New Reactivity and Selectivity in Rhodium-Catalysed Hydroacylation

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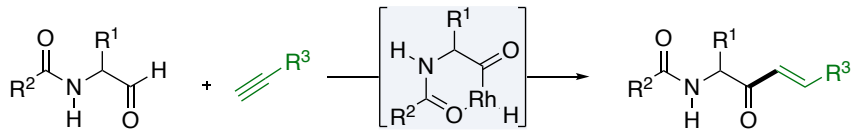
A thesis submitted for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

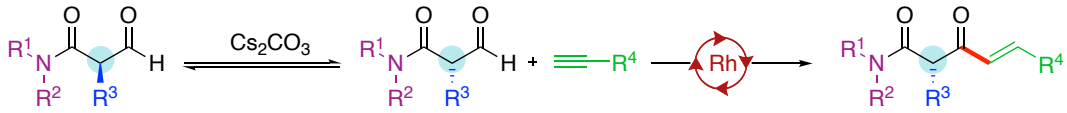
This thesis documents the development of two new rhodium(I)-catalysed methodologies. The first shows the use of 1,4-dicarbonyl systems in hydroacylation for the preparation of synthetically valuable α-*N*-amido ketones. The second method is a dynamic kinetic resolution process for the synthesis of enantiomerically enriched 1,3-dicarbonyl compounds.

Chapter 1 introduces the concept of rhodium-catalysed hydroacylation and presents a literature review covering key developments in the field of intra- and intermolecular hydroacylation, with a focus on chelating aldehydes that can be used to overcome decarbonylation. The advancement of enantioselective hydroacylation reactions has also been briefly summarised in this chapter.

Chapter 2 describes that readily available α-*N*-amidoaldehydes are effective substrates for intermolecular Rh-catalysed alkyne hydroacylation reactions. The catalyst [Rh(dppe)(C_6H_5F)][BAr^F_4], allows a broad range of aldehydes and alkynes to be used as substrates, delivering α-*N*-amido ketone products in high yields and high levels of regiocontrol. The use of α-*N*-amido aldehydes as substrates establishes that 6-membered rhodacyclic intermediates provide suitable chelating stability to enable productive hydroacylation.



Chapter 3 presents the development of enantioselective Rh-catalysed alkyne hydroacylation of β-amido aldehydes *via* dynamic kinetic resolution. The method delivers enantiomerically enriched 1,3-dicarbonyl products in a highly enantioselective fashion with good yields and high regiocontrol, using a combination of cationtic Rh, commercially available (*R*)-DMMGarphos ligand and Cs_2CO_3. To the best our knowledge, this is the first example of dynamic kinetic resolution in intermolecular hydroacylation.



Chapter 4 summarises the research work done and the potential future work.

Chapter 5 documents the experimental data and procedures.

Declaration

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

Ritashree Pal

April 2020

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Abbreviations

Ac	acetate
acac	acetylacetonate
Ar	aryl
atm	atmospheres
B	branched
BAr^F_4	tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate
Bn	benzyl
BOMCl	benzyl chloromethyl ether
Bu	butyl
°C	degrees Celcius
calc.	calculated
cbz	carboxybenzyl
cm^{-1}	wavenumber
COD	1,5-cyclooctadiene
coe	cyclooctene
COSY	correlation spectroscopy
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DIEA	*N*,*N*-diisopropylethylamine
DKR	dynamic kinetic resolution
DMSO	dimethylsulfoxide
EDCI·HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

equiv.	equivalents
er	enantiomeric ratio
ee	enantiomeric excess
ESI	electrospray ionisation
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Hex	hexyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
i	iso
^{i}PrOH	isopropyl alcohol
IR	infrared spectroscopy
J	coupling constant
L	linear
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet
M	molar
Me	methyl

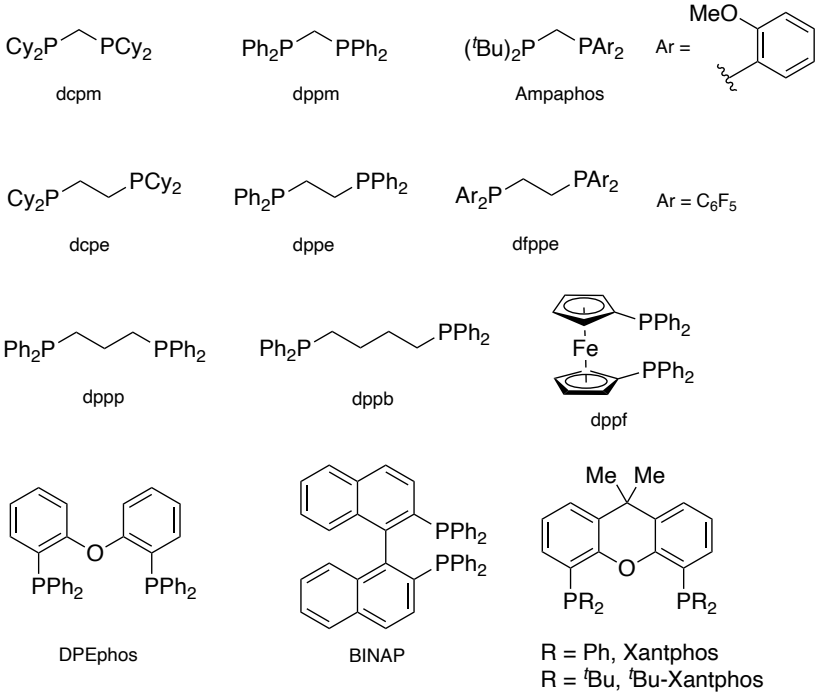
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol%	mole percentage
m.p.	melting point
MTM	methyl thiomethyl
m/z	mass to charge ratio
n	normal
N	normality
nbd	norbornadiene
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
o	ortho
p	para
P	phosphine ligand
Ph	phenyl
PMB	4-methoxy benzyl
ppm	parts per million
Pr	propyl
psi	pounds per square inch
R	generic group/substituent
r. t.	room temperature
sat.	saturated
t	tertiary
Temp.	temperature
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene

tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	tolyl
Ts	tosyl
UV	ultraviolet
X	heteroatom (unless otherwise stated)
$[\alpha]_D$	specific rotation
δ	chemical shift
μ	micro
ν_{max}	frequency
E	entgegen
Z	zusammen

NMR data

app.	apparent
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br s	broad singlet
dd	doublet of doublet
dt	doublet of triplet
ddd	doublet of doublet of doublet

Ligand Structures



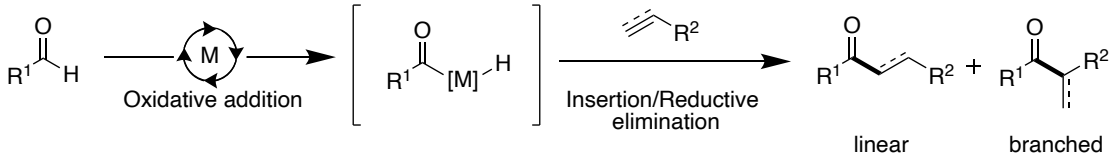
Chapter 1

Rhodium-catalysed hydroacylation

1.1 Introduction

The activation of C–H bonds has been one of the most useful and cost-effective synthetic methods for the formation of C–C bonds. In the past few decades, considerable progress has been made in the direct functionalisation of traditionally unreactive C–H bonds, enabling the direct use of the cheapest and most abundant feedstock for the synthesis of more complex organic molecules.[1–12]

A primary example of C-H activation is the hydroacylation of alkenes and alkynes. It is a process concerning the addition of an aldehyde across the C-C π-bonds of alkenes or alkynes to form ketones or enones respectively (**Scheme 1.1**).[13–16] The broad utility of ketones as versatile chemical intermediates in organic synthesis, alongside their appearance in large number of pharmaceuticals and other biologically active molecules, is testament to the general importance of transition-metal catalysed hydroacylation. Since the seminal report by Sakai and co-workers in 1972,[17]where a stoichiometric amount of Wilkinson's complex was used to cyclise 4-pentenals, the field of hydroacylation of alkenes and alkynes continues to evolve, encompassing reactions catalysed by non-transition metals (NHCs),[18–25] rhodium, ruthenium,[26–30] nickel,[31–34] cobalt[35–38] and iridium[39, 40]. However, rhodium(I)-diphosphines are most widely used, as they provide widespread reactivity. Only the development of rhodium-catalysed hydroacylation will be discussed in this thesis.

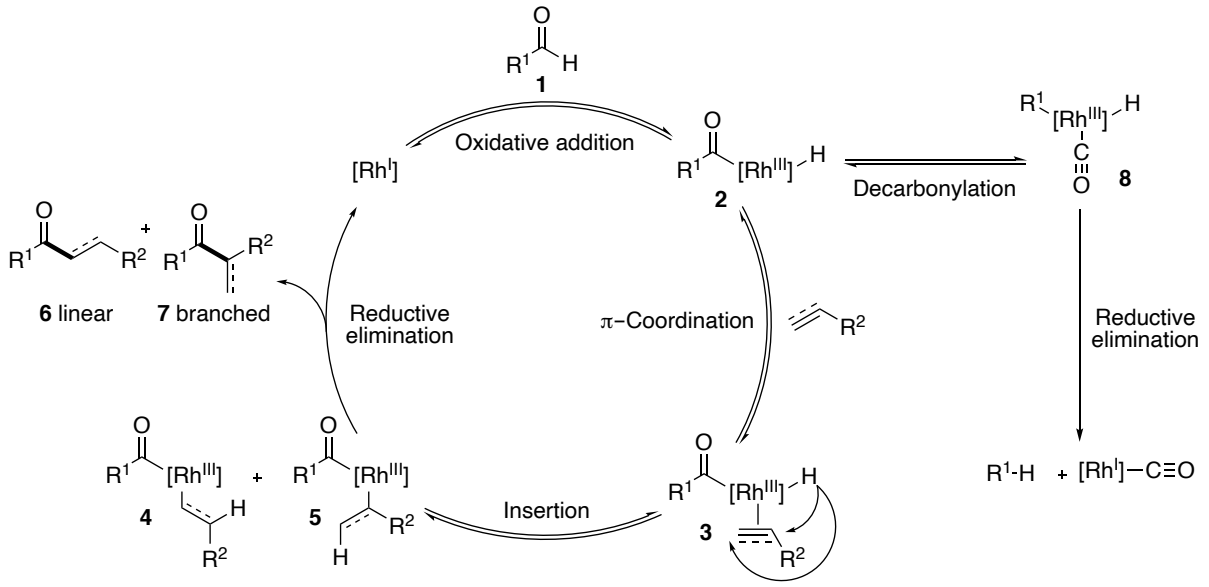


Scheme 1.1: Metal-catalysed hydroacylation reaction.

A rigorous understanding of the hydroacylation process is still relatively underdeveloped. However, a series of mechanistic studies support a commonly accepted catalytic cycle, which is shown in **Scheme 1.2**. The first isolation of a rhodium-acyl hydride complex, by Suggs in 1978,[41] was one of the earliest of these studies. Quinoline carboxaldehyde was reacted with Wilkinson's catalyst followed by treatment with silver(I) tetrafluoroborate to isolate stable rhodium-acyl-hydride complex. Later in 1988, Bosnich and co-workers used 1 mol% of cationic Rh catalyst for 4-pentenal cyclisation where the existence of an acyl-rhodium hydride intermediate was established by deuterium-labelling studies.[42] Since this early establishment of the reaction proceeding *via* an acyl hydride intermediate, an extensive range of experiments have been carried out in order to investigate the mechanism with a variety of rhodium catalysts. Willis and Weller carried out mechanistic studies with both small and wide bite angle diphosphine ligands, including isolation of key intermediate species, deuterium labelling and kinetic isotope effect experiments.[43–47] Computational calculations by Morehead and Sargent suggested reductive elimination as the rate limiting step for an intramolecular reaction.[48]

The catalytic cycle starts with coordination followed by reversible oxidative addition of the aldehyde **1** to the rhodium(I) catalyst**,** forming the acyl-hydride intermediate **2**. Coordination of the unsaturated species then occurs to form **3**, followed by migratory insertion of the hydride. This species can migrate to either the internal or terminal ends of the unsaturated species in coordinated molecule **3**, leading to intermediates, **4** and **5**. This results in regioselectivity issues, which also need to be dealt with, alongside other parameters that are more regularly

considered in synthetic methodology. Then the rate-limiting reductive elimination step gives either linear product **6** or branched product **7**, prior to catalyst regeneration. Labelling studies and spectroscopic analyses, that are inferred through techniques such as product distribution and kinetic studies, support the reversibility of the steps described above.



Scheme 1.2: Proposed mechanism for the hydroacylation of aldehydes using a Rh(I) catalyst.

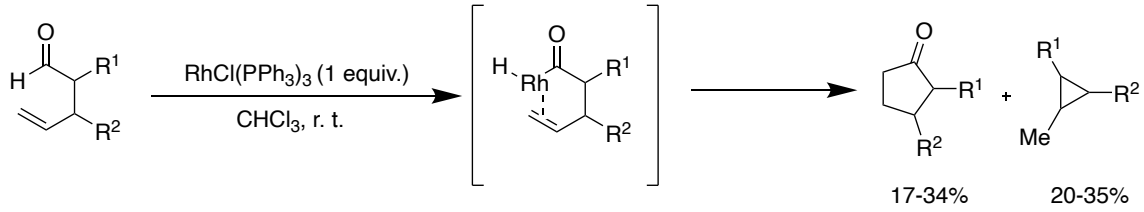
The acyl-hydride intermediate **2** can also undergo undesired decarbonylation in presence of a *cis*-vacant site at the Rh centre. Intermediate **8** is prone to undergo irreversible reductive elimination and form the reduced starting material and an inactive rhodium complex. This destructive side reaction destroys the catalyst, therefore, suppressing decarbonylation remains a key challenge in the field of rhodium-catalysed hydroacylation.

1.2 Rhodium-catalysed intramolecular hydroacylation

Initial reports on hydroacylation are mainly centred around intramolecular systems to generate cyclopentanone products. The olefin bond coordination to Rh forms stable metallacycle and

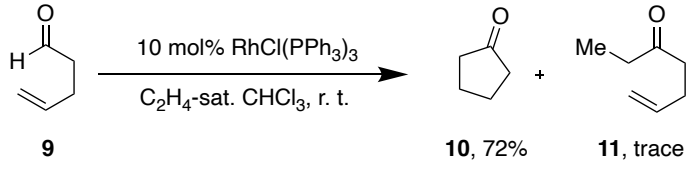
the proximity of the alkene to the aldehyde lowers the kinetic barrier of the reaction which promotes a facile transformation.

In 1972, Sakai first reported an example of intramolecular hydroacylation using a stoichiometric amount of Wilkinson's complex (**Scheme 1.3**).[17] At room temperature, substituted 4-pentenals underwent intramolecular hydroacylation to give cyclopentanones; however, a similar amount of a cyclopropane, originating from decarbonylation was also formed.



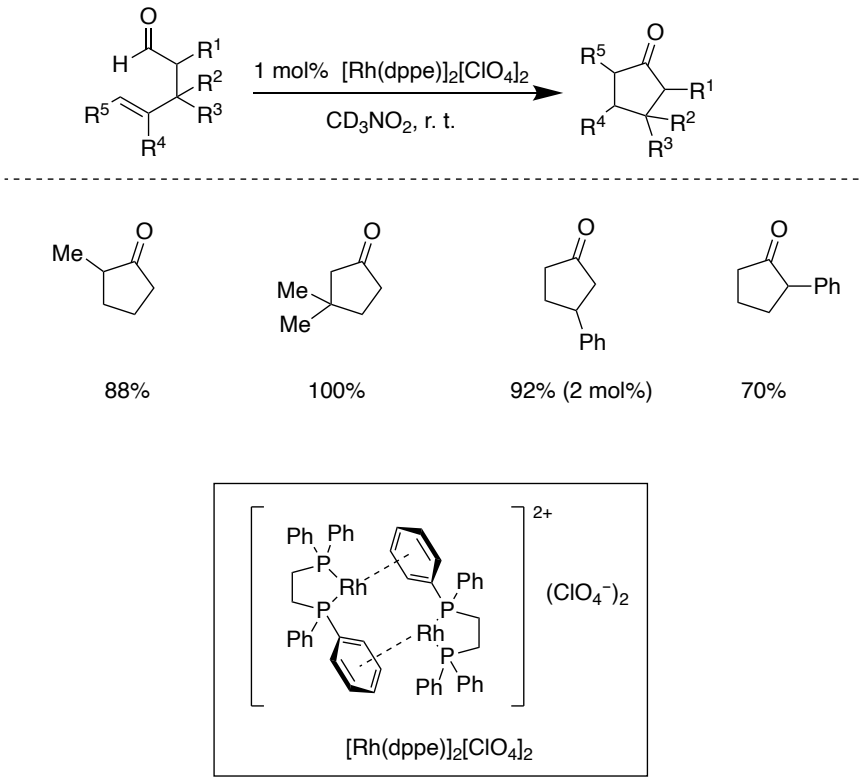
Scheme 1.3: Sakai's first example of intramolecular hydroacylation using stoichiometric Rh.

In 1976, Lochow and Miller reported the same reaction using 10 mol% of Wilkinson's complex in an ethene saturated solution of chloroform (**Scheme 1.4**).[49] A high yield (72%) of compound **10** was achieved from intramolecular hydroacylation of **9**, which indicates that ethene reduced the rate of reductive decarbonylation by occupying the vacant site of Rh intermediate that is required for decarbonylation. A trace amount of the intermolecular hydroacylation product **11** was obtained due to the presence of ethylene.



Scheme 1.4: Lochow and Miller's first example of intramolecular hydroacylation using catalytic amount of Wilkinson's complex.

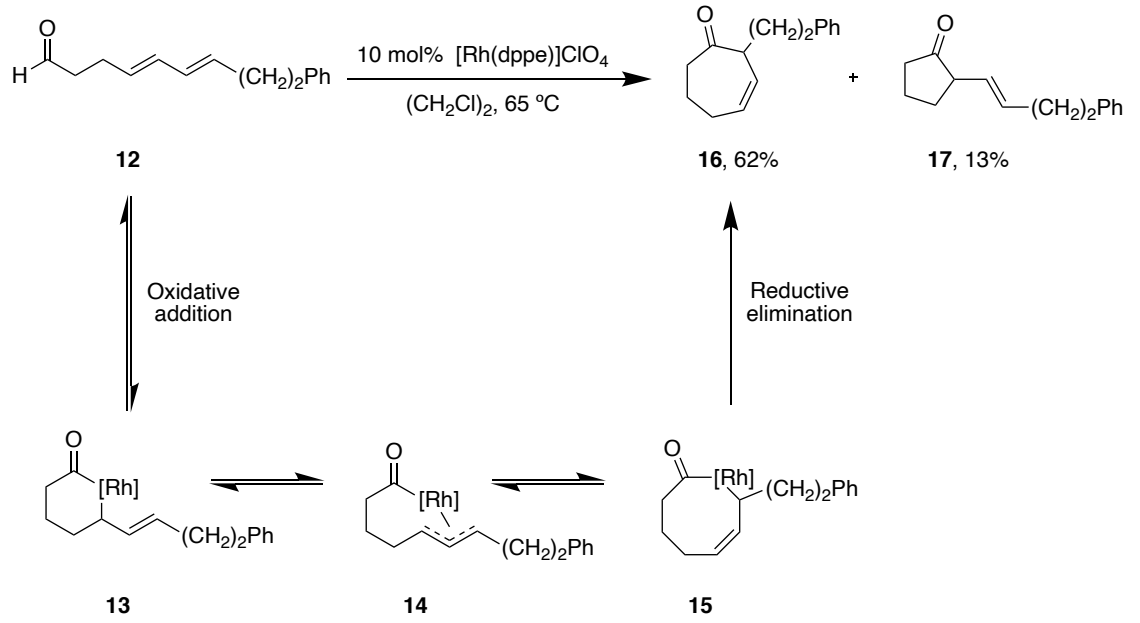
Larock continued the optimisation of this reaction in order to synthesise a broader range of cyclopentanones, however, high catalyst loading was still required and applications to larger ring sized proved unsuccessful.[50] A major breakthrough occurred when Bosnich reported the use of highly electrophilic rhodium complexes in the field of hydroacylation in 1988 (**Scheme 1.5**).[42] An efficient intramolecular hydroacylation method was achieved when $[Rh(dppe)_2][ClO_4]_2$ was used as a catalyst. Various substituted cyclopentanones were synthesised in good yields with only 1 mol% of the catalyst. It was proposed that the cationic Rh-complex was vital for high catalytic activity as it promoted the formation of coordinatively unsaturated, and therefore reactive, catalytic intermediates.

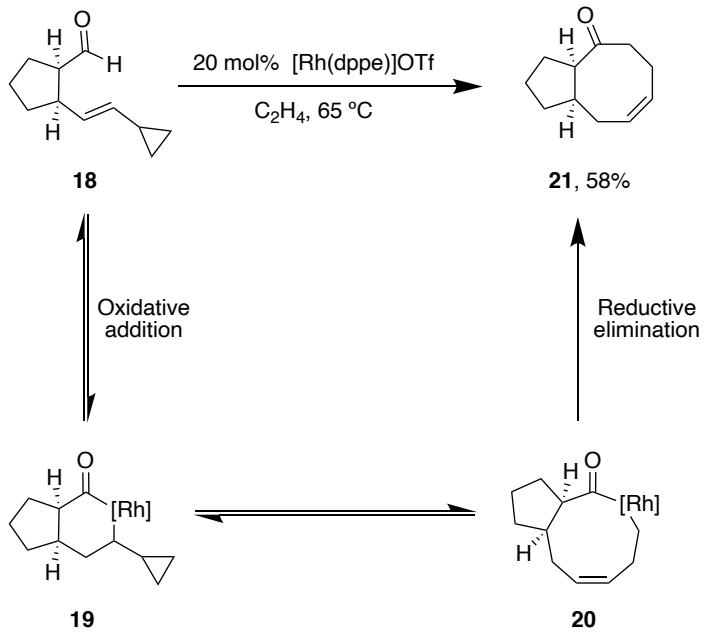


Scheme 1.5: Bosnich's cationic Rh catalyst in hydroacylation.

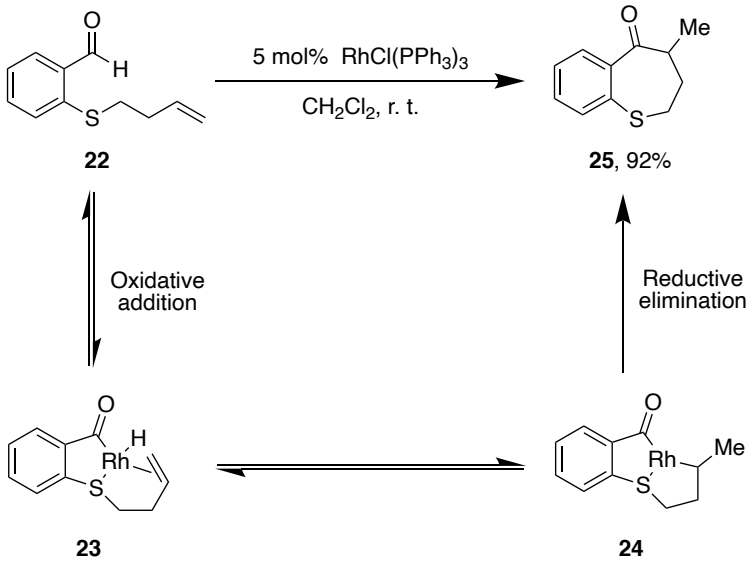
Intramolecular hydroacylation to form five-membered cyclic ketones are generally favoured due to kinetic favourability, however, synthesis of larger rings is relatively challenging and often requires incorporation of additional functionality, such as an adjacent alkenyl group

(**Scheme 1.6**),[51, 52] cyclopropane group (**Scheme 1.6**)[53] or heteroatomic chelating group (**Scheme 1.7**)[54] on the substrates to prevent decarbonylation.





Scheme 1.6: The Mori group's route to cycloheptanones and the Shair group's route to cyclooctanones.

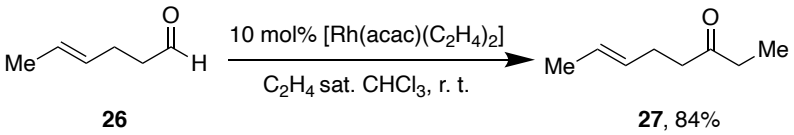


Scheme 1.7: The Bendorf group's use of sulfur chelation to promote intramolecular hydroacylation.

1.3 Rhodium-catalysed intermolecular hydroacylation and chelation-controlled strategies

Intermolecular reactions are more attractive as versatile and readily available substrates can be employed. However, these reactions are more challenging as the high entropic cost that bring the reactants together accompanies an inevitable loss of the reaction rate. The higher entropic cost additionally means that the stability of the crucial Rh-acyl hydride intermediate is less readily aided by alkyne/alkene coordination. Therefore, a major drawback of intermolecular hydroacylation reaction is that destructive decarbonylation is more readily observed. Furthermore, the stereo- and regioselectivity is more challenging to control because of the lack of cyclic transition states. Although the decarbonylation pathway can be suppressed by altering the catalyst electronics, the use of a chelating group on either of the coupling partners has emerged as a more effective strategy to overcome the reactivity issues. Chelating motifs featuring alkenes, phosphines, amines, hydroxyl groups, and sulfides are most prevalent, and will be discussed in this chapter.

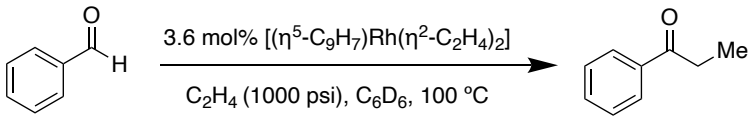
The first example of intermolecular hydroacylation was reported by Miller and coworkers in 1980 (**Scheme 1.8**).[55] Enals were employed as the aldehyde components and it was postulated that the alkene group coordinates to the Rh and acts as a chelating group which prevents the decarbonylation. Treatment of 4-hexenal (**26**) with [Rh(acac)(C_2H_4)$_2$] in C_2H_4-saturated $CHCl_3$ at 24–26 ºC produces hydroacylation adduct **27** in 84% yield after 28 h.



26 **27**, 84%

Scheme 1.8: The Miller group's first example of intermolecular hydroacylation.

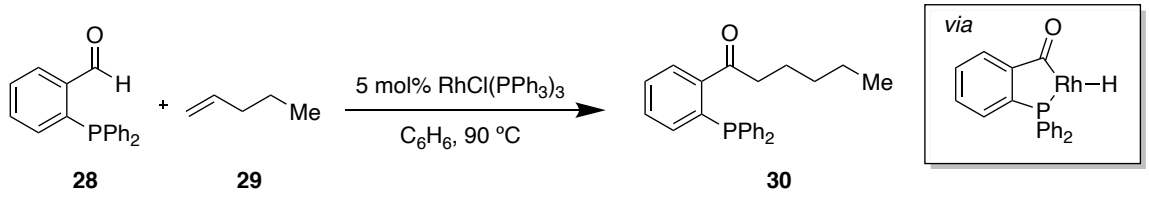
Subsequently, in 1988, Millstein and Marder published the intermolecular hydroacylation of ethylene with aryl aldehydes.[56] The reactions were performed under extremely high pressures of ethylene (1000 psi at 25 °C) by the indenyl rhodium complex [(η^5-C_9H_7)Rh(η^2-C_2H_4)$_2$] to generate ethyl ketones. The high pressure of ethylene was crucial for the reaction to proceed suggesting that a highly saturated rhodium complex, is a key property that is required for reaction progression in this case (an example is shown in **Scheme 1.9**).



Scheme 1.9: The Millstein and Marder group's intermolecular hydroacylation of ethylene with benzaldehyde.

In 1995, Jun and Lee demonstrated that 2-(diphenylphosphino)benzaldehyde (**28**) was an effective substrate in hydroacylation of unactivated alkenes (**Scheme 1.10**).[57] The putative coordination of the phosphine group, to the Rh centre, helps to overcome decarbonylation. A

5 mol% loading of Wilkinson's complex was employed in benzene at 90 °C. Alkyl-substituted alkenes were found to be more reactive compared to aryl versions.

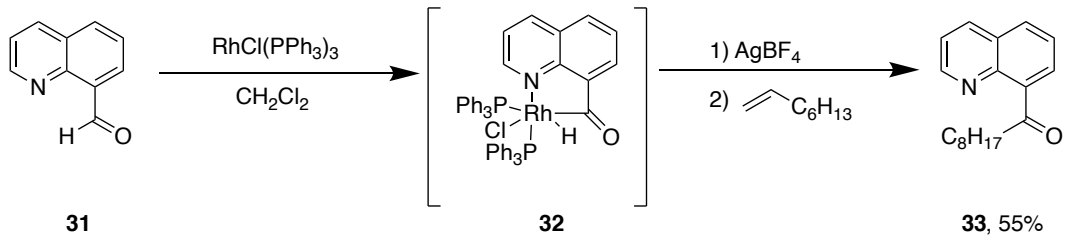


28 29 30

Scheme 1.10: The Jun group's intermolecular hydroacylation using phosphine chelating group.

1.3.1 Nitrogen-based chelating groups

In 1978, Suggs developed a first example of *N*-controlled hydroacylation which contributed enormously to the progress of this chemistry (**Scheme 1.11**).[41, 58] A five-membered rhodium-acyl-hydride complex (**32**) was isolated from the oxidative addition of quinoline-8-carboxaldehyde (**31**) with Wilkinson's complex. Treatment of the complex (**32**) with silver(I) tetrafluoroborate and 1-octene generated the hydroacylation adduct (**33**) in 55% yield. In spite of promoting successful hydroacylation, the limitation of this process was to have a large quinoline group which is difficult to further transform or remove. Also, efforts to convert this into a catalytic process were unsuccessful.

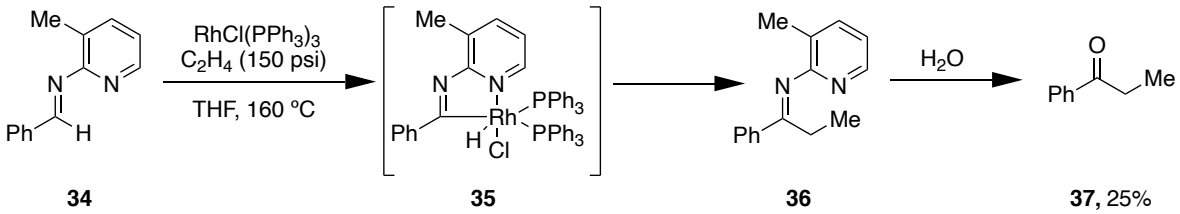


31 32 **33**, 55%

Scheme 1.11: Use of quinolines as a chelating group by Suggs.

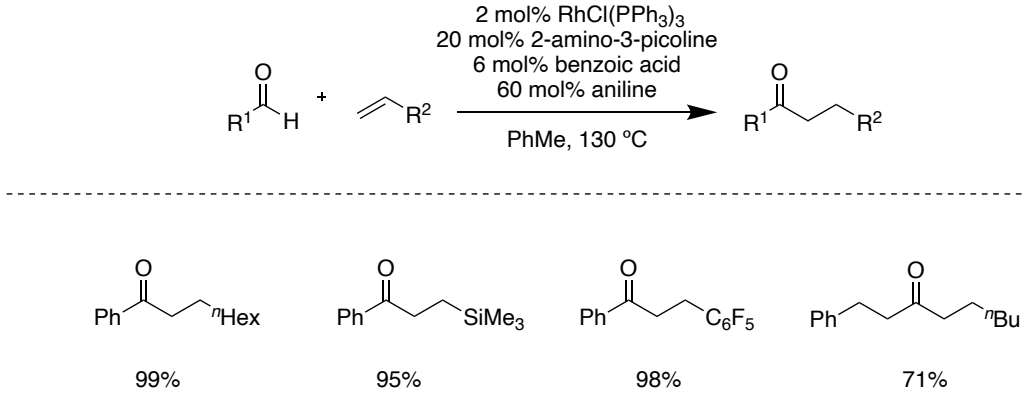
As a solution to this problem, Suggs explored a new strategy for the activation of aldehyde C-H bonds *via* formation of a 3-methyl-2-aminopyridyl aldimine (**34**) (**Scheme 1.12**).[59] This aldimine undergoes oxidative addition with Wilkinson's complex (5 mol%) where the pyridine

unit coordinates to Rh centre and stabilises the iminoacyl complex (**35**) formed, which reacts with an ethylene molecule to produce **36** and after hydrolysis provides the ketone **37** in 25% yield.



Scheme 1.12: Suggs and co-workers' attempts at using picolyl imines in hydroacylation.

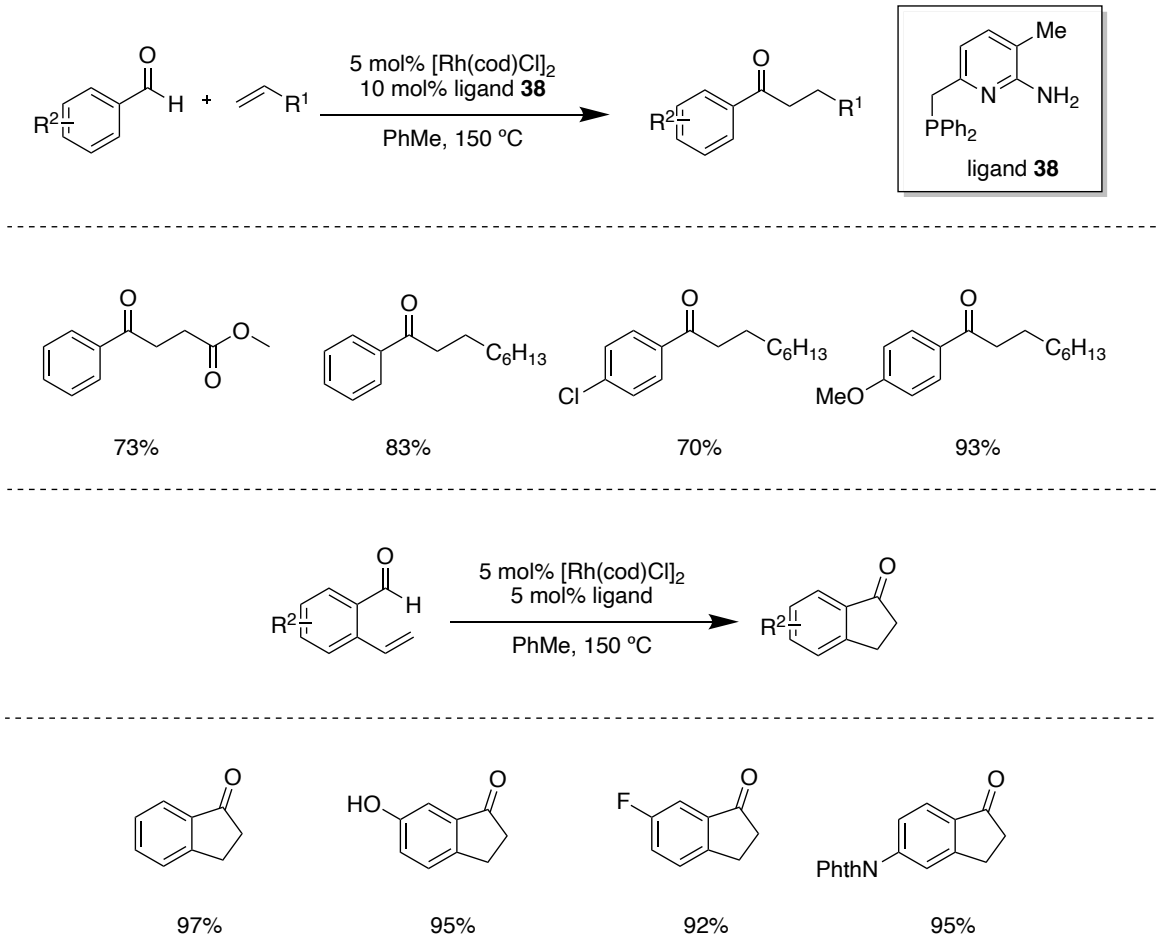
Inspired by the pioneering work by Suggs, Jun and co-workers developed a process to generate imines *in situ* from condensation of aldehydes and 2-amino-3-picoline using sub-stoichiometric benzoic acid (6 mol%) (**Scheme 1.13**).[60–66] A wide range of simple aldehydes and alkenes were combined using 2 mol% of Wilkinson's catalyst. 60 mol% of aniline was also used as a co-catalyst which was found to enhance the reactivity.



Scheme 1.13: The Jun group' *N*-chelation controlled traceless hydroacylation.

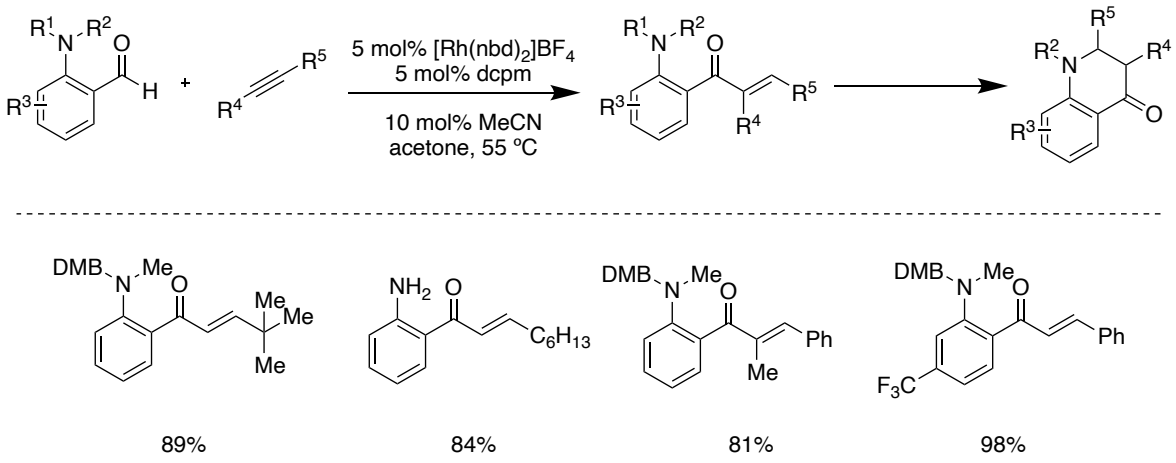
Following this, in 2011, Breit and co-workers developed a new bifunctional ligand **38** by tethering a phosphine to a pyridine ring of an amine (**Scheme 1.14**).[67] The amine condenses with the aldehyde, leaving the phosphine group and pyridine to both partake in chelation to

rhodium. This catalytic system allows both intra- and intermolecular alkene hydroacylation in an efficient manner.



Scheme 1.14: The Breit group's inter- and intramolecular hydroacylation using a bifunctional ligand.

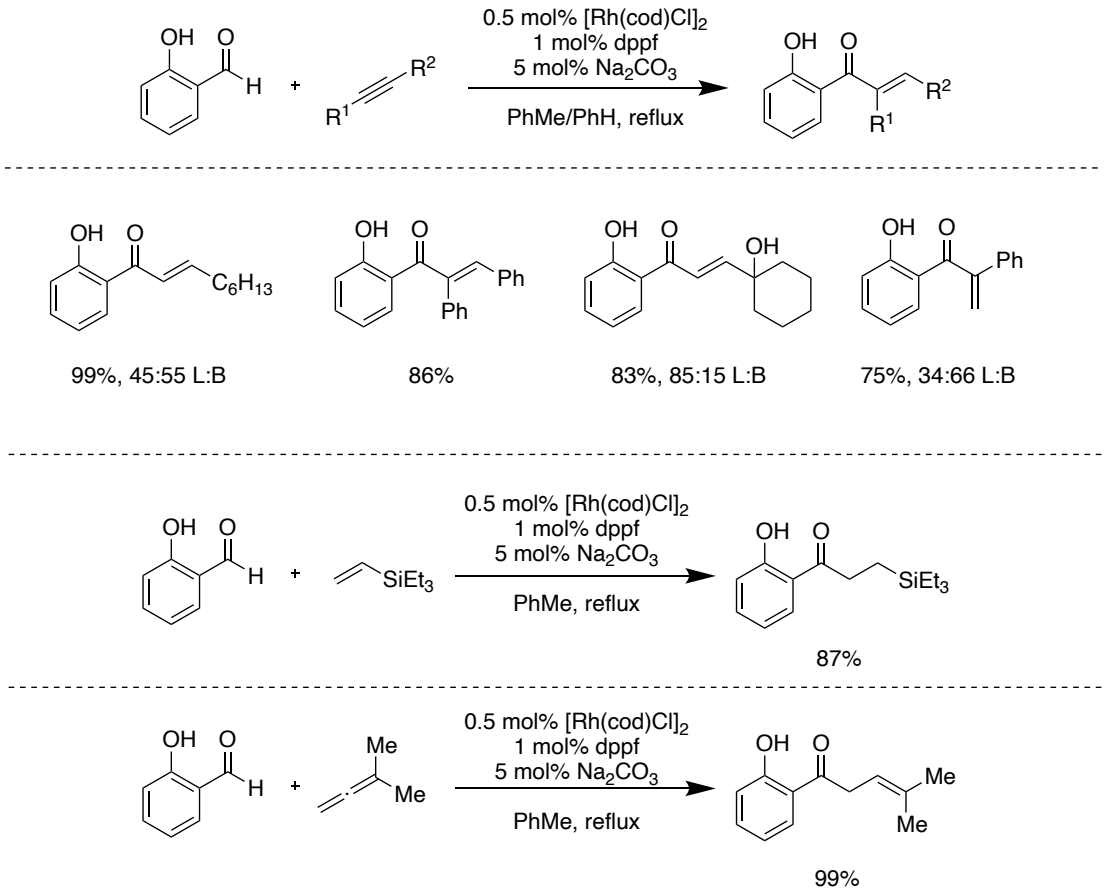
More recently, Willis and co-workers showed 2-aminobenzaldehyde derivatives as effective substrates in intermolecular alkyne hydroacylation reactions (**Scheme 1.15**).[68] Using the small bite-angle dcpm ligand, a wide range of functional groups on both terminal and internal unactivated alkynes could be tolerated in excellent to good yields with a high level of regiocontrol. Addition of 10 mol% of acetonitrile was necessary to achieve high reactivity. To illustrate the synthetic utility of the products, dihydro-4-quinolones were synthesised in a one-step cyclisation from the hydroacylation product.



Scheme 1.15: The Willis group's intermolecular hydroacylation with 2-aminobenzaldehyde derivatives.

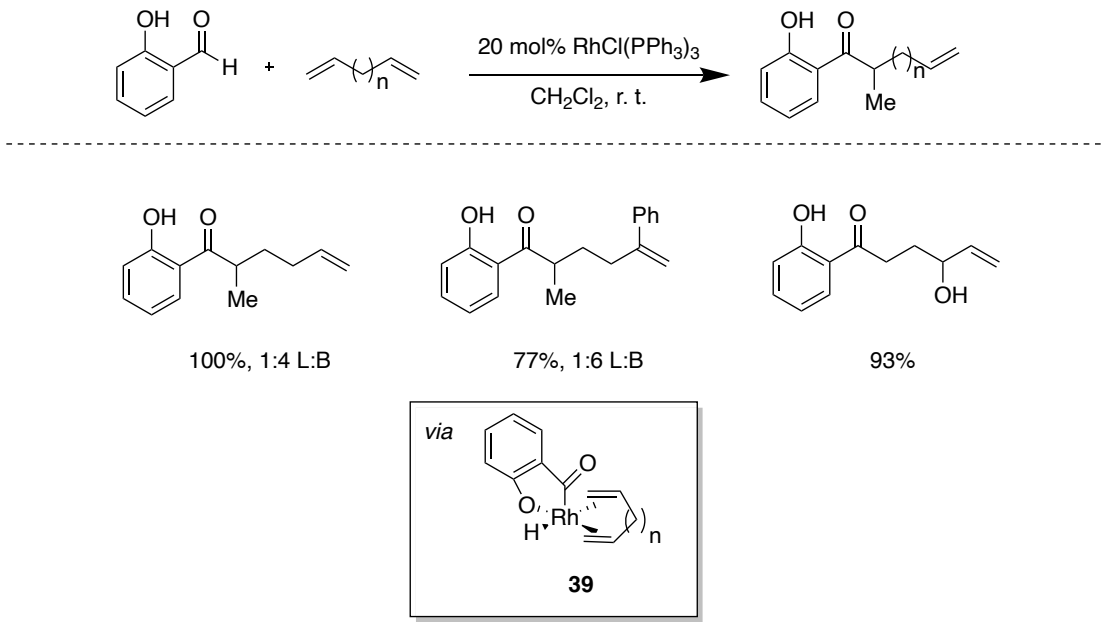
1.3.2 Oxygen-based chelating groups

Use of oxygen-based chelating substrates in hydroacylation was first developed by the Miura group in 1997 (**Scheme 1.16**).[69–70] Simple salicylaldehyde derivatives as *O*-chelating substrates are synthetically attractive, as their widespread commercial availability relinquishes the need for tether installation onto respective precursors. Using a low catalyst loading (1 mol% $[Rh(cod)Cl]_2$), dppf ligand and Na_2CO_3, alkyne hydroacylations were performed to afford enones in good to excellent yields. A sub-stoichiometric amount of base was crucial to provide sufficient deprotonation of the phenol group on salicylaldehyde, enabling the formation of a Rh-phenolate complex. Poor reactivity was observed when alkenes were subjected to hydroacylation conditions, with an exception of vinyltrimethylsilane. The other limitation of this method was a compromised regioselectivity.



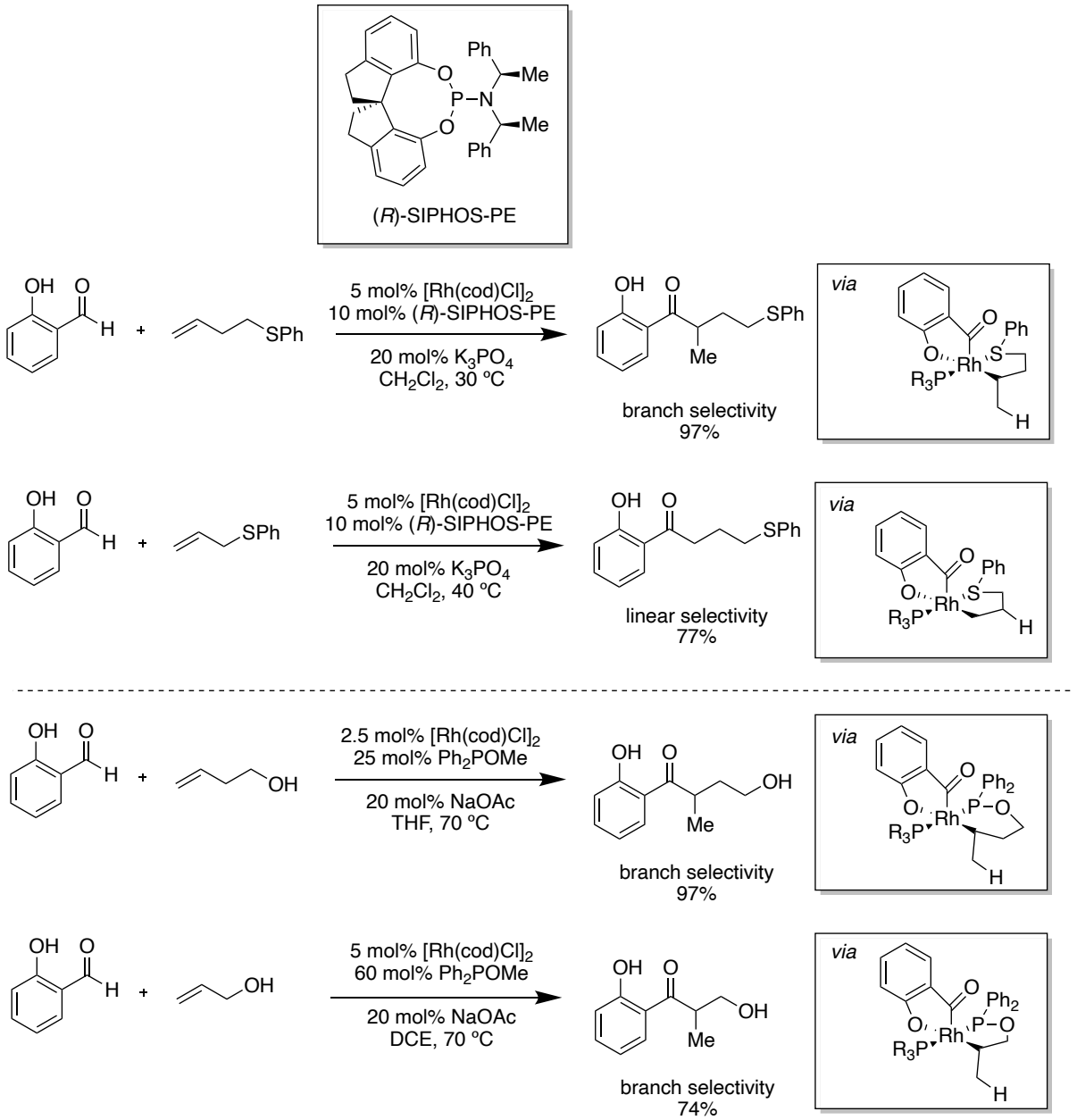
Scheme 1.16: The Miura group's oxygen-based chelating substrates in hydroacylation.

Since this initial report, remarkable progress has been made with *O*-tethered aldehydes. In 2004, Suemune and co-workers published the hydroacylation of dienes with salicylic aldehyde (**Scheme 1.17**).[71–72] High yields of regioisomeric product mixtures were isolated by using 20 mol% of Wilkinson's catalyst, where moderate branched regioselectivity could be observed when substituted dienes were used. A variety of 1,4- and 1,5-dienes reacted successfully, however, low yields were observed for 1,6-dienes. Deuterium labelling studies revealed the presence of an intermediate complex **39**, where both the diene and salicylaldehyde are datively bound to the Rh-complex.



Scheme 1.17: The Suemune group's reported hydroacylation of salicylaldehydes with dienes.

The double-chelation strategy was continued by Dong and co-workers (**Scheme 1.18**).[73–75] They replaced one of the alkene bonds with a strongly coordinating sulfide group in an attempt to increase the regioselectivity of the alkene hydroacylation reaction. Using a $[Rh(cod)Cl]_2$, chiral monodentate phosphine SIPHOS-PE ligand and K_3PO_4 catalyst system, the branched ketone products were formed in the reactions of salicylaldehyde and homoallylic sulfides. Interestingly, high linear selectivity was observed when allylic sulfides were employed. The difference in regiochemistry was rationalised by the preferred formation of 5-membered rhodacycles upon migratory insertion, over 4- and 6-membered intermediates. Subsequently, they extended this concept for the hydroacylation of allylic and homoallylic alcohols and reported highly branch selective method using Ph_2POMe which acts as ligand as well as reversibly bound directing group.

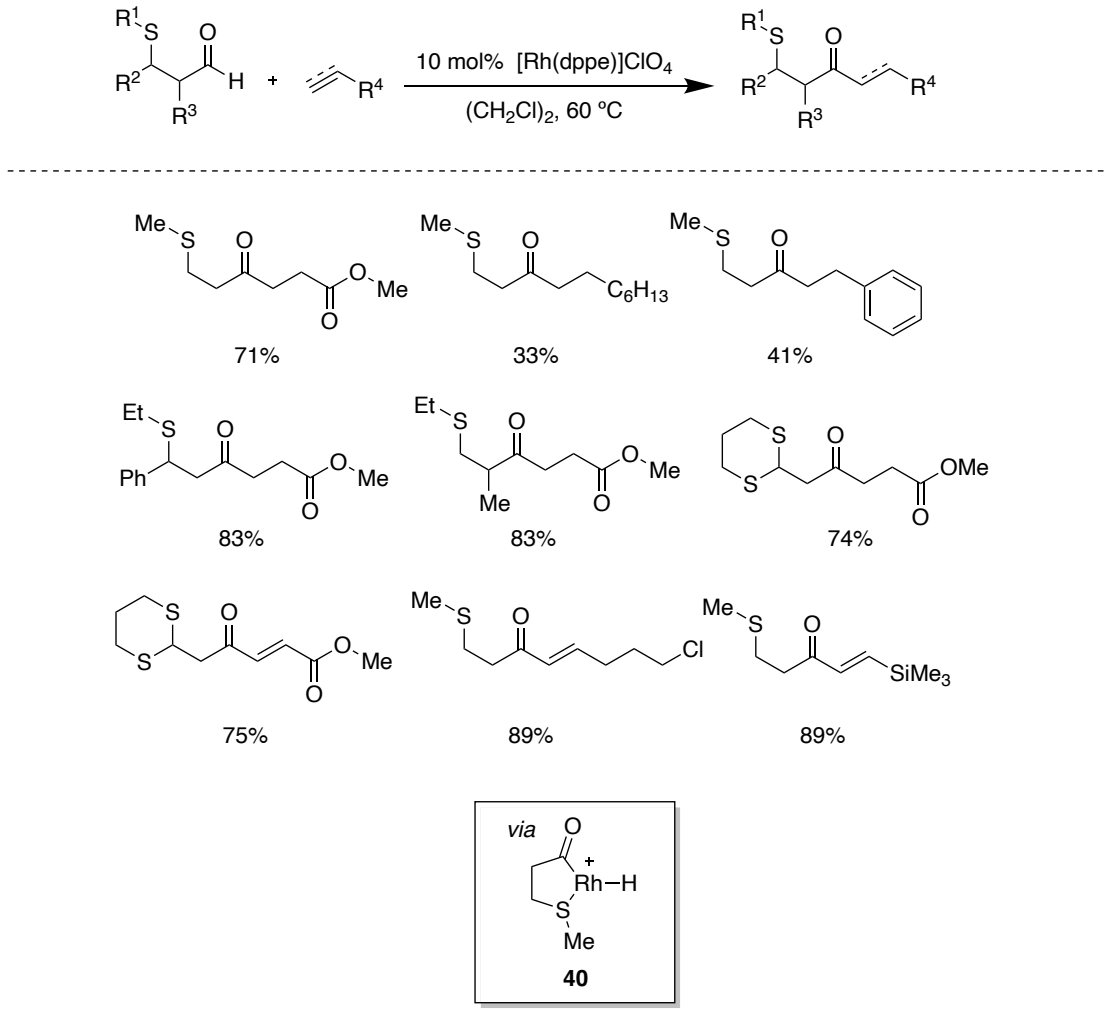


Scheme 1.18: The Dong group's *S*- and *O*-chelating alkenes in hydroacylation.

1.3.3 Sulfur-based chelating groups

Willis pioneered sulfur-based chelating groups in intermolecular hydroacylation using cationic rhodium complexes and a range of diphosphine ligands. In 2004, Willis and co-workers reported hydroacylation of alkenes and alkynes with *S*-substituted aldehydes (**Scheme 1.19**).[76] The position of the sulfur atom β to the aldehyde was found to be crucial in generating the

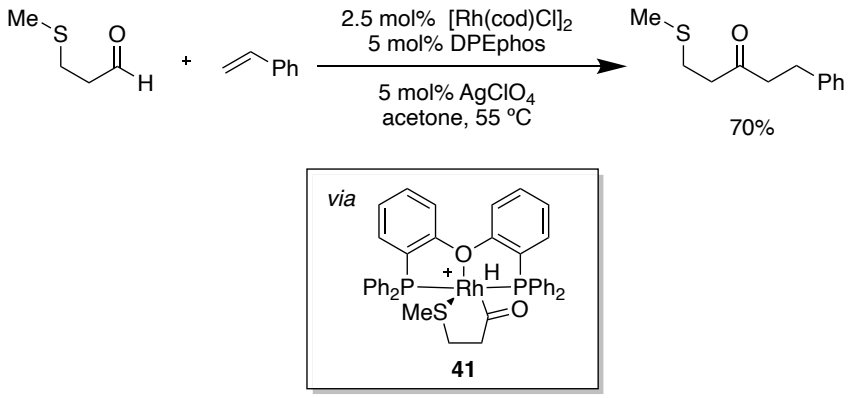
stable Rh-S bound five-membered rhodacycle **40**, which is required to overcome decarbonylation. A wide range of functionalised ketones and enones were obtained in excellent to good yields, however, unactivated alkenes had reduced reactivity.



Scheme 1.19: The Willis group's sulfur-tethered hydroacylation of alkenes and alkynes.

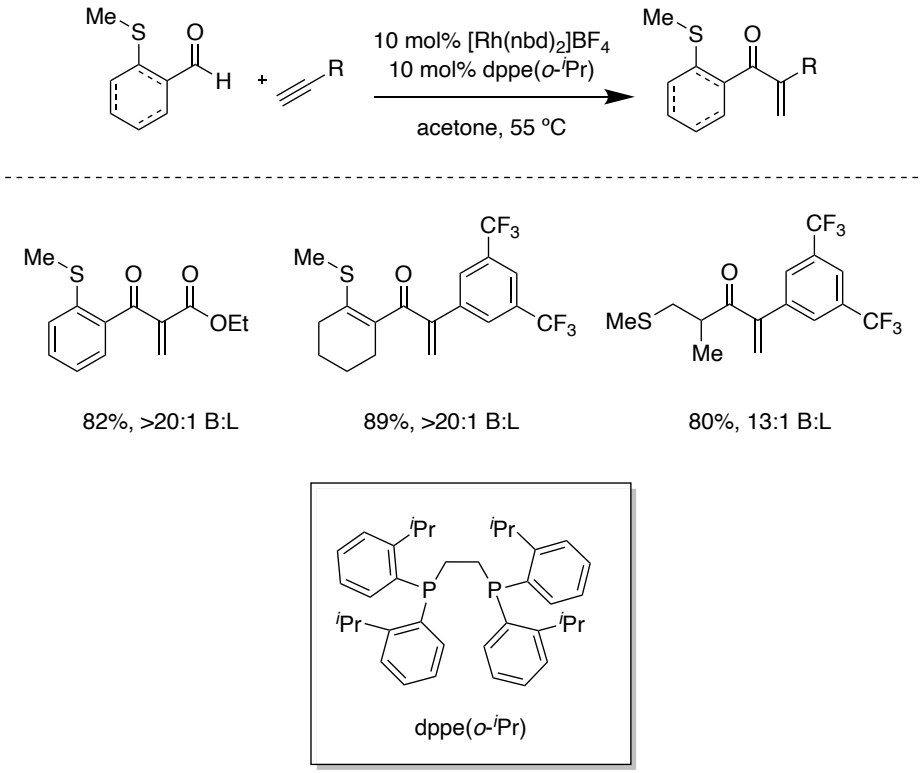
Following this report, the Willis and Weller groups turned towards the development of more active catalyst systems that increase reactivity towards unactivated alkenes and consolidate general regioselectivity. A 2nd generation catalyst system, which utilised the hemilabile DPEPhos ligand, showed improved yields when reacting β-sulfur aldehydes towards unactivated alkenes, whilst exhibiting additional benefits of decreased catalyst loading and reaction time (**Scheme 1.20 and 1.24**).[44] Mechanistic studies revealed an O-Rh interaction

between oxygen atom, in the POP backbone and Rh centre. This finding was confirmed by an X-ray crystal structure, obtained from an isolated acyl hydride complex (**41**).[43] The authors attributed the enhanced reactivity of the catalyst to this additional O-Rh reversible coordination mode, which is believed to enhance rhodium-acyl hydride stability and minimise decarbonylation.



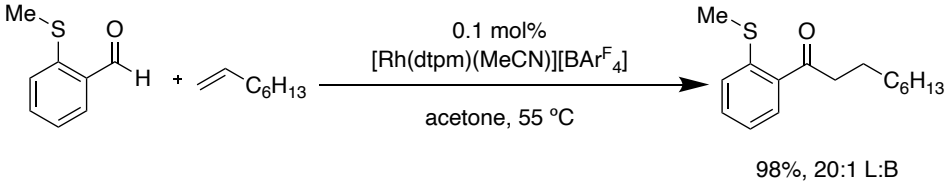
Scheme 1.20: The Willis group's alkene hydroacylation with hemilabile DPEPhos ligand.

A branch selective hydroacylation of terminal alkynes was reported in 2011, using dppe ligand with bulky phosphine substituents (**Scheme 1.21**).[77] Despite the necessity for a higher catalyst loading in this system (10 mol%), excellent reactivity and regioselectivity was observed with alkyl, vinyl and aryl sulfides, using mild reaction conditions.



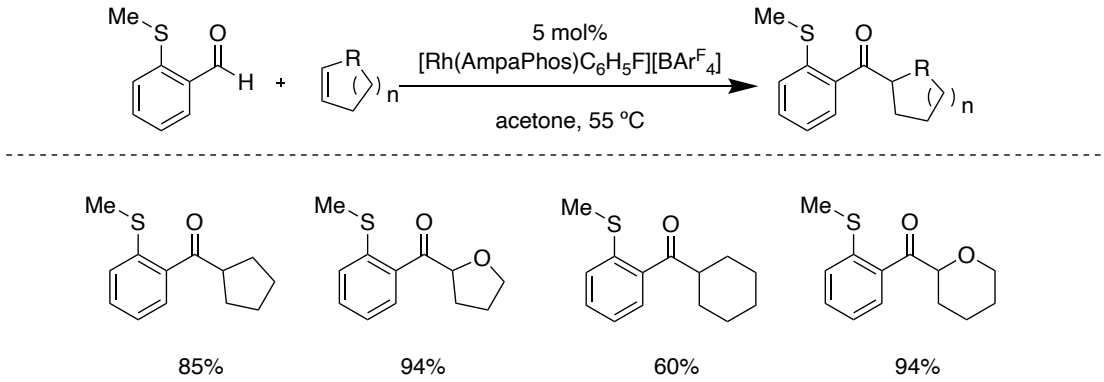
Scheme 1.21: The Willis group's branch selective hydroacylation with *S*-tethered aldehydes.

In 2012, Willis and Weller reported a 3rd generation catalyst system with another significant improvement in catalytic activity with small bite-angle ligand (**Scheme 1.22 and 1.24**).[46] A catalyst utilising small bite-angle dtpm ligand (^{t}Bu$_2$PCH$_2$P^{t}Bu$_2$), was found to promote high level of reactivity and linear selectivity. Using a catalyst loading as low as 0.1 mol%, high yields in alkene hydroacylation was achieved. It was postulated that small bite-angle ligands accelerate the rate limiting reductive elimination step of the hydroacylation reactions. This prevented the *in situ* formation of decarbonylation products, from catalytic intermediates.

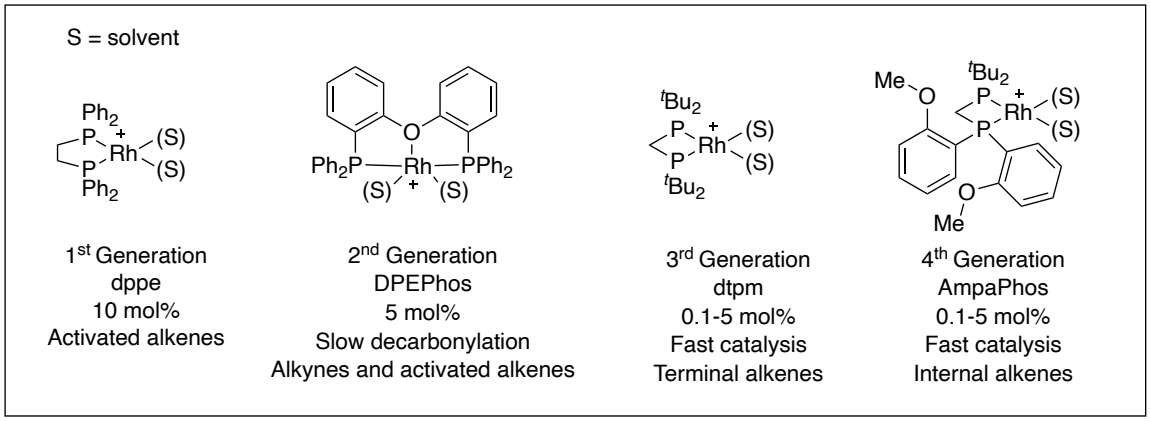


Scheme 1.22: The Willis group's hydroacylation of unactivated alkenes with very low catalyst loading.

Modification of electronics and steric properties of small bite-angle ligands led to development of a 4th generation catalyst incorporating bulky *tert*-butyl and *ortho*-anisole substituents on each phosphine; this novel ligand has been named AmpaPhos (**Scheme 1.23 and 1.24**).[78] This system allowed hydroacylation of internal alkene substrates with β-*S*-substituted aldehydes. The high reactivity of unactivated internal alkenes in presence of catalysts incorporating the AmpaPhos ligand was rationalised by bulky phosphine substituents promoting the challenging hydride insertion step in the catalytic cycle.



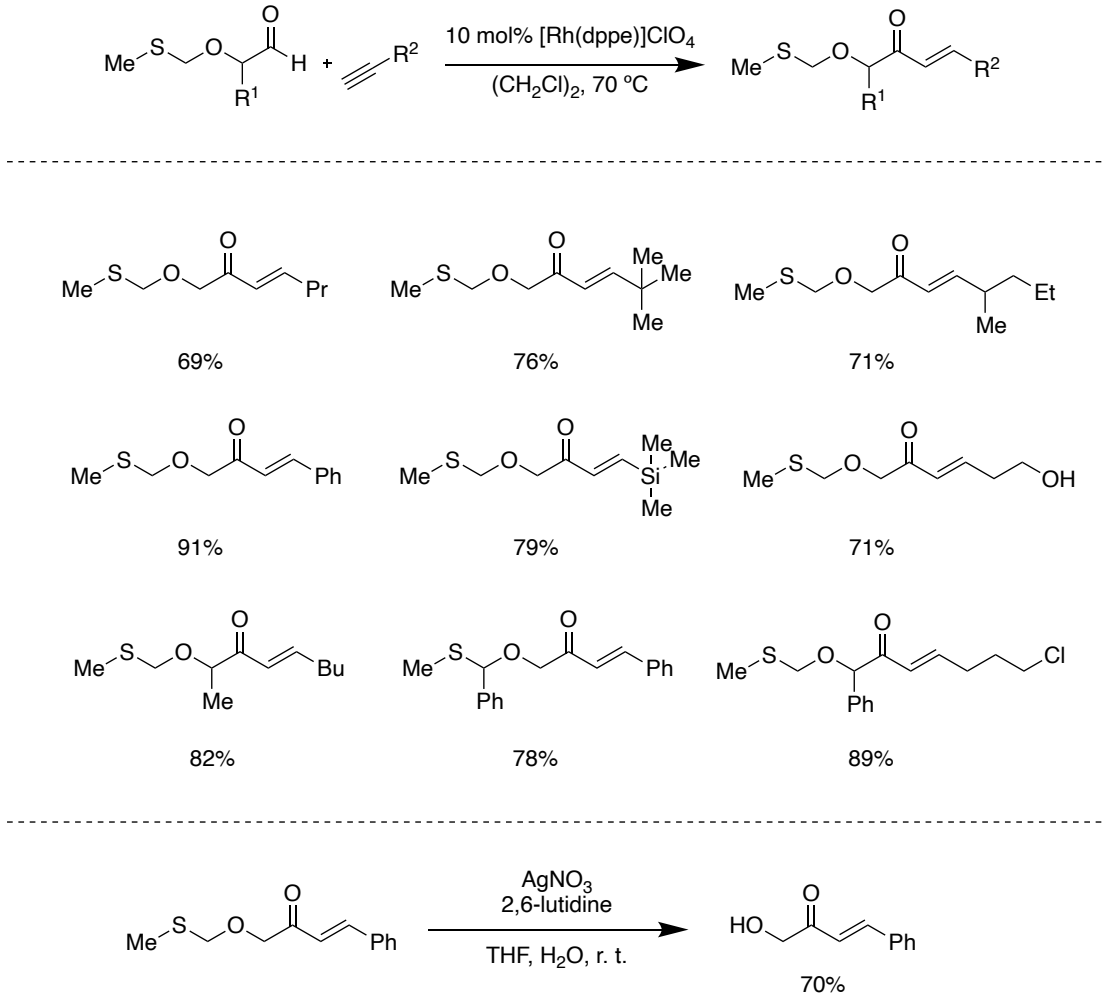
Scheme 1.23: The Willis group's hydroacylation of internal alkenes.



Scheme 1.24: The Willis group's catalyst design for hydroacylation with β-*S*-substituted aldehydes.

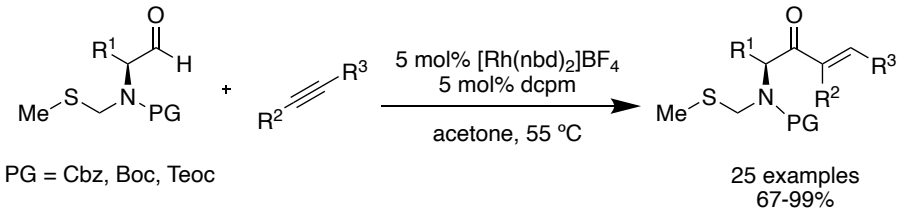
Notable advancements have been made on the use of *S*-substituted aldehydes, however the products all contain a sulfur chelating group and this is not often desirable. As a solution to

this problem, an MTM directing group was introduced in hydroacylation and facile removal of the tether was shown (**Scheme 1.25**).[79]

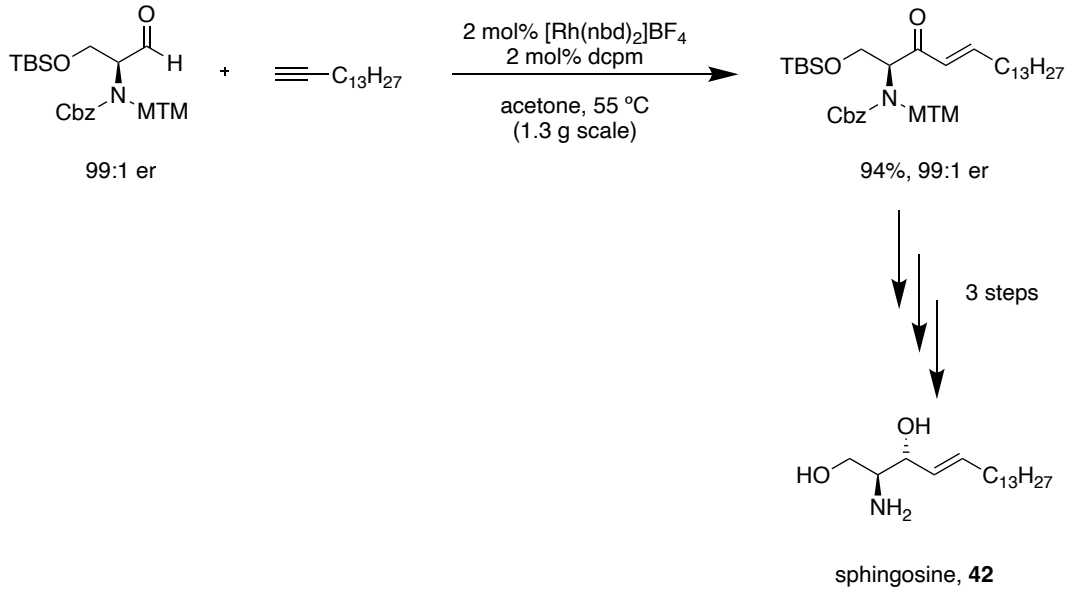


Scheme 1.25: The Willis group's MTM-controlled hydroacylation and MTM deprotection.

Enantiomerically enriched MTM-protected α-amino aldehydes were shown to be excellent substrates in alkyne hydroacylation (**Scheme 1.26**).[80] Using the small bite-angle dcpm ligand, high yields were achieved with retention of enantiopurity. To demonstrate the utility of MTM-directed hydroacylation of α-amino acid derived aldehydes, this method was used to synthesise natural product sphingosine **42**, in an efficient and economic manner (**Scheme 1.27**).



Scheme 1.26: The Willis group's hydroacylation with MTM-protected α-amino aldehydes.



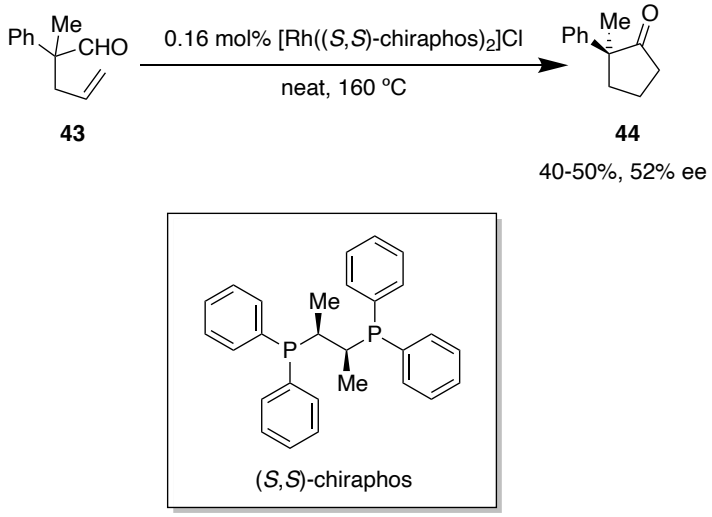
Scheme 1.27: The Willis group's application of MTM-protected α-amino aldehyde hydroacylation.

1.4 Enantioselective hydroacylation reactions

1.4.1 Enantioselective intramolecular hydroacylation reactions

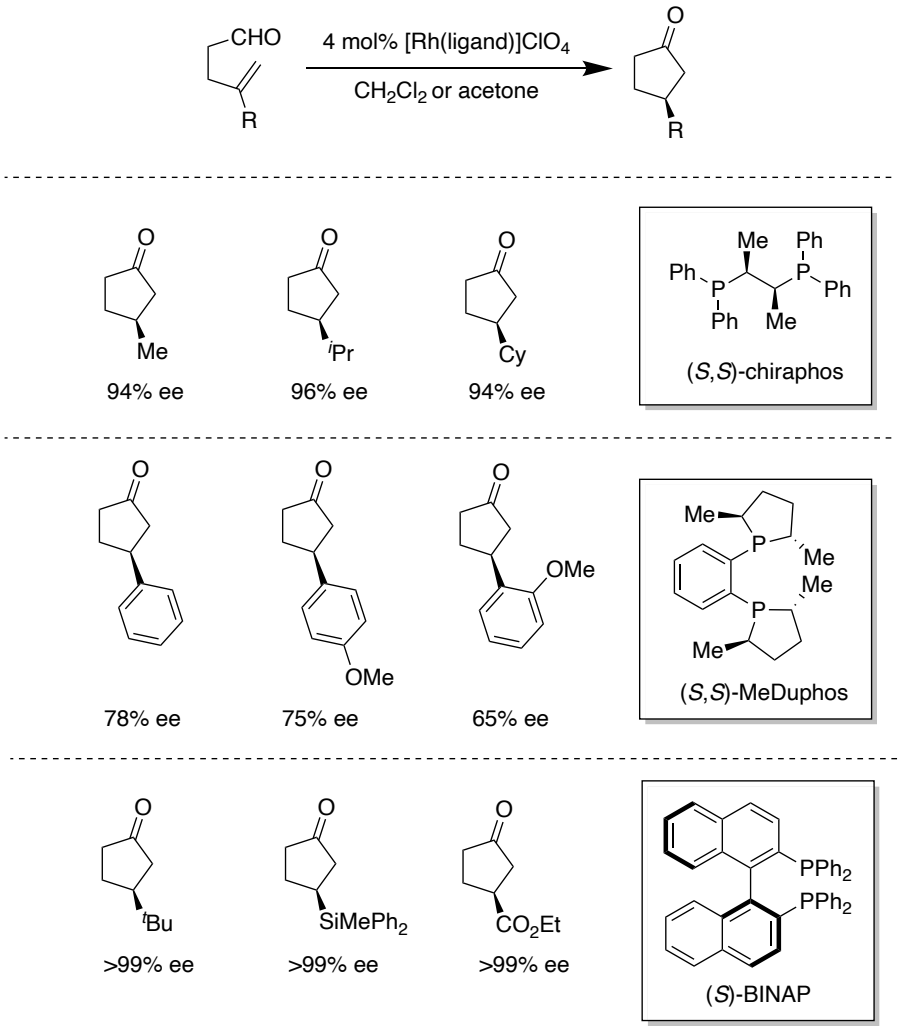
In 1983, James and Young first reported the asymmetric intramolecular hydroacylation reaction (**Scheme 1.28**).[81] The discovery was fortuitous, since they had aimed at decarbonylating racemic aldehydes to generate chiral hydrocarbons. However, treatment of 4-pentenal **43** with [Rh((*S*,*S*)chiraphos)$_2$]Cl resulted in the intramolecular addition of the aldehyde group to the alkene bond forming 3,3-disubstituted cyclopentanone **44** in 40-50% yield and with 52% ee. Despite the high temperature required, which is likely a result of the

steric hinderance at the α-position to the aldehyde, this was one of the earliest examples where only a sub-stoichiometric amount of Rh-catalyst was required for hydroacylation.



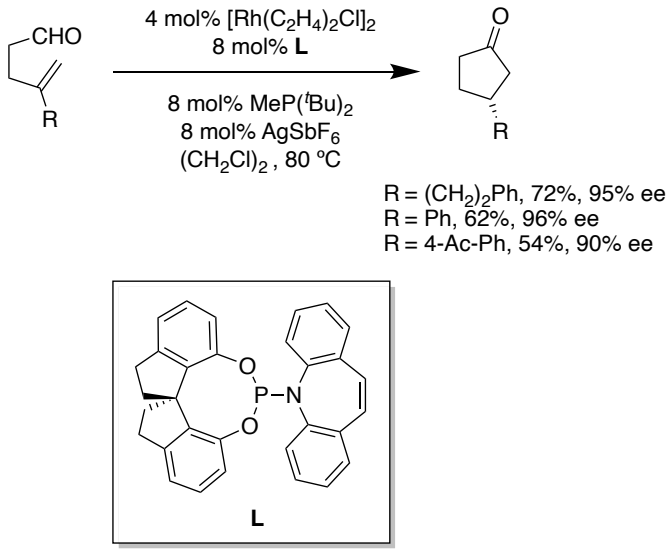
Scheme 1.28: First reported asymmetric intramolecular hydroacylation reaction by James and Young.

Bosnich and co-workers reported 4-pentenal cyclisation using cationic Rh catalysts in 1988 (**Scheme 1.29**).[42, 82] The catalysts were highly selective in promoting hydroacylation over decarbonylation as well as being effective at room temperature with low catalyst loadings (1-10 mol%). Following this, both Bosnich and Sakai reported stereoselective intramolecular cyclisation of 4-substituted-4-pentenals.[83–85] Chiral diphophine ligands (BINAP, Me-DuPhos, chiraphos) were combined with cationic Rh to achieve high enantioselectivity.



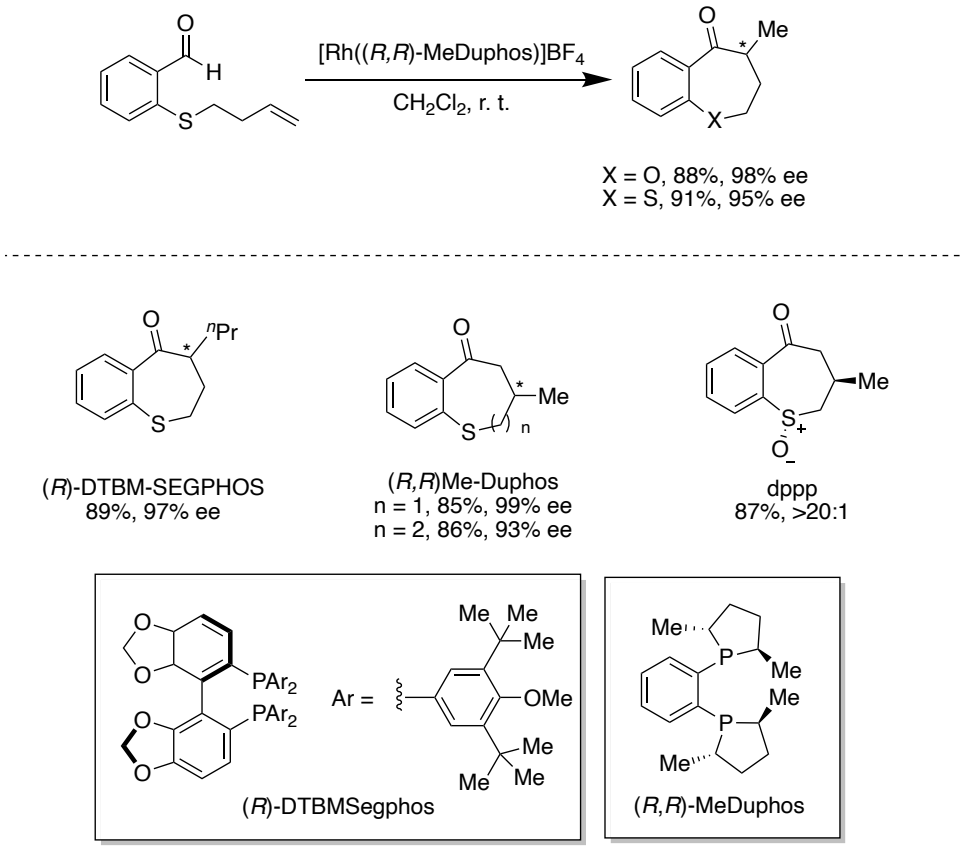
Scheme 1.29: Asymmetric cyclisation of 4-pentenals.

In 2011, Carreira and co-workers reported a highly enantioselective cyclisation of 4-aryl-substituted pentenals using a combination of cationic Rh, a phosphoramidite-olefin ligand and an achiral monodentate phosphine ligand (**Scheme 1.30**).[86] Various asymmetric processes such as desymmetrisation, kinetic resolution and dynamic kinetic resolution were also reported for the synthesis of substituted cyclopentanones.[87–91]



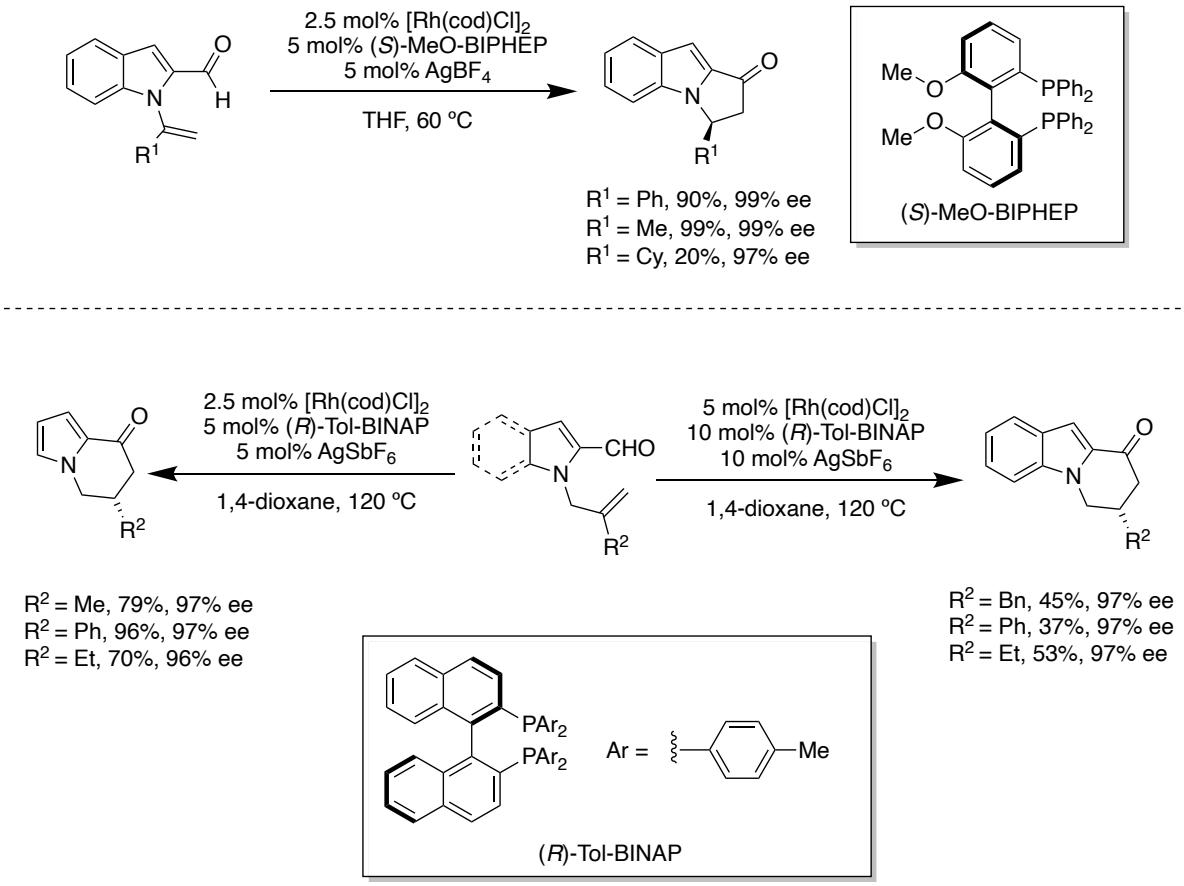
Scheme 1.30: The Carreira group's reported enantioselective cyclisation of 4-aryl-substituted pentenals.

Considerable attention has been devoted for the synthesis of larger ring systems.[51–54] Due to the difficulties in achieving high chemo and regioselectivities with homologated alkenals, tethers containing co-ordinating heteroatoms have been used to promote hydroacylation by Dong and co-workers (**Scheme 1.31**).[92] Incorporation of heteroatom tether (oxygen or sulfur) favours hydroacylation over decarbonylation and provides high yields with excellent enantioselectivities. Formation of both the regioisomers (chiral 7-membered ketones and achiral 8-membered ketones) was possible by facile choice of ligand.



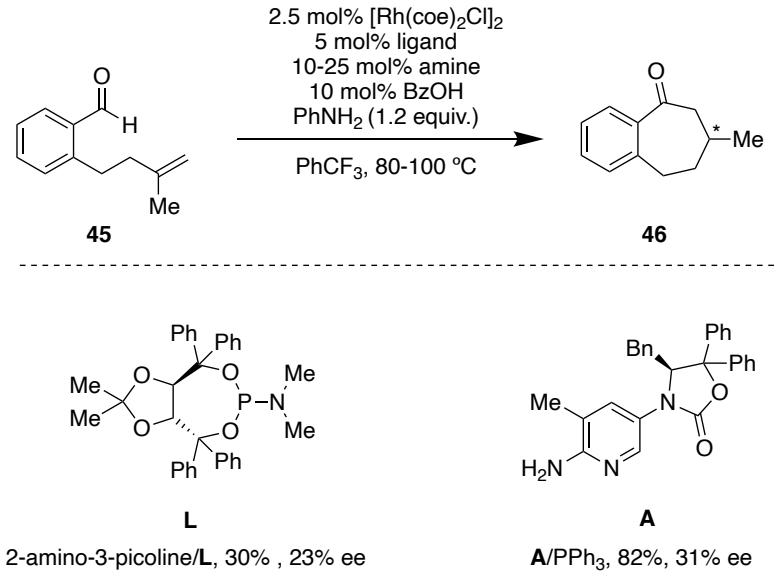
Scheme 1.31: The Dong group's reported synthesis of chiral 7- and 8-membered ketones.

Stanley and co-workers reported highly enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes, *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes (**Scheme 1.32**).[93, 94] The hydroacylations occur in the absence of chelation to synthesise *N*-containing six membered ketones. Variants of chiral BINAP ligands was used to achieve excellent yields and enantioselectivity (up to 98% ee).



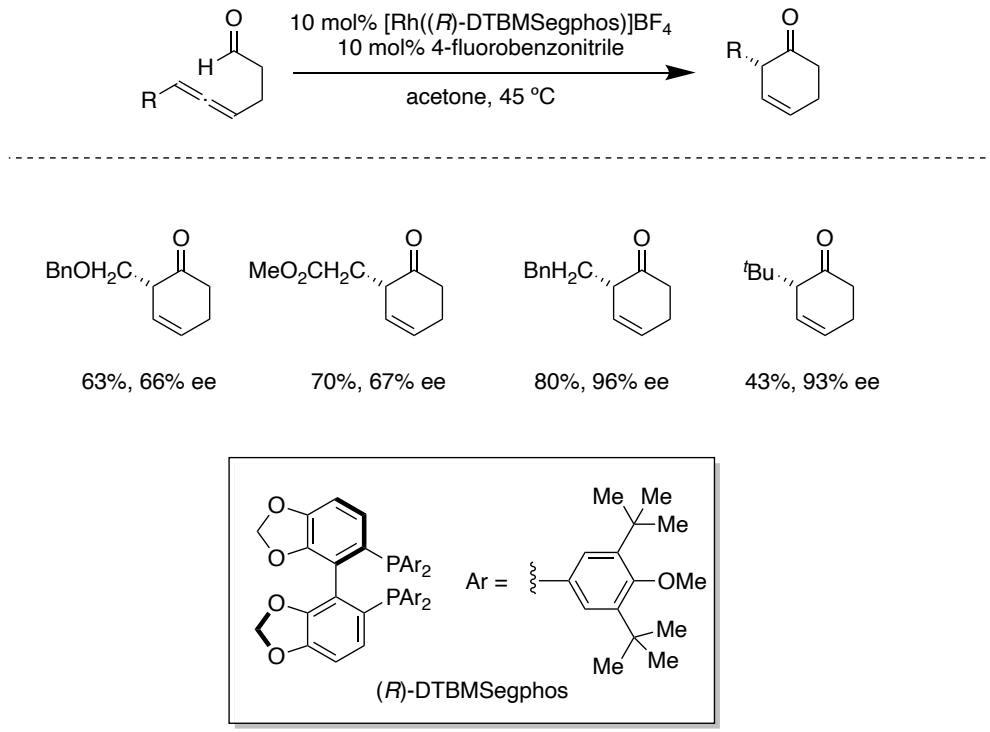
Scheme 1.32: The Stanley group's reported synthesis of *N*-containing six membered ketones.

In 2012, Douglas and co-workers reported the synthesis of 7-membered chiral ketones by hydroacylation without incorporation of any chelating atoms (**Scheme 1.33**).[95] They used a cooperative catalysis approach to hydroacylation which was first shown by Jun and co-workers.[96] Condensation of the aldehyde **45** and 2-amino-3-picoline forms an aldimine which contains a temporary pyridine chelating group to overcome decarbonylation. Using either chiral phosphorus-containing ligands or amines, enantioselective hydroacylation could be achieved to synthesise chiral 7-membered ketone **46** with moderate enantioselectivity (23% ee when chiral ligand **L** was used and 31% when chiral amine **A** was used).



Scheme 1.33: The Douglas group's synthesis of 7-membered chiral ketone.

An intramolecular version of allene hydroacylation *via* dynamic kinetic asymmetric transformation was published by Sato and co-workers in 2019 (**Scheme 1.34**).[97] Racemic allenals underwent hydroacylation to give chiral six-membered cyclic ketones in high yields and ees. Interestingly, 10 mol% of 4-fluorobenzonitrile was added to the reactions along with 10 mol% of chiral Rh catalyst, to increase the enantioselectivity of the process.



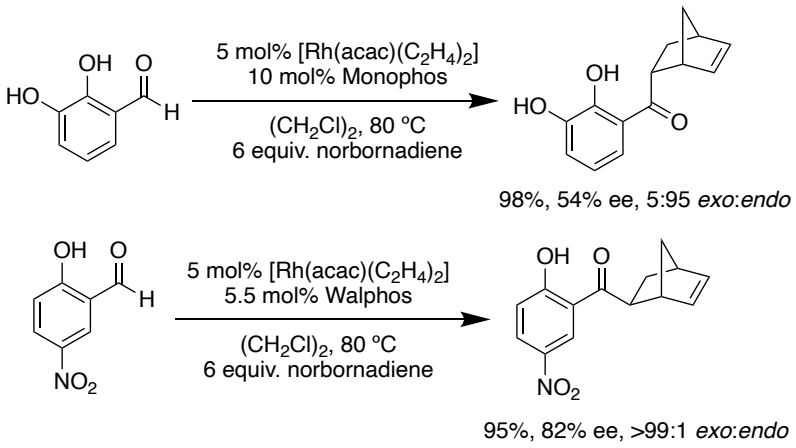
Scheme 1.34: The Sato group's intramolecular allene hydroacylation.

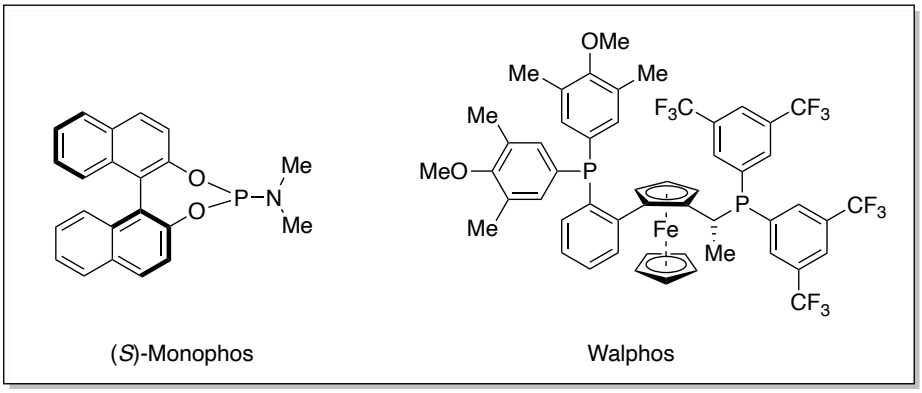
1.4.2 Enantioselective intermolecular hydroacylation reactions

Intermolecular enantioselective hydroacylations are far more challenging compared to intramolecular processes. Moreover, there are very few reports on enantioselective hydroacylations as di- and tri-substituted olefins are less reactive and branch selective hydroacylation processes are rare.

Bolm and co-workers reported the first asymmetric intermolecular hydroacylation in 2007 (**Scheme 1.35**).[98] Salicylaldehydes and norbornadiene were combined to synthesise ketones with high diastereoselectivity and moderate enantioselectivity. The hydroxyl group was deprotonated by acac anion to form phenolates which co-ordinate to the Rh and forms stable intermediate after C-H activation. It was found that mono-dentate phosphoramidite ligands were crucial to obtain *endo* selectivity with up to 54% ee, while bidentate phosphine ligands formed mainly *exo* products with high enantioselectivity (up to 82% ee). It was proposed that

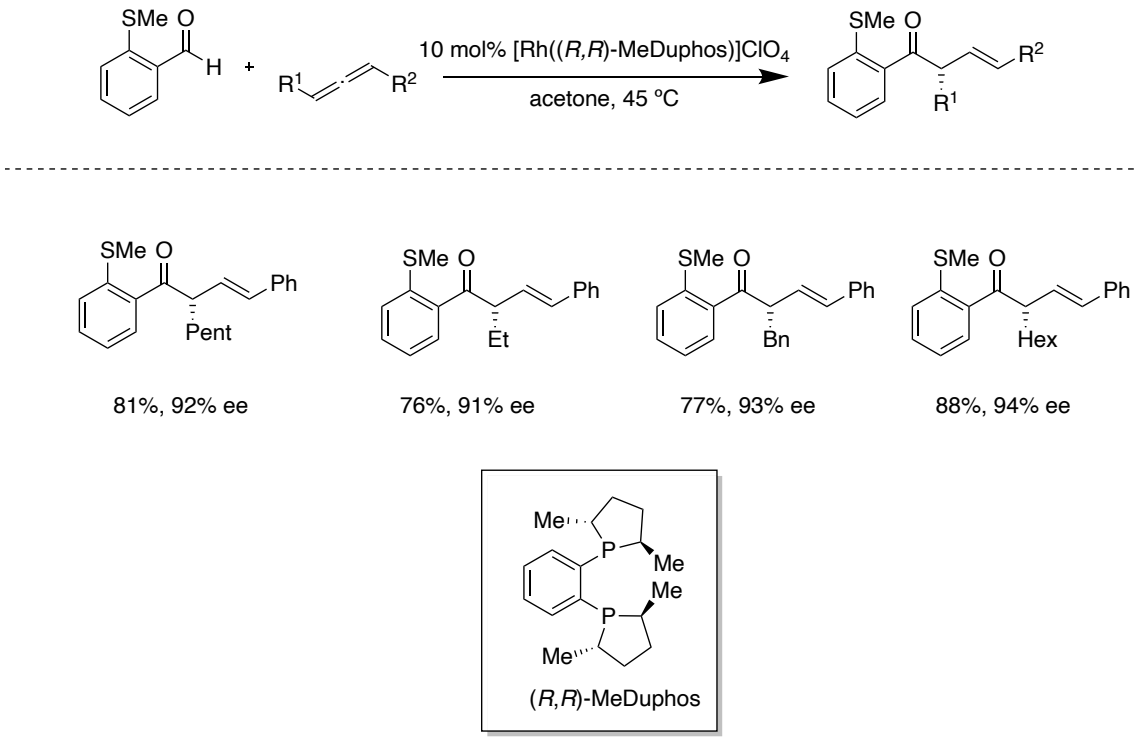
norbornadiene coordinates only with one double bond in the *exo*-like manner in presence of a bidentate ligand which occupies two of the co-ordination sites of Rh, whereas norbornadiene co-ordinates in a bidentate fashion when a monodentate phosphine was used.





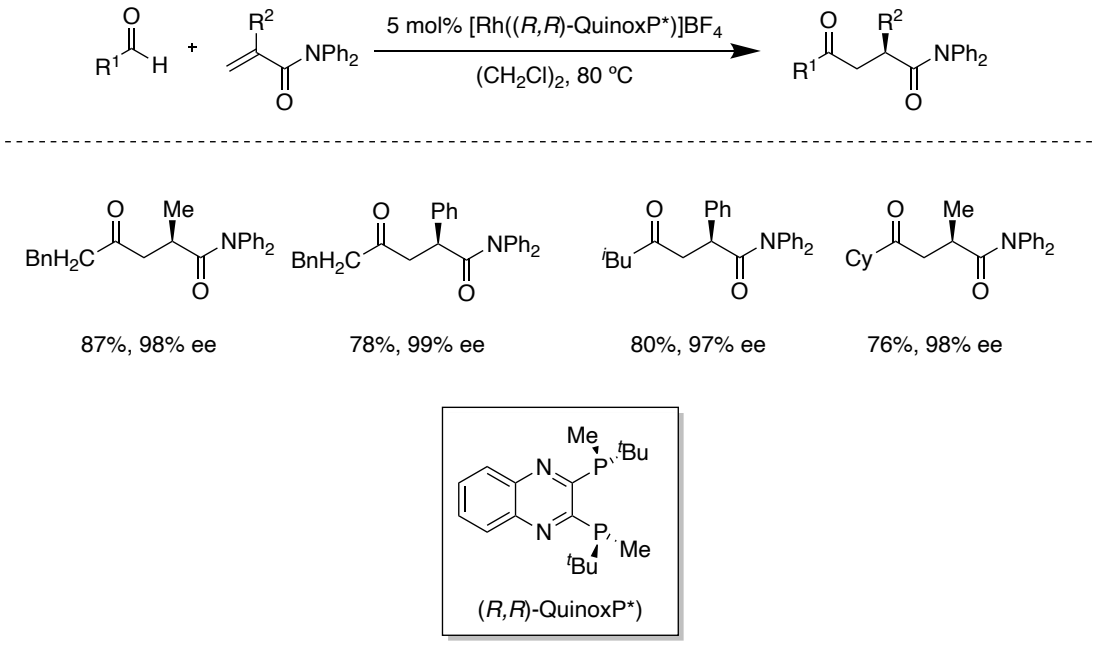
Scheme 1.35: The Bolm group's reported hydroacylation of norbornadiene.

In 2008, Willis published a dynamic kinetic asymmetric transformation in allene hydroacylation (**Scheme 1.36**).[99] The process starts with racemic allenes, which are able to racemise under the hydroacylation conditions. When undergoing hydroacylation with β-*S*-chelating aldehydes and the chiral Me-DuPhos ligand, excellent enantioselectivity (up to 96%) and high yields (up to 95%) could be accomplished. This is a highly useful method, as it relinquishes the need for less reactive di- and tri-substituted alkenes.



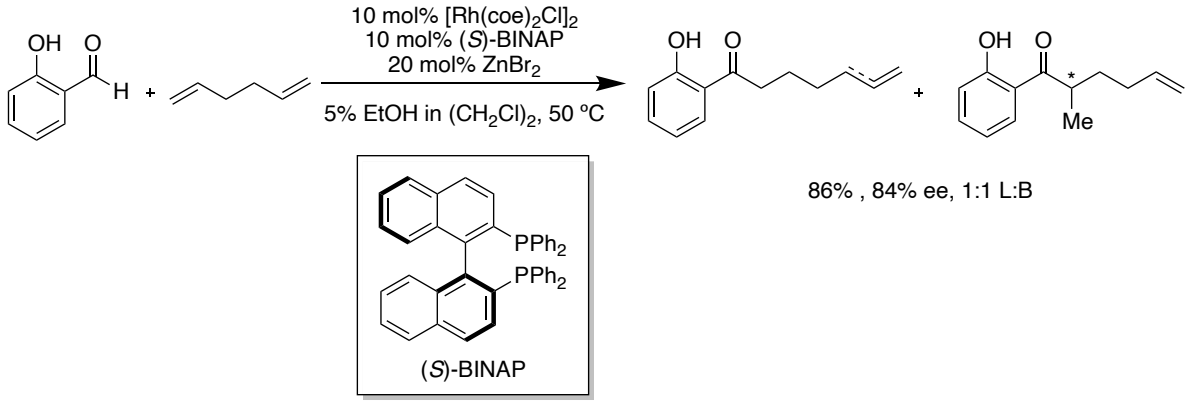
Scheme 1.36: The Willis group's dynamic kinetic asymmetric transformation in allene hydroacylation.

An example of enantioselective hydroacylation with the chelating group on the alkene was developed by Tanaka and co-workers (**Scheme 1.37**).[100] Inspired by their racemic version of this reaction,[101] enantioselective transformation was achieved by coupling alkyl-substituted aldehydes with acrylamides. It has been proposed that the presence of an amide functional group helps in stabilising the Rh-acyl-hydride intermediate by chelating to the metal centre. Chiral diphophine QuinoxP* was used as ligand and excellent enantioselectivity (up to 99% ee) with good yield was achieved.



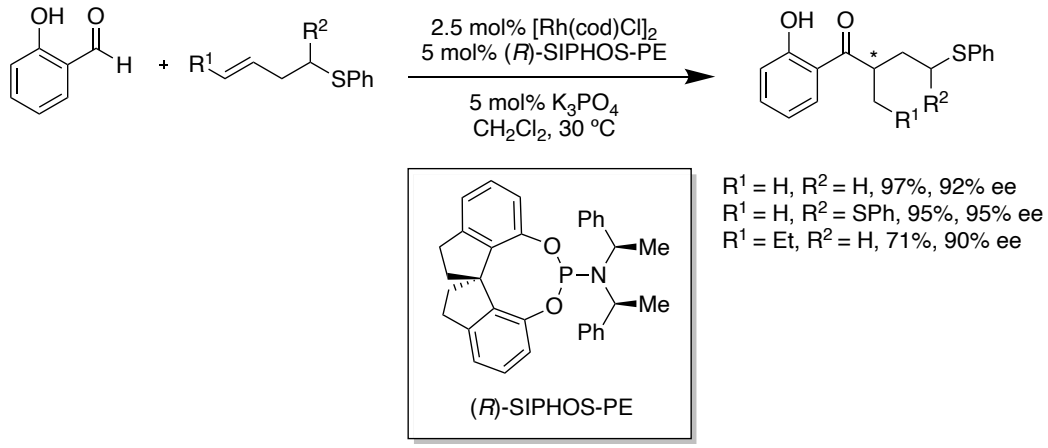
Scheme 1.37: The Tanaka group's enantioselective hydroacylation of acrylamides.

Suemune and co-workers published an asymmetric hydroacylation of 1,5-hexadienes in 2009 (**Scheme 1.38**).[102] In their previous racemic version of this reaction, branch selectivity was shown. It was proposed that chelating salicylaldehyde promotes C-H activation whereas, the diene co-ordinates Rh in bidentate fashion to provide branch selectivity (up to 12:1 regioselective ratio was obtained).[71-72] Using a combination of $[RhCl(C_8H_{14})_2]_2$, (*S*)-BINAP, and $ZnBr_2$, an 84% ee was achieved with 86% yield although the linear to branched ratio was poor (1:1).



Scheme 1.38: The Suemune group's enantioselective hydroacylation of 1,5-hexadienes.

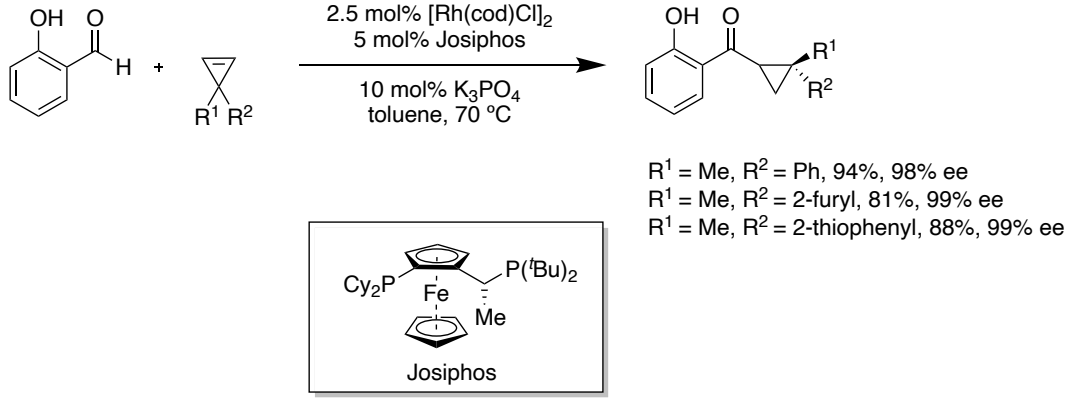
Dong and co-workers reported an asymmetric branched selective method for hydroacylation of alkenes in 2010 (**Scheme 1.39**).[73] Using their previous sulfide-directed intramolecular hydroacylation strategy, homoallylic sulfides underwent hydroacylation with salicylaldehydes. High enantioselectivity as well as regioselectivity was achieved using monodentate phosphoramidite ligands. The report shows the importance of having a sulfur atom on the alkenes, as the desired reactivity was not observed when it was replaced with a methylene group.



Scheme 1.39: The Dong group's asymmetric branched selective method for hydroacylation of alkenes.

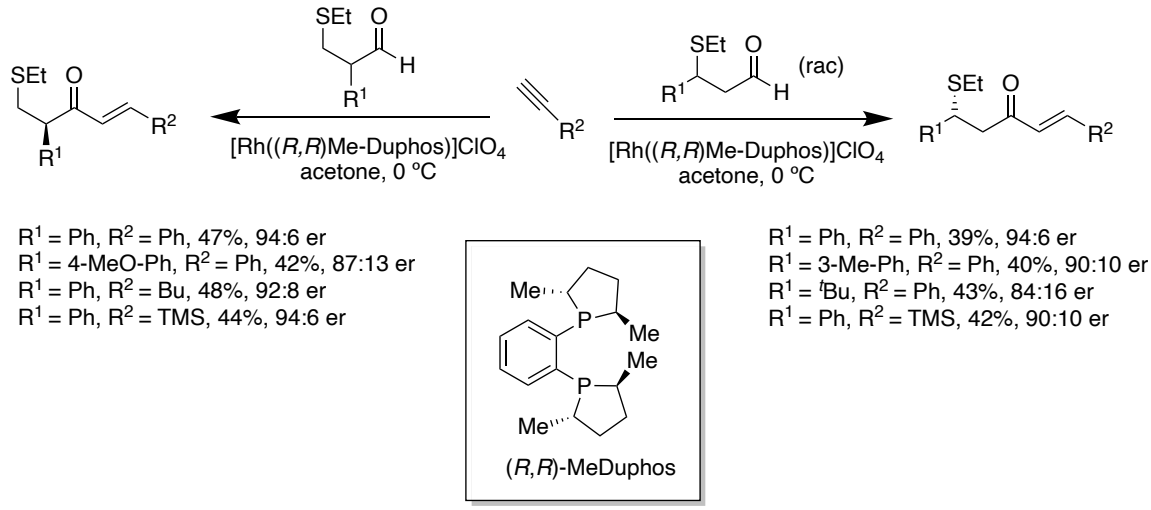
A desymmetrisation process was reported by the Dong and co-workers in the same year (**Scheme 1.40**).[103] The strategy involved using strained prochiral cycloalkenes to facilitate

hydroacylation. Salicylaldehydes and cyclopropenes were combined using a Rh-Josiphos system to achieve a wide scope with excellent enantioselectivity.



Scheme 1.40: The Dong group's desymmetrisation of cyclopropenes.

A kinetic resolution process was developed by Willis and co-workers in 2010 (**Scheme 1.41**).[104] α- and β-substituted S-chelating racemic aldehydes were coupled with alkynes to provide enantiomerically enriched enones. MeDuphos was used as chiral ligand to achieve high enantioselectivity. Using an appropriate reducing agent, it was shown that 1,2-reduction of the enone was possible to form allylic alcohols with high diastereoselectivity.



Scheme 1.41: The Willis group's reported kinetic resolution process.

1.5 Summary

Many advances in catalyst development and reaction design have been made since the first report of Rh-mediated hydroacylation by Sakai. Robust intramolecular hydroacylation processes have been developed to access five-, six- and seven-membered rings. Extensive studies have been conducted to understand the reaction mechanism, establish the catalytic cycle and isolate the key intermediates which have allowed for the development of intermolecular reactions, with low catalyst loadings and mild conditions. Tethering strategies have been a crucial asset in overcoming limitations of reactivity and selectivity; however, this involves multi-step procedures for tether installation, functionalisation or removal. Attention has been devoted to the design of traceless tethering strategies; however, these are generally accompanied by narrow substrate scopes and poor selectivities. Recently our laboratory has demonstrated that simple carbonyl groups, such as ketones, esters and amides, when positioned β to the aldehyde group, can be used to mediate rhodium-catalyzed hydroacylation reactions, to provide the β-dicarbonyl products, which are present in numerous natural products. It is therefore our aim in Chapter **2** to further investigate new applications of carbonyl coordinating groups in intermolecular hydroacylation.

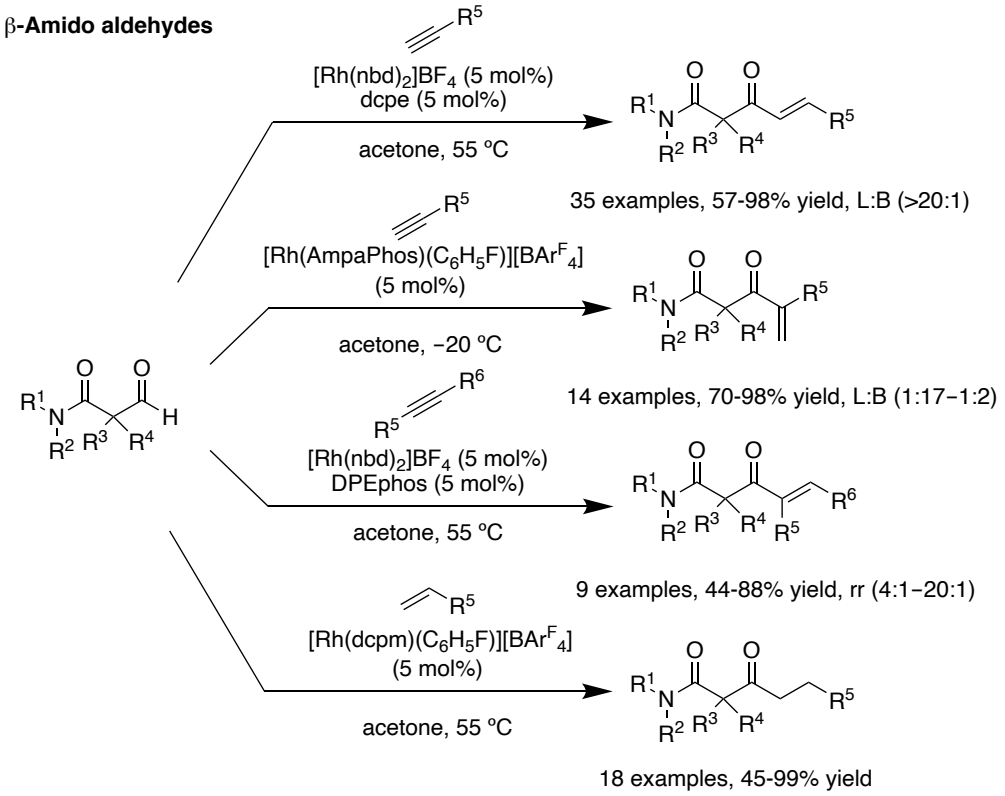
Significant progress has been made in the field of intramolecular enantioselective hydroacylation reaction, however, intermolecular processes are rarer due to the lower reactivity of internal alkenes and the lack of branch selective processes. DKR methods that install chirality on the aldehyde component, in the presence of simple alkyne hydroacylation to generate chiral enones, will be discussed in Chapter **3**. Our group's recently published carbonyl directing β-amido aldehydes[105] will be explored to facilitate this process.

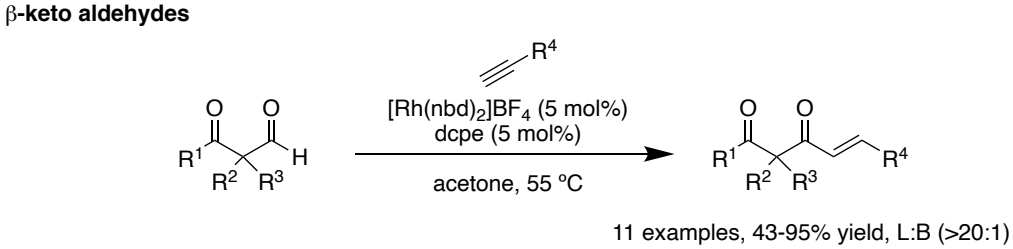
Chapter 2

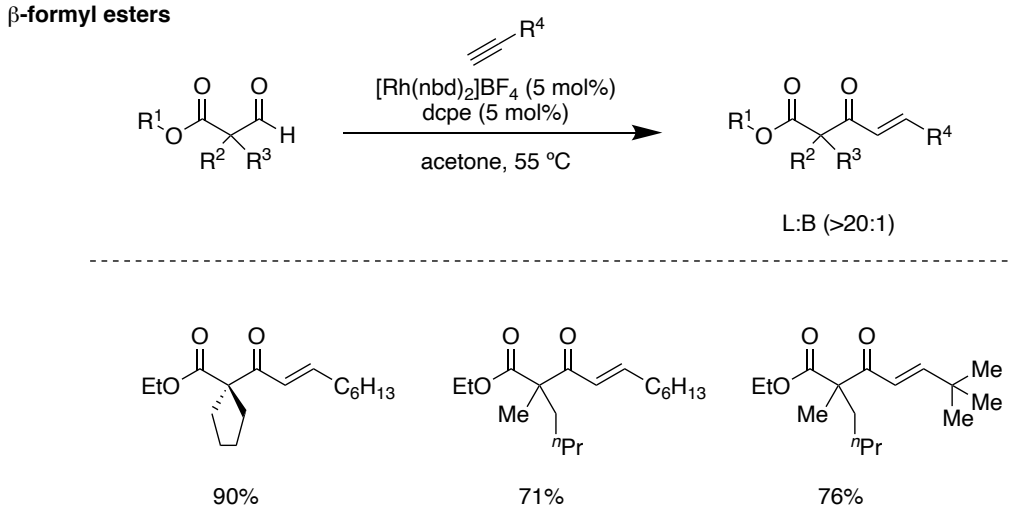
1,4-Dicarbonyls in rhodium-catalysed hydroacylation

2.1 Introduction

The majority of intermolecular hydroacylation processes rely on the use of chelating groups to deliver efficient reactivity. Although this strategy has proven effective, the installation and removal, or further transformation, of the chelating group, is an inherent limitation. One of the ways to overcome this limitation, is to employ a common functional group as a chelating motif that is desirable in the end product. Recently, our laboratory has demonstrated that simple carbonyl groups, such as ketones, esters and amides, when positioned β to the aldehyde group, can be used to mediate rhodium-catalysed hydroacylation reactions (**Scheme 2.1**).[105] A remarkable scope, with respect to both alkyne and β-amido aldehyde partners, has been reported. When dcpe was employed as a ligand, excellent yields with high linear selectivity were achieved. Switching to AmpaPhos yielded branched enones. DPEphos provided the best regioselectivity in the reaction of unsymmetrical internal alkynes, while dcpm was found to promote the reactions with terminal alkenes. α-Disubstituted β-keto aldehydes and β-ester aldehydes react with terminal alkynes in the presence of dcpe ligand to provide 1,3-dicabonyls in good yields.

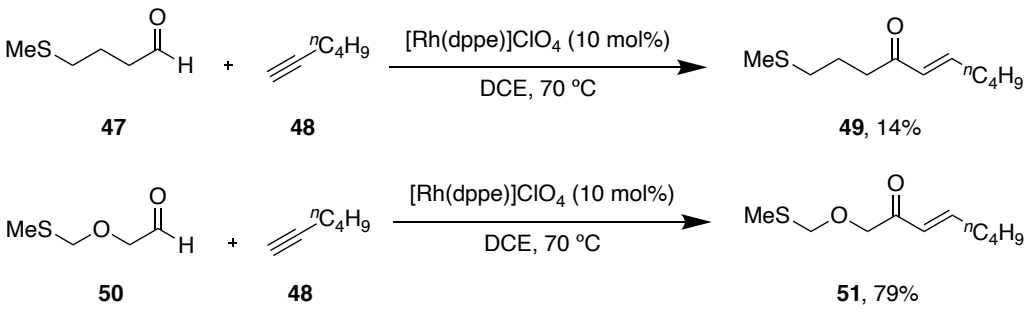




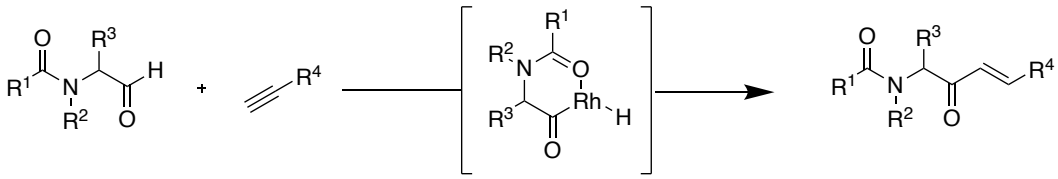


Scheme 2.1: The Willis group's β-amido, ketone and ester aldehyde hydroacylation.

Effective hydroacylations using γ- substituted systems are rare and have proved to be very challenging. It is believed that six-membered metallocycle formation, through chelation, is kinetically less favoured compared to five-membered metallocycle generation from β-substituted systems. A report from the Willis group demonstrated that a γ-sulfur substituted substrate **47** provided poor yield in hydroacylation with alkyne **48** (**Scheme 2.2**).[79] However, significant increase in reactivity was observed when an MTM tethered substrate **50** was used. This improved reactivity, was attributed to the incorporation of a heteroatom α to the aldehyde. Inspired by this observation and looking to extend the utility of the carbonyl substituent further, we decided to investigate the use of 1,4-dicarbonyl systems in rhodium-catalysed hydroacylation, with key focus on preparation of synthetically valuable α-*N*-amido ketones (**Scheme 2.3**).



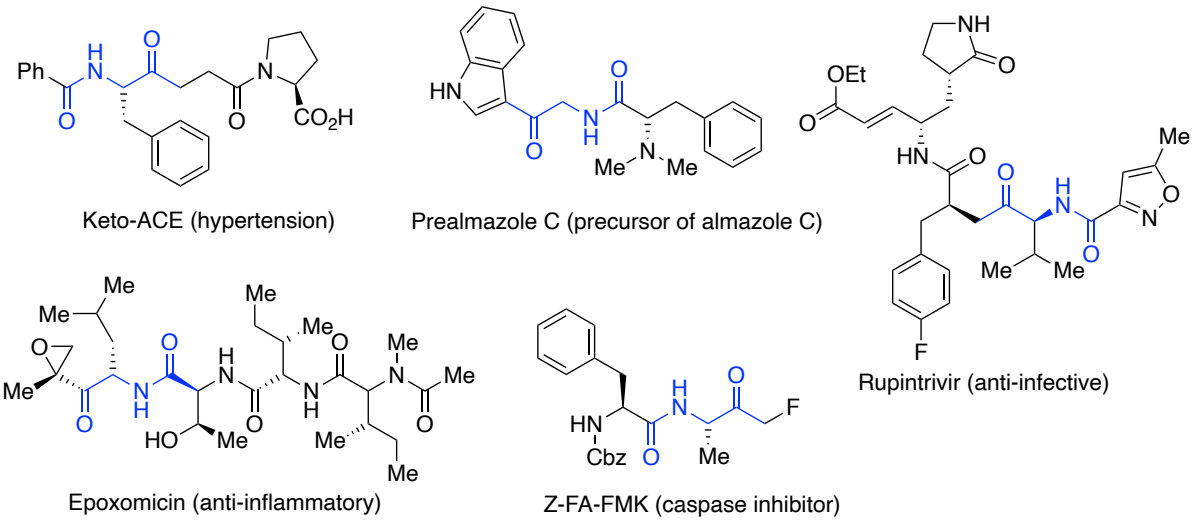
Scheme 2.2: Hydroacylation of alkynes using γ-sulfur substituted substrates.



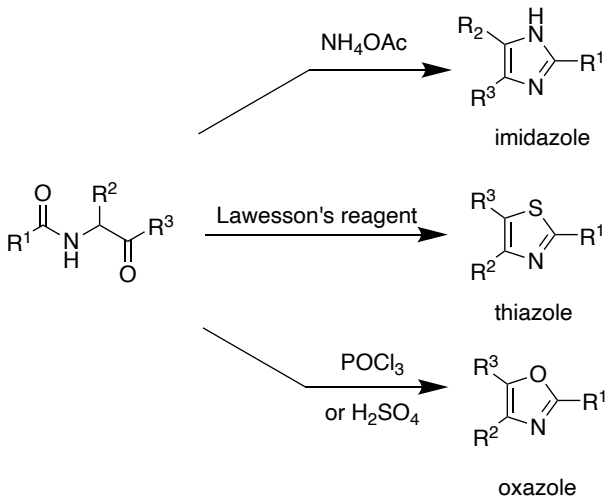
Scheme 2.3: Our proposed hydroacylation of 1,4-dicarbonyls.

2.2 Intermolecular alkyne hydroacylation of α-*N*-amido aldehydes

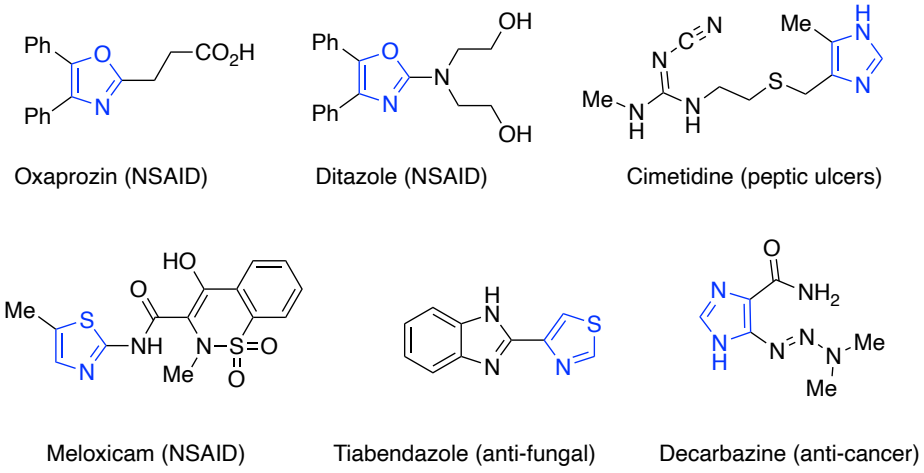
α-*N*-Amido ketones are present in many biologically relevant molecules (**Scheme 2.4**)[106–111] and are widely used as building blocks in organic synthesis.[112–114] This is exemplified by their use as precursors to oxazoles,[115–119] thiazoles[120] and imidazoles (**Scheme 2.5**), [121–123] which are among the most common heterocycles with wide applications in biology and medicine (**Scheme 2.6**).[124–126]



Scheme 2.4: Examples of medicinally relevant compounds containing an α-*N*-amido ketone motif.

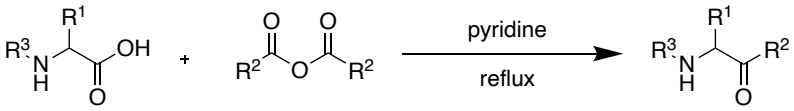


Scheme 2.5: α- *N*-Amido ketone as precursors to imidazoles, thiazoles and oxazoles.



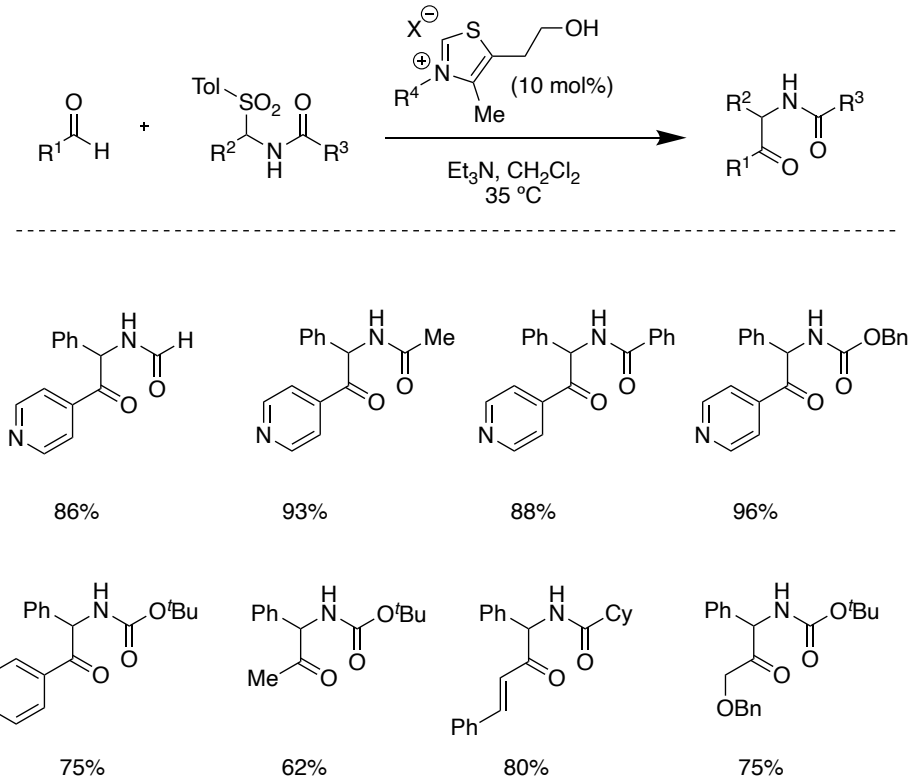
Scheme 2.6: Medicinally relevant compounds containing oxazole, thiazole and imidazole motifs.

Therefore, it is no surprise that considerable effort has been devoted to their synthesis. Dakin and West first reported the synthesis of α-*N*-amido ketones in 1928 (**Scheme 2.7**).[127] α-Amino acids were converted into α-acetylaminoalkylmethylketone using acetic anhydride and pyridine *via* evolution of CO_2. Since then, the Dakin-West reaction has been significantly advanced.[128–129] The original report described harsh reaction conditions, however, mild conditions were later developed, to provide broader scope and good yields.



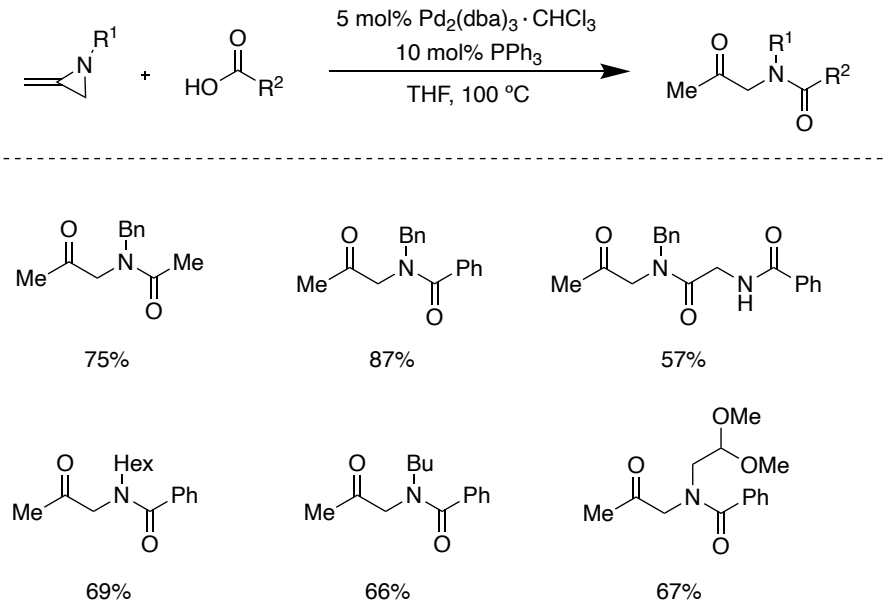
Scheme 2.7: A general outline of Dakin-West reaction.

An organocatalysed synthesis of α-*N*-amido ketones was demonstrated by Murry, Frantz and co-workers in 2001 (**Scheme 2.8**).[130] Cross-coupling between aldehydes and acylimines occurs *via* thiazolium catalysis to provide α-*N*-amido ketones. Both aliphatic and aromatic aldehydes reacted successfully with arylsulfonyl amides in excellent to low yields.



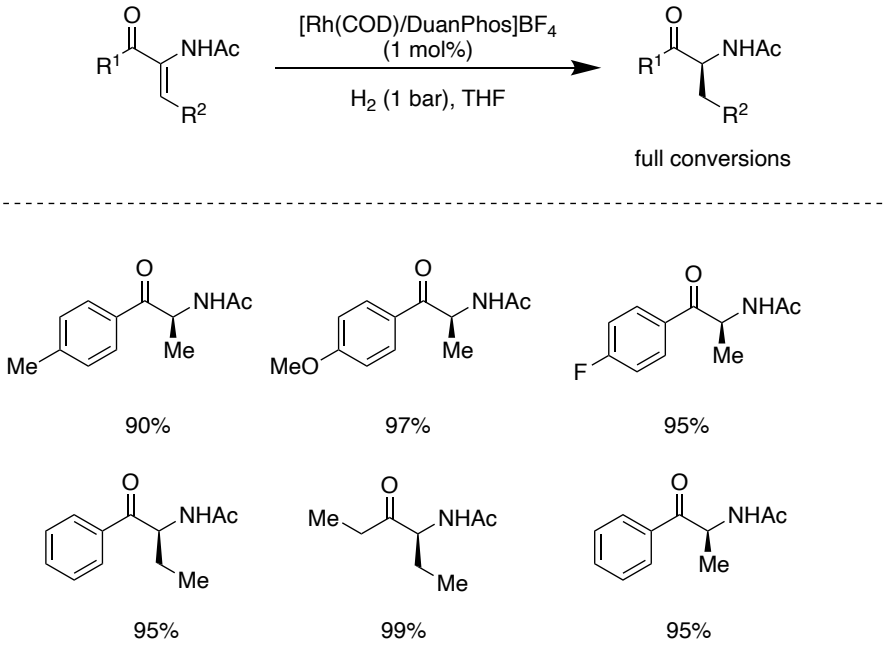
Scheme 2.8: Synthesis of α-*N*-amido ketones *via* thiazolium catalysis by Murry, Frantz and co-workers.

Yamamoto and co-workers reported synthesis of α-*N*-amido ketones *via* a palladium-catalysed ring-opening reaction in 2003 (**Scheme 2.9**).[131] The process involves hydrocarboxylation of methyleneaziridines using 10 mol% of Pd and PPh_3. Good yields were achieved, but the scope of the reaction was narrow.



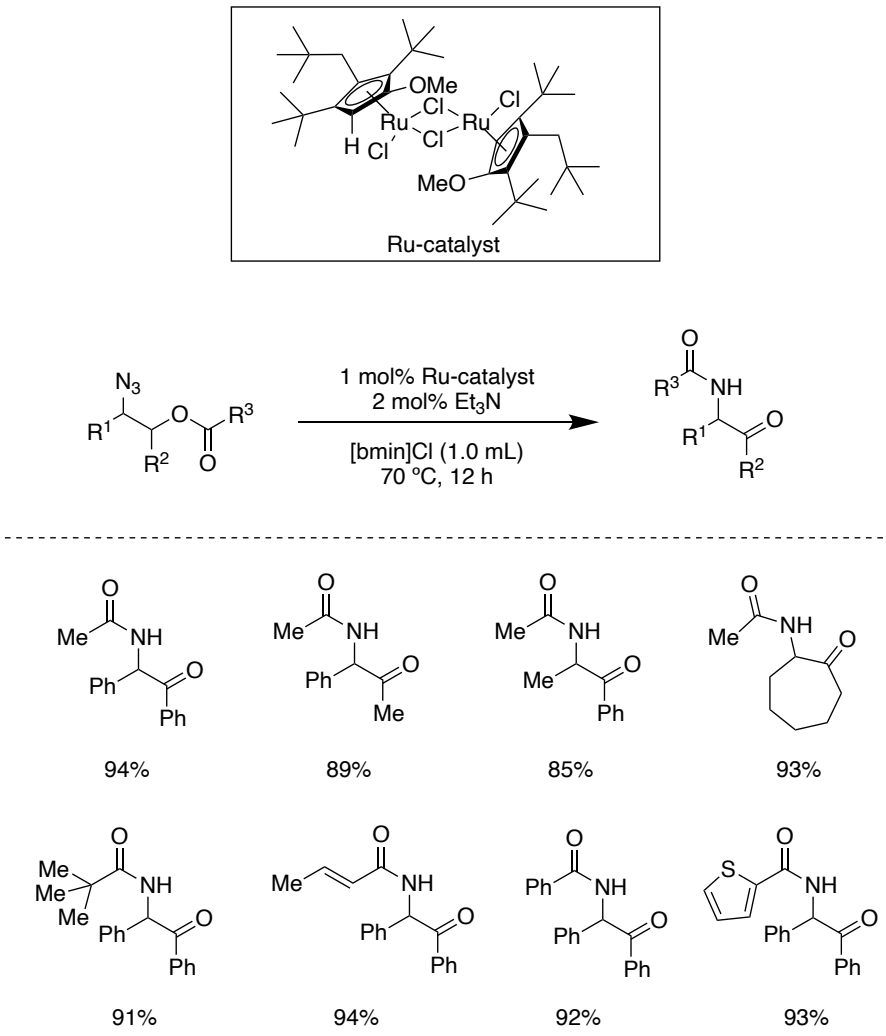
Scheme 2.9: The Yamamoto group's synthesis of α-*N*-amido ketone from methyleneaziridines.

An asymmetric hydrogenation reaction was reported in 2011 by Zhang and co-workers, which accessed enantiomerically enriched α-*N*-amido ketones (**Scheme 2.10**).[132] 1 mol% of a rhodium catalyst was used with the chiral DuanPhos ligand, affording high enantioselectivity (ees up to 99%). However, the scope of the reaction was also very limited.



Scheme 2.10: The Zhang group's asymmetric hydrogenation reaction to synthesise α-*N*-amido ketones.

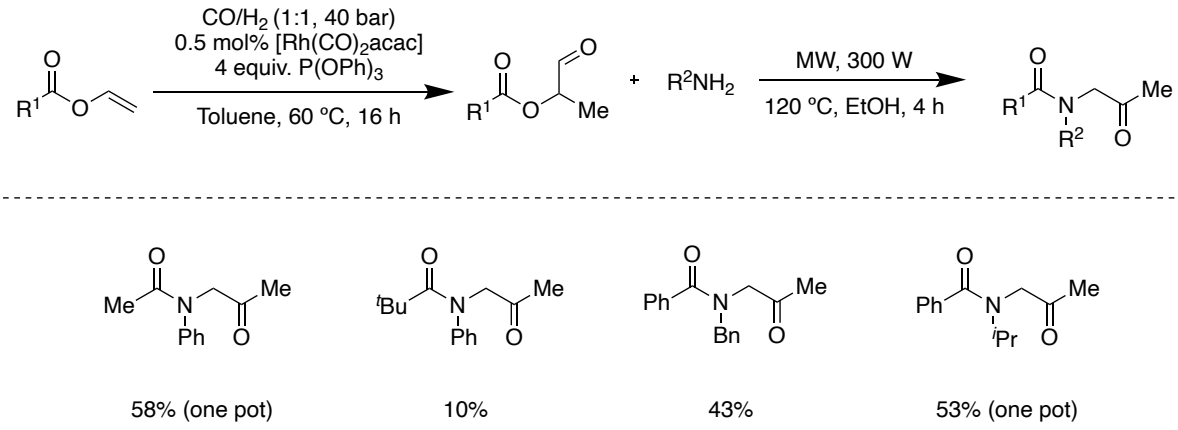
In 2016, Park, Rhee and co-workers published a method for the synthesis of α-*N*-amido ketones from the esters of 1,2-azidoalcohols.[133] The method utilises only 1 mol% of the Ru-catalyst, to deliver a wide range of multi-substituted α-*N*-amido ketones in good yields (**Scheme 2.11**). The process involves liberation of molecular nitrogen, followed by intramolecular acyl transfer.



Scheme 2.11: The Park and Rhee group's synthesis of α-*N*-amido ketone.

In the same year, an atom-efficient method for the synthesis of α-*N*-amido ketones was reported by Francio, Leitner and co-workers (**Scheme 2.12**).[134] This is a three-step process, which could be performed in one pot, starting from simple vinyl esters. The first step involves rhodium catalysed hydrofomylation of a vinyl ester. The second step is a condensation process

of an amine with the aldehyde product formed from the previous step. Finally, microwave promoted rearrangement gives the α-*N*-amido ketone product. The scope of this reaction was narrow, and the yields obtained were moderate to low.



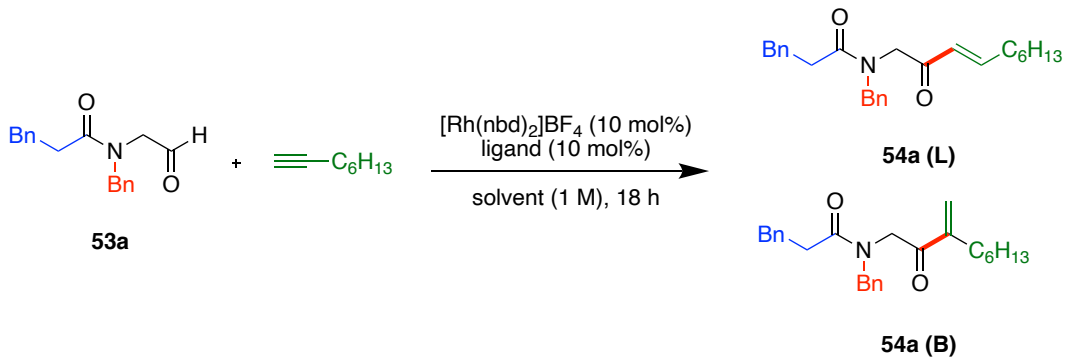
Scheme 2.12: The Francio and Leitner group's synthesis of α-*N*-amido ketone.

2.2.1 Ligand optimisation for Rh-catalysed alkyne hydroacylation

We began our study by investigating the addition of 1-octyne to aldehyde **53a** to give enone **54a,** using a variety of Rh-catalysts (**Table 2.1**). Reactions were performed using the standard practical method developed by the Willis group for hydroacylation of *S*-, *N*- and carbonyl chelating aldehydes. This involved use of bench stable rhodium precatalyst $[Rh(nbd)_2]BF_4$ and diphosphine ligands. The active catalyst was generated *in situ* by hydrogenating the nbd off $[Rh(nbd)_2]BF_4$ in dry solvent (typically DCE or acetone), in the presence of diphosphine ligand. Evaluation of a variety of commercial diphosphines was undertaken using a 10 mol% catalyst loading, starting with ligands that had previously been shown to be effective in hydroacylation chemistry. Initial results revealed that the smallest bite-angle ligand, dcpm, gave moderate conversion, with a 9:1 linear to branched ratio after 18 hours at 80 °C using 1,2-dichloroethane (DCE) as solvent (**entry 1**). The larger bite-angle ligand dcpe, resulted in very low conversion (**entry 2**); however, exchanging the cyclohexyl groups for phenyl groups significantly

improved reactivity, with dppe delivering a 93% conversion with 7:1 regioselective ratio (**entry 3**). Switching the solvent to acetone, resulted in decreased regioselectivity (4:1 L:B) (**entry 4**). Further increasing the bite angle (dppp), resulted in lower conversion, but increased regioselectivity (**entry 5**). Alternative wide bite angle ligands, such as BINAP, DPEphos and Xantphos were not effective (**entries 6-8**).

Table 2.1: Ligand screen for hydroacylation of α-*N*-amido aldehyde **53a** and 1-octyne.

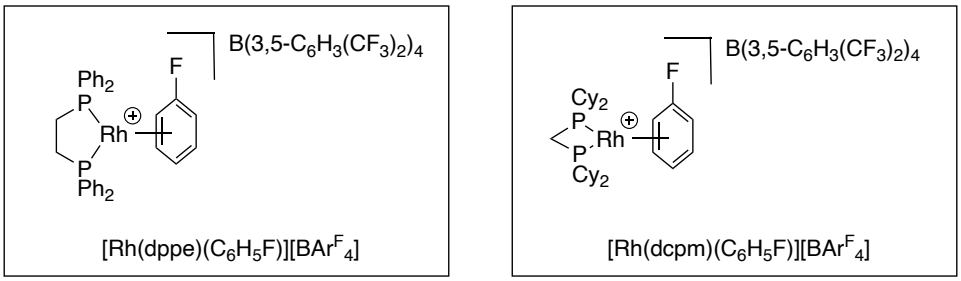


53a

Entry	Ligand	Temperature (°C)	Solvent	Conversion[a](%)	L:B[a]
1	dcpm	80	DCE	42	9:1
2	dcpe	80	DCE	2	-
3	dppe	80	DCE	93	7:1
4	dppe	55	acetone	87	4:1
5	dppp	80	DCE	27	10:1
6	(±)-BINAP	80	DCE	0	-
7	DPEphos	80	DCE	0	-
8	Xantphos	80	DCE	0	-
9[b]	dcpm	80	DCE	65	10:1
10[c]	dppe	40	CH_2Cl_2	100 (80)	10:1

Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), ligand (10 mol%), aldehyde **53a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), DCE (1.0 M), 80 °C for 18 h. [a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [b] $[Rh(dcpm)(C_6H_5F)][BAr^F{}_4]$ (10 mol%), DCE (1.0 M), 80 °C for 18 h. [c] $[Rh(dppe)(C_6H_5F)][BAr^F{}_4]$ (5 mol%), CH_2Cl_2 (2.0 M), 40 °C for 18 h, value in parentheses indicates isolated yield.

Having established dcpm and dppe as the effective ligands for the reaction, we next turned our attention to the synthesis of preformed catalysts incorporating these two ligands. [Rh(dcpm)(C_6H_5F)][$BArF_4$] and [Rh(dppe)(C_6H_5F)][$BAr^F{}_4$] were prepared using a method developed by Weller;[135, 136] the aim of using these complexes was to achieve good reactivity with a low catalyst loading (**Scheme 2.13**). Increased conversion was observed when [Rh(dcpm)(C_6H_5F)][$BAr^F{}_4$] was used, however, 10 mol% of the catalyst was still required (**entry 9**). Pleasingly, full conversion and increased regioselectivity (7:1 to 10:1) was achieved using 5 mol% catalyst of [Rh(dppe)(C_6H_5F)][$BAr^F{}_4$] (**entry 10**). The desired product was isolated in 80% yield and importantly, the reaction could be performed at 40 °C in CH_2Cl_2, compared to 80 °C needed in the original reaction.



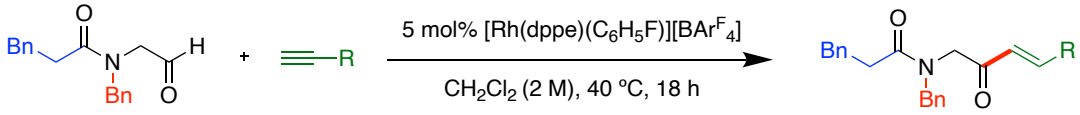
Scheme 2.13: Structure of [Rh(dppe)(C_6H_5F)][$BAr^F{}_4$] and [Rh(dcpm)(C_6H_5F)][$BAr^F{}_4$].

2.2.2 Reactivity of terminal and internal alkynes

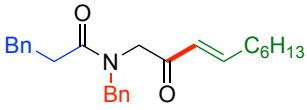
With the optimized reaction conditions in hand, the scope of this process was explored with respect to the alkyne component (**Scheme 2.14**). First, aldehyde **53a** and a range of terminal alkynes were subjected to the developed conditions. Acyclic and cyclic alkyl substituents were successfully incorporated, providing the hydroacylation adducts in good yields and regioselectivities (**54a–c**). However, hydroacylations of alkynes with cyclopropyl and benzyl substituents were found to be challenging and only moderated yields were obtained (**54d, 54e**). A cyclohexenyl substituted alkyne provided the corresponding linear enone product **54f** in 84% yield. Phenylacetylene and other arylalkynes, featuring both electron-withdrawing and

donating groups, delivered the desired products (**54g–i**) in high yields with excellent linear selectivity. A thiophene-substituted alkyne was also successfully employed, forming enone **54j** in 89% yield and with a >20:1 linear:branched (L:B) ratio. Excellent isolated yields and selectivities were obtained, when alkynes featuring sterically demanding substituents were used (**54k, 54l**). Pleasingly, many functional groups were well tolerated in the reaction, including alkyl halides, free alcohols, acetals and phthalimides, and these provide useful handles for further functionalisation (**54m–p**). Symmetric internal alkynes showed mixed results under the optimized reaction conditions. Diphenylacetylene which was proved to be a challenging substrate in hydroacylation for other tethered aldehydes, gave the desired product **54q** in 77% yield, while unactivated internal alkyne 4-octyne provided enone **54r** in only 17% yield.

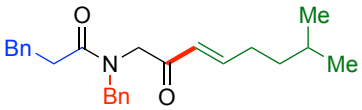
To demonstrate the robustness and scalability of this process, a gram-scale reaction was performed between aldehyde **53a** and phenylacetylene. Using a lower catalyst loading of 4 mol%, 1.03 grams of enone **54g** was isolated in 73% yield.



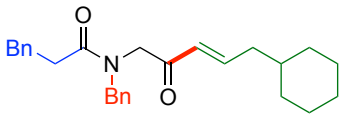
53a **54a–r**



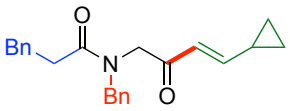
54a, 80%, 10:1 L:B



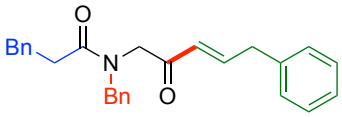
54b, 60%, 9:1 L:B



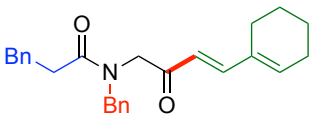
54c, 62%, 10:1 L:B



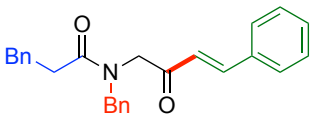
54d, 43%, >20:1 L:B



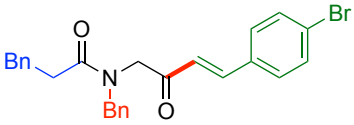
54e, 55%, 10:1 L:B



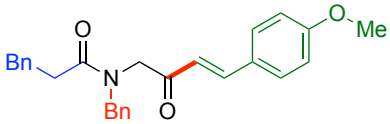
54f, 84%, >20:1 L:B



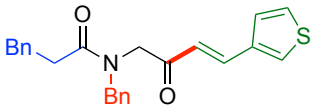
54g, 92%, >20:1 L:B
(gram scale: 73% at 4 mol%)[a]



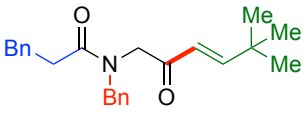
54h, 81%, >20:1 L:B



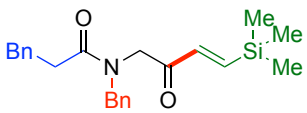
54i, 72%, >20:1 L:B



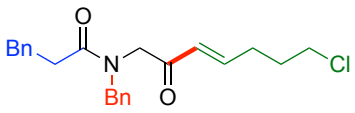
54j, 89%, >20:1 L:B



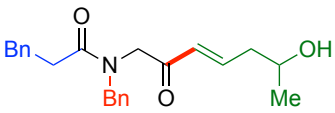
54k, 95%, >20:1 L:B



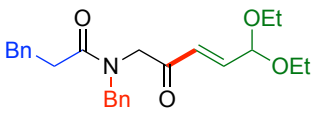
54l, 86%, >20:1 L:B



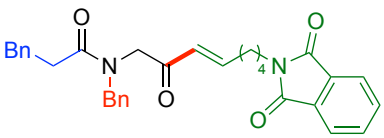
54m, 73%, 7:1 L:B



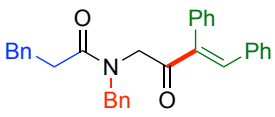
54n, 42%, 17:1 L:B



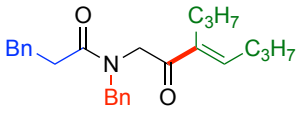
54o, 28%, >20:1 L:B



54p, 70%, >20:1 L:B



54q, 77%



54r, 17%

Reaction conditions: [Rh(dppe)(C6H5F)][BArF4] (5 mol%), aldehyde **53a** (0.2 mmol, 1.0 equiv.), alkyne (1.2 equiv.), CH_2Cl_2 (2.0 M), 40 °C for 18 h. Linear to branched ratio (L:B) determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [a] Performed with 3.7 mmol of aldehyde (1.04 g), using 4 mol% catalyst. 1.03 g of product isolated.

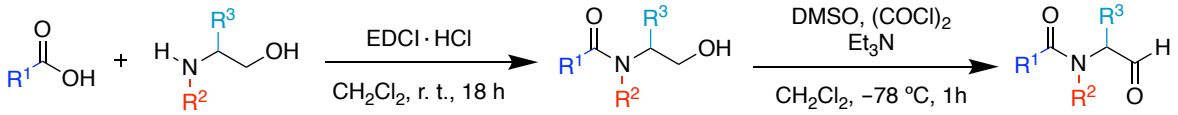
Scheme 2.14: Scope of terminal and internal alkynes in hydroacylation of α-*N*-amido aldehyde **53a.**

2.2.3 Synthesis of α-*N*-amido aldehydes

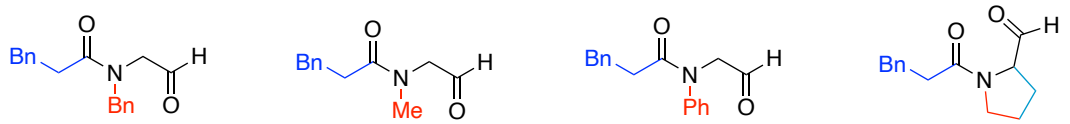
The α-*N*-amido aldehyde substrate synthesis was carried out jointly with a part II student, Sean C. O'Brien, and his contribution is also discussed here for a full understanding of the project, but the products he prepared are not included in the experimental section.

In order to assess the reaction scope with respect to the aldehyde component, we have developed a synthetic route to α-*N*-amido aldehydes. A broad range of aldehydes were prepared from commercially available aminoalcohols in two steps (**Scheme 2.15**). The first step involved an EDC coupling of an acid to an aminoalcohol, and subsequent Swern oxidation gave the desired aldehyde.

Pleasingly, good yields were achieved when hydrocinnamic acid was coupled with a variety of aminoalcohols (**52a, s–u, w–z**), however, use of alternative acids as coupling partners, gave reduced yields (**52aa, ab, ad, ae**). Swern oxidation of the amido alcohols furnished aldehydes in good to moderate yields. The reaction was tolerant towards a variety of *N*-substitutions, including alkyl, aryl and free N-H (**53a, s–u**). A wide range of alkyl substitutions at the α-position was also tolerated, including bulky groups such as isopropyl (**53w–z**). Acyl group variation of the amides was also achieved using this method (**53aa, ab, ad, ae**). However, attempts to synthesise compound **53v** by the abovementioned procedure failed as decomposition of compound occurred during purification by column chromatography. This particular compound was synthesised using a modified procedure developed by Willis (**Scheme 2.16**).[80] Hydrocinnamic acid was coupled with 2,2-dimethoxyethylamine to provide amide **52v** which was then deprotected under acidic conditions, to provide the desired compound **53v**. Aldehyde **53ac,** with carbamate protection was synthesised *via* simple cbz protection, followed by Swern oxidation starting from commercially available Cbz-Cl and 2-(benzylamino)ethan-1-ol (**Scheme 2.17**).



52 **53**

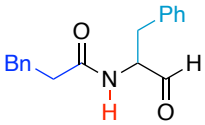


52a (79%)
53a (67%)

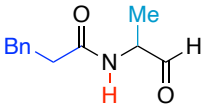
52s (76%)[a]
53s (58%)[a]

52t (79%)[a]
53t (91%)[a]

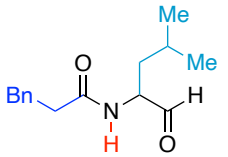
52u (79%)[a]
53u (78%)[a]



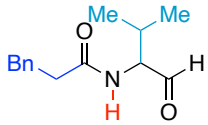
52w (72%)
53w (51%)



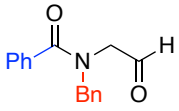
52x (37%)
53x (25%)



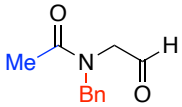
52y (60%)
53y (45%)



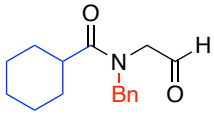
52z (64%)
53z (78%)



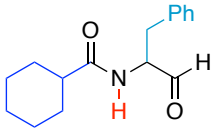
52aa (37%)[a]
53aa (49%)[a]



52ab (38%)[a]
53ab (68%)[a]



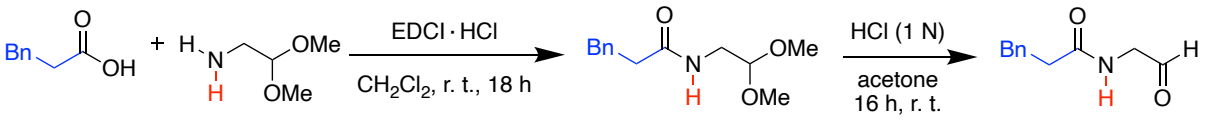
52ad (46%)
53ad (70%)



52ae (65%)
53ae (46%)

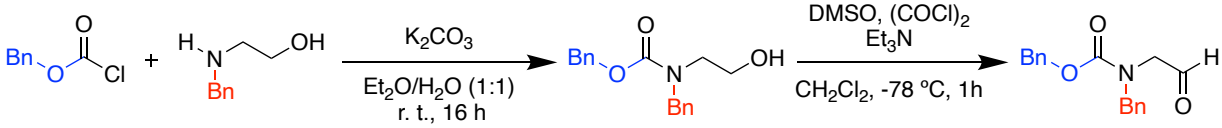
[a] Synthesised by Sean C O'Brien.

Scheme 2.15: Synthesis of α-*N*-amido aldehydes**.**



52v, 77% **53v**, 30%

Scheme 2.16: Synthesis of aldehyde **53v**.

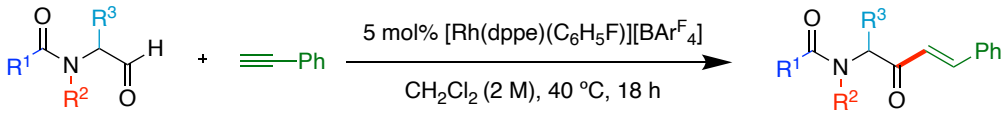


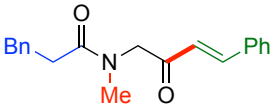
52ac, 28% **53ac**, 70%

Scheme 2.17: Synthesis of aldehyde **53ac**.

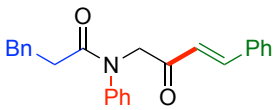
2.2.4 Reactivity of α-*N*-amido aldehyde substrates

Having established the robustness of the hydroacylation reaction towards the alkyne component, we next evaluated the scope of the aldehyde partner, in combination with phenylacetylene (**Scheme 2.18**). Variation of the *N*-substituent including methyl, phenyl and other alkyl group was well tolerated (**54s–u**). Pleasingly, an aldehyde featuring an N-H substituent reacted successfully, providing hydroacylation adduct **54v** in 80% yield and >20:1 linear selectivity. Variation of the α-substituent was then investigated; with benzyl, methyl and isobutyl substituted aldehydes worked well and delivering enones with excellent selectivities (**54w–y**). However, when the more sterically demanding isopropyl substituent was present in the α-position, the yield of the enone product **54z** decreased. Variation of the acyl moiety of the amido group gave mixed results; a benzylamide gave the desired product in high yield and excellent regioselectivity (**54aa**). In contrast, an acetylamide resulted in diminished yield (**54ab**). Use of a Cbz-carbamate, in place of an amide, delivered the corresponding ketone (**54ac**) in only 26% yield, and likely reflects the less Lewis basic nature of the group. The sterically demanding cyclohexyl amide was also a poor substrate, providing enone **54ad** in 28% yield when 10 mol% of catalyst was used. Alleviating potential allylic strain by replacing the N-Bn with a N-H group led to improved yields, with cyclohexyl amide-substituted enone **54ae** now produced in 44% yield.

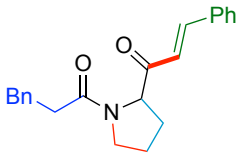




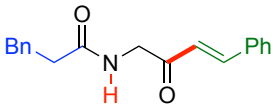
54s, 85%, >20:1 L:B



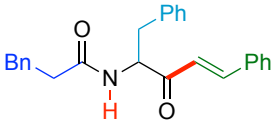
54t, 81%, >20:1 L:B



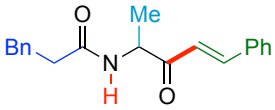
54u, 90%, >20:1 L:B



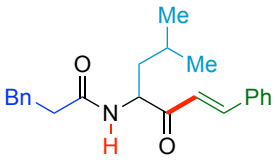
54v, 80%, >20:1 L:B



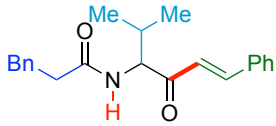
54w, 87%, >20:1 L:B



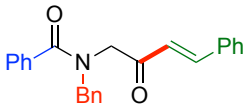
54x, 68%, >20:1 L:B



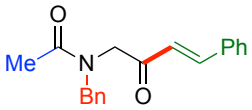
54y, 67%, >20:1 L:B



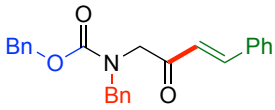
54z, 36%, >20:1 L:B



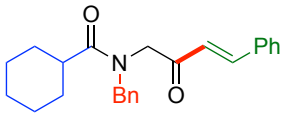
54aa, 84%, >20:1 L:B



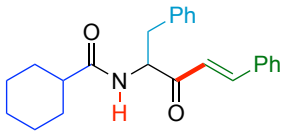
54ab, 46%, >20:1 L:B



54ac, 26%, >20:1 L:B



54ad, 28%[a], >20:1 L:B



54ae, 44%, >20:1 L:B

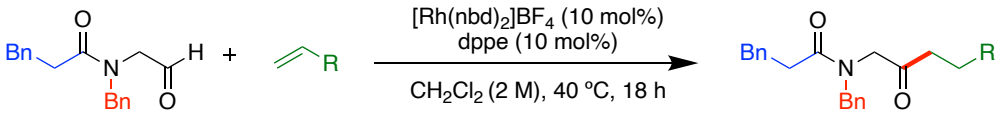
Reaction conditions: [Rh(dppe)(C_6H_5F)][BAr^F_4] (5 mol%), aldehyde (0.2 mmol, 1.0 equiv.), alkyne (1.2 equiv.), CH_2Cl_2 (2.0 M), 40 °C for 18 h. Linear to branched ratio (L:B) determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [a] Performed with 10 mol% of [Rh(dppe)(C_6H_5F)][BAr^F_4].

Scheme 2.18: Scope of α-*N*-amido aldehydes in hydroacylation of phenylacetylene.

2.3 Hydroacylation of alkenes with α-*N*-amido aldehydes

To extend the scope of the hydroacylation of α-*N*-amido aldehydes, we attempted the hydroacylation of alkenes (**Table 2.2**). Rhodium-catalysed alkene hydroacylation methods usually differ from their alkyne counterparts in that they are less reactive substrates. Alkenes often require activation,[137] higher catalyst loadings[44] or specific ligands.[78] We started our investigation with three electronically different terminal alkenes (1-octene, styrene and methyl acrylate), using a high catalyst loading of 10 mol%. Unfortunately, application of our optimal ligand failed to deliver the desired products for all three alkenes and consumption of aldehyde **53a** was not observed.

Table 2.2: Scope for hydroacylation of α-*N*-amido aldehyde **53a** and alkenes.



53a

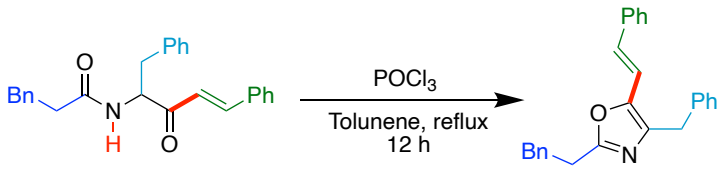
Entry	R	Conversion[a](%)
1	C_6H_{13}	0
2	Ph	0
3	CO_2Me	0

Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), dppe (10 mol%), aldehyde **53a** (0.2 mmol, 1.0 equiv.), alkene (1.2 equiv.), CH_2Cl_2 (2.0 M), 40 °C for 18 h. [a] Conversions determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.

Clearly, more investigation was required to identify an appropriate catalyst system through ligand evaluation. However, due to time constraints, further optimisation studies for the hydroacylation of alkenes substrates was suspended.

2.4 Product cyclisation to synthesise fully substituted oxazole

Having established a wide scope for both alkyne and α-*N*-amido aldehyde components, we next turned our attention to product derivatisation. To illustrate the synthetic utility of the products, we attempted to synthesise a fully substituted oxazole from hydroacylation product **54w** (**Scheme 2.19**). Using a literature procedure,[138] the desired cyclisation was achieved using $POCl_3$ in toluene under reflux conditions, producing oxazole **55** in excellent (92%) yield.



54w **55**, 92%

Reaction conditions: **54w** (0.26 mmol), $POCl_3$ (0.52 mmol) in toluene (2 mL) at reflux for 12 h.

Scheme 2.19. Synthesis of fully substituted oxazole.

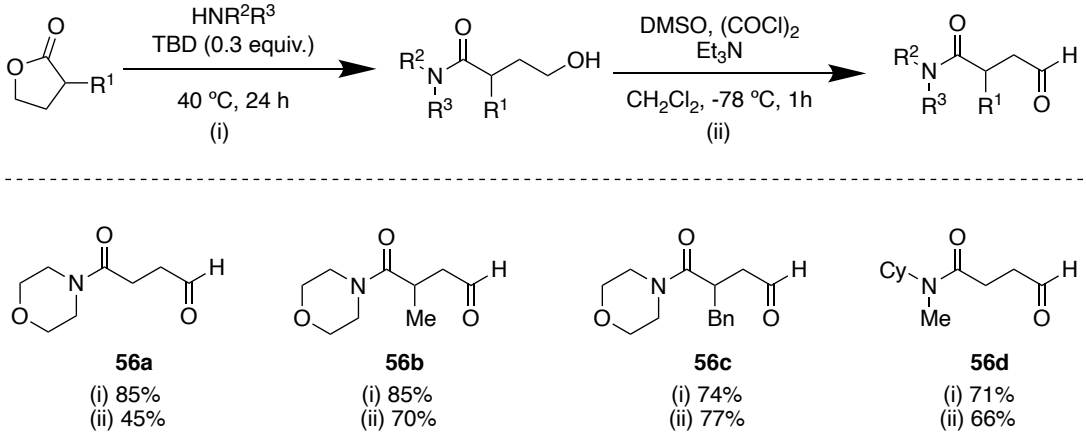
2.5 Intermolecular hydroacylation with γ-amido aldehydes

As discussed in the previous sections (**2.2.1–2.2.4**) of this chapter, α-*N*-amido aldehydes are effective substrates in alkyne hydroacylation. This suggests that 1,4 dicarbonyl motifs successfully stabilise a Rh-acyl-hydride intermediate through formation of a 6-membered metallocycle. In taking this concept forward, γ-amido aldehydes were synthesised to investigate the reactivity of this class of substrates in hydroacylation. This work was done in collaboration with a part II student Sean C. O'Brien.

2.5.1 Synthetic route to γ-amido aldehydes

We have developed a new synthetic route to γ-amido aldehydes involving two simple steps (**Scheme 2.20**). Following the procedure by Kleij,[139] γ-amido alcohols were synthesised in good yields (85-71%) *via* the ring opening of the γ-lactones (including α-substituted γ-lactones) with secondary amines catalysed by TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene). The

second step involved Swern oxidation of γ-amido alcohols and delivered the desired γ-amido aldehydes (**56a–d**) in reasonable yields.

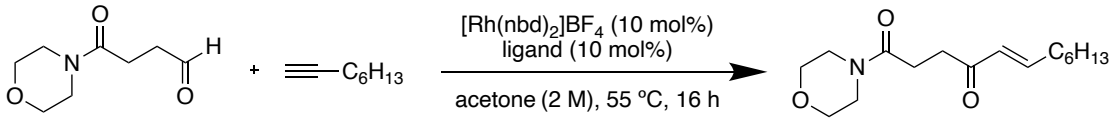


Scheme 2.20. Synthesis of γ-amido aldehydes by Sean C. O'Brien.

2.5.2 Reaction optimisation studies for hydroacylation of γ-amido aldehydes

Aldehyde **56a** and 1-octyne were chosen as model substrates for ligand optimisation because of their low steric demands and simple structures. Using 10 mol% of catalyst, a wide range of diphosphine ligands were evaluated. Disappointingly, only dppe and DPEphos gave yields above 10% (**Table 2.3, entries 1 and 9**) whereas all the other ligands very low yields as summarized in **Table 2.3**. Switching the solvent to DCE did not alter the result in the case of dppe (**entry 13**).

Table 2.3: Ligand screening for the hydroacylation of aldehyde **56a** with 1-octyne by Sean C. O'Brien.



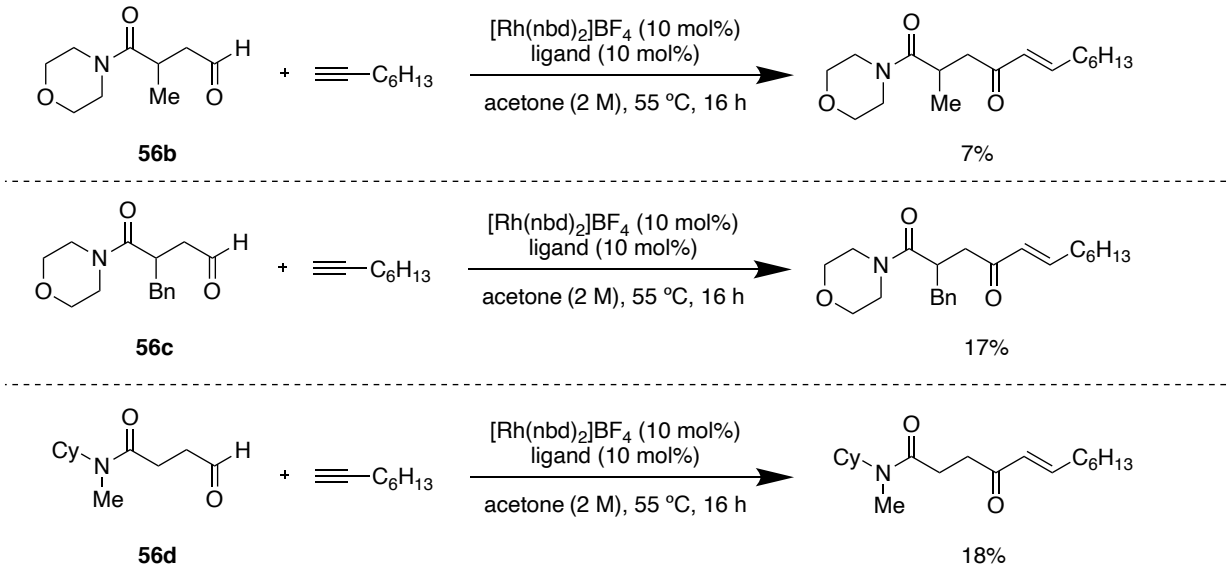
56a

Entry	Ligand	Yield of enone (%)	Decarbonylation[a] (%)
1	dppe	12	6
2	dcpe	2	17
3	dppm	5	5
4	dcpm	9	11
5	dppp	3	8
6	dppb	4	12
7	dfppe	4	9
8	dppf	5	14
9	DPEphos	18	17
10	Xantphos	3[b]	5
11	*t*-Bu-Xantphos	0	0
12	BINAP	7[c]	26
13[d]	dppe	15	5

Reaction Conditions: Aldehyde **56a** (0.20 mmol), 1-octyne (0.24 mmol), $[Rh(nbd)_2]BF_4$ (0.02 mmol), ligand (0.02 mmol), acetone (2 M with respect to the aldehyde), 55 °C, 16 h. [a] Determined by ^1H NMR spectroscopy of crude reaction mixtures using methyl 3,5-dinitrobenzoate as an internal standard. Unless otherwise stated, only the linear isomer is observed. [b] Only branched product observed. [c] L:B ratio of 1:2.5. [d] Reaction performed in 2M DCE.

In order to improve these results and hence generate a working system, substrate engineering was necessary. Aldehyde **56b** and **56c** containing methyl and benzyl substitution at β-position, respectively, and aldehyde **56d** were coupled with 1-octyne using dppe as a ligand.

Unfortunately, all of these substrates provided low yields (**Scheme 2.21**). Consequently, due to low reactivity of γ-amido aldehydes, no further optimisation was conducted.



Scheme 2.21. Hydroacylation of aldehyde **56b**, **56c** and **56d** with 1-octyne by Sean C. O'Brien.

As previously shown in **Section 2.1** (**Scheme 2.2**), the presence of a heteroatom instead of a sp^3 CH_2 centre at the β-position in γ-sulfur substituted aldehydes, significantly improved their reactivity in alkyne hydroacylation. This observation is in line with our experimental results with 1,4-dicarbonyl systems. α-*N*-Amido aldehydes containing a sp^2 nitrogen within the hydrocarbon chain react smoothly in alkyne hydroacylation reactions whereas, γ-amido aldehydes showed reduced reactivity. It is believed that the heteroatom promotes adoption of the reactive gauche conformation rather than the anti-conformation. Therefore, greater population of reactive conformation favours the formation of 6-membered metallocycle following oxidative addition.

2.6 Summary

In conclusion, we have developed the Rh(I)-catalysed hydroacylation of alkynes as a method to synthesise α-*N*-amido ketones. The use of α-*N*-amido aldehydes as substrates establishes

that 6-membered rhodacyclic intermediates provide suitable chelating stability, enabling productive hydroacylation. This robust method tolerates a wide range of functional groups, generating enones in good to excellent yields and high levels of regiocontrol. The use of preformed catalyst [Rh(dppe)(C_6H_5F)][BAr^F_4] was found to be crucial to achieving high reactivity and regioselectivity. A fully substituted oxazole has been synthesised in excellent yield from intramolecular cyclization of an α-*N*-amido enone product. Further development of a catalyst system is required for the use of alkene substrates. Despite attempts at optimisation, alkyne hydroacylation failed with γ-amido aldehydes substrates. It appears that, γ-amido aldehydes do not form the 6-membered metallocycle required for product formation.

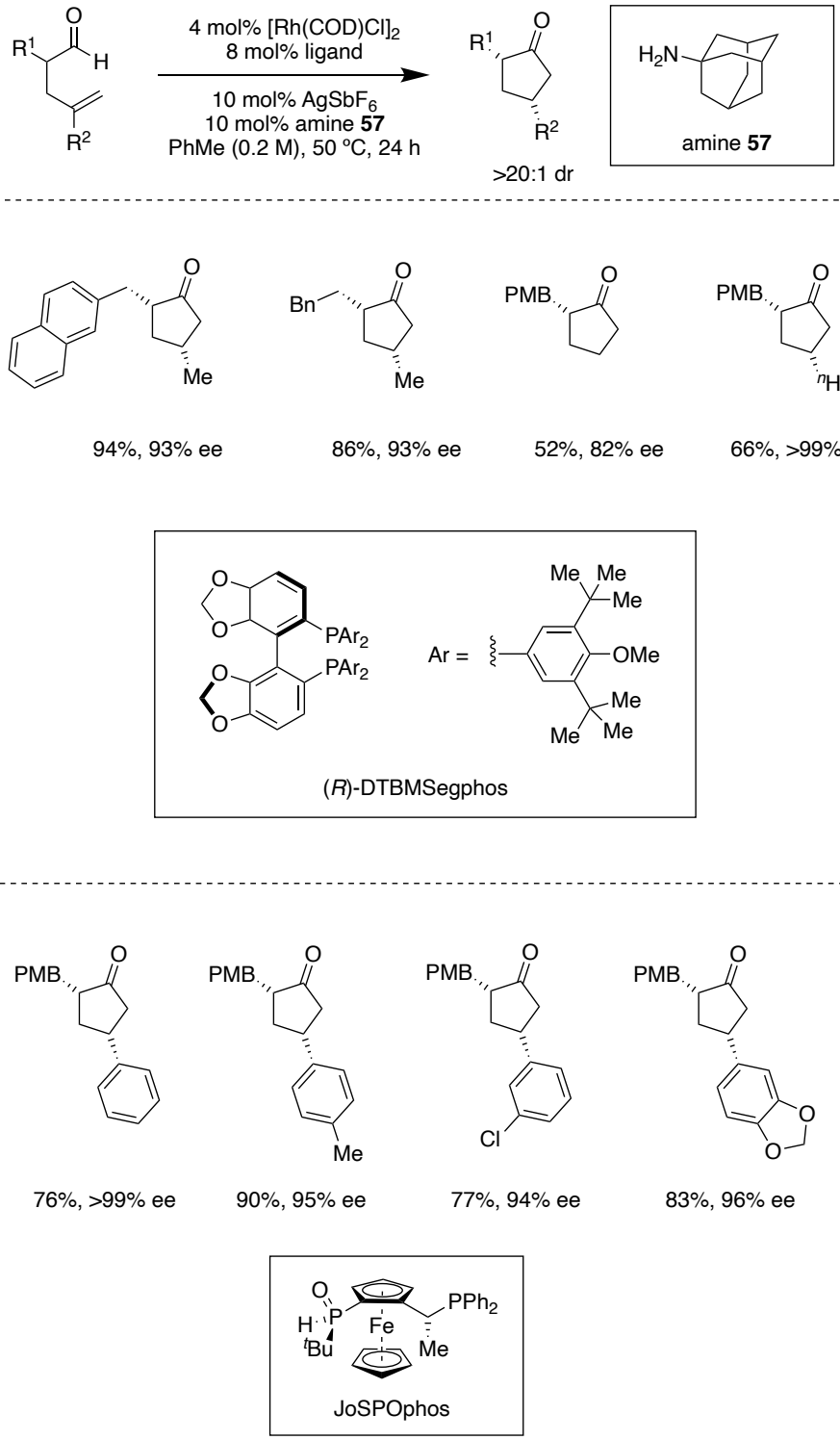
Chapter 3

Dynamic kinetic resolution in rhodium-catalysed alkyne hydroacylation

3.1 Introduction

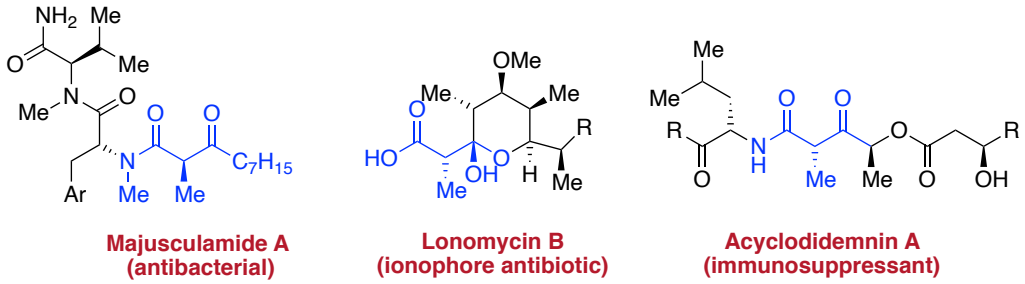
Chirality plays a vital role in drug design and therefore the synthesis of enantiomerically enriched compounds has become increasingly important due to their significant demand in pharmaceutical and agricultural industries. One of the most common methods to obtain enantiomerically pure compounds is *via* kinetic resolution. However, a major disadvantage of a kinetic resolution process is that a maximum 50% yield can be obtained, as only one enantiomer of the starting material is converted into product. Dynamic kinetic resolution (DKR) is a powerful alternative approach to asymmetric synthesis, whereby the interconversion of enantiomers of racemic starting materials possessing a stereochemically labile stereocenter allows for a theoretical yield up to 100%.

Significant advancements have been made in enantioselective hydroacylations using chiral transition metal complexes. However, DKR in Rh(I)-catalysed hydroacylation is comparatively rare. Recently, Dong and co-workers reported a DKR of chiral 4-pentenals by intramolecular olefin hydroacylation *via* dual catalysis (**Scheme 3.1**).[91] A sterically hindered primary amine **57** was used to racemise the substrates *via* enamine formation and hydrolysis. α,γ-Disubstituted cyclopentanones were synthesised with high enantio- and diastereoselectivities using chiral diphosphine ligands.



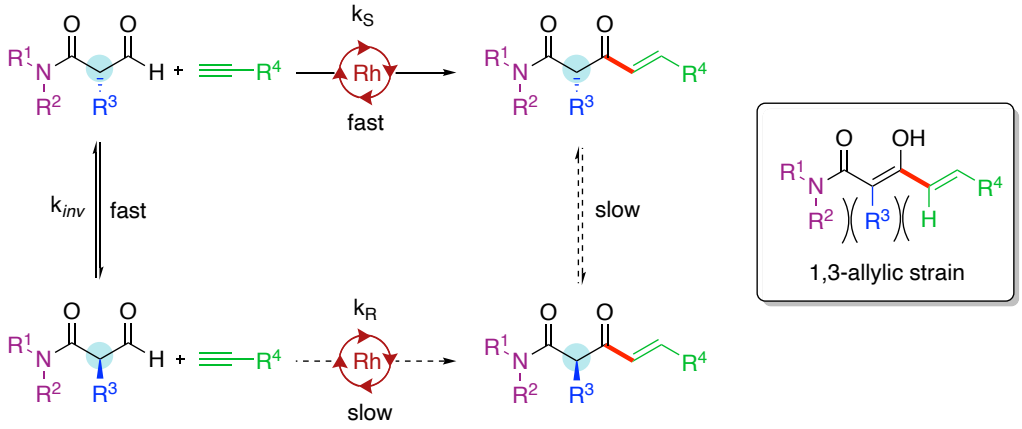
Scheme 3.1: Selected examples of Dong's intramolecular hydroacylation *via* DKR.

Encouraged by the excellent results in intermolecular hydroacylation reactions using *β*-amido aldehydes as substrates (**Chapter 2, Section 2.1, Scheme 2.1**),[105] we aimed to extend this method to access enantiomerically enriched 1,3-dicarbonyl compounds containing α-stereocentres *via* DKR. 1,3-Dicarbonyls with an α-stereocentre are an important class of compounds, broadly found in nature as components of complex natural products (**Scheme 3.2**).



Scheme 3.2: Examples of medicinally relevant compounds containing 1,3-dicarbonyl motif.

Development of a DKR process is challenging as both racemisation and resolution steps have to be carefully tuned. A successful DKR can only be achieved if the reaction rate of the fast reacting enantiomer is much greater than the reaction rate of slow reacting enantiomer i.e. $k_S >> k_R$. The rate of racemisation of the substrate enantiomers has to be at least equal to or greater than the reaction rate of the fast reacting enantiomer i.e. $k_{inv} \geq k_S$ (**Scheme 3.3**).



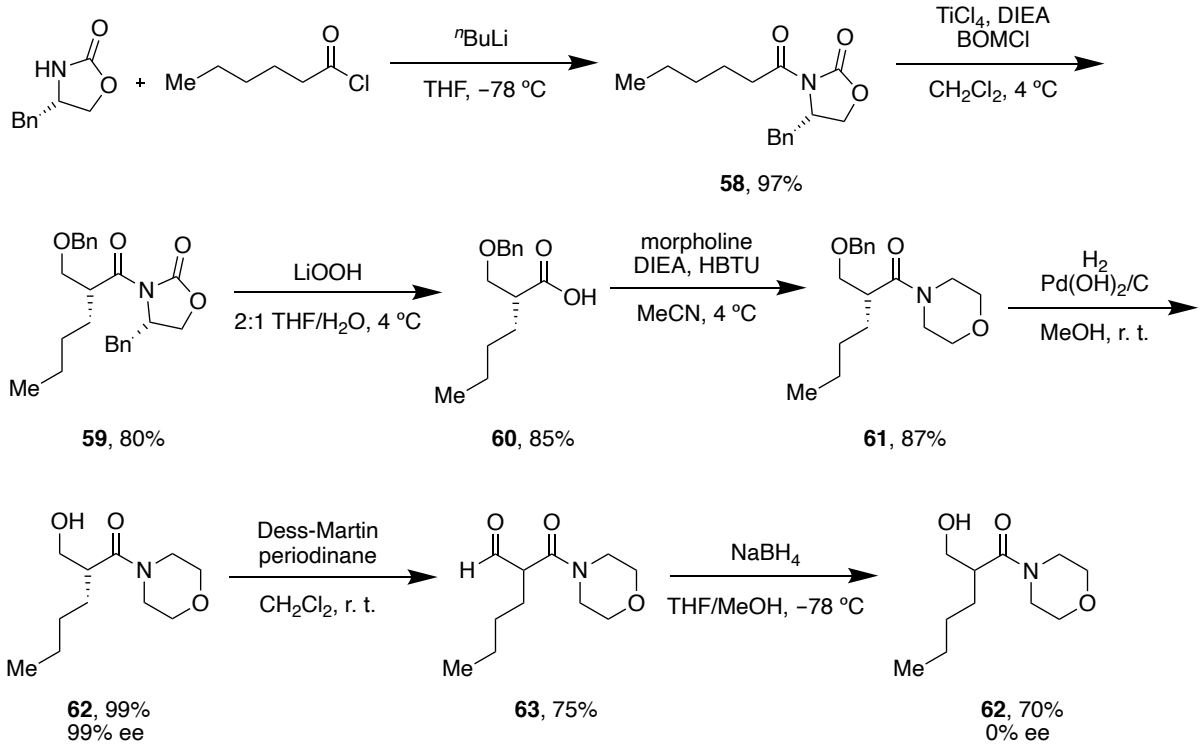
Scheme 3.3: Proposed dynamic kinetic resolution of β-amido aldehydes in alkyne hydroacylation.

We hypothesised that α-stereocentres of β-amido aldehydes would undergo rapid racemisation under hydroacylation conditions as a result of keto-enol tautomerisation. Therefore, (*R*)- and (*S*)-enantiomers of the starting material are able to interconvert throughout the reaction process. At this point, the catalyst, which is a combination of an enantiomerically enriched diphosphine ligand and cationic Rh, could selectively convert the fast reacting enantiomer of the substrate to the desired product. Importantly, racemisation of the product formed should be absent. In our case, we proposed that the rate of racemisation of the β-amido enone product would be slower compared to the aldehydes as the former would experience greater 1,3-allylic strain in the enol form as shown in **Scheme 3.3**.

3.2 Synthesis of enantiomerically enriched β-amido aldehyde

As described in section **3.1**, rapid rate of racemisation of the substrate is necessary for a successful DKR process. Therefore, synthesis of an enantioenriched β-amido aldehyde was attempted in order to study the racemisation. The six-step sequence (**Scheme 3.4**)[140] began with acylation of the lithium anion of the (*S*)-phenylalanine derived oxazolidinone with caproyl chloride to provide acyloxazolidinone **58** in 97% yield. Benzyloxymethylation of **58** provided

the benzyl ether, **59**, in 80% yield. Hydrolysis of **59** using 2 equiv. of lithium hydroperoxide at 4 °C produced carboxylic acid **60** in 85% yield which was then coupled with morpholine using HBTU in the presence of diisopropylethylamine to furnish **61** in 87% yield. Hydrogenolysis of the benzyl group was accomplished using Pearlman's catalyst and produced the primary alcohol, **62**, in 99% yield. The enantiomeric excess of this alcohol was determined to be 99% using chiral HPLC. The final oxidation step was performed using Dess-Martin periodinane, providing the desired aldehyde **63** in 75% yield. The aldehyde was subsequently reduced with $NaBH_4$ at –78 °C to the primary alcohol **62** in order to measure the enantiomeric excess, however, it was found to be racemic. It remains unclear if the racemisation happened in the oxidation, on standing, or in the reduction.



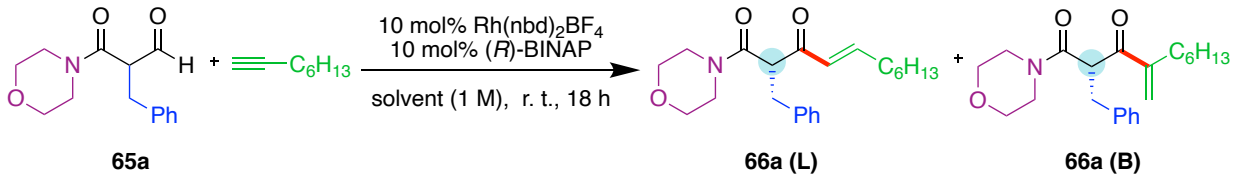
Scheme 3.4: Attempt to the synthesis of enantiomerically enriched β-amido aldehyde **63**.

3.3 Reaction optimisation for DKR of β-amido aldehydes

3.3.1 Effects of solvent on enantioselective alkyne hydroacylation

Racemic β-amido aldehyde **65a** and 1-octyne were chosen for initial optimisation of the enantioselective hydroacylation. Solvent evaluation was performed using 10 mol% of $[Rh(nbd)_2]BF_4$ and commercially available (*R*)-BINAP ligand, which is widely used in asymmetric transformations. Previously, racemic products were obtained at 55 ºC (**Chapter 2, Section 2.1, Scheme 2.1**), however, we decided to investigate the effect of solvents at room temperature as racemisation of the desired chiral product should be less favoured at lower temperature. CH_2Cl_2 was found to be the optimal solvent, providing products in 83:17 er with high regioselectivity (**entry 8**). All other solvents screened resulted in moderate enantioselectivity achieved in comparable yields (**entries 1, 3-7, 9**), whereas a toluene/CH_2Cl_2 (1:1) mixture furnished the enone product in 76% yield (**entry 9**). No reactivity was observed when MeCN was used as solvent (**entry 2**). It is believed that MeCN forms inactive catalyst species by strongly co-ordinating to the rhodium centre.

Table 3.1: Solvent screening in enantioselective hydroacylation of β-amido aldehyde **65a** and 1-octyne.

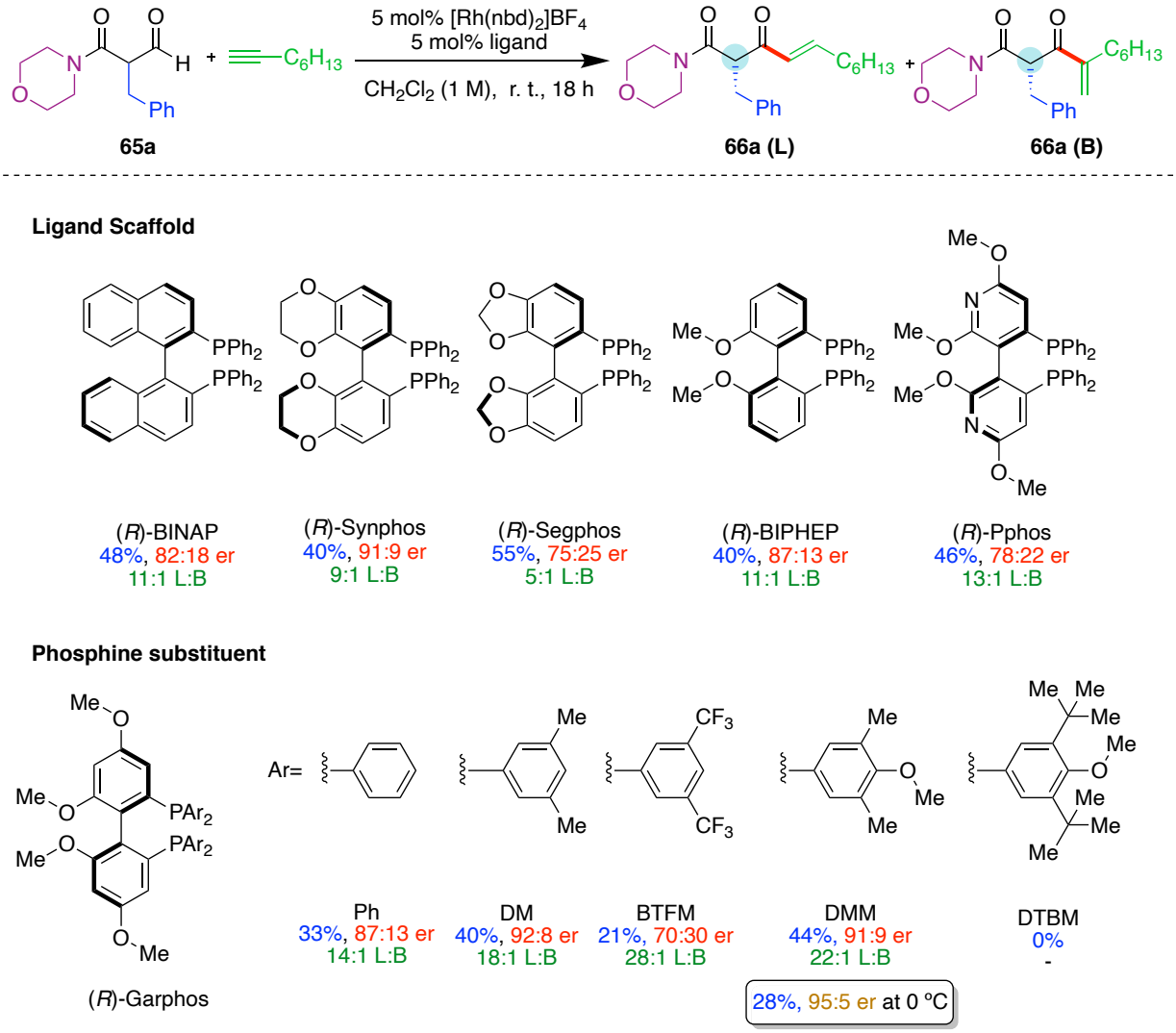


Entry	Solvent	NMR yield[a]	er[b]	L:B[a]
1	THF	68%	73:27	6:1
2	MeCN	0%	-	-
3	1,2-difluorobenzene	61%	73:27	15:1
4	1, 4-dioxane/CH_2Cl_2 (1:1)	44%	73:27	5:1
5	benzene	67%	73:27	4:1
6	acetone	66%	73:27	7:1
7	toluene/acetone (1:1)	66%	73:27	7:1
8	CH_2Cl_2	60%	83:17	14:1
9	toluene/CH_2Cl_2 (1:1)	76%	73:27	8:1

Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), (*R*)-BINAP (10 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), solvent (1.0 M), r. t. for 18 h. [a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as a standard. [b] Enantiomeric ratios are determined by chiral HPLC.

3.3.2 Ligand effects on enantioselective alkyne hydroacylation

Following solvent screening, β-amido aldehyde **65a** and 1-octyne were coupled using 5 mol% of $[Rh(nbd)_2]BF_4$ and various chiral diphosphine ligands at room temperature in CH_2Cl_2 for 18 hours. An evaluation of chiral diphosphine ligands revealed that C_2-symmetric atropisomeric diphosphines are highly effective for enantioselectivity. At first, different biaryl diphosphines bearing Ph-phosphine substituents (BINAP, Synphos, Segphos, BIPHEP, Pphos, Garphos) were explored (**Scheme 3.5,** ligand scaffold). The highest enantioselectivity was obtained using a Synphos ligand. As other variants of Synphos are not commercially available, Garphos ligands containing different aryl groups on phosphorous were evaluated to study the effect of phosphine substituents on enantioselectivity (**Scheme 3.5**, phosphine substituent). The presence of a bulkier xylyl substituent (DMGarphos) led to a significant increase in the enantiomeric ratio. The electron-deficient *bis*-trifluoromethyl analogue (BTFMGarphos) decreased both the reactivity and enantioselectivity, whereas an electron-rich aryl substituent on phosphorous (DMMGarphos) provided high enantioselectivity and regioselectivity (22:1 L:B). When the reaction using DMMGarphos was performed at lower temperature (0 ºC), excellent enantioselectivity (95:5 er) was observed, however, reactivity was significantly reduced. Consumption of the aldehyde was not observed when DTBMGarphos, possessing the bulkiest substituents, was used in hydroacylation. Therefore, DMMGarphos was found to be the most promising candidate for further optimisation as it delivered the highest enantio- and regioselectivity.



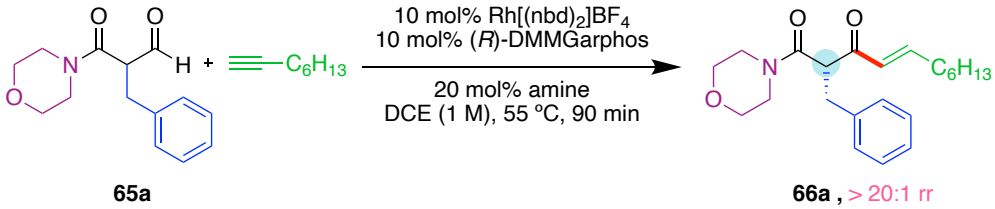
Reaction conditions: $[Rh(nbd)_2]BF_4$ (5 mol%), ligand (5 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), CH_2Cl_2 (1.0 M), r. t. for 18 h. NMR yields and L:B ratios are determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as a standard. Enantiomeric ratios are determined by chiral HPLC.

Scheme 3.5: Evaluation of chiral diphosphine ligands in enantioselective hydroacylation of **65a** and 1-octyne.

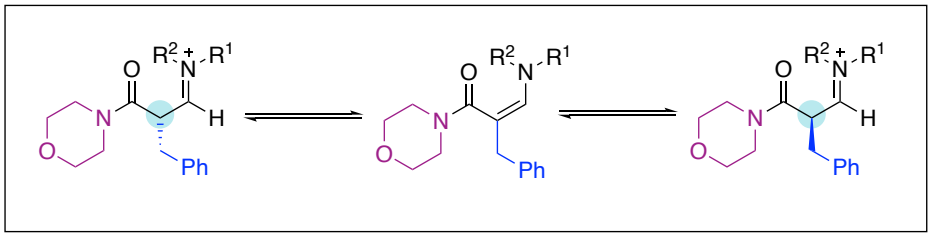
3.3.3 Effect of additives on enantioselective alkyne hydroacylation

Although we had developed a highly enantioselective transformation using DMMGarphos as ligand, however, the yield of the reaction was still low (<50%). The unreacted substrate was reduced to the corresponding alcohol using $NaBH_4$ at 0 ºC and found to have moderate enantiomeric excess. This indicated that rate of racemisation of the substrate was not fast enough and it was likely that only a kinetic resolution was taking place. Increased catalyst loading and temperature (10 mol% $[Rh(nbd)_2]BF_4$ and DMMGarphos at 55 ºC in DCE) resulted in 65% yield, however, the enantioselectivity was lower (**Table 3.2, entry 1**). Therefore, we explored the use of additives to promote interconversion of the substrate enantiomers to enable a DKR process to occur. It is well documented that aldehydes form imines when combined with amines. We hypothesised that faster racemisation of the substrate could be achieved *via* tautomerisation of an *in situ* generated imine/iminium to the corresponding enamine. We began with adding 20 mol% of secondary amines in presence of 10 mol% $[Rh(nbd)_2]BF_4$ and DMMGarphos at 55 ºC in DCE. Pleasingly, 4-methoxy-*N*-methylaniline (**entry 2**) provided the desired product in 70% yield and 90:10 er. 3-Methoxy-*N*-methylaniline and *N*-methylaniline (**entries 3 and 4**) also provided similar yields, however, lower enantioselectivity was observed. Cyclic amines (**entries 5 and 6**), tertiary amines (**entry 7 and 8**, noting that imine formation is not possible) and a sterically hindered primary amine (**entry 9**) failed to improve reactivity or enantioselectivity.

Table 3.2: Effect of amines in enantioselective hydroacylation of β-amido aldehyde **65a** and 1-octyne.



65a **66a** , > 20:1 rr

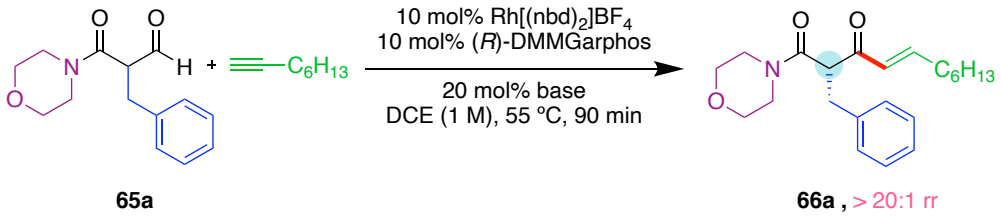


Entry	Amine	NMR yield[a]	er[b]
1	-	65%	87:13
2	4-methoxy-*N*-methylaniline	70%	90:10
3[c]	3-methoxy-*N*-methylaniline	68%	87:13
4[c]	*N*-methylaniline	70%	86:14
5[c]	pyrrolidine	65%	72:28
6	morpholine	23%	89:11
7	*N*, *N*-diisopropylethylamine	20%	88:12
8	triethylamine	41%	89:11
9	2,6-diisopropylaniline	54%	89:11

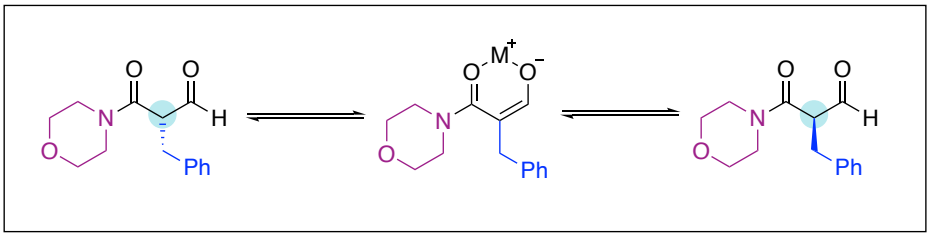
Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), (*R*)-DMMGarphos (10 mol%), amine (20 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), DCE (1.0 M), 55 ºC for 90 min. [a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as a standard. [b] Enantiomeric ratios are determined by chiral HPLC. [c] Reactions performed at r. t. for 18 h.

In an alternative approach, the addition of inorganic bases in the enantioselective hydroacylation of β-amido aldehyde **65a** was examined (**Table 3.3**). Our aim was to racemise the substrate *via* keto-enolate equilibrium. Use of $NaHCO_3$ resulted in a moderate yield with 90:10 er (**entry 1**). An improved yield was obtained when K_2CO_3 was used, however, a decrease in the enantioselectivity was observed (**entry 2**). Interestingly, complete racemisation of the product was observed when Cs_2CO_3 was used (**entry 3**). The faster racemisation of both the substrate and the product may be due to the greater solubility of Cs_2CO_3 in organic solvents. Therefore, reactions were performed for shorter periods of time (**entries 4-6**). Pleasingly, optimal conditions were obtained when the reaction was performed for 10 minutes, providing enone **66a** in 76% yield and 91:9 er (**entry 6**).

Table 3.3: Effect of bases in enantioselective hydroacylation of β-amido aldehyde **65a** and 1-octyne.



65a **66a** , > 20:1 rr

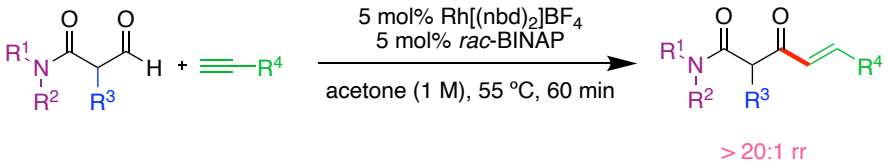


Entry	Base	NMR yield[a]	er[b]
1	$NaHCO_3$	46%	90:10
2	K_2CO_3	64%	83:17
3	Cs_2CO_3	75%	50:50
4	Cs_2CO_3 (15 min)	77%	82:18
5	Cs_2CO_3 (7 min)	68%	92:8
6	Cs_2CO_3 (10 min)	76%	91:9

Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), (*R*)-DMMGarphos (10 mol%), base (20 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), DCE (1.0 M), 55 °C for 90 min. [a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as a standard. [b] Enantiomeric ratios are determined by chiral HPLC.

3.4 Alkyne scope in enantioselective hydroacylation

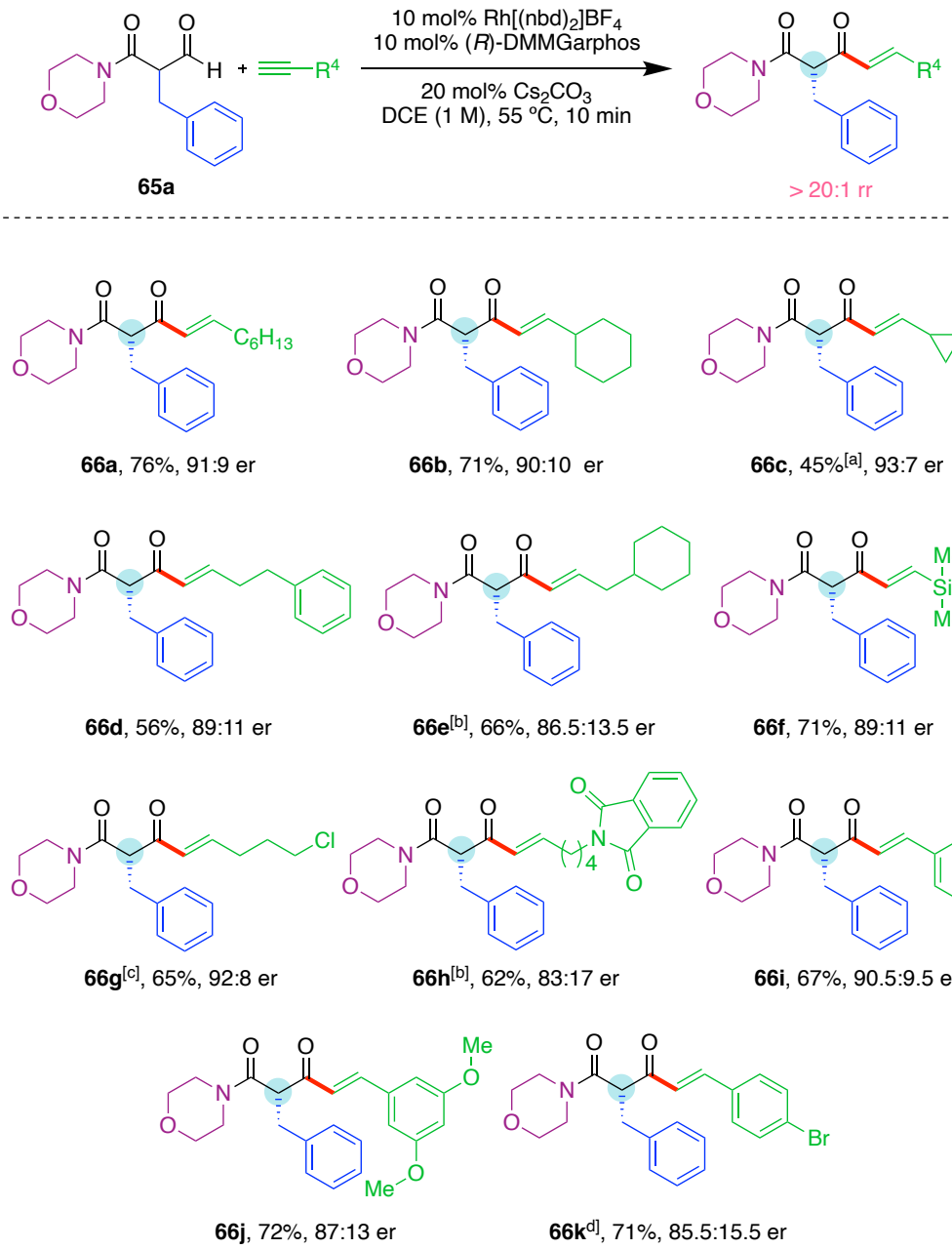
With the optimal reaction conditions in hand, we next investigated the scope of the reaction with respect to the alkyne component using aldehyde **65a** (Scheme X). Racemic products were prepared using a modified procedure developed by the Willis group,[105] 5 mol% of $[Rh(nbd)_2]BF_4$ and *rac*-BINAP were used and the reactions were performed in acetone at 55 ºC without addition of base (**Scheme 3.6**).



Scheme 3.6: The racemic version of Rh-catalysed hydroacylation of β-amido aldehydes.

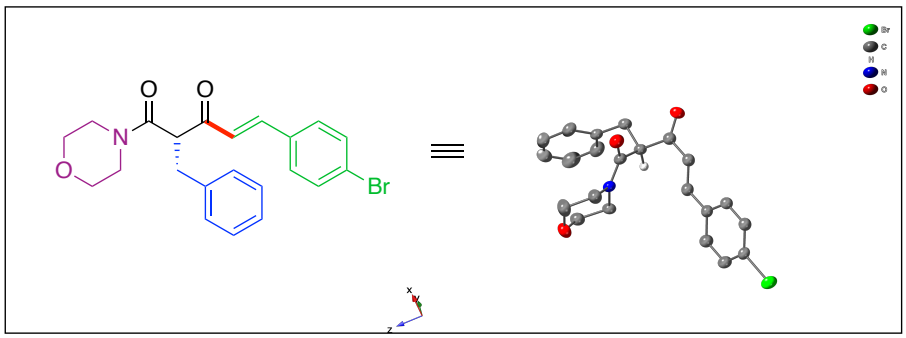
Under the optimised conditions developed in **Section 3.3.3** (**Table 3.3, entry 6**), a series of cyclic and acyclic alkyl substituted alkynes reacted successfully with aldehyde **65a**, providing the desired enones (**66a, b, d, e**) in high enantioselectivity and good yields. However, cyclopropyl substituted alkyne, which had previously proved to be a challenging substrate in racemic or achiral hydroacylation reactions, gave only moderate yield (**66c**, 45%) with high levels of stereoselectivity (93:7 er). The sterically demanding, trimethylsilyl substituted alkyne, was also well tolerated (**66f**). An alkyne containing a heteroatom functionality (chloride) was also incorporated to deliver enone **66g** with high enantioselectivity (92:8 er). A phthalimide moiety was also tolerated in the reaction, however, the enantiomeric ratio was lower (**66h**). Phenylacetylene was successfully employed (**66i**, 67% yield and 90.5:9.5 er), with other aryl alkynes featuring electron-withdrawing groups reacting in a similar manner (**66j and 66k**). An X-ray diffraction study of amide **66k** was carried out to determine the absolute

stereochemistry of the product as (*S*) (**Scheme 3.8**). The X-ray crystallography analysis was performed by Dr Alasdair I. McKay.



Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), (*R*)-DMMGarphos (10 mol%), Cs_2CO_3 (20 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), DCE (1.0 M), 55 ºC for 10 min. Enantiomeric ratios are determined by chiral HPLC. [a] Aldehyde **65a** (0.3 mmol) was used. [b] Reaction time was 8 min. [c] Aldehyde **65a** (0.3 mmol) was used and reaction time was 15 min. [d] Without addition of Cs_2CO_3.

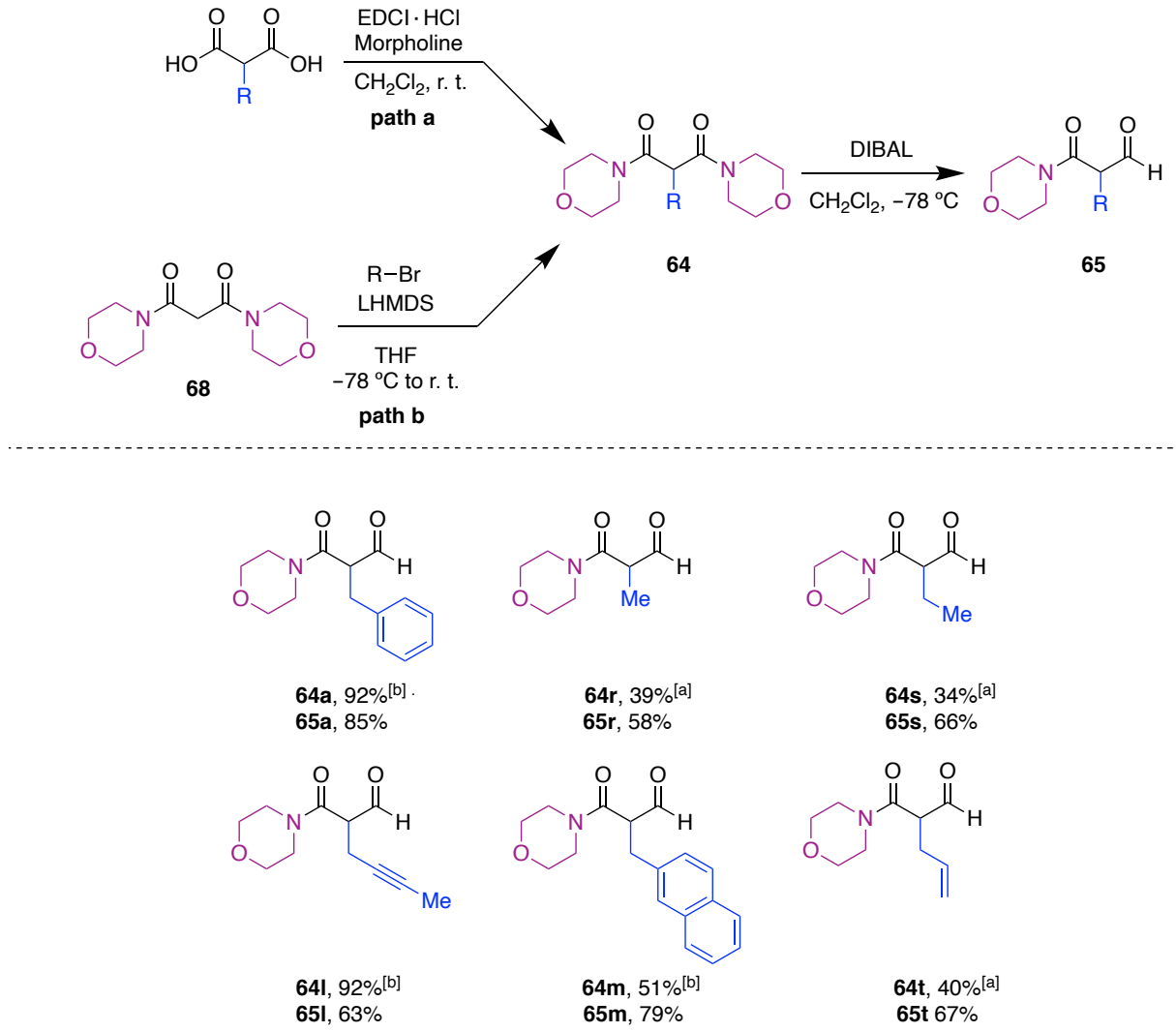
Scheme 3.7: Alkyne scope in Rh-catalysed hydroacylation of β-amido aldehyde **65a**.



Scheme 3.8: Determination of absolute configuration using X-ray diffraction study.

3.5 Synthetic route to racemic β-amido aldehydes

Due to the requirement of high purity substrates in order to obtain high catalytic activity, we designed a new synthetic route to the aldehyde substrates. Starting from commercially available monosubstituted malonic acids and morpholine, α-substituted bisamides were easily prepared *via* amide coupling in moderate yields (**Scheme 3.9, 64r, s and t**). Other bisamides (**64a, l and m**) were synthesised from **68** by simple monoalkylation using LHMDS and the corresponding alkyl bromide in excellent to good yields. In the final step of the synthesis, one of the amide functionalities in the symmetric bisamide was reduced selectively to an aldehyde using one equivalent of DIBAL in CH_2Cl_2 at –78 ºC. Excellent to good yields were achieved using this route for aldehydes with different groups at the α-position (**65a, r–t, l, m**).

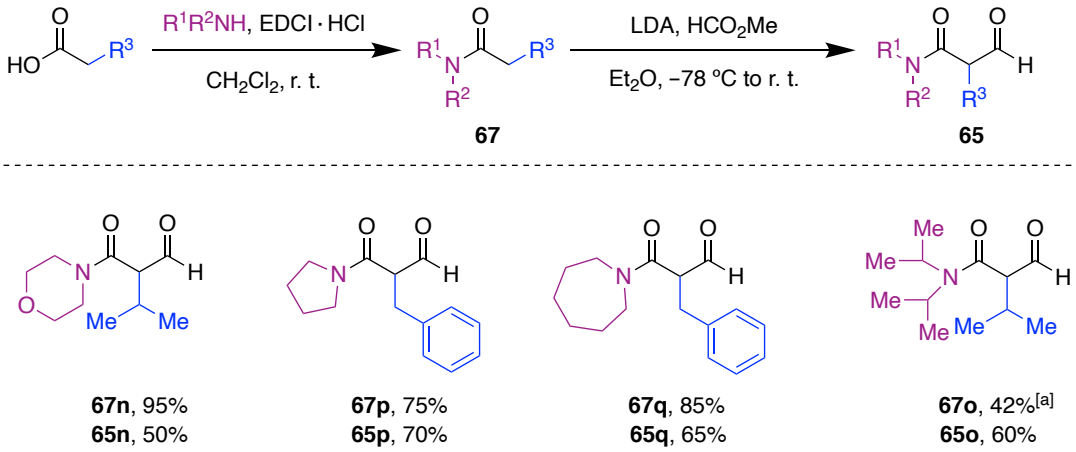


[a] Synthesised using path a. [b] Synthesised using path b.

Scheme 3.9: Synthetic route to racemic β-amido aldehydes.

Unfortunately, amide coupling of isopropylmalonic acid resulted in poor yields due to the presence of sterically bulky substitution at the α-position. Similarly, attempts to synthesise a variety of amides by coupling different amines to benzylmalonic acid also failed and decarboxylation of the malonic acid was observed. An alternative approach was taken for the synthesis of isopropyl substituted amido aldehyde **65n** and aldehydes with varying amine substituents (**65p, q, o**) (**Scheme 3.10**). Using a literature procedure reported by the Johnson group,[141] amides were synthesised first *via* amide coupling from corresponding carboxylic acids and amines in excellent to good yields (**67n, p, q, o**). This was followed by deprotonation

of the α-carbon atom of the corresponding amide with freshly prepared lithium diisopropylamide (LDA) and subsequent formylation with methyl formate to provide aldehydes in moderate yields (**65n, p, q, o**). However, as observed by the authors, the reaction was not reproducible in many cases and purification of the aldehydes proved challenging.



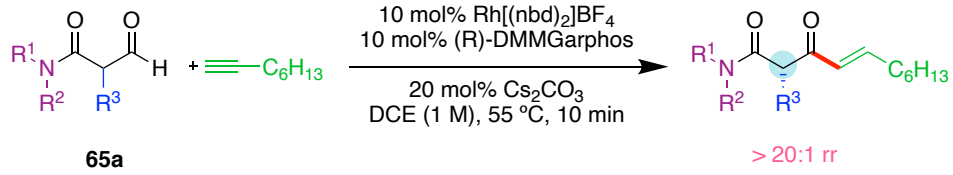
[a] *N*-methyl-2-chloropyridinium iodide was used as coupling reagent.

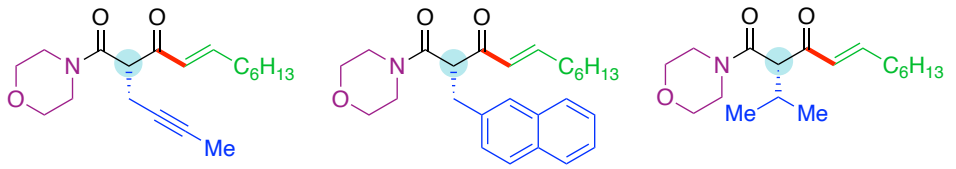
Scheme 3.10: Synthesis of racemic β-amido aldehydes using Johnson's method.

3.6 Aldehyde scope in enantioselective hydroacylation

Having established robust methods for the synthesis of aldehyde substrates, we explored the scope of the enantioselective hydroacylation reaction using 1-octyne as the coupling partner (**Scheme 3.11**). Interestingly, an aldehyde containing an internal alkyne at the α-position, **65l**, reacted smoothly with the terminal alkyne, 1-octyne, in an intermolecular fashion to provide the desired product **66l**, with no intramolecular product observed. 2-Naphthylmethyl substituent at the α-position was also well tolerated and high levels of enantioselectivity were retained (**66m**). When a sterically demanding α-isopropyl substituent was used, a significant decrease in reaction yield was observed, albeit with comparable er (**66n**). An α-isopropyl substituted aldehyde with sterically bulky diisopropyl amide also provided lower yield (46%);

however, excellent enantioselectivity (>99:1 er) was obtained (**66o**). Use of 5-membered and 7-membered cyclic amides provided good yields with good level of enantiocontrol (**66p, q**). When aldehydes containing methyl, ethyl and allyl group at the α-position were employed, the desired reactivity was not observed (**66r–t**). The reason for this was attributed to the smaller size of the substituents and it was postulated that aldehydes existed predominantly in the enolate form in presence of base.

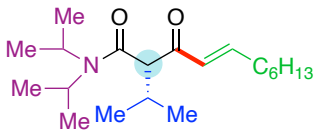




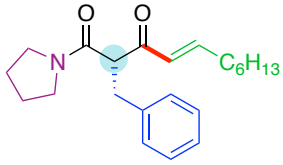
66l, 65%, 86:14 er

66m, 66%, 87:13 er

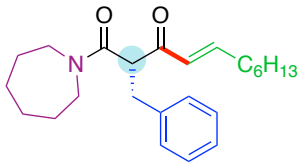
66n,40%, 87:13 er



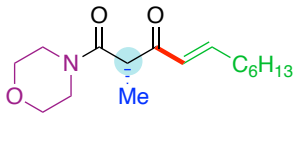
66o, 46%, >99:1 er



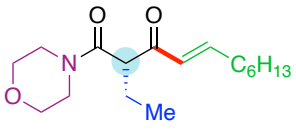
66p, 68%, 90:10 er



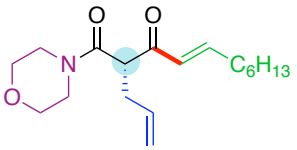
66q, 60%, 85:15 er



66r, >5%



66s, >5%



66t, 0%

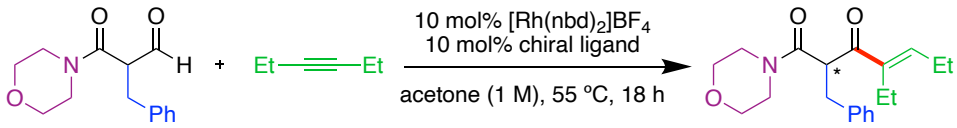
Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), (*R*)-DMMGarphos (10 mol%), Cs_2CO_3 (20 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), 1-octyne (1.2 equiv.), DCE (1.0 M), 55 ºC for 10 min. Enantiomeric ratios are determined by chiral HPLC.

Scheme 3.11: Aldehyde scope in Rh-catalysed hydroacylation with 1-octyne.

3.7 Enantioselective hydroacylation of internal alkynes

In an effort to extend the scope of enantioselective hydroacylation, we investigated the use of internal alkynes. When a symmetrical internal alkyne was tested in the hydroacylation with aldehyde **65a** (**Table 3.4**), none of the diphosphine ligands examined previously provided satisfactory enantiocontrol, although high levels of conversion were observed (**entries 1–4**). Thus, further optimisation was required. Unfortunately, time constraints meant that this was not possible.

Table 3.4: Attempts for the synthesis of enantiomerically enriched 1,3-dicarbonyls using internal alkynes.



65a **69**

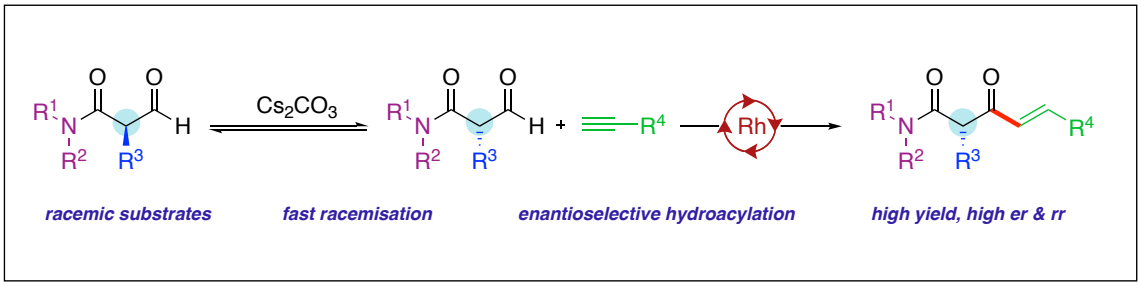
Entry	Ligand	Conversion[a]	ee[b]
1	(*R*)-SynPhos	100%	15%
2	(*R*)-BINAP	100%	5%
3	(*R*)-SegPhos	70%	11%
4	(*R*)-PPhos	90%	7%

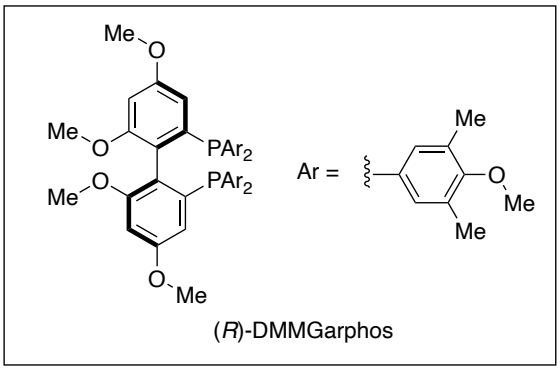
Reaction conditions: $[Rh(nbd)_2]BF_4$ (10 mol%), chiral ligand (10 mol%), aldehyde **65a** (0.2 mmol, 1.0 equiv.), hex-3-yne (1.2 equiv.), acetone (1.0 M), 55 °C for 18 h. [a] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture [b] Determined by chiral HPLC.

3.8 Summary

A successful DKR has been developed using β-amido aldehydes containing α-stereocentres which undergo rapid racemisation under hydroacylation conditions to give enantiomerically

enriched 1,3-dicarbonyl products. This is a direct catalytic route to enantiomerically enriched β-amido ketones which are an important class of chiral building block, broadly found in nature as components of complex natural products. To the best of our knowledge, this is the first example of a DKR in intermolecular hydroacylation. Rh-catalysed alkyne hydroacylation occurs in a highly enantioselective fashion with good yields and high regiocontrol. The catalyst system, which is a combination of commercially available (*R*)-DMMGarphos and cationic Rh, converts the (*S*)-enantiomer of the substrate to the desired product and Cs_2CO_3 helps in fast conversion of the (*R*)-enantiomer to (*S*)-enantiomer of the substrate in the reaction. We have also designed a new synthetic route to access α-substituted β-amido aldehydes in excellent to good yields. Despite attempts, enantioselective hydroacylation of internal alkynes proved elusive.



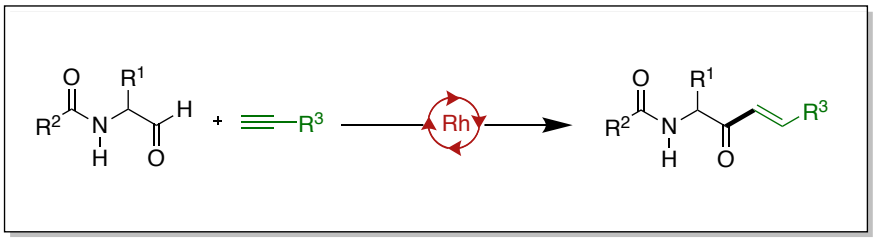


Chapter 4

Conclusions and future work

This thesis has described the development made in the field of chelate-controlled Rh-catalysed hydroacylation. The development of dynamic kinetic resolution in hydroacylation using simple readily available starting materials has been shown.

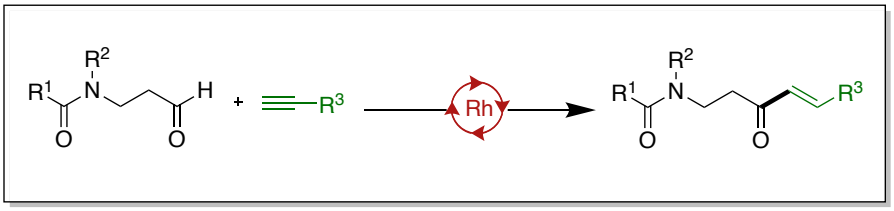
In the first project, we have presented developments of the Rh(I)-catalysed hydroacylation of alkynes as a method to synthesise α-*N*-amido ketones (**Scheme 4.1**). The use of α-*N*-amido aldehydes as substrates establishes that 1,4-dicarbonyl motifs can be used as controlling groups in Rh-catalysed hydroacylation reactions. This robust method tolerates a wide range of functional groups to form enones in good to excellent yields with generally high levels of regiocontrol. The use of preformed catalyst [Rh(dppe)(C_6H_5F)][BAr^F_4] was found to be crucial to achieve high reactivity and regioselectivity. To illustrate the synthetic utility of the products, we have also shown preparation of fully substituted oxazole from a hydroacylation product.



Scheme 4.1: Synthesis of α-*N*-amido ketones using Rh-catalysed hydroacylation.

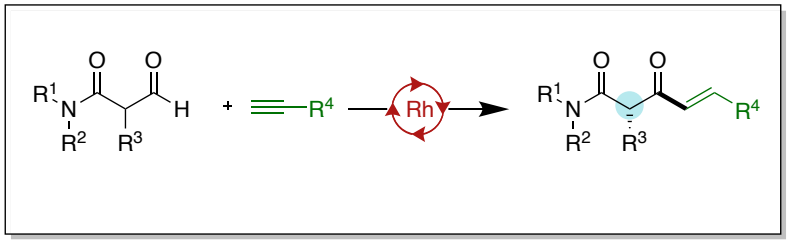
Future work includes the extension of carbonyl chelation strategy for the synthesis of 1,5-dicarbonyl systems (**Scheme 4.2**). The success of 1,4-dicarbonyl systems should be taken a further step by incorporating an additional carbon atom between aldehyde and amide functional

groups to give a 1,5-dicarbonyl system. β-*N*-Amido aldehydes can be easily made starting from a longer chain amino alcohol. Hydroacylation of alkenes or alkynes using those substrates would require formation of a 7-membered chelate formation which is very rare, and this will broaden the synthetic utility even further.



Scheme 4.2: 1,5-dicarbonyl compounds as potential substrates in Rh-catalysed hydroacylation.

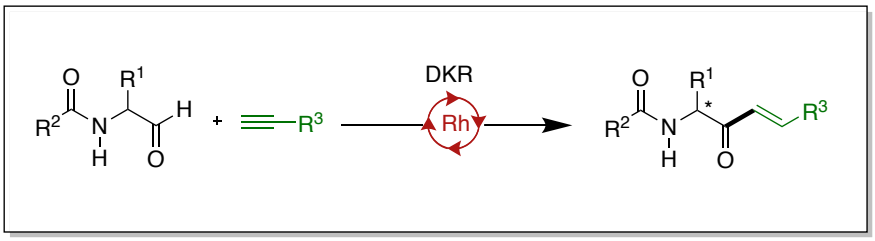
In the second project, we have described a successful dynamic kinetic resolution of β-amido aldehydes containing α-stereocentres, which undergo rapid racemisation in presence of Cs_2CO_3 (**Scheme 4.3**). The catalyst system, Rh(I)-(*R*)-DMMGarphos converts fast reacting substrate enantiomers to the desired products with high level of enantiocontrol. Rh-catalysed alkyne hydroacylation occurs with good yields and high regiocontrol to provide enantiomerically enriched 1,3-dicarbonyl products. To the best our knowledge, this is the first example of a DKR in intermolecular hydroacylation.



Scheme 4.3: Dynamic kinetic resolution of β-amido aldehydes in Rh-catalysed hydroacylation.

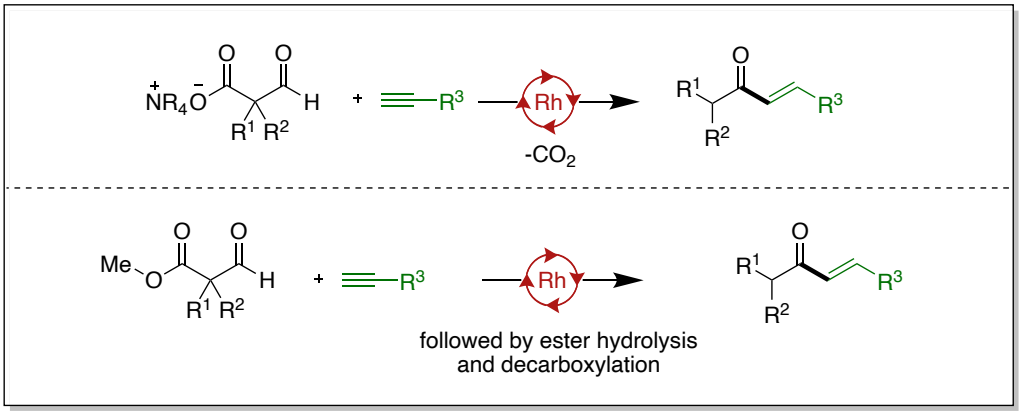
In similar way, a dynamic kinetic resolution with α-*N*-amido aldehyde substrates could be developed using chiral Rh-catalyst (**Scheme 4.4**). Therefore, the future work should explore

the possibility of developing a method to produce enantiomerically enriched α-*N*-amido ketones which are are present in many biologically relevant molecules.



Scheme 4.4: Possible dynamic kinetic resolution of α-*N*-amido aldehydes in Rh-catalysed hydroacylation.

Given the success of Rh-catalysed hydroacylation using β-amido aldehydes, it is proposed that a traceless-tethered process can be developed using β-formyl carboxylates (**Scheme 4.5**). The removal of the carboxylate group can be easily achieved following hydroacylation. However, synthesis of the substrates can be challenging as β-formyl carboxylates are prone to decarboxylation. In that case, one pot synthetic route can also be designed to achieve a traceless-tethered process using β-formyl esters. Following the hydroacylation of β-formyl esters, the ester group can be removed *via* decarboxylation in the same pot.



Scheme 4.5: Investigation of traceless-tethered processes in Rh-catalysed hydroacylation reactions.

Chapter 5

Experimental data and procedures

5.1 General considerations

Reactions were performed under inert atmosphere of nitrogen gas with anhydrous solvent unless otherwise stated. All glassware was oven dried at >80 °C, and allowed to cool to room temperature under a nitrogen argon pressure. Reactions were monitored by TLC until deemed complete using aluminum backed silica plates. Plates were visualized under ultraviolet light and/or by staining with vanillin or $KMnO_4$ stains.[142]

Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd., Alfa Aesar or Fluorochem Ltd. and used as supplied, with the exception of alkynes for use in rhodium-catalysed reactions, which were distilled before use. Dry CH_2Cl_2 was obtained by passing through anhydrous alumina columns using the Innovative Technology Inc. PS-400-7 solvent purification system, followed by degassing. Dry 1,2-Dichloroethane (DCE) and acetone, for use in rhodium reactions, distilled over Drierite® and degassed prior to use. Petrol refers to the fraction of light petroleum ether, boiling in the range 40-60 °C. Flash chromatography was carried out using matrix 60 silica. $[Rh(dppe)(C_6H_5F)][BAr^F{}_4]$ (dppe = bis(diphenylphosphino)ethane) was prepared using literature method.[135, 136] Cesium carbonate (Cs_2CO_3) was dried prior to use in a vacuum drying pistol (120 ºC, 10 mbar) for 18 hrs.

^{1}H NMR spectra were obtained on a Bruker AVIII400 (400 MHz) spectrometer using the residual solvent as an internal standard. ^{13}C NMR spectra were obtained on a Bruker AVIII400 (100 MHz) spectrometer using the residual solvent as an internal standard. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, and DEPT data and comparison with spectra of related compounds. Chemical shifts were reported in parts per million (ppm) with the multiplicities of the spectra reported as following: s, singlet; d, doublet; t, triplet; q, quartet; hept, heptet; m, multiplet; br, broad; app., apparent and coupling constants (*J*) in Hz, rounded to the nearest 0.5 Hz. Low resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High resolution ESI mass spectrometry measurements were recorded on a Brucker Daltronics microTOF (ESI) spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford. Infra-red spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1. Optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter. The enantiomeric ratio (er) of the products was determined by chiral stationary phase HPLC in a Dionex P680 chromatograph with a Dionex UVD170U detector (Daicel Chiralpak AD-H, OJ-H, OD-H, IC, IA-3, ID-3 columns).

Tertiary amides synthesised in **Chapter 2** give two sets of signals at 25 °C, owing to the presence of rotamers around the tertiary amide. At 90 °C coalescence occurs (example: ^{1}H-NMR of compound **54g** taken in DMSO-d_6). However, some signals were broad even at this temperature. Therefore, we preferred to report the spectra taken at 25 °C in $CDCl_3$.

5.2 Chapter 2 Experimental

General procedure A for the preparation of amides from carboxylic acids and aminoalcohols:

Following the procedure by the Willis group,[105] to a round bottomed flask containing the carboxylic acid (10.0 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL, 0.2 M) was added the amine (12.0 mmol, 1.2 equiv.) and EDCI·HCl (12.0 mmol, 1.2 equiv.). The reaction mixture was left to stir for 18 hours, followed by quenching with sat. aq. $NaHCO_3$ solution (50 mL). The layers were separated, and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

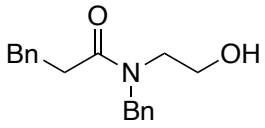
General procedure B for the preparation of aldehydes from alcohols:

To a round bottomed flask containing anhydrous DMSO (15 mmol, 2.2 equiv.) in CH_2Cl_2 (35 mL) was added oxalyl chloride (7.5 mmol, 1.1 equiv.) at −78 °C over 30 min. The reaction mixture was stirred at this temperature for 15 min, then the alcohol (7 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) was added over 30 min. The reaction mixture was stirred for a further 30 min before the addition of triethylamine (34 mmol, 4.8 equiv.) over 30 min. The reaction mixture was stirred for 15 min then allowed to warm to RT. Water (35 mL) was added and the product extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent removed in *vacuo*. The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

General procedure C for the hydroacylation of alkynes:

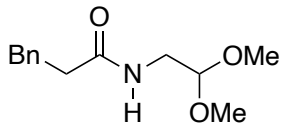
To an oven dried reaction tube containing a magnetic stirrer were added [Rh(dppe)(C_6H_5F)][BAr^F_4] (14.6 mg, 0.01 mmol, 5 mol%) and the corresponding aldehyde (0.20 mmol, 1 equiv). The tube was sealed, evacuated and backfilled with N_2 prior to dissolving in CH_2Cl_2 (0.1 mL, 2 M). Next, the corresponding alkyne (0.24 mmol, 1.2 equiv.) was added and the reaction mixture was heated at 40 °C for 18 hours. The crude was directly charged onto silica gel and subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

***N*-benzyl-*N*-(2-hydroxyethyl)-3-phenylpropanamide, 52a**



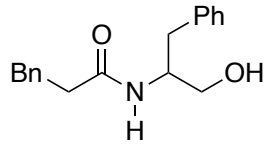
Following general procedure A, the product (2.25 g) was isolated by FC (petrol/EtOAc 1:2) in 79% yield as a colourless oil, starting from 3-phenylpropanoic acid (1.5 g, 10 mmol), 2-(benzylamino)ethan-1-ol (1.7 mL, 12 mmol) and EDCI·HCl (2.3 g, 12 mmol) in CH_2Cl_2 (50 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) (* denotes minor rotamer) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.29–7.07 (m, 8H, 8 × Ar*H*), 7.04–6.97 (m, 2H, 2 × Ar*H*), 4.60* (s, 2H, NC*H*$_2$Ph), 4.42 (s, 2H, NC*H*$_2$Ph), 3.69–3.63 (m, 2H, CH_2CH_2OH), 3.58–3.52* (m, 2H, CH_2CH_2OH), 3.51–3.43 (m, 2H, C*H*$_2$$CH_2$OH), 3.29* (t, *J* = 5.5, 2H, C*H*$_2$$CH_2$OH), 3.19 (br s, 1H, O*H*), 3.01–2.89 (m, 2H, PhC*H*$_2$$CH_2$), 2.75–2.67* (m, 2H, $PhCH_2$C*H*$_2$), 2.65–2.57 (m, 2H, $PhCH_2$C*H*$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 175.1, 173.1*, 141.6*, 141.1, 137.9*, 136.4, 129.1, 128.8*, 128.7, 128.6, 128.0*, 127.9, 127.5*, 126.4, 126.4, 126.3*, 62.4, 60.4*, 52.7, 50.3, 49.1*, 49.0*, 35.3, 35.2*, 31.8*, 31.7; **IR** (film, cm^{-1}) 3396, 3028, 1622, 1452, 1421, 1210, 1075; **LRMS** *m/z* (ESI$^+$) 284.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{18}H_{22}O_2N$ [M+H]$^+$: 284.1645, found: 284.1646.

***N*-(2,2-dimethoxyethyl)-3-phenylpropanamide, 52v**



Following general procedure A, the product (4.37 g) was isolated by FC (100% EtOAc) in 77% yield as a yellow oil, starting from 3-phenylpropanoic acid (3 g, 20 mmol), 2,2-dimethoxyethan-1-amine (618 mg, 6 mmol) and EDCI·HCl (4.6 g, 24 mmol) in CH_2Cl_2 (100 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H, 2 × Ar*H*), 7.25–7.17 (m, 3H, 3 × Ar*H*), 5.65 (s, 1H, N*H*), 4.30 (t, *J* = 5.0, 1H, C*H*$(OCH_3)_2$), 3.45–3.30 (m, 8H, C*H*$_2$CH$(OCH_3)_2$), 2.98 (t, *J* = 7.5, 2H, PhC*H*$_2$CH$_2$), 2.51 (t, *J* = 7.5, 2H, PhCH$_2$C*H*$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.3, 140.9, 128.6, 128.4, 126.3, 102.7, 54.5, 41.0, 38.4, 31.7; **IR** (film, cm^{-1}) 3304, 2980, 2833, 1646, 1545, 1496, 1453, 1384, 1128, 1058, 750, 699; **LRMS** *m/z* (ESI$^+$) 260.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{13}H_{19}O_3NNa$ [M+Na]$^+$: 260.1257, found: 260.1255.

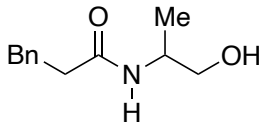
***N*-(1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide, 52w**



Following general procedure A, the product (1.02 g) was isolated by FC (100% EtOAc) in 72% yield as a white amorphous solid, starting from 3-phenylpropanoic acid (750 mg, 5 mmol), (±)-2-amino-3-phenylpropan-1-ol (907 mg, 6 mmol) and EDCI·HCl (1.15 g, 6 mmol) in CH_2Cl_2 (25 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27–7.02 (m, 10H, 10 × Ar*H*), 5.46 (d, *J* = 7.0, 1H, N*H*), 4.08–4.00 (m, 1H, NHC*H*), 3.52 (dd, *J* = 11.0, 3.5, 1H, CHCH_AH$_B$OH), 3.43 (dd, *J* = 11.0, 5.0, 1H, CHCH$_A$$H_B$OH), 2.85 (t, *J* = 7.5, 2H, CH$_2$C*H*$_2$Ph), 2.71 (dd, *J* = 7.5, 2.5, 2H, CHC*H*$_2$Ph), 2.43–2.30 (m, 2H, C*H*$_2$CH$_2$Ph); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.8, 140.8, 137.7, 129.3, 128.8, 128.7, 128.5, 126.8, 126.5, 64.1, 52.9, 38.7, 37.0, 31.8; **IR** (film, cm^{-1})

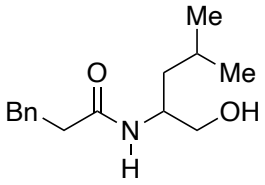
3300, 3062, 3027, 2954, 1642, 1543, 1496, 1453, 1046, 746, 699; **LRMS** *m/z* (ESI^+) 306.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{18}H_{21}O_2NNa$ $[M+Na]^+$: 306.1464, found: 306.1463;

***N*-(1-hydroxypropan-2-yl)-3-phenylpropanamide, 52x**



Following general procedure A, the product (390 mg) was isolated by FC (petrol/EtOAc 2:1) in 37% yield as a white amorphous solid, starting from 3-phenylpropanoic acid (750 mg, 5 mmol), (±)-2-aminopropan-1-ol (0.46 mL, 6 mmol) and EDCI·HCl (1.15 g, 6 mmol) in CH_2Cl_2 (25 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H, 2 × Ar*H*), 7.24–7.18 (m, 3H, 3 × Ar*H*), 5.39 (br s, 1H, N*H*), 4.07–3.96 (m, 1H, NHC*H*), 3.63–3.54 (m, 1H, CHC$H_A$$H_B$OH), 3.48–3.39 (m, 1H, CHC$H_A$$H_B$OH), 2.97 (t, J = 7.5, 2H, CH_2CH_2Ph), 2.48 (td, J = 7.5, 3.5, 2H, CH_2CH_2Ph), 1.08 (d, J = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 172.9, 140.8, 128.7, 128.5, 126.5, 67.2, 47.9, 38.8, 32.0, 17.0; **IR** (film, cm^{-1}) 3288, 3085, 3027, 2970. 1637, 1550, 1497, 1452, 987, 749, 698; **LRMS** *m/z* (ESI^+) 230.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{12}H_{17}O_2NNa$ $[M+Na]^+$: 230.1152, found: 230.1154; **m.p.** (°C): 79–81.

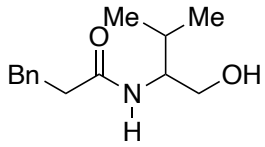
***N*-(1-hydroxy-4-methylpentan-2-yl)-3-phenylpropanamide, 52y**



Following general procedure A, the product (742 mg) was isolated by FC (petrol/EtOAc 1:1) in 60% yield as a white amorphous solid, starting from 3-phenylpropanoic acid (750 mg, 5 mmol), (±)-2-amino-4-methylpentan-1-ol (0.76 mL, 6 mmol) and EDCI·HCl (1.15 g,

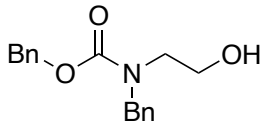
6 mmol) in CH_2Cl_2 (25 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 2H, 2 × Ar*H*), 7.26–7.18 (m, 3H, 3 × Ar*H*), 5.47 (d, *J* = 8.0, 1H, N*H*), 4.06–3.94 (m, 1H, NHC*H*), 3.64–3.54 (m, 1H, CH_AH$_B$OH), 3.51–3.40 (m, 1H, CH$_A$$H_B$OH), 3.02–2.92 (m, 2H, PhCH_2CH$_2$), 2.67–2.59 (m, 1H, O*H*), 2.56–2.49 (m, 2H, PhCH$_2$CH_2), 1.52–1.39 (m, 1H, C*H*(CH$_3$)$_2$), 1.31–1.22 (m, 2H, CH_2CH(CH$_3$)$_2$), 0.89 (app dd, *J* = 6.5, 3.0, 6H, CH(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.0, 140.8, 128.7, 128.5, 126.5, 66.3, 50.1, 40.2, 38.7, 31.9, 24.9, 23.1, 22.2; **IR** (film, cm^{-1}) 3285, 3086, 3028, 2955, 2869, 1639, 1547, 1496, 1454, 1367, 1071, 1030, 748, 698; **LRMS** *m/z* (ESI$^+$) 272.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{15}H_{23}O_2NNa$ [M+Na]$^+$: 272.1621, found: 272.1622; **m.p.** (^{o}C): 61–63.

***N*-(1-hydroxy-3-methylbutan-2-yl)-3-phenylpropanamide, 52z**



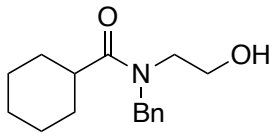
Following general procedure A, the product (750 mg) was isolated by FC (petrol/EtOAc 1:1) in 64% yield as a white amorphous solid, starting from 3-phenylpropanoic acid (750 mg, 5 mmol),n(±)-2-amino-3-methylbutan-1-ol (618 mg, 6 mmol) and EDCI·HCl (1.15 g, 6 mmol) in CH_2Cl_2 (25 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H, 2 × Ar*H*), 7.26–7.20 (m, 3H, 3 × Ar*H*), 5.51 (d, *J* = 8.0, 1H, N*H*), 3.74–3.54 (m, 3H, NHC*H*CH_2OH), 3.00 (t, *J* = 7.5, 2H, PhCH_2CH$_2$), 2.61–2.49 (m, 2H, PhCH_2CH$_2$), 2.46 (s, 1H, O*H*), 1.80 (h, *J* = 7.0, 1H, CH(CH_3)$_2$), 0.90 (d, *J* = 7.0, 3H, CH_3), 0.84 (d, *J* = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.2, 140.8, 128.7, 128.5, 126.5, 64.1, 57.3, 38.8, 32.0, 29.0, 19.5, 18.8; **IR** (film, cm^{-1}) 3294, 3028, 2960, 2873, 1637, 1545, 1496, 1454, 1075, 1028, 748, 698; **LRMS** *m/z* (ESI$^+$) 258.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{14}H_{21}O_2NNa$ [M+Na]$^+$: 258.1465, found: 258.1464; **m.p.** (^{o}C): 66–68.

Benzyl benzyl(2-hydroxyethyl)carbamate, 52ac



Following the procedure by the Willis group, [80] to a round bottomed flask containing solution of 2-(benzylamino)ethan-1-ol (0.7 mL, 5 mmol) in Et_2O (25 mL) was added potassium carbonate (2 g, 15 mmol) and water (25 mL). The reaction mixture was then cooled to 0 °C and benzyl chloroformate (0.7 mL, 5 mmol) was added. The reaction mixture was then allowed to warm to RT and stirred for 16 hours. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic layers were washed with 5% aqueous citric acid (3 × 30 mL) and brine (2 × 30 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The product (400 mg) was isolated by FC (petrol/EtOAc 2:1) in 28% yield as a colourless oil; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50–7.15 (m, 10H, 10 × Ar*H*), 5.23 (s, 2H, PhC*H*$_2$O), 4.61 (s, 2H, NC*H*$_2$Ph), 3.79–3.65 (m, 2H, CH_2CH_2OH), 3.54–3.35 (m, 2H, C*H*$_2$$CH_2$OH); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 157.6, 137.6, 136.4, 128.7, 128.6, 128.1, 128.0, 127.5, 127.3, 67.6, 61.4, 51.6, 50.0; **IR** (film, cm^{-1}) 3429, 3031, 2939, 1676, 1496, 1472, 1453, 1419, 1223, 1121, 1029, 731, 696; **LRMS** *m/z* (ESI$^+$) 308.0 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{17}H_{19}O_3NNa$ [M+Na]$^+$: 308.1257, found: 308.1255.

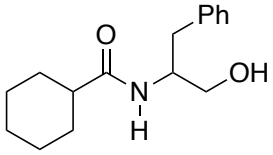
***N*-benzyl-*N*-(2-hydroxyethyl)cyclohexanecarboxamide, 52ad**



Following general procedure A, the product (600 mg) was isolated by FC (petrol/EtOAc 1:1) in 46% yield as a colourless oil, starting from cyclohexanecarboxylic acid (641 mg, 5 mmol), 2-(benzylamino)ethan-1-ol (0.85 mL, 6 mmol) and EDCI·HCl (1.15 g, 6 mmol) in CH_2Cl_2 (25 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ

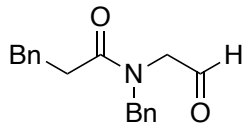
7.44–7.16 (m, 5H, 5 × Ar*H*), 4.67* (s, 2H, NCH_2Ph), 4.64 (s, 2H, NCH_2Ph), 3.78–3.68 (m, 2H, NCH$_2$CH_2OH), 3.55 (t, *J* = 5.5, 2H, NCH_2CH$_2$OH), 3.45* (t, *J* = 5.5, 2H, NCH_2CH$_2$OH), 2.68* (tt, *J* = 11.5, 3.0, 1H, C*H*(CH$_2$)$_5$), 2.52 (tt, *J* = 11.5, 3.0, 1H, C*H*(CH$_2$)$_5$), 1.87–1.72 (m, 4H, 2 × CH_2), 1.71–1.53 (m, 3H, 1.5 × CH_2), 1.37–1.10 (m, 3H, 1.5 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 179.4, 136.9, 129.1, 128.8*, 127.9, 127.8*, 127.4*, 126.5, 62.5, 60.6*, 52.5, 50.1, 48.8*, 48.7*, 41.2, 40.7*, 29.8, 25.9*, 25.8; **IR** (film, cm^{-1}) 3391, 2927, 2854, 1612, 1495, 1448, 1205, 1074, 730, 697; **LRMS** *m/z* (ESI$^+$) 284.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{16}H_{23}O_2NNa$ [M+Na]$^+$: 284.1619, found: 284.1621.

_N_-(1-hydroxy-3-phenylpropan-2-yl)cyclohexanecarboxamide, 52ae



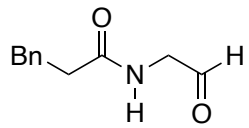
Following general procedure A, the product (842 mg) was isolated by FC (100% EtOAc) in 65% yield as a white amorphous solid, starting from cyclohexanecarboxylic acid (641 mg, 5 mmol), (±)-2-amino-3-phenylpropan-1-ol (907 mg, 6 mmol) and EDCI·HCl (1.15 g, 6 mmol) in CH_2Cl_2 (25 mL); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H, 5 × Ar*H*), 5.70 (d, *J* = 8.5, 1H, N*H*), 4.22–4.09 (m, 1H, NHC*H*), 3.74–3.64 (m, 1H, CHCH_AH$_B$OH), 3.63–3.54 (m, 1H, CHCH$_A$$H_B$OH), 3.03–2.80 (m, 3H, O*H*, CHCH_2Ph), 2.03 (tt, *J* = 11.5, 3.0, 1H, C*H*(CH$_2$)$_5$), 1.84–1.68 (m, 4H, 2 × CH_2), 1.69–1.59 (m, 1H, 0.5 × CH_2), 1.43–1.10 (m, 5H, 2.5 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 177.1, 137.8, 129.3, 128.8, 126.8, 64.9, 52.9, 45.6, 37.1, 29.8, 29.7, 25.8, 25.8; **IR** (film, cm^{-1}) 3279, 2980, 2927, 2852, 1641, 1548, 1496, 1446, 1386, 1054, 952, 752, 699; **LRMS** *m/z* (ESI$^+$) 284.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{16}H_{24}O_2N$ [M+H]$^+$: 262.1802, found: 262.1802; **m.p.** (^{o}C): 127–129.

***N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide, 53a**



Following general procedure B, the product (943 mg) was isolated by FC (petrol/EtOAc 2:1) in 67% yield as a colourless oil, starting from anhydrous DMSO (0.76 mL, 10.7 mmol) in CH_2Cl_2 (25 mL), oxalyl chloride (0.44 mL, 5.35 mmol), *N*-benzyl-*N*-(2-hydroxyethyl)-3-phenylpropanamide (**52a**) (1.417 g, 5 mmol) in CH_2Cl_2 (18 mL) and triethylamine (3.4 mL, 34 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) (* denotes minor rotamer) [the compound exists as two rotamers, in a ratio of 4:1] δ 9.51 (s, 1H, C(O)*H*), 9.38* (s, 1H, C(O)*H*), 7.40–7.28 (m, 5H, 5 × Ar*H*), 7.26–7.17 (m, 3H, 3 × Ar*H*), 7.15–7.08 (m, 2H, 2 × Ar*H*), 4.68* (s, 2H, NCH_2Ph), 4.56 (s, 2H, NCH_2Ph), 4.09 (s, 2H, NCH_2C(O)H), 3.98* (s, 2H, NCH_2C(O)H), 3.09–3.01 (m, 2H, PhCH_2CH$_2$), 2.87–2.77 (m, 2H, PhCH$_2$CH_2), 2.57–2.50* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 197.4, 197.2*, 173.3, 172.5*, 141.0, 135.9, 129.2, 128.9*, 128.7*, 128.7, 128.6*, 128.6, 128.6*, 128.2, 128.0*, 126.8, 126.4*, 126.4, 57.1*, 56.0, 52.6, 50.3*, 35.3*, 34.8, 31.5*, 31.4; **IR** (film, cm^{-1}) 3028, 1732, 1645, 1452, 1121; **LRMS** *m/z* (ESI$^+$) 282.5 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{18}H_{20}O_2N$ [M+H]$^+$: 282.1489, found: 282.1489.

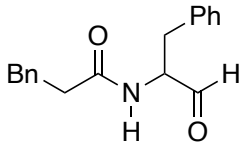
***N*-(2-oxoethyl)-3-phenylpropanamide, 53v**



Following the procedure by the Willis group,[80] to a round bottomed flask containing solution of *N*-(2,2-dimethoxyethyl)-3-phenylpropanamide (**52v**) (498 mg, 2.1 mmol) in acetone (20 mL) was added 1 N aqueous hydrochloric acid (20 mL) and stirred for 16 hours at RT. The organic and aqueous layers were separated and extracted with Et_2O (2 × 60 mL). The organic

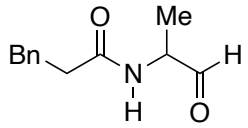
layers were combined and washed with aqueous sodium bicarbonate (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The product (121 mg) was isolated by FC (petrol/EtOAc 1:1) in 30% yield as a colourless oil; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.62 (d, J = 1.0, 1H, C(O)*H*), 7.33–7.24 (m, 2H, 2 × Ar*H*), 7.24–7.15 (m, 3H, 3 × Ar*H*), 6.13 (br s, 1H, N*H*), 4.17 (dd, J = 5.0, 1.0, 2H, NHCH_2), 3.08–2.95 (m, 2H, PhCH_2CH$_2$), 2.61–2.54 (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 196.5, 172.5, 140.7, 128.7, 128.4, 126.5, 50.4, 38.1, 31.6; **IR** (film, cm^{-1}) 3302, 3028, 2930, 1731, 1645, 1540, 1496, 1453, 1075, 750, 699; **LRMS** *m/z* (ESI$^+$) 192.0 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{11}H_{14}O_2N$ [M+H]$^+$: 192.1019, found: 192.1021.

***N*-(1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide, 53w**



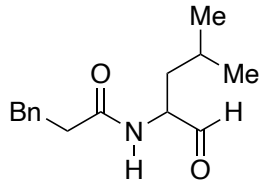
Following general procedure B, the product (289 mg) was isolated by FC (petrol/EtOAc 1:1) in 51% yield as a white amorphous solid, starting from anhydrous DMSO (0.3 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), oxalyl chloride (0.2 mL, 2.2 mmol), *N*-(1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide (**52w**) (566 mg, 2 mmol) in CH_2Cl_2 (8 mL) and triethylamine (1.4 mL, 9.6 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.58 (s, 1H, C(O)*H*), 7.37–7.13 (m, 8H, 8 × Ar*H*), 7.08–6.94 (m, 2H, 2 × Ar*H*), 5.87 (s, 1H, N*H*), 4.75–4.65 (m, 1H, C*H*C(O)H), 3.21–3.03 (m, 2H, NHCHCH_2), 3.00–2.92 (m, 2H, PhCH_2CH$_2$), 2.60–2.45 (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.9, 172.2, 140.7, 135.6, 129.4, 128.9, 128.7, 128.5, 127.3, 126.5, 59.8, 38.2, 35.2, 31.6; **IR** (film, cm^{-1}) 3332, 3027, 2929, 2829, 1726, 1633, 1532, 1496, 1453, 740, 697; **LRMS** *m/z* (ESI$^+$) 304.1 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{18}H_{20}O_2N$ [M+H]$^+$: 282.1489, found: 282.1488; **m.p.** (^{o}C): 85–87.

***N*-(1-oxopropan-2-yl)-3-phenylpropanamide, 53x**



Following general procedure B, the product (78 mg) was isolated by FC (petrol/EtOAc 1:1) in 25% yield as a yellow amorphous solid, starting from anhydrous DMSO (0.22 mL, 3.3 mmol) in CH_2Cl_2 (7.5 mL), oxalyl chloride (0.15 mL, 1.65 mmol), *N*-(1-hydroxypropan-2-yl)-3-phenylpropanamide (**52x**) (310 mg, 1.5 mmol) in CH_2Cl_2 (6 mL) and triethylamine (1 mL, 7.2 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.49 (s, 1H, C(O)*H*), 7.33–7.25 (m, 2H, 2 × Ar*H*), 7.24–7.17 (m, 3H, 3 × Ar*H*), 5.93 (br s, 1H, N*H*), 4.53–4.43 (m, 1H, NHC*H*), 2.98 (t, J = 7.5, 2H, PhCH_2CH$_2$), 2.61–2.47 (m, 2H, PhCH$_2$CH_2), 1.30 (d, J = 7.5, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 199.1, 172.1, 140.7, 128.7, 128.5, 126.5, 54.6, 38.3, 31.7, 14.6; **IR** (film, cm^{-1}) 3294, 3028, 2934, 1732, 1644, 1536, 1497, 1453, 751, 700; **LRMS** *m/z* (ESI$^+$) 228.0 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{12}H_{15}O_2NNa$ [M+Na]$^+$: 228.0995, found: 228.0997; **m.p.** (^{o}C): 66–68.

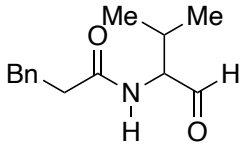
***N*-(4-methyl-1-oxopentan-2-yl)-3-phenylpropanamide, 53y**



Following general procedure B, the product (221 mg) was isolated by FC (petrol/EtOAc 2:1) in 45% yield as a yellow oil, starting from anhydrous DMSO (0.3 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), oxalyl chloride (0.2 mL, 2.2 mmol), *N*-(1-hydroxy-4-methylpentan-2-yl)-3-phenylpropanamide (**52y**) (498 mg, 2 mmol) in CH_2Cl_2 (8 mL) and triethylamine (1.4 mL, 9.6 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.45–9.42 (m, 1H, C(O)*H*), 7.24–7.18 (m, 2H, 2 × Ar*H*), 7.16–7.09 (m, 3H, 3 × Ar*H*), 5.73 (br s, 1H, N*H*), 4.52–4.39 (m, 1H, NHC*H*),

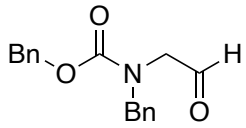
2.96–2.85 (m, 2H, PhCH_2CH$_2$), 2.58–2.41 (m, 2H, PhCH$_2$CH_2), 1.64–1.41 (m, 2H, CH_2CH(CH$_3$)$_2$), 1.30–1.20 (m, 1H, CH(CH$_3$)$_2$), 0.93–0.73 (m, 6H, CH(CH_3)$_2$); **^{13}C-NMR** (100 MHz, CDCl$_3$) δ 199.8, 172.4, 140.7, 128.7, 128.5, 126.5, 57.3, 38.2, 38.1, 31.7, 24.8, 23.2, 22.1; **IR** (film, cm^{-1}) 3291, 3028, 2956, 2869, 1733, 1643, 1537, 1496, 1453, 748, 698; **LRMS** *m/z* (ESI$^+$) 248.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{15}H_{22}O_2N$ [M+H]$^+$: 248.1645, found: 248.1650.

***N*-(3-methyl-1-oxobutan-2-yl)-3-phenylpropanamide, 53z**



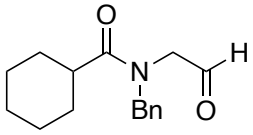
Following general procedure B, the product (363 mg) was isolated by FC (petrol/EtOAc 2:3) in 78% yield as a colourless oil, starting from anhydrous DMSO (0.3 mL, 4.4 mmol) in CH$_2$Cl$_2$ (10 mL), oxalyl chloride (0.2 mL, 2.2 mmol), *N*-(1-hydroxy-3-methylbutan-2-yl)-3-phenylpropanamide (**52z**) (538 mg, 2 mmol) in CH$_2$Cl$_2$ (8 mL) and triethylamine (1.4 mL, 9.6 mmol); **^{1}H-NMR** (400 MHz, CDCl$_3$) δ 9.51 (s, 1H, C(O)H), 7.24–7.17 (m, 2H, 2 × ArH), 7.16–7.09 (m, 3H, 3 × ArH), 5.91 (d, J = 7.0, 1H, NH), 4.48 (dd, J = 7.0, 4.5, 1H, NHCH), 2.97–2.85 (m, 2H, PhCH_2CH$_2$), 2.58–2.44 (m, 2H, PhCH$_2$CH_2), 2.17 (heptd, J = 7.0, 4.5, 1H, CH(CH$_3$)$_2$), 0.83 (d, J = 7.0, 3H, CH_3), 0.80 (d, J = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, CDCl$_3$) δ 199.9, 172.4, 140.5, 128.6, 128.3, 126.3, 63.2, 38.2, 31.6, 29.0, 18.9, 17.7; **IR** (film, cm^{-1}) 3294, 3028, 2963, 1730, 1644, 1533, 1497, 1454, 747, 698; **LRMS** *m/z* (ESI$^+$) 234.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{14}H_{20}O_2N$ [M+H]$^+$: 234.1489, found: 234.1491.

Benzyl benzyl(2-oxoethyl)carbamate, 53ac



Following general procedure B, the product (200 mg) was isolated by FC (petrol/EtOAc 4:1) in 70% yield as a colourless oil, starting from anhydrous DMSO (0.15 mL, 2.2 mmol) in CH_2Cl_2 (5 mL), oxalyl chloride (0.1 mL, 1.1 mmol), Benzyl benzyl(2-hydroxyethyl)carbamate (**52ac**) (300 mg, 1 mmol) in CH_2Cl_2 (4 mL) and triethylamine (0.7 mL, 4.8 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 1:1] δ 9.53 (s, 1H, C(O)*H*), 9.44* (s, 1H, C(O)*H*), 7.44–7.25 (m, 8H, 8 × Ar*H*), 7.24–7.18 (m, 2H, 2 × Ar*H*), 5.26 (s, 2H, PhCH_2O), 5.22* (s, 2H, PhCH_2O), 4.63 (s, 2H, PhCH_2N), 4.61* (s, 2H, PhCH_2N), 4.03 (s, 2H, NCH_2C(O)H), 3.94* (s, 2H, NCH_2C(O)H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.1, 156.7, 136.7, 136.2, 129.0, 128.7, 128.4, 128.4, 128.1, 128.0*, 127.9, 68.1, 68.0*, 56.7, 56.1*, 52.2, 51.9*; **IR** (film, cm^{-1}) 3032, 2921, 1733, 1696, 1496, 1452, 1426, 1230, 1123, 734, 697; **LRMS** *m/z* (ESI$^+$) 306.1 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{17}H_{17}O_3NNa$ [M+Na]$^+$: 306.1100, found: 306.1098.

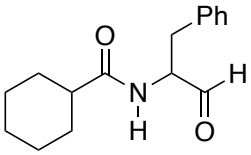
***N*-benzyl-*N*-(2-oxoethyl)cyclohexanecarboxamide, 53ad**



Following general procedure B, the product (361 mg) was isolated by FC (petrol/EtOAc 3:1) in 70% yield as a pale yellow oil, starting from anhydrous DMSO (0.3 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), oxalyl chloride (0.2 mL, 2.2 mmol), *N*-benzyl-*N*-(2-hydroxyethyl)cyclohexanecarboxamide (**52ad**) (522 mg, 2 mmol) in CH_2Cl_2 (8 mL) and triethylamine (1.4 mL, 9.6 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) (* denotes minor rotamer) [the compound exists as two rotamers, in a ratio of 4:1] δ 9.43* (s, 1H, C(O)*H*), 9.39 (s, 1H,

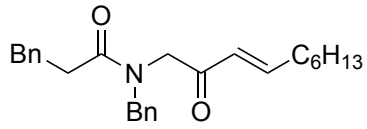
C(O)*H*), 7.35–7.16 (m, 3H, 3 × Ar*H*), 7.14–7.07 (m, 2H, 2 × Ar*H*), 4.56 (s, 2H, NC*H*$_2$Ph), 3.99* (s, 2H, NC*H*$_2$C(O)H), 3.93 (s, 2H, NC*H*$_2$C(O)H), 2.56 (tt, *J* = 11.5, 3.0, 1H, C*H*(CH$_2$)$_5$), 2.18–2.07* (m, 1H, C*H*(CH$_2$)$_5$), 1.82–1.44 (m, 7H, 7 × C*H*$_2$), 1.27–1.04 (m, 3H, 3 × C*H*$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) *δ* 197.7*, 197.5, 177.4, 176.6*, 136.9*, 136.3, 129.2, 128.9*, 128.4*, 128.1, 127.8*, 126.8, 56.9*, 55.8, 52.4, 50.0*, 41.1*, 40.6, 29.7, 29.6*, 25.8; **IR** (film, cm^{-1}) 2928, 2854, 1730, 1634, 1495, 1448, 1206, 729, 698; **LRMS** *m/z* (ESI$^+$) 260.1 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{16}H_{22}O_2N$ [M+H]$^+$: 260.1645, found: 260.1645.

_N_-(1-oxo-3-phenylpropan-2-yl)cyclohexanecarboxamide, 53ae



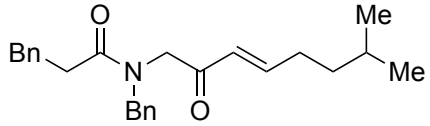
Following general procedure B, the product (237 mg) was isolated by FC (petrol/EtOAc 2:1) in 46% yield as a white amorphous solid, starting from anhydrous DMSO (0.3 mL, 4.4 mmol) in CH_2Cl_2 (10 mL), oxalyl chloride (0.2 mL, 2.2 mmol), *N*-(1-hydroxy-3-phenylpropan-2-yl)cyclohexanecarboxamide (**52ae**) (522 mg, 2 mmol) in CH_2Cl_2 (8 mL) and triethylamine (1.4 mL, 9.6 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) *δ* 9.64 (s, 1H, C(O)*H*), 7.34–7.22 (m, 3H, 3 × Ar*H*), 7.18–7.10 (m, 2H, 2 × Ar*H*), 5.96 (s, 1H, N*H*), 4.75–4.68 (m, 1H, NHC*H*), 3.18 (d, *J* = 6.5, 2H, CHC*H*$_2$Ph), 2.11 (tt, *J* = 12.0, 3.5, 1H, C*H*(CH$_2$)$_5$), 1.88–1.56 (m, 5H, 2.5 × C*H*$_2$), 1.48–1.32 (m, 2H, C*H*$_2$), 1.33–1.13 (m, 3H, 1.5 × C*H*$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) *δ* 199.0, 176.0, 135.6, 129.4, 128.7, 127.1, 59.5, 45.2, 35.1, 29.7, 29.5, 25.7, 25.6, 25.6; **IR** (film, cm^{-1}) 3303, 3029, 2928, 2854, 1732, 1638, 1530, 1450, 1257, 1216, 739, 699; **LRMS** *m/z* (ESI$^+$) 260.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{16}H_{22}O_2N$ [M+H]$^+$: 260.1645, found: 260.1642; **m.p.** (^{o}C): 97–99.

(*E*)-*N*-benzyl-*N*-(2-oxodec-3-en-1-yl)-3-phenylpropanamide, 54a



Following general procedure C, the product (63 mg) was isolated by FC (petrol/EtOAc 4:1) in 80% yield as a pale yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) (* denotes minor rotamer) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.28–7.14 (m, 5H, 5 × Ar*H*), 7.13–7.05 (m, 3H, 3 × Ar*H*), 7.04–6.96 (m, 2H, 2 × Ar*H*), 6.86–6.71 (m, 1H, C(O)CH=C*H*CH_2), 6.01 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=$CHCH_2$), 5.95* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=$CHCH_2$), 4.53* (s, 2H, NC*H*$_2$Ph), 4.47 (s, 2H, NC*H*$_2$Ph), 4.22 (s, 2H, NC*H*$_2$C(O)), 3.95* (s, 2H, NC*H*$_2$C(O)), 2.97–2.88 (m, 2H, PhC*H*$_2$$CH_2$), 2.71–2.65 (m, 2H, $PhCH_2$C*H*$_2$), 2.42–2.36* (m, 2H, $PhCH_2$C*H*$_2$), 2.14–2.04 (m, 2H, C*H*$_2$$CH_2$$(CH_2)_3CH_3$), 1.41–1.28 (m, 2H, CH_2C*H*$_2$$(CH_2)_3CH_3$), 1.27–1.14 (m, 6H, CH_2CH_2(C*H*$_2$$)_3CH_3$), 0.85–0.71 (m, 3H, $CH_2CH_2(CH_2)_3$C*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.4, 193.9*, 172.9, 172.9*, 149.9*, 148.9, 141.4*, 141.2, 137.1*, 136.5, 129.0, 128.6*, 128.5, 128.5, 128.4*, 127.8, 127.6, 127.5*, 126.7*, 126.6, 126.2*, 126.14, 54.2*, 52.7, 52.0, 49.9*, 35.1*, 34.8, 32.7*, 32.7, 31.6, 31.6*, 31.5*, 31.3, 28.9, 28.9*, 27.9, 27.9*, 22.6, 22.5*, 14.1, 14.1*; **IR** (film, cm^{-1}) 2928, 1689, 1651, 1453, 1360, 1206; **LRMS** *m/z* (ESI^+) 414.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{26}H_{33}O_2NNa$ $[M+Na]^+$: 414.2403, found: 414.2398.

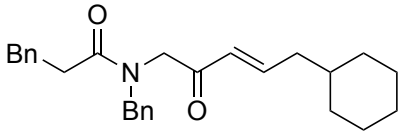
(*E*)-*N*-benzyl-*N*-(7-methyl-2-oxooct-3-en-1-yl)-3-phenylpropanamide, 54b



Following general procedure C, the product (45 mg) was isolated by FC (petrol/EtOAc 4:1) in 60% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**)

(56 mg, 0.20 mmol) and 5-methylhex-1-yne (31 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.28–7.15 (m, 5H, 5 × Ar*H*), 7.14–7.06 (m, 3H, 3 × Ar*H*), 7.05–6.97 (m, 2H, 2 × Ar*H*), 6.86–6.72 (m, 1H, C(O)CH=C*H*), 6.02 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 5.96* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 4.54* (s, 2H, NCH_2Ph), 4.48 (s, 2H, NCH_2Ph), 4.22 (s, 2H, NCH_2C(O)), 3.96* (s, 2H, NCH_2C(O)), 2.98–2.89 (m, 2H, PhCH_2CH$_2$), 2.74–2.65 (m, 2H, PhCH$_2$CH_2), 2.44–2.35* (m, 2H, PhCH$_2$CH_2), 2.16–2.06 (m, 2H, CH_2CH$_2$CH(CH$_3$)$_2$), 1.53–1.42 (m, 1H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.28–1.17 (m, 2H, CH$_2$CH_2CH(CH$_3$)$_2$), 0.81 (d, *J* = 6.5, 6H, CH$_2$CH$_2$CH(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.4, 193.9*, 172.9, 172.8*, 150.1*, 149.1, 141.3*, 141.2, 137.1*, 136.3, 128.9, 128.6*, 128.5, 128.5, 128.4*, 127.7, 127.5*, 127.5, 126.6, 126.5*, 126.1*, 126.1, 54.2*, 52.7, 52.0, 49.9*, 37.0, 36.9*, 35.1*, 34.8, 31.4*, 31.3, 30.6*, 30.5, 27.6*, 27.6, 22.4, 22.3*; **IR** (film, cm^{-1}) 3027, 2954, 2869, 1686, 1647, 1495, 1452, 1206, 734, 699; **LRMS** *m/z* (ESI$^+$) 400.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{25}H_{32}O_2N$ [M+H]$^+$: 378.2438, found: 378.2429.

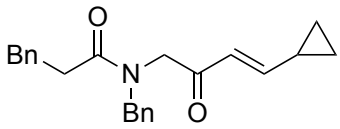
(*E*)-*N*-benzyl-*N*-(5-cyclohexyl-2-oxopent-3-en-1-yl)-3-phenylpropanamide, 54c



Following general procedure C, the product (50 mg) was isolated by FC (petrol/EtOAc 4:1) in 62% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and prop-2-yn-1-ylcyclohexane (34 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.30–7.15 (m, 5H, 5 × Ar*H*), 7.14–7.07 (m, 3H, 3 × Ar*H*), 7.06–6.94 (m, 2H, 2 × Ar*H*), 6.86–6.70 (m, 1H, C(O)CH=C*H*), 6.00 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 5.94* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 4.55* (s, 2H, NCH_2Ph), 4.49 (s, 2H, NCH_2Ph), 4.23 (s, 2H, NCH_2C(O)), 3.95*

(s, 2H, NCH_2C(O)), 3.00–2.88 (m, 2H, PhCH_2CH$_2$), 2.73–2.64 (m, 2H, PhCH$_2$CH_2), 2.45–2.37* (m, 2H, PhCH$_2$CH_2), 2.05–1.95 (m, 2H, CH_2CH(CH$_2$)$_5$), 1.71–1.50 (m, 5H, 2.5 × CH_2), 1.39–1.26 (m, 1H, CH$_2$CH(CH$_2$)$_5$), 1.21–0.98 (m, 3H, 1.5 × CH_2), 0.92–0.73 (m, 2H, CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.4, 193.9*, 173.0, 172.9*, 148.9*, 147.8, 141.4*, 141.3, 137.2*, 136.4, 129.0, 128.7, 128.6, 128.6, 128.5*, 127.8, 127.7*, 127.6*, 126.7, 126.2*, 126.2, 54.3*, 52.8, 52.1, 50.0*, 40.7, 37.4, 37.3*, 35.2*, 34.9, 33.3, 31.5*, 31.4, 26.4, 26.3*, 26.3, 26.2*; **IR** (film, cm^{-1}) 3027, 2921, 2850, 1686, 1647, 1495, 1448, 1205, 734, 698; **LRMS** *m/z* (ESI$^+$) 426.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{27}H_{34}O_2N$ [M+H]$^+$: 404.2584, found: 404.2580.

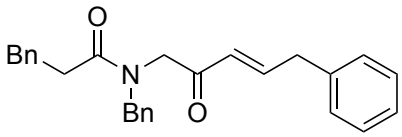
(*E*)-*N*-benzyl-*N*-(4-cyclopropyl-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54d



Following general procedure C, the product (30 mg) was isolated by FC (petrol/EtOAc 4:1) in 43% yield as a pale yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and ethynylcyclopropane (20 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2:1] δ 7.28–7.15 (m, 5H, 5 × ArH), 7.15–7.05 (m, 3H, 3 × ArH), 7.04–6.99 (m, 2H, 2 × ArH), 6.35–6.23 (m, 1H, C(O)CH=CH), 6.16–6.04 (m, 1H, C(O)CH=CH), 4.55* (s, 2H, NCH_2Ph), 4.48 (s, 2H, NCH_2Ph), 4.17 (s, 2H, NCH_2C(O)), 3.91* (s, 2H, NCH_2C(O)), 3.00–2.89 (m, 2H, PhCH_2CH$_2$), 2.74–2.64 (m, 2H, PhCH$_2$CH_2), 2.46–2.37* (m, 2H, PhCH$_2$CH_2), 1.52–1.40 (m, 1H, CH=CHCHCH$_2$), 0.98–0.85 (m, 2H, CH=CHCHCH_2), 0.64–0.52 (m, 2H, CH=CHCHCH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 193.6, 193.1*, 173.0, 155.2*, 154.1, 141.4*, 141.4, 137.2*, 136.5, 129.0, 128.7*, 128.6, 128.6, 128.6, 128.5*, 127.8, 127.6*, 126.7, 126.2*, 124.5, 123.3*, 54.5*, 52.9, 52.1, 50.0*, 35.2*, 34.9, 31.5*, 31.4, 15.3*, 15.1, 9.6*, 9.3; **IR** (film, cm^{-1}) 3027, 2924,

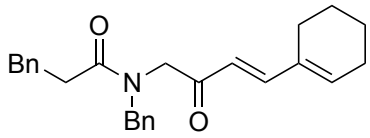
1646, 1495, 1452, 1208, 947, 736, 700; **LRMS** *m/z* (ESI^+) 370.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{23}H_{25}O_2NNa$ $[M+Na]^+$: 370.1777, found: 370.1772.

(*E*)-*N*-benzyl-*N*-(2-oxo-5-phenylpent-3-en-1-yl)-3-phenylpropanamide, 54e



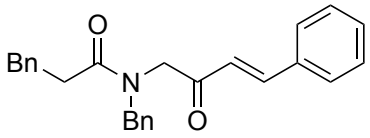
Following general procedure C, the product (44 mg) was isolated by FC (petrol/EtOAc 4:1) in 55% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and prop-2-yn-1-ylbenzene (29 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.31–6.83 (m, 16H, C(O)CH=C*H*, 15 × Ar*H*), 5.99 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 5.92* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 4.53* (s, 2H, NCH_2Ph), 4.46 (s, 2H, NCH_2Ph), 4.20 (s, 2H, NCH_2C(O)), 3.94* (s, 2H, NCH_2C(O)), 3.46–3.37 (m, 2H, CH=CHCH_2Ph), 2.98–2.88 (m, 2H, PhCH_2CH_2), 2.72–2.62 (m, 2H, PhCH_2CH_2), 2.43–2.34* (m, 2H, PhCH_2CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.4, 193.9*, 173.0, 172.9*, 147.7*, 146.7, 141.4*, 141.3, 137.4, 137.1*, 137.0*, 136.3, 129.0, 129.0, 129.0*, 128.9*, 128.9, 128.7*, 128.6, 128.6, 128.5*, 128.4, 127.9, 127.6*, 127.5*, 127.1*, 126.9, 126.7, 126.3*, 126.2, 54.4*, 52.9, 52.1, 49.9*, 39.0, 35.2*, 34.8, 31.5*, 31.4; **IR** (film, cm^{-1}) 3027, 2980, 1687, 1645, 1603, 1495, 1452, 1207, 1076, 750, 698; **LRMS** *m/z* (ESI^+) 420.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{27}H_{28}O_2N$ $[M+H]^+$: 398.2115, found: 398.2124.

(*E*)-*N*-benzyl-*N*-(4-(cyclohex-1-en-1-yl)-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54f



Following general procedure C, the product (65 mg) was isolated by FC (petrol/EtOAc 4:1) in 84% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 1-ethynylcyclohex-1-ene (28 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2:1] δ 7.28–7.14 (m, 5H, 5 × Ar*H*), 7.14–7.06 (m, 4H, C(O)CH=C*H,* 3 × Ar*H*), 7.05–6.99 (m, 2H, 2 × Ar*H*), 6.19–6.10 (m, 1H, C(O)CH=CHC=C*H*), 5.98 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 5.90* (d, *J* = 16.0, 1H, C(O)C*H*=CH), 4.55* (s, 2H, NCH_2Ph), 4.49 (s, 2H, NCH_2Ph), 4.25 (s, 2H, NCH_2C(O)), 3.99* (s, 2H, NCH_2C(O)), 2.98–2.89 (m, 2H, PhCH_2CH$_2$), 2.74–2.64 (m, 2H, PhCH$_2$CH_2), 2.45–2.38* (m, 2H, PhCH$_2$CH_2), 2.18–2.08 (m, 2H, C(O)CH=CHC=CHCH$_2$), 2.06–1.93 (m, 2H, C(O)CH=CHCCH_2), 1.67–1.45 (m, 4H, CH$_2$(CH_2)$_2$CH$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.9, 194.3*, 173.0, 147.9*, 147.2, 142.3*, 141.4*, 141.3, 141.0, 137.2*, 136.5, 135.2, 135.1*, 129.0, 128.7*, 128.6, 128.5, 128.5, 127.8, 127.6*, 126.7, 126.2*, 120.4, 119.2*, 54.6*, 53.1, 52.0, 50.0*, 35.1*, 34.9, 31.5*, 31.4, 26.8*, 26.8, 24.1, 24.1*, 22.1, 22.0, 22.0*, 21.9*; **IR** (film, cm^{-1}) 3027, 2930, 1645, 1595, 1495, 1451, 1193, 1078, 982, 733, 699; **LRMS** *m/z* (ESI$^+$) 388.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{26}H_{29}O_2NNa$ [M+Na]$^+$: 410.2101, found: 410.2088.

(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54g

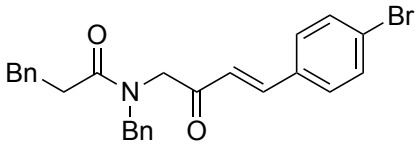


Following general procedure C, the product (71 mg) was isolated by FC (petrol/EtOAc 4:1) in 92% yield as a yellow amorphous solid, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.66 (d, *J* = 16.0, 1H, C(O)CH=C*H*), 7.61* (d, *J* = 16.0, 1H, C(O)CH=C*H*), 7.57–7.49 (m, 2H,

2 × Ar*H*), 7.47–7.10 (m, 13H, 13 × Ar*H*), 6.76 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 6.68* (d, *J* = 16.0, 1H, C(O)C*H*=CH), 4.72* (s, 2H, NCH_2Ph), 4.64 (s, 2H, NCH_2Ph), 4.46 (s, 2H, NCH_2C(O)), 4.20* (s, 2H, NCH_2C(O)), 3.12–3.02 (m, 2H, PhCH_2CH$_2$), 2.87–2.80 (m, 2H, PhCH$_2$CH_2), 2.62–2.53* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.5, 194.0*, 173.0, 172.9*, 144.5*, 143.7, 141.3*, 141.3, 137.1*, 136.3, 134.3, 133.9*, 131.2*, 130.8, 129.1*, 129.0, 128.7*, 128.6, 128.6, 128.5, 128.5, 127.9, 127.6*, 126.8, 126.2, 123.4, 122.1*, 55.0*, 53.4, 52.1, 50.0*, 35.1*, 34.8, 31.5*, 31.4; **IR** (film, cm^{-1}) 3027, 2922, 1698, 1644, 1611, 1576, 1494, 1450, 1186, 1090, 979, 748, 697; **LRMS** *m/z* (ESI$^+$) 406.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{26}H_{25}O_2NNa$ [M+Na]$^+$: 406. 1777, found: 406.1774; **m.p.** (^{o}C): 97–99.

Gram scale: Following general procedure C, the product (1.03 g) was isolated by FC (petrol/EtOAc 4:1) in 73% yield as a yellow amorphous solid, starting from *N*-benzyl-*N*-(2-oxoethyl) 3-phenylpropanamide (**1a**) (1.04 g, 3.7 mmol), ethynylbenzene (0.47 mL, 4.44 mmol) and [Rh(dppe)(C_6H_5F)][BAr$^F_4$] (216 mg, 0.15 mmol, 4 mol%) in CH_2Cl_2 (1.8 mL, 2 M).

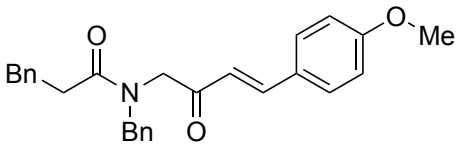
(*E*)-*N*-benzyl-*N*-(4-(4-bromophenyl)-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54h



Following general procedure C, the product (75 mg) was isolated by FC (petrol/EtOAc 4:1) in 81% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 1-bromo-4-ethynylbenzene (36 mg, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.49–7.37 (m, 3H, C(O)CH=C*H*, 2 × Ar*H*), 7.29–7.06 (m, 10H, 10 × Ar*H*), 7.05–6.97 (m, 2H, 2 × Ar*H*), 6.61 (d,

J = 16.0, 1H, C(O)C*H*=CH), 6.51* (d, *J* = 16.0, 1H, C(O)C*H*=CH), 4.58* (s, 2H, NCH_2Ph), 4.51 (s, 2H, NCH_2Ph), 4.30 (s, 2H, NCH_2C(O)), 4.06* (s, 2H, NCH_2C(O)), 2.97–2.90 (m, 2H, PhCH_2CH$_2$), 2.74–2.68 (m, 2H, PhCH$_2$CH_2), 2.46–2.40* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.3, 193.9*, 173.0, 172.9*, 143.0*, 142.2, 141.3*, 141.2, 137.0*, 136.2, 133.3, 132.8*, 132.4*, 132.3, 129.9*, 129.8, 129.1, 128.8*, 128.6, 128.5, 127.9, 127.7*, 126.8*, 126.8, 126.2, 125.1*, 123.9, 122.4*, 55.2*, 53.6, 52.1, 50.1*, 35.2*, 34.8, 31.5*, 31.4; **IR** (film, cm^{-1}) 3027, 2922, 1643, 1612, 1585, 1486, 1451, 1402, 1186, 1069, 1008, 804, 731, 699; **LRMS** *m/z* (ESI$^+$) 484.0 ([M(Br^{79})+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{26}H_{25}O_2N^{79}Br$ [M+H]$^+$: 462.1063, found: 462.1060.

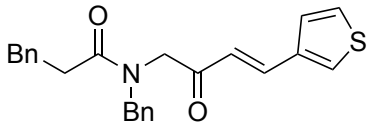
(*E*)-*N*-benzyl-*N*-(4-(4-methoxyphenyl)-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54i



Following general procedure C, the product (60 mg) was isolated by FC (petrol/EtOAc 4:1) in 72% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 1-ethynyl-4-methoxybenzene (32 mg, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2:1] δ 7.47 (app t, *J* = 16.5, 1H, C(O)CH=C*H*), 7.40–7.31 (m, 2H, 2 × Ar*H*), 7.28–7.01 (m, 10H, 10 × Ar*H*), 6.83–6.76 (m, 2H, 2 × Ar*H*), 6.52 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 6.43* (d, *J* = 16.0, 1H, C(O)C*H*=CH), 4.59* (s, 2H, NCH_2Ph), 4.51 (s, 2H, NCH_2Ph), 4.31 (s, 2H, NCH_2C(O)), 4.05* (s, 2H, NCH_2C(O)), 3.74* (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.95 (t, *J* = 8.0, 2H, PhCH_2CH$_2$), 2.75–2.65 (m, 2H, PhCH$_2$CH_2), 2.48–2.41* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.3, 193.8*, 172.9, 172.9*, 162.2*, 161.8, 144.2*, 143.4, 141.3*, 141.3, 137.1*, 136.4, 130.4*, 130.2, 129.0, 128.7*, 128.5, 128.5, 127.8, 127.6*, 127.0*, 126.7, 126.5*, 126.1, 121.2, 119.6*, 114.6*, 114.5, 55.5*, 55.4, 54.9*, 53.2, 52.0,

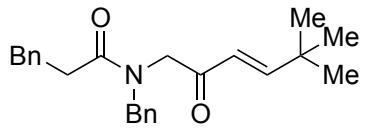
50.0*, 35.1*, 34.8, 31.4*, 31.4; **IR** (film, cm^{-1}) 3028, 2931, 1645, 1596, 1572, 1511, 1452, 1423, 1253, 1171, 1090, 1028, 816, 737, 700; **LRMS** *m/z* (ESI^+) 436.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{27}H_{28}O_3N$ $[M+H]^+$: 414.2063, found: 414.2051.

(*E*)-*N*-benzyl-*N*-(2-oxo-4-(thiophen-3-yl)but-3-en-1-yl)-3-phenylpropanamide, 54j



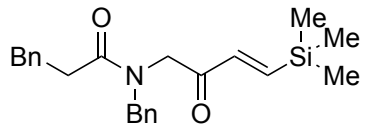
Following general procedure C, the product (70 mg) was isolated by FC (petrol/EtOAc 4:1) in 89% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 3-ethynylthiophene (23 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.57–7.38 (m, 2H, C(O)CH=C*H*, 1 × Ar*H*), 7.29–7.06 (m, 10H, 10 × Ar*H*), 7.05–7.00 (m, 2H, 2 × Ar*H*), 6.45 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.36* (d, J = 16.0, 1H, C(O)C*H*=CH), 4.58* (s, 2H, NCH_2Ph), 4.51 (s, 2H, NCH_2Ph), 4.29 (s, 2H, NCH_2C(O)), 4.04* (s, 2H, NCH_2C(O)), 2.99–2.90 (m, 2H, PhCH_2CH$_2$), 2.75–2.65 (m, 2H, PhCH$_2$CH_2), 2.47–2.38* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.7, 194.2*, 173.0, 172.9*, 141.3*, 141.3, 137.7*, 137.6, 137.3*, 137.1*, 137.0, 136.3, 130.1*, 129.4, 129.0, 128.7*, 128.6, 128.5, 127.9, 127.6*, 127.4*, 127.2, 126.7, 126.2*, 125.2, 125.1*, 123.2, 121.7*, 54.9*, 53.3, 52.1, 50.0*, 35.1*, 34.8, 31.5*, 31.4; **IR** (film, cm^{-1}) 3027, 2923, 1643, 1604, 1495, 1451, 1194, 1088, 968, 779, 732, 699; **LRMS** *m/z* (ESI^+) 412.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{24}O_2NS$ $[M+H]^+$: 390.1533, found: 390.1537.

(*E*)-*N*-benzyl-*N*-(5,5-dimethyl-2-oxohex-3-en-1-yl)-3-phenylpropanamide, 54k



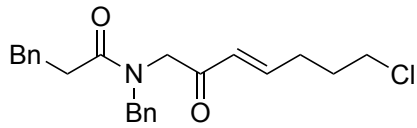
Following general procedure C, the product (69 mg) was isolated by FC (petrol/EtOAc 4:1) in 95% yield as a white amorphous solid, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 3,3-dimethylbut-1-yne (29 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.38–7.26 (m, 5H, 5 × Ar*H*), 7.26–7.18 (m, 3H, 3 × Ar*H*), 7.17–7.10 (m, 2H, 2 × Ar*H*), 6.90 (t, *J* = 16.0, 1H, C(O)CH=C*H*), 6.05 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 5.98* (d, *J* = 16.0, 1H, C(O)C*H*=CH), 4.66* (s, 2H, NCH_2Ph), 4.60 (s, 2H, NCH_2Ph), 4.35 (s, 2H, NCH_2C(O)), 4.09* (s, 2H, NCH_2C(O)), 3.09–3.01 (m, 2H, PhCH_2CH$_2$), 2.84–2.76 (m, 2H, PhCH$_2$CH_2), 2.55–2.49* (m, 2H, PhCH$_2$CH_2), 1.09 (s, 9H, C(CH_3)$_3$), 1.08* (s, 9H, C(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.9, 194.4*, 173.0, 172.9*, 159.2*, 158.2, 141.4*, 141.3, 137.2*, 136.4, 129.0, 128.7*, 128.6*, 128.5, 128.5, 128.4*, 127.8, 127.6*, 126.7, 126.2*, 126.2, 122.9, 121.9*, 54.5*, 53.0, 52.0, 49.9*, 35.1*, 34.8, 34.1*, 34.0, 31.5*, 31.4, 28.6, 28.6*; **IR** (film, cm^{-1}) 2980, 1687, 1648, 1495, 1452, 1207, 1167, 1095, 1077, 945, 735, 699; **LRMS** *m/z* (ESI$^+$) 386.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{24}H_{30}O_2N$ [M+H]$^+$: 364.2282, found: 364.2272; **m.p.** (^{o}C): 78–80.

(*E*)-*N*-benzyl-*N*-(2-oxo-4-(trimethylsilyl)but-3-en-1-yl)-3-phenylpropanamide, 54l



Following general procedure C, the product (65 mg) was isolated by FC (petrol/EtOAc 4:1) in 86% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and ethynyltrimethylsilane (33 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.23–7.11 (m, 5H, C(O)CH=C*H*, 4 × Ar*H*), 7.10–7.01 (m, 4H, 4 × Ar*H*), 7.00–6.91 (m, 2H, 2 × Ar*H*), 6.36 (d, *J* = 19.0, 1H, C(O)C*H*=CH), 6.29* (d, *J* = 19.0, 1H, C(O)C*H*=CH), 4.50* (s, 2H, NCH_2Ph), 4.44 (s, 2H, NCH_2Ph), 4.25 (s, 2H, NCH_2C(O)), 4.01* (s, 2H, NCH_2C(O)), 2.94–2.84 (m, 2H, PhCH_2CH$_2$), 2.69–2.60 (m, 2H, PhCH$_2$CH_2), 2.39–2.31* (m, 2H, PhCH$_2$CH_2), 0.00 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.1, 193.6*, 173.0, 172.9*, 149.8*, 148.5, 141.4*, 141.3, 139.7, 138.8*, 137.2*, 136.4, 129.0, 128.7*, 128.6*, 128.6, 128.6, 128.4*, 127.8, 127.6*, 126.7, 126.2*, 126.2, 53.9*, 52.6, 52.1, 49.9*, 35.2*, 34.8, 31.5*, 31.4, -1.8; **IR** (film, cm^{-1}) 3028, 2954, 1691, 1648, 1495, 1452, 1248, 1206, 1156, 1077, 994, 840, 733, 698; **LRMS** *m/z* (ESI$^+$) 402.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{23}H_{30}O_2NSi$ [M+H]$^+$: 380.2051, found: 380.2040.

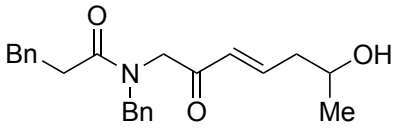
(*E*)-*N*-benzyl-*N*-(7-chloro-2-oxohept-3-en-1-yl)-3-phenylpropanamide, 54m



Following general procedure C, the product (56 mg) was isolated by FC (petrol/EtOAc 4:1) in 73% yield as a pale yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 5-chloropent-1-yne (25 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.39–7.25 (m, 5H, 5 × Ar*H*),

7.25–7.16 (m, 3H, 3 × Ar*H*), 7.15–7.05 (m, 2H, 2 × Ar*H*), 6.94–6.79 (m, 1H, C(O)CH=C*H*CH$_2$), 6.17 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CHCH$_2$), 6.10* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CHCH$_2$), 4.64* (s, 2H, NC*H*$_2$Ph), 4.58 (s, 2H, NC*H*$_2$Ph), 4.31 (s, 2H, NC*H*$_2$C(O)), 4.06* (s, 2H, NC*H*$_2$C(O)), 3.57–3.51 (m, 2H, CH$_2$CH$_2$C*H*$_2$Cl), 3.09–2.99 (m, 2H, PhC*H*$_2$CH$_2$), 2.86–2.75 (m, 2H, PhCH$_2$C*H*$_2$), 2.55–2.46* (m, 2H, PhCH$_2$C*H*$_2$), 2.44–2.27 (m, 2H, C*H*$_2$CH$_2$CH$_2$Cl), 1.99–1.85 (m, 2H, CH$_2$C*H*$_2$CH$_2$Cl); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.2, 193.7*, 173.0, 172.9*, 147.4*, 146.4, 141.4*, 141.3, 137.1*, 136.3, 129.0, 128.7*, 128.6, 128.5, 128.5, 127.9, 127.6*, 127.4*, 126.7, 126.2*, 126.2, 54.5*, 53.0, 52.1, 50.0*, 44.0*, 43.9, 35.1, 34.8,* 31.5*, 31.4, 30.7, 30.6*, 29.7*, 29.7; **IR** (film, cm^{-1}) 3027, 2922, 1686, 1640, 1495, 1451, 1205, 1107, 1076, 978, 735, 699; **LRMS** *m/z* (ESI$^+$) 406.2 ([M(Cl^{35})+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{23}H_{27}O_2N^{35}Cl$ [M+H]$^+$: 384.1725, found: 384.1723.

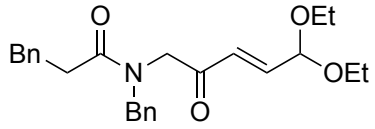
(*E*)-*N*-benzyl-*N*-(6-hydroxy-2-oxohept-3-en-1-yl)-3-phenylpropanamide, 54n



Following general procedure C, the product (31 mg) was isolated by FC (petrol/EtOAc 4:1) in 42% yield as a pale yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and pent-4-yn-2-ol (22 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.29–7.16 (m, 5H, 5 × Ar*H*), 7.15–7.06 (m, 3H, 3 × Ar*H*), 7.05–6.99 (m, 2H, 2 × Ar*H*), 6.90–6.74 (m, 1H, C(O)CH=C*H*), 6.10 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 6.03* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 4.54* (s, 2H, NC*H*$_2$Ph), 4.49 (s, 2H, NC*H*$_2$Ph), 4.23 (s, 2H, NC*H*$_2$C(O)), 3.99* (s, 2H, NC*H*$_2$C(O)), 3.92–3.81 (m, 1H, CH=CHCH$_2$C*H*(OH)CH$_3$), 2.99–2.88 (m, 2H, PhC*H*$_2$CH$_2$), 2.72–2.65 (m, 2H, PhCH$_2$C*H*$_2$), 2.45–2.36* (m, 2H, PhCH$_2$C*H*$_2$), 2.31–2.20 (m, 2H, CH=CHC*H*$_2$), 1.81

(br s, 1H, CH(O*H*)CH_3), 1.69* (br s, 1H, CH(O*H*)CH_3), 1.17–1.13 (m, 3H, CH(OH)CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.3, 193.8*, 173.1, 173.0*, 145.7*, 144.7, 141.4*, 141.3, 137.1*, 136.3, 130.0, 129.1, 128.9*, 128.7*, 128.6, 128.6, 128.5*, 127.9, 127.7*, 126.8*, 126.7, 126.3, 66.8, 66.7*, 54.4*, 53.0, 52.2, 50.0*, 42.4, 42.2*, 35.2*, 34.9, 31.5*, 31.4, 23.6*, 23.5; **IR** (film, cm^{-1}) 3412, 3028, 2925, 1686, 1631, 1495, 1452, 1209, 1077, 736, 700; **LRMS** *m/z* (ESI^+) 388.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{23}H_{28}O_3N$ $[M+H]^+$: 366.2063, found: 366.2060.

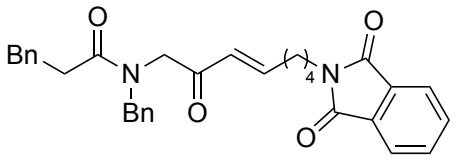
(*E*)-*N*-benzyl-*N*-(5,5-diethoxy-2-oxopent-3-en-1-yl)-3-phenylpropanamide, 54o



Following general procedure C, the product (23 mg) was isolated by FC (petrol/EtOAc 4:1) in 28% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 3,3-diethoxyprop-1-yne (34 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2:1] δ 7.28–7.17 (m, 5H, 5 × Ar*H*), 7.15–7.06 (m, 3H, 3 × Ar*H*), 7.05–6.97 (m, 2H, 2 × Ar*H*), 6.65–6.55 (m, 1H, C(O)CH=C*H*), 6.31 (dd, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 6.25* (dd, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 4.95 (dd, *J* = 4.0, 1.5, 1H, C*H*(OCH_2CH_3)$_2$), 4.93* (dd, *J* = 4.0, 1.5, 1H, C*H*(OCH_2CH_3)$_2$), 4.55* (s, 2H, NCH_2Ph), 4.48 (s, 2H, NCH_2Ph), 4.26 (s, 2H, NCH_2C(O)), 4.01* (s, 2H, NCH_2C(O)), 3.60–3.49 (m, 2H, CHOC$H_2$$CH_3$), 3.48–3.37 (m, 2H, CHOC$H_2$$CH_3$), 2.98–2.89 (m, 2H, PhC$H_2$$CH_2$), 2.73–2.66 (m, 2H, PhC$H_2CH_2$), 2.44–2.35* (m, 2H, PhCH_2CH_2), 1.14 (t, *J* = 7.0, 6H, CH(OCH_2CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.4, 194.0*, 173.1, 172.9*, 143.3*, 142.5, 141.3, 137.0*, 136.2, 129.1, 129.0*, 128.8*, 128.6, 128.6, 128.6, 128.5*, 128.0*, 127.9, 127.7*, 126.8, 126.3*, 126.3, 99.4, 99.2*, 61.9*, 61.7, 54.7*, 53.2, 52.1, 49.9*, 35.2*, 34.9, 31.5*, 31.4, 15.3; **IR** (film, cm^{-1}) 2979, 1695, 1647, 1495,

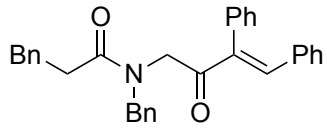
1452, 1133, 1055, 735, 700; **LRMS** *m/z* (ESI^+) 432.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{25}H_{31}O_4NNa$ $[M+Na]^+$: 432.2145, found: 432.2143.

(*E*)-*N*-benzyl-*N*-(8-(1,3-dioxoisoindolin-2-yl)-2-oxooct-3-en-1-yl)-3-phenylpropanamide, 54p



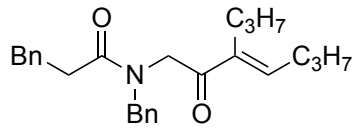
Following general procedure C, the product (71 mg) was isolated by FC (petrol/EtOAc 3:1) in 70% yield as a colourless oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 2-(hex-5-yn-1-yl)isoindoline-1,3-dione (54 mg, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.87–7.79 (m, 2H, 2 × Ar*H*), 7.75–7.67 (m, 2H, 2 × Ar*H*), 7.37–7.22 (m, 5H, 5 × Ar*H*), 7.21–7.14 (m, 3H, 3 × Ar*H*), 7.12–7.07 (m, 2H, 2 × Ar*H*), 6.94–6.77 (m, 1H, C(O)CH=C*H*), 6.10 (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 6.04* (dt, *J* = 16.0, 1.5, 1H, C(O)C*H*=CH), 4.61* (s, 2H, NCH_2Ph), 4.56 (s, 2H, NCH_2Ph), 4.29 (s, 2H, NCH_2C(O)), 4.04* (s, 2H, NCH_2C(O)), 3.71–3.64 (m, 2H, $(CH_2)_3CH_2$N), 3.07–2.95 (m, 2H, PhC$H_2$$CH_2$), 2.81–2.71 (m, 2H, Ph$CH_2CH_2$), 2.64–2.53* (m, 2H, Ph$CH_2CH_2$), 2.51–2.43* (m, 2H, C(O)CH=CHCH_2), 2.30–2.19 (m, 2H, C(O)CH=CHCH_2), 1.79–1.66 (m, 2H, C(O)CH=CH$(CH_2)_2$CH_2), 1.56–1.41 (m, 2H, C(O)CH=CHCH_2CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.4, 173.1, 168.5, 148.8*, 147.9, 141.3, 136.4, 134.1, 134.1*, 134.0*, 132.3, 132.2*, 132.2, 129.1*, 128.7*, 128.6, 128.5*, 128.0, 127.9, 127.6*, 127.2*, 126.8, 126.2, 123.4, 123.3*, 123.3*, 54.4*, 52.9, 52.1, 50.0*, 38.0*, 37.6, 37.5*, 35.2*, 34.9, 32.2, 31.5*, 31.4, 28.2, 28.2*, 25.3, 25.1*; **IR** (film, cm^{-1}) 3028, 2935, 1706, 1643, 1495, 1436, 1369, 1361, 1207, 720, 700; **LRMS** *m/z* (ESI^+) 531.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{32}H_{32}O_4N_2Na$ $[M+Na]^+$: 531.2254, found: 531.2257.

(*E*)-*N*-benzyl-*N*-(2-oxo-3,4-diphenylbut-3-en-1-yl)-3-phenylpropanamide, 54q



Following general procedure C, the product (71 mg) was isolated by FC (petrol/EtOAc 4:1) in 77% yield as a white amorphous solid, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and 1,2-diphenylethyne (36 mg, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.60 (s, 1H, C(O)C=C*H*), 7.49* (s, 1H, C(O)C=C*H*), 7.37–6.87 (m, 20H, 20 × Ar*H*), 4.54* (s, 2H, NCH_2Ph), 4.50 (s, 2H, NCH_2Ph), 4.23 (s, 2H, NCH_2C(O)), 3.92* (s, 2H, NCH_2C(O)), 2.98–2.88 (m, 2H, PhCH_2CH$_2$), 2.73–2.62 (m, 2H, PhCH$_2$CH_2), 2.43–2.34* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 195.8, 195.4, 173.1, 173.0*, 141.5*, 141.4, 139.4*, 139.1, 138.8, 137.2*, 136.5, 136.1, 135.8*, 134.5, 134.1*, 131.2*, 131.1, 129.9*, 129.7, 129.6*, 129.5*, 129.4*, 129.3, 129.0, 128.8*, 128.7*, 128.6, 128.5, 128.5*, 128.4, 128.3, 127.8, 127.6*, 126.8, 126.2, 54.3*, 53.3, 52.2, 50.0*, 35.2*, 35.0, 31.6*, 31.4; **IR** (film, cm^{-1}) 3026, 2926, 1689, 1646, 1607, 1494, 1447, 1195, 1131, 1100, 1075, 755, 732, 697; **LRMS** *m/z* (ESI$^+$) 460.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{32}H_{30}O_2N$ [M+H]$^+$: 460.2271, found: 460.2274; **m.p.** (^{o}C): 89–90.

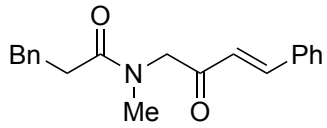
(*E*)-*N*-benzyl-*N*-(2-oxo-3-propylhept-3-en-1-yl)-3-phenylpropanamide, 54r



Following general procedure C, the product (13 mg) was isolated by FC (petrol/EtOAc 4:1) in 17% yield as a pale yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53a**) (56 mg, 0.20 mmol) and oct-4-yne (27 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2.5:1] δ 7.38–7.23 (m, 5H, 5 × Ar*H*),

7.22–7.15 (m, 3H, 3 × Ar*H*), 7.14–7.03 (m, 2H, 2 × Ar*H*), 6.55 (t, *J* = 7.5, 1H, C(O)C=C*H*), 6.35* (t, *J* = 7.5, 1H, C(O)C=C*H*), 4.60* (s, 2H, NCH_2Ph), 4.57 (s, 2H, NCH_2Ph), 4.48 (s, 2H, NCH_2C(O)), 4.20* (s, 2H, NCH_2C(O)), 3.08–2.97 (m, 2H, PhCH_2CH$_2$), 2.82–2.69 (m, 2H, PhCH$_2$CH_2), 2.48–2.39* (m, 2H, PhCH$_2$CH_2), 2.32–2.13 (m, 4H, CH_2C=CHCH_2), 1.53–1.20 (m, 4H, CH_2CH$_2$C=CH CH$_2$CH_2), 1.01–0.79 (m, 6H, 2 × CH$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) *δ* 195.6, 194.9*, 177.2*, 173.1, 143.4, 141.4, 140.7, 136.7, 129.0, 128.7*, 128.6*, 128.6, 128.6, 127.8, 126.8, 126.2, 52.1*, 51.9, 50.9, 50.0*, 35.2*, 35.0, 31.7*, 31.5, 31.0, 31.0*, 28.0, 27.9*, 22.6, 22.5*, 22.2, 22.2*, 14.3, 14.2*, 14.1, 14.1*; **IR** (film, cm^{-1}) 3028, 2959, 2930, 2870, 1680, 1650, 1495, 1453, 1205, 1104, 734, 699; **LRMS** *m/z* (ESI$^+$) 414.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{26}H_{33}O_2NNa$ [M+Na]$^+$: 414.2403, found: 414.2398.

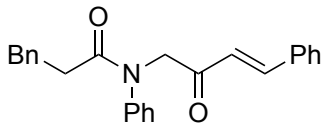
(*E*)-*N*-methyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54s



Following general procedure C, the product (52 mg) was isolated by FC (petrol/EtOAc 4:1) in 85% yield as a yellow oil, starting from *N*-methyl-*N*-(2-oxoethyl)-3-phenylpropanamide (**53s**) (41 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 5:1] *δ* 7.60–7.53 (m, 1H, C(O)CH=C*H*), 7.49–7.41 (m, 2H, 2 × Ar*H*), 7.35–7.27 (m, 3H, 3 × Ar*H*), 7.24–7.05 (m, 5H, 5 × Ar*H*), 6.70–6.60 (m, 1H, C(O)C*H*=CH), 4.39 (s, 2H, NCH_2C(O)), 4.19* (s, 2H, NCH_2C(O)), 3.16–2.85 (m, 5H, NCH_3, PhCH_2CH$_2$), 2.74–2.57 (m, 2H, PhCH$_2$CH_2), 2.45–2.30* (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) *δ* 194.7, 194.0*, 172.8, 172.8*, 144.6*, 143.8, 141.4, 141.4*, 134.3, 133.9*, 131.3*, 130.8, 129.2*, 129.1, 128.6*, 128.6, 128.6*, 128.5, 126.2, 123.3, 121.9*, 58.2*, 56.0, 36.6, 35.3*, 35.1, 35.0*, 31.4*, 31.2; **IR** (film, cm^{-1}) 3026, 2924, 1678, 1642, 1612, 1494, 1451, 1408, 1192, 1090, 980, 750, 699;

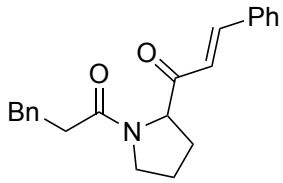
LRMS *m/z* (ESI$^+$) 330.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{20}H_{22}O_2N$ [M+H]$^+$: 308.1645, found: 308.1647.

(*E*)-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-*N*,3-diphenylpropanamide, 54t



Following general procedure C, the product (60 mg) was isolated by FC (petrol/EtOAc 4:1) in 81% yield as a yellow oil, starting from *N*-(2-oxoethyl)-*N*,3-diphenylpropanamide (**53t**) (53 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.47–7.40 (m, 2H, 2 × Ar*H*), 7.34–7.19 (m, 6H, 6 × Ar*H*), 7.18–7.11 (m, 4H, 4 × Ar*H*), 7.10–7.03 (m, 1H, Ar*H*), 7.03–6.95 (m, 2H, 2 × Ar*H*), 6.70 (d, J = 16.0, 1H, C(O)C*H*=CH), 4.63 (s, 2H, NCH_2C(O)), 2.91–2.82 (m, 2H, PhCH_2CH$_2$), 2.44–2.34 (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 193.8, 172.5, 143.6, 143.0, 141.3, 134.4, 130.8, 129.8, 129.0, 128.5, 128.5, 128.4, 128.3, 128.3, 126.1, 123.3, 58.0, 35.9, 31.6; **IR** (film, cm^{-1}) 3026, 2980, 1654, 1612, 1595, 1494, 1450, 1413, 1385, 1188, 1102, 1072, 749, 699; **LRMS** *m/z* (ESI$^+$) 392.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{25}H_{24}O_2N$ [M+H]$^+$: 370.1802, found: 370.1798.

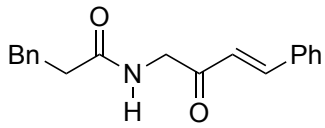
(*E*)-3-phenyl-1-(1-(3-phenylpropanoyl)pyrrolidin-2-yl)prop-2-en-1-one, 54u



Following general procedure C, the product (60 mg) was isolated by FC (petrol/EtOAc 2:1) in 90% yield as a yellow oil, starting from 1-(3-phenylpropanoyl)pyrrolidine-2-carbaldehyde (**53u**) (46 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz,

$CDCl_3$) [the compound exists as two rotamers, in a ratio of 4:1] δ 7.72 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.68–7.65* (m, 1H, 1 × Ar*H*), 7.62–7.52 (m, 2H, 2 × Ar*H*), 7.48–7.32 (m, 3H, 3 × Ar*H*), 7.36–7.11 (m, 5H, 5 × Ar*H*), 6.88 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.79* (d, J = 16.0, 1H, C(O)C*H*=CH), 4.95 (dd, J = 9.0, 4.0, 1H, C*H*C(O)CH=CH), 4.48* (dd, J = 9.0, 4.0, 1H, C*H*C(O)CH=CH), 3.77–3.67* (m, 2H, $NCH_AH_BCH_2$), 3.68–3.57 (m, 1H, $NCH_AH_BCH_2$), 3.50–3.41 (m, 1H, $NCH_AH_BCH_2$), 3.10–2.89 (m, 2H, $PhCH_2CH_2$), 2.77–2.57 (m, 2H, $PhCH_2CH_2$), 2.47–2.23* (m, 2H, $PhCH_2CH_2$), 2.24–2.08* (m, 4H, $NCH_2CH_2CH_2$), 2.11–1.78 (m, 4H, $NCH_2CH_2CH_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 197.7, 171.4*, 170.9, 145.3*, 143.8, 141.5, 141.3*, 135.9*, 135.1, 134.6, 134.0*, 131.2*, 130.6, 129.1*, 128.9, 128.7*, 128.5, 128.5, 128.4*, 127.8*, 126.1, 123.2, 120.6*, 65.3*, 63.6, 47.3, 46.9*, 36.6*, 36.4, 31.3*, 31.1*, 30.9, 28.6, 24.7, 22.7*; **IR** (film, cm^{-1}) 3026, 2971, 1636, 1609, 1575, 1495, 1428, 1331, 1176, 1101, 1075, 982, 757, 699; **LRMS** *m/z* (ESI^+) 356.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{22}H_{24}O_2N$ $[M+H]^+$: 334.1802, found: 334.1803.

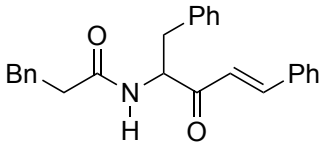
(*E*)-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54v



Following general procedure C, the product (47 mg) was isolated by FC (petrol/EtOAc 1:1) in 80% yield as a white amorphous solid, starting from *N*-(2-oxoethyl)-3-phenylpropanamide (**53v**) (38 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.60–7.51 (m, 2H, 2 × Ar*H*), 7.46–7.38 (m, 3H, 3 × Ar*H*), 7.33–7.26 (m, 2H, 2 × Ar*H*), 7.25–7.17 (m, 3H, 3 × Ar*H*), 6.74 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.44 (t, J = 4.5, 1H, C(O)N*H*), 4.44 (d, J = 4.5, 2H, $NCH_2C(O)$), 3.05–2.96 (m, 2H, $PhCH_2CH_2$), 2.66–2.56 (m, 2H, $PhCH_2CH_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.1, 172.3, 144.6, 140.9, 134.0, 131.3, 129.2, 128.7, 128.6, 128.4, 126.4, 123.2, 47.9, 38.2, 31.7; **IR** (film,

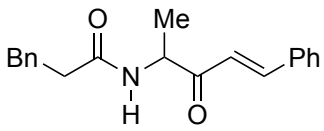
cm^{-1}) 3352, 3028, 1642, 1613, 1516, 1450, 1353, 1077, 980, 746, 690; **LRMS** *m/z* (ESI$^+$) 316.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{19}H_{19}O_2NNa$ [M+Na]$^+$: 316.1308, found: 316.1311; **m.p.** (^{o}C): 119–121.

(*E*)-*N*-(3-oxo-1,5-diphenylpent-4-en-2-yl)-3-phenylpropanamide, 54w



Following general procedure C, the product (67 mg) was isolated by FC (petrol/EtOAc 4:1) in 87% yield as a white amorphous solid, starting from *N*-(1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide (**53w**) (56 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.56–7.48 (m, 2H, 2 × Ar*H*), 7.48–7.38 (m, 3H, 3 × Ar*H*), 7.34–7.19 (m, 8H, 8 × Ar*H*), 7.07–7.00 (m, 2H, 2 × Ar*H*), 6.72 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.3 (t, J = 6.5, 1H, C(O)N*H*), 5.25 (q, J = 6.0, 1H, C(O)NHC*H*), 3.15 (d, J = 6.0, 2H, NHCHCH_2), 3.06–2.93 (m, 2H, PhCH_2CH$_2$), 2.66–2.48 (m, 2H, PhCH$_2$CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 196.9, 171.6, 144.9, 140.8, 136.0, 134.2, 131.2, 129.7, 129.1, 128.7, 128.7, 128.6, 128.5, 127.1, 126.4, 123.1, 57.8, 38.4, 38.2, 31.6.; **IR** (film, cm^{-1}) 3298, 3023, 2980, 1694, 1641, 1613, 1534, 1495, 1449, 752, 697; **LRMS** *m/z* (ESI$^+$) 406.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{26}H_{25}O_2NNa$ [M+Na]$^+$: 406.1777, found: 406.1779; **m.p.** (^{o}C): 194–196.

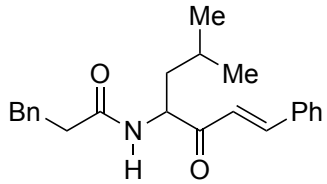
(*E*)-*N*-(3-oxo-5-phenylpent-4-en-2-yl)-3-phenylpropanamide, 54x



Following general procedure C, the product (42 mg) was isolated by FC (petrol/EtOAc 4:1) in 68% yield as a white amorphous solid, starting from *N*-(1-oxopropan-2-yl)-3-

phenylpropanamide (**53x**) (41 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.52–7.45 (m, 2H, 2 × Ar*H*), 7.38–7.28 (m, 3H, 3 × Ar*H*), 7.24–7.16 (m, 2H, 2 × Ar*H*), 7.16–7.07 (m, 3H, 3 × Ar*H*), 6.70 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.36 (d, J = 7.0, 1H, N*H*), 4.89 (p, J = 7.0, 1H, NHC*H*), 2.96–2.85 (m, 2H, PhCH_2CH$_2$), 2.55–2.41 (m, 2H, PhCH$_2$CH_2), 1.29 (d, J = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.1, 171.6, 145.0, 140.8, 134.2, 131.2, 129.2, 128.7, 128.6, 128.5, 126.4, 122.4, 52.6, 38.5, 31.8, 18.7; **IR** (film, cm^{-1}) 3292, 3027, 2930, 1644, 1607, 1532, 1495, 1449, 1069, 980, 760, 698; **LRMS** *m/z* (ESI$^+$) 330.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{20}H_{21}O_2NNa$ [M+Na]$^+$: 330.1464, found: 330.1461; **m.p.** (^{o}C): 94–96.

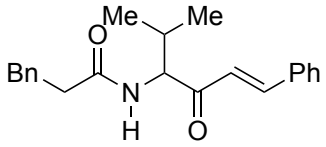
(*E*)-*N*-(6-methyl-3-oxo-1-phenylhept-1-en-4-yl)-3-phenylpropanamide, 54y



Following general procedure C, the product (47 mg) was isolated by FC (petrol/EtOAc 4:1) in 67% yield as a yellow oil, starting from *N*-(4-methyl-1-oxopentan-2-yl)-3-phenylpropanamide (**53y**) (49 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.54–7.45 (m, 2H, 2 × Ar*H*), 7.39–7.31 (m, 3H, 3 × Ar*H*), 7.23–7.17 (m, 2H, 2 × Ar*H*), 7.16–7.08 (m, 3H, 3 × Ar*H*), 6.71 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.00 (d, J = 8.0, 1H, N*H*), 5.03–4.93 (m, 1H, NHC*H*), 2.98–2.85 (m, 2H, PhCH_2CH$_2$), 2.56–2.42 (m, 2H, PhCH$_2$CH_2), 1.58–1.42 (m, 2H, CH_2CH(CH$_3$)$_2$), 1.35–1.25 (m, 1H, C*H*(CH$_3$)$_2$), 0.92 (d, J = 6.5, 3H, CH_3), 0.81 (d, J = 6.5, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.6, 171.9, 144.7, 140.8, 134.3, 131.1, 129.2, 128.7, 128.6, 128.5, 126.4, 123.1, 55.0, 42.0, 38.5, 31.7, 25.0, 23.5, 22.2; **IR** (film, cm^{-1}) 3293, 3028, 2956, 2869,

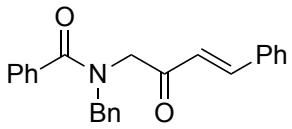
1643, 1609, 1537, 1496, 1450, 1070, 980, 755, 697; **LRMS** *m/z* (ESI^+) 372.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{23}H_{27}O_2NNa$ $[M+Na]^+$: 372.1934, found: 372.1936.

(*E*)-*N*-(2-methyl-4-oxo-6-phenylhex-5-en-3-yl)-3-phenylpropanamide, 54z



Following general procedure C, the product (24 mg) was isolated by FC (petrol/EtOAc 4:1) in 36% yield as a white amorphous solid, starting from *N*-(3-methyl-1-oxobutan-2-yl)-3-phenylpropanamide (**53z**) (47 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.52–7.47 (m, 2H, 2 × Ar*H*), 7.38–7.30 (m, 3H, 3 × Ar*H*), 7.23–7.08 (m, 5H, 5 × Ar*H*), 6.73 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.12 (d, J = 8.5, 1H, C(O)N*H*), 4.92 (dd, J = 8.5, 4.5, 1H, C(O)NHC*H*), 2.98–2.85 (m, 2H, PhCH_2CH$_2$), 2.57–2.44 (m, 2H, PhCH$_2$CH_2), 2.10 (heptd, J = 7.0, 4.5, 1H, C*H*(CH$_3$)$_2$), 0.87 (d, J = 7.0, 3H, CH_3), 0.67 (d, J = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.2, 172.2, 144.5, 140.8, 134.3, 131.1, 129.2, 128.7, 128.7, 128.5, 126.4, 123.7, 61.0, 38.5, 31.8, 31.2, 19.9, 17.1; **IR** (film, cm^{-1}) 3305, 3027, 2962, 2930, 1644, 1608, 1531, 1496, 1450, 1072, 982, 755, 698; **LRMS** *m/z* (ESI^+) 358.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{22}H_{25}O_2N^{23}Na$ $[M+Na]^+$: 358.1777, found: 358.1777; **m.p.** (°C): 86–88.

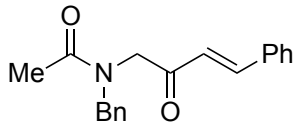
(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)benzamide, 54aa



Following general procedure C, the product (60 mg) was isolated by FC (petrol/EtOAc 4:1) in 84% yield as a white amorphous solid, starting from *N*-benzyl-*N*-(2-oxoethyl)benzamide

(**53aa**) (51 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 2:1] δ 7.65 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.61–7.50 (m, 3H, 3 × Ar*H*), 7.49–7.27 (m, 10H, 10 × Ar*H*), 7.26–7.17 (m, 2H, 2 × Ar*H*), 6.78 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.55* (d, J = 16.0, 1H, C(O)C*H*=CH), 4.86* (s, 2H, NCH_2Ph), 4.65 (s, 2H, NCH_2Ph), 4.53 (s, 2H, NCH_2C(O)), 4.20* (s, 2H, NCH_2C(O)); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.3*, 193.9, 172.6, 144.2*, 143.7, 136.8*, 136.5, 135.6, 134.3, 131.2*, 130.9, 130.0, 129.1, 129.0, 128.9*, 128.6, 128.5, 127.9, 127.2, 127.1, 126.6*, 123.5, 122.3*, 56.2*, 53.9, 52.4, 49.2*; **IR** (film, cm^{-1}) 3060, 2922, 1634, 1612, 1576, 1495, 1450, 1429, 1088, 982, 732, 698; **LRMS** *m/z* (ESI^+) 378.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{21}O_2NNa$ $[M+Na]^+$: 378.1464, found: 378.1465; **m.p.** (°C): 117–119.

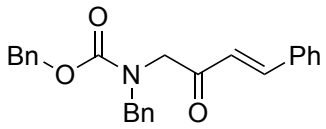
(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)acetamide, 54ab



Following general procedure C, the product (27 mg) was isolated by FC (petrol/EtOAc 4:1) in 46% yield as a yellow oil, starting from *N*-benzyl-*N*-(2-oxoethyl)acetamide (**53ab**) (38 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.58–7.49 (m, 1H, C(O)CH=C*H*), 7.47–7.40 (m, 2H, 2 × Ar*H*), 7.37–7.16 (m, 6H, 6 × Ar*H*), 7.15–7.10 (m, 2H, 2 × Ar*H*), 6.68–6.58 (m, 1H, C(O)C*H*=CH), 4.59* (s, 2H, NCH_2Ph), 4.57 (s, 2H, NCH_2Ph), 4.35 (s, 2H, NCH_2C(O)), 4.17* (s, 2H, NCH_2C(O)), 2.18 (s, 3H, CH_3), 2.00* (s, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) (* denotes minor rotamer) δ 194.5, 194.0*, 171.5, 171.4*, 144.6*, 143.7, 137.1*, 136.4, 134.4, 133.9*, 131.3*, 130.9, 129.2*, 129.1, 129.1, 128.8*, 128.7*, 128.6*, 128.5, 128.0, 127.7*, 126.9, 123.5, 122.1*, 55.9*, 53.1, 53.0, 49.9*, 21.6*, 21.4; **IR**

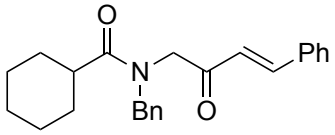
(film, cm^{-1}) 3028, 2923, 1677, 1645, 1613, 1495, 1449, 1240, 1191, 1095, 985, 749, 692; **LRMS** *m/z* (ESI^+) 316.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{19}H_{20}O_2N$ $[M+H]^+$: 294.1499, found: 294.1492.

Benzyl (*E*)-benzyl(2-oxo-4-phenylbut-3-en-1-yl)carbamate, 54ac



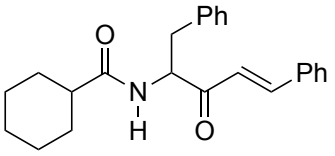
Following general procedure C, the product (20 mg) was isolated by FC (petrol/EtOAc 1:4) in 26% yield as a yellow oil, starting from benzyl benzyl(2-oxoethyl)carbamate (**53ac**) (57 mg, 0.20 mmol) and ethynylbenzene (26 µL, 0.24 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 1:1] δ 7.53 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.49–7.34 (m, 2H, 2 × Ar*H*), 7.33–7.16 (m, 11H, 11 × Ar*H*), 7.15–7.08 (m, 2H, 2 × Ar*H*), 6.63 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.57* (d, J = 16.0, 1H, C(O)C*H*=CH), 5.17 (s, 2H, OCH_2Ph), 5.11* (s, 2H, OCH_2Ph), 4.56 (s, 2H, NCH_2Ph), 4.54* (s, 2H, NCH_2Ph), 4.22 (s, 2H, NCH_2C(O)), 4.11* (s, 2H, NCH_2C(O)); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.9, 194.8*, 156.8, 156.7*, 143.8, 137.1, 136.6, 136.6*, 134.4, 134.2*, 131.0, 130.9*, 129.1, 128.8, 128.6, 128.6*, 128.6, 128.5*, 128.2, 128.1*, 128.0, 128.0*, 127.9, 127.8*, 127.7, 123.1, 122.5*, 67.9, 67.8*, 54.4, 54.3*, 51.9, 51.4*; **IR** (film, cm^{-1}) 3031, 2938, 1700, 1613, 1495, 1451, 1230, 1116, 948, 749, 697; **LRMS** *m/z* (ESI^+) 408.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{25}H_{23}O_3NNa$ $[M+Na]^+$: 408.1570, found: 408.1572.

(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)cyclohexanecarboxamide, 54ad



Following general procedure C, the product (20 mg) was isolated by FC (petrol/EtOAc 4:1) in 28% yield as a yellow oil, starting from N-benzyl-N-(2-oxoethyl)cyclohexanecarboxamide (**53ad**) (52 mg, 0.20 mmol),ethynylbenzene (26 μL, 0.24 mmol) and [Rh(dppe)(C_6H_5F)][BAr^F_4] (29 mg, 0.02 mmol, 10 mol%); **^{1}H-NMR** (400 MHz, $CDCl_3$) [the compound exists as two rotamers, in a ratio of 3:1] δ 7.60–7.49 (m, 1H, C(O)CH=C*H*), 7.48–7.40 (m, 2H, 2 × Ar*H*), 7.38–7.17 (m, 6H, 6 × Ar*H*), 7.16–7.11 (m, 2H, 2 × Ar*H*), 6.69–6.59 (m, 1H, C(O)C*H*=CH), 4.62–4.57 (m, 2H, NCH_2Ph), 4.28 (s, 2H, NCH_2C(O)), 4.18* (s, 2H, NCH_2C(O)), 2.57 (tt, J = 11.5, 3.0, 1H, C(O)C*H*(CH_2)$_5$), 2.14* (tt, J = 11.5, 3.0, 1H, C(O)C*H*(CH_2)$_5$), 1.85–1.66 (m, 4H, 2 × CH_2), 1.65–1.46 (m, 3H, 1.5 × CH_2), 1.29–1.06 (m, 3H, 1.5 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.9, 177.2, 144.5*, 143.6, 136.9, 134.5, 130.8, 129.2*, 129.1, 129.1, 128.8*, 128.7*, 128.5, 128.4*, 127.9, 127.6*, 126.9, 123.5, 122.0*, 55.1*, 53.3, 52.0, 49.8*, 41.2*, 40.7, 29.7, 29.7*, 25.9*, 25.9; **IR** (film, cm^{-1}) 2927, 2853, 1639, 1613, 1494, 1449, 1202, 1176, 1090, 749, 693; **LRMS** *m/z* (ESI$^+$) 384.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{24}H_{27}O_2NNa$ [M+Na]$^+$: 384.1934, found: 384.1930.

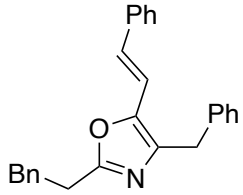
(*E*)-*N*-(3-oxo-1,5-diphenylpent-4-en-2-yl)cyclohexanecarboxamide, 54ae



Following general procedure C, the product (32 mg) was isolated by FC (petrol/EtOAc 4:1) in 44% yield as a pale yellow solid, starting from *N*-(1-oxo-3-phenylpropan-2-yl)cyclohexanecarboxamide (**53ae**) (52 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24

mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, J = 16.0, 1H, C(O)CH=C*H*), 7.48–7.37 (m, 2H, 2 × Ar*H*), 7.39–7.26 (m, 3H, 3 × Ar*H*), 7.24–7.09 (m, 3H, 3 × Ar*H*), 7.10–6.99 (m, 2H, 2 × Ar*H*), 6.65 (d, J = 16.0, 1H, C(O)C*H*=CH), 6.23 (d, J = 7.5, 1H, N*H*), 5.19–5.08 (m, 1H, NHC*H*), 3.10 (app qd, J = 14.0, 6.0, 2H, CH_2Ph), 2.05 (tt, J = 12.0, 3.5, 1H, C*H*$(CH_2)_5$), 1.83–1.49 (m, 5H, 2.5 × CH_2), 1.44–1.25 (m, 2H, CH_2), 1.27–1.05 (m, 3H, 1.5 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 197.1, 175.5, 144.7, 136.0, 134.1, 131.0, 129.6, 129.0, 128.6, 128.4, 127.0, 123.0, 57.5, 45.4, 38.1, 29.7, 29.4, 25.7, 25.6; **IR** (film, cm^{-1}) 3292, 3028, 2927, 2853, 1642, 1609, 1576, 1495. 1449, 1332, 1070, 981, 759, 729, 698; **LRMS** *m/z* (ESI$^+$) 384.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{24}H_{27}O_2NNa$ [M+Na]$^+$: 384.1934, found: 384.1926; **m.p.** (^{o}C): 111–113.

(*E*)-4-benzyl-2-phenethyl-5-styryloxazole, 55



Compound **55** was synthesised by modifying a literature procedure.[138] To a solution of (*E*)-*N*-(3-oxo-1,5-diphenylpent-4-en-2-yl)-3-phenylpropanamide (**54w**) (100 mg, 0.26 mmol) in dry toluene (2 mL) was added $POCl_3$ (0.5 mL, 0.52 mmol, 2 equiv.) at room temperature. The solution was stirred at 95 ^{o}C for 12 hours. After cooling to room temperature, the mixture was poured into water. By addition of an aqueous solution of NaOH (4 M) at 0 ^{o}C, the pH was adjusted to 7. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was subjected to FC (petrol/EtOAc 5:1) to afford the the title compound as a yellow amorphous solid (90 mg, 92%); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H, 2 × Ar*H*), 7.44–7.24 (m, 13H, 13 × Ar*H*), 7.00 (d, J = 16.0, 1H, PhC*H*=CH), 6.79 (d, J = 16.0, 1H, PhCH=C*H*), 4.02 (s, 2H, PhCH_2),

3.25–3.08 (m, 4H, PhCH_2CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 162.9, 145.6, 140.5, 138.8, 136.9, 136.6, 128.8, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 126.6, 126.4, 112.7, 33.4, 32.6, 30.4.; **IR** (film, cm^{-1}) 3026, 2360, 1601, 1572, 1494, 1453, 1428, 1157, 1075, 1029, 953, 750, 717, 694; **LRMS** *m/z* (ESI^+) 366.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{26}H_{24}ON$ $[M+H]^+$: 366.1852, found: 366.1843; **m.p.** (°C): 73–75.

5.3 Chapter 3 Experimental

General procedure D for the preparation of bisamides from malonic acids and secondary amines:

Following the procedure by the Willis group,[105] to a round bottomed flask containing the monosubstituted malonic acid (10.0 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL, 0.2 M) was added the amine (22.0 mmol, 2.2 equiv.) and EDCI·HCl (22.0 mmol, 2.2 equiv.). The reaction mixture was left to stir for 18 hours, followed by quenching with sat. aq. $NaHCO_3$ solution (50 mL). The layers were separated, and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

General procedure E for the preparation of substituted bisamides from unsubstituted bisamide 68:

A round bottomed flask containing LHMDS (12 mmol, 1.2 equiv.) in THF (48 mL, 0.25 M) was cooled to -78 °C. Compound **68** (10 mmol, 1 equiv.) was then added and stirred for 1 hour. Alkyl bromide (25 mmol, 2.5 equiv.) was then added dropwise and stirred for 1 hour at the same temperature. The solution was then warmed to room temperature and stirred until complete consumption of starting material. The reaction was quenched by addition of saturated NH_4Cl solution. The layers were separated, and the organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography to yield the corresponding product.

General procedure F for the preparation of aldehydes from substituted bisamides:

Diisobutylaluminum hydride (1.0 M in CH_2Cl_2, 3 mmol, 1.0 equiv.) was added dropwise to the solution of bisamide (3 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL, 0.1 M) at –78 °C. The solution was stirred at that temperature for 1 hour, quenched by slow addition of Rochelle Salt solution (30 mL), and the mixture was allowed to warm to RT. The organic phase was washed with Rochelle Salt solution (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

General procedure G for the preparation of amides from carboxylic acids and secondary amines:

Following the procedure by the Willis group,[105] to a round bottomed flask containing the carboxylic acid (10.0 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL, 0.2 M) was added the amine (12.0 mmol, 1.2 equiv.) and EDCI·HCl (12.0 mmol, 1.2 equiv.). The reaction mixture was left to stir for 18 hours, followed by quenching with sat. aq. $NaHCO_3$ solution (50 mL). The layers were separated, and the organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

General procedure H for the preparation of aldehydes from amides:

Following the procedure by the Johnson group, [141] a round bottomed flask containing distilled diisopropylamine (4.2 mL, 30 mmol) in Et_2O (30 mL) was cooled to –78 °C. *n*-BuLi (12.0 mL, 2.5 M, 30 mmol) was then added dropwise and the mixture was left to stir for 5 minutes. Amide (10 mmol) was subsequently added dropwise and the reaction mixture was warmed to 0 °C and stirred for 1 h. The mixture was then cooled to –78 °C followed by dropwise addition of

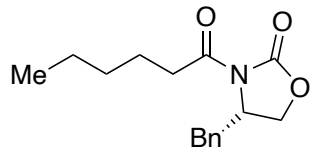
methyl formate (6.2 mL, 100 mmol). The solution was warmed to room temperature and left to stir for 16 h, followed by careful quenching with 1 N HCl (20 mL) and dilution with CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

General procedure I for the enantioselective hydroacylation of b-amido aldehydes:

$[Rh(nbd)_2]BF_4$ (7.5 mg, 0.02 mmol, 10 mol%) and (*R*)-DMMGarphos (17.5 mg, 0.02 mmol, 10 mol%) were added to a microwave vial equipped with a stirrer bar. The vial was placed under vacuum and then backfilled with nitrogen gas three times. Dry DCE (0.2 mL, 1.0 M) was added and hydrogen gas was bubbled through the solution for 2 min. The solution was then purged with nitrogen gas until dryness, and the solids were dissolved in dry DCE (0.2 mL, 1.0 M). The catalyst solution was then added to a vial containing the corresponding aldehyde (0.2 mmol, 1.0 equiv.) and Cs_2CO_3 (6.5 mg, 0.04 mmol, 20 mol%). Next, the corresponding alkyne (0.24 mmol, 1.2 equiv.) was added and the reaction mixture was heated at 55 °C for 10 min. The reaction mixture was then diluted with Et_2O and filtered through a plug of silica. The filtrate was then concentrated in *vacuo*. The crude product was subjected to flash column chromatographical purification (FC) to afford the corresponding pure product.

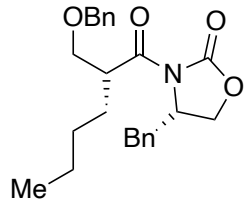
The racemic compounds (for determining the ers) were prepared using 5 mol% of $[Rh(nbd)_2]BF_4$ and 5 mol% of *rac*-BINAP as ligand, without addition of Cs_2CO_3. Acetone was used as solvent and reaction mixture was heated at 55 °C for 1 hour.

(*S*)-4-Benzyl-3-hexanoyloxazolidin-2-one, 58



A solution of (*S*)-(-)-4-benzyl-2-oxazolidinone (1.50 g, 8.46 mmol) in 10 mL of THF cooled to –78 °C was treated with a 2.2 M solution of ^{n}BuLi in hexane (3.7 mL, 8.46 mmol, 2.2 M in hexane, 1 equiv.) over 20 min. Caproyl chloride (1.19 mL, 8.71 mmol, 1.02 equiv.) was then added dropwise over 10 min, and the mixture was stirred for another 60 min at –78 °C. It was then allowed to reach ambient temperature and was stirred for 90 min before quenching with saturated aqueous NH_4Cl (6 mL). The mixture was stirred for 15 min at ambient temperature, and after dilution with H_2O (6 mL), the layers were separated. The organic layer was concentrated in *vacuo*, and the crude material was dissolved in 5:1 hexane/EtOAc (14 mL) containing 1% MeOH. This solution was washed successively with saturated aqueous NH_4Cl (6 mL) and H_2O (3 mL), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude was purified by FC (hexane/EtOAc 6:1) to afford acyl oxazolidinone **58** (2.26 g, 97%) as a colourless liquid. $[\alpha]_D^{25}$: +52.8 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.39–7.19 (m, 5H, 5 × Ar*H*), 4.69 (ddt, *J* = 10.0, 7.0, 3.5, 1H, $PhCH_2CHN$), 4.31–4.09 (m, 2H, $CHCH_2O$), 3.31 (dd, *J* = 13.5, 3.5, 1H, $PhCH_AH_B$), 3.04–2.85 (m, 2H, CH_2CH_2CO), 2.79 (dd, *J* = 13.5, 9.5, 1H, $PhCH_AH_B$), 1.79–1.64 (m, 2H, $COCH_2CH_2CH_2CH_2$), 1.46–1.27 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.01–0.87 (m, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.6, 153.6, 135.5, 129.6, 129.1, 127.5, 66.3, 55.3, 38.1, 35.7, 31.5, 24.1, 22.6, 14.1; **IR** (film, cm^{-1}) 2930, 2869, 1777, 1698, 1454, 1385, 1352, 1293, 1250, 1210, 1129, 1096, 1051, 1017, 914, 761, 731, 701; **LRMS** *m/z* (ESI^+) 298.0 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{16}H_{21}NO_3Na$ $[M+Na]^+$: 298.1413, found: 298.1428.

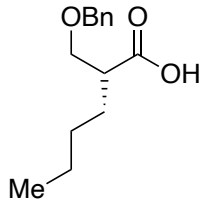
(*S*)-4-Benzyl-3-{(R)-2-[(benzyloxy)methyl]hexanoyl}oxazolidin-2-one, 59



A three-neck 100 mL flask was charged with a solution of acyl oxazolidinone **58** (1.70 g, 6.17 mmol, 1 equiv.) in CH_2Cl_2 (7 mL). The solution was cooled to 4 °C and was treated with $TiCl_4$ (0.68 mL, 6.17 mmol, 1 equiv.) over 20 min, resulting in the formation of an abundant yellow precipitate. After 10 min, diisopropylethylamine (1.11 mL, 6.38 mmol, 1.03 equiv.) was added over 10 min, and the resulting dark brown solution was stirred at 4 °C for 60 min. Then benzyl chloromethyl ether (1.06 mL, 7.65 mmol, 1.2 equiv.) was then added over 5 min. The mixture was stirred for 60 min at 4 °C, after which CH_2Cl_2 (2 mL) was added to rinse the sides of the reaction vessel and the mixture was stirred for another 5 h at 4 °C. CH_2Cl_2 (4 mL), saturated aqueous NH_4Cl (4 mL), and H_2O (4 mL) were then added sequentially, and the suspension was vigorously stirred for 30 min while warming to RT. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (2 × 4 mL), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude material was purified by FC (hexane/EtOAc 8:1) to afford 1.95 g (80%) of desired pure benzyl ether **59** as white crystals; $[\alpha]_D^{25}$: +34.4 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.40–7.17 (m, 10H, 10 × Ar*H*), 4.75 (ddt, *J* = 9.5, 8.0, 3.0, 1H, Bn(C*H*)N), 4.57 (d, *J* = 2.0, 2H, ArCH_2O), 4.27 (tdd, *J* = 8.0, 6.0, 5.0, 1H, CH_2(C*H*)CO), 4.23–4.11 (m, 2H, BnOCH_2), 3.82 (dd, *J* = 9.0, 8.5, 1H, CHCH_AH$_B$O), 3.68 (dd, *J* = 9.0, 5.0, 1H, CHCH$_A$$H_B$O), 3.26 (dd, *J* = 13.5, 3.5, 1H, ArH_AH$_B$CH), 2.70 (dd, *J* = 13.5, 9.5, 1H, ArCH$_A$$H_B$CH), 1.81–1.65 (m, 1H, CHCH_AH$_B$CH$_2$), 1.64–1.46 (m, 1H, CHCH$_A$$H_BCH_2$), 1.32 (m, 4H, $CH_2C$$H_2CH_2CH_3$), 0.97–0.82 (m, 3H, C$H_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 175.5, 153.4, 138.4, 135.6, 129.7, 129.1, 128.5, 127.9, 127.8, 127.4, 73.3, 71.7, 66.0, 55.5, 43.6, 37.9, 29.5, 29.0, 23.0, 14.1; **IR** (film, cm^{-1}) 2929, 2862, 1776, 1696, 1454, 1387, 1351, 1288, 1209,

1099, 1013, 965, 911, 737, 699; **LRMS** *m/z* (ESI^+) 418.2 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{29}NO_4Na$ $[M+Na]^+$: 418.1989, found: 418.1987; **m.p.** (°C): 57–59.

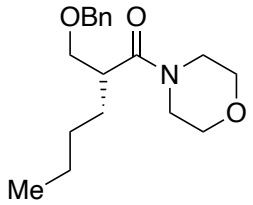
(*R*)-2-[(Benzyloxy)methyl]hexanoic acid, 60



A cold (4 °C) solution of benzyl ether **59** (1.09 g, 2.75 mmol, 1 equiv.) in 2:1 THF/H_2O (7.5 mL) was treated successively with 30% aqueous H_2O_2 (1.05 mL) and lithium hydroxide monohydrate (131 mg, 5.5 mmol, 2 equiv.). The mixture was stirred at 4 °C for 48 h and was then treated carefully, first with a solution of Na_2SO_3 (1.60 g, 13.06 mmol) in H_2O (6 mL) and then with a solution of $NaHCO_3$ (0.67 g, 8.02 mmol) in H_2O (6 mL). The mixture was stirred for 60 min at room temperature and diluted with H_2O (6 mL). The organic layer was separated from the aqueous layer and concentrated *in vacuo*. The residue was poured back into the aqueous layer, which was then extracted with CH_2Cl_2 (5 × 3 mL), cooled to 0 °C, acidified with 6 N aqueous HCl (5 mL), and extracted with CH_2Cl_2 (4 × 3 mL). The combined organic layers were then washed with brine (3 mL), dried over $MgSO_4$, and concentrated in *vacuo*, affording 554 mg (85%) of the desired carboxylic acid **60** as a colourless oil. $[\alpha]_D^{25}$: –4.5 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 11.90 (br s, 1H, CO_2H), 7.50–7.25 (m, 5H, 5 × Ar*H*), 4.61 (s, 2H, ArCH_2), 3.75 (dd, *J* = 9.0, 8.0, 1H, $PhCH_2OCH_AH_B$), 3.63 (dd, *J* = 9.0, 5.5, 1H, $PhCH_2OCH_AH_B$), 2.80 (m, 1H, $CH_2(CH)CO$), 1.79–1.66 (m, 1H, $CHCH_AH_BCH_2$), 1.66–1.55 (m, 1H, $CHCH_AH_BCH_2$), 1.39 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.03–0.90 (m, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 180.9, 138.1, 128.5, 127.8, 127.7, 73.2, 70.6, 46.2, 29.4, 28.5, 22.7, 14.0; **IR** (film, cm^{-1}) 2930, 2862, 1706, 1454, 1220, 1099, 909, 733, 697; **LRMS** *m/z*

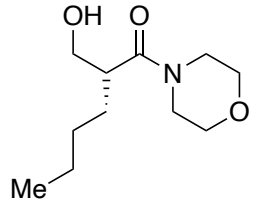
(ESI$^+$) 259.1 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{14}H_{20}O_3Na$ [M+Na]$^+$: 259.1305, found: 259.1305.

(*R*)-2-[(Benzyloxy)methyl]-1-morpholinohexan-1-one, 61



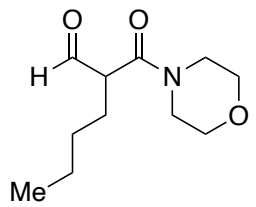
A cooled (4 °C) solution of **60** (435 mg, 1.84 mmol) in MeCN (2 mL), morpholine (0.18 mL, 2.17 mmol) and HBTU (761 mg, 2 mmol) was treated with diisopropylethylamine (0.63 mL, 3.68 mmol). The mixture was stirred at 4 °C for 2 h and then concentrated in *vacuo* and partitioned between ether (2 mL) and H_2O (10 ml). The aqueous layer was extracted with ether (2 × 2 mL), and the combined organic layers were washed successively with aqueous 1 N HCl (2 × 1 mL), saturated aqueous $NaHCO_3$ (2 mL), and brine (2 mL) and then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by FC (hexane/EtOAc 3:1) to afford pure amide **61** (480 mg 87%) as a clear, colourless oil. $[\alpha]_D^{25}$: +11.5 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34–7.11 (m, 5H, 5 × Ar*H*), 4.50–4.27 (m, 2H, ArCH_2), 3.73 (m, 1H, CHCH_AH$_B$OBn), 3.65–3.34 (m, 9H, CHCH$_A$$H_B$OBn, 2 × NC$H_2$, 2 × OC$H_2$), 2.90 (tt, *J* = 9.0, 5.0, 1H, CH$_2$(C*H*)CO), 1.65–1.49 (m, 1H, CHCH_AH$_B$CH$_2$), 1.35 (ddt, *J* = 13.0, 10.5, 5.5, 1H, CHCH$_A$$H_BCH_2$), 1.27–1.02 (m, 4H, CH$_2CH_2CH_2CH_3$), 0.80 (t, *J* = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 173.4, 138.3, 128.5, 127.8, 127.7, 73.5, 72.8, 67.2, 67.1, 46.5, 42.5, 41.7, 29.7, 29.4, 22.9, 14.1; **IR** (film, cm^{-1}) 3059, 2925, 2856, 1773, 1638, 1436, 1358, 1268, 1230, 1113, 1009, 847, 731; **LRMS** *m/z* (ESI$^+$) 328.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{18}H_{27}NO_3Na$ [M+Na]$^+$: 328.1883, found: 328.1880.

(*R*)-2-(Hydroxymethyl)-1-morpholinohexan-1-one, 62



To a solution of amide **61** (390 mg, 1.27 mmol, 1 equiv.) in MeOH (2 mL) was added 20% $Pd(OH)_2/C$ (10.0 mg, 0.05 equiv.), and the suspension was placed under an H_2 atmosphere and stirred at room temperature for 48 h. The catalyst was filtered over Celite and concentrated in *vacuo*. The crude mixture was purified by FC (10% MeOH in CH_2Cl_2) to afford alcohol **62** (270 mg 99%) as a colorless oil. $[\alpha]_D^{25}$: +1.0 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.83–3.58 (m, 8H, 2 × NC*H*$_2$, 2 × OC*H*$_2$), 3.58–3.43 (m, 2H, C*H*$_2$OH), 3.11 (dd, *J* = 7.0, 5.0, 1H, CH_2O*H*), 2.75 (m, 1H, CH_2(C*H*)CO), 1.67–1.44 (m, 2H, CHC*H*$_2$$CH_2$), 1.29 (m, 4H, CH_2C*H*$_2$C*H*$_2$$CH_3$), 0.88 (t, *J* = 7.0, 3H, C*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 174.7, 67.1, 67.0, 63.3, 46.4, 42.3, 42.2, 29.6, 28.7, 23.0, 14.1; **IR** (film, cm^{-1}) 3410, 2957, 2859, 1615, 1441, 1358, 1302, 1266, 1236, 1114, 1066, 1038, 940; **LRMS** *m/z* (ESI^+) 238.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) calc. for $C_{11}H_{22}NO_3$ $[M+H]^+$: 216.1594, found: 216.1593; The er was determined by HPLC using a Chiralpak OJ-H column [^{n}hexane/^{i}PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 9.55 min, τ_{minor} = 11.75 min (>99:1 er).

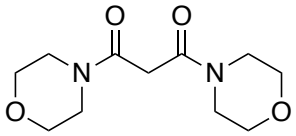
2-(Morpholine-4-carbonyl)hexanal, 63



To a solution of alcohol **62** (225 mg, 1.04 mmol, 1 equiv.) in wet CH_2Cl_2 (5.2 mL, prepared by stirring CH_2Cl_2 with water and separating the organic layer) was added Dess-Martin periodinane (650 mg, 1.56 mmol, 1.5 equiv.) in portions. The mixture was stirred at room

temperature for 60 min and then cooled to 4 °C and treated with 10 mL of 0.64 M aqueous $Na_2S_2O_3$ solution (2 mL) containing 420 mg of $NaHCO_3$. The mixture was stirred for 5 min, and then ether (10 mL) was added and the biphasic mixture was stirred vigorously for an additional 10 min at ambient temperature. The layers were separated, and the aqueous layer was extracted with 20% CH_2Cl_2/Et_2O (2 × 3 mL). The combined organic layers were then washed successively with H_2O (2 × 3 mL) and brine (2 × 3 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude mixture was purified by FC (hexane/EtOAc 1:1) to afford 168 mg (75%) of desired aldehyde **63** as colourless oil; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.53 (d, J = 3.0, 1H, C*H*O), 3.74–3.23 (m, 9H, 2 × NCH_2, 2 × OCH_2, CO(C*H*)CO), 1.86 (dt, J = 6.0, 1.5, 2H, CHCH_2CH$_2$), 1.41–1.08 (m, 4H, CH$_2$CH_2CH_2CH$_3$), 0.95–0.74 (m, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 199.2, 167.3, 66.8, 66.7, 55.3, 46.2, 42.3, 29.3, 27.3, 22.5, 13.8; **IR** (film, cm^{-1}) 2961, 2859, 1763, 1635, 1440, 1270, 1114, 1071, 1009, 848, 730, 687; **LRMS** *m/z* (ESI$^+$) 236.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{11}H_{19}NO_3Na$ [M+Na]$^+$: 236.1257, found: 236.1265.

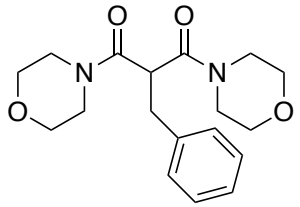
1,3-dimorpholinopropane-1,3-dione, 68



To a round bottomed flask containing morpholine (9 mL, 105 mmol, 3 equiv.) in CH_2Cl_2 (100 mL) was added a solution of malonyl chloride (5.0 g, 35.0 mmol, 1 equiv.) in CH_2Cl_2 (75 mL) at 0 ºC over 30 mins. The solution was then warmed to room temperature and stirred for 18 hours, followed by quenching with sat. aq. $NaHCO_3$ solution (100 mL). The layers were separated, and the organic layer was washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The product (3.6 g) was isolated by FC (100 % EtOAc) in 42% yield as a white solid; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.72–3.59 (m, 16H, 4 × NCH_2,

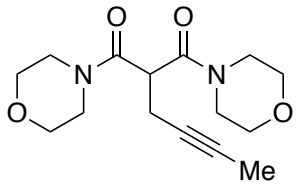
4 × OCH_2), 3.51 (s, 2H, CO(CH_2)CO); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 165.3, 66.8, 47.0, 42.5, 40.8; **IR** (film, cm^{-1}) 3451, 2859, 1620, 1438, 1271, 1110, 972, 851; **LRMS** *m/z* (ESI^+) 265.0 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{11}H_{18}N_2O_4Na$ $[M+Na]^+$: 265.1159, found: 265.1158; **m.p.** (°C): 134–136.

2-benzyl-1,3-dimorpholinopropane-1,3-dione, 64a



Following general procedure E, the product (629 mg) was isolated by FC (100 % EtOAc) in 92% yield as a white solid, starting from 1,3-dimorpholinopropane-1,3-dione (**68**) (500 mg, 2.06 mmol) and benzyl bromide (0.6 mL, 5.15 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.29–7.09 (m, 5H, 5 × Ar*H*), 3.84 (t, *J* = 7.5, 1H, CO(C*H*)CO), 3.67–3.13 (m, 18H, 4 × NCH_2, 4 × OCH_2, PhCH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.8, 138.7, 129.4, 128.8, 127.1, 66.9, 66.3, 50.5, 46.0, 42.8, 35.9; **IR** (film, cm^{-1}) 3503, 2962, 2918, 2856, 1632, 1431, 1238, 1113, 727; **LRMS** *m/z* (ESI^+) 333.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{18}H_{25}N_2O_4$ $[M+H]^+$: 333.1809, found: 333.1805; **m.p.** (°C): 173–176.

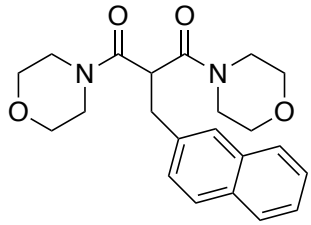
2-(but-2-yn-1-yl)-1,3-dimorpholinopropane-1,3-dione, 64l



Following general procedure E, the product (2.23 g) was isolated by FC (100 % EtOAc) in 92% yield as a white solid, starting from 1,3-dimorpholinopropane-1,3-dione (**68**) (2 g, 8.25

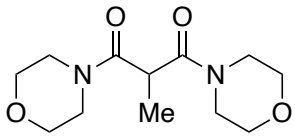
mmol) and 1-bromobut-2-yne (1.78 mL, 20.6 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.83 (t, J = 7.5, 1H, CO(C*H*)CO), 3.74–3.44 (m, 16H, 4 × NCH_2, 4 × OCH_2), 2.78 (dq, J = 7.5, 2.5, 2H, CHCH_2C≡CCH$_3$), 1.76 (t, J = 2.5, 3H, CHCH$_2$C≡CCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.2, 78.0, 75.8, 67.0, 66.6, 48.4, 46.3, 42.9, 19.6, 3.8; **IR** (film, cm^{-1}) 3507, 2920, 2855, 1633, 1433, 1112; **LRMS** *m/z* (ESI$^+$) 317.0 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{15}H_{22}O_4N_2Na$ [M+Na]$^+$: 317.1471, found: 317.1468; **m.p.** (°C): 173–176.

1,3-dimorpholino-2-(naphthalen-2-ylmethyl)propane-1,3-dione, 64m



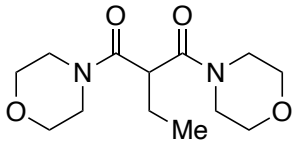
Following general procedure E, the product (800 mg) was isolated by FC (100 % EtOAc) in 51% yield as a white solid, starting from 1,3-dimorpholinopropane-1,3-dione (**68**) (1 g, 4.12 mmol) and 2-(bromomethyl)naphthalene (2.26 g, 10.3 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 3H, 3 × Ar*H*), 7.68 (s, 1H, Ar*H*), 7.51–7.41 (m, 2H, 2 × Ar*H*), 7.35 (d, J = 8.5, 1H, Ar*H*), 3.99 (t, J = 7.5, 1H, CO(C*H*)CO), 3.72–3.18 (m, 18H, 4 × NCH_2, 4 × OCH_2, ArCH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.7, 136.1, 133.6, 132.4, 128.4, 127.8, 127.8, 127.6, 127.5, 126.5, 125.9, 66.9, 66.3, 50.8, 46.1, 42.8, 36.0; **IR** (film, cm^{-1}) 3494, 2966, 2856, 1633, 1431, 1302, 1113, 1023; **LRMS** *m/z* (ESI$^+$) 405.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{22}H_{27}N_2O_4$ [M+H]$^+$: 383.1965, found: 383.1959; **m.p.** (°C): 200–203.

2-methyl-1,3-dimorpholinopropane-1,3-dione, 64r



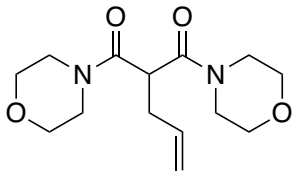
Following general procedure D, the product (1.0 g) was isolated by FC (100% EtOAc) in 39% yield as a white solid, starting from 2-methylmalonic acid (1.18 g, 10 mmol), morpholine (1.89 mL, 22 mmol) and EDCI·HCl (4.22 g, 22 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.72–3.48 (m, 17H, , 4 × NCH_2, 4 × OCH_2, CO(CH)CO), 1.42 (d, J = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.0, 67.0, 66.7, 46.2, 44.8, 42.8, 14.2; **IR** (film, cm^{-1}) 3497, 2857, 1626, 1432, 1216, 1110, 1029, 847; **LRMS** *m/z* (ESI^+) 279.2 ([M+Na]$^+$, 100%); **HRMS** (ESI^+) calc. for $C_{12}H_{21}O_4N_2Na$ [M+H]$^+$: 257.1496, found: 257.1494; **m.p.** (^{o}C): 170–172.

2-ethyl-1,3-dimorpholinopropane-1,3-dione, 64s



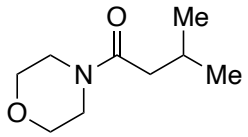
Following general procedure D, the product (1.75 g) was isolated by FC (100% EtOAc) in 34% yield as a white solid, starting from 2-ethylmalonic acid (2.5 g, 18.9 mmol), morpholine (3.57 mL, 41.5 mmol) and EDCI·HCl (7.96 g, 41.5 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.73–3.41 (m, 17H, 4 × NCH_2, 4 × OCH_2, CO(CH)CO), 1.92 (p, J = 7.5, 2H, CH_2CH$_3$), 1.00 (t, J = 7.5, 3H, CH$_2$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 168.1, 67.1, 66.8, 53.2, 46.2, 42.9, 22.4, 12.7; **IR** (film, cm^{-1}) 3506, 2964, 2855, 1623, 1428, 1266, 1111, 1034, 870; **LRMS** *m/z* (ESI^+) 293.2 ([M+Na]$^+$, 100%); **HRMS** (ESI^+) calc. for $C_{13}H_{22}O_4N_2Na$ [M+Na]$^+$: 293.1472, found: 293.1470; **m.p.** (^{o}C): 132–135.

2-allyl-1,3-dimorpholinopropane-1,3-dione, 64t



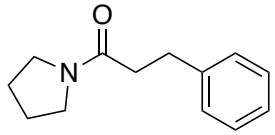
Following general procedure D, the product (2.26 g) was isolated by FC (100% EtOAc) in 40% yield as a white solid, starting from 2-allylmalonic acid (2.9 g, 20 mmol), morpholine (3.78 mL, 44 mmol) and EDCI·HCl (8.44 g, 44 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.88–5.78 (m, 1H, CH_2=C*H*CH_2), 5.17–5.03 (m, 2H, C*H*$_2$=CHCH_2), 3.72–3.48 (m, 17H, 4 × NC*H*$_2$, 4 × OC*H*$_2$, CO(C*H*)CO), 2.65 (t, *J* = 7.0, 2H, CH_2=CHC*H*$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.6, 135.1, 117.5, 67.1, 66.7, 50.7, 46.2, 42.9, 33.4; **IR** (film, cm^{-1}) 3496, 2856, 1628, 1431, 1301, 1111, 923, 847; **LRMS** *m/z* (ESI$^+$) 305.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{14}H_{22}O_4N_2Na$ [M+Na]$^+$: 305.1472, found: 305.1466; **m.p.** (^{o}C): 110–112.

3-methyl-1-morpholinobutan-1-one, 67n



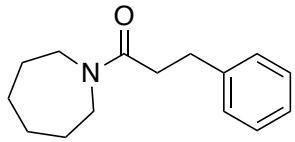
Following general procedure G, the product (4.90 g) was isolated by FC (petrol/EtOAc 1:1) in 95% yield as a colourless oil, starting from 3-methylbutanoic acid (3.31 mL, 30 mmol), morpholine (3.09 mL, 36 mmol) and EDCI·HCl (6.8 g, 36 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.71–3.57 (m, 6H, 2 × OC*H*$_2$CH$_2$N, OCH$_2$C*H*$_2$N), 3.51–3.42 (m, 2H, OCH$_2$C*H*$_2$N), 2.18 (d, *J* = 6.5, 2H, C(O)C*H*$_2$), 2.16–2.02 (m, 1H, CH$_2$C*H*(CH$_3$)$_2$), 0.96 (d, *J* = 6.5, 6H, CH$_2$CH(C*H*$_3$)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) 171.3, 67.1, 66.8, 46.4, 42.0, 41.9, 25.9, 22.8; **LRMS** *m/z* (ESI$^+$) 194.0 ([M+Na]$^+$, 100%). Data is consistent with the literature. [105, 141]

3-phenyl-1-(pyrrolidin-1-yl)propan-1-one, 67p



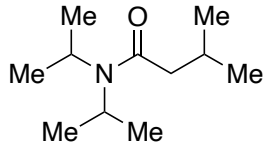
Following general procedure G, the product (4.56 g) was isolated by FC (petrol/EtOAc 1:1) in 75% yield as a colourless oil, starting from hydrocinnamic acid (4.5 g, 30 mmol), pyrrolidine (3.0 mL, 36 mmol) and EDCI·HCl (6.8 g, 36 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.34–7.17 (m, 5H, 5 × Ar*H*), 3.47 (t, J = 7.0, 2H, NCH_2), 3.29 (t, J = 7.0, 2H, NCH_2), 3.00 (t, J = 8.0, 2H, C(O)CH_2CH_2Ph), 2.57 (t, J = 8.0, 2H, C(O)C$H_2$$CH_2$Ph), 1.95–1.77 (m, 4H, 2 × NCH_2CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 170.7, 141.5, 128.4, 128.4, 126.1, 46.6, 45.6, 36.8, 31.2, 26.8, 24.4; **LRMS** *m/z* (ESI^+) 226.0 ([M+Na]$^+$, 100%). Data is consistent with the literature. [105, 141]

1-(azepan-1-yl)-3-phenylpropan-1-one, 67q



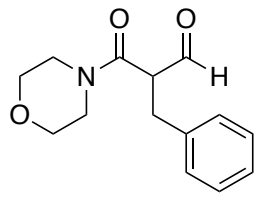
Following general procedure G, the product (2.96 g) was isolated by FC (petrol/EtOAc 2:1) in 85% yield as a colourless oil, starting from hydrocinnamic acid (2.26 g, 15.0 mmol, 1.0 equiv.), hexamethyleneimine (1.84 mL, 16.2 mmol, 1.1 equiv.) and EDCI·HCl (3.16 g, 16.2 mmol, 1.1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.35–7.14 (m, 5H, 5 × Ar*H*), 3.62–3.46 (m, 2H, NCH_2), 3.45–3.31 (m, 2H, NCH_2), 3.13–2.85 (m, 2H, C(O)CH_2CH_2Ph), 2.69–2.53 (m, 2H, C(O)C$H_2$$CH_2$Ph), 1.78–1.45 (m, 8H, 4 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.8, 141.8, 128.6, 128.6, 126.2, 47.9, 46.1, 35.3, 31.7, 29.2, 27.8, 27.1, 27.0; **IR** (film, cm^{-1}) 3026, 2925, 2854, 1633, 1425, 1193, 751, 699; **LRMS** *m/z* (ESI^-) 230.2 ([M–H]$^-$, 100%); **HRMS** (ESI^-) calc. for $C_{15}H_{20}ON$ [M–H]$^-$: 230.1550, found: 230.1549.

***N*,*N*-diisopropyl-3-methylbutanamide, 67o**



To a solution of 3-methylbutanoic acid (1.66 mL, 15.0 mmol, 1.0 equiv.) in dry CH_2Cl_2 (100 mL, 0.15 M) was added Mukaiyama's reagent (*N*-methyl-2-chloropyridinium iodide) (5.7 g, 22.5 mmol, 1.5 equiv.). The resulting suspension was stirred for 30 min prior to addition of the diisopropyl amine (6.3 mL, 45 mmol, 3 equiv.) dropwise. The reaction was stirred for 18 h at room temperature before quenching with 1 N HCl (100 mL). The layers were separated, and the organic layer was washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. The product (1.17 g) was isolated by FC (petrol/EtOAc 4:1) in 42% yield as a colourless oil; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 3.95 (hept, J = 7.0, 1H, NC*H*$(CH_3)_2$), 3.44 (app. br s, 1H, NC*H*$(CH_3)_2$), 2.21–2.03 (m, 3H, C(O)C*H*$_2$C*H*$(CH_3)_2$), 1.35 (d, J = 7.0, 6H, NCH(C*H*$_3)_2$), 1.16 (d, J = 7.0, 6H, NCH(C*H*$_3)_2$), 0.92 (d, J = 6.0, 6H, C(O)CH$_2$CH(C*H*$_3)_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 171.6, 48.6, 45.7, 44.3, 25.8, 22.8, 21.2, 20.8; **IR** (film, cm^{-1}) 3014, 2958, 2870, 1634, 1439, 1368, 1314, 1215, 1044; **LRMS** *m/z* (ESI$^+$) 186.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{11}H_{24}ON$ [M+H]$^+$: 186.1852, found: 186.1854.

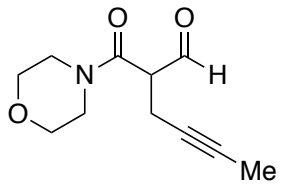
2-benzyl-3-morpholino-3-oxopropanal, 65a



Following general procedure F, the product (630 mg) was isolated by FC (petrol/EtOAc 1:1) in 85% yield as a colourless oil, starting from 2-benzyl-1,3-dimorpholinopropane-1,3-dione (**64a**) (1.0 g, 3 mmol, 1 equiv.), DIBAL (1 M in CH_2Cl_2, 3 mL, 1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.72 (d, J = 2.5, 1H, C(O)*H*), 7.36–7.17 (m, 5H, 5 × Ar*H*), 3.78–3.57 (m, 3H,

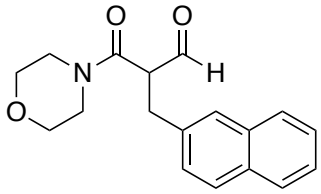
C*H*CH_2Ph, OC*H*$_A$H$_B$$CH_2N, OCH_2C*H*_AH_B$N), 3.55–3.37 (m, 3H, OC*H*$_2$$CH_2N, OCH_2C*H*_AH_B$N), 3.34–3.18 (m, 3H, OCH_2C*H*$_A$H$_B$N, CHC*H*$_2$Ph), 3.04–2.89 (m, 2H, OCH_2C*H*$_A$H$_B$N, OC*H*$_A$H$_B$$CH_2$N); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.4, 167.2, 137.5, 129.2, 129.0, 127.3, 66.7, 66.3, 56.7, 46.4, 42.4, 34.6; **LRMS** *m/z* (ESI$^+$) 270.0 ([M+Na]$^+$, 100%). Data is consistent with the literature.[105, 141]

2-(tetrahydro-2H-pyran-4-carbonyl)hex-4-ynal, 65l



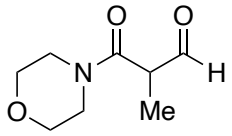
Following general procedure F, the product (393 mg) was isolated by FC (petrol/EtOAc 1:1) in 63% yield as a colourless oil, starting from 2-(but-2-yn-1-yl)-1,3-dimorpholinopropane-1,3-dione (**64l**) (883 mg, 3 mmol, 1 equiv.), DIBAL (1 M in CH_2Cl_2, 3 mL, 1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.60–9.55 (m, 1H, C(O)*H*), 3.77–3.48 (m, 9H, 2 × NC*H*$_2$, 2 × OC*H*$_2$, CO(C*H*)CO), 2.94–2.80 (m, 1H, CHC*H*$_A$H$_B$C≡CCH_3), 2.72–2.59 (m, 1H, $CHCH_A$*H*$_B$C≡CCH_3), 1.80–1.68 (m, 3H, $CHCH_2C{\equiv}CCH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 197.3, 166.1, 78.9, 74.8, 66.9, 66.8, 54.3, 46.6, 42.6, 17.6, 3.6; **IR** (film, cm^{-1}) 3392, 2980, 2920, 1726, 1620, 1439, 1234, 1112; **LRMS** *m/z* (ESI$^+$) 210.0 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{11}H_{16}O_3N$ [M+H]$^+$: 210.1125, found: 210.1125.

3-morpholino-2-(naphthalen-2-ylmethyl)-3-oxopropanal, 65m



Following general procedure F, the product (399 mg) was isolated by FC (petrol/EtOAc 1:1) in 79% yield as a colourless oil, starting from 1,3-dimorpholino-2-(naphthalen-2-ylmethyl)propane-1,3-dione (**64m**) (650 mg, 1.7 mmol, 1 equiv.), DIBAL (1 M in CH_2Cl_2, 1.7 mL, 1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.75 (d, J = 2.5, 1H, C(O)*H*), 7.84–7.74 (m, 3H, 3 × Ar*H*), 7.66 (s, 1H, Ar*H*), 7.53–7.41 (m, 2H, 2 × Ar*H*), 7.32 (dd, J = 8.5, 2.0, 1H, Ar*H*), 3.82 (ddd, J = 8.5, 7.0, 2.5, 1H, CO(C*H*)CO), 3.68–3.21 (m, 8H, 2 × NCH_2, 2 × OCH_2), 3.02–2.91 (m, 1H, CH_AH$_B$Ar), 2.87–2.77 (m, 1H, CH$_A$$H_B$Ar); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.4, 167.2, 134.9, 133.7, 132.5, 128.7, 127.8, 127.8, 127.6, 127.2, 126.6, 126.1, 66.7, 66.2, 56.8, 46.3, 42.4, 34.7; **IR** (film, cm^{-1}) 3425, 2921, 2856, 1722, 1627, 1437, 1231, 1113, 1027, 820, 749; **LRMS** *m/z* (ESI$^+$) 320.2 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{18}H_{19}O_3NNa$ [M+Na]$^+$: 320.1257, found: 320.1258.

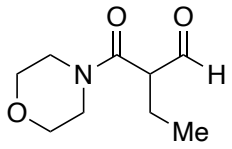
2-methyl-3-morpholino-3-oxopropanal, 65r



Following general procedure F, the product (387 mg) was isolated by FC (petrol/EtOAc 1:1) in 58% yield as a colourless oil, starting from 2-methyl-1,3-dimorpholinopropane-1,3-dione (**64r**) (1.0 g, 3.90 mmol, 1 equiv.), DIBAL (1 M in CH_2Cl_2, 3.9 mL, 1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, J = 2.0, 1H, C(O)*H*), 3.63–3.43 (m, 9H, CO(C*H*)CO, 2 × NCH_2, 2 × OCH_2), 1.34 (d, J = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.7, 168.3, 66.9, 66.7,

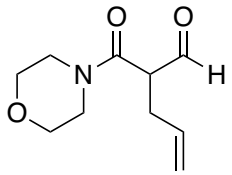
49.3, 46.4, 42.4, 11.9; **LRMS** *m/z* (ESI^+) 172.2 ($[M+H]^+$, 100%). Data is consistent with the literature. [105, 141]

2-(morpholine-4-carbonyl)butanal, 65s



Following general procedure F, the product (452 mg) was isolated by FC (petrol/EtOAc 1:1) in 66% yield as a colourless oil, starting from 2-ethyl-1,3-dimorpholinopropane-1,3-dione (**64s**) (1.0 g, 3.7 mmol, 1 equiv.), DIBAL (1 M in CH_2Cl_2, 3.7 mL, 1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.49 (d, J = 2.5, 1H, C(O)*H*), 3.65–3.33 (m, 8H, 2 × NCH_2, 2 × OCH_2), 3.27 (app. td, J = 7.0, 2.5, 1H, CO(C*H*)CO), 1.91–1.79 (m, 2H, C$H_2$$CH_3$), 0.86 (app. t, J = 7.5, 3H, CH_2CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 199.0, 167.2, 66.7, 66.5, 56.4, 46.1, 42.2, 20.8, 11.5; **IR** (film, cm^{-1}) 3422, 2970, 1722, 1625, 1438, 1271, 1224, 1112, 1032; **LRMS** *m/z* (ESI^+) 208.0 ($[M+Na]^+$, 100%); **HRMS** (ESI^+) calc. for $C_9H_{15}O_3NNa$ $[M+Na]^+$: 208.0944, found: 208.0946.

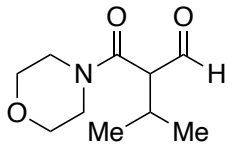
2-(morpholine-4-carbonyl)pent-4-enal, 65t



Following general procedure F, the product (470 mg) was isolated by FC (petrol/EtOAc 1:1) in 67% yield as a colourless oil, starting from 2-allyl-1,3-dimorpholinopropane-1,3-dione (**64t**) (1 g, 3.54 mmol, 1 equiv.), DIBAL (1 M in CH_2Cl_2, 3.54 mL, 1 equiv.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.56 (d, J = 2.0, 1H, C(O)*H*), 5.79–5.68 (m, 1H, CH_2=C*H*CH_2), 5.13–5.06 (m, 2H, CH_2=CHCH_2), 3.70–3.42 (m, 9H, CO(C*H*)CO, 2 × NCH_2, 2 × OCH_2), 2.66 (app. t, J = 7.0,

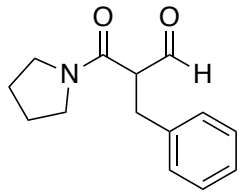
2H, CH_2=CHCH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 198.1, 166.6, 133.6, 118.0, 66.7, 66.6, 54.5, 46.2, 42.3, 31.6; **LRMS** *m/z* (ESI^+) 220.0 ([M+Na]$^+$, 100%). Data is consistent with the literature.[105, 141]

3-methyl-2-(morpholine-4-carbonyl)butanal, 65n



Following general procedure H, the product (996 mg) was isolated by FC (petrol/EtOAc 4:1) in 50% yield as a colourless oil, starting from 3-methyl-1-morpholinobutan-1-one (**67n**) (1.710 g, 10 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.60 (d, J = 4.5, 1H, C(O)*H*), 3.76–3.43 (m, 8H, 2 × NCH_2, 2 × OCH_2), 3.12 (dd, J = 9.5, 4.5, 1H, CO(C*H*)CO), 2.57 (dhept, J = 9.5, 7.0, 1H, CHC*H*(CH_3)$_2$), 0.98 (d, J = 7.0, 6H, CHCH(CH_3)$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 200.4, 167.0, 67.0, 66.8, 62.8, 46.4, 42.4, 28.7, 20.9, 20.1; **LRMS** *m/z* (ESI^+) 200.2 ([M+H]$^+$, 100%). Data is consistent with the literature.[105, 141]

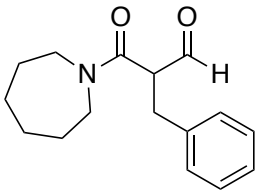
2-benzyl-3-oxo-3-(pyrrolidin-1-yl)propanal, 65p



Following general procedure H, the product (1.61 g) was isolated by FC (petrol/acetone 1:3) in 70% yield as a colourless oil, starting from 3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**67p**) (2.03 g, 10.0 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.75 (d, J = 3.0, 1H, C(O)*H*), 7.37–7.17 (m, 5H, 5 × Ar*H*), 3.60 (ddd, J = 9.0, 6.0, 3.0, 1H, CO(C*H*)CO), 3.52–3.37 (m, 2H, NCH_2), 3.36–3.15 (m, 3H, NCH_AH$_B$, CHCH_2Ph), 2.85–2.74 (m, 1H, NCH$_A$$H_B$), 1.92–1.56 (m, 4H, 2 × NCH_2CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 199.1, 166.9, 137.8, 129.1, 128.8, 127.0, 60.0,

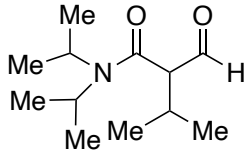
46.7, 46.0, 34.4, 26.0, 24.3; **LRMS** *m/z* (ESI^+) 254.0 ($[M+Na]^+$, 100%). Data is consistent with the literature.[105, 141]

3-(azepan-1-yl)-2-benzyl-3-oxopropanal, 65q



Following general procedure H, the product (910 mg) was isolated by FC (petrol/EtOAc 1:1) in 65% yield as a colourless oil, starting from 1-(azepan-1-yl)-3-phenylpropan-1-one (**67q**) (1.25 g, 5.4 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.69 (d, J = 3.0, 1H, C(O)*H*), 7.34–7.15 (m, 5H, 5 × Ar*H*), 3.75 (ddd, J = 9.0, 6.0, 3.0, 1H, CO(C*H*)CO), 3.64–3.54 (m, 1H, NCH_2), 3.45–3.12 (m, 5H, 1.5 × NCH_2, CH_2Ph), 1.74–1.13 (m, 8H, 4 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 199.1, 167.9, 137.9, 129.2, 128.8, 127.0, 58.3, 48.0, 46.4, 34.6, 29.1, 27.6, 26.6; **IR** (film, cm^{-1}) 3379, 2926, 2855, 1723, 1619, 1451, 750, 700; **LRMS** *m/z* (ESI^+) 260.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{16}H_{22}O_2N$ $[M+H]^+$: 260.1645, found: 260.1645.

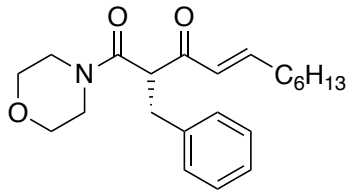
2-formyl-*N*,*N*-diisopropyl-3-methylbutanamide, 65o



Following general procedure H, the product (698 mg) was isolated by FC (petrol/EtOAc 30:1) in 60% yield as a colourless oil, starting from *N*,*N*-diisopropyl-3-methylbutanamide (**67o**) (1.00 g, 5.46 mmol); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 9.57 (d, J = 5.0, 1H, C(O)*H*), 4.13–4.00 (m, 1H, NC*H*$(CH_3)_2$), 3.54 (app. br s, 1H, NC*H*$(CH_3)_2$), 3.08 (dd, J = 9.5, 5.0, 1H, CO(C*H*)CO), 2.57 (dhept, J = 9.5, 6.5, 1H, CHC*H*$(CH_3)_2$), 1.36 (app. t, J = 6.5, 6H, NCH(C$H_3)_2$), 1.18 (app. t, J = 6.5, 6H, NCH(C$H_3)_2$), 0.96 (app. t, J = 6.5, 6H, CHCH(C$H_3)_2$);

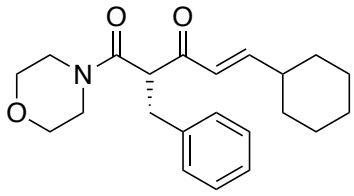
^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.6, 167.2, 65.1, 48.3, 46.4, 28.7, 20.8, 20.7, 20.5, 20.0; **IR** (film, cm^{-1}) 3006, 2964, 2935, 1721, 1625, 1440, 1371, 1328; **LRMS** *m/z* (ESI^+) 214.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{12}H_{24}O_2N$ $[M+H]^+$: 214.1802, found: 214.1804.

(*S*,*E*)-2-benzyl-1-morpholinoundec-4-ene-1,3-dione, 66a



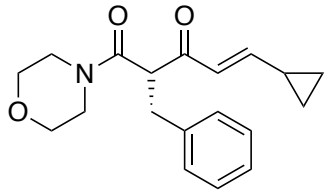
Following general procedure F, the product (54 mg) was isolated by FC (petrol/EtOAc 2:1) in 76% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); $[\alpha]_D^{25}$: +11.1 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26–7.08 (m, 5H, 5 × Ar*H*), 6.87 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.21 (dt, *J* = 15.5, 1.5, 1H, C(O)*CH*=CH), 3.87 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.60–3.03 (m, 10H, 2 × NCH_2, 2 × OCH_2, CH_2Ph), 2.19–2.07 (m, 2H, CH=CHC$H_2$$(CH_2)_4CH_3$), 1.43–1.08 (m, 8H, CH=CH$CH_2$$(CH_2)_4CH_3$), 0.82 (t, *J* = 7.0, 3H, CH=CH$CH_2$$(CH_2)_4CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.6, 167.5, 150.1, 138.7, 129.1, 128.7, 126.8, 126.6, 66.8, 66.4, 57.7, 46.4, 42.7, 35.2, 32.7, 31.7, 29.0, 28.1, 22.7, 14.2; **LRMS** *m/z* (ESI^+) 358.2 ($[M+H]^+$, 100%); the er was determined by HPLC using a Chiralpak OJ-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 26.53 min, τ_{minor} = 20.23 min (91:9 er). Data is consistent with the literature. [105]

(*S*,*E*)-2-benzyl-5-cyclohexyl-1-morpholinopent-4-ene-1,3-dione, 66b



Following general procedure F, the product (50 mg) was isolated by FC (petrol/EtOAc 3:1) in 71% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and ethynylcyclohexane (31 µL, 0.24 mmol); $[\alpha]_D^{25}$: +7.8 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) *δ* 7.32–7.13 (m, 5H, 5 × Ar*H*), 6.85 (dd, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.22 (dd, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.95 (dd, *J* = 9.0, 6.0, 1H, C*H*CH_2Ph), 3.67–3.05 (m, 10H, 2 × NCH_2, 2 × OCH_2, CH_2Ph), 2.23–2.05 (m, 1H, C*H*$(CH_2)_5$), 1.86–1.61 (m, 5H, 2.5 × CH_2), 1.38–1.01 (m, 5H, 2.5 × CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$) *δ* 195.1, 167.6, 154.7, 138.8, 129.2, 128.7, 126.8, 124.4, 66.9, 66.4, 57.6, 46.4, 42.8, 40.9, 35.2, 31.8, 31.8, 26.0, 25.7; **LRMS** *m/z* (ESI^+) 356.2 ($[M+H]^+$, 100%); the er was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 45.91 min, τ_{minor} = 49.98 min (90:10 er). Data is consistent with the literature. [105]

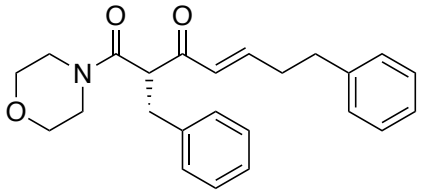
(*S*,*E*)-2-benzyl-5-cyclopropyl-1-morpholinopent-4-ene-1,3-dione, 66c



Following general procedure F, the product (41 mg) was isolated by FC (petrol/EtOAc 3:1) in 45% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (74 mg, 0.30 mmol), ethynylcyclopropane (30 µL, 0.36 mmol), Cs_2CO_3 (9.8 mg, 0.06 mmol, 20 mol%), $[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol, 10 mol%) and I-DMMGarphos (26 mg, 0.03 mmol, 10 mol%); $[\alpha]_D^{25}$: +13.9 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) *δ*

7.25–7.18 (m, 2H, 2 × Ar*H*), 7.17–7.09 (m, 3H, 3 × Ar*H*), 6.38–6.32 (m, 2H, C(O)CH=C*H*, C(O)C*H*=CH), 3.81 (dd, *J* = 9.0, 6.0, 1H, C*H*CH$_2$Ph), 3.59–3.12 (m, 9H, 2 × NC*H*$_2$, 2 × OC*H*$_2$, C*H*$_A$H$_B$Ph), 3.07 (dd, *J* = 14.0, 6.0, 1H, CH$_A$*H*$_B$Ph), 1.55–1.48 (m, 1H, C*H*(CH$_2$)$_2$), 1.03–0.89 (m, 2H, CH(C*H*$_2$)$_A$(CH$_2$)$_B$), 0.68–0.53 (m, 2H, CH(CH$_2$)$_A$(C*H*$_2$)$_B$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 193.7, 167.6, 155.6, 138.9, 129.1, 128.7, 126.8, 123.3, 66.9, 66.5, 58.1, 46.4, 42.8, 35.3, 15.4, 9.6; **LRMS** *m/z* (ESI$^+$) 314.2 ([M+H]$^+$, 100%); the er was determined by HPLC using a Chiralpak ID-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 37.92 min, τ_{minor} = 57.07 min (93:7 er). Data is consistent with the literature.[105]

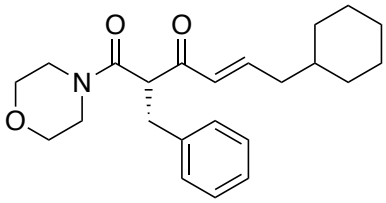
(*S*,*E*)-2-benzyl-1-morpholino-7-phenylhept-4-ene-1,3-dione, 66d



Following general procedure F, the product (41 mg) was isolated by FC (petrol/EtOAc 1:1) in 56% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and but-3-yn-1-ylbenzene (34 µL, 0.24 mmol); $[\alpha]_D^{25}$: +5.7 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33–7.12 (m, 10H, 10 × Ar*H*), 6.94 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.27 (dt, *J* = 15.5, 1.0, 1H, C(O)C*H*=CH), 3.90 (dd, *J* = 8.5, 6.0, 1H, C*H*CH$_2$Ph), 3.63–3.05 (m, 10H, 2 × NC*H*$_2$, 2 × OC*H*$_2$, C*H*$_2$Ph), 2.78 (t, *J* = 7.5, 2H, CH$_2$C*H*$_2$Ph), 2.55 (app. q, *J* = 7.5, 2H, C*H*$_2$CH$_2$Ph); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.4, 167.4, 148.5, 140.6, 138.6, 129.1, 128.7, 128.6, 128.5, 127.2, 126.8, 126.4, 66.8, 66.3, 57.6, 46.3, 42.7, 35.1, 34.3, 34.2; **IR** (film, cm^{-1}) 2980, 1684, 1628, 1453, 1434, 1270, 1232, 1114, 749, 700; **LRMS** *m/z* (ESI$^+$) 378.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{24}H_{28}O_3N$ [M+H]$^+$: 378.2064, found: 378.2062; the er was determined by HPLC using a Chiralpak IC

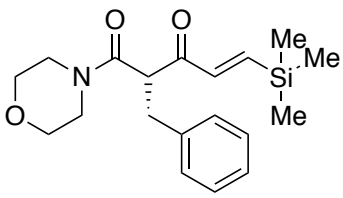
column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; τ_{major} = 32.86 min, τ_{minor} = 39.81 min (89:11 er).

(*S*,*E*)-2-benzyl-6-cyclohexyl-1-morpholinohex-4-ene-1,3-dione, 66e



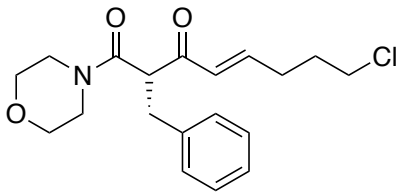
Following general procedure F, the product (49 mg) was isolated by FC (petrol/EtOAc 2:1) in 66% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and prop-2-yn-1-ylcyclohexane (34 μL, 0.24 mmol) and the reaction time was 8 min; $[\alpha]_D^{25}$: +8.3 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25–7.07 (m, 5H, 5 × Ar*H*), 6.84 (dt, *J* = 15.5, 7.5, 1H, C(O)CH=C*H*), 6.18 (dd, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.87 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.57–3.04 (m, 10H, 2 × NCH_2, 2 × OCH_2, CH_2Ph), 2.03 (app. t, *J* = 7.0, 2H, CH_2CH$(CH_2)_5$), 1.70–1.51 (m, 5H, 2.5 × CH_2), 1.41–1.26 (m, 1H, CH_2C*H*$(CH_2)_5$), 1.26–1.01 (m, 3H, 1.5 × CH_2), 0.90–0.77 (m, 2H, CH_2). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.5, 167.6, 148.9, 138.7, 129.2, 128.7, 127.7, 126.8, 66.8, 66.4, 57.6, 46.4, 42.7, 40.6, 37.5, 35.2, 33.3, 26.4, 26.3; **LRMS** *m/z* (ESI$^+$) 370.2 ([M+Na]$^+$, 100%); the er was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 38.37 min, τ_{minor} = 35.08 min (86.5:13.5 er). Data is consistent with the literature.[105]

(*S*,*E*)-2-benzyl-1-morpholino-5-(trimethylsilyl)pent-4-ene-1,3-dione, 66f



Following general procedure F, the product (49 mg) was isolated by FC (petrol/EtOAc 2:1) in 71% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and ethynyltrimethylsilane (33 µL, 0.24 mmol); $[\alpha]_D^{25}$: +8.5 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.21–7.03 (m, 5H, 5 × Ar*H*), 6.98 (d, *J* = 19.0, 1H, C(O)CH=C*H*), 6.46 (d, *J* = 19.0, 1H, C(O)C*H*=CH), 3.96 (dd, *J* = 9.0, 6.0, 1H, C*H*CH_2Ph), 3.53–2.97 (m, 10H, 2 × NCH_2, 2 × OCH_2, CH_2Ph), 0.00 (s, 9H, Si(CH_3)$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.1, 167.6, 149.2, 139.1, 138.6, 129.2, 128.7, 126.9, 66.8, 66.3, 56.2, 46.4, 42.6, 35.1, -1.8; **LRMS** *m/z* (ESI^+) 346.2 ($[M+H]^+$, 100%); the er was determined by HPLC using a Chiralpak IA-3 column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 38.20 min, τ_{minor} = 33.69 min (89:11 er). Data is consistent with the literature.[105]

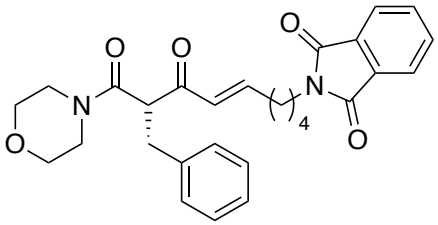
(*S*,*E*)-2-benzyl-8-chloro-1-morpholinooct-4-ene-1,3-dione, 66g



Following general procedure F, the product (68 mg) was isolated by FC (petrol/EtOAc 1:1) in 65% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (74 mg, 0.30 mmol) and 5-chloropent-1-yne (38 µL, 0.36 mmol), Cs_2CO_3 (9.8 mg, 0.06 mmol, 20 mol%), $[Rh(nbd)_2]BF_4$ (11 mg, 0.03 mmol, 10 mol%) and (*R*)-DMMGarphos (26 mg, 0.03 mmol, 10 mol%) and the reaction time was 15 min; $[\alpha]_D^{25}$: +6.8 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26–7.07 (m, 5H, 5 × Ar*H*), 6.82 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.26 (dt, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.88 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.63–3.03 (m, 12H, 2 × NCH_2, 2 × OCH_2, CH_2Ph, $CH_2CH_2CH_2Cl$), 2.42–2.21 (m, 2H, C$H_2CH_2CH_2Cl$), 1.90–1.76 (m, 2H, $CH_2CH_2CH_2Cl$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.3, 167.5, 147.3, 138.5, 129.1, 128.7, 127.6, 126.9, 66.8, 66.4, 57.6, 46.4, 44.0, 42.7, 35.1,

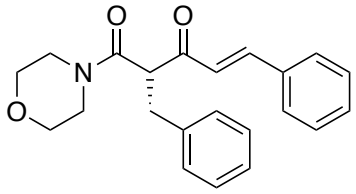
30.7, 29.6; **LRMS** *m/z* (ESI^+) 350.2 ([M (Cl^{35}) +H]$^+$, 100%); the er was determined by HPLC using a Chiralpak IA-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 30.71 min, τ_{minor} = 33.34 min (92:8 er). Data is consistent with the literature.[105]

(*S*,*E*)-2-(8-benzyl-9-morpholino-7,9-dioxonon-5-en-1-yl)isoindoline-1,3-dione, 66h



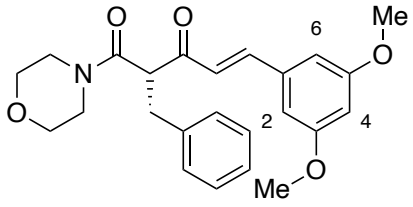
Following general procedure F, the product (57 mg) was isolated by FC (petrol/EtOAc 2:1) in 62% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and 2-(hex-5-yn-1-yl)isoindoline-1,3-dione (54 mg, 0.24 mmol) and the reaction time was 8 min; $[\alpha]_D^{25}$: +2.0 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0, 2H, 2 × Ar*H*), 7.71 (dd, *J* = 5.5, 3.0, 2H, 2 × Ar*H*), 7.29–7.15 (m, 5H, 5 × Ar*H*), 6.88 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.26 (dd, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.94 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.68 (t, *J* = 7.0, 2H, CH=CHCH_2CH_2CH_2CH_2N), 3.63–3.06 (m, 10H, 2 × NCH_2, 2 × OCH_2, CH_2Ph), 2.20–2.30 (m, 2H, CH=CHCH_2CH_2CH_2CH_2N), 1.75–1.63 (m, 2H, CH=CHCH_2CH_2CH_2CH_2N), 1.58–1.43 (m, 2H, CH=CHCH_2CH_2CH_2CH_2N); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.4, 168.5, 167.5, 148.8, 138.7, 134.1, 132.2, 129.2, 128.7, 127.1, 126.8, 123.4, 66.8, 66.4, 57.5, 46.4, 42.7, 37.6, 35.2, 32.1, 28.2, 25.4; **IR** (film, cm^{-1}) 2980, 1770, 1708, 1632, 1437, 1396, 1114, 955, 721, 702; **LRMS** *m/z* (ESI^+) 475.2 ([M+H]$^+$, 100%); **HRMS** (ESI^+) calc. for $C_{28}H_{31}O_5N_2$ [M+H]$^+$: 475.2227, found: 475.2225; the er was determined by HPLC using a Chiralpak OD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 59.19 min, τ_{minor} = 51.36 min (83:17 er).

(*S*,*E*)-2-benzyl-1-morpholino-5-phenylpent-4-ene-1,3-dione, 66i



Following general procedure F, the product (47 mg) was isolated by FC (petrol/EtOAc 3:1) in 67% yield as a pale yellow oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and ethynylbenzene (26 μL, 0.24 mmol); $[\alpha]_D^{25}$: +1.0 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0, 1H, C(O)CH=C*H*), 7.61–7.52 (m, 2H, 2 × Ar*H*), 7.47–7.34 (m, 3H, 3 × Ar*H*), 7.33–7.17 (m, 5H, 5 × Ar*H*), 6.95 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 4.05 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.69–3.18 (m, 10H, 2 × NCH_2, 2 × OCH_2, CH_2Ph); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.6, 167.4, 144.7, 138.6, 134.2, 131.1, 129.1, 129.1, 128.8, 128.7, 126.9, 122.3, 66.8, 66.5, 58.4, 46.4, 42.8, 35.3; **IR** (film, cm^{-1}) 3028, 2921, 2853, 1631, 1576, 1449, 1114, 1029, 750, 700; **LRMS** *m/z* (ESI^+) 350.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{22}H_{24}O_3N$ $[M+H]^+$: 350.1751, found: 350.1747; the er was determined by HPLC using a Chiralpak IA-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 33.46 min, τ_{minor} = 36.46 min (90.5:9.5 er).

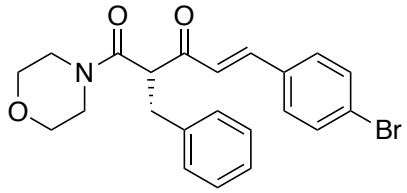
(*S*,*E*)-2-benzyl-5-(3,5-dimethoxyphenyl)-1-morpholinopent-4-ene-1,3-dione, 66j



Following general procedure F, the product (59 mg) was isolated by FC (petrol/EtOAc 2:1) in 72% yield as a colourless oil, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and 1-ethynyl-3,5-dimethoxybenzene (39 mg, 0.24 mmol); $[\alpha]_D^{25}$: +1.3 (*c* = 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 16.0, 1H, C(O)CH=C*H*),

7.32–7.26 (m, 2H, 2 × Ar*H*), 7.25–7.19 (m, 3H, 3 × Ar*H*), 6.87 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 6.67 (d, *J* = 2.0, 2H, H6, H2), 6.52 (t, *J* = 2.0, 1H, H4), 4.04 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.82 (s, 6H, 2 × OCH_3), 3.69–3.52 (m, 4H, NCH_2, OCH_2), 3.51–3.37 (m, 3H, 0.5 × NCH_2, 0.5 × OCH_2, C$H_A$$H_B$Ph), 3.33–3.17 (m, 3H, 0.5 × NCH_2, 0.5 × OCH_2, C$H_A$$H_B$Ph); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.7, 167.4, 161.2, 144.7, 138.6, 136.2, 129.2, 128.8, 126.9, 122.9, 106.7, 103.3, 66.9, 66.5, 58.4, 55.6, 46.4, 42.8, 35.4; **IR** (film, cm^{-1}) 3027, 2924, 2841, 1629, 1589, 1454, 1427, 1281, 1205, 1155, 1113, 1065, 843, 731, 701; **LRMS** *m/z* (ESI^+) 410.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{28}O_5N$ $[M+H]^+$: 410.1962, found: 410.1962; the er was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 14.01 min, τ_{minor} = 17.31 min (87:13 er).

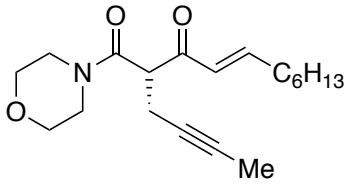
(*S*,*E*)-2-benzyl-5-(4-bromophenyl)-1-morpholinopent-4-ene-1,3-dione, 66k



Following general procedure F, the product (61 mg) was isolated by FC (petrol/EtOAc 4:1) in 71% yield as a white solid and recrystallised in CH_2Cl_2 to give **66k** as a white crystalline solid, starting from 2-benzyl-3-morpholino-3-oxopropanal (**65a**) (49 mg, 0.20 mmol) and 1-bromo-4-ethynylbenzene (36 mg, 0.24 mmol) and without using Cs_2CO_3; $[\alpha]_D^{25}$: +2.6 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 16.0, 1H, C(O)CH=C*H*), 7.46 (d, *J* = 8.5, 2H, 2 × Ar*H*), 7.34 (d, *J* = 8.5, 2H, 2 × Ar*H*), 7.26–7.18 (m, 2H, 2 × Ar*H*), 7.18–7.12 (m, 3H, 3 × Ar*H*), 6.86 (d, *J* = 16.0, 1H, C(O)C*H*=CH), 3.95 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.59–3.44 (m, 4H, NCH_2, OCH_2), 3.43–3.30 (m, 3H, 0.5 × NCH_2, 0.5 × OCH_2, C$H_A$$H_B$Ph), 3.27–3.11 (m, 3H, 0.5 × NCH_2, 0.5 × OCH_2, C$H_A$$H_B$Ph); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.5, 167.3, 143.3, 138.4, 133.2, 132.4, 130.2, 129.1, 128.8, 127.0, 125.4, 122.7, 66.9, 66.5,

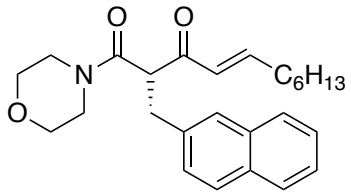
58.5, 46.5, 42.8, 35.4; **IR** (film, cm^{-1}) 3027, 2921, 2855, 1630, 1585, 1487, 1433, 1230, 1113, 1068, 1009, 815, 752, 701; **LRMS** *m/z* (ESI^+) 428.0 ([M (Br^{79}) +H]$^+$, 100%); **HRMS** (ESI^+) calc. for $C_{22}H_{23}O_3NBr^{79}$ [M (Br^{79}) +H]$^+$: 428.0856, found: 428.0850; **m.p.** (^oC): 123–125; the er was determined by HPLC using a Chiralpak IA-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 48.24 min, τ_{minor} = 63.80 min (84.5:15.5 er). Configuration of **66k** was determined *via* X-ray crystallography.

(*S*,*E*)-2-(but-2-yn-1-yl)-1-morpholinoundec-4-ene-1,3-dione, 66l



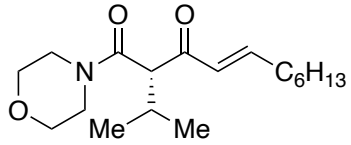
Following general procedure F, the product (41 mg) was isolated by FC (petrol/EtOAc 2:1) in 65% yield as a pale yellow oil, starting from 2-(morpholine-4-carbonyl)hex-4-ynal (**65l**) (42 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); $[\alpha]_D^{25}$: +4.9 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.18 (dt, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.77 (t, *J* = 7.5, 1H, CO(C*H*)CO), 3.69–3.41 (m, 8H, 2 × NCH_2, 2 × OCH_2), 2.76–2.61 (m, 2H, CHCH_2C≡CCH_3), 2.24–2.04 (m, 2H, CH=CHC$H_2$$CH_2$$(CH_2)_3CH_3$), 1.68 (t, *J* = 2.5, 3H, $CHCH_2$C≡CCH_3), 1.44–1.33 (m, 2H, CH=$CHCH_2$C$H_2$$(CH_2)_3CH_3$), 1.30–1.13 (m, 6H, CH=$CHCH_2CH_2$(C$H_2$$)_3CH_3$), 0.82 (t, *J* = 7.0, 3H, CH=$CHCH_2CH_2$$(CH_2)_3CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.0, 167.0, 150.5, 126.1, 78.1, 75.6, 67.0, 66.7, 55.4, 46.5, 42.9, 32.7, 31.7, 29.0, 28.1, 22.7, 19.1, 14.2, 3.7; **IR** (film, cm^{-1}) 2958, 2923, 2856, 1686, 1631, 1433, 1271, 1231, 1114; **LRMS** *m/z* (ESI^+) 320.2 ([M+H]$^+$, 100%); **HRMS** (ESI^+) calc. for $C_{19}H_{30}O_3N$ [M+H]$^+$: 320.2220, found: 320.2219; the er was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 22.11 min, τ_{minor} = 26.67 min (86:14 er).

(*S*,*E*)-1-morpholino-2-(naphthalen-2-ylmethyl)undec-4-ene-1,3-dione, 66m



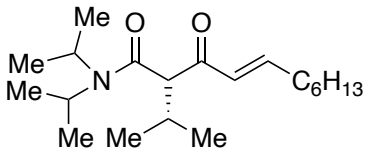
Following general procedure F, the product (54 mg) was isolated by FC (petrol/EtOAc 3:1) in 66% yield as a pale yellow oil, starting from 3-morpholino-2-(naphthalen-2-ylmethyl)-3-oxopropanal (**65m**) (59 mg, 0.20 mmol) and 1-octyne (35 μL, 0.24 mmol); $[\alpha]_D^{25}$: +15.5 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82–7.73 (m, 3H, 3 × Ar*H*), 7.64 (d, *J* = 1.5, 1H, Ar*H*), 7.49–7.40 (m, 2H, 2 × Ar*H*), 7.32 (dd, *J* = 8.5, 1.5, 1H, Ar*H*), 6.95 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.31 (dt, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 4.04 (dd, *J* = 8.5, 6.0, 1H, CO(C*H*)CO), 3.69–3.11 (m, 10H, 2 × NCH_2, 2 × OCH_2, CHCH_2Ar), 2.24–2.15 (m, 2H, CH=CHCH_2CH$_2$(CH$_2$)$_3$CH$_3$), 1.46–1.37 (m, 2H, CH=CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$), 1.35–1.23 (m, 6H, CH=CHCH$_2$CH$_2$(CH_2)$_3$CH$_3$), 0.89 (t, *J* = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.7, 167.5, 150.4, 136.2, 133.6, 132.4, 128.4, 127.8, 127.7, 127.6, 127.4, 126.6, 126.3, 125.8, 66.8, 66.4, 57.8, 46.4, 42.8, 35.4, 32.8, 31.7, 29.0, 28.1, 22.7, 14.2; **IR** (film, cm^{-1}) 2957, 2926, 2855, 1685, 1631, 1433, 1270, 1231, 1115, 857, 819, 747; **LRMS** *m/z* (ESI$^+$) 408.2 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{26}H_{34}O_3N$ [M+H]$^+$: 408.2533, found: 408.2530; the er was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 24.19 min, τ_{minor} = 26.58 min (87:13 er).

(*S*,*E*)-2-isopropyl-1-morpholinoundec-4-ene-1,3-dione, 66n



Following general procedure F, the product (25 mg) was isolated by FC (petrol/EtOAc 4:1) in 40% yield as a pale yellow oil, starting from 3-methyl-2-(morpholine-4-carbonyl)butanal (**65n**) (40 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); $[\alpha]_D^{25}$: +2.2 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.94 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.37 (dt, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.76–3.37 (m, 8H, 2 × NCH_2, 2 × OCH_2), 3.18 (d, *J* = 10.5, 1H, CO(C*H*)CO), 2.58–2.46 (m, 1H, C*H*$(CH_3)_2$), 2.17–2.08 (m, 2H, CH=CHC$H_2$$CH_2$$(CH_2)_3CH_3$), 1.42–1.31 (m, 2H, CH=CHCH_2C$H_2$$(CH_2)_3CH_3$), 1.26–1.17 (m, 6H, CH=CHC$H_2$$CH_2$(C$H_2$$)_3CH_3$), 0.90 (d, *J* = 6.5, 3H, CH(C$H_3$$)_A(CH_3)_B$), 0.85–0.75 (m, 6H, CH=CHC$H_2$$CH_2$$(CH_2)_3CH_3$, CH$(CH_3)_A$(C$H_3$$)_B$); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 195.8, 167.1, 150.2, 125.7, 67.1, 66.9, 65.7, 46.4, 42.8, 32.7, 31.7, 29.0, 28.6, 28.1, 22.7, 21.7, 20.2, 14.2; **LRMS** *m/z* (ESI^+) 332.2 ($[M+Na]^+$, 100%); the er was determined by HPLC using a Chiralpak IA-3 column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 7.70 min, τ_{minor} = 8.43 min (87:13 er). Data is consistent with the literature.[105]

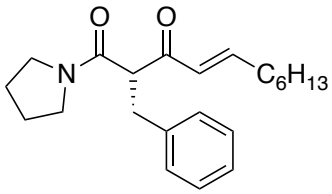
(*S*,*E*)-*N*,*N*,2-triisopropyl-3-oxoundec-4-enamide, 66o



Following general procedure F, the product (30 mg) was isolated by FC (petrol/EtOAc 50:1) in 46% yield as a pale yellow oil, starting from 2-formyl-*N*,*N*-diisopropyl-3-methylbutanamide (**65o**) (43 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); $[\alpha]_D^{25}$: +7.6 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.47 (dt, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 4.28–4.12 (m, 1H, NCH_A), 3.36 (br s, 1H, NCH_B), 3.16 (d, *J* = 10.5, 1H, CO(C*H*)CO), 2.60–2.46 (m, 1H, CHC*H*$(CH_3)_2$), 2.21–2.10 (m, 2H, CH=CHC$H_2$$CH_2$$(CH_2)_3CH_3$), 1.46–1.32 (m, 8H, CH=CHCH_2C$H_2$$(CH_2)_3CH_3$, NCH(C$H_3$$)_A$(C$H_3$$)_B$), 1.30–1.18 (m, 6H, CH=CHC$H_2$$CH_2$(C$H_2$$)_3CH_3$), 1.12 (d, *J* = 6.5, 3H,

NCH(CH_3)$_C$(CH_3)$_D$), 1.07 (d, J = 6.5, 3H, NCH(CH_3)$_C$(CH_3)$_D$), 0.94 (d, J = 6.5, 3H, CHCH(CH_3)$_A$(CH_3)$_B$), 0.88–0.79 (m, 6H, CHCH(CH_3)$_A$(CH_3)$_B$, CH=CHCH$_2$CH$_2$(CH$_2$)$_3$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 196.8, 167.1, 149.3, 126.0, 67.6, 48.5, 46.5, 32.6, 31.7, 28.9, 28.1, 22.7, 21.7, 21.0, 20.7, 20.6, 20.5, 20.3, 14.1; **IR** (film, cm^{-1}) 2979, 2970, 2931, 1731, 1624, 1443, 1375, 1331, 1259, 1158, 955; **LRMS** *m/z* (ESI$^+$) 324.3 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$) calc. for $C_{20}H_{38}O_2N$ [M+H]$^+$: 324.2897, found: 324.2898; the er was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 7.38 min, τ_{minor} = 8.38 min (99:1 er).

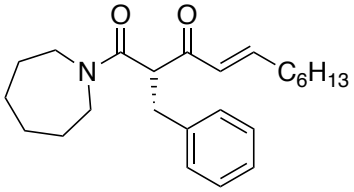
(*S*,*E*)-2-benzyl-1-(pyrrolidin-1-yl)undec-4-ene-1,3-dione, 66p



Following general procedure F, the product (47 mg) was isolated by FC (petrol/EtOAc 4:1) in 68% yield as a pale yellow oil, starting from 2-benzyl-3-oxo-3-(pyrrolidin-1-yl)propanal (**65p**) (46 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); $[\alpha]_D^{25}$: +9.2 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.24–7.05 (m, 5H, 5 × Ar*H*), 6.84 (dt, J = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.25 (dt, J = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.75 (dd, J = 8.5, 6.0, 1H, C*H*CH$_2$Ph), 3.36 (app. t, J = 6.5, 2H, NCH_2), 3.30–1.18 (m, 2H, NCH_ACH$_B$, CHCH_AH$_B$Ph), 3.05 (dd, J = 14.0, 6.0, 1H, CHCH$_A$$H_B$Ph), 2.93 (dt, J = 10.0, 6.0, 1H, NCH$_A$CH_B), 2.16–2.07 (m, 2H, CH=CHCH_2CH$_2$(CH$_2$)$_3$CH$_3$), 1.78–1.59 (m, 4H, 2 × NCH$_2$CH_2), 1.40–1.30 (m, 2H, CH=CHCH$_2$CH_2(CH$_2$)$_3$CH$_3$), 1.26–1.16 (m, 6H, CH=CHCH$_2$CH$_2$(CH_2)$_3$CH$_3$), 0.81 (t, J = 6.5, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_3$CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 194.9, 167.3, 149.5, 139.0, 129.1, 128.5, 127.1, 126.6, 60.0, 46.8, 46.2, 35.2, 32.7, 31.7, 29.0, 28.1, 26.0, 24.3, 22.6, 14.2; **LRMS** *m/z* (ESI$^+$) 364.2 ([M+Na]$^+$, 100%); the er was determined by HPLC using a Chiralpak

IA-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 26.10 min, τ_{minor} = 31.27 min (90:10 er). Data is consistent with the literature.[105]

(*S*,*E*)-1-(azepan-1-yl)-2-benzylundec-4-ene-1,3-dione, 66q



Following general procedure F, the product (44 mg) was isolated by FC (petrol/EtOAc 3:1) in 60% yield as a pale yellow oil, starting from 3-(azepan-1-yl)-2-benzyl-3-oxopropanal (**65q**) (52 mg, 0.20 mmol) and 1-octyne (35 µL, 0.24 mmol); $[\alpha]_D^{25}$: +5.5 (*c* = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.30–7.14 (m, 5H, 5 × Ar*H*), 6.96 (dt, *J* = 15.5, 7.0, 1H, C(O)CH=C*H*), 6.41 (dt, *J* = 15.5, 1.5, 1H, C(O)C*H*=CH), 3.92 (dd, *J* = 8.5, 6.0, 1H, C*H*CH_2Ph), 3.63 (dt, *J* = 14.0, 6.0, 1H, NC$H_A$$CH_B$), 3.45–3.29 (m, 3H, NC$H_2$, CHC$H_A$$H_B$Ph), 3.29–3.16 (m, 1H, NCH_ACH_B), 3.10 (dd, *J* = 14.0, 6.0, 1H, CHC$H_A$$H_B$Ph), 2.24–2.15 (m, 2H, CH=CHC$H_2$$(CH_2)_4CH_3$), 1.71–1.22 (m, 16H, CH=CHC$H_2$$(CH_2)_4CH_3$, 2 × $NCH_2CH_2CH_2$), 0.89 (t, *J* = 7.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 195.3, 168.2, 149.8, 139.1, 129.2, 128.6, 126.6, 126.5, 58.8, 48.1, 46.7, 35.7, 32.7, 31.7, 29.1, 29.0, 28.1, 27.5, 26.9, 26.5, 22.7, 14.2; **IR** (film, cm^{-1}) 3028, 2925, 2855, 1686, 1625, 1426, 1260, 1100, 1030, 803, 750, 700; **LRMS** *m/z* (ESI^+) 370.2 ($[M+H]^+$, 100%); **HRMS** (ESI^+) calc. for $C_{24}H_{36}O_2N$ $[M+H]^+$: 370.2741, found: 370.2736; the er was determined by HPLC using a Chiralpak ID-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 28.01 min, τ_{minor} = 50.32 min (85:15 er).

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Appendix: Spectra

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

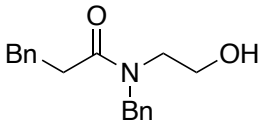
HPLC traces are also shown for chiral products and their racemates.

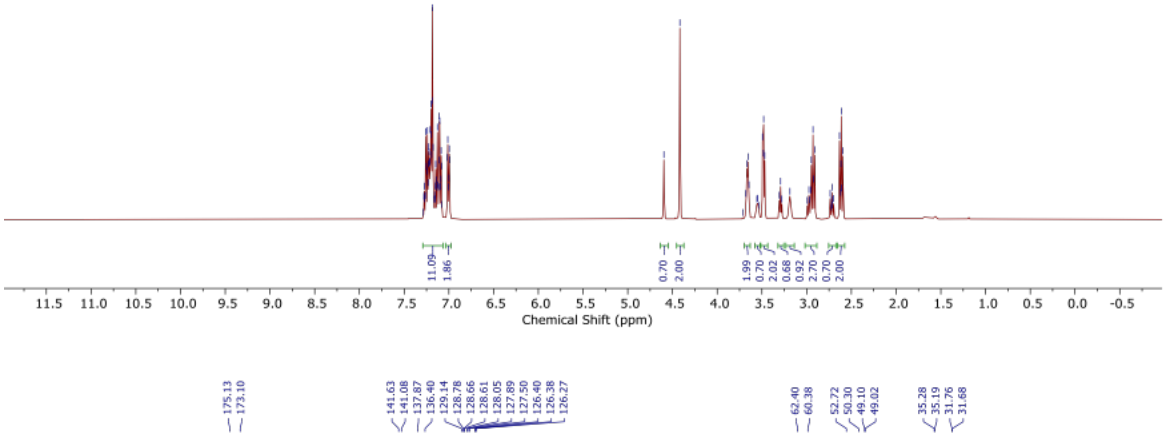
^{1}H and ^{13}C spectra of all novel compounds synthesised in Chapters 2

N-benzyl-*N*-(2-hydroxyethyl)-3-phenylpropanamide, 52a

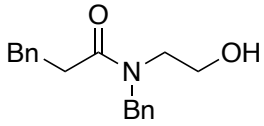


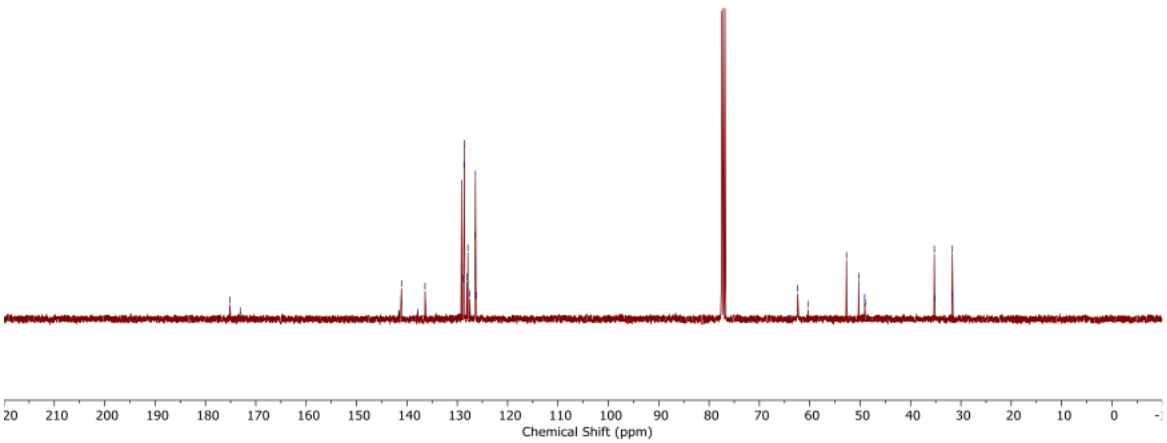
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

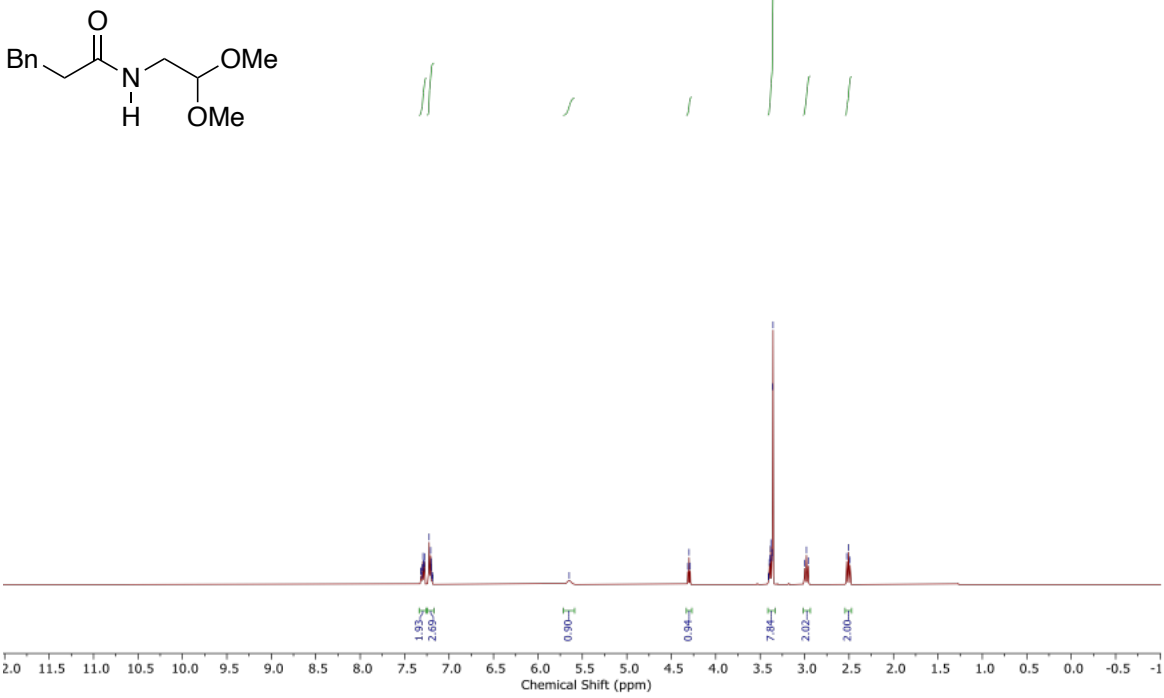




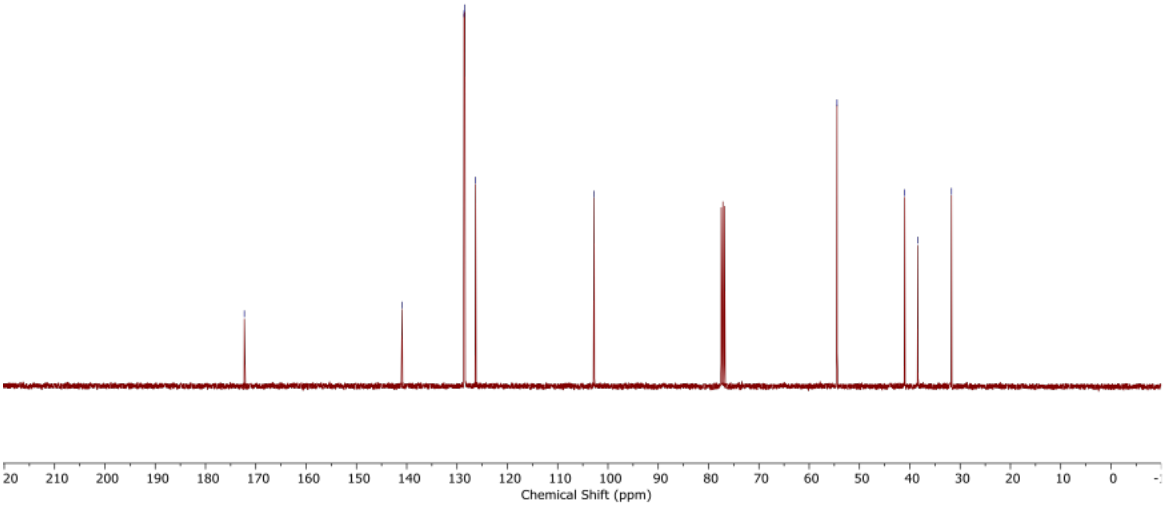
***N*-(2,2-dimethoxyethyl)-3-phenylpropanamide, 52v**



^{1}H-NMR (400 MHz, $CDCl_3$)



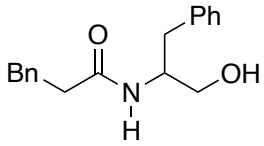
^{13}C-NMR (100 MHz, $CDCl_3$)

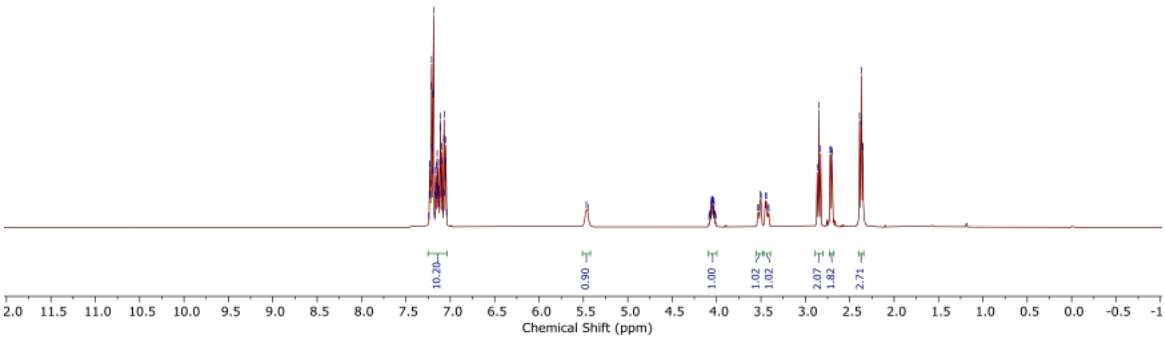


***N*-(1-hydroxy-3-phenylpropan-2-yl)-3-phenylpropanamide, 52w**

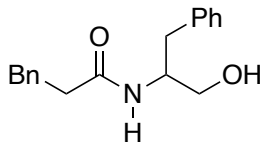


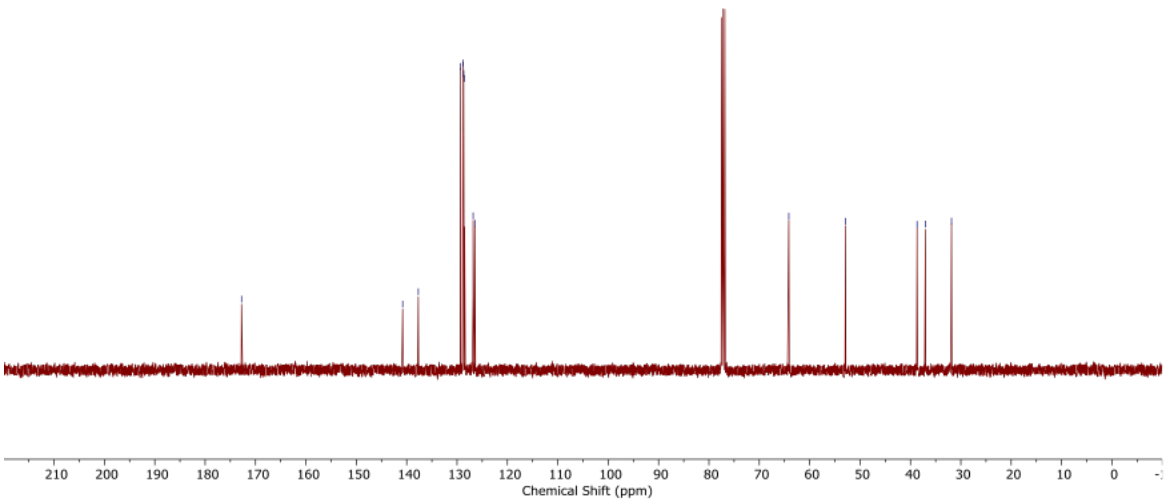
^{1}H-NMR (400 MHz, $CDCl_3$)





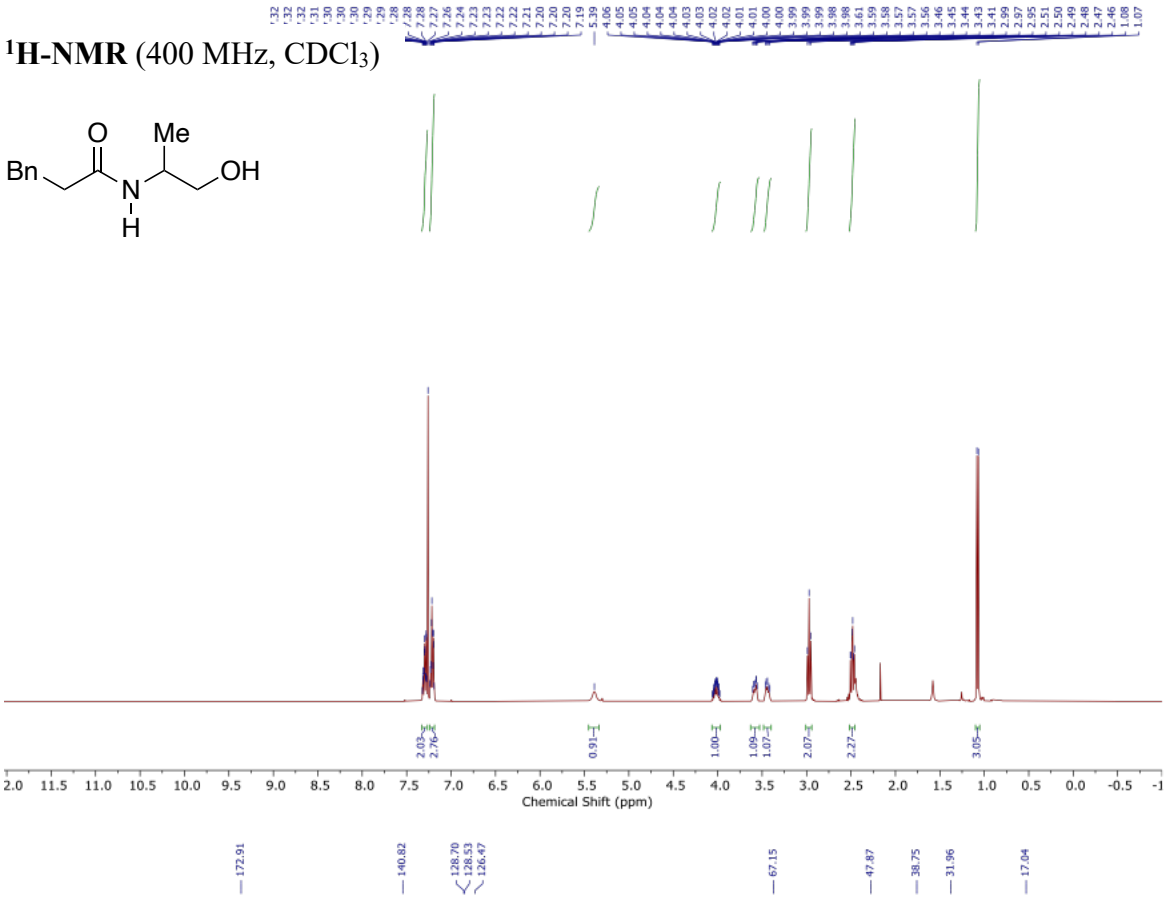
^{13}C-NMR (100 MHz, $CDCl_3$)



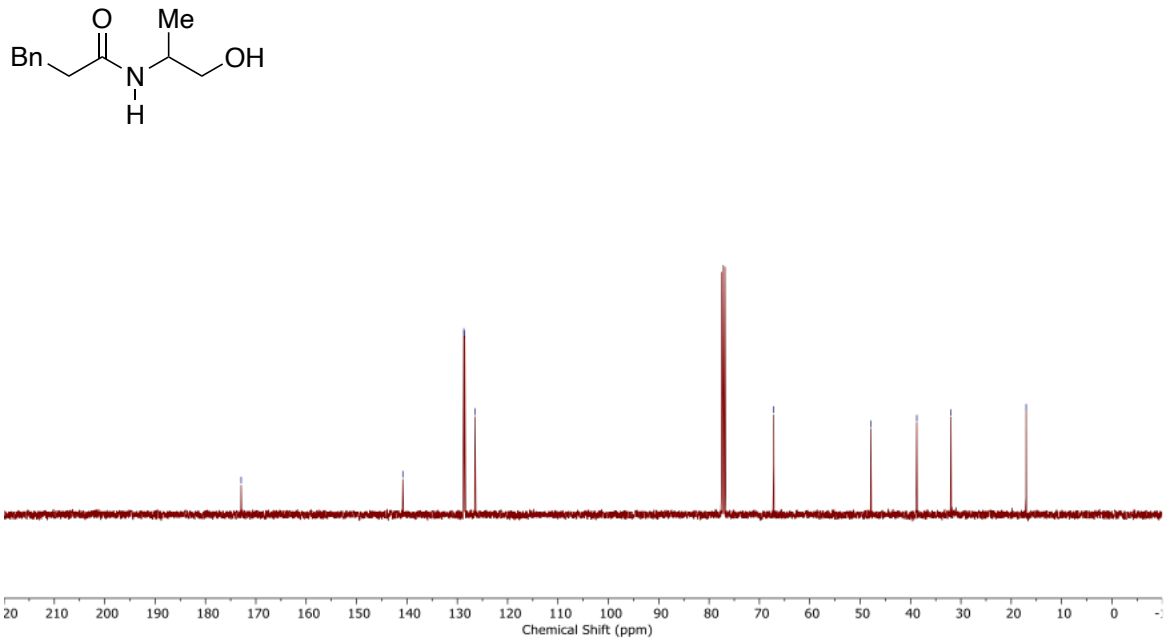


***N*-(1-hydroxypropan-2-yl)-3-phenylpropanamide, 52x**

^{1}H-NMR (400 MHz, $CDCl_3$)



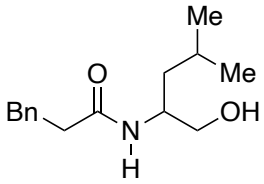
^{13}C-NMR (100 MHz, $CDCl_3$)

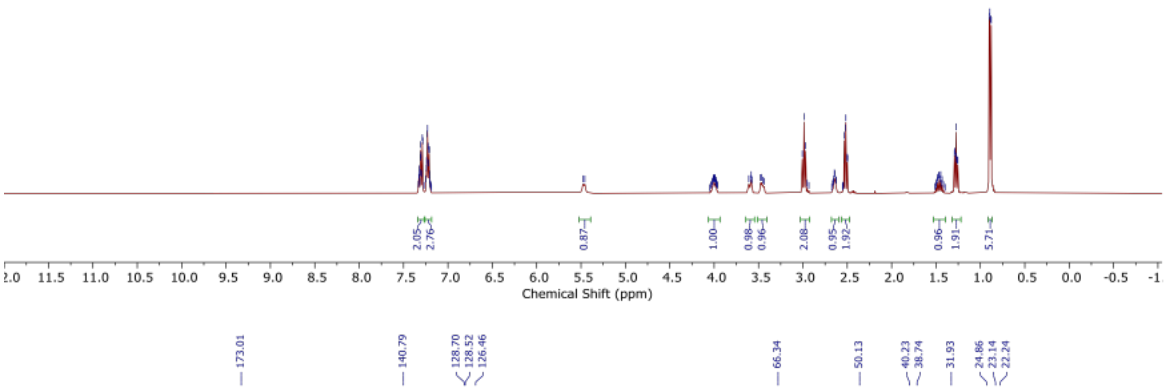


***N*-(1-hydroxy-4-methylpentan-2-yl)-3-phenylpropanamide, 52y**

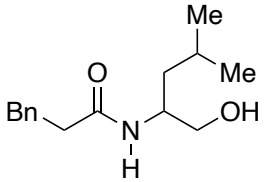


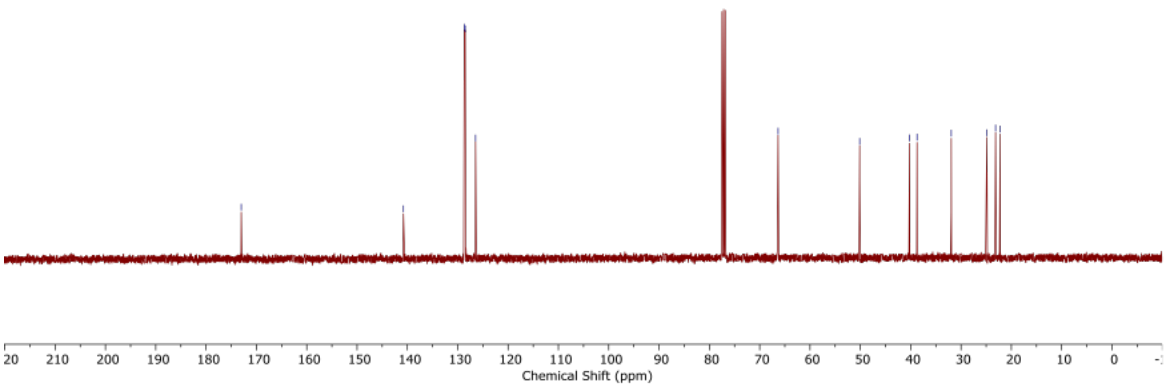
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

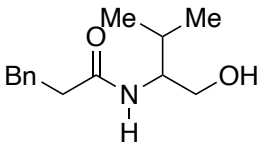


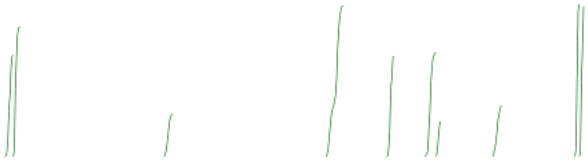


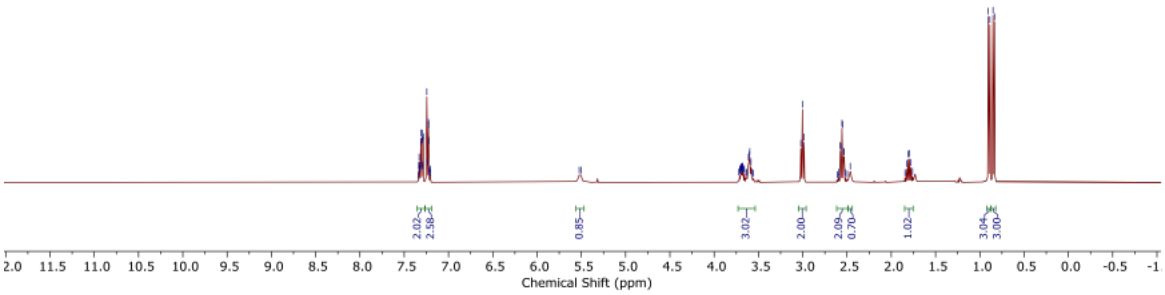
***N*-(1-hydroxy-3-methylbutan-2-yl)-3-phenylpropanamide, 52z**



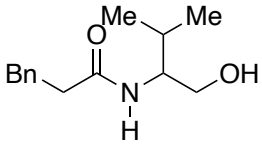
^{1}H-NMR (400 MHz, $CDCl_3$)

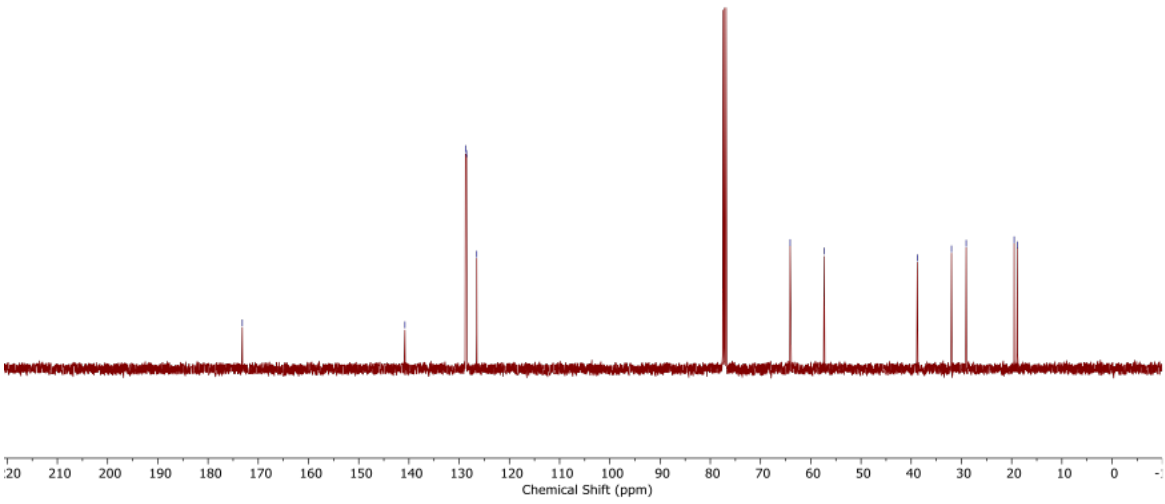






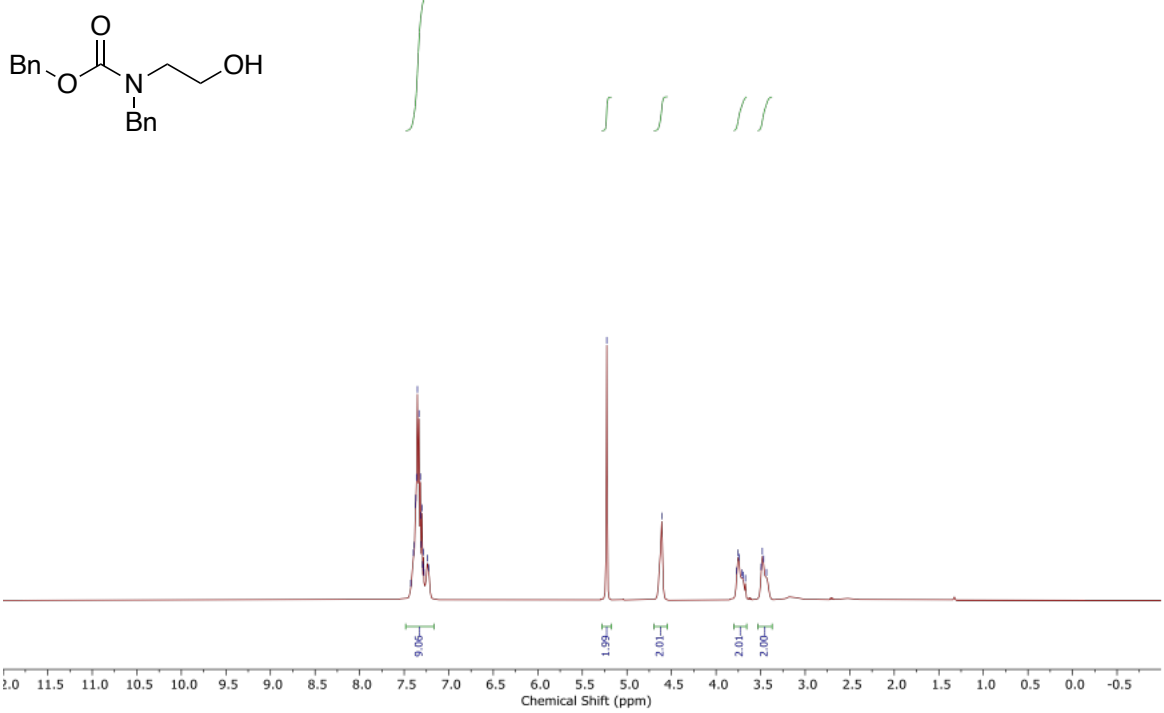
^{13}C-NMR (100 MHz, $CDCl_3$)



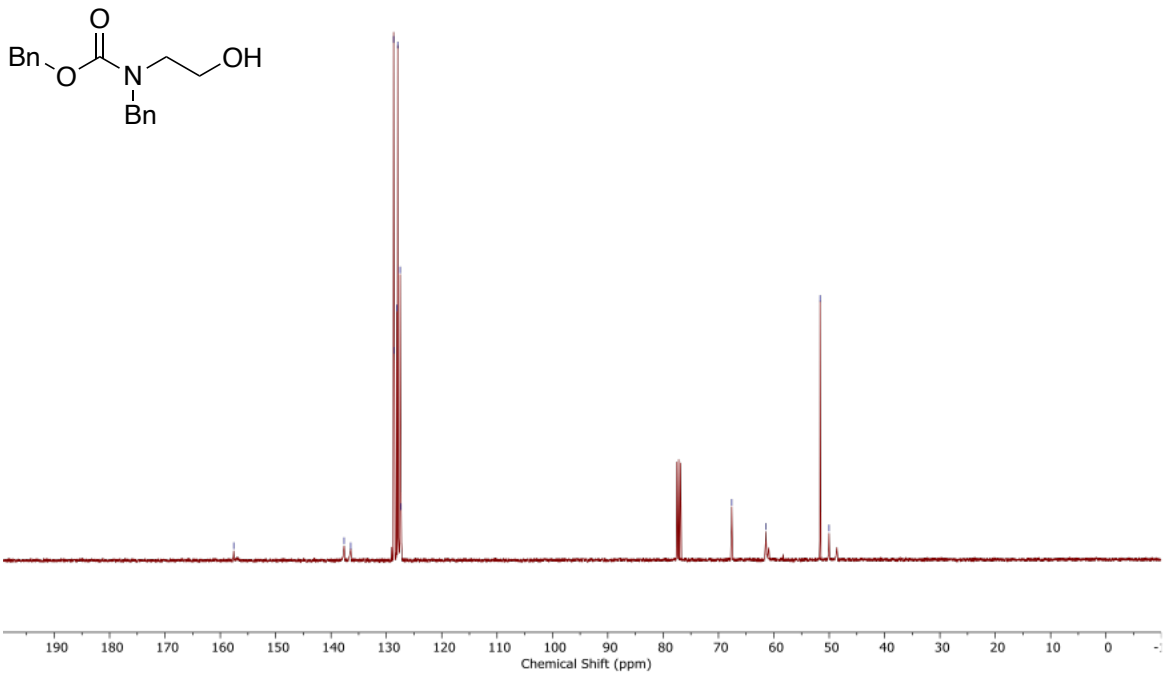


Benzyl benzyl(2-hydroxyethyl)carbamate, 52ac

^{1}H-NMR (400 MHz, $CDCl_3$)



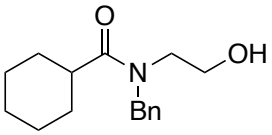
^{13}C-NMR (100 MHz, $CDCl_3$)



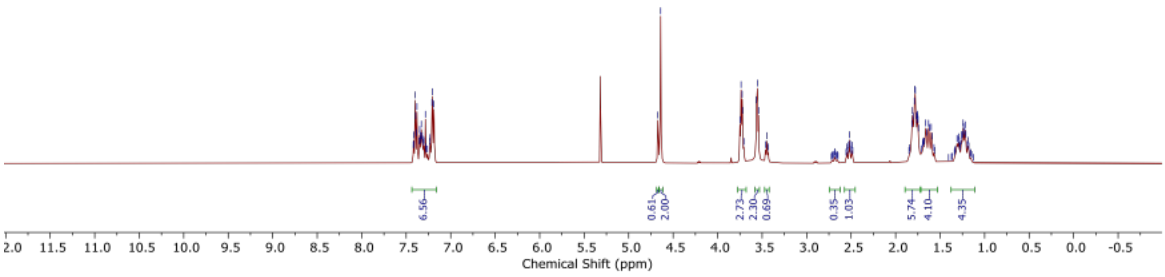
_N_-benzyl-_N_-(2-hydroxyethyl)cyclohexanecarboxamide, 52ad



^{1}H-NMR (400 MHz, $CDCl_3$)

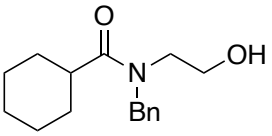


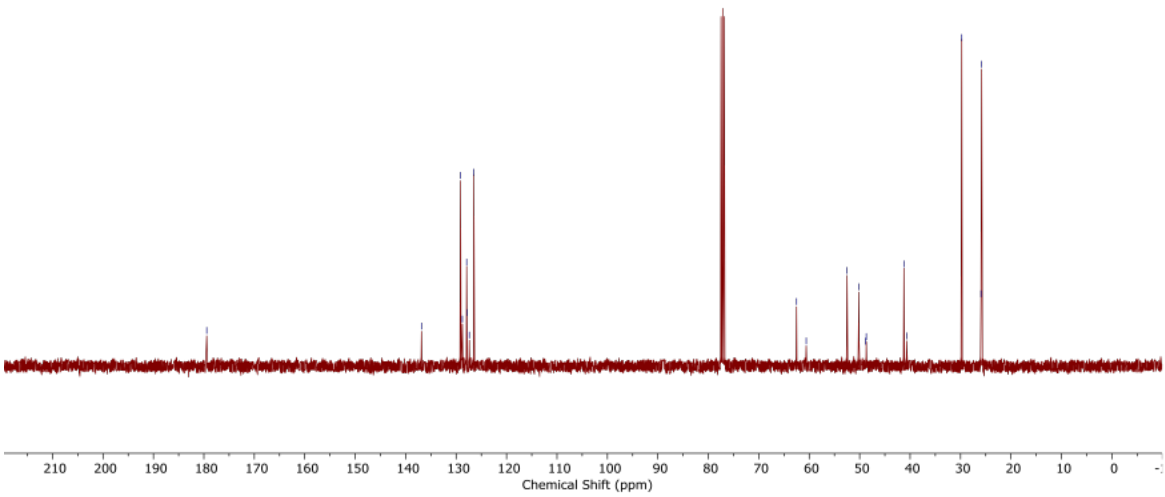






^{13}C-NMR (100 MHz, $CDCl_3$)

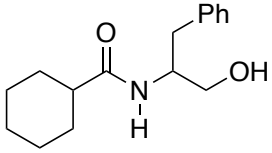


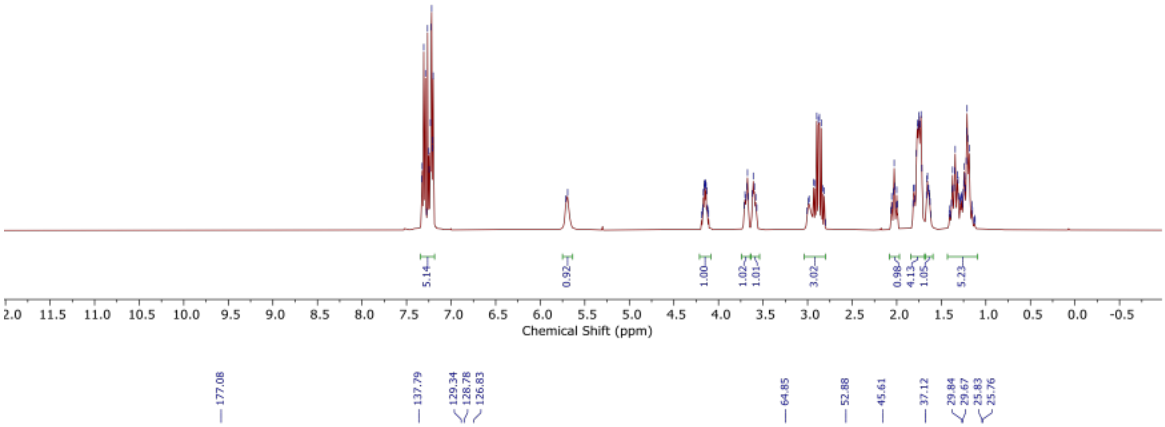


N-(1-hydroxy-3-phenylpropan-2-yl)cyclohexanecarboxamide, 52ae

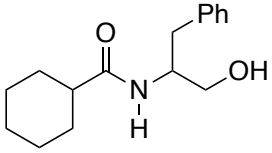


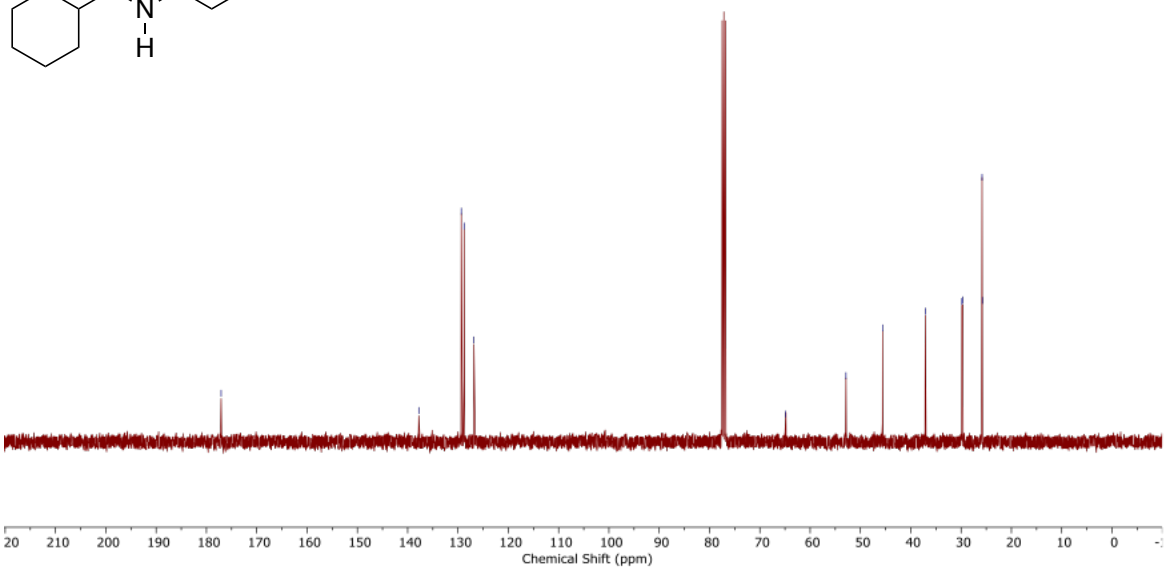
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

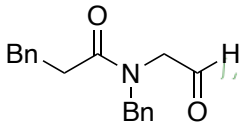




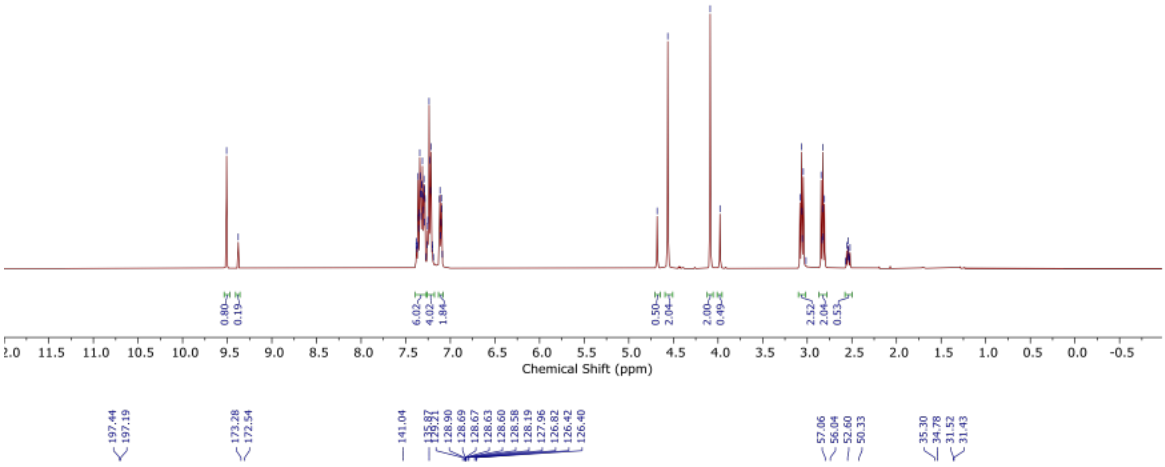
***N*-benzyl-*N*-(2-oxoethyl)-3-phenylpropanamide, 53a**



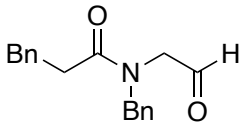
^{1}H-NMR (400 MHz, $CDCl_3$)

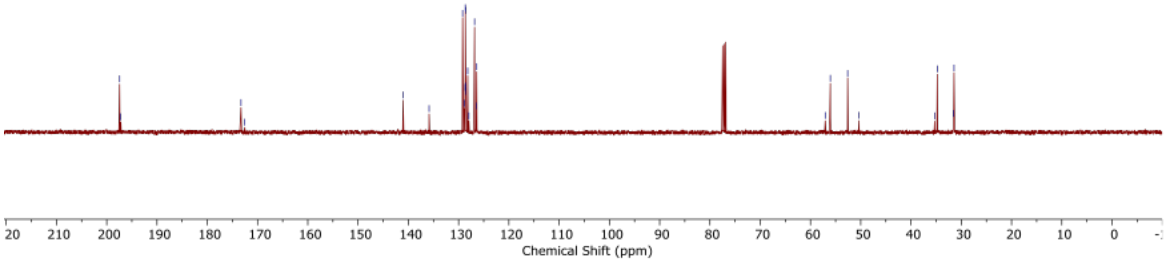






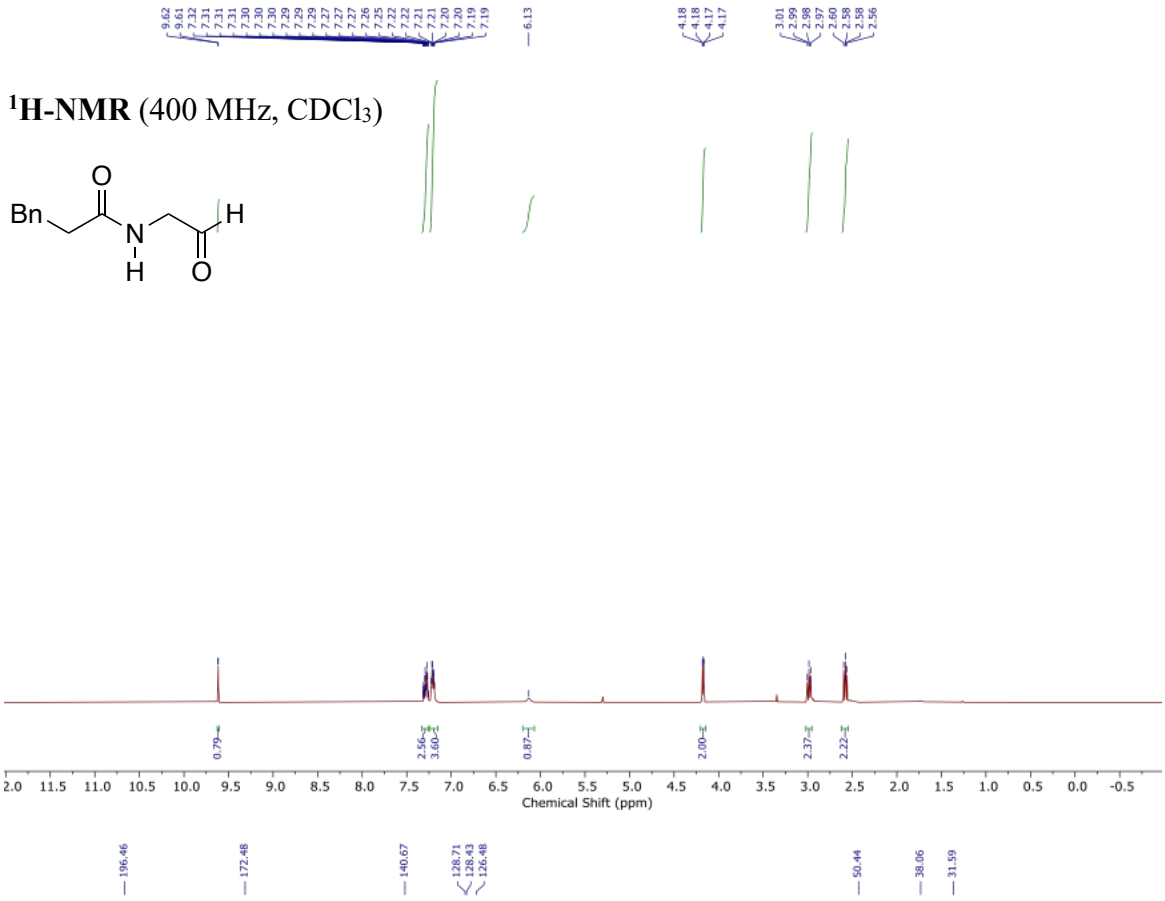
^{13}C-NMR (100 MHz, $CDCl_3$)



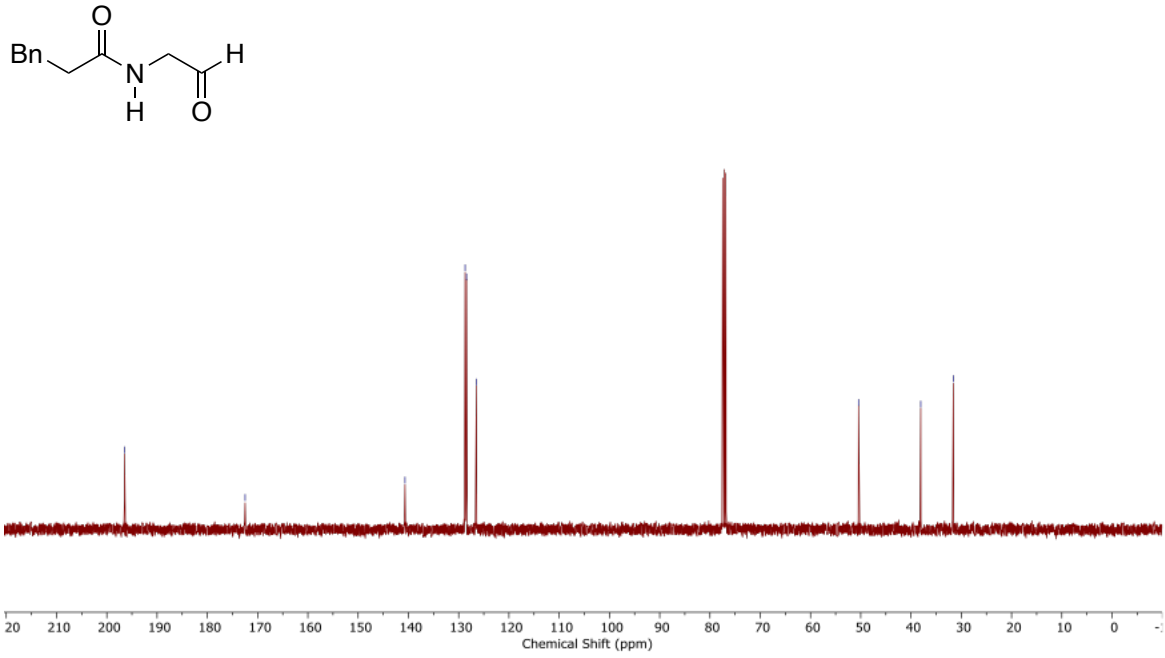


N-(2-oxoethyl)-3-phenylpropanamide, 53v

^{1}H-NMR (400 MHz, $CDCl_3$)



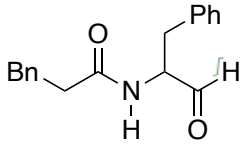
^{13}C-NMR (100 MHz, $CDCl_3$)



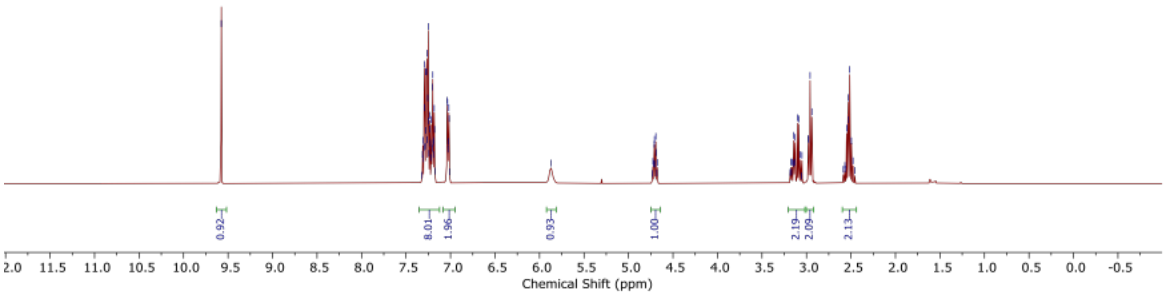
***N*-(1-oxo-3-phenylpropan-2-yl)-3-phenylpropanamide, 53w**



^{1}H-NMR (400 MHz, $CDCl_3$)

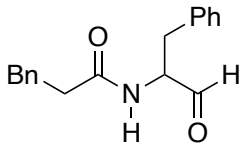


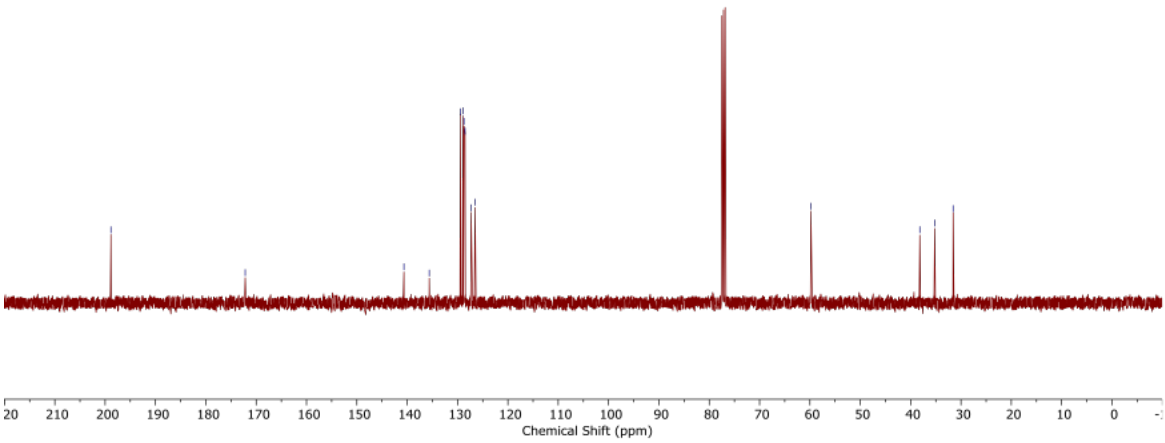






^{13}C-NMR (100 MHz, $CDCl_3$)

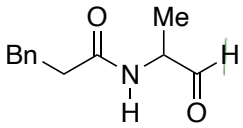




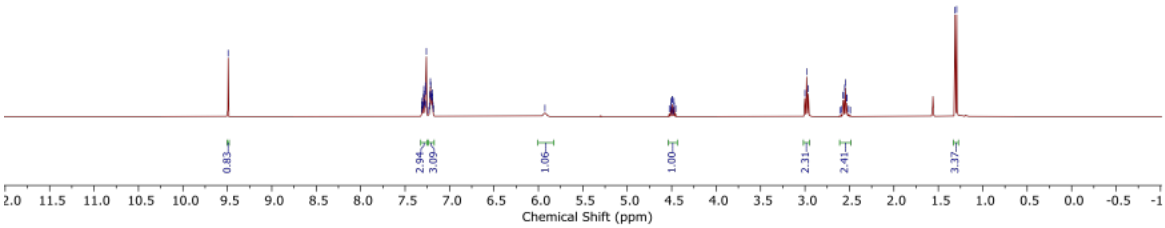
***N*-(1-oxopropan-2-yl)-3-phenylpropanamide, 53x**



^{1}H-NMR (400 MHz, $CDCl_3$)

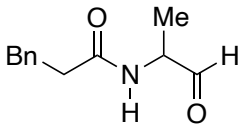


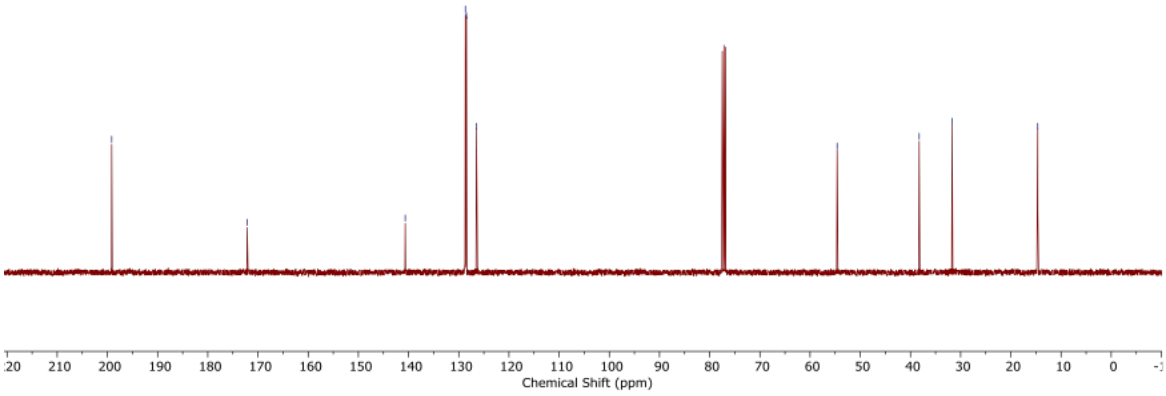






^{13}C-NMR (100 MHz, $CDCl_3$)

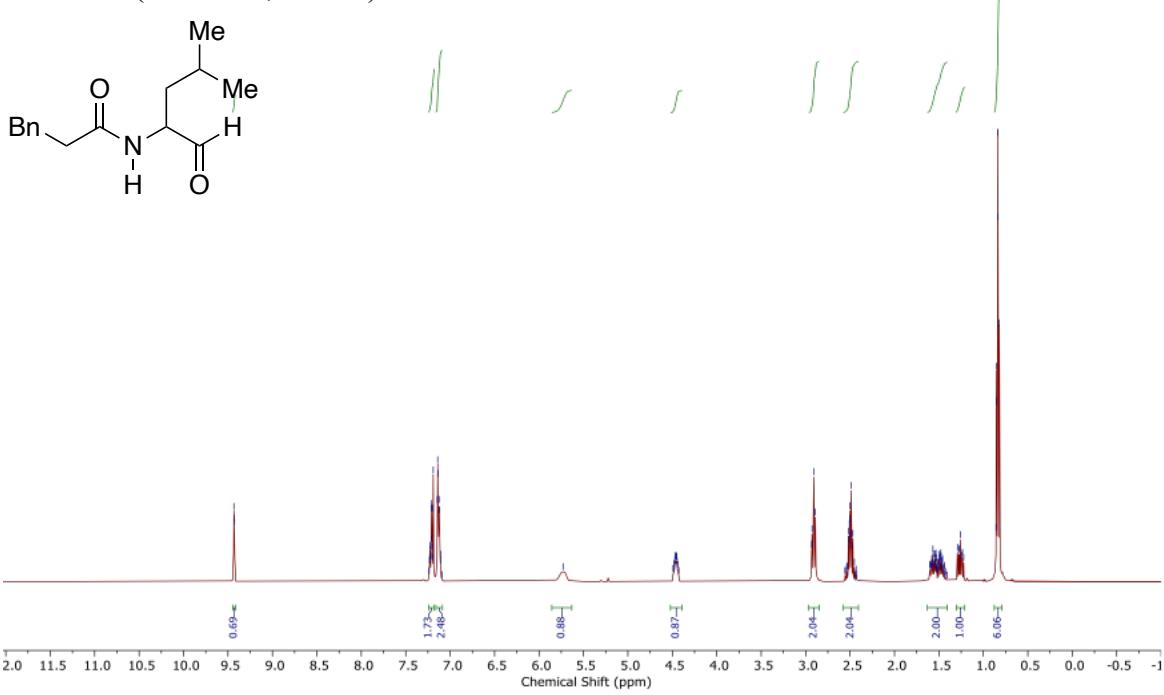




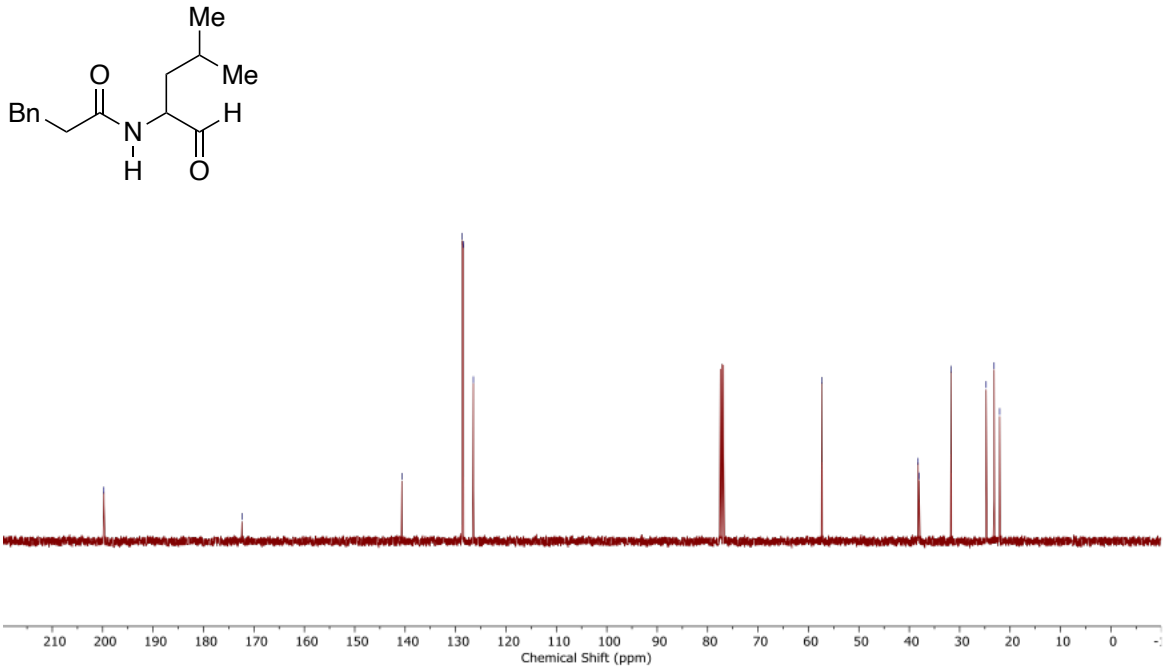
***N*-(4-methyl-1-oxopentan-2-yl)-3-phenylpropanamide, 53y**



^{1}H-NMR (400 MHz, $CDCl_3$)



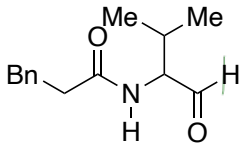
^{13}C-NMR (100 MHz, $CDCl_3$)

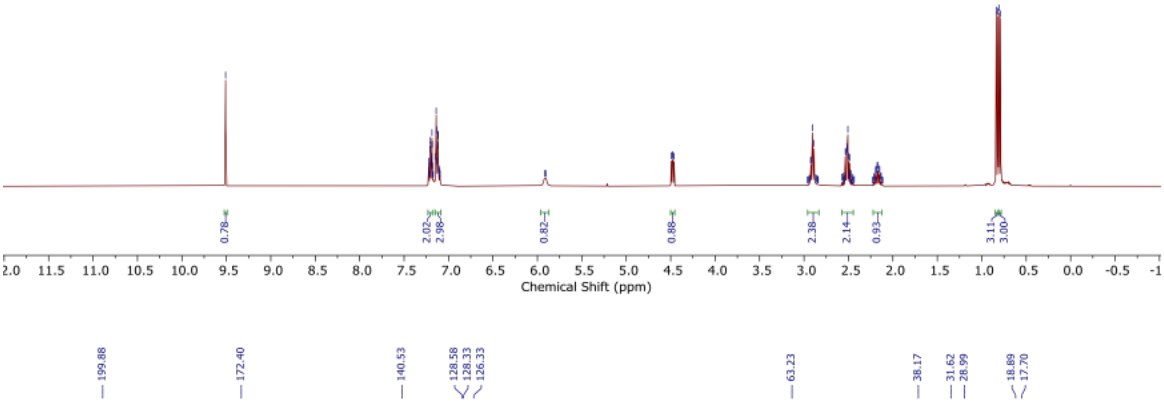


***N*-(3-methyl-1-oxobutan-2-yl)-3-phenylpropanamide, 53z**

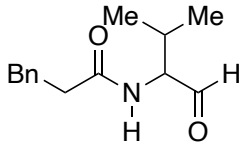


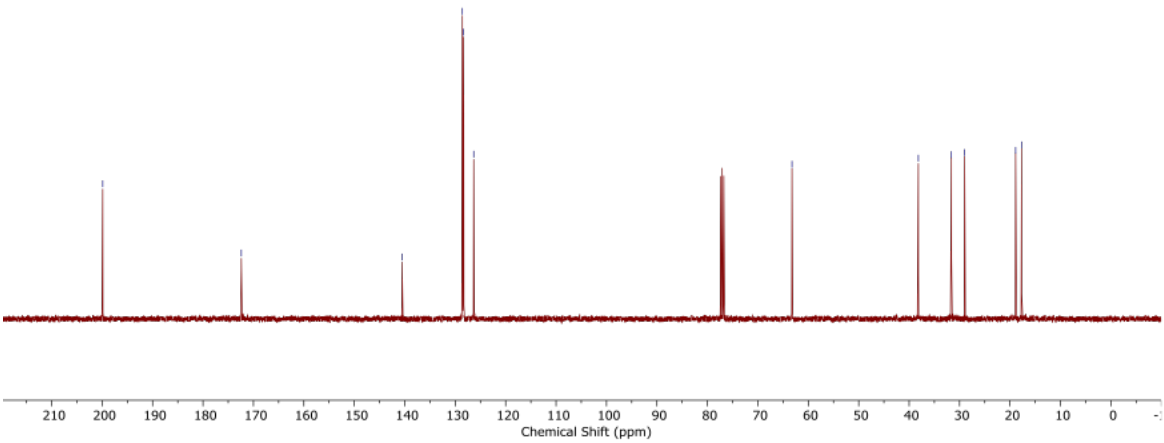
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

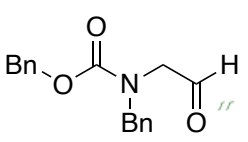


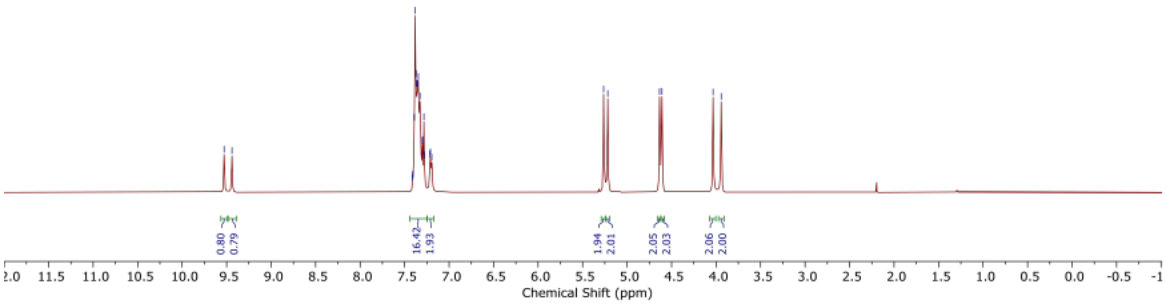


Benzyl benzyl(2-oxoethyl)carbamate, 53ac



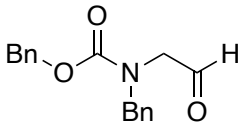
^{1}H-NMR (400 MHz, $CDCl_3$)







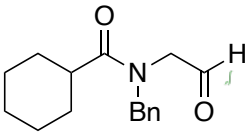
^{13}C-NMR (100 MHz, $CDCl_3$)



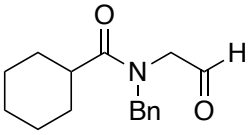
N-benzyl-*N*-(2-oxoethyl)cyclohexanecarboxamide, 53ad

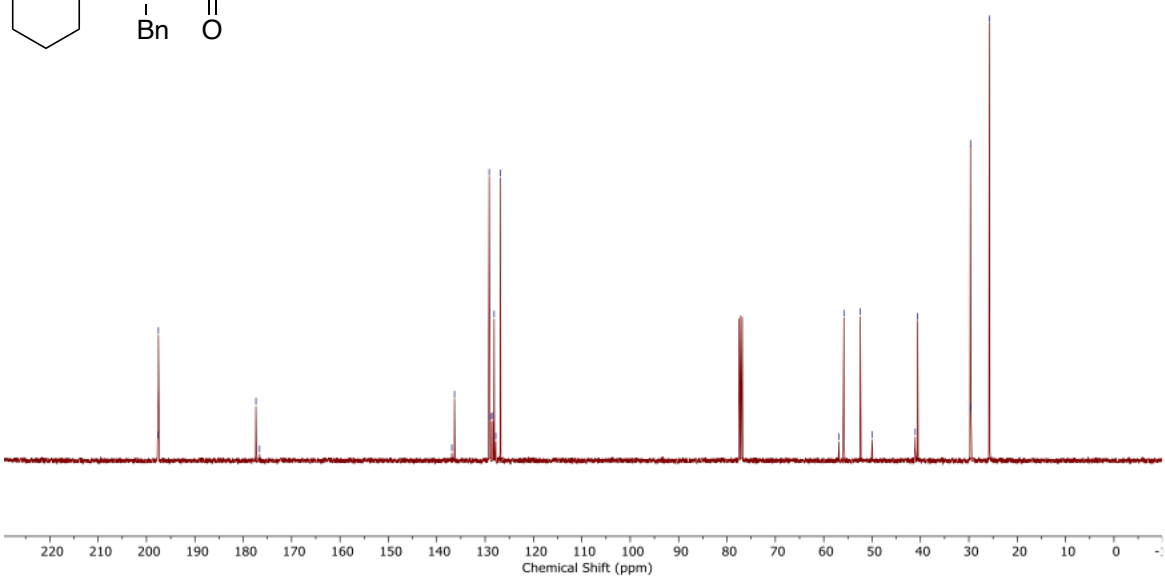


^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)

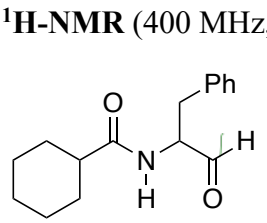




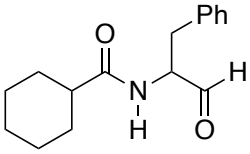
***N*-(1-oxo-3-phenylpropan-2-yl)cyclohexanecarboxamide, 53ae**

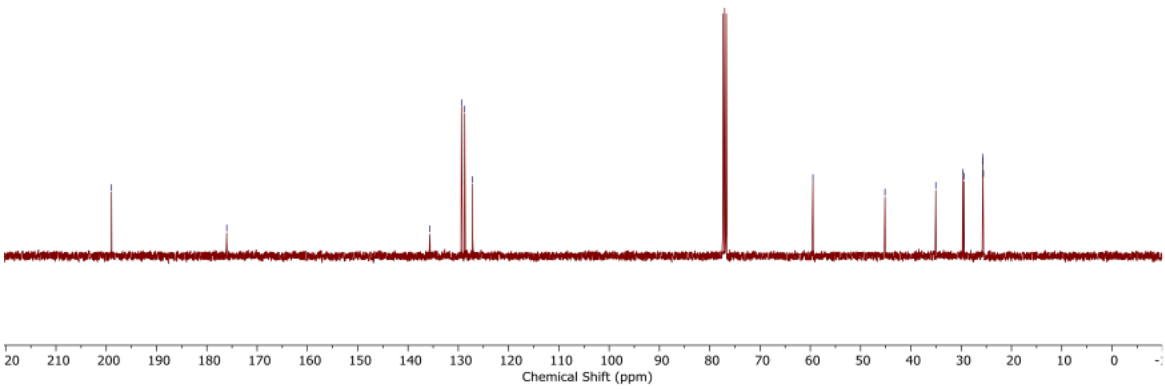


^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)

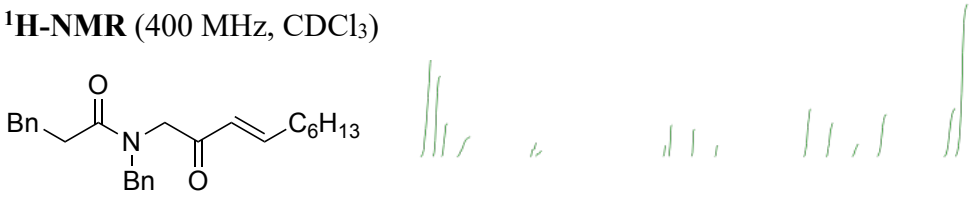


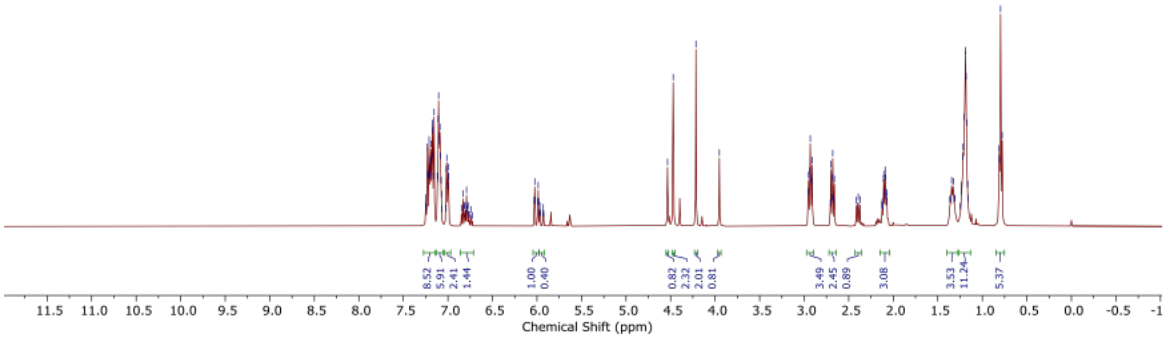


(*E*)-*N*-benzyl-*N*-(2-oxodec-3-en-1-yl)-3-phenylpropanamide, 54a



^{1}H-NMR (400 MHz, $CDCl_3$)

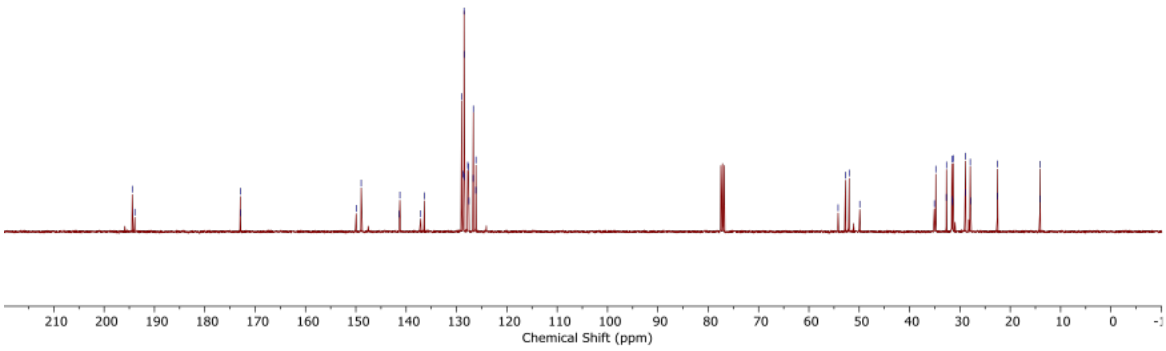






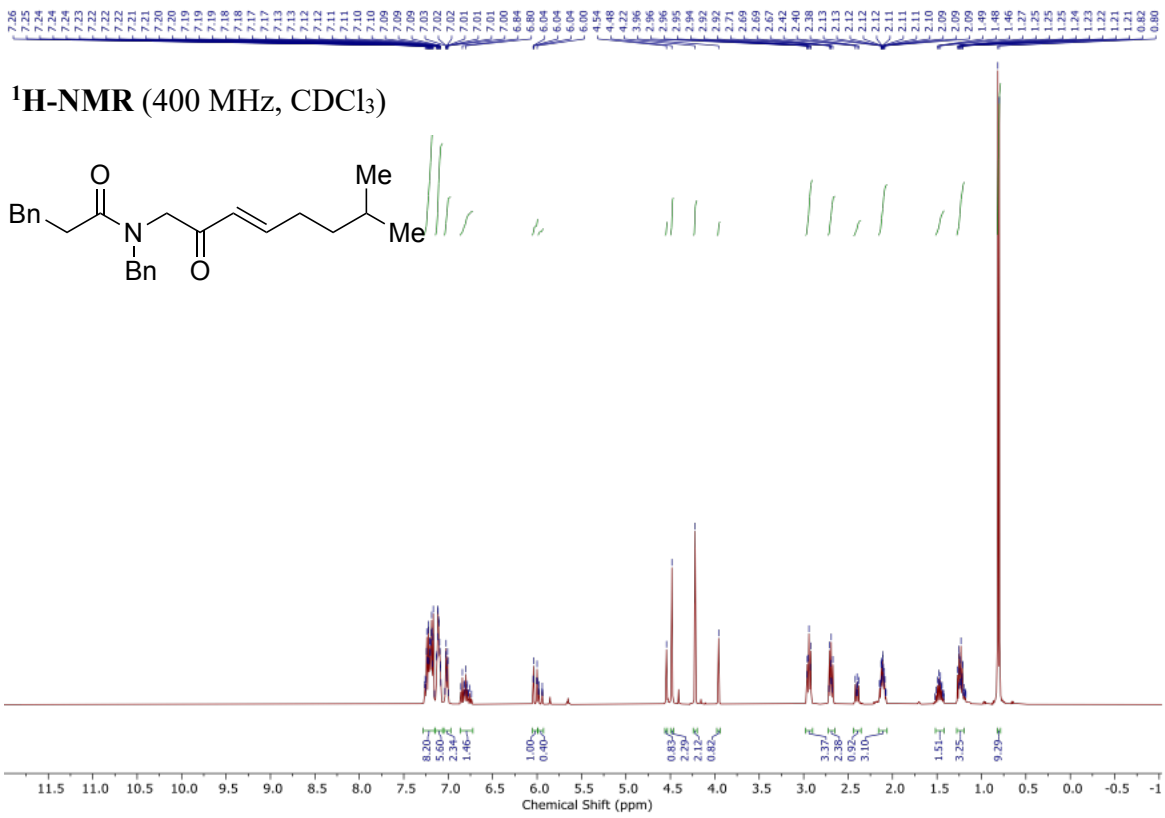
^{13}C-NMR (100 MHz, $CDCl_3$)



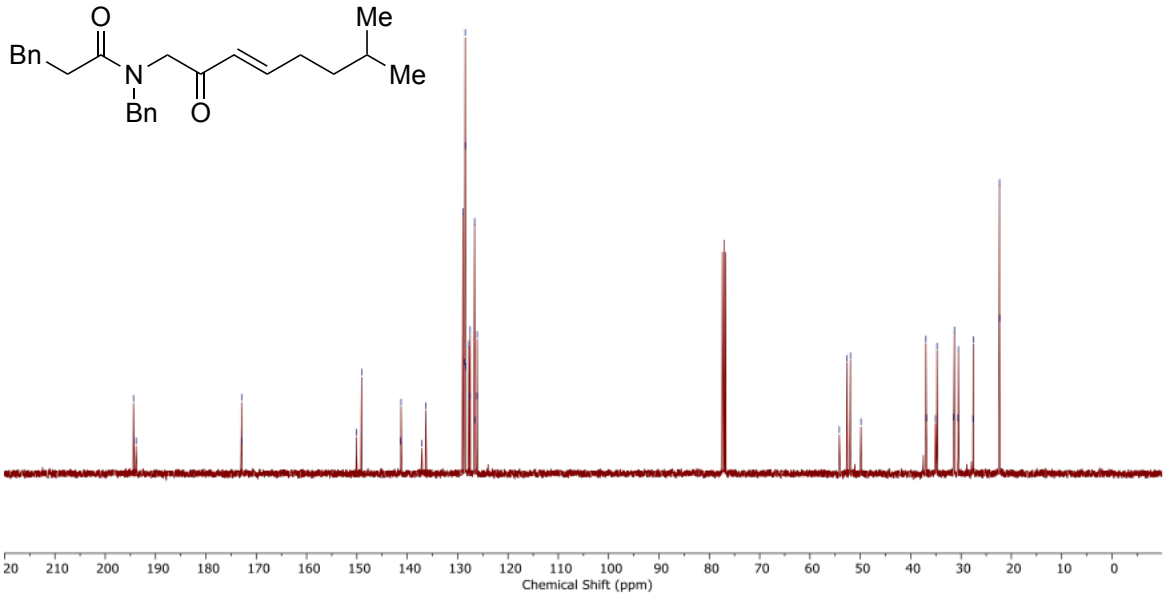


(*E*)-*N*-benzyl-*N*-(7-methyl-2-oxooct-3-en-1-yl)-3-phenylpropanamide, 54b

^{1}H-NMR (400 MHz, $CDCl_3$)



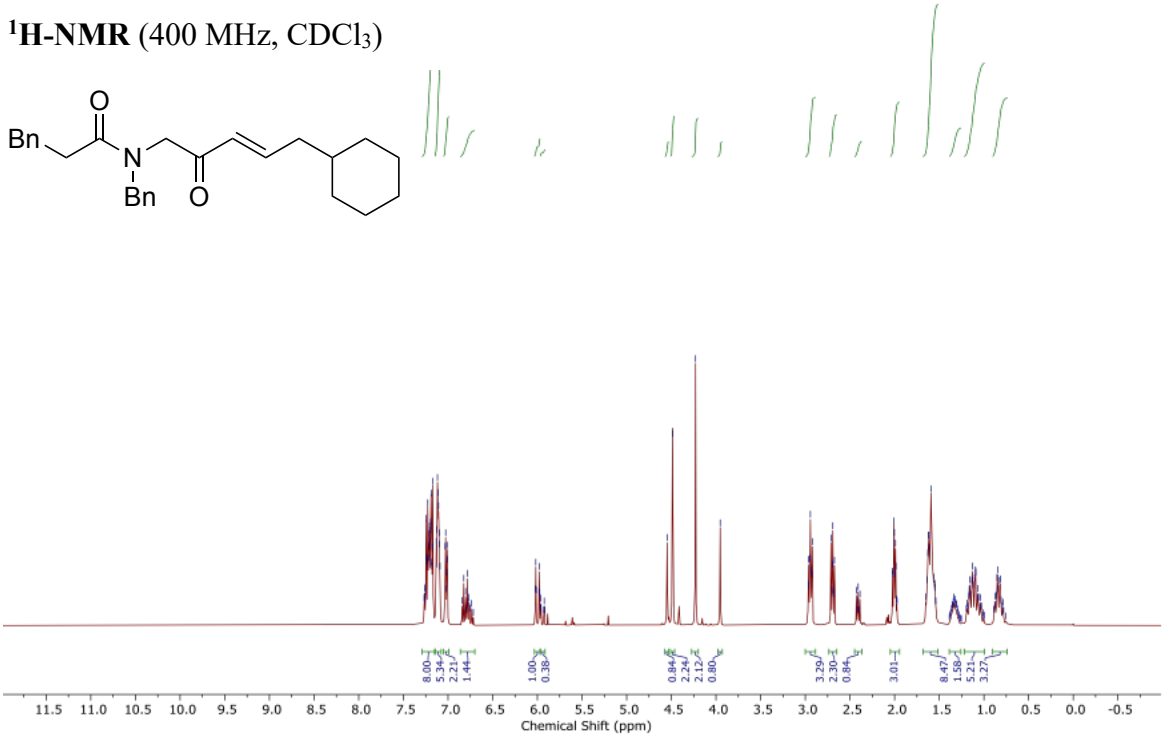
^{13}C-NMR (100 MHz, $CDCl_3$)



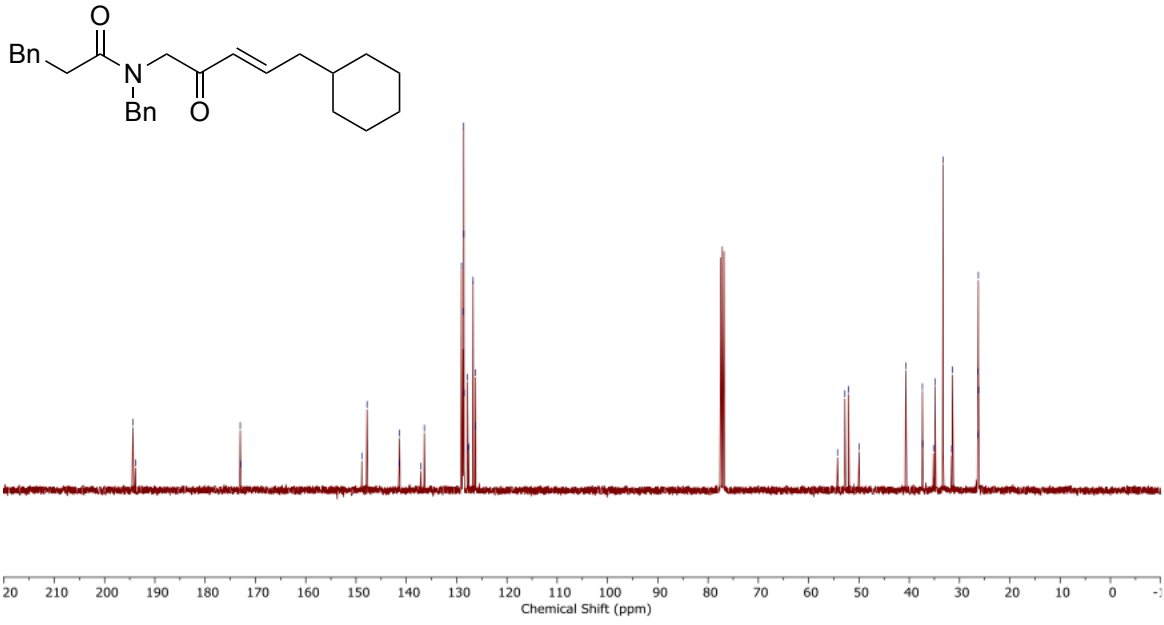
(*E*)-*N*-benzyl-*N*-(5-cyclohexyl-2-oxopent-3-en-1-yl)-3-phenylpropanamide, 54c



^{1}H-NMR (400 MHz, $CDCl_3$)



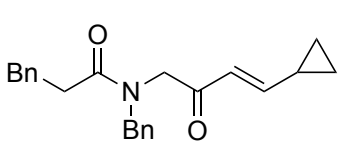
^{13}C-NMR (100 MHz, $CDCl_3$)



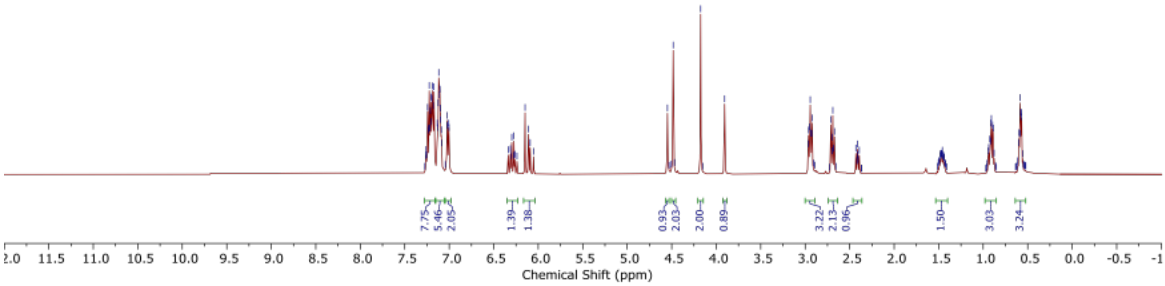
(*E*)-*N*-benzyl-*N*-(4-cyclopropyl-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54d



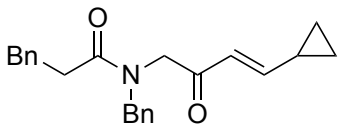
^{1}H-NMR (400 MHz, $CDCl_3$)

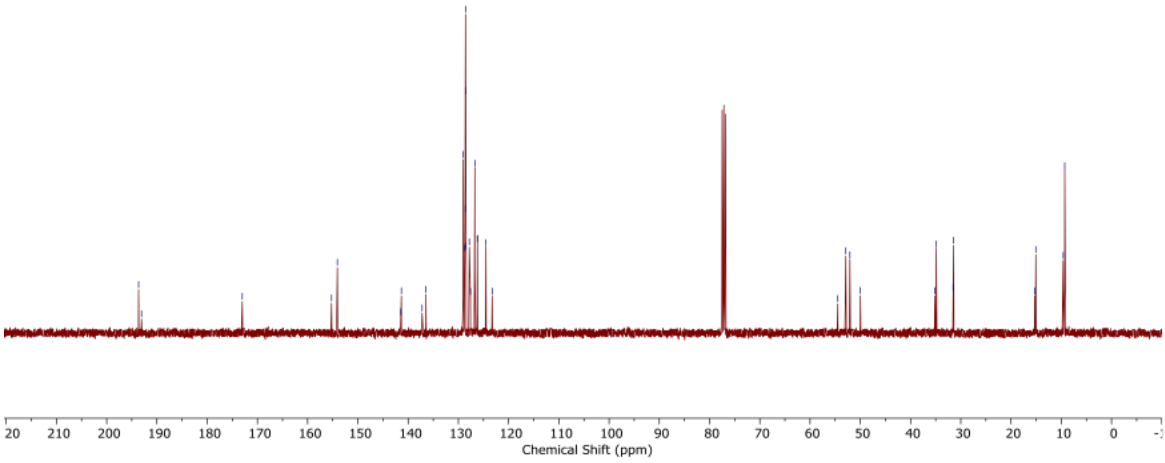






^{13}C-NMR (100 MHz, $CDCl_3$)

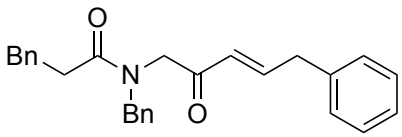


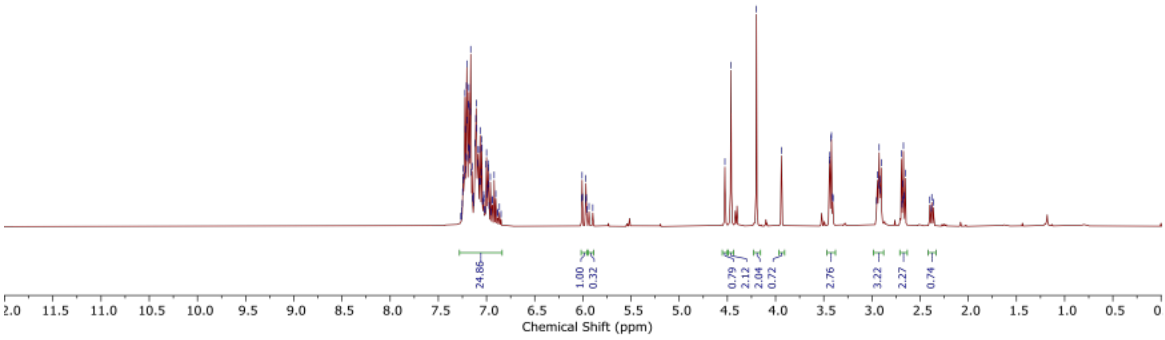


(*E*)-*N*-benzyl-*N*-(2-oxo-5-phenylpent-3-en-1-yl)-3-phenylpropanamide, 54e

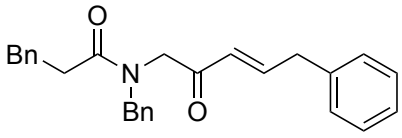


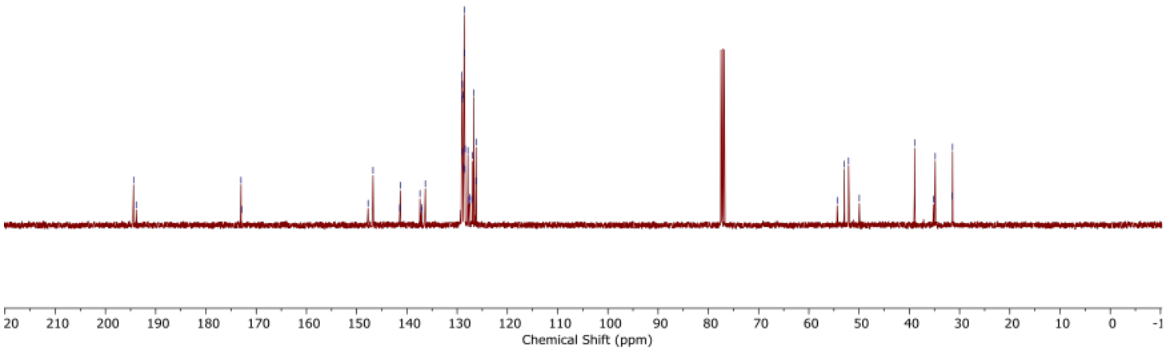
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

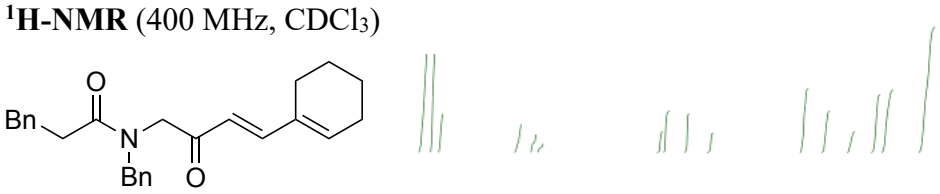


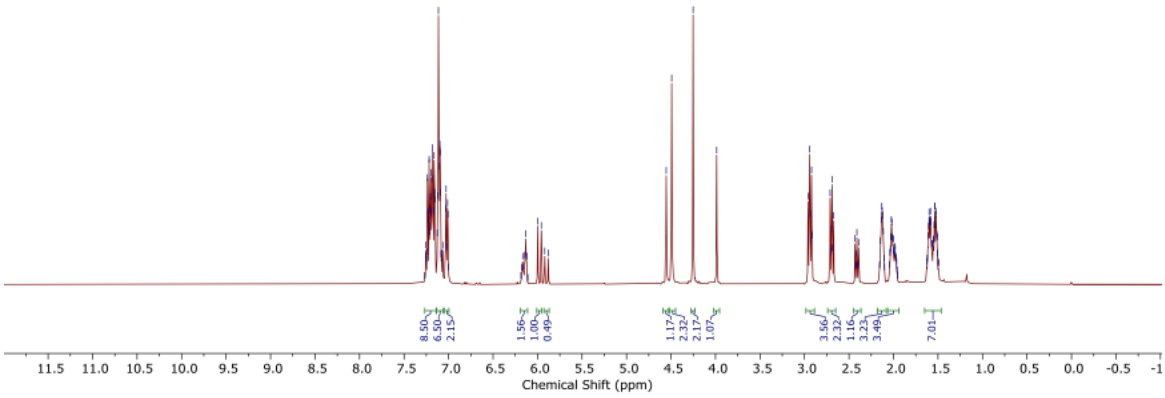


(*E*)-*N*-benzyl-*N*-(4-(cyclohex-1-en-1-yl)-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54f

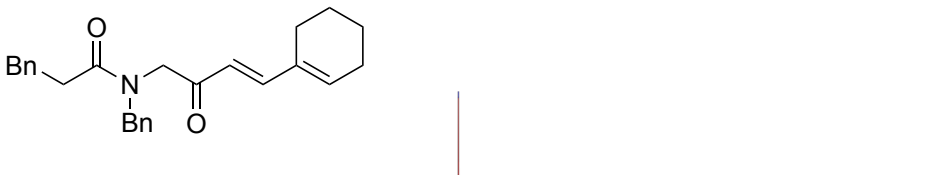


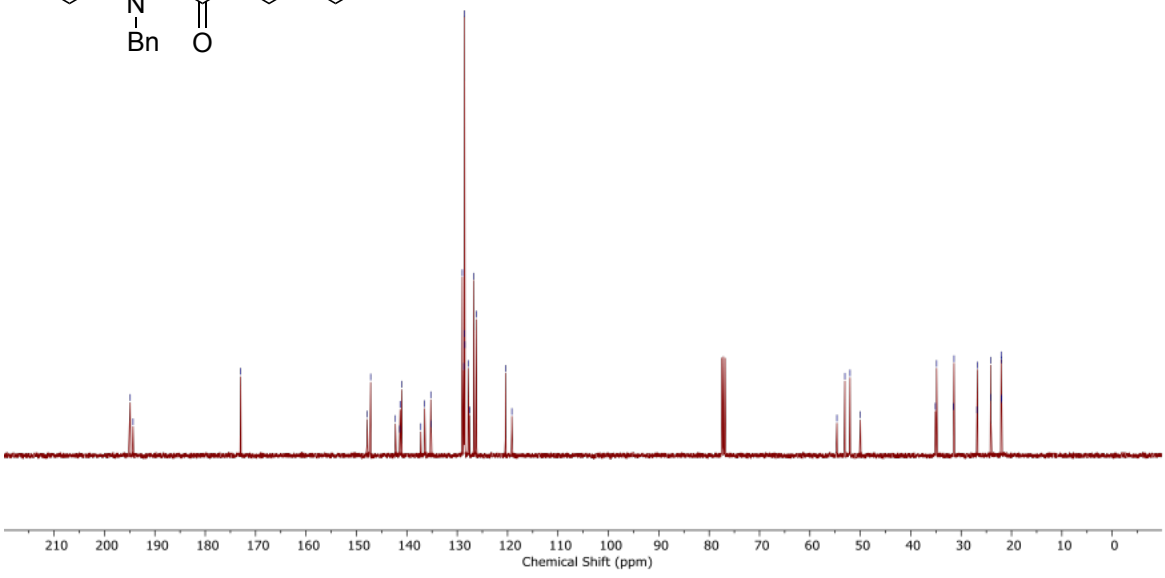
^{1}H-NMR (400 MHz, $CDCl_3$)



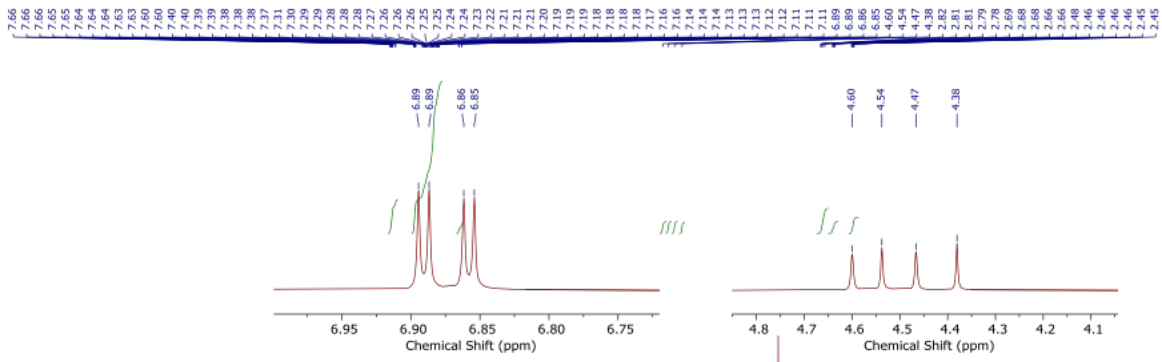


^{13}C-NMR (100 MHz, $CDCl_3$)

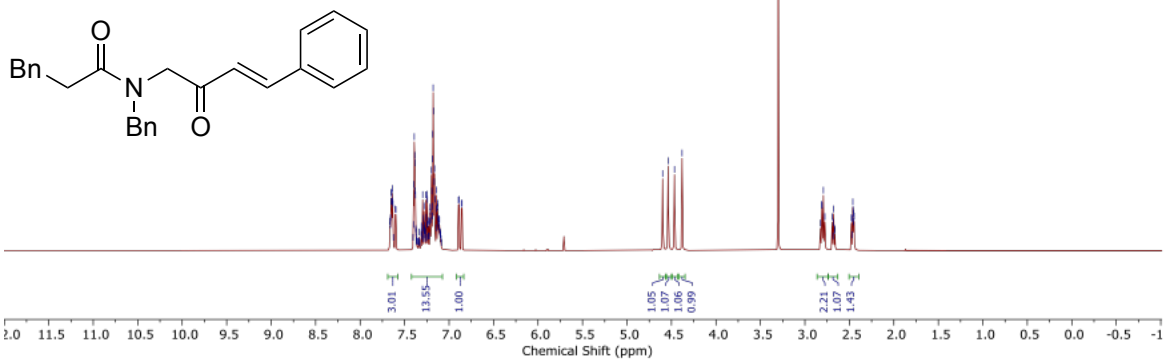


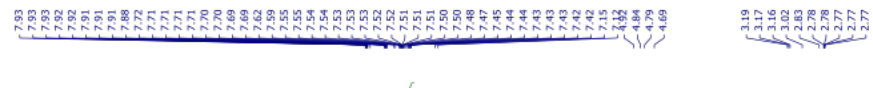


(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54g

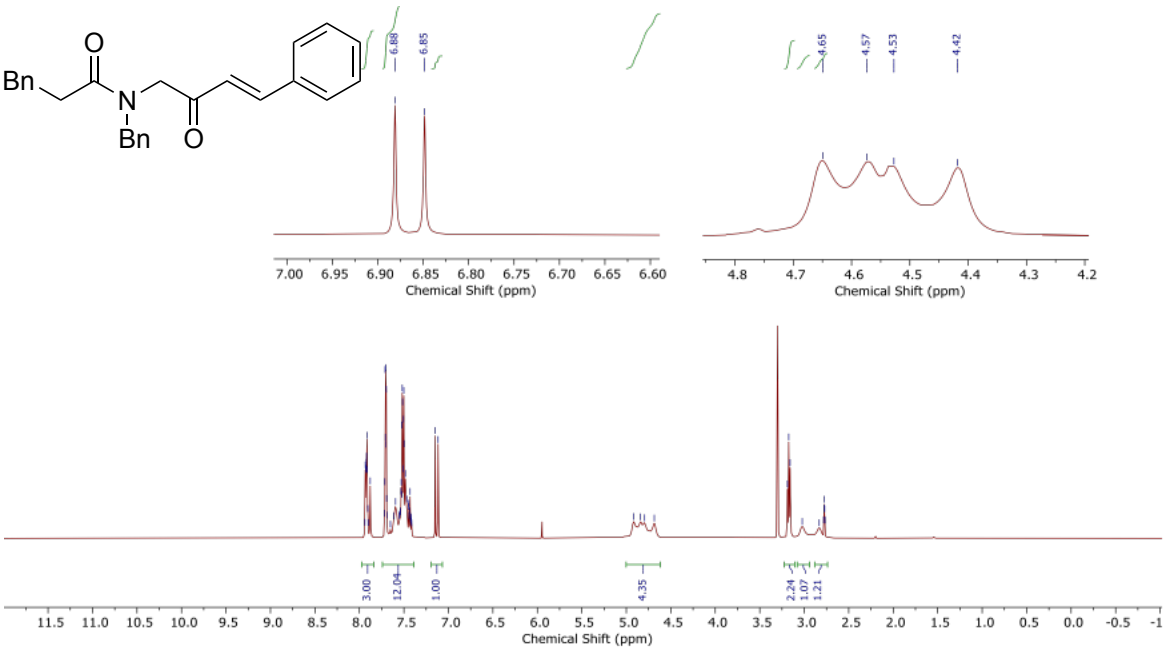


^{1}H-NMR (500 MHz, DMSO-d_6, 25 °C)





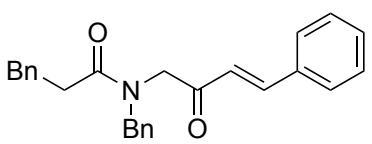
^{1}H-NMR (500 MHz, DMSO-d_6, 90 °C)

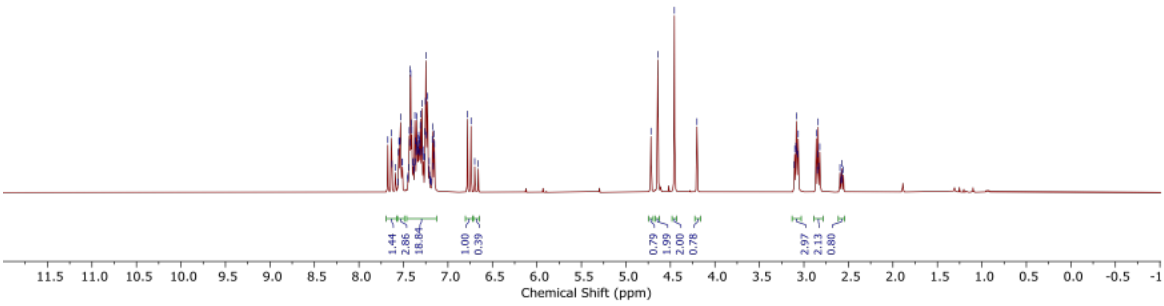


(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54g



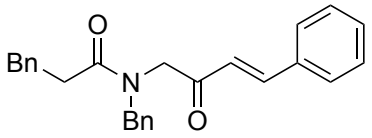
^{1}H-NMR (400 MHz, $CDCl_3$)

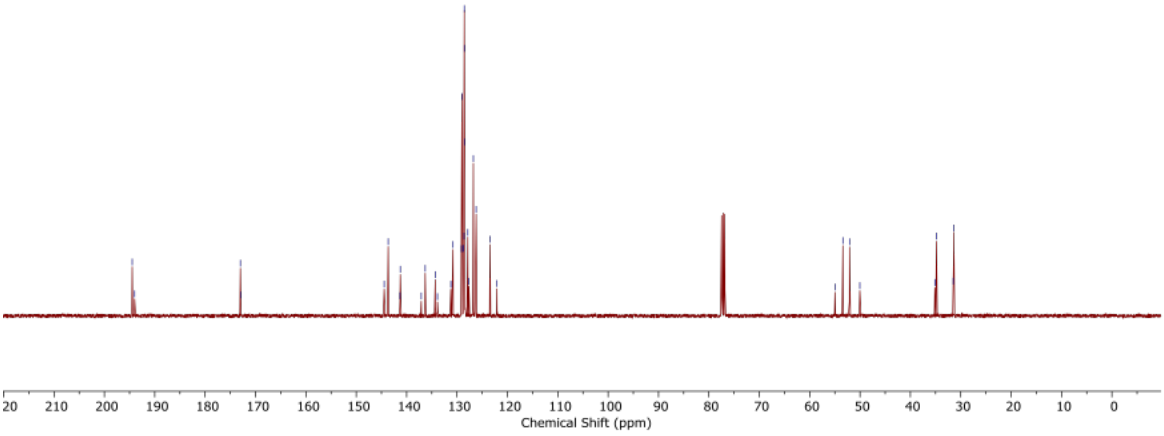






^{13}C-NMR (100 MHz, $CDCl_3$)

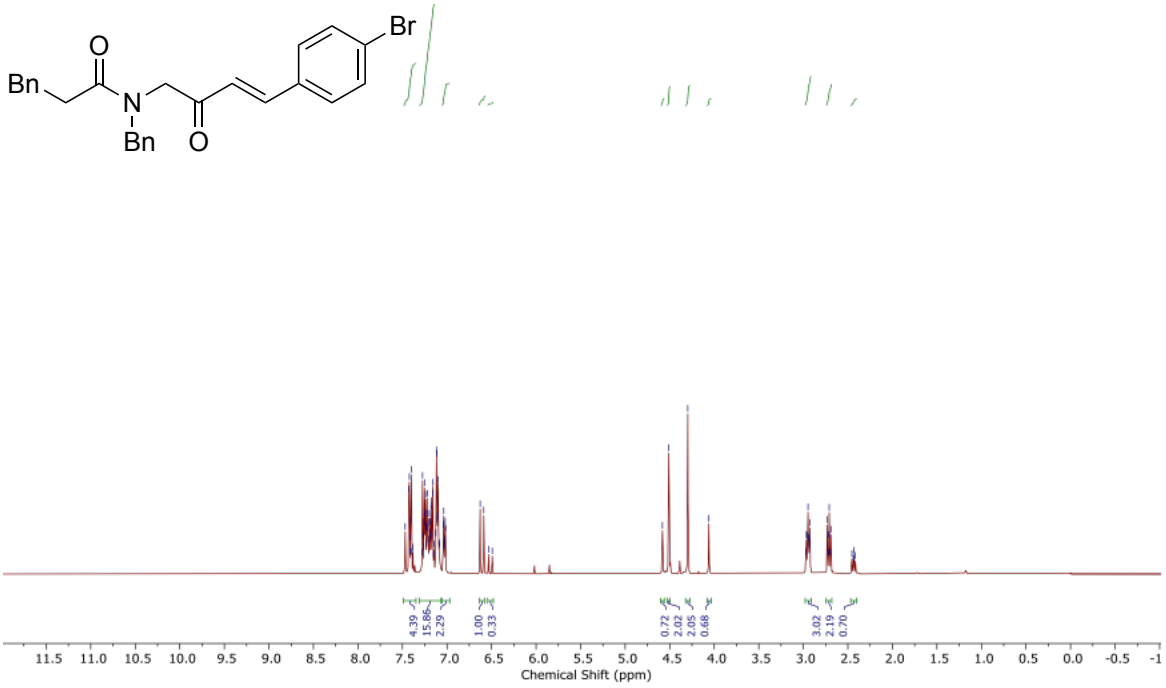




(*E*)-*N*-benzyl-*N*-(4-(4-bromophenyl)-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54h

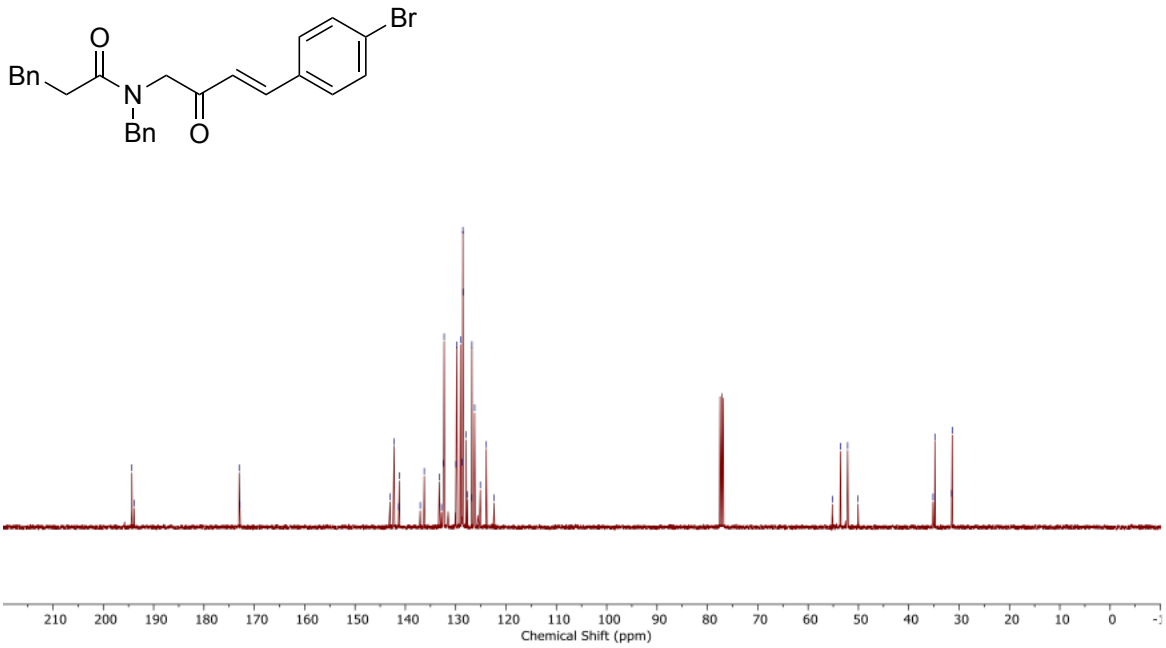


^{1}H-NMR (400 MHz, $CDCl_3$)





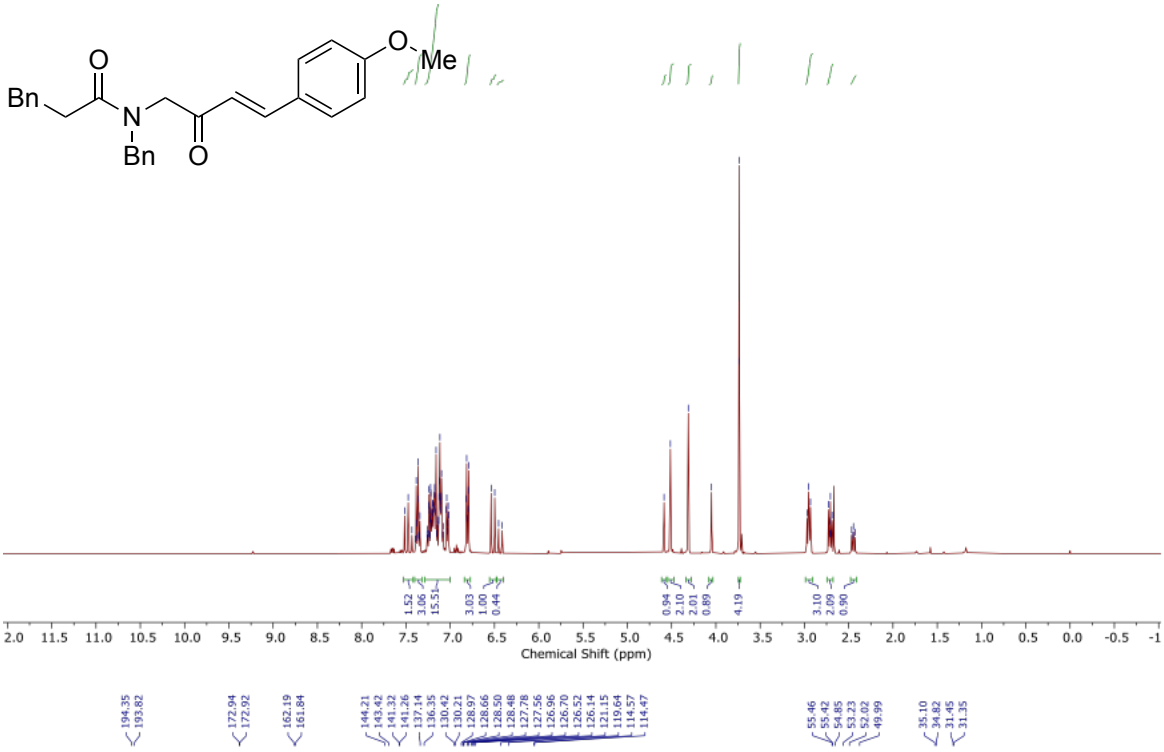
^{13}C-NMR (100 MHz, $CDCl_3$)



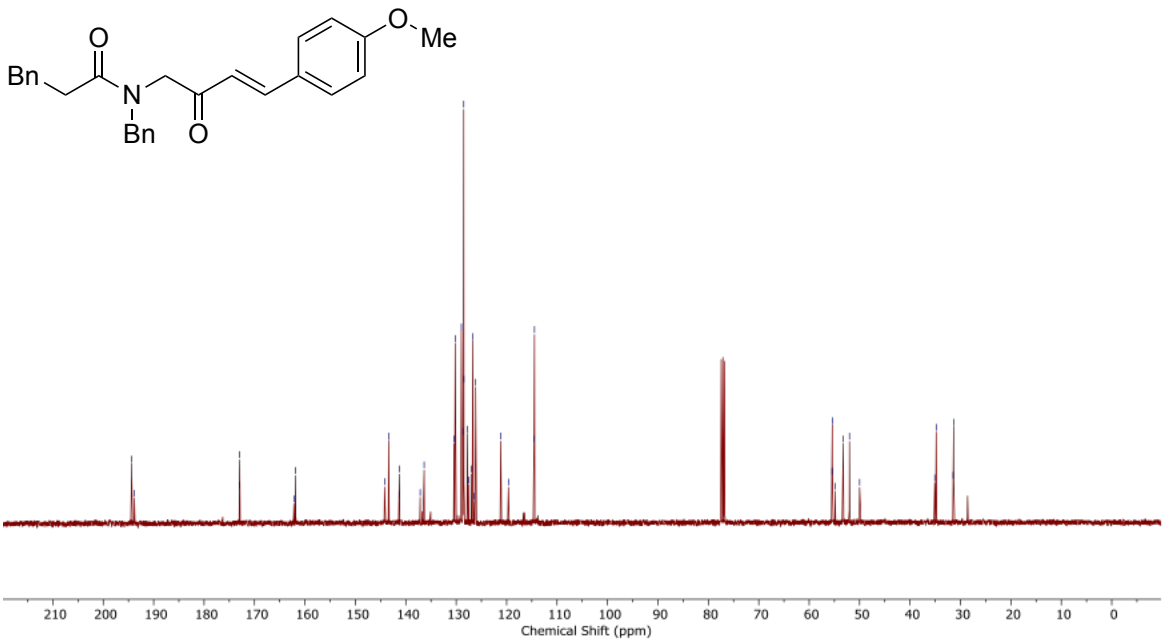
(*E*)-*N*-benzyl-*N*-(4-(4-methoxyphenyl)-2-oxobut-3-en-1-yl)-3-phenylpropanamide, 54i



^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)

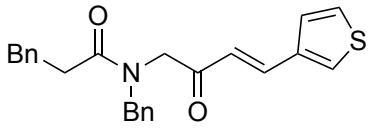


(*E*)-*N*-benzyl-*N*-(2-oxo-4-(thiophen-3-yl)but-3-en-1-yl)-3-phenylpropanamide, 54j

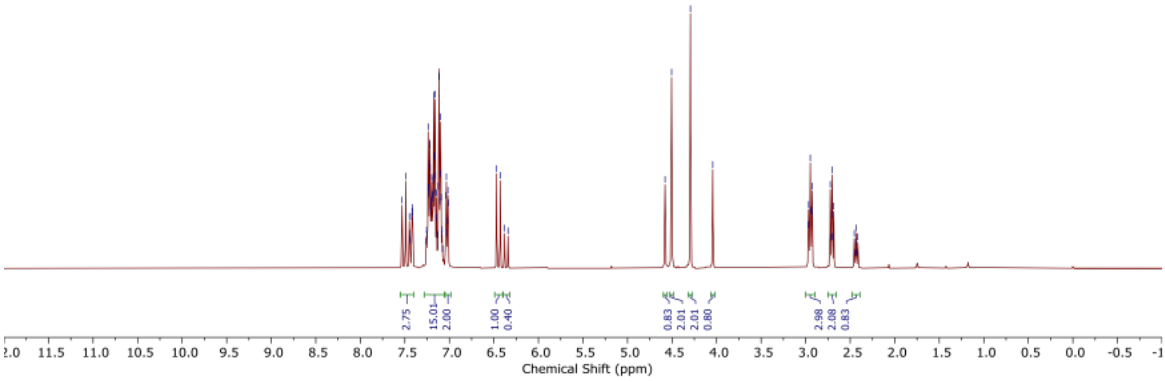




^{1}H-NMR (400 MHz, $CDCl_3$)

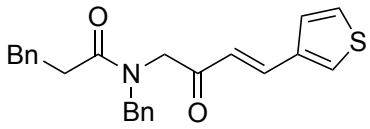


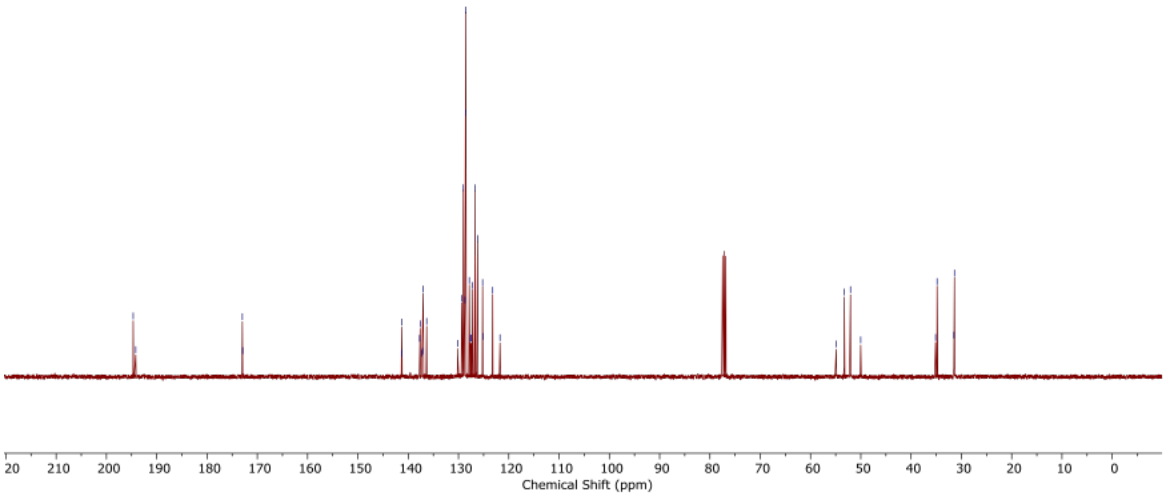






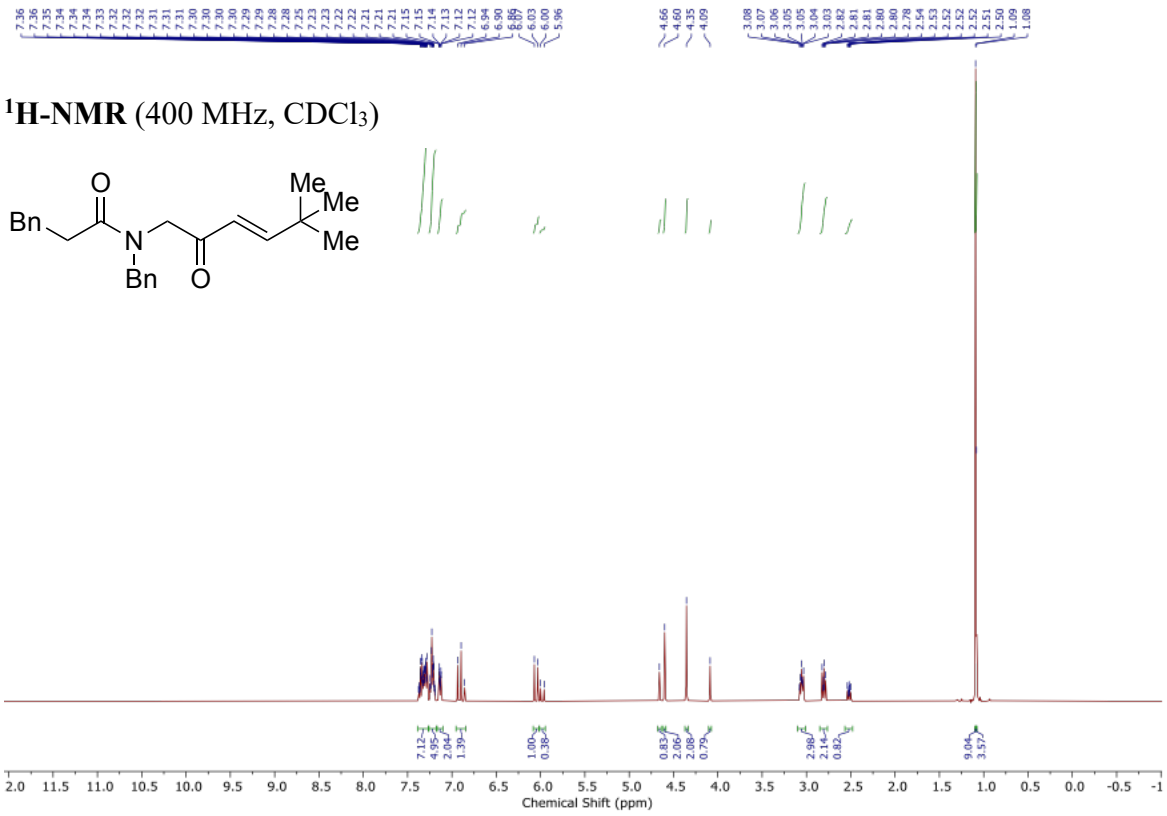
^{13}C-NMR (100 MHz, $CDCl_3$)



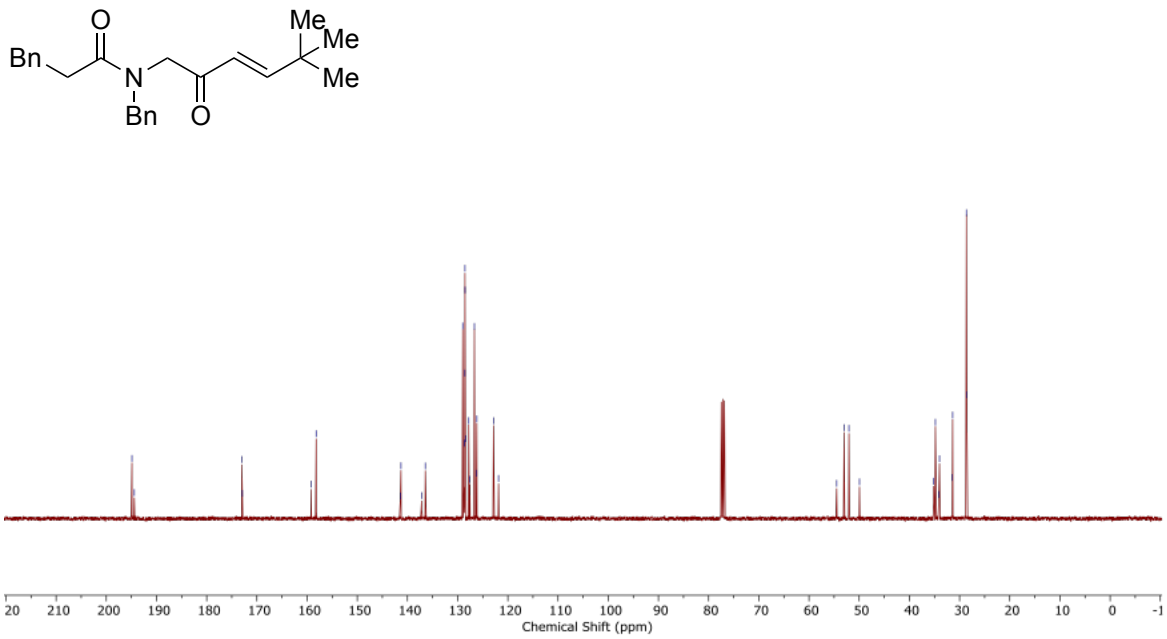


(*E*)-*N*-benzyl-*N*-(5,5-dimethyl-2-oxohex-3-en-1-yl)-3-phenylpropanamide, 54k

^{1}H-NMR (400 MHz, $CDCl_3$)



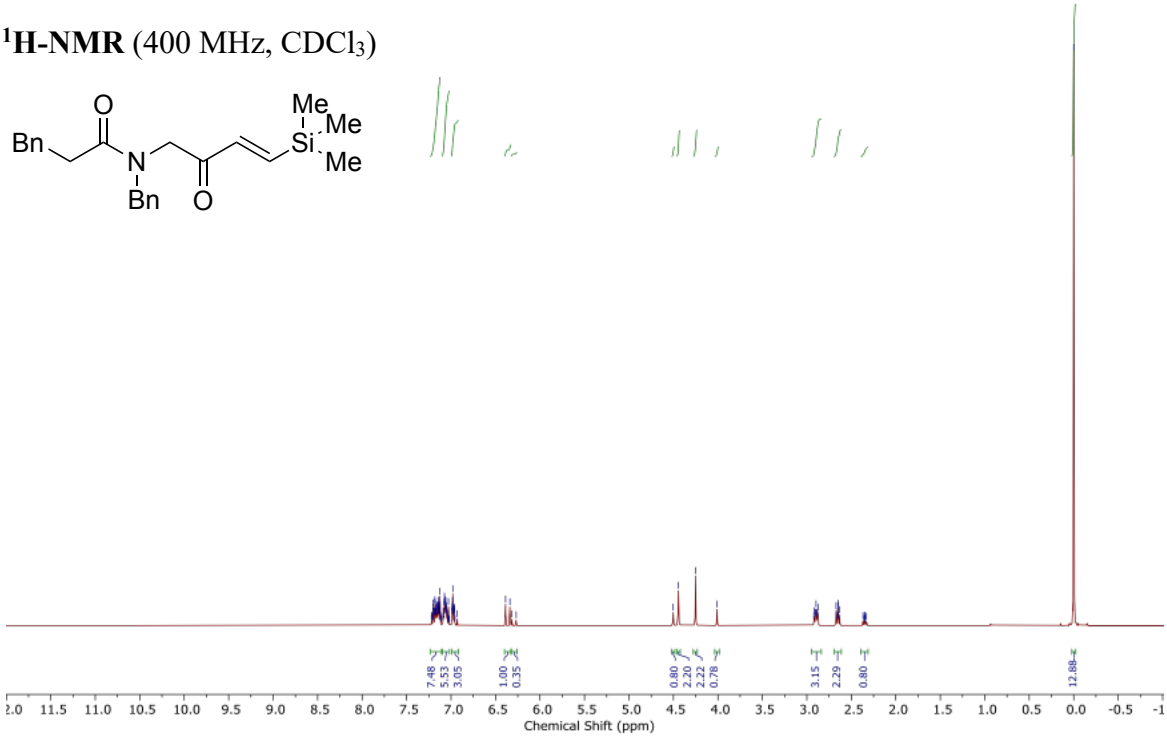
^{13}C-NMR (100 MHz, $CDCl_3$)



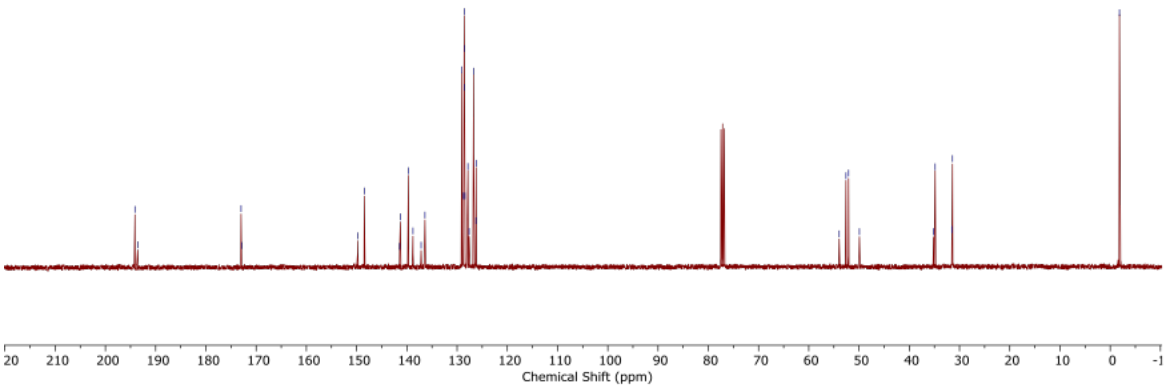
(*E*)-*N*-benzyl-*N*-(2-oxo-4-(trimethylsilyl)but-3-en-1-yl)-3-phenylpropanamide, 54l



^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)

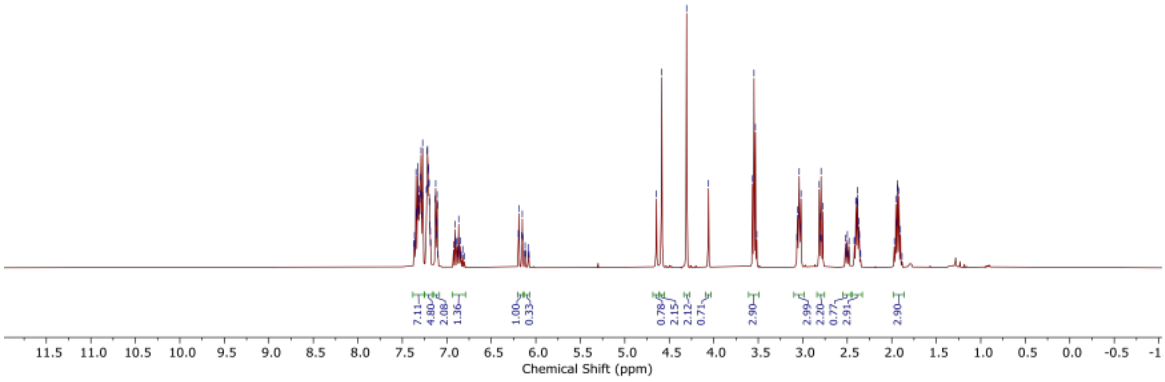


(*E*)-*N*-benzyl-*N*-(7-chloro-2-oxohept-3-en-1-yl)-3-phenylpropanamide, 54m

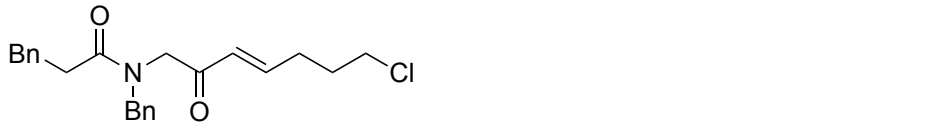


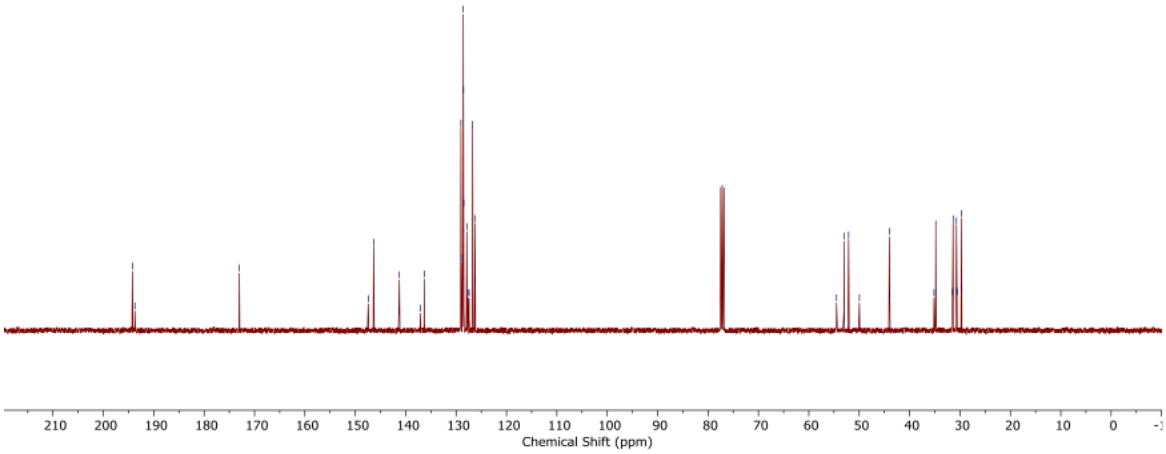
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

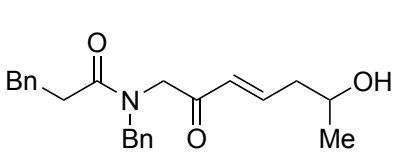


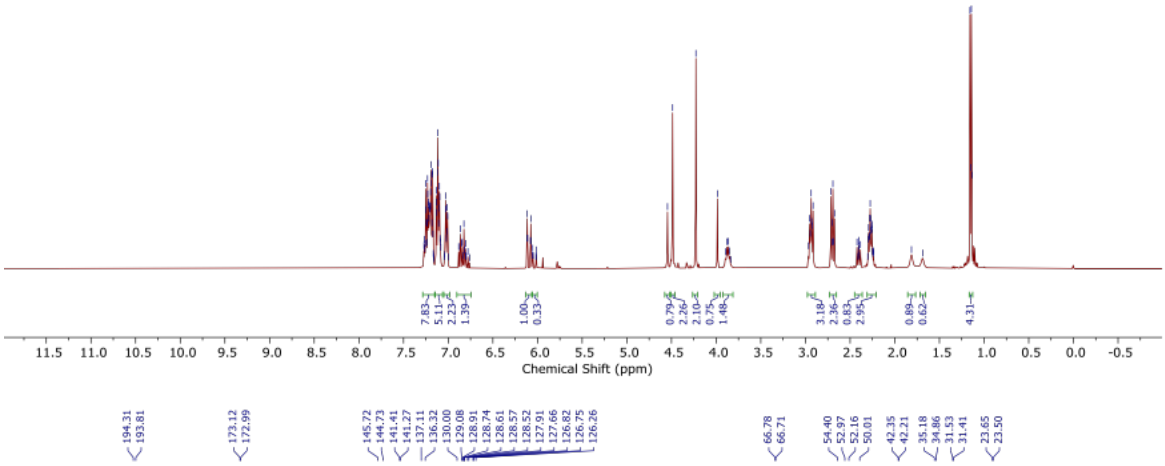


(*E*)-*N*-benzyl-*N*-(6-hydroxy-2-oxohept-3-en-1-yl)-3-phenylpropanamide, 54n

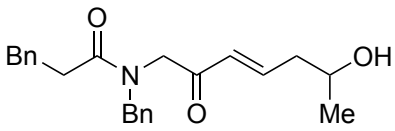


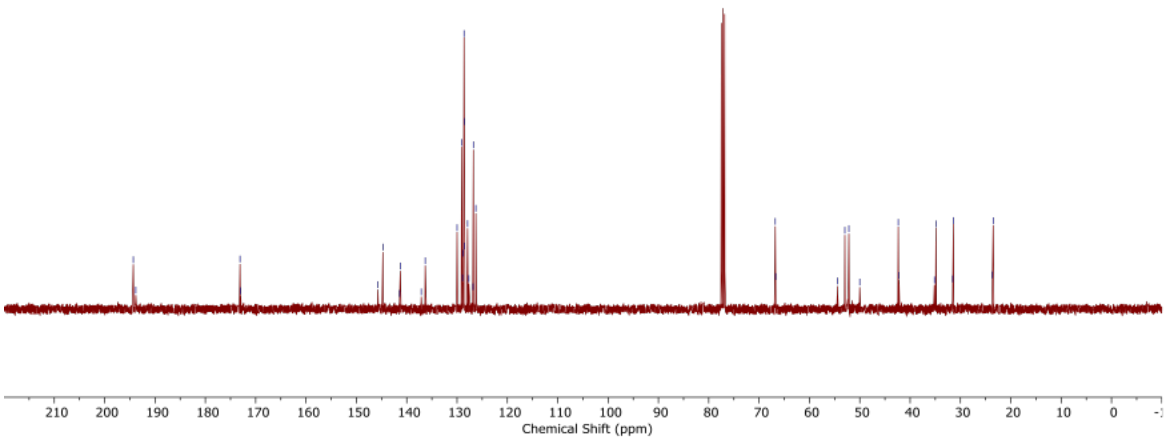
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

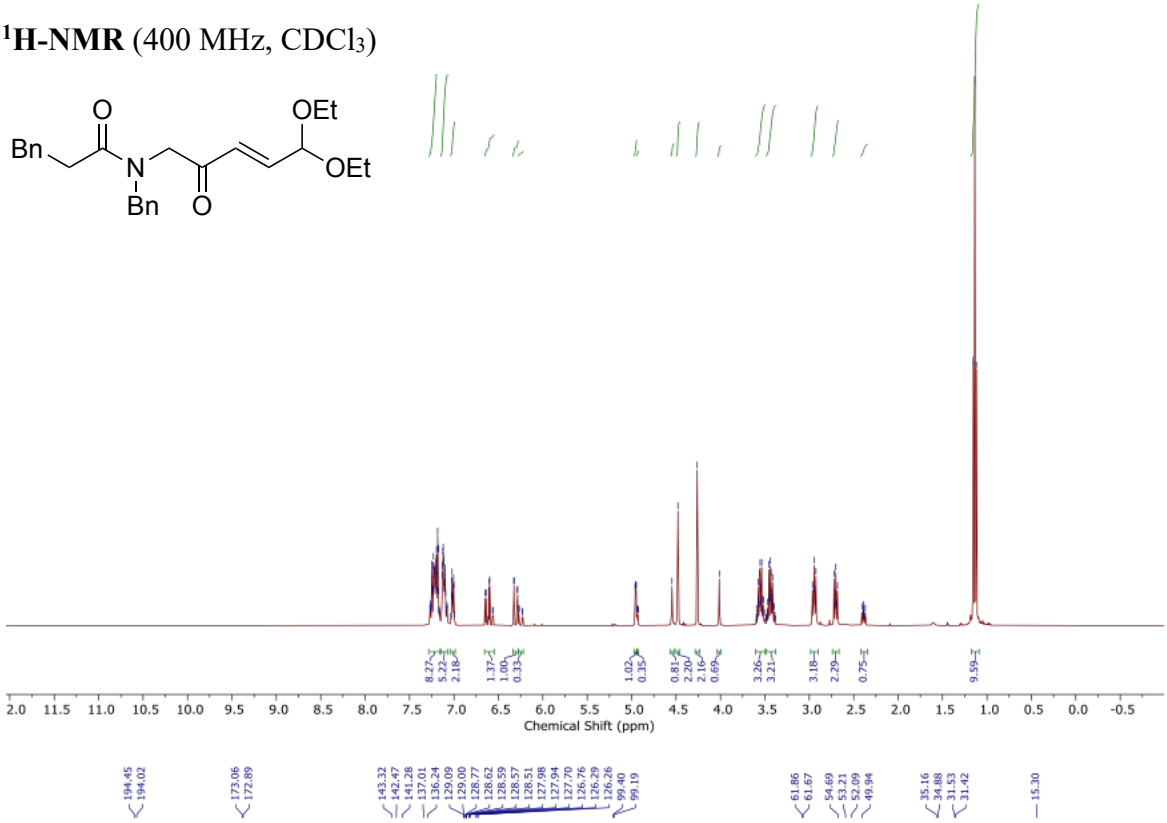




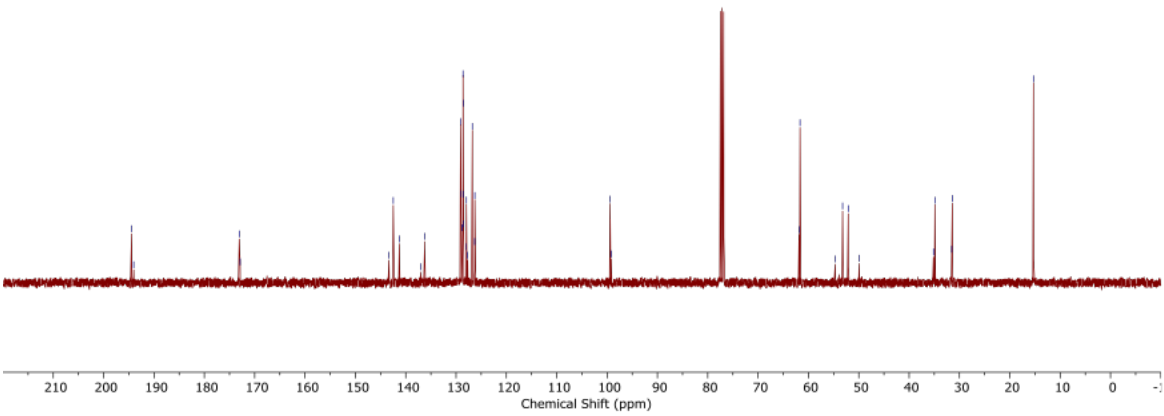
(*E*)-*N*-benzyl-*N*-(5,5-diethoxy-2-oxopent-3-en-1-yl)-3-phenylpropanamide, 54o



^{1}H-NMR (400 MHz, $CDCl_3$)



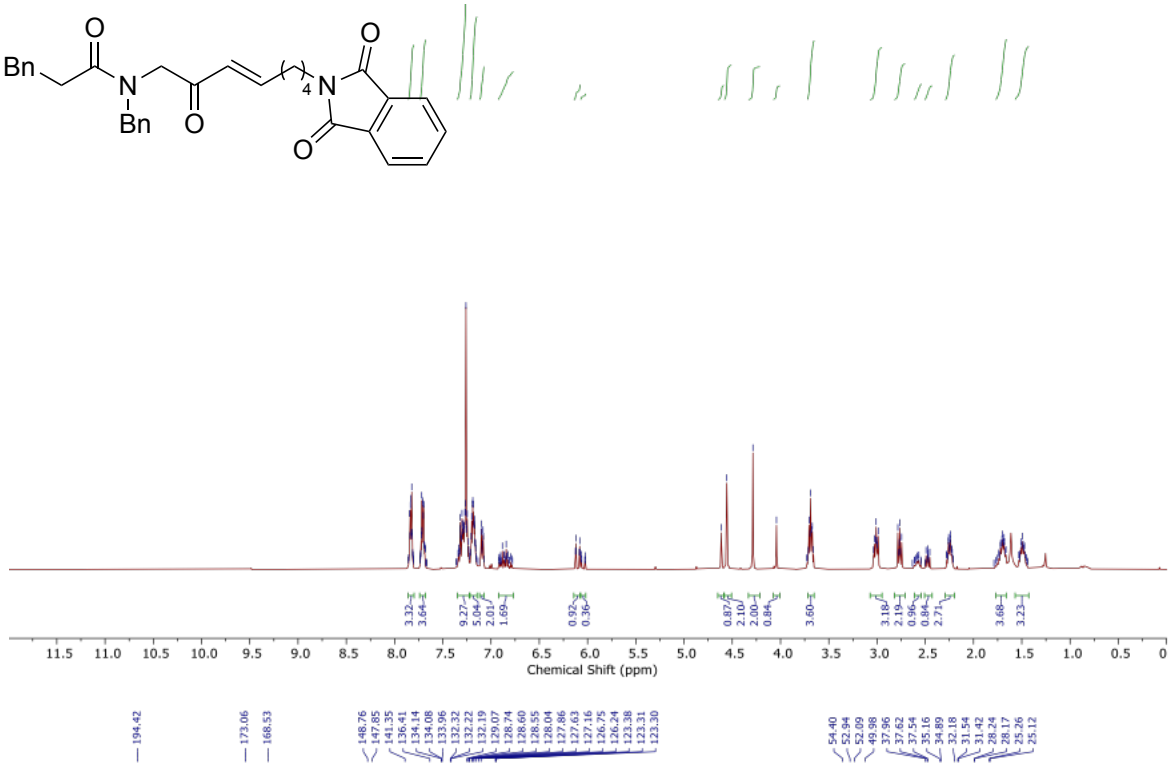
^{13}C-NMR (100 MHz, $CDCl_3$)



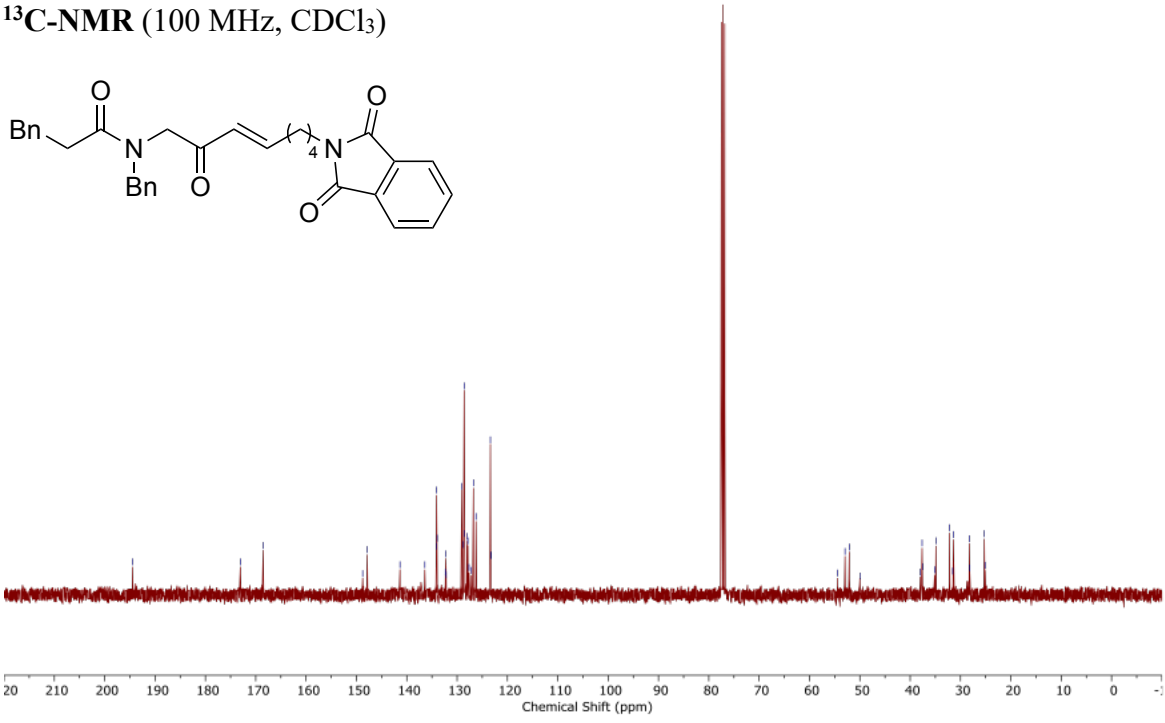
(*E*)-*N*-benzyl-*N*-(8-(1,3-dioxoisoindolin-2-yl)-2-oxooct-3-en-1-yl)-3-phenylpropanamide, 54p



^{1}H-NMR (400 MHz, $CDCl_3$)



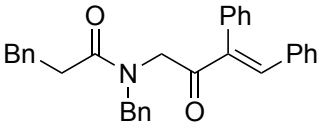
^{13}C-NMR (100 MHz, $CDCl_3$)

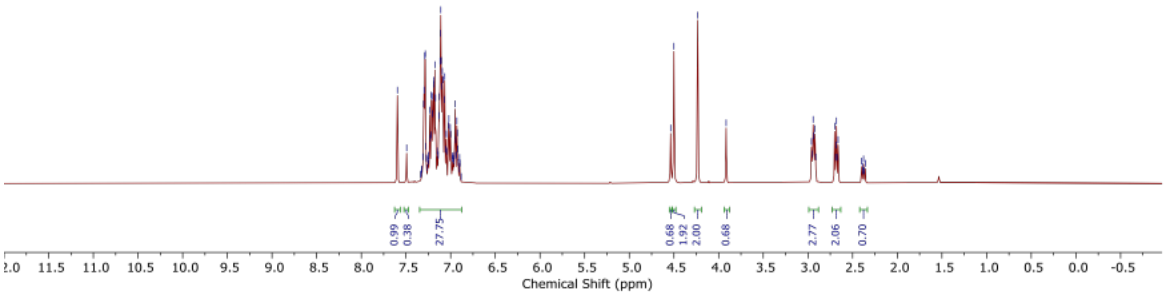


(*E*)-*N*-benzyl-*N*-(2-oxo-3,4-diphenylbut-3-en-1-yl)-3-phenylpropanamide, 54q



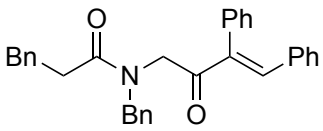
^{1}H-NMR (400 MHz, $CDCl_3$)

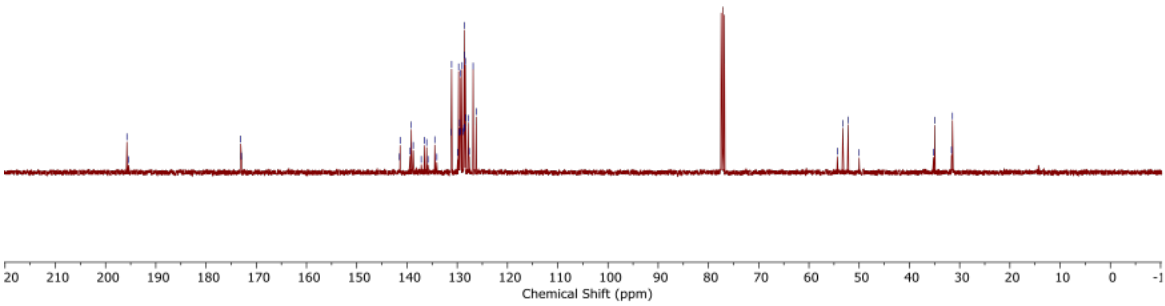






^{13}C-NMR (100 MHz, $CDCl_3$)

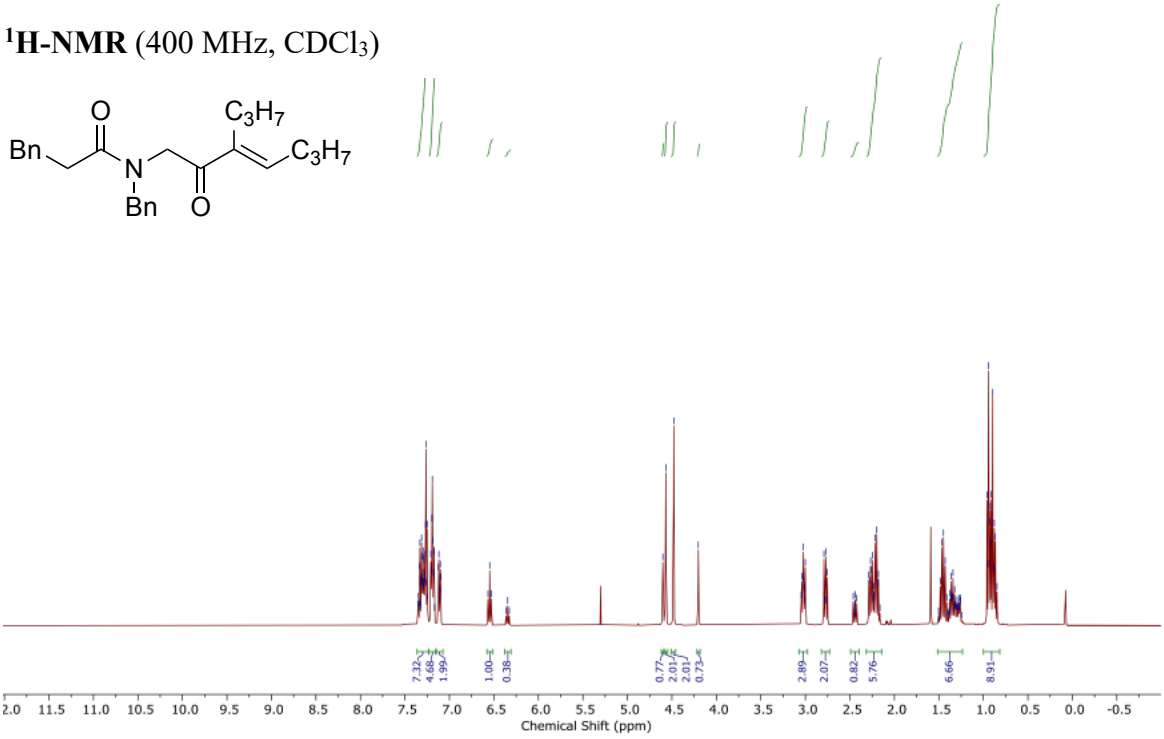




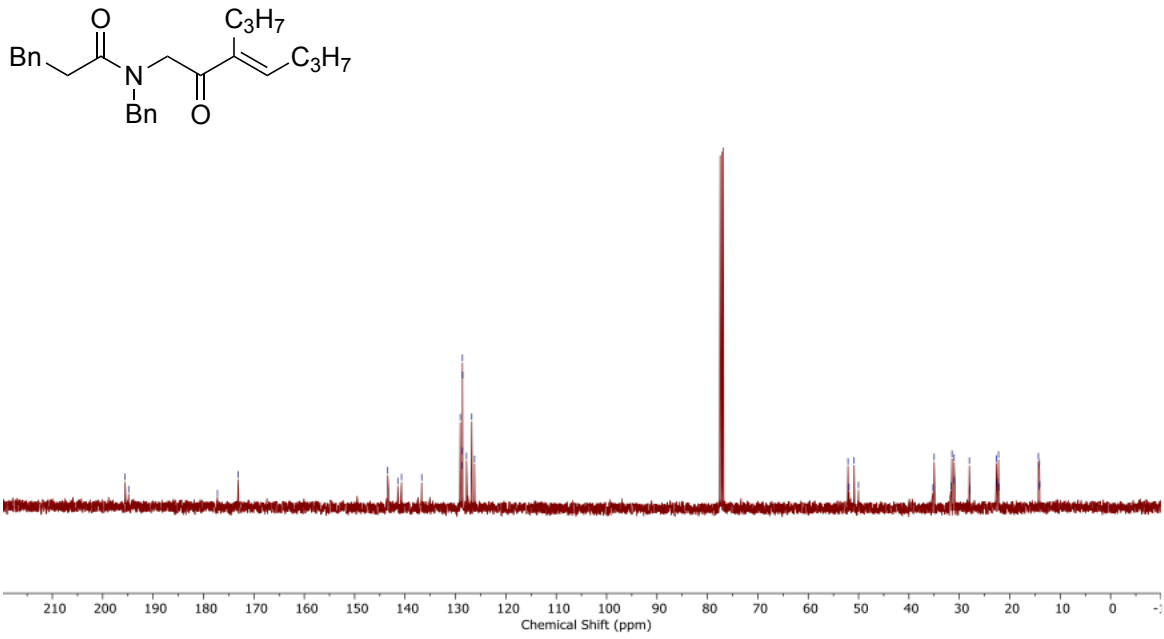
(*E*)-*N*-benzyl-*N*-(2-oxo-3-propylhept-3-en-1-yl)-3-phenylpropanamide, 54r



^{1}H-NMR (400 MHz, $CDCl_3$)



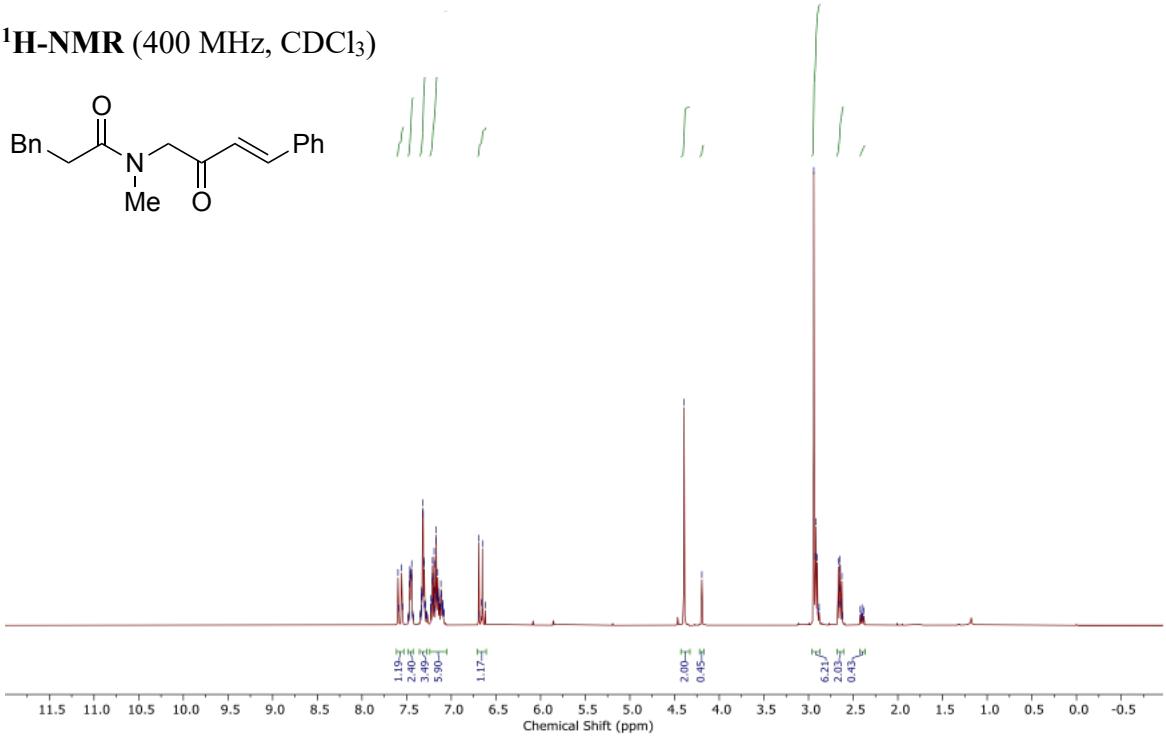
^{13}C-NMR (100 MHz, $CDCl_3$)



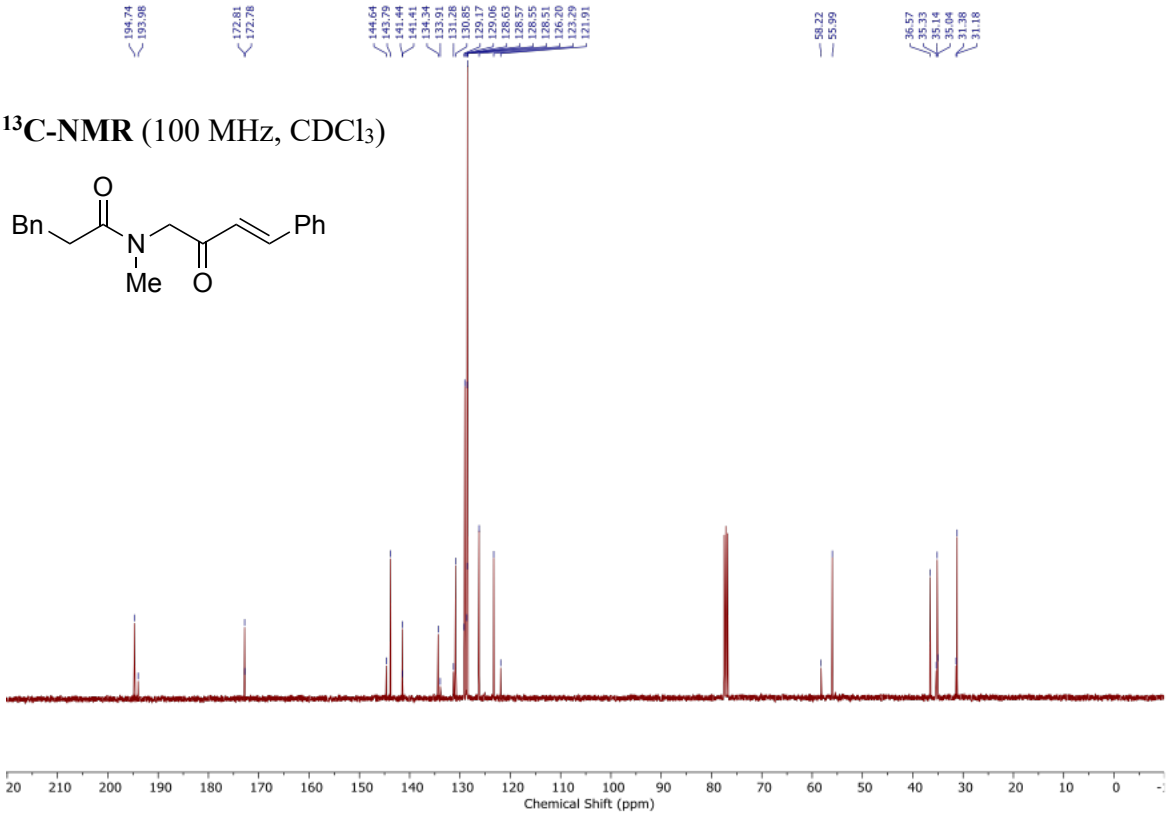
(*E*)-*N*-methyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54s



^{1}H-NMR (400 MHz, $CDCl_3$)



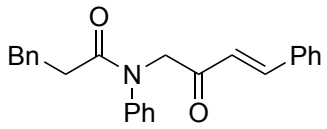
^{13}C-NMR (100 MHz, $CDCl_3$)

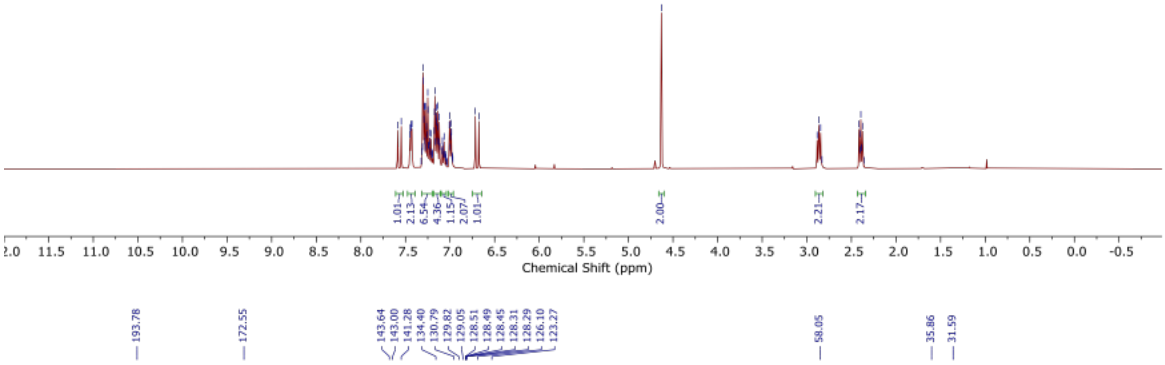


(*E*)-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-*N*,3-diphenylpropanamide, 54t

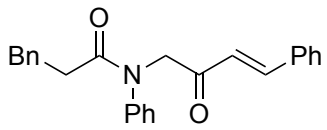


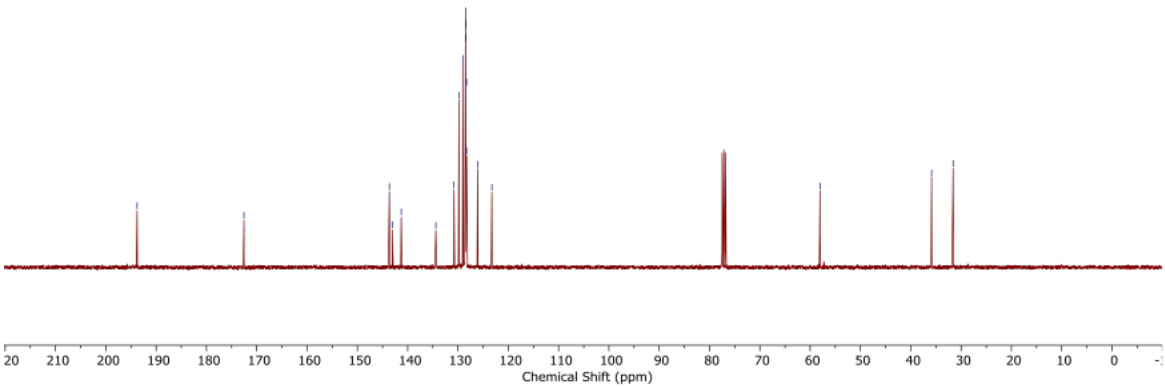
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

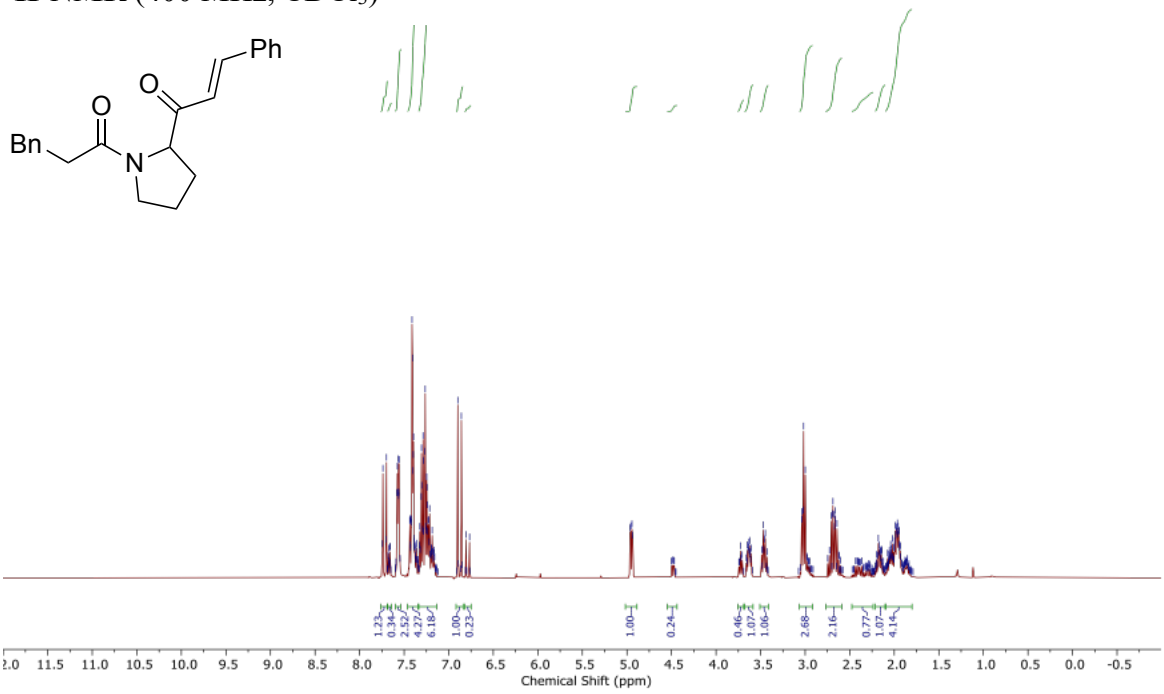




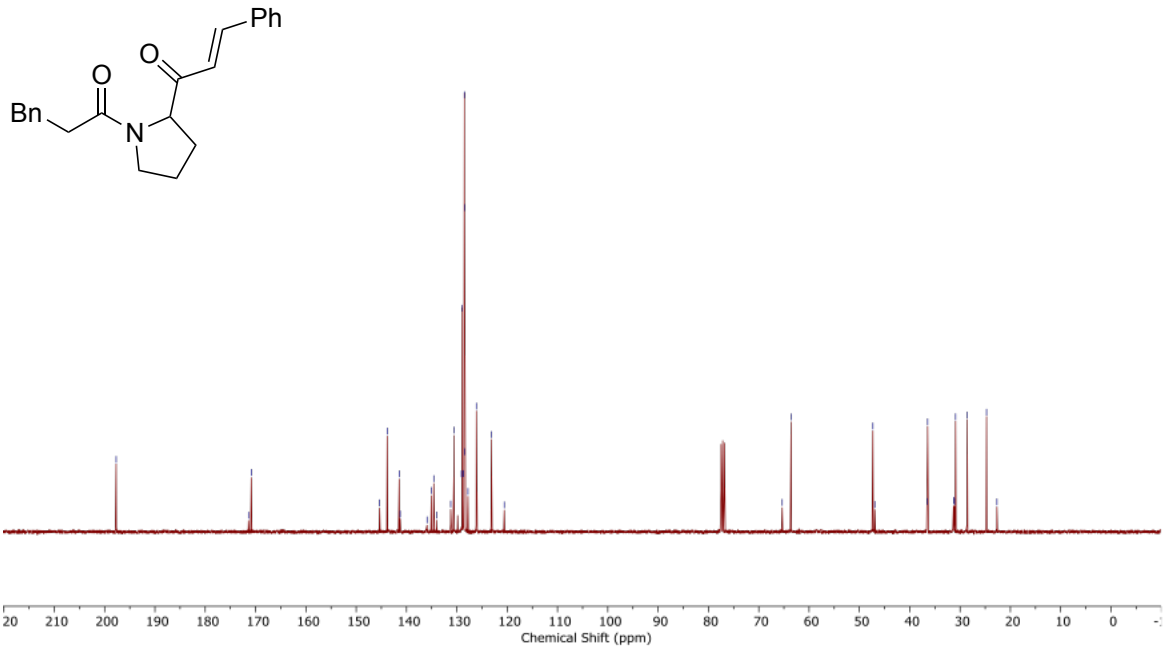
(*E*)-3-phenyl-1-(1-(3-phenylpropanoyl)pyrrolidin-2-yl)prop-2-en-1-one, 54u



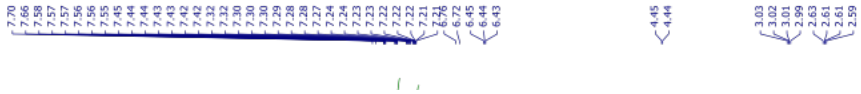
^{1}H-NMR (400 MHz, $CDCl_3$)



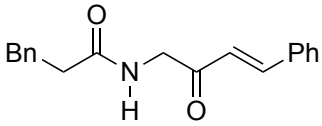
^{13}C-NMR (100 MHz, $CDCl_3$)

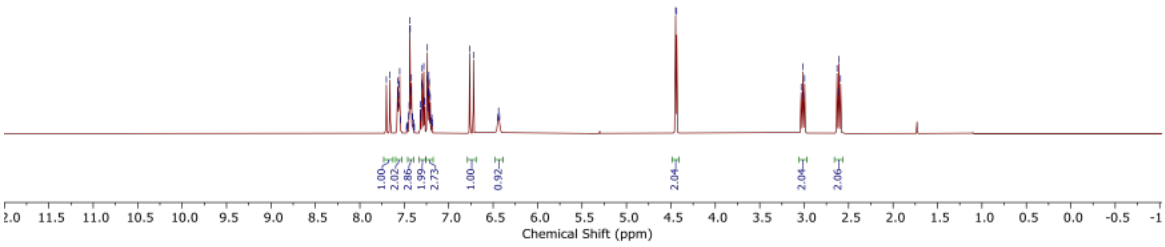


(*E*)-*N*-(2-oxo-4-phenylbut-3-en-1-yl)-3-phenylpropanamide, 54v

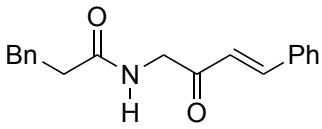


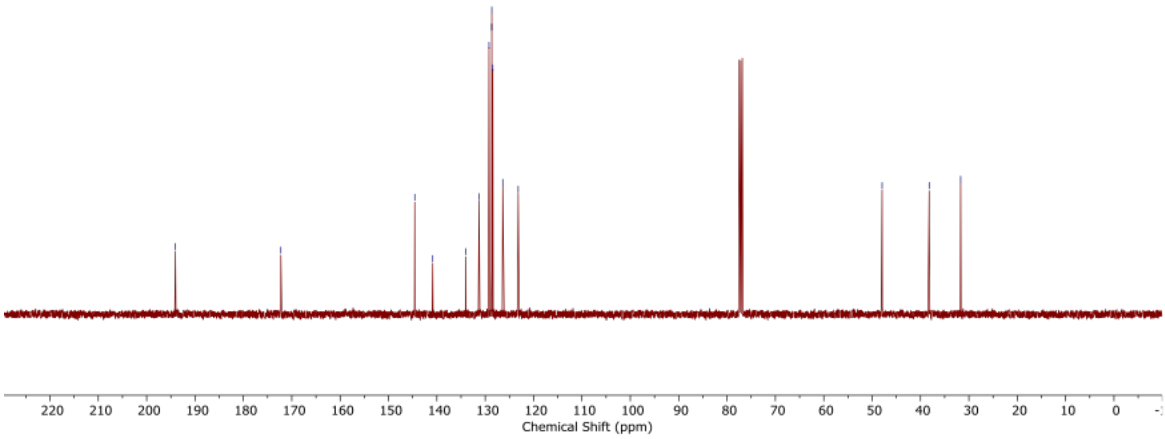
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

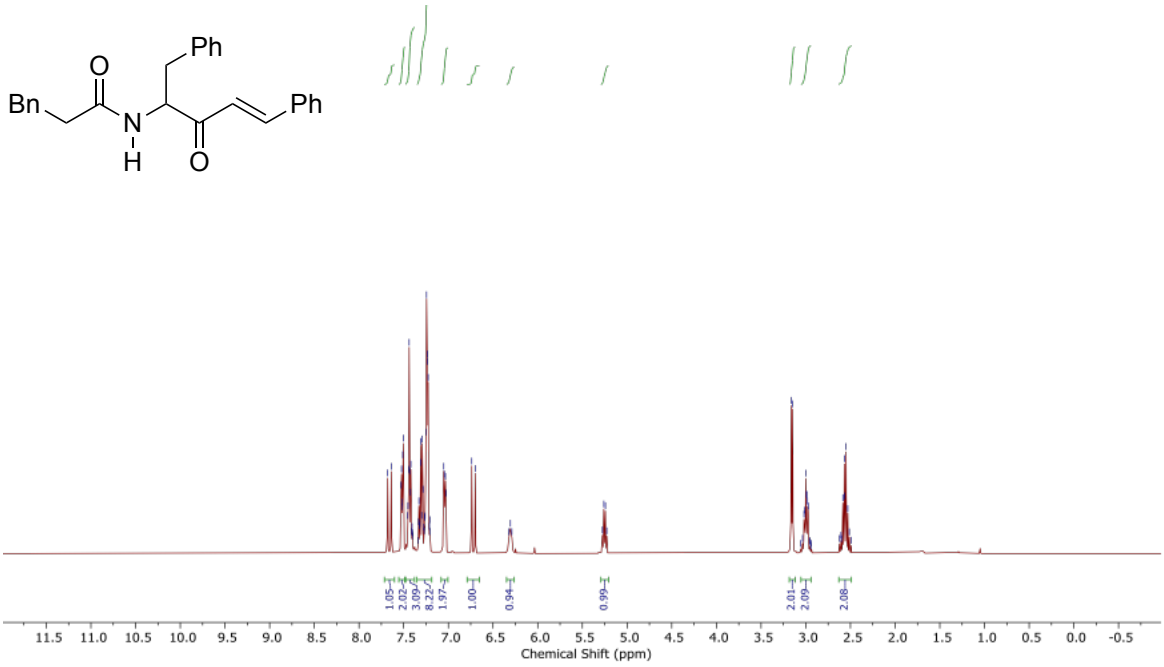




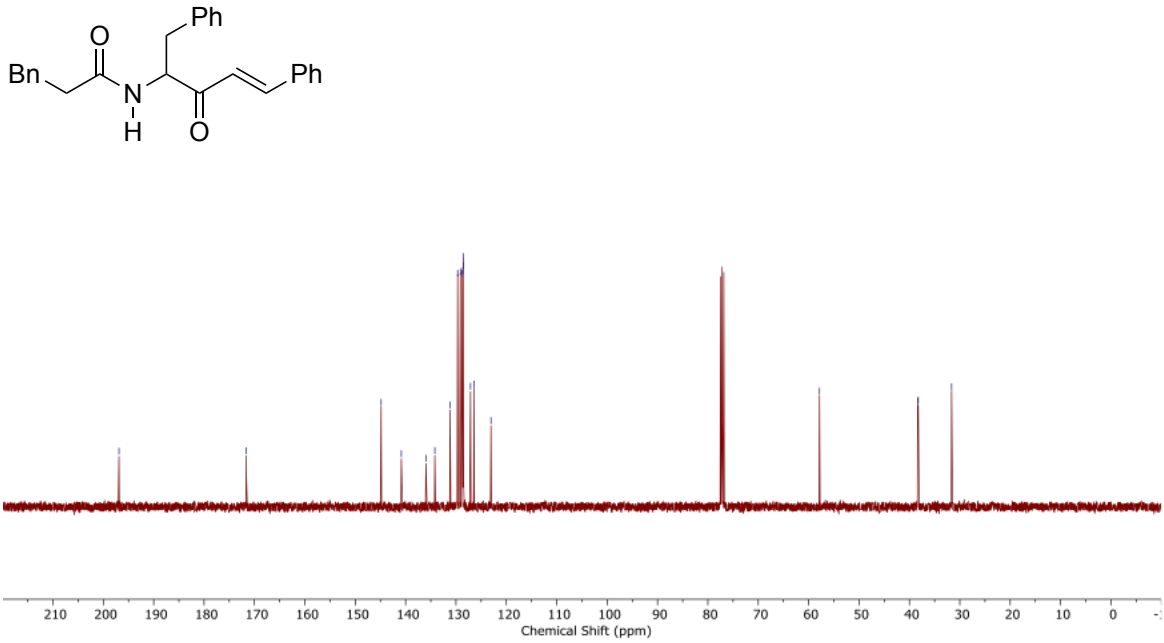
(*E*)-*N*-(3-oxo-1,5-diphenylpent-4-en-2-yl)-3-phenylpropanamide, 54w



^{1}H-NMR (400 MHz, $CDCl_3$)



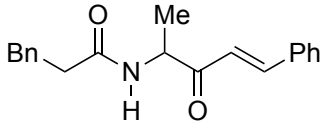
^{13}C-NMR (100 MHz, $CDCl_3$)



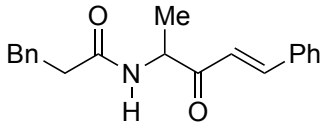
(*E*)-*N*-(3-oxo-5-phenylpent-4-en-2-yl)-3-phenylpropanamide, 54x

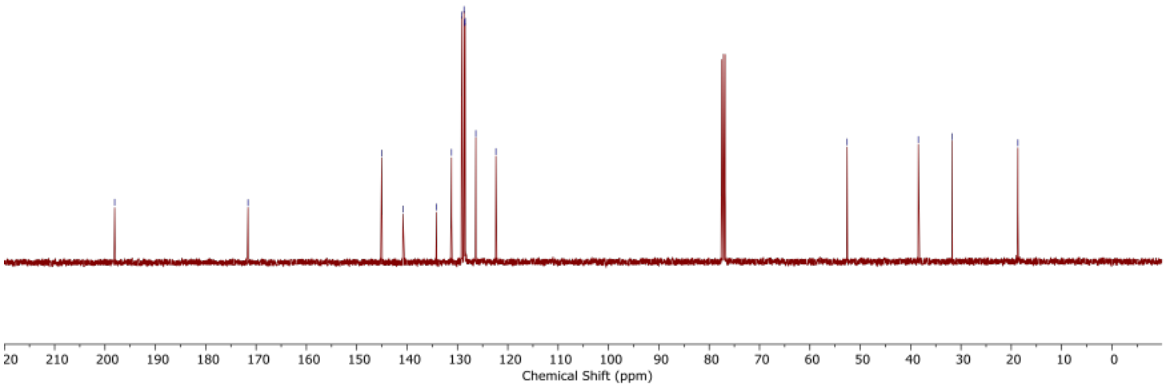


^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)



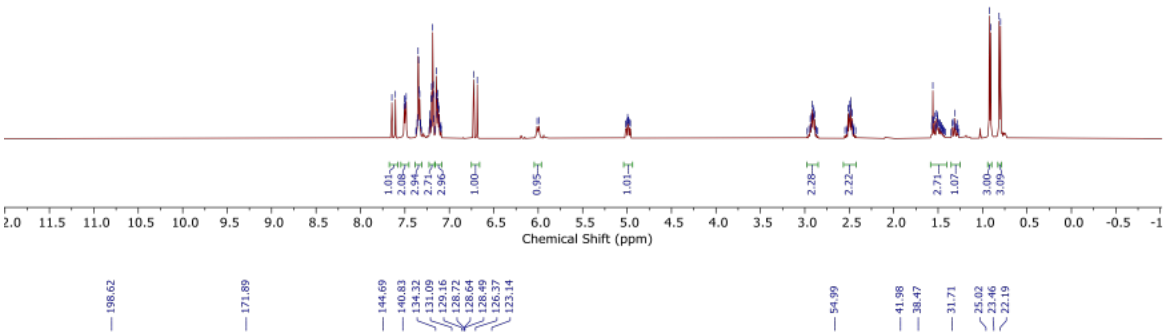


(*E*)-*N*-(6-methyl-3-oxo-1-phenylhept-1-en-4-yl)-3-phenylpropanamide, 54y



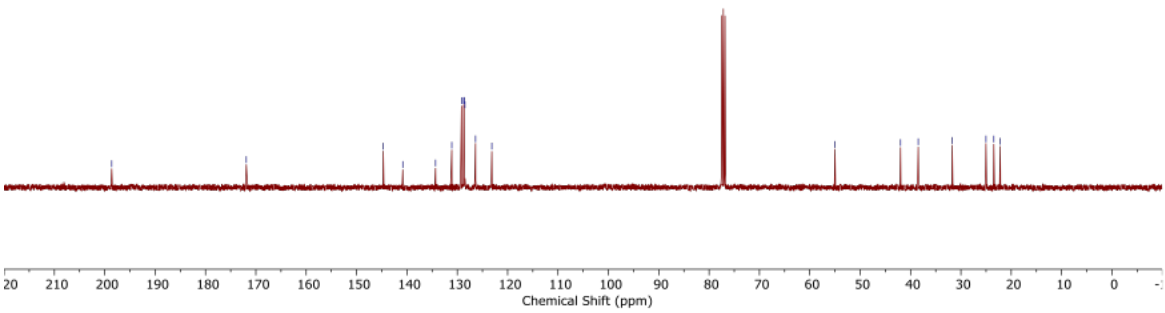
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

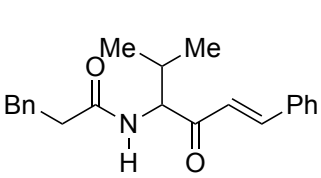




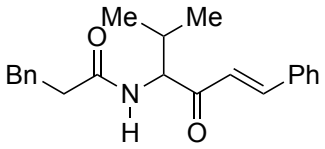
(*E*)-*N*-(2-methyl-4-oxo-6-phenylhex-5-en-3-yl)-3-phenylpropanamide, 54z

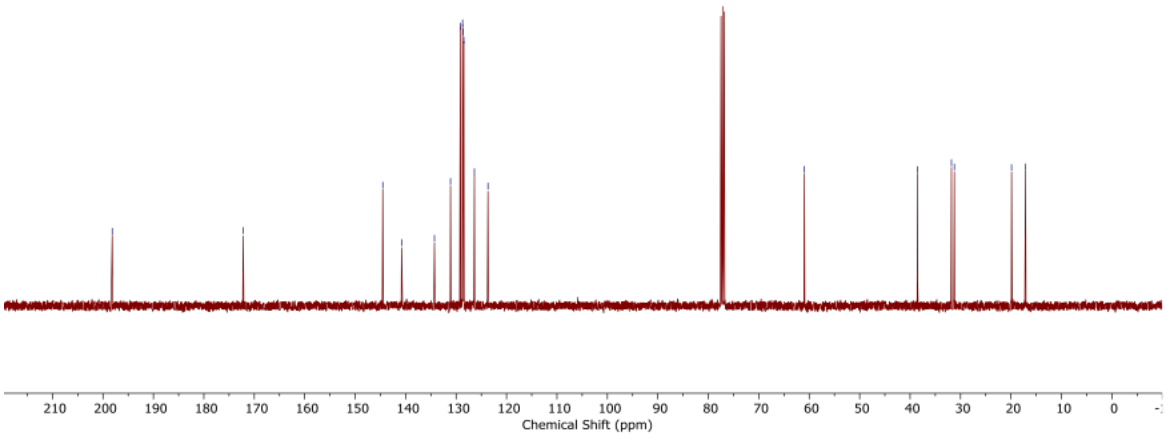


^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)

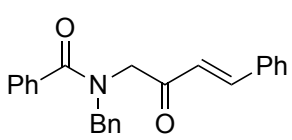


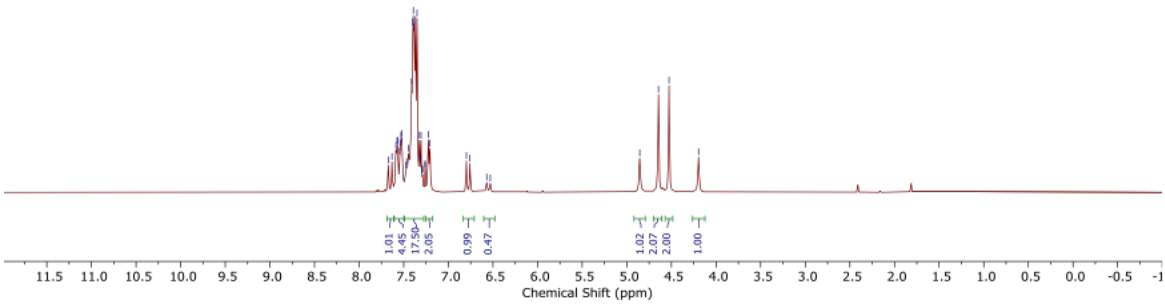


(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)benzamide, 54aa

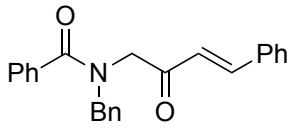


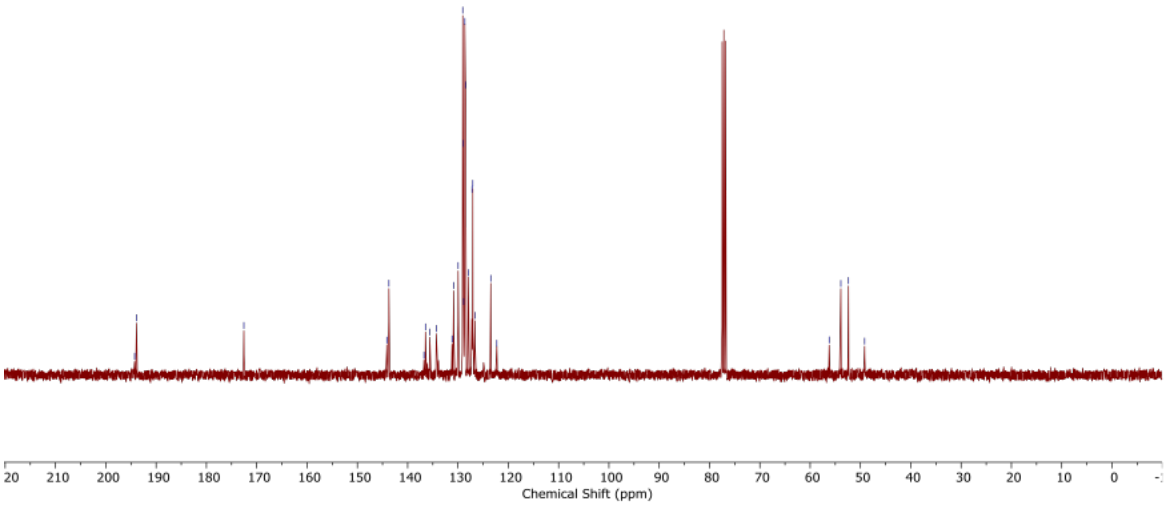
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

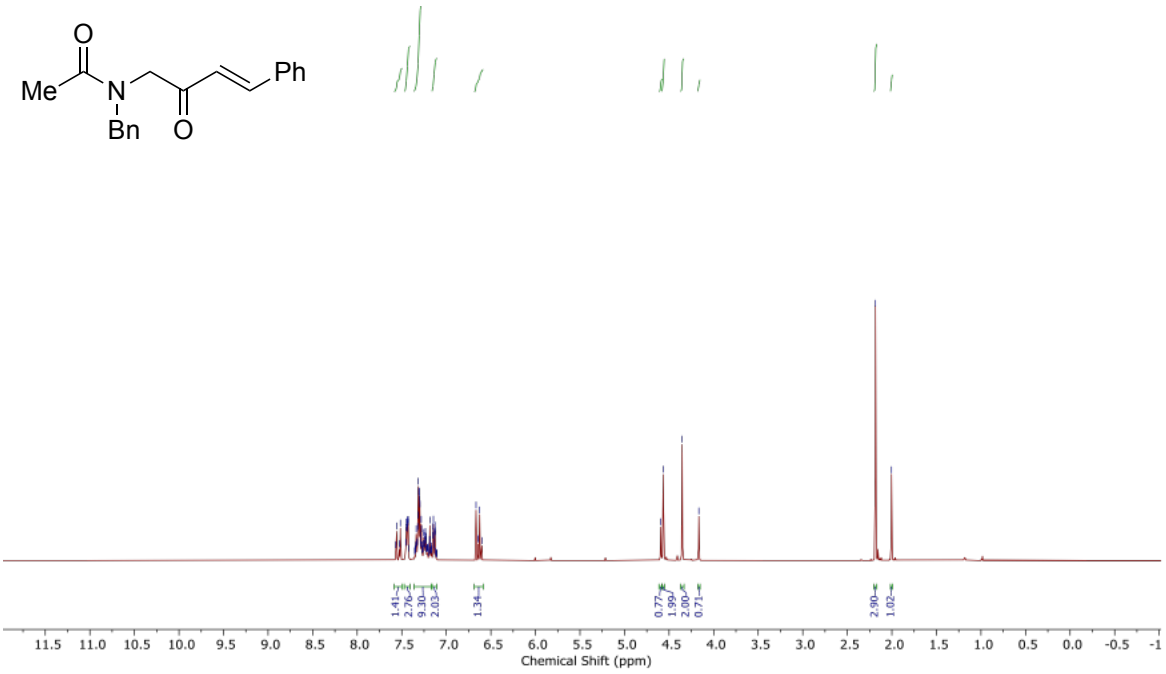




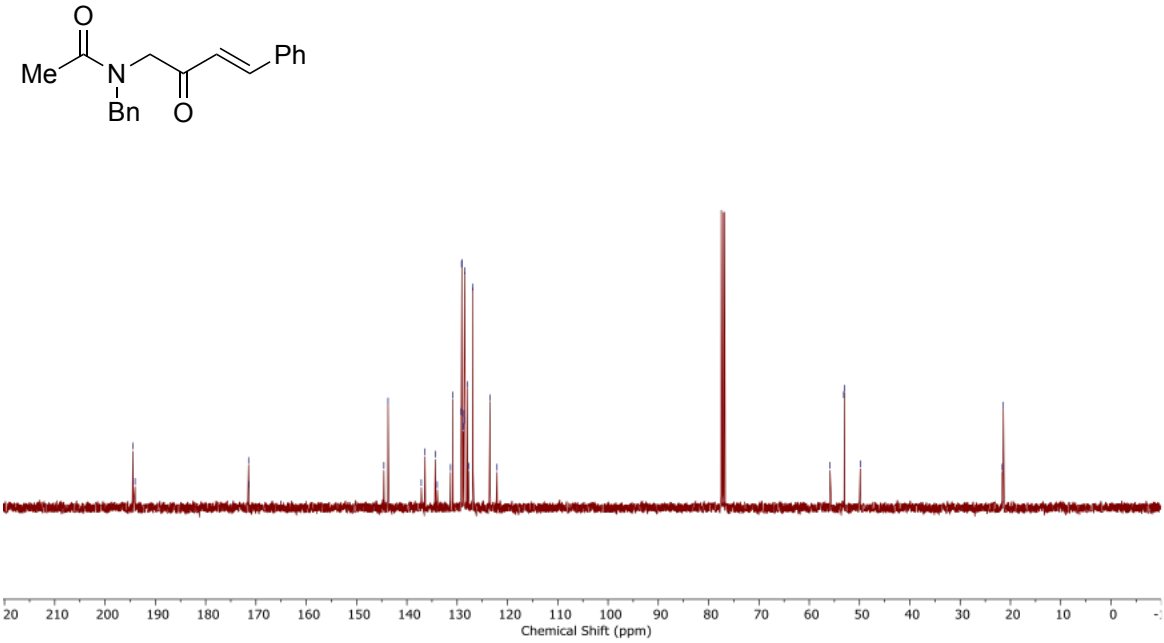
(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)acetamide, 54ab



^{1}H-NMR (400 MHz, $CDCl_3$)



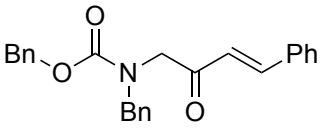
^{13}C-NMR (100 MHz, $CDCl_3$)

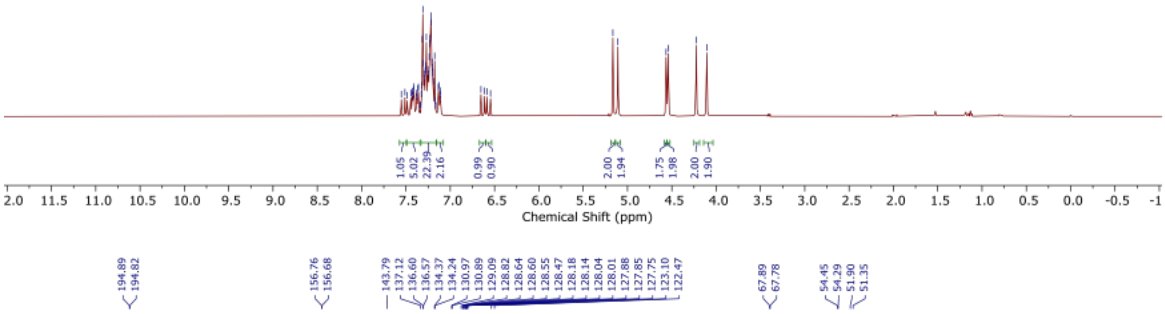


Benzyl (*E*)-benzyl(2-oxo-4-phenylbut-3-en-1-yl)carbamate, 54ac

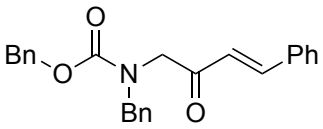


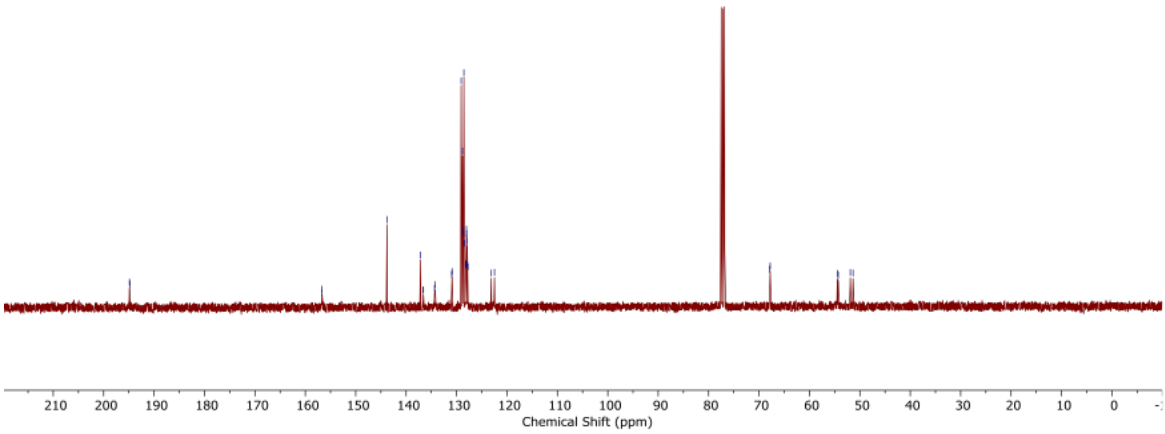
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)



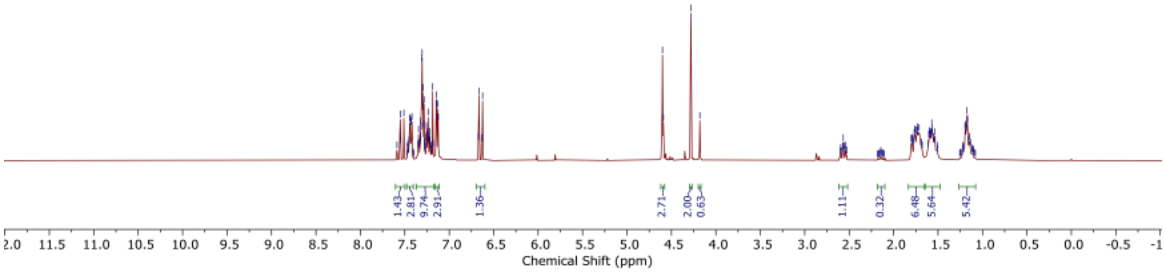


(*E*)-*N*-benzyl-*N*-(2-oxo-4-phenylbut-3-en-1-yl)cyclohexanecarboxamide, 54ad



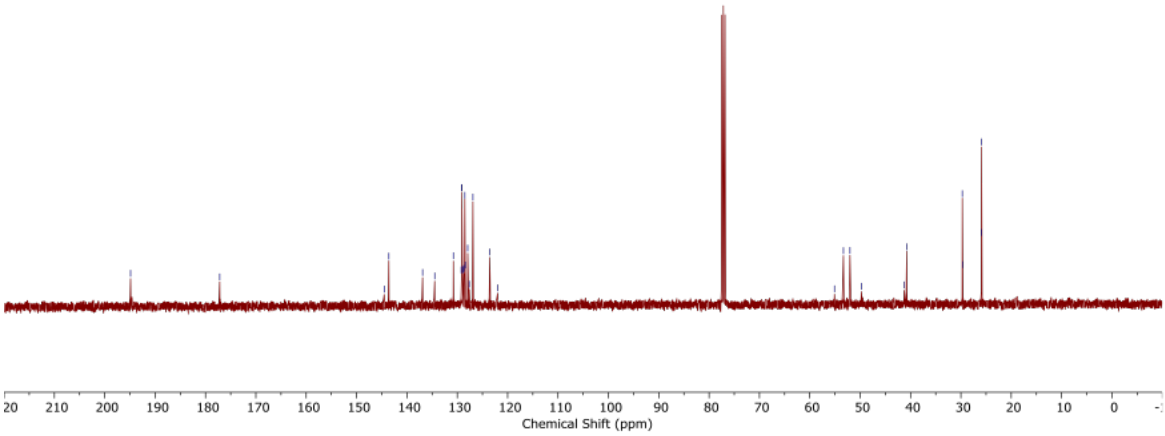
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

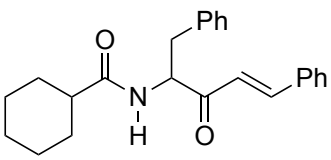


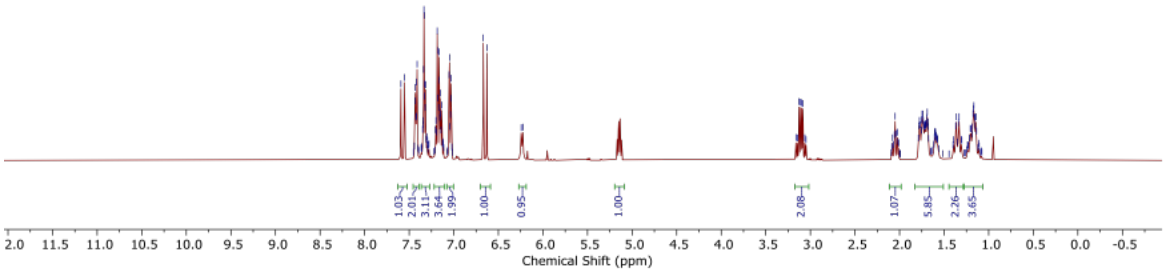


(*E*)-*N*-(3-oxo-1,5-diphenylpent-4-en-2-yl)cyclohexanecarboxamide, 54ae

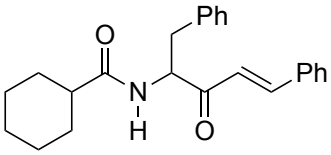


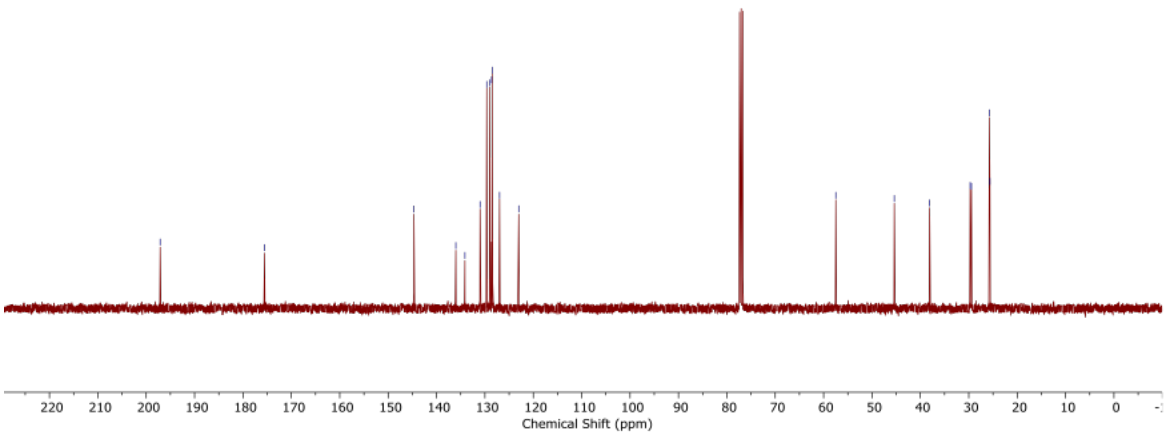
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

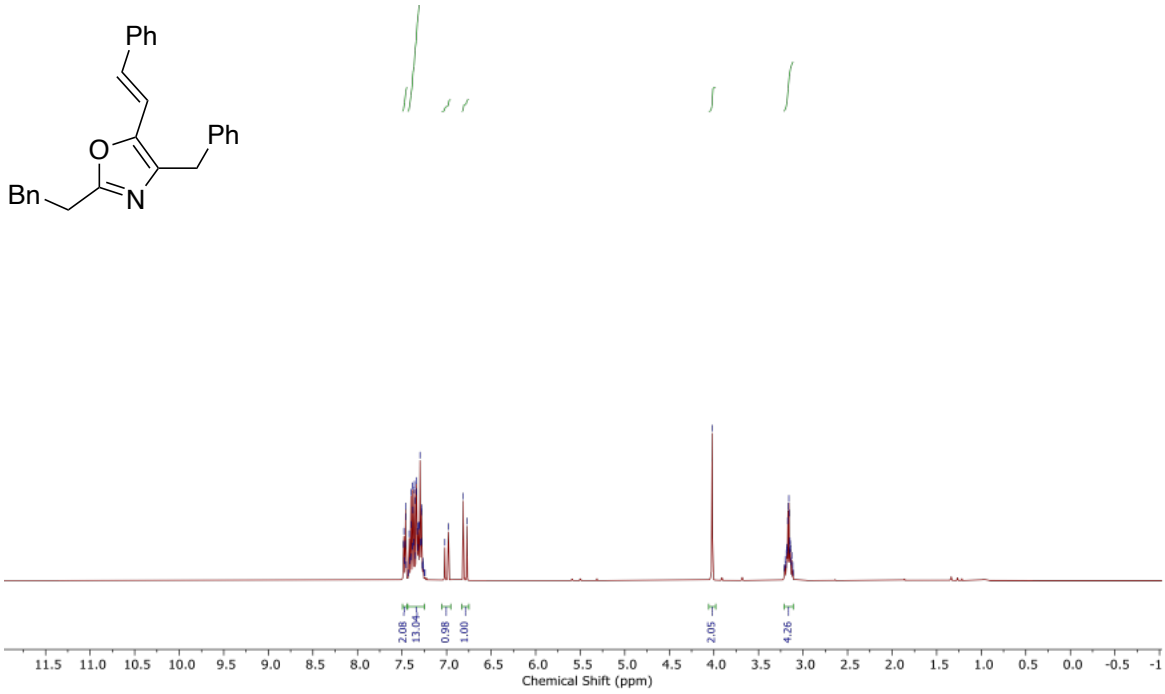




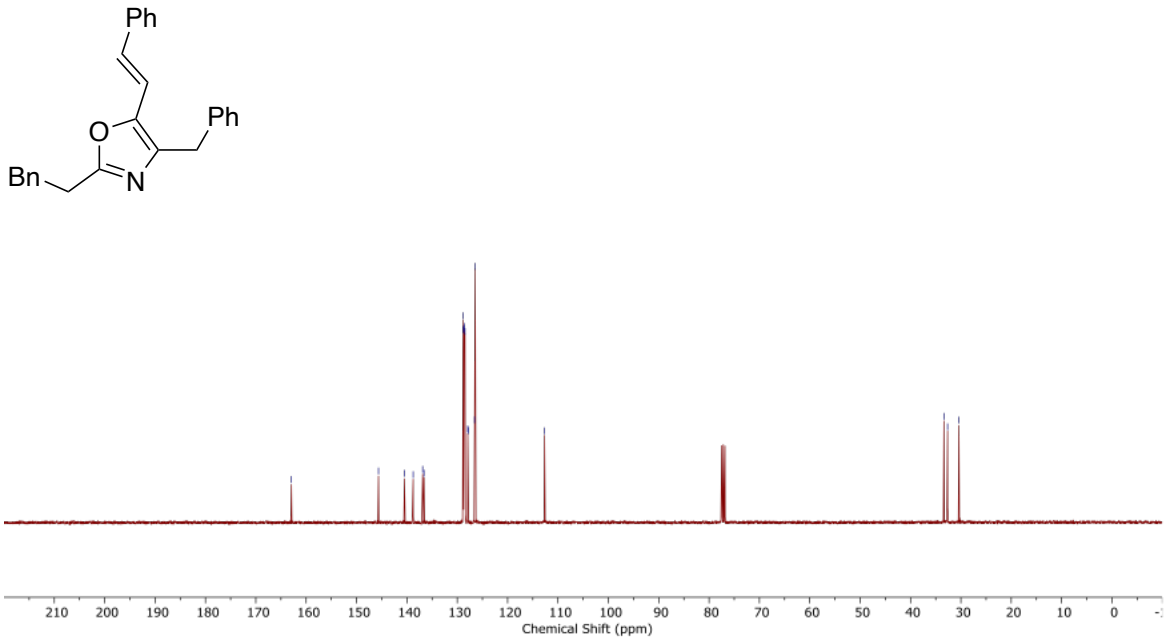
(*E*)-4-benzyl-2-phenethyl-5-styryloxazole, 55



^{1}H-NMR (400 MHz, $CDCl_3$)

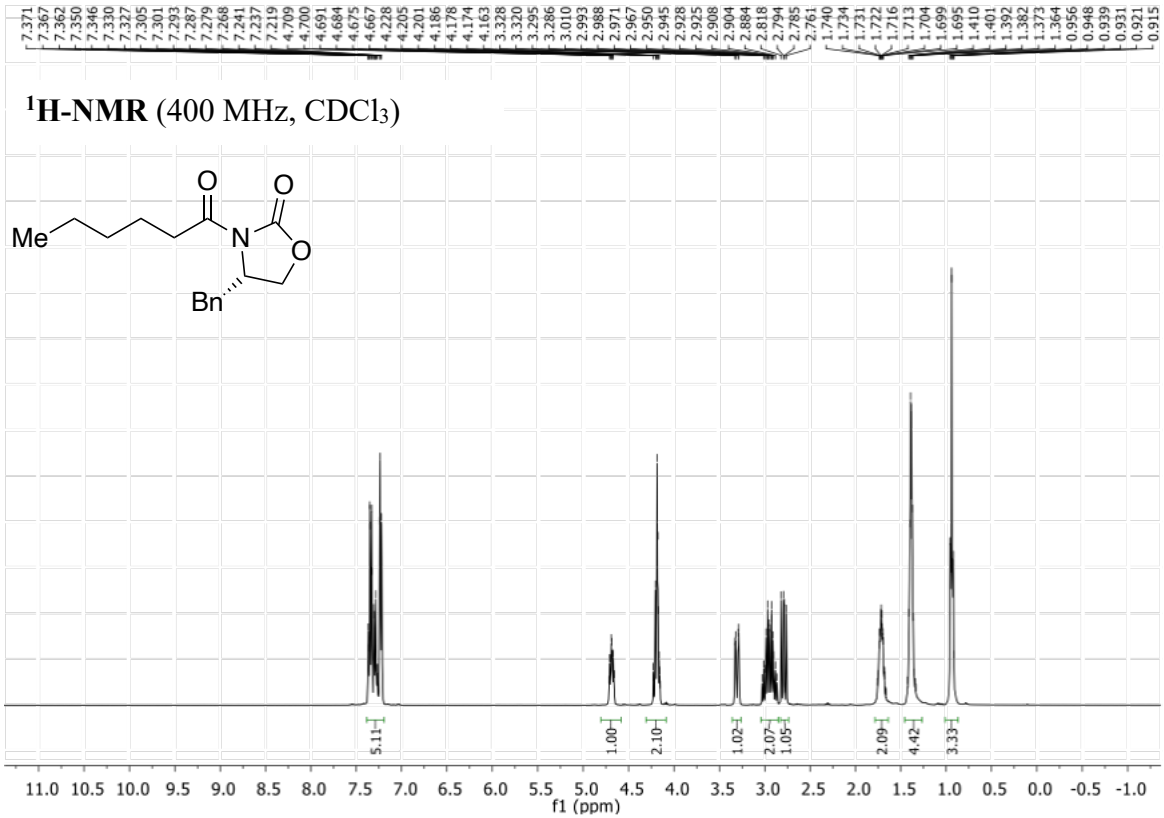


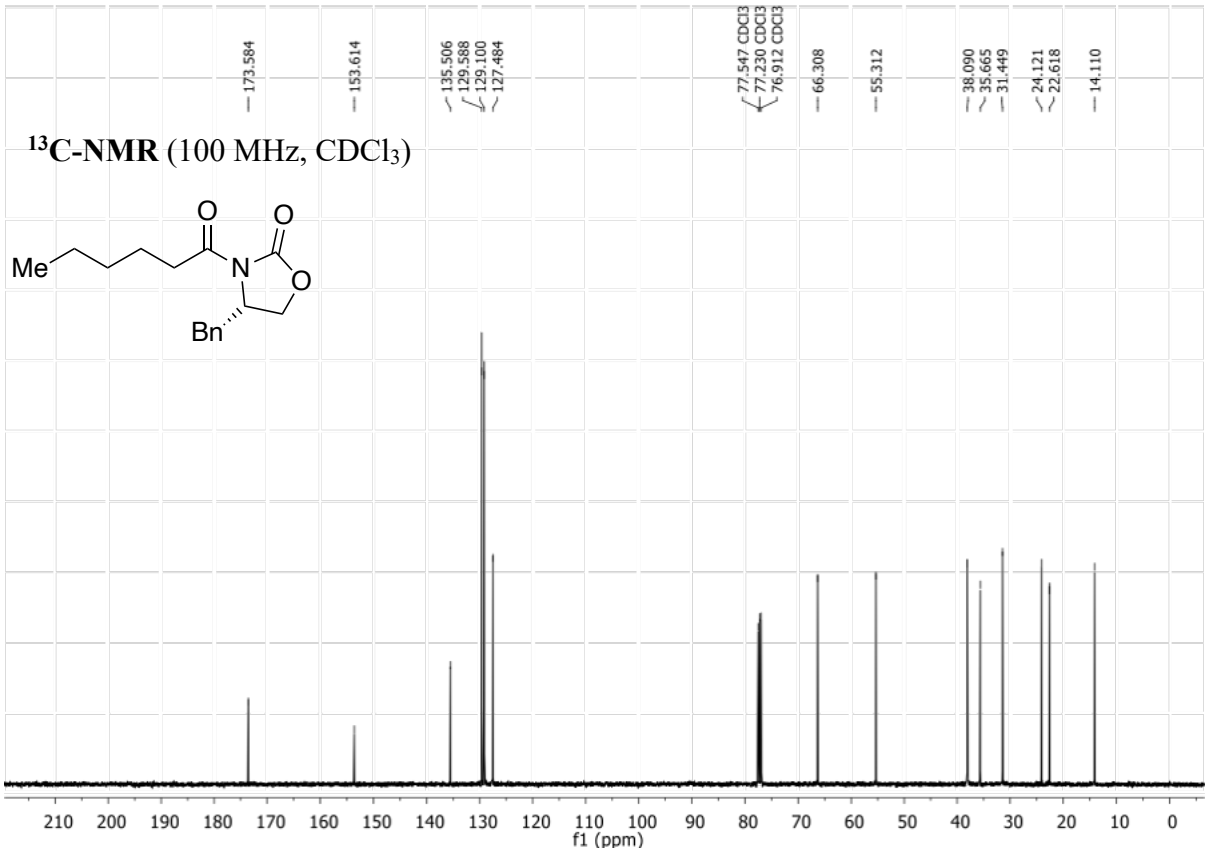
^{13}C-NMR (100 MHz, $CDCl_3$)



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

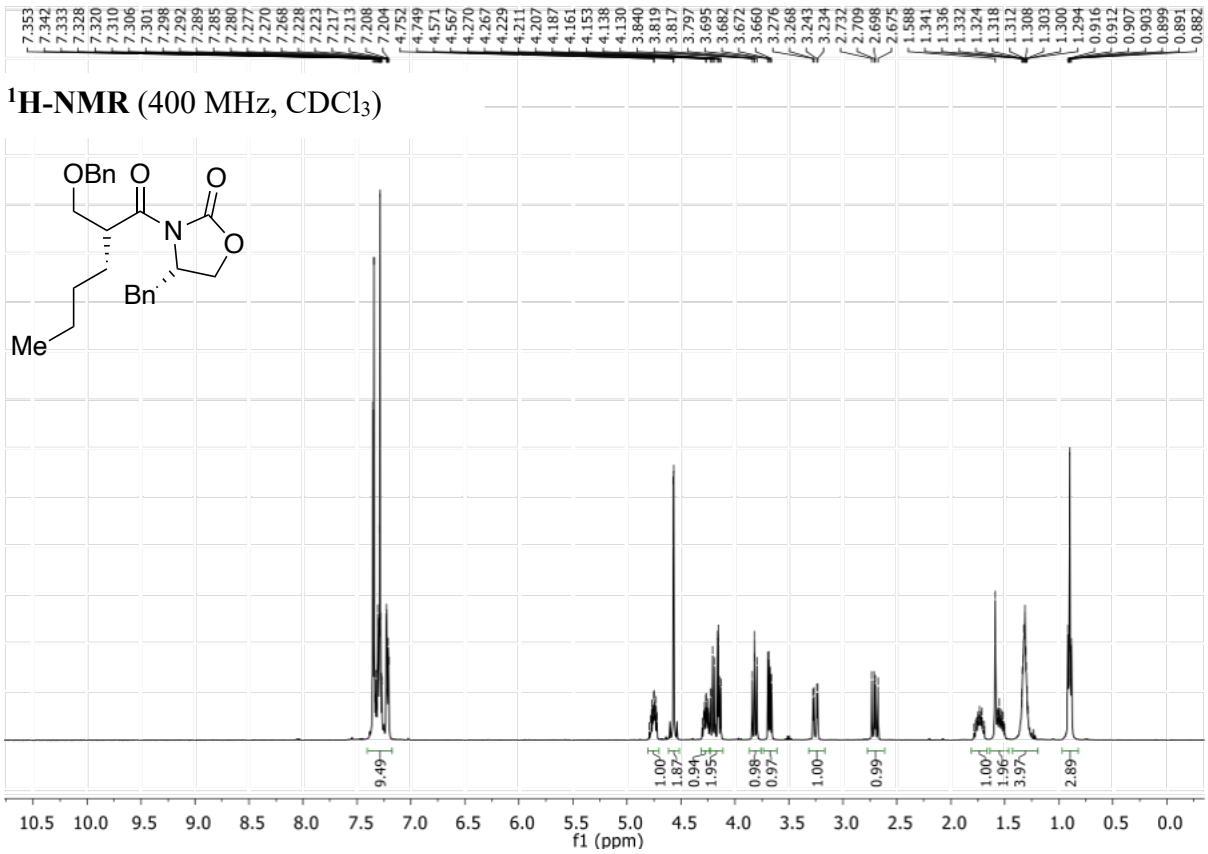
(*S*)-4-Benzyl-3-hexanoyloxazolidin-2-one, 58



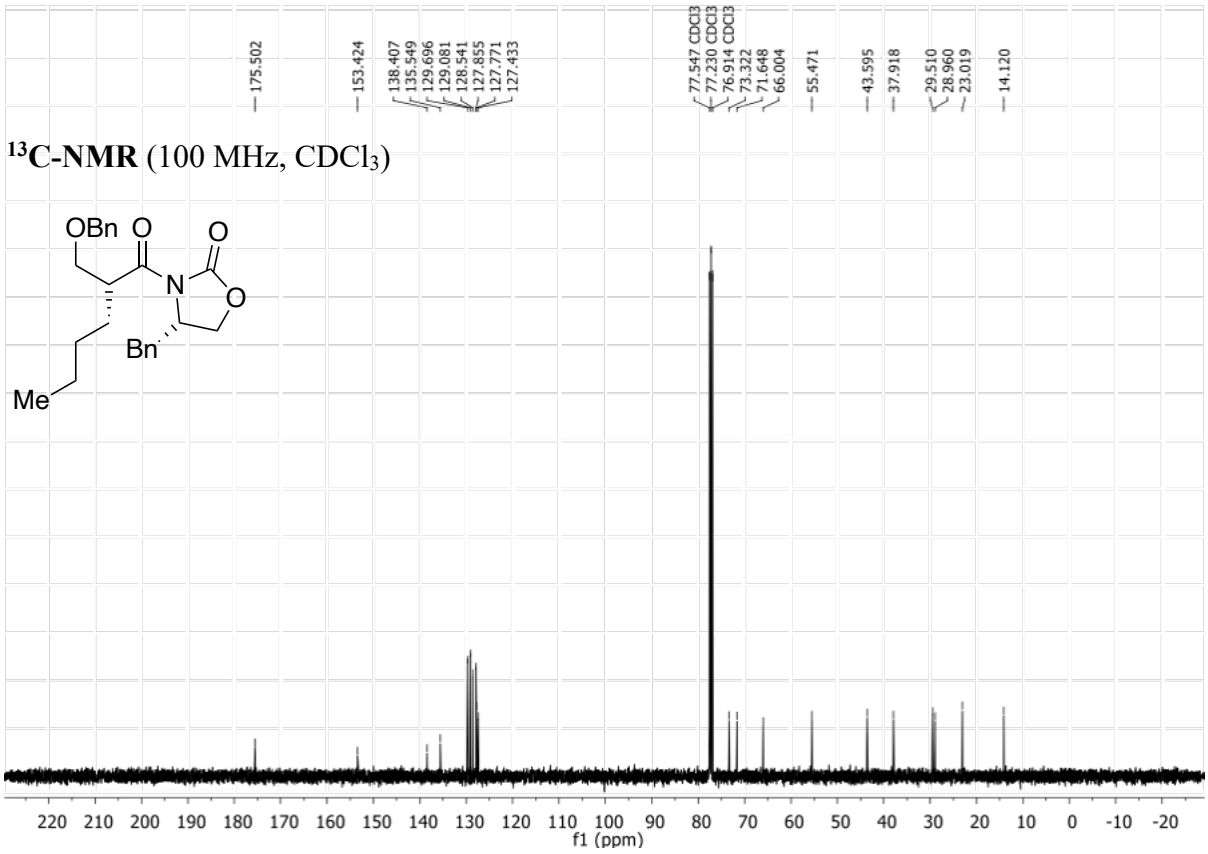


(*S*)-4-Benzyl-3-{(R)-2-[(benzyloxy)methyl]hexanoyl}oxazolidin-2-one, 59

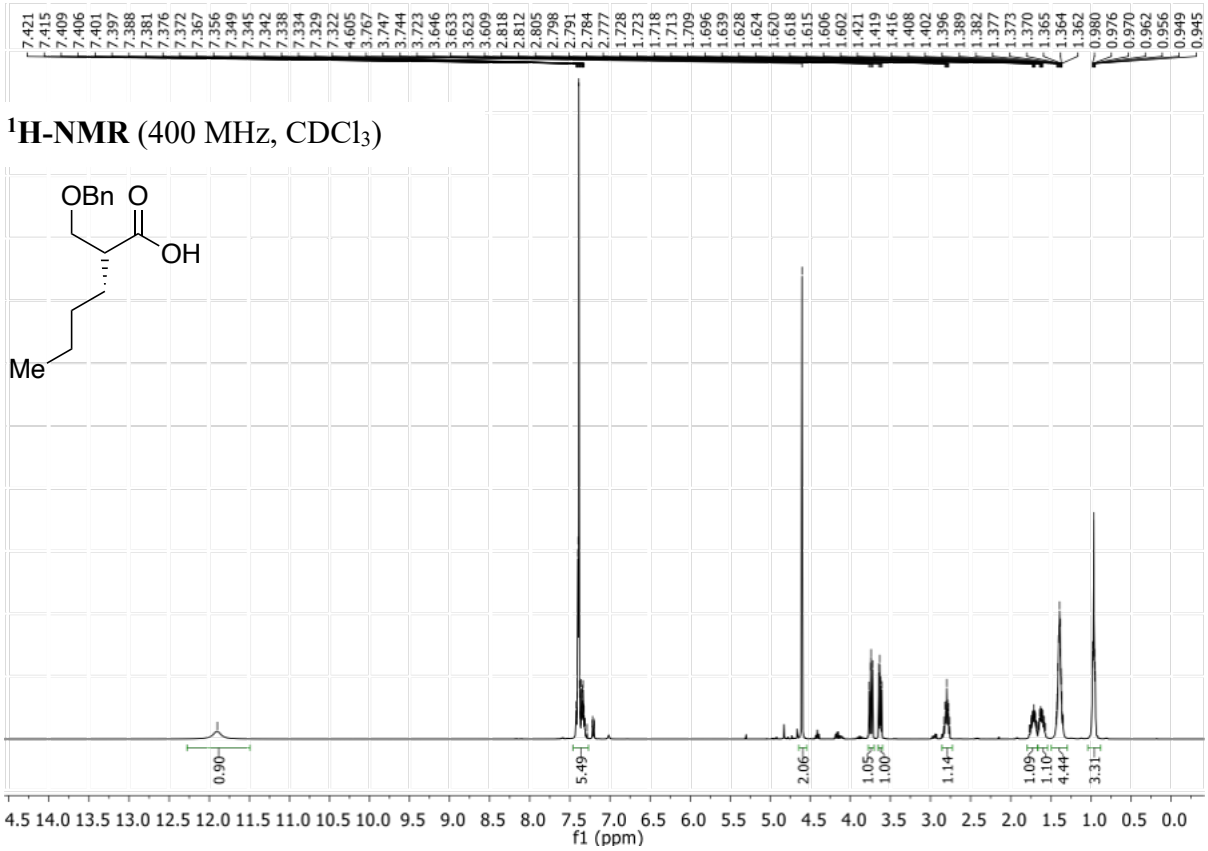
^{1}H-NMR (400 MHz, $CDCl_3$)



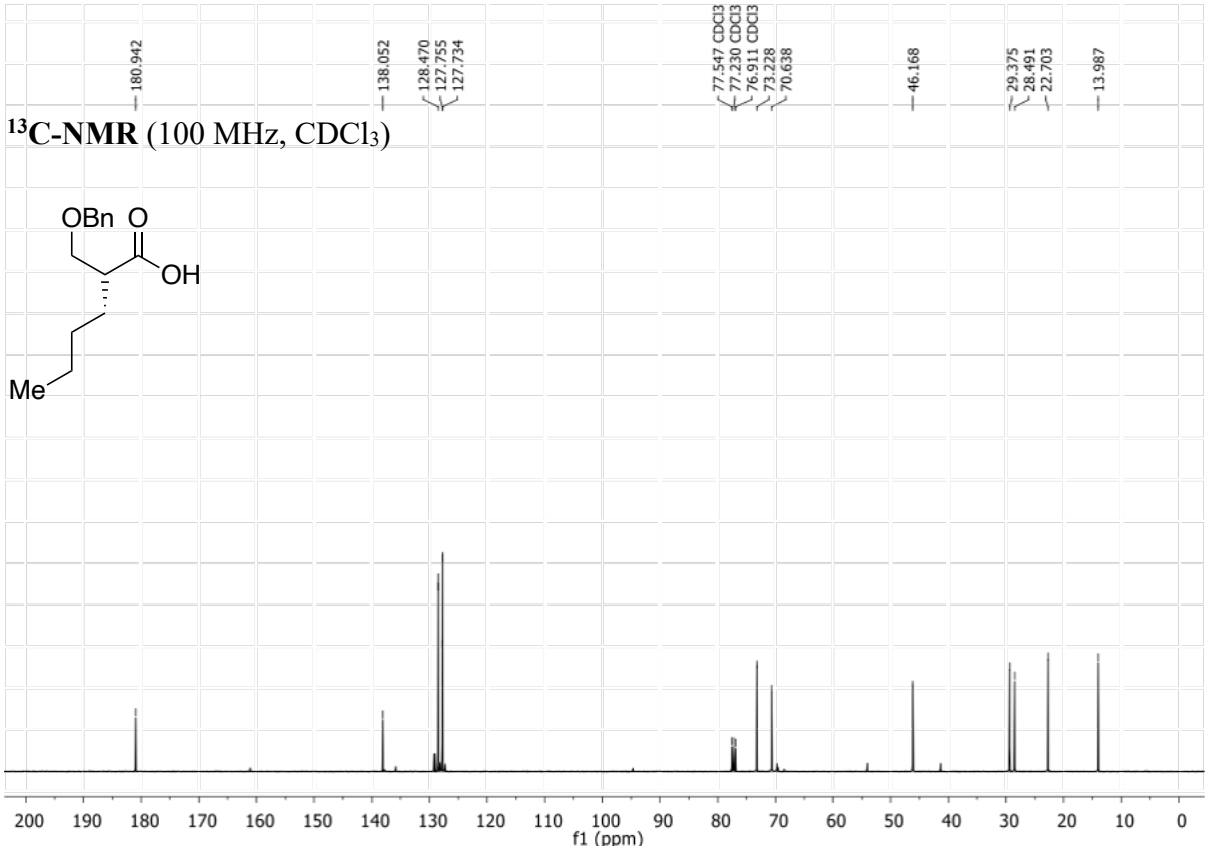
^{13}C-NMR (100 MHz, $CDCl_3$)



(*R*)-2-[(Benzyloxy)methyl]hexanoic acid, 60



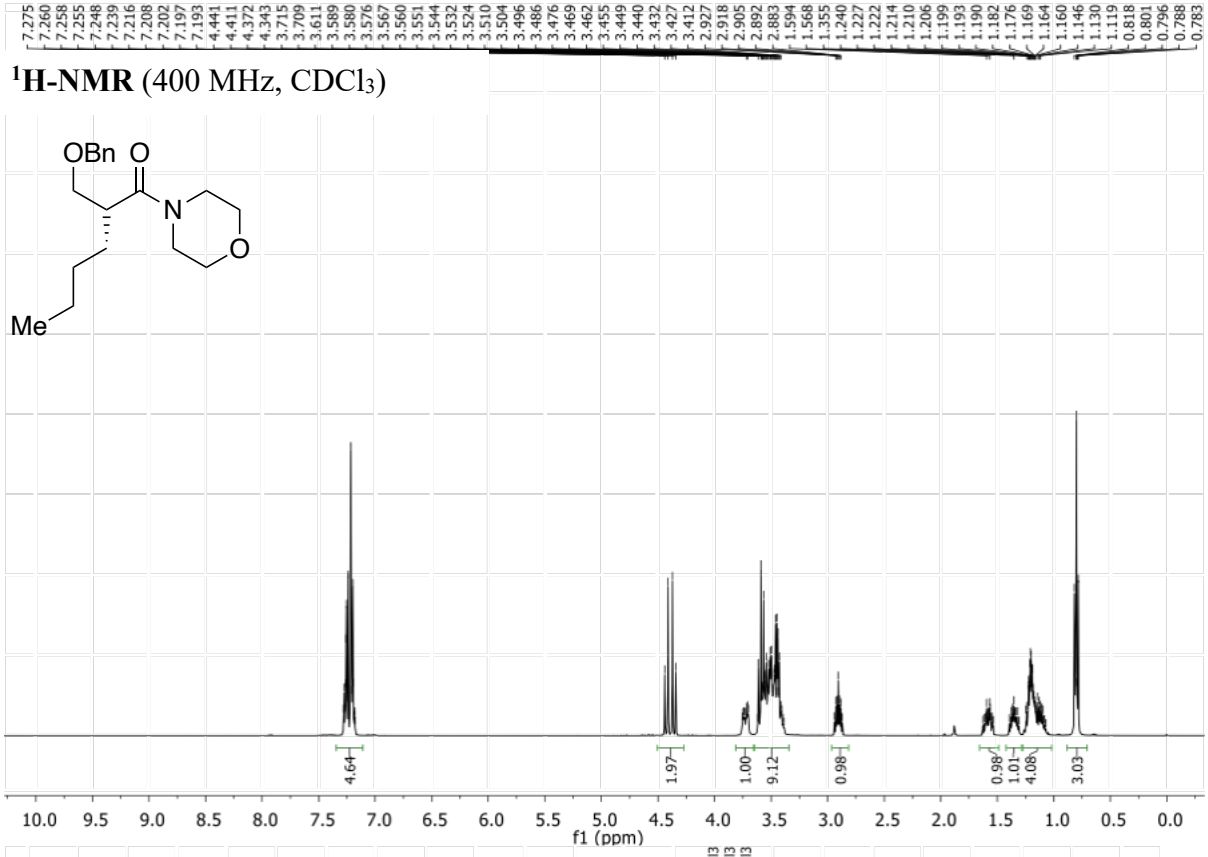
^{1}H-NMR (400 MHz, $CDCl_3$)



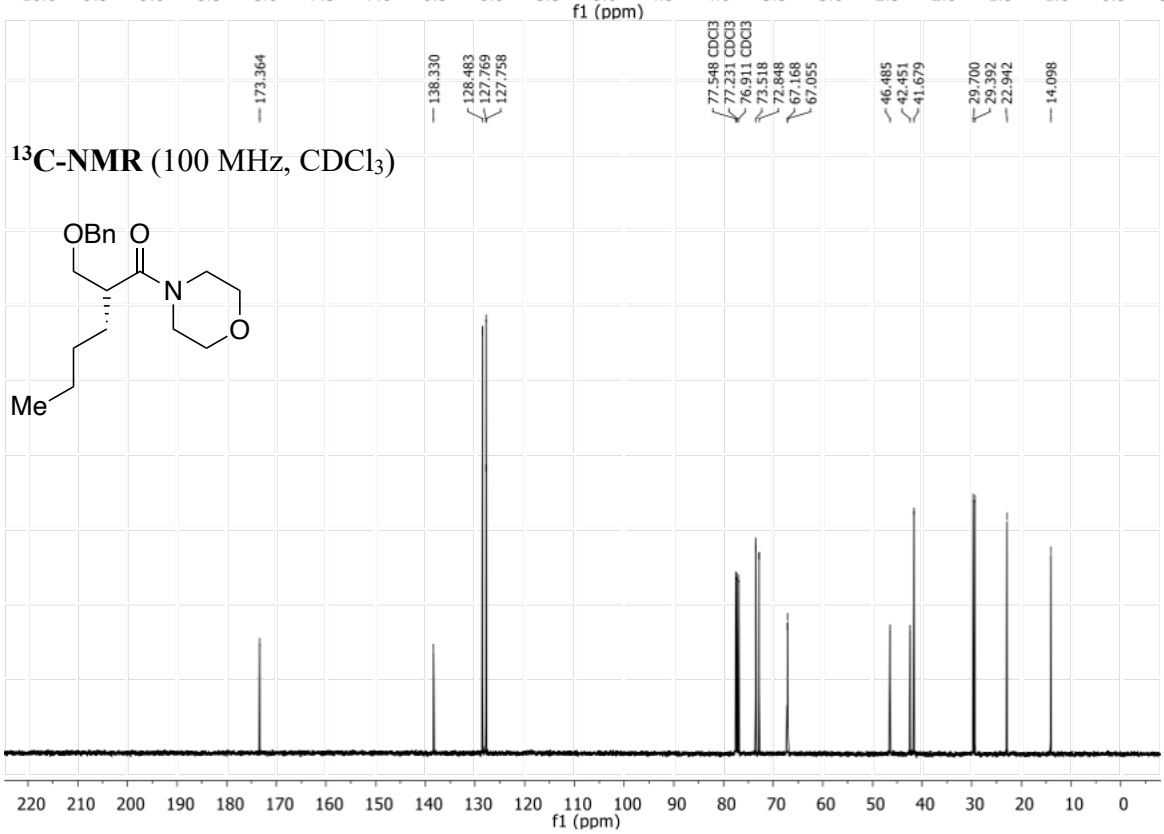
^{13}C-NMR (100 MHz, $CDCl_3$)

(*R*)-2-[(Benzyloxy)methyl]-1-morpholinohexan-1-one, 61

^{1}H-NMR (400 MHz, $CDCl_3$)

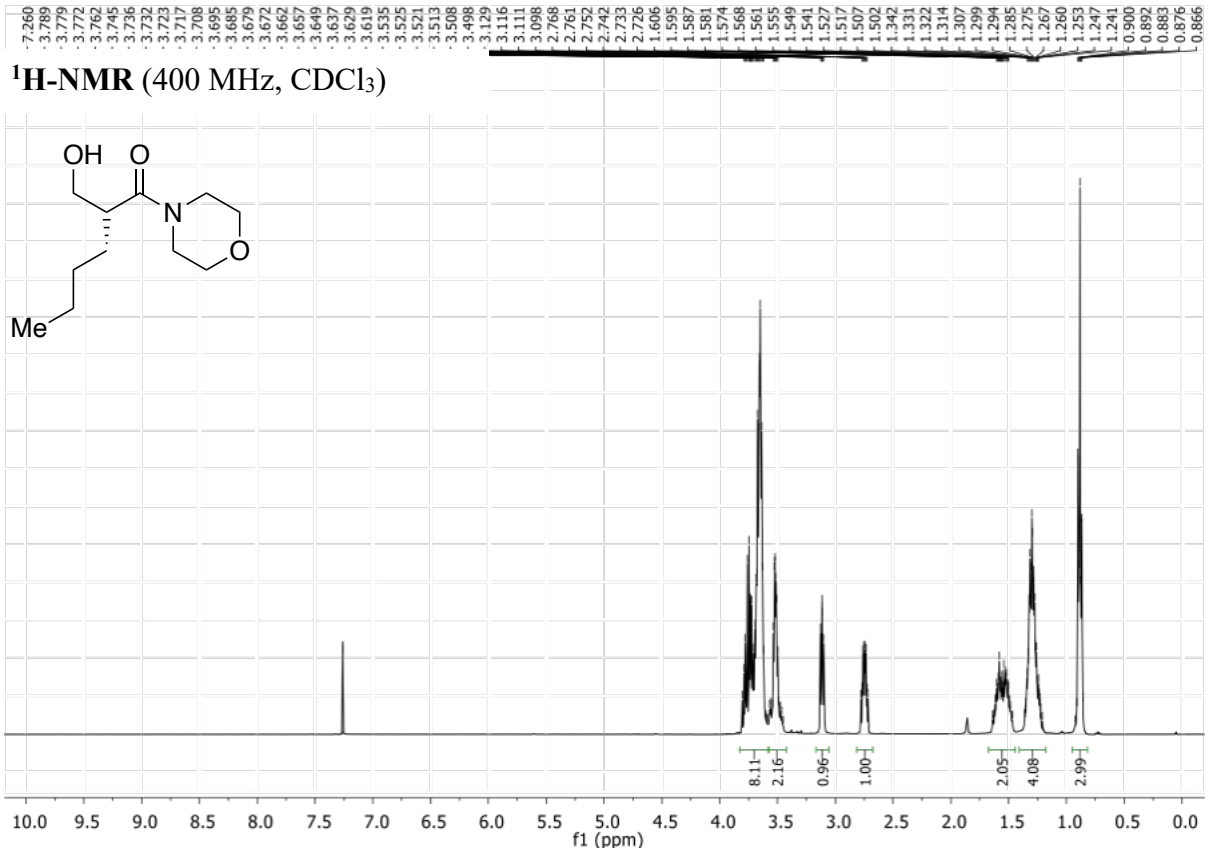


^{13}C-NMR (100 MHz, $CDCl_3$)

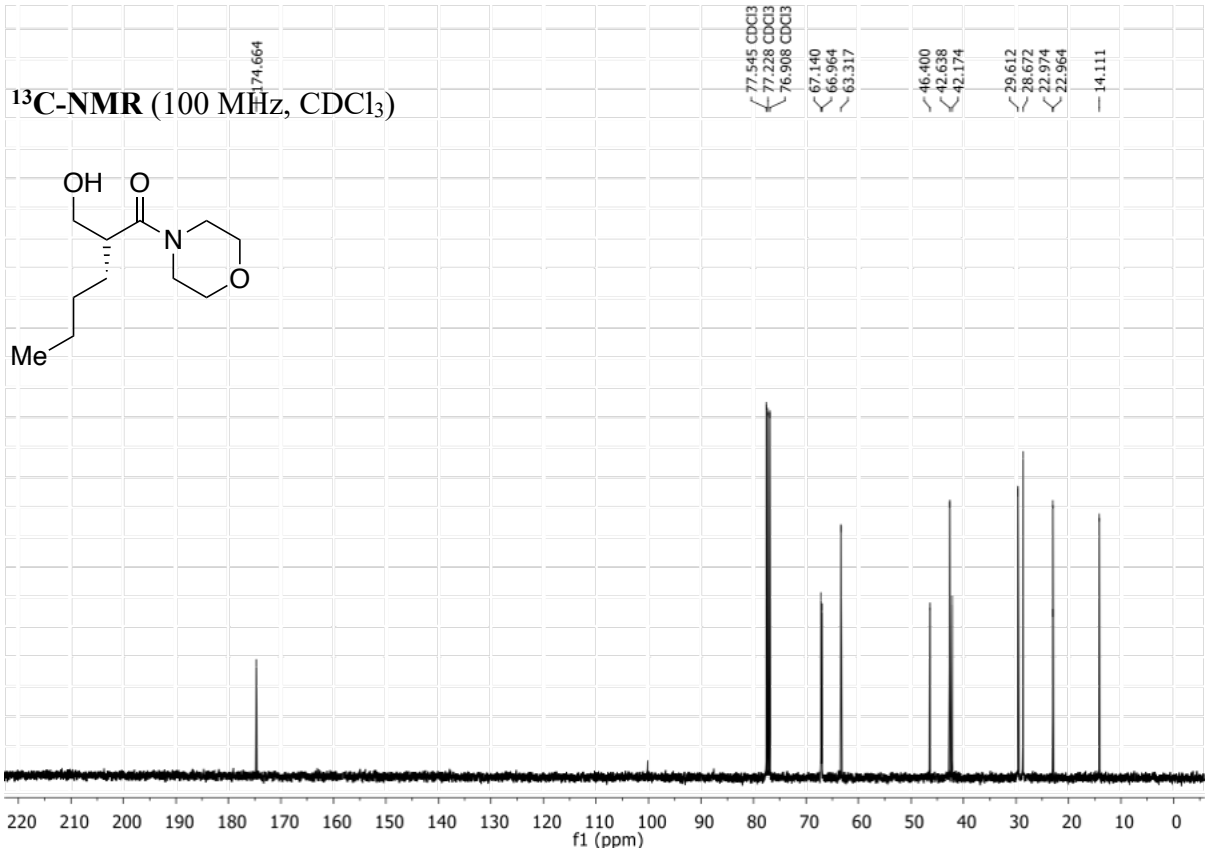


(*R*)-2-(Hydroxymethyl)-1-morpholinohexan-1-one, 62

^{1}H-NMR (400 MHz, $CDCl_3$)



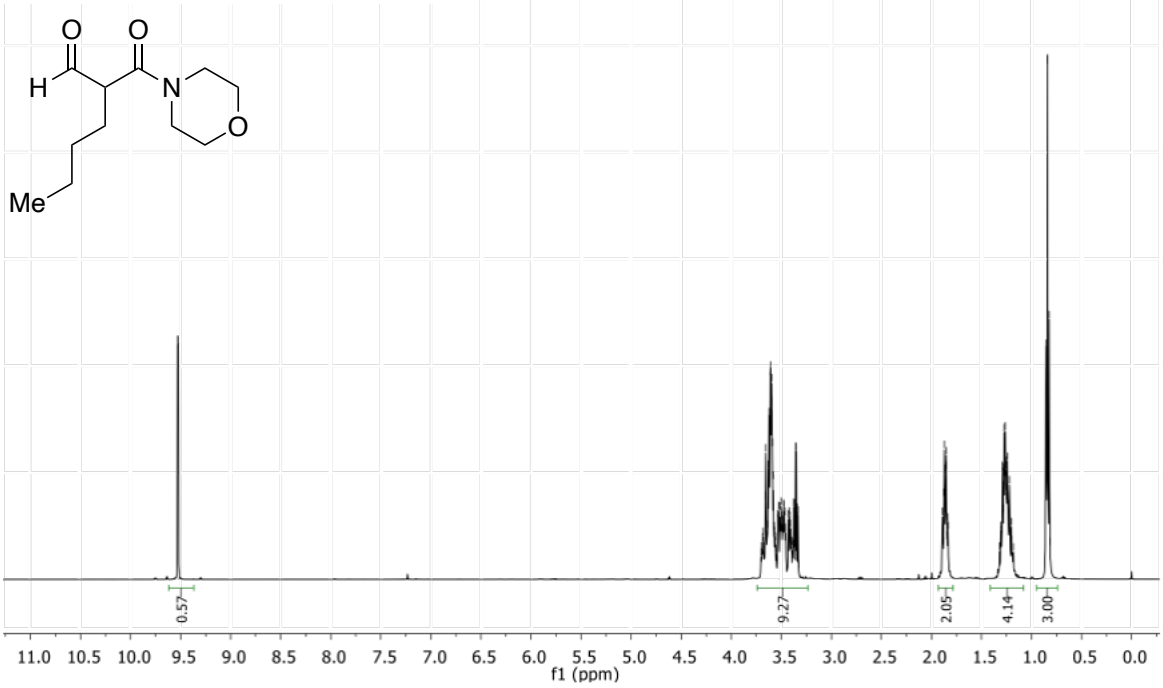
^{13}C-NMR (100 MHz, $CDCl_3$)

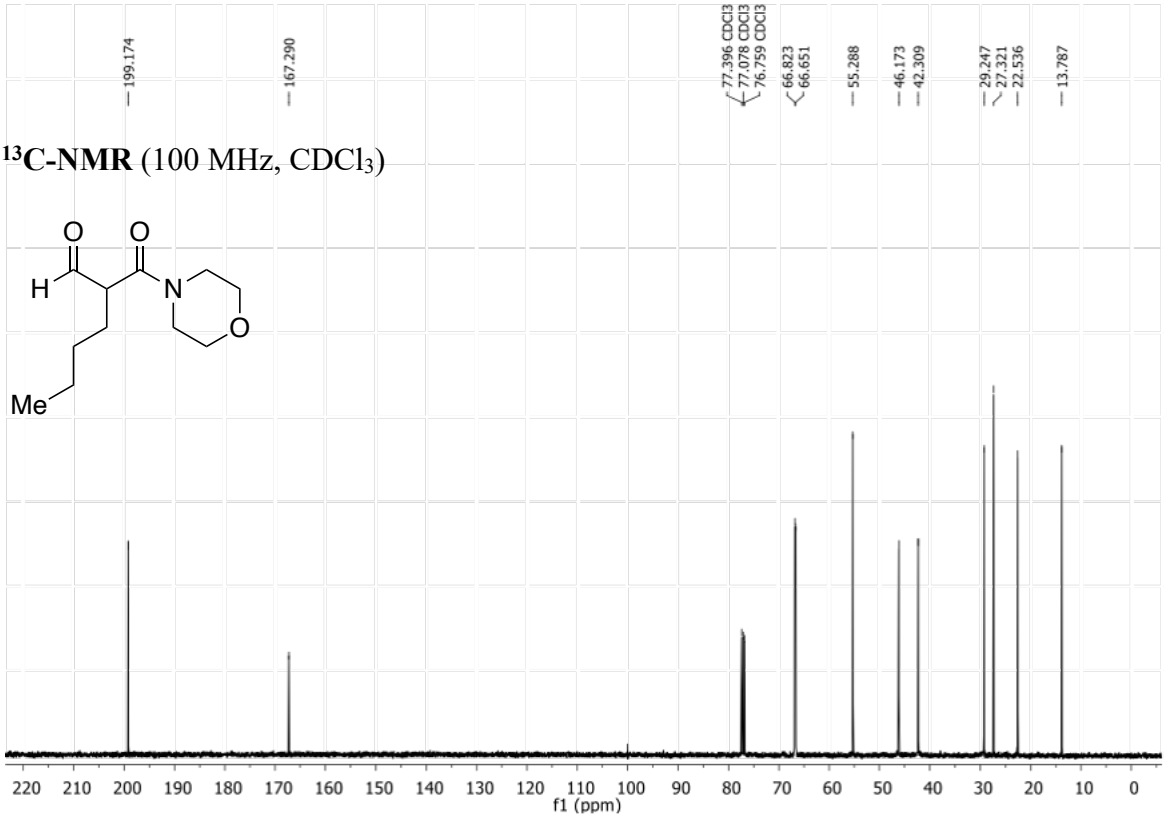


2-(Morpholine-4-carbonyl)hexanal, 63



^{1}H-NMR (400 MHz, $CDCl_3$)

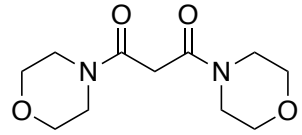




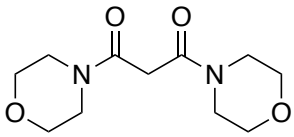
^{13}C-NMR (100 MHz, $CDCl_3$)

1,3-dimorpholinopropane-1,3-dione, 68

^{1}H-NMR (400 MHz, $CDCl_3$)

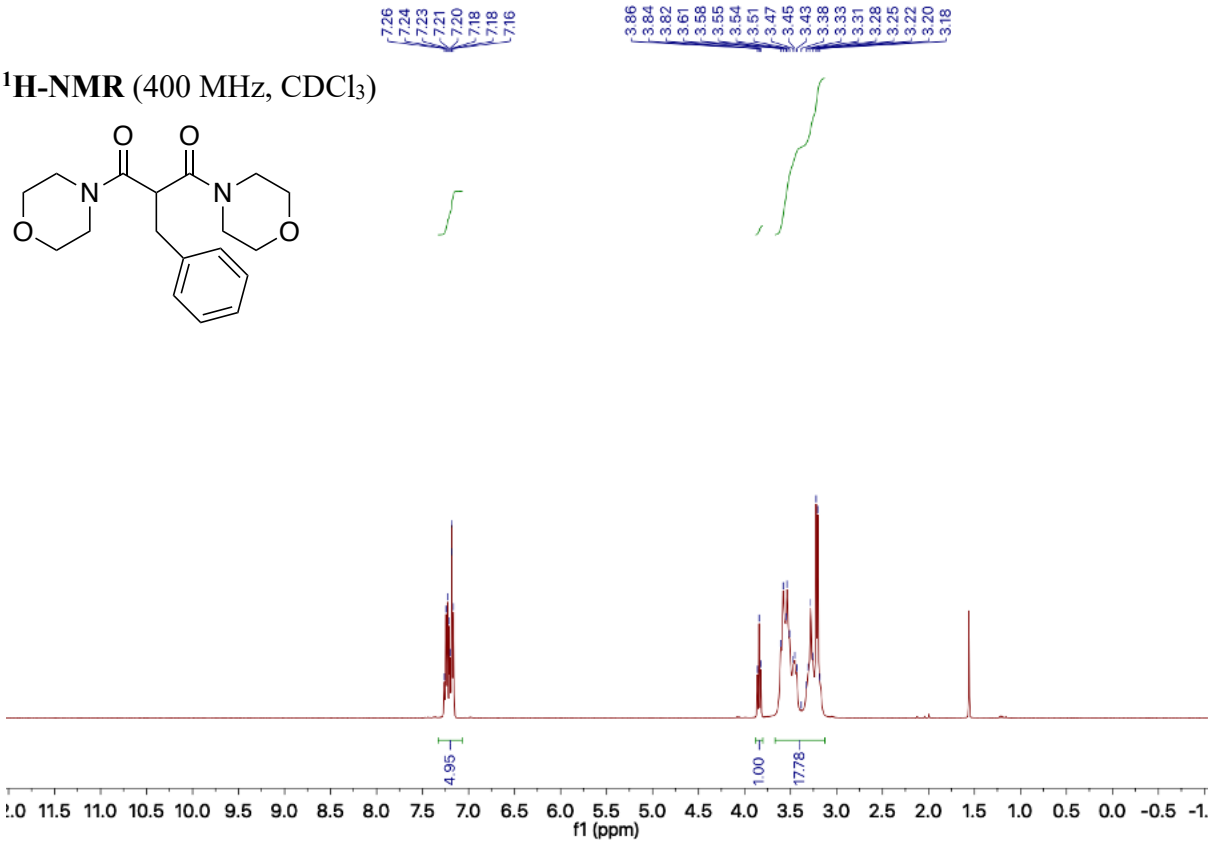


^{13}C-NMR (100 MHz, $CDCl_3$)

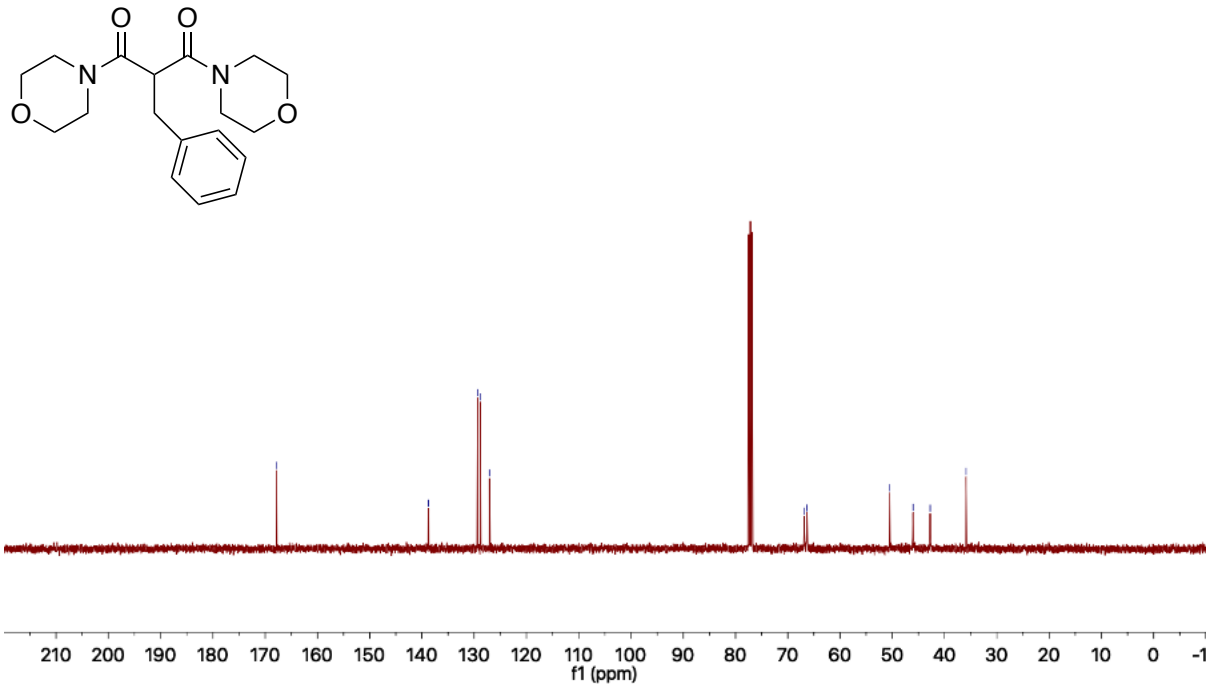


2-benzyl-1,3-dimorpholinopropane-1,3-dione, 64a

^{1}H-NMR (400 MHz, $CDCl_3$)

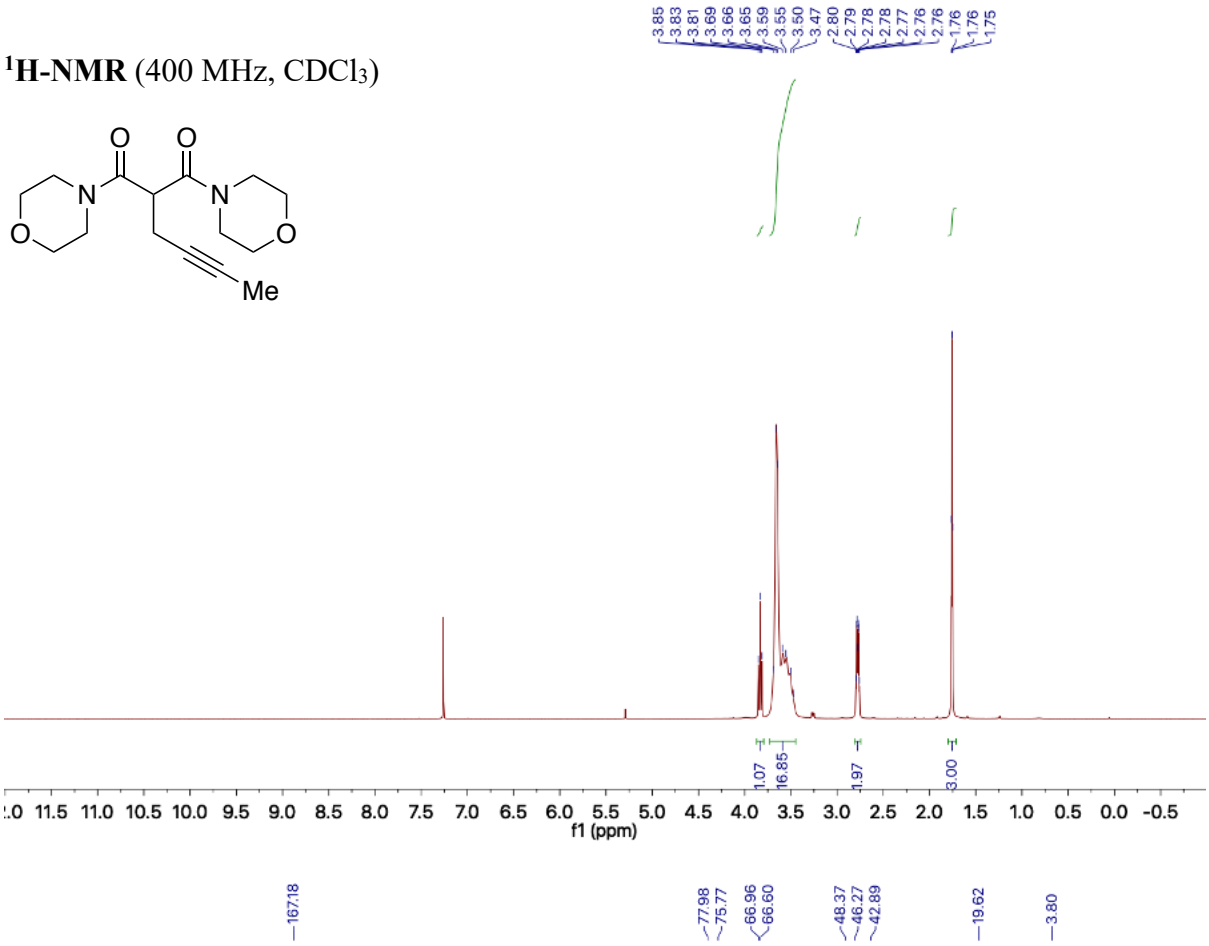


^{13}C-NMR (100 MHz, $CDCl_3$)

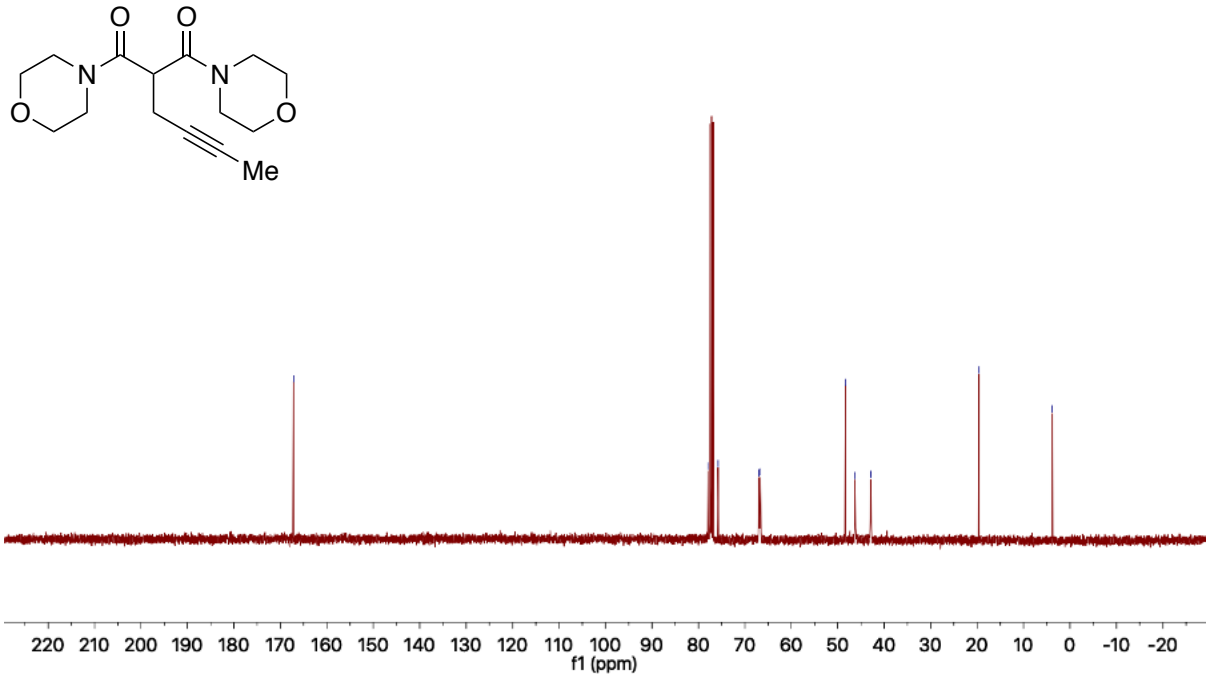


2-(but-2-yn-1-yl)-1,3-dimorpholinopropane-1,3-dione, 64l

^{1}H-NMR (400 MHz, $CDCl_3$)



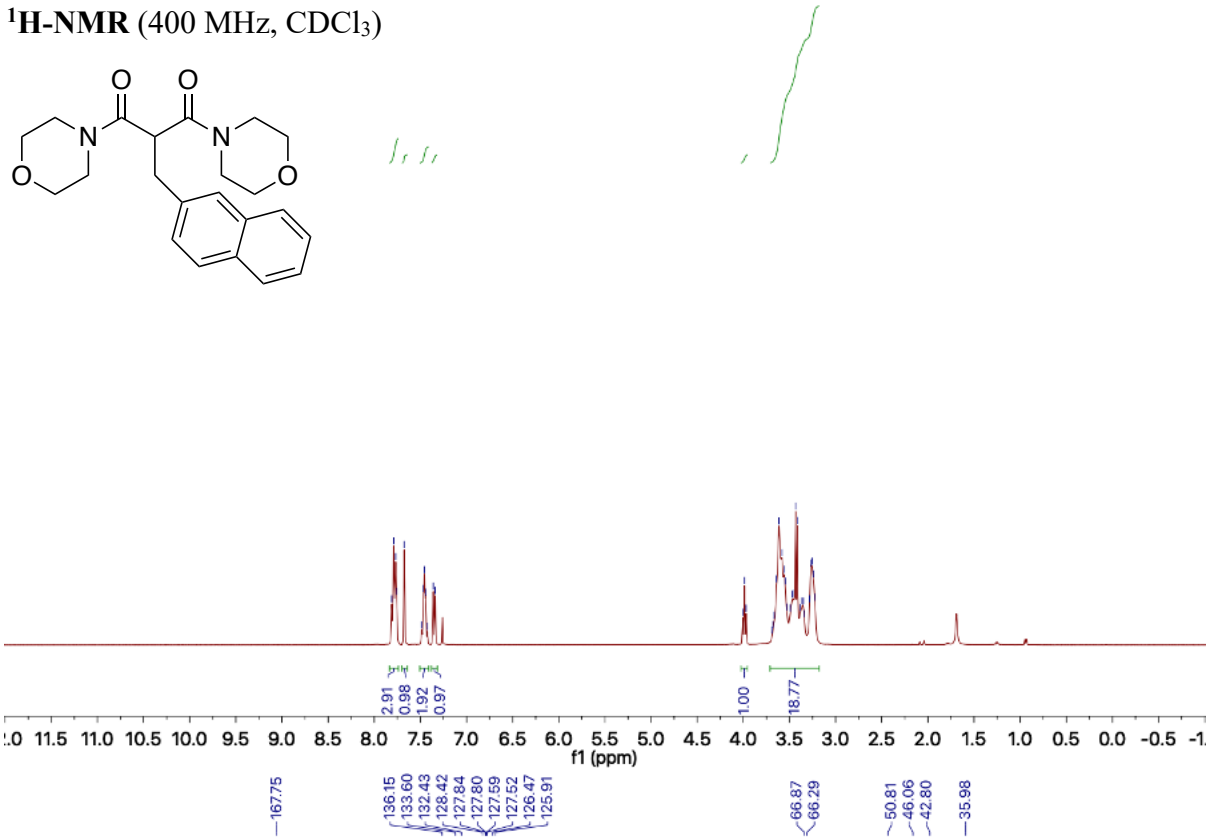
^{13}C-NMR (100 MHz, $CDCl_3$)



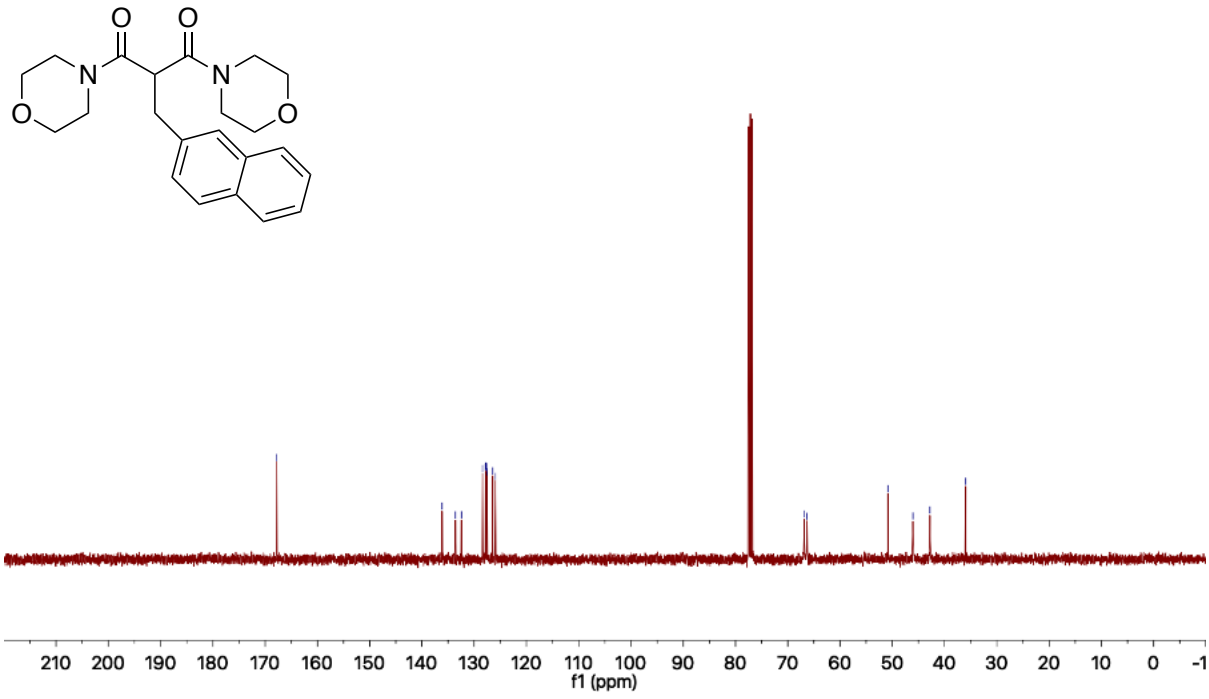
1,3-dimorpholino-2-(naphthalen-2-ylmethyl)propane-1,3-dione, 64m



^{1}H-NMR (400 MHz, $CDCl_3$)

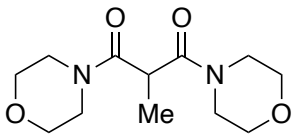


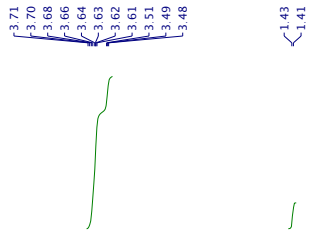
^{13}C-NMR (100 MHz, $CDCl_3$)

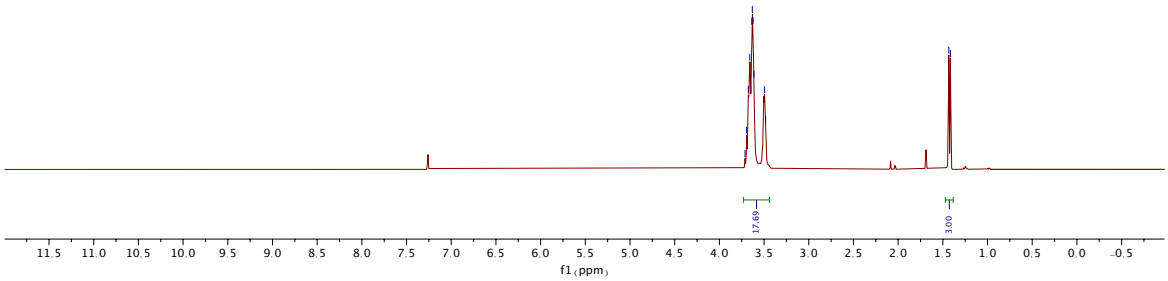


2-methyl-1,3-dimorpholinopropane-1,3-dione, 64r

^{1}H-NMR (400 MHz, $CDCl_3$)

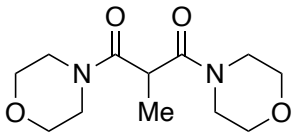


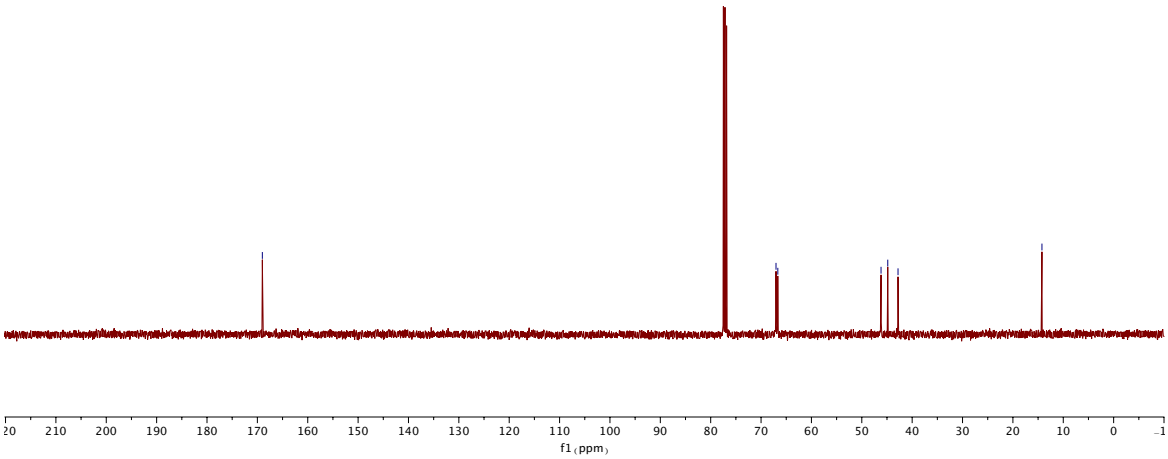






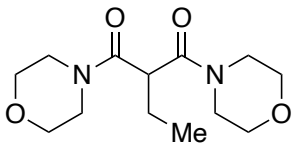
^{13}C-NMR (100 MHz, $CDCl_3$)

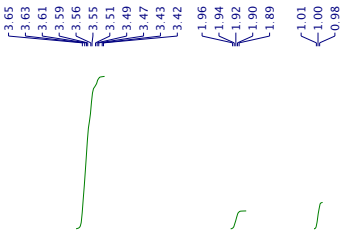


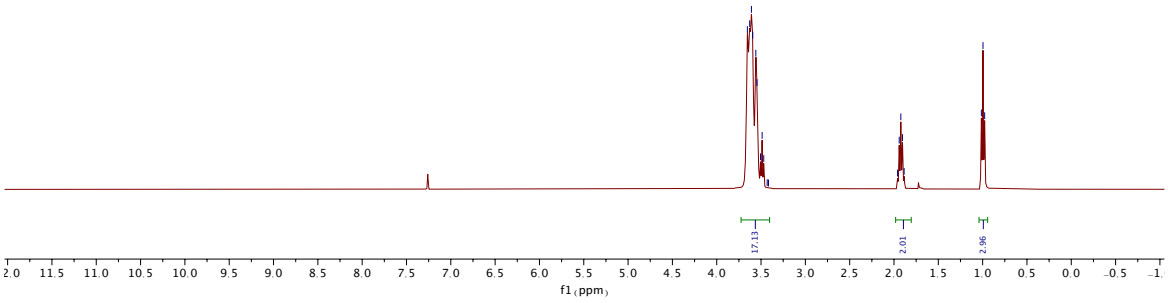


2-ethyl-1,3-dimorpholinopropane-1,3-dione, 64s

^{1}H-NMR (400 MHz, $CDCl_3$)

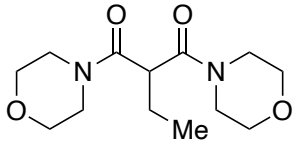


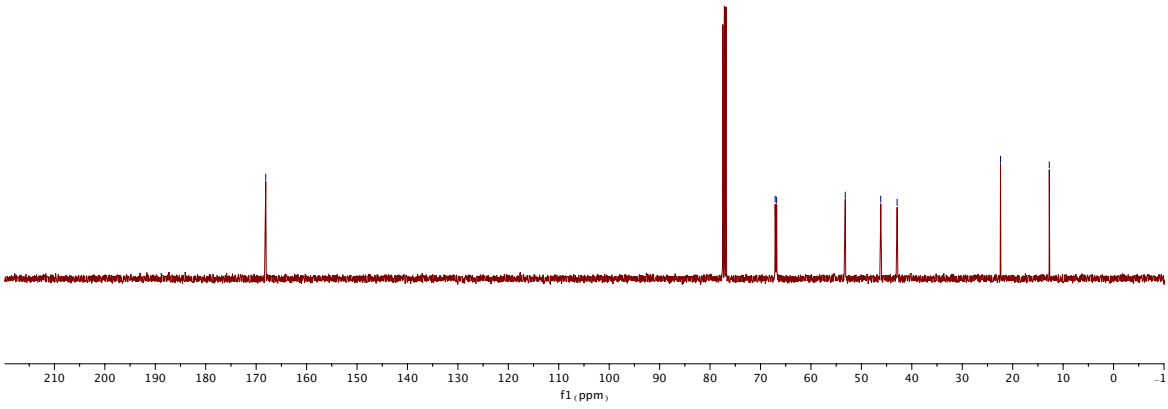






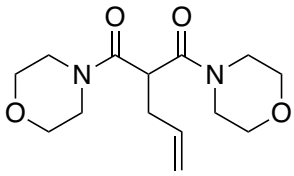
^{13}C-NMR (100 MHz, $CDCl_3$)





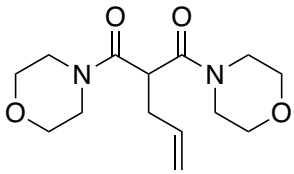
2-allyl-1,3-dimorpholinopropane-1,3-dione, 64t

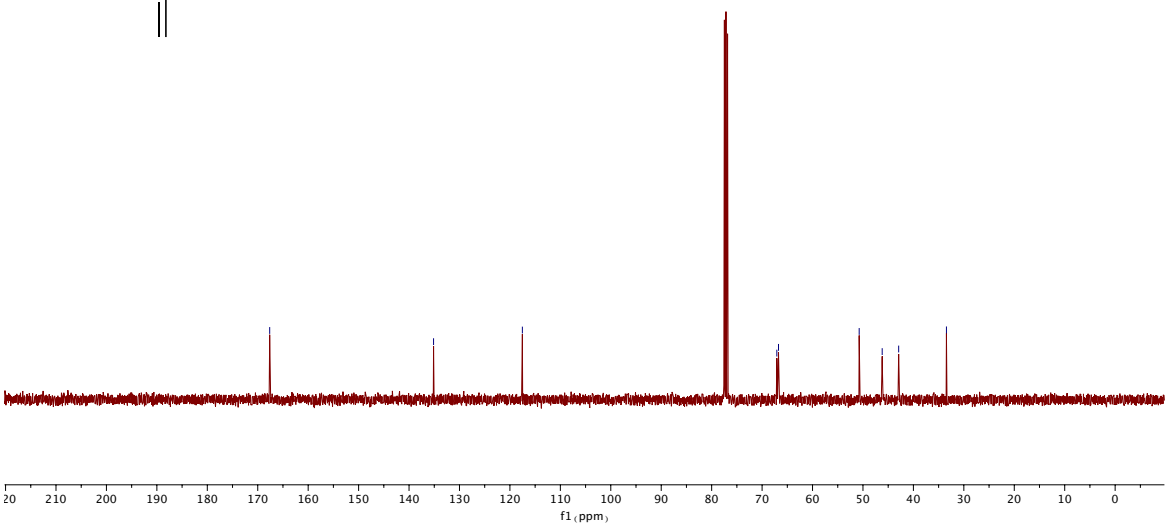
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

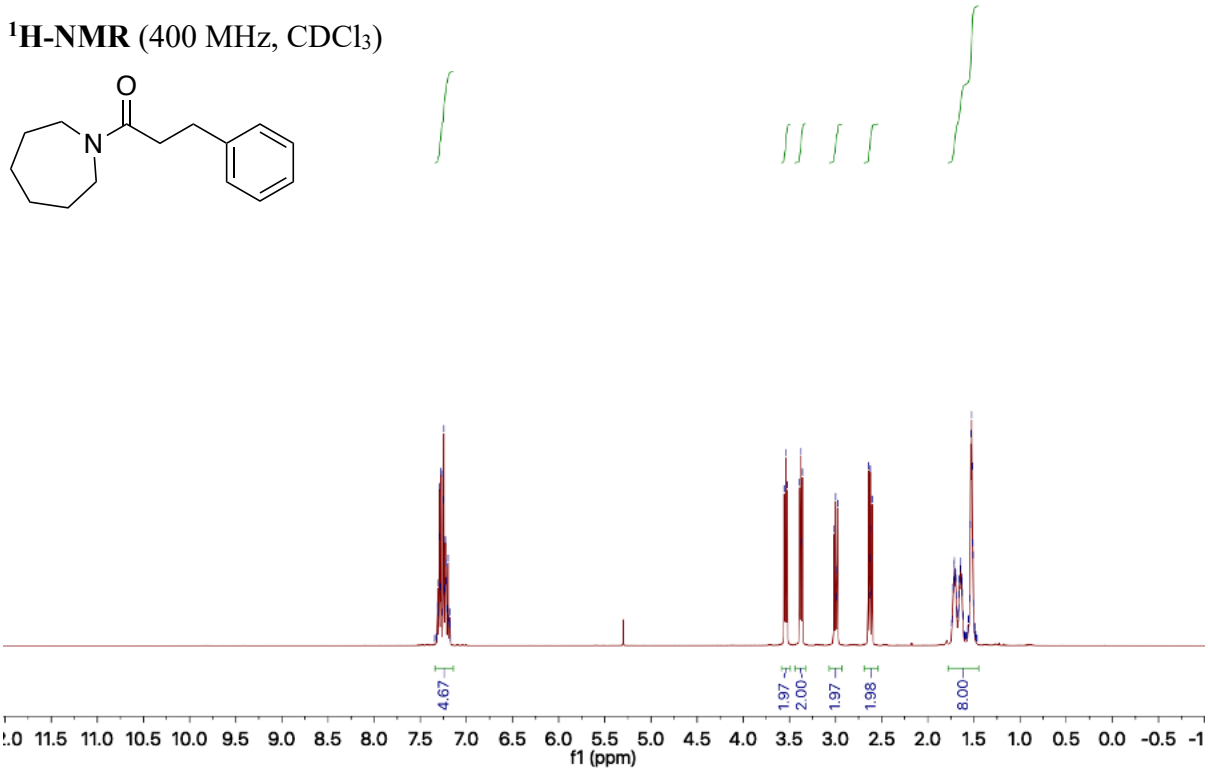




1-(azepan-1-yl)-3-phenylpropan-1-one, 67q

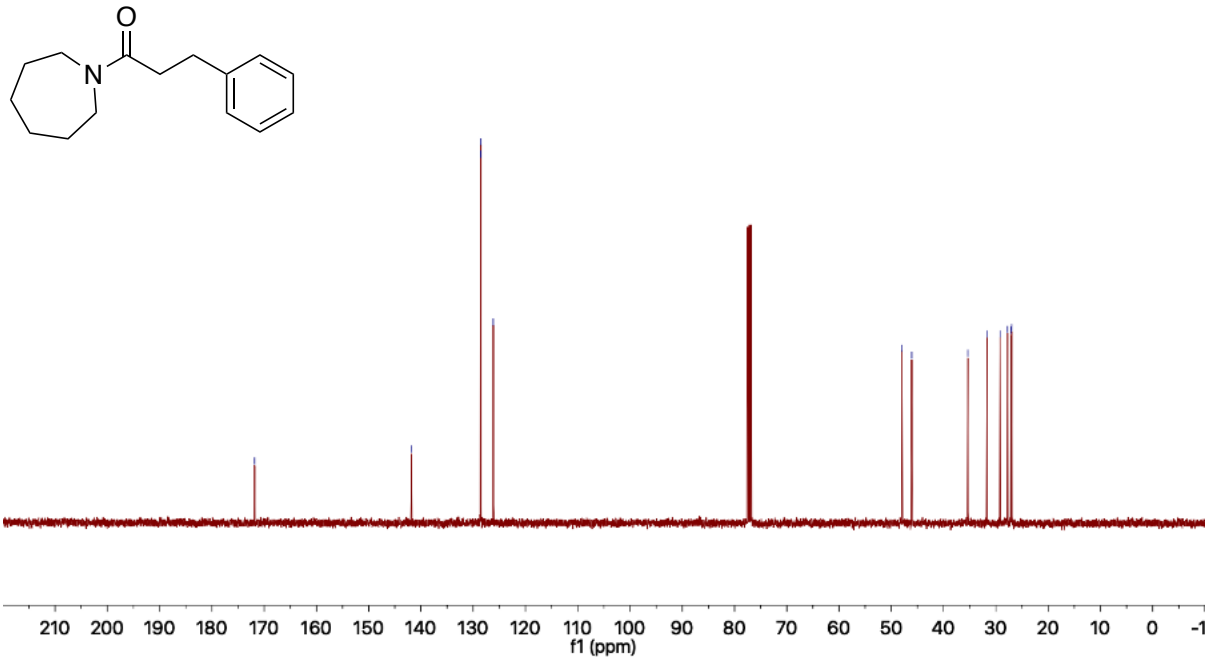


^{1}H-NMR (400 MHz, $CDCl_3$)



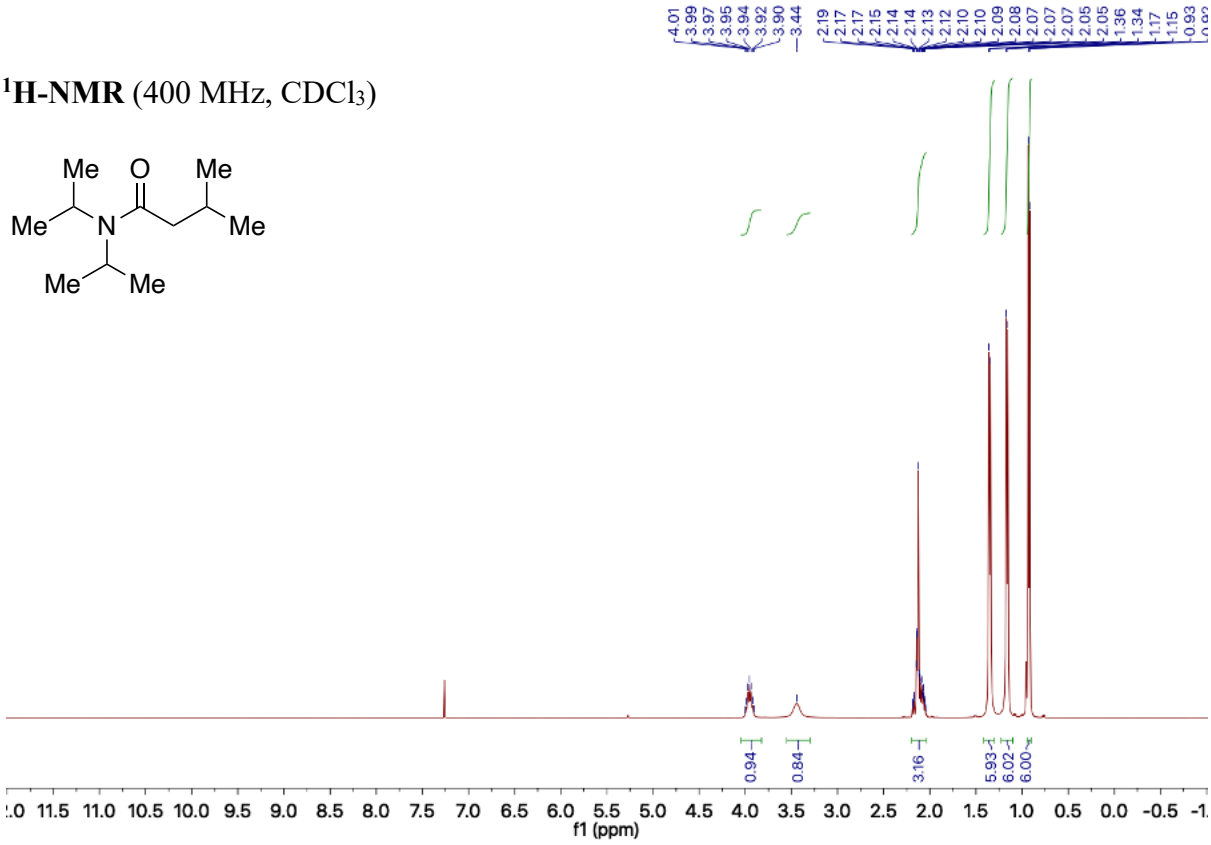


^{13}C-NMR (100 MHz, $CDCl_3$)

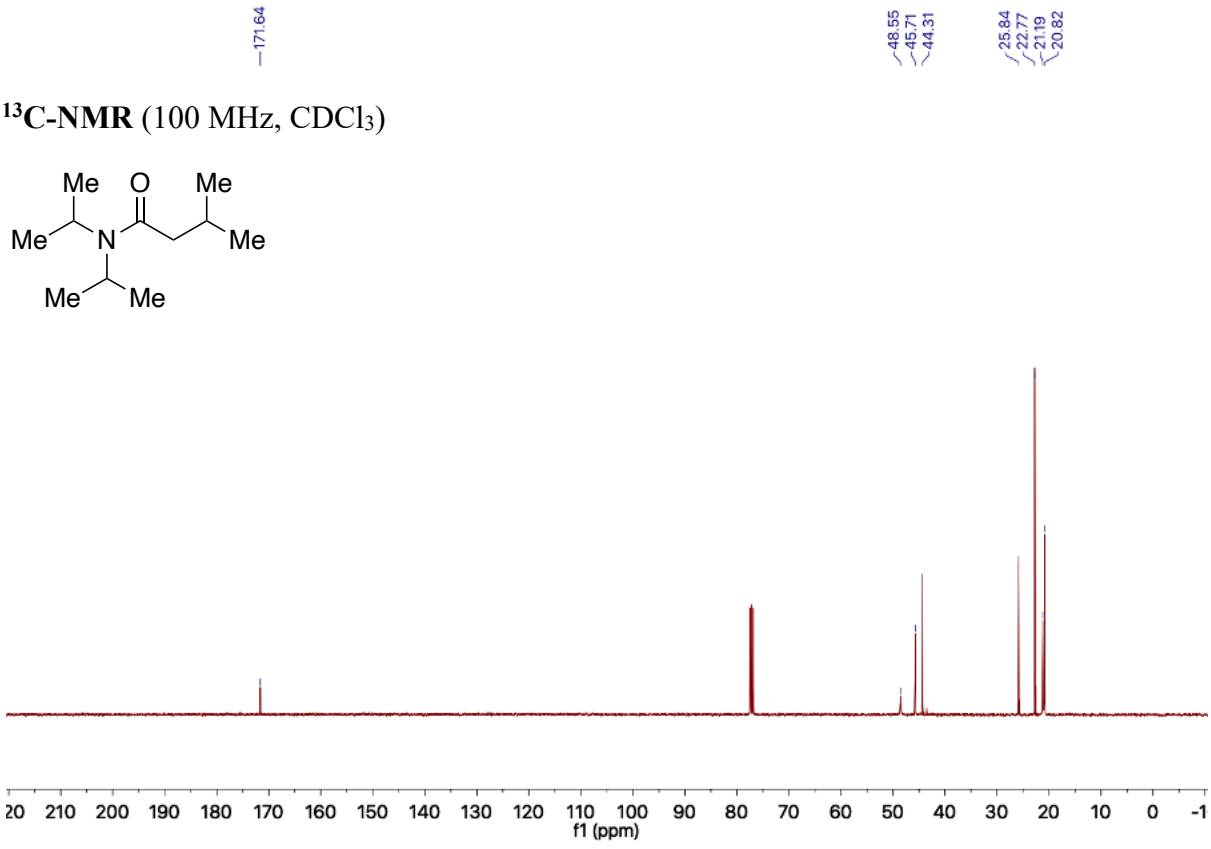


***N*,*N*-diisopropyl-3-methylbutanamide, 67o**

^{1}H-NMR (400 MHz, $CDCl_3$)



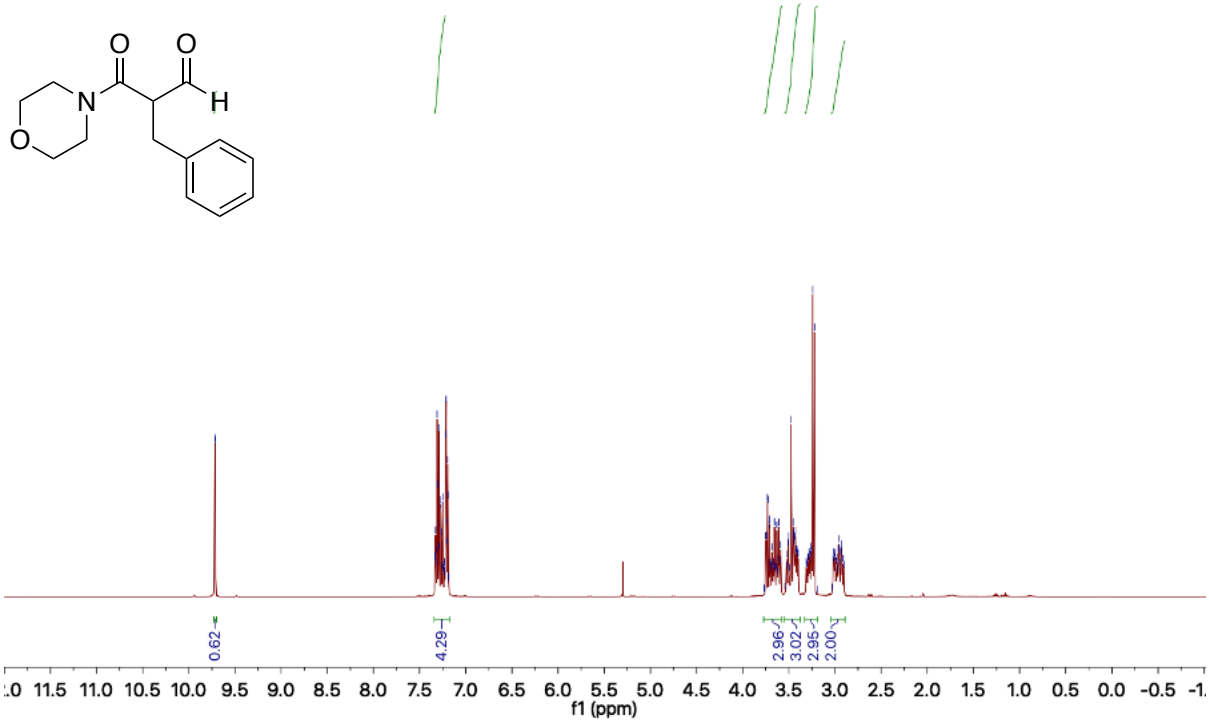
^{13}C-NMR (100 MHz, $CDCl_3$)



2-benzyl-3-morpholino-3-oxopropanal, 65a

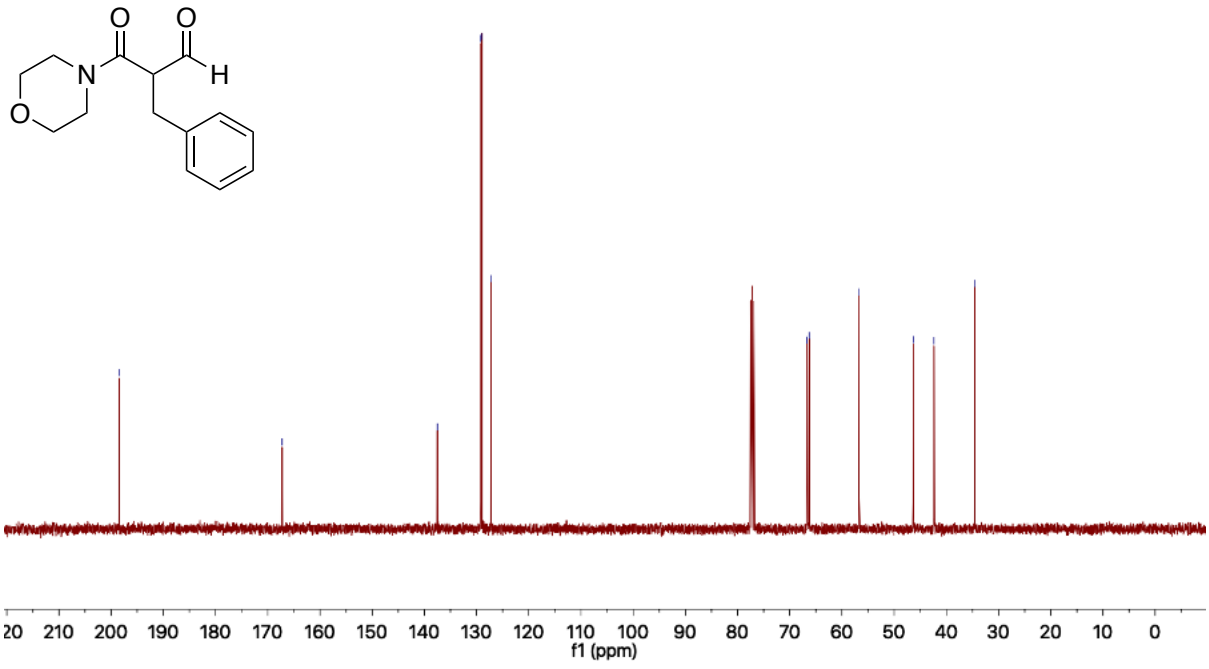


^{1}H-NMR (400 MHz, $CDCl_3$)





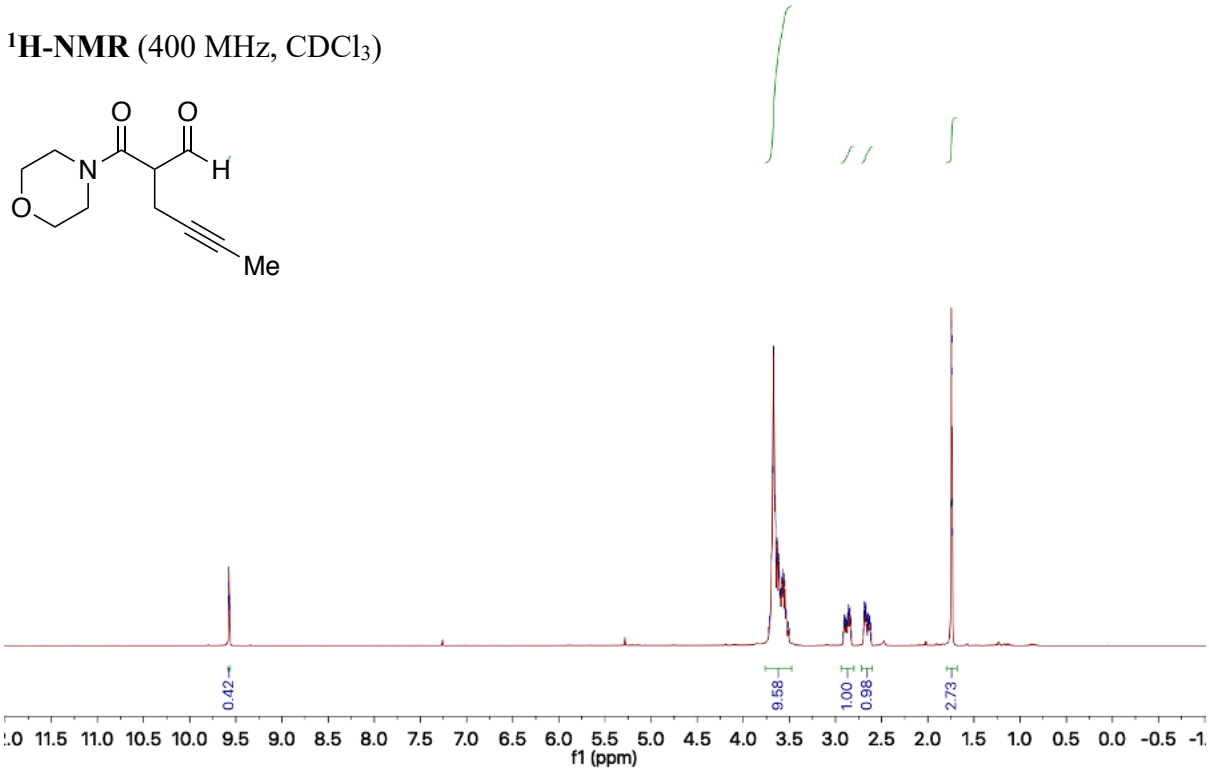
^{13}C-NMR (100 MHz, $CDCl_3$)



2-(tetrahydro-2H-pyran-4-carbonyl)hex-4-ynal, 65l

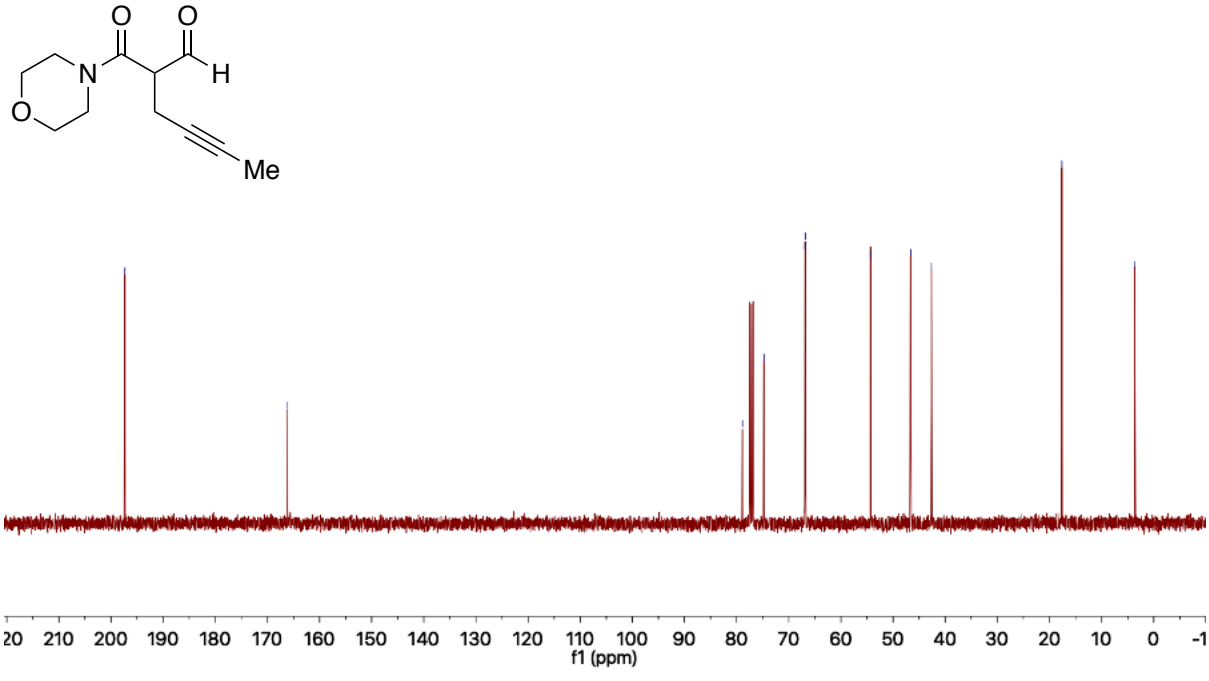


^{1}H-NMR (400 MHz, $CDCl_3$)





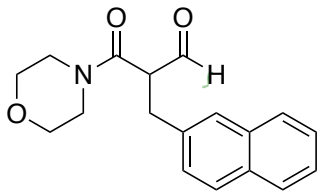
^{13}C-NMR (100 MHz, $CDCl_3$)

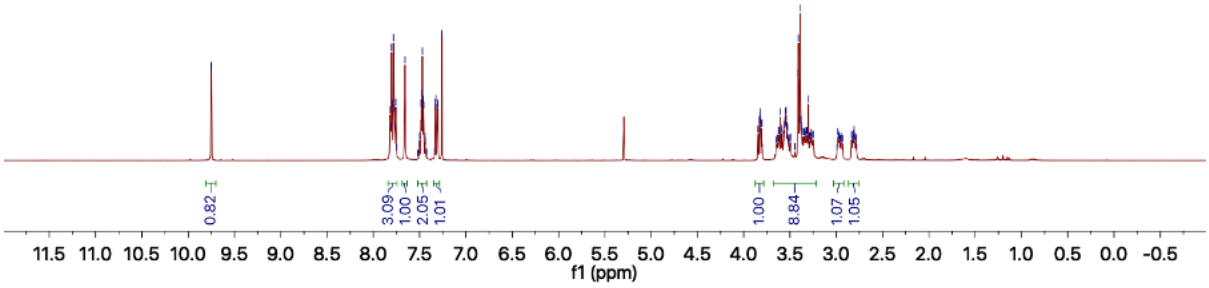


3-morpholino-2-(naphthalen-2-ylmethyl)-3-oxopropanal, 65m



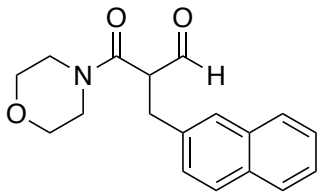
^{1}H-NMR (400 MHz, $CDCl_3$)

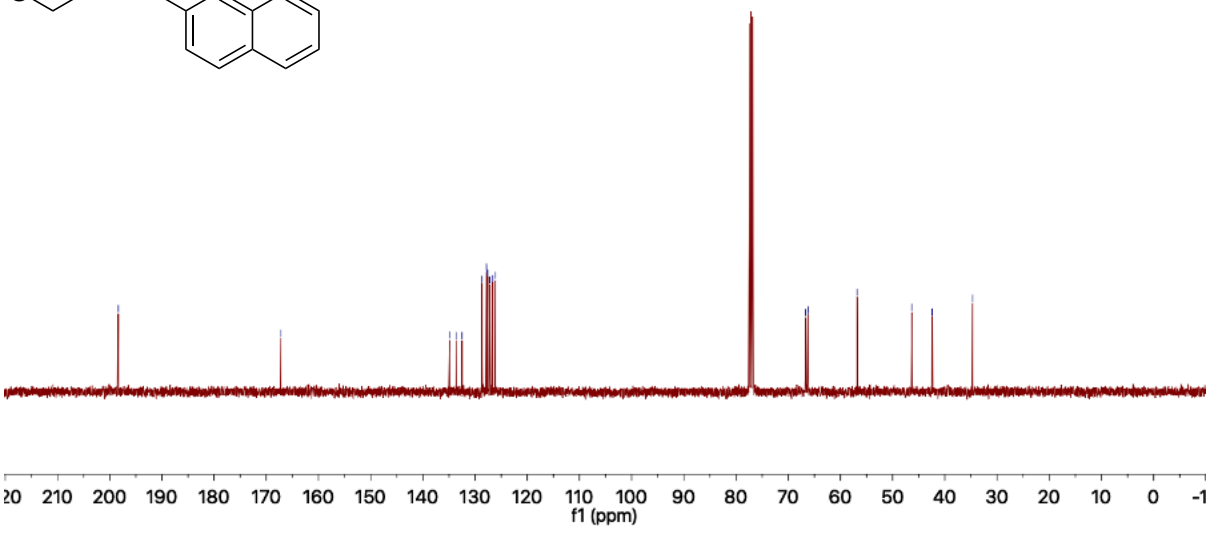






^{13}C-NMR (100 MHz, $CDCl_3$)

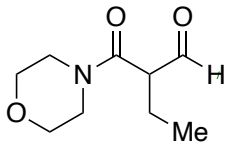


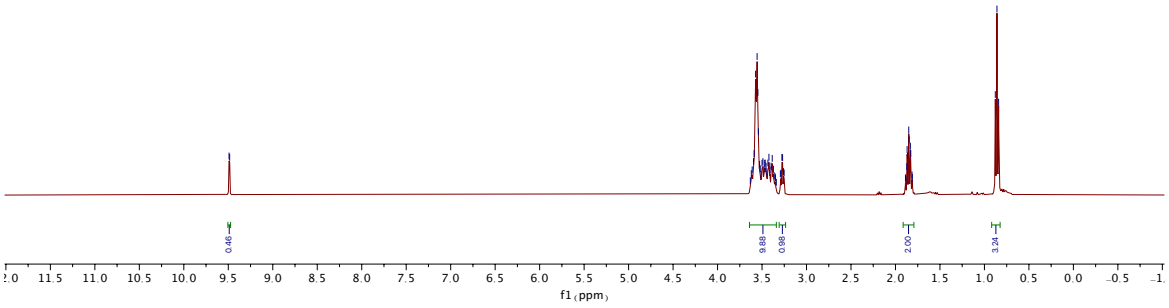


2-(morpholine-4-carbonyl)butanal, 65s



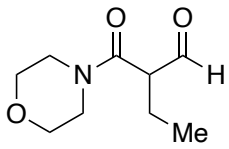
^{1}H-NMR (400 MHz, $CDCl_3$)

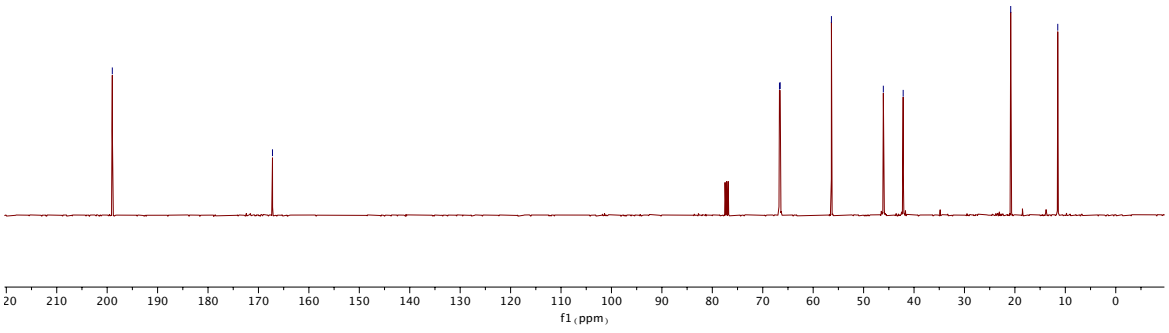






^{13}C-NMR (100 MHz, $CDCl_3$)

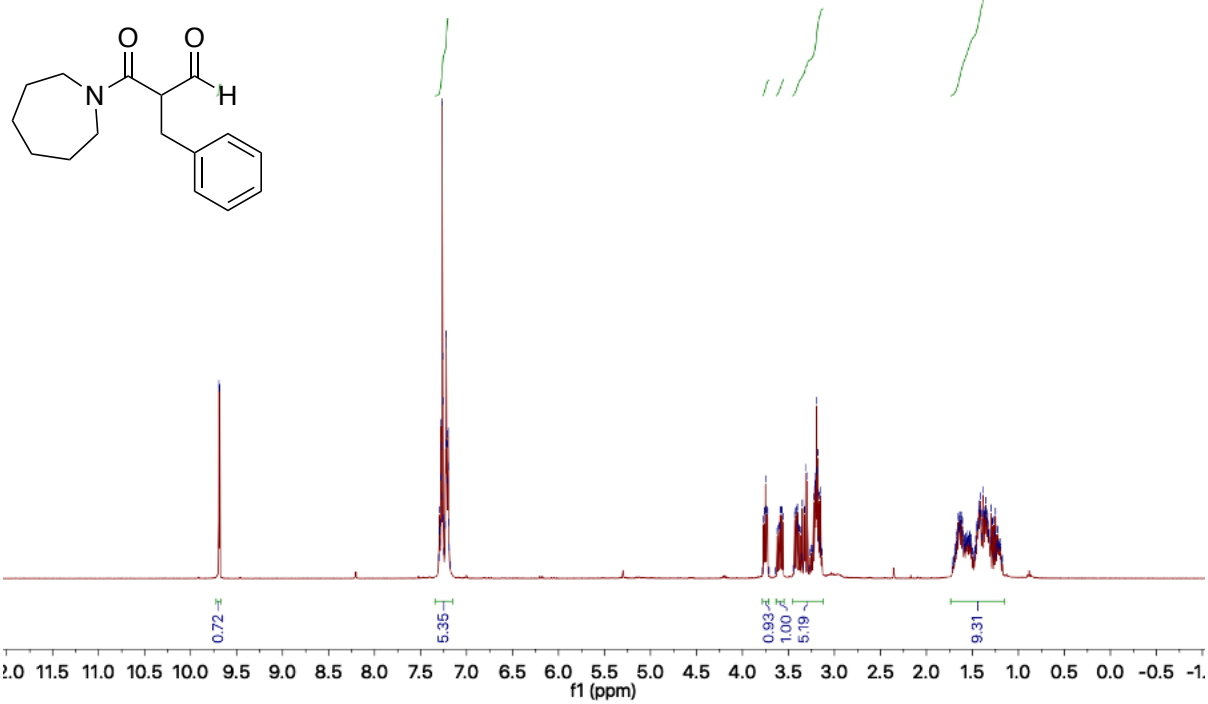




3-(azepan-1-yl)-2-benzyl-3-oxopropanal, 65q

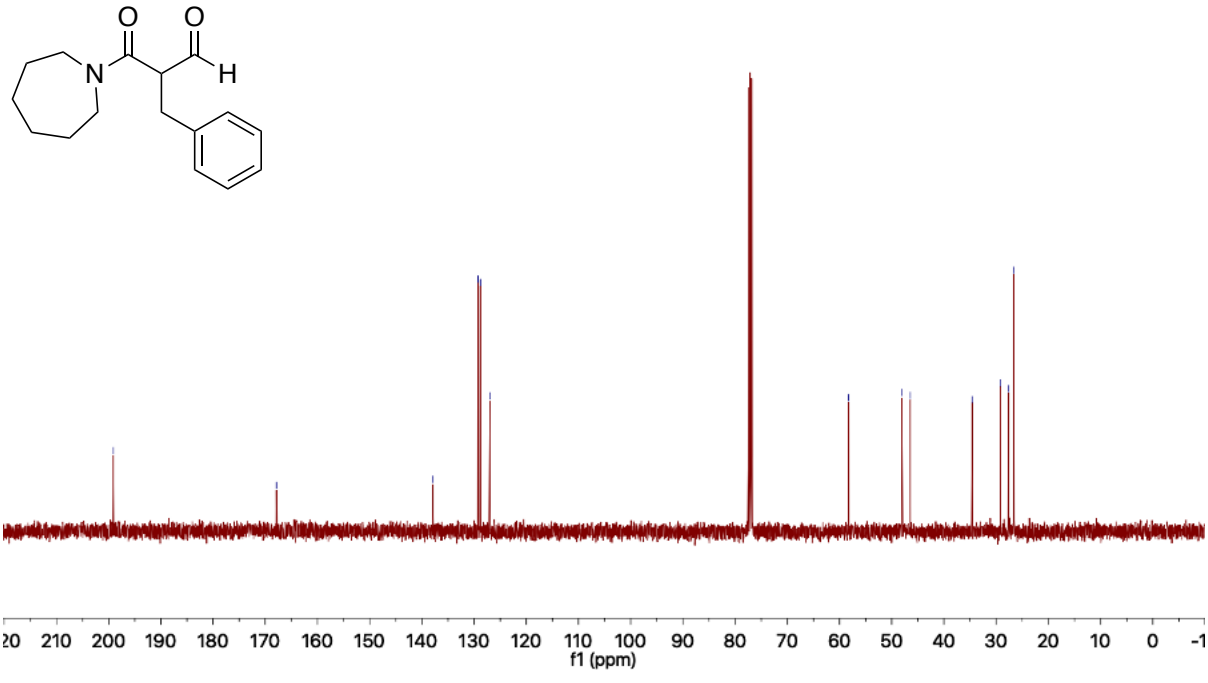


^{1}H-NMR (400 MHz, $CDCl_3$)



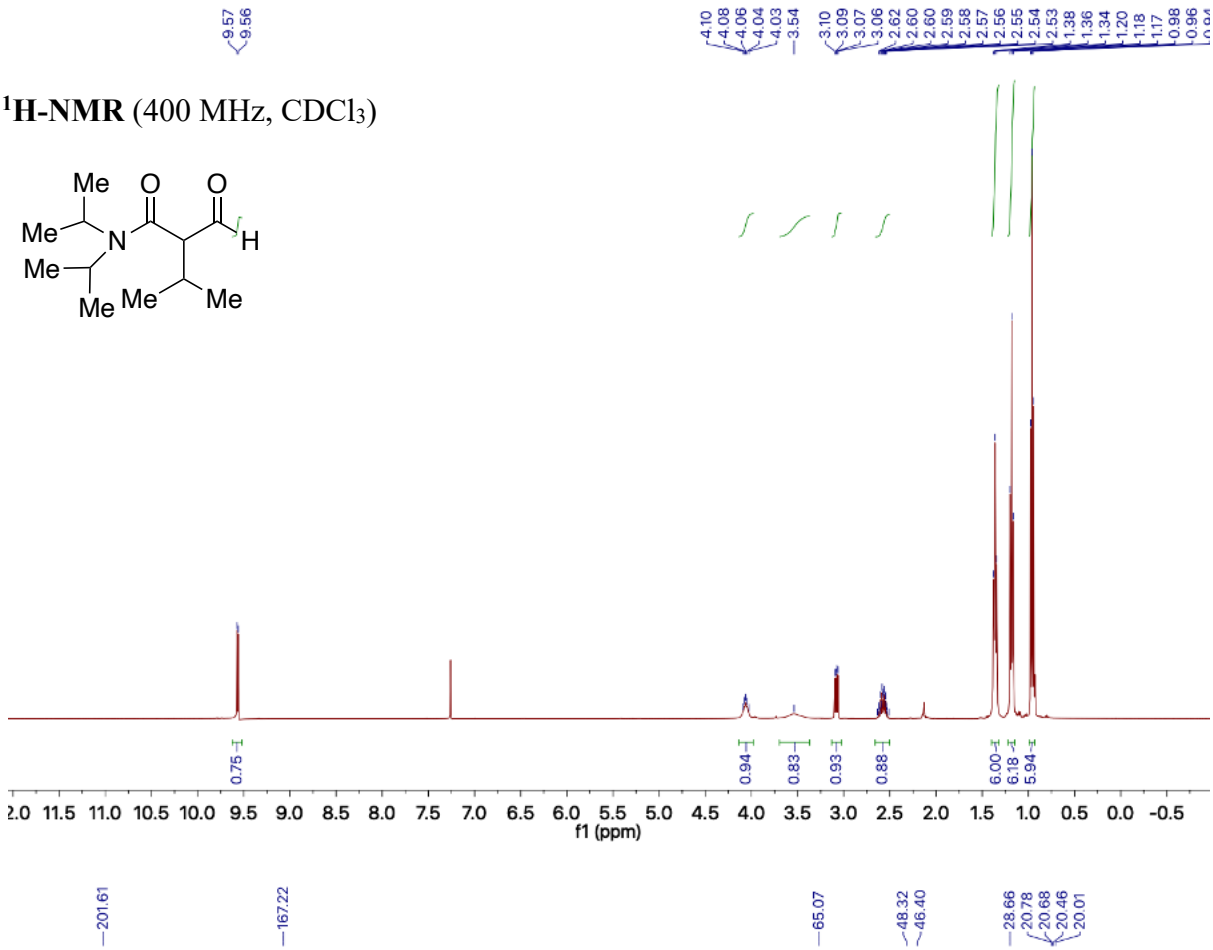


^{13}C-NMR (100 MHz, $CDCl_3$)

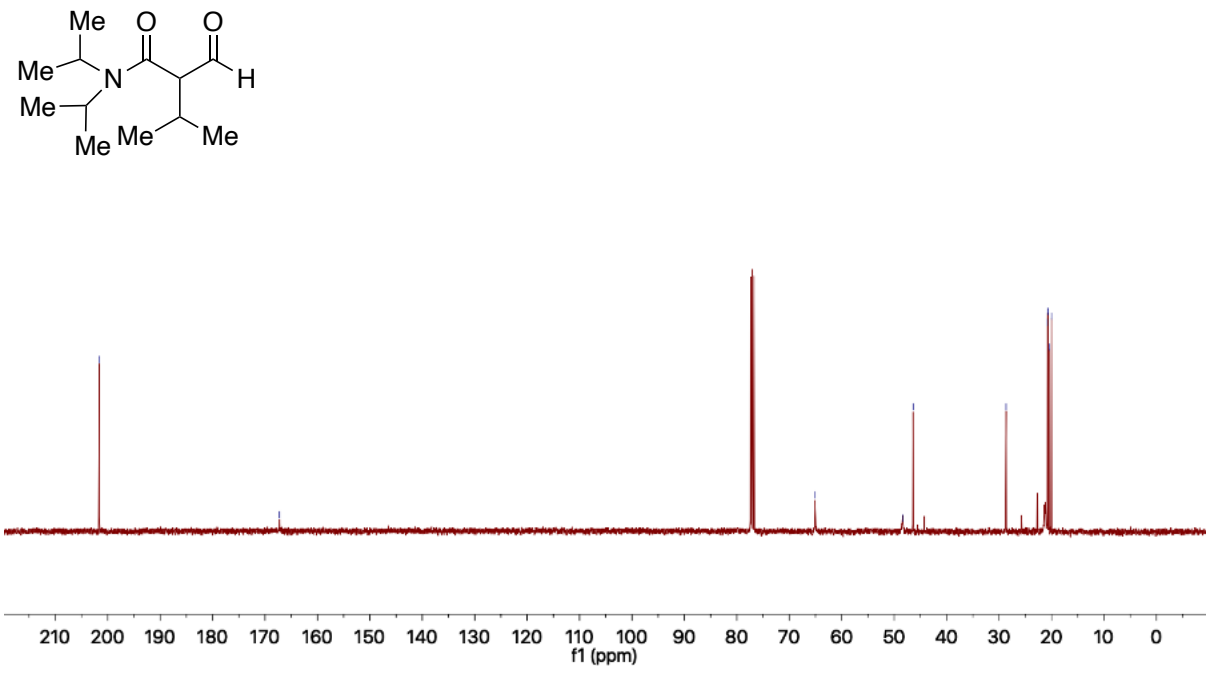


2-formyl-*N*,*N*-diisopropyl-3-methylbutanamide, 65o

^{1}H-NMR (400 MHz, $CDCl_3$)



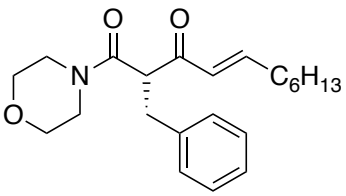
^{13}C-NMR (100 MHz, $CDCl_3$)

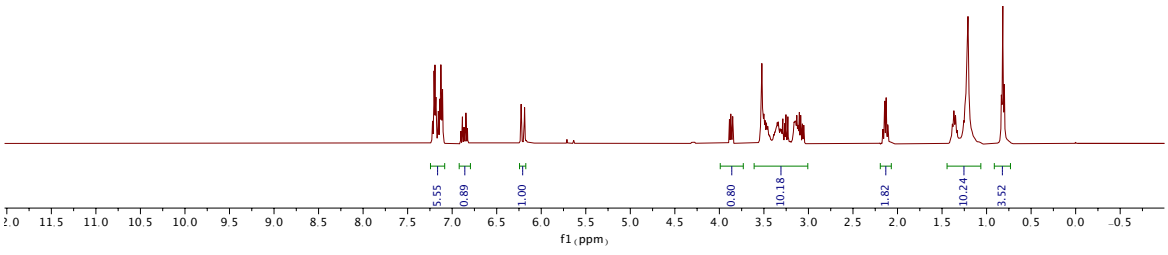


(*S*,*E*)-2-benzyl-1-morpholinoundec-4-ene-1,3-dione, 66a



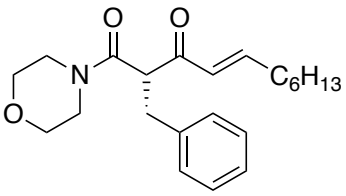
^{1}H-NMR (400 MHz, $CDCl_3$)

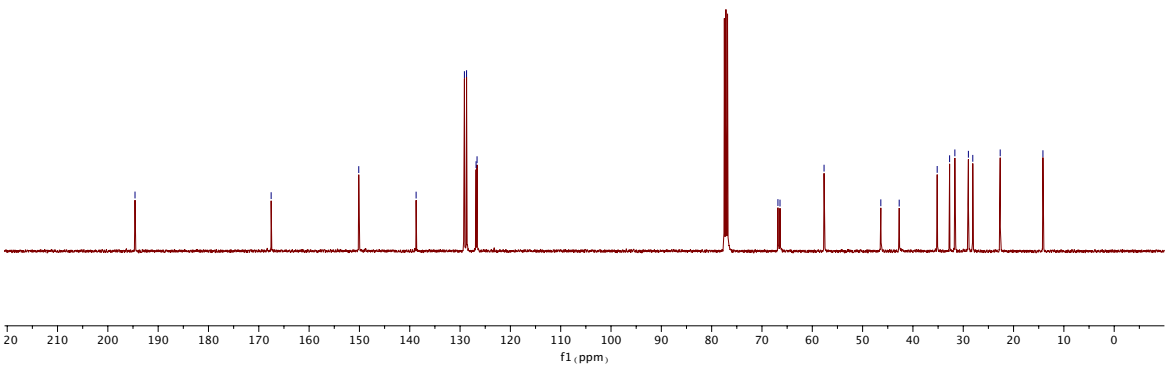






^{13}C-NMR (100 MHz, $CDCl_3$)

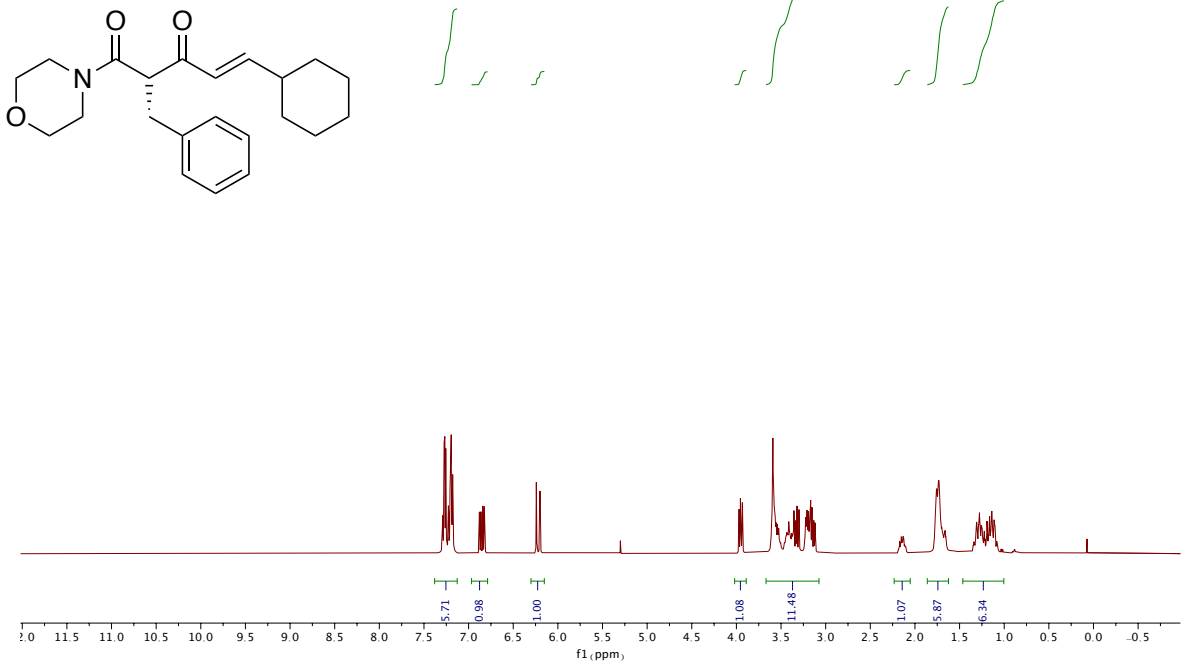




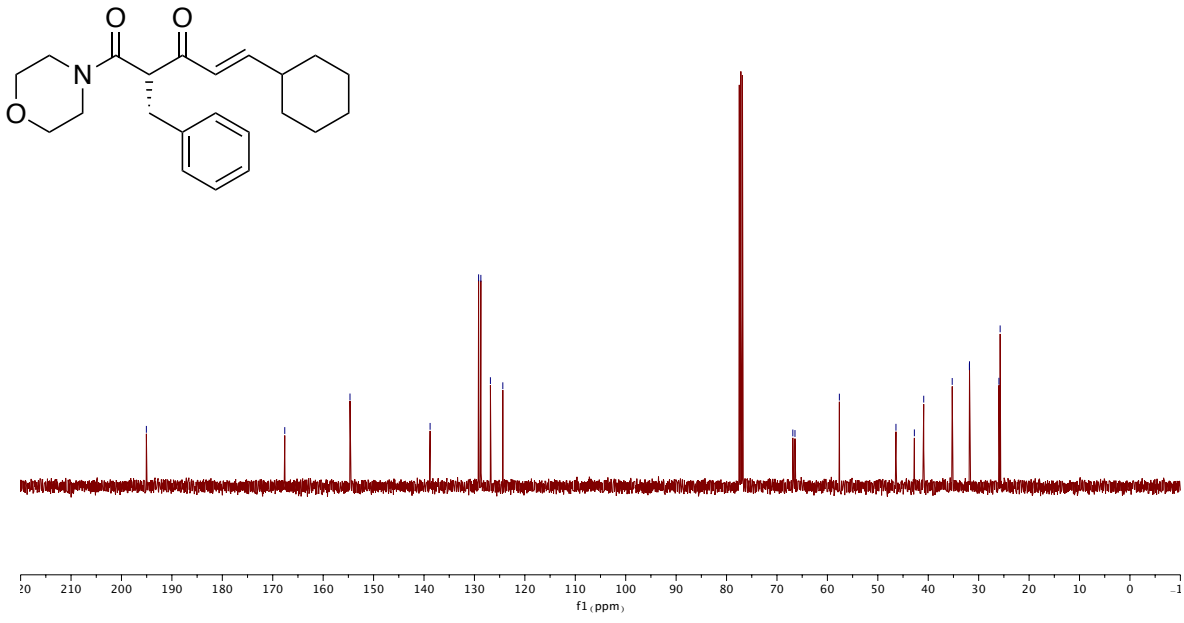
(*S*,*E*)-2-benzyl-5-cyclohexyl-1-morpholinopent-4-ene-1,3-dione, 66b



^{1}H-NMR (400 MHz, $CDCl_3$)



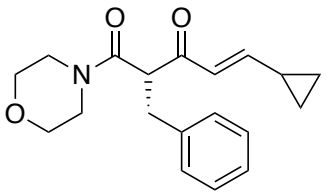
^{13}C-NMR (100 MHz, $CDCl_3$)

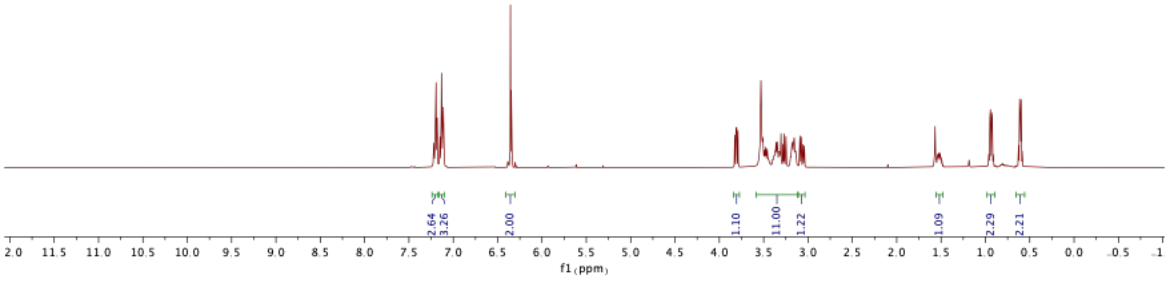


(*S*,*E*)-2-benzyl-5-cyclopropyl-1-morpholinopent-4-ene-1,3-dione, 66c



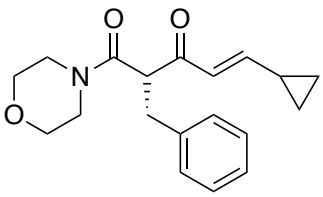
^{1}H-NMR (400 MHz, $CDCl_3$)







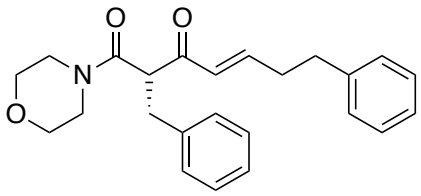
^{13}C-NMR (100 MHz, $CDCl_3$)

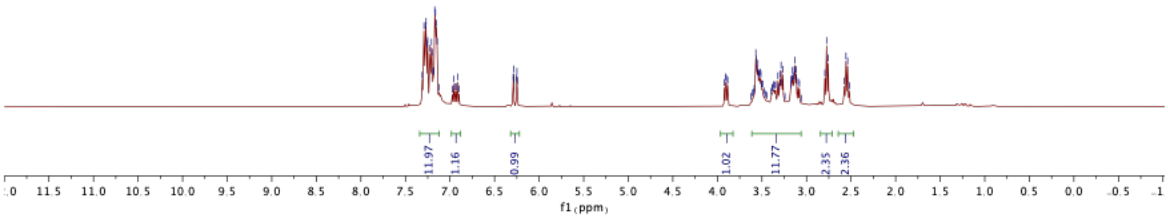


(*S*,*E*)-2-benzyl-1-morpholino-7-phenylhept-4-ene-1,3-dione, 66d



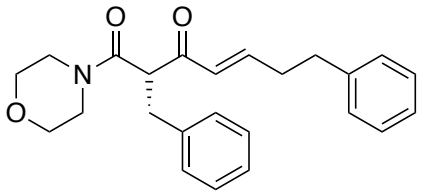
^{1}H-NMR (400 MHz, $CDCl_3$)







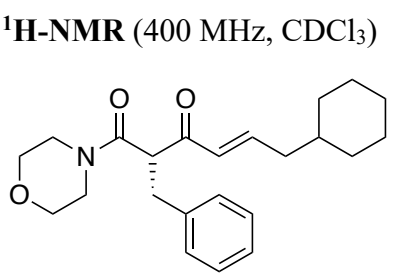
^{13}C-NMR (100 MHz, $CDCl_3$)

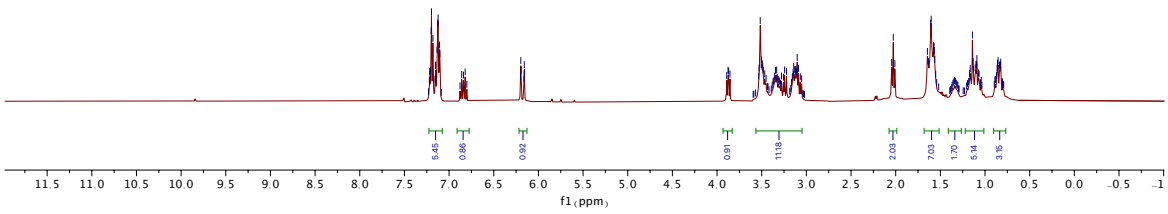


(*S*,*E*)-2-benzyl-6-cyclohexyl-1-morpholinohex-4-ene-1,3-dione, 66e



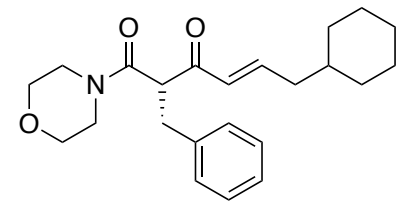
^{1}H-NMR (400 MHz, $CDCl_3$)

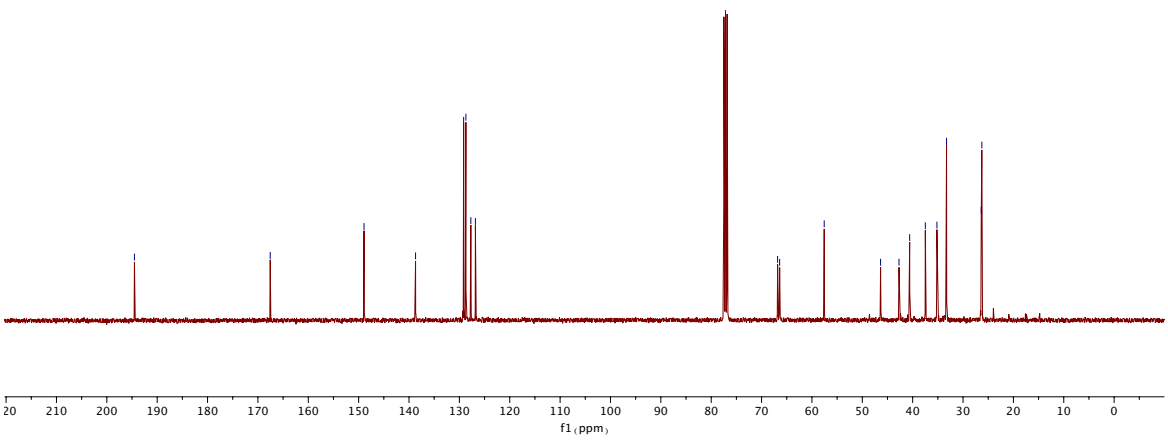




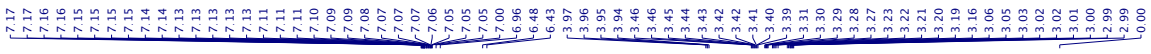


^{13}C-NMR (100 MHz, $CDCl_3$)

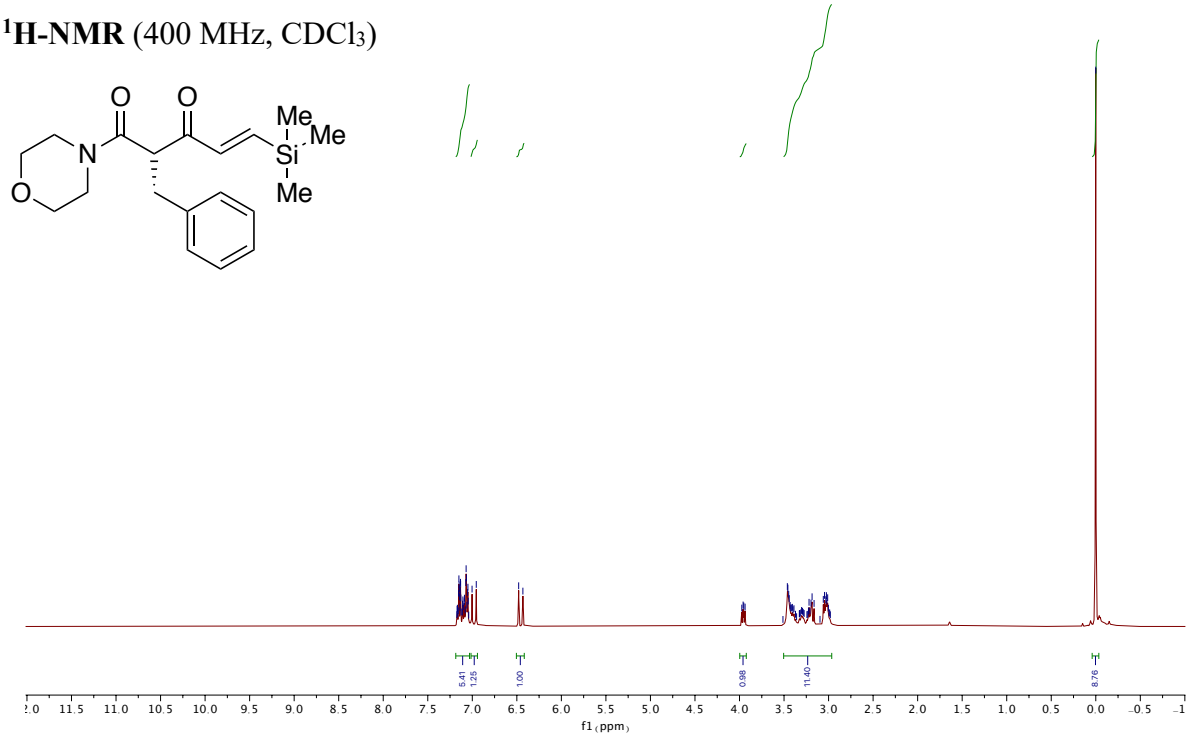




(*S*,*E*)-2-benzyl-1-morpholino-5-(trimethylsilyl)pent-4-ene-1,3-dione, 66f

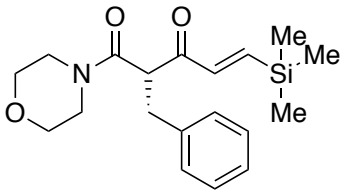


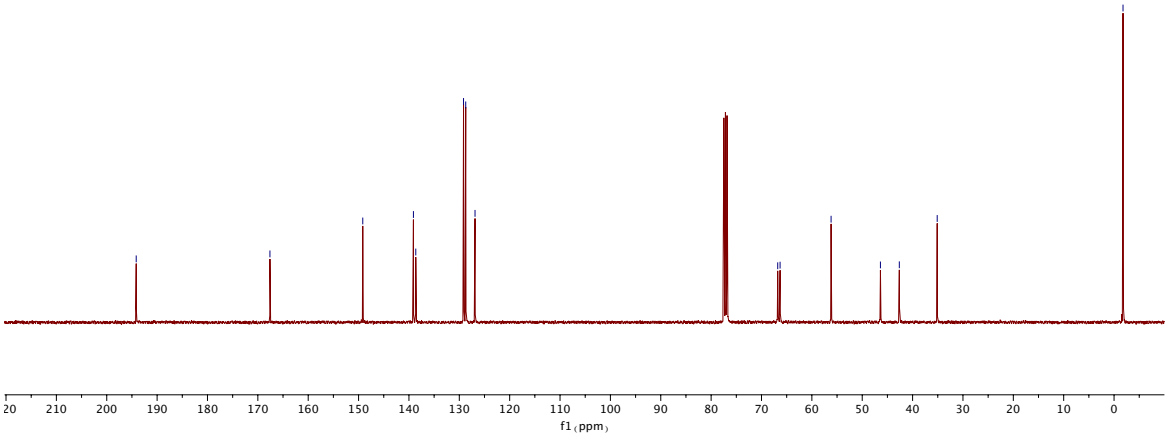
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

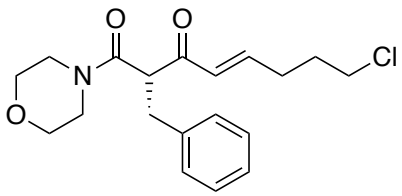


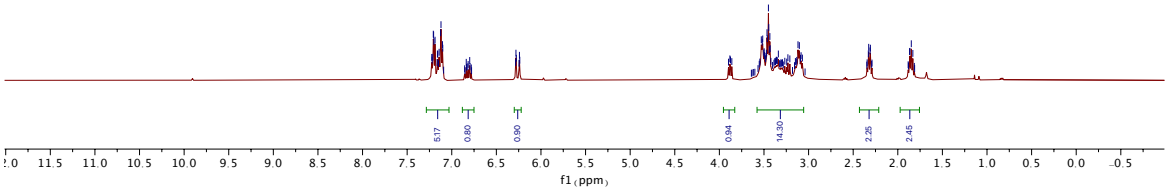


(*S*,*E*)-2-benzyl-8-chloro-1-morpholinooct-4-ene-1,3-dione, 66g



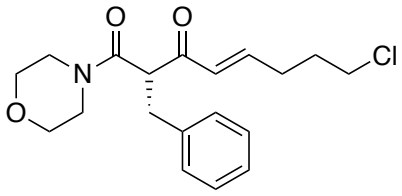
^{1}H-NMR (400 MHz, $CDCl_3$)

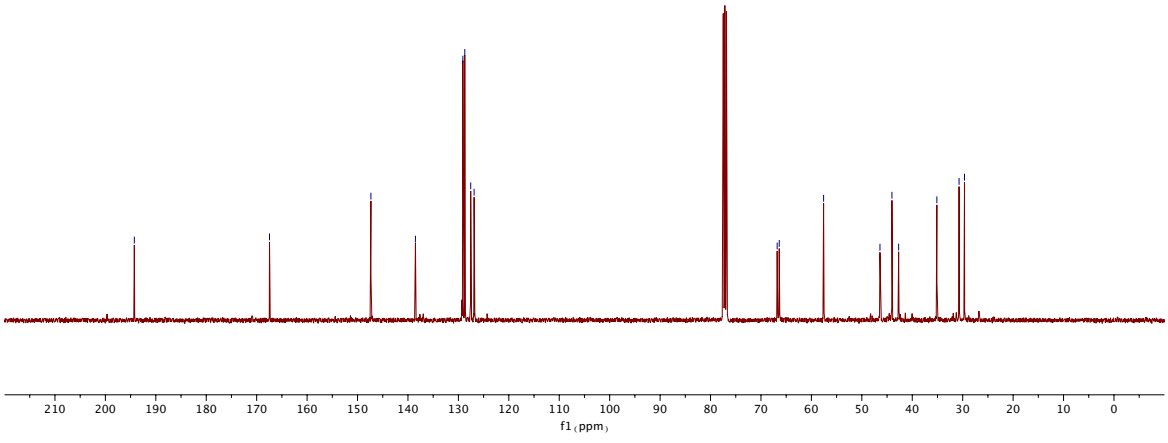






^{13}C-NMR (100 MHz, $CDCl_3$)

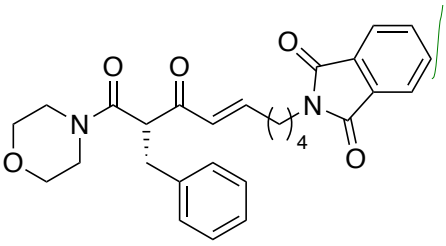


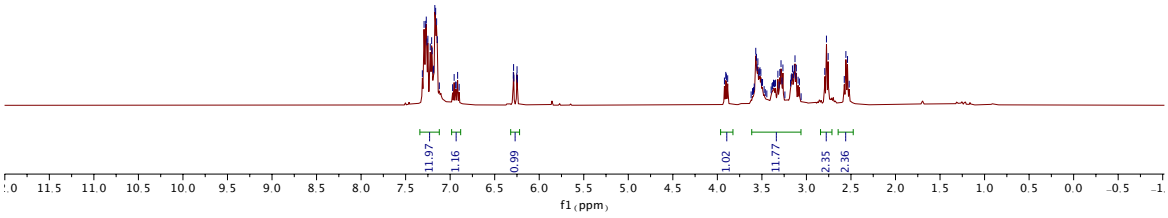


(*S*,*E*)-2-(8-benzyl-9-morpholino-7,9-dioxonon-5-en-1-yl)isoindoline-1,3-dione, 66h



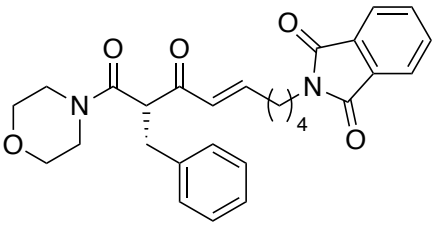
^{1}H-NMR (400 MHz, $CDCl_3$)

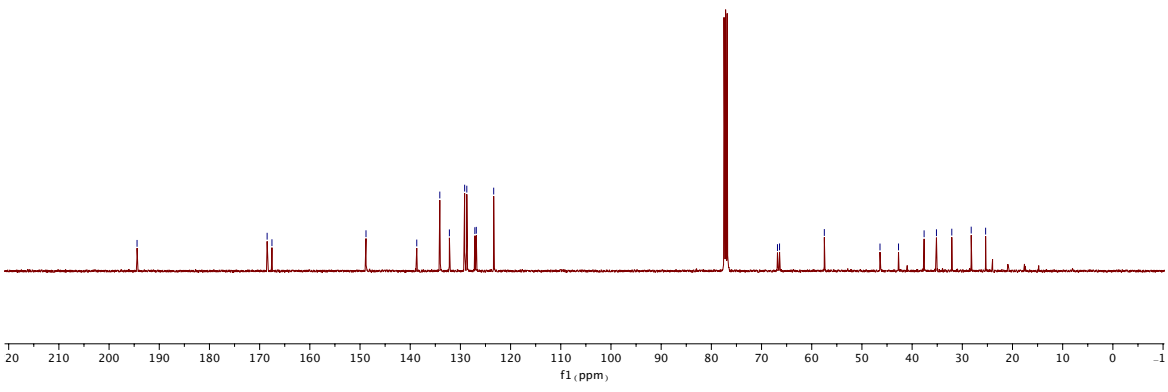




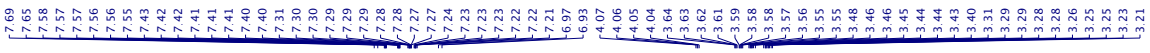


^{13}C-NMR (100 MHz, $CDCl_3$)

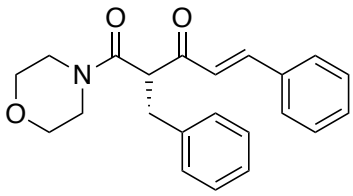


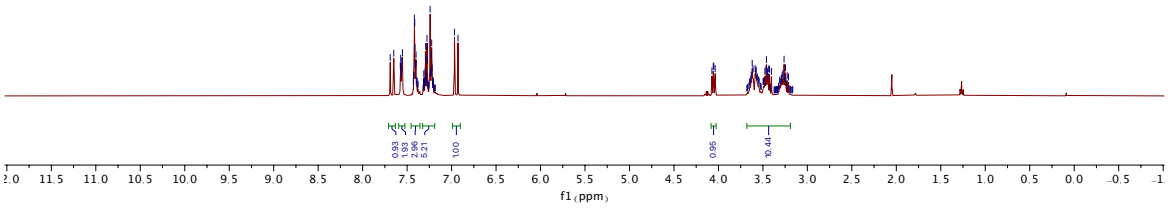


(*S*,*E*)-2-benzyl-1-morpholino-5-phenylpent-4-ene-1,3-dione, 66i



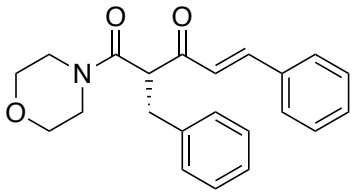
^{1}H-NMR (400 MHz, $CDCl_3$)

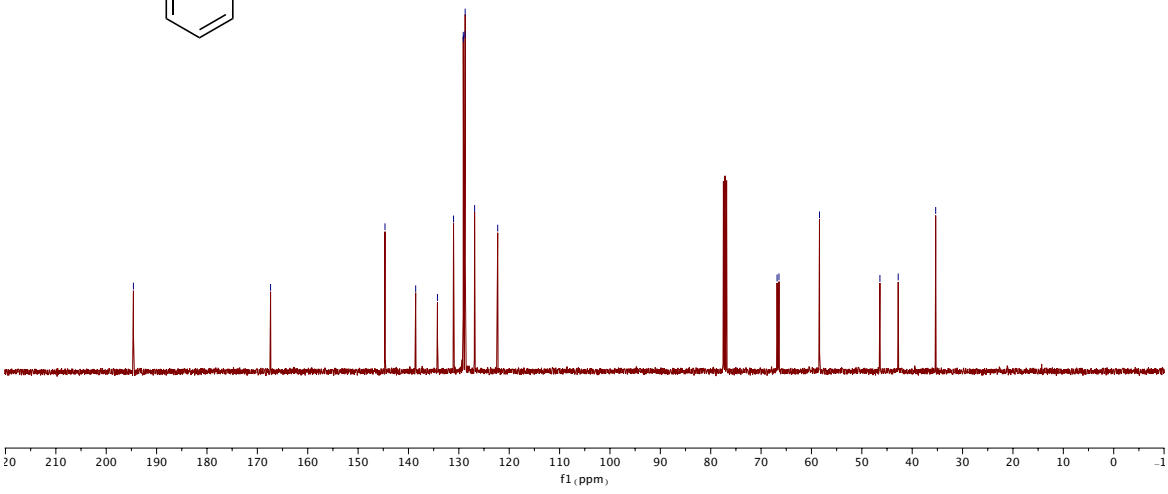






^{13}C-NMR (100 MHz, $CDCl_3$)

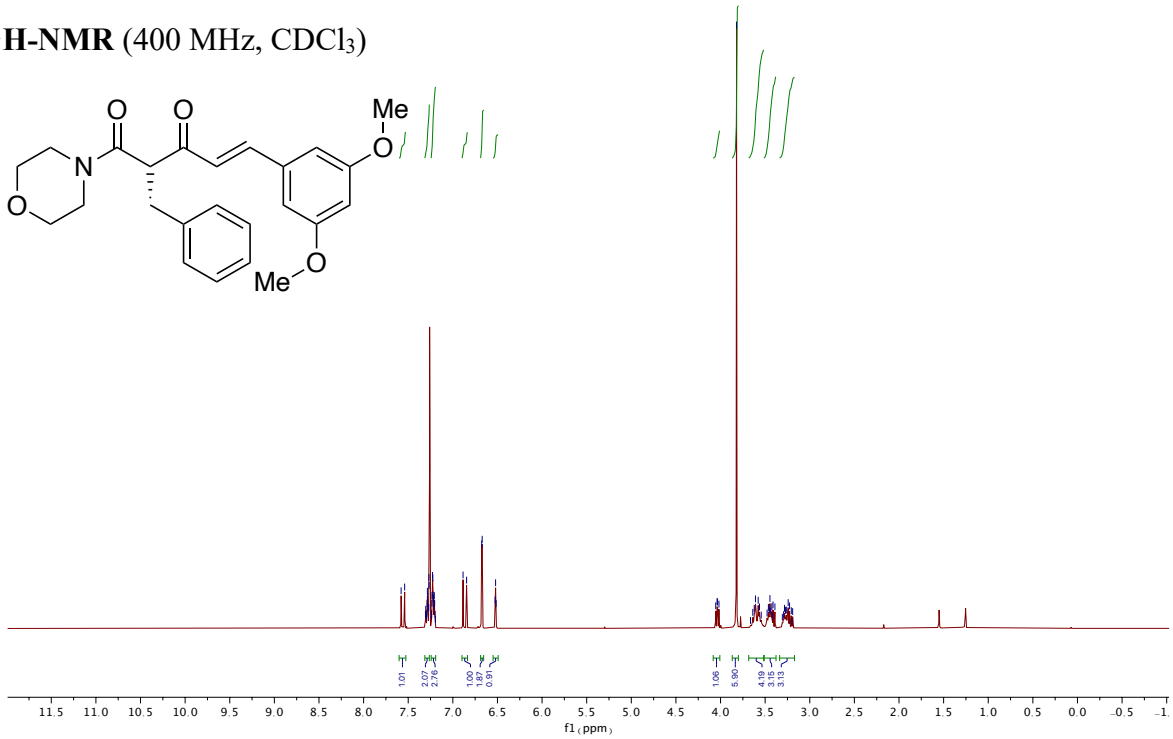


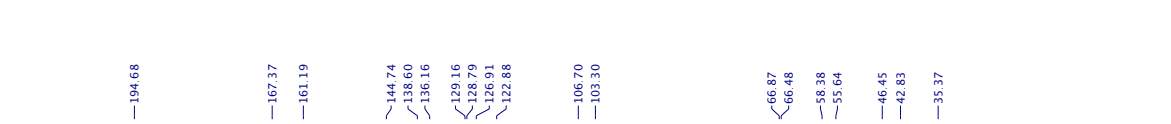


(*S*,*E*)-2-benzyl-5-(3,5-dimethoxyphenyl)-1-morpholinopent-4-ene-1,3-dione, 66j

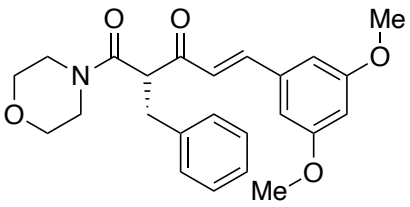


^{1}H-NMR (400 MHz, $CDCl_3$)





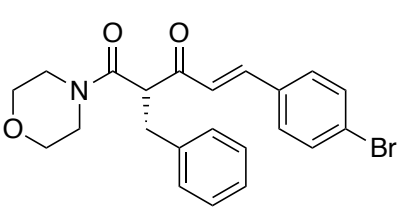
^{13}C-NMR (100 MHz, $CDCl_3$)

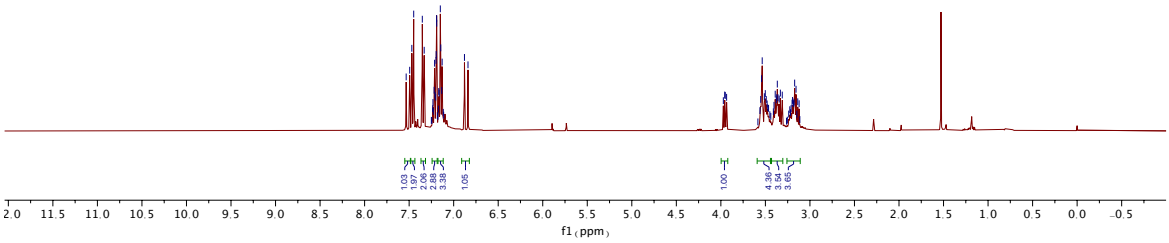


(*S*,*E*)-2-benzyl-5-(4-bromophenyl)-1-morpholinopent-4-ene-1,3-dione, 66k



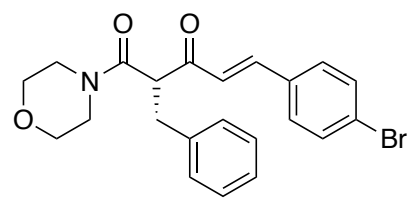
^{1}H-NMR (400 MHz, $CDCl_3$)







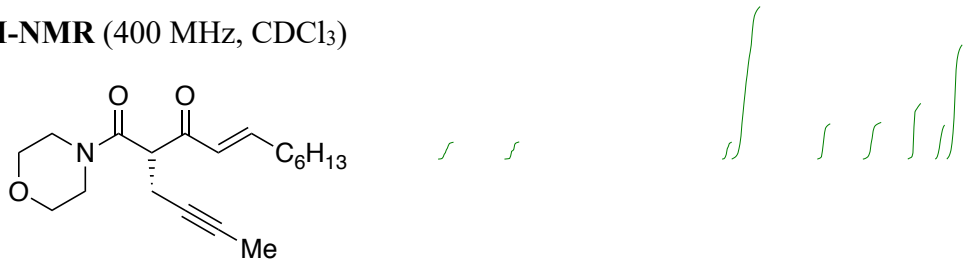
^{13}C-NMR (100 MHz, $CDCl_3$)

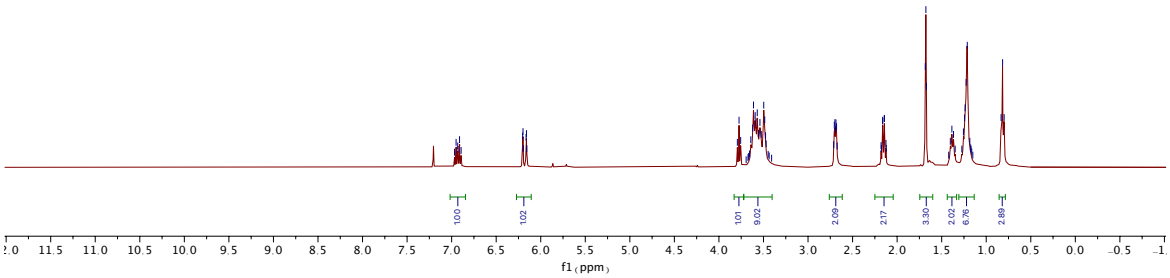


(*S*,*E*)-2-(but-2-yn-1-yl)-1-morpholinoundec-4-ene-1,3-dione, 66l

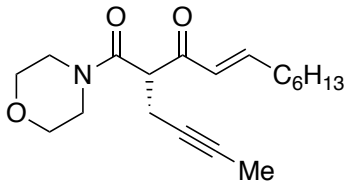


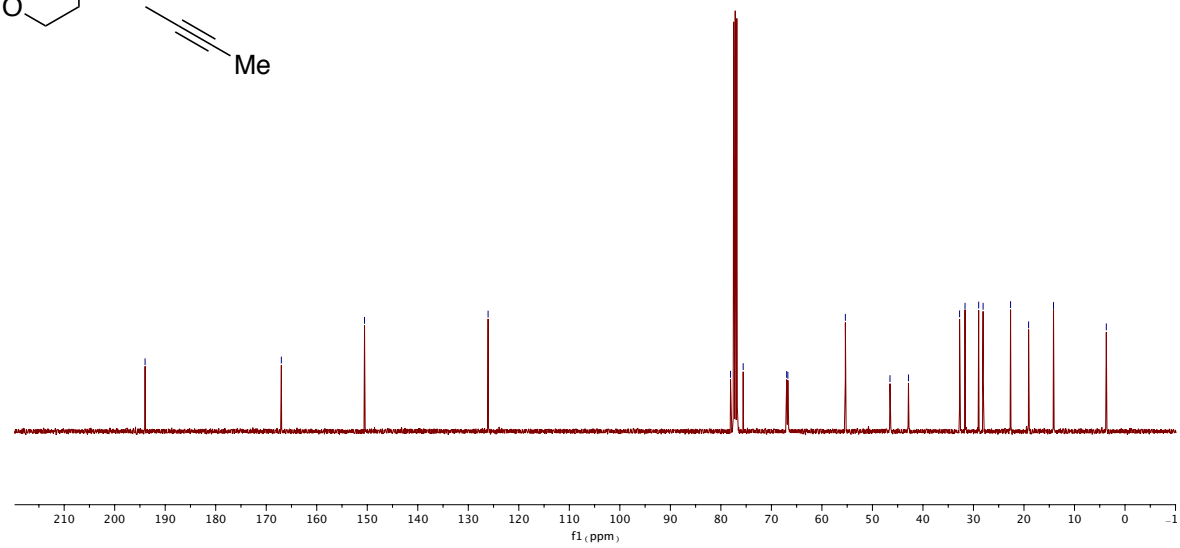
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

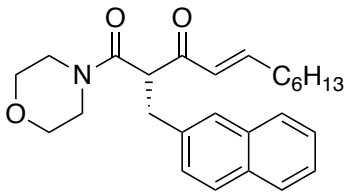




(*S*,*E*)-1-morpholino-2-(naphthalen-2-ylmethyl)undec-4-ene-1,3-dione, 66m

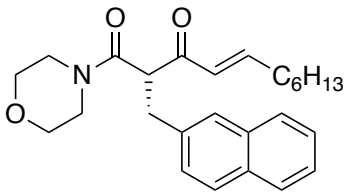


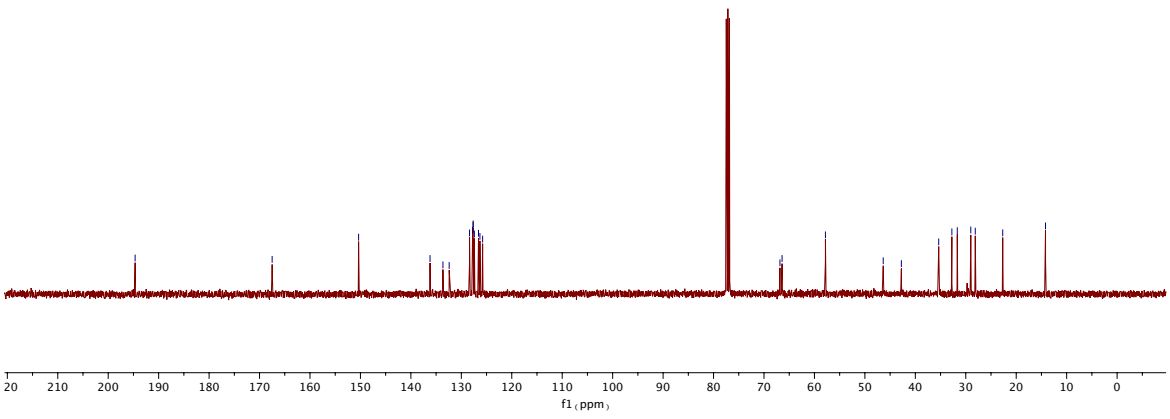
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

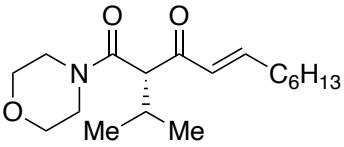


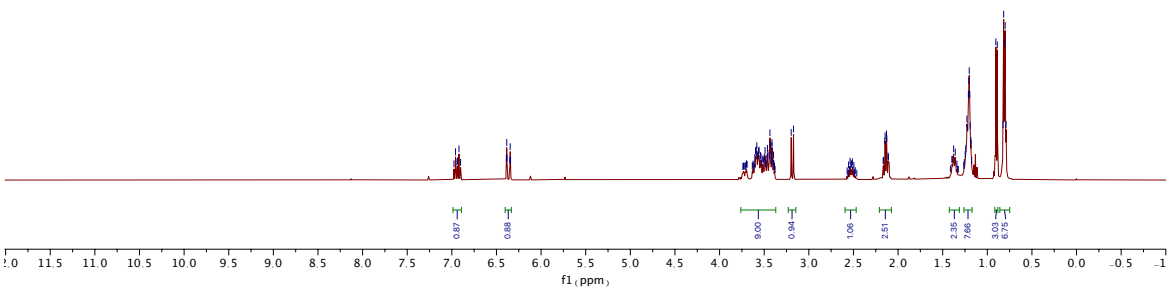


(*S*,*E*)-2-isopropyl-1-morpholinoundec-4-ene-1,3-dione, 66n



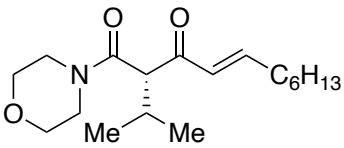
^{1}H-NMR (400 MHz, $CDCl_3$)

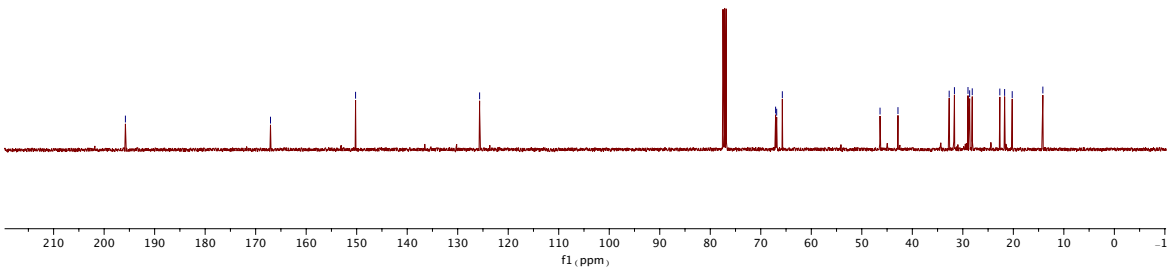






^{13}C-NMR (100 MHz, $CDCl_3$)

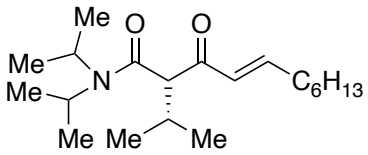


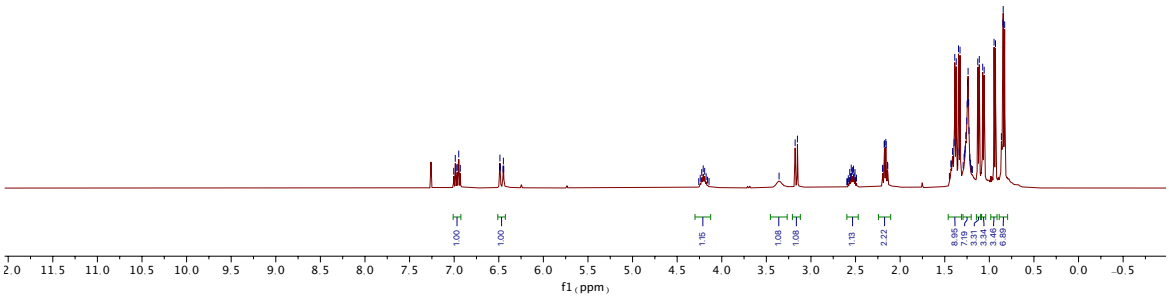


(*S*,*E*)-*N*,*N*,2-triisopropyl-3-oxoundec-4-enamide, 66o



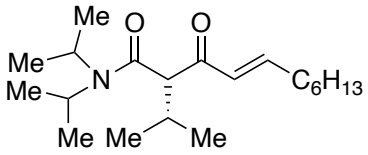
^{1}H-NMR (400 MHz, $CDCl_3$)

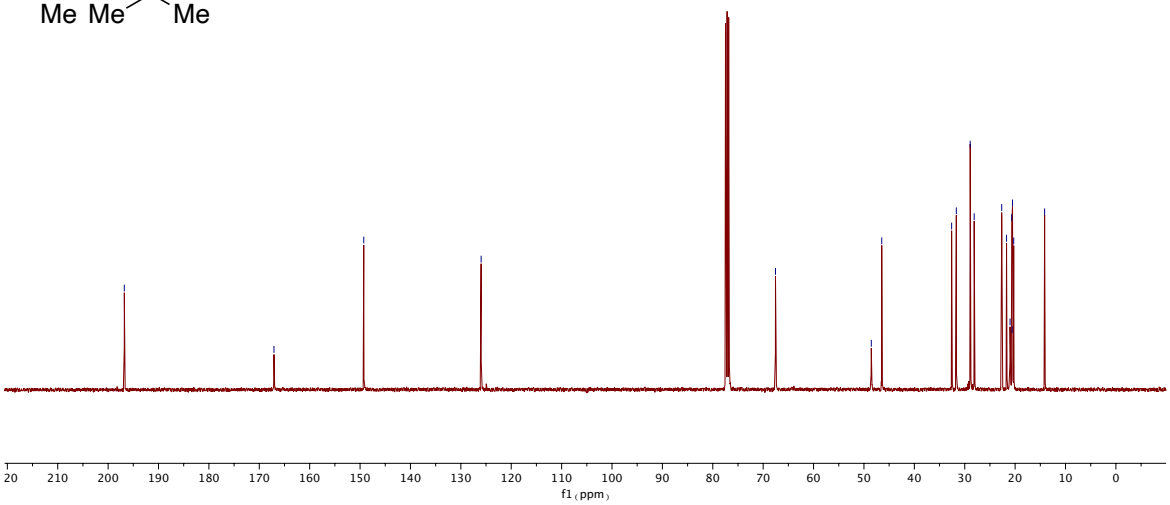






^{13}C-NMR (100 MHz, $CDCl_3$)

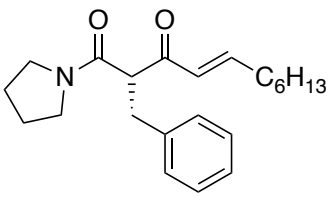




(*S*,*E*)-2-benzyl-1-(pyrrolidin-1-yl)undec-4-ene-1,3-dione, 66p

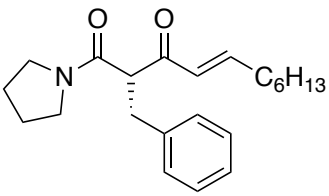


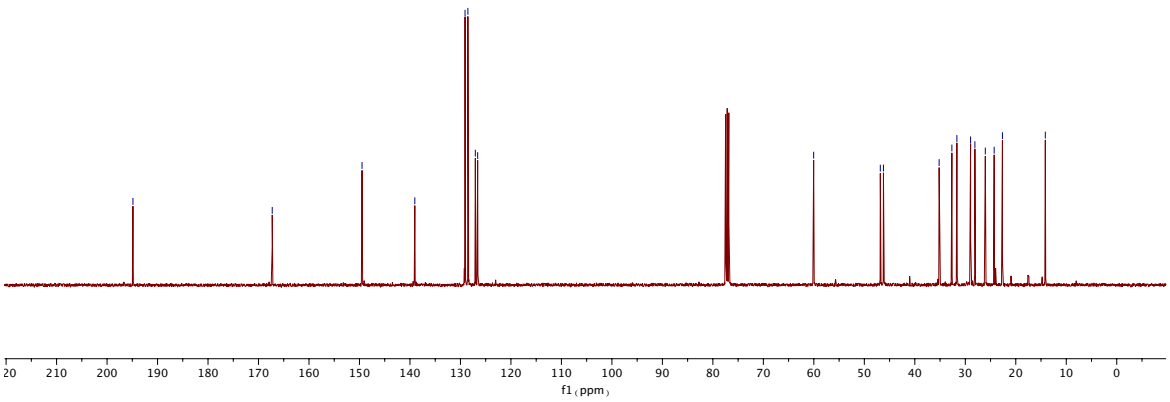
^{1}H-NMR (400 MHz, $CDCl_3$)





^{13}C-NMR (100 MHz, $CDCl_3$)

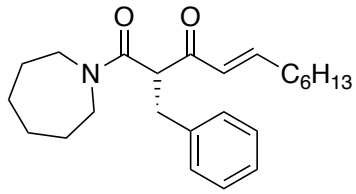


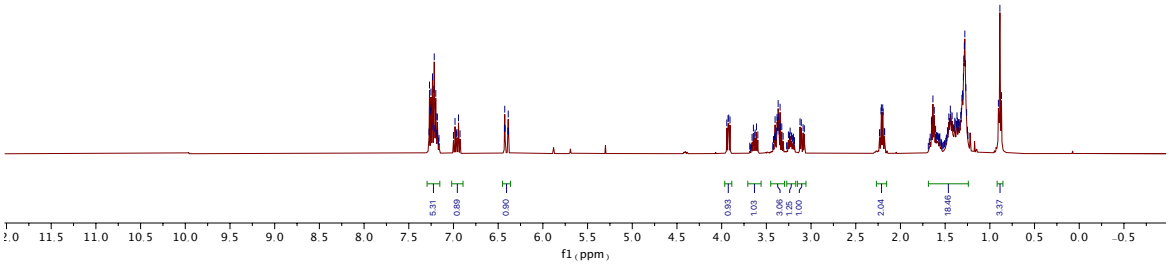


(*S*,*E*)-1-(azepan-1-yl)-2-benzylundec-4-ene-1,3-dione, 66q



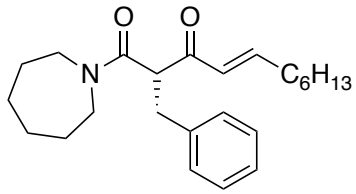
^{1}H-NMR (400 MHz, $CDCl_3$)

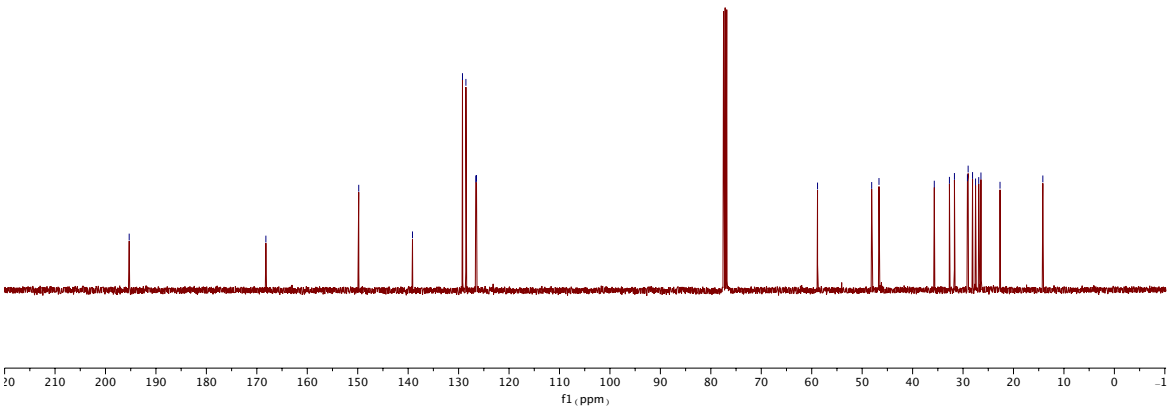






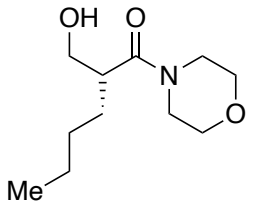
^{13}C-NMR (100 MHz, $CDCl_3$)

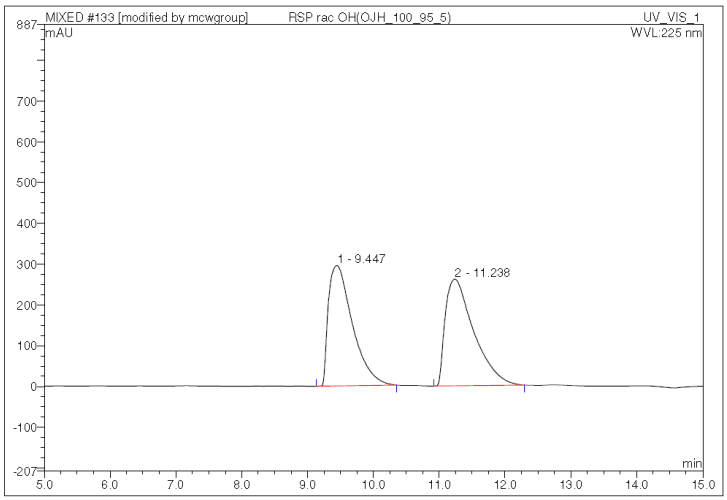




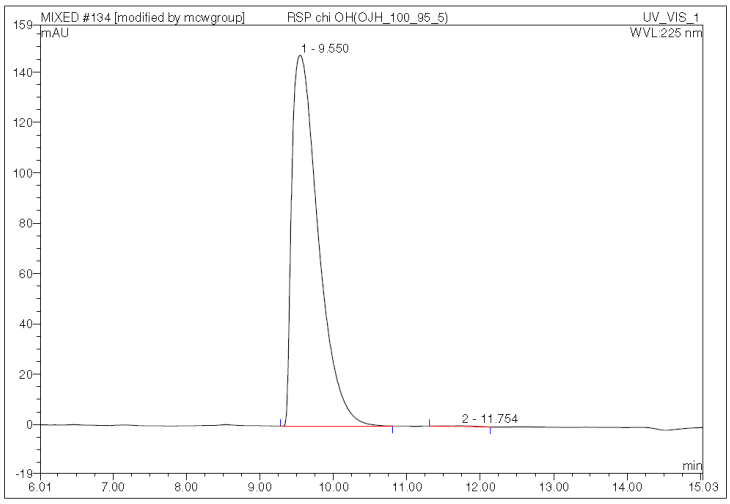
HPLC traces for chiral products and their racemates

(*R*)-2-(Hydroxymethyl)-1-morpholinohexan-1-one, 62



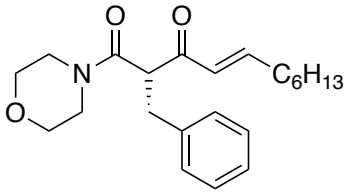


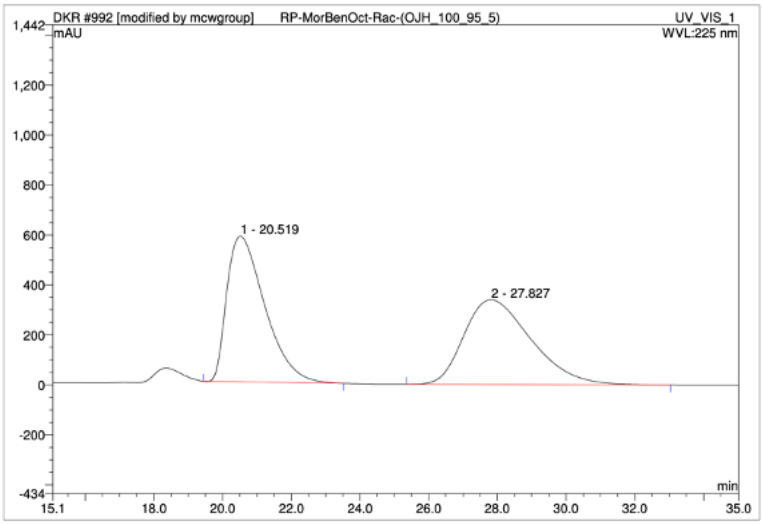
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.45	n.a.	294.670	124.801	48.77	n.a.	BMB*
2	11.24	n.a.	261.142	131.099	51.23	n.a.	BMB*
Total:			555.812	255.900	100.00	0.000	



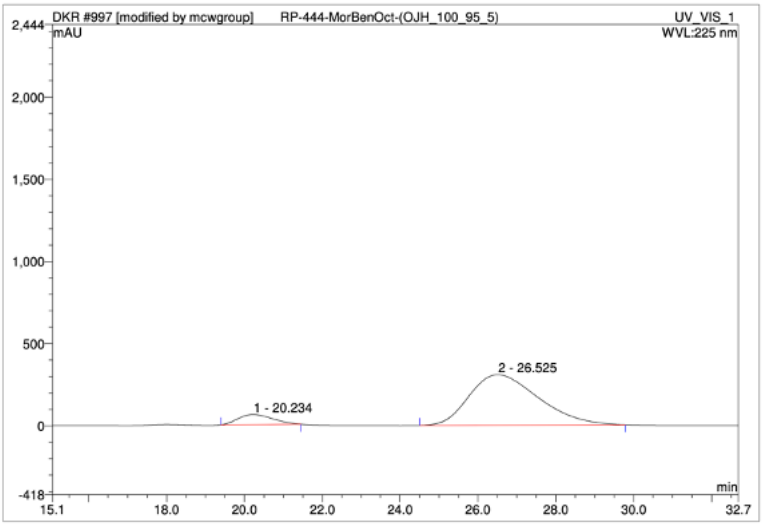
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.55	n.a.	147.186	61.420	99.76	n.a.	BMB*
2	11.75	n.a.	0.328	0.149	0.24	n.a.	BMB*
Total:			147.514	61.569	100.00	0.000	

(*S*,*E*)-2-benzyl-1-morpholinoundec-4-ene-1,3-dione, 66a



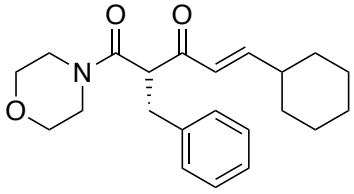


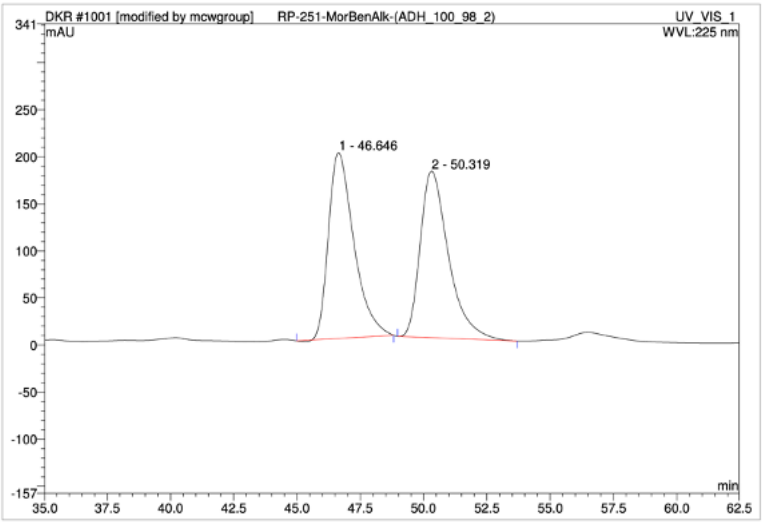
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.52	n.a.	583.262	746.655	49.38	n.a.	BMB*
2	27.83	n.a.	338.584	765.471	50.62	n.a.	BMB*
Total:			921.846	1512.126	100.00	0.000	



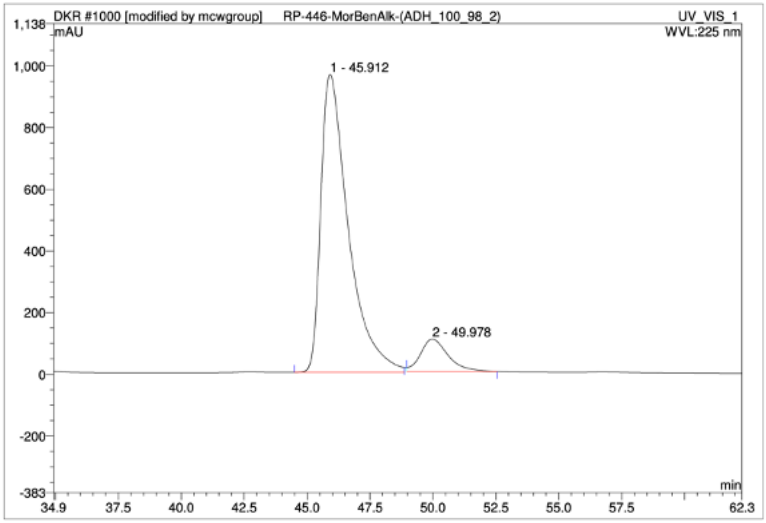
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.23	n.a.	60.954	62.538	9.03	n.a.	BMB*
2	26.53	n.a.	307.105	630.377	90.97	n.a.	BMB*
Total:			368.059	692.914	100.00	0.000	

(*S*,*E*)-2-benzyl-5-cyclohexyl-1-morpholinopent-4-ene-1,3-dione, 66b



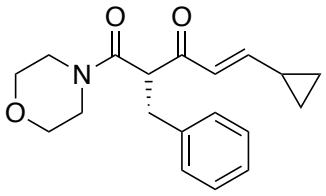


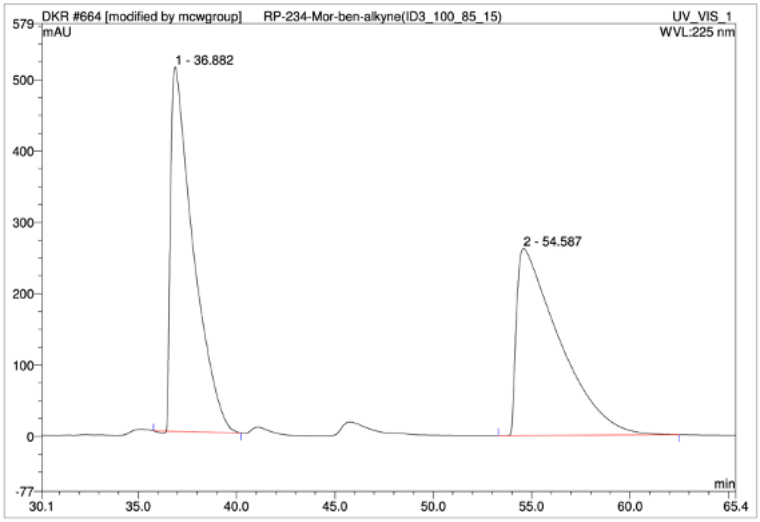
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	46.65	n.a.	197.529	230.225	50.13	n.a.	BMB*
2	50.32	n.a.	176.984	229.001	49.87	n.a.	BMB*
Total:			374.513	459.226	100.00	0.000	



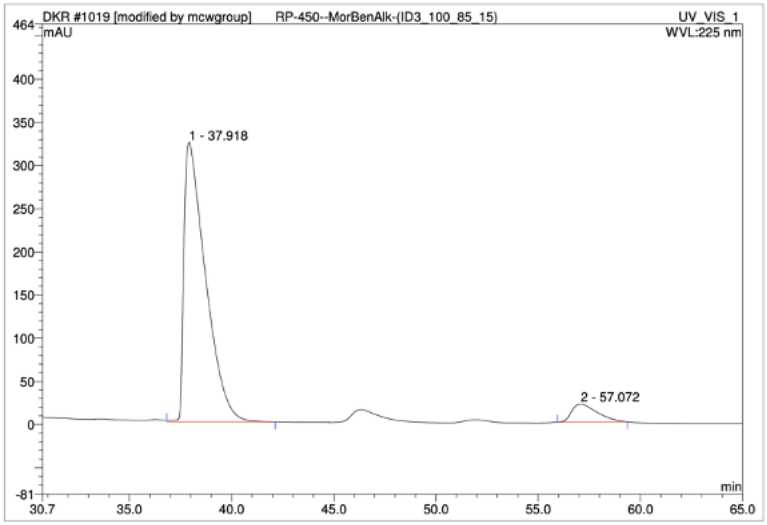
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	45.91	n.a.	966.554	1226.343	90.13	n.a.	BM *
2	49.98	n.a.	105.585	134.273	9.87	n.a.	MB*
Total:			1072.140	1360.616	100.00	0.000	

(*S*,*E*)-2-benzyl-5-cyclopropyl-1-morpholinopent-4-ene-1,3-dione, 66c



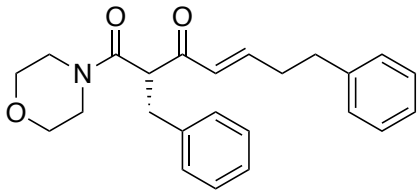


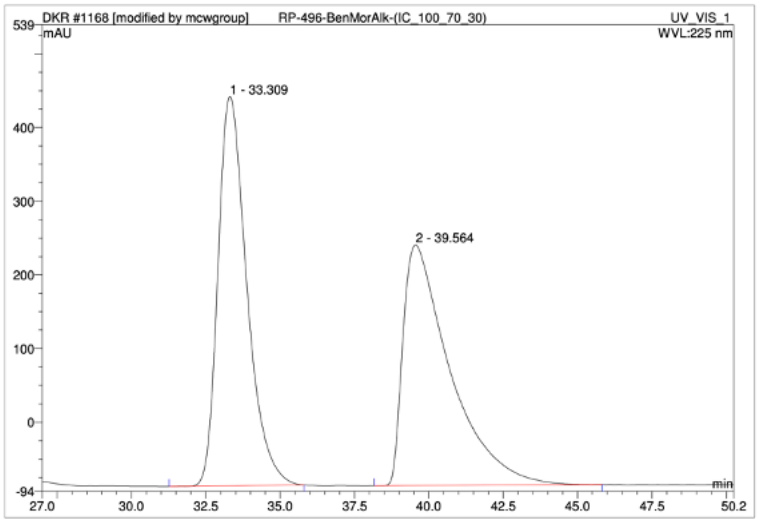
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	36.88	n.a.	511.127	679.283	50.67	n.a.	BMB*
2	54.59	n.a.	262.328	661.337	49.33	n.a.	BMB*
Total:			773.454	1340.619	100.00	0.000	



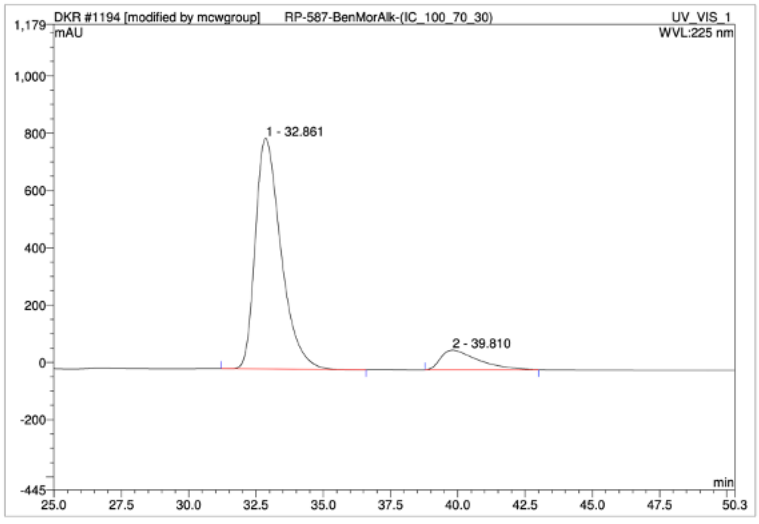
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37.92	n.a.	323.984	395.256	93.00	n.a.	MB*
2	57.07	n.a.	20.734	29.754	7.00	n.a.	BMB*
Total:			344.718	425.010	100.00	0.000	

(*S*,*E*)-2-benzyl-1-morpholino-7-phenylhept-4-ene-1,3-dione, 66d



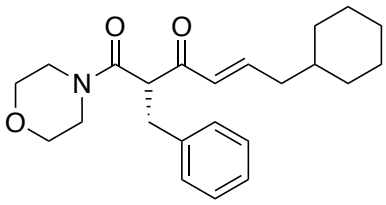


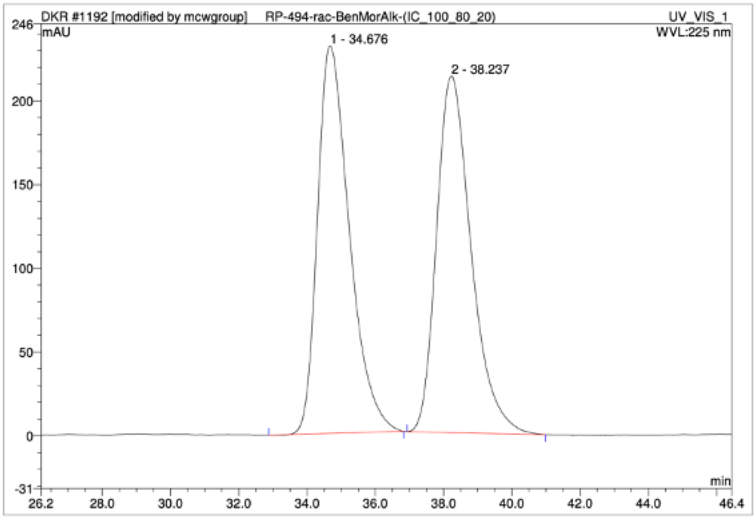
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	33.31	n.a.	528.088	593.716	49.80	n.a.	BMB*
2	39.56	n.a.	326.432	598.485	50.20	n.a.	BMB*
Total:			854.520	1192.200	100.00	0.000	



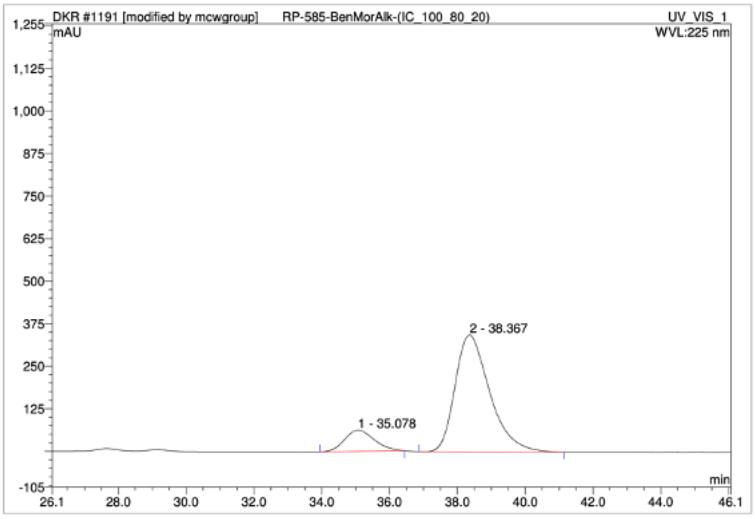
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.86	n.a.	804.085	887.190	89.12	n.a.	BMB*
2	39.81	n.a.	67.955	108.264	10.88	n.a.	BMB*
Total:			872.040	995.455	100.00	0.000	

(*S*,*E*)-2-benzyl-6-cyclohexyl-1-morpholinohex-4-ene-1,3-dione, 66e



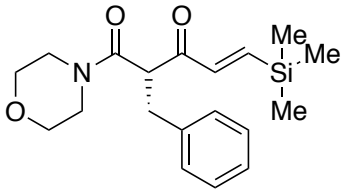


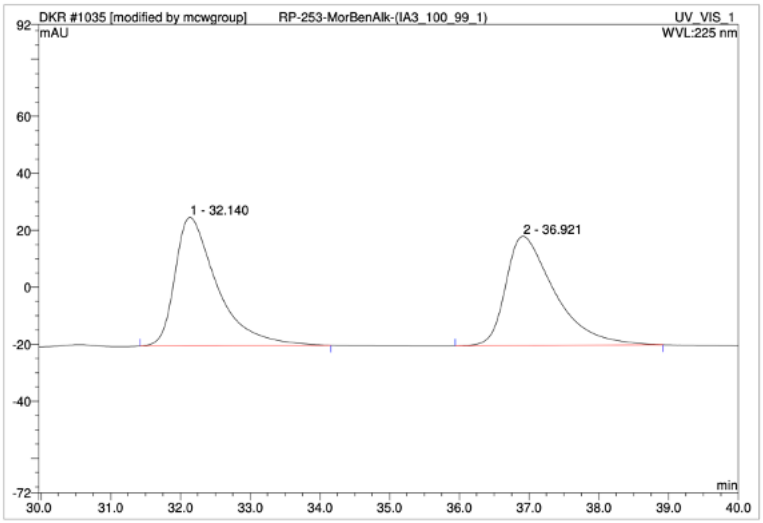
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	34.68	n.a.	231.424	250.417	50.05	n.a.	BMB*
2	38.24	n.a.	212.908	249.910	49.95	n.a.	BMB*
Total:			444.332	500.327	100.00	0.000	



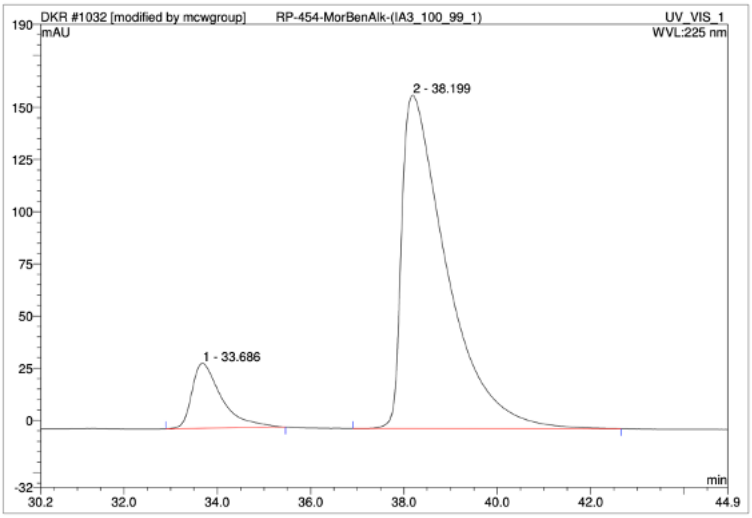
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	35.08	n.a.	62.192	63.234	13.47	n.a.	BMB*
2	38.37	n.a.	343.055	406.310	86.53	n.a.	BMB*
Total:			405.248	469.544	100.00	0.000	

(*S*,*E*)-2-benzyl-1-morpholino-5-(trimethylsilyl)pent-4-ene-1,3-dione, 66f



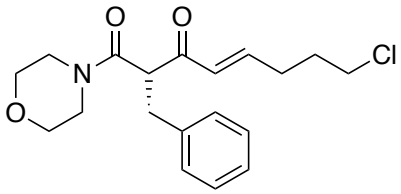


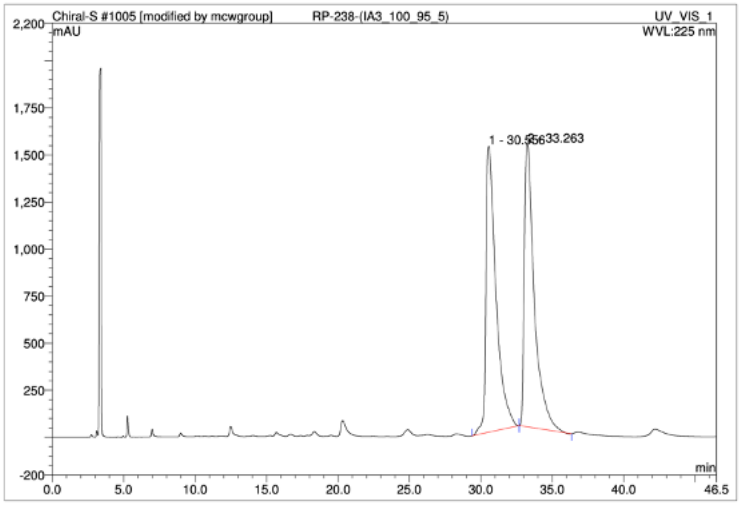
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	32.14	n.a.	45.071	31.494	50.30	n.a.	BMB*
2	36.92	n.a.	38.370	31.123	49.70	n.a.	BMB*
Total:			83.440	62.617	100.00	0.000	



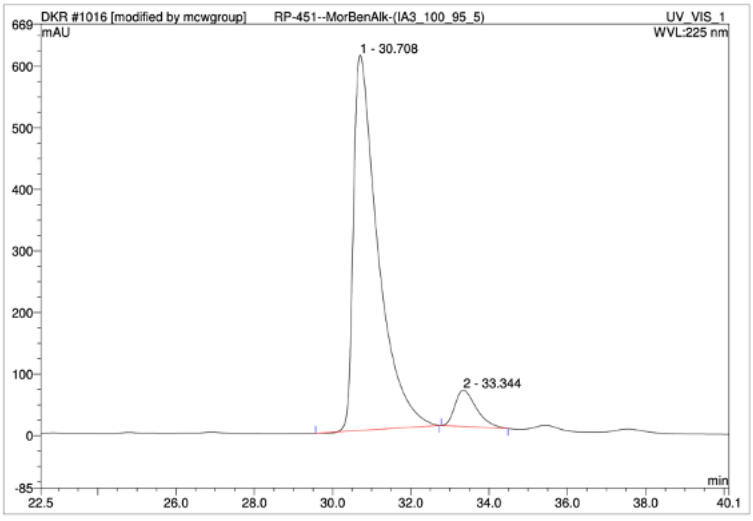
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	33.69	n.a.	31.046	22.930	11.42	n.a.	BMB*
2	38.20	n.a.	159.680	177.845	88.58	n.a.	BMB*
Total:			190.726	200.775	100.00	0.000	

(*S*,*E*)-2-benzyl-8-chloro-1-morpholinooct-4-ene-1,3-dione, 66g



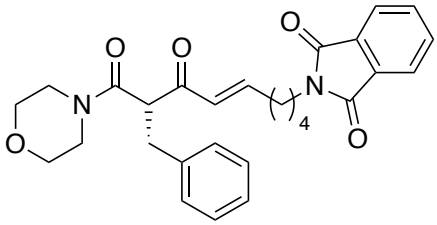


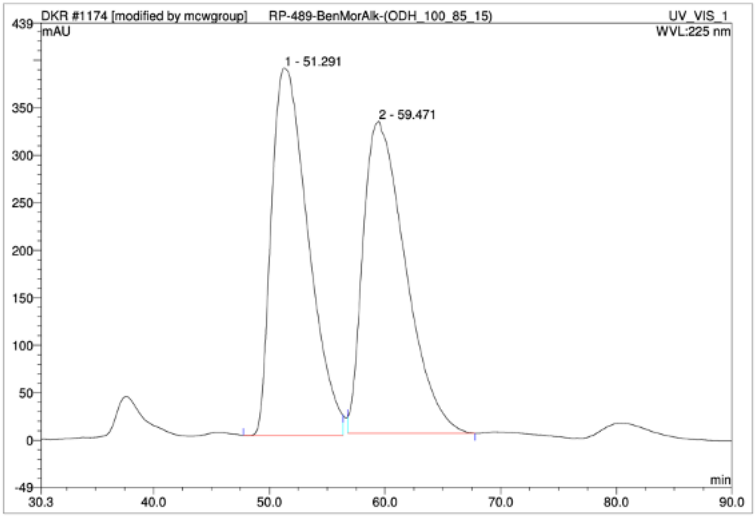
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	30.56	n.a.	1519.195	1246.190	50.44	n.a.	BMb*
2	33.26	n.a.	1499.826	1224.598	49.56	n.a.	bMB*
Total:			3019.021	2470.788	100.00	0.000	



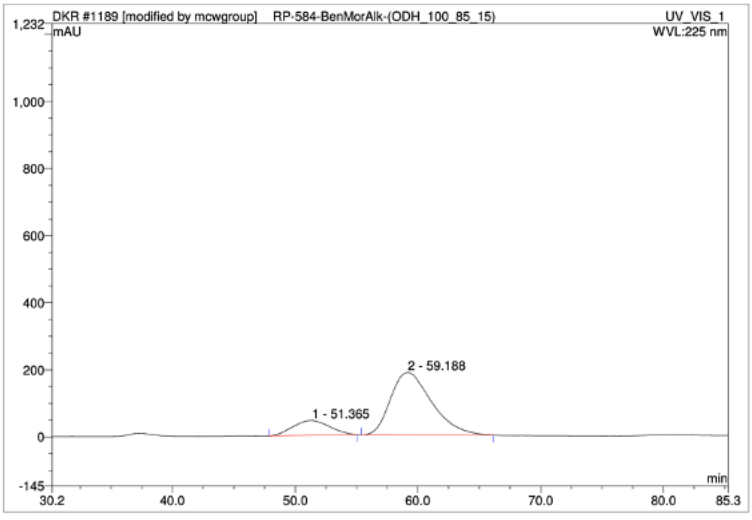
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	30.71	n.a.	609.645	444.614	92.24	n.a.	BMB*
2	33.34	n.a.	59.124	37.387	7.76	n.a.	BMB*
Total:			668.769	482.002	100.00	0.000	

(*S*,*E*)-2-(8-benzyl-9-morpholino-7,9-dioxonon-5-en-1-yl)isoindoline-1,3-dione, 66h



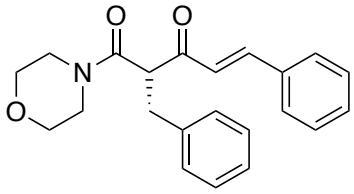


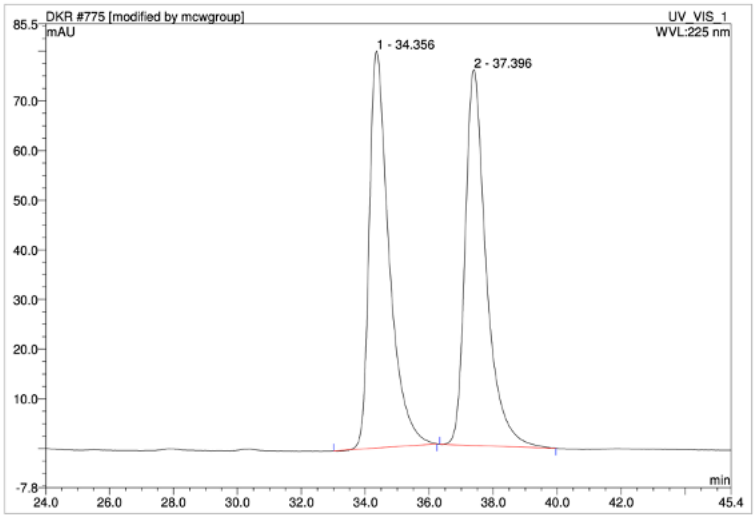
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	51.29	n.a.	386.500	1420.099	50.33	n.a.	BM *
2	59.47	n.a.	328.445	1401.722	49.67	n.a.	MB*
Total:			714.945	2821.821	100.00	0.000	



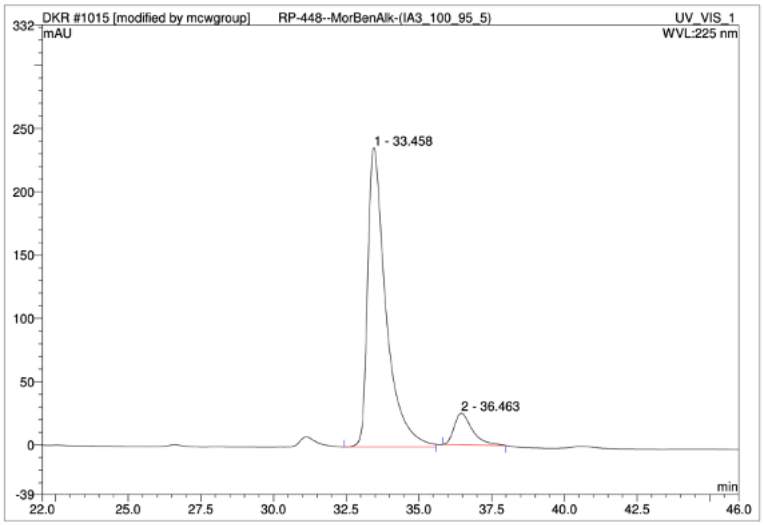
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	51.36	n.a.	43.869	152.580	17.41	n.a.	BMB*
2	59.19	n.a.	186.341	723.906	82.59	n.a.	BMB*
Total:			230.210	876.487	100.00	0.000	

(*S*,*E*)-2-benzyl-1-morpholino-5-phenylpent-4-ene-1,3-dione, 66i



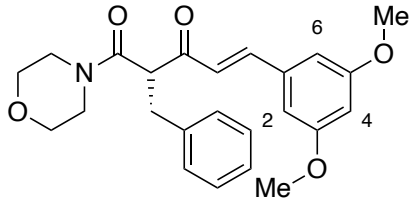


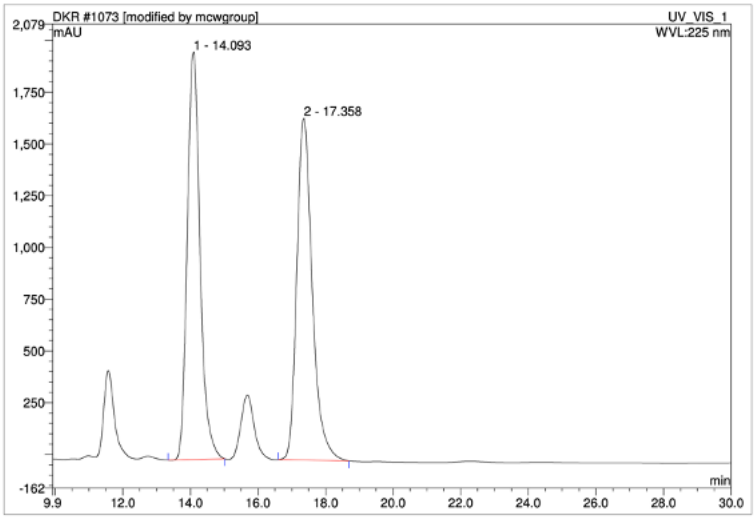
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	34.36	n.a.	79.918	57.524	49.98	n.a.	BMB*
2	37.40	n.a.	75.640	57.568	50.02	n.a.	BMB*
Total:			155.557	115.093	100.00	0.000	



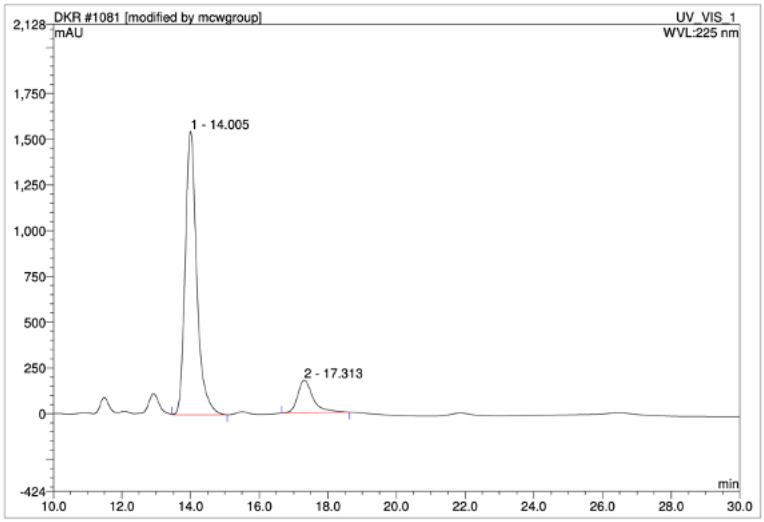
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	33.46	n.a.	236.451	173.378	90.55	n.a.	BM *
2	36.46	n.a.	24.957	18.099	9.45	n.a.	BMB*
Total:			261.408	191.477	100.00	0.000	

(*S*,*E*)-2-benzyl-5-(3,5-dimethoxyphenyl)-1-morpholinopent-4-ene-1,3-dione, 66j



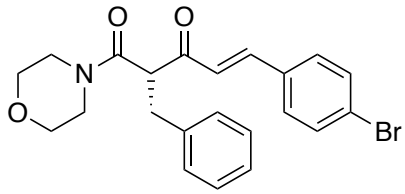


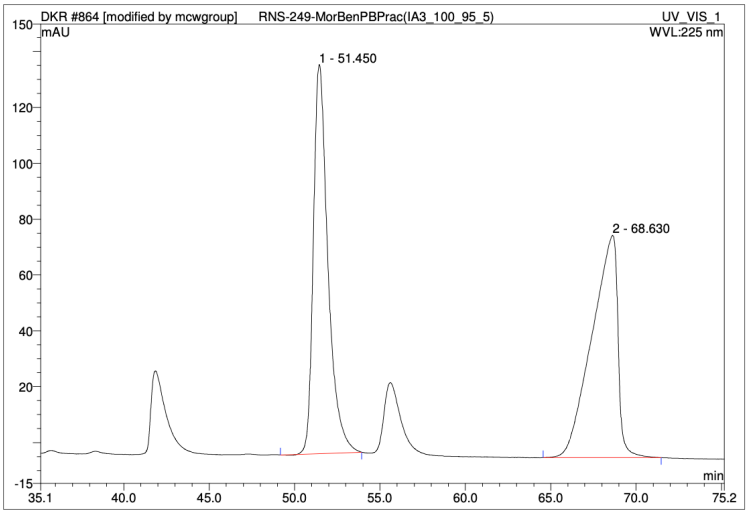
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.09	n.a.	1968.583	861.486	49.65	n.a.	BMB*
2	17.36	n.a.	1650.864	873.578	50.35	n.a.	BMB*
Total:			3619.447	1735.064	100.00	0.000	



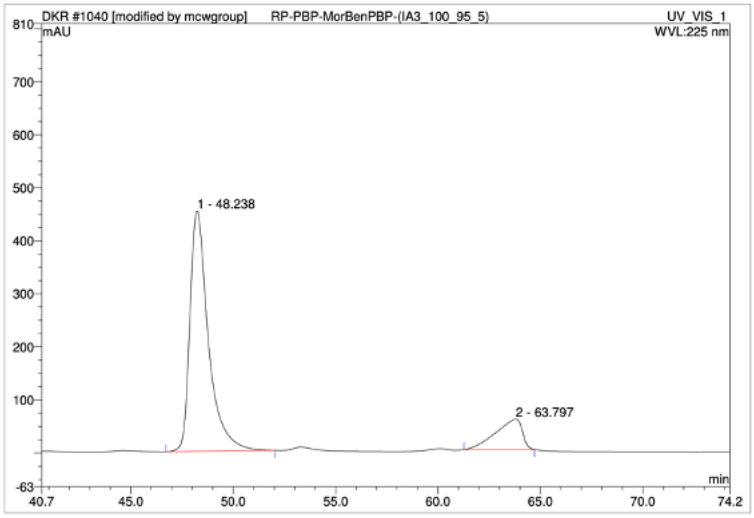
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.01	n.a.	1548.512	602.668	86.72	n.a.	MB*
2	17.31	n.a.	178.834	92.272	13.28	n.a.	BMB*
Total:			1727.346	694.939	100.00	0.000	

(*S*,*E*)-2-benzyl-5-(4-bromophenyl)-1-morpholinopent-4-ene-1,3-dione, 66k



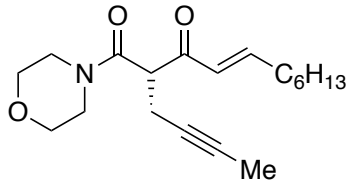


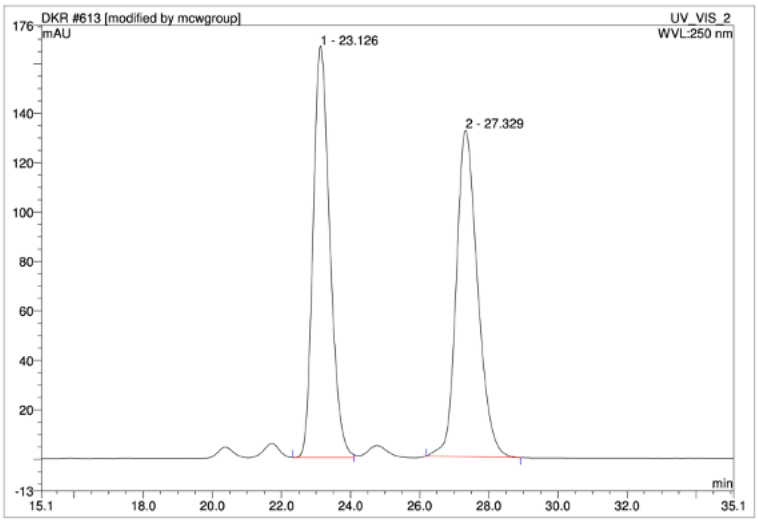
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	51.45	n.a.	139.322	137.561	49.44	n.a.	BMB*
2	68.63	n.a.	79.599	140.703	50.56	n.a.	BMB*
Total:			218.922	278.264	100.00	0.000	



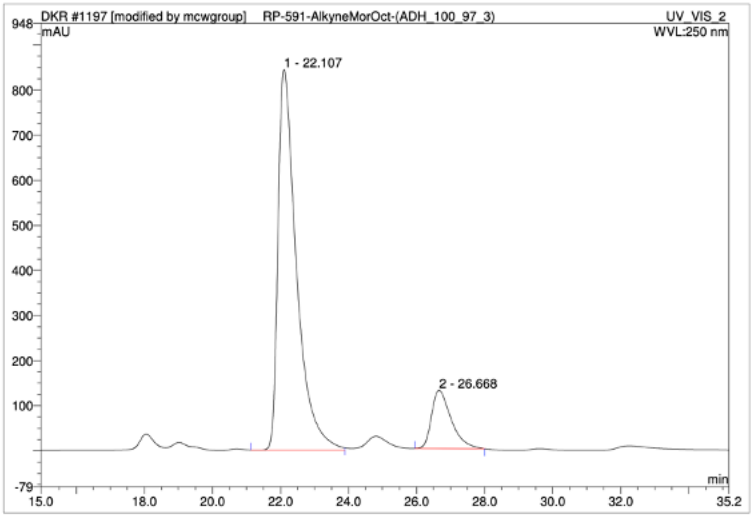
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	48.24	n.a.	453.276	472.542	84.56	n.a.	BMB*
2	63.80	n.a.	57.032	86.283	15.44	n.a.	BMB*
Total:			510.307	558.825	100.00	0.000	

(*S*,*E*)-2-(but-2-yn-1-yl)-1-morpholinoundec-4-ene-1,3-dione, 66l



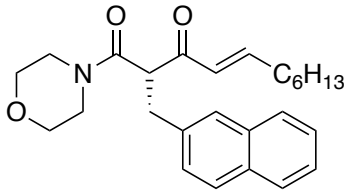


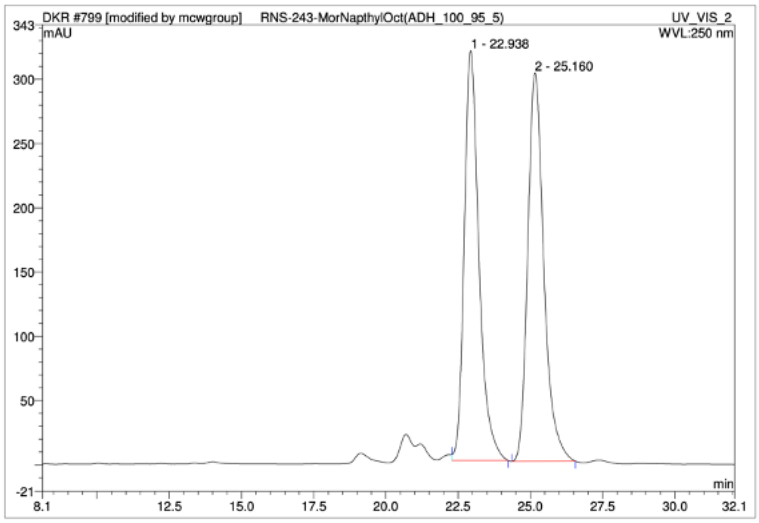
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23.13	n.a.	166.562	93.324	49.63	n.a.	BM *
2	27.33	n.a.	132.105	94.699	50.37	n.a.	BMB*
Total:			298.667	188.023	100.00	0.000	



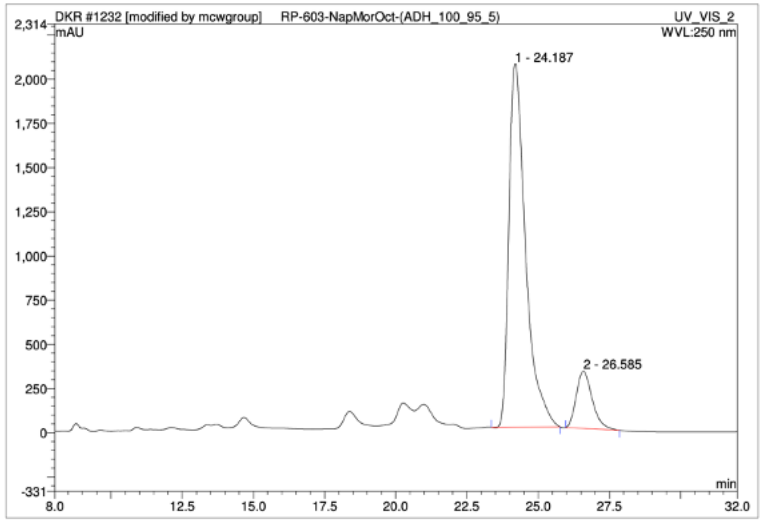
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.11	n.a.	843.826	529.145	86.02	n.a.	BM *
2	26.67	n.a.	129.132	86.008	13.98	n.a.	BMB*
Total:			972.958	615.153	100.00	0.000	

(*S*,*E*)-1-morpholino-2-(naphthalen-2-ylmethyl)undec-4-ene-1,3-dione, 66m



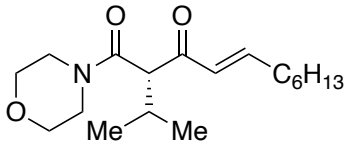


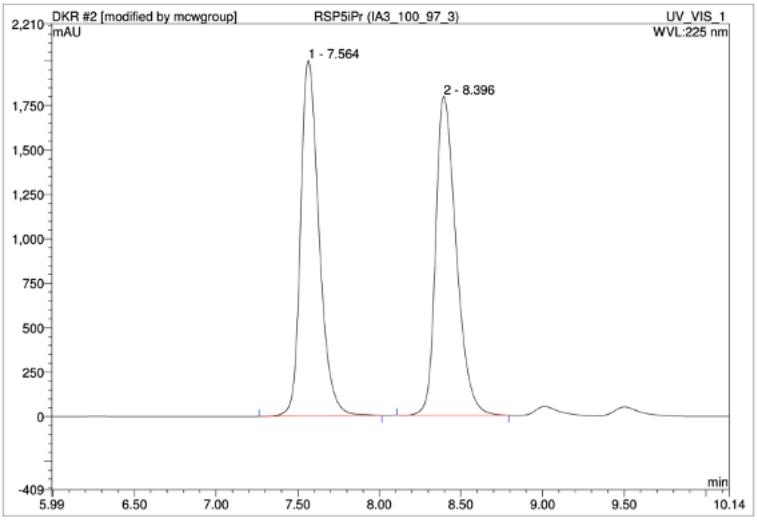
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.94	n.a.	318.876	188.055	49.13	n.a.	MB*
2	25.16	n.a.	302.170	194.734	50.87	n.a.	BMB*
Total:			621.046	382.788	100.00	0.000	



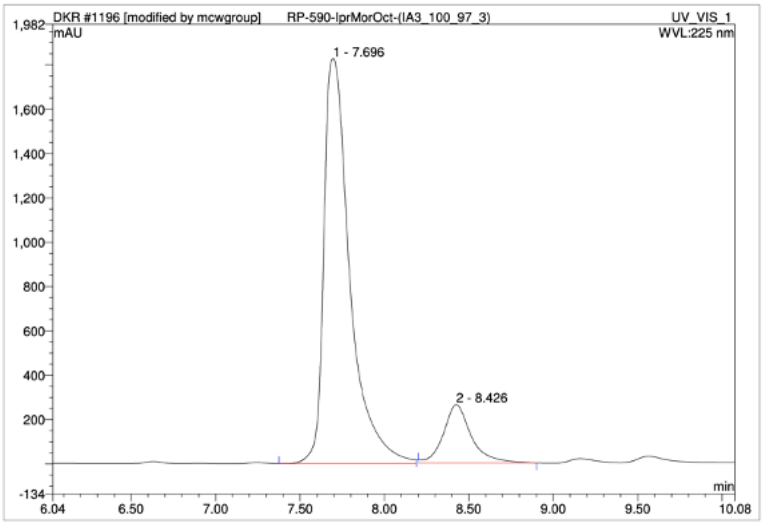
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24.19	n.a.	2054.317	1393.237	86.88	n.a.	BMB*
2	26.58	n.a.	323.044	210.365	13.12	n.a.	BMB*
Total:			2377.360	1603.602	100.00	0.000	

(*S*,*E*)-2-isopropyl-1-morpholinoundec-4-ene-1,3-dione, 66n



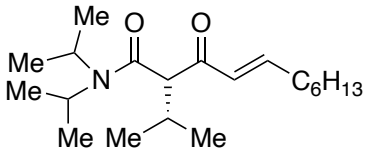


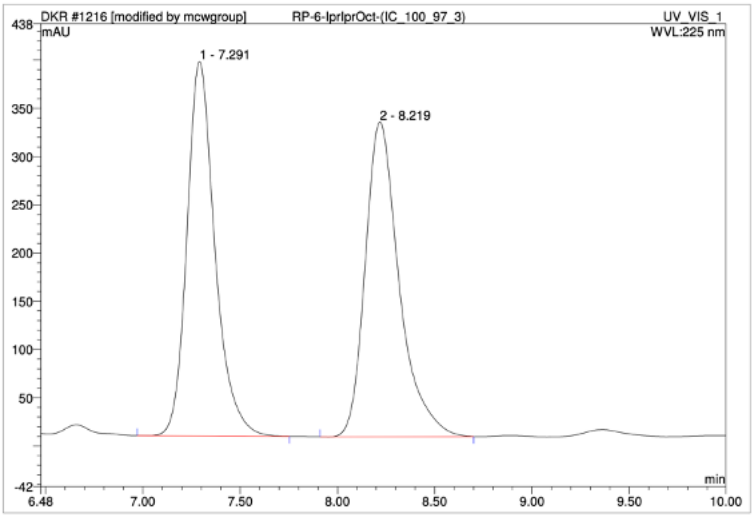
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.56	n.a.	1999.748	262.667	50.07	n.a.	BMB*
2	8.40	n.a.	1792.540	261.937	49.93	n.a.	BMB*
Total:			3792.288	524.604	100.00	0.000	



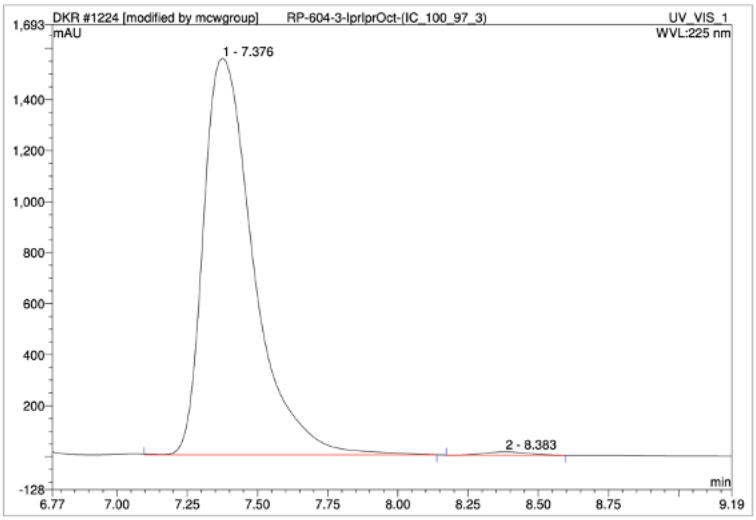
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.70	n.a.	1825.702	326.145	86.69	n.a.	BM *
2	8.43	n.a.	262.717	50.060	13.31	n.a.	MB*
Total:			2088.420	376.205	100.00	0.000	

(*S*,*E*)-*N*,*N*,2-triisopropyl-3-oxoundec-4-enamide, 66o



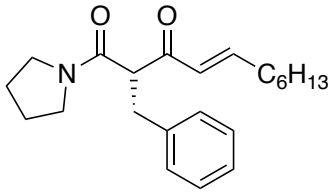


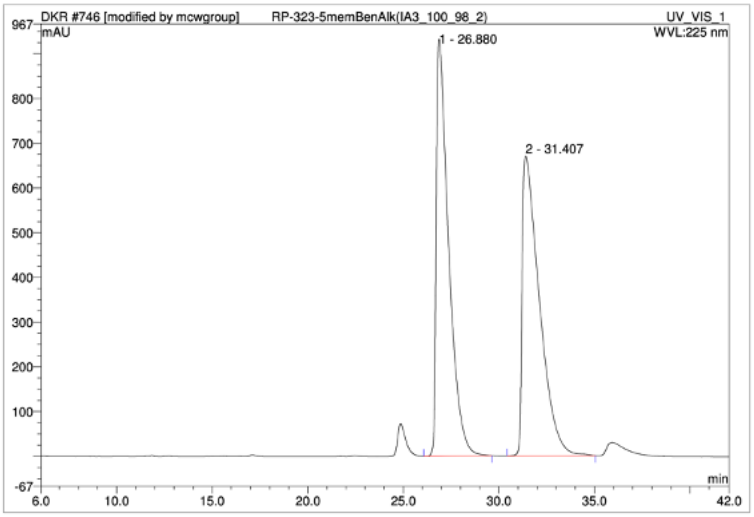
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.29	n.a.	388.016	64.671	49.48	n.a.	BMB*
2	8.22	n.a.	326.113	66.020	50.52	n.a.	BMB*
Total:			714.129	130.690	100.00	0.000	



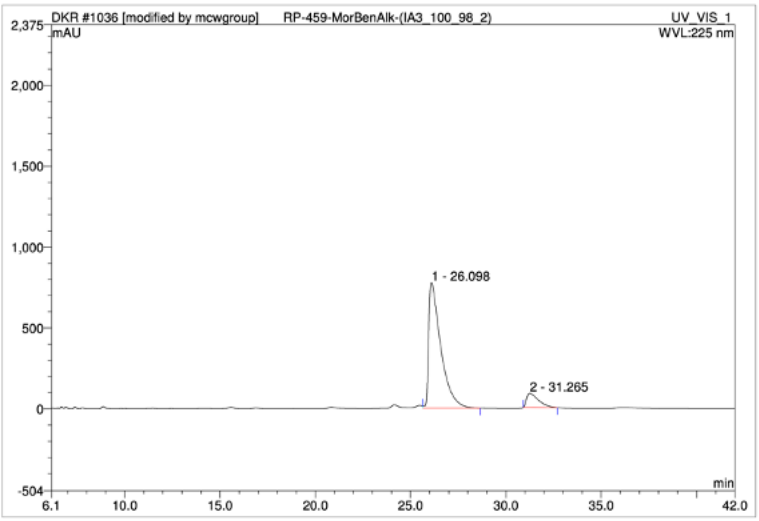
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.38	n.a.	1553.446	322.233	99.31	n.a.	MB*
2	8.38	n.a.	12.899	2.230	0.69	n.a.	BMB*
Total:			1566.346	324.463	100.00	0.000	

(*S*,*E*)-2-benzyl-1-(pyrrolidin-1-yl)undec-4-ene-1,3-dione, 66p



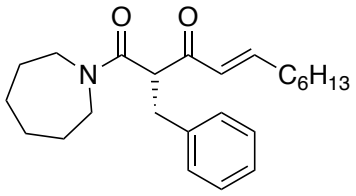


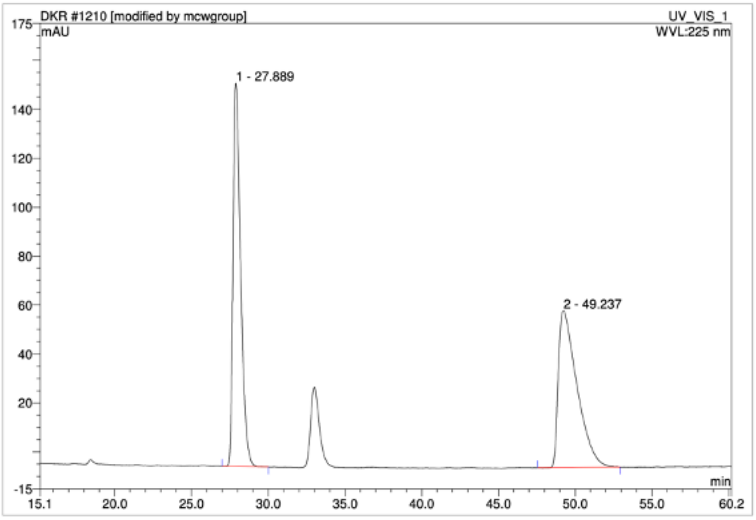
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.88	n.a.	931.935	699.065	49.93	n.a.	BMB*
2	31.41	n.a.	670.541	700.935	50.07	n.a.	BMB*
Total:			1602.476	1400.000	100.00	0.000	



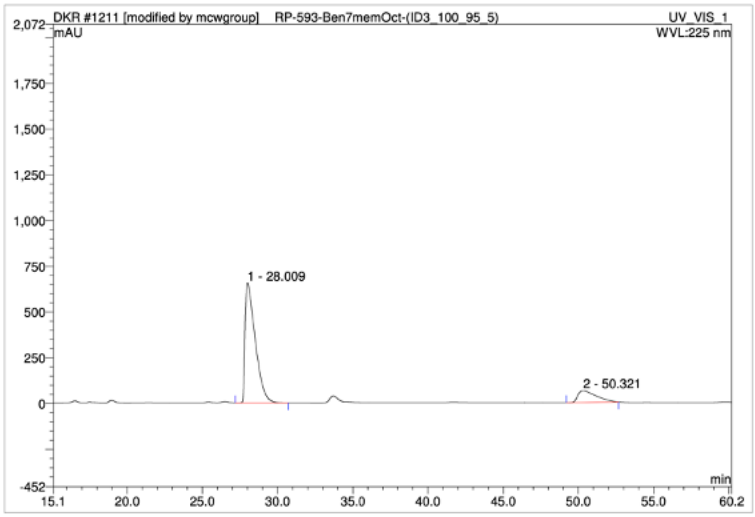
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.10	n.a.	774.355	568.754	90.06	n.a.	MB*
2	31.27	n.a.	86.161	62.743	9.94	n.a.	BMB*
Total:			860.516	631.497	100.00	0.000	

(*S*,*E*)-1-(azepan-1-yl)-2-benzylundec-4-ene-1,3-dione, 66q





No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	27.89	n.a.	156.641	89.860	49.97	n.a.	BMB*
2	49.24	n.a.	63.933	89.964	50.03	n.a.	BMB*
Total:			220.574	179.823	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.01	n.a.	654.468	512.355	85.16	n.a.	BMB*
2	50.32	n.a.	63.748	89.282	14.84	n.a.	BMB*
Total:			718.216	601.638	100.00	0.000	