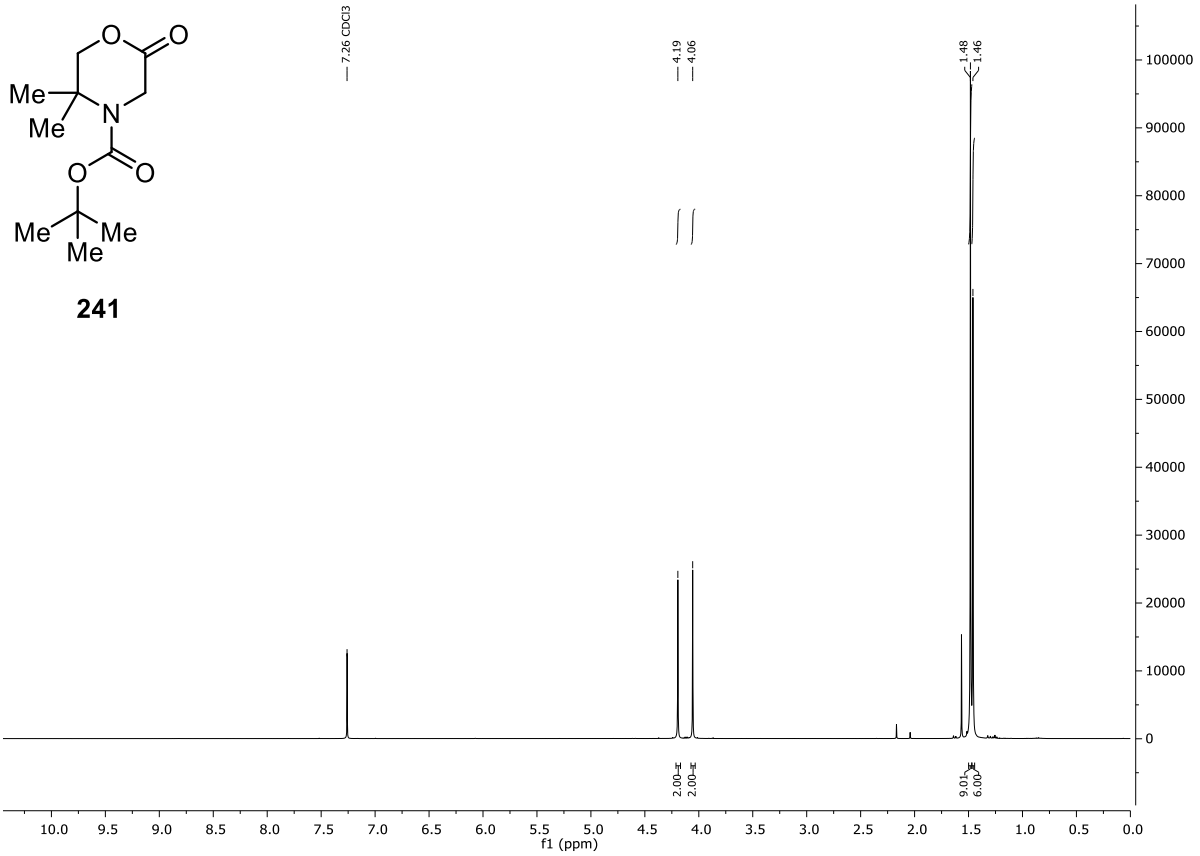
7.26 CDCl3
1.89
2.24
2.02
2.05
5.88
12.00
8.05
f1 (ppm)

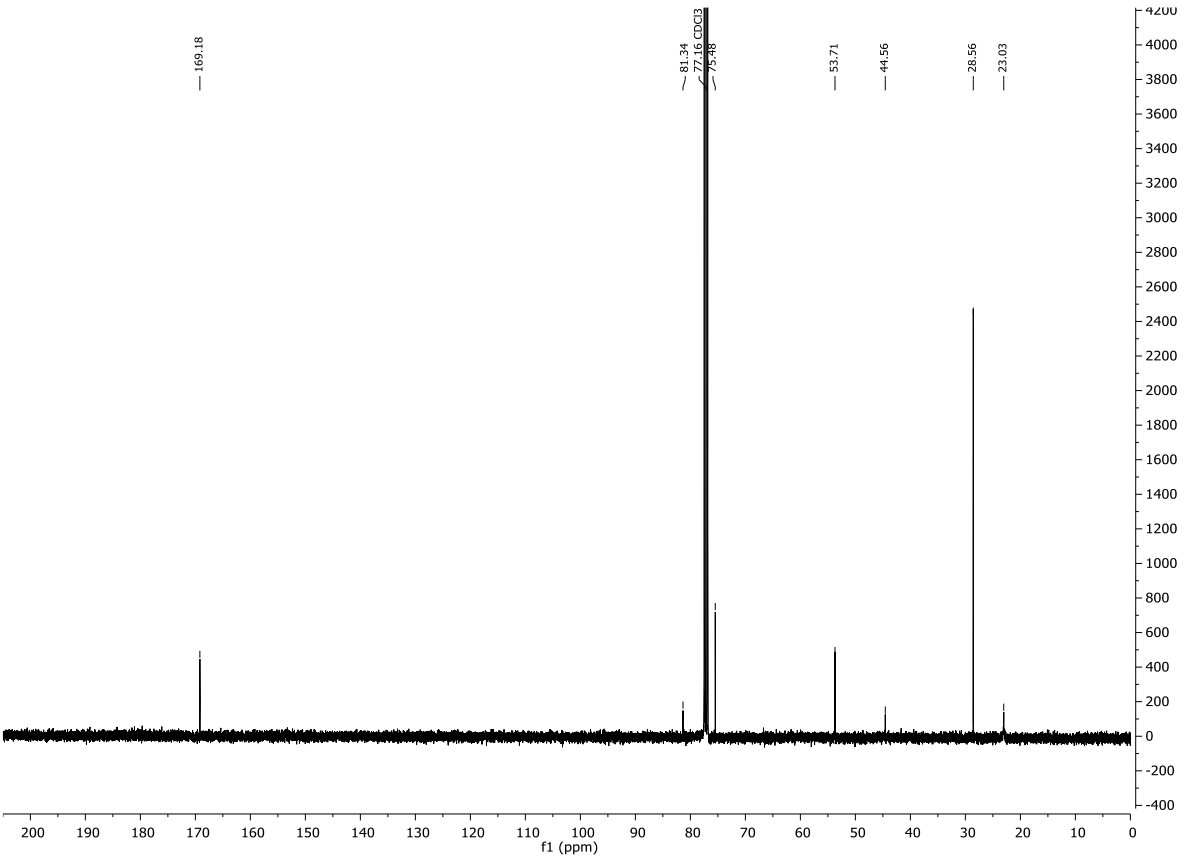

174.21
77.48
77.16 CDCl3
61.23
48.66
44.85
33.51
27.02
26.91
18.30
11.99
8.36
7.62
3.50
f1 (ppm)

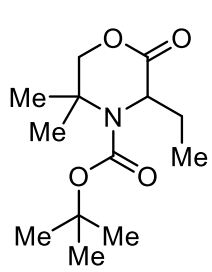

9.74
7.44
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.39
7.39
7.38
7.38
7.36
7.36
7.35
7.35
7.34
7.34
7.26 CDCl3
4.48
4.46
3.99
3.96
3.82
3.82
3.78
3.78
3.47
3.44
2.96
2.94
2.93
2.91
2.90
2.88
2.17
2.16
2.14
2.13
2.12
2.10
1.55
1.02
0.99
0.98
0.96
1.00
5.03
1.03
1.13
1.07
1.06
1.10
1.14
3.09
2.85
3.03
f1 (ppm)

240


199.00
173.79
169.24
140.51
130.22
128.40
127.47
77.16 CDCl3
75.63
65.73
55.94
46.86
30.83
27.41
26.01
9.85
f1 (ppm)

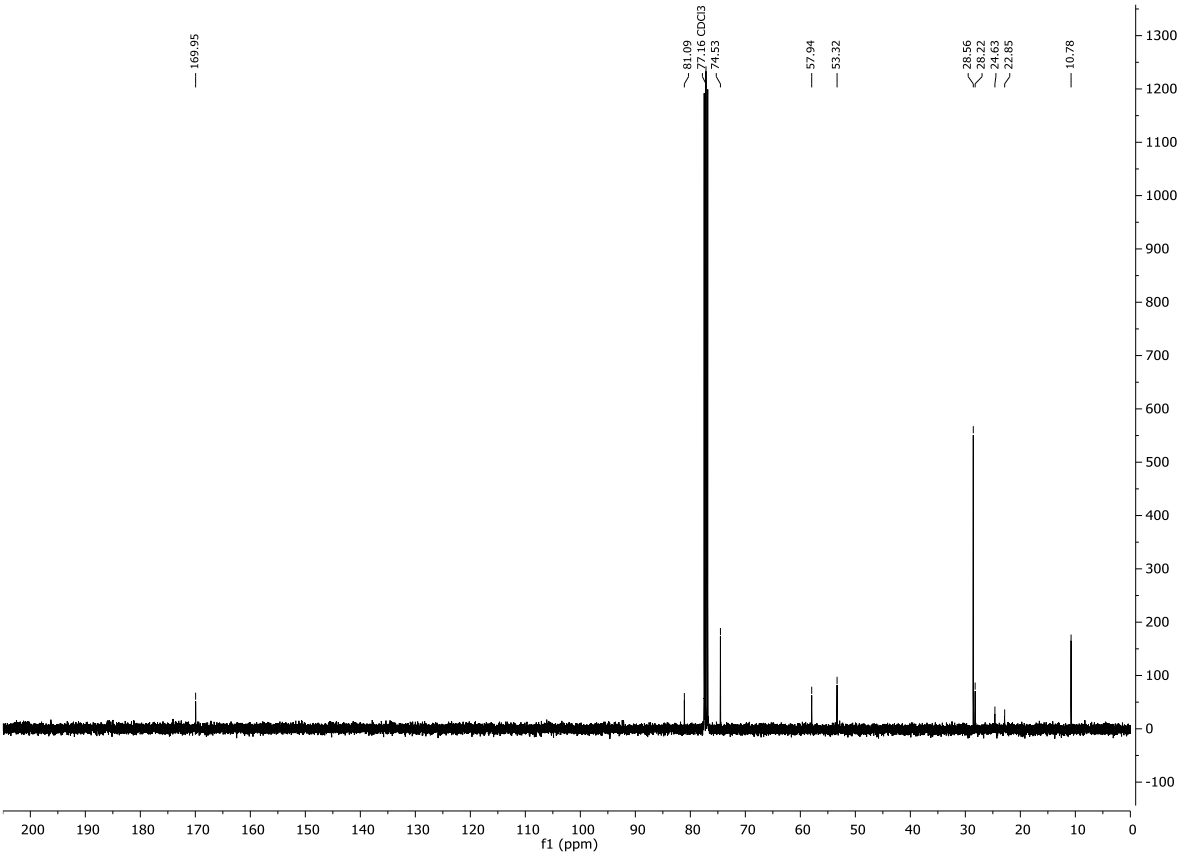

Me
Me
N
O
O
O
O
Me
Me
Me
241
7.26 CDCl3
4.19
4.06
1.48
1.46
2.00
2.00
9.01
6.00
f1 (ppm)

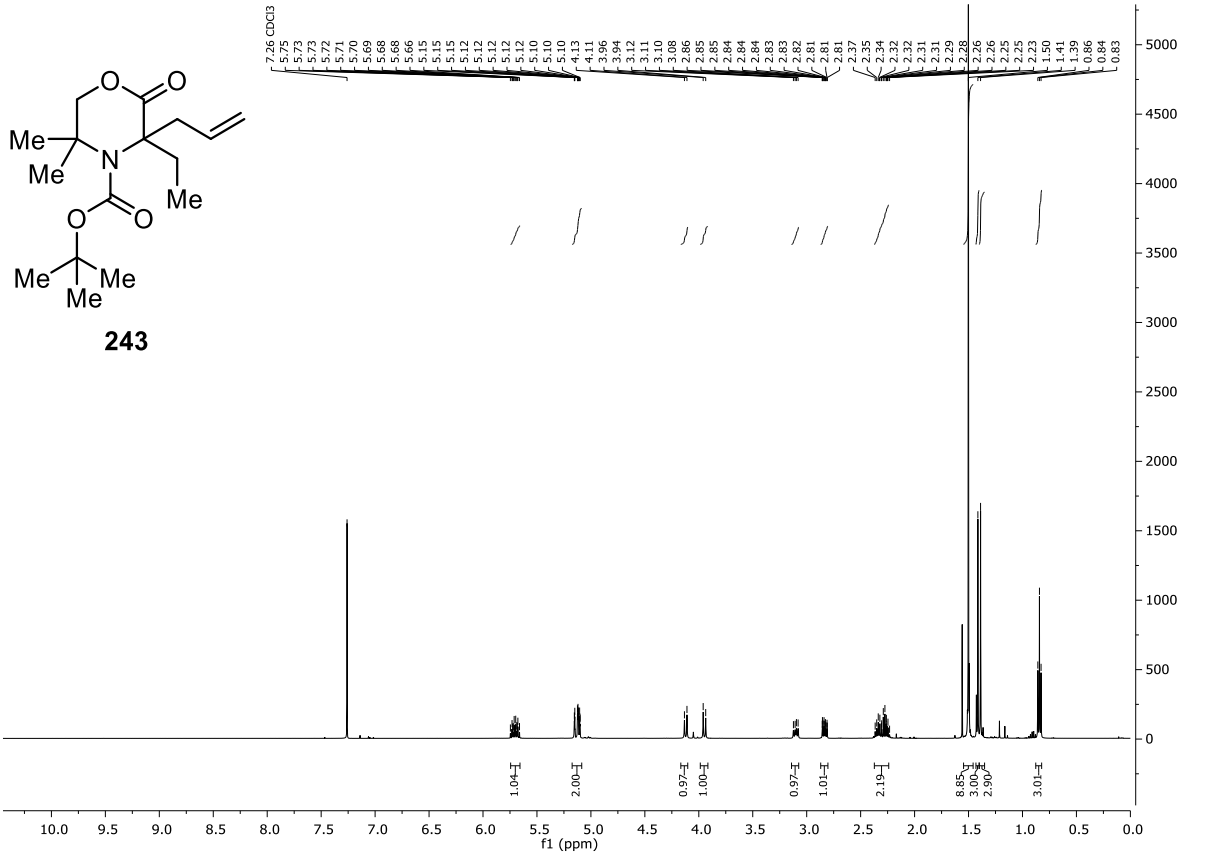

169.18
81.34
77.16 CDCl3
75.48
53.71
44.56
28.56
23.03
f1 (ppm)

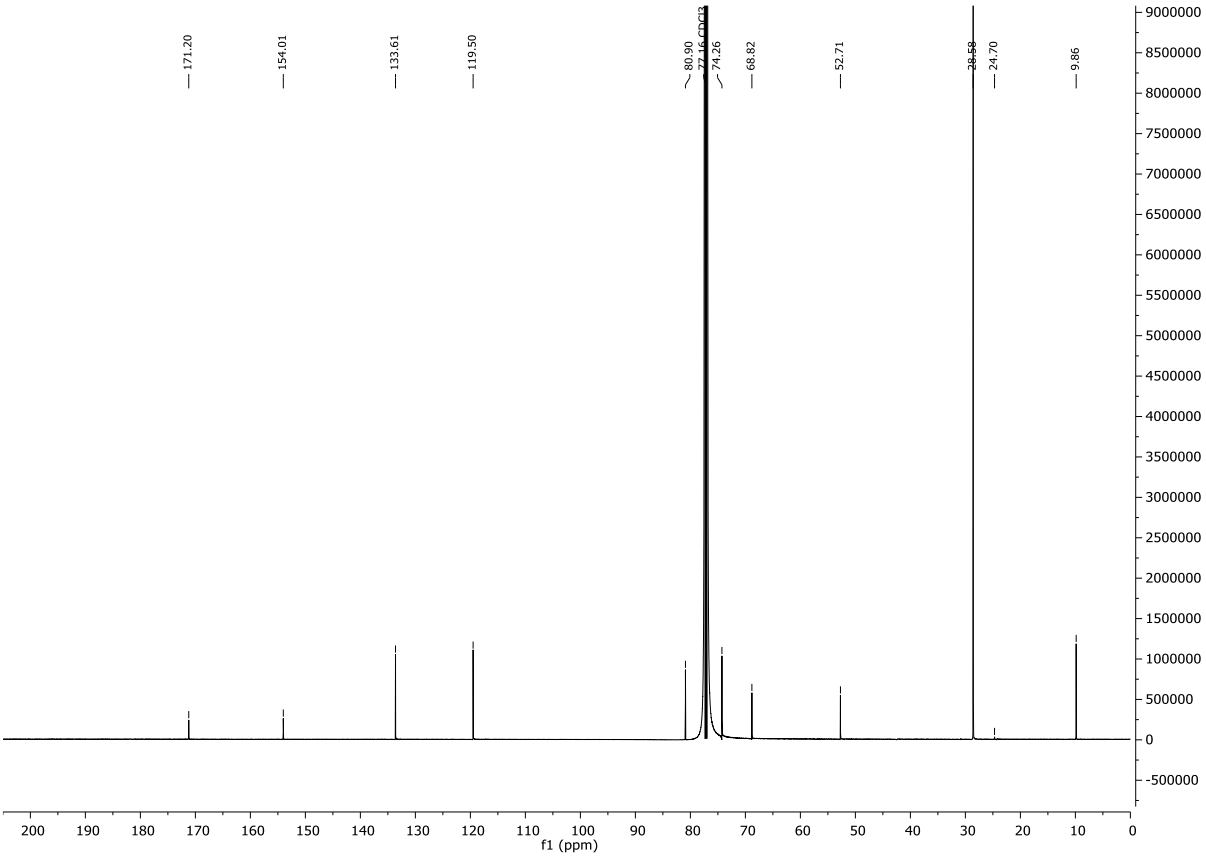

O
O
Me
Me
N
Me
O
O
Me
Me
Me

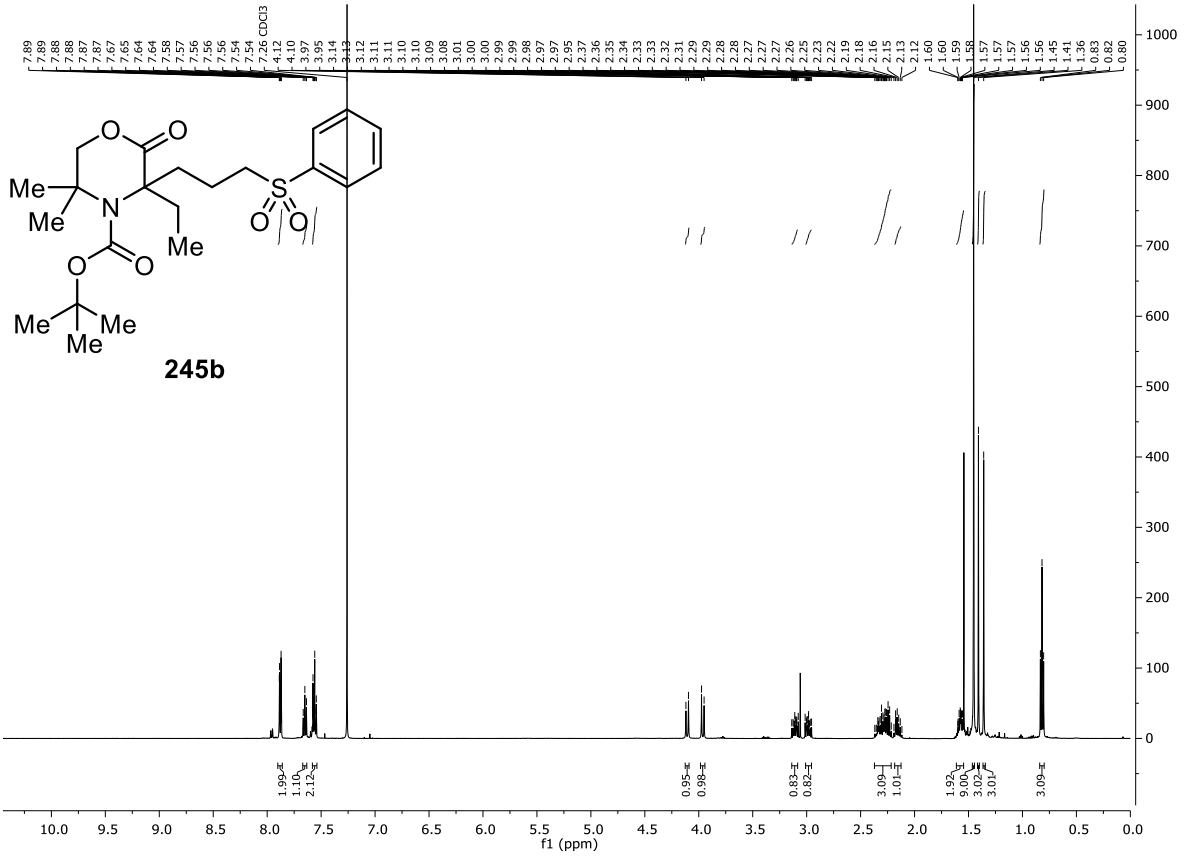
242

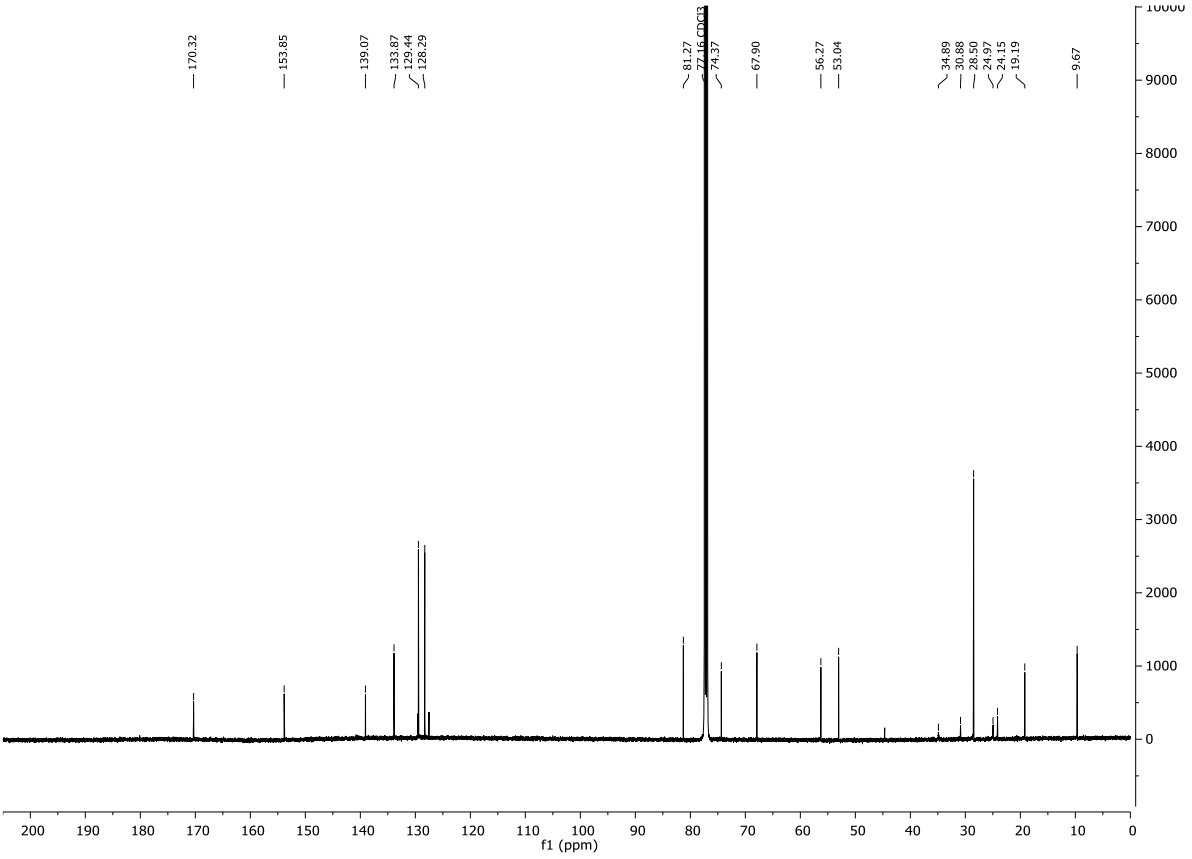
7.26 CDCl3
4.52
4.50
4.50
4.48
4.32
4.29
3.91
3.88
1.92
1.90
1.89
1.89
1.87
1.85
1.85
1.83
1.82
1.82
1.80
1.80
1.78
1.78
1.77
1.76
1.75
1.74
1.73
1.73
1.71
1.48
1.47
1.45
1.06
1.04
1.02
0.96
1.01
1.00
2.09
15.03
2.99
f1 (ppm)

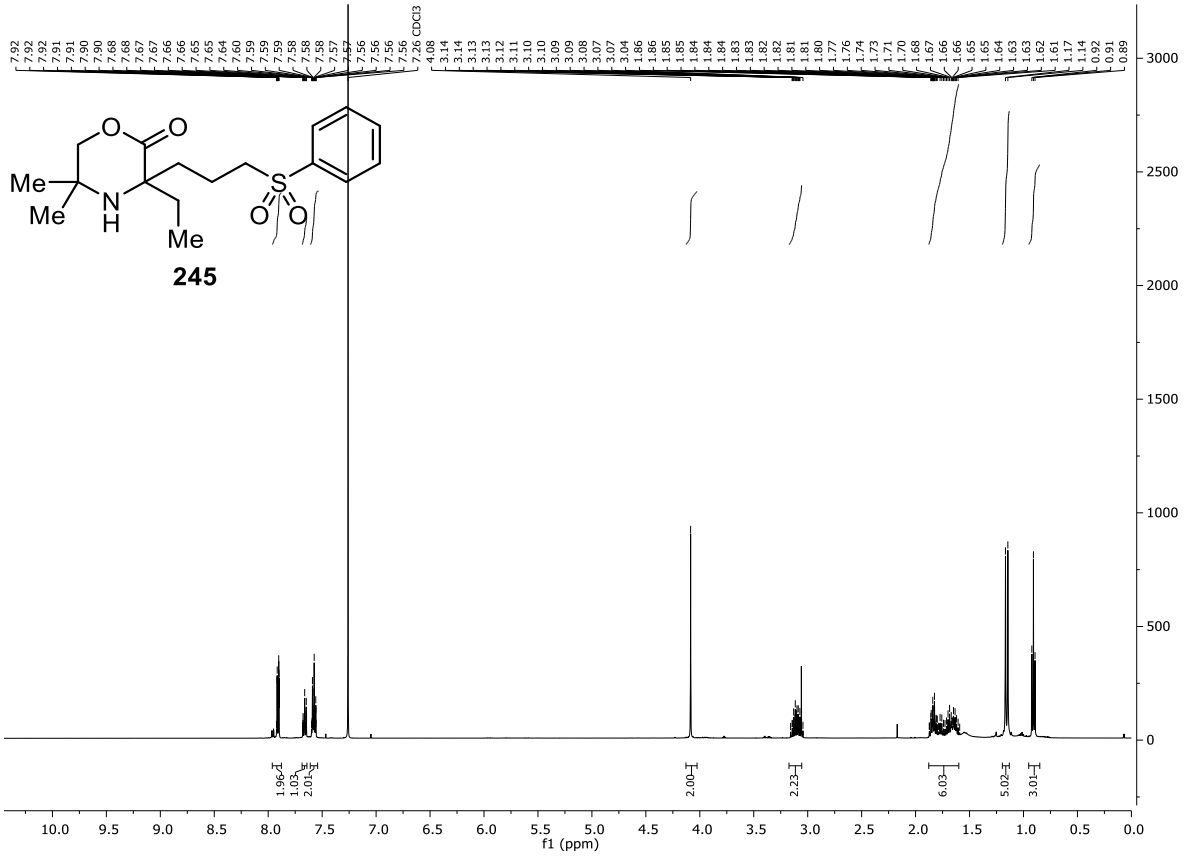

169.95
81.09
77.16 CDCl3
74.53
57.94
53.32
28.56
28.22
24.63
22.85
10.78
f1 (ppm)

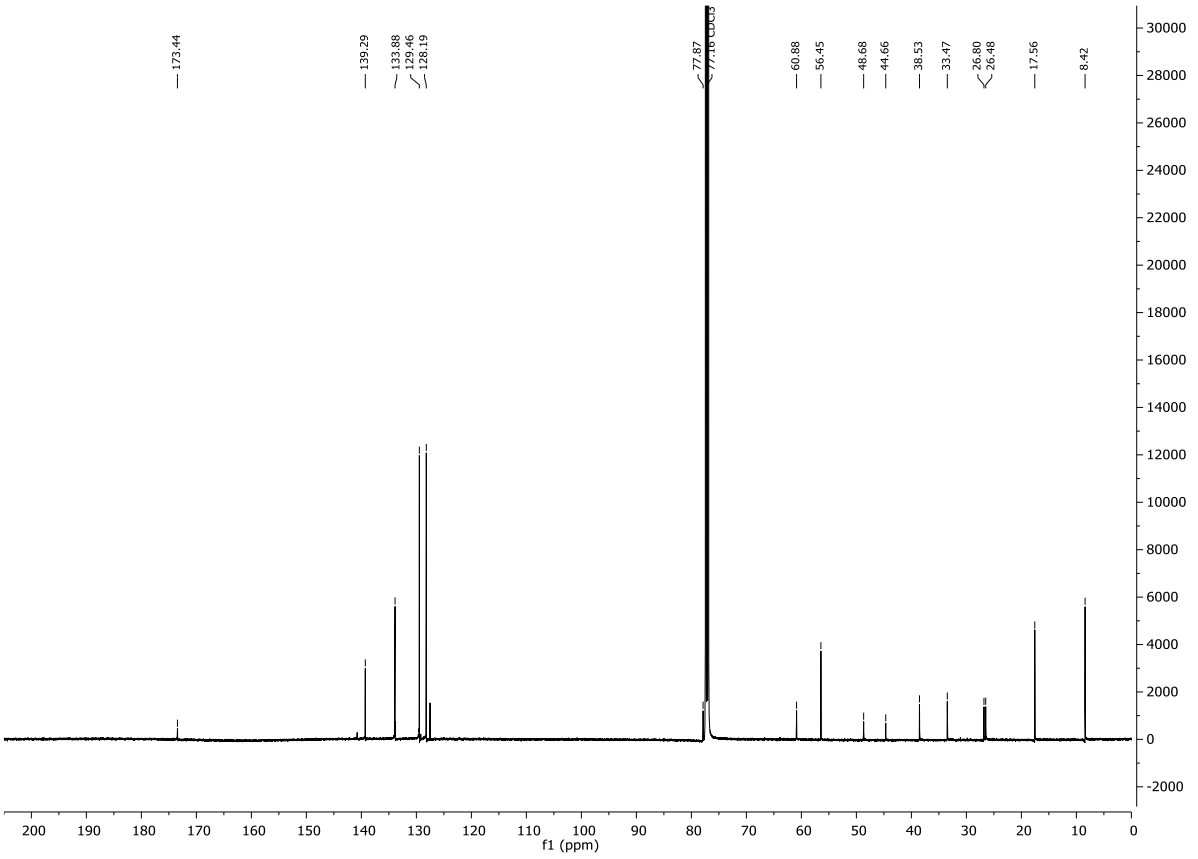

Me
Me
N
O
O
O
O
Me
Me
Me
Me
243
7.26 CDCl3
f1 (ppm)

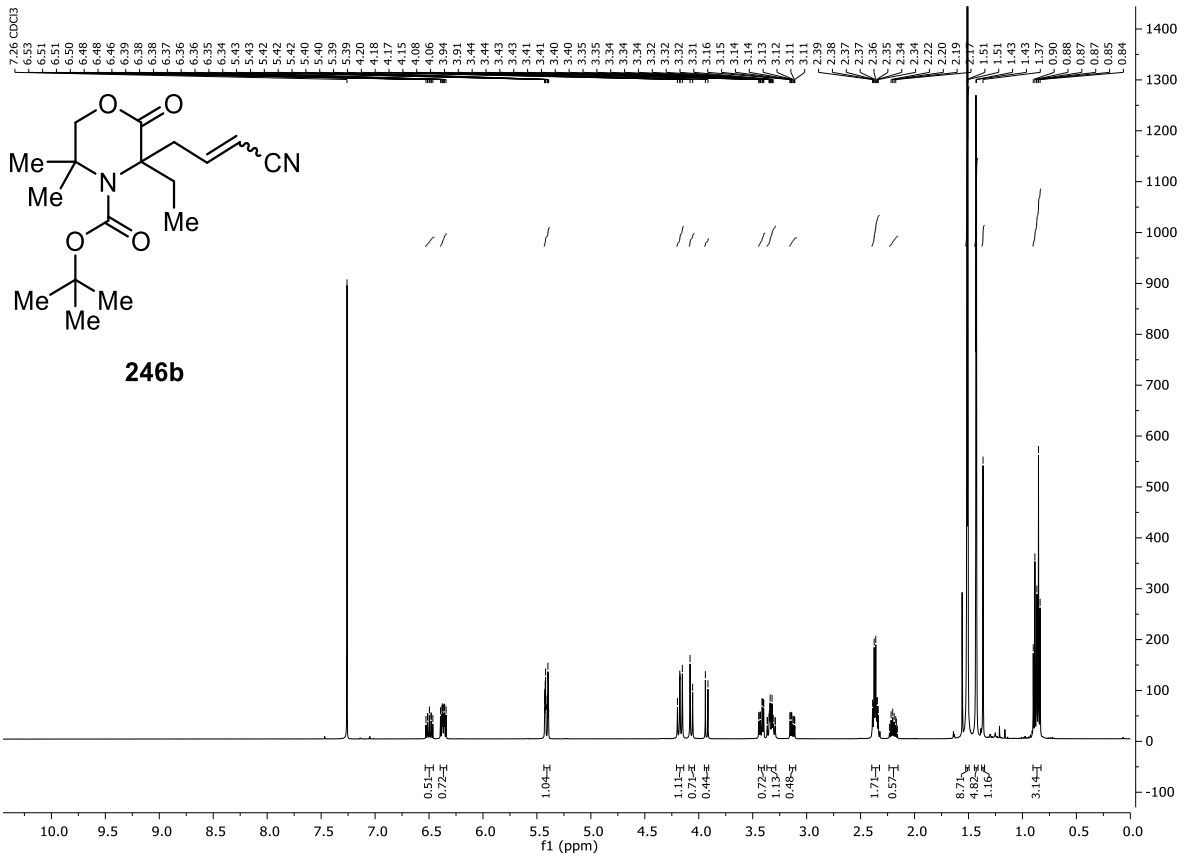

171.20
154.01
133.61
119.50
80.90
77.16 CDCl3
74.26
68.82
52.71
28.58
24.70
9.86
f1 (ppm)

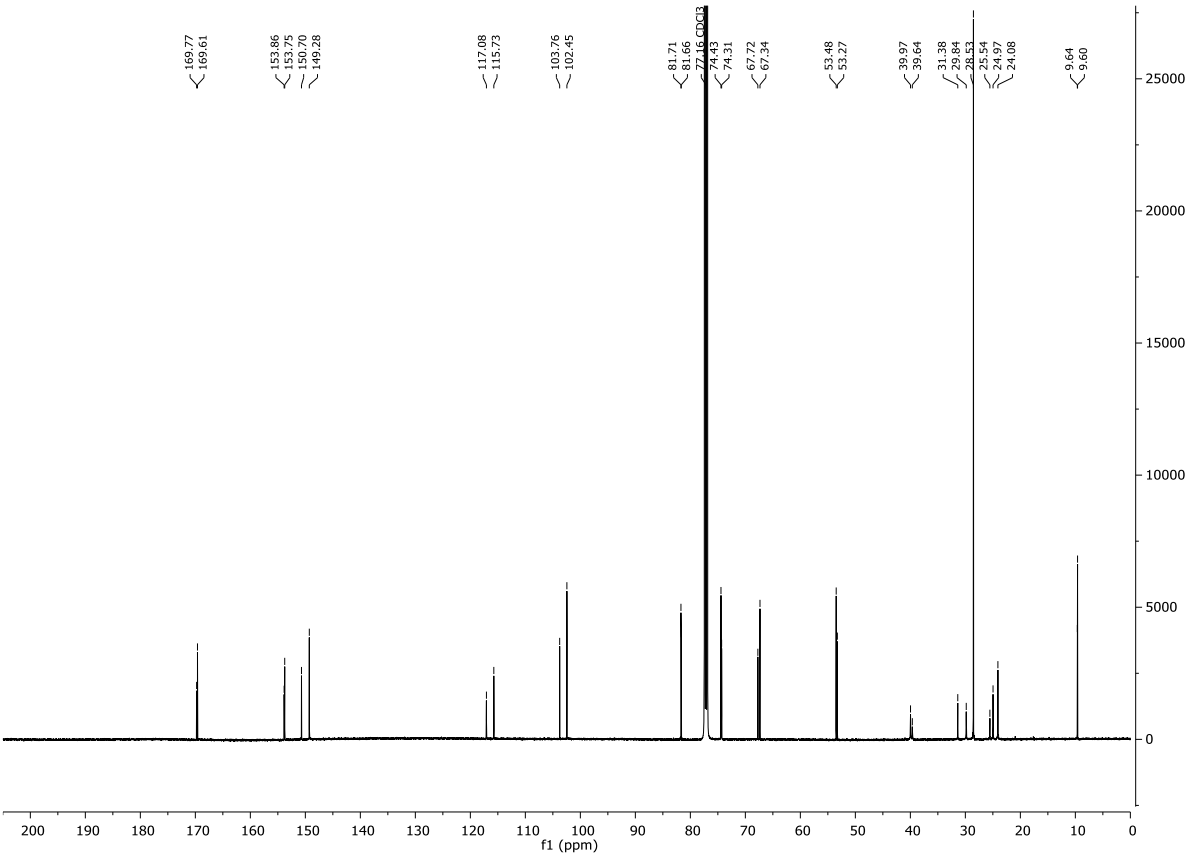

245b
f1 (ppm)

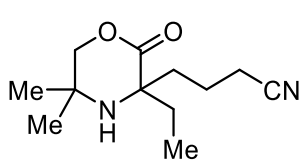

f1 (ppm)


Me
Me
N
H
O
O
S
O
O
Me
245
f1 (ppm)


173.44
139.29
133.88
129.46
128.19
77.87
77.16 CDCl3
60.88
56.45
48.68
44.66
38.53
33.47
26.80
26.48
17.56
8.42
f1 (ppm)

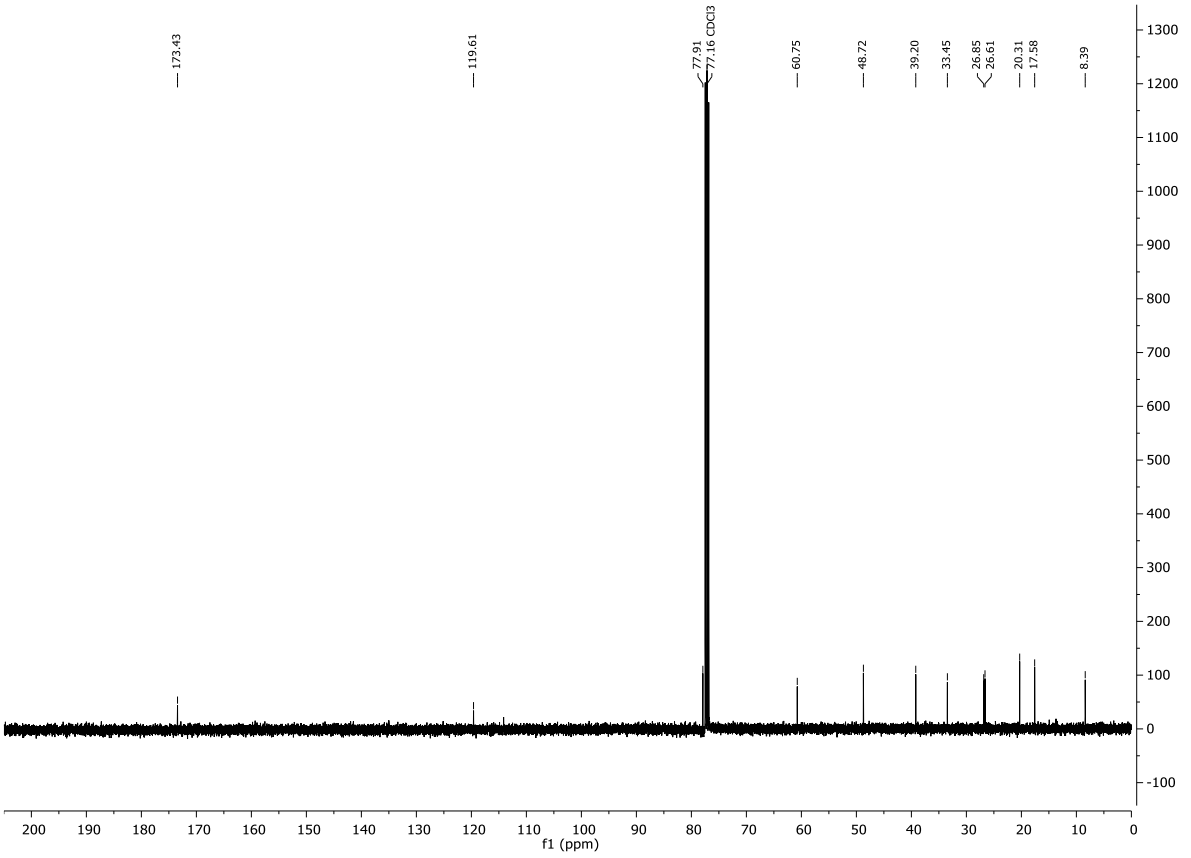

246b
f1 (ppm)

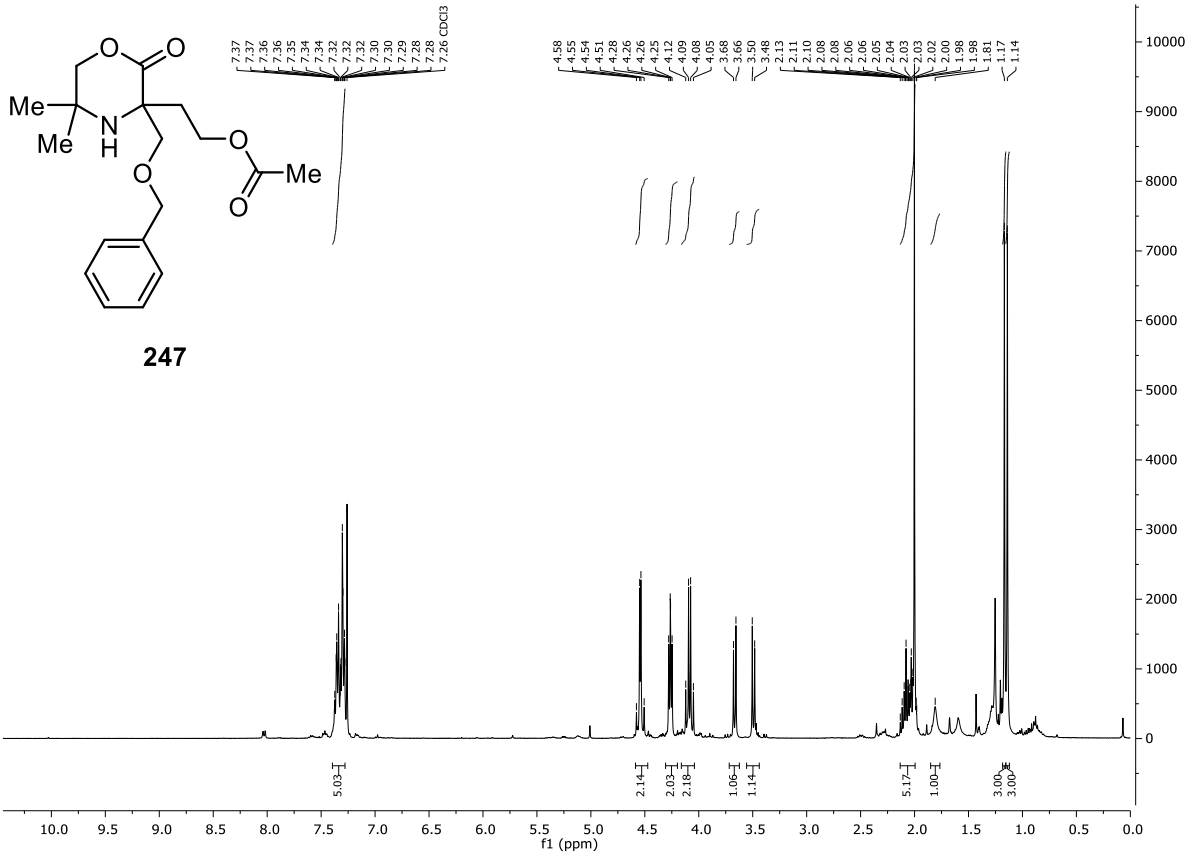

f1 (ppm)


O
O
Me
Me
N
H
Me
CN

246

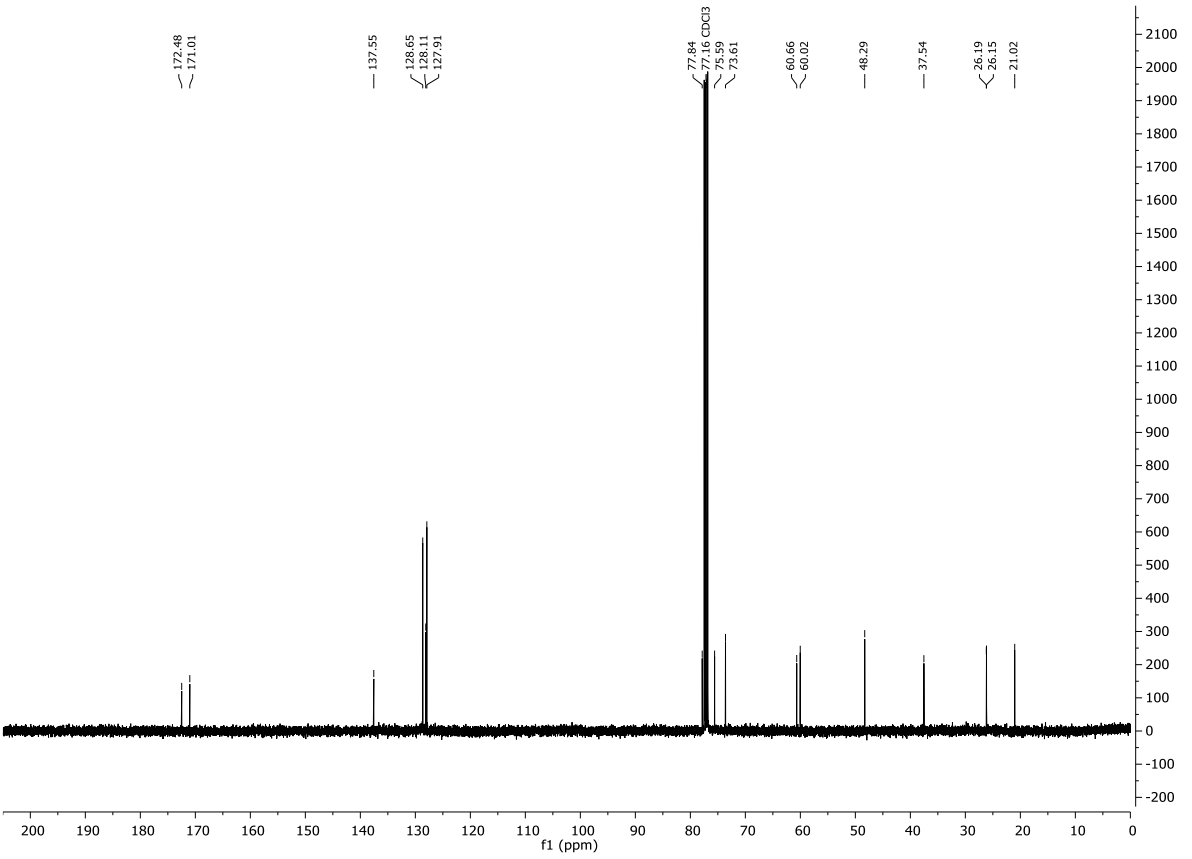
7.26 CDCl3
4.13
4.12
2.39
2.38
2.37
2.37
2.36
2.35
1.84
1.83
1.82
1.82
1.81
1.80
1.80
1.79
1.78
1.77
1.76
1.76
1.75
1.74
1.74
1.73
1.72
1.71
1.70
1.69
1.68
1.66
1.64
1.63
1.20
1.19
0.97
0.95
0.94
2.00
2.02
6.10
5.94
3.01
f1 (ppm)

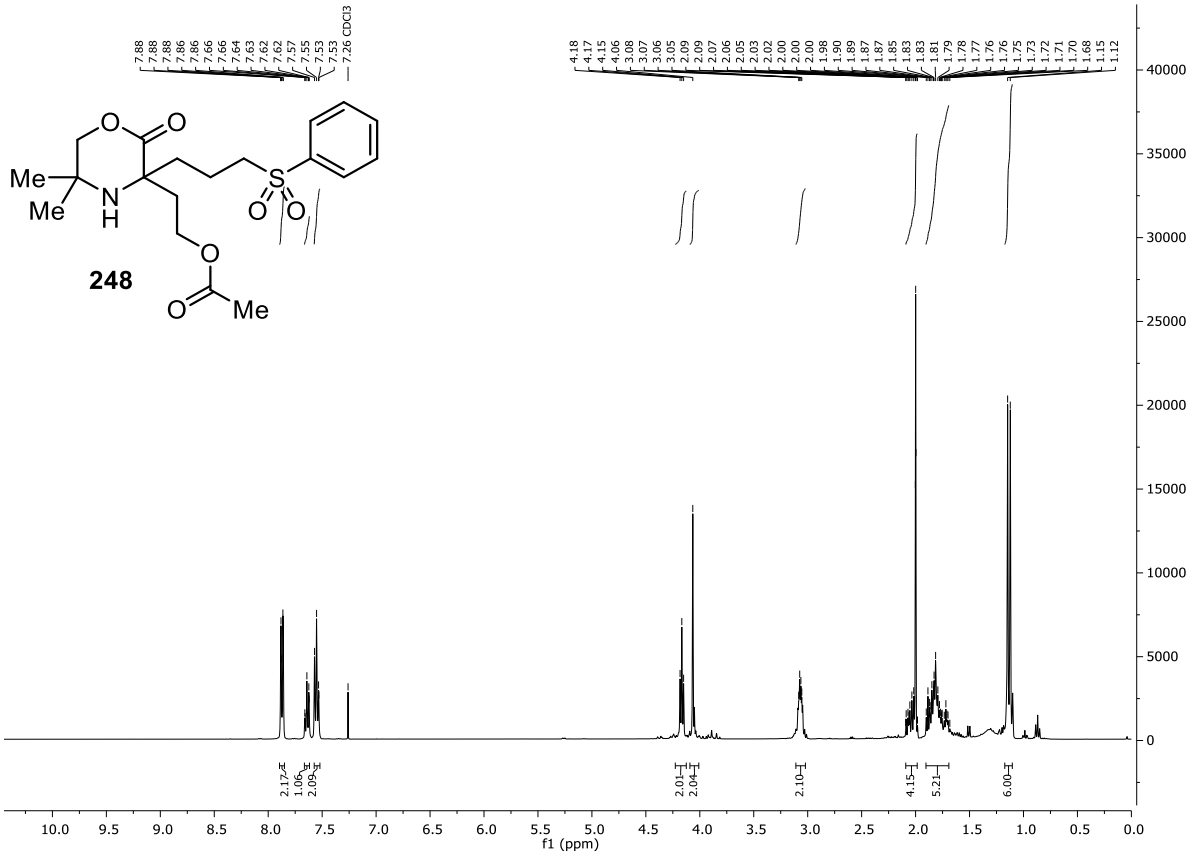

173.43
119.61
77.91
77.16 CDCl3
60.75
48.72
39.20
33.45
26.85
26.61
20.31
17.58
8.39
f1 (ppm)

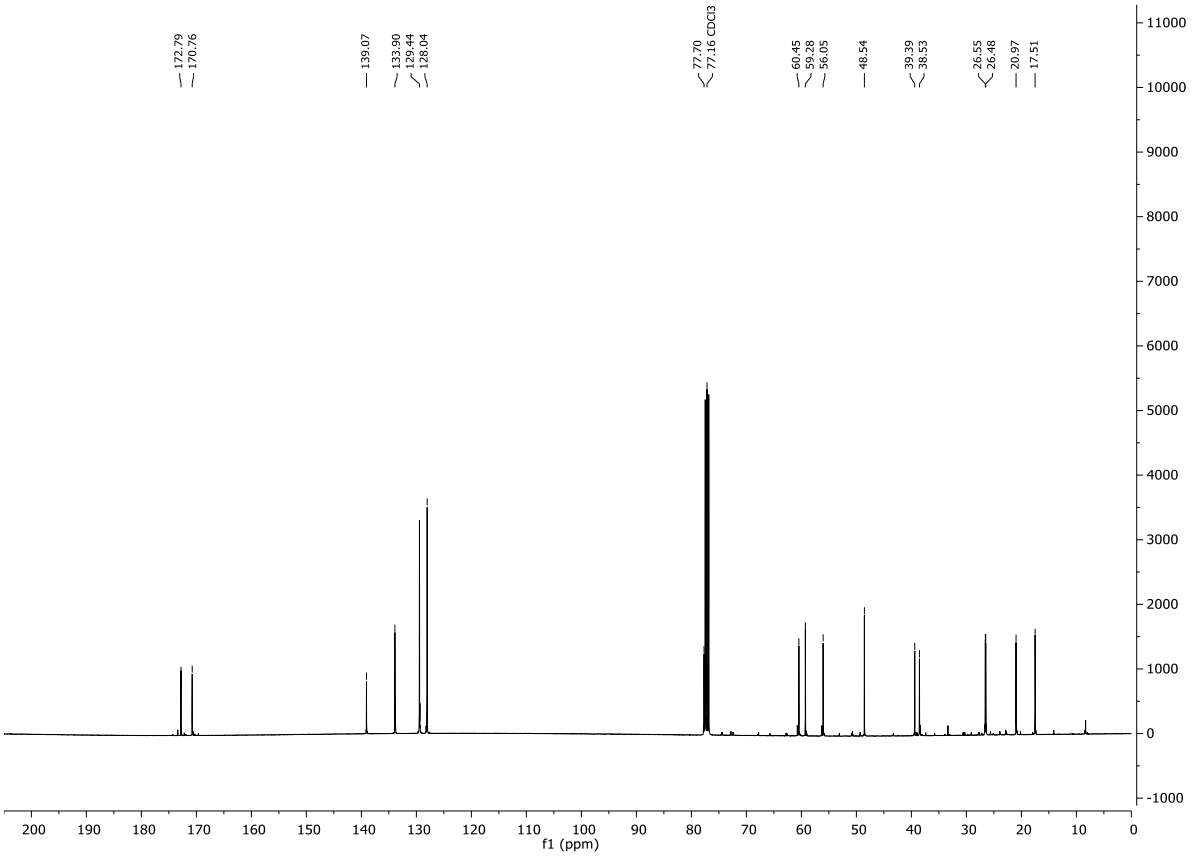

Me
Me
N
H
O
O
O
O
Me
O

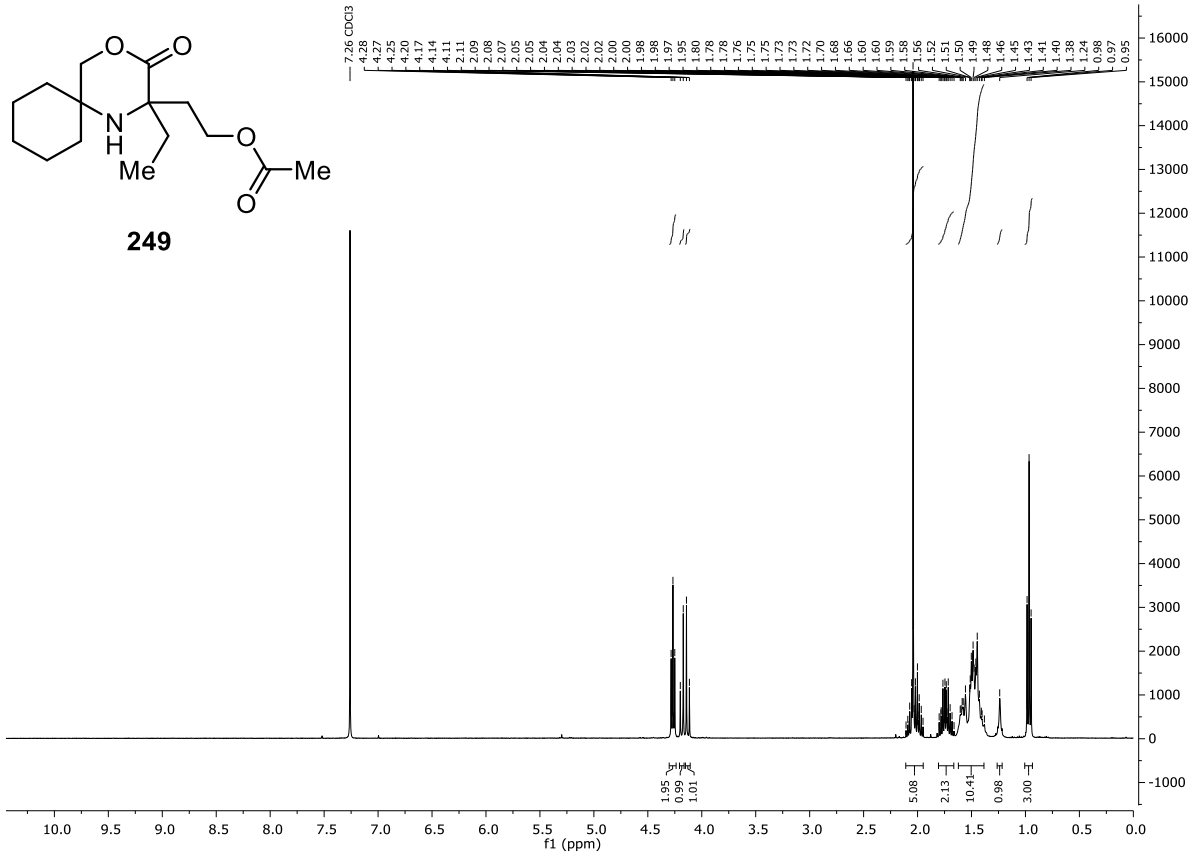
247

7.37
7.37
7.36
7.36
7.35
7.34
7.34
7.32
7.32
7.32
7.30
7.30
7.29
7.28
7.28
7.26 CDCl3
4.58
4.55
4.54
4.51
4.28
4.26
4.26
4.25
4.12
4.09
4.08
4.05
3.68
3.66
3.50
3.48
2.13
2.11
2.10
2.08
2.08
2.06
2.06
2.05
2.04
2.03
2.03
2.02
2.00
1.98
1.98
1.81
1.17
1.14
5.03
2.14
2.03
2.18
1.06
1.14
5.17
1.00
3.00
3.00
f1 (ppm)

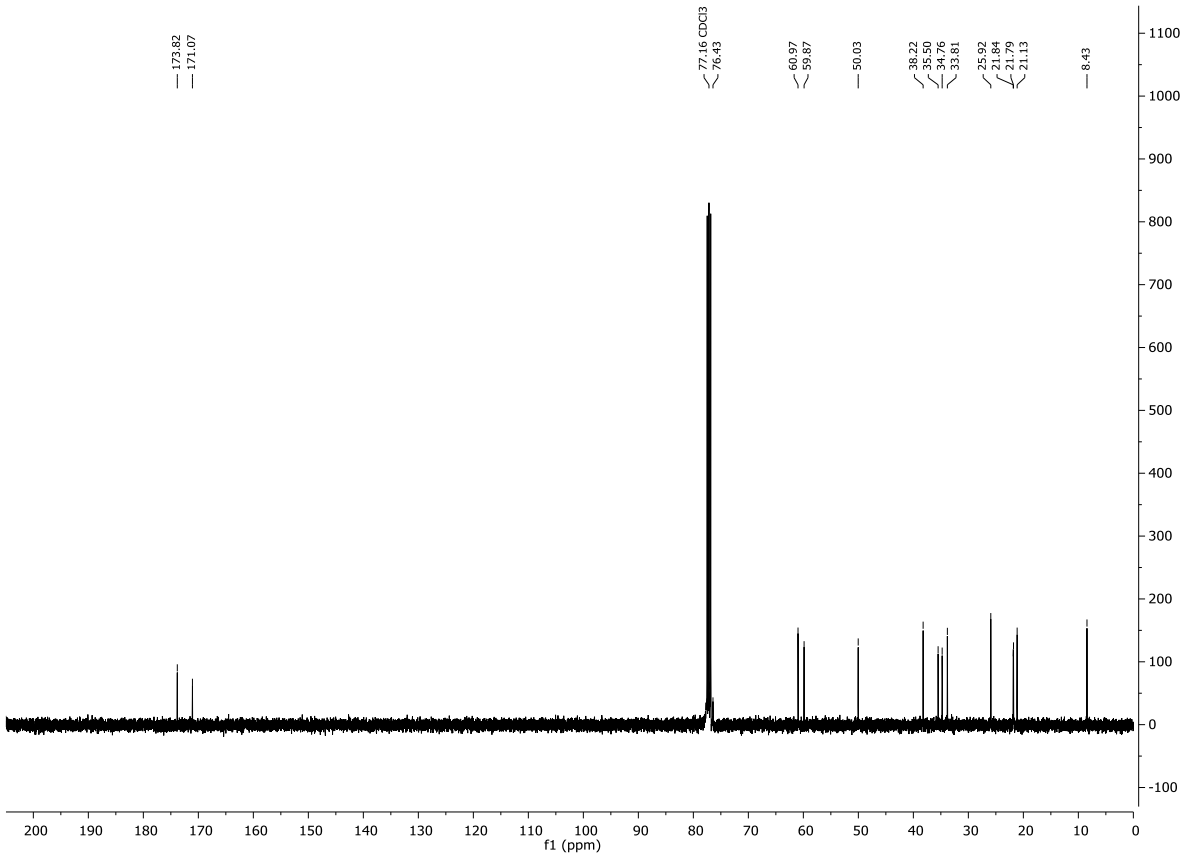

172.48
171.01
137.55
128.65
128.11
127.91
77.84
77.16 CDCl3
75.59
73.61
60.66
60.02
48.29
37.54
26.19
26.15
21.02
f1 (ppm)

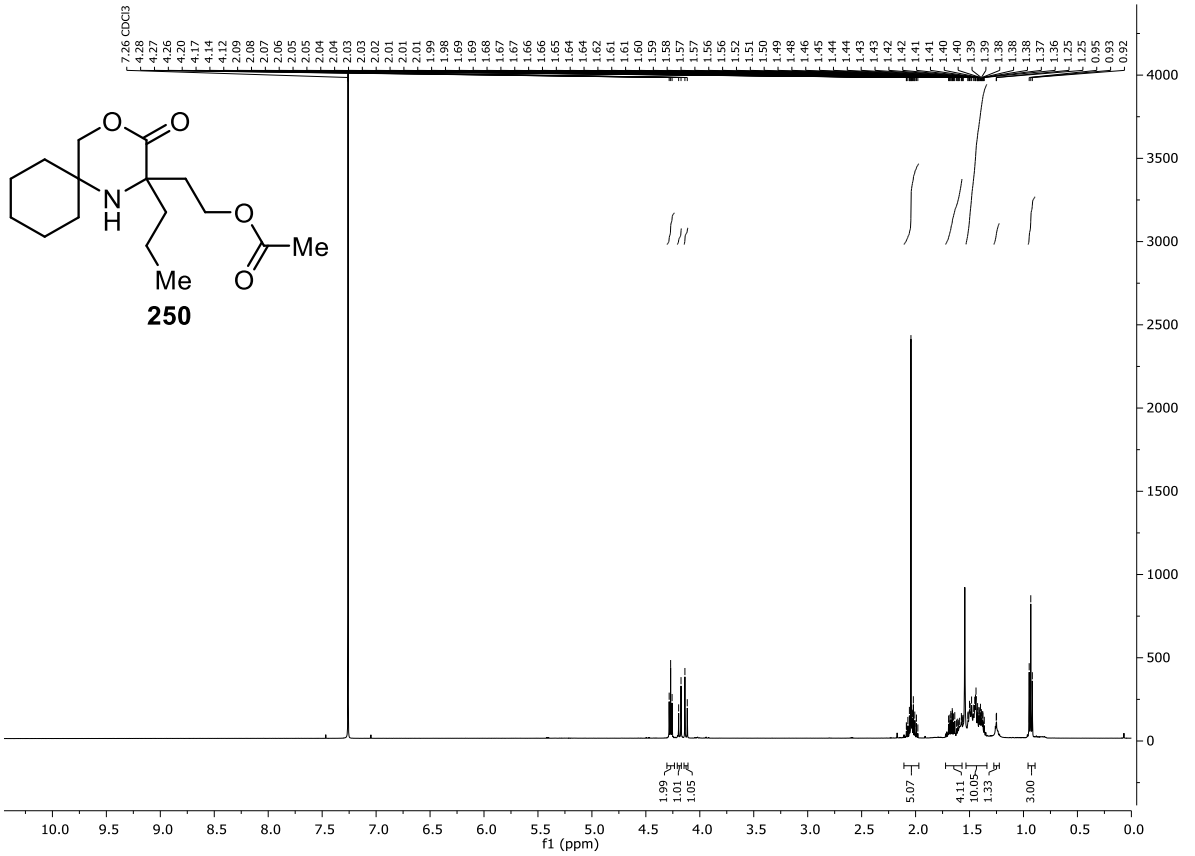

248
f1 (ppm)

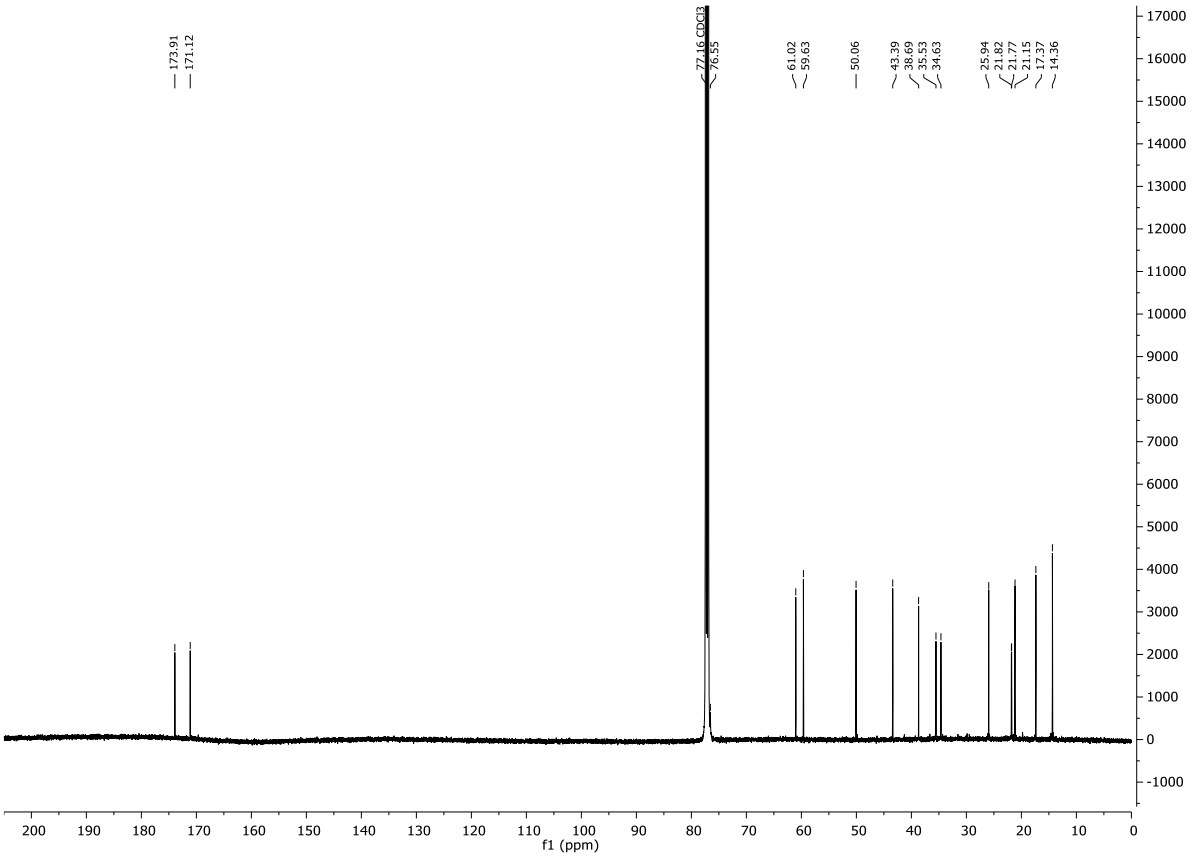

f1 (ppm)

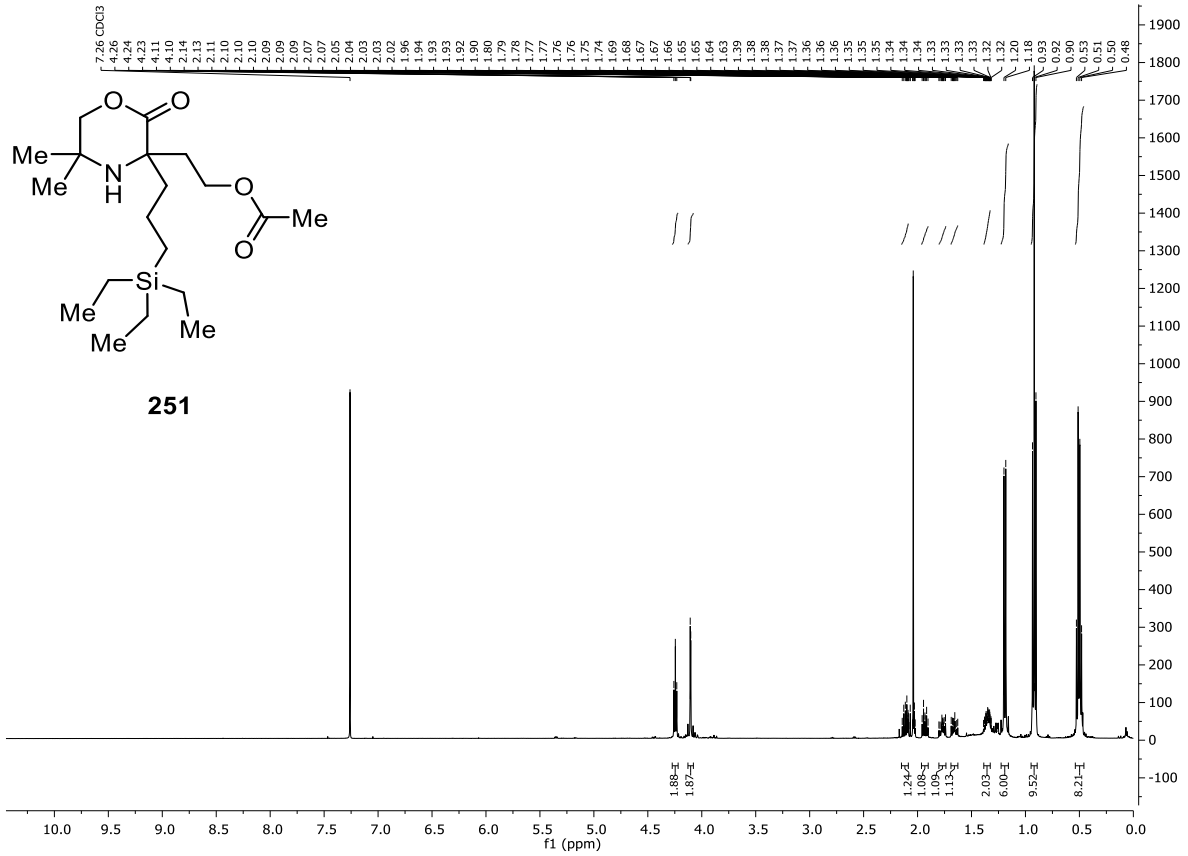

7.26 CDCl3
1.95
0.99
1.01
5.08
2.13
10.41
0.98
3.00
f1 (ppm)

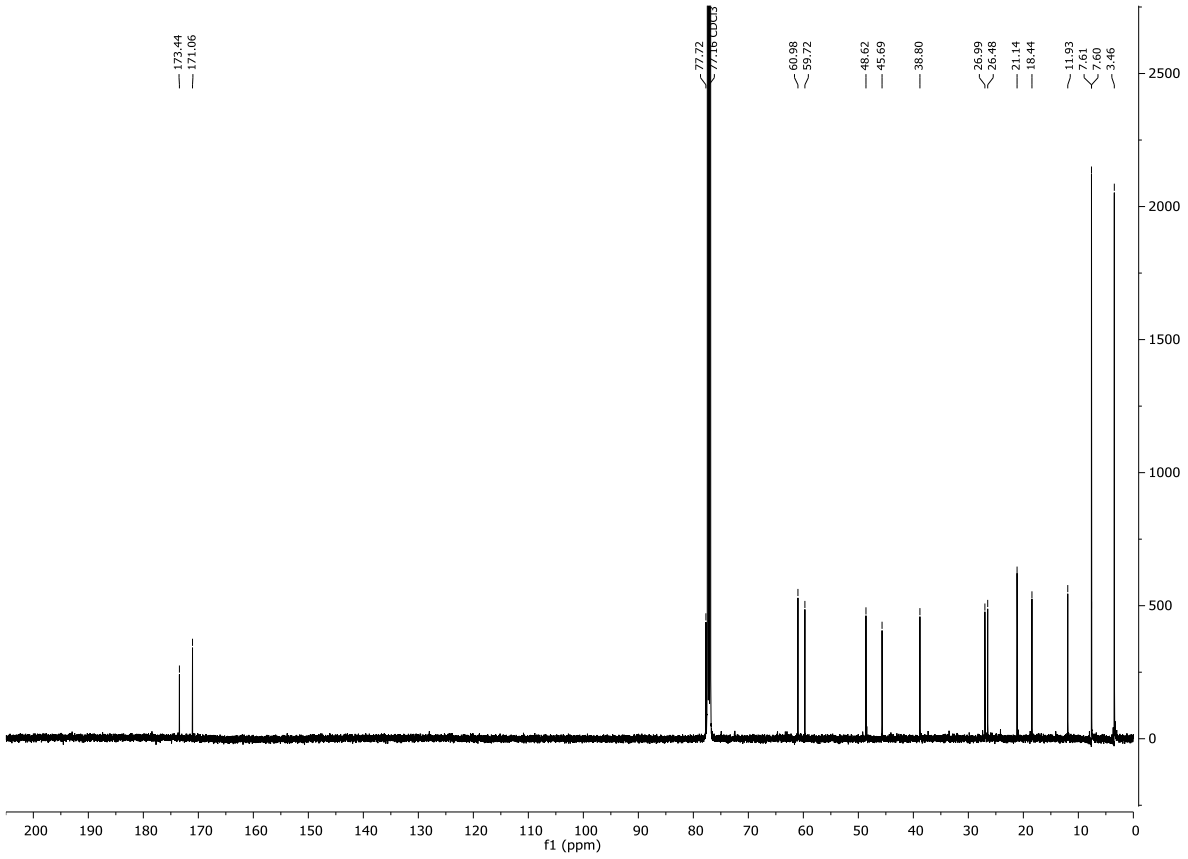
249

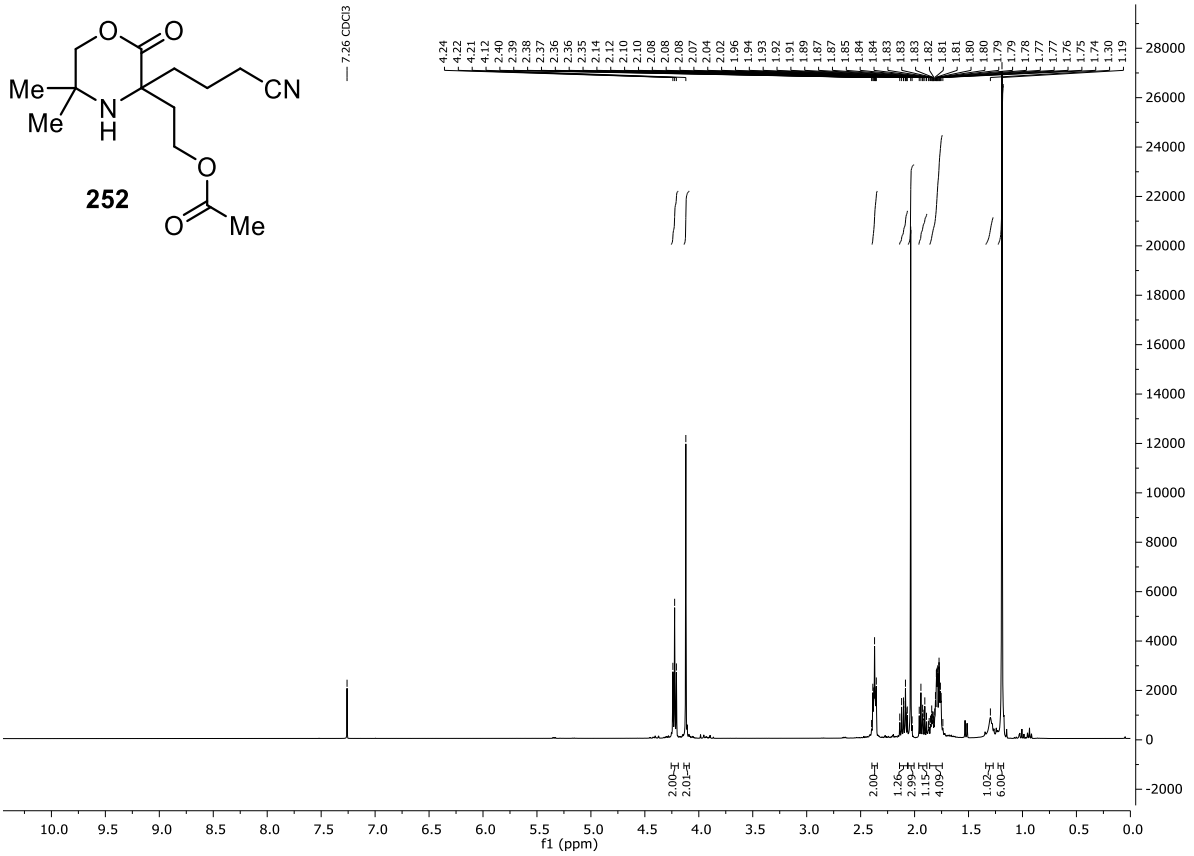

173.82
171.07
77.16 CDCl3
76.43
60.97
59.87
50.03
38.22
35.50
34.76
33.81
25.92
21.84
21.79
21.13
8.43
f1 (ppm)

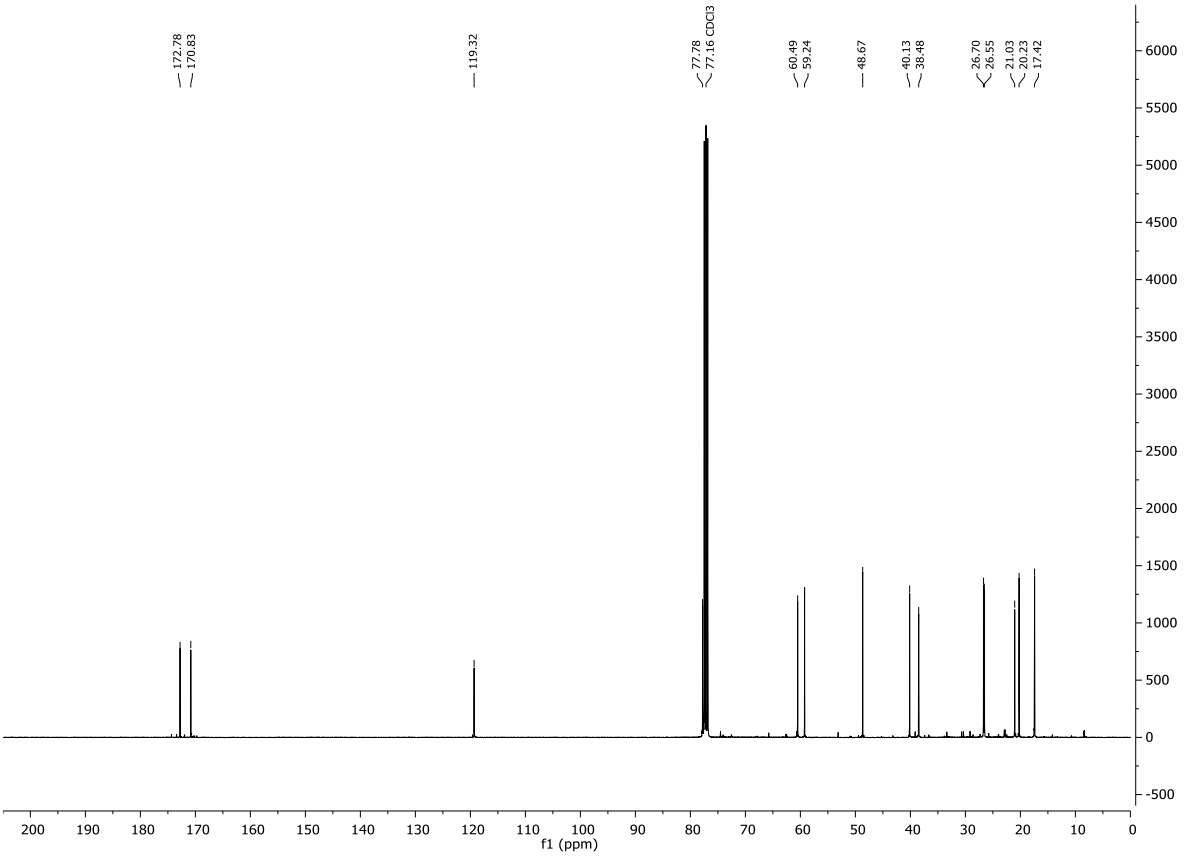

7.26 CDCl3
O
O
N
H
O
Me
Me
O
250
1.99
1.01
1.05
5.07
4.11
10.05
1.33
3.00
f1 (ppm)

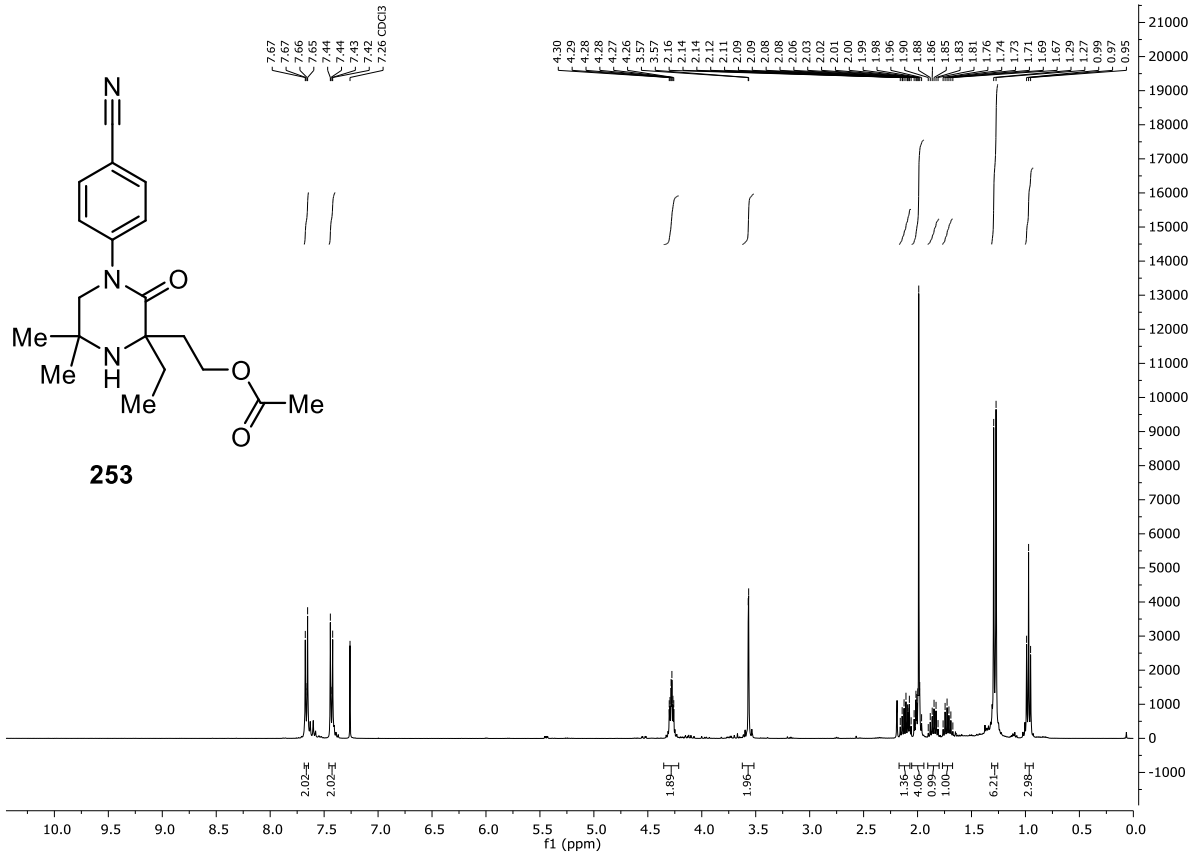

173.91
171.12
77.16 CDCl3
76.55
61.02
59.63
50.06
43.39
38.69
35.53
34.63
25.94
21.82
21.77
21.15
17.37
14.36
f1 (ppm)


Me
Me
N
H
O
O
O
Me
O
Si
Me
Me
Me
251
f1 (ppm)

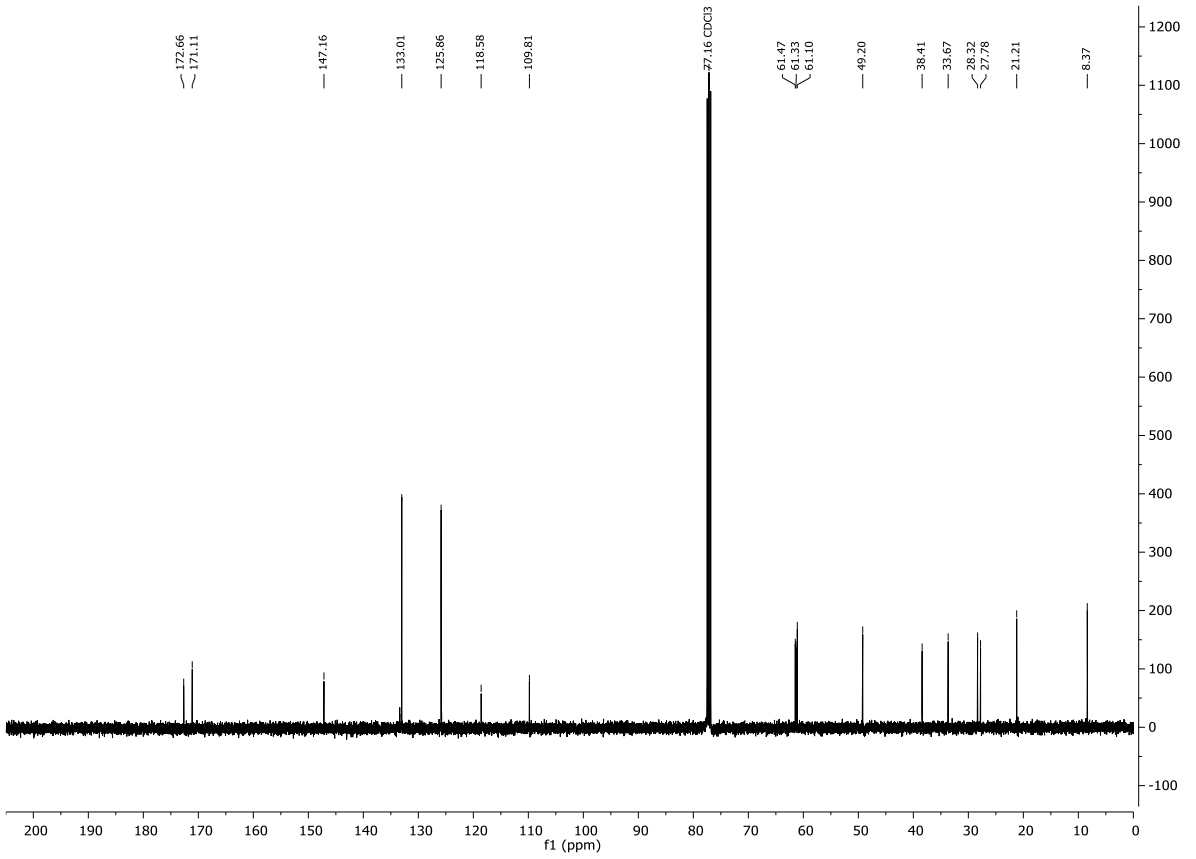

173.44
171.06
77.72
77.16 CDCl3
60.98
59.72
48.62
45.69
38.80
26.99
26.48
21.14
18.44
11.93
7.61
7.60
3.46
f1 (ppm)

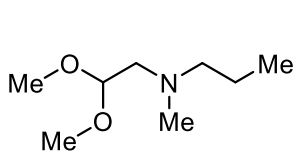

Me
Me
N
H
O
O
CN
O
O
Me
252
7.26 CDCl3
f1 (ppm)


172.78
170.83
119.32
77.78
77.16 CDCl3
60.49
59.24
48.67
40.13
38.48
26.70
26.55
21.03
20.23
17.42
f1 (ppm)


7.67
7.67
7.66
7.65
7.44
7.44
7.43
7.42
7.26 CDCl3
4.30
4.29
4.28
4.28
4.27
4.26
3.57
3.57
2.16
2.14
2.14
2.12
2.11
2.09
2.09
2.08
2.08
2.06
2.03
2.02
2.01
2.00
1.99
1.98
1.96
1.90
1.88
1.86
1.85
1.83
1.81
1.76
1.74
1.73
1.71
1.69
1.67
1.29
1.27
0.99
0.97
0.95
N
O
Me
Me
N
H
Me
O
Me
O
2.02
2.02
1.89
1.96
1.35
4.06
0.99
1.00
6.21
2.98
f1 (ppm)

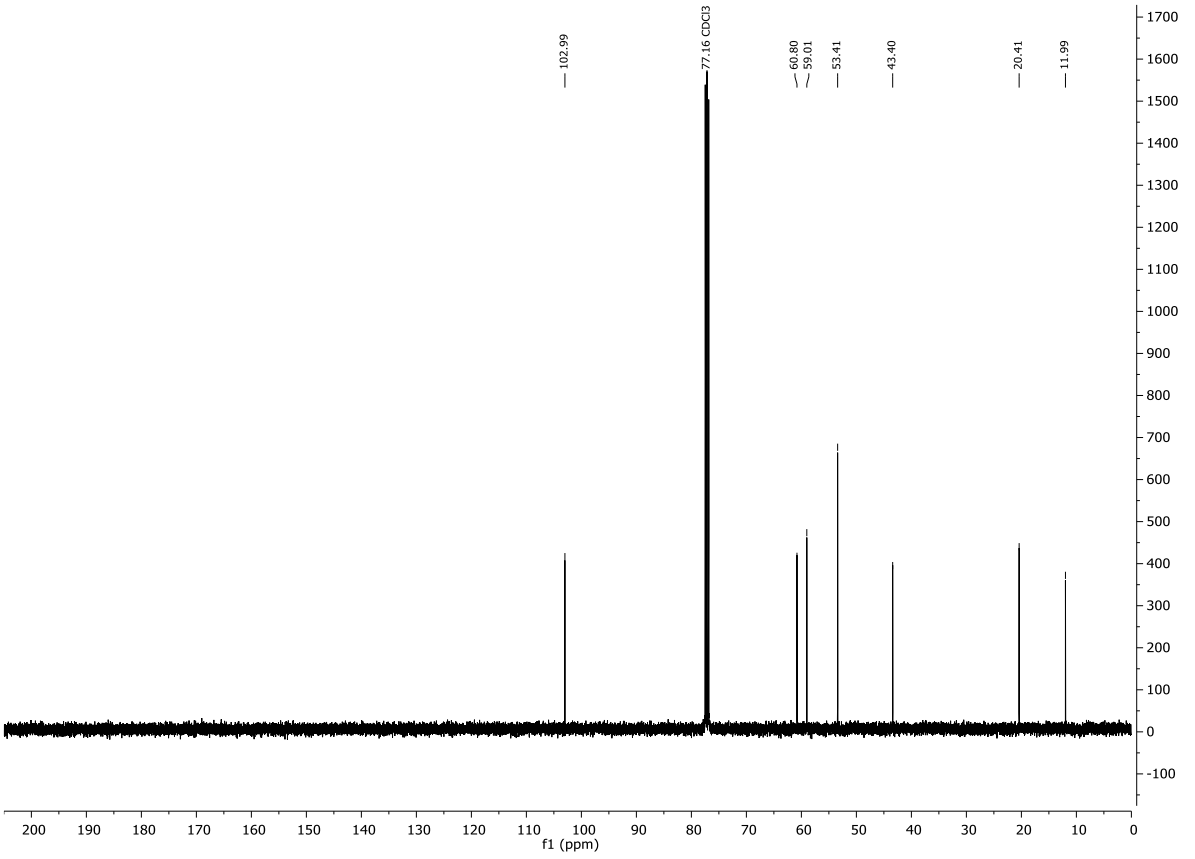
253

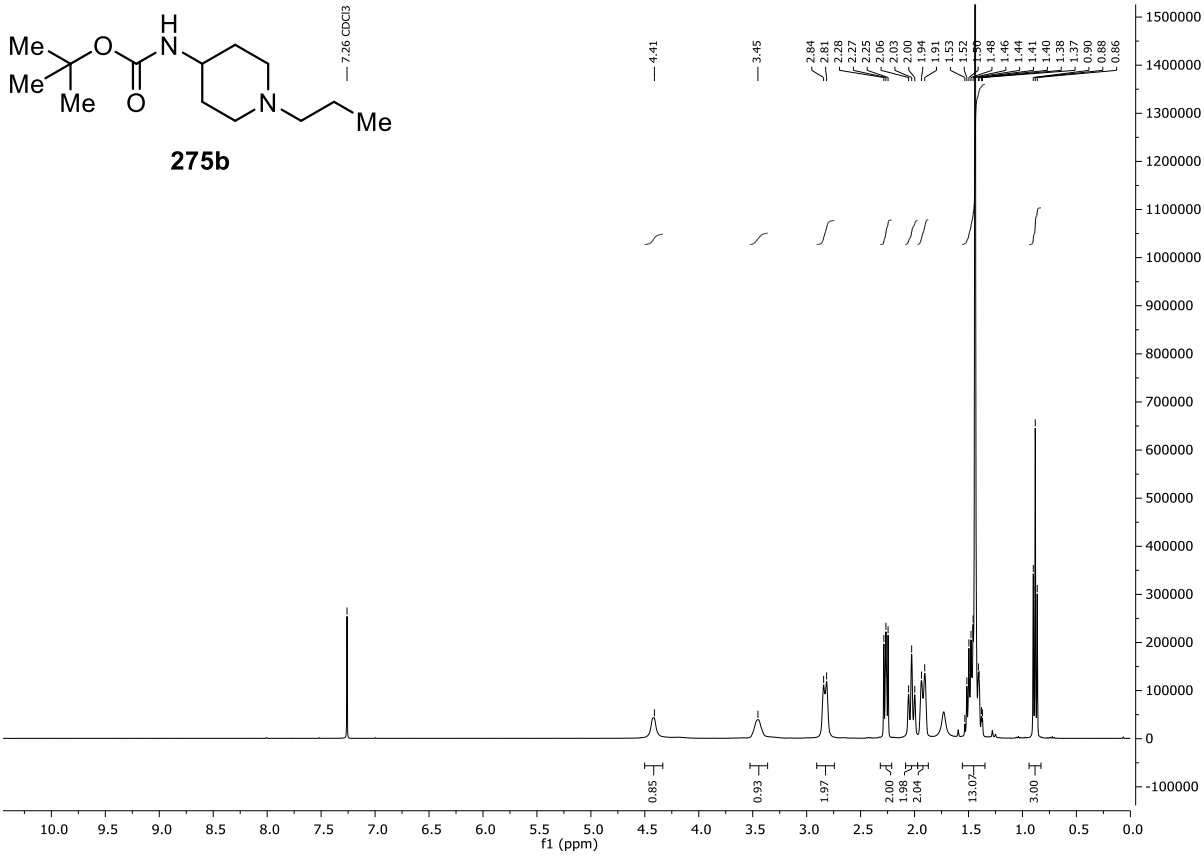

172.66
171.11
147.16
133.01
125.86
118.58
109.81
77.16 CDCl3
61.47
61.33
61.10
49.20
38.41
33.67
28.32
27.78
21.21
8.37
f1 (ppm)

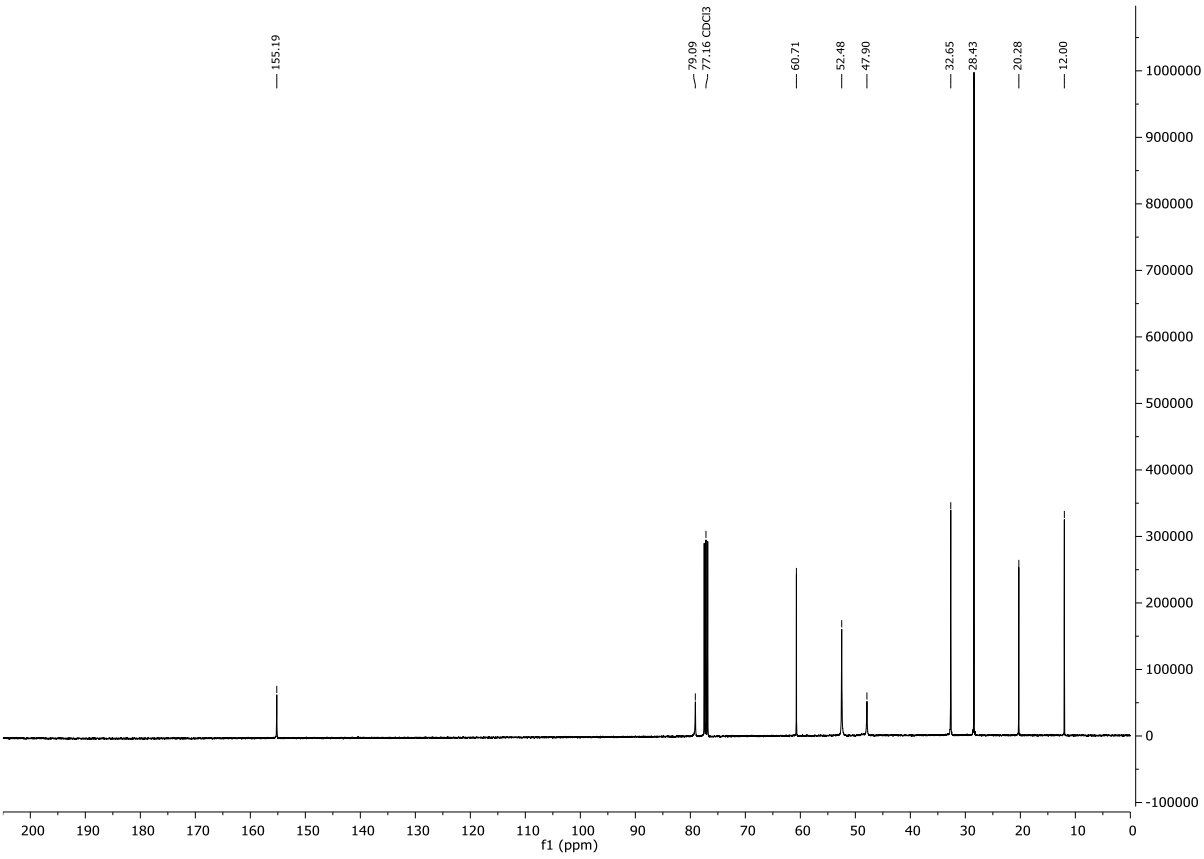

Me
O
Me
O
N
Me
Me

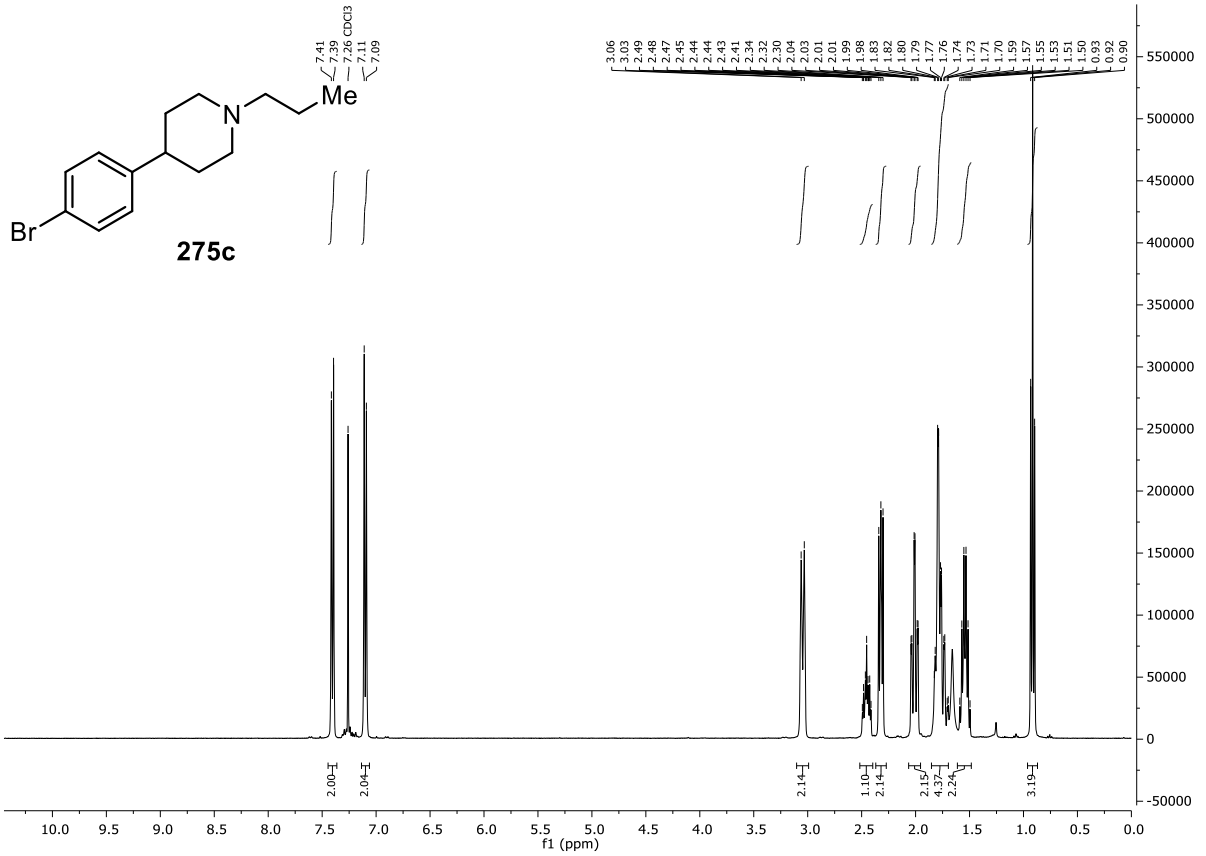
275a

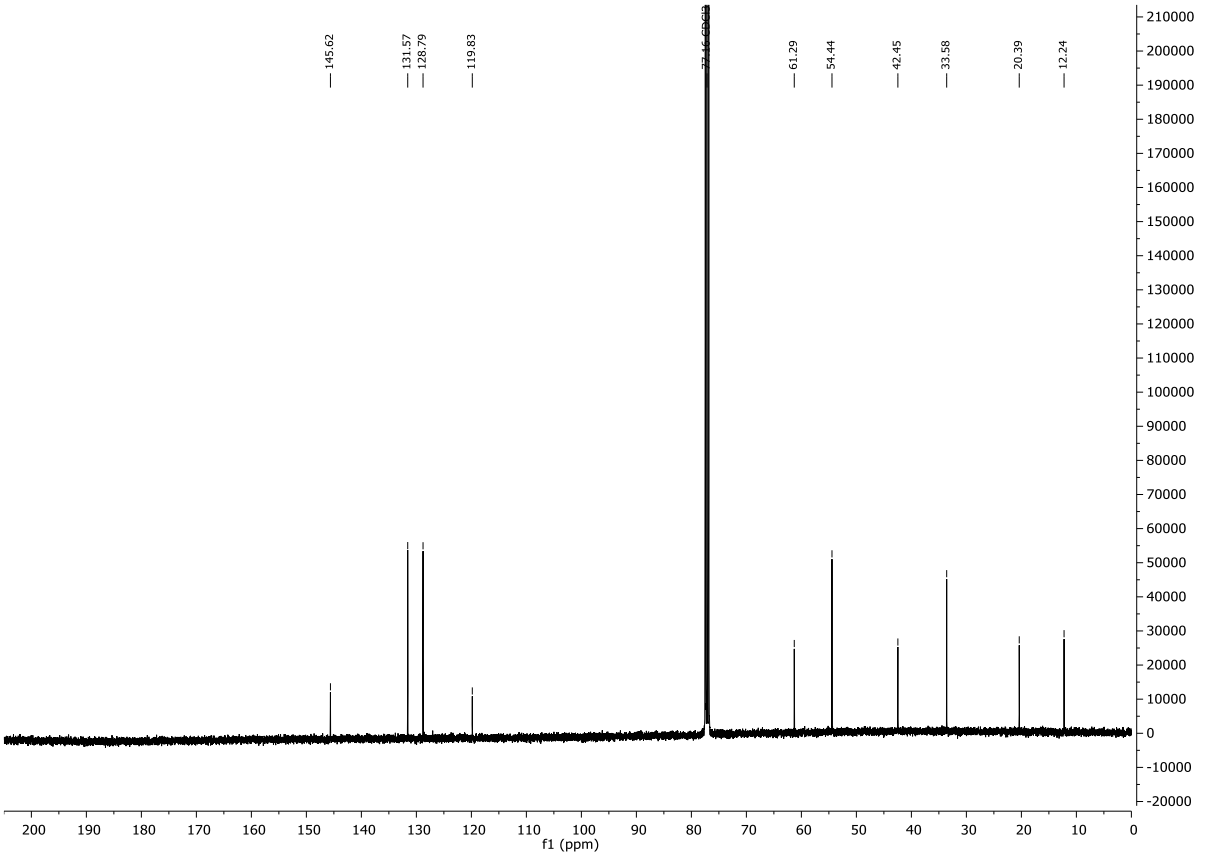
7.26 CDCl3
4.49
4.48
4.47
3.36
2.51
2.50
2.37
2.35
2.33
2.29
1.53
1.51
1.49
1.47
1.46
1.44
0.90
0.88
0.86
1.00
6.15
2.17
2.18
3.10
2.11
3.08
f1 (ppm)

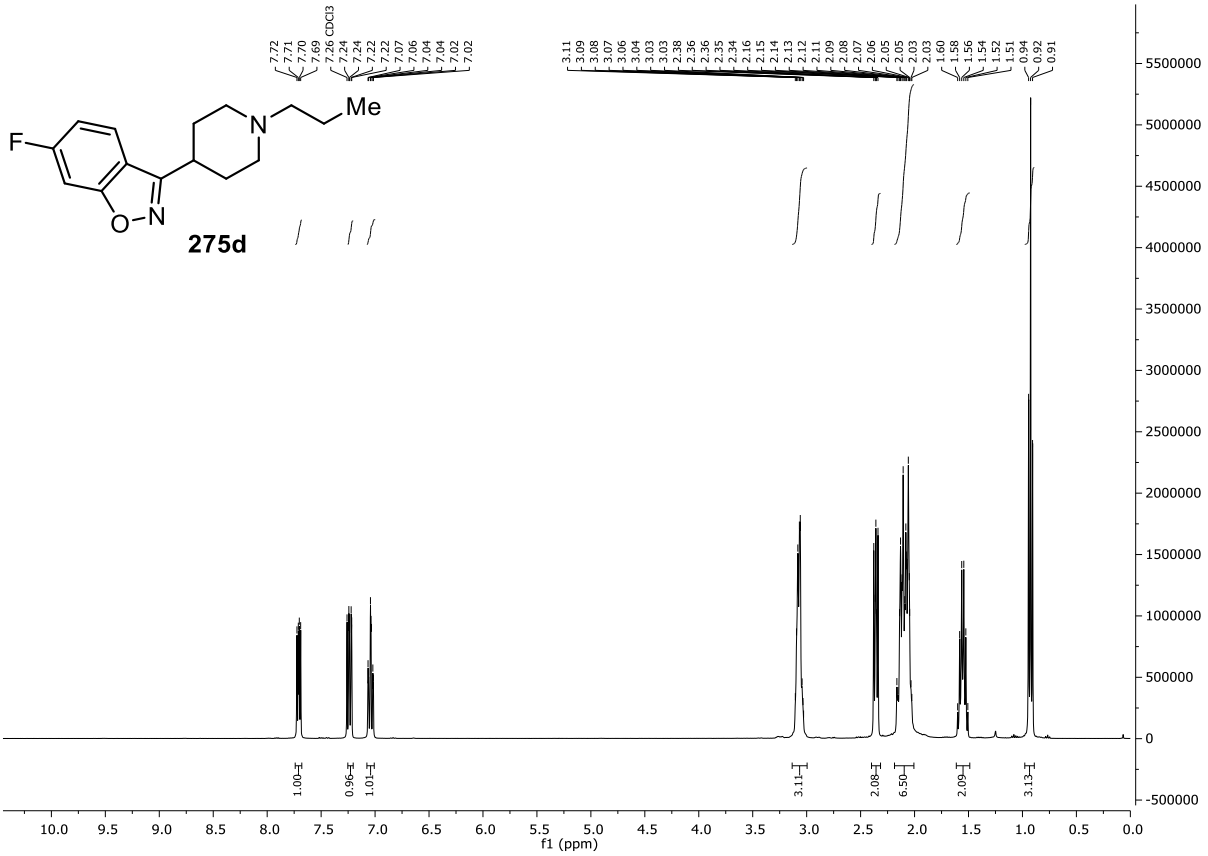

102.99
77.16 CDCl3
60.80
59.01
53.41
43.40
20.41
11.99
f1 (ppm)

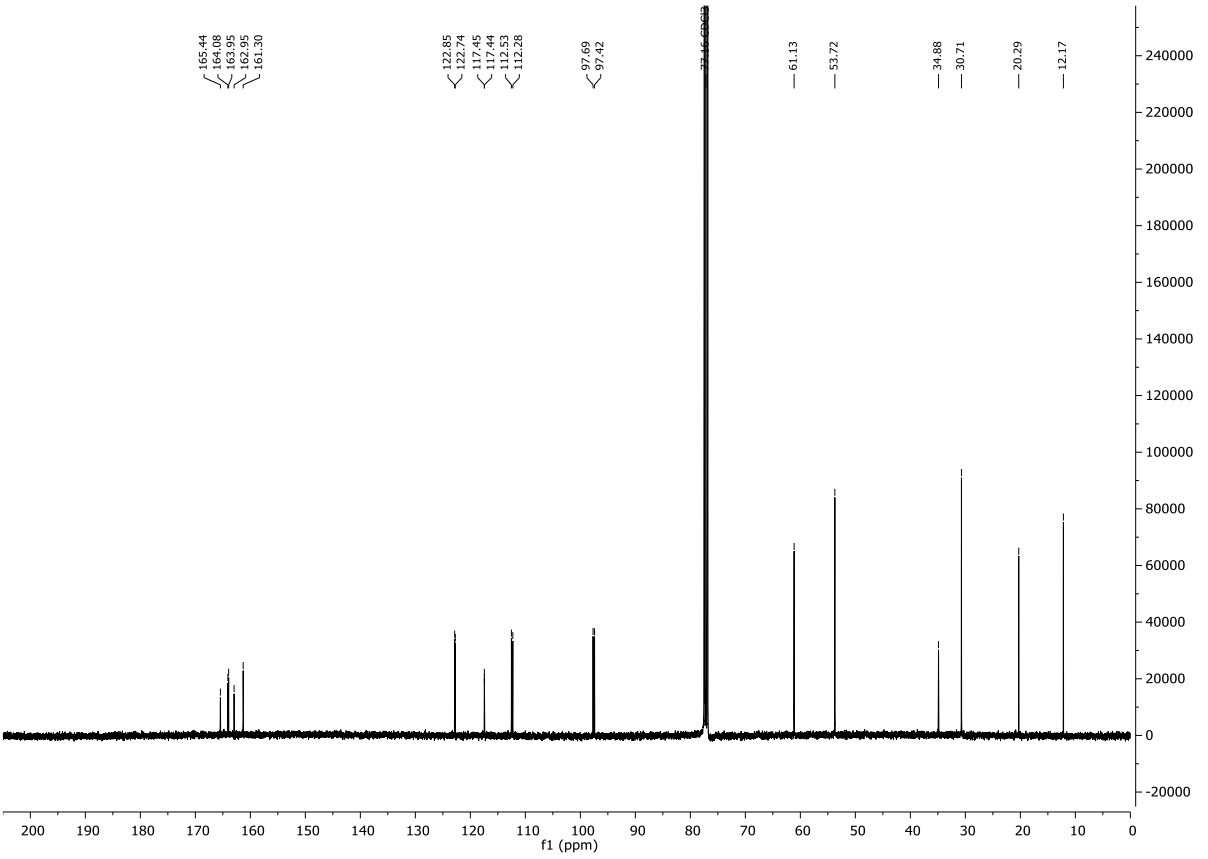

Me
Me
Me
O
O
H
N
N
Me
7.26 CDCl3
275b
4.41
3.45
2.84
2.81
2.28
2.27
2.25
2.06
2.03
2.00
1.94
1.91
1.53
1.52
1.48
1.46
1.44
1.41
1.40
1.38
1.37
0.90
0.88
0.86
0.85
0.93
1.97
2.00
1.98
2.04
13.07
3.00
f1 (ppm)

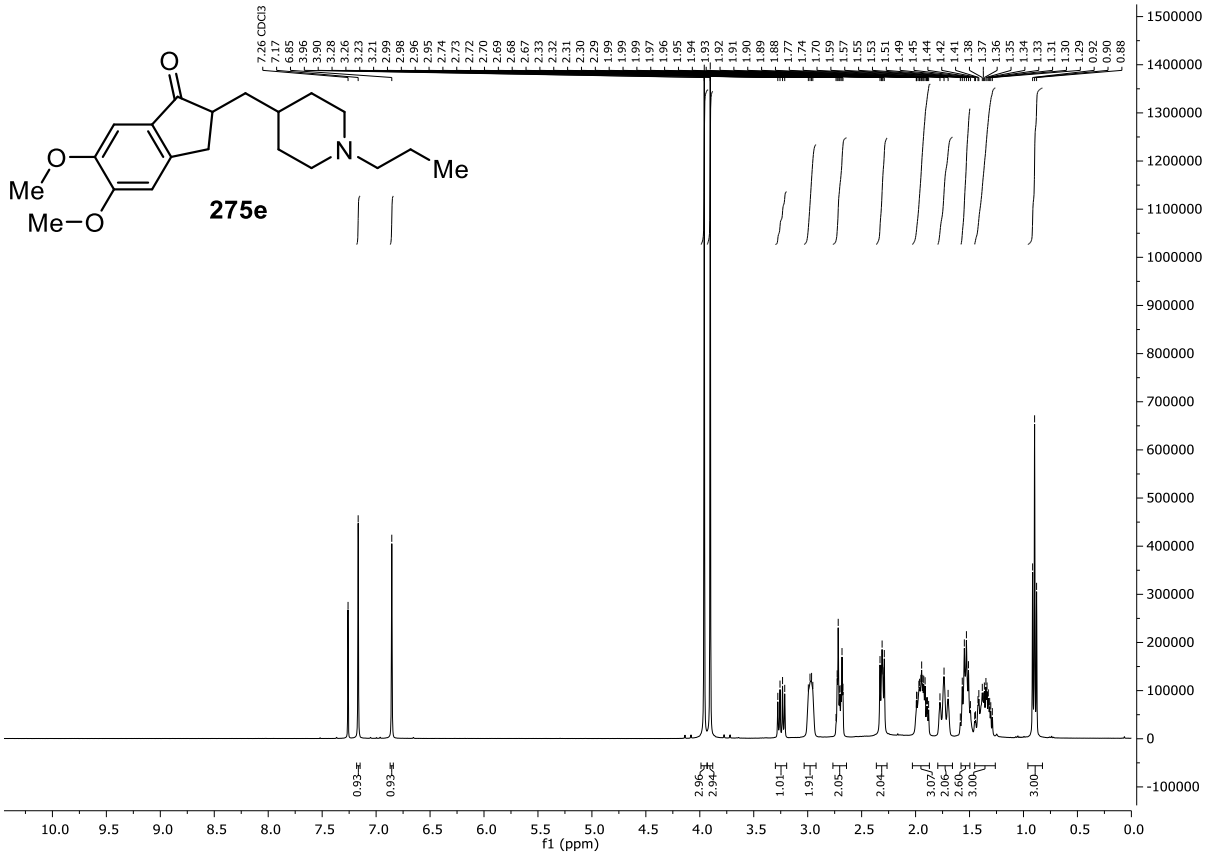

155.19
79.09
77.16 CDCl3
60.71
52.48
47.90
32.65
28.43
20.28
12.00
f1 (ppm)

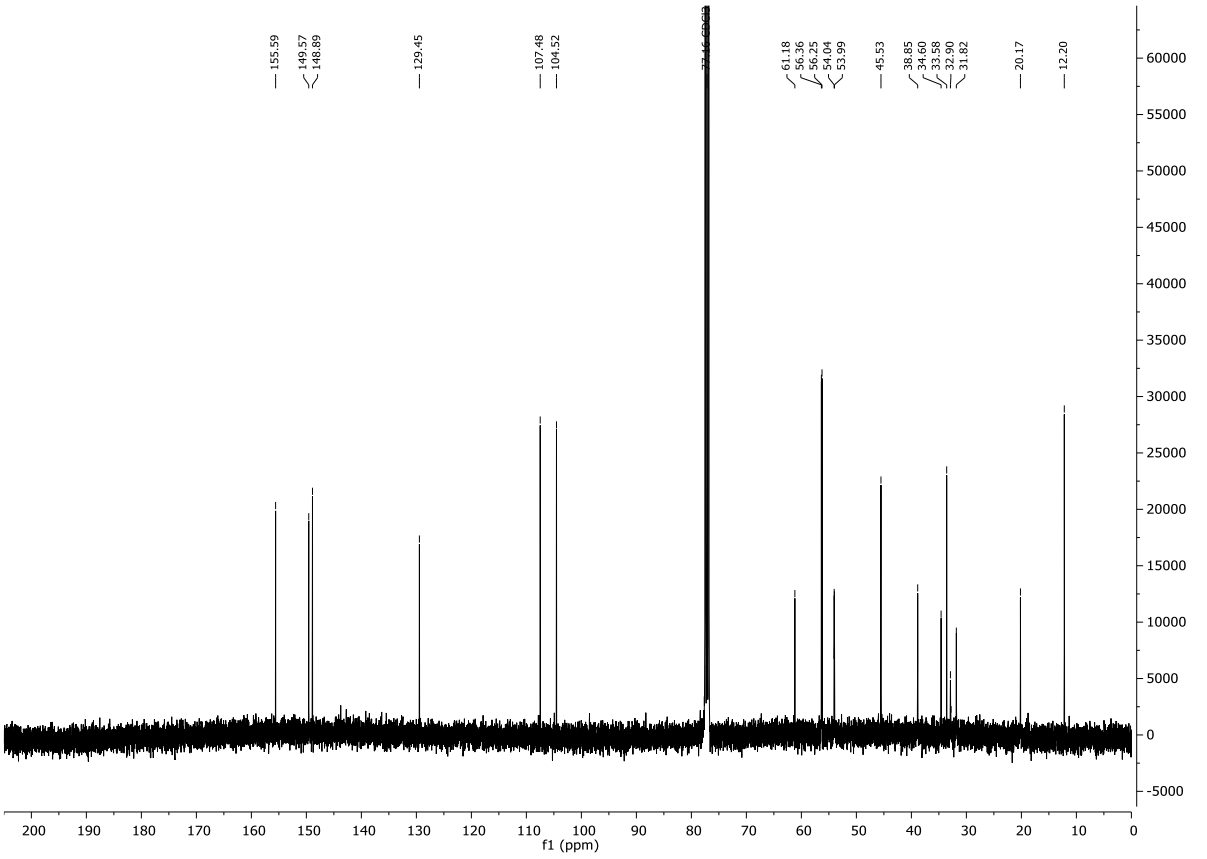

Me
N
Br
275c
f1 (ppm)

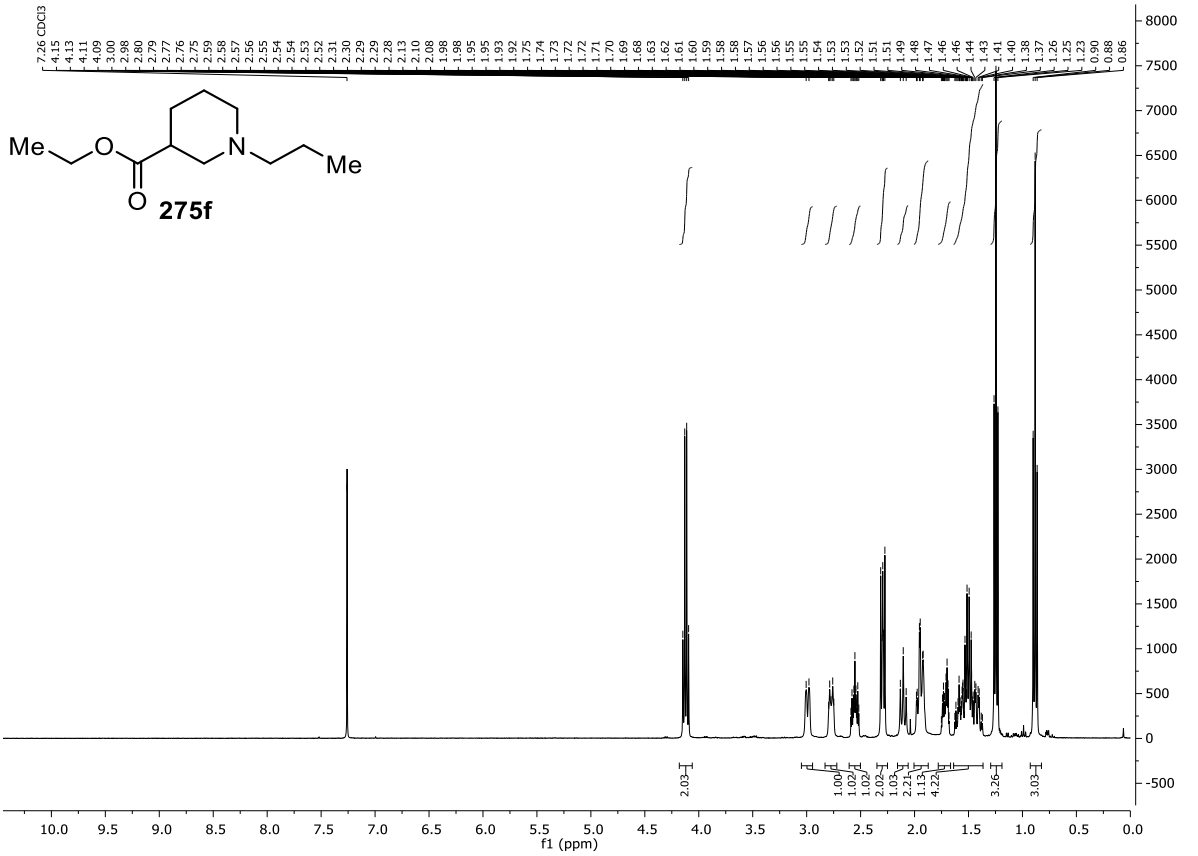

f1 (ppm)

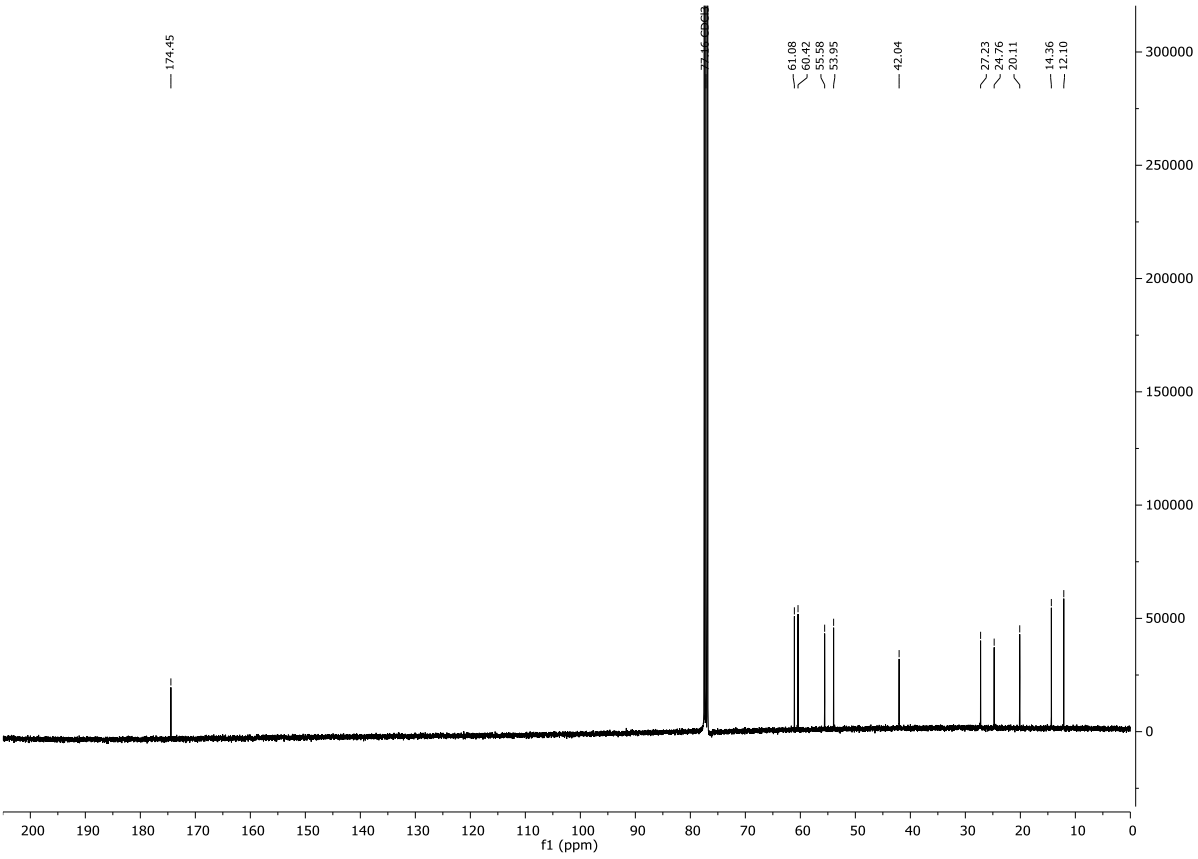

F
N
Me
O
N
275d
7.72
7.71
7.70
7.69
7.26 CDCl3
7.24
7.24
7.22
7.22
7.07
7.06
7.04
7.04
7.02
7.02
3.11
3.09
3.08
3.07
3.06
3.04
3.03
3.03
2.38
2.36
2.35
2.34
2.16
2.15
2.14
2.13
2.12
2.11
2.09
2.08
2.07
2.06
2.05
2.05
2.03
2.03
1.60
1.58
1.56
1.54
1.52
1.51
0.94
0.92
0.91
1.00
0.96
1.01
3.11
2.08
6.50
2.09
3.13
f1 (ppm)

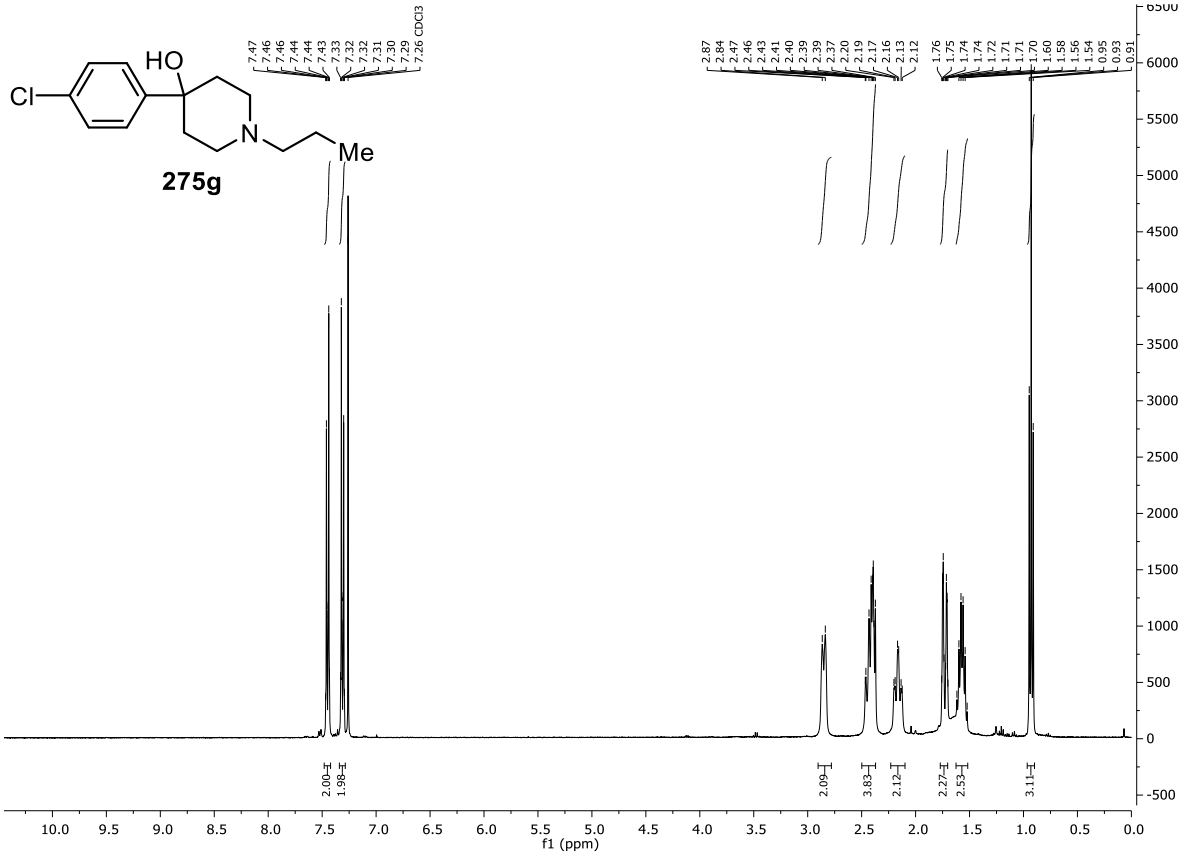

165.44
164.08
163.95
162.95
161.30
122.85
122.74
117.45
117.44
112.53
112.28
97.69
97.42
77.16 CDCl3
61.13
53.72
34.88
30.71
20.29
12.17
f1 (ppm)

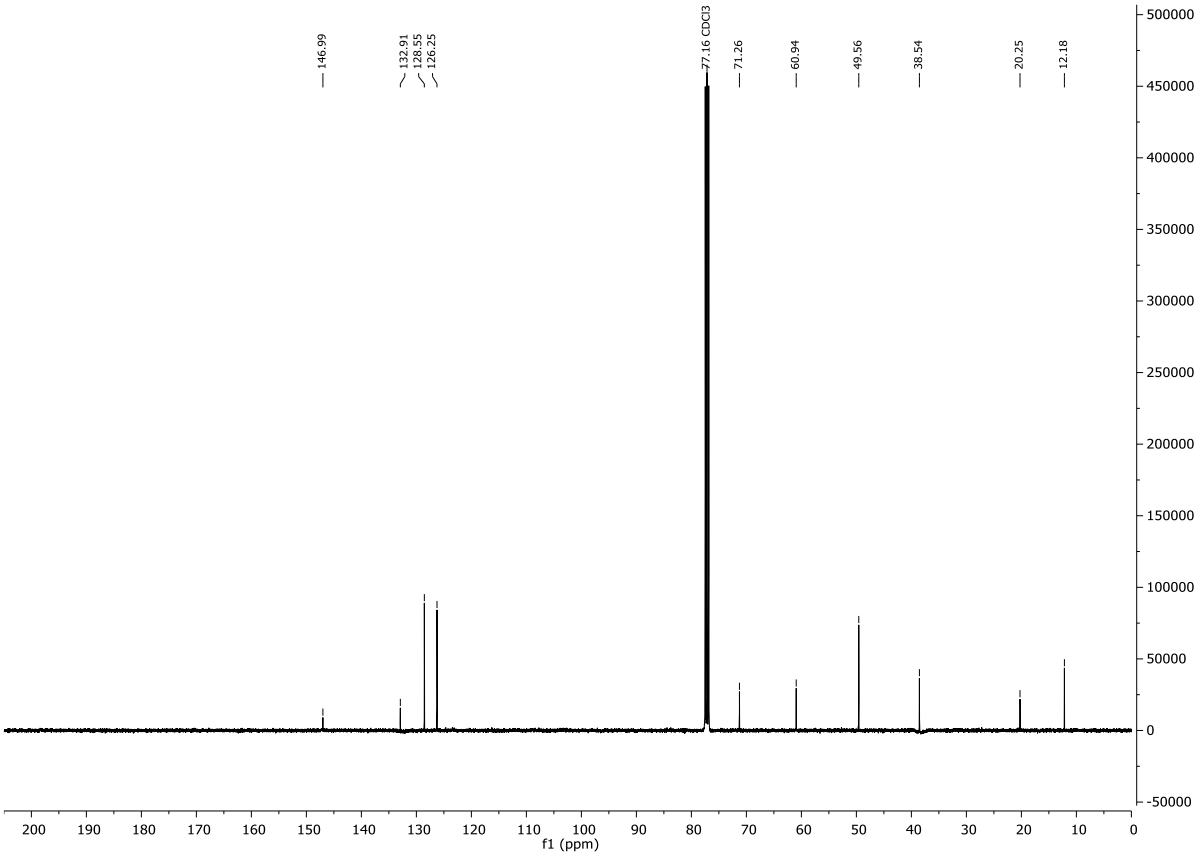

275e
Me
Me
Me
O
O
O
N
f1 (ppm)

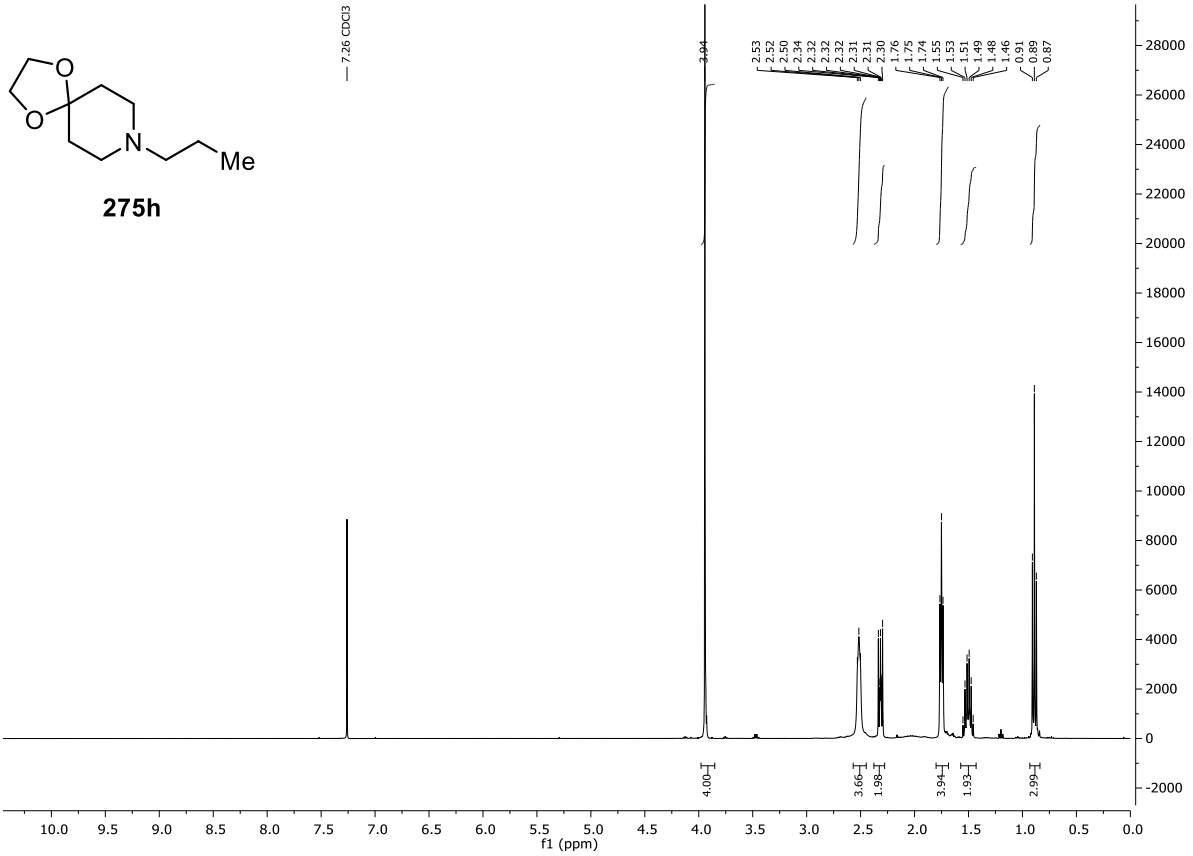

155.59
149.57
148.89
129.45
107.48
104.52
61.18
56.36
56.25
54.04
53.99
45.53
38.85
34.60
33.58
32.90
31.82
20.17
12.20
f1 (ppm)


Me
O
O
N
Me
275f
f1 (ppm)

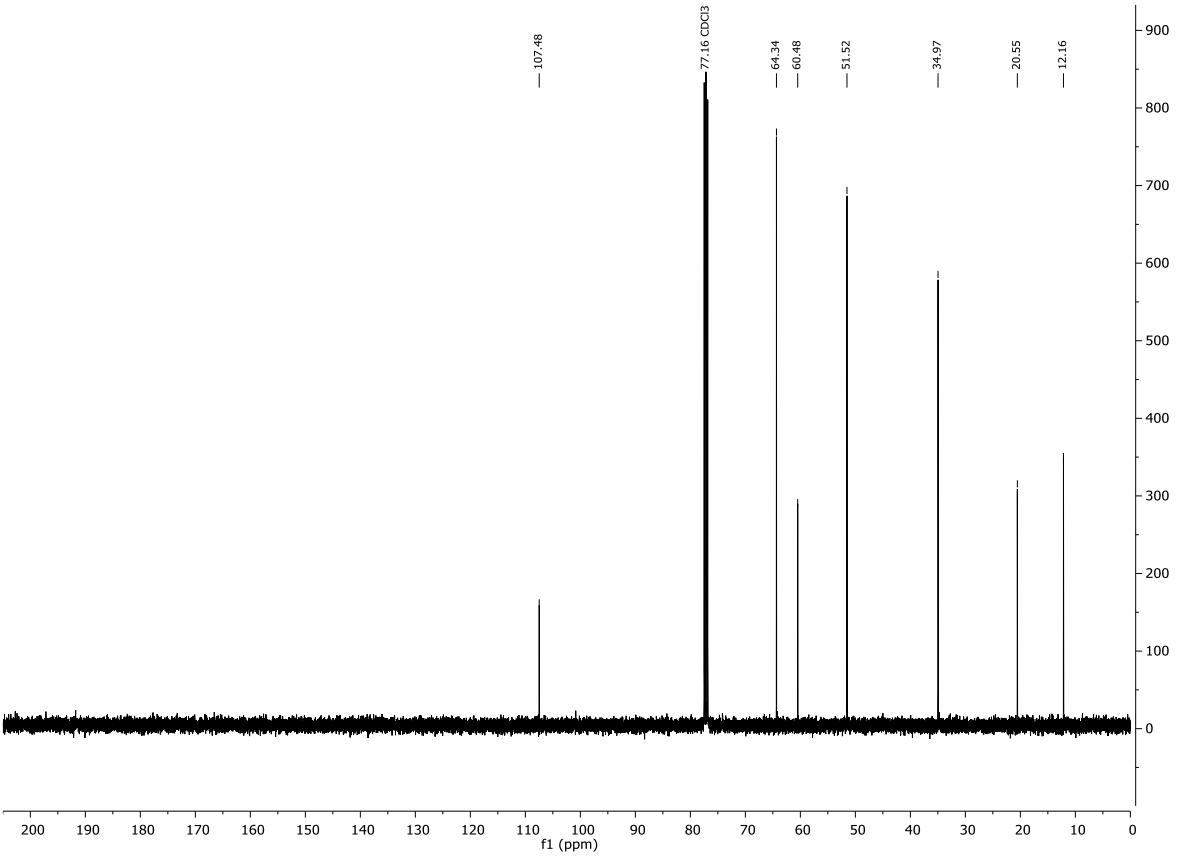

174.45
77.16 CDCl3
61.08
60.42
55.58
53.95
42.04
27.23
24.76
20.11
14.36
12.10
f1 (ppm)

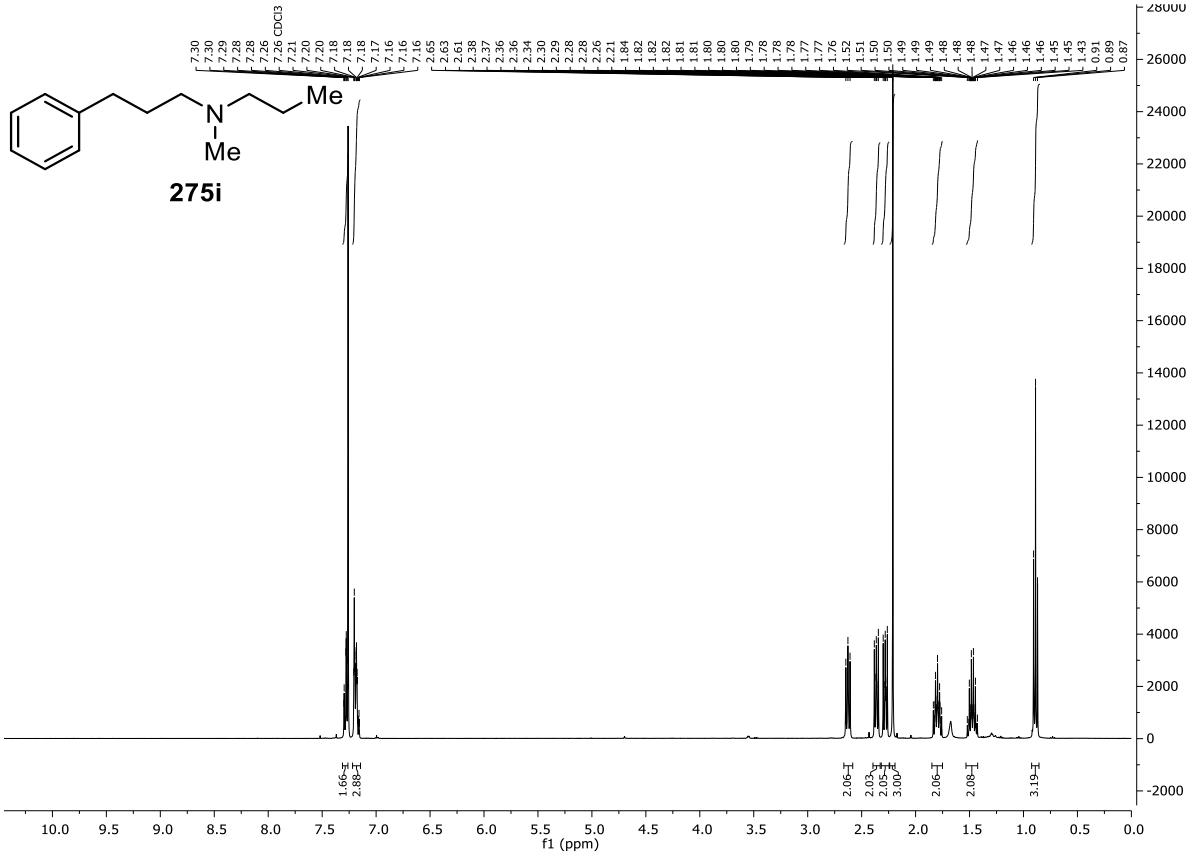

HO
Cl
N
Me
275g
7.47
7.46
7.46
7.44
7.44
7.43
7.33
7.32
7.32
7.31
7.30
7.29
7.26 CDCl3
2.87
2.84
2.47
2.46
2.43
2.41
2.40
2.39
2.39
2.37
2.20
2.19
2.17
2.16
2.13
2.12
1.76
1.75
1.74
1.74
1.72
1.71
1.71
1.70
1.60
1.58
1.56
1.54
0.95
0.93
0.91
2.00
1.98
2.09
3.83
2.12
2.27
2.53
3.11
f1 (ppm)

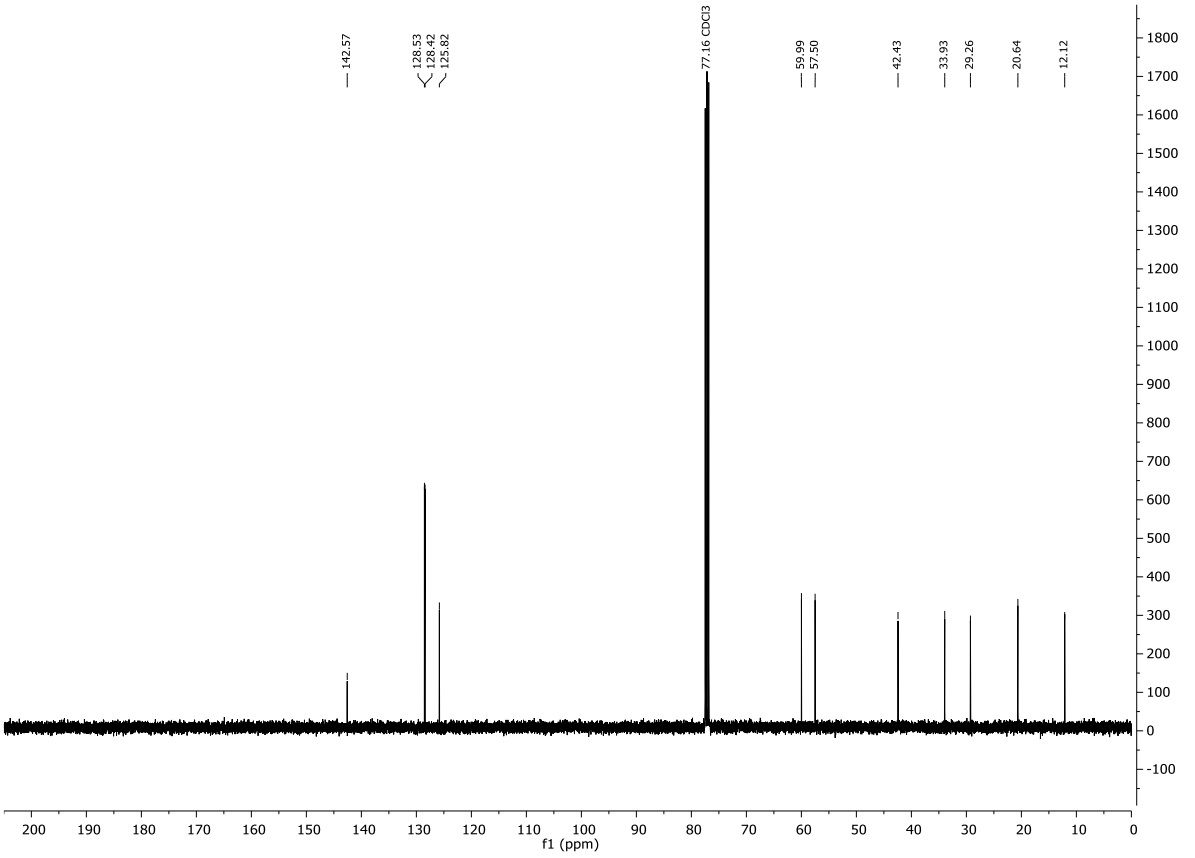

146.99
132.91
128.55
126.25
77.16 CDCl3
71.26
60.94
49.56
38.54
20.25
12.18
f1 (ppm)

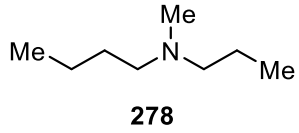

7.26 CDCl3
3.94
2.53
2.52
2.50
2.34
2.32
2.32
2.32
2.31
2.31
2.30
1.76
1.75
1.74
1.55
1.53
1.51
1.49
1.48
1.46
0.91
0.89
0.87
4.00
3.66
1.98
3.94
1.93
2.99
f1 (ppm)

275h


107.48
77.16 CDCl3
64.34
60.48
51.52
34.97
20.55
12.16
f1 (ppm)

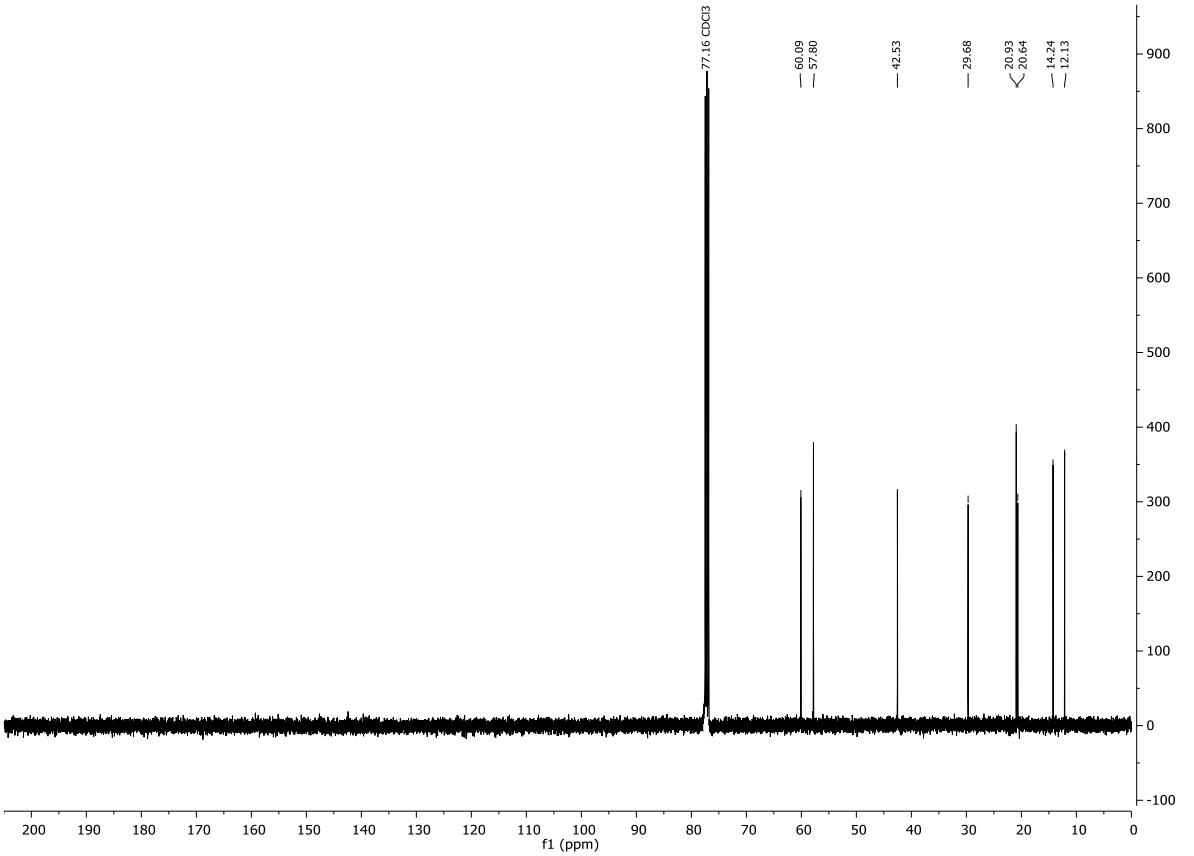

Me
N
Me
275i
f1 (ppm)

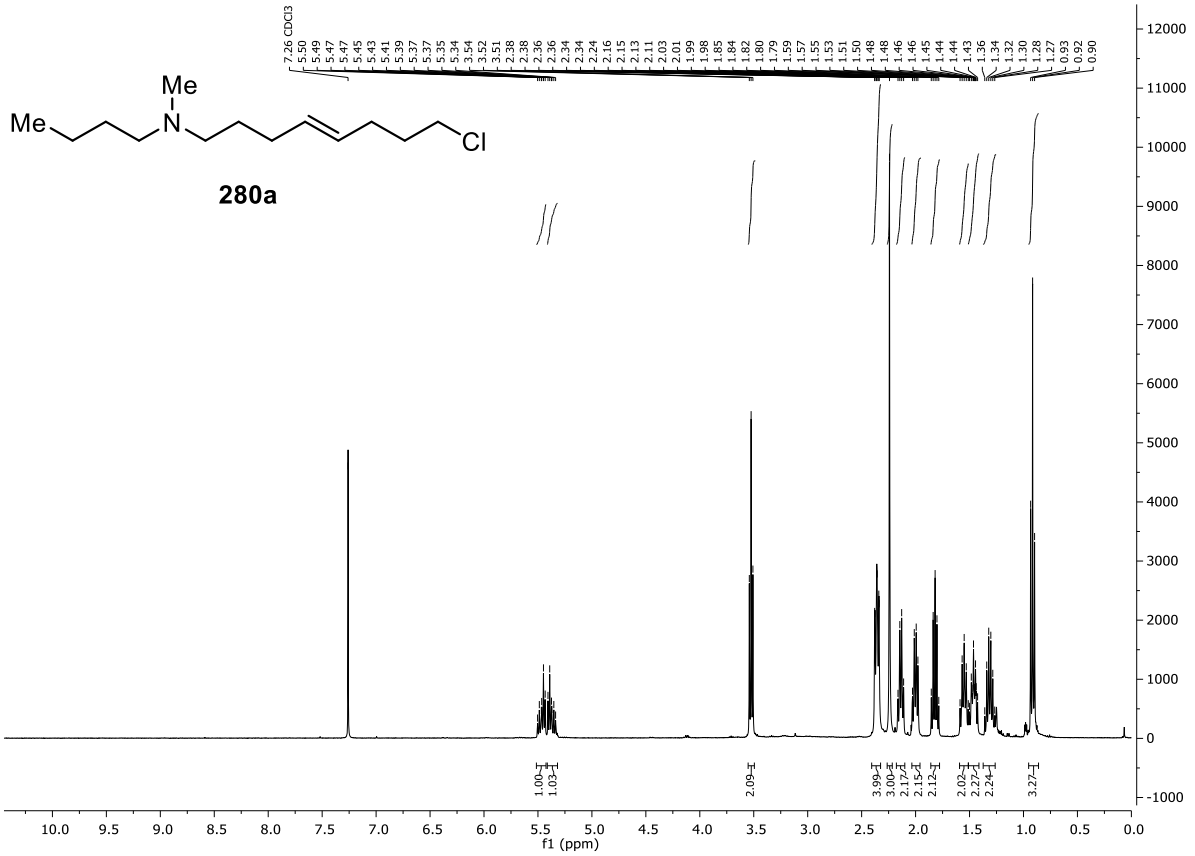

142.57
128.53
128.42
125.82
77.16 CDCl3
59.99
57.50
42.43
33.93
29.26
20.64
12.12
f1 (ppm)

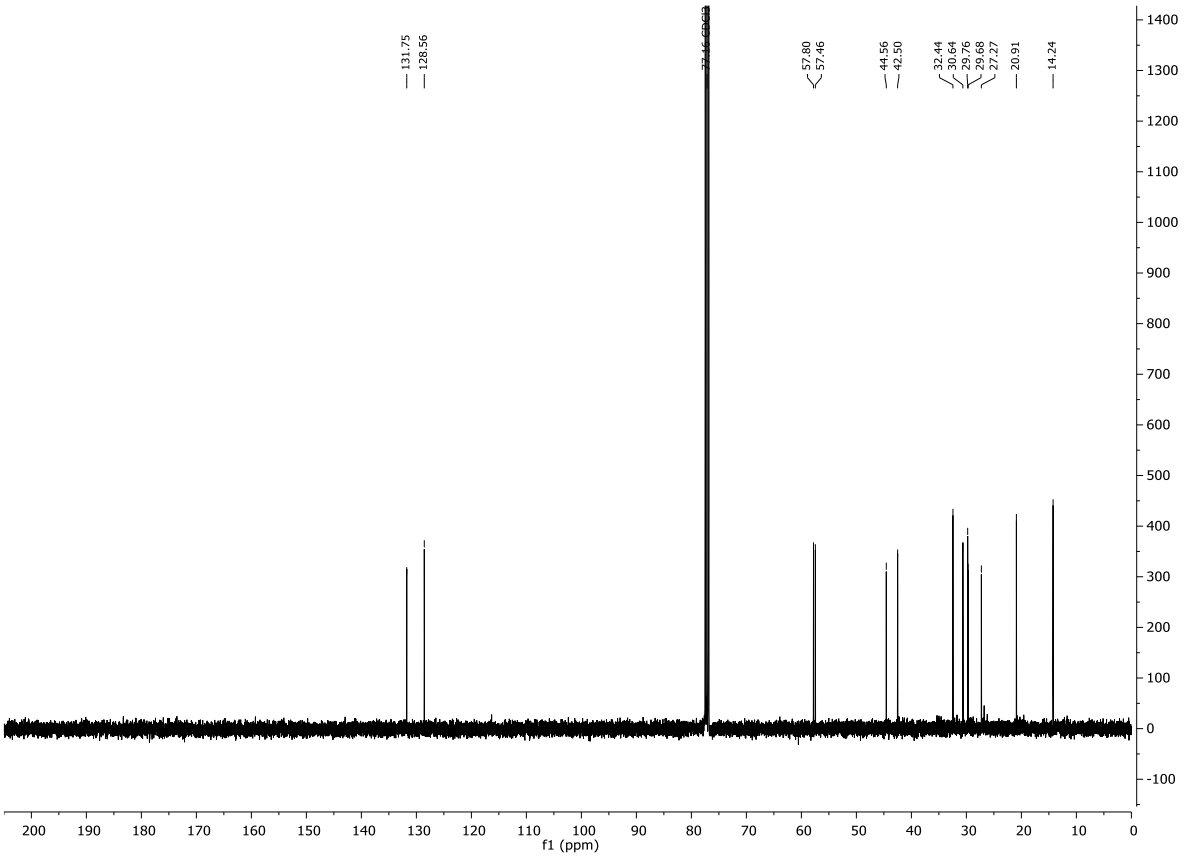

Me
N
Me
Me

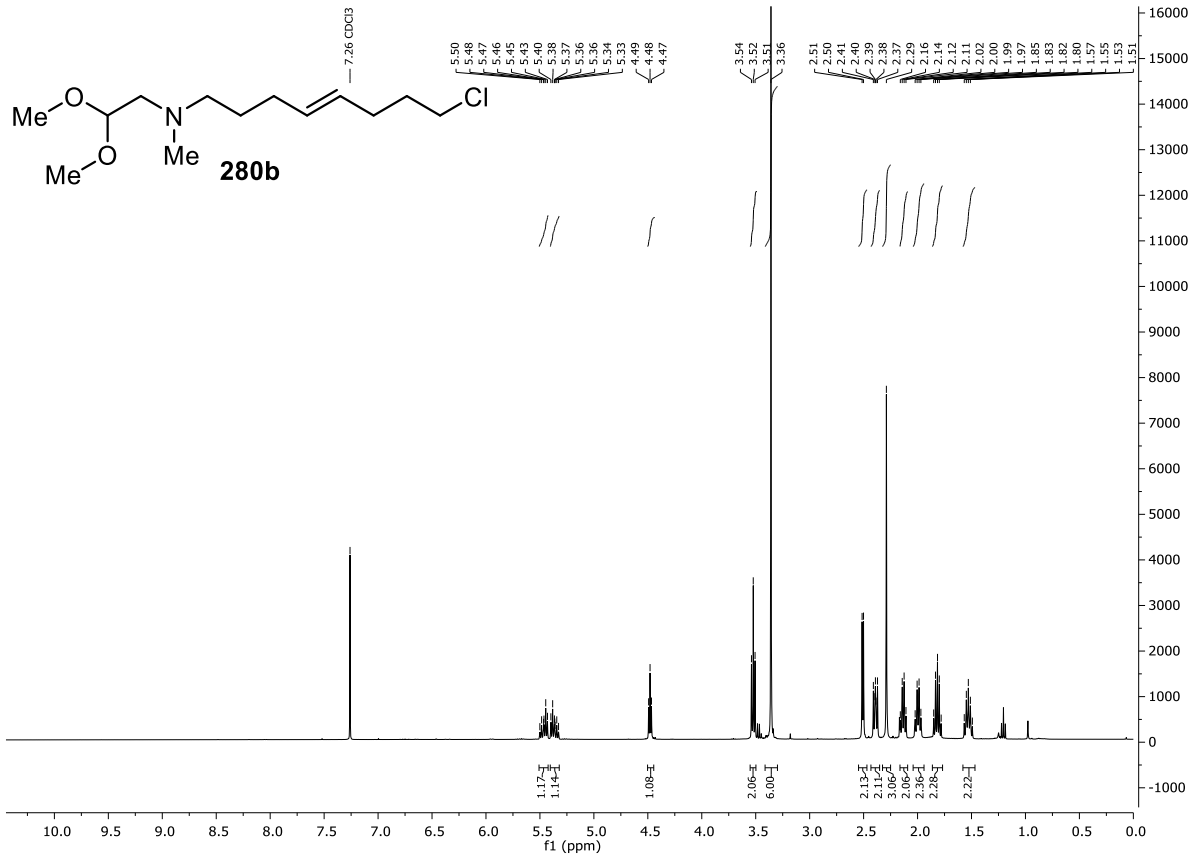
278

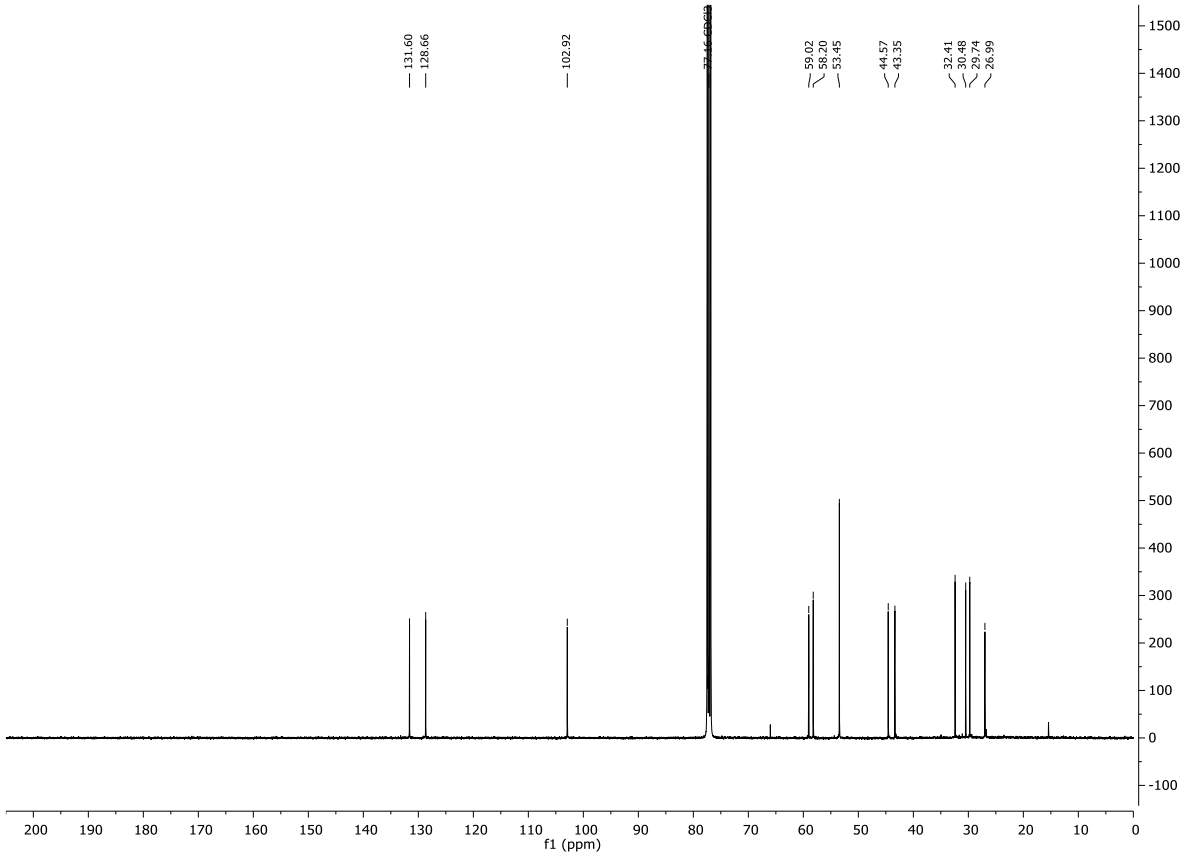
7.26 CDCl3
2.32
2.31
2.30
2.30
2.29
2.28
2.27
2.27
2.26
2.25
2.20
1.52
1.50
1.49
1.48
1.48
1.47
1.46
1.46
1.45
1.45
1.44
1.43
1.42
1.41
1.40
1.35
1.33
1.31
1.29
1.28
1.26
0.93
0.91
0.90
0.89
0.88
0.86
3.98
2.89
4.00
2.02
6.00
f1 (ppm)

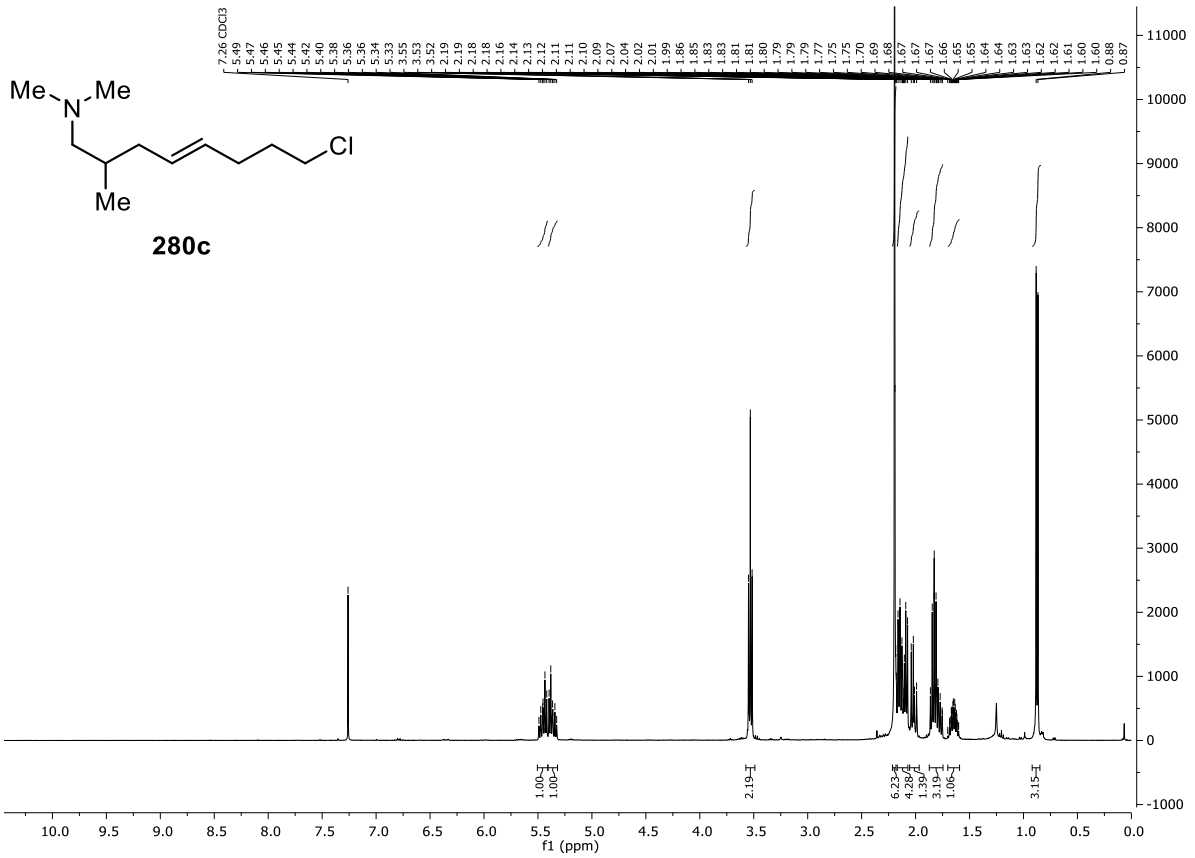

77.16 CDCl3
60.09
57.80
42.53
29.68
20.93
20.64
14.24
12.13
f1 (ppm)

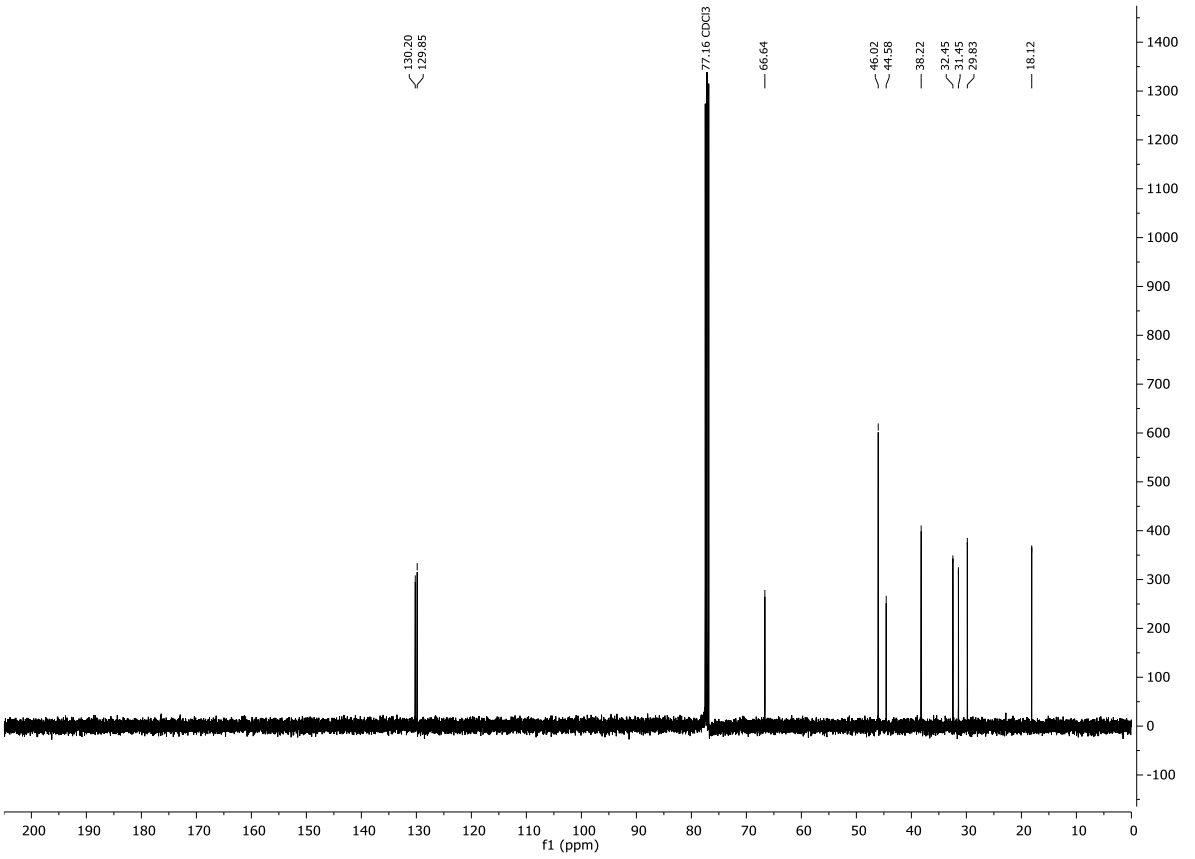

Me
N
Me
Cl
280a
7.26 CDCl3
f1 (ppm)

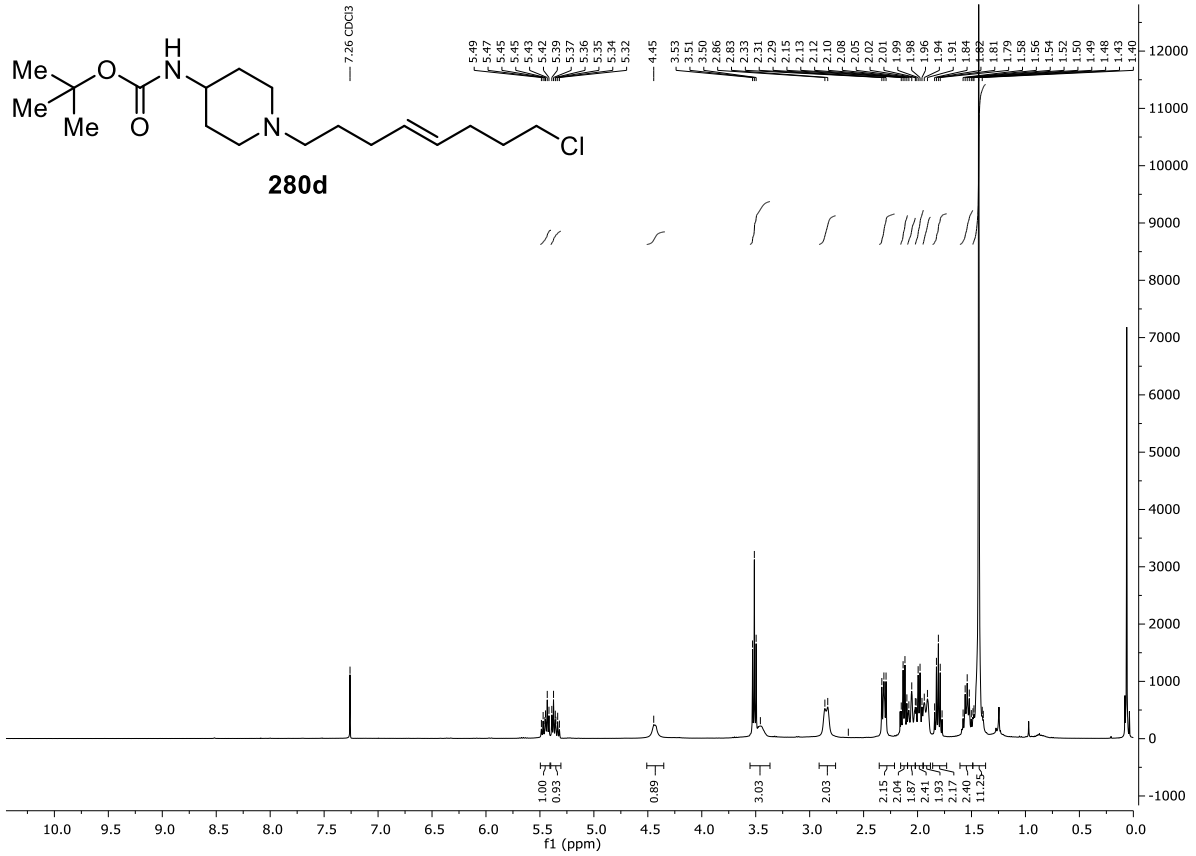

131.75
128.56
77.16 CDCl3
57.80
57.46
44.56
42.50
32.44
30.64
29.76
29.68
27.27
20.91
14.24
f1 (ppm)

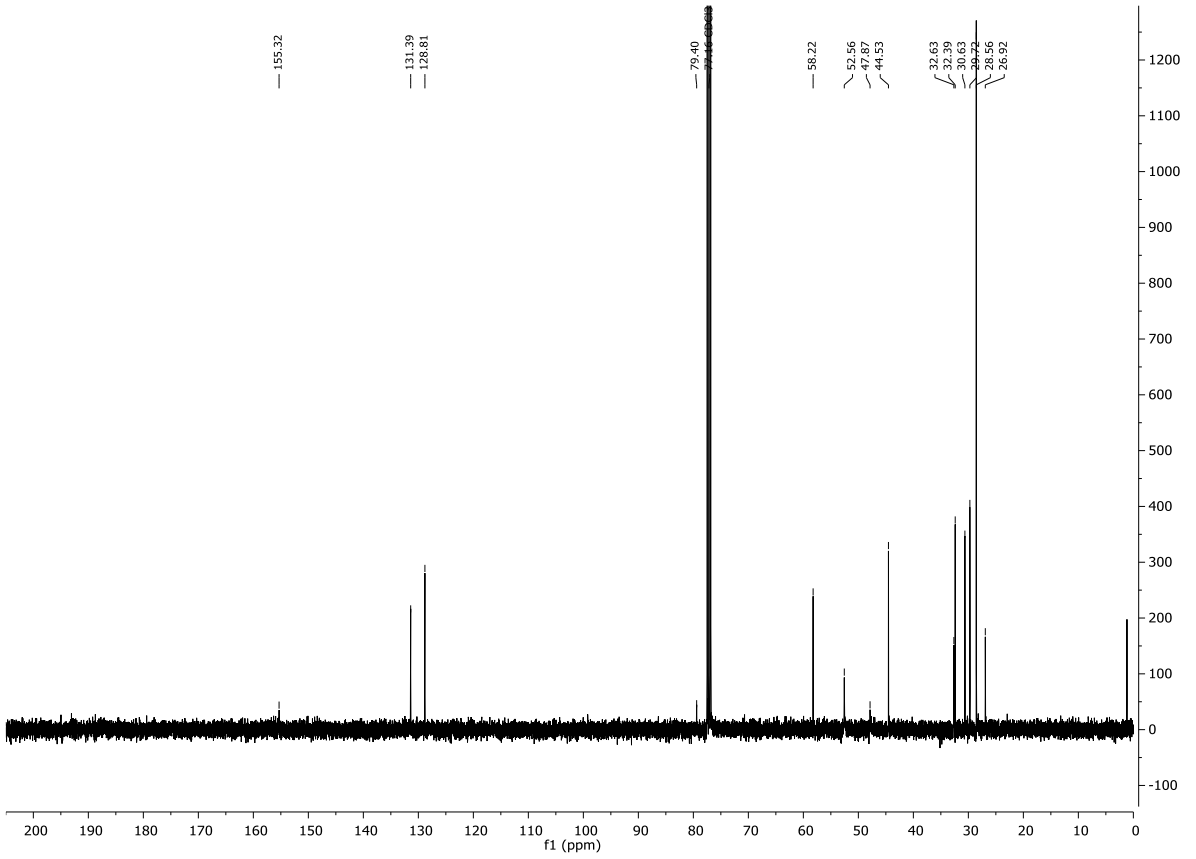

Me
O
Me
O
N
Me
Cl
280b
7.26 CDCl3
f1 (ppm)

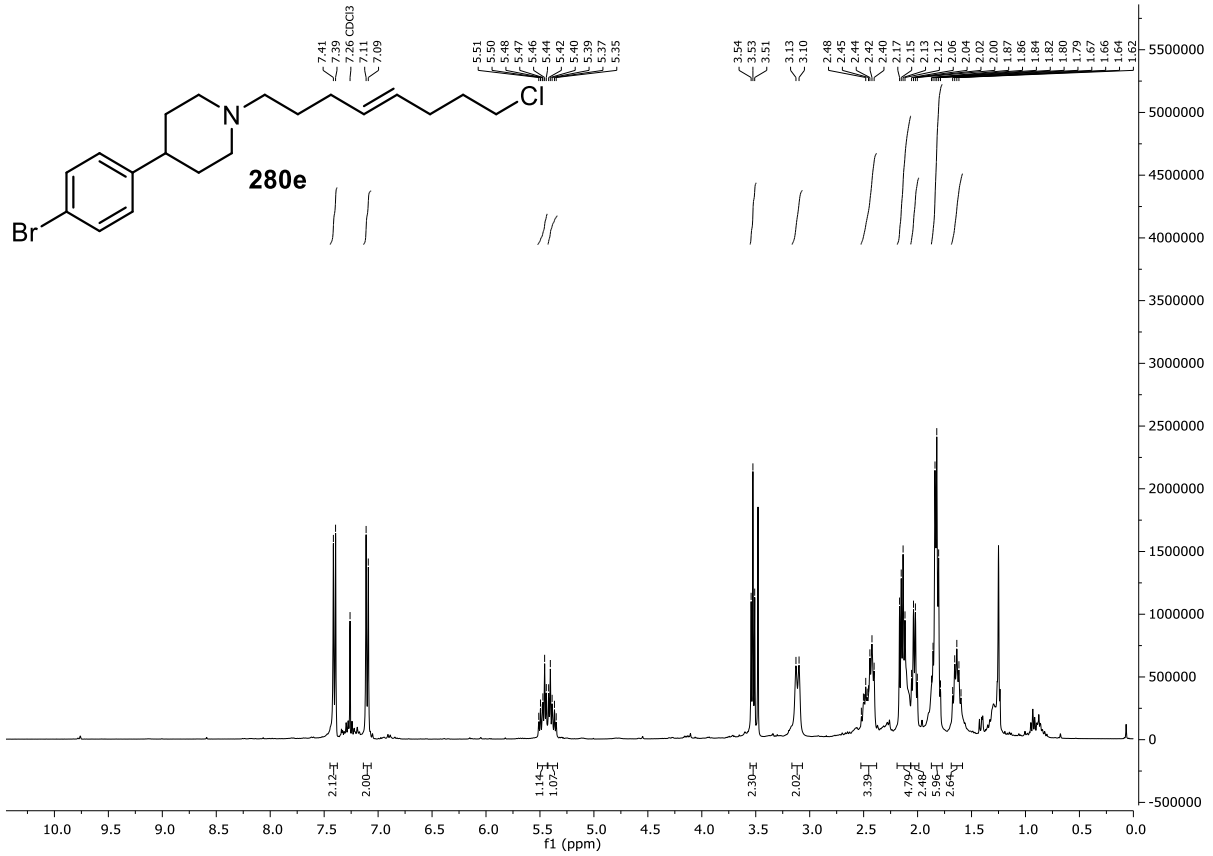

131.60
128.66
102.92
77.16 CDCl3
59.02
58.20
53.45
44.57
43.35
32.41
30.48
29.74
26.99
f1 (ppm)

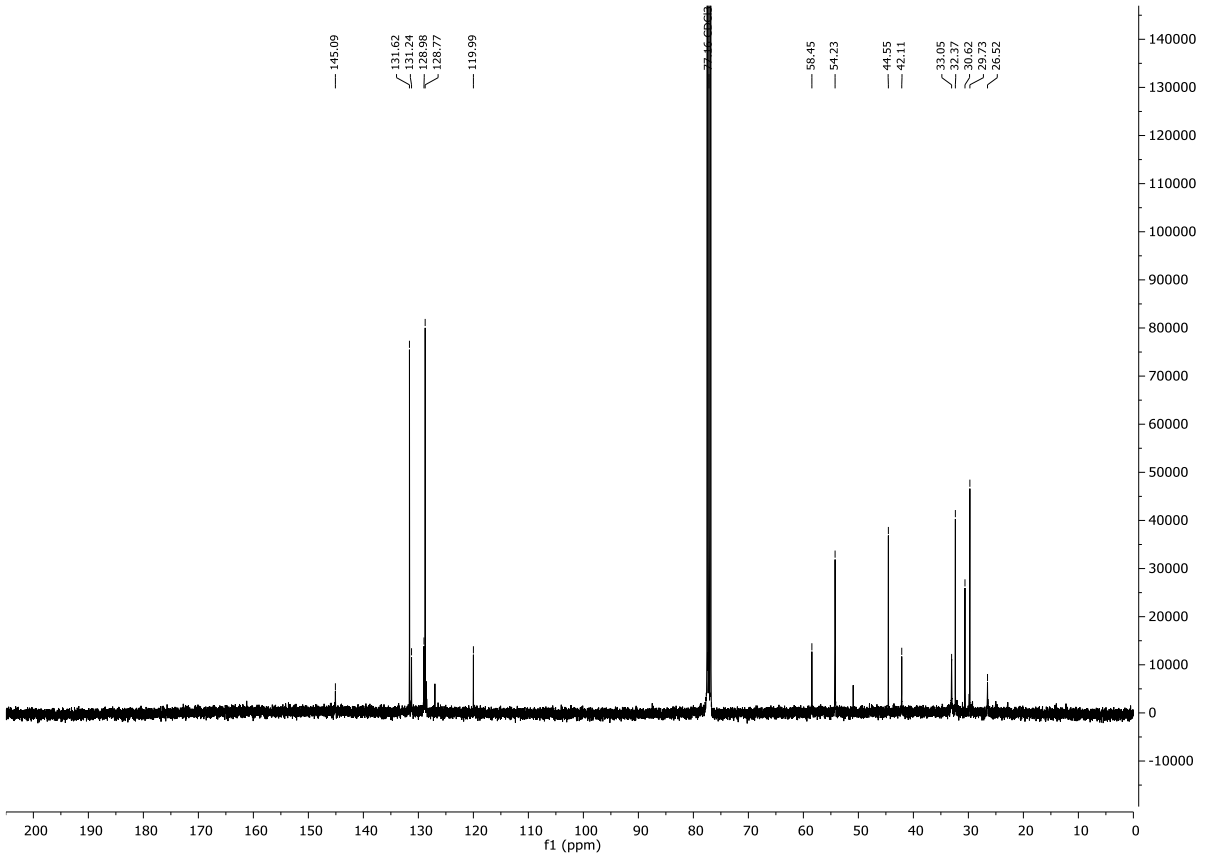

Me
N
Me
Cl
Me
280c
7.26 CDCl3
f1 (ppm)

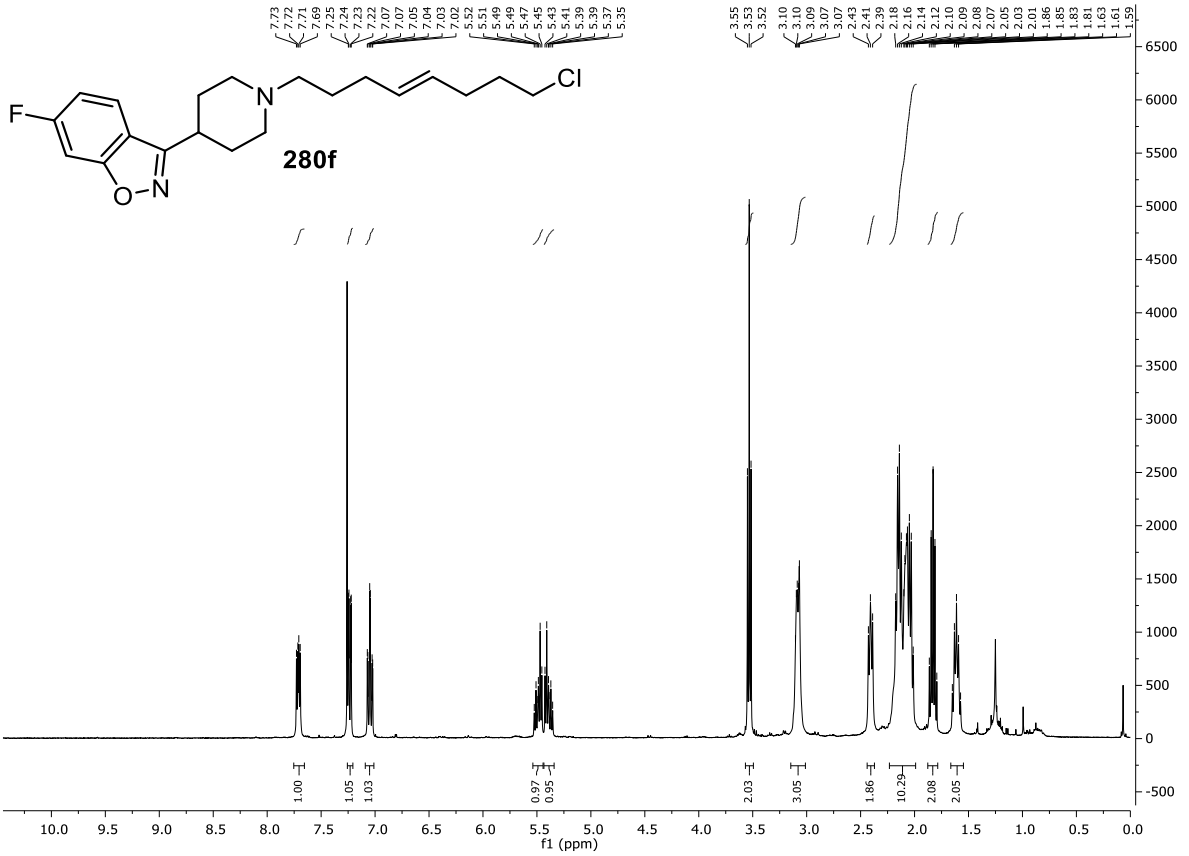

130.20
129.85
77.16 CDCl3
66.64
46.02
44.58
38.22
32.45
31.45
29.83
18.12
f1 (ppm)

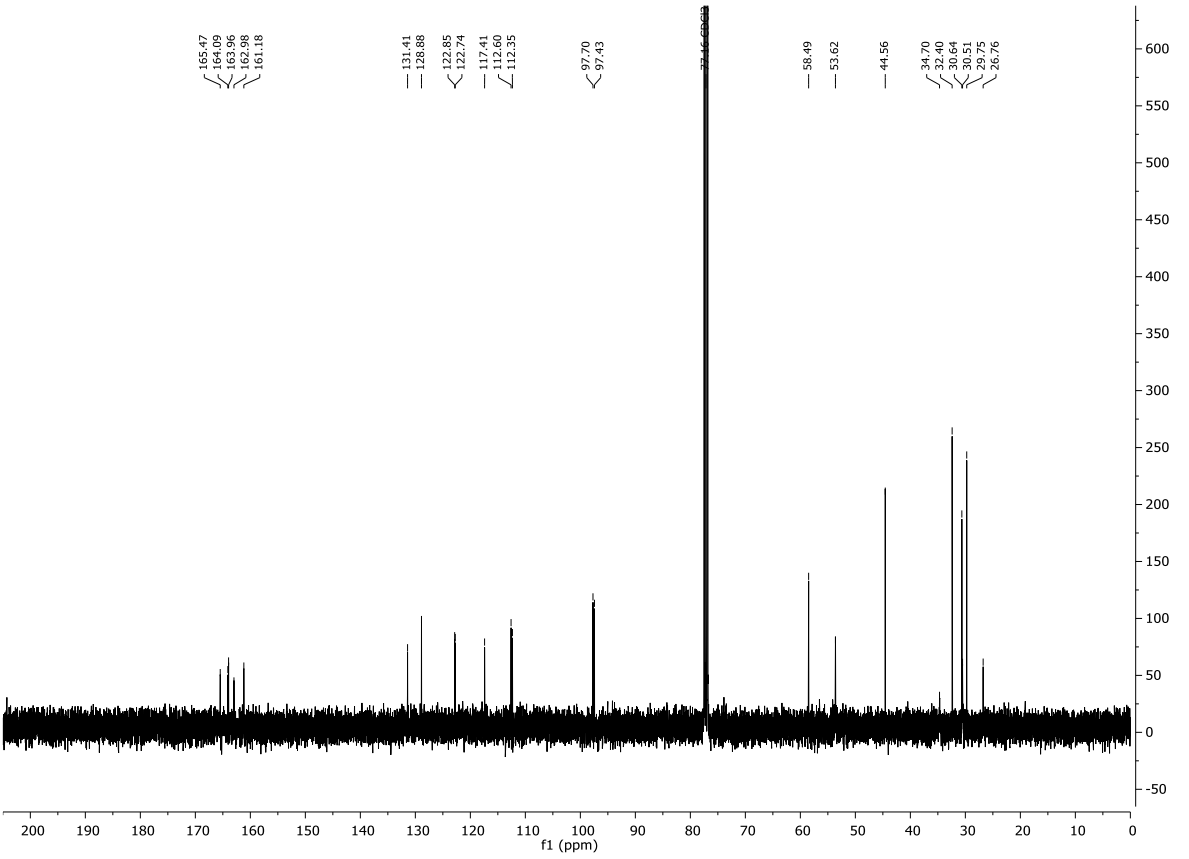

Me
Me
Me
O
O
H
N
N
Cl
280d
7.26 CDCl3
5.49
5.47
5.45
5.45
5.43
5.42
5.39
5.37
5.36
5.35
5.34
5.32
4.45
3.53
3.51
3.50
2.86
2.83
2.33
2.31
2.29
2.15
2.13
2.12
2.10
2.08
2.05
2.02
2.01
1.99
1.98
1.96
1.94
1.91
1.84
1.82
1.81
1.79
1.58
1.56
1.54
1.52
1.50
1.49
1.48
1.43
1.40
1.00
0.93
0.89
3.03
2.03
2.15
2.04
1.87
2.41
1.93
2.17
2.40
11.25
f1 (ppm)

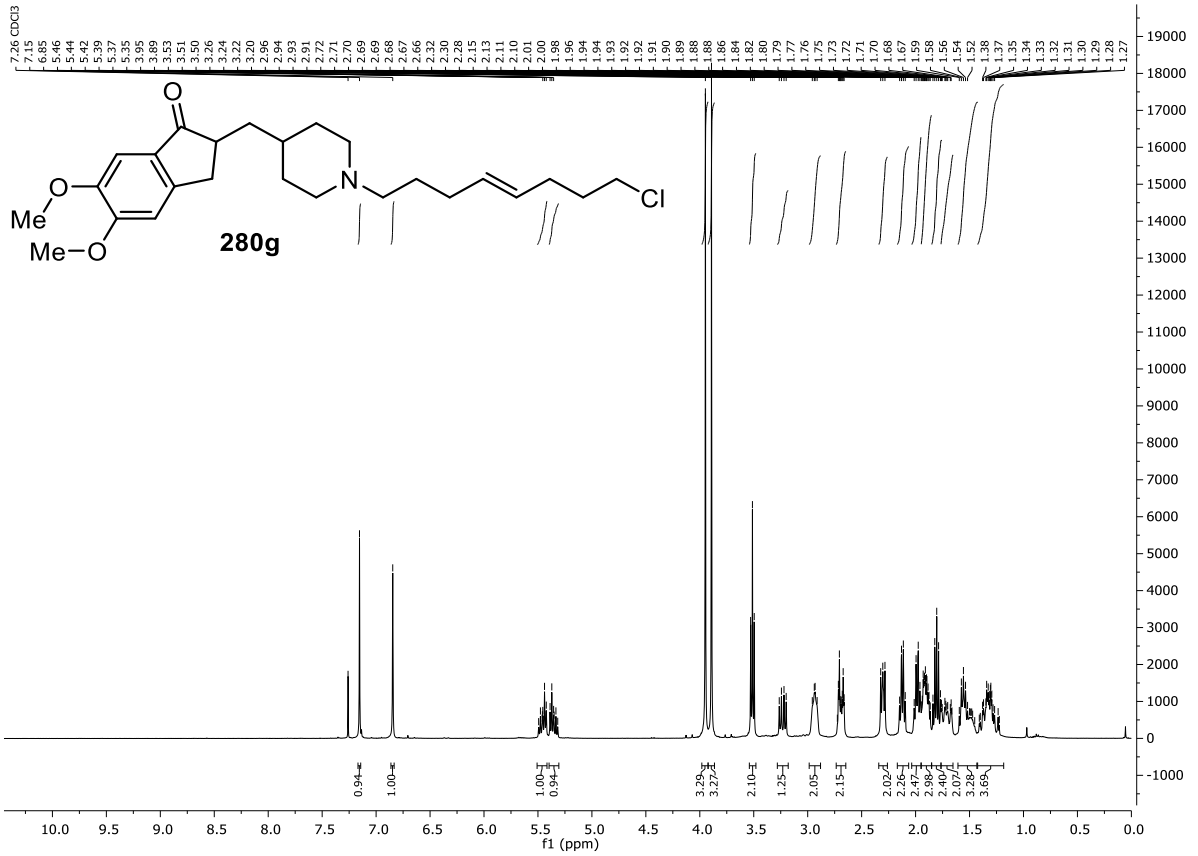

155.32
131.39
128.81
79.40
58.22
52.56
47.87
44.53
32.63
32.39
30.63
29.72
28.56
26.92
f1 (ppm)

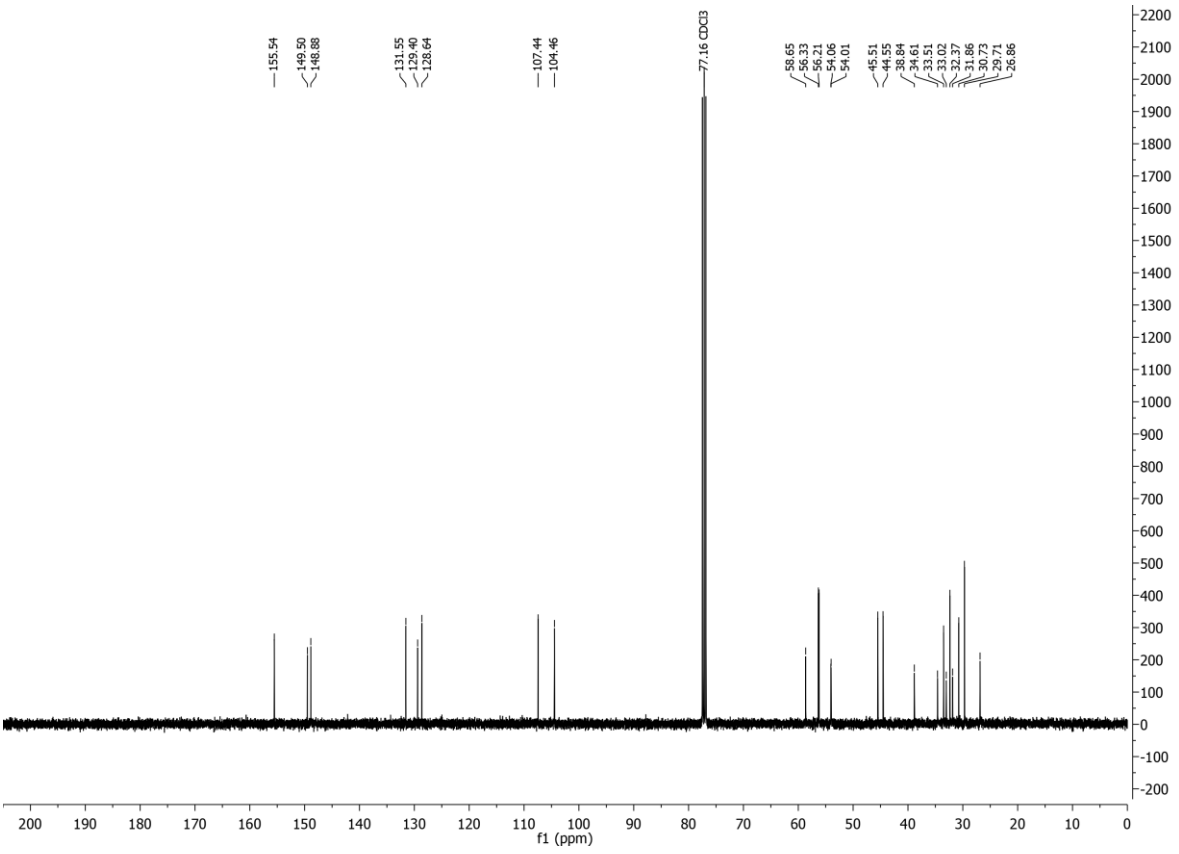

7.41
7.39
7.26 CDCl3
7.11
7.09
5.51
5.50
5.48
5.47
5.46
5.44
5.42
5.40
5.39
5.37
5.35
3.54
3.53
3.51
3.13
3.10
2.48
2.45
2.44
2.42
2.40
2.17
2.15
2.13
2.12
2.06
2.04
2.02
2.00
1.87
1.86
1.84
1.82
1.80
1.79
1.67
1.66
1.64
1.62
N
Cl
Br
280e
2.12
2.00
1.14
1.07
2.30
2.02
3.39
4.79
2.48
5.96
2.64
f1 (ppm)

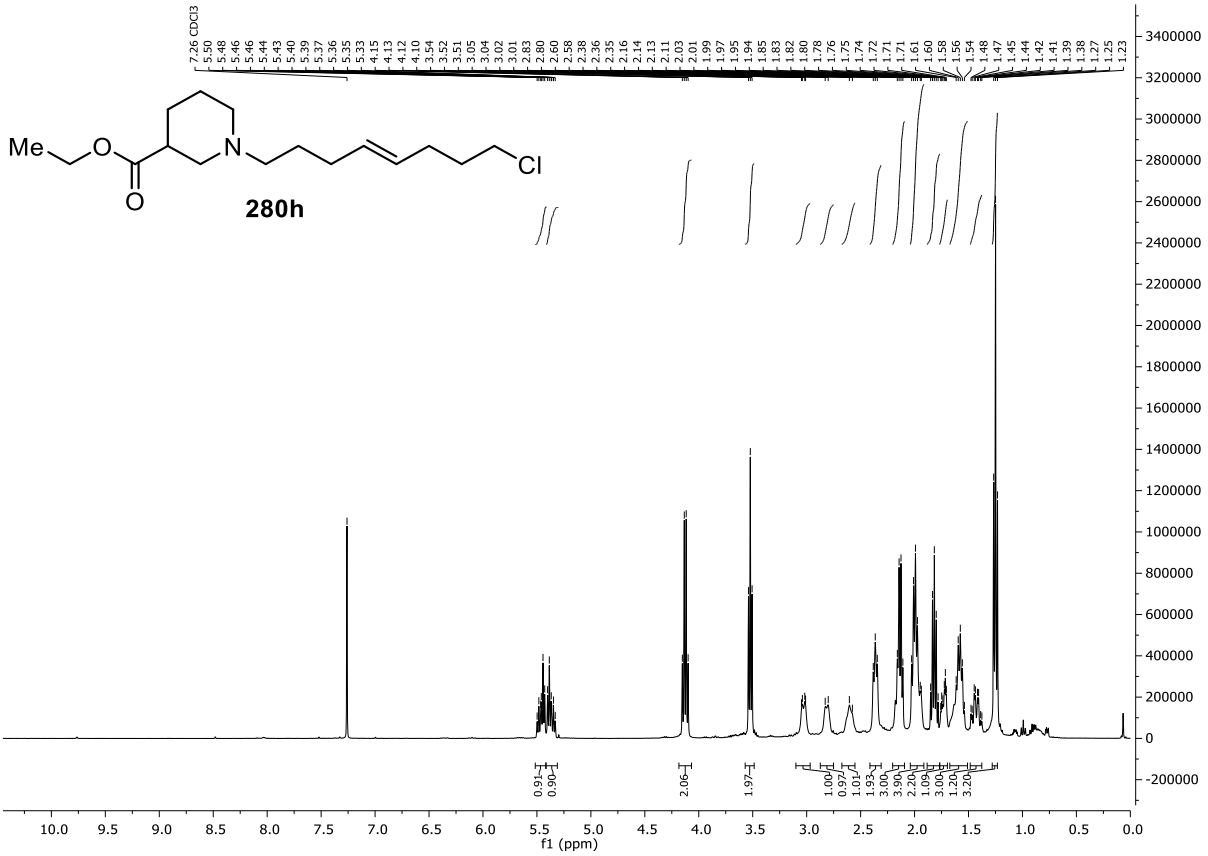

145.09
131.62
131.24
128.98
128.77
119.99
77.16 CDCl3
58.45
54.23
44.55
42.11
33.05
32.27
30.62
29.73
26.52
f1 (ppm)

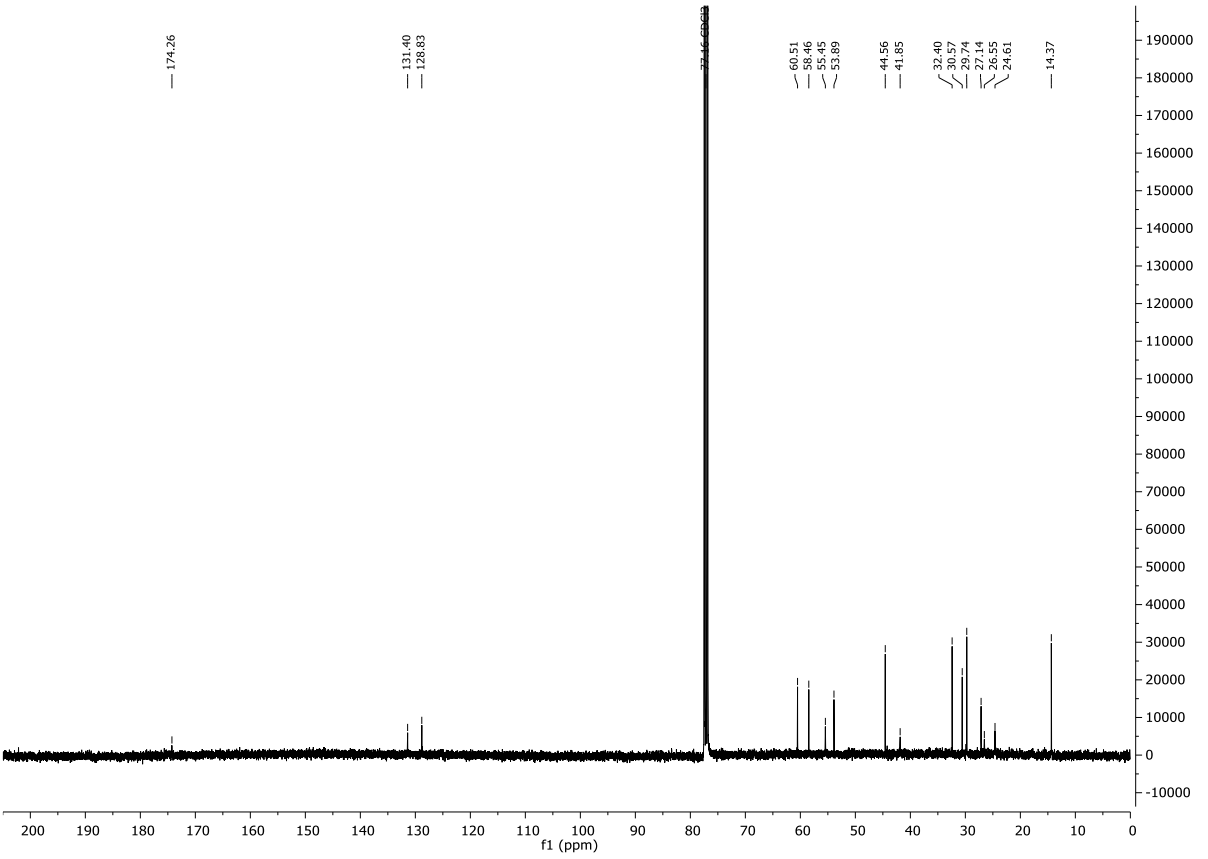

F
N
Cl
O
N
280f
f1 (ppm)

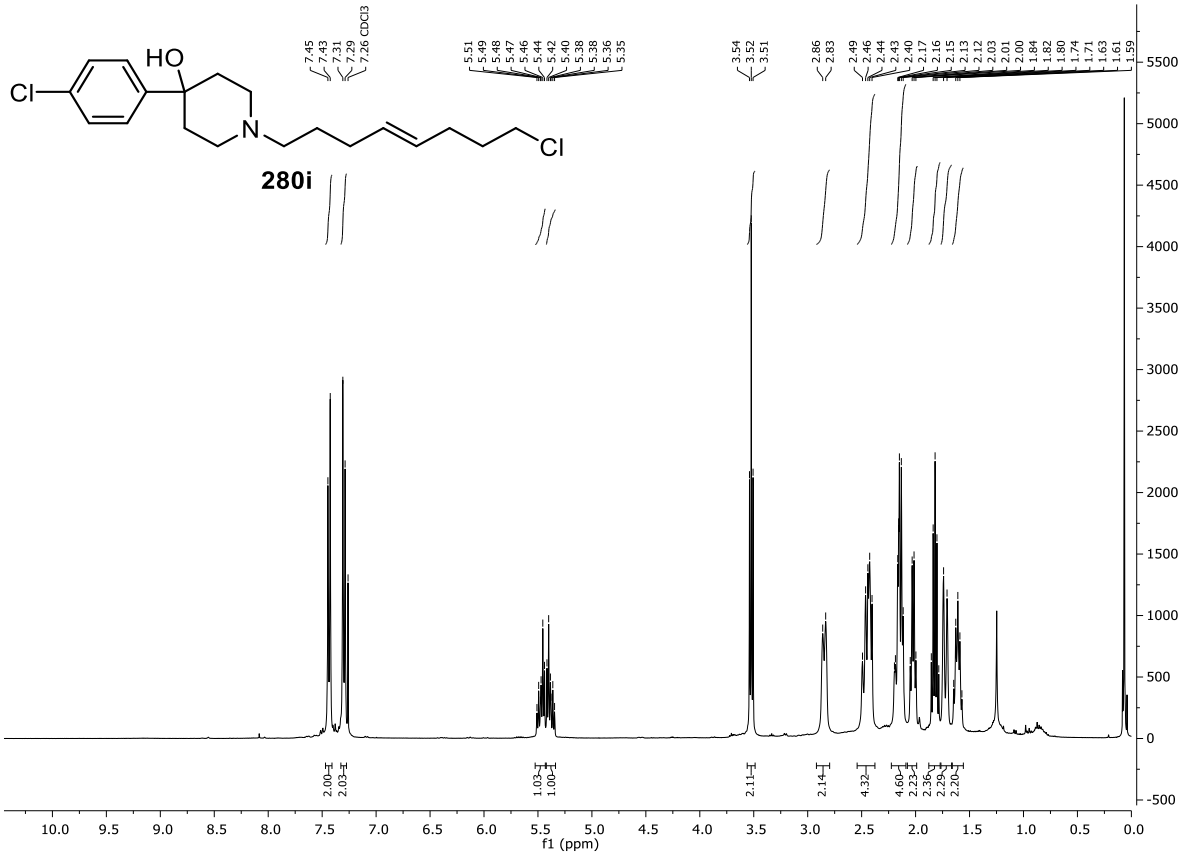

f1 (ppm)

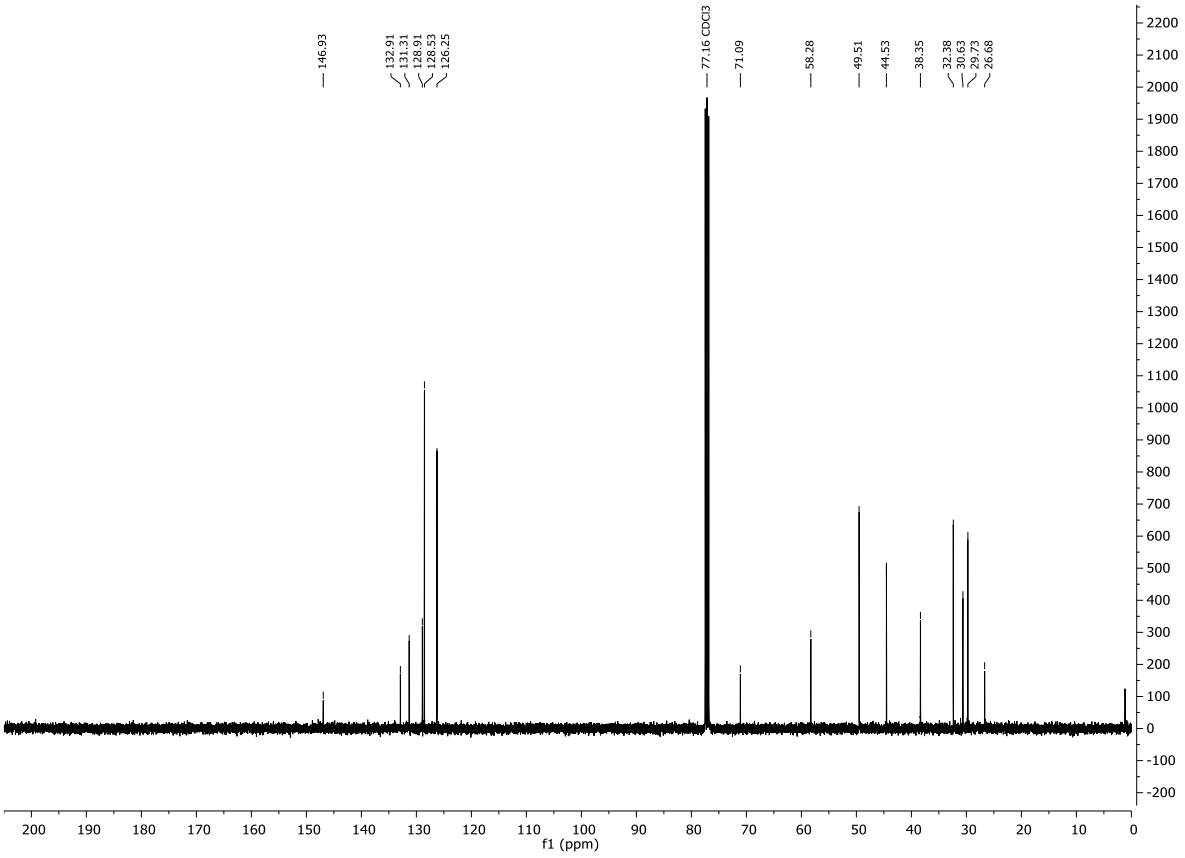

280g
f1 (ppm)

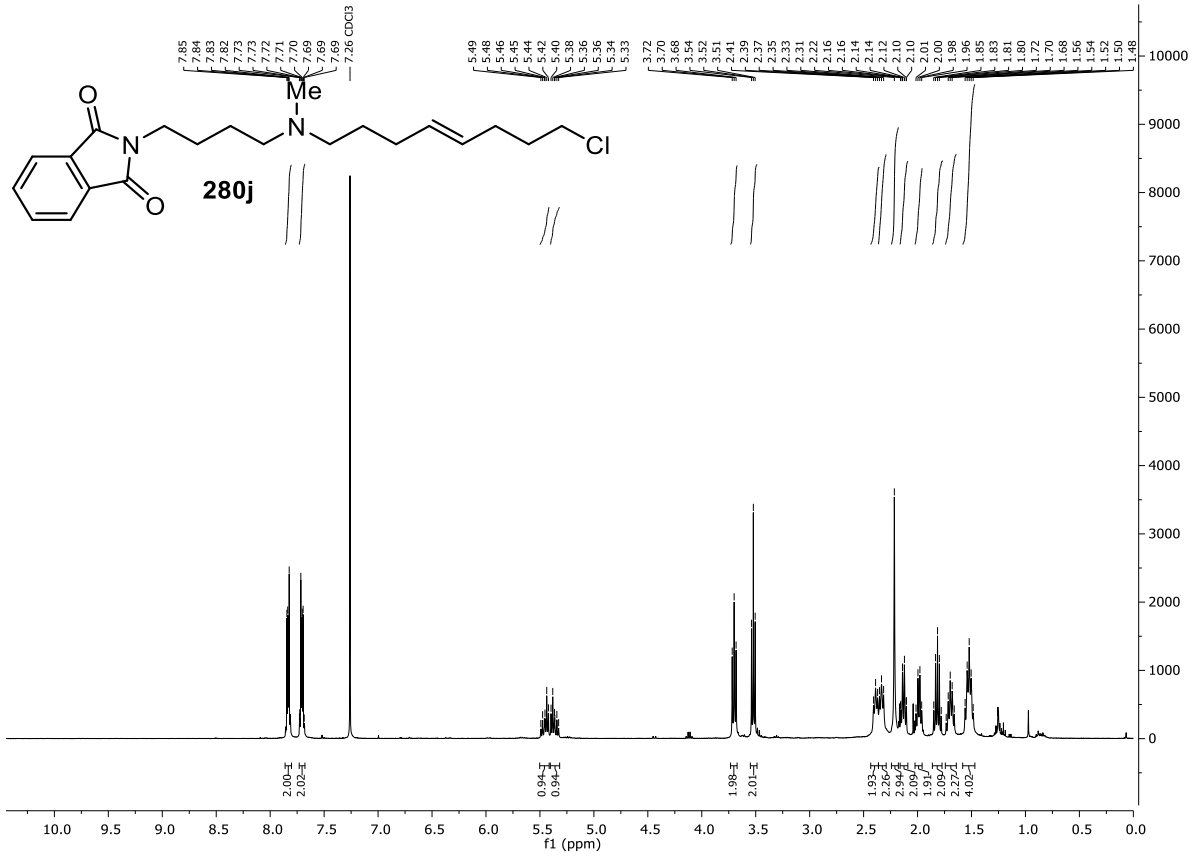

f1 (ppm)

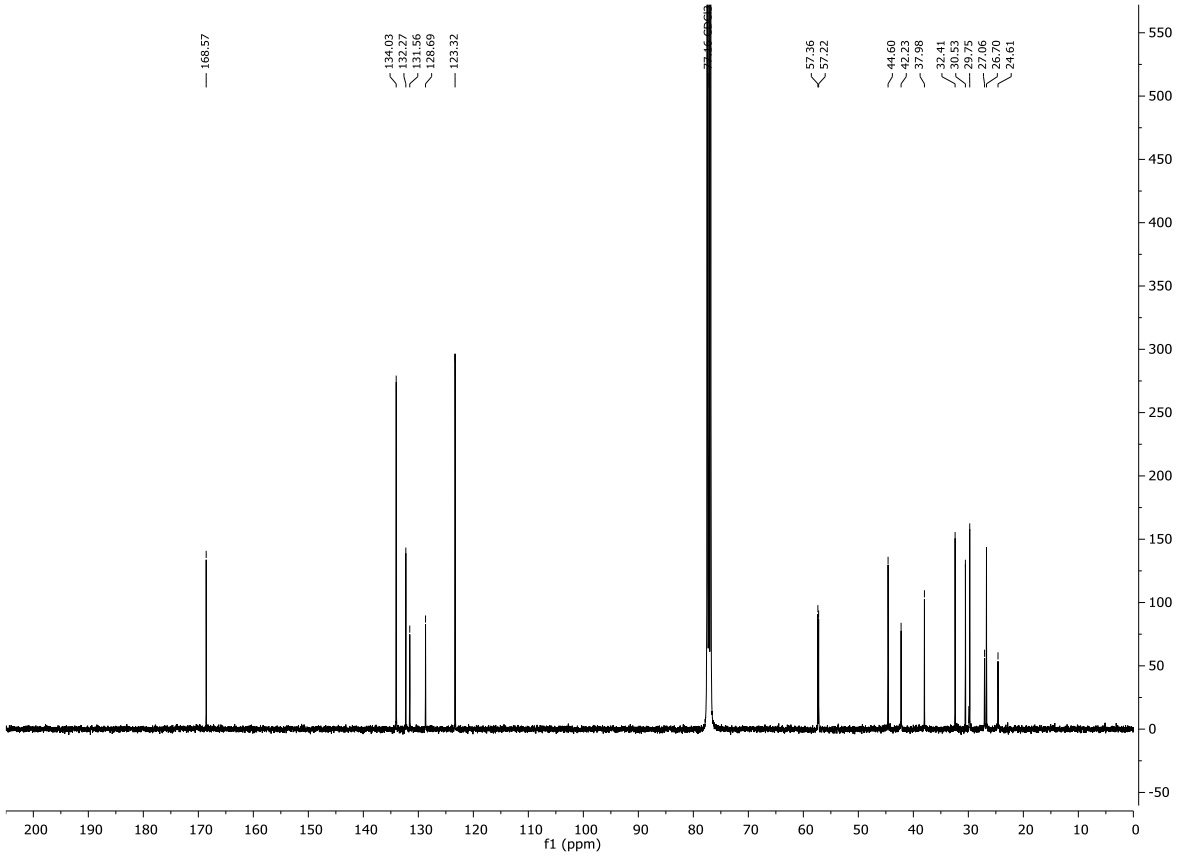

Me
O
O
N
Cl
280h
f1 (ppm)

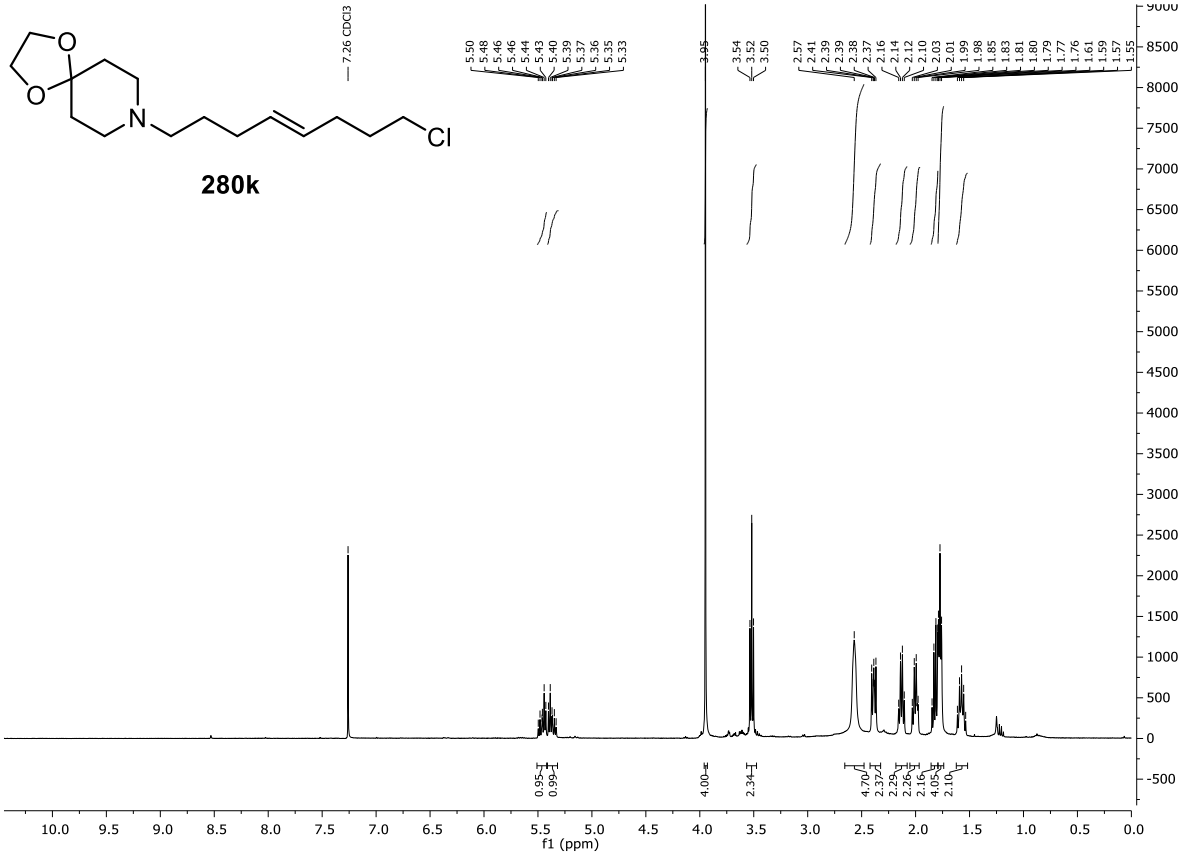

174.26
131.40
128.83
77.46 CDCl3
60.51
58.46
55.45
53.89
44.56
41.85
32.40
30.57
29.74
27.14
26.55
24.61
14.37
f1 (ppm)

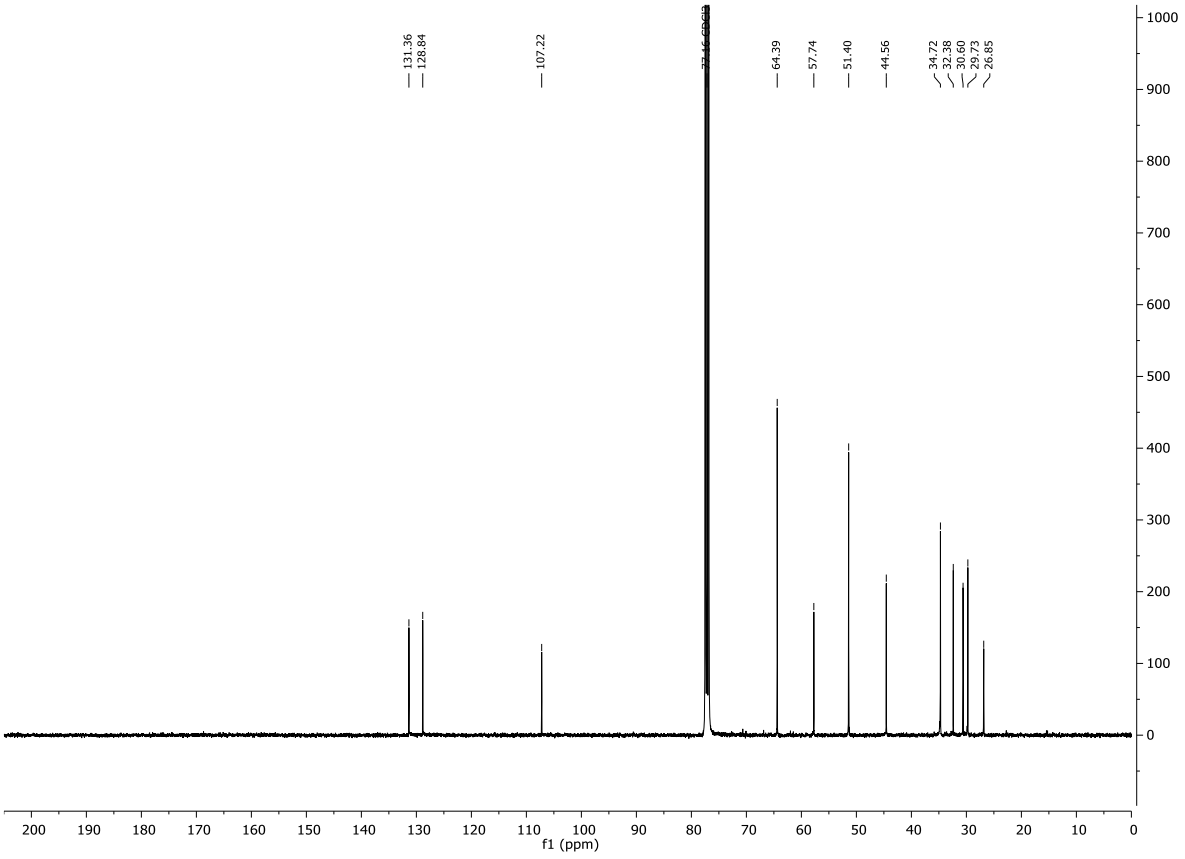

HO
Cl
N
Cl
280i
7.45
7.43
7.31
7.29
7.26 CDCl3
5.51
5.49
5.48
5.47
5.46
5.44
5.42
5.40
5.38
5.38
5.36
5.35
3.54
3.52
3.51
2.86
2.83
2.49
2.46
2.44
2.43
2.40
2.17
2.16
2.15
2.13
2.12
2.03
2.01
2.00
1.84
1.82
1.80
1.74
1.71
1.63
1.61
1.59
2.00
2.03
1.03
1.00
2.11
2.14
4.32
4.60
2.23
2.36
2.25
2.20
f1 (ppm)

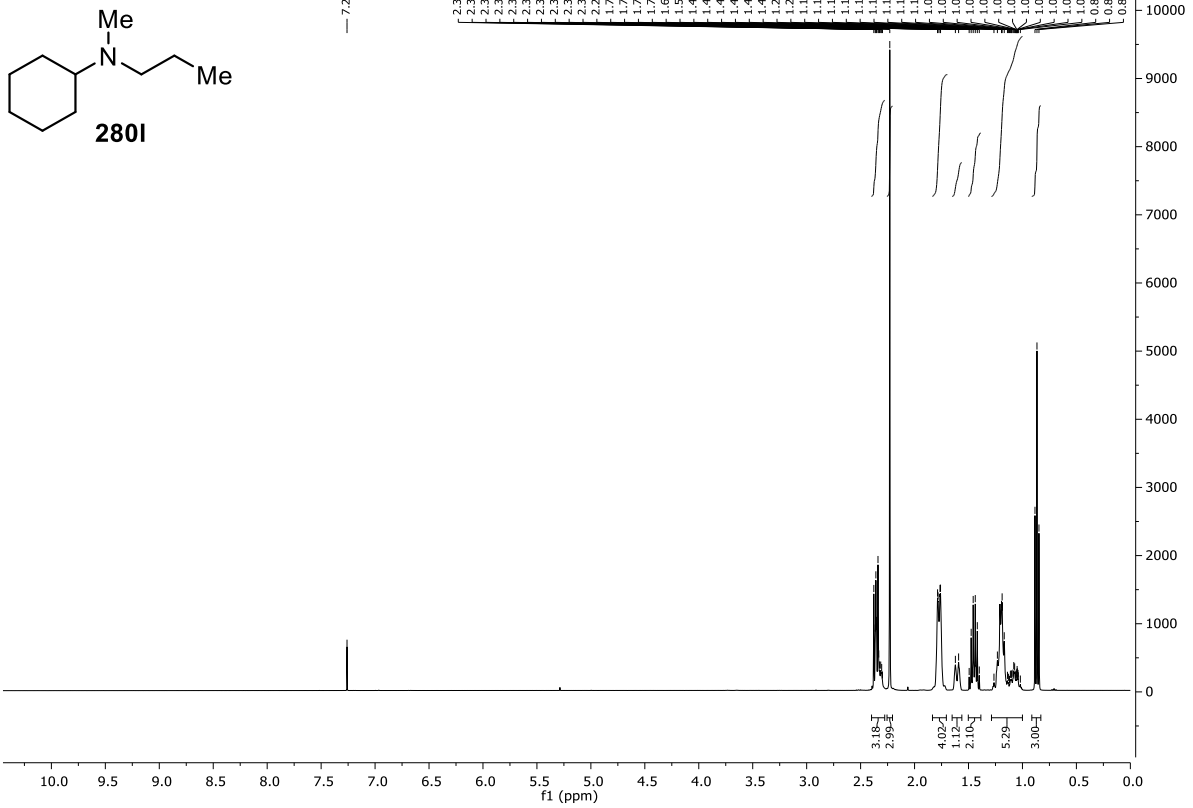

146.93
132.91
131.31
128.91
128.53
126.25
77.16 CDCl3
71.09
58.28
49.51
44.53
38.35
32.38
30.63
29.73
26.68
f1 (ppm)

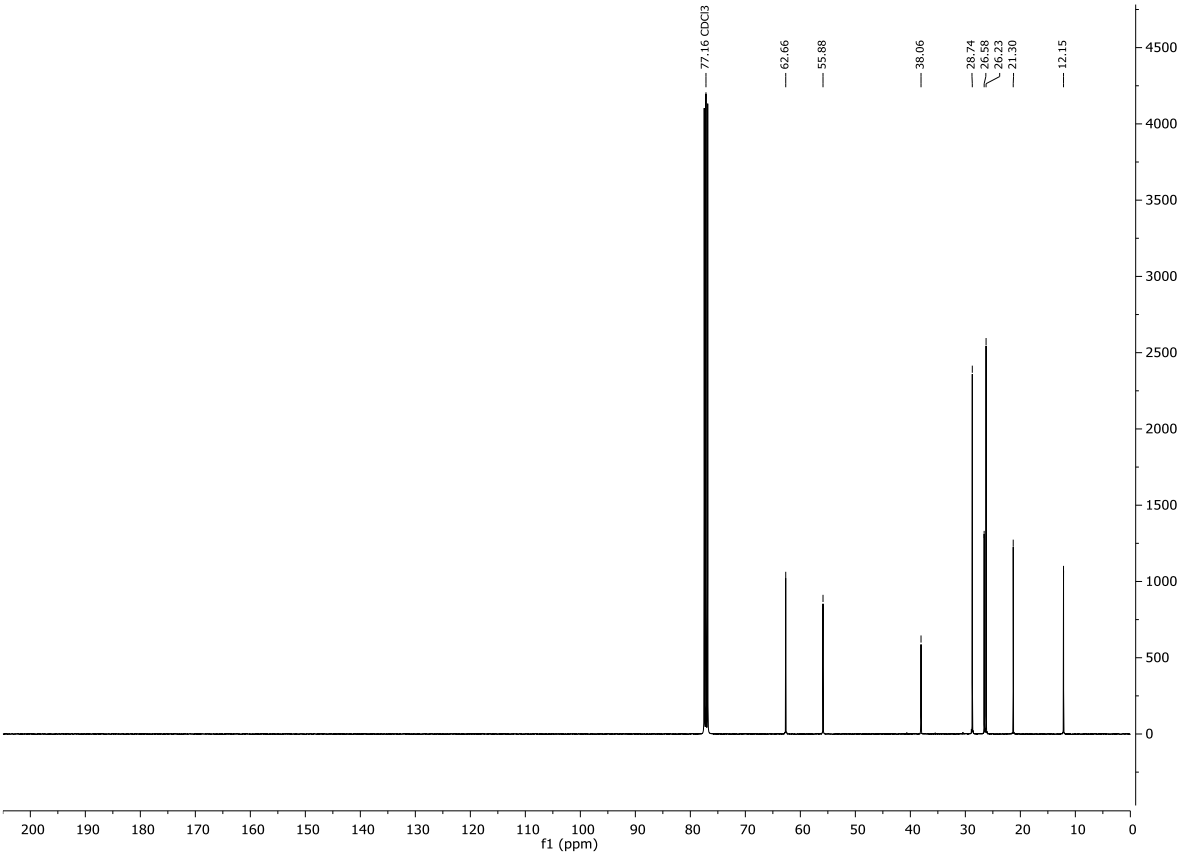

Me
N
N
O
O
Cl
280j
f1 (ppm)

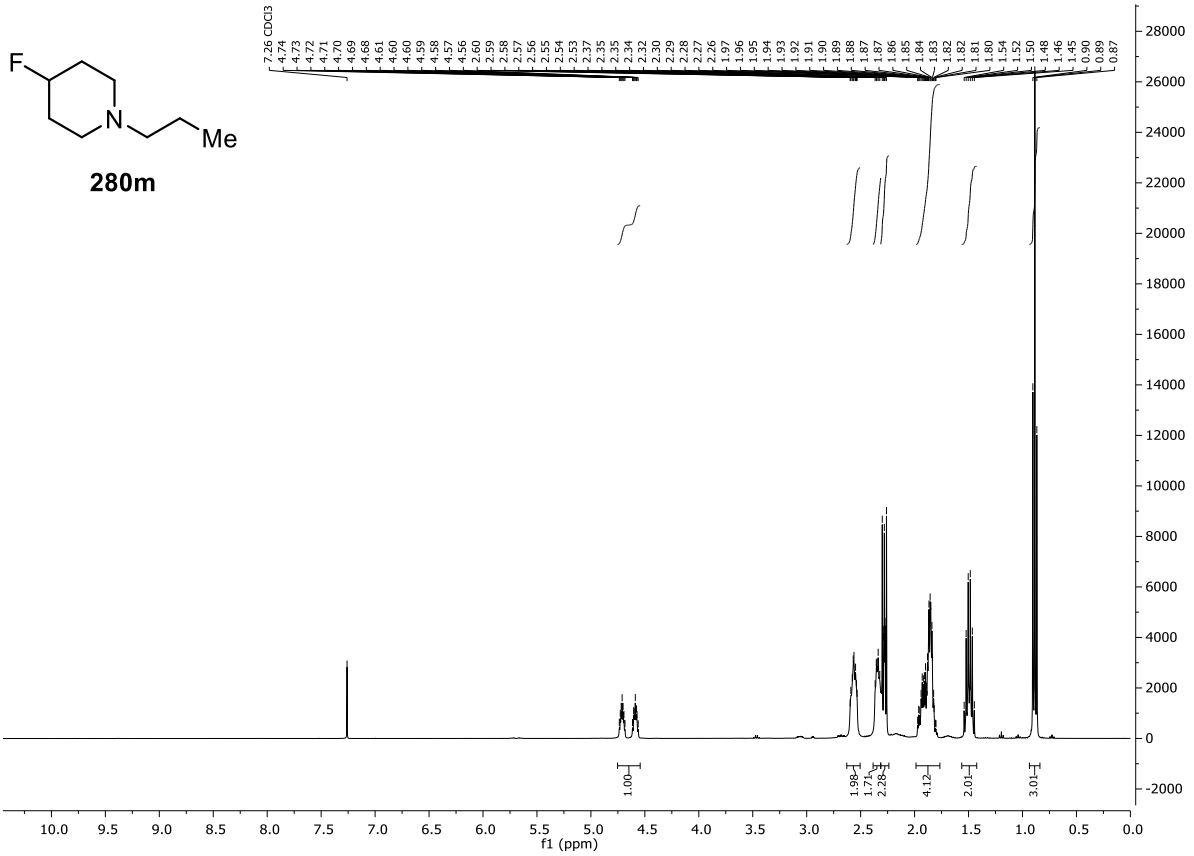

168.57
134.03
132.27
131.56
128.69
123.32
57.36
57.22
44.60
42.23
37.98
32.41
30.53
29.75
27.06
26.70
24.61
f1 (ppm)

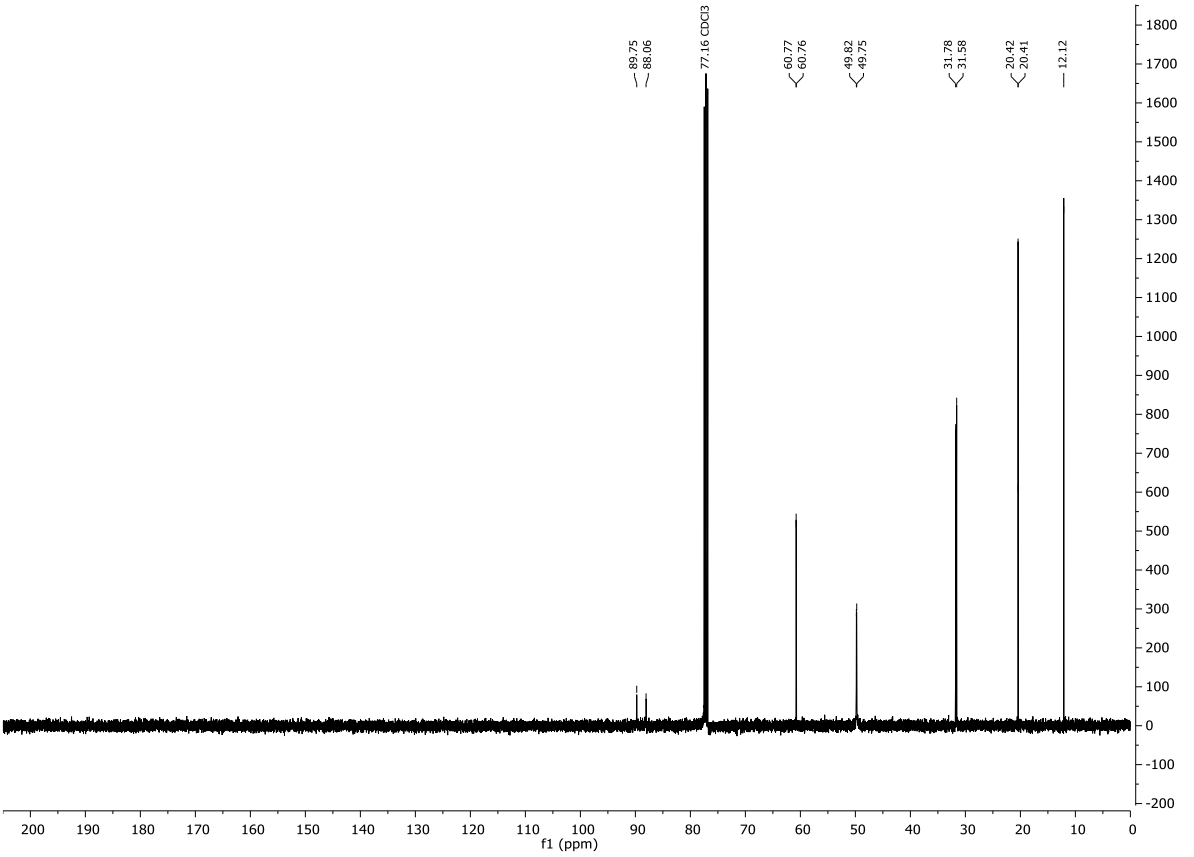

7.26 CDCl3
5.50
5.48
5.46
5.46
5.44
5.43
5.40
5.39
5.37
5.36
5.35
5.33
3.95
3.54
3.52
3.50
2.57
2.41
2.39
2.39
2.38
2.37
2.16
2.14
2.12
2.10
2.03
2.01
1.99
1.98
1.85
1.83
1.81
1.80
1.79
1.77
1.76
1.61
1.59
1.57
1.55
0.95
0.99
4.00
2.34
4.70
2.37
2.29
2.26
2.16
4.05
2.10
f1 (ppm)
O
O
N
Cl
280k

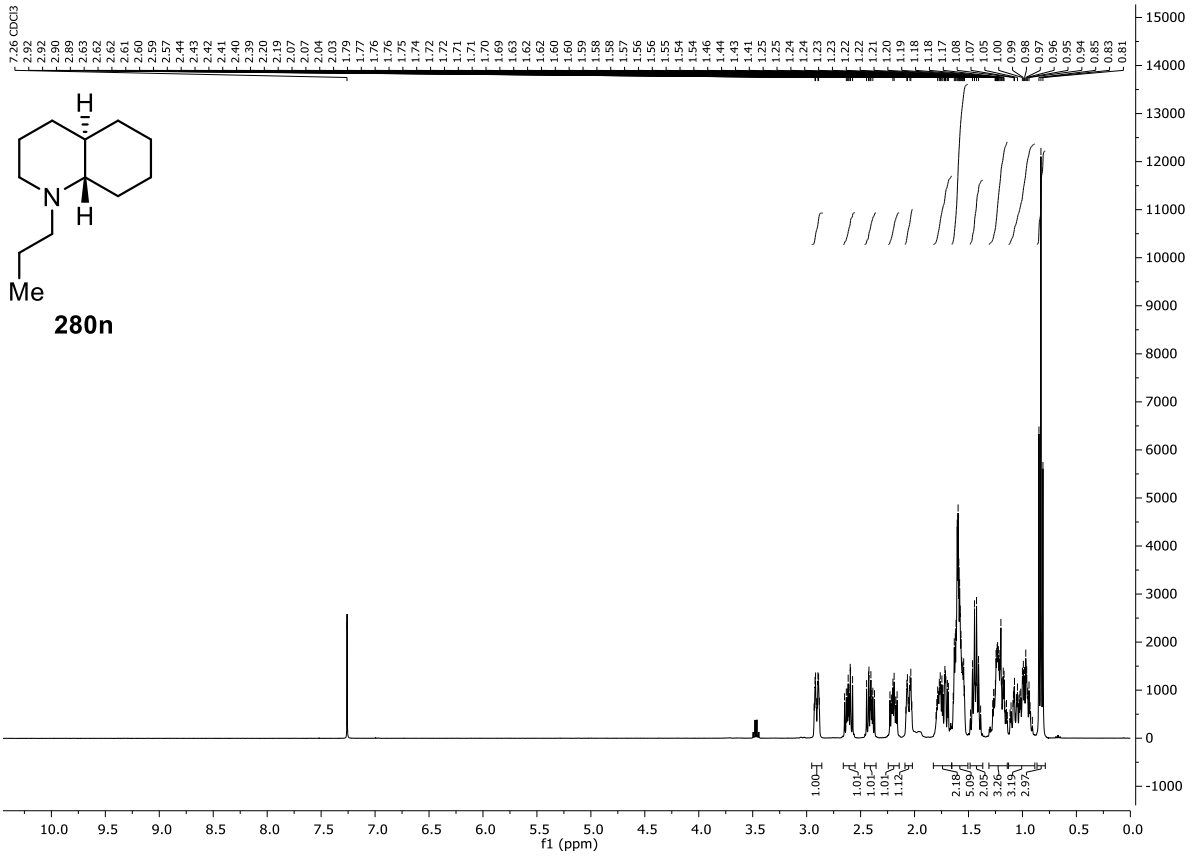

131.36
128.84
107.22
77.16 CDCl3
64.39
57.74
51.40
44.56
34.72
32.38
30.60
29.73
26.85
f1 (ppm)

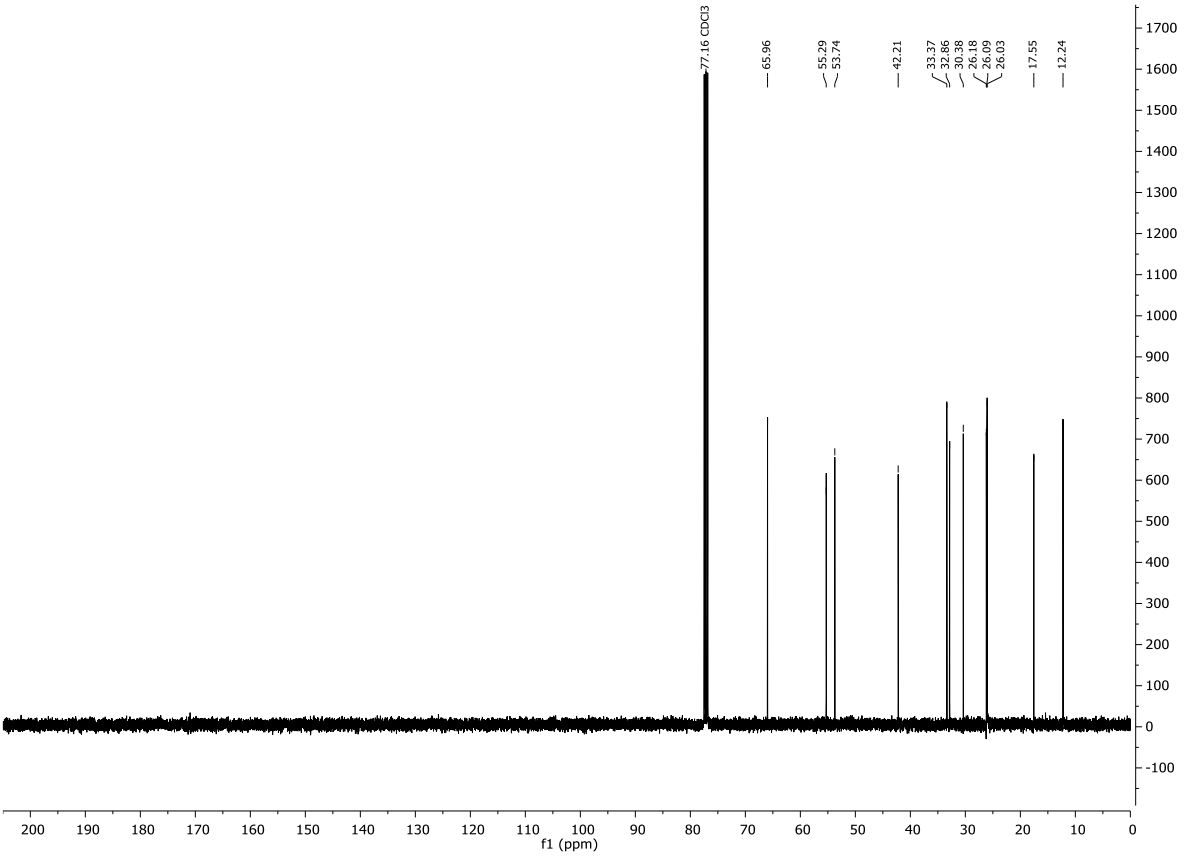

Me
N
Me
280l
7.26 CDCl3
f1 (ppm)

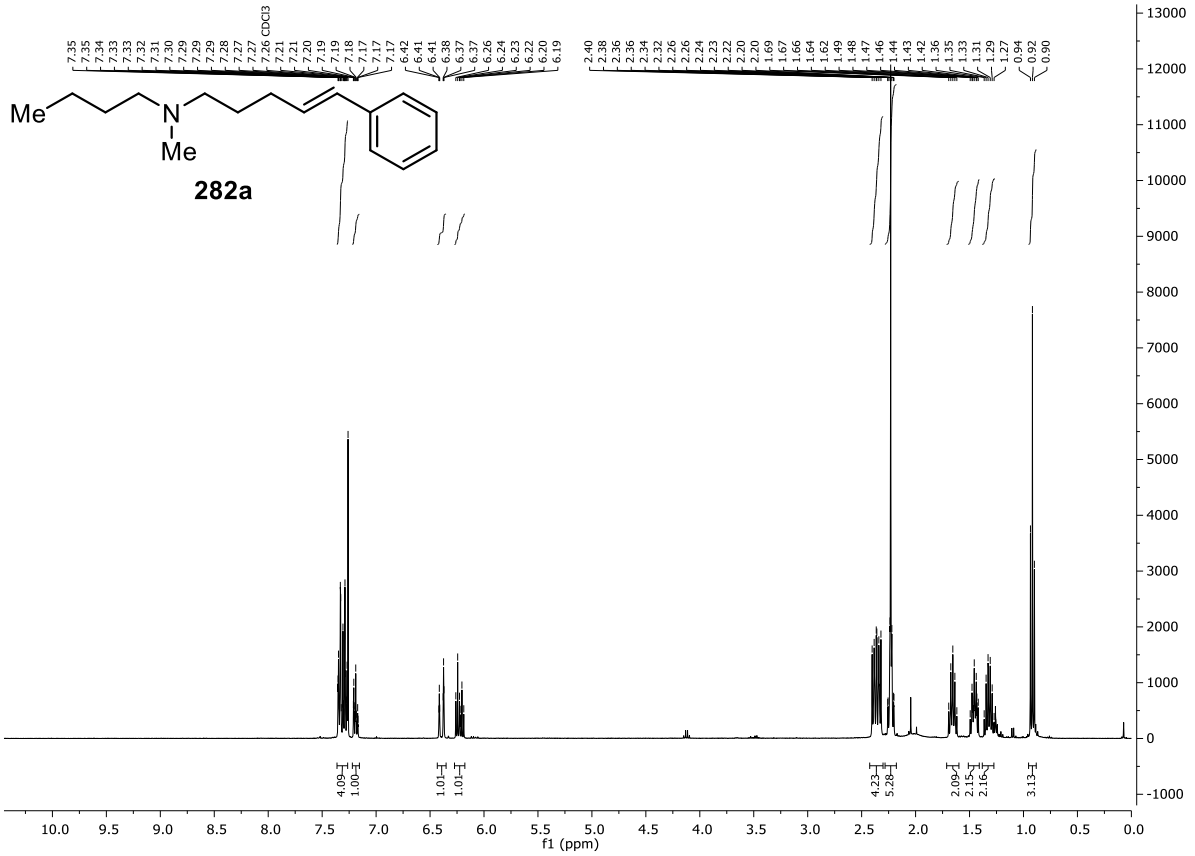

77.16 CDCl3
62.66
55.88
38.06
28.74
26.58
26.23
21.30
12.15
f1 (ppm)

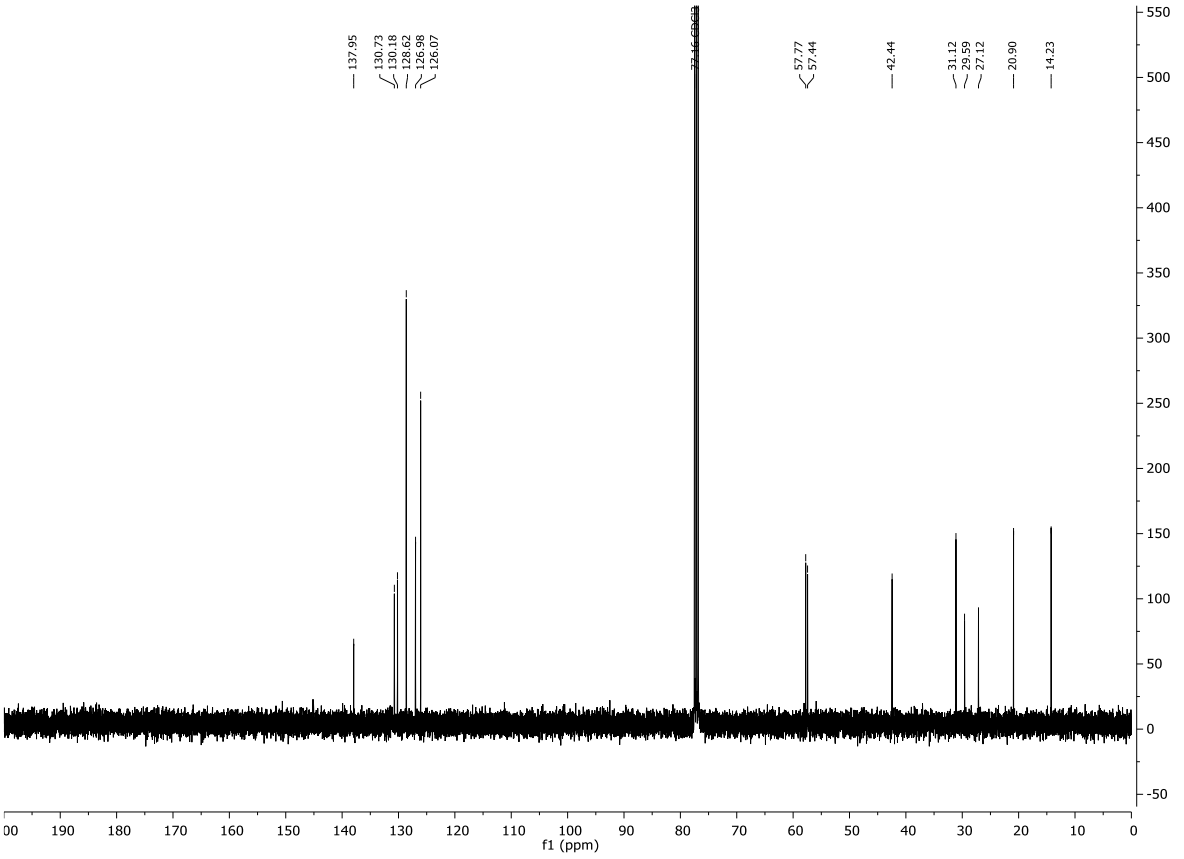

F
N
Me
280m
7.26 CDCl3
f1 (ppm)

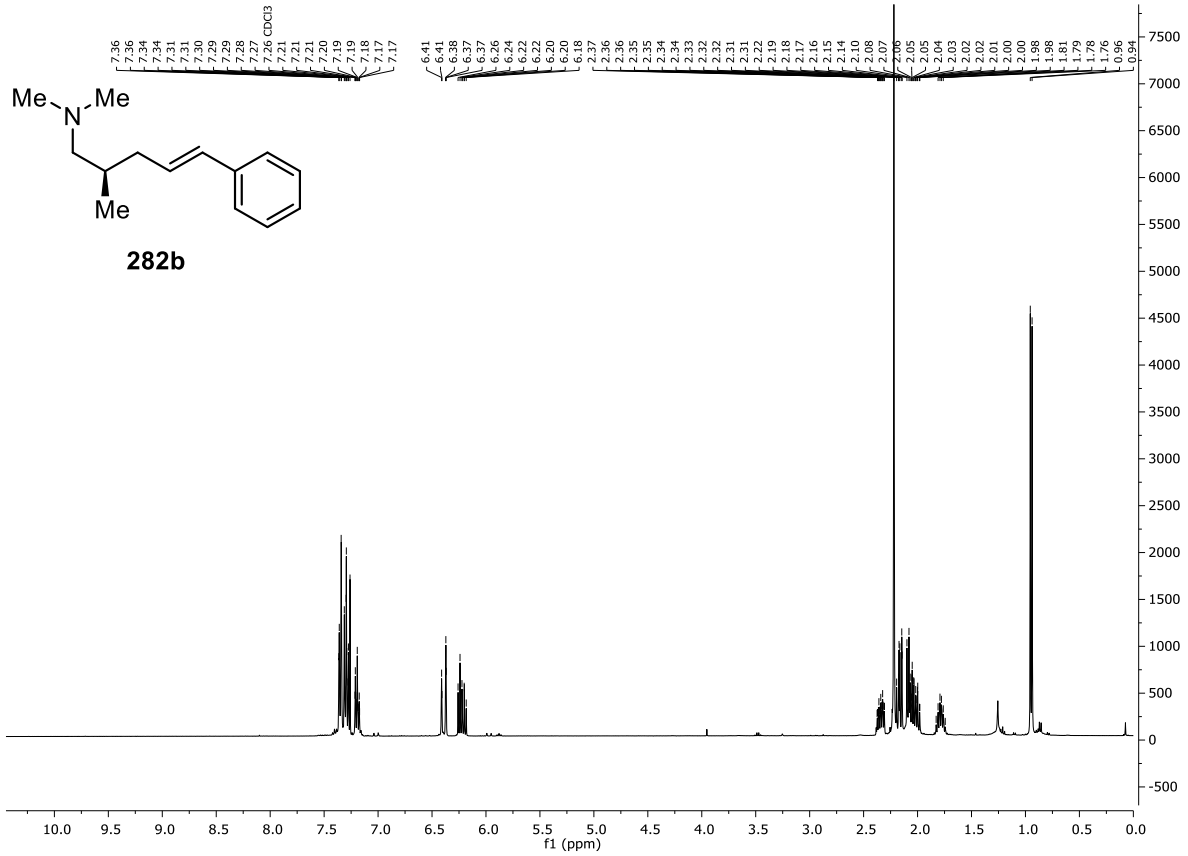

89.75
88.06
77.16 CDCl3
60.77
60.76
49.82
49.75
31.78
31.58
20.42
20.41
12.12
f1 (ppm)

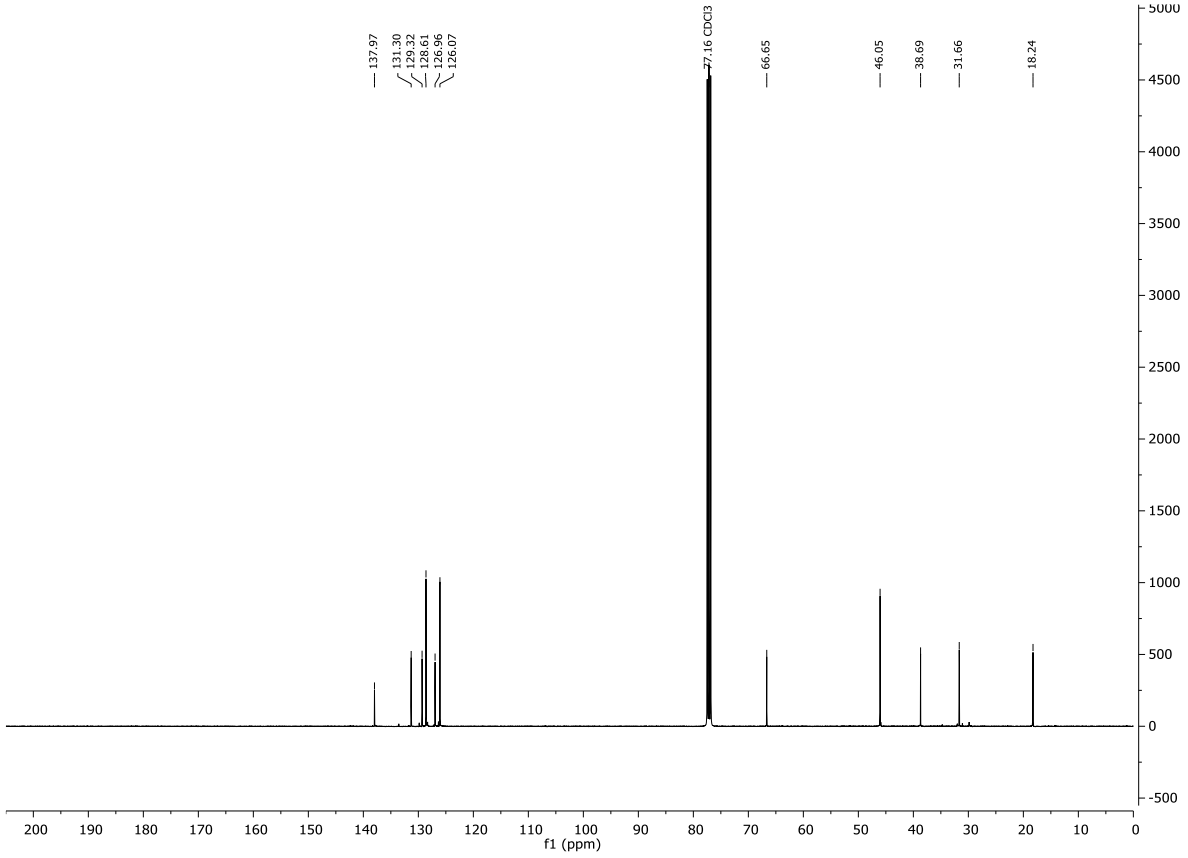

7.26 CDCl3
H
N
H
Me
280n
f1 (ppm)

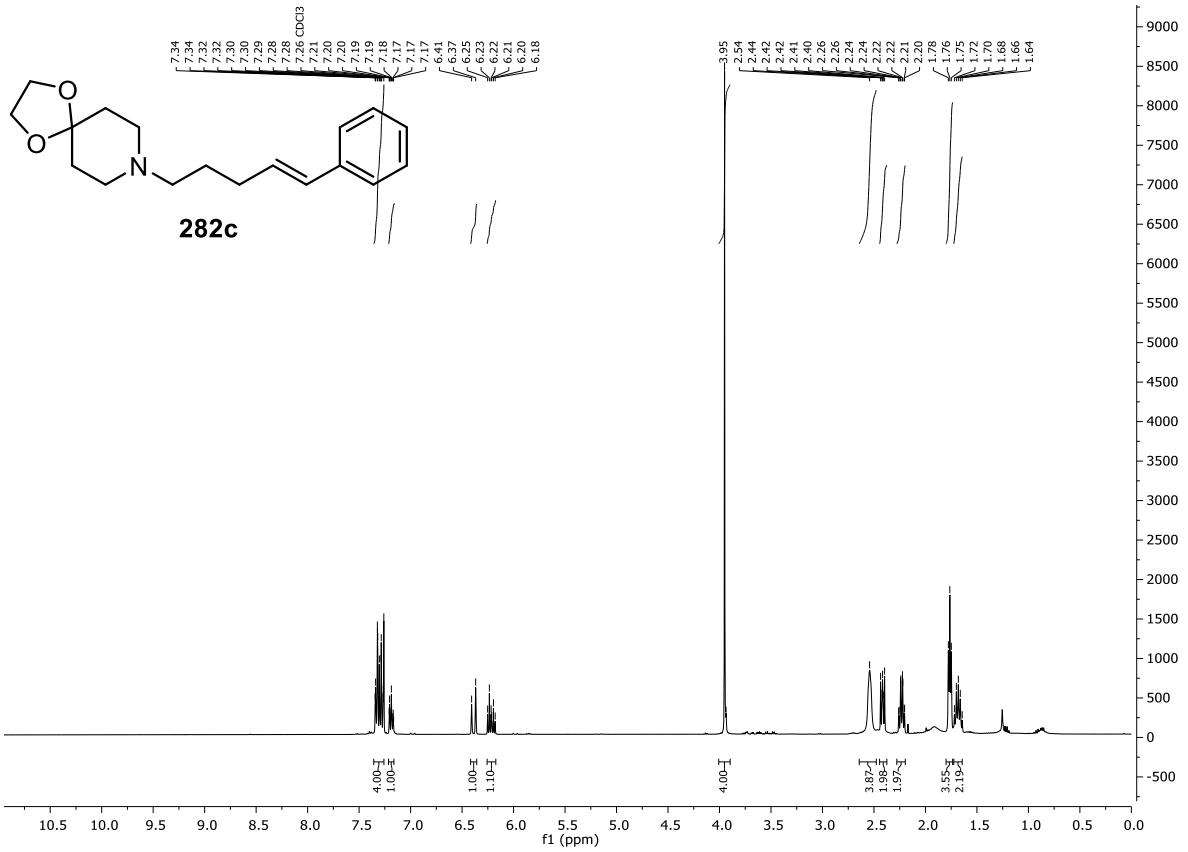

77.16 CDCl3
65.96
55.29
53.74
42.21
33.37
32.86
30.38
26.18
26.09
26.03
17.55
12.24
f1 (ppm)

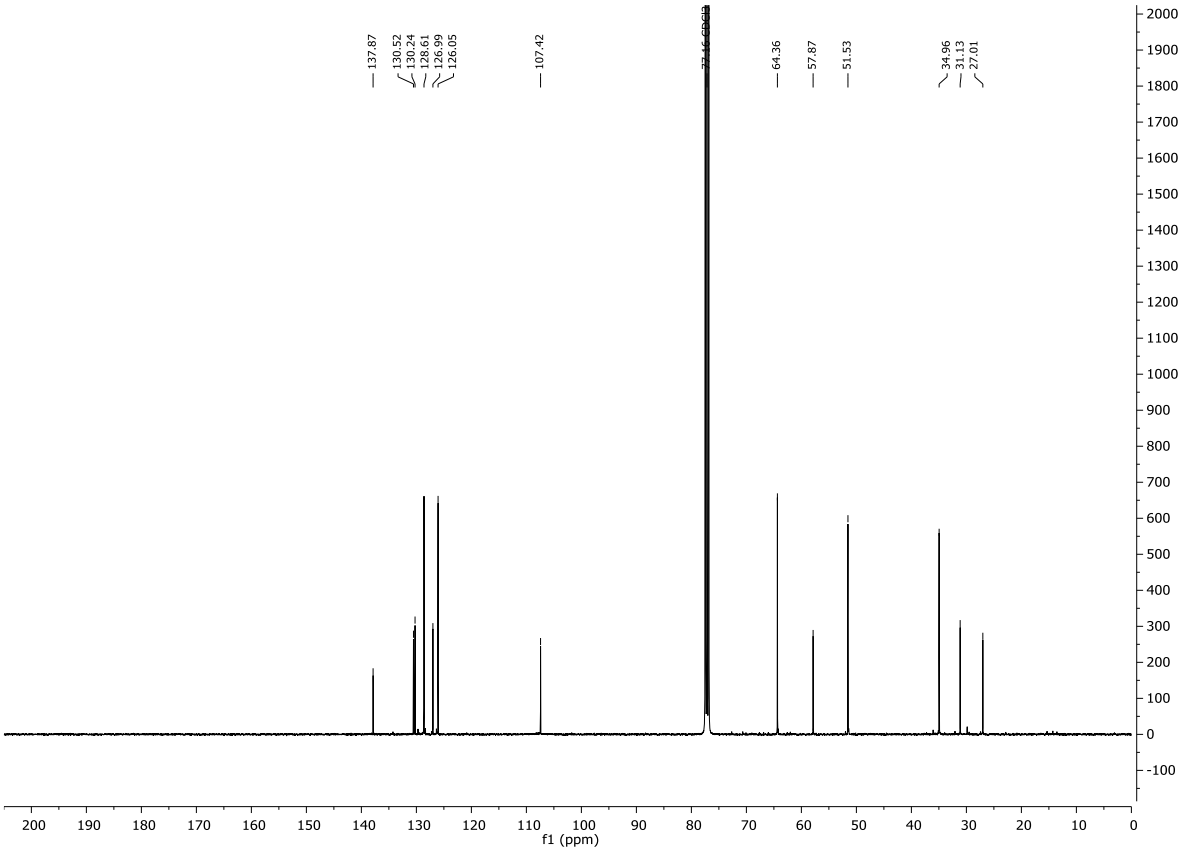

Me
N
Me
282a
f1 (ppm)

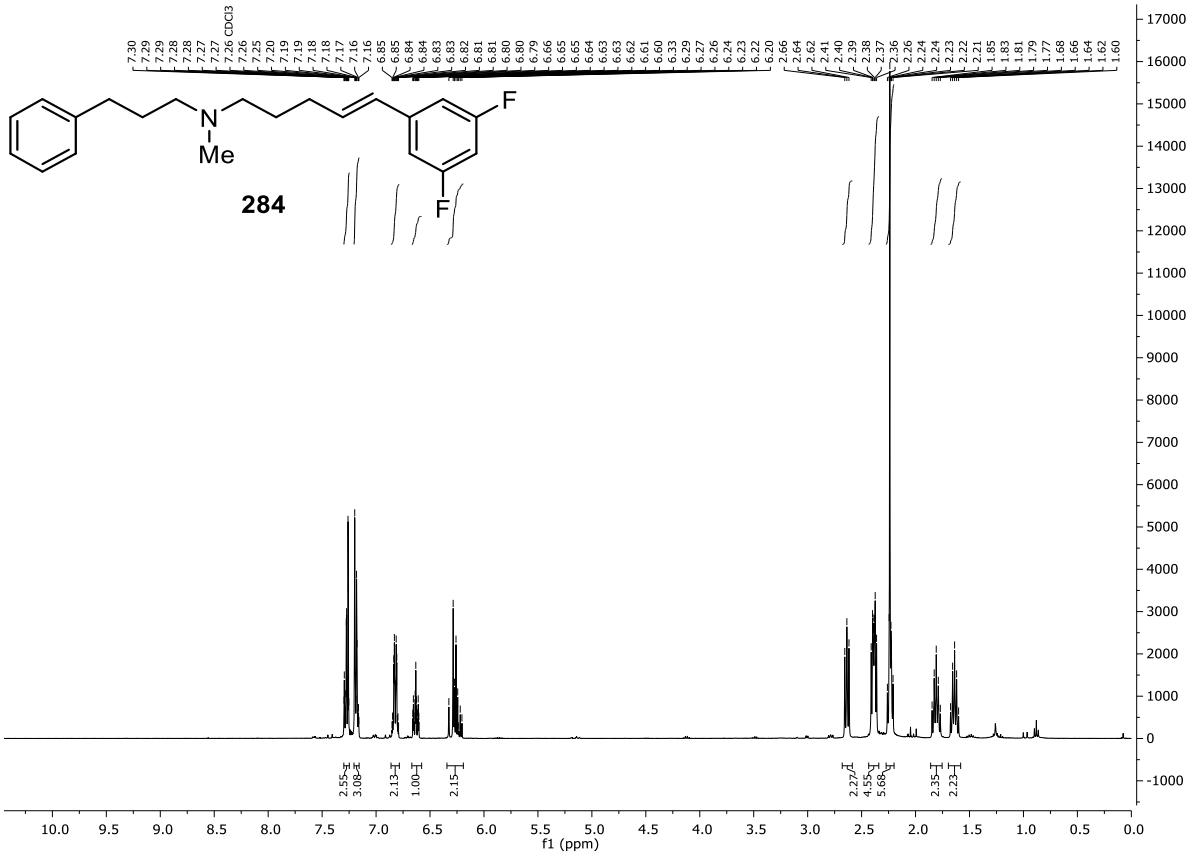

f1 (ppm)

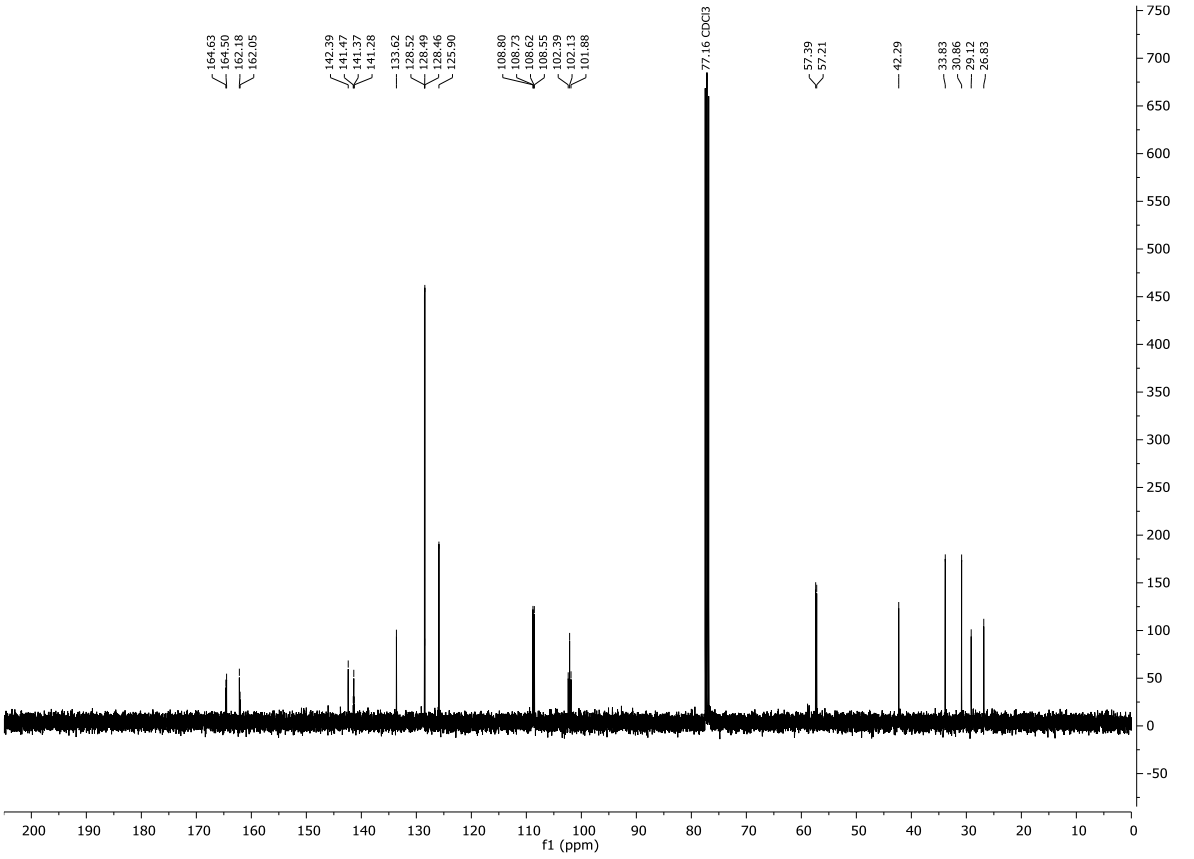

Me
N
Me
Me
282b
CDCl3
f1 (ppm)

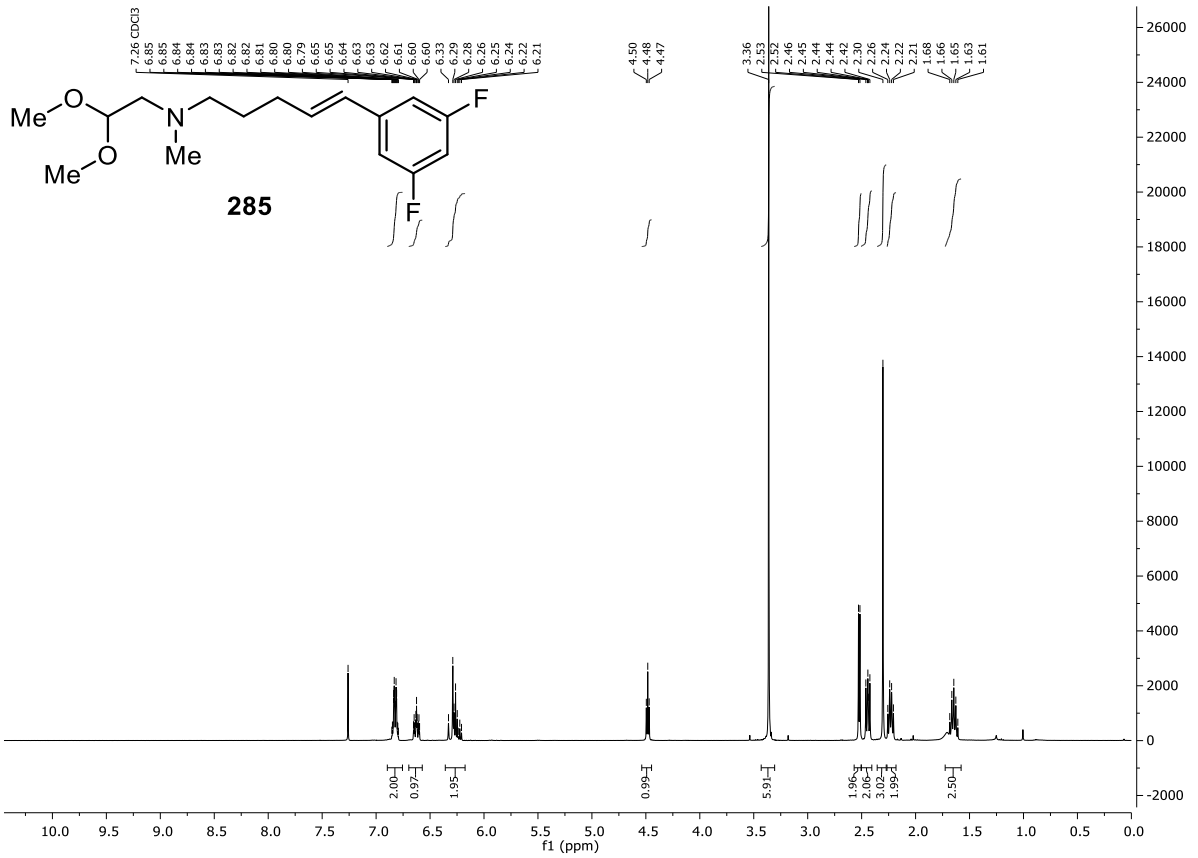

137.97
131.30
129.32
128.61
126.96
126.07
77.16 CDCl3
66.65
46.05
38.69
31.66
18.24
f1 (ppm)

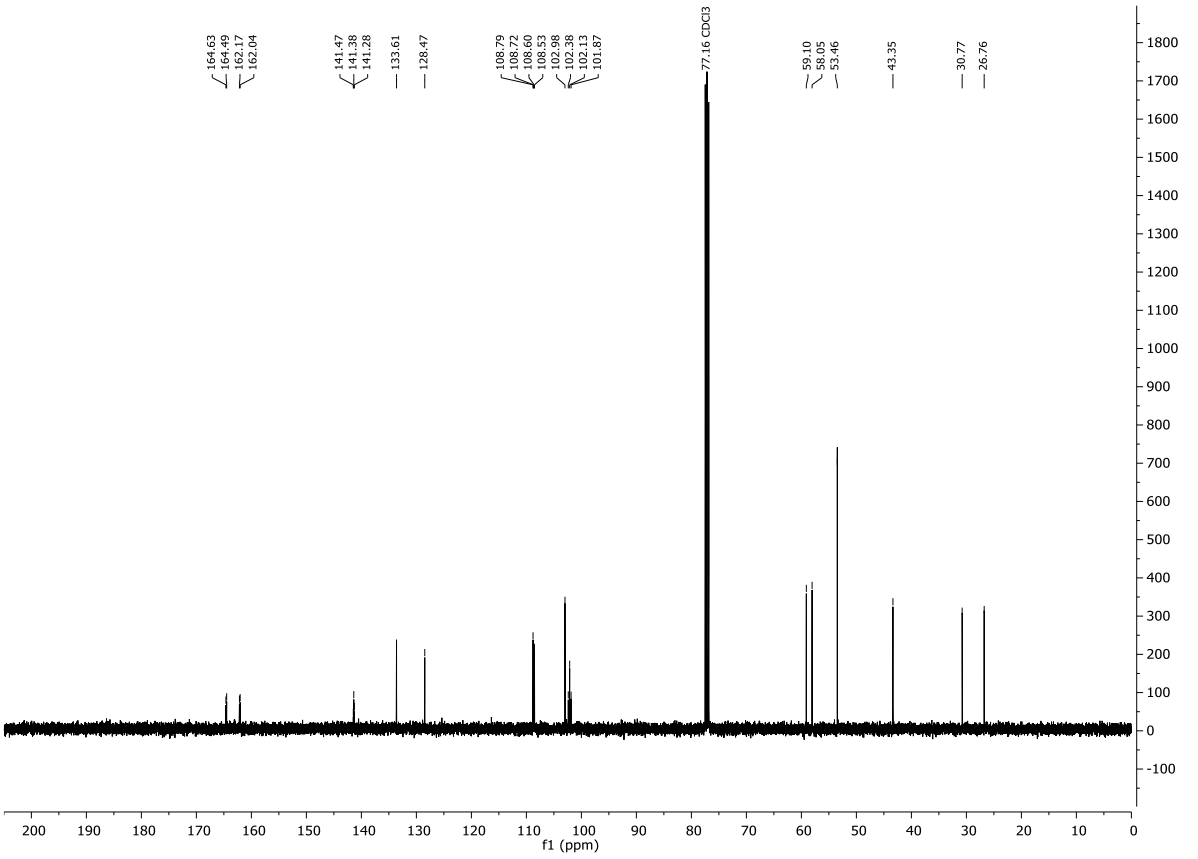

282c
f1 (ppm)

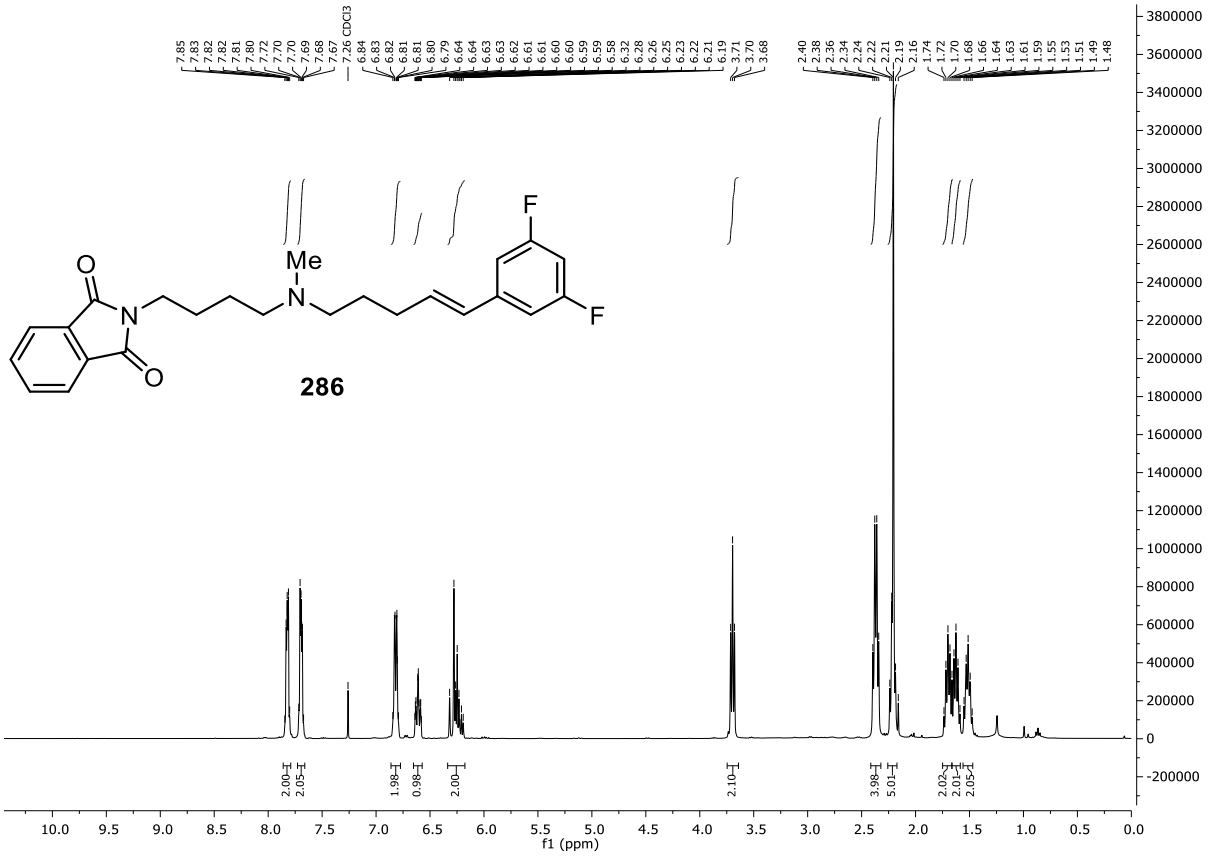

f1 (ppm)

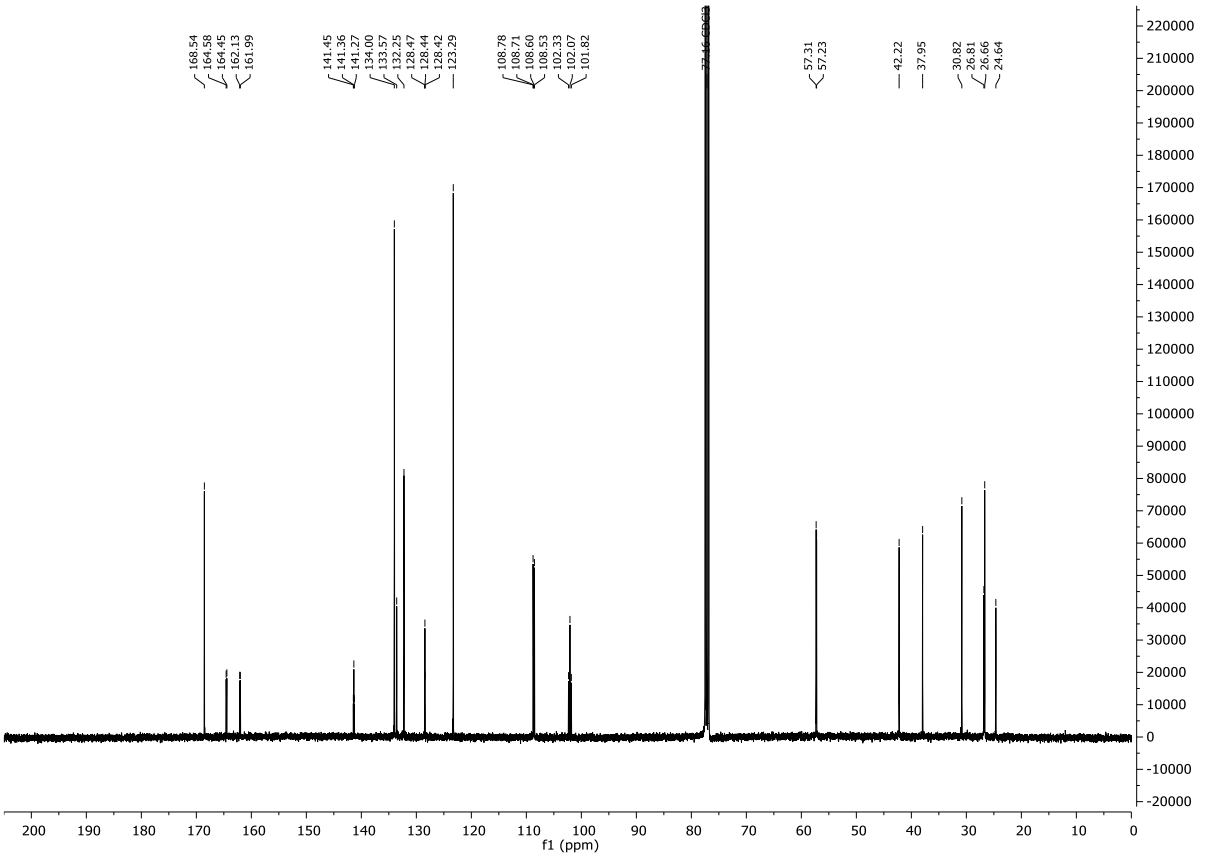

CDCl3
N
Me
F
F
284
f1 (ppm)

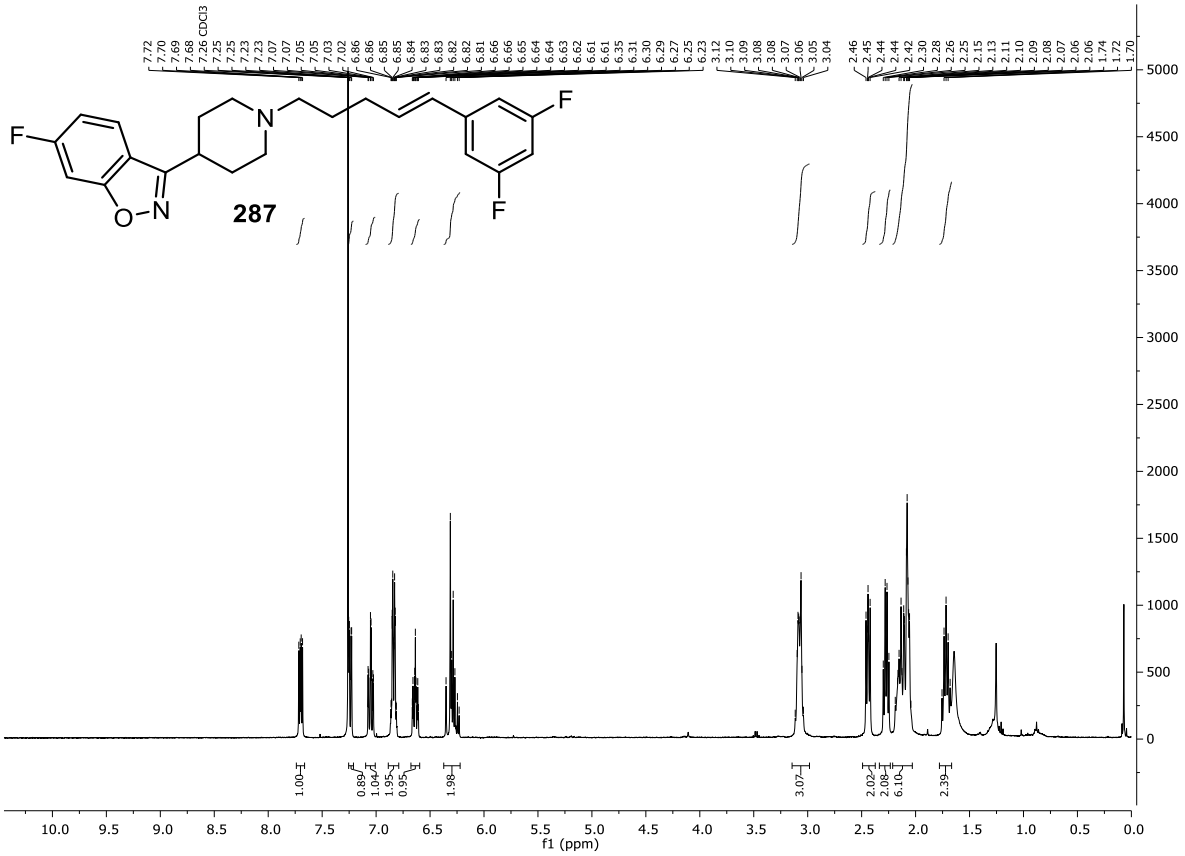

164.63
164.50
162.18
162.05
142.39
141.47
141.37
141.28
133.62
128.52
128.49
128.46
125.90
108.80
108.73
108.62
108.55
102.39
102.13
101.88
77.16 CDCl3
57.39
57.21
42.29
33.83
30.86
29.12
26.83
f1 (ppm)

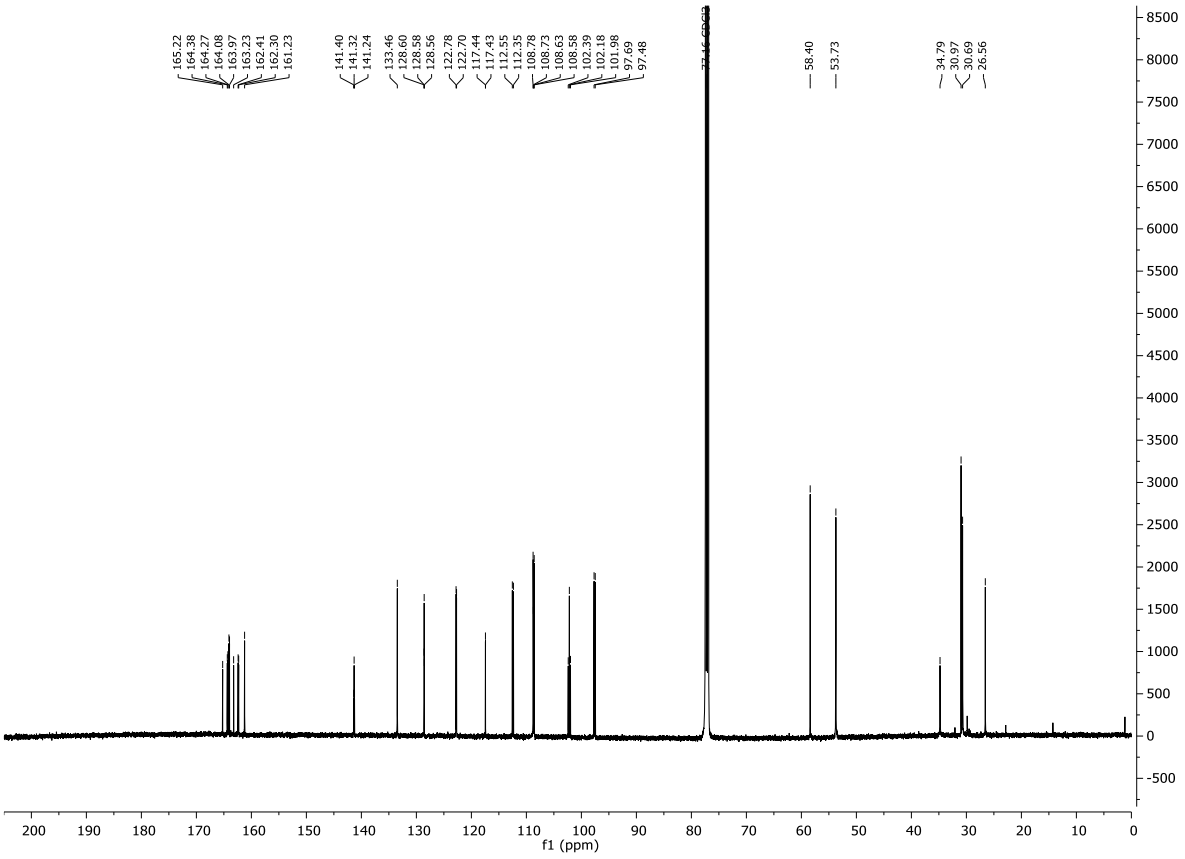

7.26 CDCl3
6.85
6.84
6.83
6.82
6.81
6.80
6.79
6.65
6.64
6.63
6.62
6.61
6.60
6.33
6.29
6.28
6.26
6.25
6.24
6.22
6.21
4.50
4.48
4.47
3.36
2.53
2.52
2.46
2.45
2.44
2.42
2.30
2.26
2.24
2.22
2.21
1.68
1.66
1.65
1.63
1.61
Me
O
Me
O
N
Me
F
F
285
2.00
0.97
1.95
0.99
5.91
1.96
2.06
3.02
1.99
2.50
f1 (ppm)

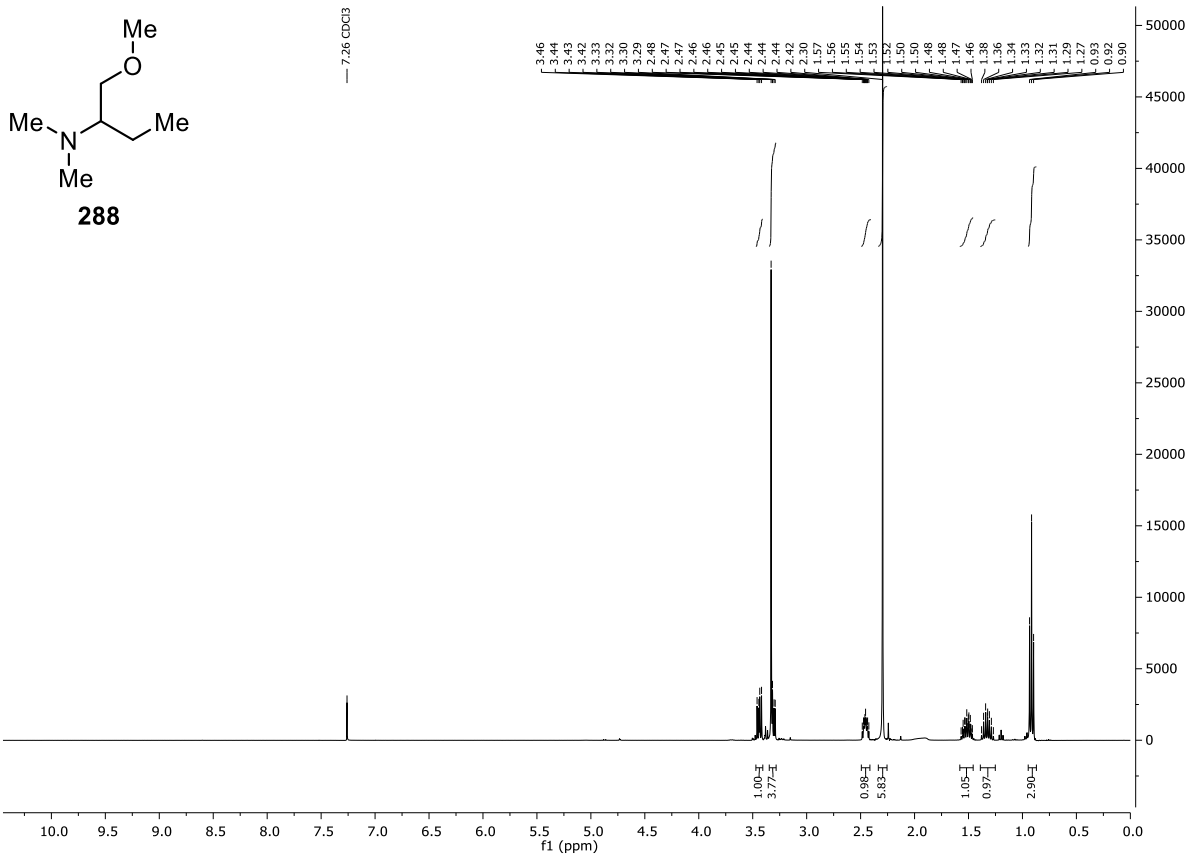

164.63
164.49
162.17
162.04
141.47
141.38
141.28
133.61
128.47
108.79
108.72
108.60
108.53
102.98
102.38
102.13
101.87
77.16 CDCl3
59.10
58.05
53.46
43.35
30.77
26.76
f1 (ppm)

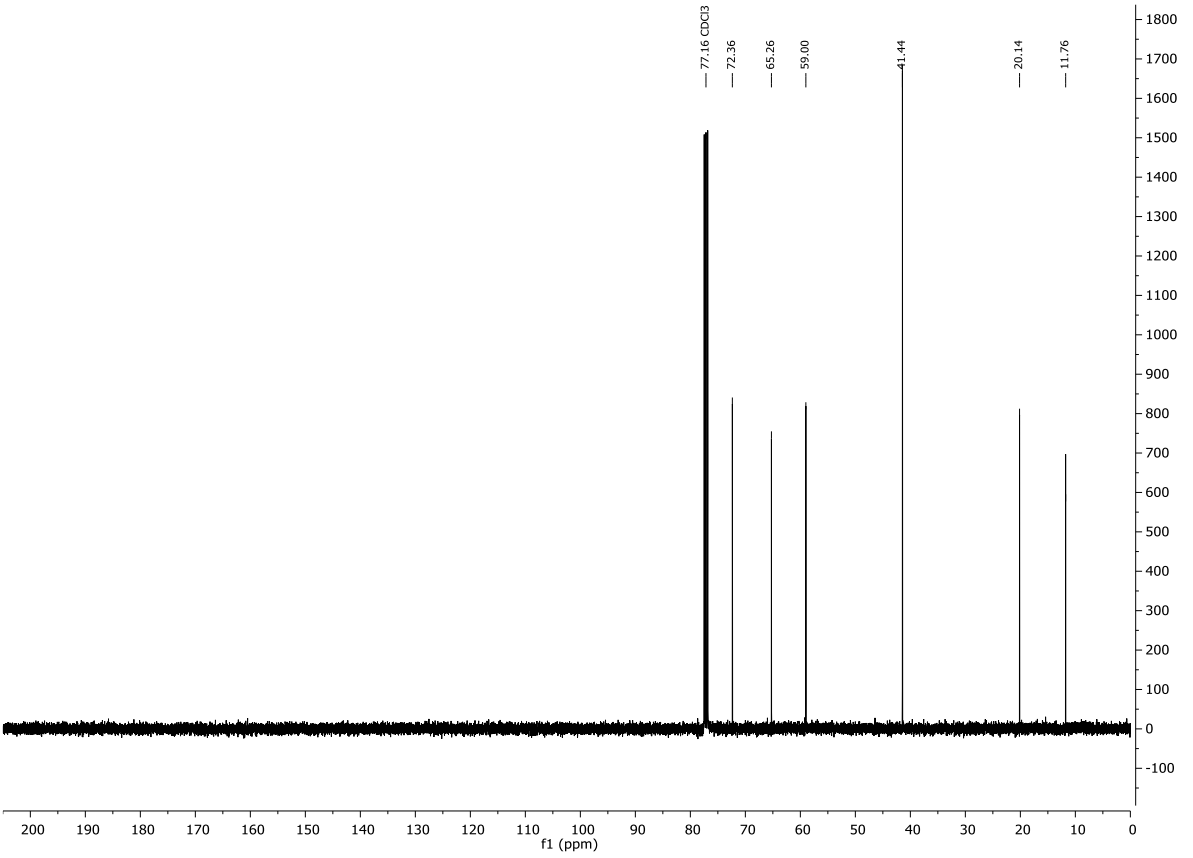

7.85 7.83 7.82 7.82 7.81 7.80 7.72 7.70 7.70 7.69 7.68 7.67 7.26 CDCl3 6.84 6.83 6.82 6.81 6.81 6.80 6.79 6.64 6.64 6.63 6.63 6.62 6.61 6.61 6.60 6.60 6.59 6.59 6.58 6.32 6.28 6.26 6.25 6.23 6.22 6.21 6.19 3.71 3.70 3.68 2.40 2.38 2.36 2.34 2.24 2.22 2.21 2.19 2.16 1.74 1.72 1.70 1.68 1.66 1.64 1.63 1.61 1.59 1.55 1.53 1.51 1.49 1.48
Me
N
O
O
N
F
F
286
2.00 2.05 1.98 0.98 2.00 2.10 3.98 5.01 2.02 2.01 2.05
f1 (ppm)

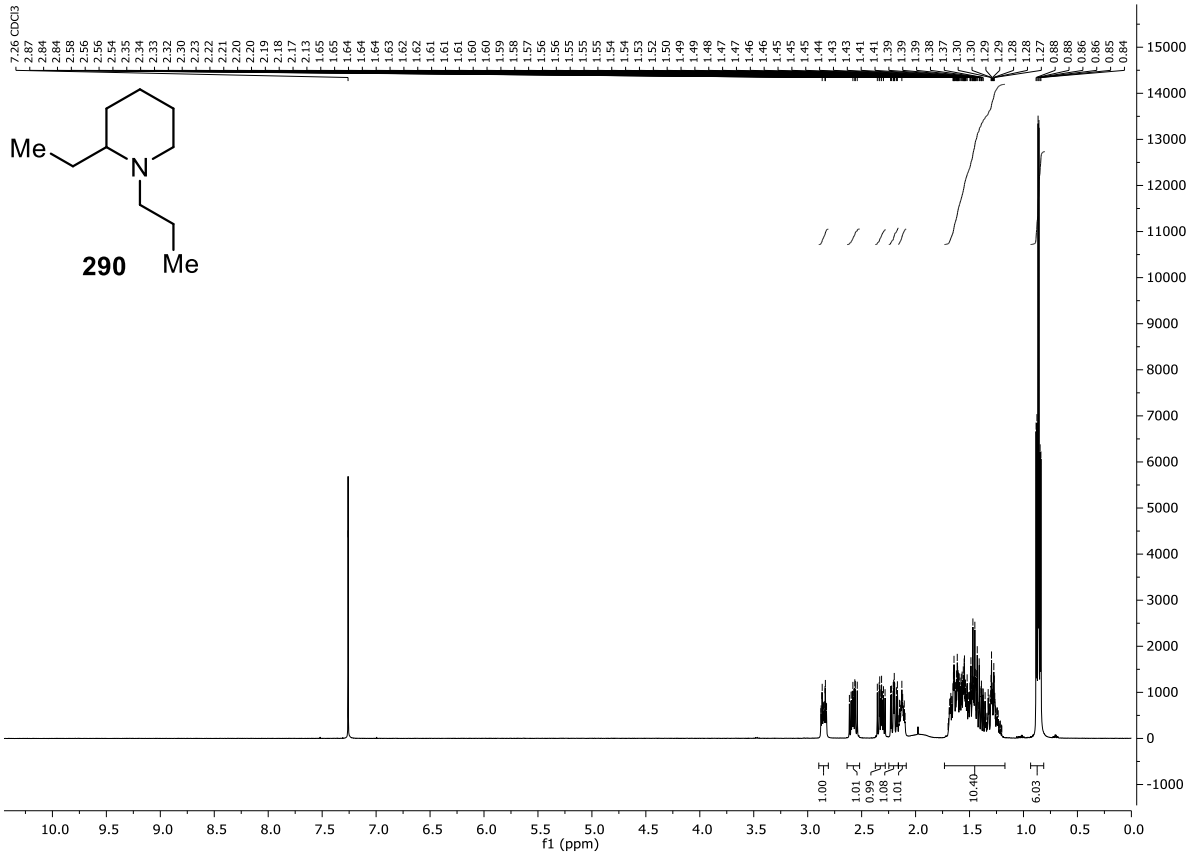

168.54 164.58 164.45 162.13 161.99 141.45 141.36 141.27 134.00 133.57 132.25 128.47 128.44 128.42 123.29 108.78 108.71 108.60 108.53 102.33 102.07 101.82 77.46 CDCl3 57.31 57.23 42.22 37.95 30.82 26.81 26.66 24.64
f1 (ppm)

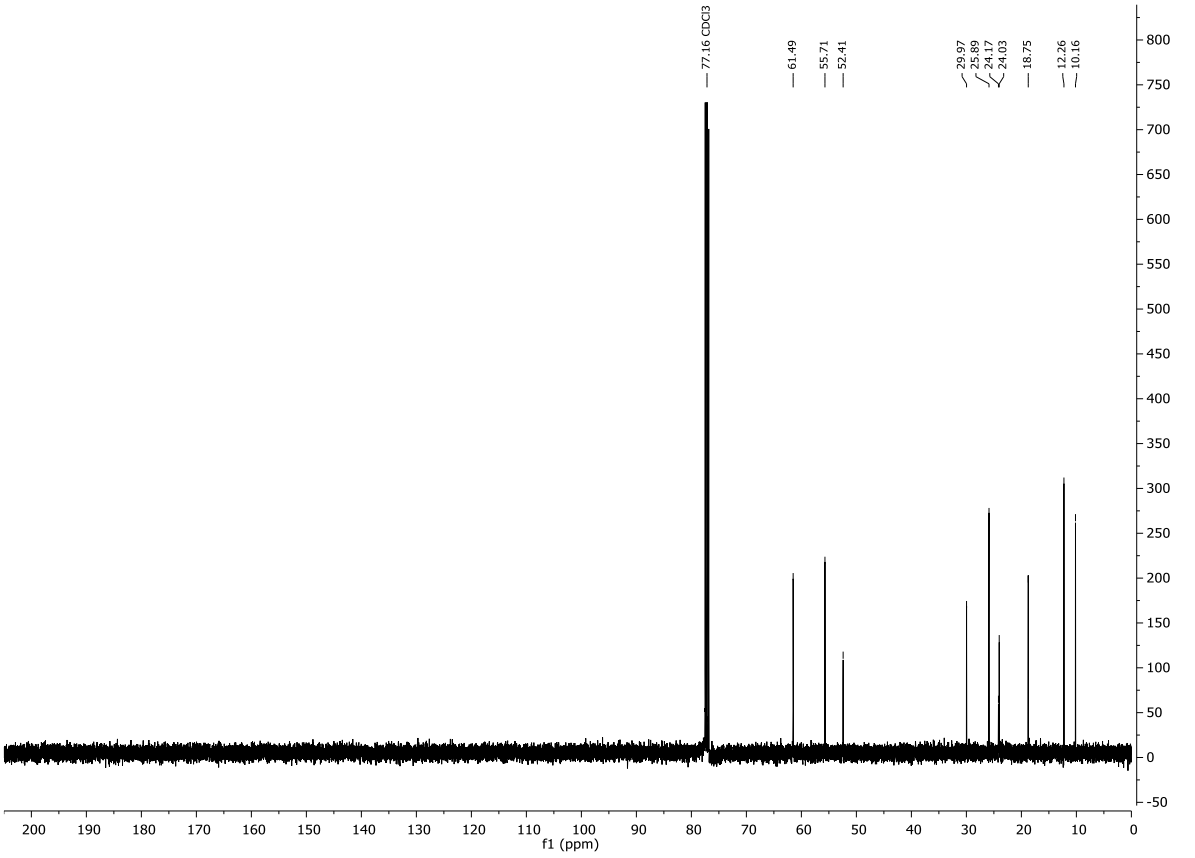

F
N
O
N
F
F
287
f1 (ppm)

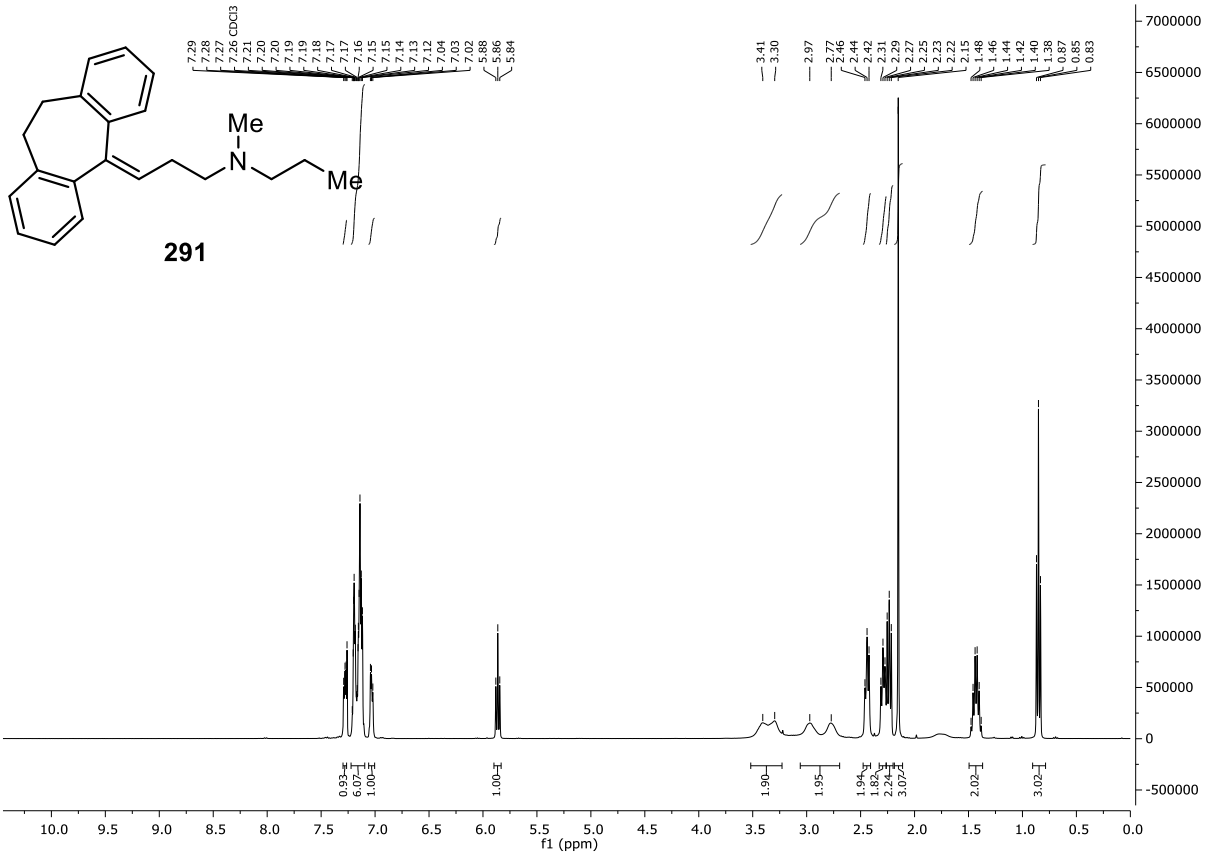

f1 (ppm)

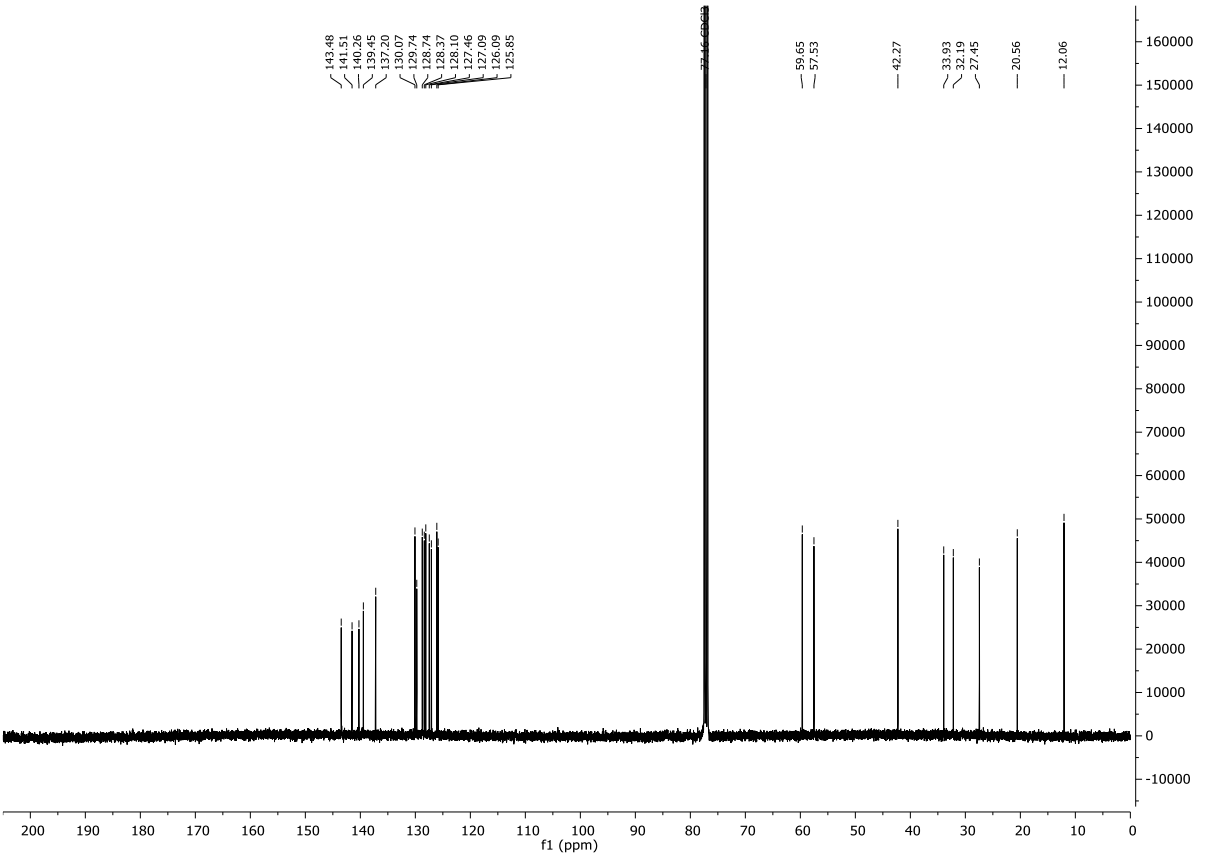

Me
O
Me
N
Me
Me
288
7.26 CDCl3
f1 (ppm)

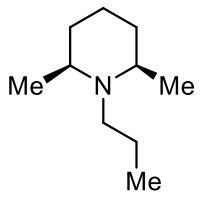

77.16 CDCl3
72.36
65.26
59.00
41.44
20.14
11.76
f1 (ppm)


Me
N
Me
290
f1 (ppm)


77.16 CDCl3
61.49
55.71
52.41
29.97
25.89
24.17
24.03
18.75
12.26
10.16
f1 (ppm)

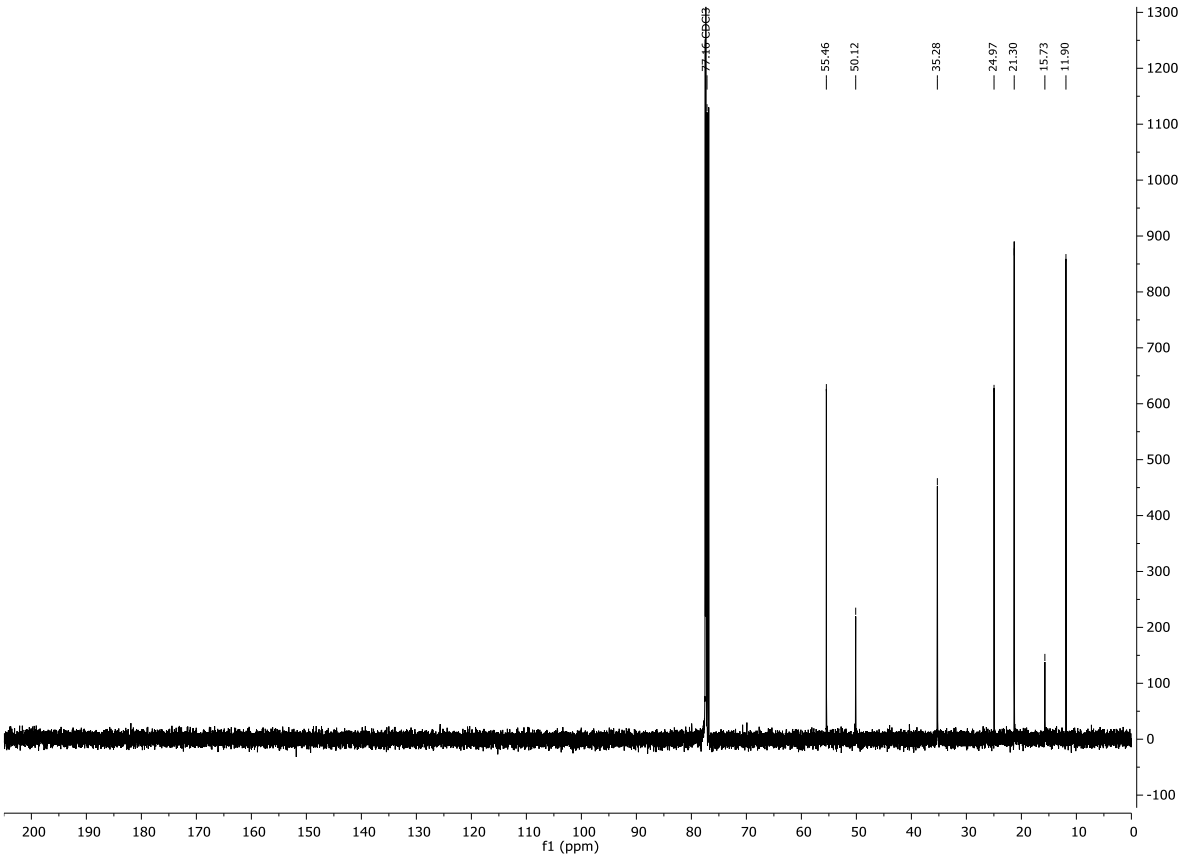

Me
N
Me
291
f1 (ppm)

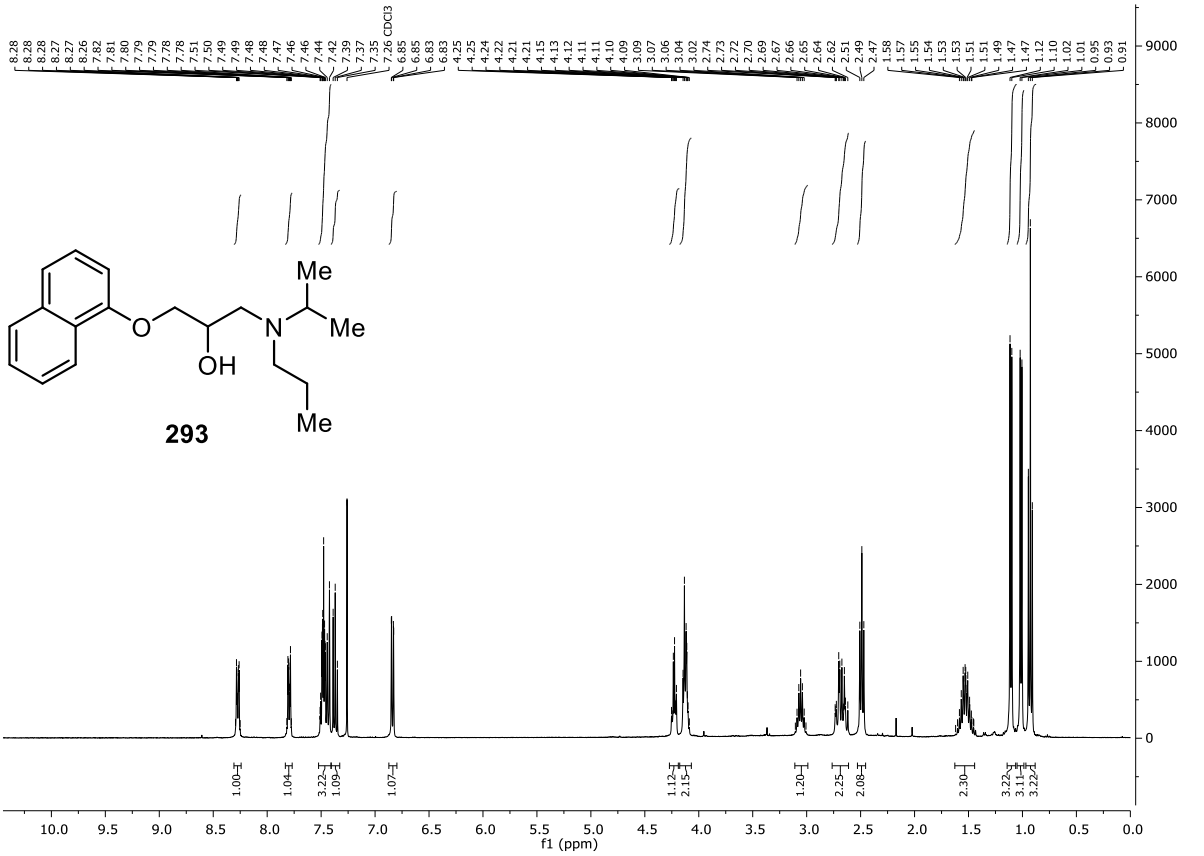

f1 (ppm)

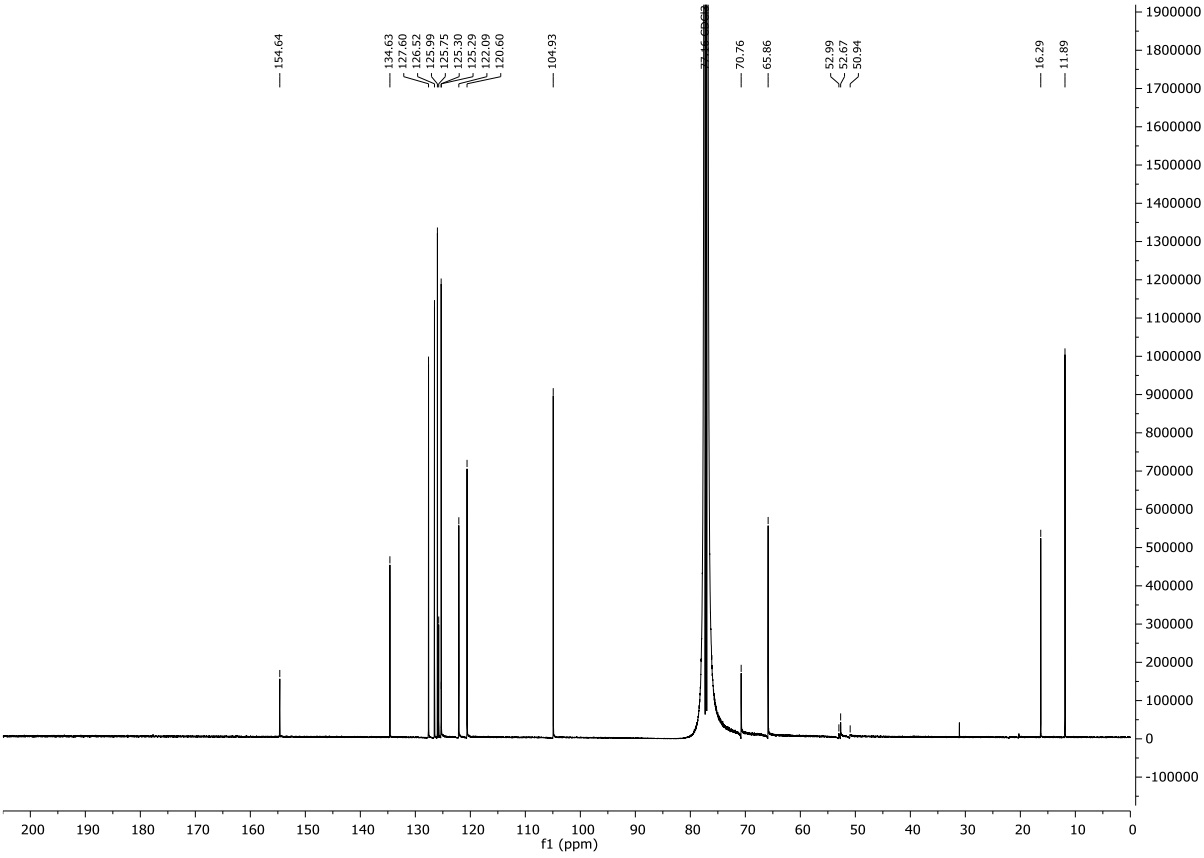

Me
N
Me
Me

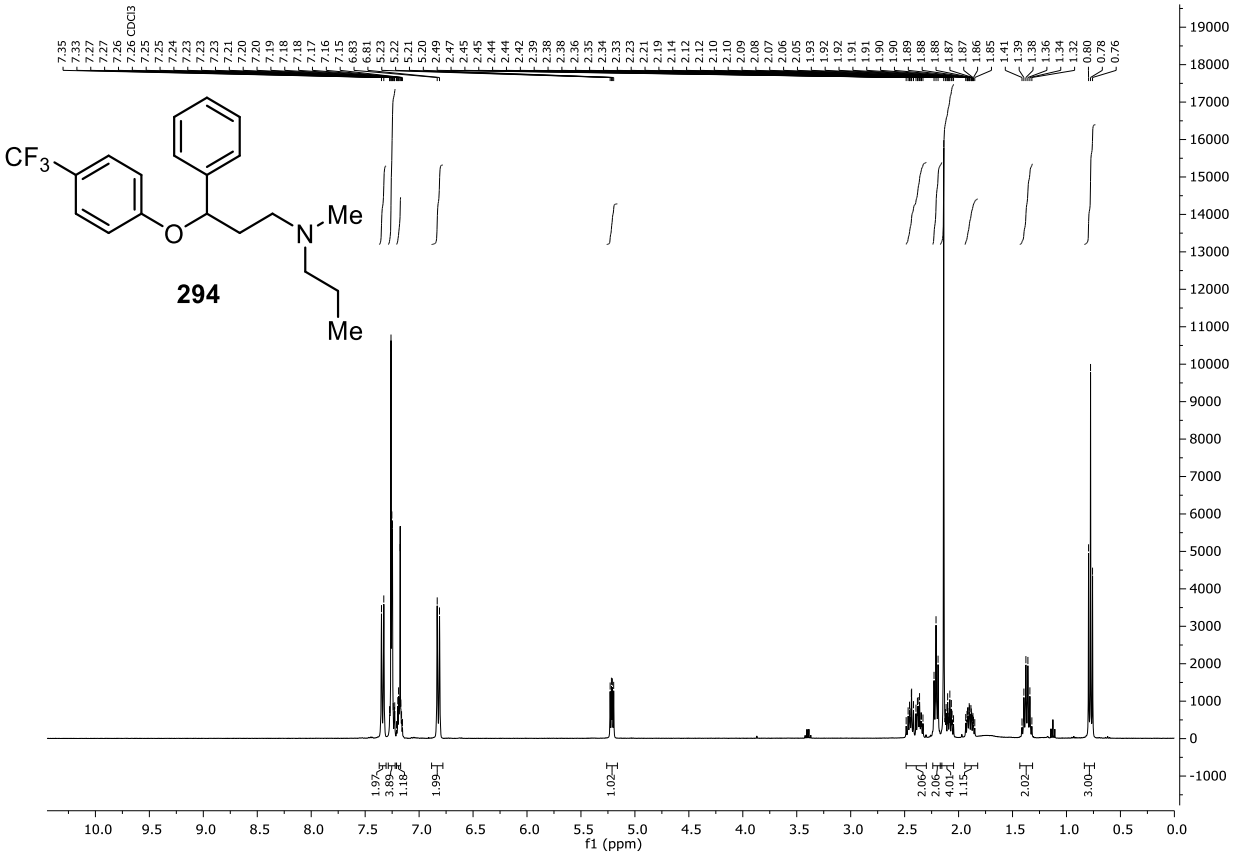
292

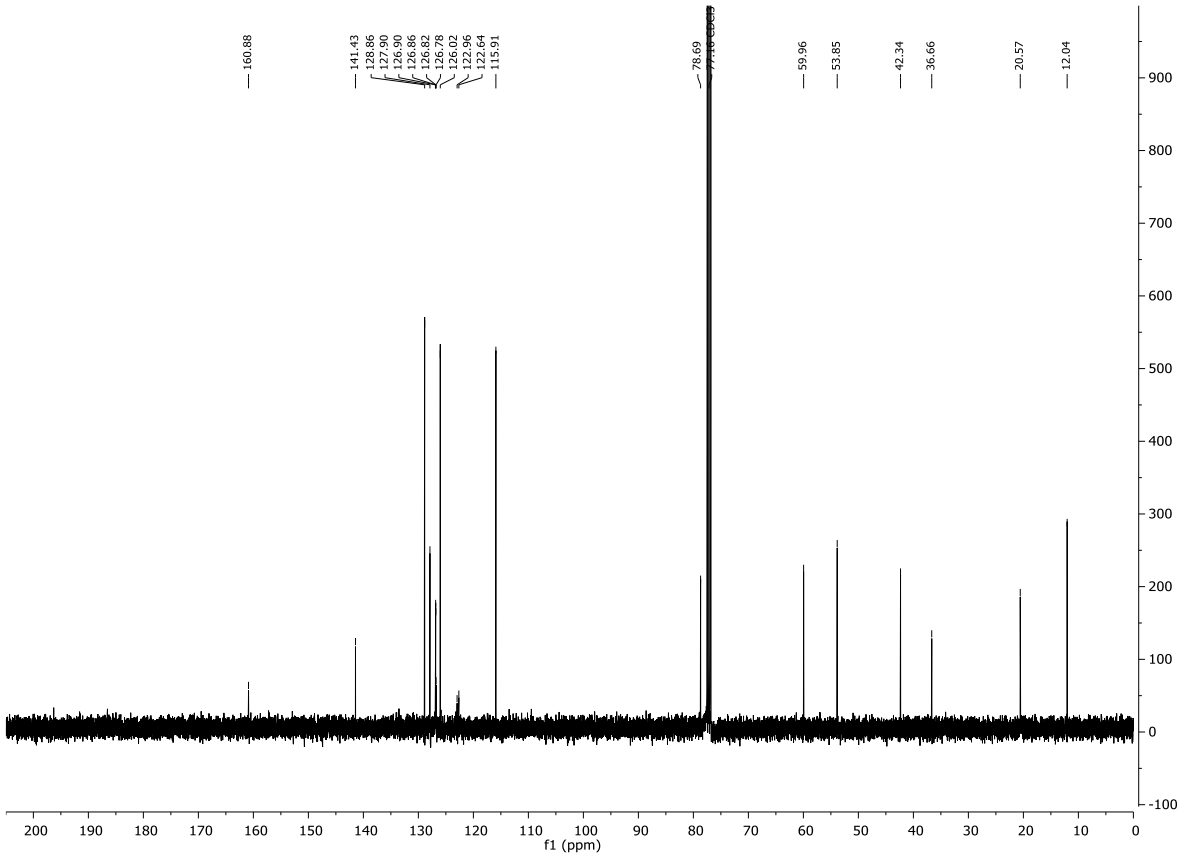
7.26 CDCl3
1.96
1.95
1.43
2.05
2.14
3.15
5.88
3.00
f1 (ppm)

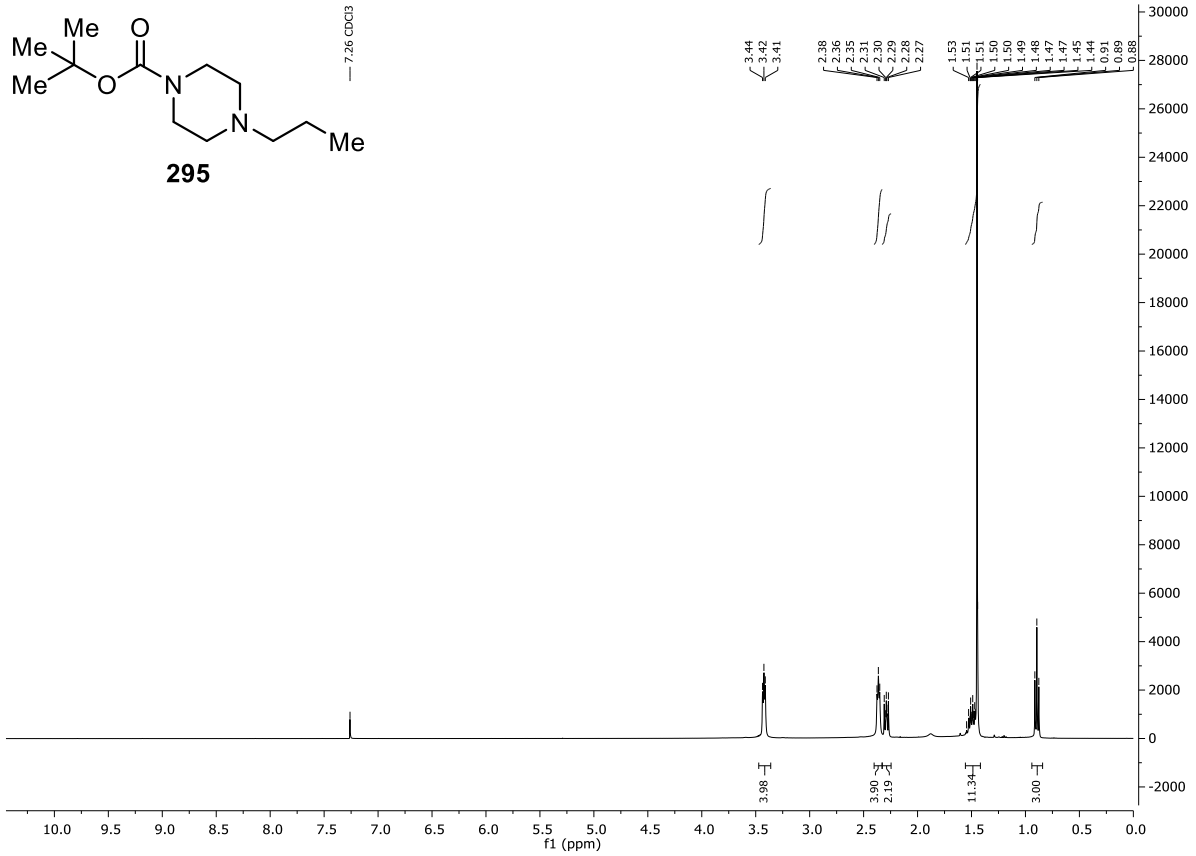

77.16 CDCl3
55.46
50.12
35.28
24.97
21.30
15.73
11.90
f1 (ppm)

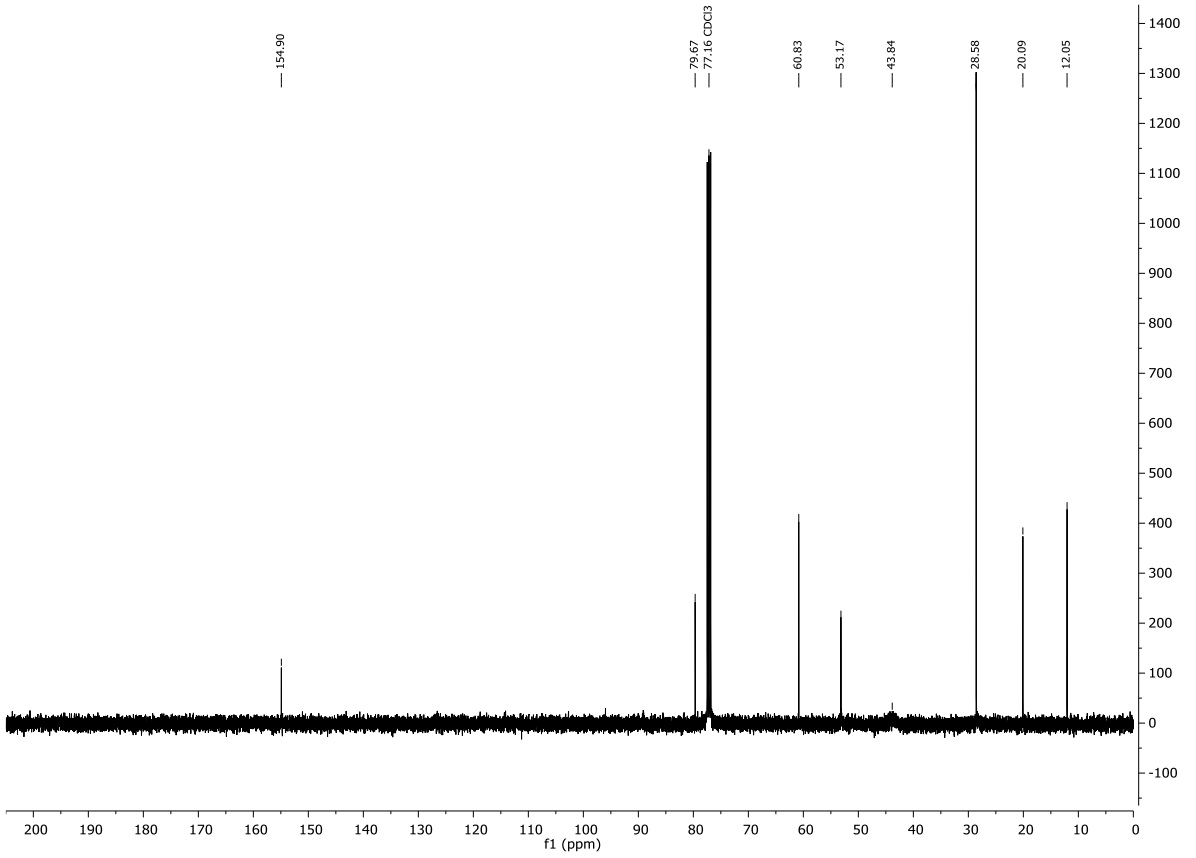

Me
Me
Me
O
N
OH
293
f1 (ppm)

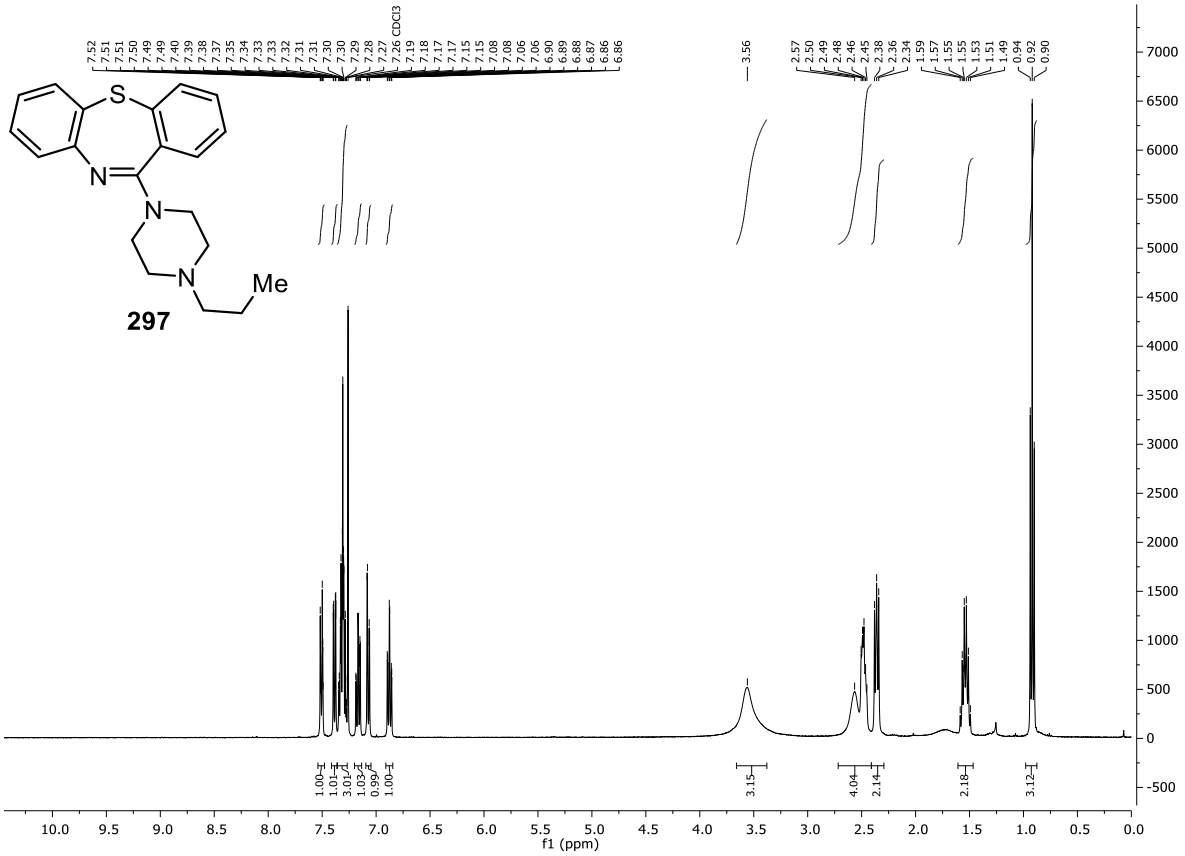

154.64
134.63
127.60
126.52
125.99
125.75
125.30
125.29
122.09
120.60
104.93
70.76
65.86
52.99
52.67
50.94
16.29
11.89
f1 (ppm)

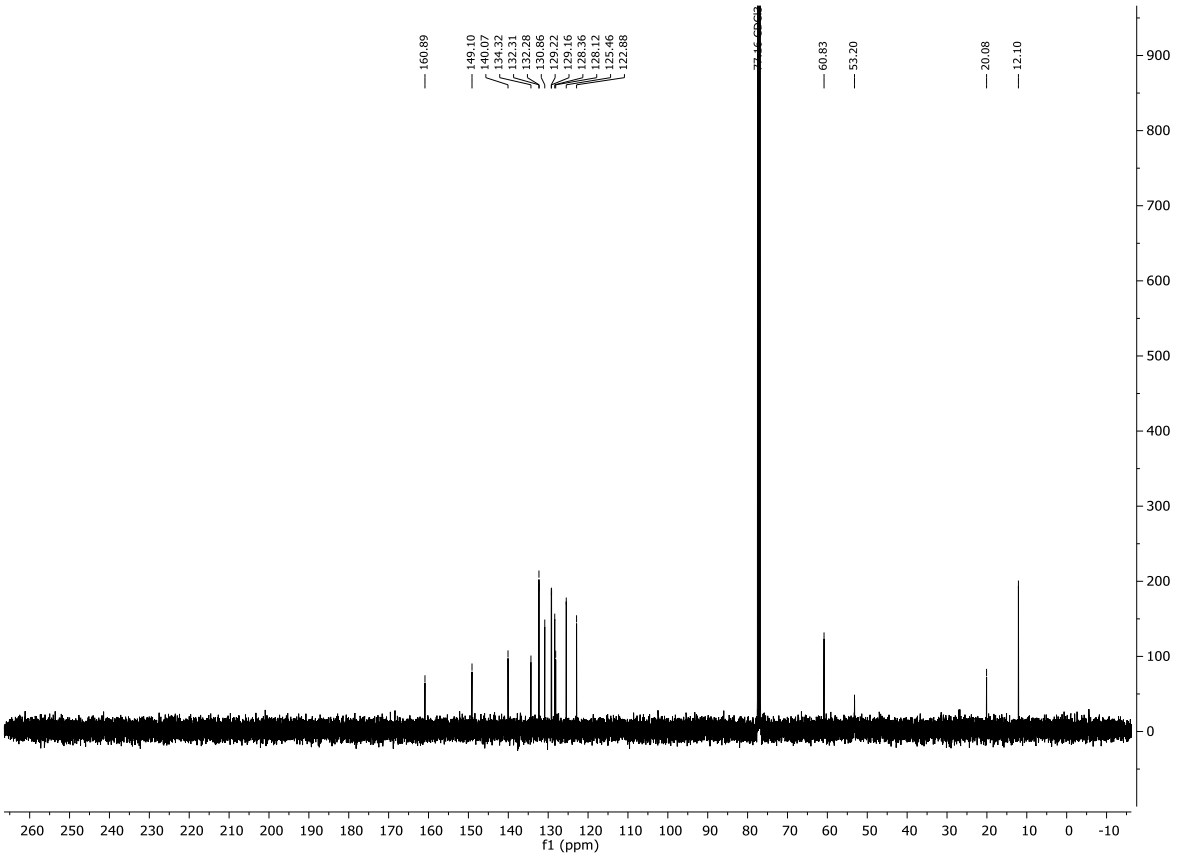

CF3
O
N
Me
Me
294
f1 (ppm)

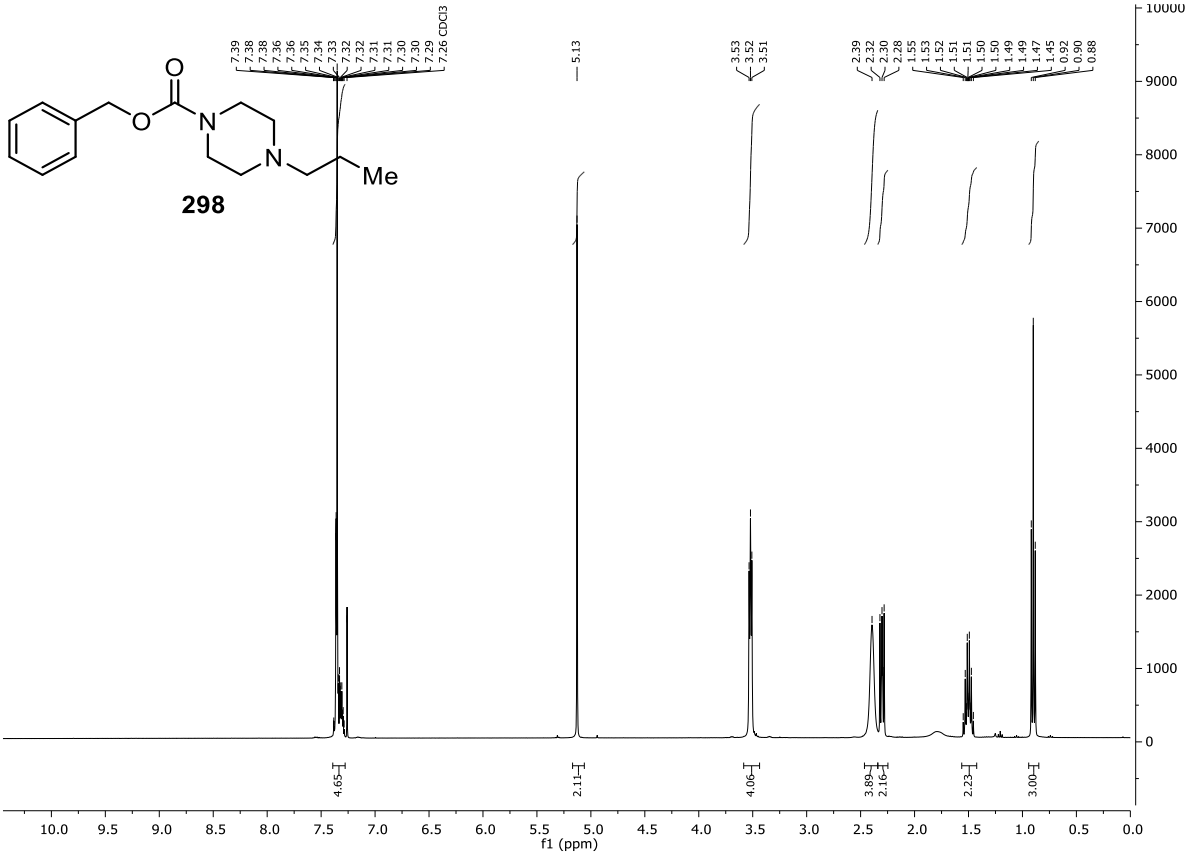

160.88
141.43
128.86
127.90
126.90
126.86
126.82
126.78
126.02
122.96
122.64
115.91
78.69
59.96
53.85
42.34
36.66
20.57
12.04
f1 (ppm)

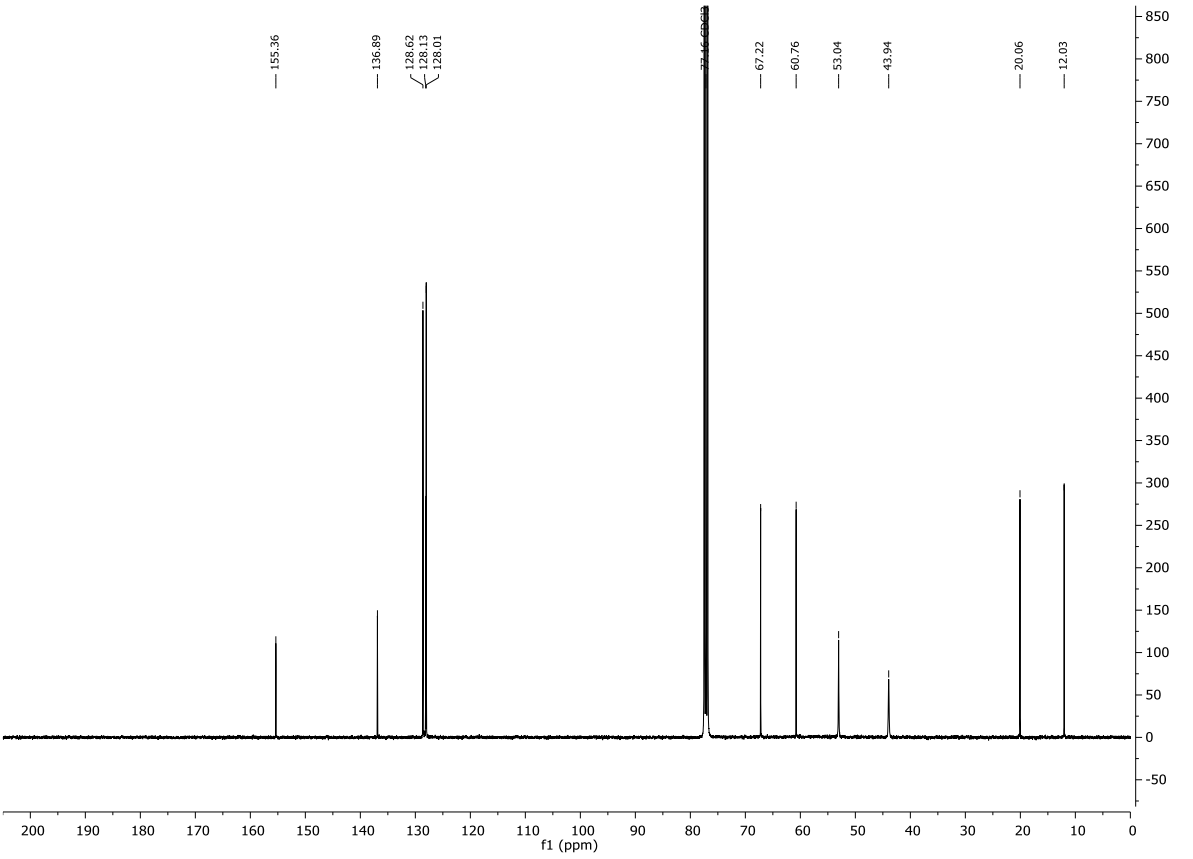

Me
O
Me
Me
O
N
N
Me
295
7.26 CDCl3
3.44
3.42
3.41
2.38
2.36
2.35
2.31
2.30
2.29
2.28
2.27
1.53
1.51
1.51
1.51
1.50
1.50
1.49
1.48
1.47
1.47
1.45
1.44
0.91
0.89
0.88
3.98
3.90
2.19
11.34
3.00
f1 (ppm)

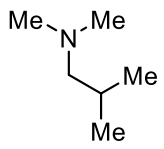

154.90
79.67
77.16 CDCl3
60.83
53.17
43.84
28.58
20.09
12.05
f1 (ppm)


7.52 7.51 7.51 7.50 7.49 7.49 7.40 7.39 7.38 7.37 7.35 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.28 7.27 7.26 CDCl3 7.19 7.18 7.17 7.17 7.15 7.15 7.08 7.08 7.06 7.06 6.90 6.89 6.88 6.87 6.86 6.86
3.56
2.57 2.50 2.49 2.48 2.46 2.45 2.38 2.36 2.34 1.59 1.57 1.55 1.55 1.53 1.51 1.49 0.94 0.92 0.90
S
N
N
N
Me
297
1.00 1.01 3.01 1.03 0.99 1.00
3.15
4.04 2.14
2.18
3.12
f1 (ppm)


160.89
149.10 140.07 134.32 132.31 132.28 130.86 129.22 129.16 128.36 128.12 125.46 122.88
77.16 CDCl3
60.83
53.20
20.08
12.10
f1 (ppm)

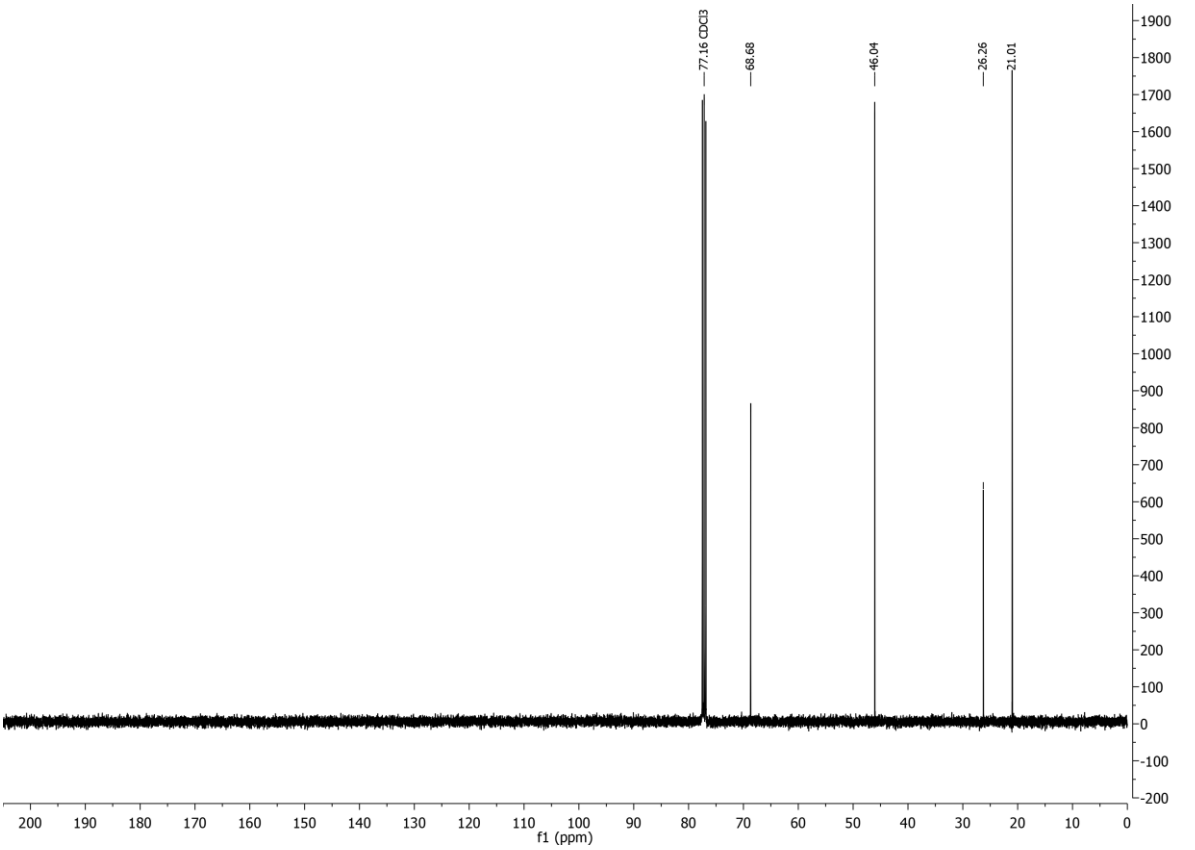

298
Me
7.39
7.38
7.38
7.36
7.36
7.35
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.26 CDCl3
5.13
3.53
3.52
3.51
2.39
2.32
2.30
2.28
1.55
1.53
1.52
1.51
1.51
1.50
1.50
1.49
1.49
1.47
1.45
0.92
0.90
0.88
4.65
2.11
4.06
3.89
2.16
2.23
3.00
f1 (ppm)

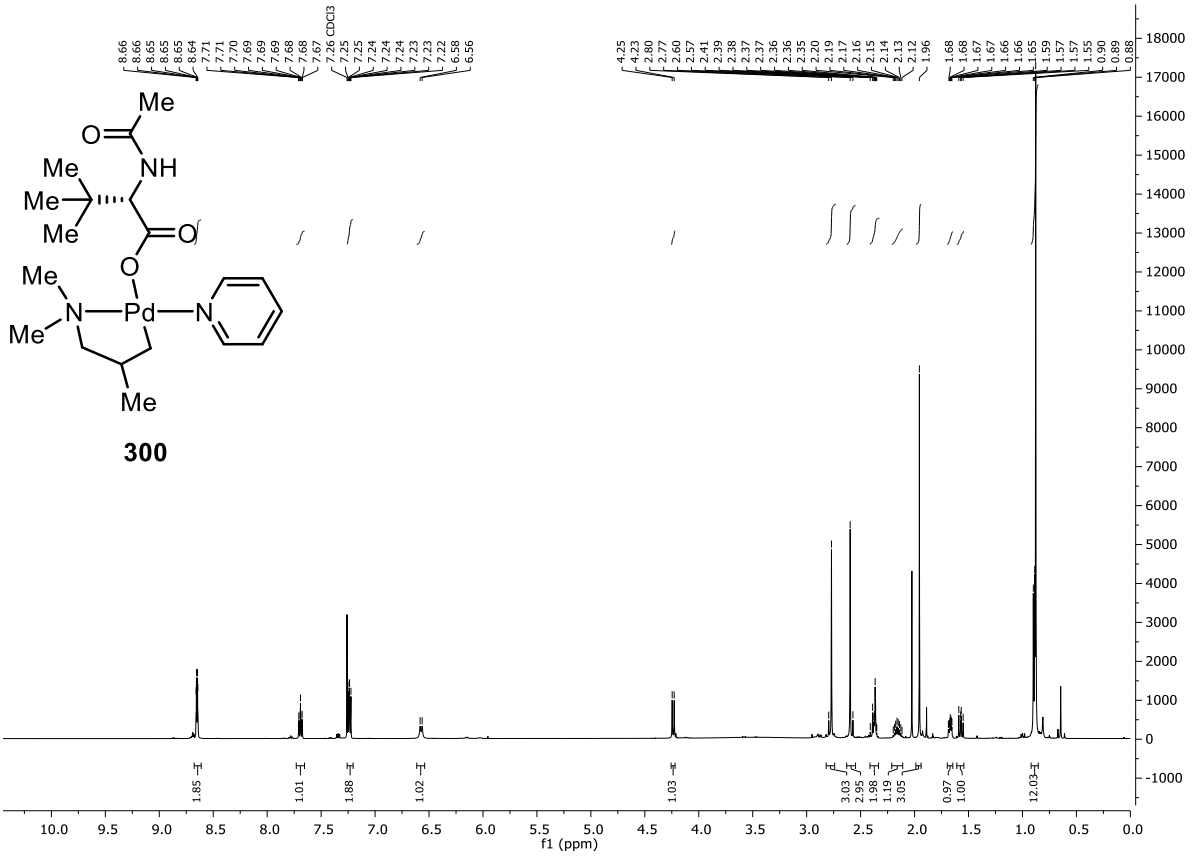

155.36
136.89
128.62
128.13
128.01
77.46 CDCl3
67.22
60.76
53.04
43.94
20.06
12.03
f1 (ppm)


Me
N
Me
Me
Me

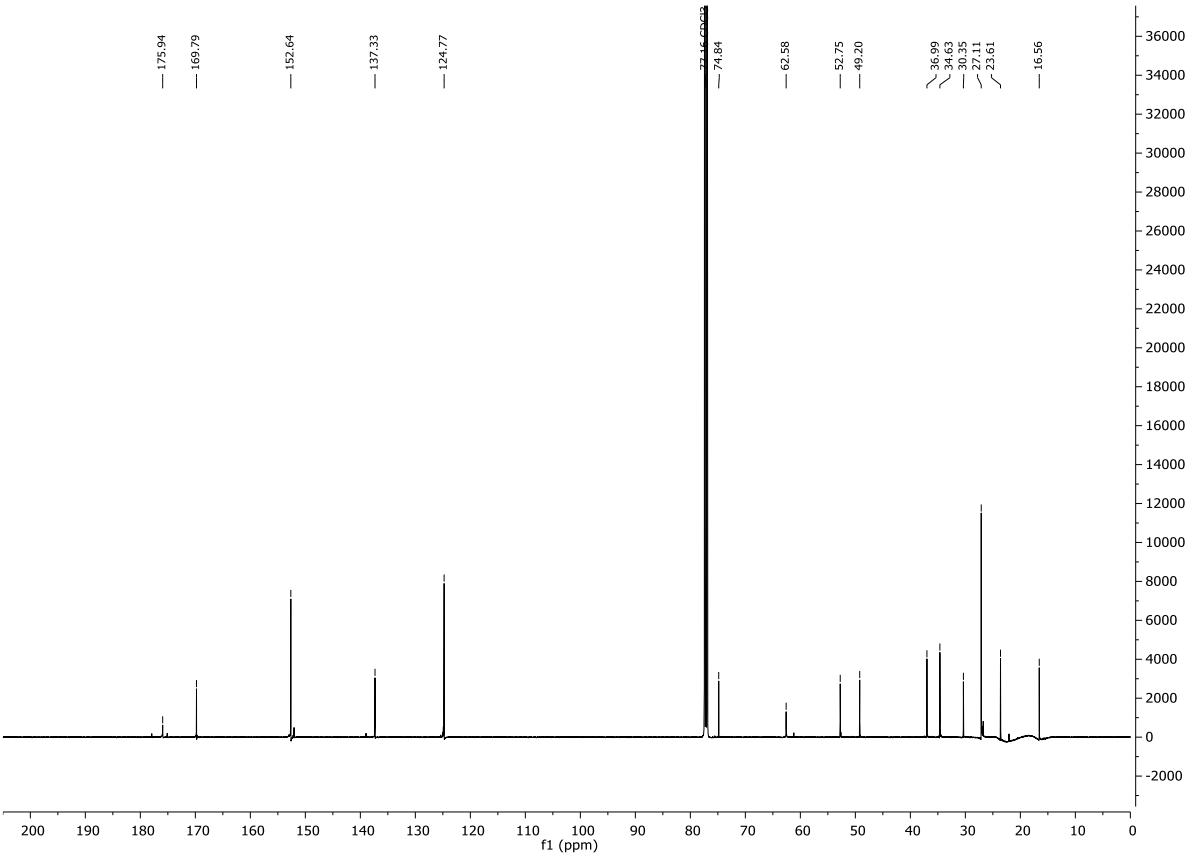
299

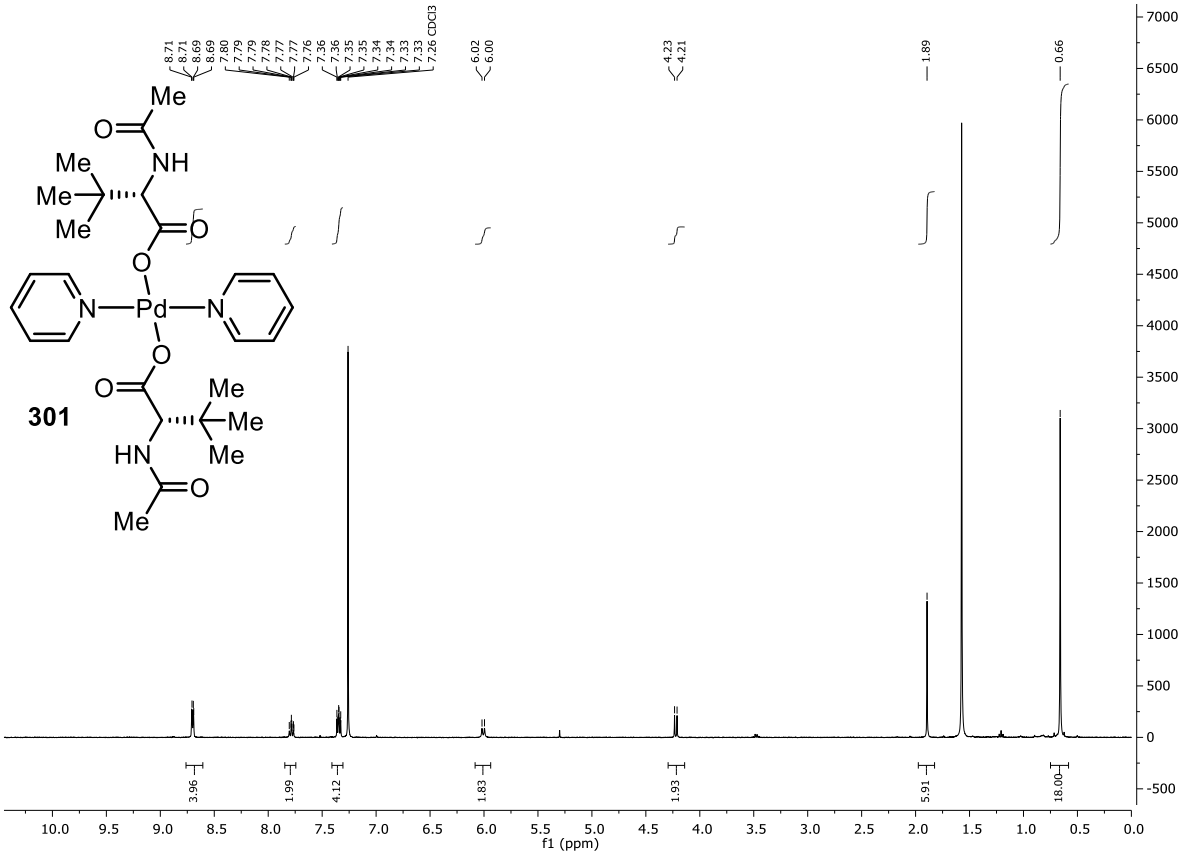
7.26 CDCl3
2.18
2.02
2.00
1.79
1.77
1.76
1.74
1.72
1.71
1.69
1.67
1.66
0.90
0.88
6.09
2.11
0.99
6.00
f1 (ppm)

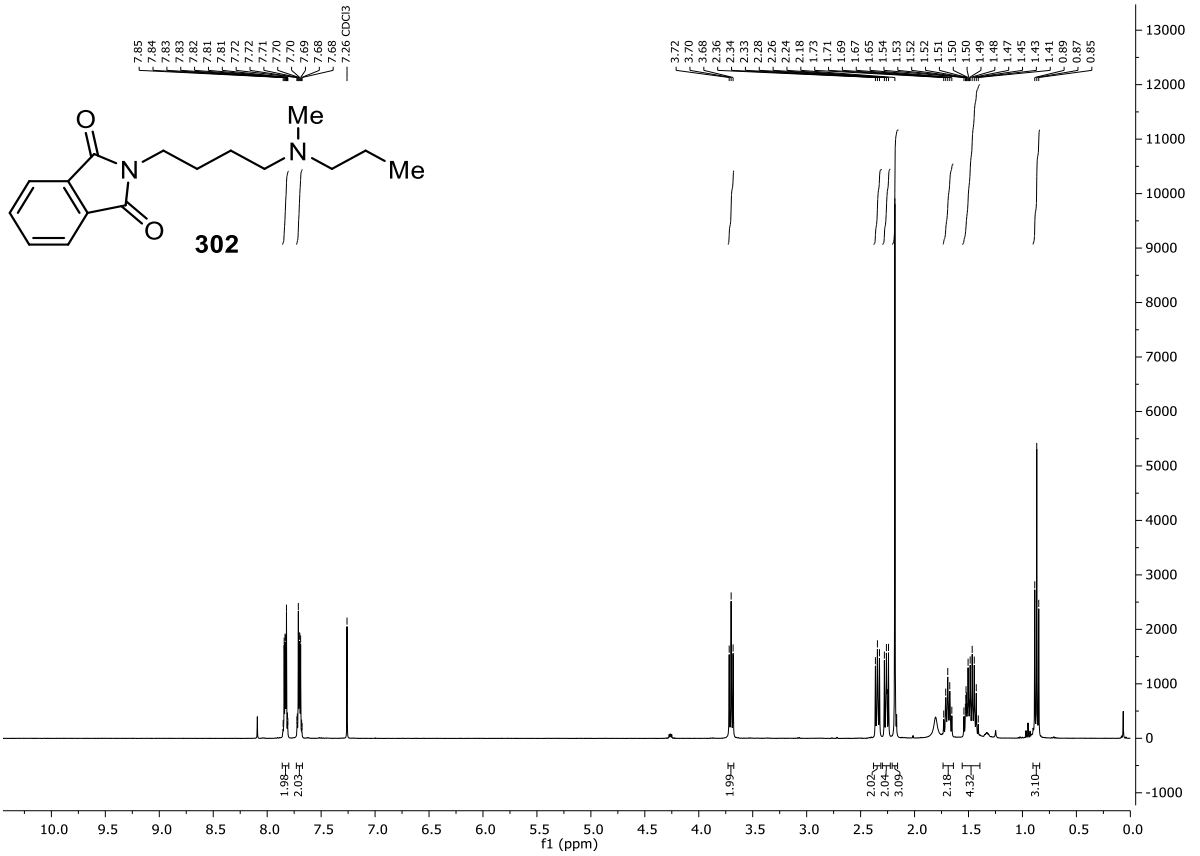

77.16 CDCl3
68.68
46.04
26.26
21.01
f1 (ppm)

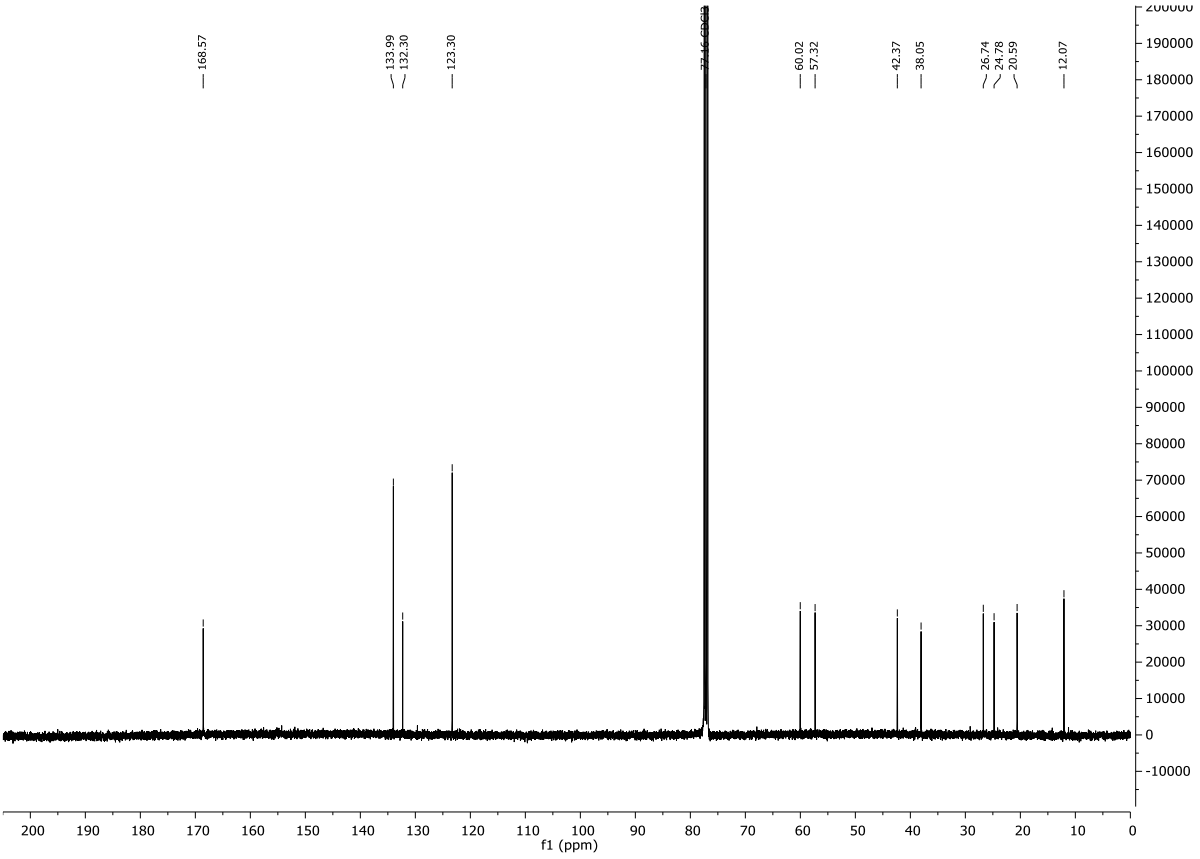


300




301
8.71
8.71
8.69
8.69
7.80
7.79
7.79
7.78
7.77
7.77
7.76
7.36
7.35
7.35
7.34
7.33
7.33
7.26 CDCl3
6.02
6.00
4.23
4.21
1.89
0.66
3.96
1.99
4.12
1.83
1.93
5.91
18.00
f1 (ppm)


7.85
7.84
7.83
7.83
7.82
7.81
7.81
7.72
7.72
7.71
7.70
7.70
7.69
7.68
7.68
7.26 CDCl3
3.72
3.70
3.68
2.36
2.34
2.33
2.28
2.26
2.24
2.18
1.73
1.71
1.69
1.67
1.65
1.54
1.53
1.52
1.52
1.51
1.50
1.50
1.49
1.48
1.47
1.45
1.43
1.41
0.89
0.87
0.85
Me
N
N
Me
O
O
O
302
1.98
2.03
1.99
2.02
2.04
3.09
2.18
4.32
3.10
f1 (ppm)


168.57
133.99
132.30
123.30
77.46 CDCl3
60.02
57.32
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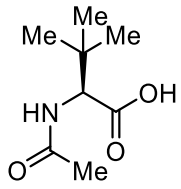
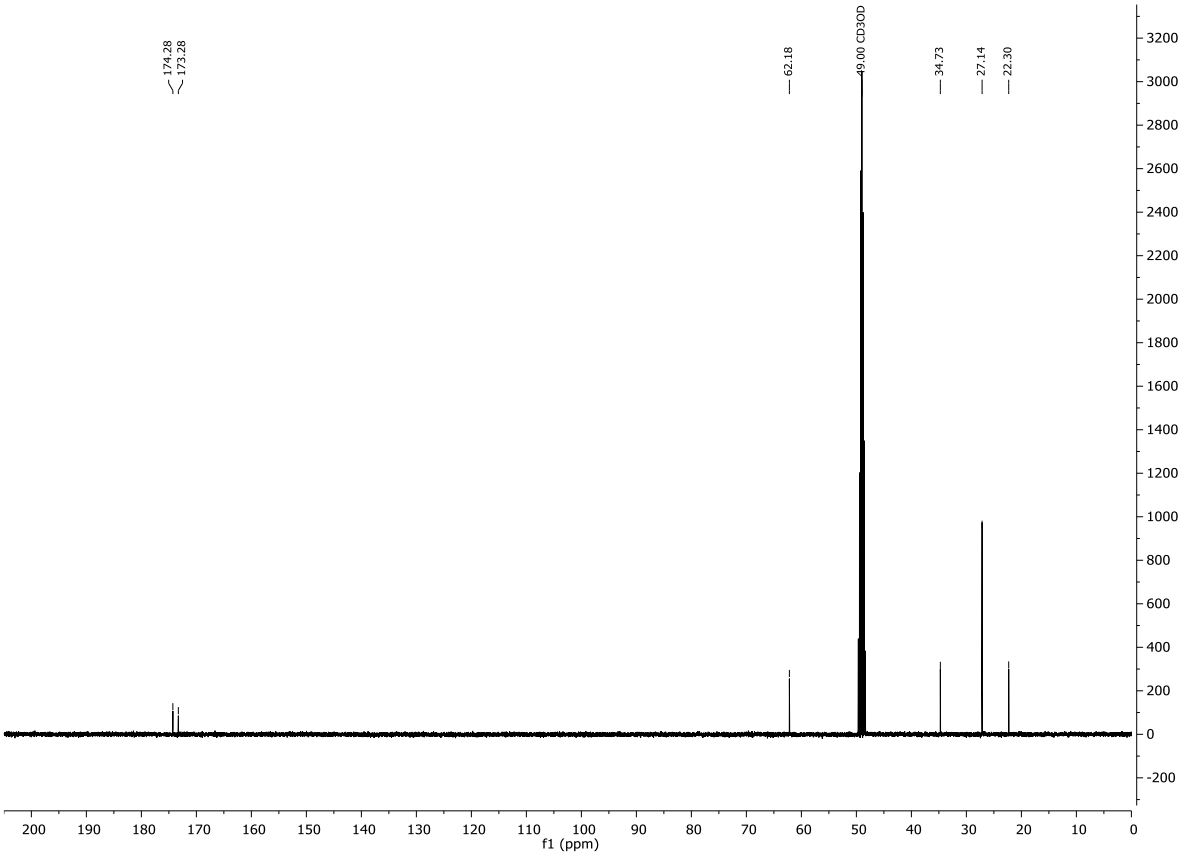
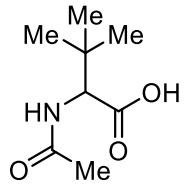
38.05
26.74
24.78
20.59
12.07
f1 (ppm)


Me
Me
Me
OH
HN
O
O
Me

(-)-304

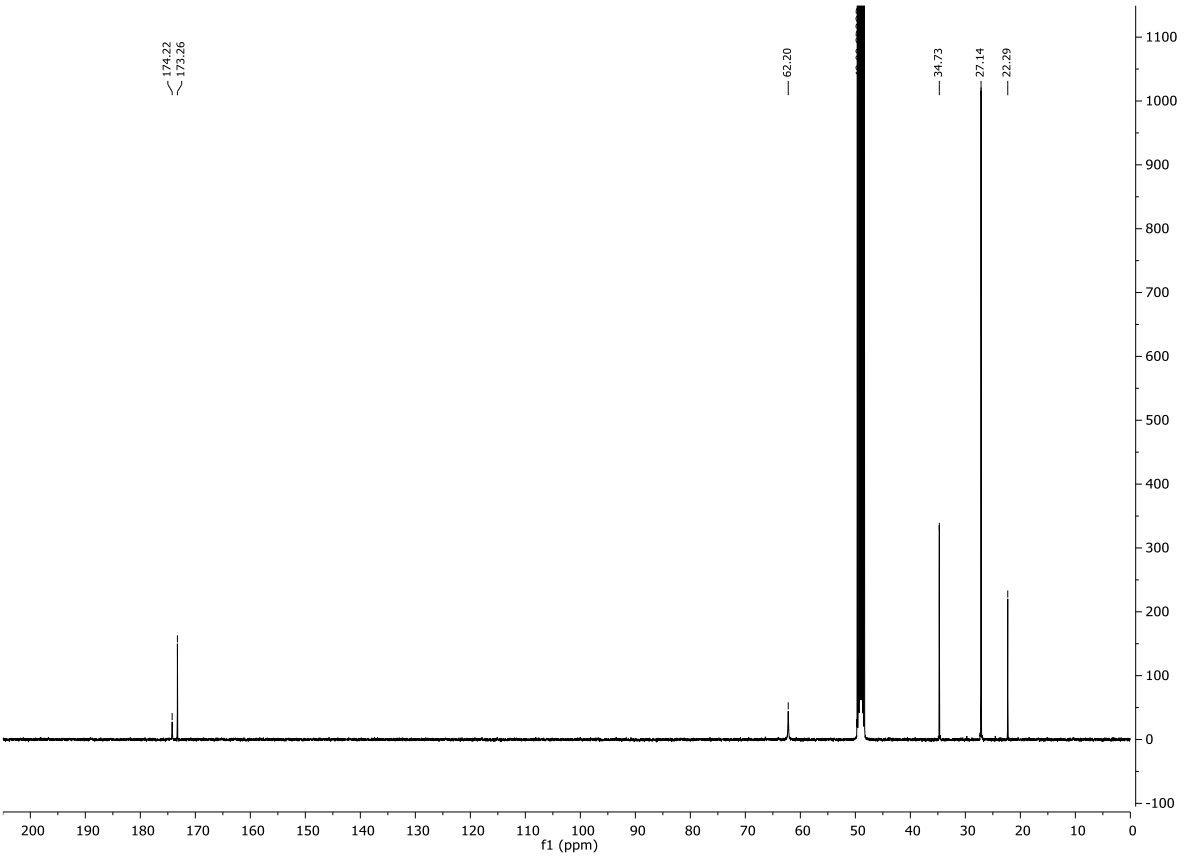
4.87 CD3OD
4.28
2.01
1.03
1.00
3.02
9.02
f1 (ppm)

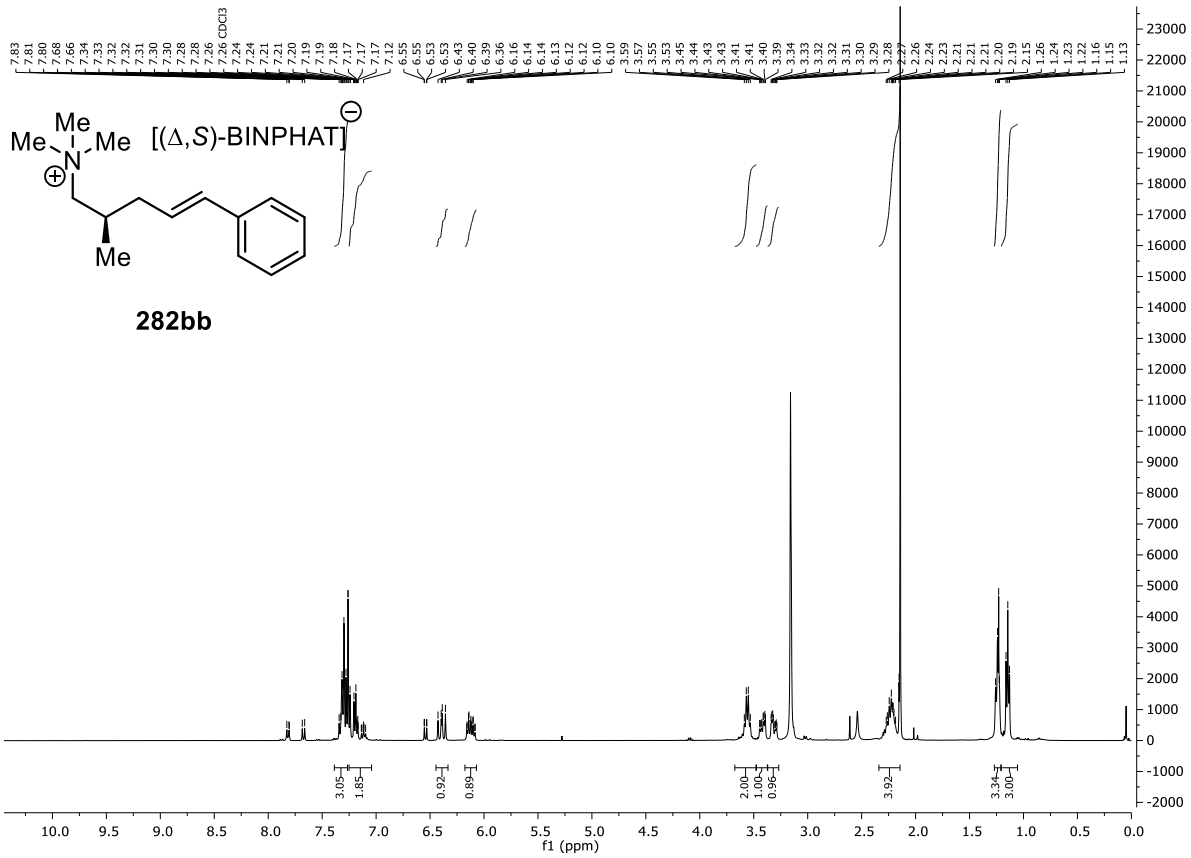

174.28
173.28
62.18
49.00 CD3OD
34.73
27.14
22.30
f1 (ppm)

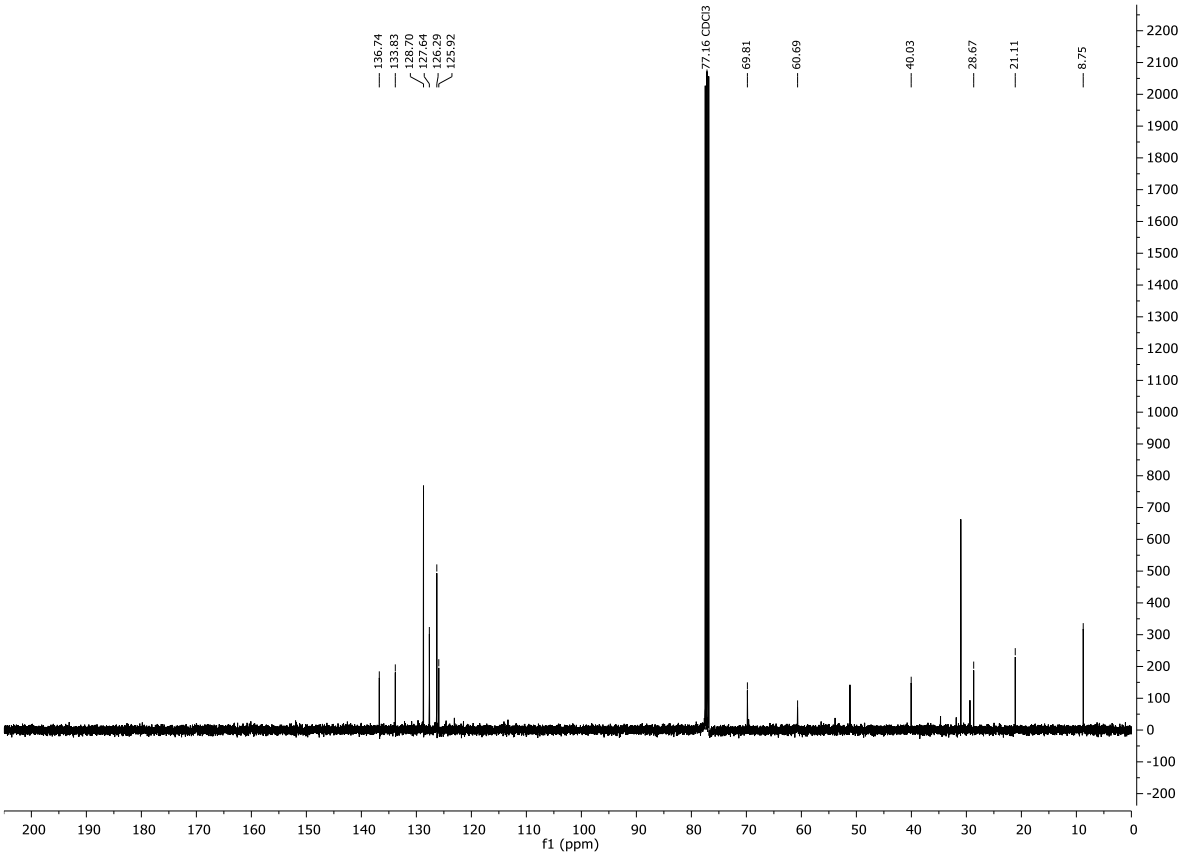

Me
Me
Me
OH
HN
O
O
Me

(±)-304

4.87 CD3OD
4.29
2.02
1.03
1.00
2.96
9.00
f1 (ppm)


174.22
173.26
62.20
34.73
27.14
22.29
f1 (ppm)


[(Δ,S)-BINPHAT]
282bb
f1 (ppm)


f1 (ppm)