

Development of Phase Transfer Catalysed amidation and cyclisation reactions

A thesis for the degree of Doctor of Philosophy

Presented to

The Royal College of Surgeons in Ireland

By

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Ph.D.

2018

Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree of Doctor of Philosophy (Ph.D.), is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed _____

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Date _____

Acknowledgments

First of all I would like to thank my supervisor Prof. Mauro Adamo, who gave me the opportunity to work in his group and provided inspiration and priceless advice, which I will treasure all over my professional career.

I would also like to thank Sir. Mauro Cortigiani, whose knowledge and friendship accompanied me throughout these three years.

I wish to thank IRC for funding my Ph.D. and all the members of the Department of Pharmaceutical and Medicinal Chemistry. In particular, thanks to Dr. Darren Griffith, for having been my examiner in many occasions.

I would also thank all my laboratory mates: Stefano Lancianesi, Eider Badiola, Sara Fradera, Alberto Tampieri, Cinzia Grotto, Reece Kenny, Elisa Floriddia, Emmet Campion, Fabio Serra, Paula Scopetta, Chiara Strinna, Graeme Kelly, Suzanne Donnelly, Dan Wu, Harrison Daly, Umberto Pennè, Gonzalo Duran, Scott McKay, Aoife McKeon, Federico Lucantoni, Salvatore Spina, Anna Maio, Muhammad Haris, Rosita Bellavita, Ilaria Biancofiore, Hasim Ibrahim, Emanuela Mandic, Roberta Pacifico, Deborah Sementa, Francesco Alletto, Grazia Bencivenni, Andrea Zandrini.

In particular I would like to thank Claudio Monasterolo, Federica Torri, Ziga Ude, Diana Salazar, Claudia Del Fiandra, Andrea Ravelli, Elena Bobbi, Donal Keogan, Eolan Kitteringham (Eooo Oh Oh), Caterina Cioffi, Rosaria Spina, who shared with me countless funny moments.

Thanks to Andrea Locatelli, for being like a brother.

Thanks to Valerio Piacenti, for our blissful jam sessions and all the good time together.

Thank you Ludovica Ferrari for your patience and dedication: we still have our scented project to finish.

Thank you Carlo Bottinelli for your invaluable help: a big herd needs a skilful shepherd.

Thanks to Daniele Canestrari, for having paid for my night updates, I would not be 3.0 without his contribution.

Thank you Martina Costanzo, for trying to correct my improper behaviour, I will take care of our entomological collection.

I would also like to thank my family, Elena, Daniele and Giulia, who always supported me from far away, giving me strength and unconditional love.

And finally, my biggest thanks go to Sandra Best Assistant, to whom I dedicate this thesis, because she is the one who brightens up my life, noisily.

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Abbreviations

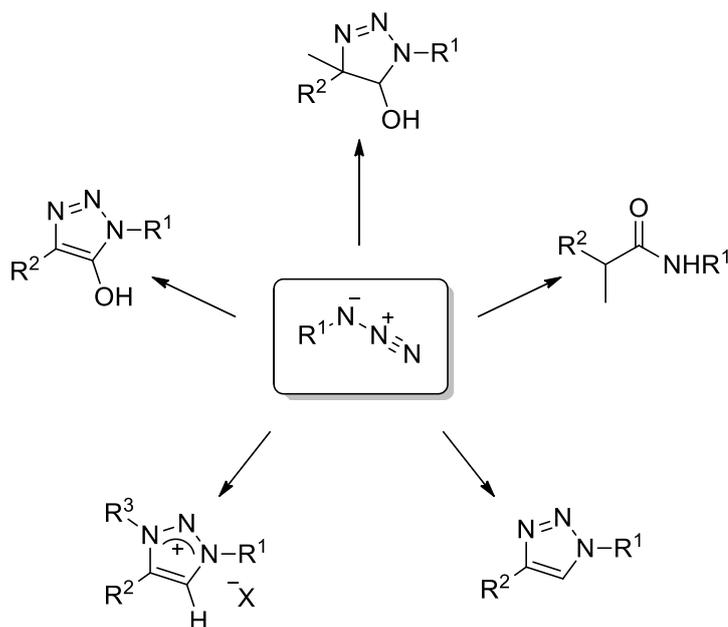
mol%	mole percent
$[\alpha]_D$	specific rotation
Ac	acetyl
ACN	acetonitrile
Act	activating group
aq	aqueous solution
Ar	aryl
BINOL	1,1'-bi-2,2'-naphthol
Boc	<i>tert</i> -butylcarbonyl
Bu	butyl
CDI	carbonyldiimidazole
conv.	conversion
CPME	cyclopentyl-methyl ether
CuAAC	copper-catalysed Azide-Alkyne Cycloaddition
DABCO	(1,4-diazabicyclo[2.2.2]octane)
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -dimethylaminopyridine
DMSO	dimethylsulfoxide
<i>dr</i>	diastereoisomeric ratio
ED	electron-donating group
eq.	molar equivalents
Et	ethyl
EWG	electron withdrawing group

Fmoc	fluorenylmethyloxycarbonyl
HMBA	hexamethylene bisacetamide
HPLC	High Performance Liquid Chromatography
<i>i</i> -Pr	<i>iso</i> -propyl
IR	infra-red
K _a	association constant
LDA	lithium diisopropylamide
<i>m</i>	<i>meta</i>
Me	methyl
MELC	murine erytroleukemia cell
mmol	millimoles
mol%	molar percentage
MTBE	methyl- <i>tert</i> -butyl ether
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	phenyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
Proton-sponge	1,8-bis(dimethylamino)naphthalene
PTC	phase transfer catalyst
<i>q</i> NMR	quantitative Nuclear Magnetic Resonance
R _f	retention factor
RT	room temperature
SAHA	suberanilic hydroxamic acid

SNAr	nucleophilic aromatic substitution
TBAB	tetrabutylammonium bromide
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TMU	tetramethylurea
TLC	thin layer chromatography
Tol	tolyl, 4-methylphenyl
tosyl	<i>p</i> -toluenesulfonyl
UV	ultraviolet

Aims

The purpose of this work is the discovery and development of new catalytic methodologies towards the synthesis of amides and cyclic compounds, with the aid of phase transfer reagents. In particular, it is focused on triazocyclic compounds, which are conveniently obtained by the reaction of organic azides with enolates, or by copper-catalysed azide-alkyne cycloaddition. Triazocyclic compounds display a wide scope of reactivity, which is still partially unexplored. Finally, we pursue the discovery of innovative applications of 1,2,3-triazoles and 1,2,3-triazolium salts in the field of organocatalysis.



Abstract

Chapter 1

A novel two-step sequence for the preparation of amides starting from azides and enolisable aldehydes. The reaction proceeded via the formation of triazoline intermediates that were converted into amides via Lewis acid catalysis. Preliminary studies on the preparation of triazolines under chiral phase transfer catalysis are also presented, demonstrating that enantioenriched amides could be prepared from achiral aldehydes in moderate to low enantioselectivity.

Chapter 2

The reactivity of ester enolates with organic azides was studied. The condensation of 2-alkylacetoacetic esters with aromatic azides under organic base catalysis provided 5-hydroxy-4-alkyl-1,2,3-triazoles, which showed strong Brønsted acidity. Three anilide-hydroxytriazoles analogue to SAHA were synthesised in order to test their activity as histone deacetylase inhibitors. In a preliminary study, different organocatalysts bearing the 5-hydroxytriazole motif were designed, and several steps towards their synthesis were made.

Chapter 3

A novel stereoselective synthesis of 3,4-dihydropyran-2-ones under phase transfer catalysis is described. The reaction of cinnamic thioesters and acetylacetone was promoted by *Cinchona*-derived quaternary ammonium salts. 3,4-Dihydropyran-2-ones were obtained in good yields and enantioselectivity when the reaction was carried out in the presence of catalytic amounts of *N*-benzylquininium bromide and phenol.

Chapter 4

Novel and chiral binaphthalene-derived-1,2,3-triazolium salts were synthesised following a simple 3-step procedure, starting from commercially available (*S*)-2,2'-diamino-1,1'-binaphthalene. Chiral triazolium salts were used as phase transfer catalysts for different organic reaction. The 1,2,3-triazolium-catalysed Michael addition of nitromethane to 5-stylylisoxazoles provided the desired nitroadduct in 90% yield and 56% enantiomeric excess.

Chapter 1

**Reaction of azides and enolisable aldehydes under
the catalysis of organic bases and Cinchona-based
quaternary ammonium salts**

1.1 Introduction

1.1.1 Amide synthesis: carboxylic acid activation

The formation of an amide bond is one of the most executed reactions in organic synthesis, forming key linkages in peptides, peptide nucleic acids (PNAs), proteins, synthetic polymers and certain pharmaceutical active ingredients (APIs). For example **Atorvastatin**, a cholesterol level lowering drug, had been the best-selling drug of the previous decade (Figure 1), **Valsartan** has extensively been used as an angiotensin receptor blocker, *N*-acetylprocainamide an antiarrhythmic agent, **Imatinib** is known as an inhibitor of tyrosine kinases and is indicated for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs).¹⁻³ In living systems most amide bonds are formed in complex structures called ribosomes, where proteins are assembled amino acid by amino acid using nucleic acid chains as a template. Synthetic chemists cannot rely on these efficient coupling systems and must instead push the reaction equilibrium by using coupling reagents and protecting groups, which generate large amounts of waste, and involve using excess of reagents or hazardous by-products.

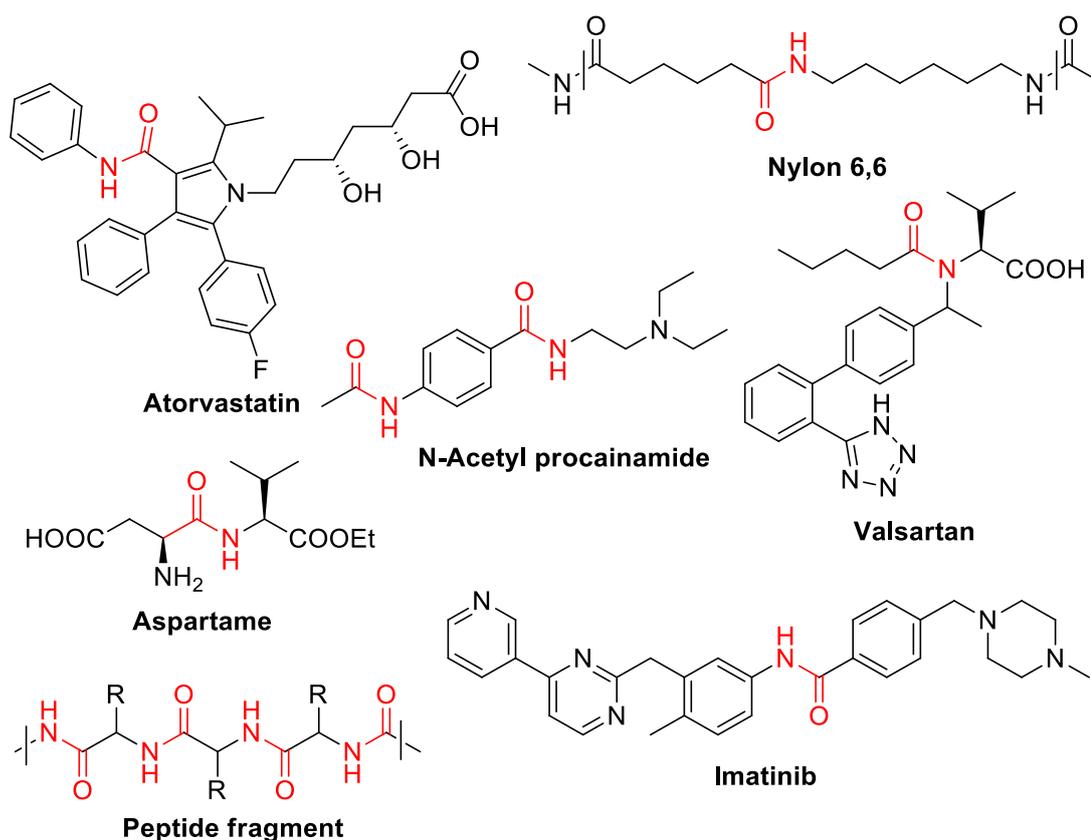
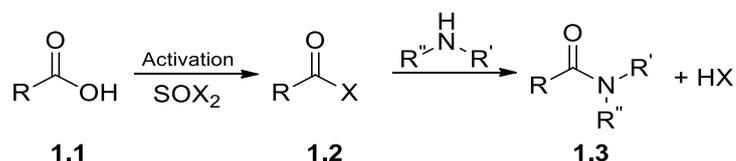


Figure 1: Importance of amide bond in organic chemistry.

Some of the most commonly used reactions and reagents employed to prepare amides are described in the following paragraph with the aim of presenting an up to date landscape of the field.

1.1.2 Coupling with acyl halides

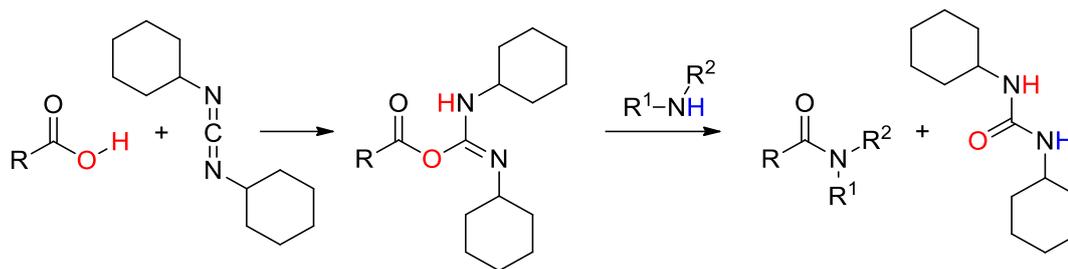
Amide bond synthesis is typically obtained by coupling a carboxylic acid with an amine: this transformation occurs with elimination of a molecule of water, which can take place at high temperatures. These harsh conditions restrict the scope of this reaction, and, when run on polyfunctional molecules, lead to decomposition. To avoid decomposition of the substrate or its racemisation, common practice is to first activate the carboxylic acid, by converting the OH group into a suitable leaving group such as a halide, for example (Scheme 1). This is done by employing chlorinating reagents like thionyl chloride or oxalyl chloride which are not expensive and excel for their high reactivity. Their employment is however restricted to substrates which do not bear additional nucleophilic sites (for example an alcohol) or acid-sensitive functional groups, such as esters and racemisable stereocenters. In case of large scale production, the use of these reagents is not ideal as they greatly increase the risk of accident: SOX₂ (or COCl₂) are toxic compounds, which may react violently with water. Also their use in the preparation of **1.2** from **1.1** generates an exothermic response that must be controlled. Hence, the preparation of amides **1.3** *via* SOX₂ activation may be useful for relatively simple substrates **1.1**, but not for fine chemical production which involves elaborating polyfunctional molecules.



Scheme 1: Principle of amide bond formation by activation of the carboxylic function.

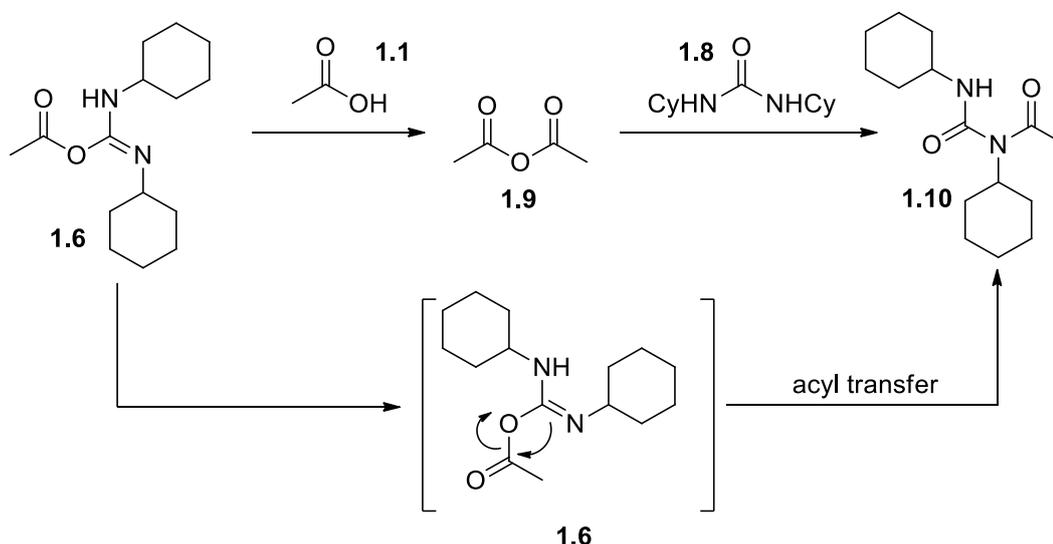
1.1.3 Carbodiimides as coupling reagents

Carbodiimides **1.5**, firstly employed in 1955 and synthesised by dehydration of ureas,⁴ are a popular alternative to the activation of carboxylic acid *via* halogenation. The electrophilic carbon in **1.5** is highly reactive towards nucleophilic carboxylic acid **1.4** (Scheme 2). The driving force of the overall process is the capture of a molecule of water by carbodiimide **1.5**, which can be considered a dehydrating reagent. The reaction of **1.4** and **1.5** to give adduct **1.6** takes place promptly at room temperature, and transforms an inert group such as an OH, into a urea, which can be displaced by an amine, with the formation of amide **1.7**.



Scheme 2: DCC as a coupling reagent.

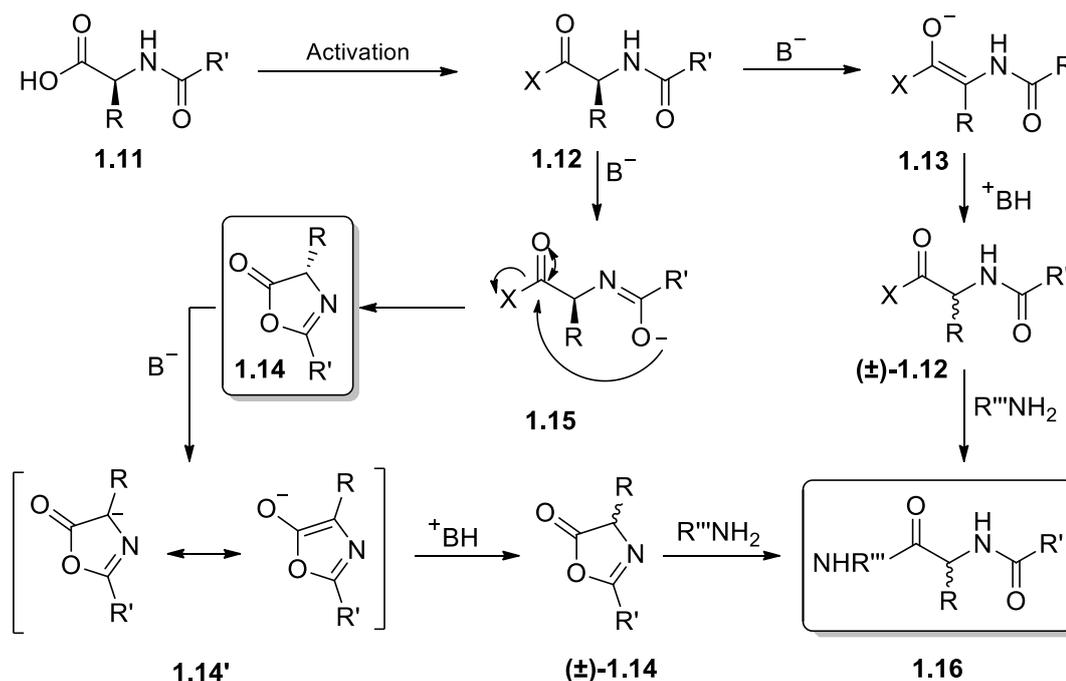
Dicyclohexylurea **1.8** (DCU) is usually insoluble in the reaction solvent: this facilitates the purification of amide **1.8**, while carrying out amidation as an homogeneous reaction. However, DCC is less suitable for most solid state syntheses, where a number of different by-products are often observed upon its use (Scheme 3). Since intermediate **1.6** is a strong acylating reagent, it may react with any nucleophilic species present in the reaction mixture, such as the anion generated from carboxylic acid **1.1**, forming anhydride **1.9**, which in turn can react with the amine, yielding the desired amide but consuming one extra equivalent of acid. Alternatively, **1.9** can react with dicyclohexylurea **1.8** yielding *N*-acylurea **1.10** which hardly precipitates, making the purification of the crude mixture problematic. The same by-product could be formed by intramolecular acyl transfer, which spontaneously occurs in **1.6**, mostly when DMF was used as the solvent.⁵



Scheme 3: Common by-products of DCC-promoted coupling.

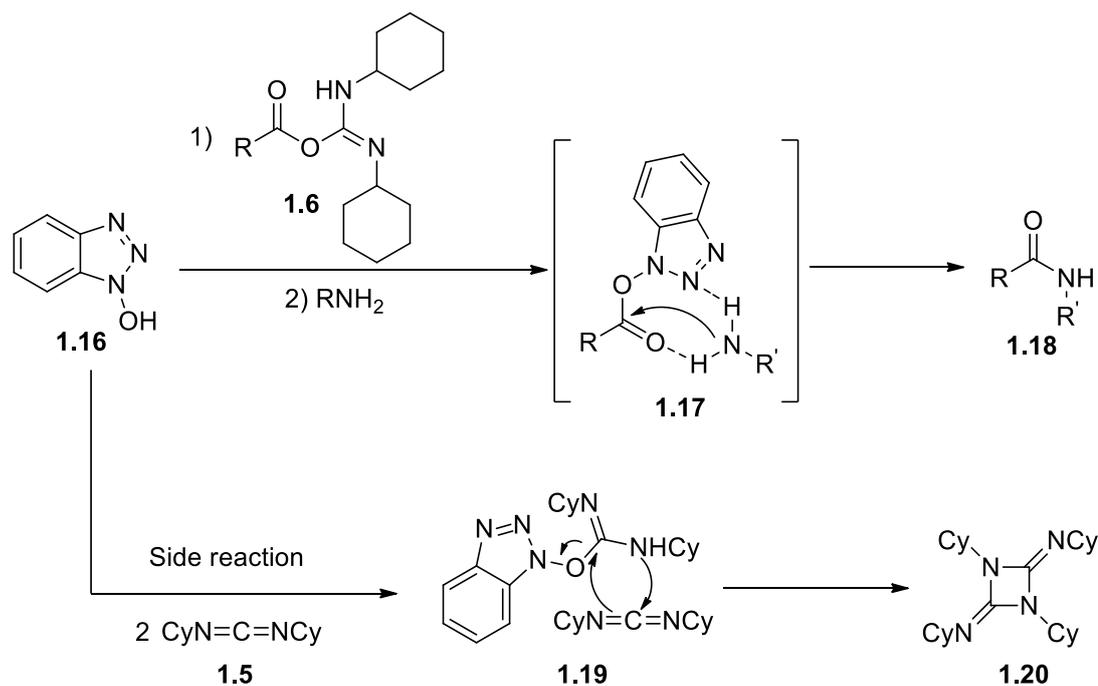
A common issue encountered in the amidation of optically active amides is the epimerisation of the α -stereocenter. It is known that very polar solvents promote α -deprotonation of activated carboxylic acids. In these cases, i.e. coupling of chiral amino acids, achieving a complete conservation of the stereochemistry could be a challenging goal.⁶ Hence, in the amidation of *N*-protected amino acid **1.11**, the activation with coupling reagents provided intermediate **1.12**

(Scheme 4). Reaction of **1.12** with a base can trigger two different reaction pathways: (a) deprotonation of N-H to compound **1.15** or (b) deprotonation of C α to enolate **1.13**. This latter produces a complete loss of existing stereochemistry, hence reprotonation of **1.13** provides racemisation of (\pm)-**1.12**, leading to a diastereoisomeric mixture **1.16** after coupling has occurred. Compound **1.15** may undergo intramolecular cyclisation to oxazolone **1.14**, which can equally lose its stereochemical identity in the presence of a base to yield racemised (\pm)-**1.14**. Once again, reaction of (\pm)-**1.14** with an amino acid provides coupled dipeptide **1.16** as a mixture of diastereoisomers.



Scheme 4: Typical racemisation pathways in peptide synthesis.

In order to reduce the racemisation rate when activating the carboxylic function with carbodiimides, a variety of additives have been developed. Hydroxybenzotriazole **1.16** (abbreviated HOBt), originally presented by Koenig and Geiger,^{7,8} enhanced the yields and lowered the epimerisation rates. The mechanism of action of **1.16** involved a fast nucleophilic acyl substitution in *N*-acylisourea **1.6**, with the formation of activated ester **1.17** which recruits and guides the approach of the amine through hydrogen bonding, in key intermediate **1.17** (Scheme 5).⁵ Evolution of **1.17** to final amide **1.18** occurred *via* addition-elimination as in other related processes.



Scheme 5: Mechanism of HOBt-mediated activation and undesired by-products.

The main drawback of this procedure is the parasitic formation of diazetidine **1.20**, via initial attack of **1.16** and **1.5**, to give adduct **1.19**, which undergoes reaction with a second equivalent of **1.5** to final dimeric **1.20** (Scheme 5). A wide diversity of carbodiimides and oximes based on DCC and HOBt had been studied and tested on model amidation reactions of small molecules and peptides (Figure 2). The result of these studies is a very large pool of reagents that can be taken into consideration while optimising the synthesis of a particular molecule or peptide sequence.

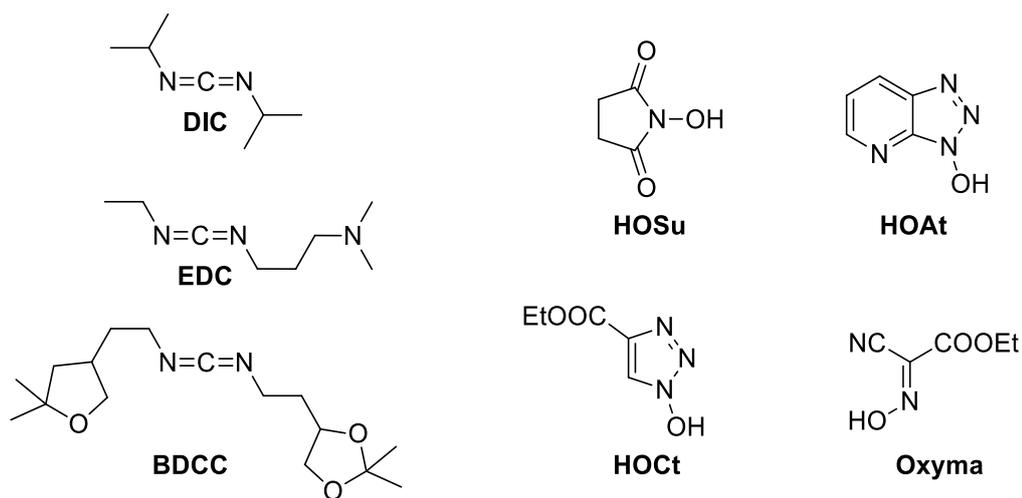
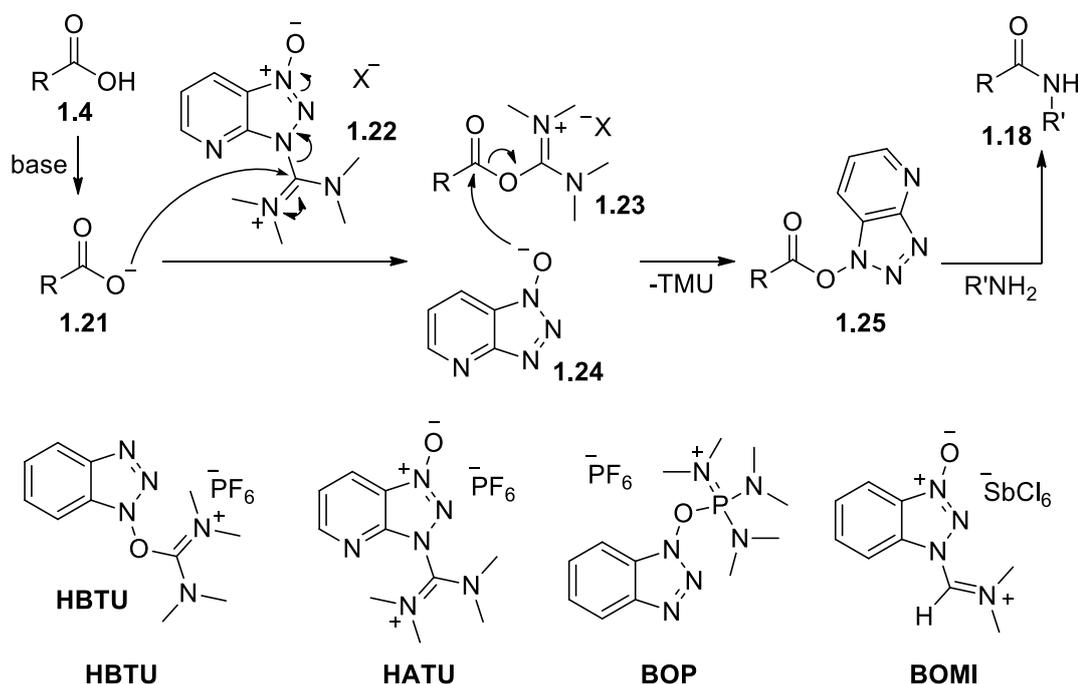


Figure 2: Coupling reagents based on DCC and HOBt.

1.1.4 Onium-type coupling reagents

A second generation of coupling reagents combines the activity and the function of both DCC and HOBt in one single compound. Uronium, guanidinium, phosphonium, amidinium salts are just some of the functional groups that can be included into such a class of products, together with the benzotriazole moiety. The mechanism of reaction follows the same principles previously described. Hence, the reaction of **1.21** with **1.22** produced activated **1.23** alongside benzotriazole-N-oxide **1.24**. In turn, **1.24** reacted with **1.23** to give **1.25**, which is thus reacted with an amine group to give final **1.18**. Several “onium” species have been reported following this design, such as HBT, HATU, BOP, BOMI (Scheme 6).

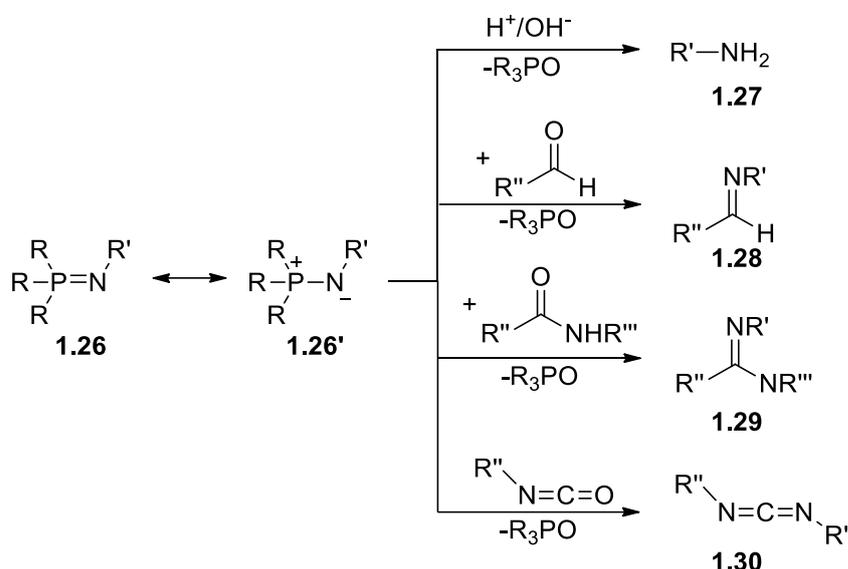


Scheme 6: Mechanism of activation with HATU and different “onium” salts.

Coupling reagents such as DCC/HOBt or HATU are in most cases the optimum for small scale peptide synthesis and for general amide bond formation, since they offer the advantage of being generally applicable.⁹ Their employment is however restricted to fine chemicals due to their high cost. Considerable safety issues connected to their chemical nature must be also considered: HATU, for example, possessing a carbon/nitrogen ratio close to 1 is potentially explosive; BOP, once reacted, converts into hexamethylphosphoramide, that is well known for its carcinogenicity; DCC and DIC are strong sensitizers and should be carefully handled.¹⁰

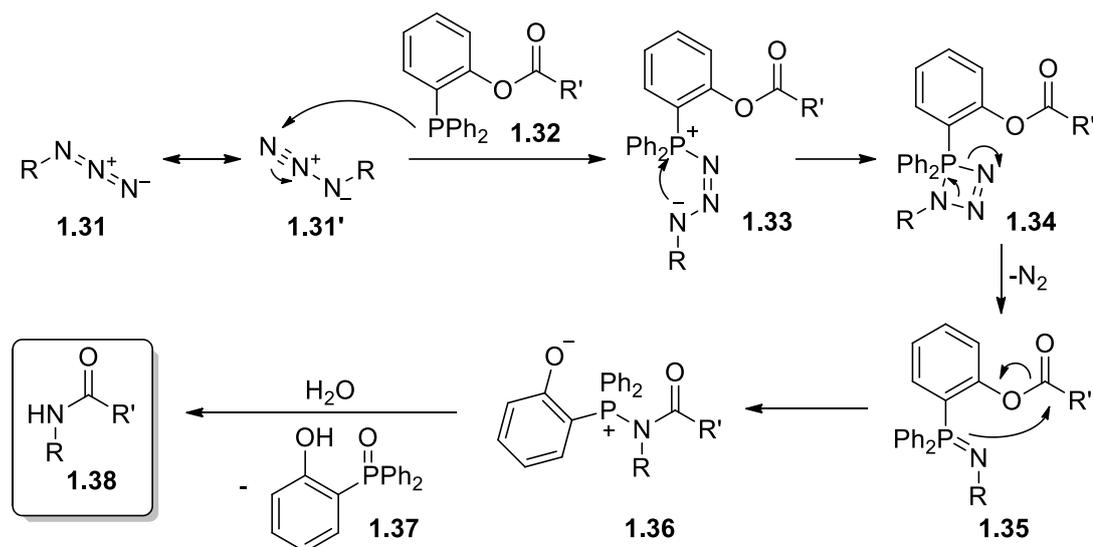
1.1.5 Alternative methods: Staudinger ligation, Schmidt reaction, oxidative amination.

In order to develop more efficient procedures that avoid using carboxylic acids and amine functionalities, other precursors have been considered. Azides are reactive compounds, which can be easily reduced to amines in presence of triphenylphosphine in an aqueous solvent (Staudinger reaction). The intermediate iminophosphorane **1.26**, generated by reacting a nucleophilic phosphine and an azide, is a strong *N*-nucleophile that promptly reacted with various electrophilic reagents, thus resulting in many reactions of significant synthetic importance (Scheme 7).¹¹ For example, reaction of **1.26** with water produced amines, while the reaction with aldehydes/ketones provided a method to obtain imines **1.28**, **1.29** without the involvement of dehydrating conditions (i.e. Dean Stark). Finally, it was demonstrated that **1.26** reacted with isocyanates to give carbodiimides **1.30**.



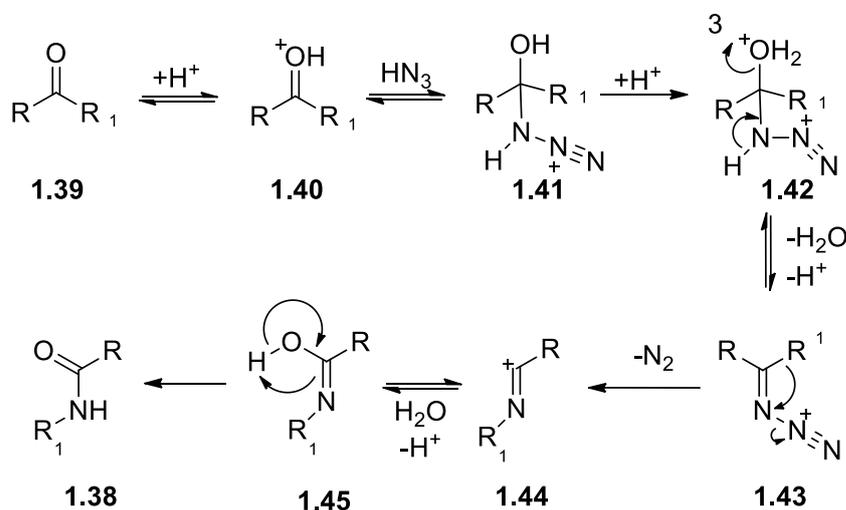
Scheme 7: Iminophosphorane reactivity.

A similar, but more attractive from a synthetic standpoint, is the so-called Traceless Staudinger Ligation, developed by Bertozzi and co-workers (Scheme 8).¹² When acylated phosphane **1.32** was treated with an azide, the nucleophilic ylide **1.35** that was formed *via* nitrogen elimination attacks the ester functionality in an intramolecular fashion, causing the cleavage of the phosphine moiety.



Scheme 8: Traceless Staudinger Ligation.

The Schmidt reaction constitutes a further example in which azides provide a source of nucleophilic nitrogen. The Schmidt reaction involved an acid-catalysed addition of hydrazoic acid to carbonyl electrophiles. When a ketone **1.39** was used as the substrate, azahydrine **1.41** was the main intermediate obtained *via* nucleophilic addition to the carbonyl. Compound **1.41** then evolved to intermediate **1.43** *via* elimination of water. Subsequent loss of N_2 and further reaction with water provided final **1.38** after 1,3-hydrogen-shift. Amide **1.38** was formed by hydrolysis of imine **1.44** (Scheme 9).¹³



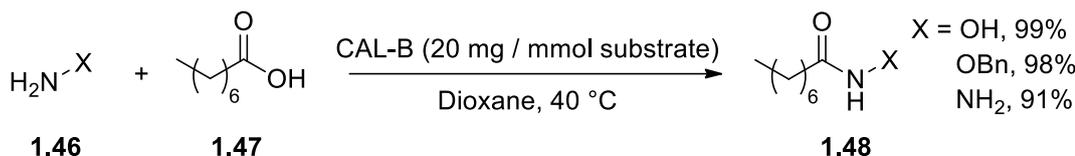
Scheme 9: Mechanism of the Schmidt reaction.

1.1.6 Catalytic amide formation

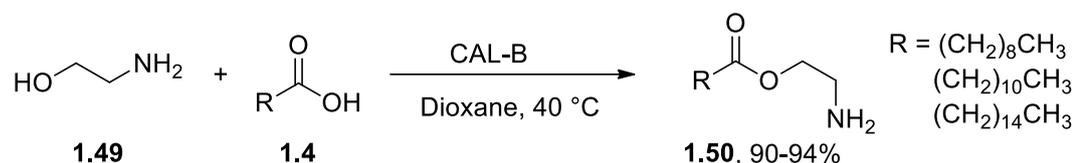
The strong demand for safe, inexpensive and waste-free amidation methods encouraged the development of several catalytic systems as valid alternatives to the traditional protocols. Enzymes have been extensively studied for the formation of the amide bond; despite the

limited scope of these methods, yields are excellent and the reaction conditions very mild. Among the many enzymatic systems proposed, *Candida antarctica* lipase B (CAL-B) was reported by several groups for its good performance, in particular when employed for the condensation of fatty acids **1.47**, **1.4** or **1.52** with amines **1.46** or aminoalcohols **1.49**.^{14,15} When amines **1.51** possessing a stereogenic centre were used as substrates, a kinetic resolution was often observed, with yields of amides **1.53a-c** close to the theoretical and high enantioselectivity (Scheme 10).^{16,17}

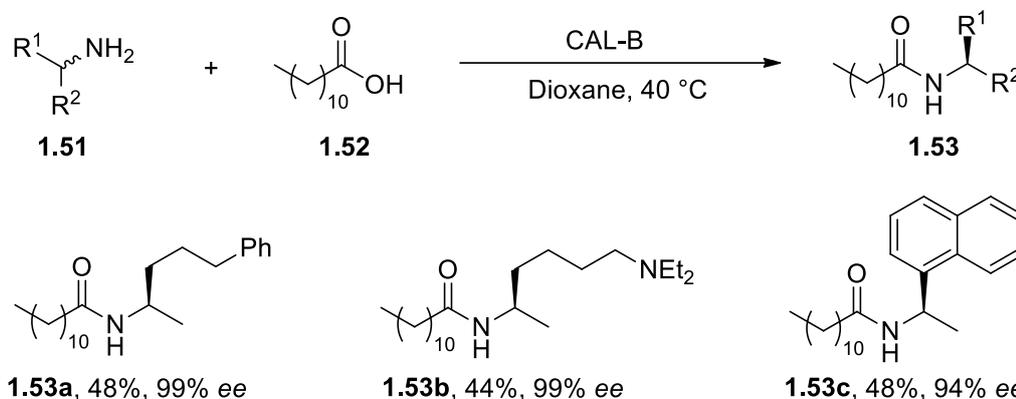
Sheldon, 2001



Fernandez-Perez, 2001



Bertrand, 2007

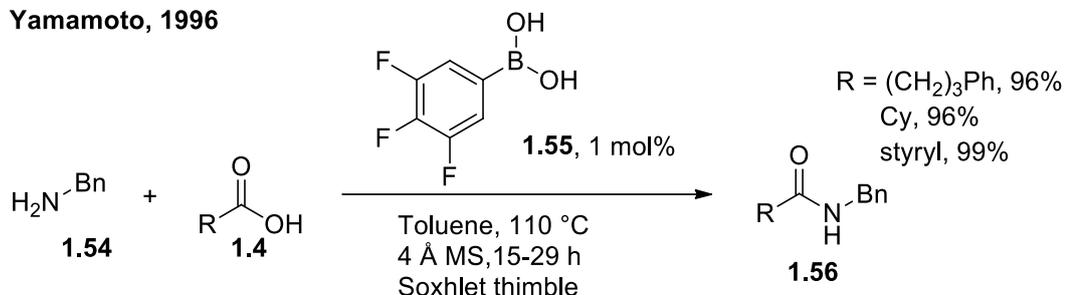


Scheme 10: Enzymatic amide bond formation.

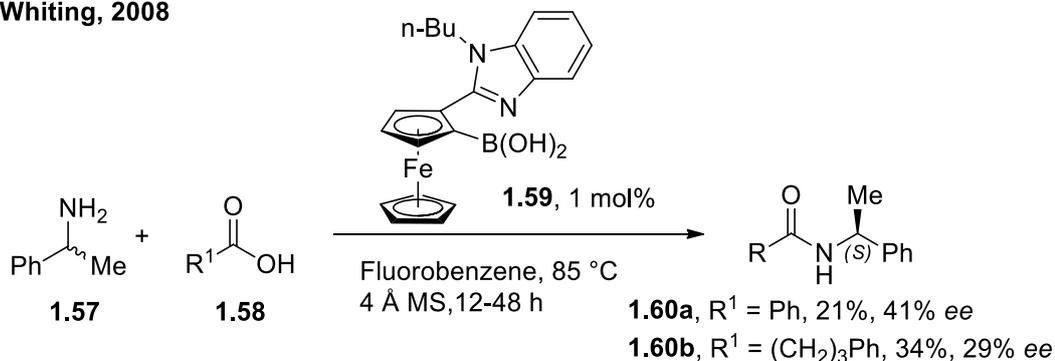
Boronic acid-promoted coupling of carboxylic acids with amines has been known for decades,¹⁸ with catalytic versions of this approach increasingly reported in recent years. For example, aromatic and aliphatic carboxylic acids were easily reacted at 110 °C with amines using electron-poor arylboronic acids such as **1.55** as the catalysts in non-polar solvents (Scheme 11): the removal of water was crucial to push the reaction equilibrium, and for this reason molecular sieves or a Soxhlet extractor were normally employed.¹⁹ More recently Whiting and co-workers reported different applications of boronic acids as amidation-promoters, such as chiral ferroceneboronic acid **1.59** which catalysed the stereoselective formation of **1.60** through an innovative kinetic resolution of racemic amines.²⁰ In spite of the

novelty of this approach, the ees of amides **1.60a,b** did not overcome 41%. The same group reported the first synthesis of dipeptides **1.64** that occurred in the presence of arylboronic acids: this transformation provided **1.64** with complete conservation of the stereochemical identity; however, stoichiometric boronic acid **1.63** was indispensable to achieve high conversion.²¹

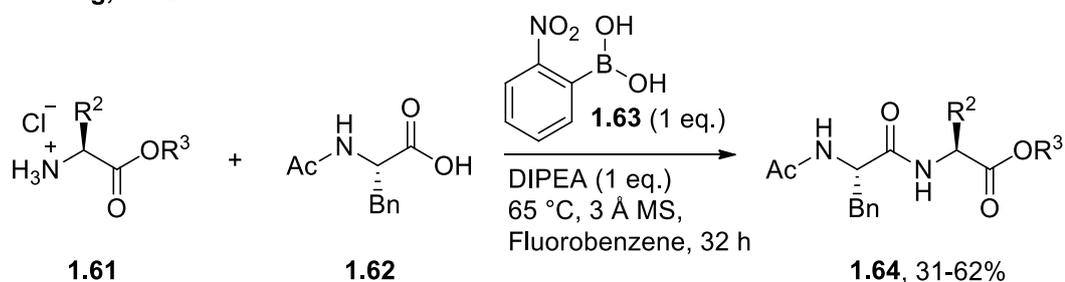
Yamamoto, 1996



Whiting, 2008



Whiting, 2013

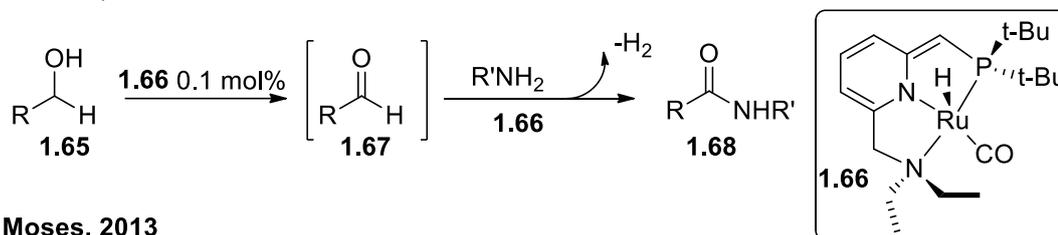


Scheme 11: Boronic acid-catalysed amidation.

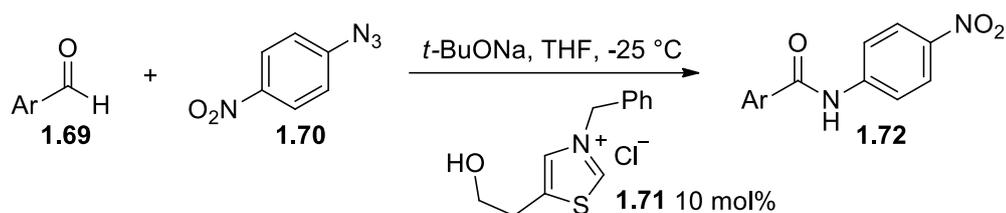
In an alternative approach, the preparation of amides has been pursued starting from precursors other than carboxylic acids and amines. For example, it has been reported that alcohols **1.65** could be oxidised *in situ* to a transient aldehyde **1.67** by palladium (II)²² or ruthenium (II)²³ complexes, which in turn reacted with amines to provide amides **1.68** (Scheme 12). Significantly, anilides such as **1.72** could be equally obtained when aldehyde **1.69** was reacted with aromatic azide **1.74** in presence of a base and *N*-heterocyclic carbenes.²⁴ This strategy offers the advantage of not using an additional oxidant, since the release of nitrogen gas provides the required thermodynamic drive for the reaction to occur. The preparation of amides from azides has also been reported by Manetsch²⁵ who showed how the reaction of

aromatic aldehydes **1.73** and benzylic azides **1.74** progressed with a strong base as the activator.

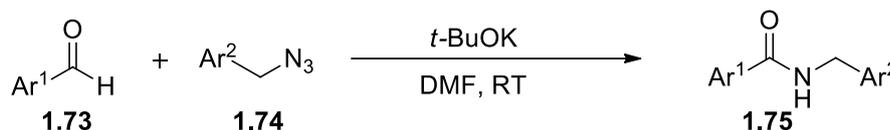
Milstein, 2007



Moses, 2013

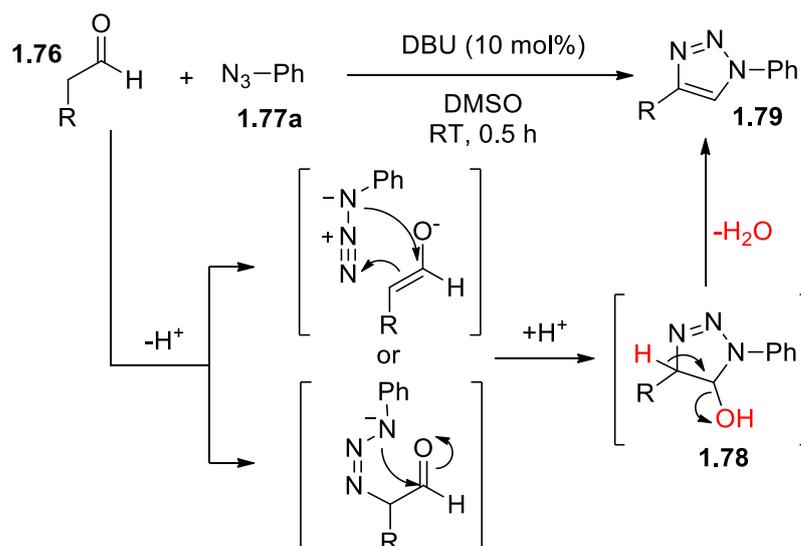


Manetsch, 2013



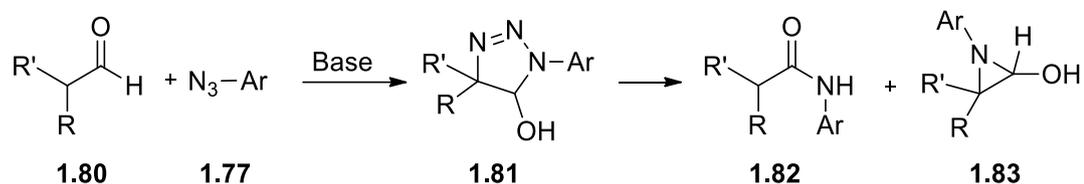
Scheme 12: Alcohols and aldehydes as synthetic analogues of carboxylic acids

These findings were followed up by Ramachary who described the first example of triazole synthesis from primary enolisable aldehydes **1.76** and azides **1.77**.²⁶ The reaction worked in the presence of a catalytic amount of an organic base, required for the generation of an enolate which reacted with **1.77** to provide triazole **1.79** upon elimination of water (Scheme 13).



Scheme 13: Triazole synthesis via enolate-azide cycloaddition.

Based on these reports and as part of ongoing studies on amidation we posed the question of whether enolisable secondary aldehydes **1.80** could be reacted with azides **1.77** under basic catalysis. Notably, 4,4-disubstituted- triazolines **1.81** cannot undergo aromatization and could provide an interesting intermediate to access not only amides **1.82** but also aziridines **1.83** by thermal or photochemical treatment (Scheme 14).



Scheme 14: Amides and aziridines as decomposition products of 4,4-disubstituted-triazolines

1.1.7 Introduction to organocatalysis and phase transfer catalysis

In 1971 Starks introduced the term “phase transfer catalysis” (PTC) to explain the role of quaternary ammonium or phosphonium salts in reactions between substances situated in different immiscible phases.²⁷ Generally, reactions between two substances placed in different phases are unsuccessful, but if a third substance was added with the purpose of transferring one of the active reactant from one phase into the other, an overall progression of the reaction would be observed. Ideally, the phase transfer catalyst is not depleted and it is able to perform the transport repeatedly. This methodology offers many advantages, such as mild reaction conditions, inexpensive and environmentally friendly reagents, low solvent consumption and the possibility to easily scale up the preparations.²⁸ The representative phase transfer reaction is constituted by a biphasic system, usually aqueous/organic phase or inorganic solid/organic phase. The organic phase normally contains a compound bearing an acidic functionality and an electrophile, instead the aqueous or solid phase contains the inorganic base, which is normally an alkali metal hydroxide, carbonate or phosphate. Heterogeneous systems such as this are not only suitable to alkylations, nucleophilic substitutions, additions and eliminations, but also functional group interconversion such as oxidations and reductions (MnO_4^- , ClO^- , BH_4^- can be easily transferred to the organic phase).²⁹ Two different mechanisms have been proposed for phase transfer reactions: Starks extraction mechanism and Makosza’s interfacial mechanism.³⁰

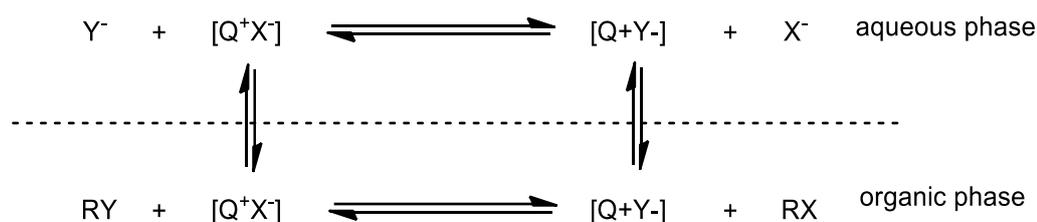


Figure 3: Starks extraction mechanism.

According to Starks, the quaternary onium salt, partitioned in both the aqueous and organic phases, transfers the reacting anion from the aqueous to the organic phase, at the same time returning the leaving group to the aqueous phase (Figure 3). Makosza's interfacial mechanism is more specific for highly lipophilic catalysts or for anions such as OH^- , which have very low extraction rate, and thus could not effectively deprotonate the substrate in the bulk of the organic phase. The actual exchange would occur only at the interface, from where the newly generated active ion pair is able to diffuse through the organic phase (Figure 4).

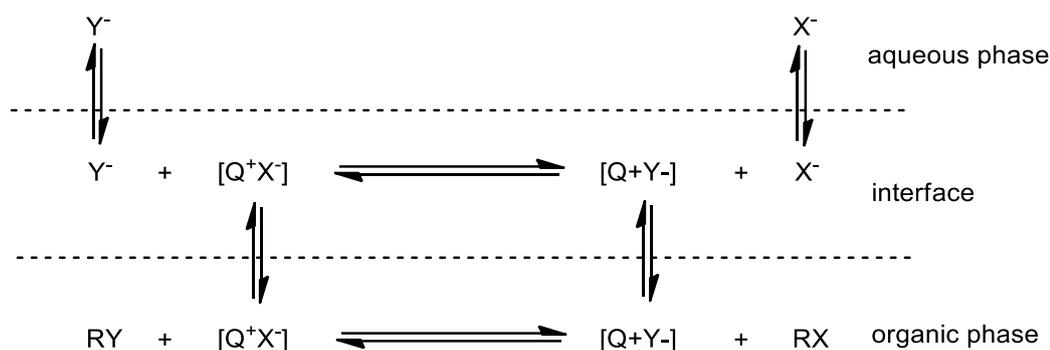


Figure 4: Makosza's interfacial mechanism.

When a chiral onium salt is employed as a phase transfer catalyst, stereoselective transformations become possible from achiral substrates. A common class of chiral phase transfer catalysts is represented by the quaternary ammonium salts derived from *Cinchona* alkaloids.³¹ Depending on their pseudoenantiomeric configuration and functional groups, four kinds of *Cinchona* alkaloid are known. *Cinchona* alkaloids have a quite unique structure involving a sterically hindered tertiary amino fraction with various functional groups, such as the 9-hydroxy group, the 6-methoxy group on the quinoline ring, and the vinyl group on the quinuclidine moiety (Figure 5).

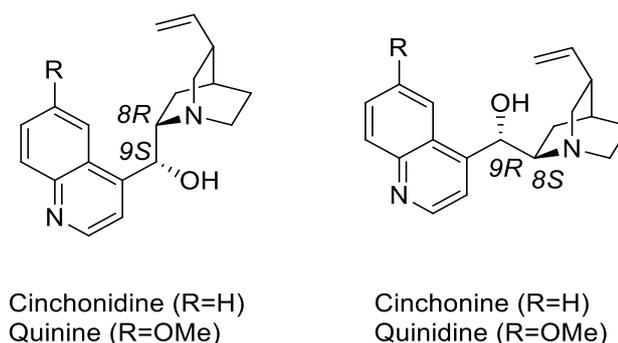
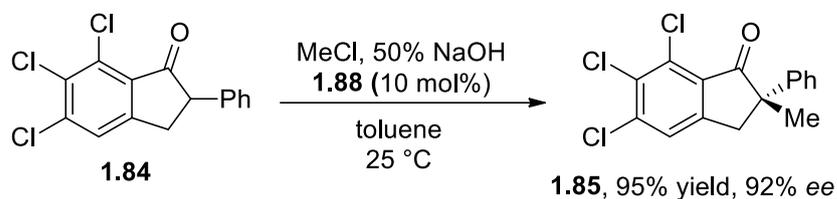


Figure 5: Structure of chinchona alkaloids.

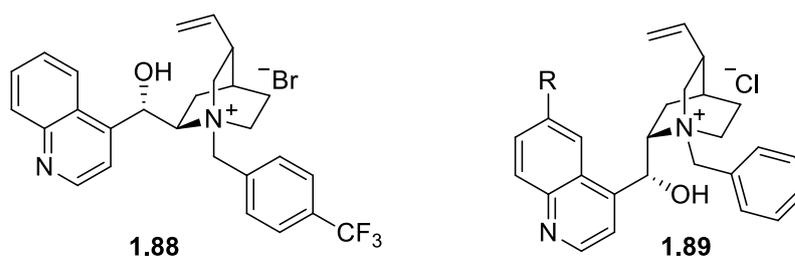
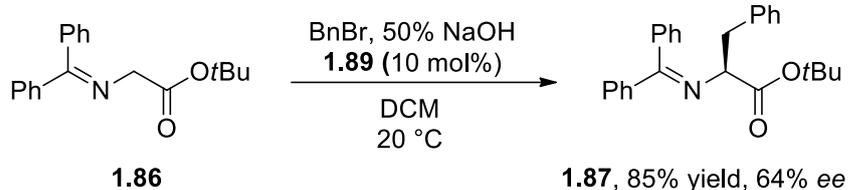
The first successful application of a *Cinchona*-derived quaternary ammonium salt as a phase transfer catalyst was reported by Dolling in 1984.³² This catalytic enantioselective alkylation of indanones was promoted by *N*-(4-trifluoromethylbenzyl)cinchoninium bromide and gave alkylated product **1.85** with good yield and enantioselectivity (Scheme 15). The first phase

transfer catalysed enantioselective synthesis of α -aminoacids was reported by O'Donnell and co-workers, who successfully reacted glycine iminoester **1.86** with benzyl bromide in the presence of *N*-benzylcinchonidinium bromide **1.89** and obtained benzylated compound **1.87** in good yield and moderate enantiomeric excess (Scheme 15).

Dolling, 1984



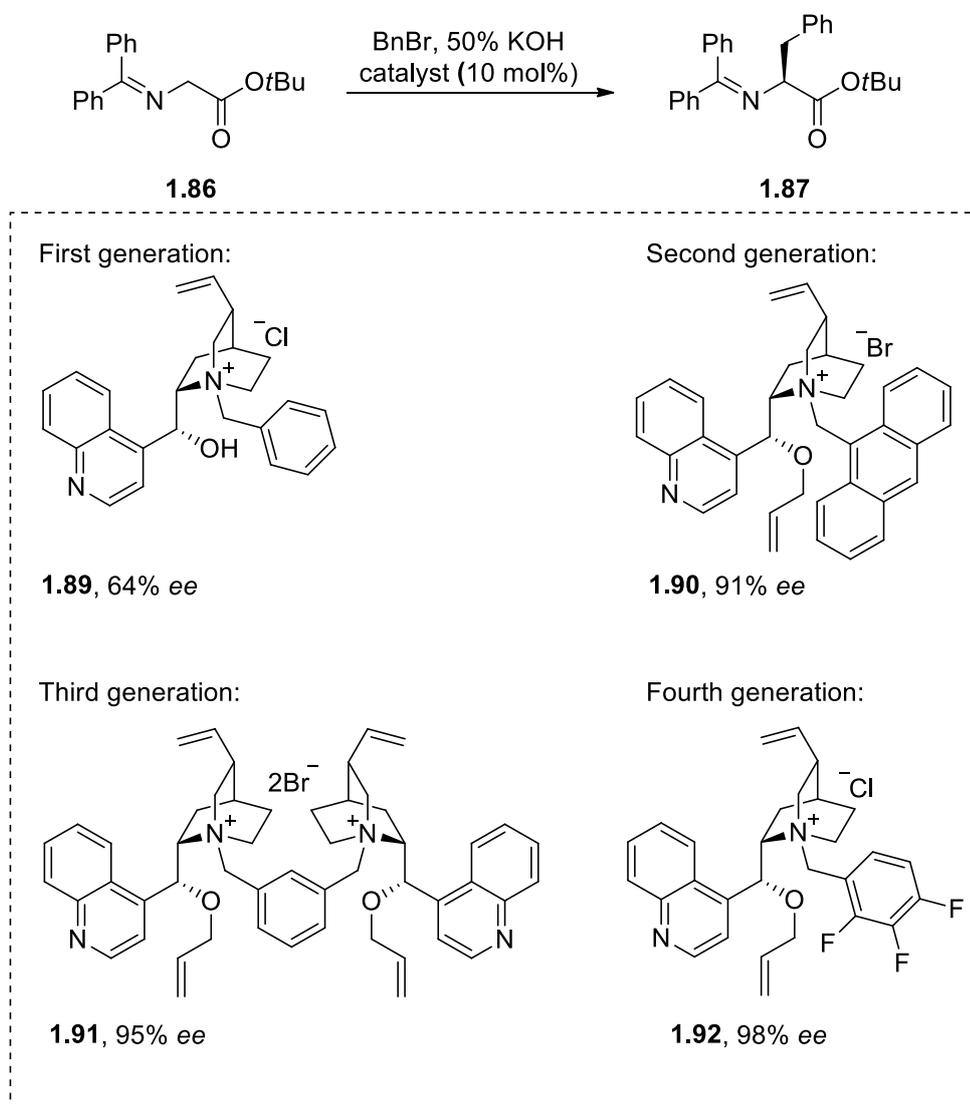
O'Donnell, 1989



Scheme 15: First applications of *Cinchona*-derived PTC.

Since the first pioneering work of Dolling, many improvements to the original structure of the *Cinchona*-derived PTC were made, increasing both enantioselectivity and the scope of substrates. These new families of quaternary salts can be divided into four generations, depending on the chronological order they were first tested and developed on the alkylation of glycine iminoester **1.86**, which is now considered a benchmark reaction in organocatalysis (Scheme 16). While trying to elaborate a model of enantioselectivity, Corey and Lygo synthesised and tested *N*-anthracenylcinchonidinium **1.90**, whose high rigidity greatly improved both stereoselectivity and yield for the alkylation reaction of glycine iminoester **1.86**.^{33,34} Excellent results were also obtained in 2001 by Jew and co-workers, who prepared a library of various dimeric species of *Cinchona*-derived quaternary ammonium salts; depending on the type and the geometry of the aromatic linker, yields and selectivities changed.³⁵ It was discovered that the two *Cinchona* units could best interact when a meta-substituted ring was selected as a linker (Scheme 16, compound **1.91**). Jew also studied the effect of various substituents, when attached to different positions of the phenyl group. Electron withdrawing or electron donating groups can respectively increase or decrease the Lewis acidity of the quaternary ammonium group, and so modify the energy of the ion-pair

bond. In particular, it was found that polar *ortho*-substituents could greatly improve stereoselectivities, by participating to the complexation of the basic counter-ion and thus increasing the overall rigidity of the transition state (Scheme 16, compound **1.92**).³⁶



Scheme 16: The four generations of the Cinchona PTC.

During the sequential pathway of a catalytic phase transfer reaction, the *Cinchona*-derived quaternary ammonium salt generates a chiral environment surrounding the nucleophilic ionic complex ($R_4N^+ Nu^-$). The quaternary ammonium salt derived from cinchona alkaloid can be seen as an imaginary tetrahedron composed of four carbons adjacent to the bridgehead nitrogen (Figure 6). In order to positively induce chirality to the reactive enolate, the *Cinchona*-derived PTC should be designed so the three faces F1-F3 of the tetrahedron are too sterically hindered and only F4 is sufficiently open to allow a close interaction between the enolate anion and the positively charged nitrogen.³⁷

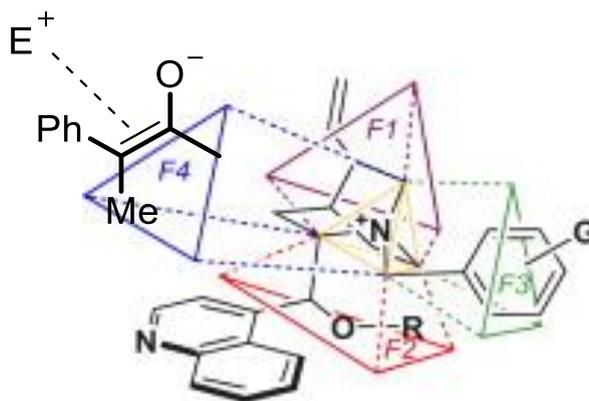


Figure 6: Origin of the stereoselectivity in *Cinchona*-derived quaternary ammonium salts.

1.1.8 Organic superbases

The use of strong organic non-nucleophilic bases constitutes an additional approach to the generation of enolates through the deprotonation of acidic C-H. The strength of the catalytic Brønsted base must be adjusted depending on the acidity of the substrate. In order to partially shift the deprotonation equilibrium of the substrate towards its anionic form, the pK_a of the conjugate acid of the chosen base must be numerically close to the pK_a of the acidic hydrogen on the substrate. Bases such as guanidines, amidines and phosphazenes excel in application scope and owe their strength to delocalisation and hydrogen bond-donors properties (Figure 7).

	trialkylamine	guanidine	amidine	triarylmino-phosphorane	P1 phos-phazene
B					
pK_{BH^+}	18.82	23.56	24.34	25.0	26.98

Figure 7: Organic superbases. Literature values of the conjugate acid pK_a in ACN.

Many chiral versions of these superbases have been developed and their application covers all types of base-promoted reactions, such as alkylation of enolates,³⁸ Nitro-Michael reaction,³⁹ Nitro-Mannich reaction,⁴⁰ Diels-Alder reaction⁴¹ (Figure 8).

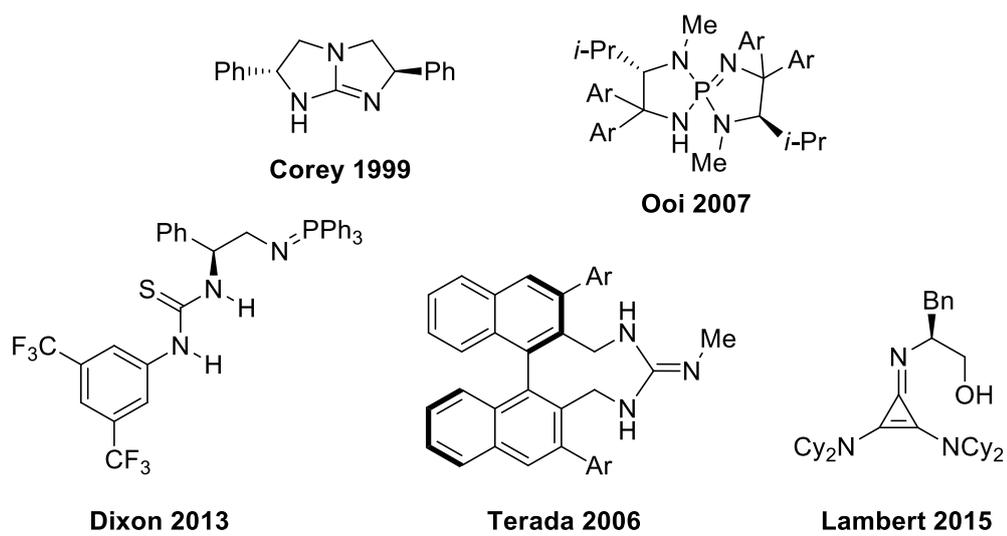


Figure 8: Chiral superbases.

1.2 Results and discussion

1.2.1 Organic base-catalysed triazoline synthesis

Preliminary investigation was carried out by reacting 2-phenylpropionaldehyde **1.80a** and azidobenzene **1.77a** in the presence of a catalytic amount of organic base in DMSO (Table 1). The reaction was carried out at room temperature and the starting material was consumed after 4 h (Table 1, entry 1), providing the desired **1.93** along with 10-15% of unwanted acetophenone side product. Since it is known that 2-phenylpropionaldehyde undergoes oxidative demethylation in the presence of atmospheric oxygen,⁴² the amount of acetophenone was reduced to 5% by briefly degassing the solvent with a nitrogen stream. During the course of this study, Ramstrom disclosed similar results to those presented in Table 1, which were generated in our laboratory as a proof of concept for the study presented in this chapter.⁴³

Table 1: Optimization of the base-catalysed triazoline formation ^a

Reaction scheme: 2-phenylpropionaldehyde (**1.80a**) + azidobenzene (**1.77a**) $\xrightarrow[\text{RT}]{\text{Base 10 mol\%}}$ 5-hydroxy-1,2,4-triazoline (**1.93**)

Entry	Base	Solvent	Time (h)	Conv. (%)
1	DBU	DMSO	4	99
2	DBU	DCM	4	0
3	DABCO	DMSO	4	0
4	Propylamine	DMSO	24	10 ^b
5	(S)-Proline	DMSO	24	30 ^b
6	Quinine	DMSO	4	0
7	BTPP ^c	DMSO	4	99

^a Reaction conditions: **1.80a** (0.36 mmol), **1.77a** (0.30 mmol), base (0.03 mmol), solvent (1.5 ml), 20 °C. ^b Aldol product recovered from the crude mixture. ^c BTPP = *tert*-Butylimino-tri(pyrrolidino)phosphorane.

5-Hydroxytriazoline **1.93** was obtained as a solid in pure form by work-up with a saturated solution of ammonium chloride. As also described by Ramstrom, who reported only spectroscopic evidence for compound **1.93**, this product could not be purified by column chromatography. However, treatment of the crude reaction mixture with hexane allowed isolating compound **1.93** in a pure crystalline form and near quantitative yields, as a 3 : 1 *anti* to *syn* mixture (Figure 9). The relative stereochemistry of *syn* and *anti* **1.93** was determined via NOESY experiments. In particular, a pronounced nOe effect was noted upon irradiation of C₅-H and C₄-H in *syn*-**1.93** (Figure 10). Compound **1.93** did not form when the reaction was carried out in a non-polar solvent such as DCM or when a weaker base *i.e.* propylamine was used (Table 1, entries 2-4). It was also confirmed that other bases with similar pKa would

equally promote the formation of **1.93**. For example, *tert*-butylimino-tri(pyrrolidino)phosphorane (BTTP) provided triazoline **1.93** in almost quantitative yields.

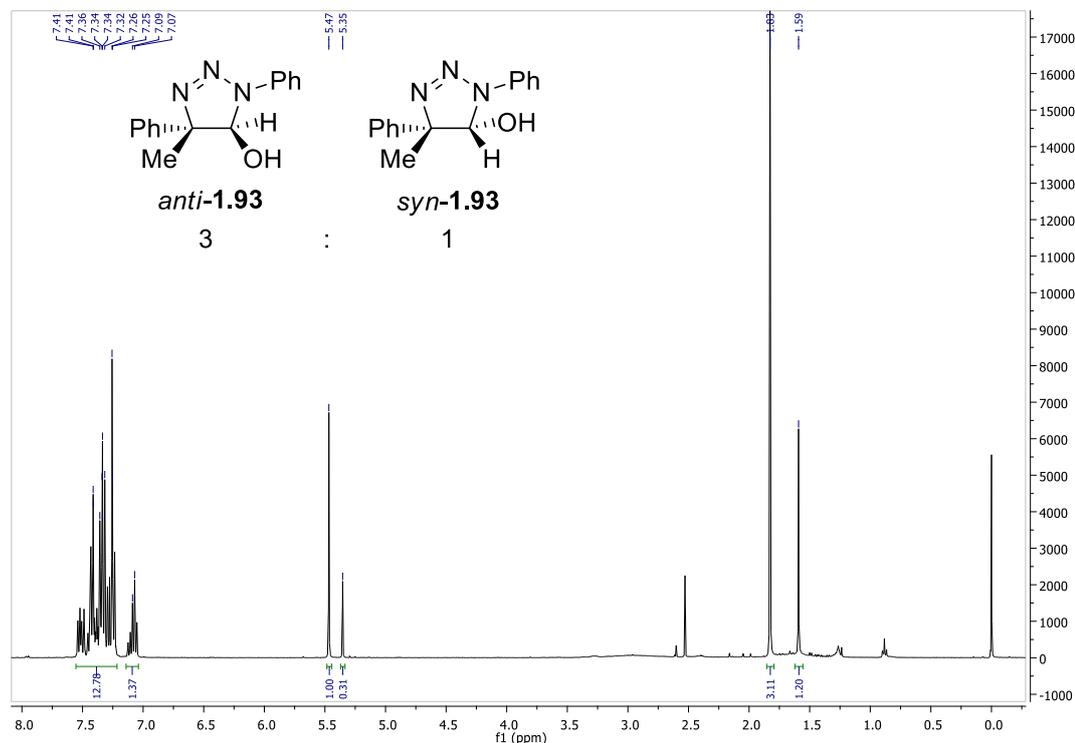


Figure 9: ¹H-NMR of **1.93**.

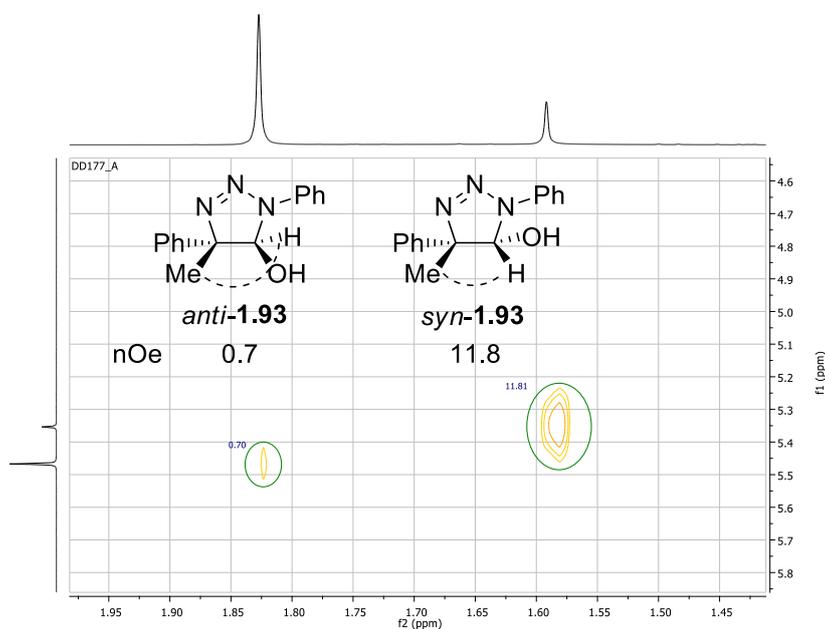
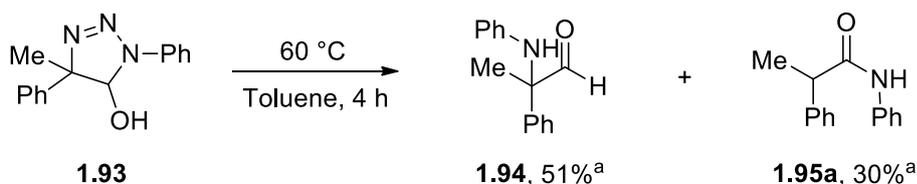


Figure 10: NOESY of **1.93**.

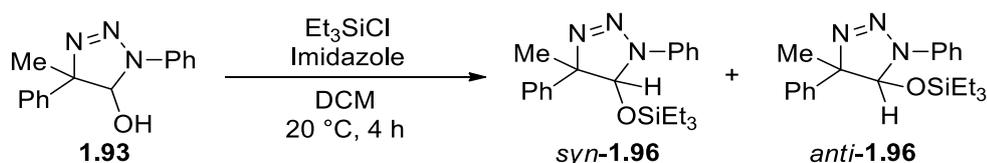
Triazolines such as **1.93** have been reported to extrude N₂ to give amides via an imine intermediate.⁴⁴ However, as confirmed by Ramstrom, this reaction requires high temperatures and provides good yields of amide only with the aid of microwave irradiation.⁴³ A literature

survey indicated that acid catalysis accelerated the decomposition of triazolines to amides, presumably *via* Brønsted acid-catalysed activation of the triazoline sp^3 nitrogen.⁴⁵ With the aim of optimising a milder, room temperature procedure, we envisaged that treatment of triazoline **1.93** with either oxo-philic or a nitro-philic Lewis acid could accelerate the rearrangement of **1.93** to an amide. Initially, to obtain workable samples of amide **1.95a**, compound **1.93** was heated at 60 °C for 3 h, providing the desired **1.95a** in 30% isolated yield along with 51% of α -anilinoaldehyde **1.94** (Scheme 17).



Scheme 17: Thermal decomposition of triazoline **1.93**. ^a Isolated yield.

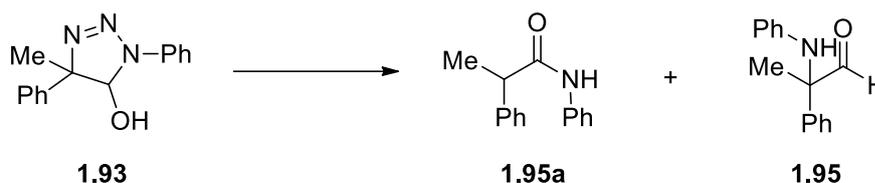
Concomitantly, crude triazoline **1.93** was derivatised to *O*-silylether by reacting it with triethylsilylchloride and an excess of imidazole (Scheme 18). Chromatographic purification of silyl ether **1.96** provided pure samples of *anti*-**1.96** and *syn*-**1.96** which were separated and fully characterised, hence confirming the presence of the triazoline core.



Scheme 18: Silylation of triazoline **1.93**. Reaction conditions: **1.93** (0.8 mmol), Et_3SiCl (1.2 mmol), imidazole (2.1 mmol), DCM (8 ml), 20 °C, 4 h, 90% yield.

1.2.2 Lewis-acid mediated triazoline decomposition

The aim of this study was to select the best catalyst and solvent required to convert **1.93** into **1.95a**, hence minimising the formation of the undesired aminoaldehyde **1.94**. Triazoline **1.93** was selected as the model substrate and reacted with a number of Lewis acids (Table 2). In our working hypothesis, metal ligation either to the O-H or the N^1 (sp^3) nitrogen in **1.93** would equally lead to an increased rate of decomposition *via* cleavage of the weak N^1 - N^2 bond,⁴⁴ leading to faster formation of **1.95a**. DMSO, DMF, THF, 1,4-dioxane and toluene were selected as a range of potential solvents. All reactions reported in Table 2 were carried out at room temperature, which was advantageous compared to the high temperature procedure described by Ramstrom.⁴³

Table 2: Lewis acid-promoted triazolone decomposition.^a

Entry	Lewis acid	Solvent	Conv. (%)	1.95a^b (%)	1.94^b (%)
1	AgCl	DMSO	0	-	-
2	LiBr	DMSO	0	-	-
3	CoSO ₄	DMSO	0	-	-
4	FeCl ₃	DMSO	75	37	12
5	FeSO ₄ ·7H ₂ O	DMSO	0	-	-
6	NiSO ₄ ·6H ₂ O	DMSO	0	-	-
7	ZnCl ₂	DMSO	0	-	-
8	CuCl	DMSO	0	-	-
9	Cu(OAc) ₂	DMSO	26	19	7
10	CuCl ₂	DMSO	99	65	26
11 ^c	CuCl ₂	DMSO	99	74	16
12	CuCl ₂	DMF	84	55	18
13	Ru(CO) ₆	THF _{dry}	41	21	9
14	BF ₃ ·Et ₂ O	THF _{dry}	90	22	0
15 ^d	AlCl ₃	THF _{dry}	99	-	-
16	Ce(SO ₄) ₂	THF _{dry}	0	-	-
17	Sc(OTf) ₃	THF _{dry}	90	46	10
18 ^d	SnCl ₄	THF _{dry}	99	-	-
19	RuCl ₃	THF _{dry}	99	60	25
20	Ti(O ^{<i>i</i>} Pr) ₄	THF _{dry}	70	54	7
21	Ti(O ^{<i>i</i>} Pr) ₄	DMSO _{dry}	18	0	20
22	Ti(O ^{<i>i</i>} Pr) ₄	Dioxane _{dry}	80	67	11
23	Ti(O ^{<i>i</i>} Pr) ₄	DCM _{dry}	99	23	5
24	Ti(O ^{<i>i</i>} Pr) ₄	Toluene _{dry}	99	85 ^e	10

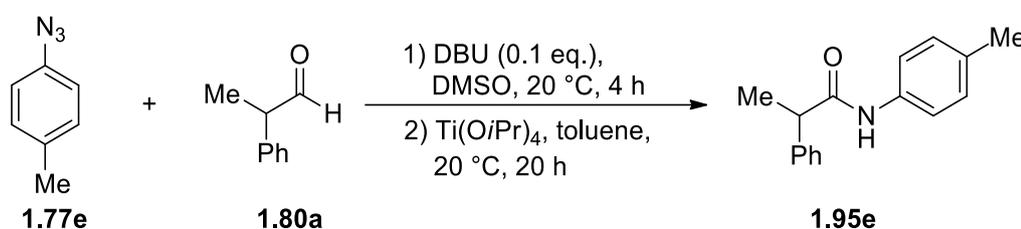
^a Reaction Conditions: **1.93** (0.80 mmol), Lewis acid (0.84 mmol), solvent (8 ml), 20 °C, 20 h.

^b Yield determined by NMR with an internal standard. ^c 1.5 eq CuCl₂. ^d Complex mixture. ^e Correspondent to 72% isolated yield.

Delightfully, when reacted with a slight excess of Lewis acid for 20 h, triazolone **1.93** was converted into products **1.95a** and **1.94**. Data showed a remarkable dependence of the amide yield on the solvent employed. For example, when DMSO was used (Table 2, entries 1-11), Cu(II) chloride was found to be the best reagent, converting **1.93** completely and providing amide **1.95a** in 74% yield (Table 2, entry 11). The reaction of **1.93** and Ti(IV) isopropoxide (Table 2, entry 24) progressed best in dry toluene, providing amide **1.95a** in 85% yield (calculated by ¹H-NMR integration) and in 72% isolated yield. The reaction did not occur under the catalysis of Fe(II), Ni(II), Cu(I) and Zn(II). The use of stronger oxo-philic Lewis acids such as Al(III) and Sn(IV) chlorides led to full conversion of **1.93**, but no amide **1.95a** or aldehyde **1.94** was detected in the crude mixture, which contained a complex mixture of compounds. Finally, Fe(III) and BF₃ provided only partial conversion of **1.93**, producing a remarkable amount of side products. In summary, this study identified Cu(II) in DMSO and

Ti(IV) in toluene as the two best conditions to obtain amide **1.95a** from triazoline **1.93**. In particular, when Ti(IV) in toluene was employed, the amount of unwanted aldehyde **1.94** could be minimised to 10%, which was advantageous compared to the microwave irradiation reported by Ramstrom.⁴³ Hence, this study determined (i) the best condition to prepare triazoline **1.93** from parent azide and aldehyde reagents and (ii) the best procedure to transform **1.93** to an amide **1.95a** at room temperature. Further optimisation of the two-step sequence was then carried out by (a) adjusting the stoichiometric ratio of aldehyde to azide reagents, (b) varying the metal loading and (c) studying the effect of varying the temperature (Table 3). For this study, DBU and Ti(IV) isopropoxide were selected and reacted with 2-phenylpropionaldehyde **1.80a** and 4-methyl-azidobenzene **1.77e** to obtain amide **1.95e**. These reactions were performed in DMSO at 20 °C. Crude triazoline was separated from DMSO and then reacted with Ti(IV) isopropoxide in toluene for the time and temperature specified (Table 3).

Table 3: Optimisation of the reaction conditions for the preparation of amides **1.95a**

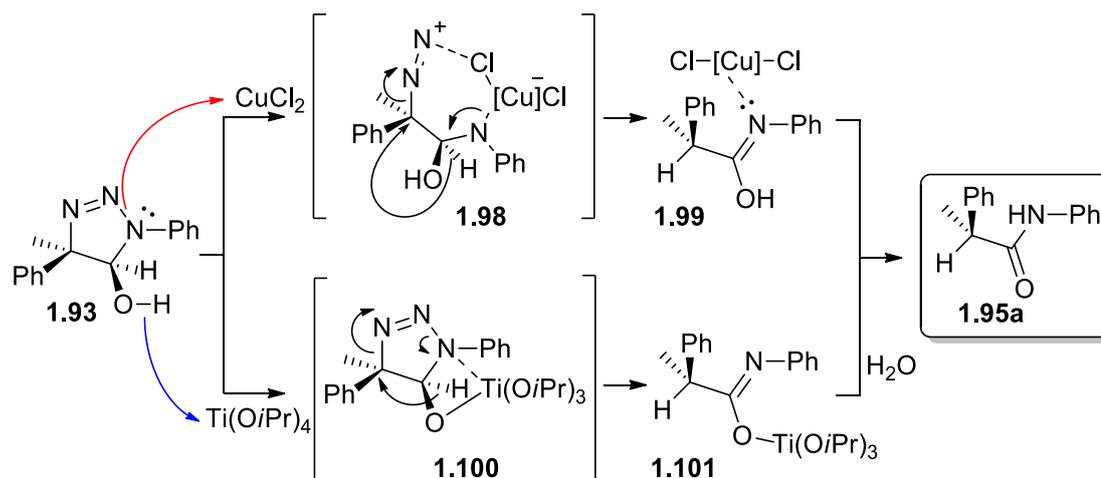


Entry	1.77e (eq.)	1.80a (eq.)	DBU (eq.)	Ti(O <i>i</i> Pr) ₄ (eq.)	Yield ^b (%)
1	1.5	1.0	0.1	1.1	60
2	1.0	2.0	0.1	2.0	61
3	1.0	1.2	0.1	1.2	59
4 ^c	1.0	1.2	0.1	1.2	65
5	1.0	1.2	0.02	1.2	35
6	1.0	1.2	0.5	1.2	59
7	1.0	1.2	0.2	1.2	65
8	1.0	1.2	0.2	2.0	62
9	1.0	1.2	0.2	0.5	49
10 ^d	1.0	1.2	0.2	1.2	68
11 ^{d,e}	1.0	1.2	0.2	1.2	66

^a Reaction conditions: **1.77e** (0.5 mmol), DMSO (1 ml), toluene (5 ml). ^b Isolated yield over two steps. ^c Workup with neutral water. ^d Second step carried out at 45 °C for 2h. ^e First step carried out at 45 °C for 2 h.

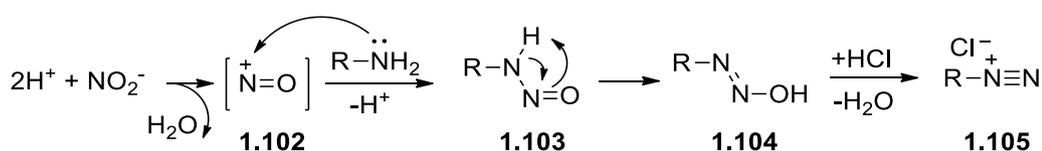
The data collected showed that **1.95e** was obtained in moderate to good yields by adjustment of the temperature at the second step. In this regard, it should be noted that an increase of temperature from 20 °C to 45 °C maximised the yield of **1.95e** and shortened the reaction time from 20 to 2 h. Conversion of **1.93** to **1.95e** proceeded best in the presence of an excess of Ti(IV), while sub-stoichiometric amounts of Ti(IV) gave reduced yields (Table 3, entries 8 and 9). It was found that neutral aqueous workup before execution of step 2 was beneficial to the overall yields of **1.95e** (Table 3, entries 3 and 4). Finally, it was noted that carrying out the first step at 45 °C was not detrimental to the reaction yield (Table 3, entry 11). A mechanism for

the metal-promoted nitrogen elimination was postulated (Scheme 19). In the case of copper (II) chloride our hypothesis is an initial coordination to the sp^3 nitrogen that would further weaken the N^1-N^2 bond. On this aspect, an interaction with the basic chloride would stabilise diazo-intermediate **1.98**. A 1,2-hydride shift triggered by nitrogen elimination would produce imine **1.99** which is the tautomer of **1.95a**. A similarly plausible mechanism involves the initial coordination of the oxygen by the metal (depicted in Scheme 19 as a more likely approach for an oxo-philic titanium (IV)), the proximity of a covalently bond strong Lewis acid could then promote the polarization of N^1-N^2 bond until its rupture.



Scheme 19: Possible mechanisms of the metal-promoted triazoline decomposition.

In order to test the scope of this optimised transformation, a library of azides was prepared, starting from commercially available anilines. The diazotation reaction is the most convenient synthetic approach to aromatic azides, but safety precautions must be taken when handling diazonium salts and organic azides as both are explosive and shock sensitive.⁴⁶ The reaction mechanism involves the *in situ* formation of nitrous acid by combination of a strong mineral acid and sodium nitrite (Scheme 20). The acid-catalysed dehydration of nitrous acid generates the reactive nitrosonium species **1.102**, which in turn is subject to nucleophilic addition by aniline. Sigmatropic rearrangement to hydroxy-azacompound **1.104** and subsequent dehydration allow the formation of diazonium salt **1.105**, which is an excellent leaving group for nucleophilic aromatic substitutions (S_NAr).



Scheme 20: Diazotation mechanism.

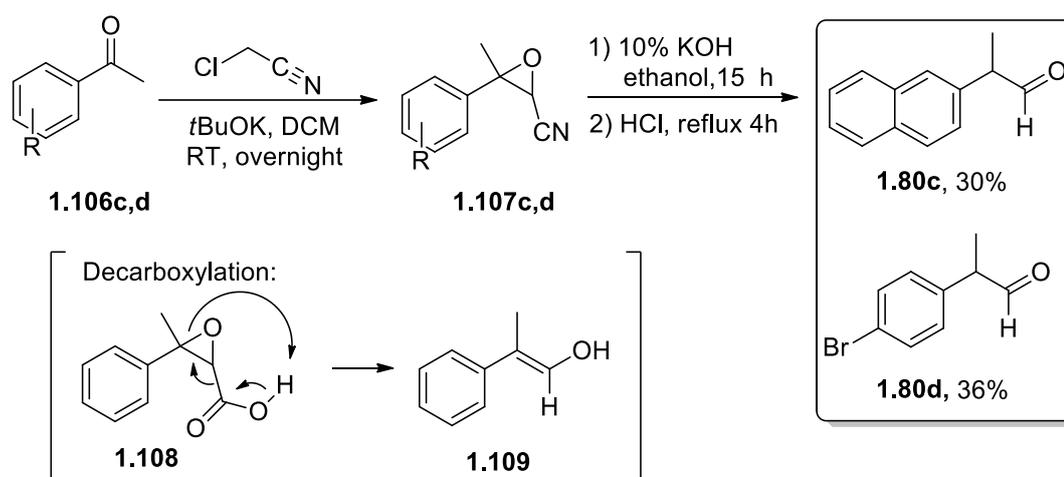
Azides **1.77a-I** were prepared by diazotation with sodium nitrite in aqueous HCl, followed by nucleophilic aromatic substitution with sodium azide (Table 4).

Table 4: Synthesis of a library of aromatic azides.^a

Entry	Product	R	Yield (%)
1	1.77a	Ph	78
2	1.77b	4-NO ₂ C ₆ H ₄	30
3	1.77c	1-naph	63
4	1.77d	4-MeOC ₆ H ₄	66
5	1.77e	4-MeC ₆ H ₄	88
6	1.77f	3,5-(CF ₃) ₂ C ₆ H ₄	53
7	1.77g	4-ClC ₆ H ₄	44
8	1.77h	2,4-(Cl) ₂ C ₆ H ₃	68
9	1.77i	4-BrC ₆ H ₄	53
10	1.77j	4-FC ₆ H ₄	60
11	1.77k	4-Me-2-NO ₂ C ₆ H ₃	79
12	1.77l	4-(SO ₂ NH ₂)C ₆ H ₄	14

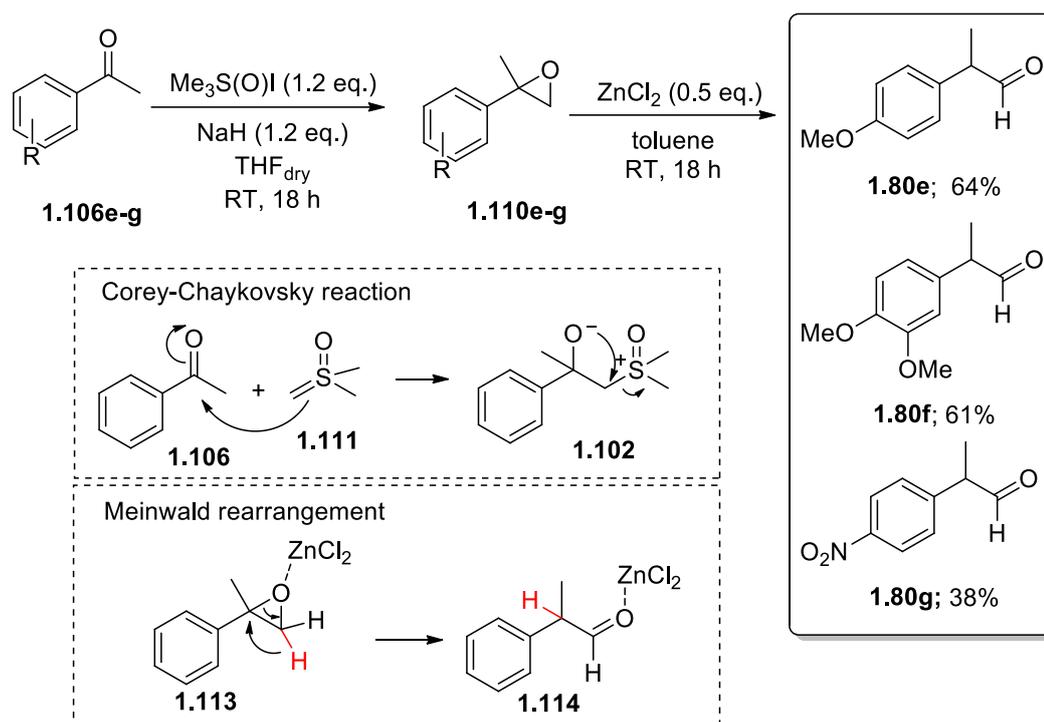
^a Reaction conditions: **1.106a-l** (16 mmol), HCl 37% (89 mmol), NaNO₂ (16 mmol), NaN₃ (16 mmol), water (20 ml) 0 °C, 1 h.

Azides **1.77a-l** were isolated by extraction with diethyl ether and simple filtration over silica gel of the crude mixture. Anilines bearing electron-withdrawing groups provided the corresponding azide with lower yields compared to the electron-rich counterparts (Table 4, entries 2, 6). This is due to the low basicity of anilines **1.106b,f**, which were not fully dissolved in water as a hydrochloric salt. A similarly low result was obtained with aniline **1.106l** whose sulfonamide substituent imparted a very low solubility in acidic aqueous media (Table 4, entry 12). Similarly to the preparation of the various azides **1.77a-l**, 2-phenylpropionaldehyde was decorated with electron donating and electron withdrawing groups. The chosen synthetic strategy was the Darzens reaction of the corresponding acetophenones **1.106** (Scheme 21).⁴⁷ Cyanoepoxide **1.107** was then hydrolysed with ethanolic potassium hydroxide and the resulting carboxylate **1.108** underwent decarboxylation when acidified and heated (Scheme 21).



Scheme 21: Synthesis of branched propionaldehydes *via* Darzens reaction; mechanism of the decarboxylation.

Unfortunately, strong electron donating and electron withdrawing groups on the phenyl ring of cyanooxiranes **1.107** prevented the decarboxylation from being successful, since starting material acetophenone was recovered from the reaction mixture, together with unidentified material. Therefore, 2-arylpropionaldehydes **1.80d-f** were prepared by Corey-Chaykovsky epoxidation of acetophenones **1.106e-g** followed by Lewis acid-promoted Meinwald rearrangement (Scheme 22). Corey-Chaykovsky ylide **1.111** was generated by deprotonation of trimethylsulfoxonium iodide; species **1.111**, which is a strong nucleophile, reacted with the carbonyl of ketone **1.106**.⁴⁸ The resulting internal salt **1.112** rapidly underwent intramolecular nucleophilic substitution to yield branched aldehyde **1.80**. Meinwald rearrangement consists of a Lewis acid-catalysed hydride shift of an epoxide such as **1.113**.⁴⁹ The most commonly employed Lewis acid for this transformation is indium (III) chloride; in this study was instead used inexpensive zinc (II) chloride, whose application on this type of transformation is not reported in the literature. Aldehydes **1.80e-g** were so obtained in moderate to good yields by reacting acetophenones **1.106e-g** with trimethylsulfoxonium iodide in presence of an excess of sodium hydride. Intermediate terminal epoxides **1.110e-g** were reacted with a catalytic amount of Zn(II) chloride in toluene and final aldehydes **1.80e-g** were isolated after column chromatography (Scheme 22).



Scheme 22: Corey Chaykovsky reaction followed by Meinwald rearrangement of acetophenones.

With a procedure and a library of substrates in hand, the scope of the reaction was studied by subjecting azides **1.77a-l** and aldehydes **1.80a-g** to the dual catalysis of DBU and Ti(IV) (Table 5). Azides **1.77a-l** employed in this study were selected to include either an electron-donating or electron-withdrawing substituent: this was deliberately planned in consideration of the known dependence of the azide reactivity on the electronic nature of the substituent directly attached. In a similar manner, electron withdrawing and electron donating groups were introduced on the aromatic portion of the aldehyde to establish the dependence of amidation on electronic factors (Table 5, entries 15-18). Notably nitro-substituted aldehyde **1.80g** was not reactive in the tested reaction condition, probably due to a too soft nucleophilic character of the delocalised enolate derived from **1.80g**. Replacement of the phenyl group with a 2-naphthyl probed the steric demand of the reaction (Table 5, entry 14). The results obtained showed that amides **1.95a-q** were obtained in good to excellent isolated yield (57-95%). This study proved the following facts: (a) electron withdrawing groups present on the azide were beneficial in providing higher yields of the resulting amides (Table 5, entries 1-11); (b) azides possessing sterically demanding substituent reacted equally well (Table 5, entry 8); (c) scarcely soluble azidosulfonamide **1.77i** provided amide **1.95i** with an equally good yield (Table 5, entry 12); (d) aldehydes possessing a weak electron withdrawing group provided amides in higher yield compared to those possessing an electron donating group (Table 5, compare entries 16-18), (e) aldehydes possessing a larger group than a methyl provided the corresponding amide in high yields (Table 5, compare entries 2 and 13).

Table 5: The study of reaction scope for the two-step preparation of amides **1.95a-r**^a

Entry	Product	Ar	Aldehyde 1.80a-f	Yield (%)
1 ^b	1.95a	Ph	1.80a , R = Ph, R ¹ = Me	76
2 ^c	1.95b	4-NO ₂ C ₆ H ₄	1.80a , R = Ph, R ¹ = Me	99
3 ^b	1.95c	1-naph	1.80a , R = Ph, R ¹ = Me	69
4 ^b	1.95d	4-MeOC ₆ H ₄	1.80a , R = Ph, R ¹ = Me	75
5	1.95e	4-MeC ₆ H ₄	1.80a , R = Ph, R ¹ = Me	72
6	1.95f	3,5-(CF ₃) ₂ C ₆ H ₄	1.80a , R = Ph, R ¹ = Me	92
7 ^b	1.95g	4-ClC ₆ H ₄	1.80a , R = Ph, R ¹ = Me	77
8	1.95h	2,4-(Cl) ₂ C ₆ H ₃	1.80a , R = Ph, R ¹ = Me	81
9	1.95i	4-BrC ₆ H ₄	1.80a , R = Ph, R ¹ = Me	75
10	1.95j	4-FC ₆ H ₄	1.80a , R = Ph, R ¹ = Me	76
11	1.95k	4-Me-2-NO ₂ C ₆ H ₃	1.80a , R = Ph, R ¹ = Me	82
12	1.95l	4-(SO ₂ NH ₂)C ₆ H ₄	1.80a , R = Ph, R ¹ = Me	72
13	1.95m	4-NO ₂ C ₆ H ₄	1.80b , R = R ¹ = Ph	89
14	1.95n	4-NO ₂ C ₆ H ₄	1.80c , R = 2-naphtyl, R ¹ = Me	72
15	1.95o	4-NO ₂ C ₆ H ₄	1.80d , R = 4-BrC ₆ H ₄ , R ¹ = Me	95
16	1.95p	4-NO ₂ C ₆ H ₄	1.80e , R = 4-MeOC ₆ H ₄ , R ¹ = Me	57
17	1.95q	4-NO ₂ C ₆ H ₄	1.80f , R = 2,4-(OMe) ₂ C ₆ H ₃ , R ¹ = Me	67
18	1.95r	4-NO ₂ C ₆ H ₄	1.80g , R = 4-NO ₂ C ₆ H ₄ , R ¹ = Me	-

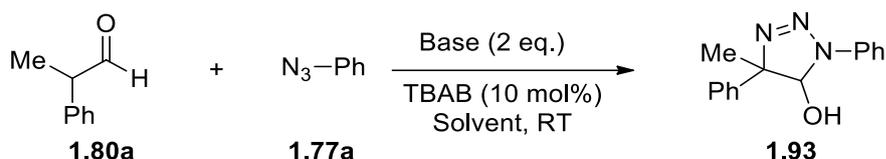
^a Reaction conditions: 1) **1.77a-l** (0.8 mmol), **1.80a-f** (1.0 mmol), DBU (0.2 mmol), DMSO (1.6 ml), 45 °C, 1 h; 2) Ti(O*i*Pr)₄ (1.0 mmol), toluene (8 ml), Isolated yield over two steps. ^b First step carried out at 20 °C for 4 h. ^c Product isolated quantitatively after first step.

1.2.2 Phase transfer catalysed triazoline formation

Phase transfer catalysis presents many advantages compared to other organic catalyses, such as mild experimental conditions and the employment of inexpensive and non-toxic reagents.⁵⁰ Our group has recently described some highly enantioselective cyclopropanations^{51–53} and Michael reactions^{52,54–56} that run in the presence of Cinchona based quaternary ammonium salts. Considering that the reaction of **1.80** and **1.77** to form triazoline **1.93** ran under a basic catalysis, we posed the question whether the use of a chiral catalyst may lead to the formation of **1.93** in a stereocontrolled fashion. As a first attempt, we reacted azidobenzene **1.77a** (0.1M in toluene) and 2-phenylpropionaldehyde **1.80a** in the presence of 2 eq. of cesium fluoride and 0.1 eq. of tetrabutylammonium bromide (TBAB) for 18 h. Delightfully, this experiment provided triazoline **1.93** in an encouraging 62% yield (Table 6, entry 1). We therefore embarked on a systematic study to determine the best solvent and inorganic base to obtain **1.93** in high yields. This set of experiments entailed reacting **1.77a**

and **1.80a** in four different solvents and in the presence of five bases of increasing strength at room temperature. The conversion of **1.77a** and **1.80a** to triazoline **1.93** was determined by $^1\text{H-NMR}$. The best result was obtained when Cs_2CO_3 was employed as the base (Table 6, entries 4,9 and 14) and dichloromethane as the solvent (Table 6, entry 19). It was also noted that carrying out the reaction at $3\text{ }^\circ\text{C}$ for an extended time of 48 h (Table 6, entry 20) provided a cleaner reaction mixture and compound **1.93** was obtained in maximised yields (up to 96%). Hence, this study determined Cs_2CO_3 as the optimal base, DCM as the preferred solvent and $3\text{ }^\circ\text{C}$ as the best temperature to convert **1.77a** and **1.80a** into the desired **1.93**.

Table 6: Solvent and base screening for phase transfer catalysed triazoline formation^a

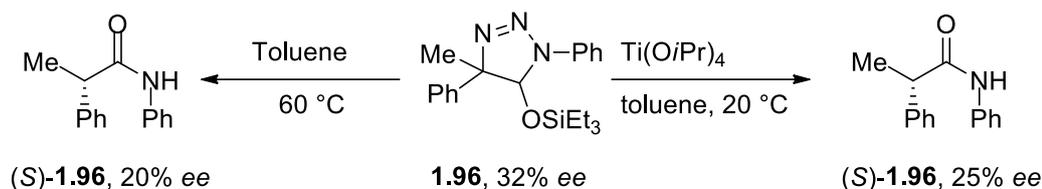


Entry	Base	Solvent	Time (h)	1.93 conv. %
1	CsF	toluene	72	62
2	K ₂ CO ₃	toluene	24	0
3	K ₃ PO ₄	toluene	24	0
4	Cs ₂ CO ₃	toluene	44	78
5	LiOH	toluene	24	0
6	CsF	CPME ^b	24	49
7	K ₂ CO ₃	CPME	24	0
8	K ₃ PO ₄	CPME	24	21
9	Cs ₂ CO ₃	CPME	24	82
9	LiOH	CPME	24	0
10	CsF	THF	24	69
11	K ₂ CO ₃	THF	24	58
12	K ₃ PO ₄	THF	24	0
13	Cs ₂ CO ₃	THF	28	87
14	LiOH	THF	28	0
15	CsF	DCM	48	32
16	K ₂ CO ₃	DCM	28	0
17	K ₃ PO ₄	DCM	28	0
18	Cs ₂ CO ₃	DCM	28	88
19 ^c	Cs ₂ CO ₃	DCM	48	96
20	LiOH	DCM	28	0

^a Reaction conditions: **1.77a** (0.5 mmol), **1.80a** (0.6 mmol), base (1.5 mmol), TBAB (0.05 mmol), solvent (5 ml), $20\text{ }^\circ\text{C}$; ^b CPME = cyclopentyl methyl ether; ^c reaction carried out at $3\text{ }^\circ\text{C}$.

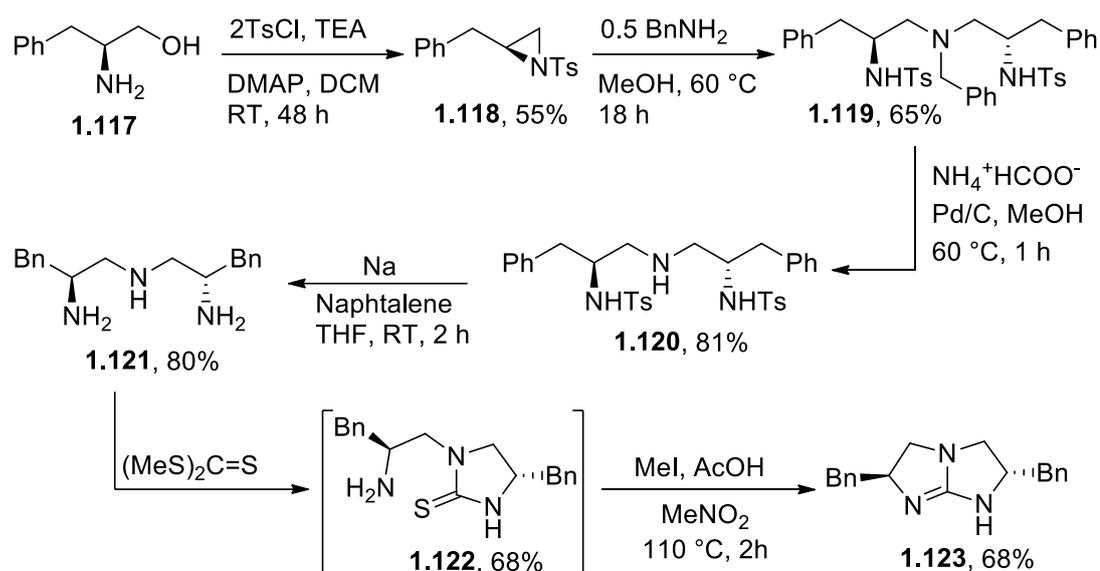
At this point, we combined the results from the study of metal-promoted decomposition of triazolines to amides (Tables 2,3) with the phase transfer catalysed procedure identified to generate triazolines from parent aldehydes and azides. (Table 6). Hence, azides **1.77a-f** and aldehyde **1.80a** went through a procedure involving the two consecutive reactions highlighted above (Table 7). This entailed allowing **1.77a-f** and aldehyde **1.80a** to react in the presence

application has been extensively studied on a wide range of base-catalysed reactions.⁵⁷ Hence, a library of chiral ammonium salts derived from four *Cinchona* alkaloids was tested under similar conditions identified for TBAB (Table 6), but with K_2CO_3 as the base which ensured best *ees* (Table 8). In order to measure the enantioselectivity of this reaction and considering the instability of **1.93** in a polar chromatographic column (compound **1.93** could not be directly analysed by chiral HPLC), it was decided to carry out the reaction to the amide and measure the *ee* on compound **1.95a**. A selection of quaternary ammonium salts **1.115a-k** and their pseudo-enantiomeric counterparts **1.116a-f** bearing three elements of diversity, namely R^1-R^3 , were tested in the reaction of azide **1.77a** and aldehyde **1.80a**. Notably, both Lygo ($R^1 = H$)³³ and Corey type ($R^1 = \text{alkyl}$)³⁴ were employed for this study. This screening revealed that compound **1.95a** could be obtained only in modest enantioselectivity, which seemed almost independent on the nature of the substituents present on the catalysts. The best results were obtained when quaternary ammonium species **1.115e** (Table 8, entry 5), **1.115i** (Table 8, entry 9) and **1.116d** were employed (Table 8, entry 15). The absolute stereochemistry of amide **1.95a** was determined to be *S* by comparison of the optical rotation of the enantioenriched compound obtained with **1.115a** ($[\alpha]_D = -70^\circ$) and the one reported for the *R* enantiomer ($[\alpha]_D = +120^\circ$).⁵⁸ Significantly, catalysts **1.115e**, **1.115i** and **1.116d** provided an excess of the same enantiomer *S* regardless of the stereochemistry of the catalyst employed with the exception of compound **1.115d** (Table 8, entry 4) that provided (*R*)-**1.95a** preferentially.

Scheme 23: Thermal and metal-catalysed rearrangement of enantioenriched **1.96**.

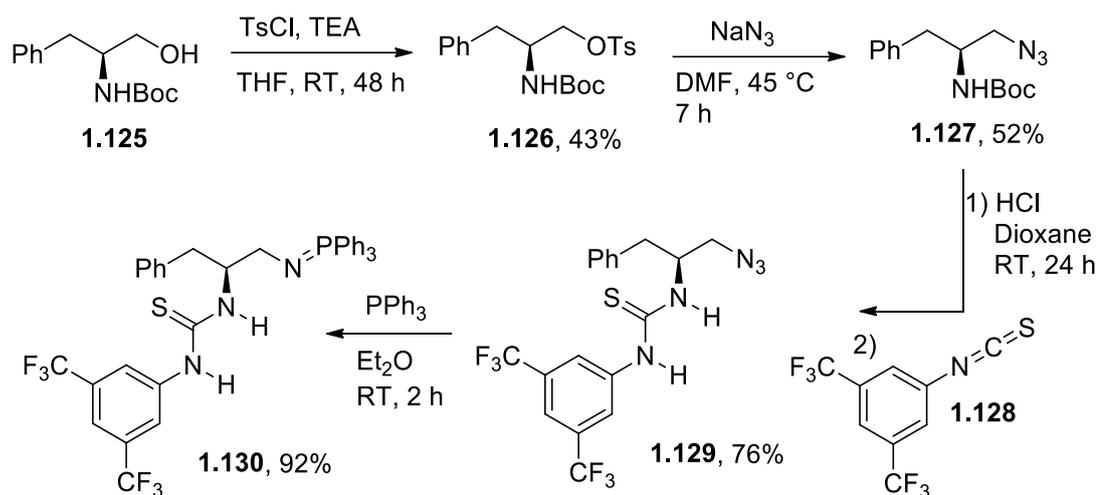
1.2.4 Chiral organic superbases-mediated synthesis of triazolines

While testing our base-catalysed triazolone formation with different organic bases and solvents (Table 1) it became evident that a strong organic base was needed, in order for the reaction to take place. The strength of a base is often expressed by the pK_a of the conjugate acid. Analysing Table 1 from this perspective, it can be said that only a base with a pK_a of the conjugate acid higher than 20 could catalyse the reaction between azide **1.77a** and aldehyde **1.80a**. This also explains why strong inorganic bases such as carbonates worked so well in a PTC reactive system. If we wanted to take this into consideration while attempting to obtain the same transformation in a homogeneous media we would inevitably have to choose a base belonging to the amidine, guanidine or phosphazene families. The possibility to produce enantiomerically-enriched triazolone **1.93** and to retain the stereochemical information in the decomposition product amide **1.95a** was validated by the catalyst screening performed on the *Cinchona*-derived chiral PTCs. It was so attempted an asymmetric version of the DBU-catalysed synthesis of triazolines, with a catalytic amount of chiral organic strong base. In order to identify the optimal catalyst structure, several chiral organic superbases were synthesised according to literature procedures. In 1999 Corey reported an innovative stereoselective Strecker synthesis of α -aminonitriles catalysed by bicyclic chiral guanidine **1.123** (Scheme 24).⁵⁹ In order to synthesise compound **1.123**, it was followed the improved synthetic pathway proposed by Tan and co-workers in 2005.^{41,60} C_2 -Symmetric guanidine **1.123** was obtained starting from (*S*)-phenylalaninol **1.117**, which was reacted with two equivalents of tosyl chloride in presence of trimethylamine and *N,N*-dimethylaminopyridine in DCM. Aziridine **1.118** was purified by column chromatography and was reacted with 0.5 molar equivalents of benzylamine in methanol. At this point, Tan's procedures suggested a detosylation with sodium in liquid ammonia, followed by a catalytic hydrogenation with hydrogen and palladium on carbon as a catalyst. Not being able to perform either due to the health and safety policies of our department, we were forced to find an alternative method. Hydrogenolysis of the benzyl groups on the secondary amine **1.119** was performed in the presence of *in situ*-generated hydrogen by combining ammonium formate and palladium on carbon in methanol.⁶¹ Detosylation of **1.120** with sodium naphthalenide in THF also proved to be a valid alternative to the published standard synthesis, and provided free triamine **1.121** in 80% yield.⁶² By condensation of **1.121** with dimethyltrithiocarbonate, intermediate thiourea **1.122** was formed and subsequent treatment with methyl iodide and acetic acid in nitromethane provided guanidine **1.123** as a brown solid (Scheme 24).



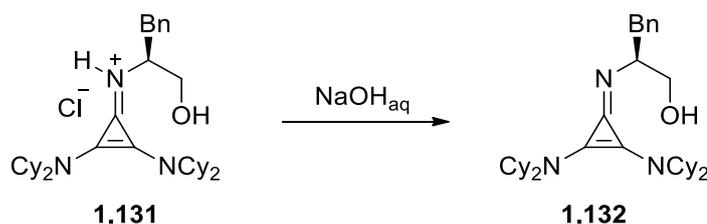
Scheme 24: Synthesis of chiral bicyclic guanidines and Corey's asymmetric Strecker synthesis.

In 2013 Dixon reported the synthesis and first application of bifunctional chiral iminophosphorane **1.130**, which combines a strongly basic Brønsted base with a thiourea motif, well known for its Lewis-acidity (Scheme 25).⁴⁰ Compound **1.130** successfully catalysed the stereoselective Mannich addition of nitromethane to *N*-phosphinyl-ketoimines. Iminophosphorane **1.130** was obtained following the experimental procedure reported by Dixon,⁴⁰ starting from (*S*)-*N*-Boc-phenylalaninol **1.125**, which was reacted with tosyl chloride in the presence of triethylamine, in order to turn the OH into a good leaving group. Tosylated **1.126** was reacted with sodium azide in DMF and the corresponding azide **1.127** was then deprotected on the amine functionality with a solution of hydrogen chloride in dioxane. The free amine was reacted with isothiocyanate **1.128** in THF at room temperature overnight. After purification via flash chromatography, azido-thiourea **1.129** was reacted with triphenylphosphine and a yellow solid corresponding to iminophosphorane **1.130** was isolated from the reaction crude after precipitation with hexane. This synthesis consisted of 5 steps with an overall yield of 16% (Scheme 25).



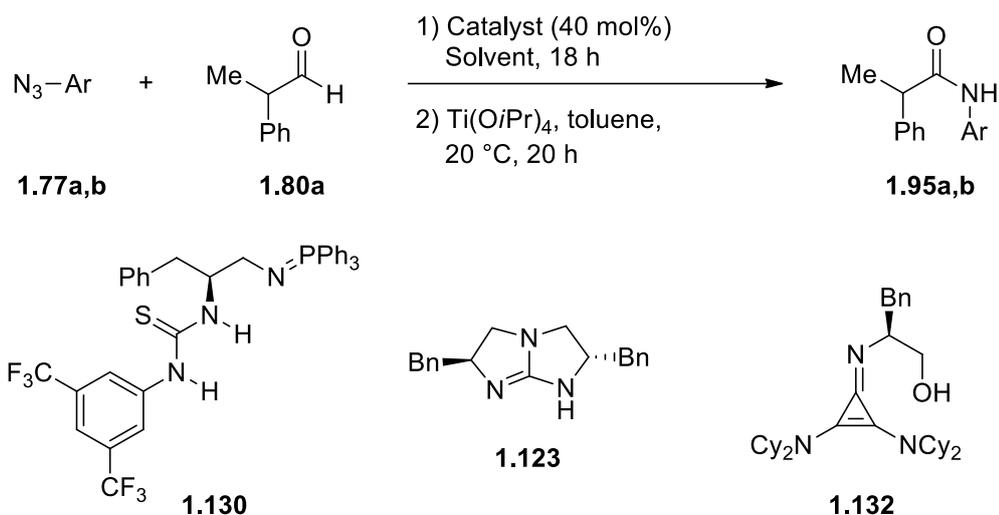
Scheme 25: Synthesis and application of Dixon's chiral iminophosphorane.

Cyclopropenimine **1.132** was firstly described by Lambert in 2015 as a highly selective catalyst for the Michael addition of glycine iminoesters to methyl acrylate (Scheme 26). The synthetic route to **1.132** is so simple that it became soon commercially available as a stable hydrochloric salt **1.131**, which can be easily converted to the active imine by washing with an aqueous solution of sodium hydroxide before use (Scheme 26).³⁸



Scheme 26: Lambert's cyclopropenimine and its application on Michael addition to methyl acrylate.

2-Phenylpropionaldehyde **1.80a** was then reacted with aromatic azides **1.77a,b** in the presence of a catalytic amount of the synthesised chiral organic superbases **1.123**, **1.130** and **1.132** (Table 9). Aprotic solvents such as DCM, AcOEt and DMSO were selected in order to maintain the reaction conditions the most similar to the optimised DBU-catalysed triazoline formation (Table 3). Intermediate triazolines were not isolated, but directly underwent decomposition towards compound **1.95a,b** when treated with Ti(IV) isopropoxide in toluene. Amides **1.95a,b** were purified by column chromatography and analysed by chiral HPLC. Catalyst **1.130** showed no activity in DCM and AcOEt, but it proved effective when a more polar solvent and a more reactive azide **1.77b** were employed (Table 9, entries 1-3). A similar trend could be observed with catalyst **1.123**, which gave the desired amide **1.95b** only when DMSO was the solvent of the reaction (Table 9, entry 5). Interestingly, when catalyst **1.132** was tested in AcOEt, heating the reaction up to 45 °C proved sufficient to obtain product **1.95b** with 50% of isolated yield, after treatment with Ti(IV) and column chromatography (table 9, entry 7).

Table 9: Synthesis of amides catalysed by chiral organic superbases^a

Entry	Product	Ar	Catalyst	Solvent	T (°C)	Yield (%) ^b	ee (%) ^c
1	1.95a	Ph	1.130	DCM	20	0	-
2	1.95a	Ph	1.130	AcOEt	20	0	-
3	1.95b	4-NO ₂ C ₆ H ₄	1.130	DMSO	20	50	0
4	1.95b	4-NO ₂ C ₆ H ₄	1.123	AcOEt	20	0	-
5	1.95b	4-NO ₂ C ₆ H ₄	1.123	DMSO	20	62	0
6	1.95b	4-NO ₂ C ₆ H ₄	1.132	AcOEt	20	0	-
7	1.95b	4-NO ₂ C ₆ H ₄	1.132	AcOEt	45	50	0

^a Reaction conditions: **1.77a,b** (0.5 mmol), **1.80a** (0.6 mmol), catalyst (0.2 mmol), solvent (2.5 ml) 18 h; ^b calculated from ¹H-NMR of the crude mixture, amide **1.95b** was directly recovered from the crude; ^c measure after flash chromatography of the crude amide (Chiralcel OD).

When amide **1.95b** was recovered from the reaction mixture, its stereochemical composition was analysed by chiral HPLC. Unfortunately, all the samples of amides **1.95a,b** coming from the reactions described in Table 9 were racemic. It could be stated that a solvent with a high dielectric constant was needed in order for the reaction to take place. DMSO could stabilise the formation of the ion-pair enolate-chiral base. This could result in a higher reaction rate due to an increased concentration of the reactive species in the reaction mixture. Moreover, the solvation of the ionic intermediate might loosen the interaction between the enolate and its counter-ion, making the former more available to the nucleophilic attack on the poorly electrophilic azide. The drawback of the pronounced solvating properties of DMSO is the excessive stabilisation not only of the enolate, but also of the transition state during the nucleophilic attack of the enolate on the azide. A strong solvation decreases the energy gap between two or more accessible transition states, thus dramatically lowering the enantiomeric control over a stereoselective transformation.

1.3 Conclusions

In conclusion, we have developed a two-step sequence for the preparation of amides **1.95a-q** starting from azides **1.77a-l** and aldehydes **1.80a-f**. We confirmed that this reaction proceeds *via* the formation of triazoline intermediate **1.93**, providing a method for its isolation and its derivatisation. Two alternative procedures that make use of Lewis-acids were optimised and provided **1.95a-q** in high isolated yields. The preparation of triazolines under achiral and chiral phase transfer catalysis was also studied and optimised, demonstrating that enantioenriched amides could be prepared from racemic aldehydes, although in low enantioselectivity. In order to obtain higher enantioselectivities, the use of chiral organic superbases was investigated, but no level of enantioselectivity was observed when the selected chiral guanidines and phosphazenes were employed in catalytic amount.

Further studies aimed at improving the enantioselectivity of this transformation have to be undertaken, along with mechanistic studies aimed at identifying a rationale for the enantiospecificity for both the triazoline formation and its decomposition to amide **1.95**.

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Chapter 2

**The base-promoted reaction of aromatic azides and
ester enolates**

2.1 Introduction

2.1.1 Properties of 1,2,3-triazoles

1,2,3-Triazole has become an important structural motif, which found application in many disciplines, such as medicinal chemistry, material science and agricultural chemistry. The rise in popularity of this heterocycle is predominantly due to the Copper catalysed Azide-Alkyne Cycloaddition (abbreviated CuAAC), which provided an efficient method of preparation and allows for biocompatible orthogonality.¹ Moreover, 1,2,3-triazoles are closely related to amides, possessing similar steric and physicochemical properties; as a consequence, 1,2,3-triazoles have been extensively used as peptidomimetics.² While 1,2,3-triazoles are not present in natural products, their bioequivalence to amides was exploited in the development of active compounds such as calcium influx inhibitor **CAI**³ or **AB2**, an HIV-1 protease inhibitor, prepared as part of a diversity oriented library, aimed at identifying HIV-1 inhibitors related to amprenavir (Figure 1).^{4,5}

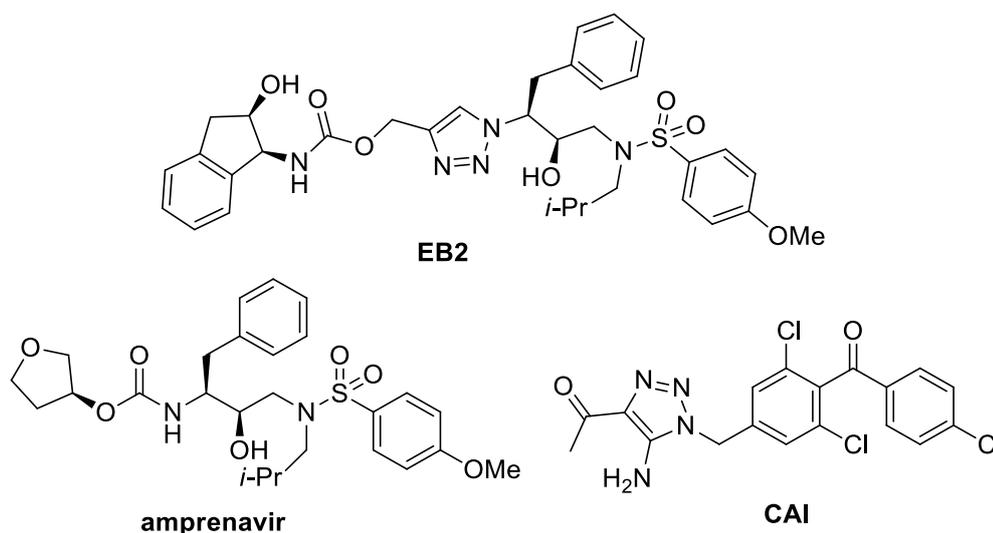


Figure 1: Biologically active 1,2,3-triazoles.

The chemical structure of 1,2,3-triazoles is constituted by an aromatic 5-membered ring where the 3 nitrogens are contiguous. The aromaticity, in accordance with Hückel's rule, derives from the presence of 6 π electrons delocalised over 5 atoms and confers to the cyclic structure remarkable stability and unique chemical reactivity, when compared to analogue heterocyclic 5-membered ring. The properties of *N*-heterocyclic compounds highly depend on the electronic configuration of the nitrogen taking part to the aromatic system. Compounds containing endocyclic aromatic nitrogens can be classified in two groups, based on whether the nitrogen lone pair is delocalised over the aromatic ring (pyrrole-type) or not (pyridine-type). In pyridine, the nitrogen lone pair is not involved in the formation of the aromatic system, hence is available to elicit a basic property. Pyridine is isoelectric to benzene, and possesses the same numbers of π electrons, but the presence of a strongly electronegative atom such as

nitrogen partially reduces the π -electron density, with a subsequent reduced reactivity over electrophilic aromatic substitution. Pyridine's nitrogen ($-N=C-$) is a weak σ -donor and a strong π -acceptor, in respect to the carbon atoms on the aromatic ring.⁶ Protonation of the nitrogen on pyridine does not disrupt the aromaticity, since it occurs on the non-shared lone pair. The π -cloud in pyrrole, on the other hand, is constituted by 4 sp^2 carbons and one nitrogen ($-NH-$). The nitrogen of pyrrole possesses low basicity, and can be easily deprotonated, since it is a σ -acceptor and π -donor. 1,2,3-Triazoles feature both pyrrole-like and pyridine-like nitrogens, therefore they can act both as acids and bases (Figure 2).

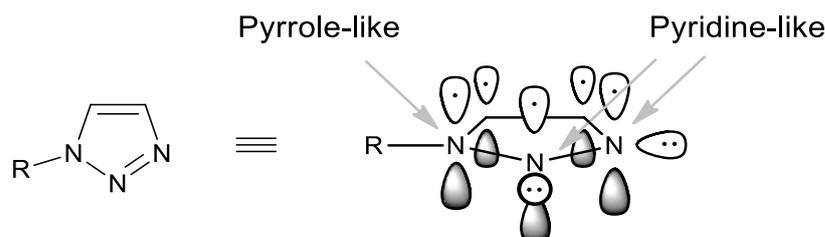


Figure 2: Electronic structure of 1,2,3-triazoles.

1,2,3-triazoles are polar molecules, having a dipole moment of 4.55 D, which makes them soluble in polar solvents,⁷ property often exploited in the pharmaceutical field. The high polarity of 1,2,3-triazoles can be explained by the resonance structures reported in Figure 3, where N-2 and N-3 have a partial negative charge, while N-1, C-4 and C-5 are partially positive, splitting the molecule in two separate sides with opposite polarisation. These considerations are backed by *ab initio* calculations and NMR studies.^{7,8}

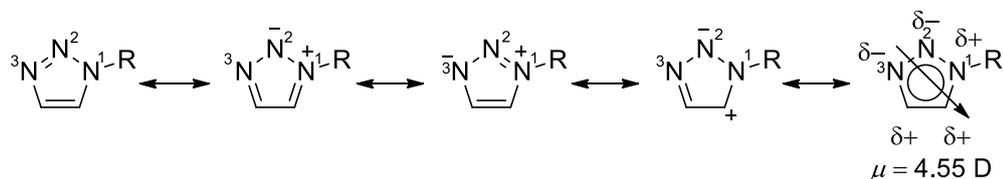


Figure 3: Selected resonance structure of 1,2,3-triazoles. Neat dipolar moment.

The acid-base properties of 1,2,3-triazoles are directly related to the electronic configuration of the molecule and therefore, the polarisation within the structure. In Table 1 is reported a comparison of the pK_a values for different azoles:⁶ it is evident that successive aza-substitution causes increasing polarisation of C-H and N-H bonds, with an increased CH- and NH-acidity as a result. The position adjacent to the pyrrole-type nitrogen possesses the highest acidity: as a result, the pK_a values for 1*H*-1,2,3-triazole are 35.0 and 27.8 for C-4 and C-5 respectively (Table 1). A base such as *n*-butyl lithium can readily deprotonate 1,2,3-triazoles, making this a common strategy for 1,2,3-triazole functionalisation.⁹ The NH-acidity is dependent on the inductive effect provided by the presence of other electron-withdrawing nitrogens in the ring (Table 1). The basicity in water of the pyridine-type nitrogen is dependent on the electronic content of the aromatic system and the presence of additional nitrogens. For example, the

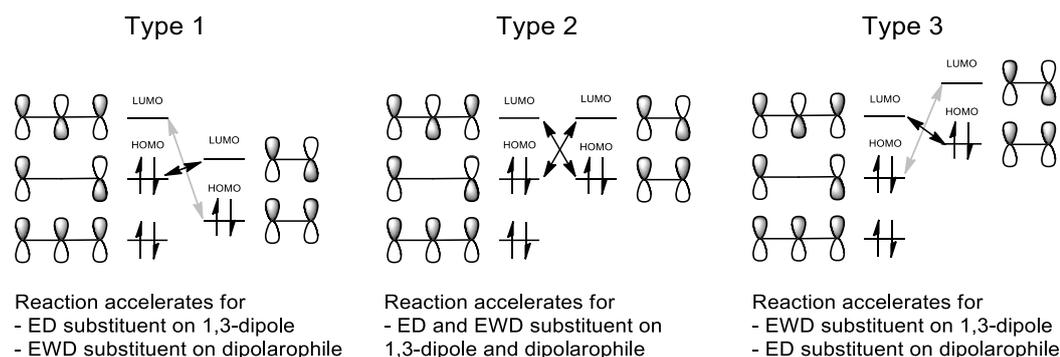
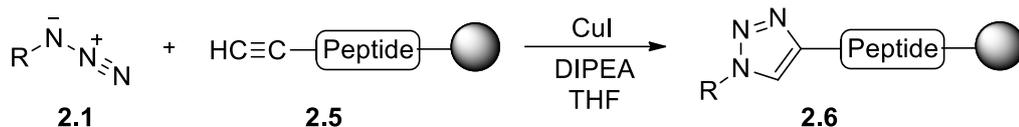


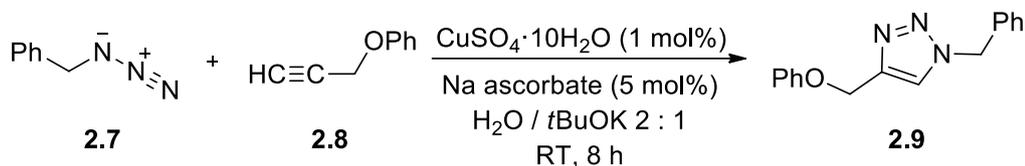
Figure 4: Classification of 1,3-dipolar cycloaddition according to Huisgen.

Dipoles of this type, are both nucleophilic and electrophilic: a typical example is the organic azide. Finally, type 3 systems are characterised by the presence of an electrophilic dipole, which therefore has a low energy LUMO, capable of interacting with the HOMO of the dipolarophile. Examples of LUMO-controlled dipoles are nitrous oxide and ozone. In the case of azide-alkyne 1,3-cycloadditions, it is possible to control the regioselectivity towards 1,4- or 1,5-disubstituted triazoles by introducing sterically demanding substituents, or by varying the electronic nature of the dipole and dipolarophile (and thus directing the reaction mechanism towards a type 1 or type 3 mechanism).¹¹ While Huisgen provided several examples of 1,3-cycloadditions, a general methodology for the preparation of 1,2,3-triazoles was published only in 2002, when Meldal and co-workers described the first Copper(I)-catalysed Azide-Alkyne Cycloaddition (CuAAC), which allowed to generate disubstituted-1,2,3-triazoles **2.6** at room temperature and with complete 1,4-regioselectivity (Scheme 2).¹² According to Meldal, copper(II) species did not accelerate this transformation, while the desired 1,2,3-triazoles were obtained in the presence of an appropriate copper(I) salt, which was employed at low catalyst loading (1 mol%) and in combination with an organic base. This transformation could be carried out on solid phase, which was a valuable feature in the perspective of peptide conjugation. Furthermore, the CuAAC showed significant chemoselectivity, since many organic functional groups were tolerated and did not react under the mild reaction conditions. In the same year, Sharpless and co-workers, independently reported a similar procedure, which involved the *in situ* generation of copper(I) species from inexpensive copper(II) sulfate and sodium ascorbate as a catalytic reductant (Scheme 2).¹³ Remarkably, this reaction could be carried out in water, giving later access to powerful bioconjugation techniques.¹⁴

Meldal, 2002

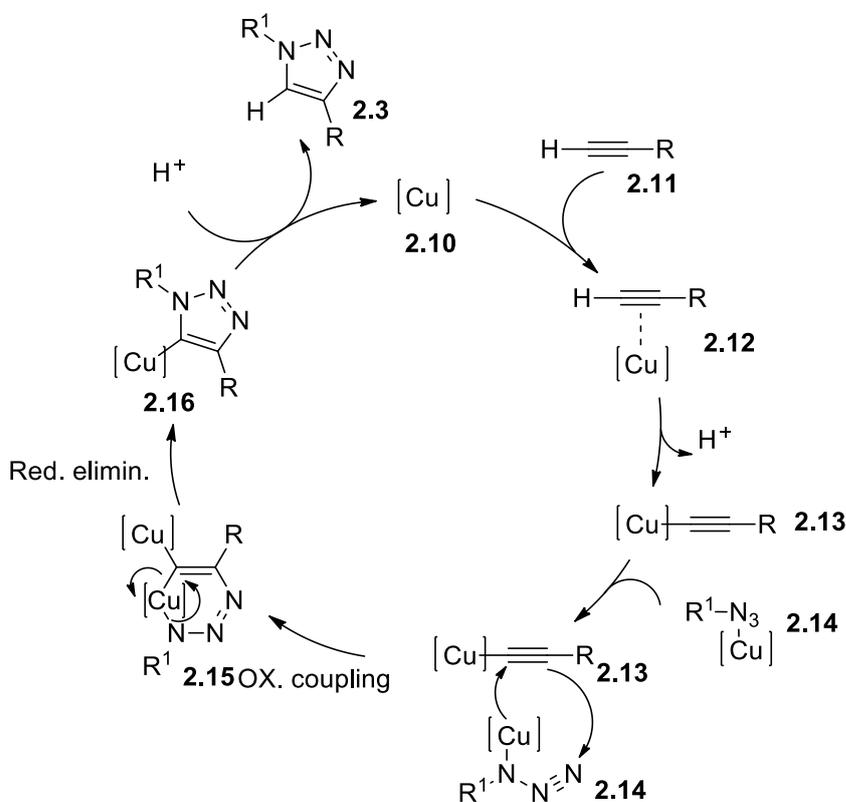


Sharpless, 2002



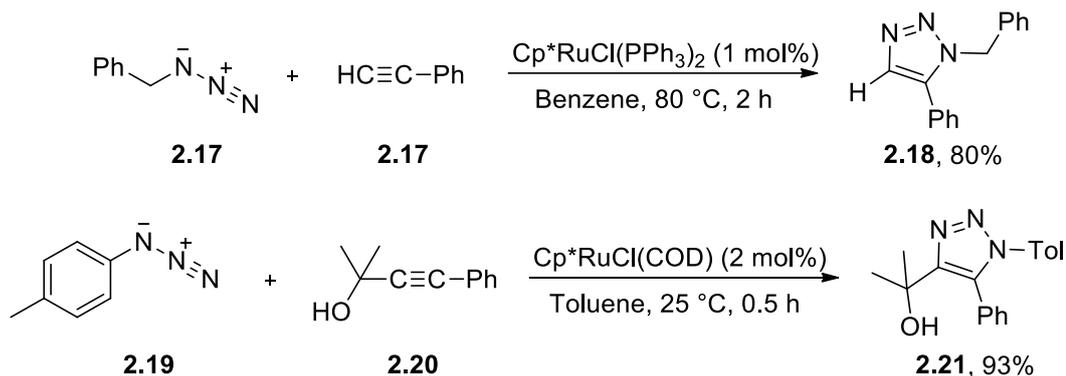
Scheme 2: Copper-catalysed azide-alkyne 1,3-cycloaddition.

The term click-chemistry was coined by Sharpless only one year before (2001), to describe a chemical transformation that is “*modular, wide in scope, high yielding, creates only inoffensive by-product (that can be removed without chromatography), is stereospecific, simple to perform and that requires benign or easily removed solvent*”.¹⁵ The fact that nowadays click-chemistry is often used as a synonym for CuAAC, is a notable indicator of the impact that this simple and efficient reaction had on the scientific community. In CuAAC, the presence of copper(I) species greatly increases the rate of the reaction, which can be carried out at room temperature.



Scheme 3: CuAAC: catalytic cycle.

The most accredited mechanism involves the initial formation of a copper(I) acetylide **2.13**, often facilitated by adding an organic base to the reaction mixture (Scheme 3). The coupling between acetylide **2.13** and coordinated azide **2.14** is believed to occur around two metal centers, with a formal oxidation of copper(I) to copper (II): kinetic studies have confirmed a second-order dependence with respect to the copper concentration.^{16,17} Ring contraction and Cu(I) extrusion *via* reductive elimination afford copper(I) triazolide **2.16** (Scheme 3). Finally, cuprated triazole **2.16** undergoes protonolysis to provide 1,4-substituted-1,2,3-triazole **2.3** (Scheme 3).

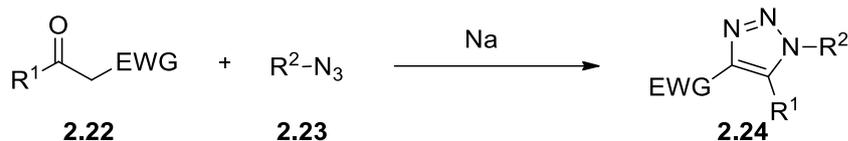


Scheme 4: Ruthenium-catalysed synthesis of 1,5-disubstituted-1,2,3-triazoles.

A few years later his first studies on CuAAC, Sharpless reported a complementary procedure for the regioselective synthesis of 1,5-disubstituted-1,2,3-triazole **2.18**;¹⁸ the use of catalytic ruthenium complexes in an organic solvent afforded 1,5-disubstituted-1,2,3-triazoles **2.18** in good yields. Conversely to CuAAC, this transformation could also be successfully applied to internal alkynes, providing 1,4,5-trisubstituted-1,2,3-triazoles **2.21** in good yield and regioselectivity. However, this variant was shown working only when polar groups were present on the alkyne portion (Scheme 4).¹⁹

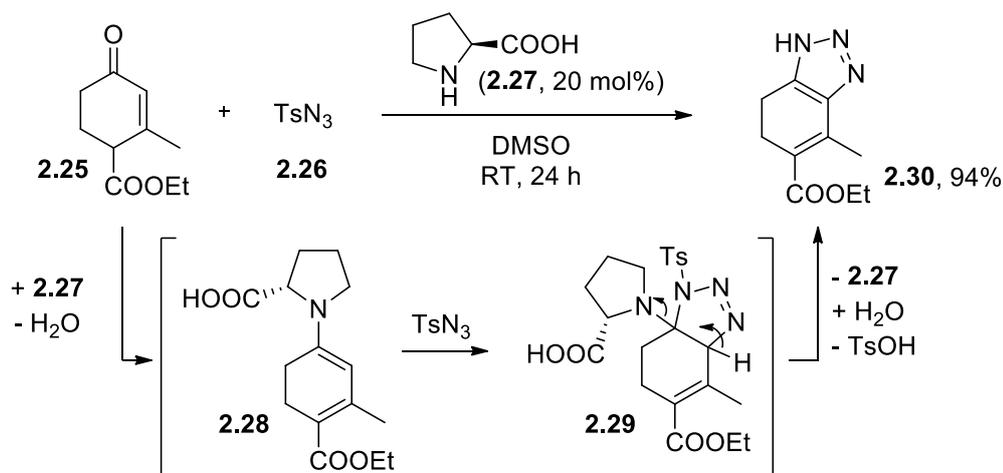
2.1.3 Organocatalytic synthesis of 1,2,3-triazoles

In the past decade, the organocatalysed synthesis of heterocyclic compounds has received much attention, especially in medicinal chemistry, where new efficient methodologies find immediate application and are used to produce chemical diversity and provide new conjugation techniques.^{20–22} The increasing popularity of the 1,2,3-triazole motif encouraged the study of new organocatalytic methods for the preparation of 1,2,3-triazoles, that may be complementary to the classic copper(I)-catalysed procedures. The majority of the organocatalysed triazole syntheses proceed *via* the formation of an enolate or enamine, which, by condensation with a molecule of organic azide, generate a triazocyclic compound. Dimroth reaction (year 1902) could be considered the first example of such a transformation, however, the harsh conditions required for the reaction to take place and the narrow substrate scope, limited the diffusion of this method (Scheme 5).²³



Scheme 5: Dimroth reaction for the synthesis of 1,2,3-triazoles.

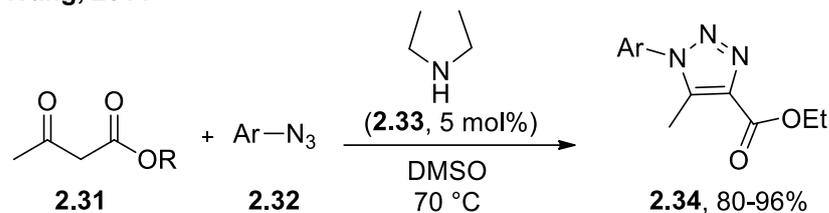
Recent methodology development has as objective the overcoming of such limitations, delivering new general catalytic syntheses of 1,2,3-triazoles; in this context, the use of mild organic amines proved successful, providing reactions with improved chemoselectivity and substrates scope.



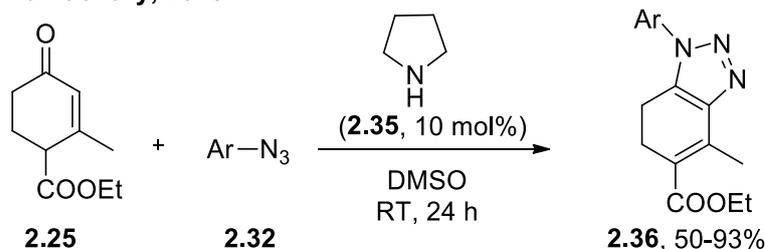
Scheme 6: First organocatalytic synthesis of 1,2,3-triazoles.

The first organocatalysed 1,2,3-triazole synthesis was described by Ramachary in 2008, as a proline-catalysed formation of bicyclic triazoles **2.30** (Scheme 6).²⁴ Hagemann's ester **2.25**²⁵ was reacted with tosylazide **2.26** in the presence of 20 mol% proline in DMSO. The mechanism of the reaction involves the formation of a nucleophilic dienamine **2.28**, which reacted with tosylazide to form intermediate triazolone **2.29**. Elimination of **2.27** afforded *N*-tosyltriazole **2.30**, which is not stable towards hydrolysis, therefore only hydrolysed 1H-1,2,3-triazole **2.30** was obtained as the product (Scheme 6). As an expansion of this work, Ramachary reported the optimised version of the enamine-catalysed cycloaddition of ketones **2.25** to aromatic azides **2.32** (Scheme 7).²⁶ The yields of this transformation were strongly dependent on the electronic content of the azide, being higher for electron-poor azides such as 4-(trifluoromethyl)azidobenzene (93% yield) and moderate for less electrophilic azides (i.e. 4-methylazidobenzene provided the correspondent triazole in only 50% yield) (Scheme 7). In 2011 Wang and co-workers applied a similar catalysis to the Dimroth reaction between β -ketoesters **2.31** or β -ketonitriles and aromatic azides **2.32** (Scheme 7). 4-Carbonyl-triazoles **2.34** were obtained in excellent yields, for both electron-rich and electron-poor azides when *N,N*-diethylamine was employed in catalytic amounts.

Wang, 2011

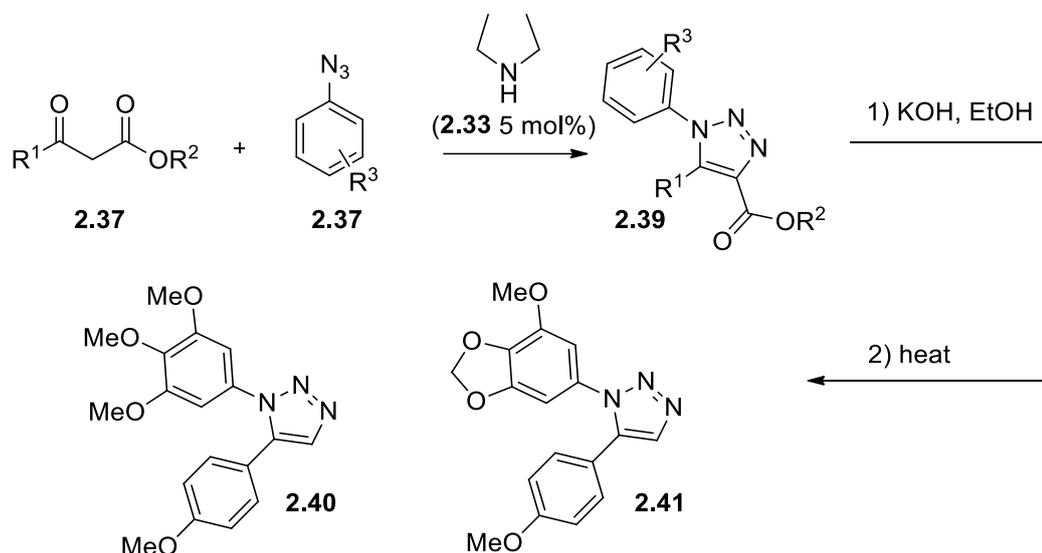


Ramachary, 2013



Scheme 7: Organocatalysed synthesis of substituted 1,2,3-triazoles.

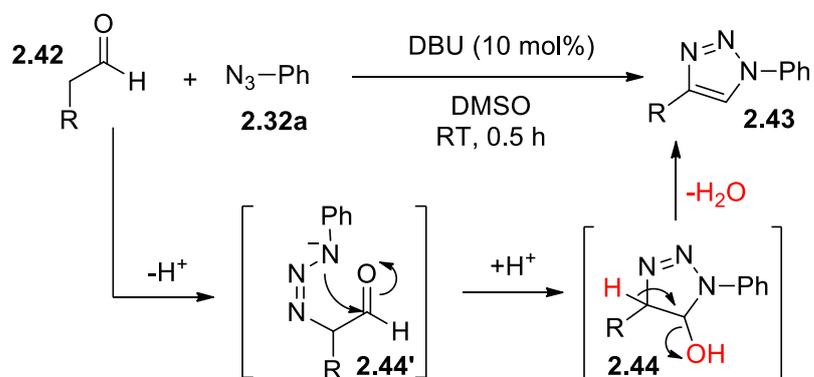
The catalytic synthesis of 4-carbonyltriazole **2.34** was successfully adapted to the preparation of biologically active compounds such as **2.40** and **2.41**, 1,2,3-triazole analogues of combretastatin.²⁷ The simplicity of this methodology, allowed Semenov and co-workers to perform a detailed study of the structure-activity relationships for 1,5-disubstituted-1,2,3-triazoles such as **2.40** and **2.41** against various human cancer cell lines (Scheme 8). Compounds **2.40** and **2.41** were found active at nanomolar concentrations ($IC_{50} = 10-20$ nM) as potent antimitotic microtubule destabilising agents.



Scheme 8: Synthesis of antitumoral combretastatin analogues.

The first organocatalysed reaction of an aldehyde **2.42** enolate with an aromatic azide **2.38** was reported by Ramachary in 2014 (Scheme 9).²⁸ The cycloaddition-elimination provided 1,4-disubstituted-1,2,3-triazoles **2.43**, and took place in the presence of a catalytic amount of

an organic base, required for the generation of intermediate **2.44'** (**Error! Reference source not found.**). This report instigated the work carried out on the synthesis of branched anilides that was described in Chapter 1.



Scheme 35: Triazole synthesis via enolate-azide cycloaddition

2.1.4 Hydroxamic acid as Histone deacetylase inhibitors

Histone proteins are responsible for organising DNA into structural units called nucleosomes. The complex DNA/proteins is called chromatin, which is made of repeating nucleosome units (Figure 5). Histone proteins are strongly basic, due to the numerous lysine and arginine residues; the basic sites are positively charged at physiological pH, and normally interact with the negatively charged phosphates constituting the DNA backbone. Acetylation of the basic sites neutralizes the positive charges on the histone by transforming amines into amides and decreases the ability of the histones to bind to DNA. When DNA is not tightly bound to the histones, gene transcription can take place. For this reason, in living systems the expression of some genes is often regulated by acetylation of the histone proteins, carried out by histone deacetylase enzymes (HDACs).²⁹

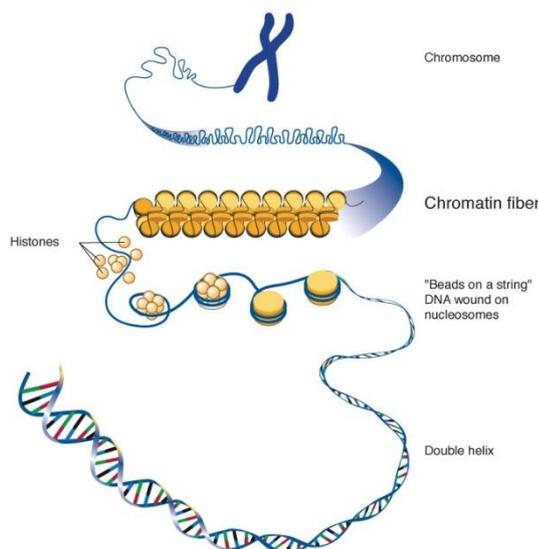


Figure 5: Nucleosomes organise the DNA into a compact structure that fits in the cell nucleus. Credit: National Human Genome Research Institute.

Aberrant expression of HDAC is characteristic of many leukemias, lymphomas and solid tumors.^{30,31} Dimethyl sulphoxide was one of the first chemicals to be identified as an inducer of transformed cell differentiation;³² it was later discovered that DMSO and other small polar organic molecules caused cytodifferentiation and growth arrest of murine erytroleukemia cell (MELC).³³ In particular, it was found that simple amides were even more potent than DMSO. By combining two amide functions, connected by a C₆ aliphatic chain, Marks and Breslow synthesised hexamethylene bisacetamide (HMBA, Figure 6). HMBA showed an increased potency of two orders of magnitude (5mM inhibited MELC growth) compared to DMSO and acetamide.³⁴ Hydroxamic acids are strong bidentate ligands that easily bind to transition metal complexes.³⁵ The hypothesis that the activity of polar molecules such as HMBA could be ascribed to the binding on a metal center present on the target, led to the synthesis of bis-hydroxamic acids SBHA and SAHA (Figure 6); SBHA proved very active at μM concentration, while SAHA was already active at nM concentrations. Suberoanilinohydroxamic acid (SAHA), features only one hydroxamic acid group and differs from SBHA for bearing a terminal lipophilic amide; it was chosen as a lead for preclinical trials as an anti-leukemia drug, due to its high potency and low toxicity profile. It was only in 1998 that histone deacetylases were identified as the main target of SAHA: the crystal structure of SAHA with a model histone deacetylase confirmed the mode of binding (Figure 6).^{36,37} The hydroxamic acid portion of the molecule was found to coordinate to a zinc atom present in a cavity of the protein, while the alkyl chain occupied a narrow lipophilic channel leading to a hydrophobic portion of the enzyme, where the anilide group was located.

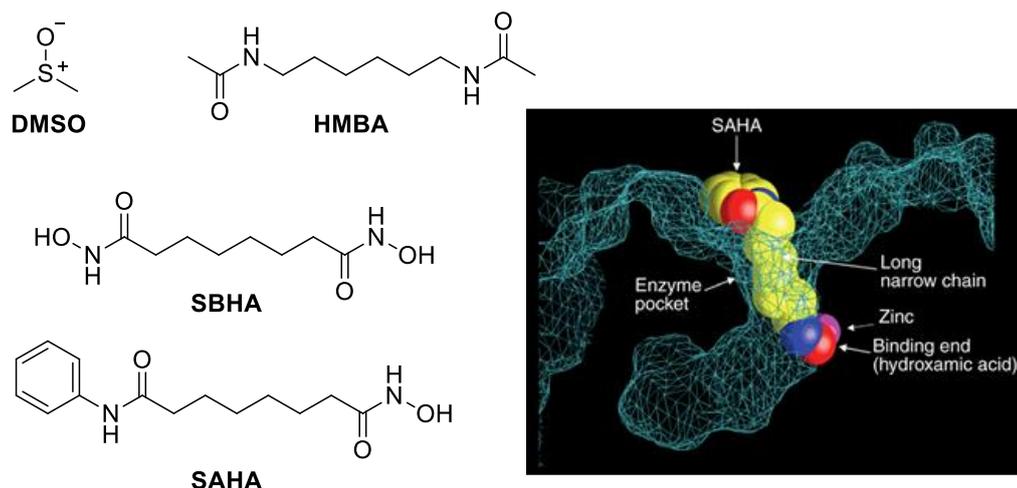


Figure 6: Small polar molecules as histone deacetylase inhibitors.

SAHA is now an FDA-approved drug for cutaneous T-cell lymphoma under the brand name Zolinza. Several clinical trials are still ongoing, in order to extend the application of SAHA, as a monotherapy or in combination with other drugs, to the treatment of renal cell carcinoma, metastatic cancers, multiple myeloma and colon cancer.³⁸ Other relevant histone deacetylase inhibitors belonging to the family of hydroxamic acid are Belinostat and Panobinostat (Figure 7), which are FDA-approved drugs for peripheral T-cell lymphoma and multiple myeloma respectively.^{39,40} Other families of polar molecules were found to selectively inhibit one class of HDACs: it is the case of benzamide Tacedinaline and tetrapeptide Romidepsin, which proved to block the activity of class I HDACs only and are currently under clinical trial for the treatment of T-cell lymphoma and solid tumors.^{41,42}

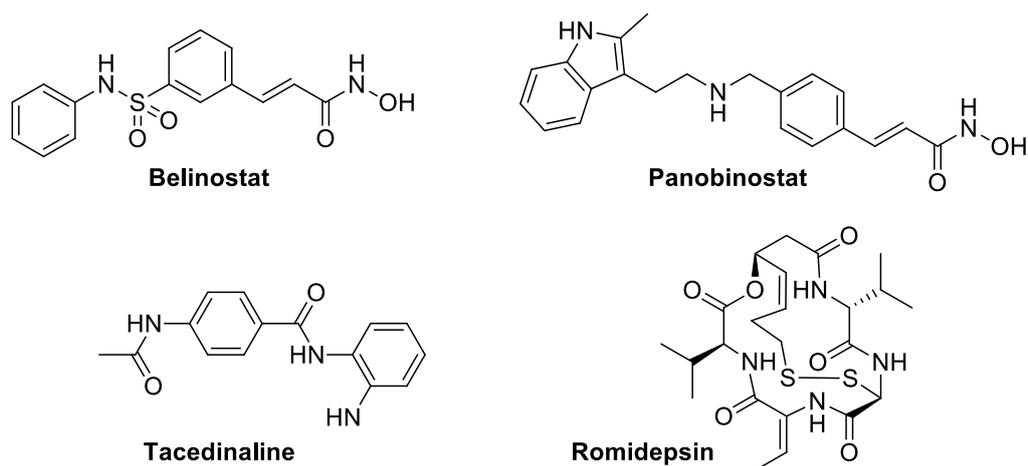


Figure 7: New generation of histone deacetylase inhibitors.

2.1.6 Introduction to strong Brønsted acid catalysis

According to the Brønsted-Lowry theory of acids and bases, a Brønsted-acid is a substance that donates a proton (H^+). Brønsted-acids have traditionally been used as a catalysts in acetal

formation reactions and, more in general, for C-O bond cleavage. More recently however, many interesting C-C bond formation reactions have been reported that include the use of a catalytic quantity of a strong protic acid.⁴³ The mechanism of action of a Brønsted-acid differs from that of a Lewis-acid for the formation of a tight ion pair, in which a neat positive charge is located on the protonated substrate; in contrast, a Lewis-acid withdraws part of the electron density of unsaturated systems, thus activating them towards a nucleophilic attack (Figure 8). One of the biggest advantages of Brønsted-acids over Lewis-acids lays in their high stability, in fact, Brønsted-acids are not water/moisture sensitive. Nowadays, chiral and non-chiral Brønsted-acid catalysis are very prolific fields of research. In this paragraph is reported a small selection of the most encountered structures and applications of this area, with particular emphasis on those catalysts possessing a pK_a between that of a carboxylic acids and a phenol ($pK_a = 5-15$, DMSO).

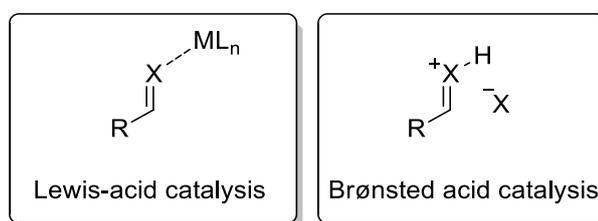


Figure 8: Lewis-acid catalysis and Brønsted-acid catalysis.

The most widely used Brønsted-acid catalysts belong to the classes of the mineral acids (HCl, H₂SO₄), carboxylic acids (acetic acid, benzoic acid, trifluoroacetic acid), sulfonic acids (*p*-toluenesulfonic acid, triflic acid) (Figure 9). A special class of Brønsted-acids are ureas and thioureas, which are characterised by a relatively low acidity, but have extraordinary H-bond donor properties, which make them ideal for carbonyl activation. A class of super strong organic Brønsted-acids is represented by nitrogen-acids and carbon-acids, whose exceptional catalytic activity has been object of several studies during the last decade.⁴⁴

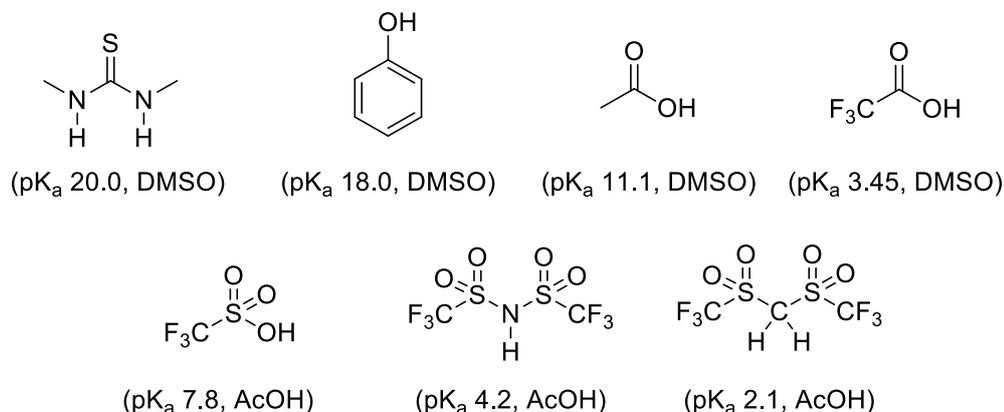
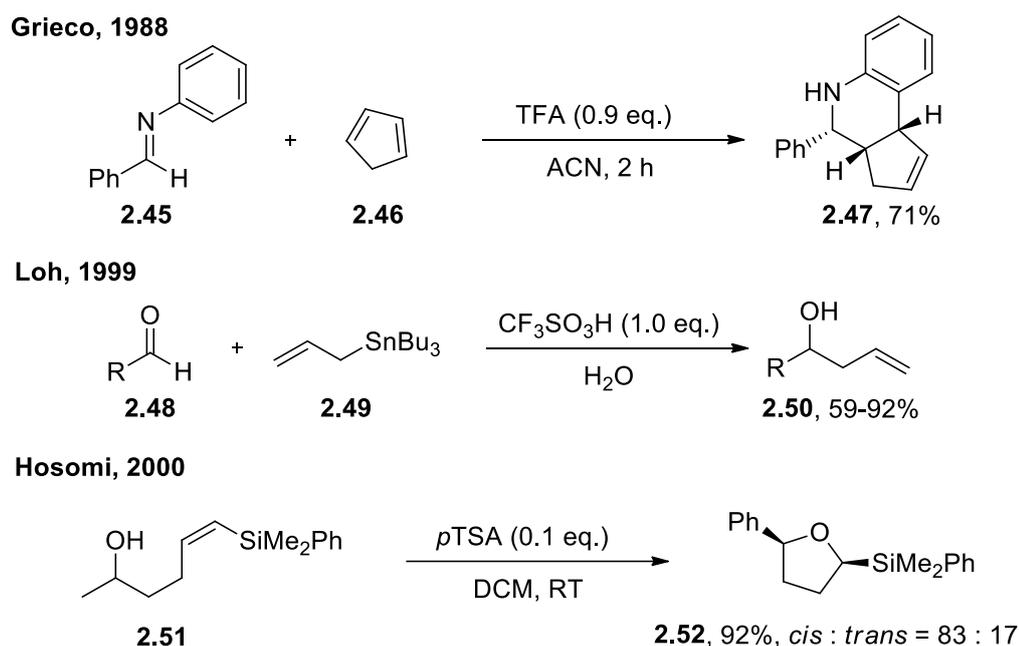


Figure 9: Examples of Brønsted-acids with their relative pK_a .⁴⁵

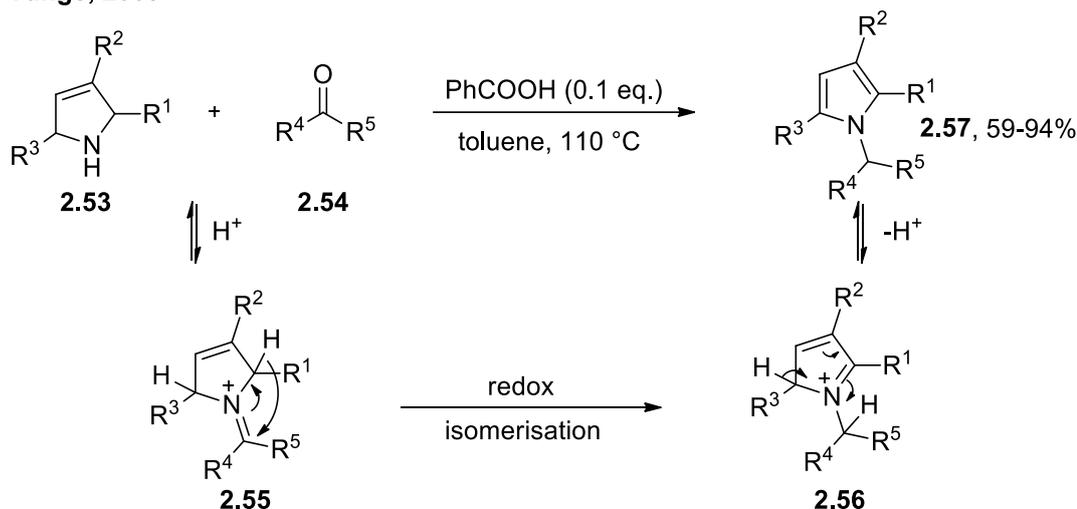
The first applications of Brønsted-acids to the C-C bond formation date back to the end of the last century; a selection of transformations promoted by achiral Brønsted-acids are reported in Scheme 10. In 1988 Grieco reported an aza-Diels-Alder reaction of *N*-arylimine **2.45** and cyclopentadiene **2.46** to give tetrahydroquinoline **2.47**; the reaction was carried out in the presence of trifluoroacetic acid in sub-stoichiometric amount (Scheme 10).⁴⁶ In 1999, Loh reported a triflic acid-catalysed Hosomi-Sakurai reaction between aldehyde **2.48** and allyl-stannane **2.49**.⁴⁷ This reaction could be carried out in water, and provided in good to excellent yields hydroxyalkenes **2.50**. Hosomi and co-workers reported a *cis*-selective intramolecular cyclisation of hydroxy-vinyl silane **2.51**, catalysed by *p*-toluenesulfonic acid (*p*TSA).⁴⁸



Scheme 10: Selection of Brønsted-acid-catalysed reactions.

More recently, benzoic acid was found to be an excellent catalyst for the intramolecular reductive amination of 3-pyrrolines **2.53** (Scheme 11).⁴⁹ The formation of 3-pyrroliniminium **2.55** *via* acid catalysis was followed by a 1,3-hydride shift. The aromatisation of **2.56** to a stable pyrrole ring provided *N*-alkylpyrroles **2.57** in good to excellent yields.

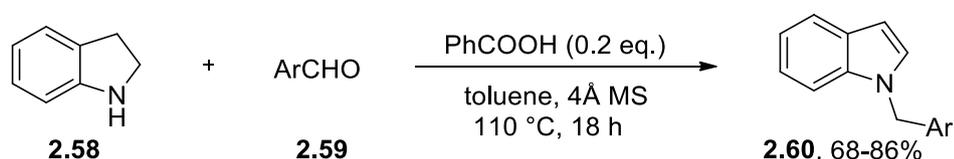
Tunge, 2009



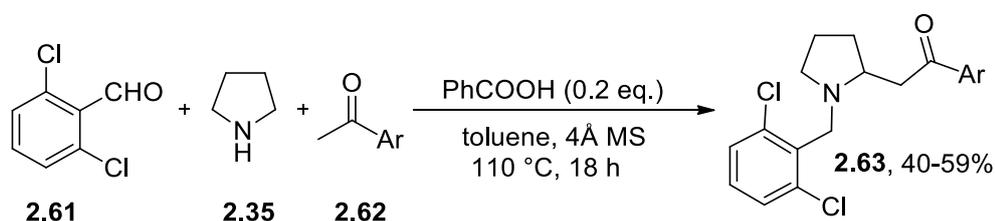
Scheme 11: Redox amination of ketones.

Similarly, *N*-alkylindoles **2.60** could be obtained from indoline **2.58** and aromatic aldehydes **2.59**, under the catalysis of benzoic acid (Scheme 12).⁵⁰ A highly dehydrating environment, provided by 4 Å MS, ensured a full conversion of **2.58** to *N*-alkylindoles **2.60**. A variation of this protocol was reported by Seidel, who described a 3-components Mannich reaction in which an internal hydride shift provided an iminium intermediate that was subsequently alkylated to give *N*,2-dialkylpyrrolidines **2.63** (Scheme 12).⁵¹

Pan, 2010



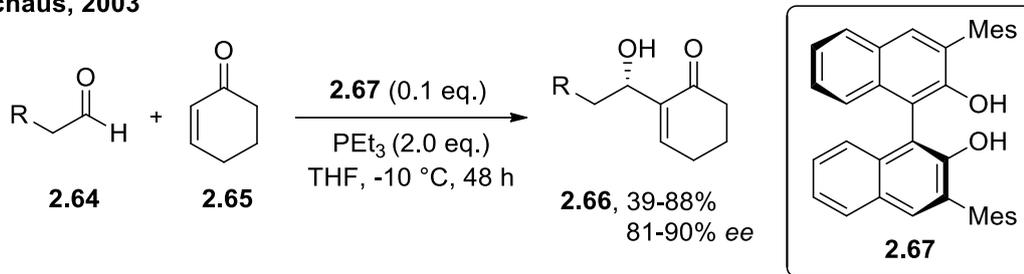
Seidel, 2014

Scheme 12: Benzoic acid-catalysed α -activation of pyrrolidinium compounds.

Since 1979, when Noyori first recognised its potential in the asymmetric reduction of ketones and aldehydes, 1,1'-bi-2-naphthol (BINOL) has been extensively used as chiral ligand for metal-mediated stereoselective transformations.⁵² Binaphthols were also adopted as the chiral scaffold of choice for one of the most important families of phase transfer catalysts.⁵³ Binaphthols acidity is relatively low (pK_a 9 in water), but their activity as Brønsted-acids could be successfully exploited in several stereoselective transformations. The first example of

BINOL-catalysed Morita-Baylis-Hillmann reaction was reported by Schaus in 2003 (Scheme 13).⁵⁴ Catalyst **2.67** was selected among a library of differently-substituted binaphthol derivatives. A catalytic quantity of BINOL derivative **2.67**, in combination with an excess of triethylphosphine, provided adduct **2.66**, for a range of aliphatic aldehydes **2.64** (Scheme 13).

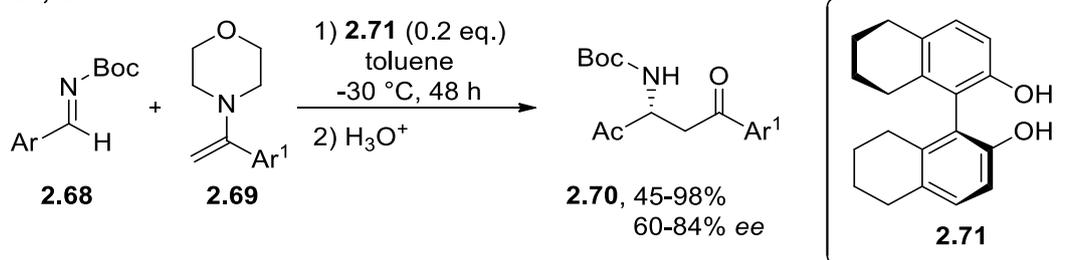
Schaus, 2003



Scheme 13: BINOL-catalysed enantioselective Morita-Baylis-Hillmann reaction.

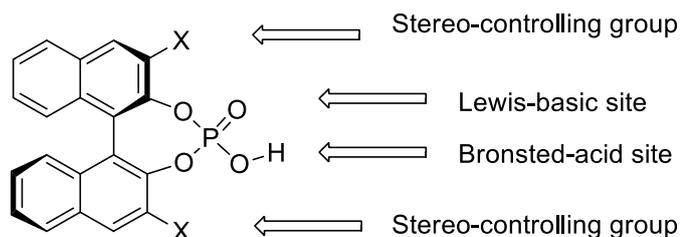
A stereoselective enamine-Mannich reaction was reported by Dixon in 2007 (Scheme 14).⁵⁵ H8-BINOL **2.71** often showed unique solubility, geometry and activity profiles compared to its fully aromatic counterpart.⁵⁶ H8-BINOL **2.71** catalysed the reaction of aldimines **2.68** and morpholino-enamines **2.69**, providing Mannich adducts **2.70** in good yield and stereoselectivity (Scheme 14).

Dixon, 2007



Scheme 14: H8-BINOL-catalysed enantioselective enamine-Mannich reaction.

BINOL-derived chiral phosphoric acids are stronger acids, compared to BINOLs, and their catalytic activity in stereoselective reactions can be tuned by increasing or decreasing the steric bulk of the X substituents on the 3,3'-positions of the binaphthyl system (Figure 10). The excellent stereocontrol obtained for certain transformations can be ascribed also to the presence of a Lewis-basic site, which increases the catalyst-substrate affinity, by the establishment of an extra hydrogen bond (Figure 10).

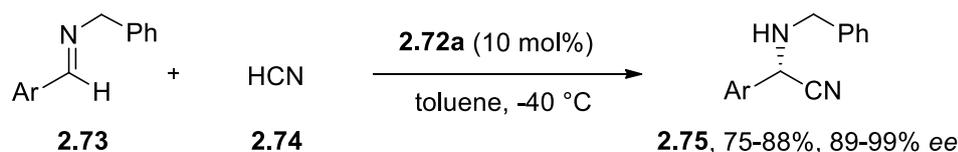


- 2.72a:** X = 9-phenantryhl
2.72b: X = 2,4,6-(*i*Pr)₃C₆H₂
2.72c: X = 4-β-naphth-C₆H₄

Figure 10: Chiral phosphoric acids.

Rueping and co-workers reported a chiral phosphoric acid-catalysed Strecker synthesis in 2006 (Scheme 15).⁵⁷ The reaction was carried out in the presence of 9-phenantryl-substituted phosphoric acid **2.72a** in a catalytic amount, and provided α-aminonitriles **2.75** in good yields and excellent enantiomeric excess, when *N*-benzylaldimine **2.73** were employed as substrates (Scheme 15).

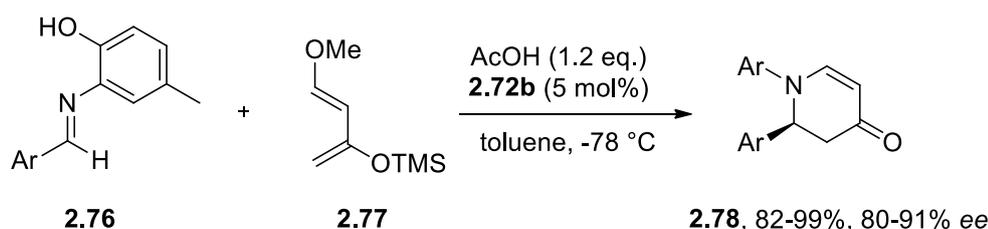
Rueping, 2006



Scheme 15: Chiral phosphoric acid-catalysed enantioselective Strecker synthesis.

The reaction of aldimines **2.76** with Danishefsky's diene **2.77**⁵⁸ was reported by Akiyama in the same year (Scheme 16).⁵⁹ The use of stoichiometric acetic acid, in combination with 5 mol% of bis-tri-isopropyl-phenyl-phosphoric acid **2.72b**, provided aza-Diels-Alder product **2.78** in very good yield and enantiomeric excess (Scheme 16). The presence of an *ortho*-hydroxyl group on imine **2.76** was essential for both the reaction rate and enantioselectivity, which was consistent with the presence of two H-bond donor-acceptor sites on phosphoric acids such as **2.72a-c** (Figure 10).

Akiyama, 2006



Scheme 16: Chiral phosphoric acid-catalysed enantioselective aza-Diels-Alder reaction.

A highly enantioselective Mannich reaction of *N*-Boc-alimine **2.68** and acetylacetone **2.79** was described by Terada and co-workers in 2006 (Scheme 17).⁶⁰ The reaction could be carried out at room temperature and with a very low catalyst loading (2 mol% of **2.72c**) and provided the desired Mannich adducts **2.80** in excellent yield and enantioselectivity.

Terada, 2006



Scheme 17: Chiral phosphoric acid-catalysed enantioselective Mannich-type reaction.

Although phosphoric acids are still among the best performing chiral Brønsted-acids, in more recent years the attention of the scientific community shifted towards new structures such as **BINSA**, **2.81**, **2.82**, **2.83**, whose catalytic activity found numerous applications on stereoselective Mannich reaction,^{61,62} Mukaiyama aldol reaction,^{63,64} imino-aza-ene reaction,^{65,66} Hosomi-Sakurai reaction (Figure 11).⁶⁷

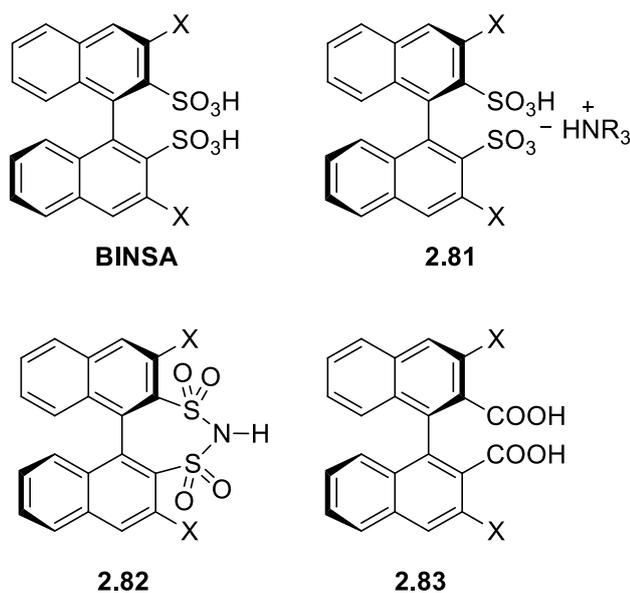


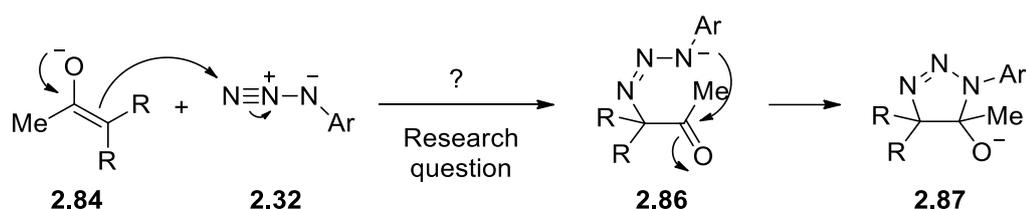
Figure 11: Most recently developed Brønsted-acid catalysts.

2.2 Results and discussion

2.2.1 Reactivity of enolate esters with aromatic azides

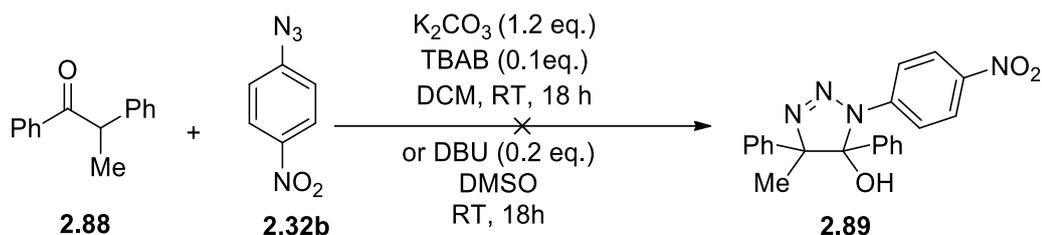
Azides are reactive organic compounds which often react following unexpected reaction pathways; for this reason they must be considered interesting and versatile building blocks in organic chemistry.⁶⁸ Organic azides were first discovered by Peter Griess in 1864 but it was Curtius, a few years later, who discovered hydrogen azide and thoroughly studied the physical property and the structure of alkyl and acyl azides.^{69,70} Although most of the azide chemistry was developed during the middle of the 20th century,⁷¹ the recent and increasing number of publications reporting undiscovered reactivities of organic azides testifies for a renewed interest in the application of azides to the development of new synthetic methodologies. Moreover, whole libraries of organic azides can be easily purchased, due to the popularity of the Copper-catalysed Azide-Alkyne Huisgen Cycloaddition (often abbreviated CuAAC), allowing the final user to avoid the sometimes hazardous syntheses and the troublesome isolation of these compounds. For these reasons, we focused our interest on the reactivity of organic azides towards carbon nucleophiles, which may be generated by deprotonation of an active methyne or methylene compound.

The results reported in this chapter are a follow up of the studies disclosed in Chapter 1, where was described a new base-catalysed reaction between the enolate of an α -disubstituted aldehyde and an aromatic azide, leading to the formation of triazocyclic compounds. We posed the question of whether the enolate of a ketone could be reacted with an aromatic azide, similarly to what was reported in Chapter 1 (Scheme 18).



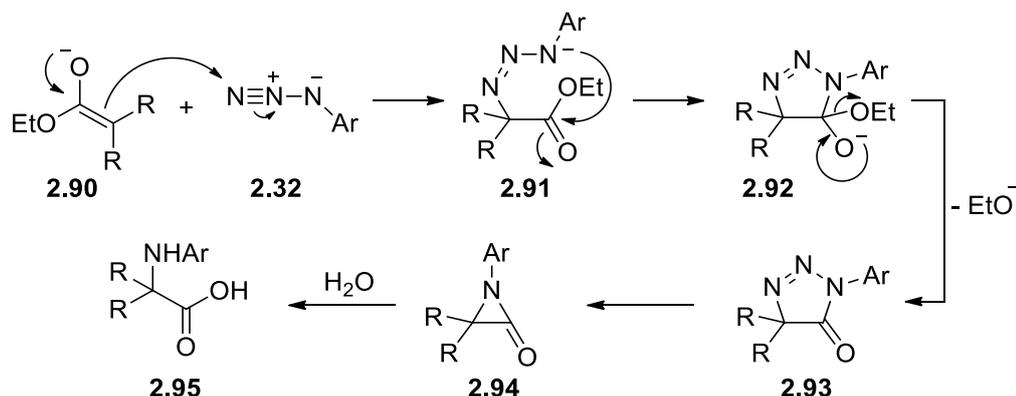
Scheme 18: Synthesis of 4,4,5-trialkyltriazoline from enolates derived from ketones and aromatic azides.

When 2-phenylpropyl phenyl ketone **2.88** was reacted with 4-nitroazidobenzene **2.32b** in the presence of a phase transfer catalyst and an excess of potassium carbonate, the formation of product triazoline **2.89** was not observed (Scheme 19). The crude mixture after 18 h still contained unreacted starting material azide **2.32b** and ketone **2.88**. The reaction was also carried out in DMSO with a catalytic amount of DBU, but the formation of the desired cyclised product was not observed in this case (Scheme 19). The lack of reactivity was explained considering that ketone enolates are notoriously less reactive than their aldehyde counterpart; it is possible that selected phenyl-ketone **2.88** was too bulky to effectively react with a poor electrophile such as an azide.



Scheme 19: Attempted synthesis of triazoline **2.89** from ketone **2.88** and azide **2.32b**.

Therefore we decided to react esters, hoping that the reaction of their enolates with an azide could generate cyclic triazolines **2.92** (Scheme 20). It was anticipated that the presence of a leaving group attached to the carbonyl could give rise to subsequent reactivities: as shown in Scheme 20, intermediate triazoline **2.92**, generated by the reaction of ester enolate **2.90** and azide **2.32**, could undergo ethanol elimination to give cyclic amide **2.93**. Thermolysis of **2.93** could then provide aziridine **2.94** (by extraction of N_2), which could be considered an α -amino acid equivalent (Scheme 20).

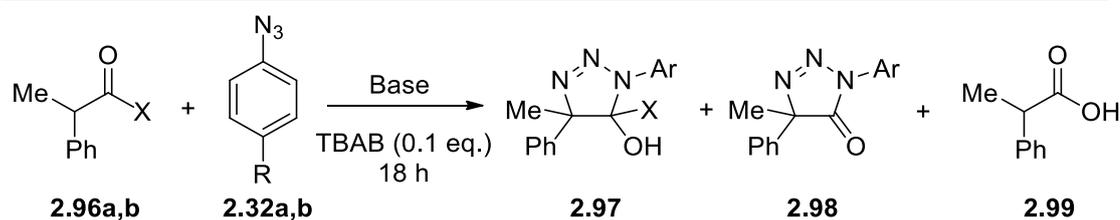


Scheme 20: Potential reaction of an ester enolate and an aromatic azide.

In order to probe this potential new synthesis, branched carboxylic acid derivatives **2.96a,b** were reacted with aromatic azides **2.32a,b** in the presence of a base (Table 2). When ethyl ester **2.96a** was reacted with azidobenzene **2.32a** in DCM with an excess of sodium hydroxide and a catalytic amount of tetrabutylammonium bromide (TBAB), the formation of cyclisation products **2.98** and **2.99** was not observed (Table 2, entry 1). The reaction was sluggish and after 18 h at room temperature **2.96a** was recovered in 10% yield, together with unreacted ester and azide. In order to promote the displacement of the X^- anion, thioesters were selected as a more reactive version of oxo-esters. Due to the higher acidity of thiophenol compared to ethanol, thiophenolate would prove a better leaving group, thus favouring the cyclisation reaction and anion extrusion over the simple hydrolysis of the ester. Unfortunately, when thioester **2.96b** was reacted with azides **2.32a,b**, under PTC conditions, no cyclisation product was observed in the reaction mixture and only carboxylic acid **2.99** and starting materials (**2.96b**, **2.32a,b**) were isolated after purification of the crude (Table 2, entries 2-4). When substrates **2.96b** and **2.32a** were reacted in DMSO, with a catalytic amount of DBU over 18

h, no starting thioester **2.96b** was recovered from the reaction mixture, instead the crude mixture was composed of a complex mixture of unidentified products (Table 2, entry 5).

Table 2: Cyclisation of azides with enolates of esters.^a



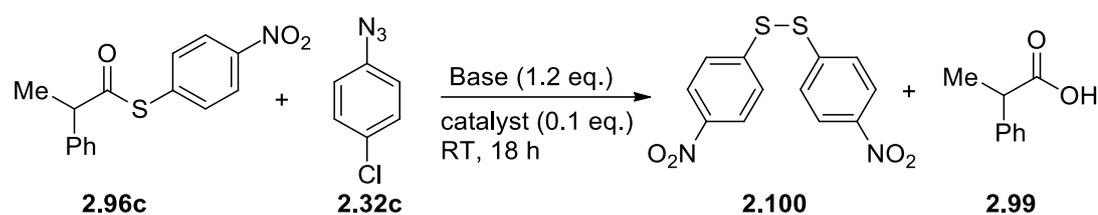
Entry	X	Ester	R	Base	Solvent	Conv. (%)	2.97 (%)	2.98 (%)	2.99 (%)
1	OEt	2.96a	H	NaOH (2.0 eq.)	DCM	5	-	-	5
2	SPh	2.96b	H	NaOH (2.0 eq.)	DCM	15	-	-	15
3	SPh	2.96b	H	K ₃ PO ₄ (2.0 eq.)	DCM	10	-	-	10
4	SPh	2.96b	NO ₂	K ₃ PO ₄ (2.0 eq.)	DCM	12	-	-	10
5 ^b	SPh	2.96b	H	DBU (0.2 eq.)	DMSO	99 ^c	-	-	-

^a Reaction conditions: **2.96a,b** (1.2 mmol), **2.32a,b** (1.0 mmol), solvent (2 ml), 20 °C, 18 h. ^b Without TBAB. ^c Complex mixture of products.

It was then decided to introduce an electron-withdrawing group (EWG) on the thiophenyl moiety, in order to render this a better leaving group. It was also reasoned that the presence of an EWG would also influence the acidity of the methyne group, providing an increased concentration of enolate nucleophile in the reaction medium. Hence 4-nitrothiophenylester **2.96c** was reacted overnight with 4-chloroazidobenzene **2.32c** (selected to have a clearer picture from the H-NMR of the crude) under the catalysis of TBAB and in the presence of a small excess of potassium phosphate. Ester **2.96c** was not found in the crude mixture, in spite of the fact that azide **2.32c** resulted completely unreacted (Table 3, entry 1). We were also able to detect 4-nitrophenyldisulfide **2.100**, originated from the oxidation of 4-nitrothiophenol, as a by-product of the hydrolysis of **2.96c**, promoted by small amounts of water, commonly found in most commercial sodium and potassium salts. The purification of the crude confirmed that **2.96c** underwent complete hydrolysis, since carboxylic acid **2.99** was recovered in 78% yield from the chromatographic column. When DBU was used, the reaction between **2.96c** and **2.32c** equally produced carboxylic acid **2.99** (46% conversion, 24% yield). The use of an even stronger base such as potassium *tert*-butoxide, resulted in the degradation of the reactants, yielding a complex mixture of compounds (Table 3, entry 3). Soft enolisation with diisopropylethylamine (DIPEA) in the presence of boron trifluoride diethyletherate did not provide sufficient activation for the cyclisation reaction between thioester **2.96c** and aromatic azide **2.32c** to occur, since these products were found unreacted in the reaction mixture (Table 3, entry 4).⁷² When the reaction was carried out in DMSO with DBU as a catalyst, in dry conditions, carboxylic acid **2.99** constituted the only reaction product (Table 3, entry 2). This information pointed out that compound **2.99** could be formed only in the workup stage, as water was required. A control experiment was performed by reacting **2.96c** and **2.32c** in the

presence of 1.1 molar equivalents of DBU, in dry ethyl acetate at room temperature (Scheme 21). After 30 min, a TLC analysis confirmed the disappearance of thioester **2.96c** from the reaction mixture. 1 Molar equivalent of benzylamine was added to the reaction, which was then stirred overnight. After column chromatography *N*-benzylamide **2.103** was isolated in 86% yield, confirming that when thioester **2.96c** was treated with DBU in a dry aprotic solvent, a transient species was formed. The reactive intermediate acts as a carbonyl electrophile, giving addition products such as carboxylic acids and amides when treated with water and amines respectively (Scheme 21).

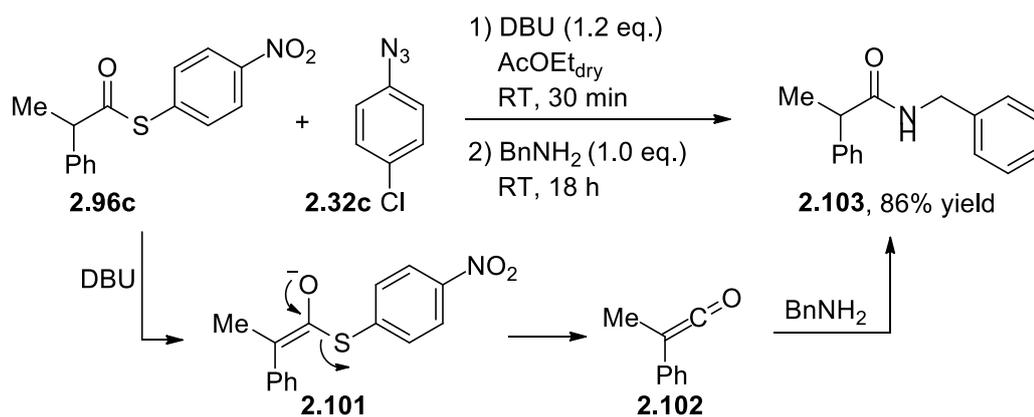
Table 3: Reaction between 4-nitrothiophenylesters and 4-chloroazidobenzene under base catalysis^a



Entry	Base	Catalyst	Solvent	Conv. (%) ^b	2.96c (%) ^c	2.100 (%) ^c	2.99 (%) ^c
1	K ₃ PO ₄	TBAB	DCM	98	-	61	78
2	DBU	-	DMSO _{dry}	46	28	7	24
3	<i>t</i> BuOK	-	THF _{dry}	99 ^d	-	-	-
4	DIPEA	BF ₃ ·Et ₂ O	DCM _{dry}	0	-	-	-

^a Reaction conditions: **2.96c** (1.0 mmol), **2.32c** (1.0 mmol), base (1.2 mmol), catalyst (0.1 mmol), solvent (2 ml), 20 °C, 18 h. ^b Conversion was measured based on the consumed mol of thioester, azide was recovered unreacted from the crude mixture. ^c Calculated from the ¹H-NMR of the crude mixture after aqueous workup. ^d Complete degradation of the substrates.

The most likely hypothesis was that a ketene intermediate was formed (Scheme 21), and this would explain the disappearance of thioester **2.96c** from the TLC but the still high reactivity towards nucleophilic addition. Confirmation for the presence of ketene **2.102** in the reaction medium was obtained by ¹H-NMR of the crude mixture before workup, which clearly shows a sharp singlet at 1.97 ppm, in accordance with the value reported in literature for phenyl methyl ketene (Figure 12).⁷³



cheme 21: Reaction of *S*-(4-nitrophenyl)-thioesters with DBU: possible formation of a transient ketene.

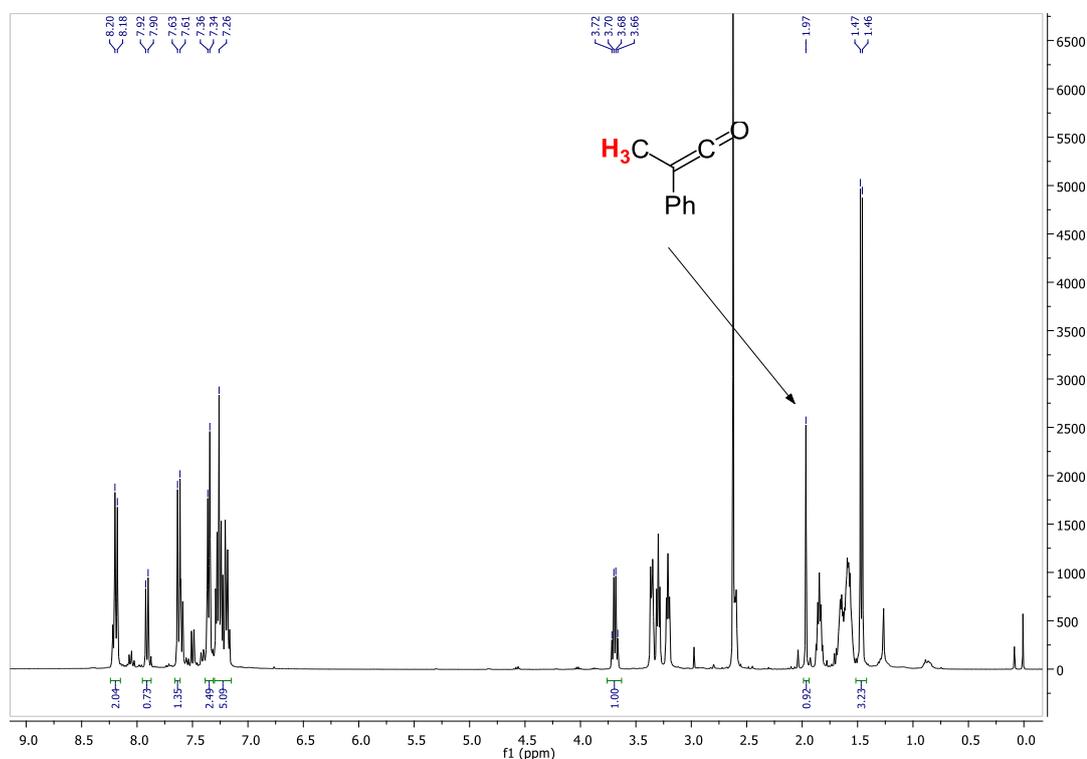
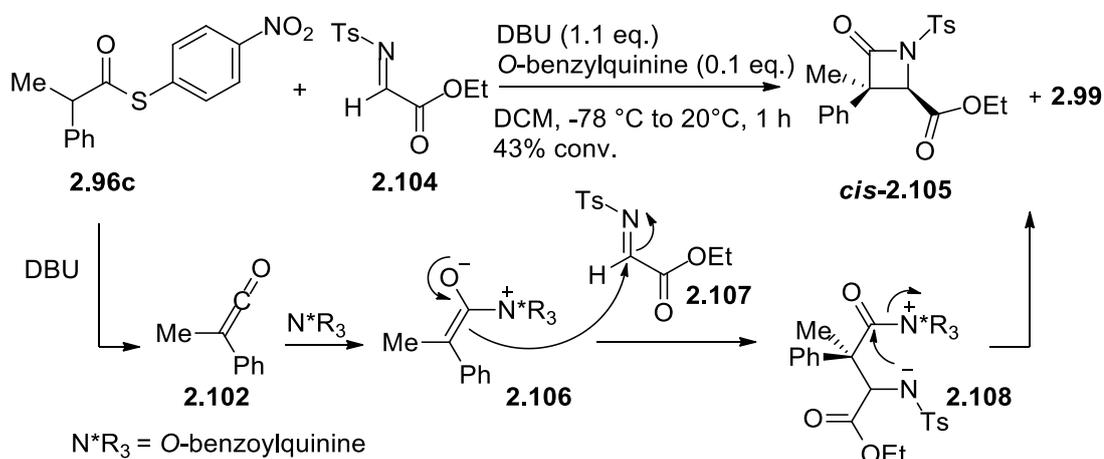


Figure 12: $^1\text{H-NMR}$ of the reaction mixture when thioester **2.96c** is reacted with DBU. The highlighted signal belongs to phenyl-methyl ketene.

2.2.2 Thioesters as ketene precursors

The *in situ* formation of ketene from electron-poor thioesters such as **2.96c** could lead to interesting applications, for example, we planned to use thioesters as a milder version of acyl chlorides or free ketenes for the synthesis of β -lactams.^{74,75} Thioester **2.96c** was reacted with iminoester **2.104** in DCM in the presence of a stoichiometric amount of DBU and catalytic *O*-benzoylquinine, following a reported procedure where a catalytic amount of *O*-benzoylquinine was added to generate chiral nucleophilic intermediate **2.106** (Scheme 22) from a solution of ketene **2.102**.⁷⁵ Based on the NMR data reported in the literature,⁷⁴ the formation of *cis*- β -

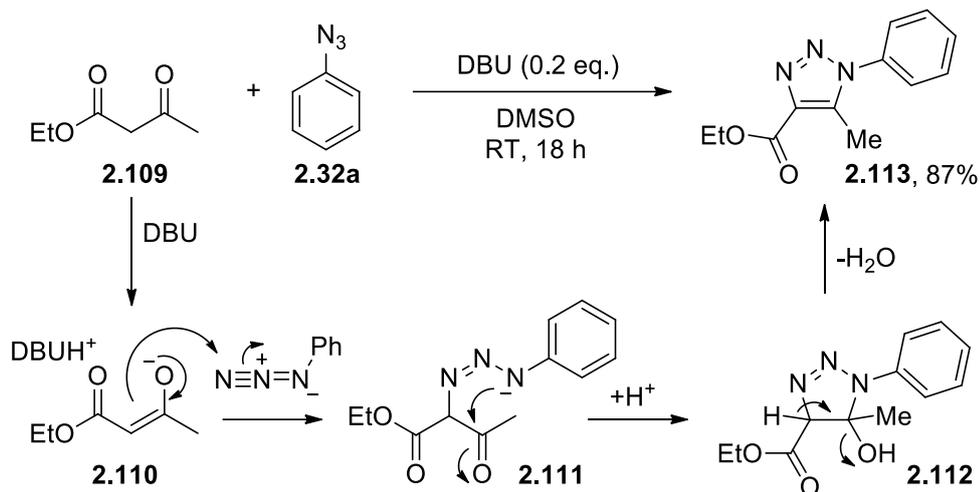
lactam **2.105** was followed by recording the $^1\text{H-NMR}$ of the crude mixture. After 18 h iminoester **2.104** was completely consumed, while thioester **2.96c** was only 43% converted. *cis*- β -Lactam **2.105** and carboxylic acid **2.99** (2 : 5 ratio) were the main products of the reaction. Obtaining a pure sample of **2.105** *via* chromatography purification of the reaction crude, was not possible due to the presence of inseparable impurities. The poor outcome of this reaction could be ascribed to the low purity of iminoester **2.104** that was used in this study. Iminoester **2.104** that was synthesised following a literature procedure,⁷⁶ was indeed difficult to isolate by distillation and had a very short shelf life, according to our experience. Through this study we were however able to further confirm that reactive ketenes can be generated *in situ* from 4-nitrophenylthioesters **2.96c** by treatment with a strong non-nucleophilic base such as DBU. Further studies may unveil the full potential of this transformation, by a careful selection of the reaction substrates and the optimisation of the reaction conditions, together with the evaluation of its stereoselectivity.



Scheme 22: Synthesis of β -lactam **2.105** *via* DBU-catalysed ketene formation.

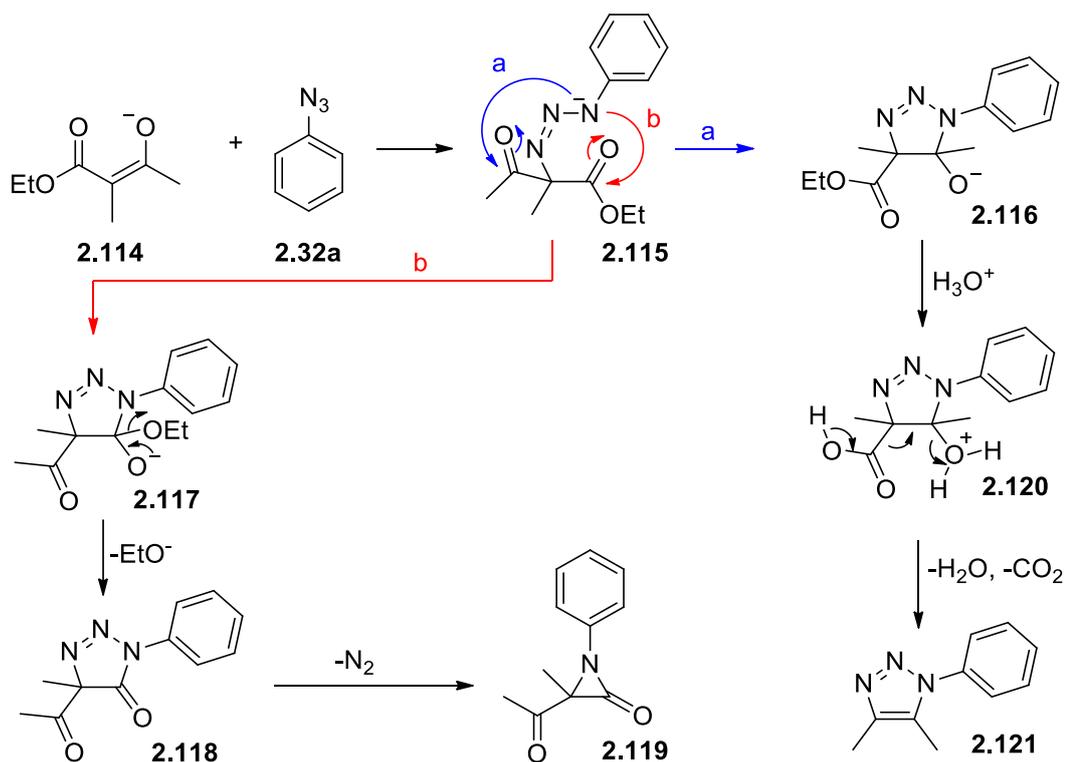
2.2.3 Reaction of ketoester enolates with aromatic azides

Among the most reactive and easily generated carbon nucleophiles, enolates of active methylene compounds found innumerable applications. In particular, the reaction of enolates and carbonyl compounds can be considered one of the most convenient method for the formation of C-C bonds.^{77,78} We reacted ethyl acetoacetate **2.109** with azidobenzene **2.32a** in DMSO and in the presence of a catalytic amount of DBU. This experiment provided triazole ester **2.113** in 87% isolated yield after aqueous workup and solvent removal (Scheme 23). We explained this result considering that the reaction of **2.109** in presence of a base generated **2.110** which, in turn, reacted with azide **2.32a** to form intermediate **2.111** (Scheme 23). Intramolecular cyclisation of **2.111** lead to triazoline **2.112**, which underwent elimination of water to give aromatised five-membered triazole **2.113**.



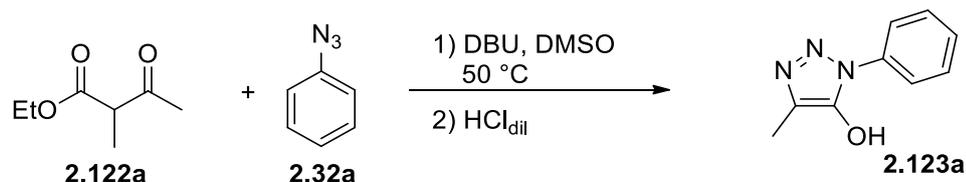
Scheme 23: DBU-catalyzed synthesis of 1,2,3-triazole ester **2.113**.

A literature survey revealed that this reaction was firstly discovered by Dimroth in 1902, who reacted ethyl acetoacetate **2.109** and azidobenzene in sodium ethoxide. The same reaction was also re-described by Wang and co-workers, in an organo-catalytic version.^{23,79} We speculated that by substituting one of the acidic methylene hydrogens on the acetoacetate, we could prevent water elimination and thus, provide access to non-aromatic compounds such as triazoline **2.116** (Scheme 24). It was speculated that, following the nucleophilic attack of enolate **2.114** on the terminal nitrogen of azide **2.32a**, key intermediate **2.115** could be formed. Depending on which carbonyl is subjected to nucleophilic addition next, the reaction may progress towards final triazole **2.121** or, alternatively, towards triazoline **2.118** and/or aziridinones **2.119**. If formed, compound **2.116** could be isolated or treated with a Lewis acid (similarly to what described in Chapter 1) and transformed into compounds such as amides **2.119** or aminoaldehydes. Alternatively, **2.116** could be hydrolysed under acidic conditions and thus undergo decarboxylation and elimination of water to yield tri-substituted triazole **2.121** (Scheme 24). If it was the ester carbonyl to be attacked by the negatively charged nitrogen of **2.115**, triazoline **2.117** could undergo ethoxide elimination and form cyclic amide **2.118** (Scheme 24, pathway b). Product **2.118** could in turn be subjected to nitrogen elimination, in favour of a transient α -lactam **2.119**, precursor of α -aminoacids by ring-opening reaction.



Scheme 24: Reaction of 2-substituted-acetoacetic ester enolates with aromatic azides.

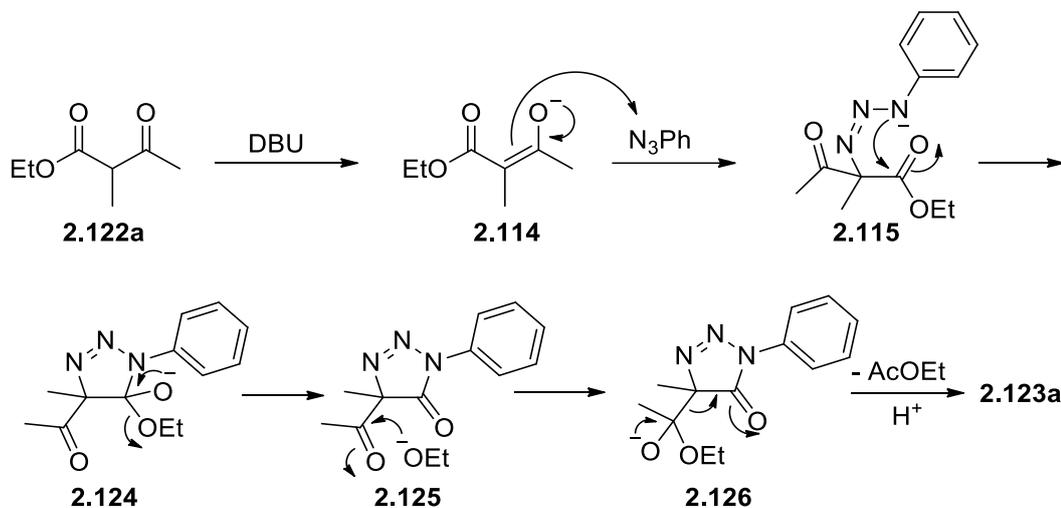
Hence we decided to start this investigation by reacting ethyl 2-methylacetoacetate **2.122a** and azidobenzene **2.32a** in the presence of 20 mol% DBU in DMSO at 50 °C. This experiment provided only low conversion of azidobenzene **2.32a** (Table 4, entry 1). The $^1\text{H-NMR}$ of the crude showed after 2 h the formation of a product possessing a sharp singlet at 2.23 ppm and aromatic signals downshifted, when compared to azidobenzene. An extension of the reaction time up to 48 h did not improve the conversion (Table 4, entry 2). However, when a slight excess of DBU was added, we observed a complete disappearance of the azide signals in the crude $^1\text{H-NMR}$ (Table 4, entry 3). The conversion could not be improved by addition of proton sponge to DBU (Table 4, entry 4). We identified the new compound that generated during this reaction as 5-hydroxytriazole **2.123a**, whose formation was explained as follows (Scheme 25).

Table 4: Cyclisation of azides with enolates of ketoesters.^a

Entry	Base	Time (h)	Conv. (%) ^b	2.123a (%)
1	DBU (0.2 eq.)	2	15	-
2	DBU (0.2 eq.)	48	24	-
3	DBU (1.2 eq.)	2	85	58 ^c
4	DBU (0.2 eq.) + proton sponge (1.1 eq.)	18	21	-

^a Reaction conditions: **2.122a** (1.0 mmol), **2.32a** (1.2 mmol), solvent (1 ml), 50 °C. ^b Calculated by ¹H-NMR. ^c isolated yield.

Ketoester **2.112a** was first enolised to **2.114** by DBU. Enolate **2.114** in turn reacted with azidobenzene **2.32a** to give adduct **2.115** (Scheme 25). Intramolecular cyclisation in **2.115** lead to ketal **2.124**, which was able to eliminate ethoxide to give triazolone **2.125**. Reaction of ethoxide with **2.125** promoted deacetylation to give final hydroxytriazole **2.123a**. Ketals such as **2.126** are known to undergo deacetylation, when the residual negative charge can be delocalised on an aromatic system bearing electron-withdrawing groups.⁸⁰

Scheme 25: Proposed mechanism for the formation of 5-hydroxytriazole **2.123a**

When crude **2.123a** was washed with water and evaporated under vacuum, ¹H-NMR showed only the residual peaks of the unreacted starting materials. Desired product **2.123a** was instead found in the water phase as a salt of DBU. The water phases were acidified to pH = 1 and the white solid that precipitated was collected and dried under vacuum. This pure sample of **2.123a** showed downshifted aromatic signals corresponding to an electron poor *ortho*-substituted phenyl ring, together with a strongly shielded proton at 13.57 ppm and a sharp singlet at 2.23 ppm (Figure 13). This surprisingly simple set of signals had to arise from the

loss of the –OEt and –COMe fragments. Mass spectroscopy confirmed a mass of 175.2 daltons, in accordance to the proposed structure of compound **2.123a**.

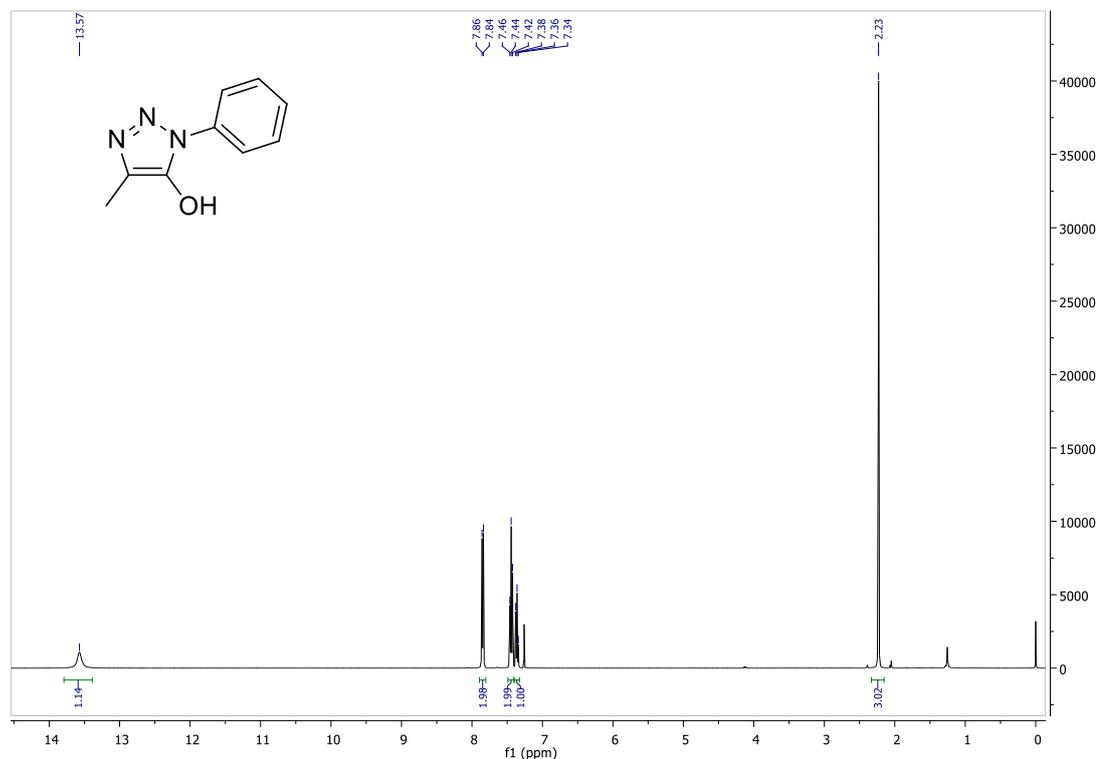


Figure 13: $^1\text{H-NMR}$ of 5-hydroxytriazole **2.123a**.

Since compound **2.123a** behaved as a relatively strong Brønsted acid, we decided to carry out a titration experiment, to better characterise its properties. Hence a 0.1 M solution of **2.123a** was titrated with 0.1 M NaOH, and the pH was recorded with a glass electrode. The titration curve was obtained by plotting the dataset obtained with the potentiometric titration (Figure 14). The curve showed the typical behaviour of a weak acid, with a buffer region at $\text{pH} \approx \text{pK}_a$. Using the graphical method we determined the equivalence point (**2.123a** is fully deprotonated at $\text{pH} = 8.4$), and consequently, the half-neutralisation point, at which the pH equals the value of pK_a . A pK_a of 4.2 in water belongs to an acid with the strength comparable to that of a carboxylic acid.

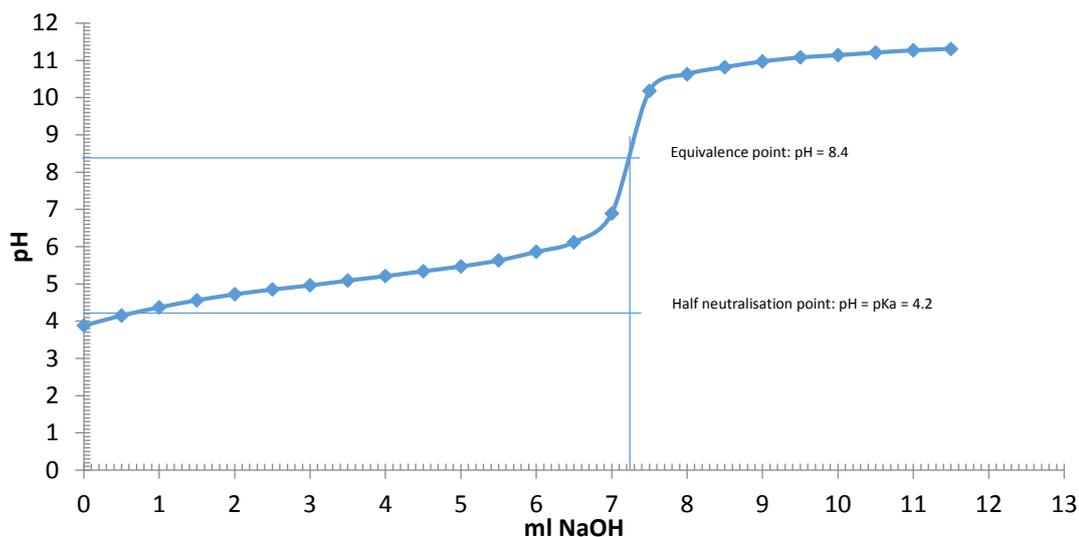
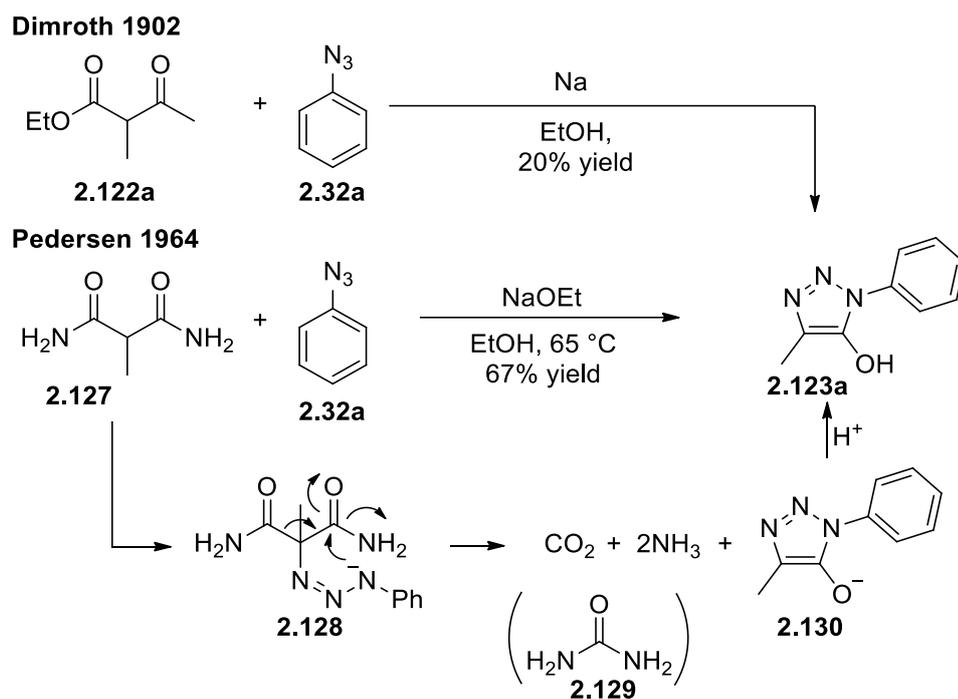


Figure 14: Potentiometric titration of 5-hydroxytriazole **2.123a**. Equivalence point: pH = 8.4, $pK_a = 4.2$.

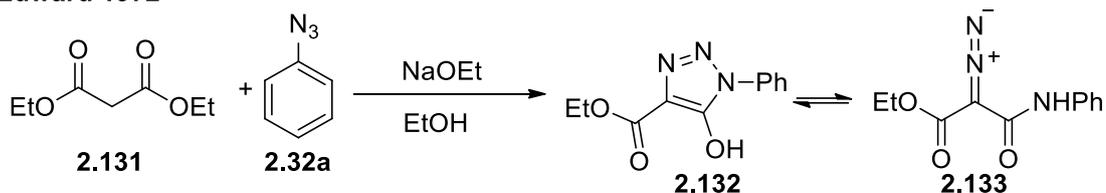
However, there is no spectroscopic data of this compound in the literature, but, as stated before, Dimroth and Pedersen reported the synthesis of **2.123a** in 1902²³ and 1964⁸¹ respectively. Dimroth obtained compound **2.123a** by treating ketoester **2.122a** with sodium in ethanol in the presence of azidobenzene, in a synthetically similar fashion to what described in Table 4 (Scheme 26). Pedersen reacted 2-methylmalonamide **2.127** and azidobenzene **2.32a** with 3 molar equivalents of sodium ethoxide in ethanol under reflux (Scheme 26).⁸¹ Pedersen's proposed mechanism involved the elimination of two molecules of ammonia and one molecule of carbon dioxide. Clearly, in respect of the mass balance, we consider the extrusion of a molecule of urea **2.129** a better interpretation of Pedersen's results (Scheme 26).



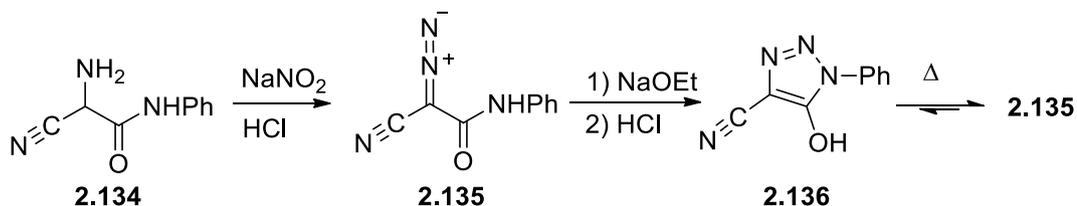
Scheme 26: Dimroth and Pedersen's synthesis of 5-hydroxytriazoles.

5-hydroxy-1,2,3-triazoles such as **2.132** could also be prepared via the Dimroth reaction, which entails reacting azidobenzene **2.32a** with diethyl malonate **2.131** in the presence of a base (Scheme 27). Alternatively, **2.132** is accessible by deprotonation of the corresponding diazomalonic-amidoester **2.133** or nitrile **2.135** as reported by Edward and Bekulev (Scheme 27).^{82,83} Diastereoisomers **2.135** were generated *via* oxidation of parent aminonitrile **2.134** using sodium nitrite. However, the presence of a carbonyl at the 4-position, made 4-carboxytriazole **2.132** and 4-cyanotriazoles **2.136** thermodynamically unstable, since they interconverted with their respective open-chain form (**2.133** and **2.135**) at room temperature (Scheme 27). Based on our experience, 4-alkyl-5-hydroxytriazoles **2.123** are not subject to such a behaviour if kept below 60 °C.

Edward 1972



Bakulev 2000

Scheme 27: Synthesis of 4-carbonyl-5-hydroxy-1,2,3-triazoles **2.132** and **2.136**.

It was decided to perform a screening of reaction conditions and thus identify the most convenient protocol for the synthesis of 4-alkyl-5-hydroxy-1,2,3-triazoles **2.123**. Moreover, the properties and reactivity of 5-hydroxytriazoles were never extensively studied, and considering their acidity, we identified a series of potential applications for these compounds as Bronsted-acids. Ethyl 2-methylacetoacetate **2.122a** and azidobenzene **2.32a** were selected as the standard reagents and a series of bases, solvents and reaction conditions were screened (Table 5). When the reaction was carried out at 50 °C in acetonitrile with a slight excess of DBU (1.2 eq.) ketoester **2.122a** was still visible in the crude ¹H-NMR after 6 h. A longer reaction time (18 h) ensured complete conversion and compound **2.123a** was obtained in 98% ¹H-NMR yield (Table 5, entries 1 and 2). It was demonstrated that **2.122a** and **2.32a** reacted equally well in solvents such as THF, toluene and acetone (Table 5, entries 3-5); however the best yields were obtained in acetonitrile. When the reaction was carried out in water, complete conversion of ketoester **2.122a** was observed, but hydrolysis to correspondent carboxylic acid was observed (Table 5, entry 6). Weaker bases such as DABCO (1,4-diazabicyclo[2.2.2]octane) and TEA did not effectively catalyse the cyclisation of **2.122a** with azidobenzene **2.32a**, also when a strong Lewis acid (e.g. BF₃·Et₂O) was added in catalytic amount (Table 5, entries 7-9). The use of inorganic base, such as excess of potassium carbonate, produced only 26% of the desired product, regardless of the polar or non-polar nature of the solvent (Table 5, entries 10 and 11). When a PTC was added to the mixture of substrates and potassium carbonate, the formation of product **2.123a** was not observed (Table 5, entries 12,13). Interestingly, when solid KOH was added to a solution of **2.122a** and **2.32a** in acetonitrile, ketoester **2.122a** was completely consumed in 1 h, and product **2.123a** was obtained as a white solid after evaporation of the solvent and acidic wash with HCl 1M (53% yield, Table 5, entry 15). Best results were obtained when the same reaction was carried out in diethyl ether as a solvent, and KOH was added to a solution of ketoester **2.122a**, azidobenzene **2.32a** and TBAB (10 mol%). In this experiment, starting materials were

consumed just after 4 h. Importantly, the potassium salt of product **2.123a** precipitated and could be isolated by simple filtration in high yields. **2.123a** in its protonated acidic form was then obtained by running the crude through a plug of silica with a DCM/MeOH/AcOH mixture (95% yield, Table 5, entry 17).

Table 5: Optimisation of the base-catalysed formation of **2.123a**.^a

Entry	Base	Additive (0.1 eq.)	Solvent	Time (h)	Temp. (°C)	Yield (%) ^b
1	DBU (1.2 eq.)	-	ACN	6	50	80
2	DBU (1.2 eq.)	-	ACN	18	50	98
3	DBU (1.2 eq.)	-	THF	7	50	82
4	DBU (1.2 eq.)	-	Acetone	7	50	60
5	DBU (1.2 eq.)	-	Toluene	7	50	15
6	DBU (1 eq.)	-	Water	18	20	-
7	DABCO (1.2 eq.)	-	DMSO	18	20	20
8	TEA (1.2 eq.)	-	DMSO	18	50	-
9	TEA (1.2 eq.)	BF ₃ ·Et ₂ O	THF	18	20	-
10	K ₂ CO ₃ (1.2 eq.)	-	DMSO	18	20	26 ^c
11	K ₂ CO ₃ (1.2 eq.)	-	MeOH	18	20	5
12	K ₂ CO ₃ (1.2 eq.)	TBAB	DCM	18	20	-
13	K ₂ CO ₃ 20% _{aq}	TBAB	DCM	18	20	-
14	NaHCO ₃ (3 eq.)	DBU	ACN	18	20	-
15	KOH (1.1 eq.)	-	ACN	1	50	53 ^c
16	KOH (1.1 eq.)	TBAB	DCM	4	20	70
17	KOH (1.1 eq.)	TBAB	Et ₂ O	4	20	95 ^c

^a Reaction conditions: **2.122a** (0.5 mmol), **2.32a** (0.6 mmol), solvent (1 ml), 50 °C. ^b Calculated by ¹H-NMR. ^c isolated yield.

Since the phase transfer catalysed reaction of ketoester **2.122a** with azidobenzene **2.32a** provided 5-hydroxytriazole **2.123a** in almost quantitative yield (Table 5, entry 17), it was decided to study the scope of this transformation (Table 6). In the phase transfer catalysed cyclisation of alkyl-ketoesters **2.122b-e** with azidobenzene **2.32a**, no reactivity was observed (Table 6, entries 10-13). Instead, **2.122b-e** were isolated from the reaction mixture as hydrolysed compounds **2.137**. This result was justified considering that nucleophilic attack on the azide and the subsequent elimination of ethyl acetate is kinetically disfavoured compared to the hydrolysis of the ester function, when sterically demanding enolates such as **2.122b** were reacted with azide **2.32a**. Ethyl 2-methylacetoacetate enolate, on the other hand, is sufficiently small, and the reaction with azidobenzene proceeded fast enough to overcome the ester hydrolysis. When more electrophilic azides such as **2.32b** and **2.32d** were employed, their reaction with **2.112a** took place under PTC condition and correspondent product could

be isolated in good yields (Table 6, entries 2 and 3). Electron rich azide **2.32e** and sterically demanding azide **2.32f**, however did not provide 5-hydroxy triazoles **2.123d,e** when reacted under the same conditions (Table 6, entries 4,5). When 2-phenylazidobenzene **2.32g** was reacted with **2.122a** correspondant **2.123f** was obtained in only 15% yield; this result further proves that the steric demand of the reaction is high and *ortho*-substituted azides gave poor yields (Table 6, entry 6). In order to overcome this limitation, a small screening of solvents was performed on bulky 2-phenylazidobenzene **2.32g**; DCM and toluene did not lead to an improvement in the yield of **2.123f** (Table 6, entries 7,8). When **2.122a** and **2.32g** were dissolved in a solution of KOH in acetonitrile without PTC, no cyclisation product **2.123f** was formed (Table 6, entry 9). Hence, it was shown that Et₂O was best solvent and PTC was indispensable for the reaction.

Table 6: Phase transfer catalysed synthesis of 5-hydroxytriazoles.^a

Entry	Product	Ketoester	Azide	R	Ar	Solvent	Time	2.123a-j (%) ^b
1	2.123a	2.122a	2.32a	Me	Ph	Et ₂ O	4 h	95
2	2.123b	2.122a	2.32b	Me	4-NO ₂ C ₆ H ₄	Et ₂ O	4 h	76
3	2.123c	2.122a	2.32d	Me	2-NO ₂ -4-MeC ₆ H ₃	Et ₂ O	4 h	83
4	2.123d	2.122a	2.32e	Me	4-OMeC ₆ H ₄	Et ₂ O	18 h	- ^c
5	2.123e	2.122a	2.32f	Me	1-napht	Et ₂ O	18 h	- ^c
6	2.123f	2.122a	2.32g	Me	2-PhC ₆ H ₄	Et ₂ O	18 h	15
7	2.123f	2.122a	2.32g	Me	2-PhC ₆ H ₄	DCM	4 h	- ^c
8	2.123f	2.122a	2.32g	Me	2-PhC ₆ H ₄	toluene	18 h	- ^c
9 ^d	2.123f	2.122a	2.32g	Me	2-PhC ₆ H ₄	ACN	18 h	- ^c
10	2.123g	2.122b	2.32a	<i>i</i> -Pr	Ph	Et ₂ O	18 h	- ^c
11	2.123h	2.122c	2.32a	Ac	Ph	Et ₂ O	18 h	- ^c
12	2.123i	2.122d	2.32a	Bn	Ph	Et ₂ O	18 h	- ^c
13	2.123j	2.122e	2.32a	Ph	Ph	Et ₂ O	18 h	- ^c

^a Reaction conditions: **2.112a-e** (1.1 mmol), **2.32a-g** (1.2 mmol), TBAB (0.1 mmol), solvent (4 ml); reaction was stirred until the spot of ketoester **2.122** disappeared from the TLC. ^b Isolated yield over two steps. ^c Only hydrolysis product **2.137** formed. ^d Without TBAB.

The screening of substrates and reaction conditions described by Table 5, showed that a slight excess of KOH and a catalytic amount of TBAB in diethyl ether were the optimal conditions for the synthesis of **2.123a**. However, when we applied these reaction conditions to different substrates (Table 6), yields were good only when electron-poor azides such as **2.32b** and **2.32d** were employed, and also the reactivity was limited to methylacetoacetates such as **2.122a**, since more bulky R substituents were not tolerated. The initial homogeneous conditions were then taken into consideration, while trying to test the reaction scope. A small library of ketoesters **2.122** and azides **2.32** were then reacted in ACN, in the presence of a slight excess of DBU at 50 °C. A reaction time of 18 h was chosen to ensure full conversion

of the less reactive substrates (Table 7). When ethyl methylacetoacetate **2.122a** was reacted with azidobenzene **2.32a** under these conditions, after 18 h starting materials were completely consumed and 5-hydroxytriazole **2.123a** was found as a DBU salt in the reaction crude (Table 7, entry 1). Protonated **2.123a** was obtained in 85% yield by filtration over silica of the reaction crude (0.5% of acetic acid was added to the eluent mixture). 4-Bromoazidobenzene **2.32h** reacted as well as azidobenzene **2.32a**, providing **2.123k** in 87% yield (Table 7, entry 2). However, *ortho*-substituted product **2.123l** was impossible to obtain under these conditions, as the 5-hydroxytriazole DBU salt decomposed into unidentified products upon acidification (Table 7, entry 3). Notably, poorly electrophilic azide **2.32e** reacted with ketoester **2.122a**, and product **2.123d** was isolated in 62% yield (Table 7, entry 4). This procedure, running under homogeneous conditions, allowed using bulkier azides such as **2.32g** and **2.32f**, which provided 5-hydroxytriazoles **2.123f** and **2.123e** in good yield (Table 7, entries 6,7). Electron poor azides **2.32b**, **2.32d**, provided triazoles **2.123b** and **2.123c** respectively, in only moderate yield, making the PTC version of this reaction a more suitable protocol (Table 7, entries 7,8). Aliphatic azides such as **2.123j** and **2.123k** were also tested, but their reaction with ketoester **2.122a** did not lead to the formation of cyclic products **2.123m** and **2.123n** (Table 7, entries 9,10). When the methyl group on ketoester **2.122a** was substituted with a carbonyl of a ketone or an ester, the reaction did not take place, and the starting materials were recovered unreacted from the reaction mixture (Table 7, entries 11-12). Ethyl isopropylacetoacetate **2.112b** was not reactive under the tested reaction conditions, while its benzyl analogue **2.112d** did provide 5-hydroxytriazole in good yield (Table 7, entries 13,14).

Table 7: DBU-promoted synthesis of 5-hydroxytriazoles.^a

Entry	Product	Ketoester	Azide	R	Ar	Yield % ^b
1	2.123a	2.122a	2.32a	Me	Ph	85
2	2.123k	2.122a	2.32h	Me	4-BrC ₆ H ₄	87
3	2.123l	2.122a	2.32i	Me	2-BrC ₆ H ₄	- ^c
4	2.123d	2.122a	2.32e	Me	4-OMeC ₆ H ₄	62
5	2.123f	2.122a	2.32g	Me	2-PhC ₆ H ₄	75
6	2.123e	2.122a	2.32f	Me	1-naphtyl	79
7	2.123b	2.122a	2.32b	Me	4-NO ₂ C ₆ H ₄	53
8	2.123c	2.122a	2.32d	Me	2-NO ₂ -4-MeC ₆ H ₃	56
9	2.123m	2.122a	2.32j	Me	<i>n</i> -Bu	- ^d
10	2.123n	2.122a	2.32k	Me	Bn	- ^d
11	2.123o	2.122f	2.32a	COOEt	Ph	- ^d
12	2.123h	2.122c	2.32a	COMe	Ph	- ^d
13	2.123g	2.122b	2.32a	<i>i</i> -Pr	Ph	- ^d
14	2.123i	2.122d	2.32a	Bn	Ph	75

^a Reaction conditions: **2.122a-f** (0.6 mmol), **2.32a-k** (0.5 mmol), DBU (0.6 mmol), ACN (2.5 ml). ^b Isolated yield. ^c Unstable product. ^d No reaction.

This screening allowed concluding that reaction of ketoesters **2.122a-f** with azidobenzenes **2.32a-k** in the presence of 1.2 eq. of DBU in acetonitrile at 50 °C for 18 h, generally provided 5-hydroxytriazoles **2.123a-o** in moderate to good yield. The reaction was however sensitive to the electronic content of the azide starting material, with electron-neutral azides **2.32a,f,g,h** giving highest yield. Electron-rich azides **2.32e** reacted equally well, although yields were lower. Aromatic azides **2.32b,d** bearing strong electron-withdrawing groups provided 5-hydroxytriazoles only in moderate yield, and they would best be reacted under PTC conditions (Table 6). Steric hindrance on the aromatic ring of the azide **2.32** did not impact on the reaction yield, while the R-group on the ketoester **2.122** had a more critical effect. In particular, when R contained a tertiary carbon the reaction did not take place, whereas proceeded well when a primary or secondary aliphatic substituent were present. To further test the synthetic potential of this transformation, we considered reacting cyclic ketoesters such as **2.138a** (Scheme 28). When acyclic ketoesters were used, the C2-C3 bond was cleaved and formal loss of a molecule of ethyl acetate was observed. It was reasoned that if the carbonyl group of compound **2.138a** was directly connected to the side chain by a cyclohexane ring, elimination of ethyl acetate would not occur, providing a method to include an aliphatic chain on the triazole, improving the atom efficiency of the reaction. When cyclic ketoester **2.138a** was reacted with azidobenzene **2.32a** under the optimised reaction conditions, 5-hydroxytriazole ester **2.142a** was obtained in 29% yield, after chromatographic purification (Scheme 28). This result further confirmed that during the aromatisation of the triazoline ring the carbonyl is eliminated in the form of an ethyl ester.

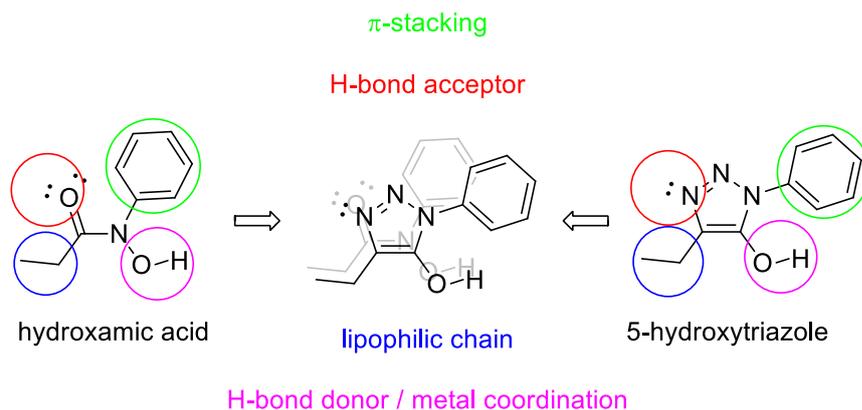
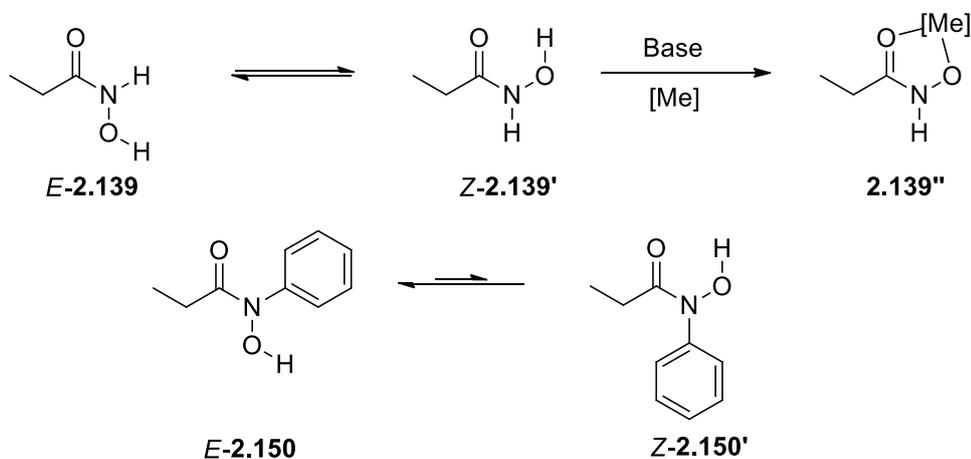


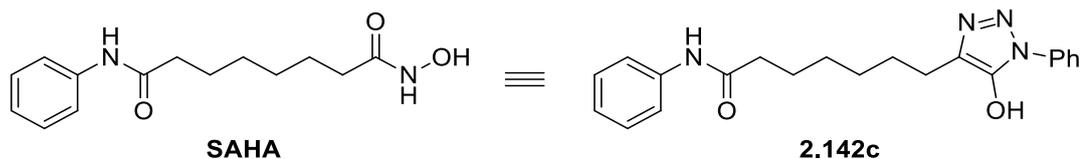
Figure 16: Isosterism between hydroxamic acids and 5-hydroxytriazoles.

Solutions of hydroxamic acids are normally constituted by two conformers, which rapidly interconvert at room temperature (**2.139**, **2.139'**, Scheme 29).⁸⁶ Notably, in order to obtain metal complexation, a small portion of the less thermodynamically favoured *Z*-isomer must be present in solution. It was also found that *E/Z* equilibrium can be shifted by acting on the polarity of the solvent. The presence of an alkyl substituent on the nitrogen proved to dramatically decrease the potency of metal-binding hydroxamic acid drugs.⁸⁷ NMR studies showed that the *E/Z* equilibrium of *N*-alkylhydroxamic acids such as **2.150** is completely shifted towards the less sterically hindered *E*-conformation, thus the impossibility of metal-chelation (Scheme 29).

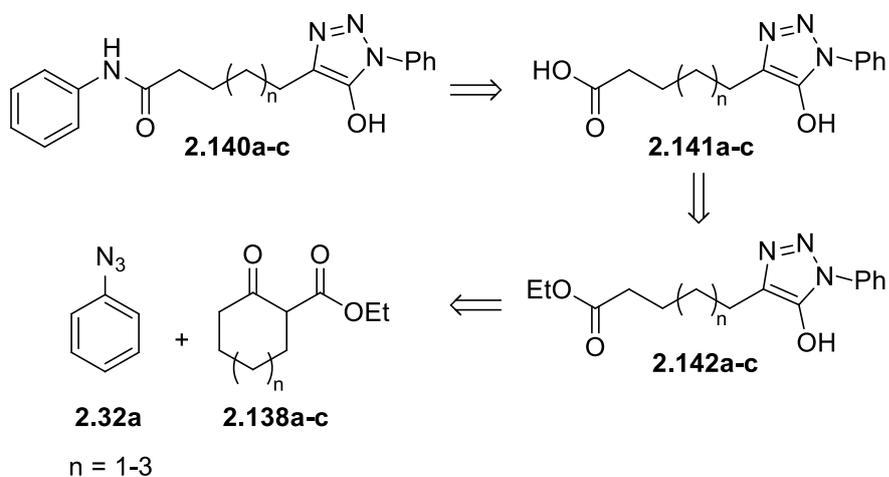


Scheme 29: Conformational equilibrium of hydroxamic acids in solution.

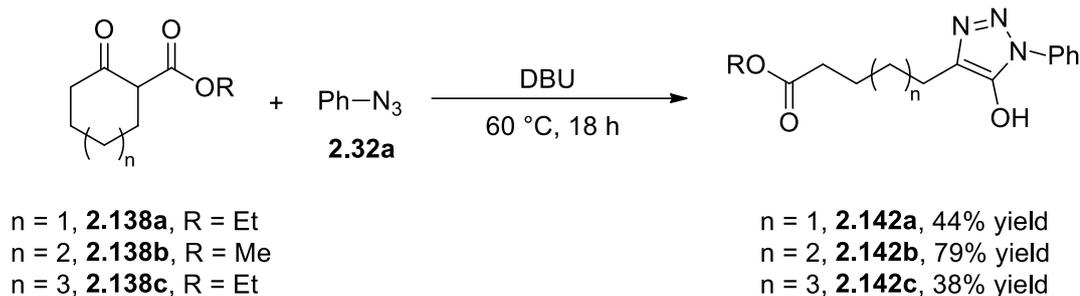
Suberanilohydroxamic acid (**SAHA**) was first discovered in 1992 by Ronald Breslow and co-workers, who reported its activity as a promoter of cell differentiation and inhibitor of histone deacetylase (Scheme 30).^{36,88} It was later discovered that this class of molecules have the ability to selectively induce cell death on some cancer cell-lines, leaving healthy cells unaltered.³⁰ Because of the structure similarity between SAHA and compound **2.142c**, we considered to include the 5-hydroxytriazole motif into the structure of SAHA, conscious that the acidic phenol on the triazole might prove a weaker ligand for the zinc centre on HDACs.

Scheme 30: Design of SAHA analogue **2.142c**.

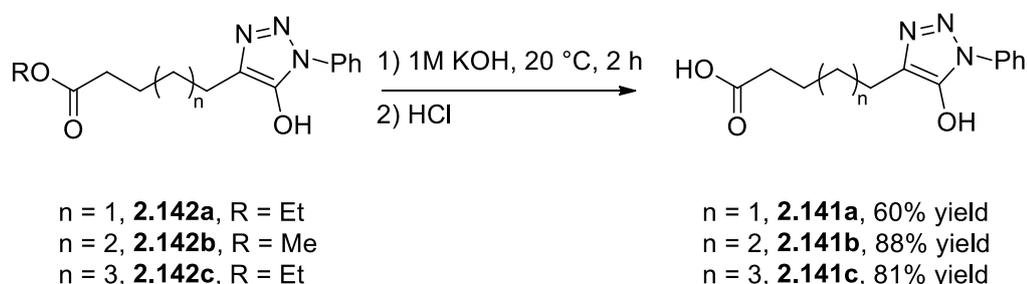
The base-promoted synthesis of 5-hydroxytriazoles **2.142a-c** from cyclic ketoesters **2.138a-c** allowed to vary the length of the aliphatic chain on final compounds **2.140a-c** by simply increasing the size of the cycloalkane ring on the starting materials **2.138a-c** (Scheme 31). Triazoloesters **2.138a-c** could be converted into final anilides **2.140a-c** by a two-step hydrolysis/amidation (Scheme 31).

Scheme 31: Retrosynthetic analysis for the preparation of compounds **2.1**

The preparation of compounds **2.142a-c** started by reacting commercially available cyclic ketoesters **2.138a-c** with azidobenzene **2.32a** and DBU (1.2 eq.). 5-hydroxytriazoles **2.142a-c** were obtained in fair to good yields after chromatography purification (Scheme 32). Notably, methyl 2-oxocycloheptanecarboxylate **2.138b** provided compound **2.142b** with a much higher yield, compared to ethyl esters **2.138a,c**. The different reactivity could be attributed to the better migratory properties of the methoxide anion compared to ethoxide, since the former is smaller and slightly less basic. Methyl ester analogues of **2.138a** and **2.138c** will be tested under the same reaction conditions, in order to establish an optimised protocol for this synthetic step.

Scheme 32: Synthesis of long-chained triazoloesters **2.142a-c**.

Ethyl and methyl esters **2.142a-c** underwent basic hydrolysis when treated with 1 M KOH for 2 h at room temperature (Scheme 33). Carboxylic acids **2.141a-c** were isolated by precipitation adding concentrate HCl to the basic solution of their respective carboxylates. The chemical yields of this step are generally good, but it is probable that a longer reaction time is necessary for the esters to fully hydrolyse.

Scheme 33: Basic hydrolysis of esters **2.142a-c**.

Carboxylic acids **2.141a-c** bear two acidic sites, which could compete in the reaction with electrophiles, making the next amidation reaction a problematic step, with no immediate solution. In fact, different reaction conditions were tested before being able to isolate amidotriazoles **2.140a-c** in barely satisfactory yields (Table 8). Carboxylic acid **2.141a** was refluxed with thionyl chloride for 2 h, and the brown oil that was obtained by evaporation of the excess thionyl chloride was added with a solution of aniline and triethylamine in DCM. After chromatography of the crude we isolated **2.140a** in 60% yield (Table 8, entry 1). However, when we applied the same protocol to the preparation of **2.140b**, we could not isolate **2.140b** from a complex reaction mixture. We explained this result considering that a polymerisation reaction may have occurred, due to the self-condensation of the phenolic hydroxyl on the reactive acyl chloride derived from the carboxylic acid (Table 8, entry 2). We also tried the direct reaction of ethyl ester **2.142a** with aniline in ACN at 70 °C; the activation barrier of this reaction is probably too high and we did not dare to further heat up compound **2.142a** (Table 8, entry 3). Dicyclohexylcarbodiimide (DCC) is one of the most used activating reagents for amide formation, but when it was reacted with **2.142a** in the presence of aniline and triethylamine, a complex mixture of products was produced (Table 8, entry 4); the main product isolated after column chromatography showed a set of $^1\text{H-NMR}$ signals corresponding to the conjugation of **2.141a** with aniline and dicyclohexylurea. Treatment of the unknown

compound with 1M HCl did not provide amide **2.140a**, but a mixture of decomposition products. The cleanest result for the of amidation step was obtained when carboxylic acids **2.142b,c** were reacted overnight with aniline in the presence of a slight excess of carbonyldiimidazole (CDI) and triethylamine. Anilides **2.140b** and **2.140c** were obtained in 34% and 48% yield respectively, after column chromatography of the reaction crude (Table 8, entries 5,6). Compounds **2.142a-c** were obtained in moderately poor yields, but after identifying CDI as a good coupling reagent for this transformation, a fine-tuning of the reaction conditions will be sufficient to greatly improve the reaction outcome.

Table 8: Preparation of long-chained triazoloamides **2.140a-c**.

Entry	Product	R	n	Activator	Temp. (°C)	Solvent	Time (h)	Yield (%)
1 ^a	2.140a	H	1	SOCl ₂	20	DCM	18	61
2 ^a	2.140b	H	2	SOCl ₂	20	DCM	88	-
3 ^b	2.140a	Et	1	-	70	ACN	48	-
4 ^c	2.140a	H	1	DCC	20	DCM	18	-
5 ^d	2.140b	H	2	CDI	20	DCM	18	35
6 ^d	2.140c	H	3	CDI	20	DCM	18	48

Reaction conditions: ^a **2.141 a,b** (0.5 mmol), SOCl₂ (15 mmol), 2 h, 60 °C. SOCl₂ was evaporated and crude acyl chloride was added with a solution of aniline (0.6 mmol) and TEA (0.6 mmol) in DCM (1 ml). ^b Ester **2.142a** (0.1 mmol), aniline (1.2 mmol), ACN (1 ml), 70 °C. ^c **2.141a** (0.2 mmol), aniline (0.2 mmol), DCC (0.21 mmol), TEA (0.21 mmol), ACN (0.5 ml). ^d **2.141b,c** (0.3 mmol), aniline (0.3 mmol), CDI (0.36 mmol), TEA (0.36 mmol), DCM (1 ml).

2.2.5 5-hydroxytriazoles as organocatalysts

5-hydroxytriazoles' central features are constituted by the rigid 5-membered aromatic ring and the phenolic group, which has proven to be a strong Brønsted acid, dissociating rapidly in water at a pH higher than 8. There are only few organic functional groups that exhibit such a high acidity, some examples are carboxylic acids, phosphoric acids, sulfonic acids and phenols. The elevated acidity of these classes of compounds has recently been exploited in the field of organocatalysis and many examples of enantioselective Brønsted acid-assisted reactions have been reported.⁴³ A preliminary study was undertaken in order to test the feasibility of a 5-hydroxytriazole-catalysed transformation (Table 9). We chose the Mannich-type reaction between a dicarbonyl compound **2.79** and protected imine **2.143** as a model transformation to evaluate the potential catalytic properties of 5-hydroxytriazole **2.123b**. Brønsted-acid-catalysed nucleophilic addition to imines is a two-step process; first the imine is protonated by the protic acid, generating a highly-electrophilic iminium salt which is then subjected to the nucleophilic attack of the enole. When a mixture of acetylacetone **2.79** and catalyst **2.123b** was added with *N*-Boc-imine **2.143** in toluene at room temperature, the full

consumption of imine **2.143** was observed after 1 h, and product **2.144a** was found in the reaction mixture (Table 9, entry 1). When substrates **2.79** and **2.143** were reacted under the same conditions but without catalyst **2.123b**, the reaction took place in 1 h and so we were not able to assert the catalytic action of **2.123b** (Table 9, entry 2). Carrying out the reaction at 0 °C did not inhibit the non-catalytic transformation, since even without catalyst, the reaction reached full conversion after only 30 min (Table 9, entry 4). Ethyl acetoacetate **2.109** was chosen as a less reactive substrate and indeed we were able to block the non-catalytic process when imine **2.143** was reacted with ethyl acetoacetate **2.109** in DCM at room temperature: without 5-hydroxytriazole **2.123b**, compound **2.109** was found unreacted in the reaction crude after 18 h of reaction (Table 9, entry 6). We were delighted to discover that if the same reaction was carried out in the presence of a catalytic amount of 5-hydroxytriazole **2.123b**, product **2.144b** formed, and was isolated in 47% yield after column chromatography (Table 9, entry 5).

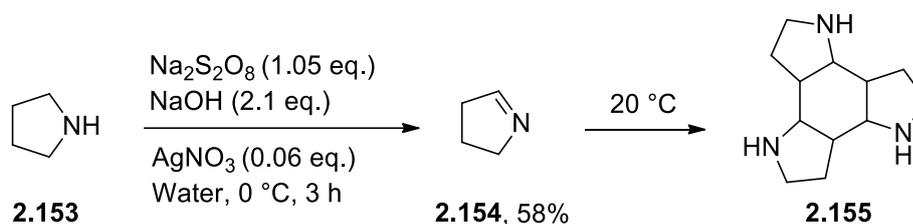
Table 9: 5-Hydroxytriazole-catalysed Mannich-type reaction.^a

Entry	Product	R	Solvent	Catalyst	Temp. (°C)	Time (h)	Conv. (%) ^b
1	2.144a	Me	toluene	2.123b	20	1	99
2	2.144a	Me	toluene	-	20	1	99
3	2.144a	Me	toluene	2.123b	0	0.5	99
4	2.144a	Me	toluene	-	0	0.5	99
5	2.144b	OEt	DCM	2.123b	20	18	99 ^c
6	2.144b	OEt	DCM	-	20	18	0

^a Reaction conditions: **2.79** or **2.109** (0.55 mmol), **2.143** (0.5 mmol), catalyst (0.05 mmol) solvent (5 ml). ^b Measured from the ¹H-NMR of the crude reaction mixture. ^c Corresponding to an isolated yield of 47%.

Having proved that a 5-hydroxytriazole **2.123b** can act as an acid catalyst in the Mannich-type reaction of ketoesters and imines, we proceeded with the design of a chiral version of **2.123b**. L-Proline **2.146** is one of the best-performing organocatalysts, and its successful application on asymmetric Mannich reactions has been reported since year 2000.⁸⁹ With the structure of proline in mind, we designed candidate catalysts **2.145** and **2.147**, which possess the 5-hydroxytriazole moiety, together with a primary or secondary amine sitting on a chiral centre (Scheme 34). Bi-functional structures **2.145** and **2.147** are not only potential acid catalysts; the presence of an aliphatic amine greatly increases the accessible mechanisms of action, because of the possibility to form imines and enamines with carbonyl compounds (Scheme 34).

aminotriazole **2.152**. Instead, in the $^1\text{H-NMR}$ of the crude mixture we could see a sharp singlet at 10.0 ppm, compatible with the formation of benzaldehyde. Crude mixture was evaporated and partitioned in AcOEt and water; acidification of the water phases afforded ketotriazole **2.151** as a white solid in 78% yield. Our mechanistic explanation for this result is that the elimination of benzaldimine is more favoured than the deacetylation reaction that we previously observed for 2-methylacetoacetates (Table 4). The first synthetical step for the preparation of 4-pyrrolidino-5-hydroxytriazole **2.147** consisted in the silver(I)-catalysed oxidation of pyrrolidine **2.153** to Δ^1 -pyrroline **2.154**, according to a published procedure (Scheme 36).⁹¹ Δ^1 -Pyrroline **2.154** spontaneously self-condenses over-time to form trimeric **2.155**. For this reason, compound **2.154** was used within a week from its preparation.



Scheme 36: Oxidation of pyrrolidine to Δ^1 -pyrroline.

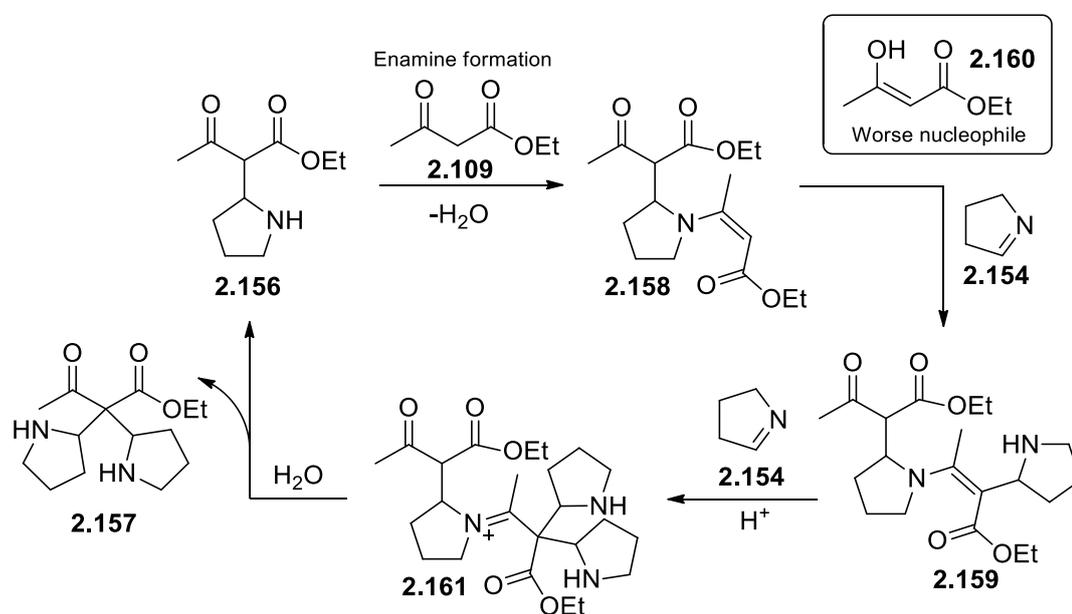
There are no examples reported in the literature of the condensation between a pyrroline such as **2.154** and ethyl acetoacetate, so several reaction conditions were tested in order to obtain mono-adduct **2.156**. When a catalytic amount of *p*TSA was added to a solution of ethyl acetoacetate and a slight excess of pyrroline **2.154**, the formation of mono-adduct was not observed over 2 h. Instead, the reaction mixture contained only 13% of bis-adduct **2.157**, together with unreacted acetoacetate **2.109** (Table 10, entry 1). Varying the stoichiometric ratio in favour of ketoester **2.109** did not change the reaction: dropwise addition of a diluted solution of Δ^1 -Pyrroline **2.154** to a solution of *p*TSA and acetoacetate **2.109** in toluene did not give better results, since the reaction carried out this way still provided bis-adduct **2.157** uniquely (Table 10, entry 2). Sodium ethoxide did not promote the transformation effectively, since unreacted starting materials **2.109** and **2.154** were the only components of the reaction mixture after 18 h. The use of a strong base in stoichiometric amount did not lead to an improvement: for example, lithium diisopropylamide only provided bis-adduct **2.157** in 44% yield, after addition at $-78\text{ }^\circ\text{C}$ and slow warming up to room temperature overnight (Table 10, entry 4). We observed that the reaction also took place in DCM, in the absence of any acid or basic promoters; in this case a great excess of acetoacetate **2.109** failed to shift the reaction selectivity towards **2.156** (Table 10, entry 5). The presence of a Lewis acid such as titanium isopropoxide also was uninformative on the relative composition of mono and bis-adducts **2.156** and **2.157**.

Table 10: Addition of ethyl acetoacetate to Δ^1 -pyrroline: screening of acids and bases.

Entry	Solvent	Additive	Ratio 2.109 : 2.154	Time	2.156 (%)	2.157 (%)
1	toluene	<i>p</i> TSA (0.1 eq.)	0.6	2 h	-	13
2 ^b	toluene	<i>p</i> TSA (0.1 eq.)	1.1	2 h	-	70
3	EtOH	EtONa (1.1 eq.)	1.1	0.5 h	-	-
4 ^c	DCM	LDA (1.0 eq.)	1.1	18 h	-	44
5	DCM	-	6.0	18 h	-	70
6	DCM	Ti(O ^{<i>i</i>} Pr) ₄ (1.1 eq.)	2.0	18 h	-	66

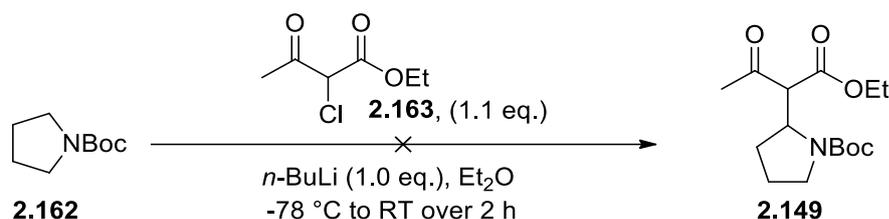
^a Reaction conditions: **2.109** (0.55 mmol), **2.154** (0.5 mmol), catalyst (0.05 mmol) solvent (5 ml). ^b Dropwise addition of a solution of pyrroline **2.154** over 1 h. ^c Reagents added at -78 °C and left warm up to room temperature overnight.

When planning this synthesis, we did not expect mono-adduct **2.156** to be in competition with acetoacetate **2.109** for the addition of pyrroline **2.154**, due to steric factors. Our interpretation of this results was that the first addition of **2.109** to **2.154** generates compound **2.156**, whose pyrrolidine residue acts as an organocatalyst and promotes the formation of enamine **2.158** by acid-catalysed nucleophilic attack on the carbonyl function of keto ester **2.109** (Scheme 37).

Scheme 37: Proposed mechanism for the formation of **2.157**.

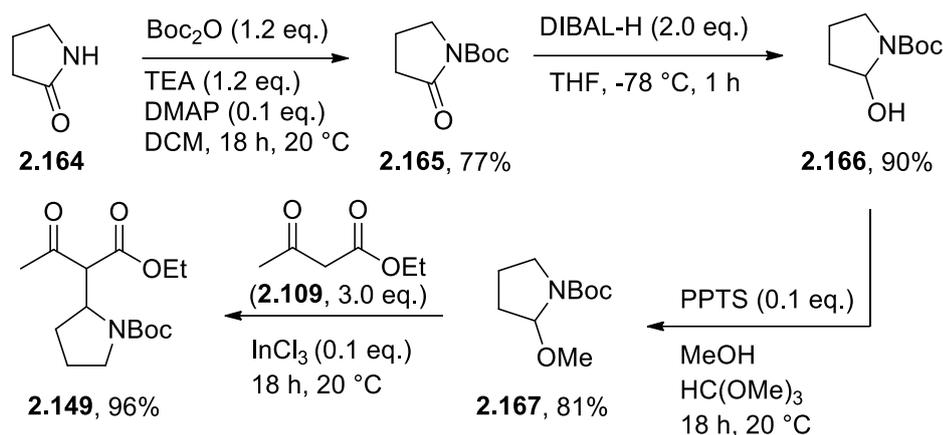
The superior nucleophilicity of secondary enamine **2.158** and tertiary enamine **2.159** (resulting from the addition of a molecule of pyrroline to **2.158**) over secondary enole **2.160** could be the reason behind the exclusive formation of bis-adduct **2.157** when reacting ketoesters such as

2.109 with Δ^1 -pyrroline **2.154**. As an evidence of this mechanism, when the reaction was carried out with an excess of Δ^1 -pyrroline **2.154**, the formation of enamine **2.158** was observed, as product **2.158** was isolated in 4% yield after column chromatography. An “umpolung” approach to the synthesis described in Table 9 was attempted by α -deprotonation of *N*-Boc-protected pyrrolidine **2.162** with *n*-butyllithium in diethyl ether at $-78\text{ }^\circ\text{C}$ (Scheme 38) and alkylation of the resulting carbanion with **2.163**. Ethyl 2-chloroacetoacetate **2.163** was added dropwise and the reaction was slowly warmed up to room temperature over 2 h. Product **2.149** did not form in these reaction conditions; it was later discovered through a literature research that *N*-Boc-pyrrolidines such as **2.162** need a stronger base (e.g. *sec*-BuLi) in order to be deprotonated and react with carbon electrophiles.

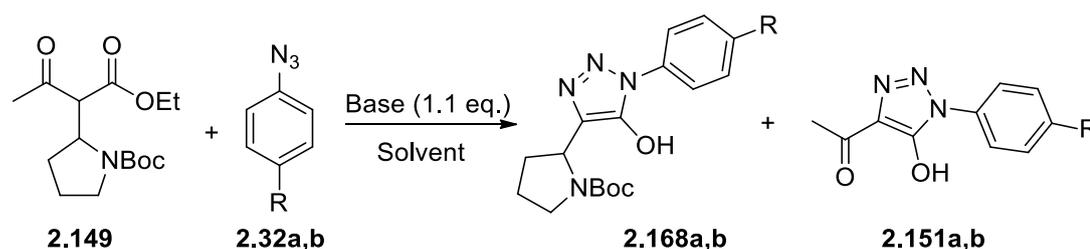


Scheme 38: Attempted synthesis of **2.149** from *N*-Boc-protected pyrrolidine.

Compound **2.149** was successfully obtained starting from pyrrolidinone **2.164**, through a longer but efficient synthesis (Scheme 39). Compound **2.164** was Boc-protected on the nitrogen following a standard protocol: a solution of **2.164** was added with a slight excess of triethylamine, Boc-anhydride and a catalytic amount of DMAP. After 18 h at room temperature and an acid/base workup *N*-Boc-pyrrolidinone **2.165** was isolated in 77% yield. The reduction of the amide function to a hemiaminal was performed by treatment with 2 equivalents of diisobutylaluminium hydride (DIBAL-H) in THF at $-78\text{ }^\circ\text{C}$ for 1 h.⁹² Hemiaminal **2.166** was isolated from the crude by column chromatography in 90% yield and directly underwent methylation to give **2.167** in 81% yield, when reacted overnight with methanol and trimethylorthoformate in the presence of a catalytic quantity of pyridinium *p*-toluenesulfonate (PPTS, Scheme 39).⁹³ Following Pilli's procedure,⁹⁴ indium(III) chloride was employed as a catalyst for the solvent-less condensation of methoxypyrroline **2.167** and ethyl acetoacetate **2.109**; a catalytic amount of indium(III) chloride was added to a mixture of **2.167** and ethylacetoacetate **2.109**; Boc-protected aminoketoester **2.149** was obtained in 96% yield as a 2 : 1 diastereomeric mixture after purification of the crude by flash column chromatography (Scheme 39).

Scheme 39: Synthesis of 2-pyrrolidinoacetacetate **2.149**.

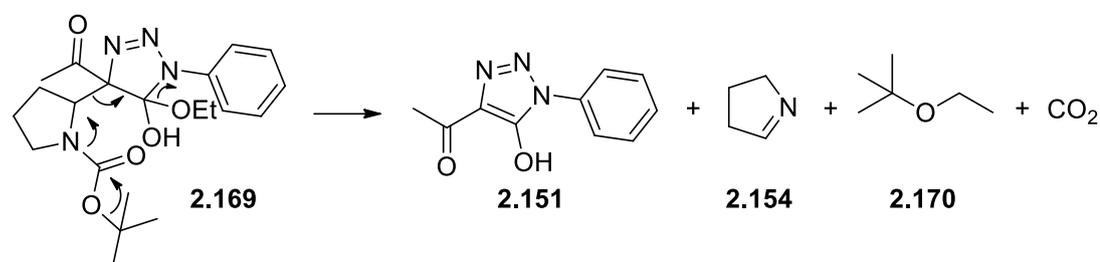
When a solution of compound **2.149** in acetonitrile was reacted with azidobenzene **2.32a** at room temperature in the presence of a slight excess of DBU, the formation of a product was not observed in the crude $^1\text{H-NMR}$ after 3 h (Table 11, entry 1). When DMSO was selected as the solvent of the reaction the starting materials did not convert after 3 h at room temperature (Table 11, entry 3). Increasing the reaction temperature to 60 $^\circ\text{C}$ and having the reaction stir for additional 3 h did not promote the conversion of the starting materials any further (Table 11, entry 3). A more strongly basic system such as EtONa / ethanol did not prove effective, since ketoester **2.149** and azide **2.32a** were found unreacted in the reaction mixture after 18 h under reflux. It was only when ketoester **2.149** was reacted with a more reactive azide such as 4-nitroazidobenzene **2.32b** that complete conversion of the starting materials was observed after only 2 h. However, partial evaporation of the solvent and the addition of conc. HCl until precipitation, did not afford aminotriazole **2.168b** as expected. Ketotriazole **2.151b** was isolated as the sole reaction product, its NMR signals in accordance with the product of the reaction described in Scheme 35. It was so evident that, if this synthetic protocol was followed, any attempt to synthesise α -chiral-hydroxytriazoles such as **2.145** and **2.157** would eventually result in the formation of 5-hydroxy-4-ketotriazole **2.151**.

Table 11: Base-promoted reaction of aromatic azides with aminoketoester **2.149**.^a

Entry	R	Product	Base	Solvent	Temp. (°C)	Time (h)	2.168a,b (%)	2.151a,b (%)
1	H	2.151a	DBU	ACN	20	3	-	-
2	H	2.151a	DBU	DMSO	20	3	-	-
3	H	2.151a	DBU	DMSO	60	3	-	-
4	H	2.151a	EtONa	EtOH	80	18	-	-
5	NO ₂	2.151b	DBU	DMSO	20	2	-	89 ^b

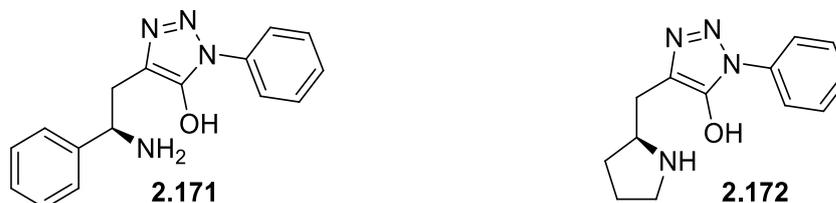
^a Reaction conditions: **2.149** (0.18 mmol), **2.32a,b** (0.20 mmol), base (0.20 mmol), solvent (0.4 ml). ^b Isolated yield after partial evaporation of the solvent and acidification with 37% HCl.

The acyl elimination mechanism described in Table 4 can only be applied when 2-alkylacetoacetate is primary or secondary and is not connected to a heteroatom (Scheme 40). However, when in the presence of β -amino groups, the elimination of the alkyl chain is preferred, with the formation of an imine, as also hypothesised in Scheme 35. The decarboxylation of Boc-protecting group could also provide the necessary thermodynamic drive and thus favour the imine elimination reaction over the desired acylation pathway (Scheme 40).

Scheme 40: Proposed mechanism for the formation of **2.151**.

From these considerations it can be concluded that target chiral 5-hydroxytriazoles cannot be obtained from the reaction between chiral 2-alkylacetoacetates such as **2.148** and **2.149** and an aromatic azide. The reaction is selective towards the formation of 4-alkyl-5-hydroxytriazoles only when the side-chain on the acetoacetate portion is primary (methyl) or secondary. When 2-amino side chains are present on the ketoester substrate the reaction follows a different mechanism and a 4-keto-5-hydroxytriazole **2.151** is formed, with simultaneous elimination of the alkyl chain in the form of an imine. In order to avoid this undesired reactivity, two alternative structures of potential bifunctional catalyst have been designed (Scheme 41). The secondary side-chains will ensure an easy preparation through base-catalysed cycloaddition of the corresponding acetoacetate with azidobenzene, although the presence of an extra carbon might partially reduce the molecule rigidity, an essential

property for an organocatalyst to be effective. The preparation of molecules **2.171** and **2.172** will be object of future work.



Scheme 41: Alternative designs for chiral aminotriazoles.

2.3 Conclusions

In conclusion, we have delved into the reactivity of ester enolates with organic azides, discovering unexpected reactivities and developing a synthetic protocol for the preparation and isolation of 1-aryl-4-alkyl-5-hydroxy-1,2,3-triazoles **2.123**. The reaction between a 2-substituted-acetoacetic ester **2.122** and an aromatic azide **2.32** in the presence of a slight excess of DBU provided 5-hydroxytriazoles **2.123** in good to excellent yield. We carried out the optimisation of this reaction and we tested its scope, by reacting differently substituted acetoacetates with aromatic and aliphatic azides. The reaction tolerates only primary or secondary substituent at the C-2 position of the acetoacetic ester, since tertiary substituents inhibited the reactivity. Aliphatic azides did not prove reactive under the tested reaction conditions. Cyclic acetoacetic esters **2.138** provided the correspondent 5-hydroxytriazoloesters **2.142** when reacted with azidobenzene in the presence of a slight excess of DBU. 5-hydroxytriazoles **2.123** can be considered sterically related to hydroxamic acids; for this reason, we synthesised a small library of SAHA-analogues, bearing a 5-hydroxytriazole group instead of a hydroxamic acid. The biological activity of compounds **2.140a,b,c** will be tested. We also tried to exploit the exceptional acidity of 5-hydroxytriazoles by testing their catalytic activity on the Mannich-type reaction of acetoacetic esters on benzaldimines. We designed and attempted the synthesis of new bifunctional chiral organocatalysts bearing a 5-hydroxytriazole group, which will be tested as chiral Brønsted acids for carbon-carbon bond formation reactions such as Mannich reaction, Michael reaction, Diels-Alder reaction.

2.4 References

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Chapter 3

Phase Transfer Catalysed enantioselective synthesis of 3,4-dihydropyran-2-ones

3.1 Introduction

3.1.1 Biological and synthetic applications of 3,4-dihydropyran-2-ones

Six-membered oxygen-containing heterocycles such as 3,4-dihydropyran-2-ones are structural subunits that appear in various natural products and biologically active compounds. For example, iridoid terpenoids often feature a tetrahydropyran or dihydropyran motif in their structure.¹ Iridoids like (-)-(7)-deoxyloganin **3.3** are involved in many biosynthetic pathways in plants, and are precursors to a wide range of alkaloids and bioactive terpenoids (Figure 1).^{2,3} Nepetalactone **3.2**, is commonly found in *Nepeta cataria*, also known as catnip, and causes behavioural effects on cats (Figure 1). Nepetalactone **3.2** is also currently under study as an insect pheromone, thanks to its repellent properties affecting many species of aphids, commonly associated with crop infestations.⁴ Isocoumarins, also found in plants, are a class of natural products containing a pyran-2-one ring; isocoumarin NM-3 **3.1** is under phase 1 clinical trial, as an inhibitor of human endothelial cell-growth *in vitro* and also inhibited tumor angiogenesis in human xenograft model (Figure 1).⁵ For these reasons, in recent years, synthetic methods that provide chiral tetrahydropyran and dihydropyran derivatives have received much interest.

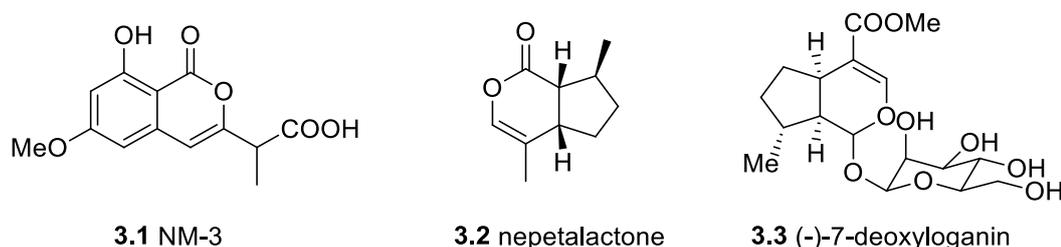
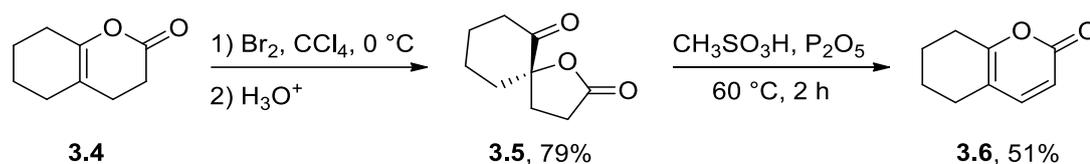


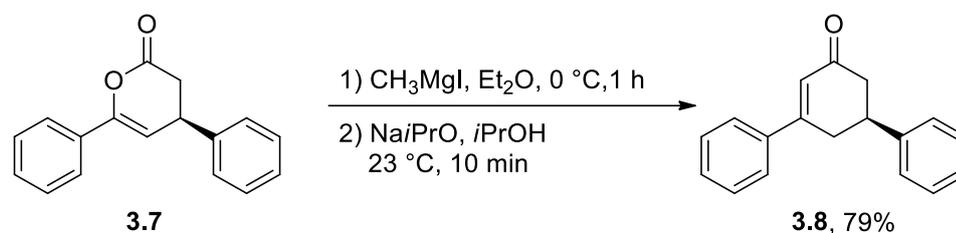
Figure 1: Biologically active pyran-2-ones.

3,4-Dihydropyran-2-ones are widely recognized as useful building blocks for the synthesis of valuable classes of organic compounds, such as 2-pyrones,^{6–8} γ -lactones,⁸ cyclic enamines,⁹ functionalised enones.¹⁰ For example, Jawalkar and co-workers reported some synthetic transformations involving the use of 3,4-dihydropyran-2-ones **3.4** as starting materials (Scheme 1).⁸ Compound **3.4** was conveniently converted to spiro-cyclic ketoester **3.5** by treatment with bromine in carbon tetrachloride. **3.5** underwent acid-catalysed rearrangement into 2-pyrone **3.6** when reacted with methanesulfonic acid and phosphorus pentoxide.



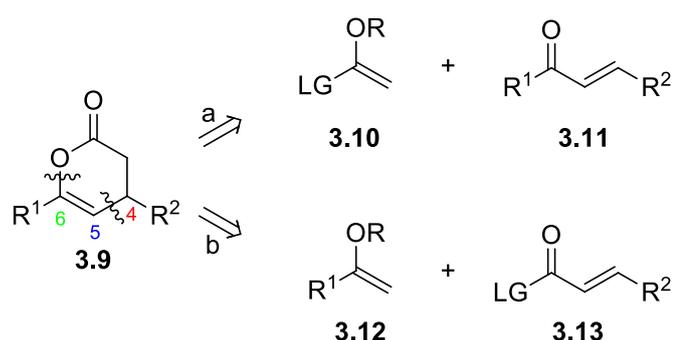
Scheme 1: Derivatisation of 3,4-dihydropyran-2-ones into 2-pyrones.

Corey and co-workers, as part of their work on PTC enantioselective Michael reactions, proposed the formation of chiral cyclohexenones **3.8** from chiral 3,4-dihydropyranone **3.7** as a profitable synthetic opportunity (Scheme 2).¹⁰ Compound **3.7** was treated with a Grignard reagent and the resulting diketone underwent intramolecular aldol condensation in the presence of a strong base, to provide cyclohexenone **3.8**, in a completely stereoconservative manner.



Scheme 2: 3,4-Dihydropyran-2-ones as precursors of substituted cyclohexanones.

The preparation of 3,4-dihydropyran-2-ones has been object of study for more than two decades.¹¹ The majority of the reported methods, involve the concerted (or stepwise, depending on the author's mechanistic interpretation) formation of the C4-C5 and C6-O1 bonds, resulting in the assembly of the 3,4-dihydropyran-2-one ring, which is normally stable under basic and neutral conditions (Scheme 3). These disconnections identified synthons **3.10** – **3.13** as the building blocks required to form desired **3.9**. Hence the reaction of an ester enolate equivalent **3.10** with an α,β -unsaturated carbonyl compound **3.11** was the most common method (Scheme 3, path a) and the presence of a good leaving group on the nucleophilic component was essential for the cyclisation to take place. An alternative route was represented by the reaction of a carbonyl enolate **3.12** and a cinnamate equivalent **3.13** (Scheme 3, path b).

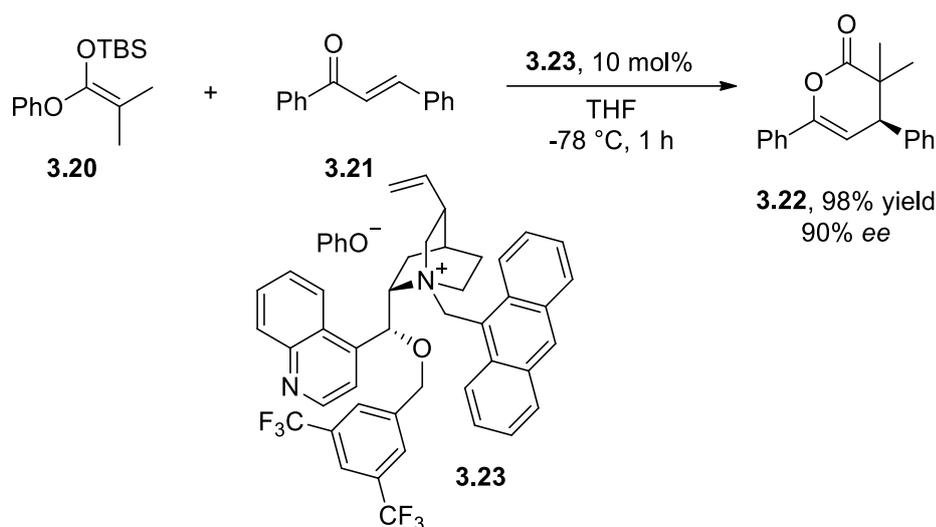


Scheme 3: Common synthetic routes for the preparation of 3,4-dihydropyran-2-ones **3.9**.

3.1.2 Ester enolate equivalents in the synthesis of 3,4-dihydropyran-2-ones

The first general synthesis of 3,4-dihydropyran-2-ones was reported by Kobayashi in 1997, who proposed a synthetic protocol involving the Michael addition of an ether-derived silyl enol ether such as **3.14** to an α,β -unsaturated carbonyl compound, under the catalysis of a tritylium

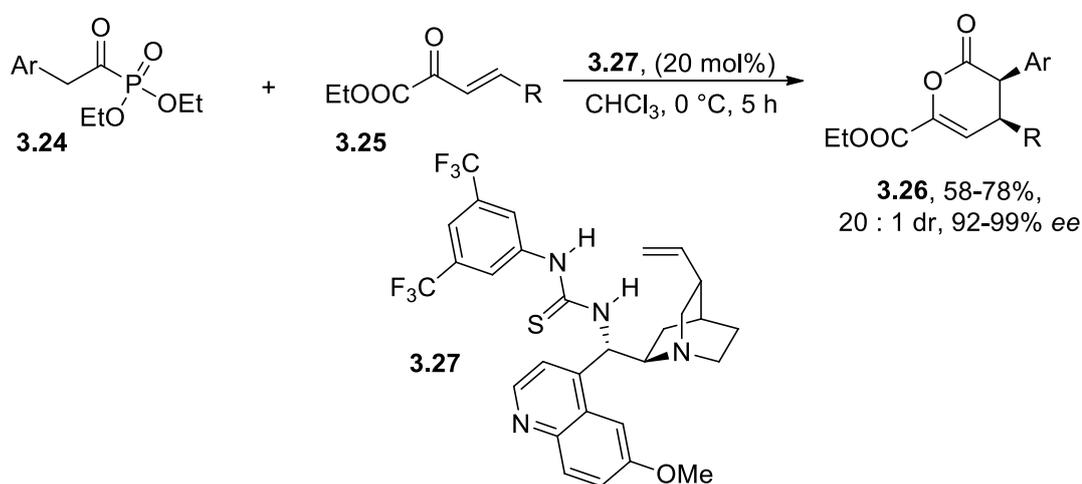
Mukaiyama, 2007



Scheme 6: Chiral PTC-catalysed Michael addition-cyclisation of silyl enol ethers and chalcones.

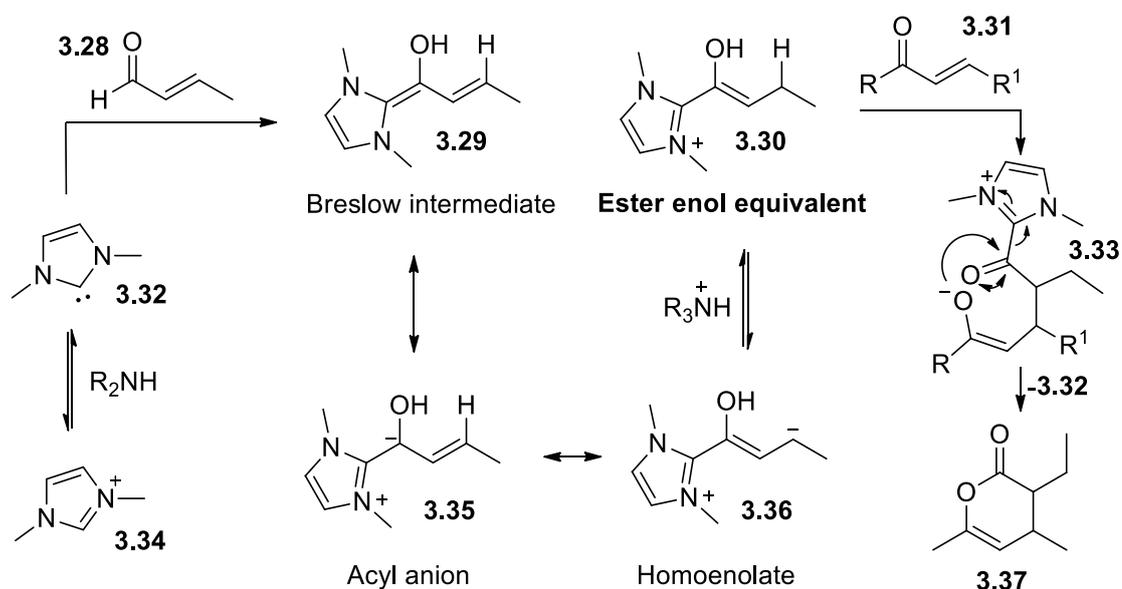
More recently, Xu and co-workers described the use of acylphosphonates **3.24** as ester enolate equivalents in the stereoselective synthesis of pyranones **3.26** (Scheme 7). The presence of 20 mol% of bifunctional *Cinchona*-derived thiourea **3.27** (also known as Soos' catalyst), promoted the cyclisation of acylphosphonate **3.24** and enone **3.25**, providing **3.26** in good yields and excellent diastereo- and enantioselectivity.¹⁵

Xu, 2016

Scheme 7: Chiral bifunctional thiourea as a catalyst for the stereoselective preparation of 3,4-dihydropyranones **3.26**.

α,β -Unsaturated aldehydes can be converted to ester enolates equivalents by reaction with a catalytic quantity of *N*-heterocyclic carbenes (NHC, Scheme 8). The reaction that involves the *umpolung* of an aldehyde to a transient species can be used in a variety of conditions. Significantly, depending on the acidity of the media, the substitution on the reactants and the eventual presence of oxidants, a range of diverse reactivities could be observed.¹¹ *N*-

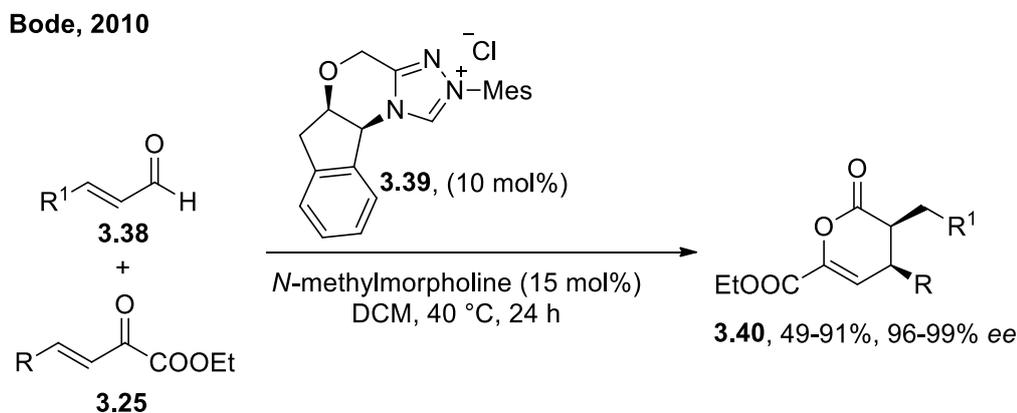
Heterocyclic carbenes are often generated by catalytic deprotonation of a thiazolium, triazolium or imidazolium salt **3.34**. NHCs are reactive singlet carbenes, so they do not react as di-radicals species; their behaviour is more similar to that of a strong nucleophilic base. The first step in the reaction between a NHC and an aldehyde is the formation of a Breslow's intermediate **3.29** (Scheme 8). Breslow's nucleophile is better described by its resonance structure **3.35**, which shows the *umpolung* of the aldehyde, which from an acceptor (a1) is turned into a donor (d1) synthon. When treated with an NHC, α,β -unsaturated aldehydes generally react as d3 nucleophiles (homoenolate **3.36**, Scheme 8), being the vinylogous position kinetically favoured. The protonation of homoenolate **3.36** is the critical step for the generation of ester enol equivalents **3.30**. In fact, if the organic base adopted for the initial deprotonation of imidazolium salt **3.34** is too strong, its conjugate acid will not be acidic enough to protonate homoenolate **3.36**, which will instead react as a d3 nucleophile. Michael addition of enol **3.30** to enone **3.31** and intramolecular cyclisation provide 3,4-dihydropyranones **3.37** with the release of a free NHC, which will again take part to the catalytic cycle (Scheme 8).



Scheme 8: NHC-catalysed formation of 3,4-dihydropyran-2-ones from α,β -unsaturated aldehydes **3.28** and enones **3.31**.

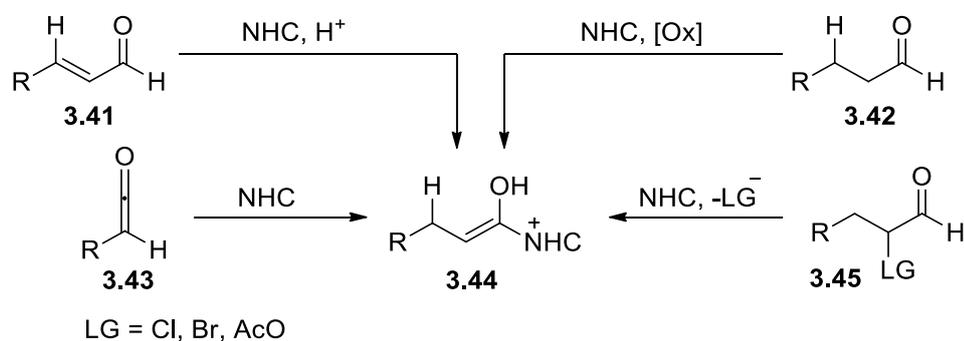
NHC-catalysed activation of α,β -unsaturated aldehydes is by far the most executed synthetic strategy towards 3,4-dihydropyran-2-ones and, considering the excellent performances of catalysts such as **3.39**, also provided the best enantioselectivities, at minimal catalyst loading, when compared to other synthetic protocols (Scheme 9). A notable application of this procedure was reported by Bode in 2010: α,β -unsaturated aldehydes **3.38** were reacted with enones **3.25** in the presence of catalytic chiral triazolium salt **3.39**.¹⁶ Organic base *N*-methylmorpholine triggered the formation of reactive NHC and, in its protonated form, served as a weak acid during the protonation of intermediate homoenolate **3.36** (Scheme 8).

Trisubstituted pyranones **3.40** were obtained in moderate to excellent yield, and high enantioselectivity (Scheme 9).



Scheme 9: Chiral NHC-catalysed enantioselective synthesis of 3,4-dihydropyran-2-ones.

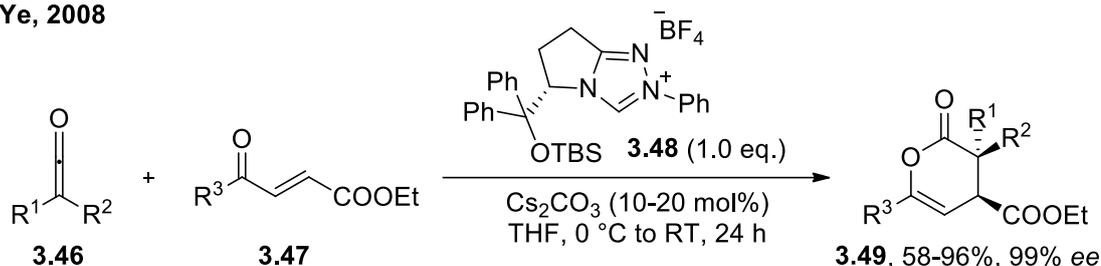
The reaction between NHC and α,β -unsaturated aldehydes is not the only method to generate reactive NHC enolates **3.44** (Scheme 10). Over the years, various methodologies have been developed, which included: (a) substrates other than α,β -unsaturated aldehydes, for example ketenes **3.43**; (b) *in situ* oxidation of aliphatic aldehydes **3.42** to α,β -unsaturated aldehydes; (c) elimination of acid from α -halogenoaldehydes **3.45** (Scheme 10).



Scheme 10: NHC-enolates can generate from a variety of substrates.

As reported by Ye, ketenes **3.46** were reacted with L-pyrogutamic acid-derived triazolium salt **3.48** in the presence of a catalytic quantity of inorganic base in polar aprotic solvent (Scheme 11);¹⁷ when Michael acceptor **3.47** was added to the reaction mixture, the formation of 3,4-dihydropyranones **3.49** bearing a quaternary stereocenter was observed. The stereoselectivity of this transformation was total for all tested substrates, while the yield varied depending on the substitution (Scheme 11).

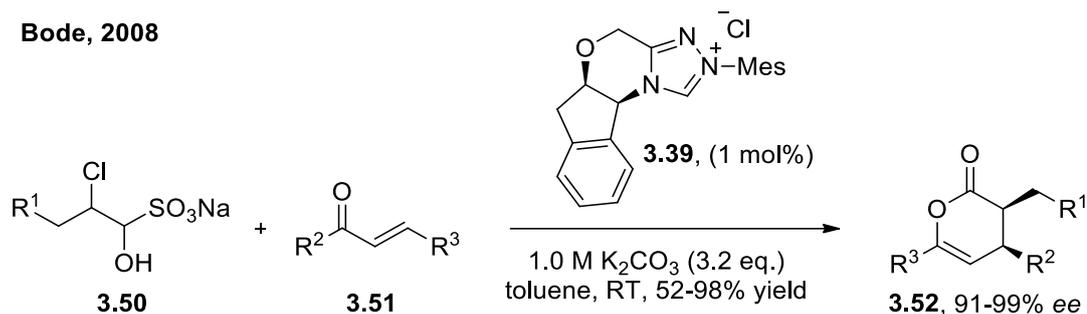
Ye, 2008



Scheme 11: Ketenes as precursors of 3,4-dihydropyran-2-ones

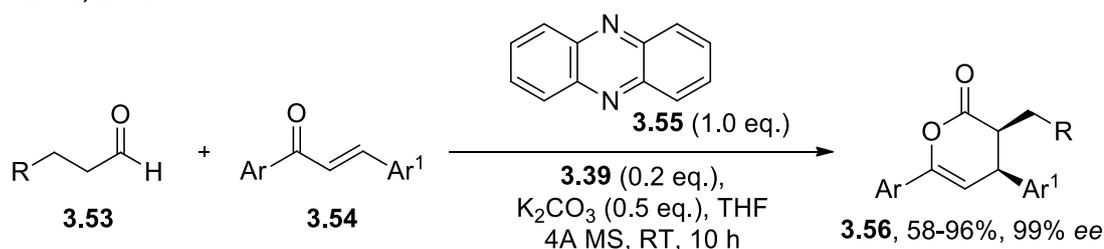
α -Chloro-aldehyde-bisulfite adducts **3.50** were successfully employed as synthetic alternatives to α,β -unsaturated aldehydes by Bode and co-workers (Scheme 12).¹⁸ α -Chloroaldehydes were generated *in situ* by treatment with aqueous potassium carbonate and their reaction with enones **3.51** provided 3,4-dihydropyran-2-ones **3.52** in excellent diastereo- and enantioselectivity, when 1 mol% of chiral triazolium **3.39** was present. Notably, the reaction could be carried out in the presence of large amounts of water, since poisoning of the catalyst was not observed, even for very low catalyst loadings.

Bode, 2008

Scheme 12: Synthesis of chiral 3,4-dihydropyran-2-ones from α -chloroaldehyde bisulfite adduct.

An oxidative procedure was reported by Rovis in 2012, which involved the stoichiometric addition of phenazine **3.55** with the consequent *in situ* formation of an α,β -unsaturated aldehyde (Scheme 13).¹⁹ The presence of chiral NHC precursor **3.39**, in combination with a sub-stoichiometric amount of potassium carbonate in THF, promoted the reaction between aldehydes **3.53** and chalcones **3.54**, to obtain products **3.56** in excellent enantioselectivities.

Rovis, 2012

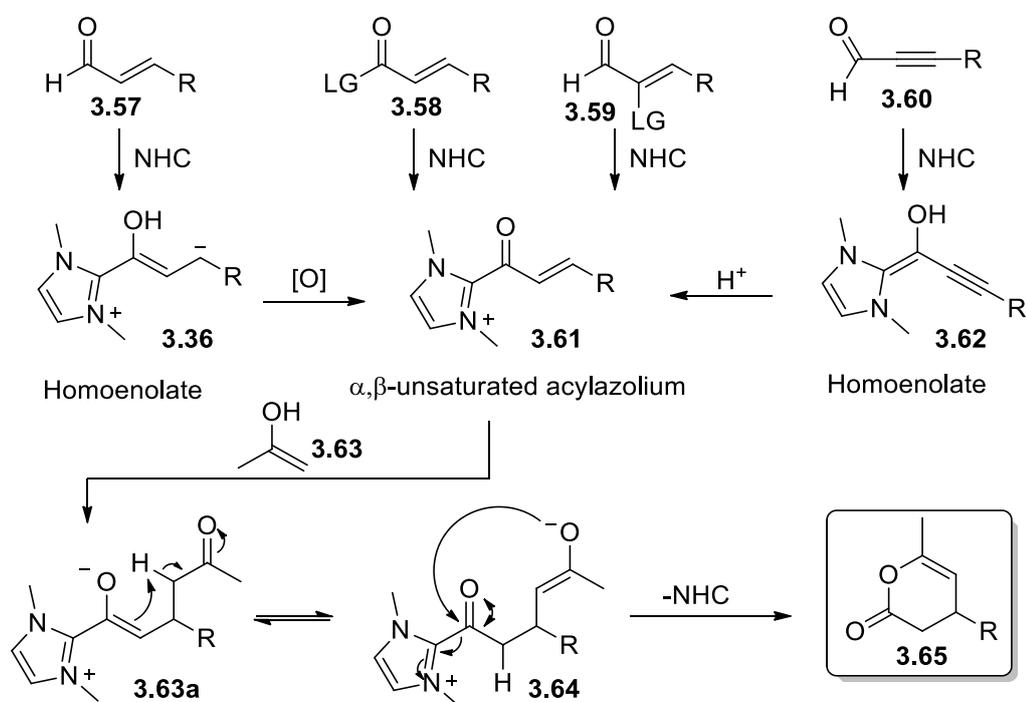


Scheme 13: Synthesis of 3,4-dihydropyran-2-ones in the presence of a mild oxidant.

1,3,4-Trisubstituted-3,4-dihydropyran-2-ones can be easily prepared from ester enolate analogues and α,β -unsaturated ketones *via* organocatalysis.^{12–19} Several examples of stereoselective reactions have been reported: the use of chiral PTCs and bifunctional thioureas provided chiral 3,4-dihydropyran-2-ones in good diastereo- and enantioselectivity.^{14,15} More recently, a series of convenient and efficient approaches involving the use of NHC catalysis have been reported. The model transformation consists in the reaction of α -functionalised aldehydes with α,β -unsaturated ketones, in the presence of a NHC precursor and an organic base.¹⁶ NHC-catalysis allowed the isolation of desired 3,4-dihydropyranones in excellent yield and stereoselectivity.¹⁶ NHC catalysts displayed exceptional activity for a large number of substrates and in various reaction conditions: notable is the possibility to apply NHC catalysis to biphasic water / organic systems.^{17–19}

2.1.2 Cinnamate equivalents in the synthesis of 3,4-dihydropyran-2-ones

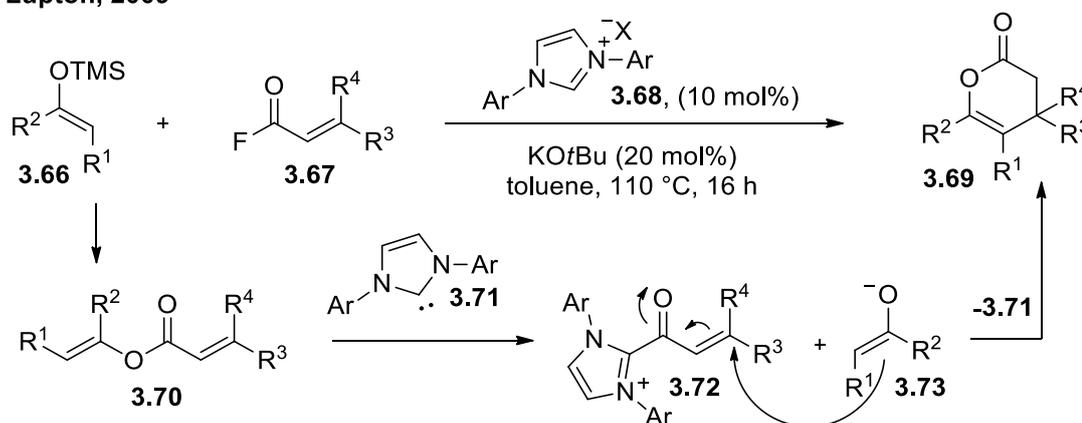
As described in Scheme 3, the reaction of cinnamate equivalent with a ketone enolate constitutes an alternative synthetic strategy to access 3,4-dihydropyran-2-ones. Activated cinnamate equivalents are normally generated *via* NHC catalysis (Scheme 14). Several NHC-catalysed transformations were reported in the last decade that took place through the formation of α,β -unsaturated acylazolium species **3.61**.^{20–24} These electrophilic intermediates acted as Michael acceptors, in 1,4-nucleophilic addition, generating the respective keto-acylazolium enolates **3.63a**. The following intramolecular proton-shift converts ester enolate **3.63a** into ketone enolate **3.64**.



Scheme 14: Synthesis of 3,4-dihydropyran-2-ones *via* α,β -unsaturated acylazolium and ketone enolate.

The cyclisation reaction takes place *via* O-nucleophilic addition-elimination with regeneration of NHC, which will re-join the catalytic cycle (Scheme 14). Methods to generate α,β -unsaturated acylazolium **3.61** are: (I) oxidation of NHC-homoenolates **3.36**, (II) nucleophilic substitution of cinnamic ester **3.58** with a NHC and (III) the protonolysis of homoenolates derived from of ynals **3.60** and enals **3.59** (Scheme 14). Silyl enol ethers **3.66** and α,β -unsaturated acyl fluorides **3.67** reacted to give compound **3.69** as the final product (Scheme 15);²⁰ the reaction was carried out in refluxing toluene with catalytic potassium *tert*-butoxide and imidazolium salt **3.68**. The mechanism of the reaction involved the fluoride-promoted deprotection of silyl enol ether **3.66** to form a vinyl acrylate **3.70**. Next, nucleophilic addition of NHC **3.71** derived from **3.68** to vinyl ester **3.70**, generated enolate **3.73** and the required acylazolium compound **3.72**. Michael addition of enolate **3.73** to acylazolium **3.72** formed a ketoester enolate, which, by subsequent proton-shift and final intramolecular nucleophilic addition-elimination, provided tetrasubstituted 3,4-dihydropyran-2-ones **3.69**.

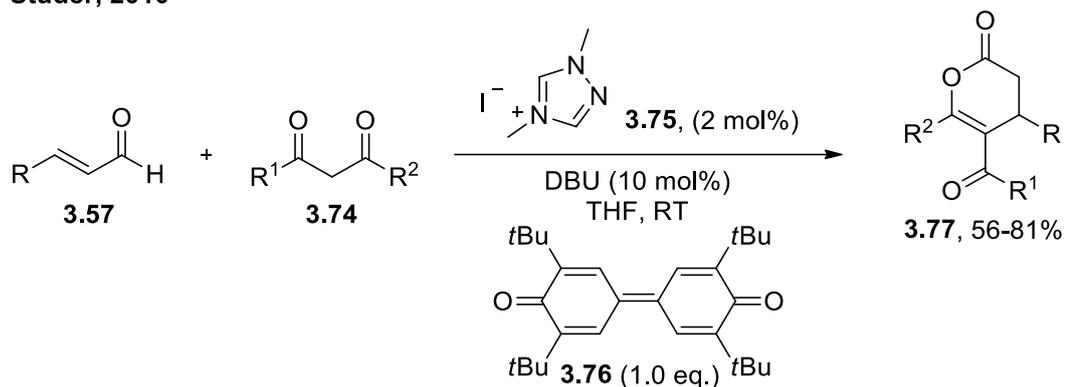
Lupton, 2009



Scheme 15: The NHC-catalysed reaction of silyl enol ethers and α,β -unsaturated acyl fluorides.

Following Lupton's report, Studer described the NHC-catalysed Michael addition-cyclisation of α,β -unsaturated aldehydes **3.57** and β -diketones **3.74** (Scheme 16).²¹ The reaction was carried out in the presence of a stoichiometric amount of quinone **3.76**, which oxidised the transient homoenolate to provide an electrophilic acylazolium.

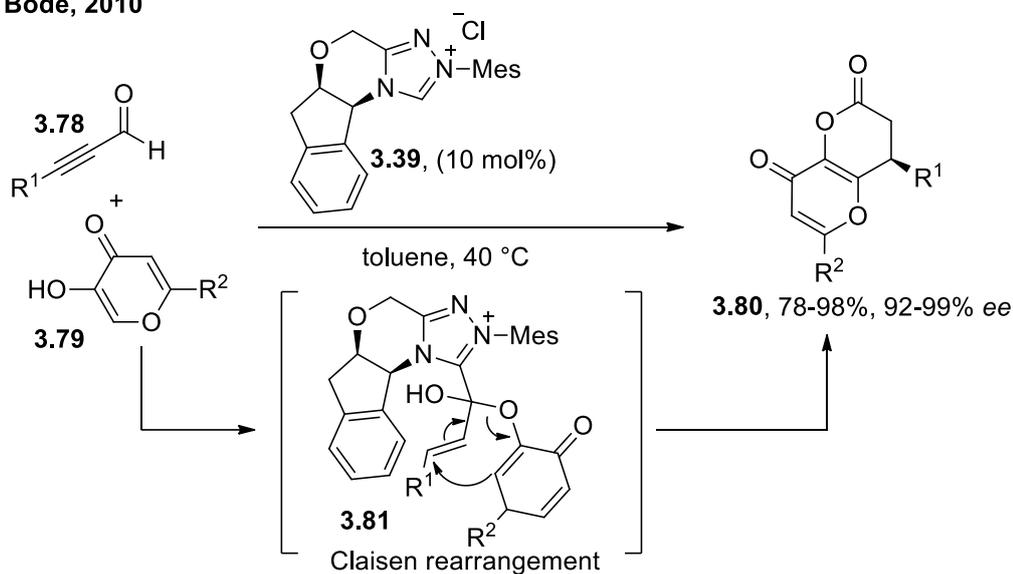
Studer, 2010



Scheme 16: NHC-catalysed synthesis of 3,4-dihydropyran-2-ones from α,β -unsaturated aldehydes and β -diketones.

A stereoselective synthesis of 3,4-dihydropyranones was reported by Bode in 2010 (Scheme 17):²² the reaction of ynals **3.78** with enols **3.79** proceeded in the presence of catalytic amounts of triazolium salt **3.80**, without the necessity of an organic base. In this context, the small quantity of NHC that was in equilibrium with protonated iminium salt **3.39** was sufficient for the reaction to take place. Bicyclic 3,4-dihydropyranones **3.80** were obtained in good yield and enantioselectivities *via* a proposed Claisen rearrangement of hemiacetal **3.81** (Scheme 17).

Bode, 2010

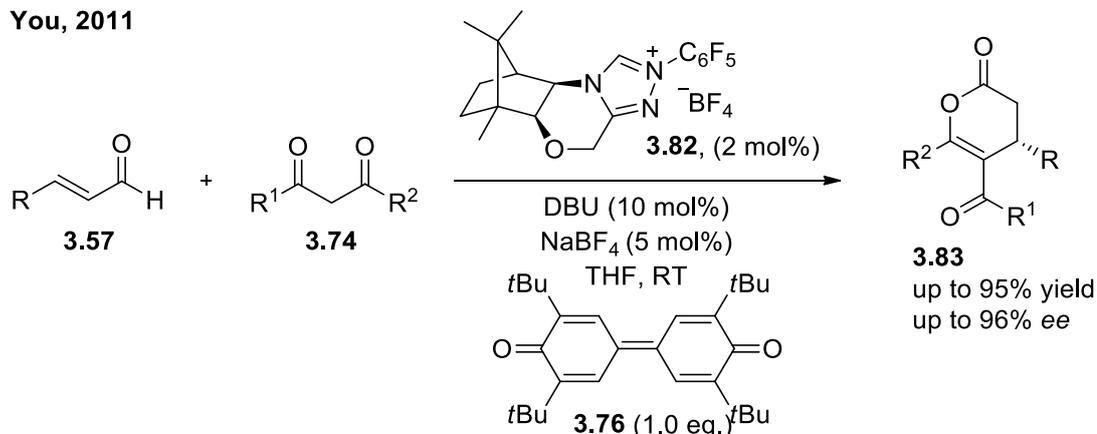


Scheme 17: Enantioselective synthesis of bicyclic 3,4-dihydropyrano-2-ones.

A stereoselective version of Studer's oxidative annulation of α,β -unsaturated aldehydes and β -diketones (Scheme 16) was reported by You in 2011 (Scheme 18).²³ Camphor-derived triazolium salt **3.82** and catalytic DBU promoted the formation of 3,4-dihydropyranones **3.83**, with quinone **3.76** as the oxidant. Interestingly, the addition of 5 mol% of sodium tetrafluoroborate enhanced both the chemical yield and the stereoselectivity; according to the

author, the interaction between NaBF_4 and the C_6F_5 group of triazolium salt **3.82** influenced the transition state of the reaction, leading to the high enantioselectivity observed.

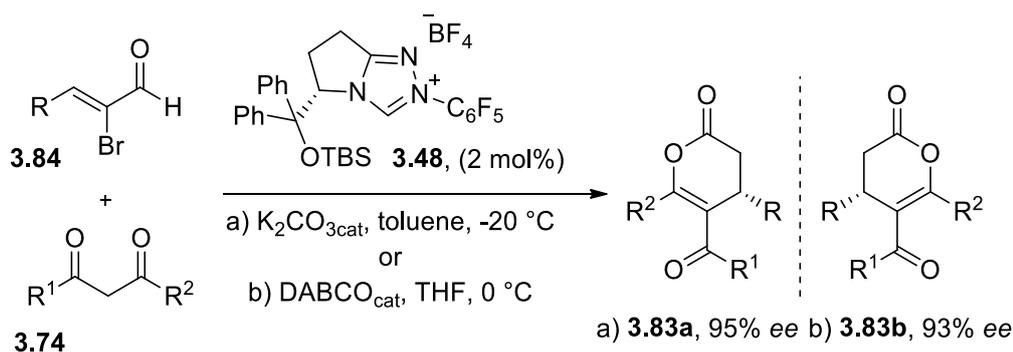
You, 2011



Scheme 18: Stereoselective oxidative annulation of α,β -unsaturated aldehydes and β -diketones.

Ye and co-workers described the generation of α,β -unsaturated acylazolium ions from α -bromoaldehydes **3.84** and chiral NHCs (Scheme 19).²⁴ Michael addition of β -dikarbonyl compounds to **3.84** in the presence of a base provided the corresponding pyranones **3.83**. Different NHC precursors were tested in order to optimise the stereoselectivity: notably, changing the nature and the strength of the base led to a reversal of the observed stereoselectivity; when the reaction was carried out in toluene and potassium carbonate as a base, product **3.83a** was obtained in 95% ee, while the same reaction, carried out in THF and DABCO as a base, provided enantiomer **3.83b** in 93% ee (Scheme 19).

Ye, 2011



Scheme 19: Synthesis of chiral 3,4-dihydropyran-2-ones from α -bromoaldehydes.

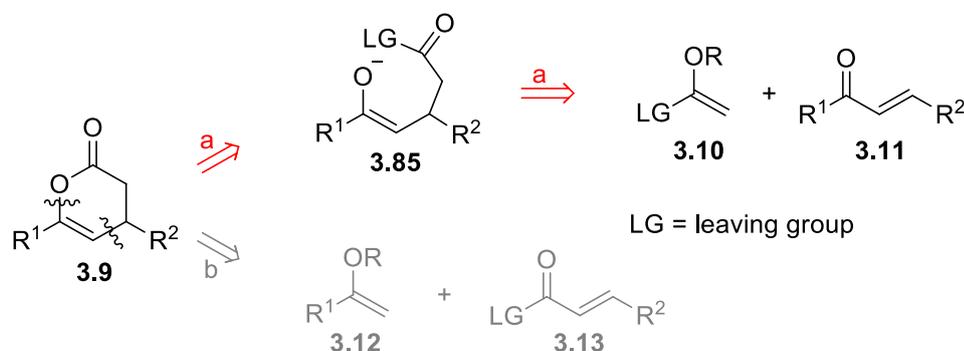
The stereoselective synthesis of substituted 3,4-dihydropyran-2-ones can be easily executed starting from cheap building blocks, with the aid of organocatalysis. Two complementary synthetic routes are available and allow the formation of chiral 3,4-dihydropyran-2-ones in high stereoselectivity. *N*-heterocyclic carbene-catalysis provided the most successful examples of synthesis of 3,4-dihydropyran-2-ones, in terms of versatility and efficiency. It should be noted that the preparation of chiral NHC involves several steps and it is unideal, in spite of the high

ees that were reported. Also, examples of phase transfer catalysed and thiourea-catalysed reactions have been reported. However, these latter often required very reactive starting materials, or the use of stoichiometric oxidants, which is not compatible with many functional groups. In this context, the development of a new and mild catalytic approach to the formation of 3,4-dihydropyranones fills a gap, providing an easy-to-execute procedure to access important compounds.

3.2 Results and Discussion

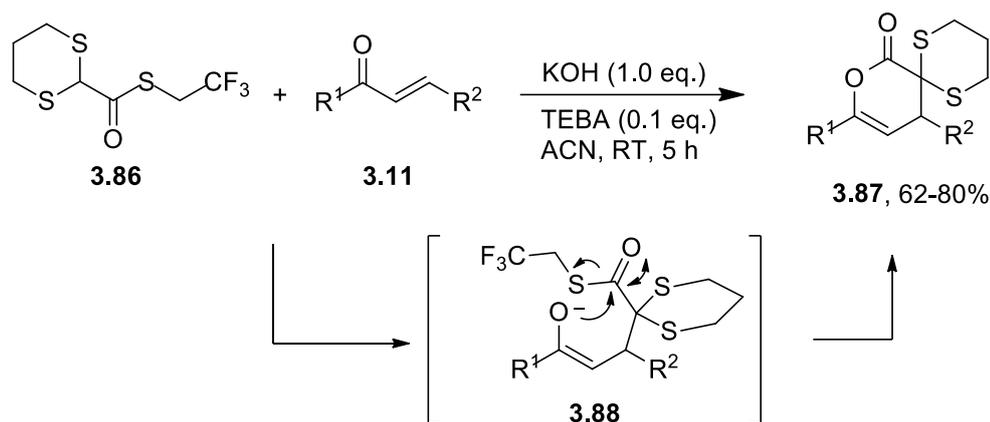
3.2.1 Phase transfer catalysed enantioselective synthesis of 3,3-dithiano-3,4-dihydropyran-2-ones *via* Michael addition-cyclisation of thioester enolates and chalcones.

3,4-Dihydropyran-2-ones are versatile synthetic intermediates in organic chemistry, widely employed in the synthesis of 2-pyrones,⁶⁻⁸ γ -lactones,⁸ cyclic enamines,⁹ functionalised enones.¹⁰ Moreover, they constitute the key functionalized subunit of isocoumarins, a family of naturally occurring compounds that show a broad spectrum of interesting pharmacological activities.²⁵ The Michael addition of enolates **3.10** bearing good leaving groups to α,β -unsaturated carbonyl compounds **3.11**, followed by intramolecular cyclization, is one of the most straightforward, efficient and simple methods for constructing the 3,4-dihydropyran-2-one skeleton and is well preceded in the literature (Scheme 20, path a).^{12,13,15}



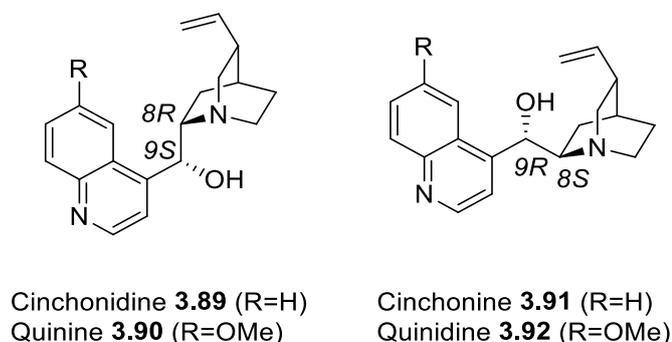
Scheme 20: Retro-synthesis of 4,6-disubstituted-3,4-dihydro pyran-2-ones.

In a previous work by Albanese and Gaggero,²⁶ 3,4-dihydropyran-2-one **3.87** was synthesized by a Michael addition-cyclization tandem procedure, which involved the reaction of the enolate of activated thioester **3.86** and chalcone **3.11**, under phase transfer catalysis (Scheme 21).



Scheme 21: Phase transfer catalysed synthesis of 3,4-dihydropyranones from activated thioesters.

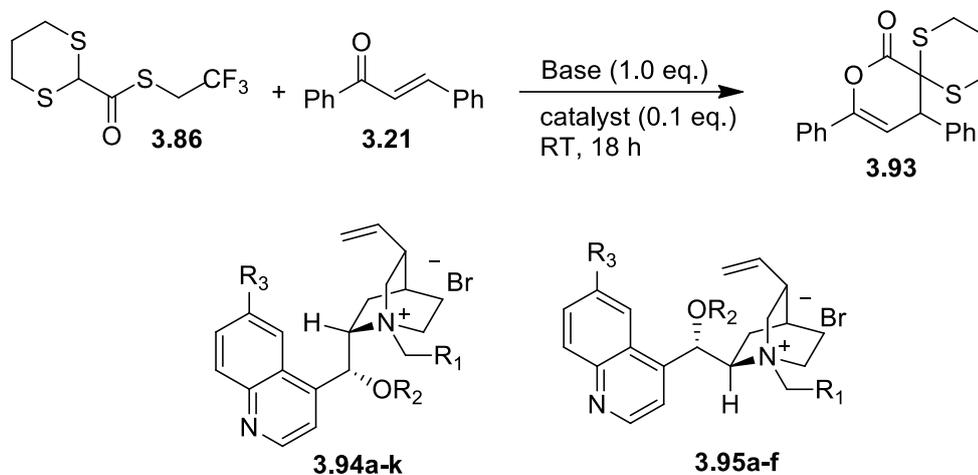
The choice of nucleophile **3.86** bearing the 1,3-dithiane moiety, stemmed from numerous evidences that pointed out the remarkable stabilising effect the two sulfur atoms may provide to an adjacent carbanion.^{27,28} As a consequence, the pK_a of simple 1,3-dithiane has been evaluated as 39.²⁹ The presence of a thioester group further increases the acidity of the α -proton, and also fulfils the role of an excellent leaving group for a next addition/elimination reaction, offering the opportunity for a final annulation step. The 1,3-dithiane is a versatile group that can be removed subsequently by means of established procedures, requiring oxidative³⁰ or reductive³¹ conditions. Hence dihydropyranones **3.87** were obtained in moderate to good yield by reacting chalcones **3.11** with thioester **3.86** in the presence of 1 molar equivalent of potassium hydroxide and a catalytic quantity of triethylbenzylammonium chloride (TEBA, Scheme 21). With this preliminary data in hand and convinced of the importance of the obtainable compounds we posed the question of how to carry out this reaction in enantioselective fashion by using a chiral phase transfer catalyst. Our research group has recently described some highly enantioselective Michael reactions and cyclopropanations, which run in the presence of chiral *Cinchona*-based quaternary ammonium salts.^{32–37} Chiral ammonium salts **3.94**, **3.95** can be prepared in a single step by quaternization of cheap, commercially available cinchona alkaloids with a variety of alkylating agents (Scheme 22).³⁸



Scheme 22: *Cinchona* alkaloids.

Cinchona alkaloids are convenient materials for organocatalysis, and they have been preferred to other classes of chiral ammonium salts, which required longer syntheses.³⁹

Table 1: Screening of *Cinchona*-based quaternary ammonium salts^a



Entry	catalyst	R ¹	R ²	R ³	Base	Solvent	Yield (%) ^b	ee (%) ^c
1 ^d	TBAB	-	-	-	KOH	DCM	74	-
2 ^d	3.94a	Ph	H	H	KOH	DCM	17	3
3	3.94a	Ph	H	H	KOH	Toluene	19	7
4	3.94a	Ph	H	H	KOH	Et ₂ O	17	3
5	3.94a	Ph	H	H	K ₃ PO ₄	DCM	32	-28
6	3.94a	Ph	H	H	K ₂ CO ₃	DCM	28	-4
7	3.94a	Ph	H	H	CsF	DCM	44	-17
8	-	-	-	-	K ₃ PO ₄	Toluene	40	-
9	3.94a	Ph	H	H	K ₃ PO ₄	Toluene	25	-3
10	-	-	-	-	K ₃ PO ₄ (aq) ^e	Toluene	0	-
11	3.94a	Ph	H	H	K ₃ PO ₄ (aq) ^e	Toluene	5	44
12	3.94a	Ph	H	H	K ₃ PO ₄ (aq) ^e	DCM	2	7
13	3.94b	Anthracenyl	H	H	K ₃ PO ₄	DCM	33	-
14	3.94c	Ph	Allyl	H	K ₃ PO ₄	DCM	31	-10
15	3.94d	C ₆ F ₅	H	H	K ₃ PO ₄	DCM	11	18
16	3.94e	2-(NO ₂)C ₆ H ₄	H	H	K ₃ PO ₄	DCM	8	-2
17	3.94f	2-(OMe)C ₆ H ₄	H	H	K ₃ PO ₄	DCM	9	-6
18	3.95a	Ph	H	H	K ₃ PO ₄	DCM	22	23
19	3.94g	Anthracenyl	H	OMe	K ₃ PO ₄	DCM	8	12
20	3.95b	C ₆ F ₅	H	OMe	K ₃ PO ₄	DCM	11	10

^a Reaction conditions: **3.86** (0.10 mmol), chalcone **3.21** (0.12 mmol), base (0.10 mmol), catalyst (0.01 mmol), solvent (5 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD), negative numbers refer to inverted enantioselectivity. ^d Reaction carried out for 5 h. ^e 1.5 M aqueous solution.

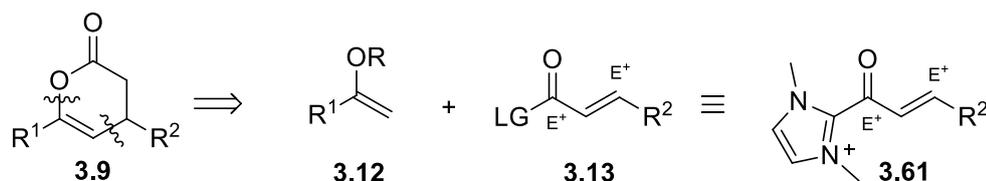
Moreover, they are available in two pseudoenantiomeric forms, which often have a complementary effect over the stereoselectivity of a reaction, when used as chiral catalysts. It was reasoned that the use of **3.94**, **3.95** would provide an advantage over the NHC catalysed reaction, as **3.94**, **3.95** are easy and fast to prepare and usually require very low catalyst loading. In addition, salts **3.94**, **3.95** are bench stable and can be used or stored without

precautions. *S*-(2,2,2-Trifluoroethyl)-1,3-dithiane-2-carbothioate **3.86** was prepared by reacting commercially available 1,3-dithiane-2-carboxylic acid and 2,2,2-trifluoro ethanethiol in the presence of HOBt and EDC·HCl as stoichiometric coupling reagents.^{40,41} Thioester **3.86** was isolated in 95% yield after aqueous workup as an air-stable solid, which could be stored in a closed vial for several months without special precautions. A series of catalysts **3.94** and **3.95** were prepared by quaternarisation of quinine (QN), quinidine (QD), cinchonine (CN) or cinchonidine (CD) with the desired alkyl halide, following a well-known synthetic protocol.³⁸ The chiral phase transfer catalysed reaction of thioester **3.86** and chalcone **3.21** was selected as the standard experiment and was run under several reaction conditions, including different bases, solvents and chiral catalysts (Table 1). This set of experiment were run at room temperature, for a time of 5 h and employing 10 mol% of catalyst. When the reaction was run under the catalysis of triethylbenzylammonium chloride and potassium hydroxide was used as an inorganic base, 3,4-dihydropyranone **3.93** was obtained in 74% yield, in accordance with Albanese's published results (Table 1, entry 1).²⁶ Under the same reaction conditions, chiral *N*-benzylcinchonidinium bromide **3.94a** provided 3,4-dihydropyranone **3.93** in only 17% yield, and no appreciable enantioselectivity (Table 1, entry 2). The results obtained using potassium hydroxide revealed to be not dependent on the solvent; indeed, when thioester **3.86** and chalcone **3.21** were reacted in toluene or diethyl ether with potassium hydroxide as a base and *N*-benzylcinchonidinium bromide **3.94a** as a catalyst, product **3.93** was obtained in similar yield, and enantiomeric excess close to 0 (Table 1, entries 3 and 4). However, when different bases such as potassium carbonate, potassium phosphate and cesium fluoride were used, compound **3.93** was obtained in higher yields and *ees* (Table 1, entries 5-7). Remarkably, it was noted that in these experiments the opposite enantiomer was consistently obtained as the major product, suggesting a catalytic transition state that is strongly dependent on the strength and dimension of the base. It is not uncommon for chiral phase transfer catalysis to provide different enantiomers depending on solvent polarity and size of the basic anion: when using the same catalyst, the reaction media can influence the geometry of the transition state to such an extent that the two different enantiomers can be obtained by simply changing the reaction conditions. When the reaction was carried out with potassium phosphate in toluene without a phase transfer catalyst, product **3.93** was obtained in 40% yield after 18 h of reaction, while the same reaction carried out in the presence of catalyst **3.94a** provided product **3.93** in only 25% yield (Table 1, entries 8, 9). This result showed that the uncatalysed background reaction displayed a comparable rate to the reaction mediated by the quaternary ammonium catalyst. In order to slow down the uncatalysed racemic process it was decided to run the reaction in a liquid-liquid biphasic system. However, when potassium phosphate was added as a 1.5 M aqueous solution, only traces of 3,4-dihydropyranone **3.93** were formed (Table 1, entries 10-12). Interestingly, when a solution of substrates **3.86** and **3.21** in toluene was reacted in the presence of catalyst **3.94a** and an aqueous solution of potassium phosphate, compound **3.93** was isolated in only 5% yield, but with an enantiomeric excess as high as 44%, the highest level of enantioselectivity found in this study (Table 1,

entry 11). From this set of experiments we identified potassium phosphate and DCM as the base and solvent that provided higher chemical yields of product **3.93**. Hence we tested the effect of the presence of different *Cinchona*-derived PTC, synthesised from the four different pseudoenantiomeric alkaloids under these reaction conditions (Table 1, entries 13-20). Bulky anthracenyl-cinchonidinium **3.94b** provided compound **3.93** in 33% yield but with no enantioselectivity (Table 1, entry 13). *N*-Pentafluorobenzyl-cinchonidinium **3.94d** provided **3.93** with an inversion of enantioselectivity, compared to simple *N*-benzylcinchonidinium bromide **3.94a** (Table 1, entries 5, 15). *Ortho*-substituted **3.94e** and **3.94f** did not perform well in terms of chemical yield and enantioselectivity (Table 1, entries 16, 17). Quaternary ammonium salts derived from the different pseudoenantiomers of the *Cinchona* alkaloids (Table 1, entries 18-20). It was also shown that cinchoninium salt **3.95a** provided product **3.93** in similar yield but inverted enantiomeric excess, compared to its cinchonidinium analogue **3.94a** (Table 1, entries 5, 18). On the other hand, quininium **3.94g** and quinidinium **3.95b**, although in pseudoenantiomeric relationship, provided the same major enantiomer and in equally low enantioselectivity (Table 1, entries 19, 20). In summary, the results outlined in Table 1 identified potassium phosphate and DCM as the best combination of base and solvent, since 3,4-dihydropyranone **3.93** was obtained in 32% yield and 28% ee, when catalyst **3.94a** was used and 18 h were chosen as the reaction time (Table 1, entry 5). Liquid-liquid PTC did not prove to be the ideal reaction medium, since the reaction carried out in this fashion showed a low chemical yield, even if a higher enantioselectivity (44% ee) was achieved when the biphasic system consisted of toluene and a potassium phosphate aqueous solution. The effect of the substitution on the quaternary ammonium salts **3.94a-g**, **3.95a,b** could not be rationalized, and therefore we were not able to improve the enantioselectivity of the reaction by catalyst design and optimisation. In conclusion, we abandoned the enantioselective PTC synthesis of 3,4-dihydropyranones from dithianethioesters **3.86**, in favour of a more promising synthetic strategy, which better adapted to the phase transfer catalysed conditions and that will be discussed in the next paragraph.

3.2.2 Enantioselective synthesis of 3,4-dihydropyran-2-ones via PTC addition-cyclisation of acetylacetone to thiocinnamates.

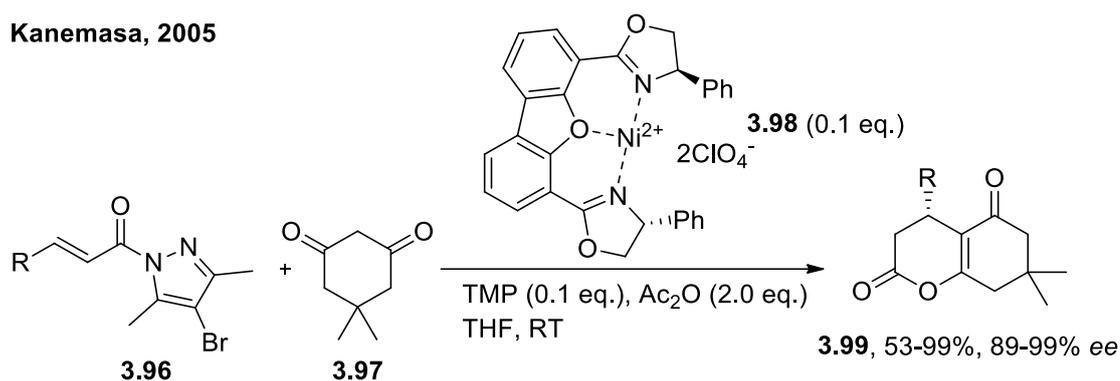
α,β -unsaturated acylazolium species **3.61**, key intermediates in the NHC-catalysed synthesis of 3,4-dihydropyran-2-ones **3.9** (Scheme 14), can be considered synthetic analogue to α,β -unsaturated activated esters **3.13**. Both compounds **3.13** and **3.61** contain two electrophilic centres (E^+) that could be selectively reacted. For this reason, the use of cinnamic acid derivatives **3.13** in combination with ketone enolates **3.12** was considered a viable synthetic option to prepare substituted 3,4-dihydropyranones (Scheme 23).



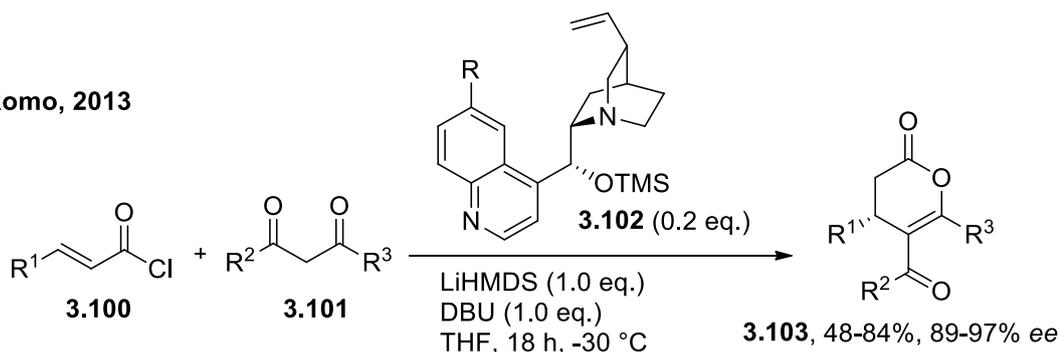
Scheme 23: Synthesis of 3,4-dihydropyran-2-ones from enolates and α,β -unsaturated activated esters.

A literature survey revealed many examples of this strategy: for instance, Kanemasa and Itoh reported the asymmetric Michael reaction between a cyclic ketone **3.97** and α,β -unsaturated acylpyrazole **3.96**, catalyzed by chiral Lewis acid **3.98** and 2,2,6,6-tetramethylpiperidine (TMP) (Scheme 24).⁴² This process required an excess of acetic anhydride as electrophilic trap for by-product pyrazole to prevent its reaction with starting material **3.96**. Romo reported a Michael reaction of acceptor **3.100** and donor 1,3-diketone **3.101**, which run under the catalysis of tertiary chiral amines **3.102** (Scheme 24).⁴³ These methods present several advantages over NHC catalysis, which often requires either a stoichiometric amount of oxidant or functionalized aldehydes as starting material.⁴⁴

Kanemasa, 2005



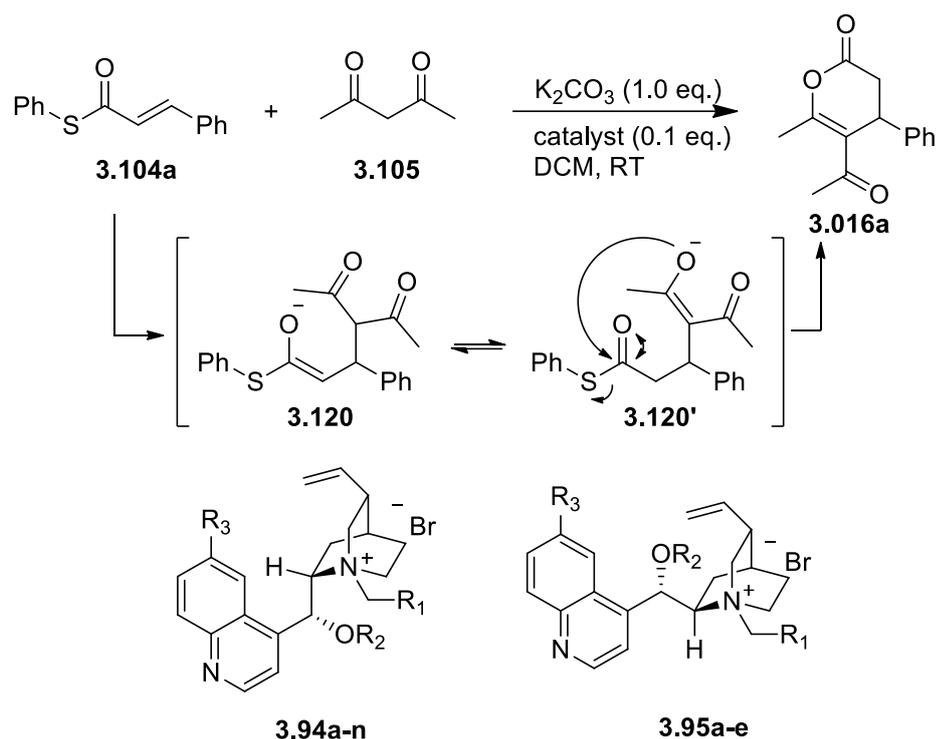
Romo, 2013



Scheme 24: Enantioselective synthesis of 3,4-dihydropyranones from acrylic acid derivatives.

To the best of our knowledge, there are no reported examples of the reaction between an enolate and an activated α,β -unsaturated carbonyl such as **3.96** and **3.100** carried out under phase transfer catalysis. We have also considered that thioesters present a thiolate moiety that could fulfil the requirement of the leaving group necessary to the tandem cyclisation. Thioesters are stable compounds, insensitive to air or moisture and their use offers an

advantage over acyl chlorides.²⁶ Hence we set out to prepare 3,4-dihydropyran-2-ones by reaction of an active methylene compound and an α,β -unsaturated thioester in the presence of a stoichiometric amount of inorganic base and a catalytic chiral quaternary ammonium salt. The addition of acetylacetone **3.105** to *S*-phenyl-(*E*)-thiocinnamate **3.104a** was chosen as a model reaction in order to probe the reactivity of α,β -unsaturated thioesters towards Michael addition and to test if thiophenolate displacement could take place under these conditions. To our delight, when cinnamic thioester **3.104a** and acetylacetone were reacted in DCM for 24 h, in the presence of 1 molar equivalent of potassium carbonate and 10 mol% of tetrabutylammonium bromide (TBAB), pyranone **3.106a** was obtained in 74% yield after column chromatography (Table 2, entry 1). Having discovered a new method to access **3.106a**, we then considered to develop an enantioselective version of it, by carrying out the reaction in presence of a chiral PTC. In addition we verified that the reaction of **3.104a** and **3.105** carried out in the absence of a quaternary ammonium salt, did not take place, and product **3.106** could not be detected in the crude ¹H-NMR after 24 h of reaction (Table 2, entry 2). When chiral *N*-benzylcinchonidinium bromide **3.94a** was used as a phase transfer catalyst, product **3.106a** was obtained in 50% yield after 24 h of reaction time (Table 2, entry 3). The enantiomeric excess of product **3.106a** proved to be 27% ee, as measured *via* chiral HPLC. Encouraged by these preliminary results, we undertook a screening of *Cinchona*-derived quaternary ammonium salts. Interestingly, when *N*-benzylcinchoninium bromide **3.95a**, pseudoenantiomer of **3.94a**, was used as a catalyst, pyranone **3.106a** was isolated from the reaction mixture in 53% yield and 18% ee after 48 h of reaction (Table 2, entry 4). The comparison of the specific optical rotation of enantioenriched compounds **3.106a** derived from the reaction with catalysts **3.94a** and **3.95a** with the literature data allowed us to determine the absolute configuration of the major enantiomer in each product mixture.⁴⁵ Accordingly, when cinchonidinium salt **3.94a** was used, an (*S*)-enantiomer-rich mixture of **3.106a** was obtained, while the pseudoenantiomer cinchoninium salt **3.95a** promoted the formation of (*R*)-**3.106a** preferentially. Quininium and quinidinium salts **3.94h**, **3.95c** proved to be better catalysts for this reaction, since product **3.106a** was obtained in higher yield and enantiomeric excess (Table 2, entries 5, 6). Similarly to what observed for the cinchonidine/cinchonine series, quininium **3.94h** promoted the formation of the (*S*)-enantiomer while quinidinium **3.95c** favoured the formation of (*R*)-enantiomer (38% and 20% ee respectively). A screening of differently substituted *Cinchona* PTCs was then performed in order to identify the steric determinants required to improve the stereoselectivity. Bulky *N*-anthracenylcinchonidinium **3.94b** did not prove a good catalyst, inhibiting the formation of **3.106a** (Table 2, entry 7). Also, the presence of a free OH on the catalyst seemed essential for the reaction to take place, since *O*-pivaloyl-*N*-benzylcinchonidinium **3.94i** allowed the formation of product **3.106a** in only 10% yield over 48 h, with no stereoselectivity (Table 2, entry 8).

Table 2: Preliminary screening of *Cinchona*-based quaternary ammonium salts^a

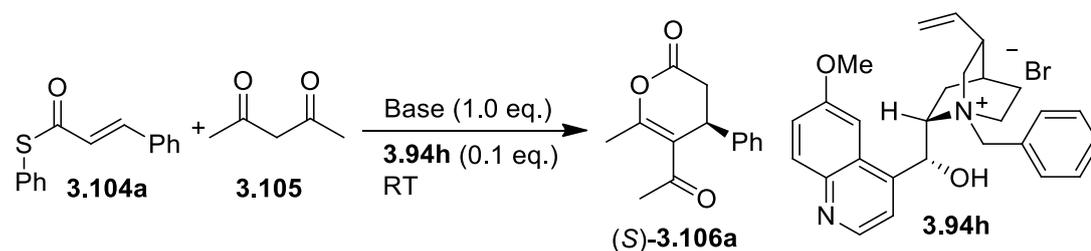
Entry	catalyst	R ¹	R ²	R ³	Time (h)	Yield (%) ^b	ee (%) ^c
1 ^d	TBAB	-	-	-	24	74	-
2 ^d	-	-	-	-	24	0	-
3	3.94a	Ph	H	H	72	50	27 (S)
4	3.95a	Ph	H	H	48	53	18 (R)
5	3.94h	Ph	H	OMe	48	63	38 (S)
6	3.95c	Ph	H	OMe	48	65	20 (R)
7	3.94b	Anthracenyl	H	H	24	-	-
8	3.94i	Ph	Pivaolyl	H	48	10	4 (S)
9	3.94j	3,5-(<i>t</i> Bu) ₂ C ₆ H ₃	H	OMe	48	60	28 (S)
10	3.94k	2-(CN)C ₆ H ₄	H	OMe	48	5	12 (S)
11	3.94l	4-(CF ₃)C ₆ H ₄	H	OMe	48	50	35 (S)
12	3.94m	2-(NO ₂)C ₆ H ₄	H	OMe	48	0	-
13	3.94n	2-(OMe)-4-(NO ₂)C ₆ H ₃	H	OMe	46	28	32 (S)
14	3.95d	3,5-(CF ₃) ₂ C ₆ H ₃	H	OMe	46	20	35 (R)
15	3.95e	2-(OMe)C ₆ H ₄	H	OMe	44	64	33 (R)

^a Reaction conditions: **3.104a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), catalyst (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD). ^d Reaction carried out for 5 h.

Quininium salts **3.94l**, bearing electron-withdrawing substituents on the *N*-benzylic portion, behaved similarly to simple *N*-benzylquininium **3.94h** (Table 2, entry 11), while *ortho*-substituted quininium **3.94k,m** proved ineffective (Table 2, entries 10 and 12). Quinidinium catalyst **3.95d** provided dihydropyranone **3.106a** in 20% yield and 32% ee; a better performance was obtained with 2-methoxyquinidinium derivative **3.95e**, which promoted the formation of (*R*)-**3.106a** in 64% yield and 33% ee. From the results of Table 2, we could

observe the detrimental effect of bulky substituents and *ortho*-EWG-substituents on the benzylic portion of the catalyst. Among the 4 *Cinchona* alkaloids, quinine- and quinidine-derived quaternary salts gave the best results in terms of both chemical yield and enantioselectivity. The addition of substituents on the benzylic moiety of catalysts **3.94**, **3.95**, did not remarkably improve the stereoselectivity of the reaction. *N*-Benzylquininium bromide **3.94h**, which gave the best results, was chosen as a model catalyst in the screening of reaction conditions (Table 3). When the reaction between thioester **3.104a** and acetylacetone **3.105** was carried out in DCM at room temperature, in the presence of catalyst **3.94h** and cesium fluoride, product **3.106a** was obtained in 10% yield and 21% enantiomeric excess, after 44 h of reaction (Table 3, entry 1). When the same reaction was carried out with potassium hydroxide, a drop of the reaction yield was observed, probably due to the competing hydrolysis of thioester **3.104a** (Table 3, entry 3). Potassium phosphate provided similar results to those obtained with potassium carbonate, while lithium hydroxide proved not reactive at all (Table 3, entries 2 and 4). Toluene, tetrahydrofuran, diethyl ether and 1,4-dioxane were tested as reaction solvents, with potassium carbonate as a base and 48 h of reaction time: none of the tested solvents gave results as good as when the reaction was carried out in the same conditions in dichloromethane (Table 3, entries 5-8).

Table 3: Screening of bases and solvents ^a



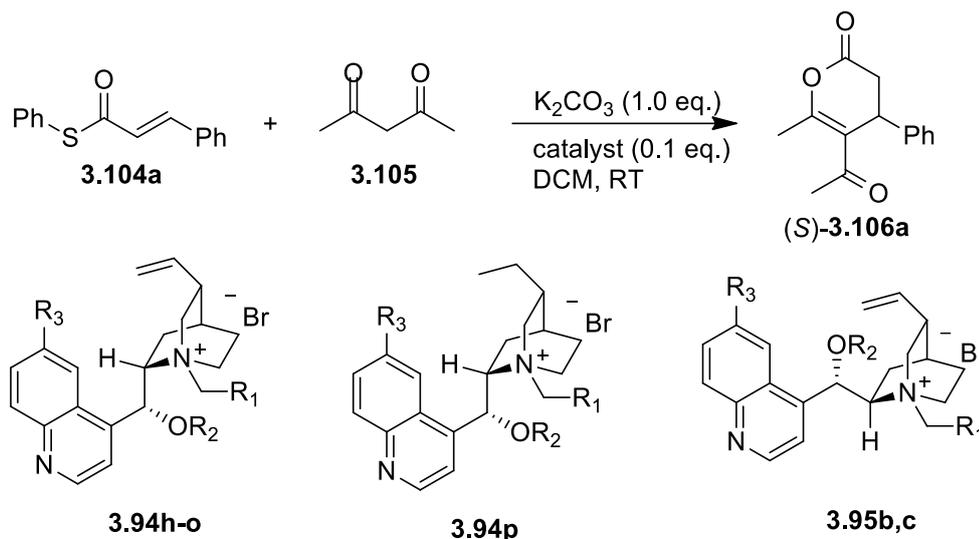
Entry	Base	Solvent	Time (h)	Yield (%) ^b	ee (S, %) ^c
1	CsF	DCM	44	10	21
2	K ₃ PO ₄	DCM	45	61	41
3	KOH	DCM	46	33	46
4	LiOH	DCM	48	-	-
5	K ₂ CO ₃	toluene	48	25	37
6	K ₂ CO ₃	THF	48	53	28
7	K ₂ CO ₃	Et ₂ O	48	11	16
8	K ₂ CO ₃	1,4-dioxane	48	58	17

^a Reaction conditions: **3.104a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **3.94h** (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD).

The optimised reaction conditions (catalyst **3.94h** in DCM with potassium carbonate as a base, Table 2, entry 5) allowed us to obtain product **3.106a** in 63% yield and 38% ee, after 48 h of reaction. In order to further improve this results, we considered the use of additives, which might prove beneficial to the reaction. There are several examples in the literature where the use of ammonium phenoxides greatly improved the performances of a stereoselective

reaction carried out under phase transfer catalysis.⁴⁶ Following the procedure described by Lygo,⁴⁷ a chiral ammonium phenoxide was generated *in situ* by stirring for 30 min a mixture of *N*-benzylquininium bromide **3.94h** (0.1 eq.) with phenol and potassium carbonate (0.1 and 1.1 molar equivalents respectively) at 0 °C in dichloromethane. Then, phenyl thioester **3.104a** and acetylacetone **3.105** were added to the mixture and the reaction was stirred for 36-48 h. The synthesis of dihydropyranone **3.106a** carried out this way took place in 36 h and provided the desired product in 62% yield and a remarkable 80% ee (Table 4, entry 1).

Table 4: Michael addition-cyclisation in the presence of a co-catalyst^a



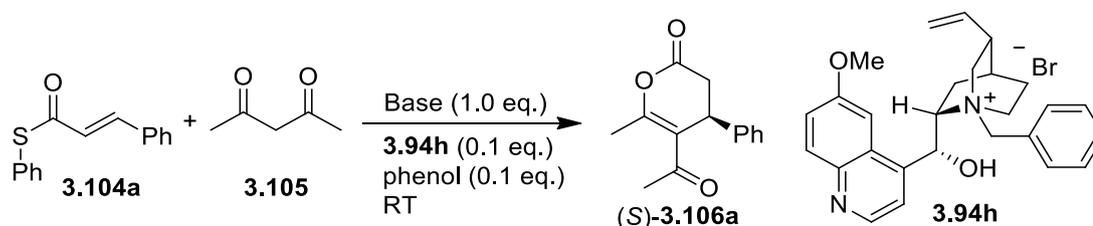
Entry	Catalyst	R ¹	R ²	R ³	Additive	Time (h)	Yield (%) ^b	ee (%) ^c
1	3.94h	Ph	H	OMe	phenol	36	62	80 (S)
2	3.95c	Ph	H	OMe	phenol	36	60	78 (R)
3	3.95b	C ₆ F ₅	H	OMe	phenol	44	0	-
4	3.94g	Antraceny	H	OMe	phenol	44	0	-
5	3.94j	3,5-(<i>t</i> Bu) ₂ C ₆ H ₃	H	OMe	phenol	44	52	80 (S)
6	3.94l	4-(CF ₃)C ₆ H ₄	H	OMe	phenol	44	30	82 (S)
7	3.94o	Ph	H	OH	-	40	41	23 (S)
8	3.94o	Ph	H	OH	phenol	40	30	45 (S)
9	3.94p	Ph	H	OMe	phenol	44	64	79 (S)

^a Reaction conditions: **3.104a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), catalyst (0.01 mmol), additive (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD).

When *N*-benzylquininium bromide **3.95c** was used, the reaction provided enantiomer (*R*)-**3.106a** in identical yield and enantioselectivity (Table 4, entry 2). Additional experiments were carried out in order to investigate the influence of the catalyst structure under these modified conditions. Phase transfer catalysts with a bulky substituent **3.94g** or pentafluorophenyl group **3.95b** did not promote the formation of desired **3.106a** (Table 4, entries 3-4). The presence of bulky *meta*-substituents or a *para*-trifluoromethyl residue did not affect the ee but reduced the chemical yield (Table 4, entries 5, 6). At this stage it was decided to also investigate the potential of cupreidine-based catalysts: cupreidine **3.94o** features a phenol group on the

quinoline ring, making it an equivalent catalytic system to PTC/phenoxide. However, when the reaction between thioester **3.104a** and acetylacetone **3.105** was carried out in the presence of catalytic cupreidinium bromide **3.94o**, dihydropyranone was obtained in only modest yield and enantioselectivity; the addition of catalytic phenol to this system only improved the ee to a small extent (Table 4, entries 7 and 8). Hydroquinine derivatives such as **3.94p** have often showed to provide slightly better performances, compared to their unsaturated counterparts. In our case, however, the use of catalyst **3.94p** did not significantly improve the result over **3.94h**, since product **3.106a** was obtained in 64% yield and 79% ee (Table 4, entry 9). This study, therefore, proved that catalyst **3.94h** was the best option, in particular when used in combination with a catalytic amount of phenol. Hence we focused on the choice of base and solvent for the phenoxide-assisted stereoselective synthesis of dihydropyranone **3.106a**. A brief screening of bases in dichloromethane showed that while potassium hydroxide and cesium carbonate provided compound **3.106a** in higher yield, the best enantiomeric ratio was obtained with potassium carbonate (Table 5, entries 1-3). When toluene, tetrahydrofuran and cyclopentyl methyl ether (CPME) were used as the solvent, yields and enantiomeric excesses were poor (Table 5 entries 4-6). The reaction carried out in chloroform provided dihydropyranone **3.106a** in high ee (87%), compared to what obtained in dichloromethane, but with a much lower chemical yield (Table 5, entry 8). It was noted that when the reaction of thioester **3.104a** and acetylacetone **3.105** was carried out in dry dichloromethane in inert conditions, a slight improvement of both yield and enantiomeric excess was observed (Table 5, entry 7).

Table 5: Optimisation of bases and solvents in the presence of phenol ^a

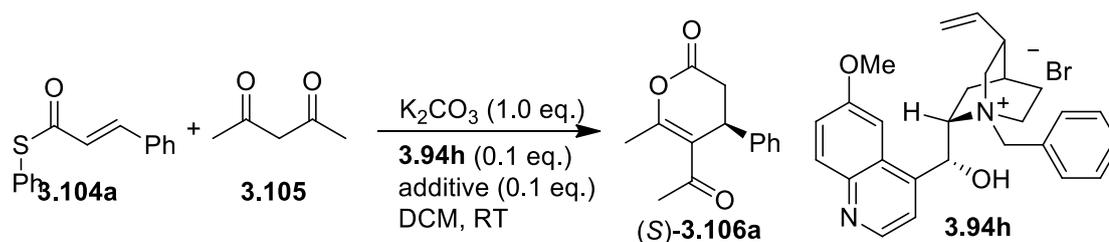


Entry	Base	Solvent	Time (h)	Yield (%) ^b	ee (S, %) ^c
1	K ₂ CO ₃	DCM	36	60	80
2	KOH	DCM	48	73	74
3	Cs ₂ CO ₃	DCM	48	71	78
4	K ₂ CO ₃	toluene	44	20	70
5	K ₂ CO ₃	THF	44	41	49
6	K ₂ CO ₃	CPME	44	16	59
7	K ₂ CO ₃	DCM _{dry} ^d	47	66	81
8	K ₂ CO ₃	CHCl ₃	50	35	86

^a Reaction conditions: **3.104a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **3.94h** (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD). ^d Nitrogen atmosphere and dry solvent.

Differently substituted phenols were next investigated as additives, in order to ascertain the influence of the phenol structure on the outcome of the reaction (Table 6). When 10 mol% thiophenol was added to a mixture of thioester **3.104a**, acetylacetone **3.105**, catalyst **3.94h** and potassium carbonate in DCM, for 36 h of reaction, compound (*S*)-**3.106a** was obtained in 40% yield and 40% *ee* after column chromatography (Table 6, entry 2). Anisole, 4-bromophenol, 4-nitrophenol and β -naphthol, when added to the reaction carried out in a similar manner, provided compound (*S*)-**3.106a** in 30-50% yield and 56-77% *ee*, thus not performing as good as simple phenol (Table 6, entries 3, 5-7). In the case of 2,4,6-trimethylphenol, however, (*S*)-**3.106a** was obtained in slightly higher yield, that was explained considering a suppression of the transesterification of starting thiocinnamate (some *O*-phenyl cinnamate was detected in the $^1\text{H-NMR}$ of the crude while carrying out the reaction in the presence of phenol as additive). The results presented in Table 6 show how the presence of substituents on the phenolic additive did not improve the yield of the reaction, meaning that, in order to obtain greater yield and enantioselectivity, non-substituted phenoxide constitutes the optimal counterion to the quaternary ammonium species.

Table 6: Effect of the substitution on the phenol additive ^a



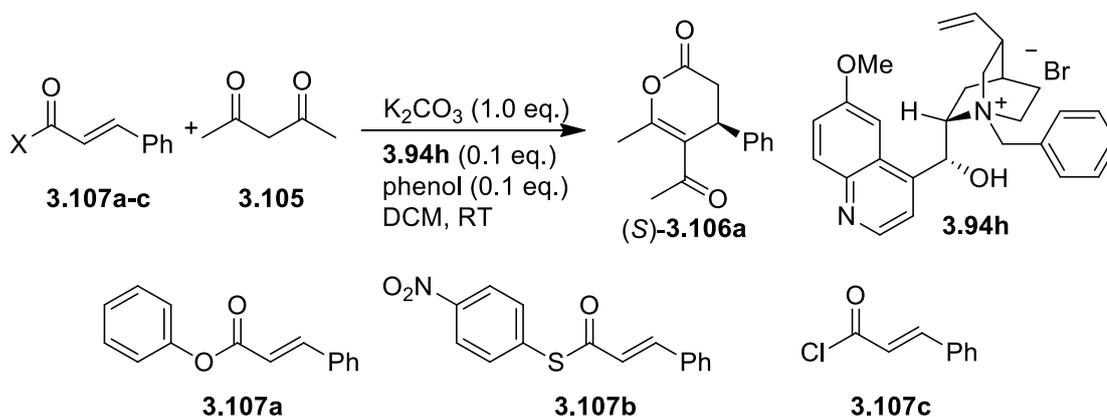
Entry	Additive	Time (h)	Yield (%) ^b	<i>ee</i> (<i>S</i> , %) ^c
1	phenol	36	60	80
2	thiophenol	48	40	40
3	anisole	48	50	73
4	2,4,6-trimethylphenol	40	75	67
5	4-bromophenol	44	45	77
6	4-nitrophenol	46	30	56
7	β -naphthol	44	54	77

^a Reaction conditions: **3.104a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **3.94h** (0.01 mmol), additive (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD). ^d Nitrogen atmosphere and dry solvent.

Michael acceptors **3.107a-c** bearing different leaving groups were tested under the optimised Michael addition-cyclisation reaction conditions (Table 7). When phenyl cinnamate **3.107a** was reacted with acetylacetone **3.105**, the reaction proved sluggish, and after 5 days we were able to recover product **3.106a** in only 10% yield, but with a high enantiomeric excess (80% *ee*, Table 7, entry 1). We synthesised 4-nitrophenylthioester **3.107b** in order to test if a more electron-withdrawed thiol would prove a better leaving group and thus increase the reaction rate. When thioester **3.107b** was reacted with acetylacetone **3.105** under the optimized

reaction conditions, dihydropyranone **3.106a** was obtained in only 56% yield and 12% ee, demonstrating that an EWG NO₂ group might interfere significantly with the transition state (Table 7, entry 2). We have also verified that the reaction of cinnamoyl chloride **3.107c** with acetylacetone **3.105** in PTC took place with formation of hydrolysed cinnamic acid, while traces of **3.106a** were only detected in the ¹H-NMR of the crude (Table 7, entry 3).

Table 7: Reaction of acetylacetone with different Michael acceptors ^a



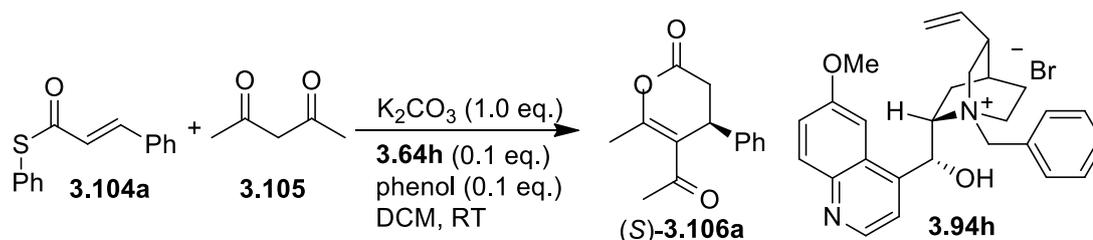
Entry	Substrate	Time (h)	Yield (%) ^b	ee (S, %) ^c
1	3.107a	120	10	80
2	3.107b	44	56	12
3	3.107c	16	trace	-

^a Reaction conditions: **3.107a-c** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **3.94h** (0.01 mmol), additive (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD).

In the attempt to further improve the enantioselectivity of this transformation, we carried out the reaction of thioester **3.104a** and acetylacetone **3.105** in the presence of different additives or in different reaction conditions (Table 8). It has been reported that the addition of ionic compounds or water could increase the performance of a phase transfer catalysed reaction through the stabilisation of the transition states by solvation.⁴⁸ In our case, the addition of small quantities of salts such as potassium and lithium chloride, or the addition of a catalytic amount of water decreased the reaction yield, while leaving the enantioselectivity unperturbed (Table 8, entries 1, 3). The rate of the reaction was substantially reduced when the reaction was carried out at 0 °C, with no appreciable improvement of stereoselectivity. It was observed that after 4 days at 0 °C thioester **3.104a** was only 59% converted and dihydropyranone **3.106a** was obtained after purification of the crude in 35% yield and 78% ee (Table 8, entry 4). When 1 molar equivalent of phenol was added to a DCM solution of reactants **3.104a** and **3.105**, in the presence of 1.0 molar equivalent of potassium carbonate and 10 mol% of **3.94h**, the reaction did not provide compound **3.106a**, but a complex mixture of products (Table 8, entry 5). The reaction carried out with 20 mol% of **3.94h** and phenol proved slower than when performed in the standard reaction conditions, probably due to the inhibiting effect of phenol when exceeding catalytic amounts (Table 8, entry 6). It should also be noted that phase

transfer catalysis using bifunctional quaternary ammonium salts runs faster when carried out at dilution lower than 0.08 M, to impede the formation of catalytically inactive aggregates.⁴⁹ When the reaction of thioester **3.104a** and acetylacetone **3.105** was carried out at a 0.01 M concentration, a drop of the rate was observed, since product **3.106a** was isolated in 31% yield after 44 h of reaction. The increased dilution did not improved the enantioselectivity (79% ee, Table 8, entry 7).

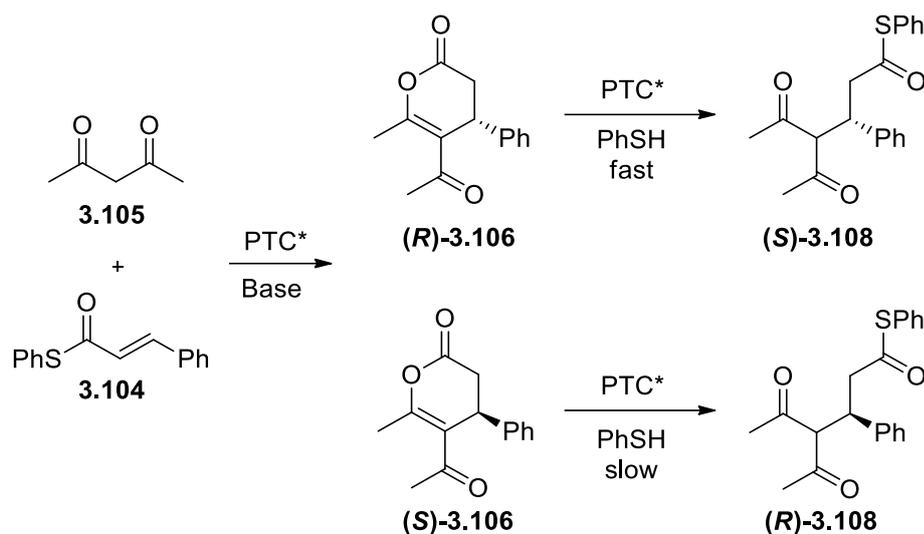
Table 8: Screening of various conditions ^a



Entry	Reaction conditions	Time (h)	Yield (%) ^b	ee (S, %) ^c
1	KCl (1.0 eq.)	47	50	78
2	LiCl (1.0 eq.)	44	18	74
3	H ₂ O (1.0 eq.)	44	49	78
4	0°C	96	35	78
5	phenol (1.0 eq.)	4	0	-
6	phenol (0.2 eq.), 3.115h (0.2 eq.)	45	30	78
7	0.01 M concentration	44	31	79
8	-	1	12	68

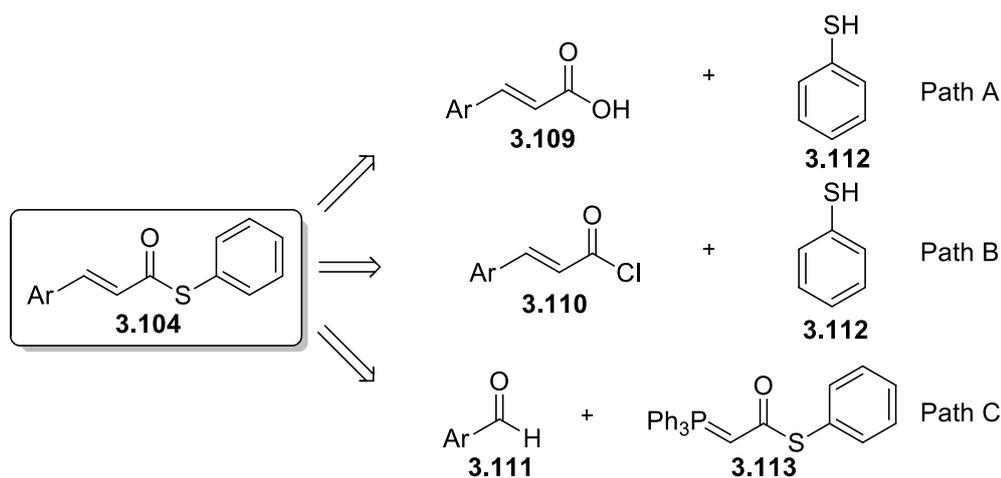
^a Reaction conditions: **3.104a** (0.10 mmol), acetylacetone (0.12 mmol), base (0.10 mmol), **3.94h** (0.01 mmol), solvent (1 ml). ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralpak AD). ^d Nitrogen atmosphere and dry solvent.

When the reaction, carried out in the optimal conditions, was stopped after 1 h, the enantiomeric excess of the isolated product **3.106a** was surprisingly lower than when the reaction was left stirring for 48 h (Table 8, entry 8). In order to explain this result, we hypothesised that a kinetic resolution could occur. Chiral phase transfer catalyst **3.64h** could promote the transesterification/hydrolysis of one of the two enantiomer products **3.106a** preferentially. If this was the case, we could observe the disappearance of one of the two enantiomeric forms of **3.106a** over time. A control experiment was carried out stirring a racemic mixture of dihydropyranone (*R*)-**3.106a** and (*S*)-**3.106a** in DCM, in the presence of chiral PTC **3.64h** (0.1 eq.), potassium carbonate (0.5 eq.), phenol (0.1 eq.) and thiophenol (0.1 eq.) (Scheme 25). After 44 h unreacted **3.106a** was recovered, together with some of its corresponding carboxylic acid. The enantiomeric composition of the recovered dihydropyranone **3.106a** was still racemic. Therefore, the hypothesis of the establishment of a phase transfer catalysed kinetic resolution was disproved.



Scheme 25: The non-constant enantioselectivity could be caused by the kinetic resolution of products **3.106**.

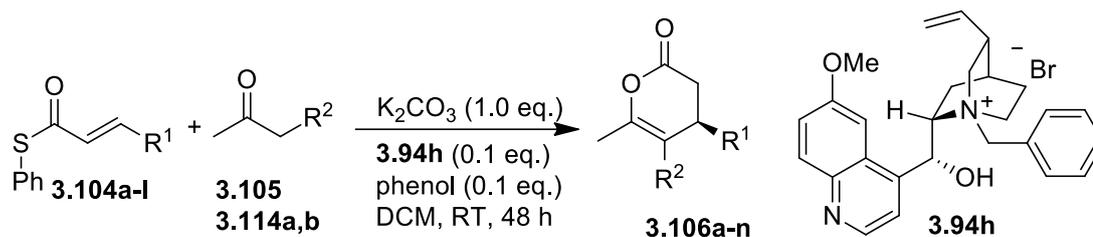
In order to test the scope of the reaction between an active methylene compound such as acetylacetone **3.105** and α,β -unsaturated thioesters **3.104a** a small library of cinnamic thioesters **3.104a-n** was synthesised (Scheme 26). Cinnamic thioesters can be prepared from the corresponding commercial cinnamic acids **3.109** by treatment with thiophenol **3.112**, in the presence of a coupling reagent such as dicyclohexylcarbodiimide (DCC) and catalytic *N,N*-dimethylaminopyridine (DMAP) (Scheme 26, path a). This reaction was performed for most cinnamic acids, but some difficulties were encountered during the separation of the final product from the dicyclohexylurea by-product. For this reason, some thioesters were prepared through chlorination of the corresponding cinnamic acid with thionyl chloride (Scheme 26, path b). The resulting cinnamoyl chloride **3.110** was reacted with thiophenol **3.112** in the presence of triethylamine, to afford the corresponding thioester **3.104**. Cinnamic acids that were not commercially available, were synthesised through pyridine-catalysed Knoevenagel condensation of malonic acid with aromatic aldehydes. An alternative synthesis of cinnamic thioesters is constituted by the Wittig reaction of phosphonium ylide **3.113** with an aromatic aldehyde **3.111** (Scheme 26, path c). However, we found this reaction rather problematic, since it worked well only for aromatic aldehydes bearing electron-withdrawing groups.



Scheme 26: Synthesis of cinnamic thioesters.

The newly synthesised thioesters **3.104a-l** were reacted with acetylacetone **3.105** in dry DCM, in the presence of potassium carbonate and a catalytic amount of phenol and *N*-benzylquininium bromide **3.94h** (Table 9). The steric effect of the substitution on the phenyl ring of the cinnamic ester portion was tested by reacting 2-, 3- and 4-chlorocinnamic thioesters **3.104b,c,d** with acetylacetone **3.105**, under the optimised reaction conditions (Table 9, entries 2-4). 2-substituted and 4-substituted **3.104b,d** provided the corresponding dihydropyranones **3.106b,d** in 78% and 67% yield respectively and very good enantioselectivity. 3-Substitution instead, seemed to have a detrimental effect on both chemical yield and enantiomeric excess (Table 9, entry 3), since 3-chloro-substituted-pyranone **3.106c** was obtained in 50% yield and 57% enantiomeric excess. The reaction did not tolerate excessive steric bulk on the cinnamic aromatic ring, as demonstrated by the reaction of 1-naphthyl-substituted thioester **3.104i** with acetylacetone **3.105** (Table 9, entry 9). Over 48 h, the starting thioester did not convert into the respective pyranone **3.106i**; **3.104i** was recovered unreacted from the reaction mixture, together with 20 mol% of its corresponding carboxylic acid. When 4-methoxythiocinnamic ester **3.104e** was reacted with acetylacetone **3.105**, 4-methoxy-dihydropyranone **3.106e** was obtained in 44% yield, and 5% ee (Table 9, entry 5). The presence of a strong electron-donating group on the aromatic ring of the thioester greatly reduced its electrophilicity, resulting in a slow Michael addition, and a loss of enantiomeric control. On the other hand, the presence of electron-withdrawing groups on the aromatic ring of thioesters **3.104f,g**, was well tolerated: for example, 4-trifluoromethylphenyl-dihydropyranone **3.106g** was obtained in 93% yield and 83% ee (Table 9, entry 7). Thioesters bearing aromatic heterocycles such as furan and thiophene reacted well, providing the corresponding dihydropyranones **3.106j-l** in good yield and enantioselectivity (Table 9, entries 10-12). Less acidic active methylene compounds were tested under the optimised reaction conditions: acetone **3.114a** was reacted with thioester **3.104a** in the presence of potassium carbonate or potassium hydroxide, but the formation of the corresponding dihydropyranone **3.106m** was not observed (Table 9, entry 13). Ethyl acetoacetate proved slightly more reactive, providing dihydropyranone **3.106n** in 21% yield when the reaction was carried out using potassium phosphate as a base (Table 9,

entry 14). Weaker potassium carbonate did not effectively deprotonate ethyl acetoacetate, while the use of potassium hydroxide caused the complete hydrolysis of starting ketoester **3.114b**. While the chemical yield of the reaction between ethyl acetoacetate and thioester **3.104a** was disappointingly low, product **3.106n** was obtained in rather high enantioselectivity (75% ee). A screening of bases and solvents will be performed in order to extend the applicability of the Michael reaction/cyclisation described in Table 9 to β -ketoesters such as ethyl acetoacetate.

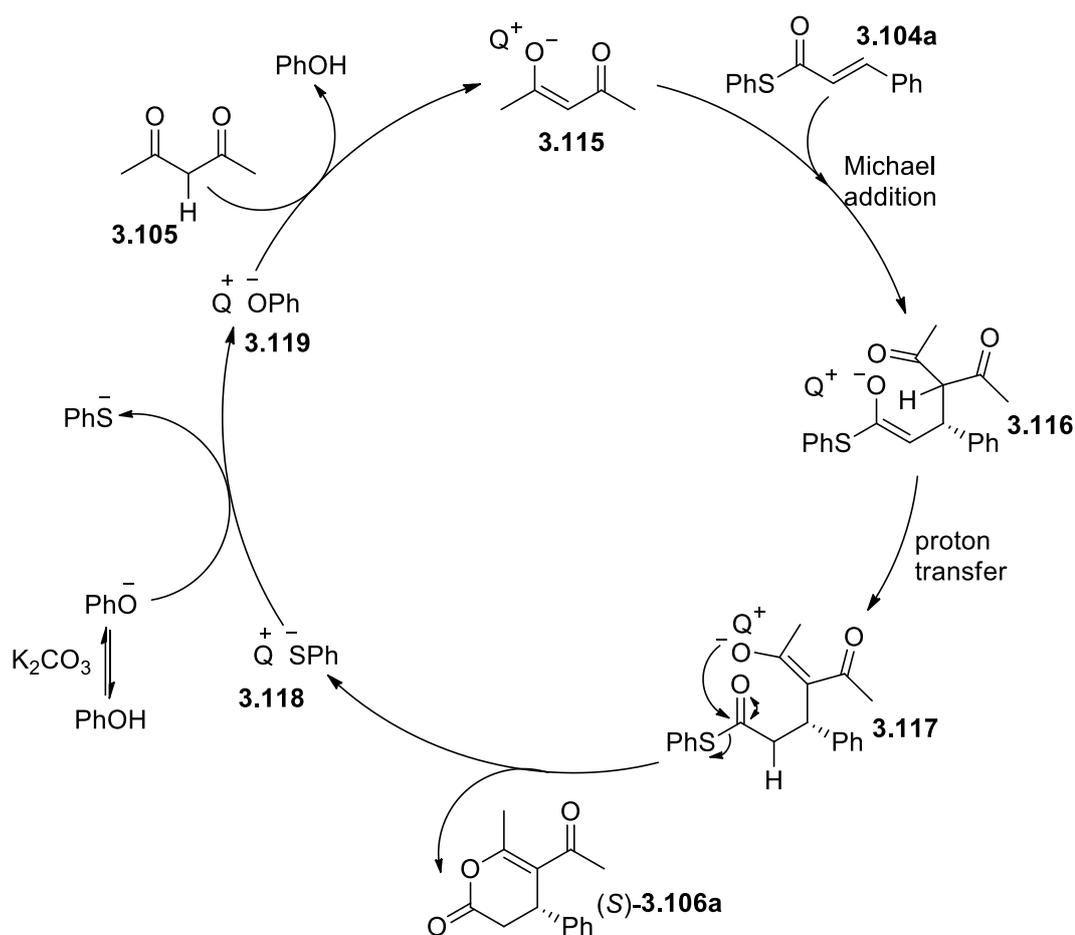
Table 9: Reaction scope ^a

Entry	Product	R ¹	R ²	Yield (%) ^b	ee (S, %) ^c
1	3.106a	Ph	COMe	82	77
2	3.106b	2-ClC ₆ H ₄	COMe	77	88
3	3.106c	3-ClC ₆ H ₄	COMe	57	57
4	3.106d	4-ClC ₆ H ₄	COMe	67	82
5	3.106e	4-(OMe)C ₆ H ₄	COMe	41	5
6	3.106f	4-FC ₆ H ₄	COMe	74	80
7	3.106g	4-CF ₃ C ₆ H ₄	COMe	93	83
8	3.106h	4-MeC ₆ H ₄	COMe	75	76
9	3.106i	1-naphtyl	COMe	-	-
10	3.106j	2-furyl	COMe	60	76
11	3.106k	5-methylfur-2-yl	COMe	55	77
12	3.106l	thiophenyl	COMe	80	88
13 ^d	3.106m	Ph	H	-	-
14 ^e	3.106n	Ph	COOEt	21	75

^a Reaction conditions: **3.104a-l** (0.20 mmol), **3.105** or **3.114a,b** (0.21 mmol), base (0.20 mmol), **3.94h** (0.02 mmol), phenol (0.02 mmol), DCM_{dry} (2 ml), 48 h under nitrogen atmosphere. ^b Isolated yield after column chromatography. ^c Determined by chiral HPLC. ^d Potassium hydroxide and potassium carbonate were tested as bases. ^e Potassium phosphate as a base.

The results presented in Table 9 showed that the synthesis of 3,4-dihydropyranones could be performed with different cinnamic thioesters **3.104a-l**. The reaction, which tolerated many substituents, provided the desired dihydropyranones in excellent yield and good enantioselectivity for thiocinnamates bearing electron-withdrawing groups on the aromatic ring. Strongly electron-donating groups such as methoxy dramatically reduced the reactivity of the cinnamic thioester towards Michael addition, thus preventing the formation of cyclic dihydropyranones. Thioesters bearing a mono-substituted aromatic ring provided the corresponding dihydropyranones in good yield and enantioselectivity, with the exception of *meta*-substituted cinnamic thioester **3.104c**, whose dihydropyranone **3.106c** was obtained in only 50% yield and 57% ee. Less reactive methylene compounds such as acetone and ethyl

acetoacetate were tested, and while the former proved totally unreactive under the optimised conditions, acetoacetate **3.114b** provided the corresponding dihydropyranone **3.106n** in low yield but good enantioselectivity. The proposed mechanism for the annulation process is shown in Scheme 27: the first step involving the deprotonation of acetylacetone **3.105** by chiral quininium phenoxide **3.119** ($Q^+ PhO^-$). Chiral species quininium enolate **3.115** is the active nucleophile, which stereoselectively performs a Michael addition to cinnamic thioester **3.104a**. Adduct enolate **3.116** is subjected to intramolecular proton transfer to form ketone enolate **3.117**, which is converted into the desired 3,4-dihydropyranone **3.106a**, by nucleophilic addition to the thioester carbonyl and thiophenolate extrusion (Scheme 26).



Scheme 27: Proposed catalytic cycle.

3.3 Conclusions

In conclusion, the enantioselective version of Albanese's synthesis of 3,4-dihydropyran-2-ones from dithiano-thioester **3.86** and chalcone was studied. Different *Cinchona*-derived quaternary ammonium salts were tested as chiral phase transfer catalysts for this transformation. A screening of reaction conditions was performed in order to outline a standard protocol that would provide dithiano-3,4-dihydropyranones **3.93** in good yield and enantioselectivity. The best result was obtained when thioester **3.86** was reacted with chalcone **3.11** in dichloromethane, in the presence of potassium phosphate as the inorganic base and *N*-benzylcinchonidinium bromide **3.94a** as catalyst. Under these reaction conditions, dihydropyranone **3.93** was obtained in 32% yield and 28% ee. A new synthesis of 3,4-dihydropyran-2-ones starting from cinnamic thioesters **3.104** and acetylacetone was discovered and optimised. The use of *Cinchona*-derived PTC, allowed the formation of chiral dihydropyranones **3.106** in yields up to 93% and enantiomeric excesses up to 88%. The best results were obtained when catalytic amounts of *N*-benzylquininium bromide **3.94h** and phenol were added to the reaction mixture containing cinnamic thioesters **3.104a**, acetylacetone **3.105** and potassium carbonate. The substrate scope of this new transformation was tested, and the reaction proved to tolerate several functional groups, providing 3,4-dihydropyranones in generally good yield and enantioselectivity for a wide range of cinnamic thioesters. The results discussed in this chapter will soon be converted into a full paper, to be submitted to the editorial board of Journal of Organic Chemistry (or ACS Catalysis).

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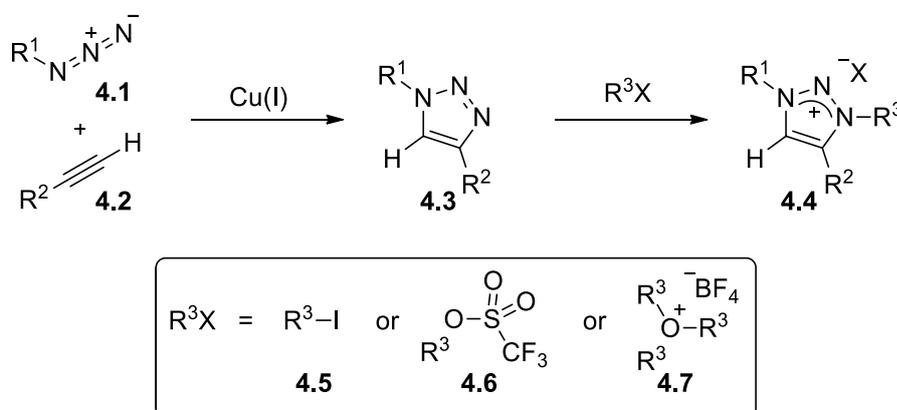
Chapter 4

Design and synthesis of novel binaphthyl-based triazolium salts as a new class of chiral Phase Transfer Catalysts

4.1 Introduction

4.1.1 Physical and chemical properties of 1,2,3-triazolium salts

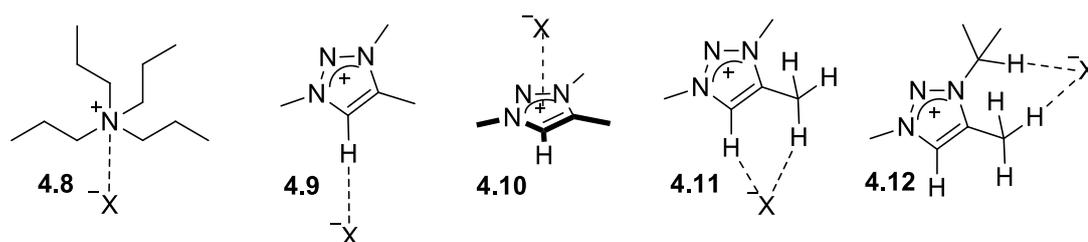
The chemistry of 1,2,3-triazoles and their derivatives has lately received much attention, as a result of the popularity of the Copper catalysed Alkyne-Azide Cycloaddition (CuAAC). Notably, CuAAC allowed the easy preparation of highly functionalised heterocyclic compounds in quantitative yields and complete regioselectivity. 1,2,3-Triazolium salts, arising from *N*-alkylation of 1,2,3-triazoles, have found application in various disciplines: for example, they have been studied as non-conventional ionic liquids,^{1,2} organocatalysts,³⁻⁵ ligands for metal complexes,⁶⁻⁸ and for their unique electronic properties, they have been engineered into anion-recognition molecular probes^{9,10} and molecular machines.¹¹⁻¹³ 1,2,3-Triazolium salts **4.4** can be conveniently synthesised in a modular fashion, by alkylation of the respective 1,2,3-triazole **4.3** with alkyl halides **4.5**, alkyl triflates **4.6** or trimethyloxonium tetrafluoroborates (Meerwein's salts) **4.7** (Scheme 1). Notably, alkylation carried out using mild conditions (i.e. methyl iodide in dichloromethane) required long reaction times and high temperature, due to the relatively low nucleophilicity of the pyridine-like N-3 nitrogen. On the contrary, stronger alkylating reagents, such as triflic esters **4.6** and trialkyloxonium reagents **4.7**, provided the corresponding 1,2,3-triazolium triflates at room temperature and in short reaction times (Scheme 1).



Scheme 1: Preparation of 1,2,3-triazolium salts.

One of the main differences between 1,2,3-triazoles and *N*-alkylated-1,2,3-triazolium salts lays in the increased C-H acidity, which arises from the electron-withdrawing properties of electron-poor aromatic system. Since the pK_a value for a triazolium salt such as **4.4** is 24 (DMSO), these compounds are easily deprotonated by alkoxides; however, when in the presence of weaker bases they can behave as strong hydrogen-bond donors.⁸ For example, when a compound such as **4.4** is treated with a fluoride salt, the difference in pK_a between 1,2,3-triazolium **4.4** and hydrofluoric acid (pK_a 15, DMSO) is so low that the hydrogen bond which is formed has a significant covalent character. In some cases, partial deprotonation in the presence of fluoride was observed, as demonstrated by a hydrogen/deuterium exchange in solution.¹⁴ The delocalisation of the positive charge over the aromatic ring and the presence

of a strongly acidic C-H bond make 1,2,3-triazolium compounds essentially different from a classical asymmetric quaternary ammonium salt **4.8**, whose positive charge is exclusively localised on the central nitrogen atom (Scheme 2); in such a case, the non-directional Coulomb attraction between N^+ and its counterion gives the highest contribution to the binding energy. On the other hand, 1,2,3-triazolium salts offer multiple binding possibilities: the direct interaction ($n \rightarrow \sigma^*$) between the anion lone pair and the anti-bond orbital of the acidic C-H is probably the predominant directional force that best describes the interaction between a 1,2,3-triazolium and its anion (Scheme 2, structure **4.9**).¹¹ It should be noted that the C-H-X dihedral angle is never 180° , due to the important contribution of other additional interactions, such as the direct charge transfer ($n \rightarrow \pi^*$) exerted by the electron-deficient π -system of the triazolium cation (Scheme 2, structure **4.10**). The strong inductive effect generated by the electron-poor triazolium ring also polarises the C-H bonds of the attached alkyl substituents, which also contribute to the binding with the anion, further increasing the accessible complexation geometries (Scheme 2, structures **4.11**, **4.12**). The multiple modes of interaction that triazolium ions can form with negatively charged species may give rise to a lack of orientational preference. However, multiple interaction increase the binding energy overall.¹⁵

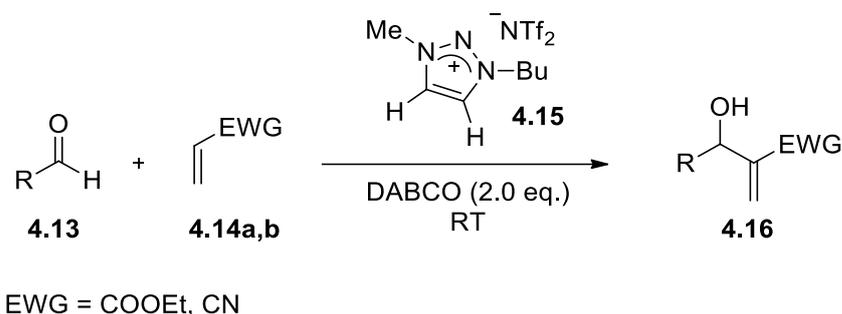


Scheme 2: Anion complexation of 1,2,3-triazolium salts.

4.1.2 Applications of triazolium salts

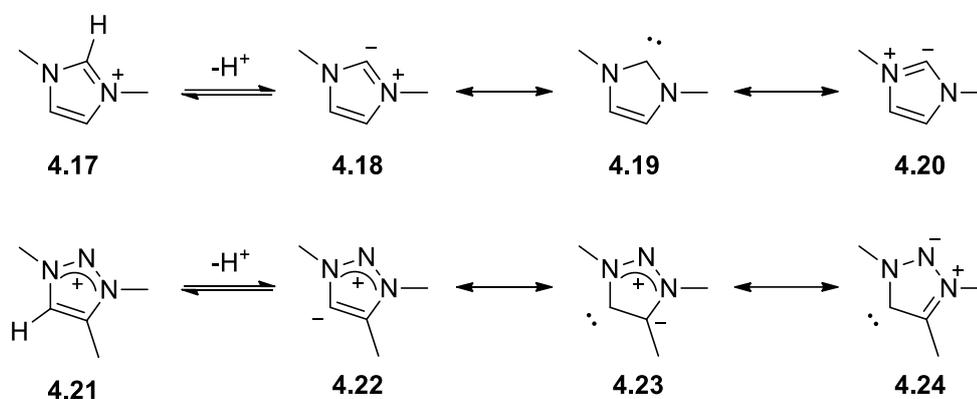
One of the first applications of 1,2,3-triazolium salts was in the synthesis of ionic liquids, as an alternative to the classic 1,3-imidazolium based salts, which have been extensively studied during the last decade as polar reaction solvents,¹⁶ electrolytes^{17,18} and catalysts.¹⁹ Ionic liquids are organic salts with a melting point lower than 100°C and a very low vapour pressure. Their ability to dissolve organic molecules and to transport ions and electric current, make them unique alternatives to water and classical organic solvents. Ionic liquids are considered “green” reaction media, because of their low volatility and solubility in water, which reduce the chances of environmental release.²⁰ However, an important limitation to the use of imidazolium-based ionic liquids lays in their tendency to be deprotonated at the C-2 position, when exposed to mildly basic conditions. For this reason, 1,2,3-triazolium salts provided an advantage over their imidazolium analogues as a more stable alternative towards bases. Their use as solvents for the Baylis-Hillman reaction was reported by Ryu in 2010 (Scheme 3).² This study demonstrated that the reaction of several aromatic aldehydes **4.13** with methyl acrylate **4.14a** or acrylonitrile **4.14b** was promoted by **4.15**: these reactions were carried out at room

temperature, in the presence of an excess of DABCO and provided the desired adducts **4.16** in good yields.



Scheme 3: 1,2,3-Triazolium salt as solvent and promoter of the Baylis-Hillman reaction.

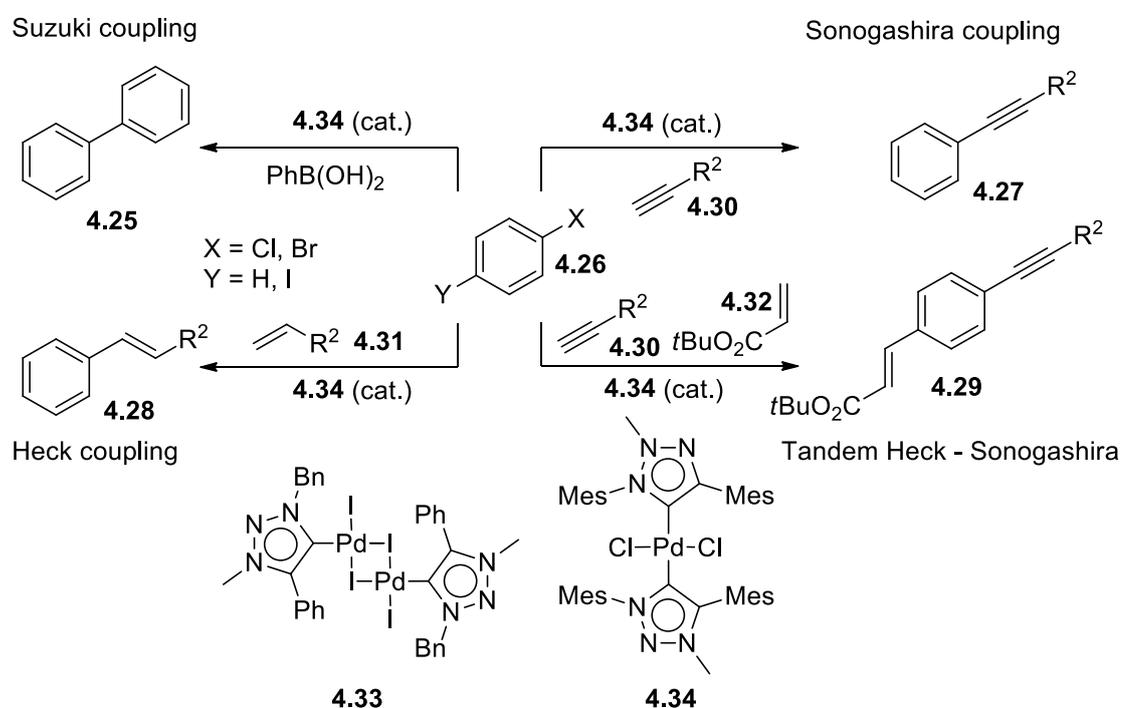
The most relevant application of 1,2,3-triazolium salts is probably their use as precursors of mesoionic carbenes, an increasingly important class of ligands with unique properties.⁶ Mesoionic carbenes, also known as abnormal carbenes, differ from classical imidazolium-derived *N*-heterocyclic carbenes for the lack of a neutral resonance structure such as **4.19**, where a divalent carbon formally bears an electron sextet (Scheme 4). The product of the deprotonation of **4.21** cannot be drawn as a non-zwitterionic resonance structure: as a result, the carbene character of **4.22** is slightly reduced, in favour of a more carbanionic character. For this reason, when bound to metals, mesoionic carbenes such as **4.19** behave as relatively inert and exceptionally strong σ -donor and moderate π -acceptor ligands.



Scheme 4: Resonance structures of 1,3-imidazolium carbenes and 1,2,3-triazolium mesoionic carbenes.

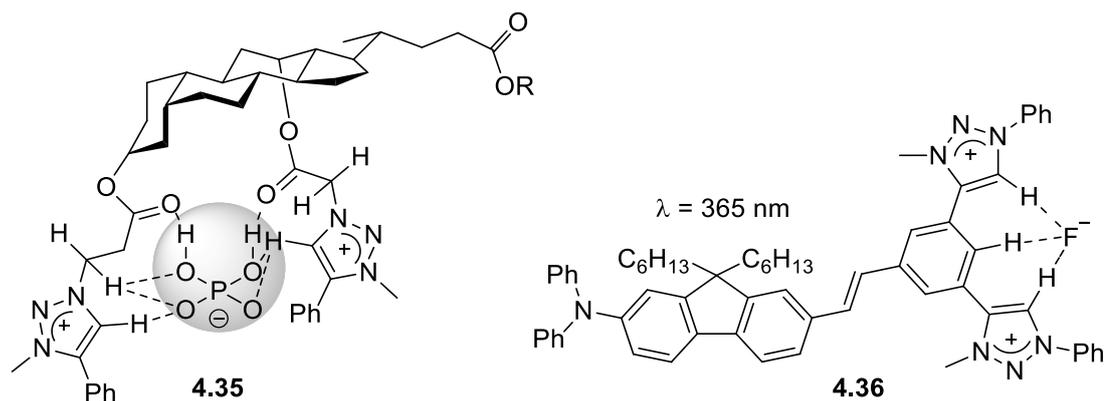
The synthesis of a 1,2,3-triazolidene metal complex was first reported by Albrecht and co-workers, who were able to obtain dimeric palladium complex **4.33** by direct C-H activation of the corresponding 1,2,3-triazolium iodide, in the presence of palladium acetate (Scheme 5).⁶ A similar approach was successfully applied to the preparation of silver, ruthenium and iridium analogues to complex **4.33**. Monomeric *trans*-bis-triazolydene palladium complex **4.34** was tested on palladium-catalysed cross-coupling reactions by the group of Fukuzawa: compound **4.34** performed better than its imidazolydene counterpart in the tested reactions (Scheme

5).²¹ For example, biphenyls **4.25** were obtained quantitatively through a Suzuki coupling of aryl halide **4.26** with phenylboronic acid, under the catalysis of 1 mol% **4.34**.²¹ 1,2,3-Triazolylidene palladium-catalysed Sonogashira coupling of terminal alkynes **4.30** and aryl halides **4.26** and the Heck coupling of aryl halides **4.26** with alkenes **4.31** were also reported (Scheme 5). Notably, Fukuzawa reported a one-pot Sonogashira-Heck tandem process of 4-chloriodobenzene with alkyne **4.30** and *tert*-butyl acrylate **4.32** that, in the presence of palladium complex **4.34** provided **4.29** in good yields (Scheme 5).²² 1,2,3-Triazolylidene ruthenium complexes were proved able to promote oxidation reactions. For example, alcohols were converted to the corresponding aldehydes in neutral conditions, by simple refluxing in toluene, in the presence of η^6 -aryl-1,2,3-triazolylidene ruthenium (II) complexes.²³ The same ruthenium complex was used to perform an alcohol – amine oxidative coupling, which provided amides in excellent yields (Scheme 5).²⁴



Scheme 5: 1,2,3-Triazolylidene palladium complexes as catalysts for coupling reactions.

1,2,3-Triazolium salts have also found many applications in the field of supramolecular chemistry (Scheme 6). Pandey developed a bile acid-derived selective anionic captor **4.35**, which showed a strong affinity for biologically relevant dihydrogenophosphate anion ($K_a = 1920 \text{ M}^{-1}$, CHCl_3).⁹ Cyclic dimeric structures, analogue to **4.35**, showed a higher selectivity for smaller anions, such as chloride, because of the reduced size of the binding cavity.¹⁰



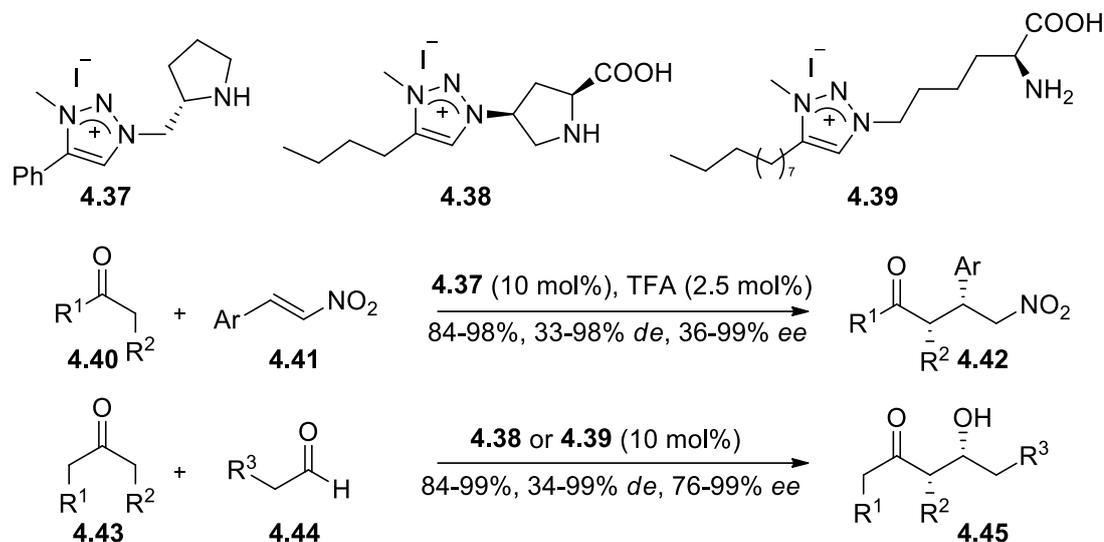
Scheme 6: 1,2,3-Triazolium salts as highly selective anion captors.

Tridentate and macrocyclic structures have also been synthesised by Schulze and co-workers, and their binding properties were tuned by acting on substitution pattern and chain length: highly selective complexation of sulfate and chloride were obtained, with association constants up to 10^5 M^{-1} .²⁵ An approach to anion detection was developed by Belfield in 2013: fluorene-derived bis-1,2,3-triazolium **4.36** displayed a strong fluorescent response when exposed to fluoride anions under UV light at 365 nm.²⁶ Compound **4.36** proved highly fluoride-selective, since no fluorescence could be detected when tested in the presence of several other anionic species. When product **4.36** was adsorbed on a test strip of paper and exposed to diluted fluoride solutions, fluorescence was detected for concentration as low as 1.9 ppm; using this method, the fluoride content of samples of drinking water was conveniently determined.

4.1.3 1,2,3-Triazolium salts in organocatalysis

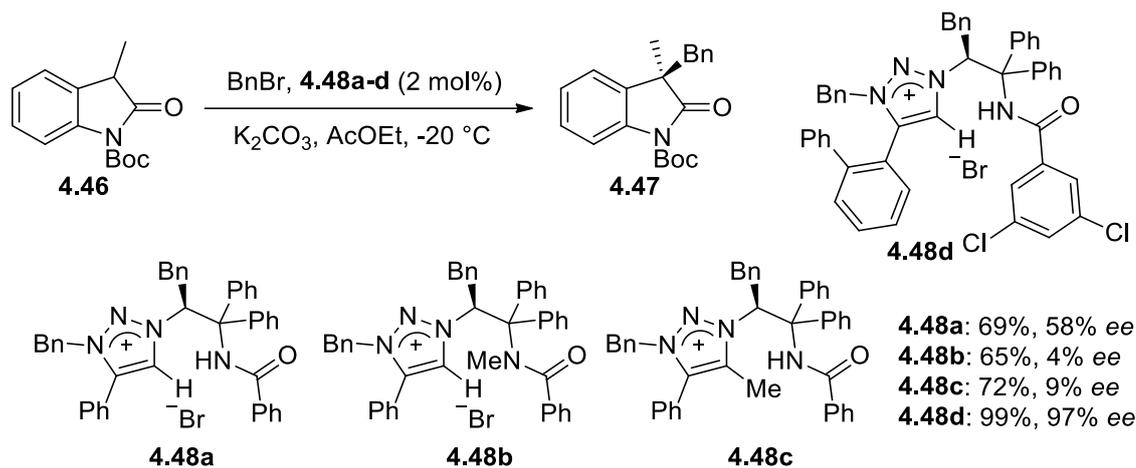
The first introduction of the 1,2,3-triazolium moiety in organocatalysis dates back to 2008, when Liebscher and co-workers reported the first examples of chiral triazolium catalysts, derived from natural aminoacids (Scheme 7).²⁷ After almost 10 years, however, 1,2,3-triazolium salts as organocatalysts are still unexplored, despite the availability of thousands of triazole precursors, which can be prepared *via* copper-catalysed azide-alkyne cycloaddition. Liebscher's original design consisted in combining the exceptional catalytic properties of proline derivatives with the newly discovered ionic liquids obtained by *N*-alkylation of 1,2,3-triazoles. Catalytic amounts of (*S*)-prolinol-derived triazolium iodide **4.37** were able to stereoselectively promote the nitro-Michael reaction of ketones **4.40** with nitroalkenes **4.41**, in the presence of small amounts of a protic acid and no additional solvent (Scheme 7). Good stereocontrol was also obtained when the aldol reaction of ketones **4.43** and aldehydes **4.44** was carried out in the presence of compounds **4.38** and **4.39**, derived from 4-hydroxyproline and L-lysine respectively.²⁸ Liebscher's work provided a proof of concept, since carrying out C-C bond formation in solventless mode is intriguing. Moreover, catalysts **4.37**, **4.38** and **4.39** were found insoluble in ethereal solvents and could be conveniently recovered by simple

extraction of the reaction mixture with diethyl ether. The recovered catalysts were re-used and their performance proved unaltered for up to 5 cycles.



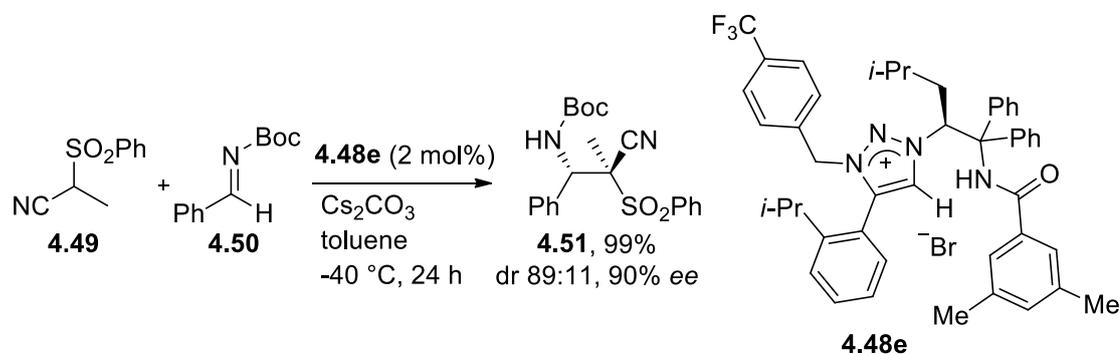
Scheme 7: Chiral 1,2,3-triazolium organocatalysts derived from natural aminoacids.

More recently, Ooi and co-workers designed a new class of chiral phase transfer catalysts, which combined the 1,2,3-triazolium salt with a chiral scaffold derived from phenylalanine (Scheme 8).³ Catalyst **4.48b** found application in the benzylation of oxindole **4.46**, in combination with potassium carbonate: compound **4.47** was obtained in good yields and enantiomeric excess, when the reaction was carried out in ethyl acetate, at -20 °C. The acidic protons of the triazolium and amide moieties had a synergic effect on the binding of the reactive enolate derived from the deprotonation of **4.46**. This was demonstrated when the methylated catalysts **4.48b,c** were tested under the same reaction conditions: in both cases, product **4.47** was obtained with poor enantioselectivity. A library of differently substituted triazolium-amides **4.48** were synthesised and, among all, compound **4.48d** proved the best, in terms of yield and enantioselectivity (Scheme 8). The benzylation reaction of **4.46**, in the presence of catalyst **4.48d**, provided compound **4.47** in quantitative yield and 97% *ee*. The effect of substitution on the substrates was also tested, and electron donating groups on the aromatic ring were well tolerated, while no results were reported for halide- or nitro-substituted oxindoles. The reaction proved highly stereoselective, also when alkylating reagents other than benzyl bromide were used: excellent results were obtained with allyl-bromides, substituted benzyl bromides and methyl bromoacetate.



Scheme 8: Alkylation of oxindoles catalysed by chiral 1,2,3-triazolium salts.

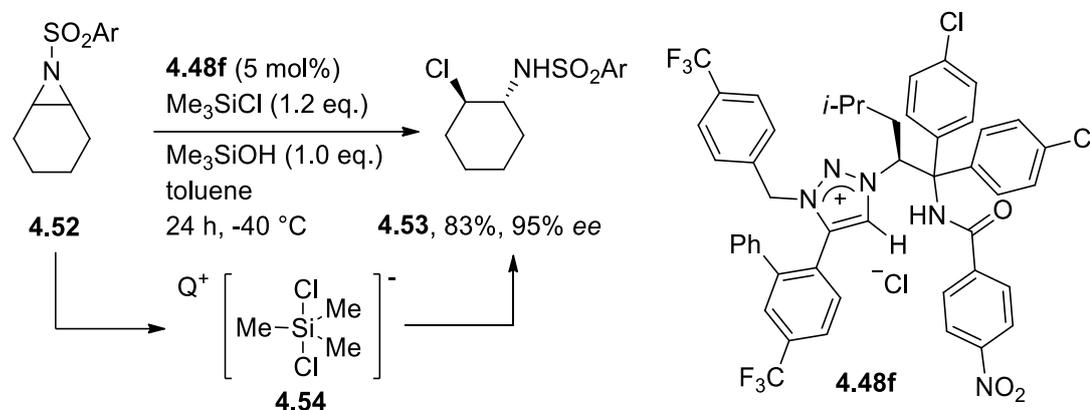
Ooi's chiral triazolium salts were also tested on other asymmetric transformations. For example, the Mannich-type reaction of cyanosulfone **4.49** with *N*-Boc-alimine **4.50** was carried out in toluene, at $-40\text{ }^\circ\text{C}$, in the presence of 2 mol% of triazolium bromide **4.48e** (Scheme 9).²⁹ Triazolium salt **4.48e** was selected screening of a family of related catalysts, which were obtained through an efficient and modular synthesis. Unfortunately, diastereoselectivity did not overcome 89 : 11 *dr* in the best case, even if compound **4.51** was obtained in up to 90% *ee*. Similar results were obtained starting from other *N*-Boc-aldimines, bearing different substituents on the aromatic ring.



Scheme 9: Mannich-type reaction of cyanosulfones catalysed by chiral triazolium salts.

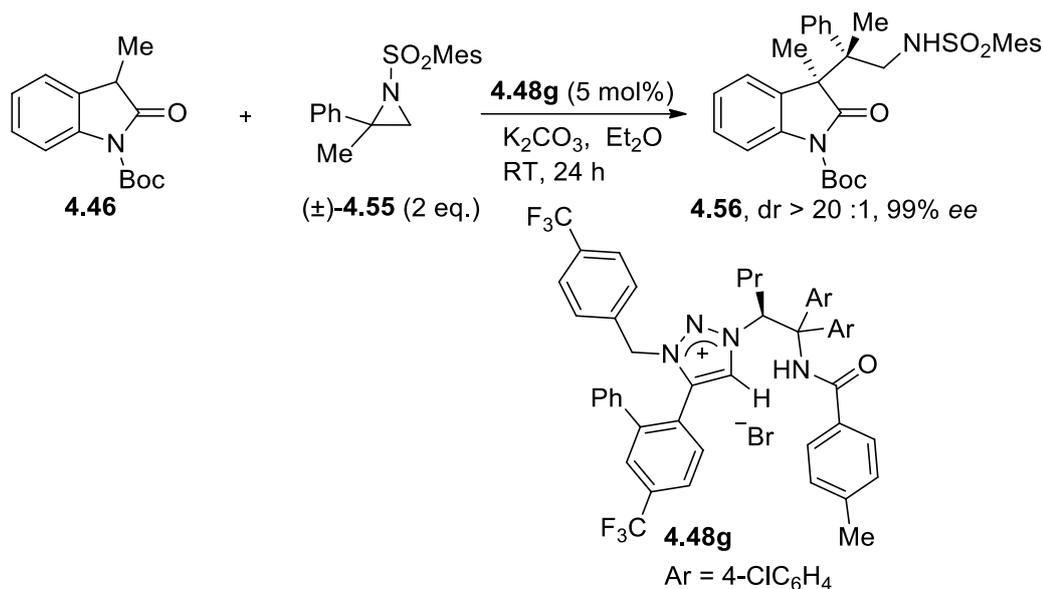
In 2012, Ooi reported an interesting desymmetrisation of meso-aziridines **4.52**, promoted by chiral triazolium chloride **4.48f**: ring-opening product **4.53** was obtained in 80% yield and 95% *ee* in the presence of a slight excess of trimethylsilyl chloride, trimethylsilanol and catalytic amounts of triazolium salt **4.48f** (Scheme 10).⁴ When the reaction was carried out with 1.0 molar equivalent of triazolium chloride **4.48f** and no silyl chloride, the formation of ring-opening product **4.53** was not observed. Similarly, when **4.52** was reacted with trimethylsilyl chloride alone, the ring-opening did not take place, meaning that the concomitant presence of a triazolium chloride and trimethylsilyl chloride were indispensable for the nucleophilic attack to occur. In light of these findings, the author proposed the formation of a hypervalent silicon species **4.54**, which acted as the final chlorinating reagent (Scheme 10). Moreover, the

presence of trimethylsilanol greatly increased the reaction rate and the enantioselectivity, presumably acting as a weak Brønsted acid, facilitating the elimination of chlorosulfonamide **4.53** from the catalyst and thus increasing the turnover number.



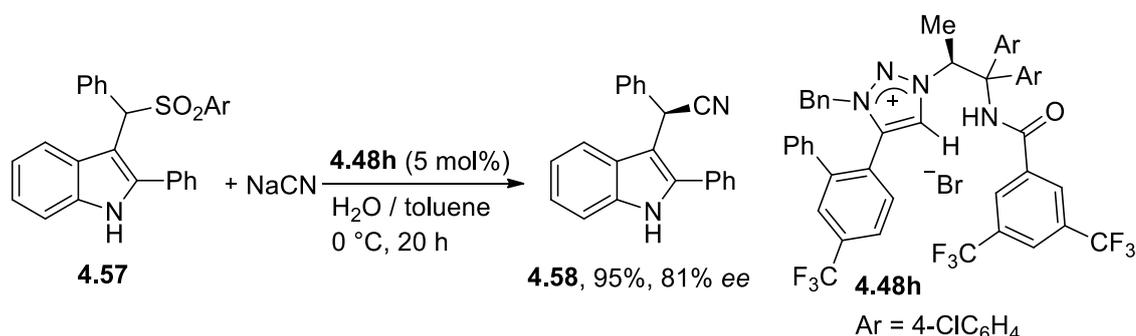
Scheme 10: Desymmetrisation of *meso*-aziridines catalysed by chiral triazolium chlorides.

The ring opening of aziridines such as **4.55** was also performed with carbon nucleophiles, generated by phase transfer catalysed deprotonation of oxindole **4.46** (Scheme 11).⁵ The reaction was carried out at room temperature in diethyl ether, with an excess of potassium carbonate: the formation of adduct **4.56** took place with complete stereoselectivity and good diastereocontrol, when 5 mol% of catalyst **4.48g** were used. The reaction was shown to be a kinetic resolution: when 2 equivalents of racemic aziridine **4.55** were added to the reaction mixture, after 24 h unreacted **4.55** was recovered as an enantiomerically enriched mixture (76% ee). It was demonstrated that, when catalyst **4.48f** was present, only (*S*)-aziridine was consumed and the ring-opening reaction took place with inversion of configuration at the quaternary carbon *via* a S_N2 stereospecific mechanism. The substrate scope of the reaction was also tested: aziridines bearing electron-withdrawing and electron-donating substituents were well tolerated; also, the substitution on the oxindole ring proved to not influence the stereochemical course of the reaction (Scheme 11).



Scheme 11: Ring-opening of aziridines with oxindole enolates, catalysed by a chiral triazolium salt.

Finally, triazolium salt **4.48h** catalysed the stereoselective cyanation reaction of alkylideneindolenines, generated *in situ* from sulfonylalkylindoles **4.57** (Scheme 12).³⁰ The reaction was carried out at 0 °C for 20 h, in a biphasic water / toluene mixture, in the presence of an excess of sodium cyanide and a catalytic amount of triazolium salt **4.48h**, selected among different 1,2,3-triazolium salts bearing various substituents. Cyanoindole **4.58** was obtained in 95% yield and 81% ee, with optimised catalyst **4.48h**. When different sulfonylindoles, analogue to **4.57**, were reacted under the same conditions, the corresponding cyanoindoles were obtained in 76-99% yield and 71-90% ee, showing that, even if the stereocontrol of the reaction was not absolute, the presence of substituents and steric bulk on the substrates did not prevent the transformation from being consistently stereoselective.



Scheme 12: Cyanation of sulfonylalkylindoles catalysed by a chiral triazolium salt.

In conclusion, 1,2,3-triazolium salts are an interesting class of organic compounds with a wide scope of applications. Preliminary investigation of their potential has been undertaken in various fields of chemistry, such as organometallic chemistry, green chemistry, supramolecular chemistry and material sciences. Among all, however, organocatalysis was the least explored, and only the synthesis of one generation of 1,2,3-triazolium-based

catalysts is published to date. Therefore, we consider of great interest the development of new classes of organocatalysts that include the 1,2,3-triazolium motif: in particular, the unique anion-recognition properties of 1,2,3-triazolium salts might prove of great impact on the activity and selectivity of new families of phase transfer catalysts.

4.2 Results and Discussion

4.2.1 Synthesis of binaphthyl-derived 1,2,3-triazoliums salts

1,1'-Bi-2-naphthol (BINOL) is probably one of the most important non-natural chiral scaffolds, and its use in both stoichiometric and catalytic asymmetric reactions has been documented since 1979, date of the first published works of Ryoji Noyori on the asymmetric hydrogenation. BINOL's chirality derives from the impeded rotation around the C-1–C-1' axis, which gives rise to two non-superimposable structures, with identical connectivity (**4.59a,b**, Figure 1). The two enantiomers possess a C_2 -rotational axis as the only element of symmetry and therefore belong to the C_2 -dissymmetric point group.³¹ When trying to induce enantioselectivity, dissymmetric reagents have several advantages compared with asymmetric reagents, including the reduced amount of possible diastereoisomerically-related transition states.³² For this reason, a wide range of BINOL-derived chiral molecules had found application in catalysis as a ligand for metal complexes or as chiral scaffolds for the synthesis of organocatalysts. Ru-BINAP complexes were first employed by Noyori in the stereoselective hydrogenation of carbonyl compounds and during the total synthesis of (-)-menthol (Figure 1).³³ Many BINOL-derived chiral Brønsted acids such as **4.61** were found to effectively catalyse a great number of stereoselective chemical transformations (see Chapter 2).³⁴

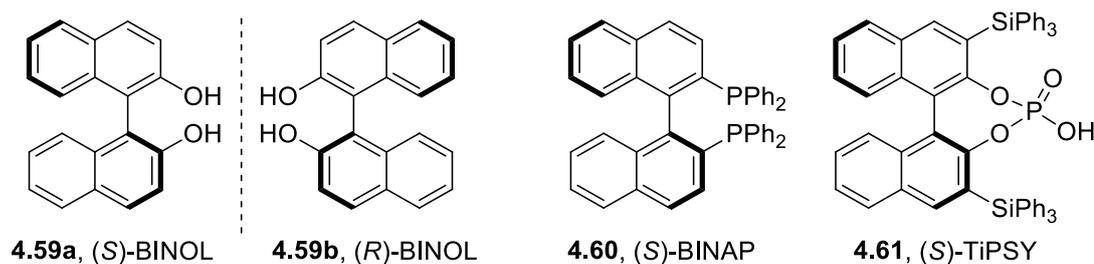


Figure 1: BINOL enantiomeric forms and important BINOL-derived chiral molecules.

1,2,3-Triazolium salts are easily accessible ionic compounds, which proved able to bind with negative ions in a unique fashion; moreover, very little work has been done on the synthesis and use of chiral triazolium salts as phase transfer catalysts. For these reasons, preliminary studies were focused on the design and synthesis of molecules such as **4.62-4.64**, which incorporate the 1,2,3-triazolium motif into the chiral structure of BINOL-derivatives (Figure 2). In this chapter we report the synthetic route to a number of novel binaphthyl-based 1,2,3-triazolium salts, which were characterised and employed in preliminary studies. Classical asymmetric organic reactions were used to benchmark the performance of the newly

synthesised compounds. In Figure 2 are reported three target structures which, in our opinion, might well serve the function of chiral phase transfers. For example, bis-1,2,3-triazolium-binaphthalene **4.62**, is a C_2 -symmetric molecule, bearing two 1,2,3-triazolium functions: the presence of two positively charged aromatic rings so close together might have an effect on the type of interaction with negatively charged carbon nucleophiles. Asymmetric aminotriazolium salt **4.56** was designed as a bifunctional catalyst: the free amino group could participate by H-bond to the binding with anionic species; alternatively, the basicity of the aniline group could act as a Brønsted base and complexate acidic groups through its protonation. We also considered the functionalization of the free amine into a sulfonamide **4.64**, which should provide an even stronger H-bond donor character to the nitrogen (Figure 2).

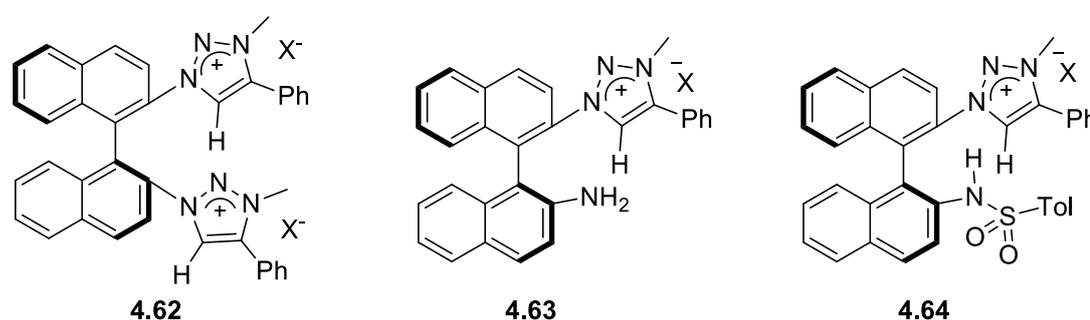
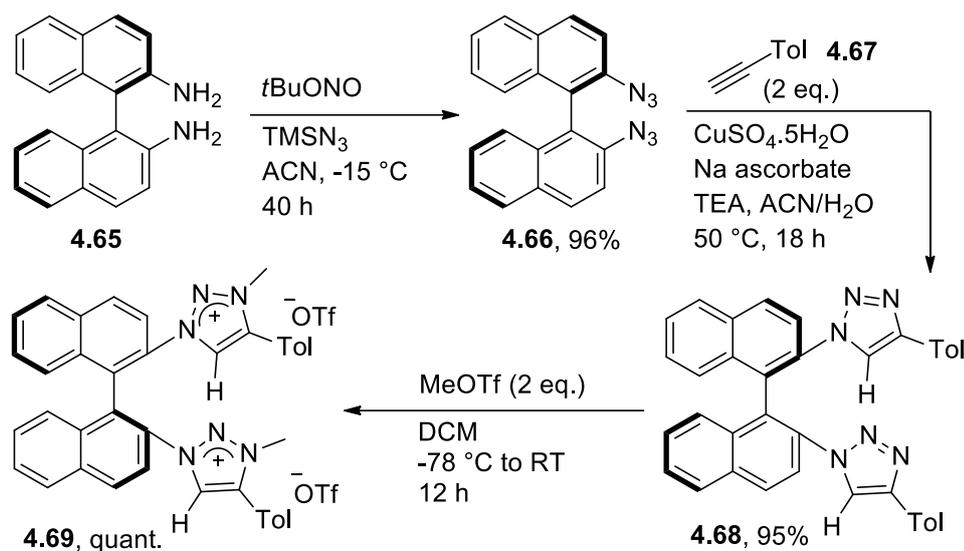
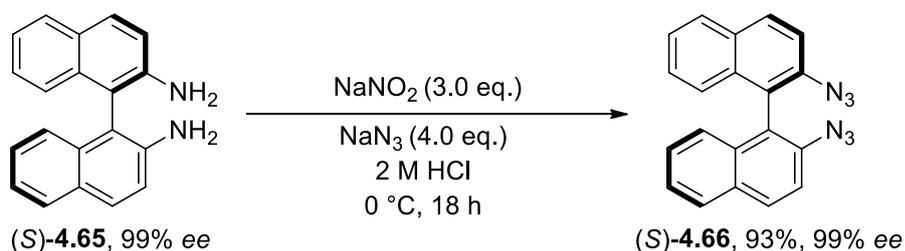


Figure 2: Design of novel binaphthyl-based 1,2,3-triazolium catalysts.

The synthesis of binaphthyl-derived bis-triazolium compounds similar to **4.62** has already been reported in 2015 by Elsevier and co-workers.³⁵ The authors were able to synthesise bis-triazolium triflate **4.69** in 91% yield over 3 steps, starting from commercially available (*R*)-2,2'-diamino-1,1'-binaphthalene (Scheme 13). Bis-azide **4.66** was obtained in 96% yield by diazotation of **4.65** with *tert*-butyl nitrite and treatment with trimethylsilylazide at low temperature. The resulting azide underwent copper-catalysed azide-alkyne cycloaddition in the presence of 2 molar equivalents of tolylacetylene and a catalytic amount of copper (II) sulfate, sodium ascorbate and triethylamine. The reaction was carried out in a 4 : 1 acetonitrile / water mixture, at 50 °C for 60 h, obtaining bis-triazolo-binaphthalene **4.68** in 95% yield. Compound **4.68** was alkylated with 2 molar equivalents of methyl trifluoromethanesulfonate in dichloromethane at low temperature: the reaction provided bis-triazolium triflate **4.69** in quantitative yield.

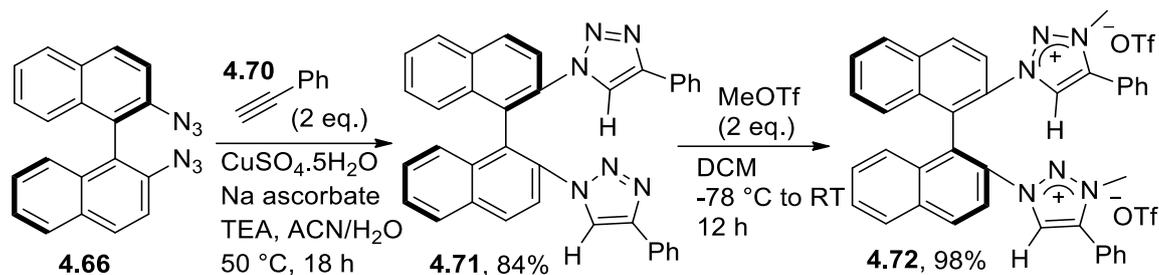
Scheme 13: Elsevier's synthesis of bis-1,2,3-triazolium triflate **4.69**.

We repeated Elsevier's synthetic protocol, making a few modifications and were able to obtain the desired 1,2,3-triazolium triflate **4.72** in 77% yield over 3 steps (Scheme 15). The azidation reaction of diamine **4.65** was carried out on the enantiopure (*S*)-enantiomer, in aqueous medium, using sodium nitrite in hydrochloric acid for the generation of the diazonium salt (Scheme 14). The reaction was carried out at 0 °C and sodium azide was used as a source of azide anion. Bis-azide **4.66** was obtained in 93% yield after extraction of the reaction mixture with dichloromethane. This alternative procedure makes use of inexpensive and solid reagents, and can be preferred over the original method, which required refrigeration over a long period. S_NA reactions such as the nucleophilic substitution of a diazonium salts can result in the partial racemisation of atropoisomeric compounds such as **4.66**: for this reason, the enantiomeric purity of **4.66**, obtained following this alternative procedure, was measured *via* chiral HPLC, and compared to that of a sample of **4.66** obtained from racemic (\pm)-**4.65**. We were able to confirm that no racemisation of the chiral scaffold occurred during the reaction.

Scheme 14: Alternative preparation of bis-azide **4.66**.

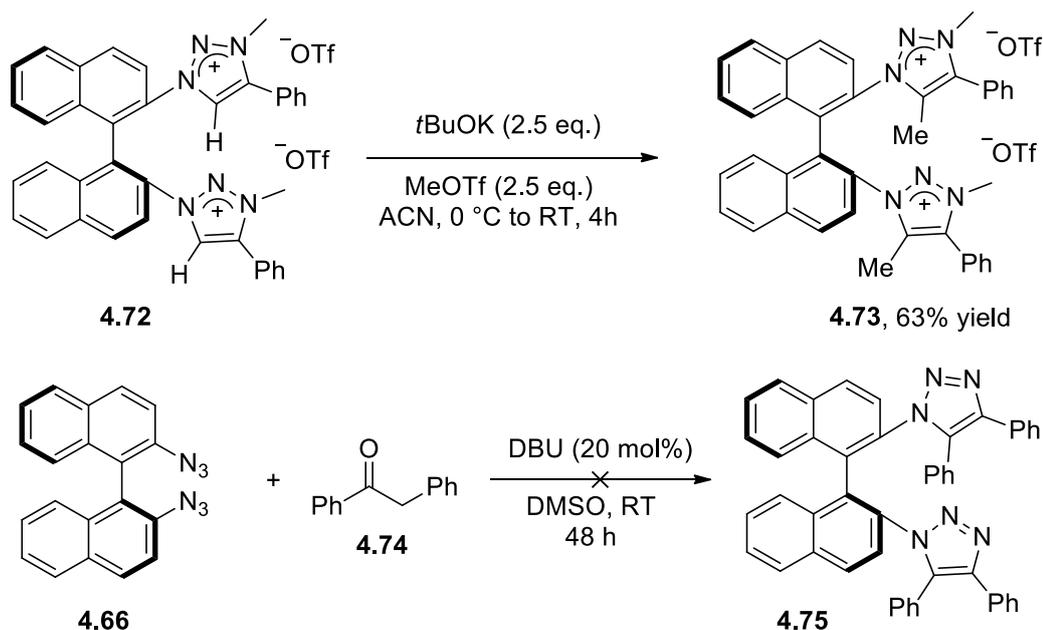
The following triazole formation and quaternarisation were carried out following Elsevier's procedure: CuAAC was carried out at 50 °C overnight, in the presence of copper sulfate, sodium ascorbate and triethylamine (Scheme 15). Notably, the reaction of bis-azide **4.66** with phenylacetylene **4.70** provided the corresponding bis-triazole **4.71** in only 84% yield. The enantiomeric purity of **4.71** was assessed *via* chiral HPLC, in order to verify that no significant

racemisation occurred when heating up to 50 °C compounds such as **4.60** and **4.71**. Bis-methylated compound **4.72** was obtained in almost quantitative yield by adding 2 molar equivalents of methyl triflate to a solution of bis-triazole **4.71** in dichloromethane at -78 °C (Scheme 15). The alkylation reaction of bis-triazole **4.71** was also attempted with weaker alkylating reagents, such as methyl iodide or benzyl bromide, in acetonitrile: these reaction failed to provide desired **4.72** and starting material **4.71** was recovered unreacted after 24 h of reaction. The alkylation with methyl iodide was attempted at 60 °C for 18 h, but it was equally proved unsuccessful.



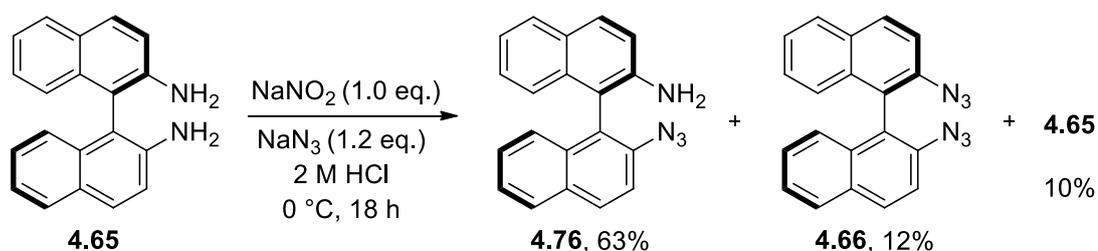
Scheme 15: Synthesis of bis-1,2,3-triazolium triflate **4.72**.

The acidity of the triazolium-C-H of compound **4.72** might influence the complexation of anions and bases during a phase transfer catalysed reaction. Moreover, the deprotonation of compound **4.72** might occur in a strongly basic media, leading to catalyst poisoning. In order to better understand this phenomenon, and prevent the base-induced deprotonation at the triazolium ring, we synthesised 4-methyl-1,2,3-triazolium triflate **4.73** by deprotonation of bis-1,2,3-triazolium triflate **4.72** with potassium *tert*-butoxide and subsequent alkylation of the resulting 1,2,3-triazolidene with methyl triflate (Scheme 16). The reaction was carried out in acetonitrile for 4 h and desired methylated compound **4.73** was obtained in 63% yield as a pale yellow solid, after chromatographic purification. It was also attempted the synthesis of bis-4,5-diphenyltriazole **4.75** via base catalysed condensation of bis-azide **4.66** and 2-phenylacetophenone **4.74**, following Ramachary's protocol (Scheme 16).³⁶ Unfortunately, due to steric factors, the reaction did not work, and after 48 h the crude contained only unreacted starting material and traces of mono- and bis-triazole.



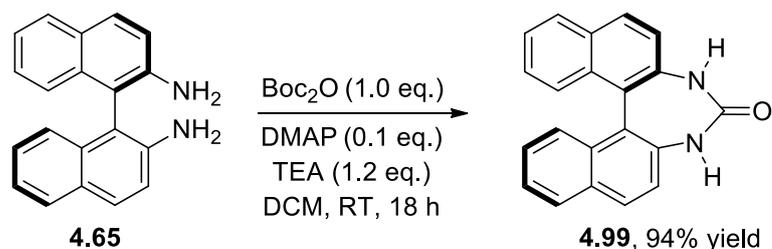
Scheme 16: Synthesis of 4-alkyl-1,2,3-triazolium triflates.

The synthesis of asymmetric bifunctional triazolium salts (**4.63**, Figure 2) was carried out starting from diamine **4.65**, which underwent selective mono-azidation when sodium nitrite and sodium azide were employed in limited amount (1 molar equivalent, Scheme 17). Mono-azide **4.76** was isolated in 63% yield after column chromatography, together with 10% of unreacted diamine **4.65** and 12% of bis-azide **4.66**. Remarkably, when the same reaction was carried out with 1 molar equivalent of *tert*-butyl nitrite and trimethylsilylazide, the yield in mono-azide **4.76** dropped to 40%.

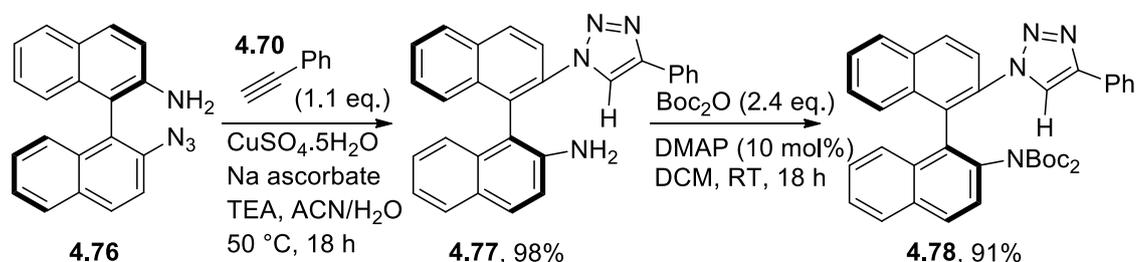


Scheme 17: Mono-azidation of 2,2'-diamino-1,1'-binaphthalene.

In an attempt to selectively protect one of the amine functions, compound **4.65** was reacted with 1 molar equivalent of di-*tert*-butyldicarbonate (Boc-anhydride) in dichloromethane, in the presence of 1.2 molar equivalents of triethylamine and a catalytic amount of DMAP (Scheme 18). Unfortunately, the mono-protection did not occur: instead, we isolated a cyclic urea **4.99**, derived from the reaction of the free amino group with the carbamate originated from the Boc-protection of the first amine. It was so decided to perform the protection of the aniline group later on in the synthesis.

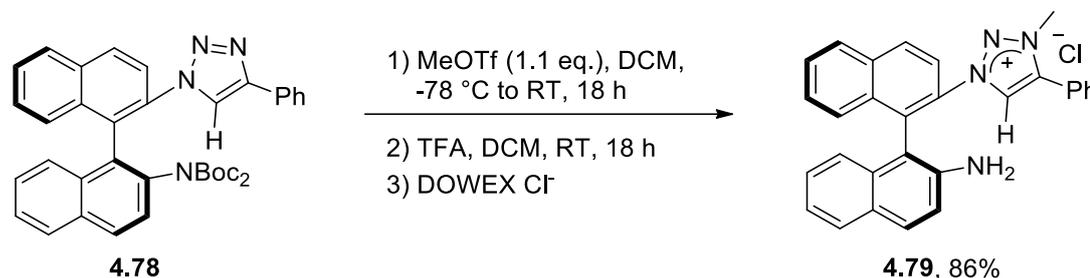
Scheme 18: Attempted mono-protection of diamine **4.65**

The CuAAC of aminoazide **4.76** with phenylacetylene **4.70** proceeded smoothly, under the same conditions adopted for bis-azide **4.66**. Aminotriazole **4.77** was obtained in almost quantitative yield after 18 h at 50 °C (Scheme 19). An attempt to carry out the methylation of the triazole ring was made on compound **4.77** using methyl triflate in dichloromethane, but a complex mixture of products with different degrees of alkylation was obtained. For this reason, aminotriazole **4.77** was reacted with 1.2 molar equivalents of Boc-anhydride in dichloromethane, and 10 mol% of DMAP. After 18 h, the reaction mixture contained di-Boc-aminotriazole **4.78**, together with unreacted **4.77**, and mono-Boc-protected-aminotriazole. For practical reasons, it was decided to add 1 extra equivalent of Boc-anhydride and let the reaction reach full completion, in favour of di-Boc-aminotriazole **4.78**. After 4 h, starting material **4.77** was fully consumed and compound **4.78** was isolated from the crude mixture in 91% yield, after silica flash chromatography (Scheme 19). At this point, we were able to directly obtain di-Boc-protected compound **4.78** by reacting **4.77** with 2.4 molar equivalents of Boc-anhydride overnight.

Scheme 19: Synthesis of *N*-protected-aminotriazole **4.78**.

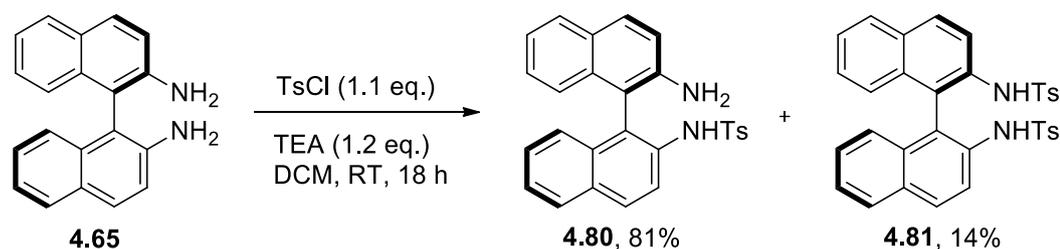
Methylation of Boc-protected-triazole **4.78** was successfully achieved by reacting **4.78** with 1.1 molar equivalents of methyl triflate in dichloromethane, in the standard conditions (Scheme 20). It was confirmed that the reaction reached full conversion by ¹H-NMR analysis of the crude reaction mixture, but also partial *N*-deprotection occurred, due to the acidic environment. For this reason, crude *N,N*-di-Boc-triazolium triflate underwent deprotection by treatment with trifluoroacetic acid (TFA) in dichloromethane. After 18 h, the crude aminotriazolium salt was treated with aqueous sodium bicarbonate and extracted with dichloromethane. However, the treatment with different anionic species during work-up complicated the ¹H-NMR of product **4.79**, which was therefore eluted through a short plug of

DOWEX 1X8 (strongly basic, chloride form), in order to displace and exchange any anion with chloride. Amino-1,2,3-triazolium chloride **4.79**, was so isolated as a brown solid in 86% yield.



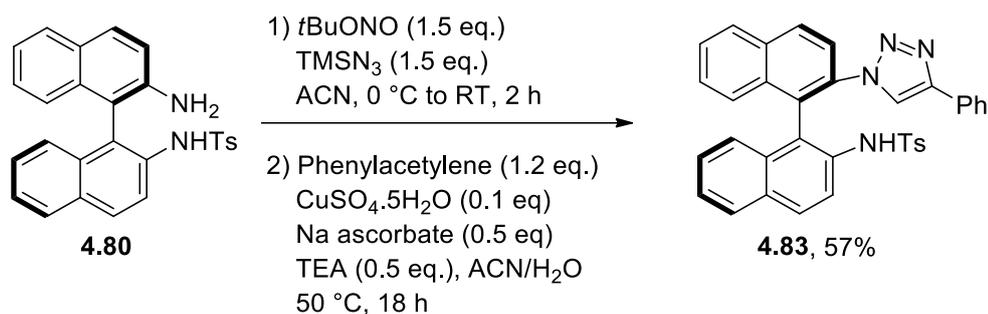
Scheme 20: Synthesis of amino-1,2,3-triazolium chloride **4.79**.

The synthesis of *N*-tosyl-1,2,3-triazolium-binaphthalene **4.84** was easily achieved, starting from the mono-tosylation of diamine **4.65** (Scheme 21). The reaction was carried out adding a slight excess of tosyl chloride to a solution of **4.65** and triethylamine in dichloromethane. After 18 h, the crude mixture was composed of mono- and bis-tosylated-amine **4.80** and **4.81**, which could not be separated by chromatography. Compounds **4.80** and **4.81** were obtained as a 6 : 1 mixture (molar ratio, calculated from H-NMR) corresponding to a yield of 81% and 14% respectively. The mixture of products was used in the following step, without attempting any further purification.

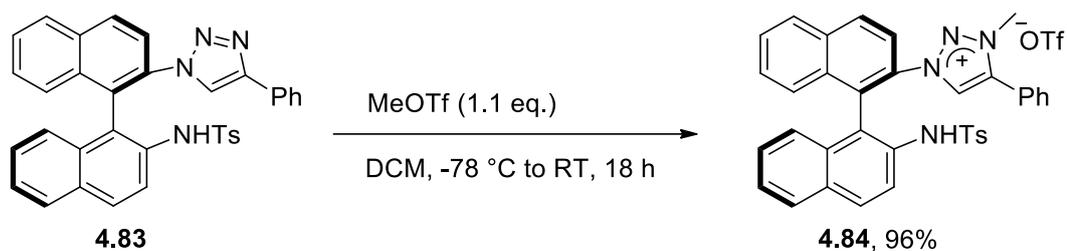


Scheme 21: Synthesis of mono-tosylated-diamine **4.80**.

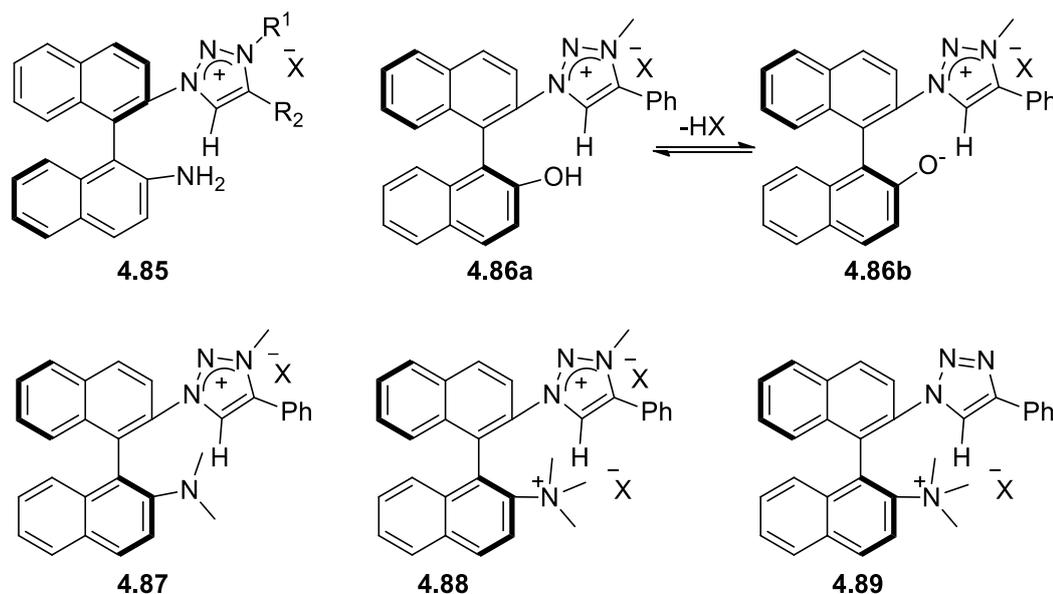
Mono-tosyl-diamine **4.80** underwent azidation when treated with *tert*-butyl nitrite and trimethylsilylazide in acetonitrile at 0 °C (Scheme 22). These mild reaction conditions were chosen in order to prevent the hydrolysis of the sulfonamide, which might occur in a strongly acidic media. The reaction was monitored *via* TLC, and after 2 h, starting material was fully converted. The resulting crude *N*-tosyl-azidoamine was then reacted with phenylacetylene in a ACN / water mixture, in the presence of copper(II) sulfate, sodium ascorbate and triethylamine, under optimised reaction conditions. After 18 h, crude *N*-tosyl-aminotriazole **4.83** was purified by flash chromatography, and it was isolated in 57% yield over two steps.

Scheme 22: Synthesis of N-tosyl-aminotriazole **4.83**

Since we were interested in the isolation of final alkylated product, we did not try to optimise the synthesis of compound **4.83**: however, a screening of different tosylation and azidation conditions will be performed in the future, in order to improve the overall chemical yield. Compound **4.83** was subjected to alkylation with methyl triflate in dichloromethane at -78 °C. The reaction was left to slowly reach room temperature overnight. Evaporation of the solvent and the residual unreacted triflate afforded compound **4.84** in 96% yield, without further purification.

Scheme 23: Synthesis of N-tosyl-aminotriazolium triflate **4.84**.

In this section, the synthesis of four different binaphthyl-derived 1,2,3-triazolium salts **4.72**, **4.73**, **4.79**, **4.84** was described. The four novel compounds were obtained in generally good yield, following a short synthetic route and starting from commercially available enantiopure (*S*)-2,2'-diamino-1,1'-binaphthalene **4.59**. Based on the preliminary results obtained with the base-promoted phase transfer catalysed reactions, described in the next paragraph, the tested catalysts will be further functionalised, in order to improve the stereoselectivity of the tested reactions.



Scheme 24: Future synthetic work - a second generation of binaphthyl-based triazolium salts.

A few examples are reported in Scheme 24: the effect of the substitution on the triazolium ring of compounds **4.85** will be studied; the corresponding triazoles will be alkylated with different triflic esters, in order to regulate the level of steric hindrance at the R^1 group. The effect of the R^2 group will also be verified: different R^2 residues will be introduced by reacting aminoazides such as **4.76** with diverse terminal alkynes. Phenolic compound **4.86a** was also designed: the possibility to generate a zwitterionic species **4.86b** by the action of a base was taken into consideration. Stability-studies of compound **4.86** in basic media will be carried out, since the formation of carbenoid species *via* deprotonation of the triazolium C-H must be avoided. Tertiary amine **4.87** might show a unique behaviour, compared to compounds **4.85**, due to the increased steric hindrance and the lack of extra H-bond donor sites. The stability of the 1,2,3-triazolium group to the Escheweiler-Clarke reaction conditions will be put to the test. Peralkylated **4.88** will be synthesised *via* treatment of compounds such as **4.85** with a large excess of methylating reagent. The presence of two cationic sites might considerably impact the interaction with anionic species. Structure **4.89** was conceived following an alternative approach: the quaternary ammonium site is located on the amine function, leaving the 1,2,3-triazole moiety unaltered (Scheme 24).

4.2.2 Binaphthyl-derived 1,2,3-triazolium salts in phase transfer catalysis.

The four 1,2,3-triazolium-based chiral catalysts **4.72**, **4.73**, **4.79** and **4.84**, whose preparation was described in the previous paragraph, were used in the screening of selected organocatalyses (Figure 3). C_2 -symmetric **4.72** and **4.73** are di-ionic species, which might be able to establish a strong interaction with inorganic basic anions: as a consequence, also organic anionic species, such as enolates, might be tightly bound and therefore may react preferentially on one of their enantiotopic faces. Compound **4.73** does not possess acidic

aromatic C-Hs, for this reason the counterions are more likely to be seated close to the *N*-methyl residue, with potential implications on stereoselectivity (see available binding sites, structure **4.12**, Scheme 2). Catalysts **4.79** and **4.84** are asymmetric and bifunctional (Figure 3): the presence of an amine (Brønsted base, H-bond donor) or sulfonamide (N-H, strong H-bond donor; S=O, H-bond acceptor) provides an additional site of interaction with substrates. Therefore, not only phase transfer catalysis is possible, but also carbonyl activation in neutral/acidic pH *via* oxonium or imine formation.

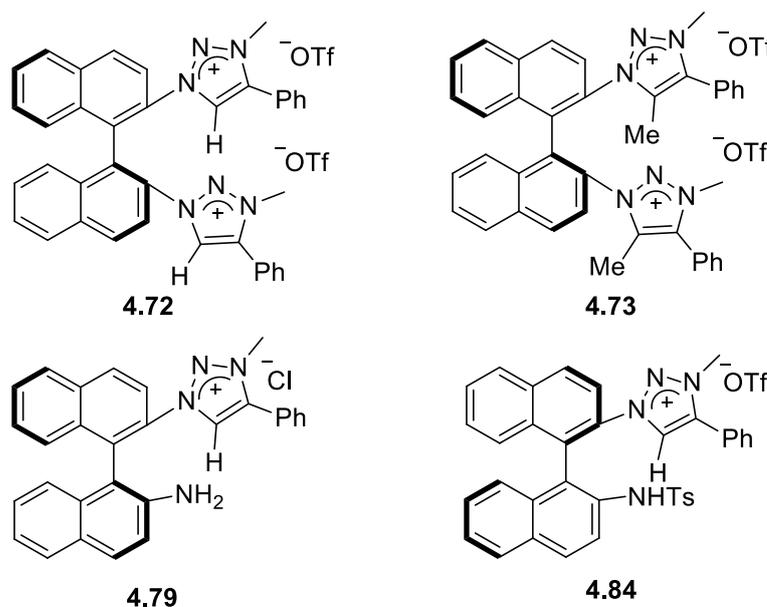


Figure 3: 1,2,3-Triazolium-based organocatalysts.

As a preliminary study, three types of organic reactions were examined: alkylation of enolates, Mannich-like reaction and nitro-Michael addition. The first test was performed on the benzylation of glycine-derived iminoester **4.90**, a common benchmark reaction in phase transfer catalysis (Table 1). First, we reacted iminoester **4.90** with benzyl bromide in a biphasic media constituted by a 50% KOH water solution and an organic solvent. When the reaction was carried out in toluene at 0 °C, in the absence of a catalytic promoter, the formation of benzylated product **4.91** was not observed (Table 1, entry 1). When catalytic amounts of (*S*)-**4.72** were added, the reaction also did not proceed, very likely due to the low solubility of **4.72** in toluene. When we dissolved triazolium salt **4.72** in 3 ml of dichloromethane and added 1 ml of 50% KOH water solution, we immediately observed a change in colour. ¹H-NMR analysis of the catalyst after basic treatment showed the complete degradation of product **4.72**. The high basicity of the media, promoted the deprotonation of the acidic aromatic C-H of compound **4.72**, resulting in the formation of carbenoid species, which have a short life if not intercepted by a metal center, and tend to decompose *via* methyl migration, with the formation of a 5-methyl-1,2,3-triazole.³⁷ As a result of the decomposition of catalyst **4.72**, the alkylation of iminoester **4.90** did not occur, when carried out in dichloromethane (Table 1, entry 4).

Racemic methyl-bis-triazolium **4.73** showed a low degree of activity, promoting the formation of **4.91** in 15% yield over 24 h of reaction (Table 1, entry 5). The same reaction, carried out in the presence of enantiomerically pure (*S*)-**4.73**, provided the corresponding benzylated product **4.91** in 11% yield and 6% ee. Catalyst **4.79** proved slightly more active, promoting the formation of the desired product in 21% yield, after 24 h of reaction (Table 1, entry 7); in this case, however, the stereoselectivity was barely appreciable. A similar result was obtained with *N*-tosyl-triazolium **4.84**, whose catalytic presence provided racemic compound **4.91** in 18 % yield (Table 1, entry 8). From the results of Table 1, we can conclude that the tested chiral triazolium salts are poor phase transfer catalyst, when employed in catalytic amounts in the alkylation of glycine iminoester **4.90**.

Table 1: Benzylation of glycine iminoester **4.90** under phase transfer catalysis ^a

$$\text{Ph}=\text{N}(\text{Ph})\text{CH}_2\text{C}(=\text{O})\text{OtBu} + \text{BnBr} \xrightarrow[\text{Solvent}]{50\% \text{ KOH}_{\text{aq}}, \text{catalyst (5 mol\%)}} \text{Ph}=\text{N}(\text{Ph})\text{CH}(\text{Bn})\text{C}(=\text{O})\text{OtBu}$$

4.90 **4.91**

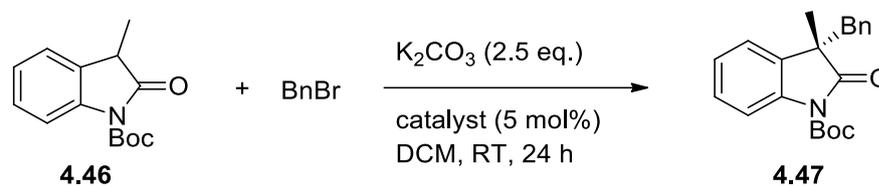
Entry	Time (h)	T (°C)	Catalyst	Solvent	Yield (%) ^b	ee (R, %) ^c
1	24	0	-	toluene	-	-
2	24	0	(<i>S</i>)- 4.72	toluene	-	-
3	72	20	-	DCM	-	-
4	72	20	(<i>S</i>)- 4.72	DCM	-	-
5	24	20	(±)- 4.73	DCM	15	0
6	24	20	(<i>S</i>)- 4.73	DCM	11	6
7	24	20	(<i>S</i>)- 4.79	DCM	21	-2
8	24	20	(<i>S</i>)- 4.84	DCM	18	0

^a Reaction conditions: **4.90** (0.10 mmol), benzyl bromide (0.12 mmol), 50% aqueous KOH (1 ml), catalyst (0.005 mmol), solvent (3 ml). ^b Isolated yield after column chromatography. ^c Determined by chiral HPLC (Chiralcel OD), absolute configuration obtained by comparison with literature data.³⁸

Next, the catalytic activity of our chiral triazolium salts was investigated in the alkylation of oxindole **4.46** with benzyl bromide, which Ooi was able to perform with excellent enantioselectivity, using amido-1,2,3-triazolium salts **4.42** as phase transfer catalysts (Scheme 8).³ We carried out the reactions in dichloromethane, using an excess of potassium carbonate as the inorganic base and 5 mol% of triazolium salts **4.72**, **4.73**, **4.79** and **4.84** (Table 2). The reaction with bis-triazolium triflate **4.72**, carried out over 24 h, provided compound **4.91** in 20% yield, after column chromatography of the crude reaction mixture: benzylated oxindole **4.91** was however composed of an equimolar mixture of enantiomers (Table 2, entry 1). When bis-methylated-triazolium triflate **4.73** was used in catalytic amounts, product **4.47** was obtained in 44% yield and 8% ee (Table 2, entry 2). The best result in terms of yield was achieved with amino-triazolium chloride **4.79**, which catalysed the formation of **4.47** in 65% yield, but with low enantioselectivity (Table 2, entry 3). *N*-Tosyl-triazolium triflate **4.84** provided the desired product with the highest enantiomeric excess, even if in poor yield

(Table 2, entry 4). Chiral 1,2,3-triazolium salts **4.72**, **4.73**, **4.79** and **4.84** did not effectively promote the stereoselective alkylation of oxindole **4.46**: the data of Table 2 showed that the best result in terms of stereoselectivity was obtained with *N*-tosyl-triazolium triflate **4.84**. In this case, however, compound **4.91**, was obtained in only 27% yield and 16% ee, which we considered too low to justify a further screening of reaction conditions.

Table 2: Phase transfer catalysed alkylation of oxindoles ^a



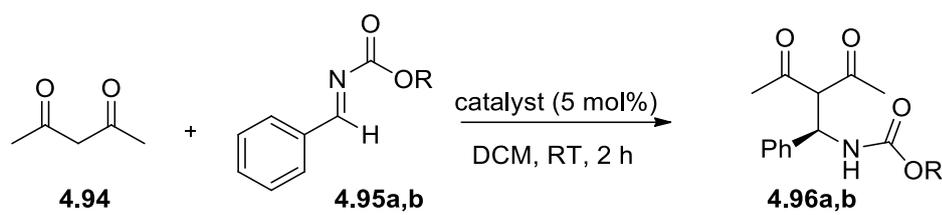
Entry	Catalyst	Yield (%) ^b	ee (S, %) ^c
1	(S)- 4.72	20	0
2	(S)- 4.73	44	8
3	(S)- 4.79	65	7
4	(S)- 4.84	27	16

^a Reaction conditions: **4.46** (1.0 mmol), benzyl bromide (1.2 mmol), catalyst (0.005 mmol) dichloromethane (1 ml), 20 °C, 24 h. ^b Isolated yield after column chromatography. ^c Determined by chiral HPLC (Chiralcel OD), absolute configuration obtained by comparison with literature data.³

The Mannich-type reaction of active methylene compounds with aldimines is a well-established C-C bond formation protocol, which can take place in a stereoselective fashion, if carried out in the presence of a suitable chiral H-bond donor (see Chapter 2). We envisaged that catalysts **4.72**, **4.79** and **4.84**, which bear acidic hydrogens, might promote this type of transformation, through the activation of aldimines **4.95a,b** by H-bonding. Acetylacetone **4.94** was reacted with *N*-Boc-aldimine **4.95a** in dichloromethane, at room temperature, in the presence of a catalytic quantity of triazolium salts **4.72**, **4.73**, **4.79** and **4.84** (Table 3, entries 2-5). After a reaction time of 2 h, the formation of product **4.96a** was observed with all the tested catalysts: compound **4.96a** was isolated in low to good yield, depending on the triazolium salt employed; in all cases, adduct **4.96a** was constituted by a racemic mixture (Table 3, entries 2-5). Notably, when the reaction was carried out for 2 h with no catalyst, 60% of starting material **4.95a** was converted into product **4.96a**, which was isolated in 48% yield (Table 3, entry 1). Therefore, the lack of enantioselectivity observed for entries 2 to 5, can be explained by the extensive contribution of the non-catalysed background reaction: in other words, if the reaction takes place when no catalyst is added, the catalytic pathway will have to be at least 100 times faster than the non-catalytic process in order to obtain good levels of stereocontrol. It is interesting, however, that in the presence of catalysts **4.72** and **4.79**, the reaction provided higher amounts of the desired product **4.96a**, even if with no appreciable stereoselectivity. We hypothesised that an excessively bulky substrate such as *N*-Boc-aldimine **4.95a** might not be able to reach the catalytic site on the already sterically hindered triazolium salts. For this reason, it was decided to react methylcarbamate **4.95b** with acetylacetone **4.94**, in the presence of triazolium salts **4.72**, **4.73**, **4.79** and **4.84**, in order to

verify the effect of the steric bulk on the catalytic performance (Table 3, entries 6-9). Indeed, product **4.96b**, was isolated in higher yields overall, meaning that a less sterically demanding substrate favoured the rate of the reaction. However, no stereoselectivity was measured, with the exception of catalyst **4.73**, which provided the desired product **4.96b** in 90% yield and 9% enantioselectivity (Table 3, entry 7). The same catalyst gave the worst performance in the reaction of *N*-Boc-alimine **4.95a**, meaning that triazolium salts **4.72**, **4.73**, **4.79** and **4.84** are indeed sensitive to the steric bulk of the substrate, and might therefore provide better results in the catalysis of reactions involving one organic substrate only.

Table 3: Mannich-type addition of acetylacetone to aldimines ^a



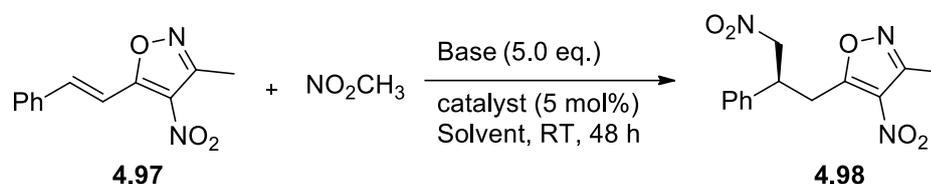
Entry	R	Product	Catalyst	Yield (%) ^b	ee (%) ^c
1	<i>t</i> Bu	4.96a	-	48	-
2	<i>t</i> Bu	4.96a	(S)- 4.72	67	0
3	<i>t</i> Bu	4.96a	(S)- 4.73	45	0
4	<i>t</i> Bu	4.96a	(S)- 4.79	74	0
5	<i>t</i> Bu	4.96a	(S)- 4.84	47	0
6	Me	4.96b	(S)- 4.72	67	0
7	Me	4.96b	(S)- 4.73	90	9
8	Me	4.96b	(S)- 4.79	87	0
9	Me	4.96b	(S)- 4.84	92	0

^a Reaction conditions: **4.84** (1.1 mmol), **4.95a,b** (1.0 mmol), catalyst (0.005 mmol), solvent (2 ml), 20 °C, 2 h. ^b Isolated yield after column chromatography. ^c Determined by HPLC (entries 1-5, Chiralpak AD; entries 6-9, Chiralpak AS).

We selected nitromethane anion as a small nucleophilic molecule, which could better be accommodated into the small positive cavity of binaphthalene-derived triazolium salts. The reaction of nitromethane with Michael acceptor 3-methyl-4-nitro-5-styryl-isoxazole **4.97**, was carried out at room temperature for 48 h, in the presence of an excess of solid potassium carbonate, following an experimental protocol that was developed in our laboratory.³⁹ When no triazolium salt was added, product **4.98** was obtained in 32% yield, meaning that, even in the absence of a phase transfer reagent, the conjugate nucleophilic addition took place (Table 4, entry 1). When 5 mol% of bis-triazolium-binaphthalene **4.72** was added to a mixture of isoxazole **4.97**, nitromethane and potassium carbonate, adduct **4.98** was obtained in 21% yield and 20% ee (Table 4, entry 2). Similarly, methytriazolium triflate **4.73** provided compound **4.98** in 17% yield and 21% ee, when the reaction was carried out in the same conditions (Table 4, entry 3). A good result was obtained with aminotriazolium chloride **4.79**, which promoted the formation of nitromethyl-adduct **4.98** in 90% yield and 56% enantioselectivity. Compound **4.98** was obtained in 82% yield and 10% ee, when the same reaction was carried out in the presence of *N*-tosyl-aminotriazolium triflate **4.84**. Catalyst **4.79** was selected for a

screening of reaction conditions, aimed at improving the stereoselectivity of this novel application of 1,2,3-triazolium salts. Potassium phosphate was tested as an alternative to potassium carbonate: the increased basicity led to a complete decomposition of the starting material (Table 4, entry 6). 5-Styrylisoxazoles are known to decompose into carboxylic acid upon treatment with strongly basic aqueous solutions. Binaphthalene-derived-triazolium salts are scarcely soluble in non-polar solvents such as toluene or ethers, but possess good solubility in chlorinated solvents. When 1,2-dichloroethane was used as a solvent, the reaction provided compound **4.98** in only 15% yield and 55% ee (Table 4, entry 7). The catalyst loading was increased to 20 mol%, but no appreciable improvement of the reaction outcome was observed (Table 4, entry 8). Also conducting the reaction at 0 °C for 48 h resulted in a lower chemical yield and enantioselectivity (Table 4, entry 9). When the reaction was carried out under anhydrous conditions, product **4.98** was obtained in 21% yield and 43% ee, as demonstration of the involvement of water in the reaction mechanism / transition state. It is known that small quantities of water can improve the performances of a phase transfer catalyst.⁴⁰ For this reason, we performed a test in a water/DCM biphasic system, with potassium carbonate dissolved in the aqueous phase (Table 4, entry 11): the presence of an excess of water did not improve the stereocontrol of the reaction, which provided the desired product in 48% yield and 39% ee (Table 4, entry 11).

Table 4: Michael addition of nitromethane to styrylisoxazole ^a



Entry	Catalyst	Base	Solvent	Yield (%) ^b	ee (S, %) ^c
1	-	K ₂ CO ₃	DCM	32	-
2	(S)- 4.72	K ₂ CO ₃	DCM	21	20
3	(S)- 4.73	K ₂ CO ₃	DCM	17	21
4	(S)- 4.79	K ₂ CO ₃	DCM	90	56
5	(S)- 4.84	K ₂ CO ₃	DCM	82	10
6	(S)- 4.79	K ₃ PO ₄	DCM	-	-
7	(S)- 4.79	K ₂ CO ₃	1,2-dichloroethane	15	55
8 ^d	(S)- 4.79	K ₂ CO ₃	DCM	85	54
9 ^e	(S)- 4.79	K ₂ CO ₃	DCM	58	36
10 ^f	(S)- 4.79	K ₂ CO ₃	DCM	21	43
11 ^g	(S)- 4.79	K ₂ CO ₃ aq	DCM	48	39

^a Reaction conditions: **4.97** (1.0 mmol), nitromethane (5.0 mmol), catalyst (0.005 mmol), solvent (1 ml), 20 °C, 48 h. ^b Isolated yield after column chromatography. ^c Determined by HPLC (Chiralcel OD), absolute configuration was obtained by comparison with literature data.³⁹ ^d 20 mol% of catalyst (S)-**4.79** were used. ^e Carried out at 0 °C for 48 h. ^f Carried out under anhydrous conditions. ^g Aqueous K₂CO₃ (50%wt, 1 ml).

Binaphthalene-derived triazolium salts **4.72**, **4.73**, **4.79** and **4.84** were tested as phase transfer catalysts in the reaction of nitromethane with Michael acceptor 5-styrylisoxazole **4.97**: aminotriazolium chloride **4.79** proved to be an excellent catalyst and, when used in

combination with solid potassium carbonate in dichloromethane, promoted the stereoselective formation of nitro-adduct **4.98**, which was isolated in 90% yield and 56% *ee*. Different attempts to improve this result were made by changing the inorganic base, the reaction solvent, the temperature, the catalyst loading and the heterogeneous medium: unfortunately, we were not able to improve the results obtained. Ongoing work is focused on the synthesis of a small library of aminotriazolium chlorides, analogue to **4.79**, but bearing different substituents on the N-1 or the C-5 of the triazolium ring. The effect of sterically demanding and polar groups at these sites will be tested on the enantioselective Michael addition of nitromethane to styrylisoxazole **4.97**.

In the future, the ability to promote stereoselective C-C bond formation of the newly synthesised binaphthalene-based-1,2,3-triazolium salts will be investigated on several other organic reactions, such as Baylis-Hillman, Strecker synthesis, dihydroxylation of alkenes, 2,3-Wittig rearrangement and asymmetric deprotonations. Furthermore, the free amine function of catalyst **4.79**, might act as an aldehyde-activator through the acid-catalysed formation of iminium species, greatly extending the field of application of these simple organocatalysts.

4.3 Conclusions

Novel and chiral binaphthalene-derived-1,2,3-triazolium salts **4.72**, **4.73**, **4.79** and **4.84** were synthesised following a simple 3 step procedure, starting from (*S*)-2,2'-diamino-1,1'-binaphthalene **4.65**, commercially available in enantiopure form. The azidation reaction was performed treating diamine **4.65** with sodium nitrite and sodium azide, at 0 °C, and provided in good yield the corresponding mono- or di-azide, depending on the molar quantities employed. Azides were easily converted to triazoles, *via* copper-catalysed azide-alkyne cycloaddition, which took place in the presence of the desired terminal alkyne and a copper(II) / ascorbate aqueous media. The methylation of binaphthalene-derived-1,2,3-triazoles was obtained in high yield by treatment with methyl triflate. 2-Amino-2'-(1,2,3-triazolium)-binaphthalene chloride **4.79** was prepared according to a modification of the general procedure, to which a protection-deprotection step of the amine function was added. *N*-Tosyl-amino-2'-(1,2,3-triazolium)-binaphthalene triflate **4.84** was obtained following a non-optimised synthesis, which consisted in the mono-tosylation of starting diamine **4.65** with tosyl chloride, followed by azidation of the corresponding mono-tosylated-diamine **4.72** with sodium nitrite and sodium azide in water. Finally, *N*-tosylaminotriazolium triflate **4.84** was obtained *via* CuAAC with phenylacetylene and methylation with methyl triflate. The general synthesis that was developed is modular, and will allow the preparation of a library of differently substituted binaphthalene-derived-1,2,3-triazolium salts. Compounds **4.72**, **4.73**, **4.79** and **4.84** were tested as chiral phase transfer catalysts in the alkylation of glycine-iminoester **4.90**, the alkylation of oxindole **4.46**, the Mannich-type reaction of acetylacetone with aldimines **4.95a,b** and the Michael addition of nitromethane to 5-styryl-4-nitro-3-methylisoxazole **4.97**. While alkylations and Mannich reactions did not afford positive results, the nitro-Michael addition to compound **4.97** provided the desired nitro-adduct **4.98** in 90% yield and 56% *ee*, when aminotriazolium chloride **4.79** was added to the reaction mixture in catalytic amounts. A small screening of reaction conditions was undertaken, in order to improve the outcome of this enantioselective transformation. Unfortunately, we were not able to improve the stereocontrol of the reaction, but future studies will focus on the synthesis and testing of decorated analogues of **4.79**, which might prove more selective catalysts for not only the nitro-Michael addition, but also for several other organic reactions, which will be object of future studies.

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General conclusions

In conclusion, a new synthesis of amides, starting from enolisable aldehydes and organic azides was discovered and optimised. The study of cyclic compounds derived from the reaction of azides with enolates was undertaken and culminated in a preliminary study of the application of 5-hydroxytriazoles in organocatalysis. Rational drug design led to the preparation of three novel compounds, which incorporate the 5-hydroxytriazole motif, and might potentially inhibit histone deacetylases: these enzymes are a relevant class of biological targets, frequently related to the treatment of cancer. Asymmetric phase transfer catalysis was used to develop a new stereoselective synthesis of 3,4-dihydropyran-2-ones, an important structural unit, often found in natural molecules. Finally, novel binaphthalene-based 1,2,3-triazolium salts were prepared and their activity in organocatalysis was tested for several organic reactions: one particular compound successfully promoted the Michael addition of nitromethane to 5-styrylisoxazole, in a stereoselective fashion. The studies herein reported, touched several branches of organic chemistry, such as organocatalysis, heterocyclic chemistry and synthesis of drug-like molecules. The discovery of undocumented reactivities led to the encounter of new chemical structures, which, in turn, provided inspiration to the development of innovative catalysts. Future work will be focused on improving the performances of the newly discovered organocatalysts, and, at the same time, extending their scope of application.

Experimental Section

General experimental

All chemicals were purchased from Sigma-Aldrich Ireland and used without further purification, unless otherwise stated. *Cinchona*-derived quaternary ammonium salts were synthesised by alkylation of *Cinchona* alkaloids with the corresponding alkyl bromides, following literature procedures.¹ NMR experiments were performed on a Bruker Avance 400 and samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 for ¹³C). Coupling constants are in Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, br, broad. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD, Chiralpak AS, Chiralcel OD), using a UV detector operating at 254 nm. All reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (from EMD/Merk KGaA, silica gel 60 F254) or by NMR (as for the case of the triazoline synthesis, where the product decomposes over silica). Retention factors are reported to ± 0.05. High resolution mass spectra were obtained analysing 0.5 mM solutions of pure products with a Waters Quattro *micro*TM LC-MS/MS System situated at CSCB Mass Spectrometry Facility. Photochemical reactions were carried out in a chamber reactor Rayonet RPR-100 (fluorescent tubes at 254, 300 and 350 nm). Infrared spectra (IR) were recorded as KBr disc using a Bruker Tensor27 FT-IR instrument. Absorption maximum (v_{max}) was reported in wave numbers (cm⁻¹) and only selected peaks are reported. Quantitative NMR (qNMR) analysis was employed to determine the purity of purchased starting materials or when the isolation of a sensitive compound wasn't possible through standard chromatography procedures. Duroquinone TraceCERT[®] (99.31% certified purity grade, δ 2.01 ppm) was adopted as our internal standard. 10.0 mg of duroquinone were dissolved into a solution of the sample in deuterated chloroform (20.0 mg/ml). The solution was sonicated for 5 min and analysed by H-NMR using an inverse-gated ¹³C-decoupled sequence. The absolute purity of a given product was calculated as follows:

$$P_{sample} = \frac{I_{sample}}{I_{ref}} \times \frac{N_{ref}}{N_{sample}} \times \frac{M_{sample}}{M_{ref}} \times \frac{m_{ref}}{m_{sample}} \times P_{ref}$$

I = sum of the integrals of the measured hydrogens;

N = number of hydrogen of the molecule;

M = molecular weight of the molecule;

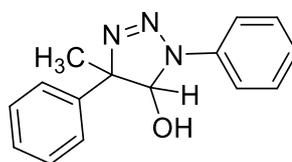
m = weighted mass;

P = purity (mass%).

¹ C. Del Fiandra, M. Moccia, V. Cerulli, M. F. A. Adamo, *Chem. Commun.*, 2016, **52**, 1697–1700.

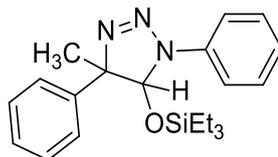
Experimental Section Chapter 1

Synthesis of 4-Methyl-(*N*,4)-diphenyl-5-hydroxytriazoline **1.93**



Azidobenzene (376 mg, 3.1 mmol) and 2-phenyl-propionaldehyde (536 mg, 3.6 mmol) were dissolved in freshly degassed DMSO (5 ml) at room temperature. DBU (0.6 mmol, 536 mg) was added to the solution which was stirred under nitrogen for 2 h at room temperature. Dichloromethane (10 ml) and water (4 ml) were added and after separating the two layers the aqueous phase was extracted with DCM (15 ml). The reunited organic layers were washed with water (4 x 10 ml), dried over sodium sulfate and evaporated under vacuum. The resulting white powder was washed three times with 10 ml of hexane and dried under vacuum yielding 756 mg of triazoline **1.93** as a 3 : 1 diastereoisomeric mixture (96% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.48 (m, 1H), 7.46 – 7.22 (m, 8H), 7.14 – 7.04 (m, 1H), 5.47 (s, 0.75H), 5.35 (s, 0.25H), 1.83 (s, 2.32H), 1.59 (s, 0.84H); ¹³C NMR (101 MHz, CDCl₃) δ 141.6, 139.6, 139.3, 136.2, 129.5, 129.4, 128.9, 128.9, 128.4, 127.9, 127.3, 125.0, 123.4, 123.3, 115.8, 115.7, 86.7, 86.2, 85.2, 84.1, 24.2, 18.8; IR (KBr, cm⁻¹): 1664, 1597, 1495, 1435, 750, 695; HRMS (ES⁺) calculated for C₁₅H₁₆N₃O ([M+H]⁺): 254.1293; found: 254.1286.

Synthesis of 4-Methyl-(*N*,4)-diphenyl-5-triethylsilyloxytriazoline **1.96**



To a solution of imidazole (78 mg, 1.14 mmol) and hydroxytriazoline **1.93** (115 mg, 0.45 mmol) in dry DCM (4.5 ml, 0.1M), triethyl silyl chloride (90 μl, 0.54 mmol) was added at 0°C. The reaction mixture was then left to stir for 18 hours at room temperature. The crude solution was evaporated and silica flash chromatography (Et₂O / Petroleum ether 1:30) allowed to separate the two diastereoisomers of the silyl-protected triazoline **1.96** (product *anti*-**1.96**, 38 mg, 23% yield; product *syn*-**1.96**, 39mg, 24% yield). Relative configuration was determined *via* NOESY experiments.

Silyl-protected anti-1.96. ¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.01 (m, 9H), 5.36 (s, 1H), 1.77 (s, 3H), 0.75 (t, *J* = 7.9 Hz, 9H), 0.53 – 0.29 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 196.7, 140.8, 139.7, 129.1, 128.8, 127.8, 125.2, 124.4, 119.4, 86.9, 19.0, 6.6, 4.9.

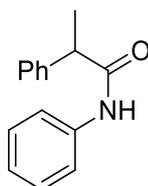
Silyl-protected *syn*-1.96. ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.28 (m, 9H), 5.33 (s, 1H), 1.56 (s, 3H), 0.54 (t, *J* = 8.0 Hz, 9H), 0.04 – -0.06 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 201.1, 135.1, 133.6, 128.9, 127.7, 127.2, 126.4, 126.2, 126.1, 65.9, 26.7, 15.3, 14.7.

General procedure A: phase-transfer catalysed triazoline synthesis followed by Lewis acid-promoted rearrangement into anilides 1.95a-f

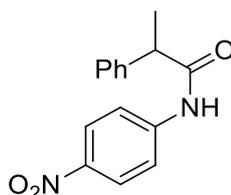
A solution of azide **1.77a-f** (1.0 mmol), aldehyde **1.80a** (2 mmol) and tetra-butylammonium bromide (0.1 mmol) in freshly degassed DCM (5 ml) was cooled down to 3 °C and added with cesium carbonate (3.0 mmol). After 48 h of vigorous stirring at 3 °C the heterogeneous reaction mixture was added with a saturated solution of ammonium chloride and extracted with dichloromethane (3 x 10 ml). The reunited organic phases were dried over sodium sulfate and evaporated under vacuum (bath temperature < 20°C, to avoid thermal decomposition of the intermediate). Crude triazoline was dissolved in dry toluene (10 ml) and titanium isopropoxide (1.1 mmol) was added under nitrogen atmosphere and the clear solution was left stirring for 20 h at room temperature. When the reaction mixture was added with water (2 ml) the formation of white titanium oxide was observed. After 30 min the heterogeneous system was filtered under vacuum and the filtrate was extracted with ethyl acetate (3 x 10 ml). The reunited organic phases were dried over sodium sulfate and evaporated. Pure anilides **1.95a-f** were obtained by trituration of the crude solid with hexane or by flash chromatography over silica gel (AcOEt / petroleum ether from 1:20 to 1:2).

General procedure B: Synthesis of anilides 1.95a-q through DBU-catalysed triazoline formation and Lewis acid-promoted decomposition

1,8-Diazabicycloundec-7-ene (DBU) (0.2 mmol) was added to a solution of azide **1.77a-l** (1.0 mmol) and aldehyde **1.80a-g** (1.2 mmol) in degassed DMSO (2 ml, 0.5M). The solution was flushed with N₂ and left stirring vigorously for 1 hour at 45°C (for products **1.95a,c,d,q** better results were obtained at 20 °C for 4 h). The reaction mixture was added with 10 ml of water and extracted with ethyl acetate (3 x 5 ml). The reunited organic phases were dried over sodium sulfate and evaporated under vacuum (bath temperature < 20°C). Dry toluene (10 ml, 0.1M) and titanium isopropoxide (1.2 mmol) were added to the crude triazoline mixture under nitrogen and the solution was left stirring for 2 hours at 45 °C. Water (2 ml) was added to the stirring solution and the formation of a white suspended solid was observed. The suspension was stirred for 30 min at room temperature, then it was filtered under vacuum and extracted with ethyl acetate (3 x 10 ml). The reunited organic phases were dried over sodium sulfate and the solvent was evaporated under vacuum. Flash chromatography (AcOEt / petroleum ether) followed by trituration with hexane yielded pure anilides **1.95a-q** as solid materials.

2,*N*-Diphenylpropionamide 1.95a

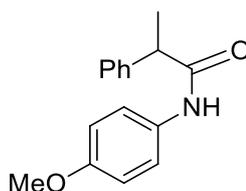
White solid, 76% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.35 (m, $J = 10.9, 7.4$ Hz, 4H), 7.35 – 7.23 (m, 4H), 7.07 (t, $J = 7.4$ Hz, 1H), 6.98 (s, 1H), 3.72 (q, $J = 7.2$ Hz, 1H), 1.61 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.3, 141.0, 138.0, 129.3, 129.1, 127.8, 127.8, 124.4, 119.8, 48.3, 18.7; IR (KBr, cm^{-1}): 3275, 1660, 1561, 1384, 1274; HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{16}\text{NO}$ ($[\text{M}+\text{CH}_3]^+$): 226.1232; found: 226.1221; Chiral HPLC (Chiralpak AD, 10:90 iPrOH/hexane, 0.5 ml/min) Retention time= 23.04 min, 27.34 min.

***N*-(4-Nitrophenyl)-2-phenylpropionamide 1.95b.**

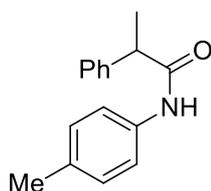
Yellow solid, 99% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 9.2$ Hz, 2H), 7.60 (d, $J = 9.2$ Hz, 2H), 7.45 – 7.32 (m, 5H), 7.30 (s, 1H), 3.76 (q, $J = 7.1$ Hz, 1H), 1.61 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.6, 143.6, 143.5, 140.1, 129.5, 128.0, 127.7, 125.0, 118.9, 48.4, 18.4; IR (KBr, cm^{-1}): 1672, 1558, 1518, 1337, 1254, 856, 699; HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_3$ ($[\text{M}+\text{CH}_3]^+$): 271.1083; found: 271.1091.

***N*-(2-Naphthyl)-2-phenylpropionamide 1.95c.**

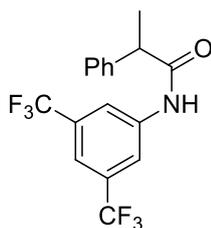
White solid, 69% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 7.5$ Hz, 1H), 7.66 (d, $J = 8.1$ Hz, 1H), 7.56 (s, 1H), 7.49 (d, $J = 8.2$ Hz, 1H), 7.35 – 7.16 (m, 9H), 3.75 (q, $J = 7.1$ Hz, 1H), 1.53 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.8, 141.1, 134.0, 132.2, 129.4, 128.7, 128.0, 127.9, 126.8, 126.2, 125.8, 125.7, 125.5, 120.1, 120.1, 48.2, 18.2; IR (KBr, cm^{-1}): 3252, 2929, 1652, 1534, 781, 691; HR-MS (ES+) calculated for $\text{C}_{19}\text{H}_{18}\text{NO}$ ($[\text{M}+\text{CH}_3]^+$): 276.1388; found: 276.1398.

***N*-(4-Methoxyphenyl)-2-phenylpropionamide 1.95d.**

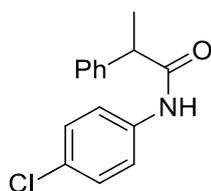
White solid, 75% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.35 (m, 5H), 7.31 (d, $J = 8.9$ Hz, 2H), 6.93 (s, 1H), 6.81 (d, $J = 9.0$ Hz, 2H), 3.76 (s, 3H), 3.70 (q, $J = 7.2$ Hz, 1H), 1.60 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.1, 156.4, 141.1, 131.1, 129.1, 127.7, 127.55, 121.6, 114.0, 55.5, 48.1, 18.6; IR (KBr, cm^{-1}): 3291, 2929, 1652, 1510, 1231; HR-MS (ES+) calculated for $\text{C}_{16}\text{H}_{17}\text{NO}_2$ ($[\text{M}]^+$): 255.1259; found: 255.1263.

***N*-(4-Methylphenyl)-2-phenylpropionamide 1.95e.**

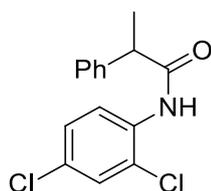
White solid, 72% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.34 (m, 4H), 7.34 – 7.28 (m, 3H), 7.12 – 7.01 (m, 3H), 3.71 (q, $J = 7.1$ Hz, 1H), 2.29 (s, 3H), 1.60 (d, $J = 7.1$ Hz, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.1, 141.0, 135.3, 133.9, 129.4, 129.2, 127.7, 127.6, 119.7, 48.1, 20.8, 18.6; IR (KBr, cm^{-1}): 1648, 1600, 1542, 1246, 813, 695; HR-MS (ES+) calculated for $\text{C}_{16}\text{H}_{18}\text{NO}$ ($[\text{M}+\text{CH}_3]^+$): 240.1388; found: 240.1399.

***N*-(3,5-Di-(trifluoromethyl)-phenyl)-2-phenylpropionamide 1.95f.**

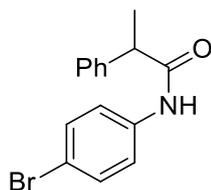
White solid, 92% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.94 (s, 2H), 7.56 (s, 1H), 7.45 – 7.33 (m, 5H), 7.31 (s, 1H), 3.75 (q, $J = 7.1$ Hz, 1H), 1.62 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.0, 139.0, 131.4 (q, $J_{\text{C-F}} = 34.3$ Hz), 128.4, 127.0, 126.6, 122.0 (q, $J_{\text{C-F}} = 272.8$ Hz), 118.4, 116.5, 47.1, 17.4; ^{19}F NMR (376 MHz, CDCl_3) δ -63.11; IR (KBr, cm^{-1}): 1656, 1585, 1546, 1487, 1435, 746, 695; HR-MS (EI+) calculated for $\text{C}_{17}\text{H}_{13}\text{F}_6\text{NO}$ ($[\text{M}]^+$): 361.0901; found: 361.0897.

***N*-(4-Chlorophenyl)-2-phenylpropionamide 1.95g.**

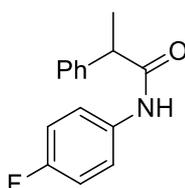
White solid, 77% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.67 (s, 1H), 7.43 – 7.27 (m, 7H), 7.19 (d, $J = 8.8$ Hz, 2H), 3.71 (q, $J = 7.1$ Hz, 1H), 1.57 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.3, 140.7, 136.4, 129.3, 129.2, 128.9, 127.7, 127.7, 120.9, 48.1, 18.5; IR (KBr, cm^{-1}): 3293, 1663, 1537, 829; HR-MS (EI+) calculated for $\text{C}_{15}\text{H}_{14}\text{NOCl}$ ($[\text{M}]^+$): 259.0764; found: 259.0772.

***N*-(2,4-Dichlorophenyl)-2-phenylpropionamide 1.95h.**

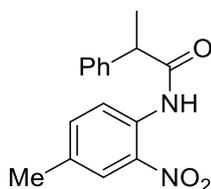
White solid, 81% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 8.35 (d, $J = 8.9$ Hz, 1H), 7.56 (s, 1H), 7.45 – 7.31 (m, 5H), 7.28 (d, $J = 2.3$ Hz, 1H), 7.21 (dd, $J = 8.9, 2.4$ Hz, 1H), 3.79 (q, $J = 7.2$ Hz, 1H), 1.64 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.4, 140.1, 133.4, 129.3, 128.9, 128.6, 127.9, 127.9, 127.8, 123.2, 121.8, 48.4, 18.0; IR (KBr, cm^{-1}): 3364 (broad), 1652, 1533, 830; HR-MS (EI+) calculated for $\text{C}_{15}\text{H}_{13}\text{NOCl}_2$ ($[\text{M}]^+$): 293.0374; found: 293.0380.

***N*-(4-Bromophenyl)-2-phenylpropionamide 1.95i.**

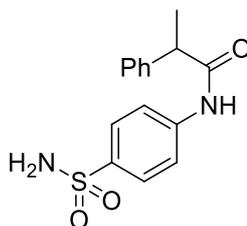
Yellow solid, 75% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.29 (m, 9H), 6.99 (s, 1H), 3.70 (q, $J = 7.1$ Hz, 1H), 1.59 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.3, 140.6, 136.9, 131.9, 129.3, 127.7, 127.7, 121.2, 116.8, 48.2, 18.5; IR (KBr, cm^{-1}): 2934, 1662, 1508; HR-MS (EI+) calculated for $\text{C}_{15}\text{H}_{14}\text{NOBr}$ ($[\text{M}]^+$): 303.0259; found: 303.0269.

***N*-(4-Fluorophenyl)-2-phenylpropionamide 1.95j.**

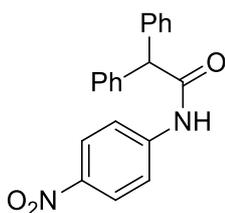
Brown solid, 76% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.29 (m, 7H), 7.03 – 6.90 (m, 3H), 3.71 (q, $J = 7.2$ Hz, 1H), 1.60 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.2, 159.3 (d, $J = 243.4$ Hz), 140.8, 129.2, 127.7 (2C), 121.6, 121.5 (d, $J = 7.8$ Hz), 115.5 (d, $J = 22.5$ Hz), 48.0, 18.5; ^{19}F NMR (376 MHz, CDCl_3) δ -118.08 (m); IR (KBr, cm^{-1}): 2786 (broad), 1648; HR-MS (EI+) calculated for $\text{C}_{15}\text{H}_{14}\text{NOF}$ ($[\text{M}]^+$): 243.1059; found: 243.1063.

***N*-(4-methyl-2-nitrophenyl)-2-phenylpropionamide 1.95k.**

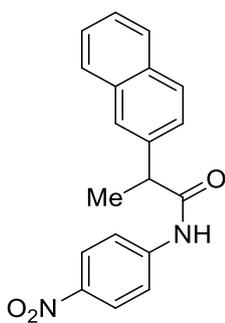
Yellow oil, 82% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 10.20 (s, 1H), 8.64 (d, $J = 8.6$ Hz, 1H), 7.90 (s, 1H), 7.47 – 7.28 (m, 6H), 3.81 (q, $J = 7.1$ Hz, 1H), 2.32 (s, 3H), 1.64 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 140.0, 136.7, 136.0, 133.3, 132.6, 129.2, 127.8, 127.8, 125.4, 121.8, 49.0, 20.5, 18.0; IR (KBr, cm^{-1}): 2384 (broad); HR-MS (EI+) calculated for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 284.1161; found: 284.1155.

***N*-(4-sulfamoylphenyl)-2-phenylpropionamide 1.95l.**

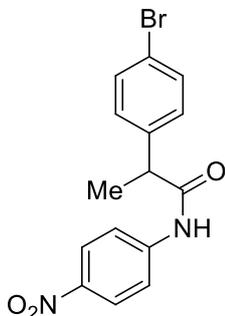
Grey solid, 72% yield (general procedure B). ^1H NMR (400 MHz, DMSO) δ 10.45 (s, 1H), 7.77 (s, 4H), 7.46 – 7.17 (m, 7H), 3.87 (q, $J = 6.9$ Hz, 1H), 3.51 (s, 6H), 1.43 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 172.8, 142.1, 141.5, 138.3, 128.4, 127.2, 126.8, 126.6, 118.7, 46.0, 18.6; IR (KBr, cm^{-1}): 3331, 3231, 1652, 1523, 1327, 1160; HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ ($[\text{M}]^+$): 304.0882; found: 304.0885.

***N*-(4-nitrophenyl)-2,2-di-phenylacetamide 1.95m.**

Yellow solid, 89% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 9.1$ Hz, 2H), 7.68 – 7.61 (m, 3H), 7.43 – 7.28 (m, 10H), 5.11 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.6, 143.7, 143.3, 138.3, 129.1, 128.9, 127.9, 125.0, 119.1, 60.1; IR (KBr, cm^{-1}): 1677, 1512, 1332, 693; HR-MS (ES+) calculated for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 271.1083; found: 271.1091

***N*-(4-Nitrophenyl)-2-(2-naphthyl)-propionamide 1.95n.**

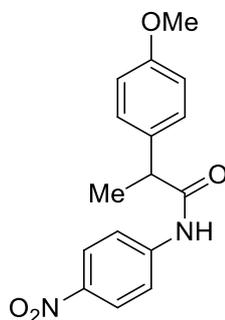
Yellow solid, 72% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H), 8.04 (d, $J = 9.1$ Hz, 2H), 7.85 – 7.73 (m, 4H), 7.62 (d, $J = 9.1$ Hz, 2H), 7.51 – 7.40 (m, 3H), 3.95 (q, $J = 7.0$ Hz, 1H), 1.67 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.2, 144.1, 143.2, 137.7, 133.5, 132.7, 129.1, 127.7 (2C), 126.6, 126.5, 126.3, 125.3, 124.9, 119.1, 48.2, 18.6; IR (KBr, cm^{-1}): 1684, 1505, 1341, 858, 744; HR-MS (ES+) calculated for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 320.1161; found: 320.1153.

***N*-(4-Nitrophenyl)-2-(4-bromophenyl)-propionamide 1.95o.**

Pale yellow solid, 95% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 9.1$ Hz, 2H), 7.63 (d, $J = 9.1$ Hz, 2H), 7.53 (t, $J = 10.8$ Hz, 2H), 7.36 (s, 1H), 7.24 (d, $J = 8.3$ Hz, 2H), 3.71 (q, $J = 7.0$ Hz, 1H), 1.58 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.0,

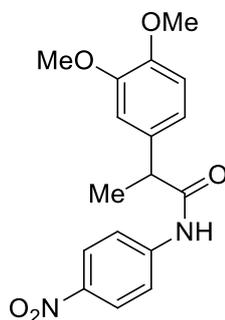
143.6, 143.4, 139.1, 132.5, 129.3, 125.1, 122.0, 119.0, 47.8, 18.6; HR-MS (ES+) calculated for $C_{15}H_{13}N_2O_3Br$ ($[M]^+$): 348.0117; found: 348.0110.

***N*-(4-Nitrophenyl)-2-(4-methoxyphenyl)-propionamide 1.95p.**

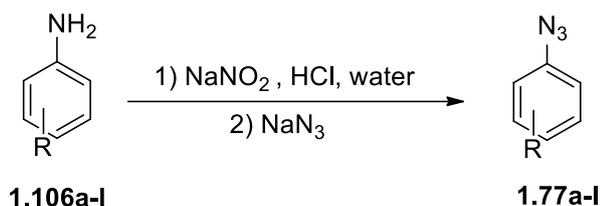


Pale green solid, 57% yield (general procedure B). 1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9.2 Hz, 2H), 7.57 – 7.49 (m, 3H), 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.73 (s, 1H), 3.69 – 3.60 (m, 1H), 1.50 (d, J = 7.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 159.2, 143.8, 143.4, 132.1, 128.8, 125.0, 119.0, 114.7, 55.3, 47.4, 18.6; IR (KBr, cm^{-1}): 1679, 1510, 1331; HR-MS (ES+) calculated for $C_{16}H_{16}N_2O_4$ ($[M]^+$): 300.1110; found: 300.1118.

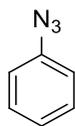
***N*-(4-Nitrophenyl)-2-(2,4-dimethoxyphenyl)-propionamide 1.95q.**



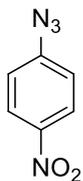
Yellow solid, 67% yield (general procedure B). 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 9.2 Hz, 2H), 7.77 (s, 1H), 7.63 (d, J = 9.2 Hz, 2H), 6.90 – 6.81 (m, 3H), 3.83 (d, J = 4.2 Hz, 6H), 3.70 (q, J = 7.1 Hz, 1H), 1.57 (d, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 149.5, 148.6, 143.9, 143.3, 132.7, 125.0, 119.8, 118.9, 111.6, 110.5, 55.9, 55.9, 47.8, 18.6; IR (KBr, cm^{-1}): 2824, 1670, 1505, 1321; HR-MS (ES+) calculated for $C_{17}H_{18}N_2O_5$ ($[M]^+$): 330.1216; found: 330.1219.

General procedure for the synthesis of azides 1.77a-l

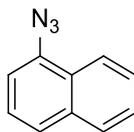
To a stirring solution of HCl in water (89 mmol, 20ml, 4.5 M), aniline **1.106a-l** (15.9 mmol) was added dropwise. After 10 min the mixture was cooled down to 0 °C and added with an aqueous solution of NaNO₂ (15.9 mmol, 3 M) over 5 min. After 40 min the pH was carefully adjusted to 7 with saturated NaHCO₃ and an aqueous solution of NaN₃ (15.6 mmol, 3 M) was slowly added. The ice bath was removed after 5 min and the mixture was left stirring for additional 30 minutes. Crude was extracted with Et₂O (1x80 ml, 2x40 ml). The reunited organic phases were dried over sodium sulfate and evaporated under vacuum (bath temperature < 20°C). Column chromatography (hexane) yielded pure azides **1.77a-l**.

Azidobenzene 1.77a

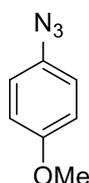
Pale yellow liquid, 78% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.34 (m, 2H), 7.17 – 7.13 (m, 1H), 7.05 – 7.03 (d, *J* = 8Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 140.0, 129.8, 124.9, 119.0. IR (KBr) (cm⁻¹) 2127, 2095, 1594, 1493, 1455, 1175, 1130, 688, 670. HR-MS (ES+) calculated for C₆H₅N₃ ([M+Na]⁺): 119.0478; found: 119.0480.

4-Nitro-azidobenzene 1.77b

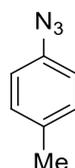
Orange oil, 30% yield. ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 146.9, 144.6, 125.6, 119.4. IR (KBr, cm⁻¹) 3111.77, 2121.20, 1589.32, 1511.28, 1487.23, 1338.33, 1285.15. ES-MS (*m/z*): 164.1 (M⁺).

1-Azidonaphthalene 1.77c

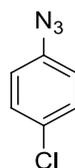
White solid, 63% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.19 – 8.10 (m, 1H), 7.89 – 7.81 (m, 1H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.59 – 7.43 (m, 3H), 7.27 (d, $J = 7.3$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.5, 134.4, 127.7, 126.9, 126.4, 126.2, 125.7, 124.7, 122.6, 113.9. IR (KBr, cm^{-1}): 2112. ES-MS (m/z): 169.0 (M^+).

4-Azidoanisole 1.77d

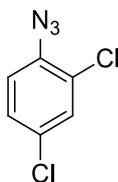
Yellow oil, 66% yield. ^1H NMR (400 MHz, CDCl_3) δ 6.96 (d, $J = 9.0$ Hz, 2H), 6.89 (d, $J = 9.0$ Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.0, 132.3, 120.0, 115.1, 55.6. IR (NaCl, cm^{-1}) 2131, 2016. ES-MS (m/z): 149.0 (M^+).

4-Azidotoluene 1.77e

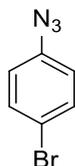
Pale yellow oil, 88% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.17 (d, $J = 8.3$ Hz, 2H), 6.94 (d, $J = 8.3$ Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 137.2, 134.3, 130.4, 118.9, 20.8. IR (KBr, cm^{-1}) 2130, 2106. ES-MS (m/z): 133.1 (M^+).

4-Chloro-azidobenzene 1.77g

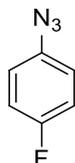
Orange oil, 44%. ^1H NMR (400 MHz, CDCl_3) δ 7.30 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 138.7, 130.2, 129.8, 120.3. IR (KBr, cm^{-1}): 2135, 1488, 1303. HR-MS (ES+) calculated for $\text{C}_6\text{H}_4\text{N}_3\text{Cl}$ ($[\text{M}]^+$): 153.0094; found: 153.0089.

2,4-Dichloro-azidobenzene 1.77h

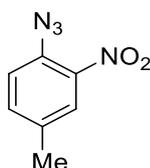
Pale yellow solid, 68% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.39 (d, $J = 2.3$ Hz, 1H), 7.27 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.10 (d, $J = 8.6$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 136.0, 130.5, 130.4, 128.1, 125.7, 120.4. IR (KBr, cm^{-1}): 2118, 1476, 1305. HR-MS (ES+) calculated for $\text{C}_6\text{H}_3\text{N}_3\text{Cl}_2$ ($[\text{M}]^+$): 186.9704; found: 186.9706.

4-Bromo-azidobenzene 1.77i

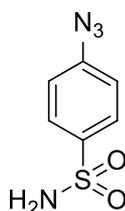
Orange solid, 53%. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 139.3, 132.8, 120.7, 117.8. IR (KBr, cm^{-1}): 2125, 1476, 1066. HR-MS (ES+) calculated for $\text{C}_6\text{H}_4\text{N}_3\text{Br}$ ($[\text{M}]^+$): 196.9589; found: 196.9598.

4-Fluoro-azidobenzene 1.77j

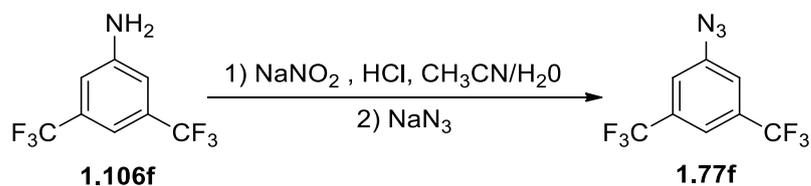
Pale yellow oil, 60%. ^1H NMR (400 MHz, CDCl_3) δ 7.09 – 7.02 (m, 2H), 7.02 – 6.95 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.2 (s), 158.8 (s), 135.9 (d, $J = 2.9$ Hz), 120.3 (d, $J = 8.3$ Hz), 116.6 (d, $J = 23.2$ Hz). ^{19}F NMR (376 MHz, CDCl_3) δ -117.74 (m). IR (KBr, cm^{-1}): 2118, 1504, 1303, 1226, 823. HR-MS (ES+) calculated for $\text{C}_6\text{H}_4\text{N}_3\text{F}$ ($[\text{M}]^+$): 137.0389; found: 137.0384.

4-Methyl-2-nitro-azidobenzene 1.77k

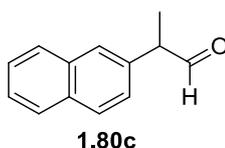
Yellow solid, 79% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.74 (s, 1H), 7.42 (d, $J = 8.3$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 140.6, 135.5, 134.8, 132.0, 126.2, 120.6, 20.6. IR (KBr, cm^{-1}): 1521, 1345, 1280, 1171, 807. Not stable under ES-MS conditions.

4-Azido-benzenesulfonamide 1.77l

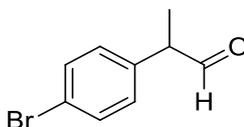
Pale brown solid, 14% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 8.6$ Hz, 2H), 7.14 (d, $J = 8.6$ Hz, 2H), 4.91 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 144.9, 138.1, 128.5, 119.4. IR (KBr, cm^{-1}): 1589, 1490, 1333, 1283, 1158. HRMS (ES+) calculated for $\text{C}_6\text{H}_6\text{N}_4\text{O}_2\text{S}$ ($[\text{M}]^+$): 198.0211; found: 198.0211.

Synthesis of azide 1.77f

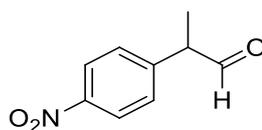
37% HCl (40 mmol, 3.3 ml) was added to a stirring solution of 3,5-di-(trifluoromethyl)-azidobenzene (1.04 g, 4.54 mmol) in acetonitrile / water 1 : 8. After 10 min, NaNO_2 (630 mg, 9.1 mmol) was slowly added and the solution was stirred for 1 h. The pH was then neutralised with NaHCO_3 sat., and the mixture was cooled down to $0\text{ }^\circ\text{C}$ with an ice bath. A water solution of NaN_3 (9.1 mmol, 10 ml) was added dropwise and the solution was stirred for 1 h. Crude was extracted with Et_2O (1x80 ml, 2x40 ml). The reunited organic phase was dried over sodium sulfate and evaporated under vacuum (bath temp $< 20\text{ }^\circ\text{C}$). Column chromatography (hexane) yielded pure azide **1.77f** as a pale yellow oil (613 mg, 53% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.64 (s, 1H), 7.44 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 142.4 (s), 133.4 (q, $J = 34.0$ Hz), 122.7 (q, $J = 273.0$ Hz), 119.2 (m), 118.5 (m). ^{19}F NMR (376 MHz, C_6D_6): δ -63.2. IR (KBr, cm^{-1}): 2117, 1463, 1372, 1282, 1183, 1132. HRMS (ES+) calculated for $\text{C}_8\text{H}_3\text{F}_6\text{N}_3$ ($[\text{M}]^+$): 255.0226; found: 255.0219.

2-(β -Naphthyl)-propionaldehyde 1.80c

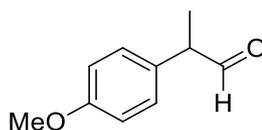
Potassium tert-butoxide (4.7 g, 42 mmol) was slowly added to a solution of methyl- β -naphthyl ketone **1.106c** (6.0 g, 35.2 mmol) and chloroacetonitrile (2.2 ml, 2.38 g, 35.2 mmol) in 30 ml of dichloromethane at 5°C. The solution was stirred overnight letting the temperature slowly rise to 20 °C. The crude mixture was added with 150 ml of ice-cold water and extracted 3 times with Et₂O (80 ml). The reunited organic phase was washed with water (50 ml) and brine (50 ml), dried over sodium sulfate and evaporated under vacuum to yield a brown oil. Crude epoxy nitrile **1.106c** was dissolved in ethanol (45 ml), added with a 10 % aqueous KOH (34 ml) and refluxed overnight. The residue was evaporated under vacuum, diluted with water (50 ml) and extracted 4 times with Et₂O (50 ml). The aqueous solution was acidified to pH=1 with 37% HCl and refluxed for 4 hours. The crude mixture then was extracted four times with Et₂O (50 ml) and the organic layer was washed with saturated NaHCO₃ solution, water and brine. After drying over sodium sulfate, the crude was evaporated under vacuum and purified by flash chromatography (Et₂O / Petroleum ether 1:20) obtaining pure 2-(β -naphthyl)-propionaldehyde **1.80c** (904 mg, 14% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H), 7.95 – 7.77 (m, 3H), 7.69 (s, 1H), 7.57 – 7.42 (m, 2H), 7.34 – 7.42 (m, 1H), 3.82 (q, *J* = 7.0, 1H), 1.55 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 201.1, 135.1, 133.6, 132.7, 128.9, 127.7, 127.2, 126.5, 126.2, 126.1, 53.1, 14.7. IR (KBr): ν (cm⁻¹) = 2923, 2853, 1712, 1504, 1453, 1387, 1273. HR-MS (ES⁺) calculated for C₁₃H₁₂O ([M+CH₃]⁺): 199.1121; found: 199.1117.

4-Bromo-phenylpropionaldehyde 1.80d

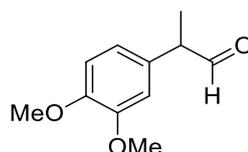
Obtained following the same procedure for **1.80c**. Yellow solid, 5.77 g, 36% yield. ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 1H), 1.33 (d, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 200.4, 136.7, 132.2, 130.0, 121.6, 52.3, 14.6. IR (KBr): ν (cm⁻¹) = 2936, 1721, 1591, 1487, 1404, 1072. HR-MS (ES⁺) calculated for C₁₀H₁₂BrO ([M+CH₃]⁺): 227.0068; found: 227.0066.

2-(4-Nitrophenyl)-propionaldehyde 1.80g

To a stirring solution of NaH (60% in mineral oil, 0.27 g, 6.75 mmol) in dry THF (6 ml), $\text{Me}_3\text{S}(\text{O})\text{I}$ (1.50 g, 6.75 mmol) was added at room temperature. The reaction mixture was left stirring for 1 h at room temperature. A solution of 4-nitro-acetophenone **1.106g** (928 mg, 5.62 mmol) in dry THF (3 ml) was added dropwise and the reaction mixture was left stirring for 24 h. The reaction mixture was diluted with H_2O (10 ml), followed by extractions with EtOAc (3 x 10 ml). The combined organic phases were dried over sodium sulfate and the solvent was evaporated under vacuum. The crude epoxide **1.110g** was then dissolved in toluene (28 ml) and added with zinc chloride (804 mg, 5.9 mmol). The mixture was refluxed at 110 °C for 1 h. Evaporation of the solvent yielded 4-nitrophenyl-propionaldehyde **1.180g** (382 mg, 38% yield). ^1H NMR (400 MHz, CDCl_3) δ 9.72 (s, 1H), 8.25 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 3.80 (q, $J = 7.2$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 199.6, 147.4, 145.3, 129.3, 124.2, 52.7, 14.7. IR (KBr): ν (cm^{-1}) = 2842, 2739, 1727, 1605, 1519, 1419, 1397. HR-MS (ES+) calculated for $\text{C}_9\text{H}_9\text{NO}_3$ ($[\text{M}+\text{CH}_3]^+$): 179.0582, found: 179.0583.

2-(4-methoxyphenyl)-propionaldehyde 1.80e

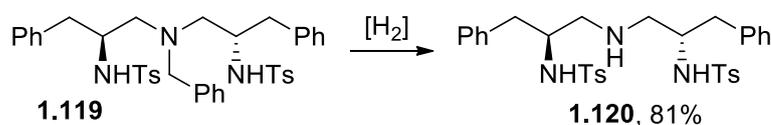
Aldehyde **1.80e** was prepared following the procedure described for the synthesis of **1.80g**. Yellow oil, 536 mg, 64 %yield. ^1H NMR (400 MHz, CDCl_3) δ 9.65 (s, 1H), 7.13 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 3.81 (s, 3H), 3.58 (q, $J = 7.1$, 1H), 1.41 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 201.2, 159.0, 129.6, 129.4, 114.5, 55.3, 52.2, 14.7. IR (KBr): ν (cm^{-1}) = 2933, 1717, 1610, 1585, 1244, 1178. HR-MS (ES+) calculated for $\text{C}_{10}\text{H}_{13}\text{O}_2$ ($[\text{M}+\text{H}]^+$): 165.0914; found: 165.0910.

2-(3,4-Di-methoxyphenyl)-propionaldehyde 1.80f

To a stirring dispersion of NaH (60% in mineral oil, 3.2 g, 80.4 mmol) in dry THF (40 ml) at room temperature, $\text{Me}_3\text{S}(\text{O})\text{I}$ (17.7 g, 80.4 mmol) was added portion wise under nitrogen flow. The mixture was refluxed at 70 °C for 1 h, added with a solution of 3,4-dimethoxyacetophenone **1.106f** (7.24 g, 40.2 mmol dissolved in 40 ml of THF) and reacted at

room temperature for 20 h. The reaction mixture was diluted with H₂O, and extracted with Et₂O. The combined organic layers were dried over sodium sulfate and the solvent was evaporated under vacuum. Crude epoxide **1.110f** was dissolved in toluene (100 ml) and added with zinc (II) chloride (523 mg, 8 mmol). The mixture was reacted at room temperature for 18 h, yielding crude 3,4-di-methoxyphenylpropionaldehyde **1.80f**. To the crude mixture were added sodium bisulfite (6.2 g, 60 mmol), ethyl acetate (50 ml), ethanol (30 ml) and water (10 ml). The heterogeneous mixture was stirred at 40 °C for 2 h then allowed to cool down to room temperature, filtered, washed with cold ethanol (10 ml) and dried to give the bisulfite adduct as white crystals. The regeneration of the aldehyde was performed adding 20 ml of saturated sodium bicarbonate and 20 ml of dichloromethane to the bisulfite adduct. The mixture was left stirring vigorously for 1 h at room temperature then it was extracted three times with dichloromethane, dried over sodium sulfate and evaporated under vacuum to yield 4.21 g of pure aldehyde **1.80f** as a yellow oil (4.76 g, 61% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.65 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.68 (d, *J* = 2.1 Hz, 1H), 3.88 (s, 6H), 3.58 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 201.0, 149.5, 148.5, 130.0, 120.5, 111.7, 111.3, 55.9 (2C), 52.6, 14.6. IR (KBr, cm⁻¹): 1721, 1520, 1267. HR MS (ES+) calculated for C₁₁H₁₄O₃Na ([M+Na]⁺): 217.0841; found: 217.0838.

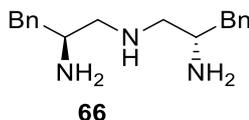
Hydrogenolysis of benzylic amines with ammonium formate ²



A solution of **1.119** (489 mg, 1.24 mmol) in methanol (10 ml) was added with ammonium formate (782 mg, 12.4 mmol) and palladium on carbon (10% wt, 0.35 g). The reaction vessel was tightly capped and heated up to 63 °C for 2 h. Overpressure of hydrogen was released every 5 min through a needle during the first 30 min of reaction. The reaction mixture was filtered and evaporated under vacuum. Crude amine **1.120** was isolated as a colorless oil without further purification (346 mg, 81% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 8.2 Hz, 4H), 7.25 – 7.16 (m, 10H), 7.01 – 6.90 (m, 4H), 3.46 – 3.36 (m, 2H), 2.71 (dd, *J* = 13.8, 6.0 Hz, 2H), 2.58 (dd, *J* = 13.8, 7.5 Hz, 2H), 2.51 – 2.37 (m, 10H). ¹³C NMR (101 MHz, CDCl₃) δ 143.3, 137.5, 137.1, 129.7, 129.3, 128.6, 127.1, 126.6, 54.6, 51.7, 39.5, 21.5.

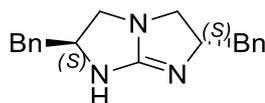
² S. Ram and R. E. Ehrenkauf, *Synthesis (Stuttg.)*, 1988, **1988**, 91–95.

Detosylation of primary amines with sodium naphthalenide: synthesis of di-((S)-2-amino-3-phenylpropyl)amine ³



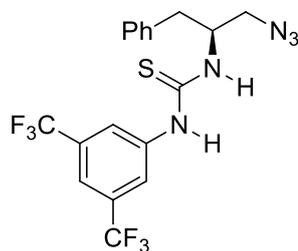
To a solution of naphthalene (928 mg, 7.24 mmol) in dry THF (10 ml) freshly cut sodium (159 mg, 6.9 mmol) was added at room temperature. After 2 h the green solution was added with a solution of secondary amine **1.120** (342 mg, 0.58 mmol) in dry THF (4 ml) and stirred for 1 h. The reaction mixture was added with ice and acidified with 1 M HCl till pH 1. The heterogeneous mixture was extracted with diethyl ether (15 ml) and the water phase was basified with 1 M NaOH until pH 11 was reached. Dichloromethane (3 x 10 ml) was used to extract free amine **66**. The extract was dried over sodium sulfate and evaporated under vacuum yielding **66** as a colorless oil (130 mg, 80% yield). No further further purification was needed. ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.10 (m, 10H), 3.17 – 3.03 (m, 2H), 2.78 (dd, J = 13.4, 4.5 Hz, 2H), 2.73 – 2.63 (m, 2H), 2.58 – 2.44 (m, 4H), 1.50 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 139.24, 129.25, 128.51, 128.48, 126.27, 56.15, 52.53, 42.78.

Chiral guanidine 1.122



Obtained from **1.121** following the experimental procedure reported by Tan.⁴ Brown solid (88 mg, 16% overall yield over 6 steps). ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.17 (m, 10H), 4.35 – 4.25 (m, 2H), 3.14 – 3.09 (m, 2H), 2.98 (dd, J = 13.5, 7.0 Hz, 2H), 2.85 (dd, J = 7.9, 6.0 Hz, 2H), 2.79 (dd, J = 13.5, 7.4 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 168.3, 138.16, 129.11, 128.60, 126.55, 65.62, 53.30, 41.86.

(S)-1-(1-azido-3-phenyl-iso-propyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea 1.129

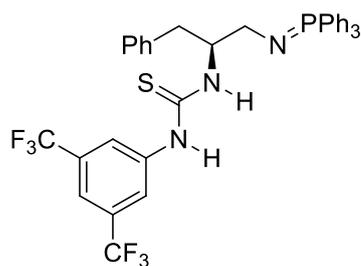


³ S. C. Bergmeier and P. P. Seth, *Tetrahedron Lett.*, 1999, **40**, 6181–6184.

⁴ J. Shen, T. T. Nguyen, Y.-P. Goh, W. Ye, X. Fu, J. Xu and C.-H. Tan, *J Am Chem Soc*, 2006, **128**, 13692–13693.

Obtained from **1.125** following the experimental procedure reported by Dixon.⁵ White solid. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 7.68 (s, 1H), 7.61 (s, 2H), 7.29 – 7.14 (m, 5H), 6.10 (s, 1H), 4.79 (s, 1H), 3.64 (dd, *J* = 12.0, 4.6 Hz, 1H), 3.40 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.98 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.78 (dd, *J* = 13.8, 8.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 180.2, 138.2, 136.3, 133.8, 133.5, 133.2, 132.8, 129.1, 129.0, 127.2, 124.1, 121.3, 119.9, 55.4, 52.3, 37.4. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.8.

(S)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(1-phenyl-3-((triphenylphosphoranylidene)amino)propan-2-yl)thiourea **1.130**⁵

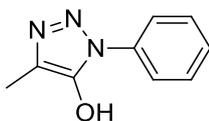


Triphenylphosphine (310 mg, 1.18 mmol) was added to a solution of azide **1.129** (512 mg, 1.18 mmol) in dry diethyl ether (3 ml) at room temperature. The reaction was stirred for 24 h, then crude mixture was evaporated and the viscous mass was triturated with hexane, yielding product **1.130** as a bright yellow solid (738 mg, 92% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.53 (m, 3H), 7.53 – 7.27 (m, 21H), 7.18 – 7.01 (m, 5H), 4.16 (s, 1H), 3.29 – 3.15 (m, 1H), 3.11 – 2.95 (m, 1H), 2.84 (s, 1H), 2.80 – 2.58 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 178.6, 157.6, 132.6, 132.5, 132.2 (d, *J*_{CP} = 3.0 Hz), 132.1 (d, *J*_{CP} = 10.0 Hz), 129.1, 128.9, 128.6 (d, *J*_{CP} = 12.0 Hz), 126.8, 124.2, 119.3, 116.7, 77.4, 61.4, 51.7, 39.5. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.8. ³¹P NMR (162 MHz, CDCl₃) δ 19.9 (bs).

⁵ M. G. Núñez, A. J. M. Farley and D. J. Dixon, *J Am Chem Soc*, 2013, **135**, 16348–16351.

Experimental Section Chapter 2

Synthesis of 5-hydroxy-1,2,3-triazoles 2.123a-j via phase transfer catalysis

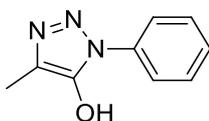


To a solution of aromatic azide **2.32a** (131 mg, 1.2 mmol) and 90% ethyl 2-methylacetoacetate **2.122a** (192 mg, 1.2 mmol) in diethyl ether (5 ml) were added tetrabutylammonium bromide (35 mg, 0.11 mmol) and finely ground KOH (123 mg, 2.2 mmol) at room temperature. After 4 h of vigorous stirring the white precipitate was collected by vacuum filtration. The solid, made of the potassium salt of **2.123a** was dispersed in 1 ml of ACN and added with acetic acid until dissolution. The mixture was evaporated and purified *via* flash column chromatography (MeOH / DCM 1 : 9) to afford 181 mg of compound **2.123a** as a white solid (95% yield). ¹H NMR (400 MHz, CDCl₃) δ 13.57 (bs, 1H), 7.85 (d, J = 7.7 Hz, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 2.23 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 152.2, 135.8, 129.1, 128.4, 122.4, 119.6, 8.3. IR (KBr, cm⁻¹): 1852, 1493, 759. m. p. 140 °C. HR-MS (ES⁺) calculated for C₉H₁₀N₃O ([M+H]⁺): 176.0824; found: 176.0819.

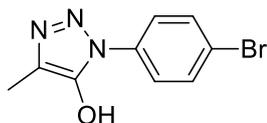
General procedure for the DBU-promoted synthesis of 5-hydroxytriazoles 2.123a-o.

To a solution of aromatic azide **2.32a-k** (0.5 mmol) and ketoester **2.112a-g** (0.6 mmol) in ACN (2.5 ml) was added DBU (0.6 mmol) and the reaction was stirred at 50 °C overnight. The crude mixture was evaporated under vacuum and purified *via* flash column chromatography (MeOH / DCM / AcOH 90 : 10 : 0.1) to afford title compounds as solids. Purified products could still contain traces of DBU salt, which were easily removed by trituration of the solid with a minimum quantity of water.

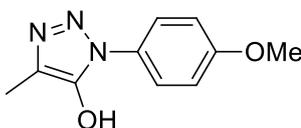
5-Hydroxy-4-methyl-1-phenyl-1,2,3-triazole 2.123a



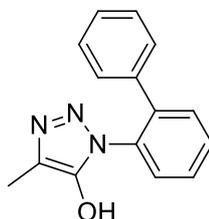
White solid, 85% yield. ¹H NMR (400 MHz, CDCl₃) δ 13.57 (bs, 1H), 7.85 (d, J = 7.7 Hz, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 2.23 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 152.2, 135.8, 129.1, 128.4, 122.4, 119.6, 8.3. IR (KBr, cm⁻¹): 1852, 1493, 759. m. p. 140 °C. HR-MS (ES⁺) calculated for C₉H₁₀N₃O ([M+H]⁺): 176.0824; found: 176.0819.

5-Hydroxy-4-methyl-1-(4-bromophenyl)-1,2,3-triazole 2.123b

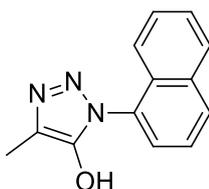
Off-white solid, 87% yield; m. p. 154 °C. ¹H NMR (400 MHz, DMSO) δ 11.75 (bs, 1H), 7.91 – 7.59 (m, 4H), 2.17 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 146.8, 135.1, 132.3, 123.7, 122.9, 120.6, 9.2. IR (KBr, cm⁻¹): 2389, 1991, 1493. HR-MS (ES+) calculated for C₉H₉BrN₃O ([M+H]⁺): 253.9929; found: 253.9935.

5-Hydroxy-4-methyl-1-(4-methoxyphenyl)-1,2,3-triazole 2.123d

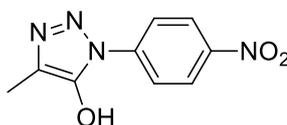
White solid, 62% yield; m. p. 153 °C. ¹H NMR (400 MHz, DMSO) δ 7.58 (d, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 3.82 (s, 1H), 2.17 (s, 1H). ¹³C NMR (101 MHz, DMSO) δ 159.3, 146.8, 129.2, 124.5, 123.2, 114.9, 55.9, 9.7. IR (KBr, cm⁻¹): 2616, 1522, 1257. HR-MS (ES+) calculated for C₁₀H₁₂N₃O₂ ([M+H]⁺): 206.0930; found: 206.0928.

5-Hydroxy-4-methyl-1-(2-phenylphenyl)-1,2,3-triazole 2.123e

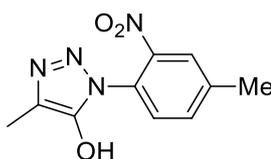
Off-white solid, 75% yield; m. p. 143 °C. ¹H NMR (400 MHz, DMSO) δ 9.87 (bs, 1H), 7.70 – 7.62 (m, 1H), 7.61 – 7.52 (m, 2H), 7.49 – 7.41 (m, 1H), 7.36 – 7.25 (m, 3H), 7.18 – 7.05 (m, 2H), 2.05 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 158.9, 147.9, 139.2, 138.3, 133.1, 131.2, 130.7, 128.9, 128.8, 128.5, 127.9, 122.0, 9.6. IR (KBr, cm⁻¹): 2315, 1597, 1478, 1271, 1232. HR-MS (ES+) calculated for C₁₅H₁₄N₃O ([M+H]⁺): 252.1137; found: 252.1129.

5-Hydroxy-4-methyl-1-(1-naphthyl)-1,2,3-triazole 2.123f

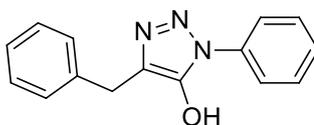
White solid, 79% yield; m. p. 119 °C. ¹H NMR (400 MHz, DMSO) δ 8.16 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.73 – 7.56 (m, 4H), 7.36 (d, *J* = 8.2 Hz, 1H), 2.26 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 148.3, 134.1, 131.9, 130.4, 129.4, 128.6, 128.0, 127.3, 125.9, 125.6, 123.1, 122.4, 9.8. IR (KBr, cm⁻¹): 3236, 2980, 2867, 2167. HR-MS (ES+) calculated for C₁₃H₁₂N₃O ([M+H]⁺): 226.0980; found: 226.0972.

5-Hydroxy-4-methyl-1-(4-nitrophenyl)-1,2,3-triazole 2.123g

Yellow solid, 53% yield; m. p. 156 °C. ¹H NMR (400 MHz, DMSO) δ 12.49 (bs, 1H), 8.42 (d, *J* = 9.1 Hz, 2H), 8.13 (d, *J* = 9.1 Hz, 2H), 2.19 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 146.3, 141.3, 125.6, 125.2, 121.9, 120.6, 9.51. IR (KBr, cm⁻¹): 3350, 2350, 1517, 1330. HR-MS (ES+) calculated for C₉H₉N₄O₃ ([M+H]⁺): 221.0675; found: 221.0679.

5-Hydroxy-4-methyl-1-(4-methyl-2-nitrophenyl)-1,2,3-triazole 2.123h

Yellow solid, 56% yield; m. p. 112 °C. ¹H NMR (400 MHz, MeOD) δ 8.00 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 2.54 (s, 3H), 2.22 (s, 3H). ¹³C NMR (101 MHz, MeOD) δ 145.8, 143.4, 137.0, 135.7, 129.6, 126.7, 126.6, 123.9, 21.0, 8.4. IR (KBr, cm⁻¹): 3088, 2921, 1183, 759. HR-MS (ES+) calculated for C₁₀H₁₁N₄O₃ ([M+H]⁺): 235.0831; found: 235.0822.

5-Hydroxy-4-benzyl-1-phenyl-1,2,3-triazole 2.123n

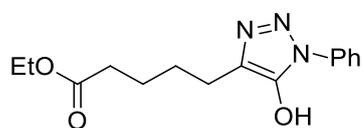
White solid, 75% yield; m. p. 146 °C. ¹H NMR (400 MHz, DMSO) δ 12.30 (bs, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.57 – 7.50 (m, 2H), 7.46 – 7.40 (m, 1H), 7.29 – 7.24 (m, 4H), 7.22 – 7.15 (m,

1H), 3.96 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 147.5, 140.2, 136.0, 129.3, 128.3, 128.2, 127.7, 126.2, 125.9, 122.0, 29.3. IR (KBr, cm^{-1}): 2783, 1596, 1493. HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}$ ($[\text{M}+\text{H}]^+$): 252.1137; found: 252.1130.

General procedure for the synthesis of long-chained 5-hydroxy-1,2,3-triazole esters 2.142a-c.

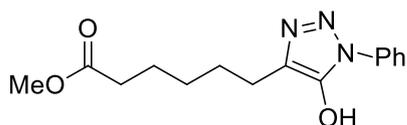
To a mixture of commercially available cyclic ketoester **2.138a-c** (2.4 mmol) and azidobenzene **2.32a** (2.0 mmol) DBU (2.4 mmol) was added. The reaction was stirred at 60 °C overnight. The crude mixture was purified by silica flash chromatography (AcOEt / petroleum ether 1 : 2 to 1 : 0) to afford 1,2,3-triazolo esters **2.142a-c** as solids.

Ethyl 5-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)pentanoic ester 2.142a

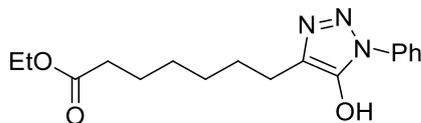


Off-white solid, 44% yield; m. p. 98 °C. ^1H NMR (400 MHz, CDCl_3) δ 13.01 (bs, 1H), 7.85 (d, $J = 7.7$ Hz, 2H), 7.45 (t, $J = 6.9$ Hz, 2H), 7.36 (t, $J = 7.4$ Hz, 1H), 4.06 (q, $J = 7.2$ Hz, 2H), 2.70 (t, $J = 7.1$ Hz, 2H), 2.24 (t, $J = 7.2$ Hz, 2H), 1.75 – 1.53 (m, 4H), 1.19 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 173.9, 152.0, 135.7, 129.1, 128.4, 123.3, 122.4, 60.4, 33.8, 27.8, 24.1, 22.4, 14.2. IR (KBr, cm^{-1}): 2507, 1734, 1604, 1570. HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 290.1505; found: 290.15019.

Methyl 6-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)hexanoic ester 2.142b



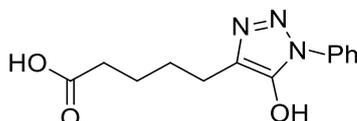
Off-white solid, 79% yield; m. p. 112 °C. ^1H NMR (400 MHz, CDCl_3) δ 10.61 (bs, 1H), 7.87 (d, $J = 7.7$ Hz, 2H), 7.49 – 7.40 (m, 2H), 7.38 – 7.33 (m, 1H), 3.61 (s, 3H), 2.65 (t, $J = 7.6$ Hz, 2H), 2.22 (t, $J = 7.4$ Hz, 2H), 1.69 – 1.61 (m, 2H), 1.60 – 1.51 (m, 2H), 1.34 – 1.24 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.5, 151.5, 136.0, 129.0, 128.2, 124.3, 122.2, 51.6, 33.8, 28.5, 28.2, 24.3, 22.7. IR (KBr, cm^{-1}): 2857, 2512, 1744, 1606. HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 290.1505; found: 290.1492.

Ethyl 7-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)heptanoic ester 2.142c

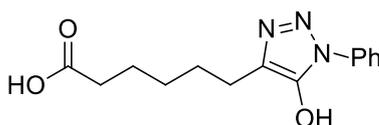
Off-white solid, 38% yield; m. p. 100 °C. ¹H NMR (400 MHz, CDCl₃) δ 13.43 (bs, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.50 – 7.42 (m, 2H), 7.40 – 7.32 (m, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.71 – 1.58 (m, 2H), 1.55 – 1.45 (m, 2H), 1.33 – 1.10 (m, 7H). ¹³C NMR (101 MHz, CDCl₃) δ 174.0, 151.9, 136.1, 129.0, 128.1, 124.1, 122.2, 60.3, 34.2, 28.8, 28.7, 28.5, 24.8, 23.0, 14.2. IR (KBr, cm⁻¹): 2869, 2524, 1732, 1599. HR-MS (ES+) calculated for C₁₇H₂₄N₃O₃ ([M+H]⁺): 318.1818; found: 318.1816.

General procedure for the synthesis of long-chained 5-hydroxy-1,2,3-triazolecarboxylic acids @a,b,c.

In a round bottom flask, a dispersion of 1,2,3-triazole ester **2.142a-c** (0.5 mmol) in water (5 ml) at 0 °C was added with KOH pellets (5.0 mmol). Upon complete dissolution of KOH and ester @ the ice bath was removed and the reaction was vigorously stirred for 2 h at room temperature. The reaction was again cooled down to 0 °C and 37% HCl was added dropwise until pH 1. The white solid was collected by vacuum filtration and dried under vacuum to afford 5-hydroxy-1,2,3-triazolecarboxylic acids **2.141a-c** in pure form.

5-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)pentanoic acid 2.141a

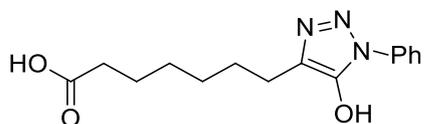
White solid, 60% yield; m. p. 122 °C. ¹H NMR (400 MHz, DMSO) δ 11.95 (bs, 1H), 11.38 (bs, 1H), 7.65 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.45 (m, 2H), 7.44 – 7.34 (m, 1H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.19 (t, *J* = 6.8 Hz, 2H), 1.65 – 1.42 (m, 4H). ¹³C NMR (101 MHz, DMSO) δ 174.5, 135.8, 129.4, 128.0, 122.2, 33.5, 28.4, 24.2, 23.1. IR (KBr, cm⁻¹): 3340, 2350, 1700, 1601, 1562. HR-MS (ES+) calculated for C₁₃H₁₆N₃O₃ ([M+H]⁺): 262.1192; found: 262.1184.

6-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)hexanoic acid 2.141b

White solid, 88% yield; m. p. 115 °C. ¹H NMR (400 MHz, DMSO) δ 11.80 (s, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.44 – 7.36 (m, 1H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.61 – 1.44 (m, 4H), 1.35 – 1.23 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 174.6, 135.9,

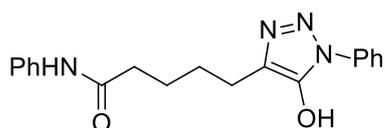
129.3, 127.9, 122.2, 33.7, 28.6, 28.3, 24.4, 23.2. IR (KBr, cm^{-1}): 3395, 2938, 1724, 1629, 1599. HR-MS (ES+) calculated for $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 276.1348; found: 276.1333.

7-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)heptanoic acid 2.141c



White solid, 81% yield; m. p. 117 °C. ^1H NMR (400 MHz, DMSO) δ 11.89 (bs, 2H), 7.71 (d, J = 7.7 Hz, 2H), 7.58 – 7.50 (m, 2H), 7.48 – 7.39 (m, 1H), 2.58 – 2.52 (m, 2H), 2.20 (t, J = 7.3 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.54 – 1.44 (m, 2H), 1.38 – 1.27 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.6, 135.8, 129.3, 128.0, 122.2, 33.7, 28.7, 28.5, 28.4, 24.5, 23.3. IR (KBr, cm^{-1}): 3223, 2948, 1717, 1599. HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 290.1505; found: 290.1518.

N-phenyl-5-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)pentanamide 2.140a



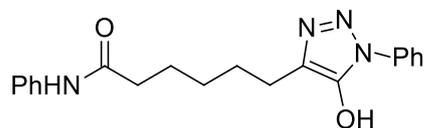
Carboxylic acid **2.141a** (0.49 mmol) was dissolved in 1 ml of thionyl chloride. The reaction was refluxed at 60 °C for 2 h. The reaction mixture was evaporated under vacuum in order to remove the excess of thionyl chloride. Crude acyl chloride was dissolved in dry DCM (1 ml) and added with aniline (49 μl , 0.54 mmol) and triethylamine (75 μl , 0.54 mmol). The reaction mixture was stirred under nitrogen overnight. The crude was diluted in AcOEt (20 ml), washed with saturated sodium bicarbonate (5 ml) and 1M HCl (5 ml). The organic phase was dried over sodium sulfate and evaporated under vacuum. Crude amide was purified by flash column chromatography (AcOEt / petroleum ether 1 : 1 to 1 : 0) to yield title compound **2.140a** in 61% yield as a white solid. m. p. 152 °C. ^1H NMR (400 MHz, DMSO) δ 9.80 (s, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.64 – 7.51 (m, 4H), 7.48 – 7.39 (m, 1H), 7.32 – 7.23 (m, 2H), 7.06 – 6.97 (m, 1H), 2.67 – 2.58 (m, 2H), 2.42 – 2.31 (m, 2H), 1.75 – 1.60 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 171.26, 139.38, 135.82, 129.34, 128.67, 127.97, 122.96, 122.23, 119.05, 36.35, 28.58, 24.94, 23.21. IR (KBr, cm^{-1}): 2372, 1649, 1590. HR-MS (ES+) calculated for $\text{C}_{19}\text{H}_{21}\text{N}_4\text{O}_2$ ($[\text{M}+\text{H}]^+$): 337.1665; found: 337.1676.

General procedure for the synthesis of long-chained N-phenyl-5-hydroxy-1,2,3-triazoleamides 2.140b,c.

In a round bottom flask, a solution of carboxylic acid **2.141b,c** (0.40 mmol) in dry DCM (2 ml) was added with TEA (67 μl , 0.48 mmol) and aniline (44 μl , 0.48 mmol). The solution was added with carbonyldiimidazole (CDI, 78 mg, 0.48 mmol) and stirred overnight at room

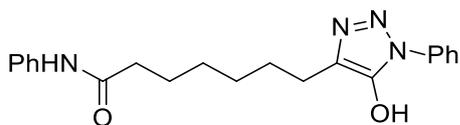
temperature. The crude mixture was diluted with AcOEt (20 ml), washed with 0.5M HCl (5 ml), dried over sodium sulfate and evaporated under vacuum. Crude amide was purified by flash column chromatography (AcOEt / petroleum ether 1 : 1 to 1 : 0) to yield title compounds **2.140b,c** as white solids.

N-phenyl-6-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)hexanamide 2.140b



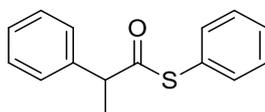
White solid, 35% yield; m. p. 148 °C. ¹H NMR (400 MHz, DMSO) δ 11.36 (bs, 1H), 9.86 (s, 1H), 7.71 (d, *J* = 6.7 Hz, 2H), 7.62 – 7.50 (m, 4H), 7.48 – 7.40 (m, 1H), 7.32 – 7.22 (m, 2H), 7.05 – 6.96 (m, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.55 (m, 4H), 1.45 – 1.33 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 171.27, 139.37, 135.83, 129.32, 128.66, 127.93, 122.92, 122.20, 119.02, 36.40, 28.67, 28.38, 24.99, 23.23. IR (KBr, cm⁻¹): 2387, 1654, 1599. HR-MS (ES⁺) calculated for C₂₀H₂₃N₄O₂ ([M+H]⁺): 351.1821; found: 351.1815.

N-phenyl-7-(5-hydroxy-1-phenyl-1,2,3-triazol-4-yl)heptanamide 2.140c



White solid, 48% yield; m. p. 142 °C. ¹H NMR (400 MHz, DMSO) δ 9.87 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.49 (m, 4H), 7.48 – 7.40 (m, 1H), 7.31 – 7.21 (m, 2H), 7.05 – 6.96 (m, 1H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.66 – 1.55 (m, 4H), 1.41 – 1.29 (m, 4H). ¹³C NMR (101 MHz, DMSO) δ 171.27, 139.38, 135.82, 129.33, 128.65, 127.94, 122.91, 122.20, 119.02, 36.43, 28.73, 28.5 (2C), 25.15, 23.30. IR (KBr, cm⁻¹): 2367, 1658, 1535. HR-MS (ES⁺) calculated for C₂₁H₂₅N₄O₂ ([M+H]⁺): 365.1978; found: 365.1991.

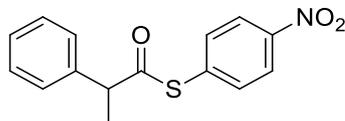
S-phenyl-2-phenylpropionic thioester 2.96b



In a round bottom flask, a solution of DCC (1.54 g, 7.5 mmol) in dry DCM (3 ml) was added with a solution of 2-phenylpropanoic acid (1.0 ml, 6.8 mmol) in dry DCM (3 ml). After 15 min thiophenol (0.70 ml, 6.8 mmol) was added dropwise and the reaction was stirred overnight. The white precipitate was filtered off by vacuum filtration and washed with DCM (10 ml). The filtrate was washed with water (5 ml) and the water phase was extracted with DCM (2 x 10 ml). The DCM solution was dried over sodium sulfate and evaporated under vacuum to yield thioester **2.96b** as a viscous colorless oil (1.60 g, 97% yield). ¹H NMR (400 MHz, CDCl₃) δ

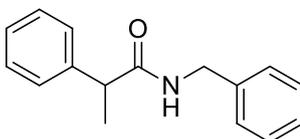
7.49 – 7.23 (m, 10H), 4.01 (q, $J = 7.1$ Hz, 1H), 1.58 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 199.0, 139.6, 134.5, 129.3, 129.1, 128.8, 128.0, 127.9, 127.6, 54.1, 18.7.

S-(4-nitrophenyl) 2-phenylpropionic thioester **2.96c**



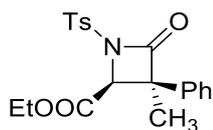
In a round bottom flask, a solution of DCC (877 mg, 4.2 mmol) in dry DCM (2 ml) was added with a solution of 2-phenylpropanoic acid (581 mg, 3.9 mmol) in dry DCM (2 ml). After 15 min 4-nitrothiophenol (600 mg, 3.9 mmol) was added dropwise and the reaction was stirred overnight. The white precipitate was filtered off by vacuum filtration and washed with DCM (10 ml). The filtrate was washed with water (5 ml) and the water phase was extracted with DCM (2 x 10 ml). The DCM solution was dried over sodium sulfate and evaporated under vacuum. Crude thioester **2.96c** was purified by flash chromatography (Et_2O / petroleum ether 1 : 20) to yield 570 mg of white solid (51% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 8.9$ Hz, 2H), 7.53 (d, $J = 8.9$ Hz, 2H), 7.42 – 7.30 (m, 5H), 4.02 (q, $J = 7.1$ Hz, 1H), 1.61 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.1, 148.2, 138.9, 136.8, 134.8, 129.1, 128.2, 128.1, 124.0, 54.8, 18.5.

N-benzyl-2-phenylpropionamide **2.103**

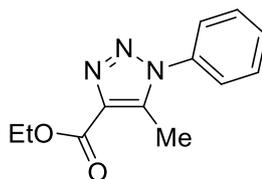


In a round bottom flask under nitrogen, a solution in dry AcOEt (4 ml) of S-(4-nitrophenyl)-2-phenylpropionic thioester **2.96c** (97 mg, 0.40 mmol) and 4-chloro-azidobenzene **2.32c** (56 mg, 0.36 mmol) was added with DBU (6 mg, 0.04 mmol) at room temperature. After 30 min, the spot of thioester @ disappeared from the TLC (AcOEt / petroleum ether 1 : 4) and 44 μl of benzylamine (0.40 mmol) were added with a syringe. After 18 h the crude mixture was washed with 1M HCl and the aqueous phase was extracted with AcOEt (2 x 10 ml). Crude was evaporated and purified by flash column chromatography (AcOEt/PE 1 : 20) to afford 82 mg of title compound **2.103** as of white solid (86% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.18 (m, 8H), 7.13 (d, $J = 6.9$ Hz, 2H), 5.67 (s, 1H), 4.48 – 4.28 (m, 2H), 3.59 (q, $J = 7.2$ Hz, 1H), 1.55 (d, $J = 7.2$ Hz, 3H). Physical and spectral data in accordance with the literature.⁶

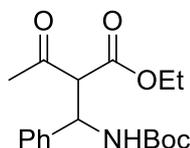
⁶ M. Terada, K. Sorimachi and D. Uruguchi, *Synlett*, 2006, **2006**, 133–136.

cis-1-*p*-Toluenesulfonyl-3-methyl-3-phenyl-4-ethoxycarbonylazetidinone lactam 2.105

To a solution of *S*-(4-nitrophenyl)-2-phenylpropionic thioester **2.96c** (23 mg, 0.09 mmol) and *O*-benzylquinine (4 mg, 0.01 mmol) in DCM_{dry} (0.5 ml) at -78 °C was added a solution of DBU (15 mg, 0.10 mmol, 0.5 ml DCM_{dry}), followed by the addition of a solution of ethyl *N*-iminoglyoxylate **2.104** (28 mg, 0.11 mmol, 0.5 ml DCM_{dry}). The reaction was slowly warmed up to room temperature overnight. The crude was purified by silica flash chromatography (AcOEt / petroleum ether 1 : 4), yielding 10 mg of white solid, which was mainly composed of compound **2.105**. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.28 (m, 5H), 4.57 (s, 1H), 3.81 – 3.70 (m, 1H), 2.47 (s, 3H), 1.79 (s, 3H), 0.78 (t, *J* = 7.2 Hz, 3H). Spectral data in accordance with the literature.⁷

Ethyl 5-methyl-1-phenyl-1,2,3-triazole 4-carboxylate 2.113

To a solution of azidobenzene **2.32a** (125 mg, 1.05 mmol) and ethyl acetoacetate **2.109** (163 mg, 1.26 mmol) in DMSO (2 ml) was added DBU (31 mg, 0.21 mmol). The reaction was stirred overnight at room temperature. The evaporation of the solvent afforded 208 mg of title compound **2.113** in 90% purity as a white solid (86% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.53 (m, 3H), 7.48 – 7.42 (m, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 2.60 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). Experimental data in accordance with the literature.⁸

Synthesis of ketoester 2.144b via 5-hydroxytriazole-catalysed Mannich-type reaction

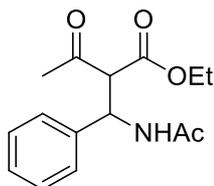
To a solution of ethyl acetoacetate **2.109** (11 mg, 0.09 mmol) and 1-(4-nitrophenyl)4-methyl-5-hydroxy-1,2,3-triazole **2.123b** (2 mg, 0.01 mmol) in DCM (1 ml) was added *N*-Boc-benzaldimine **2.143** (20 mg, 0.1 mmol) at room temperature. The reaction was stirred

⁷ A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury and T. Lectka, *J. Am. Chem. Soc.*, 2000, **122**, 7831–7832.

⁸ L. J. T. Danence, Y. Gao, M. Li, Y. Huang and J. Wang, *Chem. – A Eur. J.*, 2011, **17**, 3584–3587.

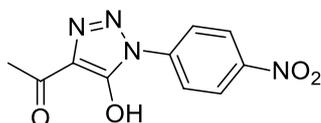
overnight, then the solvent was evaporated under vacuum. The crude mixture was purified by silica flash chromatography affording 14 mg of **2.144b** as a 50 : 50 mixture of diastereoisomers. 47% yield. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.41 – 7.22 (m, 5H), 6.26 – 6.13 (m, 1H), 5.83 (s, 0.5H), 5.56 (s, 0.5H), 5.50 – 5.33 (m, 1H), 4.19 – 4.03 (m, 2H), 2.33 (s, 1.5H), 2.17 (s, 1.5H), 1.53 - 1.31 (m, 15H), 1.25 (s, 3H), 1.18 (t, $J = 7.2$ Hz, 1.5H), 1.12 (t, $J = 7.1$ Hz, 1.5H). Physical and spectral data in accordance with the literature.⁹

Ethyl 2-(N-acyl-aminobenzyl)acetoacetate **2.148**



Following literature procedure,¹⁰ compound **2.148** was obtained in 17% yield as a white solid (0.9 : 1 diastereoisomeric mixture). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.43 – 7.20 (m, 6H), 7.04 (d, $J = 9.1$ Hz, 0.9H), 5.91 (dd, $J = 9.5, 4.2$ Hz, 0.45H), 5.76 (dd, $J = 9.2, 6.1$ Hz, 0.5H), 4.21 – 4.03 (m, 3H), 2.35 (s, 2.7H), 2.16 (s, 3H), 2.04 (s, 2.7H), 1.99 (s, 3H), 1.20 (t, $J = 6.4$ Hz, 3H), 1.14 (t, $J = 7.1$ Hz, 2.7H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 204.0, 201.5, 169.7, 169.5, 169.1, 167.3, 139.2, 134.0, 128.7, 128.7, 127.8, 127.7, 126.5, 126.1, 63.6, 62.8, 62.0, 61.6, 52.3, 50.8, 30.7, 28.9, 23.3, 13.9, 13.9.

5-hydroxy-4-acyl-1-phenyl-1,2,3-triazole **2.151b**



To a solution of aminoketoester **2.148** (322 mg, 1.2 mmol) and 4-nitroazidobenzene **2.32b** (173 mg, 1.0 mmol) in DMSO (0.5 ml) was added DBU (176 mg, 1.2 mmol). The reaction was stirred at 50 °C for 5 h. The crude mixture was diluted with methanol (5 ml) and acidified with 37% HCl. The solvent was evaporated under vacuum. Trituration with 2 ml of DCM afforded compound **2.151b** as a white solid (205 mg, 79% yield). $^1\text{H NMR}$ (400 MHz, DMSO) δ 10.66 (s, 1H), 8.24 (d, $J = 9.1$ Hz, 2H), 7.87 (d, $J = 9.1$ Hz, 2H), 2.44 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, DMSO) δ 191.5, 159.9, 144.3, 143.2, 125.6, 120.0 (2C), 27.5. Physical and spectral data in accordance with the literature.¹¹

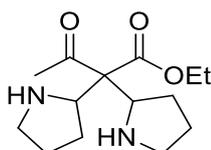
⁹ M. Hatano, T. Horibe and K. Ishihara, *J. Am. Chem. Soc.*, 2010, **132**, 56–57.

¹⁰ B. Das, K. R. Reddy, Y. Srinivas and R. A. Kumar, *Can. J. Chem.*, 2007, **85**, 479–482.

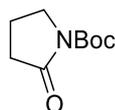
¹¹ R. A. Franich, G. Lowe and J. Parker, *J. Chem. Soc. Perkin Trans. 1*, 1972, **0**, 2034.

Δ^1 -pyrroline 2.154

Compound **2.154** was prepared according to published procedures (58% yield).¹² ¹H NMR (400 MHz, CDCl₃) δ 7.61 (s, 1H), 3.90 – 3.77 (m, 2H), 2.58 – 2.48 (m, 2H), 1.84 – 1.72 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 167.00, 61.25, 36.64, 20.50.

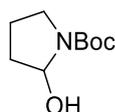
Ethyl 2,2-di-(2-pyrrolidino)acetoacetate 2.157

A solution of ethyl acetoacetate **2.109** (562 mg, 3.4 mmol) and *p*-toluenesulfonic acid (64 mg, 0.34 mmol) in toluene (3.5 ml) was added dropwise with Δ^1 -pyrroline **2.154** (355 mg, 5.1 mmol) at room temperature. The reaction was stirred overnight at room temperature. The solvent was evaporated under vacuum. The reaction crude was purified by flash column chromatography yielding 115 mg of **2.157** as a white solid (17% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.29 (t, *J* = 7.1 Hz, 1H), 4.21 – 4.00 (m, 2H), 3.92 (t, *J* = 5.9 Hz, 1H), 3.61 – 3.43 (m, 2H), 2.72 – 2.59 (m, 2H), 2.37 (s, 3H), 2.36 – 2.24 (m, 1H), 2.18 – 2.08 (m, 1H), 2.04 – 1.94 (m, 1H), 1.91 – 1.75 (m, 4H), 1.70 – 1.59 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 168.1, 153.6, 96.6, 74.6, 60.9, 58.3, 47.2, 45.1, 31.8, 29.8, 22.6, 22.5, 17.4, 14.6.

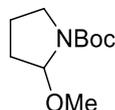
***N*-Boc-pyrrolidin-2-one 2.165**

A solution of pyrrolidin-2-one (2.8 g, 33 mmol), TEA (5.6 ml, 40 mmol) and *N,N*-dimethylaminopyridine (403 mg, 3.3 mmol) in DCM_{dry} (70 ml) was added at room temperature with Boc-anhydride (8.7 g, 40 mmol). The reaction was stirred overnight, then the organic solution washed with saturated sodium bicarbonate (20 ml), 0.1 M HCl solution (20 ml), water (10 ml) and of brine (10 ml). The organic phase was dried over sodium sulfate and evaporated under vacuum, to afford 4.73 g of pure **2.165** as a solid (77% yield). ¹H NMR (400 MHz, CDCl₃) δ 3.79 – 3.71 (m, 2H), 2.52 (t, *J* = 8.1 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.53 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 174.35, 150.24, 82.77, 46.48, 32.97, 28.03, 17.41.

¹² W. Xiao, C. Hu and M. D. Ward, *Cryst. Growth Des.*, 2013, **13**, 3197–3200.

N-Boc-pyrrolidin-2-ol 2.166

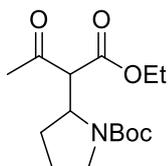
Following Gawley's procedure,¹³ compound **2.166** was obtained by dropwise addition of diisobutylaluminium hydride (22 ml, 22 mmol) to a solution of *N*-Boc-pyrrolidin-2-one **2.165** (2.0 g, 11 mmol) in THF_{dry} (25 ml) at -78 °C, under inert atmosphere. The reaction was stirred at -78 °C for 1 h, then it was let to warm up to room temperature over 1 h. 5 ml of saturated potassium acetate were added, and the reaction was stirred for 10 min. The resulting colloidal mixture was diluted with 10 ml of water and 10 ml of 15% NaOH. The mixture was filtered through a pad of celite. The filtration cake was rinsed with diethyl ether 20 ml. The biphasic filtrate was separated and the organic phase was washed with water (10 ml) and brine (10 ml). The organic phase was dried over sodium sulfate and evaporated under vacuum. Crude **2.166** was purified by silica flash chromatography (AcOEt / petroleum ether 1 : 2) to yield 1.85 g of pure **2.166** (90 % yield) as a 6 : 4 mixture of rotamers. ¹H NMR (400 MHz, CDCl₃) δ 5.50 – 5.44 (m, 0.6H), 5.39 (s, 0.4H), 3.66 (s, 0.6H), 3.57 – 3.45 (m, 1H), 3.35 – 3.20 (m, 1H), 2.88 (s, 0.4H), 2.10 – 1.71 (m, 4H), 1.50 (s, *J* = 10.8 Hz, 3.6H), 1.47 (s, 5.4H). ¹³C NMR (101 MHz, CDCl₃) δ 155.1, 81.8, 81.5, 80.0, 68.0, 45.9, 45.8, 33.5, 32.6, 28.6, 28.5, 25.6, 22.7, 22.1.

N-Boc-2-methoxy-pyrrolidine 2.167

Following Somfai's procedure,¹⁴ a mixture of hydroxypyrroline **2.166** (1.64 g, 8.76 mmol), MeOH (15 ml) and methyl orthoformate (6 ml) was added with 226 mg of pyridinium *p*-toluenesulfonate (0.90 mmol). The reaction was stirred at room temperature overnight and then added with solid sodium carbonate (1 g). The mixture was partitioned between diethyl ether (30 ml) and water (20 ml) and the phases were separated. The aqueous phase was extracted with diethyl ether (20 ml), the combined organic phases were dried over sodium sulfate and pure **2.167** was obtained by evaporation of the solvent (1.42 g, clear oil, 81% yield, 1 : 1 mixture of rotamers). ¹H NMR (400 MHz, CDCl₃) δ 5.17 (bs, 0.5H), 5.06 (bs, 0.5H), 3.49 – 3.17 (m, 5H), 2.04 (bs, 1H), 1.96 – 1.84 (m, 2H), 1.83 – 1.67 (m, 1H), 1.48 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 154.5, 88.6, 88.6, 80.9, 80.0, 79.6, 55.8, 55.5, 46.0, 45.4, 32.8, 31.9, 28.4, 22.7, 21.8.

¹³ R. E. Gawley, G. Barolli, S. Madan, M. Saverin and S. O'Connor, *Tetrahedron Lett.*, 2004, **45**, 1759–1761.

¹⁴ J. Åhman and P. Somfai, *Tetrahedron*, 1992, **48**, 9537–9544.

Ethyl 2-(*N*-Boc-2-pyrrolidino)acetoacetate **2.149**

Following Pilli's procedure,¹⁵ a mixture of ethyl acetoacetate (148 mg, 0.90 mmol) and *N*-Boc-2-methoxy-pyrrolidine **2.167** (61 mg, 0.30 mmol) was added with solid indium(III) chloride (7 mg, 0.03 mmol). The reaction was stirred overnight at room temperature. The crude mixture was purified *via* silica flash chromatography (diethyl ether / petroleum ether 1 : 4), yielding 86 mg of **2.149** as a white solid (96% yield, 1 : 2 mixture of diastereomers). ¹H NMR (400 MHz, CDCl₃) δ 4.47 – 4.09 (m, 4H), 3.61 – 3.33 (m, 1H), 3.32 – 3.19 (m, 1H), 2.24 (s, 3H), 2.19 – 1.86 (m, 2H), 1.85 – 1.72 (m, 2H), 1.46 (s, *J* = 9.7 Hz, 9H), 1.33 – 1.20 (m, 3H).

¹⁵ L. A. F. de Godoy, N. S. Camilo and R. A. Pilli, *Tetrahedron Lett.*, 2006, **47**, 7853–7856.

Experimental Section Chapter 3

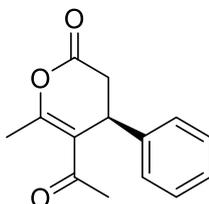
General procedure A for the stereoselective synthesis of 3,4-dihydropyran-2-ones 3.106a-n

In a 10 ml test tube *N*-benzylquininium bromide (0.02 mmol), K_2CO_3 (0.20 mmol) and phenol (0.02 mmol) were dissolved in dry DCM (1.8 ml). The resulting purple reaction mixture was stirred for 30 min at 0 °C. Thiocinnamate **3.104a-I** (0.20 mmol) and acetylacetone (41 μ l, 0.40 mmol) were added and the reaction was allowed to warm up to room temperature and stirred for 48 h under nitrogen. The solvent was evaporated *in vacuo* and the crude was purified by silica flash chromatography (AcOEt : petroleum ether, 1 : 5). Pure **3.106a-n** were obtained as solid materials.

General procedure B for the synthesis of racemic 3,4-dihydropyran-2-ones 3.106a-n

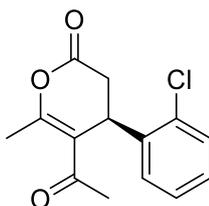
In a 10 ml test tube cinnamic thioester **3.104a-I** (0.20 mmol), TBAB (0.02 mmol), K_2CO_3 (0.20 mmol) and phenol (0.02 mmol) were dissolved in dry DCM (1.8 ml). Acetylacetone (0.40 mmol) was added and the reaction mixture was stirred for 24 h under nitrogen. After evaporation of the solvent, crude mixture was purified by silica flash chromatography (AcOEt : petroleum ether, 1 : 5). Pure **3.106a-n** were obtained as solid materials.

(*S*)-5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyran-2-one 3.106a

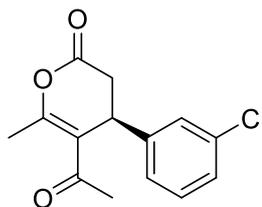


White solid, m.p. 69-71 °C, 82% yield (general procedure A), 44% yield (general procedure B). 1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 3H), 7.18 – 7.12 (m, 2H), 4.18 – 4.13 (m, 1H), 2.98 (dd, $J = 15.7, 7.2$ Hz, 1H), 2.84 (dd, $J = 15.7, 2.6$ Hz, 1H), 2.43 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 165.7, 160.4, 129.5, 127.6, 126.7, 117.3, 38.9, 38.8, 37.2, 29.6, 19.1. FTIR (cm^{-1}): 3024, 2924, 1774, 1689, 1627, 1489, 1442, 1357, 1026, 948, 864. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min, 76% ee); retention time = 12.84 min, 14.91 min. Physical and spectral data in accordance with the literature.¹⁶

¹⁶ Wu, X., Zhang, Y., Wang, Y., Ke, J., Jeret, M., Reddi, R. N., ... & Chi, Y. R., *Angewandte Chemie* **2017**, 129(11), 2988-2992.

(R)-5-Acetyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyran-2-one 3.106b

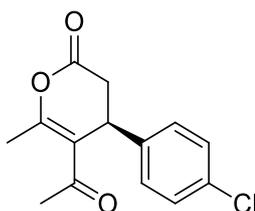
Yellow wax, 72% yield (general procedure A), 78% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.45 – 7.43 (m, 1H), 7.26 – 7.21 (m, $J = 6.4, 2.5$ Hz, 2H), 7.06 – 7.02 (m, 1H), 4.64 (dd, $J = 6.7, 2.0$ Hz, 1H), 2.96 (dd, $J = 15.8, 6.7$ Hz, 1H), 2.90 (dd, $J = 15.8, 2.0$ Hz, 1H), 2.47 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.6, 165.3, 161.6, 136.3, 133.1, 130.6, 129.5, 127.9, 127.4, 116.0, 35.6, 34.9, 29.3, 19.1. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min 88% ee); retention time = 21.31 min, 22.96 min. Physical and spectral data in accordance with the literature.¹⁷

(S)-5-Acetyl-4-(3-chlorophenyl)-6-methyl-3,4-dihydropyran-2-one 3.106c

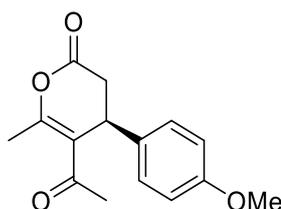
Orange wax, 72% yield (general procedure A), 50% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.26 (m, 2H), 7.14 (s, 1H), 7.06 – 7.01 (m, 1H), 4.18 – 4.13 (m, 1H), 2.97 (dd, $J = 15.7, 7.3$ Hz, 1H), 2.83 (dd, $J = 15.7, 2.5$ Hz, 1H), 2.45 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.3, 165.2, 160.9, 141.8, 135.3, 130.8, 128.3, 127.0, 124.8, 116.9, 38.4, 36.9, 30.0, 19.3. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min, 57% ee); retention time = 13.21 min, 14.43 min. Physical and spectral data in accordance with the literature.¹⁸

¹⁷ Yetra, S. R., Bhunia, A., Patra, A., Mane, M. V., Vanka, K., & Biju, A. T. *Advanced Synthesis & Catalysis* **2013**, 355(6), 1089-1097.

¹⁸ Sun, F. G., Sun, L. H., & Ye, S. *Advanced Synthesis & Catalysis* **2011**, 353(17), 3134-3138.

(S)-5-Acetyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyran-2-one 3.106d

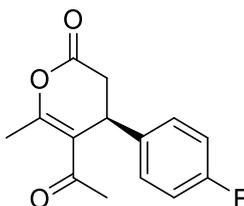
Yellow wax, 72% yield (general procedure A), 67% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.29 (m, 2H), 7.12 – 7.06 (m, 2H), 4.17 – 4.12 (m, 1H), 2.96 (dd, J = 15.7, 7.2 Hz, 1H), 2.81 (dd, J = 15.7, 2.5 Hz, 1H), 2.43 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.5, 165.3, 160.7, 138.3, 133.9, 129.6, 128.1, 117.2, 38.2, 37.0, 31.6, 29.9, 29.7, 22.7, 19.2, 14.1. Chiral HPLC (Chiralpak OD, n-hexane/ethanol 95 : 5, 1 ml/min 82% ee); retention time = 17.74 min, 22.51 min. Physical and spectral data in accordance with the literature.¹⁹

(S)-5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyran-2-one 3.106e

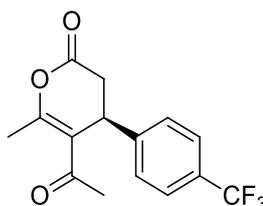
Yellow wax, 17% yield (general procedure A), 44% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.02 – 6.96 (m, 2H), 6.82 – 6.76 (m, 2H), 4.05 – 4.01 (m, 1H), 2.87 (dd, J = 15.6, 7.1 Hz, 1H), 2.74 (dd, J = 15.6, 2.6 Hz, 1H), 2.35 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 202.8, 175.6, 158.8, 131.3, 129.1, 127.8, 114.8, 114.2, 55.2, 40.5, 38.9, 29.9, 19.1. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min, 5% ee); retention time = 20.75 min, 32.00 min. Physical and spectral data in accordance with the literature.²⁰

¹⁹ Yetra, S. R., Bhunia, A., Patra, A., Mane, M. V., Vanka, K., & Biju, A. T. *Advanced Synthesis & Catalysis* **2013**, 355(6), 1089-1097

²⁰ De Sarkar, S., & Studer, A., *Angewandte Chemie International Edition* **2010**, 49(48), 9266-9269.

(S)-5-Acetyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyran-2-one 3.106f

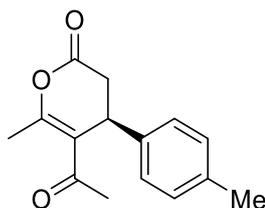
Yellow solid, 93% yield (general procedure A), 66% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.15 – 7.08 (m, 2H), 7.07 – 6.97 (m, 2H), 4.19 – 4.14 (m, 1H), 2.96 (dd, $J = 15.7, 7.2$ Hz, 1H), 2.81 (dd, $J = 15.7, 2.5$ Hz, 1H), 2.43 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.6, 165.5, 163.5, 162.3 (d, $J = 247.0$ Hz), 135.5, 135.4, 128.4 (d, $J = 8.2$ Hz), 117.4, 116.4 (d, $J = 21.6$ Hz), 38.1, 37.2, 37.2, 29.9, 19.2. ^{19}F NMR (376 MHz, CDCl_3) δ -114.37. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min, 80% ee); retention time = 14.92 min, 19.55 min. Physical and spectral data in accordance with the literature.²¹

(S)-5-Acetyl-6-methyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydropyran-2-one 3.106g

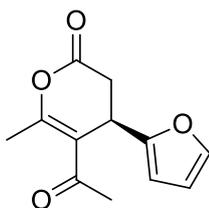
Orange solid, 93% yield (general procedure A), 75% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, $J = 8.1$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 4.28 – 4.24 (m, 1H), 3.00 (dd, $J = 15.8, 7.3$ Hz, 1H), 2.84 (dd, $J = 15.8, 2.3$ Hz, 1H), 2.46 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.1, 165.1, 161.0, 143.9, 130.3 (q, $J = 32.6$ Hz), 127.9, 127.2, 126.5 (q, $J = 3.7$ Hz), 124.5 (q, $J = 273.7$ Hz), 117.1, 125.2, 122.5, 119.8, 38.5, 36.7, 30.0, 19.3. ^{19}F NMR (376 MHz, CDCl_3) δ -62.66. FTIR (cm^{-1}): 2922, 2853, 1323, 1108, 1067, 838. HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$): 299.0895; found: 299.0888. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min, 83% ee); retention time = 12.48 min, 19.02 min. Physical and spectral data in accordance with the literature.²²

²¹ Yetra, S. R., Bhunia, A., Patra, A., Mane, M. V., Vanka, K., & Biju, A. T., *Advanced Synthesis & Catalysis* **2013**, 355(6), 1089-1097.

²² J. Mo, L. Shen and Y. R. Chi, *Angew. Chemie - Int. Ed.*, 2013, **52**, 8588–8591.

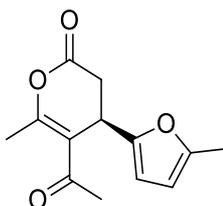
(S)-5-Acetyl-6-methyl-4-(4-tolyl)-3,4-dihydropyran-2-one 3.106h

Orange wax, 75% yield (general procedure A), 50% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.16 – 7.11 (m, 2H), 7.06 – 6.99 (m, 2H), 4.12 – 4.08 (m, 1H), 2.95 (dd, J = 15.6, 7.1 Hz, 1H), 2.81 (dd, J = 15.6, 2.7 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 198.1, 165.8, 160.2, 137.7, 136.6, 130.1, 126.6, 117.4, 38.5, 37.3, 29.7, 21.0, 19.1; FTIR (cm^{-1}): 2923, 1772, 1694, 1662, 1597, 1417, 1109, 1018, 819. HR-MS (ES+) calculated for $\text{C}_{15}\text{H}_{17}\text{O}_3$ ($[\text{M}+\text{H}]^+$): 245.1177; found: 245.1120. Chiral HPLC (Chiralpak AD, *n*-hexane/ethanol 95 : 5, 1 ml/min, 78% ee); retention time = 10.86 min, 14.05 min. Physical and spectral data in accordance with the literature.²²

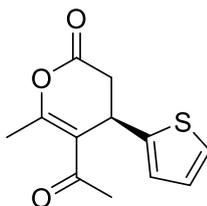
(R)-5-Acetyl-4-(furan-2-yl)-6-methyl-3,4-dihydropyran-2-one 3.106j

Orange solid, 60% yield (general procedure A), 75% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.31 (m, 1H), 6.29 – 6.25 (m, 1H), 6.08 (d, J = 3.3 Hz, 1H), 4.27 – 4.25 (m, 1H), 3.04 (dd, J = 15.9, 2.1 Hz, 1H), 2.84 (dd, J = 15.9, 6.8 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.1, 165.5, 161.0, 152.5, 142.8, 115.7, 110.4, 106.6, 33.8, 32.3, 29.8, 19.4; FTIR (cm^{-1}): 2922, 1782, 1689, 1606, 1145, 1114, 1012, 942, 740. HR-MS (ES+) calculated for $\text{C}_{12}\text{H}_{13}\text{O}_4$ ($[\text{M}+\text{H}]^+$): 221.0814; found: 221.0809. Chiral HPLC (Chiralpak OD, *n*-hexane/ethanol 95 : 5, 1 ml/min, 76% ee); retention time = 15.76 min, 19.45 min. Physical and spectral data in accordance with the literature.²³

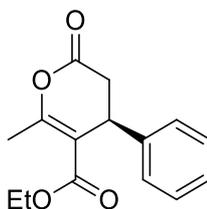
²³ D. Xie, D. Shen, Q. Chen, J. Zhou, X. Zeng and G. Zhong, *J. Org. Chem.*, 2016, **81**, 6136–6141.

(R)-5-Acetyl-6-methyl-4-(5-methylfuran-2-yl)-3,4-dihydropyran-2-one 3.106k

Orange wax, 55% yield (general procedure A), 15% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 5.94 (d, $J = 3.0$ Hz, 1H), 5.84 (d, $J = 3.0$ Hz, 1H), 4.18 (d, $J = 6.4$ Hz, 1H), 3.04 (dd, $J = 15.8, 2.1$ Hz, 1H), 2.82 (dd, $J = 15.8, 6.4$ Hz, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.1, 165.5, 161.0, 152.5, 142.8, 115.7, 110.4, 106.6, 33.8, 32.3, 29.8, 19.4. FTIR (cm^{-1}): 2922, 1782, 1689, 1606, 1145, 1114, 1012, 942, 740. HR-MS (ES+) calculated for $\text{C}_{13}\text{H}_{15}\text{O}_4$ ($[\text{M}+\text{H}]^+$): 235.0970; found: 235.0977. Chiral HPLC (Chiralpak OD, n-hexane/ethanol 95 : 5, 1 ml/min, 77% ee); retention time = 11.82 min, 15.12 min.

(R)-5-Acetyl-6-methyl-4-(thiophen-2-yl)-3,4-dihydropyran-2-one 3.106l

Yellow solid, 80% yield (general procedure A), 35% yield (general procedure B). ^1H NMR (400 MHz, CDCl_3) δ 7.21 (dd, $J = 5.1, 1.1$ Hz, 1H), 6.93 (dd, $J = 5.1, 3.6$ Hz, 1H), 6.84 (d, $J = 3.6$ Hz, 1H), 4.45 (dd, $J = 6.1, 2.9$ Hz, 1H), 3.00 (dd, $J = 15.8, 2.9$ Hz, 1H), 2.95 (dd, $J = 15.8, 6.1$ Hz, 1H), 2.41 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 197.2, 165.4, 160.8, 143.1, 127.5, 125.2, 124.8, 118.1, 37.4, 33.8, 29.8, 19.4. Chiral HPLC (Chiralpak AD, n-hexane/ethanol 95 : 5, 1 ml/min, 88% ee); retention time = 17.72 min, 28.45 min. Physical and spectral data in accordance with the literature.²⁴

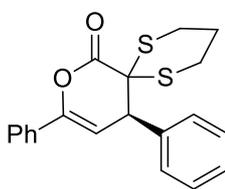
Ethyl 6-methyl-4-phenyl-3,4-dihydropyran-2-one-5-carboxylate 3.106n

In a 10 ml test tube *N*-benzylquininium bromide (10 mg, 0.02 mmol), K_3PO_4 (0.22 mmol) and phenol (2 mg 0.02 mmol) were dissolved in dry DCM (2.0 ml). The resulting purple reaction

²⁴ Wang, X. N., Winston-McPherson, G. N., Walton, M. C., Zhang, Y., Hsung, R. P., & DeKorver, K. A., *The Journal of organic chemistry* **2013**, 78(12), 6233-6244.

mixture was stirred for 30 min at 0 °C. Phenyl thiocinnamate **3.104a** (48 mg, 0.20 mmol) and ethyl acetoacetate (53 μ l, 0.60 mmol) were added and the reaction was allowed to warm up to room temperature and stirred for 48 h under nitrogen. The solvent was evaporated *in vacuo* and the crude was purified by silica flash chromatography (Et₂O : petroleum ether, 1 : 15) to afford 11 mg of **3.106n** as a white solid material (21% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.20 (m, 3H), 7.19 – 7.10 (m, 2H), 4.29 – 4.22 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.95 (dd, *J* = 15.9, 7.6 Hz, 1H), 2.83 (dd, *J* = 15.9, 2.3 Hz, 1H), 2.48 (d, *J* = 0.9 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.1, 166.0, 161.3, 140.7, 129.0, 127.5, 126.6, 110.0, 60.9, 37.9, 36.4, 18.9, 14.1. Chiral HPLC (Chiralcel OD, n-hexane/*i*-propanol 90 : 10, 1 ml/min, 75% ee (*S*)-enantiomer); retention time = 7.83 min, 14.69 min. $[\alpha]_D^{25} = +91^\circ$ (c = 0.6, CHCl₃). Physical and spectral data in accordance with the literature.²⁵

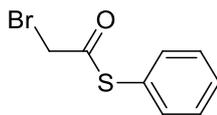
4,6-Diphenyl-2-(1,3-dithiano)-3,4-dihydropyran-2-one **3.93**



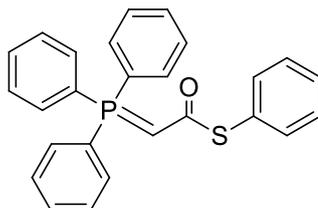
In a 10 ml test tube, a solution of 1,3-dithiane-thioester **3.86** (34 mg, 0.13 mmol) in DCM (1.5 ml) was added with *N*-benzylcinchonidinium bromide (6 mg, 0.01 mmol), K₃PO₄ (28 mg, 0.13 mmol) and chalcone (30 mg, 0.14 mmol). The mixture was stirred for 18 h. After evaporation of the solvent, crude was purified by silica flash chromatography (Et₂O : petroleum ether, 1 : 30) to afford pure **3.93** as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.35 – 7.29 (m, 3H), 7.27 – 7.22 (m, 3H), 7.20 – 7.15 (m, 2H), 5.87 (d, *J* = 6.4 Hz, 1H), 3.88 (d, *J* = 6.4 Hz, 1H), 3.54 (td, *J* = 13.5, 2.8 Hz, 1H), 3.01 (ddd, *J* = 14.8, 12.9, 2.2 Hz, 1H), 2.66 (dt, *J* = 14.8, 3.1 Hz, 1H), 2.55 (dt, *J* = 13.5, 3.2 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.80 – 1.68 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 164.8, 149.2, 135.9, 131.6, 129.4, 128.9, 128.7, 128.6, 128.6, 124.8, 101.5, 51.2, 50.6, 28.6, 28.0, 24.3. Chiral HPLC (Chiralpak AD, n-hexane/*i*-propanol 95 : 5, 1 ml/min, 28% ee); retention time = 17.46 min, 19.35 min. Physical and spectral data in accordance with the literature.²⁶

²⁵ Z.-Q. Zhu, X.-L. Zheng, N.-F. Jiang, X. Wan and J.-C. Xiao, Chem. Commun. (Camb)., 2011, 47, 8670–8672.

²⁶ N. Gaggero, D. C. M. Albanese and D. Nava, *Tetrahedron*, 2014, **70**, 8744–8749.

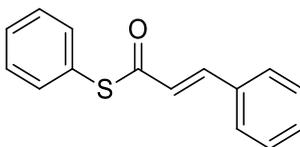
S-Phenyl-2-bromoacetate 3.120

In a 100 ml round bottom flask, triethylamine (10 ml, 71 mmol) was added dropwise to a solution of bromoacetyl bromide (10 g, 49.5 mmol) and thiophenol (4.7 ml, 45 mmol) in DCM (50 ml) at 0 °C. The immediate formation of a white solid was observed. The resulting mixture was stirred for 30 min at room temperature. The mixture was then added with 1M HCl at 0 °C until acidic pH was reached, and then extracted with DCM (3 x 20 ml). The combined organic phase was washed with saturated NaHCO₃ and NaCl, dried over anhydrous Na₂SO₄ and concentrated under vacuum. Crude mixture was purified by silica flash chromatography (petroleum ether) yielding S-phenyl-2-bromoacetate as white needles (7.6 g, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.40 (m, 5H), 4.13 (s, 1H). Physical and spectral data in accordance with the literature.²⁷

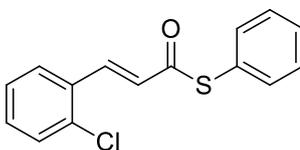
Thioacetic ester phosphorous ylide 3.121

S-phenyl-2-bromoacetate (7.6 g, 33 mmol) was added dropwise to a solution of PPh₃ (15 g, 58 mmol) in benzene (17 ml) at room temperature. The mixture was refluxed for 4 h, resulting in a precipitation of a white powder. Benzene was removed under vacuum. The obtained off-white paste was dissolved in hot water and filtered through a Buchner funnel. The filtrate was added with 10% NaOH (20 ml) and extracted with DCM. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄ and concentrated under vacuum, obtaining title compound as an orange-brown powder (6.8 g, 50% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.12 (m, 20H), 6.13 (s, 1H). Physical and spectral data in accordance with the literature.¹⁰

²⁷ Yan, Y., Chen, J., Zhang, L., Zheng, Q., Han, Y., Zhang, H., Zhang, D., Awakawa, T., Abe, I., & Liu, W. *Angew. Chem. International Edition* **2013**, 52(47), 12308-12312.

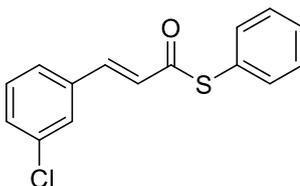
S-Phenyl (E)-3-phenylprop-2-enoate 3.104a

To a solution of cinnamoyl chloride (4.00 g, 24.0 mmol) in 30 ml of dry DCM, was added triethylamine (2.02 ml, 14.4 mmol) under nitrogen. A solution of thiophenol (1.32 g, 12.0 mmol) in 10 ml of dry DCM was added dropwise to the reaction mixture over twenty minutes. The reaction was stirred for 22 h than was diluted with 30 ml of DCM and extracted with 1M HCl (2 x 25 ml). The organic phase was than extracted with 25 ml of 5% NaHCO₃ with 20 ml of water. The organic layer was dried over sodium sulfate and was evaporated under vacuum. The crude was purified by silica flash chromatography (AcOEt : petroleum ether, 1:25) than crystallized in 40 ml of refluxing hexane. Product **3.104a** was obtained as a white solid (2.34 g, 82%). ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 15.8 Hz, 2H), 7.61 – 7.53 (m, 2H), 7.53 – 7.47 (m, 2H), 7.47 – 7.36 (m, 5H), 6.80 (d, J = 15.8 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 188.0, 141.5, 134.6, 134.0, 130.7, 129.4, 129.2, 129.0, 128.5, 127.6, 124.1. Physical and spectral data in accordance with the literature.²⁸

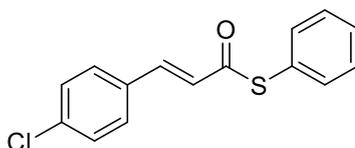
S-Phenyl (E)-3-(2-chlorophenyl)-thioprop-2-enoate 3.104b

Phosphorous ylide **3.121** was added to a solution of 2-chlorobenzaldehyde (1.0 g, 2.4 mmol) in 15 ml of dry toluene, at room temperature. The resulting mixture was stirred under N₂ atmosphere for 48 h at 60 °C. Crude was concentrated, purified *via* silica flash chromatography (AcOEt : petroleum ether 1 : 200) and crystallized with Et₂O/n-Hexane to obtain **3.104b** (131 mg, 30% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, J = 15.8 Hz, 1H), 7.66 (dd, J = 7.5, 1.9 Hz, 1H), 7.53 – 7.41 (m, 6H), 7.38 – 7.27 (m, 2H), 6.78 (d, J = 15.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 187.9, 137.4, 135.6, 134.6, 132.4, 131.5, 130.3, 129.6, 129.3, 127.7, 127.4, 127.2, 126.6. Physical and spectral data in accordance with the literature.²⁸

²⁸ Xia, Z., Lv, X., Wang, W., & Wang, X. (2011), *Tetrahedron letters* **2011**, 52(38), 4906-4910

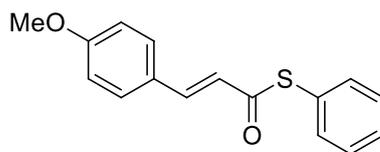
S-Phenyl (*E*)-3-(3-chlorophenyl)-thioprop-2-enoate 3.104c

Phosphorous ylide **3.121** was added to a solution of 3-chlorobenzaldehyde (1.0 g, 2.4 mmol) in 15 ml of dry toluene, at room temperature. The resulting pink reaction mixture was stirred under N₂ atmosphere for 48 h at room temperature. Crude was concentrated, purified *via* silica flash chromatography (AcOEt : petroleum ether, 1 : 100) and crystallized with Et₂O from n-hexane yielding **3.104c** as white needles (407 mg, 94% yield, m.p.128-131 °C.). ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 15.8 Hz, 1H), 7.55 (s, 1H), 7.53 – 7.41 (m, 6H), 7.41 – 7.31 (m, 2H), 6.78 (d, *J* = 15.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 187.8, 139.8, 135.9, 135.07, 134.6, 130.6, 130.3, 129.6, 129.3, 128.1, 127.3, 126.7, 125.4. FTIR (cm⁻¹): 1608, 1673, 1019, 806, 785, 749, 689. HR-MS (ES⁺) calculated for C₁₅H₁₂OCIS ([M+H]⁺): 275.0297; found: 275.0305.

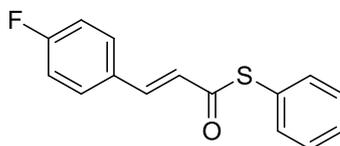
S-Phenyl-(*E*)-3-(4-chlorophenyl)thioprop-2-enoate 3.104d

4-Chlorocinnamic acid (554 mg, 3.0 mmol) was refluxed with thionyl chloride (3.0 ml, 42.5 mmol) in 17 ml of DCM overnight. The reaction mixture was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 15 ml of dry DCM, and thiophenol (0.4 ml, 4.0 mmol) and triethylamine (5.7 ml, 41.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated NaHCO₃, saturated NaCl, dried over anhydrous Na₂SO₄ and concentrated under vacuum. Crude was purified *via* silica flash chromatography (petroleum ether) yielding **3.104d** as a brown powder (205 mg, 25% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 15.8 Hz, 1H), 7.52 – 7.47 (m, 4H), 7.47 – 7.42 (m, 3H), 7.41 – 7.35 (m, 2H), 6.76 (d, *J* = 15.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 187.8, 140.0, 136.7, 134.6, 132.5, 129.6, 129.6, 129.3, 129.3, 127.4, 124.6. Physical and spectral data in accordance with the literature.²⁹

²⁹ Mohite, A. R., & Bhat, R. G. *Organic letters* **2013**, 15(17), 4564-4567.

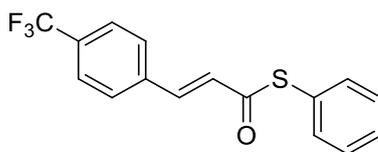
S-Phenyl-(E)-3-(4-methoxyphenyl)-thioprop-2-enoate 3.104e

(E)-4-Methoxycinnamic acid (1.0 g, 5.6 mmol) was refluxed with thionyl chloride (4.5 ml, 62.0 mmol) in 28 ml of DCM overnight. The reaction solution was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 15 ml of DCM, and thiophenol (0.6 ml, 5.6 mmol) and triethylamine (8.3 ml, 60.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated NaHCO₃, saturated NaCl, dried over anhydrous Na₂SO₄ and concentrated. Crude was purified *via* silica flash chromatography (AcOEt : petroleum ether, 1 : 20) yielding **3.104e** as a white powder (353 mg, 23% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 15.7 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.46 – 7.42 (m, 3H), 6.95 – 6.89 (m, 2H), 6.68 (d, *J* = 15.7 Hz, 1H), 3.85 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 187.9, 161.9, 141.3, 134.7, 130.3, 129.3, 129.2, 127.9, 126.7, 121.8, 114.5, 55.4. Physical and spectral data in accordance with the literature.³⁰

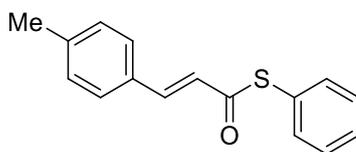
S-Phenyl (E)-3-(4-fluorophenyl)thioprop-2-enoate 3.104f

N,N-Dicyclohexylcarbodiimide (3.0 g, 14.0 mmol) was added to a stirring solution of (E)-4-fluorocinnamic acid (2.0 g, 12.0 mmol), thiophenol (1.1 ml, 11.0 mmol) and DMAP (29.0 mg, 0.24 mmol) in 5 ml of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. Crude was purified by silica flash chromatography (Et₂O : petroleum ether, 1 : 30) and then crystallized with Et₂O, obtaining compound **3.104f** as white needles (275 mg, 9% yield, m.p: 98-118 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 15.8 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.52 – 7.41 (m, 5H), 7.15 – 7.06 (m, 2H), 6.72 (d, *J* = 15.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 187.8, 164.2 (d, *J* = 252.4 Hz), 140.2, 134.6, 130.4 (d, *J* = 8.6 Hz), 130.3 (d, *J* = 3.4 Hz), 129.5, 129.3, 127.5, 123.9, 116.2 (d, *J* = 22.0 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -108.56. FTIR (cm⁻¹): 1679, 1595, 1507, 1031, 1022, 816. HR-MS (ES+) calculated for C₁₅H₁₂FOS ([M+H]⁺): 259.0593; found: 259.0581.

³⁰ Xia, Z., Lv, X., Wang, W., & Wang, X. (2011), *Tetrahedron letters* **2011**, 52(38), 4906-4910

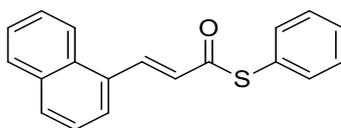
S-Phenyl-(E)-3-(4-trifluoromethylphenyl)thioprop-2-enoate 3.104g

N,N-Dicyclohexylcarbodiimide (1.0 g, 5.0 mmol) was added to a stirring solution of (*E*)-4-trifluoromethylcinnamic acid (850 mg, 4.0 mmol), thiophenol (0.4 ml, 3.6 mmol) and DMAP (8.0 mg, 0.08 mmol) in 2 ml of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. Crude was purified *via* silica flash chromatography (Et₂O : petroleum ether, 1 : 30) and then crystallized with Et₂O obtaining **3.104g** as colorless needles (170 mg, 14% yield, m.p.: 94-106 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.64 (m, 5H), 7.53 – 7.43 (m, 5H), 6.85 (d, *J* = 15.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 187.7, 139.4, 137.4, 134.6, 131.1 (q, *J* = 32.7 Hz), 129.7, 129.3, 128.6, 127.2, 126.4, 126.0 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.3 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -62.89. FTIR (cm⁻¹): 1677, 1617, 1318, 1109, 1021, 990, 821, 755, 741, 691. HR-MS (ES⁺) calculated for C₁₆H₁₂OF₃S ([M+H]⁺): 309.0561; found: 309.0550.

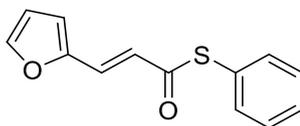
S-Phenyl (E)-3-(*p*-tolyl)thioprop-2-enoate 3.104h

N,N'-Dicyclohexylcarbodiimide (3.0 g, 14.0 mmol) was added to a stirring solution of (*E*)-4-methylcinnamic acid (2.0 g, 12.0 mmol), thiophenol (1.1 ml, 11.0 mmol) and DMAP (27.0 mg, 0.22 mmol) in 5 ml of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. Crude was purified by silica flash chromatography (Et₂O : petroleum ether, 1 : 30) yielding **3.104h** as a white/yellow powder (303 mg, 10% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 15.8 Hz, 1H), 7.53 – 7.40 (m, 7H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 15.8 Hz, 1H), 2.39 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 188.0, 141.6, 141.4, 134.7, 131.3, 129.9, 129.4, 129.2, 128.5, 127.8, 123.1, 21.6. Physical and spectral data in accordance with the literature.³¹

³¹ Wang, X., Zou, X., & Du, J. *Journal of Chemical Research* **2006**, 64.

S-Phenyl (*E*)-3-(1-naphthyl)thioprop-2-enoate 3.104i

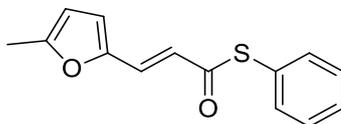
(*E*)-3-(1-Naphthyl)thioprop-2-enoic acid (916 mg, 4.7 mmol) was refluxed with thionyl chloride (4.0 ml, 52.0 mmol) in 23 ml of DCM overnight. The reaction solution was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 17 ml of dry DCM, then thiophenol (0.5 ml, 5.0 mmol) and triethylamine (7.0 ml, 49.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated NaHCO₃, saturated NaCl, dried over anhydrous Na₂SO₄ and concentrated under vacuum. Crude was purified *via* silica flash chromatography (AcOEt : petroleum ether, 1 : 50) obtaining **3.104i** as an orange powder (253 mg, 19% yield, m.p. 100-102 °C). ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 15.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.92 (dd, *J* = 15.0, 7.8 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.65 – 7.43 (m, 8H), 6.89 (d, *J* = 15.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 188.0, 138.5, 134.7, 133.7, 131.7, 131.3, 131.1, 129.5, 129.3, 129.1, 128.9, 127.1, 126.6, 126.4, 125.5, 125.3, 123.3. FTIR (cm⁻¹): 2924, 1476, 1438, 796, 685.83. HR-MS (ES+) calculated for C₁₉H₁₅OS ([M+H]⁺): 291.0844; found: 291.0845.

S-Phenyl (*E*)-3-(2-furyl)thioprop-2-enoate 3.104j

(*E*)-3-(2-Furyl)thioprop-2-enoic acid (940 mg, 7.0 mmol) was refluxed with thionyl chloride (5.5 ml, 76.0 mmol) in 34 ml of DCM overnight. The reaction solution was cooled down to room temperature and concentrated to give a yellow oily solution. The concentrated oil was dissolved in 17 ml of dry DCM, then thiophenol (0.5 ml, 5.0 mmol) and triethylamine (7.0 ml, 49.0 mmol) were slowly added. The resulting solution was stirred at room temperature overnight, washed with 2% HCl until acidic pH was reached and extracted with DCM. The combined organic layer was washed with saturated NaHCO₃, saturated NaCl, dried over anhydrous Na₂SO₄ and concentrated under vacuum. Crude was purified *via* silica flash chromatography (petroleum ether) yielding **3.104j** as an orange powder (143 mg, 9% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.45 (m, 3H), 7.45 – 7.35 (m, 4H), 6.73 – 6.63 (m, 2H), 6.52 – 6.46 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 187.6, 150.6, 145.3, 134.6, 129.4, 129.2,

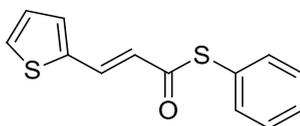
127.7, 127.5, 121.5, 116.6, 112.7. Physical and spectroscopic data in accordance with the literature.³²

S-Phenyl (*E*)-3-(5-methylfuran-2-yl)thioprop-2-enoate **3.104k**



N,N'-Dicyclohexylcarbodiimide (2.0 g, 10.0 mmol) was added to a stirring solution of (*E*)-3-(5-methylfuran-2-yl)prop-2-enoic acid (1.3 g, 8.5 mmol), thiophenol (0.7 ml, 7.6 mmol) and DMAP (21.0 mg, 0.17 mmol) in 3.5 ml of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution stirred at room temperature overnight. The precipitated solid was filtered on celite and the filtrate was concentrated. Crude was purified *via* silica gel chromatography (Et₂O : petroleum ether, 1 : 30) and then crystallized with Et₂O obtaining **3.104k** as orange needles (1.25 g, 60% yield, m.p.: 76-80 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.45 (m, 2H), 7.45 – 7.38 (m, 3H), 7.34 (d, *J* = 15.3 Hz, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.60 (d, *J* = 15.3 Hz, 1H), 6.11 (d, *J* = 3.3 Hz, 1H), 2.37 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 187.5, 156.3, 149.3, 134.6, 129.3, 129.1, 128.0, 127.5, 119.8, 118.5, 109.4, 14.0. FTIR (cm⁻¹): 2954, 2922, 2853, 1460, 1017, 964, 824, 786, 742, 709, 688, 623. HR-MS (ES+) calculated for C₁₄H₁₃O₂S ([M+H]⁺): 245.0636; found: 245.0641.

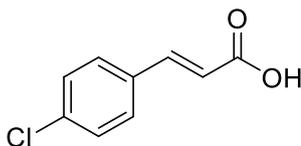
S-Phenyl (*E*)-3-(thiophen-2-yl)thioprop-2-enoate **3.104l**



N,N'-Dicyclohexylcarbodiimide (2.7 g, 13.0 mmol) was added to a stirring solution of (*E*)-3-(thiophen-2-yl)prop-2-enoic acid (1.7 g, 11.0 mmol), thiophenol (1.0 ml, 10.0 mmol) and DMAP (27.0 mg, 0.22 mmol) in 5 ml of dry DCM at 0 °C. After stirring for 1 h at 0 °C, the solution was stirred overnight at room temperature. The precipitated solid was filtered on celite and the filtrate was concentrated under vacuum. The crude was purified *via* silica gel chromatography (AcOEt : petroleum ether, 1 : 30) and then crystallized with Et₂O yielding **3.104l** as yellow crystals (801 mg, 30% yield, m.p.: 86-91 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 15.4 Hz, 1H), 7.53 – 7.40 (m, 6H), 7.33 (d, *J* = 3.7 Hz, 1H), 7.09 (d, *J* = 3.7 Hz, 1H), 6.59 (d, *J* = 15.4 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 187.5, 139.3, 134.6, 133.9, 132.3, 129.5, 129.3, 129.2, 128.4, 127.6, 122.8. FTIR (cm⁻¹): 1661, 1597, 1277, 1203, 1018, 865, 834, 823, 746, 714. HR-MS (ES+) calculated for C₁₃H₁₁OS₂ ([M+H]⁺): 247.0251; found: 247.0261.

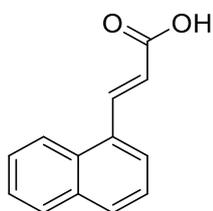
4-Chlorocinnamic acid **3.122d**

³² Xia, Z., Lv, X., Wang, W., & Wang, X. (2011), *Tetrahedron letters* **2011**, 52(38), 4906-4910



4-Chlorobenzaldehyde (0.6 g, 4.7 mmol) and piperidine (80 μ l, 0.8 mmol) were added to a solution of malonic acid (0.5 g, 4.7 mmol) and triethylamine (0.86 ml, 6.0 mmol) in toluene (5 ml). The resulting mixture was refluxed for 6 h, washed with 5% sodium bicarbonate and extracted with ethyl acetate. The combined aqueous layer was cooled down to 0 $^{\circ}$ C and washed with 37% HCl until acidic pH was reached. The resulting solid was filtered and dried *in vacuo* obtaining **3.122d** as an off-white solid (475 mg, 55% yield). ^1H NMR (400 MHz, DMSO) δ 7.71 – 7.60 (m, 2H), 7.51 – 7.34 (m, 3H), 6.57 (d, J = 16.0 Hz, 1H). Spectroscopic data is in accordance with the literature.³³

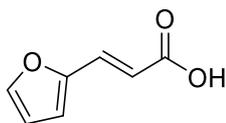
(E)-3-(1-Naphthyl)prop-2-enoic acid 3.122i



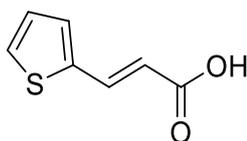
1-Naphthaldehyde (1.3 ml, 9.6 mmol) and piperidine (0.16 ml, 1.6 mmol) were added to a solution of malonic acid (1.0 g, 9.6 mmol) and triethylamine (1.75 ml, 12.5 mmol) in toluene (10 ml). The resulting mixture was refluxed overnight, washed with 5% sodium bicarbonate and extracted with ethyl acetate. The combined aqueous layer was cooled down to 0 $^{\circ}$ C and added with 37% HCl until acidic pH was reached. The resulting solid was filtered and dried *in vacuo*, obtaining **3.122i** as a yellow powder (0.92 g, 48% yield). ^1H NMR (400 MHz, DMSO) δ 12.63 (s, 3H), 8.40 (d, J = 15.8 Hz, 4H), 8.21 (d, J = 8.3 Hz, 4H), 8.06 – 7.92 (m, 12H), 7.69 – 7.54 (m, 12H), 6.61 (d, J = 15.7 Hz, 4H). Spectroscopic data is in accordance with the literature.³⁴

³³ Tang, Y. Q., Chu, C. Y., Zhu, L., Qian, B., & Shao, L. X. *Tetrahedron* **2011**, 67(49), 9479-9483.

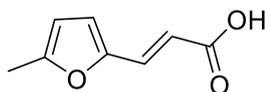
³⁴ Zhao, X., Alper, H., & Yu, Z. *The Journal of organic chemistry* **2006**, 71(10), 3988-3990.

(E)-3-(2-Furyl)prop-2-enoic acid 3.122j

Furfural (0.80 ml, 9.6 mmol) and piperidine (0.16 ml, 1.6 mmol) were added to a solution of malonic acid (1.0 g, 9.6 mmol) and triethylamine (1.75 ml, 12.5 mmol) in toluene (10 ml). The resulting mixture was refluxed overnight, washed with 5% sodium bicarbonate and extracted with ethyl acetate. The combined aqueous layer was cooled down to 0 °C and added with 37% HCl until acidic pH was reached. The resulting solid was filtered and dried *in vacuo* yielding **3.122j** as a brown powder (0.94 g, 71% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.52 (dd, *J* = 8.6, 7.1 Hz, 2H), 6.68 (d, *J* = 3.4 Hz, 1H), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.32 (d, *J* = 15.7 Hz, 1H). Spectroscopic data is in accordance with the literature.³⁵

(E)-3-(2-Thiophenyl)prop-2-enoic acid 3.122l

2-Thiophenecarboxyaldehyde (1.75 ml, 19.2 mmol) and piperidine (0.3 ml, 3.0 mmol) were added to a solution of malonic acid (2.0 g, 19.0 mmol) and triethylamine (3.5 ml, 25.0 mmol) in toluene (20 ml). The resulting mixture was refluxed overnight, washed with 5% sodium bicarbonate and extracted with ethyl acetate. The combined aqueous layer was cooled down to 0 °C and added with 37% HCl until acidic pH was reached. The resulting solid was filtered and dried under vacuum, obtaining **3.122l** as a brown/yellow powder (1.7 g, 58% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 15.7 Hz, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.08 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.25 (d, *J* = 15.6 Hz, 1H). Spectroscopic data is in accordance with the literature.³⁶

(E)-3-(5-Methylfuran-2-yl)prop-2-enoic acid 3.122k

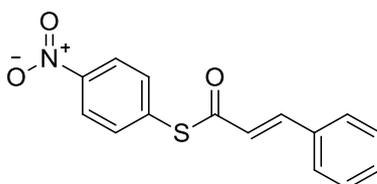
5-Methylfuran-2-carboxyaldehyde (2.0 ml, 19.0 mmol) and piperidine (0.3 ml, 3.0 mmol) were added to a solution of malonic acid (2.0 g, 19.0 mmol) and triethylamine (3.5 ml, 25.0 mmol) in toluene (20 ml). The resulting mixture was refluxed overnight, washed with 5% sodium

³⁵ Gayam, V., & Ravi, S. *European Journal of Medicinal Chemistry* **2017**, 135, 382-391.

³⁶ Xu, G., Yang, X., Jiang, B., Lei, P., Liu, X., Wang, Q. & Ling, Y. *Bioorganic & medicinal chemistry letters* **2016**, 26(7), 1849-1853.

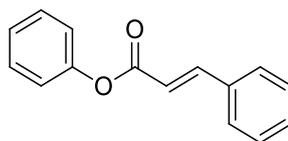
bicarbonate and extracted with ethyl acetate. The combined aqueous layer was cooled down to 0 °C and added with 37% HCl until acidic pH was reached. The resulting solid was filtered and dried under vacuum, yielding **3.122k** as a brown powder (2.5 g, 86% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 15.6 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 6.13 – 6.06 (m, 1H), 2.36 (s, 3H). Spectroscopic data is in accordance with the literature.³⁷

S-(4-Nitrophenyl) (E)-3-phenyl-thioprop-2-enate **3.107b**



Triethylamine (0.61 ml, 4.33 mmol) was added to a solution of cinnamoyl chloride (1.20 g, 7.22 mmol) in 10 ml of dry DCM,. A solution of 4-nitrobenzenethiol (0.56 g, 3.61 mmol) in 10 ml of DCM dry was added dropwise to the reaction mixture over 10 min. The reaction was stirred for 24 h under nitrogen and protected from the light, than was diluted with 100 ml of DCM and extracted with 50 ml of 1M HCl. The aqueous phase was than extracted with DCM (2 x 25 ml). The reunited organic phases were washed with 25 ml of water, dried over Na₂SO₄ and evaporated under vacuum. The crude mixture was purified by silica flash chromatography (AcOEt : petroleum ether, 1 : 40), obtaining 980 mg of **3.107b** as a yellow solid (95% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.73 (d, *J* = 15.8 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.47 – 7.39 (m, 3H), 6.79 (d, *J* = 15.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 185.6, 148.2, 143.0, 136.4, 134.8, 133.6, 131.2, 129.1, 128.7, 123.9, 123.6. Physical and spectral data in accordance with the literature.³⁸

Phenyl cinnamate **3.107a**



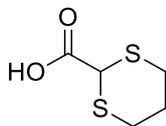
Triethylamine (1.70 ml, 12.0 mmol) and phenol (1.13 g, 12.0 mmol) were added to a solution of cinnamoyl chloride (2.00 g, 12.0 mmol) in 60 ml of AcOEt. The white suspension was stirred for 13 h, then the white solid was removed by vacuum filtration. The filtrate was evaporated under vacuum, affording crude @ as a yellow solid (2.84 g). Re-crystallisation in 5 ml of methanol afforded pure **3.107a** as white crystals (1.23 g, 46% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.65 – 7.54 (m, 2H), 7.49 – 7.35 (m, 5H), 7.31 – 7.22 (m, 1H), 7.21 – 7.13 (m, 2H), 6.63 (d, *J* = 16.0 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 165.4,

³⁷ Mohite, A. R., & Bhat, R. G. *Organic letters* **2013**, 15(17), 4564-4567.

³⁸ Y. Minami, H. Kuniyasu and N. Kambe, *Org. Lett.*, 2008, **10**, 2469–2472.

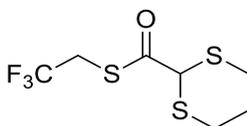
150.8, 146.6, 134.2, 130.7, 129.4, 129.0, 128.3, 125.8, 121.6, 117.4. Physical and spectral data in accordance with the literature.³⁹

1,3-Dithiane-2-carboxylic acid **3.123**



In a flask equipped with a magnetic stirring bar and condenser were added glyoxylic acid (2.00 g, 21.72 mmol), toluene (54 ml), propane-1,3-dithiol (2.53g, 23.40 mmol) and *p*-toluenesulfonic acid·H₂O (413 mg, 2.17 mmol). The reaction mixture was heated and maintained at reflux for 3 h. The mixture was then cooled down to 0 °C, added with sodium bicarbonate (2.53g, 30 mmol) and water (20 ml). After 5 min of vigorous stirring, the organic layer was separated and washed with saturated sodium bicarbonate (2 x 20 ml). The reunited aqueous layer was washed with 50 ml of Et₂O and then acidified to pH 1 with 37% HCl. The aqueous solution was extracted with AcOEt (4 x 100 ml) and the reunited organic phase was dried over sodium sulfate and evaporated under vacuum. Compound **3.123** was obtained as a white solid (3.39 g, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.16 (s, 1H), 3.52 – 3.35 (m, 2H), 2.70 – 2.53 (m, 2H), 2.26 – 2.11 (m, 1H), 2.11 – 1.96 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 175.57, 39.14, 25.61, 24.74. Physical and spectral data in accordance with the literature.⁴⁰

S-(2,2,2-Trifluoroethyl) 1,3-dithiane-2-carbothioate **3.86**



To a solution of dithiane carboxylic acid **3.123** (900 mg, 5.48 mmol) in dry dichloromethane (30 ml) hydroxybenzotriazole (709 mg, 5.25 mmol) was added at 0 °C. The resulting solution was stirred for 10 min at the same temperature. EDC·HCl (1.10 g, 5.75 mmol) was added at 0 °C and the mixture was stirred for 30 min. Finally, 2,2,2-trifluoroethanethiol (700 mg, 6.02 mmol) was added at 0 °C, and the mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (10 ml) and water (30 ml) was added. The aqueous layer was extracted with dichloromethane (2 x 15 ml) and the reunited organic phases were washed with water (2 x 10 ml) and brine (10 ml), dried over sodium sulfate, and evaporated under vacuum, to give title compound **3.86** as a white solid (1.37 g, 95% yield). ¹H NMR (300 MHz, CDCl₃) δ 4.25 (s, 1H), 3.62 (q, J=9.8 Hz, 2H), 3.24–3.16 (m, 2H), 2.68–2.60 (m, 2H), 2.20–1.96 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 192.7 (C),

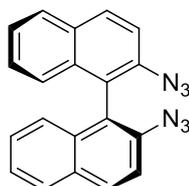
³⁹ T. Shintou, K. Fukumoto and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1569–1579.

⁴⁰ N. Gaggero, D. C. M. Albanese and D. Nava, *Tetrahedron*, 2014, **70**, 8744–8749.

124.0 (q, J=272.0 Hz), 49.5 (CH), 31.8 (q, J=33.8 Hz, CH₂), 26.4 (2 CH₂), 24.7 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ -67.2. Physical and spectral data in accordance with the literature.⁴⁰

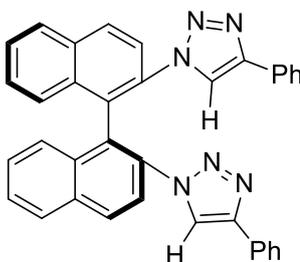
Experimental Section Chapter 4

(S)-2,2'-Diazido-1,1'-binaphthalene **4.66**



(S)-2,2'-Diamino-1,1'-binaphthalene **4.65** (511 mg, 1.80 mmol) was added to 12.5 ml of 2 M HCl in water at 0 °C. The mixture was stirred behind a blast shield and added dropwise with a water solution of sodium nitrite (5.40 mmol, 4 ml) over 15 min. After 1 h, a solution of sodium azide (7.38 mmol, 4 ml) was added dropwise at 0 °C, over 10 min. The mixture was slowly warmed up to room temperature overnight. The reaction mixture was extracted with dichloromethane (2 x 25 ml) and the reunited organic phases were dried over sodium sulfate and evaporated under vacuum, yielding 565 mg of pure **4.66** as a brown solid (93% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.32 – 7.27 (m, 2H), 7.06 (d, *J* = 8.5 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 136.0 (C_q), 133.5 (C_q), 130.9 (C_q), 130.5, 128.3, 127.5, 125.6, 125.5, 123.0 (C_q), 117.2. FTIR (cm⁻¹): 2109, 1301, 819. Physical and spectral data in accordance with the literature.⁴¹

(S)-2,2'-Bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1,1'-binaphthalene **4.71**

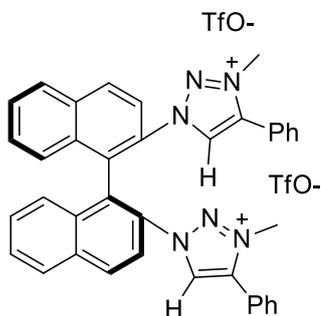


A solution of diazide **4.66** (200 mg, 0.60 mmol) in ACN (8 ml) was added with phenyl acetylene (163 μl, 1.49 mmol) and a solution of CuSO₄·5H₂O (15 mg, 0.06 mmol) and sodium ascorbate (59 mg, 0.30 mmol) in 2 ml of water. Triethylamine (42 μl, 0.30 mmol) was added and the solution was stirred at 50 °C for 48 h. The reaction crude was partially evaporated and the yellow solid that precipitated was collected by vacuum filtration. The precipitate was dried under vacuum yielding pure title compound **4.71** without further purification (272 mg, 84% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.81 (s, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.61 – 7.53 (m, 6H), 7.45 – 7.24 (m, 10H). ¹³C NMR (101 MHz, CDCl₃) δ 147.2 (C_q), 134.8 (C_q), 133.4 (C_q), 132.6 (C_q), 130.9, 130.2 (C_q), 128.9, 128.7, 128.3

⁴¹ S. N. Sluijter, L. J. Jongkind and C. J. Elsevier, *Eur. J. Inorg. Chem.*, 2015, **2015**, 2948–2955.

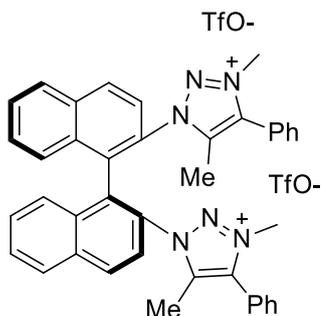
(2CH), 128.0 (C_q), 127.8, 126.4, 125.8, 123.4, 121.4. HR-MS (ES⁺) calculated for C₃₆H₂₅N₆ ([M+H]⁺): 541.2141; found: 541.2134.

(S)-2,2'-Bis(3-methyl-4-phenyl-1*H*-1,2,3-triazolium)-1,1'-binaphthalene ditriflate 4.72



A solution of (S)-bis-triazolo-binaphthalene **4.71** (100 mg, 0.18 mmol) in dry DCM (2 ml) at -78 °C, was added with methyl trifluoromethanesulfonate (58 µl, 0.51 mmol). The reaction mixture was slowly warmed up overnight. Evaporation of the solvent afforded 157 mg of pure bis-triazolium salt **4.72** as a brown solid (98% yield). ¹H NMR (400 MHz, DMSO) δ 9.52 (s, 2H), 8.65 (d, *J* = 8.9 Hz, 2H), 8.35 (d, *J* = 8.3 Hz, 2H), 8.18 (d, *J* = 8.9 Hz, 2H), 7.90 – 7.82 (m, 2H), 7.74 – 7.56 (m, 12H), 7.31 (d, *J* = 8.8 Hz, 2H), 4.04 (s, 6H). ¹³C NMR (101 MHz, DMSO) δ 142.9 (C_q), 134.1 (C_q), 132.7, 132.5 (C_q), 132.3, 132.3 (C_q), 130.6, 129.9, 129.8, 129.6, 129.4, 127.1 (C_q), 126.9, 122.6, 122.3 (C_q), 119.5 (C_q), 31.4 (CH₃). ¹⁹F NMR (376 MHz, CDCl₃) δ -78.29. HR-MS (ES⁺) calculated for C₃₉H₃₀N₆O₃F₃S ([M-TfO]⁺): 719.2047; found: 719.2040.

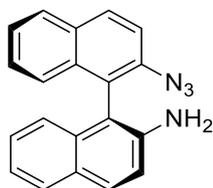
(S)-2,2'-Bis(3,5-dimethyl-4-phenyl-1*H*-1,2,3-triazolium)-1,1'-binaphthalene ditriflate 4.73



A solution of bis-triazolium-binaphthalene **4.72** (491 mg, 0.91 mmol) in dichloromethane (9 ml) at 0 °C was added with potassium *tert*-butoxide (255 mg, 2.27 mmol). The dark red solution was added with methyl trifluoromethanesulfonate (257 µl, 2.27 mmol) and slowly warmed up to room temperature over 4 h. The reaction mixture was added with water and extracted with dichloromethane (2 x 15 ml). The reunited organic phases were dried over sodium sulfate and evaporated under vacuum. Crude methyltriazolium was purified by silica flash chromatography (methanol / dichloromethane 4 : 96) obtaining 400 mg of pure title compound **4.73** as a pale yellow solid (63% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.29 (m, 4H), 8.13 (d, *J* = 8.2 Hz, 2H), 7.79 – 7.67 (m, 2H), 7.60 – 7.46 (m, 8H), 7.41 – 7.30 (m, 6H), 3.76 (s, 6H),

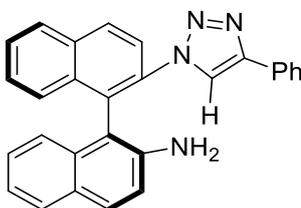
2.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 140.6 (C_q), 139.7 (C_q), 134.0 (C_q), 132.2, 131.9, 131.8 (C_q), 129.9, 129.7, 129.2, 129.1, 128.9 (C_q), 128.4, 126.5, 124.1, 121.5 (C_q), 119.0 (C_q), 38.2 (CH_3), 10.5 (CH_3). HR-MS (ES+) calculated for $\text{C}_{41}\text{H}_{34}\text{N}_6\text{O}_3\text{F}_3\text{S}$ ([M-TfO] $^+$): 747.2365; found: 747.2359.

(S)-2-Azido-2'-amino-1,1'-binaphthalene 4.76



(S)-2,2'-Diamino-1,1'-binaphthalene **4.75** (130 mg, 0.46 mmol) was added to 3.2 ml of 2 M HCl in water at 0 °C. The mixture was stirred behind a blast shield and added dropwise with a water solution of sodium nitrite (0.46 mmol, 2 ml) over 15 min. After 1 h at 0 °C, a solution of sodium azide (0.51 mmol, 2 ml) was added dropwise, over 10 min. The mixture was slowly warmed up to room temperature overnight. The reaction mixture was extracted with dichloromethane (2 x 10 ml) and the reunited organic phases were dried over sodium sulfate and evaporated under vacuum. Crude mixture was purified by silica flash chromatography (Et_2O / petroleum ether 1 : 30 to 1 : 10) obtaining 91 mg of mono-azidoaniline **4.76** as a brown solid (63% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 8.8$ Hz, 1H), 7.91 (d, $J = 8.2$ Hz, 1H), 7.85 – 7.76 (m, 2H), 7.50 (d, $J = 8.8$ Hz, 1H), 7.46 – 7.40 (m, 1H), 7.34 – 7.16 (m, 4H), 7.11 (d, $J = 8.7$ Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 1H), 3.55 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 142.1 (C_q), 136.6 (C_q), 133.9 (C_q), 133.4 (C_q), 131.5 (C_q), 130.3, 129.9, 128.4, 128.2, 128.0, 127.6 (C_q), 126.8, 125.7, 125.6, 123.8, 123.5 (C_q), 122.5, 118.0, 112.8 (C_q). FTIR (cm^{-1}): 2104, 1618, 1506, 1287, 808, 746.

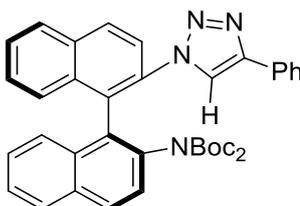
(S)-2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-2'-amino-1,1'-binaphthalene 4.77



A solution of azidoaniline **4.76** (183 mg, 0.59 mmol) in ACN (8 ml) was added with phenyl acetylene (78 μl , 0.71 mmol) and a solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (15 mg, 0.06 mmol) and sodium ascorbate (59 mg, 0.30 mmol) in 2 ml of water. Triethylamine (42 μl , 0.30 mmol) was added and the solution was stirred at 50 °C for 18 h. The reaction mixture was evaporated under vacuum, until most of ACN was removed, then it was extracted with DCM (3 x 20 ml). The reunited organic phases were dried over sodium sulfate and evaporated under vacuum, obtaining aminotriazole **4.77** without further purification (light brown solid, 238 mg, 98% yield).

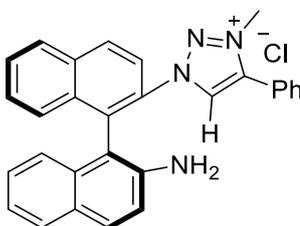
^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 8.8$ Hz, 1H), 8.11 – 8.01 (m, 2H), 7.80 – 7.70 (m, 2H), 7.65 – 7.56 (m, 1H), 7.49 – 7.37 (m, 5H), 7.32 – 7.16 (m, 5H), 7.00 (d, $J = 8.8$ Hz, 1H), 6.97 – 6.88 (m, 1H), 3.64 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.0 (C_q), 142.6 (C_q), 134.8 (C_q), 133.9 (2 C_q), 132.7 (C_q), 130.4, 130.4 (C_q), 130.2, 128.7, 128.5, 128.3, 128.0, 127.9, 127.8 (C_q), 127.6 (C_q), 127.5, 127.5, 126.8, 125.6, 123.6, 123.3, 122.7, 120.7, 118.0, 111.3 (C_q). HR-MS (ES+) calculated for $\text{C}_{28}\text{H}_{21}\text{N}_4$ ($[\text{M}+\text{H}]^+$): 413.1766; found: 413.1775.

(S)-*N,N*-di-Boc-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2'-amino-1,1'-binaphthalene 4.78



A solution of (S)-triazolo-amino-binaphthalene **4.77** (250 mg, 0.61 mmol) in dry DCM (3 ml) was added with *N,N*-dimethylaminopyridine (7 mg, 0.06 mmol), triethylamine (206 μl , 1.46 mmol), and Boc-anhydride (318 mg, 1.46 mmol). The reaction mixture was stirred overnight, then solvent was evaporated under vacuum. Crude was purified by silica flash chromatography (AcOEt / petroleum ether 1 : 4), obtaining 284 mg of *N,N*-di-Boc-triazole **4.78** as a white solid (91% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.8$ Hz, 1H), 8.09 (d, $J = 8.8$ Hz, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 7.99 (d, $J = 8.2$ Hz, 1H), 7.82 (d, $J = 8.2$ Hz, 1H), 7.65 (d, $J = 8.5$ Hz, 1H), 7.59 – 7.53 (m, 1H), 7.52 – 7.47 (m, 2H), 7.40 – 7.33 (m, 4H), 7.29 – 7.17 (m, 5H), 1.26 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 146.7 (C=O), 138.2 (C_q), 136.6 (C_q), 134.8 (C_q), 133.2 (C_q), 132.6 (C_q), 132.4 (C_q), 132.3 (C_q), 130.6 (C_q), 130.1, 130.1 (C_q), 129.8, 128.5, 127.9, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 127.0, 126.9, 125.6, 125.5 (C_q), 125.2, 123.3, 121.3, 83.0 (C_q), 82.9 (C_q), 27.8 (CH_3), 27.6 (CH_3). HR-MS (ES+) calculated for $\text{C}_{38}\text{H}_{37}\text{N}_4\text{O}_4$ ($[\text{M}+\text{H}]^+$): 613.2815; found: 613.2827.

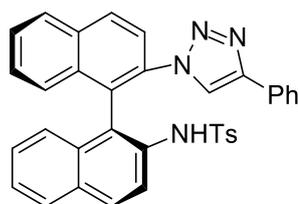
(S)-1-(2'-Amino-[1,1'-binaphthalen]-2-yl)-1-methyl-5-phenyl-1*H*-1,2,3-triazol-3-ium chloride 4.79



Under inert atmosphere, a solution of *N,N*-di-Boc-triazolo-aminobinaphthalene **4.78** (181 mg, 0.35 mmol) in dry DCM (3.5 ml) was added with methyl trifluoromethanesulfonate (44 μl , 0.39 mmol) at -78 $^\circ\text{C}$. The stirred reaction was slowly warmed up to room temperature overnight. The reaction mixture was evaporated under vacuum and crude *N,N*-di-Boc-triazolium triflate

underwent deprotection by reaction with trifluoroacetic acid (1 ml) in dichloromethane (1 ml) overnight. The reaction was diluted with 10 ml of dichloromethane and washed with saturated sodium bicarbonate until neutralisation. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the reunited organic phases were dried over sodium sulfate and evaporated under vacuum. Crude triazolium salt was dissolved in methanol (5 ml) and eluted through a short plug of DOWEX 1X8 (strongly basic, chloride form), obtaining pure title compound **4.79** as a chloride salt (brown solid, 139 mg, 86% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.38 (s, 1H), 8.24 – 8.17 (m, 2H), 8.08 (d, $J = 8.3$ Hz, 1H), 7.78 (d, $J = 8.9$ Hz, 1H), 7.75 – 7.67 (m, 2H), 7.56 – 7.37 (m, 7H), 7.29 (d, $J = 8.9$ Hz, 1H), 7.22 – 7.13 (m, 2H), 6.75 (d, $J = 7.5$ Hz, 1H), 4.38 (bs, 2H), 4.24 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 144.2 (C_q), 142.5 (C_q), 133.0 (C_q), 133.3 (C_q), 132.6 (C_q), 132.2 (C_q), 131.7, 130.9 (2 Ar-CH), 130.7 (C_q), 129.7, 129.5, 129.1, 129.0, 128.8, 128.6, 128.3, 127.5 (C_q), 127.4, 127.2, 123.1, 122.7, 122.6, 121.5 (C_q), 118.8, 108.6 (C_q), 39.1 (CH_3). HR-MS (ES+) calculated for $\text{C}_{29}\text{H}_{23}\text{N}_4$ ($[\text{M}-\text{Cl}]^+$): 427.1923; found: 427.1923.

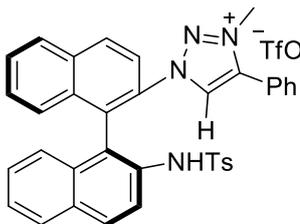
N*-Tosyl-(*S*)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2'-amino-1,1'-binaphthalene **4.83*



A solution of (*S*)-2,2'-Diamino-1,1'-binaphthalene **4.65** (50 mg, 0.176 mmol) in dry dichloromethane (4 ml) was added with triethylamine (29 μl , 0.211) and *p*-toluenesulfonylchloride (35 mg, 0.185). The reaction was stirred overnight, then the solvent was evaporated under vacuum. Purification by silica flash chromatography (AcOEt / petroleum ether 1 : 4) provided a 6 : 1 mixture of *mono*- and *bis*-tosylated diamine. The crude mixture was dissolved in 2 ml of acetonitrile and added with *tert*-butylnitrite (31 μl , 0.264 mmol) and trimethylsilylazide (35 μl , 0.264 mmol) at 0 °C. The reaction was slowly warmed up to room temperature over 2 h and then evaporated under vacuum. Crude *N*-tosyl-2-azido-2'-amino-1,1'-binaphthalene was dissolved in ACN (4 ml) and added with phenyl acetylene (23 μl , 0.211 mmol) and a solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5 mg, 0.018 mmol) and sodium ascorbate (17 mg, 0.088 mmol) in 1 ml of water. Triethylamine (13 μl , 0.088 mmol) was added and the solution was stirred at 50 °C for 18 h. The reaction mixture was evaporated under vacuum, until most of ACN was removed, then it was extracted with DCM (3 x 10 ml). The reunited organic phases were dried over sodium sulfate and evaporated under vacuum. Pure *N*-tosyl-aminotriazole **4.83** was obtained after silica flash chromatography (AcOEt / petroleum ether 1 : 4) as a white solid (46 mg, 46% yield over three steps). ^1H NMR (400 MHz, CDCl_3) δ 8.23 (d, $J = 8.9$ Hz, 1H), 8.07 (d, $J = 8.9$ Hz, 1H), 8.04 (d, $J = 8.1$ Hz, 1H), 7.99 – 7.89 (m, 2H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.62 – 7.57 (m, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 7.6$ Hz, 2H), 7.31 – 7.16 (m, 5H), 7.02 – 6.93 (m, 5H), 6.89 (d, $J = 8.5$ Hz, 1H), 6.66 (s, 1H), 2.14 (d, $J = 11.3$

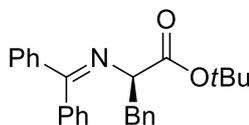
Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.1 (C_q), 144.1 (C_q), 136.4 (C_q), 134.7 (C_q), 133.7 (C_q), 133.6 (C_q), 132.7 (C_q), 132.4 (C_q), 131.2, 130.6, 130.5 (C_q), 129.9 (C_q), 129.7, 128.7, 128.6, 128.4, 128.3, 128.2, 127.8, 127.6, 127.0, 126.1, 125.6, 125.6, 125.1 (C_q), 124.6, 123.2, 120.2 (C_q), 120.0, 118.8, 21.3 (CH_3). HR-MS (ES+) calculated for $\text{C}_{35}\text{H}_{27}\text{N}_4\text{O}_2\text{S}$ ($[\text{M}+\text{H}]^+$): 567.1855; found: 567.1851.

N*-Tosyl-(*S*)-1-(2'-amino-[1,1'-binaphthalen]-2-yl)-1-methyl-5-phenyl-1*H*-1,2,3-triazol-3-ium triflate **4.84*



A solution of *N*-tosyl-triazolo-aminobinaphthalene **4.83** (46 mg, 0.08 mmol) in dry DCM (1 ml) at $-78\text{ }^\circ\text{C}$, was added with methyl trifluoromethanesulfonate (10 μl , 0.09 mmol). The reaction mixture was slowly warmed up overnight. Evaporation of the solvent afforded 53 mg of pure bis-triazolium salt **4.84** as a white solid (96% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.33 (s, 2H), 8.13 (d, $J = 8.3$ Hz, 1H), 7.92 (d, $J = 9.0$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.75 – 7.67 (m, 1H), 7.57 (d, $J = 8.2$ Hz, 2H), 7.51 (d, $J = 9.0$ Hz, 2H), 7.49 – 7.38 (m, 4H), 7.37 – 7.27 (m, 2H), 7.25 – 7.13 (m, 5H), 6.98 (d, $J = 8.5$ Hz, 1H), 6.62 (s, 1H), 4.14 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 144.6 (C_q), 142.8 (C_q), 137.0 (C_q), 134.8 (C_q), 134.1 (C_q), 132.7 (C_q), 132.6 (C_q), 132.3, 132.1 (C_q), 131.8, 131.0, 130.5, 130.0, 129.6, 129.5, 129.1, 129.0, 128.8, 128.5, 128.0, 127.9 (C_q), 127.1, 126.7, 126.3, 125.8 (C_q), 124.9, 123.5, 121.5 (C_q), 120.1 (C_q), 119.8, 38.7, 21.6 (CH_3). HR-MS (ES+) calculated for $\text{C}_{36}\text{H}_{29}\text{N}_4\text{O}_2\text{S}$ ($[\text{M}-\text{TfO}]^+$): 581.2011; found: 581.1992.

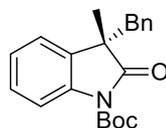
(*R*)-*N*-(Diphenylmethylene)phenylalanine *tert*-butyl ester **4.91**



An aqueous solution of KOH (50%wt, 1 ml) was added to a solution of *N*-(Diphenylmethylene)glycine *tert*-butyl ester (30 mg, 0.1 mmol), chiral triazolium catalyst (*S*)-**4.79** (2.3 mg, 0.005 mmol) and benzyl bromide (14 μl , 0.12 mmol) in dichloromethane (3 ml). The reaction mixture was vigorously stirred overnight, at room temperature. The solvent was evaporated and the residue was purified *via* silica flash chromatography (AcOEt / petroleum ether 1 : 20) to afford 3 mg of pure compound **4.82** (11% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.58 – 7.56 (m, 2H), 7.38 – 7.26 (m, 6H), 7.21 – 7.13 (m, 3H), 7.06 – 7.04 (m, 2H), 6.60 (d, $J = 8.3$ Hz, 2H), 4.10 (dd, $J = 9.2, 4.3$ Hz, 1H), 3.23 (dd, $J = 13.3, 4.3$ Hz, 1H), 3.16 (dd, $J =$

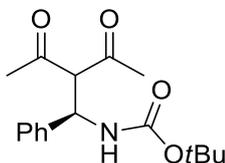
13.3, 9.2 Hz, 1H), 1.44 (s, 9H). Spectral data is in accordance with the literature.⁴² Chiral HPLC (Chiralcel OD, n-hexane / isopropanol 99 : 1, 1 ml/min, 6% ee); retention time = 6.12 min (major), 9.37 min.

(S)-tert-butyl 3-benzyl-3-methyl-2-oxindoline-1-carboxylate 4.47



Potassium carbonate (34 mg, 0.25 mmol) was added to a solution of (S)-tert-butyl 3-methyl-2-oxindoline-1-carboxylate **4.46** (23 mg, 0.1 mmol), chiral triazolium catalyst (S)-**4.84** (3.6 mg, 0.005 mmol) and benzyl bromide (14 μ l, 0.12 mmol) in dichloromethane (2 ml). The reaction mixture was vigorously stirred overnight at room temperature. The solvent was evaporated and the residue was purified *via* silica flash chromatography (AcOEt / petroleum ether 1 : 30) to afford 9 mg of pure compound **4.47** (27% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.13 – 7.04 (m, 5H), 6.83 (d, *J* = 8.0 Hz, 2H), 3.15 (d, *J* = 13.0 Hz, 1H), 3.00 (d, *J* = 13.0 Hz, 1H), 1.57 (s, 9H), 1.54 (s, 3H). Spectral data is in accordance with the literature.⁴³ Chiral HPLC (Chiralcel OD, n-hexane / isopropanol 99 : 1, 0.5 ml/min, 16% ee); retention time = 12.13 min, 13.60 min (major).

tert-butyl (2-acetyl-3-oxo-1-phenylbutyl)carbamate 4.96a

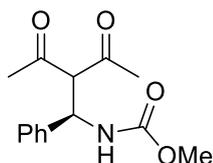


Acetylacetone (11 μ l, 0.11 mmol) was added to a solution of *N*-Boc-benzaldimine **4.95a** (35 mg, 0.1 mmol) and chiral triazolium catalyst (S)-**4.79** (2.3 mg, 0.005 mmol) in dichloromethane (2 ml). The reaction mixture for 2 h at room temperature. The solvent was evaporated and the residue was purified *via* silica flash chromatography (Et₂O / dichloromethane 1 : 20) to afford 33 mg of pure compound **4.96a** (74% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.26 (m, 5H), 5.78 (bs, 1H), 5.50 (bs, 1H), 4.22 (bs, 1H), 2.20 (s, 3H), 2.11 (s, 3H), 1.40 (s, 9H). Spectral data is in accordance with the literature.⁴⁴ Chiral HPLC (Chiralpak AD, n-hexane / isopropanol 90 : 10, 1 ml/min, racemic mixture); retention time = 12.87 min, 14.44 min.

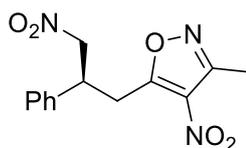
⁴² S. Shirakawa, Y. Tanaka and K. Maruoka, *Org. Lett.*, 2004, **6**, 1429–1431.

⁴³ K. Ohmatsu, M. Kiyokawa and T. Ooi, *J. Am. Chem. Soc.*, 2011, **133**, 1307–1309.

⁴⁴ T. Kano, T. Yurino, D. Asakawa and K. Maruoka, *Angew. Chemie - Int. Ed.*, 2013, **52**, 5532–5534.

Methyl (2-acetyl-3-oxo-1-phenylbutyl)carbamate 4.96b

Acetylacetone (11 μ l, 0.11 mmol) was added to a solution of *N*-methoxycarbonyl-benzaldimine (30 mg, 0.1 mmol) and chiral triazolium catalyst (**S**)-**4.73** (4.0 mg, 0.005 mmol) in dichloromethane (2 ml). The reaction mixture for 2 h at room temperature. The solvent was evaporated and the residue was purified *via* silica flash chromatography (Et₂O / dichloromethane 1 : 10) to afford 31 mg of pure compound **4.96b** (90% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.22 (m, 5H), 6.01 (s, 1H), 5.53 (s, 1H), 4.24 (bd, *J* = 5.9 Hz, 1H), 3.64 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H). Spectral data is in accordance with the literature.⁴⁵ Chiral HPLC (Chiralpak AS, n-hexane / isopropanol 90 : 10, 1 ml/min, 9% ee); retention time = 15.91 min, 26.51 min (major).

(S)-3-methyl-4-nitro-5-(3-nitro-2-phenylpropyl)isoxazole 4.98

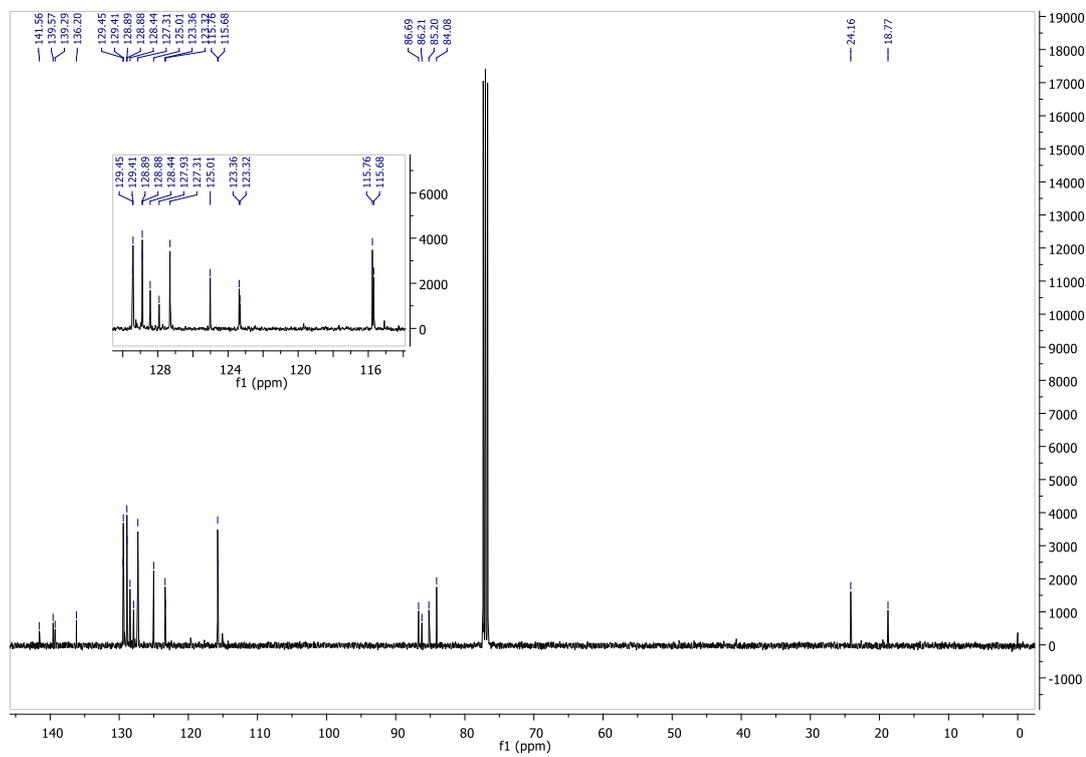
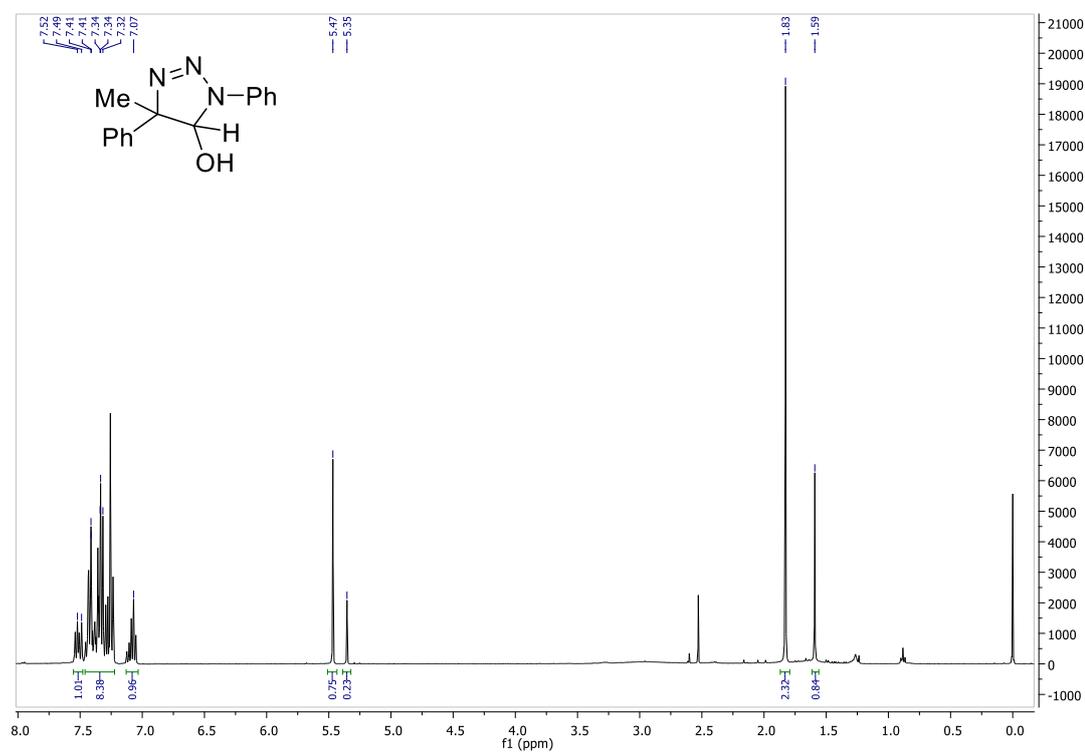
Potassium carbonate (69 mg, 0.50 mmol) was added to a solution of 3-methyl-4-nitro-5-styryl-isoxazole **4.97** (23 mg, 0.1 mmol), chiral triazolium catalyst (**S**)-**4.79** (2.3 mg, 0.005 mmol) and nitromethane (24 μ l, 0.50 mmol) in dichloromethane (1 ml). The reaction mixture was vigorously stirred for 48 h at room temperature. The solvent was evaporated and the residue was purified *via* silica flash chromatography (AcOEt / petroleum ether 1 : 20 to 1 : 4) to afford 26 mg of pure compound **4.98** (90% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.19 (m, 5H), 4.77 – 4.65 (m, 2H), 4.20 – 4.10 (m, 1H), 3.76 (dd, *J* = 15.1, 8.9 Hz, 1H), 3.58 (dd, *J* = 15.1, 6.7 Hz, 1H), 2.49 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.0, 155.6, 136.6, 129.4, 128.7, 127.1, 79.2, 41.6, 31.3, 11.5. Spectral data is in accordance with the literature.⁴⁶ Chiral HPLC (Chiralcel OD, n-hexane / isopropanol 70 : 30, 1 ml/min, 60% ee); retention time = 30.21 min, 36.62 min (major).

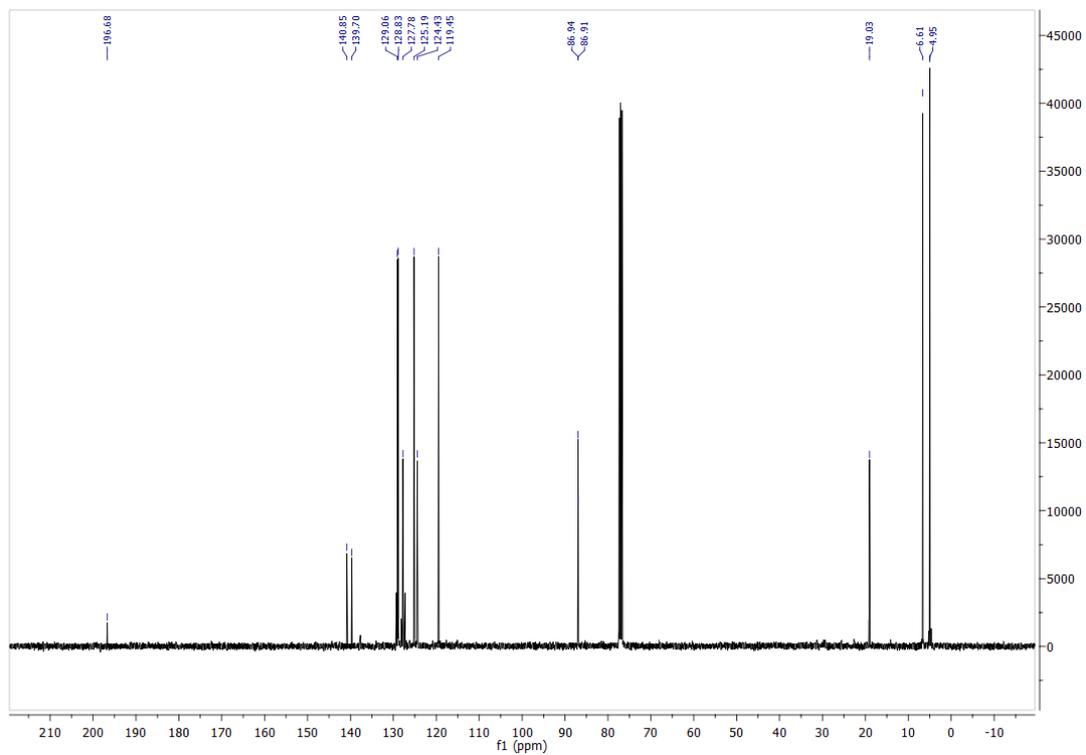
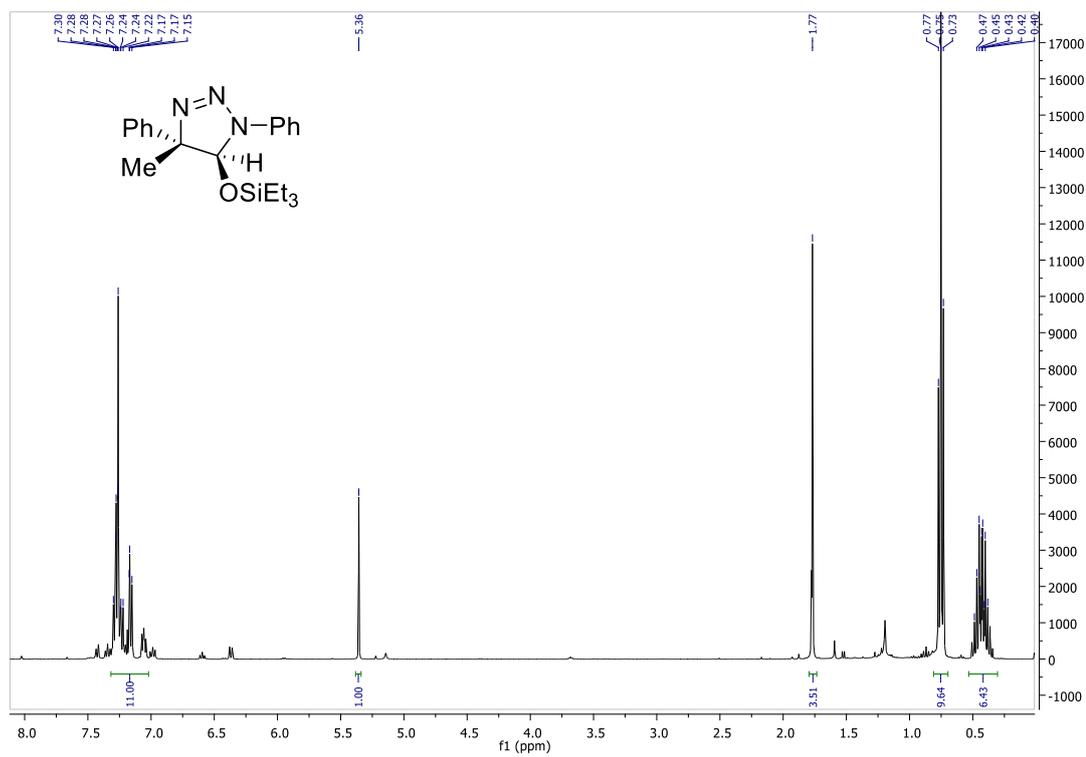
⁴⁵ I. D. Gridnev, M. Kouchi, K. Sorimachi and M. Terada, *Tetrahedron Lett.*, 2007, **48**, 497–500.

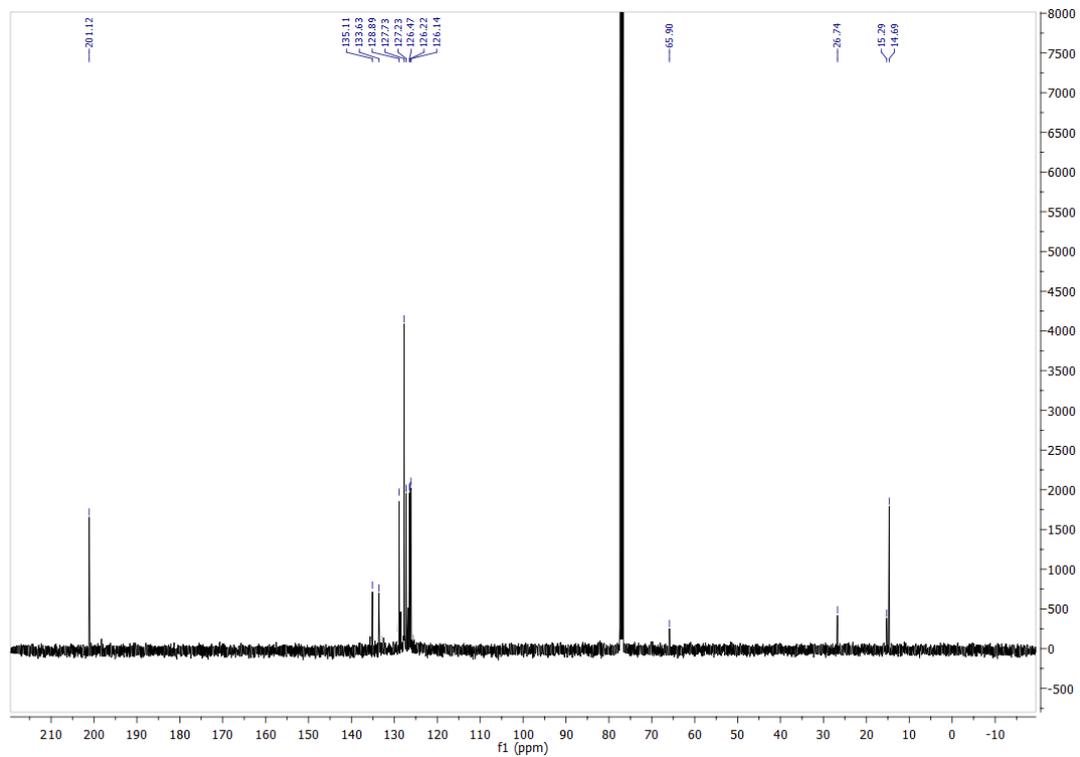
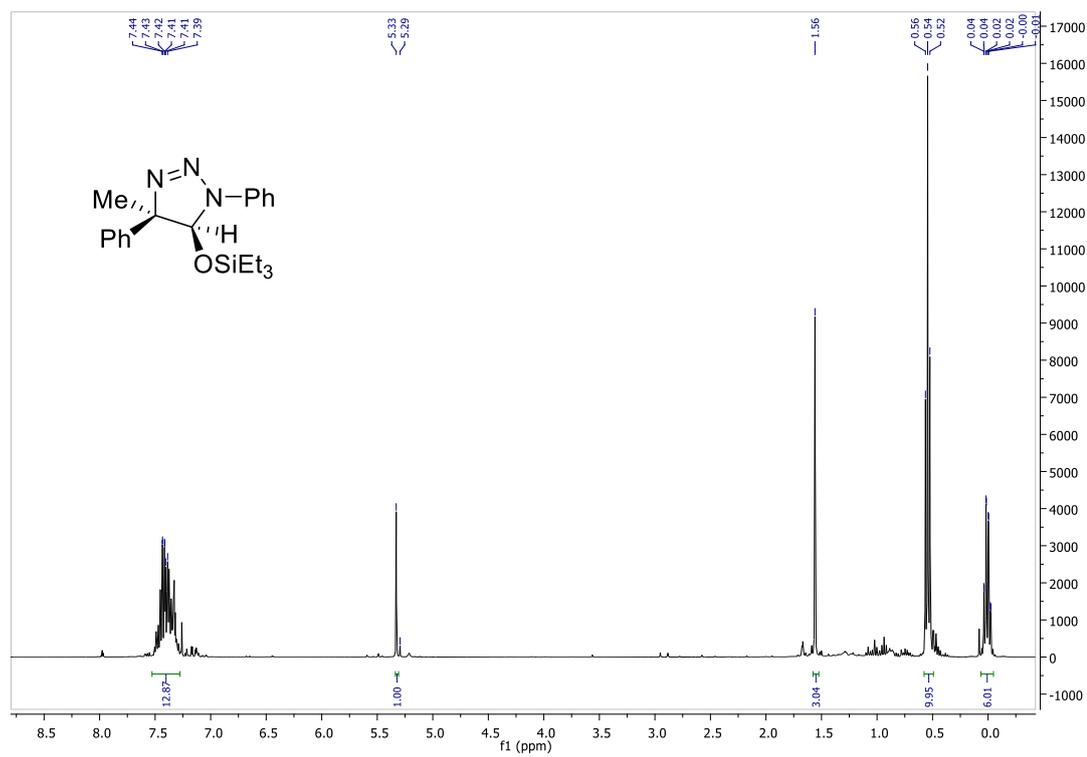
⁴⁶ A. Baschieri, L. Bernardi, A. Ricci, S. Suresh and M. F. A. Adamo, *Angew. Chemie - Int. Ed.*, 2009, **48**, 9342–9345.

Chapter 1: ^1H -NMR and ^{13}C -NMR

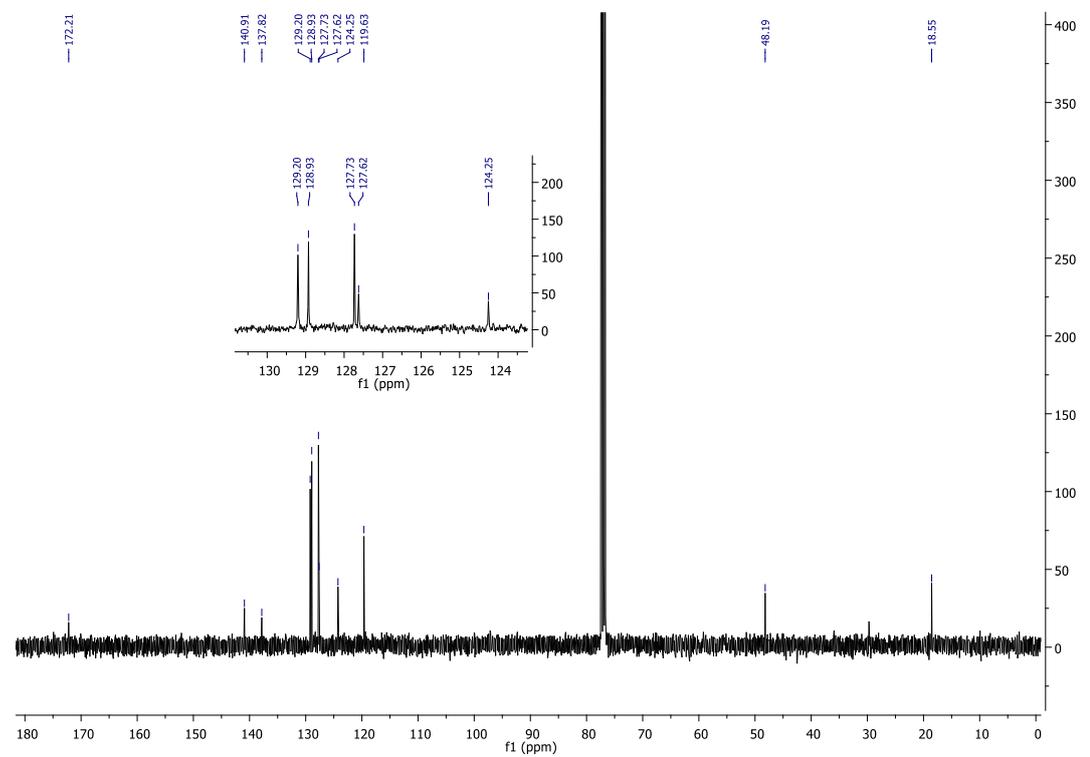
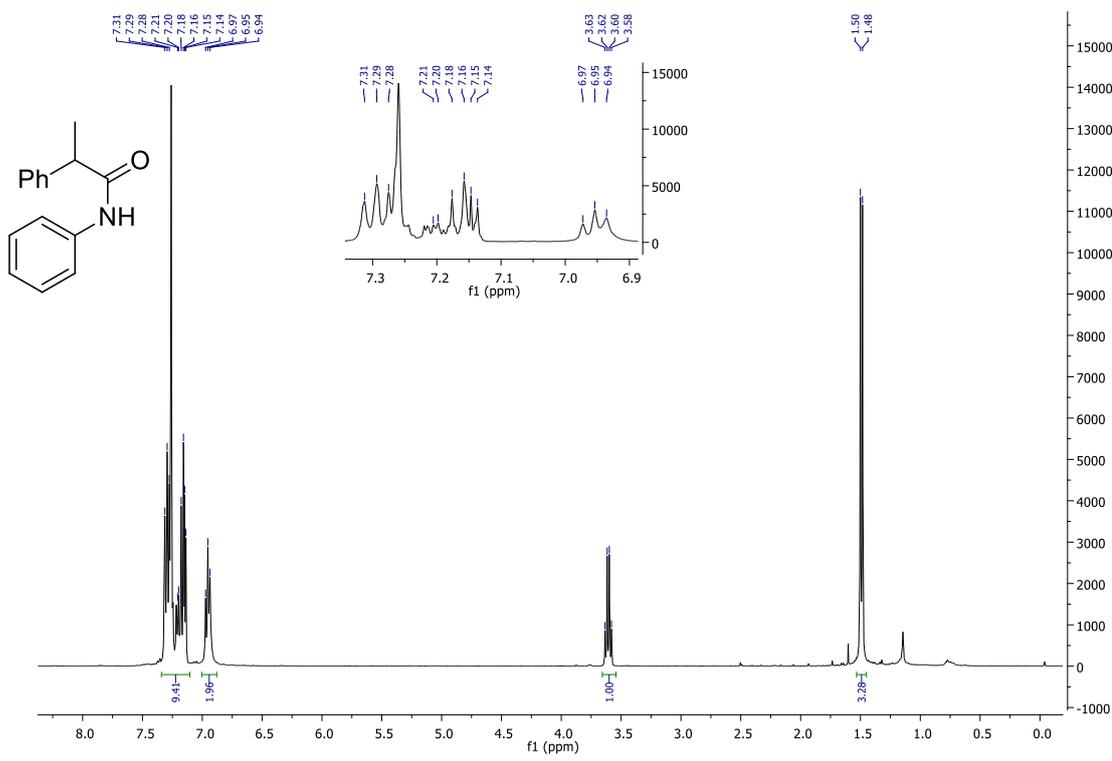
Compound 1.93



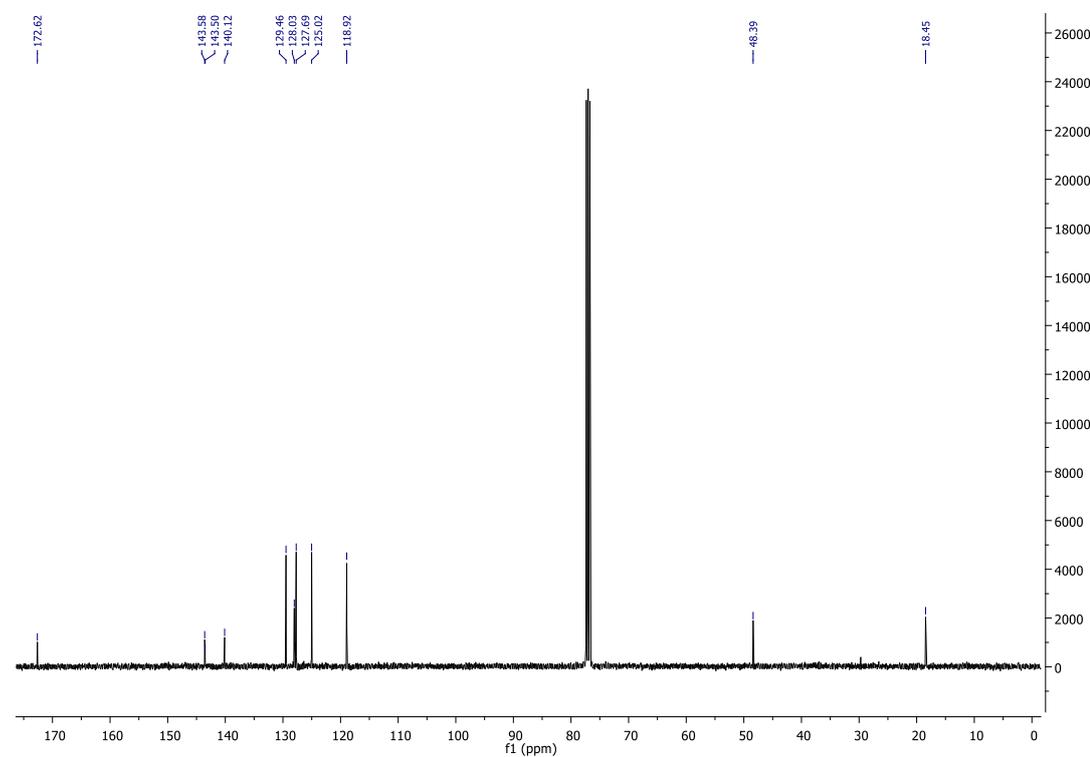
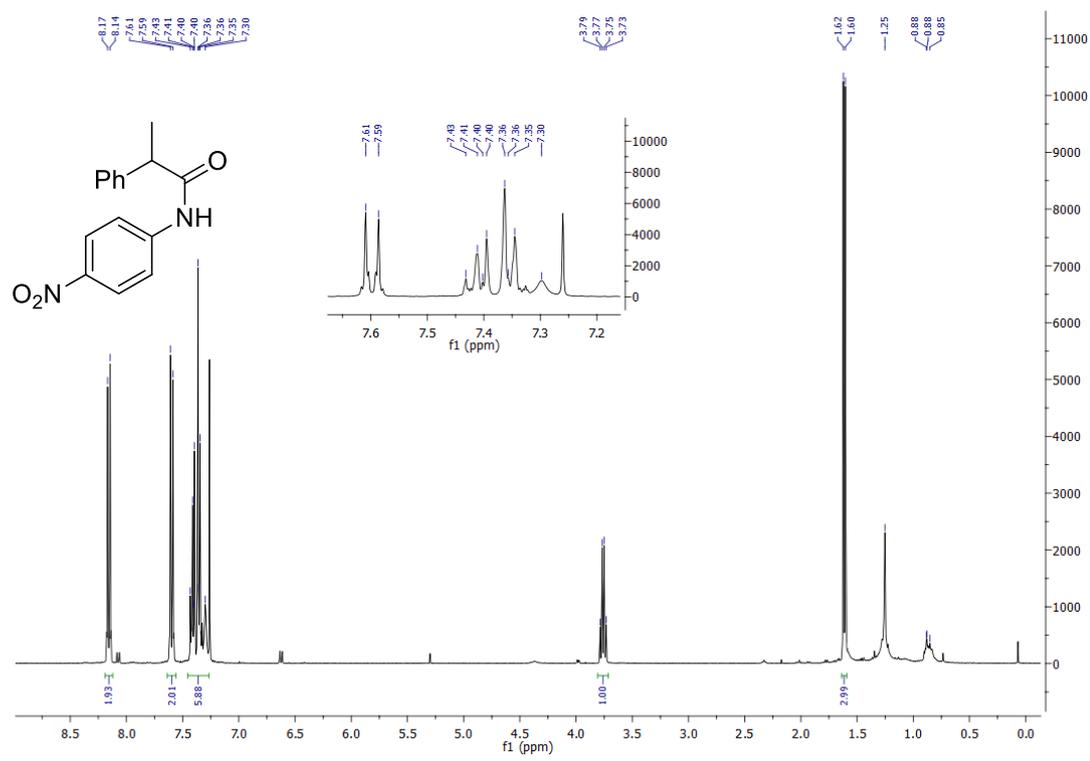
Compound *anti*-1.96

Compound *syn*-1.96

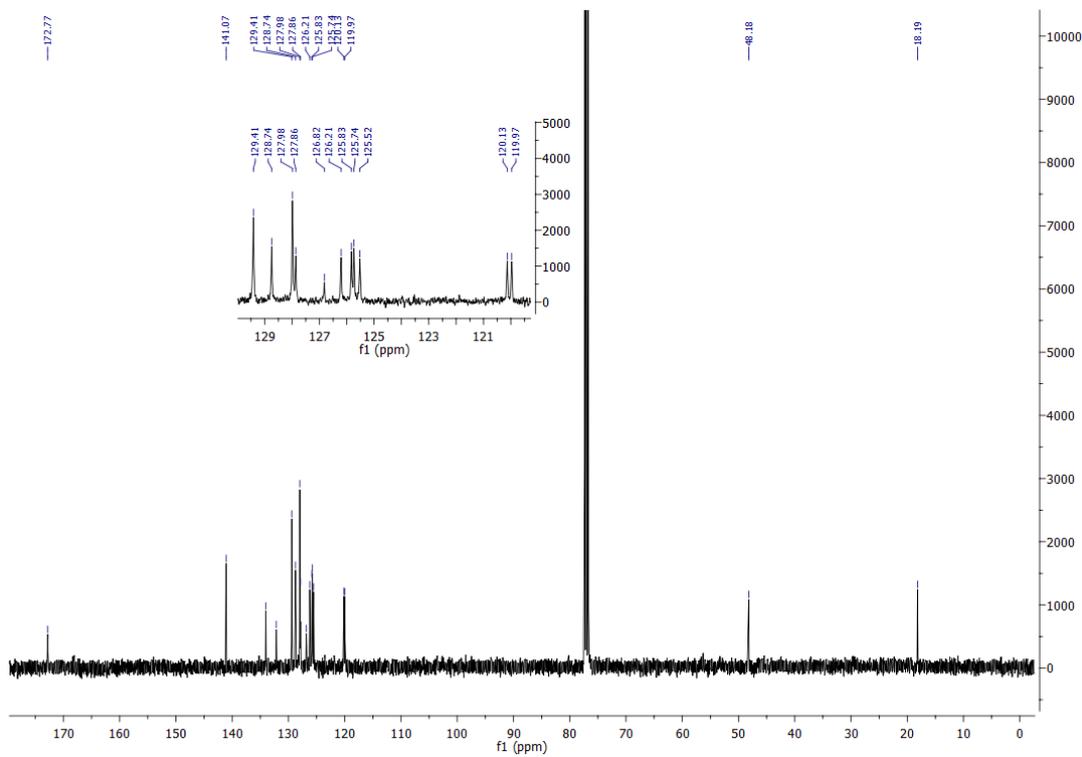
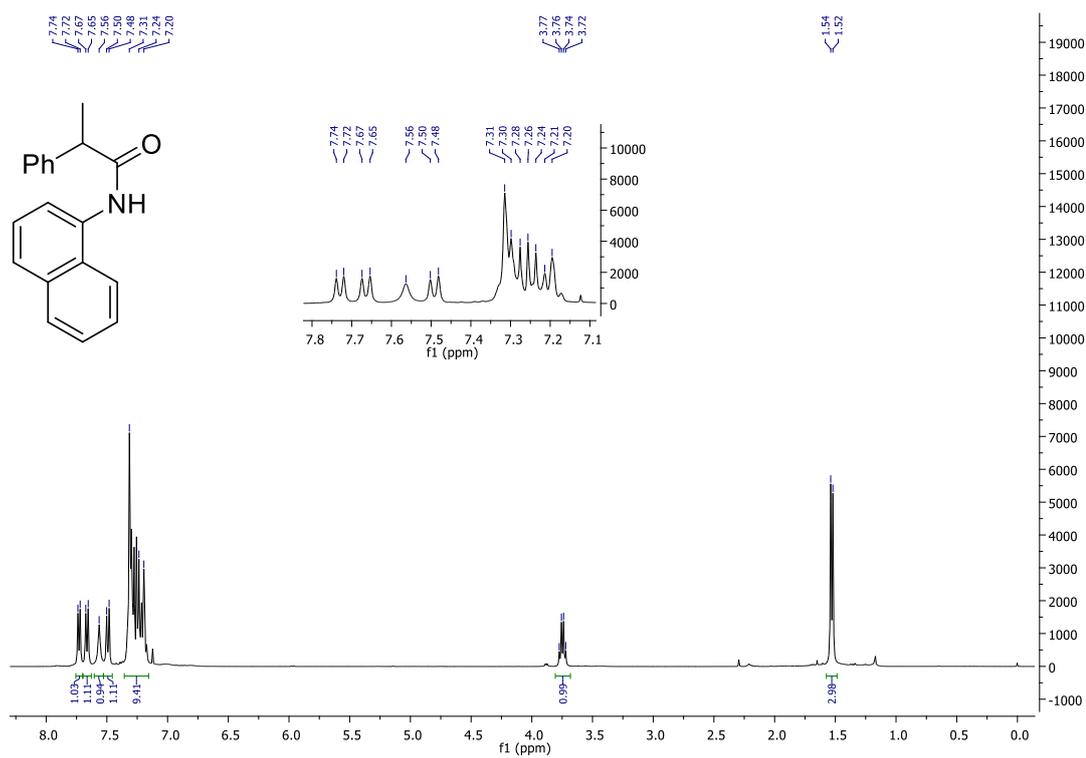
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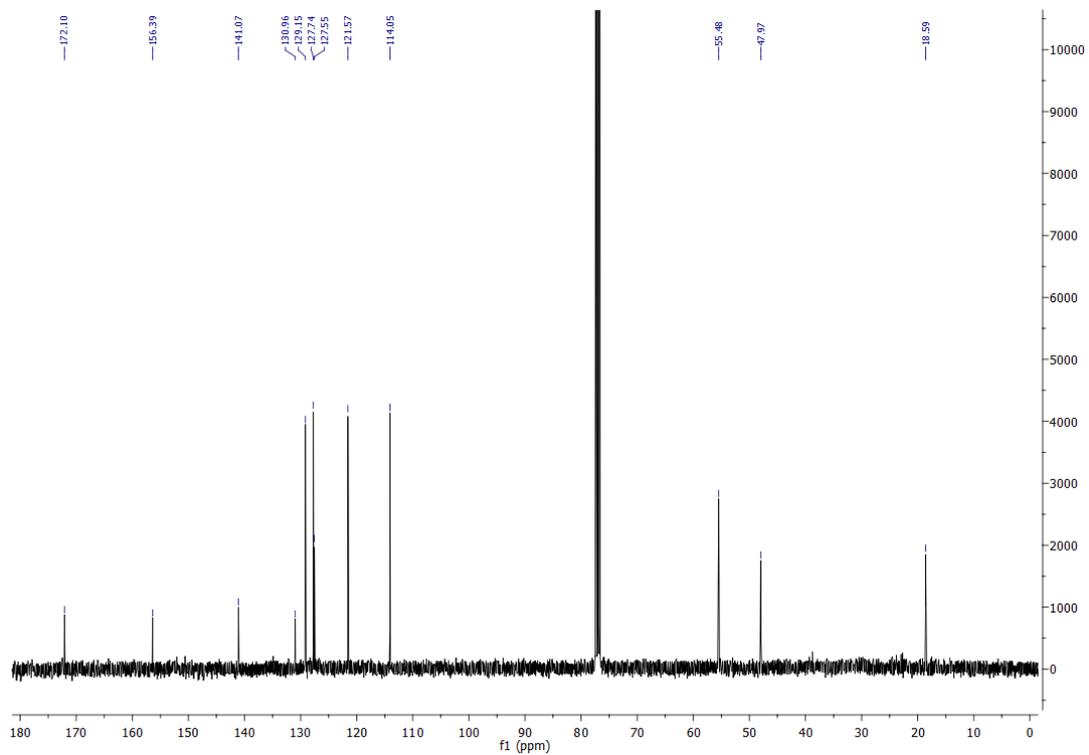
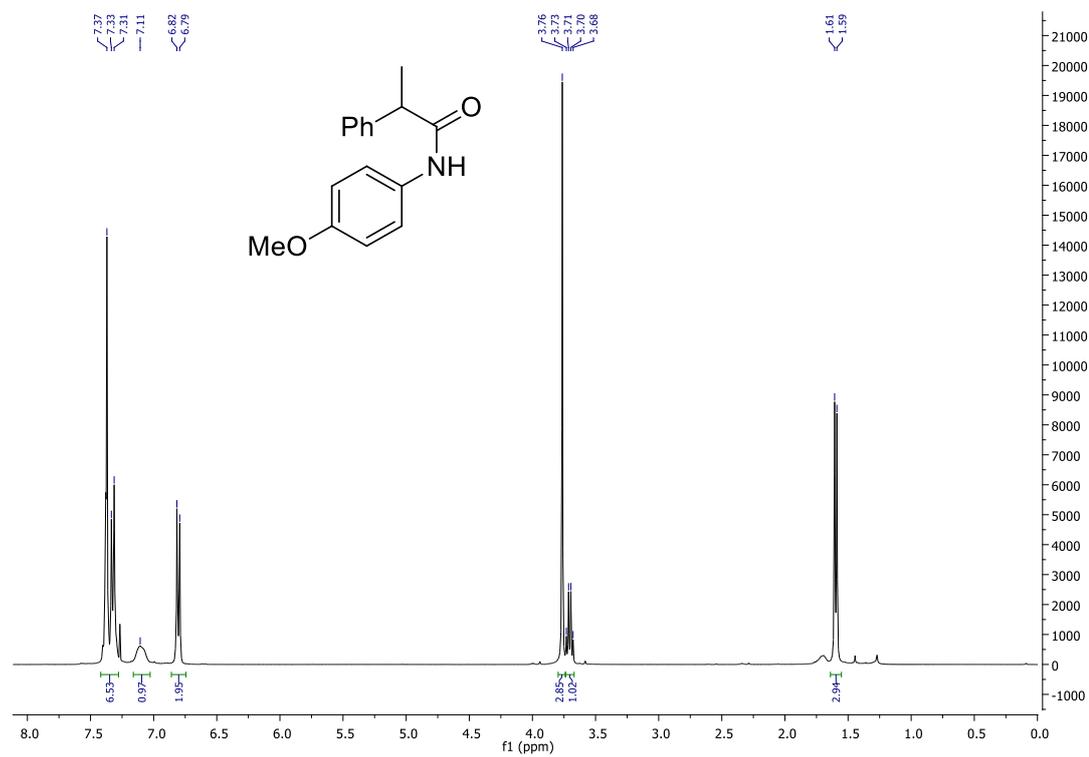
Compound 1.95b



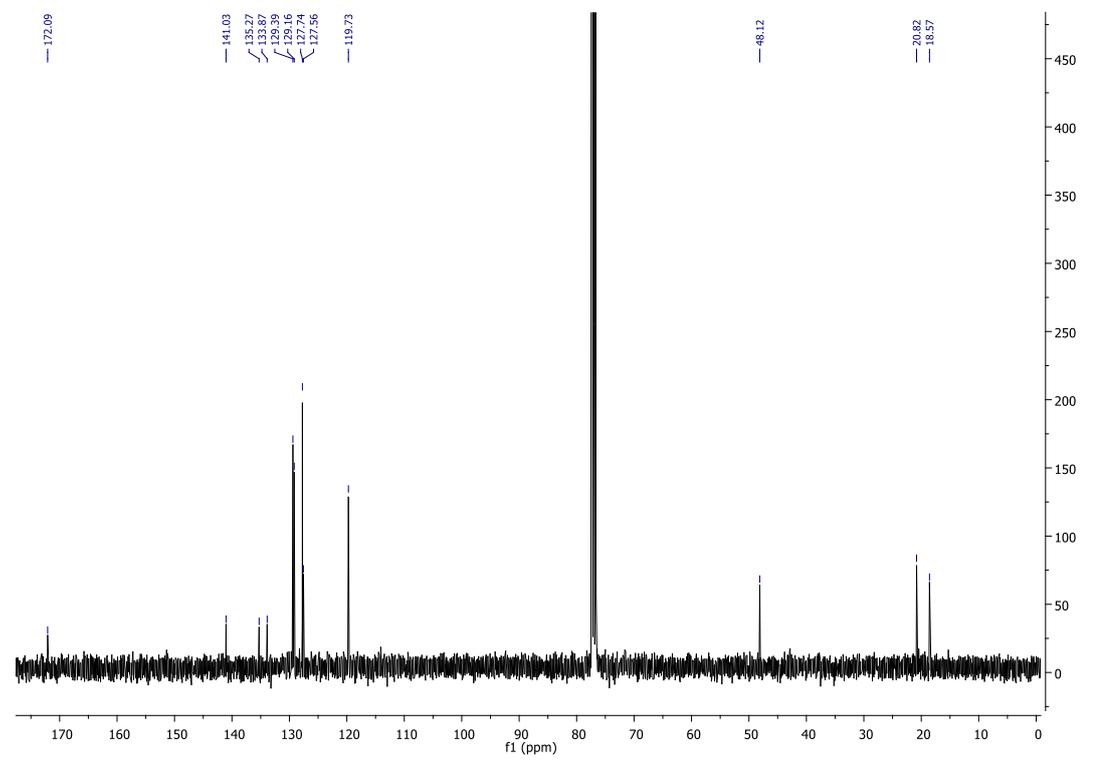
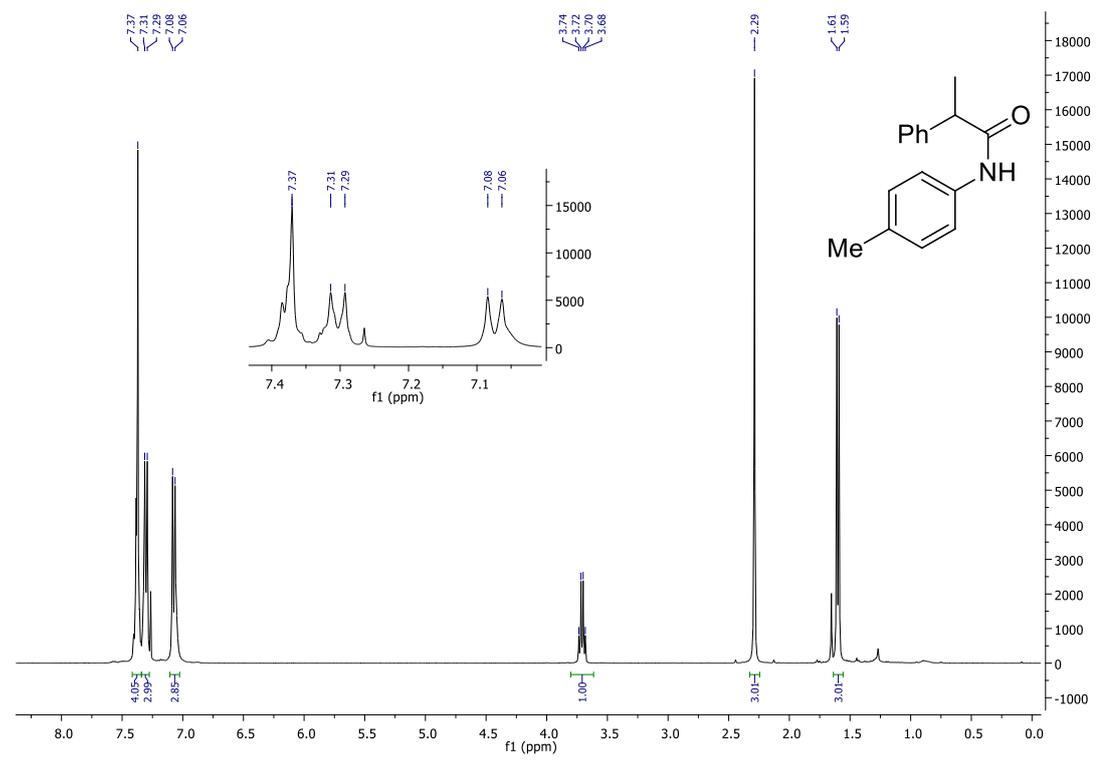
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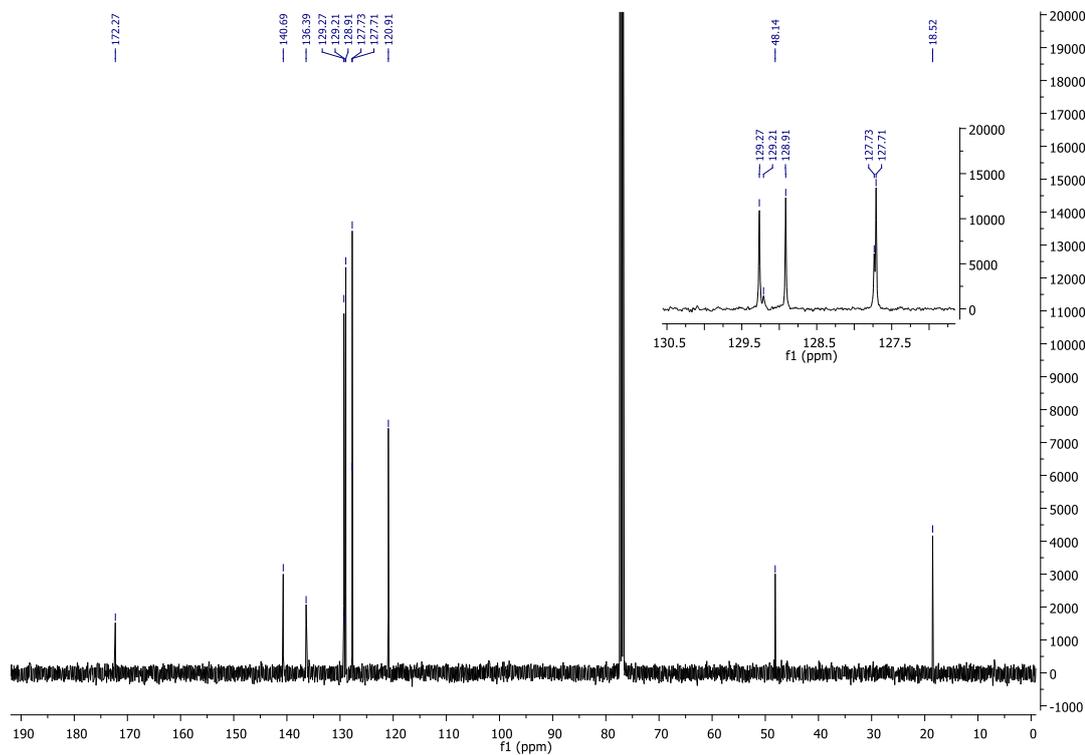
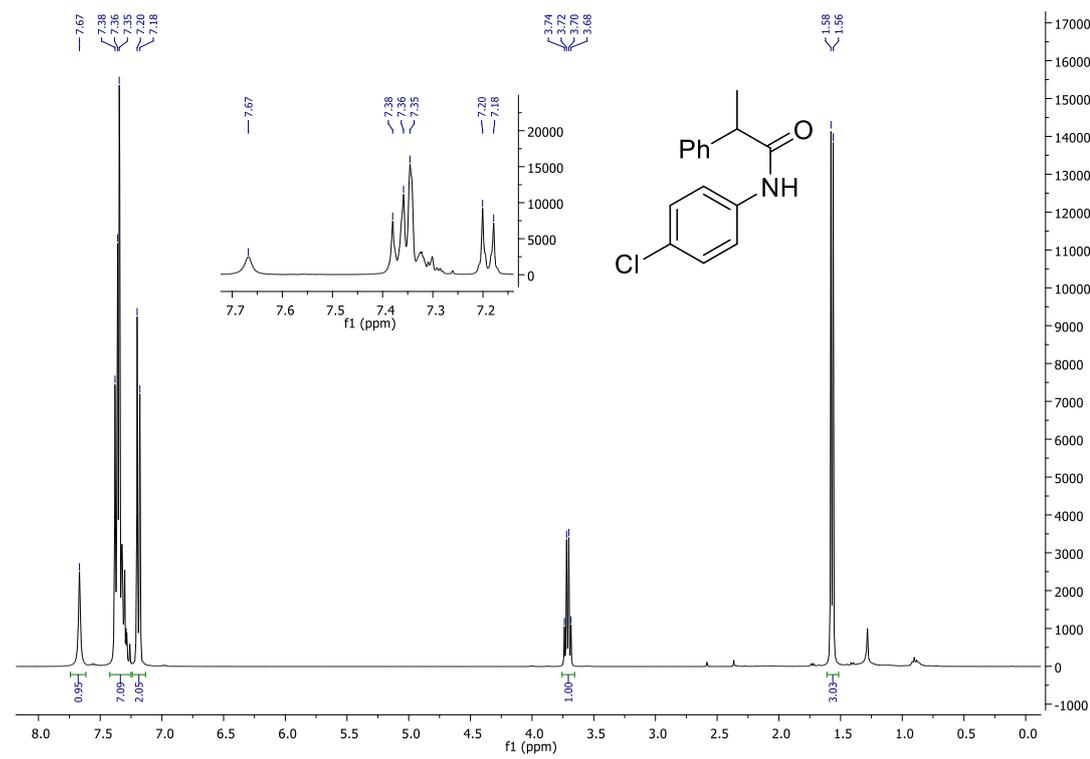
Compound 1.95d



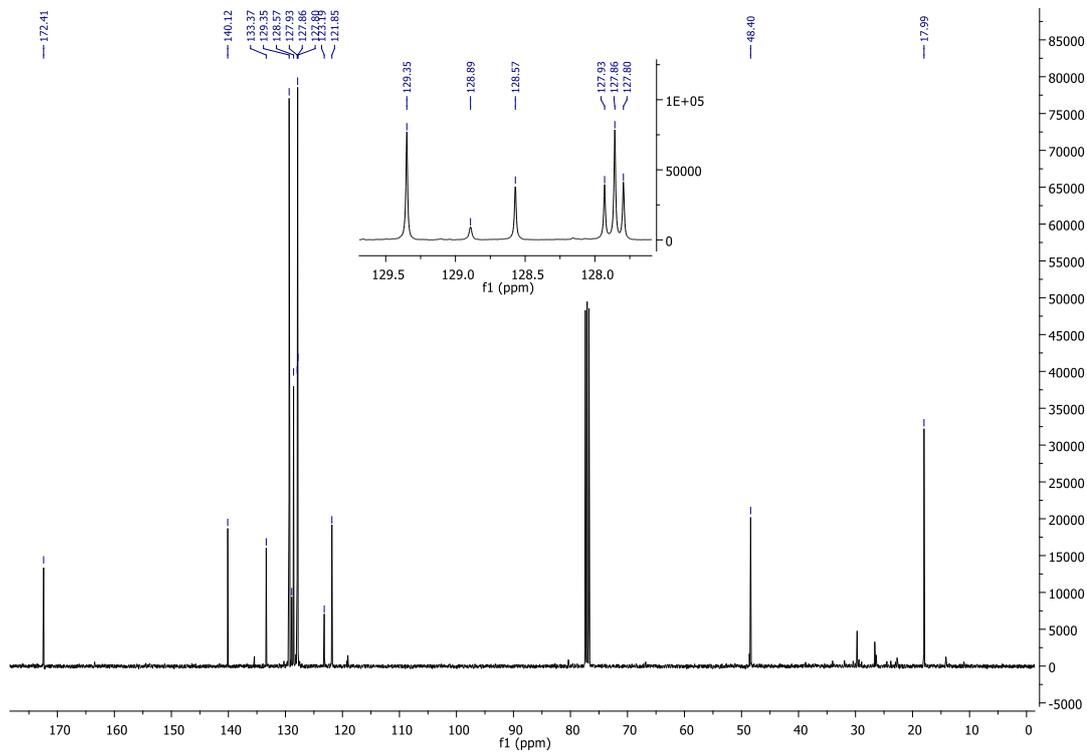
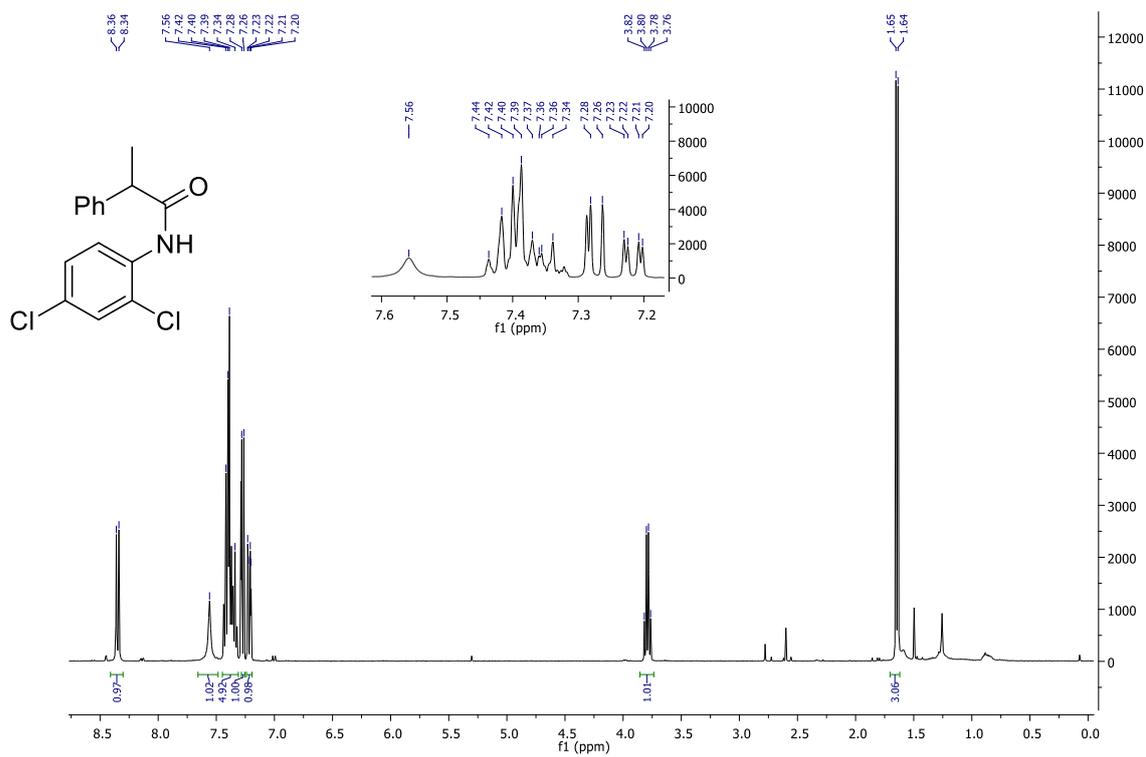
Compound 1.95e



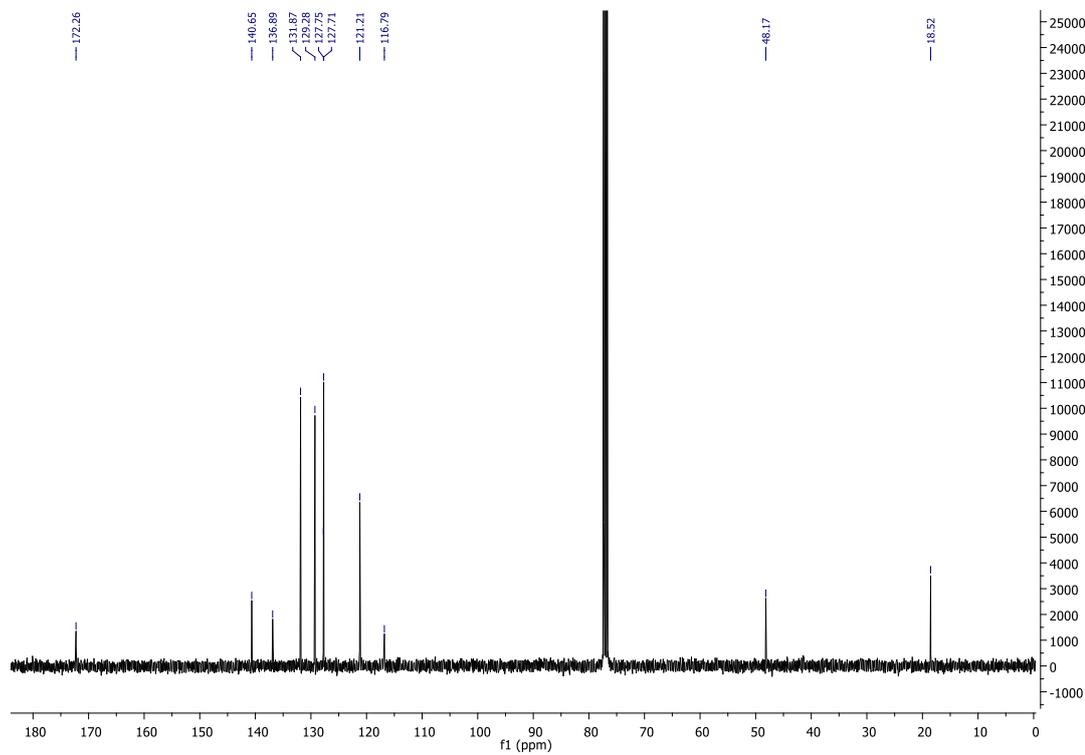
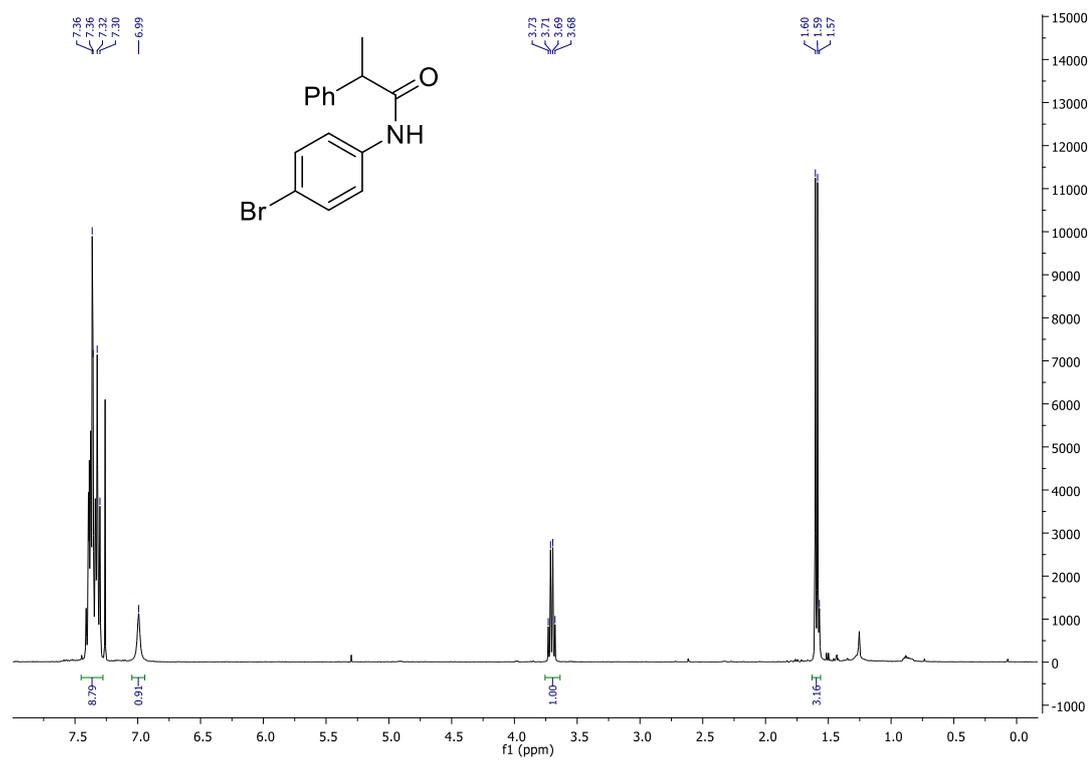
Compound 1.95g



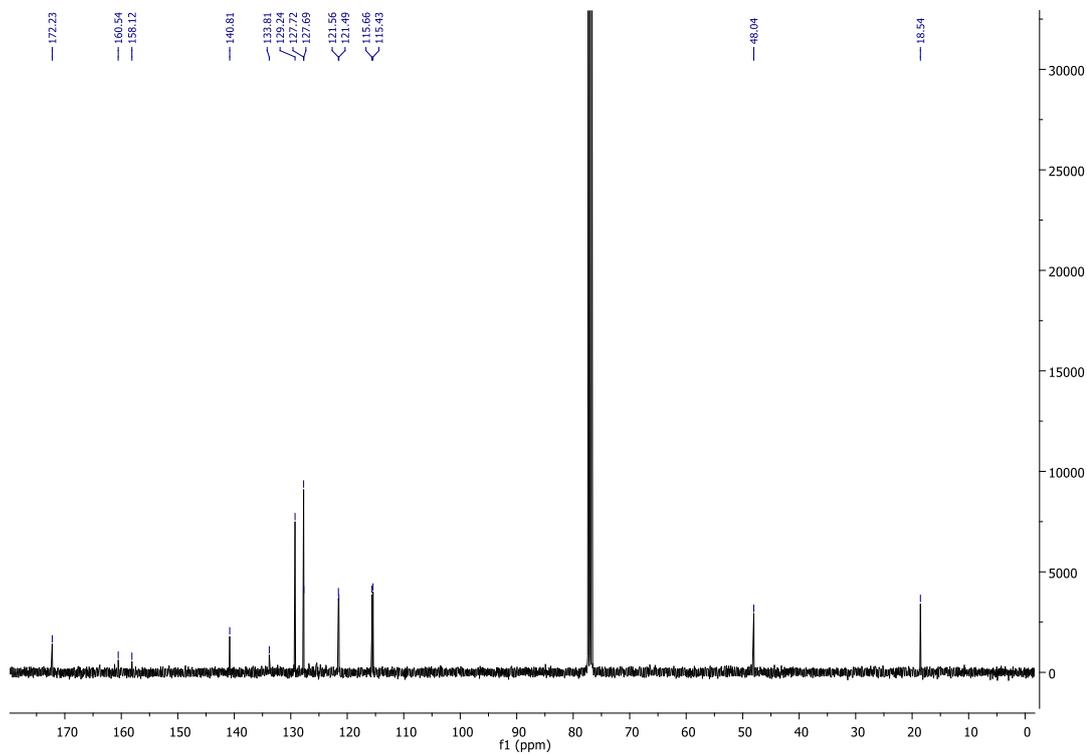
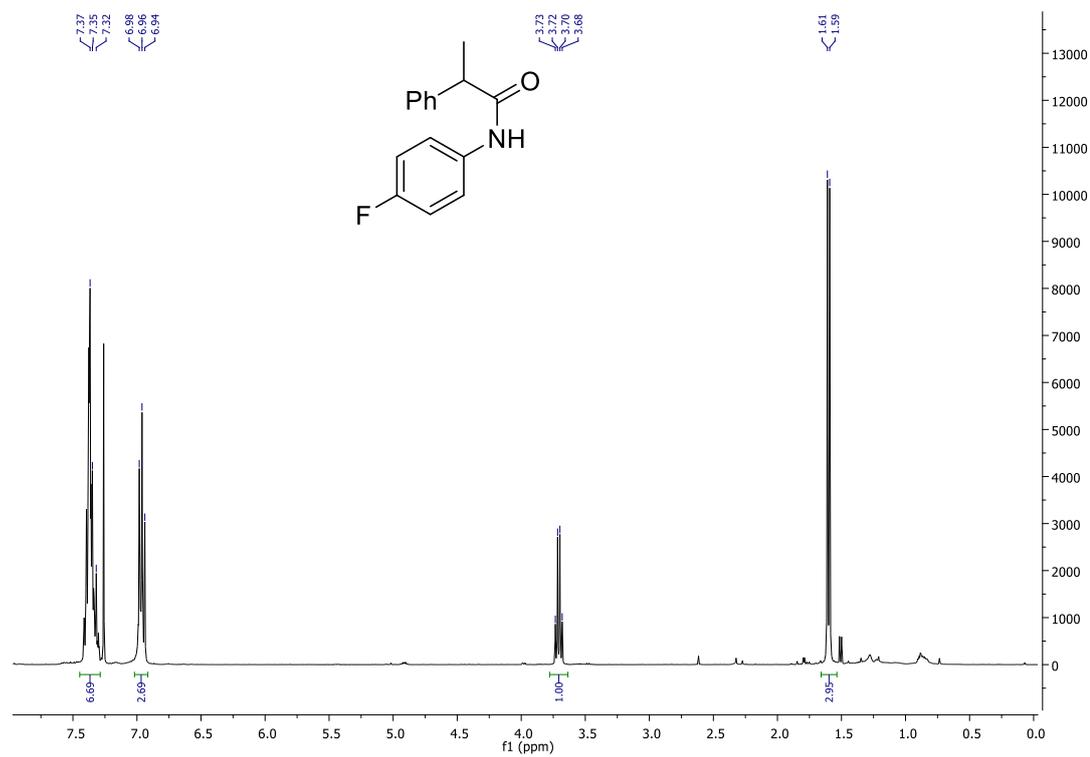
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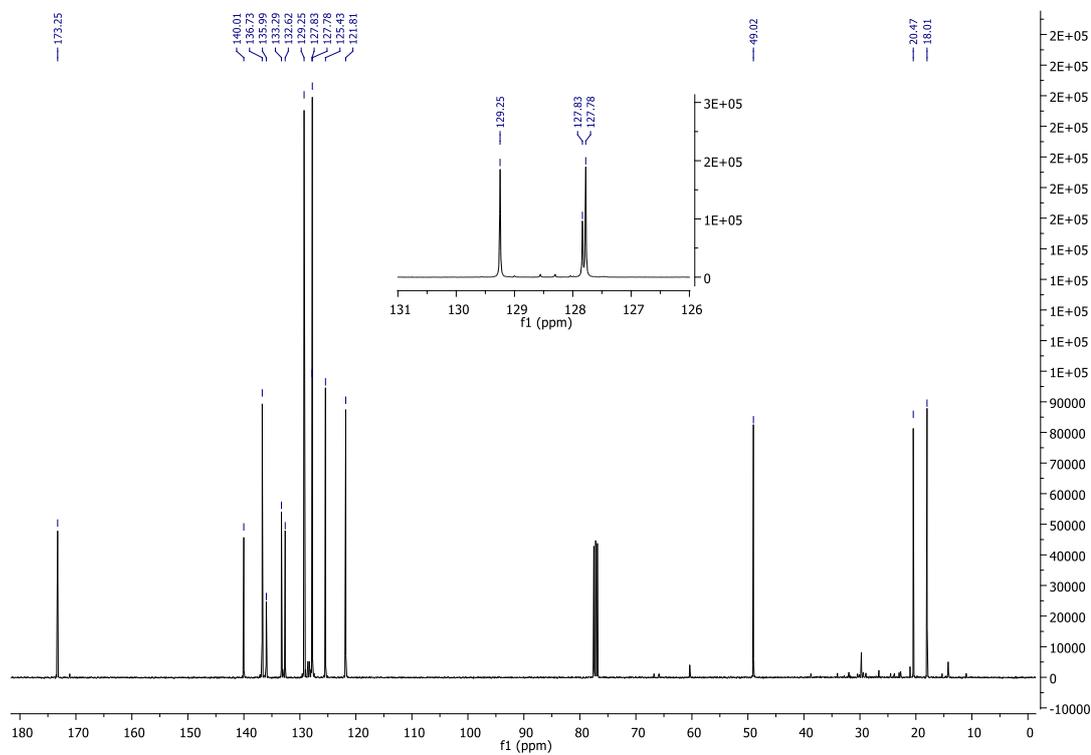
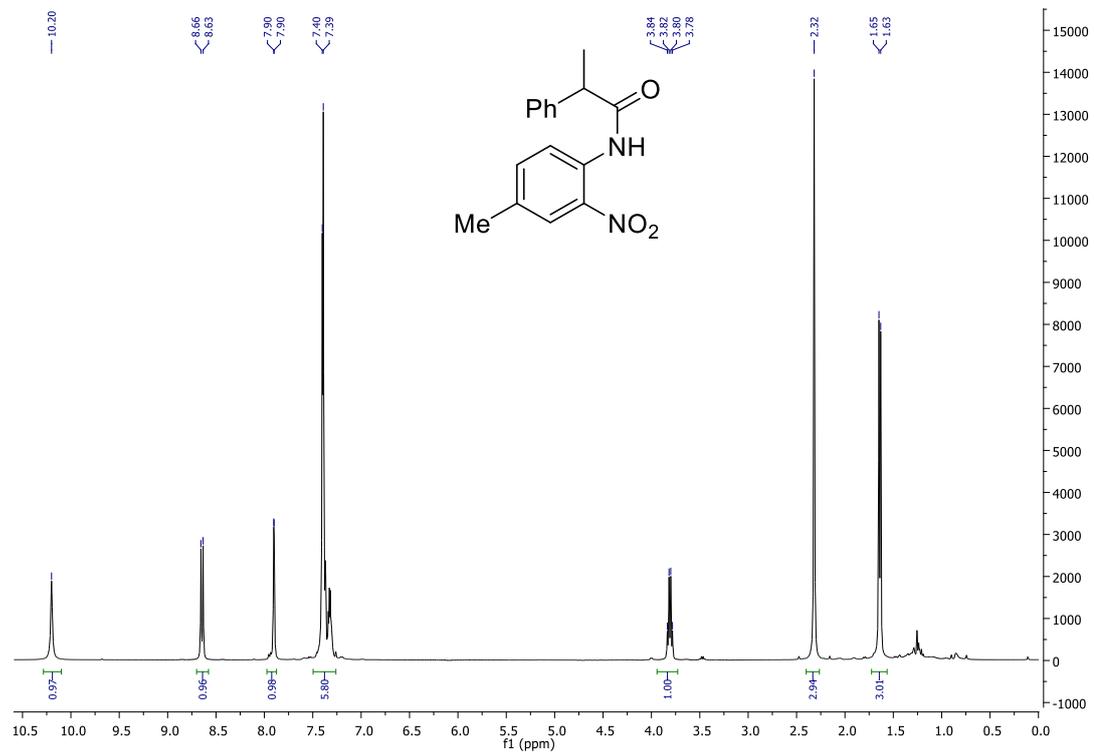


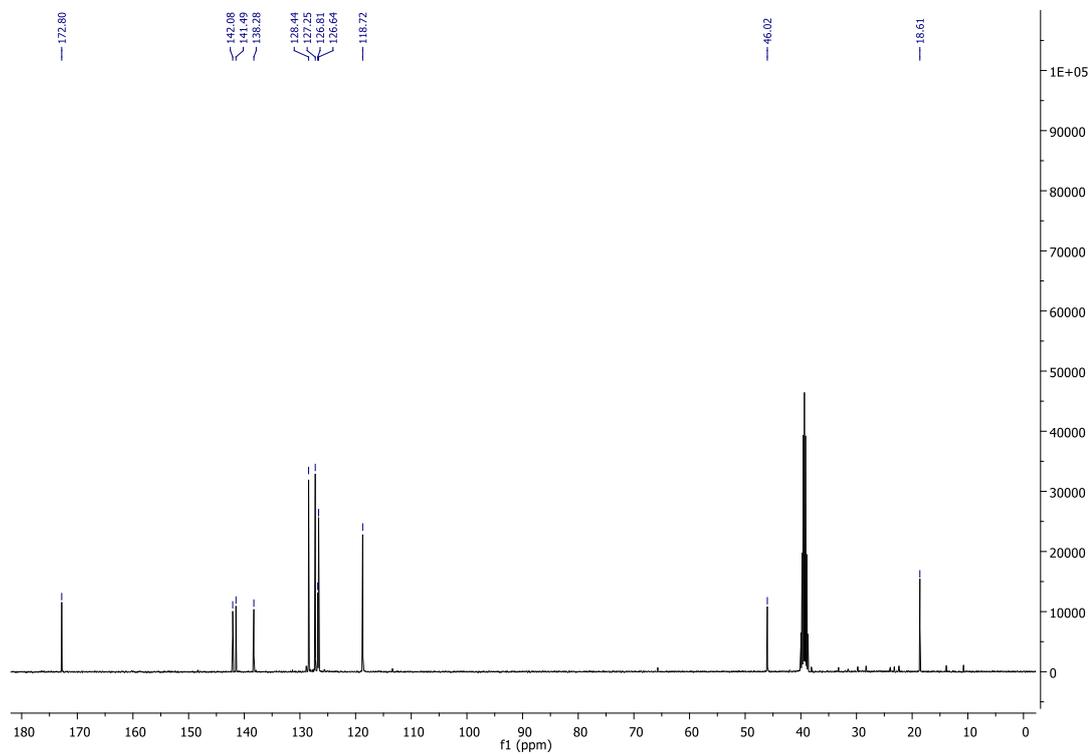
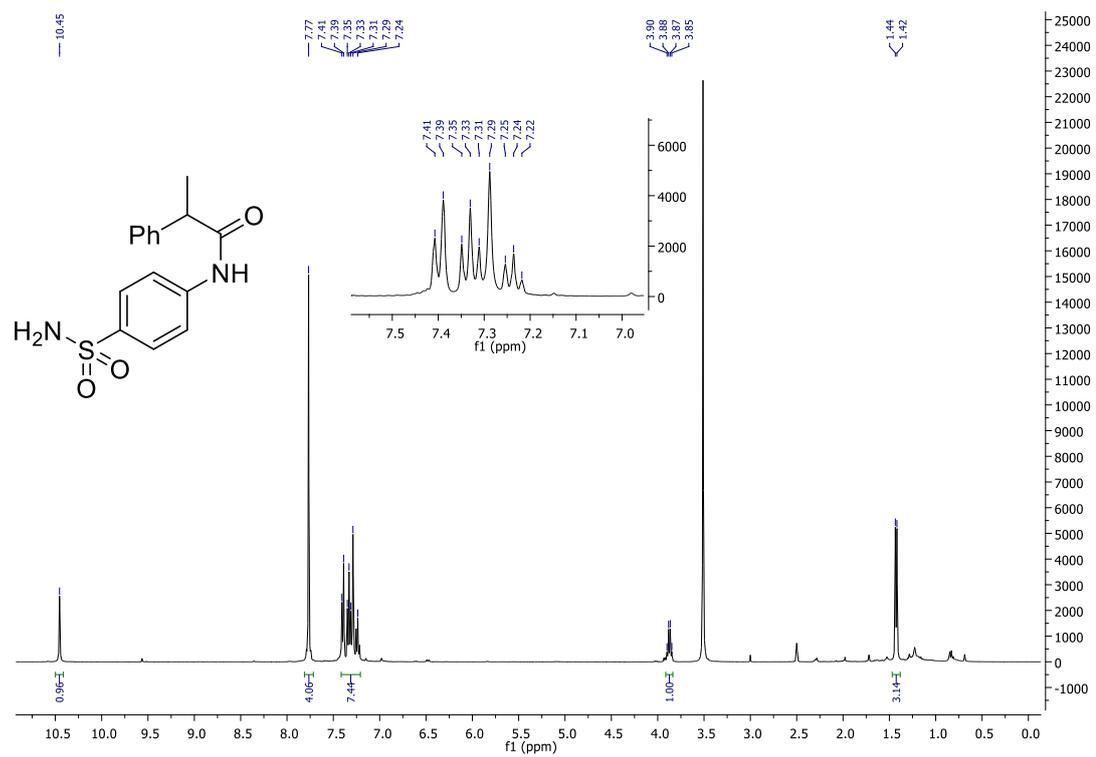
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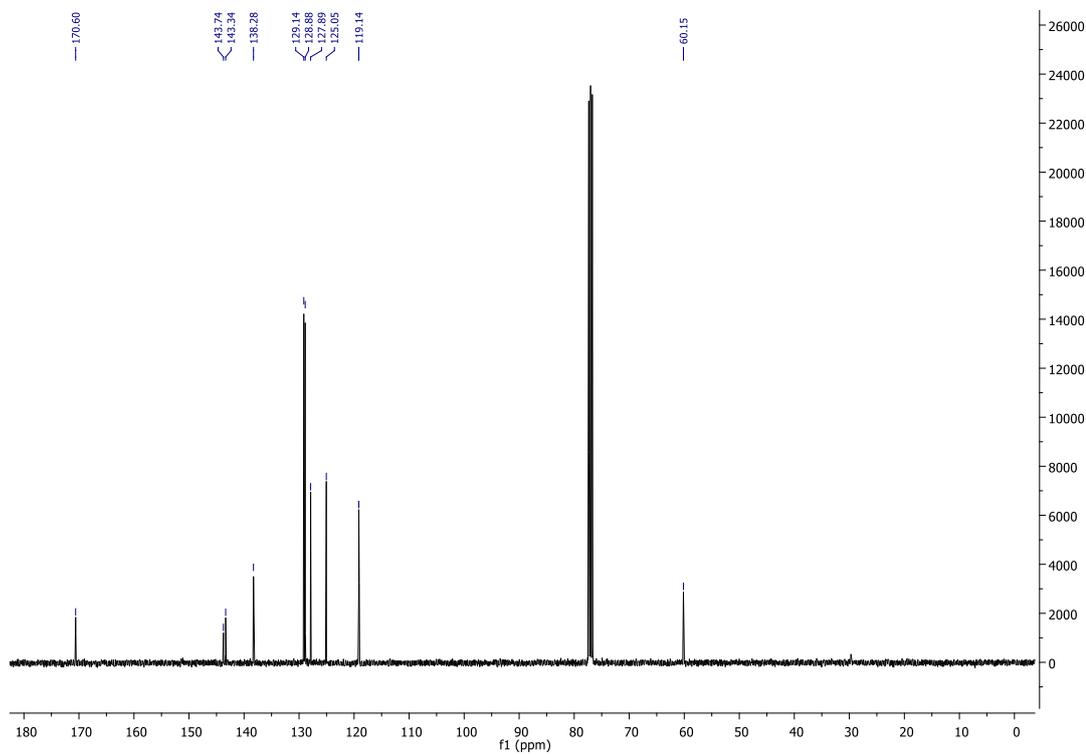
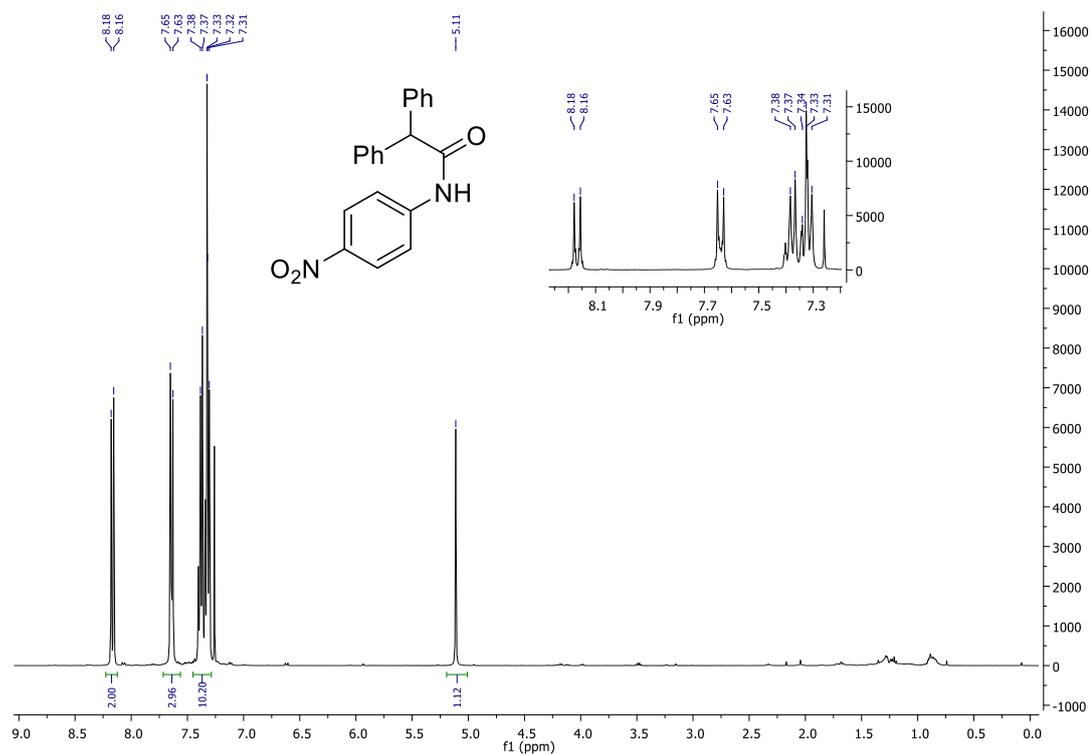
Compound 1.95j



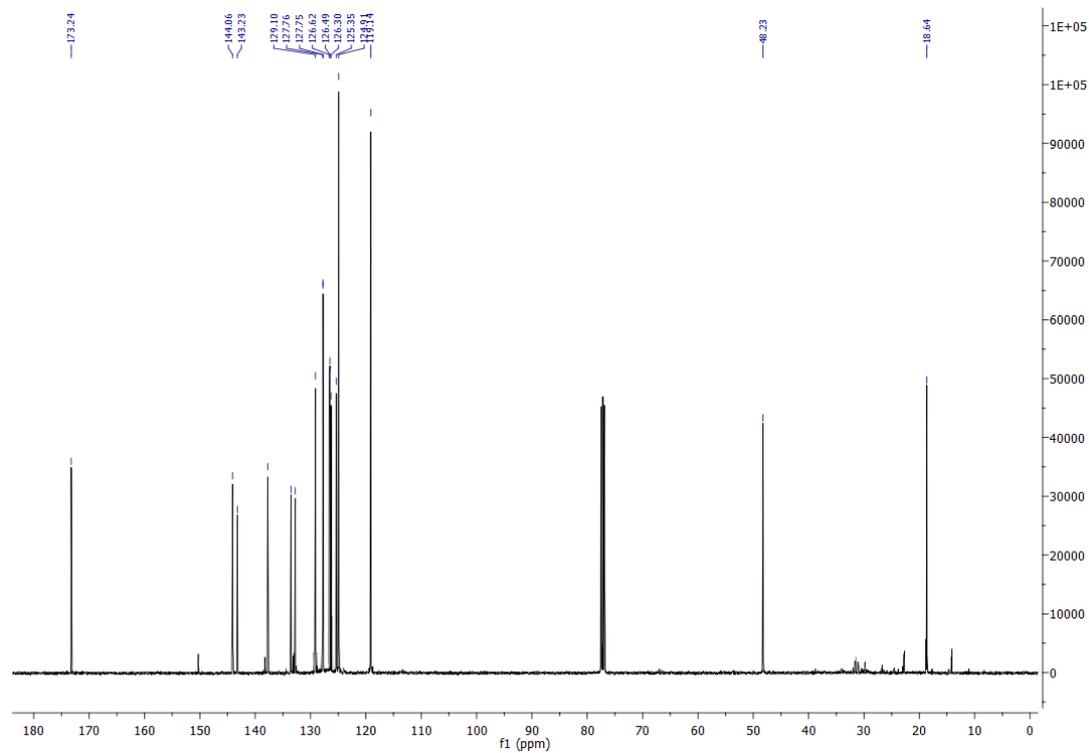
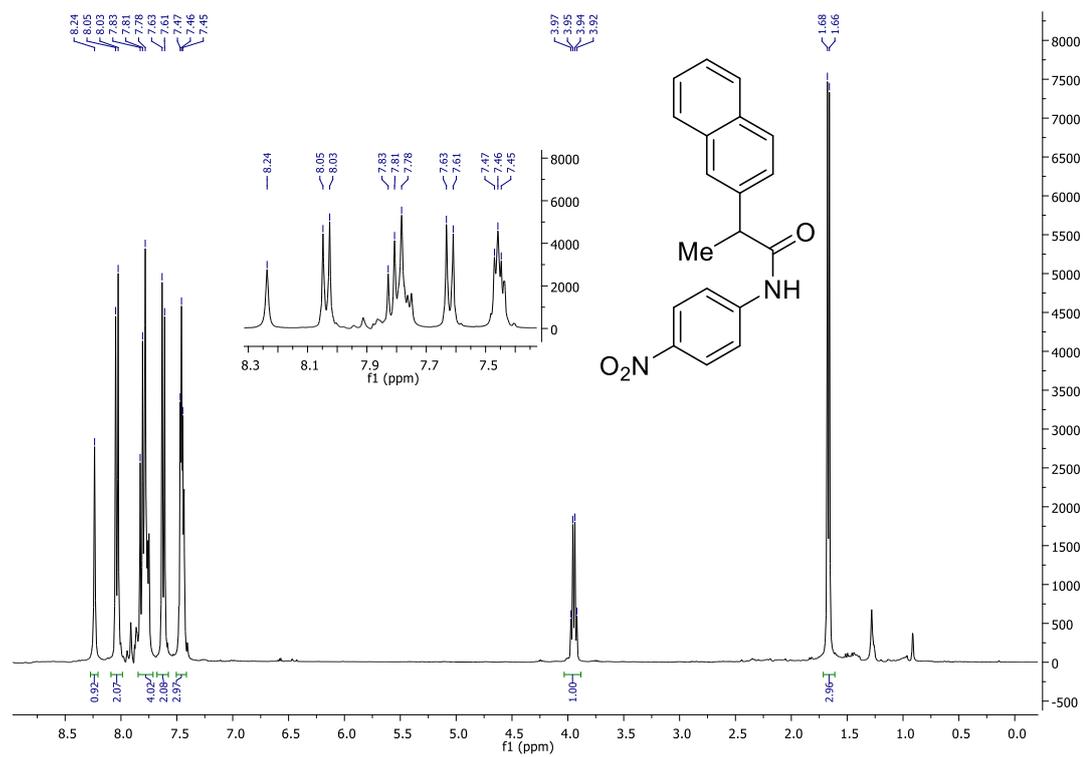
Compound **1.95k**

Compound **1.95I** (solvent DMSO-d₆)

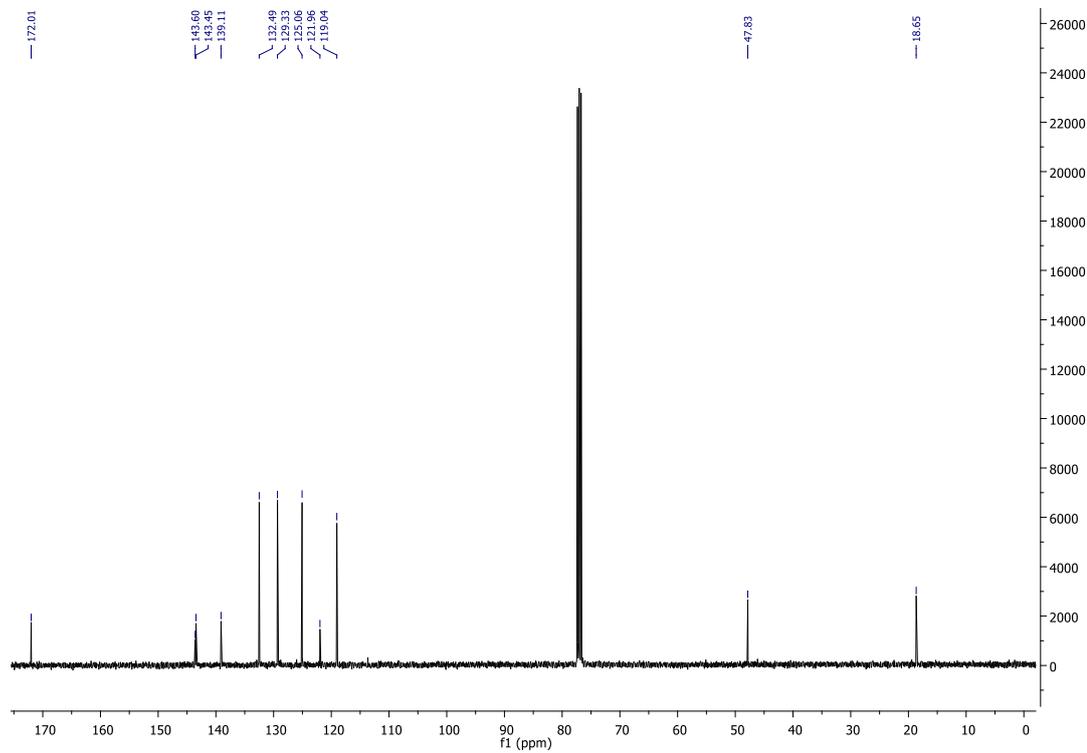
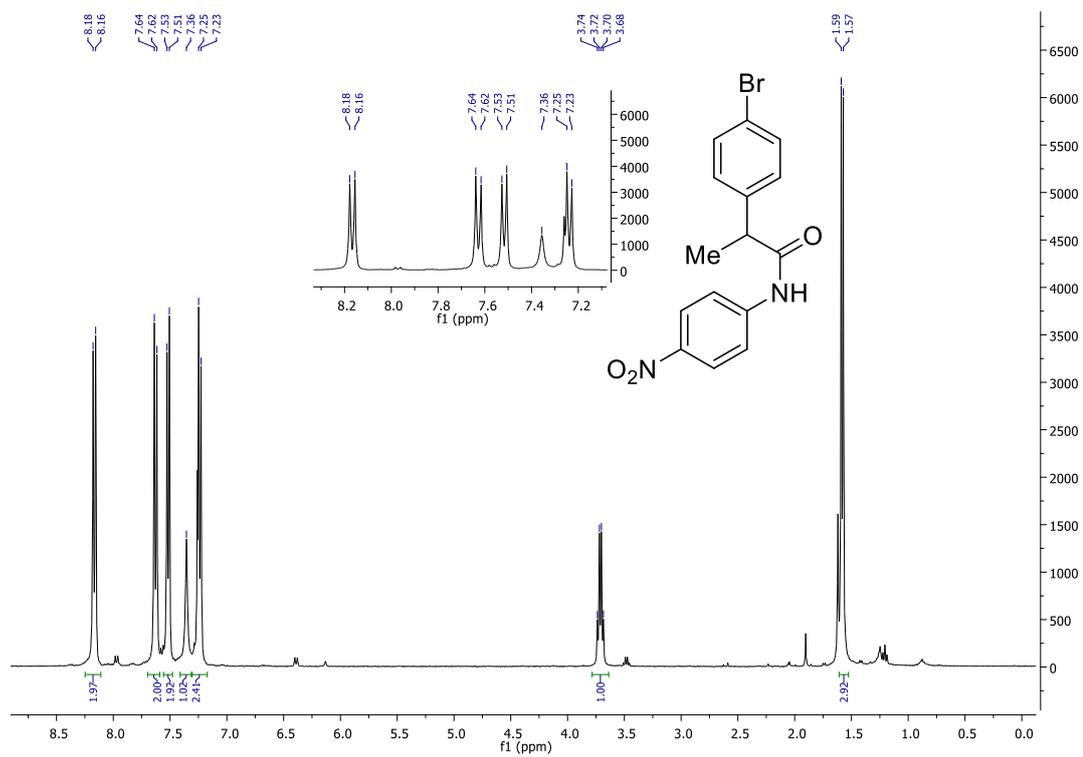
Compound 1.95m



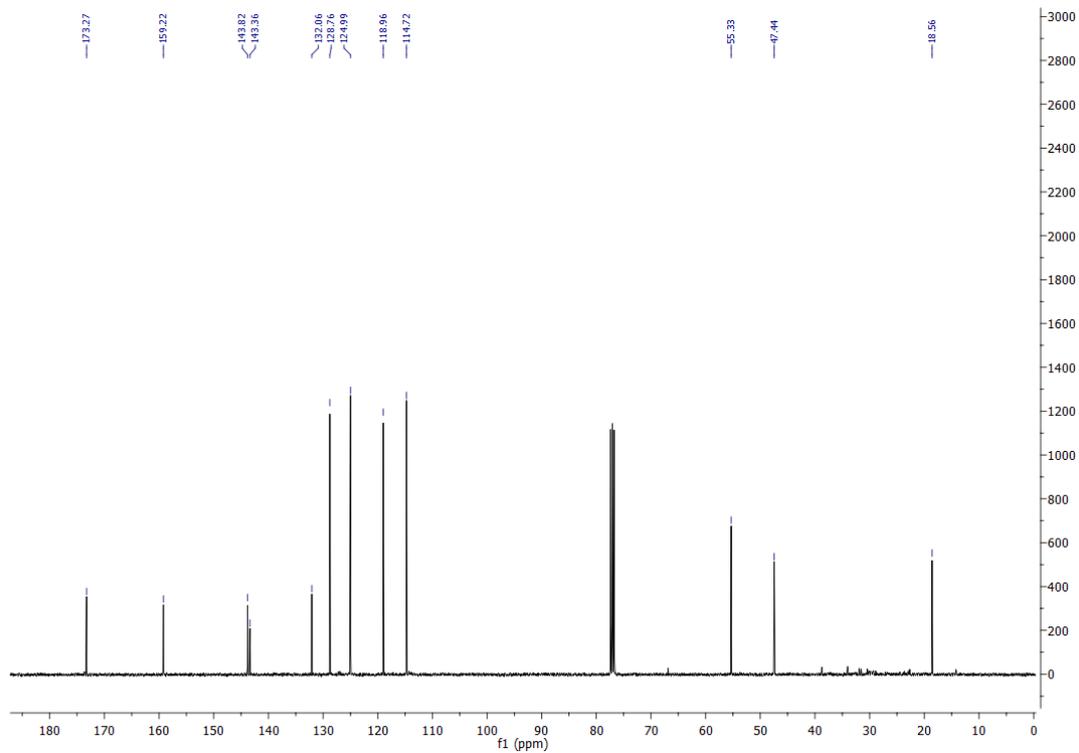
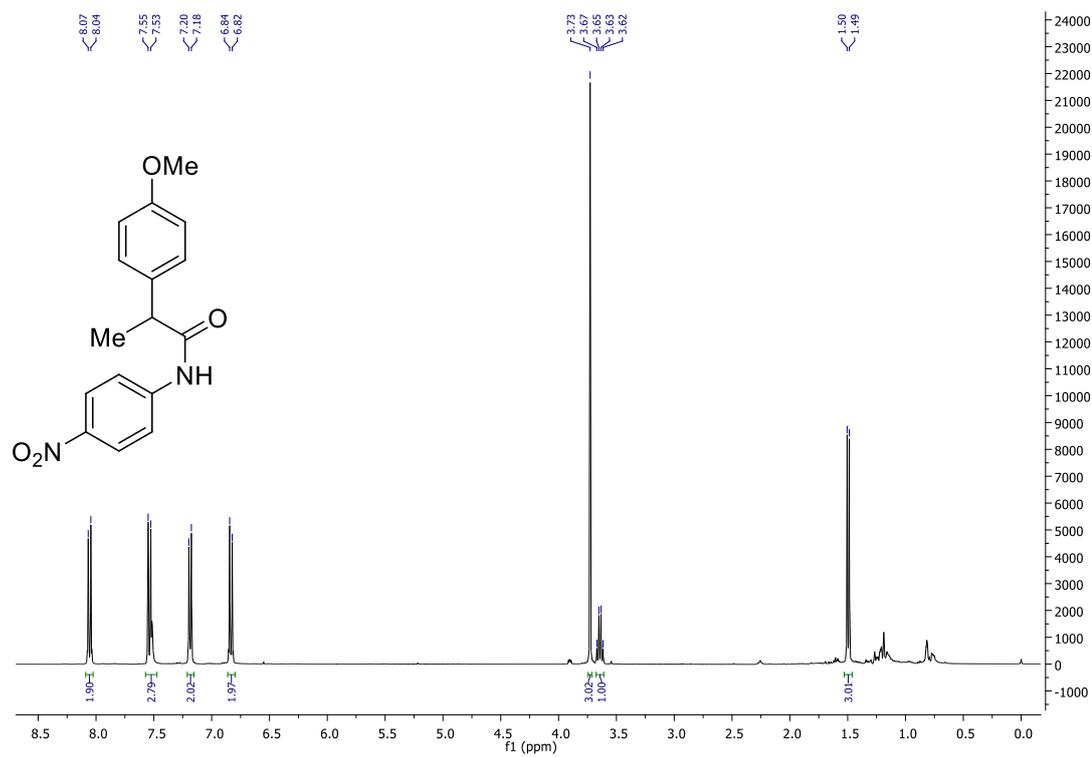
Compound 1.95n



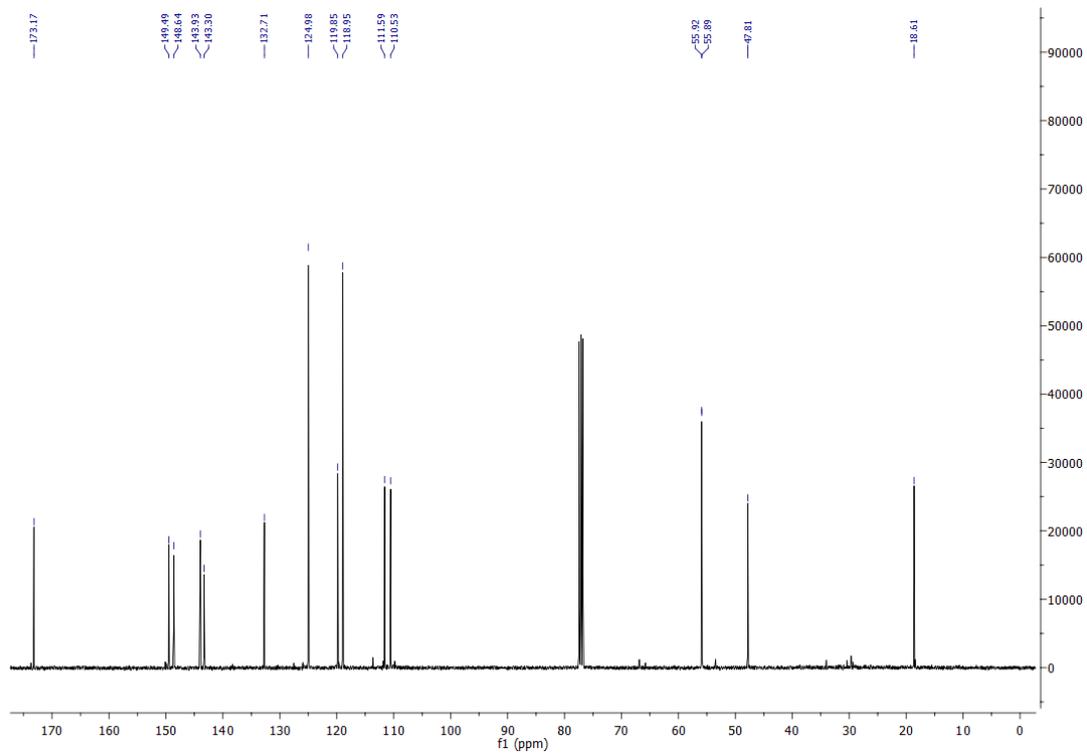
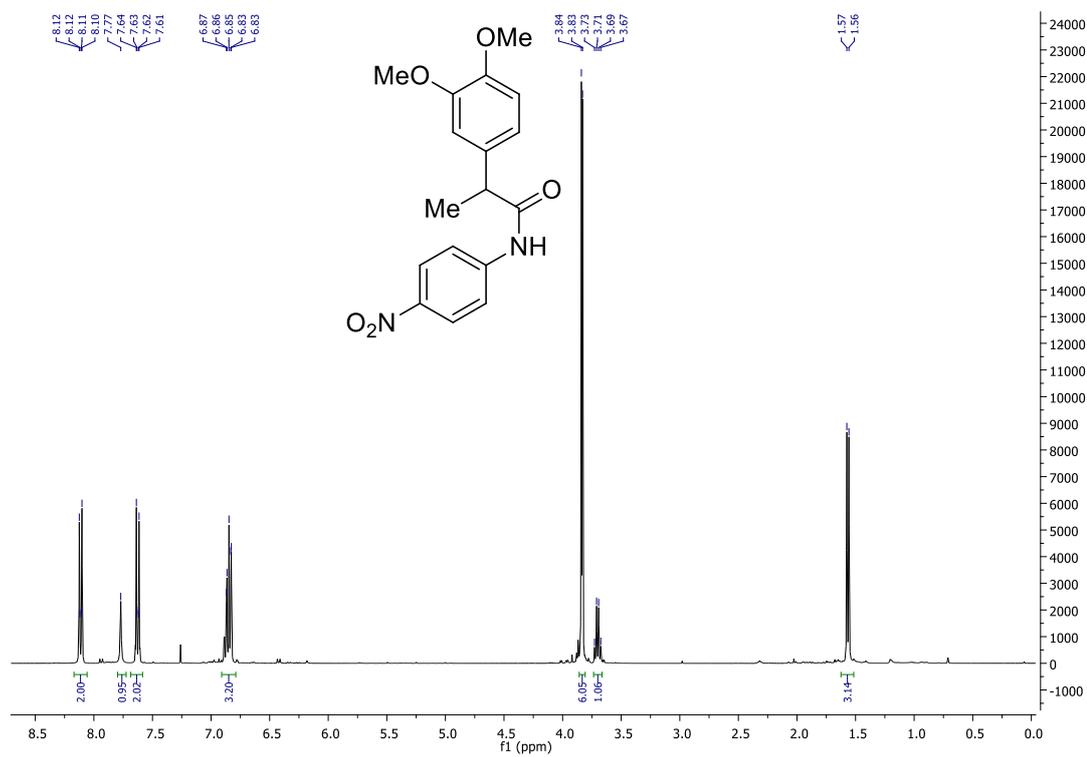
Compound 1.95o



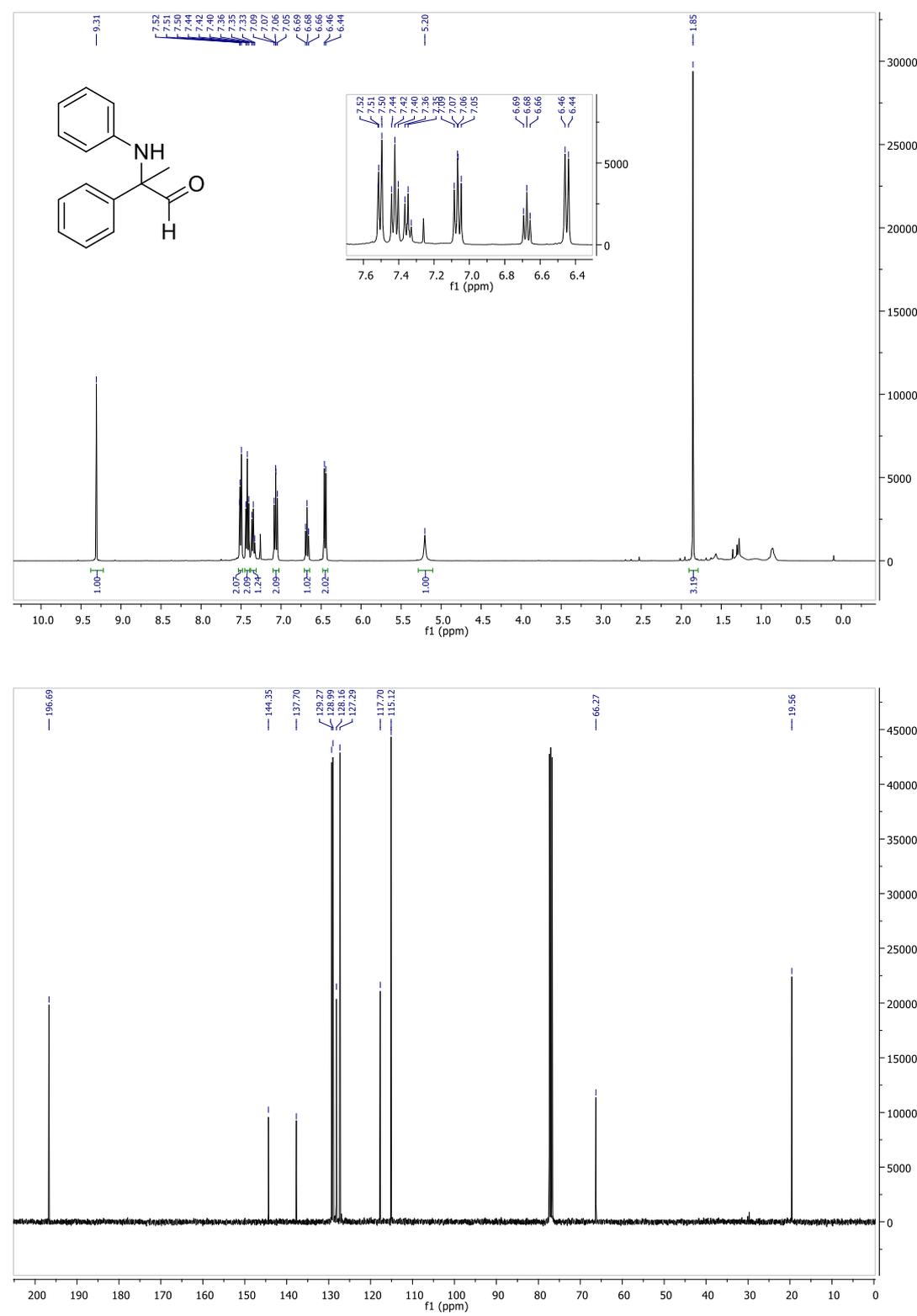
Compound 1.95p

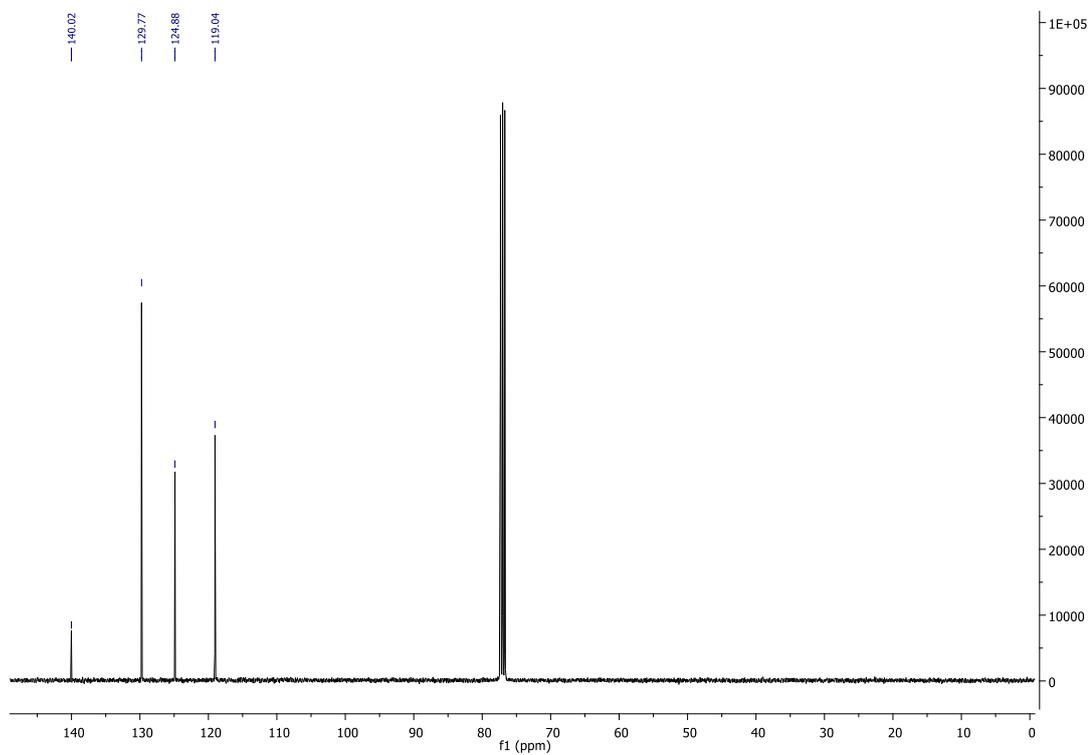
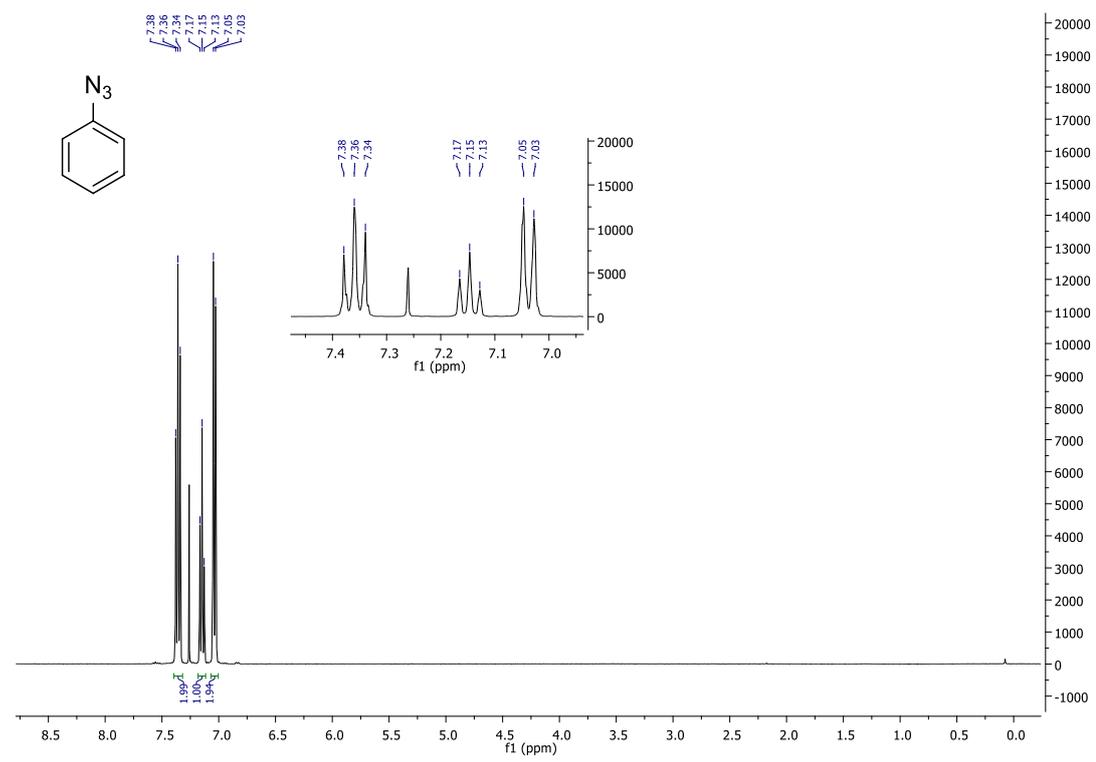


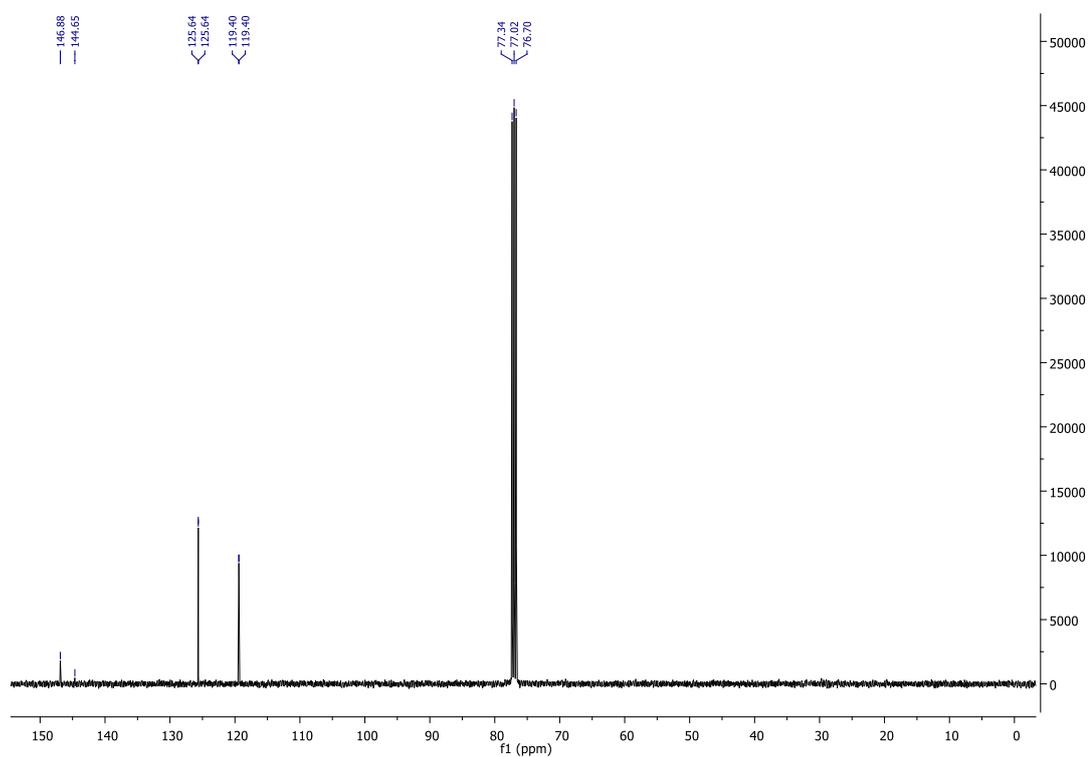
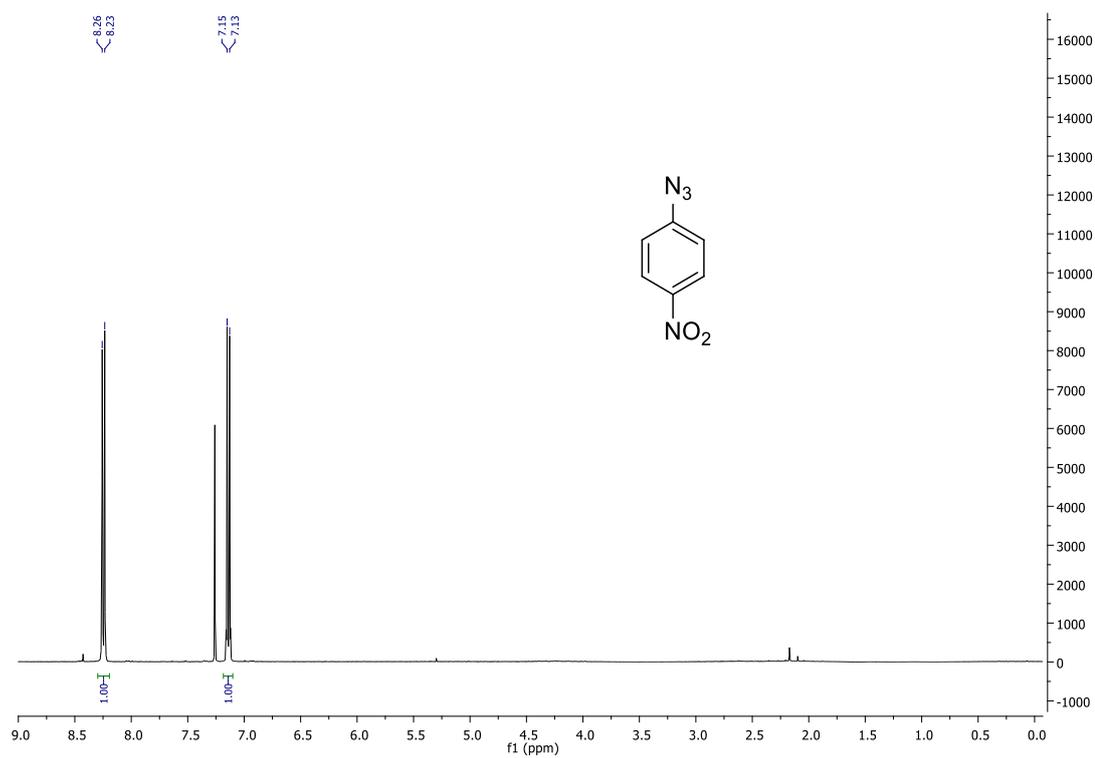
Compound 1.95q



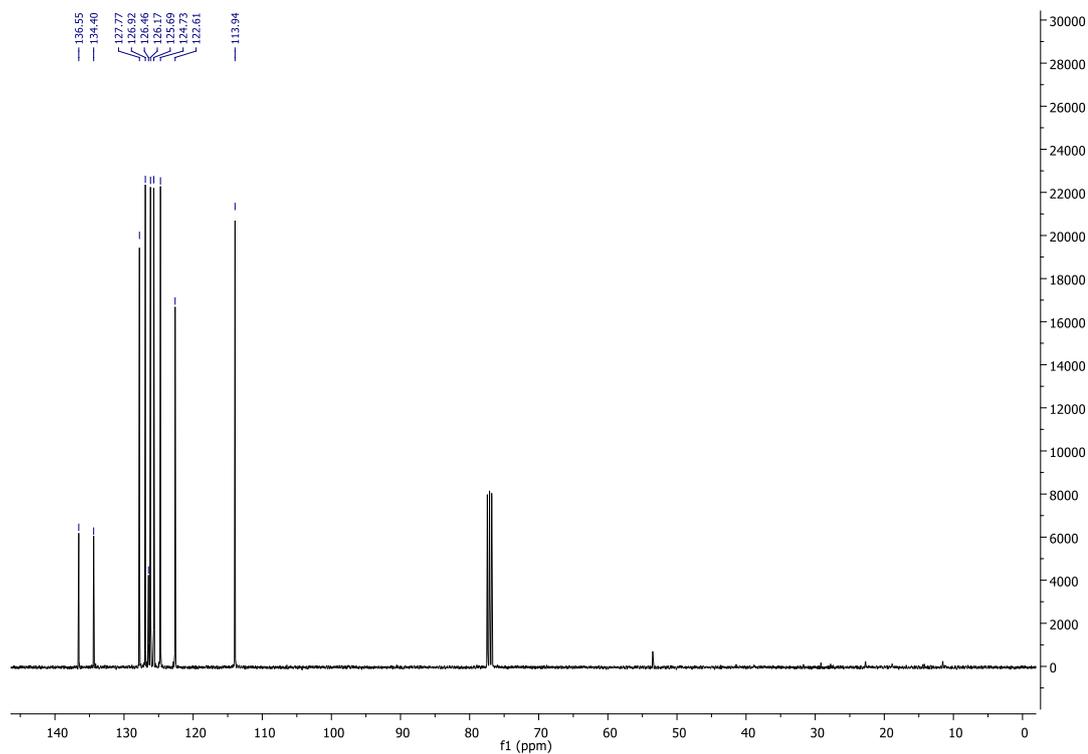
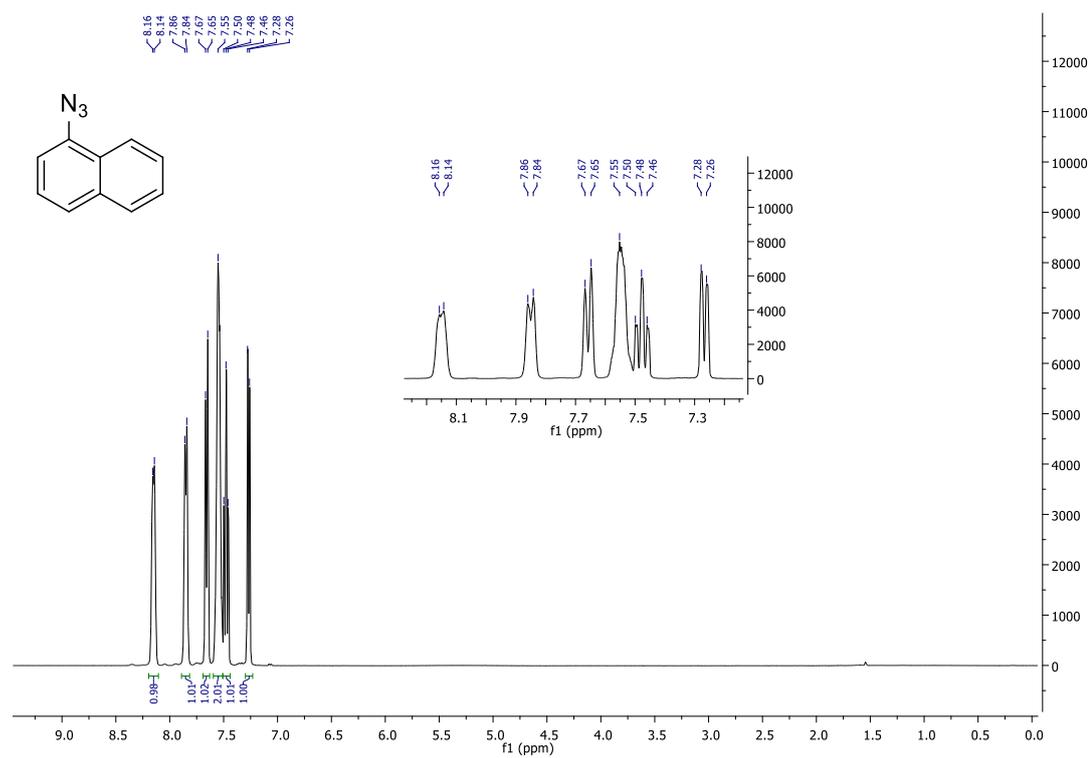
Compound 1.94



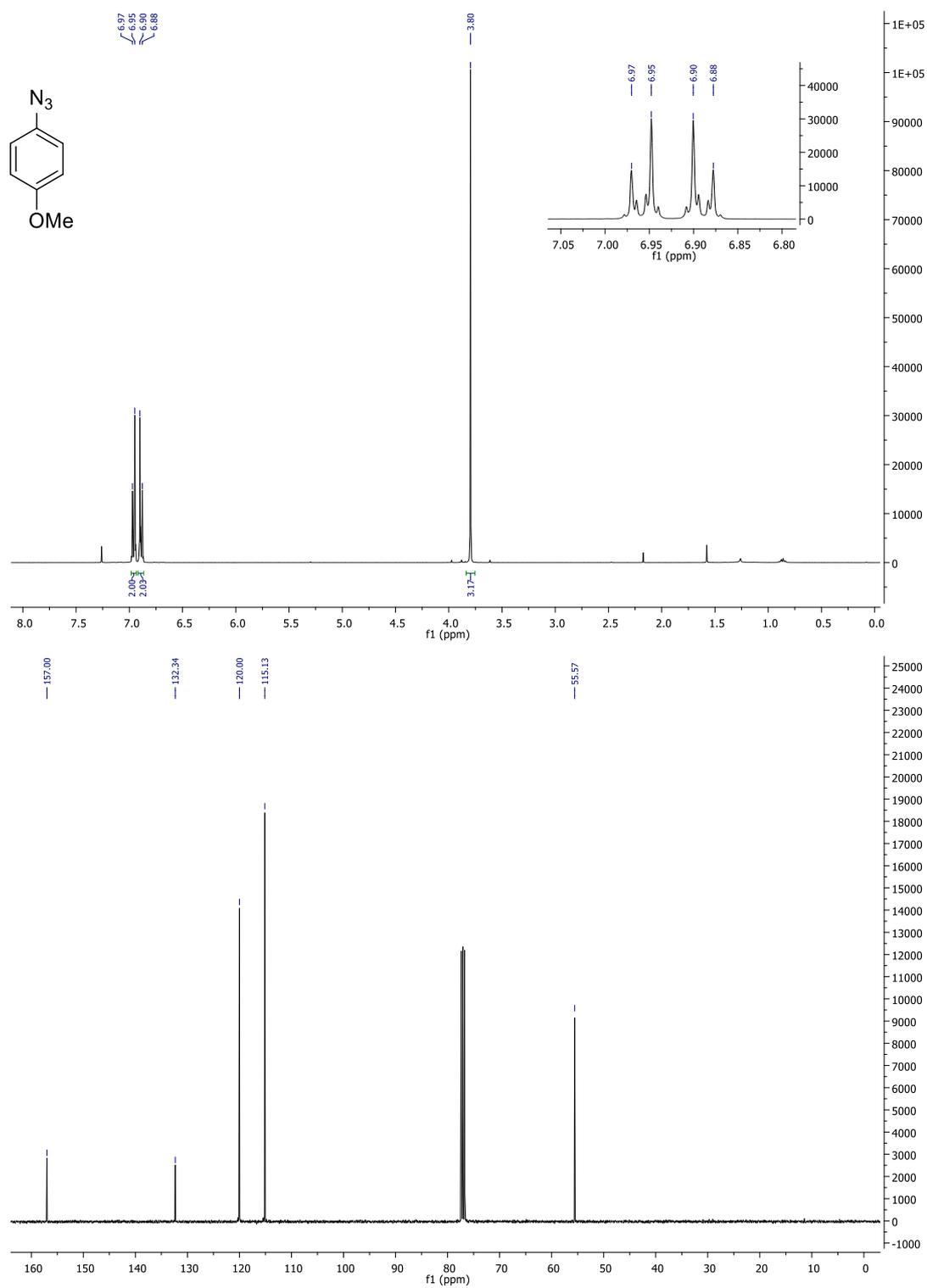
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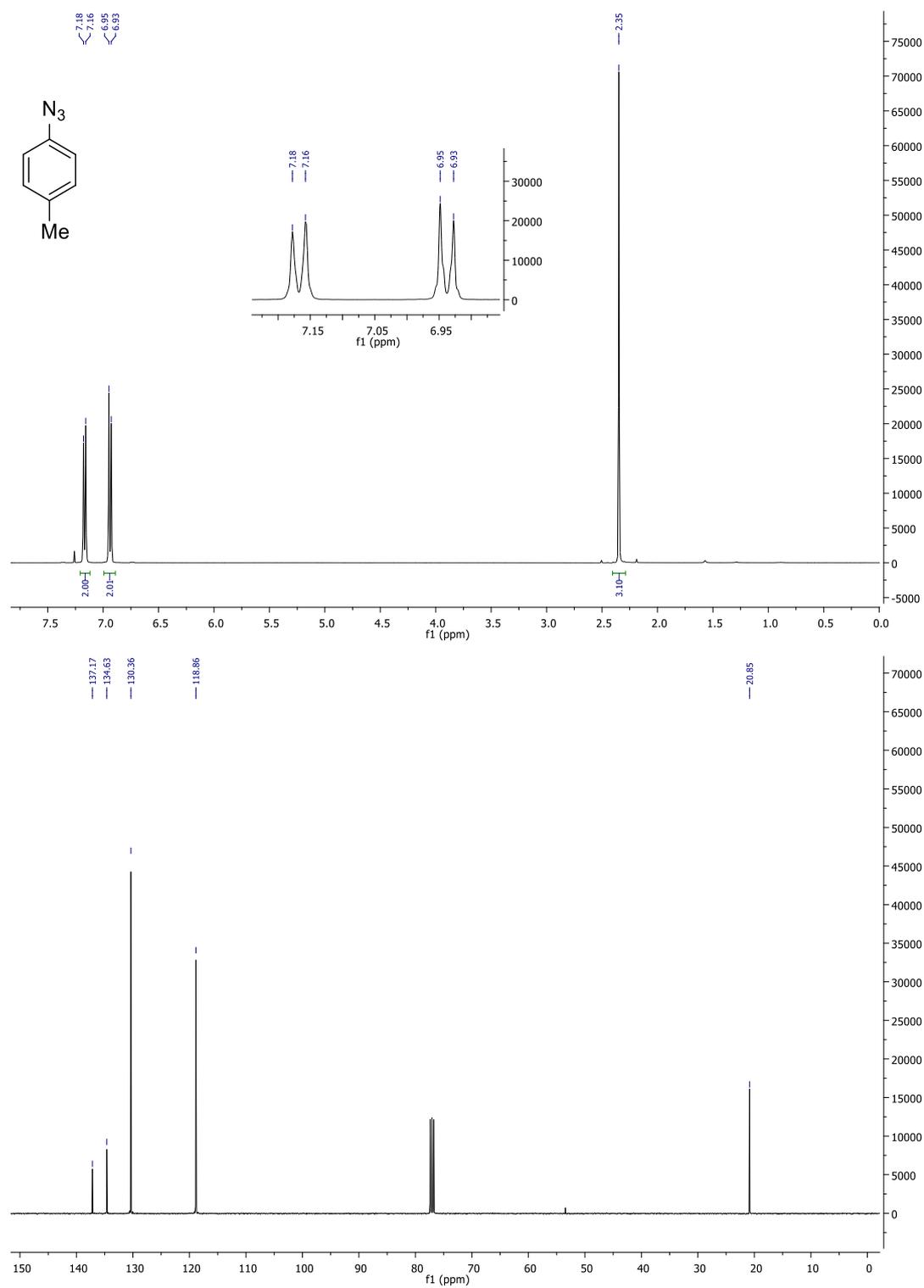
Compound **1.77b**

Compound 1.77c

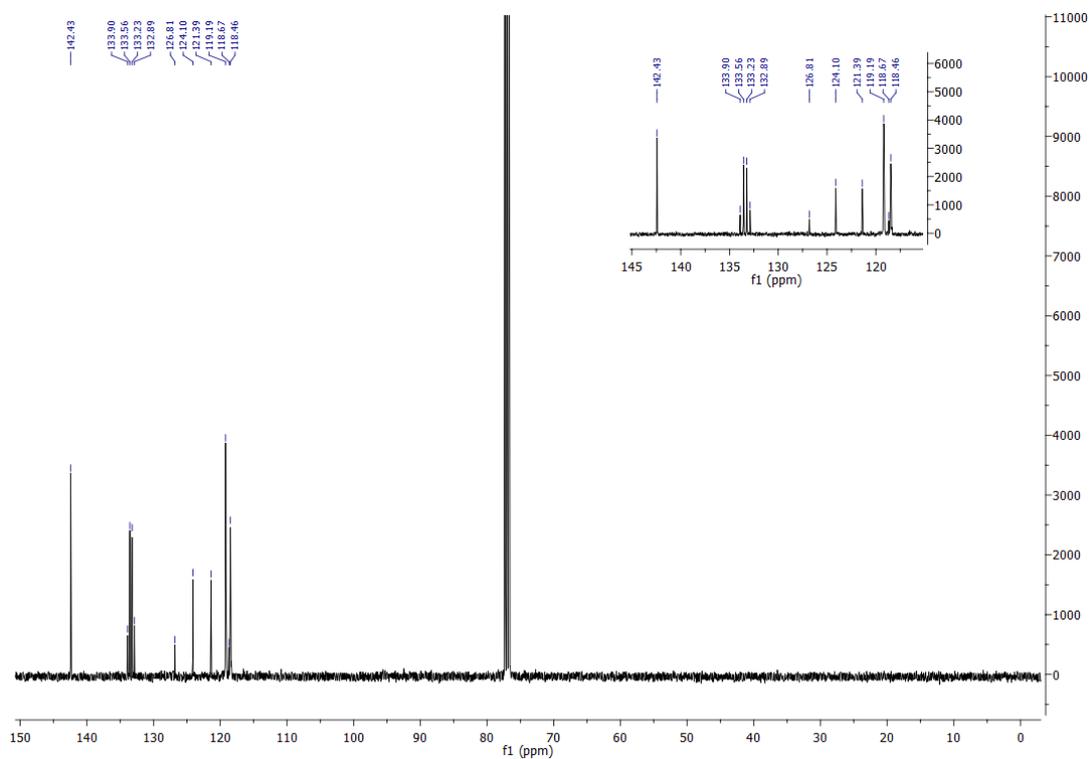
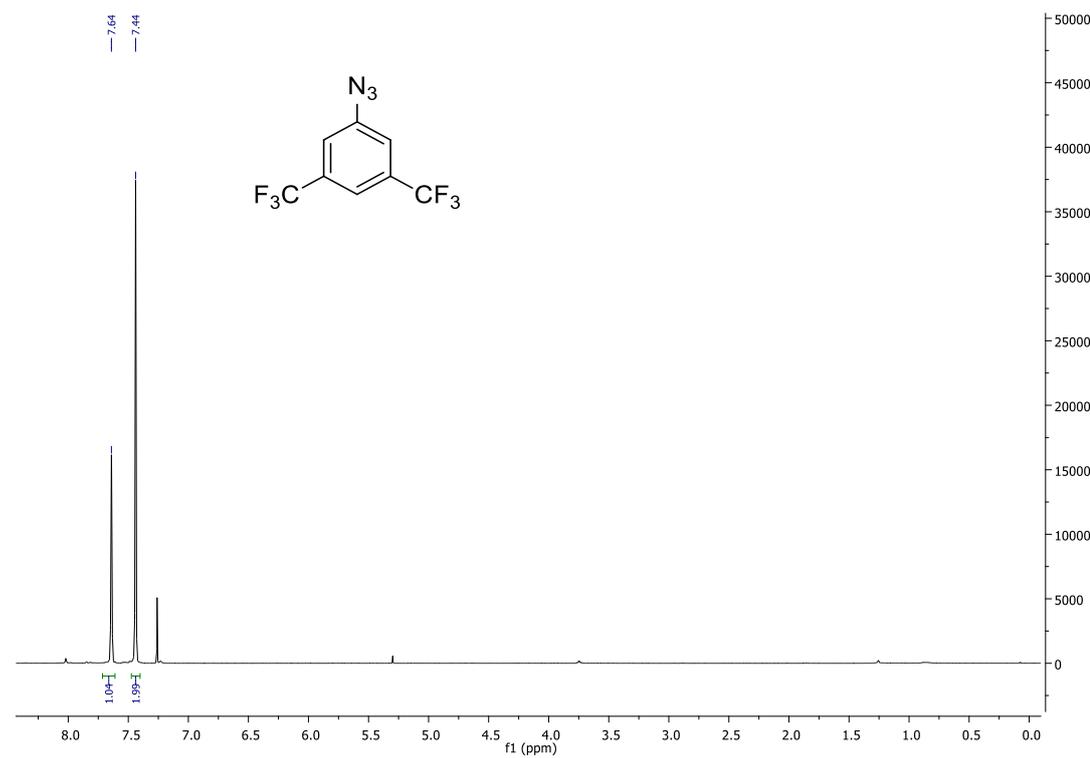


Compound 1.77d

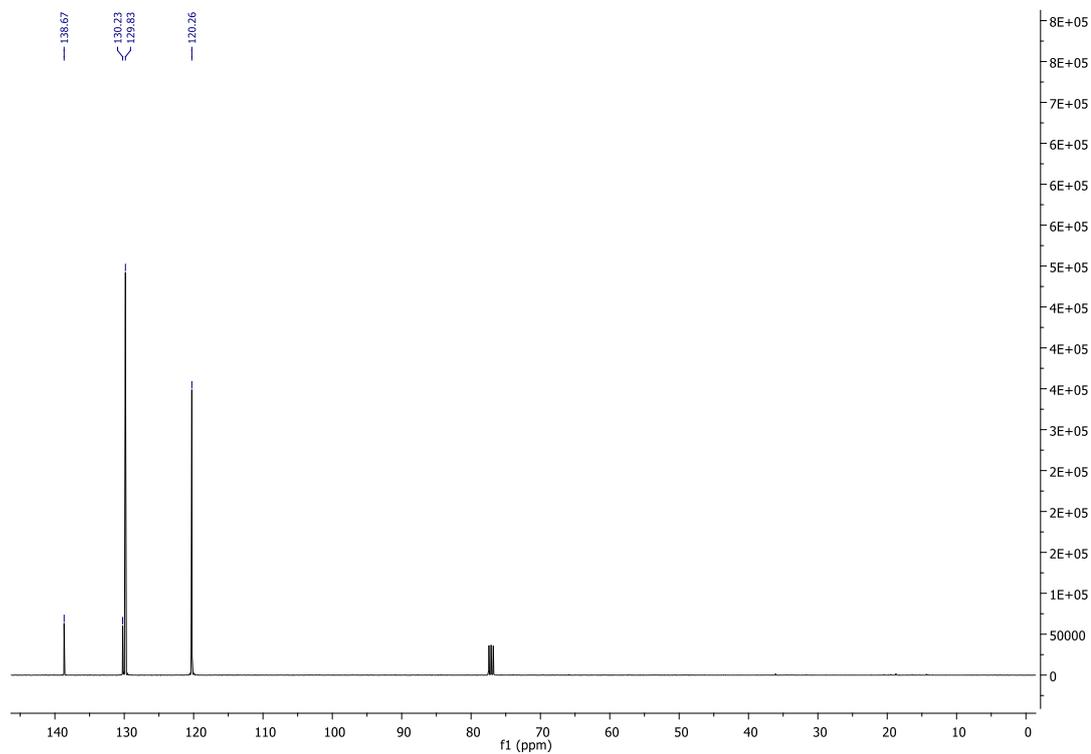
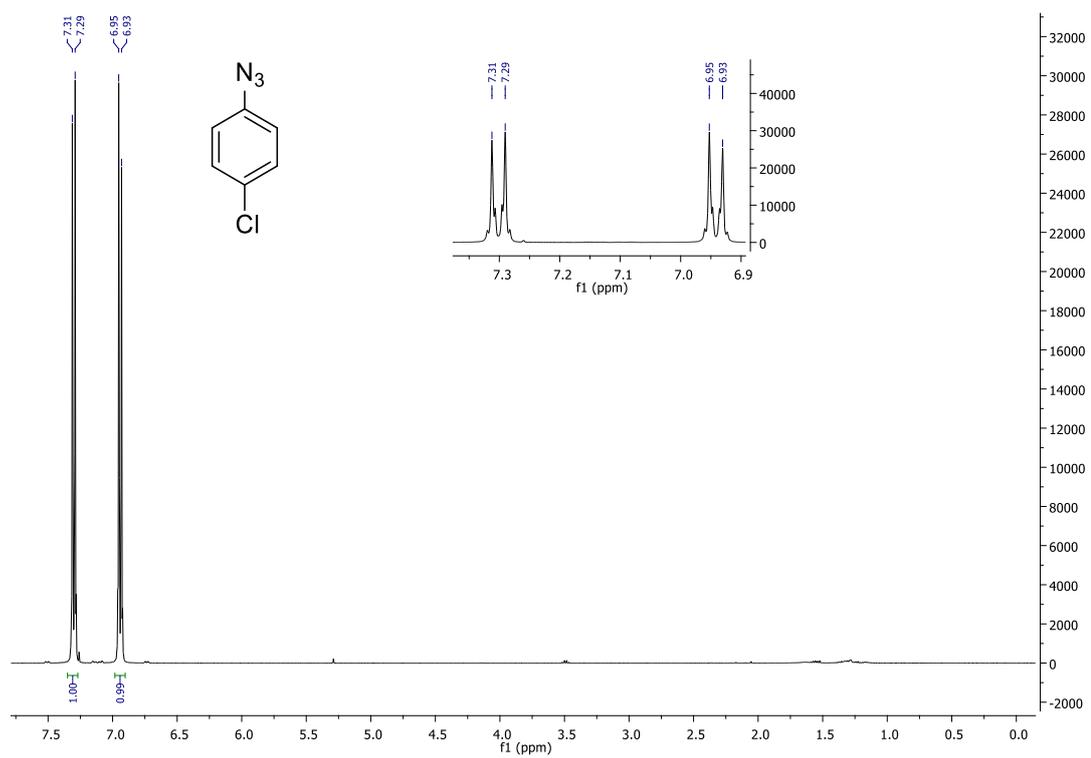


Compound **1.77e**

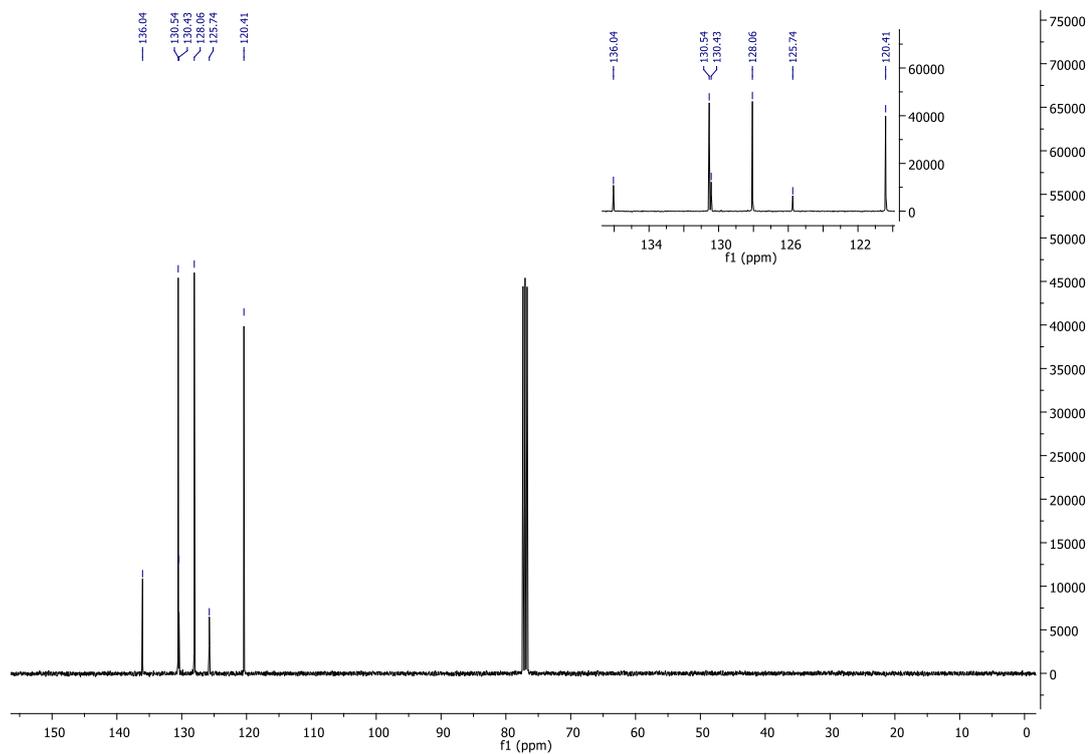
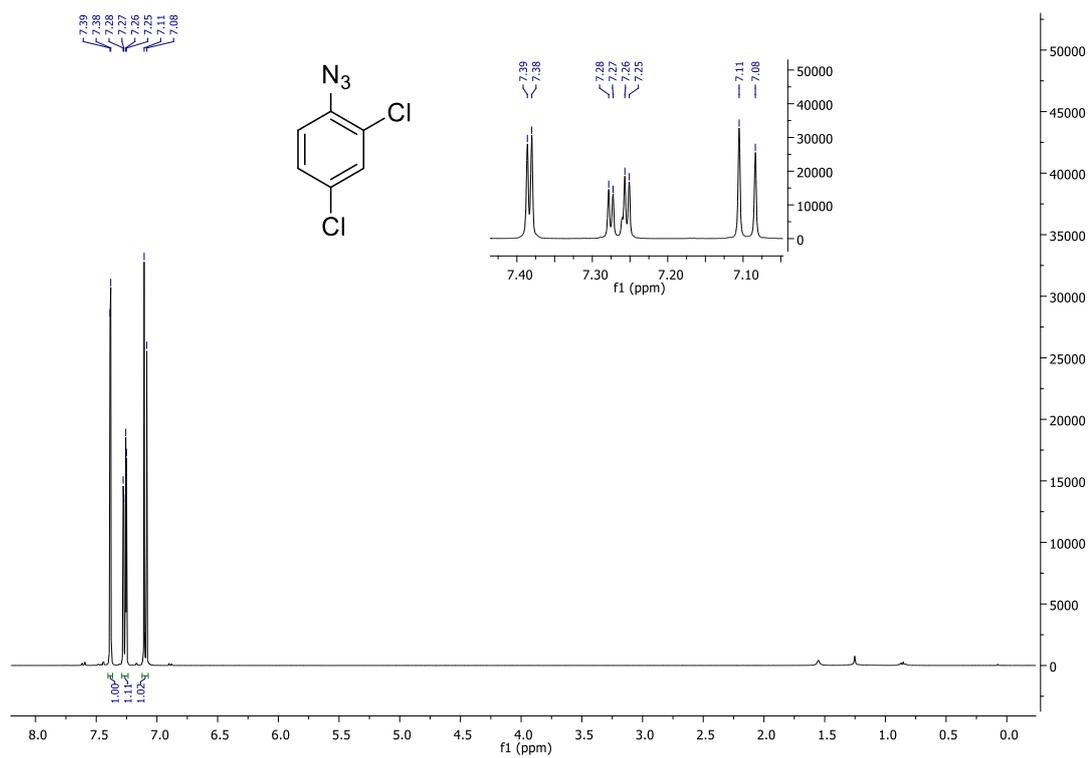
Compound 1.77f



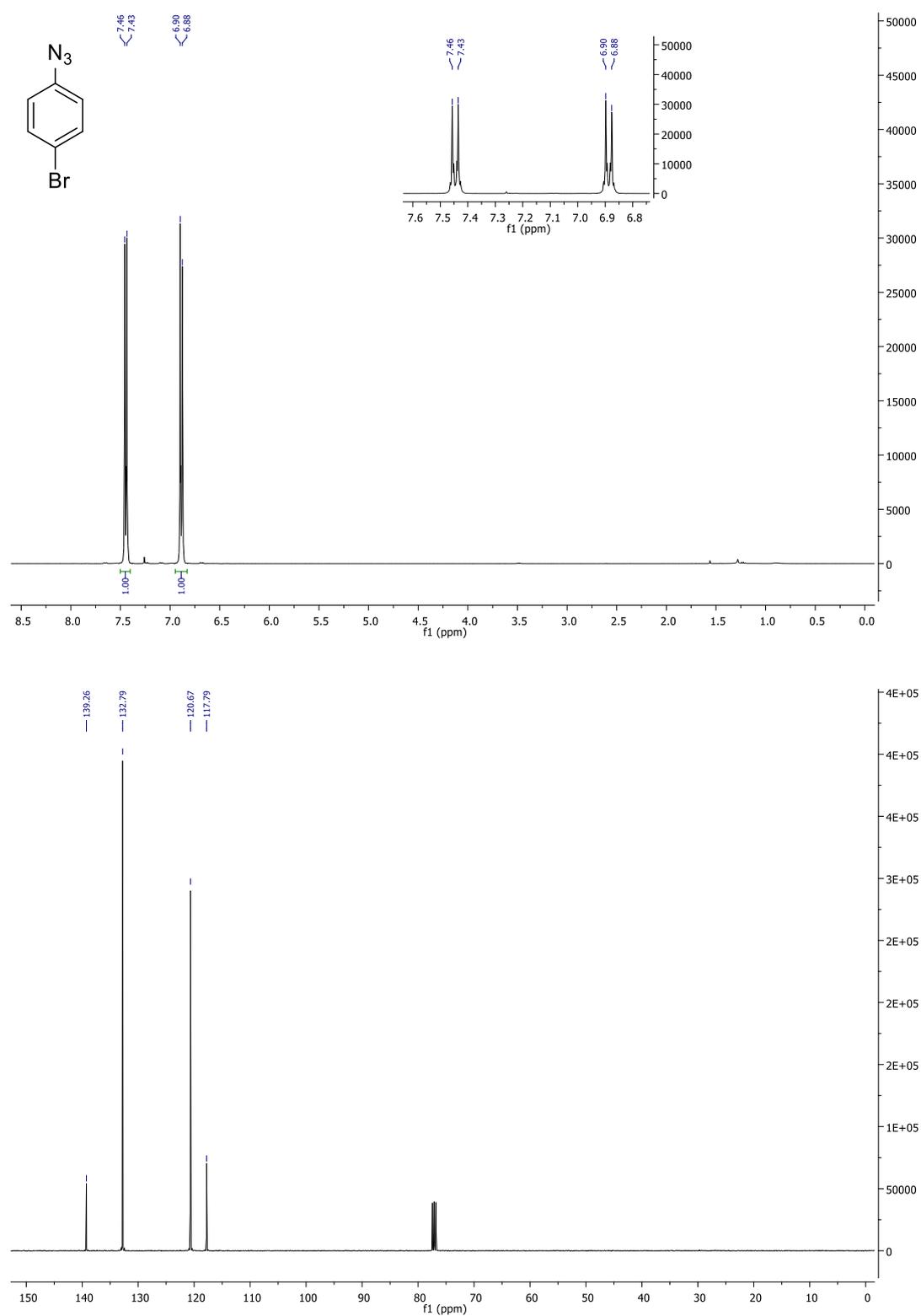
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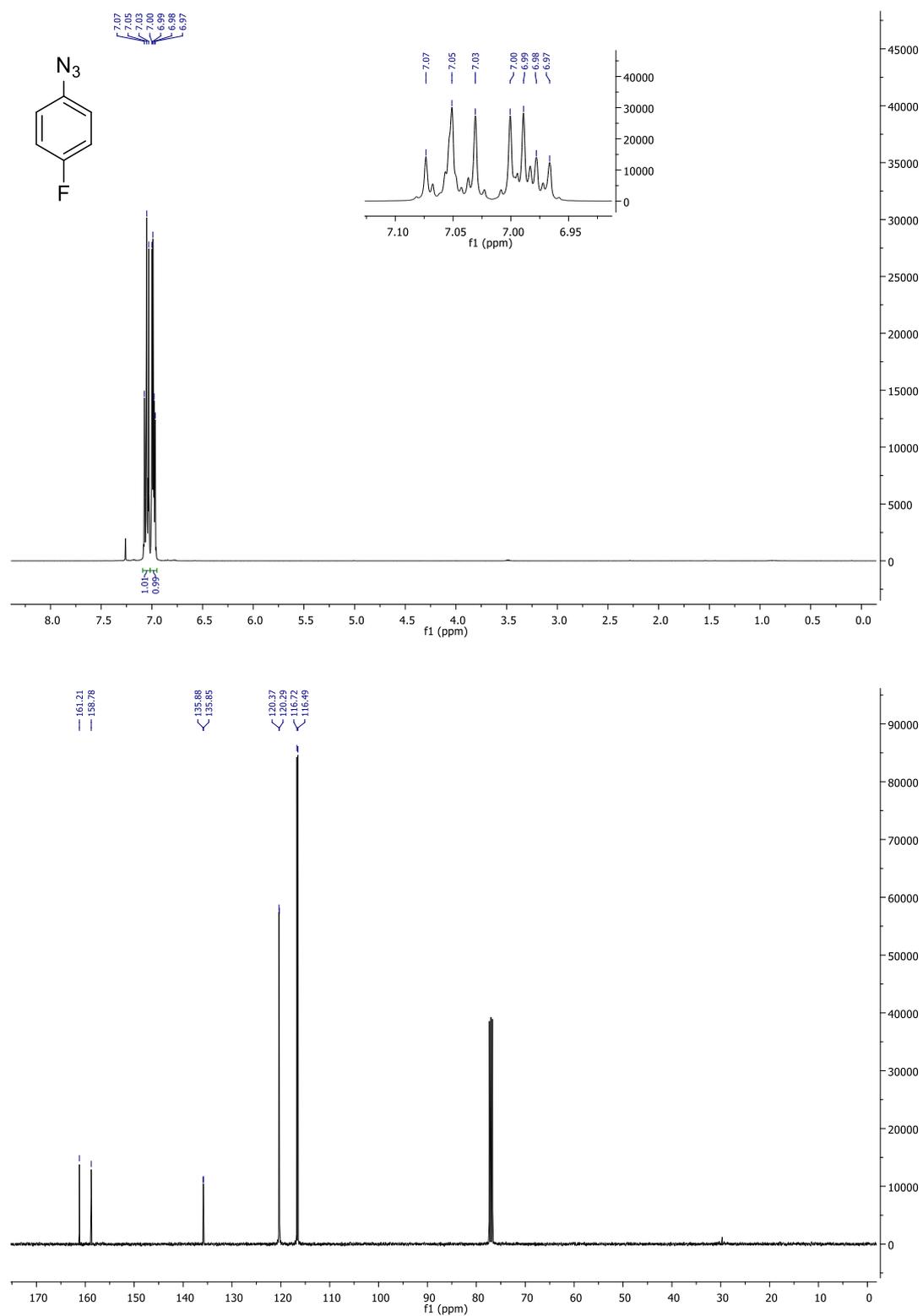
Compound 1.77h



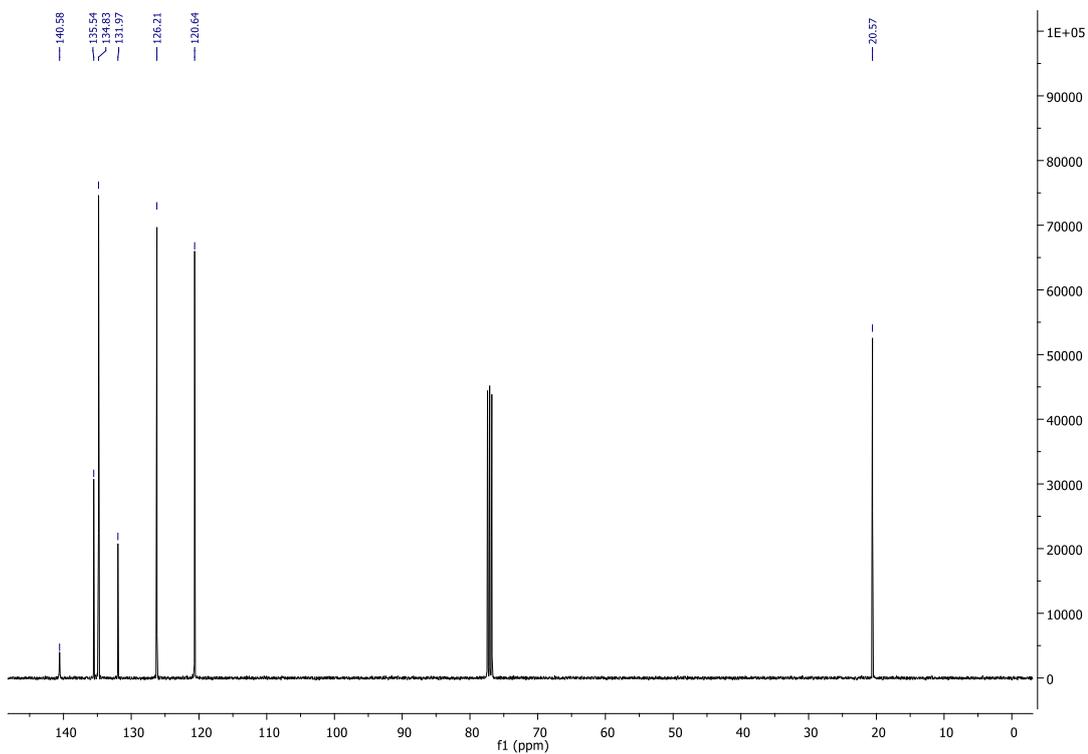
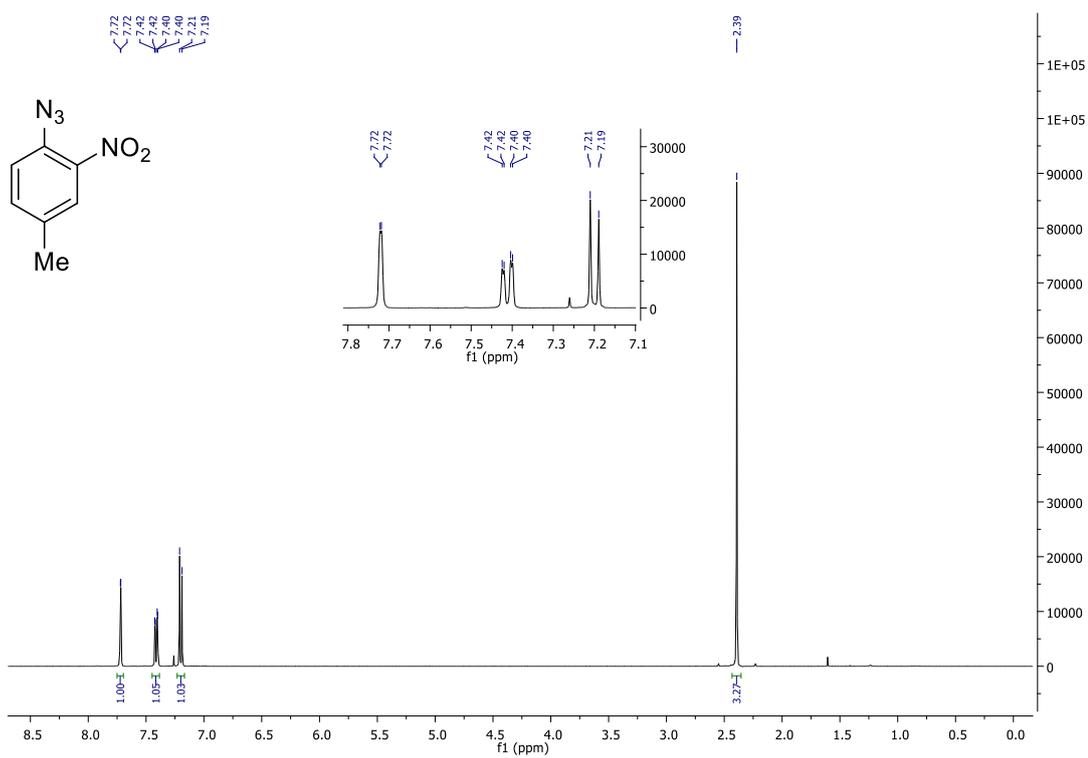
Compound 1.77i



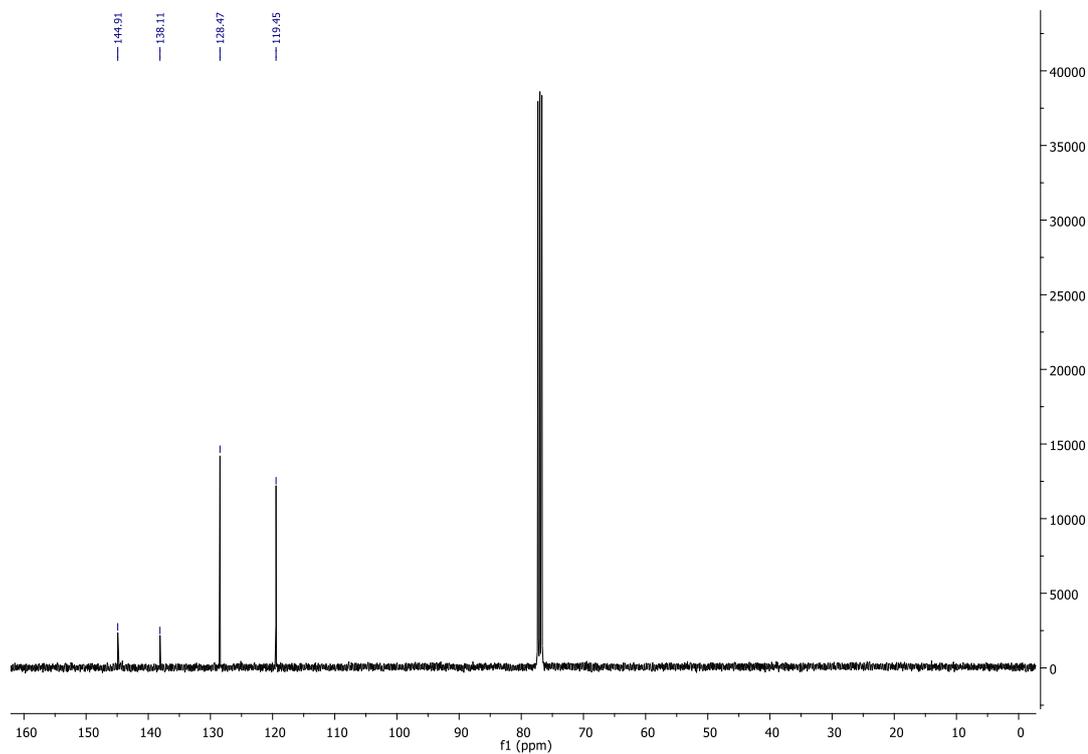
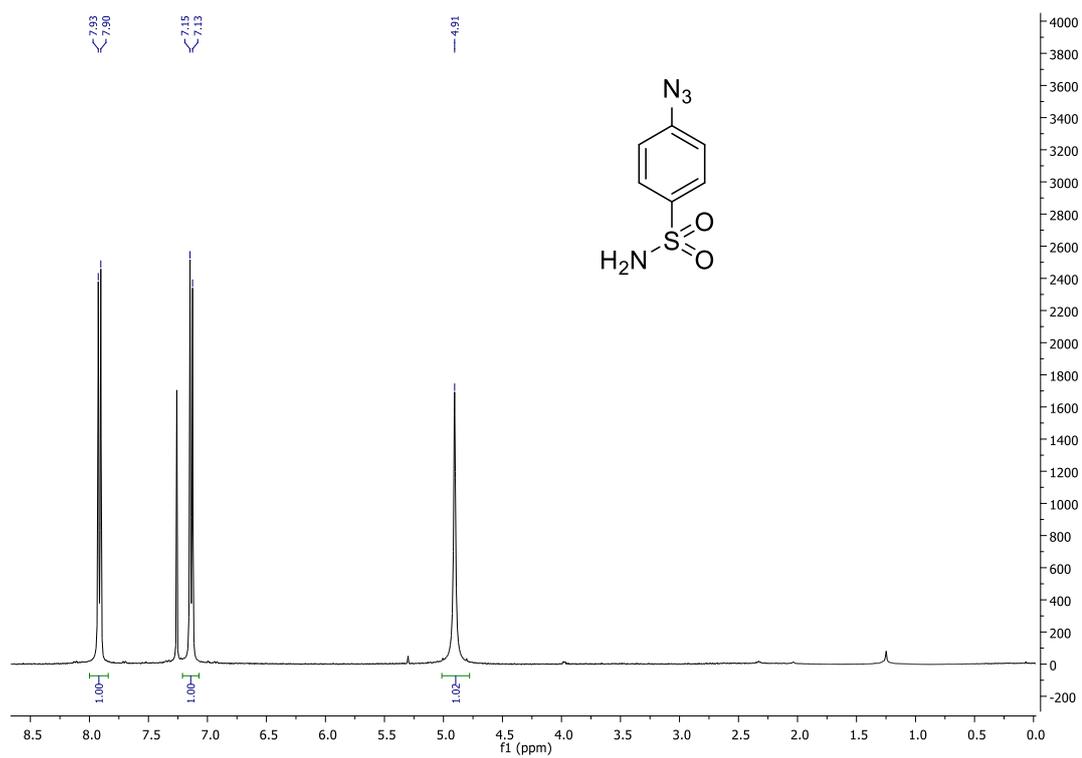
Compound 1.77j

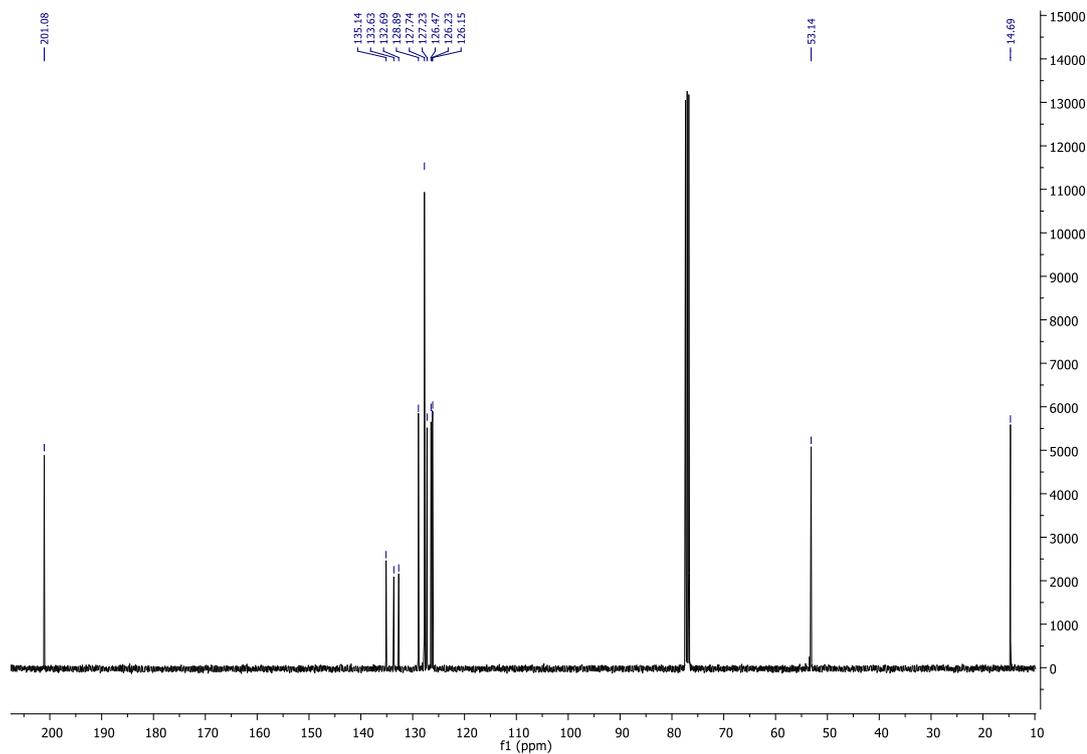
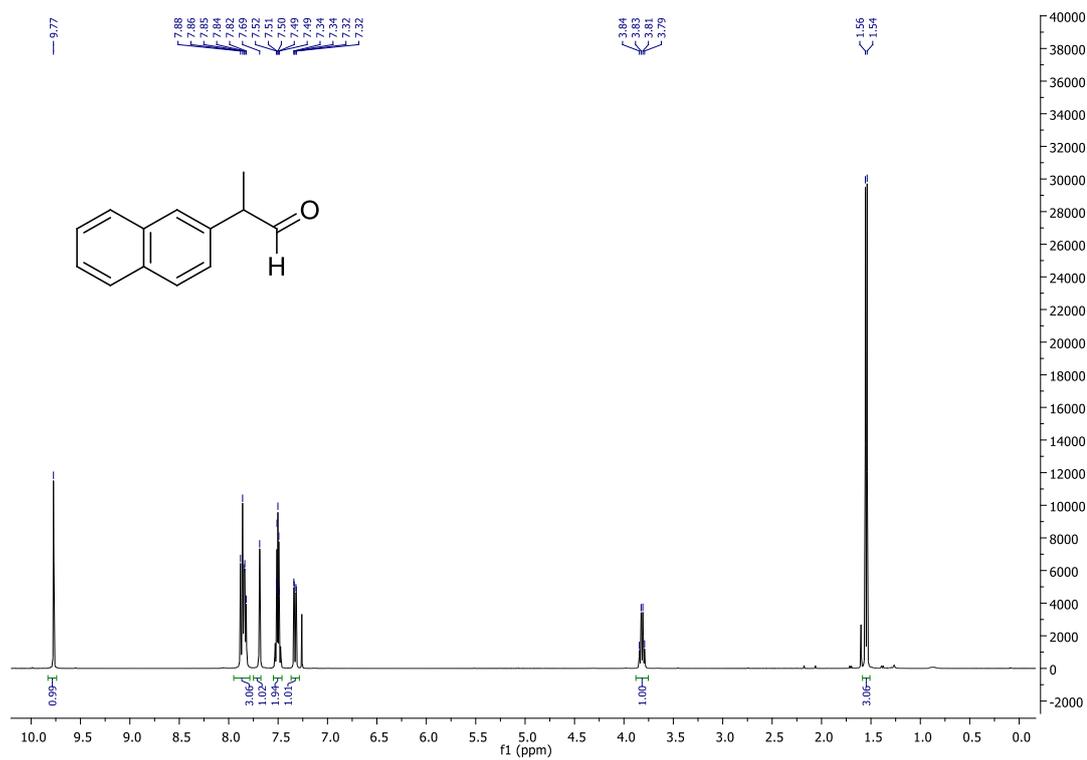


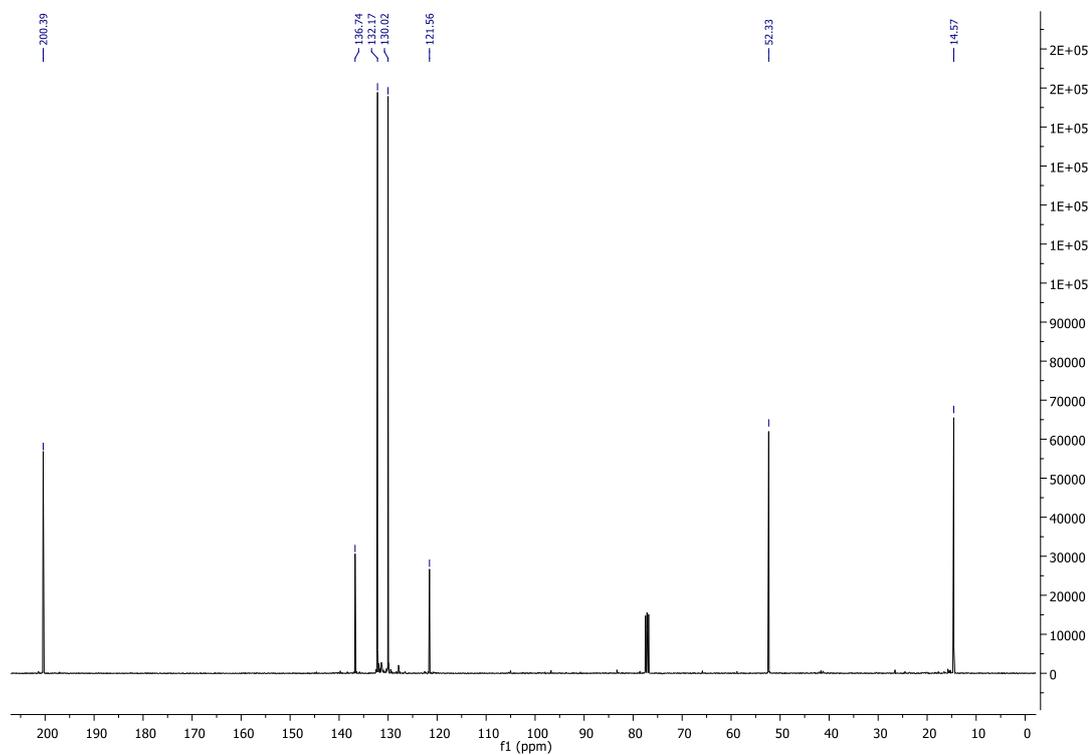
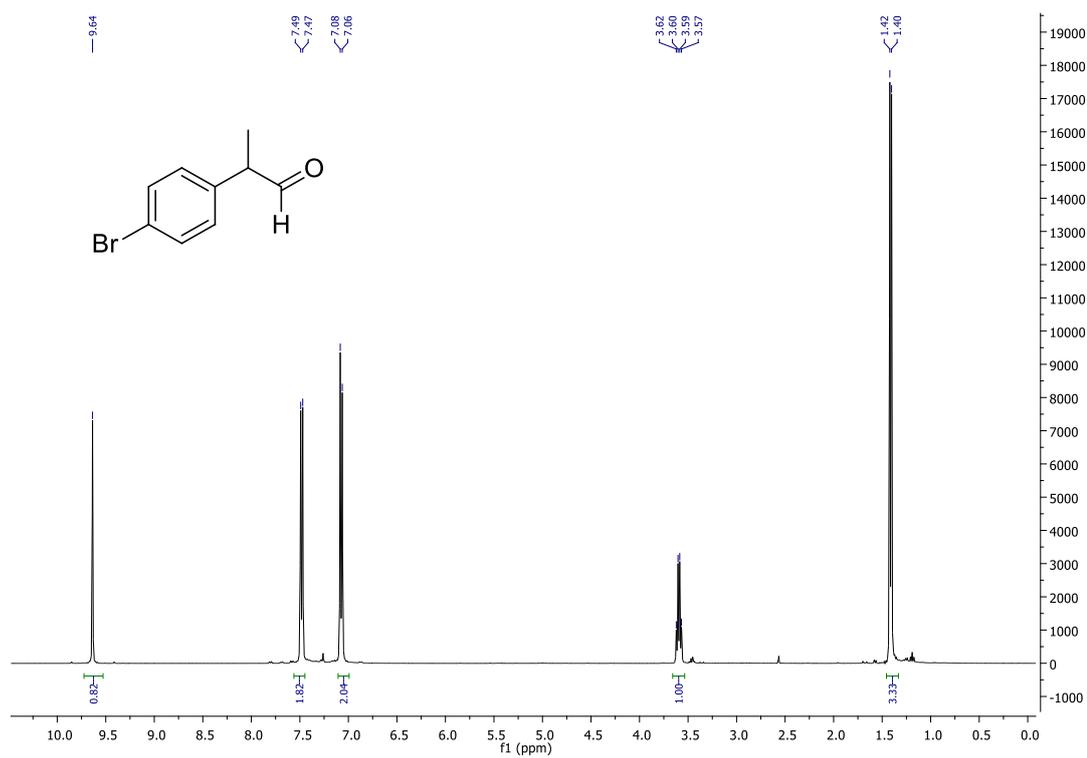
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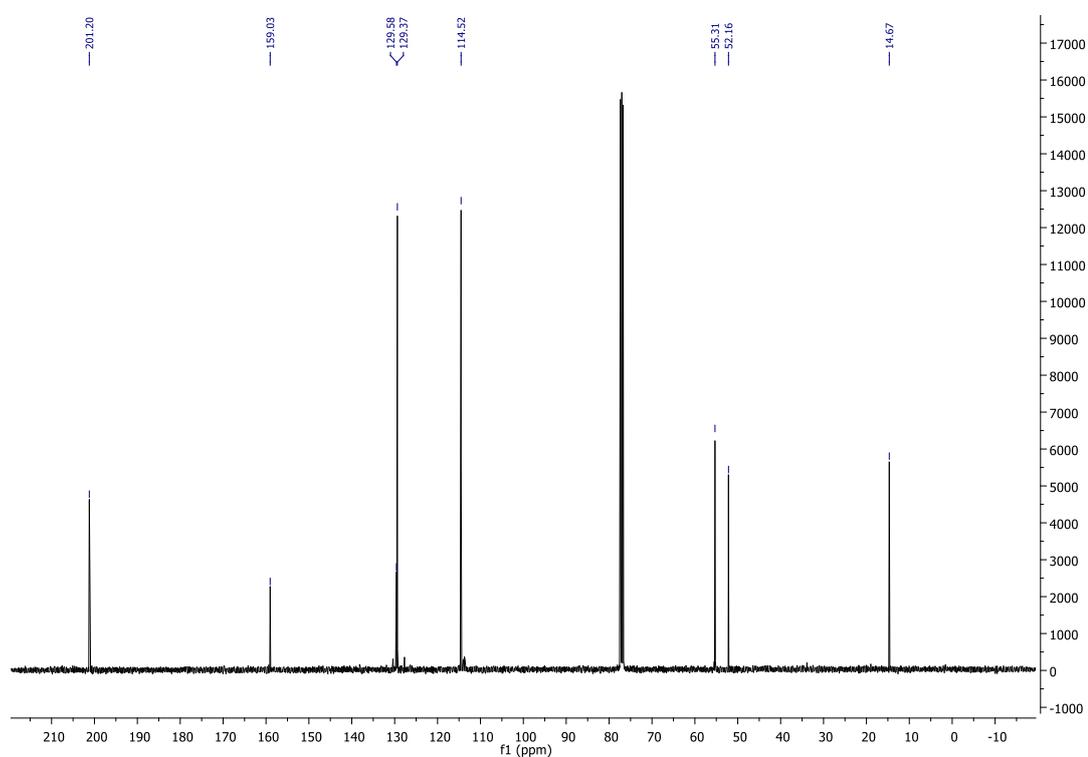
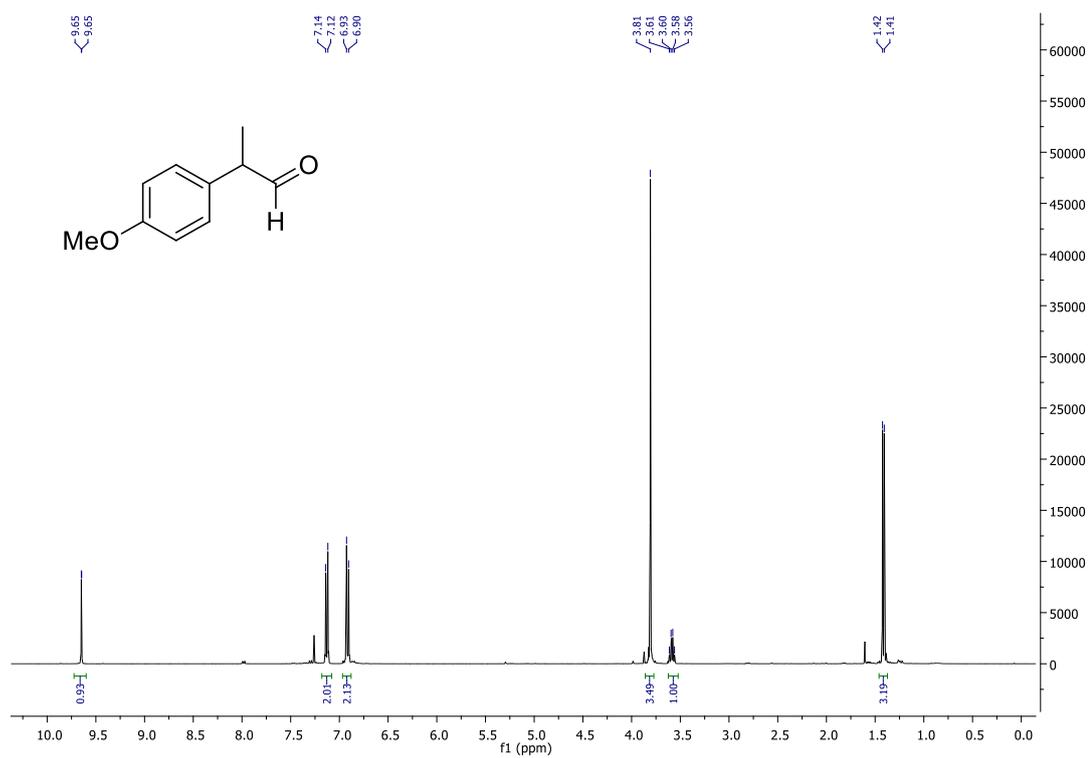


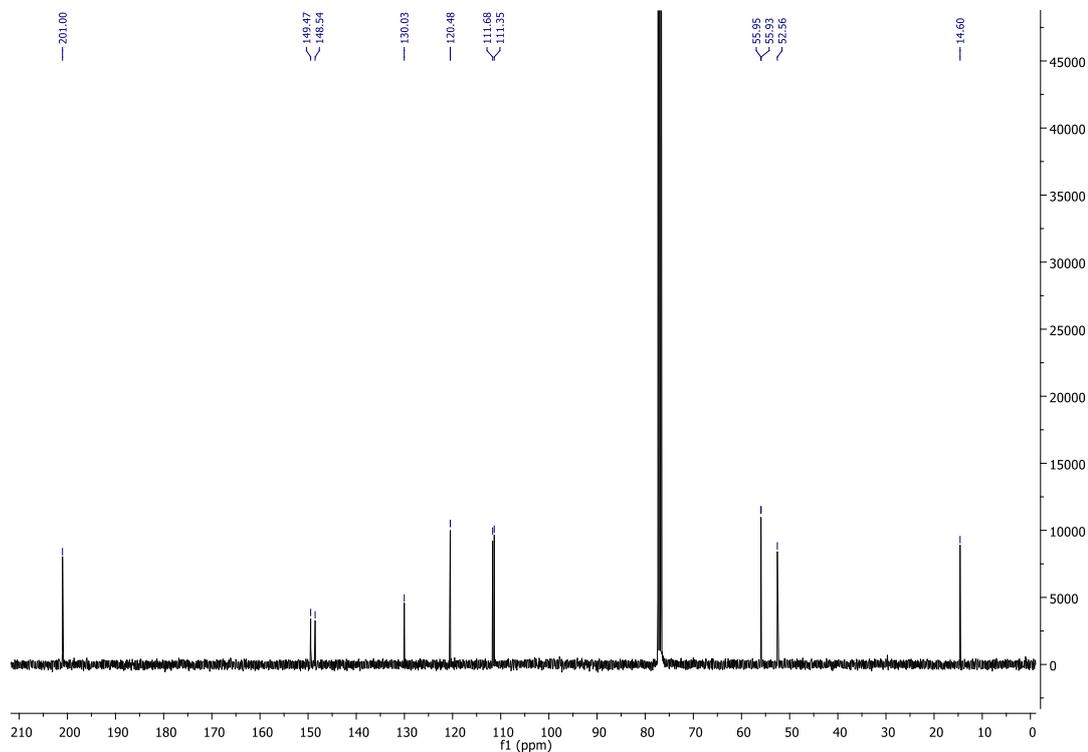
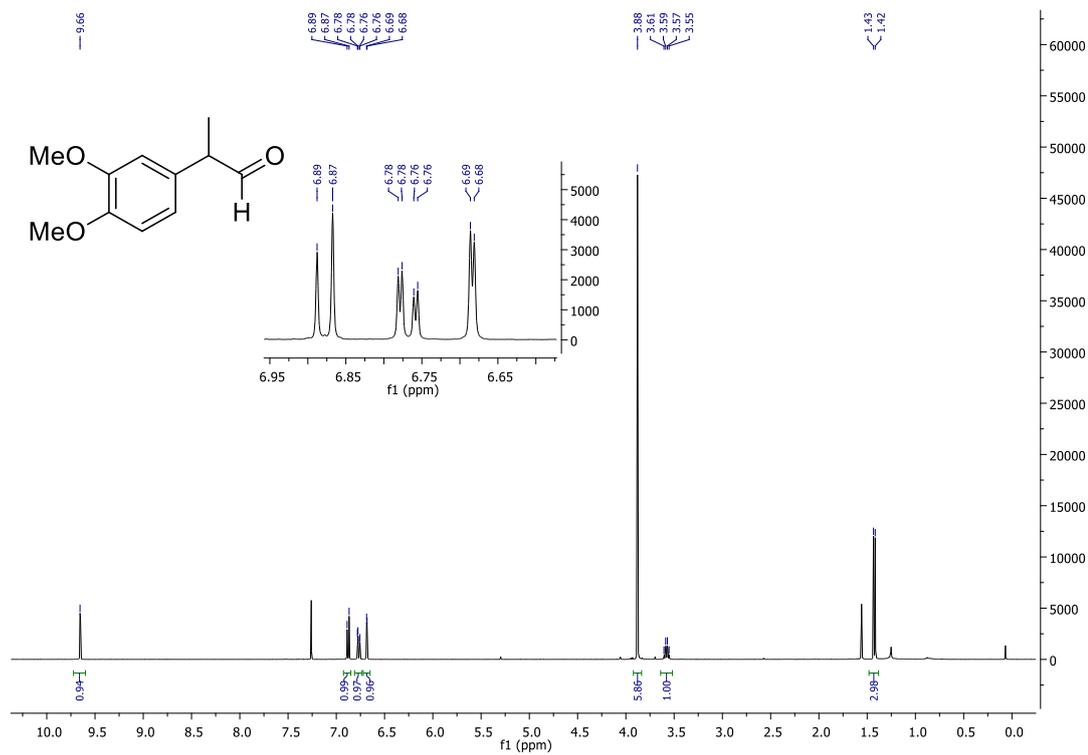
Compound 1.77I



Compound **1.80c**

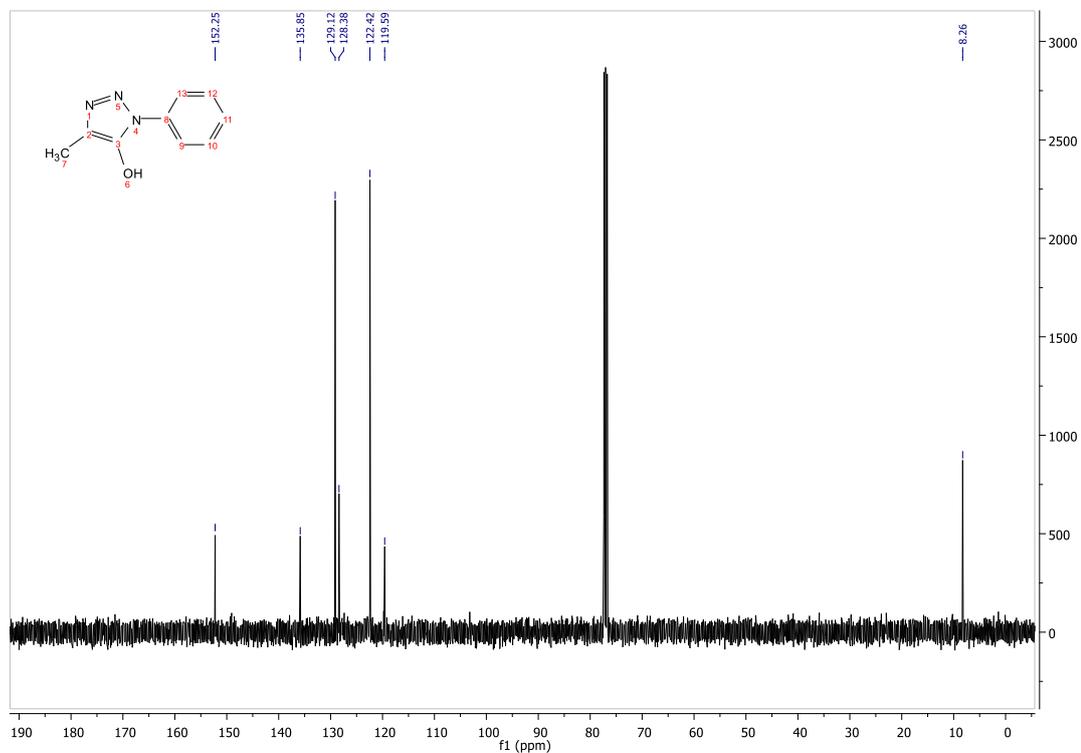
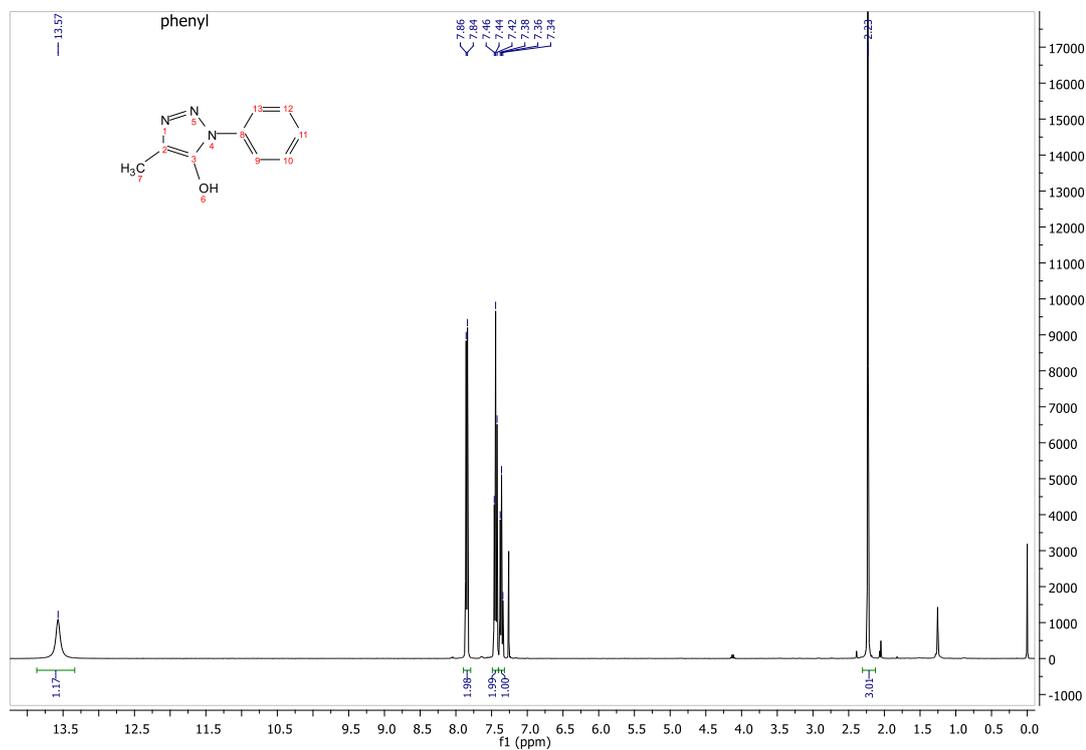
Compound **1.80d**

Compound **1.80e**

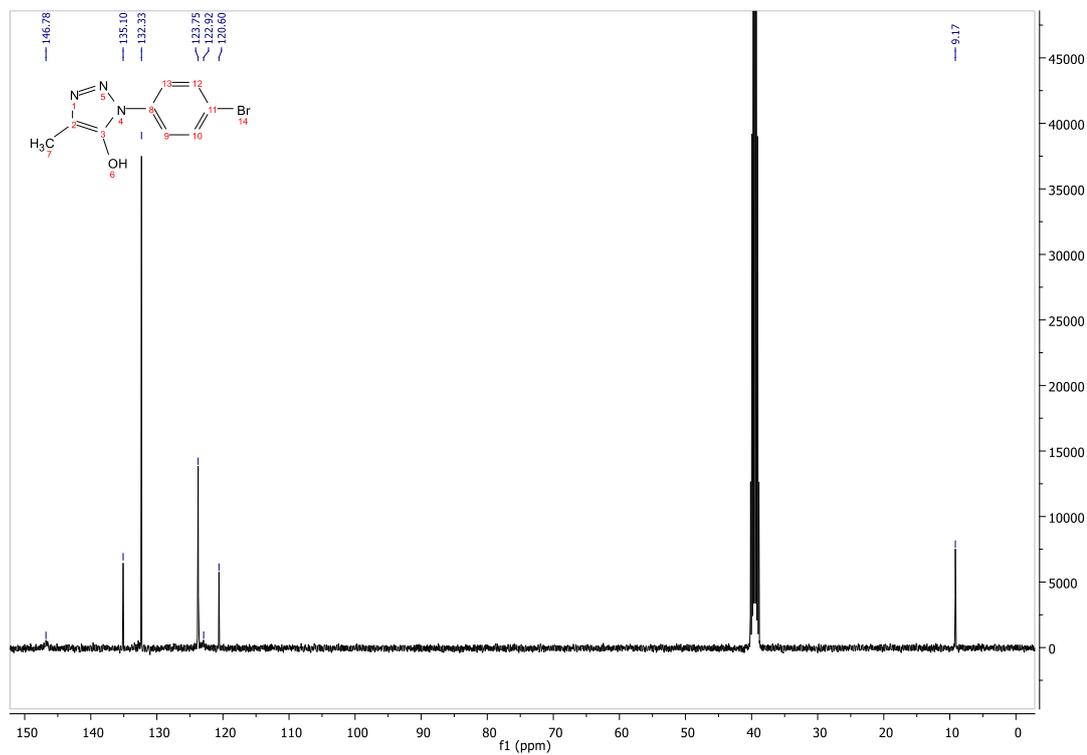
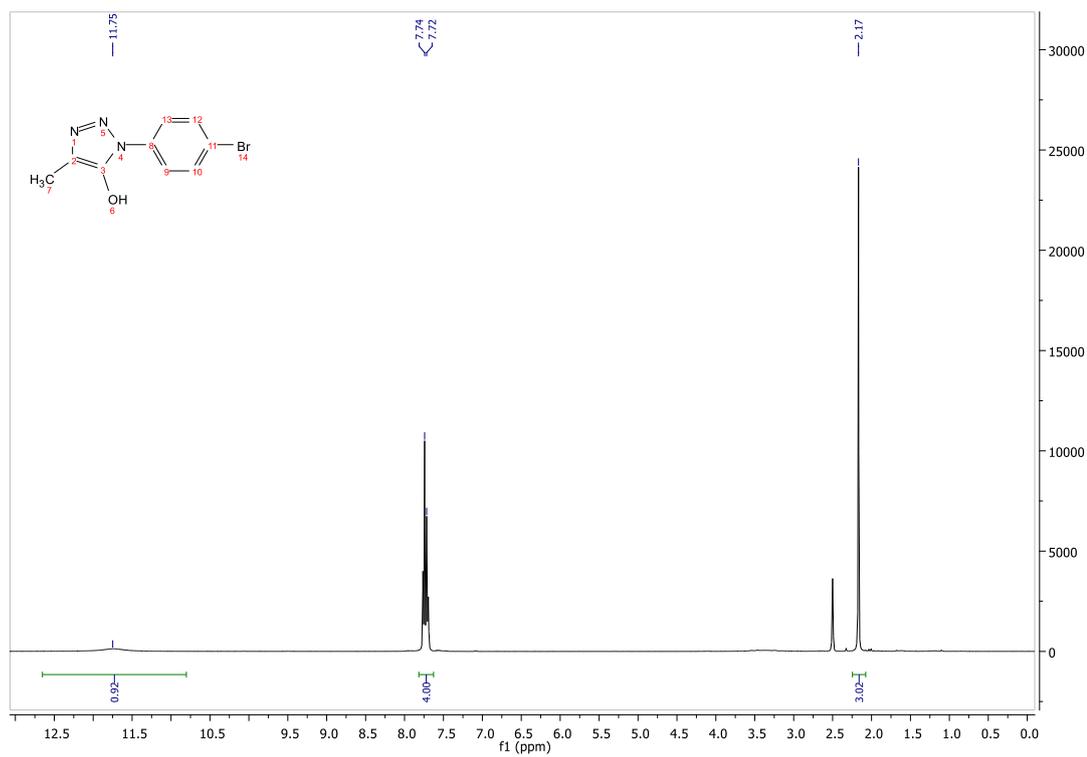
Compound **1.80f**

Chapter 2: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$

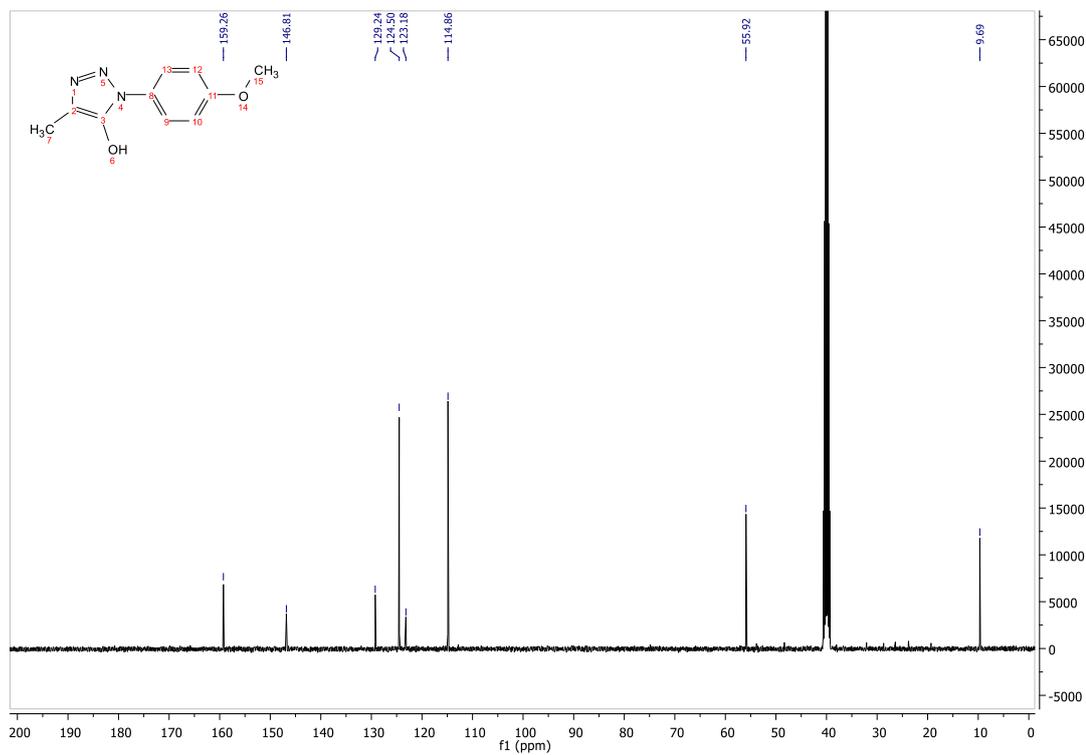
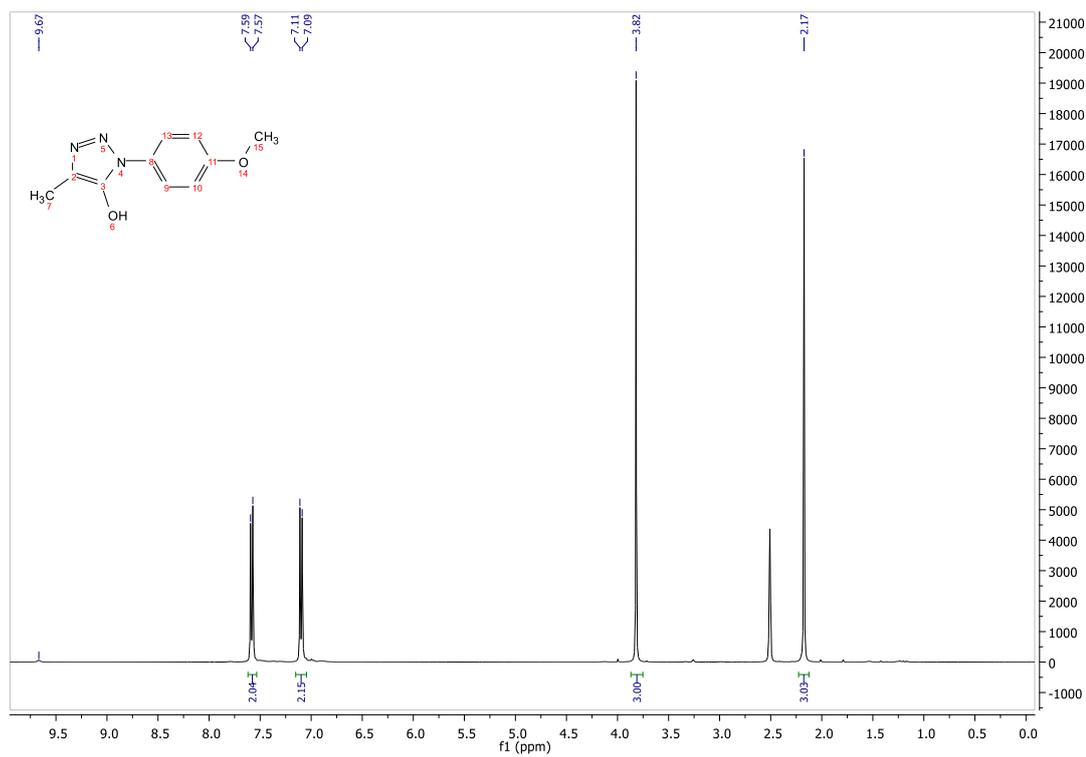
Compound 2.123a



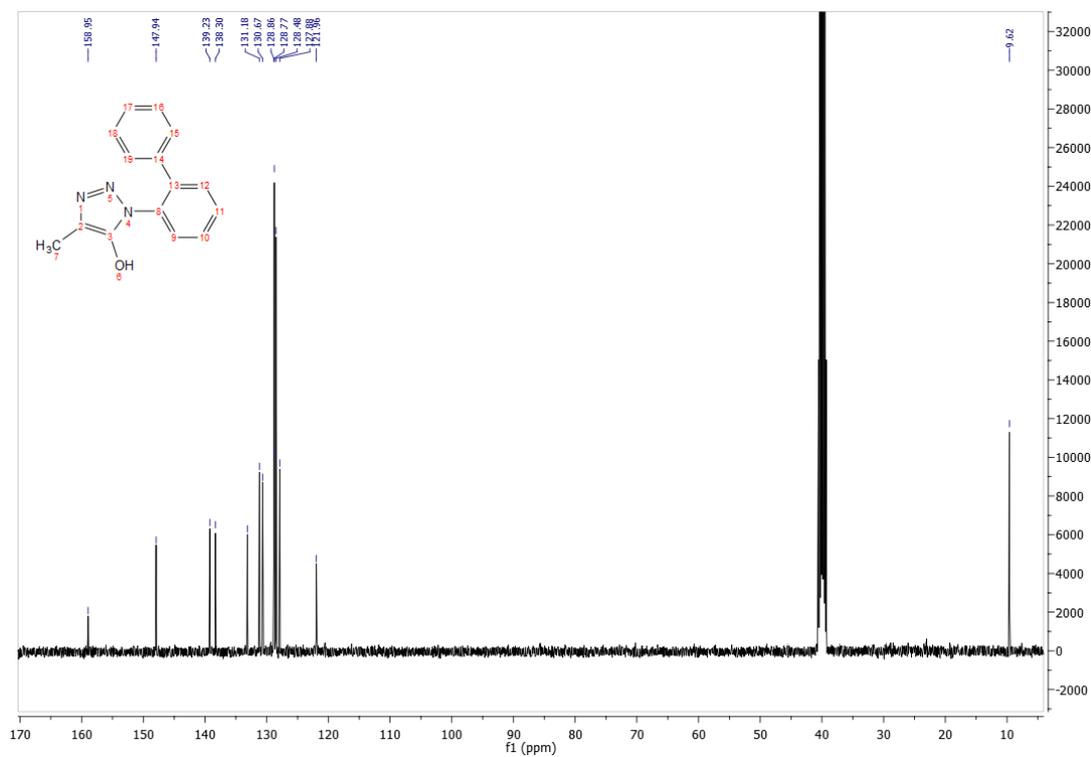
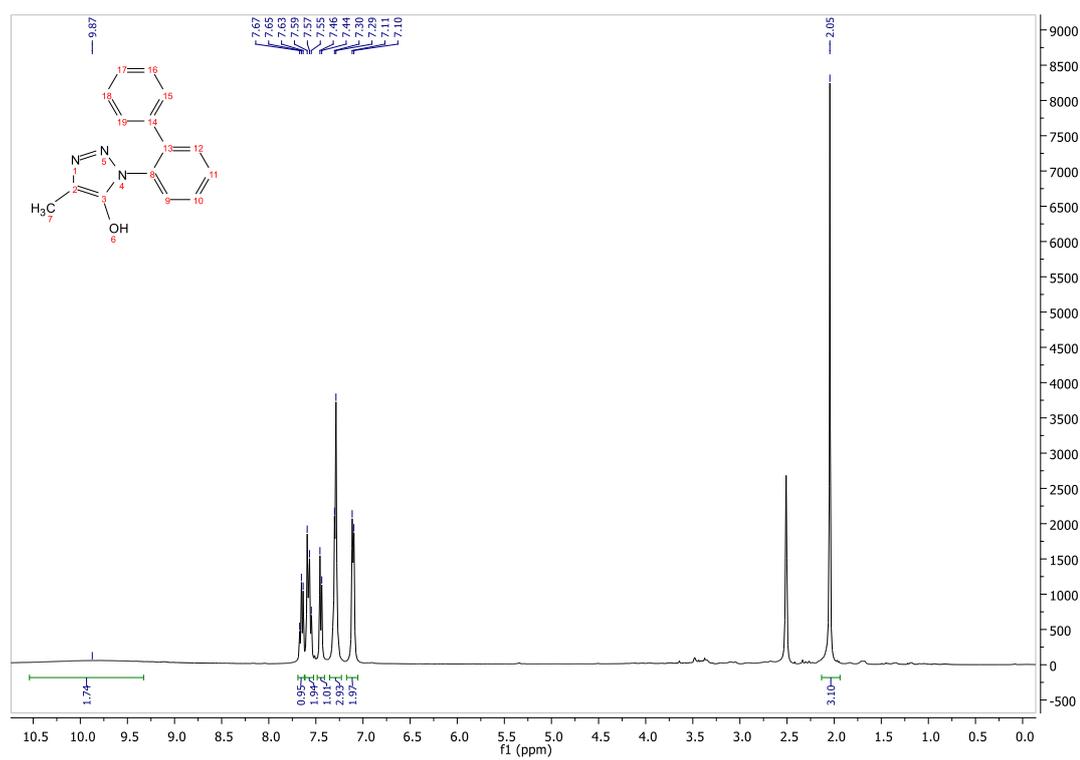
Compound 2.123b



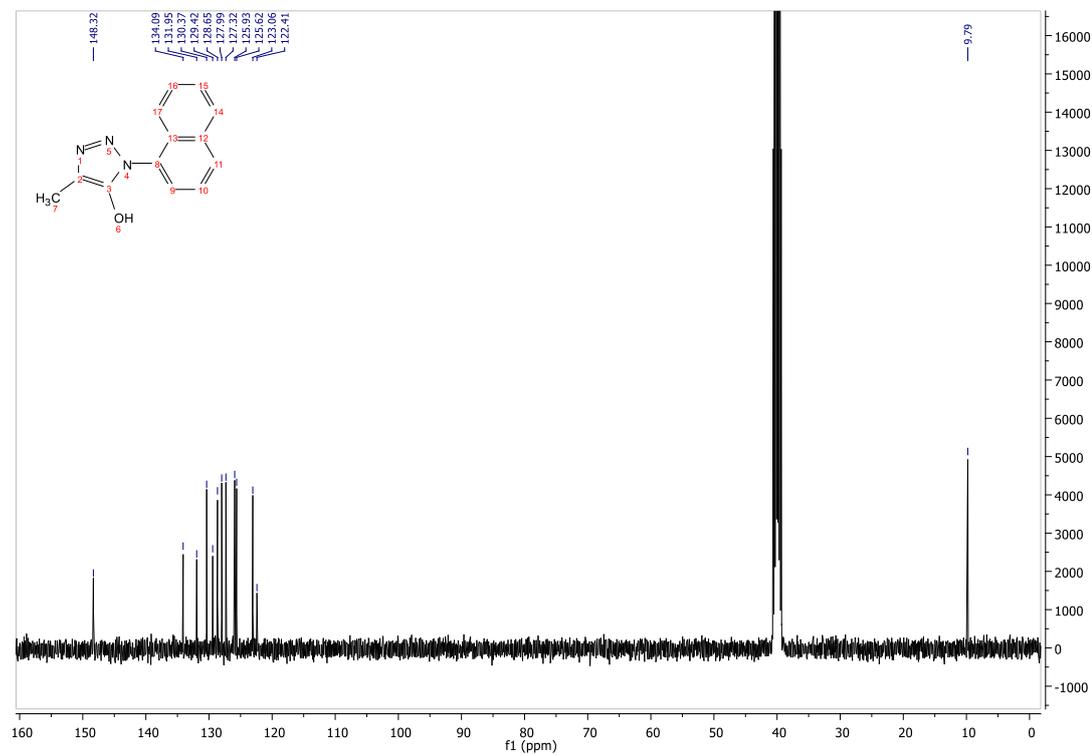
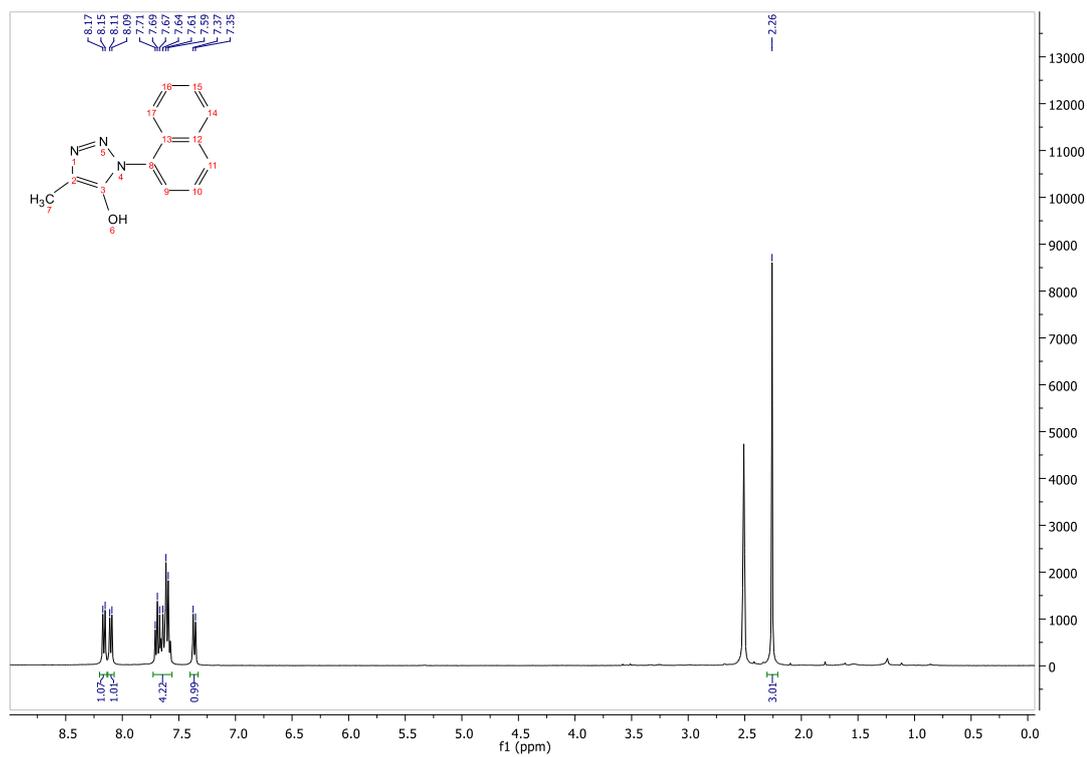
Compound 2.123d



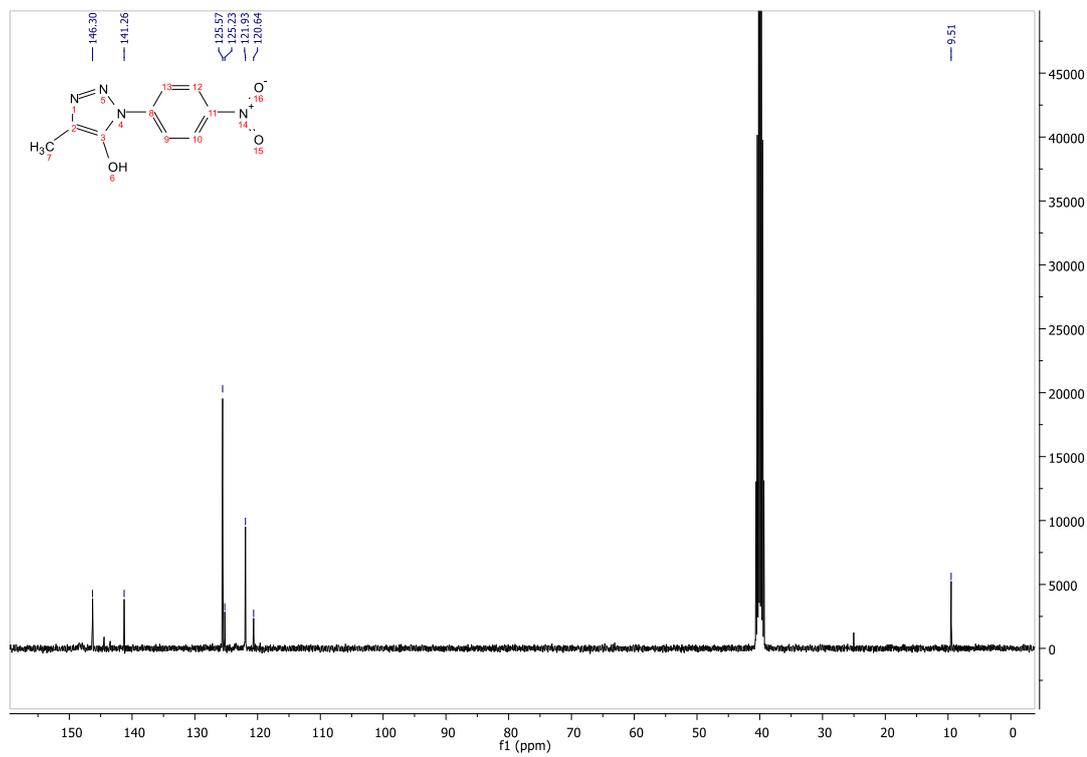
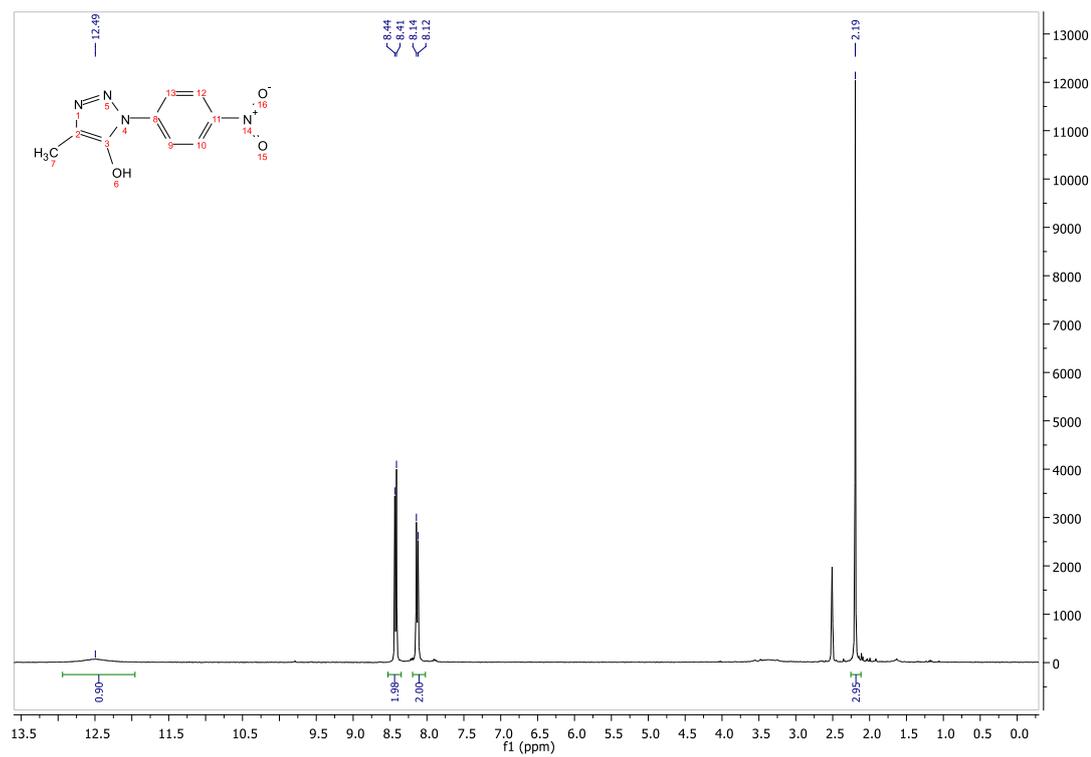
Compound 2.123e



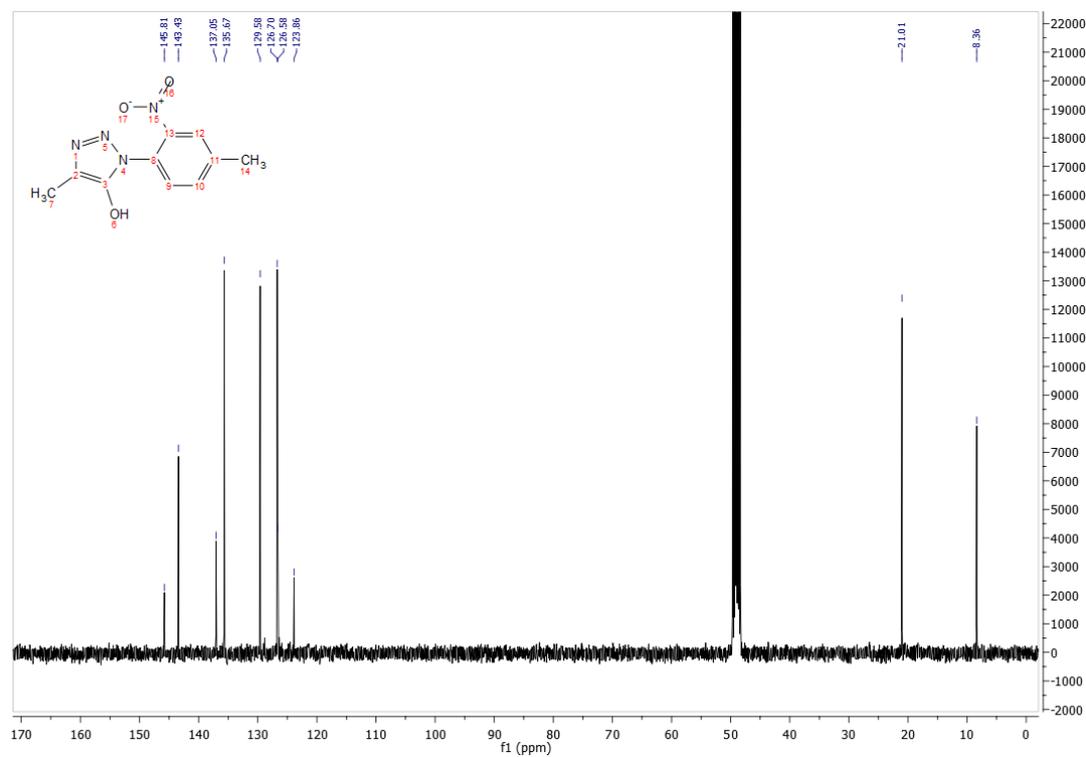
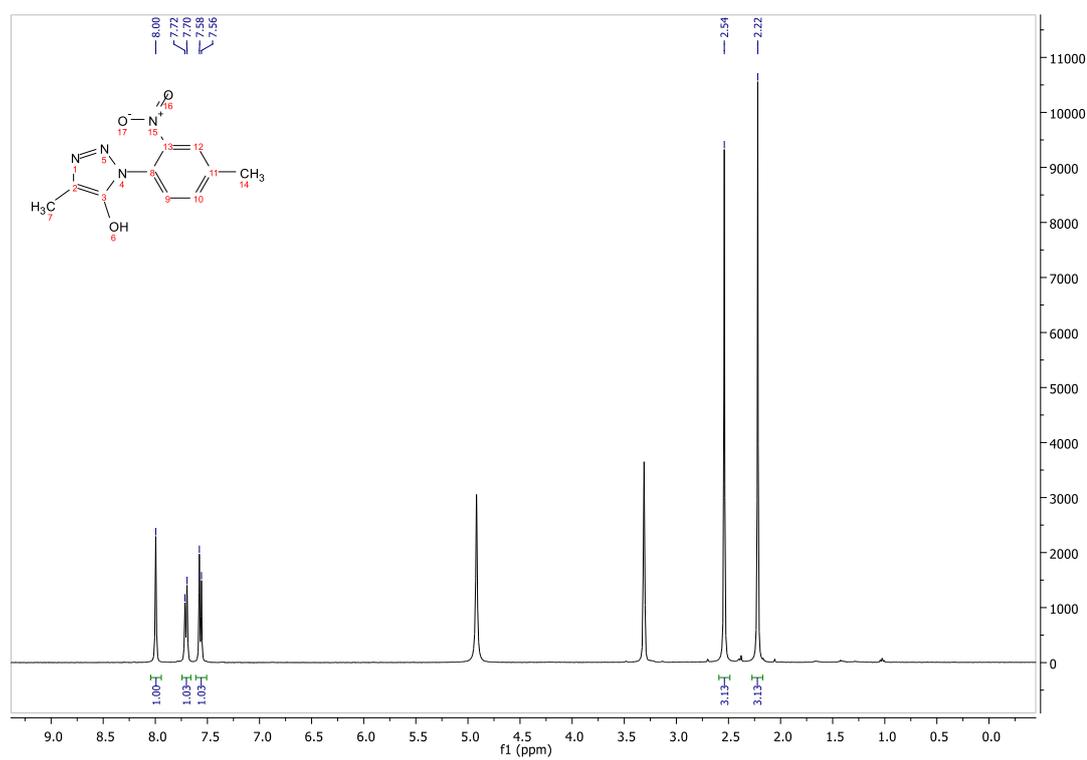
Compound 2.123f



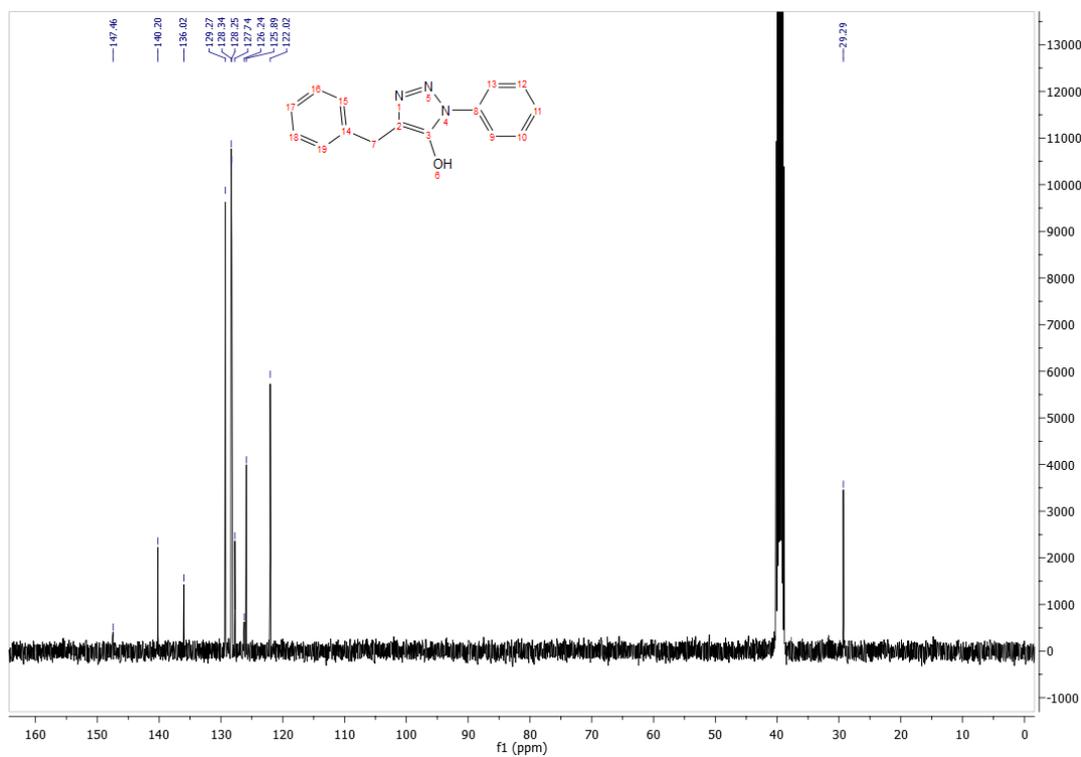
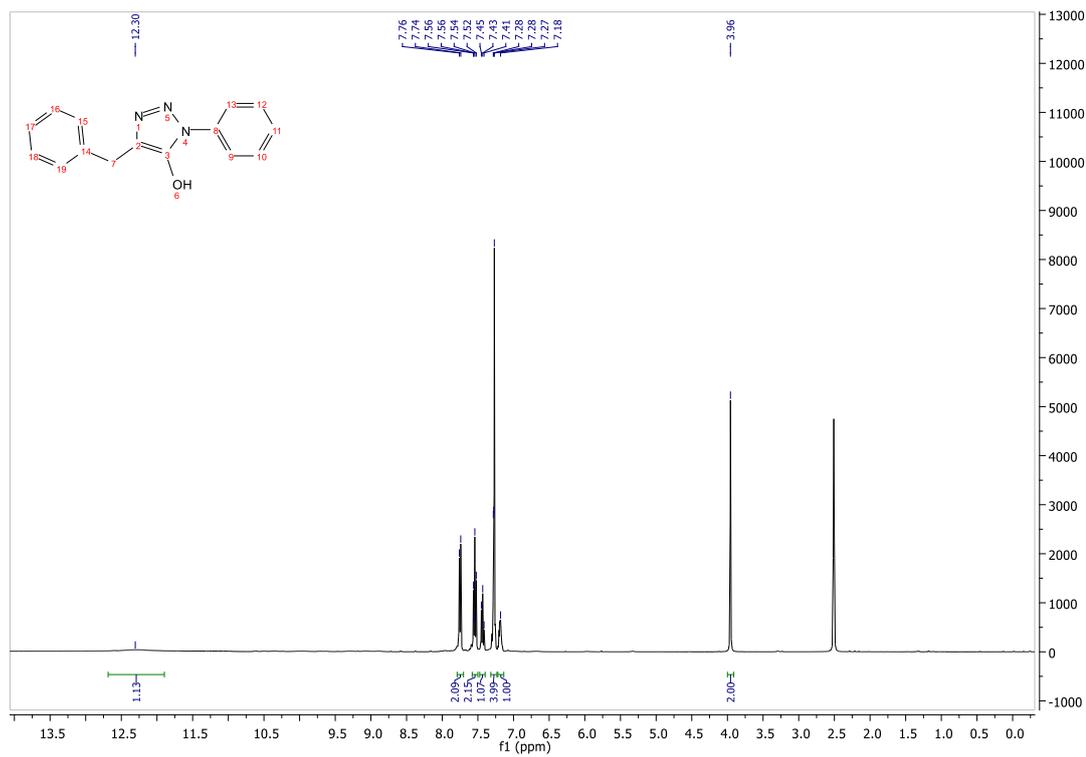
Compound 2.123g



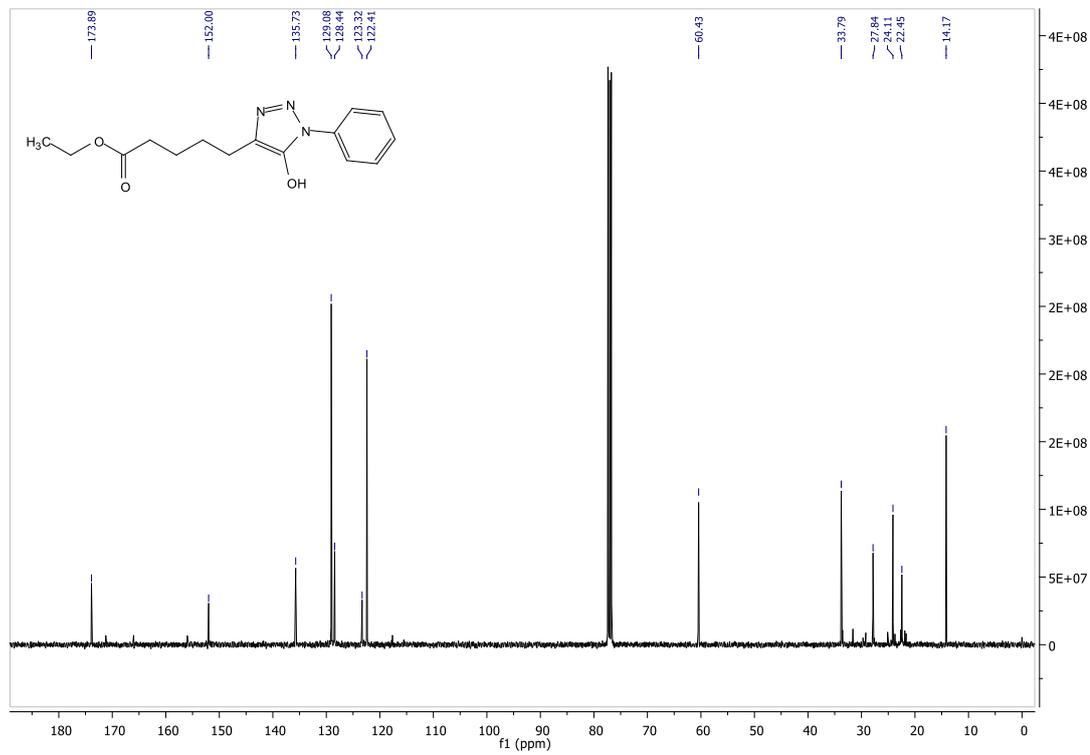
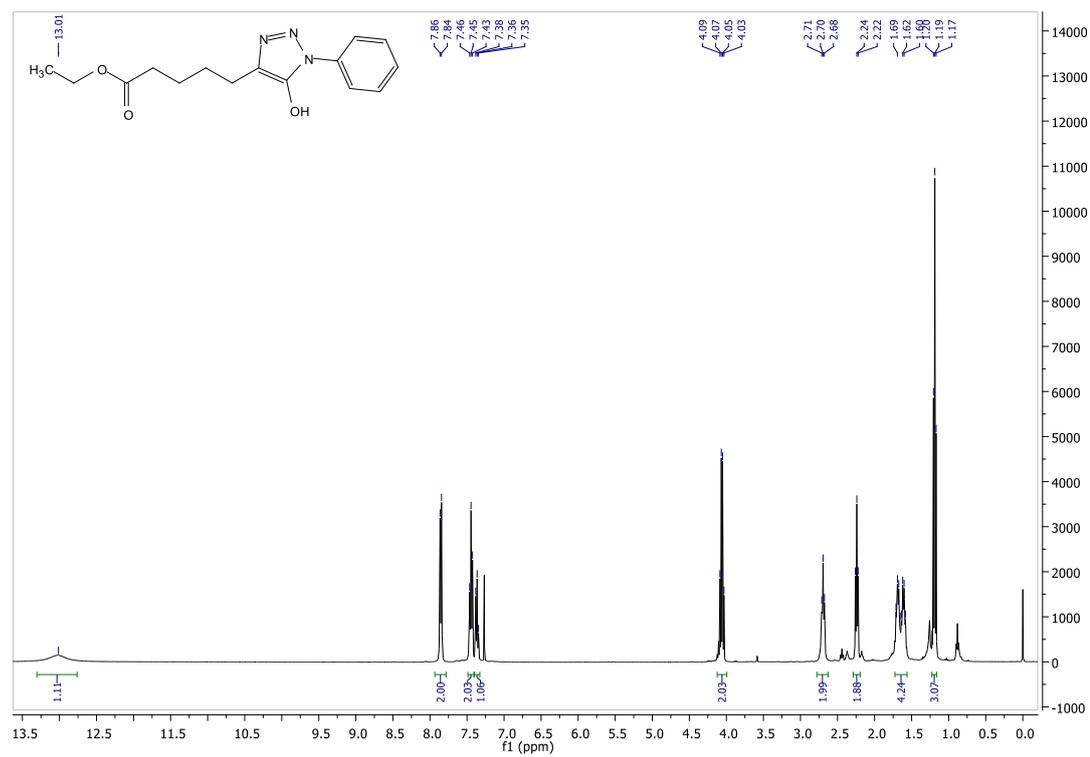
Compound 2.123h



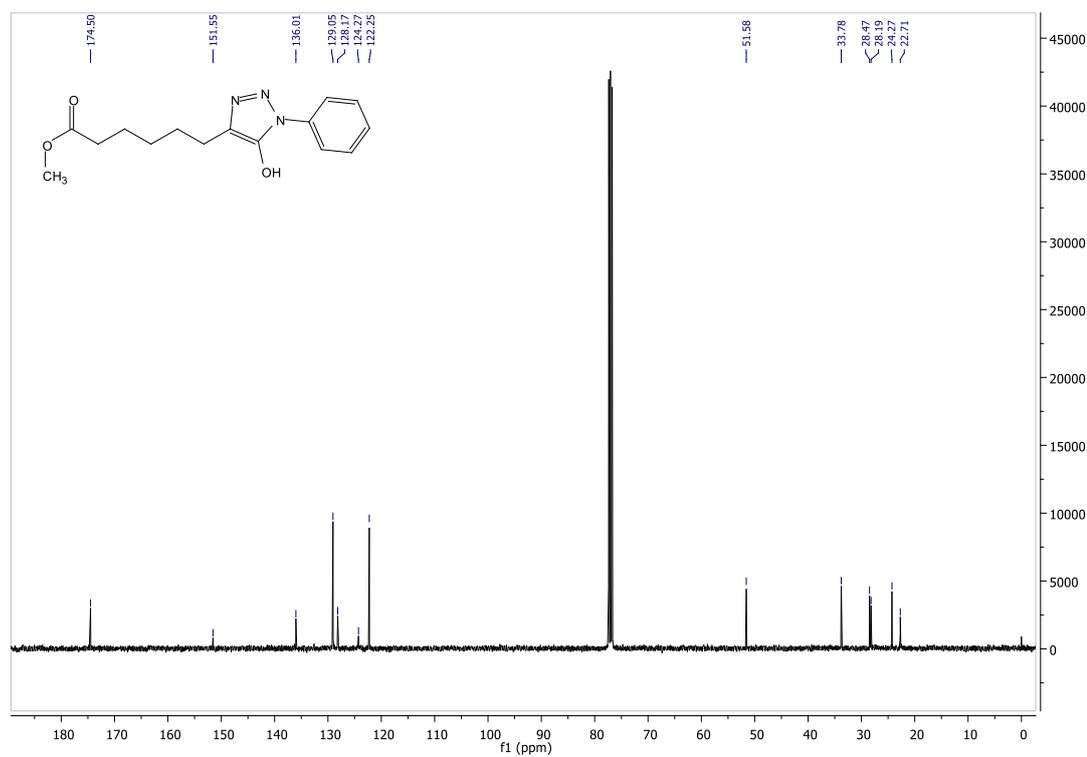
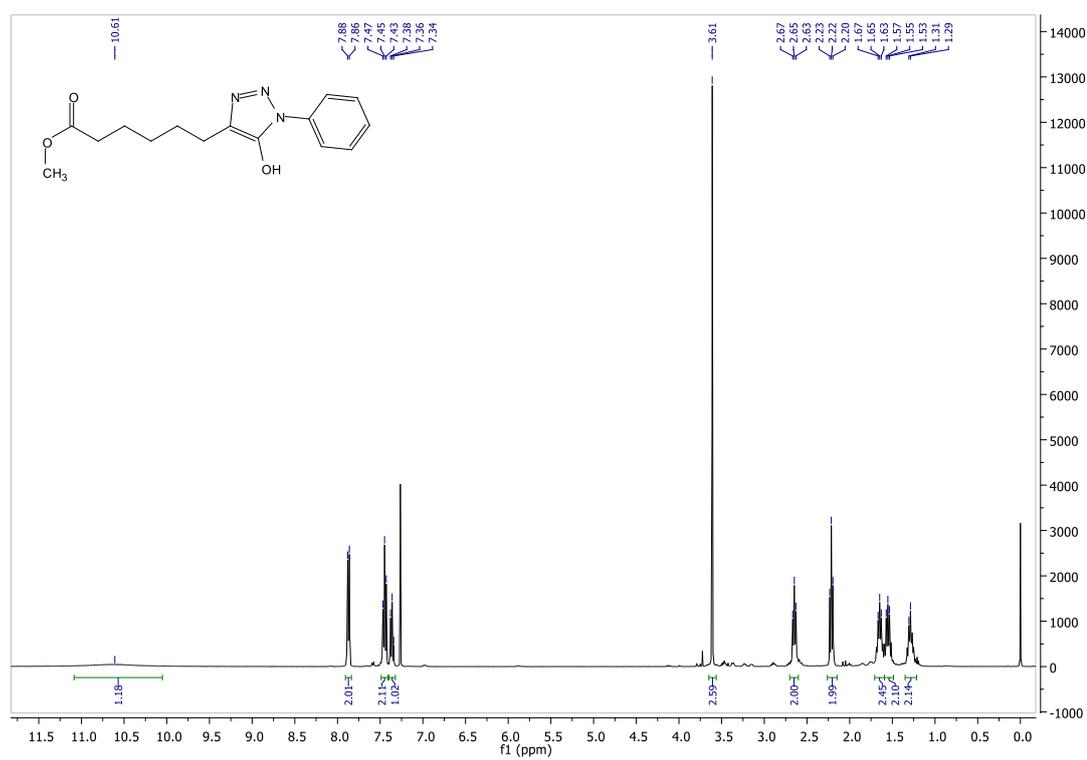
Compound 2.123n



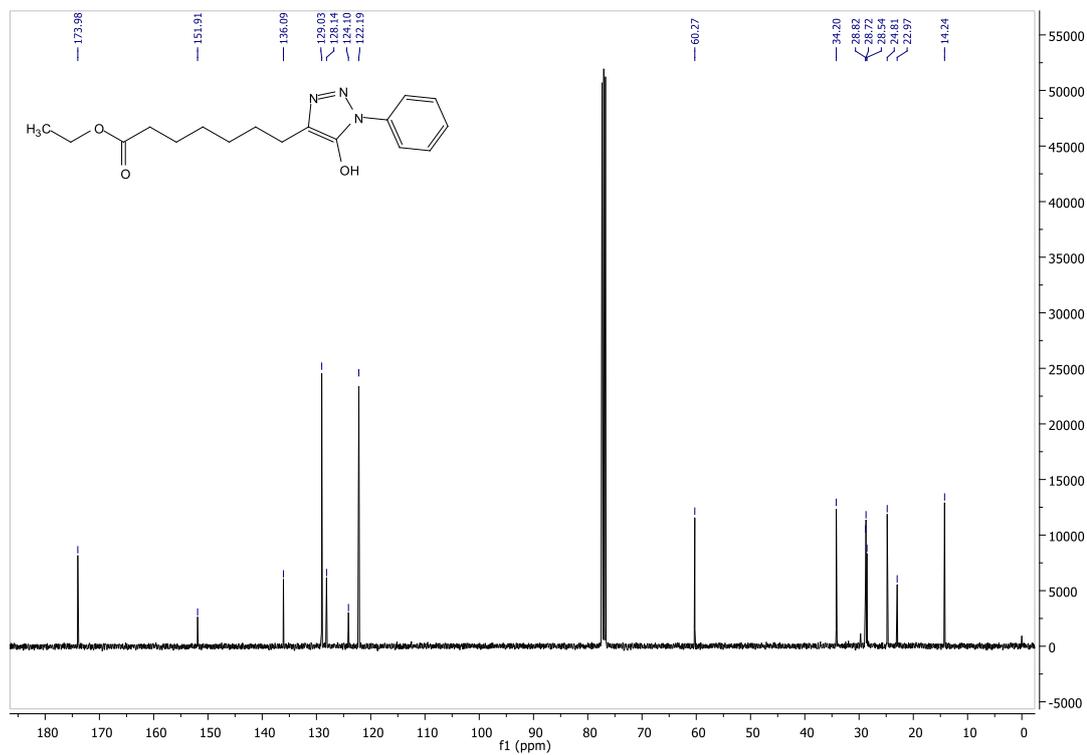
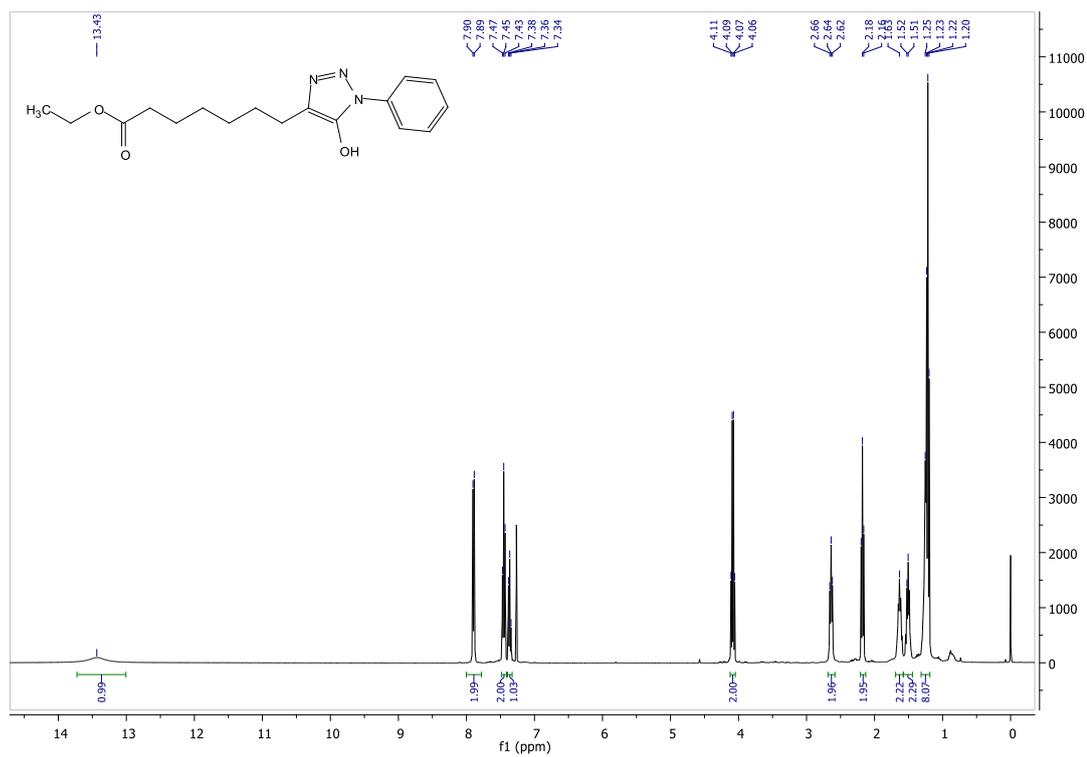
Compound 2.142a



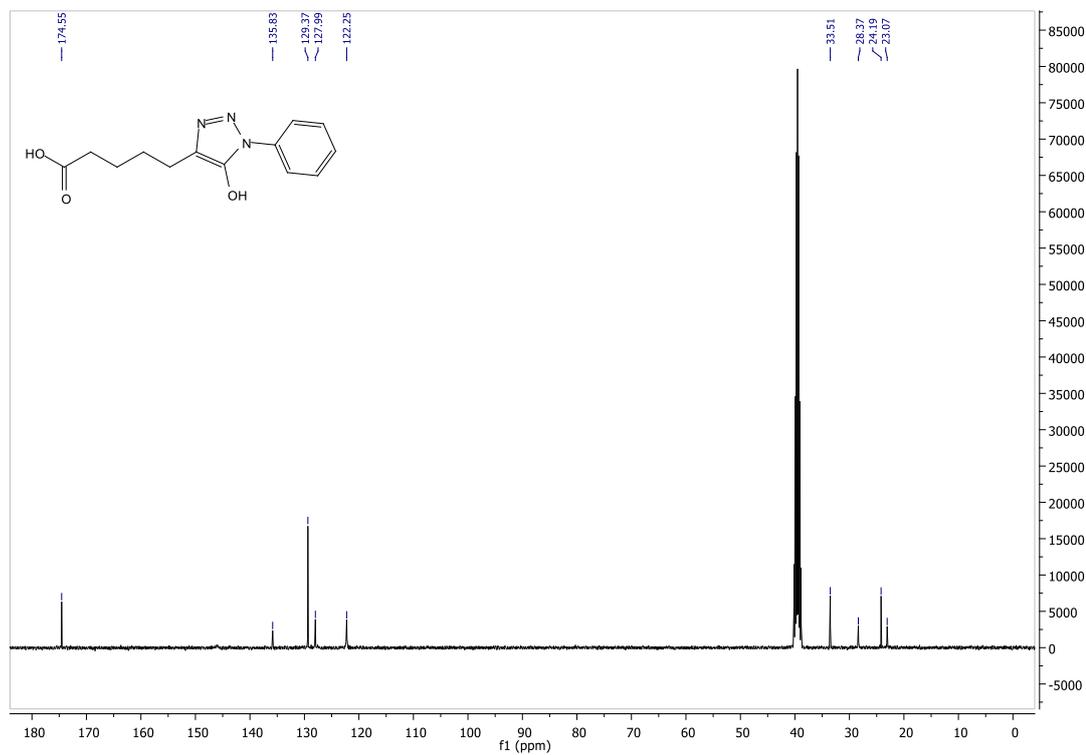
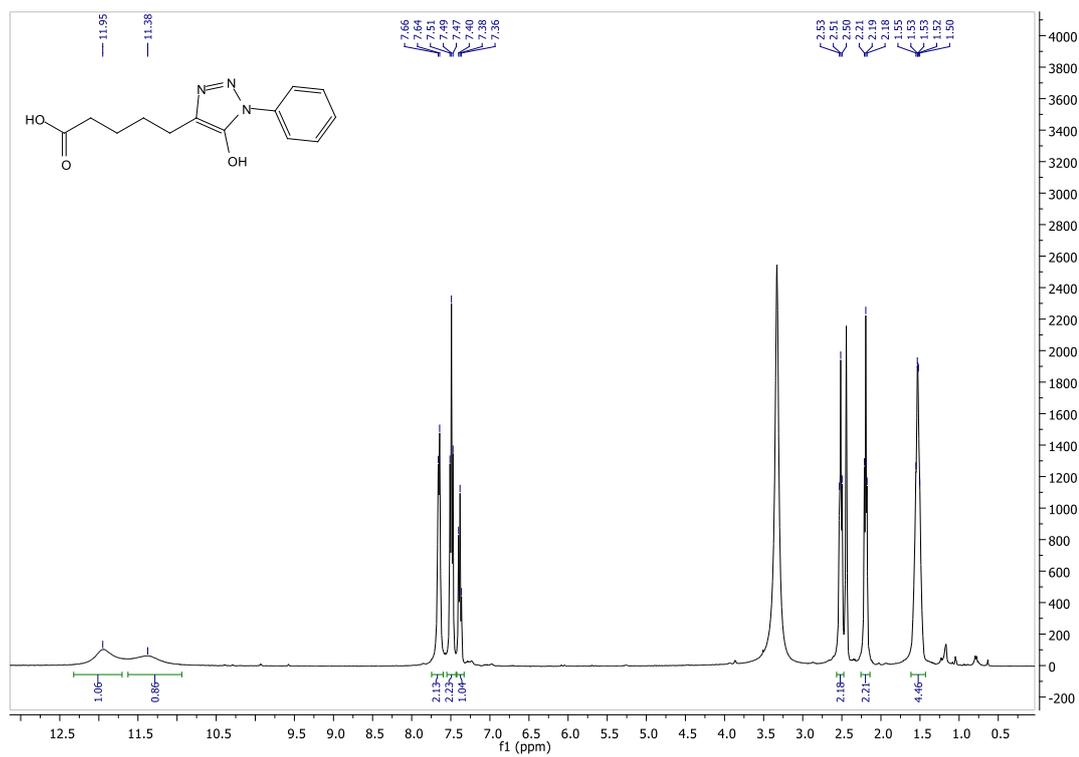
Compound 2.142b



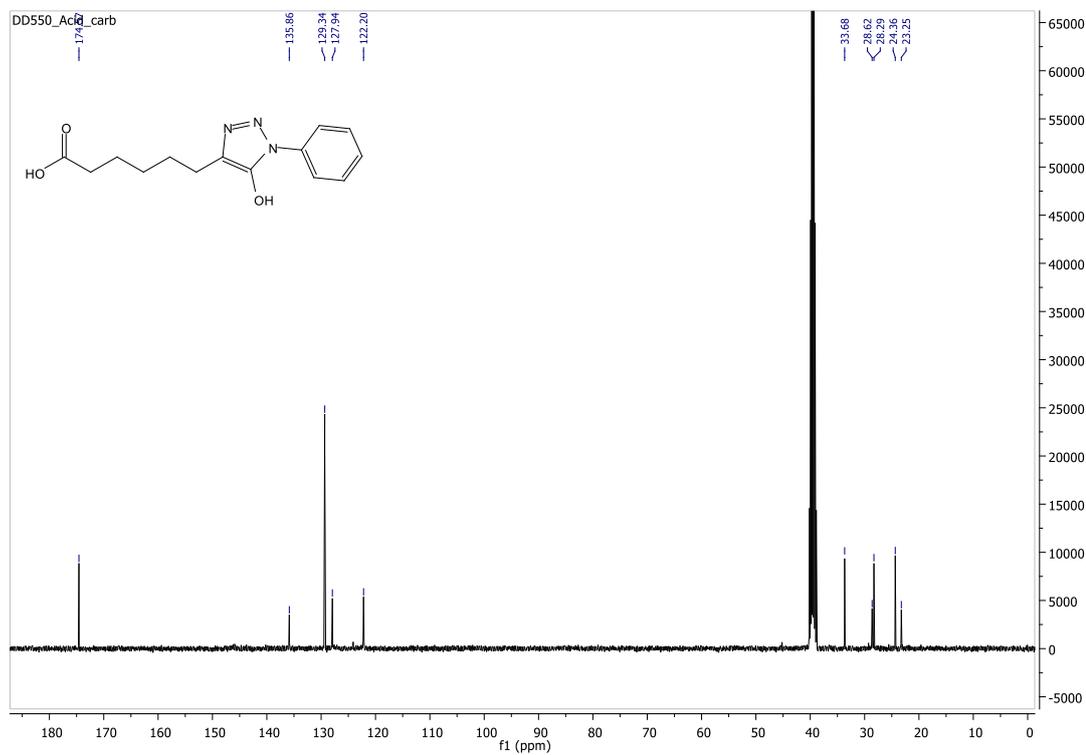
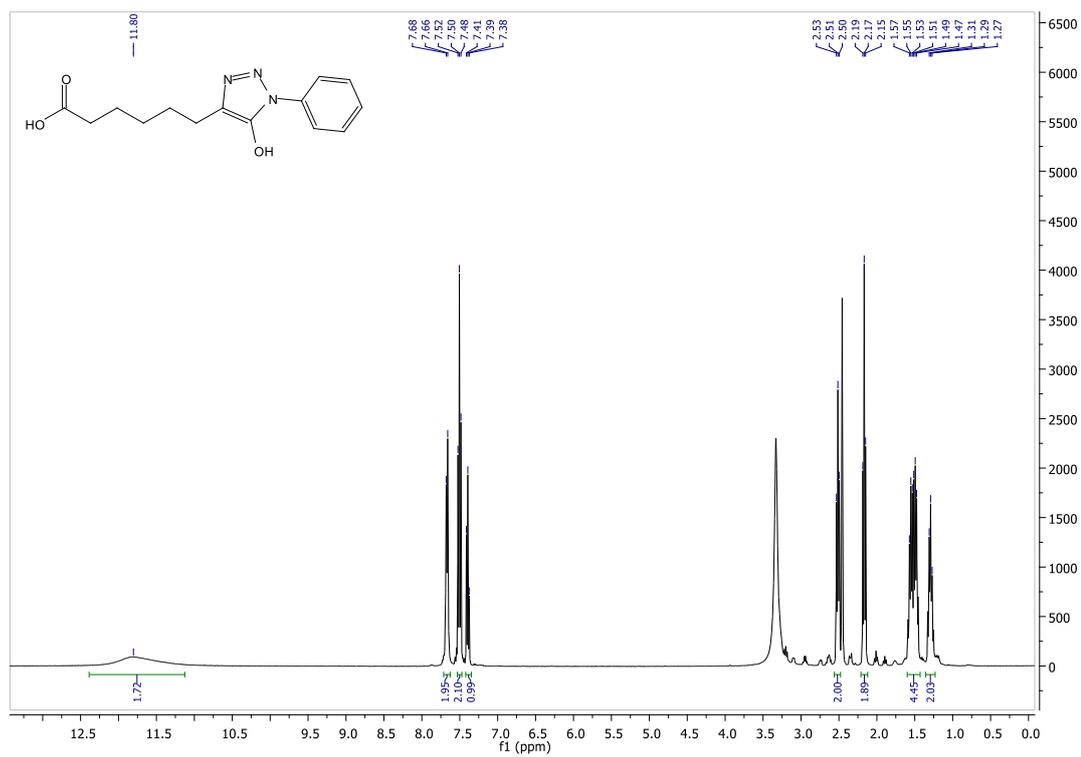
Compound 2.142c



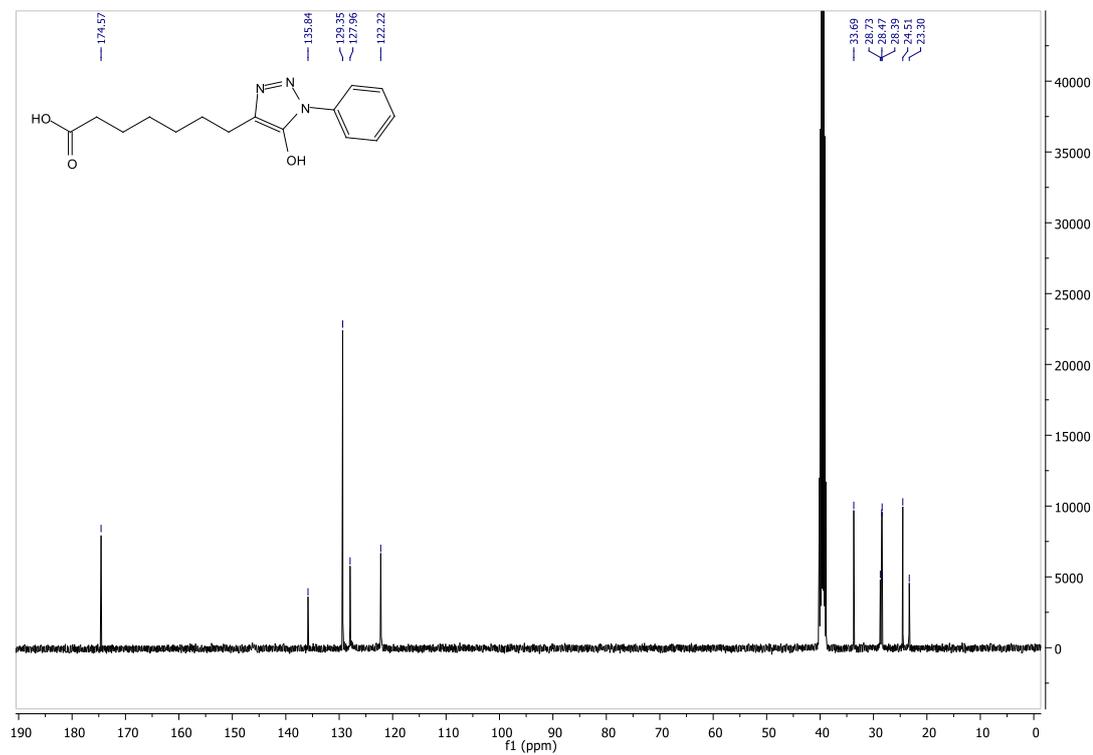
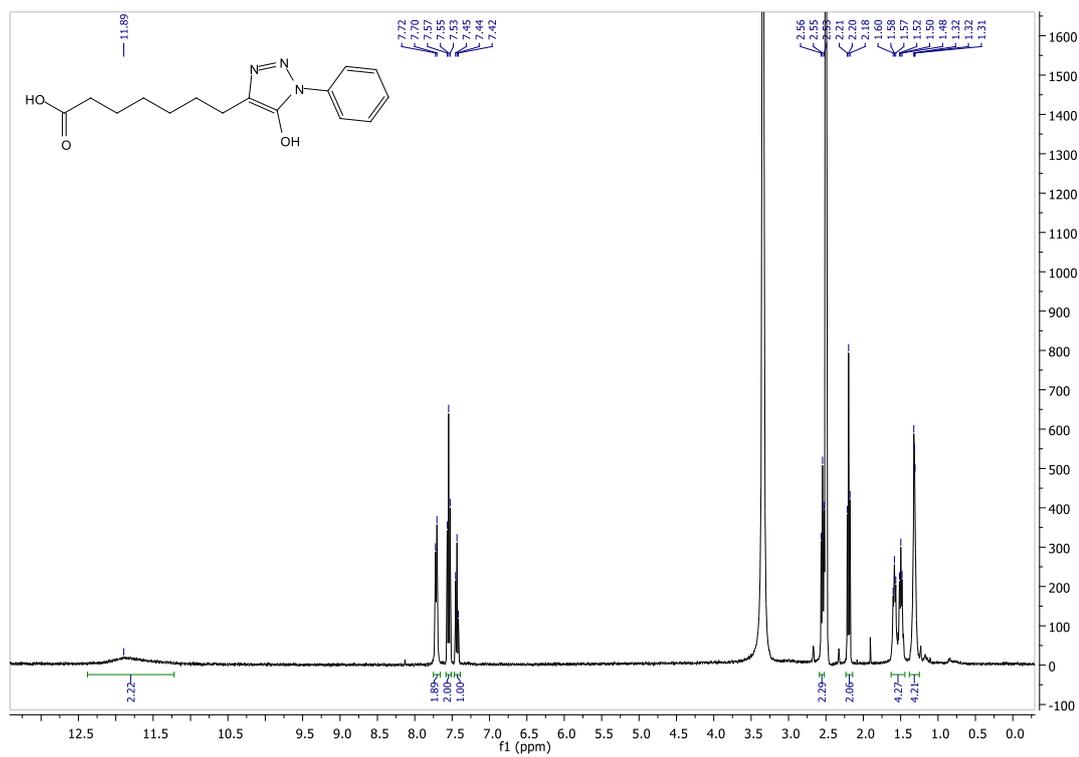
Compound 2.141a



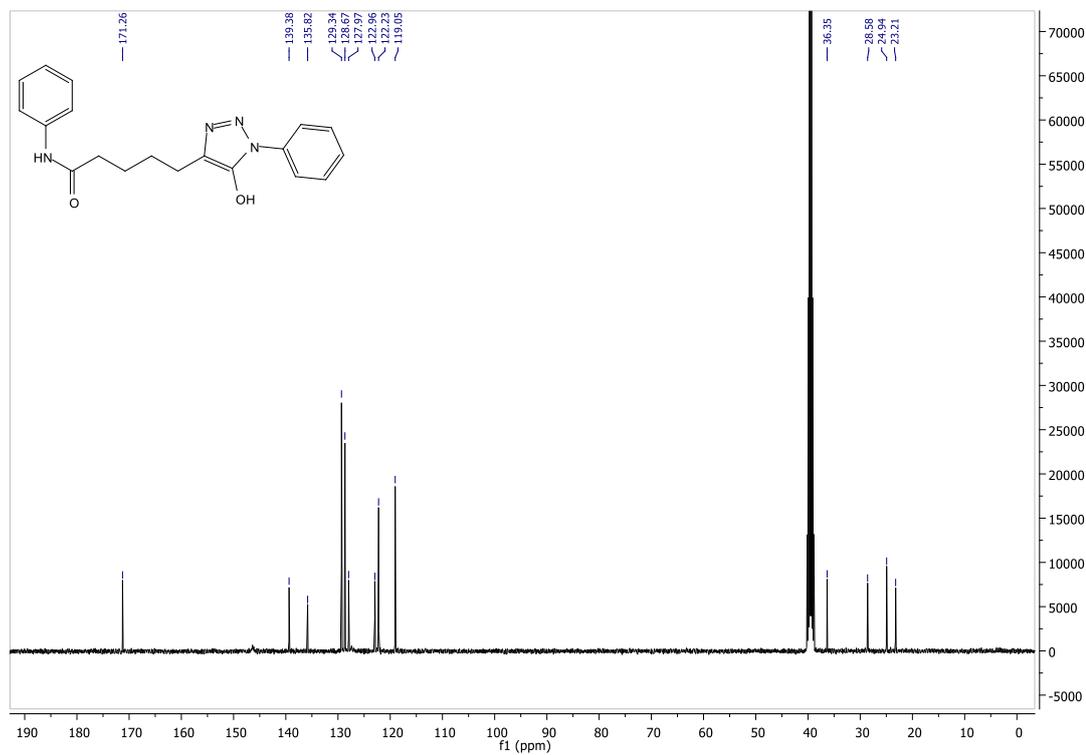
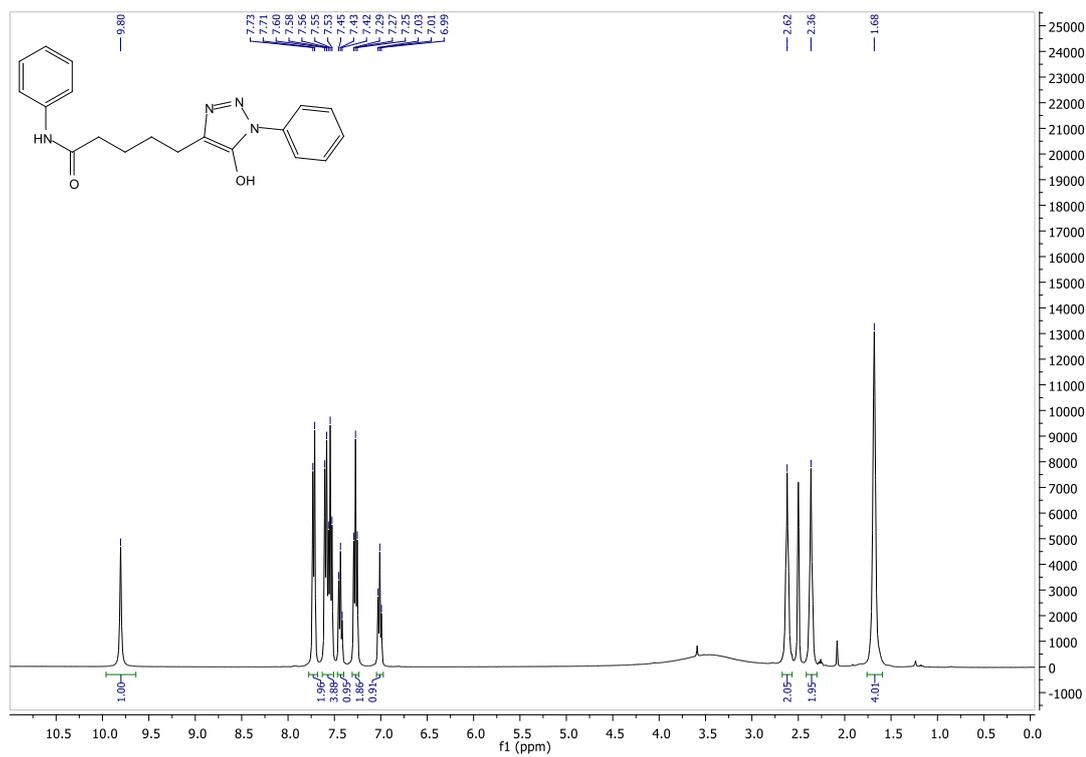
Compound 2.141b



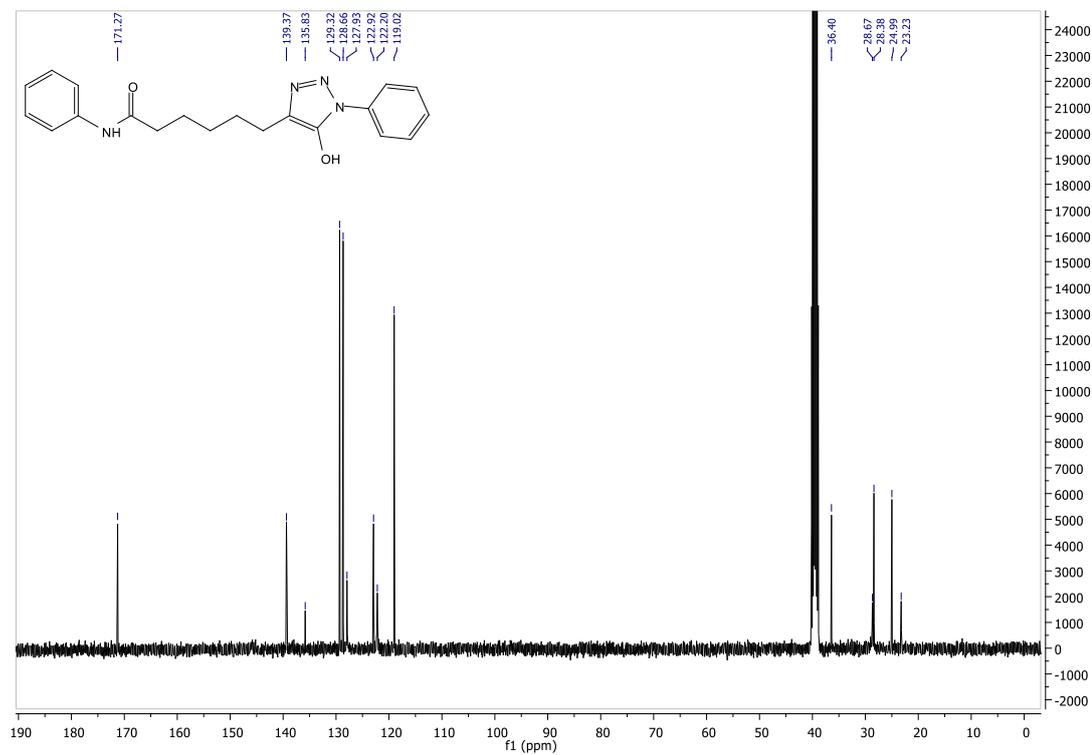
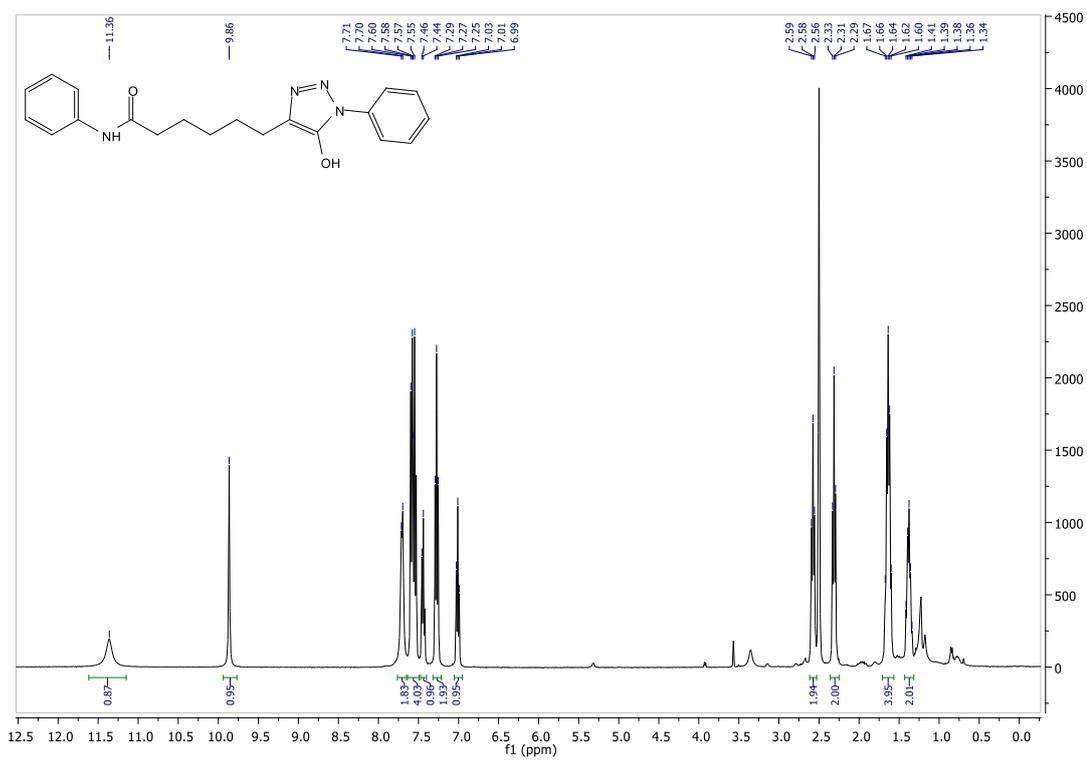
Compound 2.141c



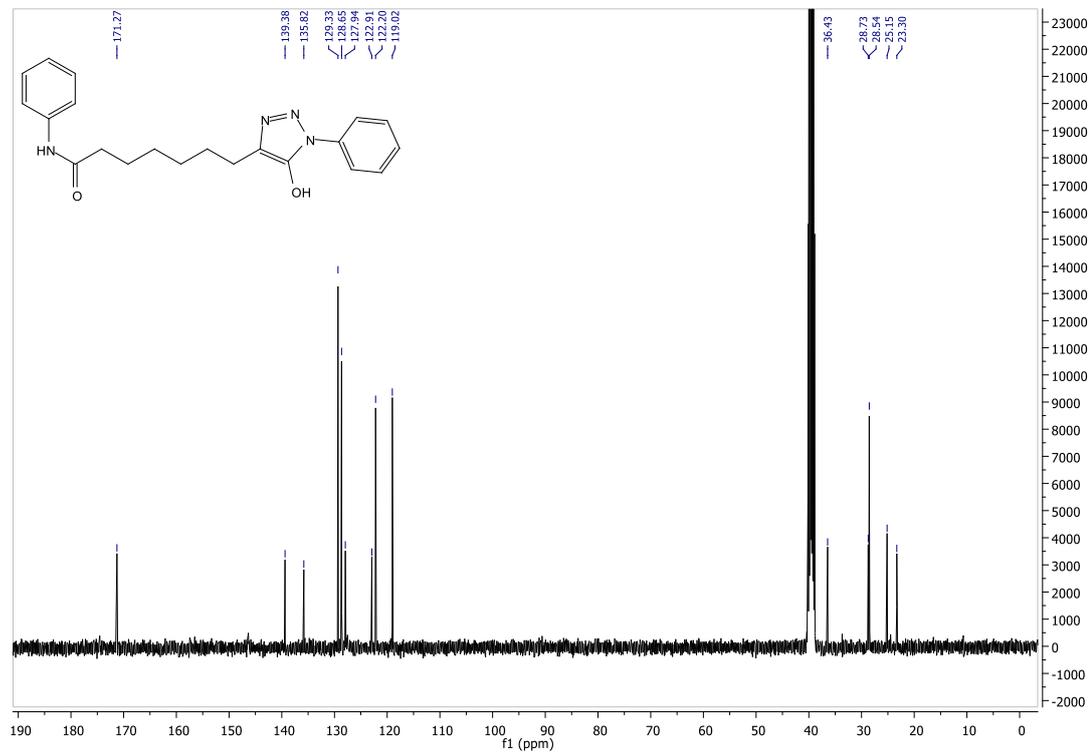
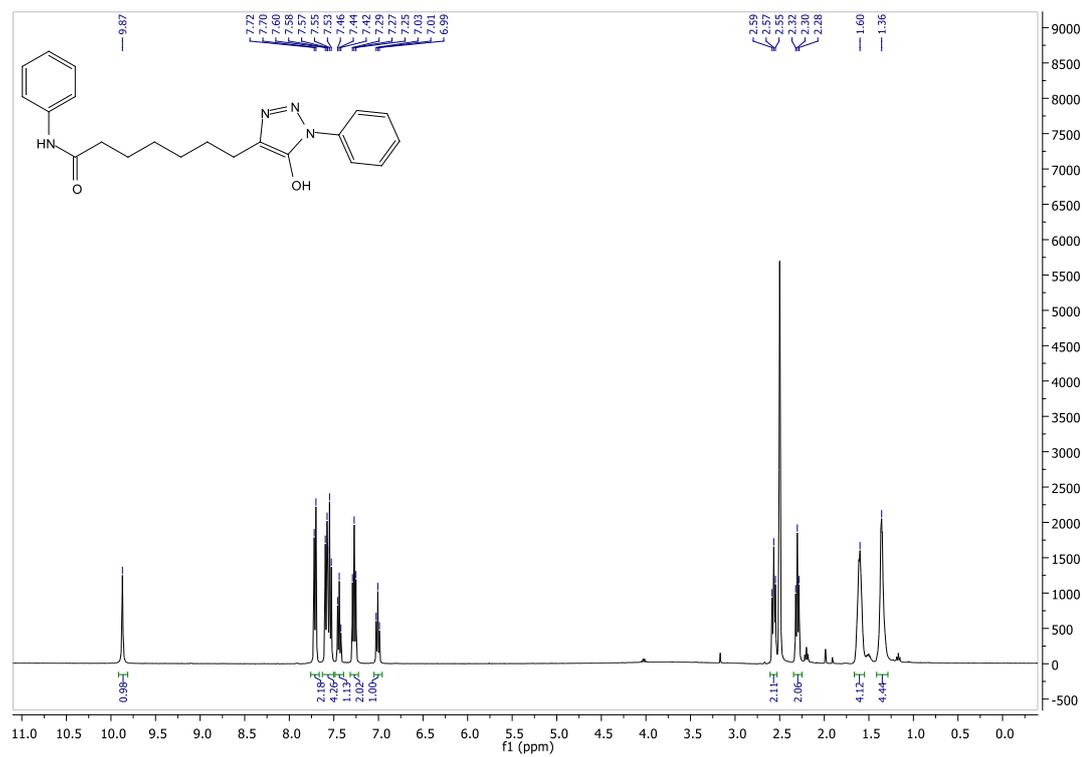
Compound 2.140a



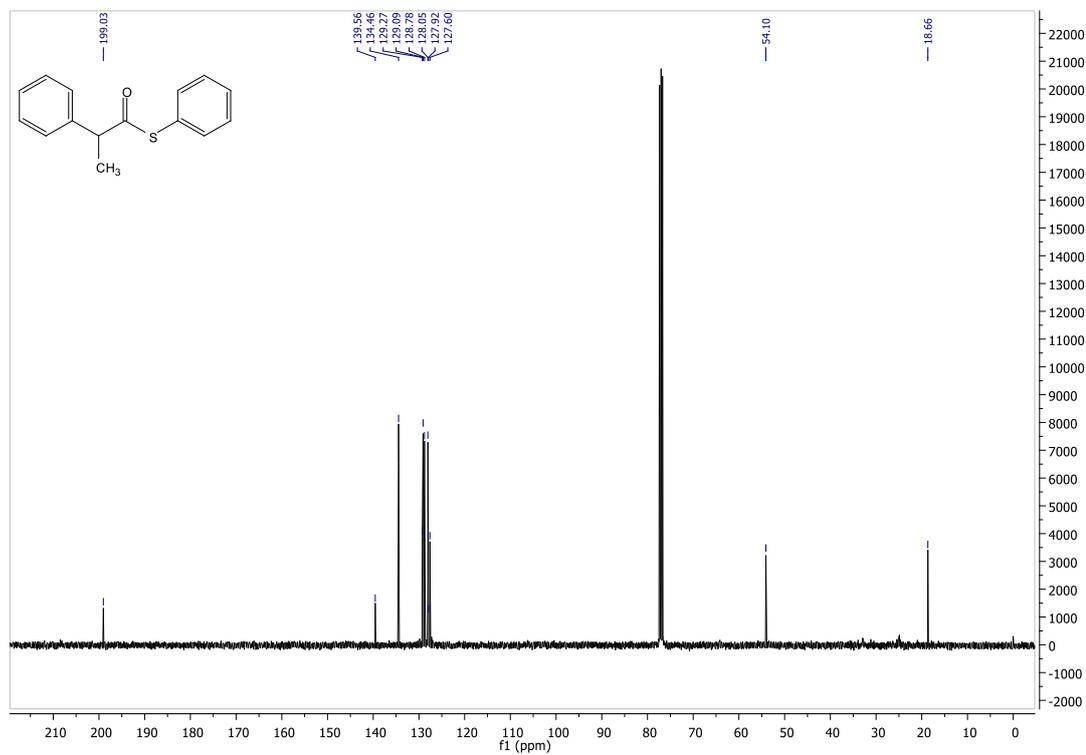
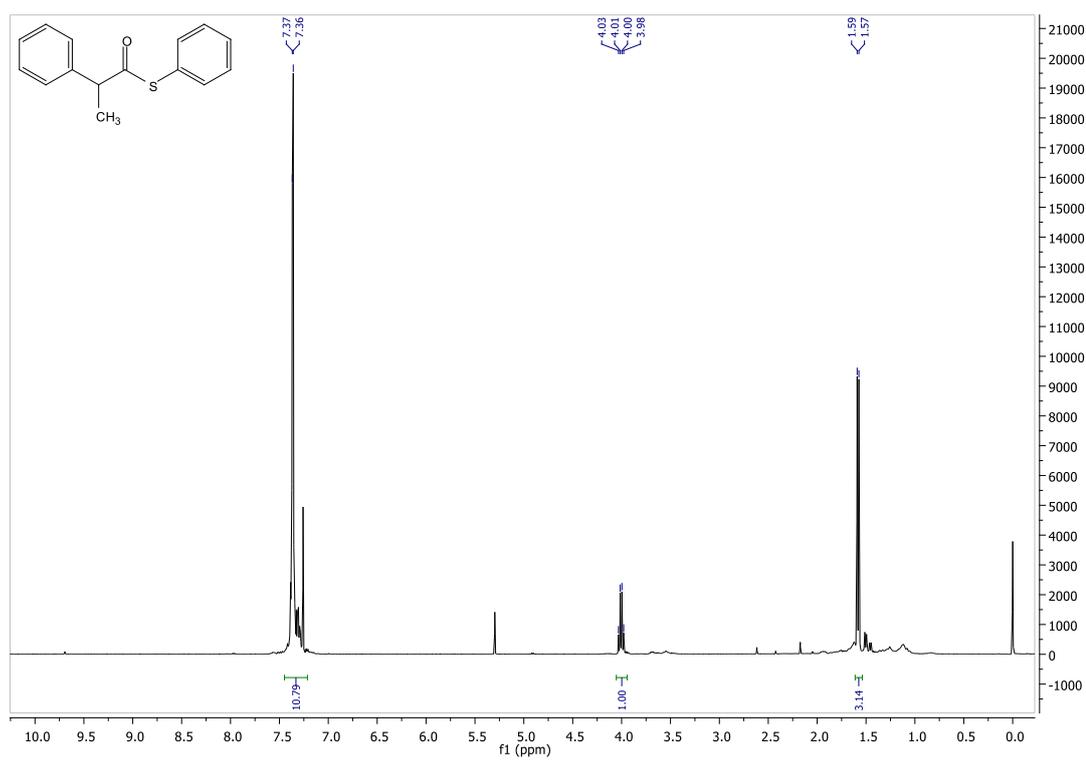
Compound 2.140b



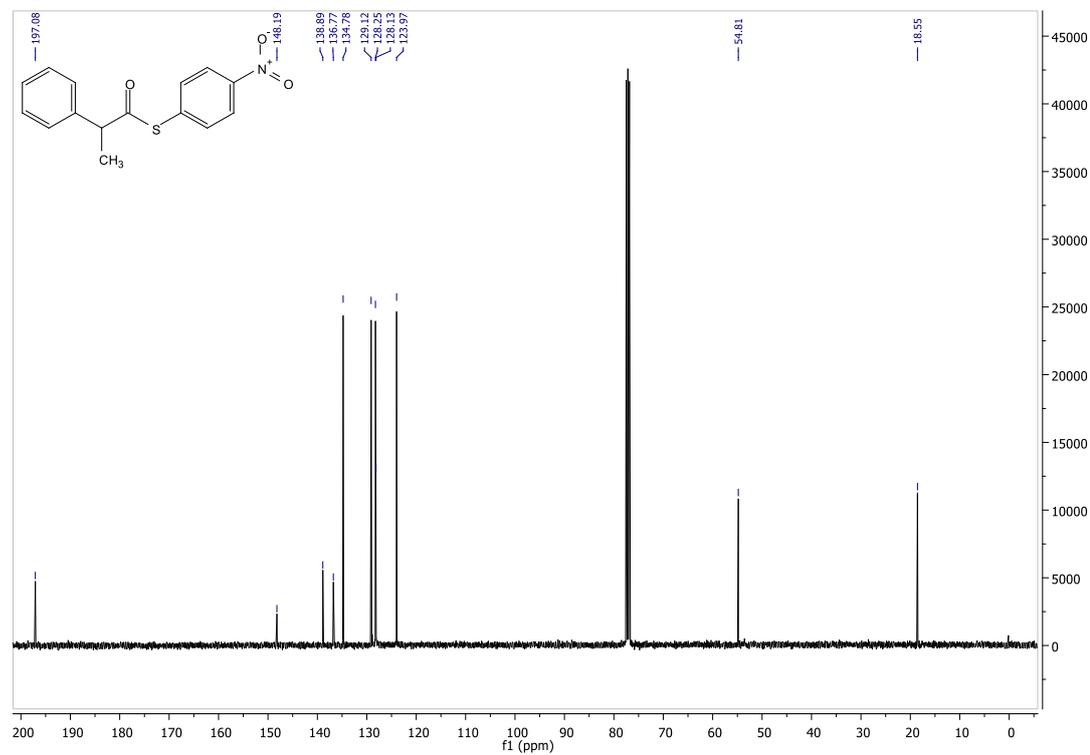
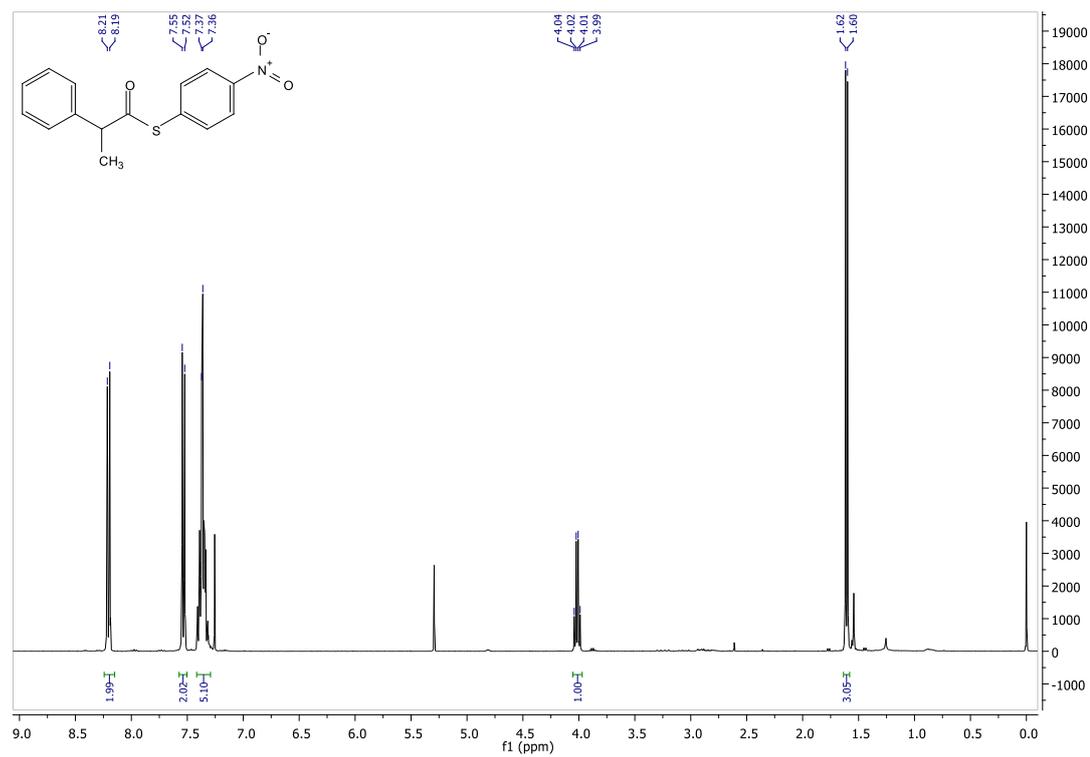
Compound 2.140c



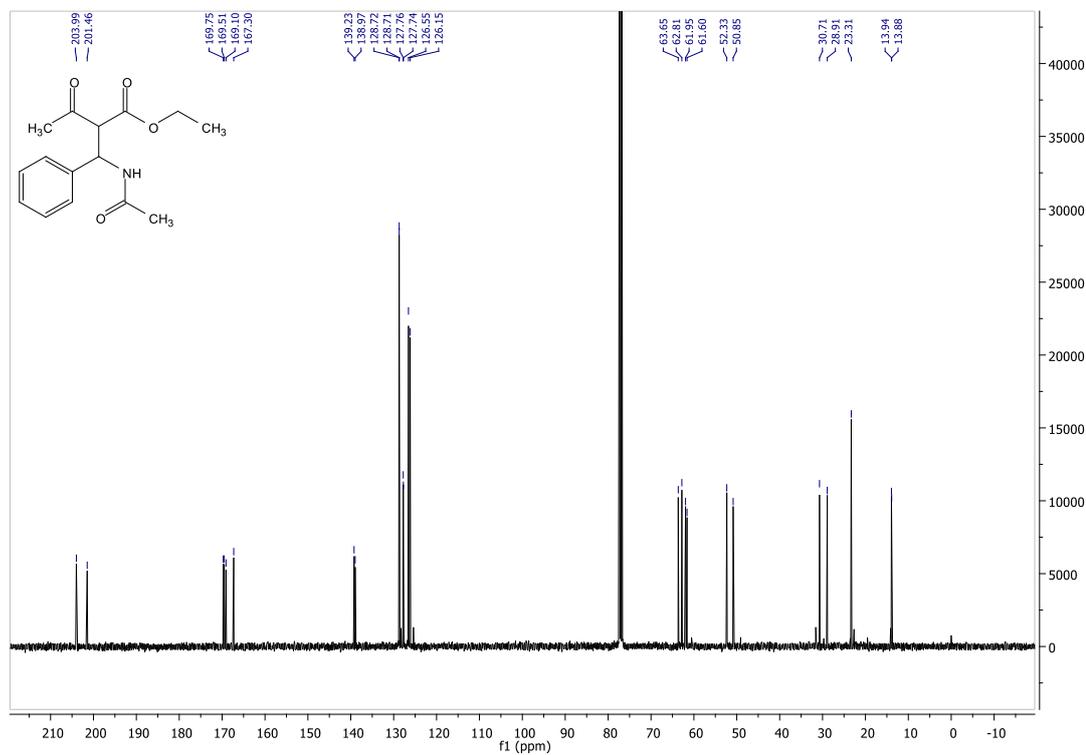
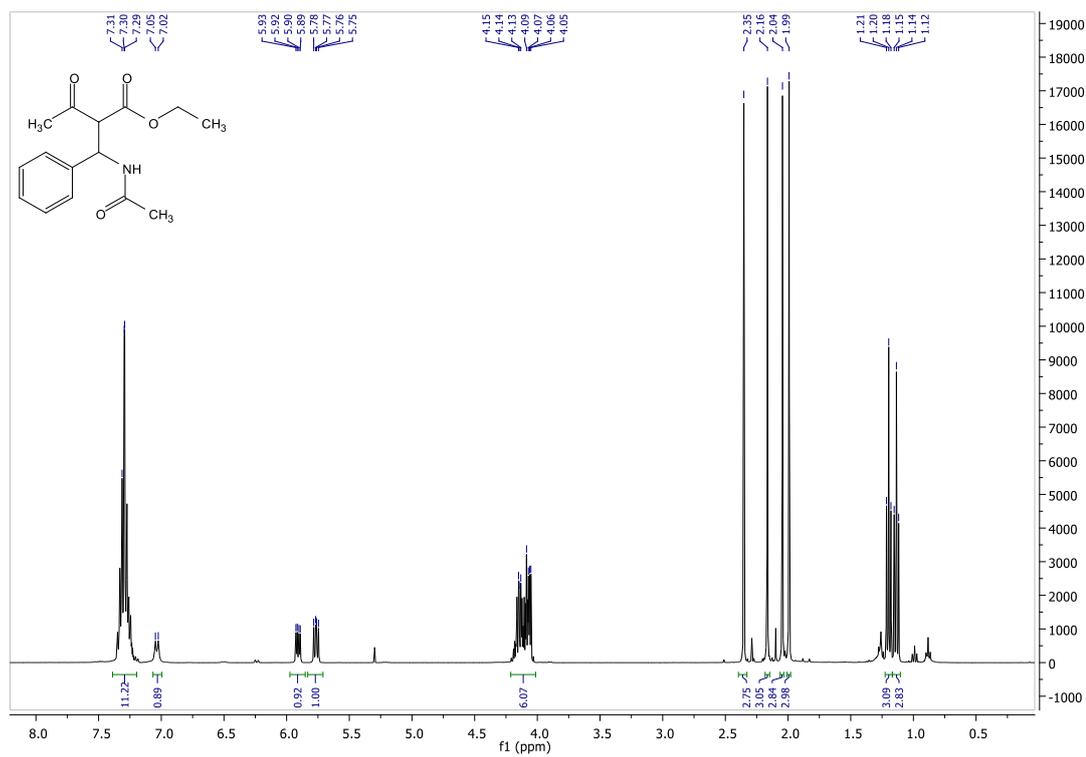
Compound 2.96b



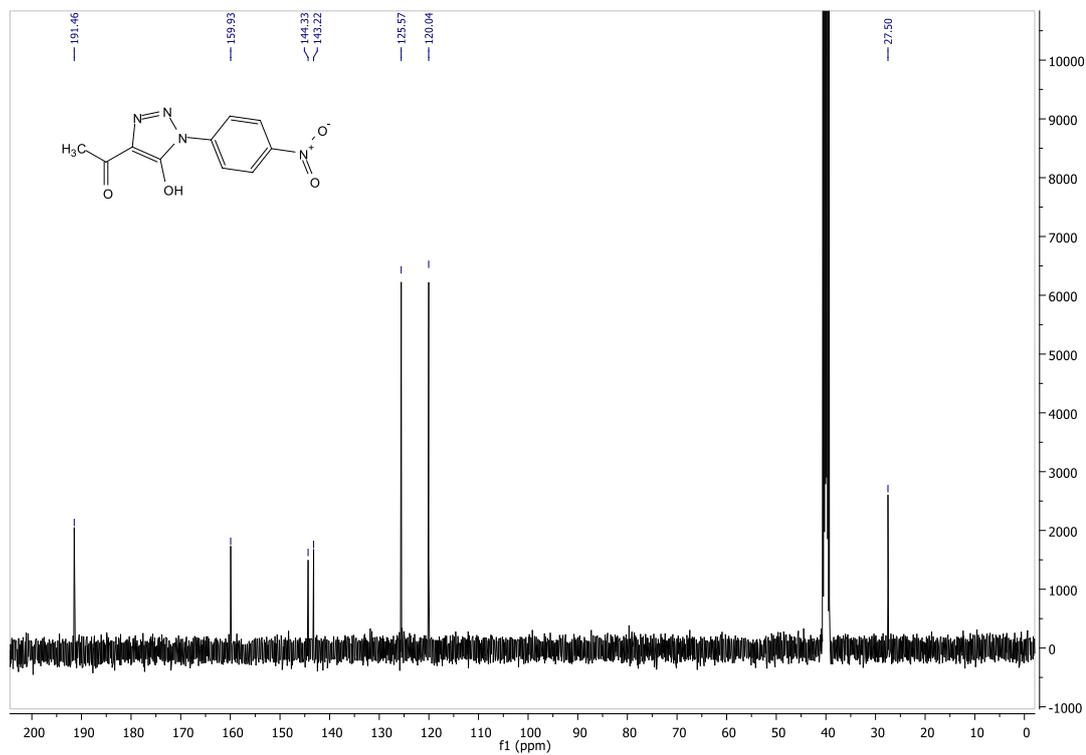
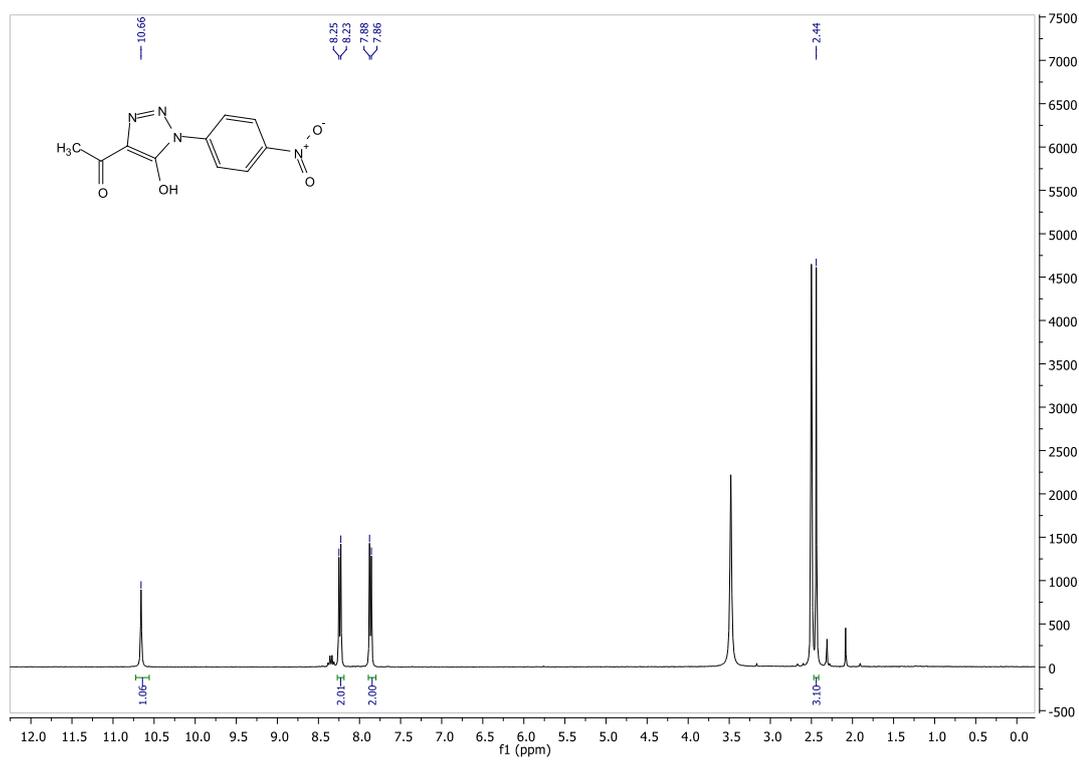
Compound 2.96c



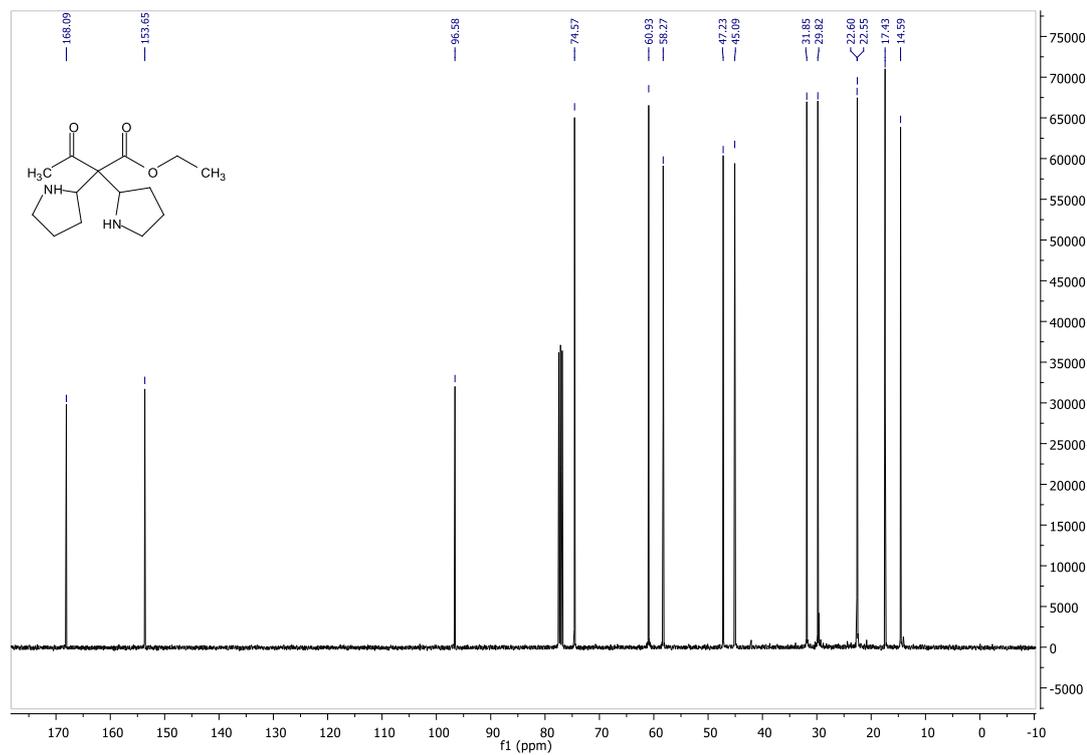
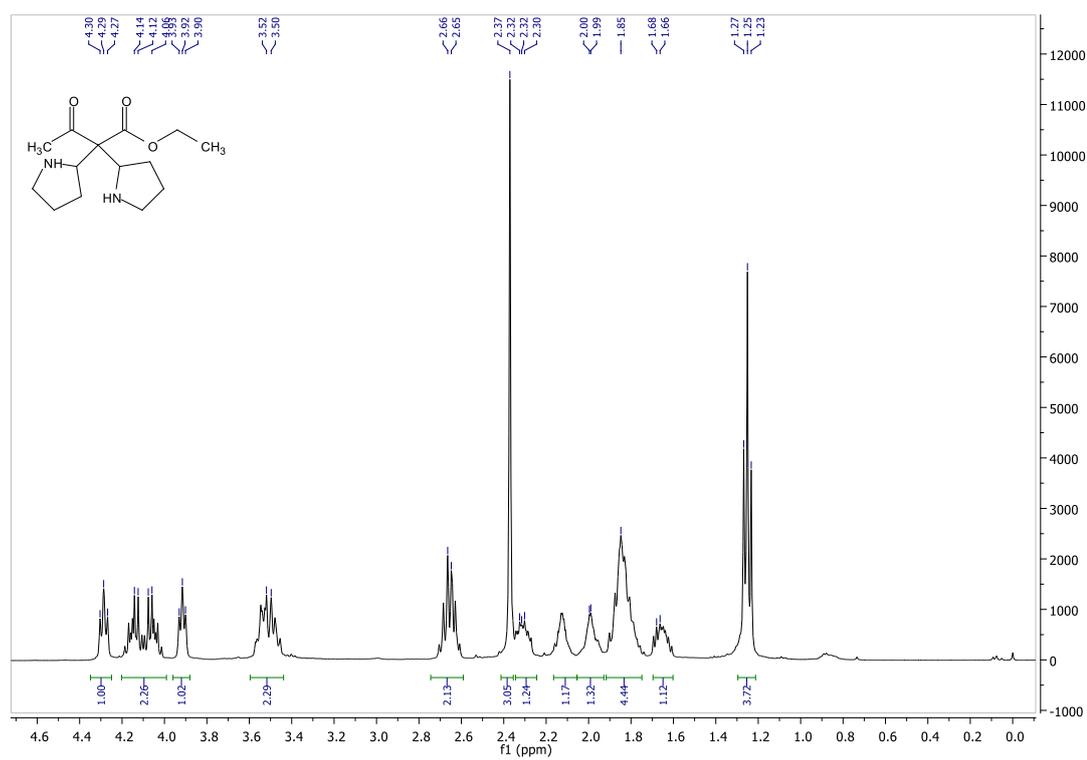
Compound 2.148



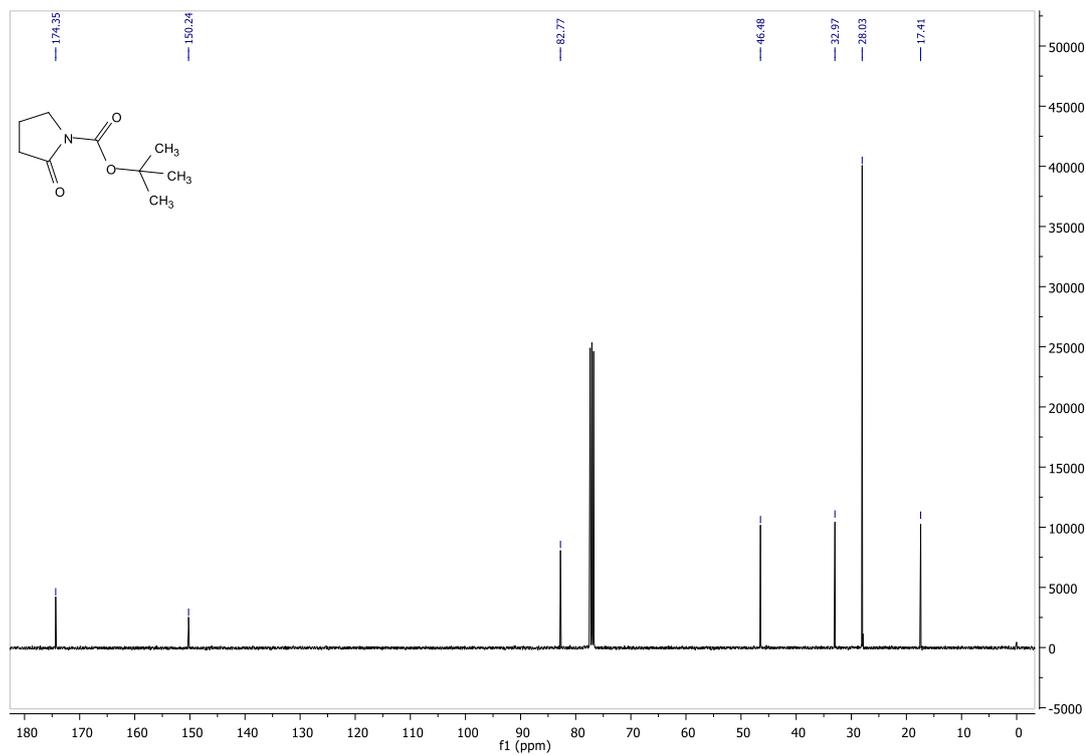
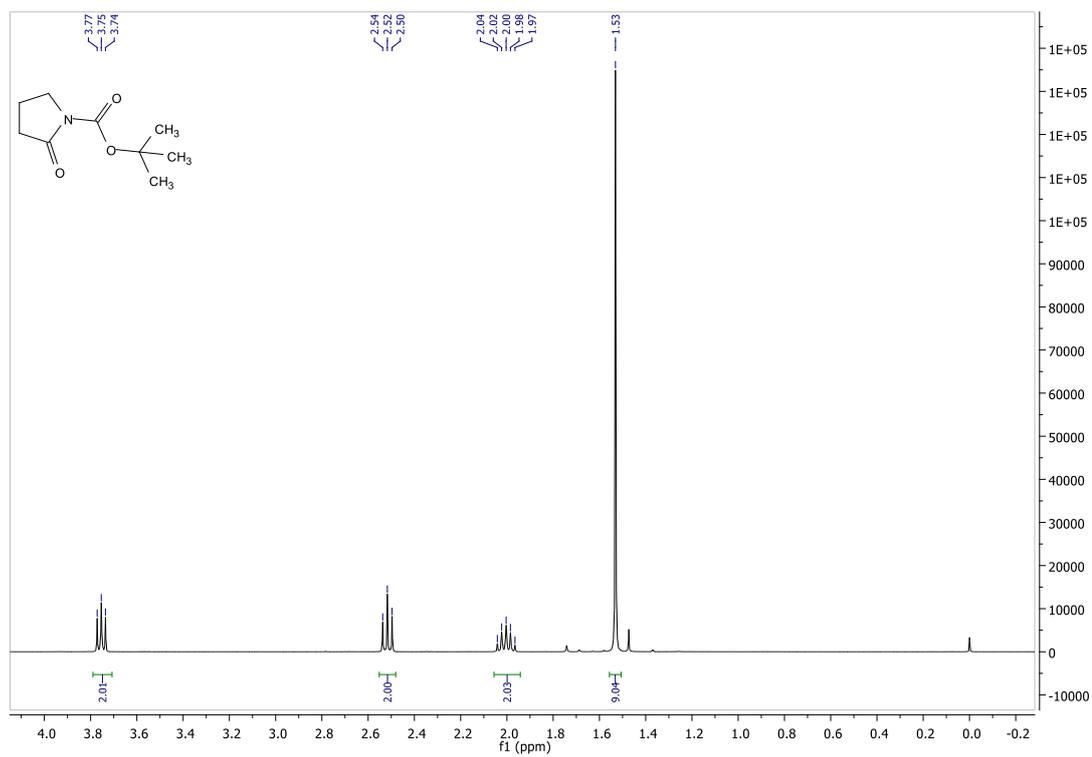
Compound 2.151b



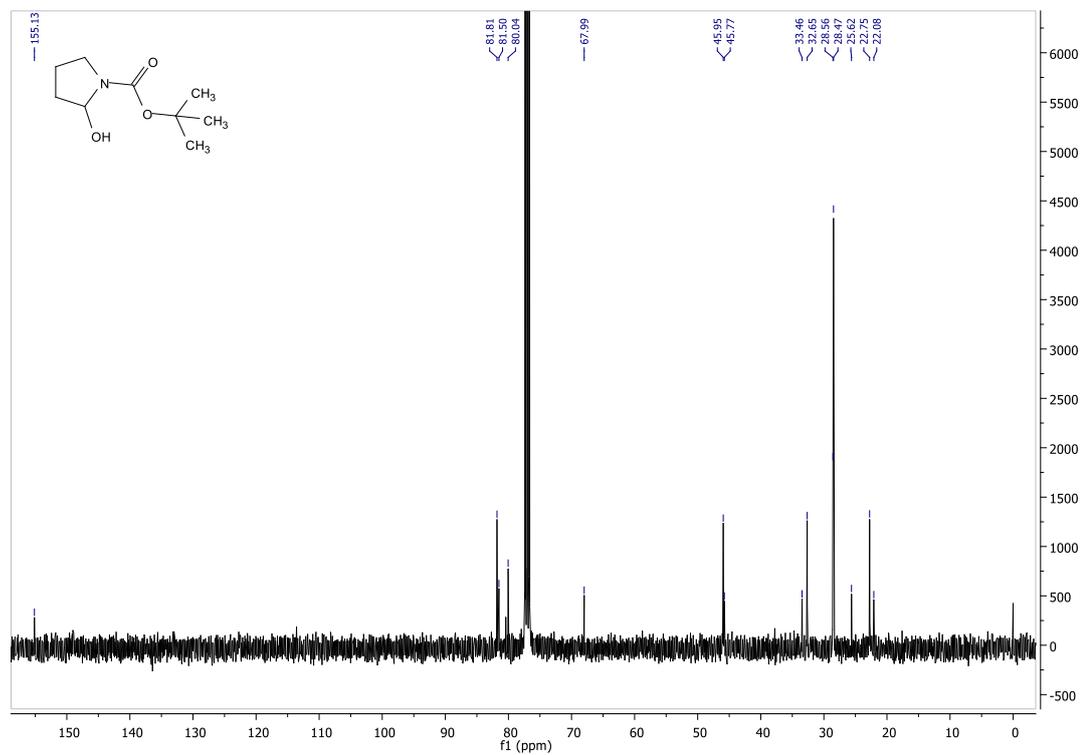
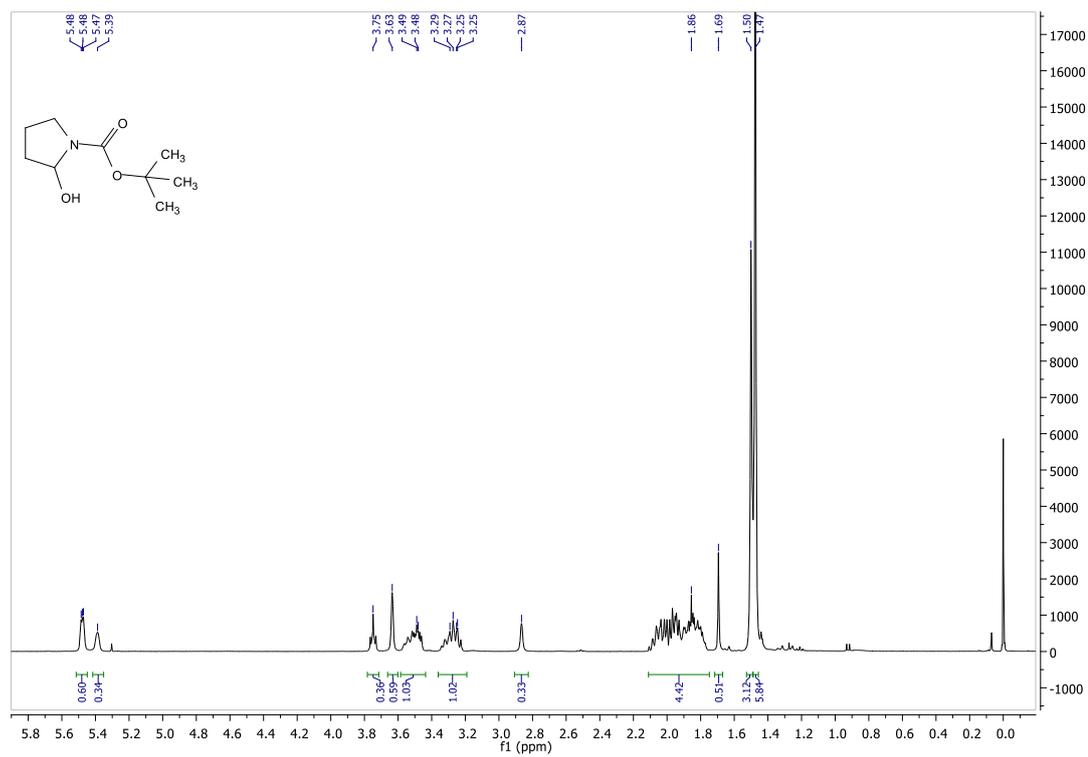
Compound 2.157



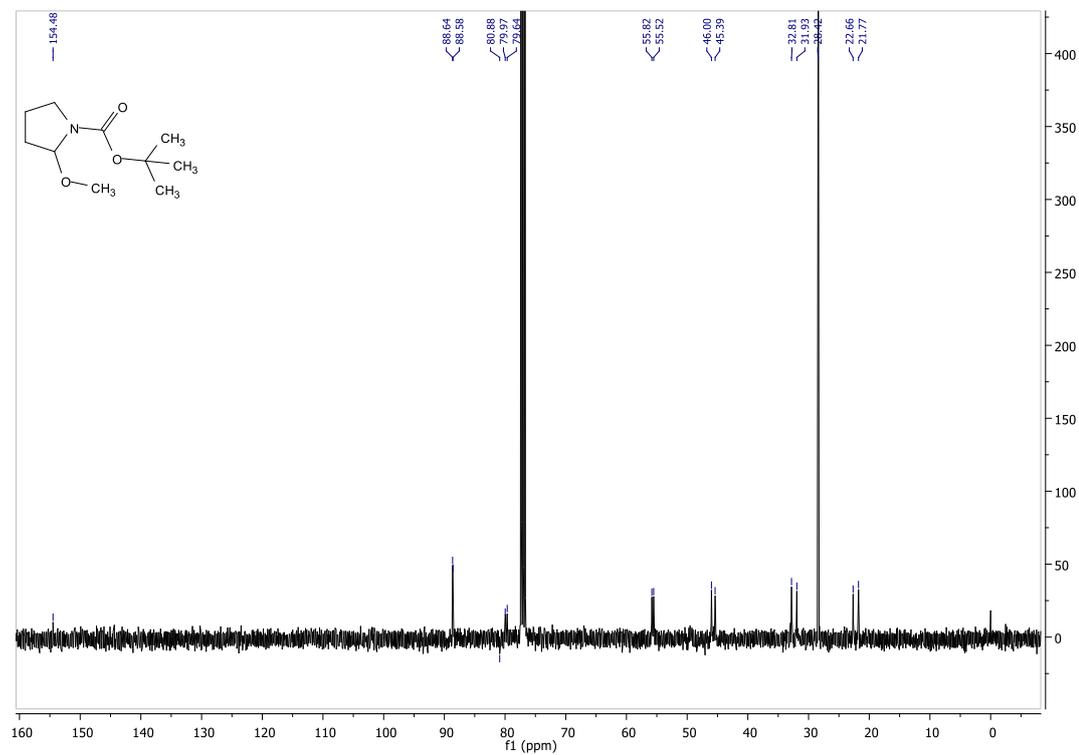
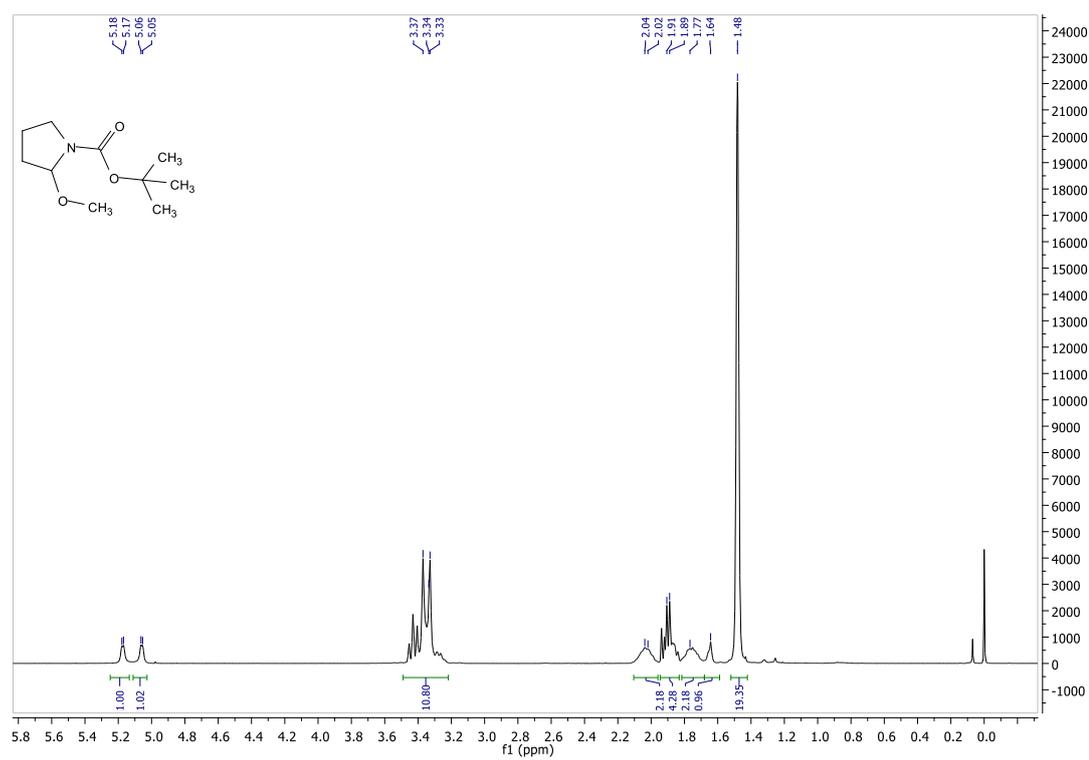
Compound 2.165



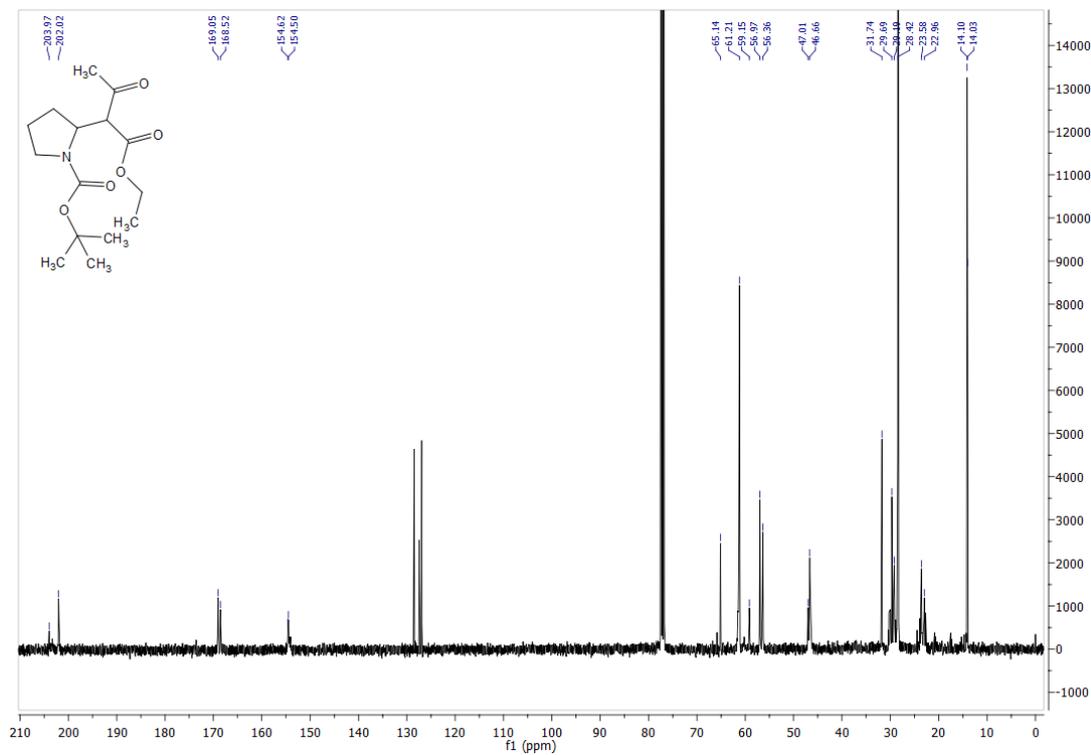
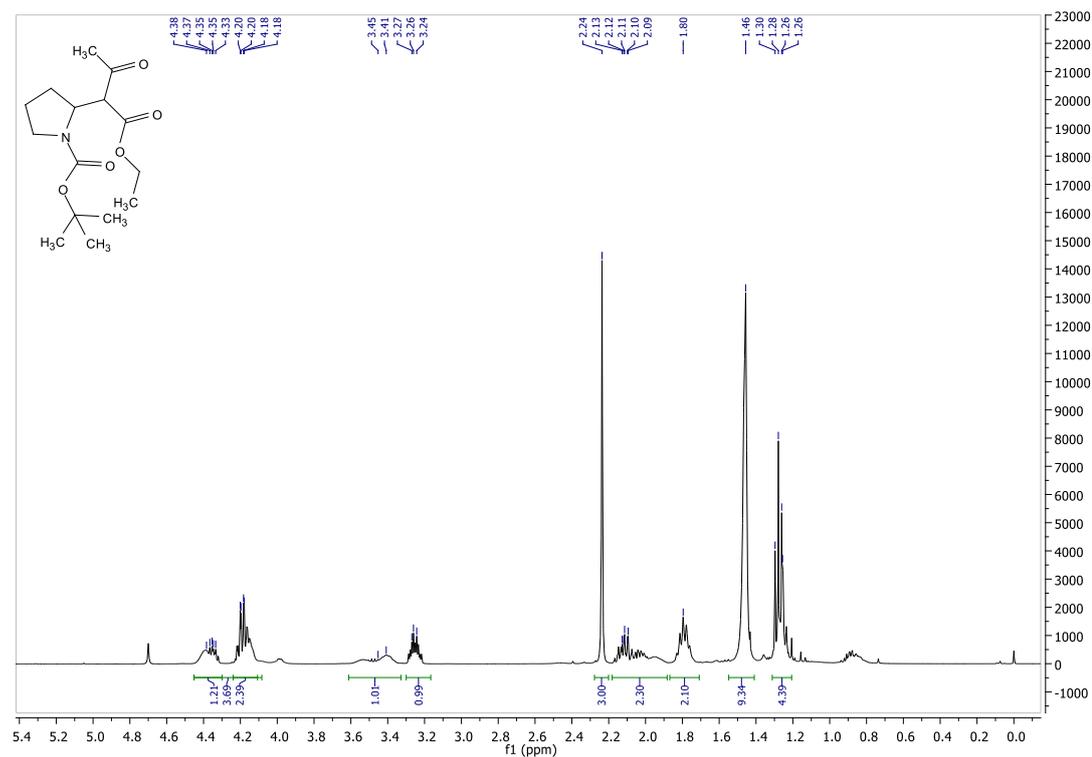
Compound 2.166



Compound 2.167

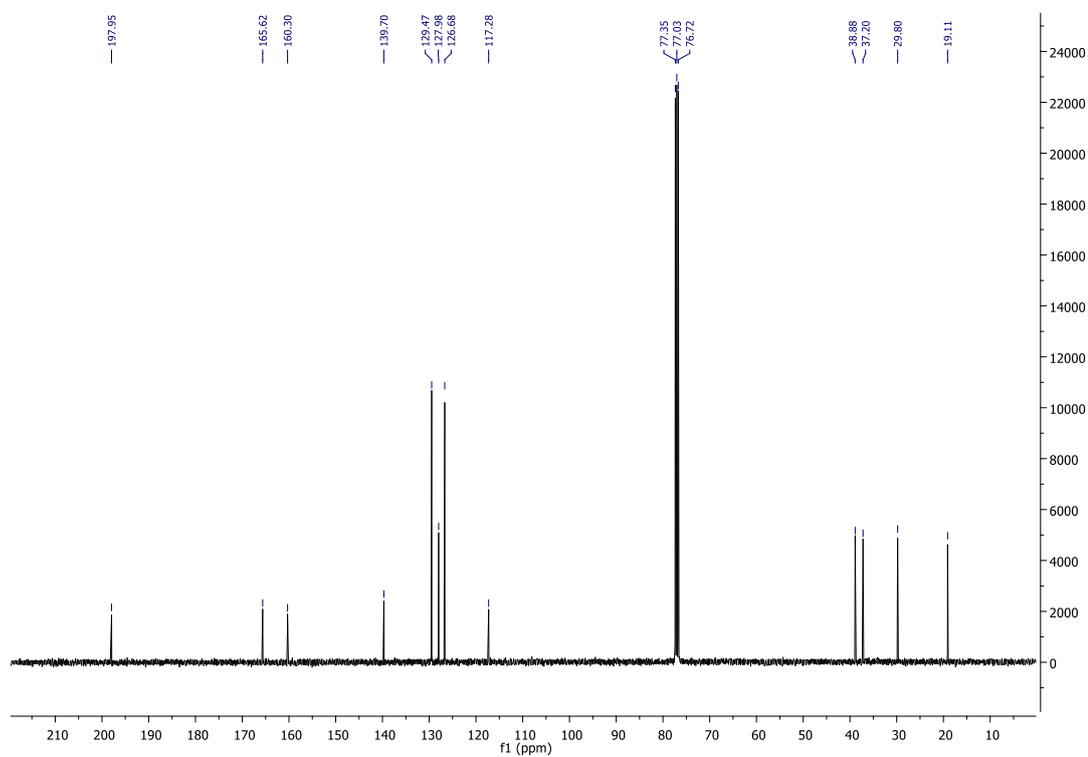
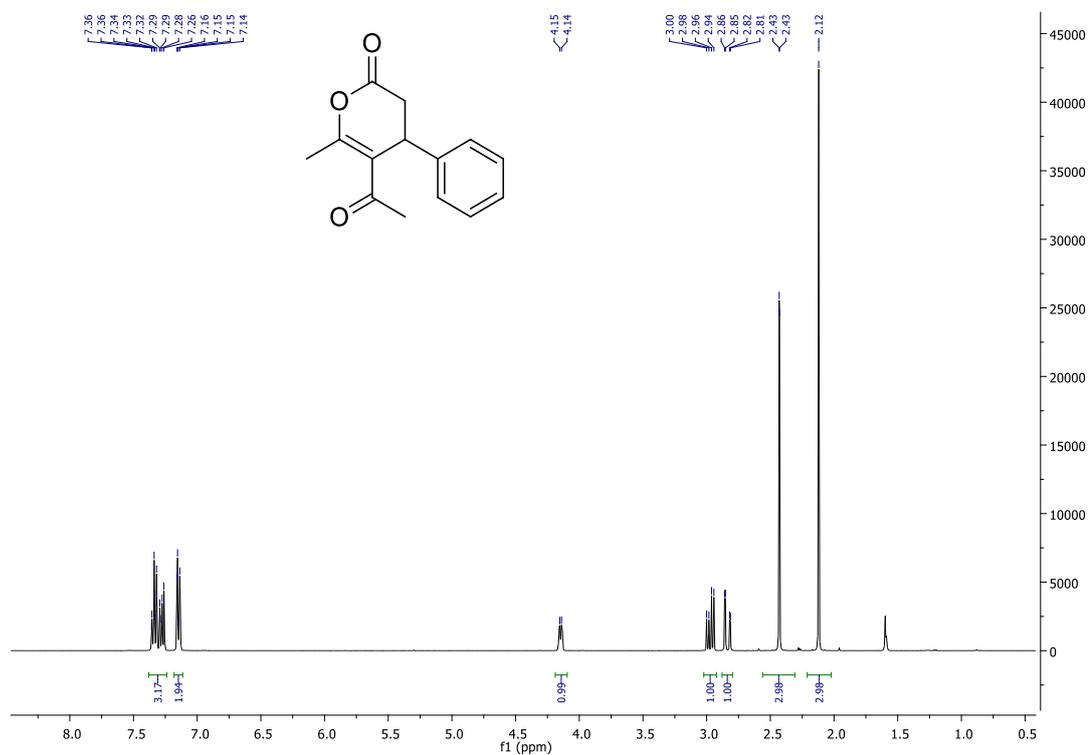


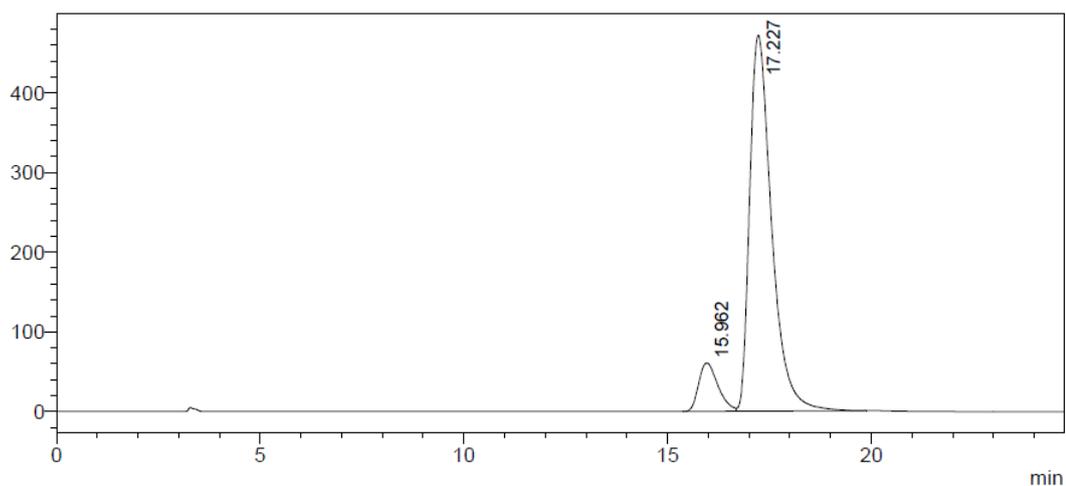
Compound 2.149



Chapter 3: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$

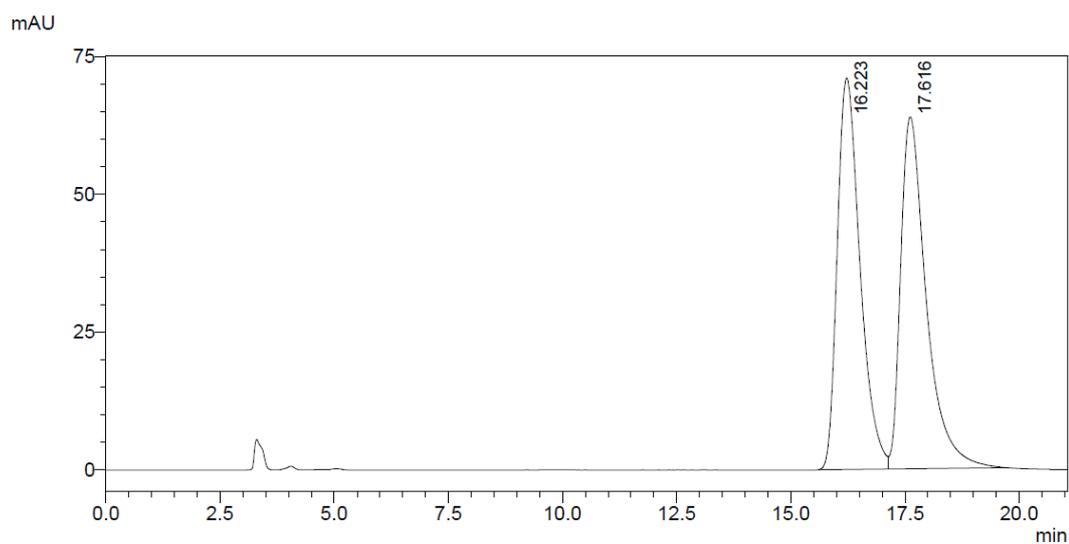
Compound 3.106a





Detector A Channel 1 254nm

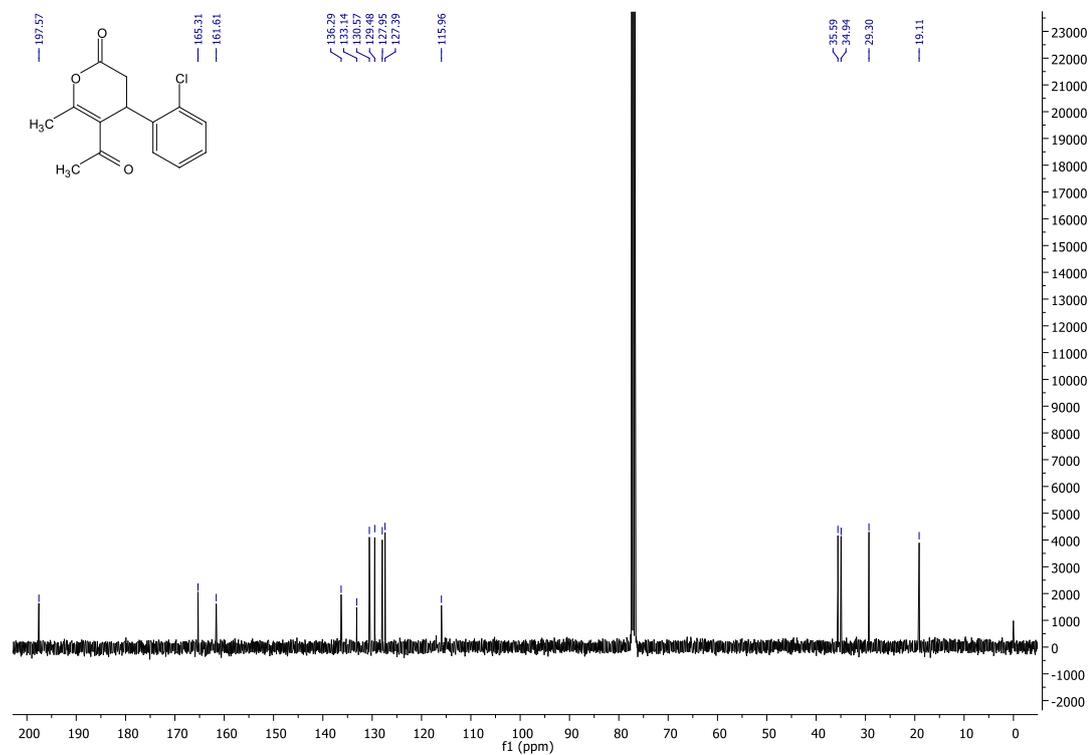
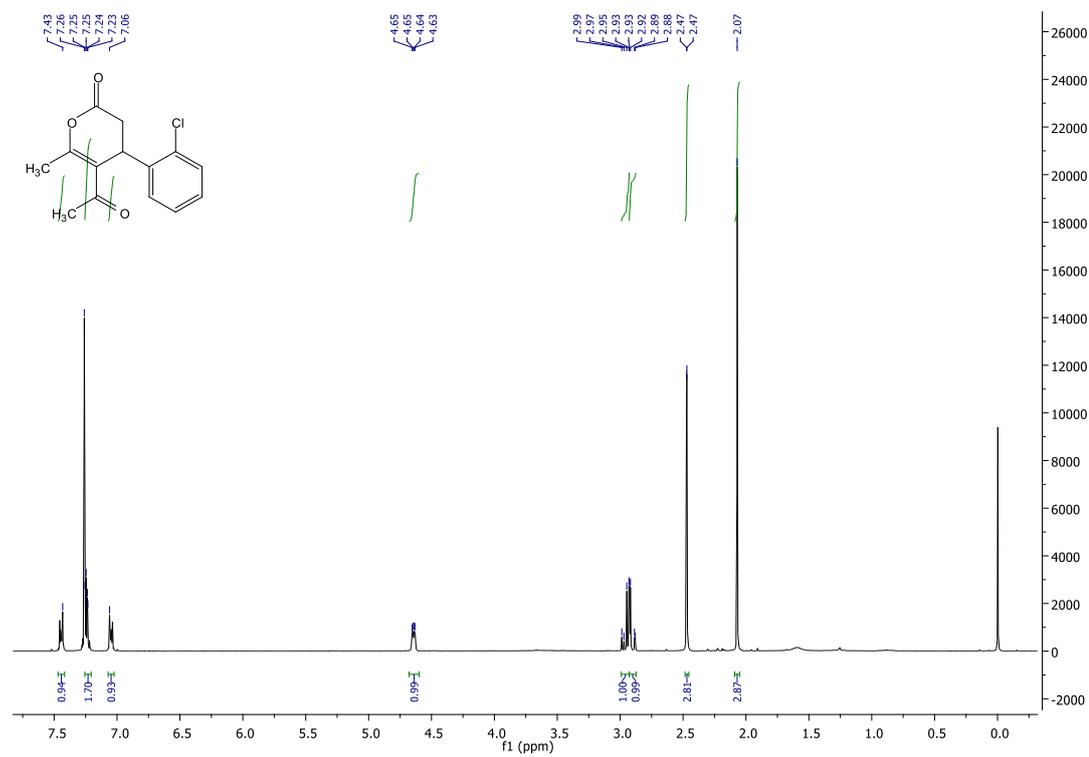
Peak#	Ret. Time	Area	Name
1	15.962	2012742	R
2	17.227	17719404	S
Total		19732146	

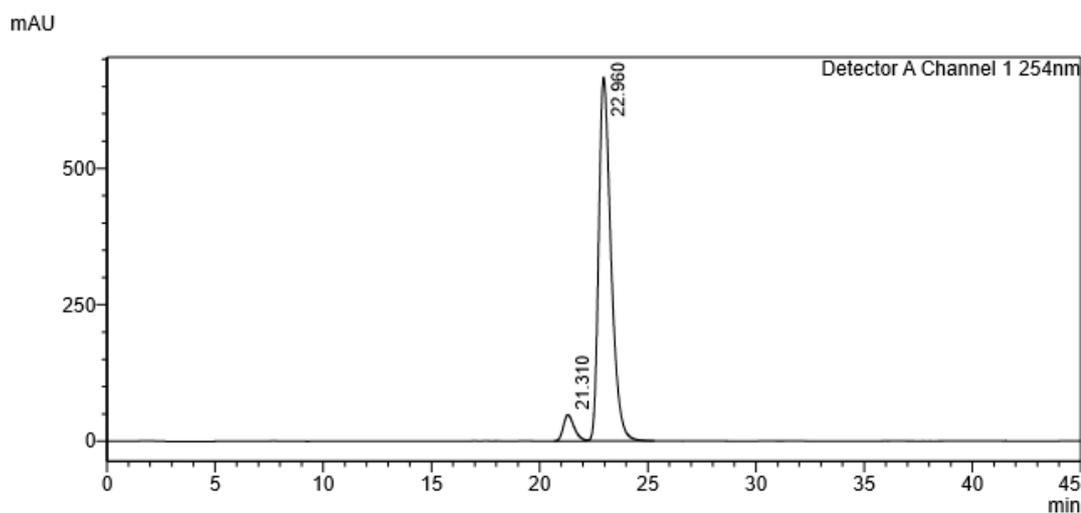


Detector A Channel 1 254nm

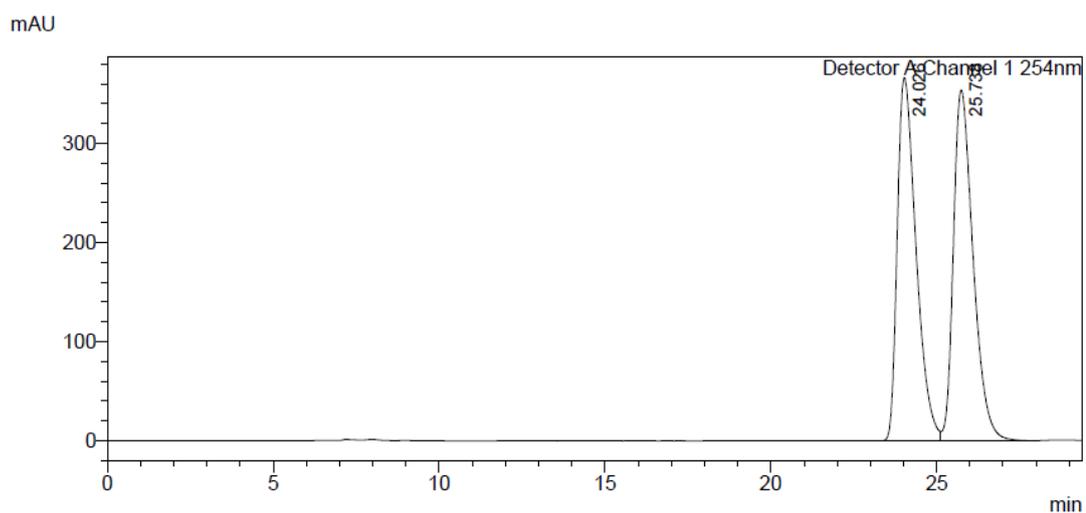
Peak#	Ret. Time	Area	Name	Area%
1	16.223	2464152	R	49.693
2	17.616	2494612	S	50.307
Total		4958764		100.000

Compound 3.106b



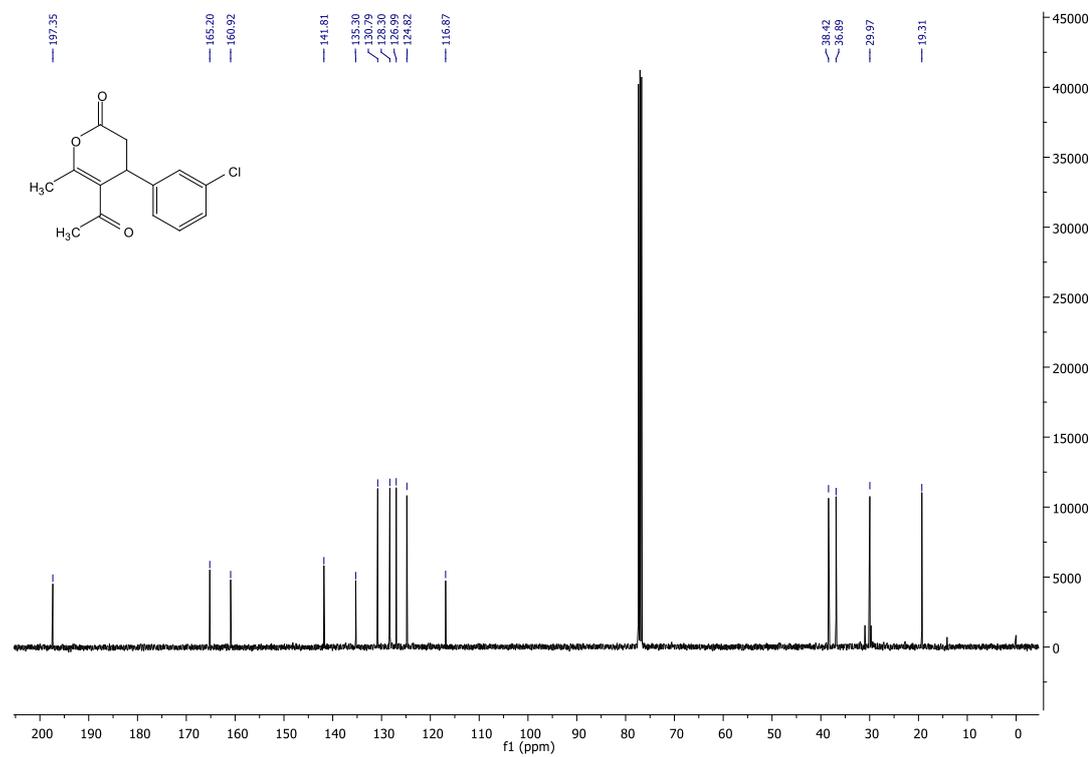
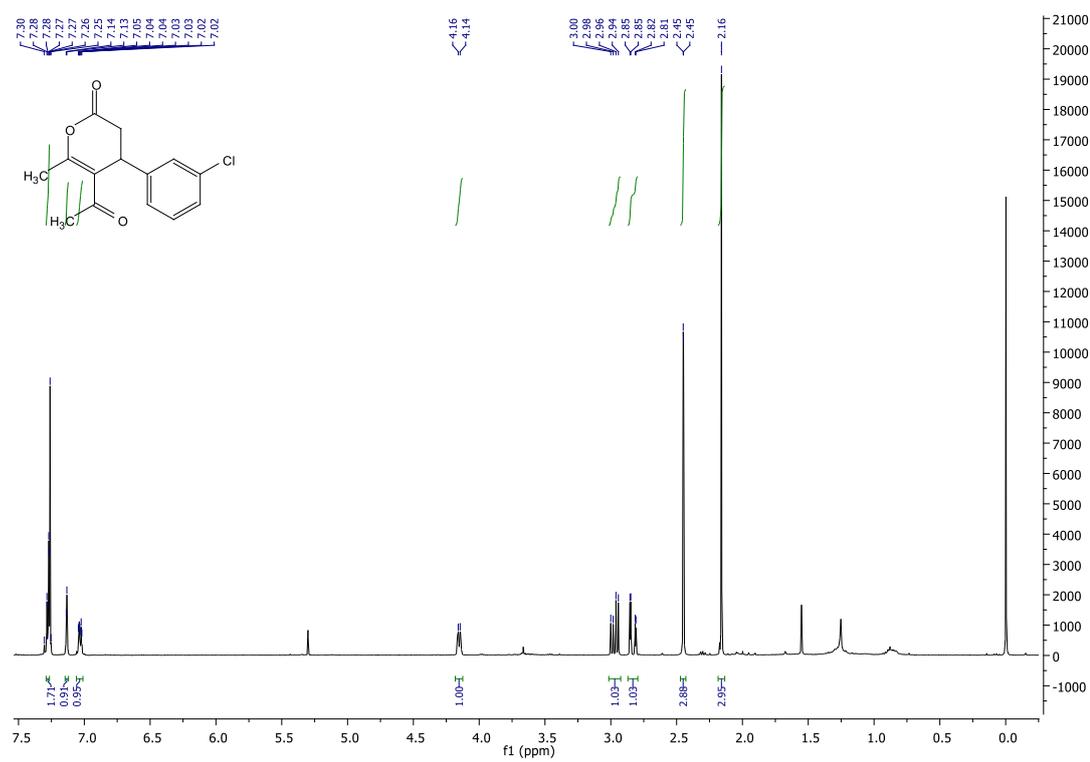


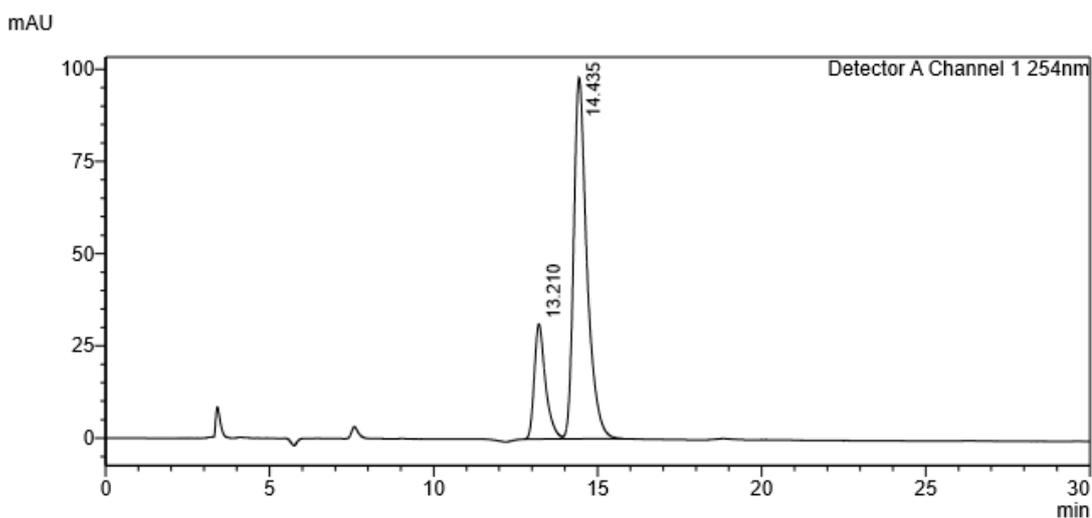
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	21.310	1685674	48076	6.018			
2	22.960	26326343	666145	93.982		V	
Total		28012017	714220				



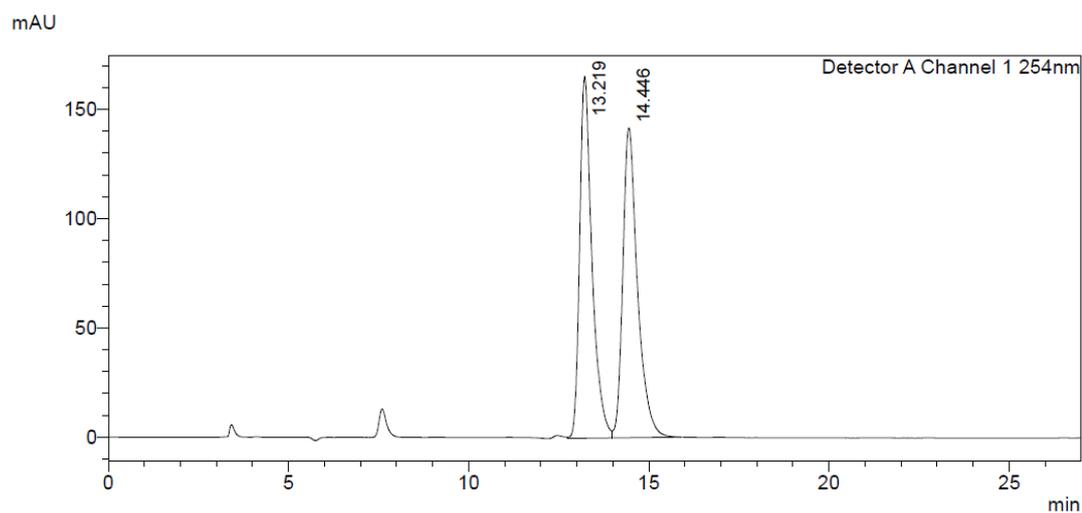
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	24.026	14432736	366589	49.727			
2	25.738	14591307	353872	50.273		V	
Total		29024043	720461				

Compound 3.106c



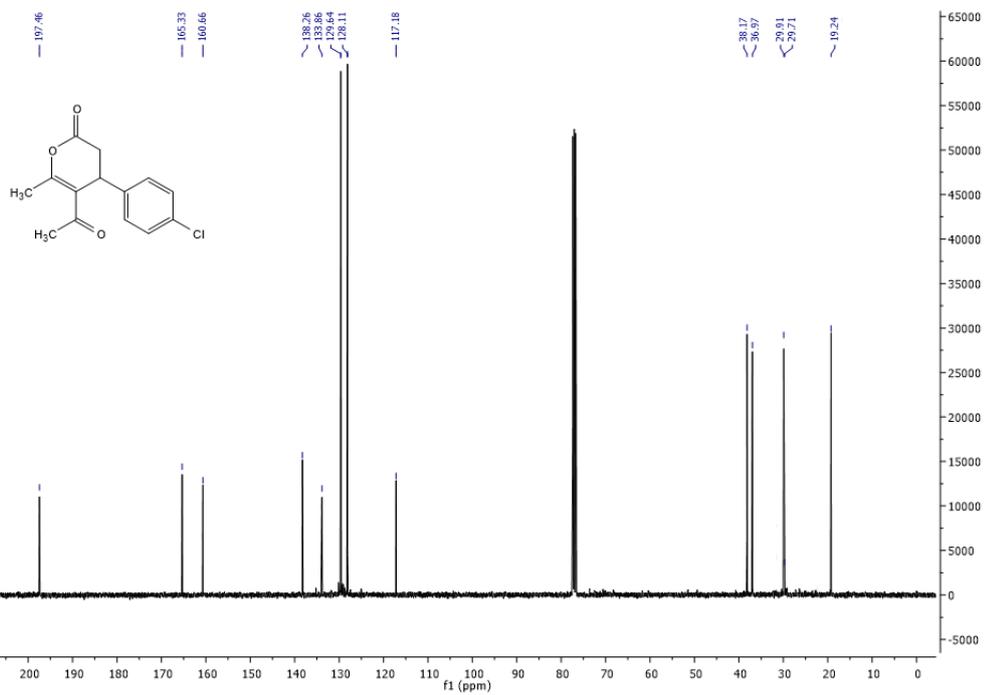
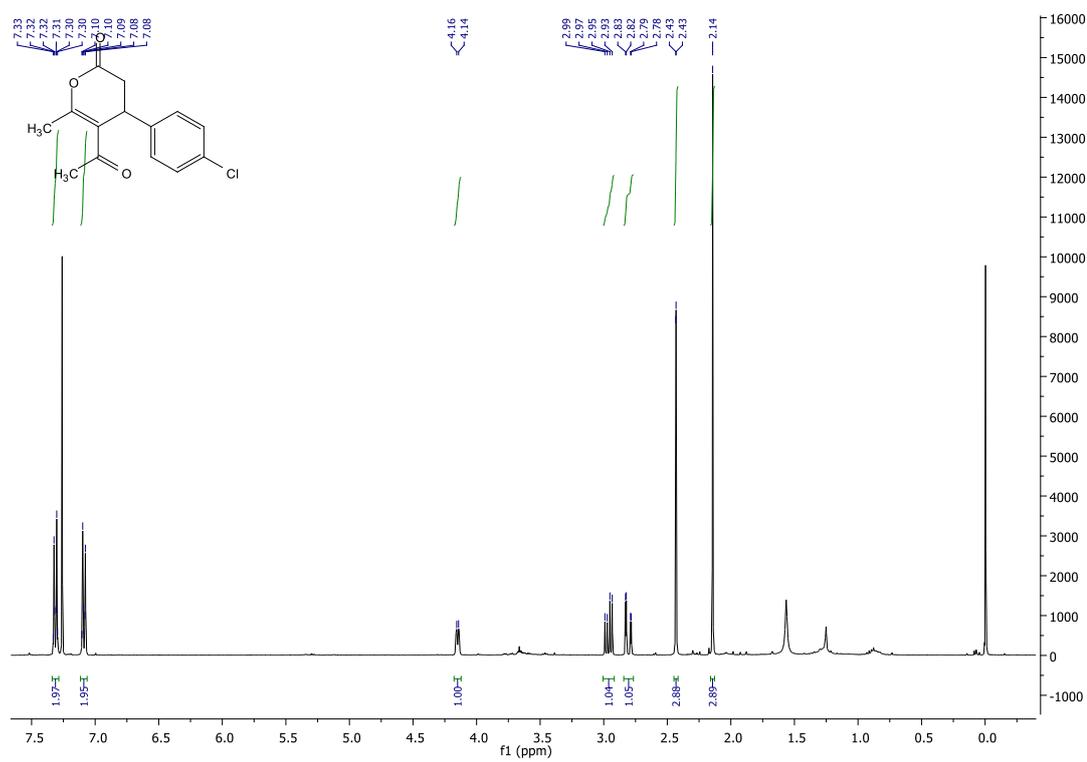


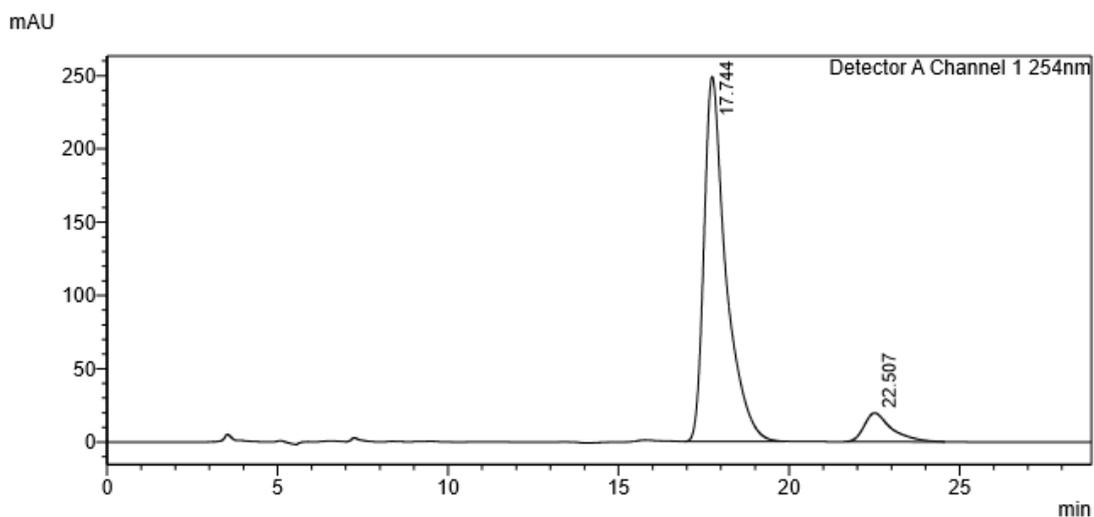
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	13.210	742500	31192	21.253			
2	14.435	2751044	97907	78.747		V	
Total		3493544	129099				



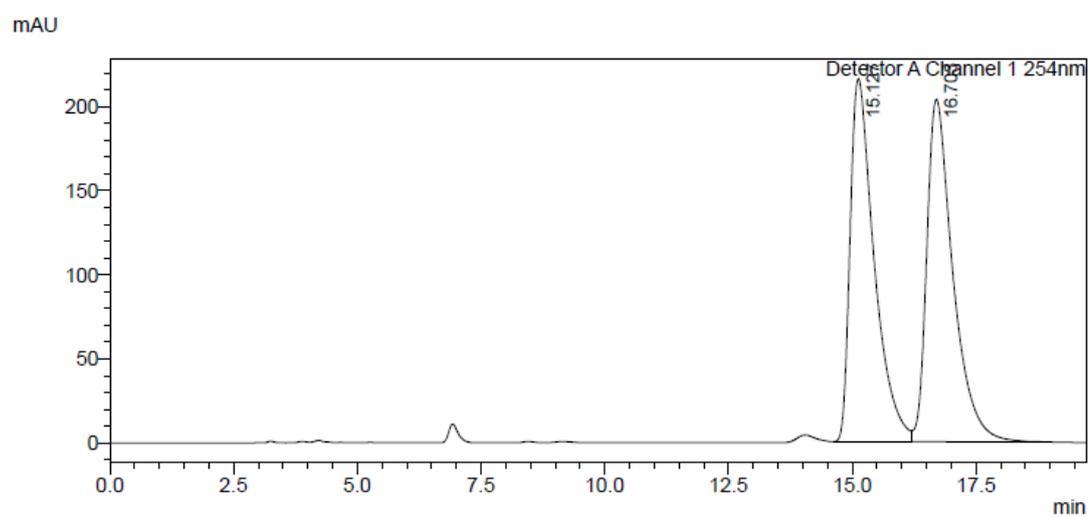
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	13.219	3970274	165642	49.802		V	
2	14.446	4001878	141804	50.198		V	
Total		7972152	307446				

Compound 3.106d



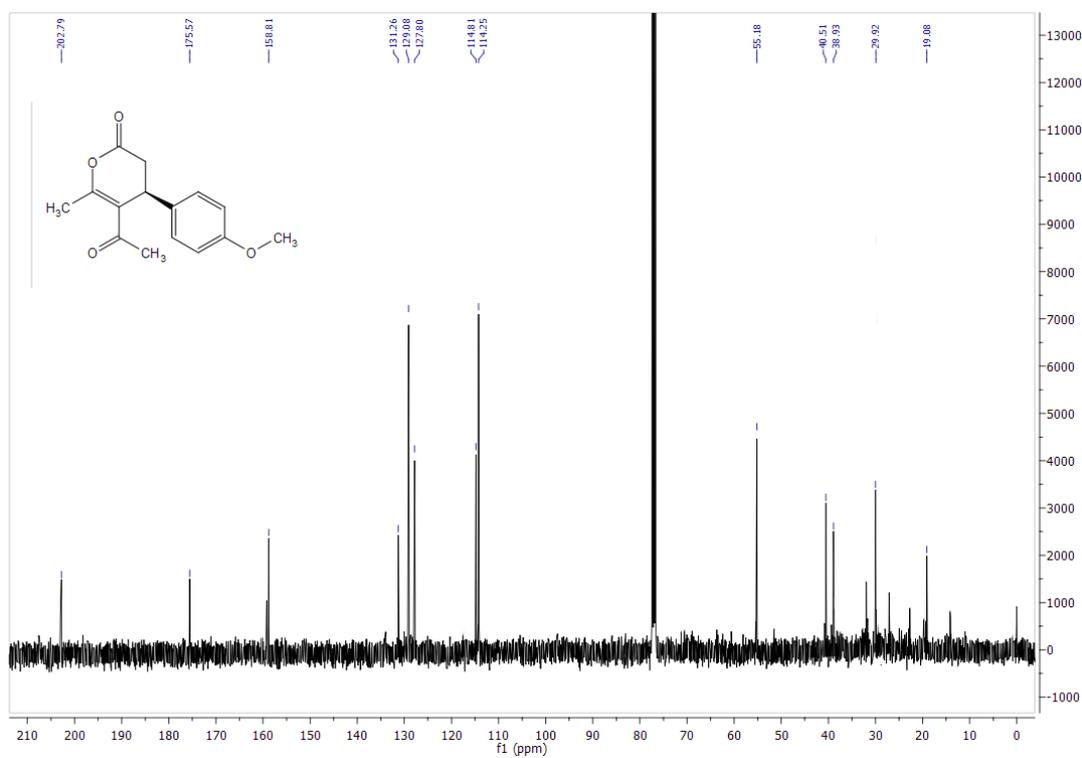
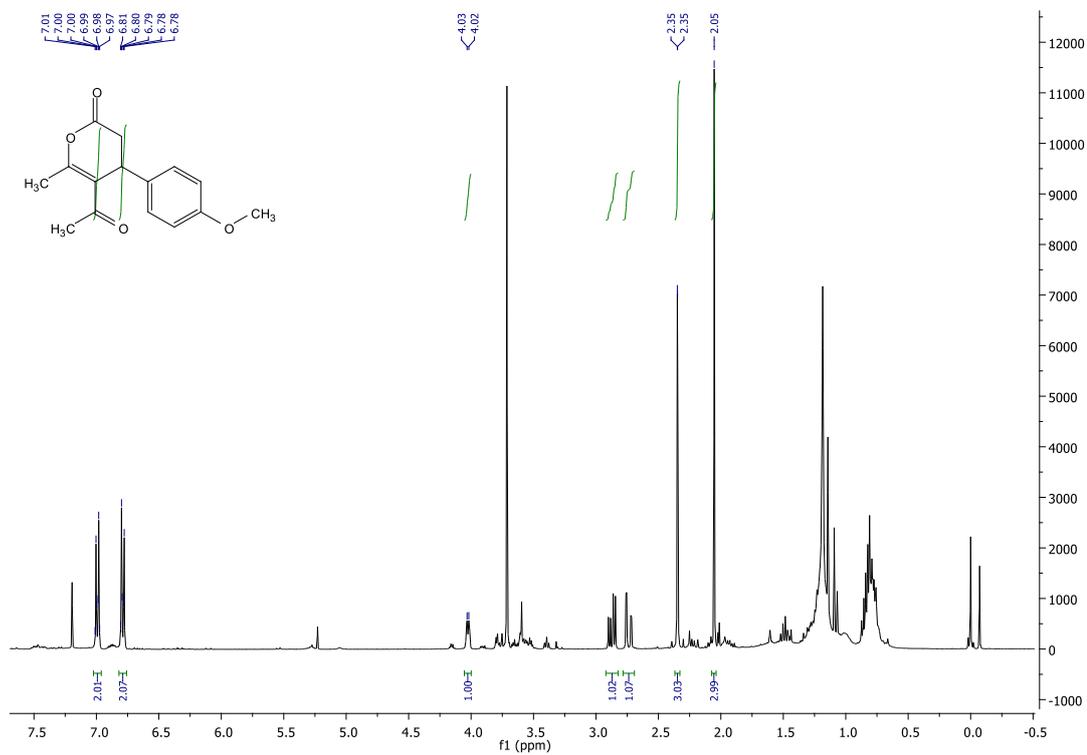


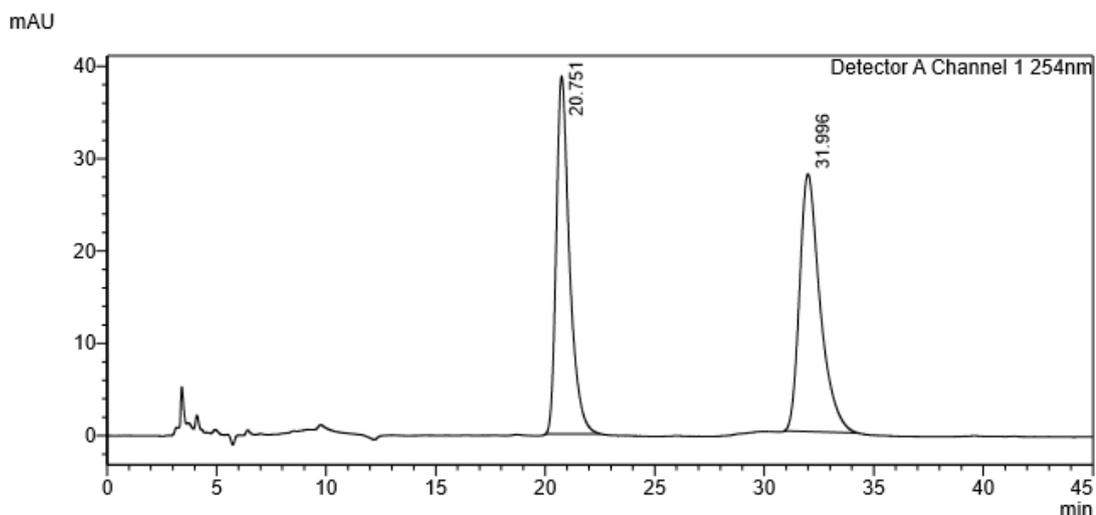
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	17.744	11121980	248969	91.097			
2	22.507	1086897	19533	8.903			
Total		12208877	268502				



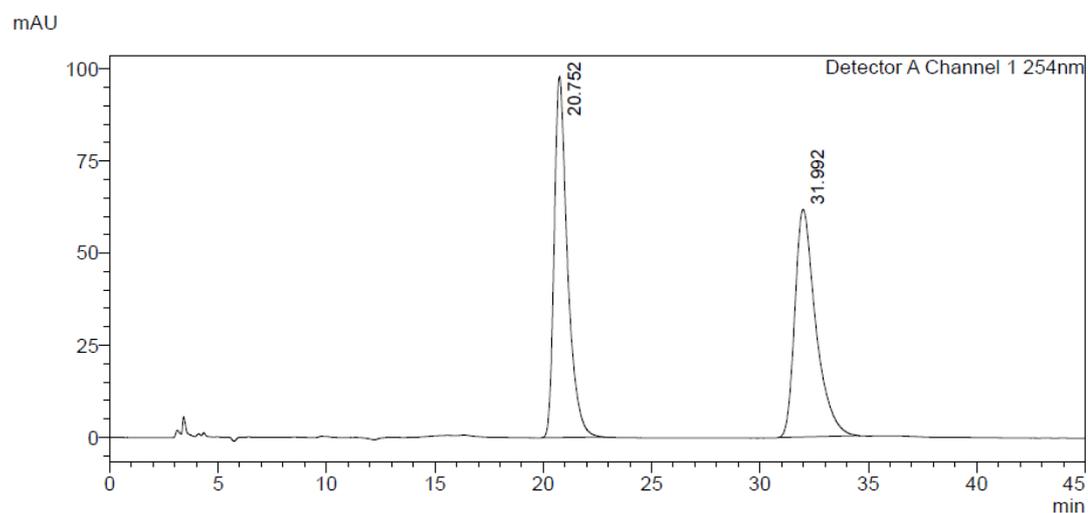
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.127	7293457	215819	49.334			
2	16.703	7490352	203659	50.666		V	
Total		14783809	419478				

Compound 3.106e



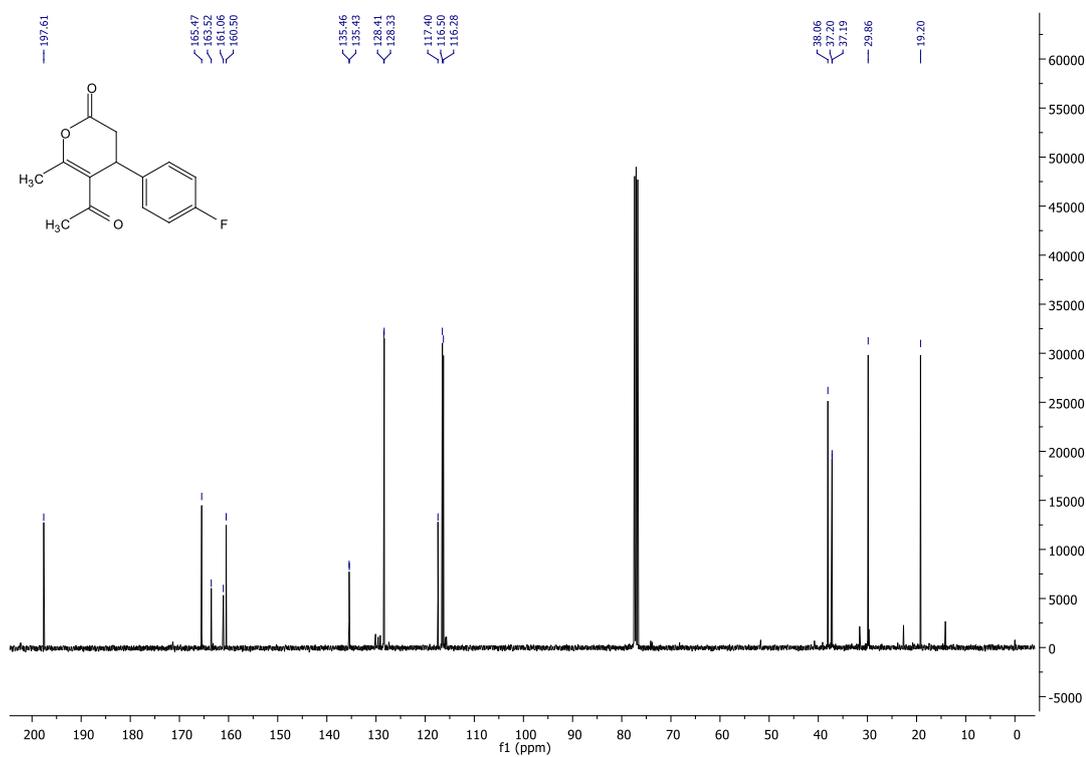
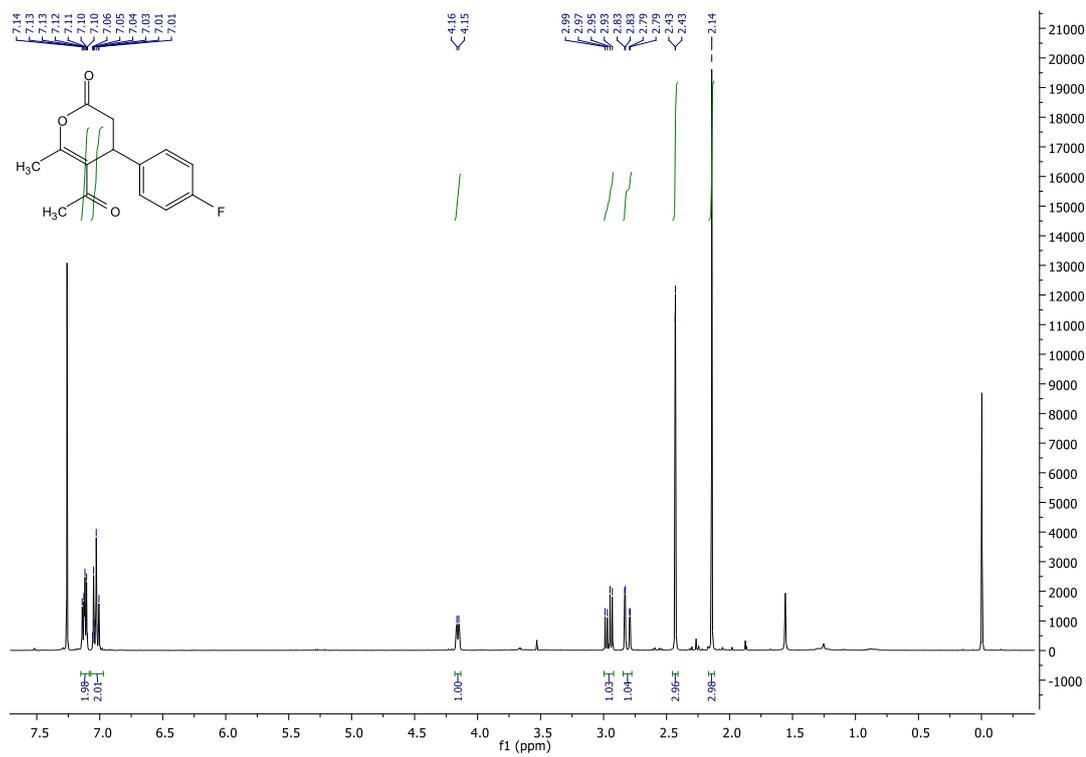


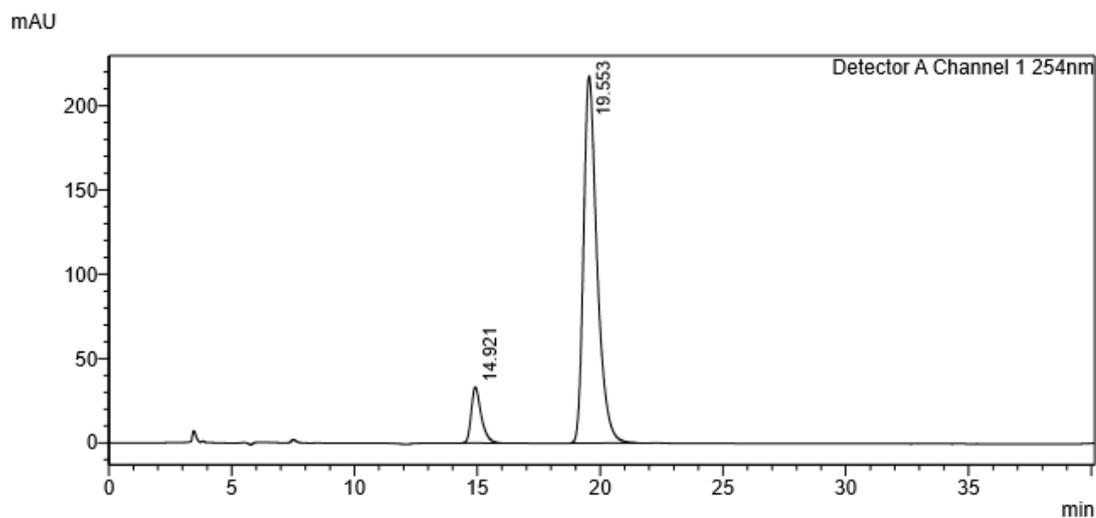
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	20.751	1628045	38715	47.286			
2	31.996	1814951	27865	52.714			
Total		3442997	66580				



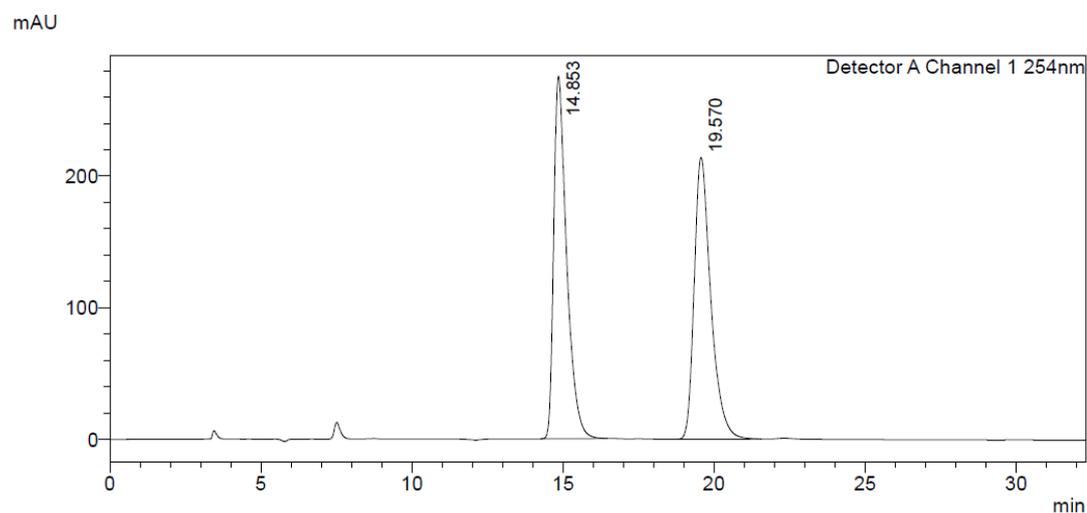
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	20.752	4173695	97870	50.186			
2	31.992	4142819	61731	49.814			
Total		8316514	159601				

Compound 3.106f



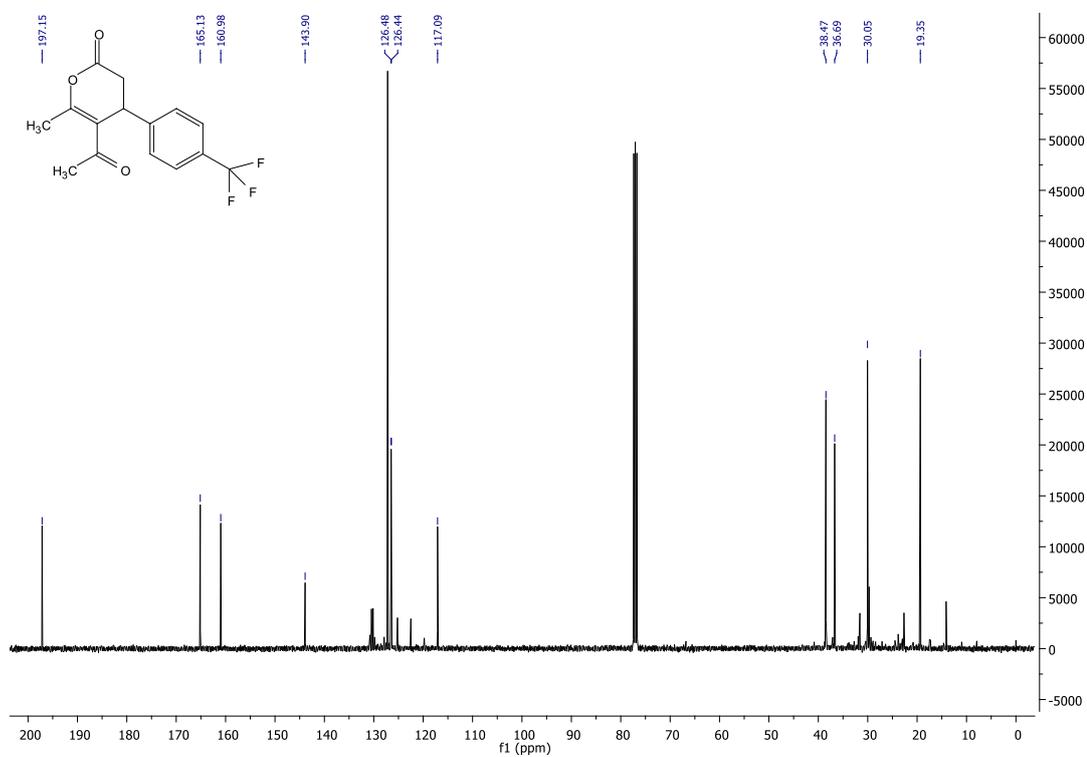
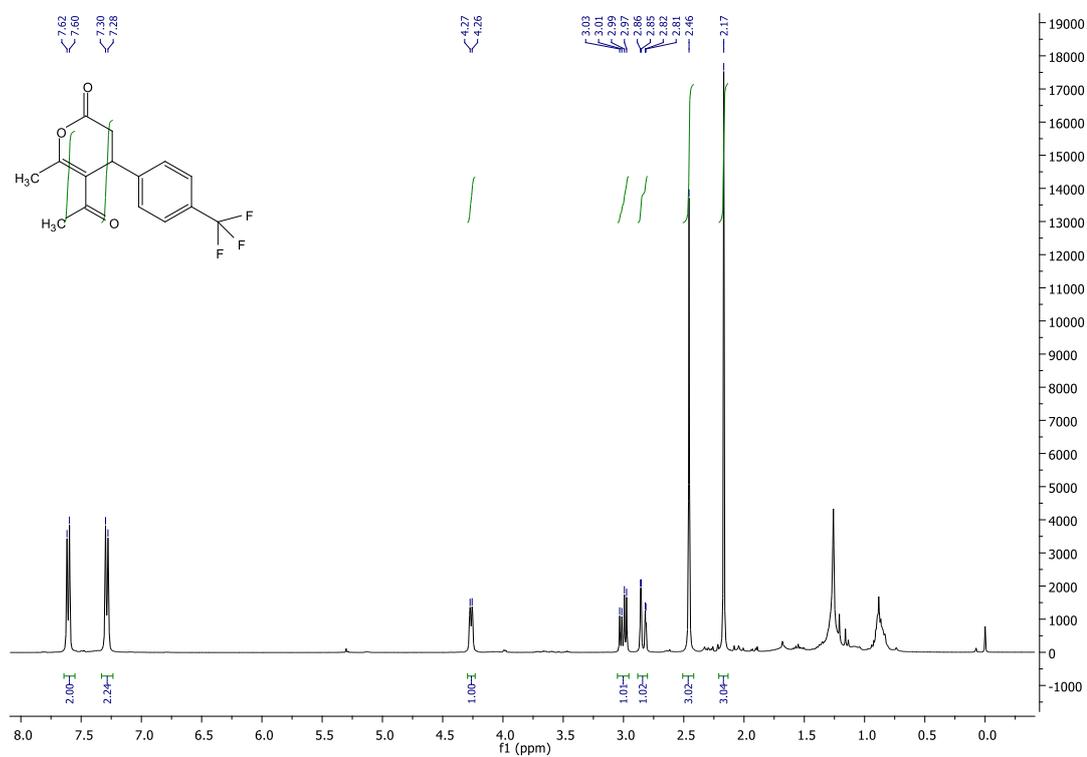


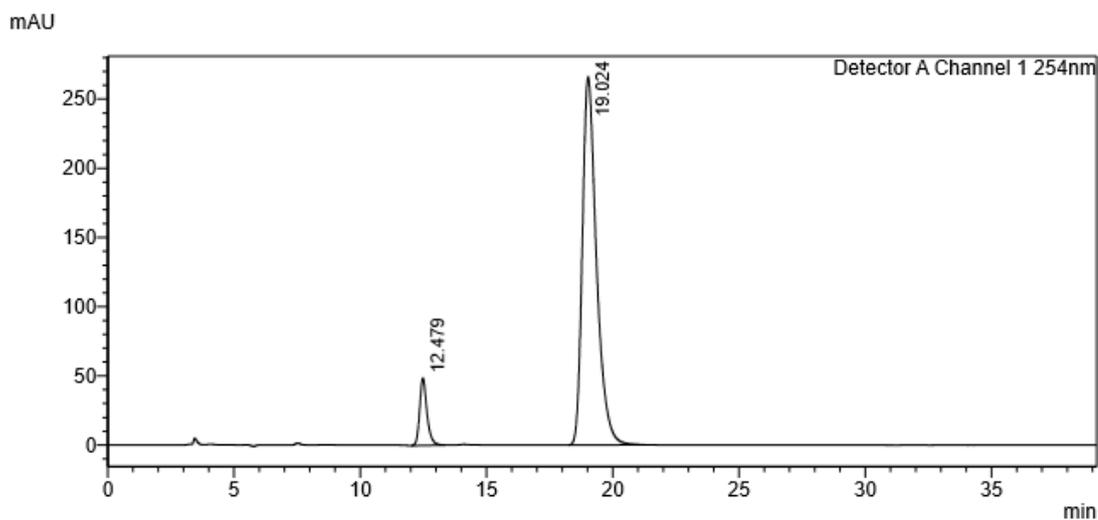
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.921	934081	33148	10.094			
2	19.553	8320131	217530	89.906			
Total		9254211	250678				



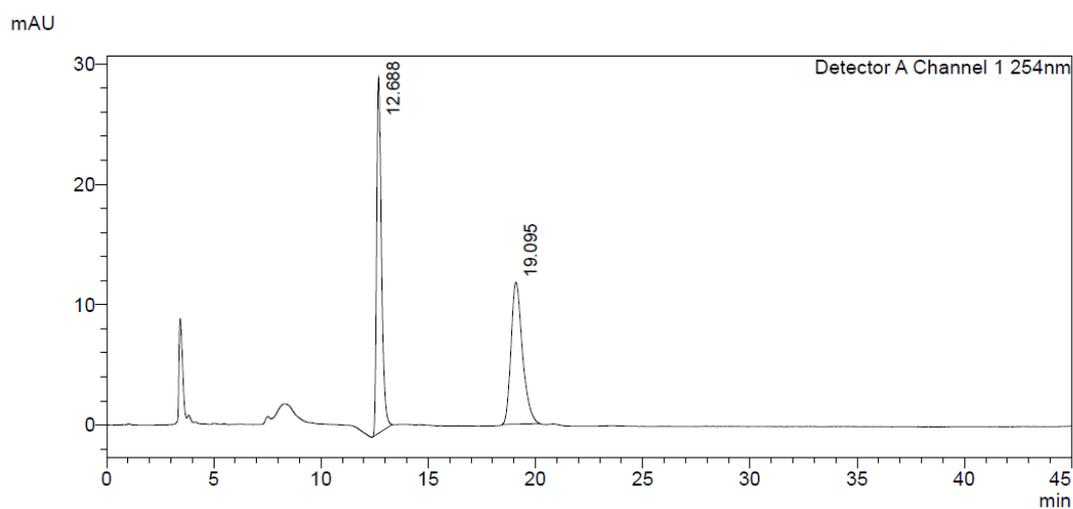
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14.853	8175762	275140	49.961			
2	19.570	8188546	213924	50.039			
Total		16364309	489064				

Compound 3.106g



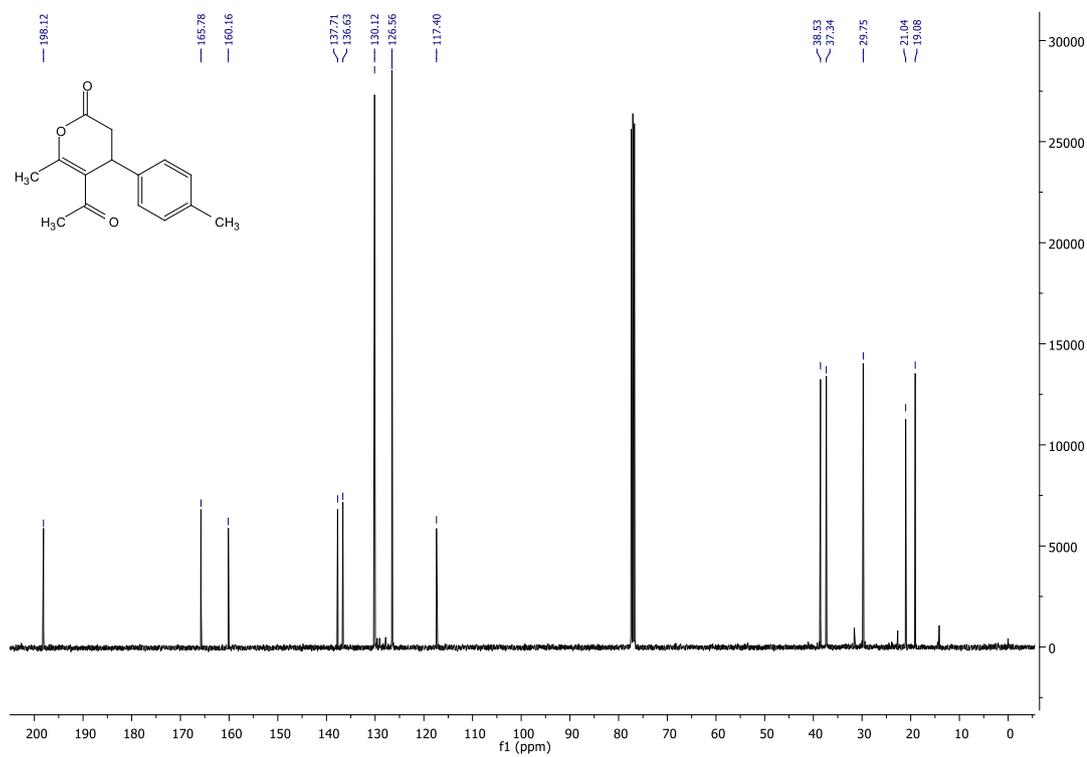
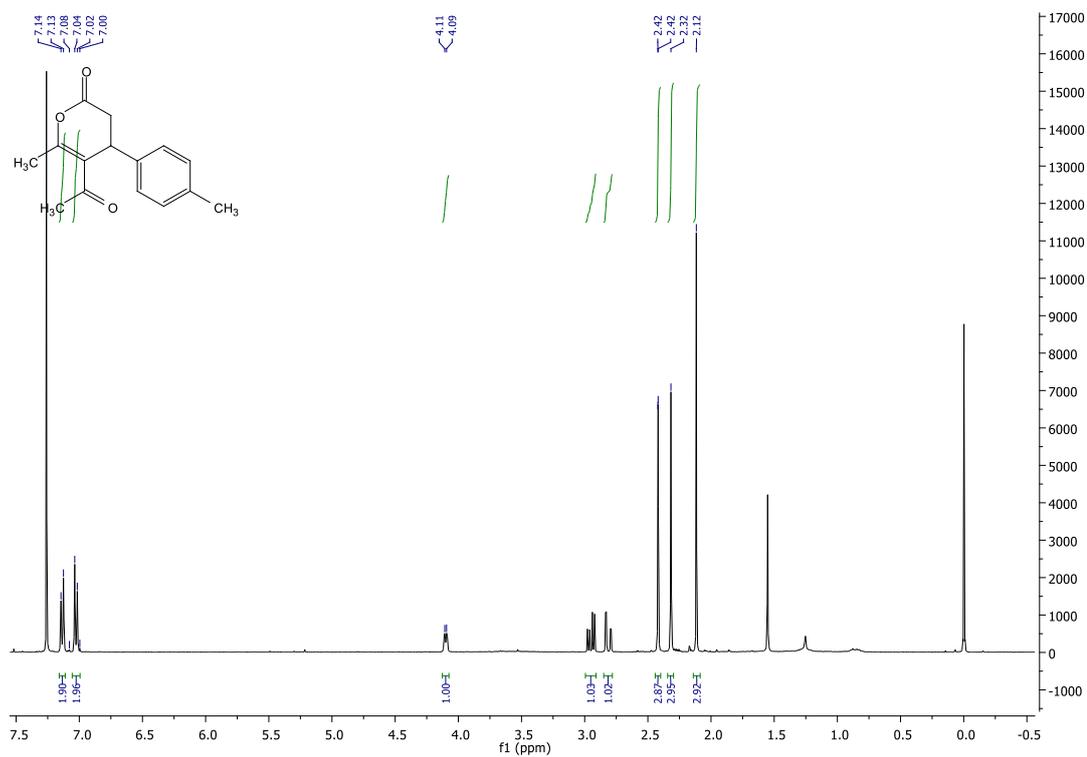


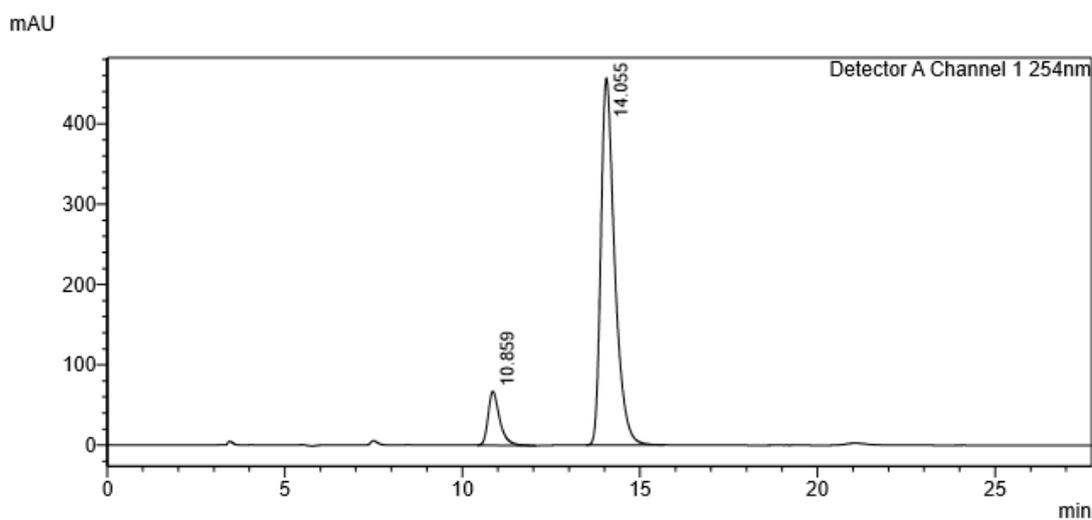
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	12.479	973655	48598	8.606			
2	19.024	10339402	266002	91.394			
Total		11313056	314600				



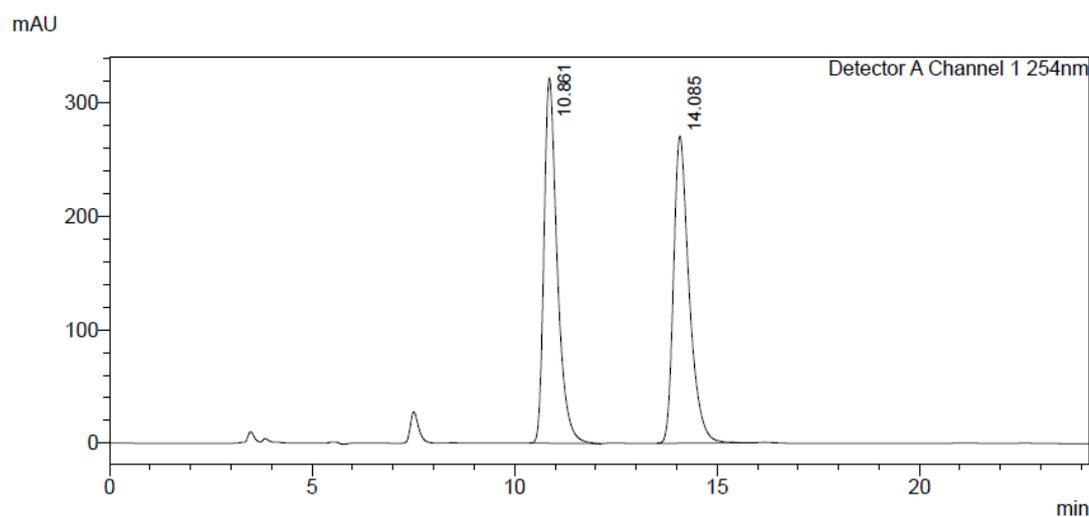
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	12.688	464559	29620	51.526			
2	19.095	437043	11789	48.474			
Total		901602	41410				

Compound 3.106h



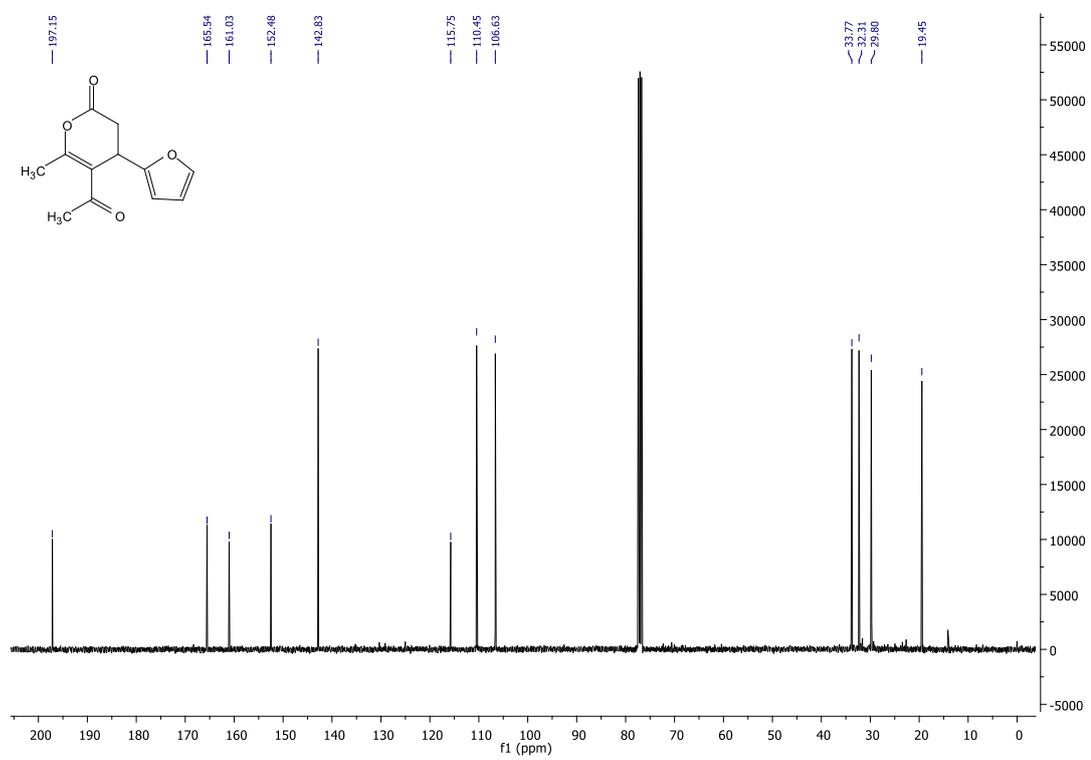
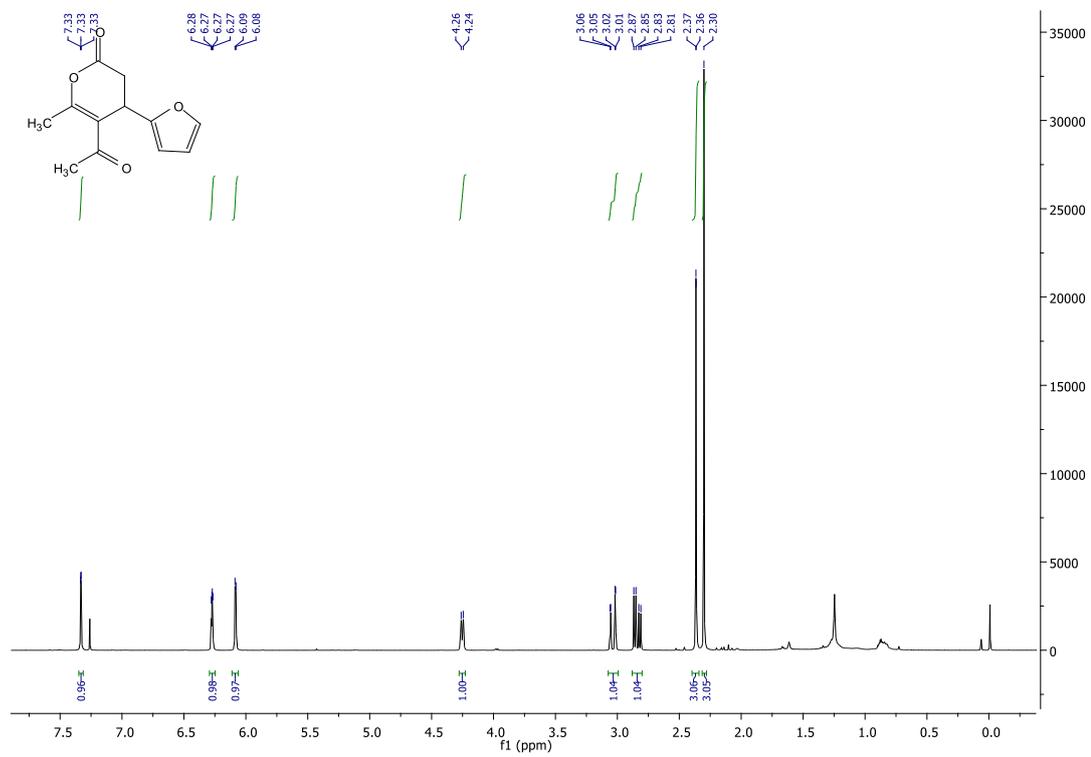


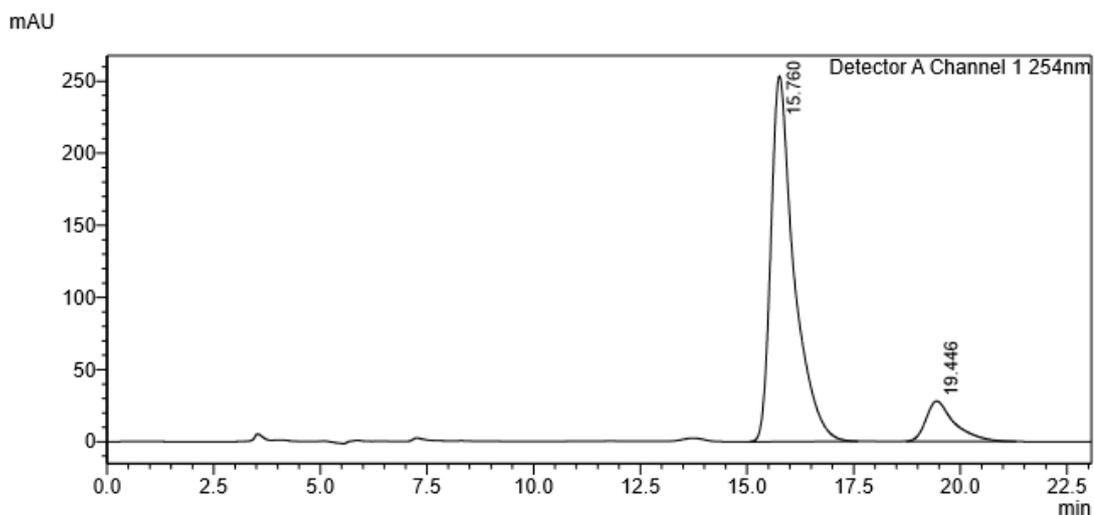
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10.859	1519524	66808	10.949			
2	14.055	12358536	456371	89.051			
Total		13878060	523179				



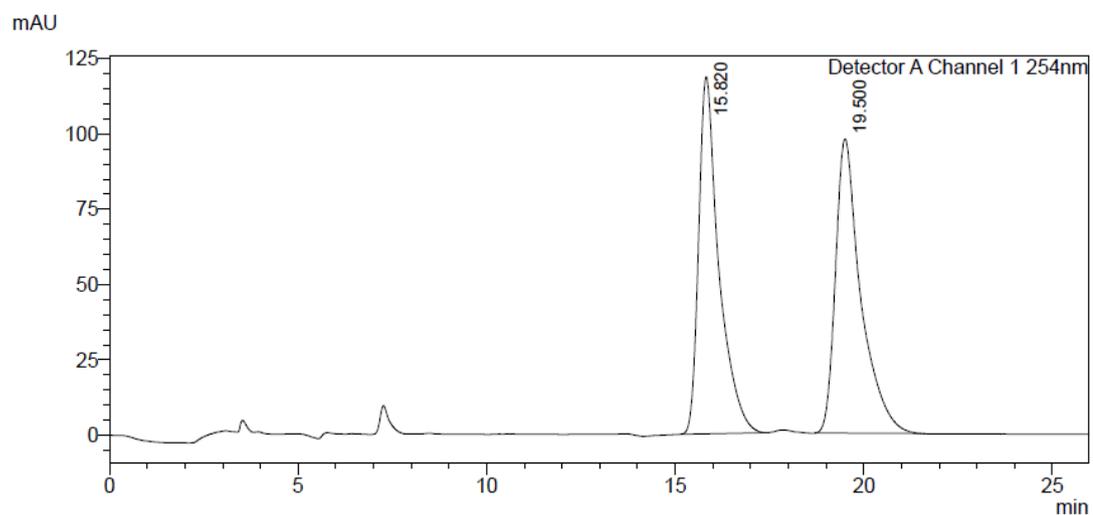
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1	10.861	7295475	322188	49.937			
2	14.085	7313964	271158	50.063			
Total		14609439	593346				

Compound 3.106j



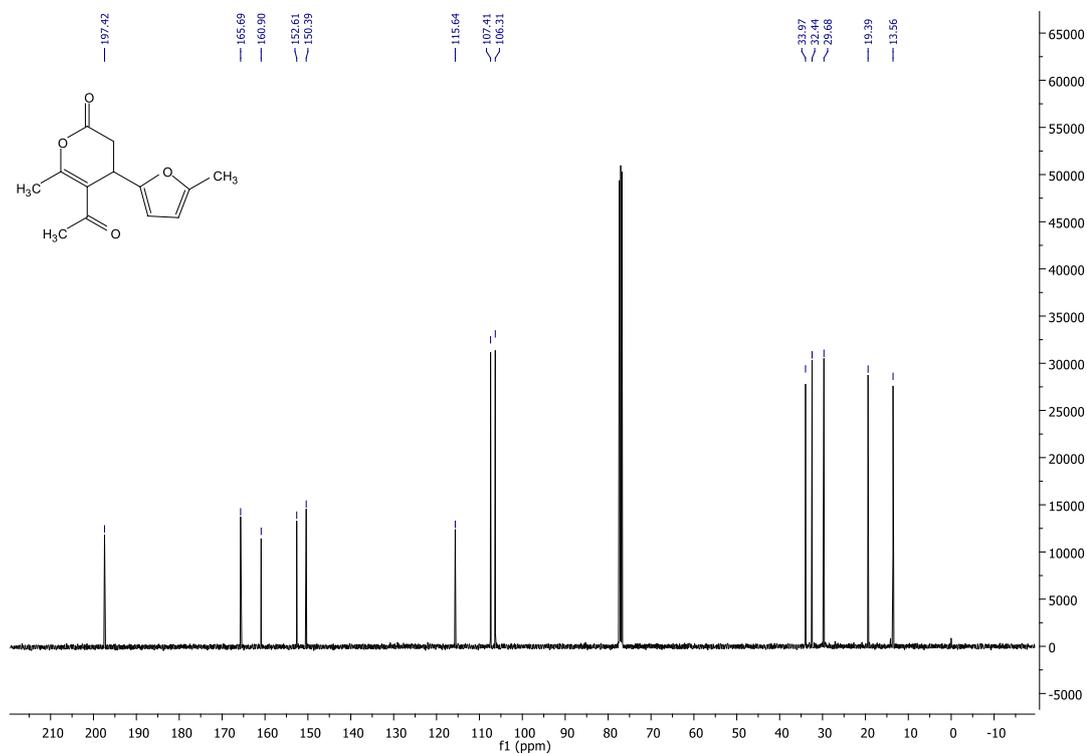
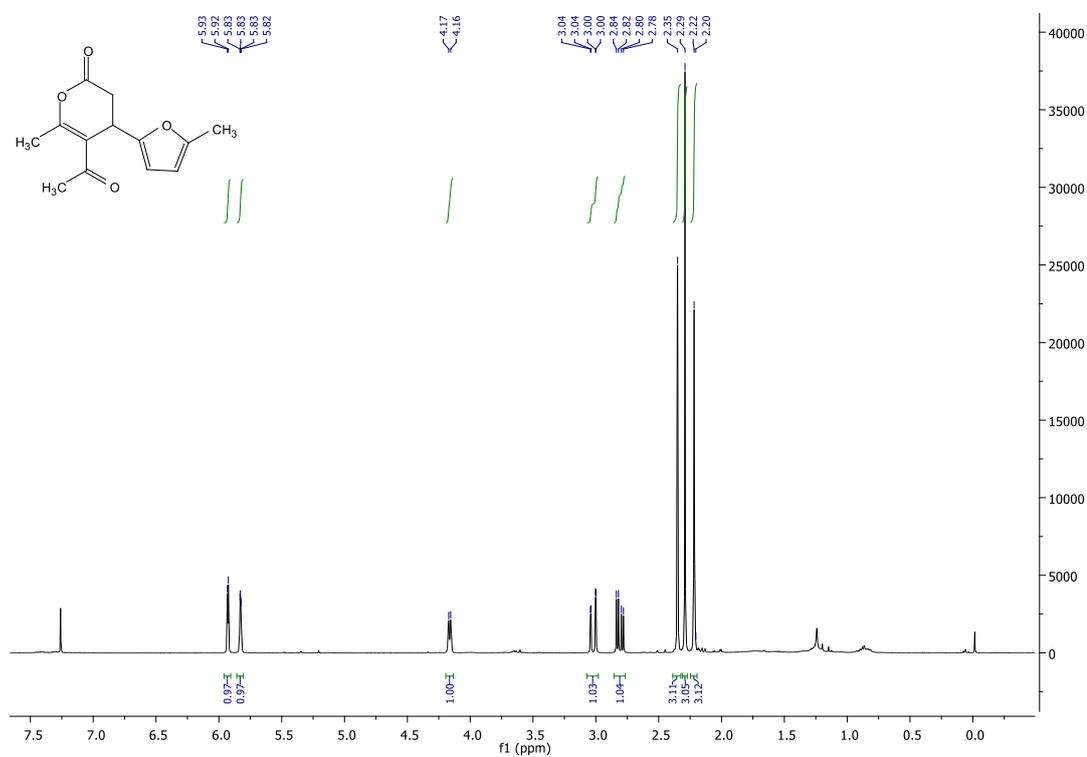


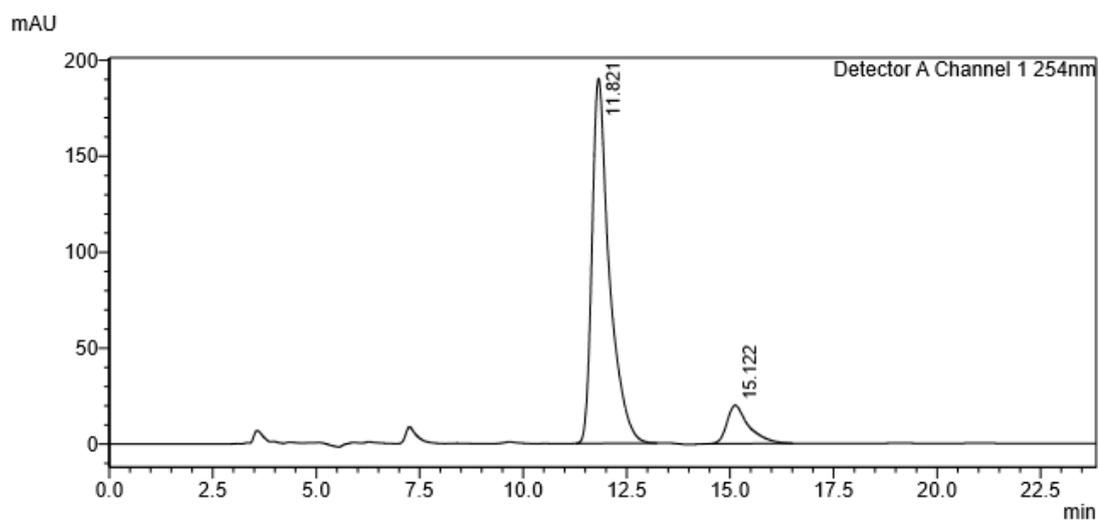
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.760	9563424	253266	88.119			
2	19.446	1289392	27855	11.881			
Total		10852816	281121				



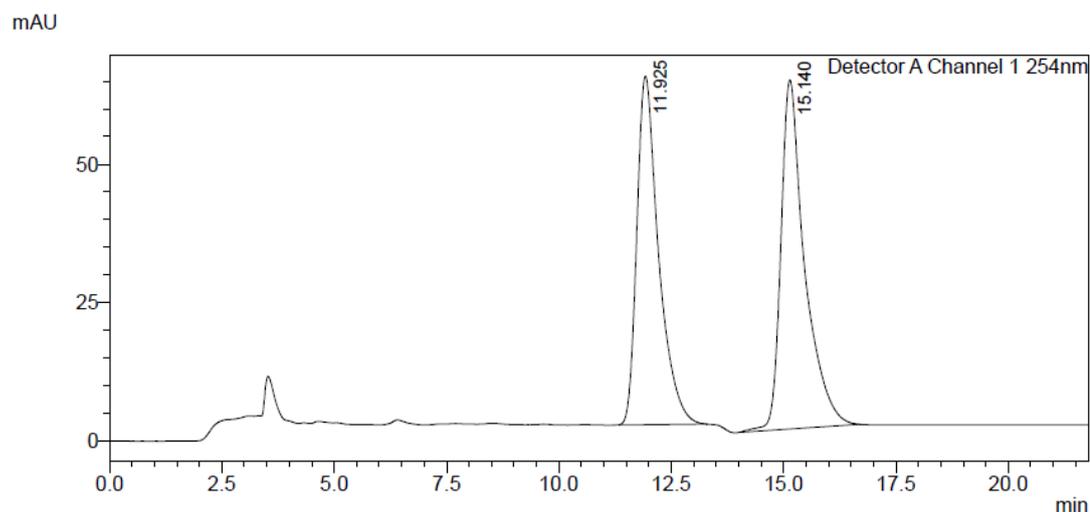
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	15.820	4430988	118588	49.275			
2	19.500	4561315	97766	50.725			
Total		8992303	216354				

Compound 3.106k

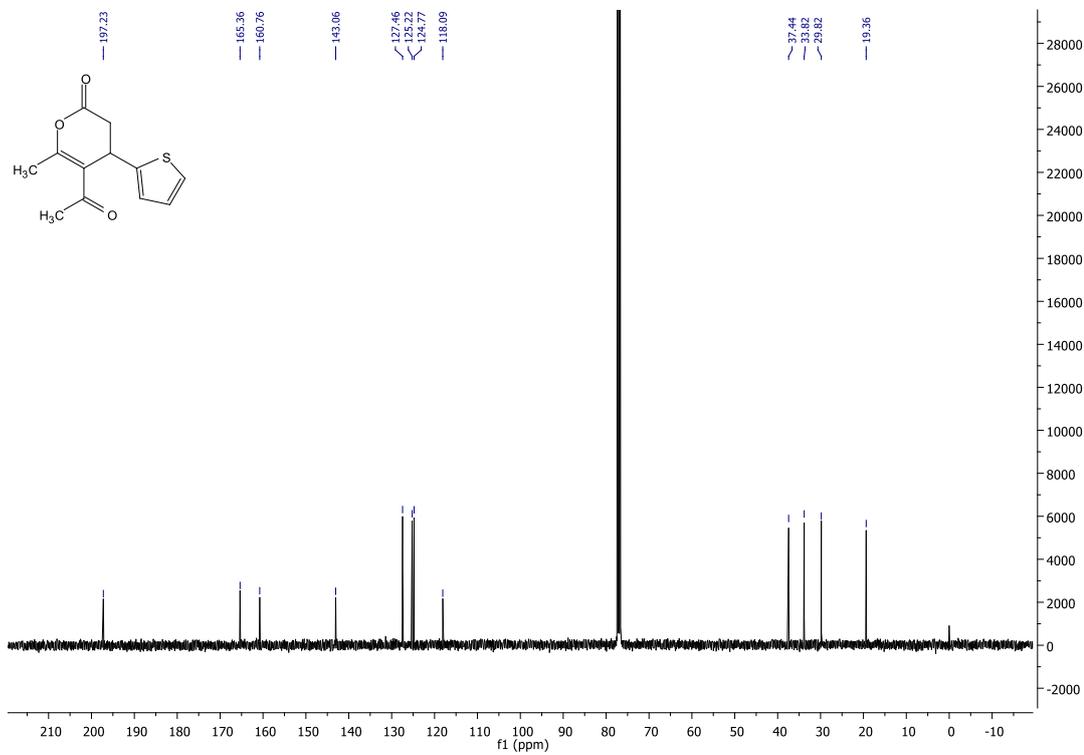
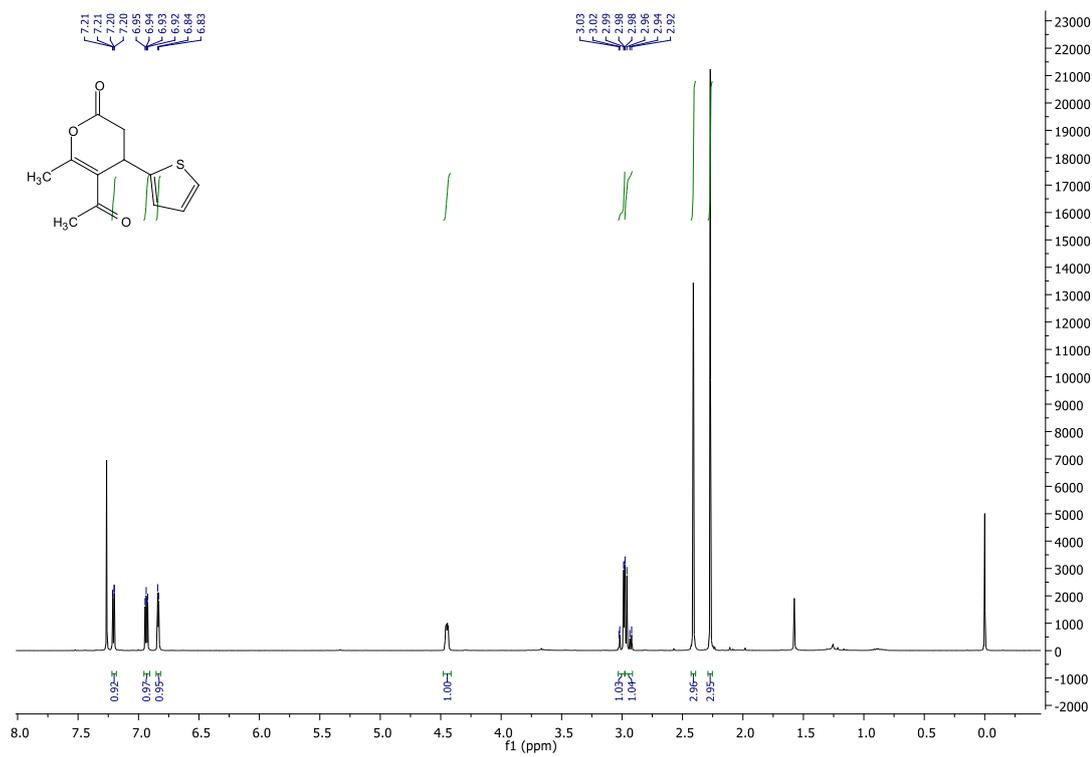


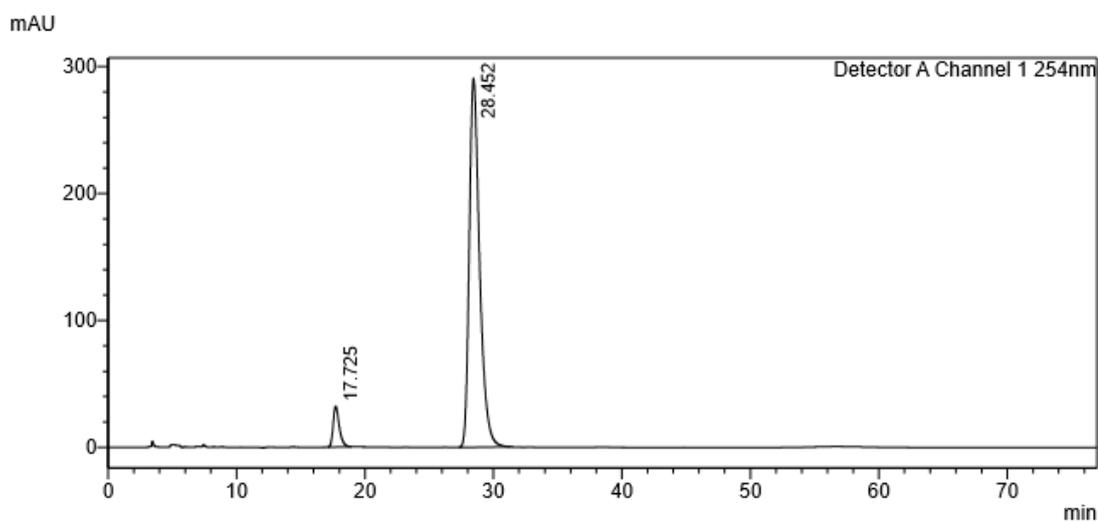


Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	11.821	5536560	190034	88.427			
2	15.122	724586	19934	11.573			
Total		6261146	209968				

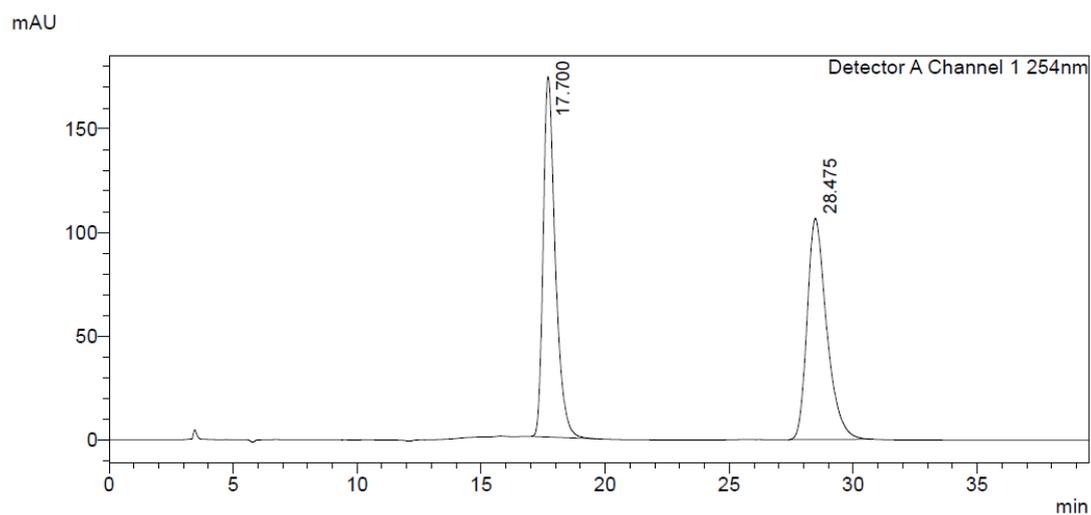


Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	11.925	2124099	62987	47.744			
2	15.140	2324811	63052	52.256			
Total		4448910	126039				

Compound **3.1061**

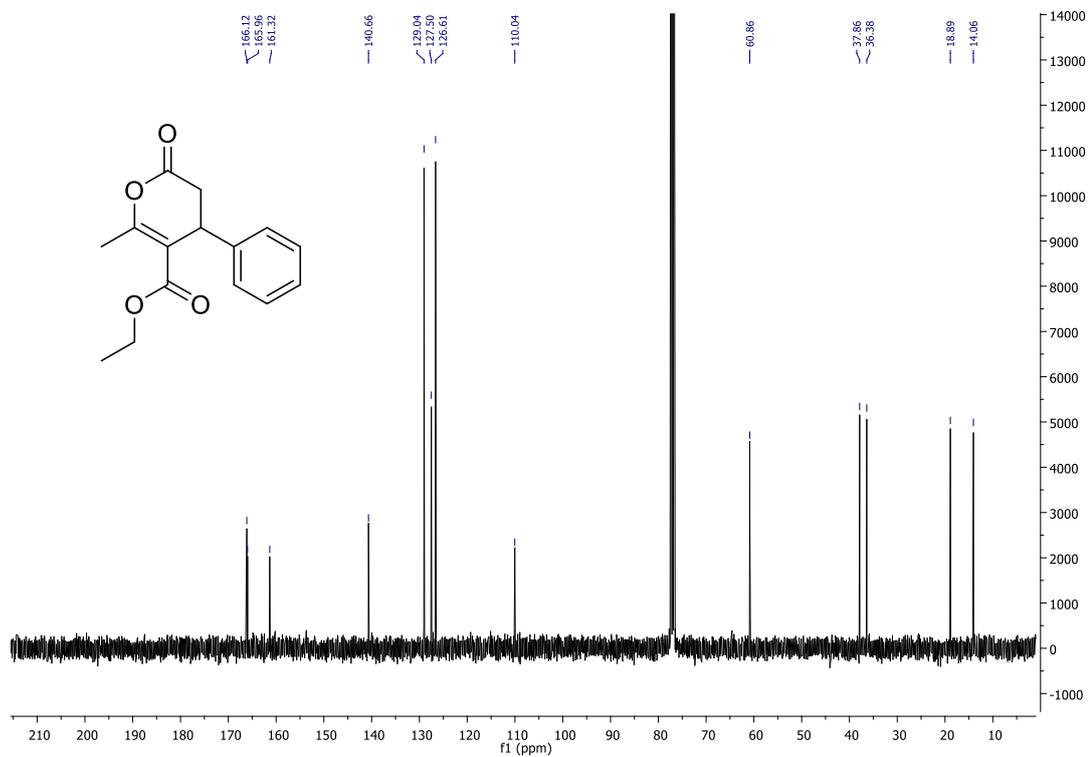
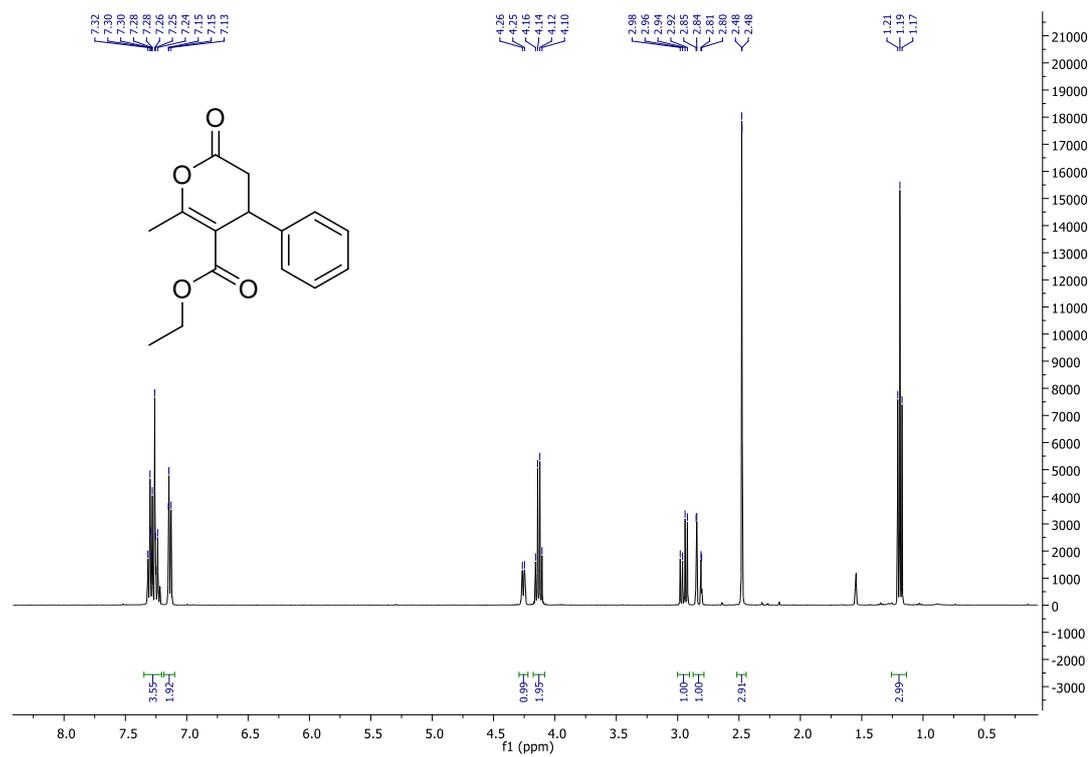


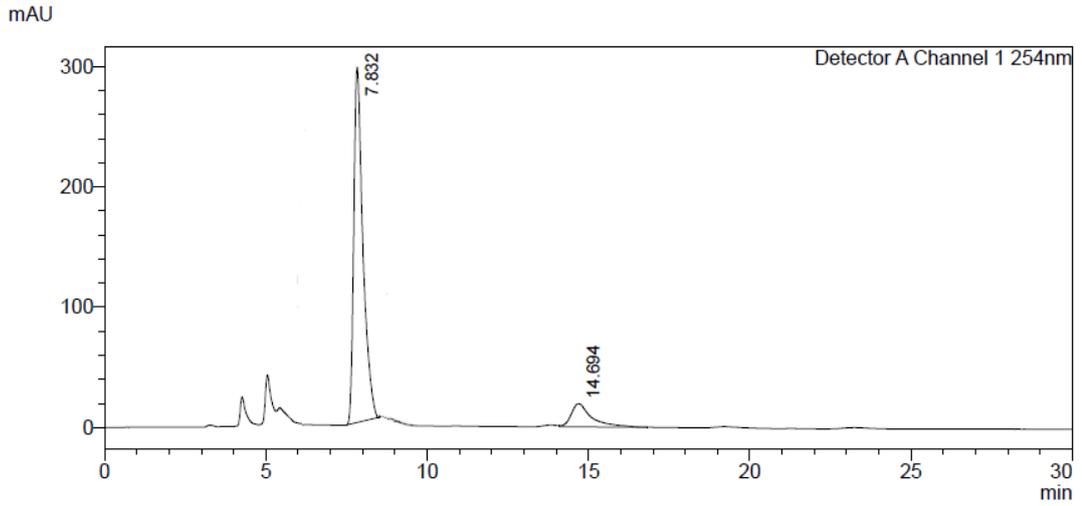
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1	17.725	1063558	31956	6.152			
2	28.452	16225462	290430	93.848			
Total		17289020	322386				



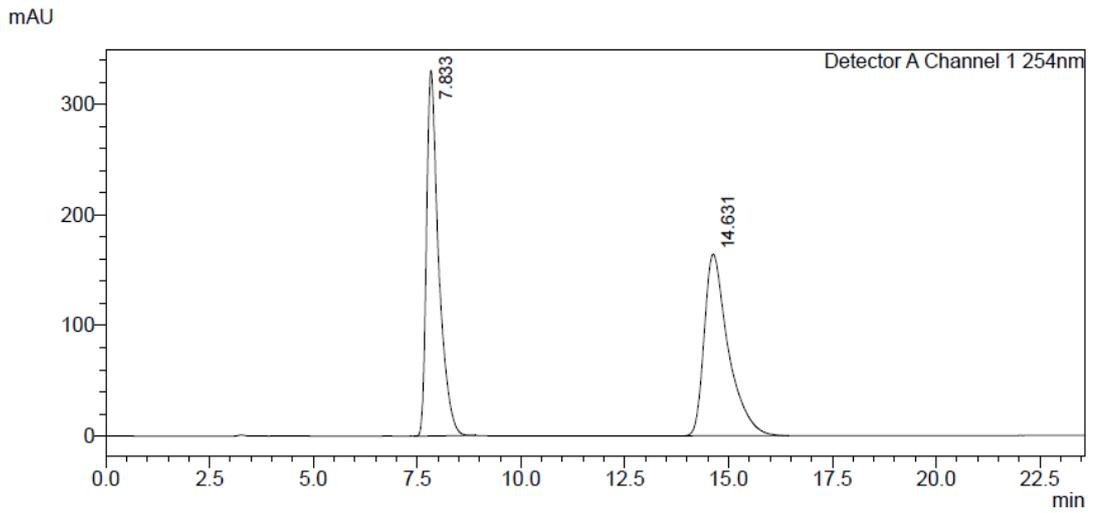
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	17.700	5912337	173718	50.204			
2	28.475	5864298	106553	49.796			
Total		11776635	280271				

Compound 3.106n



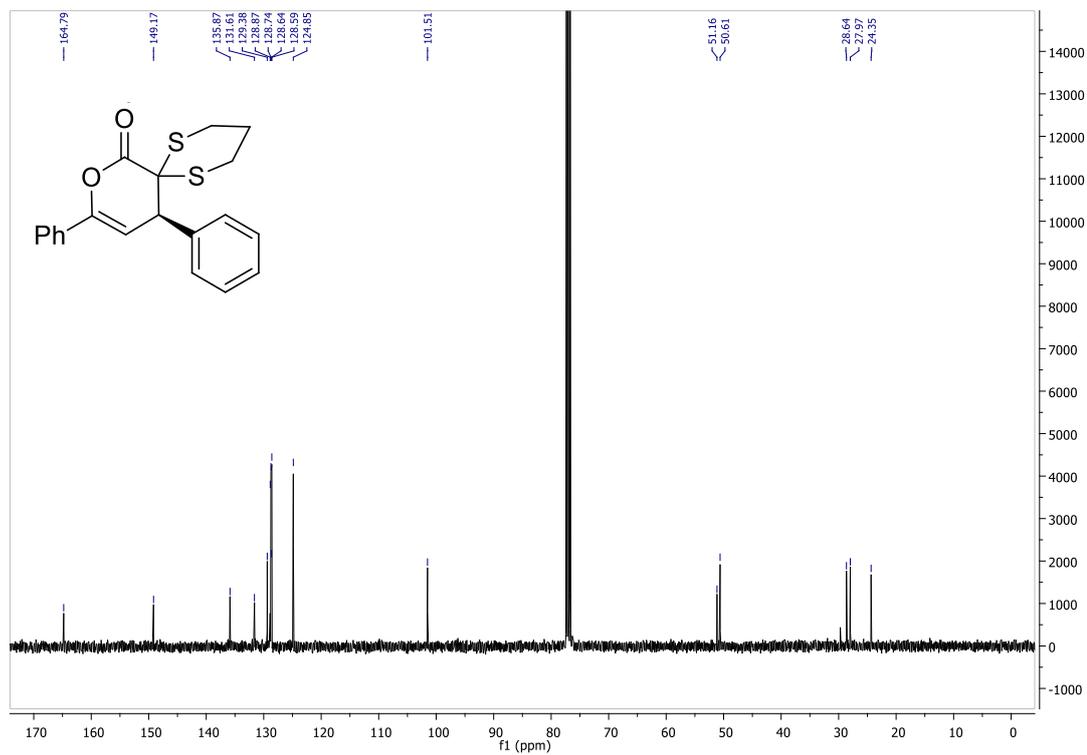
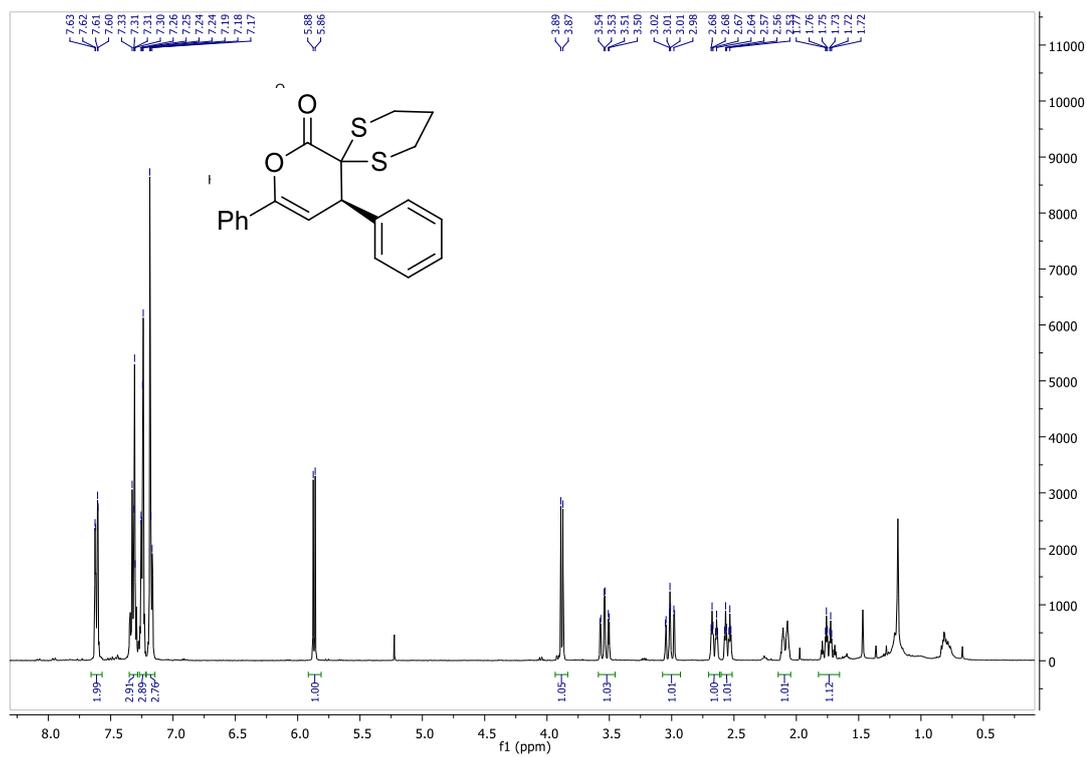


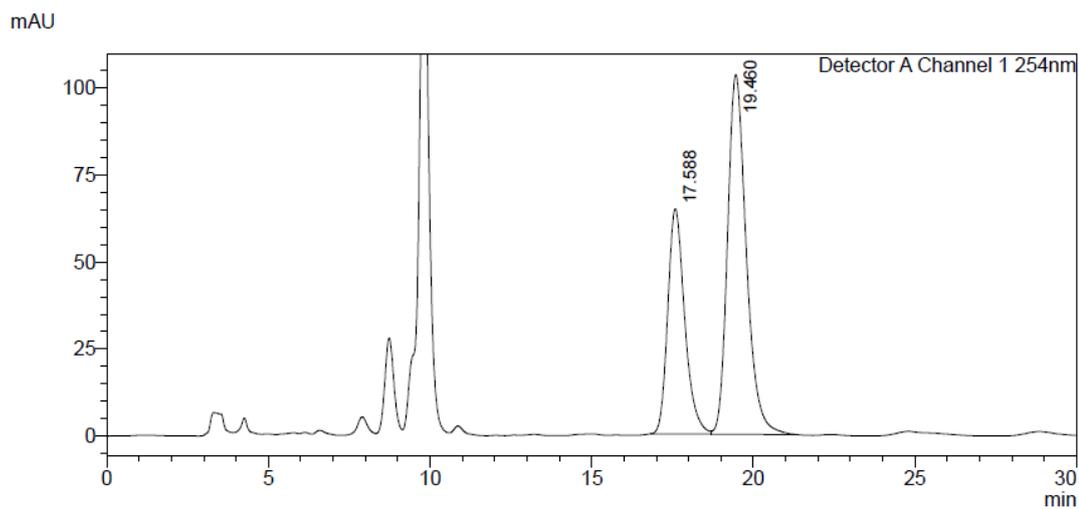
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7.832	5833952	295024	0.000	mg/L	M	R
2	14.694	849230	19254	0.000	mg/L	V	S
Total		6683182	314278				



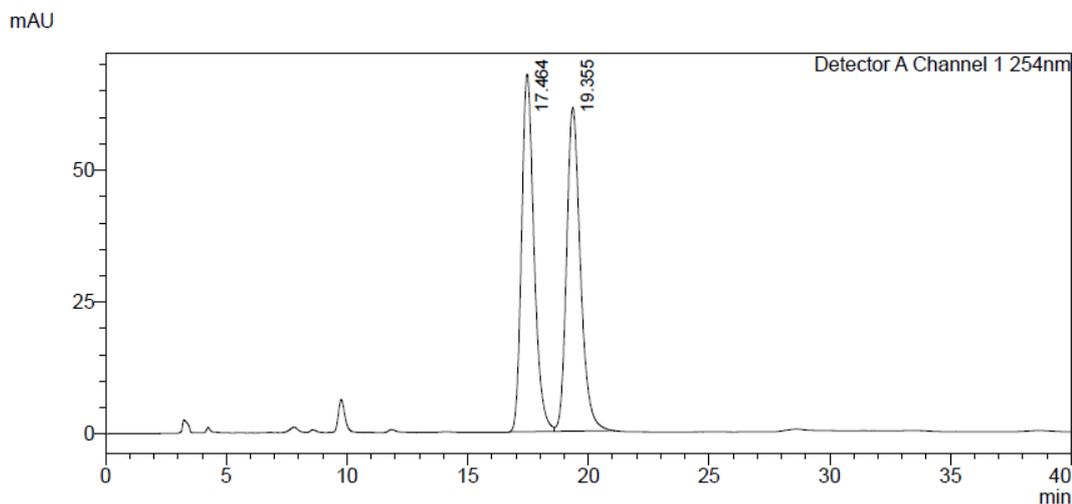
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7.833	6712581	330046	0.000	mg/L	M	R
2	14.631	6606965	164072	0.000	mg/L		S
Total		13319546	494118				

Compound 3.93



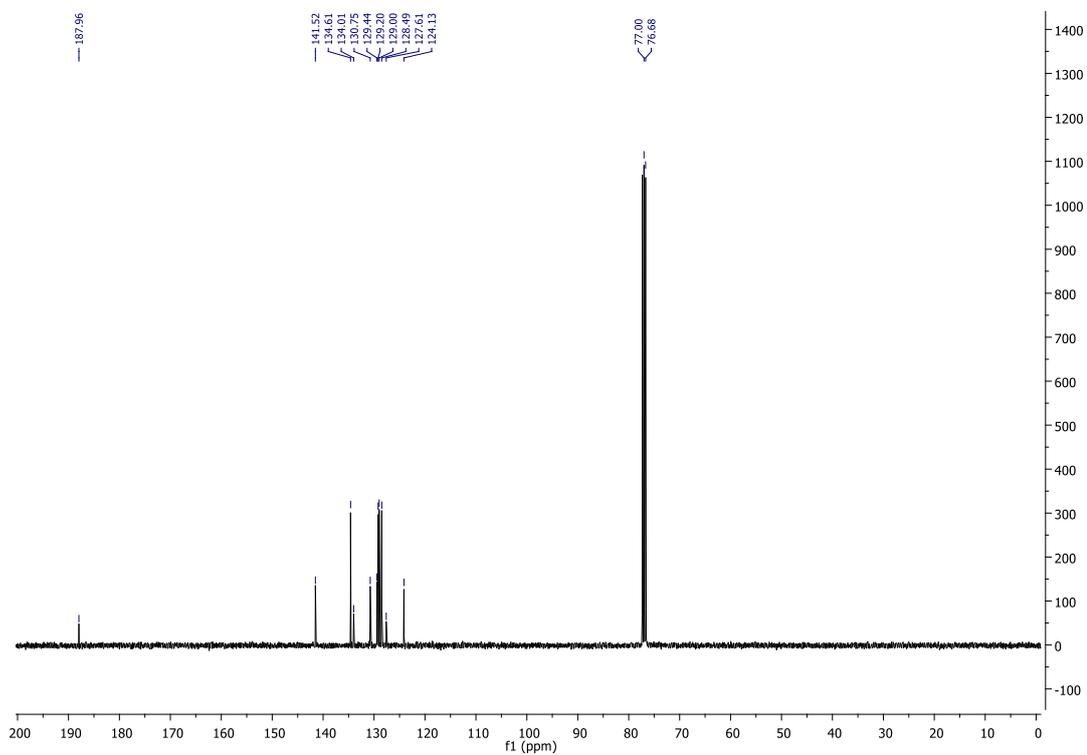
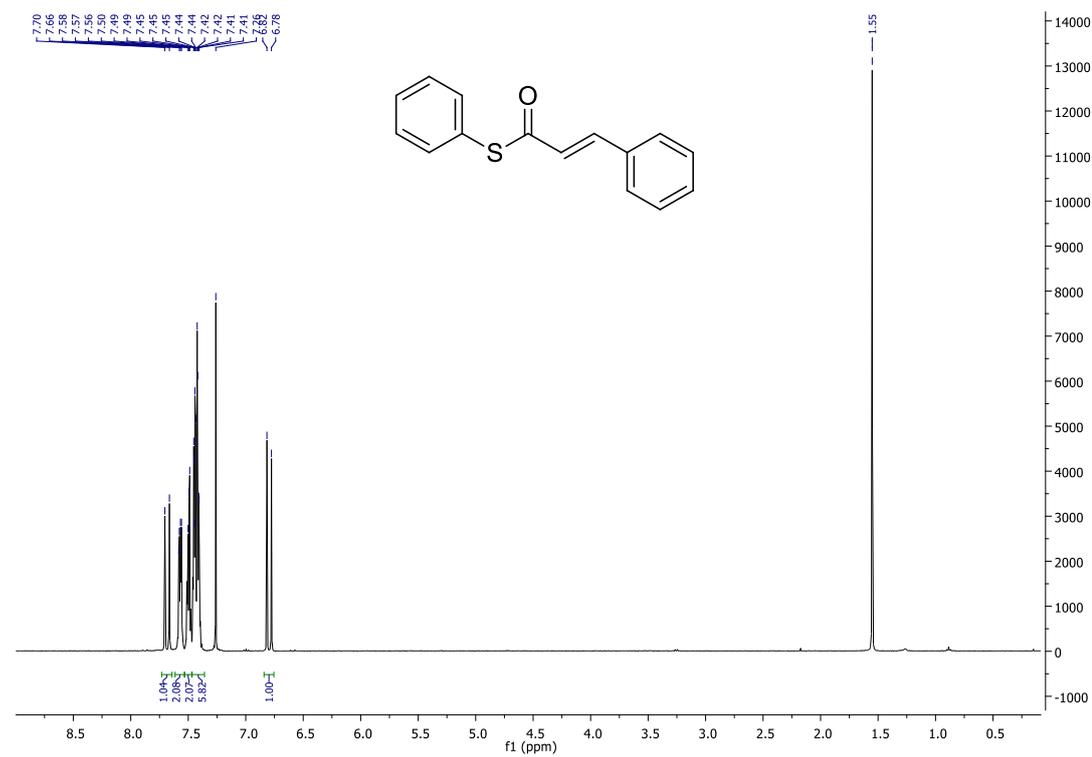


Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	17.588	2361837	64704	0.000	mg/L		R
2	19.460	4179686	103330	0.000	mg/L	V	S
Total		6541523	168034				

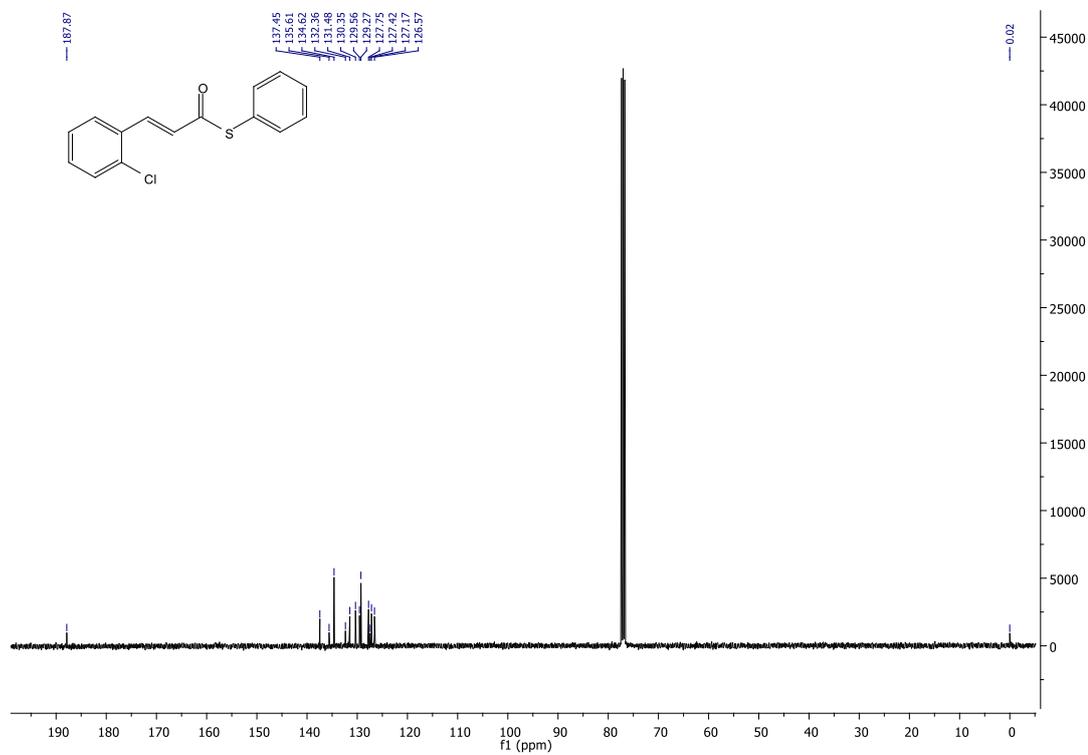
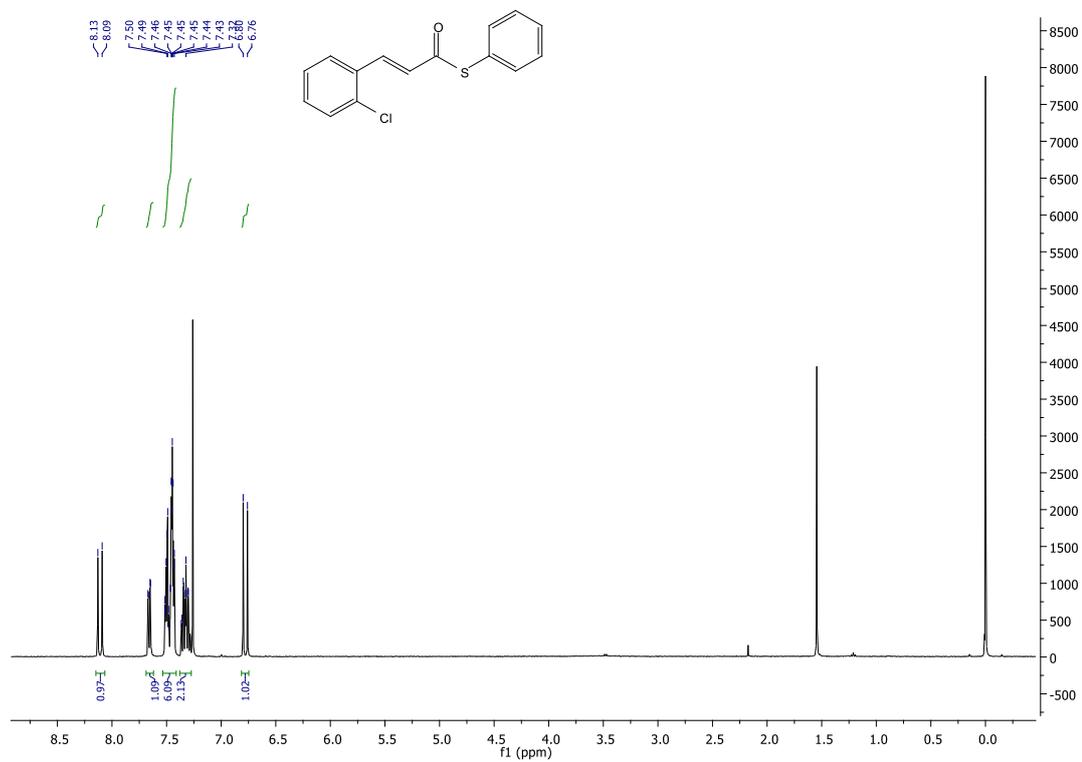


Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	17.464	2426550	67876	0.000	mg/L		a
2	19.355	2444156	61429	0.000	mg/L	V	b
Total		4870706	129304				

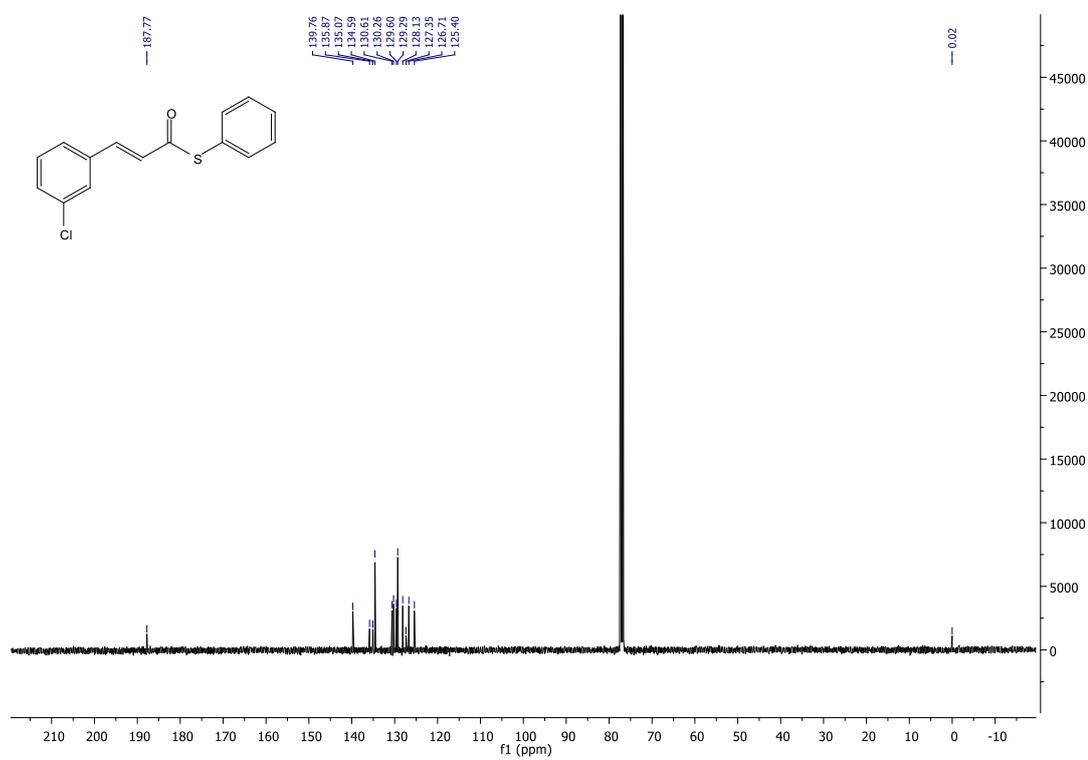
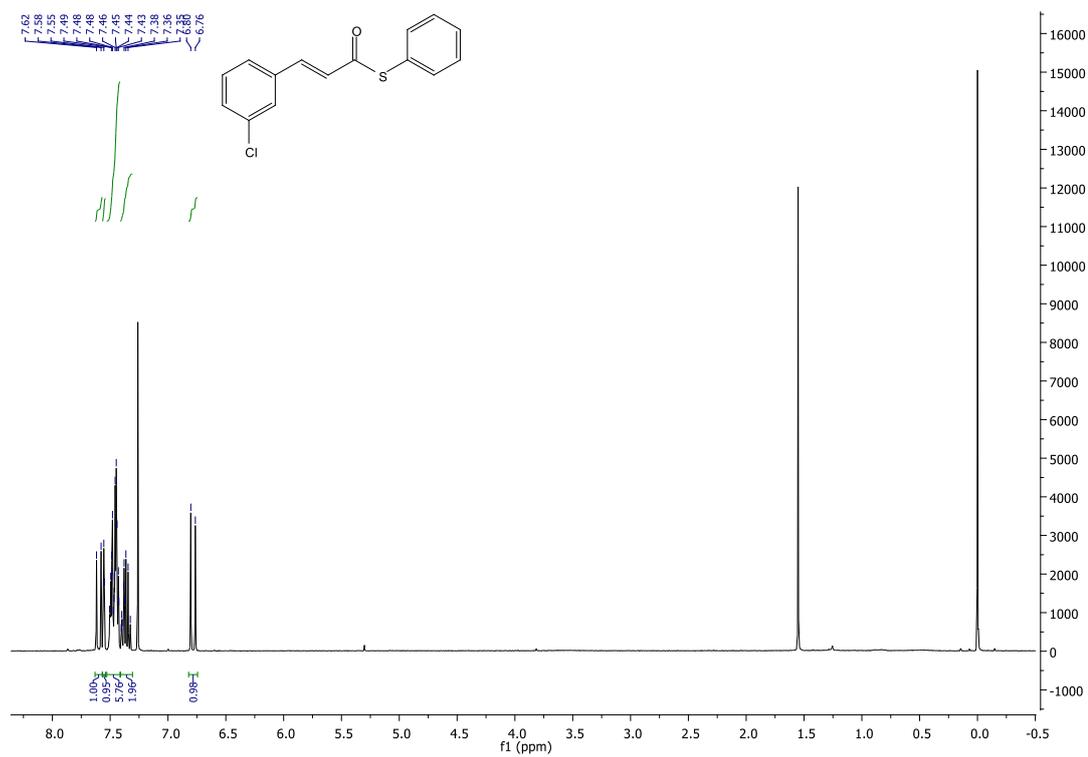
Compound 3.104a



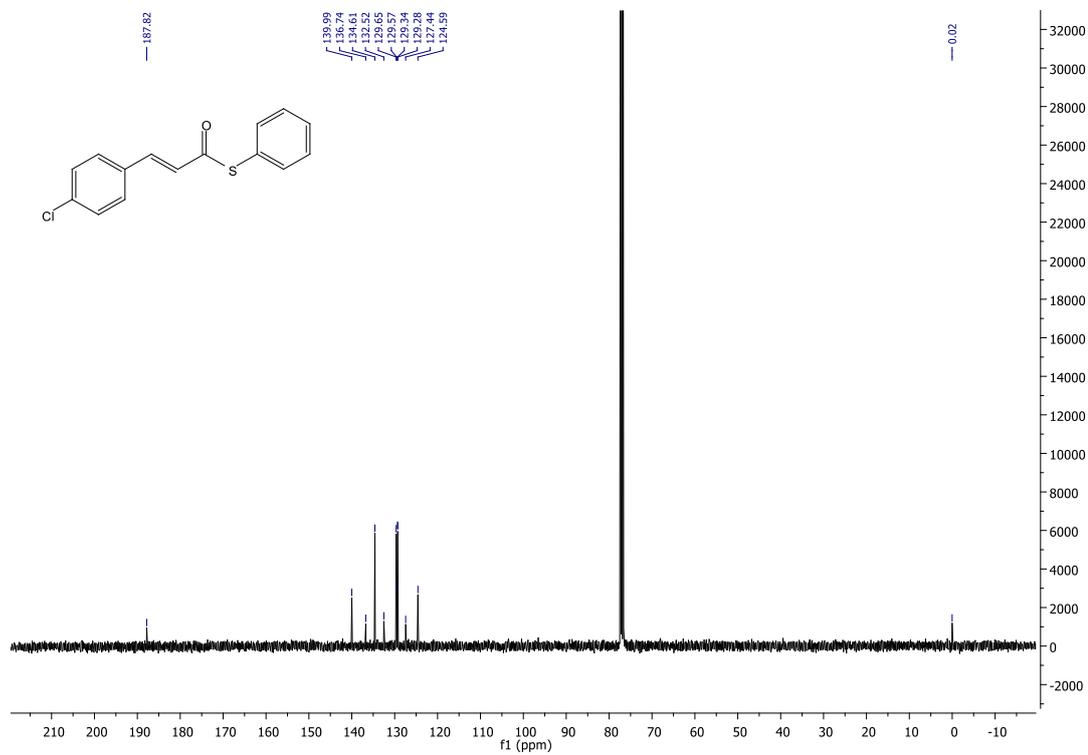
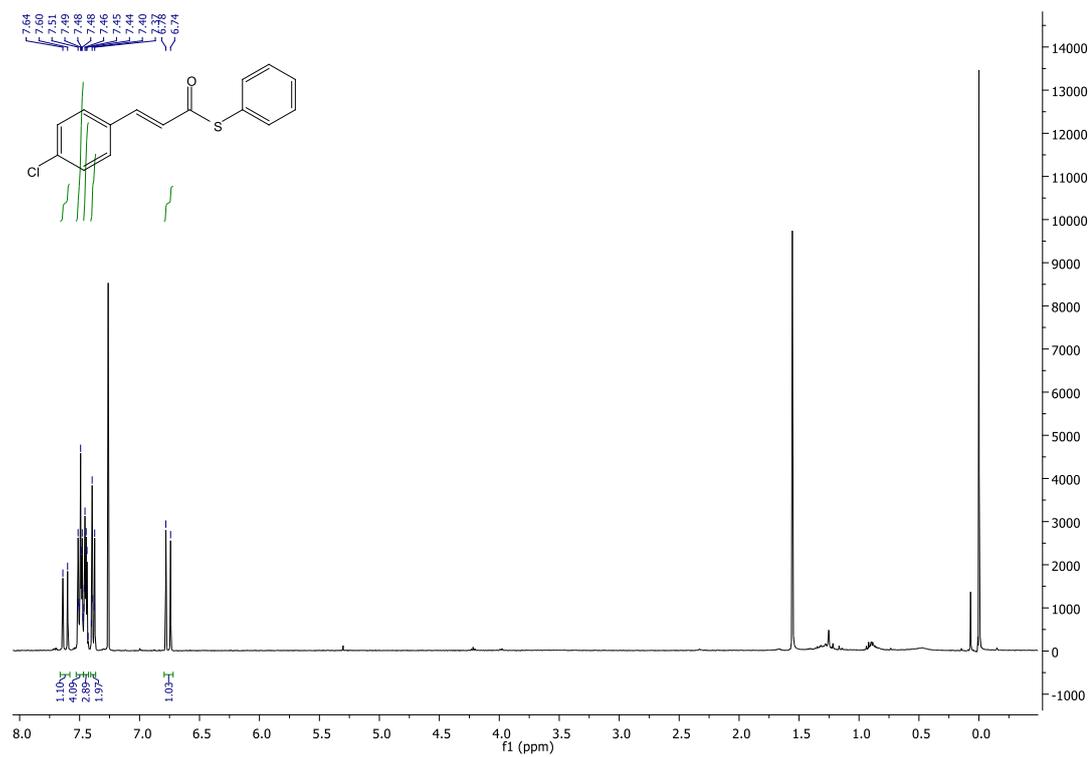
Compound 3.104b



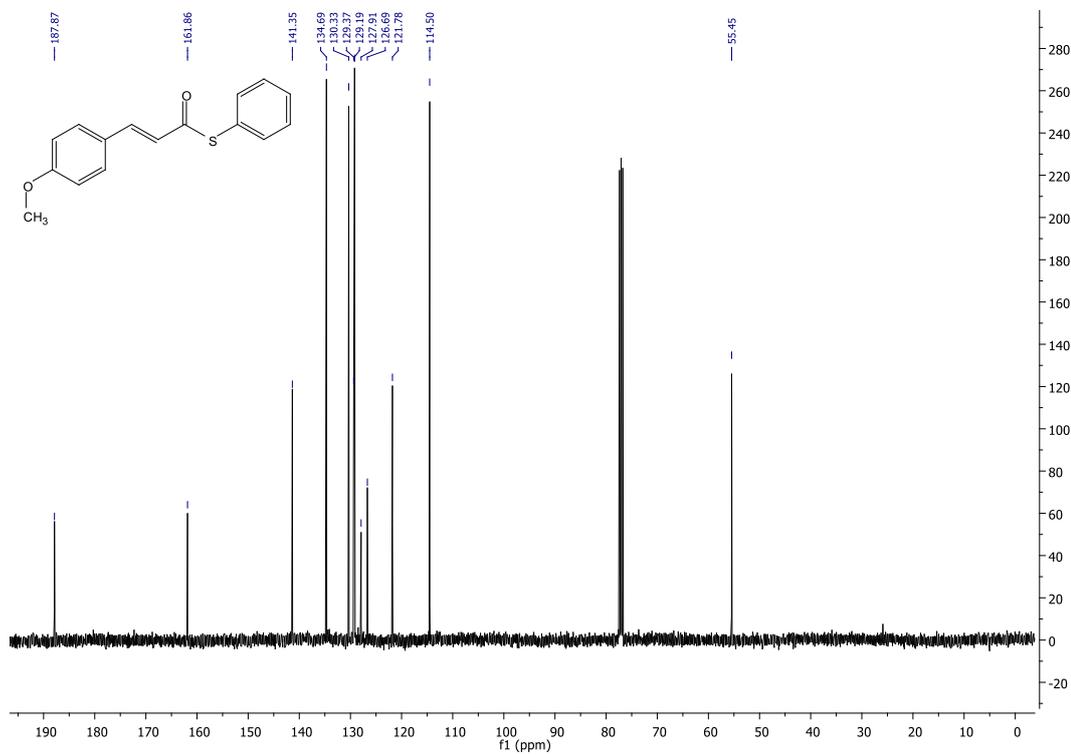
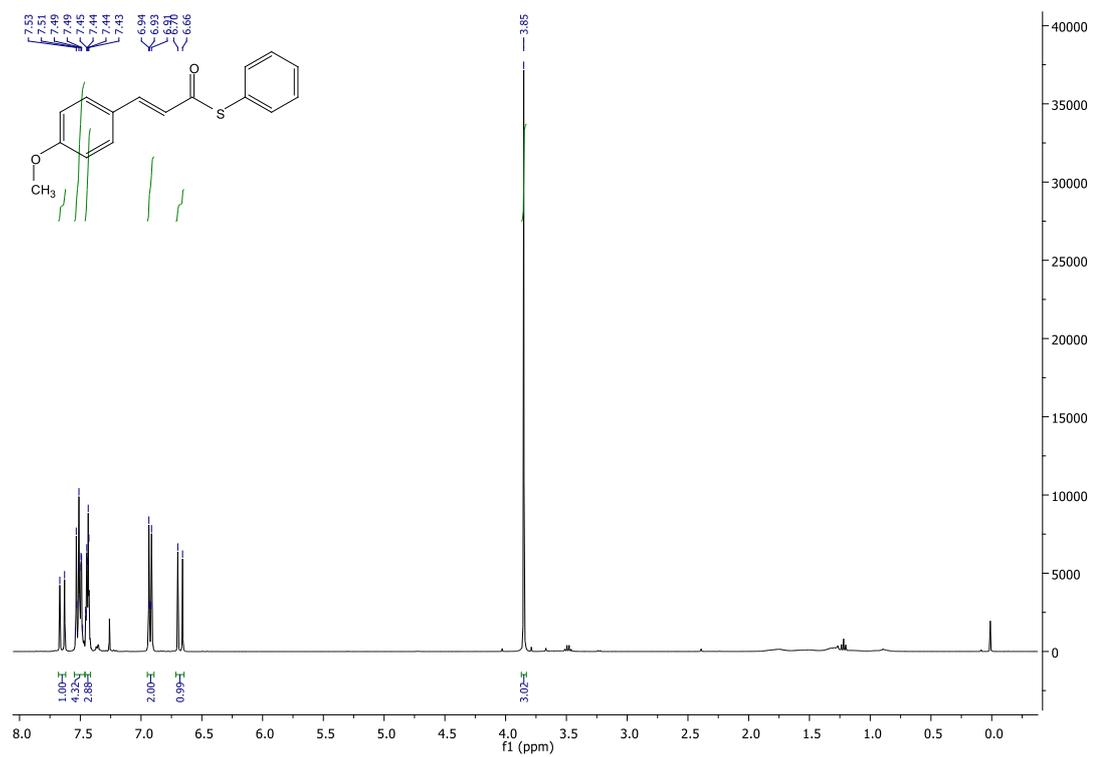
Compound 3.104c



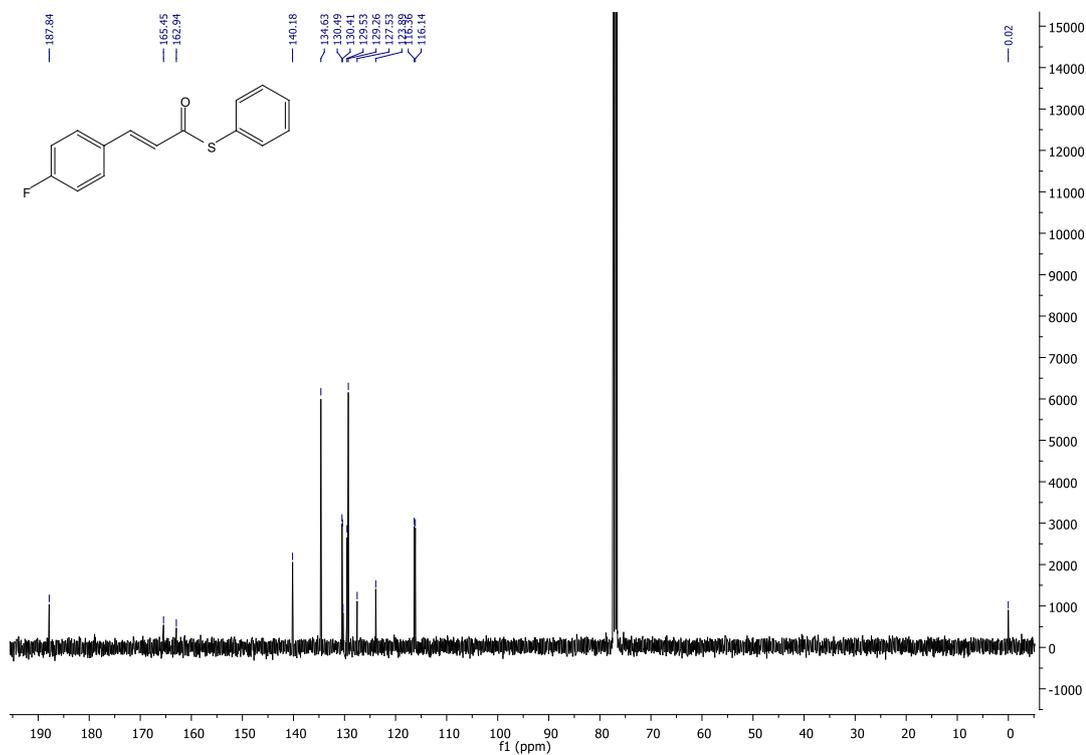
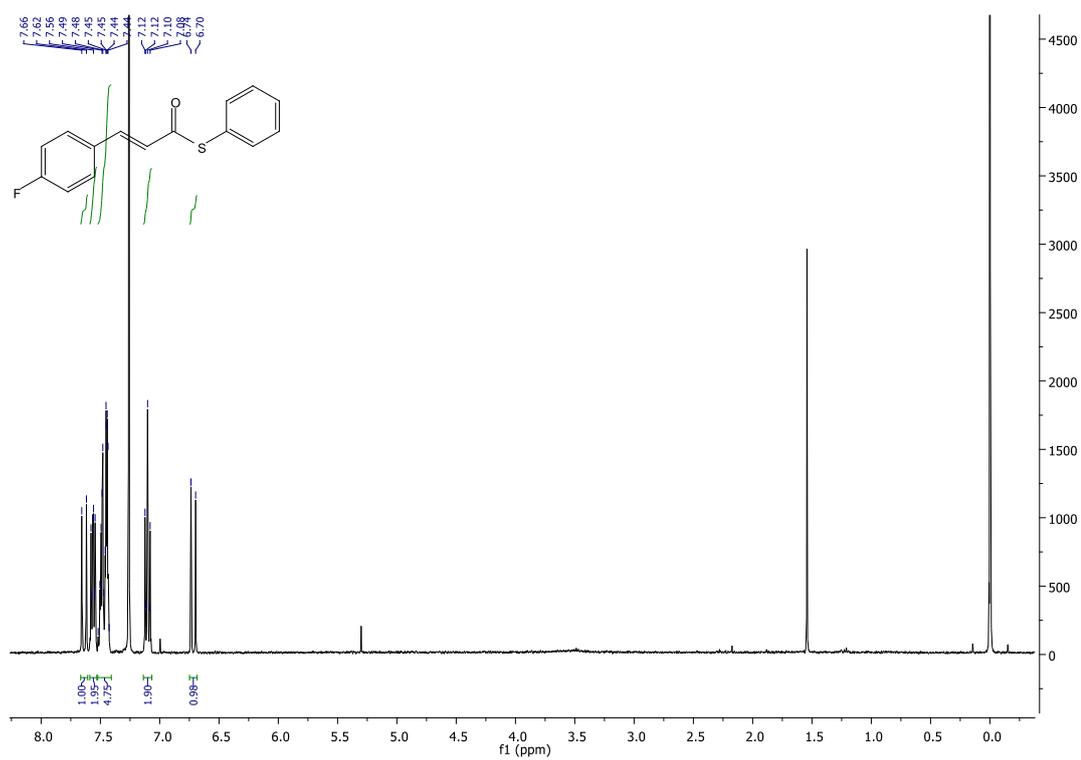
Compound 3.104d



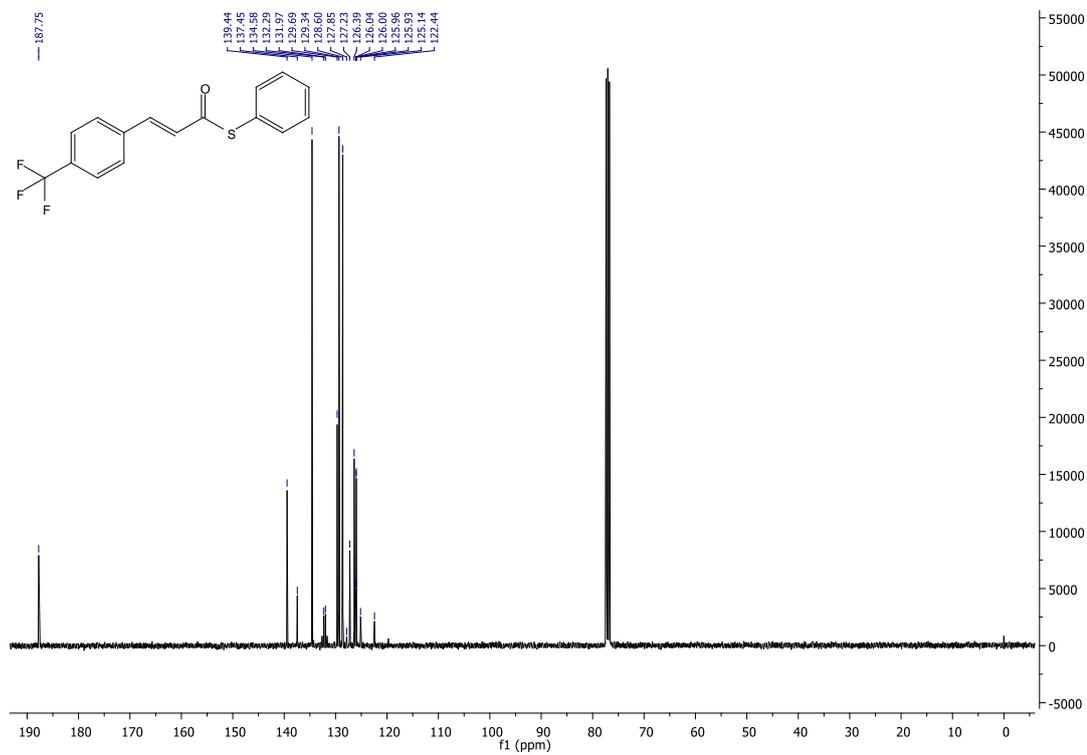
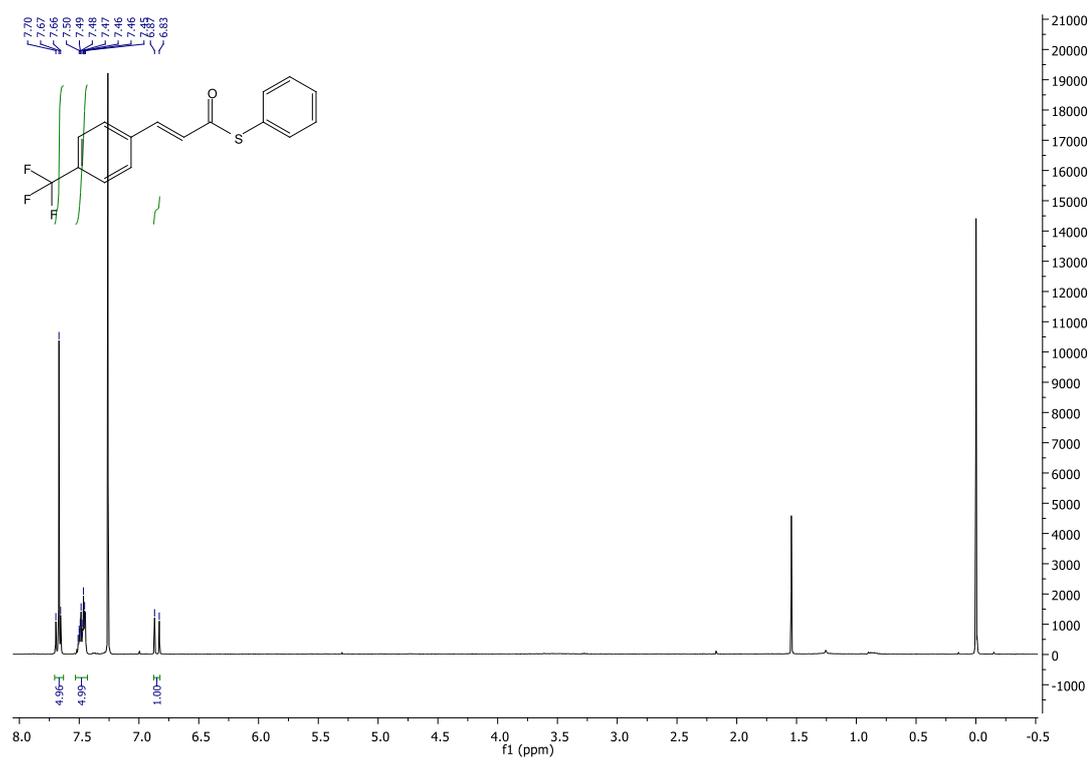
Compound 3.104e



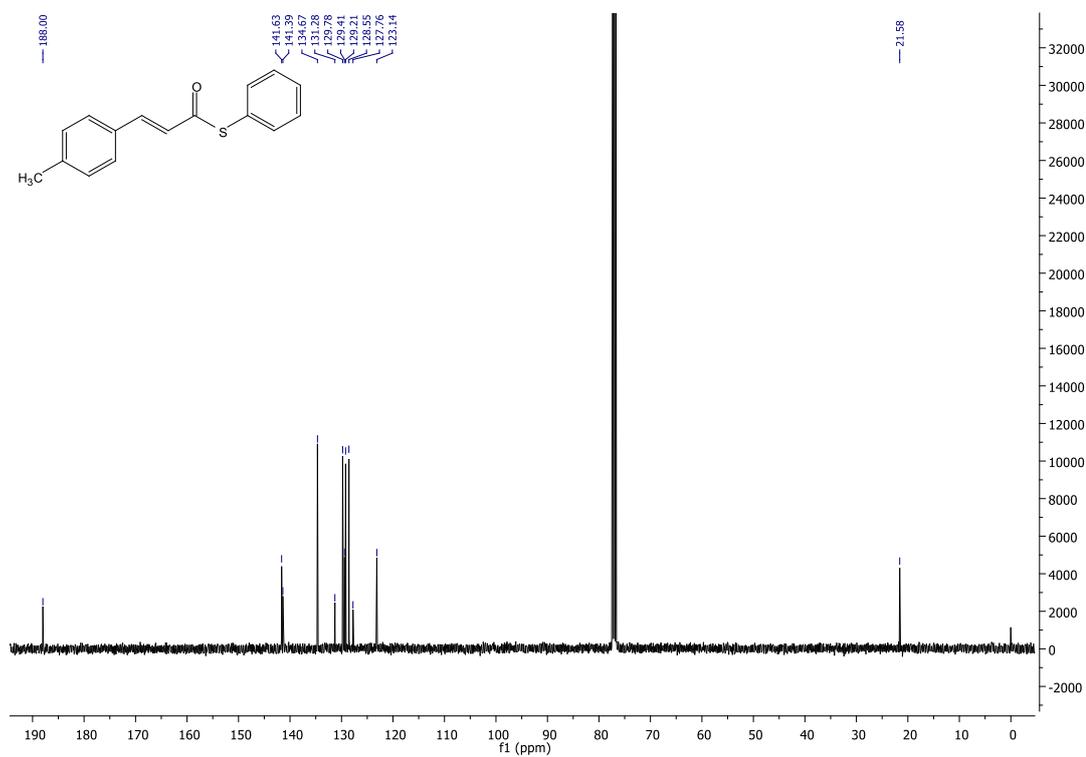
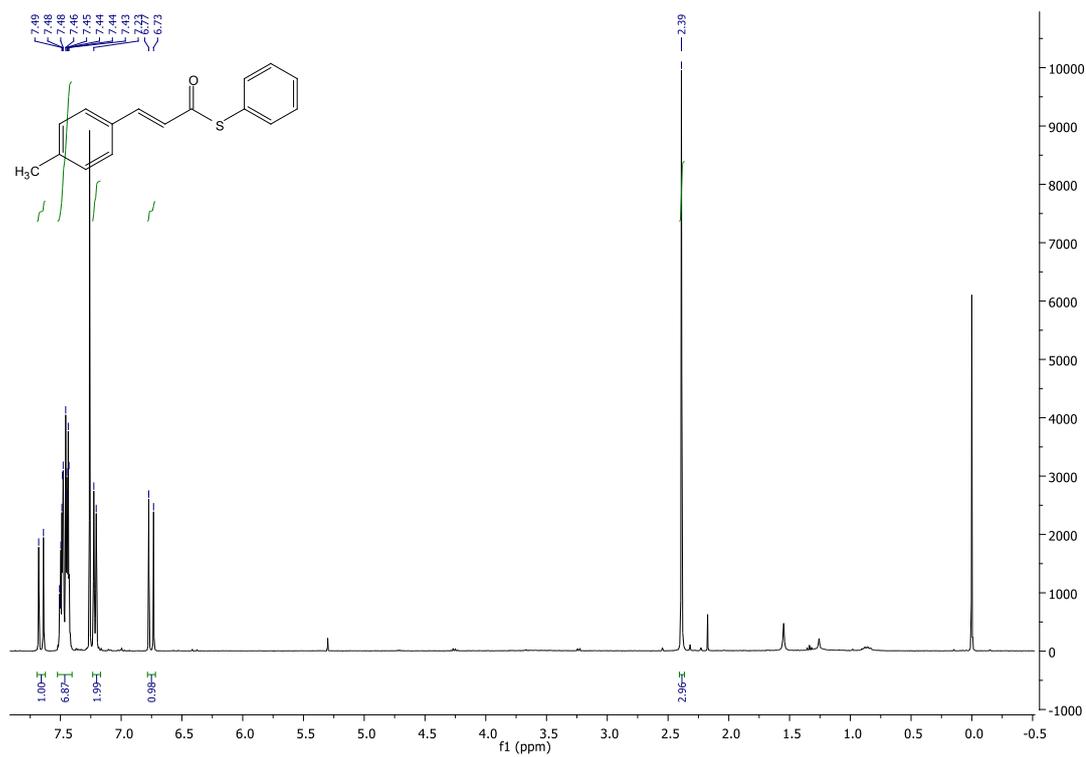
Compound 3.104f



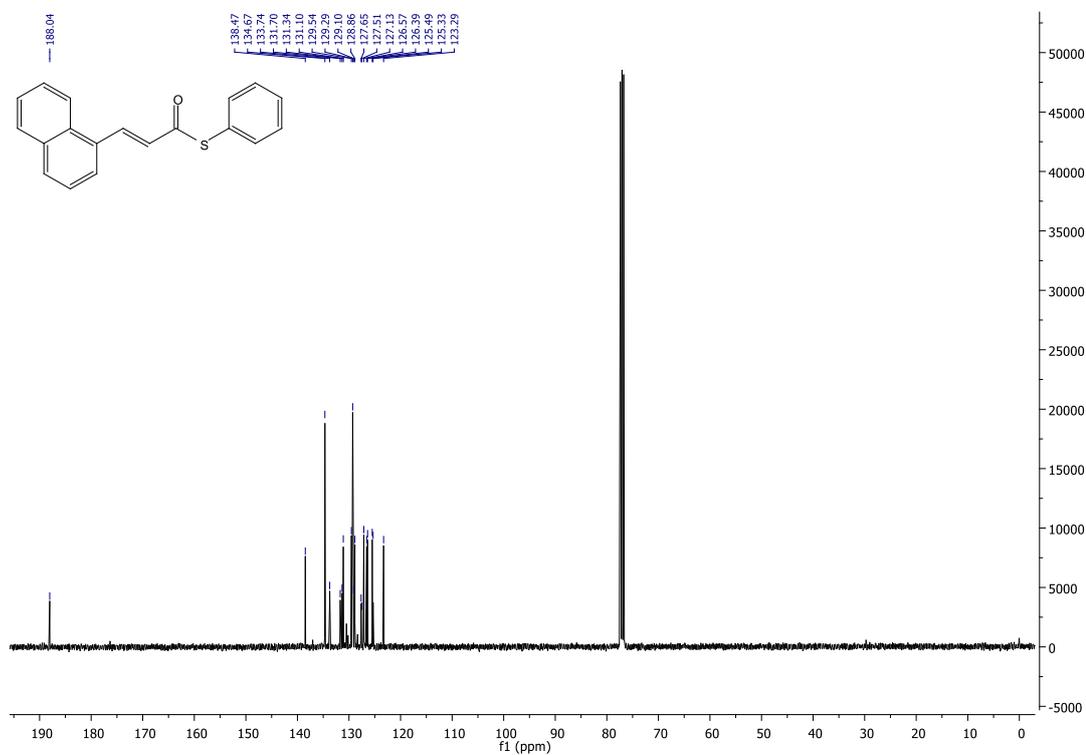
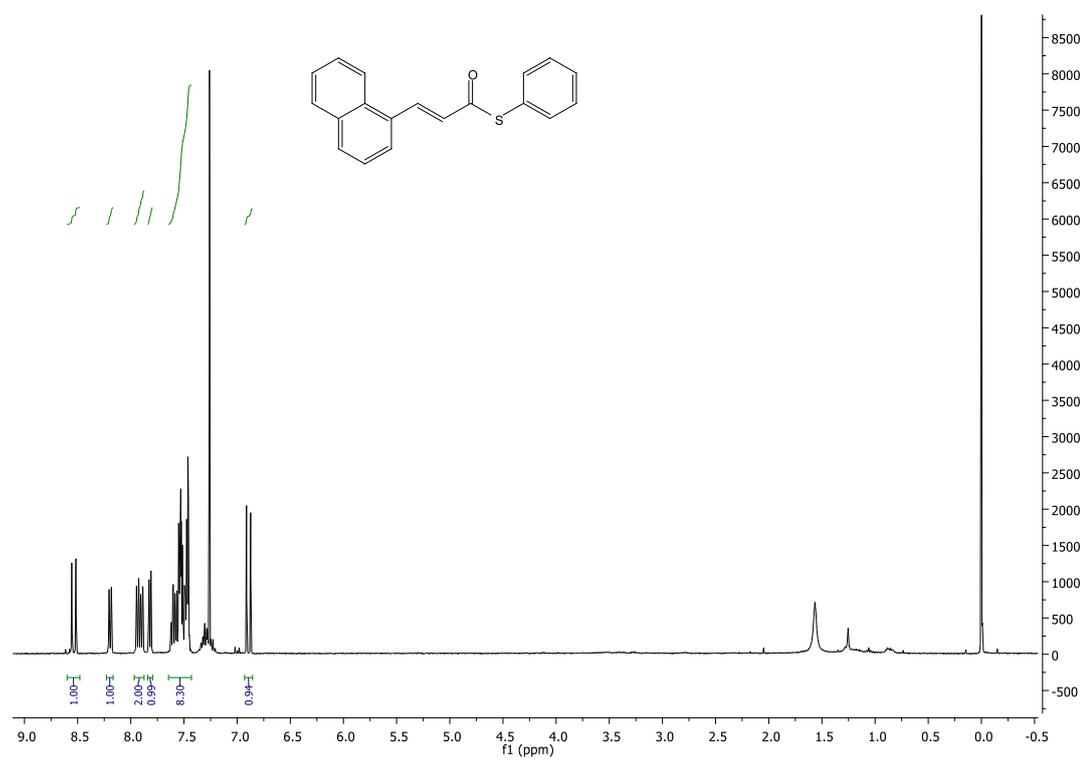
Compound 3.104g



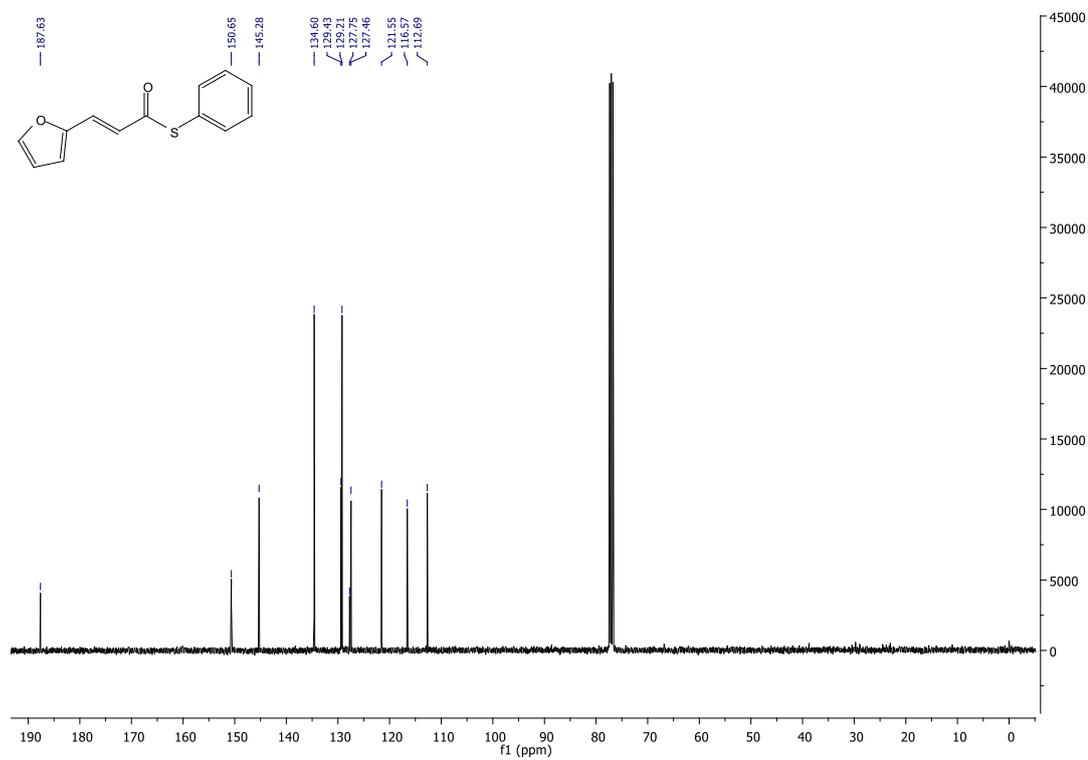
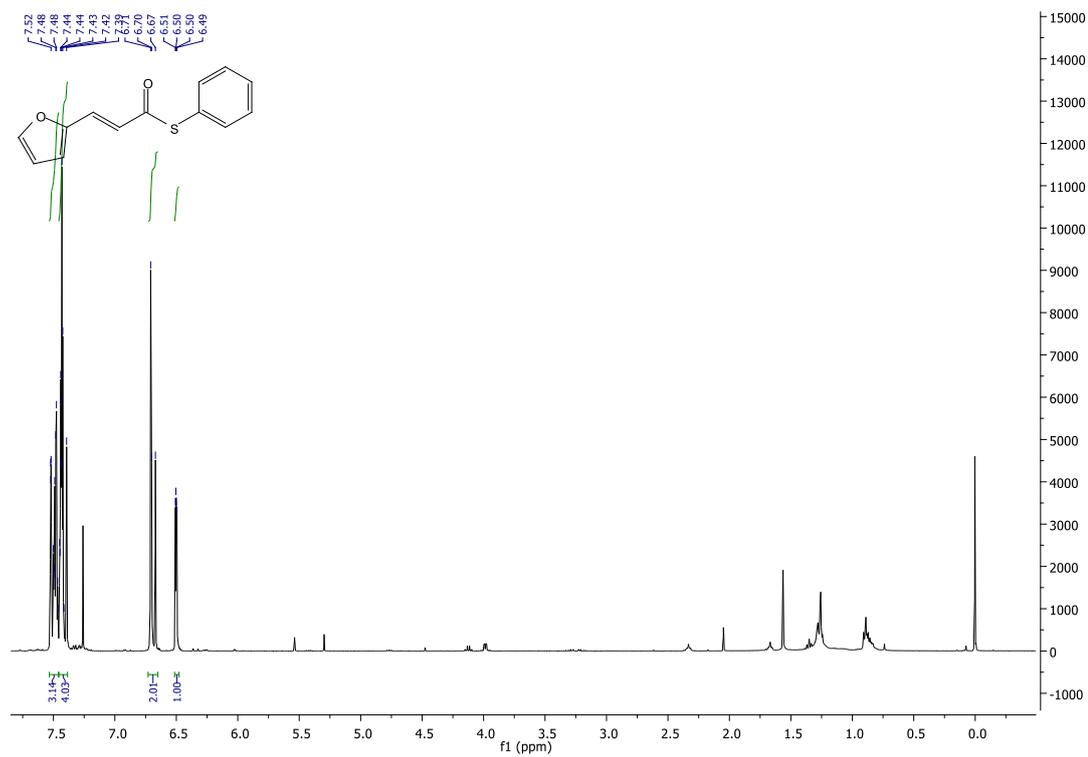
Compound 3.104h



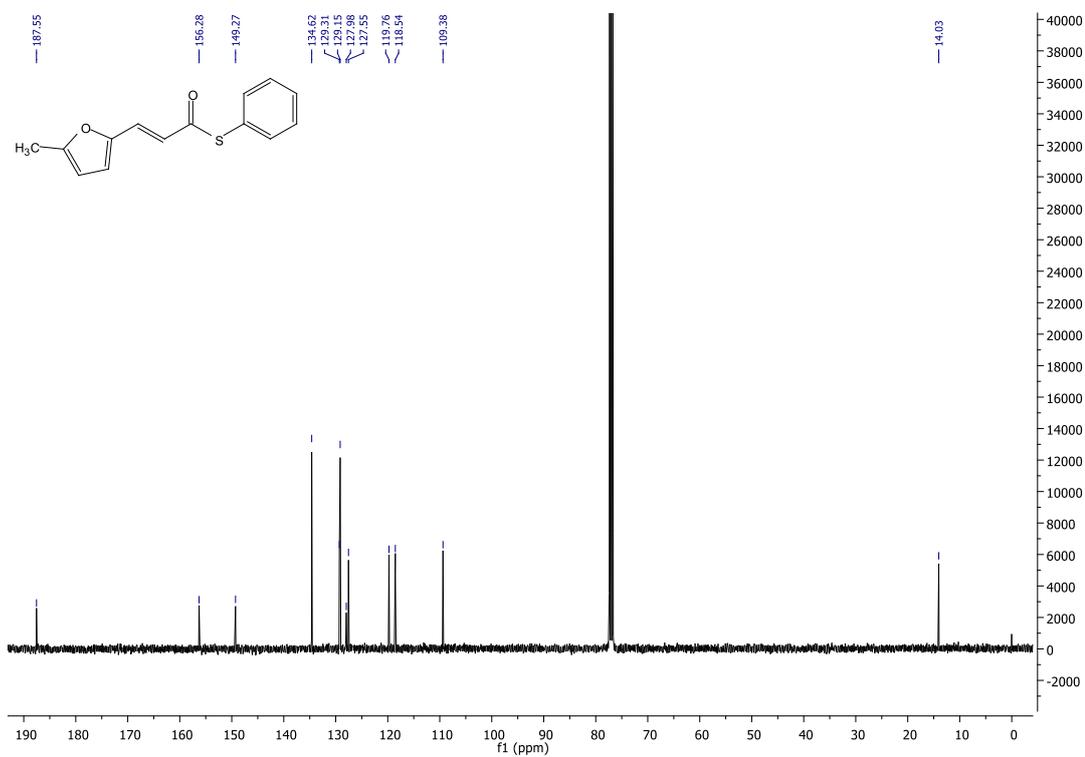
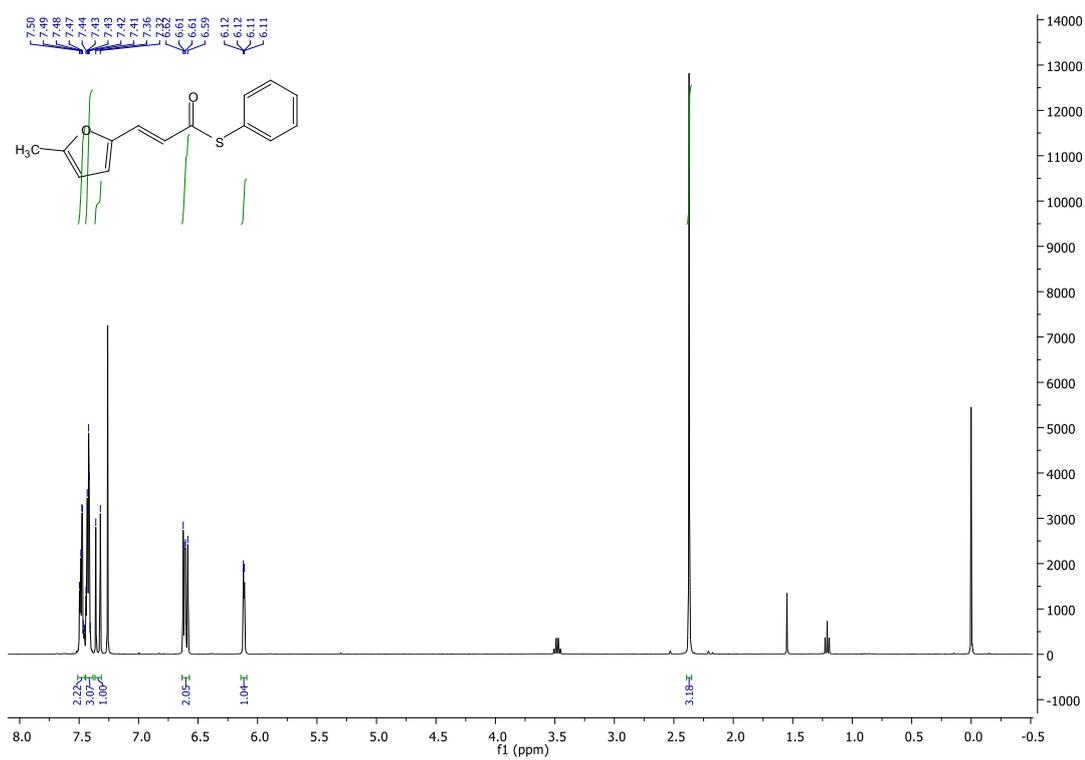
Compound 3.104i



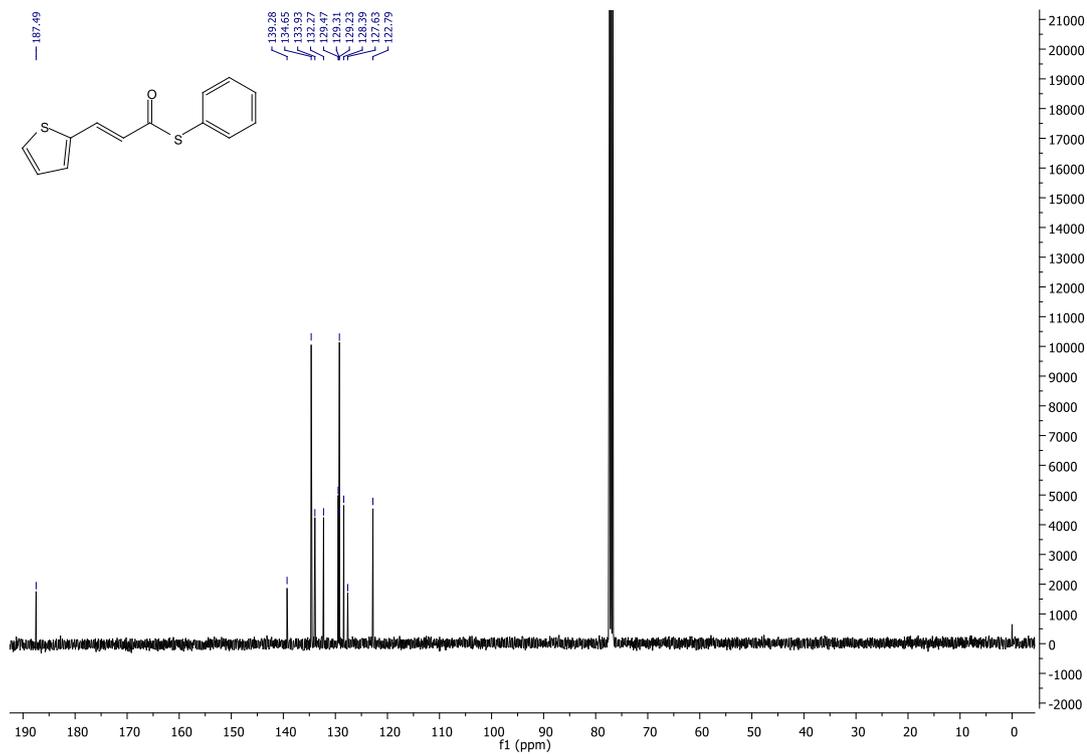
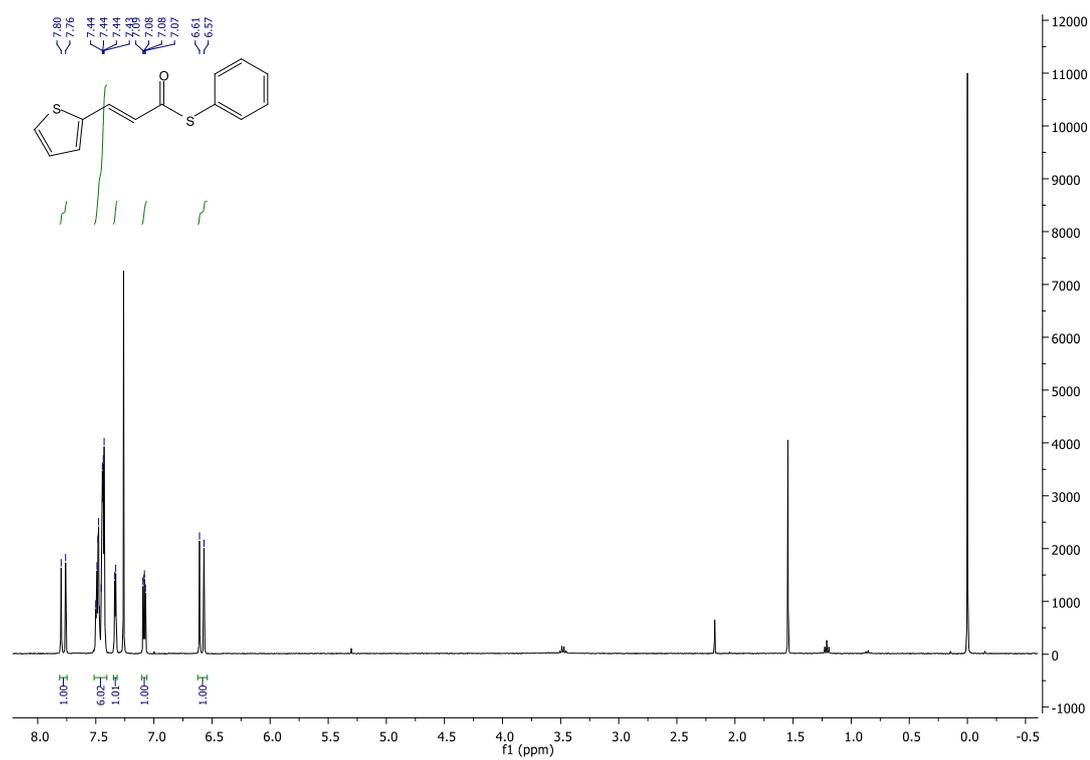
Compound 3.104j



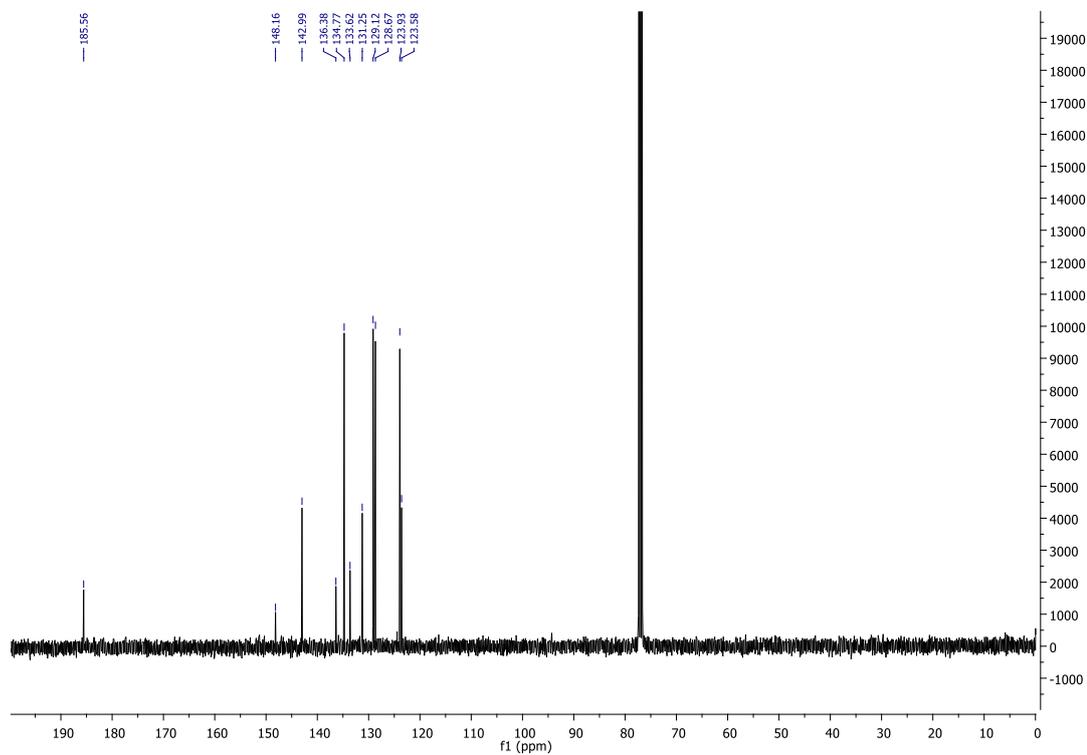
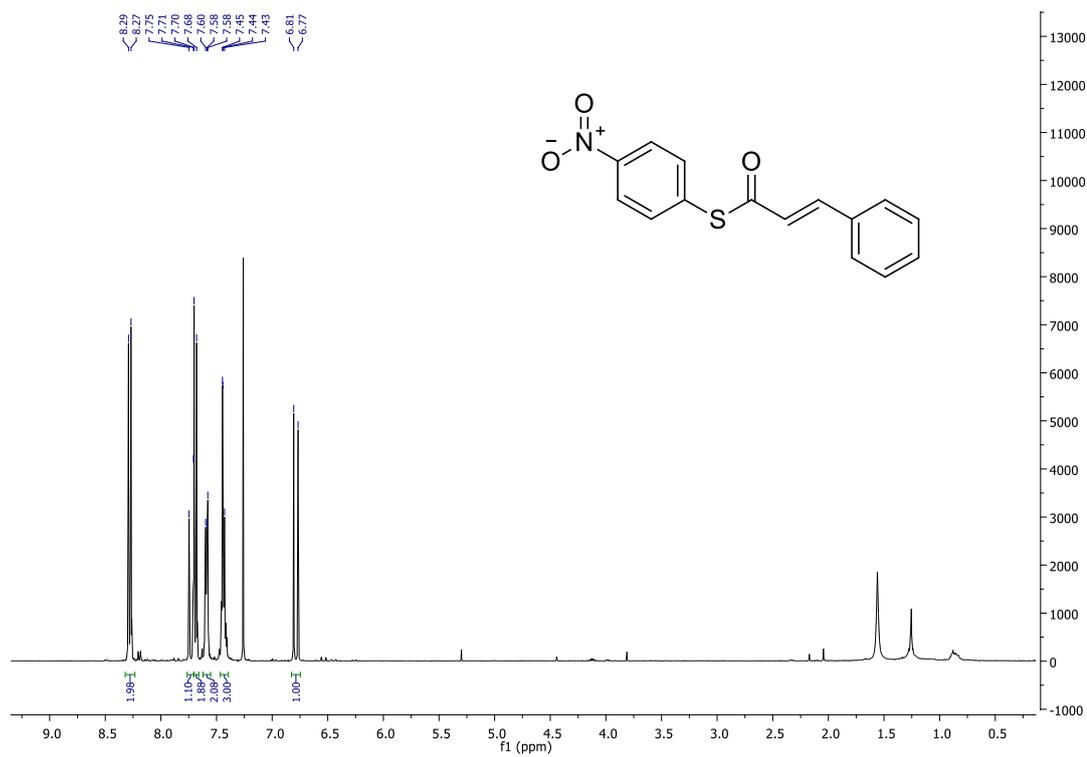
Compound 3.104k



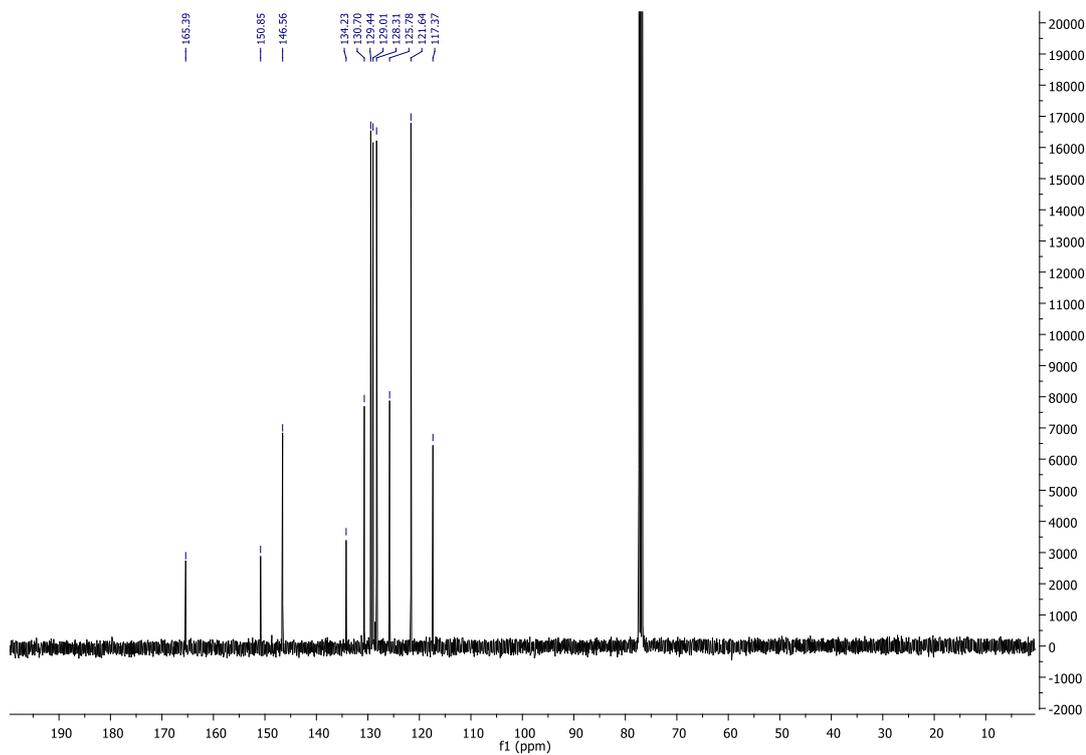
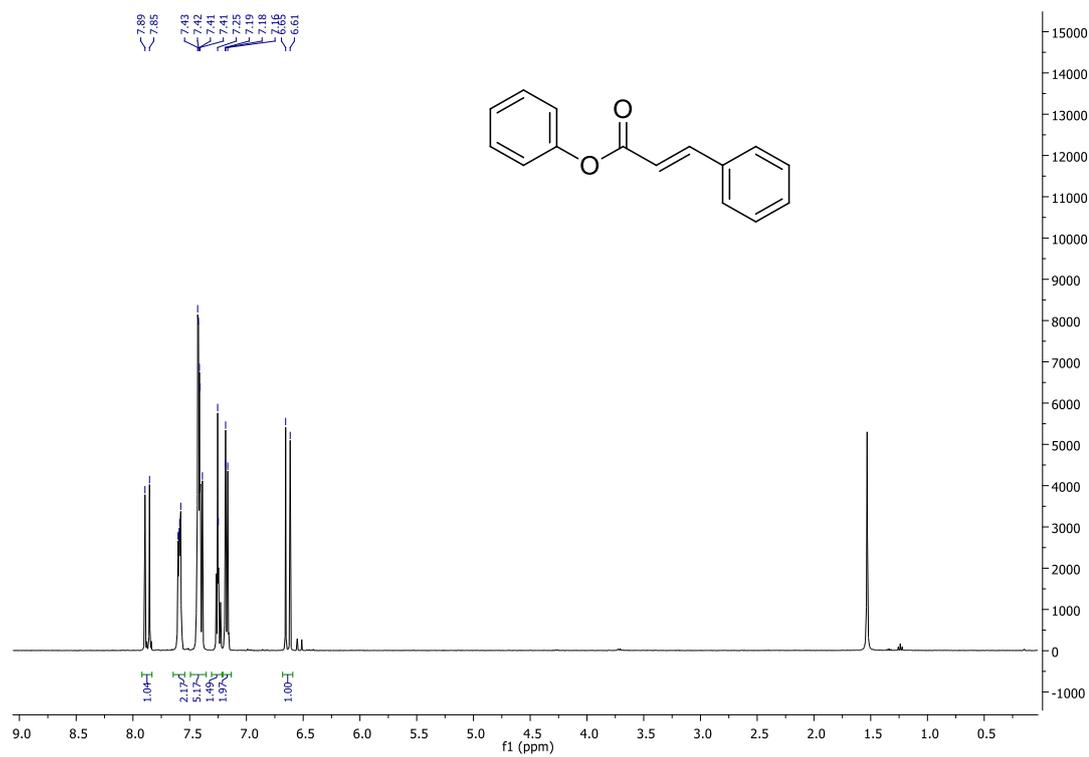
Compound 3.104I



Compound 3.107b

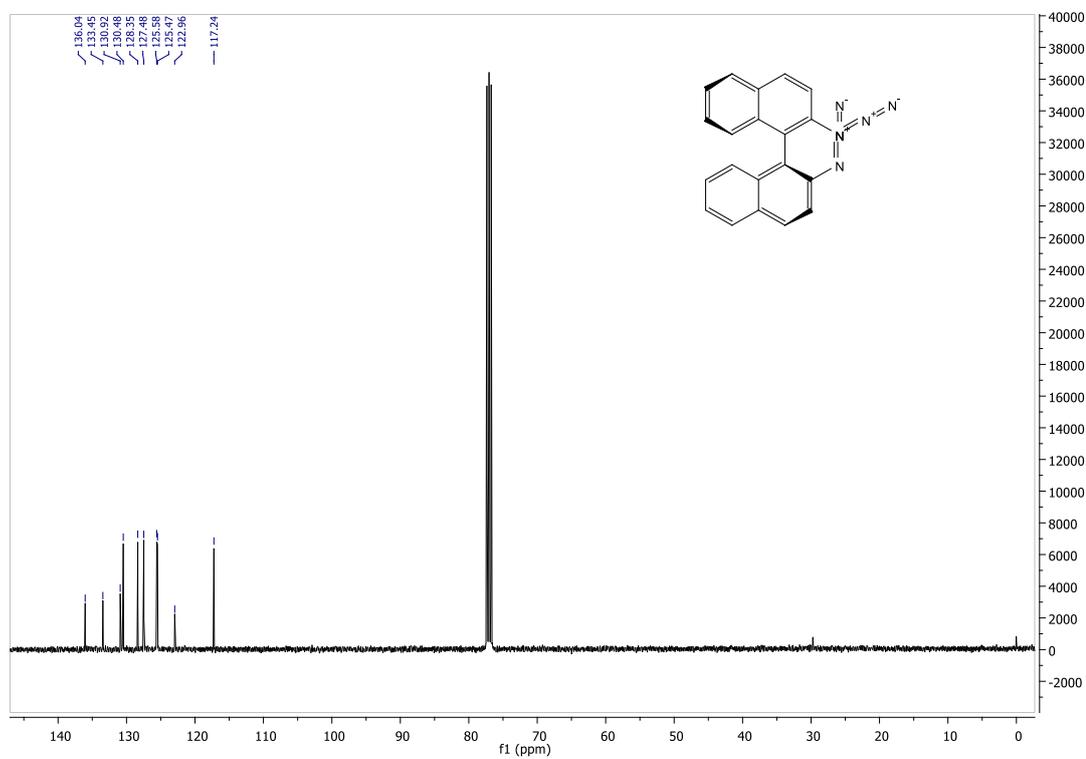
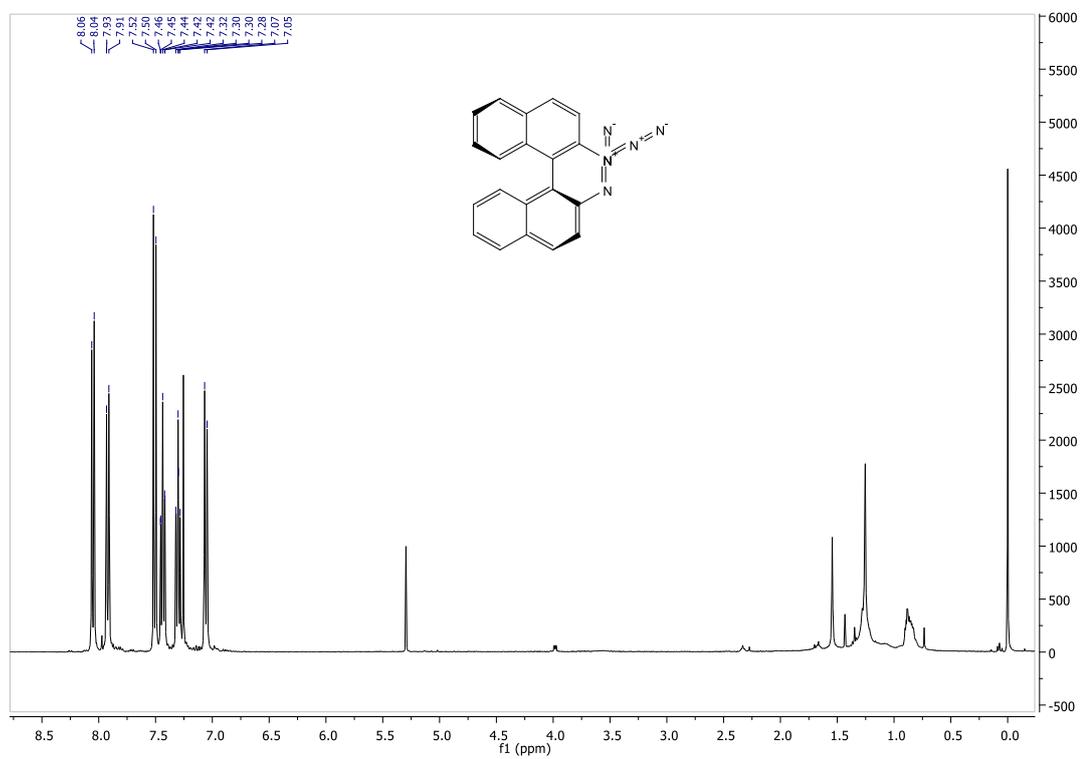


Compound 3.107a

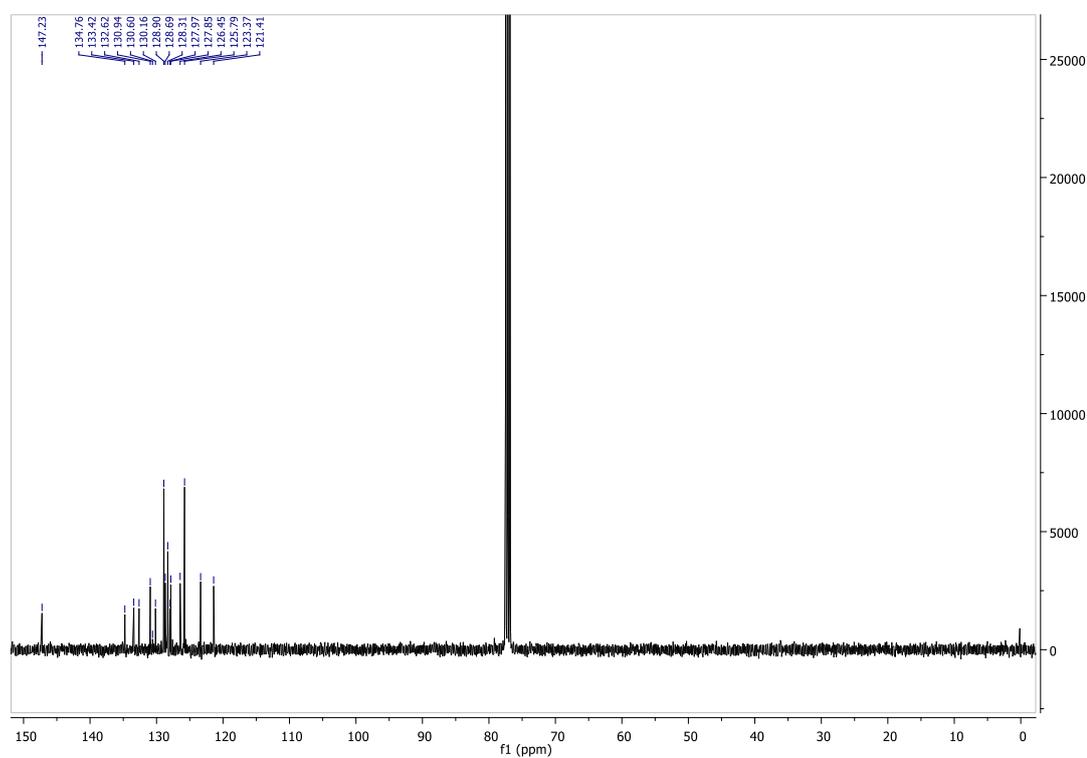
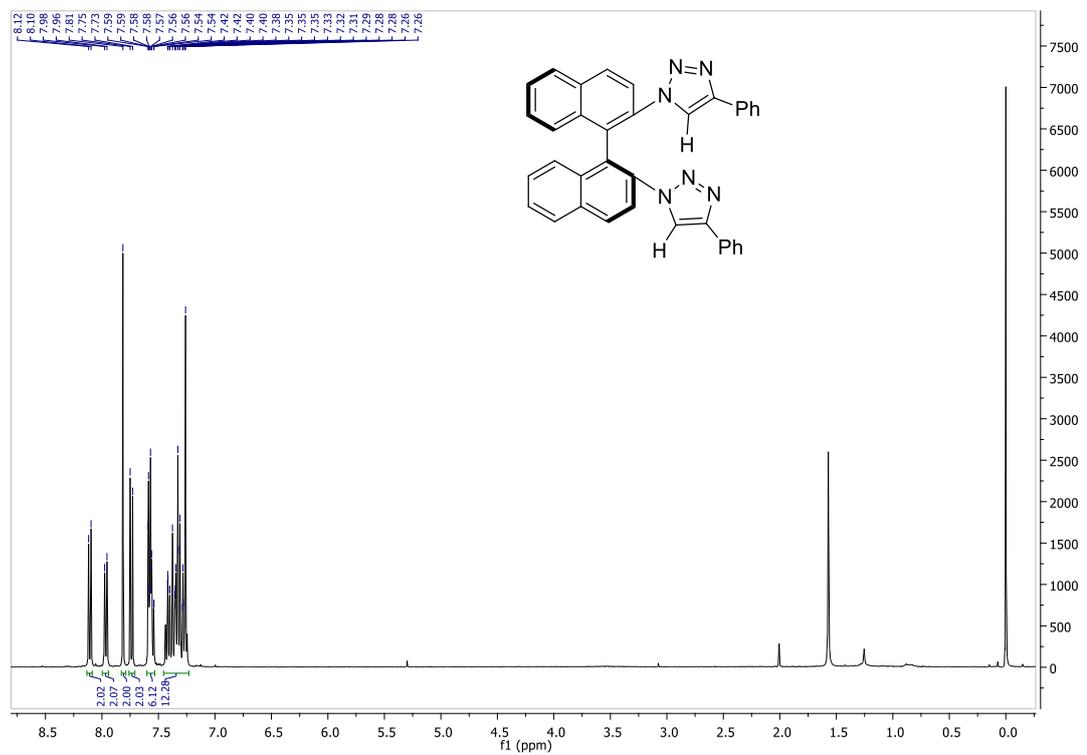


Chapter 4: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$

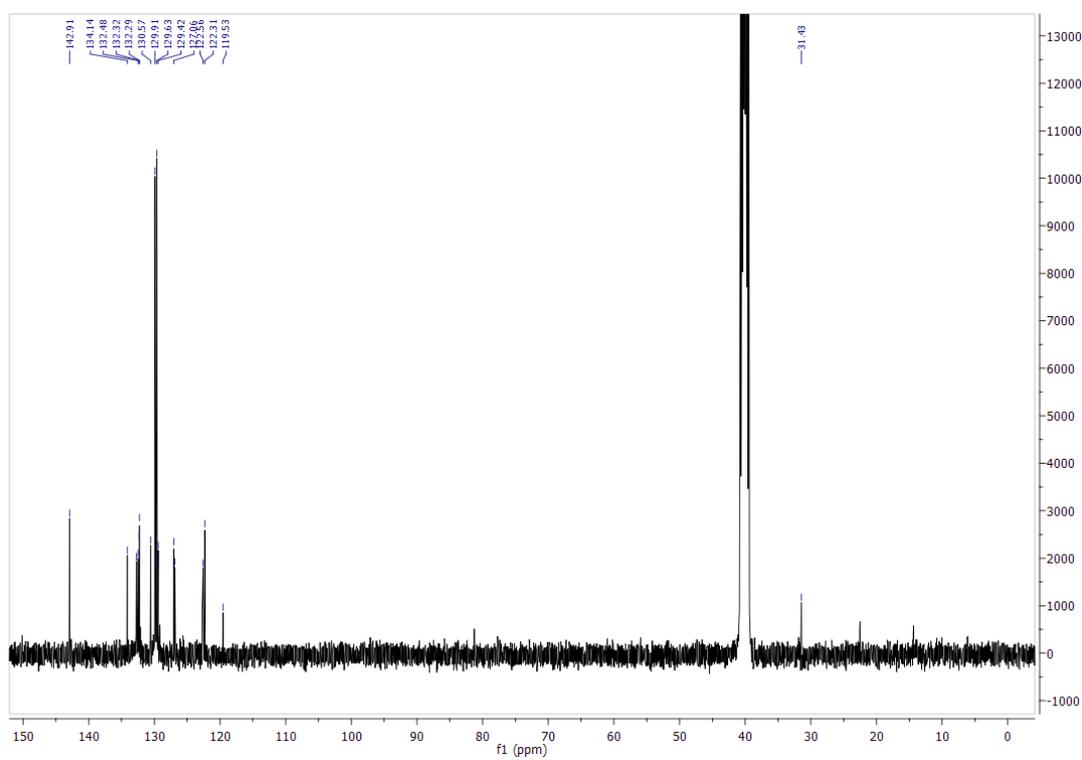
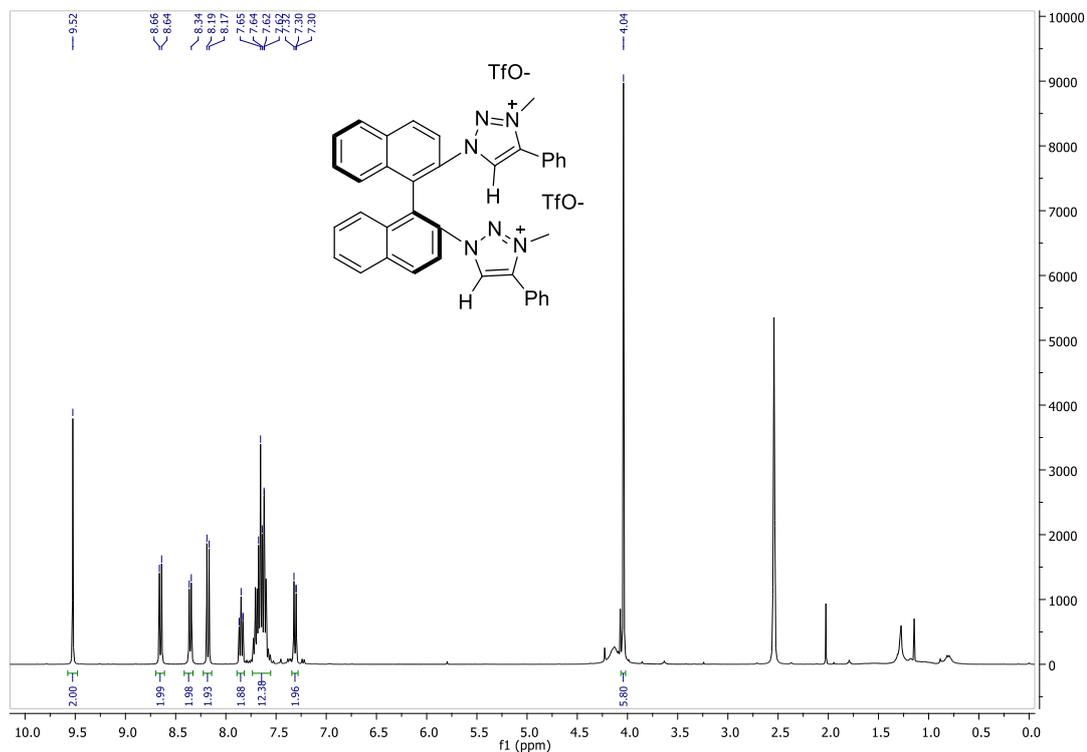
Compound 4.66



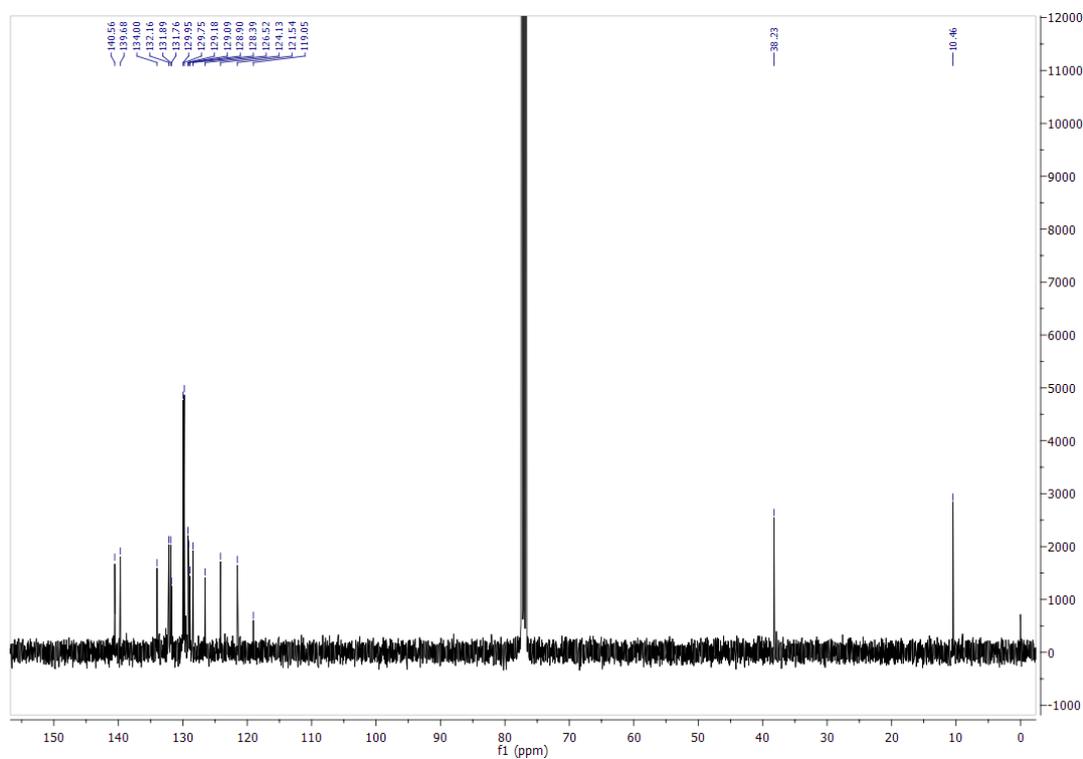
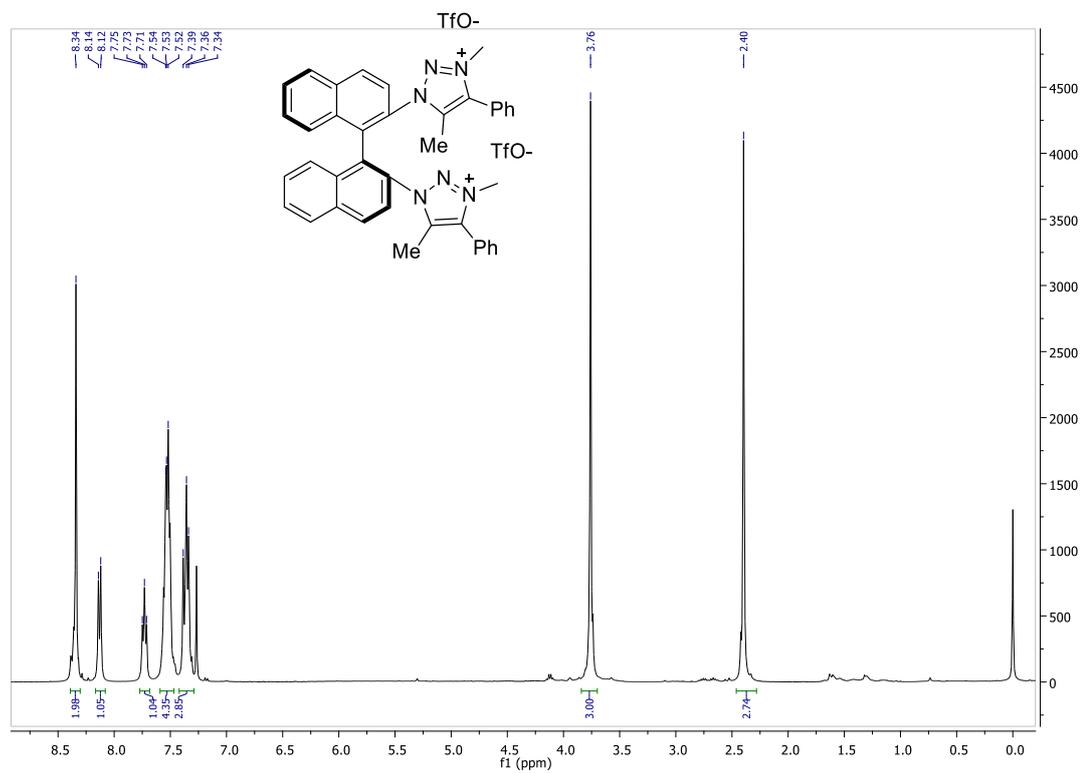
Compound 4.71



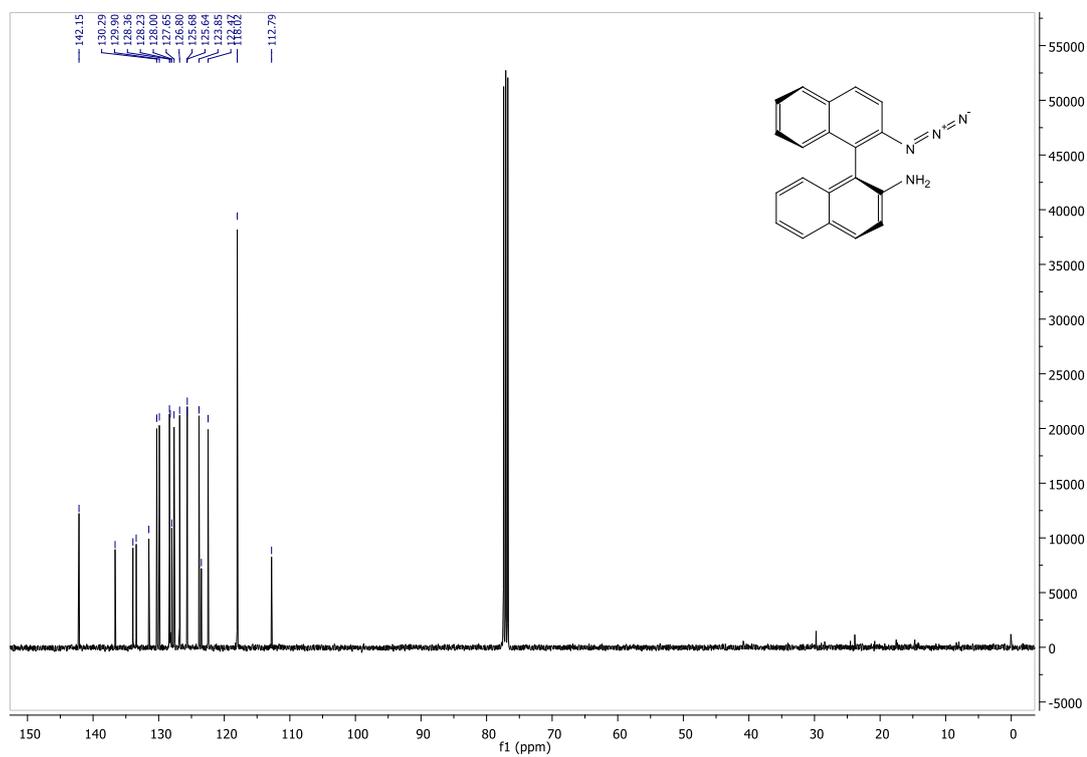
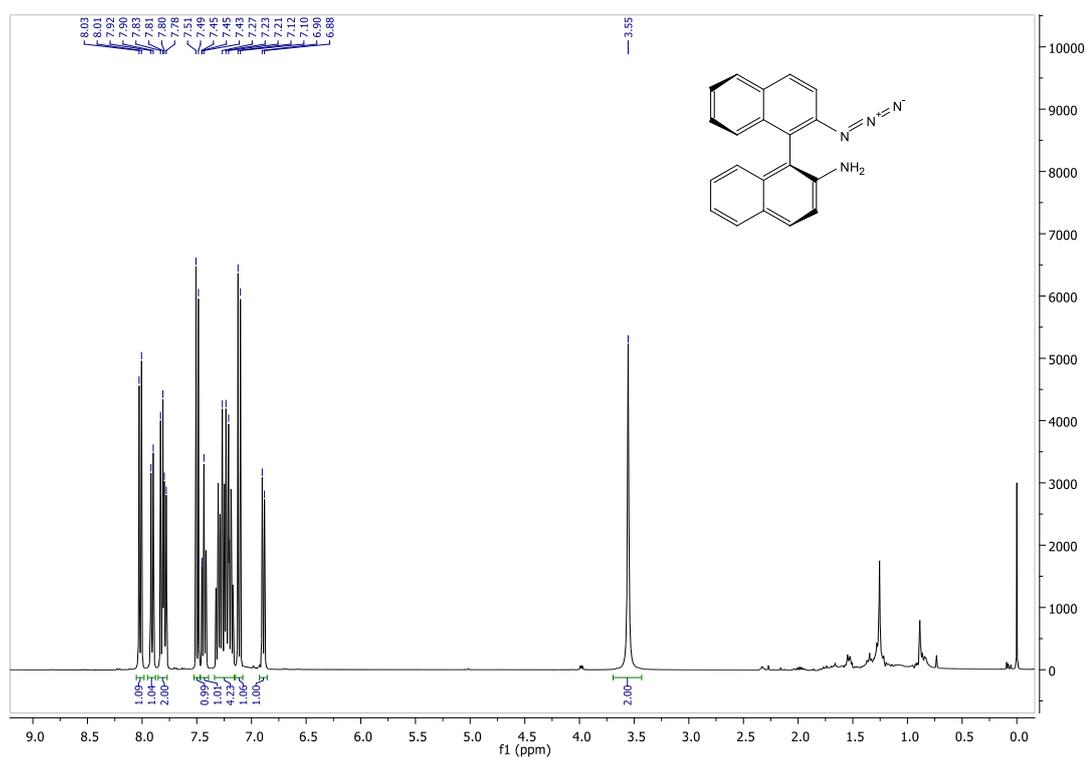
Compound 4.72



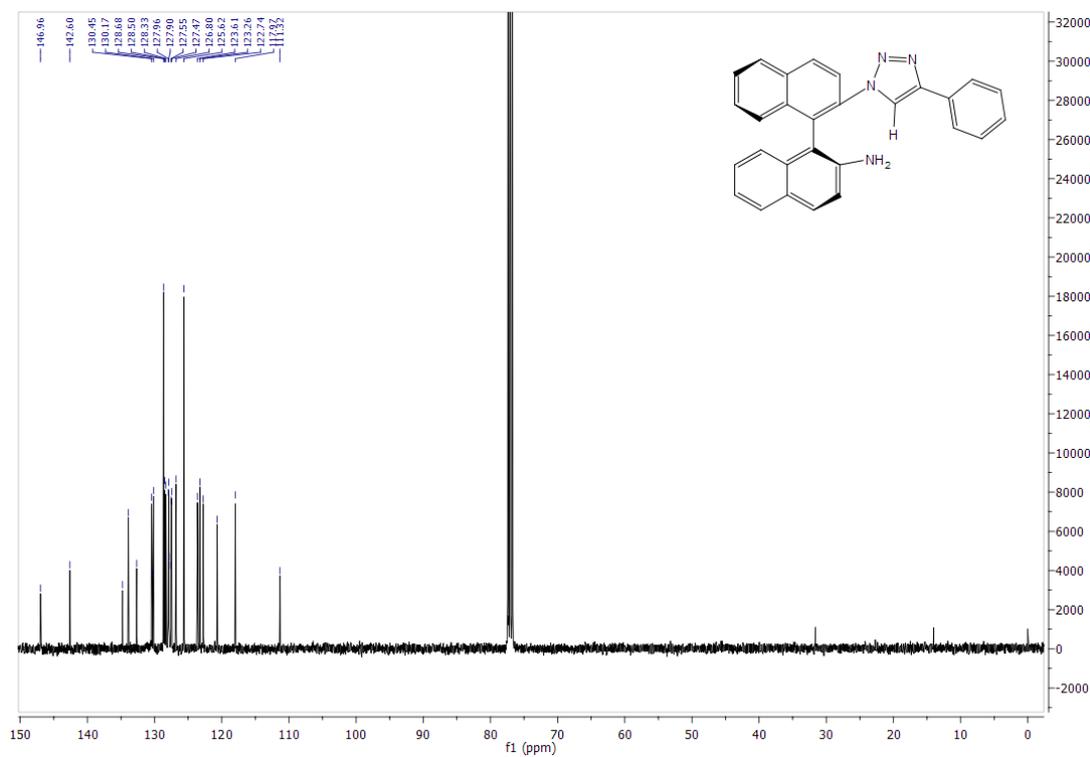
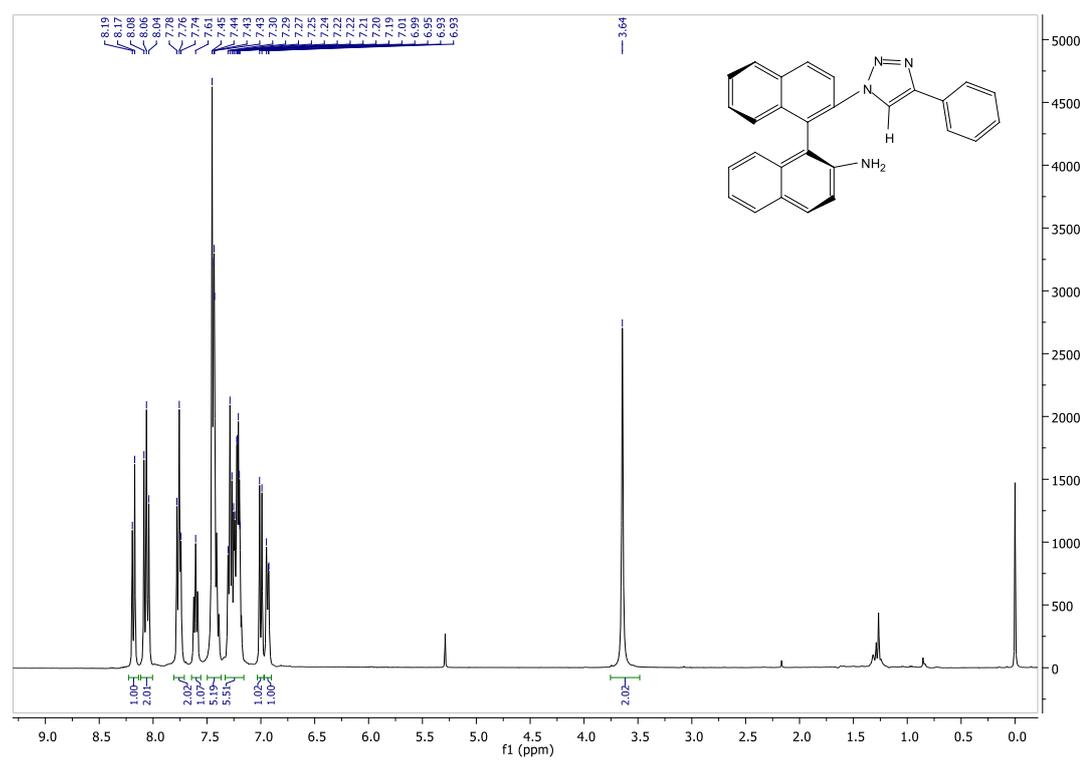
Compound 4.73



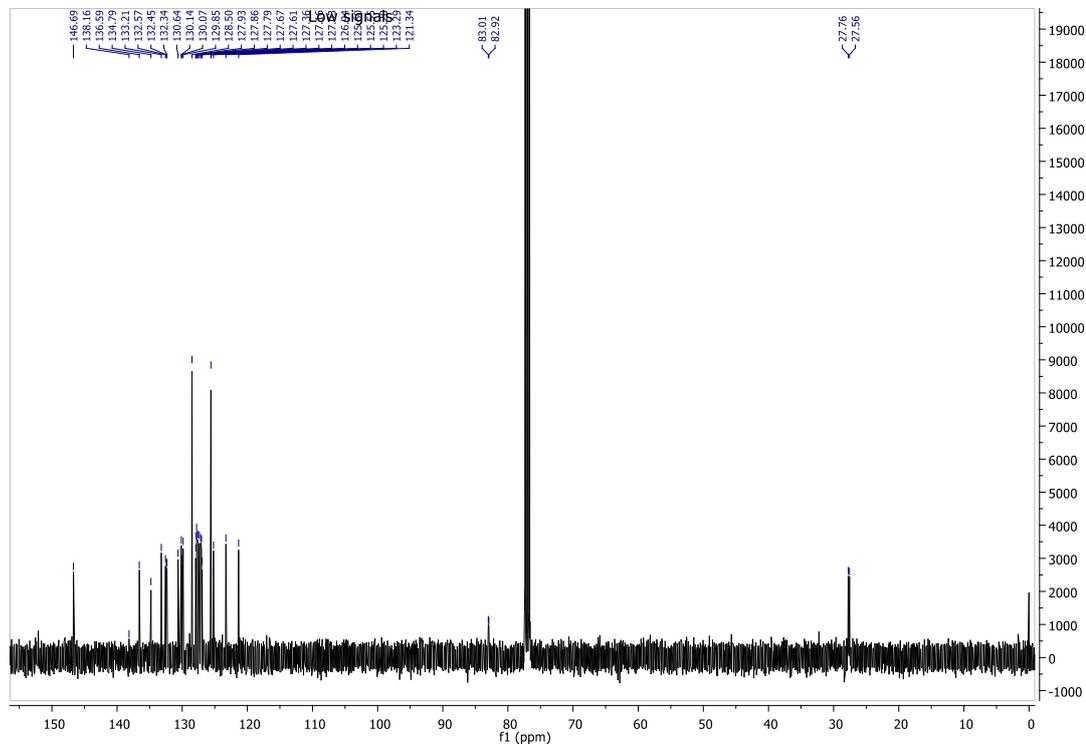
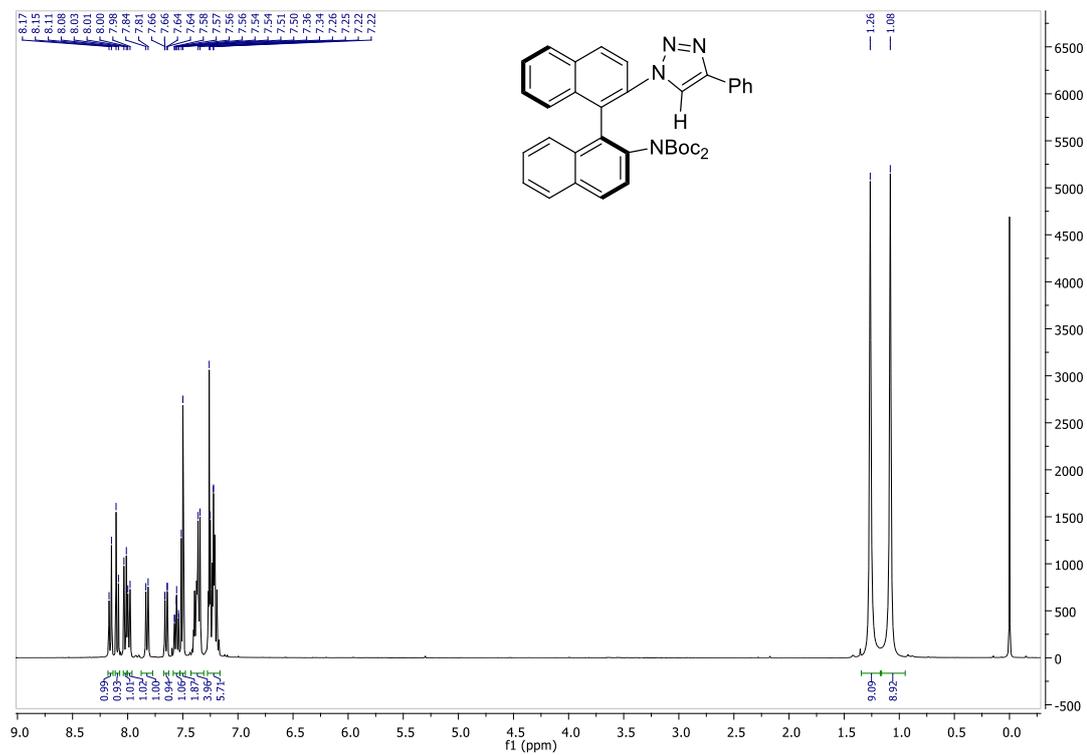
Compound 4.76



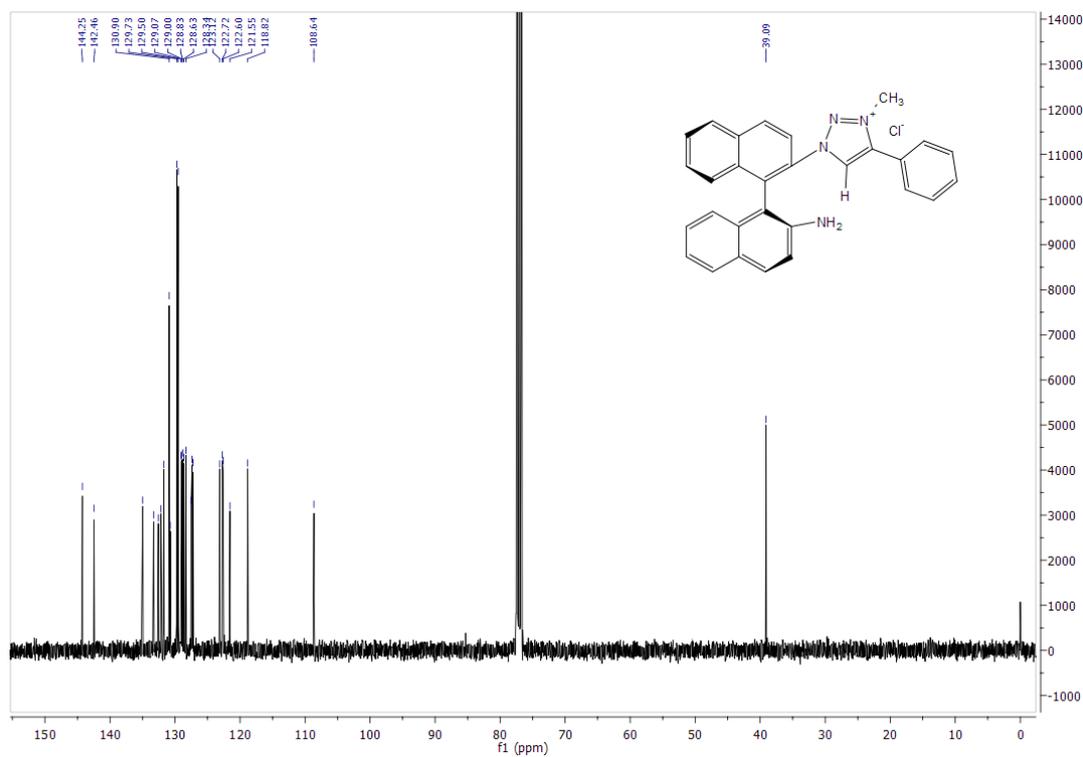
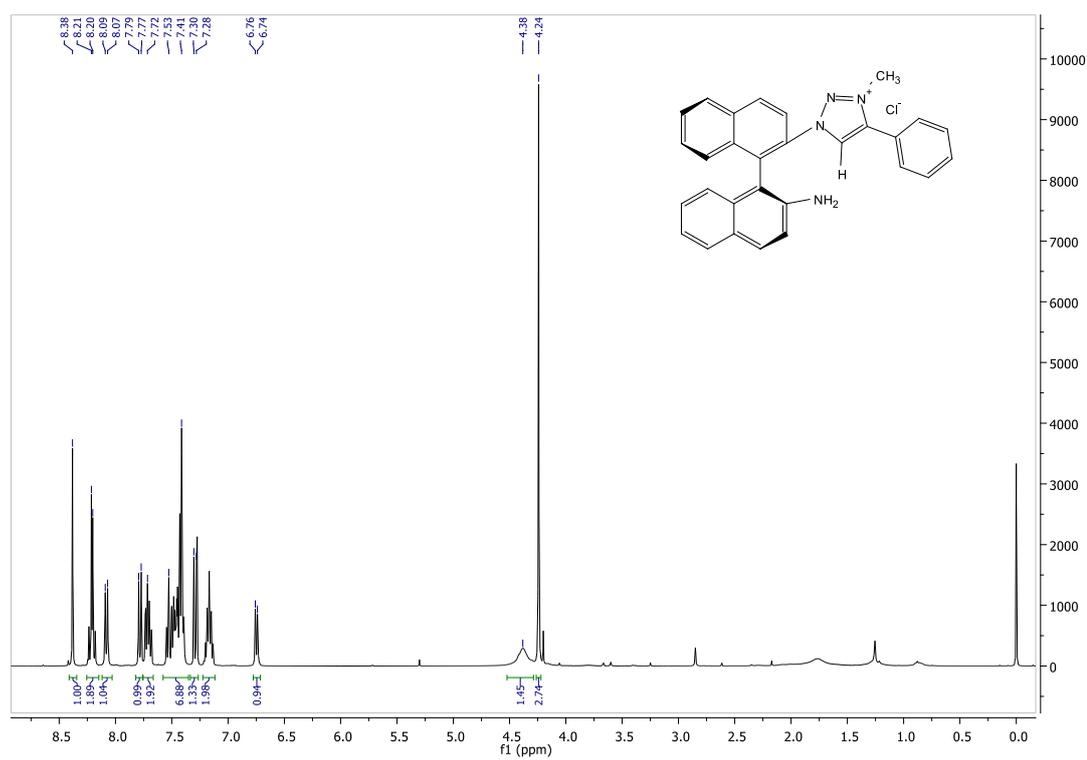
Compound 4.77



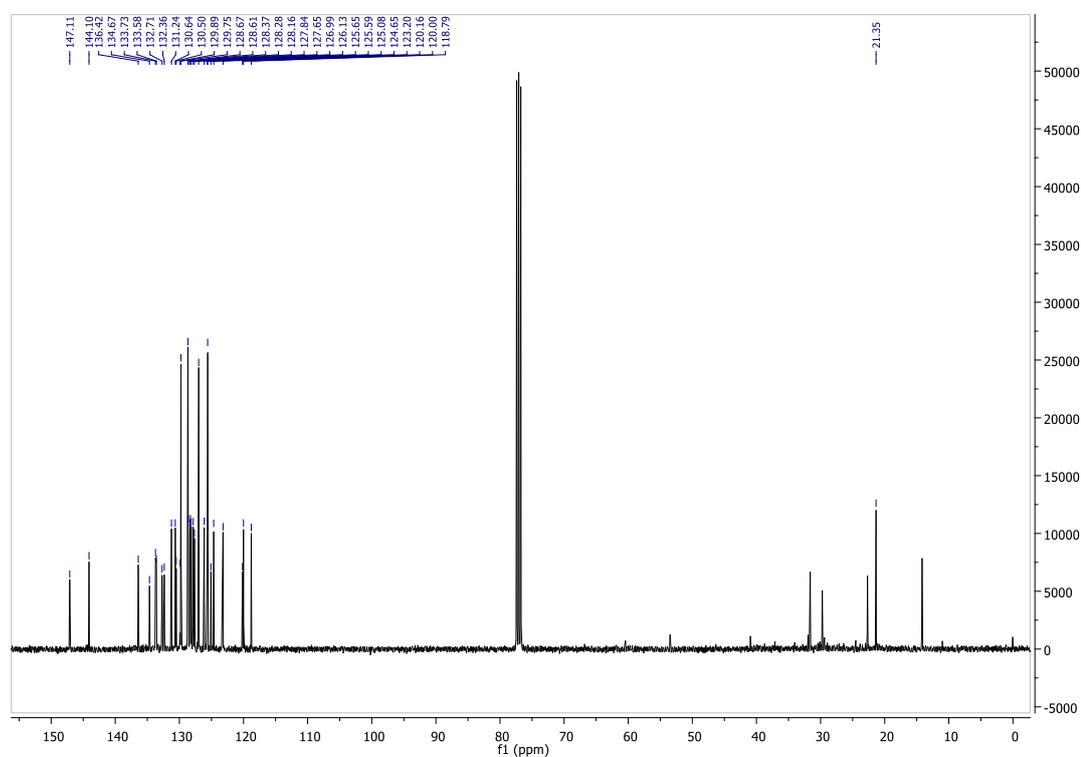
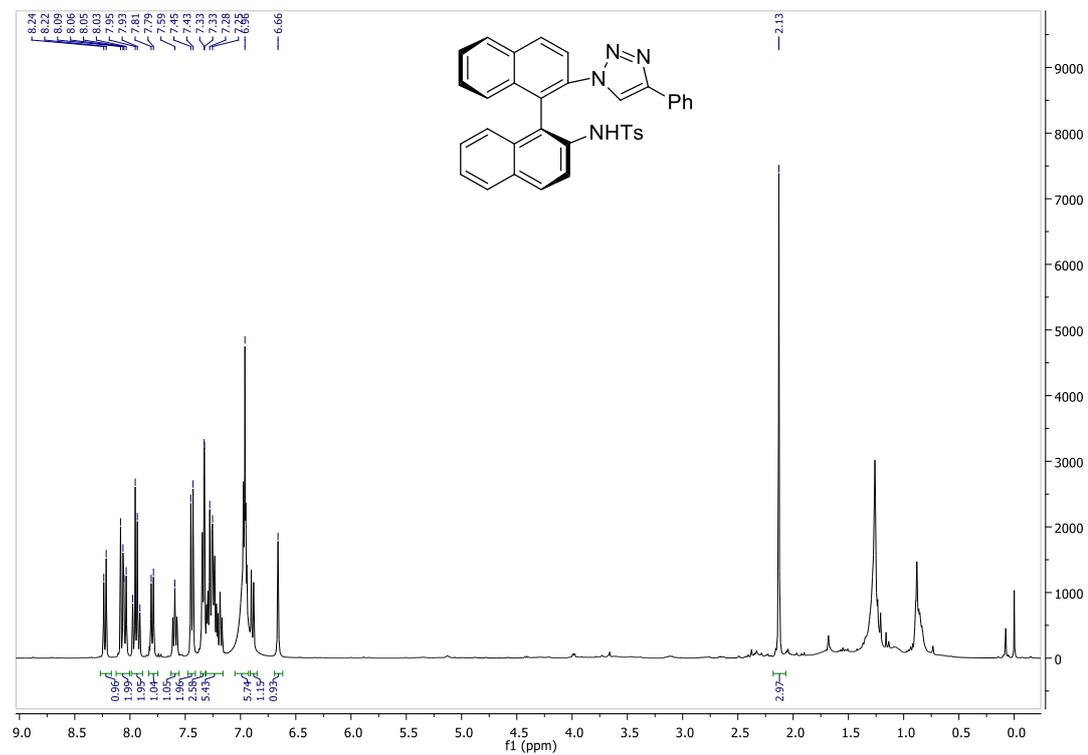
Compound 4.78



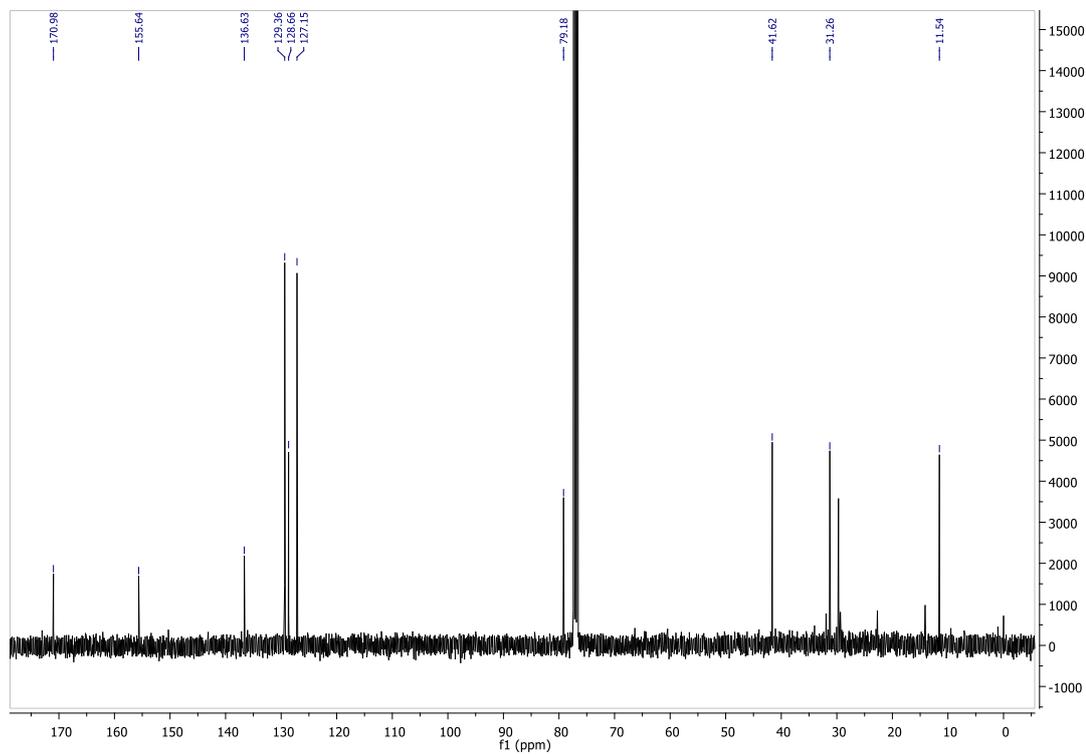
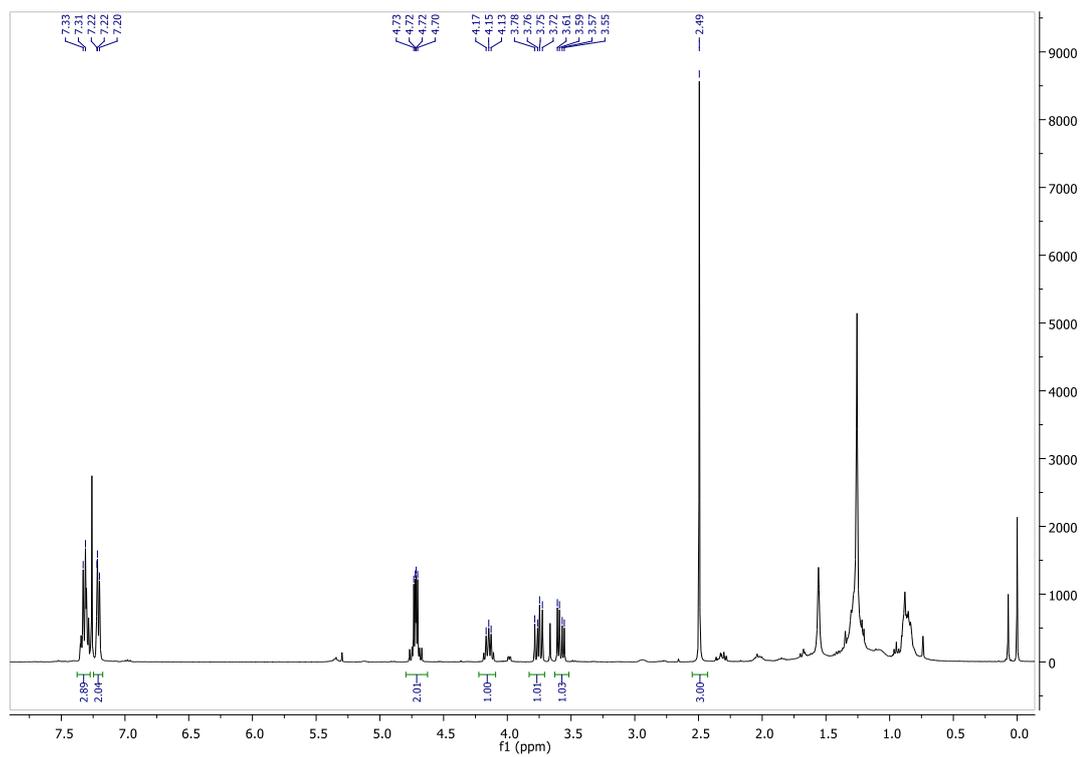
Compound 4.79

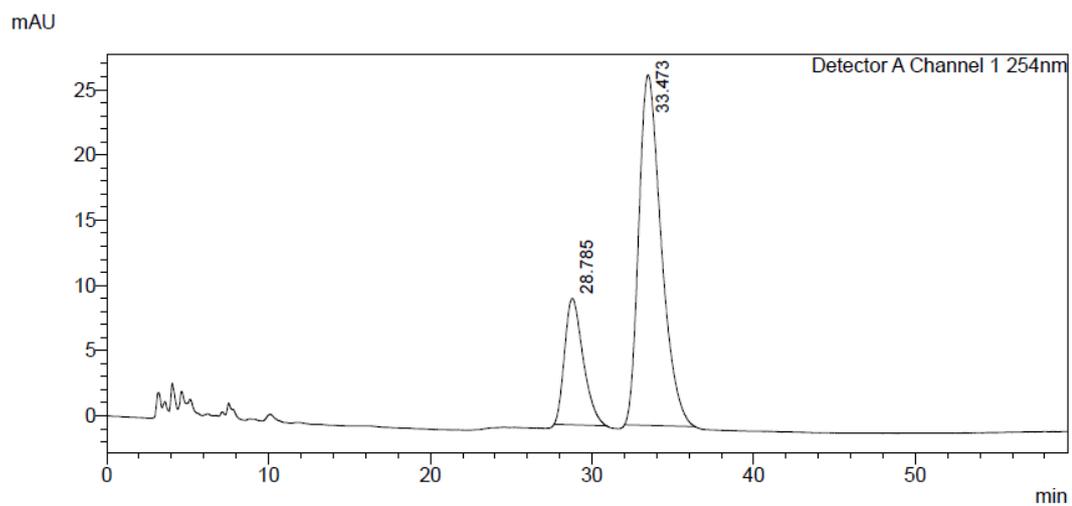


Compound 4.83



Compound 4.98





Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	28.785	773278	9692	0.000	mg/L		R
2	33.473	2591739	26857	0.000	mg/L		S
Total		3365017	36549				

