Development of Copper-Catalysed Addition Reactions to Alkynes

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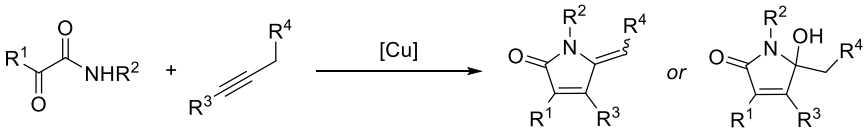
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

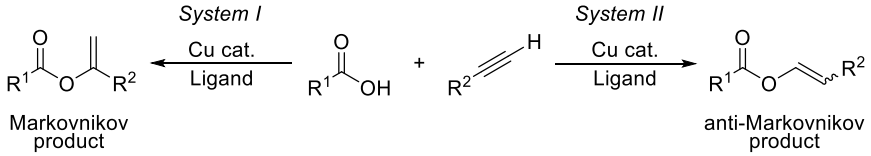
In this thesis, new copper-catalysed addition reactions to alkynes have been developed. The new methodologies exploit hydro-functionalisation to transform readily available starting materials into *N*-heterocycles and enol esters *via* addition of amides and acids to alkynes, respectively.

Chapter 1 is a literature review covering the transition metal-catalysed hydroamination and hydro-oxycarbonylation of alkynes, and some of the well-known copper-catalysed reactions.

Chapter 2 documents our new methodology on exploiting the copper-catalysed hydroamination of terminal alkynes to synthesis 5-ylidenepyrrol-2(5*H*)-ones and 5-hydroxypyrrol-2(5*H*)-ones, using readily available α-keto amides and terminal alkynes. A method towards the synthesis of asymmetric maleimides is also reported.



Chapter 3 describes two different catalyst systems for the regioselective addition of carboxylic acids to terminal alkynes, to obtain both the Markovnikov and anti-Markovnikov products. Regioselectivity was found to be dependent on the type of alkynes and ligands used. Heteroatom-alkynes are also tolerated in the Markovnikov system. Kinetics studies performed provided some insights into the mechanism.



Chapter 4 presents a conclusion on the research work done and the potential future work.

Chapter 5 provides 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.

Qian Wen Tan

October 2019

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Firstly, I would like to thank Prof. Michael Willis. I have received valuable advice, support and guidance throughout my DPhil while also getting opportunities to challenge myself. These have helped me to become a better scientist, and for that I am sincerely grateful. Thank you.

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Abbreviations and acronyms

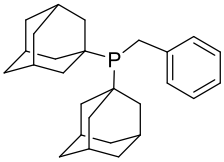
Ac	acetyl
acac	acetylacetonate
aq.	aqueous
APCI	Atmospheric Pressure Chemical Ionization
Ar	aryl
Asc	ascorbate
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bus	*tert*-butyl sulfonyl
calcd	calculated
Cat.	catalyst *or* catalytic
Cbz	carboxybenzyl
cm^{-1}	wavenumber(s)
COD	1,5-cyclooctadiene
coe	cyclooctene
Cp	cyclopentadiene
Cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
DBU	1,8-biazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*'-bicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dcpe	1,2-bis(dicyclohexylphosphino)ethane
DMA	*N*,*N*-dimethylacetamide

DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPEphos	bis[(2-diphenylphosphino)phenyl]ether
dppb	1,4-bis(diphenylphosphino)butane
dppBz	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppm	bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
equiv.	equivalent(s)
et al.	et alii (Latin: and others)
Et	ethyl
ESI	Electrospray Ionisation
FI	Field Ionisation
Fur	furyl
g	Gramme(s)
GLC	Glass Liquid Chromatography
h	hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	hertz
i	iso
^{i}Pr	isopropyl

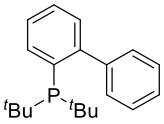
IR	Infra-Red
J	coupling constant
LRMS	Low Resolution Mass Spectrometry
Me	methyl
mesyl	methanesulfonyl
mg	milligramme(s)
MHz	megahertz
min	Minute(s)
mL	Millilitre(s)
µL	microlitre(s)
m	meta
mmol	millimole(s)
MP	melting point
MW	microwave
m/z	mass to charge ratio
n	normal
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
o	ortho
OMe	methoxy
p	para
petrol	petroleum ether
Ph	phenyl
phen	1,10-phenanthroline

ppm	parts per million
rac	racemic
rt	room temperature
s	secondary
sat.	saturated
t	tertiary
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
tosyl	*p*-toluenesulfonyl

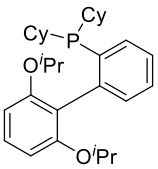
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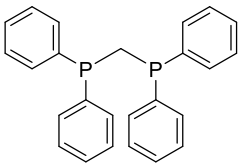
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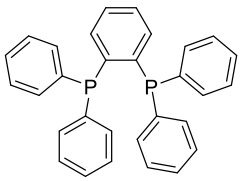
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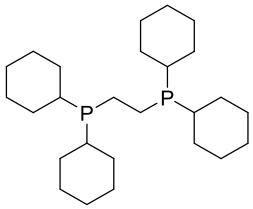
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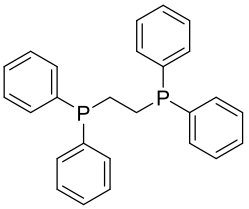
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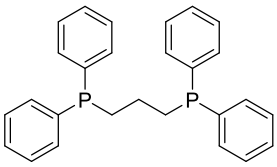
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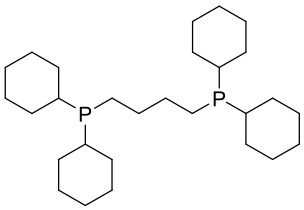
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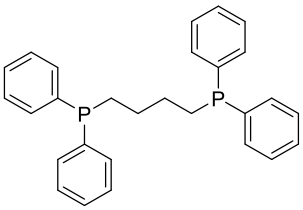
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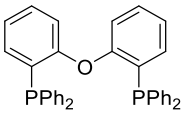
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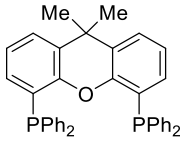
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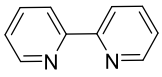
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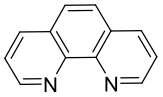
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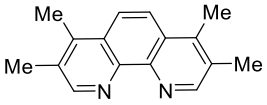
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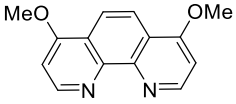
Bipyridine



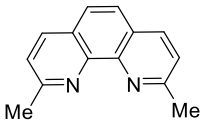
1,10-Phenanthroline



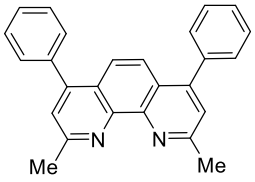
3,4,7,8-Tetramethyl-1,10-phenanthroline



4,7-Dimethoxy-1,10-phenanthroline



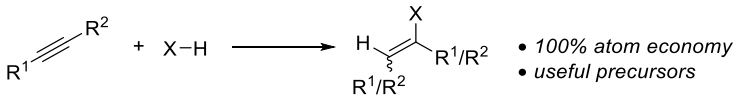
Neocuproine



Bathocuproine

Chapter 1. Introduction

The addition of a heteroatom-hydrogen bond across an unsaturated carbon-carbon bond is a powerful transformation that allows the formation of a wide range of versatile building blocks in organic chemistry (Scheme 1.1). These processes have been extensively investigated as they have excellent atom economy but require precise tuning of the reaction conditions to obtain the selectivity needed. When performed on alkynes, a great variety of alkenyl heteroatom-containing organic compounds, such as ethers, esters, sulfides, enamines, imines, phosphines and phosphonates, can be formed.[1] With intramolecular addition reactions, heterocycles can be obtained directly. These compounds have found utility in materials, pharmaceuticals, natural product synthesis, bulk chemicals and many more areas. Reactivity of the addition across the alkyne bond is dependent on a number of factors, such as the type of heteroatom used, the substituents on the heteroatom, and the substituents on the alkyne, with both electronic and steric factors coming into play.

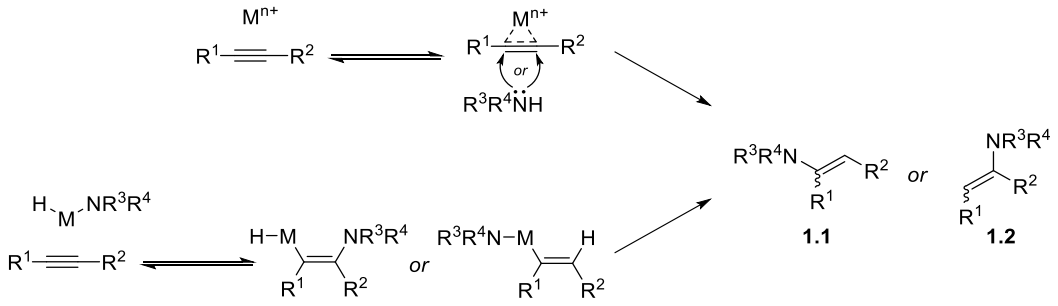


Scheme 1.1 Addition of heteroatom-hydrogen bond across an alkyne

Transition metal catalysis has transformed modern organic chemistry by introducing new mechanistic pathways that allow efficient formation of novel compounds, mostly under mild conditions. As such, the transition metal-catalysed addition of a heteroatom-hydrogen bond to alkynes has been the key to successful transformations of the variety of heteroatoms across the unsaturated bond, allowing regio-, stereo-, enantioselectivity to be tuned based on the catalyst and ligand system used.

1.1 Hydroamination

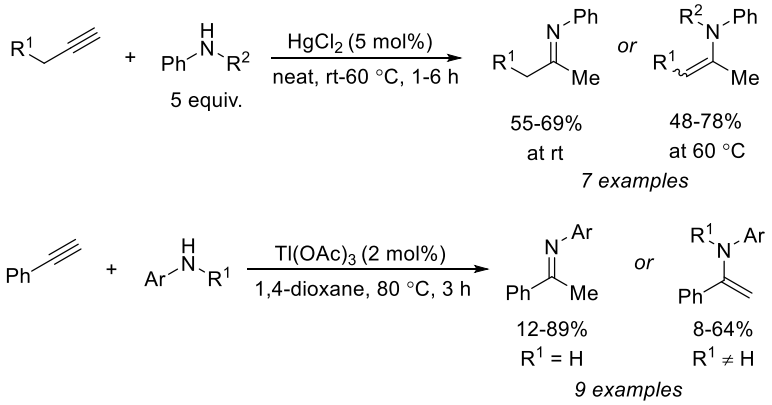
Hydroamination has often been employed to produce heterocycles or simple amino groups, as it enables the easy and direct introduction of a nitrogen atom into a molecule. When used on carbon-carbon unsaturated bonds such as alkenes and alkynes, this powerful reaction allows the formation of amines, enamines and imines, which are valuable precursors in organic chemistry. It is thus unsurprising that a wide range of transition metals has been explored as catalysts for this transformation. In this section, transition metal-catalysed hydroamination of alkynes will be discussed. The general mechanism for transition metal-catalysed hydroamination of alkynes can be broken down into two main pathways (Scheme 1.2). The metal catalyst can coordinate to the alkyne and activate it, before nucleophilic attack by the nitrogen of the amine derivative on either side of the alkyne. Alternatively, a metal-amine complex can first be formed, before insertion of the M–N or M–H bond into the alkyne. Regardless of whether the reaction proceeds *via* a *syn*- or *anti*-addition, two regioisomers can be formed in both cases. When terminal alkynes (R^2 = H) are employed, product **1.1** is defined as the Markovnikov product while product **1.2** is defined as the anti-Markovnikov product.



Scheme 1.2 Transition metal-catalysed hydroamination of alkynes

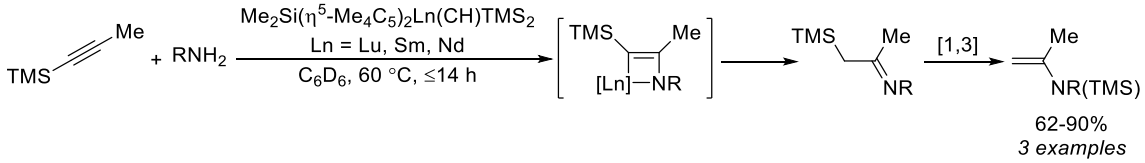
Pioneering work by Barluenga and Aznar demonstrated that sub-stoichiometric amounts of mercury and thallium salts could be used as catalysts for the hydroamination of alkynes (Scheme 1.3).[2,3] Both aromatic and aliphatic alkynes could react with aniline

derivatives to give either the enamine or the imine products with good regioselectivity, depending on the substrates and reaction conditions. However, the use of highly toxic metals was undesirable, and better metal-catalysed transformations were needed.



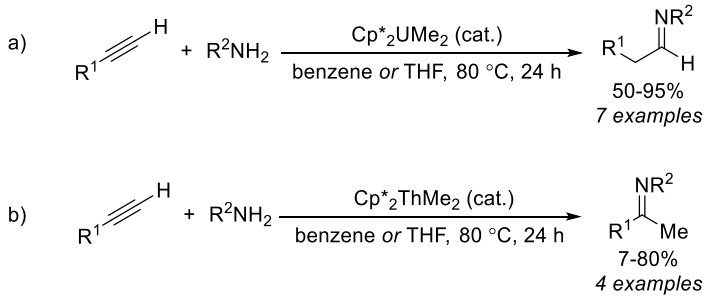
Scheme 1.3 Hg- and Tl-catalysed hydroamination of alkynes

Lanthanide and actinide salts contain highly electrophilic metal centres, allowing them to be good catalysts that can activate C–C unsaturated bonds and amines. Due to their high coordination number, activation of the alkyne and amine substrate often leads to the formation of an azametallocyclobutene intermediate that undergoes rapid metathesis to give the desired product. In 1996, Li and Marks pioneered the application of lanthanide metallocenes to the intermolecular hydroamination of silyl-substituted alkynes with primary aliphatic amines (Scheme 1.4).[4] The enamine formed initially undergoes a tautomerization to the corresponding imine before an aza-Brook rearrangement affords the final stable enamine product.



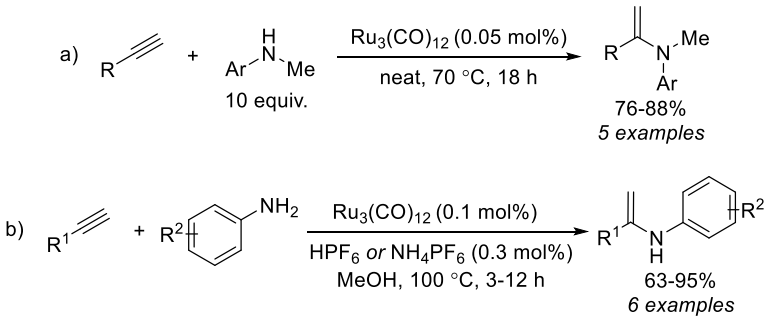
Scheme 1.4 First Ln-catalysed hydroamination of alkynes

Later, Eisen and co-workers demonstrated the use of organoactinide complexes for the hydroamination of terminal alkynes with primary amines (Scheme 1.5).[5,6] It was found that the selectivity of the addition was influenced by the catalyst, where the uranium catalyst was selective for anti-Markovnikov addition (Scheme 1.5a) while the thorium catalyst was selective for the Markovnikov addition (Scheme 1.5b).



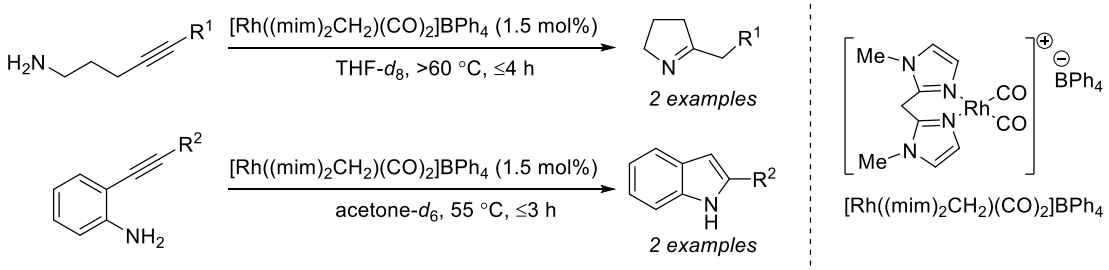
Scheme 1.5 An-catalysed hydroamination of alkynes

Other late transition metals that can also catalyse the reaction include precious metals such as ruthenium, rhodium and palladium. These metals present an advantage over other metals as they have better functional group tolerance and require lower catalyst loading. The use of $Ru_3(CO)_{12}$ for intermolecular hydroamination of alkynes was first demonstrated by Uchimaru (Scheme 1.6a).[7] While the catalyst loading was very low, the limited scope and requirement of a large excess of *N*-methylaniline were undesirable. Similarly, Wakatsuki and co-workers employed $Ru_3(CO)_{12}$ for the reaction between aniline derivatives and alkynes. Additionally, they found that using additives such as HPF_6 or NH_4PF_6 could greatly increase the rate of the reaction (Scheme 1.6b).[8] Both reactions were selective for the Markovnikov products.



Scheme 1.6 $Ru(CO_3)_{12}$-catalysed hydroamination of alkynes

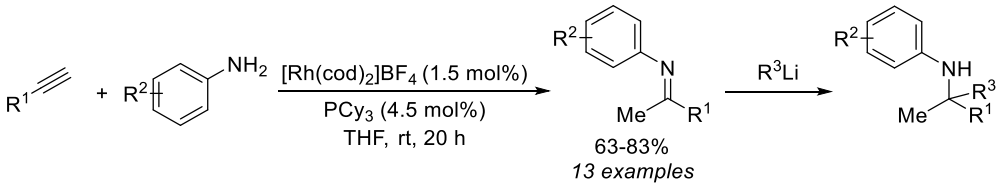
In 2000, Burling *et al.* demonstrated the use of rhodium salts for the intramolecular hydroamination of alkynes (Scheme 1.7).[9] The pre-formed cationic Rh(I) dicarbonyl complex allowed rapid formation of 3,4-dihydro-2*H*-pyrroles and indoles from the cyclisation of the aminoalkynes. Reactions were monitored by NMR spectroscopy to identify the reaction time required to reach 50% conversion, with pent-4-yn-1-amine found to be fully converted to the corresponding 3,4-dihydro-2*H*-pyrrole in 1.5 hours under reflux conditions.



Scheme 1.7 Rh-catalysed intramolecular hydroamination of alkynes

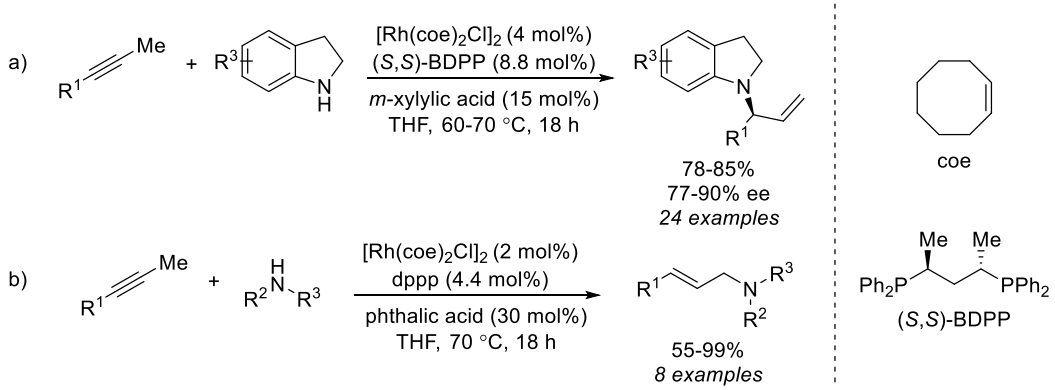
Later, Beller and co-workers showed that rhodium could also catalyse the more challenging intermolecular hydroamination of alkynes (Scheme 1.8).[10] A cationic source of rhodium catalyst and phosphine ligand were found to be necessary for good yields, with PCy_3 acting as the best ligand for their system. While aliphatic alkynes reacted well in this system, phenylacetylene was found to polymerise under the reaction conditions.

Organolithium reagents could also be added in the same pot, after formation of the imines, to give the corresponding amines.



Scheme 1.8 Rh-catalysed intermolecular hydroamination of alkynes

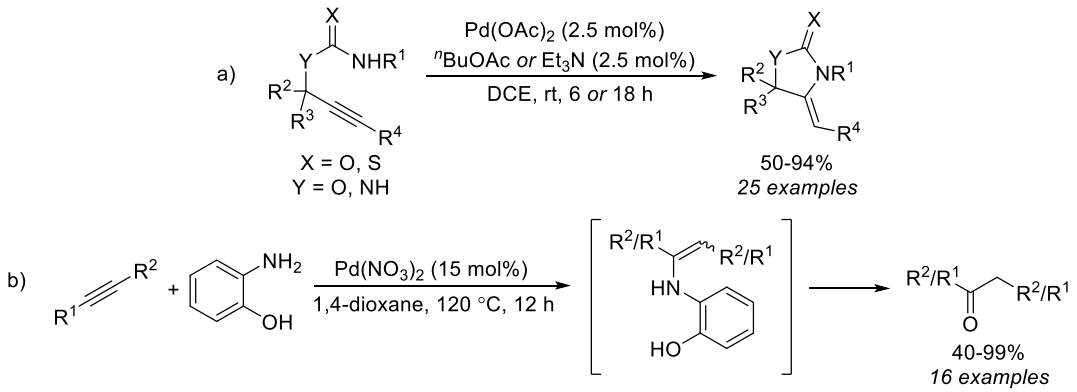
In a recent development, Dong and co-workers employed a chiral ligand for the regio- and enantioselective addition of indoles into internal alkynes (Scheme 1.9a).[11] The presence of *m*-xylylic acid was necessary for the reaction to proceed. It aided the formation of the active rhodium hydride species, directed the regioselectivity towards branched products and improved the enantioselectivity. The *N*-allylic indolines were formed in good yields and ees. At the same time, switching to a stronger acid such as phthalic acid promoted isomerisation to give good linear selectivity (Scheme 1.9b).



Scheme 1.9 Rh-catalysed regio- and enantioselective hydroamination of internal alkynes

The Bäckvall group exploited the use of palladium-catalysed hydroamination of propargylic carbamates and carbamothioates to form oxazolidinones, oxazolidinthiones, imidazolidinthiones, and imidazolidinones (Scheme 1.10a).[12] They found the choice of base was critical for the formation of their desired products, with ^{n}BuOAc giving the best

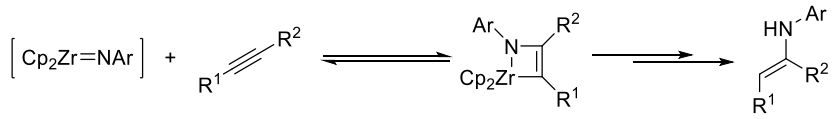
yields for the synthesis of tosyloxazolidinones, oxazolidinthiones, imidazolidinthiones and imidazolidinones. However, switching to triethylamine and increasing the reaction time to 18 hours were necessary for the cyclisation of propargylic benzoylcarbamates. Excellent stereoselectivity was obtained in all cases as only the (*Z*)-isomers were formed. While intramolecular palladium-catalysed hydroamination of alkynes has been widely explored[13–17], reports on the intermolecular equivalent have been fewer. One such example was reported by Yamamoto and co-workers, who illustrated the palladium(II)-catalysed intermolecular hydroamination of terminal and internal alkynes with *o*-aminophenol (Scheme 1.10b).[18] Hydrolysis of the enamine products afforded the corresponding ketones in moderate to excellent yields. However, the reaction presented a few limitations: regioselectivity was poor, terminal alkynes gave low yields due to cyclotrimerization and *o*-aminophenol was the only amine substrate attempted that gave good yield.



Scheme 1.10 Pd-catalysed hydroamination of alkynes

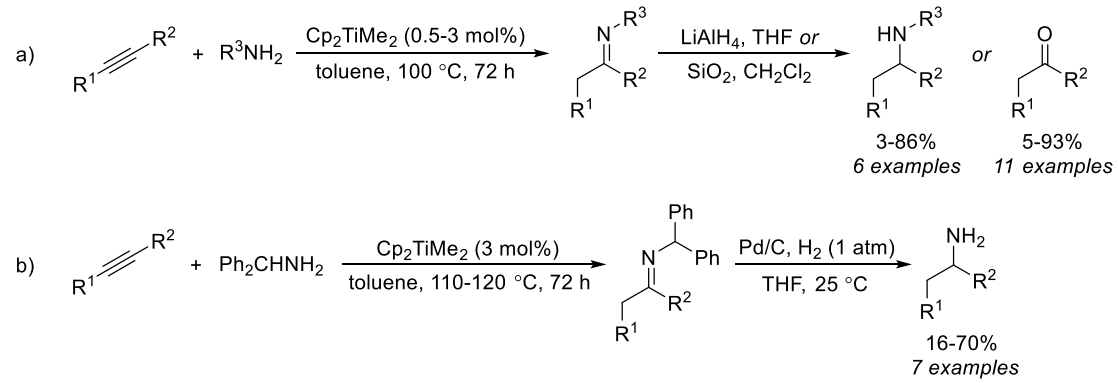
Above all, early transition metals such as titanium and zirconium have dominated the field for the hydroamination of alkynes. Initial work by Bergman *et al*. saw the use of imido-zirconium complexes to activate internal alkynes by forming azametallacyclobutenes that furnished the enamine products (Scheme 1.11).[19,20]

Regioselectivity of the addition was influenced by the size of the ligand and the substituents on the alkyne.



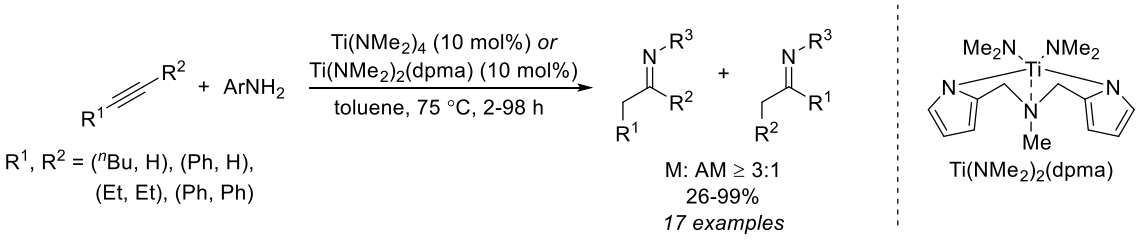
Scheme 1.11 Zr-catalysed hydroamination of internal alkynes

Titanium-catalysed hydroamination of alkynes has been studied by several groups, such as Beller,[21–24] Bergman,[25,26] Doye,[27–34] Odom[35–38] and Schaufer.[39–41] Despite the extensive work done in this area, the chemistry presents a disadvantage as a glovebox has to be used due to the high sensitivity of the active catalyst to air. Initial investigations focused on the use of Cp_2TiMe_2 as the pre-catalyst of choice as it is readily available. Doye and co-workers reported the hydroamination of internal alkynes with both aryl- and alkylamines (Scheme 1.12a).[27] The imines produced were susceptible to hydrolysis during workup, and were either reduced or hydrolysed to afford the respective amines and ketones in good yields. Yields for sterically less hindered amines and benzylamines could also be improved when $Cp^*_2TiMe_2$ was used instead.[29] The chemistry was further expanded using benzhydrylamine as an ammonia surrogate, as the imines produced could later be hydrogenated with palladium on carbon to afford primary amines (Scheme 1.12b).[28] In both examples, long reaction times were required. From here, other types of titanium complexes were explored in order to improve the reactivity and selectivity of the transformation.



Scheme 1.12 Cp_2TiMe_2-catalysed hydroamination of alkynes

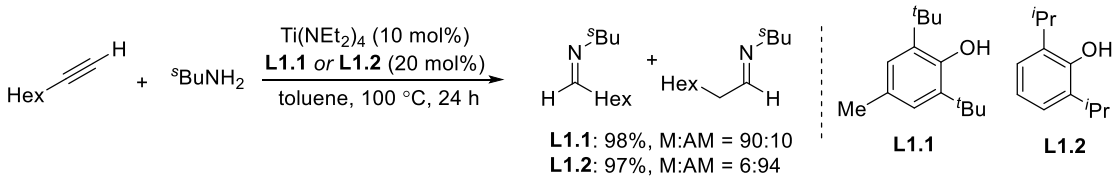
Odom and co-workers demonstrated that beyond the metallocene and Cp*-based system, commercially available $Ti(NMe_2)_4$ could also function as a pre-catalyst for the transformation using aromatic amines (Scheme 1.13).[35] Unlike the Cp_2TiMe_2 system, the use of $Ti(NMe_2)_4$ favoured the Markovnikov addition in the presence of terminal alkynes. The yield and selectivity for the Markovnikov product was later improved by using $Ti(NMe_2)_2$(dpma) as pre-catalyst. $Ti(NMe_2)_2$(dpma) can also catalyse reactions using alkylamines that were previously unreactive in the presence of $Ti(NMe_2)_4$.



Scheme 1.13 Titanium-catalysed hydroamination

Other than nitrogen-based ligands, Beller and co-workers found that aryloxotitanium complexes, formed *in situ* from commercially available $Ti(NEt_2)_4$ and phenols, could also perform the transformation (Scheme 1.14).[23,24] The choice of ligand was found to direct the selectivity of the addition, as the use of bulky ligand **L1.1** gave Markovnikov selectivity, while the use of the less hindered ligand **L1.2** gave

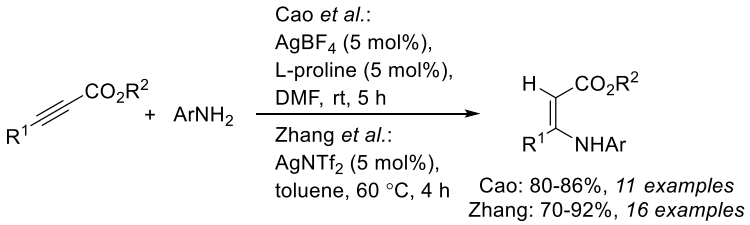
anti-Markovnikov selectivity in their model reaction between 1-octyne and ^{s}butylamine, with excellent yields obtained in both cases.



Scheme 1.14 Aryloxotitanium complexes for the hydroamination of terminal alkynes

Although coinage metals such as silver and gold have been explored extensively as catalysts for the intramolecular hydroamination of alkynes,[42–53] recent development has extended the chemistry to the more challenging intermolecular reactions.

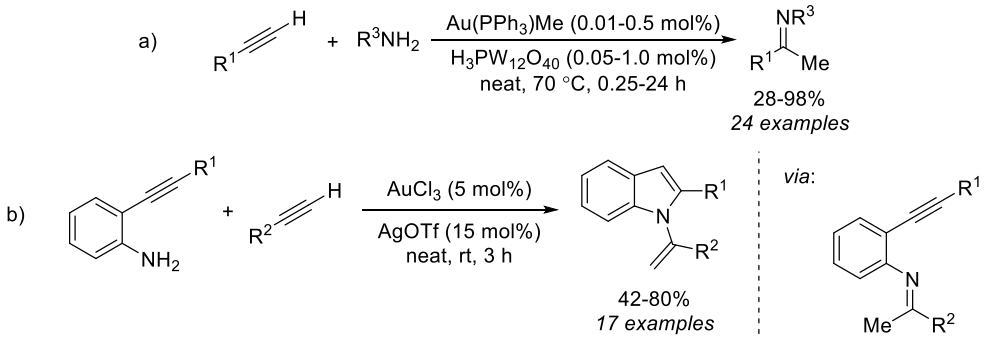
Silver salts have been found to catalyse the intermolecular hydroamination of electron-deficient alkynes and aniline derivatives. In 2008, Cao *et al*. demonstrated that the use of $AgBF_4$/L-proline in their multicomponent reaction led to excellent selectivity for a single regio-isomer**.** (Scheme 1.15).[54] The same transformation was later reported by Zhang *et al*. using $AgNTf_2$, without the need of a ligand.[55] Both silver systems used mild conditions and gave excellent selectivity for the (*Z*)-enamines.



Scheme 1.15 Ag-catalysed hydroamination of electron-deficient alkynes

Similarly, Tanaka and co-workers reported the use of $Au(PPh_3)Me$ for the hydroamination of terminal alkynes with aniline derivatives (Scheme 1.16a).[56] The presence of an acid was required to activate the Au catalyst *via* protonolysis. Zhang *et al.*

later applied double hydroamination processes for indole synthesis (Scheme 1.16b).[57] It was postulated that the *o*-alkynylaniline derivatives first undergo an intermolecular hydroamination with the terminal alkynes before cyclisation of the enamine product to furnish the final *N*-alkenylindoles in moderate to good yields.



Scheme 1.16 Au-catalysed intermolecular hydroamination of alkynes

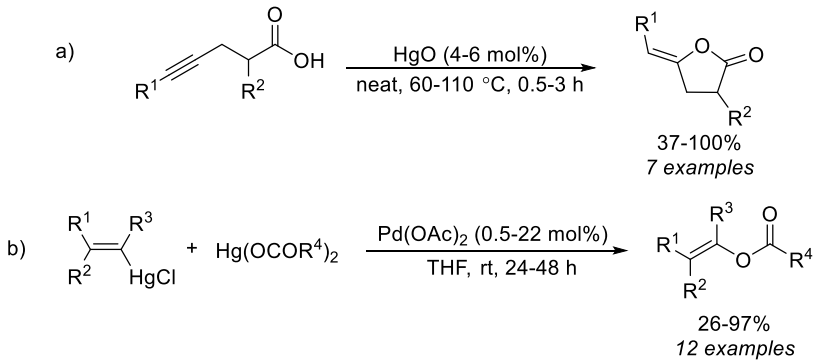
While the use of copper as a catalyst for hydroamination of unsaturated bonds such as alkenes has been widely explored,[58–69] the same application to alkynes has been much less, and will be further explored in Chapter 2.

1.2. Hydro-oxycarbonylation

Hydro-oxycarbonylation, also known as hydrocarboxylation, describes the addition of a carboxylic acid to an alkyne, giving valuable enol esters. These enol ester derivatives have found utility in many areas, mostly as building blocks for further functionalisation, such as polymerisation,[70,71] asymmetric hydrogenation,[72–75] cross-coupling[76–78] and Mannich-type reaction.[79] While the synthetic utility remains significant, decades of exploration in the types of transition metal that can catalyse such a reaction have led mostly to the development of ruthenium- and palladium-based systems. Although these precious metals are costly, they have proven to be highly efficient at

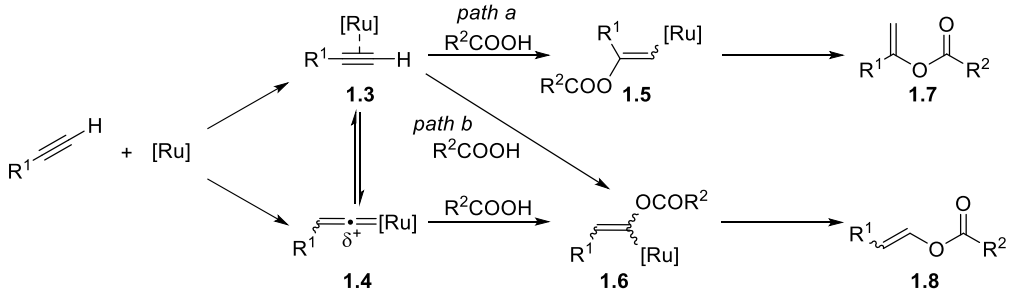
catalysing both the intra- and intermolecular hydro-oxycarbonylation of terminal and internal alkynes, with good control of selectivity.

Outdated methods for the transition metal-catalysed synthesis of enol esters include the use of mercurial substrates. Yamamoto employed the use of a small amount of mercury oxide to catalyse the intramolecular cyclisation of alkynylcarboxylic acids, giving γ-methylenebutyrolactones in good yields (Scheme 1.17a).[80,81] In 1980, Larock and co-workers demonstrated the formation of enol esters from vinyl mercurial and mercury carboxylates, catalysed by $Pd(OAc)_2$ (Scheme 1.17b).[82] In both examples, the use of toxic mercury salts made the methods very unfavourable.



Scheme 1.17 Hg-aided hydro-oxycarbonylation of alkynes

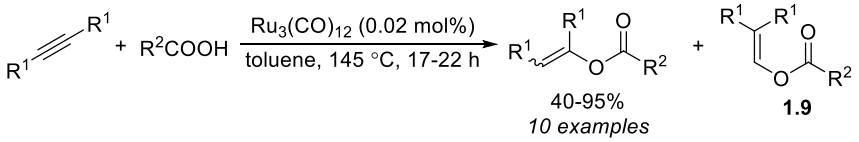
Extensive work has been performed on Ru-based systems for the hydro-oxycarbonylation of alkynes.[83–100] As a result, several systems have been developed to obtain good to excellent regioselectivity. In the presence of terminal alkynes, the selectivity for the Markovnikov or the anti-Markovnikov product was found to be influenced by the electron density at the ruthenium centre, which is affected by the ligands employed (Scheme 1.18).[86,94,97,98]



Scheme 1.18 Mechanistic pathways for the Markovnikov and anti-Markovnikov selectivity

In the presence of more σ-donating and less π-accepting ligands, the electron-rich ruthenium centre coordinates to the terminal alkyne, preferentially forming intermediate **1.3**. As a result, the incoming carboxylic acid can attack the alkyne on either alkyne carbon to give intermediate **1.5** (path a) or intermediate **1.6** (path b), where the formation of a carbocation can be stabilised by the electron-rich ruthenium centre. On the other hand, in the presence of less σ-donating and more π-accepting ligands, vinylidene intermediate **1.4** is formed and the carboxylic acid preferentially attacks the more electropositive carbon centre to give intermediate **1.6**. Protonation of intermediate **1.5** results in the formation of the formal Markovnikov product **1.7**, while protonation of intermediate **1.6** affords the formal *E*/*Z* anti-Markovnikov products **1.8**.

In 1983, Rotem and Shvo first demonstrated the use of $Ru_3(CO)_{12}$ at low catalyst loading for the addition of carboxylic acids to symmetrical internal alkynes, with good yields obtained (Scheme 1.19).[87]

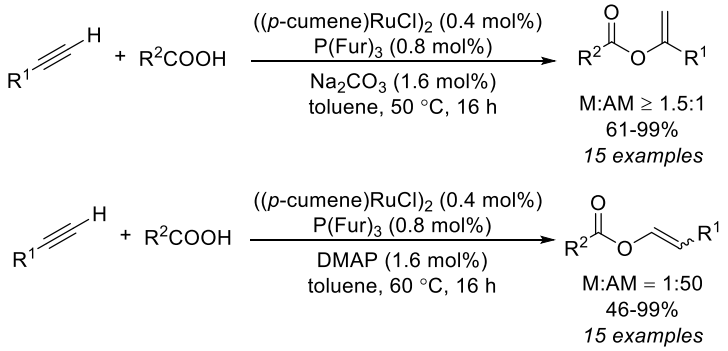


Scheme 1.19 First reported Ru-catalysed hydro-oxycarbonylation of symmetrical alkynes

Although no control of the *E*/*Z* selectivity was observed, GLC analysis indicated a slow conversion of the (*E*)-isomer to the (*Z*)-isomer. By-product **1.9** was also formed and was

found to be synthesised concurrently with the anti-Markovnikov products as subjecting a mixture of (*E*)- and (*Z*)-*α*-acetoxystilbenes back into the original reaction conditions did not yield any by-product **1.9**. It was postulated that the formation of a vinyl cation intermediate, followed by a 1,2-shift of the R^1 group led to the formation of by-product **1.9**.

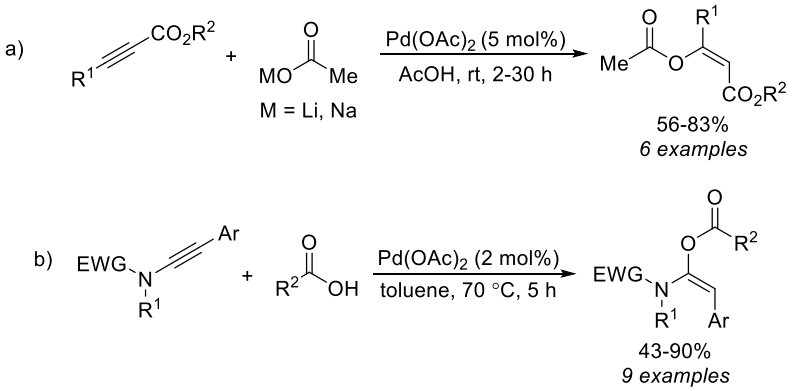
While most systems required the use of specific ligands to tune the selectivity for the transformation, Goossen and co-workers reported the use of additives to control the regioselectivity instead (Scheme 1.20).[96] When Na_2CO_3 was employed, the Markovnikov product could be obtained in good to excellent yields while the reverse selectivity was observed when DMAP was used instead. The phenomenon was postulated to be caused by the coordination of organic bases such as DMAP to the ruthenium centre.



Scheme 1.20 Control of regioselectivity *via* addition of additives

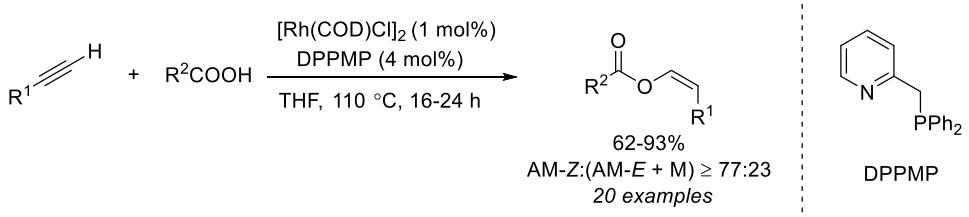
While palladium-catalysed intramolecular hydro-oxycarbonylation of alkynes has been widely demonstrated,[101–107] few examples have been shown for the intermolecular version. In the early 1990s, Zhu *et al*. described the first intermolecular Pd-catalysed transformation, where in the presence of a sub-stoichiometric amount of $Pd(OAc)_2$, acetate anion was added to 2-alkynoic acid derivatives in a regio- and stereoselective manner to yield the corresponding (*Z*)-enol esters in moderate to good yields (Scheme

1.21a).[108] Later, Lam and co-workers demonstrated the Pd-catalysed hydro-oxycarbonylation of ynamides (Scheme 1.21b).[109] Excellent regio- and stereoselectivity were obtained with this system, giving α-acyloxyenamides as single isomers. The presence of an electron-withdrawing substituent on the nitrogen atom of the ynamide was found to be necessary in order to obtain good yields.



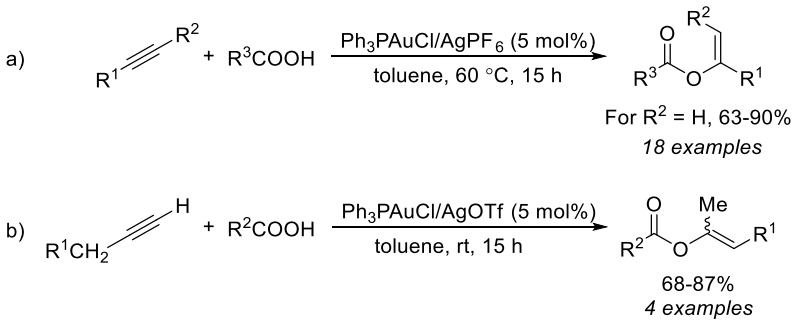
Scheme 1.21 Pd-catalysed intermolecular hydro-oxycarbonylation of alkynes

Hydro-oxycarbonylation of alkynes has also been shown to be catalysed by other precious metals. In 2010, Breit and co-workers reported the rhodium-catalysed hydro-oxycarbonylation of terminal alkynes to give anti-Markovnikov (*Z*)-enol esters selectively (Scheme 1.22).[110] They found the DPPMP ligand to be the best for obtaining the selectivity and postulated that the rhodium centre chelates to the ligand by both *N*- and *P*-coordination. Despite being unavailable commercially, DPPMP could be easily synthesised from 2-picoline and PPh_2Cl. However, the group was unhappy with the long reaction times and decided to study the reaction further. Later, they discovered that *in situ* formation of the more active rhodium catalyst from [Rh(COD)(acac)], DPPMP and the acid substrate reduced the reaction time to four hours.[111] Cs_2CO_3 could also be used as an additive to further shorten the reaction time to 1 hour.



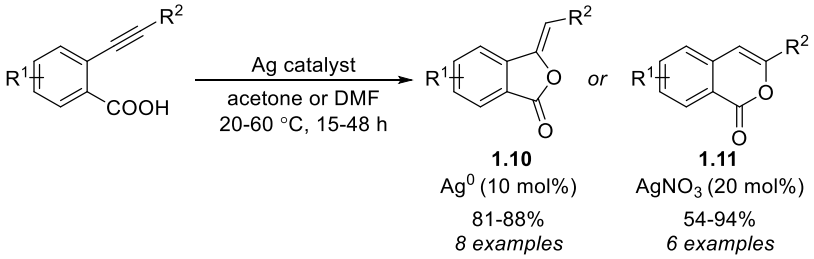
Scheme 1.22 Rh-catalysed hydro-oxycarbonylation of terminal alkynes

In 2010, gold-catalysed hydro-oxycarbonylation of alkynes was reported by Kim and Chary (Scheme 1.23).[112] In their $Au(PPh_3)Cl/AgPF_6$ system, Markovnikov selectivity was obtained. Internal alkynes were found to be less reactive but revealed that the carboxylic acids added to conjugated alkyne esters *via* conjugative anti-addition (Scheme 1.23a). When terminal alkynes were employed with AgOTf as the co-catalyst, the Markovnikov products formed were isomerised to the thermodynamic enol ester *in situ* (Scheme 1.23b).



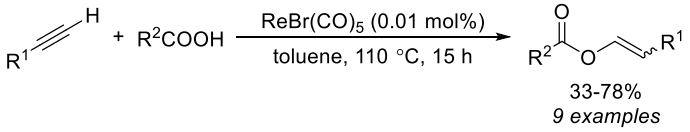
Scheme 1.23 Au-catalysed hydro-oxycarbonylation of alkynes

Silver-catalysed hydro-oxycarbonylation of alkynes remains rare. In an example, Bellina and co-workers demonstrated, with a limited substrate scope, that the regioselectivity of the intramolecular addition of carboxylic acids to alkynes could be tuned by the type of silver catalysts used (Scheme 1.24).[113] The use of Ag powder afforded (*Z*)-3-(1-alkylidene)-phthalides **1.10** while the use of $AgNO_3$ gave 3-substituted isocoumarins **1.11** in moderate to excellent yields.



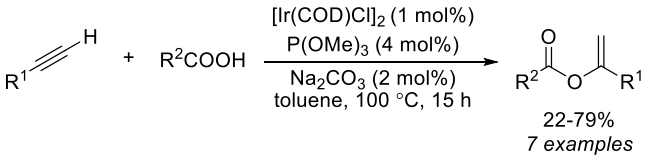
Scheme 1.24 Ag-catalysed intramolecular hydro-oxycarbonylation

Hua and Tian demonstrated the use of $ReBr(CO)_5$ for the addition of acetic, acrylic and benzoic acids to terminal alkynes with the anti-Markovnikov products formed almost exclusively (Scheme 1.25).[114] The *E*/*Z* selectivity was found to be influenced by the bulkiness of the alkyne substituents. The low catalyst loading and ability to recover the catalyst proved advantageous.



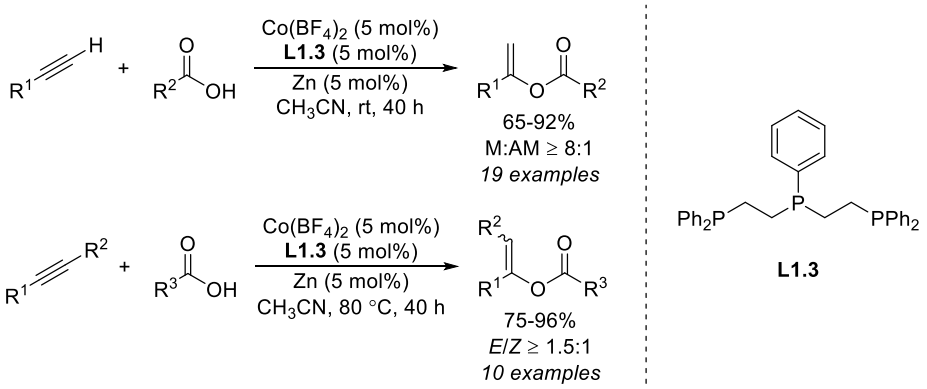
Scheme 1.25 Re-catalysed hydro-oxycarbonylation of terminal alkynes

Ishii and co-workers were the first and only researchers to demonstrate the use of iridium as a catalyst for the hydro-oxycarbonylation of terminal alkynes (Scheme 1.26).[115] While they reported the formation of the Markovnikov product as the major adduct, they demonstrated that the regioselectivity of the transformation was influenced by the phosphite ligands employed. The use of $P(OMe)_3$ or $P(O^iPr)_3$ gave Markovnikov selectivity while the use of $P(OPh)_3$ increased the amount of anti-Markovnikov products formed. The presence of base was necessary to speed up the reaction, presumably by helping to deprotonate the carboxylic acid.



Scheme 1.26 Ir-catalysed hydro-oxycarbonylation of terminal alkynes

The first cobalt-catalysed hydro-oxycarbonylation of alkynes was reported in 2018 by Chen and Li (Scheme 1.27).[116] The presence of a sub-stoichiometric amount of zinc helps to generate the active Co(I) species. Triphos ligand **L1.3** was found to be necessary for the transformation, as monodentate PPh_3 and bidentate dppm, dppb and DPEPhos ligands gave no reactivity. While the reaction gave good control of regioselectivity for both additions to terminal and internal alkynes, a long reaction time of 40 hours was necessary to obtain moderate to good yields of the enol esters formed.



Scheme 1.27 Co-catalysed hydro-oxycarbonylation of alkynes

1.3 Copper-Catalysed Reactions

The interest in the use of copper for catalysis has grown in the past decades. Copper presents advantages over precious transition metals; its abundance, low cost and low toxicity in the form of copper salts have motivated chemists to explore its capacity as a catalyst for more sustainable chemistry. Copper has four main oxidation states: Cu^0, Cu^I, Cu^{II} and Cu^{III}, and can perform both one-electron and two-electrons transfer

processes, making it a very attractive reagent. It is, hence, unsurprising that copper has gradually been sought to replace other precious metals for catalysis. Some of the notable reactions that have been widely explored include cycloaddition, cross-coupling, conjugate addition, C-H functionalisation, carbene chemistry and fluorination. In this section, copper-catalysed addition reactions to unsaturated bonds will be reviewed.

1.3.1 1,3-Dipolar Cycloaddition Reactions

Copper(I)-catalysed [3+2] cycloaddition reactions have often been demonstrated with aza-allyl type 1,3-dipoles such as nitrones, azomethine imines, azomethine ylides and azimidines, with both alkenes and alkynes as the corresponding dipolarophiles (Figure 1.1).[117] These reactions allow the synthesis of many types of nitrogen-containing heterocycles, with good enantioselectivity when suitable chiral ligands are used.

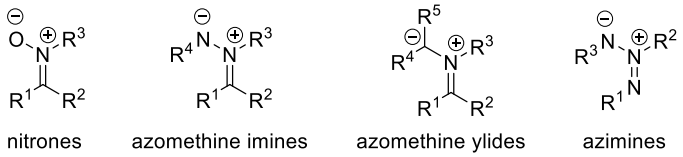
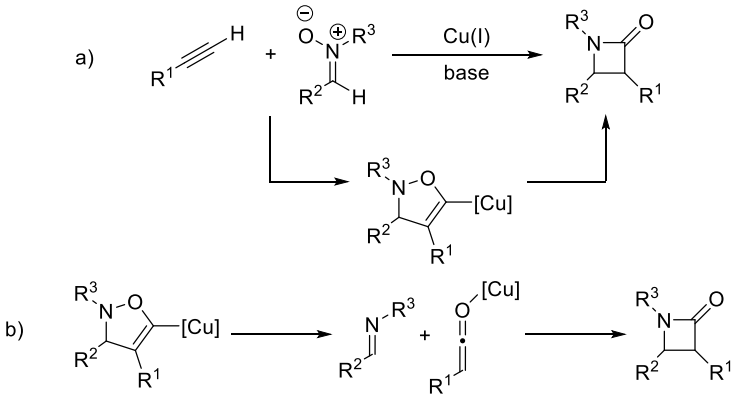


Figure 1.1 Selected 1,3-dipoles for the copper-catalysed [3+2] cycloaddition reactions

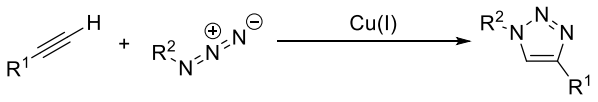
The Kinugasa reaction for the synthesis of *β*-lactams is one such example (Scheme 1.28a).[118–120] The [3+2] cycloaddition of a nitrone and an alkyne afforded the 5-membered metal complex, which later collapsed into the 4-membered ring upon protonation of the nitrogen.[117] While the Kinugasa reaction allows rapid access to *β*-lactams, by-products are often formed. In 2018, Hein and co-workers reported a revised version of the mechanism in order to explain the observations seen by other groups (Scheme 1.28b).[121] They proposed the [3+2] cycloreversion of the 5-membered metal complex to give a ketene and imine. The presence of these intermediates helped to explain the side products observed in the Kinugasa reaction and is consistent with the kinetics

data gathered for the mechanism. The intermediates then undergo a copper-aided [2+2] cycloaddition to give the desired *β*-lactams.



Scheme 1.28 Kinugasa reaction for the formation of *β*-lactams

The copper-catalysed alkyne-azide cycloaddition (CuAAC) is one of the most well-known copper-catalysed 1,3-dipolar addition reactions (Scheme 1.29). While the Huisgen cycloaddition has been known for many years,[122] the copper(I)-catalysed variant was first reported by Sharpless[123] and Meldal[124] independently in 2002. The reaction allows the regioselective formation of 1,4-disubstituted triazoles in good to excellent yields. The robust reaction is catalysed by many Cu(I) salts although the *in situ* formation of the Cu(I) catalyst from Cu(II) salts and a reductant is preferred. The reaction can tolerate a wide range of functional groups and can also be performed in an aqueous medium.



Scheme 1.29 Copper-catalysed alkyne-azide cycloaddition (CuAAC)

Initial views on the mechanism of the catalytic cycle proposed the formation of a copper(I) acetylidene, followed by coordination of the azide to the copper and nucleophilic addition of the acetylide carbon to the terminal nitrogen of the azide.

Protonation of the formed copper–triazolide generates the triazole.[124] However, recent developments have demonstrated that the reaction is in fact second order with respect to copper, suggesting the presence of polynuclear copper(I) species. Fokin and co-workers later modified the proposed mechanism to include two copper atoms (Figure 1.2).[125] They proposed that the initial formation of a copper(I) acetylidene species is driven by the coordination of another incoming copper atom. The dinuclear species then undergoes coordination to the azide after attack of the acetylidene carbon on the terminal nitrogen of the azide. The closing of the five-membered ring then prompts the loss of one copper atom, resulting in a metallocycle that gives the final triazole product after protonation.

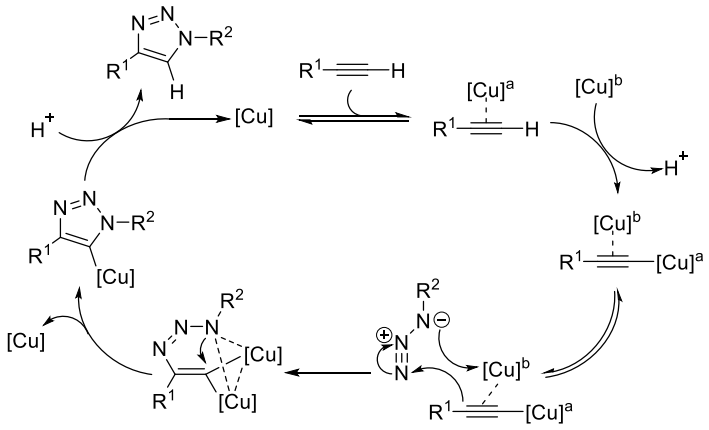
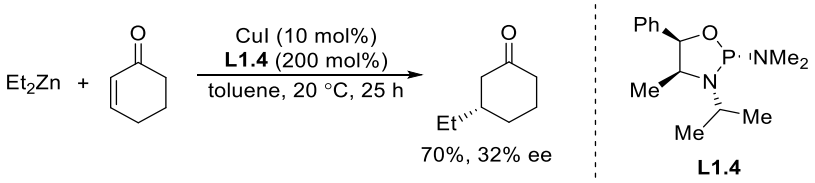


Figure 1.2 Proposed mechanism for the CuAAC reaction by Fokin and co-workers

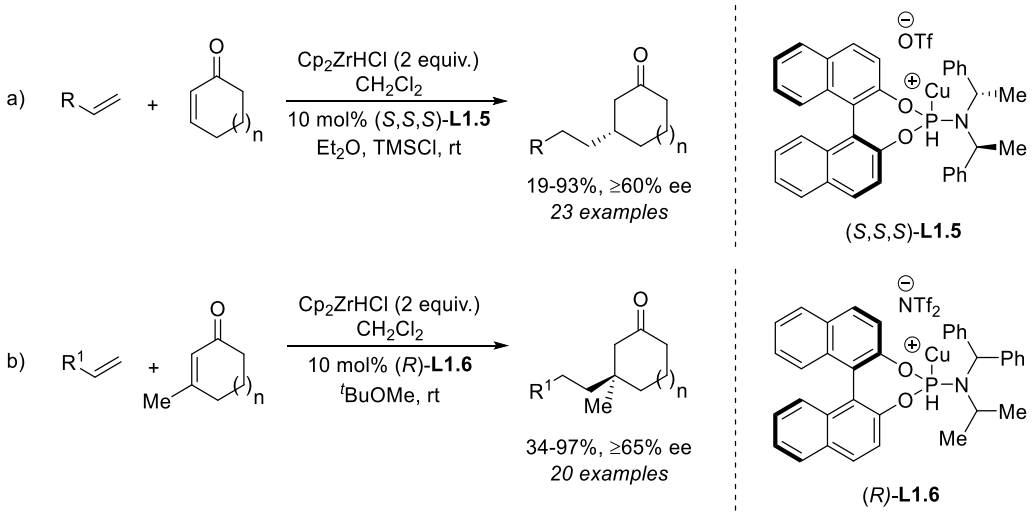
1.3.2 Asymmetric Conjugate Addition

In 1993, Alexakis and co-workers introduced the use of organozinc reagents for the copper-catalysed asymmetric conjugate addition of cyclic enones by employing a chiral phosphorus ligand **L1.4** (Scheme 1.30).[126] Since then, many phosphorus-based ligands such as phosphines, phosphoramidites, phosphites and phosphinites have been synthesised and used in conjunction with organozinc reagents, giving excellent yields and ees.[127–134] Other types of organometallic nucleophiles that have also been used included Grignard reagents, alkyl aluminiums and alkyl lithiums.



Scheme 1.30 First copper-catalysed asymmetric conjugate addition using organozinc reagents

A more recent development has extended this list of organometallic reagents to include zirconium and boron. In 2012, Fletcher and co-workers reported the strategy of using alkylzirconium reagents formed *in situ* from the hydrometallation of alkenes with the commercially available Schwartz's reagent (Scheme 1.31a).[135]

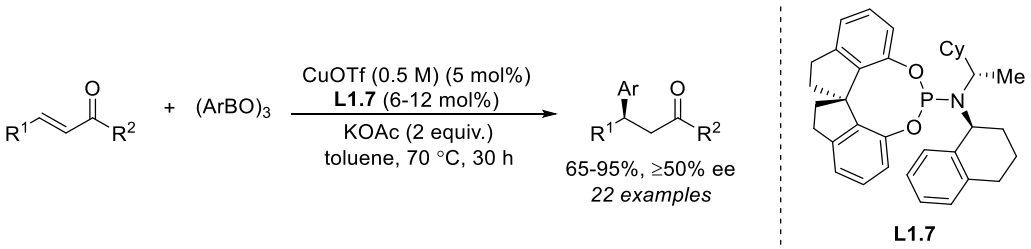


Scheme 1.31 Copper-catalysed asymmetric conjugate addition using organozirconium reagents

The reaction employed the use of a pre-formed catalyst complex that was easier to handle and less air-sensitive compared to the copper(I) triflate benzene complex. The same transformation can be applied to make quaternary centres, with a slight tweak in conditions and catalyst used (Scheme 1.31b).[136]

Takatsu *et al.*[137] and Yoshida *et al.*[138] have both reported the use of copper(I)/NHC systems to catalyse the addition of organoboron reagents to alkenes. The use of organoboron reagents presents an advantage over previous organometallic nucleophiles

used as they are generally not air-sensitive and can be handled with ease. While there was a reasonable scope for the organoboron reagents, both systems could only be used on highly activated Michael acceptors, namely α-cyanoacrylates and acroylimidazoles, respectively. In 2016, Zhou and co-workers reported an improved method using organoboron reagents which gave high yields and excellent ees (Scheme 1.32).[139] They demonstrated the copper-catalysed asymmetric conjugate addition of arylboroxines to enones using a phosphoramidite ligand.

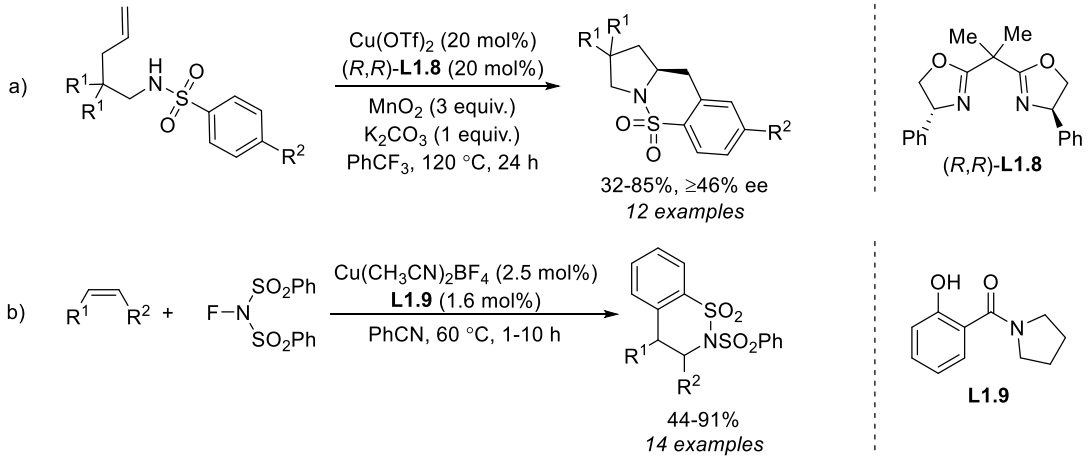


Scheme 1.32 Copper-catalysed conjugated addition with organoboron reagents

1.3.3 Heterocycle Synthesis *via* Addition of Heteroatoms to Unsaturated C–C Bonds

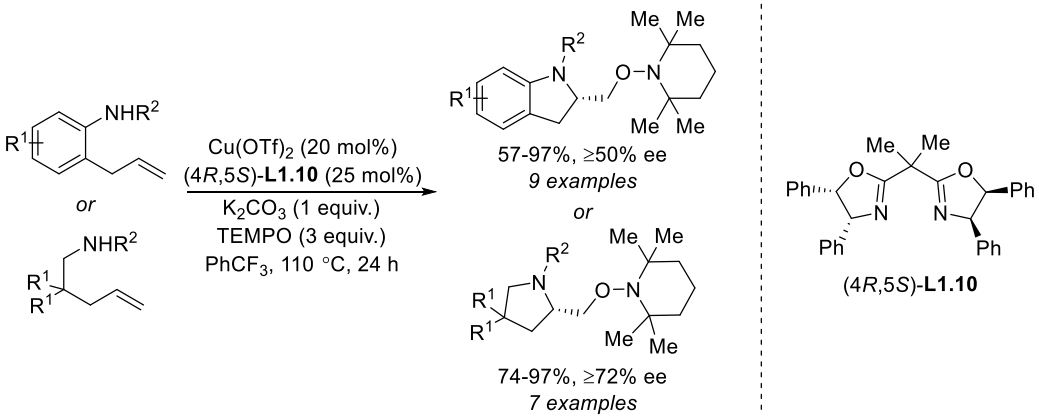
One of the more direct methods for heterocycle synthesis involves the intramolecular addition of heteroatoms into unsaturated carbon-carbon bonds. In the past several decades, copper has been developed as a catalyst for such transformations.

In 2007, Chemler and Zeng reported the first copper-catalysed asymmetric intramolecular carboamination of aryl sulfonamides to afford chiral sultams in moderate to good yields and ees (Scheme 1.33a).[140] This was an improvement from previous work in the group, where three equivalents of copper salt had to be used.[141] Later, Kanai and co-workers further extended the transformation by demonstrating that it can be done intermolecularly (Scheme 1.33b).[142] These two key reports illustrate both the ability and potential of utilising copper as a catalyst for carboamination of alkenes.



Scheme 1.33 Copper-catalysed carboamination of alkenes

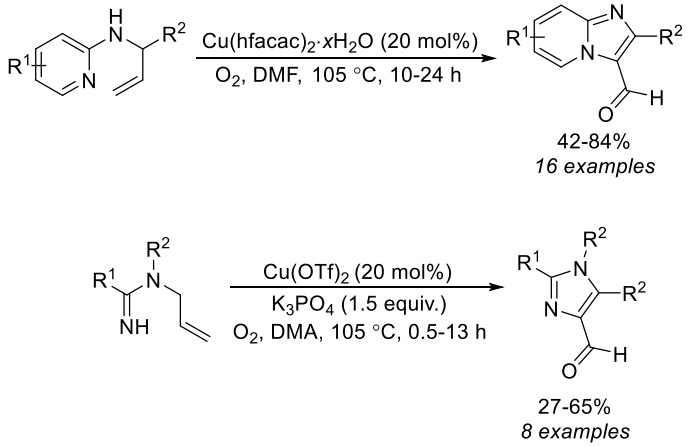
The oxyamination of unsaturated bonds is another useful transformation, as it allows the introduction of two different heteroatoms at the same time. In 2009, Chemler and co-workers reported the first copper-catalysed enantioselective intramolecular oxyamination between sulfonamides and TEMPO (Scheme 1.34).[143] By utilising *N*-sulfonyl-2-allyl aniline derivatives and 4-pentenylamine derivatives, chiral indolines and pyrrolidines could be formed in good yields.



Scheme 1.34 Copper-catalysed enantioselective intramolecular oxyamination

Zhu and co-workers reported the copper-catalysed dehydrogenative oxyamination of 2-aminopyridine derivatives to give imidazo[1,2-*a*]pyridine-3-carbaldehydes and 1,2-disubstituted imidazole-4-carbaldehydes in moderate to good yields

(Scheme 1.35).[144] Through mechanistic studies, they postulated that the oxygen atom of the corresponding aldehydes was derived from O_2. The addition aldehyde handle in the products allows further functional group interconversions.



Scheme 1.35 Copper-catalysed dehydrogenative oxyamination

1.4 Project Aims

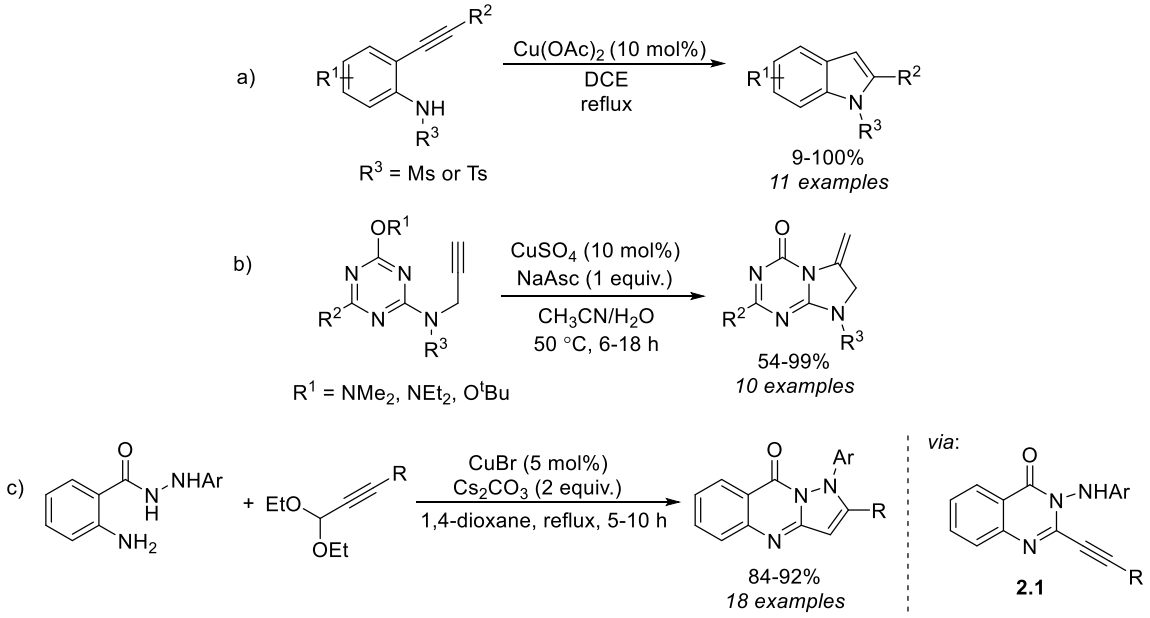
The literature review above has demonstrated the advantages in developing transition metal-catalysed reactions for both hydroamination and hydro-oxycarbonylation. However, the use of copper as a catalyst for these reactions remains scarce even though copper has certainly demonstrated its ability to act as a diverse catalyst for addition reactions to unsaturated bonds. With the move towards more sustainable chemistry, it is pertinent that we exploit copper as a catalyst and expand the types of reactions it can be applied to. With this vision in mind, the following chapters will describe our work on using copper as a catalyst for the novel hydroamination and hydro-oxycarbonylation of terminal alkynes.

Chapter 2. Copper-Catalysed Hydroamination of Alkynes, and the Development of a New Heterocycle Synthesis

2.1 Introduction

2.1.1 Copper-Catalysed Hydroamination

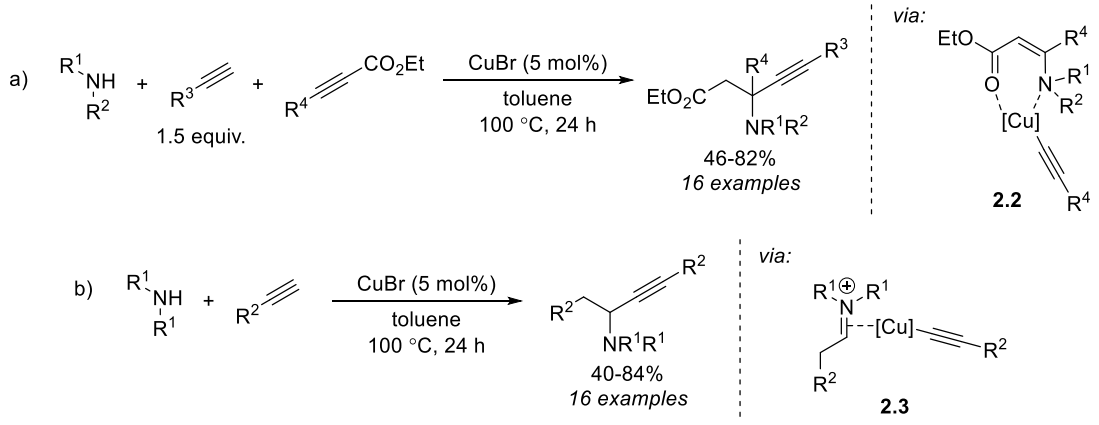
In 2004, Hiroya *et al*. introduced the use of copper(II) salts for the intramolecular cyclisation of 2-ethynylaniline derivatives for the synthesis of indoles (Scheme 2.1a).[145] $Cu(OAc)_2$ was found to activate the alkyne by acting as a Lewis acid before attack by the nitrogen lone pair for cyclisation. However, the reaction only worked well for sulfonamides. Similarly, Fokin and co-workers demonstrated the use of $CuSO_4$ on *N*-substituted hydroxylamine derivatives for the synthesis of triazinones (Scheme 2.1b).[146] Stoichiometric amounts of sodium ascorbate were necessary to achieve good conversions, as it helped to regenerate the Cu(I) species.



Scheme 2.1 Cu-catalysed hydroamination of alkynes for synthesis of heterocycles

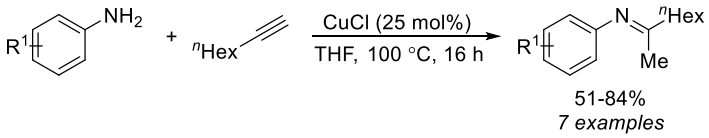
Chen *et al*. later exploited copper's ability to perform hydroaminations to form complex pyrazoloquinazolines from benzohydrazides and propynal diethyl acetals (Scheme 2.1c).[147] An initial CuBr-catalysed cyclisation and aromatisation occurs to give rise to intermediate **2.1**. From here, intermediate **2.1** undergoes a copper-catalysed intramolecular hydroamination to give the corresponding heterocycles in excellent yields. The one pot-method allowed the direct formation of two hetero-rings.

Li and co-workers reported the intermolecular hydroamination of alkynes for the synthesis of *γ*,*δ*-alkynyl-*β*-amino acid derivatives and propargyl amines (Scheme 2.2).[148,149] In both examples, the three-component reactions were catalysed by CuBr. It was postulated that the copper catalyst inserts into the terminal alkyne to form a copper-alkylidene species in both reactions. In the synthesis of *γ*,*δ*-alkynyl-*β*-amino acid derivatives, the copper-alkylidene specie coordinates to both the oxygen and nitrogen in the initial hydroamination product to give intermediate **2.2** (Scheme 2.2a), while in the synthesis of propargyl amines, the copper-alkylidene specie coordinates to the iminium product to give intermediate **2.3** (Scheme 2.2b). The formation of these key intermediates helped to facilitate the second hydroamination step.



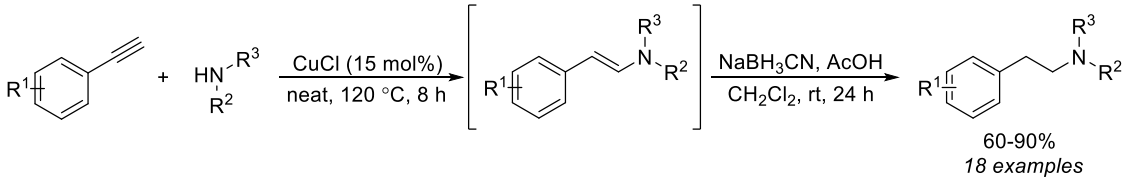
Scheme 2.2 Cu-catalysed intermolecular hydroamination

In 2011, Robbins and Hartwig exploited the efficiency of high-throughput methods to discover new reactions.[150] By screening a variety of catalysts and ligands with an assortment of substrates, they discovered a new copper-catalysed alkyne hydroamination reaction (Scheme 2.3). As a proof of concept, they demonstrated the ligand-free addition of aniline derivatives into 1-octyne using a CuCl catalyst, giving the corresponding imines in moderate to good yields, with good functional group tolerance on the aryl ring.



Scheme 2.3 Cu-catalysed intermolecular hydroamination of alkynes with aromatic amines

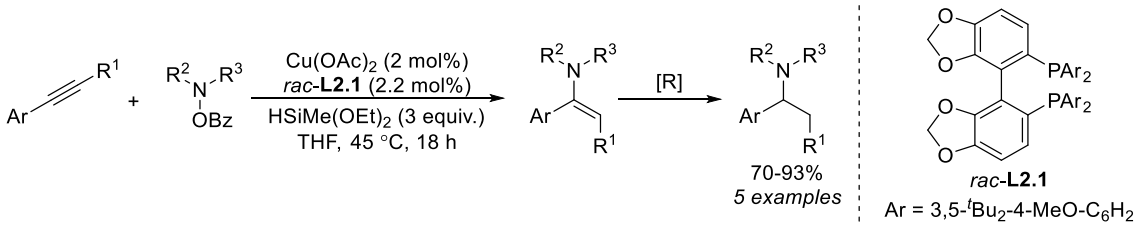
Monnier and co-workers demonstrated the ligand-free addition of secondary aliphatic amines into phenylacetylene derivatives with a CuCN catalyst to obtain (*E*)-enamines as the major product, with a small amount of the Markovnikov enamine and its corresponding hydrolysed product also obtained (Scheme 2.4).[151] As the (*E*)-enamines could not be isolated using column chromatography, reduction using $NaBH_3CN$ was performed to yield the tertiary amines in moderate to good yields.



Scheme 2.4 Cu-catalysed intermolecular hydroamination of phenylacetylene derivatives

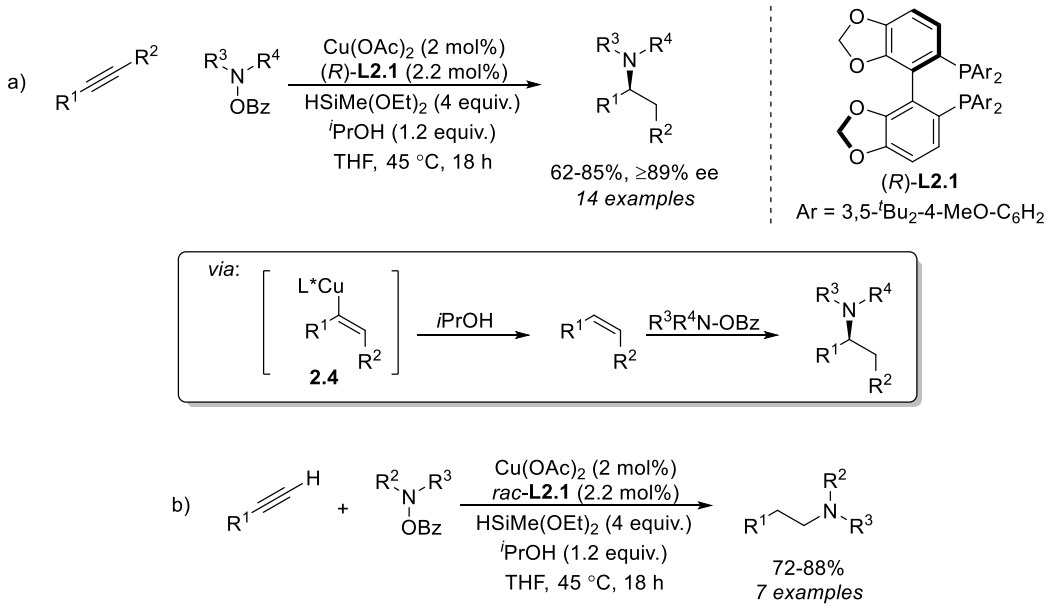
Extensive work has been done by Buchwald and co-workers in the area of Cu(I)-catalysed reactions of alkenes and alkynes.[61] Regarding copper-catalysed hydroamination of alkynes, Shi and Buchwald demonstrated the easy access to

(*E*)-enamines (Scheme 2.5), *α*-chiral branched alkylamines, and linear alkylamines (Scheme 2.6) using both internal and terminal alkynes.[152]



Scheme 2.5 Cu-catalysed hydroamination of alkynes to form (*E*)-enamines

Notably, the reaction could tolerate sterically hindered hydroxylamines and a wide range of functional groups while retaining excellent regioselectivity (>19:1) for the hydroamination of unsymmetrical internal alkynes (Scheme 2.6a). For the formation of alkylamines, an initial copper-catalysed reduction of the alkynes to alkenes occurs. The alkenes formed *in situ* then undergo hydroamination with the electrophilic amine source to furnish either the *α*-chiral branched alkylamines and linear alkylamines in moderate to good yields.

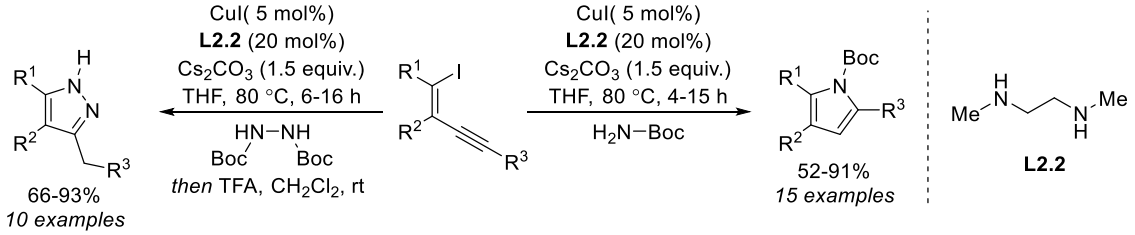


Scheme 2.6 Cu-catalysed hydroamination of alkynes to form alkylamines

The reduction was made possible by the presence of a protic source, in this case isopropanol, to protonate the vinylcopper intermediate **2.4** and give the resulting alkene

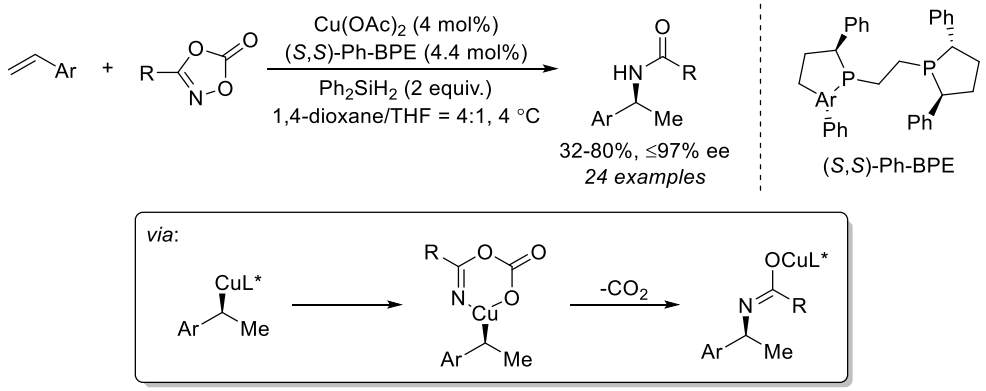
that can undergo hydroamination. Use of terminal alkynes saw regioselectivity for the terminal unsaturated carbon, giving rise to linear alkylamines (Scheme 2.6b).

While copper-catalysed addition of simple amines to alkenes and alkynes has been more apparent, the use of amides as nucleophiles for addition into alkenes and alkynes has been rare. Two examples have been reported by the Buchwald group.[153,154] In the first example, a domino sequence of copper-catalysed C–N coupling and hydroamidation furnishes pyrazoles and pyrroles in moderate to excellent yields (Scheme 2.7). The transformation exploited copper's ability to couple amides to C–I bonds, and by employing bis(Boc)hydrazine and ^{t}butyl carbamate as nucleophiles, afforded amido-alkynes that undergo an intramolecular hydroamidation to give the two different heterocycles. The formation of pyrroles occurs through a 5-*endo-dig* cyclisation while the formation of the pyrazoles occurs through a 5-*exo-dig* cyclisation followed by TFA deprotection.



Scheme 2.7 Cu-catalysed C–N coupling/hydroamidation for heterocycle synthesis

In the second example, copper-catalysed hydroamidation of styrene derivatives was illustrated using 1,4,2-dioxazol-5-ones as the electrophilic amidating reagents (Scheme 2.8). In the presence of the chiral ligand (*S*,*S*)-Ph-BPE, moderate to good yields of chiral amides were furnished with good to excellent enantioselectivity. The formation of a alkylcuprate specie first occurs from the insertion of Cu(I) into the styrene, before a N–O bond insertion and the loss of CO_2 led to the imine intermediate.



Scheme 2.8 Cu-catalysed asymmetric hydroamidation of styrene derivatives

2.1.2 Pyrrolinone Synthesis

Nitrogen-containing heterocycles are in high demand due to their frequent presence in pharmaceuticals and agrochemicals.[155–157] In the 1994 FDA-approved drugs database, 59% of the small-molecule drugs were found to contain at least one nitrogen-based heterocycle. In addition, five-membered *N*-heterocycles are ubiquitous in both synthetic and natural molecules with good biological activities.[158] It is, hence, undoubtable, that the development of *N*-heterocycle synthesis methods remains important. Pyrrolinone is a five-membered *N*-heterocycle with an amide functional group (Figure 2.1a). We are interested in the synthesis of 5-ylidenepyrrol-2(5*H*)-ones as they can be found in complex biologically active molecules (Figure 2.1b).[159–163] In addition, the presence of additional alkene unsaturated bonds allows them to be intermediates towards synthesis of other useful pharmaceutical molecules such as antibiotics.[164]

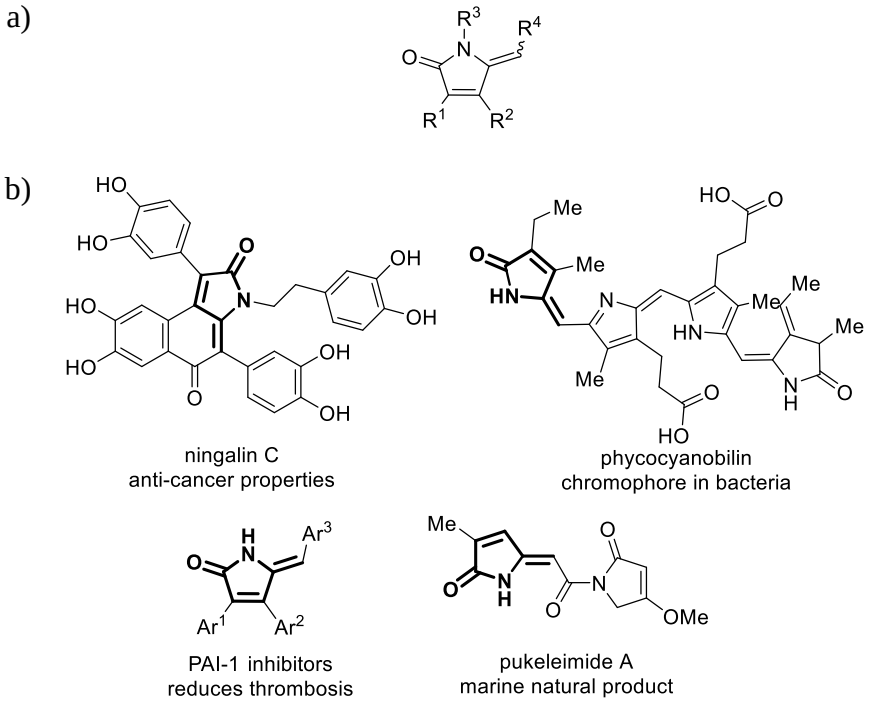
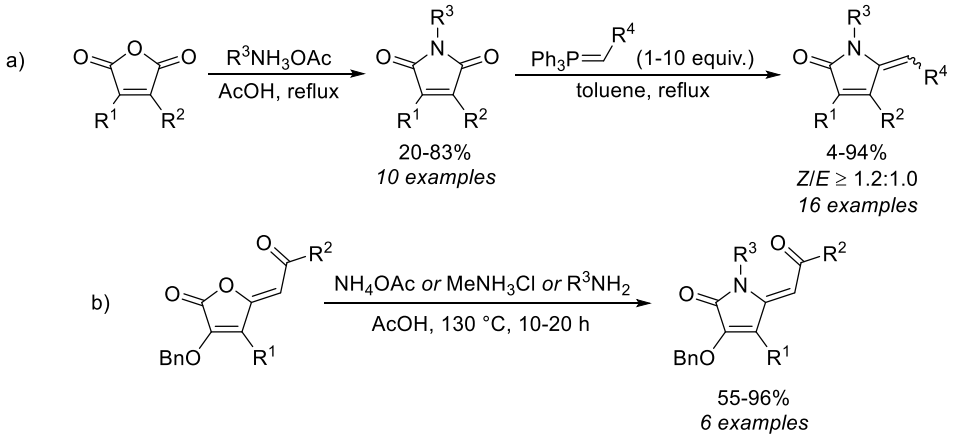


Figure 2.1a) Structure of 5-ylidenepyrrol-2(5*H*)-ones **b)** Biologically relevant compounds containing the 5-ylidenepyrrol-2(5*H*)-one core

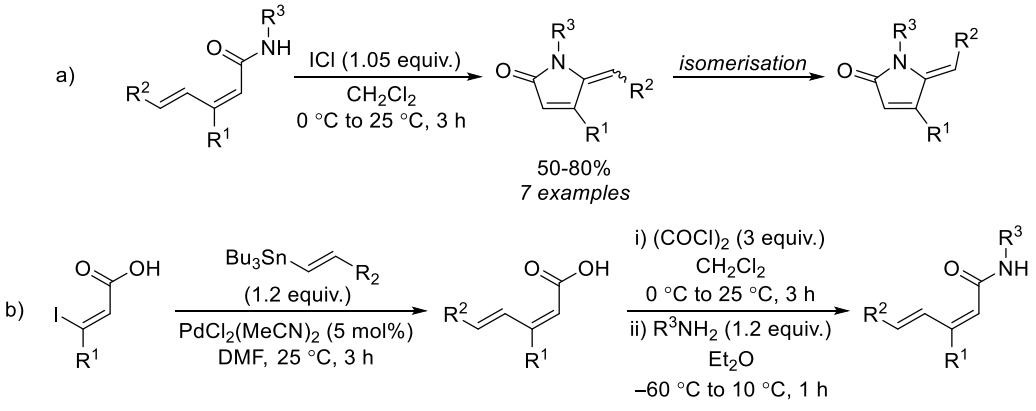
However, methods for making such structures remain few. One of the first methods for the synthesis of 5-ylidenepyrrol-2(5*H*)-ones involved the Wittig reaction of maleimides, as demonstrated by Pattenden and co-workers (Scheme 2.9a).[165] The reaction presented two main disadvantages; the maleimides had to first be obtained from the corresponding maleic anhydride and harsh reaction conditions were required to attain low to moderate yields of the final pyrrolinone derivatives.



Scheme 2.9 Early methods for synthesis of 5-ylidenepyrrol-2(5*H*)-ones

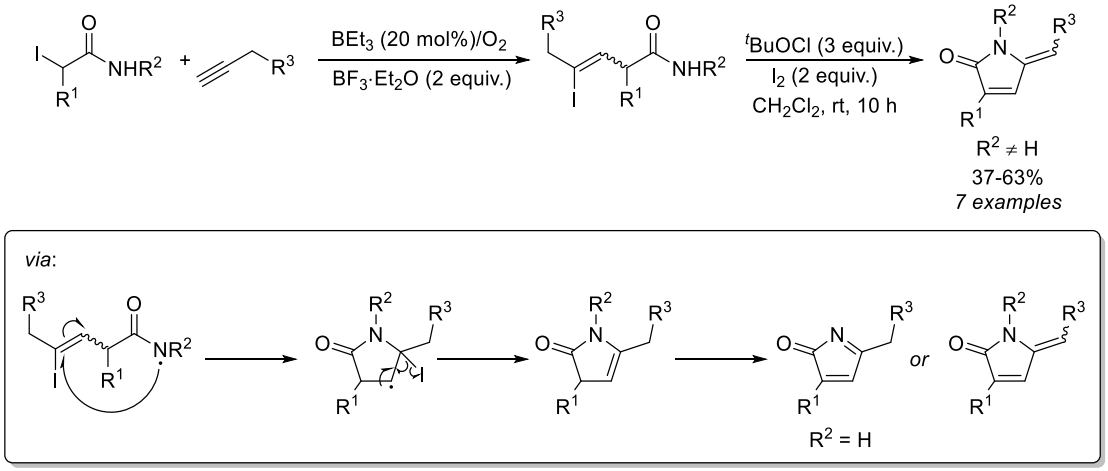
Alternatively, the 5-ylidenepyrrol-2(5*H*)-ones can be obtained directly from their oxygen-counterpart but required the benzyl protection of the free alcohol first (Scheme 2.9b). The late-stage functionalisation also demanded that any required substituents on the ring must be present from the start.[166]

Abarbri and co-workers exploited the electrophilic cyclisation of dienamides to obtain 5-ylidenepyrrol-2(5*H*)-ones (Scheme 2.10).[167,168] The regioselective transformation gave only the five-membered heterocycles *via* 5-*exo* cyclisation (Scheme 2.10a). Solvent effects were observed, with CH_2Cl_2 being the best option due to its excellent ability to dissolve the electrophile, ICl. Although initial product formation tended towards (*E*)-selectivity, they found the (*E*)-isomers easily isomerise to give only the thermodynamically favoured (*Z*)-isomers when left standing at room temperature. While the method provided an easy one-step conversion to obtain the desired pyrrolinones, the starting dienamides had to be obtained in two steps (Scheme 2.10b). An unfavourable Stille coupling of the iodo-alkenyl acids provided the corresponding (2*Z*,4*E*)-dienoic acids, which are later transformed into the dienamides *via* an amide coupling.



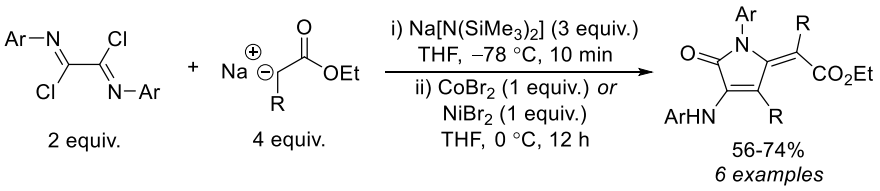
Scheme 2.10 Electrophilic cyclisation for the formation of 5-ylidenepyrrol-2(5*H*)-ones

In 2004, Li and Tang demonstrated that the cyclisation of a vinyl amide chain to obtain the corresponding *N*-heterocycles can also be performed *via* radical chemistry (Scheme 2.11).[169] The atom transfer radical addition (ATRA) of the iodoamide to a terminal alkyne afforded the corresponding vinyl amide. Upon treatment with ^{t}BuOCl and iodine, the vinyl amide forms an amidyl radical that undergoes the favoured 5-*exo* cyclisation to give the pyrrolinones in moderate yields. Notably, the use of primary amides afforded cyclic iminoketones instead while the use of phenyl substituted amide gave excellent selectivity for the (*E*)-isomers.



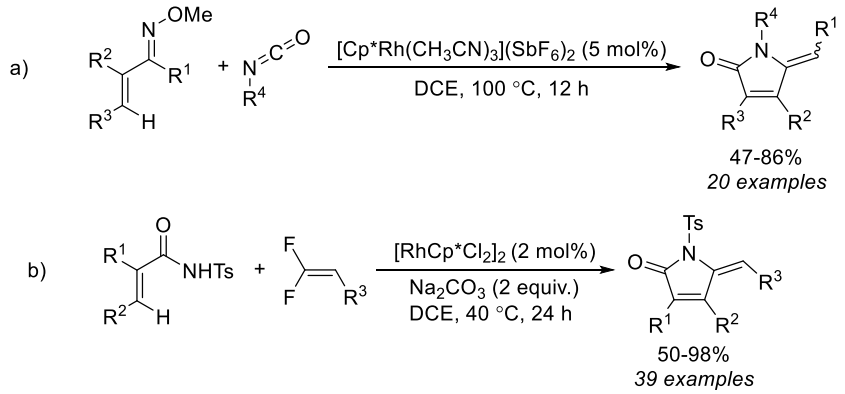
Scheme 2.11 Radical cyclisation to give 5-ylidenepyrrol-2(5*H*)-ones

Transition metals have also played a role in the synthesis of 5-ylidenepyrrol-2(5*H*)-ones. In 1999, Wuckelt *et al*. demonstrated the use of cobalt and nickel salts for the cyclisation of bis(imidoyl)chlorides with sodium diethyl malonate or sodium ethyl cyanoacetate to give the corresponding 5-ylidenepyrrol-2(5*H*)-ones (Scheme 2.12).[170] The metal salts were found to be crucial as only the linear product is formed in their absence. Unfortunately, the method presented poor atom economy as a stoichiometric amount of metal salts had to be used and an excess of reagents is required.



Scheme 2.12 Co and Ni salts mediated cyclisation to give 5-ylidenepyrrol-2(5*H*)-ones

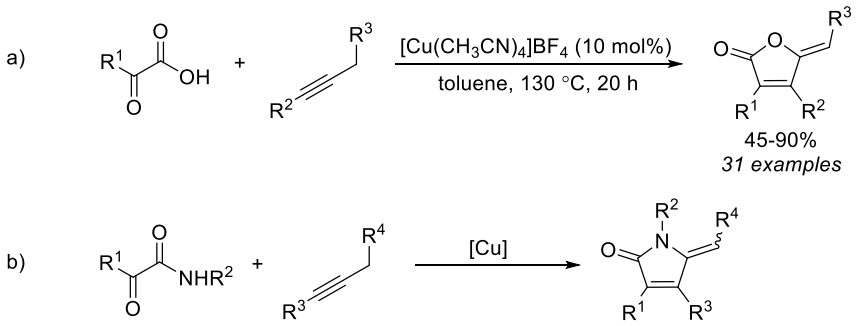
More recently, both Hou *et al*. and Liu *et al*. found that rhodium can catalyse the formation of these *N*-heterocycles (Scheme 2.13).[171,172] Hou *et al*. demonstrated that Rh(III) catalyst could be used to activate the alkenyl C–H bond of *α,β*-unsaturated oximes towards addition into isocyanates (Scheme 2.13a). Although 5-ylidenepyrrol-2(5*H*)-ones were formed in moderate to good yields with good functional-group tolerance, the *E*/*Z* selectivity was poor. On the other hand, Liu *et al*. exploited a rhodium-catalysed [4+1] annulation of *gem*-difluoroacrylates (Scheme 2.13b). As the transformation relied on the cleavage of both C–F bonds under mild conditions, the mechanism is similar to a formal dehydrogenative alkylidene carbene insertion. The reaction had a large functional group tolerance and gave only the (*E*)-isomers in moderate to excellent yields.



Scheme 2.13 Rh-catalysed cyclisation for the synthesis of 5-ylidenepyrrol-2(5*H*)-ones

2.1.3 Project Aims

The above methods illustrated the need to invent better transformations for easy access to 5-ylidenepyrrol-2(5*H*)-ones. With this desire in mind, we believed that we could exploit the capacity of copper to act as a base metal for addition reactions, allowing us to start from simple starting materials to furnish complex heterocycles. The use of addition reactions to obtain complex molecules presents an advantage due to its excellent atom economy. We previously reported the copper-catalysed addition and cyclisation of α-ketoacids and alkynes to give γ-ylidenebutenolides in moderate to good yields (Scheme 2.14a).[173]



Scheme 2.14 Cu-catalysed synthesis of γ-ylidenebutenolides and 5-ylidenepyrrolones

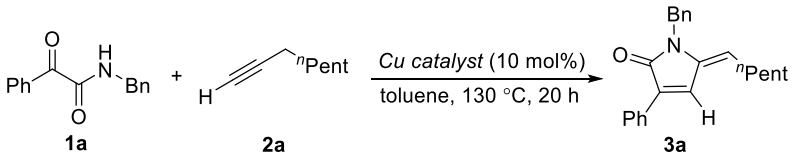
From here, we wanted to explore how extensive the reaction is, and what types of nucleophiles it can tolerate. We envisaged that the use of α-keto amides will afford the corresponding 2-pyrrolinone derivatives if the reaction undergoes the same pathway (Scheme 2.14b). Although the reaction could prove tricky as α-keto amides are much less acidic than the α-ketoacids, the novel copper-catalysed transformation would allow quick access to pyrrolinone motifs from readily accessible starting materials

.

2.2 Optimisation of Reaction Conditions

We first started the optimisation by attempting the reaction with different copper salts (Table 2.1). *α*-Ketoamide **1a** and 1-octyne **2a** were chosen as model substrates for the optimisation.

Table 2.1 Selected copper catalyst screening for the reaction between **1a** and **2a**[a]



Entry	Copper sources	Yield[b] (%)
1	$Cu(OAc)_2$	0
2	$CuBr_2$	0
3	$Cu(acac)_2$	0
4	$Cu(OTf)_2$	0
5	CuBr	0
6	CuOAc	0
7	Copper(I) 3-methylsalicylate	2
8	$CuBr(PPh_3)_3$	0
9	$(CuOTf)_2 \cdot C_6H_6$	5
10	$CuCO_3 \cdot Cu(OH)_2$	0
11	$[Cu(MeCN)]_4BF_4$	60
12	$[Cu(MeCN)]_4PF_6$	0
13	$[Cu(MeCN)]_4OTf$	0
14	$Cu(BF_4)_2.xH_2O$	27
15	$AgBF_4$	0
16	$NaBF_4$	0
17[c]	$[Cu(MeCN)]_4BF_4$	57

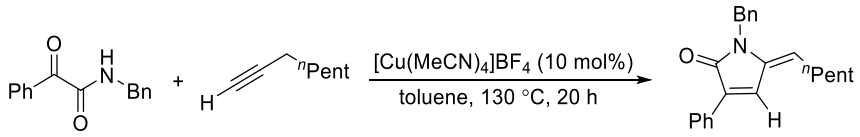
[a]Reaction conditions: *α*-ketoamide **1a** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), catalyst (0.030 mmol, 10 mol%), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard, obtained from single experiments. [c]$NaBF_4$ (0.30 mmol, 1.0 equiv.) added.

Interestingly, we found that the transformation with α-keto amides was very dependent on the choice of copper salt. While most of the copper(II) salts (entries 1–4) did not give any productive reaction, copper(I) 3-methylsalicylate, $(CuOTf)_2$ benzene complex and $[Cu(MeCN)]_4BF_4$ (entries 7, 9, 11) gave some reactivity out of all the copper (I) salts attempted (entries 5–13). Notably, the presence of PPh_3 as a ligand (entries 5 and 8) did not improve the reactivity of the copper(I) catalyst. In addition, the switch in counter anion from tetrafluoroborate to hexafluorophosphate (entry 12) and triflate (entry 13) did not yield any products. While the former is likely due to the insolubility of $[Cu(MeCN)_4]PF_6$ in toluene, the presence of tetrafluoroborate anion appeared to be necessary, as attempting the reaction with $Cu(BF_4)_2.xH_2O$ gave a 27% yield (entry 14). Through 1D NOESY experiment, we identified that the reaction gave only the (*E*)-isomer for pyrrolinone **3a**, rendering the reaction stereoselective. In order to confirm that the reaction was catalysed by copper, we also attempted the reaction with $AgBF_4$ and $NaBF_4$ (entries 15 and 16). The lack of reactivity suggested that the tetrafluoroborate anion may help to stabilise the intermediates formed during the reaction. Unfortunately, adding another equivalent of tetrafluoroborate anion in the form of $NaBF_4$ did not help to boost the yield (entry 17).

We next evaluated the equivalents of reagents and the concentrations to see if they have any effects on the yield of the reaction (Table 2.2). We found the reaction concentration to have a great effect on the yield, with a >4 fold increase in yield when the concentration was increased by 3 fold (entries 1 and 2). Although using a slight excess of α-ketoamide **1a** gave a good yield, further increasing the equivalent did not make much difference (entries 3 and 4). In addition, further increasing the concentration only gave a slight improvement of yield (entry 5). It was important to keep α-ketoamide **1a** in excess as

reversing the stoichiometric ratios of the reagents saw a significant drop in yields (entries 6 and 7).

Table 2.2 Equivalent and concentration screen for the reaction between **1a** and **2a**[a]



1a **2a** **3a**

Entry	**1a** (equiv.)	**2a** (equiv.)	Toluene (M)	Yield[b] (%)
1	1.2	1.0	0.2	13
2	1.2	1.0	0.6	60
3	1.5	1.0	0.6	63
4	2.0	1.0	0.6	61
5	2.0	1.0	1.0	69
6	1.0	1.5	0.6	32
7	1.0	2.0	0.6	30

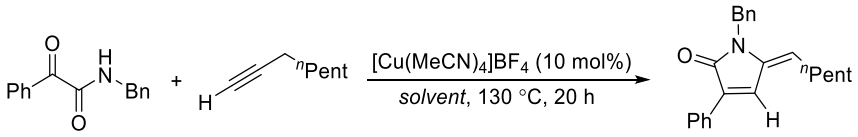
[a]Reaction conditions: $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), toluene, 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard, obtained from single experiments.

Ultimately, we chose to use 1.2 equivalents of *α*-ketoamide **1a**, 1.0 equivalent of 1-octyne **2a** at a reaction concentration of 0.6 M as our optimised conditions (entry 2). This was to prevent the solid amide reagent from being trapped at the side of the reaction vial before dissolving in toluene at 130 °C.

We also performed a solvent screen in order to determine the best solvent for the reaction (Table 2.3). We were surprised to see poor yields obtained when all isomers of xylene (entries 1–3) were used, as they have similar polarity to toluene. When we moved towards halogenated solvents (entries 4–7), the yields employing 1,1,2-trichlorobenzene, chlorobenzene and *α*, *α*, *α*-trifluorobenzene were poor, but 1,2-dichlorobenzene gave a moderate yield of 52%. Polar solvents such as MeCN and DMF (entries 8 and 9) resulted

in poor reactivity, especially for MeCN, where no reactivity was observed. This suggested that the MeCN ligands in the commercially available $[Cu(MeCN)_4]BF_4$ catalyst could be affecting the yield of the reaction. We next screened several phosphine- and nitrogen-based ligands (entry 10). However, attempts to improve the product yield were to no avail as all the ligands (dppm, dppe, dppp, dppb, dppBz, dcpe, bypyridyl, phenanthroline) used led to a very poor ≤10% yield. This indicated that the reaction performed best when the copper catalyst is not obstructed. Moreover, the use of inorganic bases (K_2CO_3, K_3PO_4, KH_2PO_4, NaOAc) as additives completely shut down the reaction (entry 11).

Table 2.3 Solvent, ligand and base screen for the reaction between **1a** and **2a**[a]



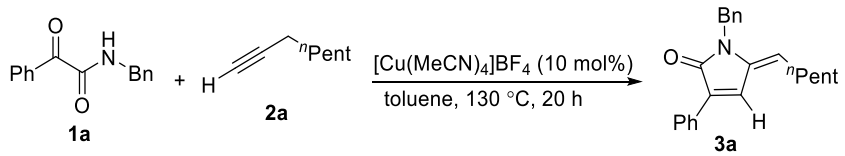
1a **2a** **3a**

Entry	Solvent	Yield[b] (%)
1	*o*-xylene	15
2	*p*-xylene	24
3	*m*-xylene	18
4	1,1,2-trichloroethane	2
5	chlorobenzene	23
6	1,2-dichlorobenzene	52
7	*α*, *α*, *α*-trifluorobenzene	39
8	acetonitrile	0
9	DMF	4
10[c]	toluene	≤10
11[d]	toluene	0

[a]Reaction conditions: *α*-ketoamide **1a** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), solvent (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard, obtained from single experiments. [c]10 mol% ligand (dppm, dppe, dppp, dppb, dppBz, dcpe, bypyridyl, phenanthroline) added. [d]1.0 equiv. of base (K_2CO_3, K_3PO_4, Et_3N, KH_2PO_4, NaOAc) added.

A final series of variations were also performed in order to understand the reaction better and improve its yield (Table 2.4). We first varied the reaction time and found that although the reaction did not go to completion after 5 and 10 hours (entries 1 and 2), prolonging the time to 30 hours (entry 3) saw no further improvement. Raising the temperature to 140 ºC was not beneficial (entry 4). We added an equivalent of H_2O to see if the byproduct obtained from the *N*-heterocycle synthesis was impeding the reactivity of the reaction but did not see a significant decrease in yield (entry 5). Performing the reaction under air led to a drop in yield to 49% (entry 6). Together with the lack of reactivity when copper(II) salts were used, we eliminated the possibility of a copper(II) species being the active catalyst in the reaction.

Table 2.4 Further screen for the reaction between **1a** and **2a**[a]



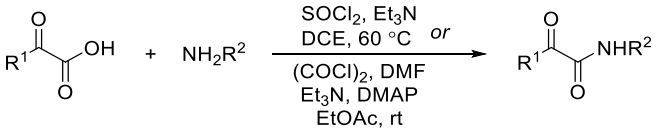
Entry	Variations	Yield[b] (%)
1	5 h	11
2	10 h	32
3	30 h	53
4	140 ºC	59
5	H_2O (1 equiv.)	52
6	Under air	49
7[c]	After 20 h, added 5 mol% of $[Cu(MeCN)_4]BF_4$	61
8[c]	After 20 h, added 1 equiv. of **2a**	53
9	0.25 equiv. of **2a** added every 5 h	50

[a]Reaction conditions: *α*-ketoamide **1a** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard, obtained from single experiments. [c]Reaction ran for another 20 h after addition.

In order to ensure that catalyst death was not the cause for the stagnation in product yield, an additional 5 mol% of $[Cu(MeCN)_4]BF_4$ was added after 20 hours, but no increase in yield was observed (entry 7). We later speculated the possibility of the loss of the alkyne reagent through copper-catalysed dimerisation as a side reaction. However, adding another equivalent of 1-octyne **2a** after 20 hours (entry 8) or adding 1-octyne **2a** periodically every 5 hours (entry 9) did not improve the yield. In addition, no dimerised products were observed in the NMR spectrum of the crude reaction mixture.

2.3 Substrate Scope

Having established the optimised conditions for the transformation, we turned our attention to the scope for the amides. While the *α*-ketoamides have to be prepared, they are readily accessed from the *α*-ketoacids *via* an amide coupling (Scheme 2.15). In both methods of amide coupling used, a chlorinating agent, either thionyl chloride or oxalyl chloride, was used to form the acid chloride before substitution of the acyl chloride by the respective amine.



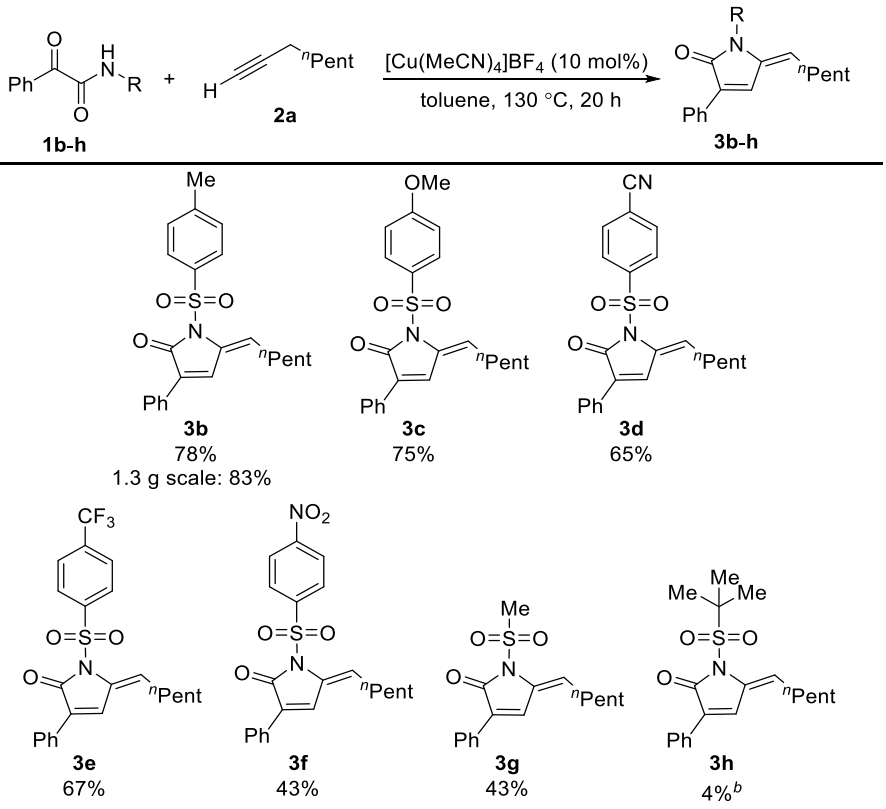
Scheme 2.15 Preparation of *α*-ketoamides

2.3.1 *N*-Substituted *α*-Ketoamide Scope

We first looked at the scope by synthesising several sulfonamides (Table 2.5). Notably, in all cases, only the (*E*)-isomers were obtained, rendering this transformation stereoselective. We found that amides with *N*-substituted sulfonamides gave moderate to good yields, depending on the electron density of the ring. Aryl groups containing electron-donating substituents (**3b** and **3c**) were better yielding than aryl groups

containing electron-withdrawing substituents (**3d**–**3f**). While having a simple methyl substituent (**3g**) gave modest yield, the reaction was affected by the steric bulk of the substituents as switching to the ^{t}butyl group drastically dropped the yield (**3h**). We were also happy to see that the synthesis of pyrrolinone **3b** could be achieved with no loss in yield on a 1.3 gramme scale.

Table 2.5 *N*-Sulfonamide scope[a]

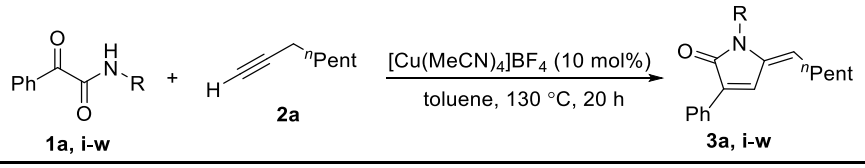


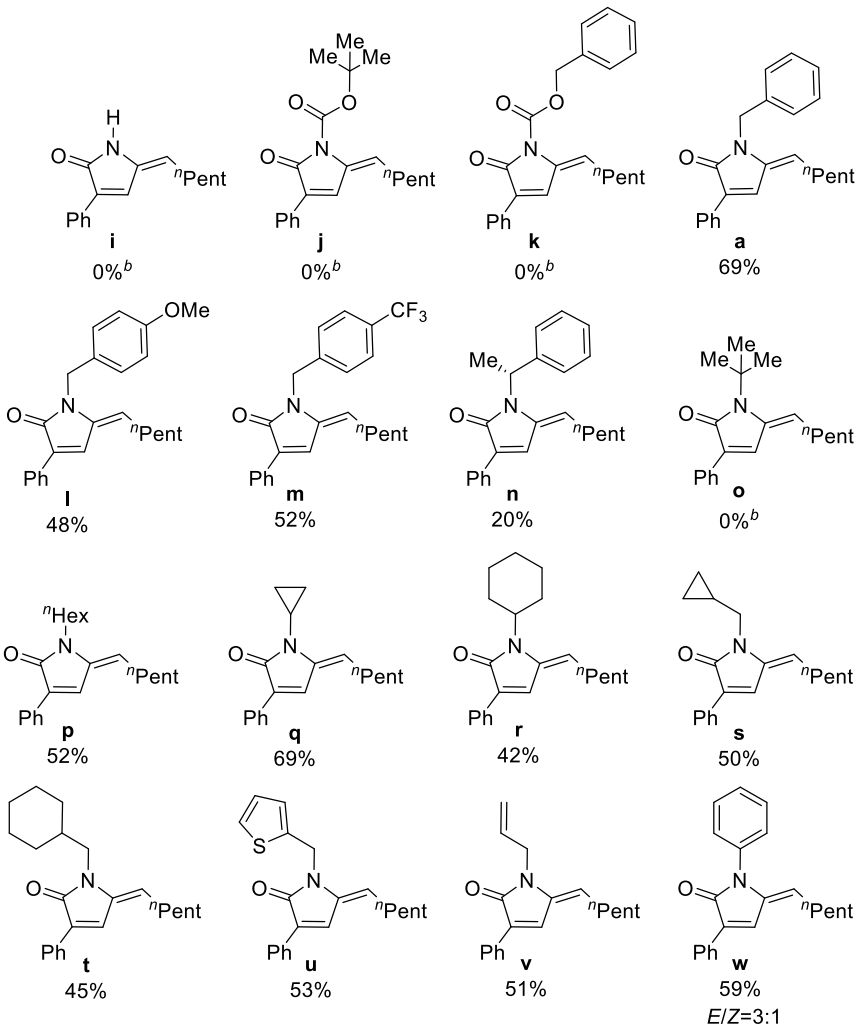
[a]Reaction conditions: *α*-ketoamide **1** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yield determined by ^{1}H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard, obtained from single experiments.

While the sulfonamide-protected amides performed well in the reaction, we wanted to see if it could be further extended to the other types of *α*-keto-amides (Table 2.6). We started by attempting the reaction with the primary *α*-keto-amide **1i** but found no reactivity after 20 hours. Unfortunately, Boc- and Cbz-protected amides **1j** and **1k** did not yield any productive reaction. In fact, the Boc protecting group was removed

under the reaction conditions as the primary α-keto-amide **1i** was observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Table 2.6 Scope for other *N*-substituted α-keto-amides[a]





[a]Reaction conditions: α-ketoamide **1a** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yield determined by ^{1}H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard, obtained from single experiments.

After repeating the reaction for the model substrate, an isolated yield of 69% was obtained for pyrrolinone **3a**. However, no trend was observed when either an electron-donating (**3l**) or an electron-withdrawing group (**3m**) was placed on the *para*-position of the benzyl

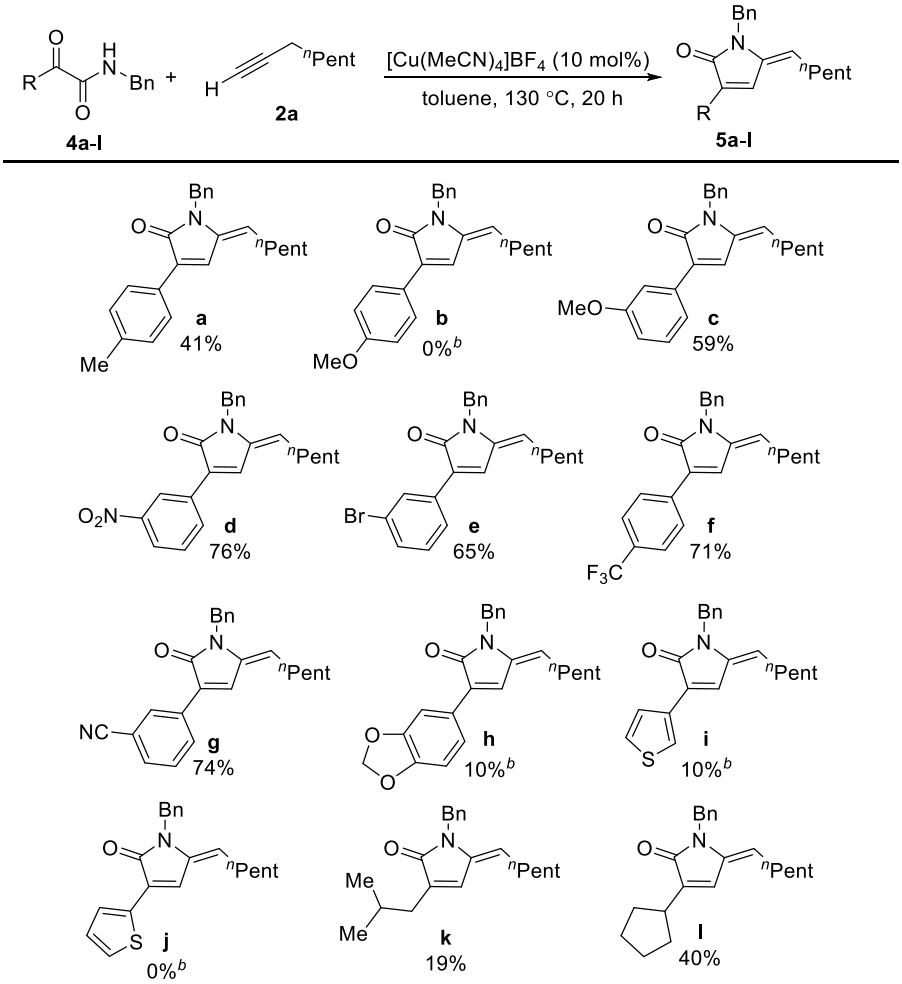
ring. Notably, the bulk around the nitrogen of the amide affected the reactivity as in the presence of an additional benzylic methyl group (**3n**), the yield dropped significantly. As a result, we were unsurprised to see that the presence of a sterically hindered ^{t}butyl group (**3o**) gave no reactivity. However, upon attempting the reaction with ^{n}hexyl α-keto-amide **1p** instead, we were happy to find that the corresponding product **3p** was obtained with a 52% yield. We later moved on to *N*-carbocycle α-keto-amides (**3q** and **3r**) as these rings are frequently present in potential drug compounds. While no observable trend based on the size of the carbocycle could be determined, a good 69% yield for pyrrolinone **3q** and no observation of any side products demonstrated that the reaction is not based on radical chemistry. Carbocycles (**3s** and **3t**) gave moderate yields and the thiophene group (**3u**) could also be tolerated. The use of *N*-allyl α-keto-amide **1v** afforded the corresponding pyrrolinone **3v** in 51% yield. The additional alkenyl functional group allows potential for further extension of the heterocycle. In the presence of a phenyl substituent (**1w**), we noted that although a good yield of 59% was obtained, some of the (*Z*)-isomer was observed, giving an *E*/*Z* ratio of 3:1.

2.3.2 β-Substituted α-Ketoamide Scope

The variation of the substituents at the β-position of the α-ketoamides was next investigated (Table 2.7). Attempts at using arene rings substituted with electron-donating groups saw moderate yields (**5a**–**c**) and we noted that the more electron dense is the ring, the poorer the reactivity. This was evident as an initial attempt at placing a methoxy group at the *para*-position of the ring (**5b**) gave no yield, but an improvement to 59% was observed when it was shifted to the *meta*-position (**5c**). In contrast, lowering the electron density of the aryl ring by placing different types of electron-withdrawing groups saw an improvement in yields (**5d**–**g**). We were delighted to see that the reaction could tolerate

the nitro (**5d**), bromo (**5e**), trifluoromethyl (**5f**) and nitrile (**5g**) groups with no issue. Attempts at using heterocycles such as benzodioxole (**5h**) and thiophenes (**5i** and **5j**) gave very low yields. Since thiophene displays similar aromaticity to benzene, we postulated that due to its close proximity to the carbonyl group, the sulfur atom present coordinated to the copper and hindered its ability to coordinate to the carbonyl group. Following the trend, we found the alkyl-substituted α-ketoamides (**4k** and **4l**) to be more challenging substrates but were still able to obtain moderate yields for the transformation.

Table 2.7 Variation at the β-position of the α-ketoamides[a]

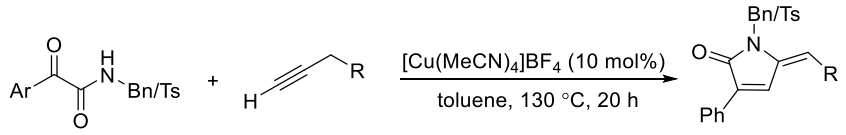


[a]Reaction conditions: α-ketoamide **4** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2.

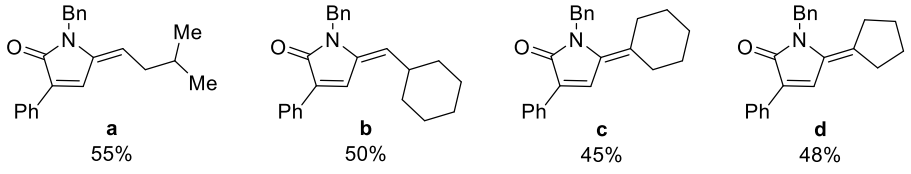
2.3.3 Alkyne Scope

Finally, we investigated the types of alkynes that could be tolerated in the reaction (Table 2.8). We found that other aliphatic alkynes gave moderate yields (**7a** and **7b**) and were happy to see that bulky carbocycles (**7c** and **7d**) and the presence of an aromatic ring (**7e**) could also be tolerated. With the less reactive alkynes, we had to switch to the more reactive *N*-tosyl *α*-ketoamide **1b** (**7f** and **7g**), and were happy to see that as a proof of concept, internal alkyne such as 4-octyne (**7h**) can react under the reaction conditions. With our understanding of how to improve reactivity of the *α*-keto amide, we synthesised a nitro-substituted keto amide with a tosyl substituent on the nitrogen (**6**) and demonstrated that an excellent yield of 81% (**7i**) can be obtained when reacted with a phthalimide-substituted alkyne.

Table 2.8 Alkyne scope[a]



1a-b, 6 **2b-j** **7a-i**



a 55% **b** 50% **c** 45% **d** 48%

e 46% **f** 27% **g** 25%

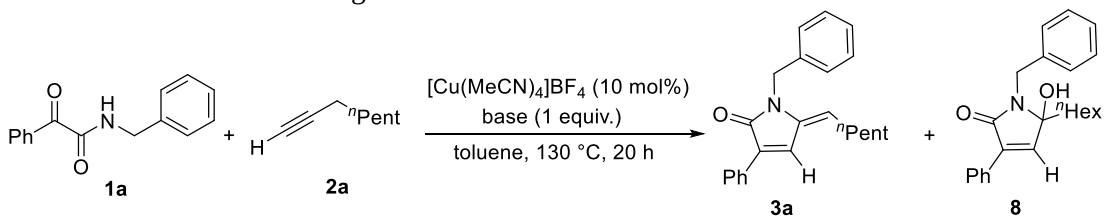
h 13%[b] **i** 81%

[a]Reaction conditions: *α*-ketoamide **1** *or* **6** (0.36 mmol, 1.2 equiv.), alkyne **2** (0.3 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2.

2.4 Formation of 5-hydroxypyrrol-2(5*H*)-ones

During our optimisation of the reaction between α-keto amide **1a** and 1-octyne **2a**, we investigated the use of organic bases as additives (Table 2.9), and were surprised to observe that the use of either DBU or DMAP led to the formation of a previously unobserved product **8** in 15% and 43% yield, respectively (entry 2 and 3). By-product **8** was identified to be a 5-hydroxypyrrol-2(5*H*)-one.

Table 2.9 Organic bases as an additive in the formation of **8**[a]

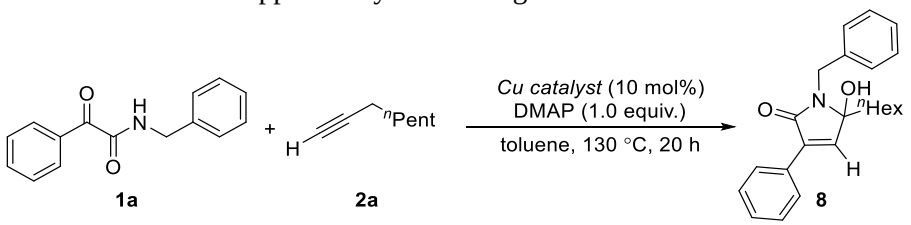


Entry	Base	Yield[b] of **3a** (%)	Yield[b] of **8** (%)
1	Et_3N	-	-
2	DBU	-	15
3	DMAP	-	43
4[c]	DMAP	-	27
5[d]	DMAP	-	50
6	4-(Methyl)aminopyridine	-	20
7	4-Aminopyridine	-	30
8	3-Aminopyridine	-	20
9	2-Aminopyridine	-	-
10	Pyridine	3	-
11	*N*-Methylaniline	46	-
12	*N*,*N*,-Dimethylaniline	6	-
13	2,6-Di-tert-butylpyridine	12	-

[a]Reaction conditions: α-ketoamide **1a** (0.36 mmol, 1.2 equiv.), 1-octyne **2a** (0.30 mmol, 1.0 equiv.), $[Cu(MeCN)_4]BF_4$ (0.030 mmol, 10 mol%), base (0.30 mmol, 1.0 equiv.), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as internal standard, obtained from single experiments. [c]DMAP (0.10 mmol, 0.33 equiv.) used. [d]DMAP (0.60 mmol, 2.0 equiv.) used.

We were intrigued by the formation of 5-hydroxypyrrol-2(5*H*)-ones and decided to investigate further. We varied the amount of DMAP present in order to identify its role. Although decreasing the amount of DMAP to 0.33 equivalents did reduce the yield to 27%, there was no significant increase in yield when 2.0 equivalents of DMAP was added. We also screened similar bases and observed that although bases with higher pKa values tend to lead to the formation of 5-hydroxypyrrol-2(5*H*)-one **8**, it was not the only factor. We noted that pyridine and aniline type-bases only gave varying amounts of 5-ylidenepyrrol-2(5*H*)-one **3a**, suggesting that both nitrogen atoms present in the base were necessary. This could also explain why the presence of DBU also resulted in the formation of 5-hydroxypyrrol-2(5*H*)-one **8**. Further optimisation was carried out to improve the yield of 5-hydroxypyrrol-2(5*H*)-one **8**. We first investigated the type of copper salts that can catalyse this reaction (Table 2.10).

Table 2.10 Copper catalyst screening for the formation of **8**[a]



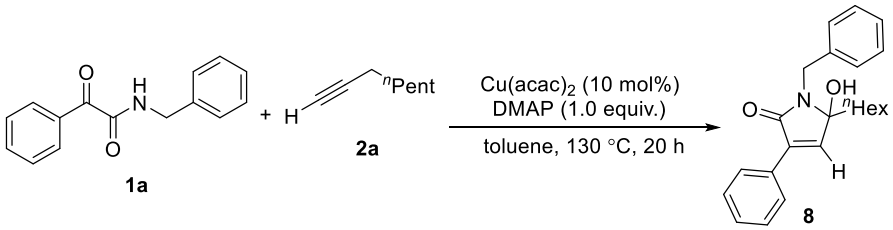
Entry	Copper sources	Yield[b] of **8** (%)
1	$Cu(BF_4)_2 \cdot H_2O$	43
2	$Cu(OAc)_2$	40
3	$CuBr_2$	11
4	$Cu(acac)_2$	54
5	$Cu(OTf)_2$	43
6	$CuCO_3 \cdot Cu(OH)_2$	18

[a]Reaction conditions: *α*-ketoamide **1a** (0.36 mmol, 1.2 equiv.), **2a** (0.30 mmol, 1.0 equiv.), catalyst (0.030 mmol, 10 mol%), base (0.30 mmol, 1.0 equiv.), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yields determined by ^{1}H NMR spectra of the crude reaction mixtures using nitromethane as internal standard, obtained from single experiments.

Our initial hit of 43% yield with $Cu(BF_4)_2 \cdot H_2O$ (entry 1) led us to believe that unlike our copper(I)-catalysed formation of 5-ylidenepyrrol-2(5*H*)-ones, copper(II) salts are also able to catalyse the formation of 5-hydroxypyrrol-2(5*H*)-ones. After further attempts with other Cu(II) salts (entries 2–6), $Cu(acac)_2$ (entry 4) gave the best yield of 54%.

Further screening (Table 2.11) indicated that while changing the stoichiometric ratio of *α*-ketoamide to alkyne to 1:2 (entry 1) did not make a difference, the reverse led to an increased isolated yield of 72% (entry 2). Addition of 1.0 equivalent of H_2O (entry 3) appeared to boost the yield slightly but the reaction was still sensitive to air (entry 4), suggesting that a Cu(I)/Cu(II) system may be present in the mechanism.

Table 2.11 Variations of conditions for the formation of **8**[a]

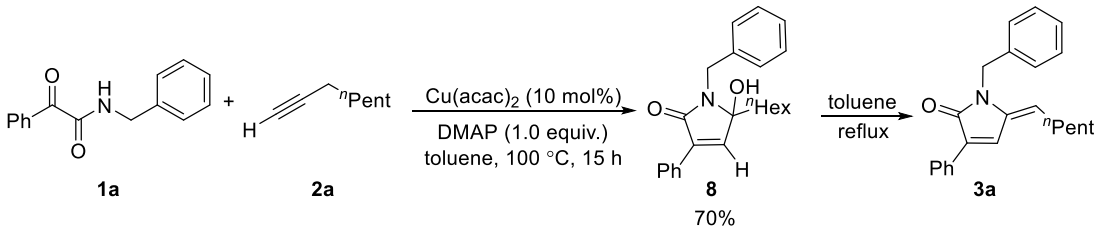


Entry	Variations	Yield[b] of **8** (%)
1	Amide: alkyne = 1:2	55
2	Amide: alkyne = 2:1	75 (72)[c]
3	H_2O (1.0 equiv.)	60
4	Under air	33
5	5 h	47
6	10 h	53
7	15 h	54
8[d]	*α*, *α*, *α*-Trifluorobenzene, DMF, DMSO, dioxane	<54
9[d]	80 °C	-
10[d]	100 °C	70

[a]Reaction conditions: *α*-ketoamide **1a** (0.36 mmol, 1.2 equiv.), **2a** (0.30 mmol, 1.0 equiv.), $Cu(acac)_2$ (0.030 mmol, 10 mol%), DMAP (0.30 mmol, 1.0 equiv.), toluene (0.5 mL, 0.6 M), 130 °C, 20 h, N_2. [b]Yields determined by ^{1}H NMR spectra of the crude reaction mixtures using nitromethane as internal standard, obtained from single experiments. [c]Isolated yield in parenthesis. [d]**1a** (0.60 mmol, 2.0 equiv.) used.

When the reaction time (entries 5–7) was investigated, we found that it could be reduced to 10 hours with no drop in yield but decided to keep it at 15 hours for easier experimentation. Solvent screening (entry 8) indicated that toluene remained the best solvent for the system, and that polar solvents proved to be detrimental. Finally, attempts at reducing the reaction temperature (entries 9 and 10) saw that the reaction was equally effective at 100 ºC but did not yield any products at 80 ºC.

Ultimately, we decided on the optimised conditions of 2.0 equivalents of *α*-ketoamide, 10 mol% $Cu(acac)_2$, 1.0 equivalent of DMAP, 100 °C, 15 hours in toluene under N_2, giving us a good isolated yield of 70% (Scheme 2.16). While we were initially surprised that 5-hydroxypyrrol-2(5*H*)-ones could be isolated without any elimination of the hydroxyl group, we wanted to ensure that the corresponding 5-ylidenepyrrol-2(5*H*)-ones could be obtained from the 5-hydroxypyrrol-2(5*H*)-ones. To that extent, we left the isolated 5-hydroxypyrrol-2(5*H*)-one **8** to reflux under toluene and found that it was completely converted to the 5-ylidenepyrrol-2(5*H*)-one **3a**.

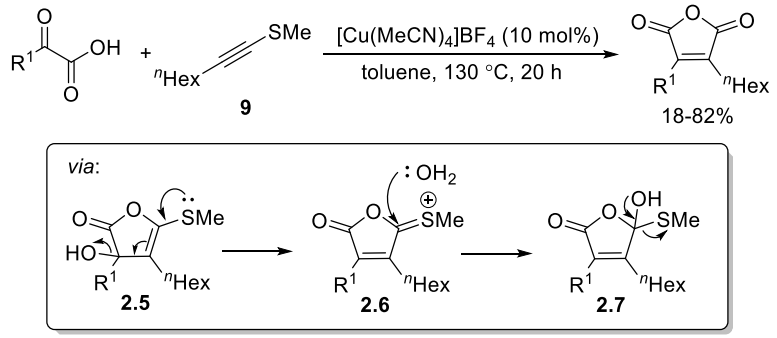


Scheme 2.16 Optimised conditions for the formation of **8**

2.5 Towards Non-Symmetric Maleimides

Work done in collaboration with a part II student Michael Findlay saw that the copper-catalysed addition of *α*-ketoacids to alkynes can also be applied to methyl(oct-1-yn-1-yl)sulfane **9** (Scheme 2.17).[174] The proposed formation of maleic anhydride follows the initial formation of intermediate **2.5**, from the addition and

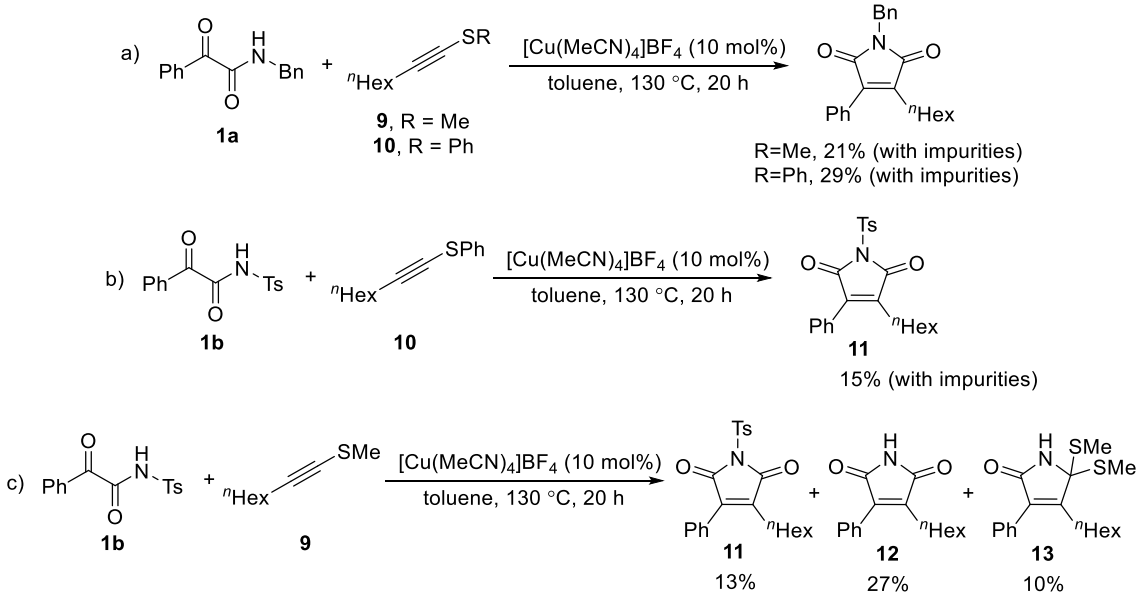
annulation of α-ketoacid to methyl(oct-1-yn-1-yl)sulfane **9**. This is followed by the facile attack of the lone pair on sulfur into the ring in order to gain conjugation in the heterocycle. The positively charged intermediate **2.6** is then attacked by a H_2O molecule, giving intermediate **2.7**. The corresponding asymmetric maleic anhydride is obtained with the loss of a SMe ion.



Scheme 2.17 Cu-catalysed addition of α-ketoacids to methyl(oct-1-yn-1-yl)sulfane by Michael Findlay

As a result, the reaction was attempted using *N*-benzyl α-ketoamide **1a** and *N*-tosyl α-ketoamide **1b** with both methyl(oct-1-yn-1-yl)sulfane **9** and phenyl(oct-1-yn-1-yl)sulfane **10** in an attempt to synthesise the corresponding maleimides (Scheme 2.18). Unfortunately, in the presence of both alkynes, the use of *N*-benzyl α-ketoamide **1a** only led to low NMR spectroscopy yields where the product could not be isolated cleanly due to an impurity having a similar R_f value to the maleimide (Scheme 2.18a). This was similarly observed when *N*-tosyl α-ketoamide **1b** was reacted with phenyl(oct-1-yn-1-yl)sulfane **10** (Scheme 2.18b). However, in the reaction of *N*-tosyl α-ketoamide **1b** with methyl(oct-1-yn-1-yl)sulfane **10**, maleimide **11** could be isolated cleanly in 13% yield after recrystallisation (Scheme 2.18c). In addition, by-products **12** and **13** were also isolated in 27% and 10% yield respectively. The presence of the deprotected maleimide **12** suggests that the thiolate ion formed *in situ* is capable of attacking the aryl ring of the tosyl group, resulting in its removal together with the release

of SO_2. The presence of byproduct **13** supports the mechanism proposed in Scheme 2.17, where in this case a thiolate ion acts as the nucleophile attacking the positively charged intermediate **2.6** instead. These initial findings suggest that with the right conditions, we can also synthesise non-symmetric maleimides *via* our copper-catalysed hydroamidation transformation.

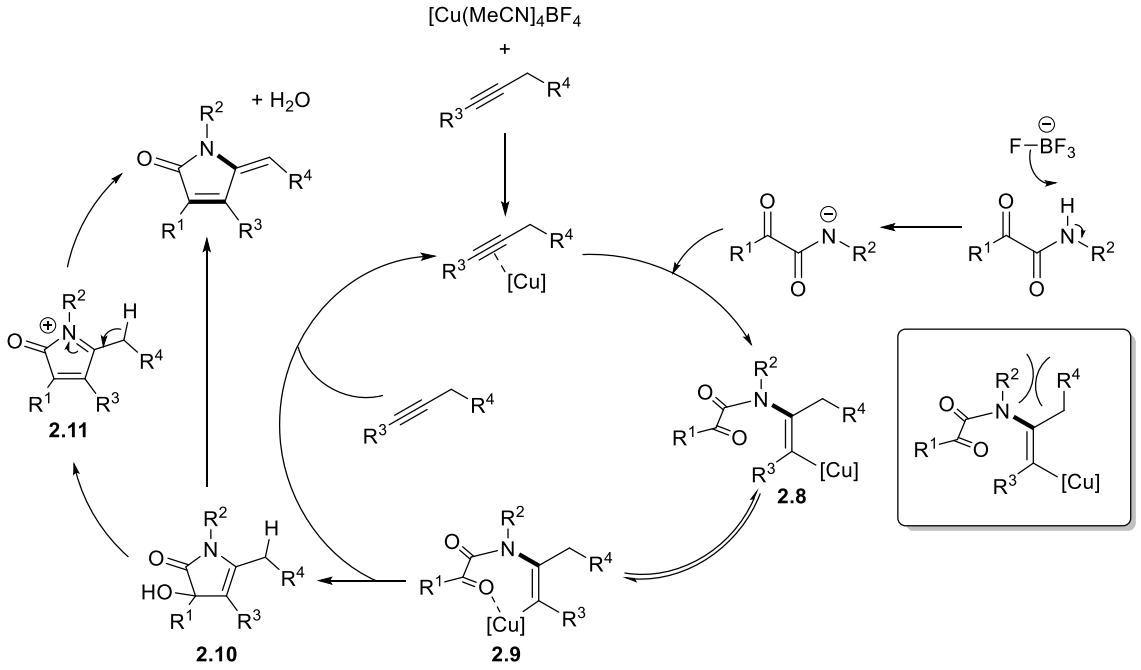


Scheme 2.18 Cu-catalysed hydroamidation of sulfane-alkynes with *α*-ketoamides

2.6 Proposed Mechanism

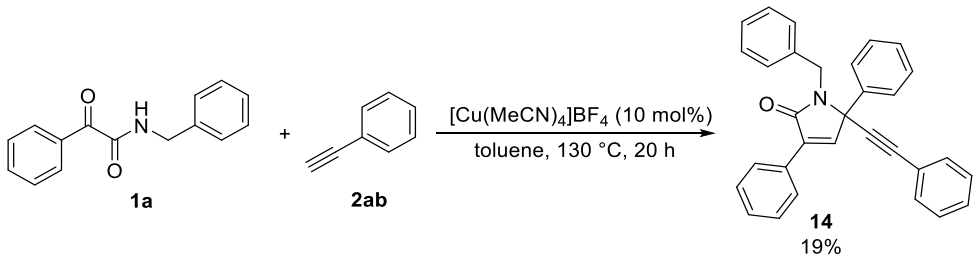
The proposed mechanism for the copper-catalysed hydroamidation of alkynes (Scheme 2.19) was modified from the one reported previously in the group for copper-catalysed hydrocarboxylation of alkynes by Dr Seo.[173] The alkyne was first activated *via* coordination of the copper(I) catalyst. As the presence of tetrafluoroborate ion was observed to be necessary, we postulated that it could act as a fluoride source[175] that deprotonates the *α*-ketoamide. This facilitates the anti-amidocupration of the alkyne to give intermediate **2.8**. The conformation of intermediate **2.8** has substituents R^3 and R^4 away from each other in order to prevent 1,3-allylic strain, resulting in (*E*)-

stereoselectivity observed for the final product. Isomerisation of intermediate **2.8** gives intermediate **2.9**, where the coordination of copper to the carbonyl oxygen sets up a facile cyclisation to give intermediate **2.10**. From here, there are two possible pathways to reach the final pyrrolinone. A direct dehydration of intermediate **2.10** or donation of the lone pair on nitrogen to give intermediate **2.11** followed by neutralising the charge on the nitrogen can occur. Under the modified conditions for the synthesis of 5-hydroxypyrrol-2(5*H*)-ones, we postulated that the presence of DMAP promoted the formation of hydroxide ions. The hydroxide ions can either intercept intermediates **2.10** or **2.11** to give 5-hydroxypyrrol-2(5*H*)-ones or add into 5-ylidenepyrrol-2(5*H*)-one to give 5-hydroxypyrrol-2(5*H*)-one.



Scheme 2.19 Proposed mechanism for the Cu-catalysed hydroamidation of alkynes

Although no intermediates were isolated, reaction of *N*-benzyl *α*-ketoamide **1a** with phenyl acetylene **2ab** saw the formation of pyrrolinone **14** in 19% yield (Scheme 2.20). Pyrrolinone **14** can be formed *via* a nucleophilic attack of phenylacetylene **2ab** on either intermediate **2.10** or **2.11** (Scheme 2.19).



Scheme 2.20 Cu-catalysed hydroamidation of phenylacetylene

2.7 Summary and Outlook

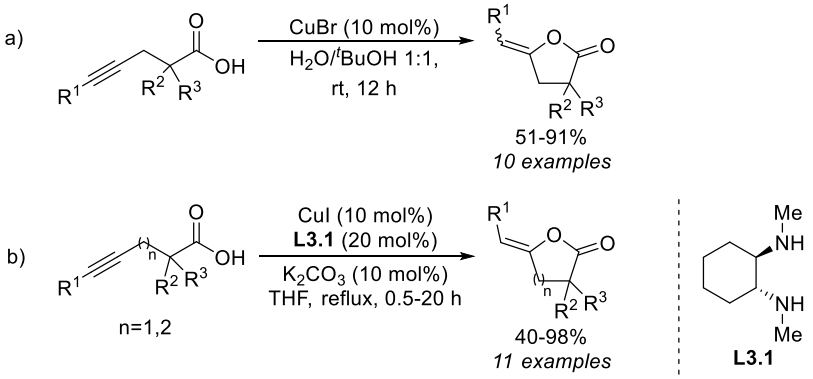
In conclusion, we have developed a novel copper-catalysed hydroamidation of terminal alkynes with α-keto amides, employing readily accessible substrates and commercially available $[Cu(MeCN)]_4BF_4$ catalyst to give 5-ylidenepyrrol-2(5*H*)-ones in moderate to good yields. Excellent stereoselectivity is obtained with only the (*E*)-isomers formed in almost all cases. The methodology covers a good substrate scope and can be scaled up to gramme-scale with no issue. In addition, the transformation presents the opportunity to form other heterocycles such as 5-hydroxypyrrol-2(5*H*)-ones or asymmetric maleimides by simple variation of reaction conditions or using sulfane-substituted alkynes. The utility of copper as a catalyst for addition reactions in alkynes will be further demonstrated in the next chapter.

Chapter 3. Hydro-Oxycarbonylation of Terminal Alkynes

3.1 Introduction

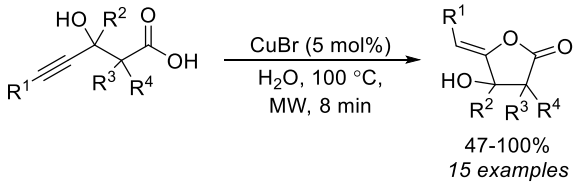
3.1.1 Copper-Catalysed Hydro-Oxycarbonylation

There have been few reports of the intramolecular variant of copper-catalysed hydro-oxycarbonylation of alkynes. In a seminal work, Schibli and Mindt described the cyclisation of alkynoic acids catalysed by CuBr (Scheme 3.1a).[176] Notably, the reactions were performed in an aqueous medium and required the copper catalyst to be in the +1 oxidation state. While the reaction could be performed under mild conditions, the use of 5-hexynoic acid or 6-heptynoic acid did not yield the corresponding 6- and 7-membered lactones, and the *E*/*Z* selectivity was poor when an internal alkyne was used. Later, Sun *et al*. reported another copper-catalysed cyclisation of alkynoic acids to form the previously inaccessible 5- and 6-membered *exo*-lactones (Scheme 3.1b).[177] In the presence of internal alkynes, selectivity for the (*Z*)-isomers was obtained. As Sun's method was performed in THF, it was complementary to Schibli's and Mindt's as substrates that have poor solubility in water could now be tolerated.



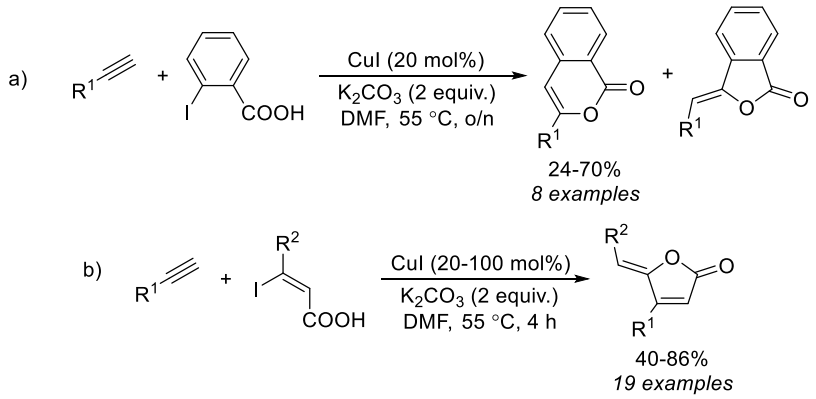
Scheme 3.1 Cu-catalysed cyclisation of alkynoic acids

Alvarez-Toledano and co-workers later exploited the use of microwave irradiation in their CuBr-catalysed cyclisation of *β*-hydroxy-*γ*-alkynoic acids in an aqueous medium (Scheme 3.2).[178] H_2O was found to be the optimal solvent for obtaining a short reaction time as the use of other polar solvents such as THF and MeCN gave only moderate yields after 40 minutes. Overall, the reaction gave (*Z*)-enol lactones selectively in moderate to excellent yields.



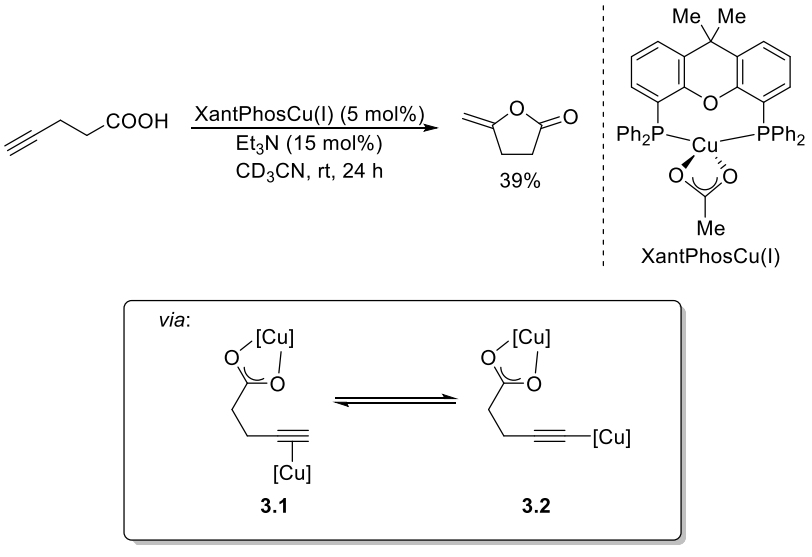
Scheme 3.2 Microwave irradiation-assisted Cu-catalysed cyclisation of alkynoic acids

The intramolecular addition of a carboxylic acid to an alkyne was also observed in a one-pot synthesis of isocoumarins and *γ*-alkylidenebutenolides from terminal alkynes and *β*-iodopropenoic acid derivatives (Scheme 3.3).[179] Inack-Ngi *et al*. demonstrated that in the presence of *β*-iodopropenoic acid derivatives, the copper first catalysed a Sonogashira-type coupling of the terminal alkyne with the vinyl iodide. The alkynoic acids formed *in situ* then cyclise to give the corresponding isocoumarins and *γ*-alkylidenebutenolides. In the reaction with (*Z*)-3-iodoacrylic acids, the temperature had to be kept at 55 °C or below in order to avoid formation of the pyranones, allowing exclusively the formation of *γ*-alkylidenebutenolides with good selectivity for the (*Z*)-isomers (Scheme 3.3b).



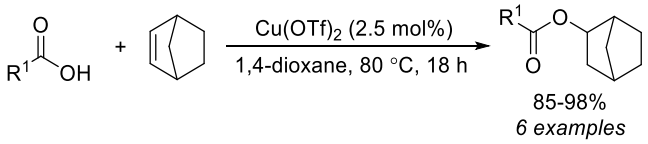
Scheme 3.3 Cu-catalysed synthesis of isocoumarins and γ-alkylidenebutenolides

Gonell *et al.* also demonstrated the use of copper as a catalyst for the cyclisation of alkynoic acids (Scheme 3.4).[180] Using a pre-formed XantPhosCu(I) catalyst, the reaction was monitored using ^{1}H NMR spectroscopy. Triethylamine was found to improve the yield from 12% to 39%. Mechanistic studies indicated that the rate order with respect to the copper catalyst was 2, signifying the presence of a binuclear active species. As a result, they postulated that the copper ion coordinates to both the acid and the alkyne components, giving intermediates **3.1** and **3.2** interchangeably.



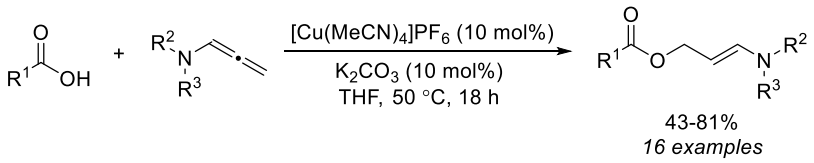
Scheme 3.4 Cu-catalysed cyclisation of alkynoic acids

Reports of copper-catalysed hydro-oxycarbonylation of alkenes are rare, with an example from Taylor *et al*.,[181] where the addition of carboxylic acids to norbornene was demonstrated (Scheme 3.5). Both aromatic and aliphatic carboxylic acids were tolerated with excellent yields obtained, but the reaction was limited to norbornene as a substrate.



Scheme 3.5 Cu-catalysed hydro-oxycarbonylation of norbonene

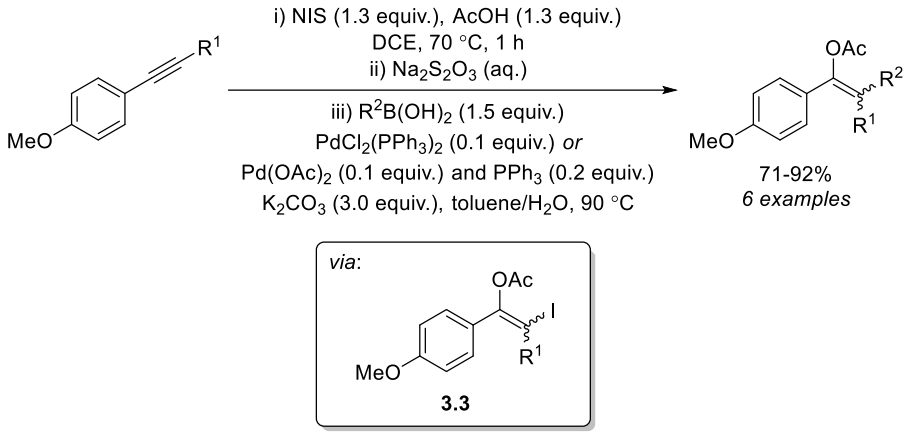
In a very recent development by the Monnier group, the first demonstration of using copper as a catalyst for the hydro-oxycarbonylation of *N*-allenes was reported (Scheme 3.6).[182] Different *N*-allenes such as allenamide, *N*-allenyl-sulfonamides, *N*-allenyloxazolidinone and *N*-allenyl-azoles could be tolerated and excellent control of regioselectivity was obtained, with linear allylic esters formed in moderate to good yields.



Scheme 3.6 Cu-catalysed hydro-oxycarbonylation of *N*-allenes

3.1.2 Enol Esters Synthesis

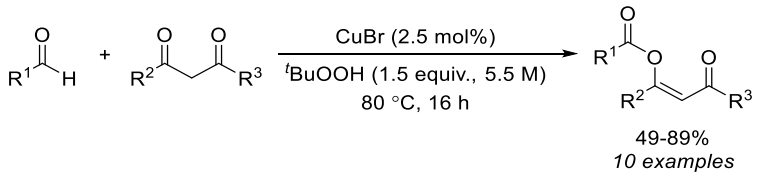
While enol esters have mostly been synthesised *via* transition metal-catalysed addition of carboxylic acids to alkynes, less classical routes have been also been reported. In 2011, Yanada and co-workers demonstrated the synthesis of enol esters *via* conversion of an alkyne to an iodo-alkene, followed by a Suzuki cross-coupling to give multi-substituted enol esters. (Scheme 3.7).[183]



Scheme 3.7 Multi-substituted enol esters synthesis by Yanada and co-workers

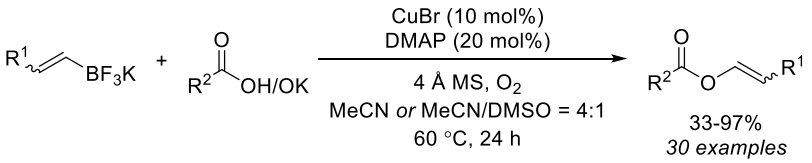
The stereoselectivity for the initial formation of iodo-alkenes **3.3** was found to be influenced by the substituent on the alkyne. While aliphatic substituents gave exclusively the (*E*)-isomers, aromatic substituents gave preferentially the (*Z*)-isomers. Although the method allowed stepwise introduction of functionality on the enol esters, the process required multiple operations and had poor overall atom economy.

Yoo and Li demonstrated the oxidative esterification of aldehydes and *β*-dicarbonyl compounds for the synthesis of enol esters containing a ketone or ester group *α* to the alkene functional group (Scheme 3.8).[184] It was important to keep the reaction temperature at 80 °C as any further increase in temperature led to a loss in stereoselectivity of the products. Under these conditions, *β*-ketoesters were found to be highly selective for the (*Z*)-enol esters with complete stereoselectivity obtained. The substituents on the aldehyde did not have any significant effect on the yields, as demonstrated by both aromatic and aliphatic aldehydes giving similar yields in the reaction.



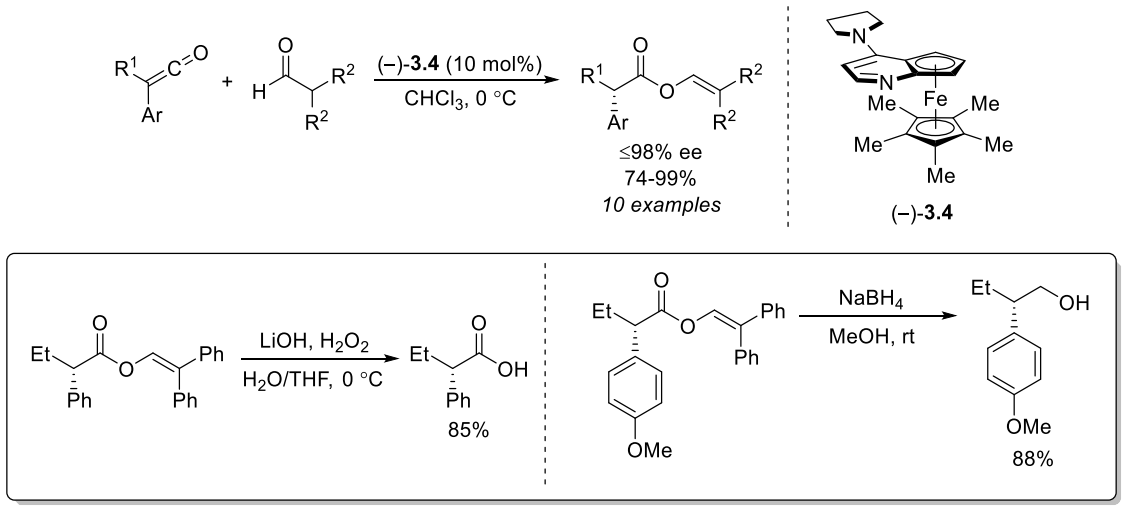
Scheme 3.8 Oxidative esterification of aldehydes and *β*-dicarbonyl compounds

Later, Huang *et al*. reported the use of CuBr for the cross-coupling of alkenylborate salts with carboxylic acids or potassium carboxylates (Scheme 3.9).[185] Although the alkenylborate salts had to be prepared from the corresponding boronic acids and KHF_2, the reaction presented an advantage as retention of the stereochemistry in the alkenylborate salts was observed. In cases where the reaction was low-yielding, DMSO could be added as a solvent to increase the yield by improving the solubility of the starting materials.



Scheme 3.9 Cu-catalysed cross coupling for the synthesis of enol esters

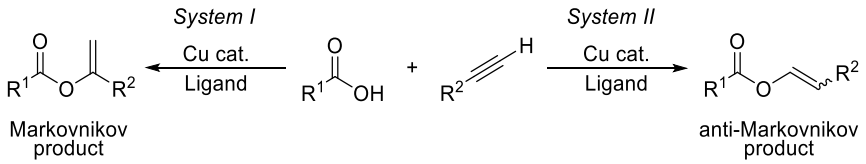
Another method for the formation of enol esters was reported by Fu and co-workers (Scheme 3.10).[186] By utilising a chiral ferrocene catalyst **3.4**, enantioselectivity could be conferred to the carbon *α* to the carbonyl group. While the method was limited to symmetrical aldehydes, the chiral enol esters were obtained in good to excellent enantioselectivity and yields. These products could also be converted to the corresponding acid or alcohol without any loss in enantiopurity.



Scheme 3.10 Asymmetric coupling of ketenes and aldehydes for the synthesis of enol esters

3.1.3 Project Aims

Given the reported literature for copper-catalysed intramolecular hydro-oxycarbonylation of alkynes shown above, we conjectured that an intermolecular variant would also be possible. The use of earth-abundant copper as a catalyst presents a significant cost advantage over the expensive metal catalysts that are commonly used for this transformation. We envisioned that with the right catalyst and ligand system (Scheme 3.11), we would be able to control the regioselectivity for the addition of carboxylic acids to terminal alkynes to obtain both the Markovnikov and the anti-Markovnikov products selectively.



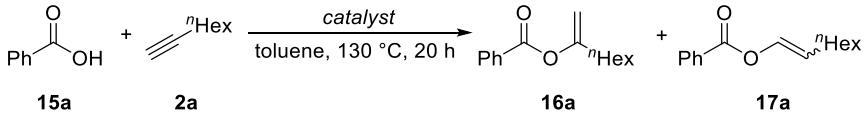
Scheme 3.11 Cu-catalysed regioselective hydro-oxycarbonylation of alkynes

3.2 Markovnikov Addition

3.2.1 Optimisation

Inspired by our earlier intramolecular reactions, we first looked at the types of copper catalysts that could successfully catalyse the reaction, using benzoic acid **15a** and 1-octyne **2a** as model substrates (Table 3.1).

Table 3.1 Copper catalyst screening for the reaction between **15a** and **2a**[a]



15a **2a** **16a** *Markovnikov* **17a** *anti-Markovnikov*

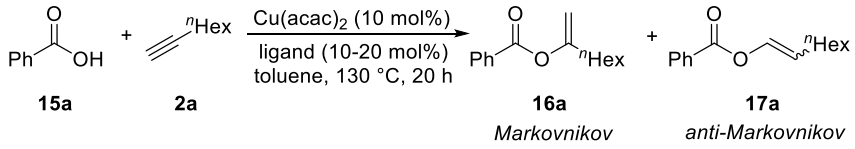
entry	catalyst (mol%)	Combined yield[b] (%)	**16a**:**17a**[c]
1	Cu_2O (10)	55	87:13
2	CuI (10)	3	-
3	$CuCl_2$ (10)	0	-
4	$Cu(OTf)_2$ (10)	0	-
5	$[Cu(MeCN)]_4BF_4$ (5)	<5	-
6	$Cu(OAc)_2$ (10)	29	79:23
7	$Cu(acac)_2$ (10)	67	78:22

[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), 1-octyne **2a** (0.60 mmol, 2.0 equiv.), copper catalyst (0.015–0.030 mmol, 5–10 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard. [c]Ratios of **16a**:**17a** obtained by comparing their crude NMR yields.

Preliminary copper catalyst screening was conducted by Dr. Seo, with selected examples illustrated above (Table 3.1, entries 1–5). We found that out of the copper salts attempted, Cu_2O, $Cu(OAc)_2$ and $Cu(acac)_2$ (entries 1, 6 & 7) gave low to moderate yields of enol esters **16a** and **17a**, with a good selectivity for the Markovnikov product. We were content with the moderate yields and selectivity obtained for both Cu_2O and $Cu(acac)_2$ and decided to move forward with both catalysts for further optimisation.

In order to improve the selectivity for the Markovnikov product, a series of phosphine ligands were evaluated, with $Cu(acac)_2$ as the catalytic system (Table 3.2).

Table 3.2 Ligand screening for the reaction between **15a** and **2a**[a]



15a **2a** **16a** *Markovnikov* **17a** *anti-Markovnikov*

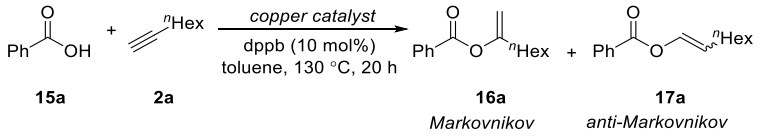
entry	Ligand (mol%)	Combined yield[b] (%)	**16a**:**17a**[c]
1	PPh_3 (20)	-	-
2	PPh_3 (10)	87	71:29
3	PPh_2H (20)	90	70:30
4	PPh_2Me (20)	91	66:34
5	PPh_2Et (20)	88	75:25
6	$P(^iPr)_3$ (10)	79	69:31
7	$HBF_4.P(^tBu)_3$ (10)	47	96:4
8	PCy_3 (10)	77	63:37
9	cataCXium ABn (10)	77	83:17
10	JohnPhos (10)	30	97:3
11	$P(Fur)_3$ (20)	96	81:19
12	dppBen (10)	92	73:27
13	dppp (10)	82	82:18
14	dppb (10)	100	92:8
15	DPEPhos (10)	97	88:12
16	XantPhos (10)	43	55:45
17	dcpb (10)	46	91:9
18[d]	dppb (10)	100	91:9
19[e]	dppb (10)	2	-

[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), 1-octyne **2a** (0.60 mmol, 2.0 equiv.), $Cu(acac)_2$ (0.030 mmol, 10 mol%), ligand (0.030–0.060 mmol, 10–20 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard. [c]Ratios of **16a**:**17a** obtained by comparing their crude NMR yields. [d]Using Cu_2O (10 mol%) instead. [e]Using Cu_2O (5 mol%) instead.

We started by exploring monodentate ligands (entries 1–10). Our attempt with PPh_3 at 20 mol% (entry 1) gave no reactivity, but when the amount of PPh_3 used was lowered to 10 mol% (entry 2), a yield of 87% was obtained, suggesting that having two PPh_3 ligands per copper ion generated an inactive catalyst. Unfortunately, despite the good yield obtained, the regioselectivity was diminished. Replacing one of the phenyl groups on the phosphine ligand with H, methyl or ethyl group (entries 3–5) saw excellent yields obtained for the transformation but selectivity remained poor. When non-aromatic substituents were placed on the phosphine ligand (entries 6–8), a slight drop in yield and selectivity was observed. We attributed the low yield, but good selectivity obtained when $HBF_4.P(^tBu)_3$ (entry 7) was used to the poor solubility of the salt in toluene and noted that the bulkier cyclohexyl groups (entry 8) were not favourable. Bulky ligands such as CatacXium ABn (entry 9) and JohnPhos (entry 10) were also attempted, with JohnPhos giving poor yield but excellent selectivity. Using an electron-poor ligand $P(Fur)_3$ (entry 11) gave an excellent yield of 96% with a slightly improved selectivity. We next looked at the bidentate phosphine ligands (entries 12–19). In the presence of 10 mol% of dppBen (entry 12), the yield increased to 92% but the selectivity dropped. When we chose to increase the bite angle of the ligand employed, we were pleased to see that dppp (entry 13) gave an improved yield of 82% but retained the selectivity that was observed when $Cu(acac)_2$ was used without any ligand. When we switched to dppb (entry 14), a ligand which has a greater bite angle, we were happy to obtain a 100% yield with excellent selectivity of **16a**:**17a** = 92:8. However, further increasing the bite angle by using DPEphos (entry 15) and Xantphos (entry 16) saw no further improvement in selectivity, suggesting that we had reached the optimum bite angle for the system. When we changed the phenyl substituents on the dppb ligand to bulkier cyclohexyl substituents (entry 17), we noted that although the selectivity was retained, the yield dropped significantly. When

we attempted the reaction with 10 mol% of Cu_2O (entry 18) instead, we found that the yield and selectivity obtained was close to identical to that obtained for $Cu(acac)_2$. However, almost no reactivity was observed when the catalyst loading was lowered to 5 mol% of Cu_2O. Other copper salts were also investigated using dppb as ligand but did not give better results (Table 3.3).

Table 3.3 Further copper screening for the reaction between **15a** and **2a**[a]



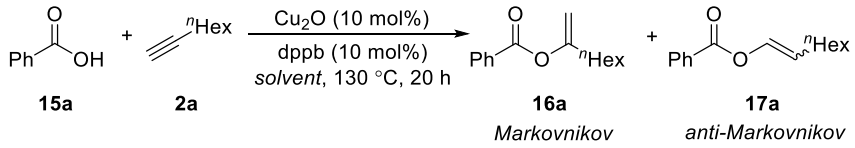
15a **2a** **16a** *Markovnikov* **17a** *anti-Markovnikov*

entry	Catalyst (10 mol%)	Combined yield[b] (%)	**16a**:**17a**[c]
1	CuBr	2	-
2	CuSCN	0	-
3	Cu powder	0	-
4	$CuCl_2$	0	-
5	$CuCO_3{\cdot}Cu(OH)_2$	64	91:9
6	$Cu(OH)_2$	95	88:12
7	$Cu(NO_3)_2{\cdot}2.5H_2O$	54	74:26
8	Cu(I)thiophene-2-carboxylate	59	92:8
9	$CuSO_4$	62	82:18
10	$Cu(OMe)_2$	83	90:10
11	$[Cu(MeCN)_4]PF_6$	27	92:8
12	Copper(I) 3-methylsalicylate	80	91:9
13	$Cu(BF_4)_2{\cdot}xH_2O$	66	85:15

[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), 1-octyne **2a** (0.60 mmol, 2.0 equiv.), catalyst (0.030 mmol, 10 mol%), dppb (0.030 mmol, 10 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h. [b]Yields determined by ^{1}H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard. [c]Ratios of **16a**:**17a** obtained by comparing their crude NMR yields.

The reaction conditions were further investigated using Cu_2O as catalyst (Table 3.4).

Table 3.4 Conditions screening for the reaction between **15a** and **2a**[a]



15a **2a** **16a** *Markovnikov* **17a** *anti-Markovnikov*

entry	**15a** (equiv.)	**2a** (equiv.)	solvent (M)	Combined yield[b] (%)	**16a**:**17a**[c]
1	1.0	2.0	toluene (0.3)	100	91:9
2	1.0	1.0	toluene (0.3)	60	92:8
3	1.5	1.0	toluene (0.3)	66	92:8
4	1.0	2.0	toluene (0.2)	100	92:8
5	1.0	2.0	toluene (0.6)	98	90:10
6	1.0	2.0	chlorobenzene (0.3)	100	90:10
7	1.0	2.0	DMF (0.3)	29	93:7
8	1.0	2.0	DMSO (0.3)	8	92:8
9	1.0	2.0	1,4-dioxane (0.3)	22	91:9
10[d]	1.0	2.0	toluene (0.2)	75	91:9
11[e]	1.0	2.0	toluene (0.3)	79	90:10
12[f]	1.0	2.0	toluene (0.3)	94	90:10
13[g]	1.0	2.0	toluene (0.3)	54	81:19

[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), 1-octyne **2a** (0.60 mmol, 2.0 equiv.), Cu_2O (0.030 mmol, 10 mol%), dppb (0.030 mmol, 10 mol%), 130 °C, 20 h, N_2. [b]Yields determined by ^1H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard. [c]Ratios of **16a**:**17a** obtained by comparing their crude NMR yields. [d]120 °C. [e]15 h. [f]H_2O saturated toluene used. [g]Under air.

The ratio of benzoic acid **15a** to 1-octyne **2a** was first set at 1:2 (entry 1), respectively. We lowered the amount of alkyne **2a** used from 2 equivalents to 1 equivalent but saw a drop in yield after 20 hours of reaction time (entry 2). A similar observation was made when we attempted the reaction with excess benzoic acid **15a** instead (entry 3). Increasing the concentration of the reaction helped to improve the selectivity (entry 4), which also dropped slightly when the reaction was diluted (entry 5). During our solvent screen, we found that chlorobenzene (entry 6) gave similar results but polar solvents such as DMF,

DMSO and 1,4-dioxane (entries 7–9) led to very poor yields. A slight reduction of the reaction temperature to 120 °C (entry 10) saw a drop in yield to 75%, while shortening the reaction time to 15 hours (entry 11) led to incomplete conversion of benzoic acid **15a**. Furthermore, running the reaction with toluene saturated with H_2O (entry 12) did not result in any significant changes but performing the reaction under air (entry 13) led to a significant drop in yield and poorer selectivity, implying that copper in a +1 oxidation state is likely to be involved in the mechanistic cycle.

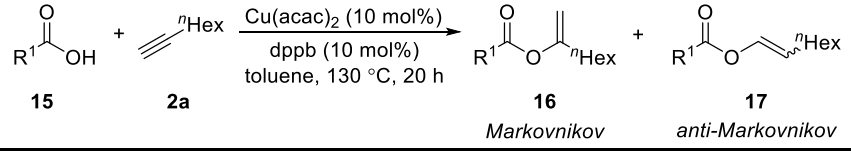
With these results at hand, we decided to move forward with our optimised conditions using 10 mol% $Cu(acac)_2$, 10 mol% dppb, toluene (0.3 M), at 130 °C for 20 hours (Table 3.2, entry 14).

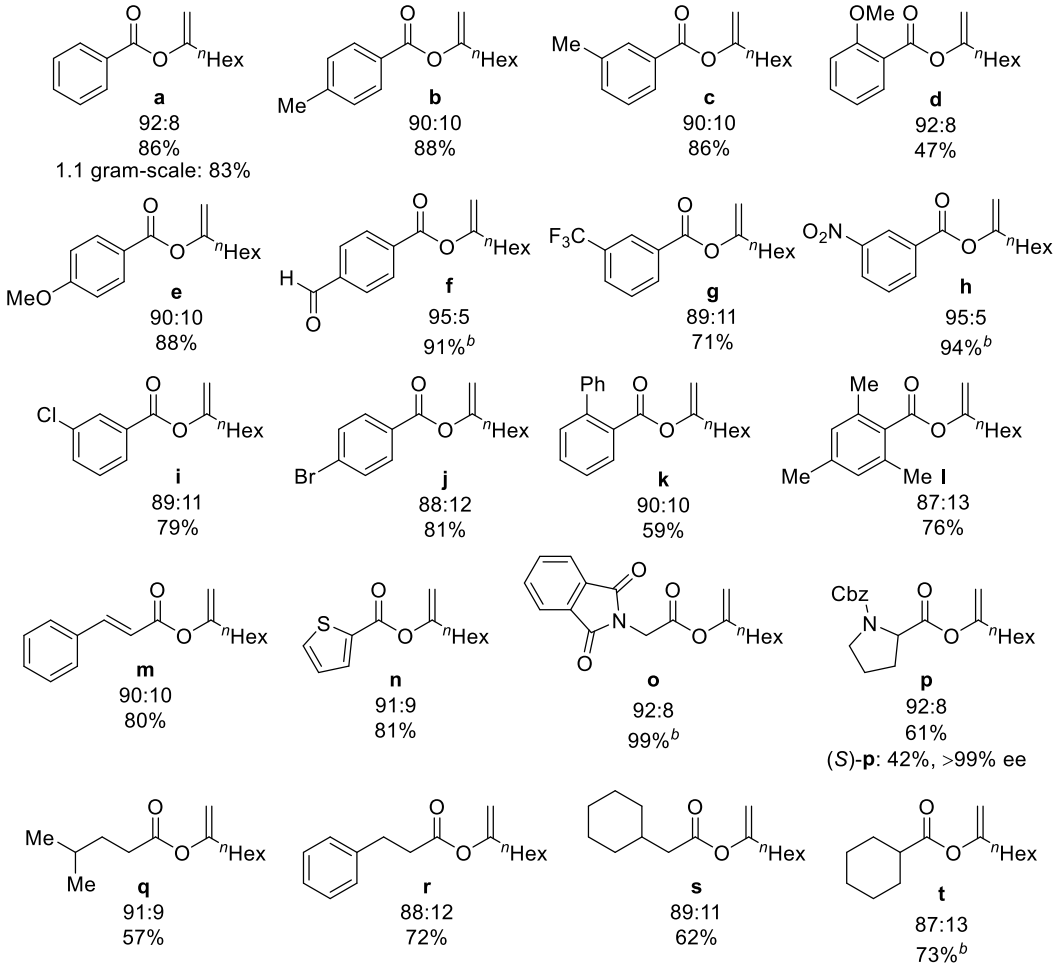
3.2.2 Acid Scope

We first looked at varying the acid component of the reaction (Table 3.5). Enol ester **16a**, synthesised using our model substrates, was isolated in an excellent 86% yield. The reaction could also be scaled up, as employing 1.10 g (9.0 mmol) of benzoic acid **15a** gave 1.84 g (7.5 mmol) of enol ester **16a**, corresponding to an isolated 83% yield. When electron-donating substituents were placed on the ring of the benzoic acid, we saw that a methyl functional group was tolerated at both the *para*- (**16b**) and *meta*- (**16c**) positions with similar yields and selectivity. While the methoxy group was also tolerated without any loss in selectivity, positioning it at the *ortho*-position (**16d**) led to a significant drop in yield compared to the *para*-position (**16e**). This could be due to either steric hindrance or interference through coordination to copper. We next attempted the reaction with electron-withdrawing substituents on the aryl ring of the benzoic acid. We were happy to observe that different functional groups such as aldehyde (**16f**), trifluoromethyl (**16g**),

nitro (**16h**), and halogens (**16i** and **16j**) were all tolerated, giving good to excellent yields with little loss in selectivity. More sterically hindered substrates (**16k** and **16l**) also gave moderate to good yields while maintaining selectivity. A vinyl substrate such as *trans*-cinnamic acid (**16m**) was also tolerated, with excellent yield and good selectivity.

Table 3.5 Acid scope for Markovnikov selectivity[a]





[a]Reaction conditions: acid **15** (0.30 mmol, 1.0 equiv.), 1-octyne **2a** (0.60 mmol, 2.0 equiv.), $Cu(acac)_2$ (0.030 mmol, 10 mol%), dppb (0.030 mmol, 10 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h, N_2, with **16**:**17** ratios obtained by comparing their crude NMR yields and isolated yields of **16** reported. [b]Indicates inseparable mixtures of **16** and **17**, with total isolated yields of **16** and **17** reported.

Heterocycles-containing carboxylic acids were next investigated. The thiophene carboxylic acid (**16n**) gave similar yield and selectivity to that of the model substrate. We were please to find that amino acid derivatives also gave good selectivity, with an

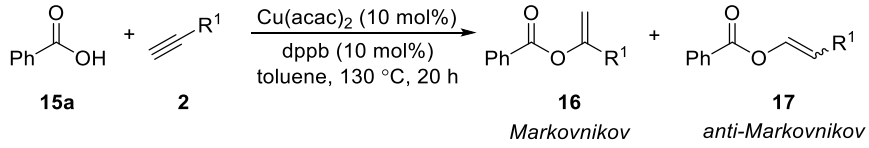
excellent yield obtained for *N*-phthaloylglycine (**16o**) and a moderate yield for Cbz-protected proline (Z-DL-proline) (**16p**). We noted that proline had to be protected with a suitable protecting group as attempts using proline and Boc-protected proline were unsuccessful. Importantly, when chiral Cbz-protected proline (Z-L-proline) was subjected to our reaction conditions, there was no loss in enantiopurity as >99% ee was obtained for (*S*)-**16p**. We were also pleased to see that the aliphatic carboxylic acids (**16q**–**16s**) were tolerated in this reaction, even with phenyl (**16r**) or cyclohexane (**16s**) substituents. Although the yields tend to be slightly lower than the aromatic carboxylic acids, selectivity remained high. Cyclohexanecarboxylic acid gave the corresponding enol ester **16t** in a good yield of 73%, with a slight drop in selectivity likely due to the steric bulk of the cyclohexane ring. Overall, the substrate scope demonstrated good functional group tolerance of the acid component in the reaction.

3.2.3 Alkyne Scope

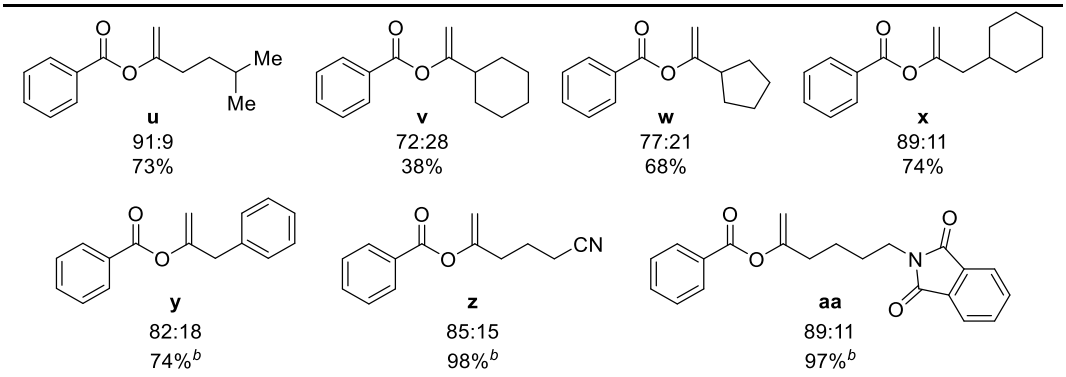
We next investigated the types of alkynes that could be tolerated in the reaction (Table 3.6). Other than 1-octyne **2a**, simple aliphatic 5-methylhex-1-yne also gave enol ester **16u** with good selectivity and yield. However, the selectivity and yield dropped when cyclohexylacetylene (**16v**) and cyclopentylaceylene (**16w**) were used. We attributed this to the steric hindrance caused by the carbocycles; this is supported by the less bulky cyclopentyl ring producing improved selectivity. Moreover, when the cyclohexane ring was shifted one carbon length away (**16x**), both the yield and selectivity improved, presumably due to less crowding around the alkyne carbon. Although a slight drop in selectivity was observed when the cyclohexane ring was switched to a phenyl ring (**16y**), the yield remained good. Lastly, the nitrile (**16z**) and phthalimide group (**16aa**) could also be tolerated and obtained in excellent yields with only a slight loss in selectivity. Overall,

the Markovnikov products were obtained in moderate to excellent yields with good selectivity in the presence of aliphatic alkynes.

Table 3.6 Alkyne scope for Markovnikov selectivity[a]



15a **2** **16** *Markovnikov* **17** *anti-Markovnikov*



u	**v**	**w**	**x**
91:9	72:28	77:21	89:11
73%	38%	68%	74%

y	**z**	**aa**
82:18	85:15	89:11
74%[b]	98%[b]	97%[b]

[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), alkyne **2** (0.60 mmol, 2.0 equiv.), $Cu(acac)_2$ (0.030 mmol, 10 mol%), dppb (0.030 mmol, 10 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h, N_2, with **16**:**17** ratios obtained by comparing their crude NMR yields and isolated yields of **16** reported. [b]Indicates inseparable mixtures of **16** and **17**, with total isolated yields of **16** and **17** reported.

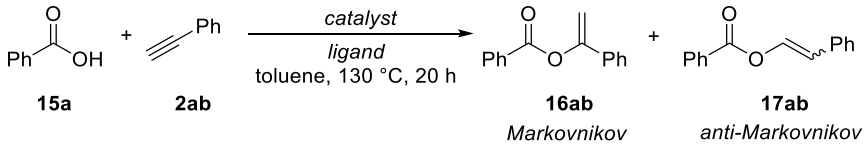
3.3 Anti-Markovnikov addition

3.3.1 Optimisation

When we first subjected phenylacetylene (**2ab**) to our optimised conditions for the Markovnikov product (Table 3.7, entry 1), we observed that the selectivity was poor, with a ~1:2 selectivity towards the anti-Markovnikov product despite the high yield of 92%. It came to our attention that aryl-alkynes preferentially form the anti-Markovnikov product **17**. This was similarly observed in some of the previously reported ruthenium systems.[93,96] As a result, we decided to develop a different copper/ligand system to synthesise anti-Markovnikov products selectively. Using benzoic acid **15a** and phenylacetylene **2ab** as model substrates, we investigated our best phosphine ligand for anti-Markovnikov selectivity found previously (Table 3.2, entry 16); Xantphos gave a better selectivity but the yield was poor (entry 2). On the other hand, switching to a

nitrogen-based ligand, such as 1,10-phenanthroline (entry 3), gave an excellent selectivity of 6:94 for enol ester **17ab**, however, the 65% yield was unsatisfactory.

Table 3.7 Optimisation of reaction between **15a** and **2ab**[a]



15a **2ab** **16ab** *Markovnikov* **17ab** *anti-Markovnikov*

entry	catalyst	ligand	Combined yield[b] (%)	**16ab**:**17ab**[c]	*E*:*Z*[d]
1	$Cu(acac)_2$	dppb	92	38:62	1.0:30.0
2	$Cu(acac)_2$	XantPhos	36	22:78	1.0:67.0
3[e]	$Cu(acac)_2$	phen	65	6:94	1.0:1.0
4	CuOAc	phen	92	7:93	1.0:3.0
5	$Cu(OAc)_2$	phen	23	9:91	1.0:0.5
6	Cu_2O	phen	91	7:93	1.0:1.5
7	Cu_2O	phen	95	6:94	1.0:2.3
8	Cu_2O	-	10	-	-
9	Cu_2O	bypyridine	47	6:94	1.0:1.2
10	Cu_2O	neocuproine	92	6:94	1.0:1.7
11[f]	Cu_2O	tmphen	86	9:91	1.0:3.0
12	Cu_2O	bathocuproine	89	3:97	1.0:0.8
13[g]	Cu_2O	4,7-(OMe)phen	81	10:90	1.0:1.8
14[h]	Cu_2O	phen	98	42:58	1.0:1.5

[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), phenylacetylene **2ab** (0.60 mmol, 2.0 equiv.), catalyst (0.030 mmol, 10 mol% (entries 1-6), 0.015 mmol, 5 mol% (entries 7-12)), ligand (0.030 mmol, 10 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h, N_2. [b]Yields determined by ^{1}H NMR spectra of the crude reaction mixtures using nitromethane as an internal standard. [c]Ratios of **16ab**:**17ab** obtained by comparing their crude NMR yields. [d]*E*:*Z* ratios obtained by comparing their crude NMR yields. [e]phen refers to 1,10-phenanthroline. [f]tmphen refers to 3,4,7,8-tetramethyl-1,10-phenanthroline. [g]4,7-(OMe)phen refers to 4,7-dimethoxy-1,10-phenanthroline. [h]Using 1-octyne **2a** instead.

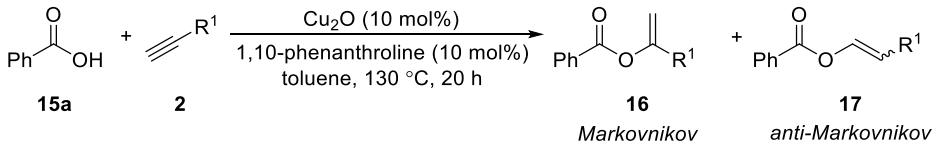
We decided to examine other copper salts (entries 4–6) and found that CuOAc and Cu_2O both gave excellent yields with no loss in selectivity. When we lowered the catalyst loading for Cu_2O to 5 mol% (entry 7), we obtained our best yield of 95%, with 6:94 selectivity for enol ester **17ab**. Removing the ligand from the system produced a very low

10% yield (entry 8), implying that it plays an important role in the catalytic cycle. We also attempted the reaction with bypyridine (entry 9) but saw that it was inferior to 1,10-phenanthroline. Other phenanthroline-type ligands were also investigated (entries 10–13). However, making the ligand more sterically demanding and electron-rich did not cause any significant improvement. As a result, our optimised conditions were Cu_2O (5 mol%), 1,10-phenanthroline (10 mol%), toluene (0.3 M) at 130 °C for 20 hours (entry 7). With these conditions, we also attempted the reaction with 1-octyne **2a** (entry 14). Although the reaction was high yielding, a poor selectivity of **16a**:**17a** ~2:3 was obtained, indicating that aliphatic alkynes have a strong preference for Markovnikov selectivity. We also observed that while the phosphine-based ligands are selective for (*Z*)-**17ab**, no strong preference was observed for either (*Z*)-**17ab** or (*E*)-**17ab** when the nitrogen-based ligands were employed.

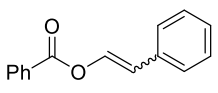
3.3.2 Alkyne Scope

We next looked at the aromatic alkynes that could be tolerated in this system (Table 3.8). In general, we found that the (*Z*)-isomers were synthesised preferentially, but the *E*/*Z* ratio increases after isolation of product due to isomerisation during column chromatography. Varying the electronic properties of the aromatic ring in the alkyne substrate was shown to have no substantial effect on the *E*/*Z* ratio. Our model substrate gave enol ester **17ab** in an excellent yield of 89%, with an excellent selectivity of 6:94. Adding electron-donating groups such as methoxy (**17ac**) and methyl (**17ad**) substituents on the *para*-position led to a decrease in yield with the selectivity slightly decreasing for the methoxy substrate. However, when 5-ethynylbenzo[*d*][1,3]dioxole was subjected to the reaction, an excellent yield and selectivity of 92% and 8:92 were obtained respectively (**17ae**).

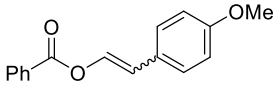
Table 3.8 Alkyne scope for anti-Markovnikov selectivity[a]



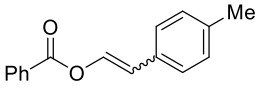
15a **2** **16** *Markovnikov* **17** *anti-Markovnikov*



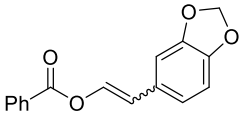
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89%
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E:*Z** = 1.0:2.4



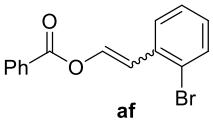
ac
13:87
63%
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E:*Z** = 1.0:8.0



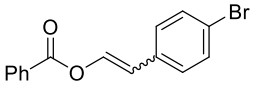
ad
7:93
70%
E:*Z* = 1.0:1.6
E:*Z** = 1.0:1.8



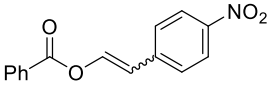
ae
8:92
92%
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E:*Z** = 1.0:1.0



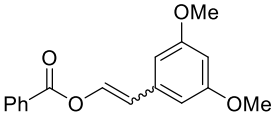
af
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88%
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E:*Z** = 1.0:2.0



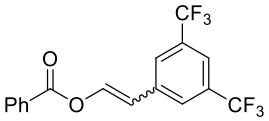
ag
4:96
92%
E:*Z* =1.0:3.4
E:*Z** = 1.0:3.5



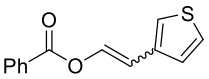
ah
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80%[b]
E:*Z* = 1.0:0.7
E:*Z** = 1.0:0.7



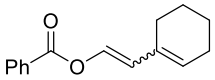
ai
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88%
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E:*Z** = 1.0:1.0



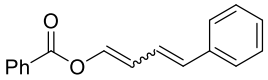
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63%
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ak
7:93
75%
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E:*Z** = 1.0:2.8



al
16:84
79%
E:*Z* = 1.0:0.5
E:*Z** = 1.0:0.5



am
2:98
63%
E:*Z* = 1.0:1.3
E:*Z** = 1.0:1.7

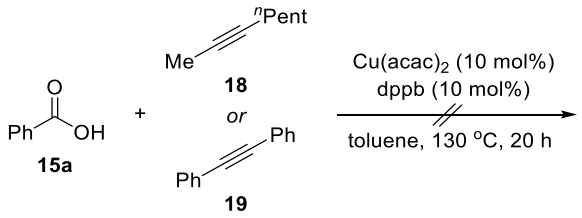
[a]Reaction conditions: benzoic acid **15a** (0.30 mmol, 1.0 equiv.), alkyne **2** (0.60 ool, 2.0 equiv.), Cu_2O (0.015 mmol, 5 mol%), 1,10-phenanthroline (0.030 mmol, 10 mol%), toluene (1.0 mL, 0.3 M), 130 °C, 20 h, N_2, with **16**:**17** ratios obtained by comparing their crude NMR yields and isolated yields of **17** reported. [b]Indicates inseparable mixtures of **16** and **17** with total isolated yields of **16** and **17** reported. *Indicates *E*/*Z* ratios obtained after column chromatography.

When we moved towards electron-poor substituents on the aromatic ring, we find that these substrates gave better selectivity, compared to the model substrate **17ab**. We were happy to see that the bromide substituent could be tolerated at both the *ortho*- (**17af**) and *para*-positions (**17ag**) with excellent yields obtained. Enol ester **17ah** containing a *para*-nitro group was obtained in a good yield of 80% with an almost exclusive anti-Markovnikov selectivity. Di-substituted aromatic rings could also be tolerated. Both

3,5-methoxy (**17ai**) and 3,5-trifluoromethyl (**17aj**) substituents gave excellent selectivity, but the latter could only give a moderate yield of 63%. We were pleased to find no loss in selectivity when the benzene ring was replaced with a thiophene, with a good yield of 75% obtained for enol ester **17ak**. When we attempted the reaction with cyclohexeneacetylene (**17al**), the decrease in electron density in the ring led to a poorer selectivity. More importantly, 4-phenylbut-3-ene-1-yne also gave an excellent selectivity (**17am**), despite being less sterically hindered around the alkyne *β*-carbon. This implies that the anti-Markovnikov selectivity is influenced by the electron density of the alkyne and not from steric control, further supporting our observation that aryl-alkynes preferentially form the anti-Markovnikov products.

3.4 Reactivity with Hetero-Alkynes

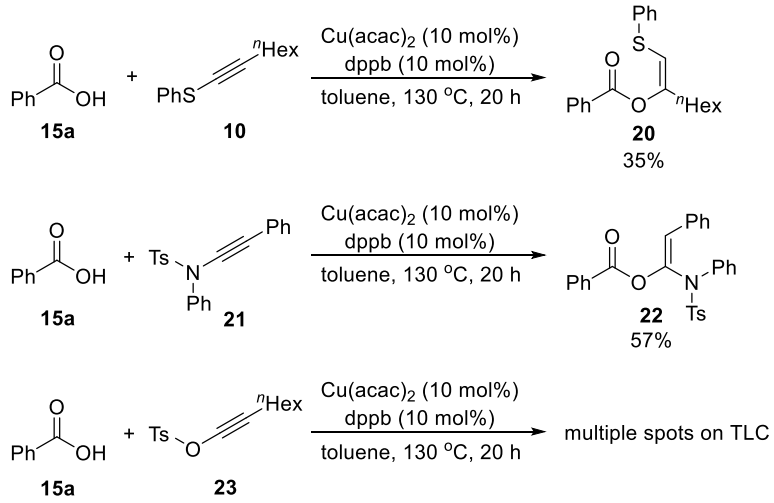
Attempts at expanding the scope for the reaction using internal alkynes with our $Cu(acac)_2$/dppb system were unsuccessful as 2-octyne **18** and diphenylacetylene **19** were unreactive under our optimised conditions (Scheme 3.12). Internal alkynes **18** and **19** were not attempted with our Cu_2O/phen system.



Scheme 3.12 Attempted reactions with 2-octyne **18** and diphenylacetylene **19**

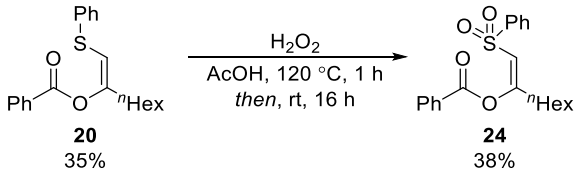
However, when we switched to heteroatom-containing alkynes (Scheme 3.13), we discovered that both sulfane alkyne **10** and ynamide **21** gave enol esters **20** and **22**, respectively, as the major product. Unfortunately, attempting the reaction with ynol ether

23 led to multiple spots on the TLC plate and no obvious product peaks were observed in the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 3.13 Reactivity with hetero-alkynes

To confirm the identity of enol ester **20**, we decided to oxidise it to the corresponding sulfone **24**, with the belief that that product would be a solid (Scheme 3.14). Unfortunately, sulfone **24** remained an oil and could not be analysed using X-ray crystallography.



Scheme 3.14 Oxidation of enol ester **20** to enol ester **24**

Enol ester **20** is a novel compound that has yet to be reported, with an alkene C–H chemical shift of 5.94 ppm, and a minute amount of a minor product present with a chemical shift of 6.10 ppm. Montevecchi and co-workers described the synthesis of similar *β*-acetoxyvinyl sulfides in 1989.[187] In their synthesis of 2-acetoxy-l-phenyl-thiohex-2-ene **25**, both the (*E*)- and (*Z*)-isomers were made and

characterised by NMR spectroscopy, with the alkene C–H having distinct chemical shifts of 5.94 ppm and 5.81 ppm respectively (Figure 3.1). Assignment of the chemical shifts to the respective regio-isomers was done based on NOESY analysis performed on similar substrates reported in the same paper. Additionally, regio-isomer (*E*)-**25'** was reported to have a chemical shift of 7.50 ppm for the C–H alkene. With this knowledge, we eliminated the possibility that we were forming the other two regioisomers for enol ester **20** and deduced that it was synthesised with an *E*/*Z* = 1:15.

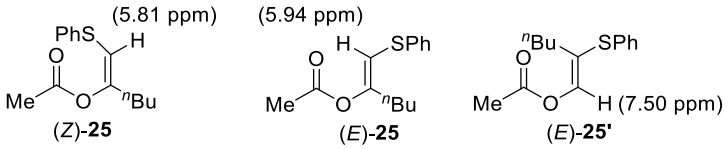


Figure 3.1 Isomers of enol ester **25** and their respective chemical shifts from Montevecchi *et al*.

Additionally, 2D NOESY analysis indicated that alkene proton H_A is correlated to both protons H_B, supporting that enol ester **20** is in the *Z*-configuration as such a correlation would not be observed in the (*E*)-isomer (Figure 3.2).

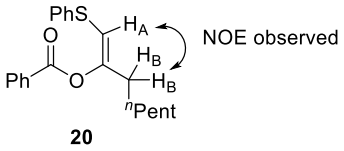


Figure 3.2 2D NOESY analysis of enol ester **20**

To further support our deduction, we also subjected benzoic acid **15a** and sulfane alkyne **10** to gold-catalysed hydro-oxycarbonylation conditions reported by Kim and Chary (Scheme 3.15),[112] with the understanding that the anti-addition product will be formed. Enol ester **20** formed in this reaction gave identical ^{1}H, ^{13}C, HSQC, HMBC and NOESY spectra to those obtained for enol ester **20** formed in our reaction conditions. From these analyses, we confirmed that enol ester (*Z*)-**20** is the major product.



Scheme 3.15 Au-catalysed hydro-carbonylation of alkyne **10**

Fortunately, enol ester **22** was a solid that could be easily recrystallised to give colourless crystals. X-ray crystallography analysis performed by Antoine de Gombert (Figure 3.3) indicated that enol ester **22** had a different regio-chemistry as compared to enol ester **20**. This came as no surprise as addition of heteronucleophiles to ynamides has often been found to be regioselective for the α-carbon.[188–192]

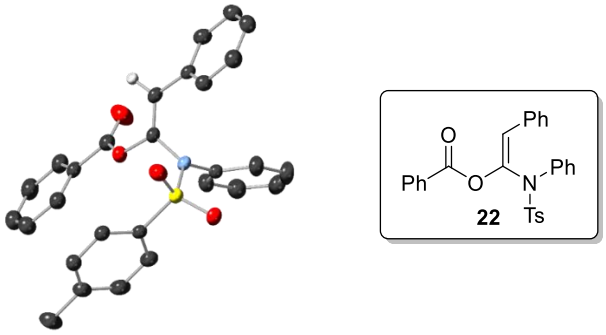


Figure 3.3 X-ray crystal structure of enol ester **22**

3.5 Mechanistic Discussions

In order to get a better understanding of the mechanism behind our reactions, kinetics studies were performed on our Markovnikov system which utilises $Cu(acac)_2$/dppb. Performing kinetics studies on the Cu_2O/phen system produced inconsistent data, potentially due to the catalyst forming solid precipitates, making aliquots, obtained for analysis, non-homogeneous.

3.5.1 Rate Order

The rate order with respect to $Cu(acac)_2$/dppb was derived by studying the rate of consumption of benzoic acid **15a** while varying the concentration of $Cu(acac)_2$ and dppb, with the ratio of $Cu(acac)_2$ to dppb maintained. 1-Octyne **2a** was chosen as the alkyne reagent. With three repeats obtained, a plot of ln(rate) against ln[Cu] was drawn, with a gradient of 0.625 (Figure 3.4). The fractional order of 0.625 obtained may suggest the formation of a monomer-dimer complex equilibrium, with the monomer complex being the active species.[193]

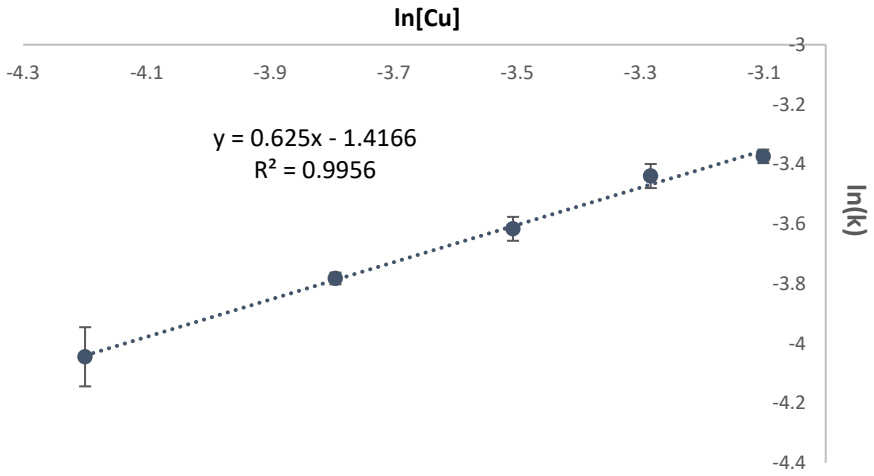


Figure 3.4 Graph of ln(k) against ln[Cu]

In 2016, Bures described a method of obtaining the rate order of the reaction without having to derive the rate after collecting the data for the consumption of starting material over time.[194]

In the graphical analysis method reported, data obtained for the consumption of starting material, A, can be plotted against a normalised time scale, $t[cat]_T^n$ (Figure 3.5), where t = time, $[cat]_T$ = catalyst concentration, T= total concentration of catalyst, n = rate order. By introducing time as a factor in the x-axis, adjustment of the time scale can be

made, and the graphs plotted for different catalyst concentrations can be compared without any loss in the integrity of the shape of graph. This means that $t[cat]_T^n$ is now a parameter for a function that describes the amount of starting material at each time point. It is important to note that the method works with the assumption that the catalyst concentration remains the same throughout the reaction. In short, graphs plotted for different catalyst concentrations will overlap when the correct rate order is applied.

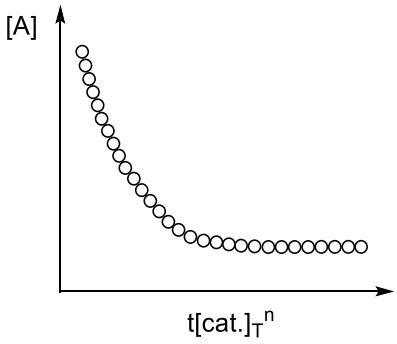


Figure 3.5 Normalised time scale method for the analysis of rate order

When we applied the normalised time-scale method, we found that we had a good overlap of all the plots with catalyst concentrations ranging from 5 mol% to 15 mol% (Figure 3.6). This verified that the fraction order obtained above is accurate.

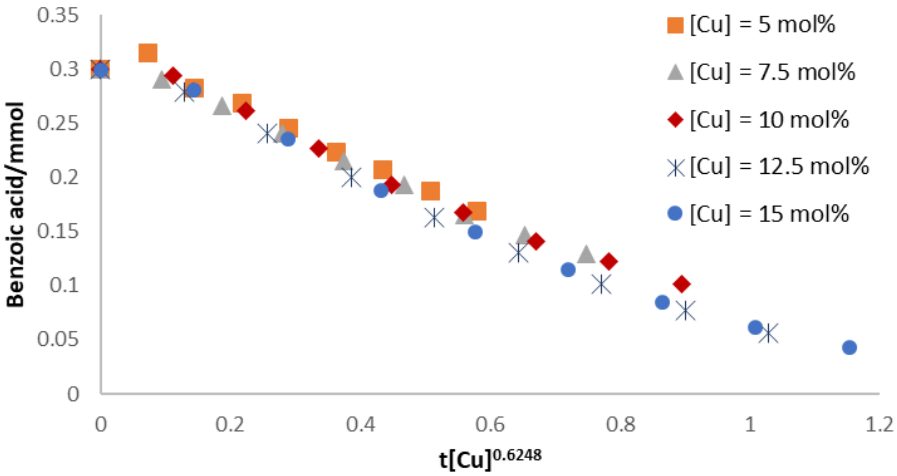
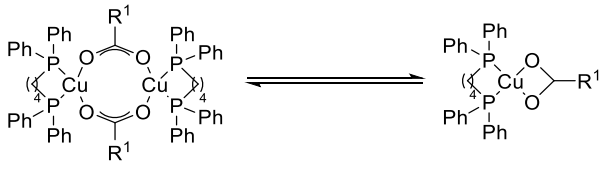


Figure 3.6 Normalised time-scale graph using rate order of 0.625

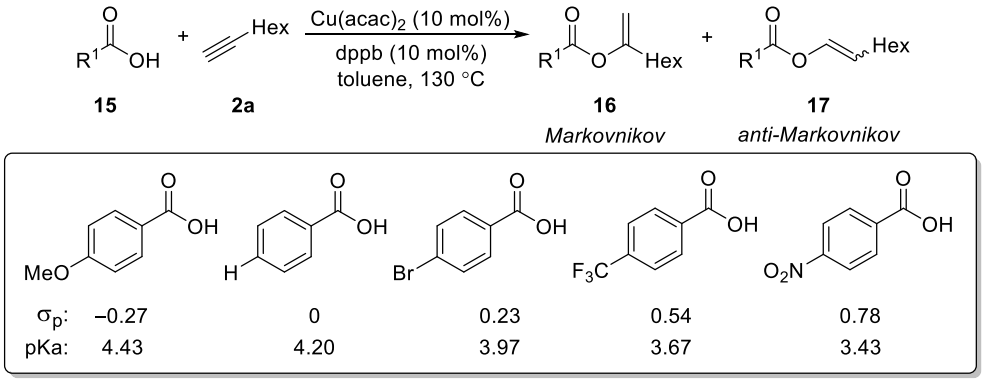
Given the fractional order obtained for the $Cu(acac)_2$/dppb system, we postulated that a copper carboxylate complex is formed in the reaction. We know from the reactions with the hetero-alkynes, that insertion of copper into the terminal alkyne to form a copper-alkylidene intermediate is not likely to be occurring, as internal alkynes could be tolerated in our system. In addition, copper carboxylates have been well studied and they have been found to exist usually in a binuclear state, with polynuclear states possible.[195–199] Typical binuclear copper complexes consist of ligands (L) and anions (X) bound in different combinations, examples include $(L_2CuX)_2$, $(L_{1.5}CuX)_2$ and $(L_2CuX_2)_2$. When the anion is a carboxylate ion, the complexity increases due to the coordination of copper ranging from one to six. To simplify the explanation, we envisioned a $(L_2CuX_2)_2$ system, where dinuclear complex **3.5** is in equilibrium with mononuclear complex **3.6** (Scheme 3.16). In this equilibrium, complex **3.6** is the active catalyst for the reaction.



Scheme 3.16 Copper carboxylate complexes in equilibrium

3.5.2 Hammett Plots

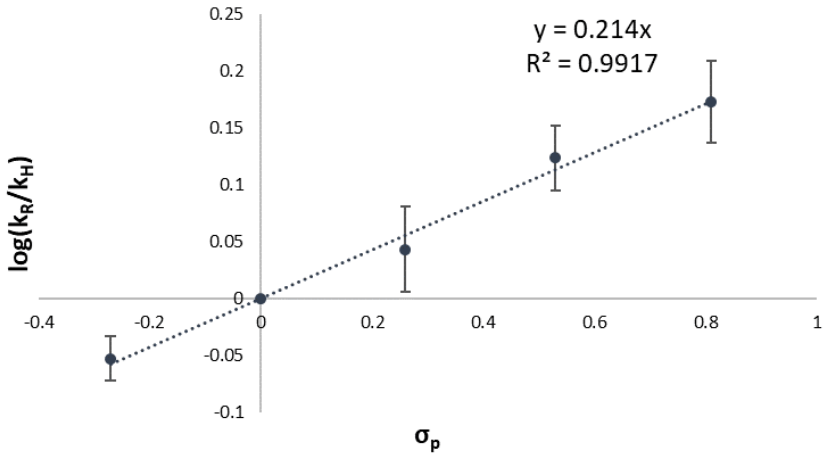
We decided to construct Hammett plots for our Markovnikov system in order to gain further insight into the reaction mechanism. We first looked at using our model substrate **2a** (Scheme 3.17).



Scheme 3.17 Kinetics studies using 1-octyne **2a**

Five different benzoic acids (R^1 = OMe, H, Br, CF_3, NO_2) with a range of σ_p values were evaluated and their concentration was tracked for the first six hours of the reaction. The ρ value obtained from the Hammett plot was 0.21 (Figure 3.7a). With a positive value that is less than 1, we can infer that the substituents on the benzoic acid have little influence on the rate determining step. The positive ρ value implied that there is a build up of negative charge on the benzoic acid during the rate determining step, which is perceivable due to the loss of a proton. With the same raw data collected, a graph of the rate of reaction against the pK_a of the benzoic acids can also be plotted (Figure 3.7b). From here, we observed that the initial rate of the reaction is influenced by the pK_a of the acid, the more acidic the benzoic acid used, the faster the initial rate of reaction.

a)



b)

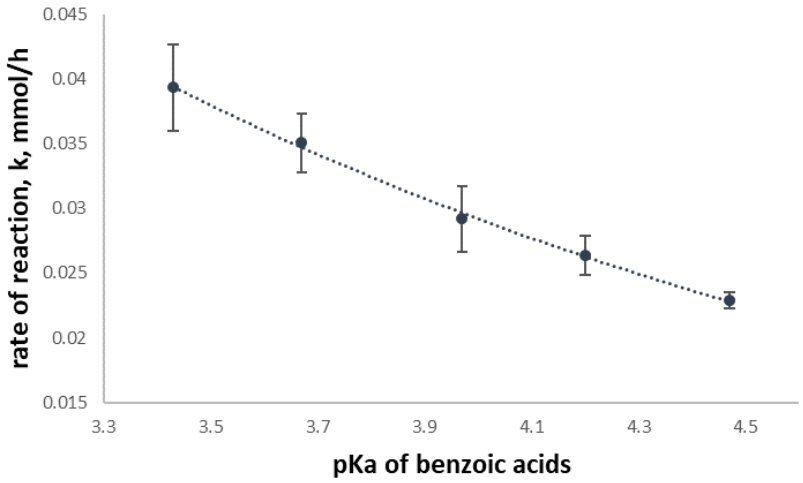
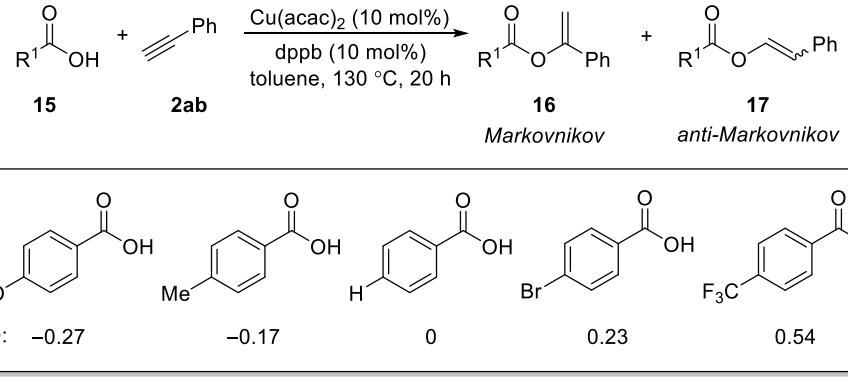


Figure 3.7a) Hammett plot, **b)** Graph of rate of reaction against pKa values of benzoic acids

We next looked at the reaction rates using phenylacetylene **2ab** (Scheme 3.18). In the $Cu(acac)_2$/dppb system, phenylacetylene still preferentially forms the anti-Markovnikov product **17**, with a ~2:1 selectivity obtained when benzoic acid **15a** is used.



Scheme 3.18 Kinetics studies using phenylacetylene **2ab**

The Hammett plot obtained from studying the rate of reaction using five different benzoic acids (R^1 = OMe, Me, H, Br, CF_3) gave a ρ value of 0.45 (Figure 3.8). This is similar to the one obtained for 1-octyne **2a**, with both falling in the range of a positive $\rho<1$.

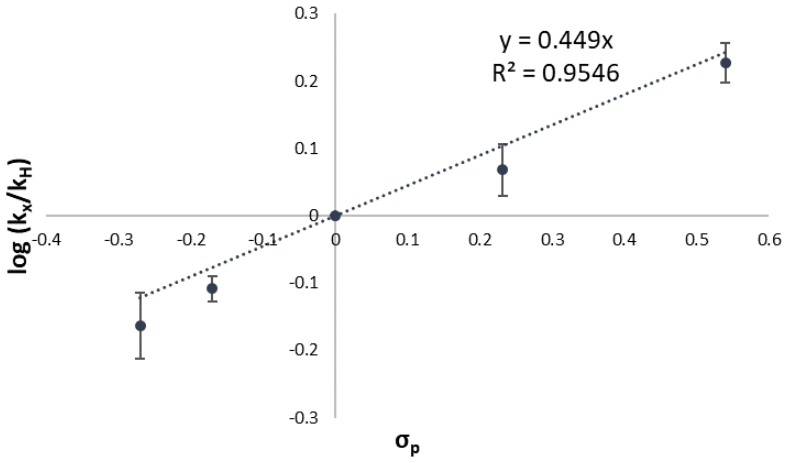


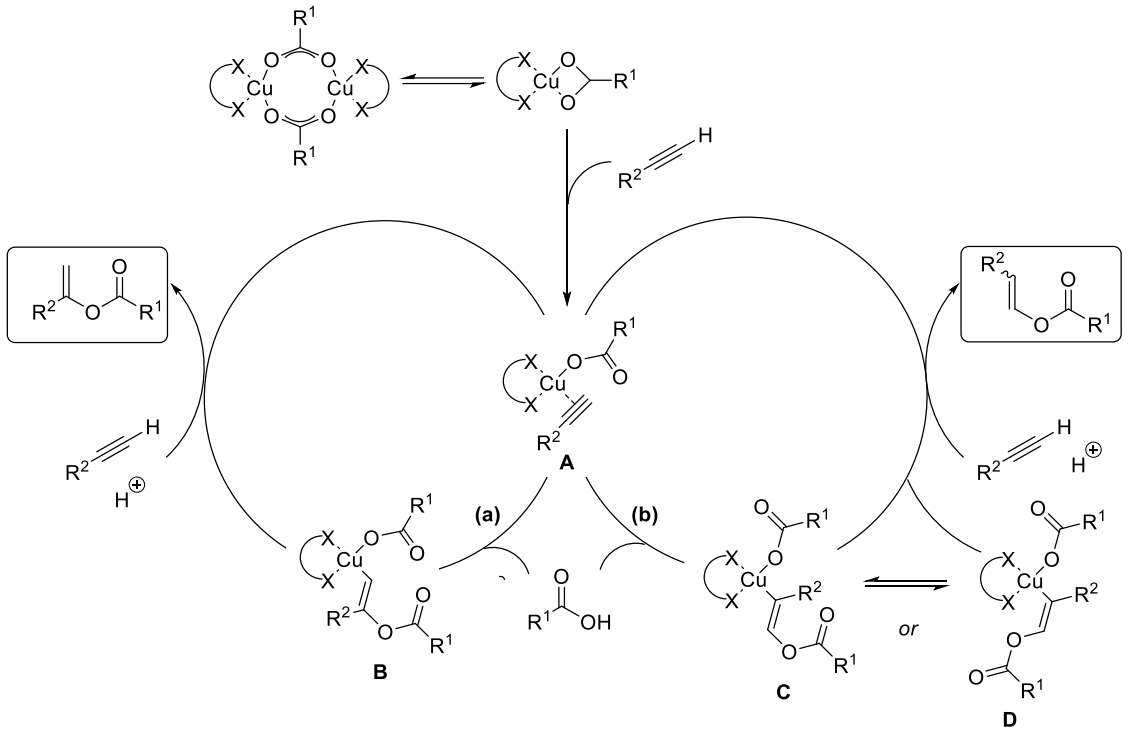
Figure 3.8 Hammett plot using phenylacetylene **2ab**

This suggests that the mechanistic pathway formation of the anti-Markovnikov product is likely to be very similar to that for the Markovnikov product, and regioselectivity is not influenced by the electronics of the benzoic acid.

3.5.3 Proposed Mechanism

A simplistic view of the possible mechanism for the copper-catalysed hydro-oxycarbonylation of alkynes was proposed (Scheme 3.19). The mechanistic cycle started from an initial copper carboxylate complexes equilibrium, with the monomer complex coordinating with a terminal alkyne to give intermediate **A**. Depending on the choice of alkyne and ligand employed, intermediate **A** can go *via* pathway (a) or (b) to reach the final product, as regioselectivity is dependent on the electronic effect. In the presence of dppb and aliphatic alkynes, pathway (a) is preferred, and the anti-addition of a carboxylic acid resulted in the formation of intermediate **B**. Protodecupration of intermediate **B** provided the Markovnikov product. On the other hand, in the presence of 1,10-phenanthroline and aromatic or alkenyl alkynes, pathway (b) is preferred. Anti-addition of a carboxylic acid to intermediate **A** gave either intermediate **C** or **D**, with isomerisation between the two intermediates possible. Protodecupration of intermediates

C and **D** led to the formation of the both (*E*)- and (*Z*)-isomers of the anti-Markovnikov product.



Scheme 3.19 Proposed mechanism for the Cu-catalysed hydro-oxcarbonylation of alkynes

3.6 Summary and Outlook

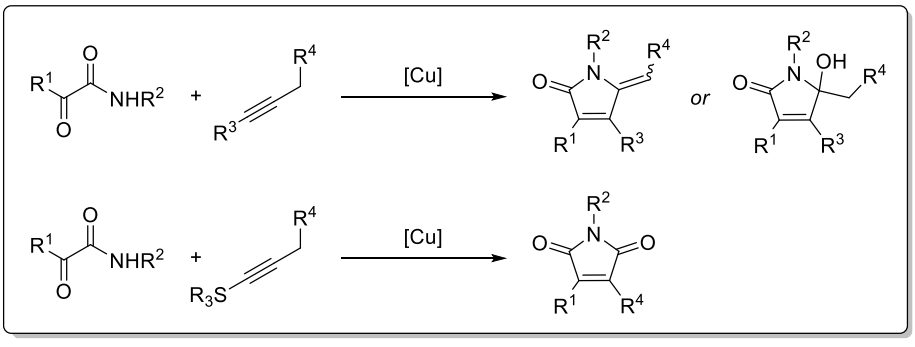
In conclusion, we have reported the first intermolecular copper-catalysed hydro-oxycarbonylation of alkynes. The reaction uses commercially available copper catalysts and allows good control of regioselectivity by choosing a suitable ligand. The methodology covers a wide range of substrates, with both aromatic and aliphatic carboxylic acids tolerated, giving good to excellent yields of enol esters. In addition, the transformation can be scaled up with no loss in yield or selectivity. Applying the transformation to heteroatom-containing alkynes such as sulfane alkynes and yanamides gives access to a wider variety of enol esters. Mechanistic studies have shown that the rate order with respect to copper is fractional, suggesting a monomer-dimer complexes equilibrium. The initial rate of reaction is influenced by the acidity of the carboxylic acid

used, where the more acidic is the acid, the faster is the reaction. Hammett plots have also shown that substituents on the benzoic acid have little influence on rate determining step and the regioselectivity.

Chapter 4. Conclusions and Future Work

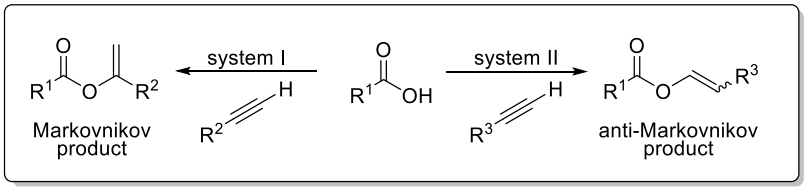
As transition metal catalysis provides alternative mechanistic pathways to useful and versatile building blocks, heavy reliance on these catalysts has led to a need to use cheaper metals in order to improve sustainability. To that effect, the work detailed in this thesis describes the development of low-cost and earth-abundant copper as a catalyst for addition reactions to alkynes. The use of different nucleophiles in these reactions gave rise to *N*-heterocycles and enol esters.

Our initial effort led to the development of copper-catalysed hydroamidation of alkynes with α-keto amides. By using readily available starting materials, the transformation provided an alternative method for producing 5-ylidenepyrrol-2(5*H*)-ones, with excellent stereoselectivity for the (*E*)-isomers. A serendipitous discovery saw the use of DMAP as an additive resulted in the formation of 5-hydroxypyrrol-2(5*H*)-ones. Asymmetric maleimides could also be formed in the presence of sulfane-substituted alkynes. These examples illustrated good utility of copper as catalyst for the formation of *N*-heterocycles.

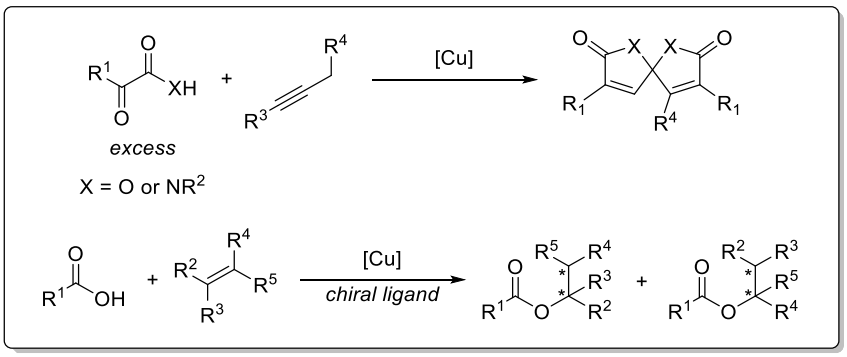


To the best of our knowledge, we have also demonstrated the first copper-catalysed intermolecular hydro-oxycarbonylation of alkynes to give both the Markovnikov and anti-Markovnikov products in good to excellent yields.

Regioselectivity was found to be dependent on the catalyst system and the alkynes. While some mechanistic insights were provided through kinetics studies for system I ($Cu(acac)_2$/dppb), further investigations can be done on system II, which may help to elucidate the source of regiocontrol obtained by using different ligands.



Future work includes extending the type and complexity of heterocycles that can be obtained from the addition reactions. By fine-tuning the reaction conditions, a second α-keto acid or amide can add into the unsaturated γ-ylidenebutenolides or pyrrolinones to give asymmetric spiro-compounds. While the reaction conditions for the addition of carboxylic acids to hetero-alkynes require further optimisation, the transformation can also be extended to alkenes. The use of alkenes requires both regio- and enantiocontrol due to the formation of two stereogenic centres, of which one is a quaternary centre. These transformations will further stretch the potential of copper as a catalyst.



Chapter 5. Experimental Data and Procedures

5.1 General Considerations

Reactions were performed under an inert N_2 atmosphere with anhydrous solvent unless otherwise stated. All glassware was oven dried at >100 °C and allowed to cool to rt under a positive N_2 pressure. Reactions were monitored by TLC until deemed complete using aluminium-backed silica plates. Plates were visualized under ultraviolet light (254 nm) and/or by staining with $KMnO_4$. Cooling of reaction mixtures to 0 °C was achieved using an ice water bath.

Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Alfa Aesar, Acros Organics Ltd., Fluorochem Ltd. or Strem Chemicals Inc. and were used as supplied. All alkynes were distilled and degassed with N_2 before use (Note: Care required as some low molecular weight alkynes are thermally unstable and can decompose explosively upon heating). Anhydrous solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system, and were degassed with N_2 flow before use. Column chromatography was carried out using matrix 60 silica. petrol refers to the fraction of light petroleum ether boiling in the range of 40–60 °C.

^{1}H NMR spectra were obtained on a Bruker AVIII400 (400 MHz) or AVIII500 (500 MHz) spectrometer using the residual solvent as an internal standard. Proton-decoupled ^{13}C NMR spectra were obtained on a Bruker AVIII400 (101 MHz) spectrometer using the residual solvent as an internal standard. Chemical shifts (δ) are

reported in parts per million (ppm) with the multiplicities of the spectra reported as following: bs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; h, sextet; m, multiplet; app., apparent. For substrates with *para*-substituted aryl rings, app. d is used for the second order effects in AA'BB' spin systems. Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz.

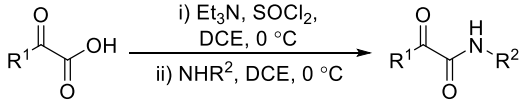
Low-resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High resolution mass spectrometry measurements were recorded on a Bruker Daltronics MicroTOF (ESI) spectrometer or on a Micromass LCT (FI) spectrometer by the internal service at Chemistry Research Laboratory, University of Oxford. Infrared spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC in a Dionex P680 chromatograph with a Dionex UVD170U detector (Daicel Chiralpak OD-H column). Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

5.2 Data for Chapter 2

5.2.1 Synthesis of Starting Materials

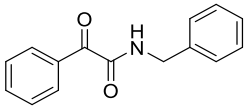
α-Keto acids were either commercially purchased or prepared by oxidation of the corresponding methyl ketones using SeO_2.[200] The crude mixture was filtered through a plug of celite, dried under vacuum and used without further purification.

General Procedure A:[201]



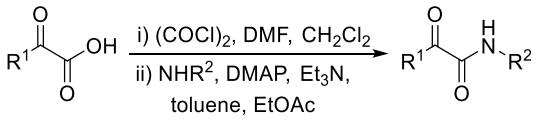
To a solution of α-keto acid (1.0 equiv.) and Et_3N (2.0 equiv.) in 1,2-dichloroethane (0.38 M) at 0 °C under a N_2 atmosphere was added thionyl chloride (2.0 equiv.) dropwise for 15 min. The mixture was stirred at rt for 20 min before a solution of amine (1.0 equiv.) in 1,2-dichloroethane was added at 0 °C for 15 min. The solution was heated to 60 °C and left to stir for 2–16 h, with the reaction checked for completion by TLC periodically. The stirring solution was cooled to rt before addition of aqueous solution of $NaHCO_3$. The organic layer was washed with water (3×), dried over $MgSO_4$, filtered and concentrated under vacuum.

_N_-Benzyl-2-oxo-2-phenylacetamide, **1a**



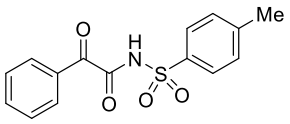
Prepared according to general procedure A using benzoylformic acid (675 mg, 4.5 mmol), Et_3N (1.3 mL, 9.0 mmol), 1,2-dichloroethane (12 mL), followed by thionyl chloride (650 µL, 9.0 mmol), benzylamine (490 µL, 4.5 mmol), 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/EtOAc = 9:1) and recrystallised (petrol/CH_2Cl_2) to give amide **1a** as a crystalline white solid (578 mg, 2.4 mmol, 54%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.36 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.63 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.49 (2H, t, *J* = 7.5 Hz, Ar-*H*), 7.45 (1H, bs, N-*H*), 7.39–7.29 (5H, m, Ar-*H*), 4.58 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.7, 161.7, 137.2, 134.6, 133.4, 131.4, 129.0, 128.6, 128.0, 127.9, 43.6; **LRMS (ESI) m/z**: 262.1 [$C_{15}H_{13}NO_2Na$, $(M+Na)^+$]. These data are consistent with literature.[202]

General Procedure B:[203]



To a solution of α-keto acid (1.0 equiv.) and 1 drop of DMF in CH_2Cl_2 (0.5 M) was added oxalyl chloride (1.2 equiv.) dropwise for 15 min, and the yellow mixture was left to stir at rt for 3 h. The solvent was removed under vacuum and the residue was dissolved in toluene. The resulting solution was then added dropwise for 20 min to a solution of amine (1.0 equiv.), DMAP (0.5 mol%) and Et_3N (2.0 equiv.) in EtOAc (same as the amount of CH_2Cl_2 used) at 0 °C. The mixture was left to stir at rt for 18 h. An aqueous solution of HCl (1 M) was added to the mixture until a clear organic layer was obtained. The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum.

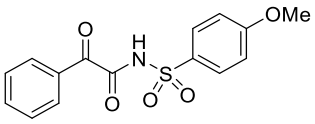
***N*-Tosyl-2-oxo-2-phenylacetamide**, **1b**



Prepared according to general procedure B using benzoylformic acid (1.50 g, 10 mmol), oxalyl chloride (1.0 mL, 12 mmol), 1 drop of DMF in CH_2Cl_2 (20 mL), toluene (10 mL), 4-methylbenzenesulfonamide (1.71 g, 10 mmol), DMAP (6.1 mg, 0.05 mmol), Et_3N (2.8 mL), and EtOAc (20 mL). The residue was purified by column chromatography (CH_2Cl_2/EtOAc/AcOH = 90:10:2) to give amide **1b** as a light yellow solid (1.91 g, 6.3 mmol, 63%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.64 (1H, bs, N-*H*), 8.25 (2H, d, J = 7.5 Hz, Ar-*H*), 8.03 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.0 Hz, Ar-*H*), 7.64 (1H, t, J = 7.5 Hz, Ar-*H*), 7.45 (2H, app. t, J = 7.5 Hz, Ar-*H*), 7.36 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 8.0 Hz, Ar-*H*), 2.43 (3H, s, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 184.1,

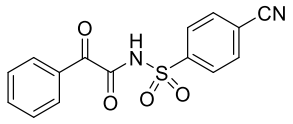
158.2, 145.8, 135.5, 135.0, 131.9, 131.5, 129.9, 128.9, 128.7, 21.8; **LRMS (ESI) m/z**: 326.0 [$C_{15}H_{13}NO_4SNa$, $(M+Na)^+$]. These data are consistent with literature.[203]

N-((4-Methoxyphenyl)sulfonyl)-2-oxo-2-phenylacetamide, 1c



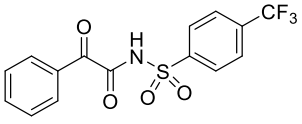
Prepared according to general procedure B, using benzoylformic acid (300 mg, 2.0 mmol), oxalyl chloride (200 µL, 2.4 mmol), 1 drop of DMF in CH_2Cl_2 (4.0 mL), toluene (2.0 mL), 4-methoxybenzenesulfonamide (190 mg, 2.0 mmol), DMAP (1.2 mg, 0.01 mmol), Et_3N (560 µL, 4.0 mmol) and EtOAc (4.0 mL). The residue was purified by column chromatography (100% Et_2O) to give amide **1c** as a white solid (250 mg, 0.79 mmol, 40%) **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.55 (1H, bs, N-*H*), 8.26 (2H, d, *J* = 7.0 Hz, Ar-*H*), 8.08 (2H, app. d (AA'BB'), J_{AB} + J_{AB}' = 9.0 Hz, Ar-*H*), 7.65 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.46 (2H, dd, *J* = 7.5, 7.0 Hz, Ar-*H*), 7.02 (2H, app. d (AA'BB'), J_{BA} + J_{BA}' = 9.0 Hz, Ar-*H*), 3.88 (3H, s, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 184.2, 164.5, 158.1, 135.5, 131.9, 131.6, 131.2, 129.2, 128.9, 114.4, 55.9; **MP (Et_2O)**: 112–116 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3649, 3247, 2980, 2844, 2361, 2342, 1718, 1678, 1595, 1578, 1498, 1419, 1354, 1317, 1265, 1191, 1166, 1089, 1023, 1002, 977, 872, 835, 805, 771, 744, 687, 676, 665, 627; **LRMS (ESI) m/z**: 342.0 [$C_{15}H_{13}NNaO_5S$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{15}H_{13}NNaO_5S$, $(M+Na)^+$]: 342.0407; found 342.0408.

***N*-((4-Cyanophenyl)sulfonyl)-2-oxo-2-phenylacetamide**, **1d**



Prepared according to general procedure B, using benzoylformic acid (600 mg, 4.0 mmol), oxalyl chloride (410 µL, 4.8 mmol), 1 drop of DMF in CH_2Cl_2 (8.0 mL), toluene (4.0 mL), 4-cyanobenzenesulfonamide (730 mg, 4.0 mmol), DMAP (2.4 mg, 0.02 mmol), Et_3N (1.1 mL, 8.0 mmol) and EtOAc (8.0 mL). The residue was purified by recrystallisation (petrol/EtOAc) to give amide **1d** as a white solid (823 mg, 2.6 mmol, 66%). **^{1}H NMR (400 MHz, acetone-d_6)** δ 11.68 (1H, bs, N-*H*), 8.32 (2H, app. d (AA'BB'), J_{AB} + J_{AB}' = 8.5 Hz, Ar-*H*), 8.13 (2H, app. d (AA'BB'), J_{BA} + J_{BA}' = 8.5 Hz, Ar-*H*), 8.00 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.74 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.60–7.51 (2H, dd, *J* = 8.0, 7.5 Hz, Ar-*H*); **^{13}C NMR (101 MHz, acetone-d_6)** δ 186.4, 162.6, 143.7, 135.9, 134.1, 133.0, 131.1, 129.9, 129.8, 118.4, 118.0; **MP (petrol/EtOAc)**: 181–183 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 3265, 3098, 2981, 2888, 2233, 1738, 1673, 1594, 1473, 1462, 1447, 1430, 1383, 1359, 1270, 1172, 1117, 1085, 1003, 967, 955, 879, 846, 831, 803, 746, 686, 671, 643; **LRMS (ESI) m/z**: 313.0 [$C_{15}H_9N_2O_4S$, $(M\text{-}H)^-$]; **HRMS (ESI)**: calcd for [$C_{15}H_9N_2O_4S$, $(M\text{-}H)^-$]: 313.0289; found 313.0288.

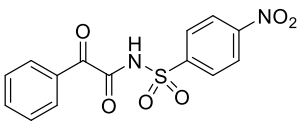
***N*-((4-(Trifluoromethyl)phenyl)sulfonyl)-2-oxo-2-phenylacetamide**, **1e**



Prepared according to general procedure B, using benzoylformic acid (300 mg, 2.0 mmol), oxalyl chloride (200 µL, 2.4 mmol), 1 drop of DMF in CH_2Cl_2 (4.0 mL), toluene (2.0 mL), 4-(trifluoromethyl)benzenesulfonamide (450 mg, 2.0 mmol), DMAP (1.2 mg, 0.01 mmol), Et_3N (560 µL, 4.0 mmol) and EtOAc (4.0 mL). The residue was

purified by column chromatography (CH_2Cl_2/EtOAc/AcOH = 90:10:2) to give amide **1e** as a white solid (573 mg, 1.6 mmol, 80%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.71 (1H, bs, N-*H*), 8.34–8.23 (4H, m, Ar-*H*), 7.85 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.67 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.48 (2H, dd, *J* = 8.0, 7.5 Hz, Ar-*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 183.6, 158.1, 141.3, 136.1 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 135.8, 131.7, 131.6, 129.4, 129.0, 126.5 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 123.1 (q, $^1J_{C\text{-}F}$ = 277.0 Hz); **^{19}F NMR (377 MHz, chloroform-*d*)** −63.3; **MP (CH_2Cl_2/EtOAc/AcOH)**: 124–127 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 2981, 2972, 2930, 2890, 2859, 1742, 1684, 1597, 1461, 1449, 1375, 1323, 1242, 1172, 1139, 1110, 1092, 1063, 1019, 967, 956, 877, 845, 845, 796, 771, 744, 713, 688; **LRMS (ESI) m/z**: 380.0 [$C_{15}H_{10}F_3NNaO_4S$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{15}H_{10}F_3NNaO_4S$, $(M+Na)^+$]: 380.0175; found 380.0175.

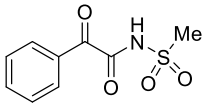
N-((4-Nitrophenyl)sulfonyl)-2-oxo-2-phenylacetamide, 1f



Prepared according to general procedure B, using benzoylformic acid (750 mg, 5.0 mmol), oxalyl chloride (510 µL, 6.0 mmol), 1 drop of DMF in CH_2Cl_2 (10 mL), toluene (5.0 mL), 4-nitrobenzenesulfonamide (1.01 g, 5.0 mmol), DMAP (3.0 mg, 0.025 mmol), Et_3N (1.4 mL, 10 mmol) and EtOAc (10 mL). The residue was purified by recrystallisation (petrol/CH_2Cl_2) to give amide **1f** as a white solid (1.27 g, 3.8 mmol, 76%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.68 (1H, bs, N-*H*), 8.39–8.33 (4H, m, Ar-*H*), 8.28 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.72–7.63 (1H, m, Ar-*H*), 7.49 (2H, dd, *J* = 8.0, 8.0 Hz, Ar-*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 183.4, 158.0, 151.2, 143.3, 135.9, 131.64, 131.61, 130.3, 129.1, 124.5; **MP (petrol/CH_2Cl_2)**: 143–145 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 3240, 2981, 2888, 2163, 1736, 1674, 1594, 1527, 1473, 1462, 1449, 1384, 1355,

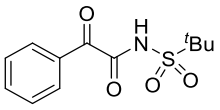
1313, 1270, 1252, 1171, 1086, 1002, 967, 956, 913, 890, 854, 823, 798, 737, 684, 672, 623; **LRMS (ESI) m/z**: 357.0 [$C_{14}H_{10}N_2NaO_6S$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{14}H_{10}N_2NaO_6S$, $(M+Na)^+$]: 357.0152; found 357.0155.

N-(Methylsulfonyl)-2-oxo-2-phenylacetamide, 1g



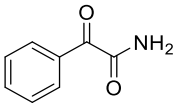
Prepared according to general procedure B, using benzoylformic acid (300 mg, 2.0 mmol), oxalyl chloride (200 µL, 2.4 mmol), 1 drop of DMF in CH_2Cl_2 (4.0 mL), toluene (10 mL), methanesulfonamide (190 mg, 2.0 mmol), DMAP (1.2 mg, 0.01 mmol), Et_3N (560 µL, 4.0 mmol) and EtOAc (4.0 mL). The residue was purified by column chromatography (CH_2Cl_2/EtOAc/AcOH = 80:20:2) to give amide **1g** as a white solid (95 mg, 0.42 mmol, 21%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.44 (1H, bs, N-*H*), 8.33 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.70 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.52 (2H, t, *J* = 8.0 Hz, Ar-*H*), 3.39 (3H, s, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 183.5, 159.1, 135.5, 131.5, 131.3, 128.7, 41.4; **MP (CH_2Cl_2/EtOAc/AcOH)**: 128–131 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3238, 3045, 2981, 1714, 1687, 1598, 1432, 1400, 1332, 1320, 1279, 1135, 989, 970, 886, 684, 669, 607; **LRMS (ESI) m/z**: 226.0 [$C_9H_8NO_4S$, $(M-H)^-$]; **HRMS (ESI)**: calcd for [$C_9H_9NNaO_4S$, $(M+Na)^+$]: 250.0145; found 250.0147. These data are consistent with literature.[203]

N-(*tert*-Butylsulfonyl)-2-oxo-2-phenylacetamide, 1h



Prepared according to general procedure B, using benzoylformic acid (450 mg, 3.0 mmol), oxalyl chloride (310 µL, 3.6 mmol), 1 drop of DMF in CH_2Cl_2 (9.0 mL), toluene (4.5 mL), 2-methylpropane-2-sulfonamide (412 mg, 3.0 mmol), DMAP (1.8 mg, 0.015 mmol), Et_3N (840 µL, 6.0 mmol) and EtOAc (9.0 mL). The residue was purified by column chromatography (CH_2Cl_2/EtOAc/AcOH = 80:20:2) to give amide **1h** as a yellow solid (261 mg, 0.97 mmol, 32%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.46 (1H, s, N*H*), 8.31–8.21 (2H, m, Ar-*H*), 7.73–7.58 (1H, m, Ar-*H*), 7.54–7.42 (2H, m, Ar-*H*), 1.53 (9H, s, 3 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.4, 164.4, 134.9, 133.0, 131.3, 128.8, 49.8, 28.8; **MP (CH_2Cl_2/EtOAc/AcOH)**: 48–51 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 2981, 2889, 2253, 1710, 1573, 1362, 1223, 1136, 1093, 909, 771, 728, 648; **LRMS (ESI) m/z**: 292.0 [$C_{12}H_{15}NNaO_4S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{12}H_{15}NNaO_4S$, $(M+Na)^+$]: 292.0614; found 292.0614.

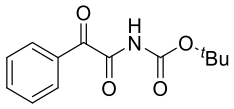
2-Oxo-2-phenylacetamide, 1i



Prepared according to a literature procedure.[204] To a solution of I_2 (1.9 g, 7.5 mmol) in DMSO (20 mL) was added acetophenone (590 µL, 5.0 mmol) and formamide (300 µL, 7.5 mmol) at rt. The resulting mixture was stirred at 100 °C for 39 h. The solution was cooled to rt before the addition of water (50 mL). The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic layer was washed with 10% Na_2SO_3 (aq., 50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by

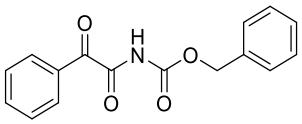
column chromatography (petrol/EtOAc = 5:1) to give amide **1i** as an orange solid (122 mg, 0.82 mmol, 16%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.29 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.63 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.48 (2H, app. t, *J* = 8.0 Hz, Ar-*H*), 7.08 (1H, s, NH_AH_B), 6.54 (1H, s, NH_AH_B); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.6, 164.4, 134.7, 133.1, 131.2, 128.7; **HRMS (ESI) m/z**: calcd for $[C_8H_8NO_2]^+$: 150.0550; found 150.0552. These data are consistent with literature.[204]

tert-Butyl(2-oxo-2-phenylacetyle)carbamate, 1j



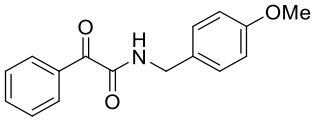
Prepared according to a literature procedure.[205] To a solution of *α*-oxo-benzenacetamide (104 mg, 0.7 mmol) in 1,2-dichloroethane (7.0 mL) was added di-*tert*-butyl dicarbamate (153 mg, 0.7 mmol) and DMAP (86.0 mg, 0.7 mmol). The solution was stirred and heated at 50 °C for 4 h before it was left to stir at rt overnight. The solution was concentrated under vacuum and purified by column chromatography (petrol/EtOAc = 4:1) to give amide **1j** as a yellow solid (65 mg, 0.26 mmol, 37%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.62 (1H, s, N*H*), 8.10 (2H, app. bs, Ar-*H*), 7.67–7.58 (1H, m, Ar-*H*), 7.48 (2H, app. t, *J* = 8.0 Hz, Ar-*H*), 1.42 (9H, s, 3 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 186.7, 149.9, 149.6, 134.8, 132.4, 130.4, 128.9, 28.1, 27.9; **MP**: 139–141 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3198, 2981, 1753, 1681, 1597, 1454, 1368, 1245, 1222, 1147, 968, 815, 773, 704; **LRMS (ESI) m/z**: 272.0 [$C_{13}H_{15}NNaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{16}NO_4$, $(M+H)^+$]: 250.1074; found 250.1071.

Benzyl(2-oxo-2-phenylacetyl)carbamate, **1k**



Prepared according to general procedure A, using benzoylformic acid (450 mg, 3.0 mmol), Et_3N (840 µL, 6.0 mmol), 1,2-dichloroethane (20 mL), followed by thionyl chloride (440 µL, 6.0 mmol), benzylcarbamate (454 mg, 3.0 mmol) and 1,2-dichloroethane (10 mL). The residue was purified by column chromatography (petrol/Et_2O = 4:1) and recrystallisation (petrol/Et_2O) to give amide **1k** a light yellow solid (480 mg, 1.8 mmol, 60%). **^{1}H NMR (400 MHz, chloroform-*d*)**; δ 8.86 (1H, bs, N*H*), 8.17 (2H, m, Ar-*H*), 7.66 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.50 (2H, app. t, *J* = 8.0 Hz, Ar-*H*), 7.39–7.33 (5H, m, Ar-*H*), 5.21 (2H, s, C*H*$_2$). **^{13}C NMR (101 MHz, chloroform-*d*)** δ 150.8, 135.1, 134.5, 132.2, 130.8, 129.0, 128.83, 128.78, 128.7, 128.4, 128.3, 68.7; **MP**: 64–67 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3263, 3066, 3034, 2981, 2889, 1757, 1682, 1596, 1481, 1451, 1377, 1348, 1290, 1199, 1176, 1069, 1028, 1001, 957, 913, 813, 772, 745, 719, 696, 686, 632; **LRMS (ESI) m/z**: 306.0 [$C_{16}H_{13}NNaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{13}NNaO_4$, $(M+Na)^+$]: 306.0737; found 306.0737.

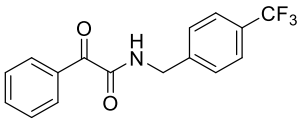
***N*-(4-Methoxybenzyl)-2-oxo-2-phenylacetamide**, **1l**



Prepared according to general procedure A, using benzoylformic acid (450 mg, 3.0 mmol), Et_3N (840 µL, 6.0 mmol), 1,2-dichloroethane (8.0 mL), followed by thionyl chloride (440 µL, 6.0 mmol), 4-methoxybenzylamine (390 µL, 3.0 mmol) and 1,2-dichloroethane (4.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) and recrystallization (petrol/Et_2O) to give amide **1l** as a white

crystalline solid (435 mg, 1.6 mmol, 54%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.38 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.65 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.51 (2H, dd, *J* = 8.0, 7.5 Hz, Ar-*H*), 7.38 (1H, bs, N*H*), 7.29 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.5 Hz, Ar-*H*), 6.91 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 8.5 Hz, Ar-*H*), 4.53 (2H, d, *J* = 6.0 Hz, CH_2), 3.83 (3H, s, OCH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.7, 161.6, 159.4, 134.6, 133.5, 131.4, 129.5, 129.3, 128.6, 114.3, 55.4, 43.1; **MP (petrol/Et$_2$O)**: 78–80 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3324, 3068, 2981, 2837, 1661, 1612, 1596, 1512, 1462, 1449, 1382, 1359, 1318, 1303, 1286, 1249, 1218, 1176, 1112, 1071, 1032, 942, 918, 827, 745, 688, 670, 615; **LRMS (ESI) m/z**: 292.0 [$C_{16}H_{15}NNaO_3$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{16}H_{15}NNaO_3$, $(M+Na)^+$]: 292.0944; found 292.0945.

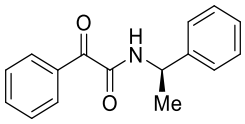
***N*-(4-(Trifluoromethyl)benzyl)-2-oxo-2-phenylacetamide**, **1m**



Prepared according to general procedure A, using benzoylformic acid (450 mg, 3.0 mmol), Et_3N (840 µL, 6.0 mmol), 1,2-dichloroethane (8.0 mL), followed by thionyl chloride (440 µL, 6.0 mmol), 4-trifluoromethylbenzylamine (430 µL, 3.0 mmol) and 1,2-dichloroethane (4.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) and recrystallisation (petrol/Et_2O) to give amide **1m** as a white crystalline solid (790 mg, 2.6 mmol, 86%). **^{1}H NMR (400 MHz, acetone-*d*$_6$)** δ 8.74 (1H, bs, N*H*), 8.21 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.0 Hz, Ar-*H*), 7.74–7.67 (3H, m, Ar-*H*), 7.64 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.55 (2H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 4.71 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, acetone-*d*$_6$)** δ 189.6, 164.5, 144.4, 135.2, 134.4, 131.3, 129.7 (q, $^2J_{C\text{-}F}$ = 31.0 Hz), 129.5, 129.1, 126.2 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 125.4 (q, $^1J_{C\text{-}F}$ = 272.0 Hz), 43.0; **^{19}F NMR (377 MHz, chloroform-*d*)** −62.6; **MP (petrol/Et$_2$O)**: 122–

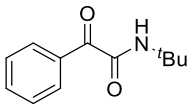
123 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 3255, 3070, 2981, 2888, 1677, 1658, 1620, 1595, 1527, 1473, 1449, 1418, 1383, 1334, 1237, 1222, 1156, 1113, 1070, 1033, 1020, 1000, 955, 942, 838, 819, 754, 729, 689, 671, 639; **LRMS (ESI) m/z**: 330.0 [$C_{16}H_{12}F_3NNaO_2$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{16}H_{12}F_3NNaO_2$, $(M+Na)^+$]: 330.0712; found 330.0713.

N-(1-Phenylethyl)-2-oxo-2-phenylacetamide, 1n



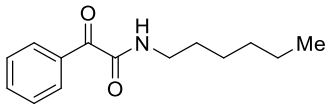
Prepared according to general procedure A, using benzoylformic acid (450 mg, 3.0 mmol), Et_3N (840 µL, 6.0 mmol), 1,2-dichloroethane (20 mL), followed by thionyl chloride (440 µL, 6.0 mmol), (*R*)-(+)-1-phenylethylamine (380 µL, 3.0 mmol) and 1,2-dichloroethane (10 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) and recrystallisation (petrol/Et_2O) to give amide **1n** as white crystals (528 mg, 2.1 mmol, 70%).**^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.34 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.62 (1H, t, *J* = 7.0 Hz, Ar-*H*), 7.47 (2H, dd, *J* = 8.5, 7.0 Hz, Ar-*H*), 7.40 (1H, bs, N*H*), 7.38–7.35 (4H, m, Ar-*H*), 7.33–7.27 (1H, m, Ar-*H*), 5.19 (1H, dq, *J* = 8.0, 7.0 Hz, C*H*), 1.61 (3H, d, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.7, 160.8, 142.4, 134.5, 133.4, 131.4, 128.9, 128.6, 127.8, 126.3, 49.2, 21.8; **MP (petrol/Et_2O)**: 111–112 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 3262, 3067, 2981, 2888, 1654, 1637, 1595, 1546, 1494, 1449, 1377, 1317, 1273, 1219, 1177, 1123, 1092, 1073, 1019, 1005, 967, 912, 851, 761, 746, 697, 671, 616; **LRMS (ESI) m/z**: 276.0 [$C_{16}H_{15}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{16}H_{15}NNaO_2$, $(M+Na)^+$]: 276.0995; found 276.0996. These data are consistent with literature.[206]

_N_-(_tert_-Butyl)-2-oxo-2-phenylacetamide, **1o**



Prepared according to general procedure A, using benzoylformic acid (180 mg, 1.2 mmol), Et_3N (340 µL, 2.4 mmol), 1,2-dichloroethane (4.0 mL), followed by thionyl chloride (170 µL, 2.4 mmol), *tert*-butylamine (130 µL, 1.2 mmol) and 1,2-dichloroethane 2.0 mL). The residue was purified by column chromatography (petrol/EtOAc = 7:3) to give amide **1o** as a yellow solid (130 mg, 0.63 mmol, 53%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.24 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.54 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.40 (2H, app. t, *J* = 8.0 Hz, Ar-*H*), 6.96 (1H, s, N*H*), 1.41 (9H, s, 3 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 188.6, 161.3, 134.1, 133.3, 131.1, 128.3, 51.6, 28.3; **LRMS (ESI) m/z**: 228.0 [$C_{12}H_{15}NNaO_2$, $(M+Na)^+$]. These data are consistent with literature.[202]

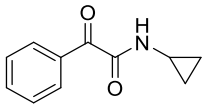
_N_-Hexyl-2-oxo-2-phenylacetamide, **1p**



Prepared according to general procedure A, using benzoylformic acid (750 mg, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), 1,2-dichloroethane (14 mL), followed by thionyl chloride (730 µL, 10.0 mmol), hexylamine (660 µL, 5.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) to give amide **1p** as a yellow oil (1.0 g, 4.3 mmol, 86%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.29 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.58 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.43 (2H, dd, *J* = 7.5, 7.5 Hz, Ar-*H*), 7.30 (1H, bs, N*H*), 3.35 (2H, dt, *J* = 6.5, 6.5 Hz, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.62–1.49 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.40–1.21 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.87 (3H, t, *J* = 6.0 Hz, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 188.1, 162.0, 134.3, 133.4,

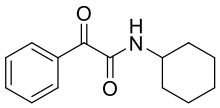
131.1, 128.4, 39.5, 31.4, 29.2, 26.5, 22.5, 14.0; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 3308, 2981, 2931, 2889, 1659, 1597, 1523, 1449, 1381, 1318, 1260, 1216, 1177, 1155, 1073, 954, 816, 745, 687, 672; **LRMS (ESI) m/z**: 234.2 [$C_{14}H_{20}NO_2$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{14}H_{20}NO_2$, $(M+H)^+$]: 234.1489; found 234.1491. These data are consistent with literature.[206]

N-Cyclopropyl-2-oxo-2-phenylacetamide, 1q



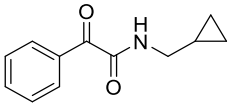
Prepared according to general procedure A, using benzoylformic acid (600 mg, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), 1,2-dichloroethane (10 mL), followed by thionyl chloride (580 µL, 8.0 mmol), cyclopropylamine (280 µL, 4.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) and recrystallisation (petrol/Et_2O) to give amide **1q** as a white solid (374 mg, 2.0 mmol, 49%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.33 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.61 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.46 (2H, dd, *J* = 8.0, 7.5 Hz, Ar-*H*), 7.17 (1H, bs, N*H*), 2.89–2.83 (1H, m, NHC*H*), 0.92–0.85 (2H, m, CH_2), 0.67–0.62 (2H, m, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.7, 163.2, 134.5, 133.3, 131.4, 128.6, 22.7, 6.7, 6.6; **MP (petrol/Et_2O)**: 69–71 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3275, 3068, 2981, 1653, 1596, 1519, 1449, 1362, 1284, 1234, 1202, 1180, 1051, 931, 850, 792, 747, 688, 670; **LRMS (ESI) m/z**: 188.1 [$C_{11}H_{10}NO_2$, $(M-H)^-$]; **HRMS (ESI)**: calcd for [$C_{11}H_{12}NO_2$, $(M+H)^+$]: 190.0863; found 190.0863.

N-Cyclohexyl-2-oxo-2-phenylacetamide, 1r



Prepared according to general procedure A, using benzoylformic acid (450 mg, 3.0 mmol), Et_3N (840 µL, 6.0 mmol), 1,2-dichloroethane (8.0 mL), followed by thionyl chloride (440 µL, 6.0 mmol), cyclohexanamine (340 µL, 3.0 mmol) and 1,2-dichloroethane (4.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) and recrystallisation (petrol/Et_2O) to give amide **1r** as a white solid (295 mg, 1.3 mmol, 43%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.33 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.61 (1H, t, *J* = 7.0 Hz, Ar-*H*), 7.47 (2H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 6.99 (1H, bs, N*H*), 3.85 (1H, tdt, *J* = 11.0, 8.0, 4.0 Hz, NHC*H*), 2.02–1.93 (2H, m, CH_2), 1.79–1.73 (2H, m, CH_2), 1.67–1.62 (1H, m, CH_AH$_B$), 1.47–1.33 (2H, m, CH_2), 1.31–1.19 (3H, m, CH_2, CH$_A$$H_B$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 188.2, 161.0, 134.4, 133.6, 131.3, 128.6, 48.6, 32.8, 25.5, 24.8; **MP (petrol/Et_2O)**: 114–116 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3274, 3085, 2935, 2855, 1680, 1664, 1640, 1596, 1551, 1449, 1246, 1217, 1179, 1153, 1088, 961, 838, 752, 693, 672; **HRMS (FI)**: calcd for [$C_{14}H_{18}NO_2$, $(M+H)^+$]: 232.1332; found 232.1334. These data are consistent with literature.[207]

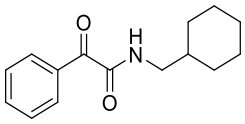
N-(Cyclopropylmethyl)-2-oxo-2-phenylacetamide, 1s



Prepared according to general procedure A, using benzoylformic acid (600 mg, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), 1,2-dichloroethane (10 mL), followed by thionyl chloride (580 µL, 8.0 mmol), cyclopropylmethanamine (350 µL, 4.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography

(petrol/Et_2O = 95:5) and recrystallisation (petrol/Et_2O) to give amide **1s** as a white solid (381 mg, 1.9 mmol, 47%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.33 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.61 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.47 (2H, dd, *J* = 7.5, 8.0 Hz, Ar-*H*), 7.21 (1H, bs, N*H*), 3.25 (2H, dd, *J* = 6.5, 6.5 Hz, NHCH_2), 1.11–0.96 (1H, m, C*H*), 0.61–0.50 (2H, m, CH(CH_2)), 0.30–0.24 (2H, m, CH(CH_2)); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 188.1, 161.7, 134.5, 133.5, 131.3, 128.6, 44.4, 10.6, 3.7; **MP (petrol/Et_2O)**: 38–40 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3305, 3080, 2981, 1657, 1596, 1523, 1449, 1268 1217, 1023, 833, 746, 688, 672; **LRMS (ESI) m/z**: 226.0 [$C_{12}H_{13}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{12}H_{13}NNaO_2$, $(M+Na)^+$]: 226.0839; found 226.0842.

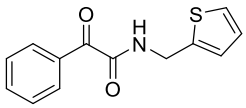
N-(Cyclohexylmethyl)-2-oxo-2-phenylacetamide, 1t



Prepared according to general procedure A, using benzoylformic acid (600 mg, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), 1,2-dichloroethane (10 mL), thionyl chloride (580 µL, 8.0 mmol), cyclohexylmethanamine (510 µL, 4.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 95:5) and recrystallisation (petrol/Et_2O) to give amide **1t** as a white solid (720 mg, 2.9 mmol, 73%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.34 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.62 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.47 (2H, dd, *J* = 8.0, 7.5 Hz, Ar-*H*), 7.15 (1H, bs, N*H*), 3.24 (2H, dd, *J* = 6.5, 6.5 Hz, NHCH_2), 1.81–1.72 (4H, m, Cy-CH_2), 1.71–1.63 (1H, m, Cy-CH_AH$_B$), 1.51–1.64 (1H, m, NHCH$_2$C*H*), 1.33–1.08 (3H, m, Cy-CH_2, Cy-CH$_A$$H_B$), 1.04–0.94 (2H, m, Cy-CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 188.1, 161.9, 134.5, 133.5, 131.4, 128.6, 45.7, 38.0, 30.9, 26.4, 25.9; **MP (petrol/Et_2O)**: 94–96 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3273, 2981, 2926, 2854, 1664, 1597, 1524, 1449, 1225, 1178, 905, 726, 688, 672,

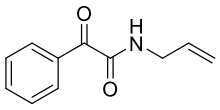
648; **LRMS (ESI) m/z**: 244.1 [$C_{15}H_{18}NO_2$, $(M-H)^-$]; **HRMS (ESI)**: calcd for [$C_{15}H_{20}NO_2$, $(M+H)^+$]: 246.1489; found 246.1487.

N-(Thiophen-2-ylmethyl)-2-oxo-2-phenylacetamide, 1u



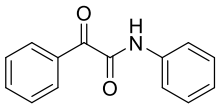
Prepared according to general procedure A, using benzoylformic acid (750 mg, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), 1,2-dichloroethane (14 mL), followed by thionyl chloride (730 µL, 10 mmol), 2-(aminomethyl)thiophene (513 µL, 5.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 4:1) and recrystallisation (petrol/Et_2O) to give amide **1u** as a white solid (655 mg, 2.7 mmol, 53%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.30 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.58 (1H, t, *J* = 7.5 Hz, Ar-*H*), 7.44 (2H, app. t, *J* = 7.5, 7.0 Hz, Ar-*H*), 7.41 (1H, bs, N*H*), 7.21 (1H, d, *J* = 5.0 Hz, Ar-*H*), 6.99 (1H, d, *J* = 3.5 Hz, Ar-*H*), 6.92 (1H, dd, *J* = 5.0, 3.5 Hz, Ar-*H*), 4.69 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.4, 161.4, 139.5, 134.6, 133.3, 131.4, 128.6, 127.1, 126.7, 125.8, 38.2; **MP (petrol/Et_2O)**: 95–97 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3661, 3255, 3085, 2981, 2888, 1681, 1639, 1595, 1563, 1533, 1451, 1431, 1371, 1347, 1219, 1179, 1053, 1041, 1022, 1001, 940, 928, 853, 800, 749, 688, 630; **LRMS (ESI) m/z**: 244.0 [$C_{13}H_{10}NO_2S$, $(M-H)^-$]; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{10}NO_2S$, $(M-H)^-$]: 244.0438; found 244.0436.

N-Allyl-2-oxo-2-phenylacetamide, 1v



Prepared according to general procedure A, using benzoylformic acid (450 mg, 3.0 mmol), Et_3N (840 µL, 6.0 mmol), 1,2-dichloroethane (8.0 mL), followed by thionyl chloride (440 µL, 6.0 mmol), allylamine (340 µL, 3.0 mmol) and 1,2-dichloroethane (4.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) and recrystallisation (petrol/Et_2O) to give amide **1v** as a white solid (229 mg, 1.2 mmol, 40%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.35 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.63 (1H, t, *J* = 7.0 Hz, Ar-*H*), 7.48 (2H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 7.18 (1H, bs, N*H*), 5.90 (1H, ddt, *J* = 17.0, 10.0, 5.5 Hz, C*H*=CH_AH_B), 5.28 (1H, dd, *J* = 17.0, 1.0 Hz, CH=C*H*$_A$$H_B$), 5.22 (1H, dd, *J* = 10.0, 1.0 Hz, CH=CH_AH_B), 4.02 (2H, dd, *J* = 5.5, 1.5 Hz, NCH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.7, 161.7, 134.6, 133.4, 133.1, 131.4, 128.7, 117.4, 41.8; **MP (petrol/Et_2O)**: 58–60 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3259, 3098, 2918, 1681, 1653, 1635, 1595, 1571, 1451, 1430, 1265, 1227, 1179, 1018, 993, 943, 928, 892, 690; **HRMS (FI)**: calcd for [$C_{11}H_{12}NO_2$, $(M+H)^+$]: 190.0863; found 190.0863. These data are consistent with literature.[208]

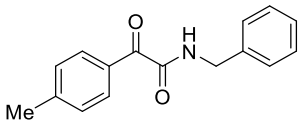
N-Phenyl-2-oxo-2-phenylacetamide, 1w



Prepared according to general procedure A, using benzoylformic acid (600 mg, 4.0 mmol), Et_3N (1.1 mL, 8.0 mmol), 1,2-dichloroethane (10 mL), followed by thionyl chloride (580 µL, 8.0 mmol), aniline (360 µL, 4.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O = 9:1) to give

amide **1w** as a yellow solid (788 mg, 3.5 mmol, 87%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.04 (1H, bs, N*H*), 8.40 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.71 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.64 (2H, dd, *J* = 8.0, 7.0 Hz, Ar-*H*), 7.49 (1H, t, *J* = 7.0 Hz, Ar-*H*), 7.39 (2H, dd, *J* = 8.5, 7.5 Hz, Ar-*H*), 7.20 (1H, t, *J* = 7.5 Hz, Ar-*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.5, 159.1, 136.7, 134.7, 133.1, 131.5, 129.3, 128.6, 125.3, 120.0; **MP (petrol/Et$_2$O)**: 59–61 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3346, 3062, 1667, 1595, 1530, 1495, 1445, 1278, 1241, 1171, 1080, 1030, 1004, 989, 907, 879, 789, 744, 688; **HRMS (FI)**: calcd for [$C_{14}H_{12}NO_2$, $(M+H)^+]^+$: 226.0863; found 226.0863. These data are consistent with literature.[207]

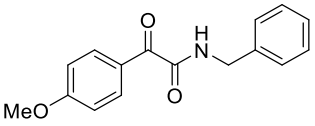
N-Benzyl-2-oxo-2-(*p*-tolyl)acetamide, 4a



Prepared according to general procedure A, using crude 2-oxo-2-(*p*-tolyl)acetic acid (985 mg, 6.0 mmol), Et_3N (1.7 mL, 12.0 mmol), 1,2-dichloroethane (16 mL), followed by thionyl chloride (870 µL, 12.0 mmol), benzylamine (660 µL, 6.0 mmol) and 1,2-dichloroethane (8.0 mL). The residue was purified by column chromatography (100% CH_2Cl_2) and recrystallised in petrol/Et_2O to give amide **4a** as white crystals (341 mg, 1.3 mmol, 22%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.29 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.45 (1H, s, N*H*), 7.39–7.26 (7H, m, Ar-*H*), 4.57 (2H, d, *J* = 6.0 Hz, CH_2), 2.43 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.1, 161.9, 145.8, 137.3, 131.5, 130.9, 129.4, 128.9, 128.0, 127.9, 43.6, 22.0; **MP (petrol/Et$_2$O)**: 82–84 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3267, 3092, 2925, 1675, 1642, 1605, 1567, 1497, 1454, 1431, 1409, 1382, 1364, 1308, 1226, 1210, 1176, 1118, 1083, 1060, 1031, 1017, 939, 904, 839, 790, 767, 730, 697, 680, 618; **LRMS (ESI) m/z**: 276.0 [$C_{16}H_{15}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI)**

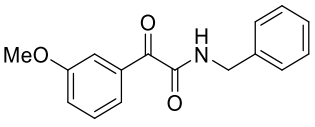
m/z: calcd for [$C_{16}H_{15}NNaO_2$, $(M+Na)^+$]: 276.0995; found 276.0995. These data are consistent with literature.[209]

N-Benzyl-2-oxo-2-(3-methoxyphenyl)acetamide, 4b



Prepared according to general procedure A, using crude 2-(4-methoxyphenyl)-2-oxoacetic acid (900 mg, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), 1,2-dichloroethane (14 mL), followed by thionyl chloride (730 µL, 10 mmol), benzylamine (550 µL, 5.0 mmol) and 1,2-dichloroethane (5.0 mL). The residue was purified by column chromatography (100% CH_2Cl_2) to give amide **4b** as a white solid (478 mg, 1.8 mmol, 35%). **^{1}H NMR (400 Mz, chloroform-*d*)** δ 8.33 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.45 (1H, bs, N*H*), 7.31–7.18 (5H, m, Ar-*H*), 6.84 (2H, app. d, $J_{BA} + J_{BA'}$ = 8.5Hz, Ar-*H*), 4.46 (2H, d, *J* = 6.0 Hz, CH_2), 3.78 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 185.6, 164.8, 162.3, 137.4, 134.0, 128.9, 127.9, 127.8, 126.4, 113.9, 55.6, 43.5; **MP (petrol/Et_2O)**: 88–90 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3353, 3300, 2950, 1655, 1596, 1512, 1455, 1423, 1315, 1261, 1167, 1027, 932, 850, 802, 773, 728, 699, 651, 618; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{16}NO_3$, $(M+H)^+$]: 270.1125; found 270.1125.

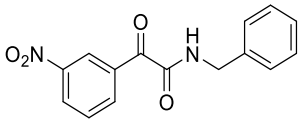
N-Benzyl-2-oxo-2-(3-methoxyphenyl)acetamide, 4c



Prepared according to general procedure A, using crude 2-(3-methoxyphenyl)-2-oxoacetic acid (1.26 g, 7.0 mmol), Et_3N (2.0 mL, 14 mmol),

1,2-dichloroethane (18 mL), followed by thionyl chloride (1.0 mL, 14 mmol), benzylamine (770 µL, 7.0 mmol) and 1,2-dichloroethane (10 mL). The residue was purified by column chromatography (100% CH_2Cl_2) to give amide **4c** as an orange oil (893 mg, 3.3 mmol, 47%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.01 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.86 (1H, s, Ar-*H*), 7.43 (1H, bs, N*H*), 7.42–7.28 (6H, m, Ar-*H*), 7.18 (1H, d, *J* = 8.0 Hz, Ar-*H*), 4.57 (2H, d, *J* = 6.0 Hz, CH_2), 3.86 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 187.4, 161.7, 159.6, 137.2, 134.5, 129.7, 129.0, 128.00, 127.95, 124.3, 121.7, 114.8, 55.6, 43.6; **IR (cm^{-1})** $\tilde{\nu}$ = 3307, 3066, 3031, 2980, 2836, 2361, 1658, 1596, 1580, 1521, 1485, 1454, 1429, 1360, 1324, 1288, 1252, 1195, 1174, 1082, 1042, 994, 952, 876, 823, 782, 765, 730, 699, 683; **LRMS (ESI) m/z**: 292.0 [$C_{16}H_{16}NNaO_3$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{16}NNaO_3$, $(M+Na)^+$]: 292.0944; found 292.0942.

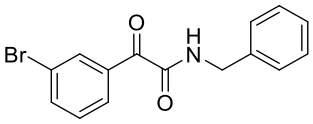
N-Benzyl-2-oxo-2-(3-nitrophenyl)acetamide, 4d



Prepared according to general procedure A, using crude 2-(3-nitrophenyl)-2-oxoacetic acid (1.4 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), 1,2-dichloroethane (14 mL), followed by thionyl chloride (730 µL, 10 mmol), benzylamine (550 µL, 5.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/CH_2Cl_2 1:1) and recrystallised in petrol/Et_2O to give amide **4d** as light yellow crystals (380 mg, 1.3 mmol, 30%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.21 (1H, s, Ar-*H*), 8.75 (1H, d, *J* = 8.0 Hz, Ar-*H*), 8.47 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.70 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.52 (1H, bs, N*H*), 7.41–7.28 (5H, m, Ar-*H*), 4.59 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 185.3, 160.4, 148.3, 137.0, 136.8, 134.6, 129.9, 129.1, 128.6, 128.2, 128.1, 126.3, 43.8; **MP (petrol/Et_2O)**: 106–108 °C; **IR (cm^{-1})**

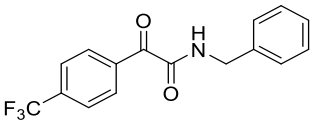
$\tilde{\nu}$ = 3385, 2980, 2888, 1669, 1613, 1530, 1497, 1474, 1455, 1437, 1382, 1349, 1251, 1214, 1153, 1081, 1030, 953, 801, 732, 700, 670; **LRMS (ESI) m/z**: 307.0 [$C_{15}H_{12}N_2NaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{12}N_2NaO_4$, $(M+Na)^+$]: 307.0689; found 307.0690.

N-Benzyl-2-oxo-2-(3-bromophenyl)acetamide, 4e



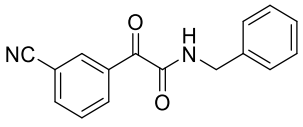
Prepared according to general procedure A, using crude 2-(3-bromophenyl)-2-oxoacetic acid (1.6 g, 7.0 mmol), Et_3N (2.0 mL, 14 mmol), 1,2-dichloroethane (18 mL), followed by thionyl chloride (1.0 mL, 14 mmol), benzylamine (770 µL, 7.0 mmol) and 1,2-dichloroethane (10 mL). The residue was purified by column chromatography (petrol/Et_2O 95:5) and recrystallised in petrol/Et_2O to give amide **4e** as white crystals (839 mg, 2.6 mmol, 38%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.53 (1H, bs, Ar-*H*), 8.35 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.77 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.49 (1H, bs, N*H*), 7.40–7.32 (6H, m, Ar-*H*), 4.58 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 186.2, 161.0, 137.4, 137.0, 135.1, 134.06, 134.04, 130.2, 130.0, 129.0, 128.0, 122.8, 43.7; **MP (petrol/Et_2O)**: 70–71 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3308, 3065, 2981, 2889, 1680, 1663, 1587, 1561, 1521, 1497, 1455, 1414, 1383, 1361, 1289, 1242, 1211, 1166, 1070, 1029, 999, 950, 900, 776, 720, 698, 677; **LRMS (ESI) m/z**: 340.0 [$C_{15}H_{13}{}^{79}BrNO_2$, $(M(^{79}Br)+H)^+$]], 342.0 [$C_{15}H_{13}{}^{81}BrNO_2$, $(M(^{81}Br)+H)^+$]]; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{13}{}^{79}BrNO_2$, $(M(^{79}Br)+H)^+$]: 318.0124; found 318.0125, calcd for [$C_{15}H_{13}{}^{81}BrNO_2$, $(M(^{81}Br)+H)^+$]: 320.0104; found 320.0103.

_N_-Benzyl-2-oxo-2-(4-(trifluoromethyl)phenyl)acetamide, **4f**



Prepared according to general procedure A, using crude 2-oxo-2-(4-(trifluoromethyl)phenyl)acetic acid (1.31 g, 6.0 mmol), Et_3N (1.7 mL, 12 mmol), 1,2-dichloroethane (16 mL), followed by thionyl chloride (870 µL, 12 mmol), benzylamine (660 µL, 6.0 mmol) and 1,2-dichloroethane (8.0 mL). The residue was purified by column chromatography (petrol/Et_2O 95:5) and recrystallised in petrol/Et_2O to give amide **4f** as light orange crystals (454 mg, 1.5 mmol, 25%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.47 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.74 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.51 (1H, bs, N*H*), 7.41–7.27 (5H, m, Ar-*H*), 4.58 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 186.7, 160.9, 137.0, 136.1, 135.4 (q, ^2J = 33.0 Hz), 131.7, 129.0, 128.1, 128.0, 125.6 (q, ^3J = 4.0 Hz), 123.6 (q, ^1J = 273.0 Hz), 43.7; **^{19}F NMR (377 MHz, chloroform-*d*)** −63.3; **MP (petrol/Et_2O)**: 104–106 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3377, 2981, 2889, 1665, 1532, 1506, 1455, 1409, 1323, 1248, 1213, 1167, 1124, 1110, 1068, 1029, 1016, 937, 901, 863, 830, 802, 765, 731, 698, 640; **LRMS (ESI) m/z**: 330.2 [$C_{16}H_{12}F_3NNaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{13}F_3NO_2$, $(M+H)^+$]: 308.0893; found 308.0894. These data are consistent with literature.[209]

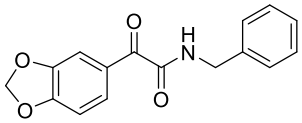
_N_-Benzyl-2-oxo-2-(3-cyanophenyl)acetamide, **4g**



Prepared according to general procedure A, using 2-(3-cyanophenyl)-2-oxoacetic acid (1.05 g, 6.0 mmol), Et_3N (1.7 mL, 12 mmol), 1,2-dichloroethane (18 mL), followed by thionyl chloride (870 µL, 12 mmol), benzylamine (660 µL, 6.0 mmol) and

1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O 4:1) and recrystallised in petrol/Et_2O to give amide **4g** as white crystals (390 mg, 1.5 mmol, 25%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.73 (1H, s, Ar-*H*), 8.61 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.89 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.62 (1H, dd, *J* = 8.0, 8.0 Hz, Ar-*H*), 7.49 (1H, s, N*H*), 7.41–7.30 (5H, m, Ar-*H*), 4.57 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 185.4, 160.5, 137.2, 136.8, 135.3, 135.1, 134.2, 129.6, 129.1, 128.2, 128.1, 117.9, 113.2, 43.8; **MP (petrol/Et_2O)**: 70–71 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3350, 3068 2981, 2233, 1668, 1599, 1523, 1498, 1476, 1455, 1426, 1361, 1292, 1238, 1159, 1070, 1029, 953, 828, 788, 762, 730, 700, 680; **LRMS (ESI) m/z**: 287.0 [$C_{16}H_{12}N_2NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{13}N_2O_2$, $(M+H)^+$]: 265.0972; found 265.0973.

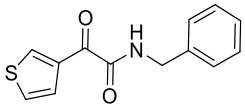
2-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-benzyl-2-oxoacetamide, **4h**



Prepared according to general procedure A, using crude 2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoacetic acid (1.36 g, 7.0 mmol), Et_3N (2.0 mL, 14 mmol), 1,2-dichloroethane (18 mL), followed by thionyl chloride (1.0 mL, 14 mmol), benzylamine (770 µL, 7.0 mmol) and 1,2-dichloroethane (10 mL). The residue was purified by column chromatography (100% CH_2Cl_2) to give amide **4h** as an orange solid (619 mg, 2.2 mmol, 31%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.08 (1H, dd, *J* = 8.5 Hz, Ar-*H*), 7.67 (1H, s, Ar-*H*), 7.45 (1H, bs, N*H*), 7.29–7.14 (5H, m, Ar-*H*), 6.75 (1H, d, *J* = 8.5 Hz, Ar-*H*), 5.94 (2H, s, OCH_2), 4.44 (2H, d, *J* = 6.0 Hz, NCH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 185.3, 162.1, 153.2, 148.0, 137.3, 129.2, 128.9, 127.9, 127.8, 110.3, 108.2, 102.1, 43.5; **MP (petrol/Et_2O)**: 74.5–76 °C; **IR (cm^{-1})**

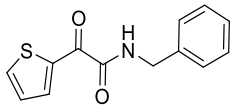
$\tilde{\nu}$ = 3366, 2981, 2889, 1652, 1602, 1502, 1486, 1440, 1382, 1358, 1246, 1148, 1110, 1081, 1036, 954, 935, 882, 831, 798, 776, 729, 699, 654; **MS (ESI) m/z**: 306.0 [$C_{16}H_{13}NNaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{13}NNaO_4$, $(M+Na)^+$]: 306.0737; found 306.0736.

_N_-benzyl-2-oxo-2-(thiophen-3-yl)acetamide, **4i**



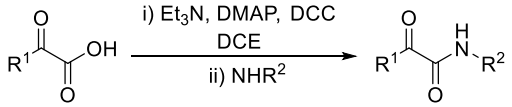
Prepared according to general procedure A, using crude 2-oxo-2-(thiophen-3-yl)acetic acid (781 mg, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), 1,2-dichloroethane (14 mL), followed by thionyl chloride (730 µL, 5.0 mmol), benzylamine (550 µL, 5.0 mmol) and 1,2-dichloroethane (6.0 mL). The residue was purified by column chromatography (petrol/Et_2O 9:1) and recrystallised in petrol/Et_2O to give amide **4i** as white needle-like crystals (777 mg, 3.2 mmol, 63%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.16 (1H, s, Ar-*H*), 7.78 (1H, d, *J* = 5.0 Hz, Ar-*H*), 7.63 (1H, s, N*H*), 7.40–7.26 (6H, m, Ar-*H*), 4.55 (2H, d, *J* = 6.0 Hz, NC*H*$_2$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 180.0, 161.2, 139.9, 137.20, 137.17, 123.0, 128.8, 128.0, 127.9, 125.9, 43.6; **MP (petrol/Et_2O)**: 82–84 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3368, 3158, 3098, 3033, 2981, 2889, 1674, 1640, 1528, 1506, 1455, 1442, 1417, 1386, 1358, 1282, 1240, 1218, 1148, 1079, 1054, 1029, 1011, 951, 911, 884, 864, 843, 793, 764, 739, 712, 691, 635, 613; **MS (ESI) m/z**: 268.0 [$C_{13}H_{11}NNaO_2S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{12}NO_2S$, $(M+H)^+$]: 246.0583; found 246.0585.

***N*-Benzyl-2-oxo-2-(thiophen-2-yl)acetamide**, **4j**



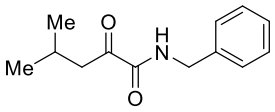
Prepared according to general procedure A, using crude 2-oxo-2-(thiophen-2-yl)acetic acid (1.09 g, 7.0 mmol), Et_3N (2.0 mL, 14 mmol), 1,2-dichloroethane (18 mL), followed by thionyl chloride (1.0 mL, 14 mmol), benzylamine (770 µL, 7.0 mmol) and 1,2-dichloroethane (10 mL). The residue was purified by column chromatography (petrol/CH_2Cl_2 1:1) and recrystallised in petrol/Et_2O to give amide **4j** as white needle-like crystals (725 mg, 2.9 mmol, 42%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.43 (1H, d, *J* = 4.5 Hz, Ar-*H*), 7.84 (1H, d, *J* = 4.5 Hz, Ar-*H*), 7.64 (1H, bs, N*H*), 7.39–7.28 (5H, m, Ar-*H*), 7.20 (1H, t, *J* = 4.5 Hz, Ar-*H*), 4.57 (2H, d, *J* = 6.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 178.4, 160.7, 138.9, 138.3, 137.1, 136.9, 129.0, 128.4, 128.04, 128.00, 43.7; **MP (petrol/Et_2O)**: 90.5–92 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3374, 2981, 2889, 1680, 1638, 1525, 1496, 1455, 1405, 1358, 1241, 1187, 1155, 1062, 1034, 954, 908, 861, 802, 768, 734, 700, 679; **MS (ESI) m/z**: 268.0 [$C_{13}H_{11}NNaO_2S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{11}NNaO_2S$, $(M+Na)^+$]: 268.0403; found 268.0403.

General Procedure C:[210]



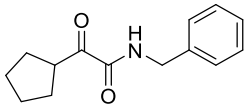
A solution of *α*-ketoacid (1.0 equiv.), Et_3N (1.0 equiv.), DMAP (0.1 equiv.), *N,N'*-dicyclohexylcarbodiimide (1.0 equiv.) in 1,2-dichloroethane (0.3 M) was stirred at rt until effervescence was no longer observed. Benzylamine (1.0 equiv.) was then added dropwise and the reaction mixture was left to stir at rt overnight before heating at 60 °C for 4 h.

_N_-Benzyl-4-methyl-2-oxopentanamide, **4k**



Prepared according to general procedure C, using 4-methyl-2-oxovaleric acid (370 µL, 3.0 mmol), Et_3N (420 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol), *N*,*N'*-dicyclohexylcarbodiimide (470 µL, 3.0 mmol), benzylamine (330 µL, 3.0 mmol) and 1,2-dichloroethane (10 mL). The crude mixture was then filtered through a plug of celite, purified by column chromatography (petrol/Et_2O 95:5) and recrystallisation (petrol/Et_2O) to give amide **4k** as a white solid (125 mg, 0.6 mmol, 19%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.39–7.24 (5H, m, Ar-*H*), 4.46 (2H, d, *J* = 6.0 Hz,NCH_2), 2.83 (2H, d, *J* = 7.0 Hz, CH_2), 2.24–2.12 (1H, m, C*H*), 0.95 (6H, dd, *J* = 7.0 Hz, 2 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 198.9, 160.2, 137.2, 129.0, 128.03, 127.99, 45.5, 43.5, 24.5, 22.7; **MP (petrol/Et_2O)**: 68–70 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3281, 2981, 2889, 1721, 1671, 1530, 1457, 1433, 1383, 1252, 1149, 1078, 954, 816, 750, 699, 679; **LRMS (ESI) m/z**: 220.2 [$C_{13}H_{18}NO_2$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{18}NO_2$, $(M+H)^+$]: 220.1332; found 220.1334.

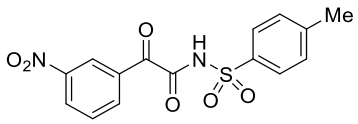
_N_-Benzyl-2-cyclopentyl-2-oxoacetamide, **4l**



Prepared according to general procedure C, using 2-cyclopentyl-2-oxoacetic acid (713 mg, 5.0 mmol), Et_3N (700 µL, 5.0 mmol), DMAP (61.0 mg, 0.5 mmol), *N*,*N'*-dicyclohexylcarbodiimide (780 µL, 5.0 mmol), benzylamine (550 µL, 5.0 mmol) and 1,2-dichloroethane (15 mL). The crude mixture was then filtered through a plug of celite, purified by column chromatography (petrol/Et_2O 95:5) and recrystallisation

(petrol/Et_2O) to give amide **4l** as white crystals (94 mg, 0.4 mmol, 7%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.39–7.25 (5H, m, Ar-*H*), 4.48 (2H, d, *J* = 6.0 Hz, NCH_2), 3.81 (1H, tt, *J* = 9.0, 7.0 Hz, C*H*), 2.00–1.87 (2H, m, CH_2), 1.81–1.70 (2H, m, CH_2), 1.69–1.57 (4H, m, 2 × CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 200.9, 160.3, 137.2, 129.0, 128.01, 127.95, 44.8, 43.6, 29.1, 26.4; **MP (petrol/Et_2O)**: 47–49 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3328, 2980, 2889, 1717, 1680, 1666, 1534, 1496, 1473, 1453, 1428, 1382, 1252, 1153, 1126, 1070, 1028, 954, 881, 817, 781, 724, 695; **LRMS (ESI) m/z**: 254.2 [$C_{14}H_{17}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{14}H_{18}NO_2$, $(M+H)^+$]: 232.1332; found 232.1331.

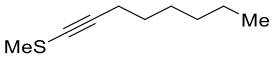
N-Tosyl-2-(3-nitrophenyl)-2-oxo-acetamide, 6



Prepared according to general procedure B, using crude 2-(3-nitrophenyl)-2-oxoacetic acid (1.95 g, 10 mmol), oxalyl chloride (1.0 mL, 12 mmol), 1 drop of DMF in CH_2Cl_2 (20 mL), toluene (10 mL), 4-methylbenzenesulfonamide (1.71 g, 10 mmol), DMAP (6 mg, 0.05 mmol), Et_3N (2.8 mL, 20 mmol) and EtOAc (20 mL). The residue was purified by recrystallisation (petrol/acetone) to give amide **6** as a light yellow solid (1.21 g, 3.5 mmol, 35%). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.53 (1H, d, *J* = 8.0 Hz, Ar-*H*), 8.49 (1H, s, Ar-*H*), 8.23 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.92–7.82 (4H, m, Ar-*H*), 7.49 (2H, d, *J* = 8.0 Hz, Ar-*H*), 2.43 (3H, s, CH_3); **^{13}C NMR (101 MHz, DMSO-d_6)** δ 185.3, 163.3, 148.3, 145.3, 136.6, 136.0, 133.7, 131.4, 130.3, 129.4, 128.1, 124.6, 21.6; **MP (petrol/Acetone)**: 189–190 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3292, 3111, 3068, 2981, 1726, 1686, 1611, 1575, 1530, 1428, 1348, 1287, 1258, 1190, 1172, 1136, 1086, 1010, 948, 890, 861, 831, 816, 798, 786, 733,

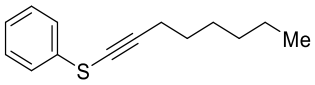
695, 676; **LRMS (ESI) m/z**: 371.0 [$C_{15}H_{12}N_2NaO_6S$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{15}H_{12}N_2NaO_6S$, $(M+Na)^+$]: 371.0308; found 371.0309.

Methyl(oct-1-yn-1-yl)sulfane, **9**



Prepared according to a procedure reported by Michael Finlay in his thesis.[174] To a solution at −78 °C, containing 1-octyne (1.8 mL, 12 mmol) in THF (40 mL), ^{n}BuLi (4.8 mL, 2.5 M in hexane, 12 mmol) was added slowly for 15 min. The reaction mixture was stirred at this temperature before addition of dimethyl disulfide (1.1 mL, 12 mmol), and the reaction miture was warmed to rt and stirred for 2 h. A saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction. The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (100% petrol) to give alkyne **9** as a pale yellow oil (1.56 g, 10.0 mmol, 83%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 2.34 (3H, s, SCH_3), 2.27 (2H, t, J = 7.0 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.56–1.44 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.44–1.35 (2H, m, CH_2CH$_2$CH$_2$CH$_3$), 1.39–1.19 (4H, m, CH_2CH_2CH$_3$), 0.92–0.84 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 93.5, 69.9, 31.5, 28.9, 28.6, 22.7, 20.2, 19.5, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2956, 2927, 2857, 1465, 1434, 1378, 1313, 976, 725; **HRMS (ESI)**: calcd for [$C_9H_{17}S$, $(M+H)^+$]: 157.1045; found 157.1048. These data are consistent with literature.[211]

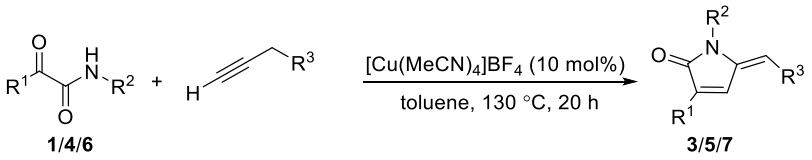
Oct-1-yn-1-yl(phenyl)sulfane, **10**



Prepared according to a literature procedure.[211] To a solution of 1-octyne (2.7 mL, 18.0 mmol) in THF (40 mL) was added ^{n}BuLi (7.9 ml, 19.0 mmol, 2.4 M) was added at 0 °C. The mixture was stirred for 30 min. Diphenyl disulfide (3.5 g, 16.0 mmol) was then added to the solution and the mixture was stirred for 2 h. The reaction was quenched with 2-bromoethanol (1.4 mL, 20 mmol) and stirred for an additional 2 h. Water (20 mL) was added and the product was extracted with EtOAc (3 × 40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography (100% petrol) to give alkyne **10** as a colourless oil (2.85 g, 13.0 mmol, 73%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.50–7.43 (2H, m, Ar-*H*), 7.43–7.31 (2H, m, Ar-*H*), 7.27–7.18 (1H, m, Ar-*H*), 2.50 (2H, t, *J* = 7.0 Hz, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.71–1.59 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.56–1.40 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.39–1.34 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 1.01–0.90 (3H, m, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 133.9, 129.1, 126.1, 125.8, 100.2, 64.7, 31.4, 28.74, 28.69, 22.7, 20.4, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 3062, 2955, 2929, 2857, 1584, 1479, 1441, 1378, 1325, 1087, 1024, 736, 687; **HRMS (APCI) m/z**: calcd for [$C_{14}H_{19}S$, $(M+H)^+$]: 219.1202; found 219.1203.

5.2.2 Synthesis of Pyrrolinones

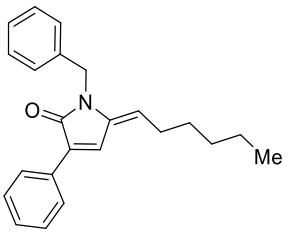
General Procedure D:



1/**4**/**6** **3**/**5**/**7**

To an oven-dried, round-bottomed 10 mL microwave reaction vial equipped with a stirrer bead was added $[Cu(MeCN)_4]BF_4$ (9.4 mg, 0.03 mmol) and *α*-keto amide **1**/**4**/**6** (0.36 mmol, 1.2 equiv.) and alkyne (0.30 mmol, 1.0 equiv.) if solid. The vial was sealed with a microwave vial cap, and then evacuated under vacuum (<1 mbar) and back-filled with N_2 gas for 3 times. Degassed dry toluene (0.5 mL) and degassed alkyne (0.30 mmol, 1.0 equiv.) if liquid were then added sequentially. The solution was stirred and heated at 130 °C for 20 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through a plug of celite and concentrated under reduced pressure. The residue was purified by column chromatography to give the resulting product.

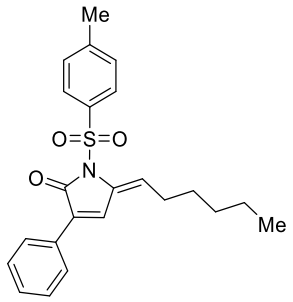
(*E*)-1-Benzyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3a**



Prepared according to general procedure D using *α*-keto amide **1a** (86 mg, 0.36 mmol), 1-octyne **2a** (44 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 95:5) to give pyrrolinone **3a** as a yellow oil (60 mg, 0.18 mmol, 60%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.06–7.99 (2H, m, Ar-*H*), 7.44–7.38 (3H, m, 2 × Ar-*H*, C=C*H*), 7.37–7.28 (3H, m, Ar-*H*), 7.26–7.20 (3H, m, Ar-*H*), 5.39 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.92 (2H, s, NCH_2), 2.32 (2H, app. q, *J* = 8.0 Hz, C=CHCH_2), 1.44–1.39

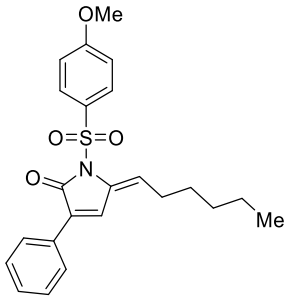
(2H, m, C=CHCH$_2$CH_2), 1.35–1.13 (4H, m, CH_2CH_2CH$_3$), 0.86 (3H, t, J = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.8, 137.9, 137.6, 133.4, 131.7, 128.8, 128.7, 128.6, 127.4, 127.2, 127.0, 125.2, 116.4, 42.9, 31.3, 30.0, 27.7, 22.5, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2927, 2858, 1683, 1494, 1402, 1346, 1177, 1075, 1029, 848, 751, 694, 668; **LRMS (ESI) m/z**: 354.2 [$C_{23}H_{25}NONa$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{26}NO$, $(M+H)^+$]: 332.2009; found 332.2007. (*E*)-isomer configuration was confirmed by 1D NOESY experiments. Configuration of other compounds was assigned by analogy.

(*E*)-5-Hexylidene-3-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one, **3b**



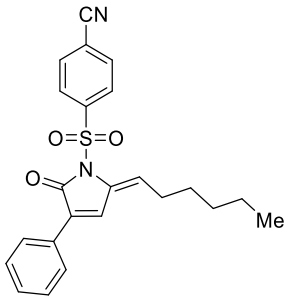
Prepared according to general procedure D using α-keto amide **1b** (109 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 9:1) to give pyrrolinone **3b** as a yellow oil (98 mg, 0.25 mmol, 83%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.94 (2H, d, J = 8.5 Hz, Ar-*H*), 7.83–7.78 (2H, m, Ar-*H*), 7.58 (1H, s, C=C*H*), 7.39–7.29 (5H, m, Ar-*H*), 6.88 (1H, t, J = 8.5 Hz, C=C*H*CH$_2$), 2.43 (2H, q, J = 8.5 Hz, C=CHCH_2), 2.40 (3H, s, Ar-CH_3) 1.61–1.52 (2H, m, C=CHCH$_2$CH_2), 1.39–1.32 (4H, m, CH_2CH_2CH$_3$), 0.94–0.90 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.9, 145.2, 135.9, 134.5, 131.4, 130.04, 130.01, 129.8, 129.4, 128.7, 128.1, 127.3, 122.9, 31.5, 29.7, 28.5, 22.6, 21.8, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2970, 2927, 1698, 1635, 1597, 1493, 1447, 1306, 1220, 1171, 1145, 1124, 1092, 1006, 991, 814, 773; **LRMS (ESI) m/z**: 396.2 [$C_{23}H_{26}NO_3S$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{26}NO_3S$, $(M+H)^+$]: 396.1628; found 396.1623.

(*E*)-5-Hexylidene-1-((4-methoxyphenyl)sulfonyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3c**



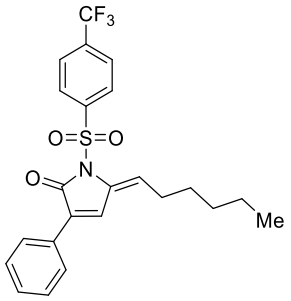
Prepared according to general procedure D using α-keto amide **1c** (115 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 4:1) to give pyrrolinone **3c** as a yellow solid (92 mg, 0.22 mmol, 75%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.00 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.80 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.57 (1H, s, C=C*H*), 7.41–7.23 (3H, m, Ar-*H*), 6.96 (2H, app. d, J_{BA} + $J_{BA'}$ = 8.5 Hz, Ar-*H*), 6.88 (1H, t, *J* = 8.0 Hz, C=C*H*CH$_2$), 3.83 (3H, s, OC*H*$_3$), 2.43 (2H, q, *J* = 8.5 Hz, C=CHC*H*$_2$), 1.60–1.52 (2H, m, C=CHCH$_2$C*H*$_2$), 1.41–1.27 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.92 (3H, t, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 167.0, 164.0, 134.6, 131.4, 130.4, 130.3, 130.1, 129.9, 129.3, 128.7, 127.3, 122.9, 114.3, 55.8, 31.5, 29.7, 28.5, 22.6, 14.1; **MP (petrol/Et$_2$O)**: 96–98 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3084, 2955, 2927, 2857, 1718, 1635, 1595, 1578, 1498, 1461, 1449, 1417, 1388, 1364, 1305, 1264, 1246, 1190, 1168, 1143, 1122, 1092, 1025, 1007, 994, 920, 866, 834, 804, 785, 750, 718, 692, 666, 647, 627, 615; **LRMS (ESI) m/z**: 412.2 [$C_{23}H_{26}NO_4S$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{26}NO_4S$, $(M+H)^+$]: 412.1577; found 412.1576.

(*E*)-5-Hexylidene-1-((4-cyano)sulfonyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3d**



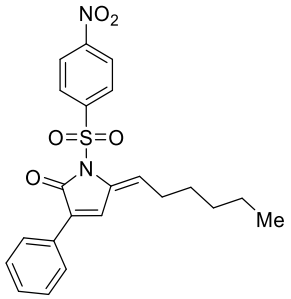
Prepared according to general procedure D, using α-keto amide **1d** (113 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 9:1) to give pyrrolinone **3d** as a white solid (79 mg, 0.19 mmol, 65%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.18 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.82 (2H, app. d (AA'BB'), J_{BA} + $J_{BA'}$ = 8.5 Hz, Ar-*H*), 7.77 (2H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.62 (1H, s, C=C*H*), 7.42–7.30 (3H, m, Ar-*H*), 6.88 (1H, t, *J* = 8.5 Hz, C=C*H*CH_2), 2.50–2.39 (2H, m, C=CHC*H*$_2$), 1.66–1.53 (2H, m, C=CHCH_2C*H*$_2$), 1.41–1.31 (4H, m, C*H*$_2$C*H*$_2$$CH_3$), 0.93 (3H, t, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.8, 142.5, 134.2, 132.9, 131.3, 130.6, 129.7, 129.6, 128.83, 128.82, 127.3, 123.4, 117.7, 117.2, 31.5, 29.6, 28.6, 22.6, 14.1; **MP (petrol/Et_2O)**: 112–114 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3095, 2956, 2928, 2858, 2234, 1722, 1635, 1490, 1449, 1394, 1369, 1305 1285, 1244, 1189, 1174, 1120, 1090, 1007, 995, 867, 838, 785, 750, 720, 692, 631; **LRMS (ESI) m/z**: 407.2 [$C_{23}H_{23}N_2O_3S$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{23}N_2O_3S$, $(M+H)^+$]: 407.1424; found 407.1418.

(*E*)-5-Hexylidene-3-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,5-dihydro-2*H*-pyrrol-2-one, **3e**



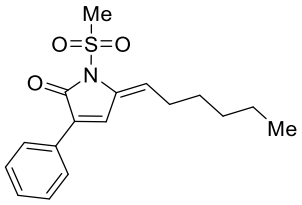
Prepared according to general procedure D, using α-keto amide **1e** (129 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 9:1) to give pyrrolinone **3e** as a yellow solid (94 mg, 0.21 mmol, 70%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.21 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.0 Hz, Ar-*H*), 7.80–7.77 (4H, m, Ar-*H*), 7.62 (1H, s, C=C*H*), 7.41–7.31 (3H, m, Ar-*H*), 6.90 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 2.51–2.40 (2H, m, C=CHCH_2), 1.63–1.52 (2H, m, C=CHCH_2CH_2), 1.42–1.31 (4H, m, CH_2C$H_2$$CH_3$), 0.94 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.8, 142.1, 135.5 (q, ^2J = 34.0 Hz), 134.3, 131.4, 130.5, 129.7, 129.6, 128.8, 128.7, 127.3, 126.3 (q, ^3J = 3.0 Hz), 123.3, 123.1 (q, ^1J = 273.0 Hz), 31.5, 29.6, 28.5, 22.6, 14.1; **^{19}F NMR (377 MHz, chloroform-*d*)** −63.3**; MP (petrol/Et_2O)**: 85–87 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2960, 2930, 2255, 1720, 1492, 1450, 1406, 1371, 1322, 1243, 1176, 1140, 1109, 1094, 1063, 1007, 995, 905, 843, 785, 726, 692, 649, 607; **LRMS (ESI) m/z**: 450.2 [$C_{23}H_{23}F_3NO_3S$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{23}F_3NO_3S$, $(M+H)^+$]: 450.1345; found 450.1344.

(*E*)-5-Hexylidene-1-((4-nitrophenyl)sulfonyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3f



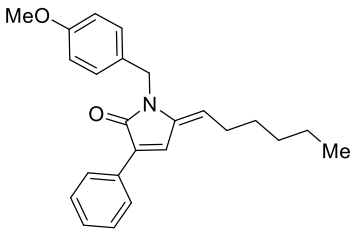
Prepared according to general procedure D, using α-keto amide **1f** (120 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 4:1) to give pyrrolinone **3f** as a yellow solid (55 mg, 0.13 mmol, 43%). **^{1}H NMR (400 MHz, chloroform-*d*)**; δ 8.36 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 9.0 Hz , Ar-*H*), 8.27 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 9.0 Hz , Ar-*H*), 7.80–7.73 (2H, m, Ar-*H*), 7.62 (1H, s, C=C*H*), 7.41–7.32 (3H, m, Ar-*H*), 6.90 (1H, t, J = 8.0 Hz, C=C*H*CH_2), 2.53–2.39 (1H, m, C=CHC*H*$_2$), 1.65–1.53 (2H, m, C=CHCH_2C*H*$_2$), 1.44–1.33 (4H, m, C*H*$_2$C*H*$_2$$CH_3$), 0.93 (3H, t, J = 7.0 Hz, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.8, 150.9, 144.0, 134.2, 131.5, 130.6, 129.8, 129.7, 129.6, 128.9, 127.3, 124.4, 123.5, 31.6, 29.7, 28.6, 22.6, 14.2; **MP (petrol/Et_2O)**: 90–92 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3658, 2981, 2889, 1721, 1636, 1607, 1532, 1473, 1462, 1382, 1251, 1151, 1089, 1073, 1007, 955, 855, 816, 785, 741, 683, 669, 648, 609; **LRMS (ESI) m/z**: 427.2 [$C_{22}H_{23}N_2O_5S$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{22}H_{23}N_2O_5S$, $(M+H)^+$]: 427.1322; found 427.1323.

(*E*)-5-Hexylidene-1-(methylsulfonyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3g**



Prepared according to general procedure D, using α-keto amide **1g** (82 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 9:1) to give pyrrolinone **3g** as a yellow oil (41 mg, 0.13 mmol, 43%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.89–7.85 (2H, m, Ar-*H*), 7.64 (1H, s, C=C*H*), 7.47–7.33 (3H, m, Ar-*H*), 6.74 (1H, t, *J* = 8.0 Hz, C=C*H*CH$_2$), 3.41 (3H, s, SO$_2$C*H*$_3$), 2.47–2.36 (2H, m, C=CHC*H*$_2$), 1.56–1.50 (2H, m, C=CHCH$_2$C*H*$_2$), 1.37–1.32 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.92 (3H, t, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 167.7, 134.3, 131.2, 130.0, 129.9, 129.5, 128.5, 127.3, 123.4, 41.9, 31.5, 29.5, 28.5, 22.5, 14.0; **IR (cm^{-1})** $\tilde{\nu}$ = 2929, 2960, 1714, 1492, 1449, 1355, 1325, 1220, 1165, 1124, 995, 963, 865, 772, 691; **LRMS (ESI) m/z**: 342.0 [C$_{17}$H$_{21}$NNaO$_3$S, (M+Na)$^+$]; **HRMS (ESI)**: calcd for [C$_{17}$H$_{22}$NO$_3$S, (M+H)$^+$]: 320.1315; found 320.1314.

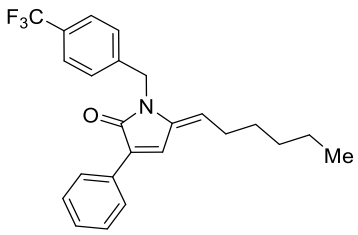
(*E*)-5-Hexylidene-1-(4-methoxybenzyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3l**



Prepared according to general procedure D, using α-keto amide **1l** (97 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et$_2$O = 95:5) to give pyrrolinone **3l** as a yellow oil (50 mg, 0.14 mmol, 48%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.00 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 8.0 Hz, Ar-*H*), 7.44–7.38 (2H,

m, Ar-*H*, C=C*H*), 7.37–7.33 (2H, m, Ar-*H*), 7.17 (2H, d, *J* = 8.5 Hz, Ar-*H*), 6.83 (2H, app. d, $J_{BA} + J_{BA'}$ = 8.0 Hz, Ar-*H*), 5.46–5.37 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.84 (2H, s, NCH_2), 3.77 (3H, s, OCH_3), 2.36–2.29 (2H, m, C=CHCH_2), 1.47–1.37 (2H, m, C=CHCH_2CH_2), 1.34–1.14 (4H, m, $CH_2CH_2CH_3$), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.9, 158.8, 137.9, 133.4, 131.8, 129.8, 128.8, 128.6, 128.4, 127.4, 125.2, 116.4, 114.1, 55.4, 42.4, 31.3, 30.0, 27.8, 22.6, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 3650, 3064, 2981, 2971, 2930, 1684, 1613, 1586, 1513, 1491, 1462, 1447, 1395, 1345, 1291, 1279, 1248, 1176, 1156, 1111, 1073, 1035, 953, 845, 808, 789, 748, 693, 669, 649, 630, 614; **LRMS (ESI) m/z**: 384.2 [$C_{24}H_{27}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{24}H_{27}NNaO_2$, $(M+Na)^+$]: 384.1934; found 384.1934.

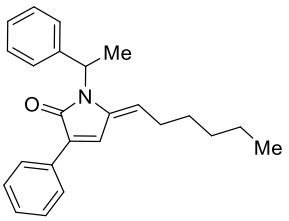
(*E*)-5-Hexylidene-3-phenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2*H*-pyrrol-2-one, **3m**



Prepared according to general procedure D, using *α*-keto amide **1m** (111 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 90:10) to give pyrrolinone **3m** as a yellow oil (62 mg, 0.16 mmol, 52%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.01 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 7.5 Hz, Ar-*H*), 7.57 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.46–7.40 (3H, m, 2 × Ar-*H*, C=C*H*), 7.39–7.35 (1H, m, Ar-*H*), 7.35–7.30 (2H, m, Ar-*H*), 5.32 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.97 (2H, s, NCH_2), 2.39–2.29 (2H, m, C=CHCH_2), 1.47–1.35 (2H, m, C=CHCH_2CH_2), 1.32–1.18 (4H, m, $CH_2CH_2CH_3$), 0.86 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.9, 141.7, 137.8, 133.5, 131.5, 129.7 (q, ^2J = 30.0 Hz), 129.0, 128.7, 127.4, 127.3,

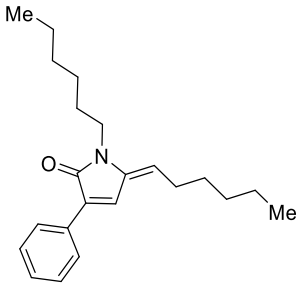
125.7 (q, ^{3}J = 4.0 Hz), 125.4, 124.2 (q, ^{1}J = 270.0 Hz), 116.4, 42.5, 31.3, 30.0, 27.8, 22.6, 14.5; **^{19}F NMR (377 MHz, chloroform-*d*)** −62.7; **IR (cm^{-1})** $\tilde{\nu}$ = 2989, 2931, 2889, 1704, 1620, 1493, 1400, 1324, 1165, 1125, 1067, 1019, 927, 857, 792, 752, 694, 672, 665, 651; **LRMS (ESI) m/z**: 400.2 [$C_{24}H_{25}F_3NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{24}H_{25}F_3NO$, $(M+H)^+$]: 400.1883; found 400.1881.

(*E*)-5-Hexylidene-3-phenyl-1-(1-phenylethyl)-1,5-dihydro-2*H*-pyrrol-2-one, **3n**



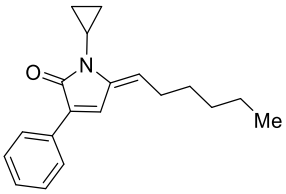
Prepared according to general procedure D, using α-keto amide **1n** (91 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 7:3) to give pyrrolinone **3n** as a brown oil (22 mg, 0.06 mmol, 20%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.00–7.92 (2H, m, Ar-*H*), 7.40–7.33 (3H, m, Ar-*H*), 7.32–7.23 (5H, m, 4 × Ar-*H*, C=C*H*), 7.22–7.16 (1H, m, Ar-*H*), 5.80 (1H, q, *J* = 7.0 Hz, NC*H*), 5.14 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 2.24–2.13 (2H, m, C=CHCH_2), 1.76 (3H, d, *J* = 7.0 Hz, NCH(CH_3)), 1.29–1.12 (4H, m, CH_2C$H_2$$CH_2$$CH_3$), 1.06 (2H, m, C$H_2$$CH_3$), 0.79 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.0, 141.2, 136.4, 132.6, 131.9, 128.7, 128.6, 128.5, 127.5, 127.0, 126.6, 125.6, 118.3, 48.4, 31.1, 30.0, 28.0, 22.6, 17.8, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 3063, 2956, 2929, 2857, 2162, 1683, 1493, 1449, 1403, 1376, 1182, 1072, 1023, 957, 851, 788, 753, 696, 652; **LRMS (ESI) m/z**: 368.2 [$C_{24}H_{27}NNaO$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{24}H_{28}NO$, $(M+H)^+$]: 346.2165; found 346.2169.

(*E*)-1-Hexyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3p**



Prepared according to general procedure D, using *α*-keto amide **1p** (84 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3p** as a yellow oil (51 mg, 0.16 mmol, 52%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.98 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.44–7.30 (4H, m, 3 × Ar-*H*, C=C*H*), 5.45 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 3.66 (2H, t, *J* = 7.5 Hz, NCH_2), 2.46–2.35 (2H, m, C=CHCH_2), 1.65–1.58 (2H, m, NCH_2CH_2), 1.57–1.46 (2H, m, $C{=}CHCH_2CH_2$), 1.41–1.22 (10H, m, $N(CH_2)_2CH_2CH_2CH_2$, $CH_2CH_2CH_3$), 0.96–0.84 (6H, m, $N(CH_2)_5CH_3$, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.7, 138.3, 133.5, 131.9, 128.7, 128.6, 127.4, 124.7, 114.9, 39.3, 31.7, 31.5, 30.2, 29.0, 27.9, 26.7, 22.7, 22.6, 14.17, 14.15; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 2981, 2931, 2889, 1684, 1647, 1461, 1382, 1251, 1153, 1073, 956, 818, 787, 748, 693, 649; **LRMS (ESI) m/z**: 326.2 [$C_{22}H_{32}NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{22}H_{32}NO$, $(M+H)^+$]: 326.2478; found 326.2474.

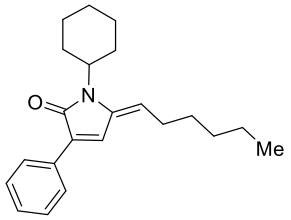
(*E*)-1-Cyclopropyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3q**



Prepared according to general procedure D, using *α*-keto amide **1q** (68 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3q** as a yellow oil (58 mg, 0.21 mmol, 69%). **^{1}H NMR (400 MHz,**

chloroform-*d*) δ 7.93 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.38 (2H, dd, *J* = 7.5, 7.5 Hz, Ar-*H*), 7.35–7.29 (2H, m, Ar-*H*, C=C*H*), 5.83 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 2.54 (1H, tt, *J* = 7.0, 4.0 Hz, NC*H*), 2.44–2.34 (2H, m, C=CHCH_2), 1.58–1.48 (2H, m, C=CHCH_2CH_2), 1.40–1.29 (4H, m, CH_2C$H_2$$CH_3$), 1.06–0.98 (2H, m, NCHCH_2), 0.94–0.88 (5H, m, CH_3, NCHCH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.4, 139.2, 133.0, 131.9, 128.6, 128.6, 127.4, 124.7, 116.1, 31.5, 30.2, 27.9, 22.6, 21.4, 14.2, 6.4; **IR (cm^{-1})** $\tilde{\nu}$ = 3661, 2981, 2889, 1681, 1462, 1421, 1382, 1241, 1152, 1073, 904, 788, 724, 649; **LRMS (ESI) m/z**: 282.2 [$C_{19}H_{24}NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{19}H_{24}NO$, $(M+H)^+$]: 282.1852; found 282.1849.

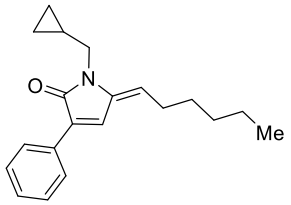
(*E*)-1-Cyclohexyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3r**



Prepared according to general procedure D, using *α*-keto amide **1r** (83 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3r** as a yellow oil (41 mg, 0.13 mmol, 42%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.95 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.43–7.27 (4H, m, 3 × Ar-*H*, C=C*H*), 5.61 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 3.96 (1H, p, *J* = 12.0 Hz, $C_{cy}H$), 2.43–2.37 (2H, m, C=CHCH_2), 2.26–2.11 (2H, m, $C_{cy}H_2$), 1.92–1.82 (2H, m, $C_{cy}H_2$), 1.77–1.68 (4H, m, 2 × $C_{cy}H_2$), 1.58–1.48 (2H, m, C=CHCH_2CH_2), 1.42–1.31 (4H, m, CH_2C$H_2$$CH_3$), 1.31–1.15 (2H, m, $C_{cy}H_2$), 0.92 (3H, t, *J* = 6.5 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.9, 138.0, 133.3, 131.9, 128.6, 128.5, 127.5, 125.1, 115.5, 52.2, 31.6, 30.4, 30.3, 28.2, 26.6, 25.6, 22.6, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 3661, 2981, 2933, 1676, 1640, 1450, 1308, 1347, 1259, 1205, 1152, 1073, 905, 788, 726, 693, 648; **LRMS (ESI) m/z**: 346.2

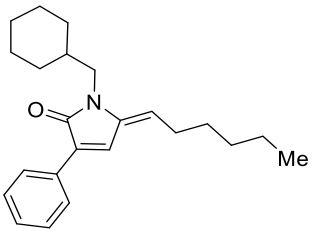
[$C_{22}H_{29}NNaO$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{22}H_{30}NO$, $(M+H)^+$]: 324.2322; found 324.2320.

(*E*)-1-(Cyclopropylmethyl)-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3s**



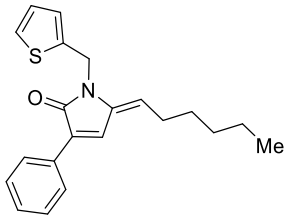
Prepared according to general procedure D, using α-keto amide **1s** (73 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3s** as a yellow oil (44 mg, 0.15 mmol, 50%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.97 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.42–7.37 (3H, m, 2 × Ar-*H*, C=C*H*), 7.33 (1H, t, *J* = 7.5 Hz, Ar-*H*), 5.54 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 3.58 (2H, d, *J* = 7.0 Hz, NCH_2), 2.48–2.37 (2H, m, C=CHCH_2), 1.60–1.46 (2H, m, C=CHCH_2CH_2), 1.40–1.30 (4H, m, CH_2C$H_2$$CH_3$), 1.15–1.01 (1H, m, C*H*$(CH_2)_2$), 0.96–0.87 (3H, m, CH_3), 0.54–0.44 (2H, m, 1 × CH(CH_2)$_2$), 0.43–0.34 (2H, m, 1 × CH(CH_2)$_2$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.8, 138.6, 133.6, 131.9, 128.7, 128.6, 127.4, 124.8, 115.1, 43.3, 31.5, 30.2, 27.9, 22.6, 14.2, 10.9, 3.9; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 2981, 2889, 1687, 1491, 1461, 1383, 1252, 1153, 1073, 1021, 955, 789, 749, 694, 650; **LRMS (ESI) m/z**: 296.2 [$C_{20}H_{26}NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{20}H_{26}NO$, $(M+H)^+$]: 296.2009; found 296.2006.

(*E*)-1-(Cyclohexylmethyl)-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3t**



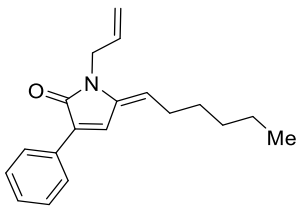
Prepared according to general procedure D, using α-keto amide **1t** (88 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3t** as a yellow oil (46 mg, 0.14 mmol, 45%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.98 (2H, d, *J* = 7.5 Hz, Ar-*H*), 7.43–7.35 (3H, m, 2 × Ar-*H*, C=C*H*), 7.32 (1H, t, *J* = 7.0 Hz, Ar-*H*), 5.45 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 3.51 (2H, d, *J* = 7.0 Hz, NCH_2), 2.48–2.35 (2H, m, C=CHCH_2), 1.78–1.69 (5H, m, $C_{cy}H$, 2 × $C_{cy}H_2$), 1.68–1.61 (2H, m, $C_{cy}H_2$), 1.56–1.47 (2H, m, C=CHCH_2CH_2), 1.40–1.30 (4H, m, $CH_2CH_2CH_3$), 1.22–1.14 (2H, m, $C_{cy}H_2$), 1.08–0.95 (2H, m, $C_{cy}H_2$), 0.95–0.88 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.1, 138.8, 133.3, 131.9, 128.7, 128.6, 127.4, 124.6, 115.3, 45.5, 37.7, 31.5, 31.1, 30.2, 27.9, 26.0, 25.9, 22.6, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 2981, 2928, 1678, 1646, 1448, 1381, 1345, 1251, 1153, 1073, 956, 906, 838,787, 727, 693, 649; **LRMS (ESI) m/z**: 338.2 [$C_{23}H_{32}NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{32}NO$, $(M+H)^+$]: 338.2478; found 338.2476.

(*E*)-5-Hexylidene-3-phenyl-1-(thiophen-2-ylmethyl)-1,5-dihydro-2*H*-pyrrol-2-one, **3u**



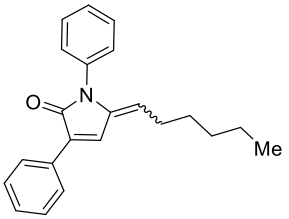
Prepared according to general procedure D, using α-keto amide **1u** (88 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3u** as a yellow oil (54 mg, 0.16 mmol, 53%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.94 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.39–7.31 (3H, m, Ar-*H*), 7.29 (1H, d, *J* = 7.0 Hz, Ar-*H*), 7.12 (1H, d, *J* = 5.0 Hz, Ar-*H*), 6.93 (1H, s, C=C*H*), 6.87 (1H, dd, *J* = 5.0, 3.5 Hz, Ar-*H*), 5.51 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.99 (2H, s, NCH_2), 2.32 (2H, q, *J* = 8.0 Hz, C=CHCH_2), 1.48–1.36 (2H, m, C$H_2CH_2CH_2CH_3$), 1.32–1.17 (4H, m, C$H_2CH_2CH_3$), 0.84 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.3, 140.2, 137.5, 133.3, 131.6, 128.8, 128.6, 127.4, 126.8, 125.9, 125.3, 125.0, 116.0, 37.8, 31.3, 30.0, 27.8, 22.6, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 3369, 3069, 2955, 2927, 2857, 1685, 1491, 1431, 1410, 1340, 1238, 1180, 1128, 1074, 924, 852, 789, 747, 694, 649; **MS (ESI) m/z**: 338.2 [$C_{21}H_{24}NOS$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{24}NOS$, $(M+H)^+$]: 338.1573; found 338.1569.

(*E*)-1-Allyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3v**



Prepared according to general procedure D, using *α*-keto amide **1v** (68 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3v** as a yellow oil (43 mg, 0.15 mmol, 51%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.98 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.43–7.30 (4H, m, 3 × Ar-*H*, C=C*H*), 5.90–5.78 (1H, m, NCH_2CH=CH_2), 5.46 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 5.19–5.08 (2H, m, NCH_2CH=CH_2), 4.35–4.27 (2H, m, NCH_2), 2.44–2.34 (2H, m, C=CHCH_2), 1.55–1.45 (2H, m, C=$CHCH_2CH_2$), 1.41–1.28 (4H, m, CH_2C$H_2$$CH_3$), 0.91 (3H, t, *J* = 6.5 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.5, 138.0, 133.4, 133.3, 131.8, 128.8, 128.6, 127.4, 125.0, 116.4, 116.0, 41.6, 31.5, 30.1, 27.9, 22.6, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 3661, 2981, 2889, 1681, 1647, 1382, 1251, 1153, 1073, 942, 905, 727, 693, 648; **LRMS (ESI) m/z**: 304.2 [$C_{19}H_{23}NNaO$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{19}H_{23}NNaO$, $(M+Na)^+$]: 304.1672; found 304.1673.

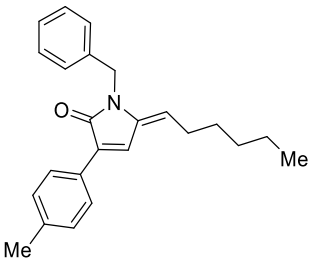
(*E*,*Z*)-5-Hexylidene-1,3-diphenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3w**



Prepared according to general procedure D, using *α*-keto amide **1w** (81 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **3w** as a yellow oil containing an inseparable mixture of isomers (56 mg, 0.18 mmol, 59%), *E*/*Z* ratio 3:1. *(E)-isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)**

δ 8.12 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.65 (1H, s, C=C*H*), 7.59–7.36 (8H, m, Ar-*H*), 5.50 (1H, t, *J* = 8.5 Hz, C=C*H*CH_2), 2.53–2.42 (2H, m, C=CHC*H*$_2$), 1.59–1.48 (2H, m, C*H*$_2$$CH_2CH_2CH_3$), 1.46–1.36 (4H, m, C*H*$_2$C*H*$_2$$CH_3$), 1.05–0.94 (3H, m, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** 168.3, 139.4, 134.8, 132.97, 131.7, 129.3, 128.9, 128.64, 128.4, 127.8, 127.51, 125.3, 117.0, 31.5, 29.9, 27.9, 22.6, 14.1; *(Z)-isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.08–7.98 (2H, m, Ar-*H*), 7.76–7.67 (1H, m, Ar-*H*), 7.65–7.34 (7H, m, Ar-*H*), 7.25 (1H, s, C=C*H*), 5.38 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 1.83–1.72 (2H, m, C=CHC*H*$_2$), 1.46–1.26 (4H, m, C*H*$_2$C*H*$_2$$CH_2CH_3$), 1.28–1.10 (2H, m, C*H*$_2$$CH_3$), 0.94–0.86 (3H, m, 3H, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** 170.2, 138.1, 137.1, 133.04, 131.6, 129.2, 128.7, 128.60, 128.56, 128.2, 127.50, 127.2, 119.7, 31.4, 29.3, 27.4, 22.4, 14.0; **IR (cm^{-1})** $\tilde{\nu}$ = 3065, 2955, 2927, 2856, 1693, 1597, 1500, 1449, 1404, 1352, 1224, 1159, 1120, 1073, 1027, 964, 909, 851, 785, 749, 730, 693, 651; **LRMS (ESI) m/z**: 318.2 [$C_{22}H_{24}NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{22}H_{24}NO$, $(M+H)^+$]: 318.1852; found 318.1849. *E*/*Z* ratio obtained from comparing the integrals of the alkenyl C-H of each isomer.

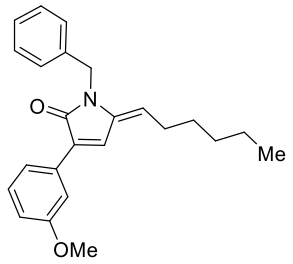
(*E*)-1-Benzyl-5-hexylidene-3-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one, **5a**



Prepared according to general procedure D, using *α*-keto amide **4a** (91 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **5a** as a yellow oil (42 mg, 0.12 mmol, 41%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.05 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.50 (1H, s, C=C*H*), 7.45–7.40 (2H, m,

Ar-*H*), 7.38–7.31 (5H, m, Ar-*H*), 5.48 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 5.03 (2H, s, NCH_2), 2.50 (3H, s, Ar-CH_3), 2.47–2.40 (2H, m, C=CHCH_2), 1.55–1.48 (2H, m, C$H_2$$CH_2$$CH_2$$CH_3$), 1.42–1.32 (4H, m, C$H_2CH_2$$CH_3$), 0.98 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.0, 138.8, 138.0, 137.7, 133.3, 129.4, 128.9, 128.7, 127.8, 127.2, 127.0, 124.3, 115.9, 42.9, 31.3, 30.0, 27.7, 22.5, 21.5, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 2889, 1699, 1512, 1495, 1458, 1393, 1252, 1153, 1077, 954, 823, 748, 701, 648; **LRMS (ESI) m/z**: 346.2 [$C_{24}H_{28}NO$, $(M+H)^+$]; **HRMS (ESI)**: calcd for [$C_{24}H_{28}NO$, $(M+H)^+$]: 346.2165; found 346.2163.

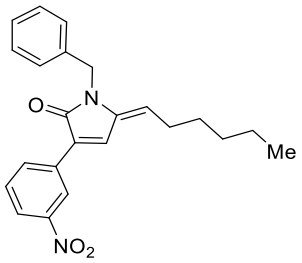
(*E*)-1-Benzyl-5-hexylidene-3-(3-methoxyphenyl)-1,5-dihydro-2*H*-pyrrol-2-one, **5c**



Prepared according to general procedure D, using *α*-keto amide **4c** (97 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **5c** as a yellow oil (64 mg, 0.18 mmol, 59%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.67 (1H, s, Ar-*H*), 7.55 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.41 (1H, s, C=C*H*), 7.34–7.25 (3H, m, Ar-*H*), 7.25–7.17 (3H, m, Ar-*H*), 6.90 (1H, d, *J* = 8.0 Hz, Ar-*H*), 5.38 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.90 (2H, s, NCH_2), 3.84 (3H, s, OCH_3), 2.30 (2H, q, *J* = 8.0 Hz, C=CHCH_2), 1.44–1.32 (2H, m, C$H_2$$CH_2$$CH_2$$CH_3$), 1.32–1.13 (4H, m, C$H_2CH_2$$CH_3$), 0.84 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.8, 159.8, 137.9, 137.6, 133.1, 133.0, 129.6, 128.7, 127.3, 127.0, 125.5, 119.8, 116.6, 115.1, 112.3, 55.4, 42.9, 31.3, 29.9, 27.8, 22.5, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2928, 2857, 2012, 1722, 1683, 1575, 1534, 1488, 1455, 1434, 1412, 1371, 1336, 1287, 1252, 1207, 1180,

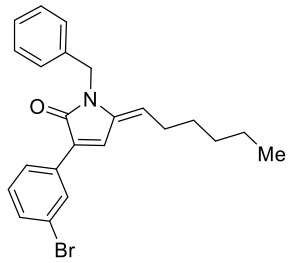
1153, 1112, 1044, 1012, 963, 842, 790, 729, 695, 649; **LRMS (ESI) m/z**: 362.2 [$C_{24}H_{28}NO_2$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{24}H_{28}NO_2$, $(M+H)^+$]: 362.2115; found 362.2115.

(*E*)-1-Benzyl-5-hexylidene-3-(3-nitrophenyl)-1,5-dihydro-2*H*-pyrrol-2-one, **5d**



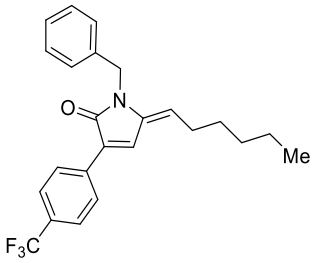
Prepared according to general procedure D, using α-keto amide **4d** (102 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 9:1) to give pyrrolinone **5d** as a light yellow solid (86 mg, 0.23 mmol, 76%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.80 (1H, s, Ar-*H*), 8.49 (1H, d, *J* = 8.0 Hz, Ar-*H*), 8.19 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.65–7.57 (2H, m, Ar-*H*, C=C*H*), 7.36–7.20 (5H, m, Ar-*H*), 5.52 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.93 (2H, s, NCH_2), 2.37 (2H, q, *J* = 8.0 Hz, C=CHCH_2), 1.48–1.38 (2H, m, C$H_2CH_2CH_2CH_3$), 1.34–1.18 (4H, m, C$H_2CH_2CH_3$), 0.86 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.1, 148.6, 137.6, 137.2, 133.4, 133.3, 131.0, 129.7, 128.8, 127.5, 127.1, 127.0, 123.3, 122.1, 118.8, 43.1, 31.3, 29.9, 28.0, 22.6, 14.1; **MP (petrol/Et$_2$O)**: 80–82 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2889, 1724, 1686, 1529, 1473, 1462, 1382, 1350, 1252, 1152, 1073, 955, 810, 732, 701; **LRMS (ESI) m/z**: 377.2 [$C_{23}H_{25}N_2O_3$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{23}H_{25}N_2O_3$, $(M+H)^+$]: 377.1860; found 377.1858.

(*E*)-1-Benzyl-3-(3-bromophenyl)-5-hexylidene-1,5-dihydro-2*H*-pyrrol-2-one, **5e**



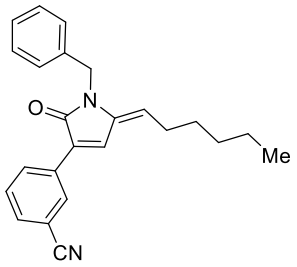
Prepared according to general procedure D, using *α*-keto amide **4e** (115 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **5e** as a brown oil (80 mg, 0.20 mmol, 65%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.08 (1H, s, Ar-*H*), 7.90 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.41–7.33 (2H, m, Ar-*H*), 7.25–7.09 (6H, m, Ar-*H*, C=C*H*), 5.34 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.81 (2H, s, NCH_2), 2.29–2.16 (2H, m, C=CHCH_2), 1.37–1.25 (2H, m, C$H_2CH_2CH_2CH_3$), 1.25–1.05 (4H, m, C$H_2CH_2CH_3$), 0.77 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.3, 137.7, 137.4, 133.7, 131.8, 131.6, 130.14, 130.13, 128.7, 127.3, 127.0, 126.1, 126.0, 122.8, 117.5, 42.9, 31.3, 29.9, 27.8, 22.5, 14.1; **MP (petrol/Et_2O)**: 65–67 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2889, 1724, 1683, 1556, 1473, 1462, 1382, 1252, 1152, 1074, 954, 790, 729, 696; **LRMS (ESI) m/z**: 410.0 [$C_{23}H_{25}{}^{79}$BrNO, $(M+H)^+$]], 412.0 [$C_{23}H_{25}{}^{81}$BrNO, $(M+H)^+$]]; **HRMS (ESI) m/z**: calcd for [$C_{23}H_{25}{}^{79}$BrNO, $(M+H)^+$]: 410.11140; found 410.11127, calcd for [$C_{23}H_{25}{}^{81}$BrNO, $(M+H)^+$]: 412.1094; found 412.1091.

(*E*)-1-Benzyl-5-hexylidene-3-(4-(trifluoromethyl)phenyl)-1,5-dihydro-2*H*-pyrrol-2-one, **5f**



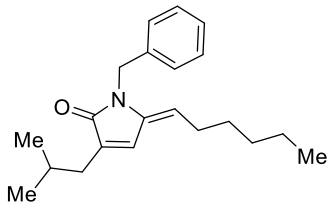
Prepared according to general procedure D, using *α*-keto amide **4f** (111 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **5f** as a brown oil (85 mg, 0.21 mmol, 71%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.07 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.59 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.45 (1H, s, C=C*H*), 7.28–7.20 (2H, m, Ar-*H*), 7.21–7.12 (3H, m, Ar-*H*), 5.40 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.85 (2H, s, NCH_2), 2.28 (2H, q, *J* = 8.0 Hz, C=CHCH_2), 1.40–1.29 (2H, m, C$H_2CH_2CH_2CH_3$), 1.28–1.08 (4H, m, CH_2CH_2CH_3), 0.79 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.4, 137.7, 137.4, 135.2, 132.0, 130.4 (q, ^2J = 32.0 Hz), 128.8, 127.6, 127.4, 127.0, 126.9, 125.5 (q, ^3J = 4.0 Hz), 124.2 (q, ^1J = 273.0 Hz), 118.1, 43.0, 31.3, 29.9, 27.9, 22.6, 14.1; **^{19}F NMR (377 MHz, chloroform-*d*)** −62.7; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2889, 1684, 1616, 1461, 1382, 1324, 1251, 1164, 1126, 1070, 1018, 954, 842, 757, 729, 698, 612; **LRMS (ESI) m/z**: 400.2 [$C_{24}H_{25}F_3NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{24}H_{25}F_3NO$, $(M+H)^+$]: 400.1883; found 400.1879.

(*E*)-3-(1-Benzyl-5-hexylidene-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)benzonitrile, **5g**



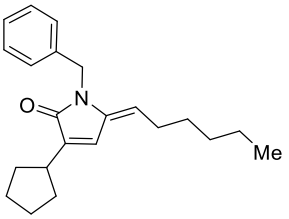
Prepared according to general procedure D, using *α*-keto amide **4g** (95 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 9:1) to give pyrrolinone **5g** as a yellow solid (79 mg, 0.22 mmol, 74%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.34 (1H, s, Ar-*H*), 8.25 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.59 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.54–7.45 (2H, m, Ar-*H*, C=C*H*), 7.36–7.16 (5H, m, Ar-*H*), 5.49 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.90 (2H, s, NCH_2), 2.34 (2H, q, *J* = 8.0 Hz, C=CHCH_2), 1.48–1.34 (2H, m, C$H_2CH_2CH_2CH_3$), 1.29–1.17 (4H, m, C$H_2CH_2CH_3$), 0.84 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.1, 137.5, 137.2, 132.9, 131.8, 131.5, 131.0, 130.8, 129.4, 128.7, 127.4, 127.0, 126.7, 118.7, 118.5, 112.8, 42.9, 31.2, 29.8, 27.9, 22.5, 14.0; **MP (petrol/Et_2O)**: 72–74 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2889, 2230, 1683, 1649, 1473, 1461, 1382, 1252, 1154, 1073, 955, 803, 729, 687, 655; **LRMS (ESI) m/z**: 357.2 [$C_{24}H_{25}N_2O$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{24}H_{25}N_2O$, $(M+H)^+$]: 357.1961; found 357.1961.

(*E*)-1-Benzyl-5-hexylidene-3-isobutyl-1,5-dihydro-2*H*-pyrrol-2-one, **5k**



Prepared according to general procedure D, using α-keto amide **4k** (79 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **5k** as a brown oil (18 mg, 0.06 mmol, 19%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.26–7.11 (3H, m, Ar-*H*), 7.11–7.06 (2H, m, Ar-*H*), 6.82 (1H, s, C=C*H*), 5.13 (1H, t, *J* = 8.0 Hz, C=C*H*CH_2), 4.75 (2H, s, NCH_2), 2.23 (2H, d, *J* = 7.0 Hz, CHCH_2), 2.15 (2H, q, *J* = 8.0 Hz, C=CHCH_2), 2.00–1.85 (1H, m, C*H*CH_2), 1.34–1.05 (6H, m, CH_2CH_2C$H_2$$CH_3$), 0.89 (6H, d, *J* = 6.5 Hz, 2 × CH_3), 0.77 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 170.6, 138.3, 137.9, 136.8, 128.6, 127.2, 127.0, 126.9, 114.1, 42.9, 34.9, 31.3, 30.0, 27.50, 27.48, 22.7, 22.5, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2889, 1690, 1473, 1462, 1383, 1252, 1153, 1074, 954, 819, 728, 697; **LRMS (ESI) m/z**: 312.2 [$C_{21}H_{30}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{30}NO$, $(M+H)^+$]: 312.2322; found 312.2316.

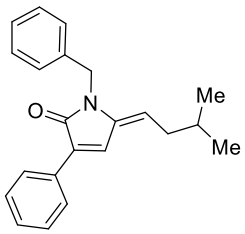
(*E*)-1-Benzyl-3-cyclopentyl-5-hexylidene-1,5-dihydro-2*H*-pyrrol-2-one, **5l**



Prepared according to general procedure D, using α-keto amide **4l** (83 mg, 0.36 mmol), 1-octyne (44 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 95:5) to give pyrrolinone **5l** as a yellow oil (39 mg, 0.12 mmol, 40%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.27–7.07 (5H, m, Ar-*H*), 6.78 (1H, s, C=C*H*), 5.12 (1H, t, *J* = 8.0 Hz,

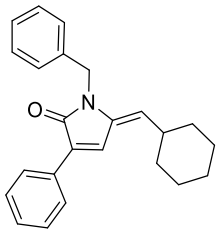
C=C*H*CH_2), 4.75 (2H s, NCH_2), 2.93–2.80 (1H, m, C*H*), 2.22–2.08 (2H, m, C=CHCH_2), 2.06–1.91 (2H, m, $C_{cyclopentane}H_2$), 1.75–1.43 (6H, m, 2 × $C_{cyclopentane}H_2$, CH_2CH_2CH_2CH_3), 1.34–1.07 (6H, m, $C_{cyclopentane}H_2$, CH_2CH_2CH_3), 0.78 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 170.2, 142.1, 138.3, 137.9, 128.6, 127.2, 127.0, 124.1, 114.0, 42.8, 37.0, 32.2, 31.3, 30.0, 27.5, 25.4, 22.6, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2889, 1704, 1679, 1456, 1393, 1252, 1152, 1072, 955, 817, 700; **LRMS (ESI) m/z**: 324.2 [$C_{22}H_{30}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{22}H_{30}NO$, $(M+H)^+$]: 324.2322; found 324.2322.

(*E*)-1-Benzyl-5-(3-methylbutylidene)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **7a**



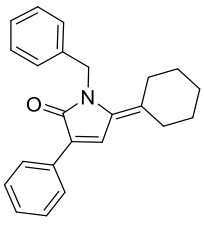
Prepared according to general procedure D using *α*-keto amide **1a** (86 mg, 0.36 mmol) and 5-methyl-1-hexyne (40 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 95:5) to give pyrrolinone **7a** as yellow solid (52 mg, 0.16 mmol, 55%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.02 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.45–7.40 (3H, m, Ar-*H*), 7.37–7.28 (3H, m, 2 × Ar-*H*, C=C*H*), 7.26–7.20 (3H, m, Ar-*H*), 5.39 (1H, t, *J* = 8.5 Hz, C=C*H*CH_2), 4.93 (2H, s, NCH_2), 2.22 (2H, dd, *J* = 8.5, 7.0 Hz, C=CHCH_2), 1.73–1.59 (1H, m, C*H*$(CH_3)_2$), 0.84 (6H, d, *J* = 7.0 Hz, 2 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.9, 138.5, 137.6, 133.5, 131.8, 128.8, 128.71, 128.67, 127.5, 127.3, 127.0, 125.4, 115.2, 43.0, 36.7, 29.4, 22.3; **MP (petrol/Et_2O)**: 81–82 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2889, 1683, 1648, 1490, 1462, 1383, 1296, 1252, 1153, 1073, 953, 854, 786, 749, 730, 694, 649; **LRMS (ESI) m/z**: 318.2 [$C_{22}H_{24}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{22}H_{24}NO$, $(M+H)^+$]: 318.1852; found 318.1853.

(*E*)-1-Benzyl-5-(cyclohexylmethylene)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **7b**



Prepared according to general procedure D using *α*-keto amide **1a** (86 mg, 0.36 mmol) and 3-cyclohexyl-1-propyne (43 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 9:1) to give pyrrolinone **7b** as a yellow oil (52 mg, 0.15 mmol, 50%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.06–7.98 (2H, m, Ar-*H*), 7.45–7.39 (3H, m, 2 × Ar-*H*, C=C*H*), 7.38–7.27 (3H, m, Ar-*H*), 7.25–7.20 (3H, m, Ar-*H*), 5.27 (1H, d, *J* = 10.0 Hz, C=C*H*CH), 4.90 (2H, s, NCH_2), 2.57–2.43 (1H, m, C=CHC*H*), 1.78–1.61 (5H, m, 2 × CH_2, CH_AH$_B$), 1.40–1.24 (2H, m, CH_2), 1.24–1.05 (3H, m, CH_2, CH$_A$$H_B$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.9, 137.6, 136.7, 133.5, 128.8, 128.70, 128.65, 127.4, 127.3, 127.1, 125.5, 122.0, 42.9, 37.3, 34.1, 25.8, 25.7; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2889, 1685, 1473, 1462, 1383, 1252, 1153, 1073, 954, 816, 695; **LRMS (ESI) m/z**: 344.2 [$C_{24}H_{26}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{22}H_{24}NO$, $(M+H)^+$]: 344.2009; found 344.2009.

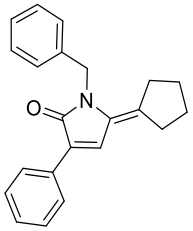
1-Benzyl-5-cyclohexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **7c**



Prepared according to general procedure D using *α*-keto amide **1a** (86 mg, 0.36 mmol) and cyclohexylacetylene (39 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 95:5) to give pyrrolinone **7c** as a yellow solid (45 mg, 0.14 mmol, 46%).

^{1}H NMR (400 MHz, chloroform-*d*) δ 8.06–8.00 (2H, m, Ar-*H*), 7.63 (1H, s, C=C*H*), 7.46–7.38 (2H, m, Ar-*H*), 7.37–7.28 (3H, m, Ar-*H*), 7.27–7.18 (1H, m, Ar-*H*), 7.12 (2H, d, *J* = 7.5 Hz, Ar-*H*), 5.18 (2H, s, NCH_2), 2.53–2.45 (2H, m, CH_2), 2.44–2.34 (2H, m, CH_2), 1.70–1.60 (2H, m, CH_2), 1.59–1.48 (2H, m, CH_2), 1.31–1.19 (2H, m, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 170.9, 138.4, 132.6, 132.1, 131.8, 130.3, 128.7, 128.6, 128.3, 128.2, 127.2, 126.9, 126.0, 45.9, 33.0, 31.0, 29.1, 28.0, 26.5; **MP (petrol/Et$_2$O)**: 117–119 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 2889, 2854, 1673, 1492, 1449, 1381, 1352, 1327, 1251, 1224, 1168, 1074, 1028, 997, 947, 892, 854, 787, 749, 725, 694, 652; **LRMS (ESI) m/z**: 330.2 [$C_{23}H_{24}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{23}H_{24}NO$, $(M+H)^+$]: 330.1852; found 330.1850.

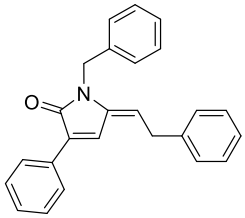
1-Benzyl-5-cyclopentylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **7d**



Prepared according to general procedure D using *α*-keto amide **1a** (86 mg, 0.36 mmol) and cyclopentylacetylene (35 µL, 0.30 mmol), purified by column chromatography (petrol/Acetone = 95:5) to give pyrrolinone **7d** as a white solid (46 mg, 0.15 mmol, 48%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.03 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.46–7.18 (7H, m, Ar-*H*, C=C*H*), 7.13 (2H, d, *J* = 7.0 Hz, Ar-*H*), 5.13 (2H, s, NCH_2), 2.76–2.69 (2H, m, CH_2), 2.55–2.47 (2H, m, CH_2), 1.75–1.61 (4H, m, 2 × CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.9, 138.8, 133.9, 132.2, 131.7, 130.5, 128.8, 128.7, 128.6, 128.4, 127.2, 127.0, 125.9, 44.4, 33.0, 30.9, 27.2, 25.8; **MP (petrol/Et$_2$O)**: 143–146 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2888, 1674, 1490, 1473, 1462, 1383, 1252, 1152, 1073, 954, 816,

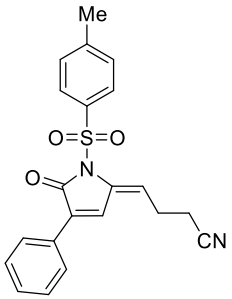
787, 748, 725, 694, 669, 652; **LRMS (ESI) m/z**: 316.2 [$C_{22}H_{22}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{22}H_{22}NO$, $(M+H)^+$]: 316.1696; found 316.1697.

(*E*)-1-Benzyl-3-phenyl-5-(2-phenylethylidene)-1,5-dihydro-2*H*-pyrrol-2-one, **7e**



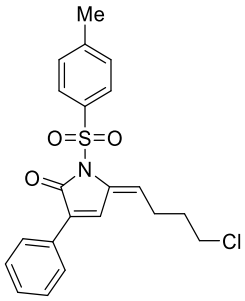
Prepared according to general procedure D using α-keto amide **1a** (86 mg, 0.36 mmol) and 4-phenyl-1-butyne (42 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 95:5) to give pyrrolinone **7e** as an off-white solid (48 mg, 0.14 mmol, 46%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.01 (2H, d, *J* = 7.0 Hz, Ar-*H*), 7.50 (1H, s, C=C*H*), 7.42 (2H, t, *J* = 7.0 Hz, Ar-*H*), 7.38–7.33 (1H, m, Ar-*H*), 7.31–7.18 (8H, m, Ar-*H*), 7.06 (2H, d, *J* = 7.0 Hz, Ar-*H*), 5.52 (1H, t, *J* = 8.5 Hz, C*H*CH_2), 4.92 (2H, s, NCH_2), 3.67 (2H, d, *J* = 8.5 Hz, CHCH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.0, 139.4, 138.7, 137.5, 134.3, 131.6, 129.1, 128.79, 128.77, 128.7, 128.4, 127.5, 127.4, 127.1, 126.7, 125.1, 113.4, 43.0, 33.6; **MP (petrol/EtOAc)**: 116–118 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3085, 3062, 3029, 2918, 2850, 2166, 2038, 1979, 1683, 1648, 1603, 1585, 1524, 1494, 1453, 1435, 1412, 1384, 1345, 1298, 1279, 1239, 1172, 1128, 1098, 1075, 1029, 1001, 974, 947, 906, 856, 786, 729, 695, 649, 609; **LRMS (ESI) m/z**: 352.2 [$C_{25}H_{22}NO$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{25}H_{22}NO$, $(M+H)^+$]: 352.1696; found 352.1697.

(*E*)-4-(5-Oxo-4-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-ylidene)butanenitrile, **7f**



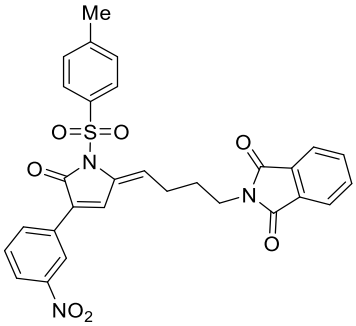
Prepared according to general procedure D using α-keto amide **1b** (109 mg, 0.36 mmol) and hex-5-ynenitrile (32 µL, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 7:3) to give pyrrolinone **7f** as a yellow solid (31 mg, 0.08 mmol, 27%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.95 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.84–7.74 (2H, m, Ar-*H*), 7.54 (1H, s, C=C*H*), 7.39–7.34 (3H, m, Ar-*H*), 7.34–7.30 (2H, m, Ar-*H*), 6.80 (1H, t, *J* = 8.5 Hz, C=C*H*CH$_2$), 2.85–2.74 (2H, m, C=CHC*H*$_2$), 2.63 (2H, t, *J* = 7.0 Hz, C*H*$_2$CN), 2.40 (3H, s, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.7, 145.6, 136.8, 135.5, 132.9, 129.94, 129.90, 129.5, 129.0, 128.8, 128.1, 127.6, 118.6, 115.7, 24.5, 21.8, 18.1; **MP (petrol/EtOAc)**: 120–122 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3090, 2981, 2929, 2889, 2246, 1725, 1540, 1492, 1389, 1364, 1307, 1190, 1176, 1135, 1092, 1006, 994, 814, 785, 692, 660; **LRMS (ESI) m/z**: 379.1 [$C_{21}H_{19}N_2O_3S$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{19}N_2O_3S$, $(M+H)^+$]: 379.1111; found 379.1110.

(*E*)-5-(4-Chlorobutylidene)-3-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one, **7g**



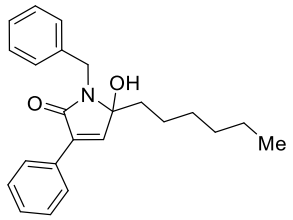
Prepared according to general procedure D using α-keto amide **1b** (109 mg, 0.36 mmol) and 6-chlorohex-1-yne (36 µL, 0.30 mmol), purified by column chromatography (petrol/Et_2O = 4:1) to give pyrrolinone **7g** as a light yellow oil (30 mg, 0.07 mmol, 25%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.94 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.86–7.76 (2H, m, Ar-*H*), 7.63 (1H, s, C=C*H*), 7.42–7.26 (5H, m, Ar-*H*), 6.80 (1H, t, *J* = 8.5 Hz, C=C*H*CH_2), 3.60 (2H, t, *J* = 6.0 Hz, CH_2Cl), 2.64 (2H, dt, *J* = 8.5, 7.0 Hz, C=CHCH_2), 2.41 (3H, s, CH_3), 2.10–1.97 (2H, m, CH_2CH_2Cl); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.8, 145.3, 135.8, 135.6, 131.9, 129.8, 129.75, 129.73, 129.5, 128.7, 128.0, 127.3, 119.6, 44.0, 32.0, 25.2, 21.7; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2889, 1723, 1492, 1473, 1387, 1366, 1306, 1250, 1188, 1175, 1135, 1092, 1006, 994, 870, 785, 750, 711, 692, 660; **LRMS (ESI) m/z**: 402.1 [$C_{21}H_{21}{}^{35}ClNO_3S$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{21}{}^{35}ClNO_3S$, $(M+H)^+$]: 402.0925; found 402.0924.

(*E*)-2-(4-(4-(3-Nitrophenyl)-5-oxo-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-ylidene)butyl)isoindoline-1,3-dione, **7i**



Prepared according to general procedure D using α-keto amide **6** (125 mg, 0.36 mmol) and *N*-(5-hexynyl)phthalimide (68 mg, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 1:1) to give pyrrolinone **7i** as a white solid (135 mg, 0.24 mmol, 81%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.67 (1H, t, *J* = 2.0 Hz, Ar-*H*), 8.27–8.23 (1H, m, Ar-*H*), 8.20–8.16 (1H, m, Ar-*H*), 7.99–7.91 (2H, m, Ar-*H*), 7.86–7.84 (2H, m, Ar-*H*), 7.80 (1H, s, C=C*H*), 7.74–7.22 (2H, m, Ar-*H*), 7.56 (1H, t, *J* = 8.0 Hz, Ar-*H*), 7.33 (2H, d, *J* = 8.0 Hz, Ar-*H*), 6.95 (1H, t, *J* = 8.2 Hz, C=C*H*CH$_2$), 3.79 (2H, t, *J* = 7.0 Hz, C*H*$_2$N), 2.60–2.48 (2H, m, C=CHC*H*$_2$), 2.41 (3H, s, C*H*$_3$), 2.02 (2H, p, *J* = 7.0 Hz, C=CHCH$_2$C*H*$_2$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.6, 166.2, 148.5, 145.6, 135.6, 134.9, 134.3, 133.3, 132.1, 131.9, 131.7, 130.0, 129.9, 129.4, 128.2, 123.9, 123.5, 123.1, 122.3, 37.3, 28.7, 26.2, 21.9; **MP (petrol/EtOAc)**: 196–197 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3660, 2981, 2888, 1770, 1709, 1529, 1395, 1351, 1251, 1152, 1090, 1023, 955, 893, 774, 720, 699; **LRMS (ESI) m/z**: 580.2 [$C_{29}H_{23}N_3NaO_7S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{29}H_{23}N_3NaO_7S$, $(M+Na)^+$]: 580.1149; found 580.1148.

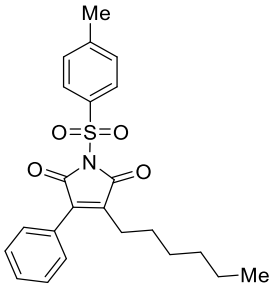
1-Benzyl-5-hexyl-5-hydroxy-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, **8**



Prepared according to general procedure D, using α-keto amide **1a** (86 mg, 0.36 mmol), 1-octyne **2a** (44 µL, 0.30 mmol), DMAP (36.6 mg, 0.30 mmol), purified by column chromatography (petrol/EtOAc = 95:5) to give pyrrolinone **8** as a yellow solid (44 mg, 0.13 mmol, 42%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.88 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.42–7.36 (5H, m, Ar-*H*), 7.31–7.20 (3H, m, Ar-*H*), 6.93 (1H, s, C=C*H*), 4.63 (1H, d, *J* = 15.0 Hz, NC*H*$_A$H$_B$), 4.35 (1H, d, *J* = 15.0 Hz, NCH$_A$*H*$_B$), 2.79 (1H, s, O*H*), 1.83 (1H, ddd, *J* = 14.0, 12.0, 4.5 Hz, OH-C-C*H*$_A$H$_B$), 1.67 (1H, ddd, *J* = 14.0, 12.0, 4.5 Hz, OH-C-CH$_A$*H*$_B$), 1.21–1.04 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.08–0.94 (4H, m, C*H*$_2$C*H*$_2$CH$_2$CH$_3$), 0.93–0.70 (5H, m, C*H*$_2$C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 169.1, 141.4, 138.4, 135.8, 130.8, 129.2, 128.7, 128.6, 128.5, 127.5, 127.4, 90.4, 42.1, 36.0, 31.6, 29.1, 23.7, 22.6, 14.1; **MP (petrol/Et$_2$O)**: 110–114 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3657, 3367, 3064, 2981, 2930, 2889, 1678, 1493, 1383, 1252, 1152, 1073, 954, 860, 789, 749, 695, 669, 649; **LRMS (ESI) m/z**: 372.2 [$C_{23}H_{27}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI)**: calcd for [$C_{23}H_{27}NNaO_2$, $(M+Na)^+$]: 372.1934; found 372.1935.

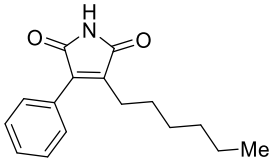
5.2.3 Synthesis of Asymmetric Maleimides

3-Hexyl-4-phenyl-1-tosyl-1*H*-pyrrole-2,5-dione, **11**



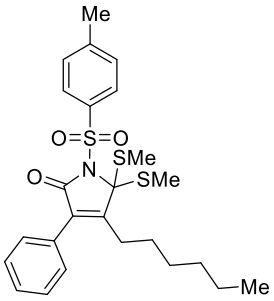
Prepared according to general procedure D, using α-keto amide **1b** (364 mg, 1.2 mmol), oct-1-yn-1-yl(phenyl)sulfane **10** (218 mg, 1.0 mmol), $[Cu(MeCN)_4]BF_4$ (31.5 mg, 0.1 mmol), toluene (1.7 mL), purified by column chromatography (petrol/Et_2O = 90:10) and recrystallisation (petrol/Et_2O) to give maleimide **11** as a white solid (16 mg, 0.04 mmol, 13%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.07–8.00 (2H, m, Ar-*H*), 7.55–7.39 (5H, m, Ar-*H*), 7.43–7.33 (2H, m, Ar-*H*), 2.61–2.50 (2H, m, C=CCH_2), 2.44 (3H, s, Ar-CH_3), 1.59–1.50 (2H, m, C=CCH$_2$CH_2), 1.36–1.16 (6H, m, CH_2CH_2CH_2CH$_3$), 0.93–0.80 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.2, 165.6, 146.1, 143.0, 139.0, 135.6, 130.5, 130.1, 129.5, 128.9, 128.5, 127.8, 31.3, 29.4, 28.3, 24.6, 22.5, 21.9, 14.1; **MP (petrol/Et$_2$O)**: 106–108 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3100, 2955, 2928, 2858, 1731, 1597, 1494, 1446, 1384, 1250, 1190, 1177, 1091, 1058, 883, 815, 799, 785, 750, 704, 693, 669, 645; **MS (ESI) m/z**: 412.2 [$C_{23}H_{26}NO_4S$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{23}H_{26}NO_4S$, $(M+H)^+$]: 412.1577; found 412.1577.

3-Hexyl-4-phenyl-1*H*-pyrrole-2,5-dione, **12**



Prepared according to general procedure D, using *α*-keto amide **1b** (364 mg, 1.2 mmol), oct-1-yn-1-yl(phenyl)sulfane **10** (218 mg, 1.0 mmol), $[Cu(MeCN)_4]BF_4$ (31.5 mg, 0.1 mmol), toluene (1.7 mL) purified by column chromatography (petrol/Et_2O = 90:10) to give maleimide **12** as a yellow oil (21 mg, 0.08 mmol, 27%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.79 (s, 1H, N-*H*), 7.54–7.39 (5H, m, Ar-*H*), 2.61–2.53 (2H, m, C=CCH_2), 1.67–1.53 (2H, m, C=CCH$_2$CH_2), 1.39–1.31 (2H, m, CH_2CH$_2$CH$_2$CH$_3$), 1.31–1.19 (4H, m, CH_2CH_2CH$_3$), 0.91–0.81 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 171.7, 171.1, 142.2, 138.4, 129.8, 129.4, 128.83, 128.77, 31.5, 29.5, 28.7, 24.4, 22.6, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 3284, 3105, 2956, 2927, 2858, 1711, 1496, 1446, 1346, 1209, 1112, 1067, 980, 769, 698, 618; **MS (ESI) m/z**: 256.2 [$C_{16}H_{18}NO_2$, $(M-H)^-$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{18}NO_2$, $(M-H)^-$]: 256.1343; found 256.1341.

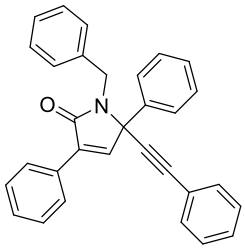
4-Hexyl-5,5-bis(methylthio)-3-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one, **13**



Prepared according to general procedure D, using *α*-keto amide **1b** (364 mg, 1.2 mmol), oct-1-yn-1-yl(phenyl)sulfane **10** (218 mg, 1.0 mmol), $[Cu(MeCN)_4]BF_4$ (31.5 mg, 0.1 mmol), toluene (1.7 mL) purified by column chromatography (petrol/Et_2O = 90:10) to give pyrrolinone **12** as a yellow oil (15 mg, 0.03 mmol, 10%). **^{1}H NMR (400 MHz,**

chloroform-*d*) δ 8.23–8.15 (2H, m, Ar-*H*), 7.40–7.33 (5H, m, Ar-*H*), 7.31–7.27 (2H, m, Ar-*H*), 2.63–2.53 (2H, m, C=CCH_2), 2.41 (3H, s, Ar-CH_3), 1.88 (6H, s, 2 × SCH_3), 1.42–1.35 (2H, m, C=CCH$_2$CH_2), 1.27–1.21 (2H, m, CH_2CH$_2$CH$_2$CH$_3$), 1.18–1.08 (4H, m, CH_2CH_2CH$_3$), 0.80 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 166.9, 159.0, 145.2, 136.1, 132.5, 129.8, 129.4, 129.2, 129.1, 129.0, 128.7, 83.1, 31.1, 29.8, 27.5, 26.4, 22.5, 21.8, 14.1, 13.7; **IR (cm^{-1})** $\tilde{\nu}$ = 3105, 3100, 2954, 2925, 2856, 1724, 1597, 1494, 1445, 1372, 1173, 1088, 1053, 991, 816, 782, 700, 663; **MS (ESI) m/z**: 512.2 [$C_{25}H_{31}NNaO_3S_3$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{25}H_{31}NNaO_3S_3$, $(M+Na)^+$]: 512.1358; found 512.1357.

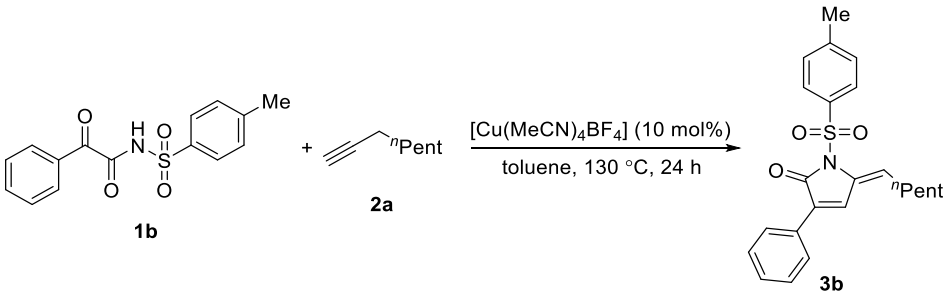
1-Benzyl-3,5-diphenyl-5-(phenylethynyl)-1,5-dihydro-2*H*-pyrrol-2-one, **14**



Prepared according to general procedure D, using *α*-keto amide **1a** (86 mg, 0.36 mmol), phenylacetylene **2ab** (33 µL, 0.30 mmol), purified by column chromatography (petrol/Et$_2$O = 9:1) to give pyrrolinone **14** as a light brown oil (12 mg, 0.03 mmol, 19%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.05–7.97 (2H, m, Ar-*H*), 7.50–7.46 (2H, m, Ar-*H*), 7.45–7.37 (3H, m, Ar-*H*), 7.37–7.30 (5H, m, Ar-*H*), 7.29–7.22 (6H, m, Ar-*H*), 7.20 (1H, s, C=C*H*), 7.17–7.12 (2H, m, Ar-*H*), 4.88 (1H, d, *J* = 15.0 Hz, CH_2), 4.25 (1H, d, *J* = 15.0 Hz, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 170.0, 143.1, 137.3, 135.8, 133.7, 131.9, 131.0, 129.2, 120.0, 128.92, 128.88, 128.85, 128.7, 128.4, 128.2, 127.6, 127.1, 127.0, 121.9, 89.1, 83.4, 65.5, 44.7; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2888, 1692, 1473, 1462, 1383, 1252, 1152, 1073, 954, 816, 757, 693; **MS (ESI) m/z**: 448.2 [$C_{31}H_{23}NNaO$,

(M+Na)$^+$]; **HRMS (ESI) m/z**: calcd for [$C_{31}H_{23}NNaO$, (M+Na)$^+$]: 448.1672; found 448.1670.

5.2.4 Gramme-scale Synthesis of Pyrrolinone 3b

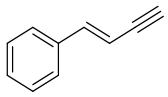


Commercially purchased 1-octyne was purified prior to use by distillation. α-Keto amide **1b** was synthesised and purified as before. An oven-dried round bottom flask (100 mL) was charged with *N*-tosyl-2-oxo-2-phenylacetamide **1a** (1.31 g, 4.32 mmol, 1.2 equiv.) and $[Cu(MeCN)_4]BF_4$ (113 mg, 0.36 mmol, 0.10 equiv.). The flask was then evacuated under vacuum and back-filled with N_2 three times. Degassed dry toluene (6.0 mL) and degassed 1-octyne (530 µL, 3.6 mmol, 1.0 equiv.) were added sequentially under N_2 atmosphere, and the mixture was heated at 130 °C for 20 h under N_2. It was then cooled to rt, filtered through silica (washed down with CH_2Cl_2), concentrated *in vacuo*, and purified by column chromatography (5% Et_2O/petrol to 10% Et_2O/petrol) to give pyrrolinone **3b** (1.18 g, 3.0 mmol, 83%) as a yellow oil. The data are consistent with those obtained for the small-scale reaction.

5.3 Data for Chapter 3

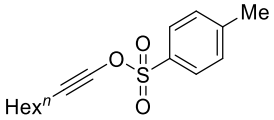
5.3.1. Synthesis of Alkynes

(*E*)-But-1-en-3-yn-1-ylbenzene, **2am**



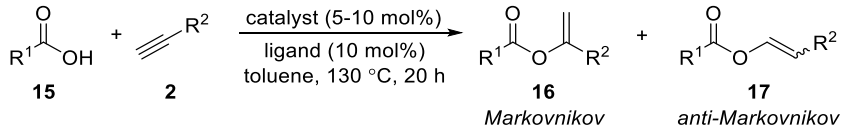
Prepared according to a literature procedure.[212] To a stirred solution of cinnamaldehyde (252 µL, 2.0 mmol) and tetrabromomethane (995 mg, 3.0 mmol) in anhydrous MeCN (4 mL), tri-*iso*propyl phosphite (990 µL, 4.0 mmol) was added dropwise over a period of 5 min at 0 °C. After 15 min, DBU (1.2 mL, 8.0 mmol) was added to the reaction mixture dropwise over a period of 10 min at 0 °C. The reaction mixture was then allowed to reach ambient temperature over 30 min with stirring. Powdered NaOH (800 mg, 20 mmol) was added to the reaction mixture and the mixture allowed to stir for 14 h. After completion of the reaction, the reaction mixture was quenched with water (20 mL), extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography (100% pentane) to give (*E*)-but-1-en-3-yn-1-ylbenzene **2am** as a yellow oil (185 mg, 72%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.43–7.27 (5H, m, Ar-*H*), 7.06 (1H, dd, *J* = 16.5, 0.5 Hz, ArC*H*=CH), 6.15 (1H, dd, *J* = 16.5, 2.5 Hz, ArCH=C*H*), 3.06 (1H, dd, *J* = 2.5, 0.5 Hz, C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 143.2, 135.9, 128.9, 128.8, 126.4, 107.0, 82.9, 79.2; **IR (cm^{-1})** $\tilde{\nu}$ = 3290, 3032, 1613, 1575, 1491, 1448, 1298, 1270, 1206, 1074, 955, 748, 689, 643, 616; **HRMS (ESI) m/z**: calcd for [$C_{10}H_9$, $(M+H)^+$]: 129.0700; found 129.0700. These data are consistent with literature.[212]

3-Oxo-oct-1-yn-1-yl-4-methylbenzenesulfonate, **23**



Prepared according to a modified literature procedure.[212] A solution of toluenesulfonic acid monohydrate (3.8 g, 20 mmol) in MeCN (30 mL) was added to a suspension of **(**diacetoxyiodo)benzene (4.0 g, 10 mmol) in MeCN (20 mL) and the reaction mixture was left to stir for 20 min, with the formation of precipitate observed. The solid was filtered and washed acetone and Et_2O to give phenylhydroxyiodonium tosylate (2.9 g, 73%). To an oven-dried flask containing the phenylhydroxyiodonium tosylate (2.7g, 7.0 mmol) and powdered 3.0 Å MS (5.0 g) under N_2, was added 1-octyne (1.2 mL, 8.0 mmol) and CH_2Cl_2 (15 mL) and the reaction mixture was left to stir at rt for 16 h. The mixture was filtered over celite and concentrated under reduced pressure. The crude mixture obtained (est. 2.0 mmol of product) was added to a solution of copper(I) triflate benzene complex (403 mg, 0.8 mmol) in MeCN (20 mL) under N_2 and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was filtered through celite, concentrated under reduced pressure, and purified by column chromatography (10% CH_2Cl_2 in pentane) to give alkyne **23** as a light yellow oil (220 mg, 0.75 mmol, 10%) **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.87 (2H, app. dd (AA'BB'), *J* = 8.5, 1.5 Hz, Ar-*H*), 7.39 (2H, app. dd (AA'BB'), *J* = 8.5, 1.5 Hz, Ar-*H*), 2.48 (3H, s, Ar-CH_3), 2.08 (2H, t, *J* = 7.0 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.44–1.35 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.33–1.16 (6H, m, CH_2CH_2CH_2CH$_3$), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 146.9, 130.1, 130.0, 129.1, 78.7, 47.9, 34.1, 31.3, 28.6, 28.3, 22.5, 16.9, 14.0; **IR (cm^{-1})** $\tilde{\nu}$ = 3005, 2955, 2929, 2858, 1689, 1597, 1458, 1386, 1194, 1180, 1075, 814, 749, 705, 690, 665; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{19}O_4S$, $(M+H)^+$]: 295.0999; found 295.1001.

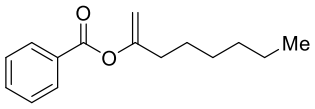
5.3.2 Synthesis of Enol Esters



General Procedure E:

To an oven-dried, round-bottomed 10 mL microwave reaction vial equipped with a stirrer bead was added catalyst (0.03 mmol), ligand (0.03 mmol), carboxylic acid **15** (0.30 mmol, 1.0 equiv.) and alkyne **2** (0.60 mmol, 2.0 equiv.) if solid. The vial was sealed with a microwave vial cap, and then evacuated under vacuum (<1 mbar) and back-filled with N_2 gas 3 times. Degassed, dry toluene (1.0 mL) and degassed alkyne **2** (0.60 mmol, 2.0 equiv.) if liquid were then added respectively. The solution was stirred and heated at 130 °C for 20 h. The reaction mixture was then diluted with EtOAc (10 mL), filtered through a plug of silica gel and concentrated under reduced pressure. The residue was purified by column chromatography to give the resulting product.

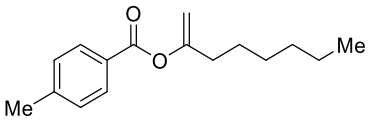
Oct-1-en-2-ylbenzoate, **16a**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16a** as a colourless oil (60 mg, 0.26 mmol, 86%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.13–8.05 (2H, m, Ar-*H*), 7.64–7.55 (1H, m, Ar-*H*), 7.51–7.42 (2H, m, Ar-*H*), 4.86 (1H, d, *J* = 1.5 Hz, C=CH_AH$_B$), 4.84 (1H, app. q, *J* = 1.0 Hz, C=CH$_A$$H_B$), 2.34 (2H, t, *J* = 8.0 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.59–1.47 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.42–1.21 (6H, m, CH_2CH_2CH_2CH$_3$), 0.95–0.83 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)**

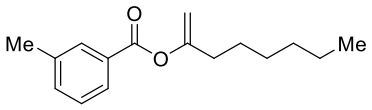
δ 164.9, 157.0, 133.4, 130.05, 130.04, 128.6, 101.4, 33.6, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2929, 2858, 1733, 1667, 1602, 1452, 1314, 1270, 1221, 1171, 1105, 1091, 1068, 1026, 866, 705; **LRMS (ESI) m/z**: 255.2 [$C_{15}H_{20}NaO_2$, $(M+Na)^+$]. These data are consistent with literature.[84]

Oct-1-en-2-yl-4-methylbenzoate, **16b**



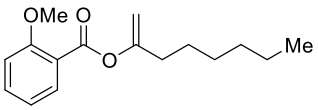
Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), *p*-toluic acid (40.8 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol to 0.5% EtOAc/petrol) to give enol ester **16b** as a light yellow oil (65 mg, 0.26 mmol, 88%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.98 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.26 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 8.5 Hz, Ar-*H*), 4.84 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.82 (1H, app. q, *J* = 1.0 Hz, C=CH_AH_B), 2.42 (3H, s, Ar-CH_3), 2.37–2.29 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.58–1.47 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.39–1.25 (6H, m, CH_2CH_2CH_2CH$_3$), 0.90–0.86 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 165.0, 157.0, 144.1, 130.1, 129.3, 127.3, 101.3, 33.6, 31.7, 28.8, 26.6, 22.7, 21.8, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2929, 1732, 1666, 1613, 1462, 1381, 1270, 1224, 1174, 1087, 1020, 955, 864, 837, 750, 687; **LRMS (ESI) m/z**: 269.2 [$C_{16}H_{22}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{23}O_2$, $(M+H)^+$]: 247.1693; found 247.1694.

Oct-1-en-2-yl-3-methylbenzoate, **16c**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), *m*-toluic acid (40.8 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16c** as a light yellow oil (64 mg, 0.26 mmol, 86%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.99 (1H, dd, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.43 (1H, td, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.32–7.23 (2H, m, Ar-*H*), 4.84 (2H, app. q, *J* = 1.0 Hz, C=CH_2), 2.63 (3H, s, Ar-CH_3), 2.38–2.30 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.63–1.48 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.44–1.30 (2H, m, CH_2CH$_2$CH$_2$CH$_3$), 1.34–1.20 (4H, m, CH_2CH_2CH$_3$), 0.95–0.79 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 165.7, 157.0, 141.0, 132.5, 132.0, 131.0, 129.1, 125.9, 101.4, 33.6, 31.7, 28.8, 26.7, 22.7, 22.0, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2929, 1733, 1666, 1603, 1459, 1382, 1292, 1249, 1217, 1168, 1139, 1064, 955, 865, 736, 691; **LRMS (ESI) m/z**: 269.2 [$C_{16}H_{22}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{22}NaO_2$, $(M+Na)^+$]: 269.1512; found 269.1513.

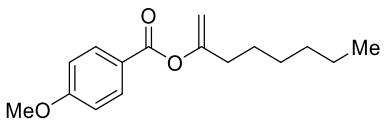
Oct-1-en-2-yl-2-methoxybenzoate, **16d**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 2-methoxybenzoic acid (46.0 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (0.1% EtOAc/petrol to 0.2% EtOAc/petrol) to give enol ester **16d** as a light yellow oil (27 mg, 0.14 mmol, 47%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.86 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.50 (1H, ddd, *J* = 8.0, 7.0, 2.0 Hz,

Ar-*H*), 7.04–6.93 (2H, m, Ar-*H*), 4.84 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.80 (1H, app. q, *J* = 1.0 Hz, C=CH_AH_B), 3.91 (3H, s, OCH_3), 2.38–2.29 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.60–1.48 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.42–1.30 (2H, m, CH_2CH$_2$CH$_2$CH$_3$), 1.40–1.21 (4H, m, CH_2CH_2CH$_3$), 0.94–0.78 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.2, 159.7, 157.0, 134.1, 132.1, 120.2, 119.7, 112.2, 101.4, 56.1, 33.6, 31.8, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 1740, 1666, 1601, 1583, 1491, 1463, 1382, 1300, 1252, 1214, 1164, 1126, 1062, 1025, 954, 865, 755, 699, 658; **LRMS (ESI) m/z**: 285.1 [$C_{16}H_{22}NaO_3$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{22}NaO_3$, $(M+Na)^+$]: 285.1461; found 285.1462.

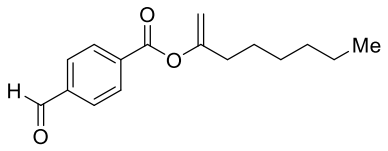
Oct-1-en-2-yl-4-methoxybenzoate, **16e**



Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 4-methoxybenzoic acid (46.0 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (0.1% EtOAc/petrol to 0.2% EtOAc/petrol) to give enol ester **16e** as a light yellow oil (69 mg, 0.26 mmol, 88%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.03 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 9.0 Hz, Ar-*H*), 6.94 (2H, app. d (AA'BB'), J_{BA} + $J_{BA'}$ = 9.0 Hz, Ar-*H*), 4.83 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.81 (1H, app. q, *J* = 1.0 Hz, C=CH_AH_B), 3.87 (3H, s, OCH_3), 2.36–2.28 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.56–1.46 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.41–1.22 (6H, m, CH_2CH_2CH_2CH$_3$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.7, 163.8, 157.0, 132.1, 122.4, 113.8, 101.3, 55.6, 33.6, 31.7, 28.8, 26.7, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2929, 1726, 1666, 1606, 1582, 1510, 1462, 1381, 1316, 1254, 1222, 1162, 1086, 1030, 955, 846, 766, 691, 617; **LRMS (ESI) m/z**: 285.1 [$C_{16}H_{22}NaO_3$,

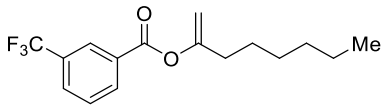
(M+Na)$^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{22}NaO_3$, (M+Na)$^+$]: 285.1461; found 285.1462. These data are consistent with literature.[74]

Oct-1-en-2-yl-4-formylbenzoate, **16f**



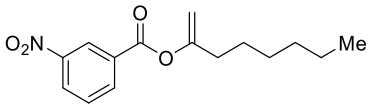
Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 4-formylbenzoic acid (45.0 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (10% EtOAc/petrol) to give enol ester **16f** as a light yellow oil with the Markovnikov and anti-Markovnikov isomers inseparable (71 mg, 0.27 mmol, 91%). M:AM = 91:9; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 10.11 (1H, s, C*H*O), 8.24 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.97 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 8.5 Hz, Ar-*H*), 4.88 (1H, d, *J* = 2.0 Hz, C=C*H*$_A$H$_B$), 4.86 (1H, dd, *J* = 2.0, 1.0 Hz, C=CH$_A$*H*$_B$), 2.38–2.31 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.58–1.41 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.44–1.18 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.91–0.82 (3H, m, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 191.7, 163.9, 156.8, 139.5, 135.0, 130.6, 129.7, 101.8, 33.4, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 1730, 1707, 1578, 1462, 1382, 1270, 1165, 1091, 1018, 954, 875, 829, 758, 728; **HRMS (APCI) m/z**: calcd for [$C_{16}H_{21}O_3$, (M+H)$^+$]: 261.1485; found 261.1473.

Oct-1-en-2-yl-3-(trifluoromethyl)benzoate, **16g**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 3-(trifluoromethyl)benzoic acid (57.0 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16g** as a light yellow oil (64 mg, 0.21 mmol, 71%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.34 (1H, d, *J* = 1.5 Hz, Ar-*H*), 8.27 (1H, app. dt, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.85 (1H, app. dq, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.62 (1H, t, *J* = 7.5 Hz, Ar-*H*), 4.90–4.84 (2H, m, C=CH_2), 2.38–2.30 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.57–1.47 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.42–1.22 (6H, m, CH_2CH_2CH_2CH$_3$), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 156.8, 133.3, 131.3 (q, ^3J = 33.0 Hz), 130.2, 129.9 (q, ^3J = 4.0 Hz), 129.32, 126.9 (q, ^3J = 4.0 Hz), 123.8 (q, ^1J = 273.0 Hz), 101.8, 33.4, 31.7, 28.8, 26.6, 22.7, 14.2; **^{19}F NMR (377 MHz, chloroform-*d*)** δ −62.8; **IR (cm^{-1})** $\tilde{\nu}$ = 2961, 2931, 1739, 1668, 1618, 1462, 1381, 1336, 1249, 1215, 1168, 1132, 1073, 925, 871, 818, 753, 695, 651; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{19}F_3NaO_2$, $(M+Na)^+$]: 323.1229; found 323.1229.

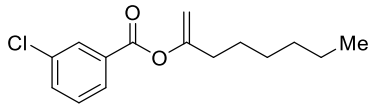
Oct-1-en-2-yl-3-nitrobenzoate, **16h**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 3-nitrobenzoic acid (50.1 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (10% EtOAc/petrol) to give enol ester **16h** as a light yellow oil with the Markovnikov and anti-Markovnikov isomers inseparable (78 mg, 0.28 mmol, 94%). M:AM = 89:11; *Markovnikov*: **^{1}H NMR (400 MHz,**

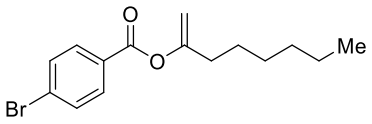
chloroform-*d*) δ 8.91–8.89 (1H, m, Ar-*H*), 8.50–8.36 (2H, m, Ar-*H*), 7.75–7.61 (1H, m, Ar-*H*), 4.92–4.85 (2H, m, C=CH_2), 2.39–2.31 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.57–1.49 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.41–1.21 (6H, m, CH_2CH_2CH_2CH$_3$), 0.92–0.83 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 162.8, 156.7, 148.5, 135.7, 131.8, 129.9, 127.9, 125.0, 102.0, 33.4, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 1738, 1668, 1617, 1534, 1463, 1440, 1381, 1351, 1321, 1291, 1258, 1219, 1165, 1127, 1068, 953, 874, 819, 771, 717; **LRMS (ESI) m/z**: 276.1 [$C_{15}H_{18}NO_4$, $(M-H)^-$]; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{18}NO_4$, $(M-H)^-$]: 276.1241; found 276.1240.

Oct-1-en-2-yl-3-chlorobenzoate, **16i**



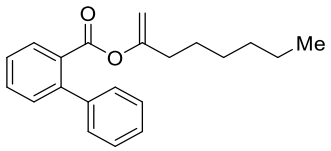
Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 3-chlorobenzoic acid (36.6 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16i** as a light yellow oil (63 mg, 0.24 mmol, 79%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.06 (1H, t, *J* = 2.0 Hz, Ar-*H*), 7.97 (1H, dt, *J* = 8.0, 1.0 Hz, Ar-*H*), 7.56 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, Ar-*H*), 7.41 (1H, t, *J* = 8.0 Hz, Ar-*H*), 4.85 (2H, dt, *J* = 4.0, 2.0 Hz, C=CH_2), 2.38–2.28 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.55–1.46 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.42–1.22 (6H, m, CH_2CH_2CH_2CH$_3$), 0.93–0.84 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.7, 156.8, 134.8, 133.4, 131.8, 130.1, 129.9, 128.2, 101.7, 33.5, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2929, 1737, 1668, 1576, 1468, 1426, 1380, 1281, 1252, 1217, 1164, 1122, 1071, 1012, 936, 870, 807, 744, 673; **LRMS (ESI) m/z**: 267.8 [$C_{15}H_{20}{}^{35}ClO_2$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{19}{}^{35}ClNaO_2$, $(M+Na)^+$]: 289.0972; found 289.0966.

Oct-1-en-2-yl-4-bromobenzoate, **16j**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 4-bromobenzoic acid (60.3 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16j** as a light yellow oil (76 mg, 0.24 mmol, 81%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.93 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 9.0 Hz, Ar-*H*), 7.68 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 9.0 Hz, Ar-*H*), 4.87–4.81 (2H, m, C=CH_2), 2.36–2.27 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.57–1.45 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.41–1.28 (2H, m, CH_2CH$_2$CH$_2$CH$_3$), 1.32–1.21 (4H, m, CH_2CH_2CH$_3$), 0.96–0.80 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.2, 156.8, 131.9, 131.5, 128.9, 128.6, 101.6, 33.5, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2928, 2858, 1733, 1666, 1590, 1484, 1465, 1398, 1268, 1219, 1169, 1090, 1070, 1012, 867, 845, 752, 730, 679, 627; **HRMS (APCI) m/z**: calcd for [$C_{15}H_{20}{}^{79}BrO_2$, (M(^{79}Br)+H)$^+$]: 311.0641; found 311.0625; calcd for [$C_{15}H_{20}{}^{81}BrO_2$, (M(^{81}Br)+H)$^+$]: 313.0621; found 313.0604. These data are consistent with literature.[74]

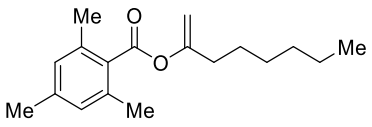
Oct-1-en-2-yl-[1,1'-biphenyl]-2-carboxylate, **16k**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), biphenyl-2-carboxylic acid (59.5 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16k** as a light yellow oil (55 mg, 0.18 mmol, 59%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.87

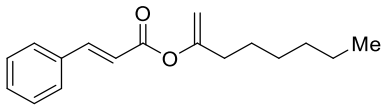
(1H, dd, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.55 (1H, dd, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.47–7.42 (1H, m, Ar-*H*), 7.42–7.33 (6H, m, Ar-*H*), 4.64 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.59 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 2.06–1.96 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.35–1.14 (8H, m, CH_2CH_2CH_2CH_2CH$_3$), 0.88 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 167.1, 156.8, 142.6, 141.3, 131.5, 131.0, 130.9, 130.0, 128.6, 128.3, 127.5, 127.3, 100.8, 33.3, 31.7, 28.8, 26.4, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2957, 2929, 2858, 1732, 1666, 1598, 1451, 1437, 1380, 1276, 1241, 1218, 1168, 1120, 1095, 1074, 1046, 1009, 956, 866, 775, 746, 699, 663, 616; **LRMS (ESI) m/z**: 331.2 [$C_{21}H_{24}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{24}NaO_2$, $(M+Na)^+$]: 331.1669; found 331.1669.

Oct-1-en-2-yl-2,4,6-trimethylbenzoate, **16l**



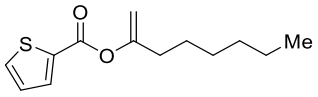
Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 2,4,6-trimethylbenzoic acid (49.3 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16l** as a light yellow oil (63 mg, 0.23 mmol, 76%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 6.88 (2H, s, Ar-*H*), 4.87 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.84 (1H, app. q, *J* = 1.0 Hz, C=CH_AH_B), 2.37 (6H, s, 2 x Ar-CH_3), 2.38–2.27 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.30 (3H, s, Ar-CH_3), 1.63–1.50 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.43–1.22 (6H, m, CH_2CH_2CH_2CH$_3$), 0.94–0.86 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.4, 156.9, 139.7, 135.2, 130.6, 128.6, 101.4, 33.7, 31.7, 28.8, 26.6, 22.7, 21.3, 19.9, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2958, 2929, 2860, 1741, 1666, 1613, 1459, 1380, 1258, 1221, 1162, 1067, 955, 853; **LRMS (ESI) m/z**: 297.1 [$C_{18}H_{26}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{18}H_{26}NaO_2$, $(M+Na)^+$]: 297.1825; found 297.1828.

Oct-1-en-2-ylcinnamate, **16m**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), *trans*-cinnamic acid (44.4 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16m** as a light yellow oil (62 mg, 0.24 mmol, 80%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.75 (1H, d, *J* = 16.0 Hz, Ar-CH=C*H*), 7.60–7.51 (2H, m, Ar-*H*), 7.45–7.35 (3H, m, Ar-*H*), 6.49 (1H, d, *J* = 16.0 Hz, Ar-C*H*=CH), 4.83–4.73 (2H, m, C=CH_2), 2.32–2.25 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.57–1.44 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.38–1.24 (6H, m, CH_2CH_2CH_2CH$_3$), 0.95–0.82 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 165.2, 156.8, 146.0, 134.4, 130.7, 129.07, 128.3, 117.8, 101.2, 33.6, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2929, 1725, 1666, 1636, 1579, 1450, 1381, 1310, 1252, 1200, 1140, 979, 864, 764, 706, 683; **LRMS (ESI) m/z**: 281.1 [$C_{17}H_{22}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{17}H_{22}NaO_2$, $(M+Na)^+$]: 281.1512; found 281.1513. These data are consistent with literature.[112]

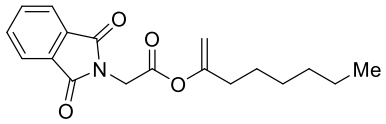
Oct-1-en-2-ylthiophene-2-carboxylate, **16n**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 2-thiophenecarboxylic acid (38.5 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16n** as a light yellow oil (58 mg, 0.24 mmol, 81%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.86 (1H, dd, *J* = 5.0, 1.5 Hz, Ar-*H*), 7.60 (1H, dd, *J* = 5.0, 1.5 Hz, Ar-*H*), 7.13 (1H, dd, *J* = 5.0,

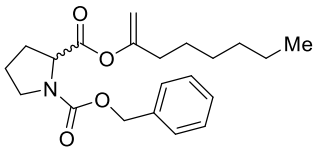
5.0 Hz, Ar-*H*), 4.87 (1H, d, *J* = 1.5 Hz, C=CH_2), 4.82 (1H, d, *J* = 1.5 Hz, C=CH_2), 2.36–2.27 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.58–1.46 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.42–1.21 (6H, m, CH_2CH_2CH_2CH$_3$), 0.92–0.83 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 160.4, 156.6, 134.2, 133.5, 133.1, 128.0, 101.6, 33.6, 31.7, 28.8, 26.6, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2929 2858, 1723, 1667, 1524, 1417, 1255, 1219, 1085, 1071, 863, 744, 720; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{18}NaO_2S$, $(M+Na)^+$]: 261.0920; found 261.0921.

Oct-1-en-2-yl-2-(1,3-dioxoisoindolin-2-yl)acetate, **16o**



Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), *N*-phthaloylglycine (61.6 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (2% EtOAc/petrol) to give enol ester **16o** as a light yellow oil with the Markovnikov and anti-Markovnikov isomers inseparable (94 mg, 0.30 mmol, 99%). M:AM = 92:8; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.92–7.83 (2H, m, Ar-*H*), 7.79–7.69 (2H, m, Ar-*H*), 4.78 (1H, d, *J* = 2.0 Hz, C=CH_AH$_B$), 4.72 (1H, app. dt, *J* = 2.0, 1.0 Hz, C=CH$_A$$H_B$), 4.50 (2H, s, NC$H_2$), 2.23–2.15 (2H, m, C$H_2CH_2CH_2CH_2CH_2CH_3$), 1.49–1.37 (2H, m, C$H_2CH_2CH_2CH_2CH_3$), 1.35–1.16 (6H, m, C$H_2CH_2CH_2CH_3$), 0.90–0.82 (3H, m, C$H_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 167.4, 165.5, 156.4, 134.4, 132.1, 123.7, 101.6, 39.1, 33.2, 31.6, 28.6, 26.3, 22.6, 14.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2930, 2859, 1763, 1719, 1669, 1468, 1415, 1394, 1165, 1114, 954, 874, 714; **LRMS (ESI) m/z**: 338.2 [$C_{18}H_{21}NNaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{18}H_{21}NNaO_4$, $(M+Na)^+$]: 338.1363; found 338.1364.

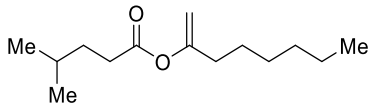
1-Benzyl-2-(oct-1-en-2-yl)pyrrolidine-1,2-dicarboxylate, **16p**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), *Z*-Pro-OH (74.8 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (5% EtOAc/petrol) to give enol ester **16p** as a light orange oil (66 mg, 0.18 mmol, 61%); **^{1}H NMR (400 MHz, chloroform-*d*)** (* denotes minor rotamer) δ 7.40–7.27 (5H, m, Ar-*H*), 5.22–5.10 (2H, m, CH_2Ar), 4.75 (1H, d, *J* = 2.0 Hz, *C=CH_AH$_B$), 4.72 (1H, app. q, *J* = 1.5 Hz, *C=CH$_A$$H_B$), 4.66 (1H, app. q, *J* = 1.5 Hz, C=CH$_A$$H_B$), 4.54 (1H, d, *J* = 2.0 Hz, C=CH_AH$_B$), 4.43 (1H, ddd, *J* = 17.0, 8.5, 4.0 Hz, NC*H*CO_2), 3.72–3.58 (1H, m, NCH_2), 3.58–3.45 (1H, m, *NCH_2), 2.37–2.25 (2H, m, NCH$_2$CH_2), 2.26–2.17 (1H, m, NCH$_2$CH$_2$CH_2), 2.08 (2H, t, *J* = 7.5 Hz, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.00–1.81 (4H, m, *NCH$_2$CH_2, *NCH$_2$CH$_2$CH_2), 1.54–1.40 (2H, m, *CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.41–1.30 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.32–1.20 (6H, m, CH_2CH_2CH_2CH$_3$), 0.88 (3H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** (* denotes minor rotamer) δ 170.9, *170.8, *156.5, 156.3, *154.8, 154.3, *136.7, 136.5, *128.45, 128.43, 128.0, *127.9, *127.83, 127.78, *101.1, *101.0, 67.1, *67.0, *59.4, 58.9, 47.0, *46.4, *33.2, 33.1, *31.59, 31.6, 31.0, *30.0, *28.60, 28.55, *26.3, 26.2, *24.3, 23.5, 22.54, *14.1, 14.0; **IR (cm^{-1})** $\tilde{\nu}$ = 2956, 2929, 1760, 1709, 1668, 1454, 1414, 1353, 1153, 1120, 1087, 985, 874, 768, 698; **LRMS (ESI) m/z**: 382.2 [$C_{21}H_{29}NNaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{29}NNaO_4$, $(M+Na)^+$]: 382.1989; found 382.1992. Procedure repeated with Z-L-proline (74.8 mg, 0.30 mmol) to give enol ester (*S*)-**16p** as a light orange oil (45 mg, 0.13 mmol, 42%): $[\alpha]_D^{25}$: -45.8 (*c* = 1.0, $CHCl_3$); The ee was determined by HPLC using a Chiralpak OD-H column

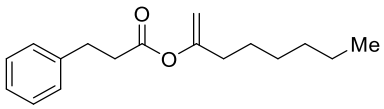
[^{n}hexane/^{i}PrOH (98:2)]: flow rate 1.0 mL/min; τ_{major} = 16.5 min, τ_{minor} = 28.6 min (>99% ee).

Oct-1-en-2-yl-4-methylpentanoate, **16q**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), 4-methylvaleric acid (38 µL, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (1% EtOAc/petrol) to give enol ester **16q** as a light yellow oil with the Markovnikov and anti-Markovnikov isomers inseparable (39 mg, 0.17 mmol, 57%). M:AM = 91:9; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 4.71 (1H, app. q, *J* = 1.5 Hz, C=CH_AH_B), 4.68 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 2.42–2.36 (2H, m, CH_2CO_2), 2.21–2.16 (2H, m, C$H_2CH_2CH_2CH_2CH_2CH_3$), 1.66–1.52 (3H, m, C$H_2CH(CH_3)_2$), 1.49–1.40 (2H, m, C$H_2CH_2CH_2CH_2CH_3$), 1.36–1.21 (6H, m, C$H_2CH_2CH_2CH_3$), 0.91 (6H, d, *J* = 6.0 Hz, CH(CH_3)$_2$), 0.90–0.85 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 172.4, 156.8, 101.1, 33.9, 33.5, 32.6, 31.7, 28.8, 27.8, 26.5, 22.7, 22.4, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2980, 2958, 2929, 2872, 1754, 1666, 1465, 1383, 1251, 1150, 1122, 957, 866; **LRMS (ESI) m/z**: 227.2 [$C_{14}H_{27}O_2$, $(M+H)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{14}H_{27}O_2$, $(M+H)^+$]: 227.2006; found 227.2008.

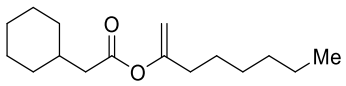
Oct-1-en-2-yl-3-phenylpropanoate, 16r



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), hydrocinnamic acid (45.0 mg, 0.30 mmol) and 1-octyne **2a**

(89 µL), purified by column chromatography (100% petrol) to give enol ester **16r** as a yellow oil (56 mg, 0.22 mmol, 72%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.35–7.27 (2H, m, Ar-*H*), 7.23 (3H, dd, *J* = 7.5, 2.5 Hz, Ar-*H*), 4.71 (1H, d, *J* = 1.5 Hz, C=CH_AH$_B$), 4.67 (1H, d, *J* = 1.5 Hz, C=CH$_A$$H_B$), 3.01 (2H, t, *J* = 8.0 Hz, CH_2CO), 2.73 (2H, dd, *J* = 8.0 Hz, CH_2CH$_2$CO), 2.21–2.12 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.47–1.35 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.34–1.20 (6H, m, CH_2CH_2CH_2CH$_3$), 0.94–0.86 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 171.2, 156.7, 140.3, 128.6, 128.4, 126.5, 101.1, 36.1, 33.4, 31.7, 31.1, 28.8, 26.5, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 1752, 1666, 1455, 1380, 1134, 1078, 956, 868, 750, 699; **LRMS (ESI) m/z**: 283.2 [$C_{17}H_{24}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{17}H_{24}NaO_2$, $(M+Na)^+$]: 283.1669; found 283.1668.

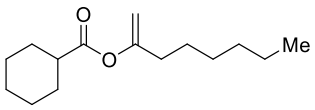
Oct-1-en-2-yl-2-cyclohexylacetate, **16s**



Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), cyclohexylacetic acid (42.7 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (100% petrol) to give enol ester **16s** as a light yellow oil (47 mg, 0.19 mmol, 62%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 4.70 (1H, app. q, *J* = 1.0 Hz, C=CH_AH$_B$), 4.68 (1H, d, *J* = 1.5 Hz, C=CH$_A$$H_B$), 2.25 (2H, d, *J* = 7.0 Hz, CH_2C=O), 2.22–2.14 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.89–1.62 (5H, m, C*H*-cy, 2 × C$_{cy}H_2$), 1.50–1.39 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.38–1.21 (9H, m, 1.5 × C$_{cy}H_2$, CH_2CH_2CH_2CH$_3$), 1.21–1.07 (1H, m, C$_{cy}H_2$), 1.06–0.92 (2H, m, C$_{cy}H_2$), 0.91–0.84 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 171.4, 156.8, 101.1, 42.3, 35.1, 33.5, 33.1, 31.7, 28.8, 26.6, 26.2, 26.1, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2926, 2855, 1753, 1666, 1450, 1381, 1214, 1153, 1114, 955, 866; **LRMS (ESI) m/z**: 275.0 [$C_{16}H_{28}NaO_2$,

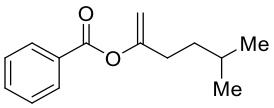
(M+Na)$^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{28}NaO_2$, (M+Na)$^+$]: 275.1982; found 275.1983.

Oct-1-en-2-ylcyclohexanecarboxylate, **16t**



Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), cyclohexanecarboxylic acid (38.5 mg, 0.30 mmol) and 1-octyne **2a** (89 µL), purified by column chromatography (1% EtOAc/petrol) to give enol ester **16t** as a light yellow oil with the Markovnikov and anti-Markovnikov isomers inseparable (52 mg, 0.22 mmol, 73%). M:AM = 87:13; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 4.74–4.64 (2H, m, C=CH_2), 2.38 (1H, tdt, *J* = 11.0, 7.0, 4.0 Hz, C_{cy}H), 2.23–2.14 (2H, m, CH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 2.00–1.90 (2H, m, $C_{cy}H_2$), 1.81–1.70 (2H, m, $C_{cy}H_2$), 1.67–1.58 (1H, m, 0.5 × $C_{cy}H_2$), 1.56–1.40 (4H, m, $C_{cy}H_2$, CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.36–1.24 (9H, m, 1.5 × $C_{cy}H_2$, CH$_2$CH$_2$CH$_2$CH$_3$), 0.93–0.84 (3H, m, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 174.4, 156.8, 100.9, 43.4, 33.5, 31.7, 29.1, 28.8, 26.5, 25.9, 25.5, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2930, 2857, 1749, 1666, 1452, 1374, 1311, 1244, 1153, 1127, 1034, 866; **LRMS (ESI) m/z**: 261.1 [$C_{15}H_{26}NaO_2$, (M+Na)$^+$]; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{26}NaO_2$, (M+Na)$^+$]: 261.1825; found 261.1827.

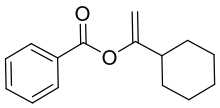
5-Methylhex-1-en-2-ylbenzoate, **16u**



Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 5-methyl-1-hexyne

(79 µL), purified by column chromatography (100% petrol) to give enol ester **16u** as a light yellow oil (48 mg, 0.22 mmol, 73%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.13–8.06 (2H, m, Ar-*H*), 7.59 (1H, ddt, *J* = 8.0, 7.0, 1.5 Hz, Ar-*H*), 7.52–7.41 (2H, m, Ar-*H*), 4.86 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.84 (1H, app. q, *J* = 1.5 Hz, C=CH_AH_B), 2.39–2.30 (2H, m, CH_2CH_2CH$(CH_3)_2$), 1.63 (1H, dt, *J* = 13.5, 6.5 Hz, C$H(CH_3)_2$), 1.49–1.39 (2H, m, CH_2CH$(CH_3)_2$), 0.91 (6H, d, *J* = 6.5 Hz, 2 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.9, 157.2, 133.4, 130.07, 130.05, 128.6, 101.3, 35.7, 31.5, 27.7, 22.6; **IR (cm^{-1})** $\tilde{\nu}$ = 2956, 2870, 1730, 1666, 1452, 1275, 1262, 1226, 1173, 1105, 1090, 1068, 1026, 867, 704; **HRMS (ESI) m/z**: calcd for [$C_{14}H_{19}O_2$, $(M+H)^+$]: 219.3180; found 219.1383.

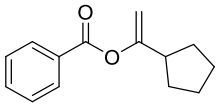
1-Cyclohexylvinyl benzoate, **16v**



Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and cyclohexylacetylene (78 µL), purified by column chromatography (100% petrol) to give enol ester **16v** as a light yellow oil (46 mg, 0.20 mmol, 67%); **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.14–8.06 (2H, m, Ar-*H*), 7.64–7.54 (1H, m, Ar-*H*), 7.52–7.43 (2H, m, Ar-*H*), 4.85–4.84 (1H, m, C=CH_AH_B), 4.83 (1H, d, *J* = 2.0 Hz, C=CH_AH_B), 2.30–2.19 (1H, m, H_2C=CC*H*), 2.04–1.93 (2H, m, CH_2), 1.84–1.72 (2H, m, CH_2), 1.72–1.63 (1H, m, CH_ACH_B), 1.36–1.10 (5H, m, CH_ACH_B, 2 × CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 165.0, 160.9, 133.4, 130.2, 130.1, 128.6, 99.8, 42.0, 30.8, 26.2, 26.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2929, 2854, 1732, 1660, 1451, 1382, 1269, 1239, 1216, 1193, 1167, 1132, 1090, 1067, 1025, 954, 871, 705;

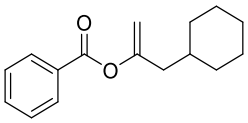
HRMS (ESI) m/z: calcd for [$C_{15}H_{19}O_2$, $(M+H)^+$]: 231.1380; found 231.1382. These data are consistent with literature.[94]

1-Cyclopentylvinylbenzoate, 16w



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), using benzoic acid **15a** (36.6 mg, 0.30 mmol) and cyclopentylacetylene (70 µL), purified by column chromatography (100% petrol) to give enol ester **16w** as a yellow oil (44 mg, 0.20 mmol, 68%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.13–8.06 (2H, m, Ar-*H*), 7.63–7.54 (1H, m, Ar-*H*), 7.51–7.42 (2H, m, Ar-*H*), 4.93–4.88 (1H, m, C=CH_AH$_B$), 4.85 (1H, d, *J* = 2.0 Hz, C=CH$_A$$H_B$), 2.78 (1H, p, *J* = 7.5 Hz, C*H*), 1.97–1.82 (2H, m, CH_2), 1.78–1.64 (2H, m, CH_2), 1.65–1.51 (4H, m, 2 × CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 165.0, 159.3, 133.4, 130.2, 130.0, 128.6, 100.0, 44.0, 30.7, 25.1; **IR (cm^{-1})** $\tilde{\nu}$ = 2958, 2870, 1731, 1660, 1451, 1314, 1267, 1225, 1175, 1092, 1067, 1026, 881, 865, 705; **HRMS (ESI) m/z**: calcd for [$C_{14}H_{17}O_2$, $(M+H)^+$]: 217.1223; found 217.1226.

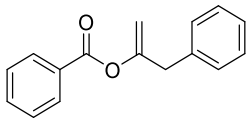
3-Cyclohexylprop-1-en-2-ylbenzoate 16x



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 3-cyclohexyl-1-propyne (87 µL), purified by column chromatography (100% petrol) to give enol ester **16x** as a yellow oil (54 mg, 0.22 mmol, 74%). **^{1}H NMR (400 MHz,**

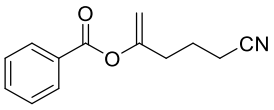
chloroform-*d*) δ 8.13–8.05 (2H, m, Ar-*H*), 7.64–7.55 (1H, m, Ar-*H*), 7.52–7.43 (2H, m, Ar-*H*), 4.89 (1H, d, *J* = 1.0 Hz, C=C*H*$_A$H$_B$), 4.81 (1H, d, *J* = 1.0 Hz, C=CH$_A$*H*$_B$), 2.27–2.21 (2H, m, CH$_2$=CC*H*$_2$), 1.86–1.76 (2H, m, C*H*$_2$), 1.80–1.59 (3H, m, 3 × C*H*$_2$), 1.59–1.41 (1H, m, CH$_2$=CCH$_2$C*H*), 1.31–1.07 (3H, m, 3 × C*H*$_2$), 1.01–0.86 (2H, m, C*H*$_2$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.9, 155.4, 133.4, 130.08, 130.05, 128.6, 102.7, 41.6, 35.4, 33.1, 26.5, 26.3; **IR (cm^{-1})** $\tilde{\nu}$ = 2923, 2851, 1733, 1666, 1450, 1272, 1252, 1221, 1189, 1174, 1091, 1068, 1026, 935, 865, 705; **LRMS (ESI) m/z**: 267.1 [$C_{16}H_{20}NaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{20}NaO_2$, $(M+Na)^+$]: 267.1356; found 267.1357. These data are consistent with literature.[94]

3-Phenylprop-1-en-2-ylbenzoate, **16y**



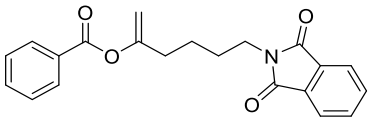
Prepared according to general procedure E using Cu(acac)$_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 3-phenyl-1-propyne (75 µL), purified by column chromatography (100% petrol) to give enol ester **16y** as a white solid with the Markovnikov and anti-Markovnikov isomers inseparable (53 mg, 0.22 mmol, 74%). M:AM = 82:18; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.05–7.98 (2H, m, Ar-*H*), 7.61–7.53 (1H, m, Ar-*H*), 7.47–7.40 (2H, m, Ar-*H*), 7.36–7.19 (5H, m, Ar-*H*), 4.99 (1H, d, *J* = 1.5 Hz, C=C*H*$_A$H$_B$), 4.82 (1H, d, *J* = 1.5 Hz, C=CH$_A$*H*$_B$), 3.68 (2H, s, C*H*$_2$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.9, 155.8, 137.0, 133.5, 130.10, 130.06, 129.4, 128.63, 128.57, 126.9, 103.3, 40.1; **MP (petrol)** = 48–50 °C**; IR (cm^{-1})** $\tilde{\nu}$ = 3062, 3028, 2981, 2927, 1731, 1452, 1266, 1228, 1166, 1092, 1027, 746, 700; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{14}NaO_2$, $(M+Na)^+$]: 261.0886; found 261.0887. These data are consistent with literature.[116]

5-Cyanopent-1-en-2-ylbenzoate, **16z**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 5-cyano-1-pentyne (63 µL), purified by column chromatography (0.1% EtOAc/petrol) to give enol ester **16z** as a yellow oil with the Markovnikov and anti-Markovnikov isomers inseparable (63 mg, 0.29 mmol, 98%). M:AM = 85:15; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.09–8.03 (2H, m, Ar-*H*), 7.65–7.56 (1H, m, Ar-*H*), 7.54–7.42 (2H, m, Ar-*H*), 5.03–4.90 (2H, m, C=CH_2), 2.52 (2H, td, *J* = 7.0, 1.0 Hz, CH_2CH$_2$CH$_2$CN), 2.45 (2H, t, *J* = 7.0 Hz, CH_2CN), 1.89 (2H, p, *J* = 7.0 Hz, CH_2CH$_2$CN); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 164.8, 153.9, 136.1, 133.7, 130.0, 128.7, 119.3, 103.6, 32.5, 22.5, 16.3; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2888, 1728, 1451, 1383, 1267, 1222, 1156, 1091, 1069, 954, 886, 706; **LRMS (ESI) m/z**: 238.0 [$C_{13}H_{13}NNaO_2$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{13}NNaO_2$, $(M+Na)^+$]: 238.0839; found 238.0843.

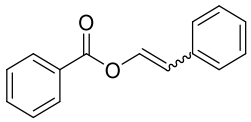
6-(1,3-Dioxoisoindolin-2-yl)hex-1-en-2-ylbenzoate, **16aa**



Prepared according to general procedure E using $Cu(acac)_2$ (7.9 mg, 0.03 mmol), dppb (12.8 mg, 0.03 mmol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and *N*-(5-hexynyl)-phthalimide (136.4 mg), purified by column chromatography (0.5% EtOAc/petrol) to give enol ester **16aa** as a white solid with the Markovnikov and anti-Markovnikov isomers inseparable (102 mg, 97%). M:AM = 89:11; *Markovnikov*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.05–8.00 (2H, m, Ar-*H*), 7.84–7.78 (2H, m,

Ar-*H*), 7.71–7.66 (2H, m, Ar-*H*), 7.57 (1H, ddt, *J* = 9.0, 7.0, 1.5 Hz, Ar-*H*), 7.46–7.38 (2H, m, Ar-*H*), 4.87 (1H, d, *J* = 1.5 Hz, C=CH_AH_B), 4.84 (1H, app. q, *J* = 1.5 Hz, C=CH_AH_B), 3.70 (2H, t, *J* = 7.5 Hz, CH_2N), 2.43–2.35 (2H, m, CH_2CH$_2$CH$_2$CH$_2$N), 1.76 (2H, tt, *J* = 7.5, 6.5 Hz, CH_2CH$_2$N), 1.65–1.54 (2H, m, CH_2CH$_2$CH$_2$N); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 168.5, 164.8, 156.0, 134.0, 133.4, 132.24, 132.23, 130.0, 128.6, 123.3, 102.11, 37.7, 33.1, 28.0, 23.9; **MP (petrol)** = 67–68 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3063, 2942, 2865, 1771, 1712, 1709, 1396, 1271, 1093, 924, 868, 708; **LRMS (ESI) m/z**: 372.2 [$C_{21}H_{19}NNaO_4$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{19}NNaO_4$, $(M+Na)^+$]: 372.1206; found 372.1208.

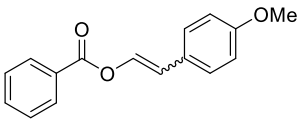
Styrylbenzoate, **17ab**



Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and phenylacetylene **2ab** (66 µL, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **17ab** as a yellow oil (60 mg, 0.27 mmol, 89%); *E*:*Z* = 1.0:2.4; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.23–8.15 (2H, m, Ar-*H*), 7.72–7.61 (3H, m, Ar-*H*), 7.57 (1H, d, *J* = 7.0 Hz, CO_2C*H*=CH), 7.56–7.49 (2H, m, Ar-*H*), 7.46–7.39 (2H, m, Ar-*H*), 7.40–7.32 (1H, m, Ar-*H*), 5.88 (1H, d, *J* = 7.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 134.31, 134.2, 133.9, 130.3, 129.3, 129.0, 128.85, 128.6, 127.5, 112.8; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.21–8.16 (2H, m, Ar-*H*), 8.13 (1H, d, *J* = 12.5 Hz, CO_2C*H*=CH), 7.67–7.61 (1H, m, Ar-*H*), 7.56–7.49 (2H, m, Ar-*H*), 7.45–7.40 (2H, m, Ar-*H*), 7.32–7.27 (2H, m, Ar-*H*), 6.62 (1H, d, *J* = 12.5 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.8, 136.6,

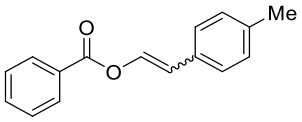
134.29, 133.8, 130.1, 129.1, 128.87, 128.7, 127.6, 126.4, 116.0; **IR (cm^{-1})** $\tilde{\nu}$ = 3061, 2981, 1732, 1658, 1602, 1493, 1450, 1315, 1263, 1177, 1117, 1092, 1070, 1026, 933, 781, 751, 705; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{13}O_2$, $(M+H)^+$]: 225.0910; found 225.0912. These data are consistent with literature.[114,213]

4-Methoxystyrylbenzoate, 17ac



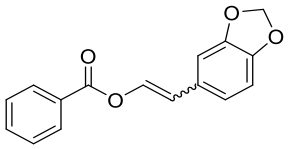
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 4-ethynylanisole (79.3 mg, 0.60 mmol), purified by column chromatography (1% EtOAc/petrol) to give enol ester **17ac** as a yellow solid (48 mg, 0.19 mmol, 63%); *E*:*Z* = 1.0:8.0; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.18 (2H, app. d (AA'BB'), J_{AB} + $J_{AB'}$ = 9.0 Hz, Ar-*H*), 7.67–7.60 (3H, m, Ar-*H*), 7.55–7.51 (2H, m, Ar-*H*), 7.47 (1H, d, *J* = 7.0 Hz, CO_2CH=CH), 6.95 (2H, app. d (AA'BB'), J_{BA} + $J_{BA'}$ = 9.0 Hz, Ar-*H*), 5.81 (1H, d, *J* = 7.0 Hz, CO_2CH=C*H*), 3.85 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.7, 158.9, 133.8, 132.9, 130.6, 130.2, 129.2, 128.9, 126.9, 114.1, 112.4, 55.4; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.17–8.14 (2H, m, Ar-*H*), 8.01 (2H, d, *J* = 13.0 Hz, CO_2CH=CH), 7.67–7.62 (3H, m, Ar-*H*), 7.36–7.31 (2H, m, Ar-*H*), 6.92–6.82 (2H, m, Ar-*H*), 6.58 (2H, d, *J* = 13.0 Hz, CO_2CH=C*H*), 3.82 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.9, 160.4, 135.2, 134.2, 133.7, 130.1, 128.7, 127.6, 115.6, 114.4, 114.2, 55.5; **MP (petrol)** = 36–38 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3099, 2920, 1732, 1606, 1511, 1263, 1175, 1093, 1070, 1027, 836, 706, 617; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{15}O_3$, $(M+H)^+$]: 255.1016; found 255.1018.

4-Methylstyrylbenzoate, **17ad**



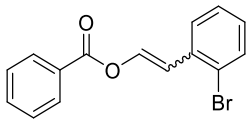
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 4-ethynyltoluene (69.7 mg, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **17ad** as a white solid (50 mg, 0.21 mmol, 71%); *E*:*Z* = 1.0:1.8; *AM-Z isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.23–8.13 (2H, m, Ar-*H*), 7.67–7.60 (1H, m, Ar-*H*), 7.61–7.54 (2H, m, Ar-*H*), 7.55–7.46 (2H, m, Ar-*H*), 7.52 (1H, d, *J* = 7.5 Hz, CO_2CH=CH), 7.23 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.0 Hz, Ar-*H*), 5.85 (1H, d, *J* = 7.5 Hz, CO_2CH=C*H*), 2.39 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 137.3, 133.8, 133.73, 131.39, 130.3, 129.34, 129.26, 129.2, 128.8, 112.8, 21.4; *AM-E isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.22–8.13 (2H, m, Ar-*H*), 8.08 (1H, d, *J* = 13.0 Hz, CO_2CH=CH), 7.68–7.60 (1H, m, Ar-*H*), 7.55–7.46 (m, 2H), 7.31 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.0 Hz, Ar-*H*), 7.16 (2H, d, *J* = 8.0 Hz, Ar-*H*), 6.58 (1H, d, *J* = 13.0 Hz, CO_2CH=C*H*), 2.36 (3H, s, CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.8, 137.5, 136.0, 133.71, 131.37, 130.1, 129.6, 129.1, 128.7, 126.3, 115.9, 21.3; **MP (petrol)** = 39–40 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2981 2889, 1733, 1661, 1602, 1452, 1384, 1262 1176, 1118, 1092, 1070, 1026, 947, 828, 705; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{15}O_2$, $(M+H)^+$]: 239.1067; found 239.1068.

2-(benzo[*d*][1,3]dioxol-5-yl)vinylbenzoate, **17ae**



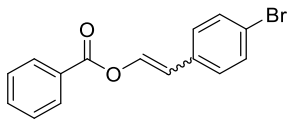
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 5-ethynylbenzo[*d*][1,3]dioxole (87.6 mg, 0.60 mmol), purified by column chromatography (0.1% EtOAc/petrol) to give enol ester **17ae** as a white solid (74 mg, 0.28 mmol, 92%); *E*:*Z* = 1.0:1.0; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.18–8.15 (2H, m, Ar-*H*), 7.67–7.62 (1H, m, Ar-*H*), 7.55–7.51 (2H, m, Ar-*H*), 7.45 (1H, d, *J* = 7.0 Hz, CO_2CH=CH), 7.30 (1H, d, *J* = 2.0 Hz, Ar-*H*), 7.06 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 6.85–6.83 (1H, m, Ar-*H*), 5.99 (2H, s, CH_2), 5.77 (1H, d, *J* = 7.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 147.9, 146.9, 133.9, 133.1, 130.2, 120.9, 129.08, 128.9, 112.5, 109.4, 108.5, 101.2 (only 13 C environments observed); *AM-E isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.14 (2H, dt, *J* = 8.5, 1.5 Hz, Ar-*H*), 7.97 (1H, d, *J* = 12.5 Hz, CO_2CH=CH), 7.64–7.59 (1H, m, Ar-*H*), 7.53–7.45 (2H, m, Ar-*H*), 6.93 (1H, d, *J* = 2.0 Hz, Ar-*H*), 6.83–6.80 (1H, m, Ar-*H*), 6.78 (1H, d, *J* = 8.0 Hz, Ar-*H*) 6.52 (1H, d, *J* = 12.5 Hz, CO_2CH=C*H*), 5.97 (2H, s, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.8, 148.3, 147.3, 135.5, 133.7, 130.1, 129.08, 128.7, 128.4, 123.5, 115.9, 108.7, 105.9, 101.3; **MP (petrol)** = 55–57 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2891, 1732, 1503, 1488, 1447, 1250, 1105, 1070, 1039, 936, 863, 814, 707; **HRMS (ESI) m/z**: calcd for [$C_{16}H_{13}O_4$, $(M+H)^+$]: 269.0808; found 269.0810.

2-Bromostyrylbenzoate, **17af**



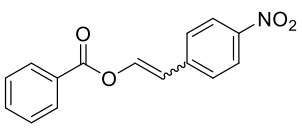
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 2-bromophenylacetylene (75 µL, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **17af** as a white solid (80 mg, 0.26 mmol, 88%); *E*:*Z* = 1.0:2.0; *AM-Z isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.12–8.07 (2H, m, Ar-*H*), 7.95 (1H, dd, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.66 (1H, d, *J* = 7.5 Hz, CO_2CH=CH), 7.65–7.61 (2H, m, Ar-*H*), 7.52–7.48 (2H, m, Ar-*H*), 7.38 (1H, td, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.20–7.10 (1H, m, Ar-*H*), 6.20 (1H, d, *J* = 7.5 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.3, 135.5, 134.0, 133.0, 131.1, 130.29, 129.0, 128.85, 128.75, 127.8, 127.3, 124.0, 111.5; *AM-E isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.22–8.14 (2H, m, Ar-*H*), 8.05 (1H, d, *J* = 13.0 Hz, CO_2CH=CH), 7.62–7.59 (1H, m, Ar-*H*), 7.58–7.52 (2H, m, Ar-*H*), 7.52–7.46 (2H, m, Ar-*H*), 7.32–7.27 (1H, m, Ar-*H*), 7.16–7.08 (1H, m, Ar-*H*), 6.94 (1H, d, *J* = 13.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.7, 138.1, 134.4, 133.9, 133.2, 130.26, 128.83, 128.80, 128.78, 127.5, 127.0, 123.8, 115.2; **MP (petrol)** = 42–43 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3010, 2923, 1736, 1656, 1601, 1468, 1452, 1435, 1260, 1128, 1107, 1091, 1070, 1026, 750, 705; **LRMS (ESI) m/z**: 326.0 [$C_{15}H_{11}NaO_2{}^{79}Br$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{12}O_2{}^{79}Br$, $(M(^{79}Br)+H)^+$]: 303.0015; found 303.0017; calcd for [$C_{15}H_{12}O_2{}^{81}Br$, $(M(^{81}Br)+H)^+$]: 304.9995; found 304.9996.

4-Bromostyrylbenzoate, **17ag**



Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 4-bromophenylacetylene (108.6 mg, 0.60 mmol), purified by column chromatography (0.1% EtOAc/petrol) to give enol ester **17ag** as a white solid (86 mg, 0.29 mmol, 95%); *E*:*Z* = 1.0:3.5; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.15 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.70–7.63 (1H, m, Ar-*H*), 7.58 (1H, d, *J* = 7.0 Hz, CO_2CH=CH), 7.54 (6H, bs, Ar-*H*), 5.81 (1H, d, *J* = 7.0 Hz, CO_2CH=CH); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.4, 134.9, 134.0, 133.9, 132.0, 131.8, 130.8, 130.2, 128.94, 121.3, 111.6; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.10 (1H, d, *J* = 13.0 Hz, CO_2CH=CH), 7.66–7.62 (2H, m, Ar-*H*), 7.54–7.51 (3H, m, Ar-*H*), 7.50–7.44 (2H, m, Ar-*H*), 7.30–7.25 (2H, m, Ar-*H*), 6.54 (1H, d, *J* = 13.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 137.1, 133.3, 133.2, 132.0, 128.88, 128.8, 128.7, 127.9, 114.9 (only 10 C environments observed); **MP (petrol)** = 65–66 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3101, 2981, 1733, 1658, 1486, 1452, 1262, 1241, 1176 1090, 1071, 1009, 835, 701; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{12}{}^{79}BrO_2$, (M(^{79}Br)+H)$^+$]: 303.0015; found 303.0016; calcd for [$C_{15}H_{12}{}^{81}BrO_2$, (M(^{81}Br)+H)$^+$]: 304.9995; found 304.9996.

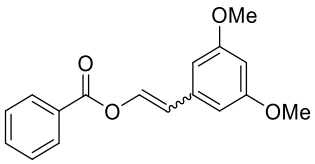
4-Nitrostyrylbenzoate, **17ah**



Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and

4-nitrophenylacetylene (88.3 mg, 0.60 mmol), purified by column chromatography (0.1% EtOAc/petrol) to give enol ester **17ah** as a white solid with the Markovnikov and anti-Markovnikov isomers inseparable (65 mg, 0.24 mmol, 80%); M:AM 1:99, *E*:*Z* = 1.0:0.7; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.25 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 9.0 Hz, Ar-*H*), 7.83–7.77 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 9.0 Hz, Ar-*H*), 7.71 (1H, d, *J* = 7.0 Hz, CO_2CH=CH), 7.69–7.62 (2H, m, Ar-*H*), 7.57–7.49 (3H, m, Ar-*H*), 5.92 (1H, d, *J* = 7.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.1, 146.5, 140.9, 137.4, 134.4, 129.8, 129.1, 128.42, 128.39, 124.0, 110.6, AM-*E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.24 (1H, d, *J* = 13.0 Hz, CO_2CH=CH), 8.21–8.17 (2H, m, Ar-*H*), 8.17–8.12 (3H, m, Ar-*H*), 7.58–7.48 (4H, m, Ar-*H*), 6.63 (1H, d, *J* = 13.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.4, 146.9, 141.4, 139.7, 134.2, 130.29, 130.27, 128.8, 126.8, 124.3, 114.0; **MP (petrol)** = 166–168 °C**; IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2889, 1717, 1656, 1579, 1511, 1473, 1462, 1382, 1344, 1252, 1152, 1073, 954, 858, 707; **HRMS (APCI) m/z**: calcd for [$C_{15}H_{12}NO_4$, $(M+H)^+$]: 270.0761; found 270.0761.

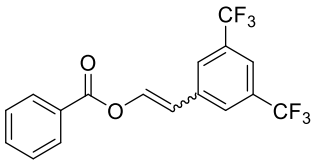
3,5-Dimethoxystyrylbenzoate, **17ai**



Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 3,5-dimethoxyphenylacetylene (97.3 mg, 0.60 mmol), purified by column chromatography (0.05% EtOAc/petrol) to give enol ester **17ai** as a white solid (75 mg, 0.26 mmol, 88%); *E*:*Z* = 1.0:1.0; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.23–8.18 (2H, m, Ar-H), 7.54 (1H, d, *J* = 7.0 Hz, CO_2CH=CH), 7.53–7.44 (3H, m, Ar-

H), 6.86 (2H, d, *J* = 2.5 Hz, Ar-*H*), 6.43 (1H, t, *J* = 2.5 Hz, Ar-*H*), 5.80 (1H, d, *J* = 7.0 Hz, CO_2CH=C*H*), 3.82 (6H, s, 2 × CH_3)**; ^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.7, 161.2, 136.2, 135.9, 133.8, 130.15, 129.0, 128.7, 16.1, 104.5, 100.0, 55.5; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.18–8.11 (2H, m, Ar-*H*), 8.10 (1H, d, *J* = 12.5 Hz, CO_2C*H*=CH), 7.69–7.56 (3H, m, Ar-*H*), 6.55 (2H, *J* = 2.0 Hz, Ar-*H*), 6.53 (1H, d, *J* = 12.5 Hz, CO_2CH=C*H*), 6.39 (1H, t, *J* = 2.0 Hz, Ar-*H*), 3.82 (6H, s, 2 × CH_3); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.4, 160.9, 137.0, 134.6, 133.9, 130.23, 29.1, 128.8, 112.8, 107.4, 100.3, 55.4; **MP (petrol)** = 52–53 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 2936, 2839, 1734, 1659, 1592, 1454, 1426, 1391, 1301, 1262, 1237, 1205, 1177, 1155, 1094, 1069, 1024, 929, 844, 707, 685; **HRMS (ESI) m/z**: calcd for [$C_{17}H_{17}O_4$, $(M+H)^+$]: 285.1121; found 285.1123.

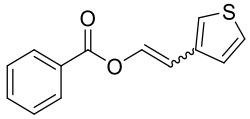
3,5-Bis(trifluoromethyl)styrylbenzoate, **17aj**



Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 3,5-di-(trifluoromethyl)phenylacetylene (106 µL, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **17aj** as a yellow oil (68 mg, 0.19 mmol, 63%); *E*:*Z* = 1.0:1.7; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.19–8.13 (3H, m, Ar-*H*), 7.82–7.72 (2H, m, Ar-*H*), 7.76 (1H, d, *J* = 7.0 Hz, CO_2C*H*=CH), 7.67–7.62 (1H, m, Ar-*H*), 7.56–7.52 (2H, m, Ar-*H*), 5.92 (1H, d, *J* = 7.0 Hz, Ar-*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 162.9, 137.1, 136.3, 134.4, 132.0 (q, ^{2}J = 33.0 Hz), 123.5 (q, ^{3}J = 273.0 Hz), 129.05, 128.9, 128.3, 126.12, 120.8 (app. q, ^{3}J = 4.0 Hz), 109.7; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.23 (1H, d,

J = 13.0 Hz, CO_2CH=CH), 8.18–8.13 (3H, m, Ar-*H*), 7.81–7.77 (2H, m, Ar-*H*), 7.66–7.63 (1H, m, Ar-*H*), 7.54–7.49 (1H, m, Ar-*H*), 6.64 (1H, d, *J* = 13.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.5, 139.3, 136.8, 134.2, 132.3 (q, ^2J = 33.5 Hz), 129.08, 129.03, 128.4, 126.16, 123.4 (q, ^1J = 273.0 Hz) 121.0 (app. q, ^3J = 4.0 Hz), 113.5; **^{19}F NMR (377 MHz, Chloroform-*d*)** δ −63.0, −63.1; **IR (cm^{-1})** $\tilde{\nu}$ = 3098, 2928, 1745, 1360, 1278, 1259, 1239, 1178, 1132, 1090, 897, 682; **HRMS (APCI) m/z**: calcd for [$C_{17}H_{11}F_6O_2$, $(M+H)^+$]: 361.0658; found 361.0661.

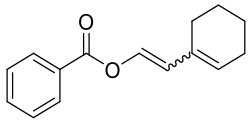
2-(Thiophen-3-yl)vinylbenzoate, **17ak**



Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 3-ethynylthiophene (59 µL, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **17ak** as a yellow oil (52 mg, 0.23 mmol, 75%); *E*:*Z* = 1.0:2.8; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.21–8.16 (2H, m, Ar-*H*), 7.68–7.63 (1H, m, Ar-*H*), 7.57–7.52 (3H, m, Ar-*H*), 7.49 (1H, d, *J* = 7.0 Hz, CO_2CH=CH), 7.44 (1H, dd, *J* = 5.0, 1.0 Hz, Ar-*H*), 7.35 (1H, dd, *J* = 5.0, 3.0 Hz, Ar-*H*), 5.96 (1H, d, *J* = 7.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 136.7, 135.0, 133.9, 133.4, 130.2, 128.9, 128.6, 125.6, 124.4, 107.4; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.16–8.12 (2H, m, Ar-*H*), 8.02 (1H, d, *J* = 13.0 Hz, CO_2CH=CH), 7.63–7.60 (1H, m, Ar-*H*), 7.52–7.50 (2H, m, Ar-*H*), 7.34–7.31 (1H, m, Ar-*H*), 7.23 (1H, dd, *J* = 5.0, 1.5 Hz, Ar-*H*), 7.18 (1H, dd, *J* = 3.0, 1.5 Hz, Ar-*H*), 6.62 (1H, d, *J* = 13.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.8, 135.6, 133.8, 130.1, 129.2, 129.1, 128.7, 126.6, 124.9, 122.0, 110.7; **IR (cm^{-1})** $\tilde{\nu}$ = 3103, 2981,

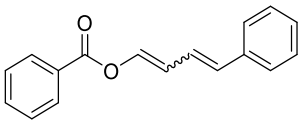
1731, 1602, 1451, 1416, 1264, 1176, 1092, 1070, 1027, 929, 795, 706; **HRMS (ESI) m/z**: calcd for [$C_{13}H_{11}O_2S$, $(M+H)^+$]: 231.0474; found 231.0477.

2-(Cyclohex-1-en-1-yl)vinylbenzoate, **17al**



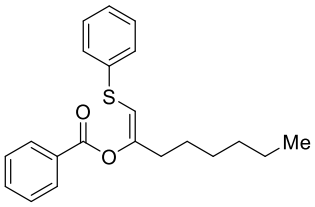
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and cyclohexylphenylacetylene (71 µL, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **17al** as a white solid (54 mg, 0.24 mmol, 79%); *E*:*Z* = 1.0:0.5; *AM-Z isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.11–8.08 (2H, m, Ar-*H*), 7.63–7.59 (1H, m, Ar-*H*), 7.51–7.44 (2H, m, Ar-*H*), 7.15 (1H, dd, *J* = 7.0, 1.0 Hz, CO_2CH=CH), 5.89 (1H, dp, *J* = 4.0, 2.0, 1.5 Hz, C=C*H*CH_2), 5.38 (1H, dd, *J* = 7.0, 1.0 Hz, CO_2CH=C*H*), 2.58 (2H, tq, *J* = 6.5, 2.5 Hz, CH_2), 2.23–2.12 (2H, m, CH_2), 1.78–1.67 (2H, m, CH_2), 1.67–1.58 (2H, m, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*) δ** 163.6, 133.5, 133.2, 131.1, 130.0, 129.92, 129.3, 128.6, 116.2, 28.3, 26.0, 22.9, 21.9; *AM-E isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.12–8.09 (2H, m, Ar-*H*), 7.63–7.57 (1H, m, Ar-*H*), 7.53 (1H, d, *J* = 12.5 Hz, CO_2CH=CH), 7.50–7.44 (2H, m, Ar-*H*), 6.23 (1H, d, *J* = 12.5 Hz, CO_2CH=C*H*), 5.77 (1H, tdd, *J* = 4.5, 3.5, 3.0, 1.5 Hz, C=C*H*CH_2), 2.23–2.12 (4H, m, 2 × CH_2), 1.78–1.67 (2H, m, CH_2), 1.67–1.58 (2H, m, CH_2); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.9, 133.9, 133.4, 132.2, 130.3, 129.90, 129.2, 128.5, 119.7, 25.9, 24.7, 22.4, 22.3; **MP (petrol)** = 61–62 °C**; IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 2889, 1729, 1472, 1383, 1262, 1243, 1175, 1165, 1093, 1070, 954, 802, 704; **HRMS (ESI) m/z**: calcd for [$C_{15}H_{16}NaO_2$, $(M+Na)^+$]: 251.0425; found 251.0434.

4-Phenylbuta-1,3-dien-1-ylbenzoate, **17am**



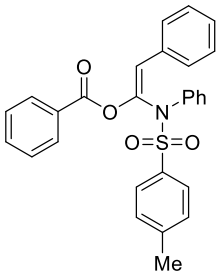
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and (*E*)-but-1-en-3-yn-1-ylbenzene **2am** (77 mg, 0.60 mmol), purified by column chromatography (2% EtOAc/petrol) to give enol ester **17am** as a yellow solid (47 mg, 0.19 mmol, 63%); *E*:*Z* = 1.0:1.7; *AM-Z isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.23–8.18 (2H, m, Ar-*H*), 7.69–7.62 (1H, m, Ar-*H*), 7.61–7.47 (2H, m, Ar-*H*), 7.58–7.54 (1H, m, CO_2CH=CH), 7.45–7.27 (5H, m, Ar-*H*), 7.32–7.28 (1H, m, C*H*=CHAr) 6.66 (1H, d, *J* = 16.0 Hz, CH=C*H*Ar), 5.83 (1H, ddd, *J* = 11.0, 6.5, 1.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.2, 137.26, 134.7, 133.82, 133.0, 129.2, 128.89, 128.85, 128.8, 128.0, 126.7, 121.0, 113.9; *AM-E isomer*: **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.15 (2H, dd, *J* = 8.5, 1.5 Hz, Ar-*H*), 7.81 (1H, dd, *J* = 12.0, 1.0 Hz, CO_2CH=CH), 7.68–7.58 (1H, m, Ar-*H*), 7.55–7.47 (2H, m, Ar-*H*), 7.47–7.27 (5H, m, Ar-*H*), 6.87–6.77 (1H, m, C*H*=CHAr), 6.62 (1H, d, *J* = 16.0 Hz, CH=C*H*Ar), 6.43 (1H, ddd, *J* = 12.0, 11.0, 1.0 Hz, CO_2CH=C*H*); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.5, 139.1, 137.29, 133.77, 132.5, 130.1, 129.0, 128.86, 128.7, 127.7, 126.3, 123.9, 116.6; **IR (cm^{-1})** $\tilde{\nu}$ = 3060, 3026, 1731, 1648, 1600, 1492, 1450, 1262, 1205, 1133, 1116, 1068, 1025, 1001, 745, 706, 691; **HRMS (ESI) m/z**: calcd for [$C_{17}H_{15}O_2$, $(M+H)^+$]: 251.1067; found 251.1067. No melting point obtained as solid is not stable.

(*Z*)-1-(Phenylthio)oct-1-en-2-ylbenzoate, **20**



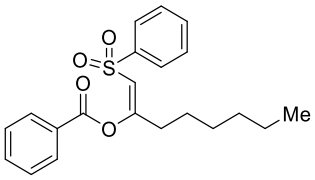
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 1-(phenylthio)oct-1-yn-3-one (131 mg, 0.60 mmol), purified by column chromatography (100% petrol) to give enol ester **20** as a light yellow oil (36 mg, 0.11 mmol, 35%), *E*/*Z* = 1.0:15. *(Z)-isomer:* **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.19–8.08 (2H, m, Ar-*H*), 7.65–7.58 (1H, m, Ar-*H*), 7.54–7.44 (2H, m, Ar-*H*), 7.41–7.35 (2H, m, Ar-*H*), 7.34–7.27 (2H, m, Ar-*H*), 7.23–7.17 (1H, m, Ar-*H*), 5.96 (1H, d, *J* = 1.0 Hz, SC*H*), 2.53–2.43 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.63–1.51 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.43–1.22 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.89 (t, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.9, 151.8, 135.8, 133.6, 132.1, 130.3, 129.3, 129.1, 128.6, 126.6, 110.3, 34.2, 31.7, 28.9, 26.7, 22.7, 14.2; **IR (cm^{-1})** $\tilde{\nu}$ = 2981, 2930, 1734, 1479, 1452, 1363, 1235, 1139, 1083, 1065, 1025, 955, 740, 706, 690; **LRMS (ESI) m/z**: 363.0 [$C_{21}H_{24}NaO_2S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{24}NaO_2S$, $(M+Na)^+$]: 363.1389; found 363.1390. The stereochemistry of the product was confirmed by NOESY experiment.

(*E*)-1-((4-methyl-*N*-phenylphenyl)sulfonamido)-2-phenylvinylbenzoate, **22**



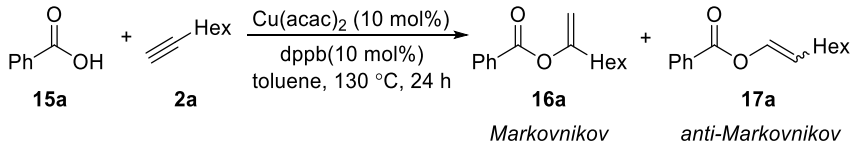
Prepared according to general procedure E using Cu_2O (2.1 mg, 0.03 mmol), 1,10-phenanthroline (5.4 mg, 0.03 mol), benzoic acid **15a** (36.6 mg, 0.30 mmol) and 4-methyl-*N*-phenyl-*N*-(phenylethynyl)benzenesulfonamide (104 mg, 0.60 mmol), purified by column chromatography (5% EtOAc/petrol) and recrystallised in pentane/Et_2O to give enol ester **22** as a white crystalline solid (80 mg, 0.17 mmol, 57%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.89 (2H, app. d (AA'BB'), $J_{AB} + J_{AB'}$ = 8.5 Hz, Ar-*H*), 7.70 – 7.65 (2H, m, Ar-*H*), 7.63 (1H, app. t, *J* = 9.0 Hz, Ar-*H*), 7.56–7.49 (2H, m, Ar-*H*), 7.49–7.41 (2H, m, Ar-*H*), 7.38–7.33 (2H, m, Ar-*H*), 7.33–7.27 (3H, m, Ar-*H*), 7.25–7.18 (3H, m, Ar-*H*), 7.04 (2H, app. d (AA'BB'), $J_{BA} + J_{BA'}$ = 8.5 Hz, Ar-*H*), 6.66 (1H, s, C=C*H*), 2.32 (3H, s, CH_3)**; ^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.6, 144.0, 139.3, 138.8, 136.6, 133.9, 132.3, 130.3, 129.4, 129.2, 129.14, 129.12, 128.6, 128.5, 128.4, 128.3, 128.0, 127.1, 122.2, 21.6; **MP (Pentane/Et_2O)** = 117–118 °C; **IR (cm^{-1})** $\tilde{\nu}$ = 3063, 2924, 1744, 1598, 1491, 1450, 1361, 1244, 1228, 1213, 1166, 1091, 1077, 1053, 1002, 904, 814, 753, 732, 692, 664, 609; **LRMS (ESI) m/z**: 492.2 [$C_{28}H_{23}NNaO_4S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{28}H_{23}NNaO_4S$, $(M+Na)^+$]: 492.1240; found 492.1240. Configuration of enol ester **22** was determined *via* X-ray crystallography.

(*Z*)-1-(phenylsulfonyl)oct-1-en-2-yl benzoate, **24**



Prepared according to a modified literature procedure.[214] To an oven-dried, round-bottomed 10 mL microwave reaction vial equipped with a stirrer was added enol ester **20** (68.0 mg, 0.2 mmol) in acetic acid (1 mL). Hydrogen peroxide (30% w/w in H_2O, 1.5 ml) was added carefully before the vial was sealed with a microwave vial cap, and the resulting mixture was heated at 120 °C for 1 h before stirring at rt for 16 h. The resulting crude mixture was extracted with CH_2Cl_2 (2 mL), dried over $MgSO_4$ and purified by column chromatography (10% EtOAc/petrol) to give enol ester **24** as a light brown oil (29 mg, 0.08 mmol, 38%). **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.06–7.98 (2H, m, Ar-*H*), 7.89–7.81 (2H, m, Ar-*H*), 7.68–7.60 (1H, m, Ar-*H*), 7.59–7.50 (1H, m, Ar-*H*), 7.53–7.45 (2H, m, Ar-*H*), 7.49–7.36 (2H, m, Ar-*H*), 6.25 (1H, t, *J* = 1.0 Hz, SC*H*), 2.48–2.40 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.57–1.45 (2H, m, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.36–1.16 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.87–0.81 (3H, m, C*H*$_3$)**; ^{13}C NMR (101 MHz, chloroform-*d*)** δ 163.1, 162.9, 14d1.6, 134.2, 133.4, 130.5, 129.1, 128.8, 128.6, 127.8, 119.2, 34.6, 31.5, 28.6, 25.9, 22.5, 14.1; **IR (cm^{-1}) $\tilde{\nu}$** = 2981, 2930, 2889, 1741, 1462, 1449, 1382, 1323, 1237, 1151, 1060, 1024, 955, 754, 706, 688; **LRMS (ESI) m/z**: 395.2 [$C_{21}H_{24}NaO_4S$, $(M+Na)^+$]; **HRMS (ESI) m/z**: calcd for [$C_{21}H_{24}NaO_4S$, $(M+Na)^+$]: 395.1288; found 395.1287.

5.3.3 Gramme-scale Synthesis of Enol Ester 16a

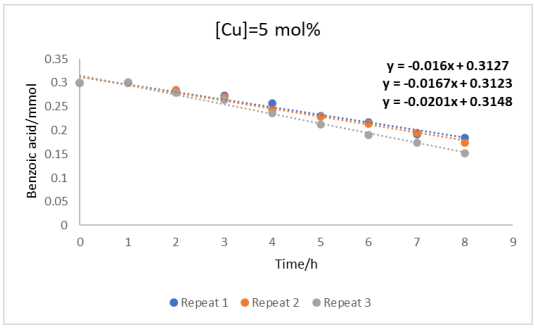


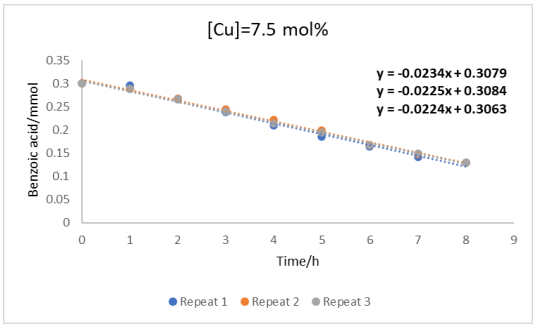
Commercially purchased 1-octyne **2a** was purified prior to use by distillation. An oven-dried round bottom flask (100 mL) fitted with a reflux condenser was charged with benzoic acid **15a** (1.10 g, 9.0 mmol, 1.0 equiv.), $Cu(acac)_2$ (235.5 mg, 0.90 mmol, 0.10 equiv.) and dppb (383.8 mg, 0.90 mmol, 0.10 equiv.). The flask was then evacuated and back-filled with N_2 three times. Degassed dry toluene (30 mL) and degassed 1-octyne (2.7 mL, 18.0 mmol, 2.0 equiv.) were added sequentially under N_2 atmosphere, and the mixture was heated at 130 °C for 24 h under N_2. It was then cooled to rt, filtered through silica (washed down with EtOAc), concentrated *in vacuo*, and purified by column chromatography (100% petrol) to give enol ester **16a** (1.84 g, 7.5 mmol, 83%) as a yellow oil. The data are consistent with those obtained for the small-scale reaction.

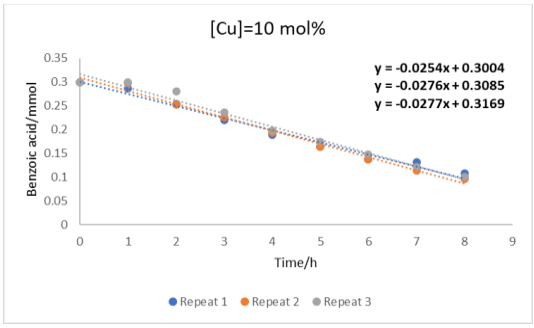
5.3.4 Kinetics Studies

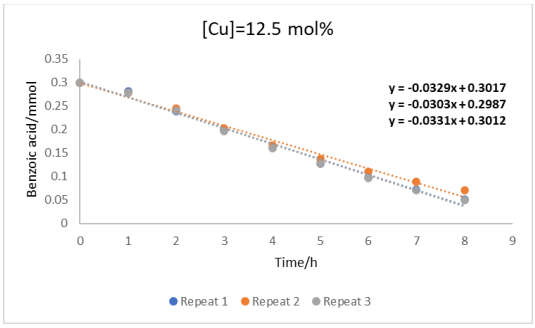
i) Calculation of rate order with respect to $Cu(acac)_2$/dppb:

Prepared according to general procedure E for enol ester synthesis. Aliquots were obtained every hour for 8 hours and analysed using HPLC to observe consumption of benzoic acid **15a**. 5 different $Cu(acac)_2$/dppb amount used: 5 mol%, 7.5 mol%, 10 mol%, 12.5 mol% and 15 mol%, with the ratio of $Cu(acac)_2$:dppb maintained at 1:1. The average ln(k) values were obtained and plotted against ln[Cu] to obtain the rate order (Table 5.1).









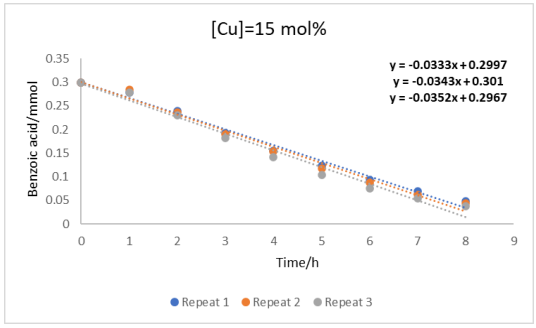


Table 5.1. Data calculation to obtain average ln(rate) values

	[Cu(acac)$_2$/dppb]									
	5 mol%		7.5 mol%		10 mol%		12.5 mol%		15 mol%	
Repeats	Rate, k	ln(k)	Rate, k	ln(k)	Rate, k	ln(k)	Rate, k	ln(k)	Rate, k	ln(k)
1	0.0160	-4.14	0.0234	-3.76	0.0254	-3.67	0.0325	-3.41	0.0333	-3.40
2	0.0167	-4.09	0.0225	-3.79	0.0276	-3.59	0.0303	-3.50	0.0343	-3.37
3	0.0201	-3.91	0.0224	-3.80	0.0277	-3.57	0.0331	-3.41	0.0352	-3.35
Average	0.0176	-4.04	0.0228	-3.78	0.0269	-3.62	0.0321	-3.44	0.0343	-3.37
SD	0.0990		0.0196		0.0400		0.0403		0.0227	
ln[Cu]	-4.20		-3.79		-3.51		-3.28		-3.10	

ii) Plot of rate of reaction, k against pK_a of benzoic acids, and Hammett plot using 1-octyne 2a

Prepared as stated in (i). Aliquots were obtained every hour for 6 hours and analysed using HPLC to observe benzoic acid consumption. 5 different *para*-substituted benzoic acids used (R= OMe, H, Br, CF_3, NO_2). The average k values were obtained (method as in (i)) and plotted against pK_a. Derived data was also used to plot the Hammett plot.

iii) Hammett plot using phenylacetylene 2ab

Prepared as stated in (i). Aliquots were obtained every 15 min for 2 hours and analysed using HPLC to observe benzoic acid consumption. 5 different *para*-substituted benzoic acids used (R= OMe, Me, H, Br, CF_3). The rate, k values obtained (method as in (i)) were used to plot the Hammett plot.

References

1. F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, **2004**, *104*, 3079–3159.
2. F. Aznar, R. Liz, R. Rodes and J. Barluenga, *J. Chem. Soc. Perkin Trans 1*, **1980**, 2732–2737.
3. F. Aznar and J. Barluenga, *Synthesis*, **1977**, 195–196.
4. Y. Li and T. J. Marks, Organometallics, **1996**, *15*, 3770–3772.
5. A. Haskel, T. Straub and M. S. Eisen, *Organometallics*, **1996**, *15*, 3773–3775.
6. T. Straub, A. Haskel, T. G. Neyroud, M. Kapon, M. Botoshansky and M. S. Eisen, *Organometallics*, **2001**, *20*, 5017–5035.
7. Y. Uchimaru, *Chem. Commun.*, **1999**, 1133–1134.
8. M. Tokunaga, M. Eckert and Y. Wakatsuki, *Angew. Chem. Int. Ed.*, **1999**, *38*, 3222–3225.
9. S. Burling, L. D. Field and B. A. Messerle, *Organometallics*, **1999**, *19*, 87–90.
10. C. G. Hartung, A. Tillack, H. Trauthwein and M. Beller, *J. Org. Chem.*, **2001**, *66*, 6339–6343.
11. Q. Chen, Z. Chen and V. M. Dong, *J. Am. Chem. Soc.*, **2015**, *137*, 8392–8395.
12. S. K. Alamsetti, A. K. A. Persson and J. E. Bäckvall, *Org. Lett.*, **2014**, *16*, 1434–1437.
13. K. Utimoto, H. Miwa and H. Nozaki, *Tetrahedron Lett.*, **1981**, *22*, 4277–4278.
14. K. Iritani, S. Matsubara and K. Utimoto, *Tetrahedron Lett.*, **1988**, *29*, 1799–1802.
15. D. E. Rudisill and J. K. Stille, *J. Org. Chem.*, **1989**, *54*, 5856–5866.
16. Y. Fukuda, S. Matsubara and K. Utimoto, *J. Org. Chem.*, **1991**, *56*, 5812–5816.
17. H. Sashida and A. Kawamukai, *Synthesis*, **1999**, *7*, 1145–1148.
18. T. Shimada and Y. Yamamoto, *J. Am. Chem. Soc.*, **2002**, *124*, 12670–12671.

19. P. J. Walsh, A. M. Baranger and R. G. Bergman, *J. Am. Chem. Soc*., **1992**, *114*, 1708–1719
20. A. M. Baranger, P. J. Walsh and R. G. Bergman, *J. Am. Chem. Soc*., **1993**, *115*, 2753–2763.
21. A. Tillack, I. G. Castro, C. G. Hartung and M. Beller, *Angew. Chem. Int. Ed*., **2002**, *41*, 2541–2543.
22. I. G. Castro, A. Tillack, C. G. Hartung and M. Beller, *Tetrahedron Lett.*, **2003**, *44*, 3217–3221.
23. A. Tillack, V. Khedkar and M. Beller, *Tetrahedron Lett.*, **2004**, *45*, 8875–8878.
24. A. Tillack, V. Khedkar, H. Jiao and M. Beller, *Eur. J. Org. Chem.*, **2005**, 5001–5012.
25. B. F. Straub and R. G. Bergman, *Angew. Chem. Int. Ed*., **2001**, *40*, 4632–4635.
26. J. S. Johnson and R. G. Bergman, *J. Am. Chem. Soc*., **2001**, *123*, 2923–2924.
27. E. Haak, I. Bytschkov and S. Doye, *Angew. Chem. Int. Ed*., **1999**, *38*, 3389–3391.
28. E. Haak, H. Siebeneicher and S. Doye, *Org. Lett.*, **2000**, *2*, 1935–1937.
29. A. Heutling and S. Doye, *J. Org. Chem*., **2002**, *67*, 1961–1964.
30. A. Heutling, F. Pohlki and S. Doye, *Chem. Eur. J.*, **2004**, *10*, 3059–3071.
31. K. Marcsekova, B. Wegener and S. Doye, *Eur. J. Org. Chem*., **2005**, 4843–4851.
32. A. Heutling, F. Pohlki, I. Bytschkov and S. Doye, *Angew. Chem. Int. Ed.*, **2005**, *44*, 2951–2954.
33. S. Doye, *Synlett*, **2005**, *10*, 1653–1672.
34. A. Heutling, R. Severin and S. Doye, *Synthesis*, **2005**, *7*, 1200–1204.
35. Y. Shi, J. T. Ciszewski and A. L. Odom, *Organometallics*, **2001**, *20*, 3967–3969.
36. C. Cao, J. T. Ciszewski and A. L. Odom, *Organometallics*, **2001**, *20*, 5011–5013.
37. Y. Shi, J. T. Ciszewski and A. L. Odom, *Organometallics*, **2002**, *21*, 5148.

38. Y. Li, Y. Shi and A. L. Odom, *J. Am. Chem. Soc*., **2004**, *126*, 1794–1803.
39. C. Li, R. K. Thomson, B. Gillon, B. O. Patrick and L. L. Schafer, *Chem. Comm*., **2003**, 2462–2463.
40. Z. Zhang and L. L. Schafer, *Org. Lett*., **2003**, *5*, 4733–4736.
41. A. V. Lee and L. L. Schafer, *Organometallics*, **2006**, *25*, 5249–5254.
42. Y. Fukuda, K. Utimoto and H. Nozaki, *Heterocycles*, **1987**, *25*, 297–300.
43. Y. Fukuda and K. Utimoto, *Synthesis*, **1991**, *11*, 975–978.
44. X. Zhang, Y. Zhou, H. Wang, D. Guo, D. Ye, Y. Xu, H. Jiang and H. Liu, *Green Chem*., **2011**, *13*, 397–405.
45. V. H. L. Wong, T. S. A. Hor and K. K. (Mimi) Kuok, *Chem. Comm*., **2013**, *49*, 9272–9274.
46. A. Arcadi, S. Di Giuseppe, F. Marinelli and E. Rossi, *Tetrahedron Lett*., **2001**, *12*, 2715–2720.
47. A. Arcadi, G. Bianchi and F. Marinelli, *Synthesis*, **2004**, *4*, 610–618.
48. D. Kadzimirsz, D. Hildebrandt, K. Merz and G. Dyker, *Chem. Comm.*, **2006**, *49*, 661–662.
49. J. Kang, H. Kim, J. Lee and S. Shin, *Org. Lett.*, **2006**, *8*, 3537–3540.
50. D. Ye, X. Zhang, Y. Zhou, D. Zhang, L. Zhang, H. Wang, H. Jiang and H. Liu, *Adv. Synth. Catal.*, **2009**, *351*, 2770–2778.
51. J. M. Carney, P. J. Donoghue, W. M. Wuest, O. Wiest and P. Helquist, *Org. Biomol. Chem.*, **2008**, *10*, 3905–2906.
52. J. Hee, S. Bin, W. Koo, D. Yoon and H. Ha, *Tetrahedron*, **2011**, *67*, 3553–3558.
53. H. M. Wisniewska and E. R. Jarvo, *Chem. Sci*., **2011**, *2*, 807–810.
54. H. Cao, X. Wang, H. Jiang, Q. Zhu, M. Zhang and H. Liu, *Chem. Eur. J*., **2008**, *14*, 11623–11633.

55. X. Zhang, B. Yang, G. Li, X. Shu, D. C. Mungra and J. Zhu, *Synlett*, **2012**, *23*, 622–626.
56. E. Mizushima, T. Hayashi and M. Tanaka, *Org. Lett.*, **2003**, *5*, 3349–3352.
57. Y. Zhang, J. P. Donahue and C. Li, *Org. Lett.*, **2007**, *9*, 627–630.
58. Y. Xi, T. W. Butcher, J. Zhang and J. F. Hartwig, *Angew. Chem. Int. Ed.*, **2016**, *55*, 776–780.
59. Y. Miki, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.*, **2013**, *52*, 10830–10834.
60. K. D. Hesp, *Angew. Chem. Int. Ed.*, **2014**, *53*, 2034–2036.
61. M. T. Pirnot, Y. M. Wang and S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2016**, *55*, 48–57.
62. D. Nishikawa, K. Hirano and M. Miura, *J. Am. Chem. Soc.*, **2015**, *137*, 15620–15623.
63. Y. Miki, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, **2014**, *16*, 1498–1501.
64. H. Ohmiya, T. Moriya and M. Sawamura, *Org. Lett.*, **2009**, *11*, 2145–2147.
65. C. Michon, F. Medina, F. Capet, P. Roussel and F. Agbossou-Niedercorn, *Adv. Synth. Catal.*, **2010**, *352*, 3293–3305.
66. S. Zhu, N. Niljianskul and S. L. Buchwald, *J. Am. Chem. Soc.*, **2013**, *135*, 15746–15749.
67. S. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, **2014**, *136*, 15913–15916.
68. Y. Yang, S. Shi, D. Niu, P. Liu and S. L. Buchwald, *Science*, **2015**, *349*, 62–66.
69. N. Niljianskul, S. Zhu and S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2015**, *54*, 1638–1641.
70. H. Ito and M. Ueda, *Macromolecules*, **1990**, *23*, 2885–2894.
71. K. Yamada, T. Nakano and Y. Okamoto, *Macromolecules*, **1998**, *31*, 7598–7605.

72. M. T. Reetz, L. J. Goossen, A. Meiswinkel, J. Paetzold and J. F. Jensen, *Org. Lett.*, **2003**, *5*, 3099–3101.

73. T. M. Konrad, P. Schmitz, W. Leitner and G. Franciò, *Chem. Eur. J.*, **2013**, *19*, 13299–13303.

74. P. Kleman, P. J. Gonzalez-Liste, S. E. García-Garrido, V. Cadierno and A. Pizzano, *Chem. Eur. J*., **2013**, *19*, 16209–16212.

75. P. Kleman, P. J. Gonzalez-Liste, S. E. Garcia-Garrido, V. Cadierno and A. Pizzano, *ACS Catal.*, **2014**, *4*, 4398–4408.

76. L. J. Gooßen and J. Paetzold, *Angew. Chem. Int. Ed*., **2004**, *43*, 1095–1098.

77. J. Yu and R. Kuwano, *Angew. Chem. Int. Ed.*, **2009**, *48*, 7217–7220.

78. C. Sun, Y. Wang, X. Zhou, Z. Wu, B. Li, B. Guan and Z. Shi, *Chem. Eur. J*., **2010**, *16*, 5844–5847.

79. N. Isambert, M. Cruz, M. J. Arevalo, E. Gomez and R. Lavilla, *Org. Lett*., **2007**, *9*, 4199–4202.

80. M. Yamamoto, *Jpn. Chem. Soc. Chem. Comm*., **1978**, 649–650.

81. M. Yamamoto, *J. Chem. Soc. Perkin Trans 1*, **1981**, 582–587.

82. R. C. Larock, K. Oertle and K. M. Beatty, *J. Am. Chem. Soc*., **1980**, *102*, 1966–1974.

83. E. Musengimana and C. Fatakanwa, *J. Iran. Chem. Soc*., **2016**, *13*, 253–259.

84. J. Jeschke, C. Gäbler and H. Lang, *J. Org. Chem.*, **2016**, *81*, 476–484.

85. H. Doucet, B. Martin-Vaca, C. Bruneau and P. H. Dixneuf, *J. Org. Chem*., **1995**, *60*, 7247–7255.

86. M. J. Stark, D. T. Tang, N. P. Rath and E. B. Bauer, *Tetrahedron Lett*., **2018**, *59*, 873–877.

87. M. Rotem, I. Goldberg, U. Shmueli and Y. Shvo, *J. Organomet. Chem*., **1986**, *314*, 185–212.
88. M. Rotem and Y. Shvo, *Organometallics*, **1983**, *2*, 1689–1691.
89. H. Doucet, J. Hofer, C. Bruneau and P. H. Dixneuf, *J. C. S. Chem. Comm*., **1993**, 850–851.
90. B. Maity, T. Mondal, K. Dey and S. Biswas, *J. Chem. Sci*., **2015**, *127*, 281–293.
91. J. Tripathy and M. Bhattacharjee, *Tetrahedron Lett*., **2009**, *50*, 4863–4865.
92. T. Opstal and F. Verpoort, *Tetrahedron Lett*., **2002**, *43*, 9259–9263.
93. M. Rotem and Y. Shvo, *J. Organomet. Chem*., **1993**, *448*, 189–204.
94. V. Cadierno, J. Francos and J. Gimeno, *Organometallics*, **2011**, *30*, 852–862.
95. C. Ruppin and P. H. Dixneuf, *Tetrahedron Lett*., **1986**, *27*, 6323–6324.
96. L. J. Goossen, J. Paetzold and D. Koley, *Chem. Comm.*, **2003**, 706–707.
97. F. Nicks, R. Aznar, D. Sainz, G. Muller and A. Demonceau, *Eur. J. Org. Chem.*, **2009**, 5020–5027.
98. S. T. Tan and W. Y. Fan, *Eur. J. Inorg. Chem.*, **2010**, 4631–4635.
99. T. Mitsudo, Y. Hori and Y. Watanabe, *J. Org. Chem*., **1985**, *50*, 1566–1568.
100. T. Mitsudo, Y. Hori, Y. Yamakawa and Y. Watanabe, *J. Org. Chem*., **1987**, *52*, 2230–2239.
101. D. H. Camacho, S. Saito and Y. Yamamoto, *Tetrahedron Lett*., **2002**, *43*, 1085–1088.
102. T. Wakahayashi, Y. Ishii, T. Murata, Y. Mizobe and M. Hidai, *Tetrahedron Lett*., **1995**, *36*, 5585–5588.
103. T. Wakabayashi, Y. Ishii, K. Ishikawa and M. Hidai, *Angew. Chem. Int. Ed*., **1983**, *35*, 2123–2124.

104. L. B. Wolf, K. C. M. F. Tjen, T. Brink, R. H. Blaauw, H. Hiemstra, H. E. Schoemaker and P. J. T. Rutjes, *Adv. Synth. Catal.*, **2002**, *344*, 70–83.

105. J. Hou, J. Xie and Q. Zhou, *Angew. Chem. Int. Ed.*, **2015**, *54*, 6302–6305.

106. C. Lambert, H. Nozaki and K. Utimoto, *Tetrahedron Lett.*, **1984**, *25*, 5323–5326.

107. W. Zhang, A. R. Haight and M. C. Hsu, *Tetrahedron Lett.*, **2002**, *43*, 6575–6578

108. G. Zhu, S. Ma and X. Lu, *Tetrahedron Lett.*, **1992**, *33*, 7205–7206.

109. D. L. Smith, W. R. F. Goundry and H. W. Lam, *Chem. Comm.*, **2012**, *48*, 1505–1507.

110. A. Lumbroso, N. R. Vautravers and B. Breit, *Org. Lett.*, **2010**, *12*, *5498*–5501.

111. 1 S. Wei, J. Pedroni, A. Meißner, A. Lumbroso, H. Drexler, D. Heller and B. Breit, *Chem. Eur. J.*, **2013**, *19*, 12067–12076.

112. B. C. Chary and S. Kim, *J. Org. Chem.*, **2010**, *75*, 7928–7931.

113. D. Ciucci, P. Vergamini, R. Rossi and F. Bellina, *Tetrahedron*, **2000**, *56*, 2533–2545.

114. R. Hua and X. Tian, *J. Org. Chem.*, **2004**, *69*, 5782–5784.

115. H. Nakagawa, Y. Okimoto, S. Sakaguchi and Y. Ishii, *Tetrahedron Lett.*, **2003**, *44*, 103–106.

116. J. Chen and C. Li, *Org. Lett.*, **2018**, *20*, 6719–6724.

117. L. M. Stanley and M. P. Sibi, *Chem. Rev.*, **2008**, *108*, 2887–2902.

118. S. Hashimoto and M. Kinugasa, *Jpn. Chem. Soc. Chem. Comm.*, **1972**, 466–467.

119. K. Okuro, M. Enna, M. Miura and M. Nomura, *Jpn. Chem. Soc. Chem. Comm.*, **1993**, 1107–1108.

120. M. Miura, M. Enna, K. Okuro and M. Nomura, *J. Org. Chem.*, **1995**, 60, 4999–5004.

121. T. C. Malig, D. Yu and J. E. Hein, *J. Am. Chem. Soc.*, **2018**, *140*, 9167–9173.

122. R. Huisgen, *Proc. Chem. Soc. London*, **1961**, 357–396.

123. V. V. Rostovtsev, L. G. Green, V. V Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596–2599.

124. C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, **2002**, *67*, 3057–3064.

125. B. T. Worrell, J. A. Malik and V. V. Fokin, *Science*, **2013**, *340*, 457–461.

126. A. Alexakis, J. Frutos and P. Mangeney, *Tetrahedron Asymmetry*, **1993**, *4*, 2427–2430.

127. M. Yan, Z. Zhou and A. S. C. Chan, *Chem. Comm.*, **2000**, 115–116.

128. B. L. Feringa, *Acc. Chem. Res.*, **2000**, *33*, 346–353.

129. I. H. Escher and A. Pfaltz, *Tetrahedron*, **2000**, *56*, 2879–2888.

130. M. Dieguez, S. Deerenberg, O. Pamies, C. Claver, P. W. N. M. van Leeuwen and P. Kamer, *Tetrahedron Asymmetry*, **2000**, *11*, 3161–3166.

131. E. Guimet, M. Dieguez, A. Ruiz and C. Claver, *Tetrahedron Asymmetry*, **2005**, *16*, 2161–2165.

132. T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, **2009**, *38*, 1039–1075.

133. H. Fernandez-Perez, P. Etayo, A. Panossian and A. Vidal-Ferran, *Chem. Rev.*, **2011**, *111*, 2119–2176.

134. K. Endo, D. Hamada, S. Yakeishi, M. Ogawa and T. Shibata, *Org. Lett.*, **2012**, *14*, 2342–2345.

135. R. M. Maksymowicz, P. M. C. Roth and S. P. Fletcher, *Nat. Chem.*, **2012**, *4*, 649–654.

136. M. Sidera, P. M. C. Roth, R. M. Maksymowicz and S. P. Fletcher, *Angew. Chem. Int. Ed.*, **2013**, *52*, 7995–7999.

137. K. Takatsu, R. Shintani and T. Hayashi, *Angew. Chem. Int. Ed*., **2011**, *50*, 5548–5552.

138. M. Yoshida, H. Ohmiya and M. Sawamura, *J. Am. Chem. Soc*., **2012**, *134*, 11896–11899.

139. C. Wu, G. Yue, C. D. Nielsen, K. Xu, J. Hirao and J. S. Zhou, *J. Am. Chem. Soc*., **2016**, *138*, 742–745.

140. W. Zeng and S. R. Chemler, *J. Am. Chem. Soc*., **2007**, *129*, 12948–12949.

141. E. S. Sherman, T. B. Tan, O. Gerlits and S. R. Chemler, *Org. Lett*., **2004**, *6*, 1573–1575.

142. K. Kaneko, T. Yoshino, S. Matsunaga and M. Kanai, *Org. Lett*., **2013**, *15*, 2502–2505.

143. P. H. Fuller, J. Kim and S. R. Chemler, *J. Am. Chem. Soc*., **2008**, *130*, 17638–17639.

144. H. Wang, Y. Wang, D. Liang, L. Liu, J. Zhang and Q. Zhu, *Angew. Chem. Int. Ed.*, **2011**, *50*, 5678–5681.

145. K. Hiroya, S. Itoh and T. Sakamoto, *J. Org. Chem*., **2004**, *69*, 1126–1136.

146. L. B. Krasnova, J. E. Hein and V. V Fokin, *J. Org. Chem*., **2010**, *75*, 8662–8665.

147. D. Chen, M. Zhang, Y. Li, Y. Liu and X. Wang, *Tetrahedron*, **2014**, *70*, 2889–2893.

148. H. Jiang and C. Li, *Adv. Synth. Catal*., **2008**, *350*, 2226–2230.

149. L. Zhou, D. S. Bohle, H. Jiang and C. Li, *Synlett*, **2009**, *6*, 937–940.

150. D. W. Robbins and J. F. Hartwig, *Science*, **2011**, *333*, 1423–1428.

151. J. Bahri, B. Jamoussi, M. Taillefer and F. Monnier, *Chem. Comm.*, **2015**, *51*, 11210–11212.

152. S. Shi and S. L. Buchwald, *Nat. Chem.*, **2014**, *7*, 38–44.

153. R. Martín, M. R. Rivero and S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2006**, *45*, 7079–7082.

154. Y. Zhou, O. D. Engl, J. S. Bandar, E. D. Chant and S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2018**, *57*, 6672–6675.

155. C. Lamberth, S. Jeanmart, T. Luksch and A. Plant, *Science*, **2013**, *341*, 742–747.

156. C. Lamberth, Pest Manag. Sci., **2013**, *69*, 1106–1114.

157. E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, **2014**, *57*, 10257–10274.

158. J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, **2016**, *14*, 10134–10156.

159. R. Rico-Ferreira and F. A. Bermejo, *J. Org. Chem.*, **2001**, *66*, 8287–8292.

160. G. D. James, S. D. Mills and G. Pattenden, *J. Chem. Soc. Perkin Trans 1*, **1993**, 2581–2584.

161. H. Miyazaki, T. Miyake, Y. Terakawa, H. Ohmizu, T. Ogiku and A. Ohtani, *Bioorg. Med. Chem. Lett*., **2010**, *20*, 546–548.

162. C. Peschko and W. Steglich, *Tetrahedron Lett*., **2000**, *41*, 9477–9481.

163. M. L. Méndez, I. Vilacosta, C. Sarriá, C. Fernández and A. S. Román, *J. Am. Chem. Soc*., **1967**, *57*, 3643.

164. S. Hashiguchi, H. Natsugari and M. Ochiai, *J. Chem. Soc. Perkin Trans 1*, **1988**, 2345–2352.

165. B. Gill, G. D. James, K. V. Oates and G. Pattenden, *J. Chem. Soc. Perkin Trans 1*, **1993**, 2567–2578.

166. C. Haase and P. Langer, *Synlett*, **2004**, *3*, 453–456.

167. K. Cherry, J. Thibonnet, A. Duchêne, J. Parrain and M. Abarbri, *Tetrahedron Lett*., **2004**, *45*, 2063–2066.

168. K. Cherry, A. Duchene, J. Thibonnet, J. Parrain, E. Anselmi and M. Abarbri, *Synthesis*, **2009**, *2*, 257–270.

169. Y. Tang and C. Li, *Org. Lett.*, **2004**, *6*, 3229–3231.

170. J. Wuckelt, M. Doring, P. Langer, R. Beckert and H. Gorls, *J. Org. Chem.*, **1999**, *64*, 365–372.

171. W. Hou, B. Zhou, Y. Yang, H. Feng and Y. Li, *Org. Lett.*, **2013**, *15*, 1814–1817.

172. H. Liu, S. Song, C. Wang, C. Feng and T. Loh, *ChemSusChem*, **2017**, *10*, 58–61.

173. S. Seo and M. C. Willis, *Org. Lett.*, **2017**, *19*, 4556–4559.

174. M. Findlay, Part II thesis.

175. A. J. Cresswell, S. G. Davies, P. M. Roberts and J. E. Thomson, *Chem. Rev.*, **2015**, *115*, 566–611.

176. T. L. Mindt and R. Schibli, *J. Org. Chem.*, **2007**, *72*, 10247–10250.

177. C. Sun, Y. Fang, S. Li, Y. Zhang, Q. Zhao, S. Zhu and C. Li, *Org. Lett.*, **2009**, *11*, 4084–4087.

178. M. E. López-reyes, R. A. Toscano, J. G. López-cortøs and C. Alvarez-Toledano, *Asian J. Org. Chem.*, **2015**, *4*, 545–551.

179. S. Inack-ngi, R. Rahmani, L. Commeiras, G. Chouraqui, J. Thibonnet, A. Duchene, M. Abarbri and J. Parrain, *Adv. Synth. Catal.*, **2009**, *351*, 779–788.

180. S. Gonell, X. Caumes, N. Orth, I. Ivanovic-Burmazovic and J. N. H. Reek, *Chem. Sci.*, **2019**, *10*, 1316–1321.

181. J. G. Taylor, N. Whittall and K. K. (Mimi) Hii, *Chem. Comm.*, **2005**, 5103–5105.

182. R. Blieck, M. Taillefer and F. Monnier, *J. Org. Chem.*, **2019**, *84*, 11247–11252.

183. N. Okamoto, Y. Miwa, H. Minami, K. Takeda and R. Yanada, *J. Org. Chem.*, **2011**, *76*, 9133–9138.

184. W. Yoo and C. Li, *J. Org. Chem.*, **2006**, *71*, 6266–6268.

185. F. Huang, T. D. Quach and R. A. Batey, *Org. Lett*., **2013**, *15*, 3150–3153.

186. C. Schaefer and G. C. Fu, *Angew. Chem. Int. Ed*., **2015**, *44*, 4606–4608.

187. L. Benati, D. Casarini and P. C. Montevecchi, *J. Chem. Soc. Perkin Trans 1*, **1989**, 1113–1116.

188. J. A. Mulder, R. P. Hsung, M. O. Frederick, M. R. Tracey and C. A. Zificsak, *Org. Lett*., **2002**, *4*, 1383–1386.

189. S. Kanemura, A. Kondoh, H. Yasui, H. Yorimitsu and K. Oshima, *Bull. Chem. Soc. Jpn*., **2008**, *81*, 506–514.

190. H. Yasui, H. Yorimitsu and Oshima, *Chem. Lett*., **2008**, *37*, 40–41.

191. S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottlander and T. Skrydstrup, *Org. Lett*., **2009**, *11*, 4208–4211.

192. K. A. Dekorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev*., **2010**, *110*, 5064–5106.

193. R. G. Wilkins, *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, VCR Verlagsgesellschaft mbH, Weinheim; VCR Publishers, Inc., New York, Second Edition., 1991.

194. J. Bures, *Angew. Chem. Int. Ed*., **2016**, *55*, 2028–2031.

195. M. Kato, H. B. Jonassen and J. C. Fanning, *Chem. Rev*., **1964**, *64*, 99–128.

196. W. E. Hatfield, C. S. Fountain and R. Whyman, *Inorg. Chem.*, **1966**, *5*, 1855–1858.

197. M. Pasquali, P. Leoni, C. Floriani and A. Gaetani-Manfredotti, *Inorg. Chem*., **1982**, *21*, 4324–4328.

198. M. Kato, *Coord. Chem. Rev*., **1988**, *92*, 45–83.

199. A. Karaliota, O. Kretsi and C. Tzougraki, *J. Inorg. Biochem.*, **2001**, *84*, 33–37.

200. J. Zhuang, C. Wang, F. Xie and W. Zhang, *Tetrahedron*, **2009**, *65*, 9797–9800.

201. N. C. Mamillapalli and G. Sekar, *Adv. Synth. Catal*., **2015**, *357*, 3273–3283.

202. M. Bouma, G. Masson and J. Zhu, *J. Org. Chem.*, **2010**, *75*, 2748–2751.

203. M. Hatano and T. Nishimura, *Angew. Chem. Int. Ed*., **2015**, *54*, 10949–10952.

204. Q. Gao, X. Wu, Y. Li, S. Liu, X. Meng and A. Wu, *Adv. Synth. Catal*., **2014**, *356*, 2924–2930.

205. M. K. Kim, H. Shin, S. Y. Cho and Y. Chong, *Bioorg. Med. Chem.*, **2014**, *22*, 1156–1162.

206. Z. Zhang, J. Su, Z. Zha and Z. Wang, *Chem. Comm*., **2013**, *49*, 8982–8984.

207. D. Wang, K. Zhang, L. Jia, D. Zhang, Y. Zhang, Y. Cheng, C. Lin and B. Wang, *Org. Biomol. Chem*., **2017**, *15*, 3427–3434.

208. S. M. Nicolle and C. J. Moody, *Chem. Eur. J*., **2014**, *20*, 4420–4425.

209. S. B. Salunke, N. S. Babu and C. T. Chen, *Adv. Synth. Catal*., **2011**, *353*, 1234–1240.

210. C. D. R. M. D'Oca, T. Coelho, T. G. Marinho, C. R. L. Hack, R. da Costa Duarte, P. A. da Silva and M. G. M. D'Oca, *Bioorg. Med. Chem. Lett*., **2010**, *20*, 5255–5257.

211. L. Hu, Q. Gui, X. Chen, Z. Tan and G. Zhu, *J. Org. Chem*., **2016**, *81*, 4861–4868.

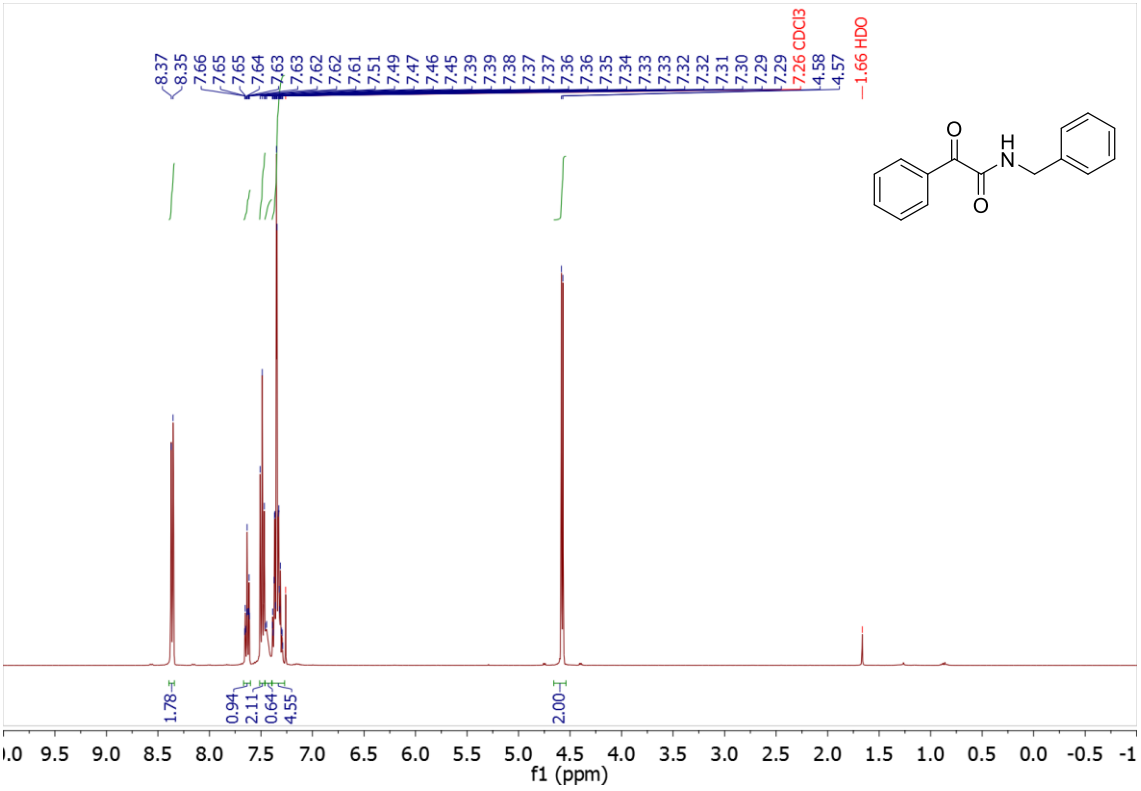
212. J. Stang, B. W. Surber, Z. Chen, K. A. Roberts and A. G. Anderson, *J. Am. Chem. Soc*., **1987**, *109*, 228–235.

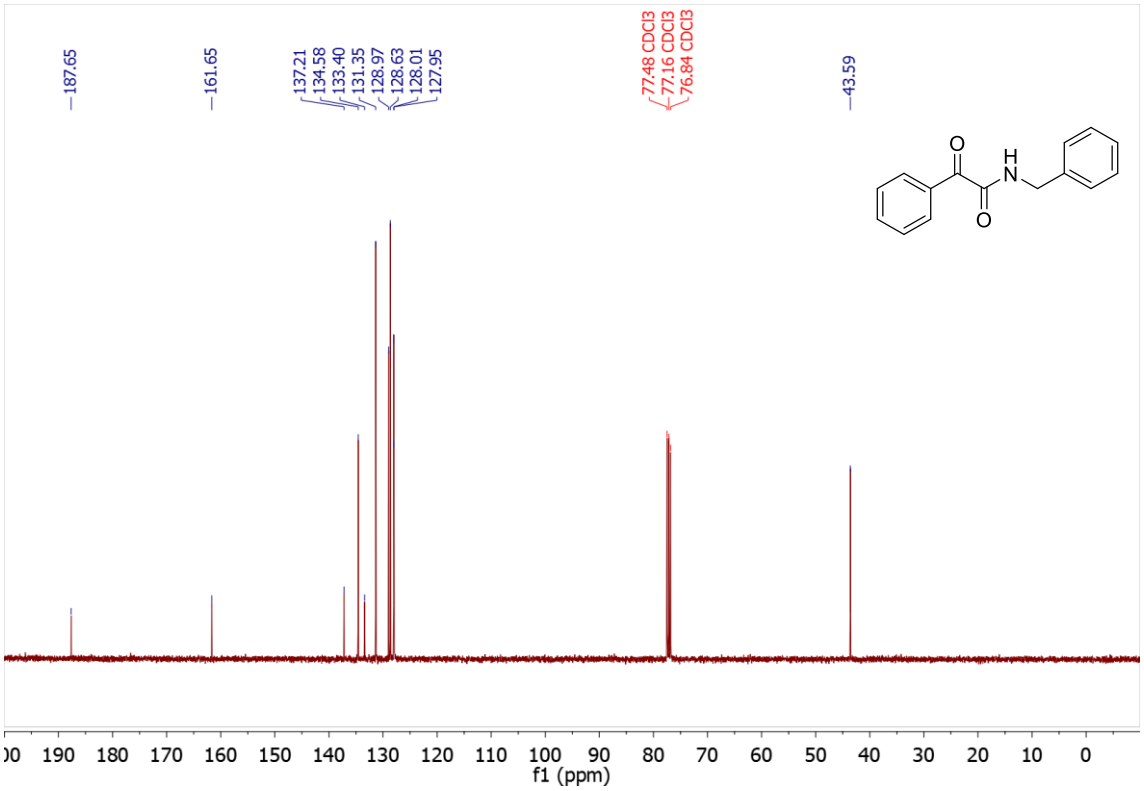
213. S. Wang, H. Song, X. Wang, N. Liu, H. Qin and C. Zhang, *Chem. Comm*., **2016**, *52*, 11893–11896.

214. W. E. Parham, F. D. Blake and D. R. Theissen, *J. Org. Chem*., **1962**, *27*, 2415–2419.

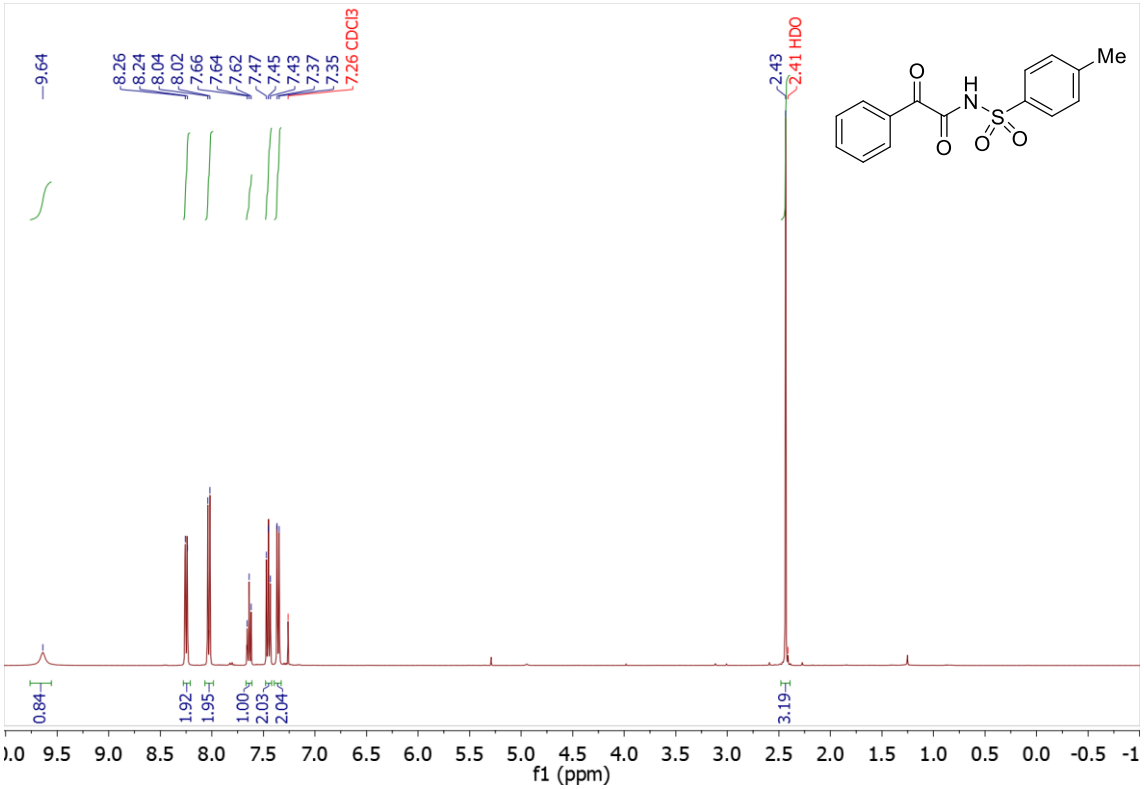
5.4 Spectra of Compounds

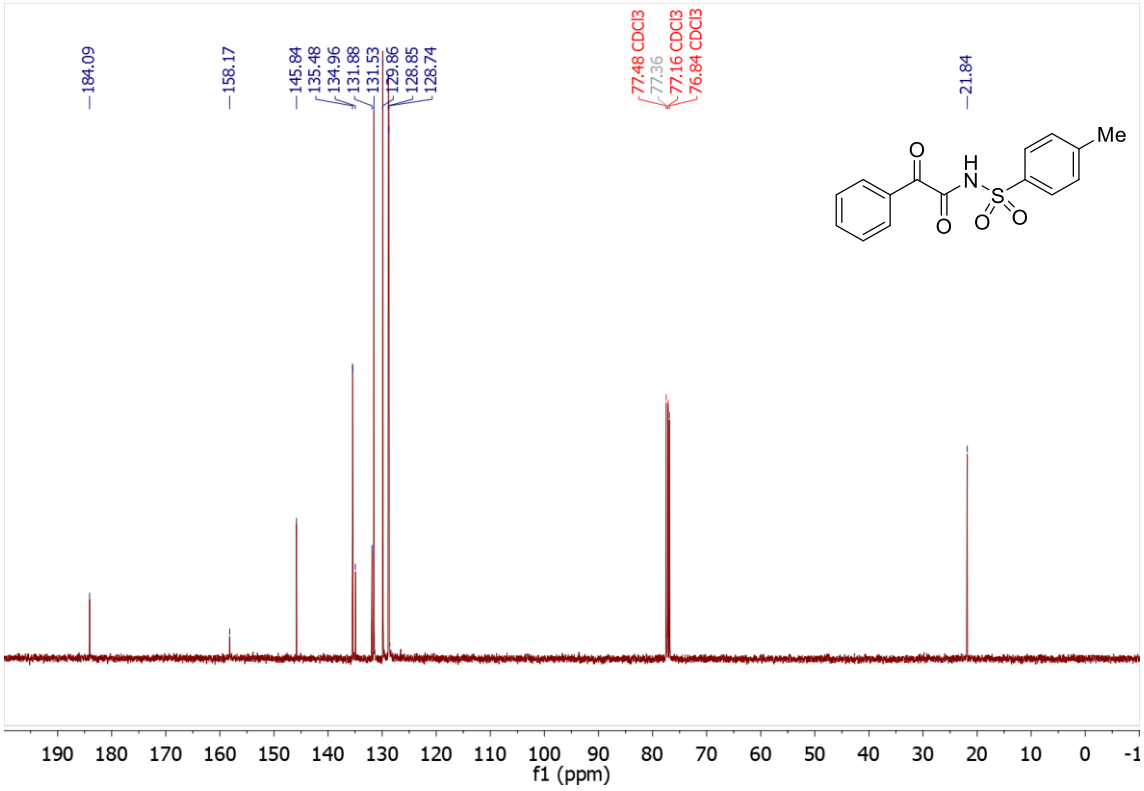
N-Benzyl-2-oxo-2-phenylacetamide, 1a



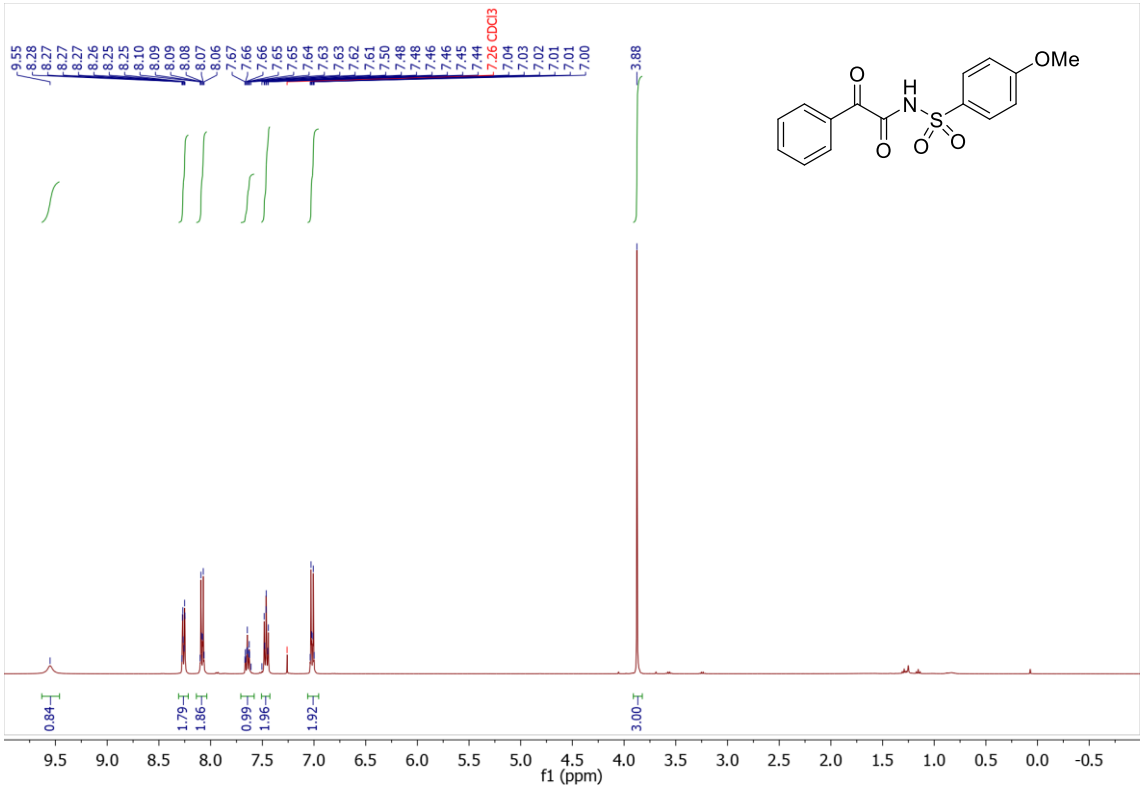


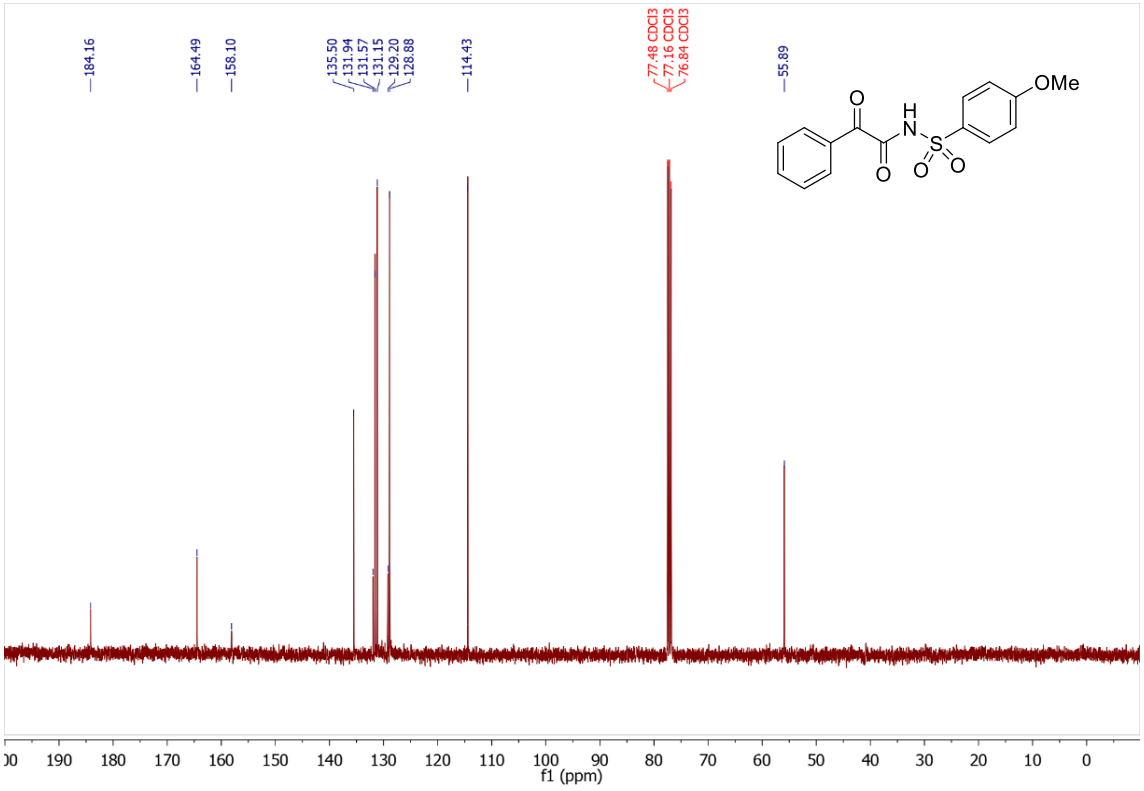
N-Tosyl-2-oxo-2-phenylacetamide, 1b



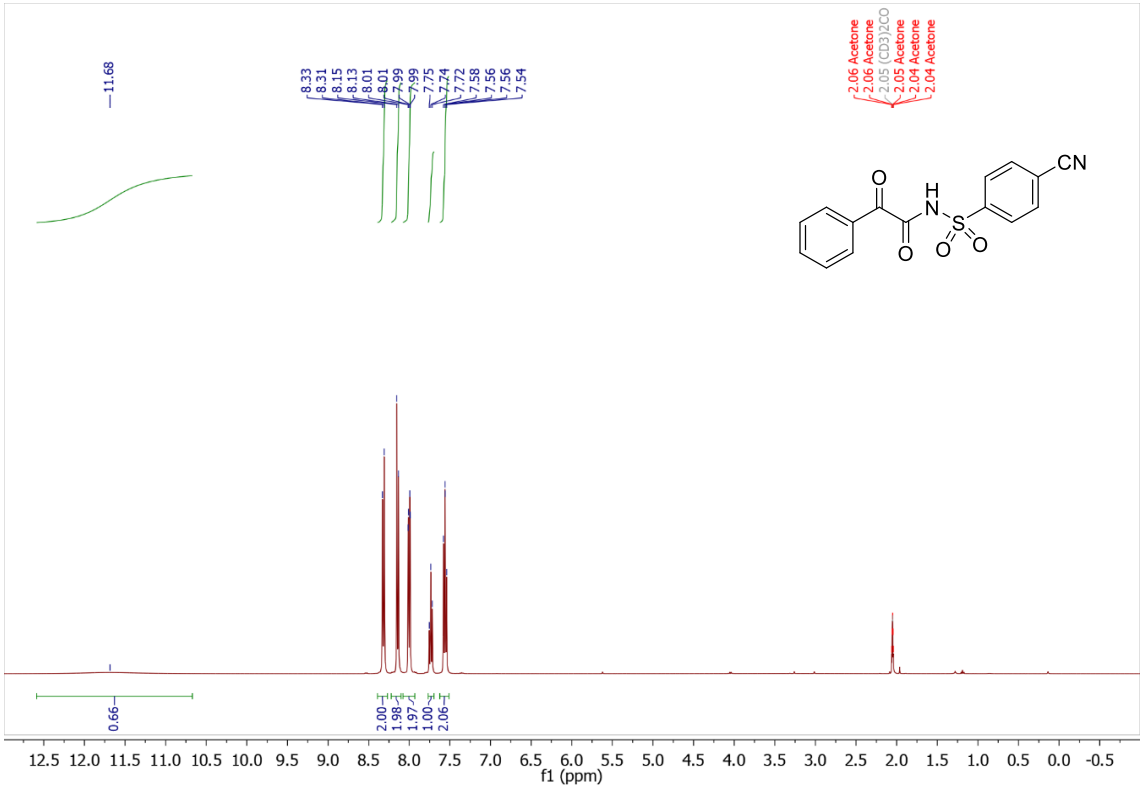


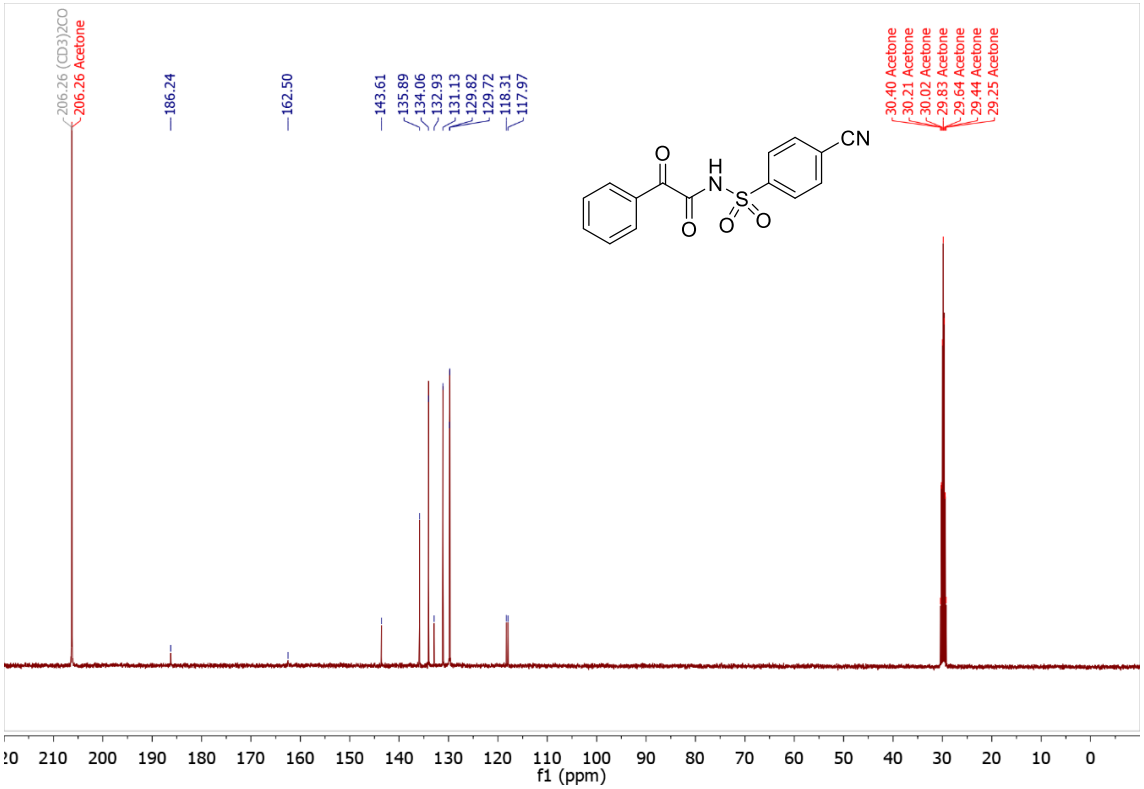
_N_-((4-Methoxyphenyl)sulfonyl)-2-oxo-2-phenylacetamide, 1c



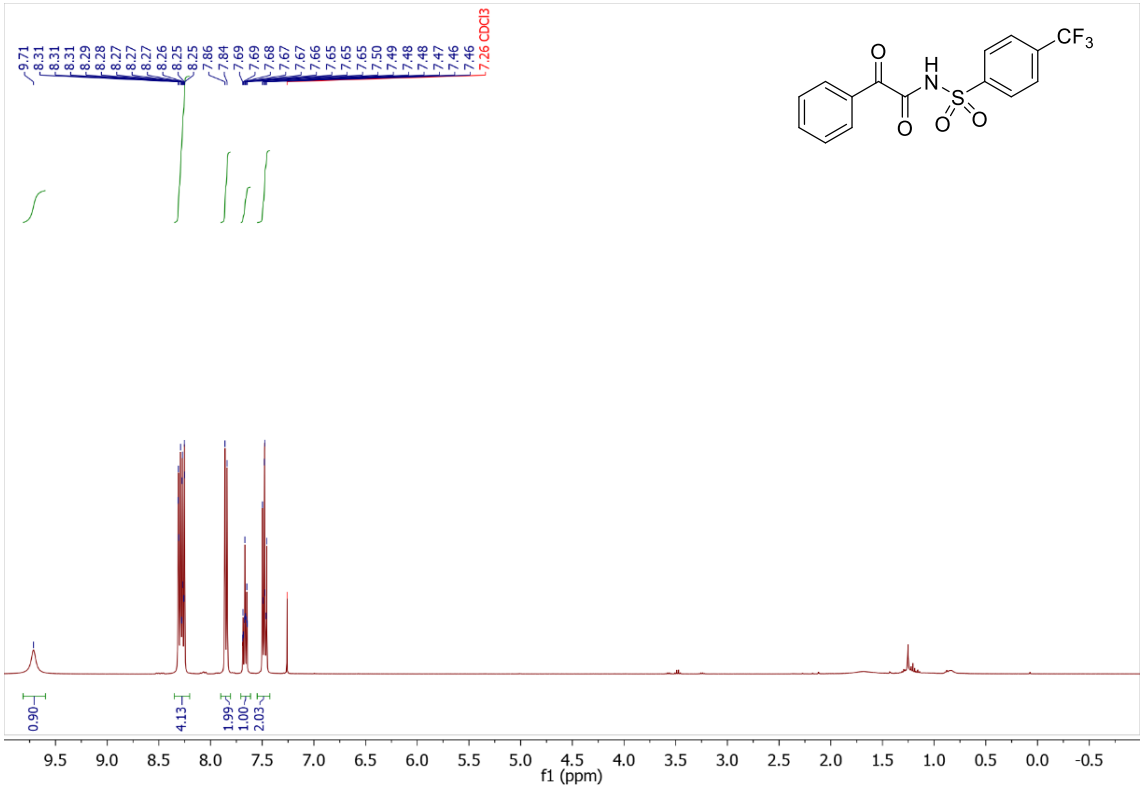


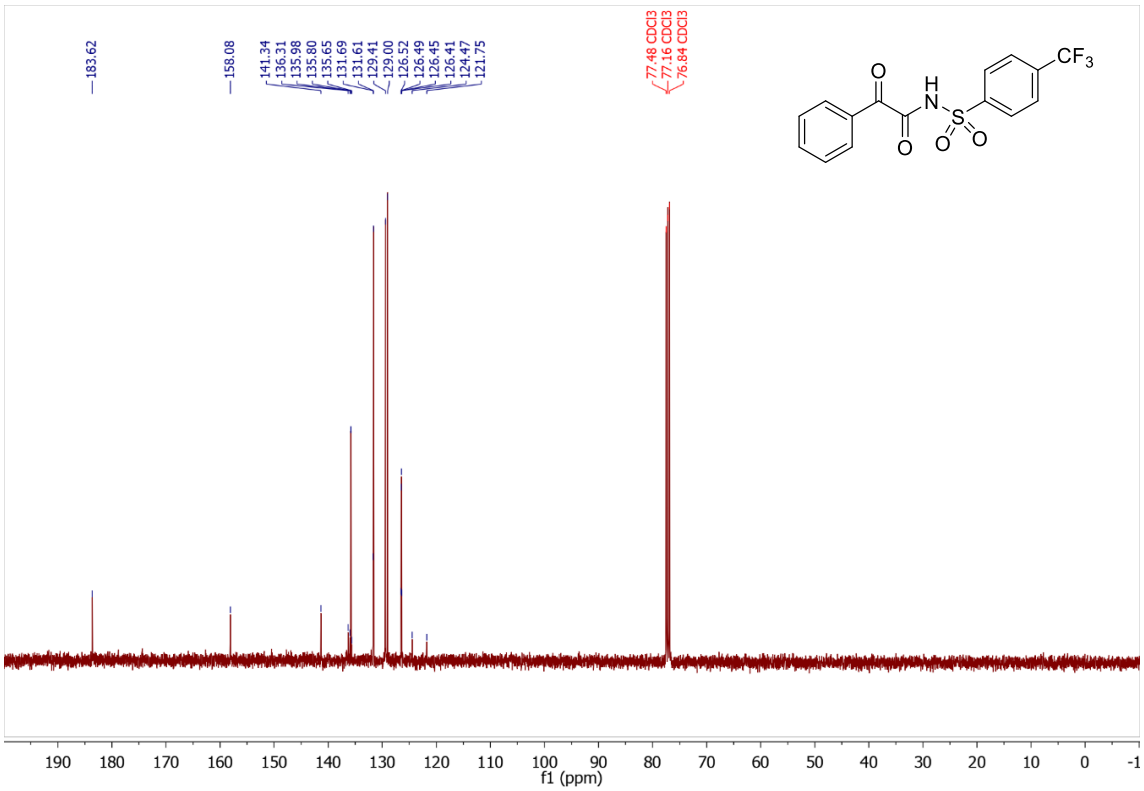
N-((4-Cyanophenyl)sulfonyl)-2-oxo-2-phenylacetamide, 1d



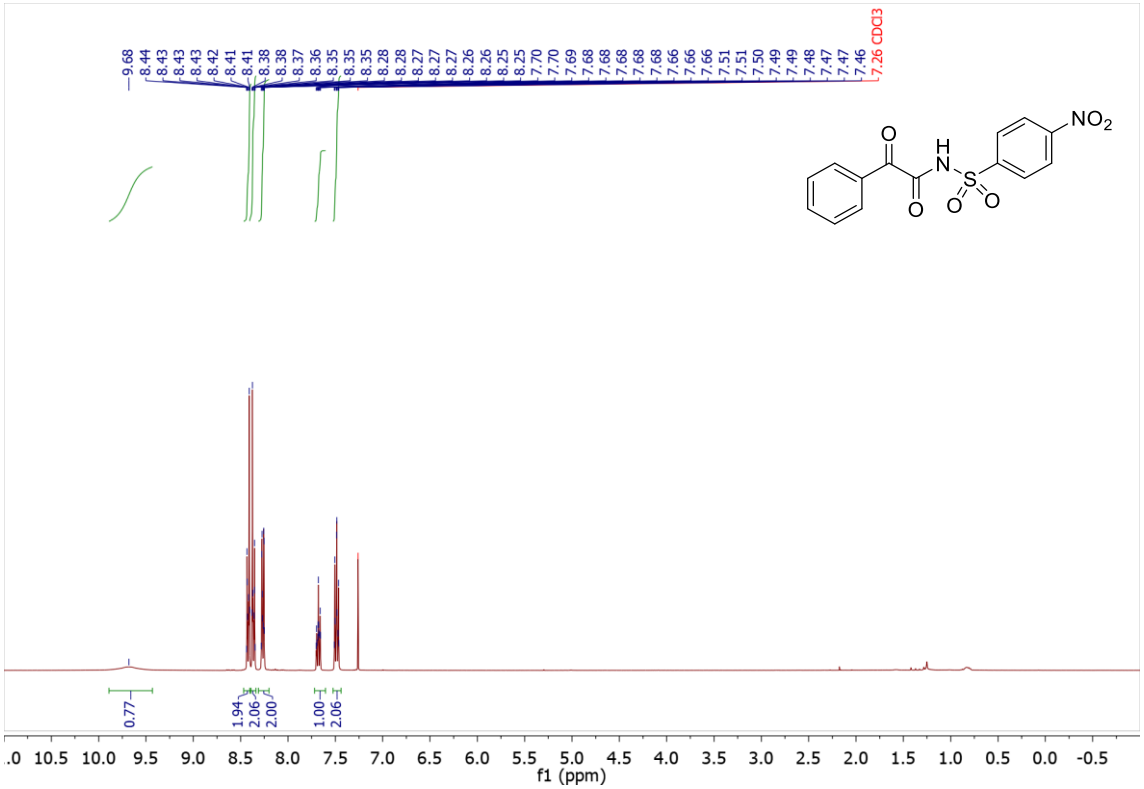


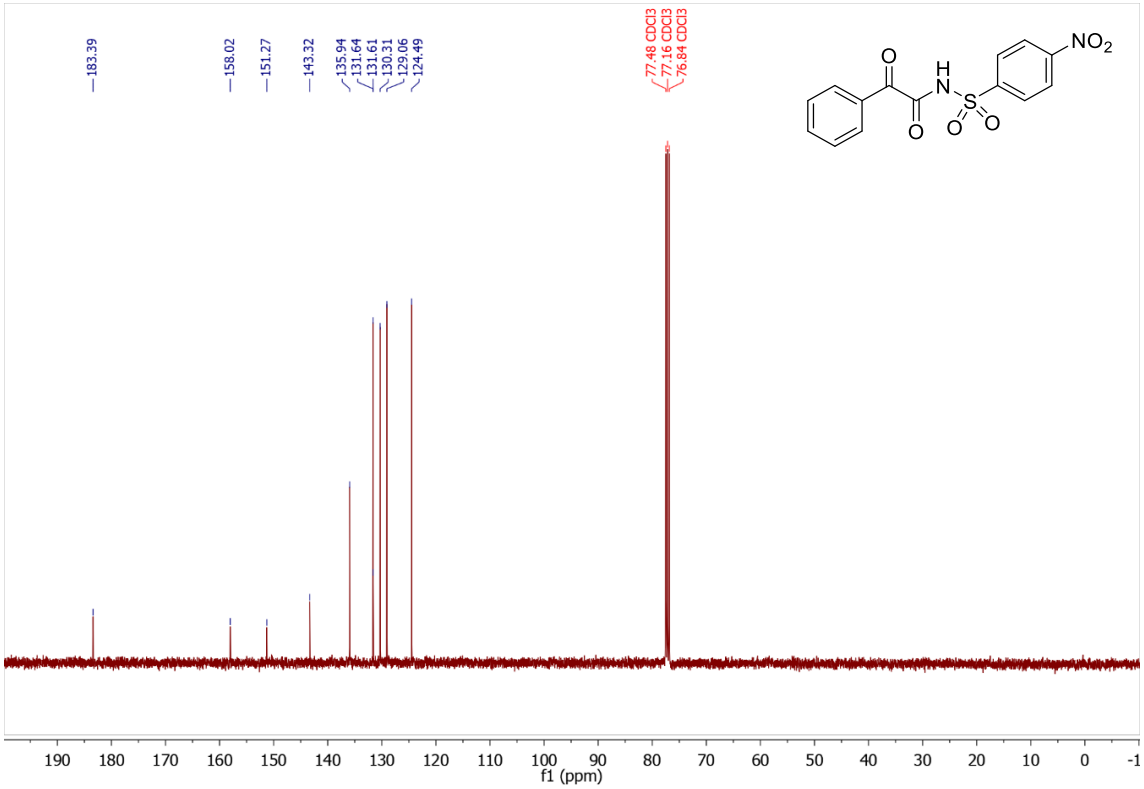
_N_-((4-(Trifluoromethyl)phenyl)sulfonyl)-2-oxo-2-phenylacetamide, 1e



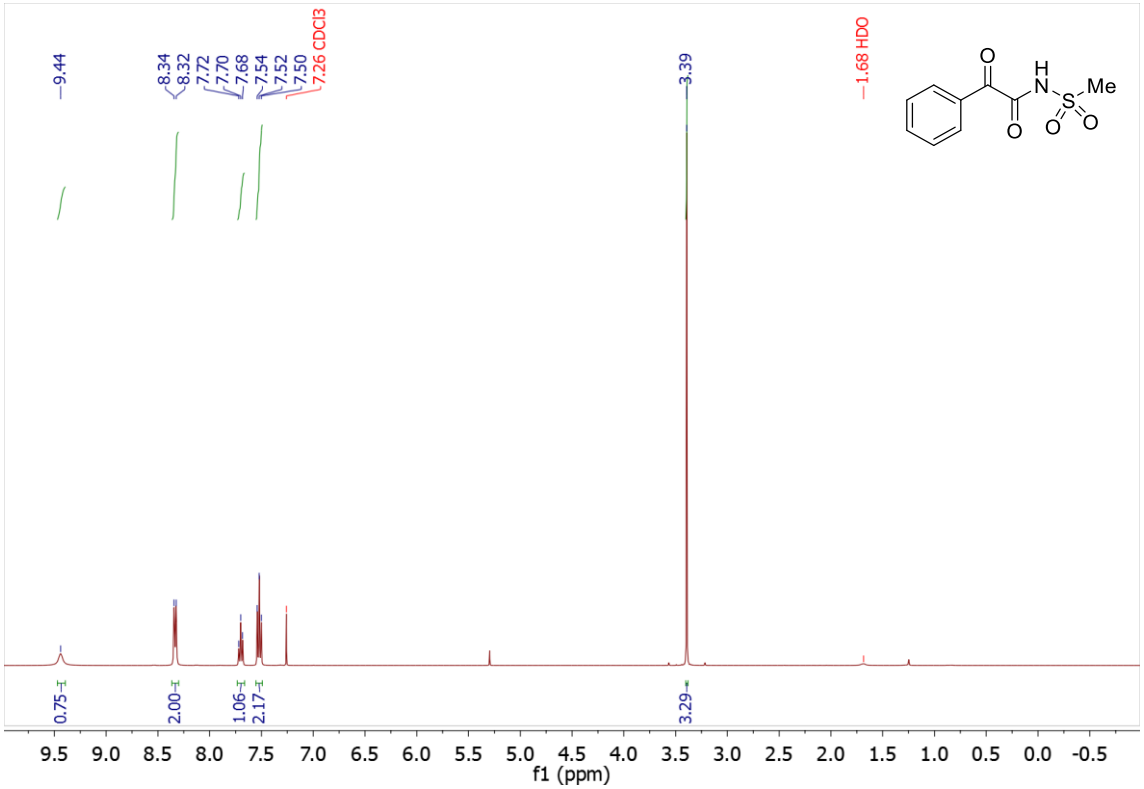


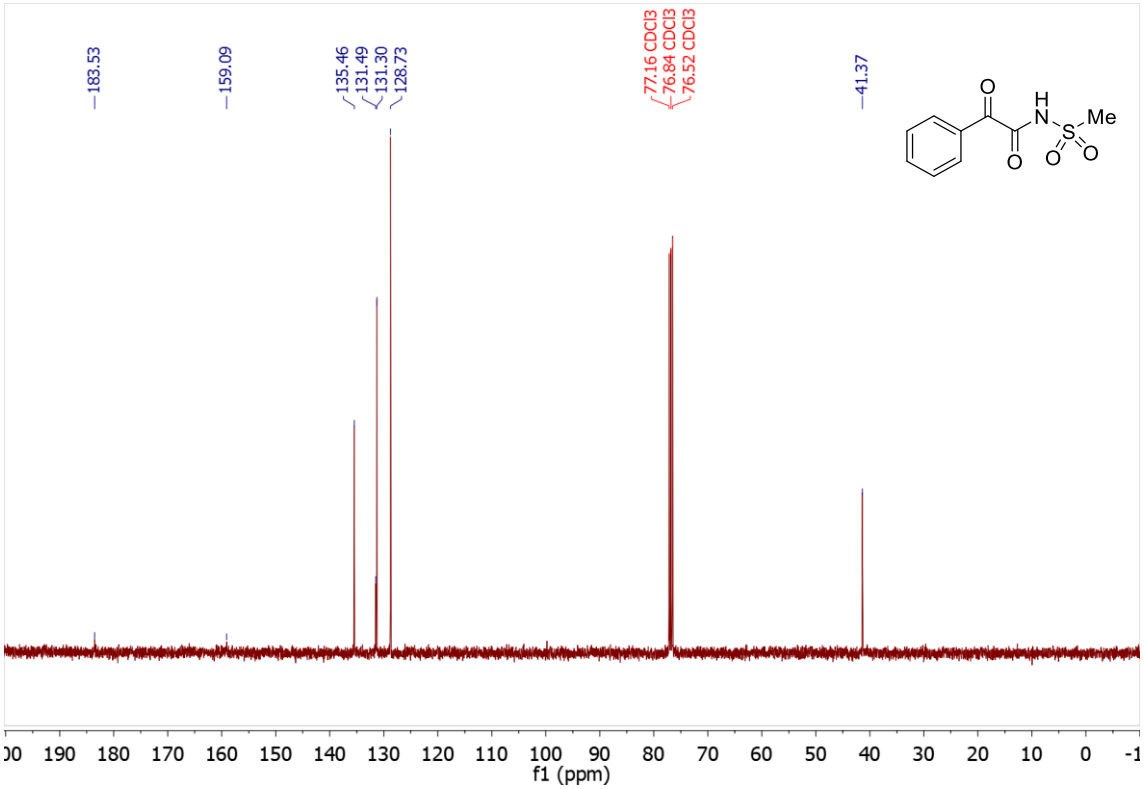
_N_-((4-Nitrophenyl)sulfonyl)-2-oxo-2-phenylacetamide, 1f



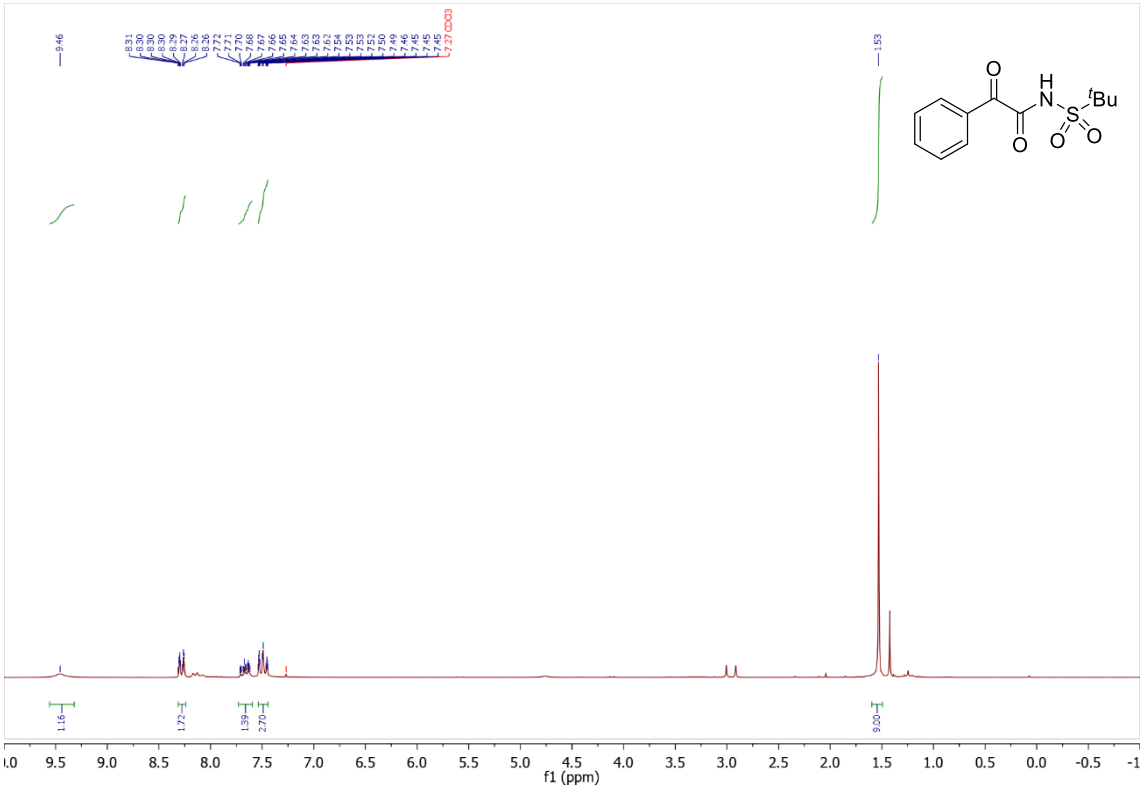


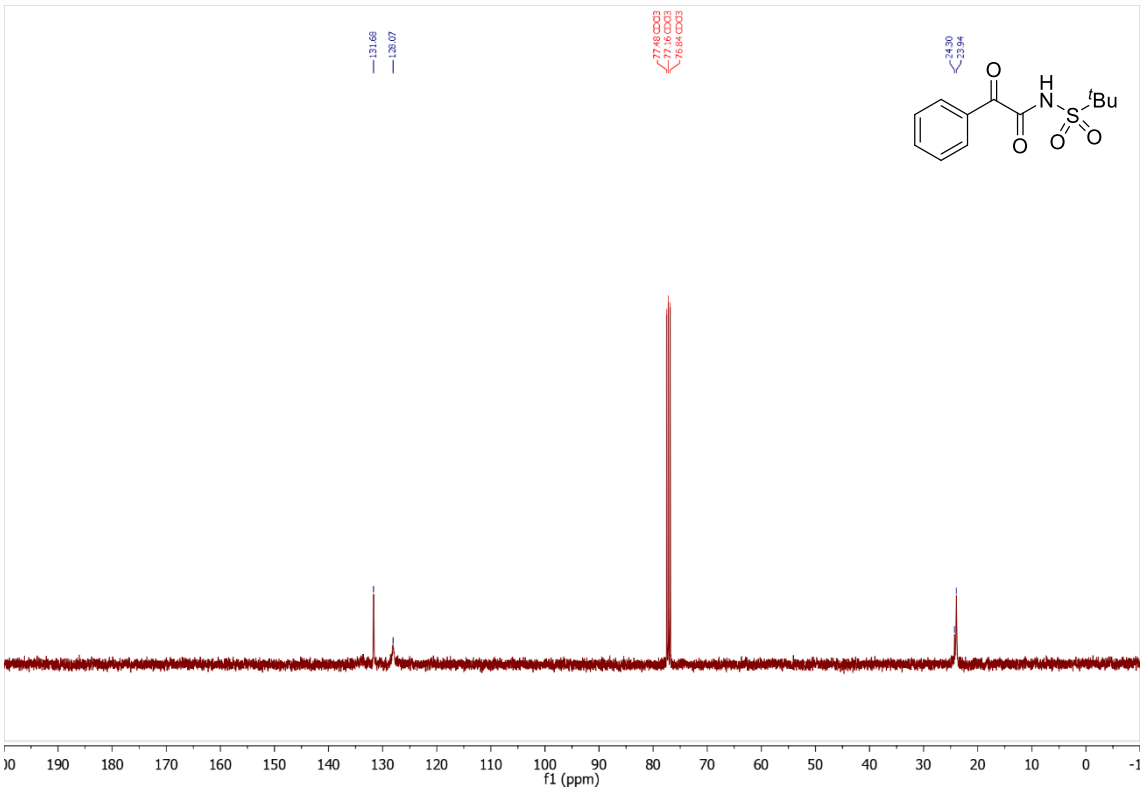
N-(Methylsulfonyl)-2-oxo-2-phenylacetamide, 1g



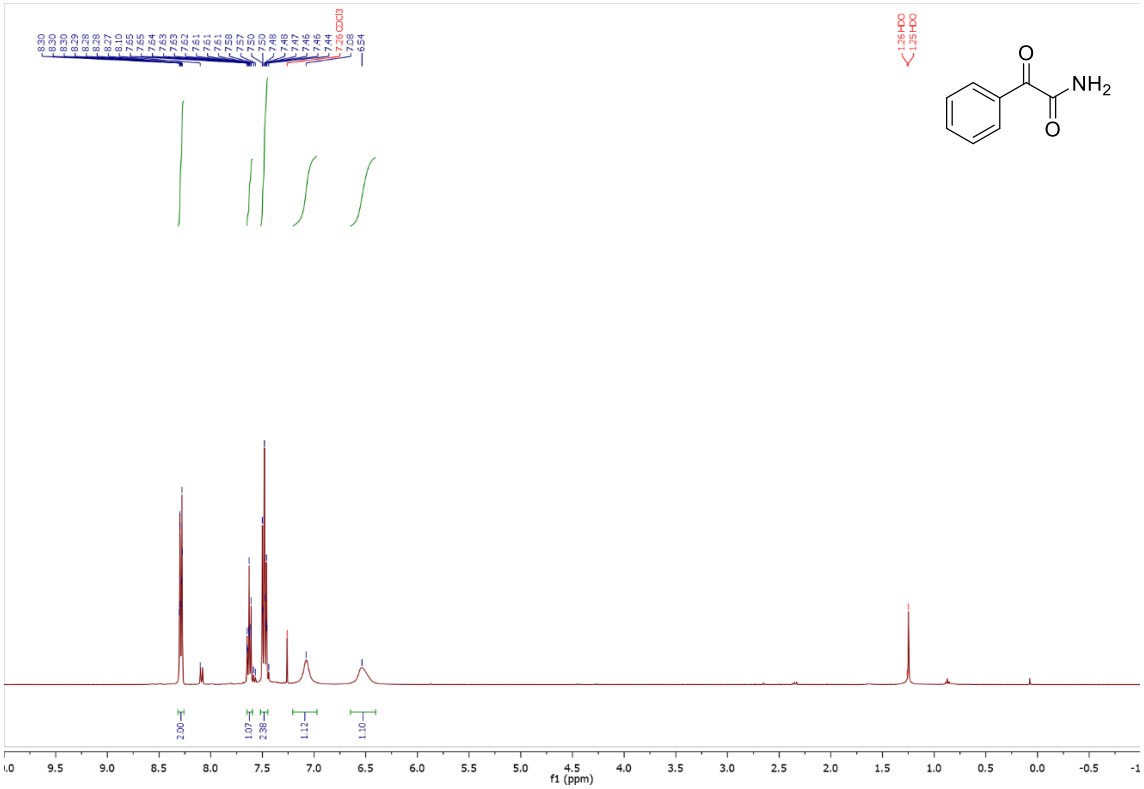


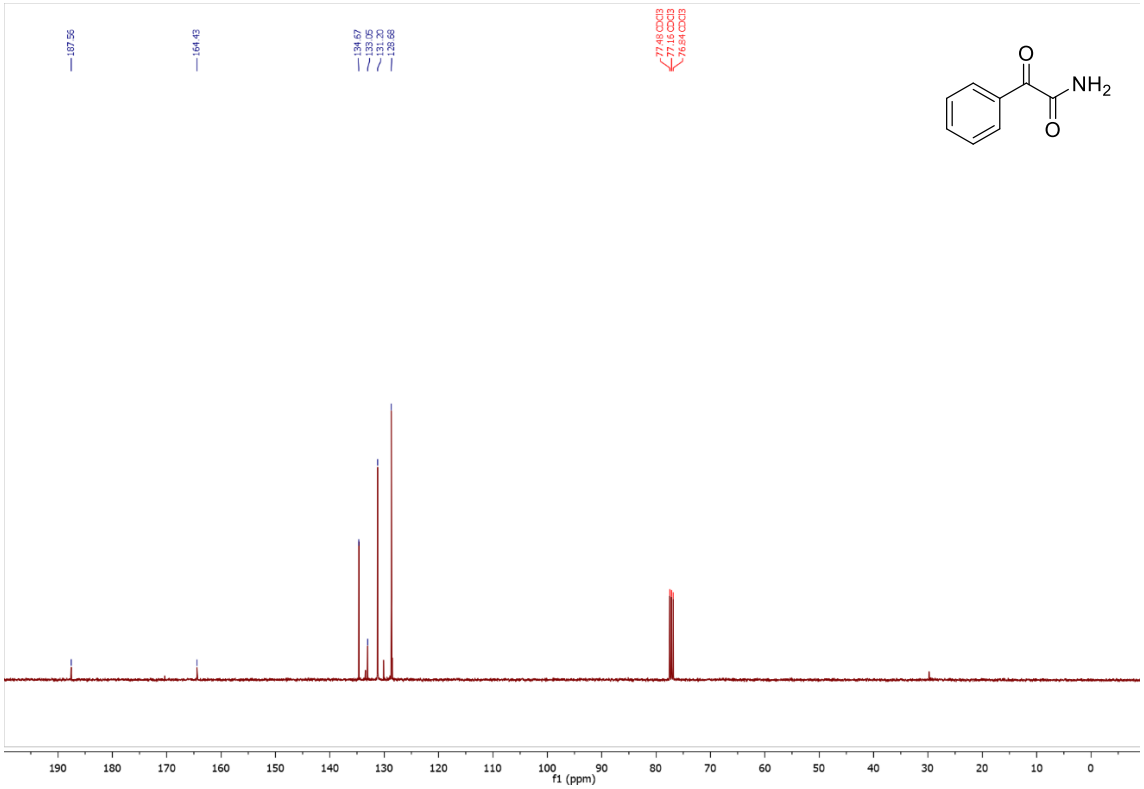
_N_-(_tert_-Butylsulfonyl)-2-oxo-2-phenylacetamide, 1h



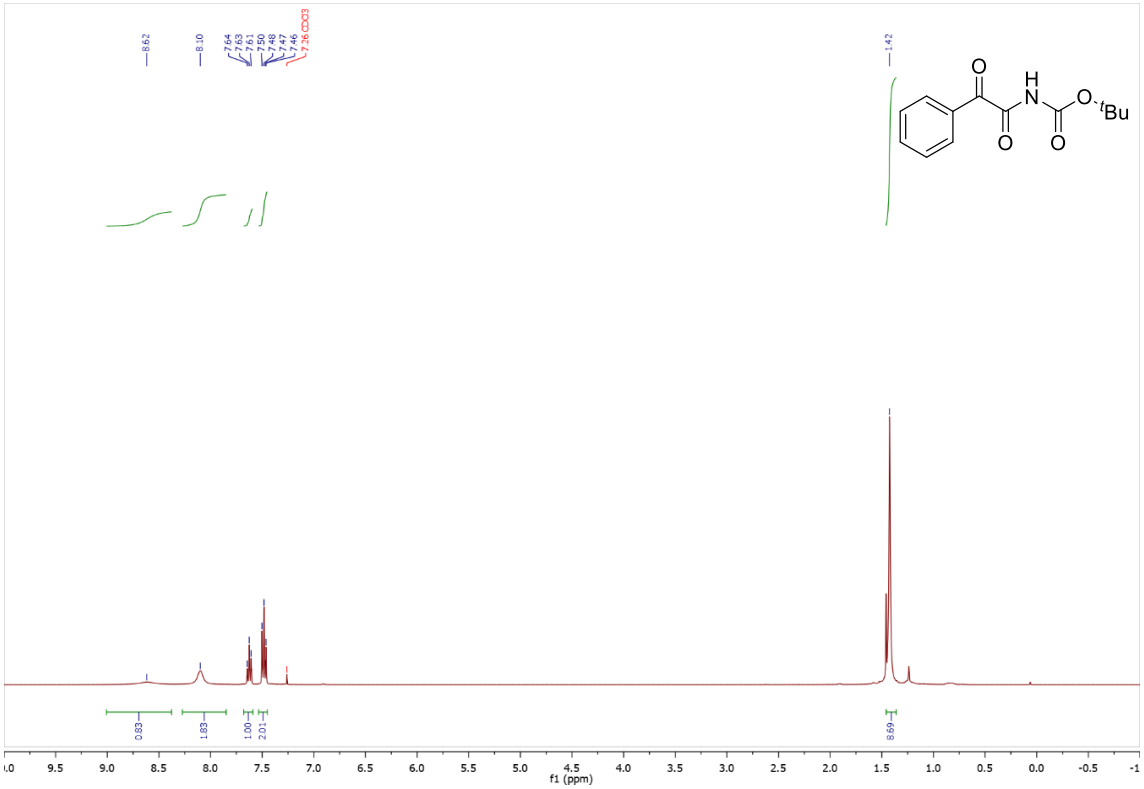


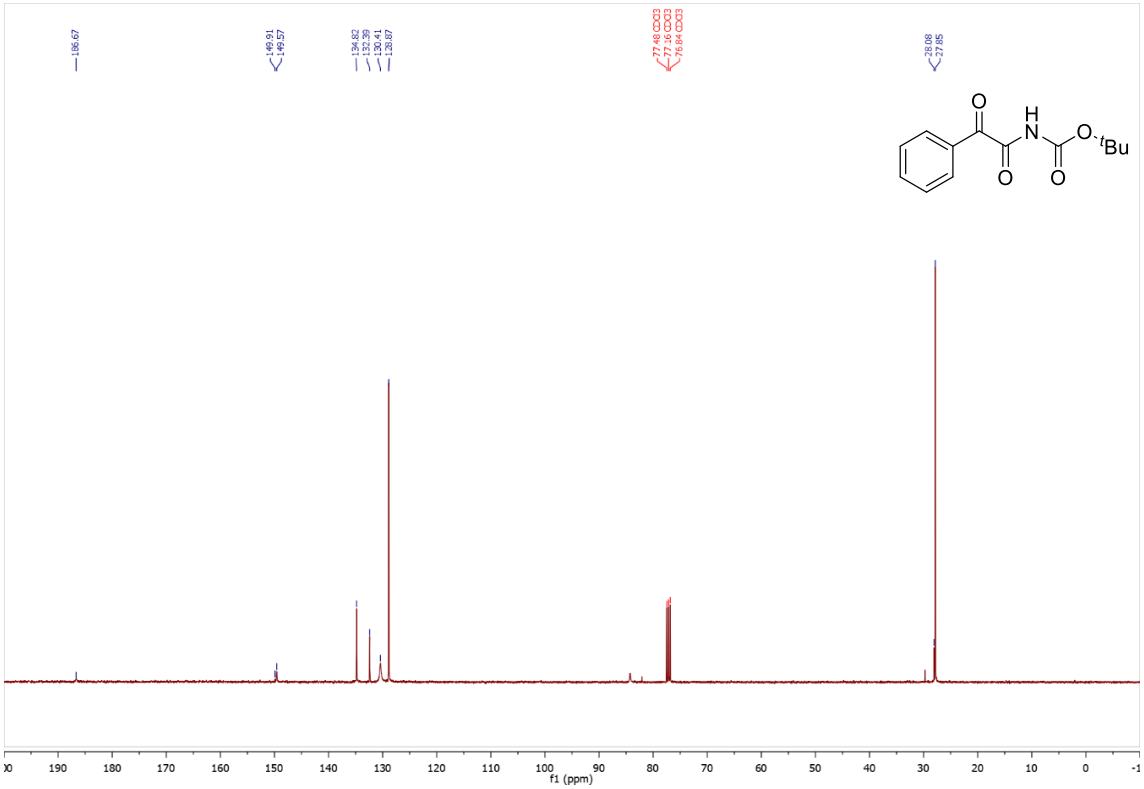
2-Oxo-2-phenylacetamide, 1i



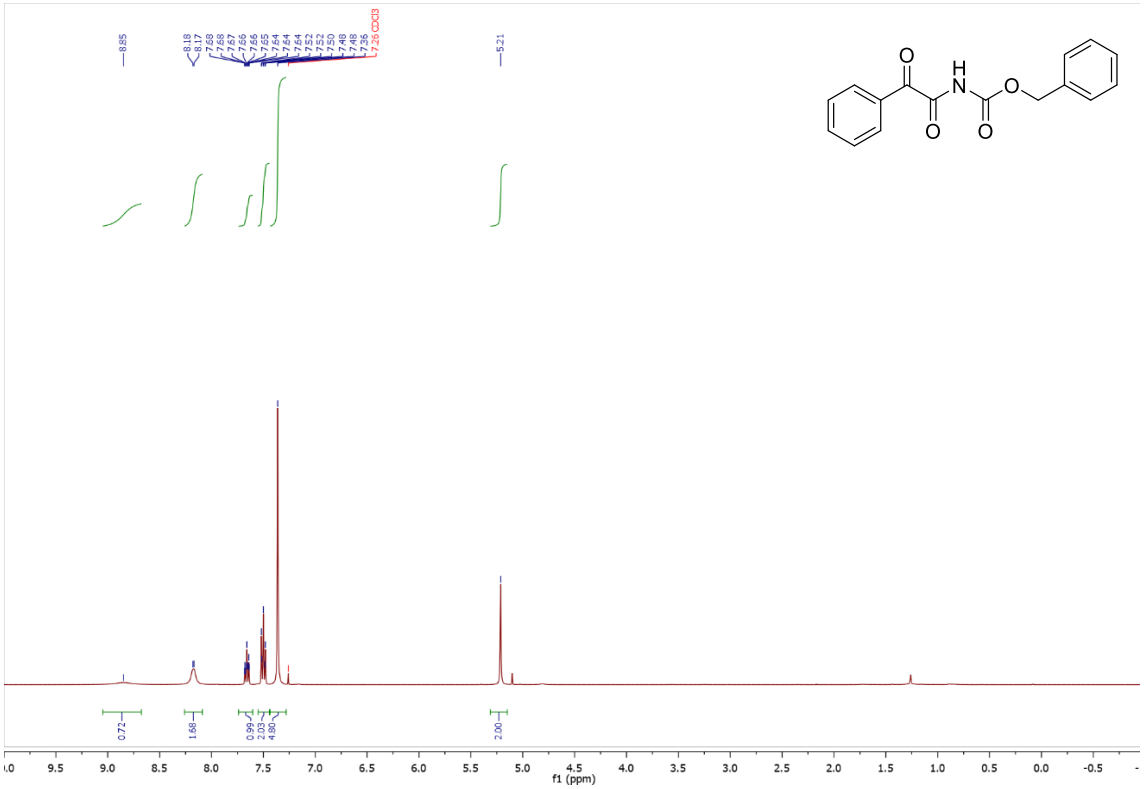


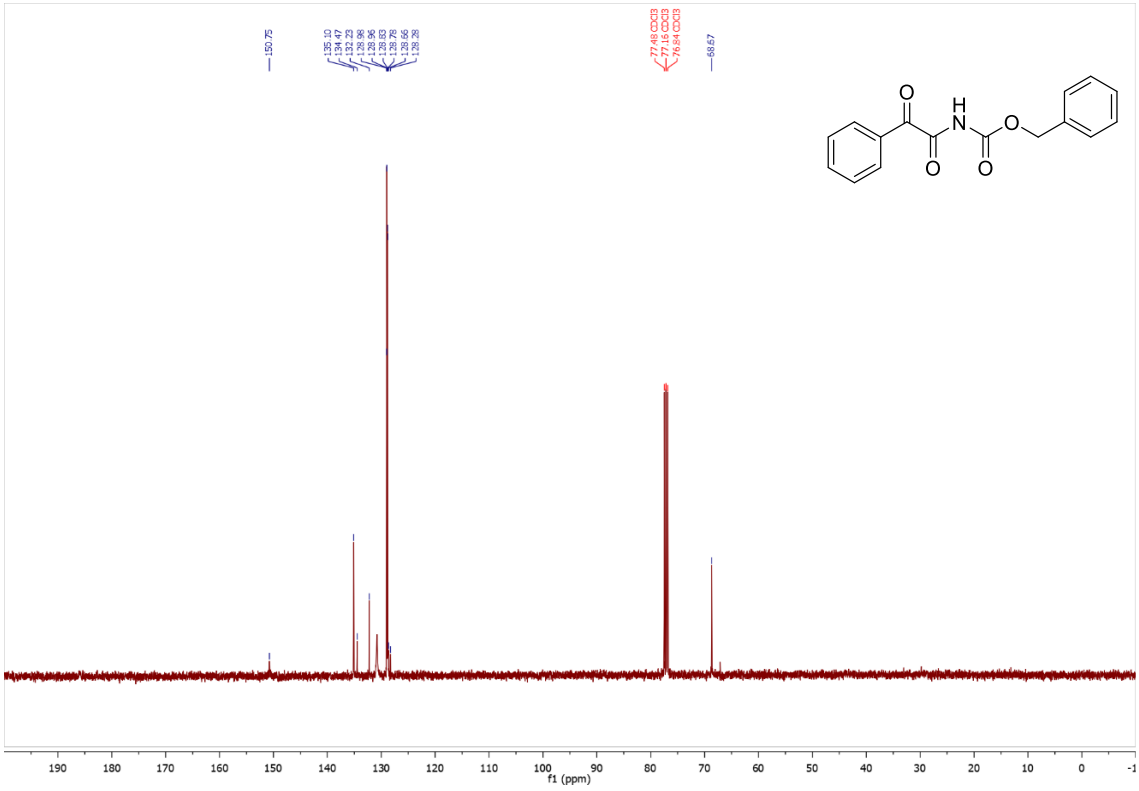
tert-Butyl(2-oxo-2-phenylacetyle)carbamate, 1j



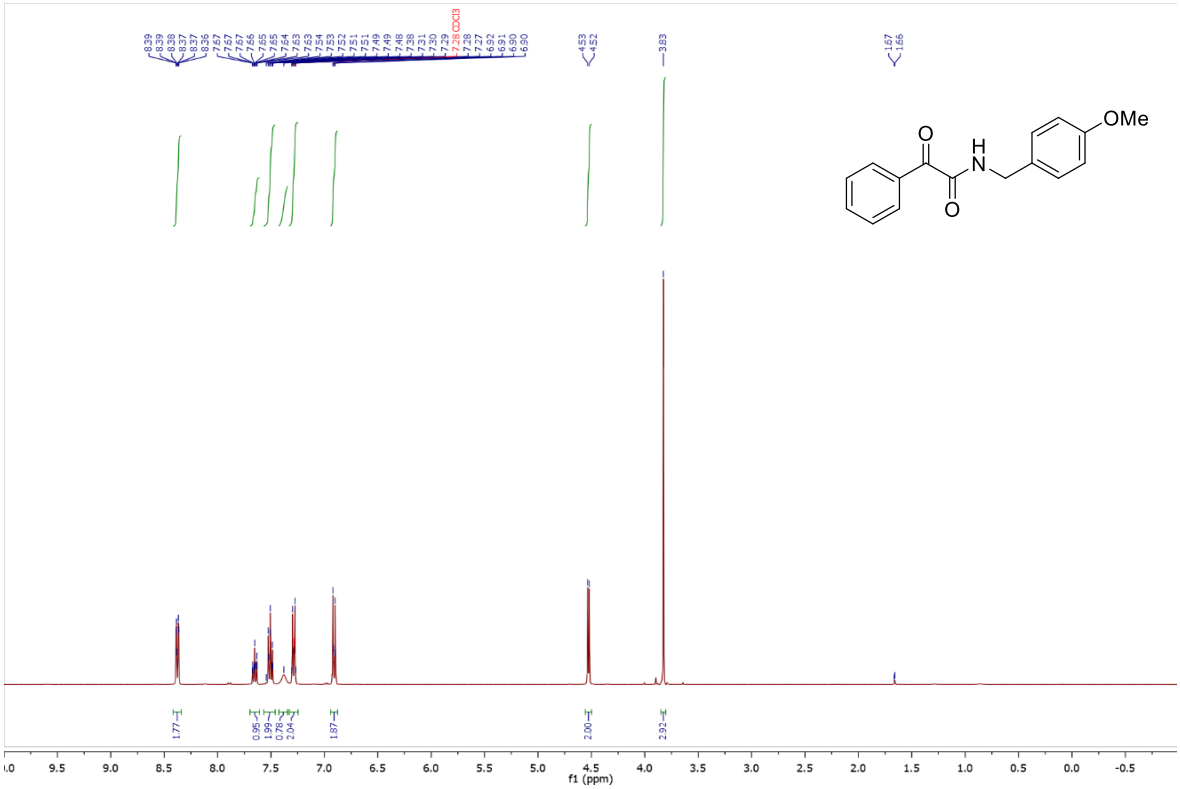


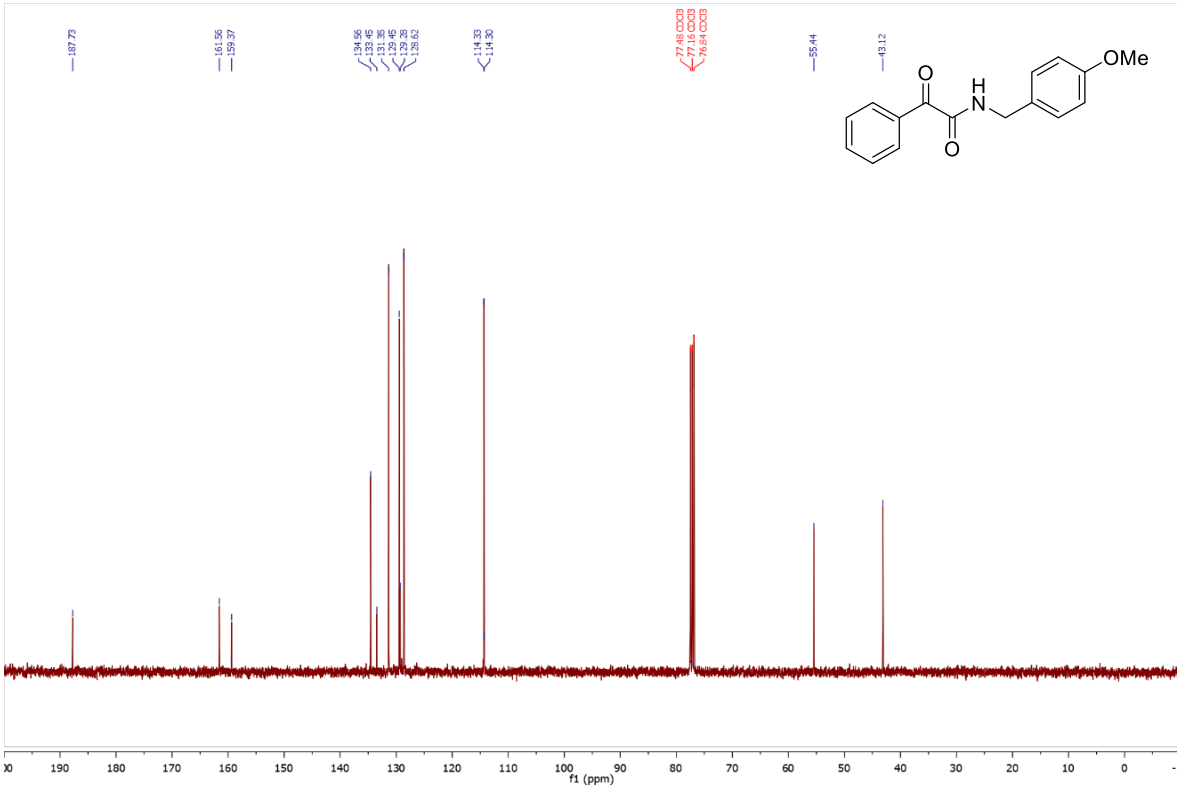
Benzyl(2-oxo-2-phenylacetyl)carbamate, 1k



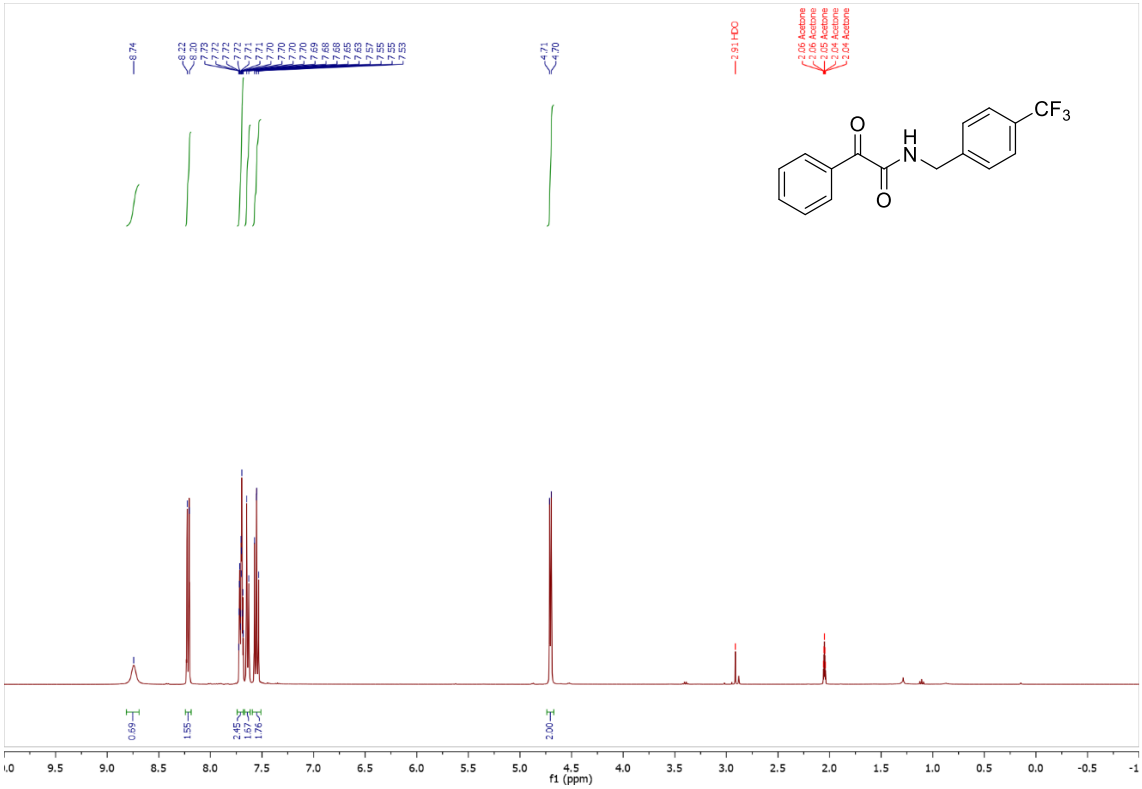


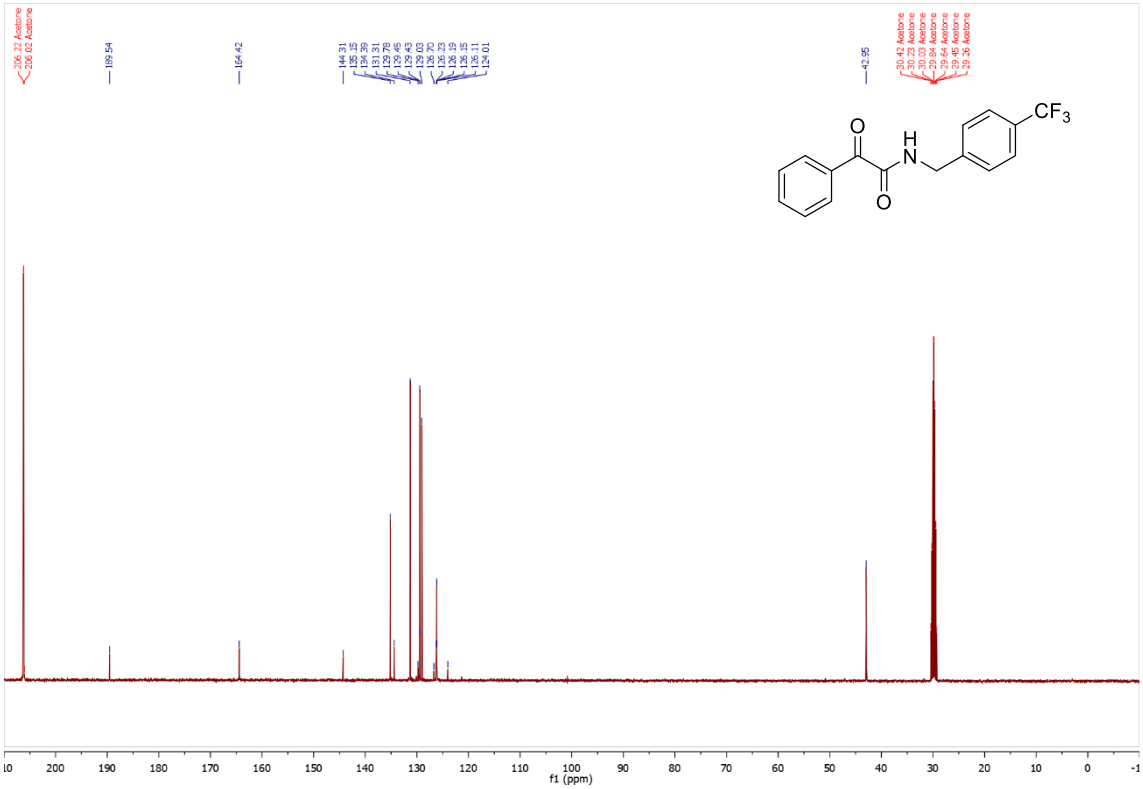
N-(4-Methoxybenzyl)-2-oxo-2-phenylacetamide, 1l



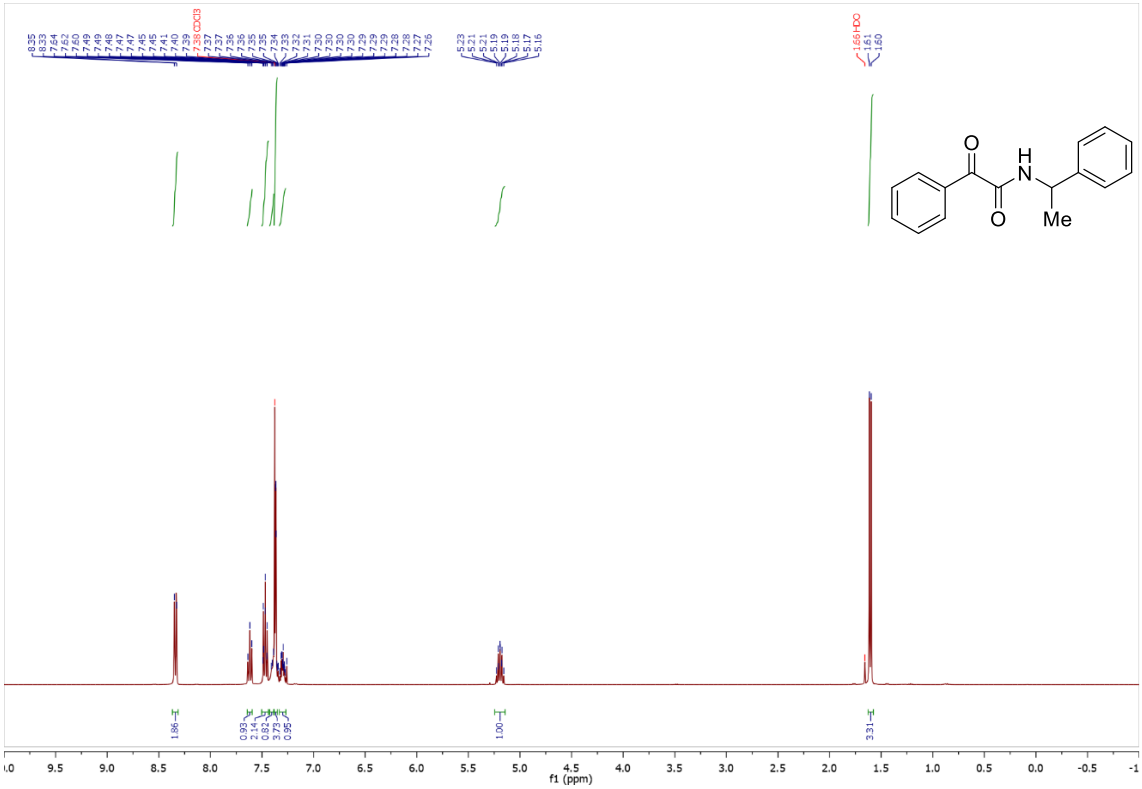


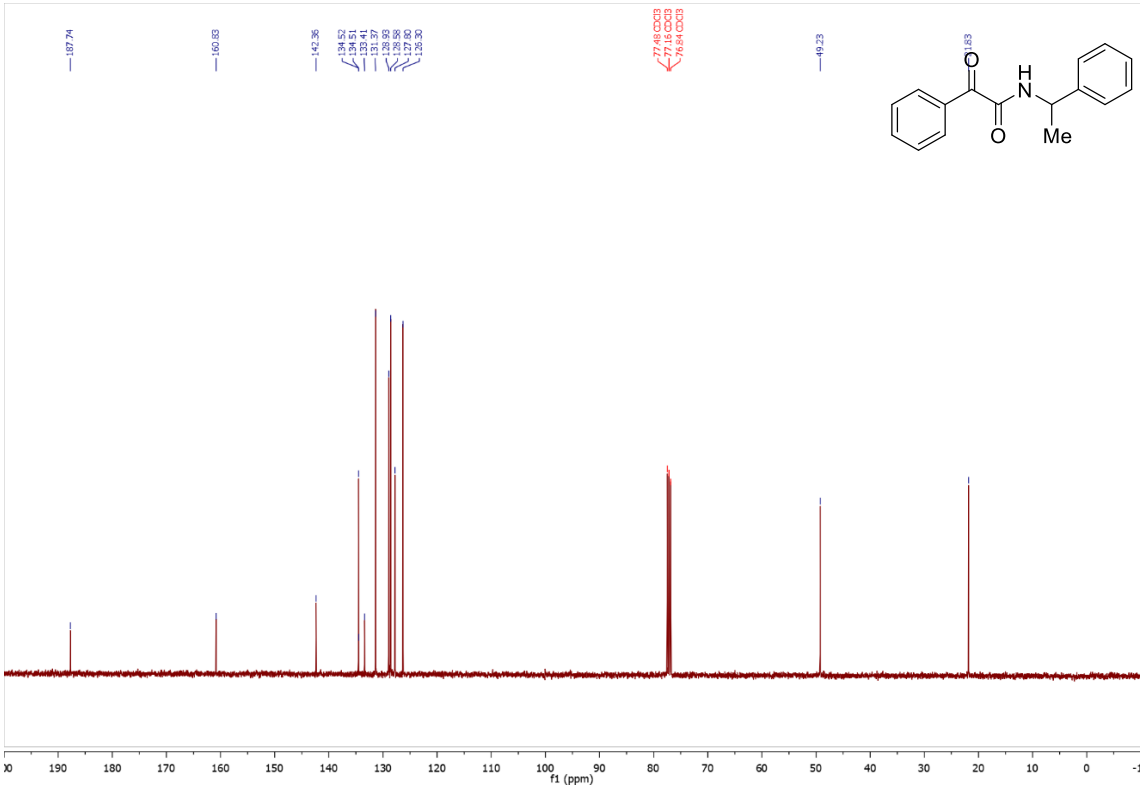
N-(4-(Trifluoromethyl)benzyl)-2-oxo-2-phenylacetamide, 1m



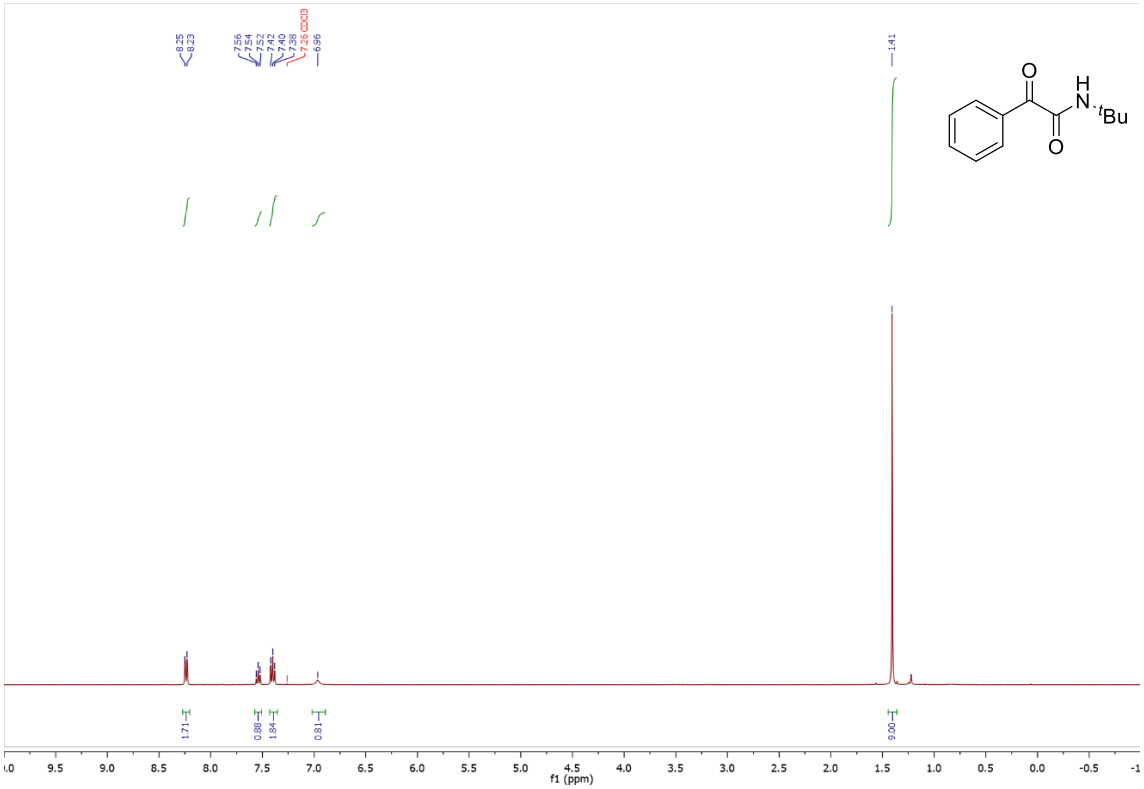


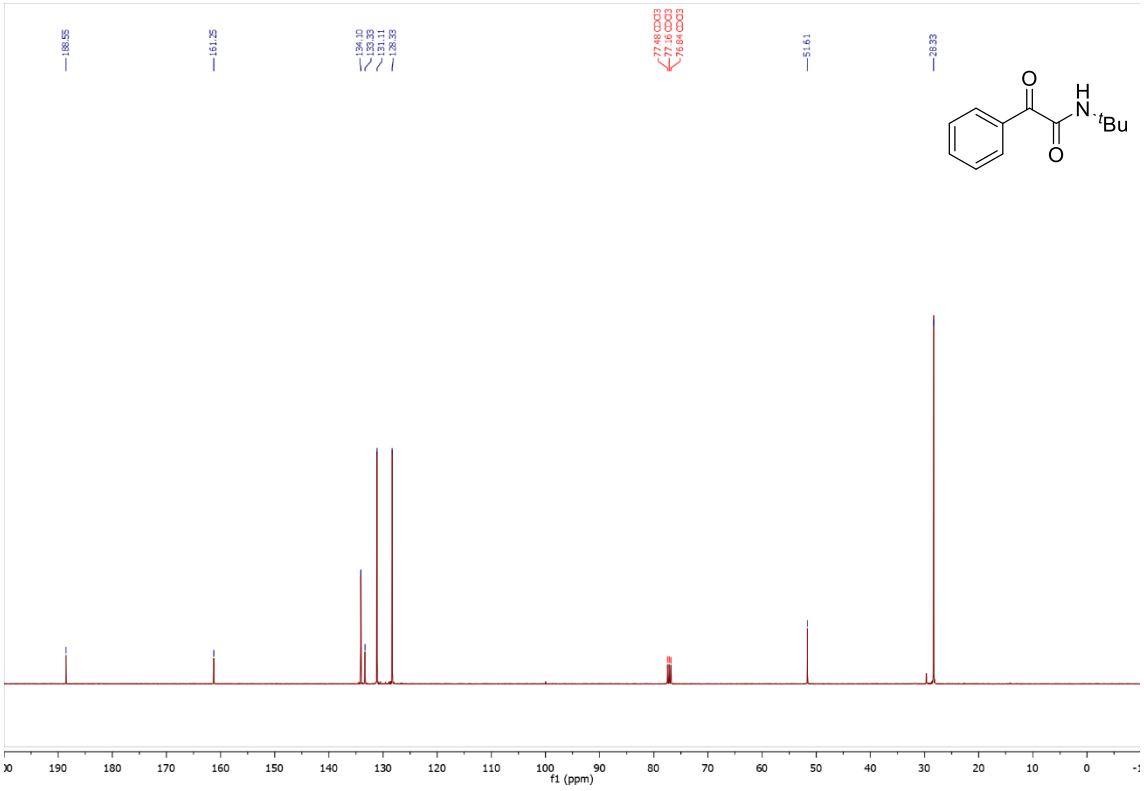
N-(1-Phenylethyl)-2-oxo-2-phenylacetamide, 1n



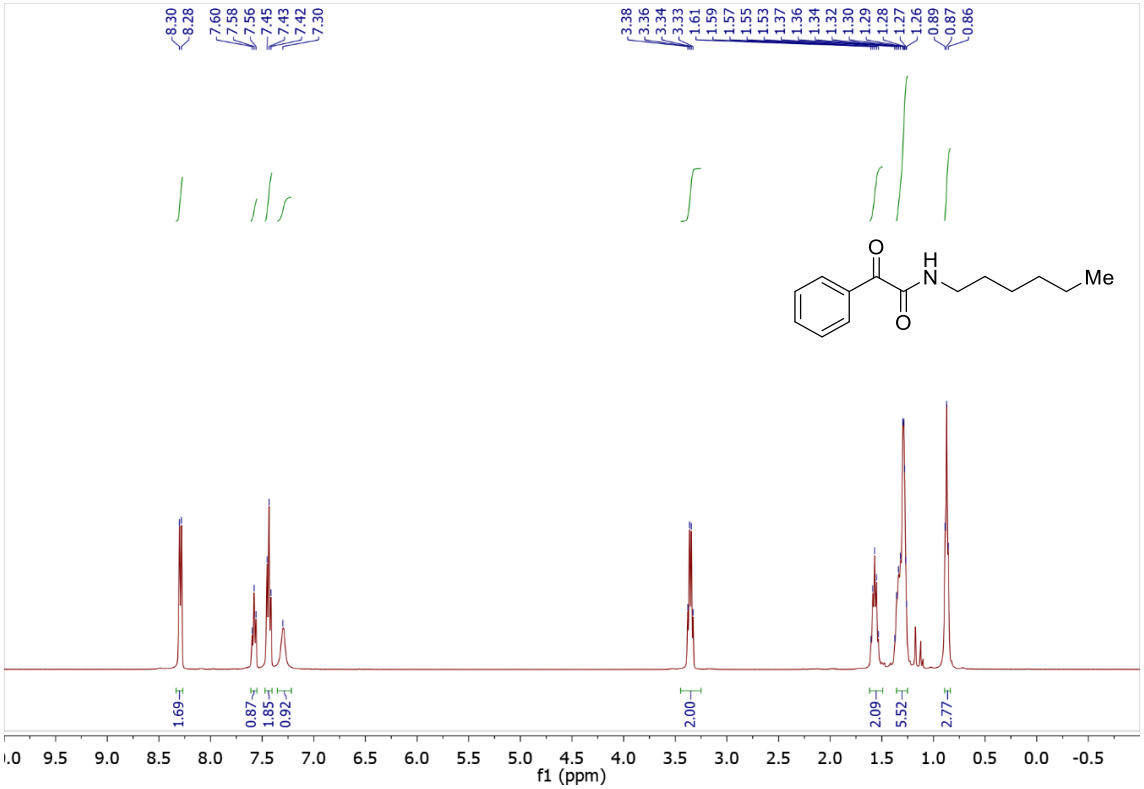


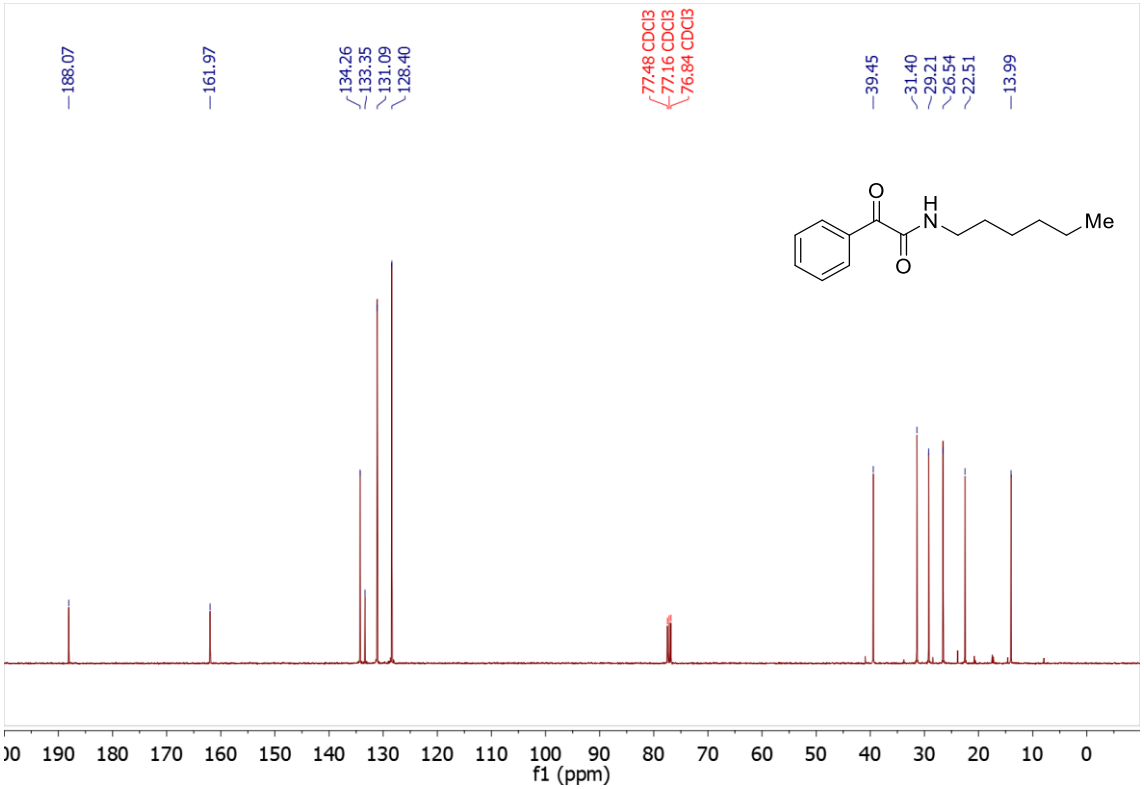
N-(*tert*-Butyl)-2-oxo-2-phenylacetamide, 1o



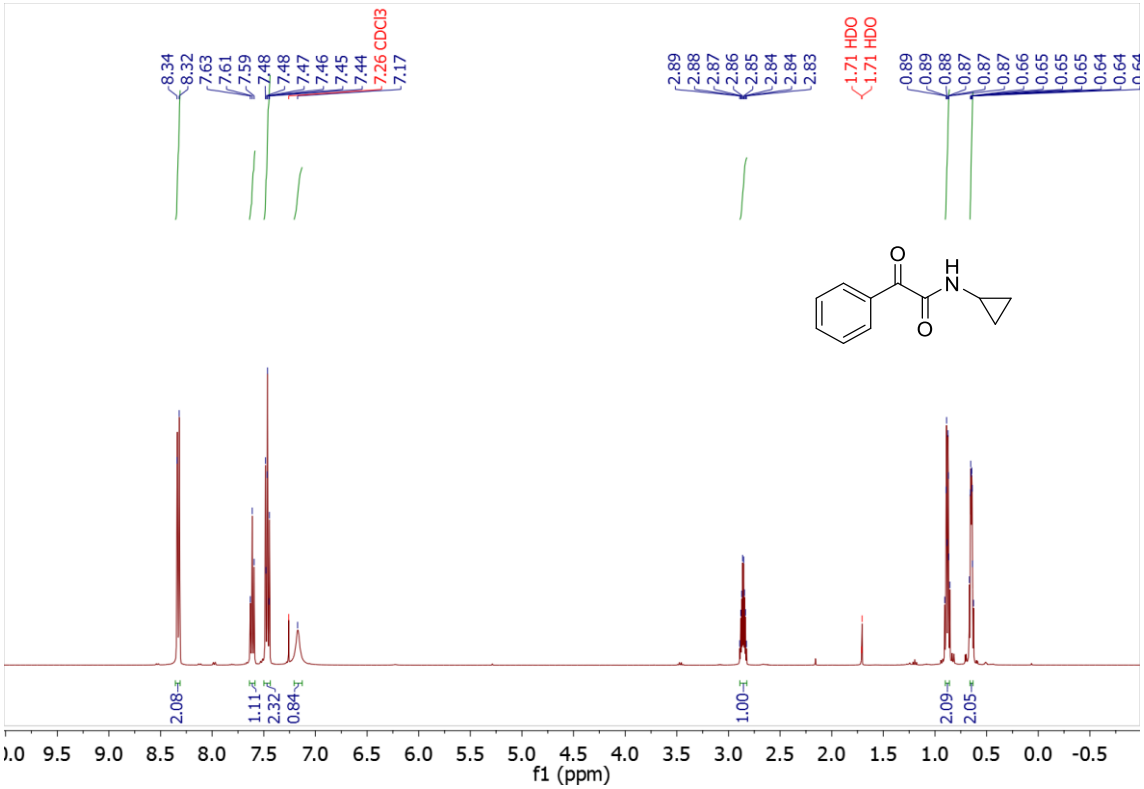


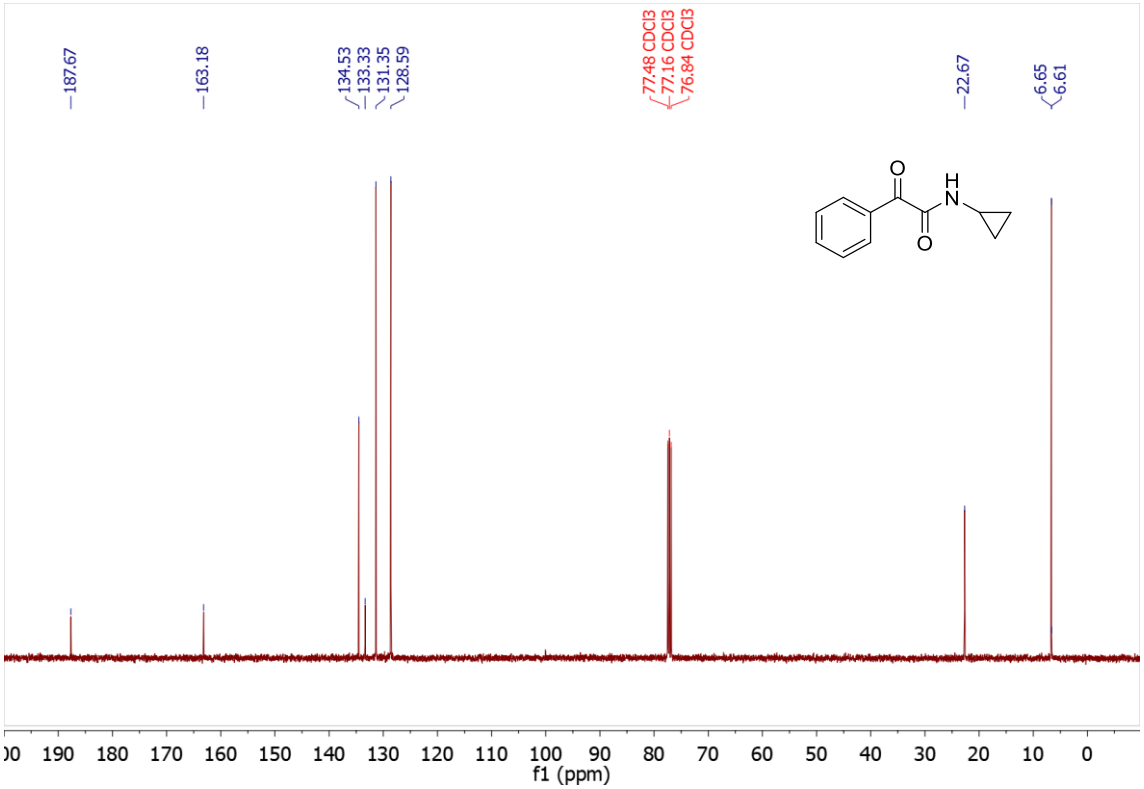
N-Hexyl-2-oxo-2-phenylacetamide, 1p



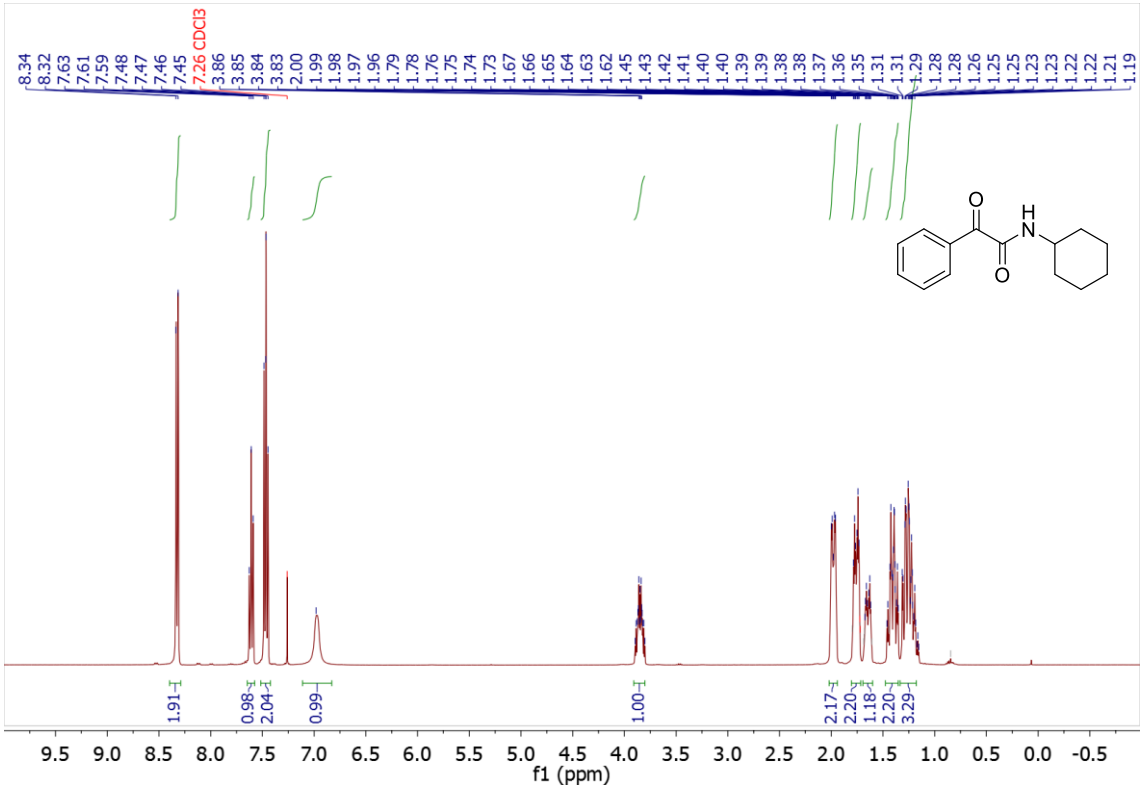


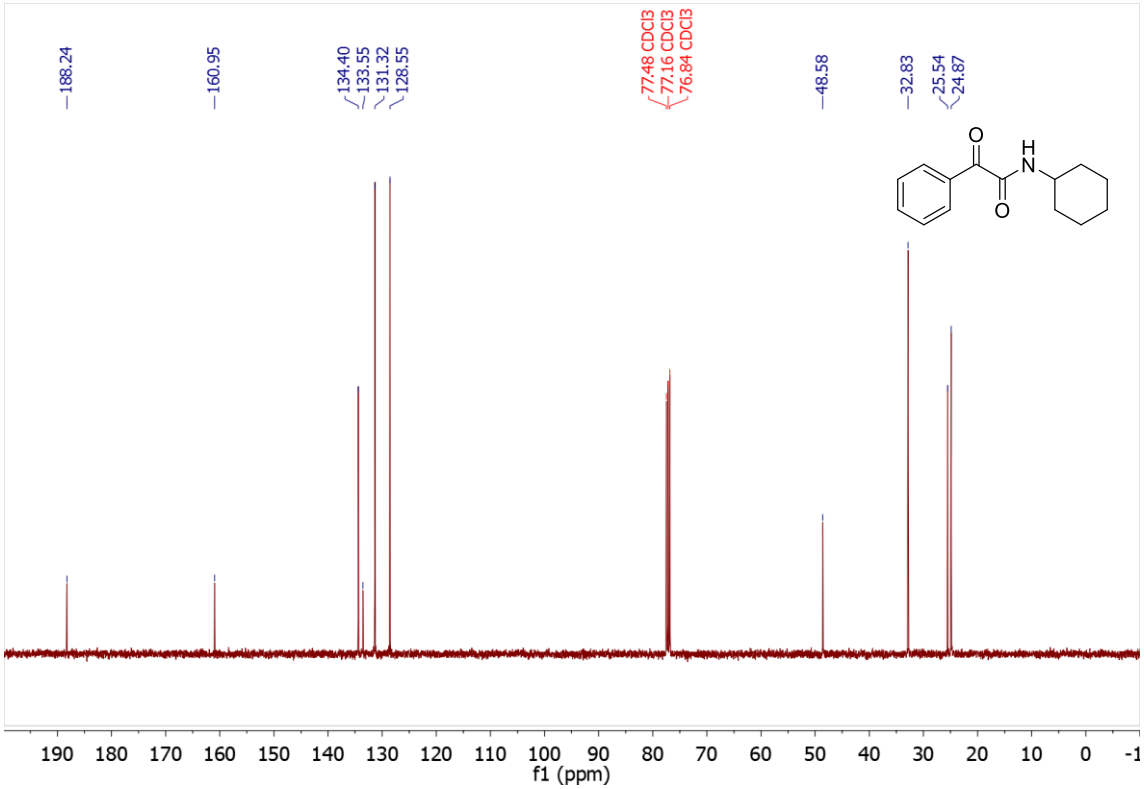
N-Cyclopropyl-2-oxo-2-phenylacetamide, 1q



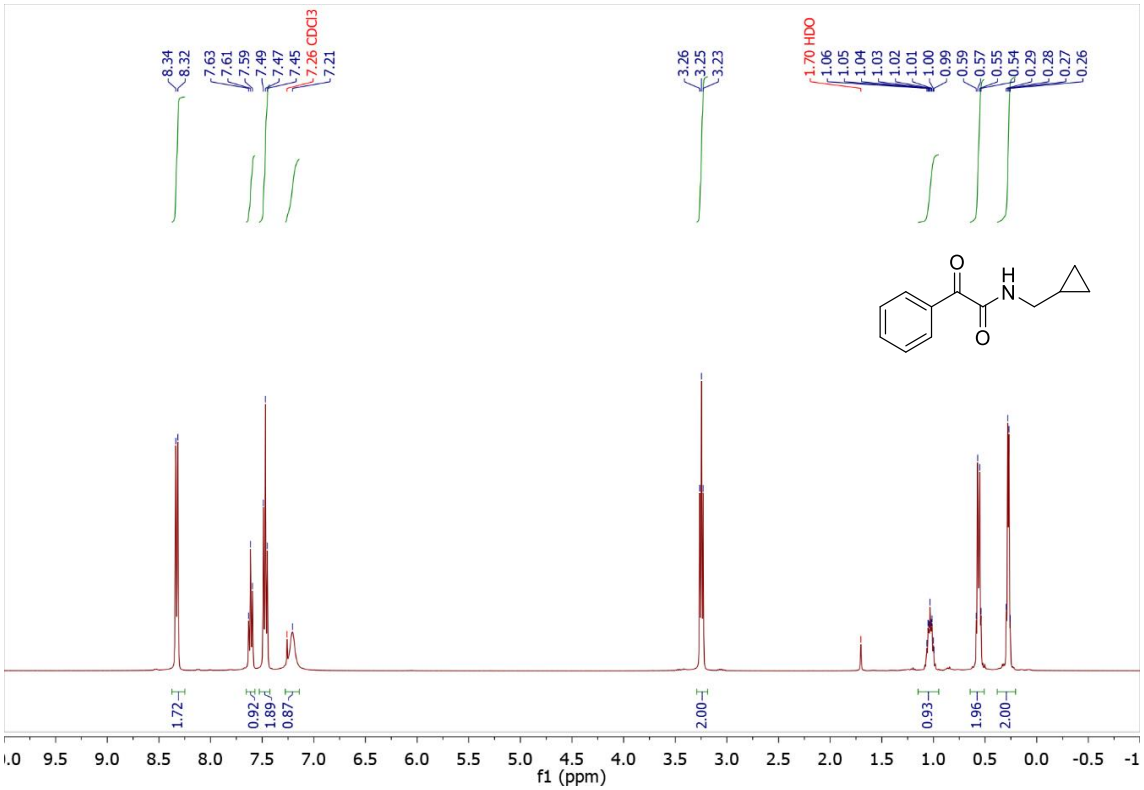


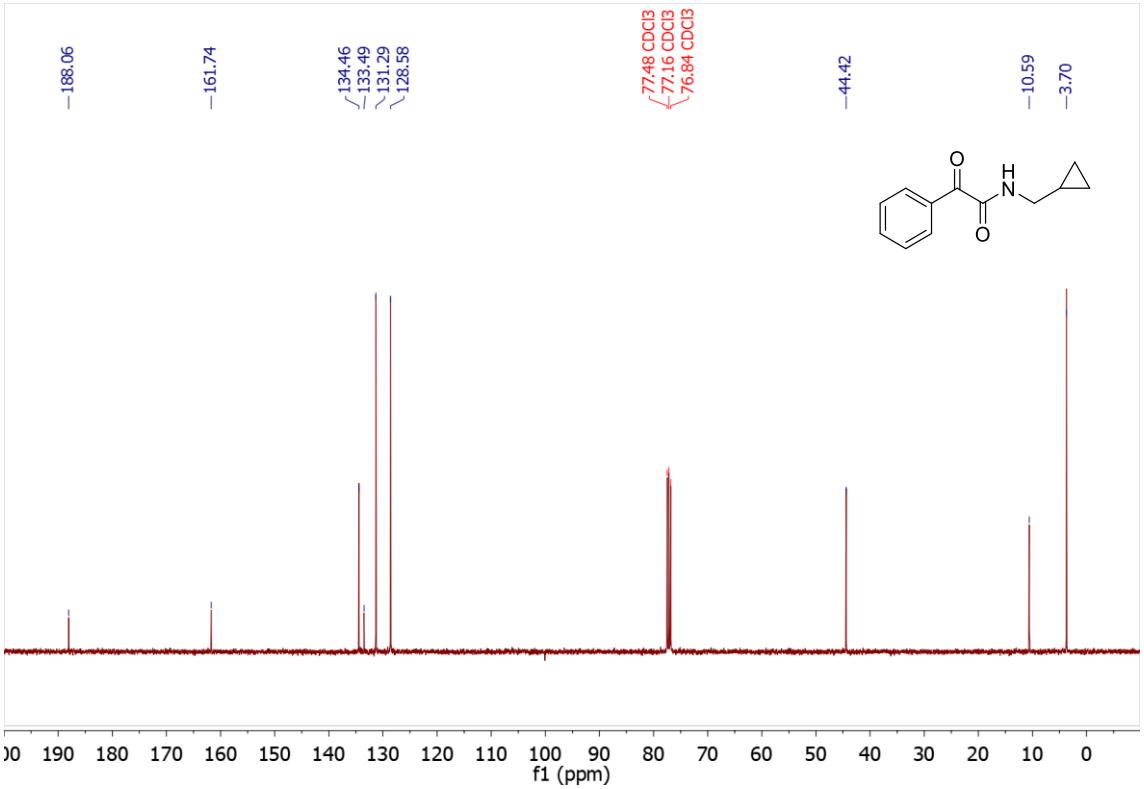
N-Cyclohexyl-2-oxo-2-phenylacetamide, 1r



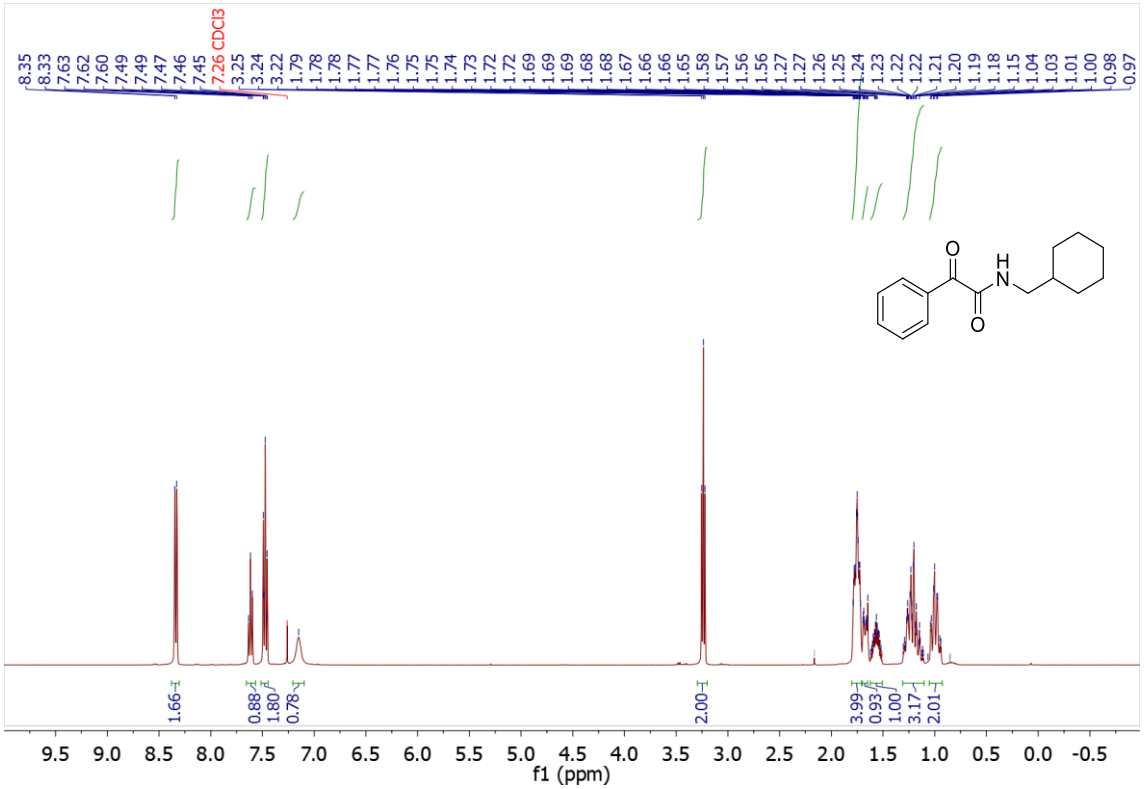


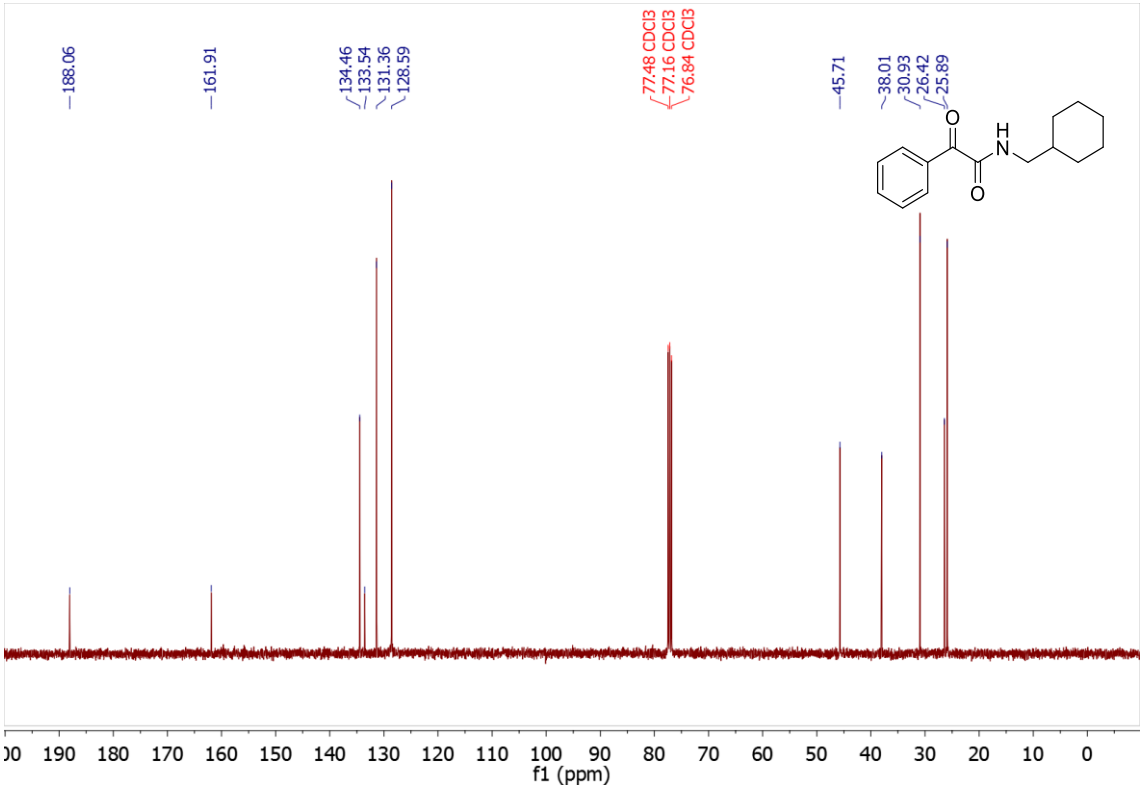
N-(Cyclopropylmethyl)-2-oxo-2-phenylacetamide, 1s



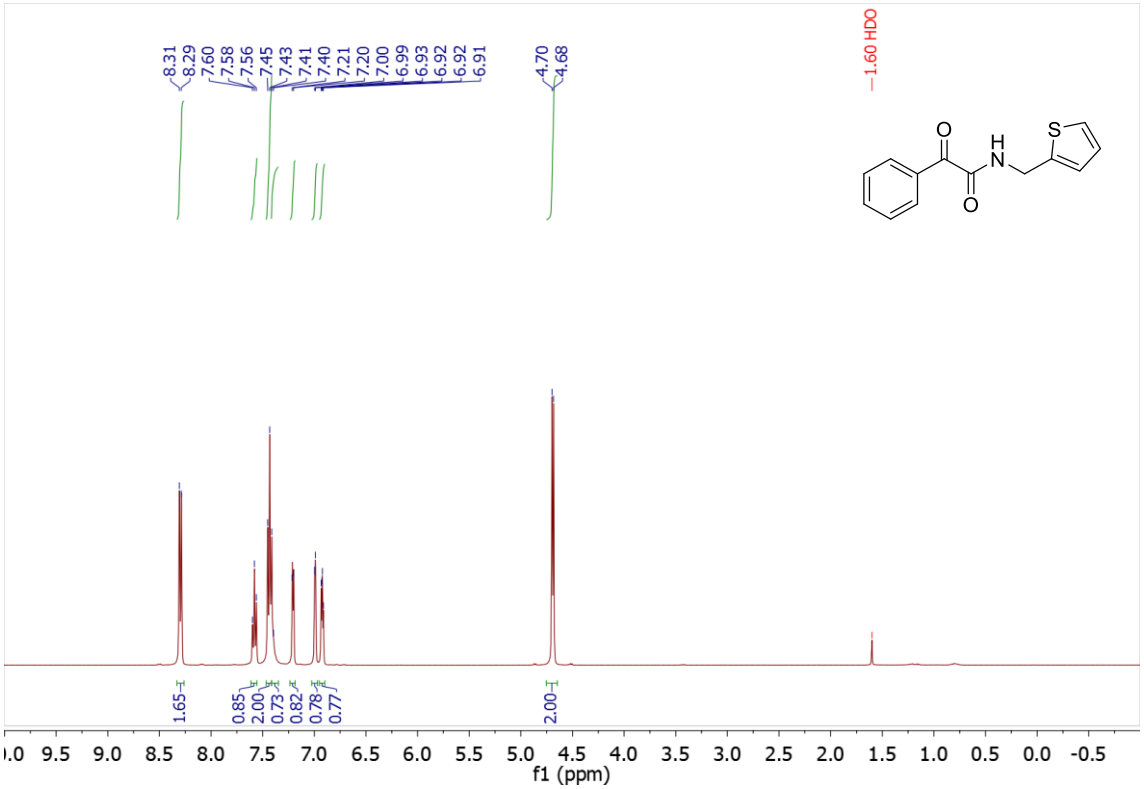


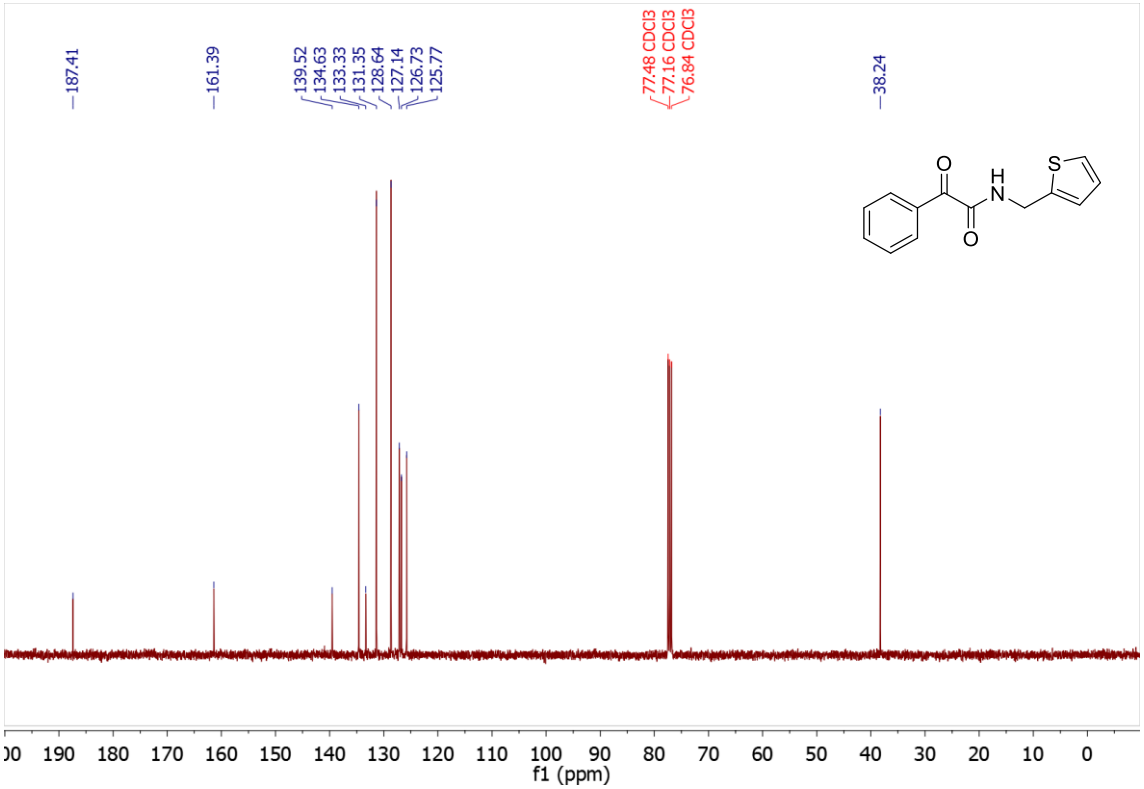
_N_-(Cyclohexylmethyl)-2-oxo-2-phenylacetamide, 1t



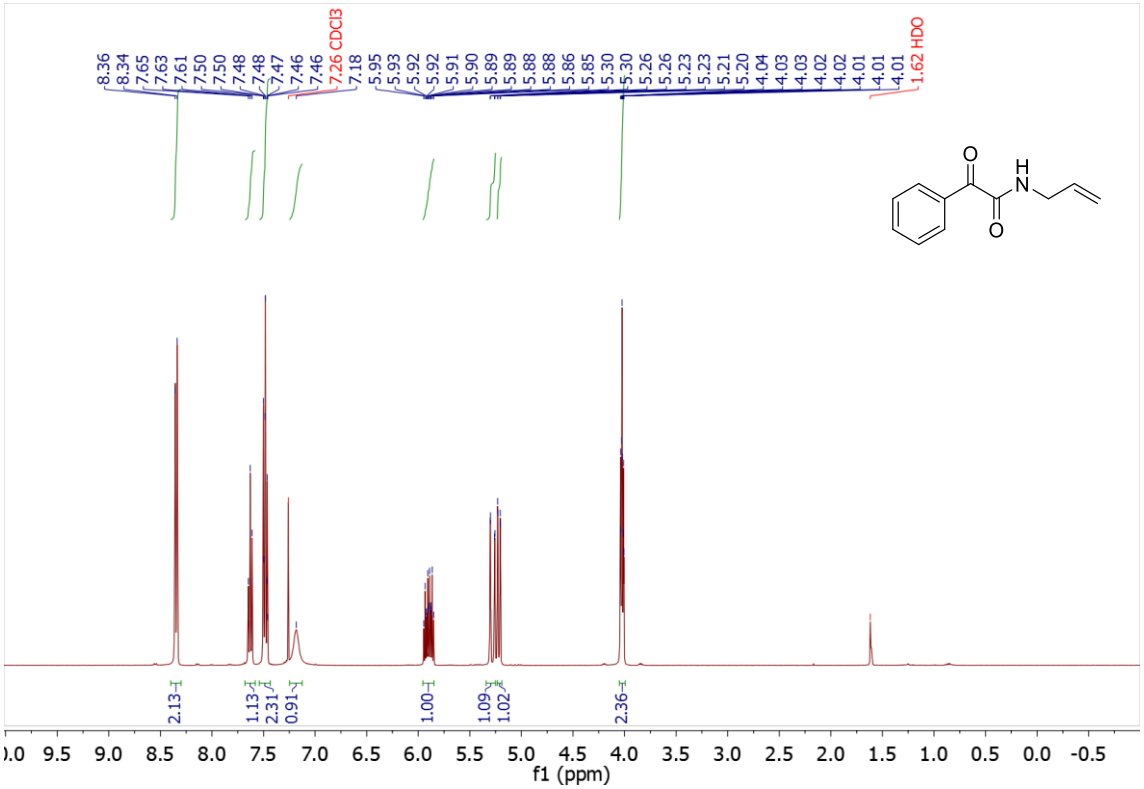


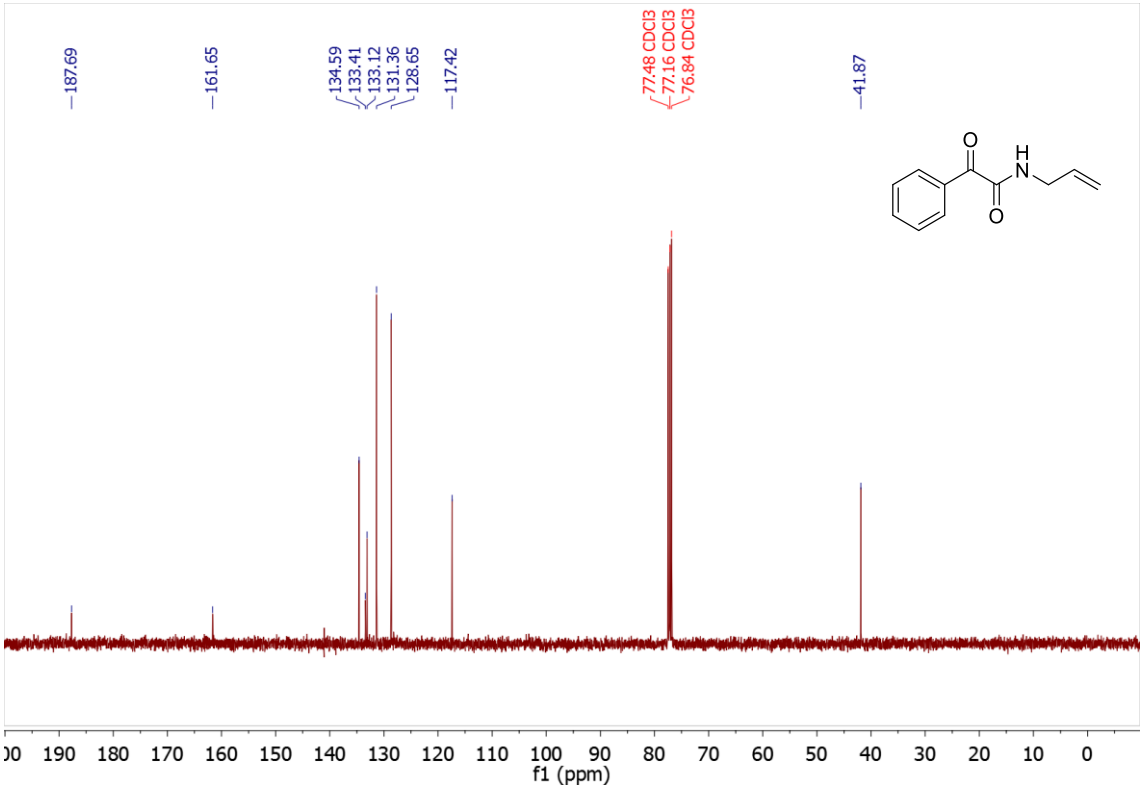
N-(Thiophen-2-ylmethyl)-2-oxo-2-phenylacetamide, 1u



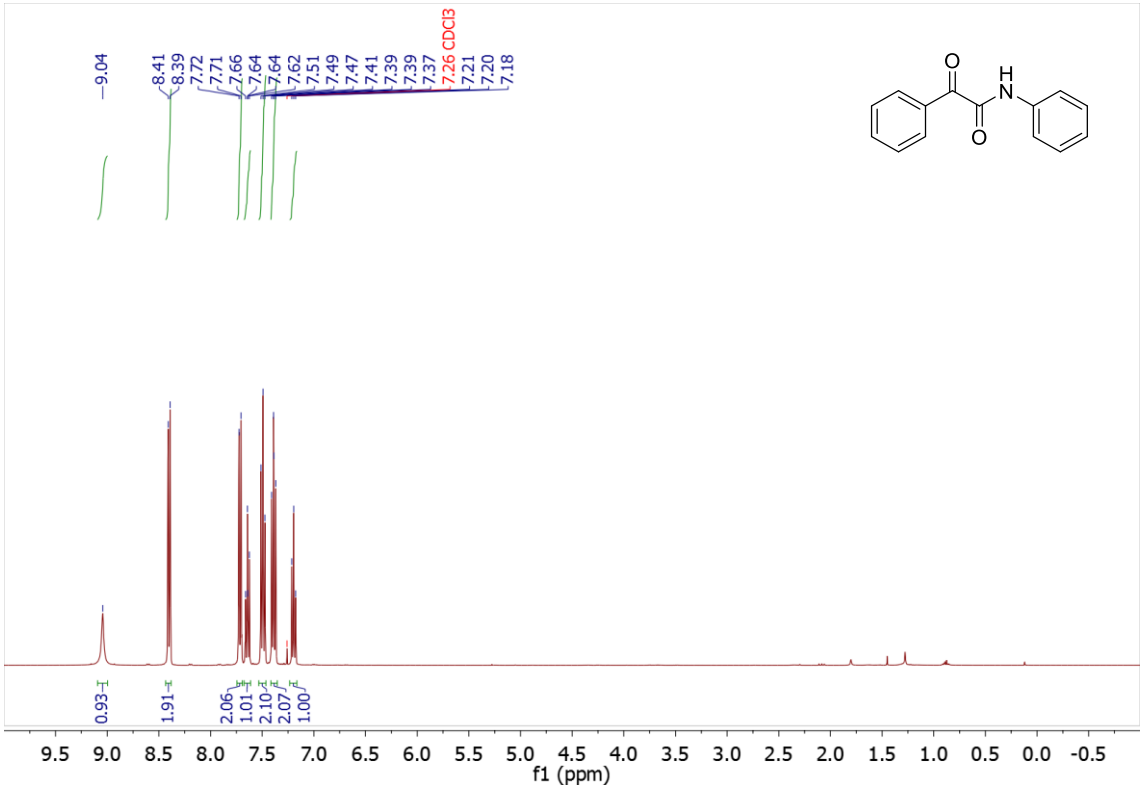


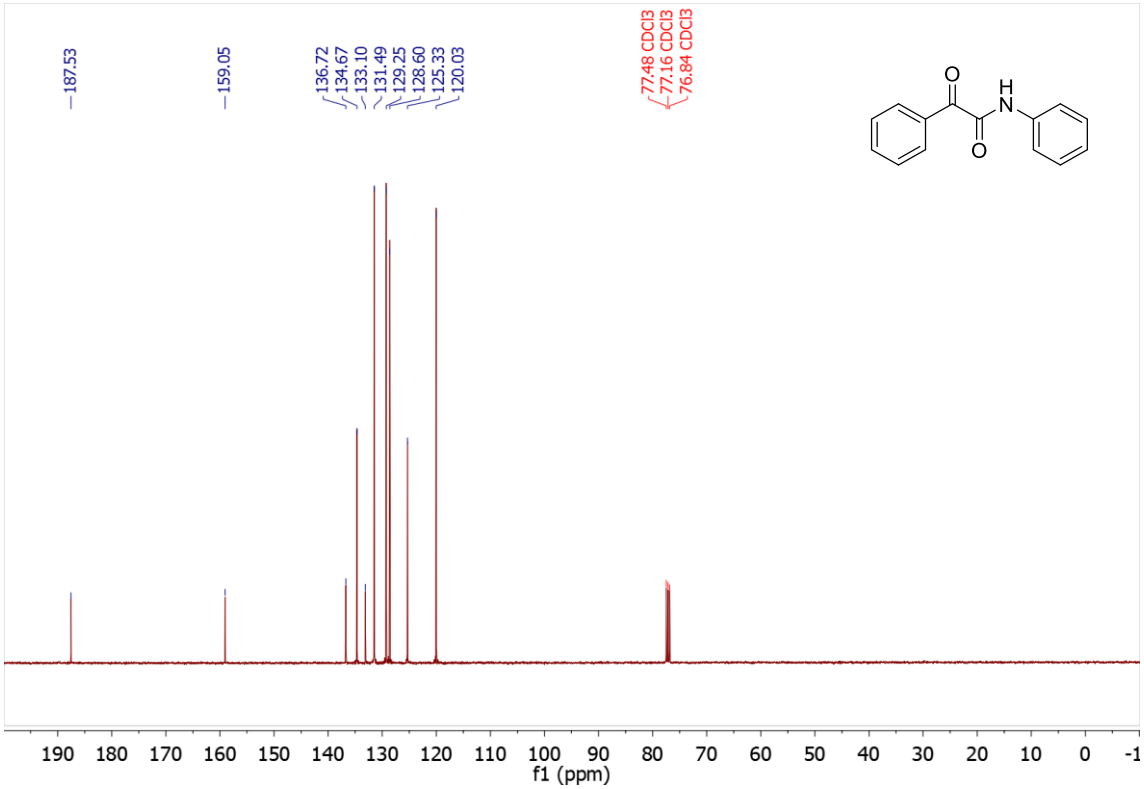
N-Allyl-2-oxo-2-phenylacetamide, 1v



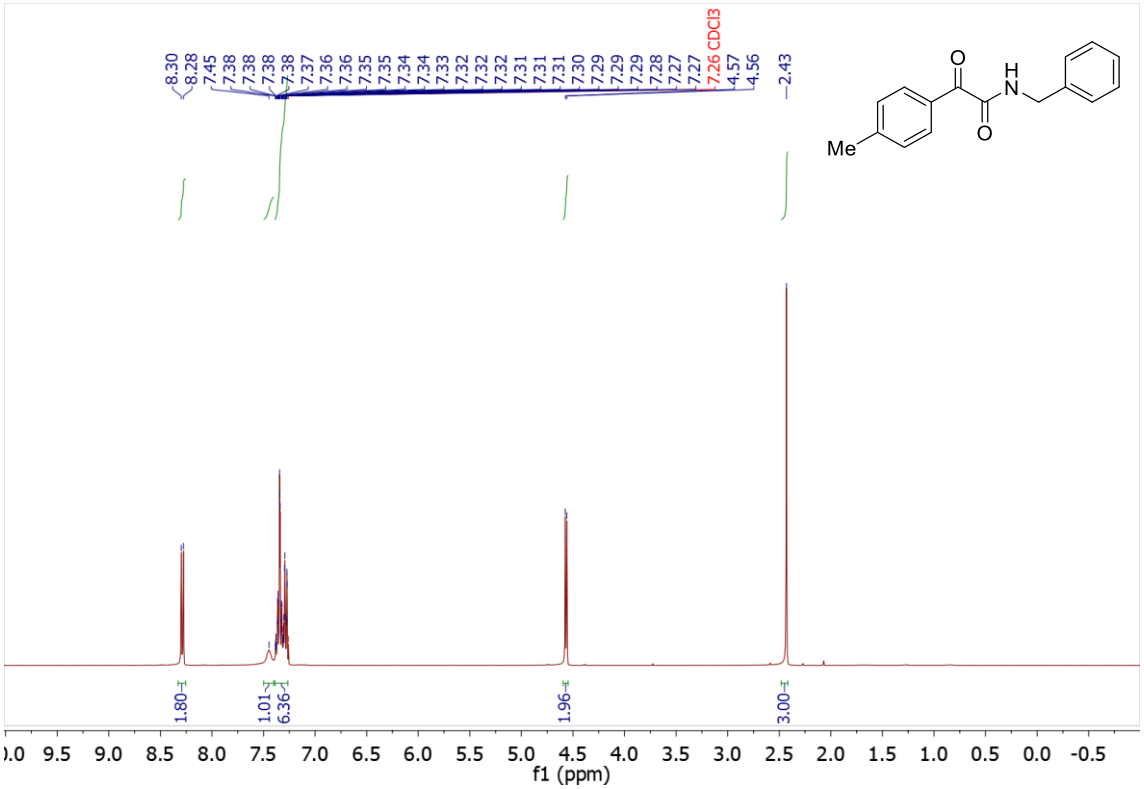


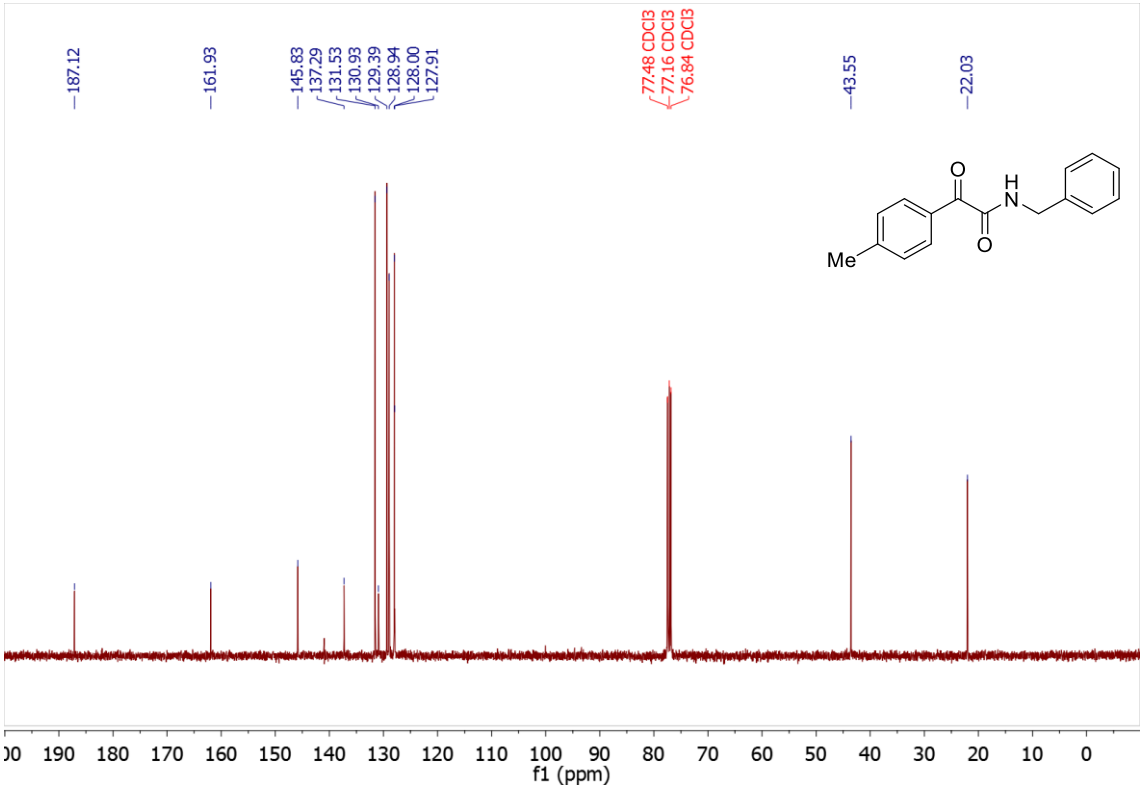
N-Phenyl-2-oxo-2-phenylacetamide, 1w



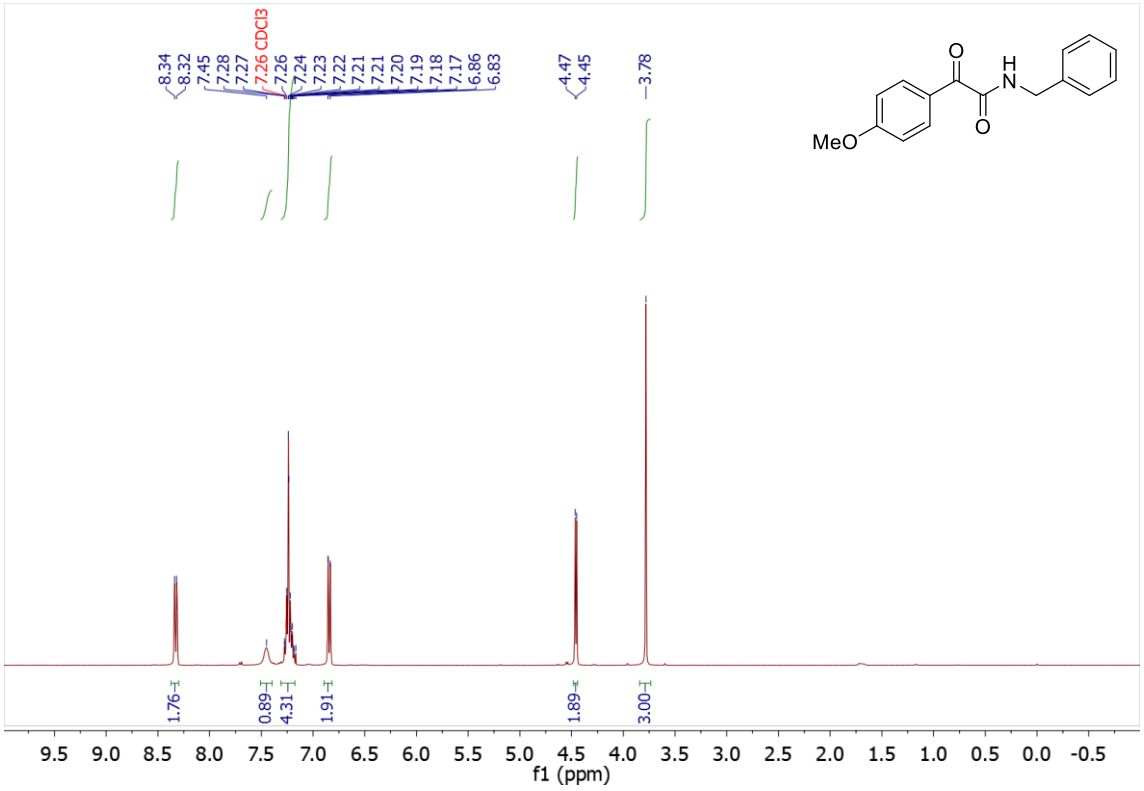


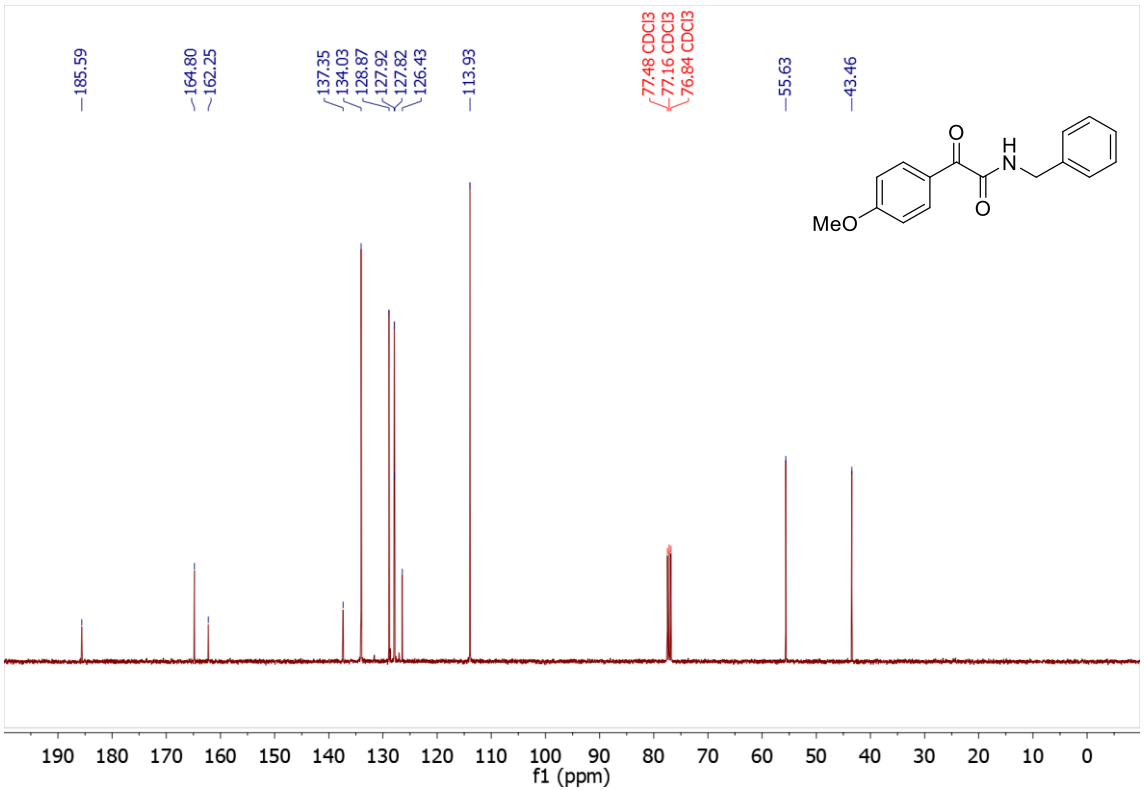
_N_-Benzyl-2-oxo-2-(_p_-tolyl)acetamide, 4a



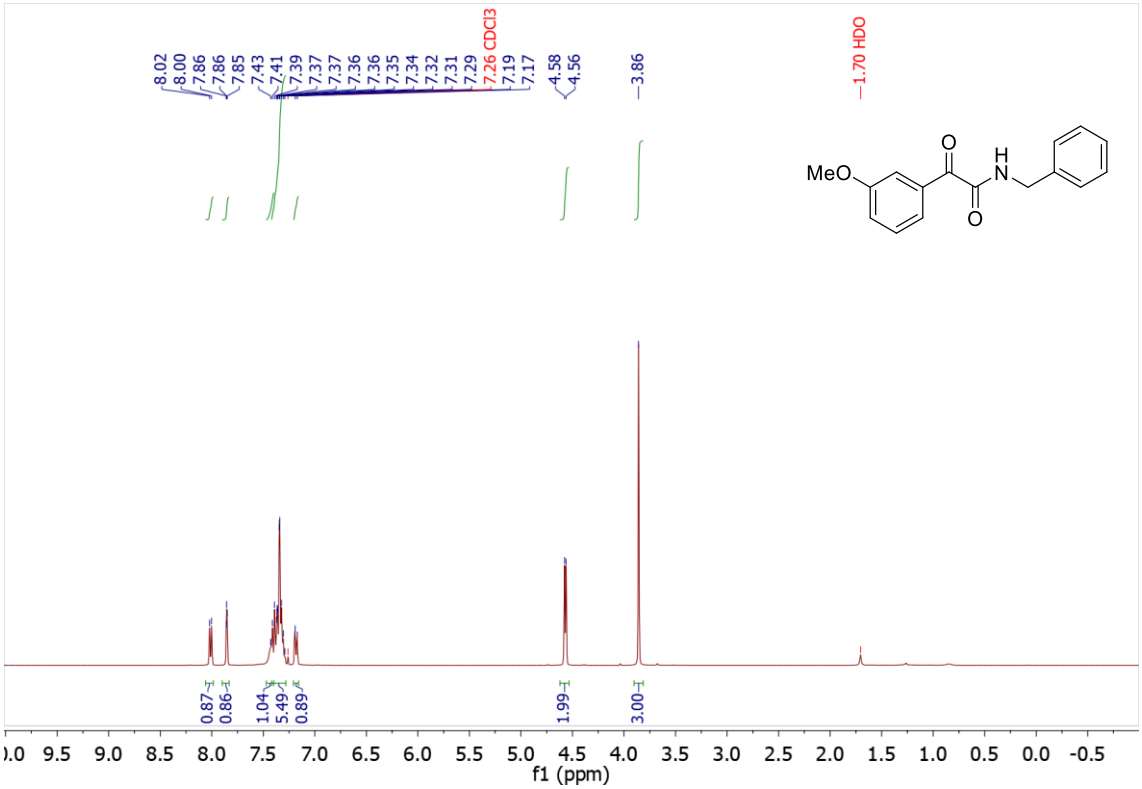


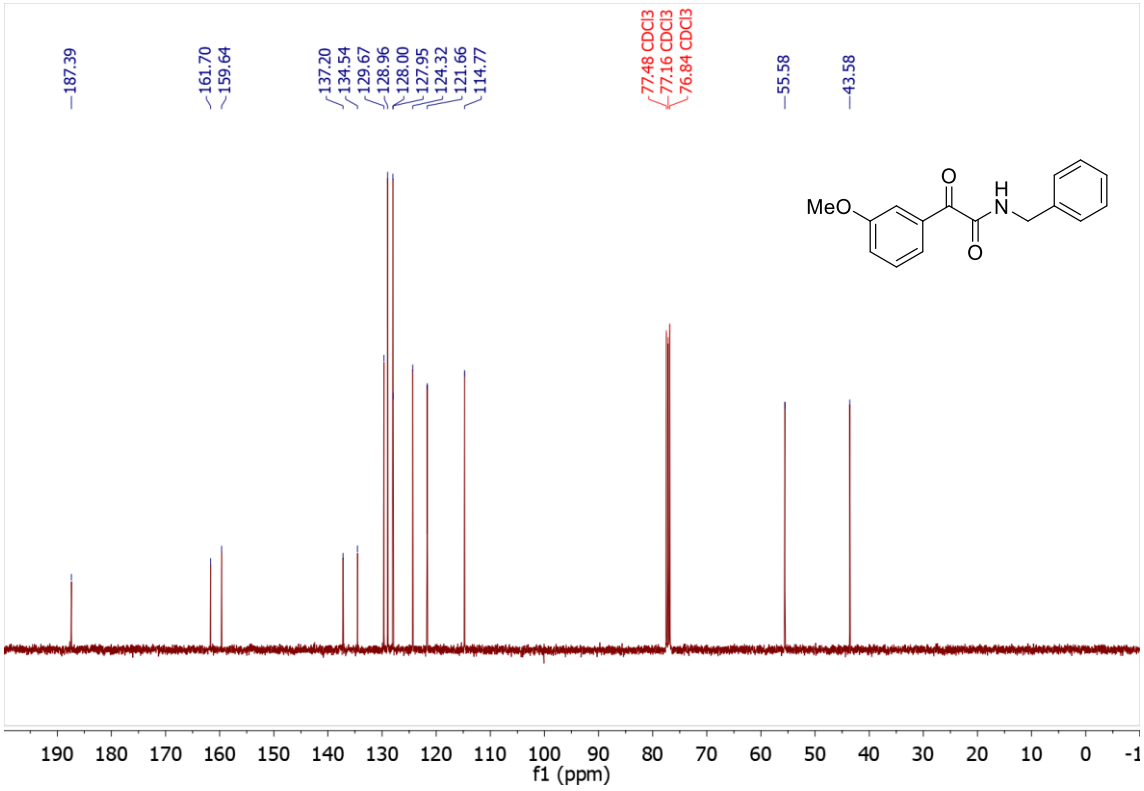
_N_-Benzyl-2-oxo-2-(3-methoxyphenyl)acetamide, 4b



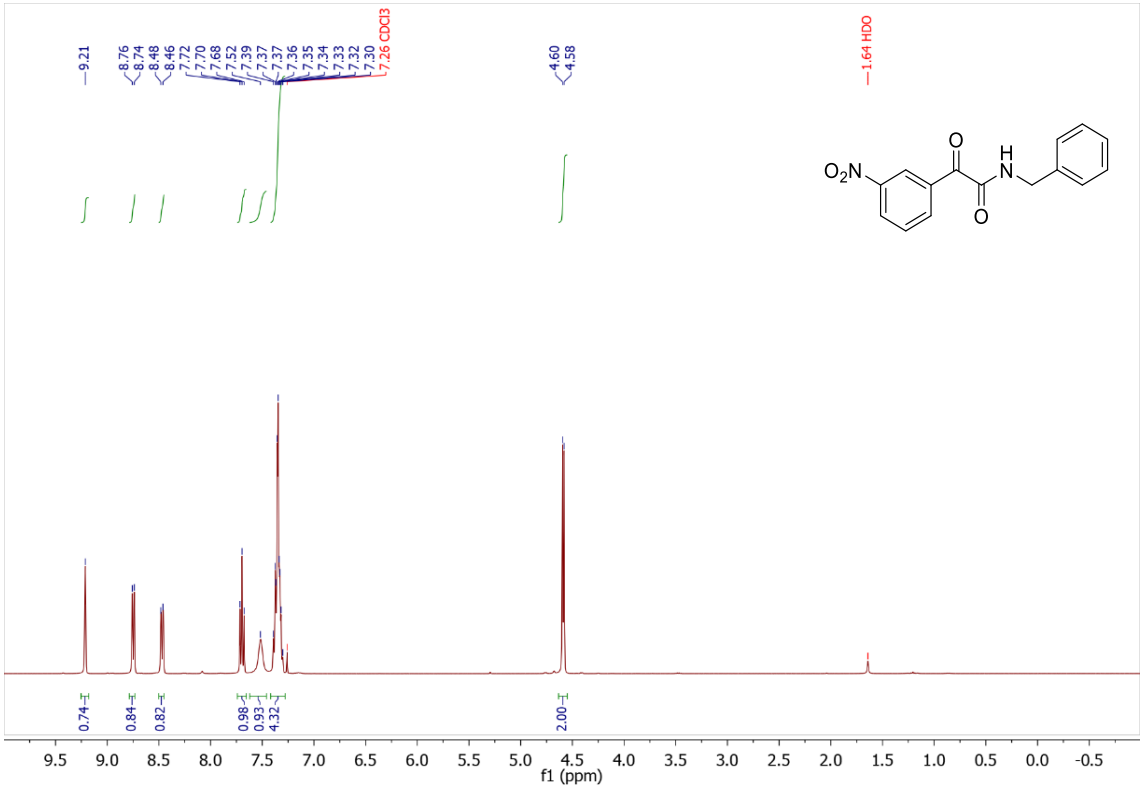


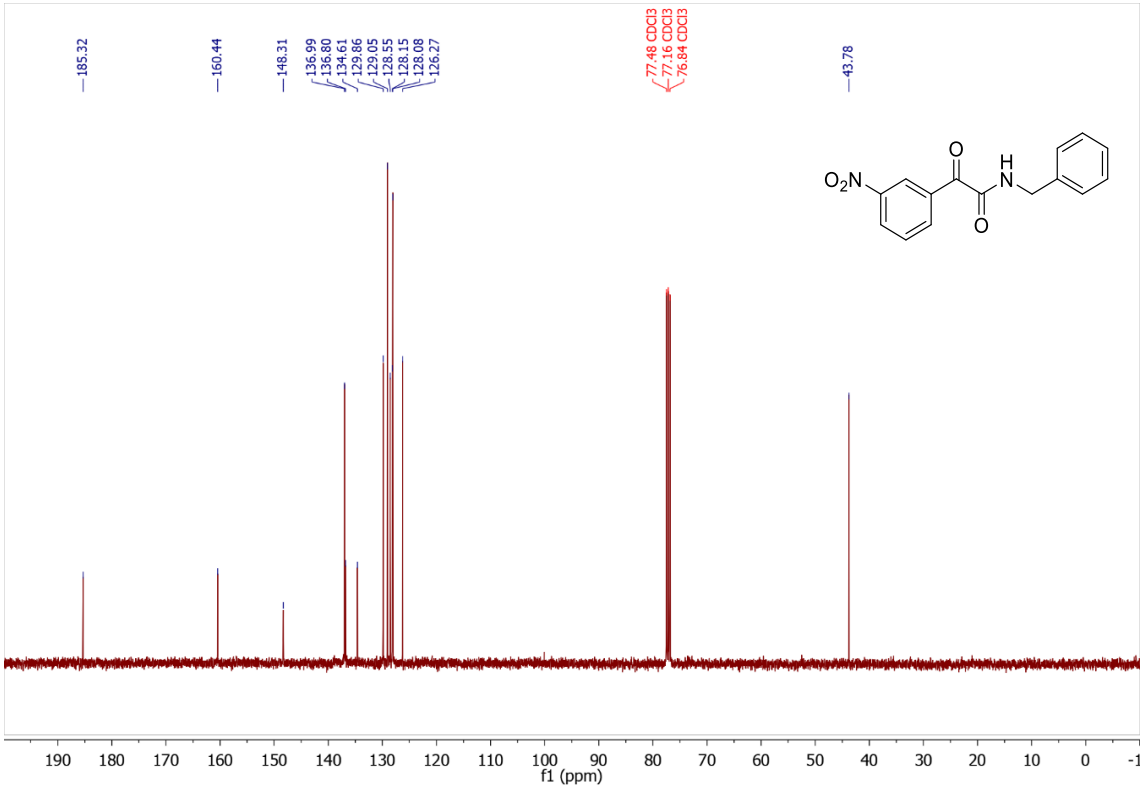
_N_-Benzyl-2-oxo-2-(3-methoxyphenyl)acetamide, 4c



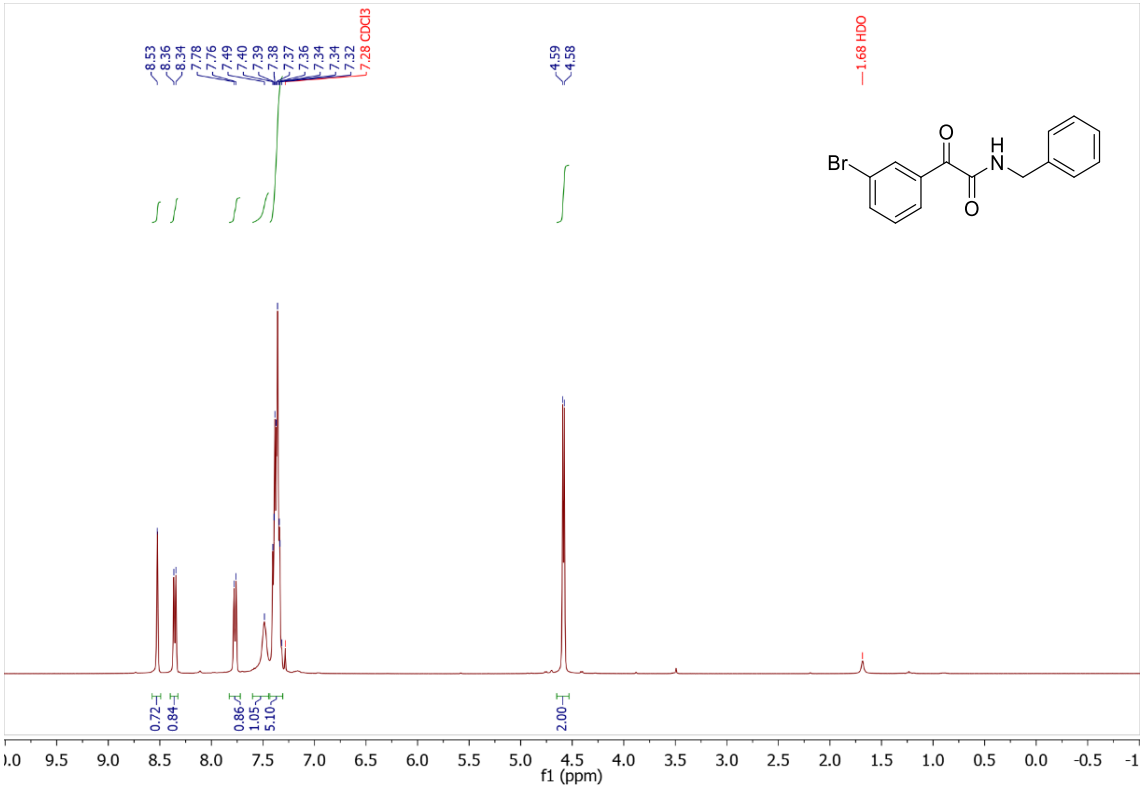


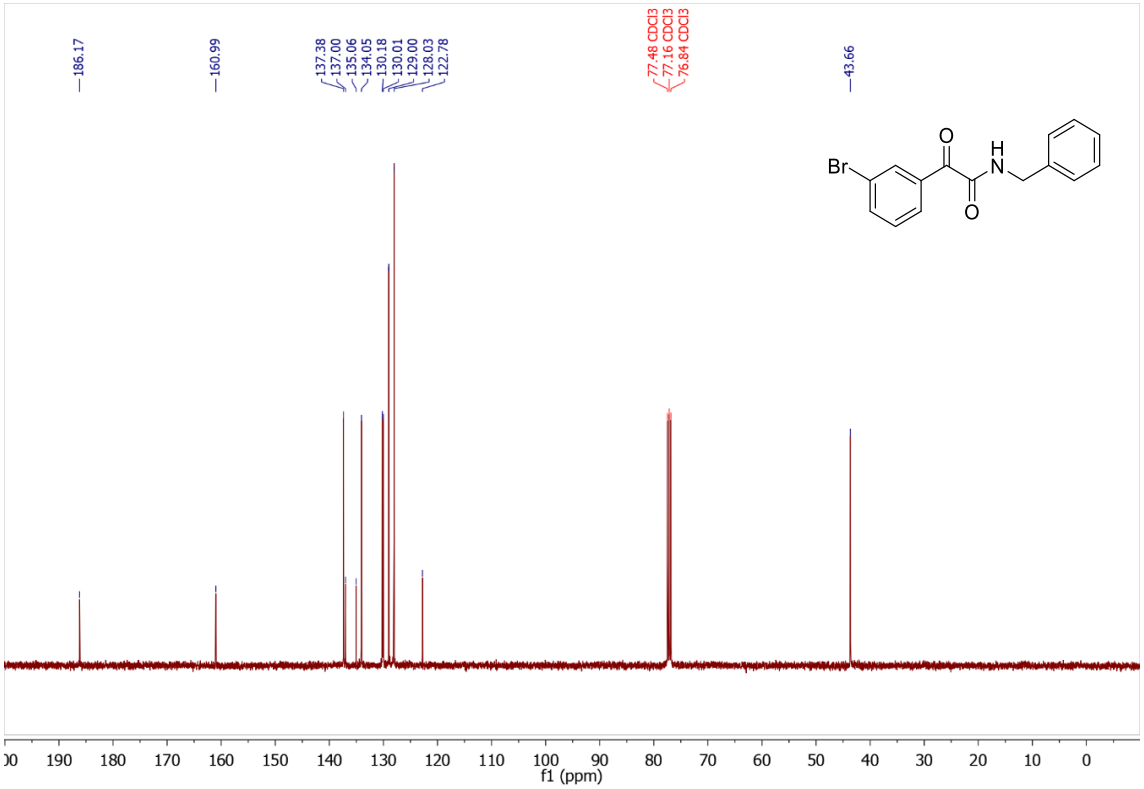
N-Benzyl-2-oxo-2-(3-nitrophenyl)acetamide, 4d



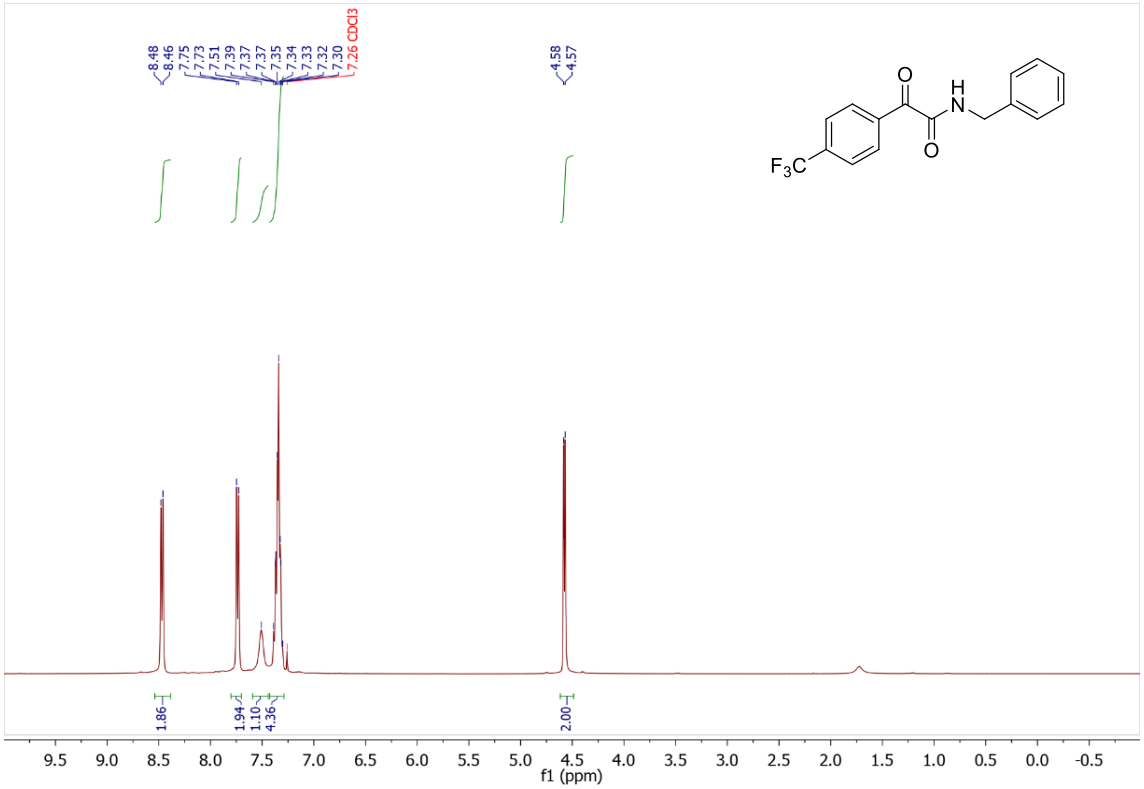


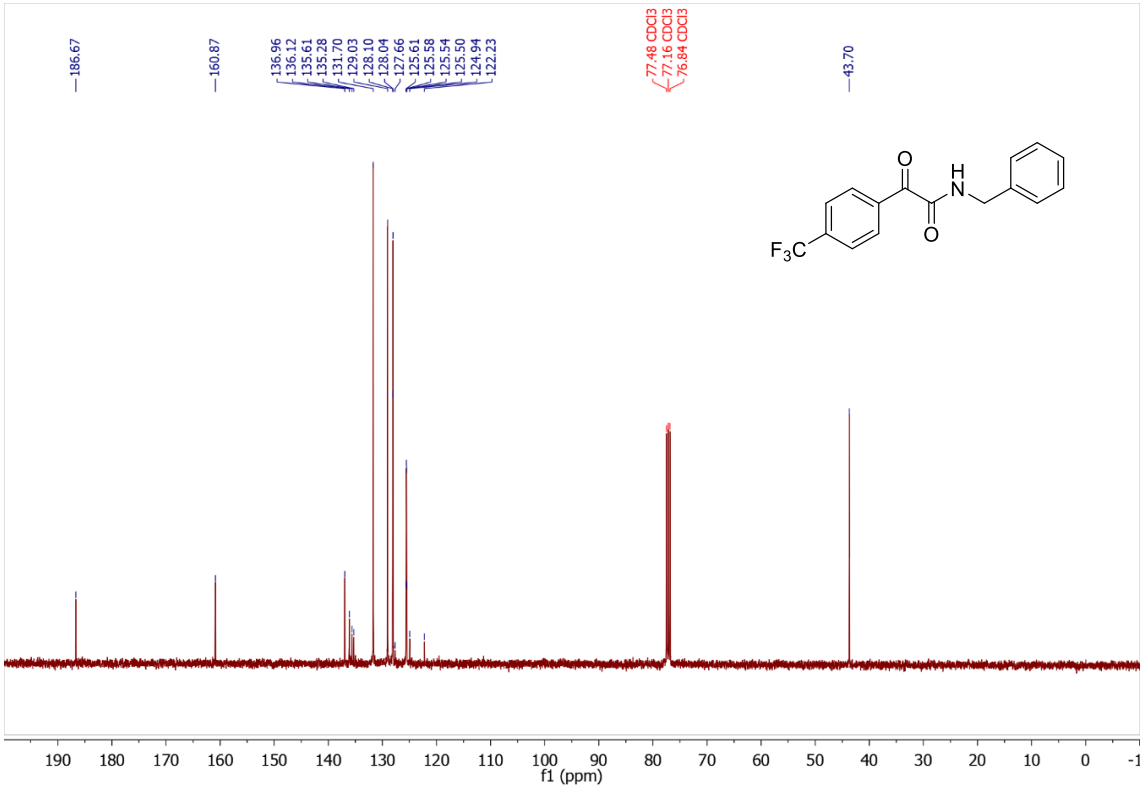
N-Benzyl-2-oxo-2-(3-bromophenyl)acetamide, 4e



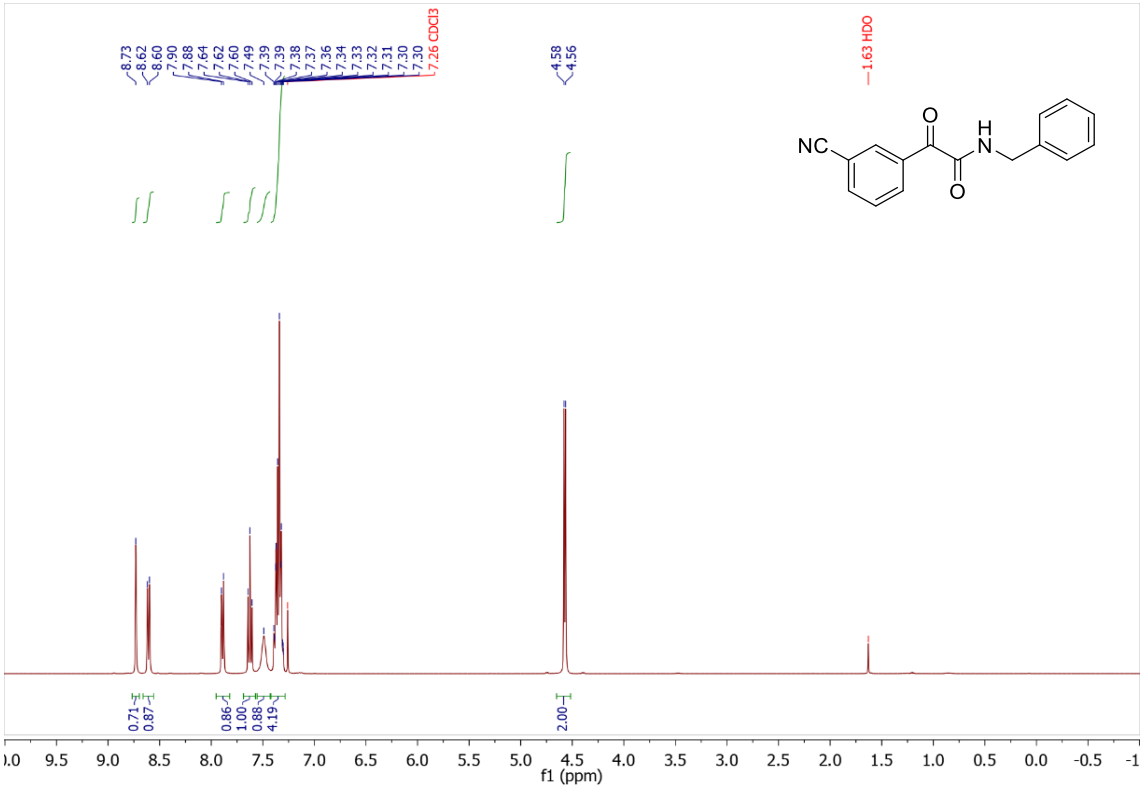


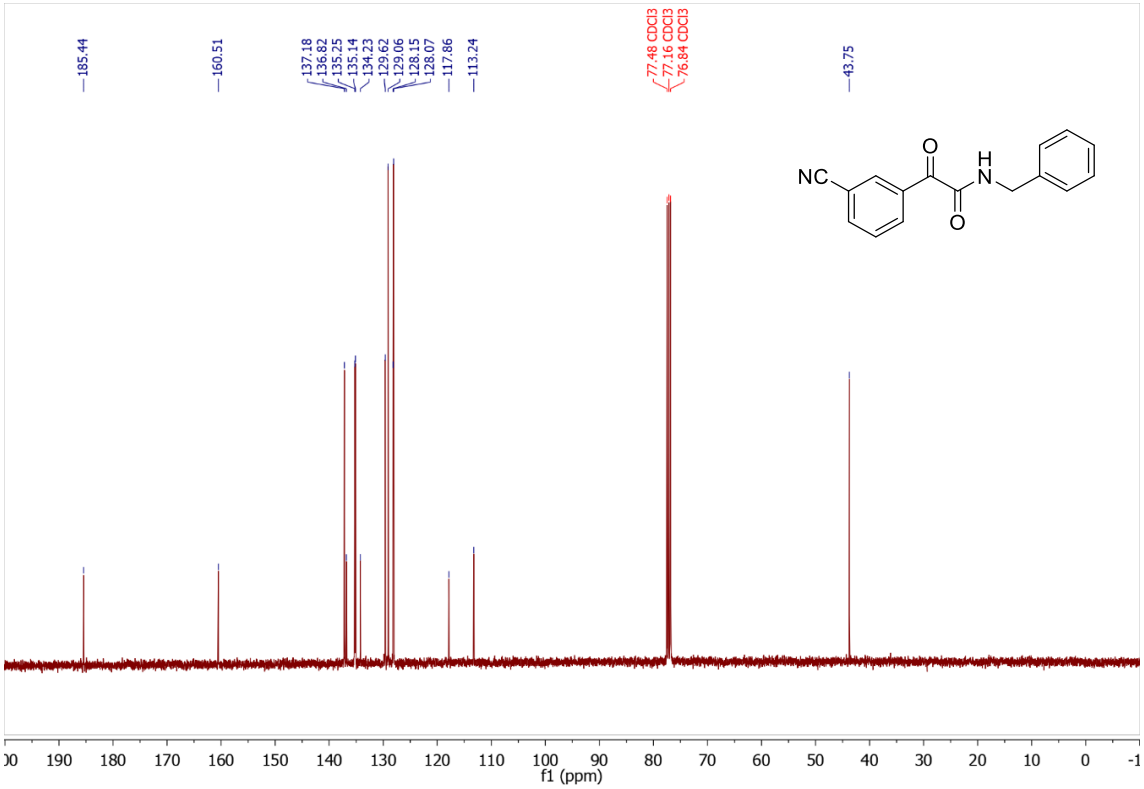
_N_-Benzyl-2-oxo-2-(4-(trifluoromethyl)phenyl)acetamide, 4f



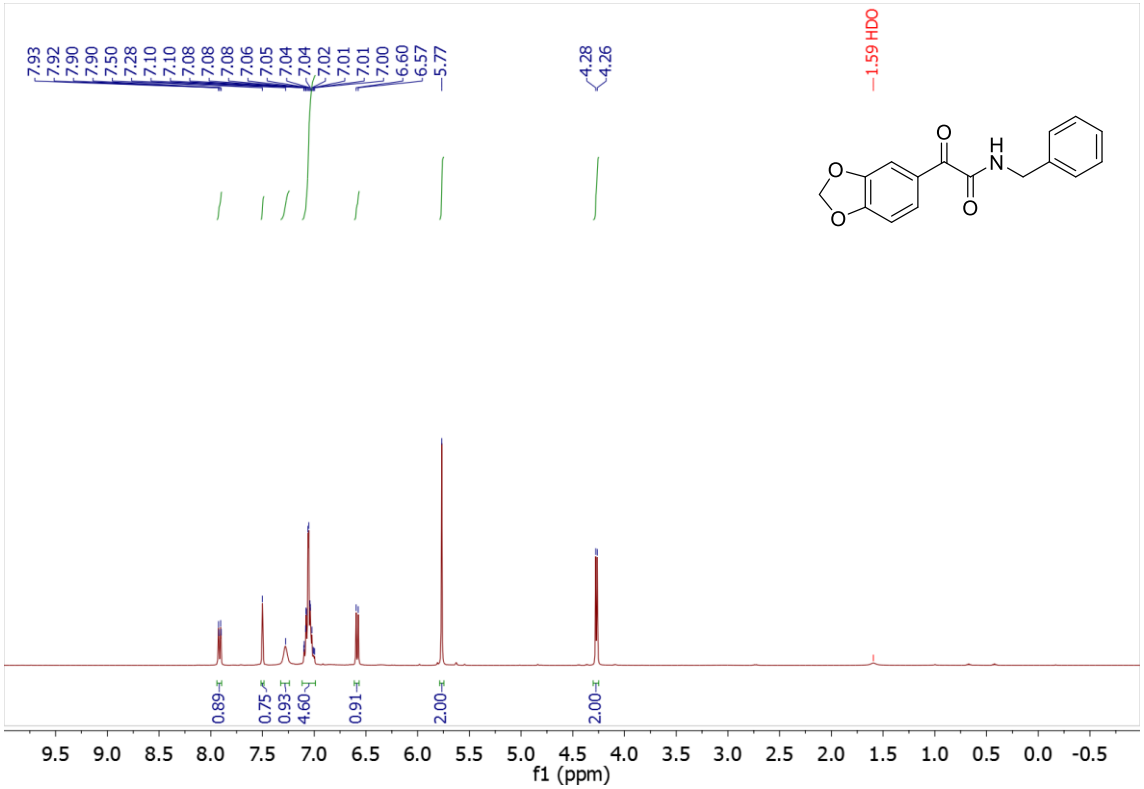


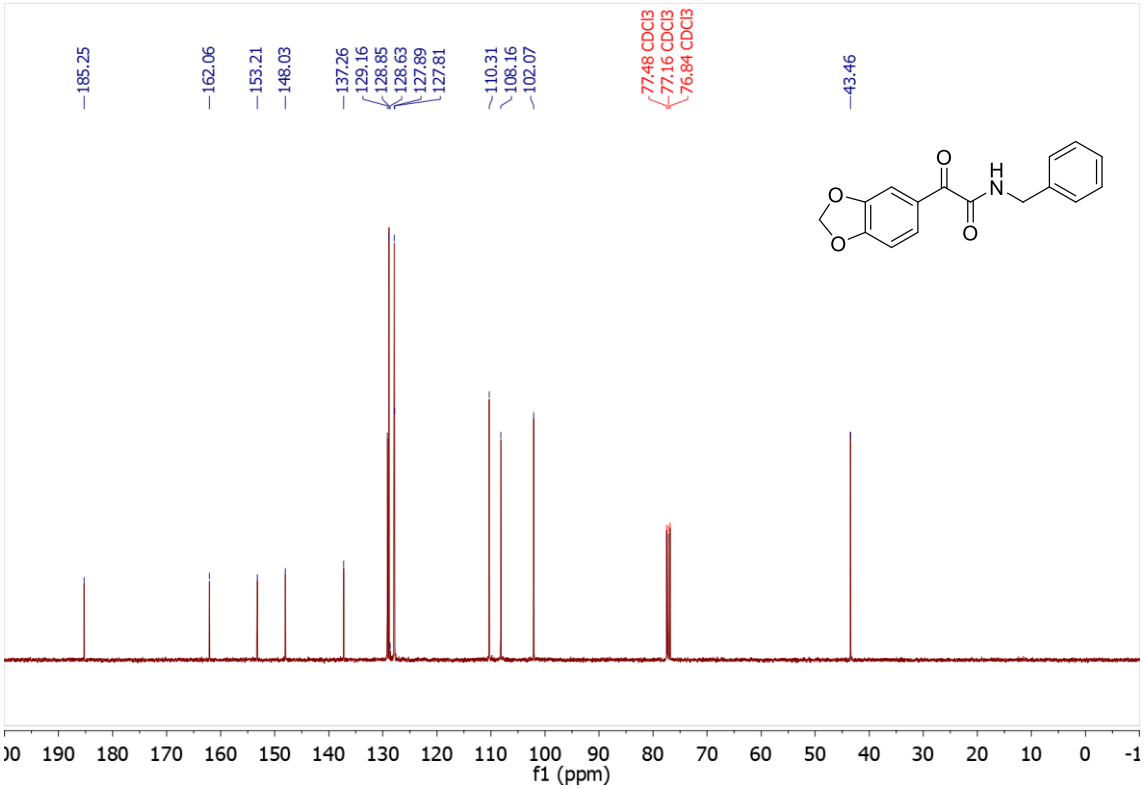
N-Benzyl-2-oxo-2-(3-cyanophenyl)acetamide, 4g



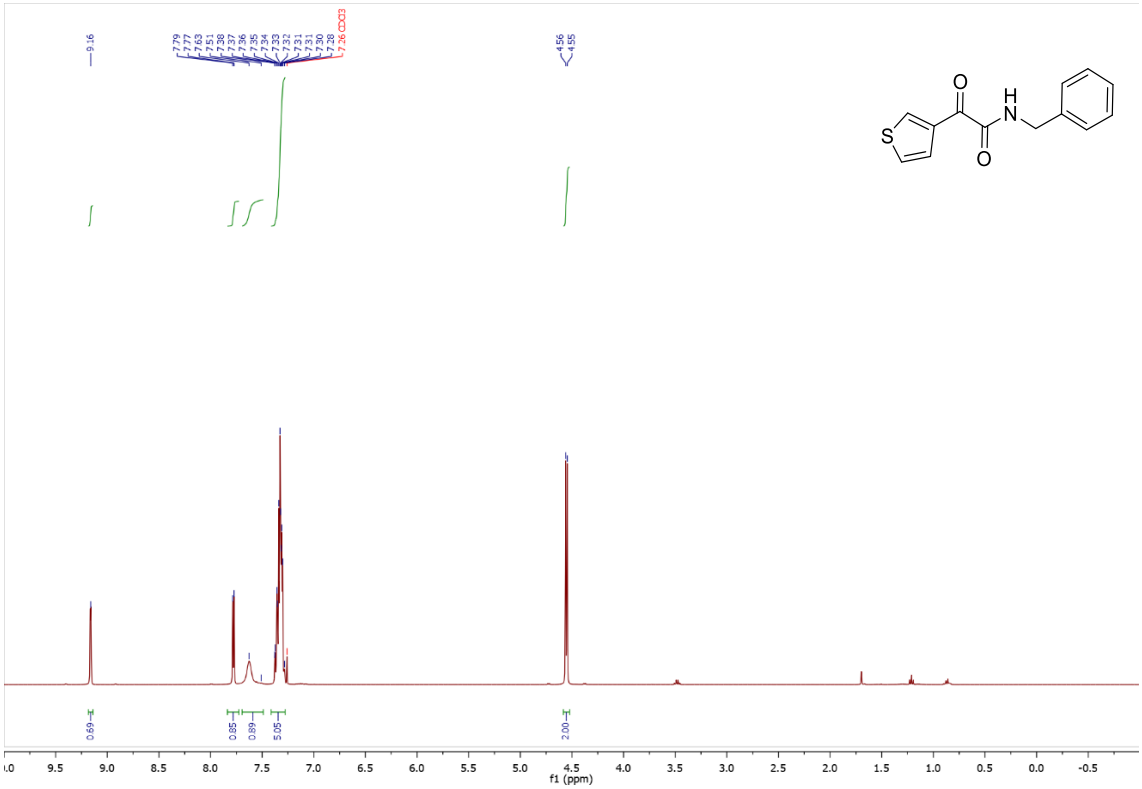


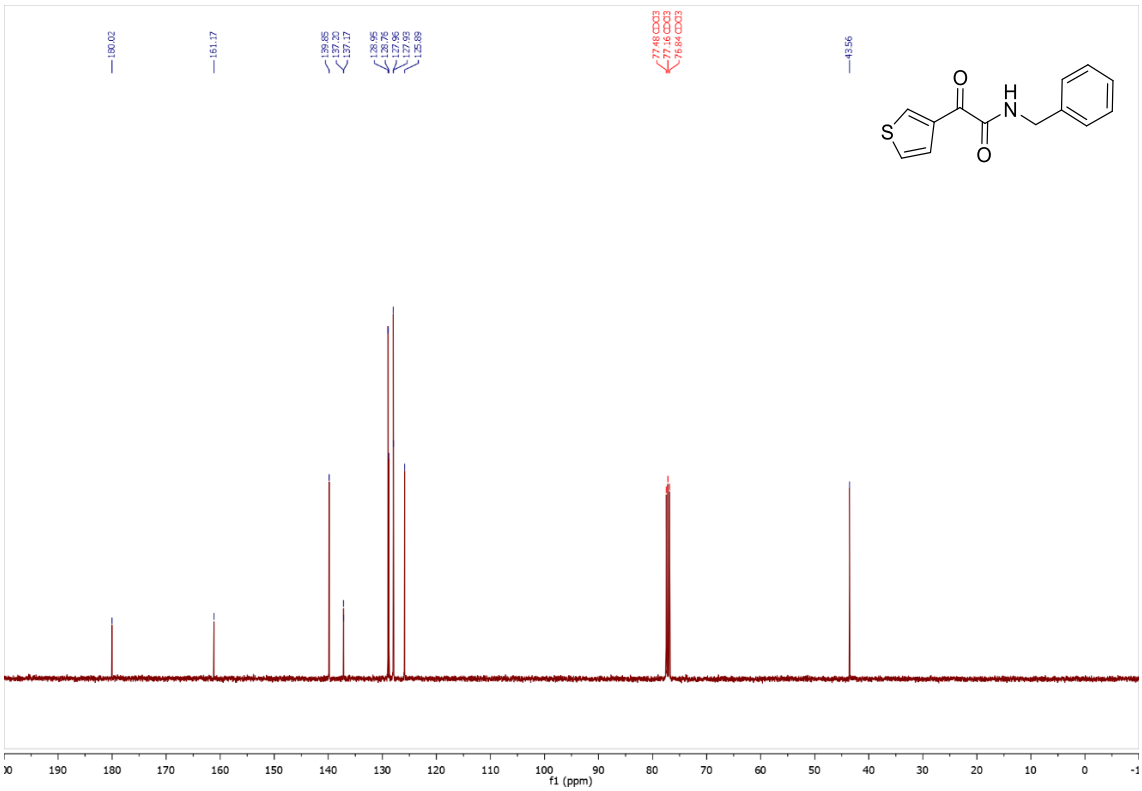
2-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-benzyl-2-oxoacetamide, 4h



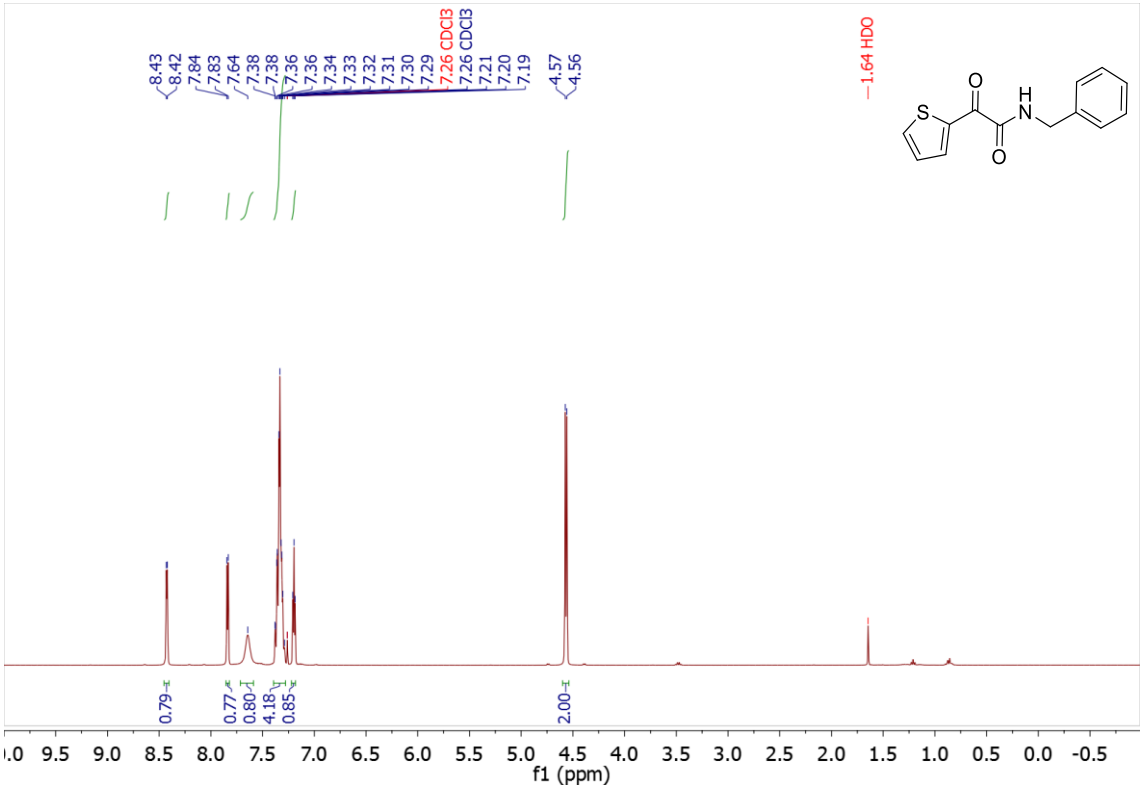


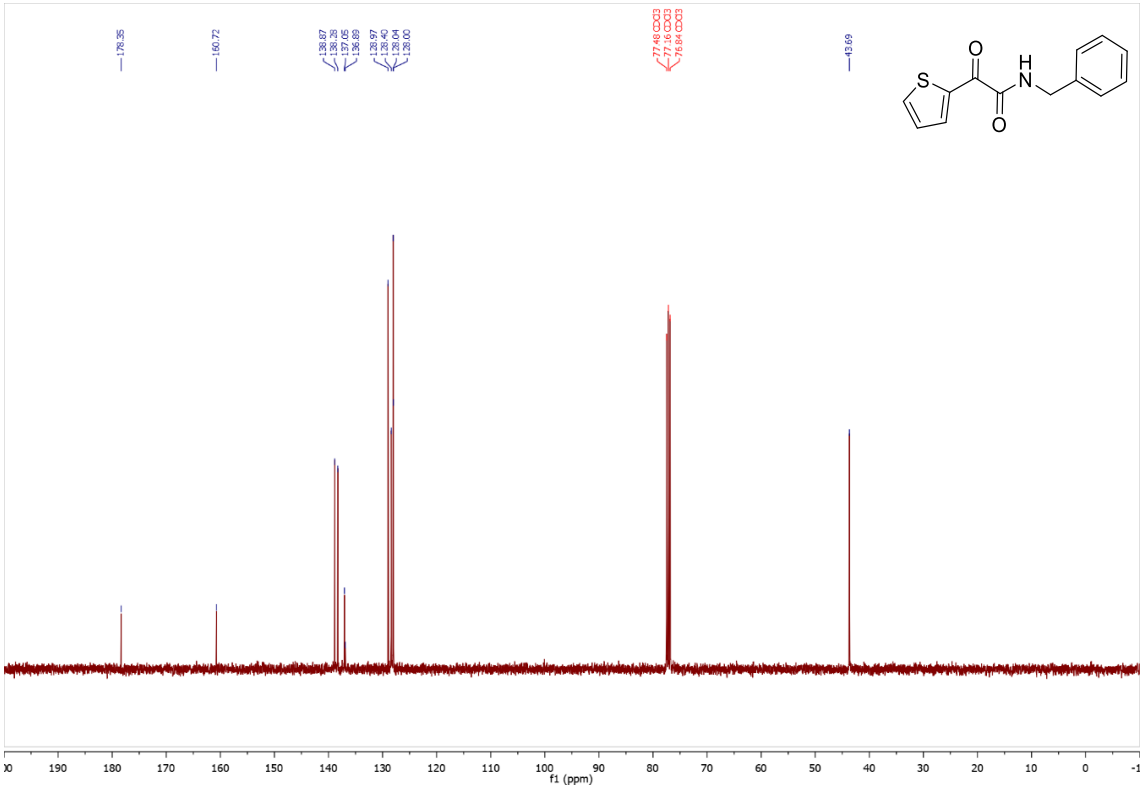
N-benzyl-2-oxo-2-(thiophen-3-yl)acetamide, 4i



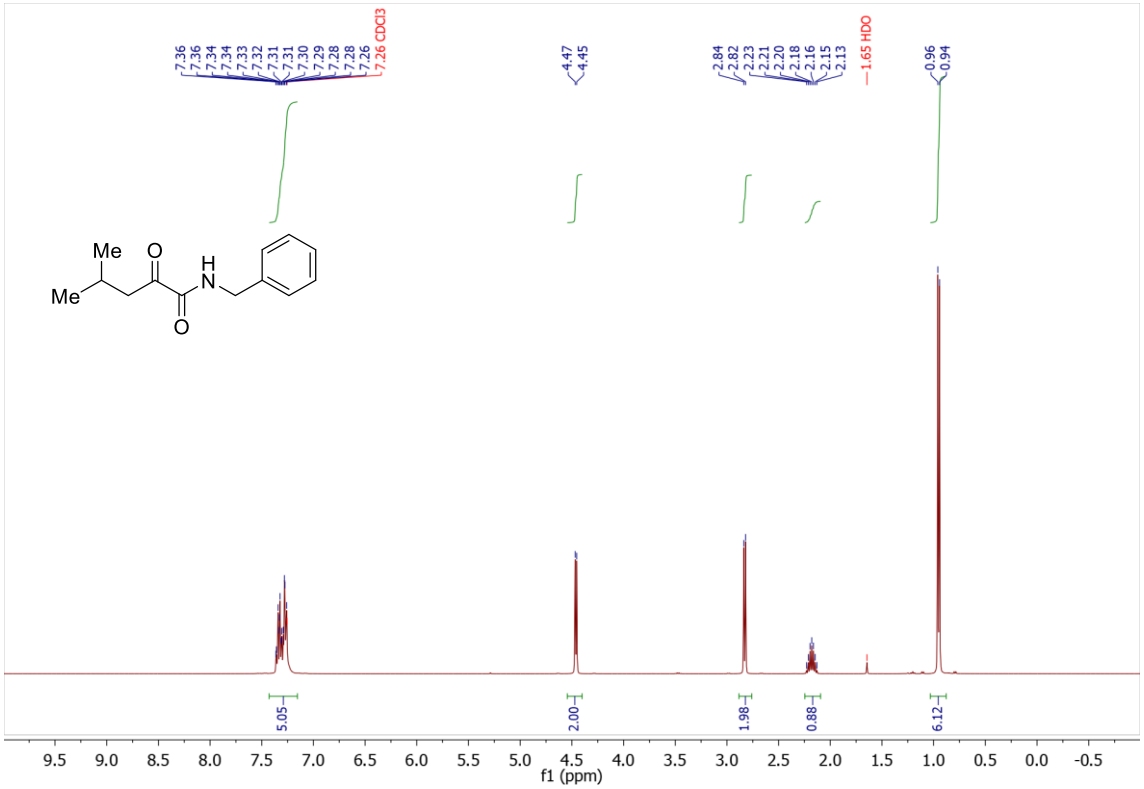


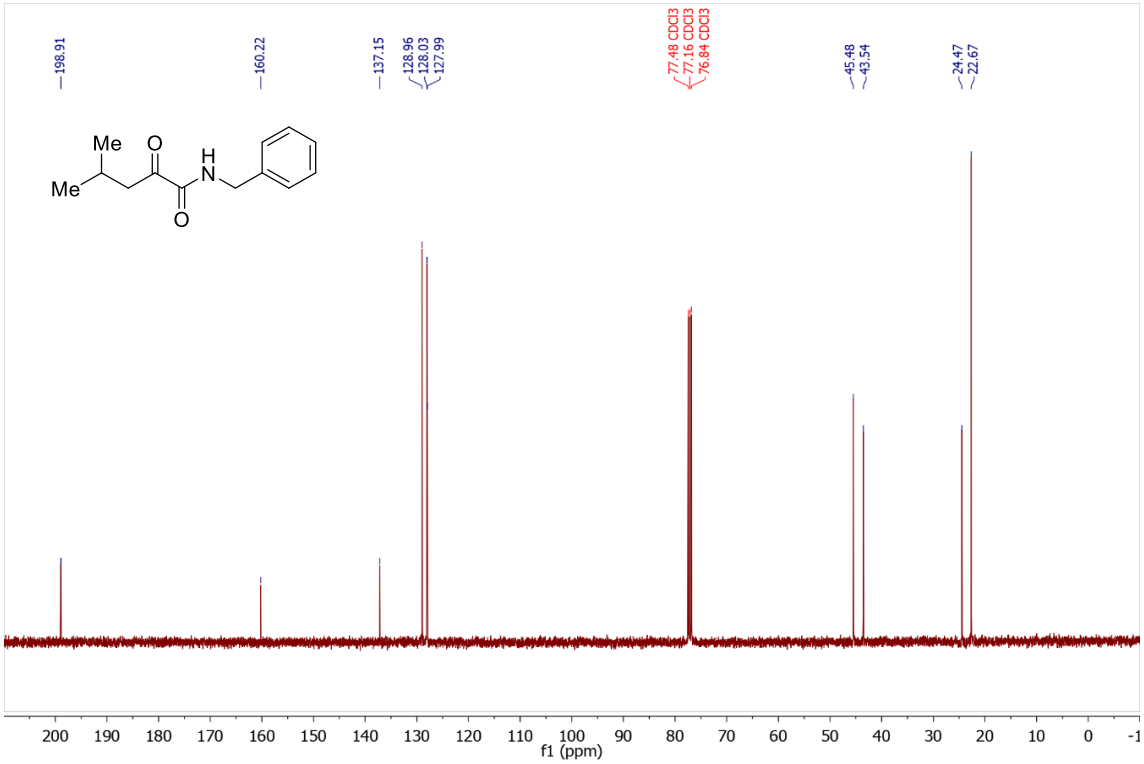
N-Benzyl-2-oxo-2-(thiophen-2-yl)acetamide, 4j



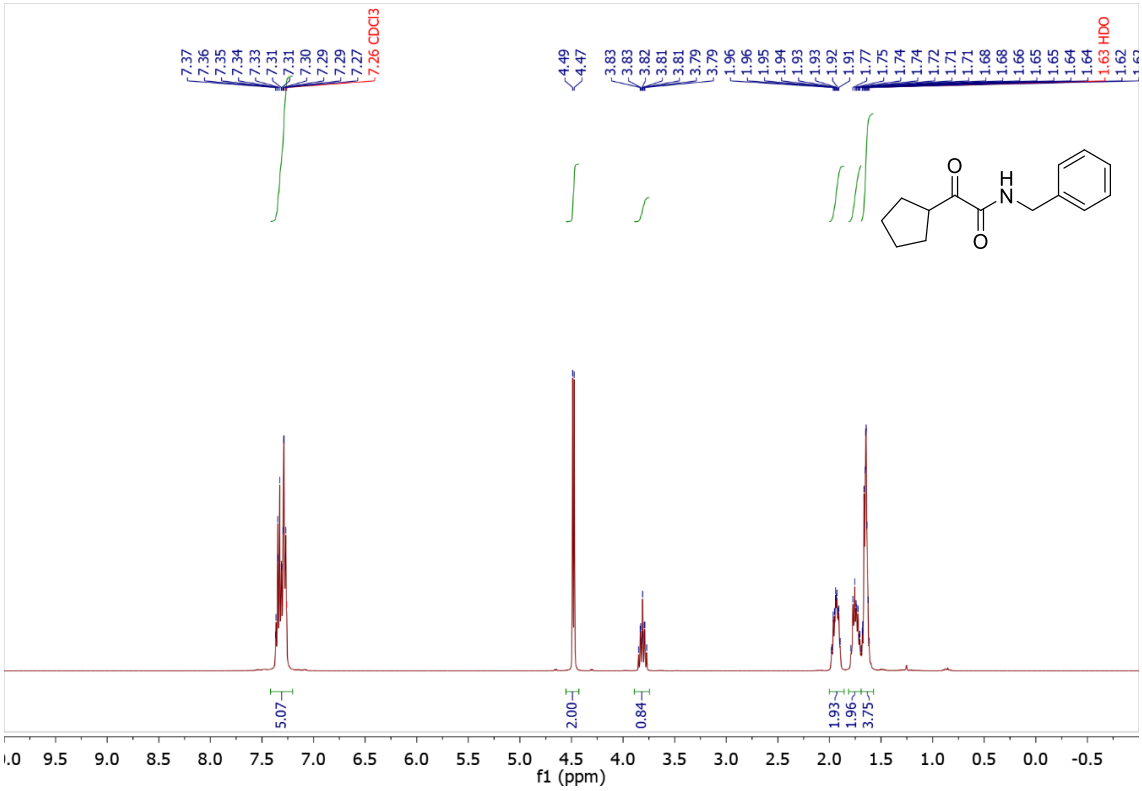


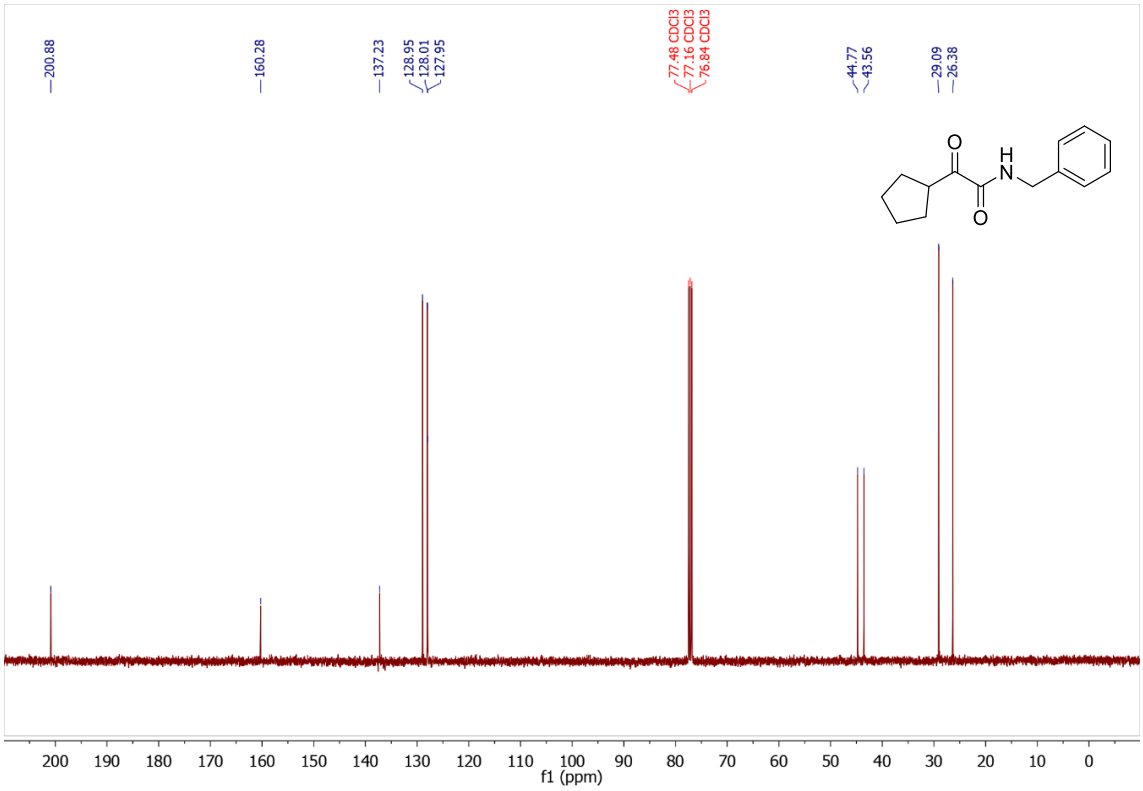
N-Benzyl-4-methyl-2-oxopentanamide, 4k



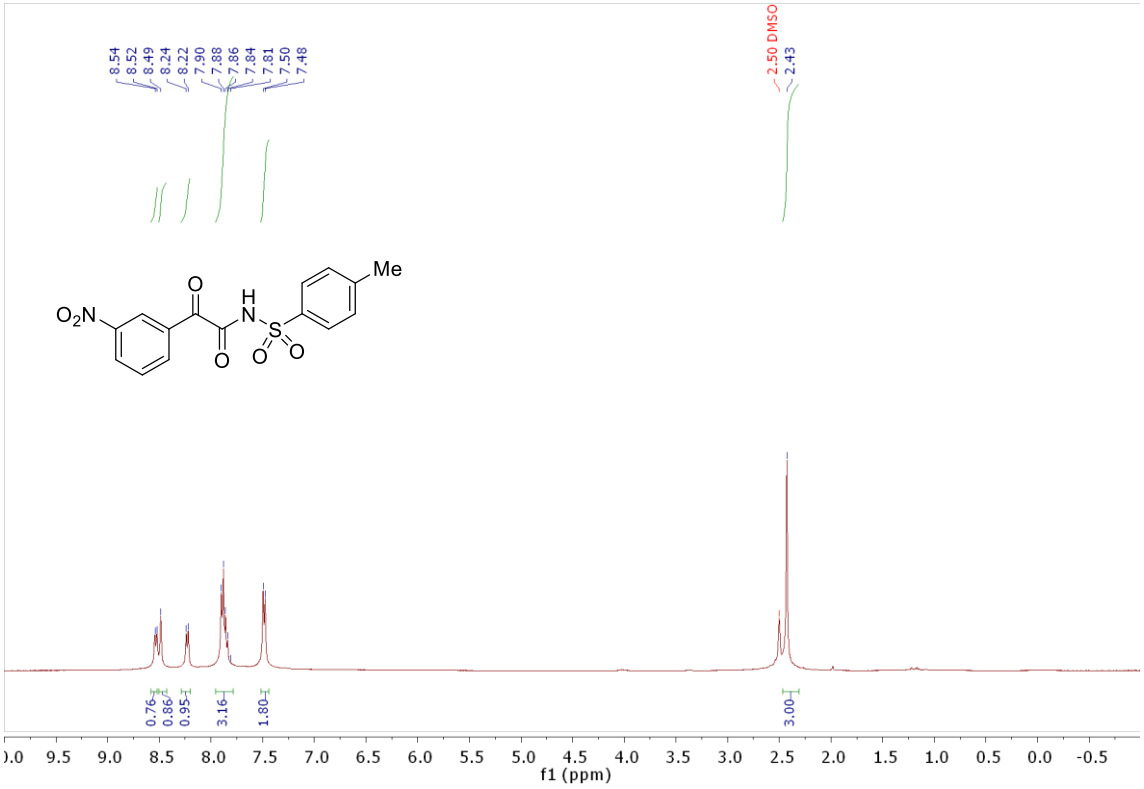


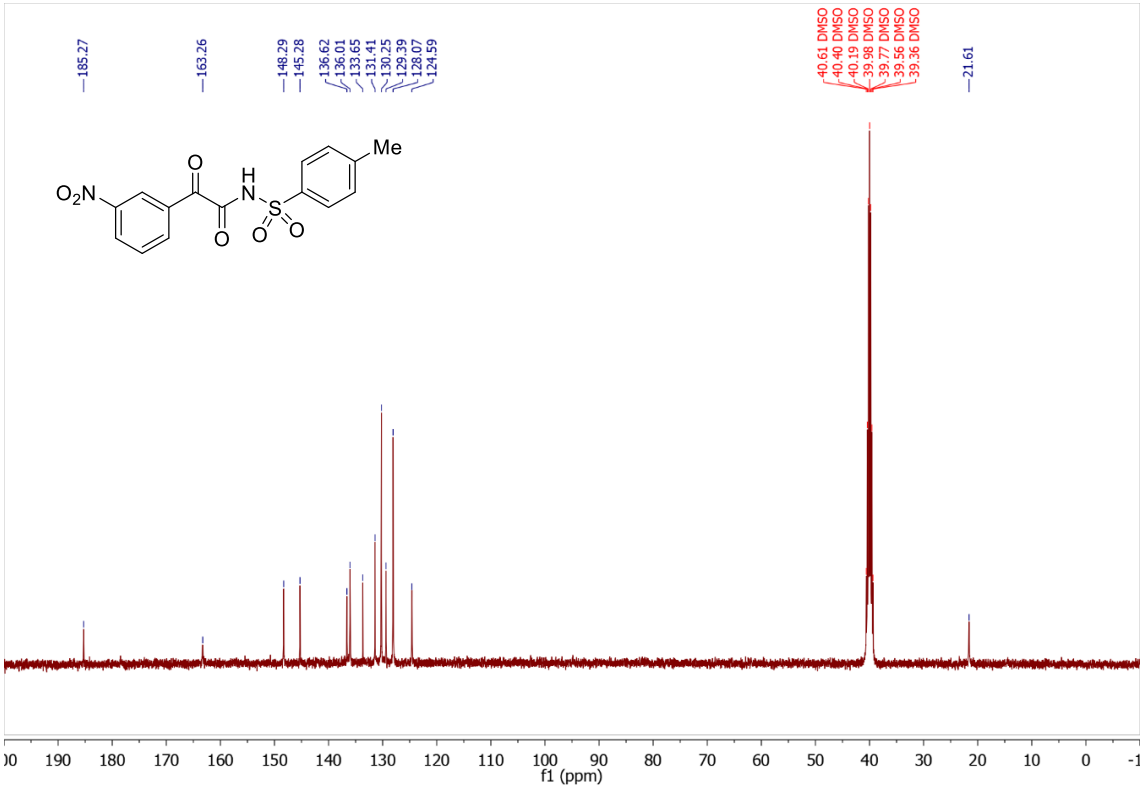
N-Benzyl-2-cyclopentyl-2-oxoacetamide, 4l



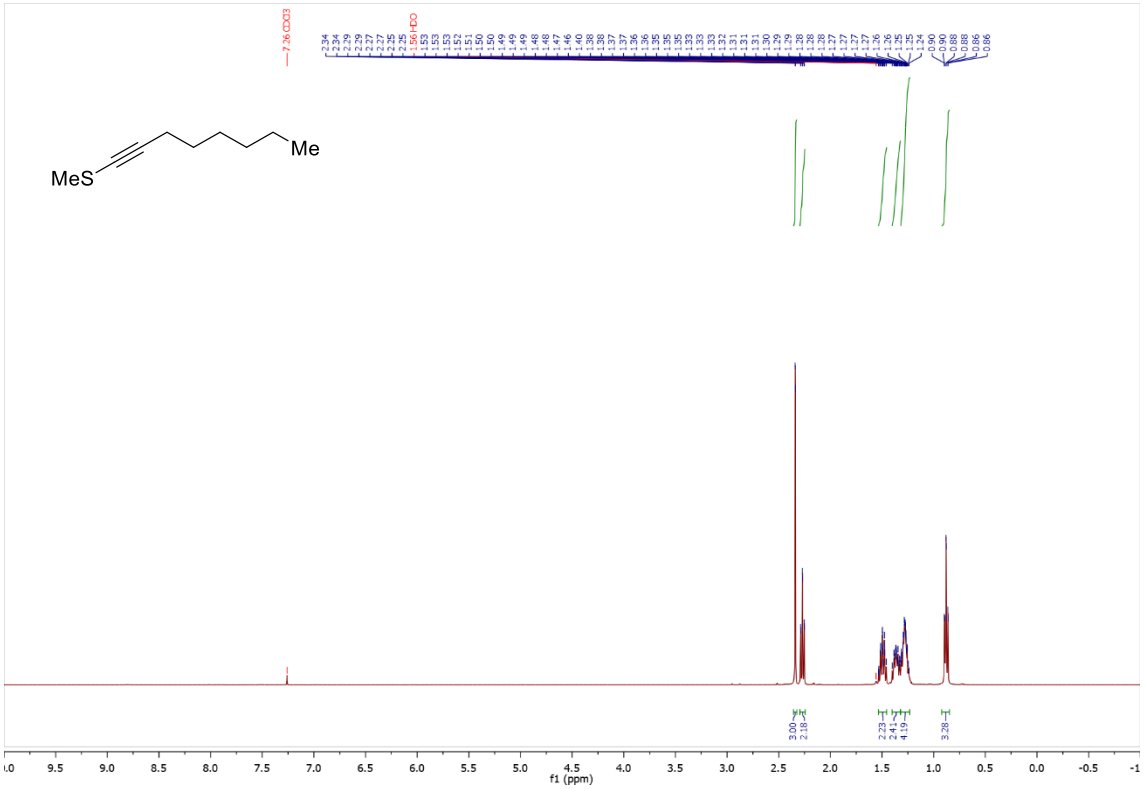


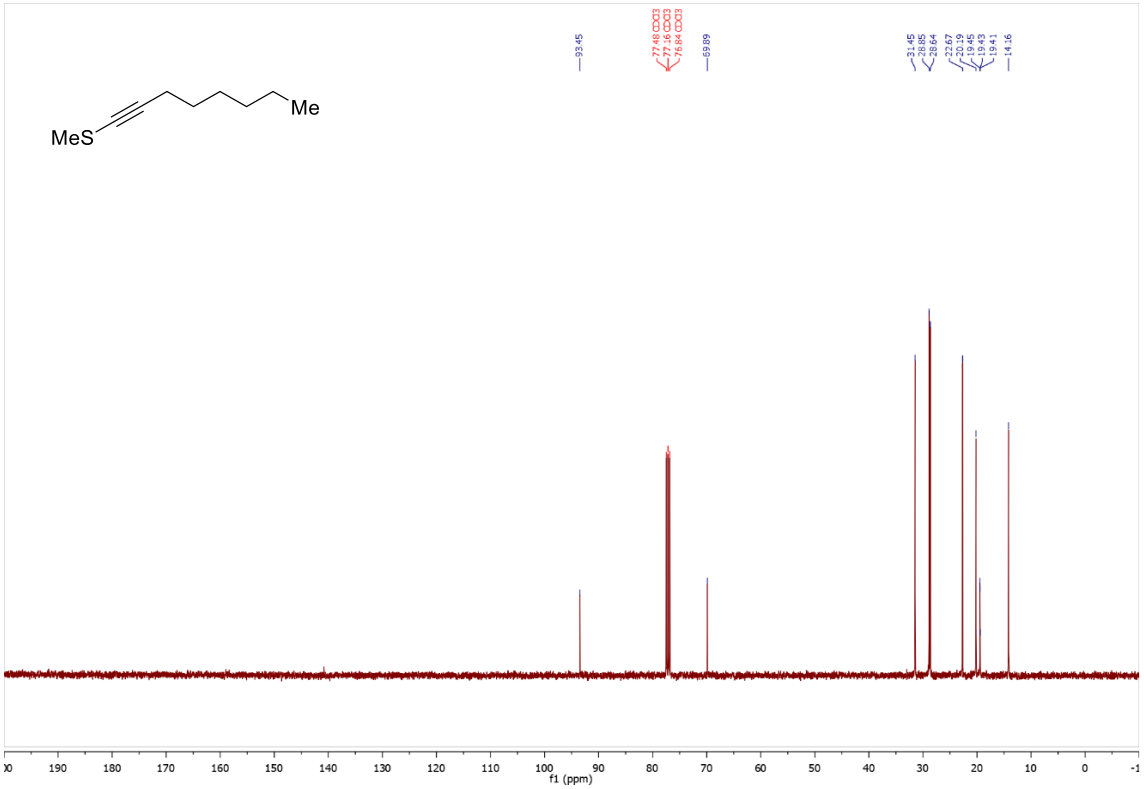
N-Tosyl-2-(3-nitrophenyl)-2-oxo-acetamide, 6



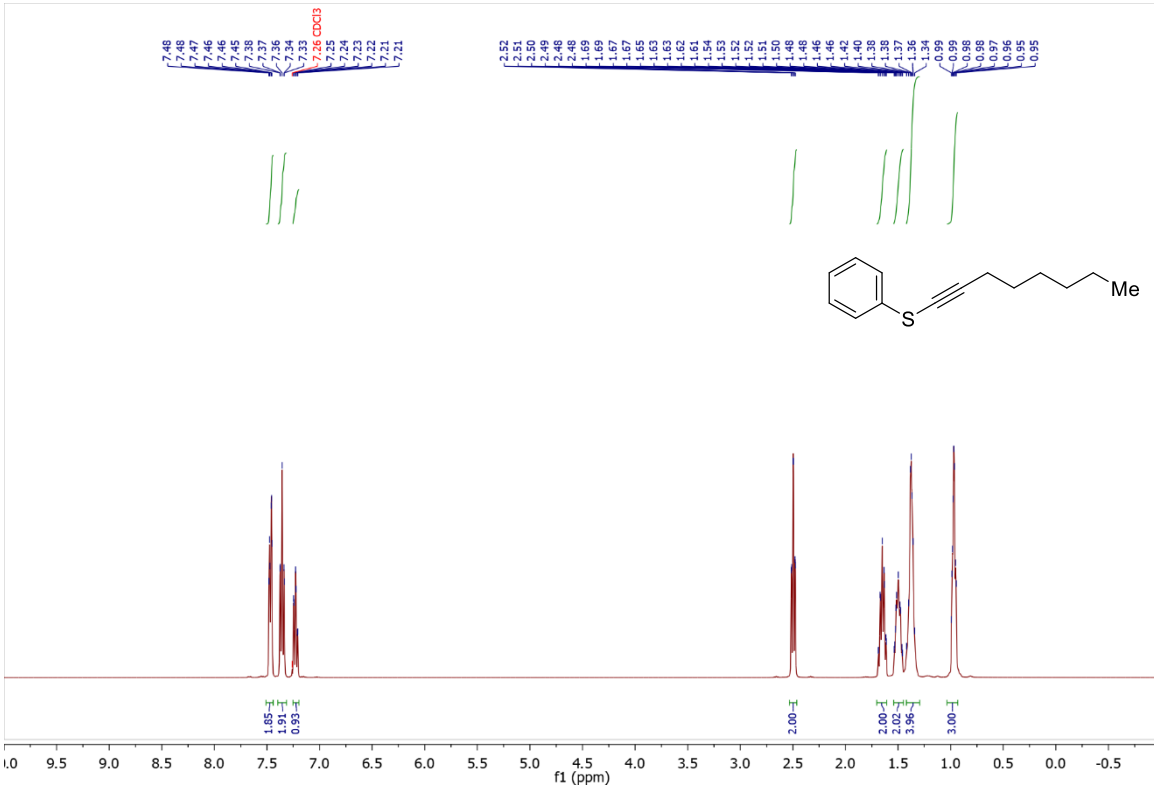


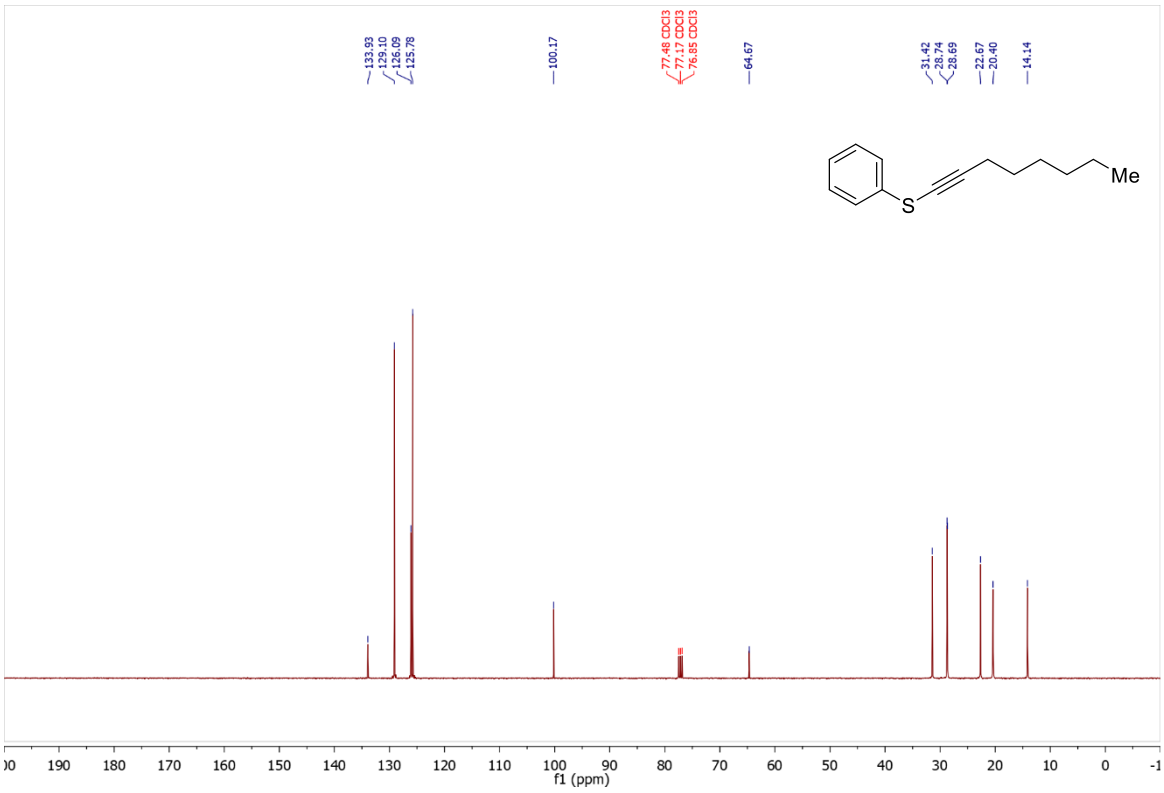
Methyl(oct-1-yn-1-yl)sulfane, 9



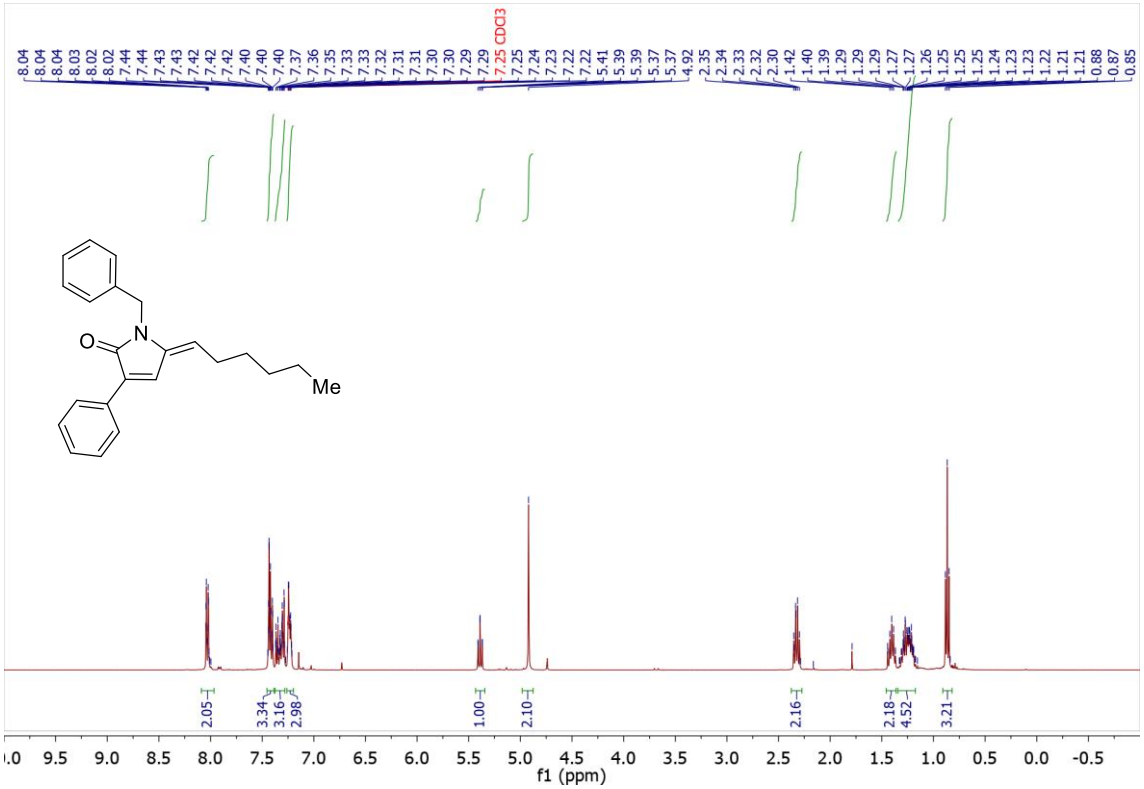


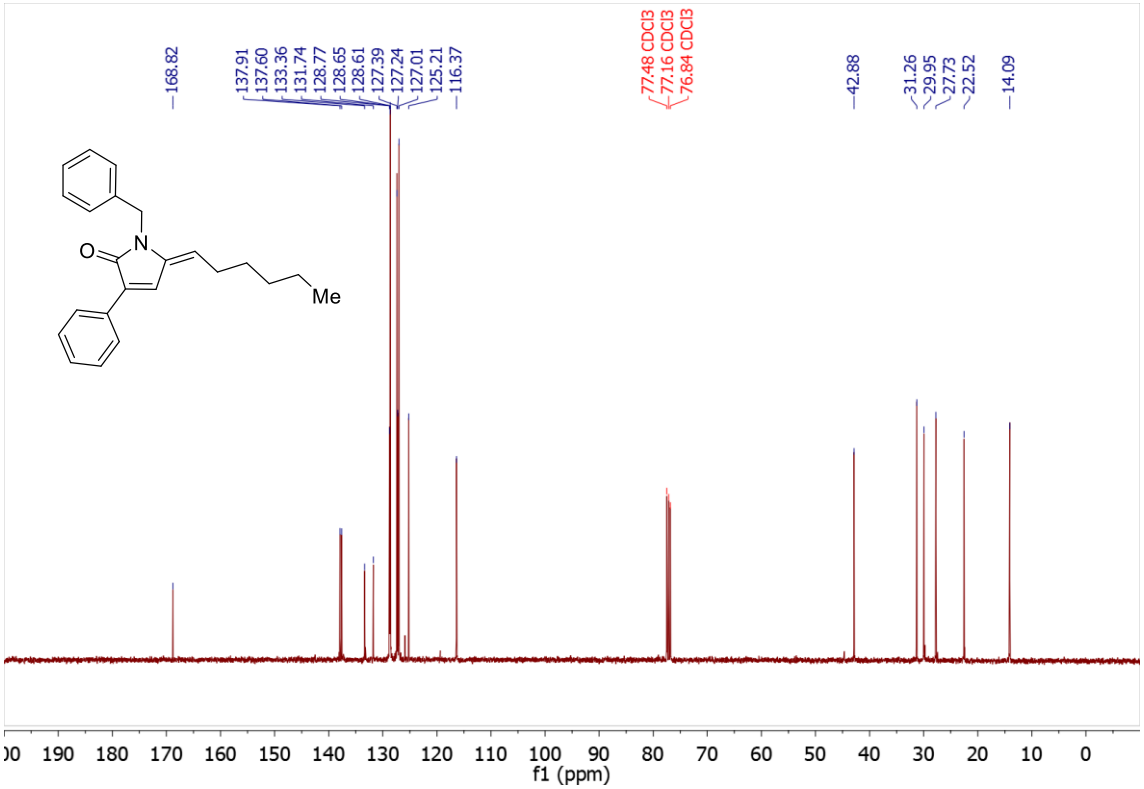
Oct-1-yn-1-yl(phenyl)sulfane, 10



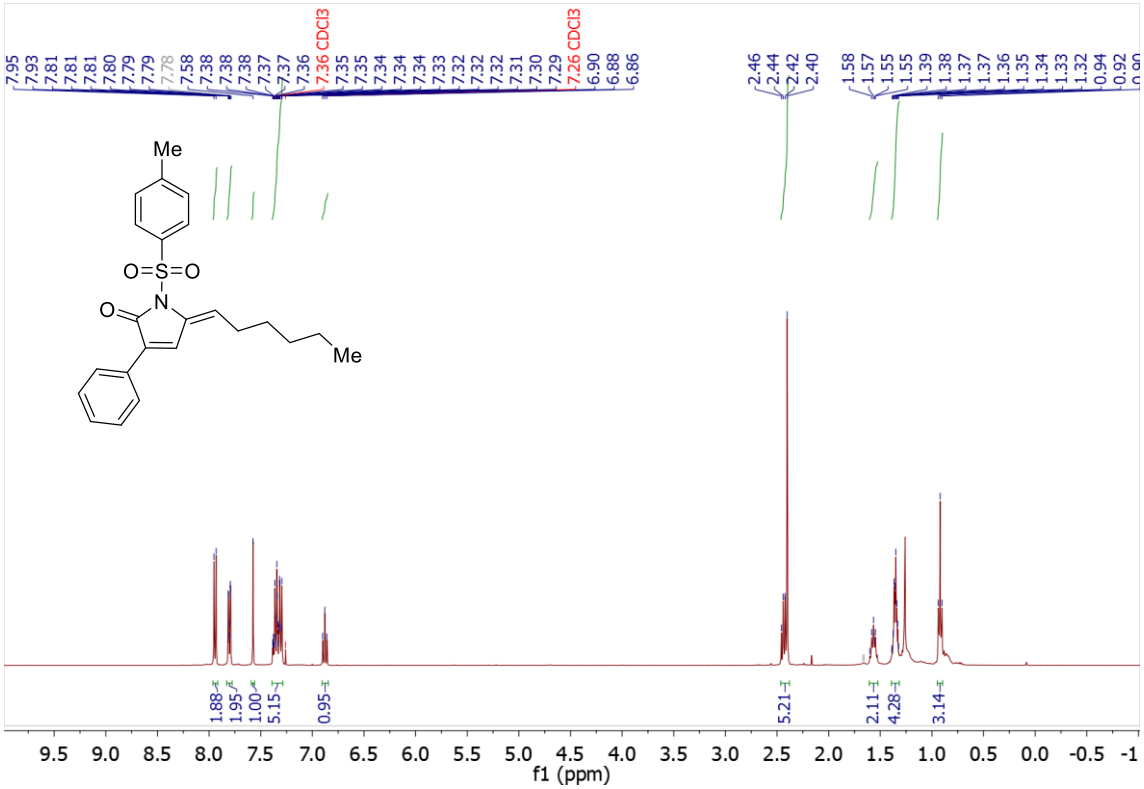


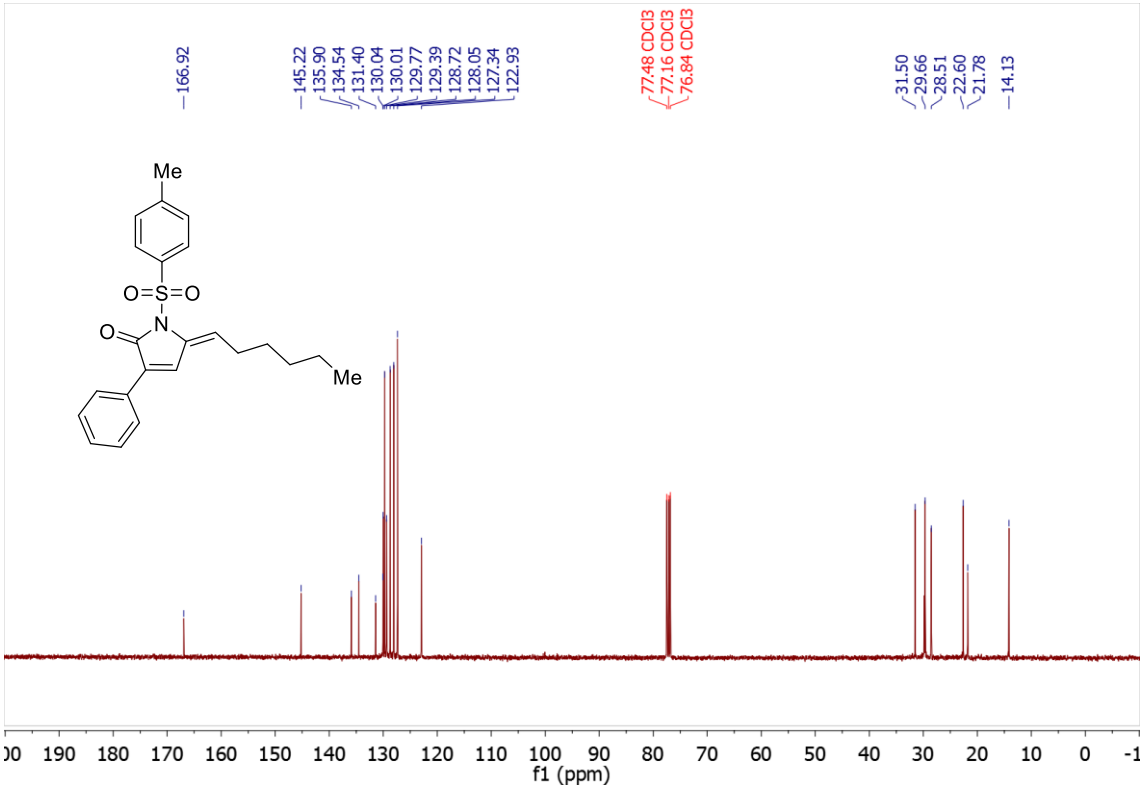
(*E*)-1-Benzyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3a



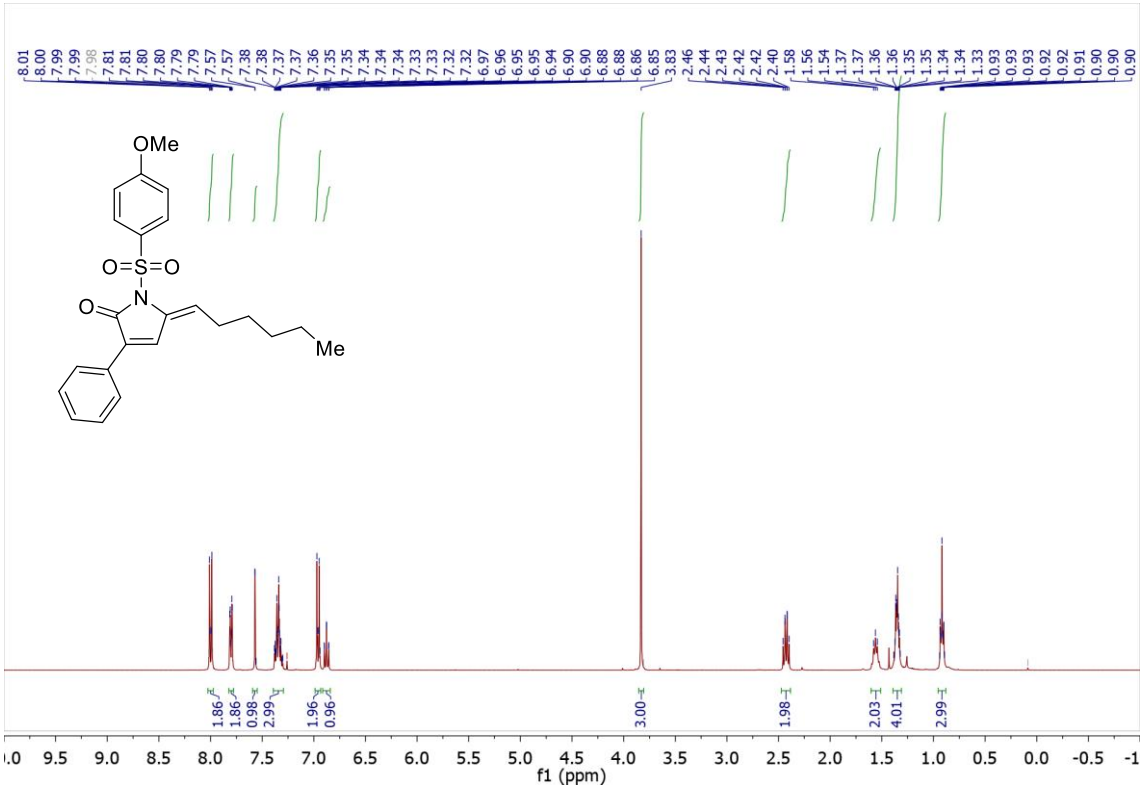


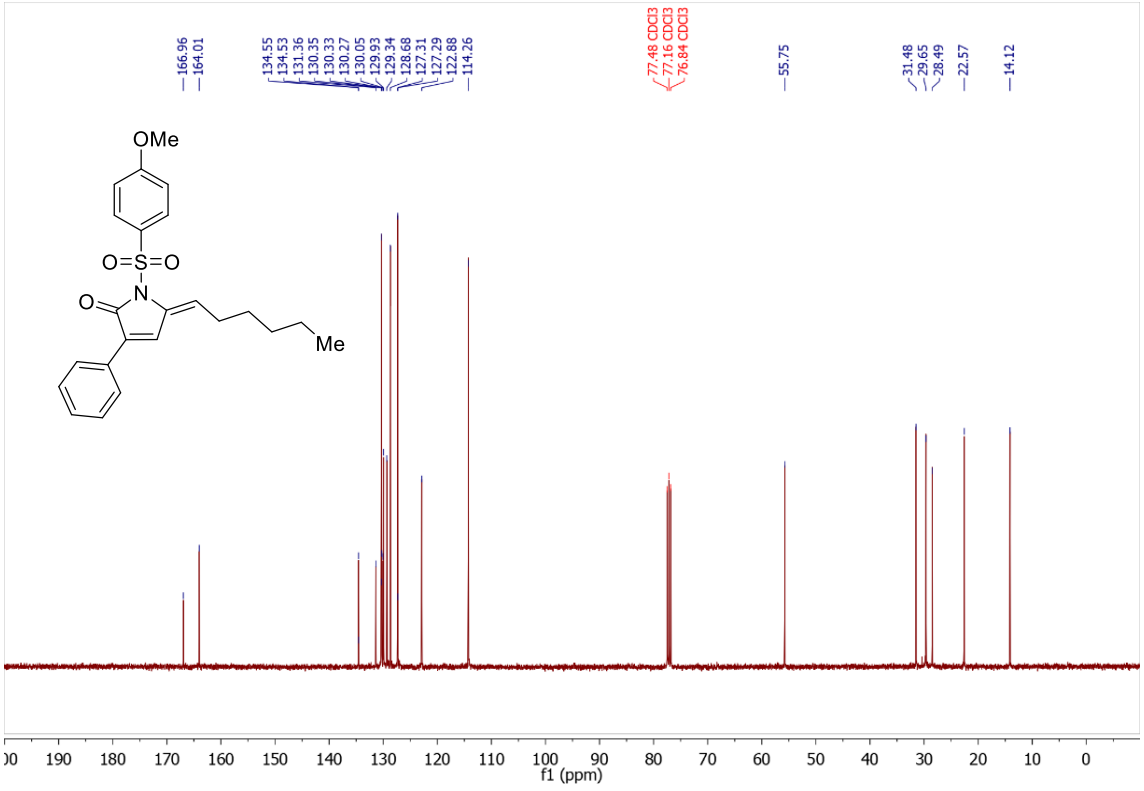
(*E*)-5-Hexylidene-3-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one, **3b**



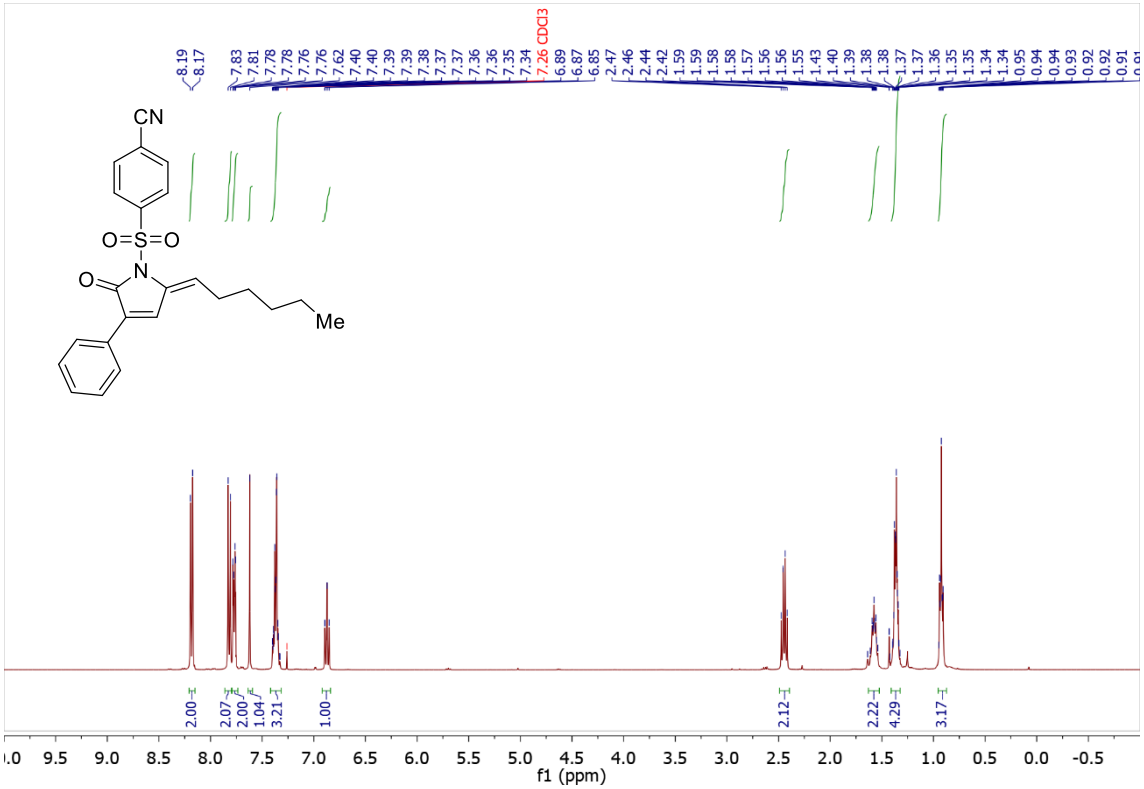


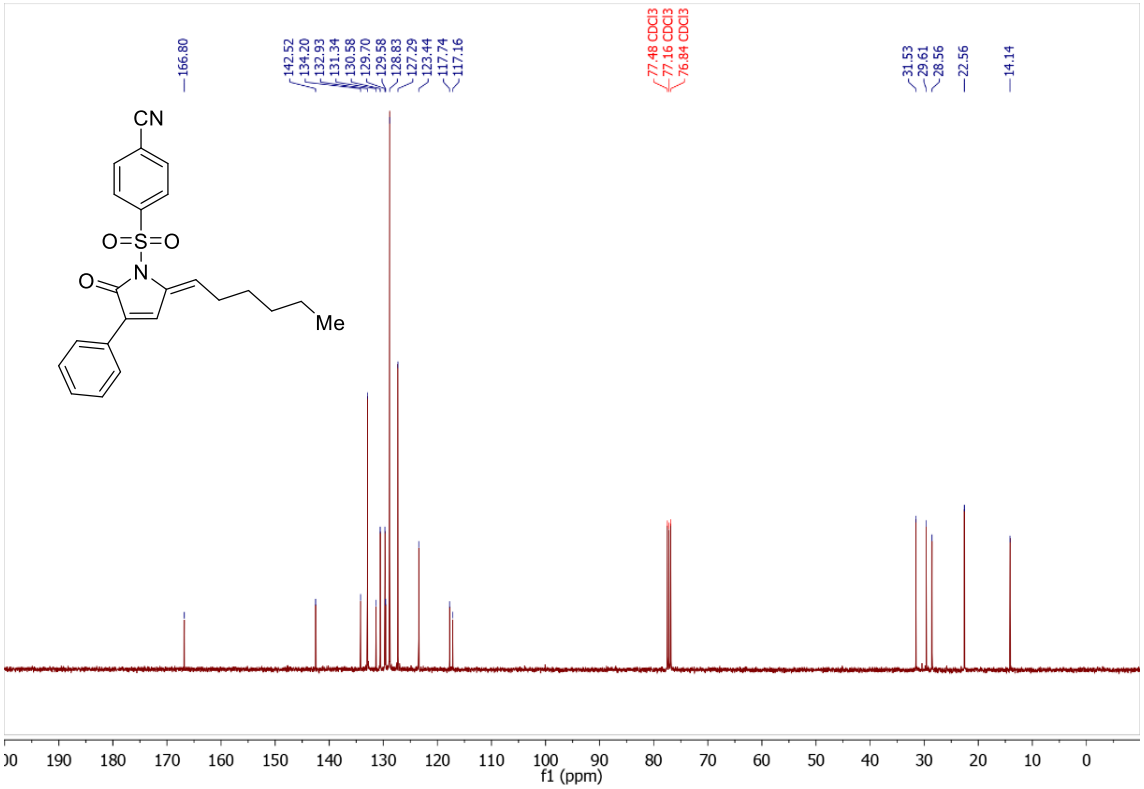
(*E*)-5-Hexylidene-1-((4-methoxyphenyl)sulfonyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3c



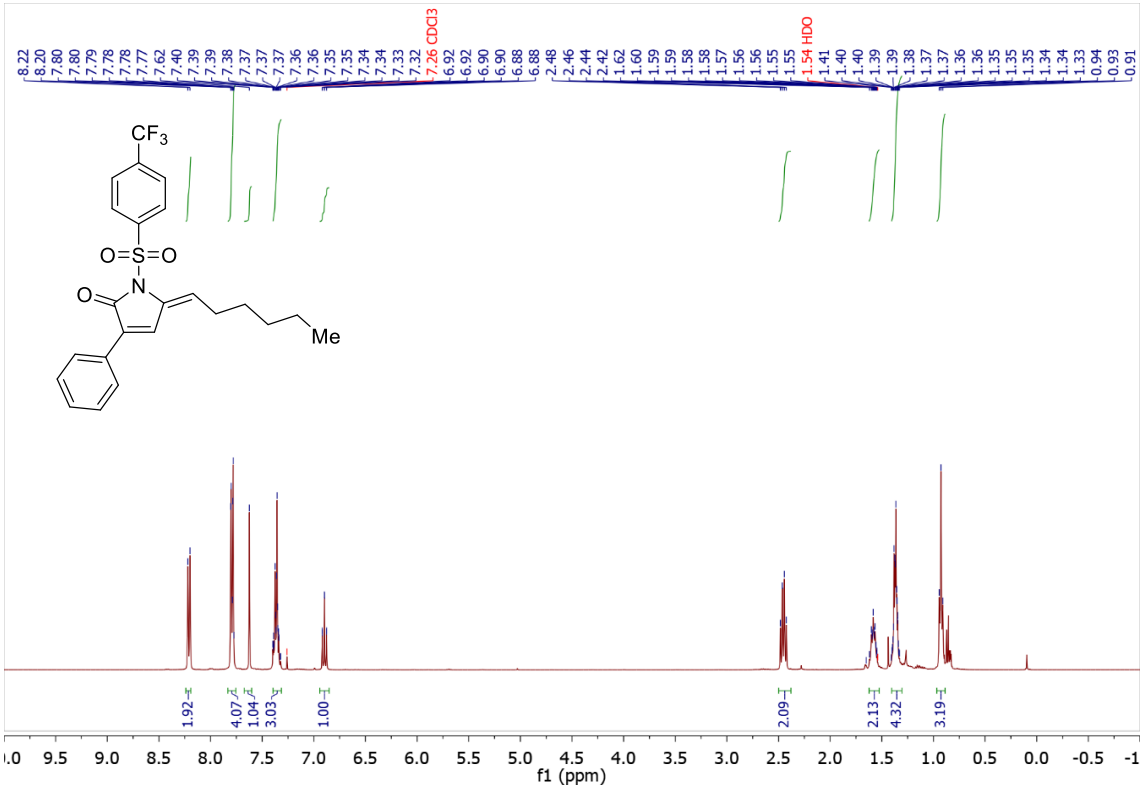


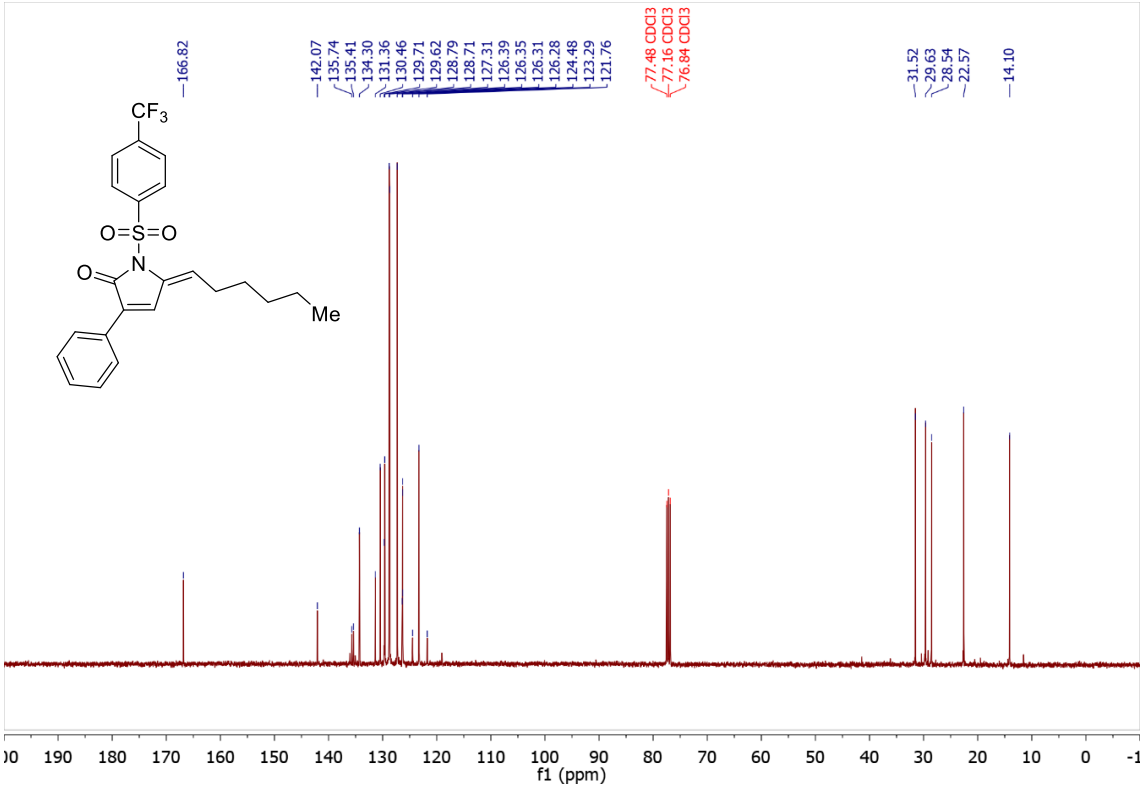
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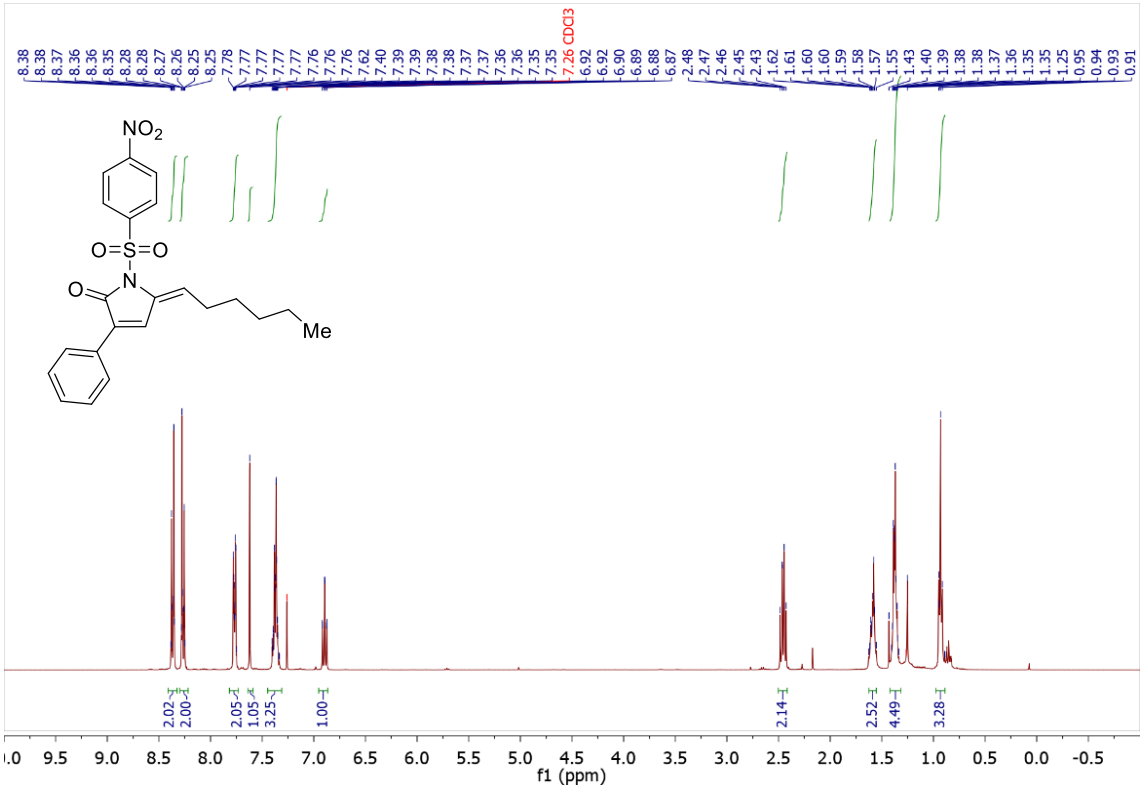


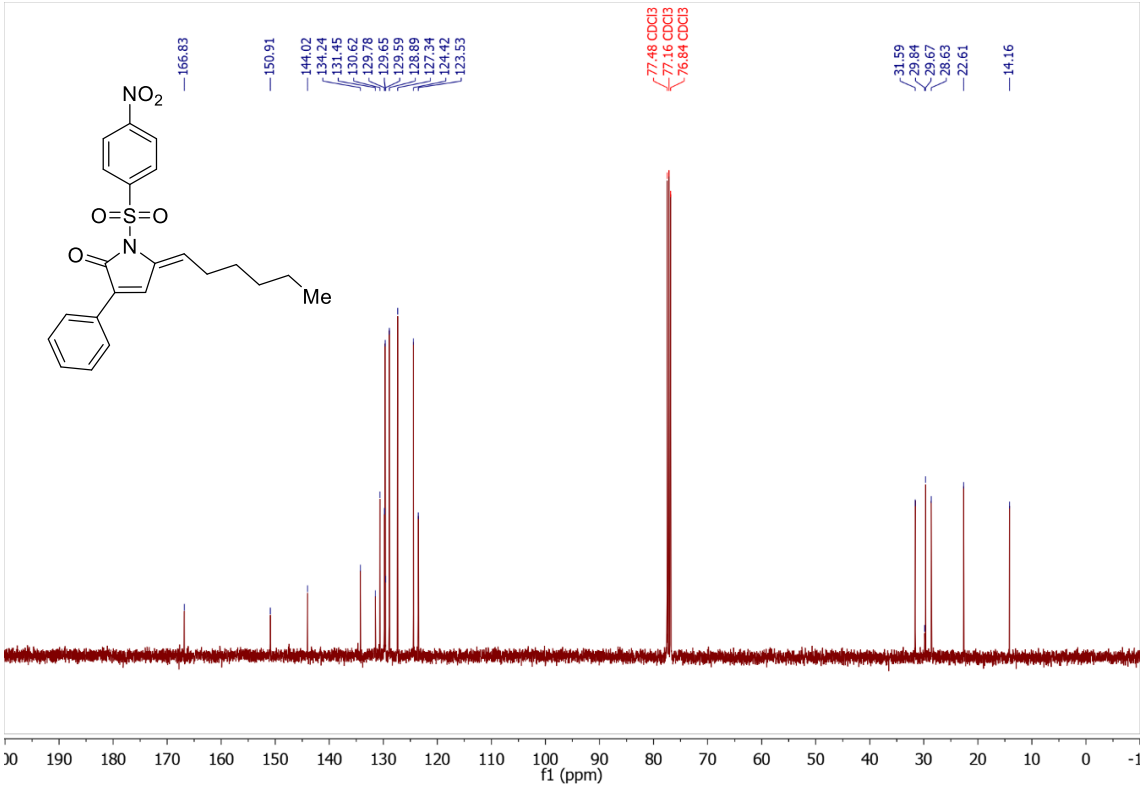
(*E*)-5-Hexylidene-3-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-1,5-dihydro-2*H*-pyrrol-2-one, 3e



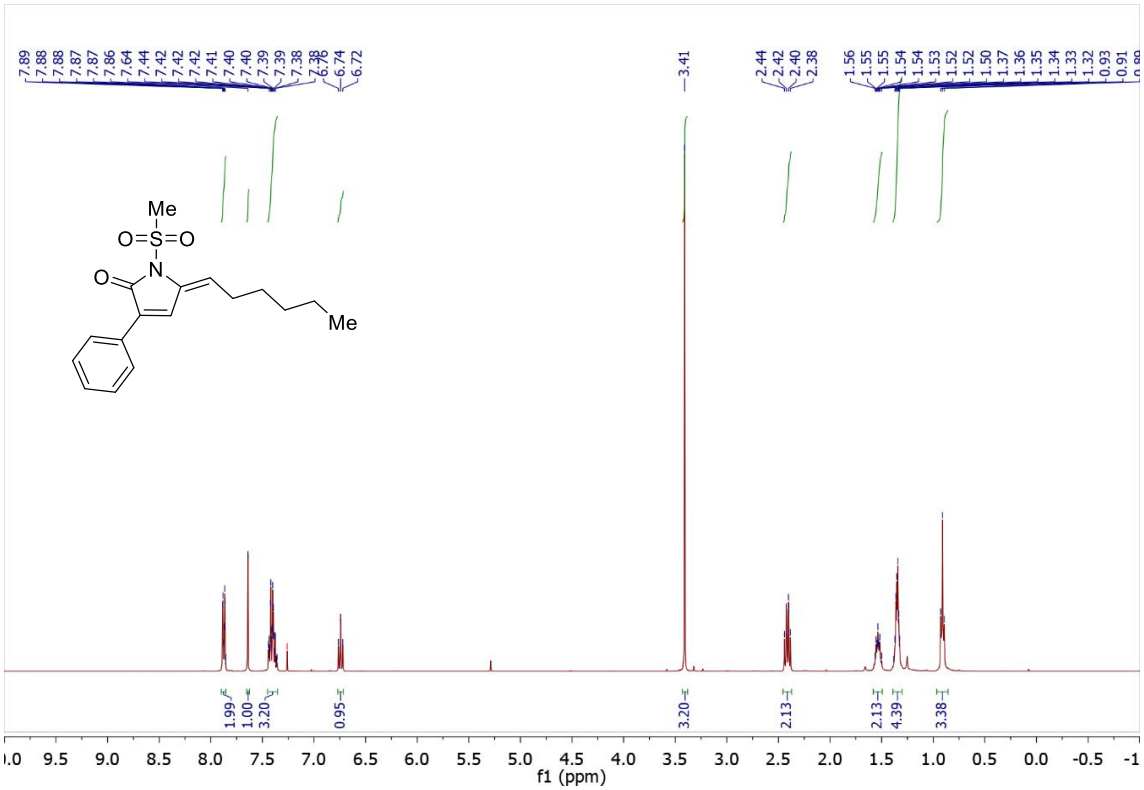


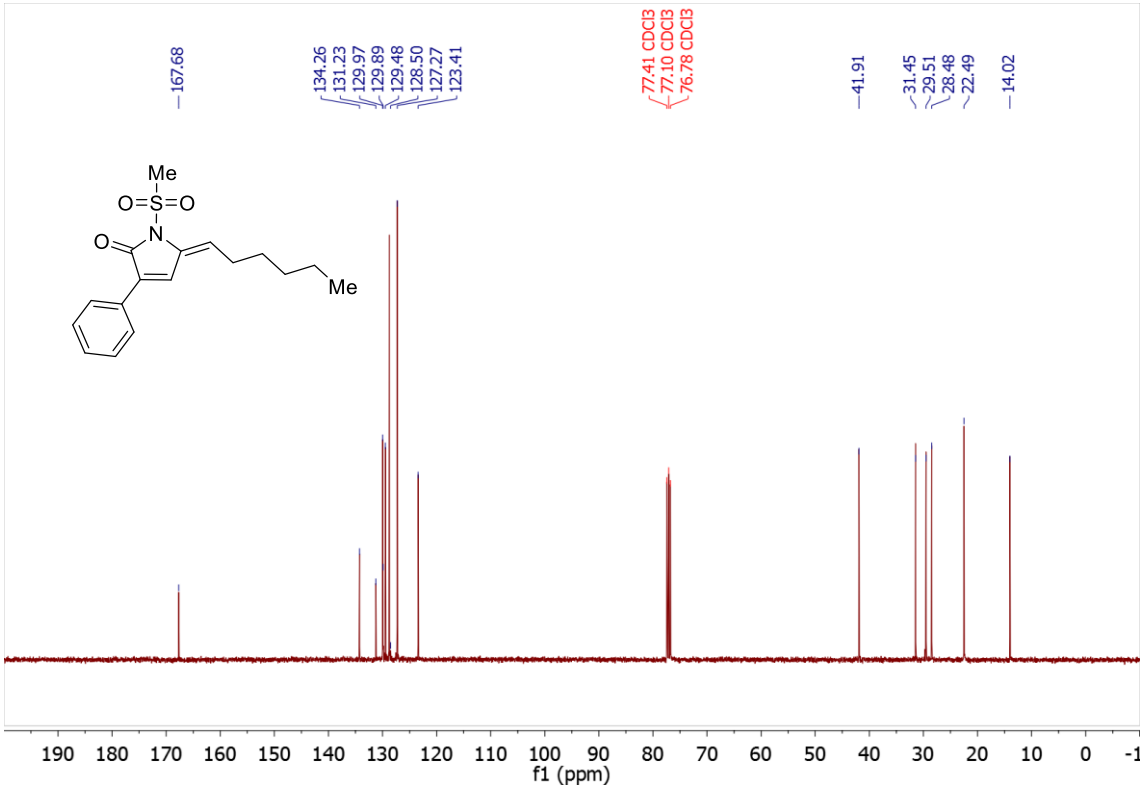
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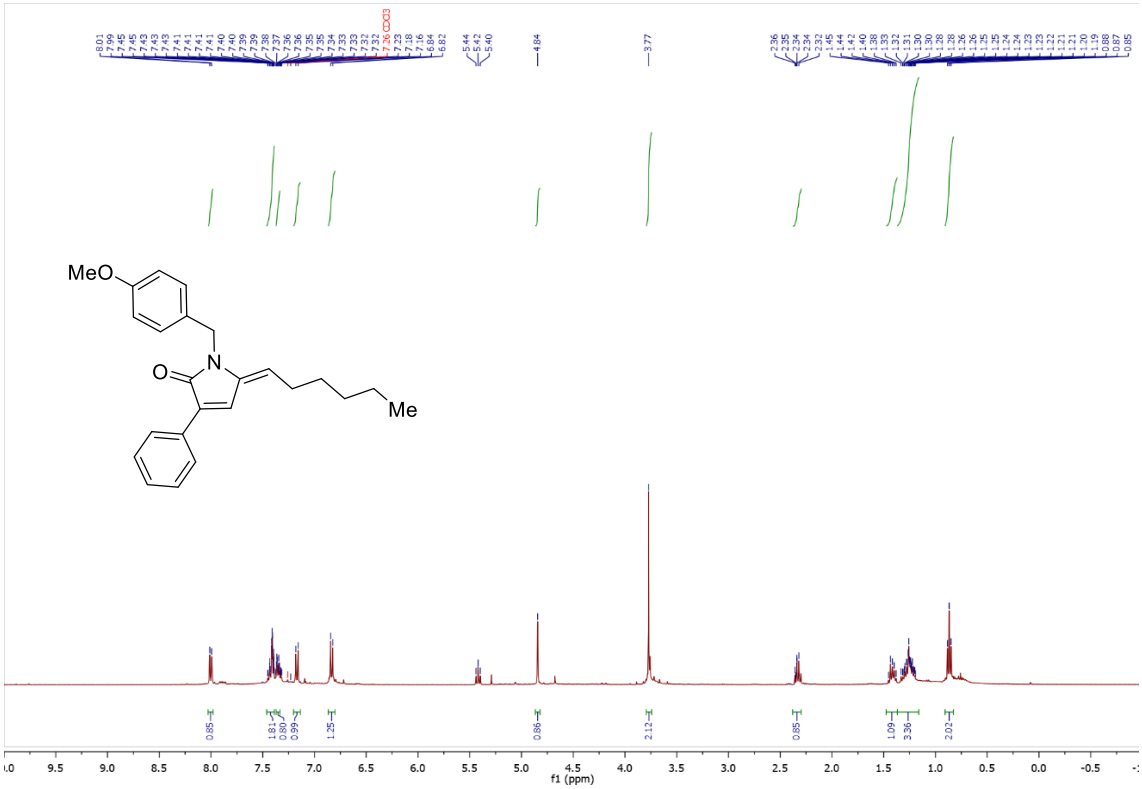


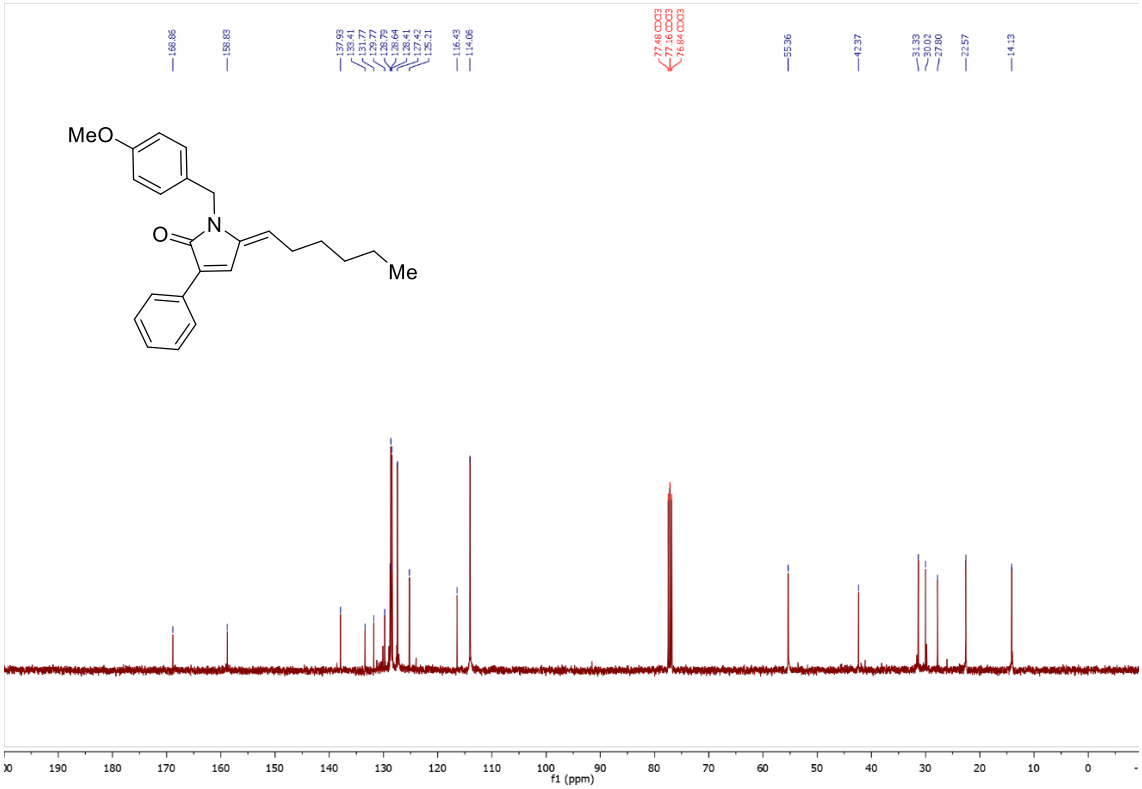
(*E*)-5-Hexylidene-1-(methylsulfonyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3g



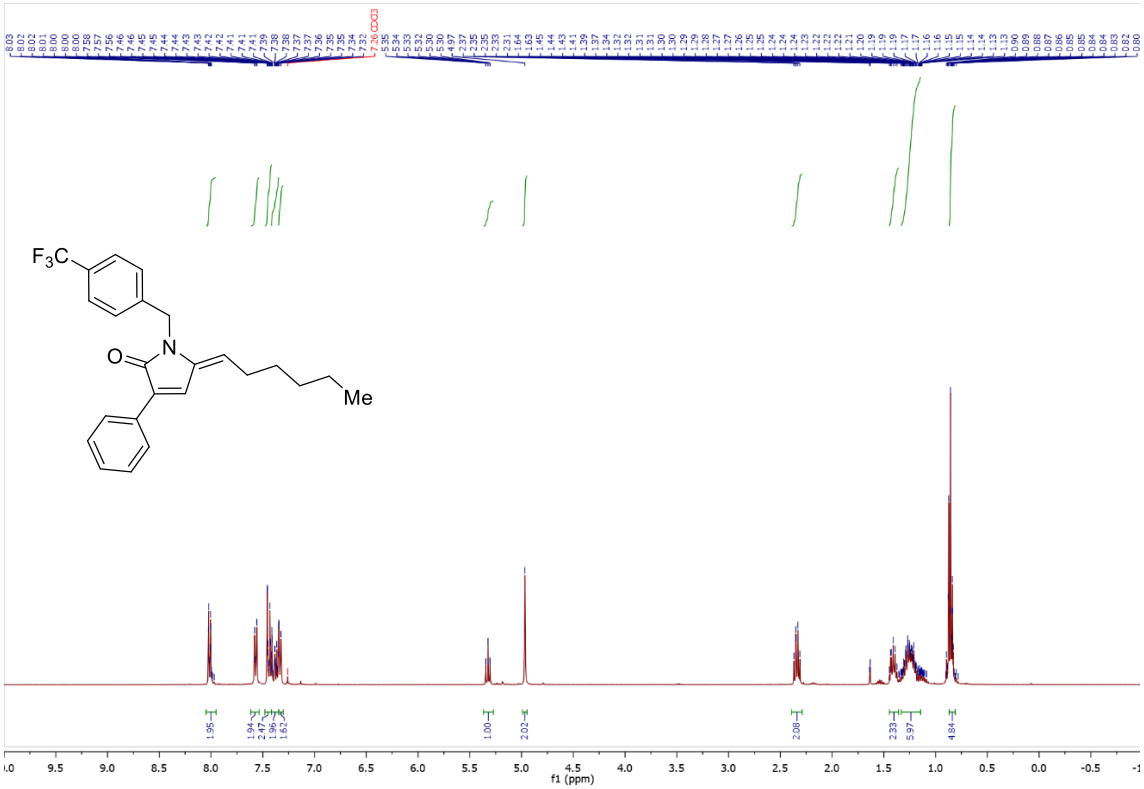


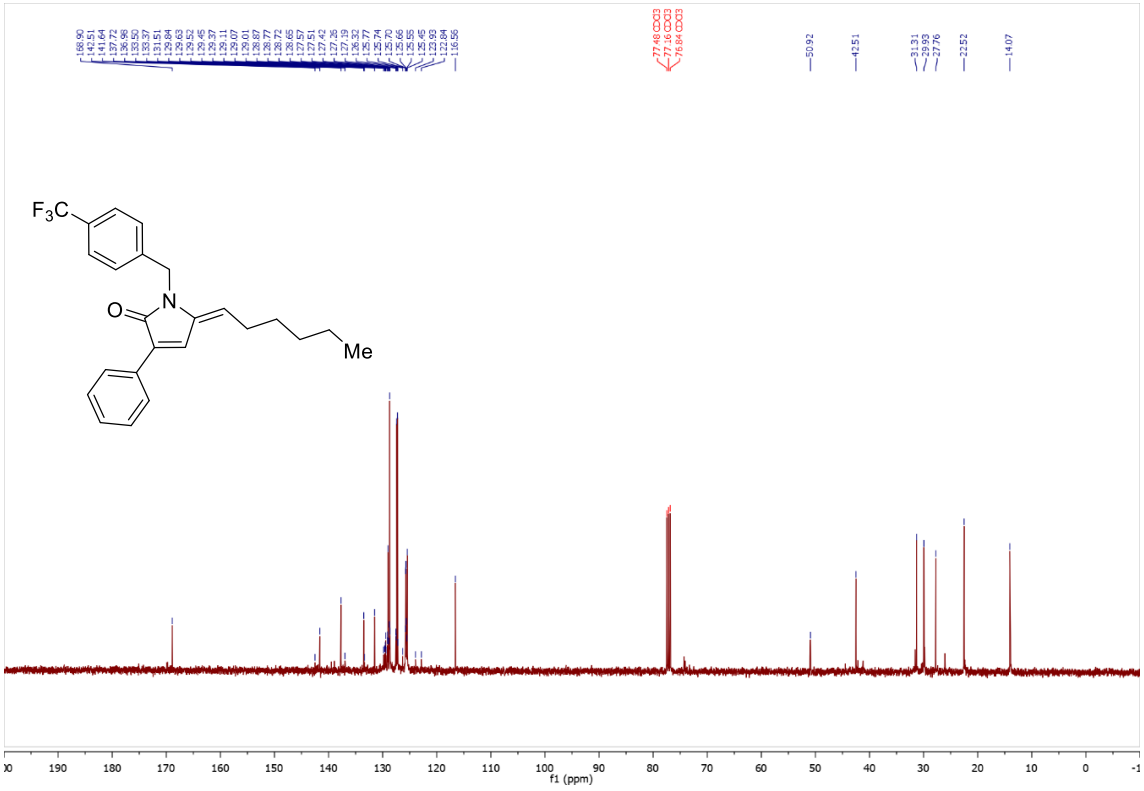
(*E*)-5-Hexylidene-1-(4-methoxybenzyl)-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3l



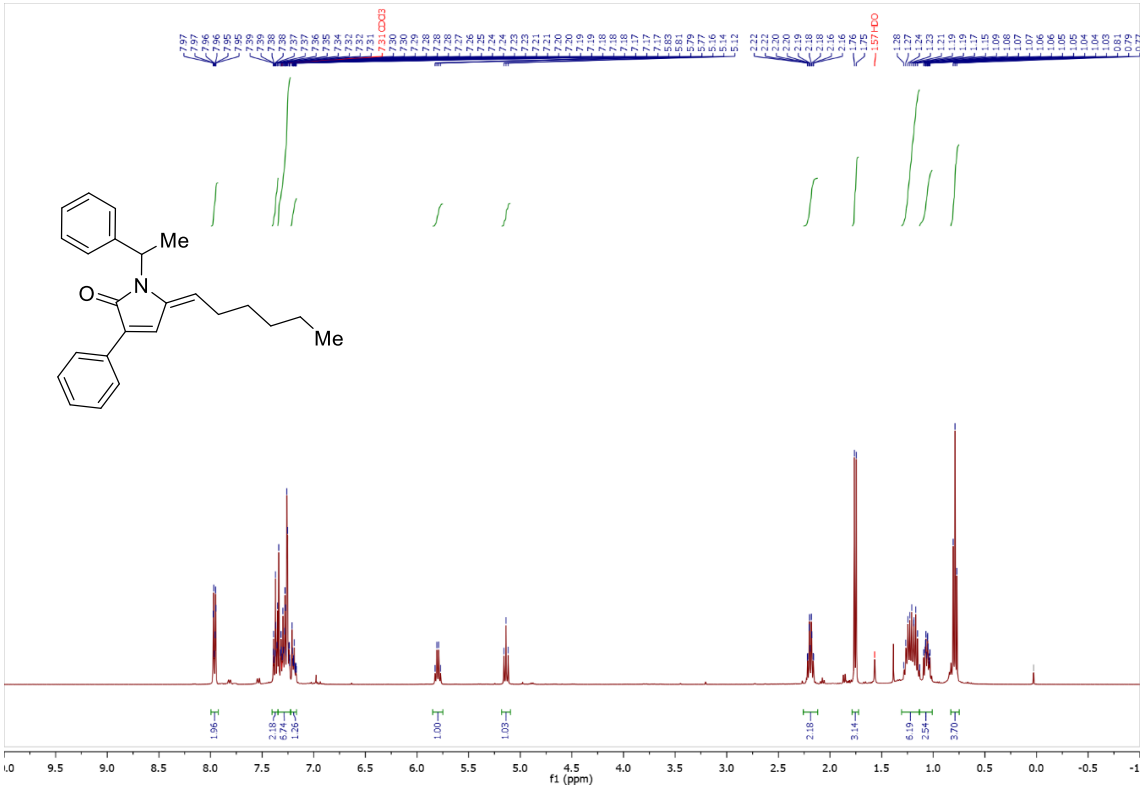


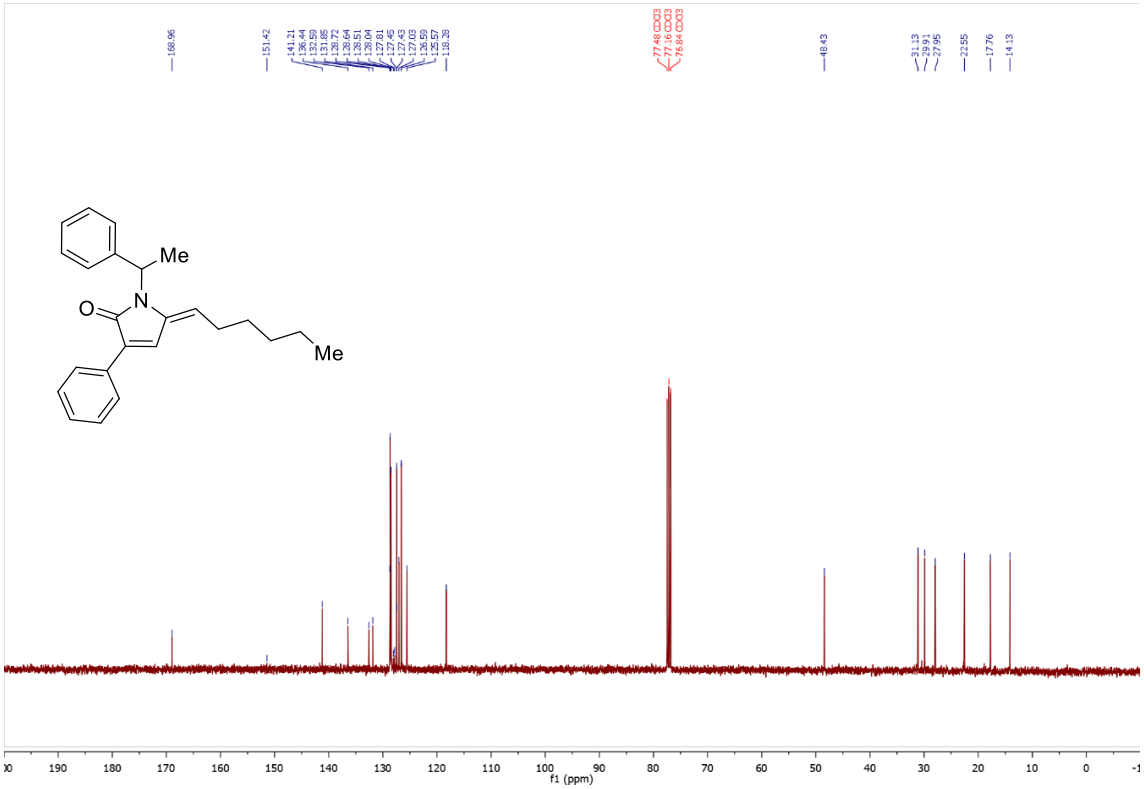
(*E*)-5-Hexylidene-3-phenyl-1-(4-(trifluoromethyl)benzyl)-1,5-dihydro-2*H*-pyrrol-2-one, 3m



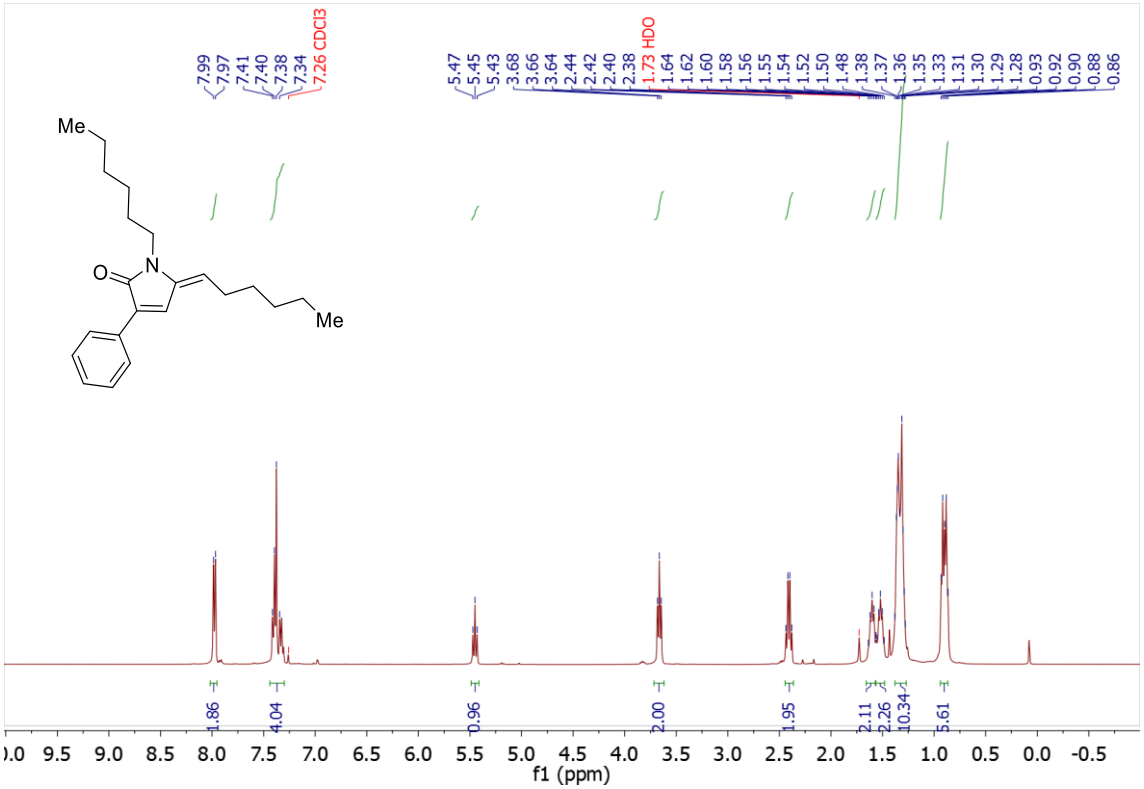


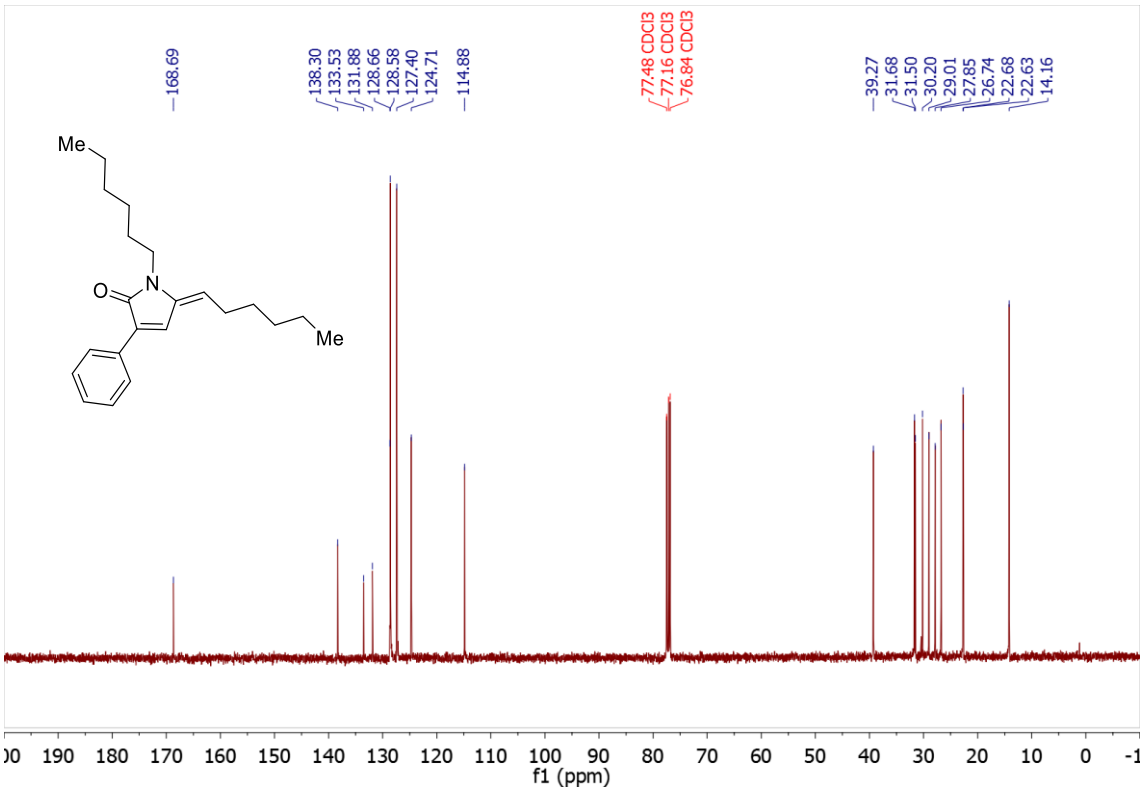
(*E*)-5-Hexylidene-3-phenyl-1-(1-phenylethyl)-1,5-dihydro-2*H*-pyrrol-2-one, 3n



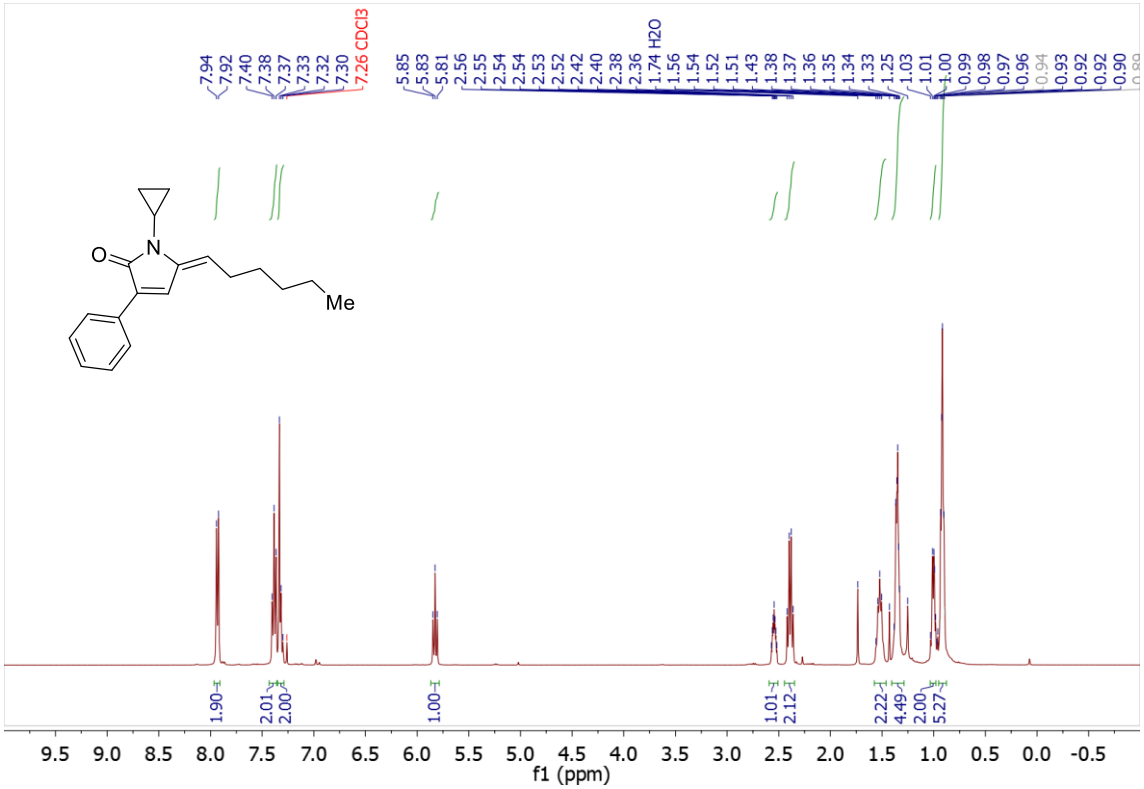


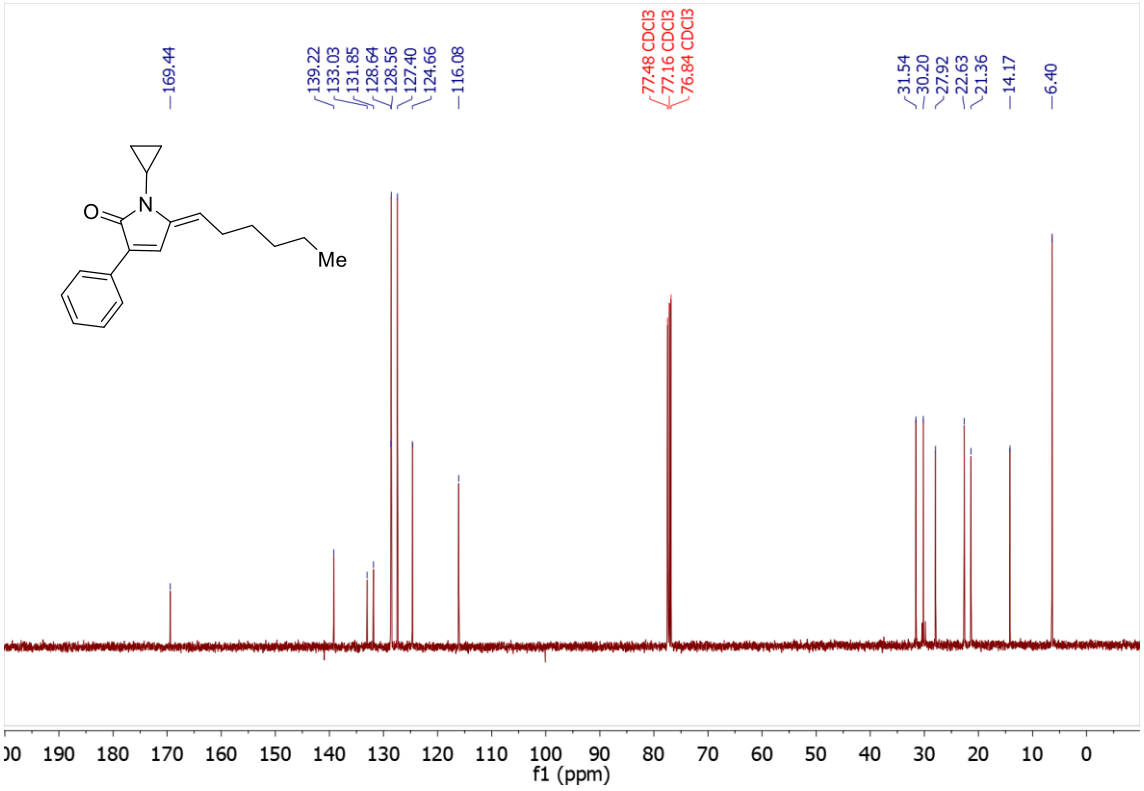
(*E*)-1-Hexyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3p



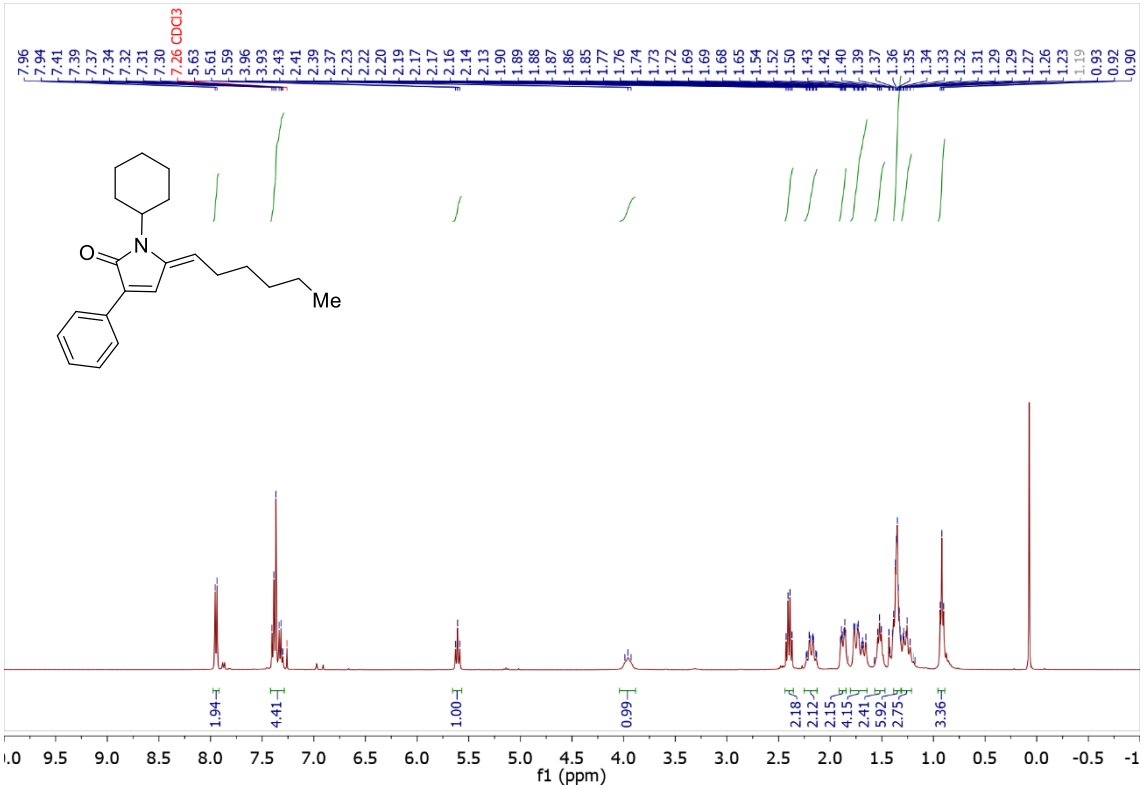


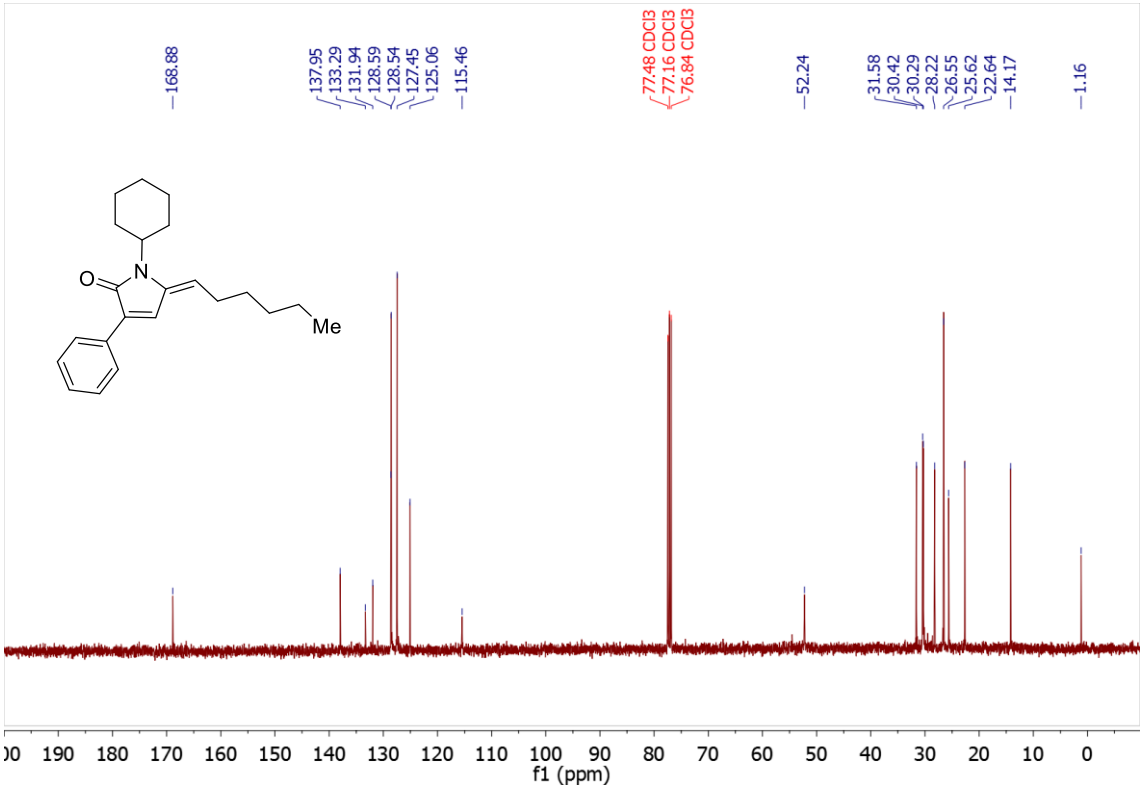
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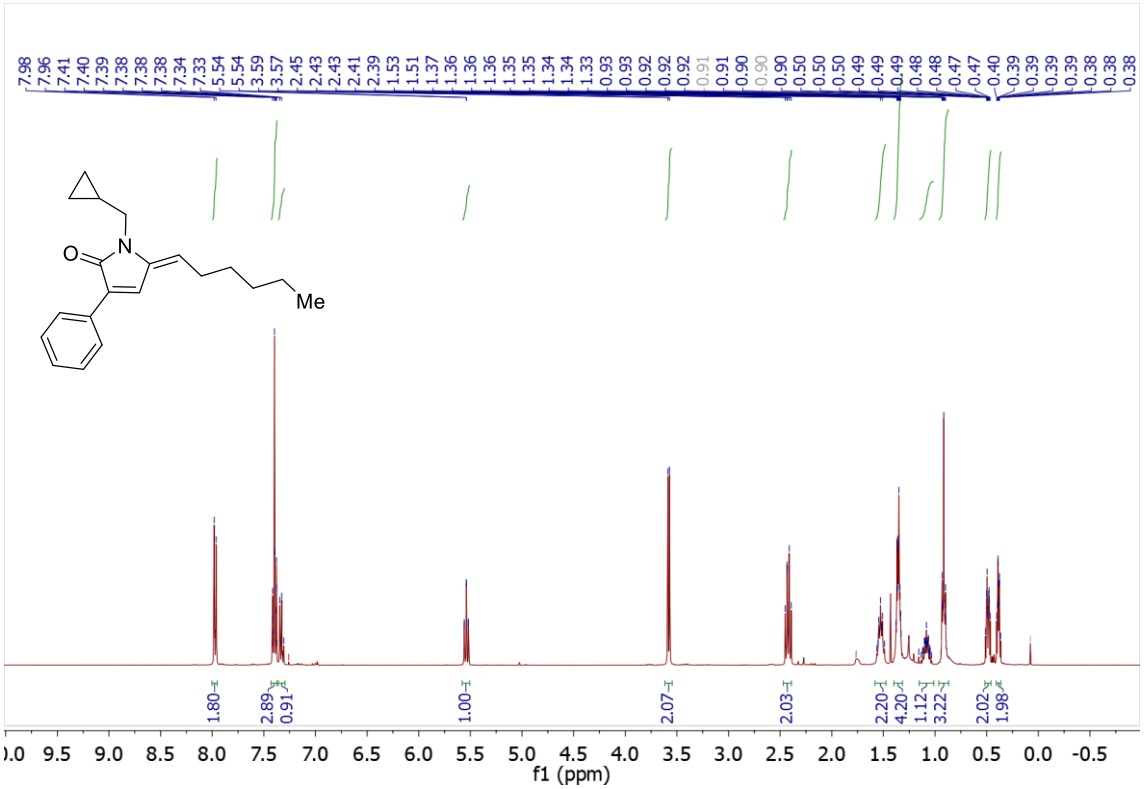


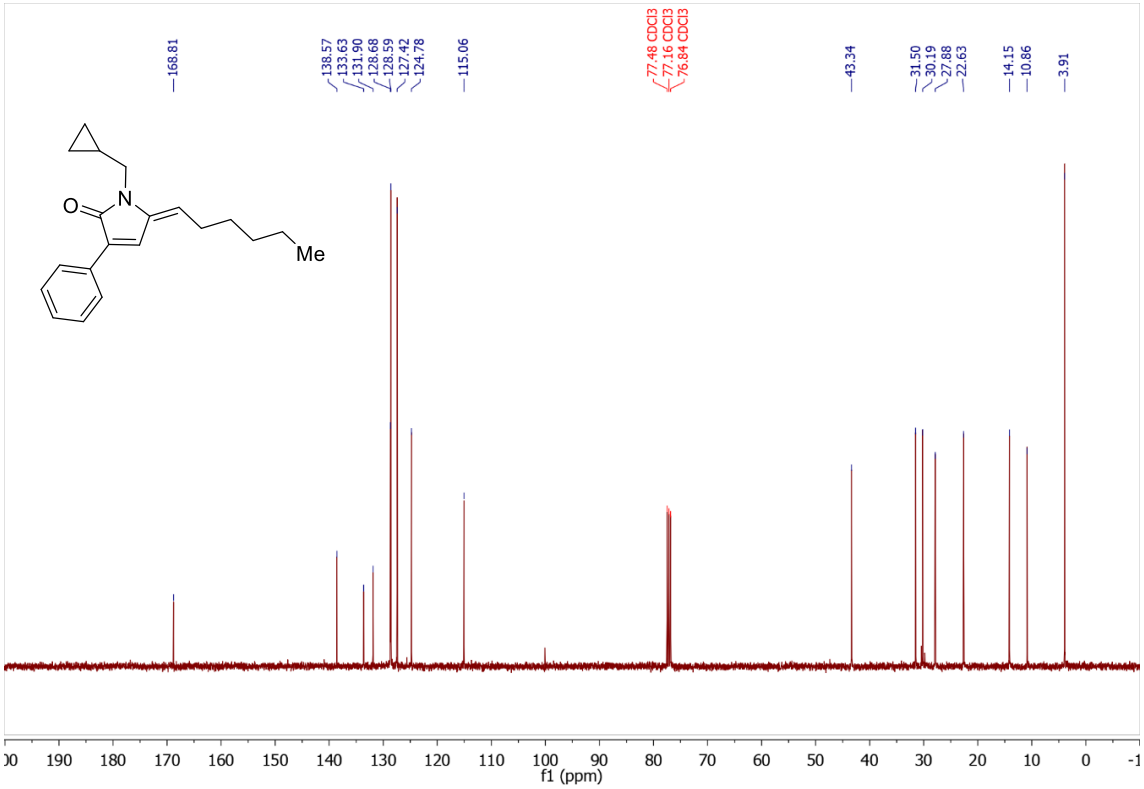
(*E*)-1-Cyclohexyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3r



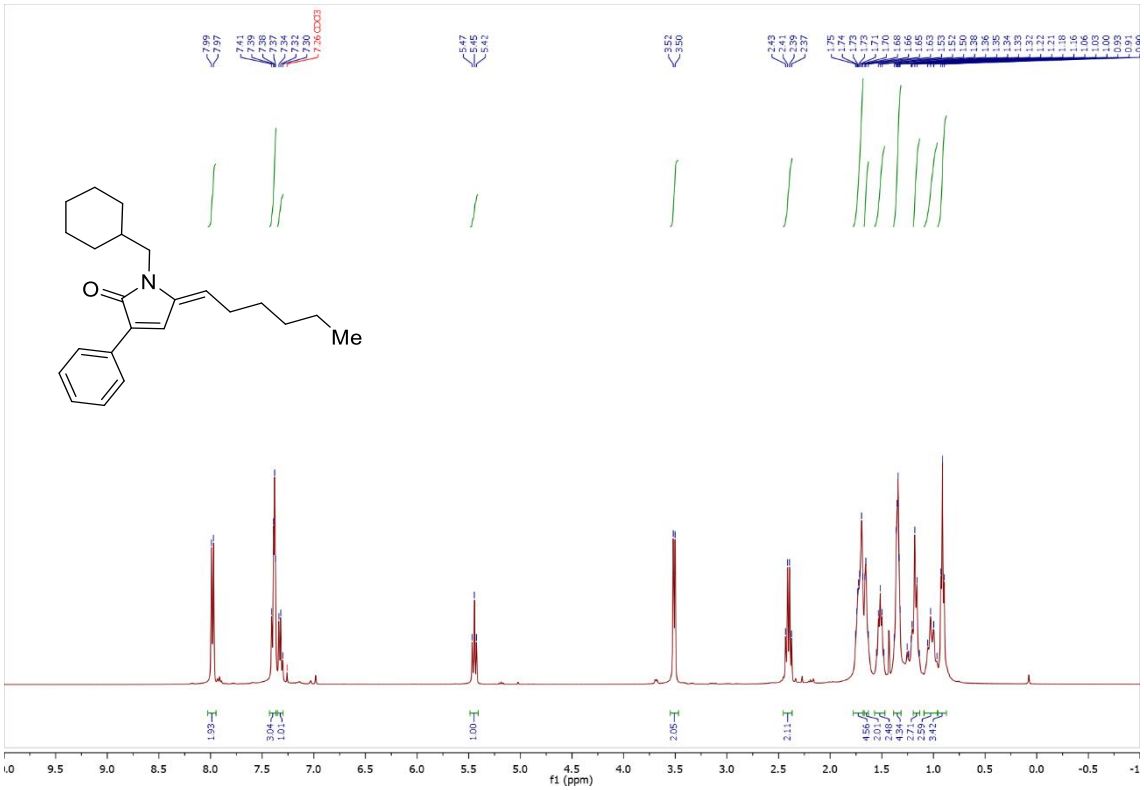


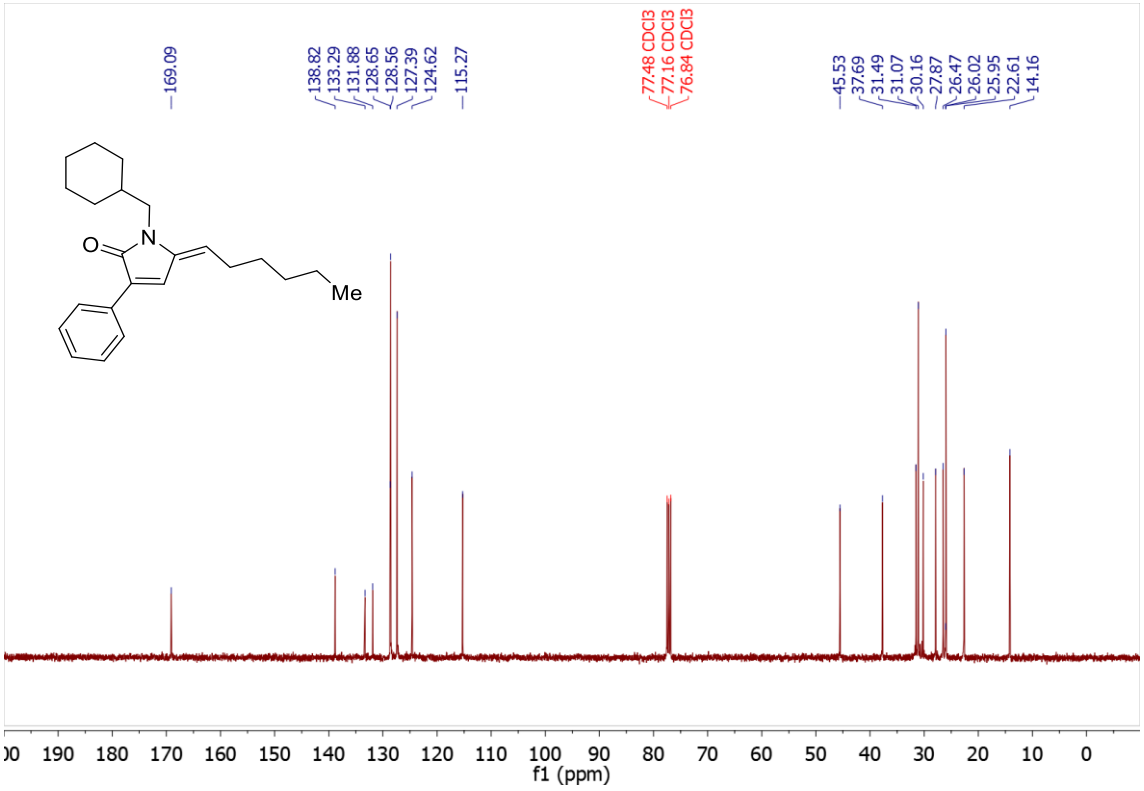
(*E*)-1-(Cyclopropylmethyl)-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3s



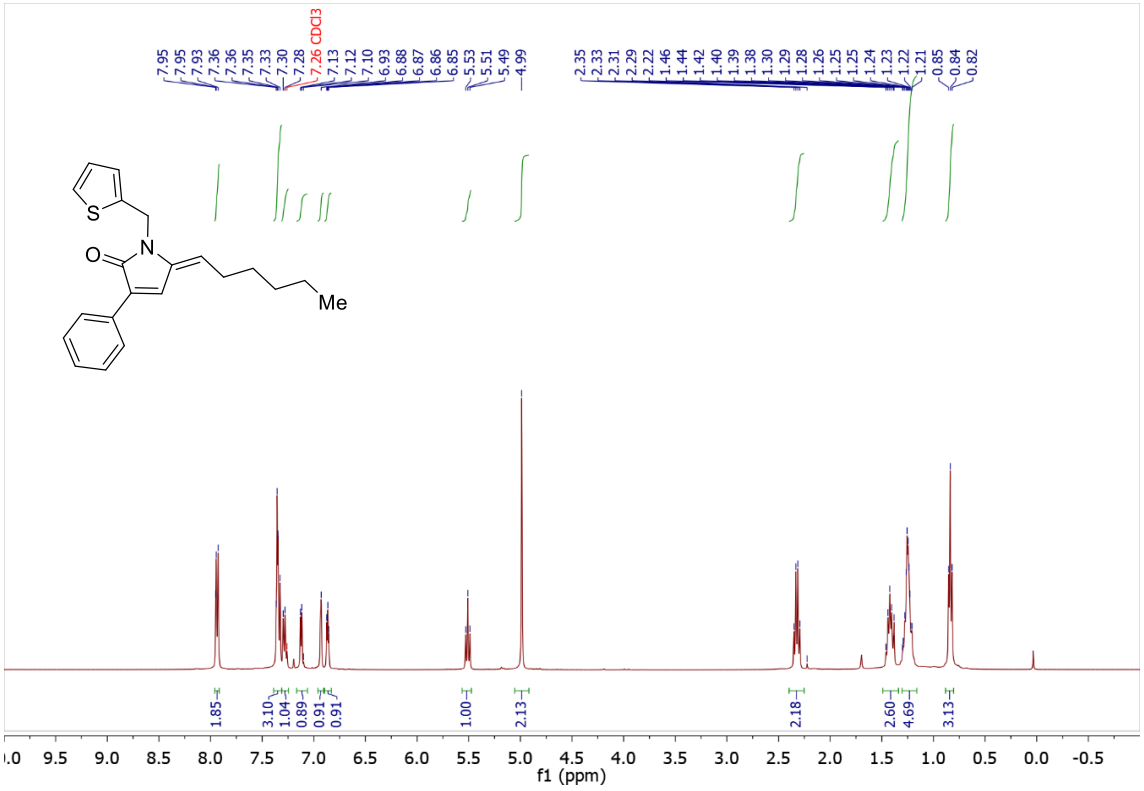


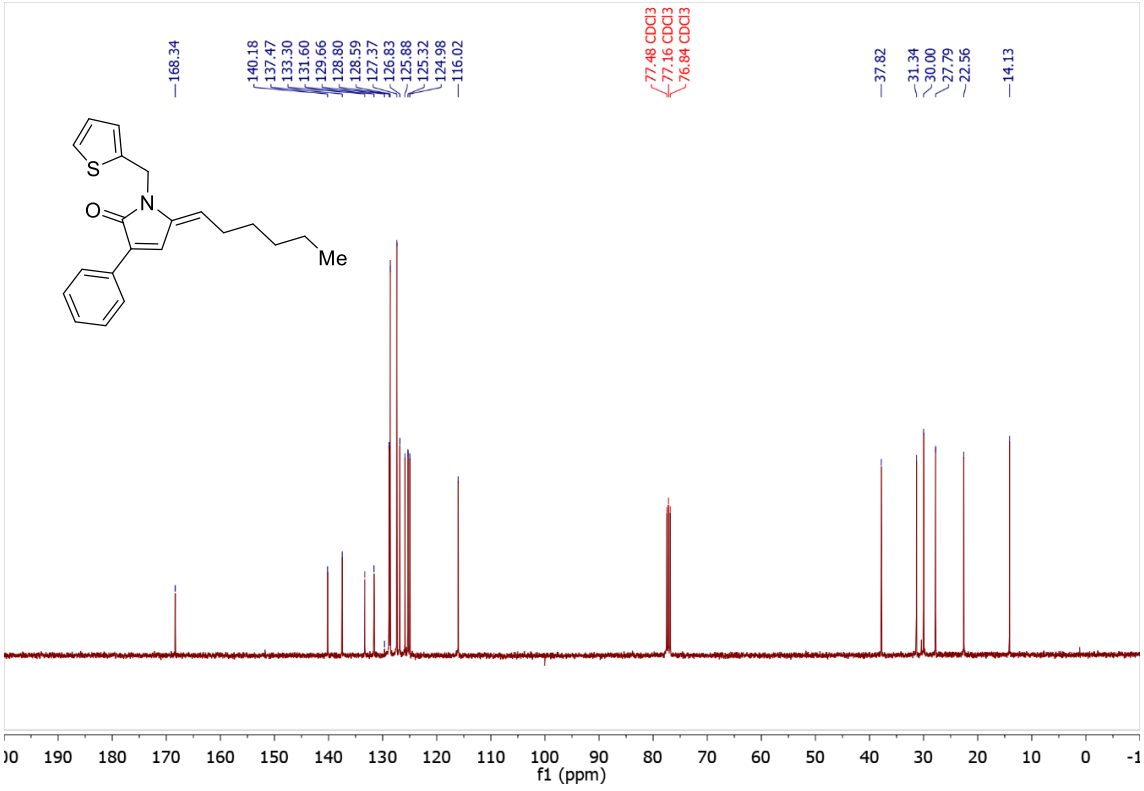
(*E*)-1-(Cyclohexylmethyl)-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3t



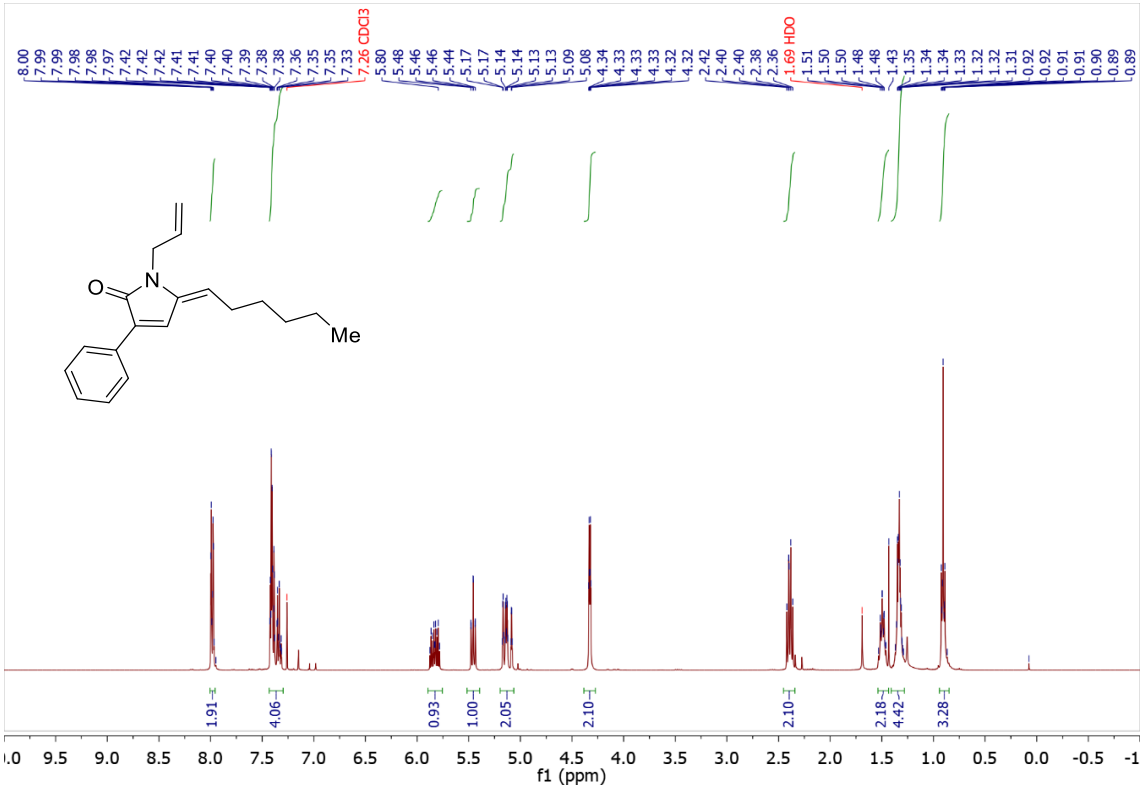


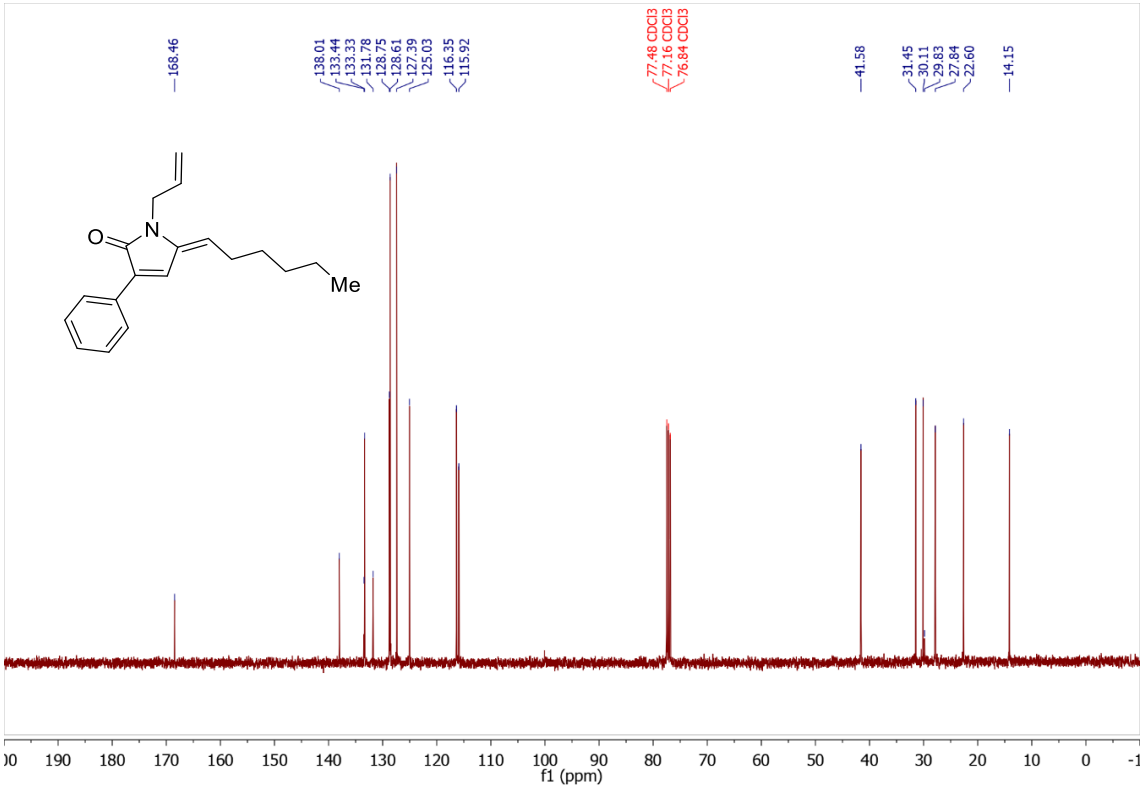
((*E*)-5-Hexylidene-3-phenyl-1-(thiophen-2-ylmethyl)-1,5-dihydro-2*H*-pyrrol-2-one, 3u



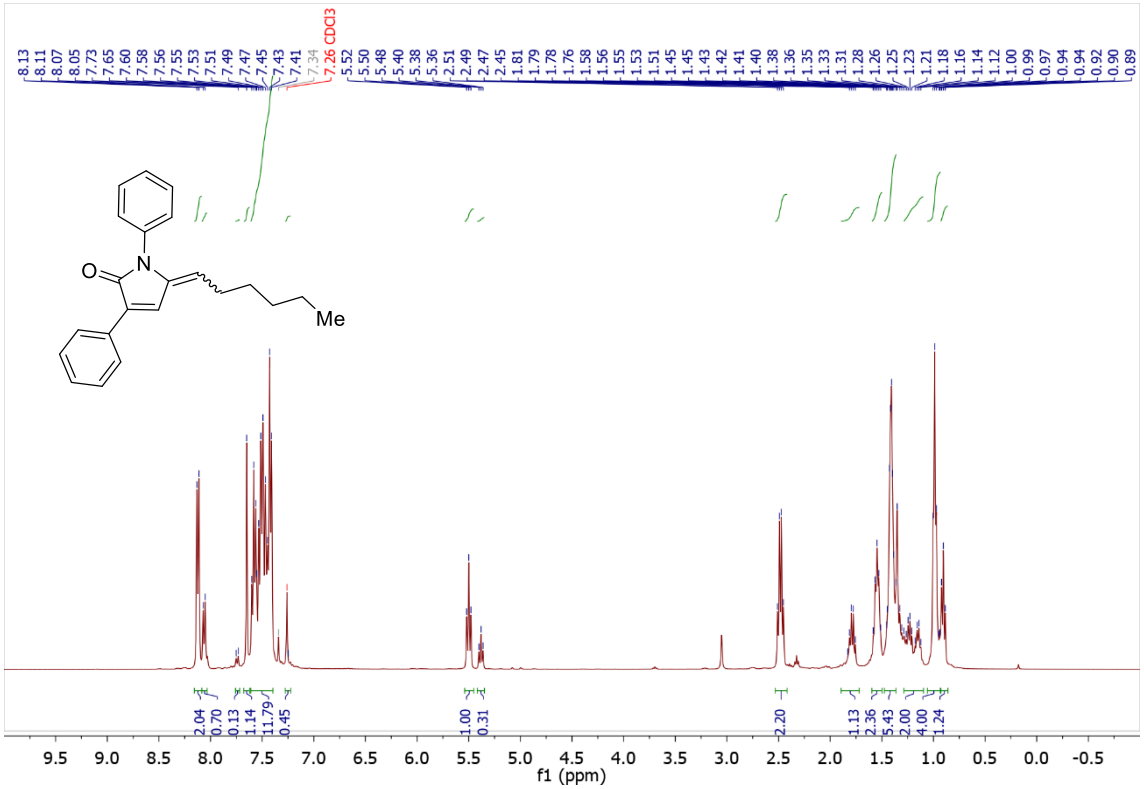


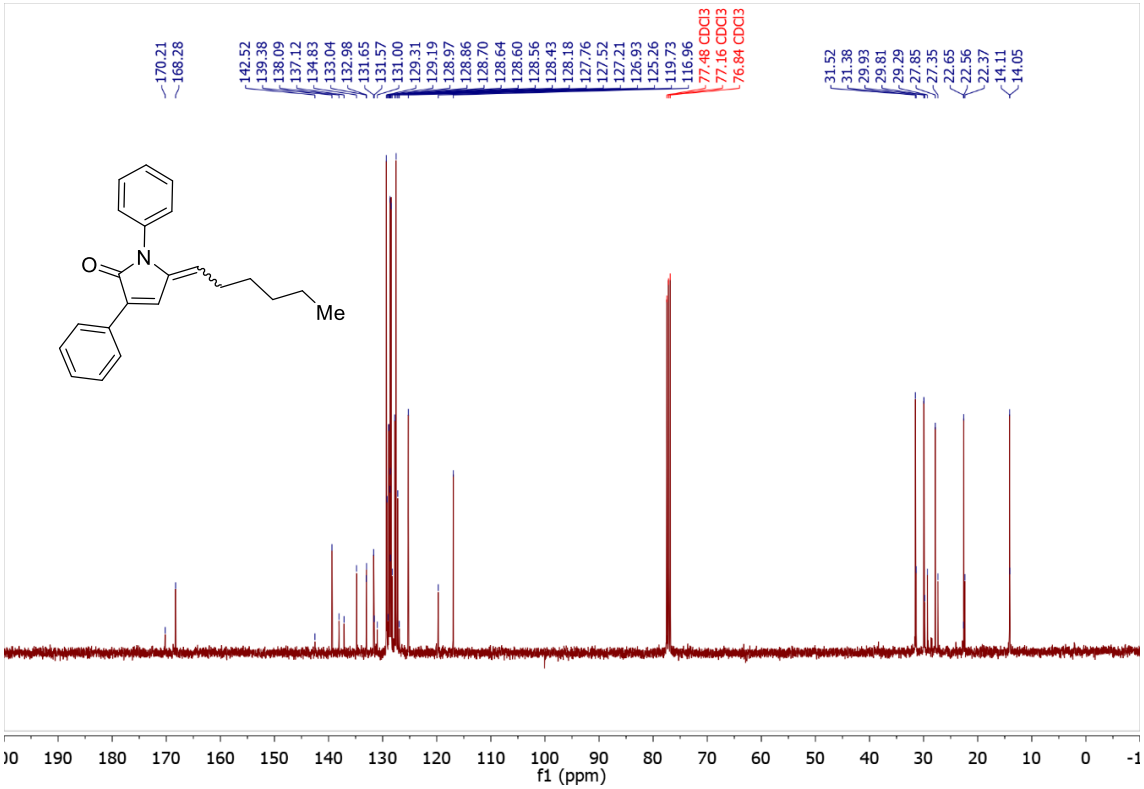
(*E*)-1-Allyl-5-hexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 3v



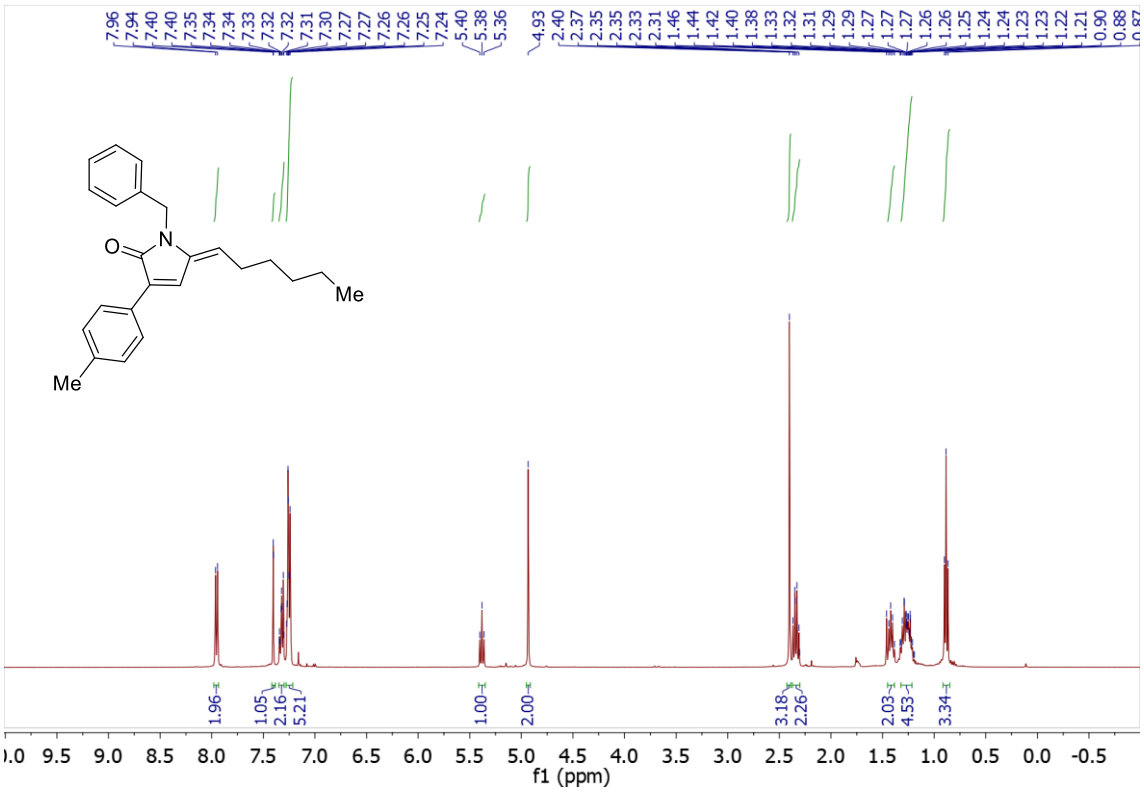


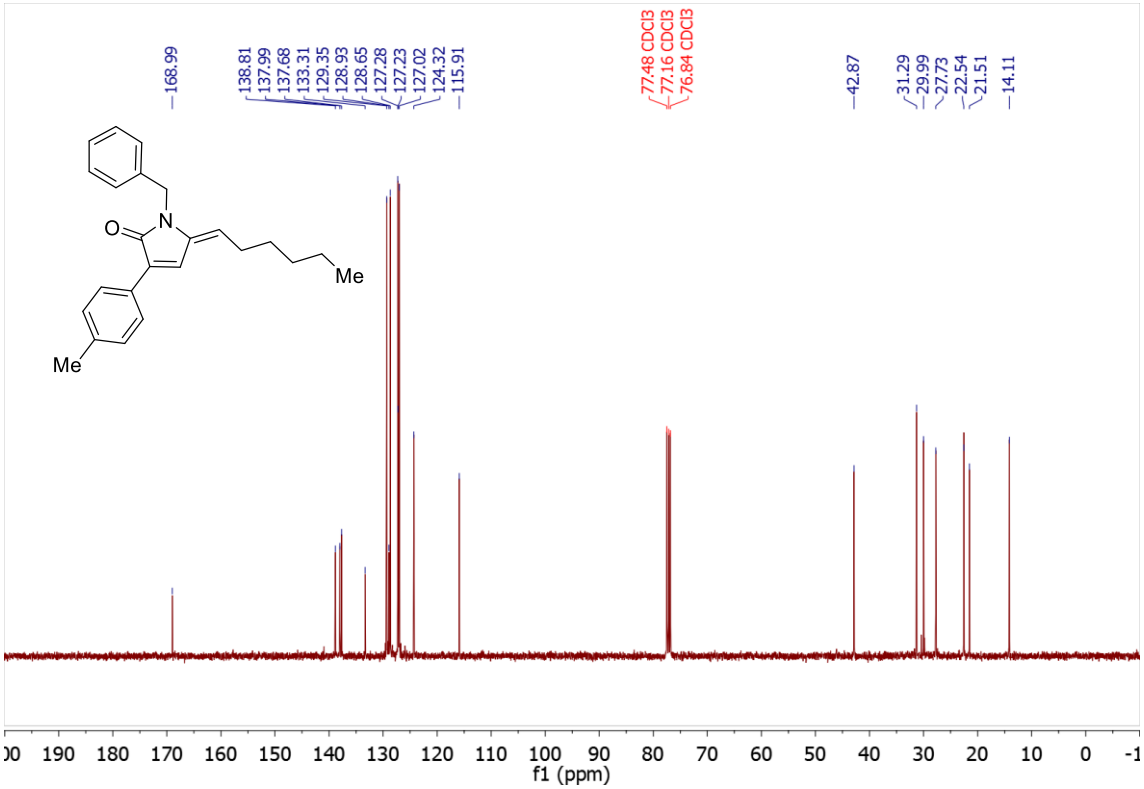
(*E*,*Z*)-5-Hexylidene-1,3-diphenyl-1,5-dihydro-2*H*-pyrrol-2-one, **3w**



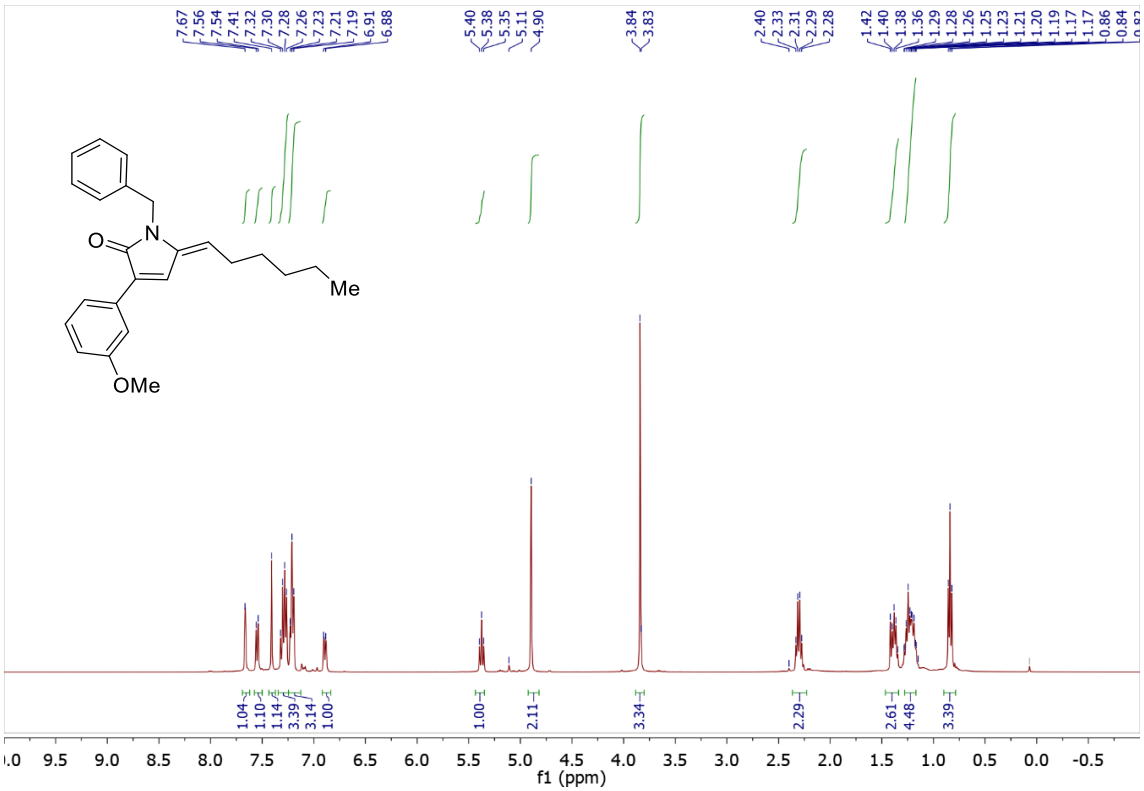


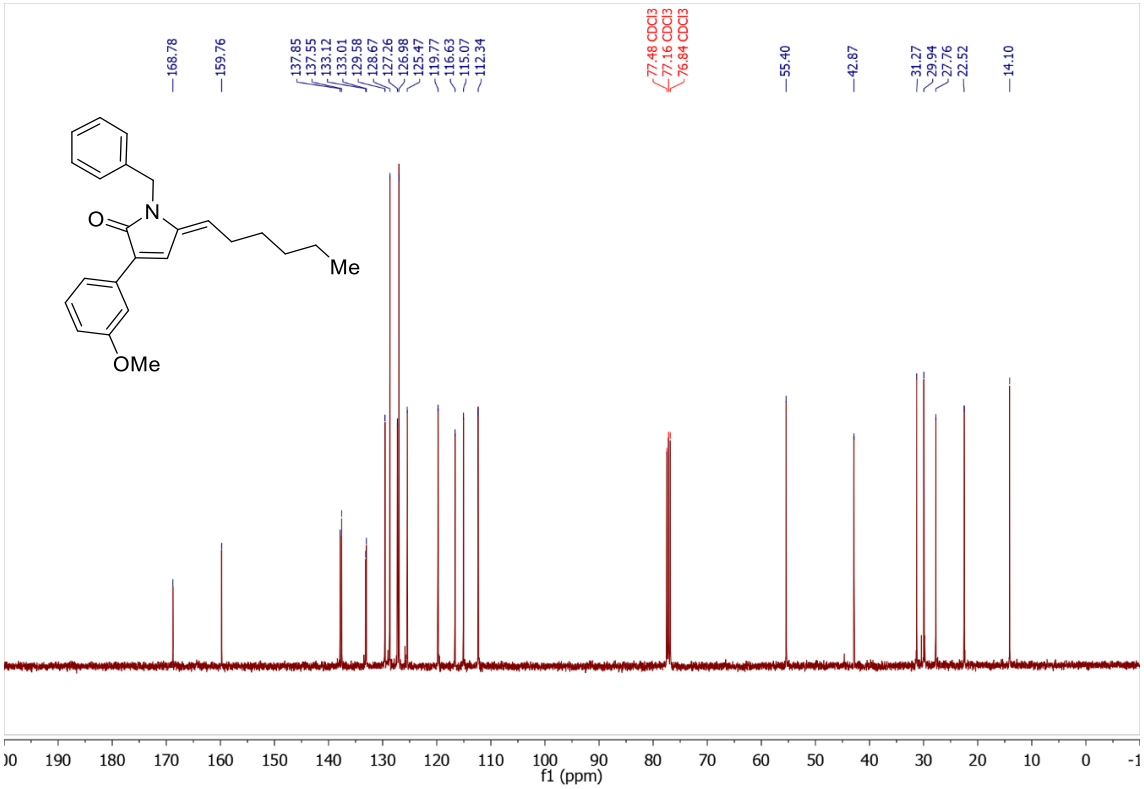
(*E*)-1-Benzyl-5-hexylidene-3-(*p*-tolyl)-1,5-dihydro-2*H*-pyrrol-2-one, 5a



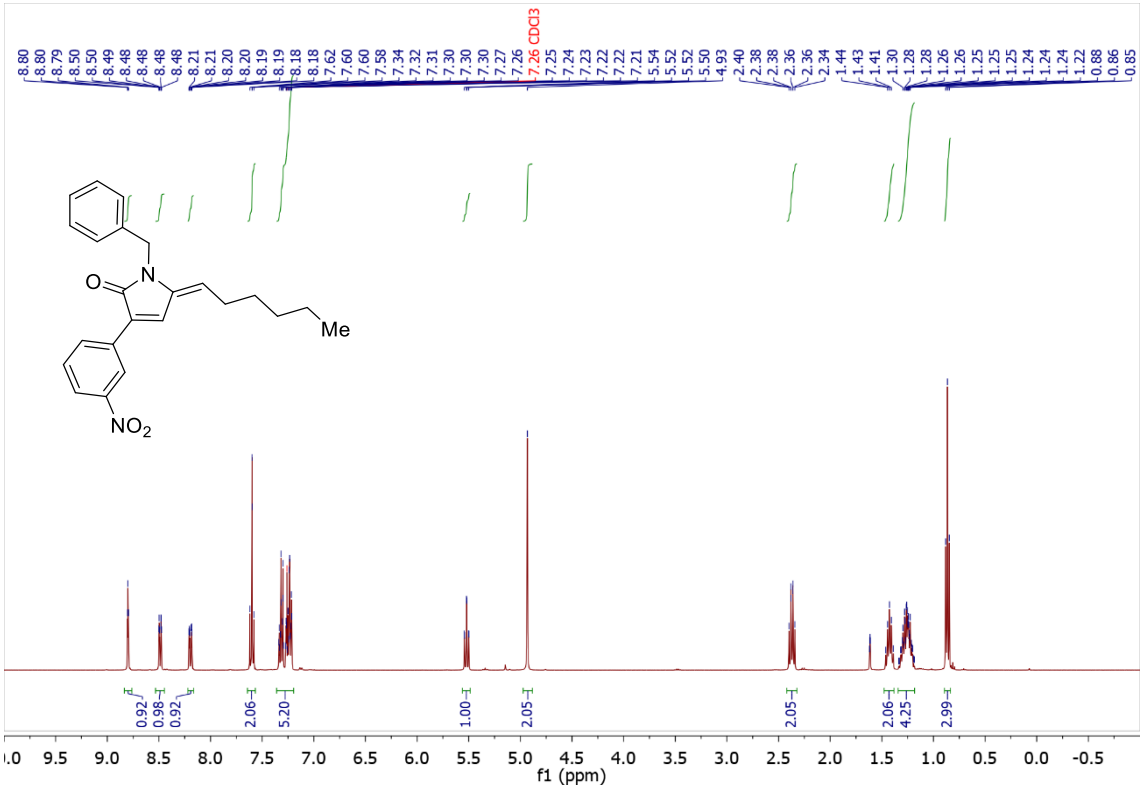


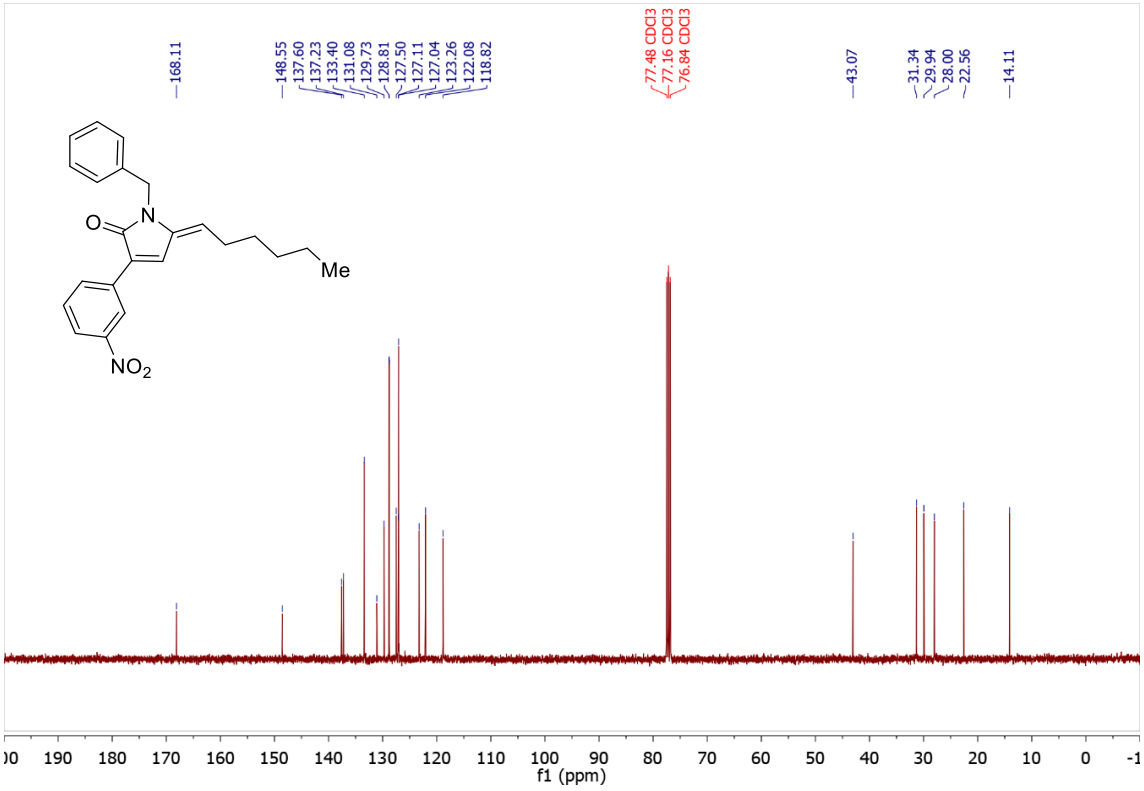
(*E*)-1-Benzyl-5-hexylidene-3-(3-methoxyphenyl)-1,5-dihydro-2*H*-pyrrol-2-one, 5c



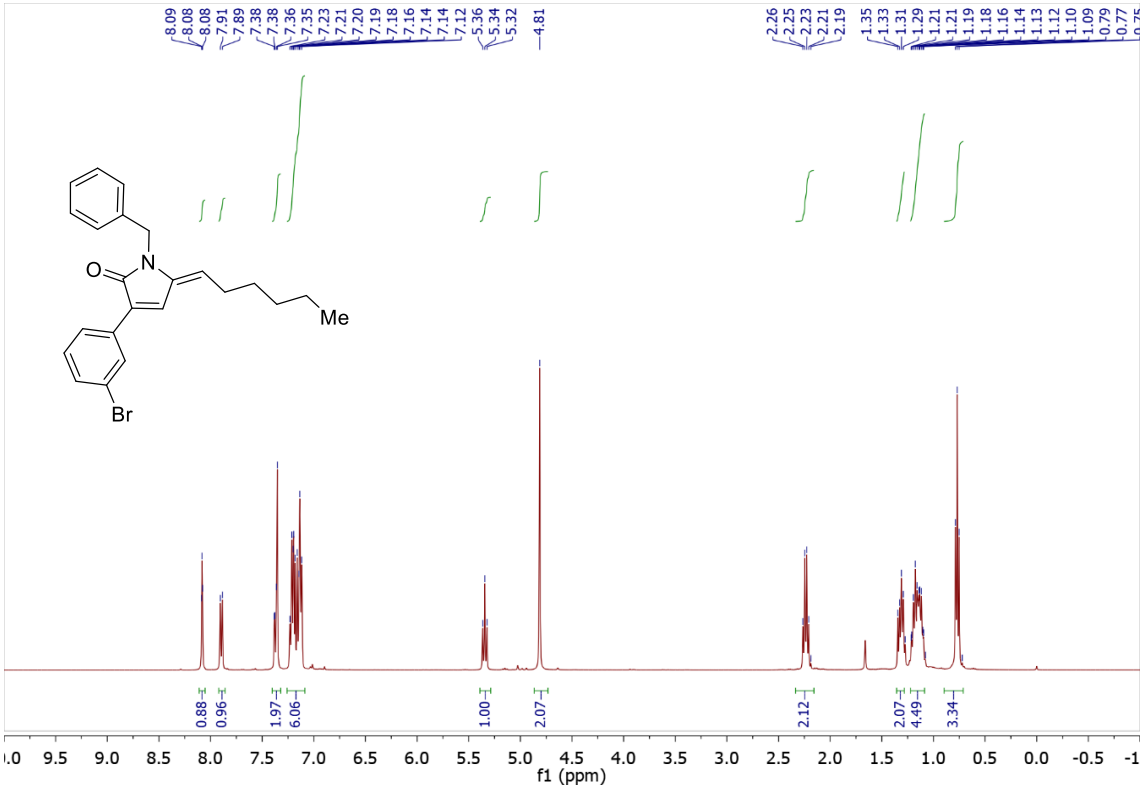


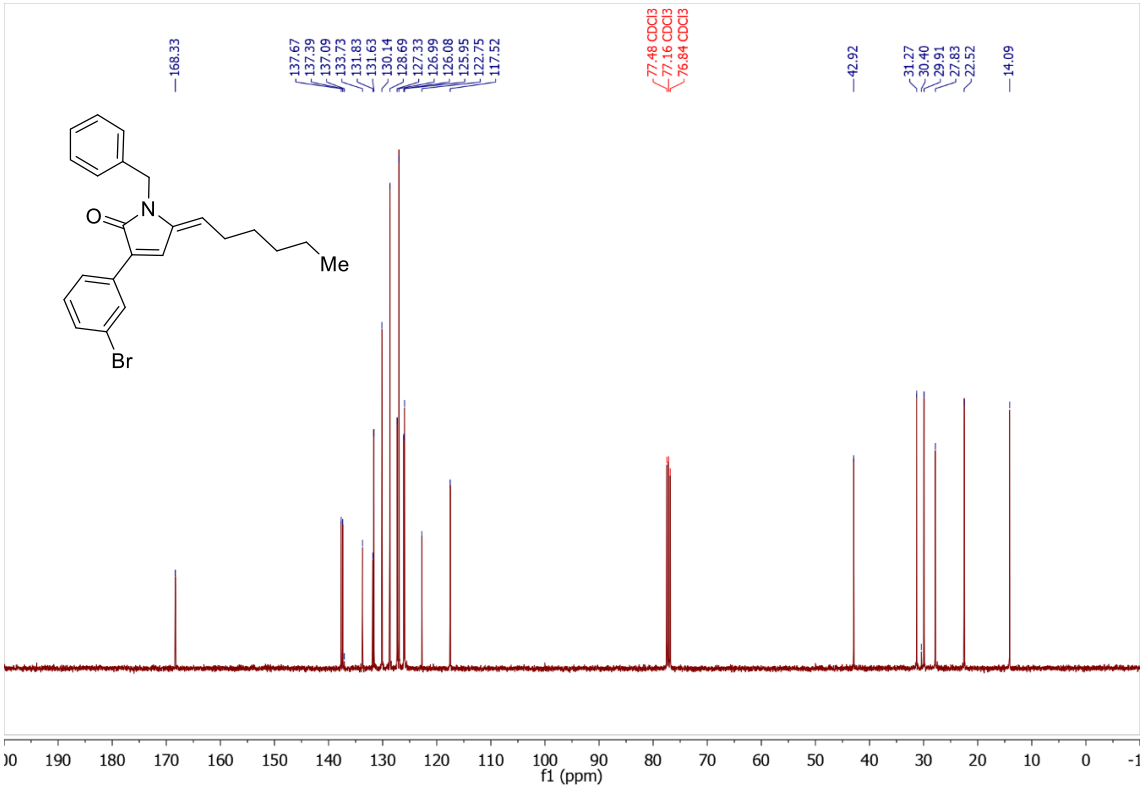
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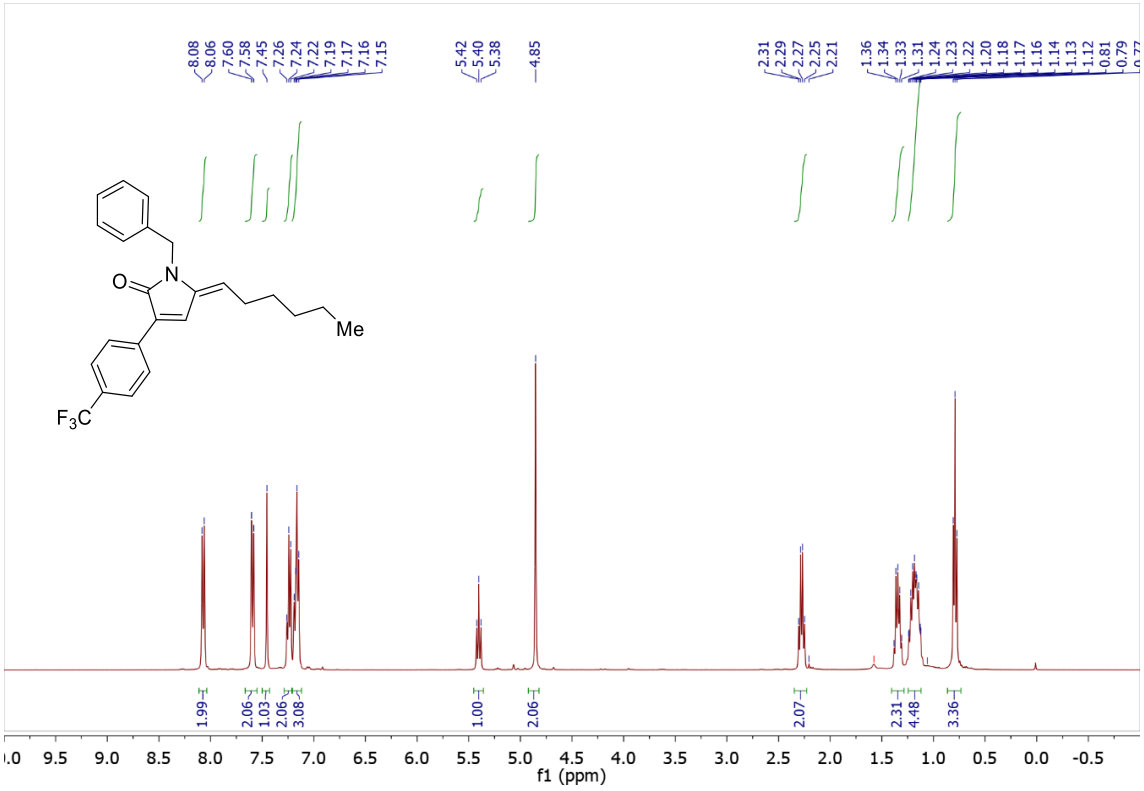


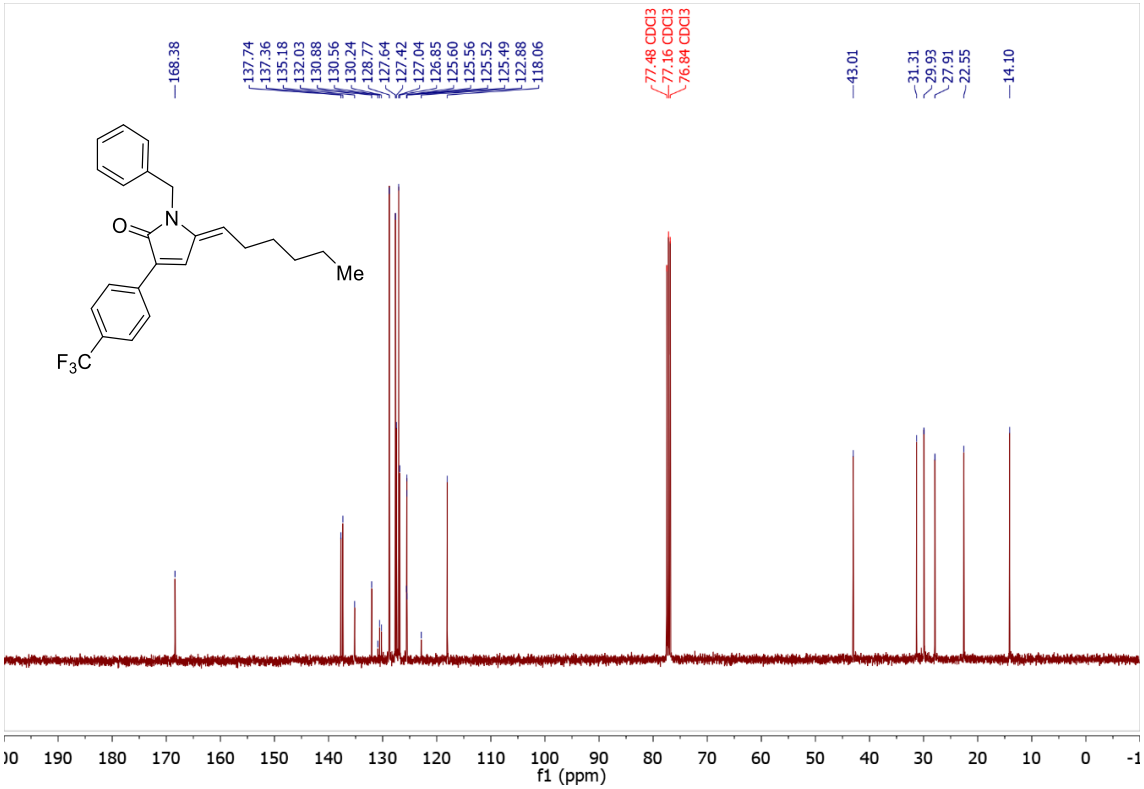
(*E*)-1-Benzyl-3-(3-bromophenyl)-5-hexylidene-1,5-dihydro-2*H*-pyrrol-2-one, 5e



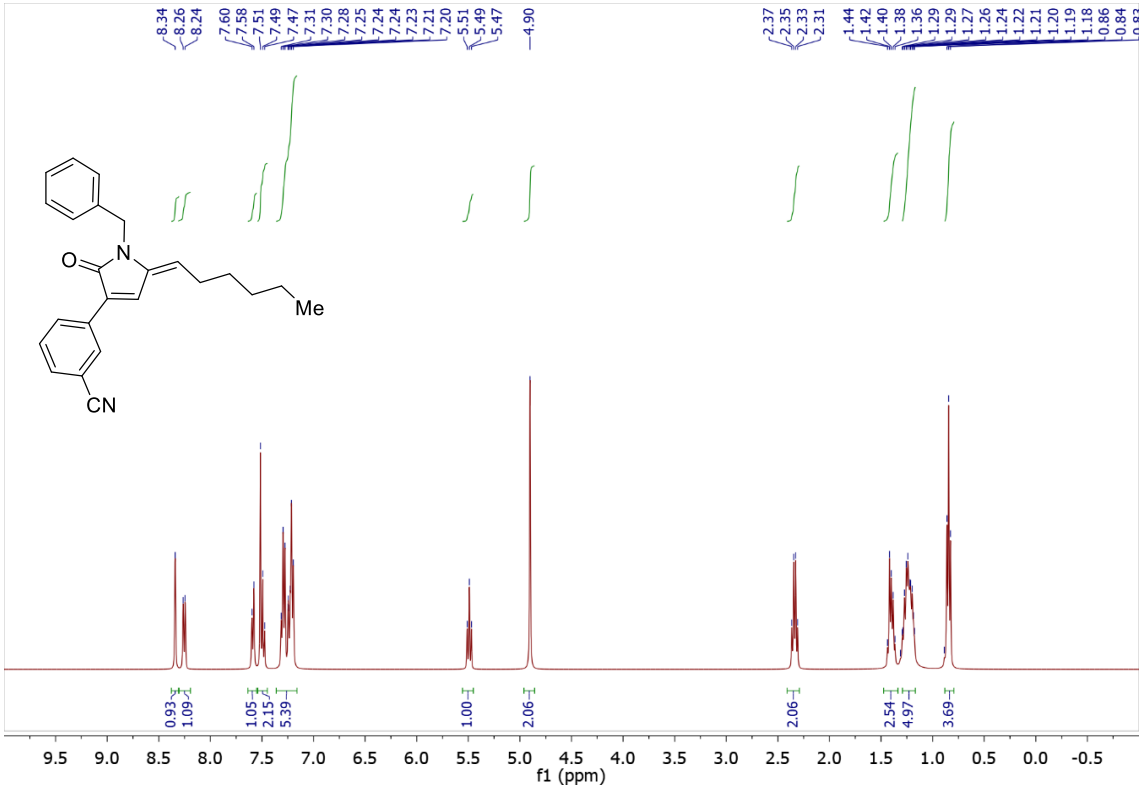


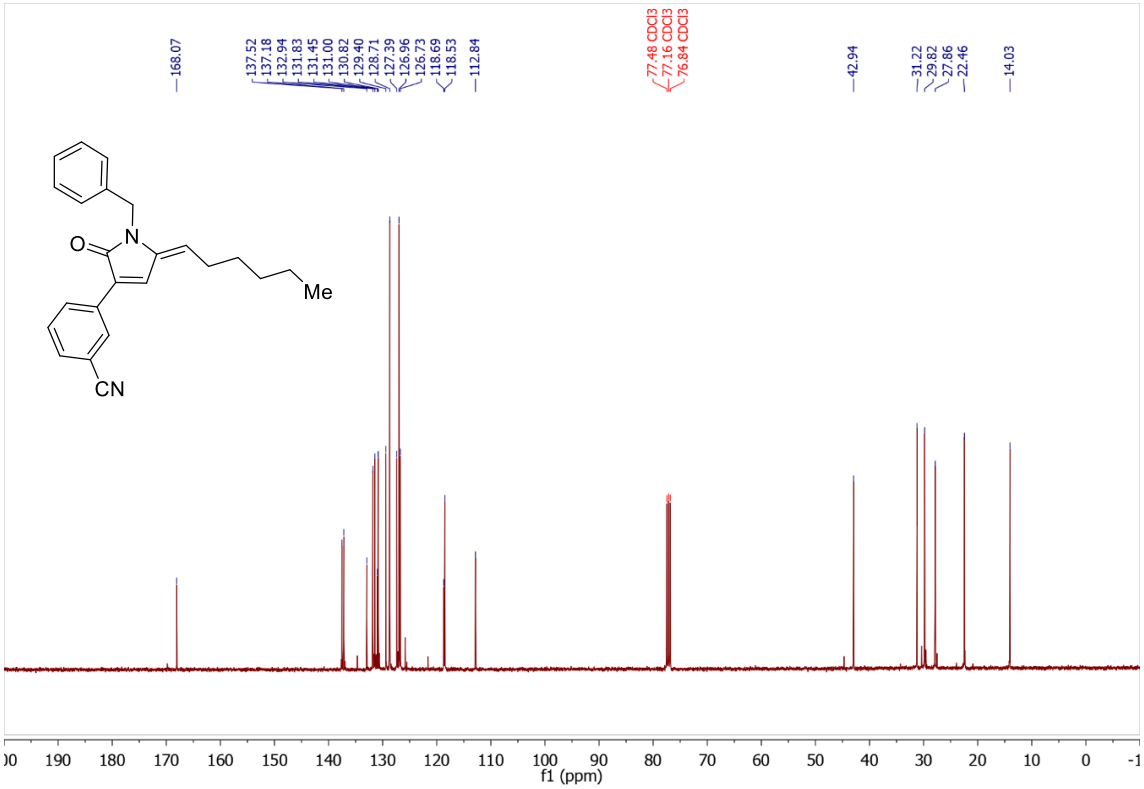
(*E*)-1-Benzyl-5-hexylidene-3-(4-(trifluoromethyl)phenyl)-1,5-dihydro-2*H*-pyrrol-2-one, 5f



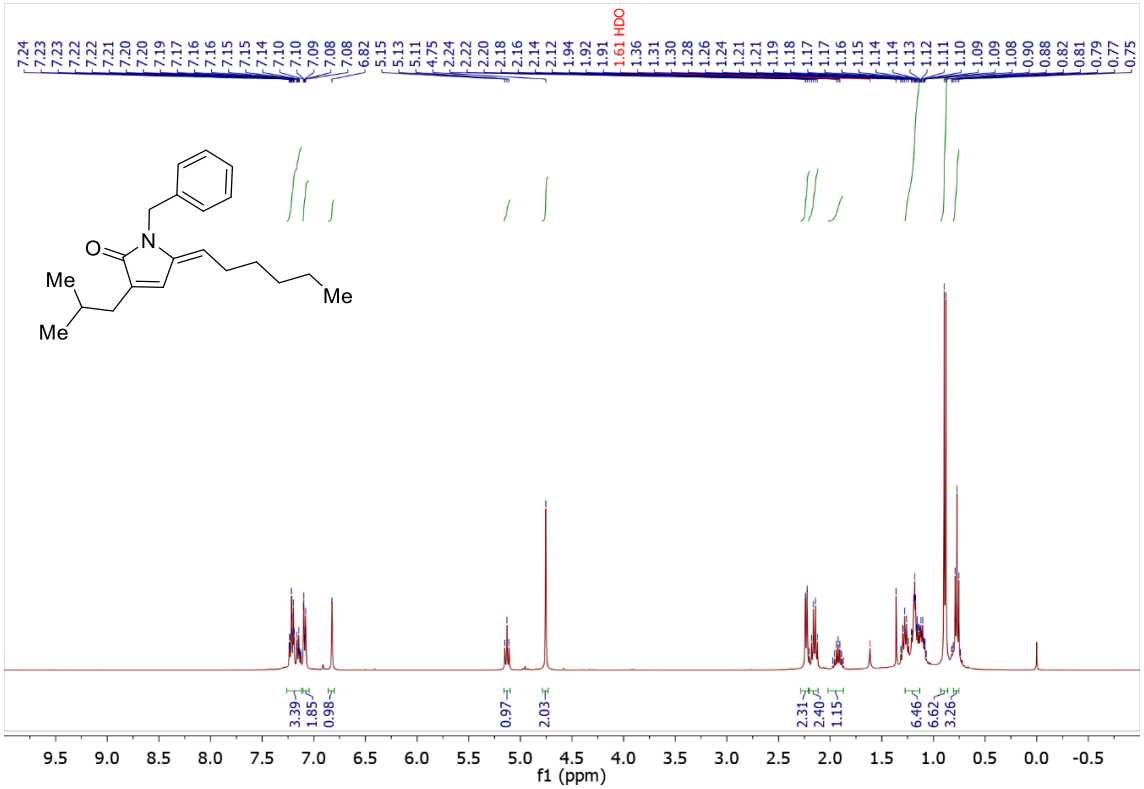


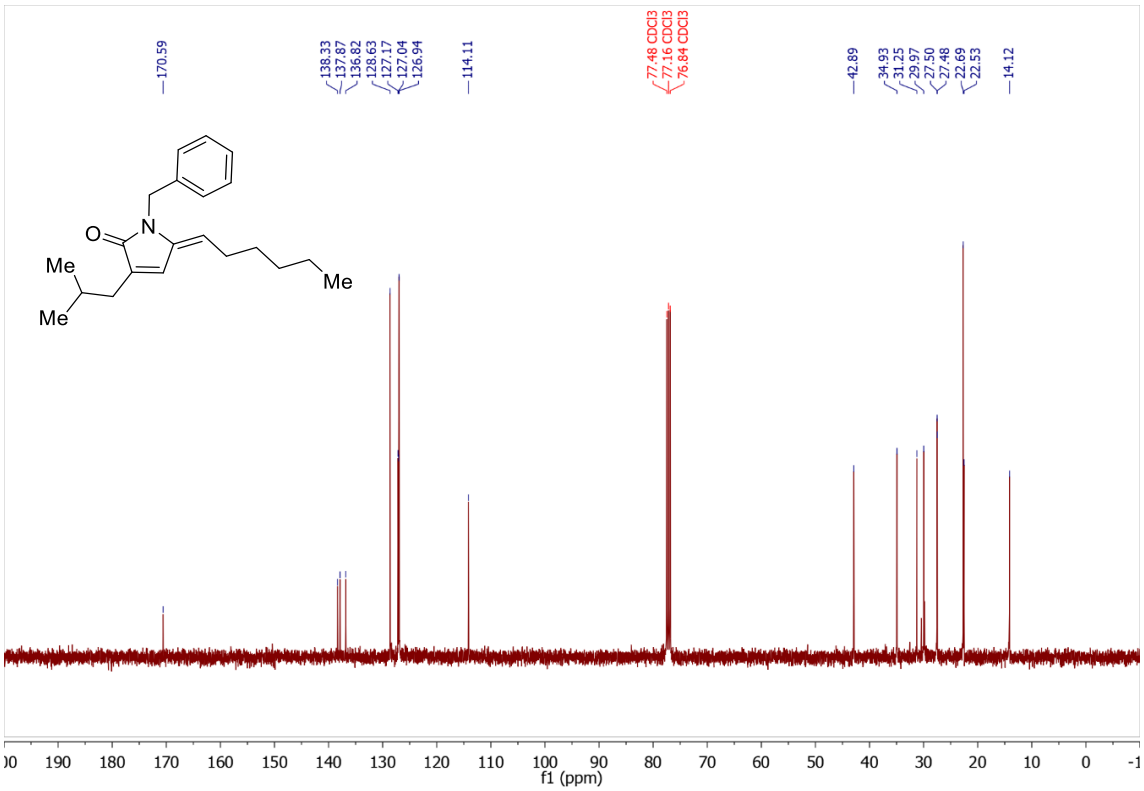
(*E*)-3-(1-Benzyl-5-hexylidene-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)benzonitrile, 5g



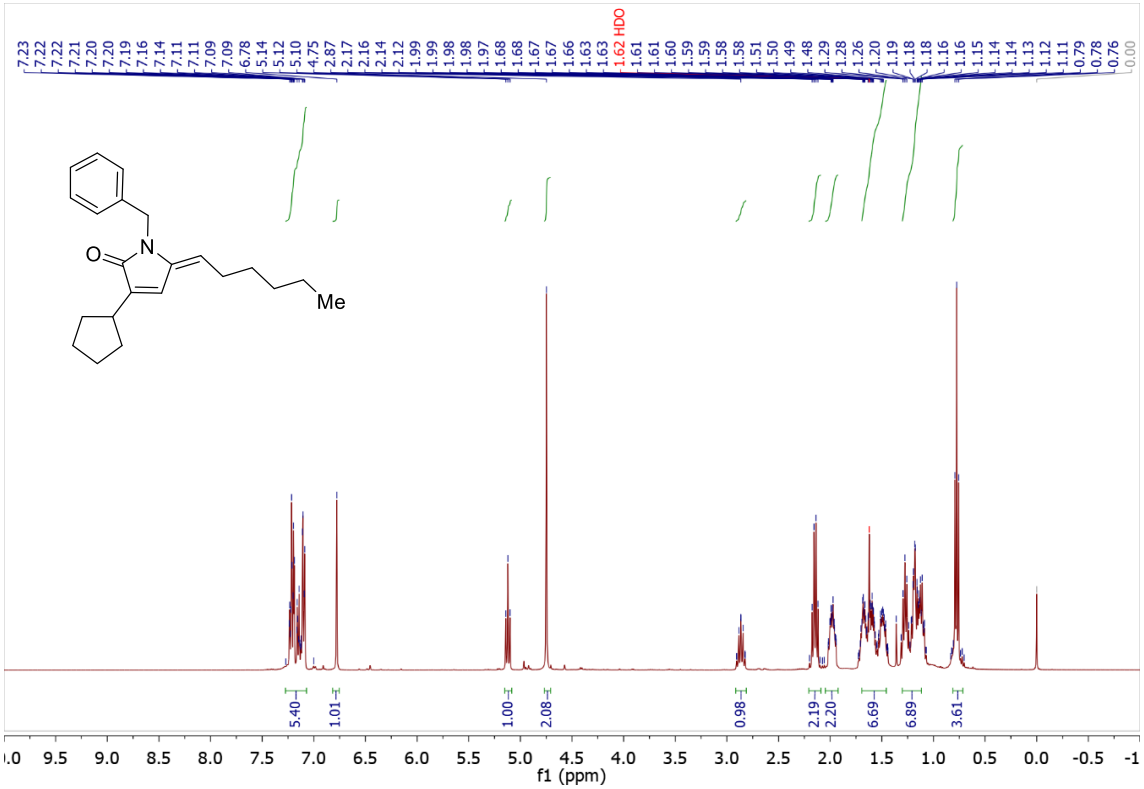


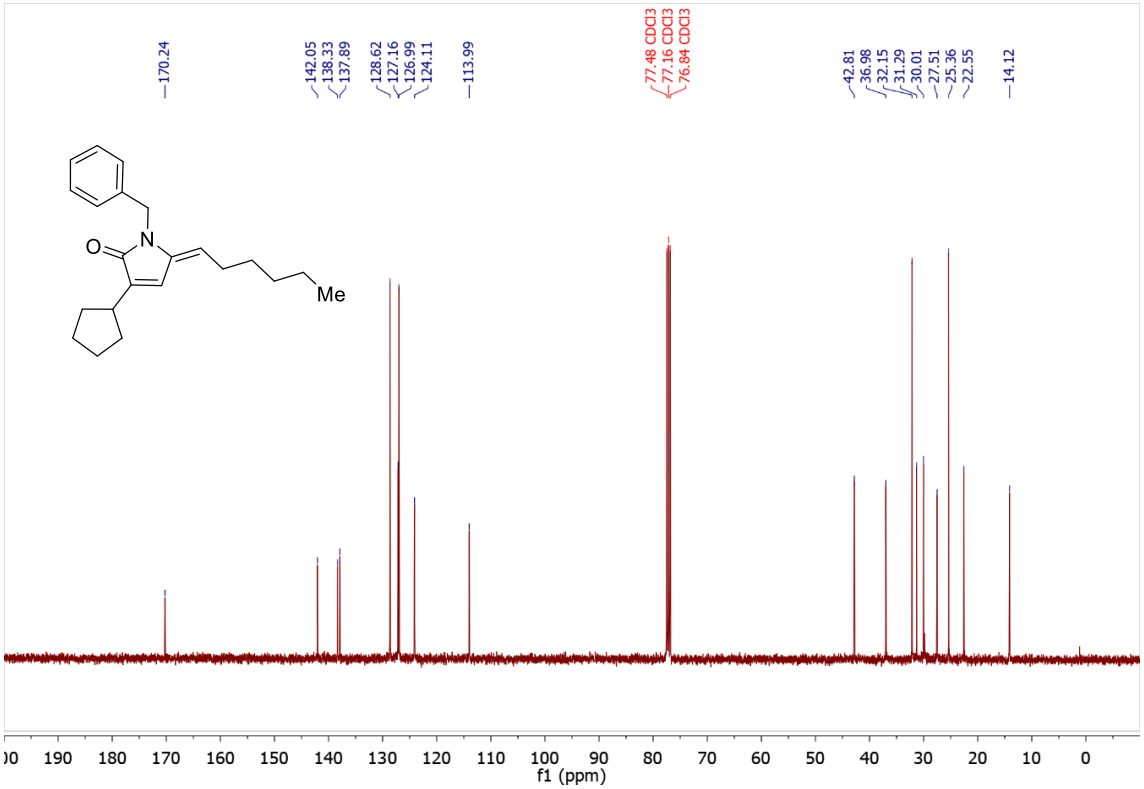
(*E*)-1-Benzyl-5-hexylidene-3-isobutyl-1,5-dihydro-2*H*-pyrrol-2-one, 5k



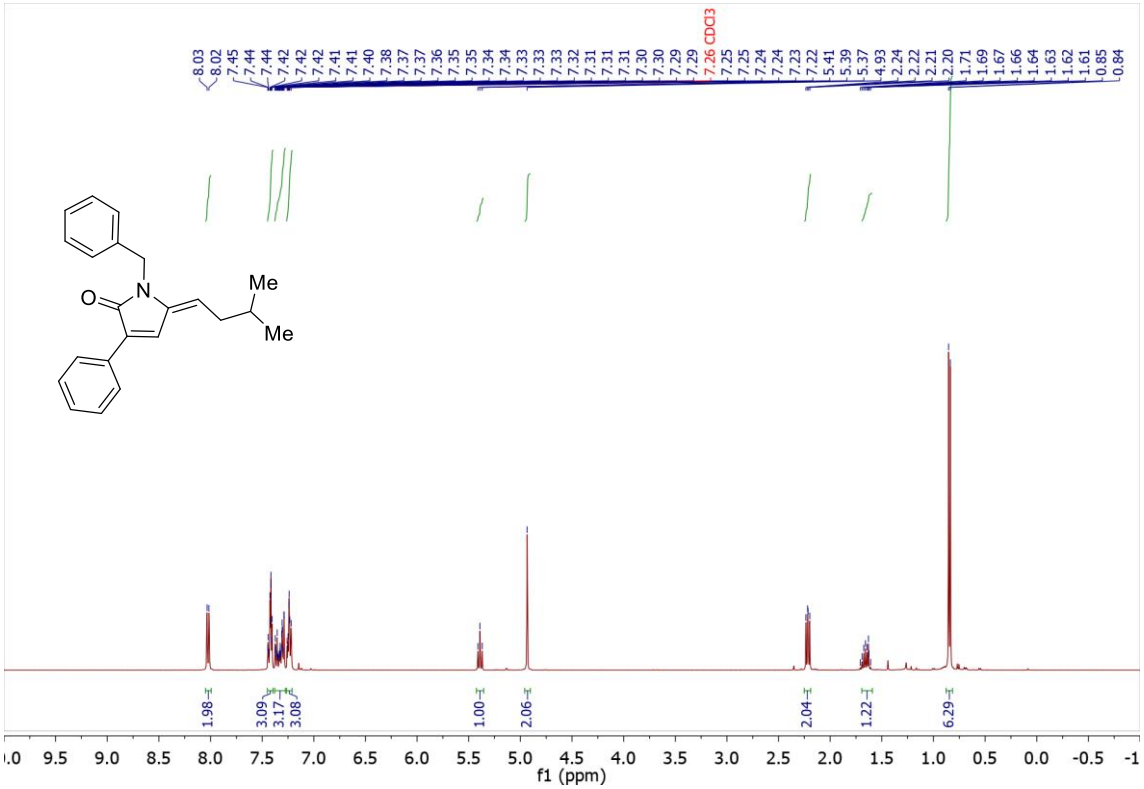


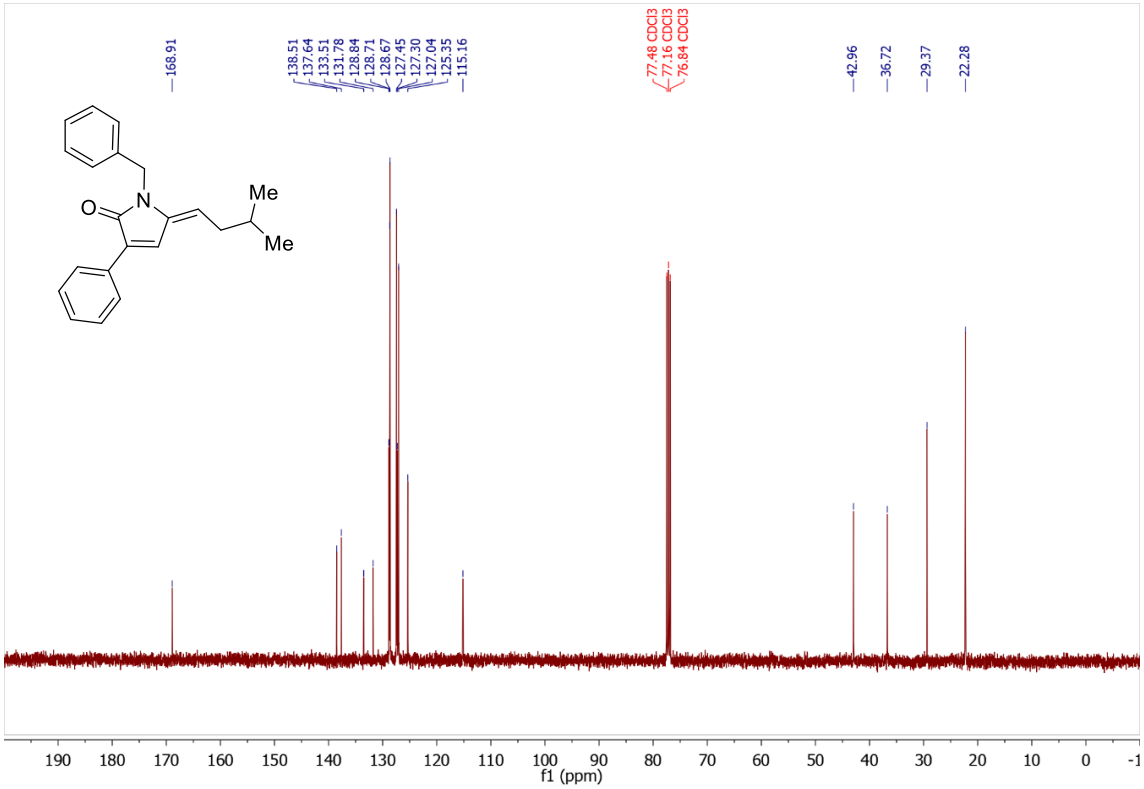
(*E*)-1-Benzyl-3-cyclopentyl-5-hexylidene-1,5-dihydro-2*H*-pyrrol-2-one, 5l



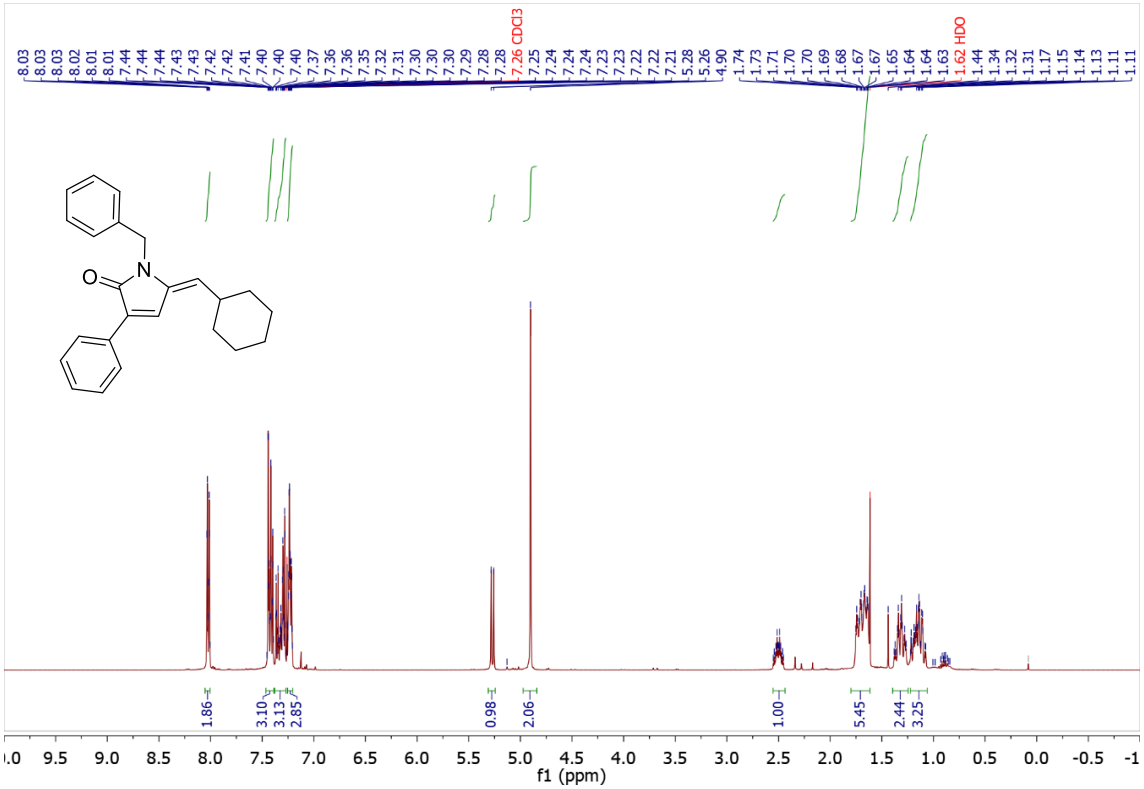


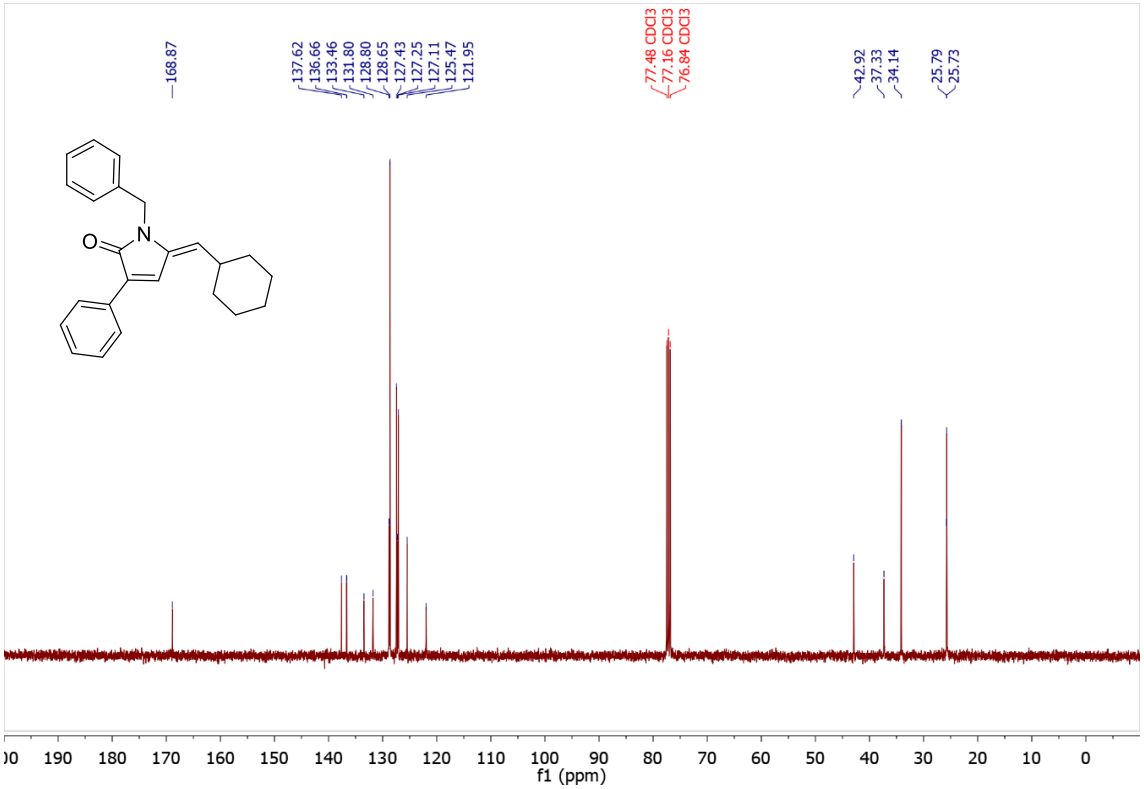
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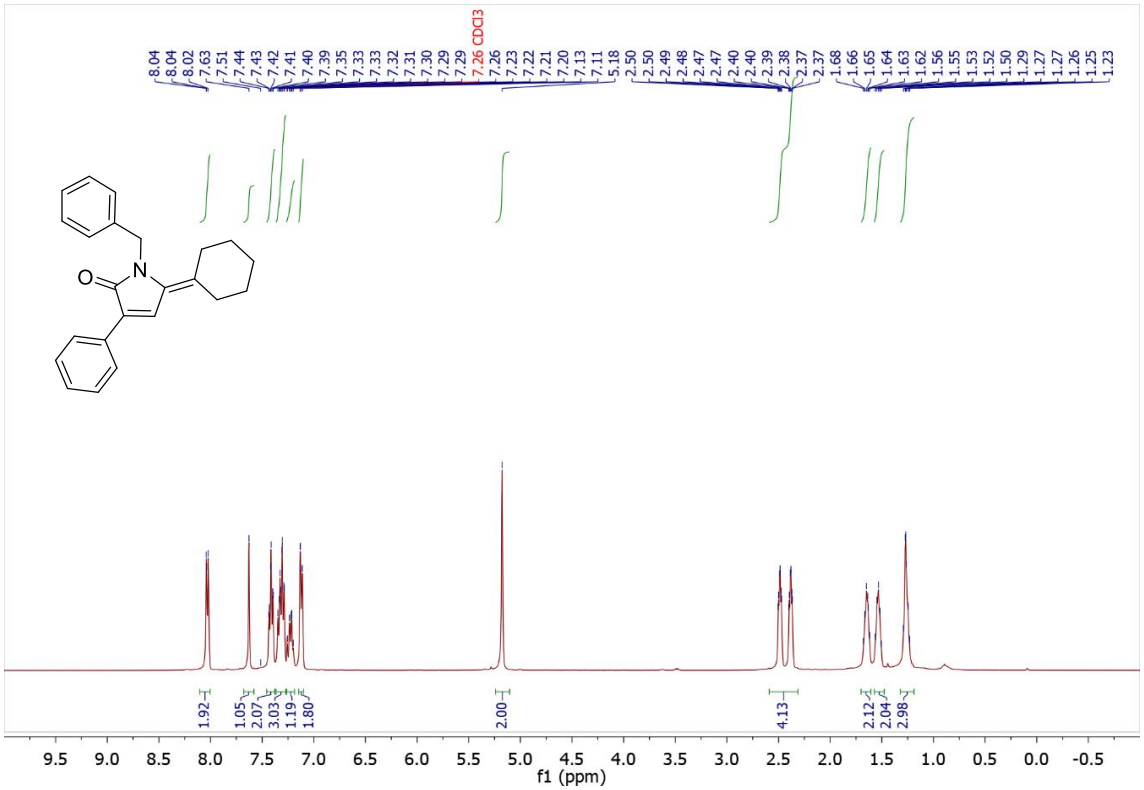


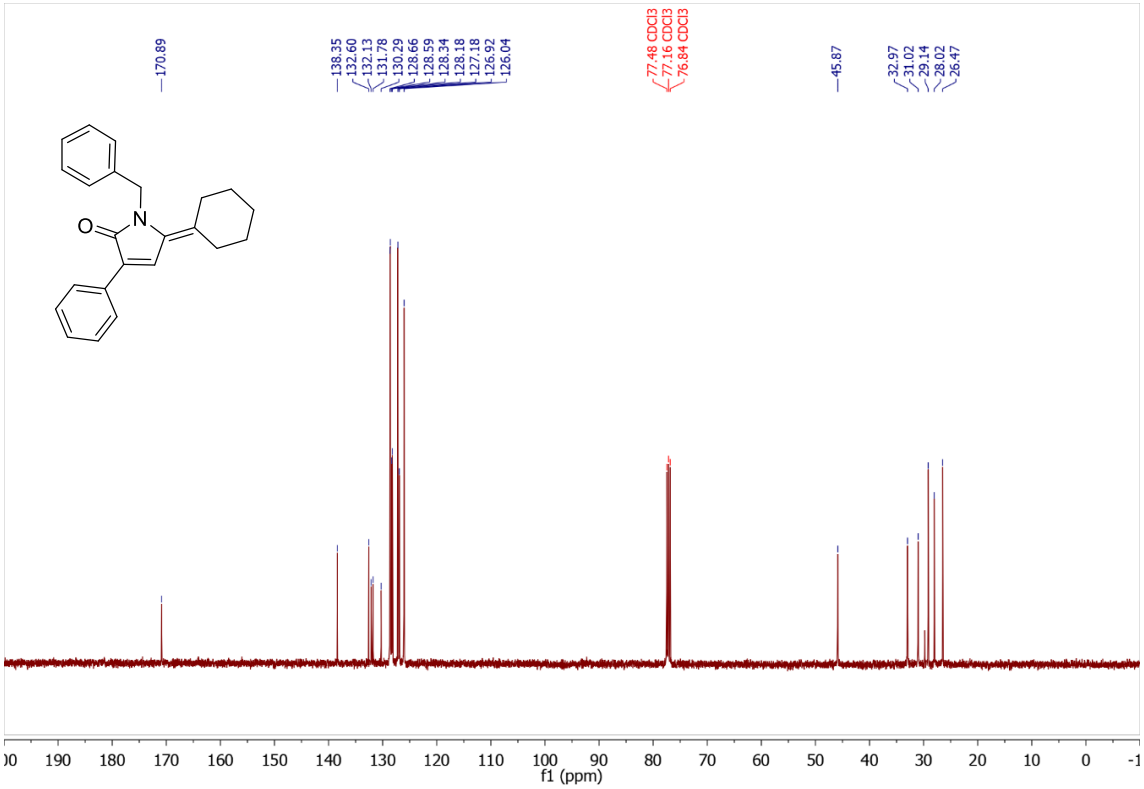
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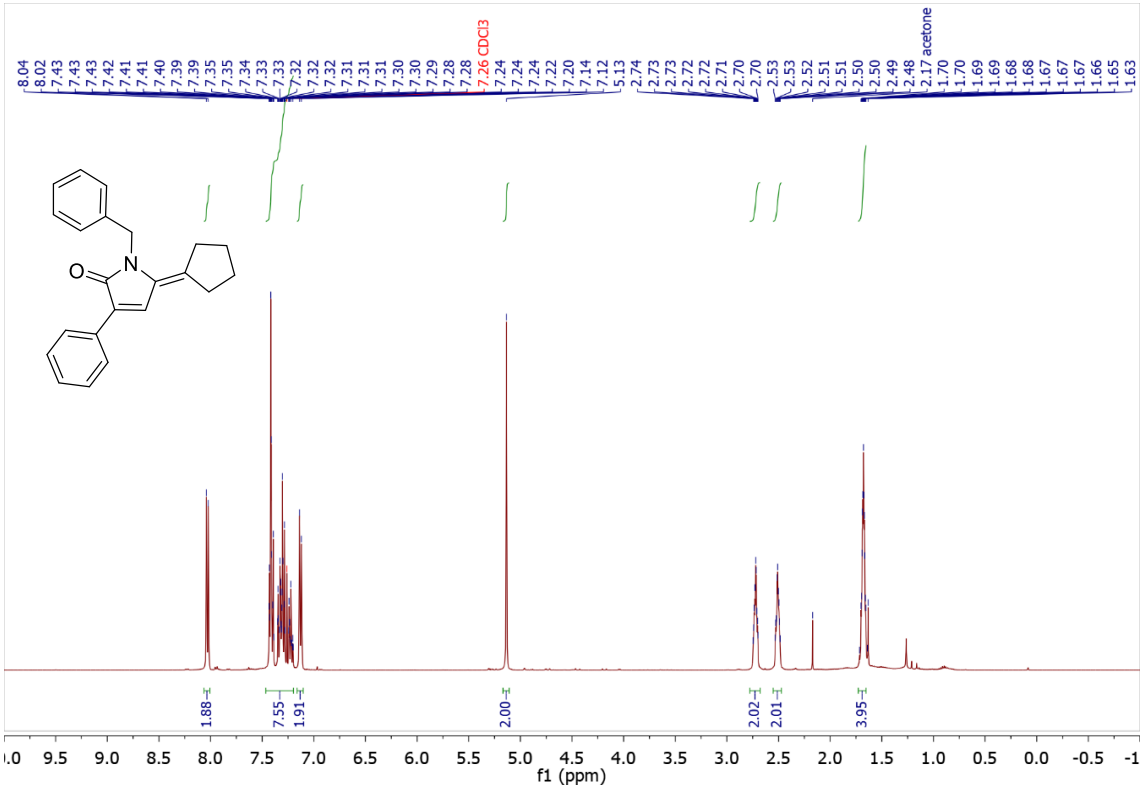


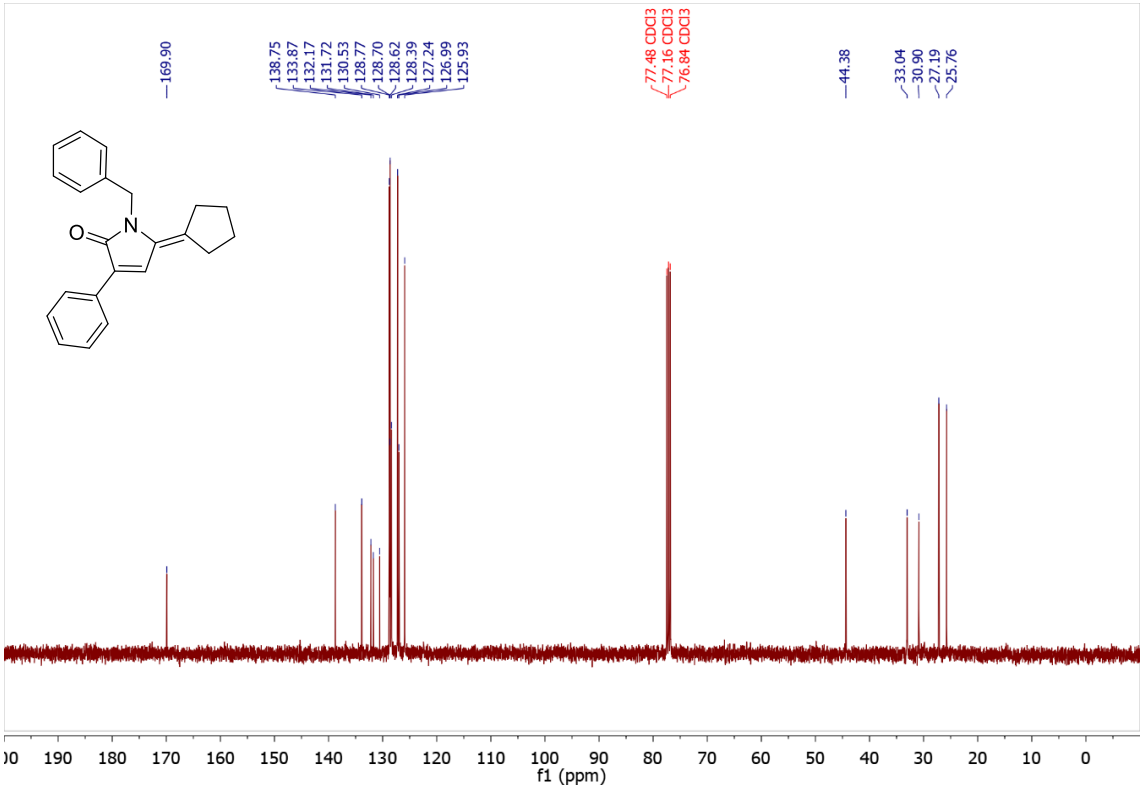
1-Benzyl-5-cyclohexylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 7c



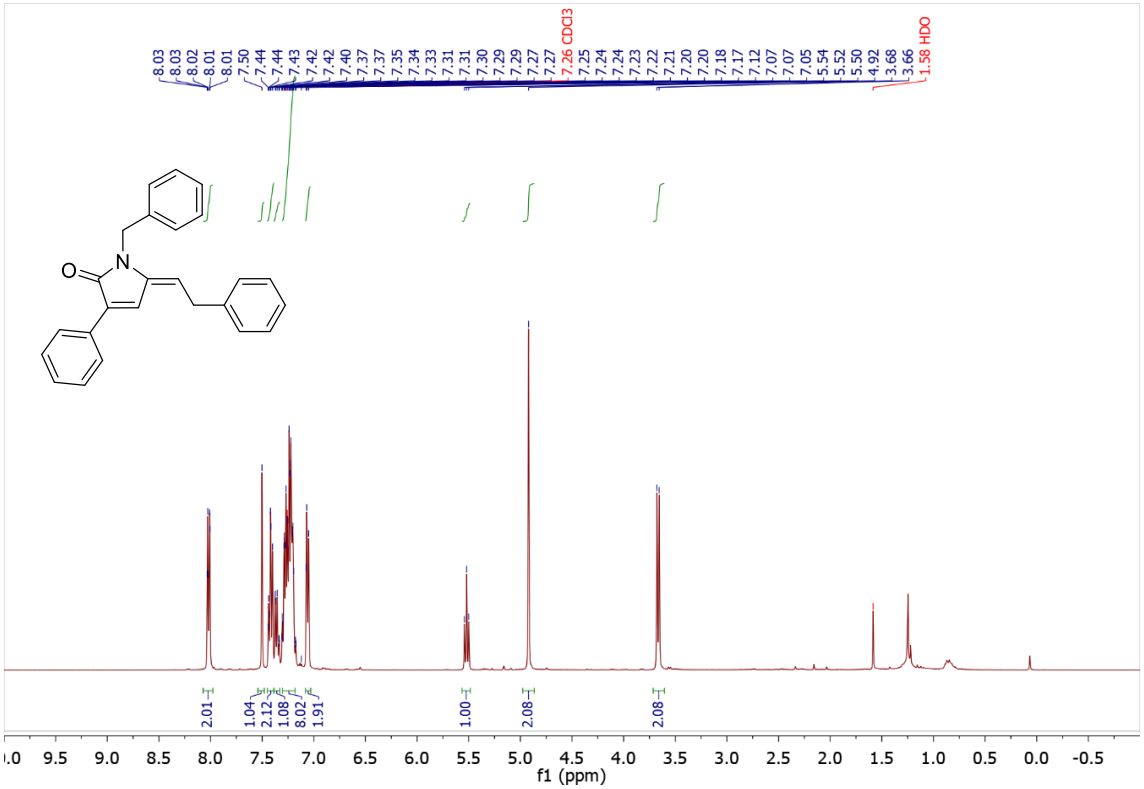


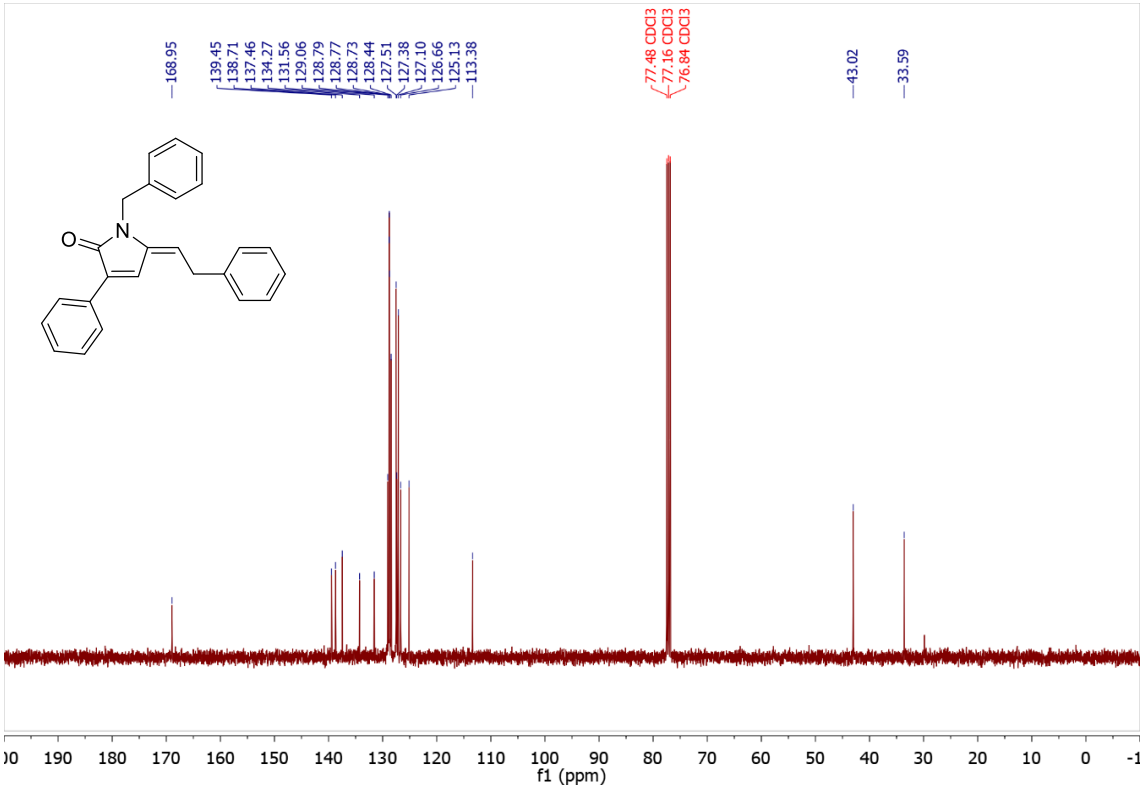
1-Benzyl-5-cyclopentylidene-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 7d



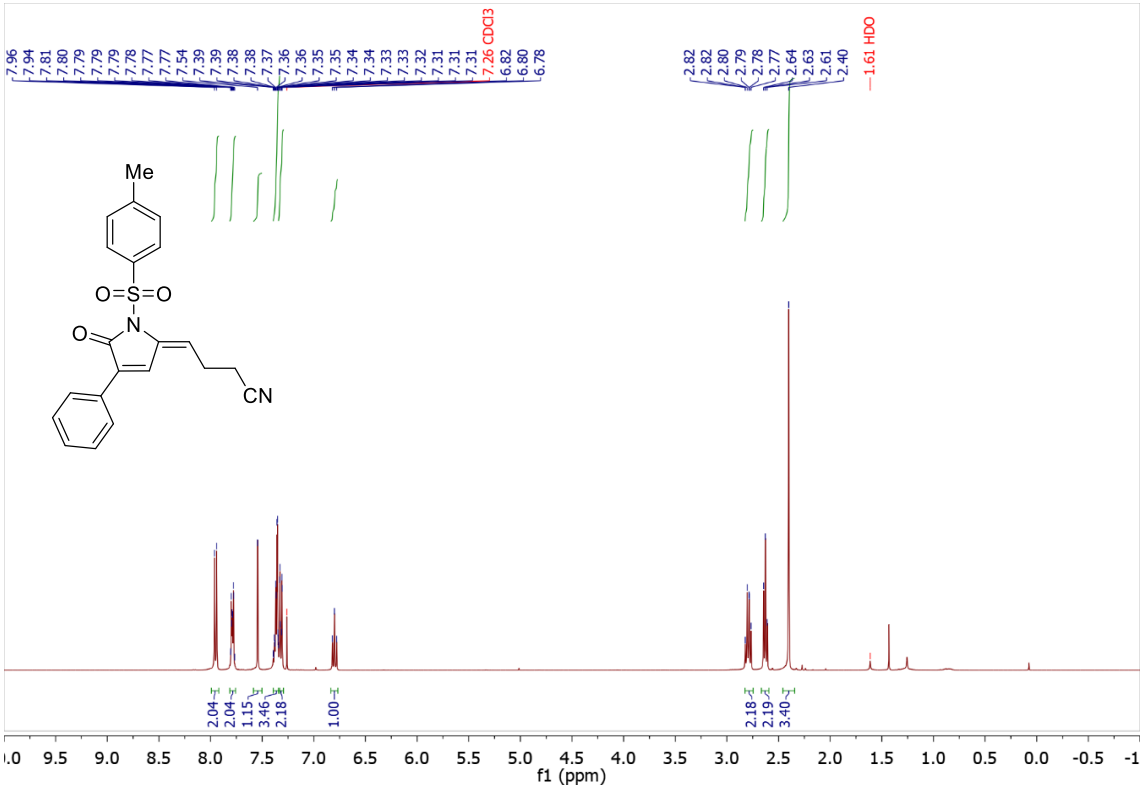


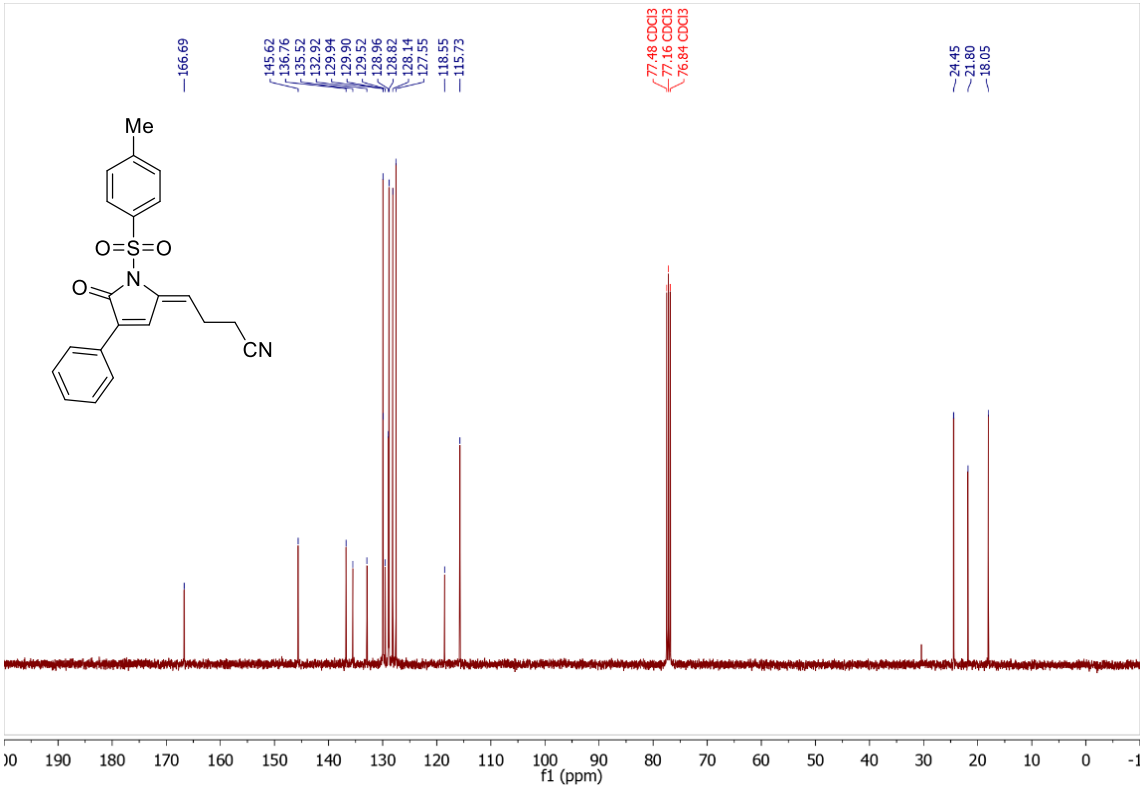
(*E*)-1-Benzyl-3-phenyl-5-(2-phenylethylidene)-1,5-dihydro-2*H*-pyrrol-2-one, 7e



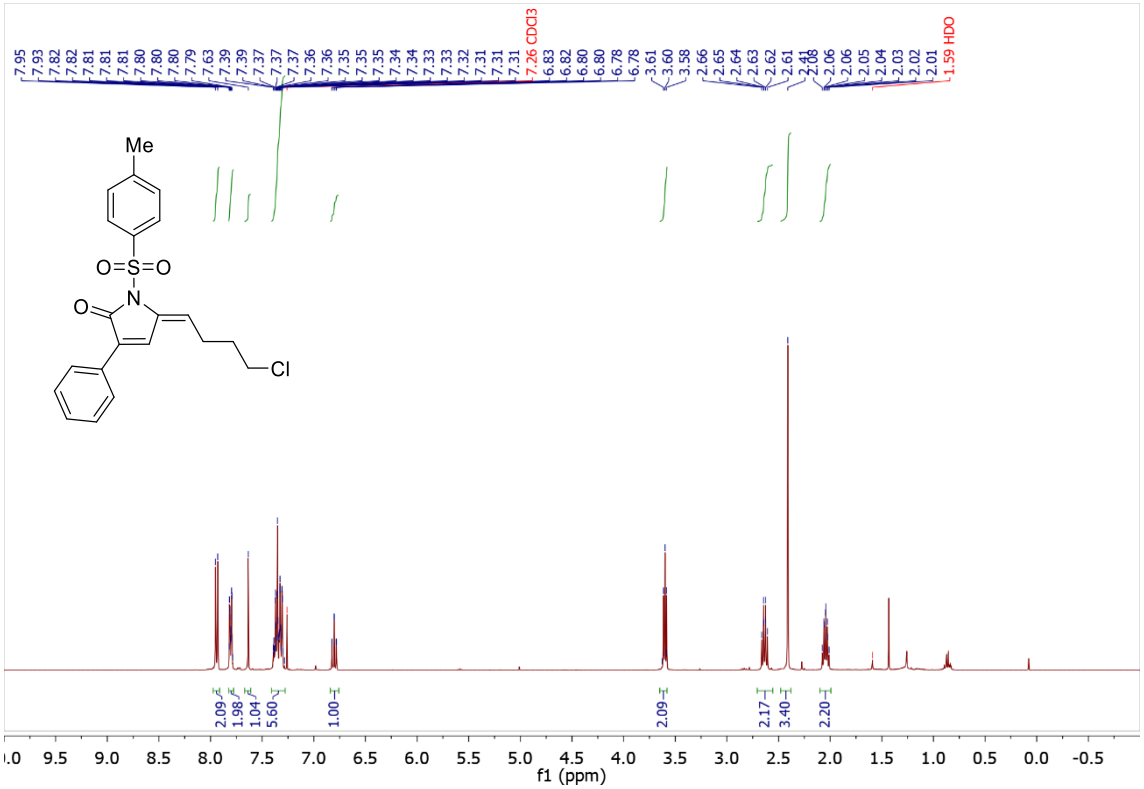


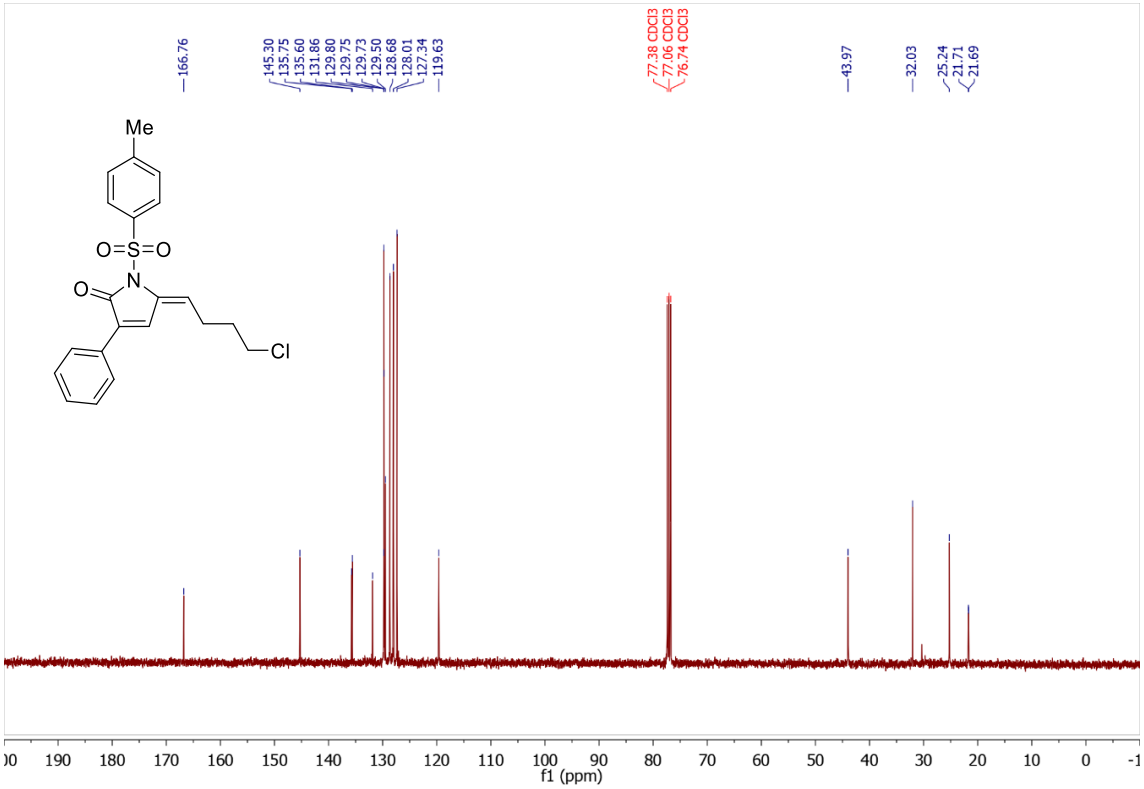
(*E*)-4-(5-Oxo-4-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-ylidene)butanenitrile, 7f



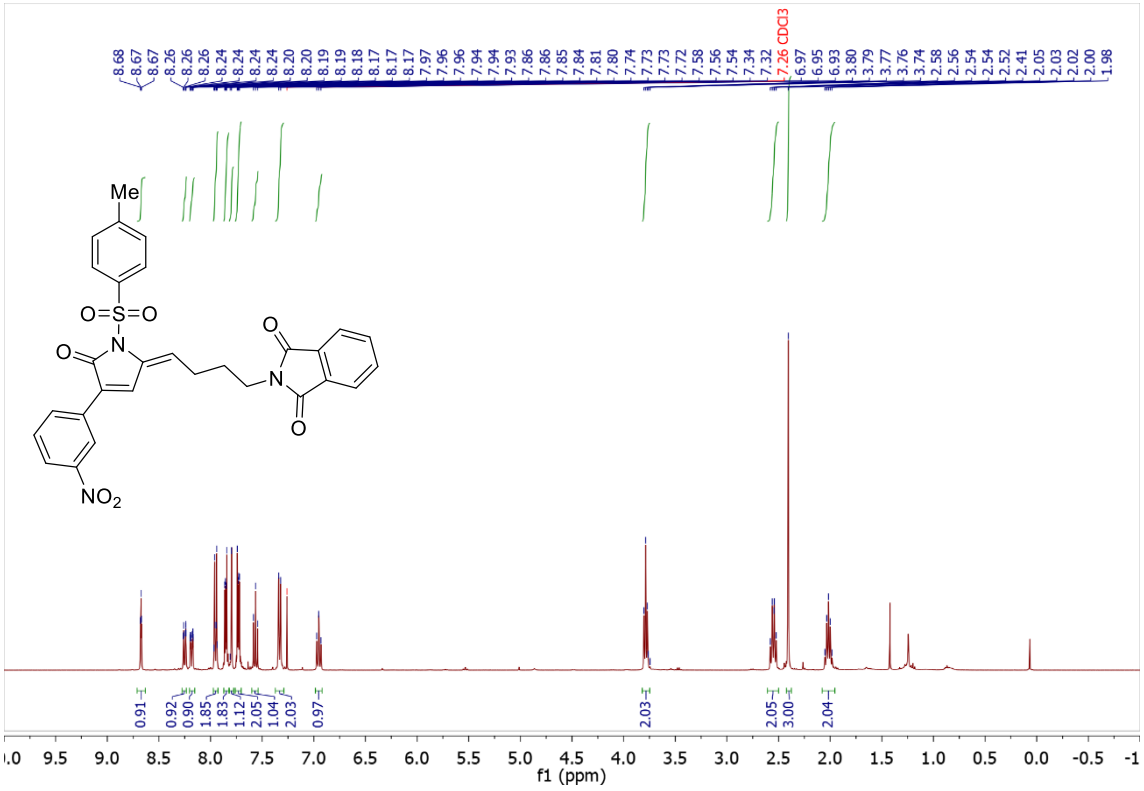


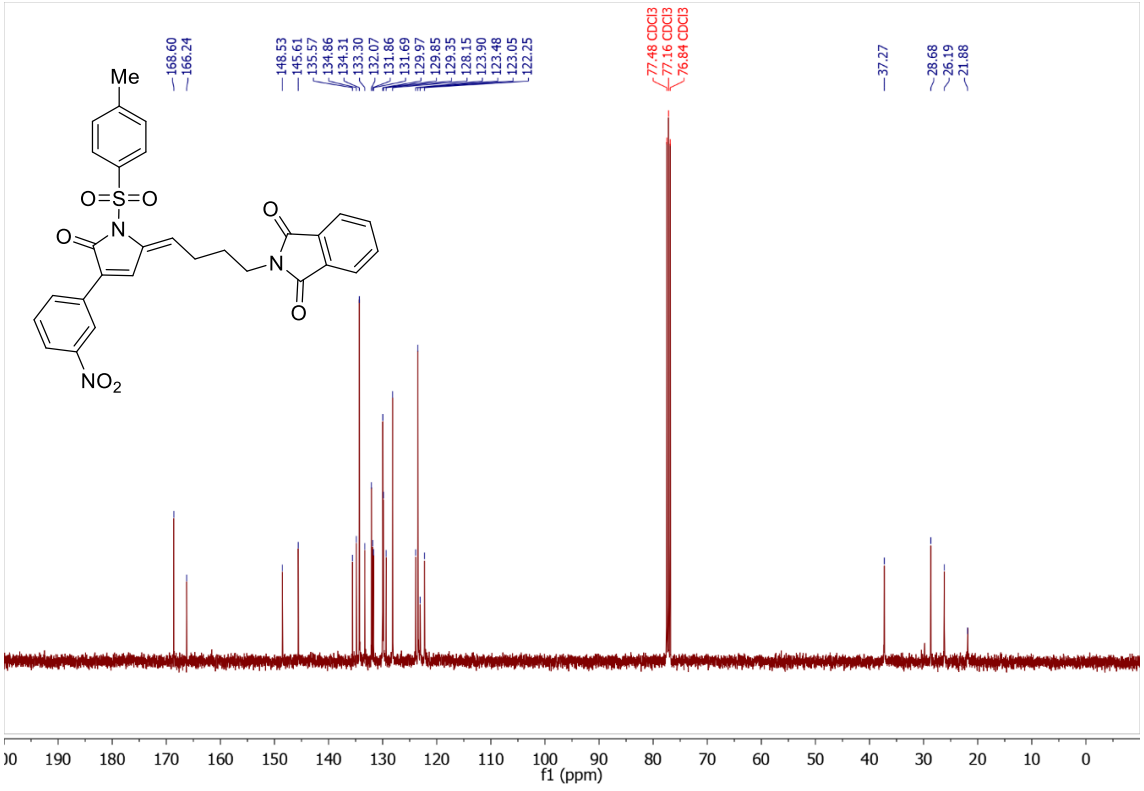
(*E*)-5-(4-Chlorobutylidene)-3-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one, 7g



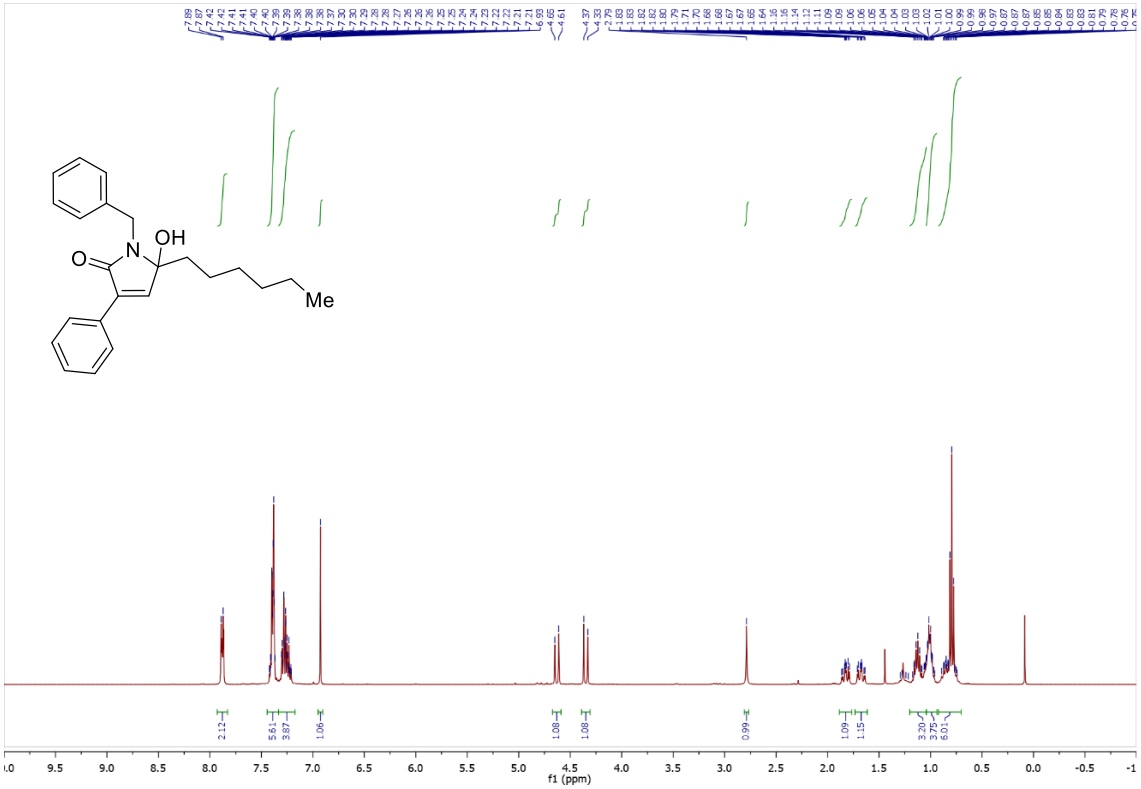


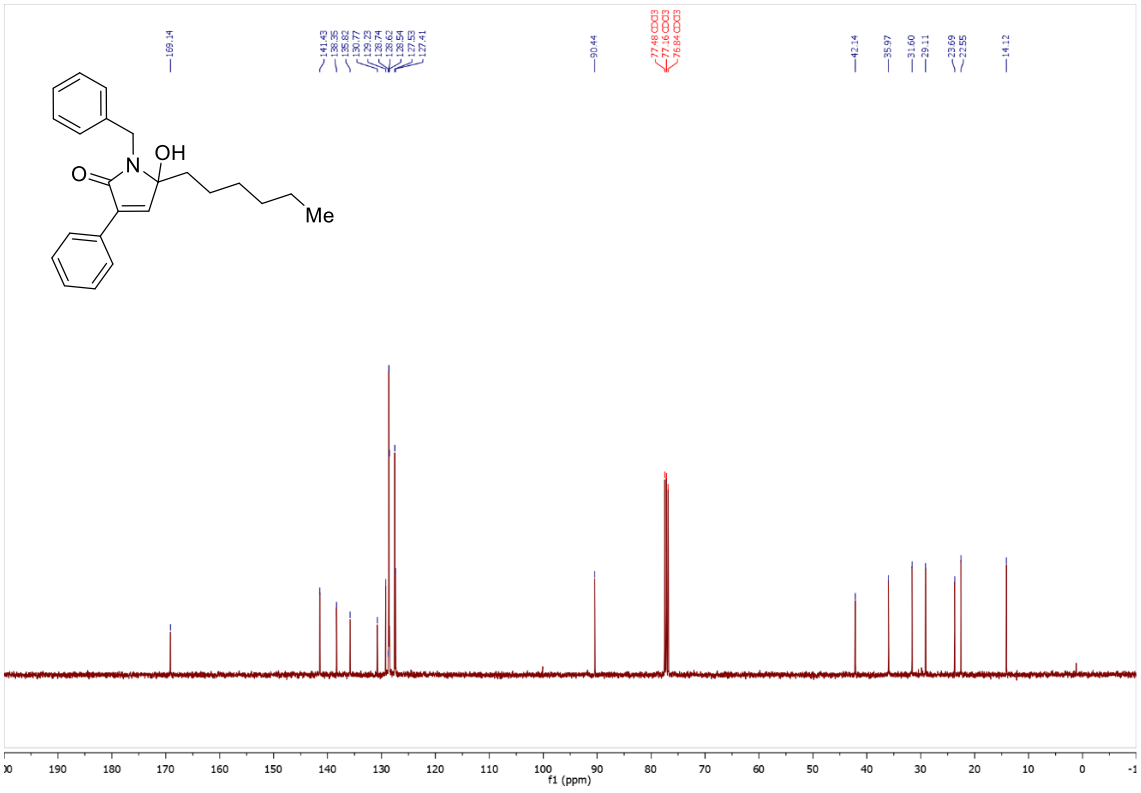
(*E*)-2-(4-(4-(3-Nitrophenyl)-5-oxo-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-ylidene)butyl)isoindoline-1,3-dione, 7i



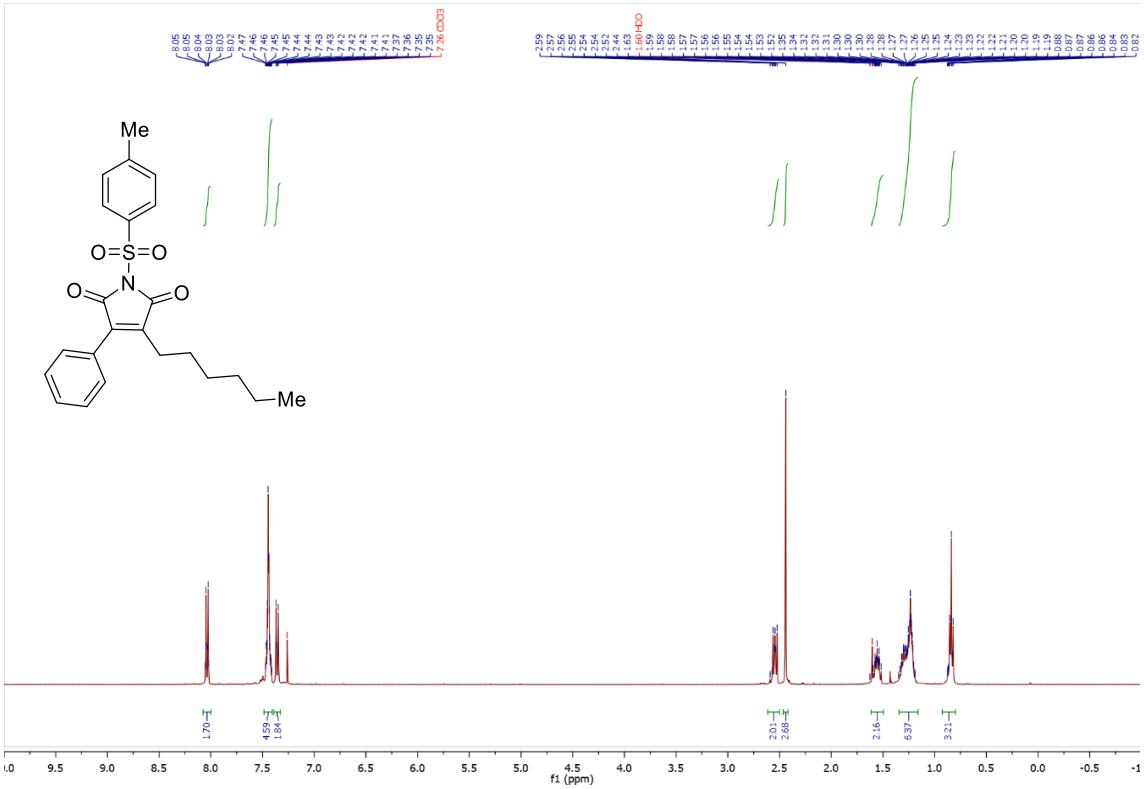


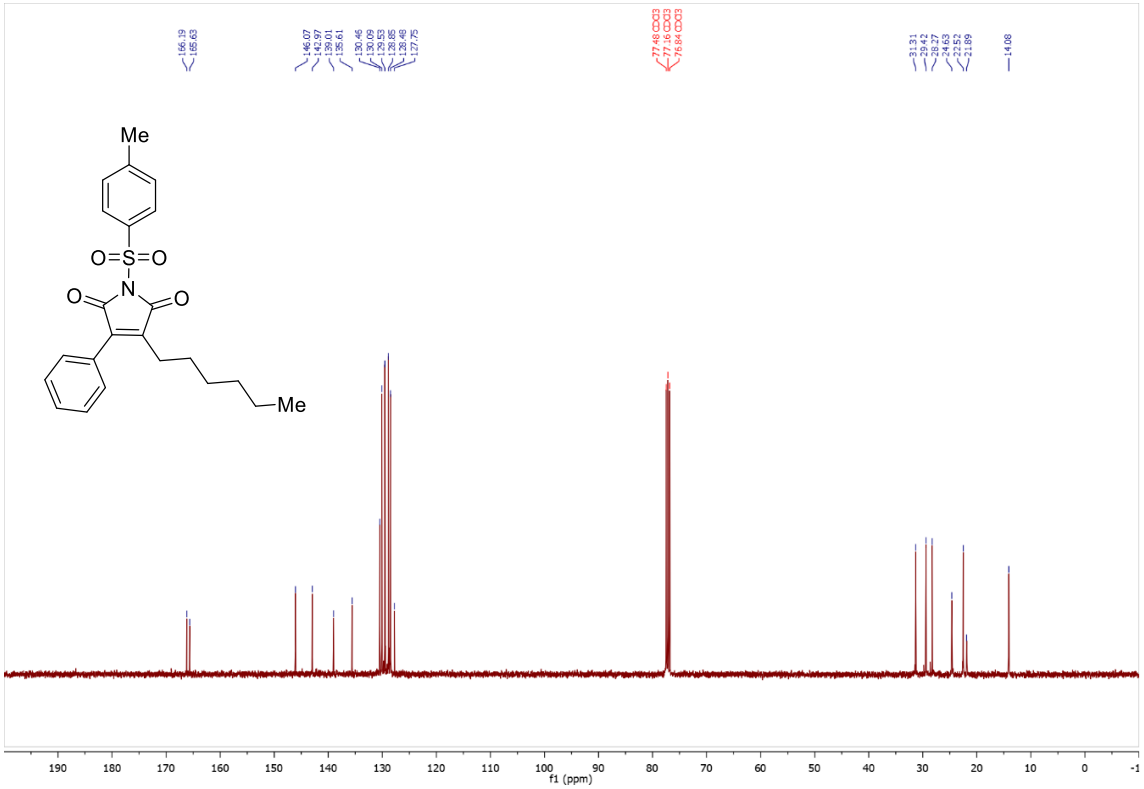
1-Benzyl-5-hexyl-5-hydroxy-3-phenyl-1,5-dihydro-2*H*-pyrrol-2-one, 8



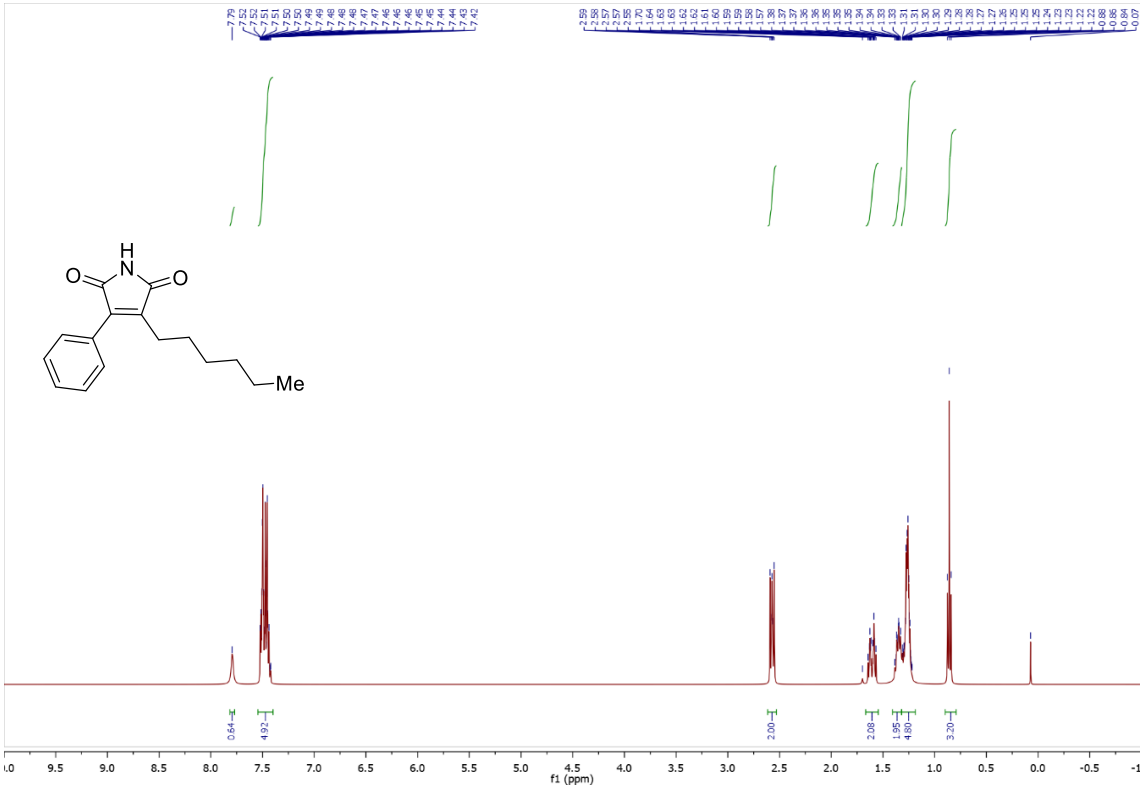


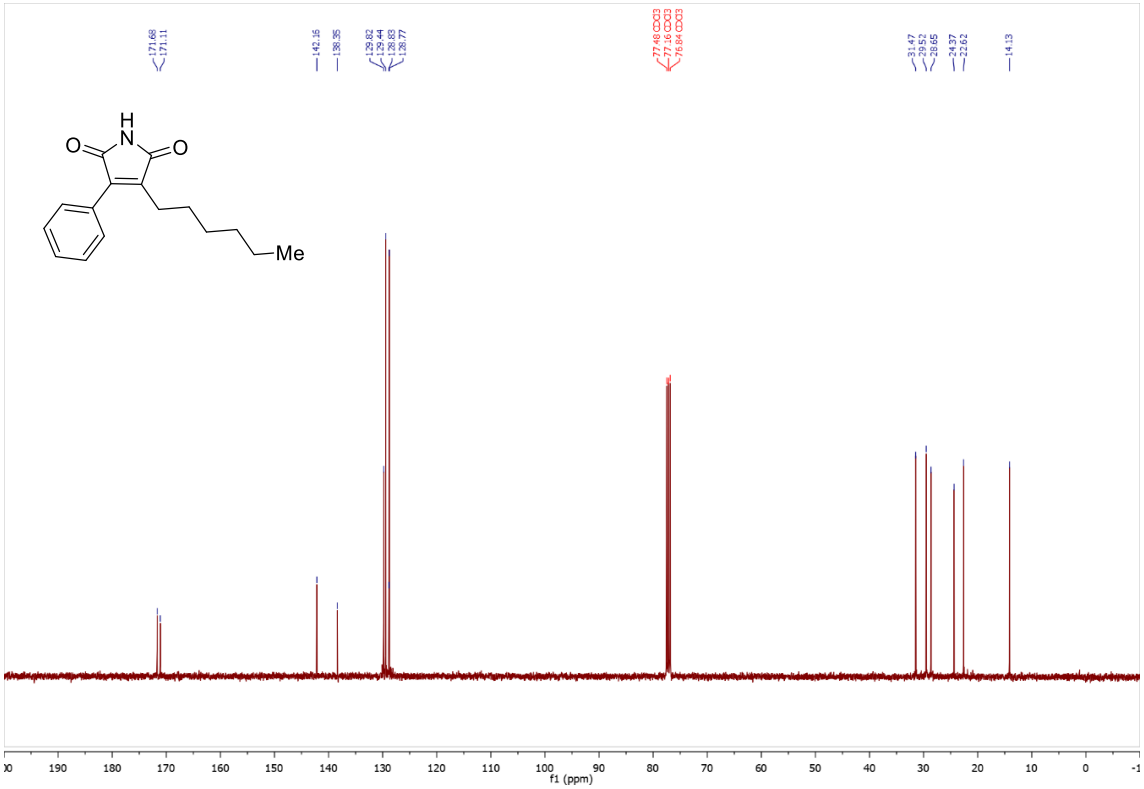
3-Hexyl-4-phenyl-1-tosyl-1*H*-pyrrole-2,5-dione, 11



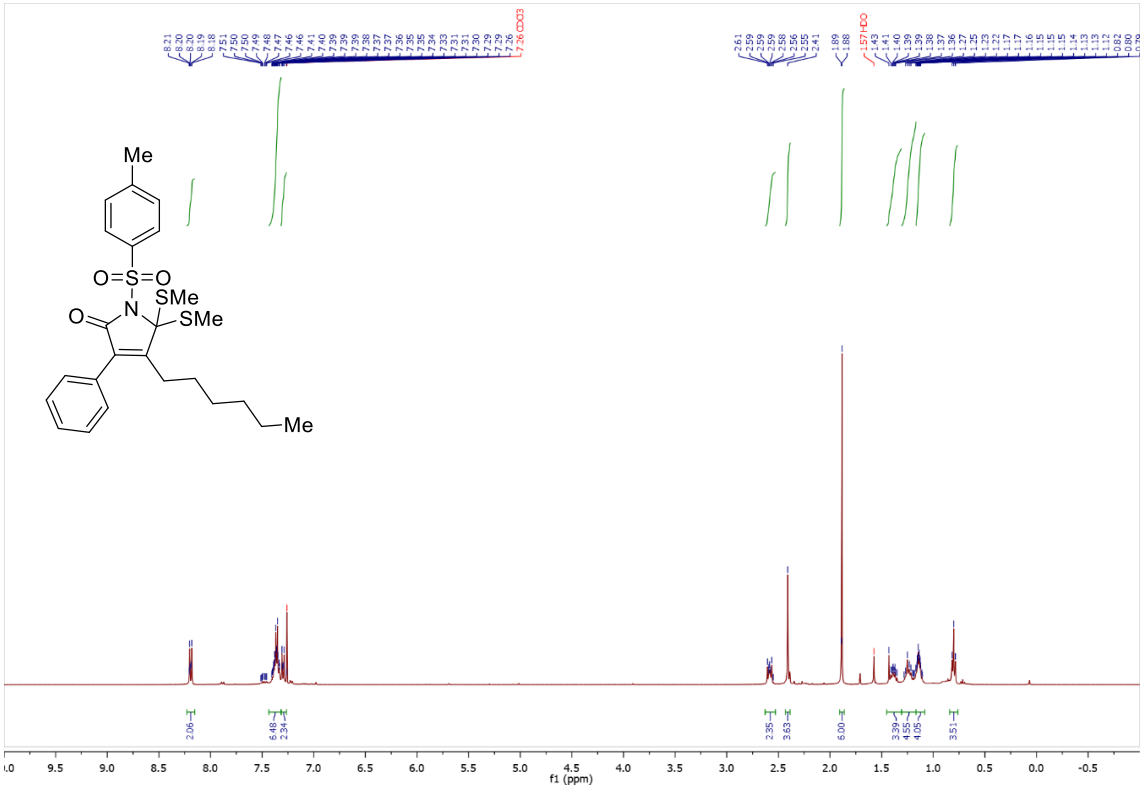


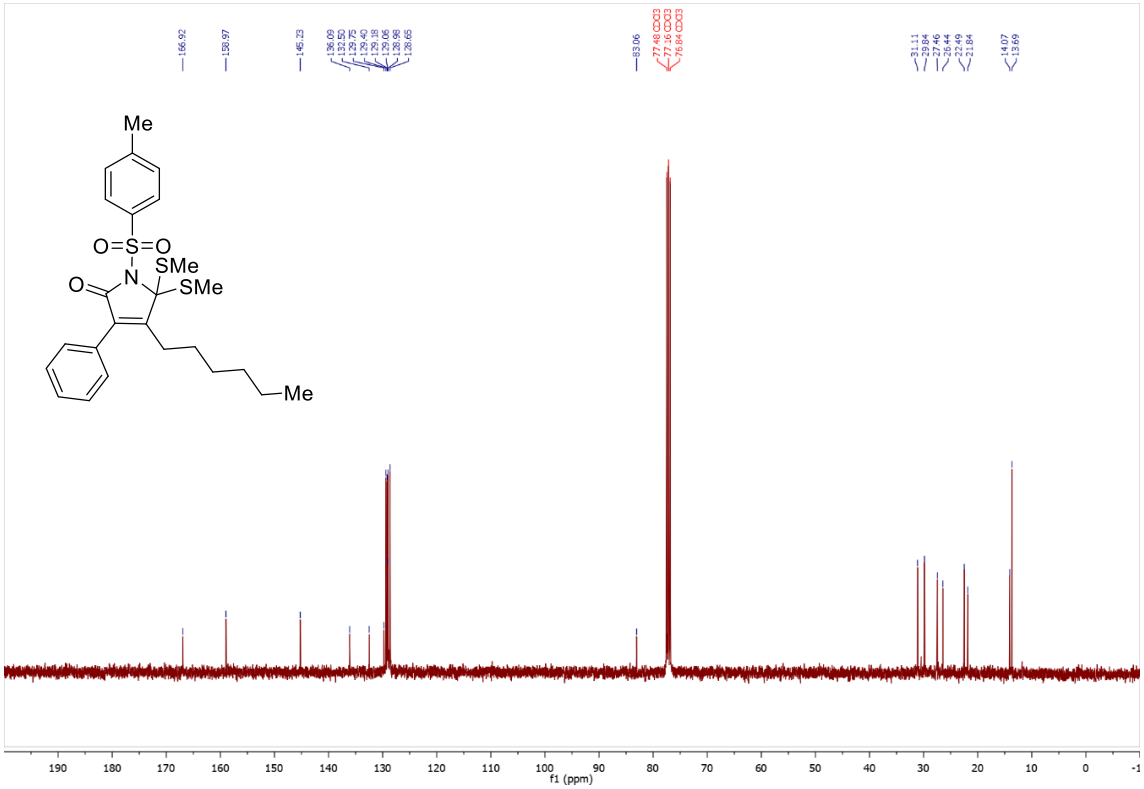
3-Hexyl-4-phenyl-1*H*-pyrrole-2,5-dione, 12



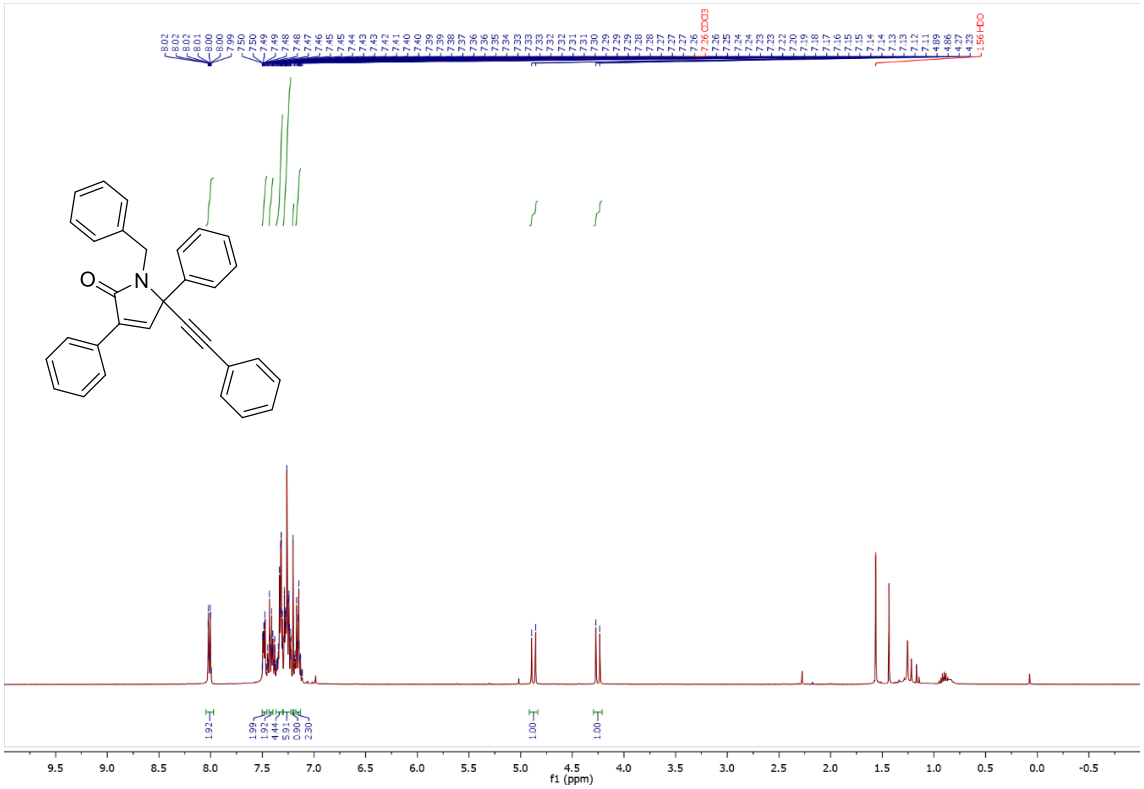


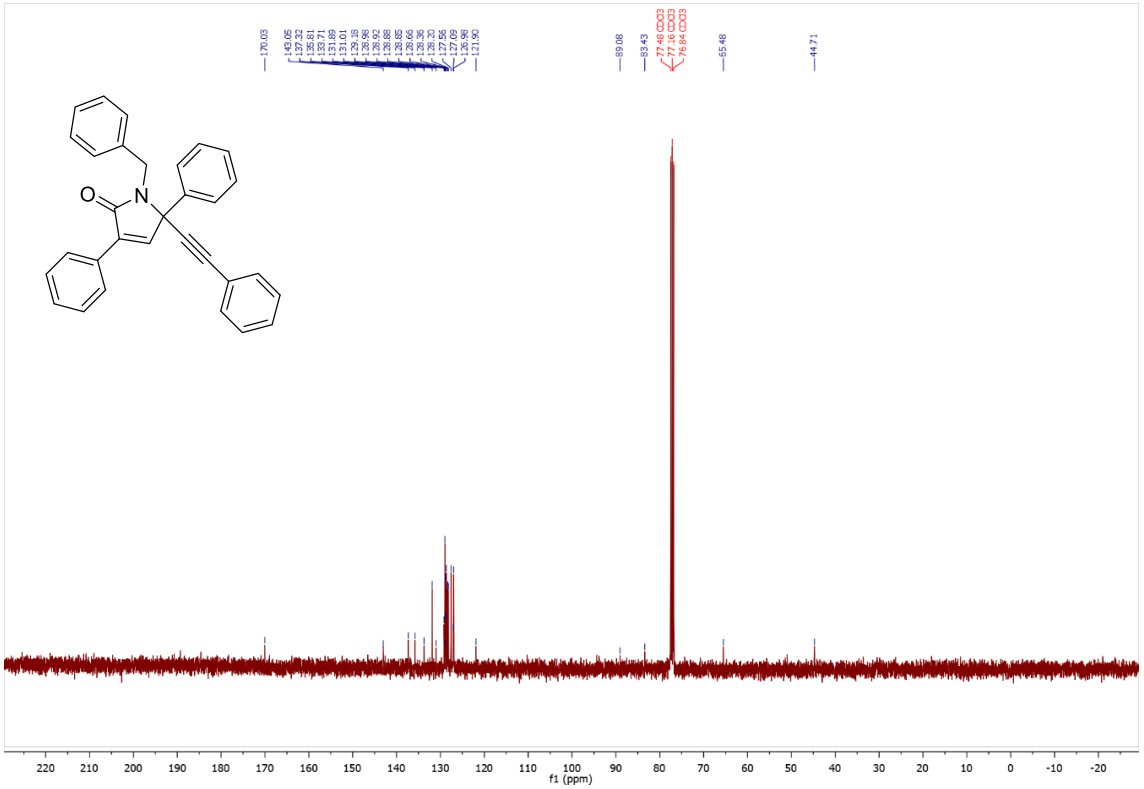
4-Hexyl-5,5-bis(methylthio)-3-phenyl-1-tosyl-1,5-dihydro-2*H*-pyrrol-2-one, 13



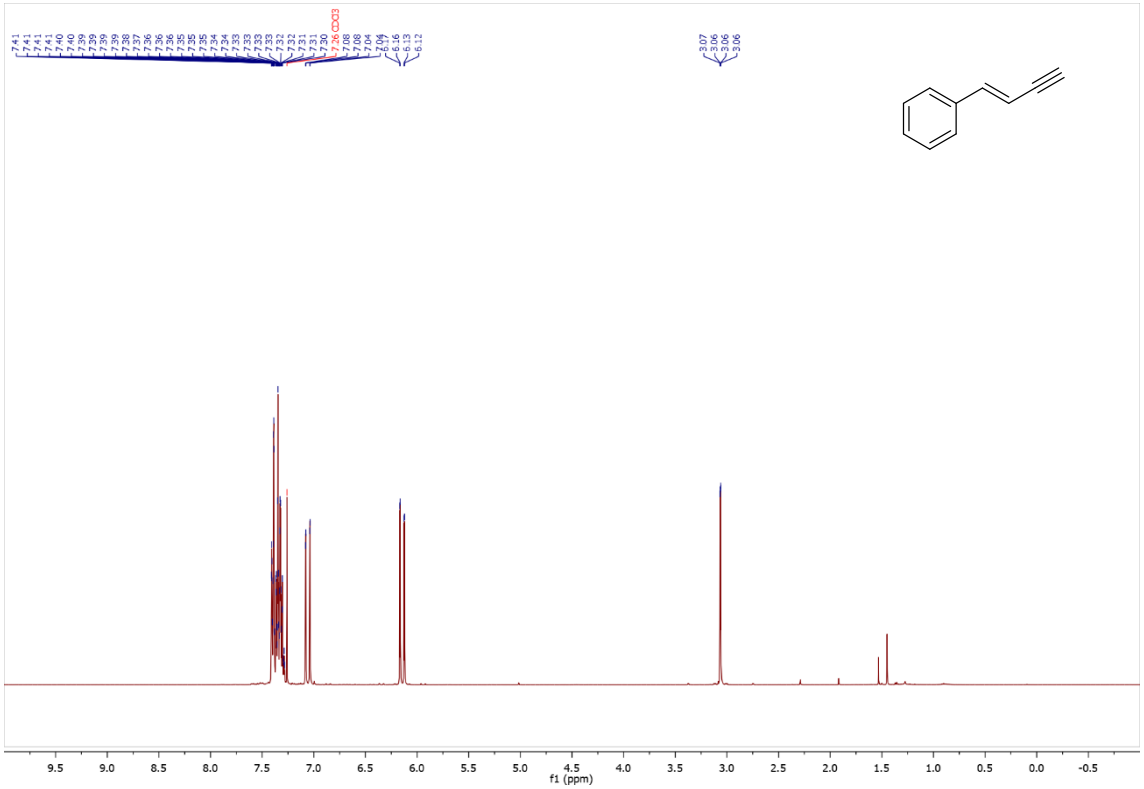


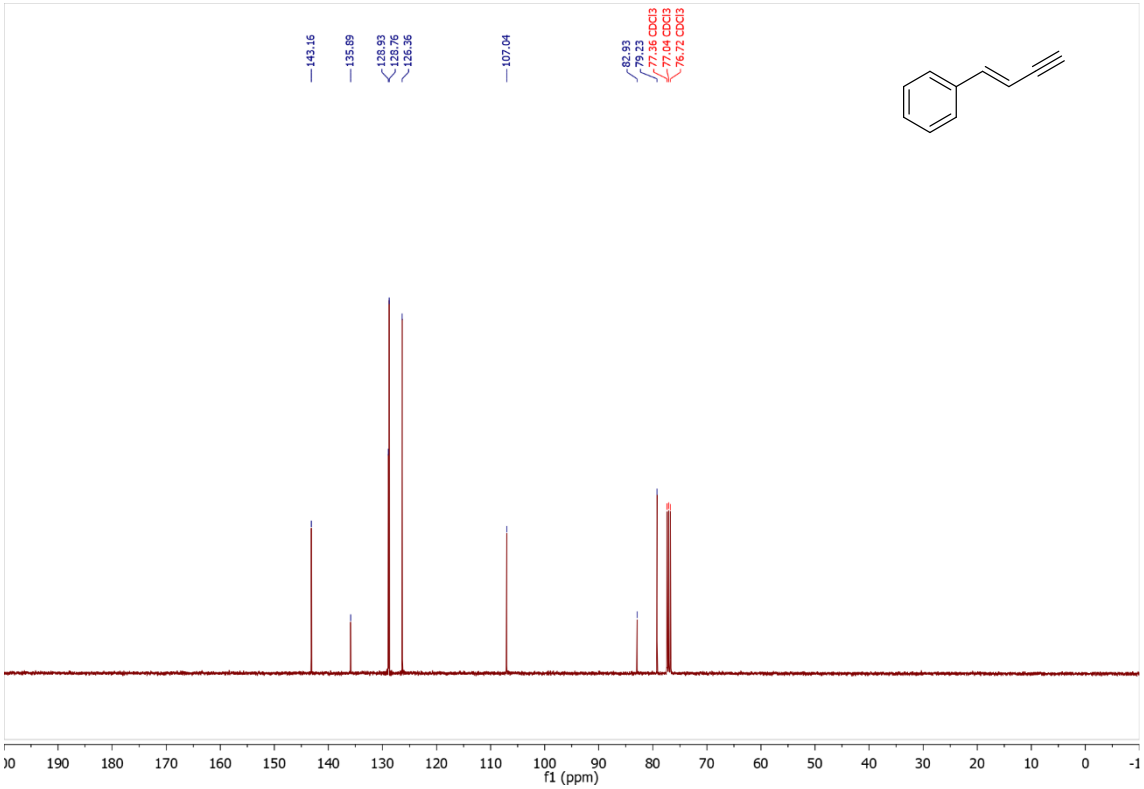
1-Benzyl-3,5-diphenyl-5-(phenylethynyl)-1,5-dihydro-2*H*-pyrrol-2-one, 14



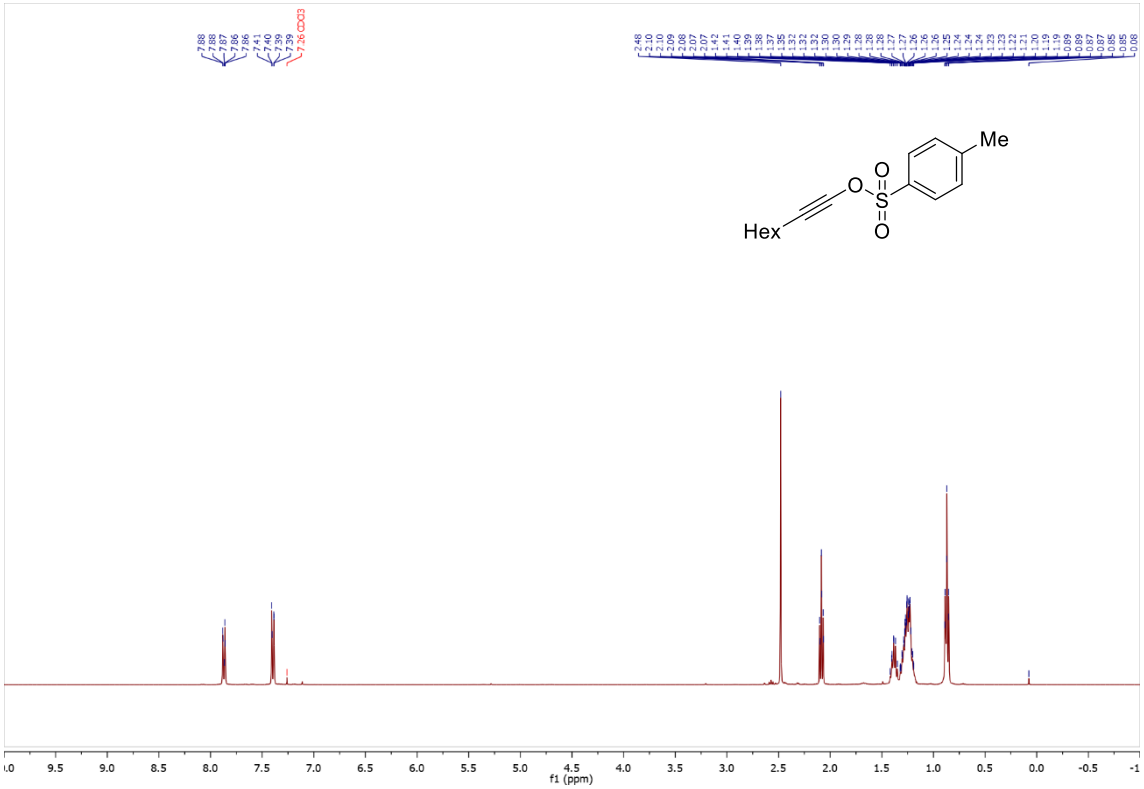


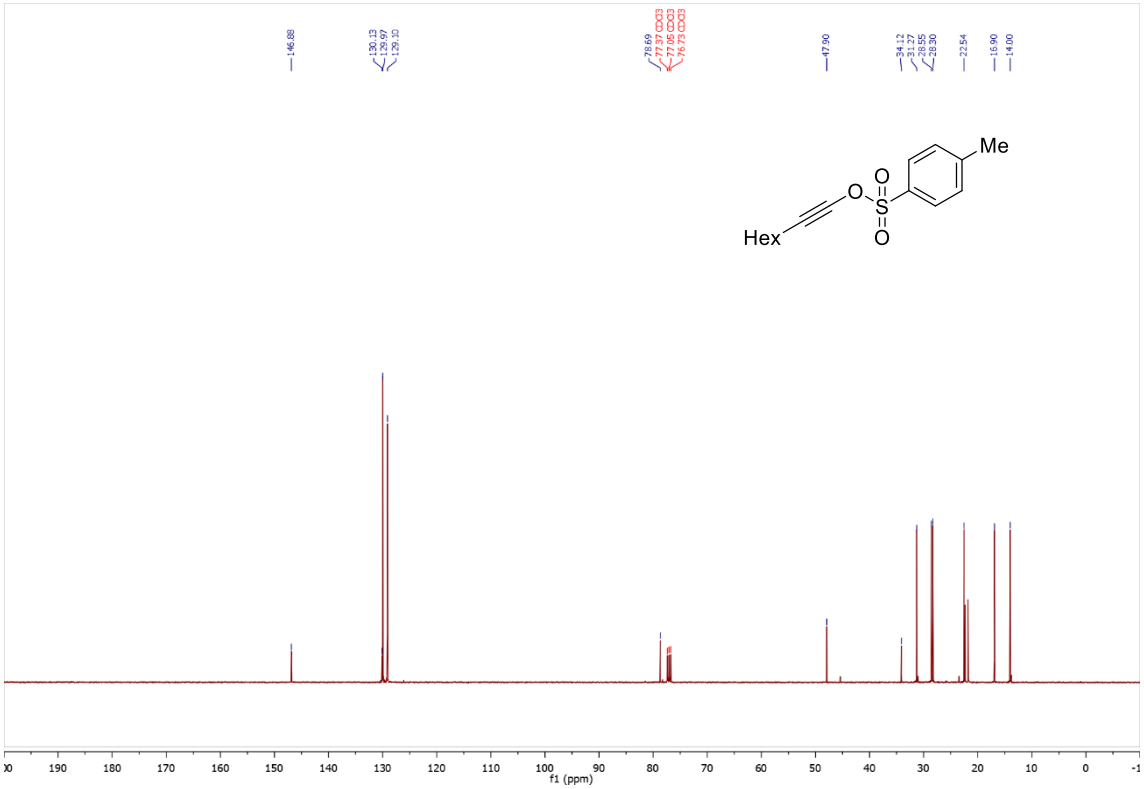
(*E*)-But-1-en-3-yn-1-ylbenzene, 2am



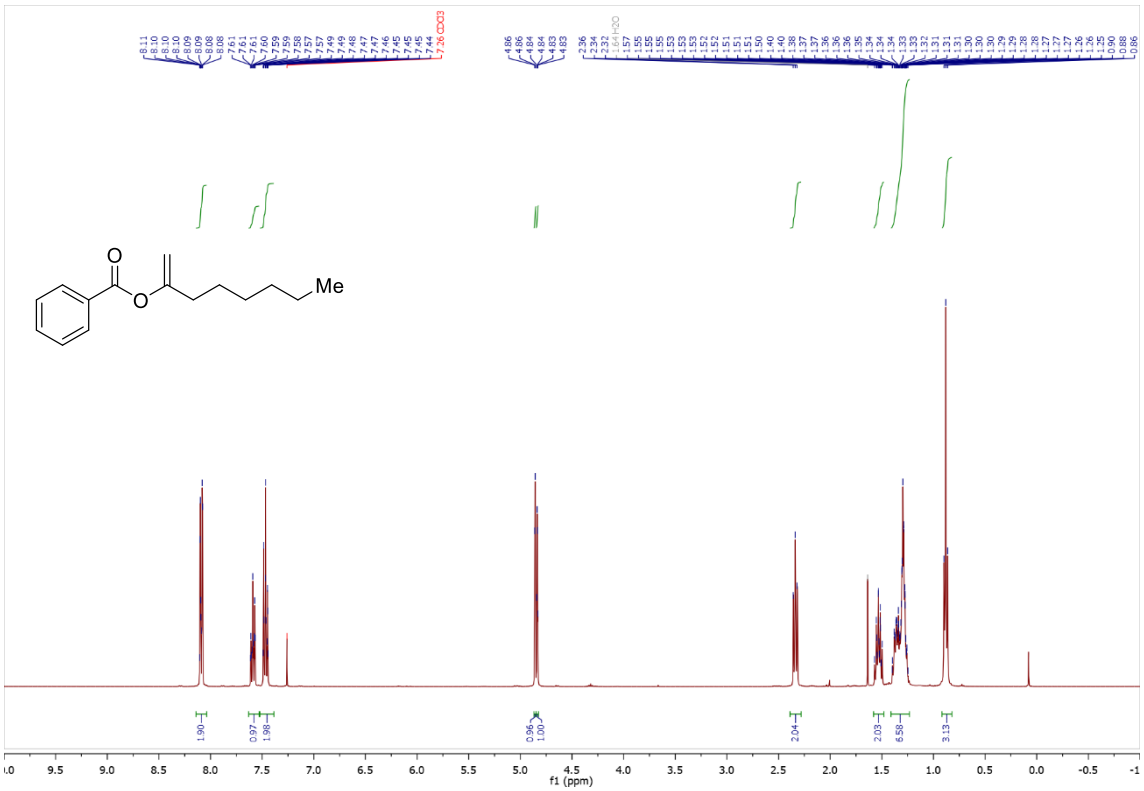


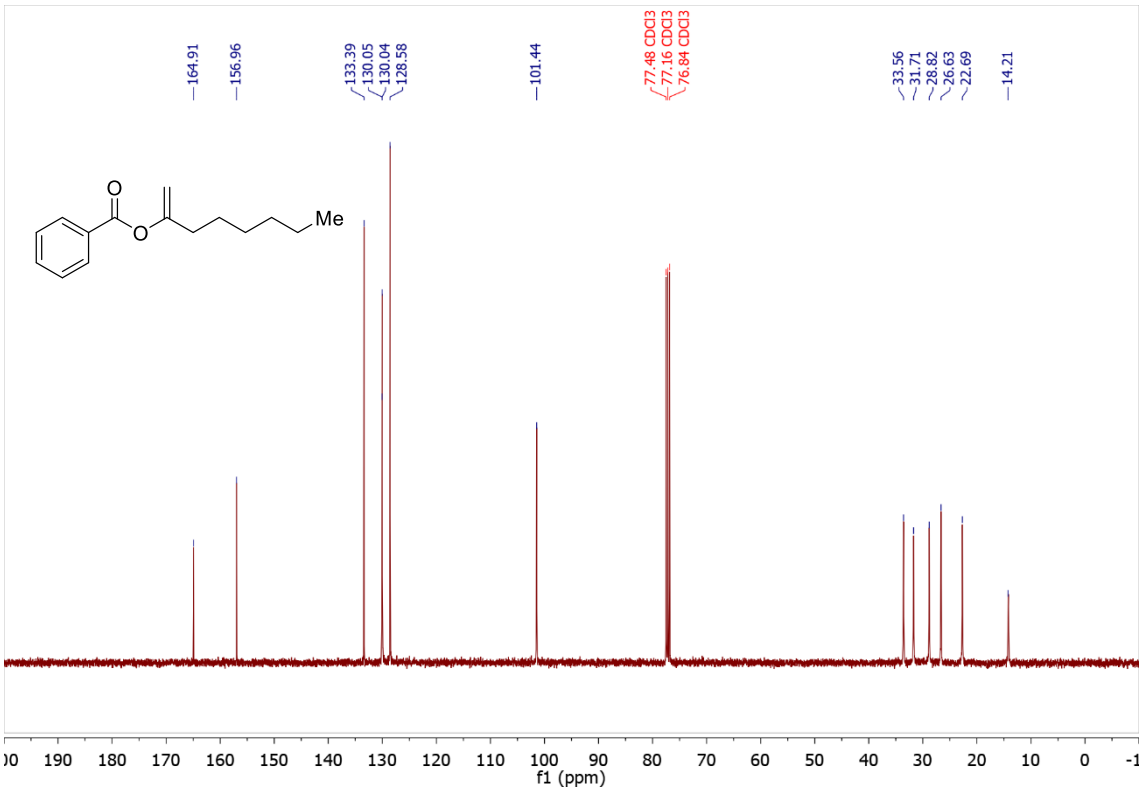
3-Oxo-oct-1-yn-1-yl 4-methylbenzenesulfonate, 23



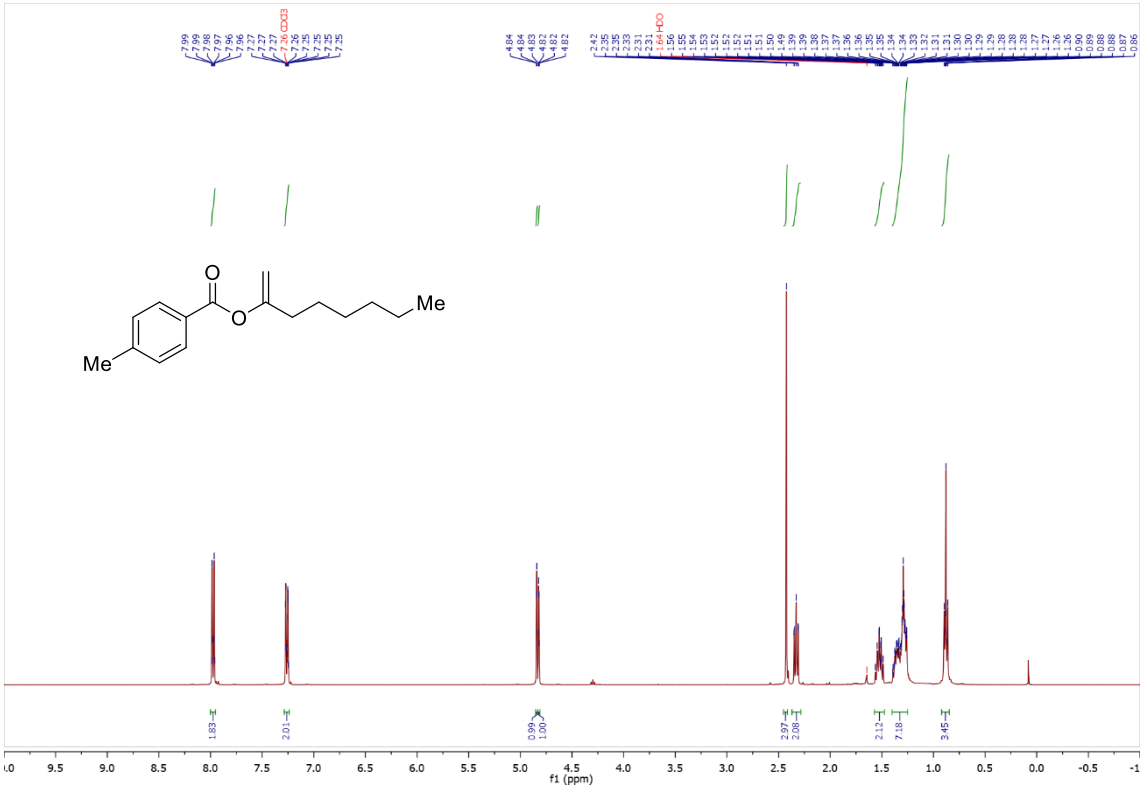


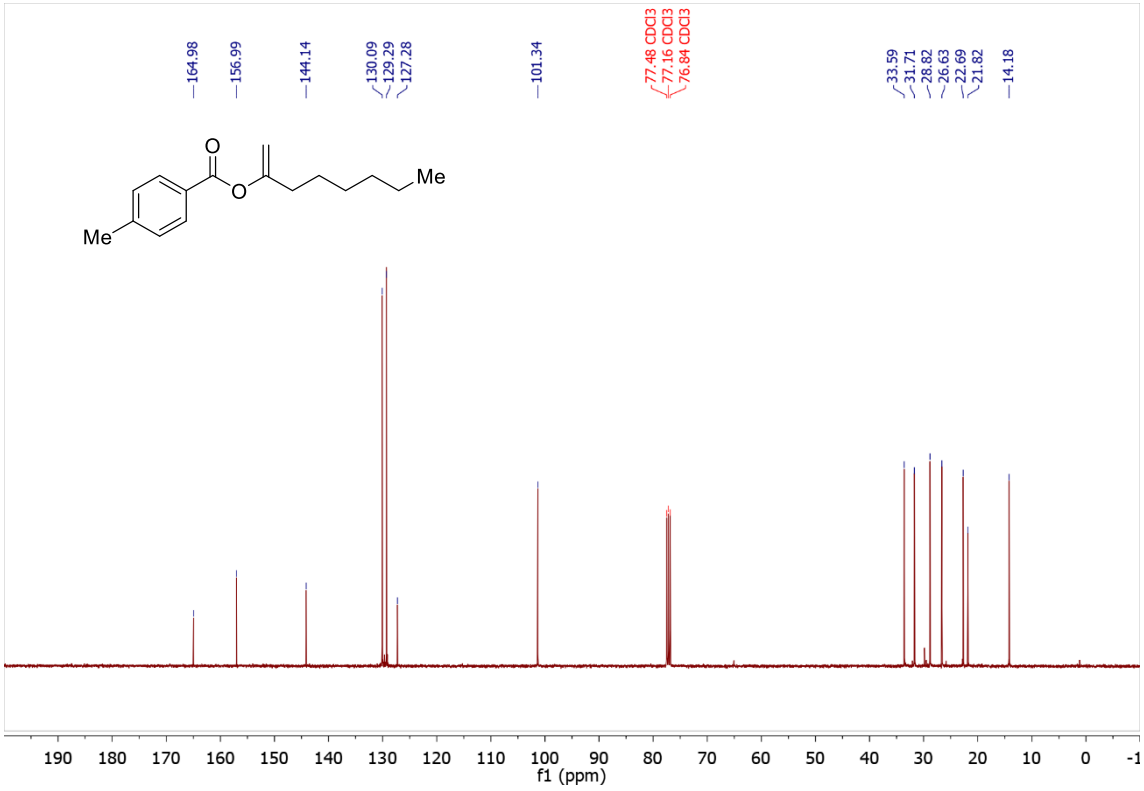
Oct-1-en-2-ylbenzoate, 16a



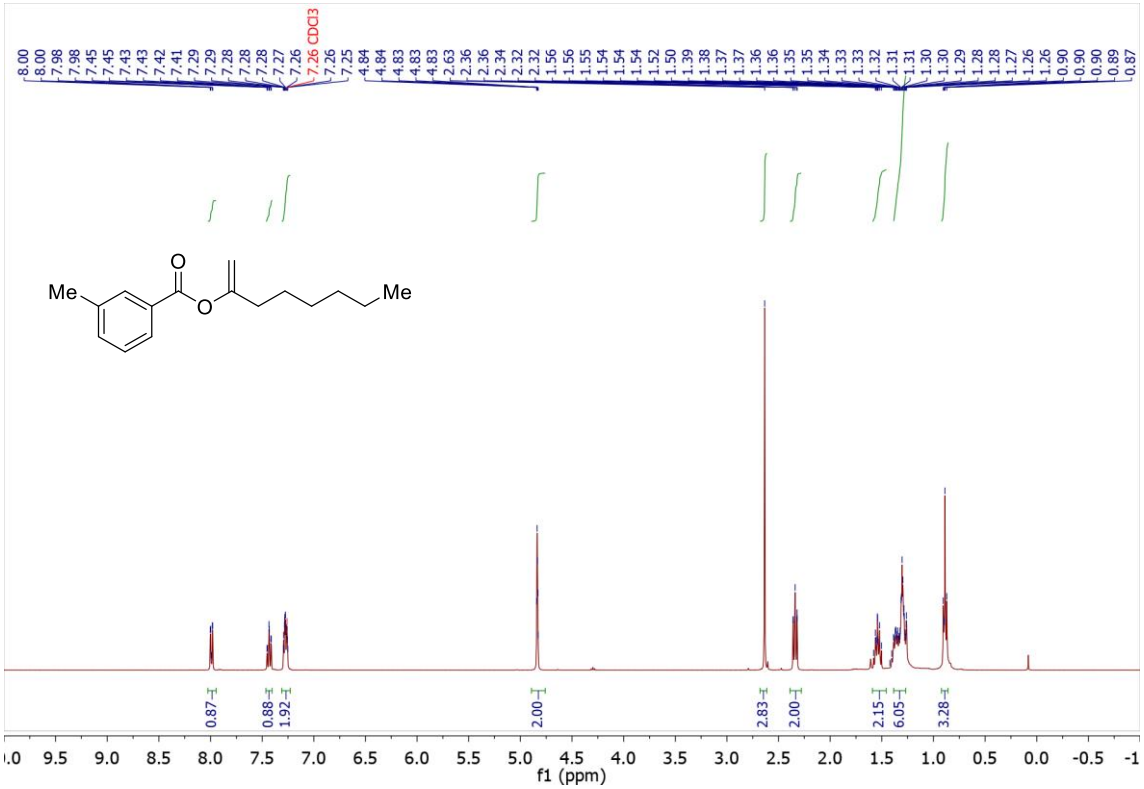


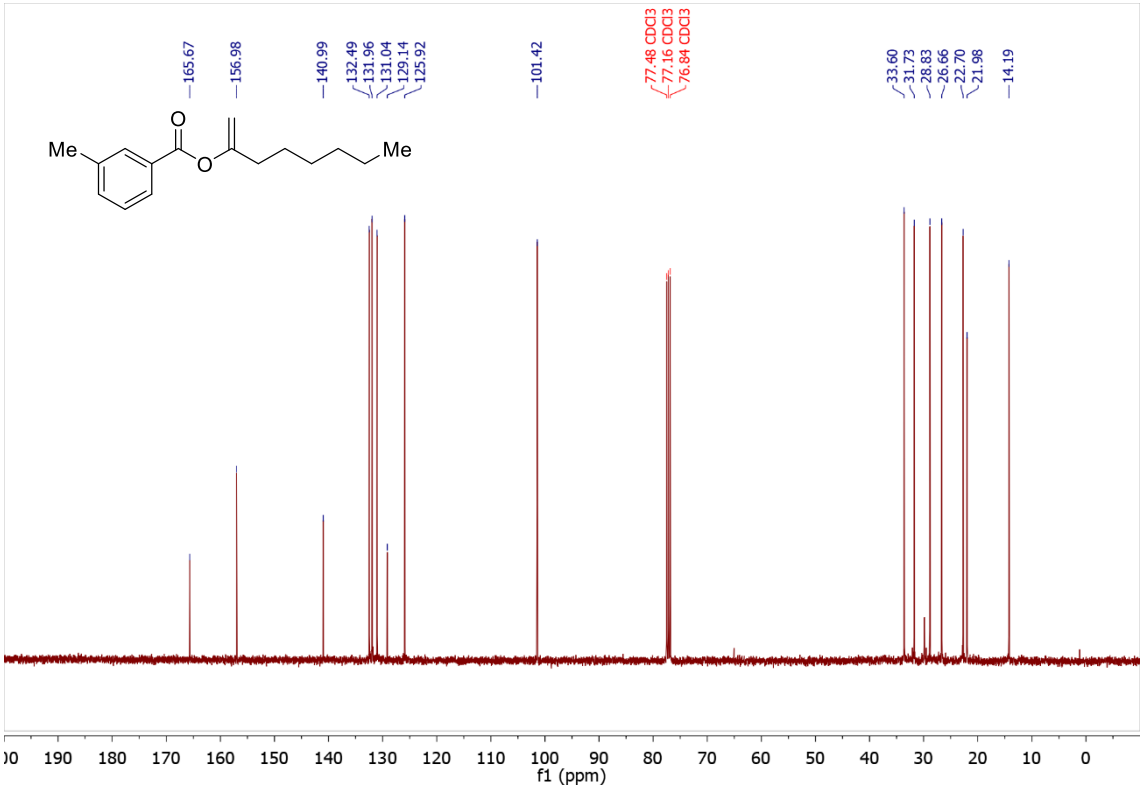
Oct-1-en-2-yl-4-methylbenzoate, 16b



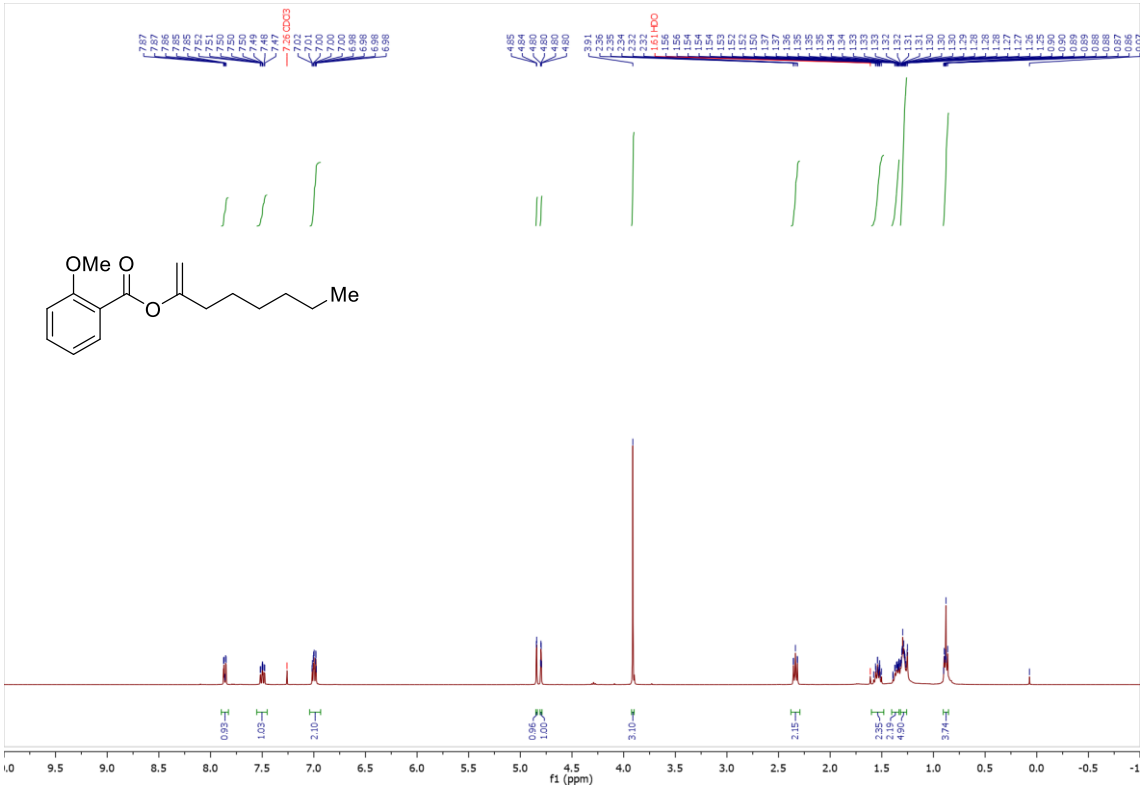


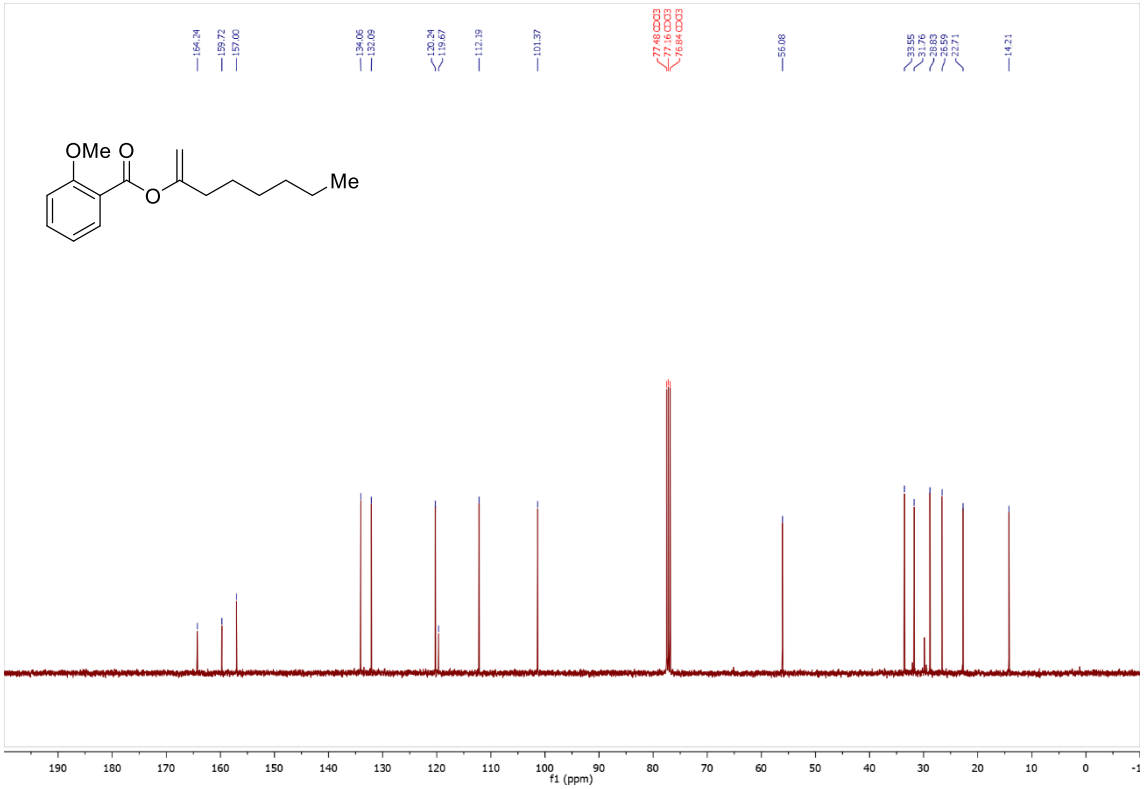
Oct-1-en-2-yl-3-methylbenzoate, 16c



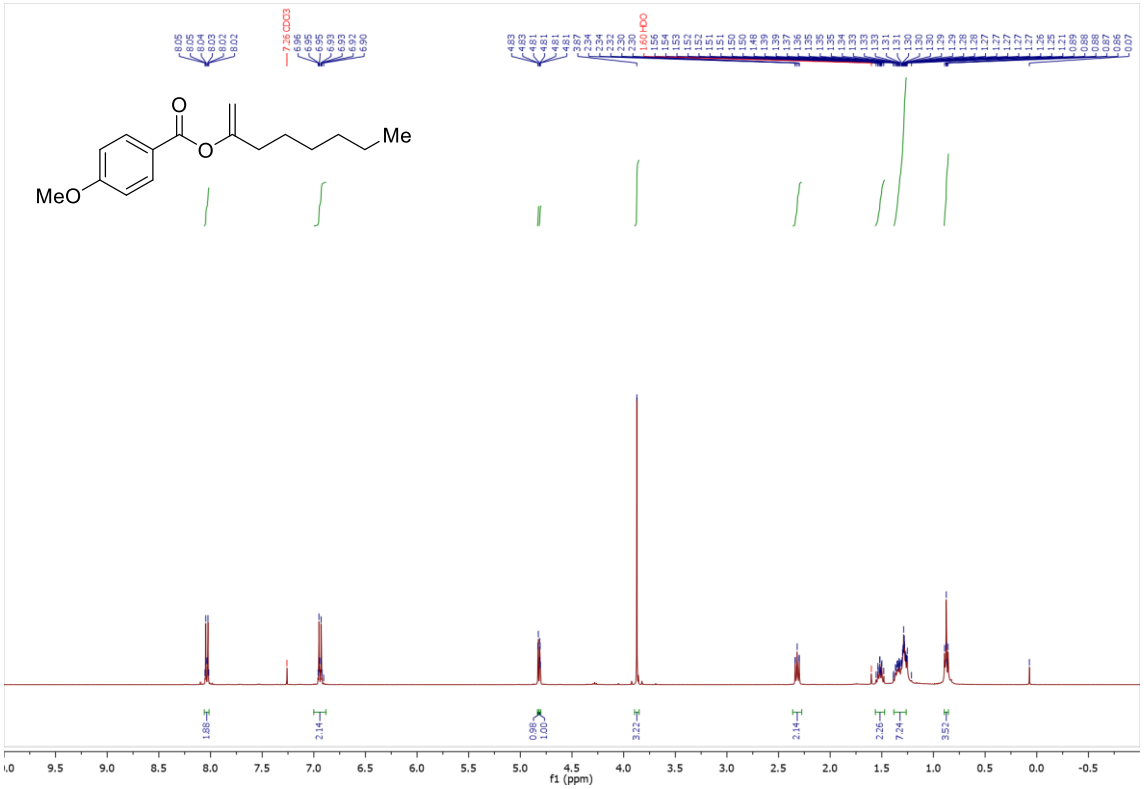


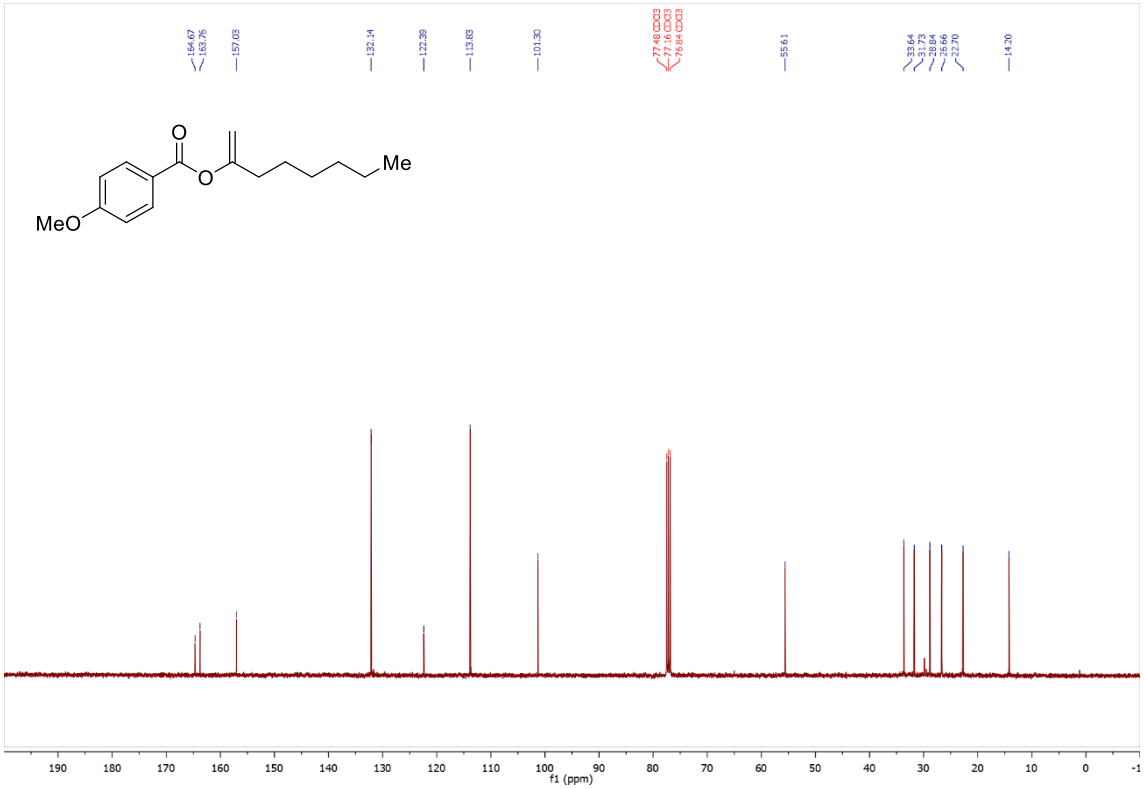
Oct-1-en-2-yl-2-methoxybenzoate, 16d



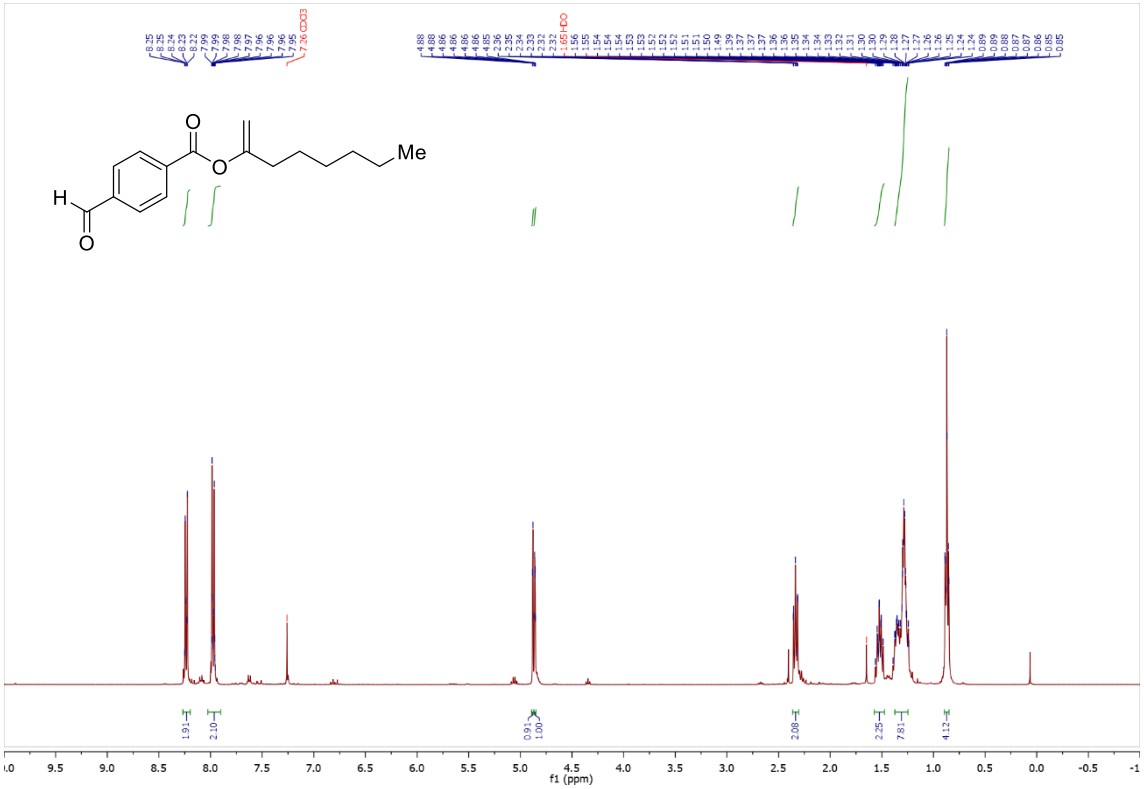


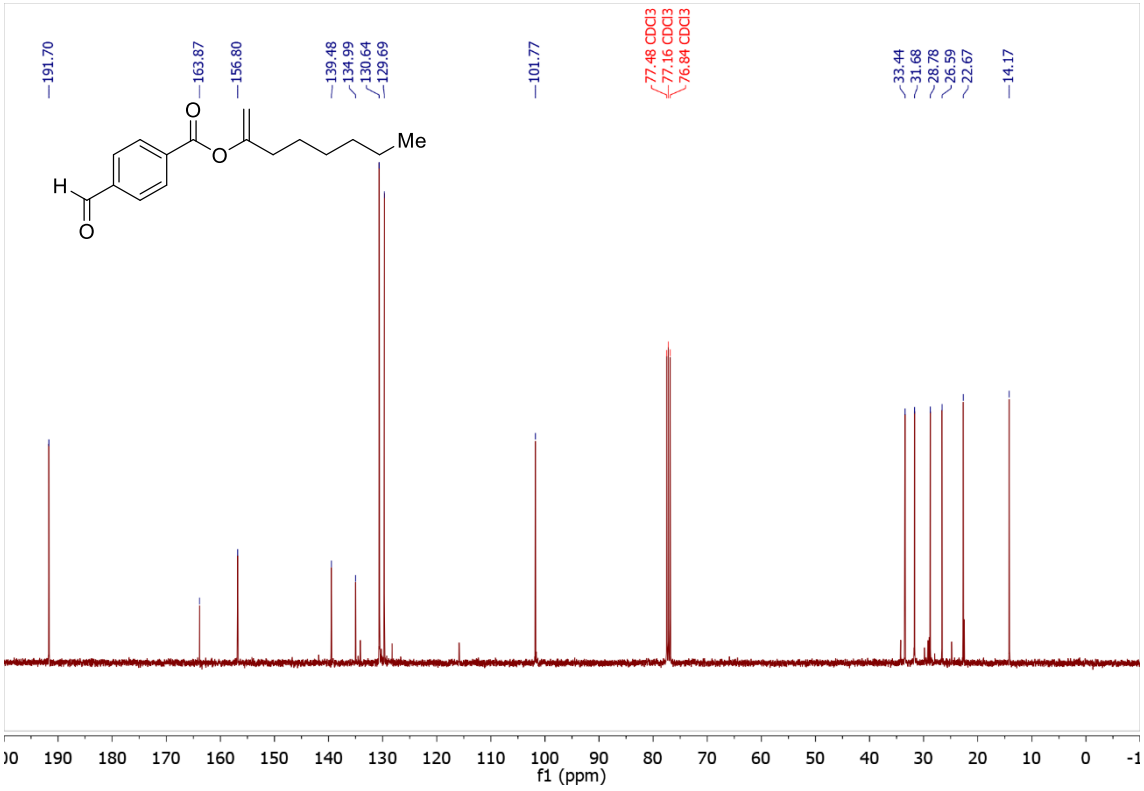
Oct-1-en-2-yl-4-methoxybenzoate, 16e



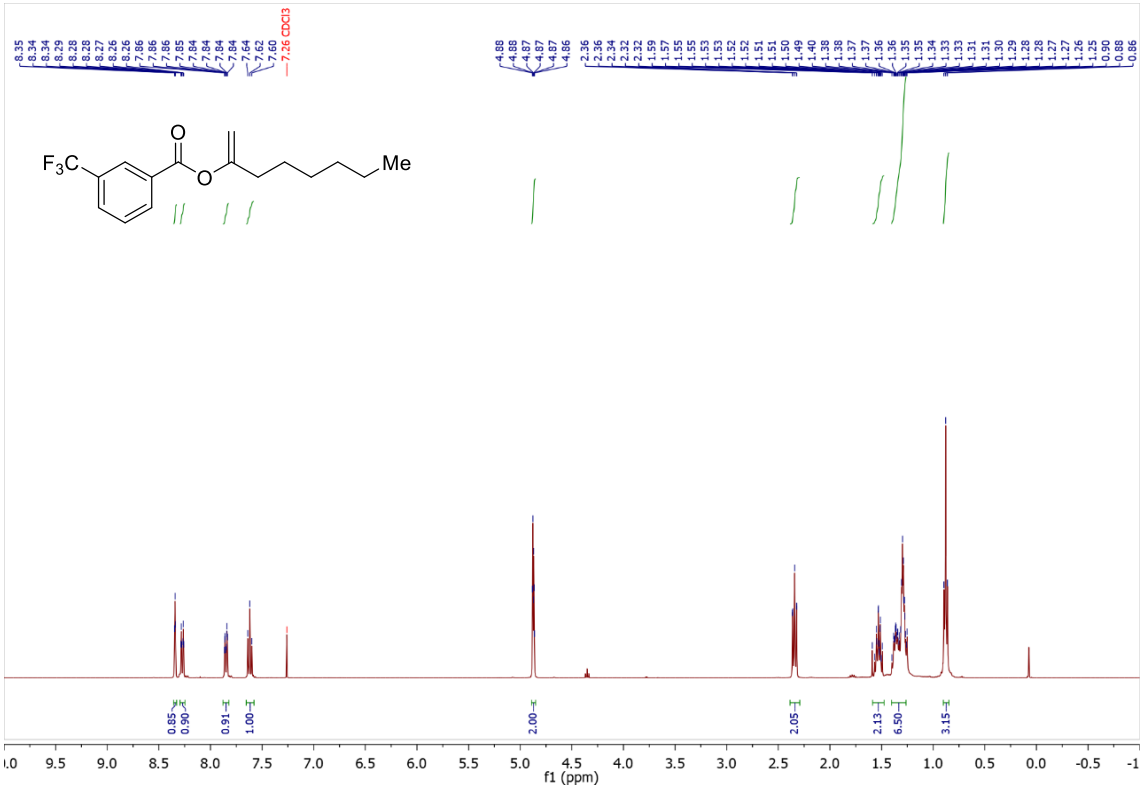


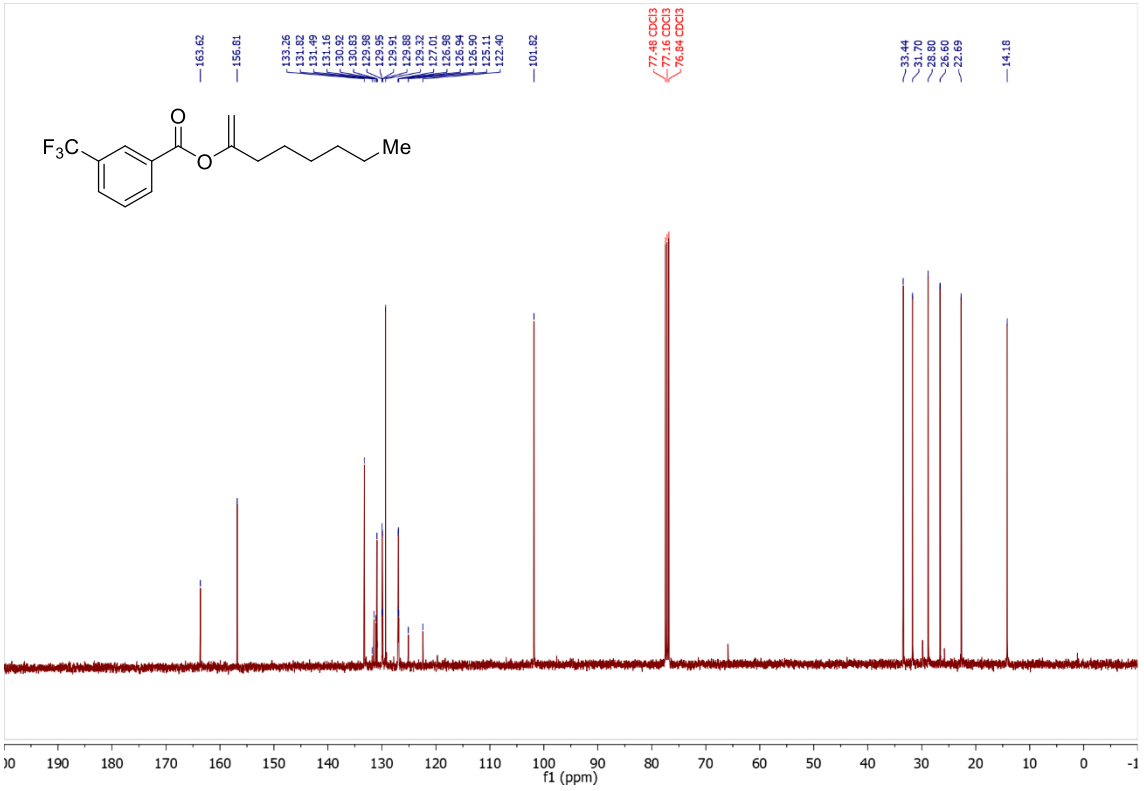
Oct-1-en-2-yl-4-formylbenzoate, 16f



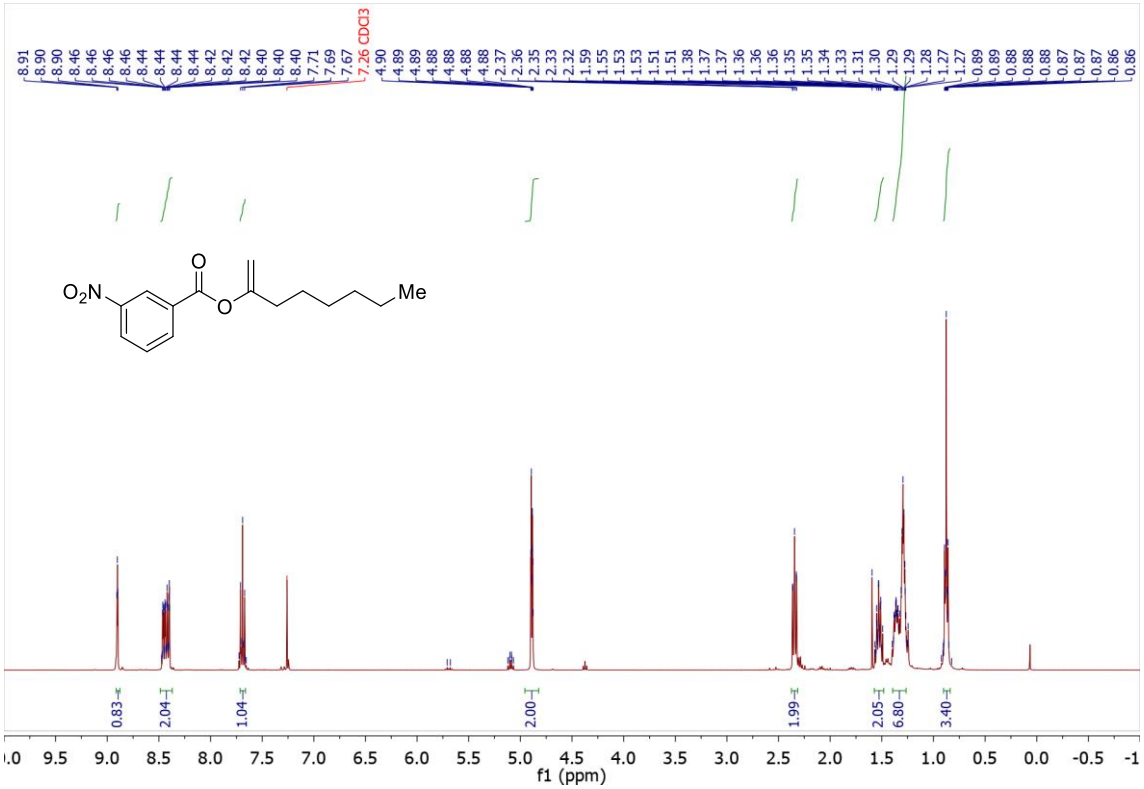


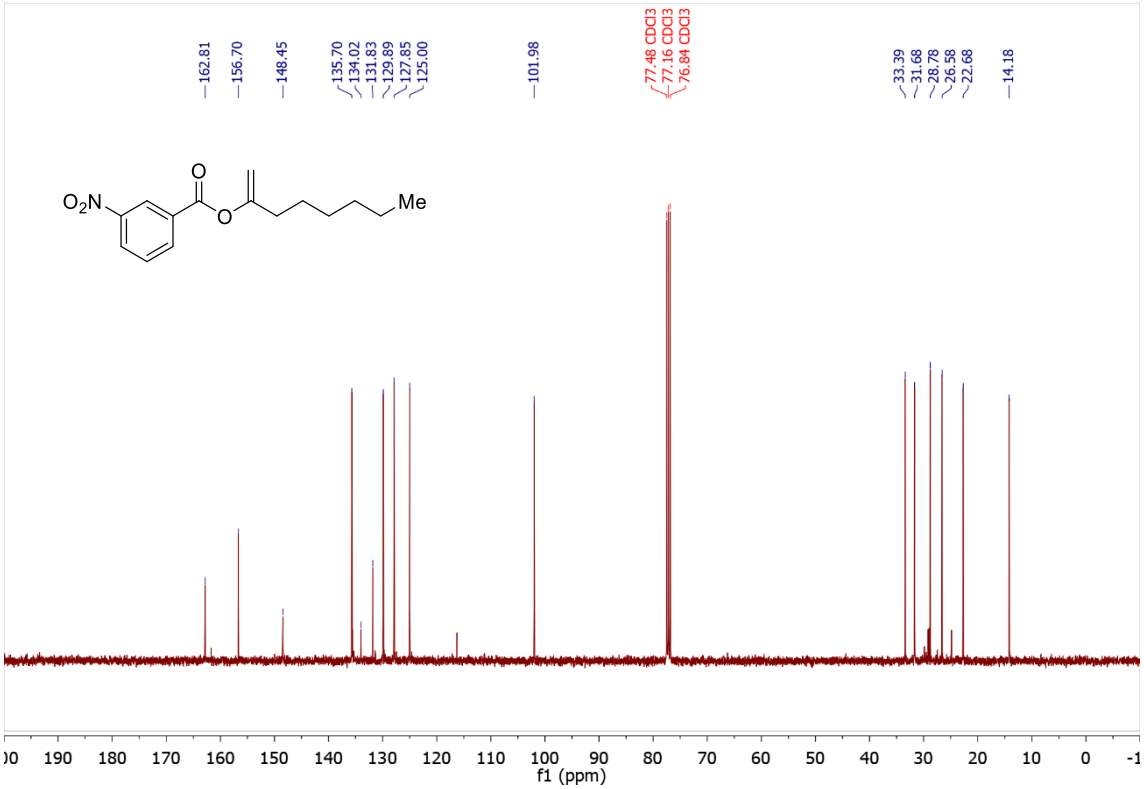
Oct-1-en-2-yl-3-(trifluoromethyl)benzoate, 16g



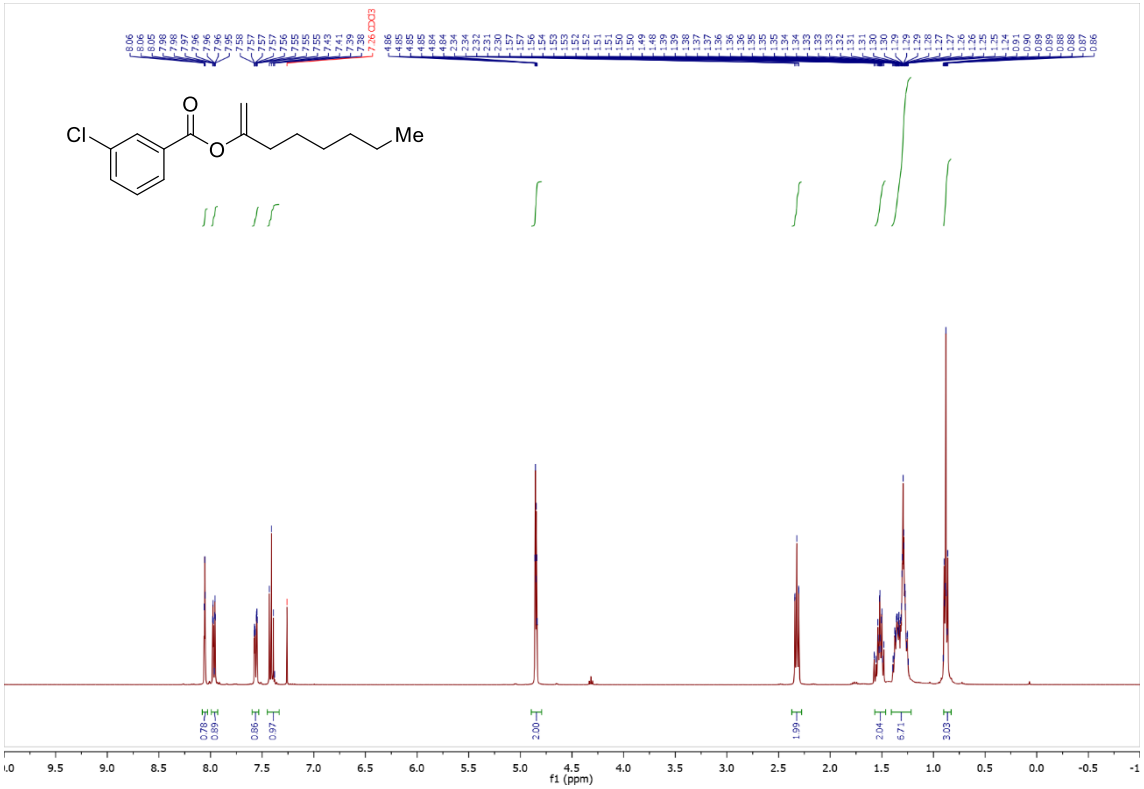


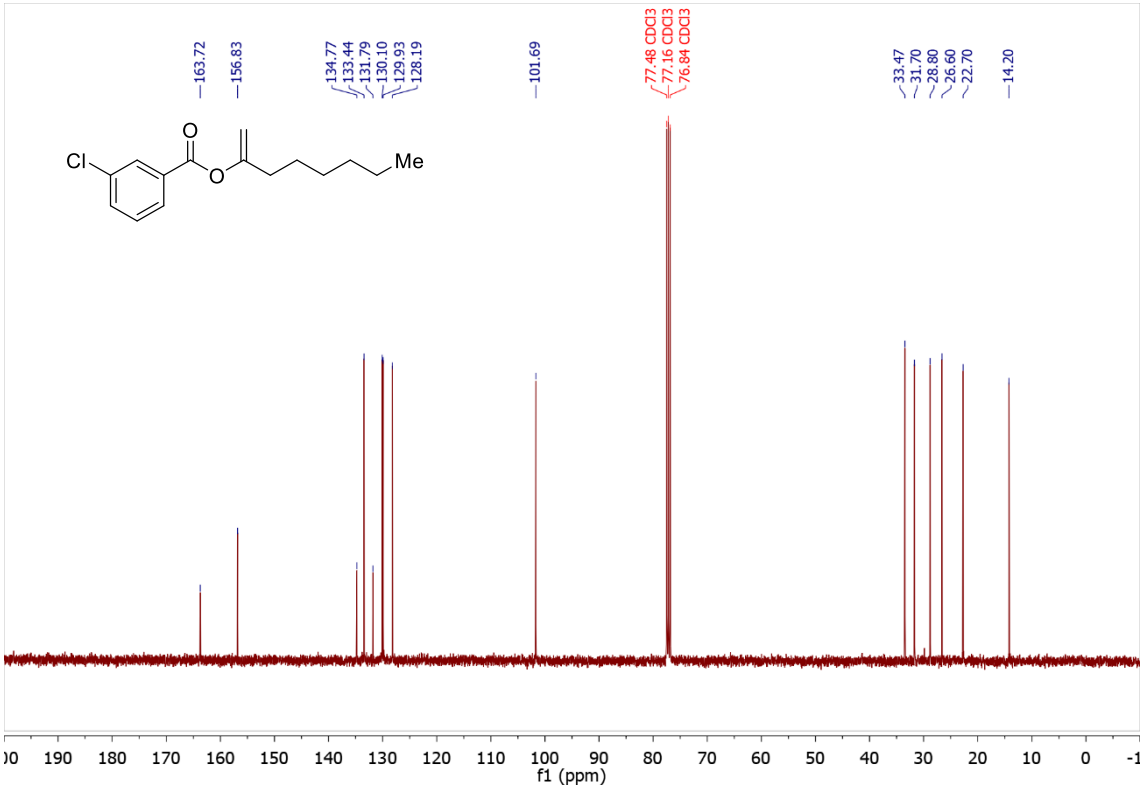
Oct-1-en-2-yl-3-nitrobenzoate, 16h



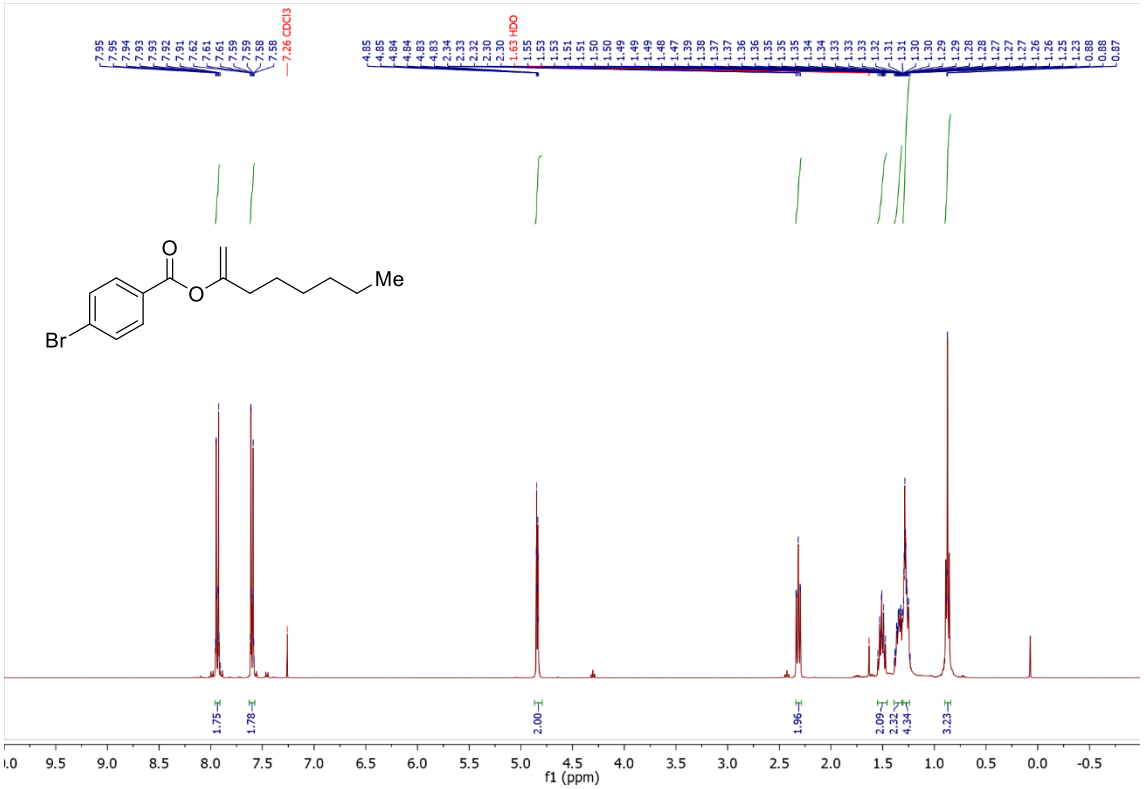


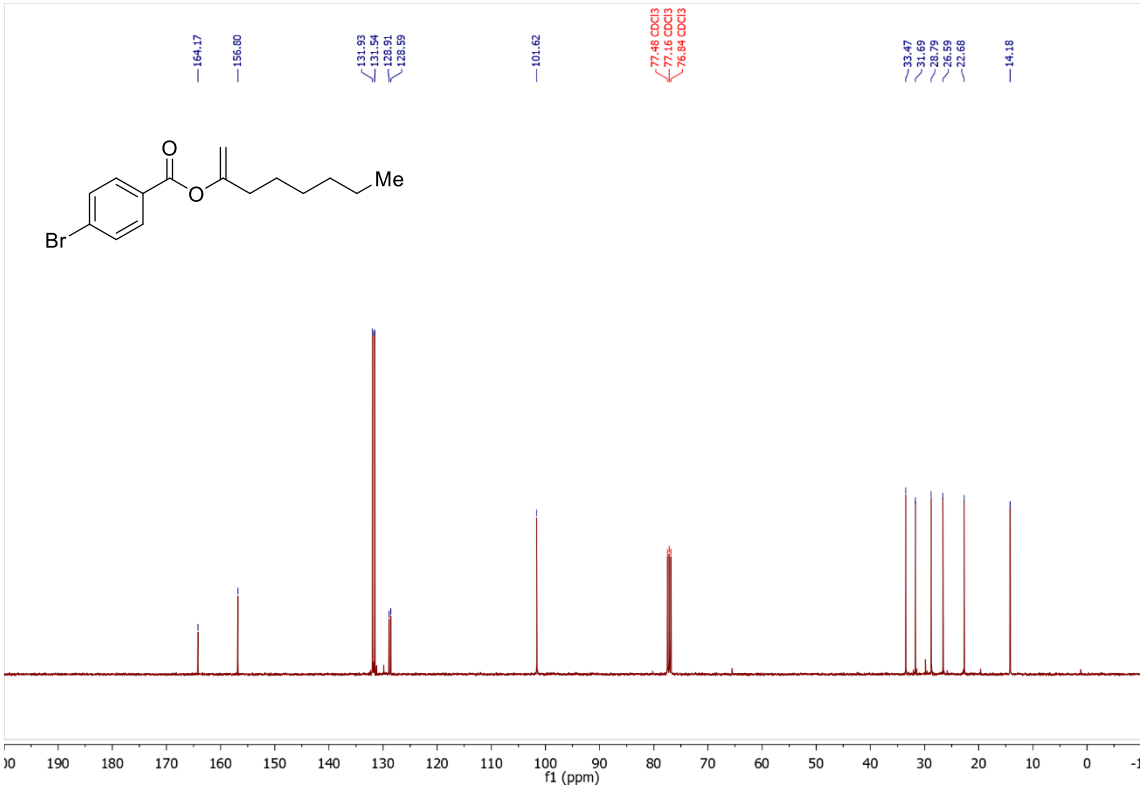
Oct-1-en-2-yl-3-chlorobenzoate, 16i



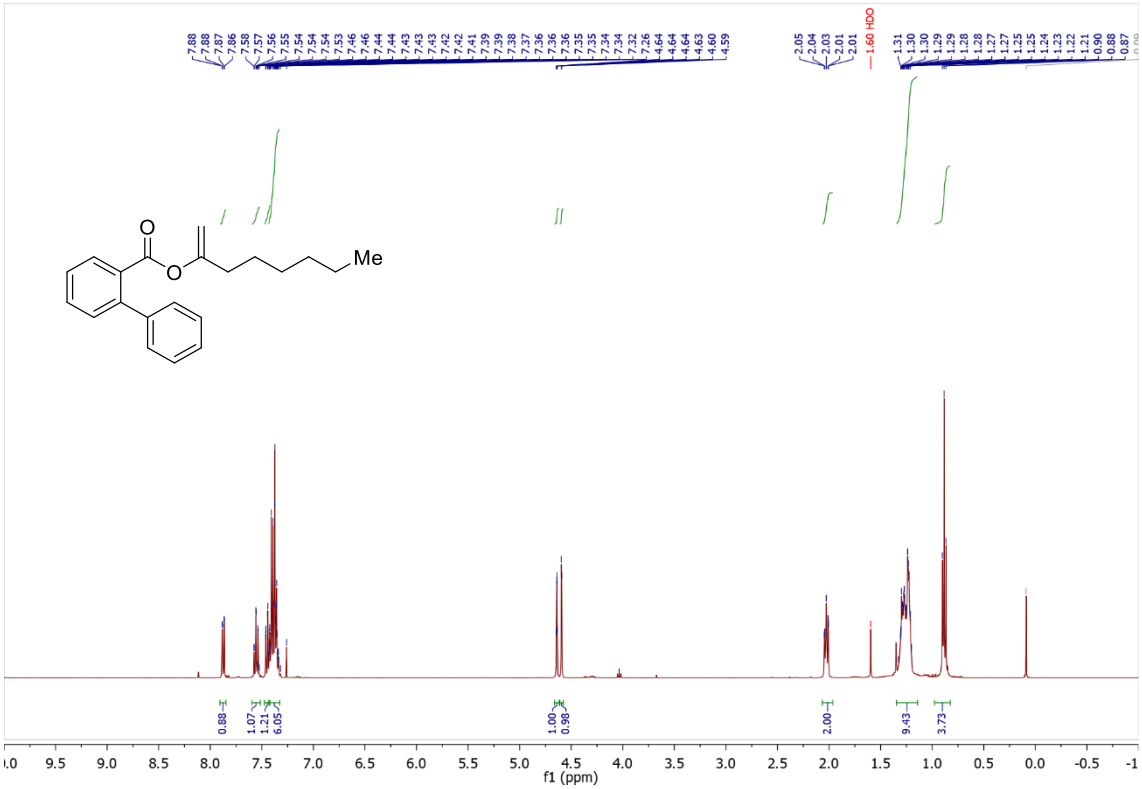


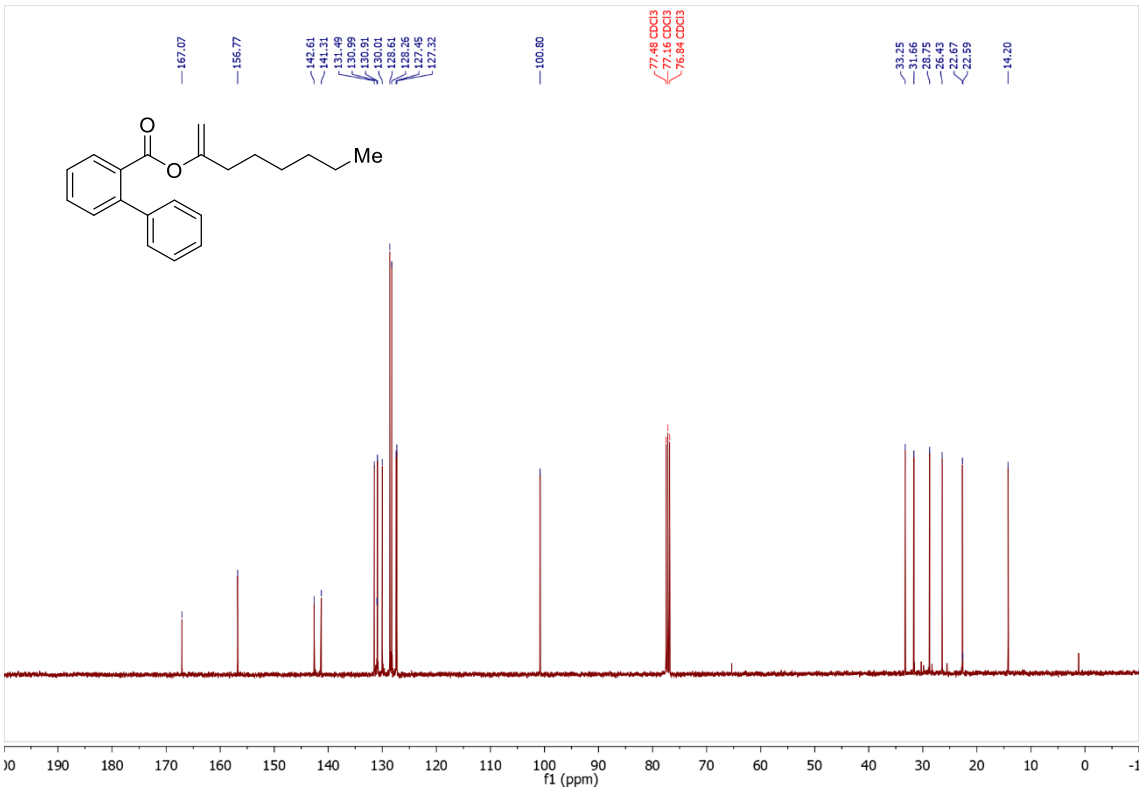
Oct-1-en-2-yl-4-bromobenzoate, 16j



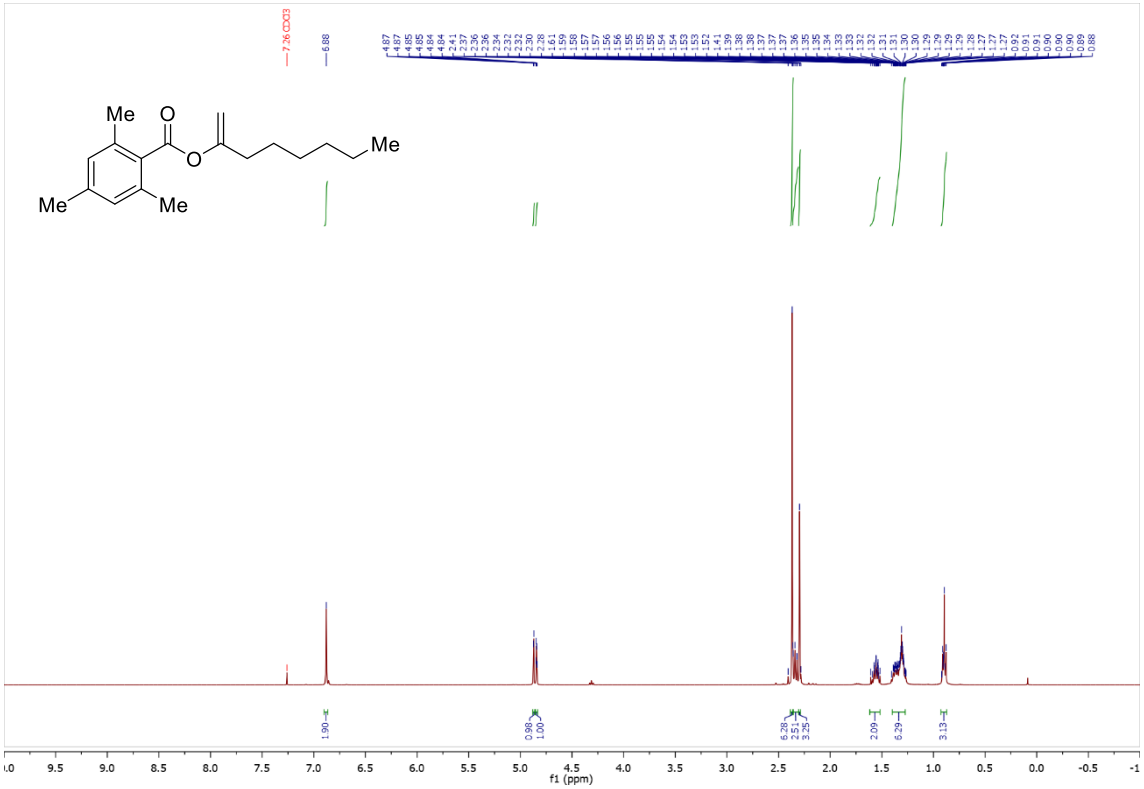


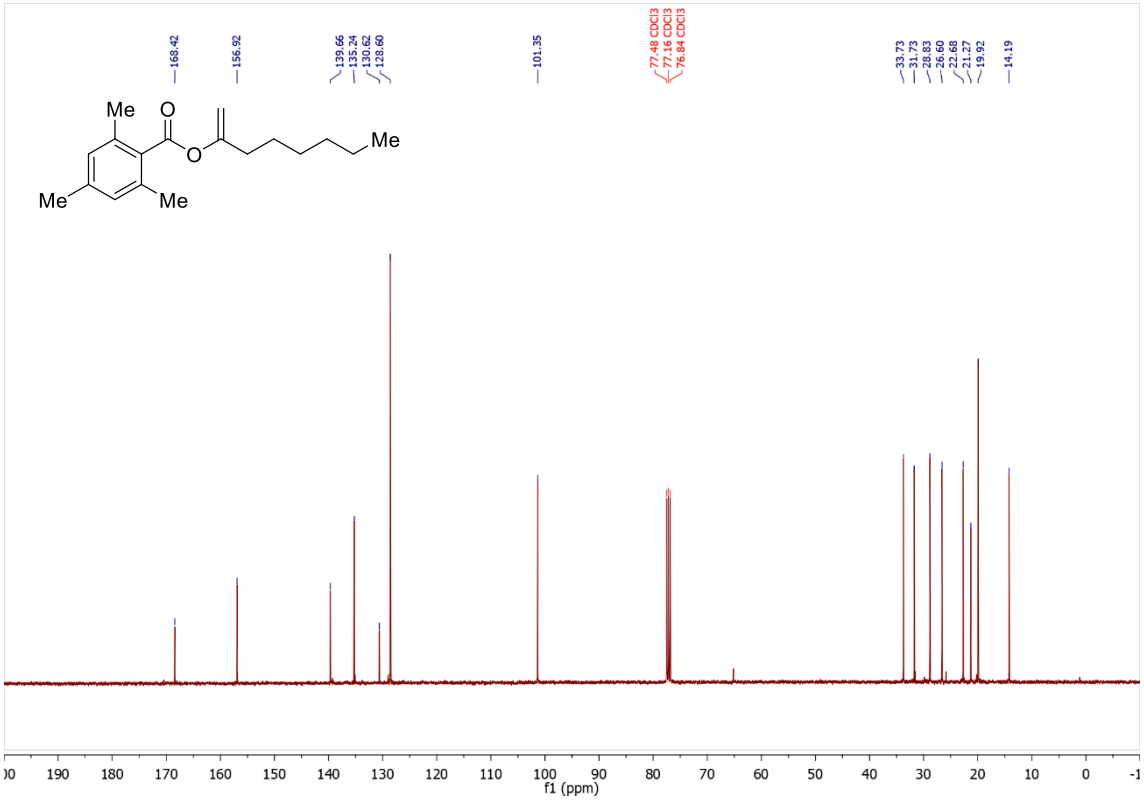
Oct-1-en-2-yl-[1,1'-biphenyl]-2-carboxylate, 16k



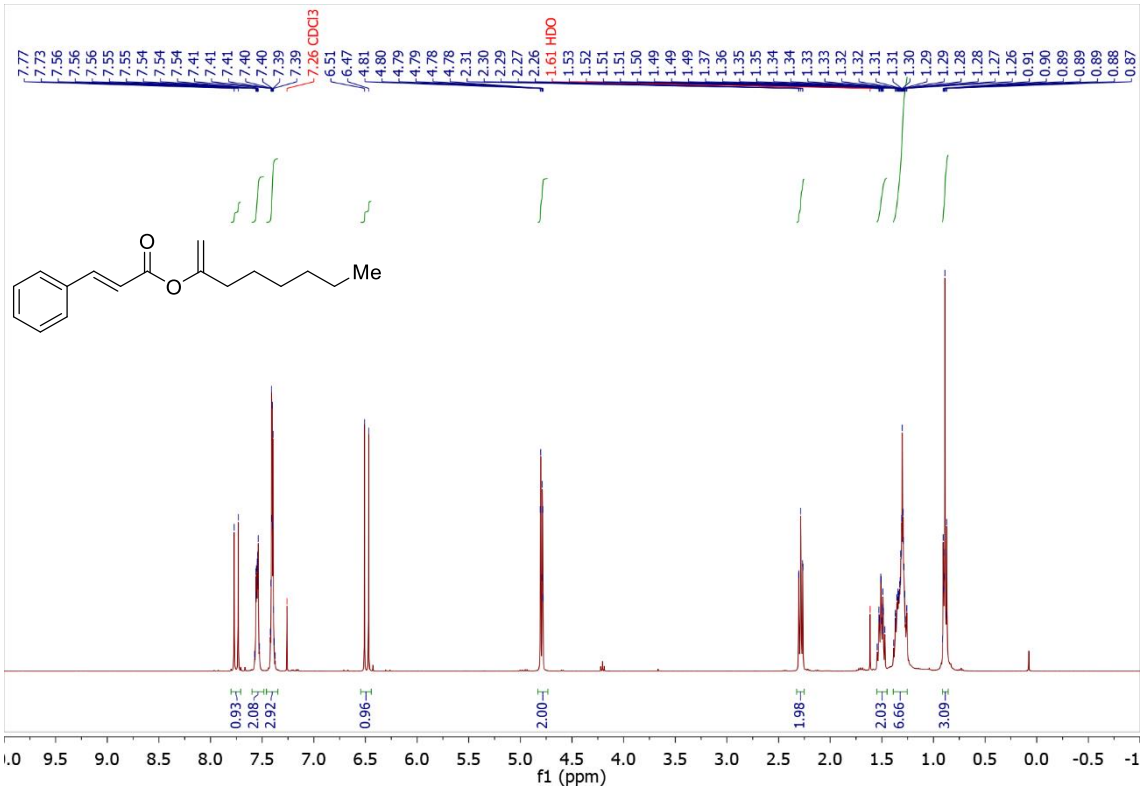


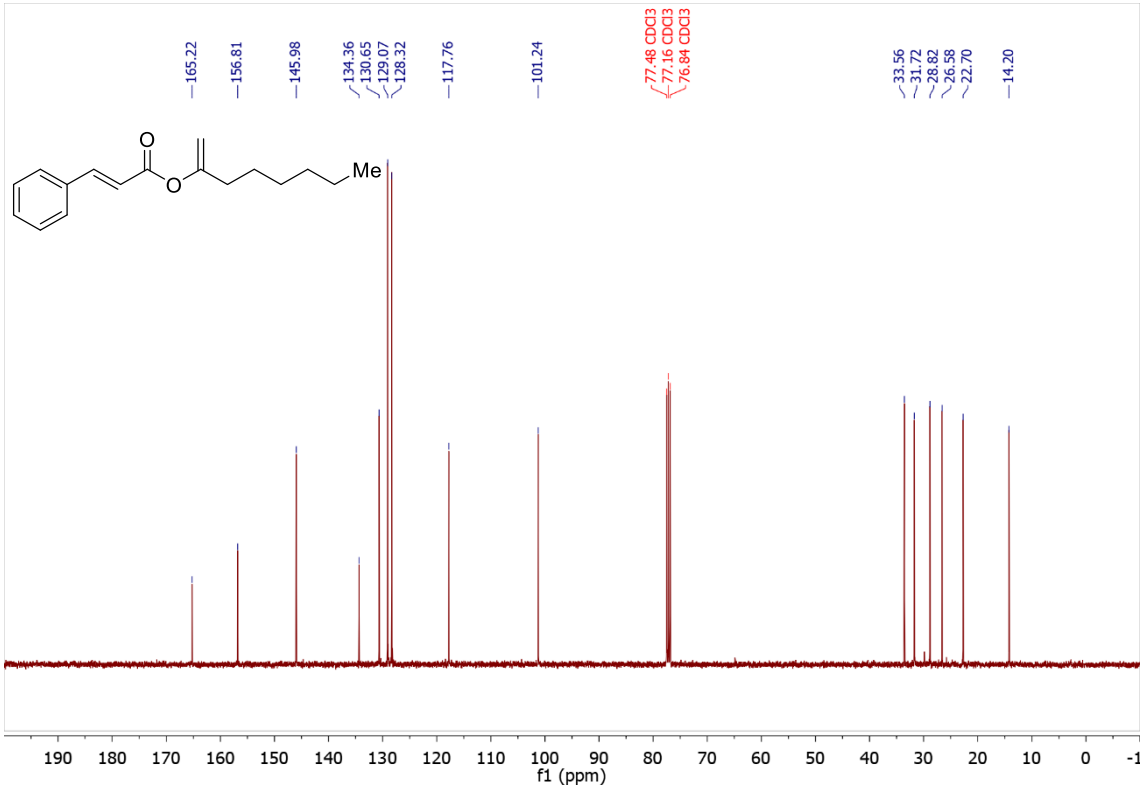
Oct-1-en-2-yl-2,4,6-trimethylbenzoate, 16l



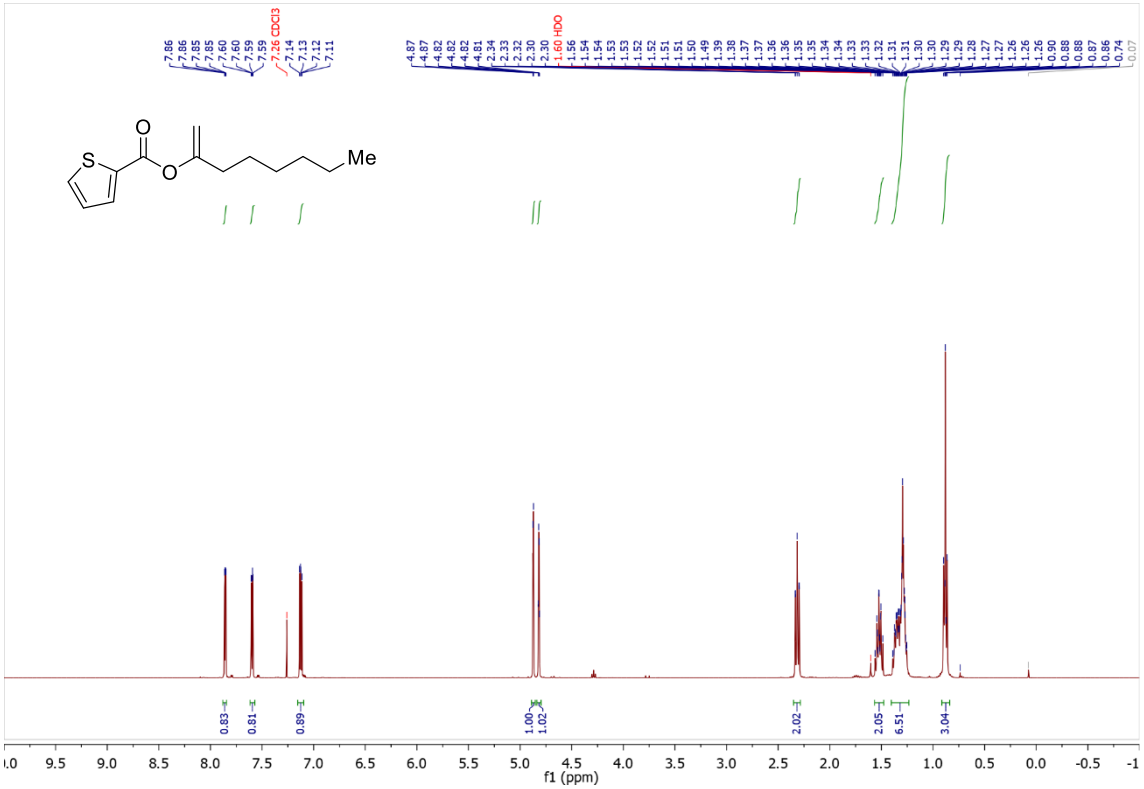


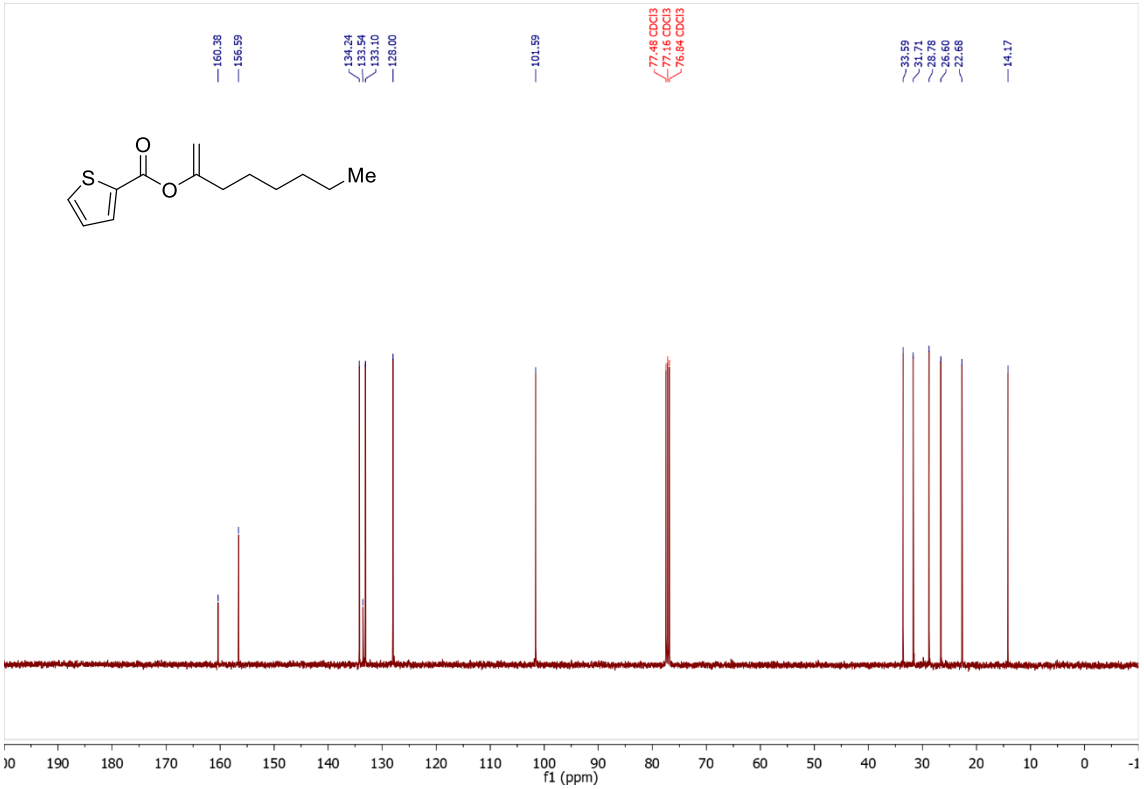
Oct-1-en-2-ylcinnamate, 16m



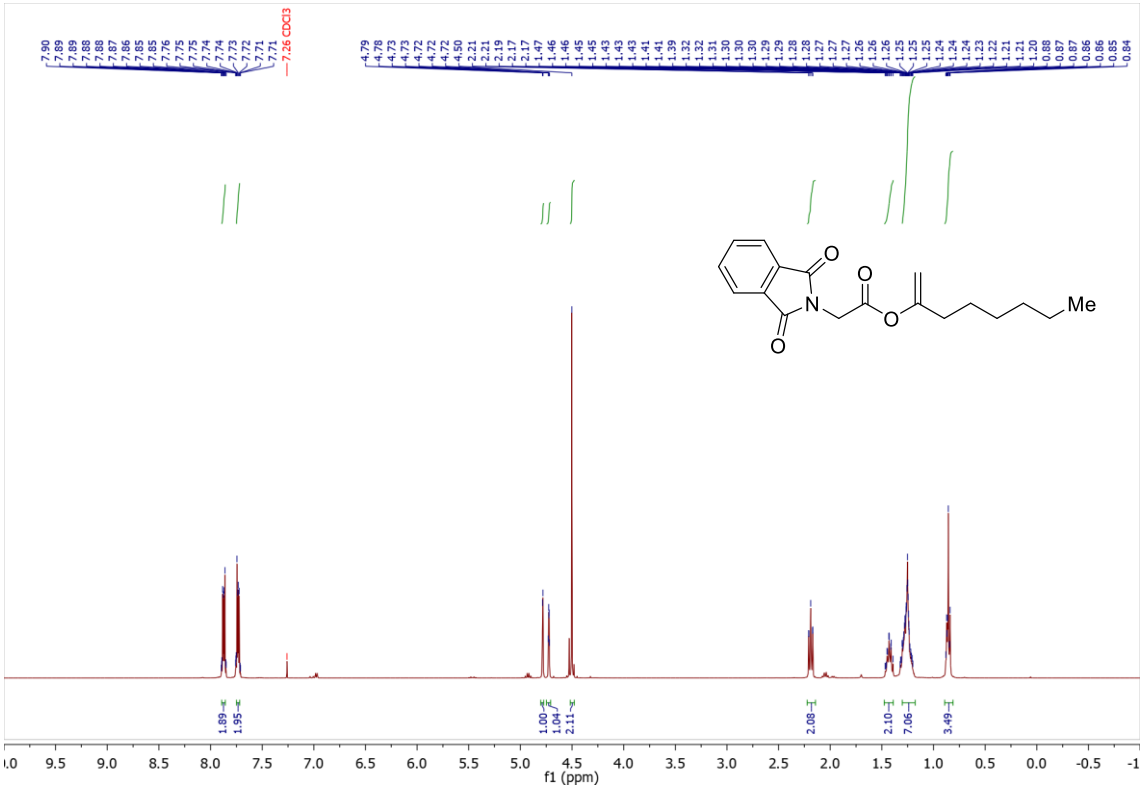


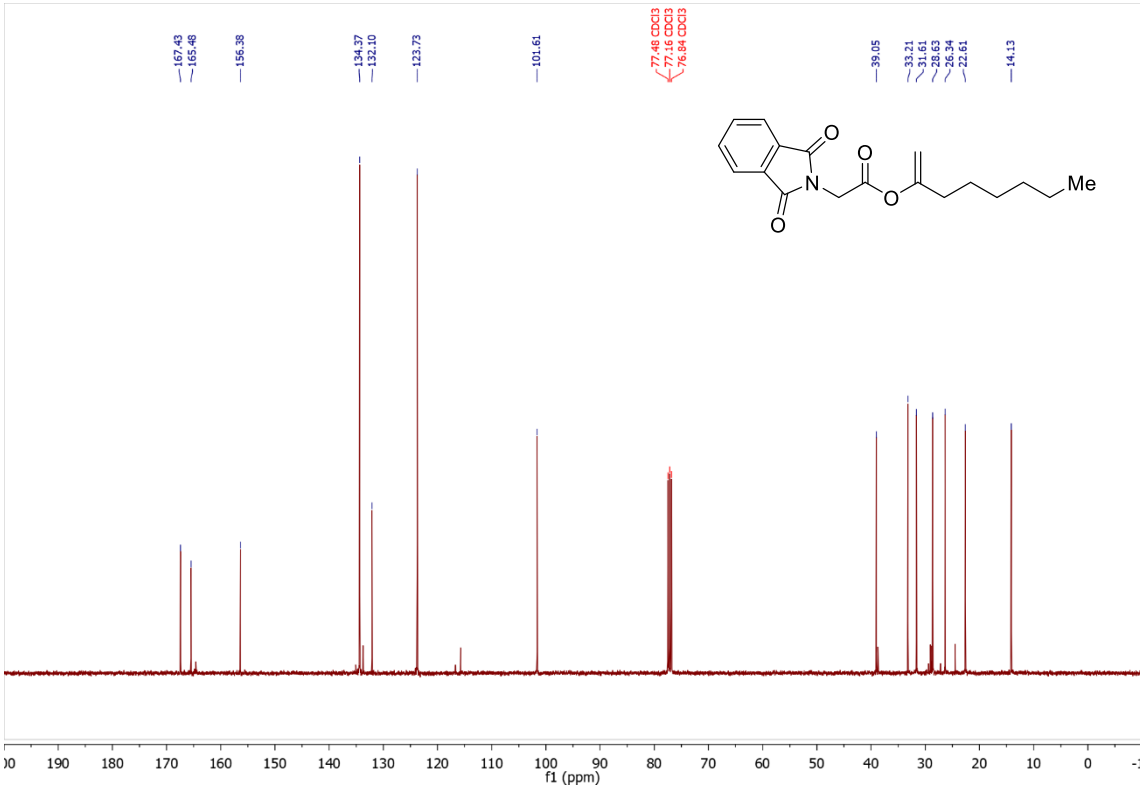
Oct-1-en-2-ylthiophene-2-carboxylate, 16n



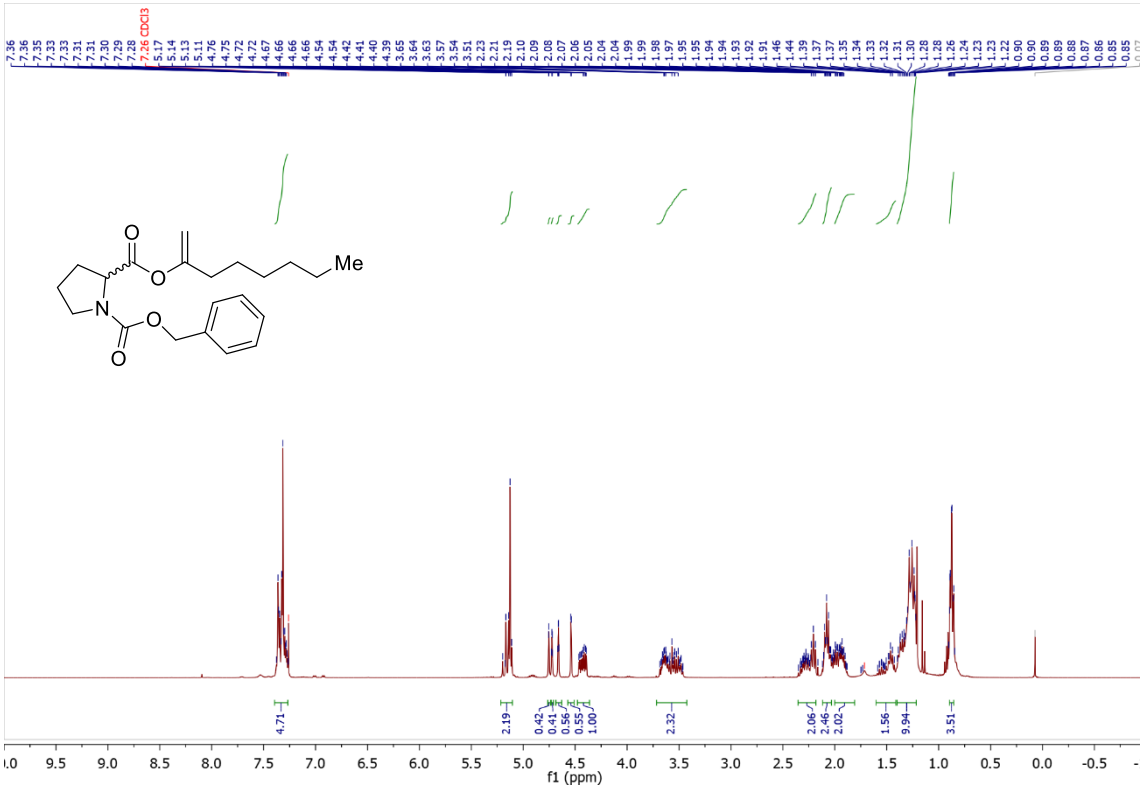


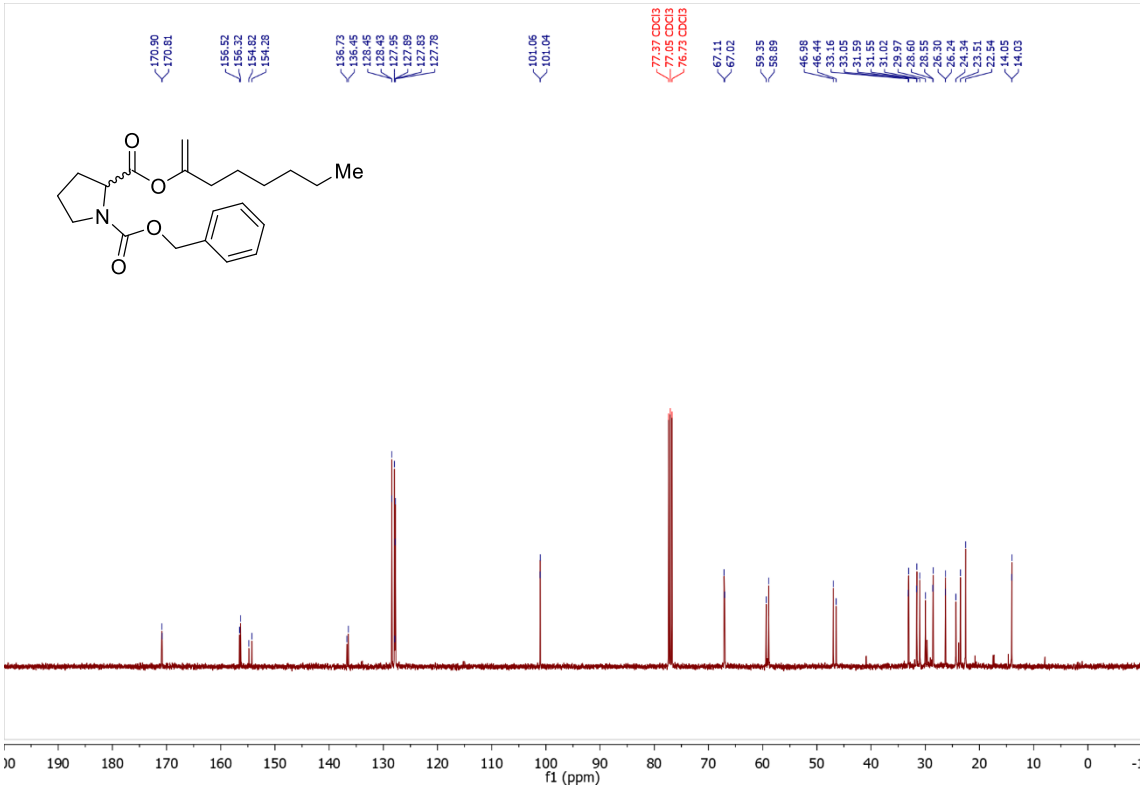
Oct-1-en-2-yl-2-(1,3-dioxoisoindolin-2-yl)acetate, 16o



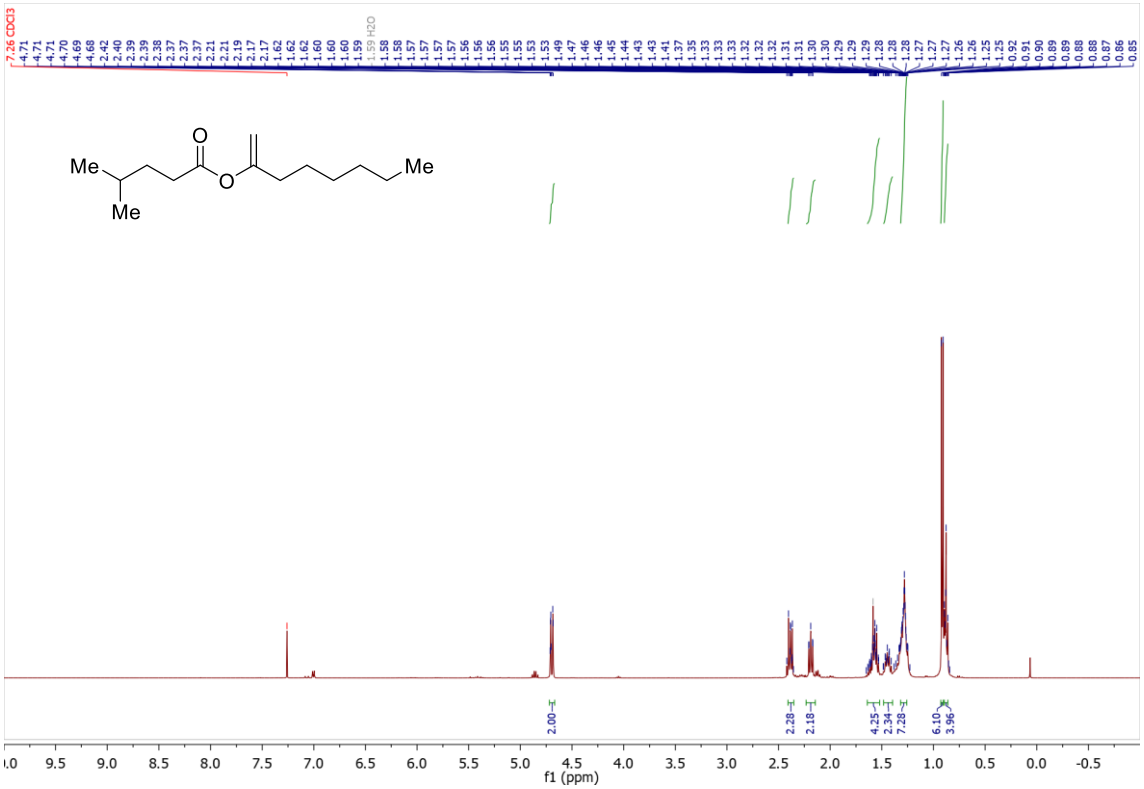


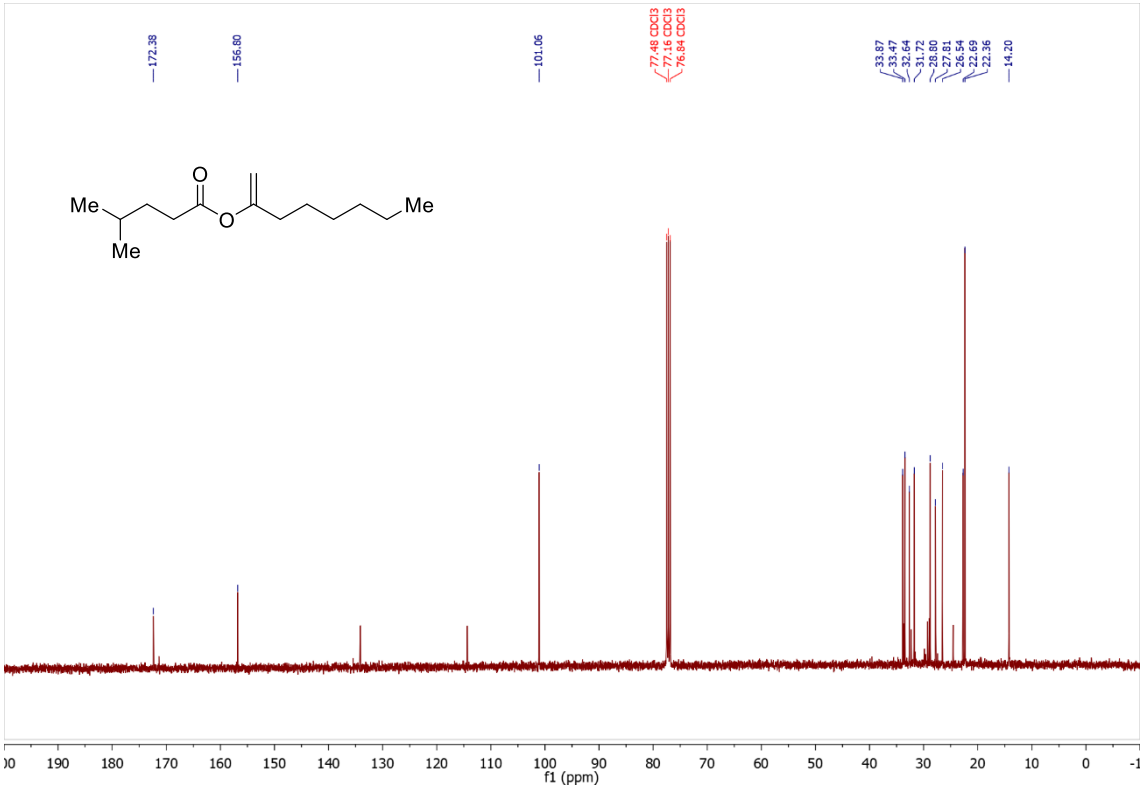
1-Benzyl-2-(oct-1-en-2-yl)pyrrolidine-1,2-dicarboxylate, 16p



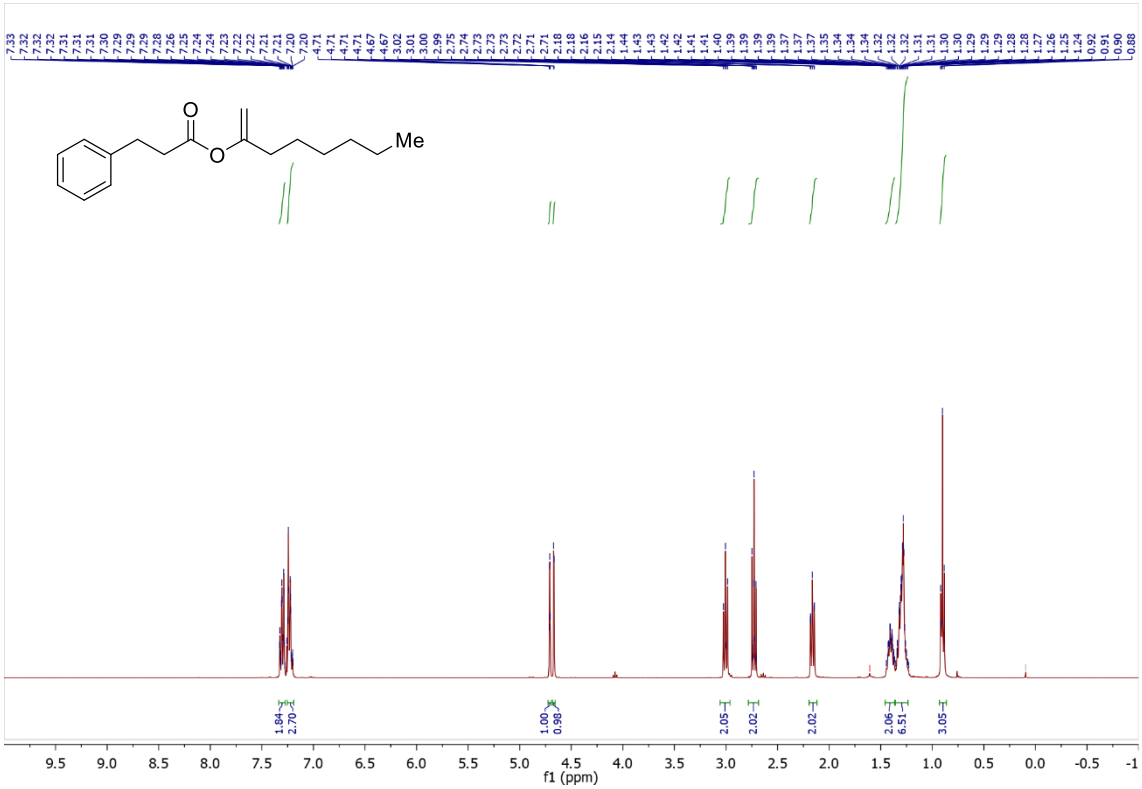


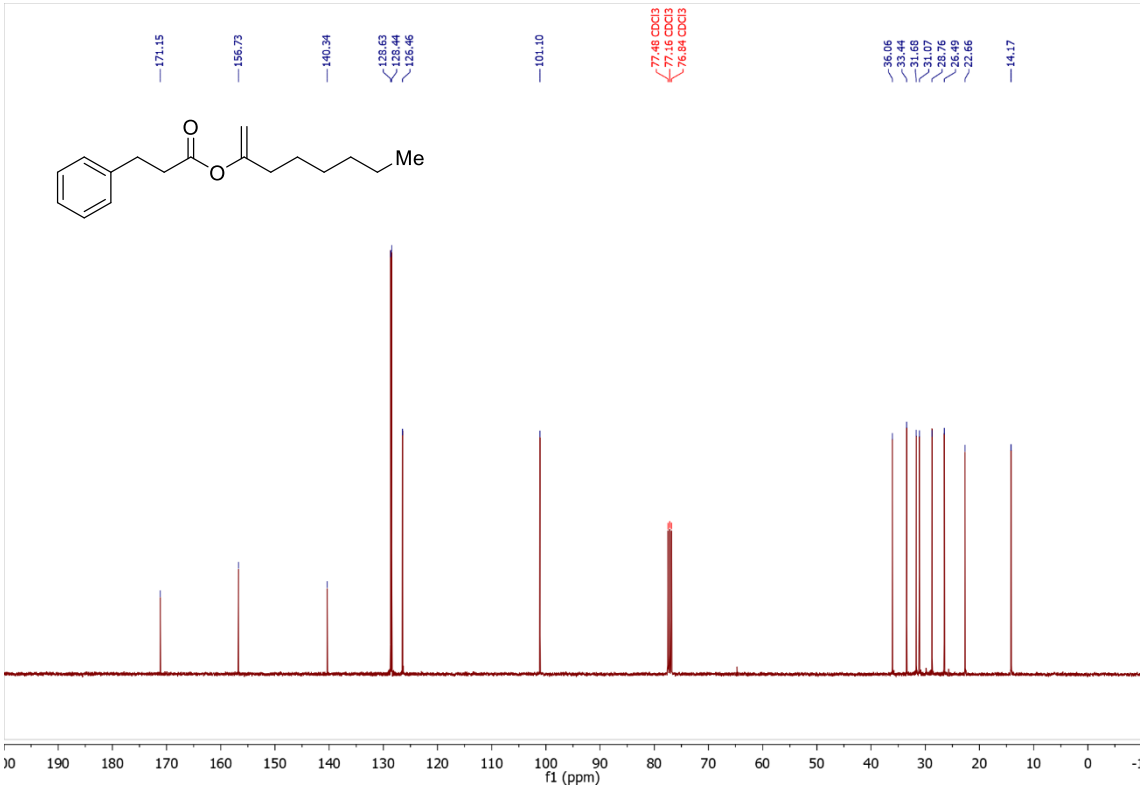
Oct-1-en-2-yl-4-methylpentanoate, 16q



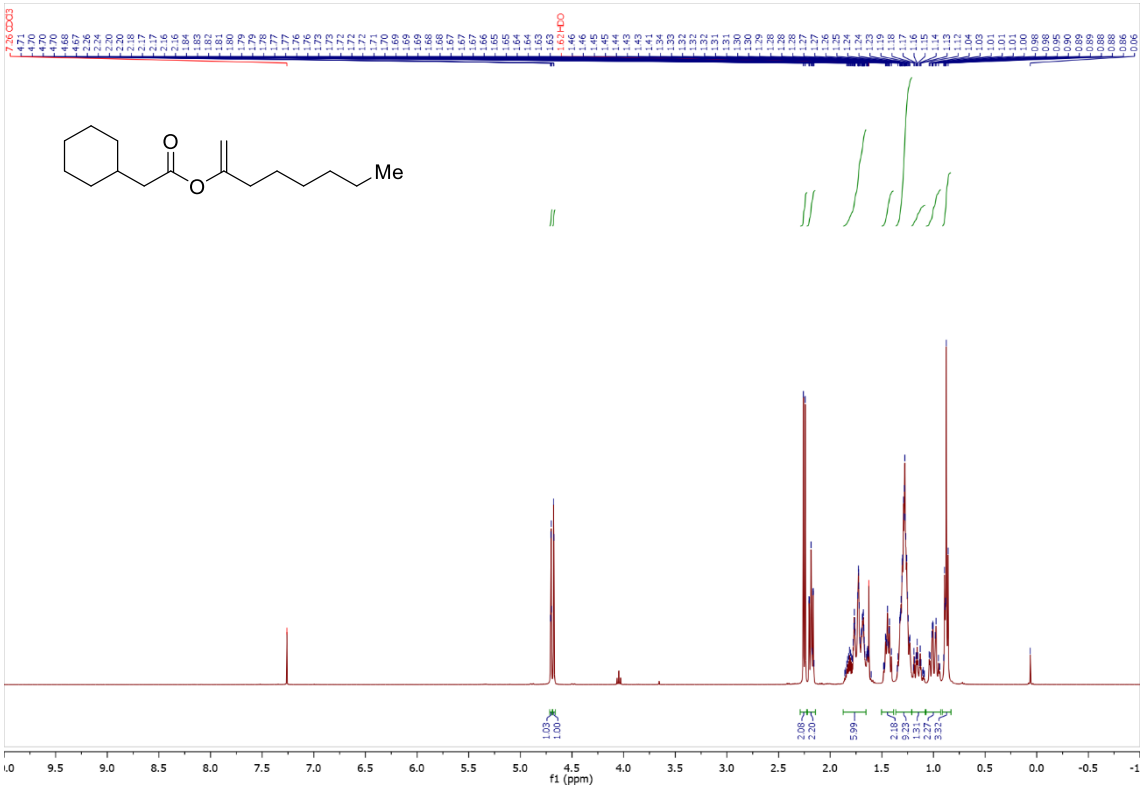


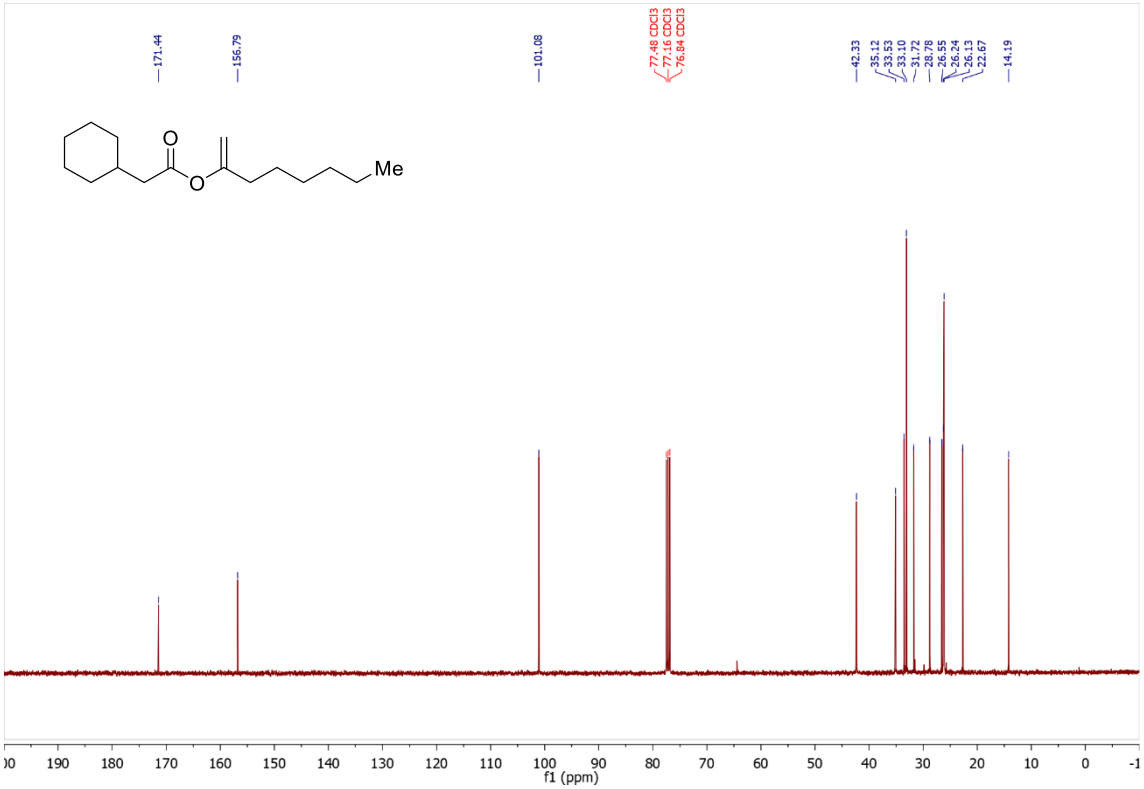
Oct-1-en-2-yl-3-phenylpropanoate, 16r



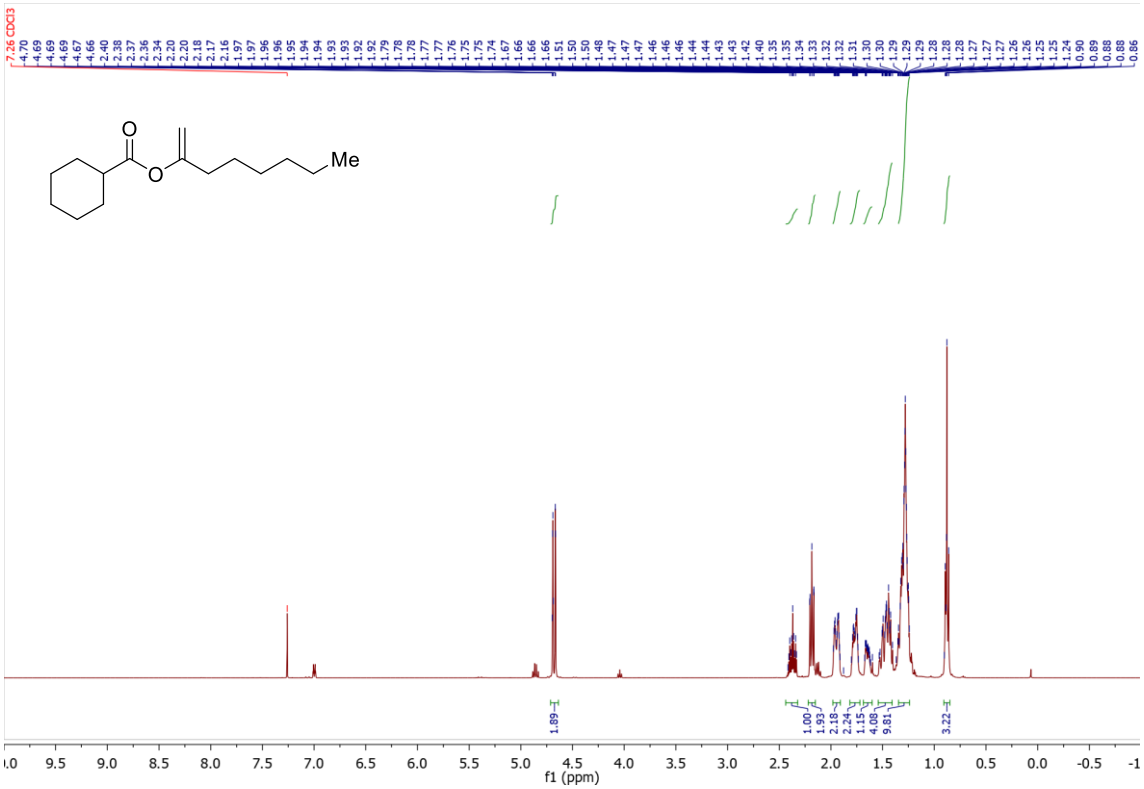


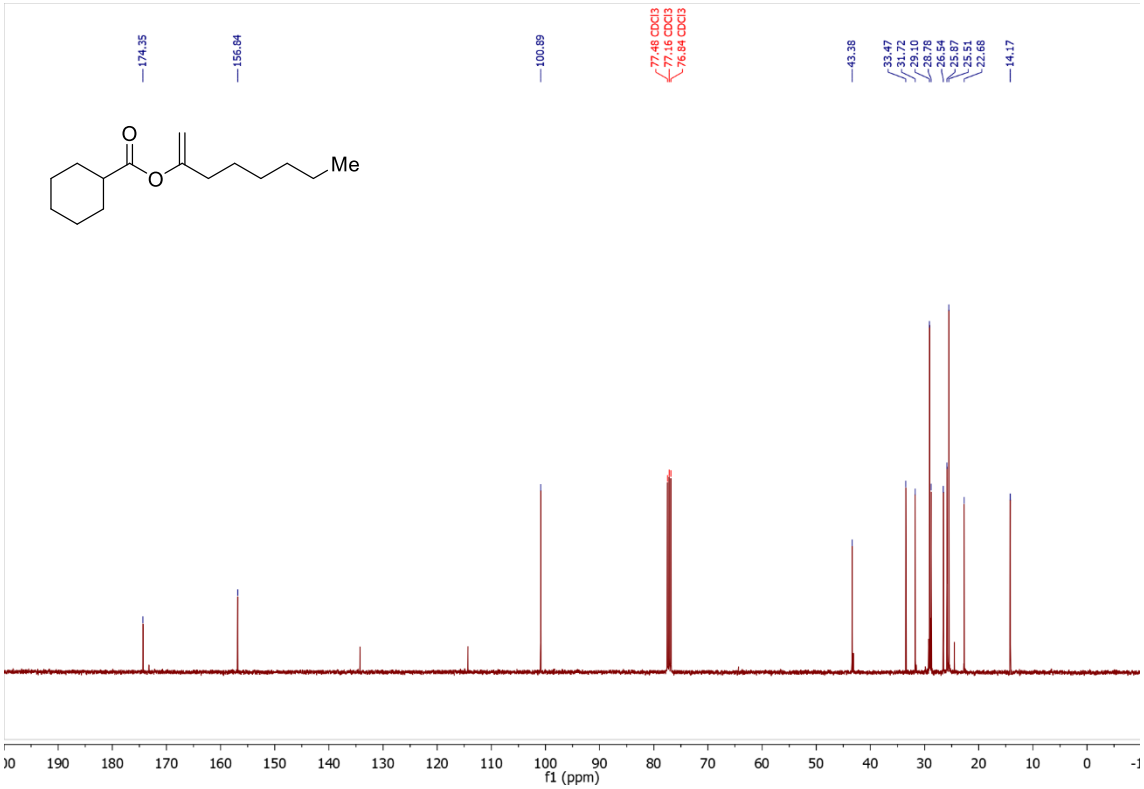
Oct-1-en-2-yl-2-cyclohexylacetate, 16s



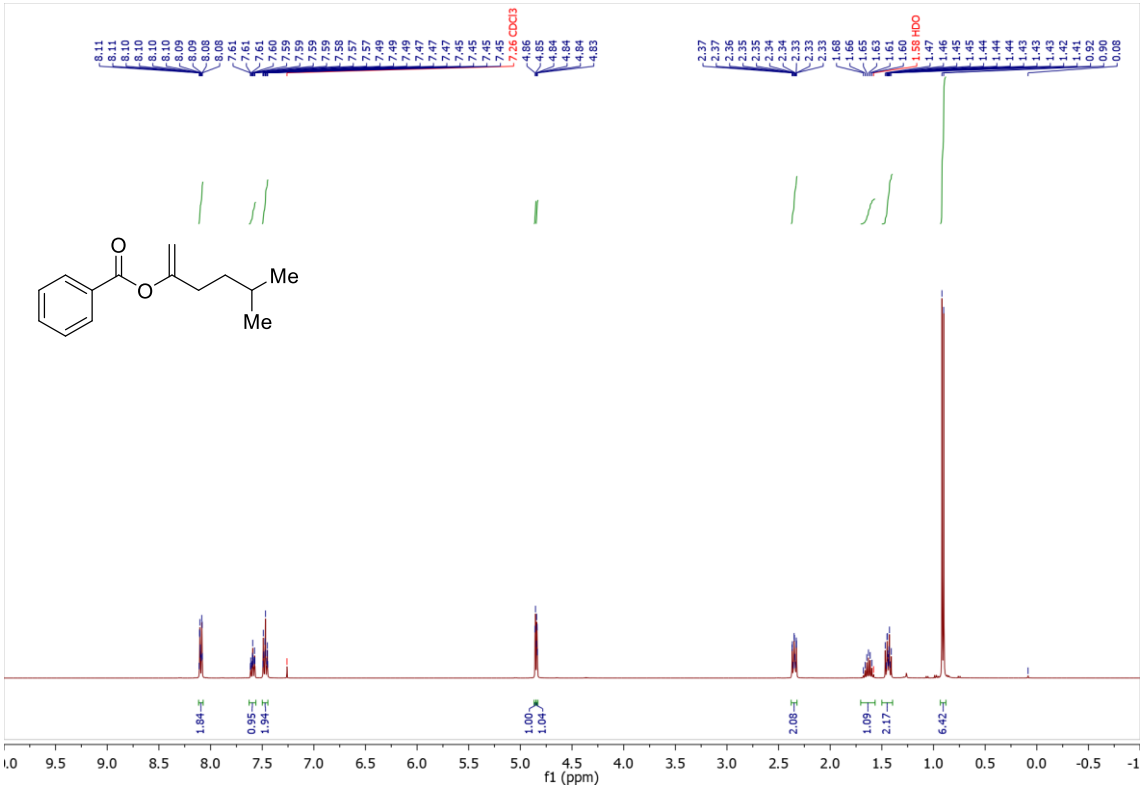


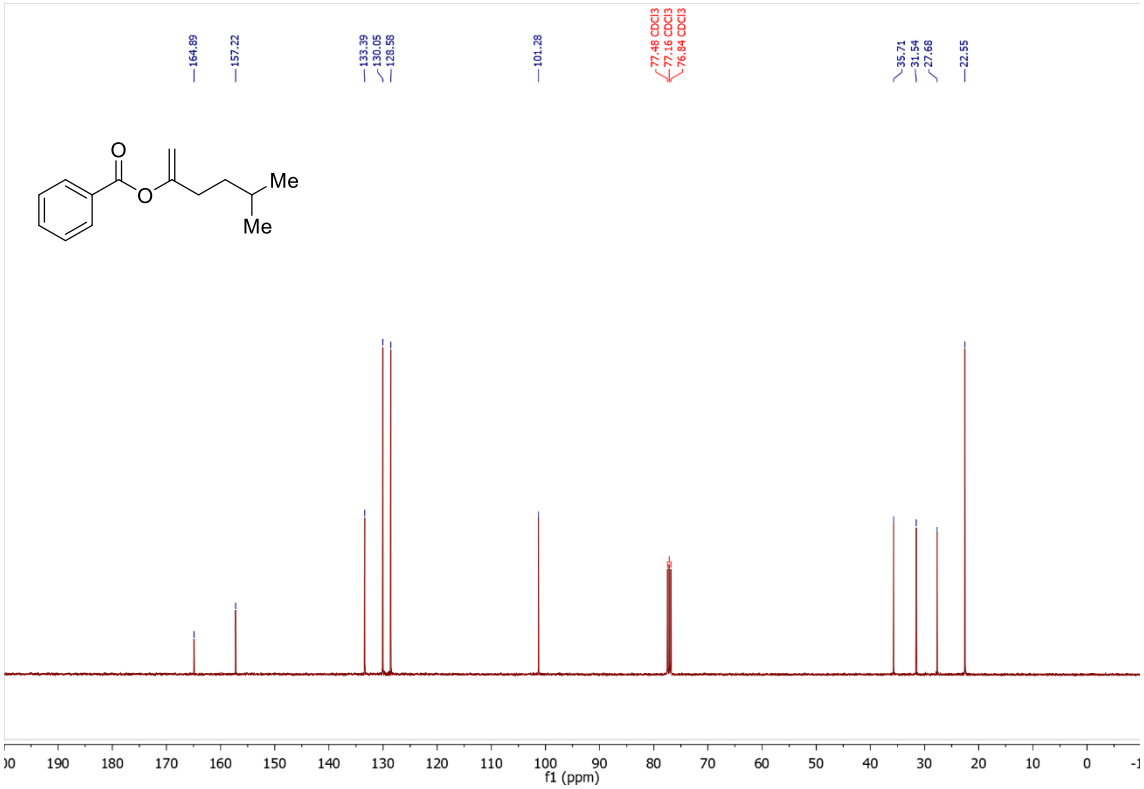
Oct-1-en-2-ylcyclohexanecarboxylate, 16t



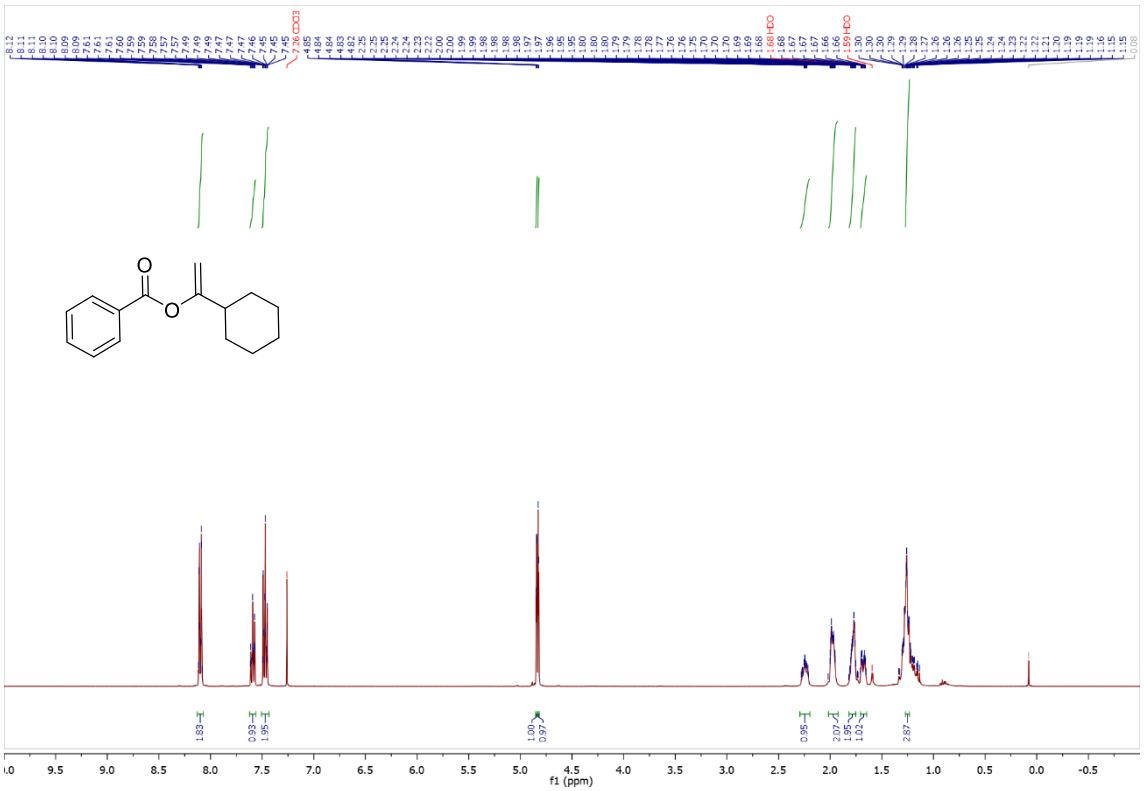


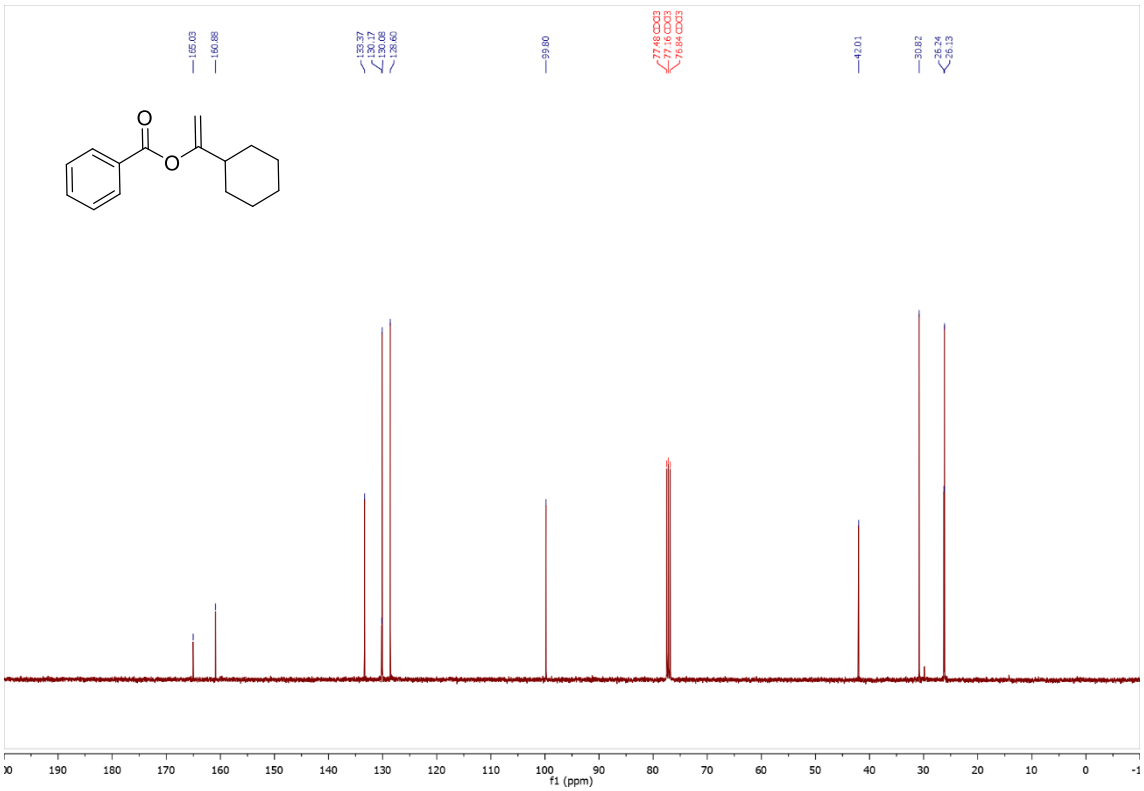
5-Methylhex-1-en-2-ylbenzoate, 16u



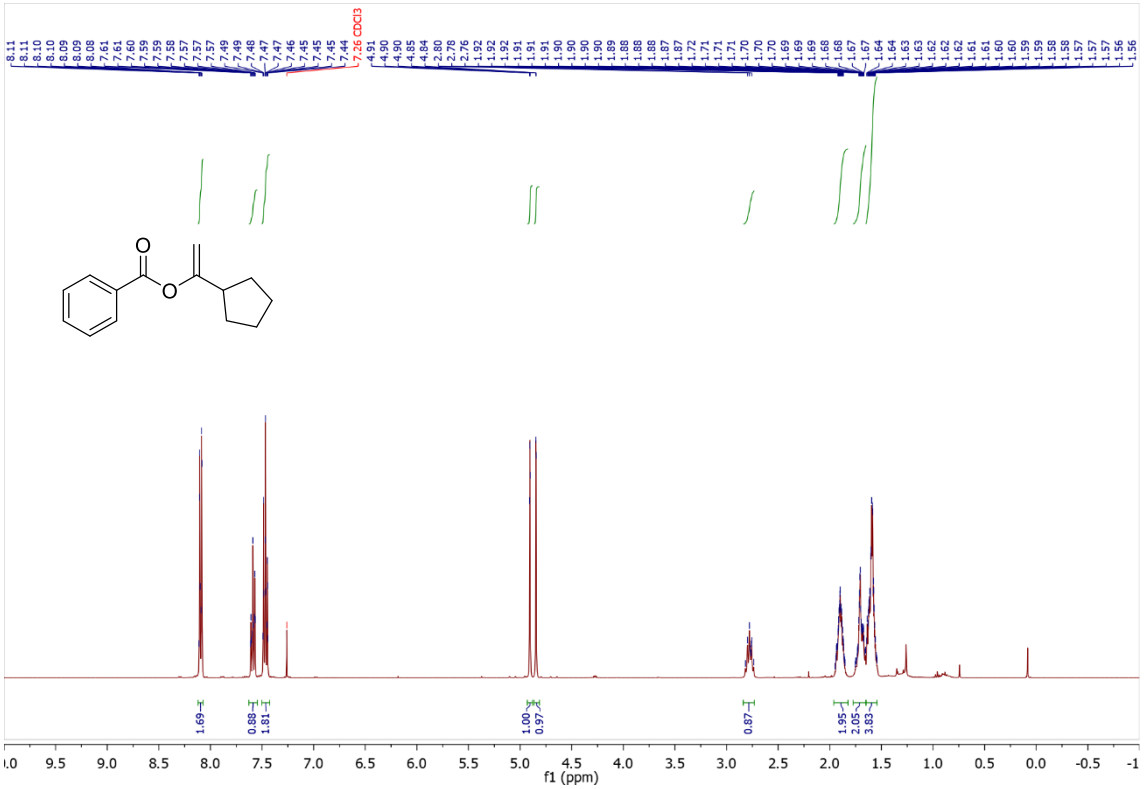


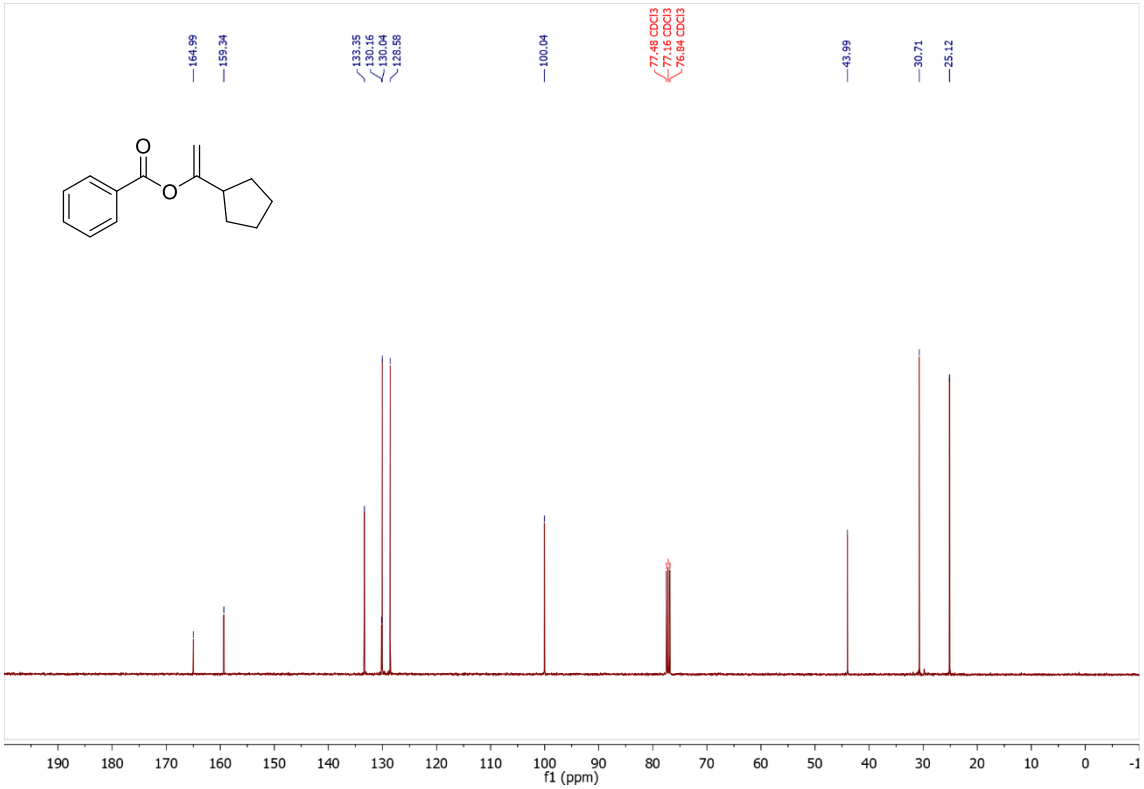
1-Cyclohexylvinyl benzoate, 16v



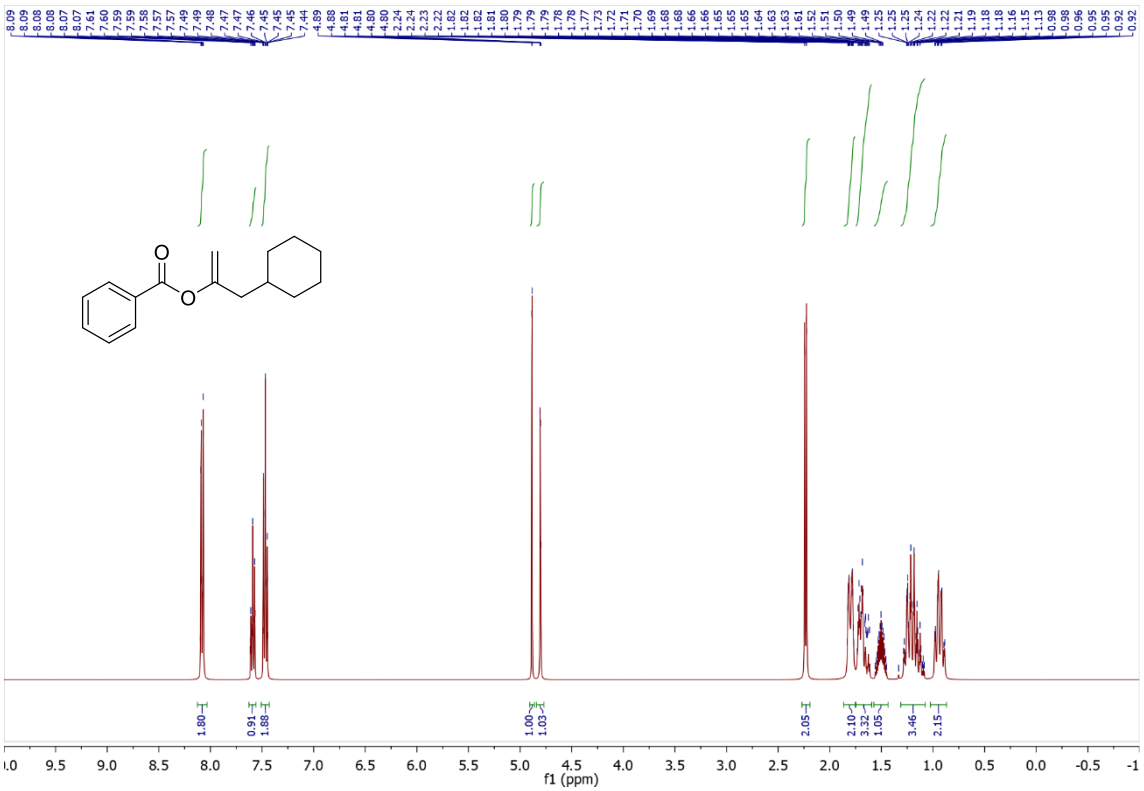


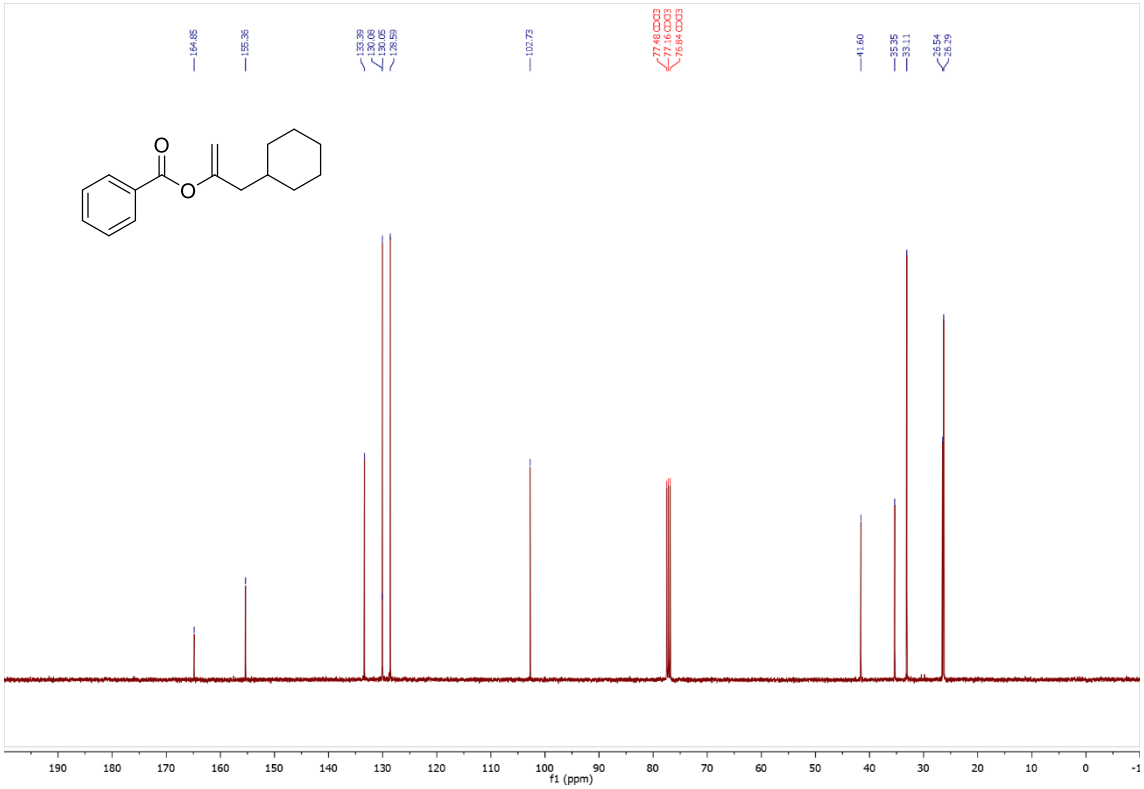
1-Cyclopentylvinylbenzoate, 16w



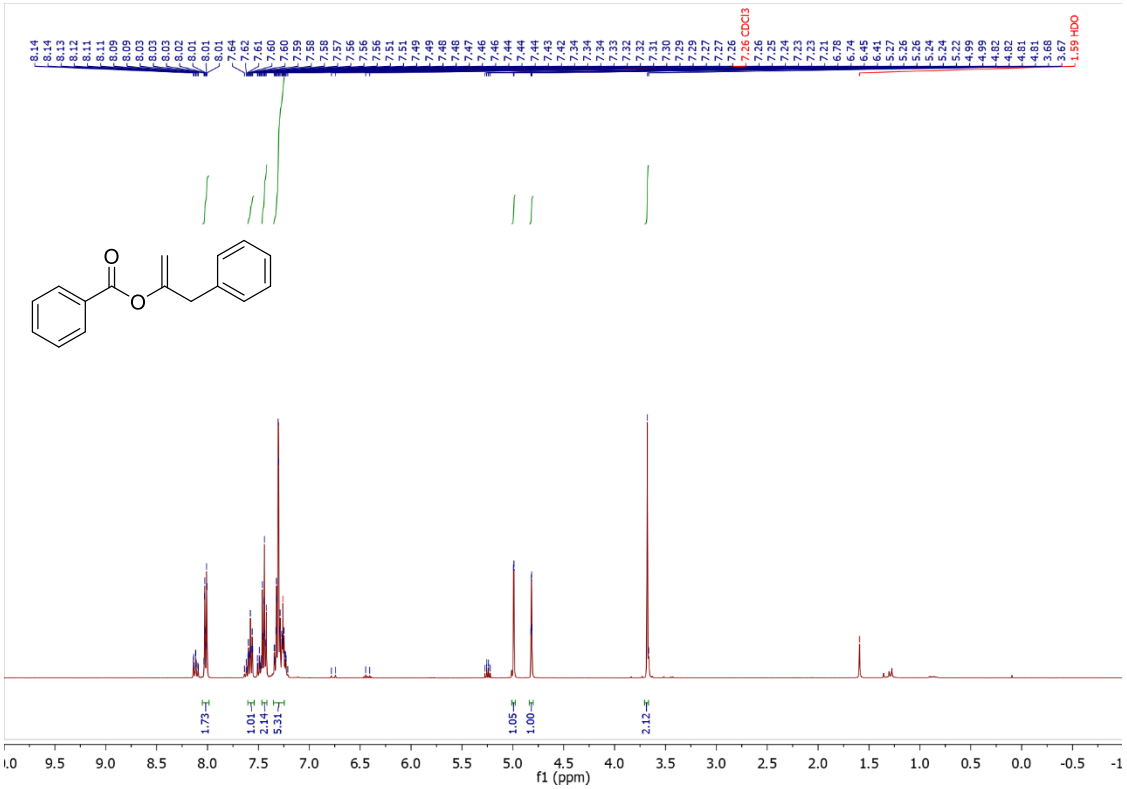


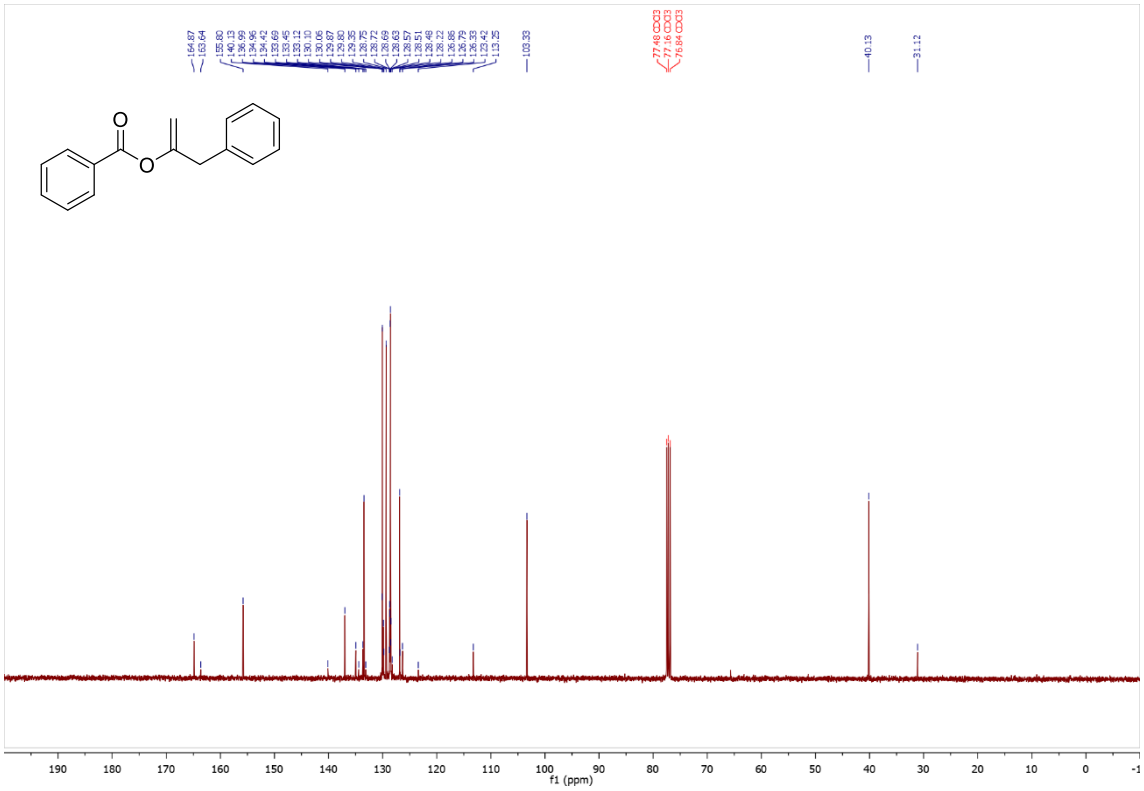
3-Cyclohexylprop-1-en-2-ylbenzoate 16x



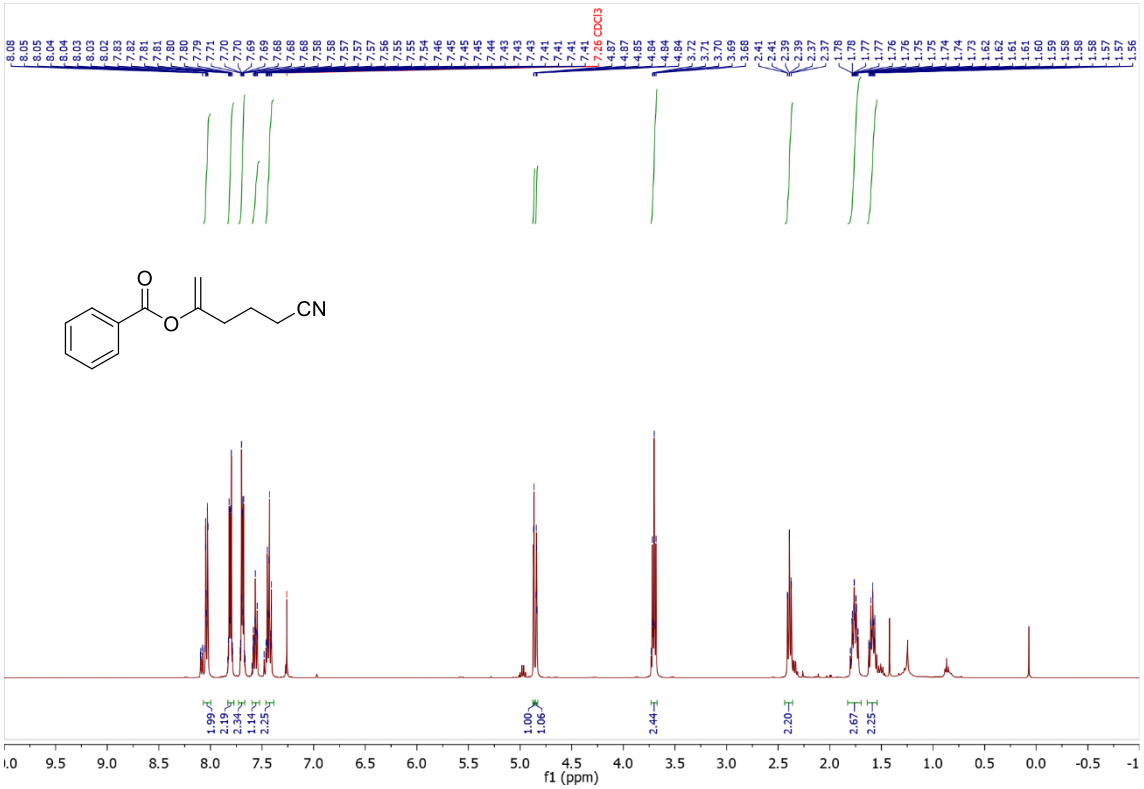


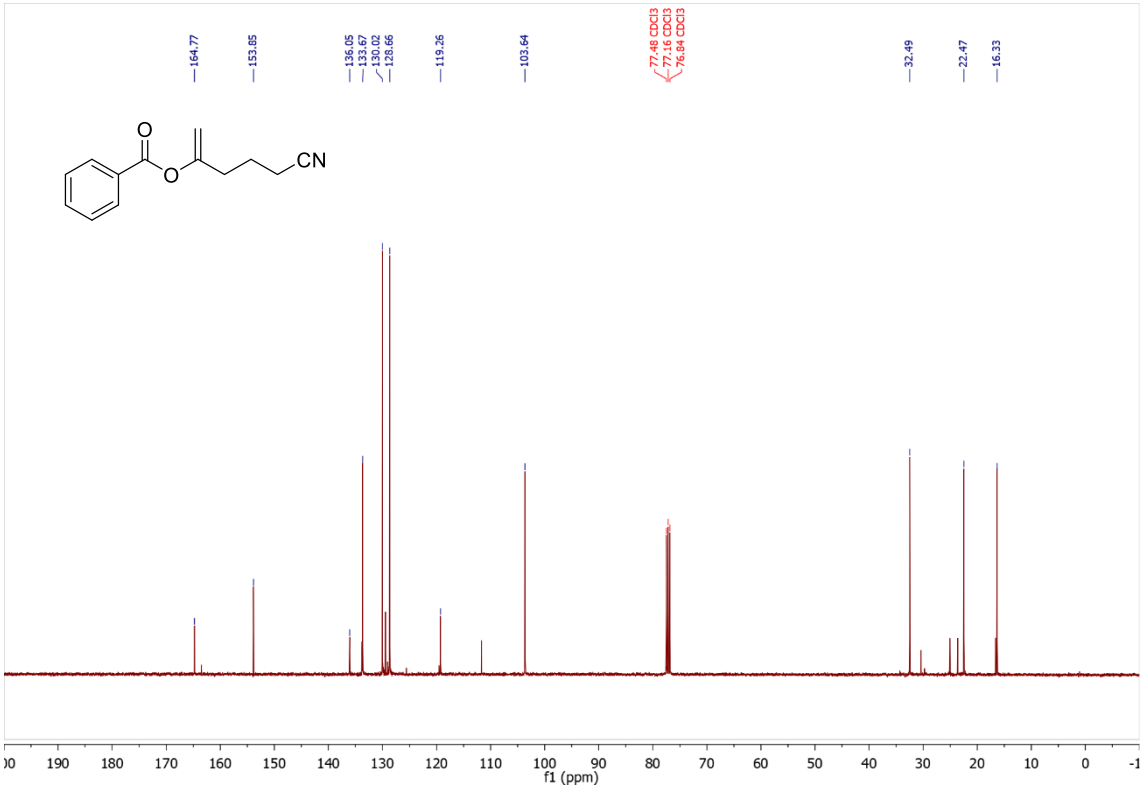
3-Phenylprop-1-en-2-ylbenzoate, 16y



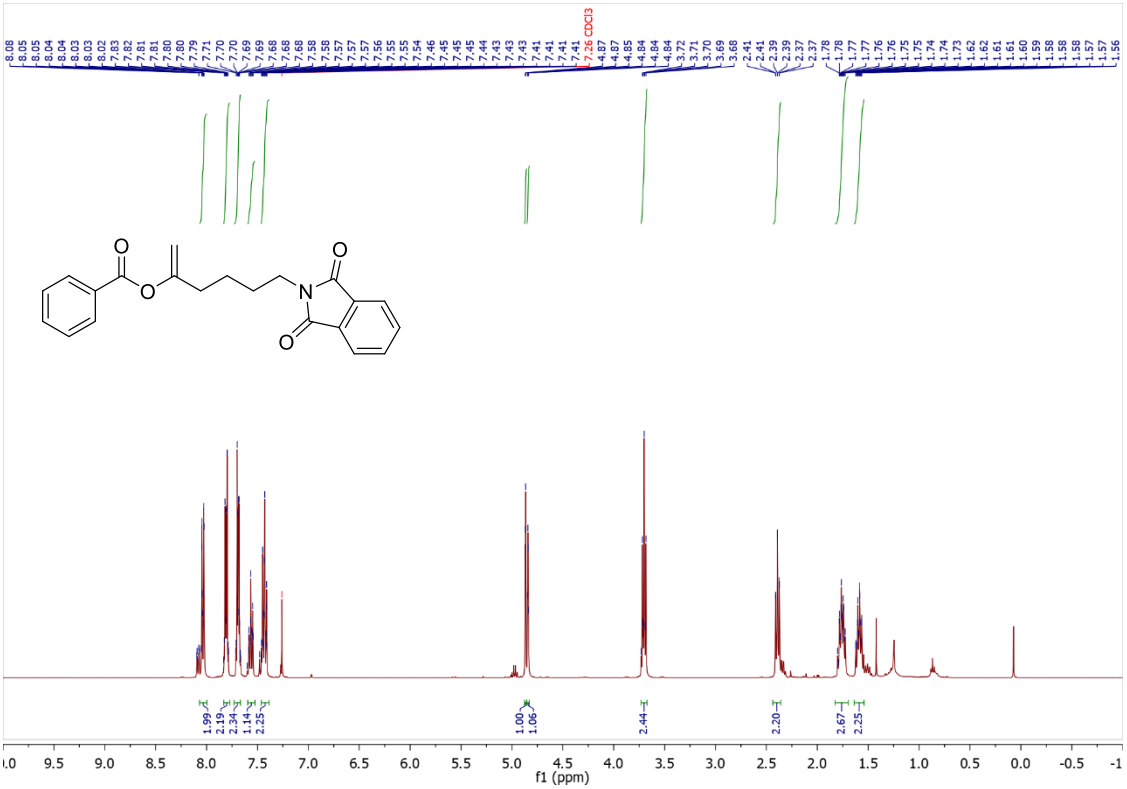


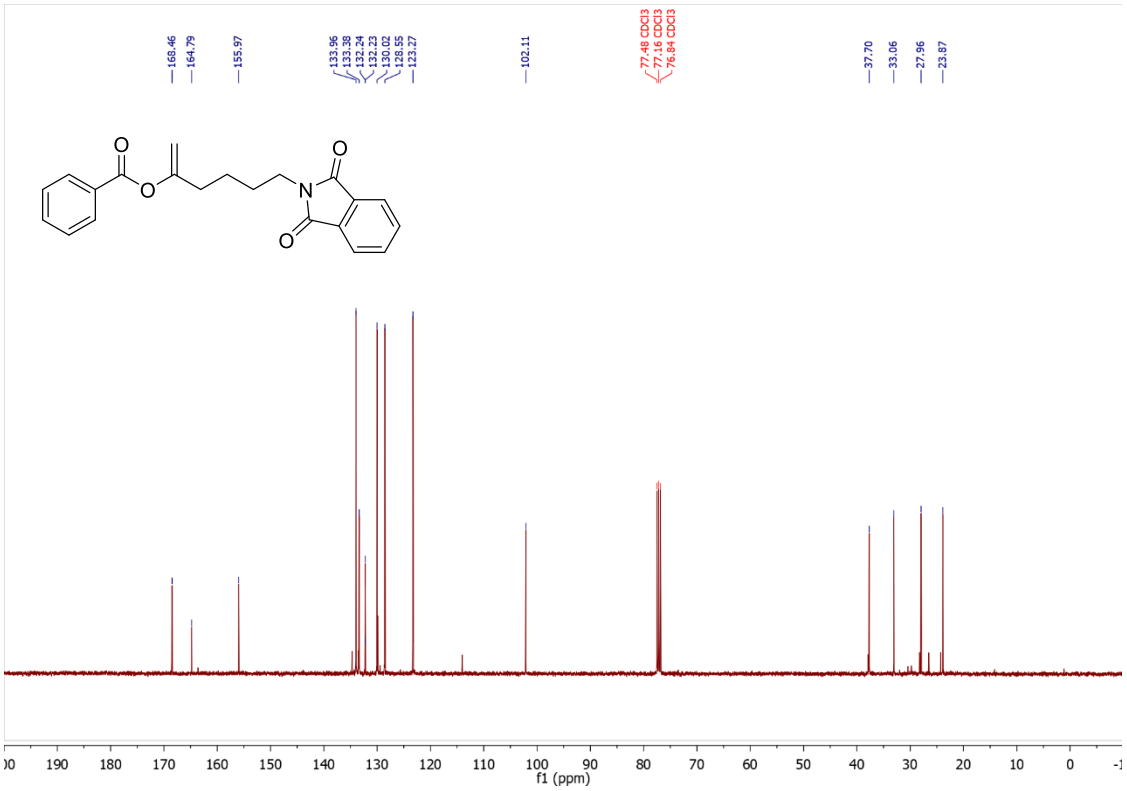
5-Cyanopent-1-en-2-ylbenzoate, 16z



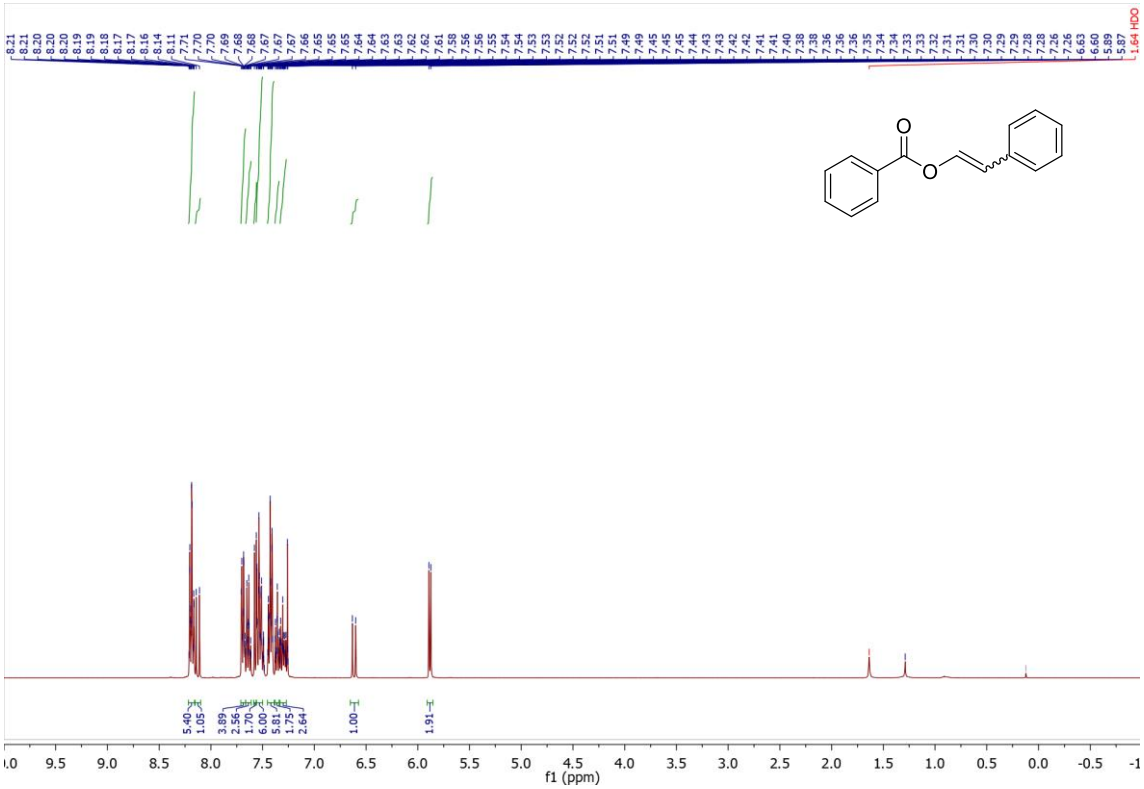


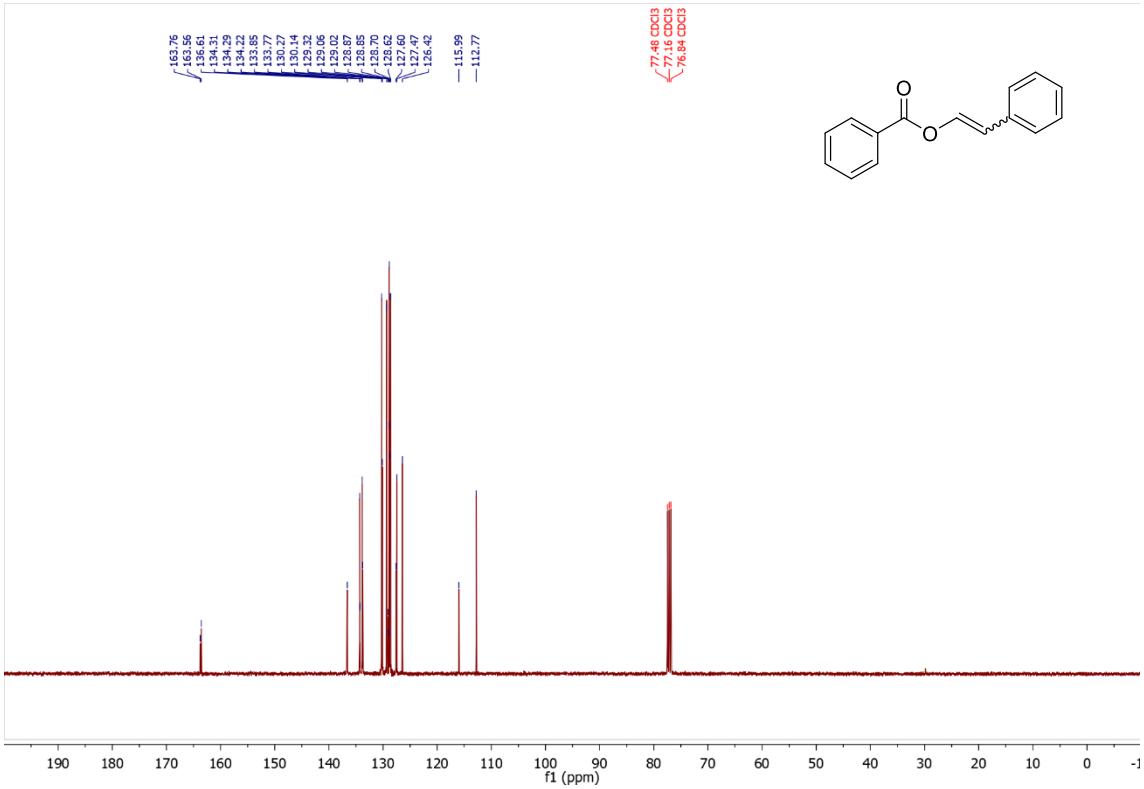
6-(1,3-Dioxoisoindolin-2-yl)hex-1-en-2-ylbenzoate, 16aa



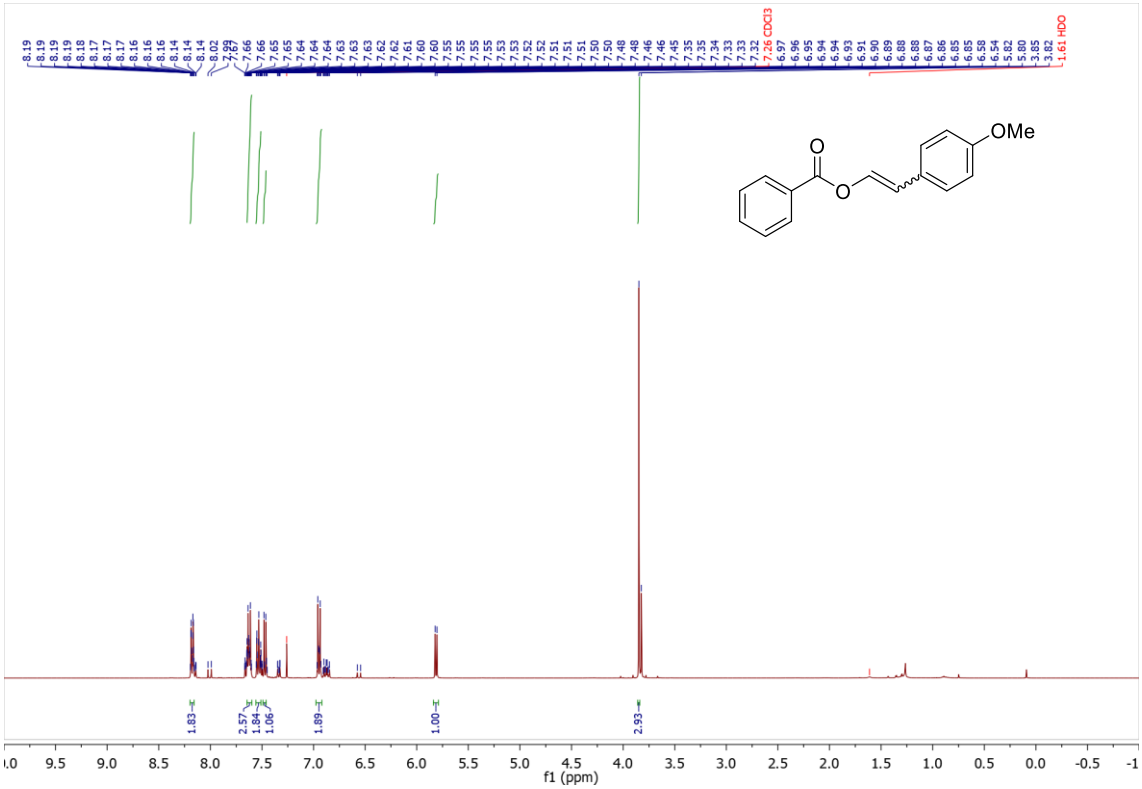


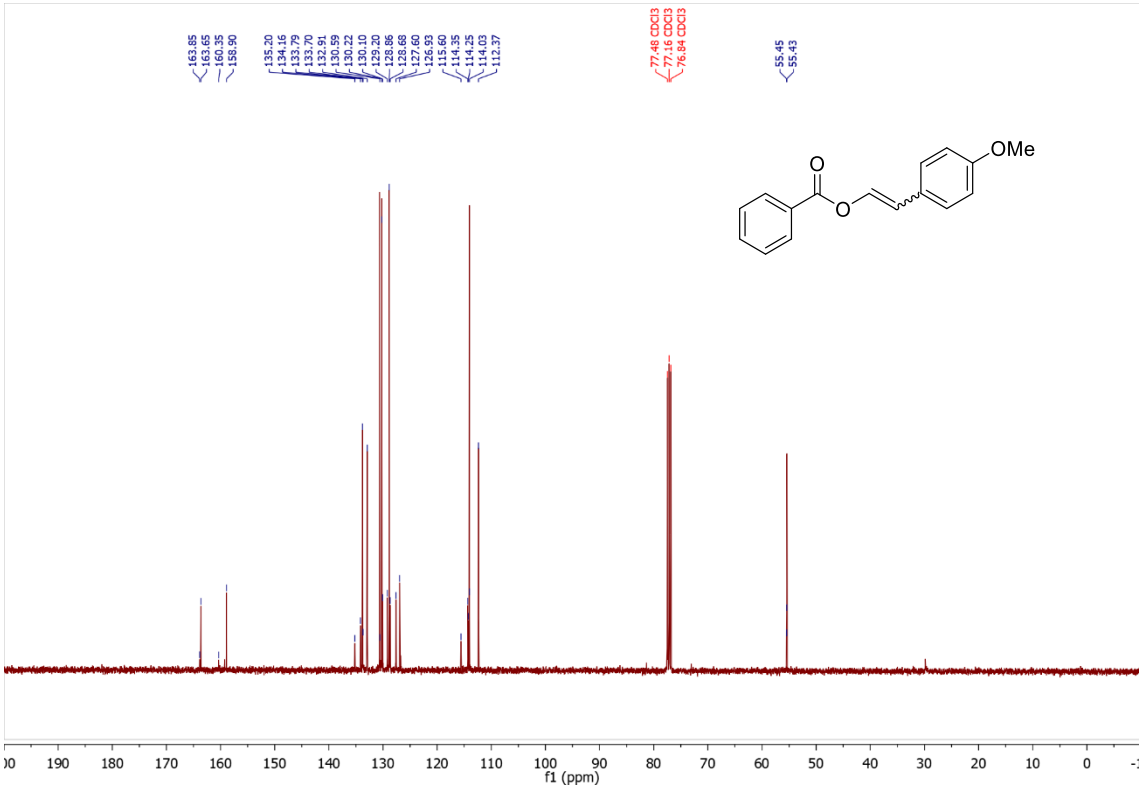
Styrylbenzoate, 17ab



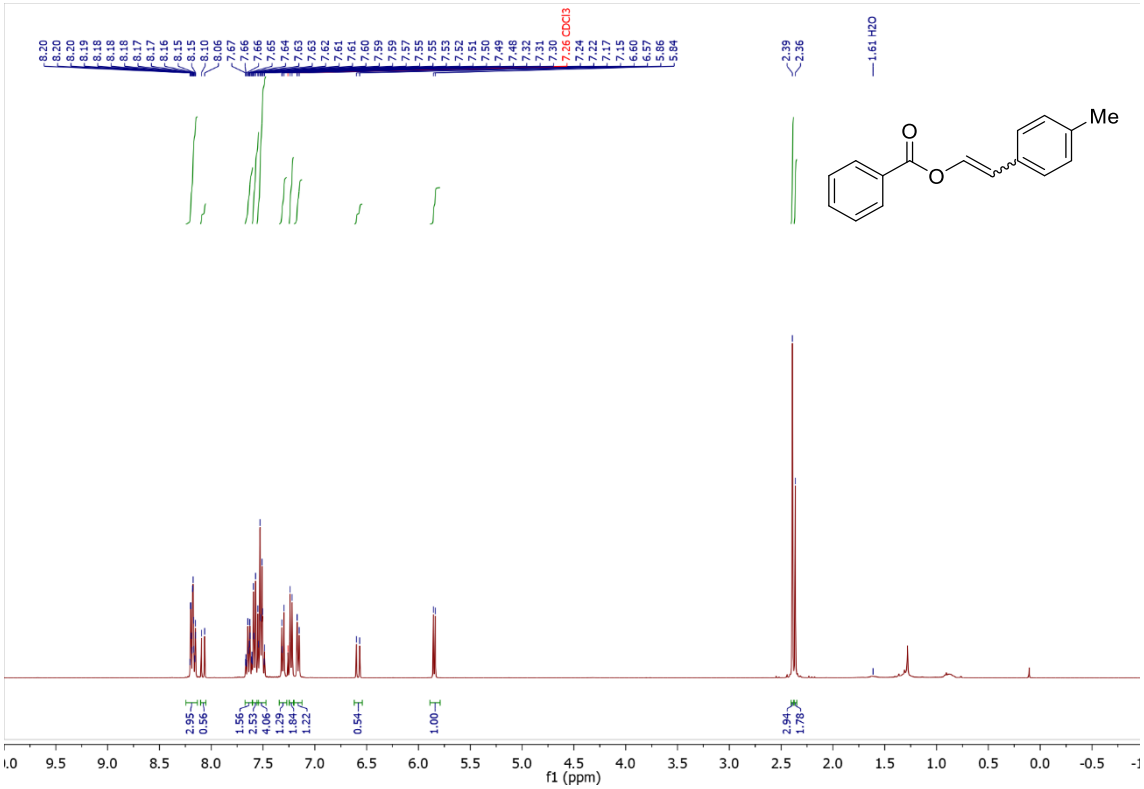


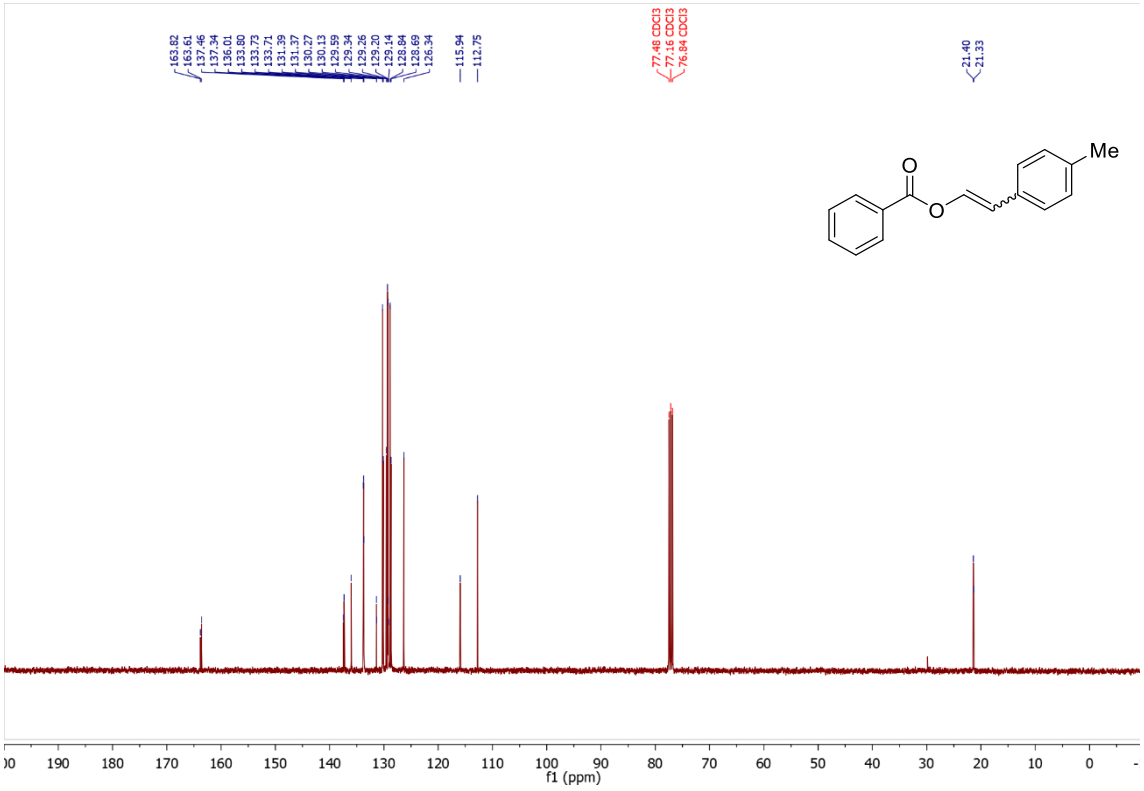
4-Methoxystyrylbenzoate, 17ac



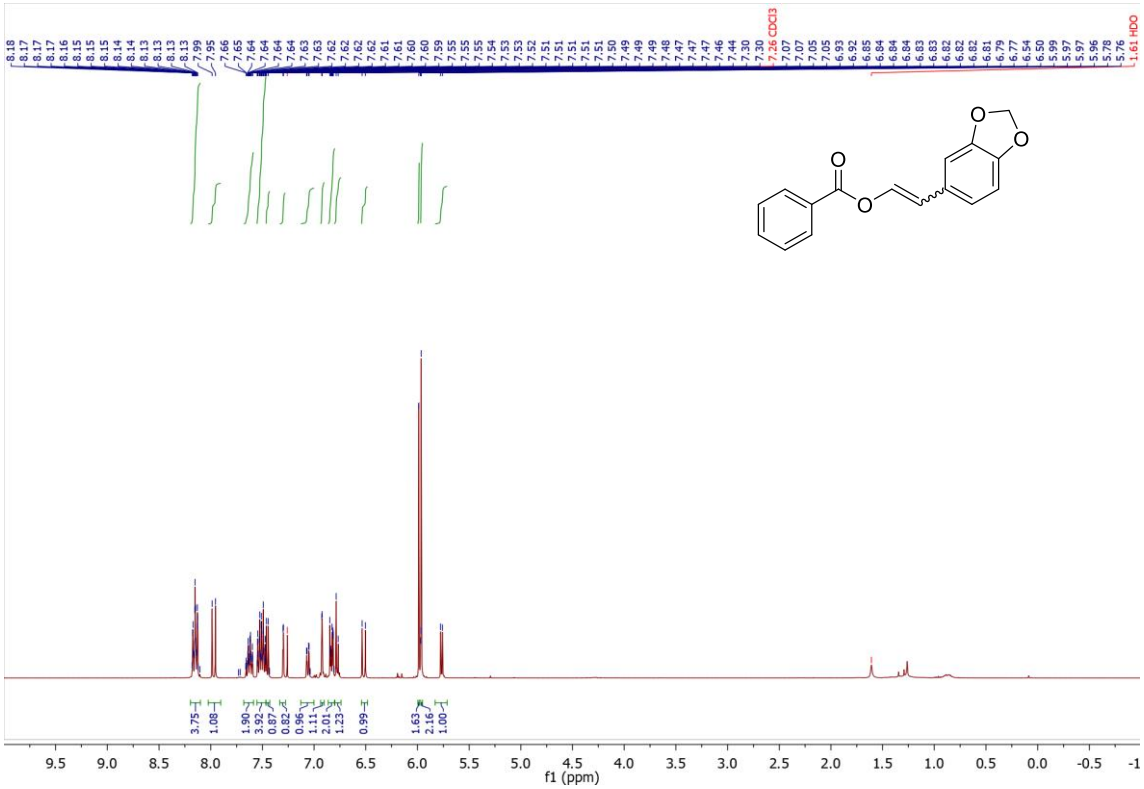


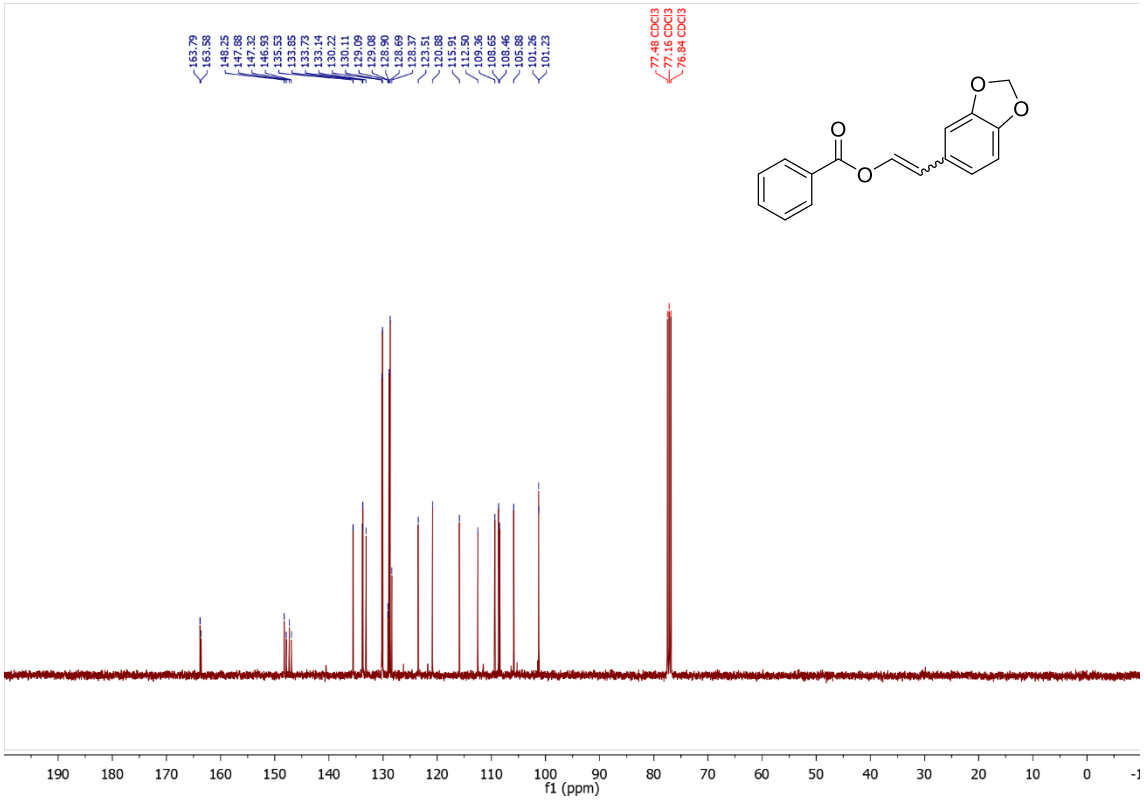
4-Methylstyrylbenzoate, 17ad



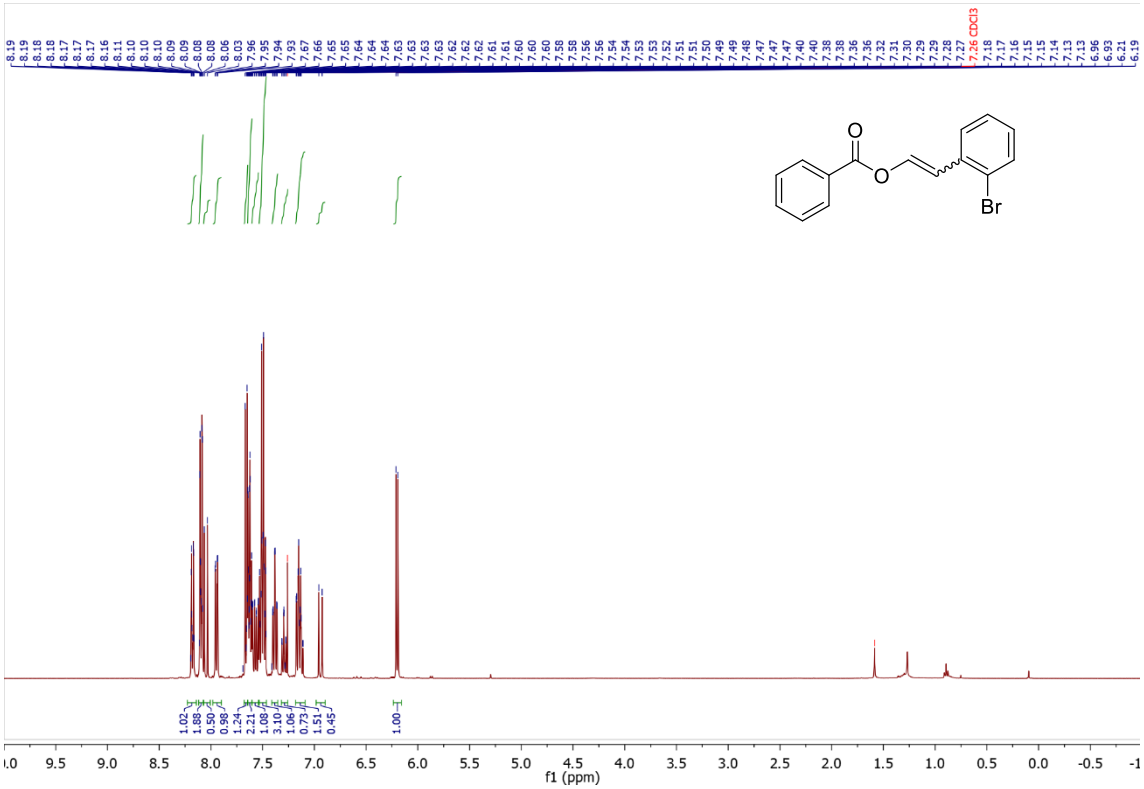


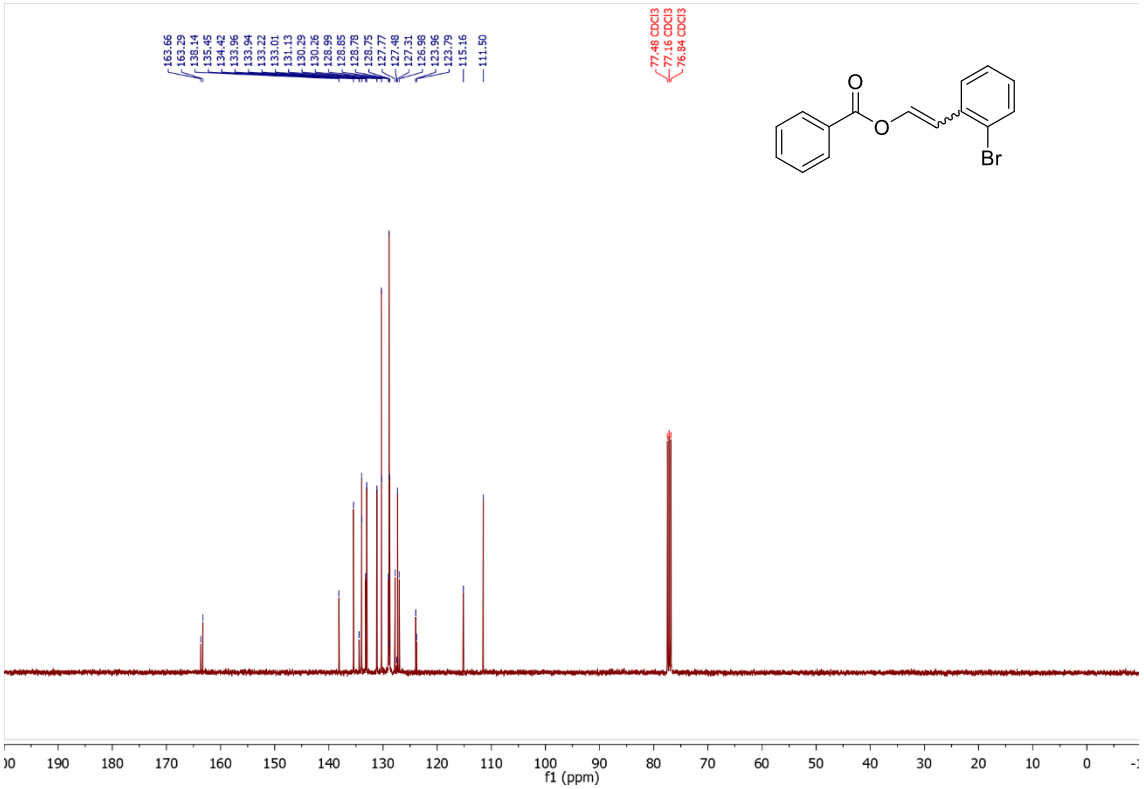
2-(Benzo[*d*][1,3]dioxol-5-yl)vinylbenzoate, 17ae



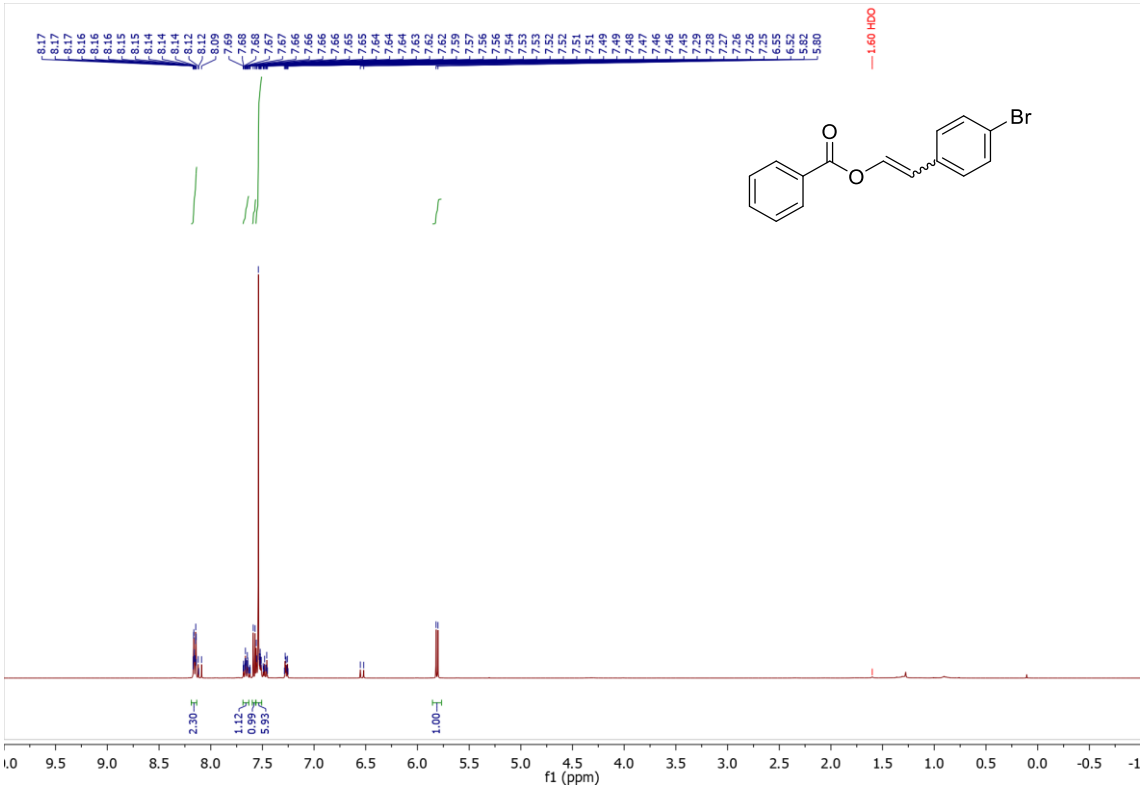


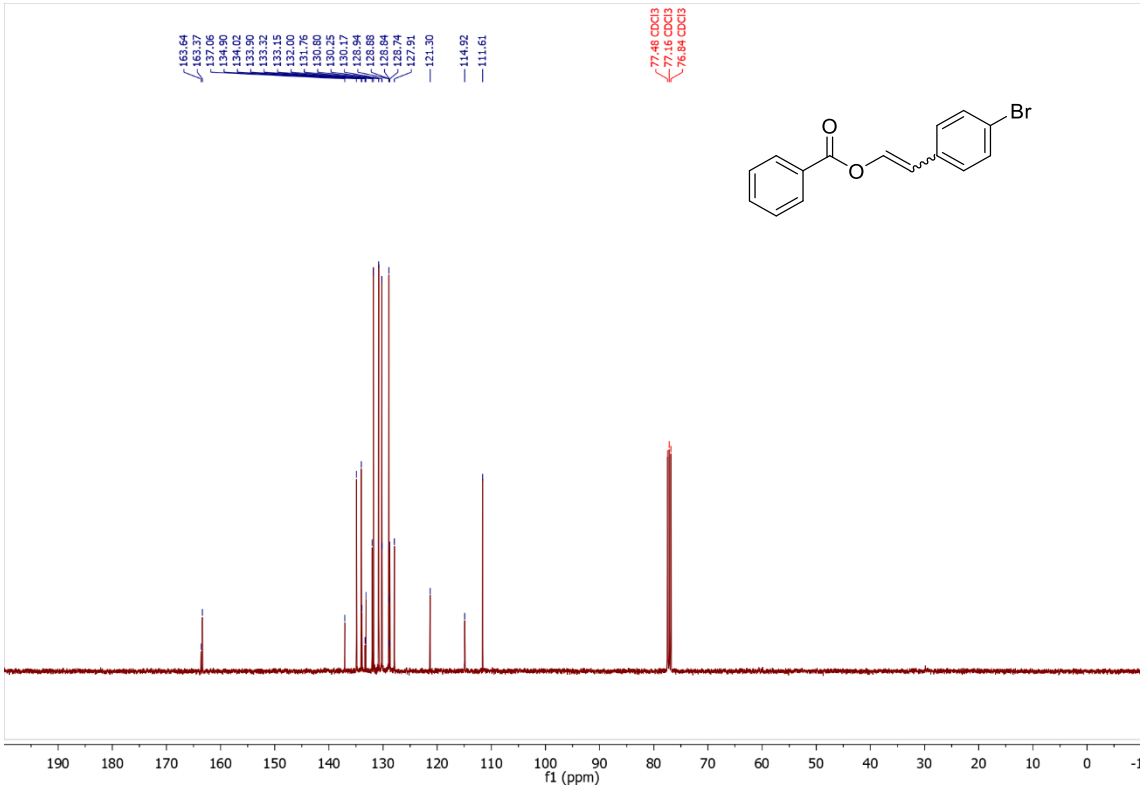
2-Bromostyrylbenzoate, 17af



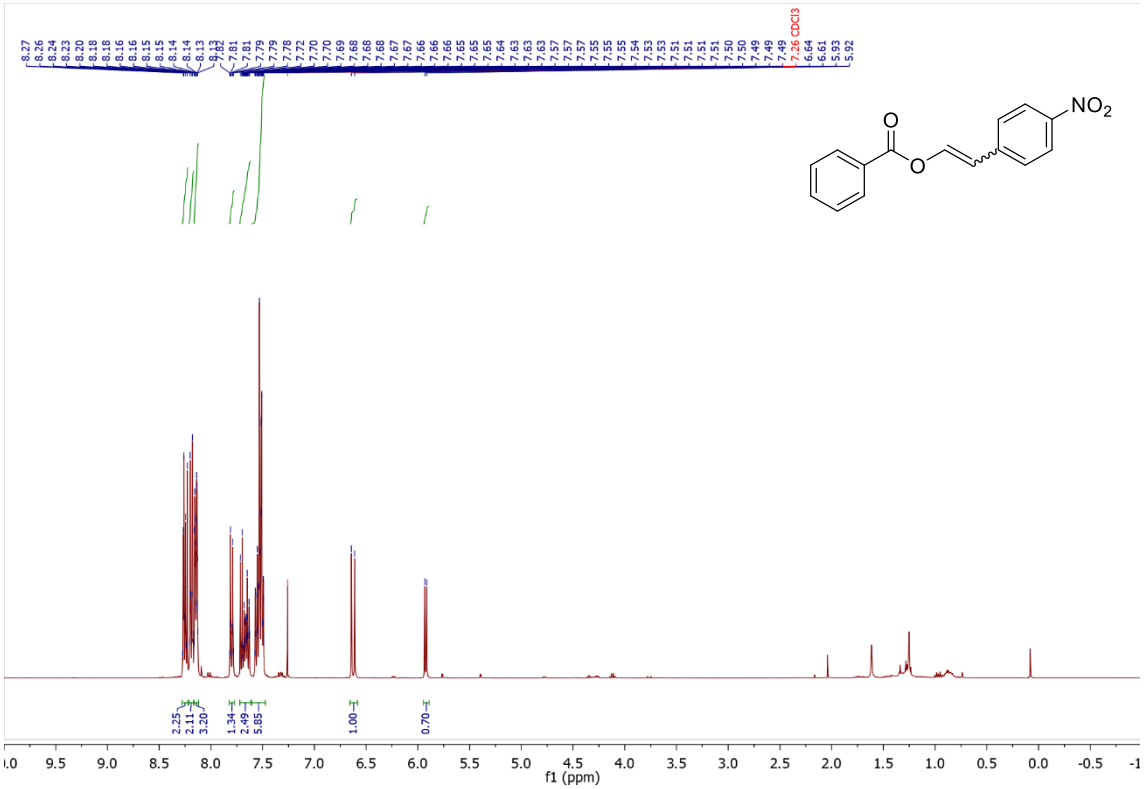


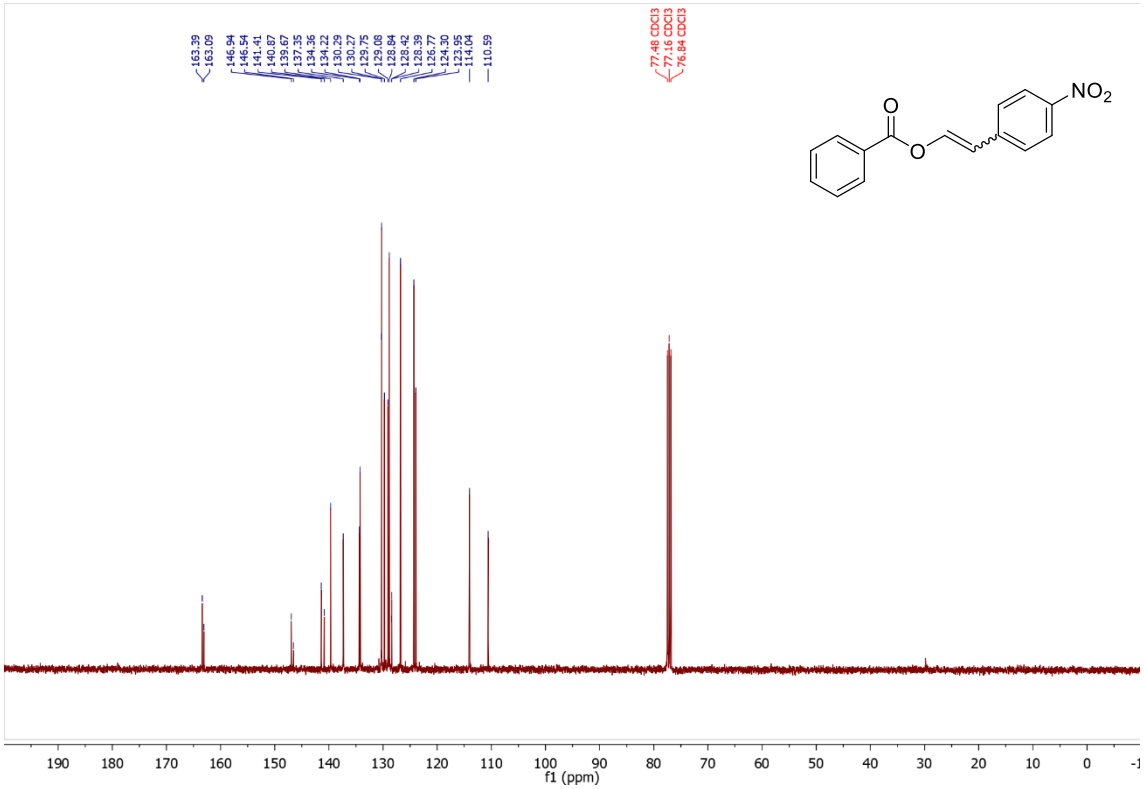
4-Bromostyrylbenzoate, 17ag



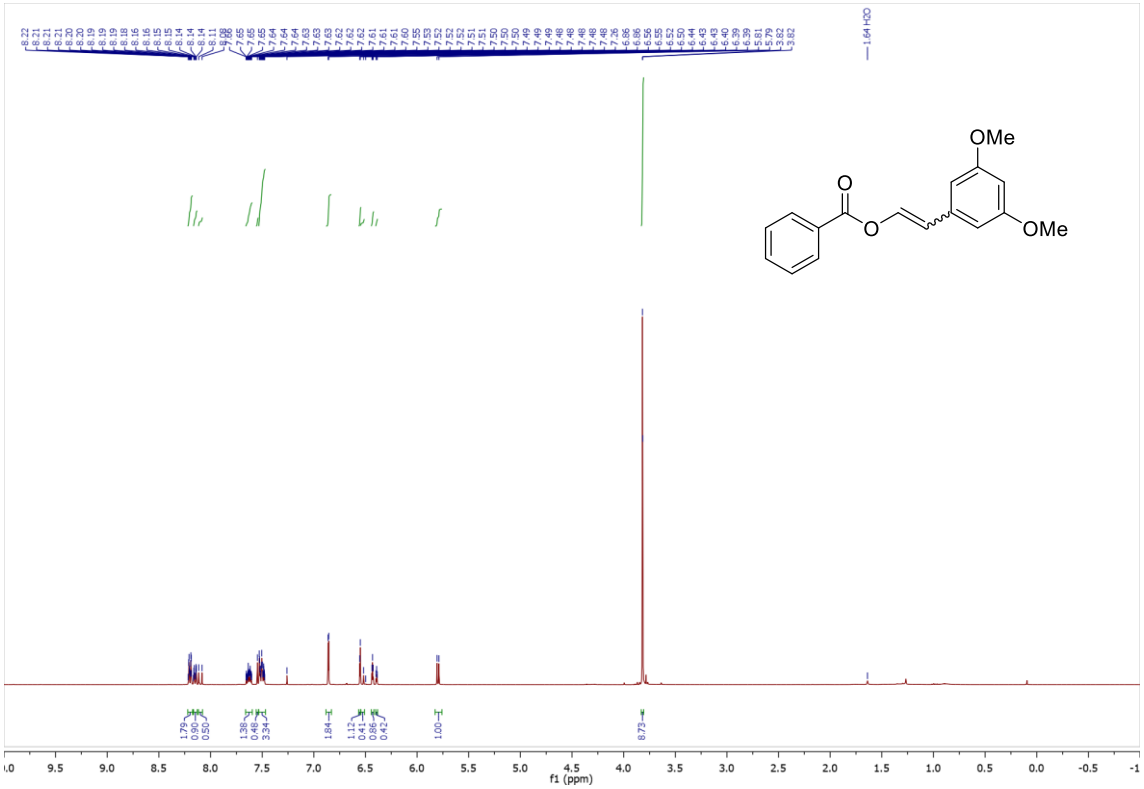


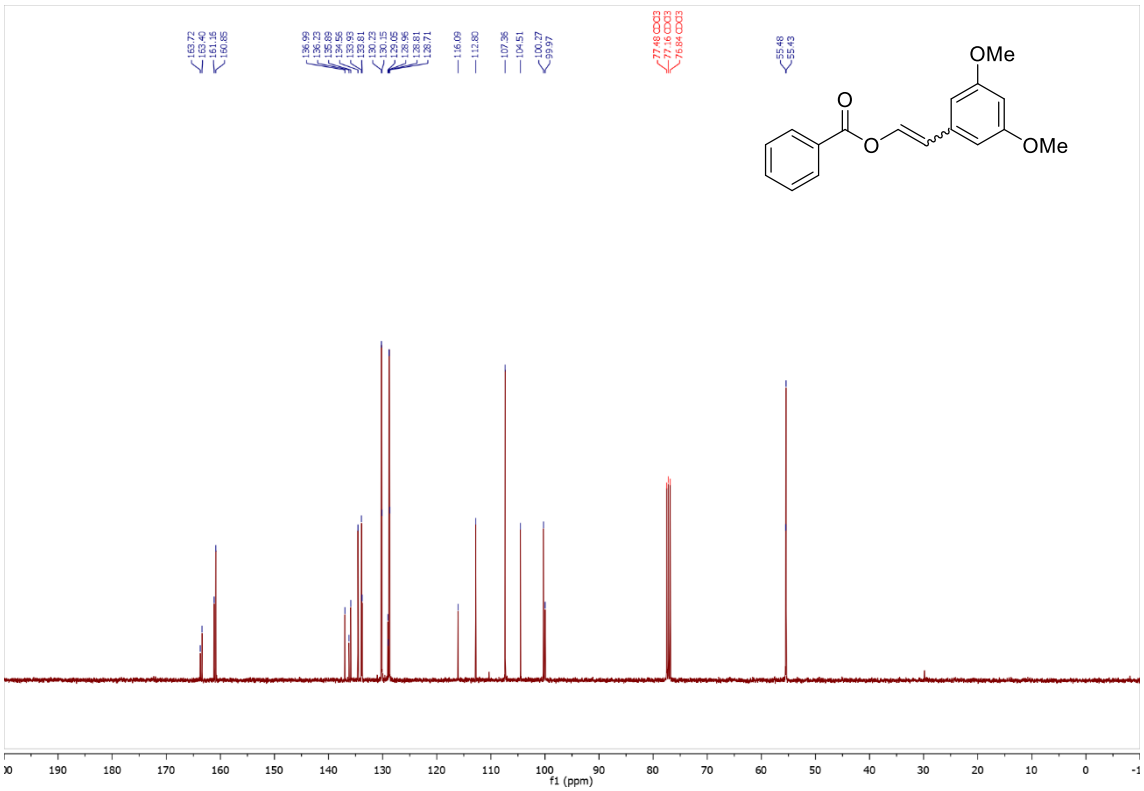
4-Nitrostyrylbenzoate, 17ah



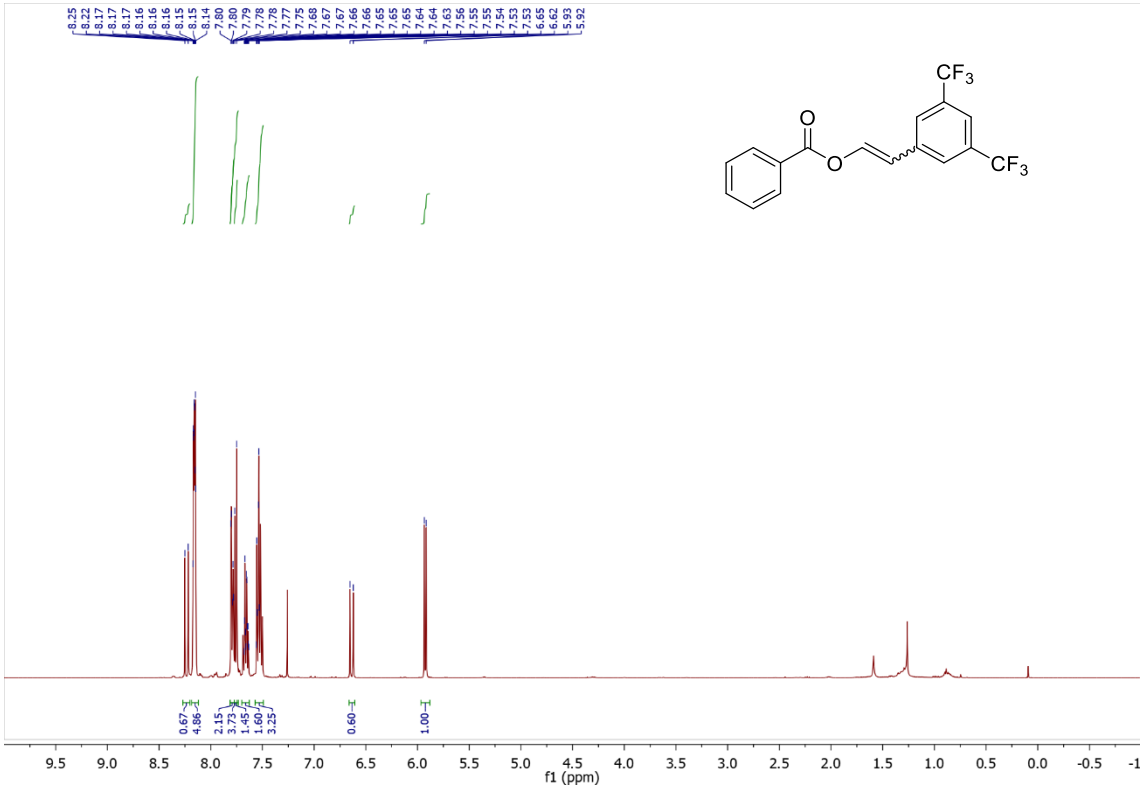


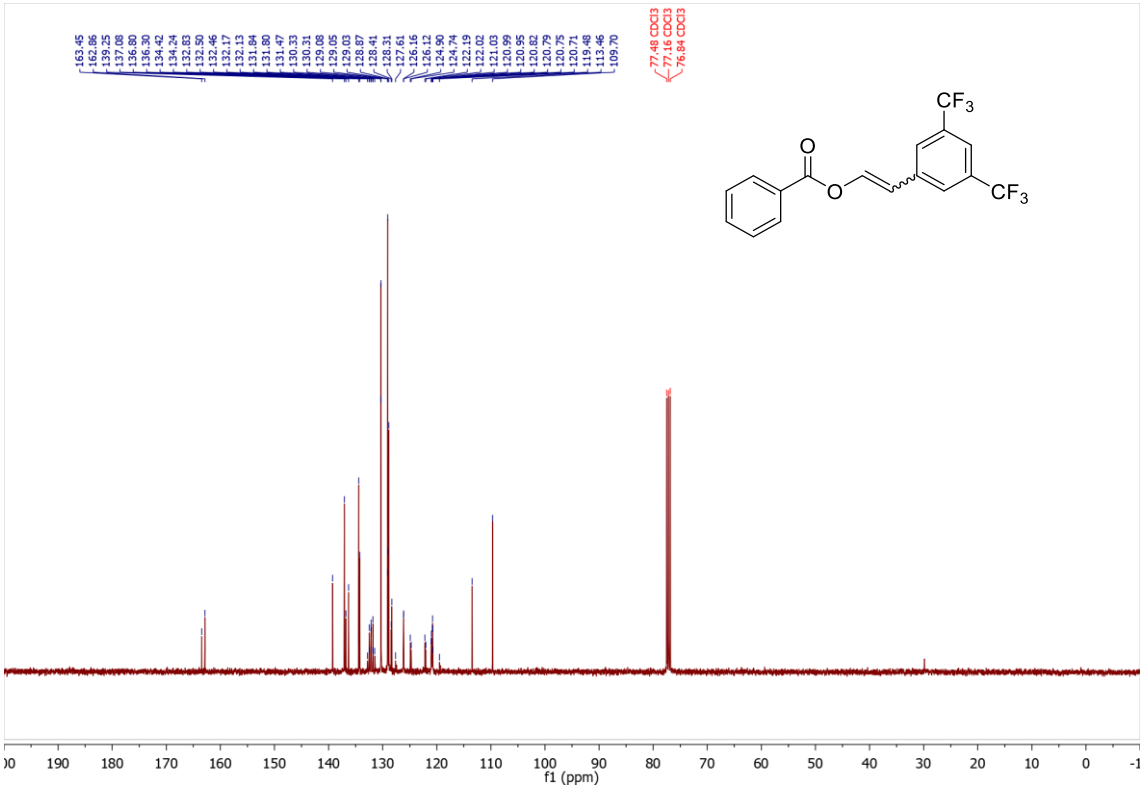
3,5-Dimethoxystyrylbenzoate, 17ai



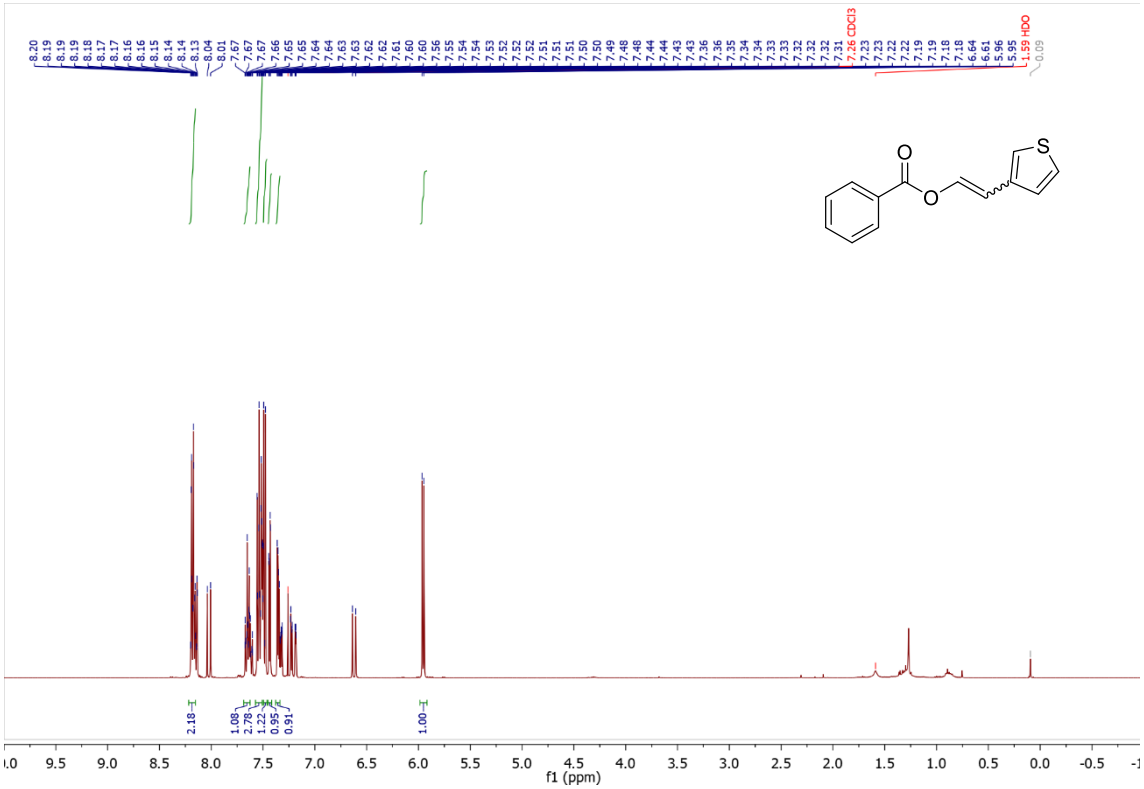


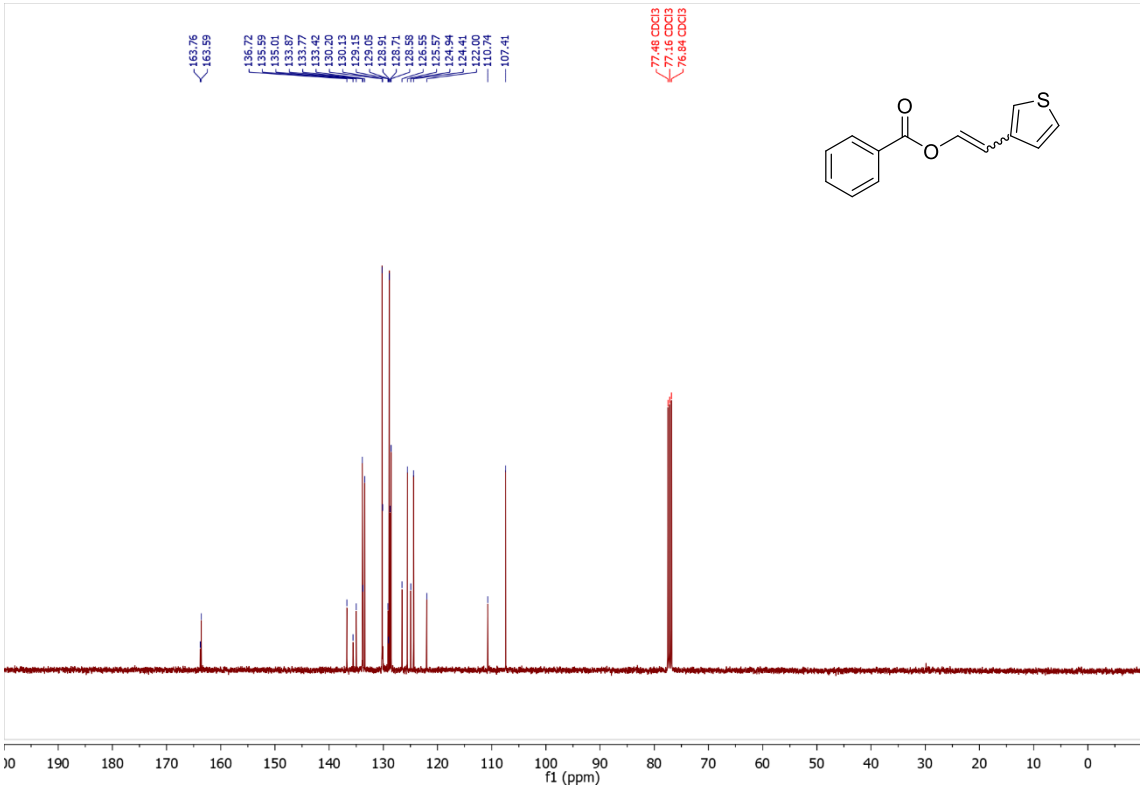
3,5-Bis(trifluoromethyl)styrylbenzoate, 17aj



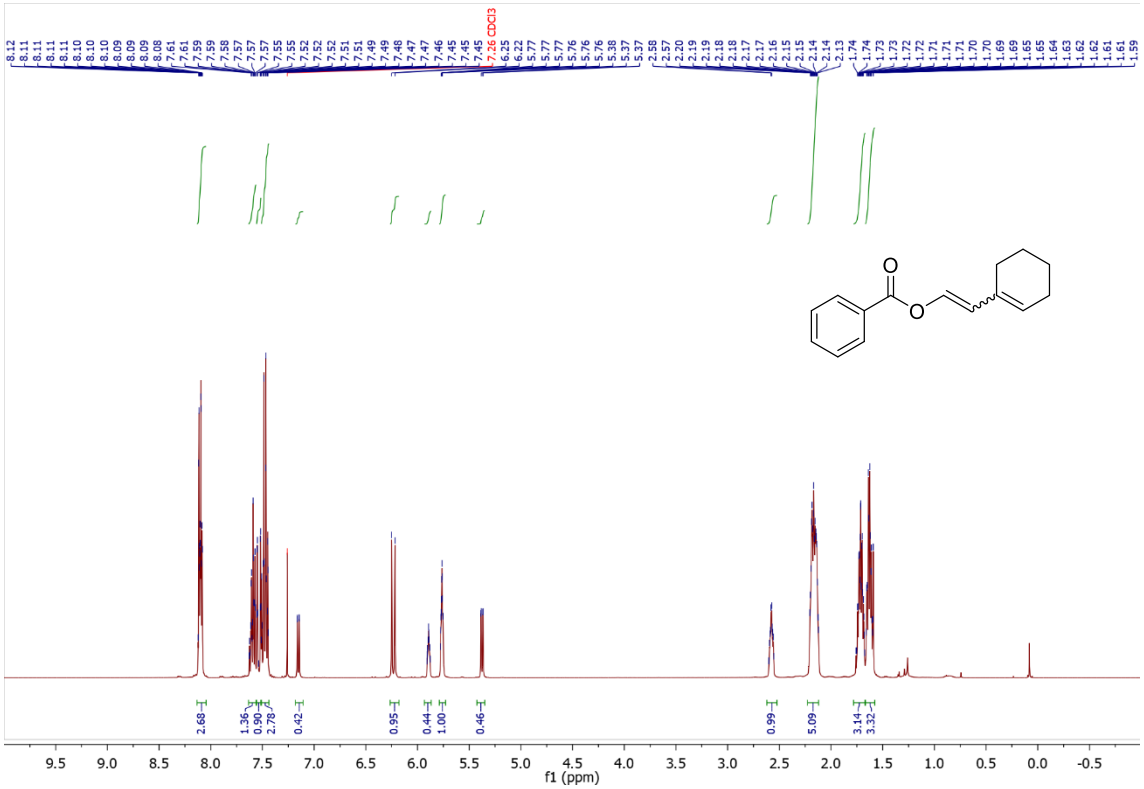


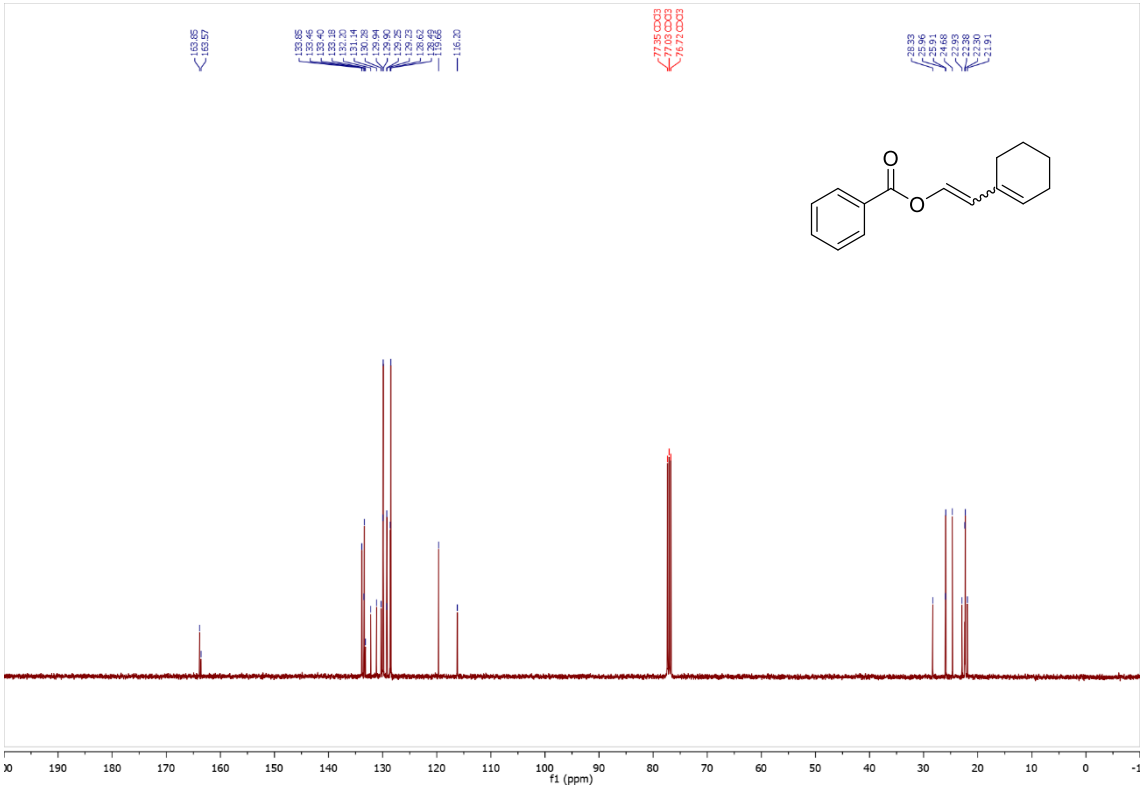
2-(Thiophen-3-yl)vinylbenzoate, 17ak



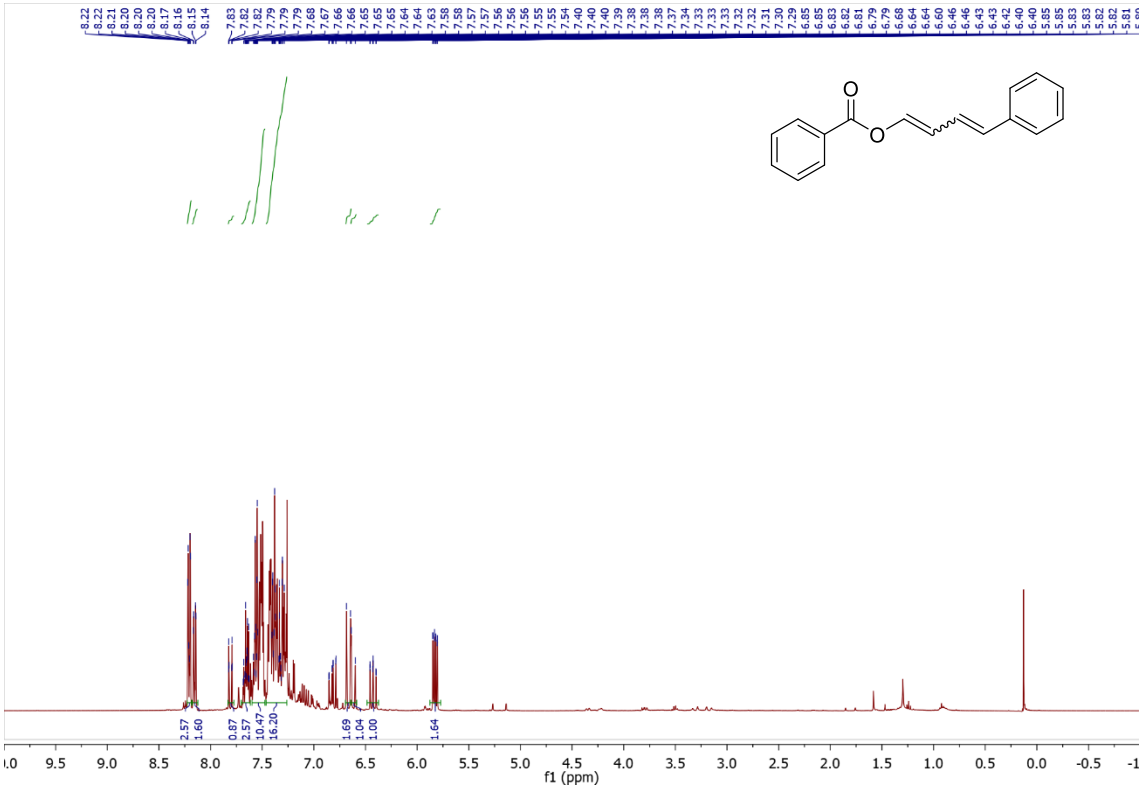


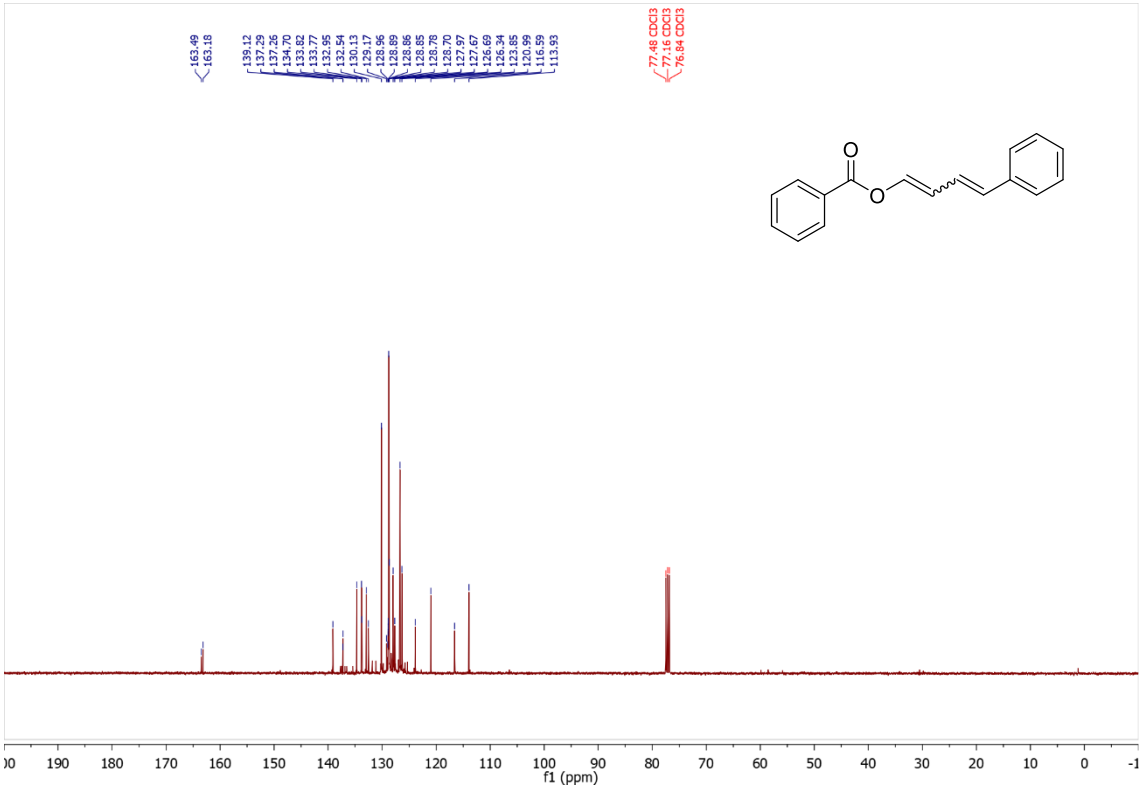
2-(Cyclohex-1-en-1-yl)vinylbenzoate, 17al



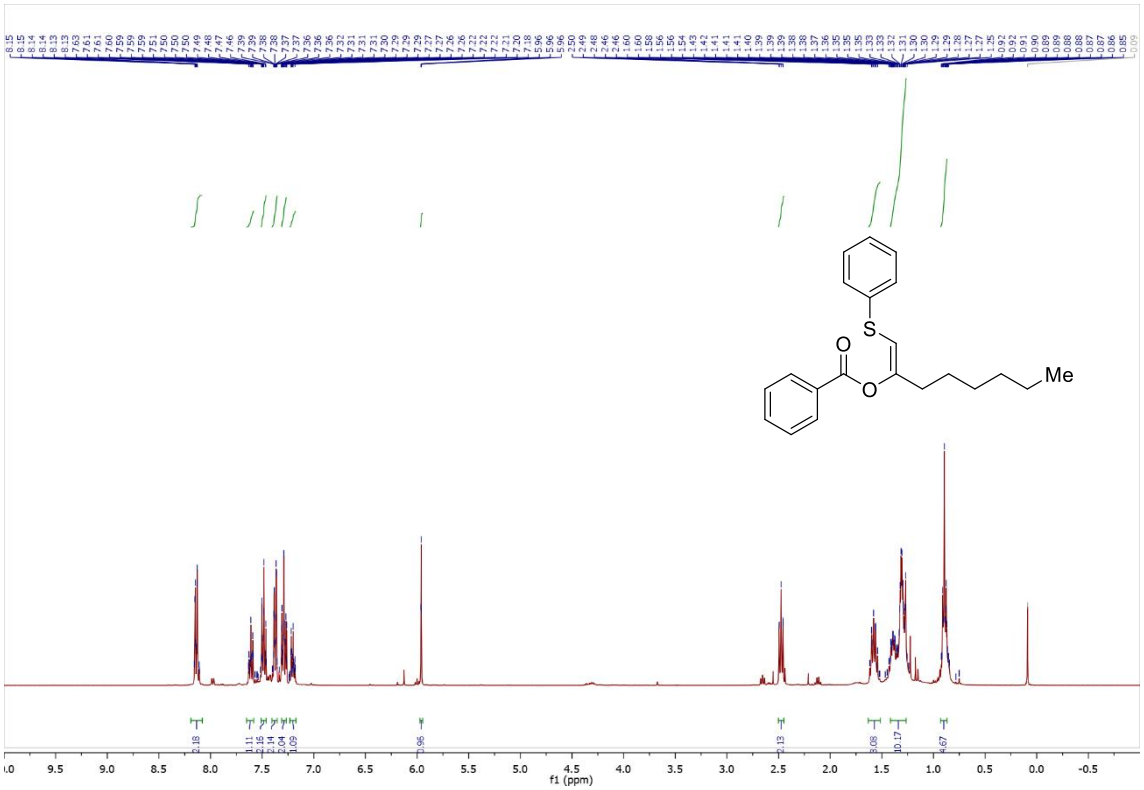


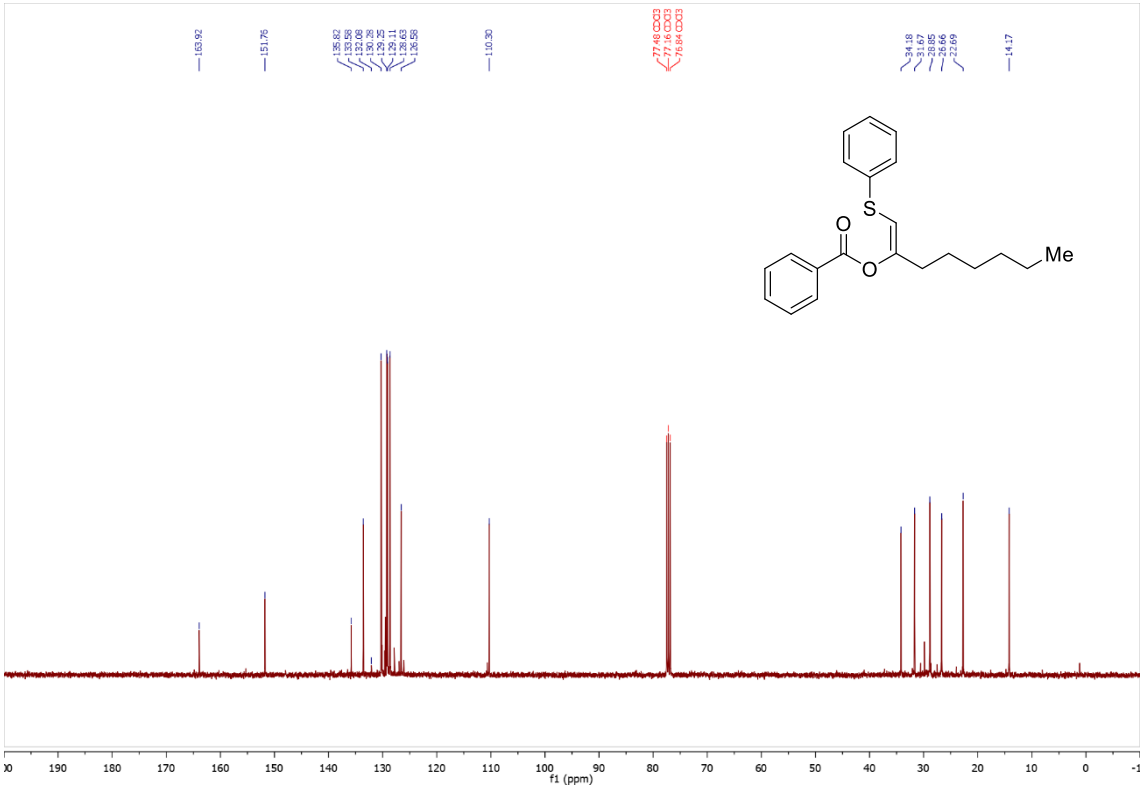
4-Phenylbuta-1,3-dien-1-ylbenzoate, 17am



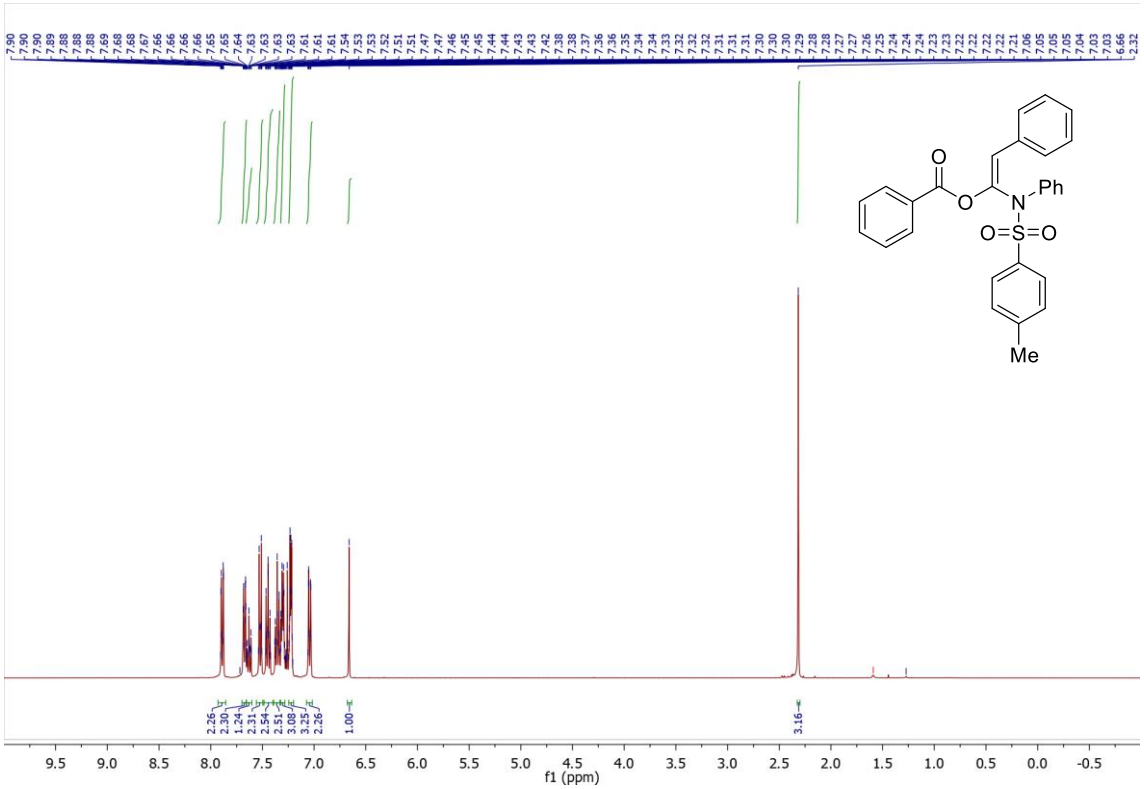


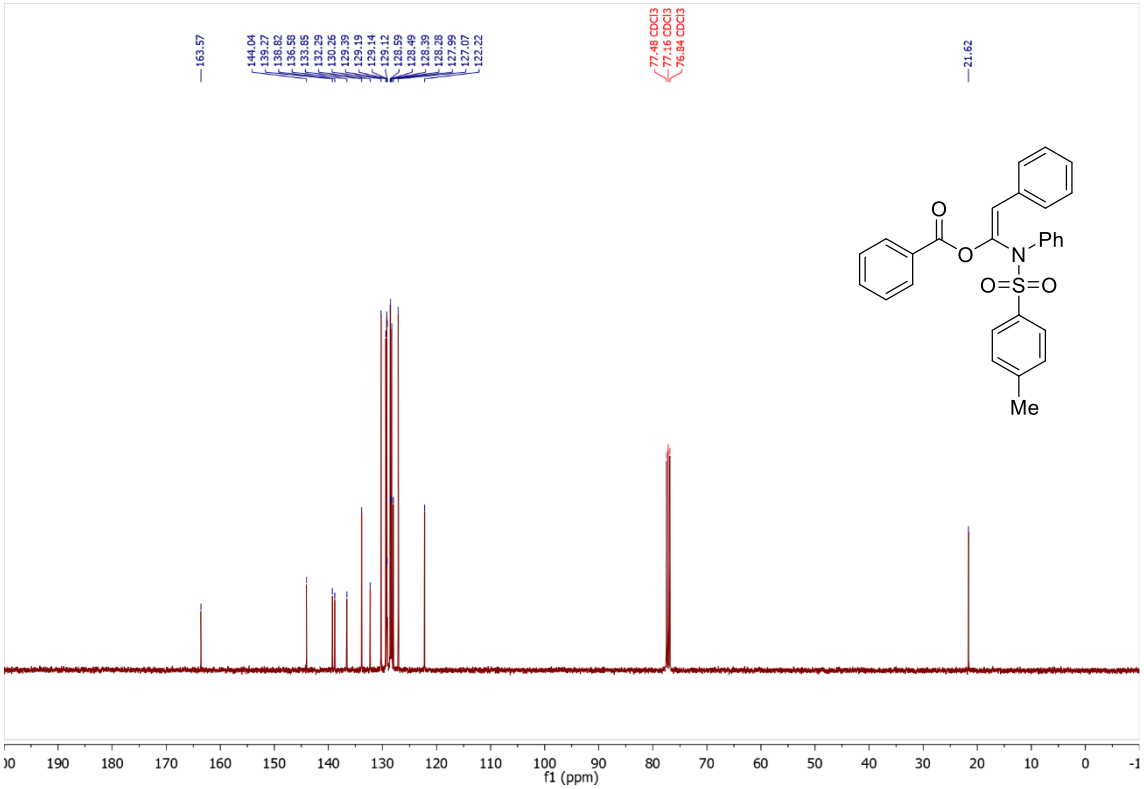
(*Z*)-1-(Phenylthio)oct-1-en-2-ylbenzoate, 20





(*E*)-1-((4-methyl-*N*-phenylphenyl)sulfonamido)-2-phenylvinylbenzoate, 22





(*Z*)-1-(phenylsulfonyl)oct-1-en-2-yl benzoate, 24

