The Investigation of Methylmagnesium Chloride as a Non-Nucleophilic Base

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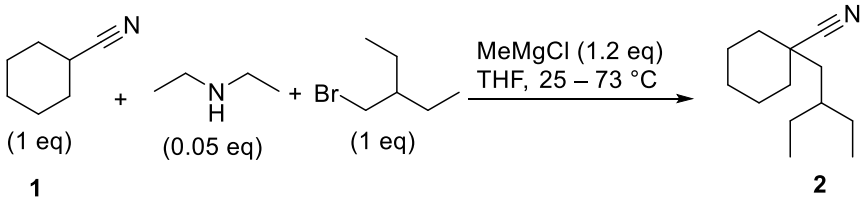
Abstract

The use of methylmagnesium chloride (MeMgCl) as a non-nucleophilic base is explored in this thesis.

Grignard reagents react in nucleophilic addition reactions with nitriles yielding a ketone upon work-up, but in the research discussed in this thesis, they are employed in deprotonation alpha to the nitrile resulting in the formation of an anion which can then undergo a S_N2 reaction with an alkyl halide.

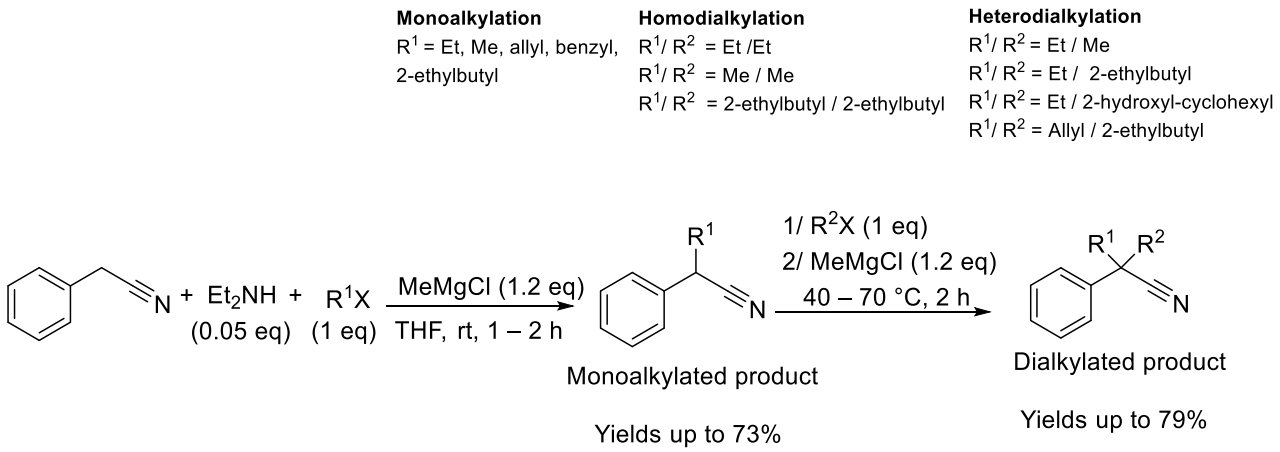
The pharmaceutical company Roche Ireland Ltd developed a new convenient synthetic procedure for the synthesis of 1-(2-ethylbutyl) cyclohexane-1-carbononitrile **2**, where MeMgCl plays the role of a non-nucleophilic base when used with catalytic amounts of an amine. The main objective of this thesis was to explore extending the applications of the MeMgCl methodology shown in Scheme 1 by replacing ethylbutyl bromide with other electrophiles and by substituting cyclohexanecarbonitrile with other nitriles and substrates bearing other electron-withdrawing groups.



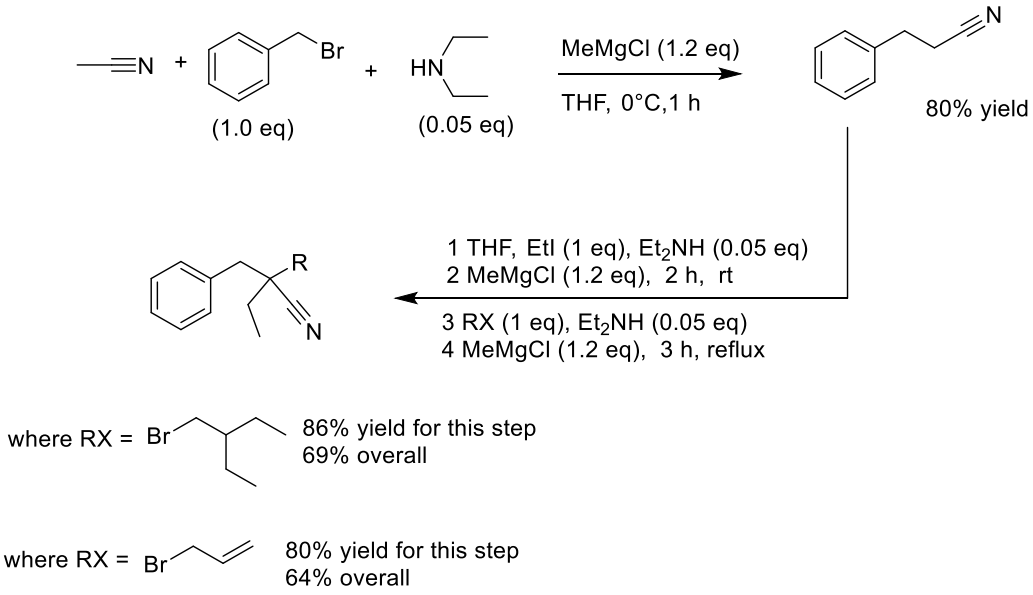
Scheme 1: Alkylation of cyclohexanecarbonitrile **1**.

The introductory chapter includes an overview of the different reaction types studied in this thesis where we used Grignard reagents, describing their importance, their applications and previously reported synthetic methods.

Chapter Two begins by discussing our initial work to explore the range and scope of this methodology in the formation of quaternary centres *via* the alkylation of cyclohexanecarbonitrile **1** and isobutyronitile with different alkyl halides, followed by the mono- and dialkylation of phenylacetonitrile (Scheme 2) and trialkylation of acetonitrile (Scheme 3). The reactions gave the desired product in excellent conversions (>90%) and moderate to high yields.



Scheme 2: Mono- and di-alkylation of phenylacetonitrile



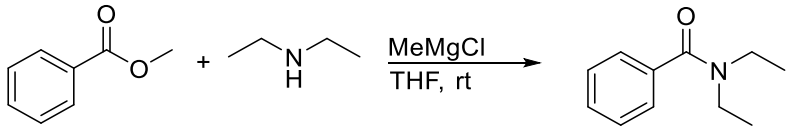
Scheme 3: Alkylation of acetonitrile.

Addition reactions with oxygen-containing electrophiles as well as electrophiles with conjugated systems are also explored. The addition of a copper salt in addition reactions involving conjugated systems promoted reaction in a 1,4 manner. In some cases, 1,4-addition reactions were observed without the addition of a copper salt.

Asymmetric alkylation was investigated by the incorporation of a chiral amine and/or a bis(oxazoline) ligand and a second metal into the reaction without being able to demonstrate enantioselectivity.

The efficient and clean one-pot synthesis of several secondary and tertiary amides using a method similar to the Bodroux reaction is described. The amides were formed from precursor

carboxylic acid esters by reaction with an amine deprotonated by the Grignard reagent (Scheme 4). The scope and efficiency of this reaction was demonstrated by coupling a variety of amines and esters using MeMgCl. The reaction of ethanolamine with methyl benzoate to form *N*-(2-hydroxyethyl)-benzamide is also reported.



Scheme 4: Amide formation.

The use of dialkyl carbonates in place of esters opened a synthetic route for the formation of carbamates and both symmetrical and non-symmetrical ureas. All reactions were monitored by GC-MS and gave the product in moderate to good yields.

The operational and environmental advantages of methylmagnesium chloride over the commonly used non-nucleophilic bases such as lithium diisopropylamine are discussed.

The final chapter contains the full experimental details, including the spectral and analytical data for the compounds synthesised during this research.

Abbreviations

br	broad
br s	broad singlet
$BMIMBF_4$	1-butyl-3-methylimidazolium tetrafluoroborate
°C	degrees Celsius
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublet
dq	doublet of quartet
dtd	doublet of triplet of doublets
d.r.	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIPA	diisopropylamine
DMPU	*N*,*N*′-dimethylpropyleneurea
ee	enantiomeric excess
e.r.	enantiomeric ratio
eq	equivalent
g	grams
GC-MS	gas chromatography – mass spectrometry
h	hours
HPLC	high performance liquid chromatography
HMQC	heteronuclear shift multiple quantum coherence
HRMS	high-resolution mass spectrometry
IR	infrared spectroscopy
mmol	millimoles
min	minutes
m	multiplet
M	molar
mg	milligrams
MHz	megahertz
mL	millilitre
mm Hg	millimetres of mercury
mol	moles
m/z	mass/charge ratio
mp	melting point
MPa	megapascal

MS	molecular sieves
NaBARF	sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NMR	nuclear magnetic resonance
ppm	parts per million
PMB	para-methyloxybenzyl
Pdt	product
q	quartet
rt	room temperature
s	singlet/Seconds
SM	starting material
t	triplet
TBDMS	tert-Butyldimethylsilyl
TLC	thin layer chromatography
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMPMgCl	2,2,6,6-tetramethylpiperidinylmagnesium chloride

Chapter 1: Introduction

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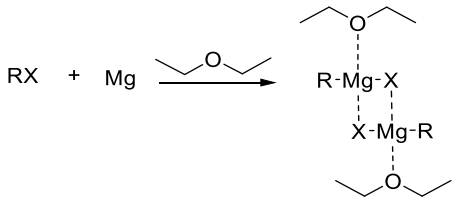
Grignard reagents in organic chemistry

Grignard reagents, named after the Nobel prize-winning French chemist Victor Grignard,[1] are organomagnesium halides with the formula RMgX, where X is a halogen and R is an alkyl, alkenyl or aryl group. Organomagnesium compounds are among the most useful organometallic reagents and have proved to be an extremely powerful synthetic tool in organic synthesis because of their easy accessibility and high reactivity.[2] The chemistry of organomagnesium compounds is characterized by the polarized carbon-magnesium bond, which leads to a negatively charged carbon atom or "carbanion". Grignard reagents are commonly prepared by reacting magnesium metal with an organic halide in an ethereal solvent (diethyl ether or THF) which stabilises the positive charge on the magnesium (Scheme 5).[3,4]



Scheme 5: Grignard complex.

Additionally, there have been several other methods developed for the preparation of Grignard reagents such as: transmetalation,[5] sulfoxide/magnesium exchange[4] and carbenoid-homologation.[6] Grignard reagents are very reactive nucleophiles. They are widely used as carbanionic species in nucleophilic additions, substitution reactions (Figure 1) and in a range of other transformations.

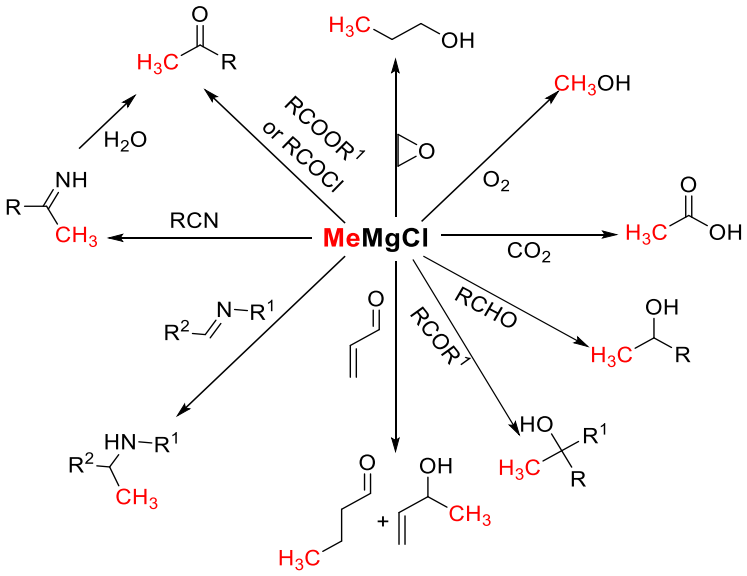
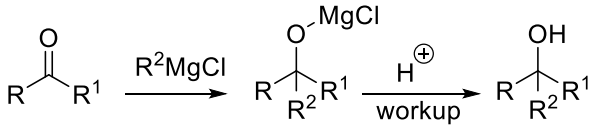


Figure 1: Applications of Grignard reagents.

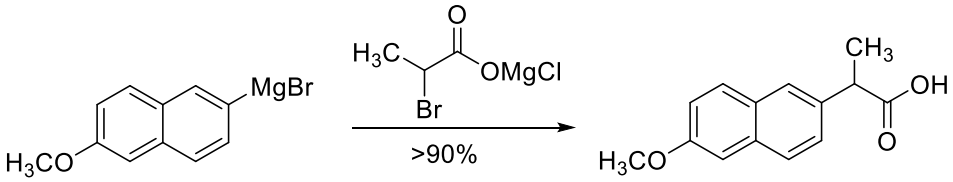
The reaction of Grignard reagents with carbonyl compounds (aldehydes, ketones, esters, carbon dioxide (CO_2)) and epoxides are amongst the most useful reactions in organic chemistry for the formation of new carbon-carbon bonds. Carbon-carbon bonds constitute the "backbone" of molecules in organic chemistry thus formation of these bonds is a key synthetic objective.

The formation of alcohols by reaction of a Grignard reagent with aldehydes or ketones is a common reaction in industry[7] (Scheme 6). The reaction is versatile and has a very broad scope where the Grignard is concerned as they can be aliphatic, aromatic or heteroaromatic.



Scheme 6: Alcohol formation *via* addition of a Grignard reagent to a carbonyl.

The reaction of Grignard reagents with alkyl halides is quite rare. In certain cases Grignard reagents can undergo nucleophilic substitution with alkyl halides.[8] Scheme 7 shows an example of the coupling of a Grignard reagent with an alkyl halide in the synthesis of naproxen.[9]

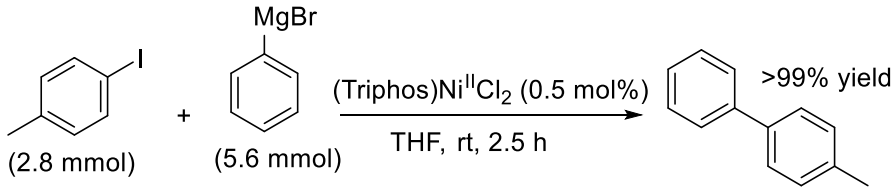


Scheme 7: Grignard reaction with an alkyl halide.

Though in some cases it is possible for Grignard reagents to react with alkyl halides, the reaction usually produces a mixture of products. Effective coupling methods have since been developed, involving the presence of metal catalysts. The reaction of Grignard regents with alkyl halides/tosylates in the presence of a metal catalyst is known as the Kumada coupling.[10,11] The Kumada coupling developed in 1972, was the first cross coupling reaction and widely employs the use of nickel and palladium catalysts (Scheme 8). When nickel is the chosen catalyst, the catalytic cycle begins with oxidative addition of the organohalide to Ni(0) to form a Ni(II) complex, this is followed by transmetalation with the Grignard reagent, where the group on the Grignard reagent replaces the halide anion on the nickel complex and makes

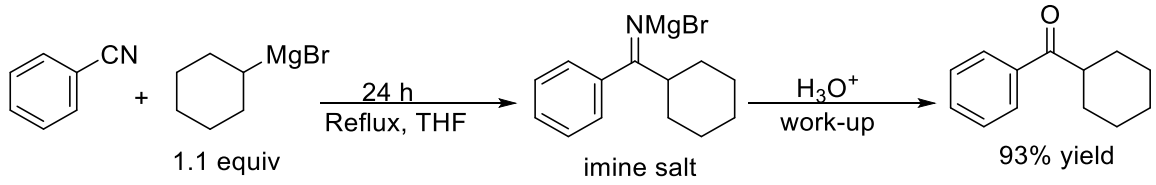
a magnesium(II) halide salt. The final step is the reductive elimination which gives the final coupled product and regenerates the catalyst.

In these reactions, the halide partner is limited to use of aryl or vinyl halides.



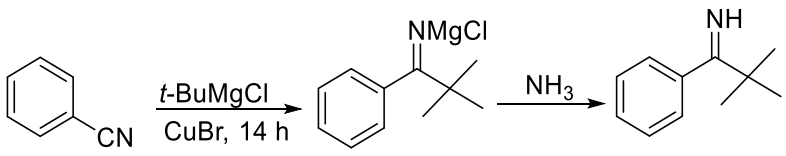
Scheme 8: Nickel-catalysed Kumada cross coupling reaction.[12]

The reaction of Grignard reagents with nitriles yields imines which on hydrolysis give ketones (Scheme 9). Although the addition of Grignard reagents to nitriles has been known for a long time, these reactions can require harsh conditions such as refluxing in high boiling solvents such as toluene[13,14] or the use of excess amounts of the Grignard reagent.[15]



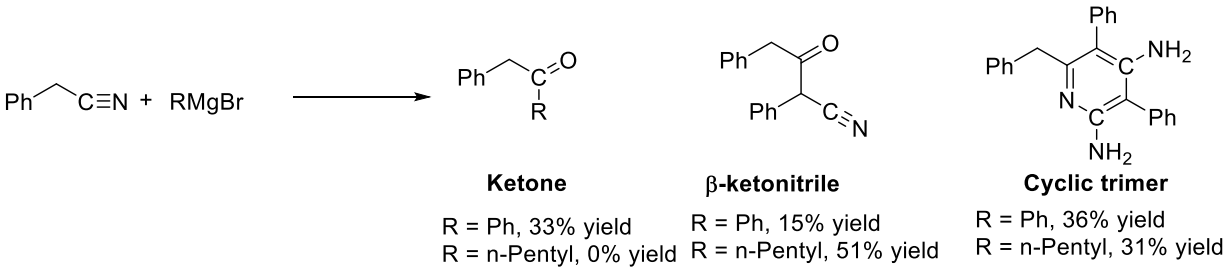
Scheme 9: Ketone synthesis from Grignard addition to a nitrile.

Though often the ketone is the target product the imine intermediate can, if required, be isolated from the reaction of nitriles with Grignard reagents.[16] Previous research on this suggests the need for refined conditions to obtain the desired product in high yield. In the reaction of *t*-butylmagnesium chloride with benzonitrile at reflux a low yield of 14% for the ketimine was obtained after 14 hours. However, when CuBr, a nucleophile activator, was added the yield increased to 83% after reacting for 1 hour and 95% after 14 hours.[17] These reactions were worked up by addition of anhydrous ammonia (Scheme 10).[13,18]



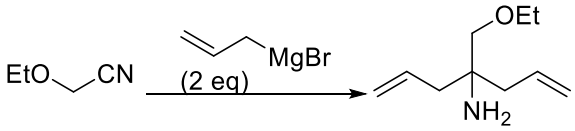
Scheme 10: Ketimine from *t*-butylmagnesium chloride and a benzonitrile.

Where nitriles bear α-hydrogen(s), there is competition between α-deprotonation and nucleophilic attack of the nitrile.[19] Hauser et al., showed that aromatic Grignard reagents favour nucleophilic attack while aliphatic Grignard reagents promote deprotonation (Scheme 11). This is observed in the reaction of phenylacetonitrile with n-pentylmagnesium bromide, where the yield of ketone product from nucleophilic attack by Grignard on the nitrile was 0%, while the combined yields of β-keto nitrile and heterocyclization product arising from α-deprotonation of the nitrile was 82%. When phenylmagnesium bromide is used, the yield of ketone product was 33%, and the combined yields of ß-ketonitrile and heterocyclization product was 51% (Scheme 11).



Scheme 11: Reaction of Grignard reagents with phenylacetonitrile.

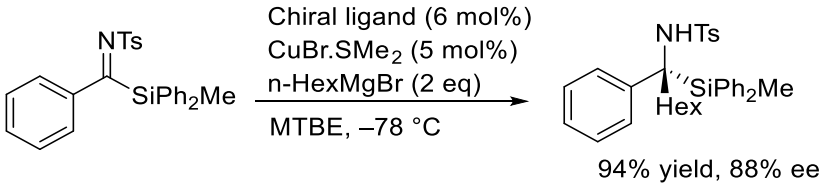
Double addition of Grignard reagents to a nitrile can be employed in the synthesis of amines (Scheme 12).[20,21] The amine products are produced from the intermediate imines. The use of excess amounts of Grignard allows for total conversion of the nitrile and a high yield of the amine product.



Scheme 12: Double addition of Grignard reagent with a nitrile.

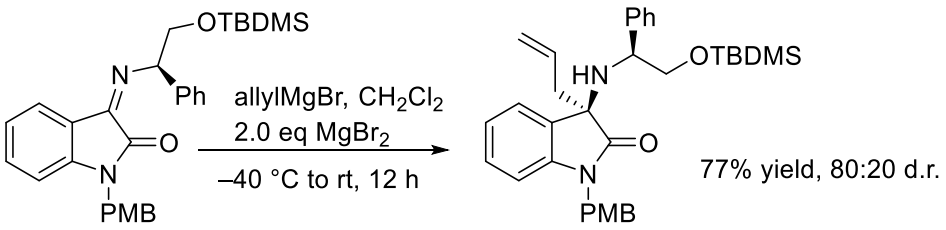
The reaction of imines with Grignard reagents has shown potential in the field of enantioselective synthesis.[20,22,23] Chiral amines are extremely important and are commonly seen in bioactive molecules.

Rong[22] reports the synthesis of *N*-sulfonyl protected α-chiral silyl amines from the addition of Grignard reagents to aromatic silyl ketimines (Scheme 13). The reaction is promoted by a copper-based chiral catalyst and produces the chiral amine in high yields and high enantioselectivity.



Scheme 13: Asymmetric alkylation of a ketimines.

Silvani and co-workers reported the synthesis of optically enriched 3-substituted 3-aminooxindoles from the reaction of a Grignard reagent and an imine derived from isatine (Scheme 14) in moderate yields and in good diastereoselectivity.[24]



Scheme 14: Addition of Grignard reagents to a derived imine.

3-Substituted 3-amino-2-oxindoles are a useful class of compounds and are found in several drug candidates, examples include AG-041R,[25] a gastrin/CCK-B antagonist and SSR149415,[26,27] a vasopressin V_{1B} receptor antagonist (Figure 2).

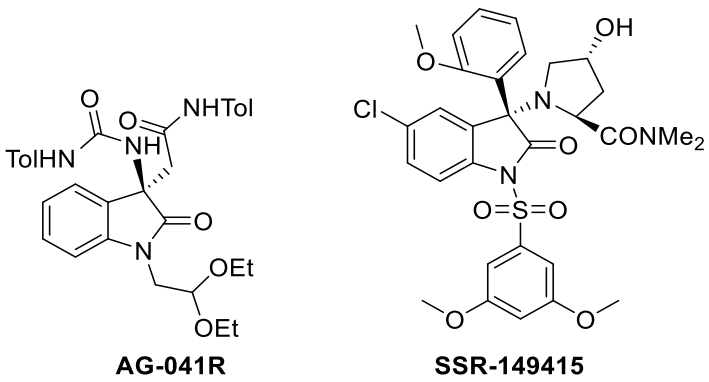


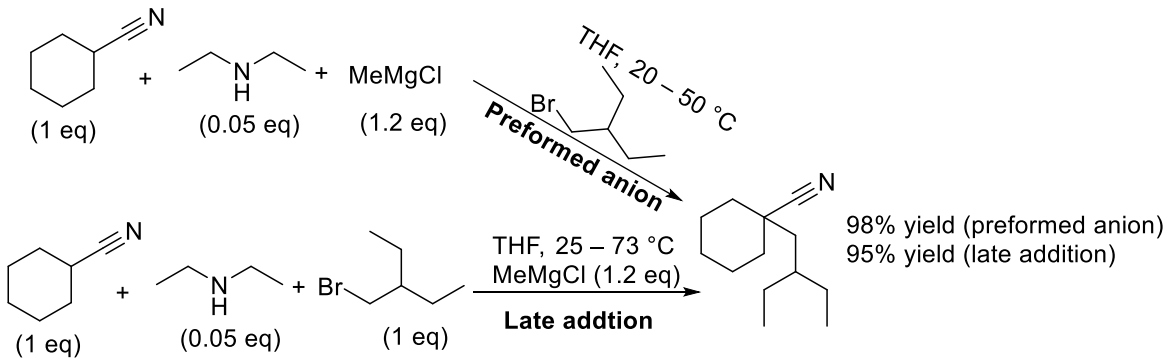
Figure 2: Bioactive aminooxindole compounds.

The use of Grignard reagents offers an advantage over other organometallic reagents as they are easy to handle, inexpensive and readily available.[22]

1.1 Methylmagnesium chloride as a non-nucleophilic base

Methylmagnesium chloride (MeMgCl) has gained importance in synthesis as it can be used as a cheap, accessible and relatively stable reagent. MeMgCl is a key reagent industrially and in research. It is applied in a wide variety of synthetic applications.[28] In 2009 and 2012, the pharmaceutical company Roche published patents for a new process in which they described the use of methylmagnesium chloride with a an amine mediator in the deprotonation of cyclohexanecarbonitrile, the resulting anion being successfully alkylated (Scheme 15). The two patents dealt with the same reaction, the difference being whether the Grignard was added prior to the alkylating agent resulting in formation of the anion first[29] or whether the Grignard was added last in a so called 'late addition' method (Scheme 15).[30] The advantages of the "late addition" method were that it simplified manufacturing operations and minimised formation of by-products arising from reaction of the preformed anion with the precursor nitrile.[19]

In general, basic reagents are defined as having a strong affinity for protons while nucleophilic reagents are defined as having a strong affinity for electron deficient carbons in a molecule. Grignard reagents are generally known to undergo nucleophilic additions with nitriles but, although only 5 mol% of the amine mediator was used, there was virtually no direct attack by MeMgCl on the nitrile. The absence of the amine promotes a nucleophilic addition reaction which produces the ketone, acetylcyclohexane.



Scheme 15: Synthetic route by Roche.

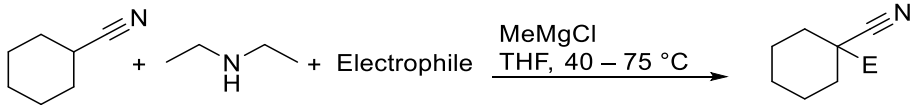
The traditional method for this type of alkylation involves the use of lithium diisopropylamide (LDA) which is generated by the reaction of *n*-butyllithium (*n*-BuLi) with diisopropylamine. BuLi, which is available only in hexanes or similar solvents, is difficult to handle on a lab scale and represents a serious risk on plant scale. BuLi and THF are incompatible on industrial scale as BuLi reacts with THF above about 0 °C to give acetaldehyde lithium enolate (CH_2CHOLi).[31] The use of LDA involves the use of a full equivalent of amine base which increases costs, waste and isolation issues. Although LDA has low nucleophilicity and high kinetic basicity, it

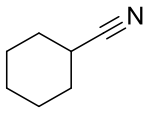
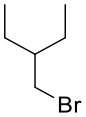
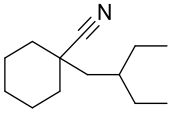
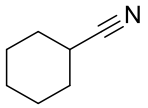
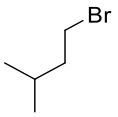
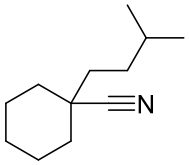
is pyrophoric, as are the alkyllithiums used to prepare it. Therefore, use of Grignard reagents in these applications is attractive industrially as they are easily prepared and are more acceptable in terms of compatible solvents, such as THF, and the reactions are conducted at temperatures between 25 – 75 °C.

At the start of this project a number of smaller preliminary studies had been conducted in our research group. The results obtained from those preliminary studies indicated that MeMgCl acting as a non-nucleophilic base offered a method for alkylation of nitrile compounds.

Tables 1a and 1b detail these, as yet unpublished,[32] preliminary reactions studying alkylation reactions *via* the 'late addition' of Grignard and *via* the 'preformed anion' method on cyclohexanecarbonitrile using a variety of electrophiles.

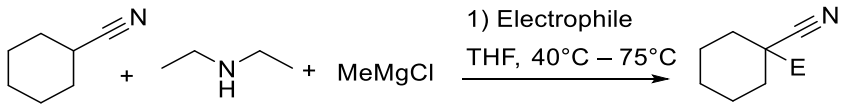
Table 1a: Alkylation of nitriles *via* 'late addition'

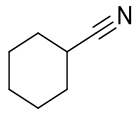
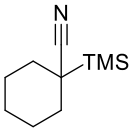
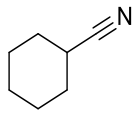
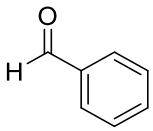
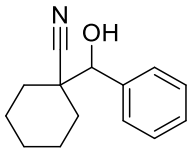


Substrate	Electrophile	Expected product	Yield[a]	Conversion[b]
			89%	100%
			65%	100%

a) Based on yield of isolated product **b)** Based on GC-MS; **Reaction conditions:** 1 eq cyclohexanecarbonitrile, 1 eq electrophile, 0.05 eq diethylamine 1.2 eq MeMgCl, at 40 to 75 °C.

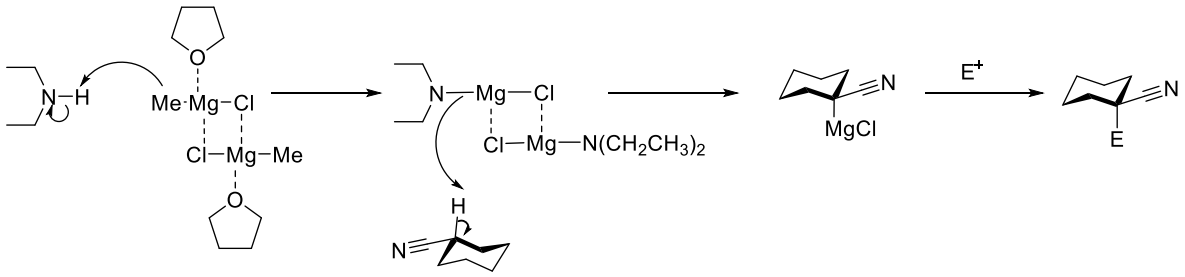
Table 1b: Alkylation of nitriles *via* 'preformed anion'



Substrate	Electrophile	Expected product	Yield[a]	Conversion[b]
	TMSCl		23%	26%
			71%	100%

a) Based on yield of isolated product **b)** Based on GC-MS; **Reaction conditions:** 1 eq cyclohexanecarbonitrile, 1 eq electrophile, 0.05 eq diethylamine 1.2 eq MeMgCl, at 40 °C to 75 °C.

A simple mechanism for this reaction begins with methylmagnesium chloride acting as a base and deprotonating diethylamine. The resulting diethylamide species deprotonates the cyclohexanecarbonitrile at the C-2 position. The anion then undergoes an S_N2 reaction with the alkyl halide or other electrophiles (Scheme 16).



Scheme 16: Deprotonation of cyclohexanecarbonitrile with MeMgCl and diethylamine.

In Roche, the reaction outlined in entry 1 of Table 1a gave yields of ≥96% at plant scale and this reaction was used to produce a precursor for the pharmaceutically active drug dalcetrapib (Figure 3).

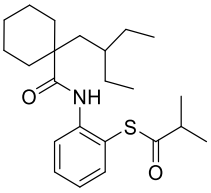
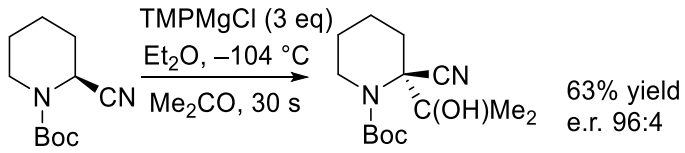


Figure 3: Dalcetrapib.

Dalcetrapib, a CETP (cholesteryl ester transfer protein) inhibitor[33] was designed to improve cardiac health by increasing the ratio between the high-density lipoprotein (HDL, “good cholesterol”) and low-density lipoprotein (LDL, “bad cholesterol”). Unfortunately, this compound was withdrawn from trial by Roche in 2012 after failing in clinical trials due to issues relating to the efficacy of the drug.[34]

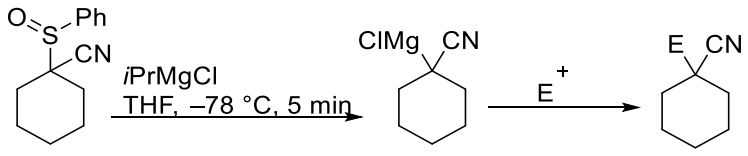
Besides the work reported by Roche, there are a few isolated examples in the literature where a Grignard acts as a non-nucleophilic base. The main difference between these reports and the work described in this thesis is that previous reports involve nitriles adjacent to activating groups[35–37] whereas the work carried out for this thesis does not depend on activating groups. The example shown in Scheme 17 is from a paper where Coldham[37] reports the rapid deprotonation of a chiral nitrile with TMPMgCl and subsequent reaction of the deprotonated species with a variety of electrophiles showing very little scrambling of the chirality, yielding highly enantiomerically enriched 2-substituted nitrile products. He also reports similar reactions with carbamate groups adjacent to the nitrile and different electrophiles.[35]



Scheme 17: Coldham et al’s deprotonation *via* magnesium bases.

Another example is shown by Fleming, albeit not involving a deprotonation but a sulfinyl-metal exchange with sulfinylnitriles and an organomagnesium. He reports the use of *i*-PrMgCl in a rapid exchange with quaternary, tertiary, and sp^2-hybridized sulfinylnitriles into C-magnesiated nitriles. The resulting species react with a diverse array of electrophiles and potentially acidic functionalities (Scheme 18).[38,39]

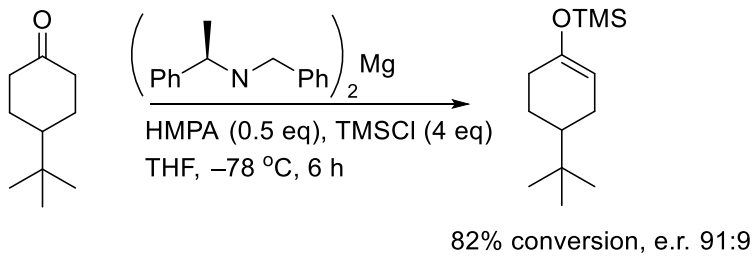
In both examples shown no addition of the Grignard reagent to the nitrile is reported.



Scheme 18: Nitrile alkylation through sulfinyl–metal exchange

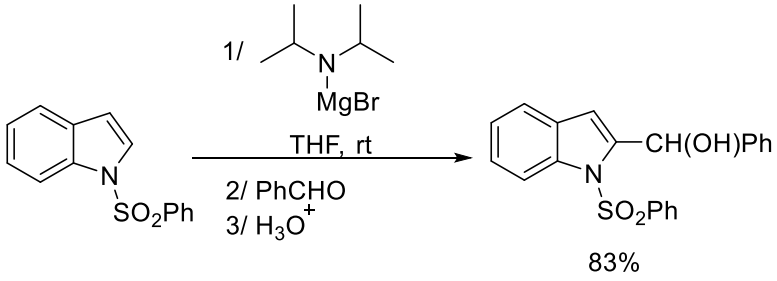
Searching the literature, we found related magnesium amide bases have been used in deprotonating adjacent to other functional groups such as ketones and carboxylic acids.[40,41]

Kerr reports the use of chiral magnesium bisamide reagents in the enantioselective deprotonation of prochiral ketones obtaining high enantioselectivity in the formation of the enol ether product (82% ee) (Scheme 19).



Scheme 19: Silyl enol ether formation with a magnesium amide base.

Magnesium amide bases have also been used to deprotonate C-H of aromatics.[42] Sakomoto reports the use of Hauser base in the deprotonation of an indole derivative (Scheme 20).



Scheme 20: Substitution of indole derivatives with a magnesium amide base.

1.2 Nitriles

Nitriles, also known as cyano compounds, are organic compounds with a (C≡N) functional group. Nitriles are useful compounds and have found use in daily life life e.g. cyanoacrylates are used in super-glue.[43] Another widely used nitrile is acrylacetonitrile which when converted into a polymer is useful in synthetic rubbers and in thermoplastic resins.[44]

Nitriles are invaluable intermediates in synthesis and can be converted into a range of diverse organic compounds because of the unique and versatile reactivity of the cyano functional group. The nitrile functional group can be transformed into other functional groups, such as esters, amines, carboxylic acids, amides, aldehydes, and heterocycles.[45,46]

Alkylnitrile moieties are found in many pharmaceuticals[47] and natural products[48] (Figure 4). Many of them exhibit remarkable bioactivities which allow them to be used extensively in the pharmaceutical industry hence are of great interest both in research and industrally.[47] Figure 4 shows examples of biologically active compounds used as drugs. They all contain nitriles and the nitrile is key to their interactions in the body. Interestingly some of the nitrile compounds exhibit different types of interaction, showing the versatility of the nitrile in drug compounds. The two nitriles present in the anticancer drug, anastrozole **3**, have been reported to potentially engage in two key hydrogen bonds with an adjacent serine residue,[49] while the nitrile in cilomilast **4** interacts with the amino acids, methionine and leucine.[47]

Syntheses of many nitrile-containing pharmaceuticals typically involve elaboration of a simpler nitrile using multiple alkylations. This is particularly true in the synthesis of those bearing quaternary centres, such as anastrozole **3** and the cyclohexylnitriles cilomilast **4** and levocabastine **6**.

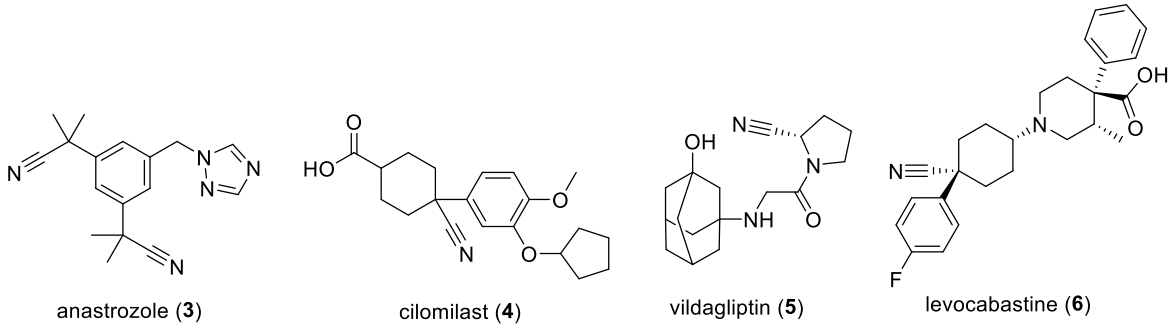
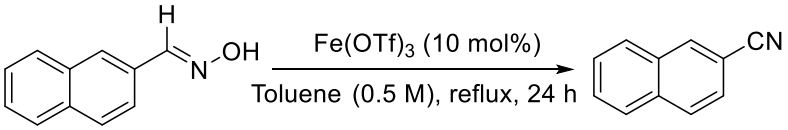


Figure 4: Bioactive pharmaceutical nitriles.

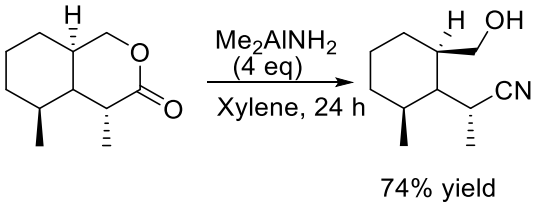
Synthetically, the nitrile functional group can be accessed *via* numerous routes such as substitution reactions of alkyl halides with cyanide salts,[50,51] which involve phase-transfer reactions using an ammonium salt.

Nitriles can also be accessed through catalytic dehydration reactions of aldoximes.[52–54]
In the past, this reaction was performed normally in nitrile-containing solvents, but in recent years Hyodo reports optimising conditions for the reaction where the use of neither stoichiometric reagents nor a nitrile containing solvent is required (Scheme 21).[55]



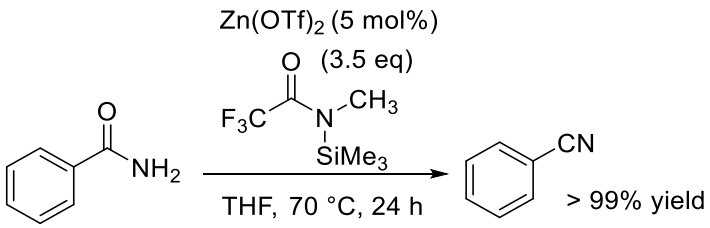
Scheme 21: Dehydration of an aldoxime to a nitrile.

The reaction of esters with aminodimethylalane[56,57] is another known route to nitriles. Weinreb[58] reports a one-step conversion of a lactone to a nitrile using excess amounts of dimethylaluminum amide in refluxing xylene. This method offers a broad functional group scope and has been utilised as part of the total synthesis of tetronomycin (Scheme 22).



Scheme 22: Direct conversion of a lactone to a nitrile.

Amide dehydration is one of the fundamental methods to produce nitriles.[59,60] In the past, amide dehydration reactions have been performed using strongly acidic dehydrating agents such as thionyl chloride, phosphorus pentoxide and phosphorus oxychloride.[61] Sodium borohydride has also been used in this type of reaction.[62]
A more recent report by Enthaler[59] shows the use of the commercially available *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) as a dehydration reagent in zinc-catalysed dehydration of amides to the corresponding nitriles (Scheme 23) in high yields.

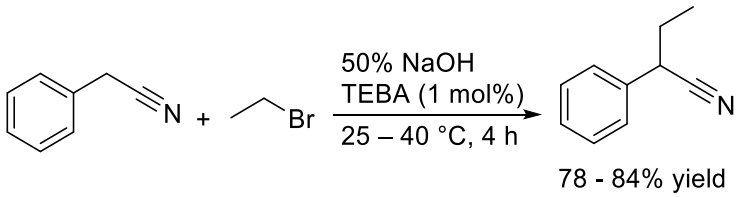


Scheme 23: A zinc–catalysed dehydration of a primary amide to a nitrile.

As previously mentioned, existing nitriles can be elaborated *via* deprotonation α to the nitrile using a strong base and alkylation of the resulting anion[63] or using other methods involving catalytic generation of metalated alkylnitriles.[64]

1.2.1 Base promoted α-deprotonation of nitriles

The most convenient method for the generation of nitrile anions is by deprotonation. This has been achieved using an array of different bases.[65] As the *pKa* values of nitriles span a wide range, the choice of base is substratedependent. In general, more acidic nitriles such as arylacetonitrile (phenylacetonitrile *pKa* 21.9) are deprotonated by bases such as hydroxide, alkoxide or solid K_2CO_3 under phase-transfer conditions. The procedure used in the alkylation of phenylacetonitrile is shown below (Scheme 24).[66–69]



Scheme 24: Phase transfer catalysed alkylation of phenylacetonitrile.

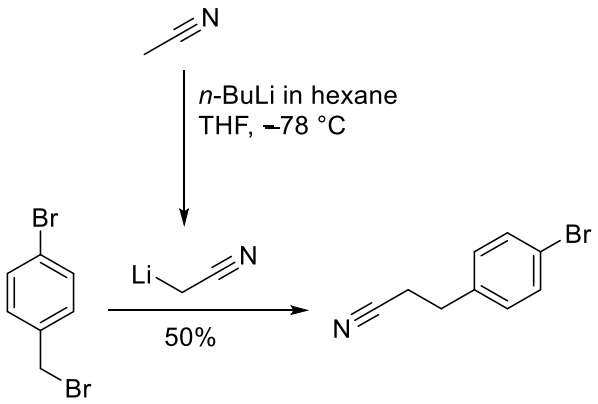
This reaction requires alkylammonium ions [benzyl triethylammonium chloride (TEBA) or tetra-n-butylammonium bromide, TBAB] as the phase-transfer catalyst and is carried out in a two-phase mixture (water and an immiscible organic solvent) to prevent the hydroxide and alkyl halide from reacting together in an S_N2 reaction to give an alcohol. The hydroxide stays in the aqueous layer, and the other reagents stay in the organic layer. Some hydroxide interacts with the phase-transfer catalyst and thus can pass into the organic layer allowing the deprotonation to occur.

Less acidic nitriles such as alkylnitriles (acetonitrile, *pKa* 31.3) require the use of strong bases such as metal amides ($NaNH_2$[70] or organolithium reagents) generating metalated nitriles.[8]

Lithium reagents such alkyllithiums and lithium amides[71] are the most common bases employed in the deprotonation of alkylnitriles. Of the two, lithium amides are most often employed.

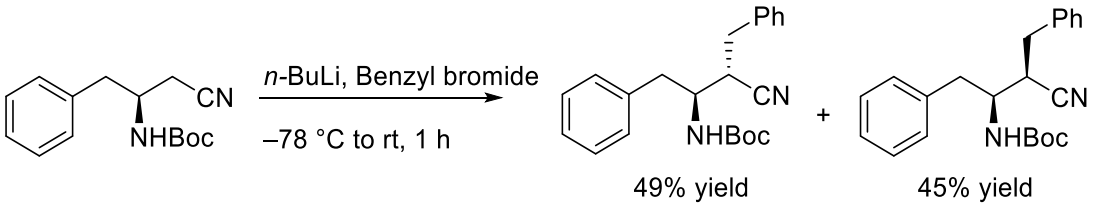
Alkyllithium bases, such as *n*-BuLi, although strong bases, are also powerful nucleophiles. Compared to *t*-butyllithium and *s*-butyllithium, *n*-butyllithium is less basic.[72]

There are very few examples reported of the use of *n*-BuLi in the deprotonation of nitriles. One example, reported by Taber,[73] is shown in Scheme 25, where he reports the direct alkylation of lithioacetonitrile. The lithioacetonitrile was prepared by the addition of *n*-BuLi to acetonitrile. The reaction was conducted at –78 °C and gave a 50% yield.



Scheme 25: Alkylation of acetonitrile using n-BuLi.

Another example is shown by Longobardo,[74] where he reports the use n-BuLi as base in the alkylation of *N*-(Boc)-β^3-amino nitriles to give equimolecular mixtures of *syn*- and *anti*-disubstituted β-amino nitriles (Scheme 26).



Scheme 26: Use of n-BuLi in the alkylation of β-amino nitriles.

As previously stated, the use of sterically hindered lithium amide bases such as lithium diisopropylamide (LDA) (diisopropylamine *pKa* ≈ 36), lithium hexamethyldisilazide[75] (LHMDS) (bis(trimethylsilyl)amine *pKa* ≈ 30) and lithium tetramethylpiperidide[76] (LTMP) (tetramethylpiperidine *pKa* ≈ 37) are commonly employed for the deprotonation of carbonyl compounds that have an acidic proton (Figure 5). These bases can be considered to exist as $Li^+NR_2^-$ and are generally known as non-nucleophilic bases due to their bulky, sterically hindered substituents.

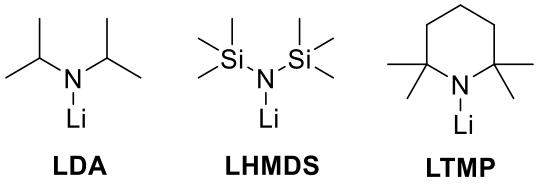
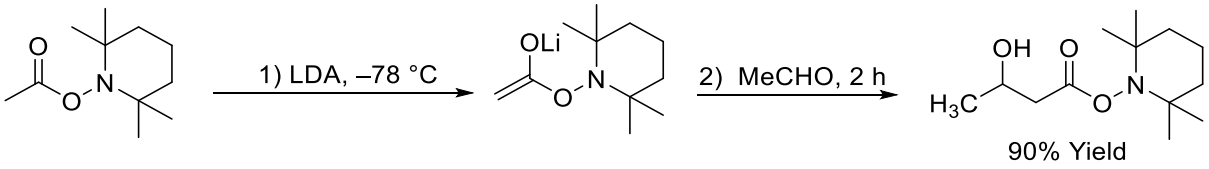


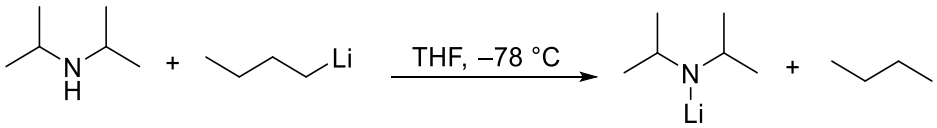
Figure 5: Lithium amide bases.

Of the three, LDA is the cheapest and most convenient base for deprotonations of carbonyl compounds (Scheme 27).[77] With LDA, deprotonation at low temperatures (–78 °C) in THF leads to the corresponding kinetic lithium enolate,[78] which then reacts with an alkyl halide or other electrophile *via* an S_N2 pathway.



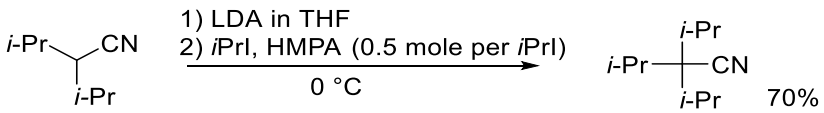
Scheme 27: Use of LDA in an Aldol reaction.

The formation of LDA is shown in Scheme 28, where LDA is prepared from the reaction of diisopropylamine (*i*-Pr_2NH) and *n*-BuLi.



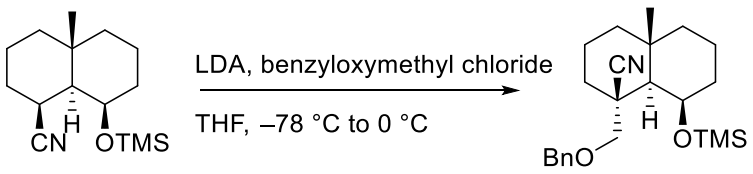
Scheme 28: Formation of LDA.

As the nitrile group mirrors the general reactivity of carbonyl groups, lithium amide bases[79] are also used to deprotonate alkylnitriles generating metalated nitriles, which are largely stabilized by inductive electron withdrawal rather than through resonance as is the case with enolates. Dubois[80] reports the alkylation of a sterically demanding nitrile (Scheme 29), where LDA is used in deprotonating diisopropylacetonitrile followed by subsequent alkylation with isopropyl iodide. The reaction was conducted at 0 °C and produced the nitrile product in a 70% yield.



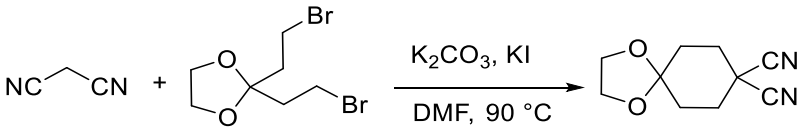
Scheme 29: Deprotonation and alkylation of diisopropylacetonitrile.

Tanaka[81] also reports the use of LDA in the high yielding alkylation of a cyclic nitrile in the total synthesis of scopadulin. This reaction was conducted at low temperatures (Scheme 30).



Scheme 30: Alkylation of a cyclic nitrile.

Where a methylene compound such as malononitrile is the starting nitrile, the reaction proceeds under mild conditions using a weak base, as the anion can be delocalized into the two nitrile groups. Weak bases such as primary and secondary amines[82] or carbonates[83,84] are sufficiently basic for deprotonation (Scheme 31).



Scheme 31: Reaction of malononitrile *via* initial deprotonation.

The use of organolithium reagents pose some issues on a large or manufacturing scale given the hazards/supply issues involved.

Alkyllithium compounds are pyrophoric, extremely flammable on exposure to air, and are generally sold as a solution in hexanes. The danger associated with alkyllithiums was tragically highlighted in a well-known fatal incident that occurred in a UCLA research lab in 2009,[85] where a research assistant, Sheharbano Sangji, died from burn wounds which arose from the ignition of *t*-BuLi as a result of its exposure to air.

Pyrophoric reagents are challenging to use and require many safety considerations for reaction set-up. A simple set-up has been developed to improve safety during fume hood transfer of air-sensitive and pyrophoric reagents from sure/seal bottles.[86] Although this set-up is applicable on laboratory scale, it is quite difficult to achieve on plant scale as this process requires the use of special containers and the appropriate engineering of the plant in order to manage the reaction vessels.

Another aspect to the use of alkyllithium regents is the choice of solvents in which they are available for use. *n*-BuLi is available only in alkane solvents such as hexanes or similar solvents, which are not green and not great solvents for polar molecules.[87] *n*-BuLi is incompatible with ether solvents such as THF on industrial scale and leads to the formation of acetaldehyde lithium enolate (CH_2CHOLi).[31] *n*-BuLi is also difficult to handle on a lab scale and represents a serious risk on plant scale. *n*-BuLi is nucleophilic and has a half-life in THF

of 1.8 hours at 20 °C.[88] Often, alkyllithiums are used to prepare LDA for use as a non-nucleophilic base.

At commercial scale, recycling of solvents is an economic and environmental essential.

Commercial LDA is only available in mixtures of solvents (typically THF, ethyl benzene and heptane) and the recovery of THF from the mixture of solvents from processes involving LDA is often not feasible without incurring excessive cost.

LDA in a THF/ethyl benzene mixture stored at 0 ˚C will decompose by 1% in 100 weeks but at 20 ˚C will decompose by 1% in 1.5 weeks.[89]

In addition, a common decomposition product of both LDA and alkyllithiums is lithium hydride (LiH). At a large scale the LiH can be deposited on storage vessels and transfer lines and its removal, deactivation and disposal can be highly hazardous and costly.

1.2.2 Metalated nitriles

Carbanions are organic intermediates that are commonly generated by proton abstraction. As carbanions are electron rich, they can react with electrophiles leading to the formation of carbon–carbon bonds. The general structure for carbanions is shown in Figure 6.

Figure 6: General carbanion structure.

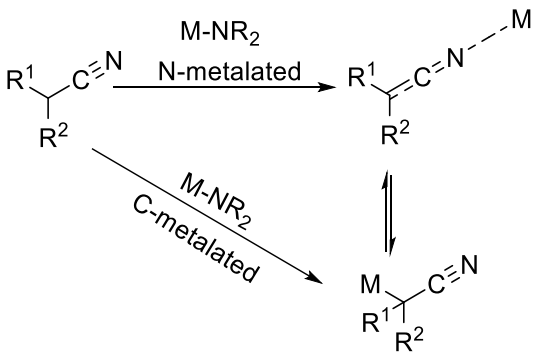
Enolates are one of the most-used type of carbanions and as nitriles have similar reactivity to carbonyls, deprotonation of a nitrile with a base also forms a carbanion. This carbanion is known as a metalated nitrile as the anion has a metal counter-ion.[62]

Metalated nitriles are powerful nucleophiles and are commonly employed in the alkylation of sterically hindered nitriles.[90,91] Metalated nitriles are chemical chameleons and exhibit unique reactivity in providing chemo, regio-, and stereo-selectivities.[64] The precise structure of metalated nitriles depends upon the metal, solvent, temperature and ligands.

The exceptional nucleophilicity of the metalated nitrile stems from the nitrile's high polar-inductive effect,[92] their excellent hydrogen bond acceptor properties,[93] and the extremely small steric demand of the CN group, with an A-value of only 0.2 kcal mol^{-1}. A-values are numerical values which aid in predicting the steric effect of a substituent.

Metalated nitriles can be generated from lithium amide bases or through organometallic-induced halogen−metal exchange.[94]

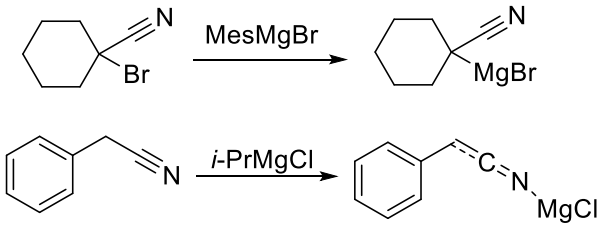
Metalated nitriles have two potential metal coordination sites (Scheme 32): N-metalation at the nitrile nitrogen and C-metalation at the formally anionic carbon.[18]



Scheme 32: Metalated nitrile.

In general, electropositive metals, such as lithium, and high-valent transition metals favour coordination to the electron-rich nitrile nitrogen, whereas less electropositive metals, and low-valent transition metals such as boron, magnesium, and zinc favour coordination at the nucleophilic carbon.[95]

One refinement of this general rule is magnesiated nitriles, which tend towards N-magnesiation of benzylnitriles and C-magnesiation of alkylnitriles (Scheme 33).[95]



Scheme 33: C- and N- magnesiation of a nitrile.

There are other reports in the literature which highlight some other reaction conditions that can influence the major magnesiated species present. When metal ligand complexes are involved the choice of the ligand can dictate the metal coordination site as illustrated in the ruthenium N- and C-phenylsulfonylacetonitriles **7** and **8** that can interconvert upon heating (Figure 7).[96] The position of equilibrium of **7** and **8** depends on the nature of the specific phosphine ligands used.

Solvent choice also has a dramatic influence on the metal coordination site.

NMR spectral analysis of lithiated acetonitrile with a chelating chiral amino ether ligand identified only the N-lithiated nitrile **9** in THF at −87 °C (Figure 7). However, in diethyl ether at −100 °C an equilibrium exists between **9** and the C- and N-lithiated nitrile **10**.[97]

The use of ^{13}C NMR spectra provides an excellent method for determining the metal coordination in metalated nitriles because the chemical shift of the nitrile carbon is sensitive to the local environment.[98] The ^{13}C NMR signal for the nitrile carbon of N-metalated nitriles containing a transition metal counter ion, lies in the range δ = 140–157 ppm whereas for the corresponding C-metalated nitriles it lies between δ = 115–138 ppm.[95]

These chemical shift ranges correlate to those seen for the ruthenium-complexed phenylsulfonylacetonitriles **7** and **8,** where the ranges are δ = 140–155 ppm for the N-coordinated, **7** and δ = 110–125 ppm for the C-phenylsulfonylacetonitriles **8**.

In contrast, the chemical shifts of the nitrile carbon in the equilibrating lithiated acetonitrile **9** and **10** are δ = 155.3 ppm for the N-lithiated nitrile and δ 148.5 ppm for the C-lithiated nitrile (Figure 7). The C-lithiated nitrile **10** resonance shows that while not purely N-lithiated it is not purely C-lithiated either showing the complexity of these systems.

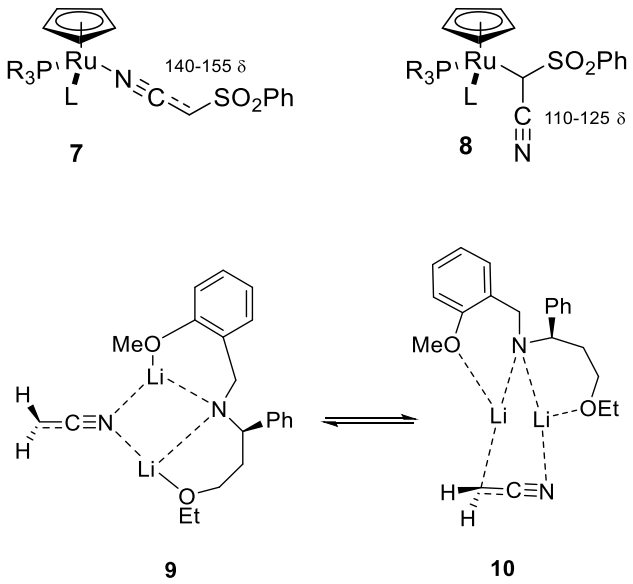


Figure 7: N- and C-metalated nitrile structures.

The use of X-ray crystallography has been a great tool for coherent understanding of the reactivity and structure of metalated nitriles albeit in the solid phase. The inductive stabilization of nitriles is made clear in the bond distances in the solid state.

Surprisingly, metalated nitriles show minimal elongation of the C≡N bond length (1.14-1.20 Å), compared to the C≡N bond length of neutral nitriles (1.14 Å).[93] Whereas, the bond length between the nitrile carbon and the formal anionic carbon (C-CN) (1.36-1.45 Å) is intermediate to a C-C and C=C bond,[99] reflecting the electrostatic attraction between the negatively charged "carbanion" and the strongly electron-withdrawing nitrile group. A specific example is shown in Figure 8.

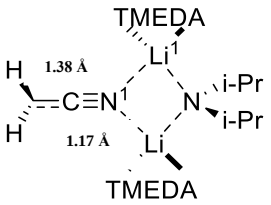
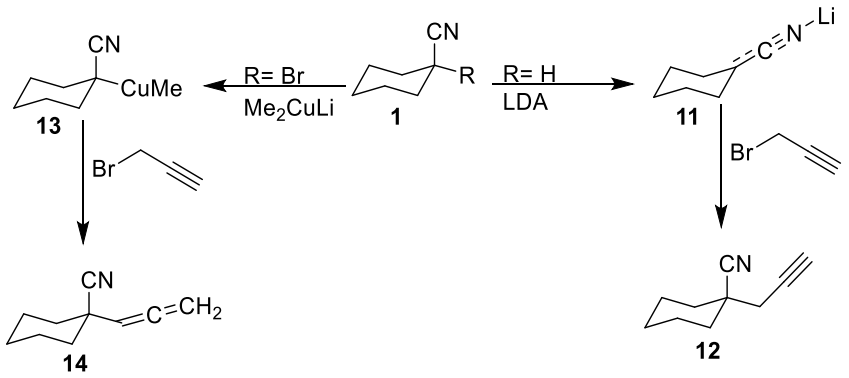


Figure 8: X-ray structure of a metalated nitrile.

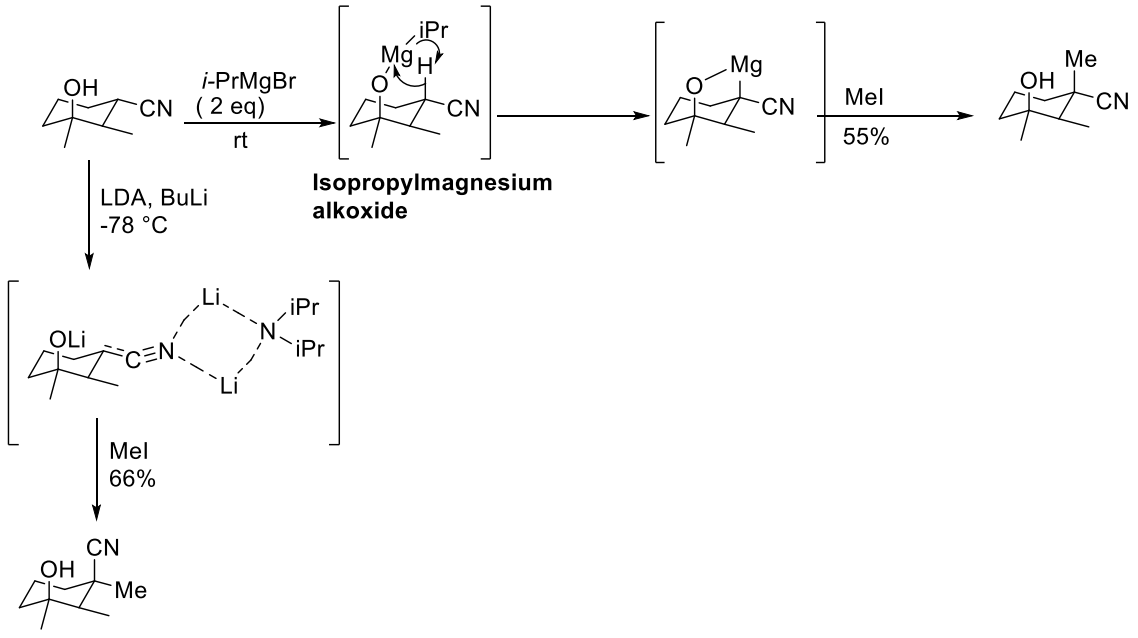
Selective formation of C- and N-metalated nitriles offers the possibility for controlling regio- and stereoselective alkylation. One example where the reaction outcome is dependent on the nature of the metal co-ordination to the deprotonated nitrile is seen below (Scheme 34). The deprotonation of cyclohexanecarbonitrile **1** (R = H) with LDA affords the N-lithiated cyclohexanecarbonitrile, which reacts with propargyl bromide to afford alkyne nitrile **12,**

whereas bromine−copper exchange of **1b** generates cuprated nitrile **13**, which affords allenenitrile **14** with propargyl bromide.[8]



Scheme 34: Regio- and stereoselectivities of N- and C-metalated nitriles.

Fleming[100] also reports the sequential addition of *i*-PrMgBr and methyl iodide to a solution of a cyclic hydroxynitrile to afford exclusively the axially methylated nitrile (Scheme 35). The reaction initially generates an isopropyl magnesium alkoxide, whose coordination directs internal deprotonation and geometrically prevents internal alkyl delivery to the electrophilic nitrile group. In contrast, with organolithium reagents (LDA and BuLi) equatorial alkylation of N-lithiated cyclohexanecarbonitrile is observed.

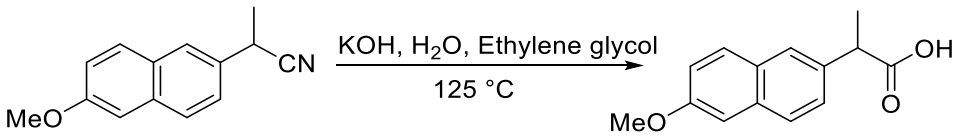


Scheme 35: Reaction regioselectivity derived from preferential formation of N- and C-metalated nitriles.

1.2.3 Asymmetric synthesis of nitriles

Racemic compounds are equimolar mixtures of enantiomers which can exhibit different effects on biological entities. As a result, the preparation of enantiomerically pure compounds has become a major endeavour for organic chemists.[101]

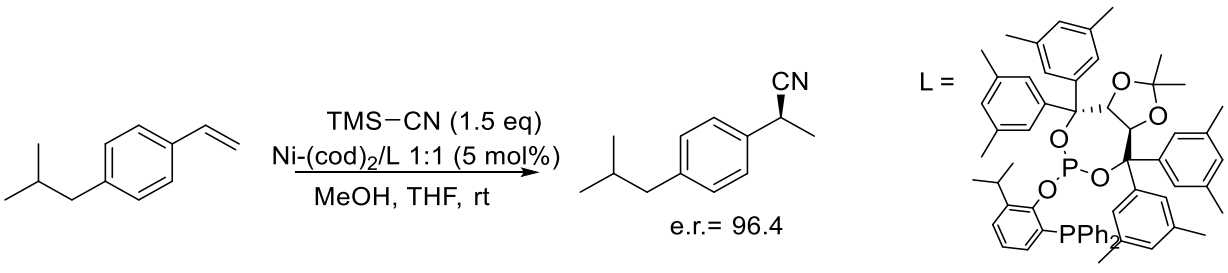
In the syntheses of chiral nitrile compounds, synthetic routes are known but are limited in application and highly enantioselective routes are elusive. As stated earlier the nitrile moiety serves as a versatile precursor to an array of other functional groups, therefore enantio-enriched α-substituted benzylnitriles are of interest as they can be transformed into α-aryl carboxylic acids such as α-benzylpropionic acids which are widely used as non-steroidal anti-inflammatory drugs (e.g., ibuprofen and naproxen) (Scheme 36).[102,103]



Scheme 36: Synthesis of (*R,S*)-naproxen.

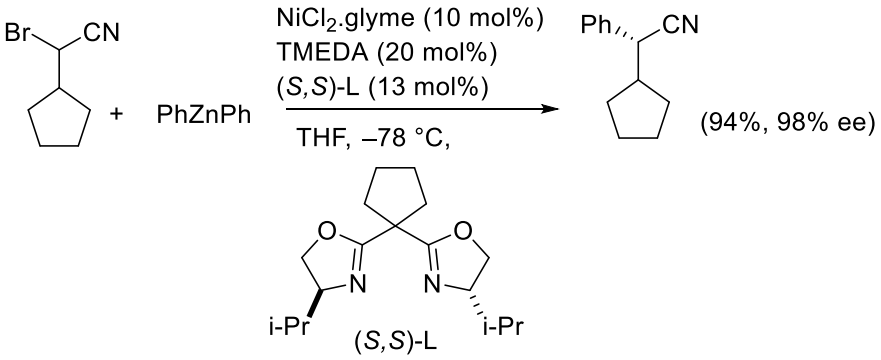
There have been many methods reviewed in literature for the catalytic asymmetric synthesis of alpha-substituted benzylnitriles.[102,104]

One example is shown in Scheme 37 where Schmalz[105] reports the use of phosphine–phosphite ligands in nickel-catalyzed hydrocyanation of vinylarenes, generating α- methylbenzylnitriles with high enantioselectivity (up to 97% ee). However, the scope of this method is limited to producing nitriles that bear α-alkyl substituents no larger than an isopropyl group.



Scheme 37: Hydrocyanation of an alkene.

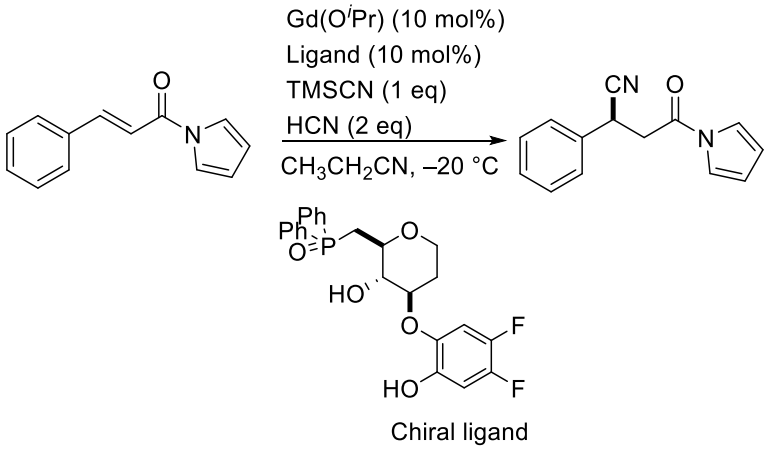
Fu has reported a stereoconvergent method for the cross-coupling of racemic α-halonitriles, using nickel-catalyzed Negishi arylations and alkenylations to generate a variety of secondary α-benzylnitriles and allylic nitriles in high enantioselectivity (up to 98% ee, Scheme 38).[106] The use of the Negishi cross coupling reaction in this process is attractive due to the compatibility of zinc with a wide range of functional groups.[107]



Scheme 38: Stereoconvergent Negishi phenylation of a racemic α-bromonitrile.

The use of transition metal-based catalysts which while effective on a small scale present a problem on larger scale where the cost of the metal and ligands become more problematic. Complete removal of the metal catalyst from the product also presents an issue for any pharmaceutical synthesis.

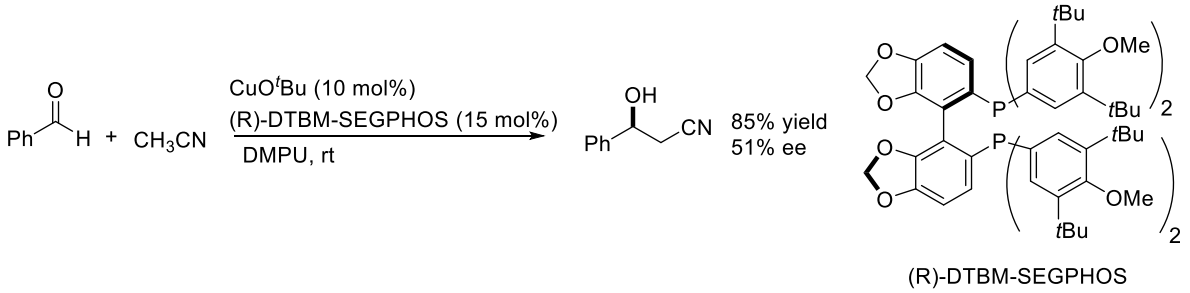
Another synthetic method for the synthesis of chiral nitrile compounds are reported by Shibasaki where he discusses the use of polymetallic Gd(III) catalysts in the cyanation of α,β-unsaturated carbonyl compounds (Scheme 39) obtaining high enantioselectivity (up to 98% ee).[108,109] Not only does this method produce α-substituted nitriles, the cyanide and *N*-acylpyrrole present in the product are synthetically versatile and can be extended to synthesize several chiral pharmaceuticals such as pregabalin.[110]



Scheme 39: Conjugate addition of cyanide to an α, β-unsaturated *N*-acylpyrroles.

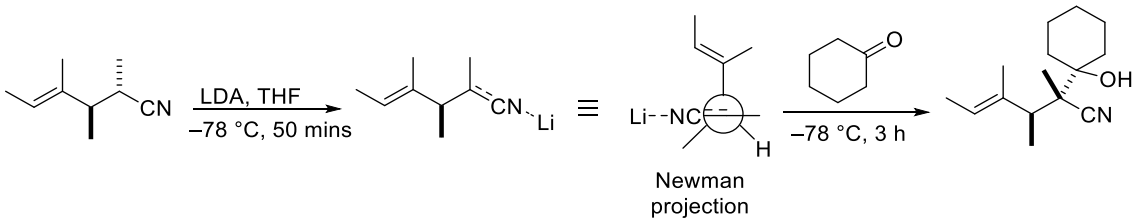
A mini-review by Paloma reports asymmetric cyanation reactions mostly in the context of nitrile aldol or similar reactions using transition metal catalysts (Scheme 40)[63,111] In this review he

concludes; ‘There is essentially no asymmetric methodology, based on the catalytic generation of metalated alkylnitriles, and further development is clearly needed.’



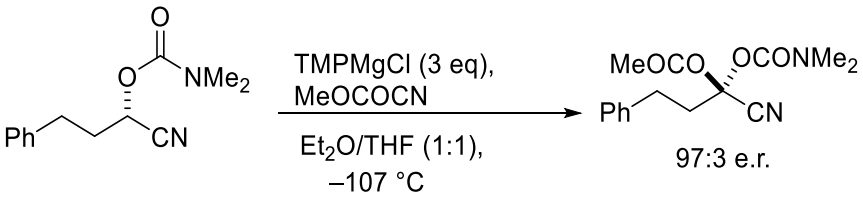
Scheme 40: An example of a copper-catalyzed enantioselective aldol-type reaction.[112]

Fleming reports the alkylation of substituted nitriles, generating quaternary centres by internal 1,2-asymmetric induction obtaining excellent stereoselectivity. The importance of metalated nitriles in the alkylation of sterically hindered nitriles is shown in Scheme 41, where the favoured conformer is seen in the Me–CN interaction because of the extremely small steric demand of a nitrile group.[113] The enantiomeric excess for these compounds was not reported and only one diastereomer is detectable in the crude reaction mixture.



Scheme 41: Diastereoselective alkylation of a nitrile.

Coldham reported the rapid deprotonation of enantioenriched nitriles adjacent to a carbamate group using a magnesium base at very low temperature, followed by subsequent alkylation with a variety of electrophiles showing very little scrambling of the chirality.[35]

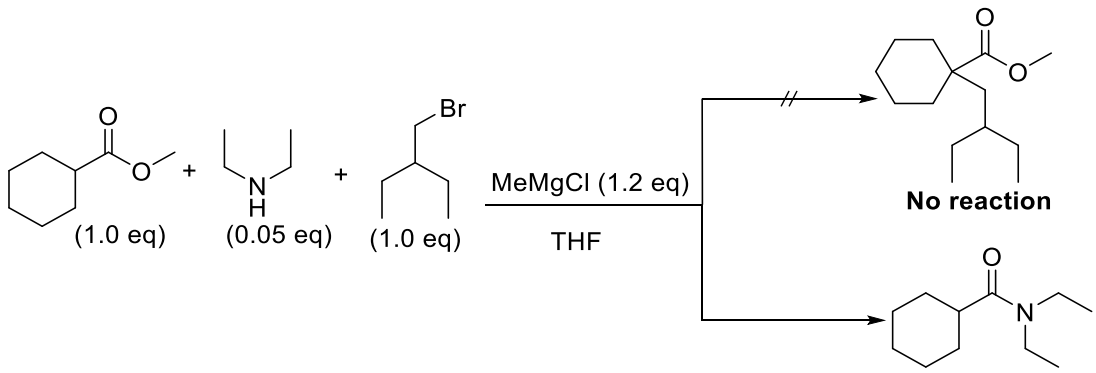


Scheme 42: Deprotonating of an enantioenriched nitrile using a magnesium base.

While impressive, the methods reported by Fleming and Coldham have significant constraints regarding the starting materials used in that full equivalents of chiral material are required. The ultra-low temperature is also an issue.

Grignard reagents in amide synthesis.

The extension of the MeMgCl deprotonation methodology to further functional groups was explored. The initial idea was to conduct an alkylation reaction; however, this approach did not lead to the formation of the desired coupled product as shown in Scheme 43. After studying the GC-MS traces, it was discovered the deprotonation of ester failed but amide formation was observed. The direct synthesis of amides from esters and amines is very attractive for its simplicity and availability of starting materials. The use of methylmagnesium chloride is explored in the synthesis of amides from readily available ester starting material.



Scheme 43: Amide formation

1.3 Amide synthesis

Amides are derivatives of carboxylic acids where the hydroxyl group is replaced by ammonia or an amine. The general structure of amides is shown below.

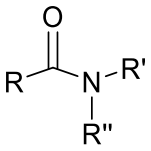


Figure 9: General amide.

This structural modification produces a significant change in physicochemical properties of amides versus amines. The strongly electron-withdrawing nature of the carbonyl group allows for resonance delocalization of the lone pair of nitrogen as shown below (Figure 10). This gives the carbon nitrogen bond partial double bond character and makes the carbonyl derivative less reactive as the carbonyl group is less electrophilic. For this reason, the amide group is the least reactive of the common carboxylic acid derivatives.[114]

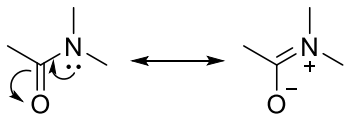


Figure 10: Resonance stabilization.

The amide functionality is one of the most fundamental chemical building blocks found in nature. Amides and amide bonds are essential to life and play a significant role in the composition of biological systems. They are the main chemical bonds that link together amino acids to make different proteins. Proteins play a central role in many biological processes such as enzymatic catalysis, transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen).[115] Applications of amide bonds are not limited to biological systems but are extended to drug molecules, with amide bonds being one of the most prolific moieties in pharmaceuticals,[116] agrochemicals and natural products. Amide bonds are increasingly important in pharmaceutical chemistry, being present in 25% of available drugs.[117,118] Some examples of these drugs are atorvastatin, a top selling drug worldwide since 2003, valsartan, and penicillin G.

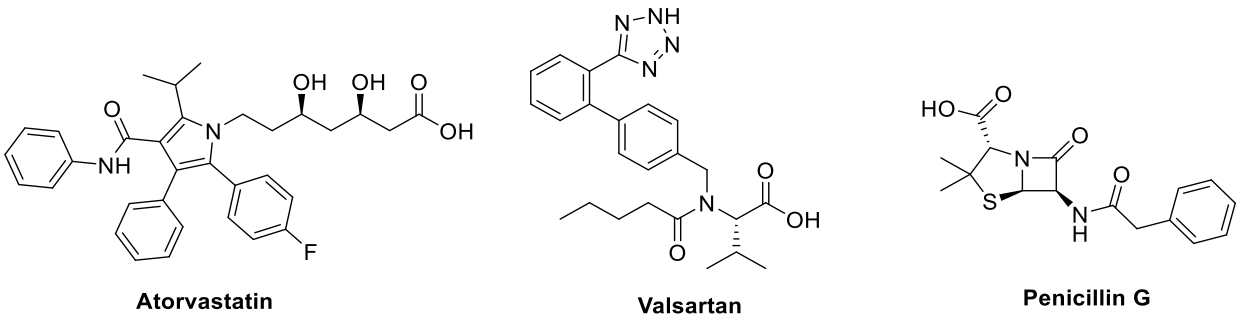


Figure 11: Drug compounds containing an amide moiety.

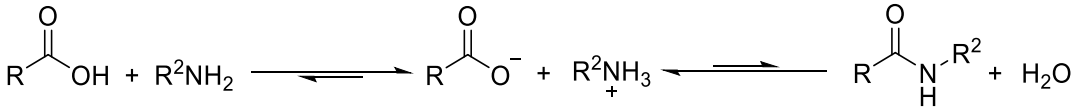
Despite the huge importance of amides, it has been said that amide synthesis is the most common, yet most difficult synthesis in the pharmaceutical industry.[119,120] Most of the well-established methods for their formation are not considered ideal and are less ‘‘atom economical’’ by virtue of their generating of large quantities of problematic waste products.
There are also difficulties associated with purification of the desired amide products.[118] As a result, there has been great interest in the development of new approaches for amide bond formation and organizations such as the ACS Green Chemistry Institute Pharmaceutical Roundtable have identified amide bond formation as one of the most important reactions used in industry for which better reagents are required.[119]

The most popular and common methods for the generation of amides involve the reaction of activated carboxylic acid derivatives, such as chlorides, anhydrides or esters, with amines.[115,116] Alternative strategies toward the synthesis of amides include; the Bodroux reaction,[121] Staudinger reaction,[122] Schmidt reaction,[123] Beckmann rearrangement,[124] aminocarbonylation of haloarenes,[125] alkenes[126] and alkynes,[127] oxidative amidation of aldehydes,[128] hydrative amide synthesis with alkynes[129] and amidation of thioacids with azides.[130]

1.3.1 Amidation with carboxylic acid and derivatives

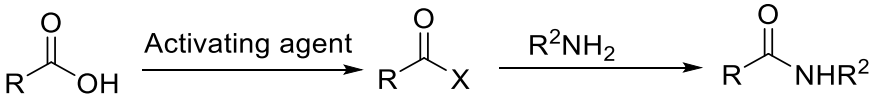
There are many methods available for the formation of amides, but on paper the most common and simplest approach for amide bond formation is generally a condensation reaction between a carboxylic acid and an amine. Although a very simple concept, the initial reaction is an acid base reaction leading to an ammonium salt which is quite stable (Scheme 44).[131]

The necessary elimination of water to form the amide occurs at elevated temperatures (160 – 180 °C), temperatures which can be incompatible with the presence of other labile functionalities.[132]



Scheme 44: Direct reaction of carboxylic with an amine.

Activation of the acid by the attachment of a leaving group to the acyl carbon of the acid prior to treatment with the amine means the amide formation is no longer dependent on equilibrium steps. The attachment of the leaving group makes for a better electrophile (Scheme 45).



Scheme 45: Amide formation *via* activation of acid.

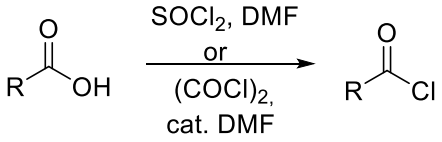
Numerous activation methods have been developed, such as the generation of acid chlorides, (mixed) anhydrides, or active esters (carbodiimides: *N,N'*-dicyclohexylcarbodiimide (DCC),

N,N′-diisopropylcarbodiimide (DIC), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC·HCl) with or without additives.[116]

Amide bond formation by reaction of an activated carboxylic acid derivative with an amine can be achieved in three ways:

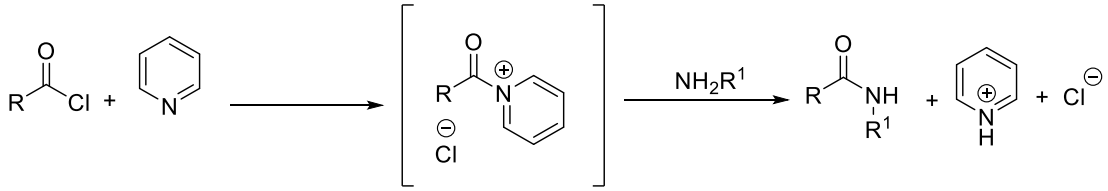
1. A sequential reaction, where the intermediate acylating agent is formed and isolated then subjected to aminolysis.
2. The formation of the reactive acylating agent in a separate step, prior to the reaction with the amine.
3. A one-pot process, where the activated carboxy derivative is generated *in situ* from the acid in the presence of the amine.

Activation of a carboxylic acid to the acid chloride and subsequent reaction with an amine is one of the oldest approaches to amide bond formation (Scheme 46). Formation of the acid chloride is often promoted by the addition of small amounts of dimethylformamide (DMF).



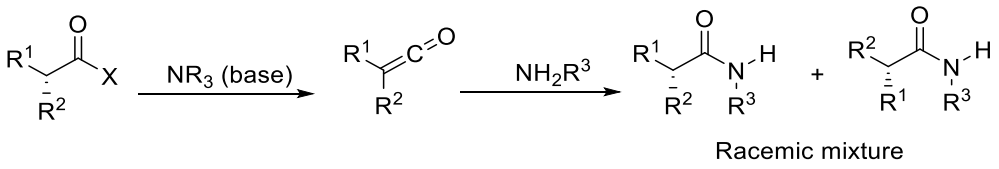
Scheme 46: Acid activation to acid chloride.

Reagents such as thionyl chloride ($SOCl_2$), oxalyl chloride ($(COCl)_2$), phosphorus oxychloride ($POCl_3$), and the Vilsmeier reagent are often employed in generating the acid chloride from the corresponding acid. $SOCl_2$ and $(COCl)_2$ are the two most widely employed reagents.[133] Subsequent reaction of the acid chloride with the amine is carried out under anhydrous conditions using organic bases such as triethylamine and pyridine to react with the HCl by-product. The reaction leading to the amine occurs via an intermediate pyridinium salt (Scheme 47).



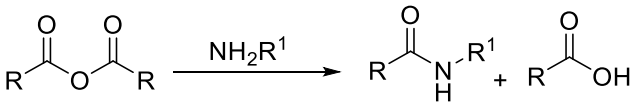
Scheme 47: Base catalysed amidation.

The formation of the HCl by-product limits the application of this method somewhat especially in peptide synthesis due to incompatibility with acid-sensitive functional groups.
Also, under the basic conditions for the coupling, epimerization is a potential problem if the acid chloride contains an α-stereocentre. Epimerization occurs *via* elimination of HX form a ketene. The ketene then further reacts with an amine to yield the addition product with an obvious loss of chiral integrity (Scheme 48).[134]



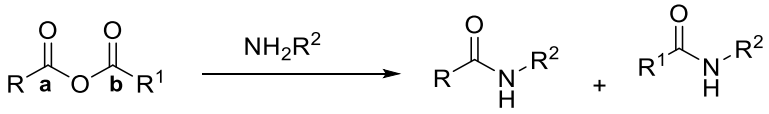
Scheme 48: Epimerisation *via* ketene formation.

Formation of amide bonds *via* anhydrides is another established activation method. Simple symmetrical anhydrides (Scheme 49) as well as mixed anhydrides have been employed. However, the major problem associated with the symmetrical anhydride is waste, as only 50% of the acid is effectively coupled.



Scheme 49: Amide synthesis *via* symmetric anhydride.

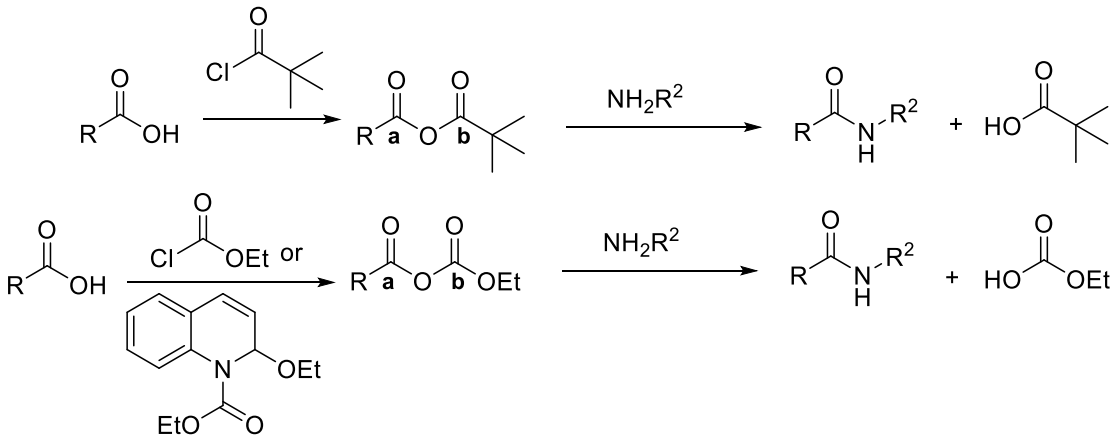
The use of mixed carboxylic anhydrides has been employed to minimise the waste problem encountered using symmetrical anhydrides. Another advantage of the mixed anhydride is that it does not produce the HCl by-product as seen using an acid chloride.[115]
However, regioselectivity is a major problem with mixed anhydrides, as the addition of the amine can potentially occur at either carbonyl group (position a or position b Scheme 50).



Scheme 50: Regioselectivity problems in mixed anhydrides.

Formation of mixed anhydrides is the result of carboxylic acids undergoing reaction with reagents such as pivaloyl chloride,[135] ethyl chloroformate[136] and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ).[137] The mixed anhydrides formed are commonly carried into coupling with the amine without isolation.

The use of mixed anhydrides such as pivalic and ethyl carbonic anhydride are seen to overcome the selectivity issue, as the reaction occurs at the desired carbonyl group due to the steric hindrance of the *t*-butyl group and due to resonance stabilisation of the carbonic carbonyl by the ethoxy group respectively (Scheme 51).



Scheme 51: Selective aminolysis *via* mixed anhydrides.

Carbodiimides are coupling reagents used for activating carboxyl groups. They are also very important agents for the synthesis of peptide links and for the efficient preparation of amide bonds (used in the preparation of activated species such as anhydrides or esters).

The use of *N,N′*-dicyclohexylcarbodiimide (DCC), for the formation of peptide and other amide bonds was first reported by Sheehan and Hess in 1955.[138] Since the first report, DCC has been one of most important reagents for activating carboxyl groups.

Based on availability, cost, product isolation procedures, and environmental considerations, dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylamino)carbodiimide HCl salt [EDC or WSC (water-soluble carbodiimide)] are frequently used for amide bond formation (Figure 12).

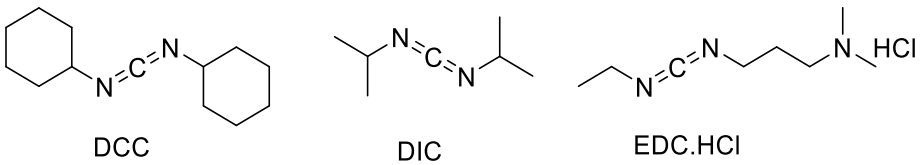
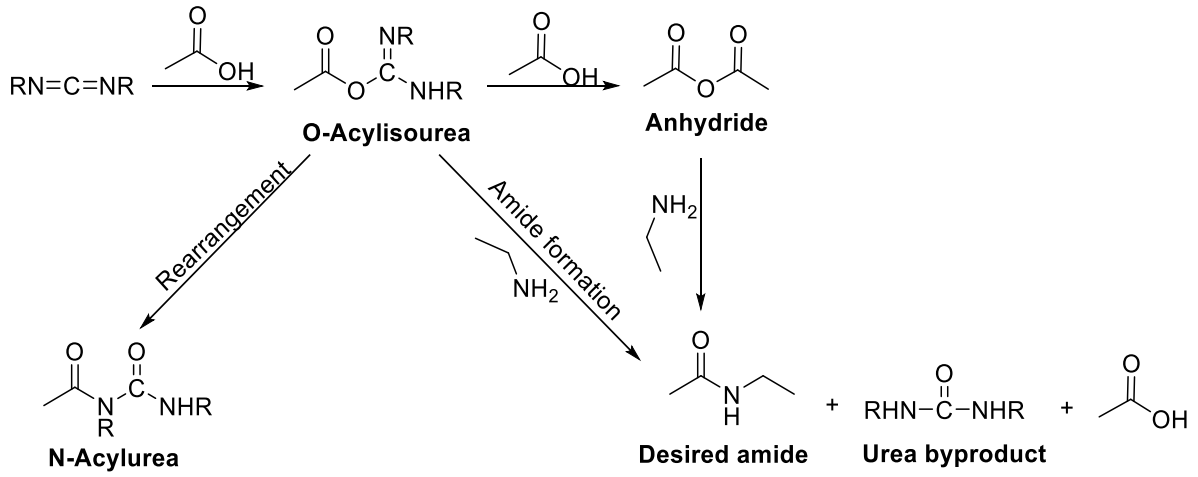


Figure 12: Carbodiimides used in amide synthesis.

All three coupling reagents act in the same way, the carbodiimide reacting with the carboxylic acid to form the O-acylisourea. The reactive acylating agent, O-acylisourea then reacts with the amine to yield the desired amide and the urea by-product.

In some cases, the O-acylisourea may rearrange to the unreactive *N*-acylurea or attack another carboxylic acid to form the symmetrical anhydride, which is also an acylating agent as stated earlier (Scheme 52).

A primary consideration when selecting a carbodiimide is the preferred workup since the method for removal of the urea by-product can vary widely. For example, dicyclohexylurea from DCC has very limited solubility in most organic solvents and, therefore, is typically removed by filtration. Diisopropylurea from DIC has reasonable solubility in CH_2Cl_2 and is removed by CH_2Cl_2 extraction. Finally, the by-product urea from EDC is water-soluble and can be removed by aqueous workup. Due to the limited solubility of DCU (the by-product of DCC) in typical organic solvents, the latter two can have an advantage over DCU depending on the solubility of the amide product.

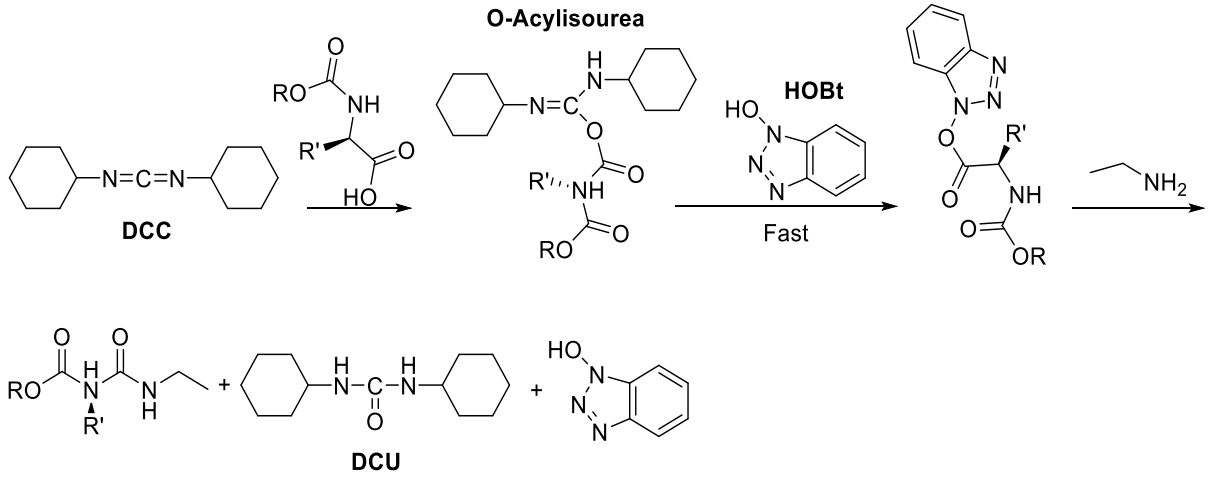


Scheme 52: Activation of carboxylic acids by carbodiimides.

In the carbodiimide amide coupling reaction, the formation of the unreactive *N*-acylurea is often observed (Scheme 52). The use of selected nucleophiles such as DMAP (4-dimethylaminopyridine) and hydroxybenzotriazole (HOBt) that react faster than the competing acyl transfer prevent the side reaction leading to the formation of *N*-acylurea.

The use of a base such as DMAP with DCC can result in the deprotonation of the O-acylisourea adjacent to the carbonyl, and should this site be chiral in the starting material this process would lead to racemisation. DCC in combination with HOBt can be used to avoid the use of base, thus minimising racemisation.

Since the successful launch of DCC/HOBt in peptide synthesis,[139] the use of carbodiimides has expanded with the aid of other additives such as 1-hydroxy-7-azabenzotriazole (HOAt),[140] HOSu (*N*-hydroxylsuccinimide) and more recently 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HODHBt).[141] In addition to minimising racemisation they increase the reaction rate allowing the reactions to be conducted at lower temperature which is highly beneficial in limiting the formation of the unreactive side product, *N*-acylurea (Scheme 53).

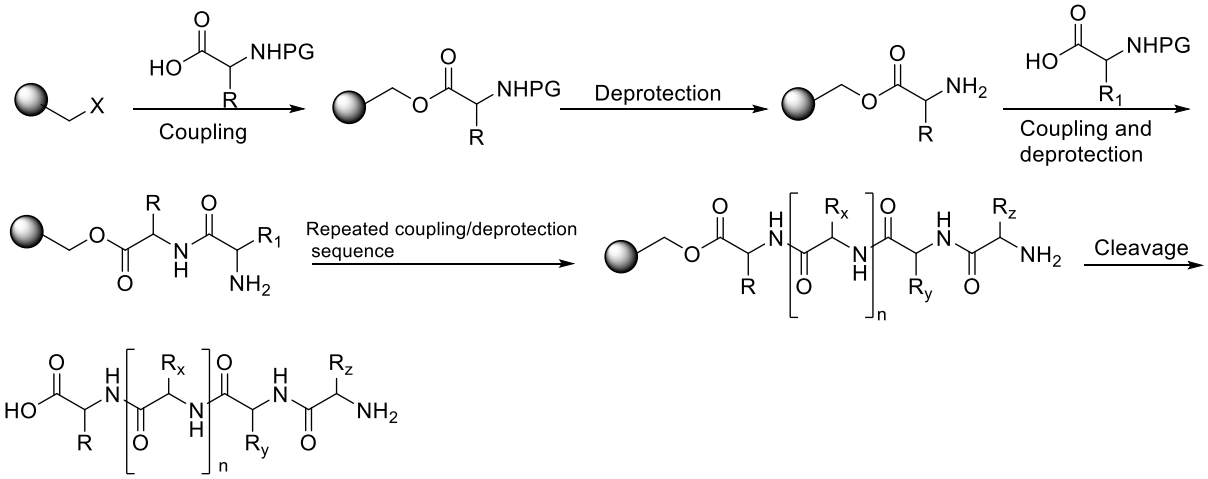


Scheme 53: Use of HOBt additive to minimise the formation of unreactive *N*-acylurea and control racemization.

1.3.2 Solid phase peptide synthesis

Solid phase peptide synthesis (SPPS), developed by Merrifield, is the established method in large-scale production of peptides and small proteins.[142,143] The reaction involves a covalent attachment step that links the nascent peptide chain to an insoluble polymeric support resin bead.

Subsequently, the anchored peptide is extended by consecutive coupling of amino acids, and finally the peptide is removed from the solid support. The general principle of polymer-supported peptide synthesis is shown in Scheme 54.

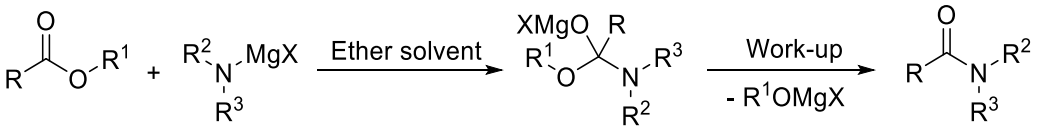


Scheme 54: General approach to solid-phase peptide synthesis.

1.3.3 Bodroux reaction

The direct synthesis of amides from esters is very attractive for its simplicity and availability of starting materials. In addition, esters are stable functional groups, usually easily accessible from a synthetic point of view, and hence are often available from commercial suppliers. The direct synthesis of amides from esters requires high temperatures and can involve the use of an autoclave. Enhancement of the reactivity of the amine through preformation of metallic amides from strong organometallic bases has been developed.[144,145]

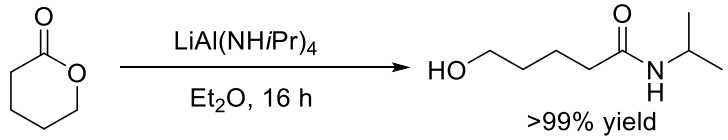
The preparation of substituted amides from the reaction between a simple aliphatic or aromatic ester and an aminomagnesium halide (1:2 ratio) obtained by treatment of a primary or secondary amine with a Grignard reagent at rt is known as the Bodroux reaction[121] (Scheme 55).



Scheme 55: The Bodroux reaction.

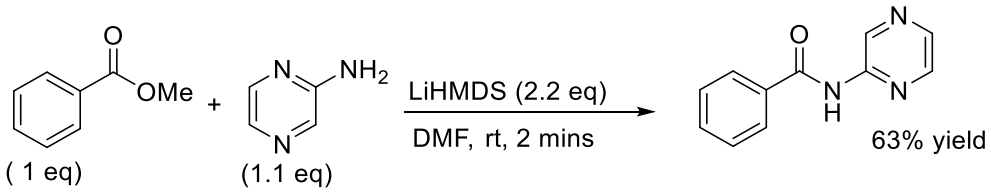
Since the first report,[121] this reaction has been extended to the reaction between esters and lithium aluminium amide (Scheme 56). The lithium aluminium amide is prepared from the $LiAlH_4$ and amines (1:5 ratio of $LiAlH_4$ to amine for the best result) at 25 °C in Et_2O.[145]

Although this reaction can produce the amide in excellent yield, this method requires an extra step for the formation of the intermediate.



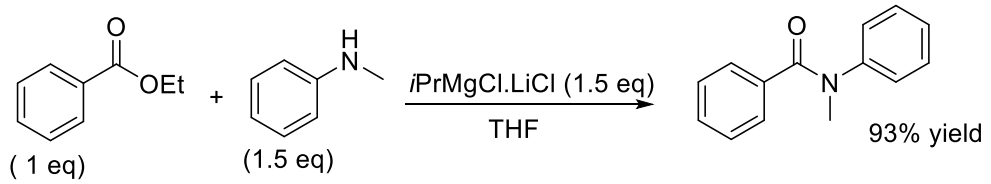
Scheme 56: Synthesis of amides from an ester and lithium aluminium amide.

Another report by Alcázar[146] demonstrates the use of lithium bis(trimethylsilyl)amide (LHMDS) in the formation of amides under continuous conditions (Scheme 57). This method, however, requires an excess of the amine and lithium amide base to afford the amide product in good yields. This reaction is also carried out in an unfavourable solvent, DMF.



Scheme 57: Amide formation mediated by LiHMDS under continuous flow conditions.

Alcázar[147] has also reported a greener procedure for the Bodroux reaction. He reports the use of an isopropylmagnesium chloride lithium chloride complex (turbo Grignard) in the formation of amides (Scheme 58). This method produces the amides in good to excellent yields and with the advantage of simultaneous mixing of all reagents at once. This method has been applied to alkyl, aryl and cyclic esters, and alkyl, aryl, primary and secondary amines.
Although this method offers a broad scope and good functional group tolerance, an excess of the amine is required for the reaction to go to completion.



Scheme 58: Amide formation mediated by isopropylmagnesium chloride under continuous flow conditions.

Although there are several coupling reagents available for amide bond formation, the available methods are far from universally applicable. These methods possess their own advantages,

nonetheless they all suffer from certain disadvantages such as use of stoichiometric amounts of coupling agents , which can be toxic and/or expensive and they or their derivatives end up in the waste stream after a possibly difficult separation process.[134,148]

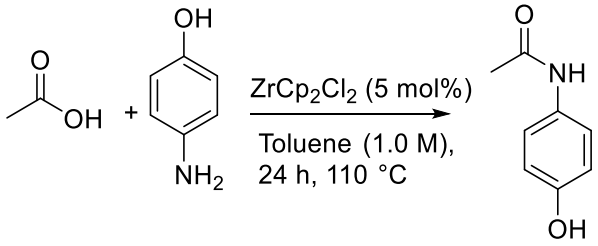
These methodologies are also often associated with significant drawbacks such as long reaction times, harsh reaction conditions, and low to moderate yields as in the case of hindered or less reactive reagents, not to mention the moderate reactivity associated with peptide synthesis.[149]

Therefore, there is a need for the development of new reagents and/or methods for the synthesis of amides.

1.3.4 Catalyst induced direct amidation of carboxylic acid

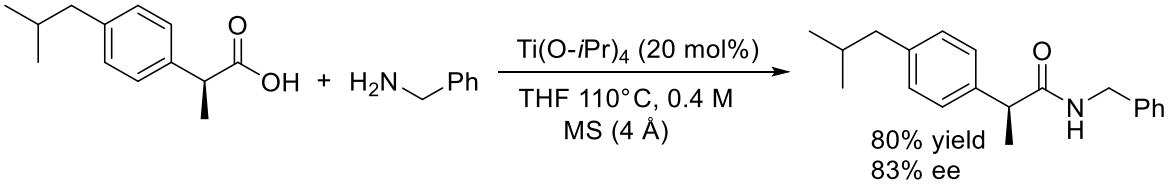
The most desirable method for the synthesis of amides involves direct condensation of carboxylic acids with amines but, as indicated earlier, direct reaction often requires severe conditions. The development of catalytic processes for amide bond formation has seen a resurgence in recent years and was highlighted as a reaction of importance from a 'green chemistry' perspective.[150]

Catalyst induced amidation of carboxylic acids eliminates the use of coupling agents in the formation of amides. In recent years, there have been many metal-based catalytic systems reported. One example involves the use of a zirconium catalyst,[151] as reported by William where 5 mol% of bis(cyclopentadienyl)zirconium(IV) dichloride catalyst (Cp_2ZrCl_2) led to a 100% conversion of the acetic acid and *para*-aminophenol to the pharmaceutical drug, paracetamol in 24 h.



Scheme 59: Direct catalysed formation of an amide.

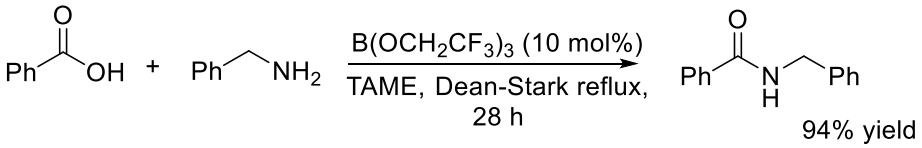
Titanium catalysts have also been used in amide formation.[152,153] Reports by Adolfsson[152] describe the use of titanium(IV) isopropoxide as a catalyst in the synthesis of a number of secondary and tertiary amides in good to excellent yields. This reaction has also been applied to acids that contain adjacent chiral centres, where the stereointegrity is largely retained with 83% ee obtained in the product.



Scheme 60: An example of a titanium catalysed amidation.

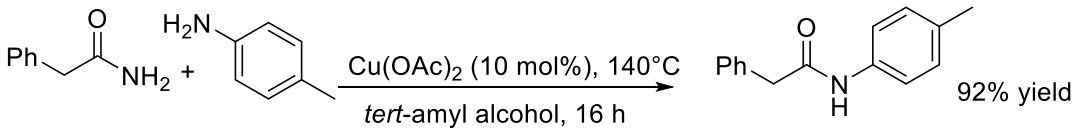
Boron mediated amidation reactions have attracted considerable attention in recent years, and boronic acids have been shown to be effective catalysts for direct amide formation from carboxylic acids and amines.[154–156]

A boronic catalyst, 2,2,2-trifluoroethanol-derived ester $B(OCH_2CF_3)_3$, developed by Sheppard[155,157] has been applied to the direct amidation of aliphatic, α-hydroxyl, aromatic and heteroaromatic acids, and *N*-Boc-protected amino acids, with primary, secondary, and heterocyclic amines under reflux conditions in *t*-amyl methyl ether (TAME). An example is shown in Scheme 61 where the reaction produces the amide in high yield.



Scheme 61: An example of a borate-mediated amidation reaction.

Transamidation has emerged as a useful alternative strategy for the synthesis of amides. The use of catalysts such as boron[158], zirconium[159] and copper[160] have enabled this process to take place under high temperatures and long reactions time, and with a range of substrates, obtaining good to excellent yield for the synthesised amides. One example is shown in Scheme 62, where Beller[160] reports a copper-catalysed transamidation of primary amides with amines in excellent yields.



Scheme 62: An example of a copper-catalysed transamidation.

These catalytic methods also have their limitations, with difficulties in separating and recycling the catalyst from the reaction mass, making their environmental profile unfavourable. These methods also require long reaction times as shown in the examples above, and most often cumbersome work-up procedures.[149]

1.4 Carbamates

Carbamates are organic compounds structurally related to amides, and are important constituents of many drug molecules and biomacromolecules.[114] Organic carbamates, identified by the presence of the linkage RO-CO-NHR, are a class of stable compounds derived from the unstable carbamic acid (H_2N-COOH) by functionalisation of the amino and acid moieties with different alkyl/aryl, aryl/alkyl or substituted alkyl/aryl & aryl/alkyl groups. Compounds with the carbamate linkage in a cyclic system are known as cyclic carbamates[161] and when the carbamate group is attached to any inorganic atom either metal or non-metal, they are referred to as inorganic carbamates.

Structurally, the carbamate functionality is an amide-ester hybrid and, in general, displays very good chemical and proteolytic stabilities.[162,163]

As amide-like structures, they do not behave as acids or bases because of delocalization of nitrogen lone pair into the carbonyl moiety. Carbamates, however, are more electrophilic than amides because of the presence of an additional electronegative "ether" oxygen atom (Figure 13).

The presence of the additional oxygen of the carbamate functionality exerts unique steric and electronic perturbations, causing the C−N bond rotational barriers of amide resonance in carbamates to be about 3−4 kcal mol^{-1} lower than those of amides.[164,165]

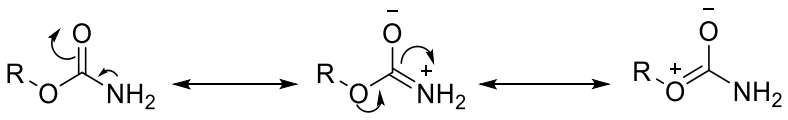


Figure 13: Resonance structures for the carbamate moiety.

Carbamates have widespread application in pharmaceuticals[166,167] and agrochemicals (pesticides, fungicides, and herbicides).[168] Carbamates are also used to produce polyurethanes polymers.

Organic carbamates have frequently been employed in pharmaceuticals, in drugs and prodrugs.[165,166] In recent years there have been several reports which indicate that the presence of a carbamate moiety increases biological activity in many synthetic and natural product molecules.[169–172] Furthermore, extensive study of the role of the carbamate moiety in natural product and semisynthetic molecules indicated that they can have activity against many diseases; such as cancer,[173] bacterial infections,[174] diabetes,[175] Alzheimer's disease[176] and diseases which affect the CNS.[169] Figure 14 shows examples of some important biologically active drug molecules bearing carbamate groups.

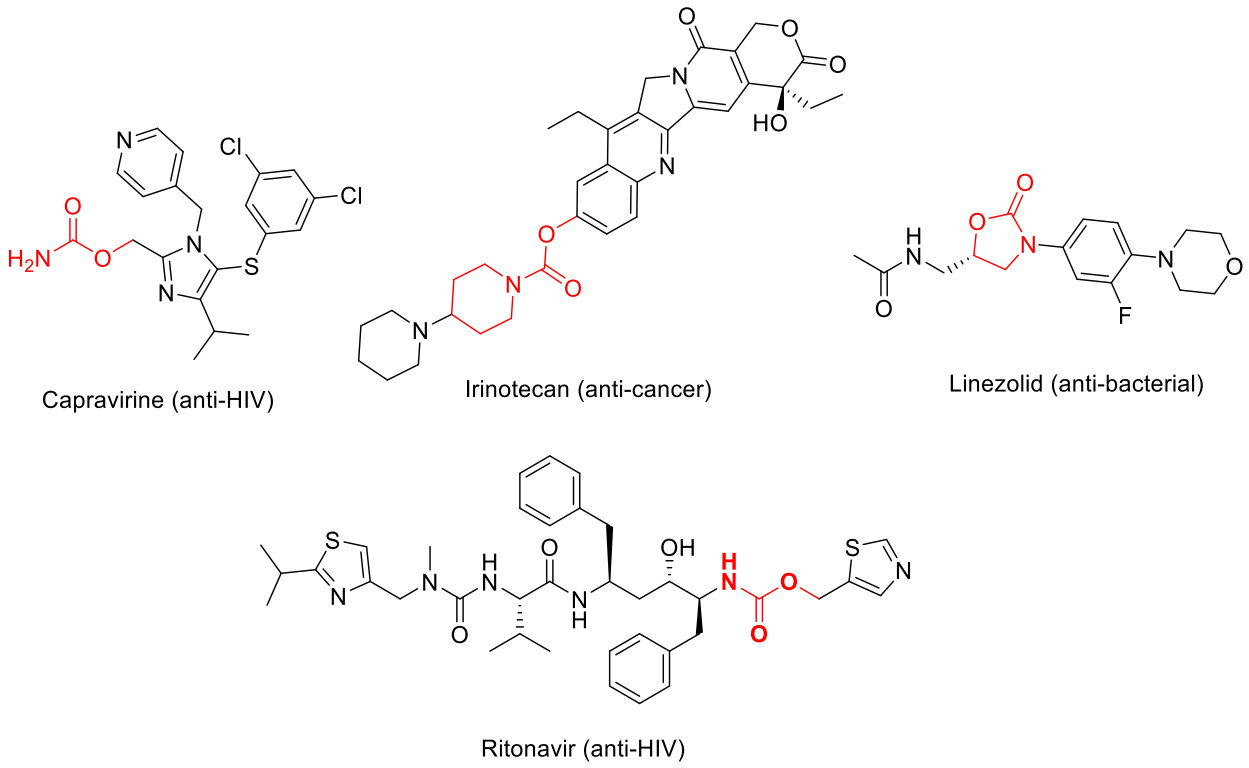


Figure 14: Biologically active drug molecules bearing carbamate linkage.

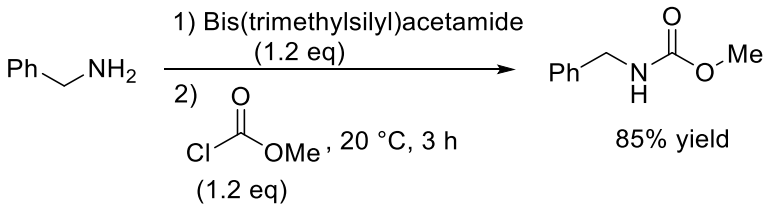
Organic carbamates also play an important role in the area of synthetic organic chemistry primarily as key intermediates,[162] as protection for amino groups in peptide chemistry[177] and as linkers in combinatorial chemistry.

The carbamate motif plays an important role in medicinal chemistry and is widely utilized as a peptide bond surrogate. The use of peptide bond surrogates is an established approach to overcoming the poor stability, lack of oral absorption and marginal ability to cross the blood-brain barrier of some peptides when used as therapeutic agents.[178,179]

Carbamates are used for their chemical stability and capability to permeate cell membranes.[171] In addition, the ability of carbamates to modulate inter- and intramolecular interactions with the target enzymes or receptors is another unique feature.

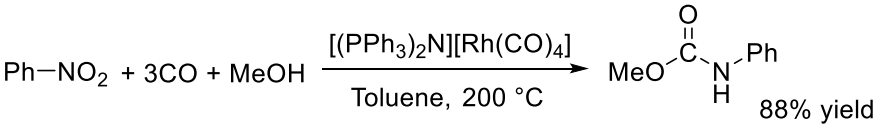
The carbamate functionality also participates in hydrogen bonding through the carboxyl group and the NH backbone. Therefore, substitution on the O- and N-terminus of a carbamate offers opportunities for modulation of biological properties and improvement in stability and pharmacokinetic properties.[165]

The conventional process for carbamate synthesis is based on phosgenation of amines.[180,181] This process is limited by operational complexity due to the involvement of either toxic or cumbersome reagents such as phosgene or phosgene equivalents such as isocyanates or di- and triphosgene and chloroformates (Scheme 63). The formation of large quantities of hydrogen chloride as a side product is also a major disadvantage for this process. Because of the toxicity of these materials, in recent years special attention has been devoted to the development of more efficient and safe methodologies for carbamate synthesis.



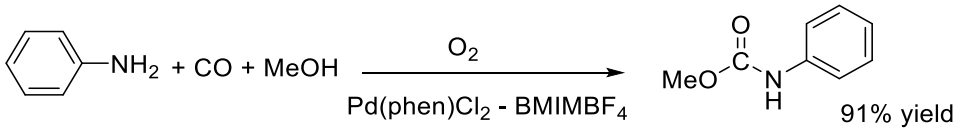
Scheme 63: Carbamate synthesis *via* a chloroformate.[182]

Efforts are continuously being made for the replacement of phosgene-based technology with environmentally benign routes such as reductive carbonylation of nitro compounds.[183]
The synthesis of carbamates *via* reductive carbonylation of nitro compounds is known as an indirect method due to the presence of an alcohol which traps an isocyanate intermediate. This method has the disadvantage of using carbon monoxide as a reagent.
This exothermic reaction is catalysed by a transition metal complex based on metals such as palladium, ruthenium[184] and rhodium,[185] and is high yielding (Scheme 64).



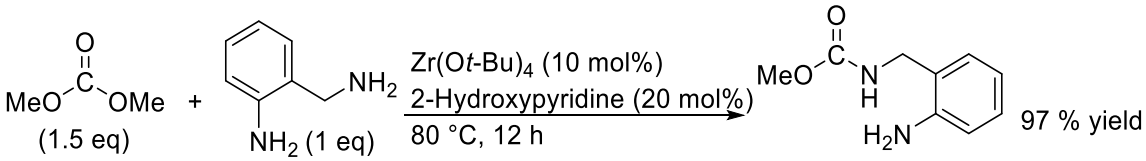
Scheme 64: Metal catalysed reductive carbonylation of a nitro aromatic compound.

Similar to the above method, oxidative carbonylation of amines[186,187] also affords carbamates in good to excellent yields through the reaction of amines, alcohols, carbon monoxide and oxygen in the presence of metal based complexes (Scheme 65). This method however again involves the use of carbon monoxide and generates water as a stoichiometric by-product, which could hydrolyse the carbamate product at high temperatures.[188]

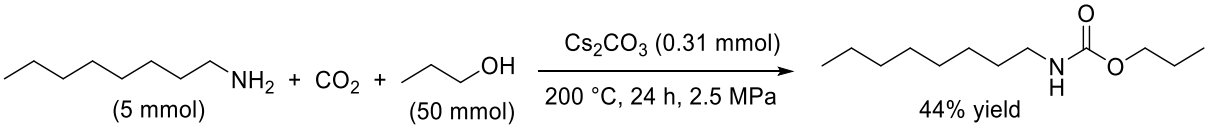


Scheme 65: Oxidative carbonylation of an amine catalysed with a palladium complex.

Carbonylation of amines using organic carbonates (Scheme 66)[189–191] or carbon dioxide (Scheme 67)[192,193] requires the use of a suitable catalyst to get high conversion rates and moderate yields. In particular, the carbonylation reaction of amines with organic carbonates is often used for the synthesis of carbamates in drug design.[194,195]

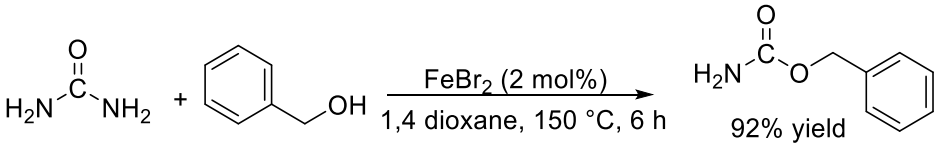


Scheme 66: Preparation of carbamates from an amine and a carbonate.[190]



Scheme 67: Synthesis of carbamates from CO_2, an amine and an alcohol.[196]

Alcoholysis of ureas[197] also affords carbamates in excellent yields, utilising catalysts such as TiO_2/SiO_2,[197] zeolite[198] and iron[199] (Scheme 68). This method is, however, limited to the use of aliphatic ureas and low molecular weight alcohols.



Scheme 68: Carbamate syntheses *via* alcoholysis of an urea.

Although these methods are effective and are a substitute for phosgene-based technology, the toxicity of carbon monoxide used as one of the reagents, high operation cost, deactivation

tendency of noble metals used as catalysts, and the formation of amines and alcohol by-products are problems associated with the above methods.

In addition, the use of carbon dioxide as the source of the carbonyl moiety requires demanding reaction conditions due to the thermodynamic inertness of CO_2, making those methods uneconomical. Thus, development of widely applicable efficient environmentally friendly methods for the synthesis of carbamates is an important task in chemical research.

1.5 Ureas

Ureas [$CO(NR_2)_2$], also known as carbamides, have similar physico-chemical properties to amides. The non-bonding electrons on the two nitrogen atoms in the urea structure are in conjugation with the adjacent carbonyl group as shown in Figure 15.[114]

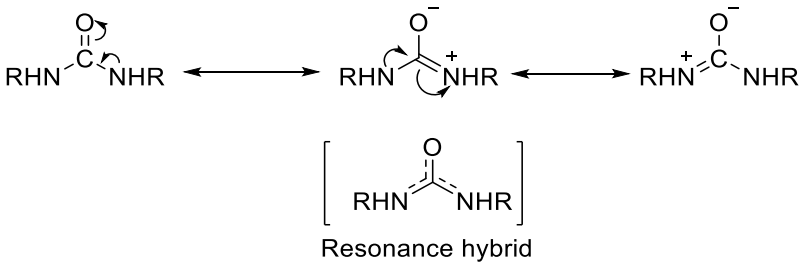


Figure 15: Resonance structures of the urea functional group.

Substituted ureas have attracted attention due to the number of natural products[200] in which they appear, and the wide variety of their applications, as dyes for cellulose fibres, as antioxidants in gasoline, as synthetic intermediates in the production of carbamates which are used in agrochemistry and as pesticides and plant growth regulators.[201]

The urea functionality plays an important role in organic and medicinal chemistry and is a common motif in many biologically active compounds [202] (Figure 16) due to their hydrolytic stability and molecular rigidity.[203]

Cyclic ureas are common and important heterocyclic motifs observed in biologically active molecules (Figure 15)[204–206] with antineoplastic,[205] anti-viral,[206,207] and anti-arrhythmic activity.[208]

Like carbamates, the urea moiety has been used for the synthesis of peptidomimetic compounds. The replacement of the amide bond of the peptide increases bioavailability as the urea bond is not susceptible to proteolytic cleavage.

The resistance to protease degradation and its interesting H-bonding properties make the urea moiety promising for drug discovery and biomedical applications.[209,210]

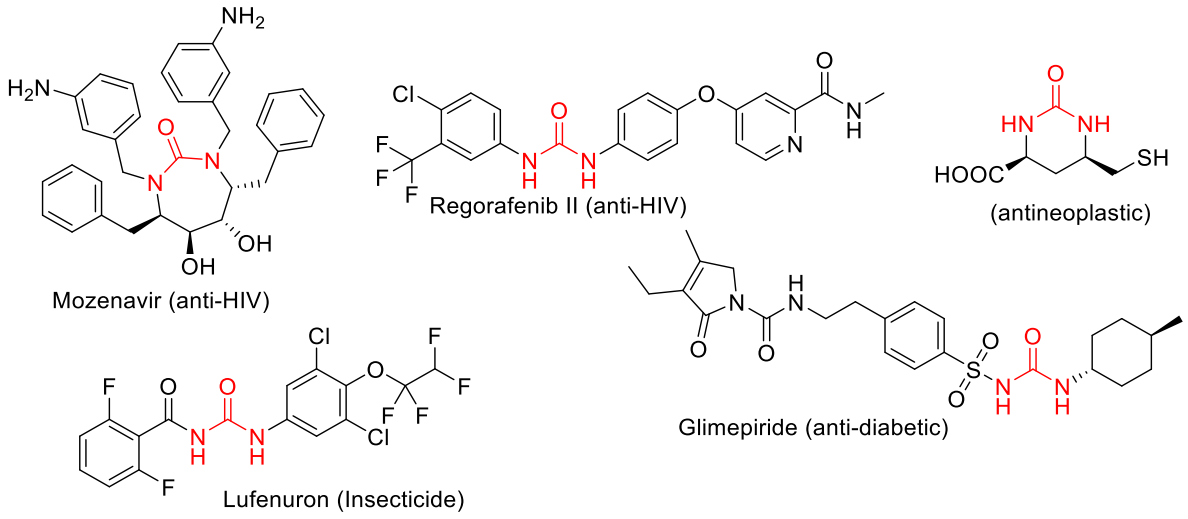
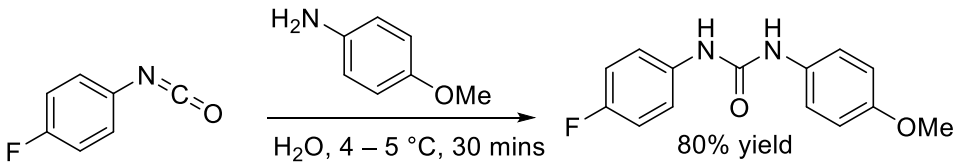


Figure 16: Examples of urea compounds with biological activity.

Due to the increasing importance of urea compounds, there has been considerable interest toward the development of new efficient, selective, and environmentally friendly protocols for their preparation.

Just like carbamates, the traditional synthetic approach to ureas have been based on hazardous reagents such as phosgene and its derivatives such as isocyanates (Scheme 69).



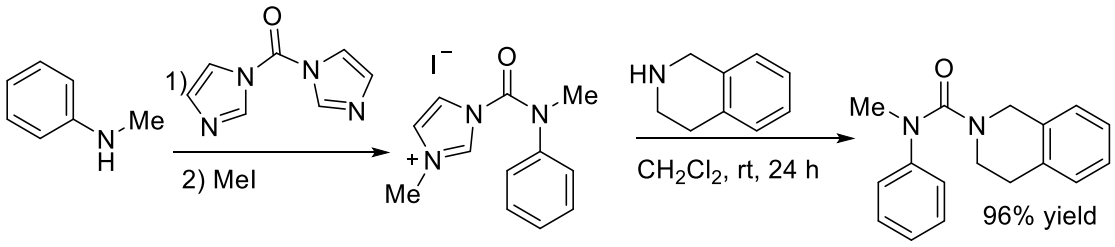
Scheme 69: Di-substituted urea from an isocyanate.[211]

Unfortunately, as said in section 1.4, these methods pose a lot of problems. The production and use of phosgene opens many worrying toxicological and environmental problems, such as the use and storage of large amounts of chlorine, production of a lot of chloride-containing aqueous waste and the safety and environmental risks involved in storage, transportation and use of a reagent characterised by high toxicity and volatility.[212]

Numerous methods mainly based on the use of carbamoyl cation equivalents (such as carbamates, carbamoyl chlorides, carbonyldibenzotriazole, carbamoylimidazolium and its salt derivatives) have been reported in the literature as cleaner and inherently safer alternatives for the synthesis of ureas.[212–215]

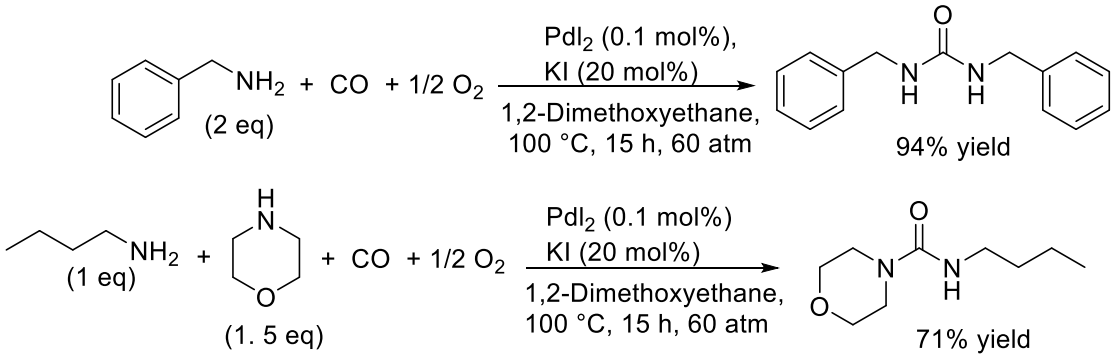
Although these newer methods are effective, the use of some carbonyl derivatives still presents some disadvantages from the standpoint of atom economy.

Carbamoyl chlorides have limited commercial availability and are synthesised from phosgene, carbonyldibenzotriazole is not commercially available and must be synthesised from benzotriazole and phosgene. These drawbacks make these methods unattractive and useable only in lab-scale preparations. Of all carbonyl derivatives listed above, the use of carbamoylimidazolium salts offers a greener pathway to the synthesis of ureas[214] (Scheme 70).



Scheme 70: Carbamoylimidazolium salt in the synthesis of ureas.

As carbamates and ureas are related compounds, the same methods are generally used in the synthesis of both. Substituted ureas can be synthesised by the carbonylation reaction of amines or nitro compounds with CO and transition metal complexes.[216] This reaction employs the use of transition metals such as Ni,[217] Co,[218] W,[219,220] Ru,[221] and Pd complexes, with Pd complexes being the most commonly used in oxidative carbonylation of amines (Scheme 71).[222,223]

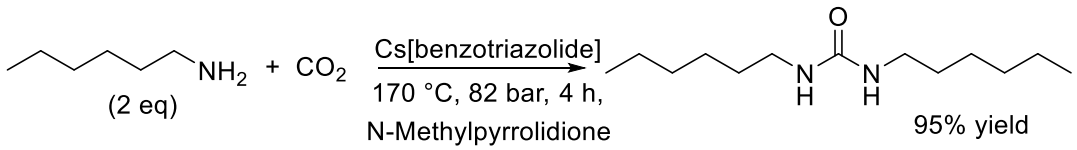


Scheme 71: Examples of palladium catalysed oxidative carbonylation of amines.

Although this reaction has advantages over those which use phosgene it requires extreme care due to the hazards associated with the use of CO and O_2 and the high pressures involved.

From an environmental viewpoint, carboxylation reactions of amines with CO_2 provide an alternative, efficient and atom friendly method for the synthesis of ureas.[224,225]

The use of dehydrating agents (carbodiimides[226]) or a metal catalyst[227,228] (Scheme 72) is often employed. However, the use of extremely high pressures used in this reaction is an operational challenge.



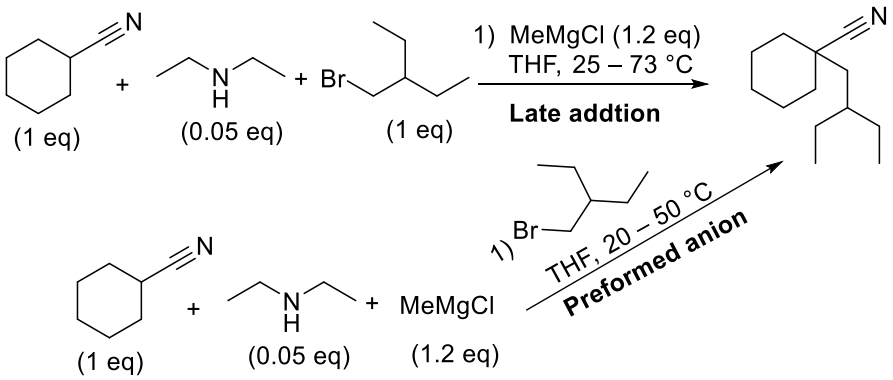
Scheme 72: Caesium catalysed carboxylation of CO_2 with an amine.

1.6 Aims and Objectives

The use of methylmagnesium chloride as a non-nucleophilic base is explored in this thesis. The idea behind this project is based on a discovery by the pharmaceutical company Roche in Clarecastle, Co. Clare, Ireland in which they developed a new convenient synthetic procedure for the synthesis of 1-(2-ethylbutyl)cyclohexane-1-carbononitrile. In 2009[29] and 2012[30] Roche published patents in which they described the use of methylmagnesium chloride as a non-nucleophilic base in conjunction with of an amine mediator to deprotonate alpha to a nitrile in alkylation reactions.

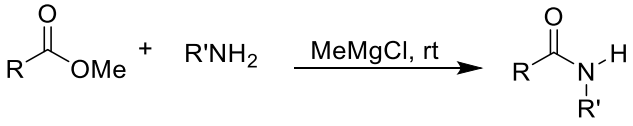
The two patents dealt with the same reaction, the difference being whether the Grignard was added prior to the alkylating agent resulting in formation of the anion (Scheme 73) or whether the Grignard was added to a mixture of all the other reagents in the so-called 'late addition' method.

The advantage of the "late addition" method was that it simplified manufacturing operations and minimised by-product formation. There are isolated examples in the literature of the use of Grignard reagents in deprotonation adjacent to nitriles, but these have often been in cases where adjacent groups activate the reaction site for deprotonation.



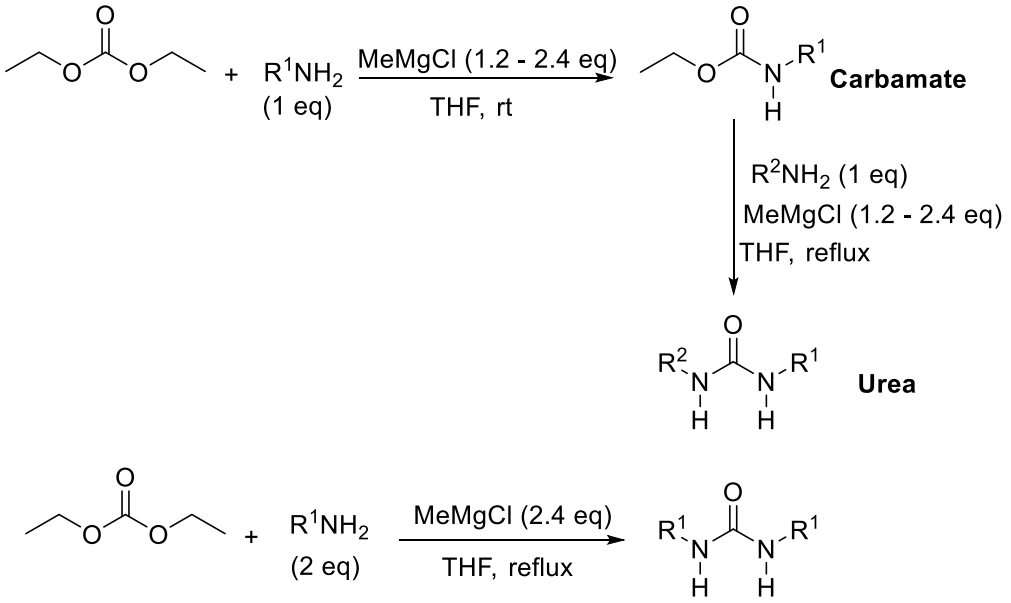
Scheme 73: Synthesis of 1-(2-ethylbutyl) cyclohexane-1-carbononitrile.

The aim of this project was to expand the recently developed methodology for the alkylation of nitriles; by varying the electrophile and nucleophiles, substituting cyclohexanecarbonitrile with other nitriles and substrates bearing other electron withdrawing groups. Its application to key synthetic concepts such as the control of sequential alkylation and the control of asymmetric reactions using chiral mediators such as chiral amines was also to be explored. In addition, we wanted to explore the extension of the methodology to other functional groups, for example in deprotonation adjacent to esters. As will be discussed, the deprotonation of esters was not successful, but these attempted reactions opened a synthetic route to the synthesis of amides involving amines (Scheme 74) and esters.



Scheme 74: Amide synthesis.

Once this chemistry was discovered we aimed to exploit it to synthesise a variety of amides and amide related functional groups such as ureas and carbamates (Scheme 75).



Scheme 75: Synthesis of carbamates and ureas.

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Chapter 2: Results and Discussion

2.1 Alkylation reactions

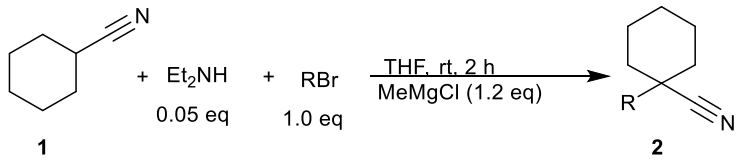
In this chapter the numbering of compounds is restarted. The numbers used in this chapter are used in the experimental chapter.

The report by Roche was of great interest to us due to its simplicity and scalability. Roche has done this reaction at 4700 mol scale, and this chemistry does not appear to be affected by the addition of the Grignard reagent to the nitrile.

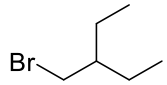
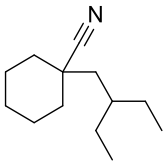
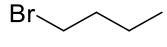
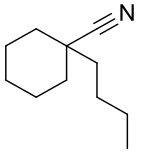
This thesis discusses exploratory work done using MeMgCl as a base in deprotonating α to nitriles, followed by alkylation of the resulting anion with various electrophiles.

The study began by looking at the same nitrile **1** used by Roche (Table 2.1). At the early stages of the investigation, we looked at straightforward alkylation using an alkyl halide and late addition of methylmagnesium chloride to a solution of the other reagents. Alkylation using the same alkyl halide as Roche proceeded well under the reaction conditions shown in Table 2.1 with 100% conversion to nitrile **2a** according to GC-MS analysis (though a yield of 63% of nitrile **2a** was obtained). The conversion value is based on the area of GC peak for the starting material in comparison with that of the peaks due to all other species detected. There was no evidence of reaction of the Grignard reagent with the nitrile group or the alkyl halide.

Table 2.1: Alkylation reactions of cyclohexanecarbonitrile **1**.



1 **2**

Electrophile	Product structure	Product Number	Conv[a] (%)	Yield[b] (%)
		**2a**	100	63
		**2b**	100	81

a) Based on GC-MS **b)** Based on the yield of isolated product.

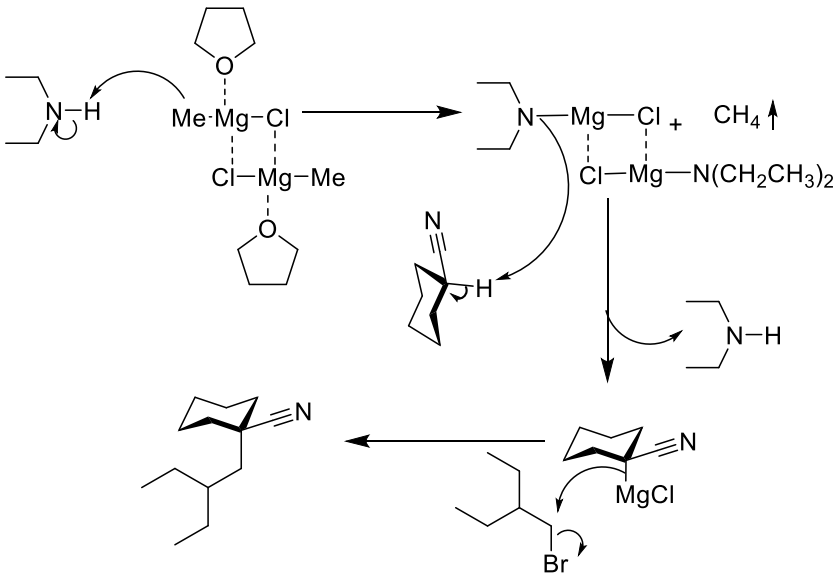


Figure 2.1: Proposed mechanism by Roche for alkylation reaction.

The proposed mechanism for this reaction is shown in Figure 2.1. The mechanism begins with methylmagnesium chloride acting as a base and deprotonating diethylamine. The resulting diethylamide then attacks the cyclohexanecarbonitrile by deprotonating it at the C-2 position. The anion then undergoes an S_N2 reaction with 2-ethylbutyl bromide.

Given the small loading of the amine in the reaction and the lack of any significant reaction between the Grignard reagent with the nitrile directly, this cycle of amine to amide and deprotonation of nitrile to reform the amine must be very rapid. Indeed, on addition of Grignard, we see rapid evolution of a gas consistent with rapid turnover of the amine.

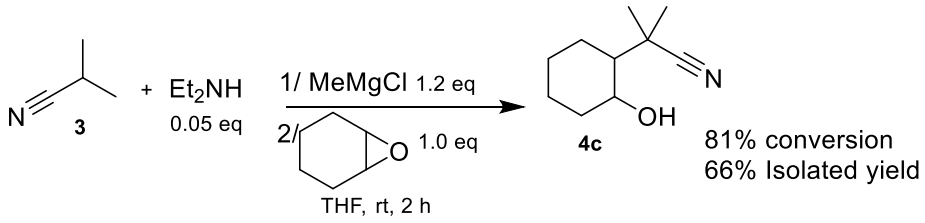
Throughout this study, we did not make exhaustive efforts to optimise yields. Our primary focus was on studying the scope of the reaction and our reactions were conducted on a relatively small scale. As a result, our yields are not as high as the initial report by Roche which was optimised and on large scale. For that reason, the conversion values reported are more significant in terms of assessing the efficiency of the reaction. That said, many of the isolated yields are very high without extensive optimisation.

In those reactions where the conversion and yield are lower, we suspected an elimination reaction from the alkyl halide could potentially be taking place (loss of HX) forming an alkene as alkyl halides are prone to undergo elimination. However, an alkene side product was only observed in the reaction involving acetonitrile, MeMgCl and (2-bromoethyl)benzene, where styrene was detected.

Having successfully repeated the reaction done by Roche to give the product **2a**, an initial scoping study was done to see if the reaction would work with other alkyl halides. The reaction

of cyclohexanecarbonitrile **1** with n-butyl bromide under the reaction conditions shown in Table 2.1 also worked well giving compound **2b** in 100% conversion and 81% yield.
The study was extended by using a different methine nitrile, isobutyronitrile **3** (Table 2.2). Alkylation using the same alkyl halide as Roche proceeded well with 100% conversion to nitrile **4a** according to GC-MS analysis and yield of 74% was obtained. Again, there was no evidence of an attack on the nitrile by the Grignard reagent. Benzyl bromide reacted well giving compound **4b** in 100% conversion and 38% crude yield.

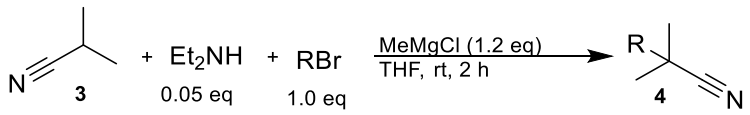
Having tested the versatility in terms of the nitrile, it was decided to move from alkyl halide alkylating reagents to oxygen-containing electrophiles. The reaction of isobutyronitrile **3** and cyclohexene oxide proceeded to give the addition product, however, only 61% conversion to the product **4c** was obtained when the reaction was conducted by late addition of the MeMgCl, with the remainder of the crude mixture being 2-chlorocyclohexanol. A general workup is carried out on all reaction mixtures. This is done by the reaction quenching with 1 M HCl followed by Et_2O, the separated ether layer is then dried over Na_2SO_4. The formation of 2-chlorocyclohexanol arises on work up, from the reaction of unreacted cyclohexene oxide with HCl. When the reaction with cyclohexene oxide was conducted by preforming the anion and adding the electrophile after all other reagents have been added (Scheme 2.1), the product was formed in 81% conversion and a yield of 66%.

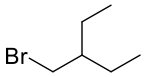
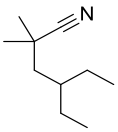
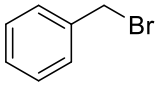
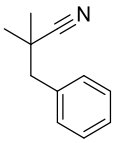
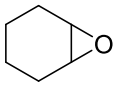
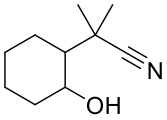
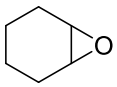
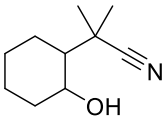


Scheme 2.1: Reaction of isobutyronitrile with cyclohexene oxide *via* preformed anion.

In both the late addition and the preformed anion method, there was no indication of Grignard addition to the cyclohexene oxide by GC-MS or ^{1}H NMR spectroscopy.

Table 2.2: Alkylation reactions of isobutyronitrile.



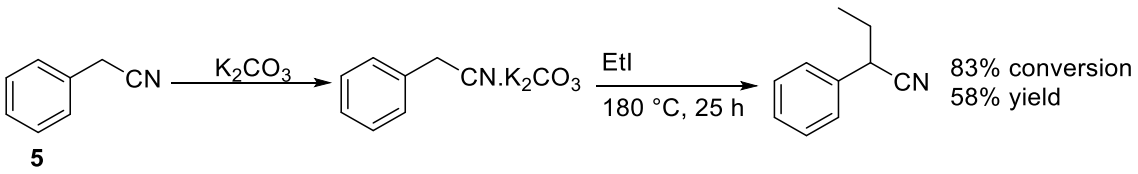
Electrophile	Product structure	Product number	Conv[a] (%)	Yield[b] (%)
		**4a**	100	74
		**4b**	100	38
		**4c**	61	40
		**4c**	81[c]	66[c]

a) Based on GC-MS **b)** Based on the yield of isolated product **c)** Reaction *via* preformed anion.

2.1.1 Monoalkylation of phenylacetonitrile

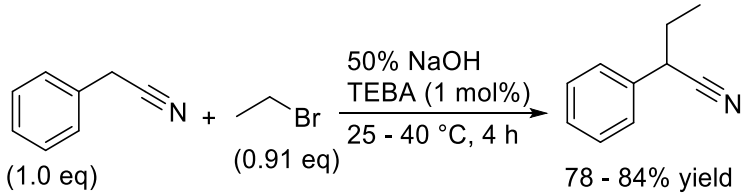
Having established that we could deprotonate and functionalise methine carbons, we next decided to investigate if the methodology could be employed in the functionalisation of methylene carbons. The alkylation of phenylacetonitrile **5** with alkyl halides using the same reaction conditions as above (shown in Table 2.3) was attempted. This would allow us to also evaluate whether an adjacent aromatic group would change the reaction outcome.

Aryl nitriles such as phenylacetonitrile are generally deprotonated by weaker bases such as hydroxide, alkoxide or carbonates. A review of literature reveals the use of potassium carbonate as a base in the alkylation of phenylacetonitrile *via* an intermediate potassium carbonate complex (Scheme 2.2).[1] This method, however, requires the use of 1:2 molar ratio of phenylacetonitrile to potassium carbonate and requires long reaction times and high temperatures to obtain high conversions.



Scheme 2.2: Alkylation of phenylacetonitrile using K_2CO_3.[1]

Alkylation of phenylacetonitrile can also be achieved under phase-transfer conditions (Scheme 2.3).[2,3] This method involves isolation of the product from the organic phase and use of 0.01 eq of the phase-transfer catalyst; the reaction uses unfavourable benzene as part of the workup process.[3]



Scheme 2.3: Phase transfer catalysed alkylation of phenylacetonitrile.

Throughout our investigation, GC-MS allowed us to identify the ratio of unreacted starting material to the monoalkylated product. The GC-MS analysis was achieved by performing a short workup on a sample of the reaction mixture. This was done by taking a sample from the reaction mixture then quenching with the addition of 1 M aqueous HCl followed by Et_2O, the separated ether layer was then dried over Na_2SO_4 and a sample was then injected into the GC-MS. The GC-MS trace was examined and any compounds evident on the GC were identified. The GC-MS is connected to a database from which the fragmentation pattern of the analytes may be correlated to the ESI(*m/z*) mass spectra of known compounds.

Although these reactions were conducted at rt, the reaction temperature generally increases to around 40 °C after initial addition of MeMgCl before decreasing back to rt.

The alkylation of phenylacetonitrile **5** with iodomethane was initially carried out at rt without the application of external heating or cooling. After 2 hours, the mixture consisted of nitrile **5**, monoalkylated product **6a** and dialkylated product **7a** in the ratio 11:82:7 which was measured by GC-MS. Due to similarities in the polarity and boiling point of the nitrile **5,** monoalkylated product **6a** and the dimethylated product **7a**, the monoalkylated product could not be isolated *via* column chromatography or bulb to bulb distillation. The 66% yield reported for the monoalkylated product **6a** is based on crude weight isolated and composition by GC-MS.

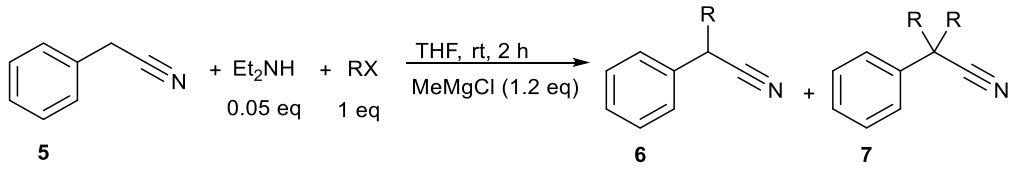
The reaction of phenylacetonitrile **5** with iodoethane also proceeded well. The reaction produced a mixture of nitrile **5**, monoalkylated **6b** and dialkylated product **7b** in the ratio 3:96:1. The monoalkylated product was isolated by column chromatography giving a 73% yield.

The reaction of nitrile **5** with 1-bromo-2-ethylbutane gave the monoalkylated product **6c** in 91% conversion and a yield of 70% after column chromatography. The remainder of the crude reaction mixture being nitrile **5** (8%) and the dialkylated product **7c** (1%).

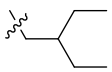
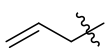
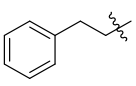
The reaction of phenylacetonitrile **5** with allyl bromide also proceeded well to give the monoalkylated product **6d** in 92% conversion, with the remainder of the reaction mixture being nitrile **5** (4%) and the dialkylated product (4%) **7d**. The monoalkylated product **6d** was obtained in a yield of 70% after column chromatography. Phenylacetonitrile **5** reacted with (2-bromoethyl)benzene to give the monoalkylated product **6e** in 90% conversion and a yield of 56%. The remainder of the crude mixture was nitrile **5** (4%) and 2-(bromoethyl) benzene (6%). In most reactions conducted we observed by GC-MS a small amount of dialkylated product and we noticed that in most cases, dialkylation decreases as the alkyl halide becomes larger; (2-bromoethyl)benzene gave no dialkylation product.

The mono-alkylation products could be separated successfully from the starting material and the dialkylated product by column chromatography giving yields ranging from 56 to 73% of the monoalkylated product representing a reasonable return on the 82 to 96% conversion.

Table 2.3: Alkylation reactions of phenylacetonitrile at rt.



5 6 7

Entry (Product)	R[c]	Ratio[b] (%) SM:Mono:Di	Yield[a] (%)
1 (**6a**)	Me	11:82:7	66[d]
2 (**6b**)	Et	3:96:1	73
3 (**6c**)		8:91:1	70
4 (**6d**)		4:92:4	70
5 **(6e)**		4:90:6[e]	56

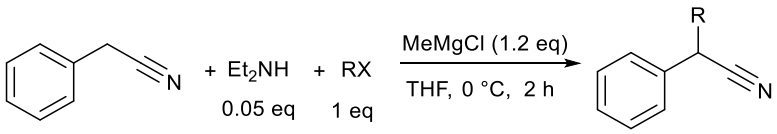
a)Based on the yield of isolated yield or monoalkylation **b)** Based on GC-MS. Starting material (SM): Monoalkylated:Dialkylated product **c)** X= I for entries 1 and 2 and X= Br for entries 3-5 **d)** Yield of monoalkylated product based on crude weight and composition by GC-MS as this compound was not pure. **e**) Ratio of phenylacetonitrile **5**, product **6e** and 2-(bromoethyl) benzene.

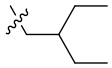
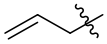
Due to the presence of small amounts of dialkylated product (observed by GC-MS), the reaction conditions were varied in the hope of eliminating the formation of the dialkylated product (Table 2.3.1).

The monoalkylated product should be less reactive than the starting nitrile and thus by conducting the reaction at lower temperature we may be able to gain better control. We wondered if we could eliminate the presence of the dialkylated product by conducting the reaction at a lower temperature.

The reaction to produce **6b** was carried out using different conditions to that reported in Table 2.3. When phenylacetonitrile **5** (1 eq) was reacted with diethylamine (0.05 eq), iodoethane (1.0 eq) and MeMgCl (1.2 eq) at 0 °C, the reaction gave a mixture of phenylacetonitrile SM **5**, monoalkylated **6b** product and dialkylated product **7b** in the ratio 4:95:1 observed by GC-MS. This was not significantly different to the reaction conducted at rt. The reaction of phenylacetonitrile **5** with allyl bromide at 0 °C gave a mixture of phenylacetonitrile SM **5**, monoalkylated **6d** product and dialkylated product **7d** in the ratio 19:80:1 observed by GC-MS. Under the same conditions, we repeated the reaction of phenylacetonitrile **5** with 1-bromo-2-ethylbutane. The reaction again gave a mixture of phenylacetonitrile SM **5**, monoalkylated **6c** product and dialkylated product in the ratio 24:75:1 observed by GC-MS. Although in both these cases the percentage of the dialkylated product present was reduced, conducting the reaction at 0 °C lead to an overall increase in the amount of unreacted starting material remaining in the reaction mixture. Taking these results into account along with the fact that, with one exception, the monoalkylated nitriles could be isolated from the mixture by chromatography we adopted reaction at rt (with temporary increase in temperature on Grignard addition) as the standard reaction conditions for monoalkylation of phenylacetonitrile **5**. As these compounds were previously isolated, during this study we made no attempts to isolate the monoalkylated product. GC-MS was used to identify the product mixture.

Table 2.3.1: Alkylation reactions of phenylacetonitrile at 0°C.



Entry (Product)	R[b]	Ratio[a](%) SM:Mono:Di
1 (**6b**)	Et	4:95:1
2 (**6c**)		24:75:1
3 (**6d**)		19:80:1

a) Based on GC-MS. Starting material (SM): Monoalkylated:Dialkylated product **b)** X= I for entry 1 and X= Br for entries 2 and 3.

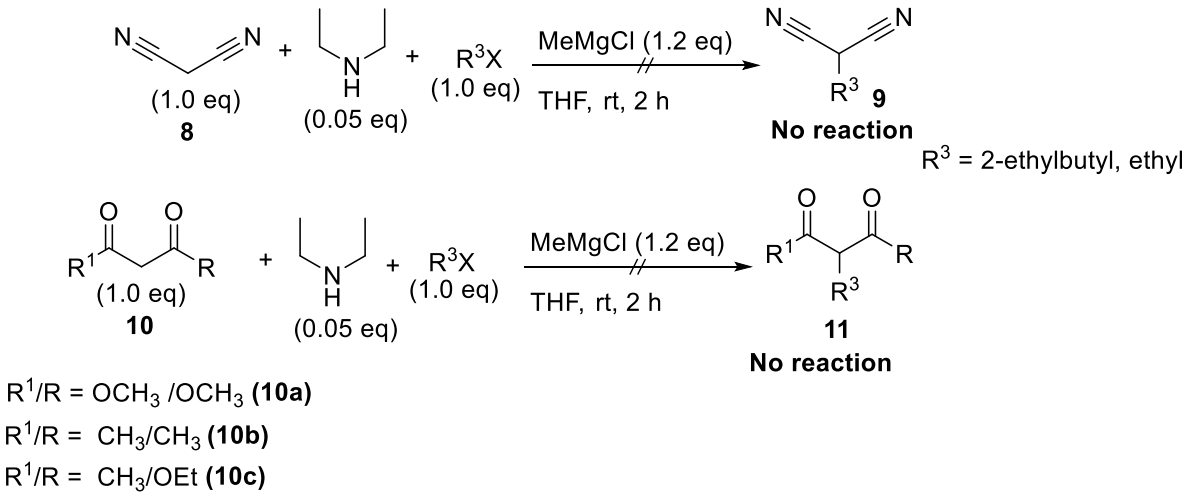
After successful deprotonation and functionalisation of a methylene carbon, in phenylacetonitrile **5**, we wondered if the alkylation of doubly-activated methylene carbons such as malononitrile **8**, dimethyl malonate **10a**, pentane-2,4-dione **10b** and ethyl acetoacetate **10c** would be possible.

The investigation was initiated by looking at the use of malononitrile; the reaction of malononitrile **8** with 1-bromo-2-ethylbutane under the conditions outlined in Table 2.3 was unsuccessful and did not lead to the desired product. The product mixture only contained unreacted starting material. This reaction was repeated at reflux and at 0°C but all to no avail.

The generation and reaction of anions derived from dimethyl malonate, ethyl acetoacetate and pentane-2,4-dione were also explored in reaction with alkylation reagents. Just as observed with malononitrile, these compounds did not react with the alkyl halide, and unreacted starting material was isolated. No direct attack of the Grignard on the nitrile or carbonyl was observed in these cases. The reaction of these nucleophiles, if indeed the anion was generated, with a different alkyl halide was then attempted. Ethyl iodide was chosen as iodide is a slightly better leaving group than bromide and because the ethyl group is smaller than the 2-ethylbutyl group (Scheme 2.4). On examination of the GC-MS and ^{1}H NMR spectrum there was no indication of the desired product, nor was there evidence of a direct attack of the Grignard on the iodoethane.

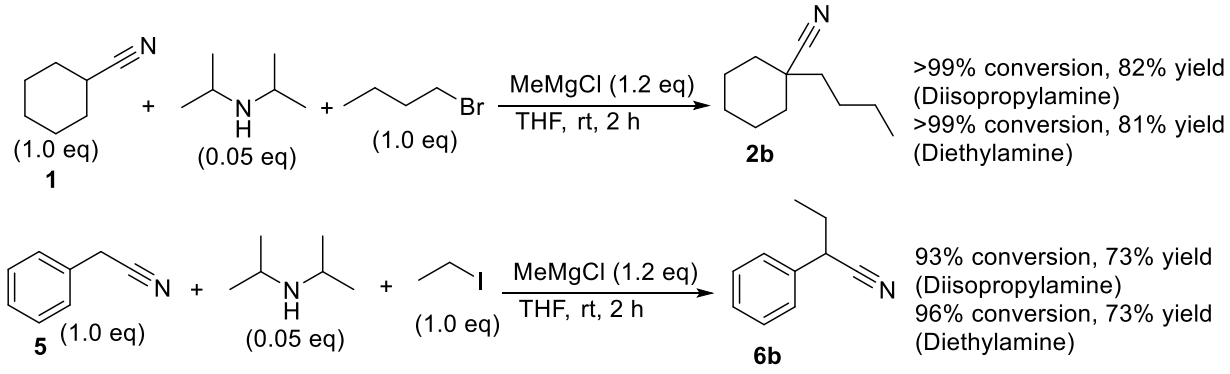
Alkylation of the methylene carbons were carried out *via* the 'late addition' and the 'preformed anion' methodologies. In all cases, they failed to react with alkyl halides.

We later revisited the use of these methylene carbon-based anions. We recognise that these are soft nucleophiles and later in the study, we deal with reaction with softer electrophiles.



Scheme 2.4: Attempted alkylation of doubly-activated methylene carbons.

During our initial reactions, where we sought to establish some feel for the scope and robustness of this reaction methodology, the use of a different amine was explored. Diisopropylamine was examined and we found that the reaction proceeded in the same manner as with diethylamine to give the product in excellent conversions. The use of diisopropylamine was applied to a few reactions; we started by repeating the reaction of cyclohexanecarbonitrile **1** with n-butylbromide to give the product **2b**. Using diisopropylamine as the amine modifier we achieved a conversion of >99% and 82% yield. The use of diisopropylamine was also applied to the reaction of phenylacetonitrile **5** with iodoethane. The product **6b** was obtained in 93% conversion and 73% yield. In both cases, the results are comparable to those using diethylamine (Scheme 2.5).

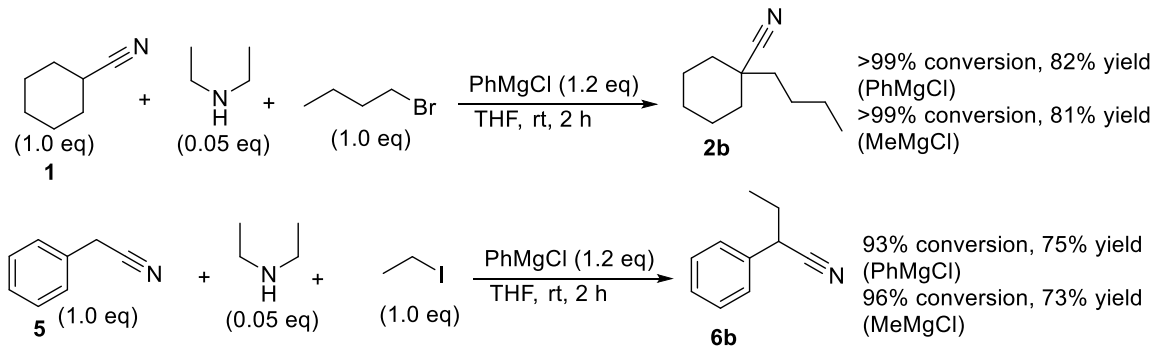


Scheme 2.5: Use of diisopropylamine in alkylation of nitriles.

As well as the use of diisopropylamine, the use of another Grignard reagent in the alkylation reactions was explored (Scheme 2.6).

When phenylmagnesium chloride was used in the place of the methylmagnesium chloride in the reaction to produce **2b** the outcome of the reaction was no different. The reaction gave the alkylated product **2b** in >99% conversion and 82% yield.

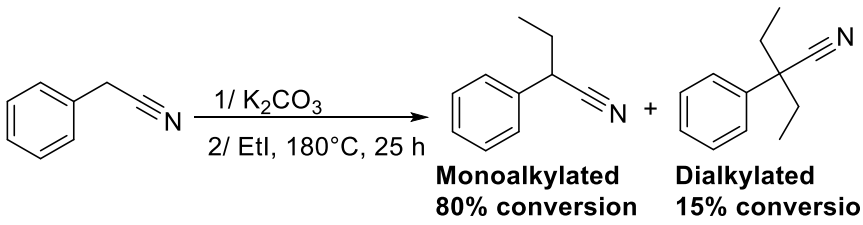
Applying the use of phenylmagnesium chloride to the reaction to produce **6b,** the reaction gave a mixture of starting material nitrile **5**, monomethylated product **6b** and diethylated product **7b** in the ratio 3:93:4 measured by GC-MS and a yield of 75% after column chromatography. The results obtained for the reactions with phenylmagnesium chloride were comparable with the results obtained with MeMgCl, again showing the versatility and robustness of this method (Scheme 2.6).



Scheme 2.6: Phenylmagnesium chloride in alkylation of nitrile **5** and **1**.

2.1.2 Dialkylation of phenylacetonitrile

A common problem, encountered in literature reports, associated with the alkylation of phenylacetonitrile is overalkylation, which occurs as a result of alkyl halide reacting twice with phenylacetonitrile **5**.[1,4] An example is shown in Scheme 2.7 where a conversion of 15% to the dialkylated product is observed in the attempted monoalkylation of phenylacetonitrile.



Scheme 2.7: Overalkylation problem in ethylation of phenylacetonitrile.[1]

A reasonable level of control was achieved in the monoalkylation of phenylacetonitrile and the monoalkylated product could be isolated. We did note however that some dialkylation took place. This led us to speculate as to whether we could gain control over the dialkylation reaction. This would lead to the possibility of producing quaternary nitriles which would be synthetically useful (Figure 2.2).

Figure 2 shows examples of biologically active quaternary nitriles compounds used as drugs molecules. Anastrozole is used in the treatment of breast cancer and verapamil is used for the treatment of angina.[5]

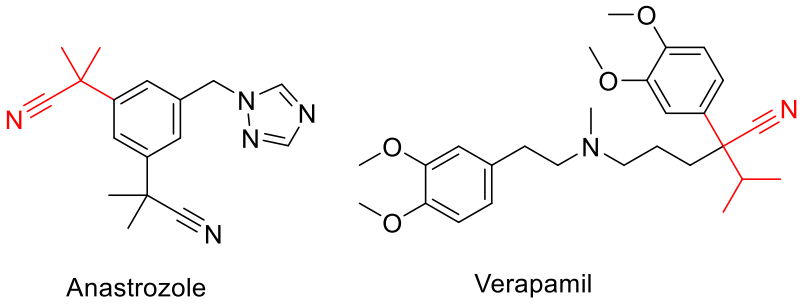


Figure 2.2: Examples of quaternary nitriles in drug molecules.

The monoalkylated products could be prepared by reaction of 1 eq of the nitrile and alkyl halide, 1.2 eq of MeMgCl and 0.05 eq of the amine at rt. A series of reactions were conducted to achieve the optimum reaction conditions for the preparation of the dialkylated product.

The monoalkylation reactions which produced dialkyl products as side products were looked at first. Reacting phenylacetonitrile **5** (1 eq) with iodoethane (2 eq), MeMgCl (2.4 eq) and maintaining the same amount of amine modifier at 0.05 eq, we achieved the diethylated product **7b** in 100% conversion when the reaction was conducted at reflux. When the same conditions were applied to the reaction of phenylacetonitrile **5** with 1-bromo-2-ethylbutane, the dialkylated product **7c** was obtained in 90% conversion, with the remainder of the isolated mixture being unreacted nitrile **5** and the monoalkylated product **6c** represented in 3% and 7% respectively. Increasing the number of eq of the alkyl halide and Grignard reagent to 3 and keeping the temperature at reflux, the reaction to produce the dialkylated 2-ethylbutyl product **7c** was achieved in 100 % conversion.

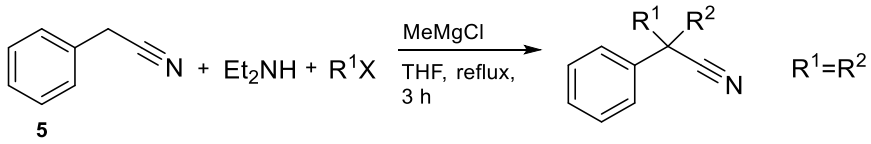
The results obtained from this enabled us to establish standard conditions for one-pot homodialkylation reactions.

The 'one-pot' (**OP**) reactions were conducted using 3 eq of the Grignard reagent and the alkyl halide, maintaining the amount of amine modifier at 0.05 eq. In all cases, we achieved conversions >99% to the quaternary nitrile after three hours at reflux.

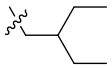
The reaction conditions devised above were applied to the reaction of phenylacetonitrile **5** with iodomethane leading to the dimethylated product **7a**. The dimethylated product was obtained in 100% conversion and 77% yield. Following this, the reaction with iodoethane leading to **7b** and the more complex 1-bromo-2-ethylbutane giving nitrile **7c** were then conducted. Both reactions were successful, with 100% conversion in both cases (Table 2.4).

One-pot homodialkylation

Table 2.4: Dialkylation of phenylacetonitrile.

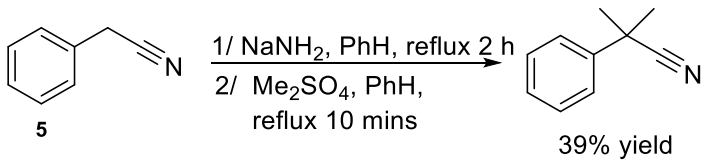


5

Electrophile (R^1)	MeMgCl/Alkyl halide[a]/Amine	Product	Conversion (%)[b]	Yield (%)[c]
Me	3 eq/3 eq/0.05 eq	**7a**	100%	77%
Et	3 eq/3 eq/0.05 eq	**7b**	100%	75%
	3 eq/3 eq/0.05 eq	**7c**	100%	79%

a) Ethyl iodide, methyl iodide, 2-ethylbutyl bromide **b**) Percentage of targeted product in the final reaction mixture by GC-MS **c)** Isolated product yield.

The syntheses of similar dialkylated compounds are reported in the literature. We feel however our method may have advantages over many of the reported methods. For example, in the example shown below, the synthesis is low yielding and not as straightforward as the MeMgCl method. The method requires the use of reagents such as dimethyl sulphate in the presence of sodamide in solvents such as benzene[6] (Scheme 2.8).



5

Scheme 2.8: Synthesis of 2-methyl-2-phenylpropanonitrile.

These dialkylated compounds are useful intermediates in the synthesis of pharmaceutically active drugs, as seen in the case of dimethyl phenylacetonitrile **7a** which is used in the preparation of antihistaminic piperidine derivatives.

Figure 2.3 shows the antihistamine drug, fexofenadine, which synthetically is derived from 2-methyl-2-phenylpropanonitrile.[7]

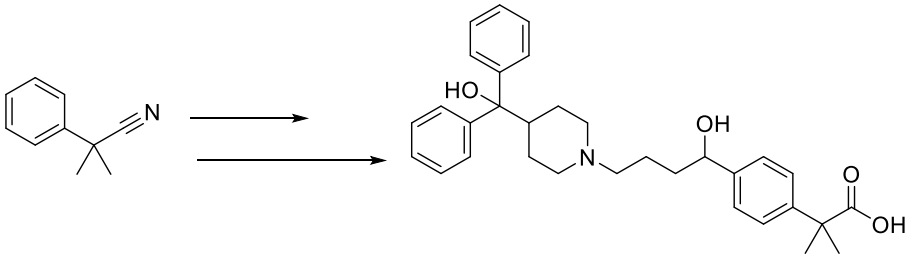


Figure 2.3: Dimethylated nitrile intermediate in the synthesis of fexofenadine.

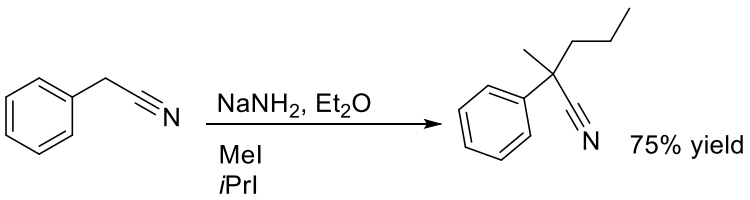
Sequential addition

The natural progression from the one-pot homodialkylation would involve developing routes which would allow dialkylation with different alkyl groups (heterodialkylation). This would open synthetic routes to many different nitriles of interest.

A review of the literature revealed that heterodialkylation of phenylacetonitrile using alkyl halides has been reported very rarely and for a limited number of molecules. [8–11]

There is no general method for the heterodialkylation of phenylacetonitrile. The methods for the heterodialkylation of phenylacetonitrile reported involve the use of sodamide in ether (Scheme 2.9) or the use of LDA at –40 °C.[11]

The dialkylated nitriles reported involve an initial isolation step to produce the monoalkylated nitrile followed by further reaction to afford the heterodialkylated product.



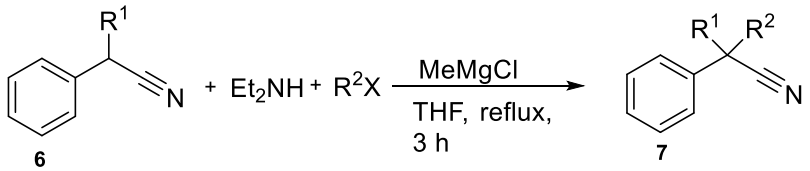
Scheme 2.9: Heterodialkylation of phenylacetonitrile.[9]

The ways in which we might make heterosubstituted quaternary nitriles was then investigated. The work preparing the homosubstituted quaternary nitriles in a one-pot reaction established that there did not seem to be a barrier in the formation of quaternary nitriles using the MeMgCl method. We decided to start with tertiary nitriles (prepared in Table 2.3) and attempt

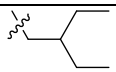
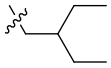
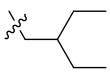
deprotonation and alkylation to produce the quaternary product in a 'Sequential Alkylation' (**SA**) route which ultimately, we could trace back to phenylacetonitrile **5**.

Three examples are shown in Table 2.5. In previous reactions where we prepared quaternary nitriles (homodialkylation) an excess of alkyl halide and Grignard was used. As we were starting with a monoalkylated nitrile product to produce a quaternary nitrile product we wondered if we could use just 1 eq of the incoming alkyl halide and conduct the reaction at reflux. We started by looking at the reaction of 2-allyl-2-phenylacetonitrile **6d** with 1-bromo-2-ethylbutane. It was found the reaction proceeded well giving 96% conversion after refluxing for 3 hours and a yield of the isolated product **7d** in 78% after column chromatography. No direct addition of Grignard to the nitrile or reaction with the halide was observed. The remainder of the crude reaction mixture was unreacted starting material **6d**. This result was very encouraging, and we decided to employ the same general method in adding an ethyl group to 4-ethyl-2-phenylhexanenitrile **6c**. The reaction was again successful giving 94% conversion to nitrile **7e** and 71% yield. Again, the remainder of the crude reaction mixture was the unchanged starting material **6c**. The product was also prepared reversing the order of addition, adding the ethylbutyl group to 2-phenylbutyronitrile **6b**. The reaction proceeded to give the heterodialkylated product **7e** in 96% conversion and a yield of 77%.

Table 2.5: Sequential addition with phenylacetonitrile **5**.

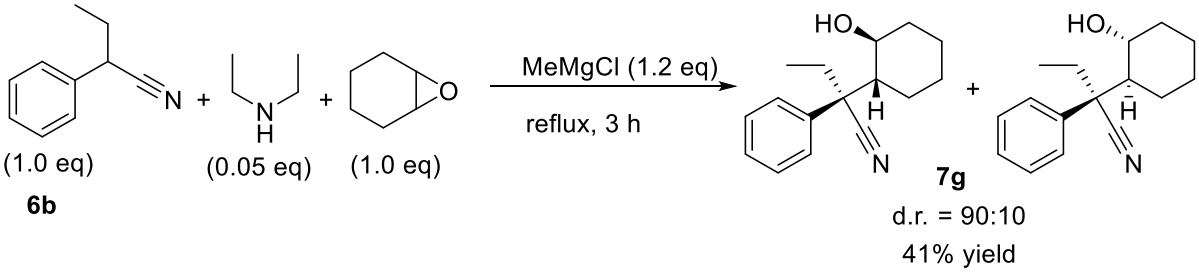


6 **7**

R^1	R^2	MeMgCl/Alkyl halide[a]/Amine	Product	Conversion (%)[b]	Yield (%)[c]
Allyl		1.2 eq/1.0 eq/0.05 eq	**7d**	96%	78%
	Et	1.2 eq/1.0 eq /0.05 eq	**7e**	94%	71%
Et		1.2 eq/1.0 eq /0.05 eq	**7e**	96%	77%

a) Allyl bromide, iodoethane, 2-ethylbutyl bromide **b**) Percentage of targeted product in the final reaction mixture by GC-MS **c)** Isolated product yield.

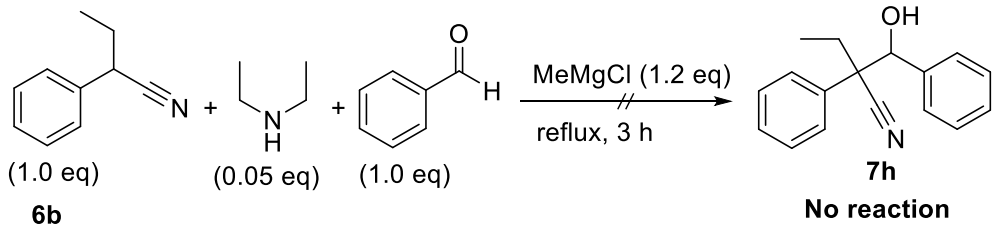
The MeMgCl chemistry was extended further to use other electrophiles such as cyclohexene oxide (Scheme 2.10). The same route was employed adding the MeMgCl to the solution containing 2-phenylbutyronitrile **6b**, diethylamine and cyclohexene oxide. The reaction produced the diastereomeric products **7g** in 70% conversion. The remainder of the mixture was unchanged starting material **6b** and 2-chlorocyclohexanol. The presence of the 2-chlorocyclohexanol is as result of the reaction of unreacted cyclohexene oxide with HCl during the workup process. The diastereomeric products **7g** could not be separated thus it was hard to be absolute in assigning spectral features to one diastereomer. The diastereomeric ratio was 90:10, measured by ^{1}H NMR spectroscopy. An isolated product yield of 41% was obtained for a mixture of the diastereomeric products **7g** after column chromatography (Scheme 2.10).



Scheme 2.10: Sequential addition with cyclohexene oxide.

With the success of cyclohexene oxide as an electrophile, we wondered if it would be possible to repeat the above reaction but this time replacing the cyclohexene oxide with benzaldehyde. We started by trying to react benzaldehyde with 4-ethyl-2-phenylhexanenitrile **6c**. This reaction was unsuccessful and yielded unchanged starting materials. The reaction of benzaldehyde with 2-phenylbutyronitrile **6b** was then attempted. The reaction again was unsuccessful. Conducting the reaction *via* the late addition method and *via* the preformed anion, the method had no positive effect on the outcome of the reaction. The reaction produced unreacted starting materials in all cases.

Although the addition of the 4-ethyl-2-phenylhexanenitrile **6c** and 2-phenylbutyronitrile **6b** to benzaldehyde were unsuccessful, there was no direct attack of the Grignard on the benzaldehyde observed, which tells us that the Grignard was used in generating the anion, but the anion was not reacting with the benzaldehyde (Scheme 2.11). It could also be possible that the anion did react then regenerated nitrile **6b**.



Scheme 2.11: Attempted reaction of 2-phenylbutyronitrile **6b** with benzaldehyde.

The results obtained were quite surprising as we have successfully reacted benzaldehyde with cyclohexanecarbonitrile **1** to produce quaternary products, a result we will discuss later.

One-Pot Heterodialkylation

Following on from successfully synthesising heterodialkylated products *via* the sequential addition route where we added, isolated and added again, we then wondered if it would be possible to go directly from phenylacetonitrile **5** to the heterosubstituted quaternary nitrile in a 'One-Pot Heterodialkylation' (**OPHD**). From previous work, rt was found to be the optimum temperature to selectively obtain the monoalkylated product. We started the investigation of **OPHD** by carrying out an initial monoalkylation at rt to minimise formation of the dialkylation product. This reaction was not worked up and the second different alkyl halide along with a second portion of Grignard was added. The second alkylation reaction was conducted at an elevated temperature (Table 2.6). Reaction of phenylacetonitrile **5** with iodoethane at rt to produce the monoalkylated product **6b** under the monoalkylation conditions was first attempted. After the addition of iodoethane, GC-MS analysis was conducted to determine the product composition at this intermediate stage. The mixture contained SM, monoalkylated nitrile **6b** and dialkylated product **7b** in the ratio 3:96:1. We then added 1-bromo-2-ethylbutane, a second portion of the amine and the Grignard reagent. The reaction temperature was then raised to reflux.

The results obtained using the one-pot (**OPHD**) method from the sequence where the ethyl group is added first before the addition of the 2-ethylbutyl group gave the nitrile product **7e** in 94% conversion and a yield of 76%.

The result from the **OPHD** compares favourably with the sequential addition method (Table 2.5, entry 2) which gave a conversion of 94% and a yield of 71% but involves one more step.

The **OPHD** reaction where the ethyl group is added first followed by the addition of the methyl group was also successful. In this case, it was necessary to add 2 eq of iodomethane for the reaction to go to completion.

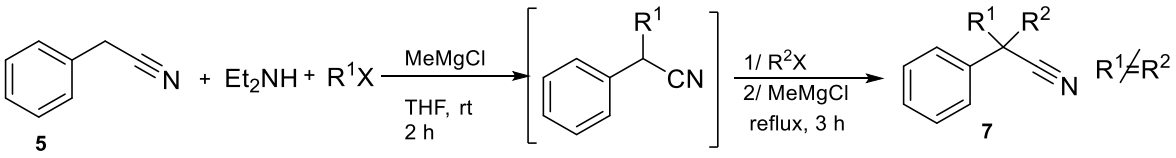
When just 1 eq of iodomethane was added to 2-phenylbutyronitrile **6b,** the heterodialkylated nitrile product was obtained in 68% conversion. When 2 eq of iodomethane was used the product **7f** was formed with 94% conversion. The main side product was the diethylated product **7b** at 5%. A chromatographic separation to produce an analytical sample proved difficult and the yield of **7f** was only 29%. The possible reason behind the need for an excess of the iodomethane is its relative volatility and the fact that the second addition involves reaction at reflux.

In general, for the **OPHD** procedure, we included a second charge of 0.05 eq of the amine in the second alkylation step. As the amine has a catalytic role, this second charge should not be necessary and when the reaction to produce the product **7e** was repeated (ethyl addition followed by 2-ethylbutyl) without the second charge of amine the outcome was unaffected (97% conversion, 79% yield)

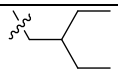
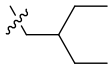
We carried out one study to see if the order of the addition of the alkyl groups was critical. When the order in which the alkyl halides leading to the ethyl, 2-ethylbutyl nitrile **7e** were added was reversed and the 2-ethylbuthyl group was added before the ethyl group, this reaction sequence gave the heterodialkylated product **7e** in just 47% conversion. The remainder of the reaction mixture contained 1-iodo-2-ethylbutane, monoethylated product **6b**, diethylated product **7b**, mono-ethylbutyl product **6c**, and di-ethylbutyl product **7c** in the ratio 8:2:26:16:1.

From our study of the OPHD, it can be concluded that in the heterodialkylation reaction of phenylacetonitrile **5** with ethyl and 2-ethylbutyl group, it was better to install the smaller ethyl group first. This is admittedly based on one reaction type.

Table 2.6: One-pot Heterodialkylation.



5 7

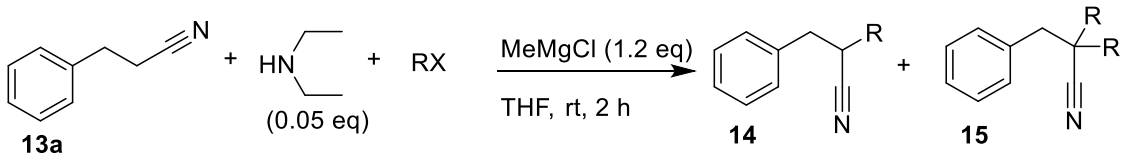
R^1	R^2	MeMgCl/Alkyl halide[a]/Amine	Product	Conversion (%)[b]	Yield (%)[c]
Et		1.2 eq/1.0 eq/0.05 eq (addn R^1) 1.2 eq/1.0 eq/0.05 eq (addn R^2)	**7e**	94%	76%
Et		1.2 eq/1.0 eq/0.05 eq (addn R^1) 1.2 eq/ 1.0 eq/ residual amine from first addn (addn R^2)	**7e**	97%	79%
Et	Me	1.2 eq/1.0 eq/0.05 eq (addn R^1) 1.2 eq/2.0 eq/0.05 eq (addn R^2)	**7f**	94%	29%

a) Iodoethane, iodomethane and 2-ethylbutyl bromide **b**) Percentage of targeted product in the final reaction mixture by GC-MS **c)** Based on yield of isolated product

Having successfully functionalised the phenylacetonitrile it was decided to see if it was possible to control alkylation of a different type of methylene carbon. Specifically, we wanted to see if a non-benzyl nitrile could be alkylated. We chose to alkylate hydrocinnamonitrile **13a**, where the aromatic group is further away from the hydrogens alpha to the nitrile. Success in the functionalisation of this nitrile would open synthetic routes for building up further complexity on the nitrile. An initial alkylation of hydrocinnamonitrile **13a** with iodomethane under the same conditions used in the monoalkylations (Table 2.7, entry 1) was carried out. It was found that when 1 eq of iodomethane was used, the conversion to the product **14a** was only 30%, measured by GC-MS analysis. At elevated temperatures (reflux) and a longer reaction time, we observed no change to the conversion. When we increased the amount of iodomethane used to 2 eq, the conversion increased significantly to 87% and a yield of 68% of nitrile **14a**

was achieved. The remainder of the crude mixture was the nitrile starting material **13a** and some dimethylated product **15a** representing 10% and 3% of the crude product mixture respectively. Hydrocinnamonitrile **13a** also reacted well with 1 eq of iodoethane with a conversion of 90% achieved and a yield of 70% of the ethylated nitrile **14b**.

Table 2.7: Alkylation reactions of hydrocinnamonitrile **13a**.



13a 14 15

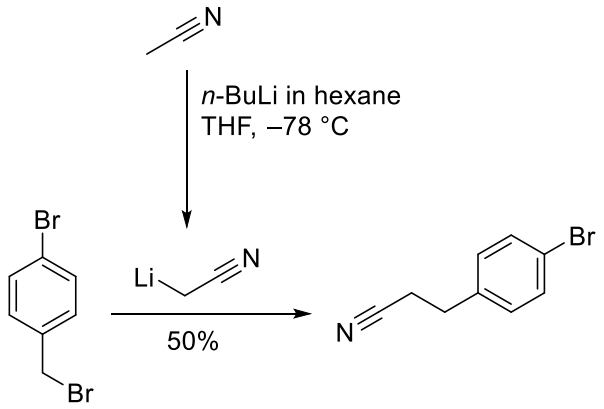
Entry (Product)	R[c]	Alkyl halide (eq)	Ratio[b] (%) SM:Mono:Di	Yield[a] (%)
1 (**14a**)	Me	2.0 eq	10:87:3	68
2 (**14b**)	Et	1.0 eq	1:90:8	70

a) Based on yield of isolated product for monoalkylation **b)** Based on GC-MS. Starting material (SM): monoalkylated:dialkylated product.**c)** Iodomethane and iodoethane

The reactions above show initial work done with hydrocinnamonitrile **13a**. We revisit this chemistry later and show that we could further build up the complexity on hydrocinnamonitrile **13a,** starting from the readily available acetonitrile.

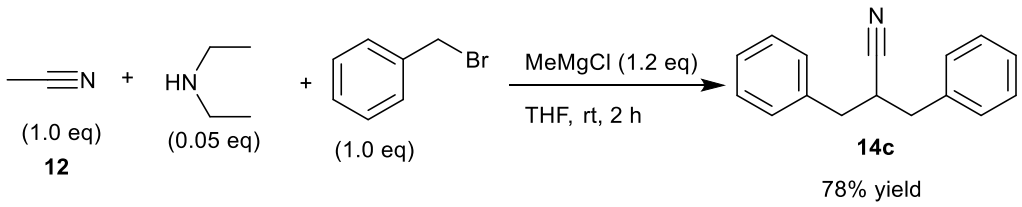
2.1.3 Trialkylation of acetonitrile

With the success of alkylating methine and methylene carbons, the method was challenged further by using the simplest available alkyl nitrile as the starting material. Publications on the alkylation of acetonitrile are quite rare although Taber reports reasonable yields for the direct alkylation of lithioacetonitrile at –78 °C (Scheme 2.12).[12] The lithioacetonitrile was prepared by the addition of *n*-BuLi to acetonitrile and gave a 50% yield in reaction with a benzyl bromide.



Scheme 2.12: Alkylation of acetonitrile using *n*-BuLi.

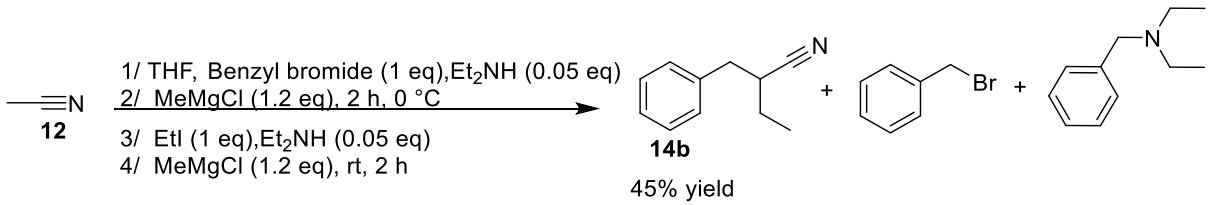
Using acetonitrile, we could potentially add three different alkyl groups *via* either sequential or one-pot processes. We started this part of the study by trying to add one group by alkylating acetonitrile using the same conditions as we had previously used for monoalkylation of phenylacetonitrile (as seen in Table 2.3). However, when we alkylated acetonitrile **12** with 1 eq of benzyl bromide at rt, the reaction proceeded to give a mixture a substantial proportion of which was 2,2-dibenzyl acetonitrile, which results from the benzyl bromide reacting twice with acetonitrile (Scheme 2.13).



Scheme 2.13: Dialkylation of acetonitrile with benzyl bromide.

From the results obtained, it was evident that the conditions used previously weren't appropriate for the monoalkylation of acetonitrile. It was decided to reduce the reaction temperature to 0 °C. We carried out a test reaction, where we reacted acetonitrile with 1 eq of benzyl bromide at the lower temperature. The reaction proceeded to give the monoalkylated

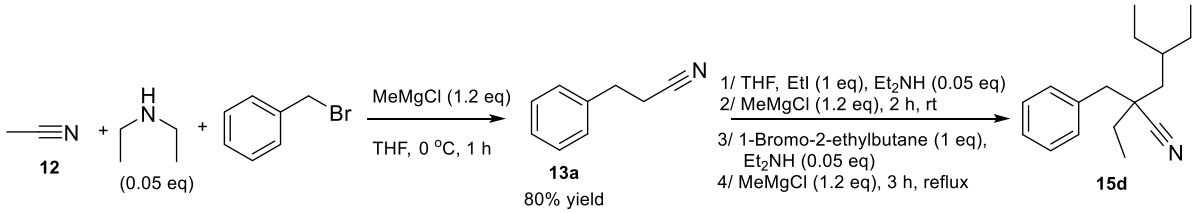
product in 95% conversion. Having improved the conditions to selectively monoalkylate acetonitrile, we wondered if it was possible to add more than one group in a one-pot manner. We started by doing an initial monoalkylation; the reaction of acetonitrile with 1 eq of benzyl bromide at 0 °C. After 1 hour the mixture was analysed on GC-MS and the reaction mixture contained benzyl bromide, monoalkylated product **13a** and *N*,*N*-diethylbenzylamine in the ratio 3:93:4. The diethylbenzylamine results from reaction of the amide anion in a nucleophilic fashion with the alkyl halide. This reaction was not worked up and was followed by the addition of iodoethane and a second portion of the Grignard reagent at rt. After 2 hours this reaction sequence gave a mixture of benzyl bromide, *N*,*N*-diethylbenzylamine, ethyl alkylated nitrile **14b** and some unknown peaks in the ratio 5:4:78:13 (Scheme 2.14). The ethyl substituted nitrile **14b** was isolated in 45% yield after column chromatography.



Scheme 2.14: One-pot alkylation reaction with acetonitrile.

From this reaction, we found that although the addition of the second and different alkyl group in a 'one-pot' manner to acetonitrile leads to formation of the product, a lot of side products were also formed. As we saw the build-up of side product in the second addition step, we didn't attempt the addition of a third group in one pot.

Simplifying the sequence somewhat we initially alkylated acetonitrile **12** with 1 eq of benzyl bromide to give the nitrile **13a** and followed this initial alkylation, was the addition of an ethyl group and a 2-ethylbutyl group (Scheme 2.15).



Scheme 2.15: Synthetic elaboration of acetonitrile.

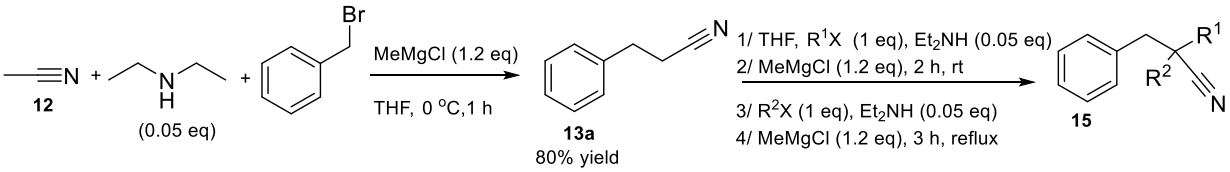
Reaction of acetonitrile with benzyl bromide at 0 °C gave a crude mixture which contained a mixture of benzyl bromide SM, product **13a** and *N*,*N*-diethylbenzylamine in the ratio 6:92:2 as measured by GC-MS. The alkylated product **13a** was isolated in 80% yield after column

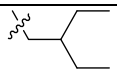
chromatography. Two different alkyl groups (Table 2.8) were then added under the established reaction conditions used in the one-pot heterodialkylation process.

The preparation of nitrile **15d** was carried out by putting the ethyl group on prior to the 2-ethylbutyl group. The isolated product **13a** was alkylated in a one-pot process initially with iodoethane at rt and then with 1-bromo-2-ethylbutane at reflux, in both cases amine (0.05 eq) and MeMgCl (1.2 eq) were used to affect the required deprotonation. The trisubstituted product **15d** made up 98% of the crude product with the other product being nitrile that had been di-substituted by the ethyl group. Following chromatography, the product **15d** was isolated in 86% yield. The overall yield from acetonitrile was thus 69% (Table 2.8). When the isolated product **13a** was alkylated in a one-pot process initially with iodoethane at rt followed by the addition of allyl bromide at reflux, the trisubstituted product **15e** made up 92% of the crude product with the other products being nitrile that had been monosubstituted and disubstituted by the ethyl group. Following chromatography, the required product **15e** was isolated in 80% yield. The overall yield from acetonitrile was thus 64%.

When the reaction was repeated reversing the order at which the reagents were added (allyl bromide addition first followed by iodoethane), the outcome of the reaction was unaffected. The trisubstituted product **15e** was formed with 90% conversion and a yield of 81% after column chromatography. The overall yield from acetonitrile was 65%.

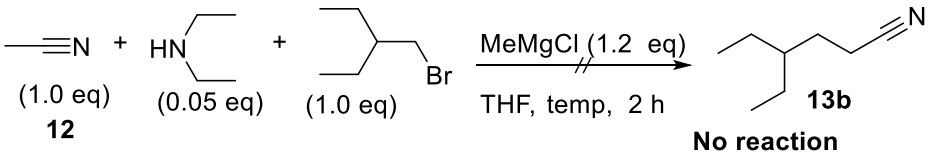
Table 2.8: Alkylation of acetonitrile **12**.



R^1	R^2	MeMgCl/Alkyl halide[a]/Amine	Product	Conversion (%)[b]	Yield (%)[c]
Et		1.2 eq/1.0 eq/0.05 eq	**15d**	98%	69%
Et	Allyl	1.2 eq/1.0 eq /0.05 eq	**15e**	92%	64%
Allyl	Et	1.2 eq/1.0 eq /0.05 eq	**15e**	90%	65%

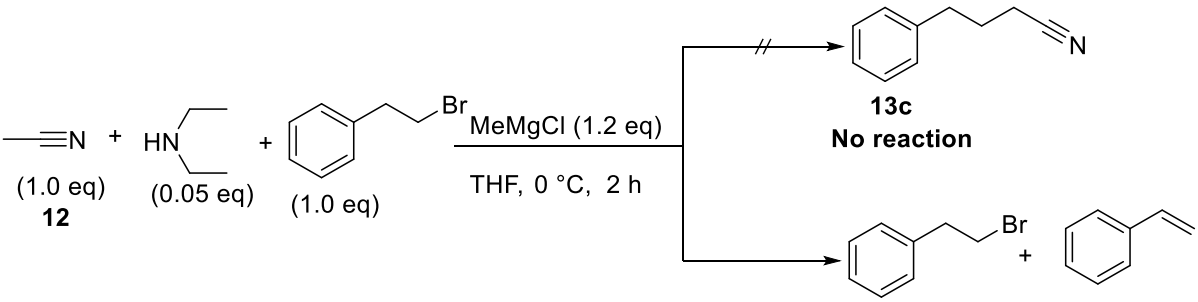
a) Allyl bromide, 2-ethylbutyl bromide, iodoethane **b**) Percentage of targeted product in final reaction mixture by GC-MS **c)** overall yield from acetonitrile.

The versatility of this method was further explored by alkylating acetonitrile with a different agent besides benzyl bromide. Having established the conditions for the mono-alkylation of acetonitrile, we attempted to alkylate acetonitrile with 1 eq of 1-bromo-2-ethylbutane. However, this reaction was unsuccessful and starting material was recovered. The outcome remained unchanged when the reaction of acetonitrile with 1-bromo-2-ethylbutane was repeated at different temperatures (rt and reflux), unreacted bromoethylbutane was recovered each time (Scheme 2.16).



Scheme 2.16: Attempted alkylation of acetonitrile with 1-bromo-2-ethylbutane.

Reaction of acetonitrile **12** and 1 eq of (2-bromoethyl)-benzene was also attempted and failed, and GC-MS analysis of the reaction mixture showed the presence of unreacted (2-bromoethyl)-benzene and styrene, due to HBr elimination, representing 66% and 34% of the crude product mixture respectively (Scheme 2.17).



Scheme 2.17: Attempted alkylation of acetonitrile with (2-bromoethyl)-benzene.

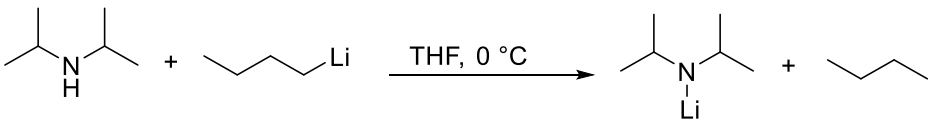
MeMgCl has been used along with an amine modifier as a base in the trialkylation of acetonitrile. We have been able to alkylate acetonitrile with benzyl bromide. After isolation further functionalisation of hydrocinnamonitrile **13a** to generate the tri-substituted nitriles **15d-e** has been successfully achieved. So far, however, this method has only been successfully demonstrated with benzyl bromide. It seems certain that the initial group added must be relatively large to ensure the product is not easily lost on workup due to its volatility. Although our success to this point is limited by only being able to add one group in the first addition to acetonitrile we can elaborate in quite a few directions from there. A literature search

of alkylations of acetonitrile returned no reported reactions involving tri-alkylation of acetonitrile.

2.1.4 Green chemistry considerations in alkylation reactions

As mentioned in the introductory chapter, bases such as lithium diisopropylamide (LDA) are typically used in deprotonating α to the nitrile. However, the use of these lithium-based reagents poses some issues on a large or manufacturing scale given the hazards/supply issues involved.

The use of the MeMgCl chemistry offers many advantages over LDA at manufacturing scale, whether LDA is sourced commercially or manufactured in-house using n-BuLi (Scheme 2.18). n-BuLi is pyrophoric and thus represents a severe fire risk. Its use to prepare LDA involves an additional synthetic step which needs to be conducted at a low temperature and with extreme safety controls in place.



Scheme 2.18: Formation of LDA from BuLi.

The manufacturing process for MeMgCl is simpler than that for LDA or n-BuLi; magnesium is cheaper and more naturally abundant than lithium; and magnesium presents fewer environmental issues than lithium.[13]

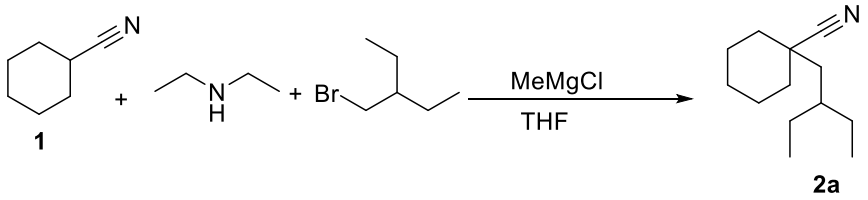
Another environmental advantage of the use of MeMgCl with an amine mediator over the use of LDA is the amount of amine used. The reduction in amine loading from 1 eq with LDA to 0.05 eq in both the “late MeMgCl” and the “preformed anion” process simplifies management of waste streams.

At commercial scale recycling of solvents is an economic and environmental essential. MeMgCl is commercially available, or can be prepared on site, in neat THF and this simplifies solvent recycling in THF-based processes. Commercial LDA is only available in mixtures of solvents (typically THF, ethyl benzene and heptane) and n-BuLi is usually only available in alkanes such as hexanes. Recovery of THF from the mixture of solvents from processes involving LDA is often not feasible without incurring excessive cost.

MeMgCl in THF is also more stable than commercial preparations of LDA, which are reported to decompose by 1% over 1.5 weeks at 20 °C.[14] The decomposition of LDA complicates supply chain management at industrial scale and the removal, deactivation and disposal of the decomposition product lithium hydride can be highly hazardous and costly.

The E Factor of a reaction is defined as the mass ratio of waste to desired product in a process, the lower the number the better. It has become one of the methods along with atom efficiency by which reactions are assessed for their environmental impact.[15]

Several Roche patents[16–18] report the transformation outlined in Scheme 2.19 being carried out in three ways *via* 'preforming' the anion prior to addition of the alkylating agent, *via* 'late addition' of the Grignard to all other reagents and *via* the traditional method involving the use of LDA.[18]

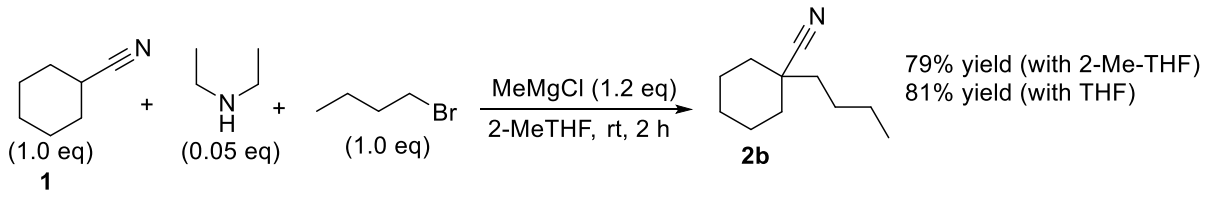


Scheme 2.19: Alkylation of cyclohexanecarbonitrile **1**.

Using the scales reported by Roche the E-Factors for the conversion of cyclohexanecarbonitrile **1** to alkylated nitrile **2a** using LDA, 'preforming the anion' and 'late addition' were calculated. The E-Factors for each method are 13.9, 12.9 and 9.7 respectively. The scales reported by Roche in the patents for the conversion of cyclohexanecarbonitrile **1** to alkylated nitrile **2a** using LDA, 'preforming the anion' and 'late addition' were 24 g, 11 g and 50 g respectively.

Another "green" advantage of the reported MeMgCl alkylation is that energy requirements are lower because extreme temperatures are not required. The chemistry works well between 0 °C and 70 °C and most often we have worked without heating or cooling in place, whereas organolithium reagents, including LDA, often require sub-zero temperatures (–78 °C).

During our development studies as part of the workup process diethyl ether was used as a diluent of the reaction mixture to allow for water extraction. This was necessary as the THF solvent is substantially soluble in water. We wanted to make the process more environmentally friendly and thus turned to the greener solvent 2-Me-THF. 2-Me-THF is considered to be the greenest of the widely available ether solvents due to the fact it can be made from sugar sources.[20] Its low water solubility allowed us to complete the work-up without addition of diethyl ether. The use of 2-Me-THF was applied in the reaction of cyclohexanecarbonitrile **1** with n-butyl bromide to give compound **2b** (Scheme 2.20). The reaction worked well, and the product was isolated in 79% yield with >99% purity without a purification step. This compares well with the same reaction using THF which gave 81% yield with >99% purity.



Scheme 2.20: Alkylation reaction in 2-MeTHF.

Part of our standard diethyl ether work-up had involved a sodium sulphate drying step, but we found it was unnecessary to dry the 2-Me-THF extract with sodium sulphate prior to solvent removal as any water present (up to 4.5%) is removed during distillation as an azeotrope (10.5% water) with the solvent.[19] When the reaction to produce **2b** was repeated with no drying agent, the product was isolated in 79% yield. This result compares well with that obtained using THF and significantly reduces waste.

It can be concluded from the above discussions that the methylmagnesium chloride chemistry has significant advantages over the lithium-based reagent with regards to safety on an industrial and research lab scale and is also well aligned with Paul Anastas's 12 Principles of Green Chemistry (Figure 2.4).[20]

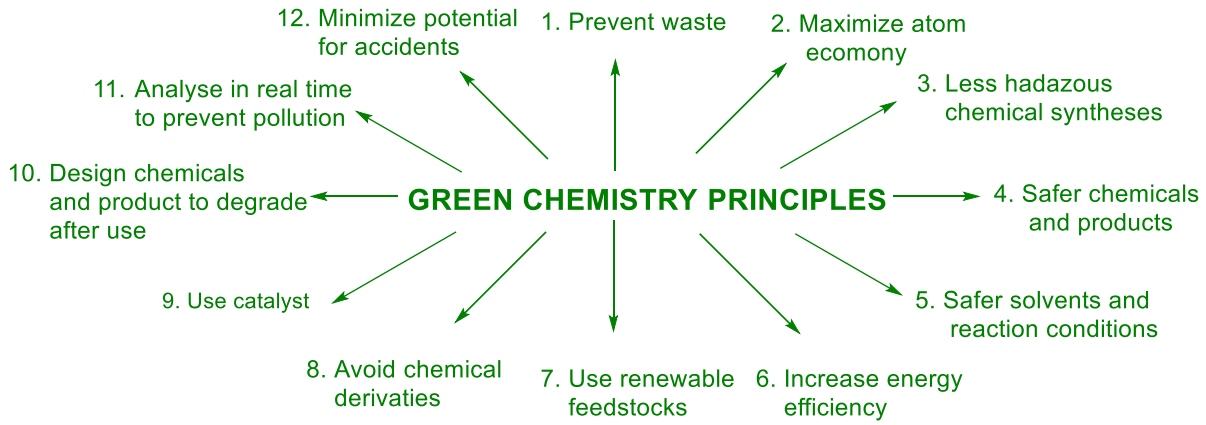


Figure 2.4: Green chemistry principles by Paul Anastas.[20]

Our process has advantages over the existing technology with respect to principles 1-9 and 12 as outlined by Paul Anastas.

The manufacturing of MeMgCl from magnesium and methyl chloride is perfectly atom economical. In the MeMgCl alkylation process, the amine mediator is used in less than stoichiometric amounts and in some cases can be reused in sequential steps. The use of the 2-Me-THF is considered a green solvent. The use of 2-Me-THF in MeMgCl alkylation

eliminates the need for diethyl ether in the work-up and the use of drying agents, which prevents waste.

The MeMgCl alkylation has minimal energy requirements, reactions are conducted at 0 °C, rt and sometimes at reflux. MeMgCl is also commercially available in THF which can be recovered without incurring excessive cost.

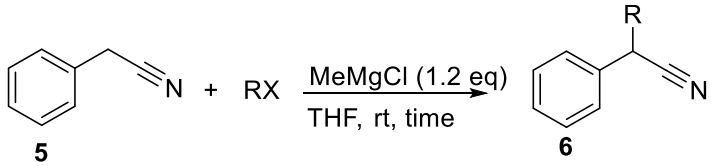
2.1.5 Mechanistic study of alkylation reactions

In general, for all alkylation reactions a charge of 0.05 eq of the amine was included.

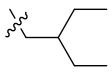
As the amine has a catalytic role, we wondered if the amine actively supressed direct addition of the Grignard reagent to the nitrile and whether the presence of the amine makes the deprotonation faster.

This study began by repeating the reaction to produce the monoalkylated product **6b** without the amine. After 2 hours the outcome of the reaction was unaffected (97% conversion, 78% yield) and no formation of phenylacetone (from addition of MeMgCl to the nitrile) was observed. When the reaction to produce the monoalkylated product **6c** was repeated, it was found that after 2 hours the reaction produced a mixture of 1-bromo-2-ethylbutane and product **6c** in the ratio 32:68 observed by GC-MS. After a reaction time of 18 hours the conversion improved and gave the product **6c** in 81% conversion. The remainder of the mixture being 1-bromo-2-ethylbutane and the dialkylated product **7c**. This result differs from that obtained when the diethylamine was present (91% conversion after 2 hours). Even with extended reaction time the conversion suffered although no evidence of phenylacetone was found (Table 2.9).

Table 2.9: Alkylation of phenylacetonitrile **5** without an amine mediator.



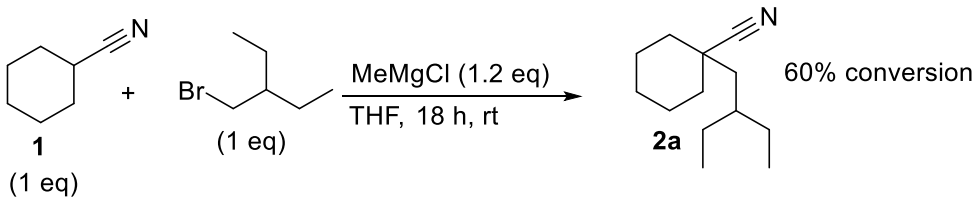
5 **6**

R	Reaction time/Product Number	Conversion[a] (%) SM:Mono:Di	Yield[b] %
Et	2 h (**6b**)	1:95:3	78
	18 h (**6c**)	17[c]:81:2	-

a) Percentage of targeted product in final reaction mixture by GC-MS **b)** based on yield of isolated product **c)** alkyl halide SM **Reaction condition:** 1 eq nitrile, 1 eq alkyl halide and 1.2 eq MeMgCl at rt.

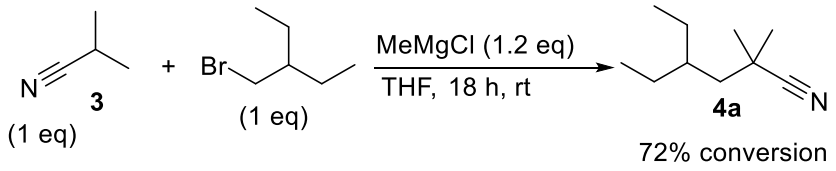
We wondered if the absence of the amine would affect the reactivity of the aliphatic nitriles. When the reaction to produce product **2a** was repeated under the same reaction conditions as previously reported in Table 2.1 except the amine was omitted, the reaction gave a mixture of alkyl halide, nitrile SM **1**, acetylcyclohexane, product **2a** in the ratio 66:26:2:6 after 2 hours. In the reaction where the amine had been employed 100% conversion and 63% yield were achieved after 2 hours.

With a longer reaction time (18 hours) it was found that the conversion to the product had increased to 60% (Scheme 2.21, Table 2.10). We did not isolate the product of this reaction however the GC-MS analysis was carried out in duplicate and the results were consistent.



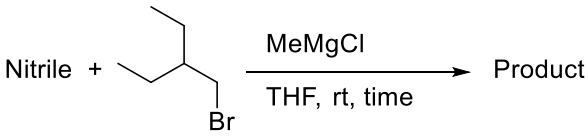
Scheme 2.21: Alkylation of cyclohexane carbonitrile **1** without an amine mediator.

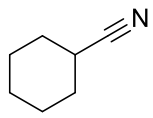
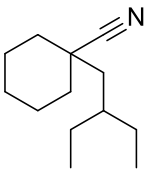
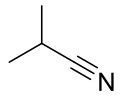
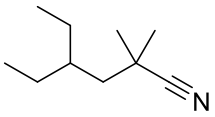
The reaction to produce **4a** was carried out in the absence of diethylamine and we found the reaction to be extremely slow. We observed the conversion to the product **4a** to be 72% after 18 hours with the remainder being nitrile **3** (10%) and 1-bromo-2-ethylbutane (18%). In this reaction we suspect again the formation of a ketone however due to the size and volatility of the likely ketone product (3-methylbutan-2-one) we were unable to observe this on the GC-MS (Scheme 2.22, Table 2.10).



Scheme 2.22: Alkylation of isobutyronitrile **3** without an amine mediator.

Table 2.10: Alkylation of alkylnitrile without an amine mediator.



Nitrile	Reaction time/Product number	Product	Product mixture[a] (%) Alkyl halide:nitrile:ketone:pdt
	18 h (**2a**)		28:10:2:60
	18 h (**4a**)		18:10:0:72

a) Percentage of each compound in final reaction mixture by GC-MS; **Reaction conditions**: 1 eq nitrile, 1 eq alkyl halide and 1.2 eq MeMgCl at rt.

To understand the chemistry further, a series of experiments were conducted to gain an insight into possible mechanisms by which this reaction may be operating. We monitored a series of experiments using a Mettler Toledo in-process FTIR.

A ReactIR™ 15 (Figure 2.5) spectrometer was used to measure changes in infrared absorption as the reaction progressed and provide specific information about reaction initiation, intermediates and endpoint.

Figure 2.5: Mettler Toledo in-process FTIR instrument.

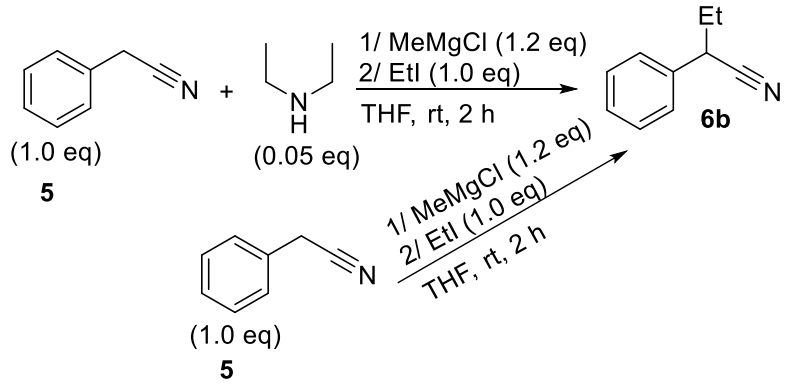
In this study both the DiComp (diamond) and SiComp (silicon) probe were used for monitoring. We carried out *in situ* IR studies and started this study by repeating the reaction to produce nitrile **6b**, from phenylacetonitrile **5** and ethyl iodide.

This reaction was carried out *via* the preformed anion route, where the anion is generated before the electrophile is added. We initially monitored this reaction using a diamond probe. This probe however had a blind spot which was in the nitrile stretching region ($\sim$ 2000 – 2300 cm^{-1}). Using the diamond probe, the only information we obtained was that the addition of MeMgCl causes an exothermic reaction which results in an increase in temperature.

A silicon probe was used to overcome this problem. Using the silicon probe, we repeated the reaction to produce **6b**. Although with this probe the peak for the starting nitrile **5** was not observed, we were able to observe the presence of the nitrile anion species generated upon reaction of the starting nitrile with MeMgCl in the presence of diethylamine.

During the study the reaction to produce **6b** was conducted both with and without an amine (Scheme 2.23). In the presence of the amine a peak which is due to the nitrile of the intermediate (peak at 2100 cm^{-1}) and a corresponding aromatic aryl signal (peak at 1590 cm^{-1}) appeared instantaneously as the MeMgCl was added. In the presence and absence of the amine, the addition of MeMgCl causes an exothermic reaction which results in an increase in temperature as shown in Figure 2.6. The reaction where the amine is omitted gave quite a different temperature profile. An addition exotherm is observed upon addition of alkyl halide (Figure 2.6). Although the reasons for this difference is not completely clear, we believe it may be due to a slower reaction in the absence of the amine base.

As the instrument was on loan we did not further investigate that aspect. In both cases, the intermediate formed was stable and disappeared immediately once the electrophile was added (Figure 2.6). The same peaks were observed when the reaction to produce **6b** was carried out without the amine present. However, in the absence of an amine base, the formation of the intermediate is slower.



Scheme 2.23: Reaction to produce **6b** with and without an amine.

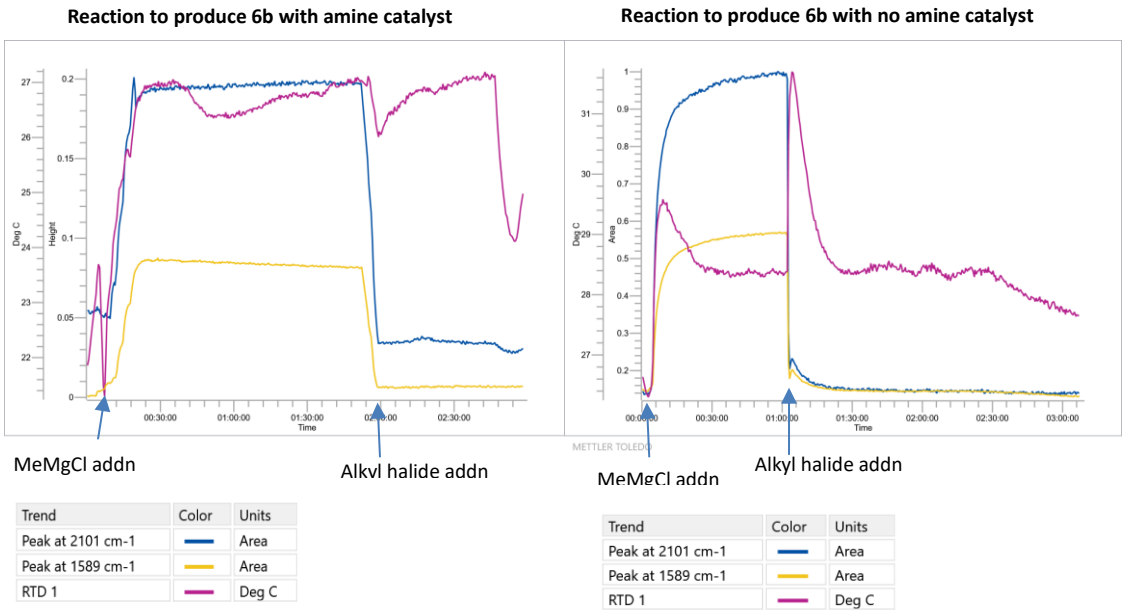


Figure 2.6: Comparison of FTIR trend of the reaction to produce **6b** with amine vs no amine.

Moving away from the aromatic nitrile, we decided to monitor the reaction of an aliphatic nitrile. When the reaction to produce **2a** was monitored on the FTIR, the formation of the nitrile anion (peak at 2035 cm^{-1}) (Figure 2.7) was observed to be lot slower than the nitrile anion formed from phenylacetonitrile by a factor of 10. Upon addition of the electrophile, the intermediate peak disappeared almost immediately as before. It was noted that there is a difference in the wavelength of absorbance between the anions of the aromatic and aliphatic nitriles. The anion generated from phenylacetonitrile is observed at 2101 cm^{-1}, while the anion generated from cyclohexane carbonitrile is observed 2035 cm^{-1} (Figure 2.6, 2.7 and 2.9). Figure 2.7 shows the FTIR trend of the reaction to produce **2a** in the presence of an amine.

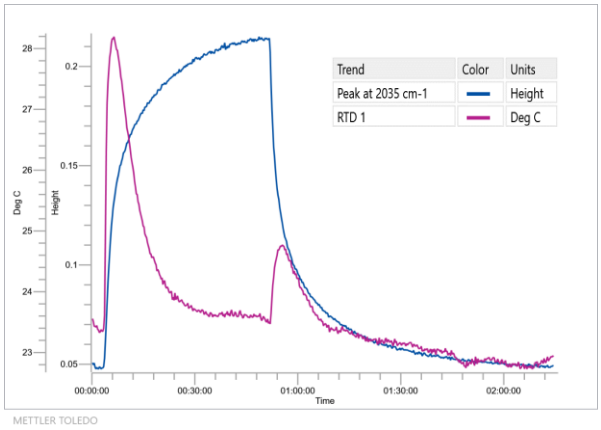


Figure 2.7: FTIR trend of reaction to produce **2a** with amine.

When the reaction to produce **2a** was repeated without the amine mediator, the signal due to the formation of the anion was found to be less intense than that seen with the amine present. These results are consistent with the GC-MS conversions obtained for **2a** after 2 hours (6% conversion). Throughout our study on the FTIR, the peak for the starting nitrile in solution was not observed. However, during the reaction to produce **2a** without the amine mediator, in addition to the nitrile anion peak, we also observed the presence of a new peak at 2245 cm^{-1} (Figure 2.8). It is unclear what this peak represents but it may be related to reaction involving attack at the nitrile by the Grignard, which we know from the presence of ketone in the product mixture does occur in this case, or due to the formation of aggregates which don't form with the amine present.

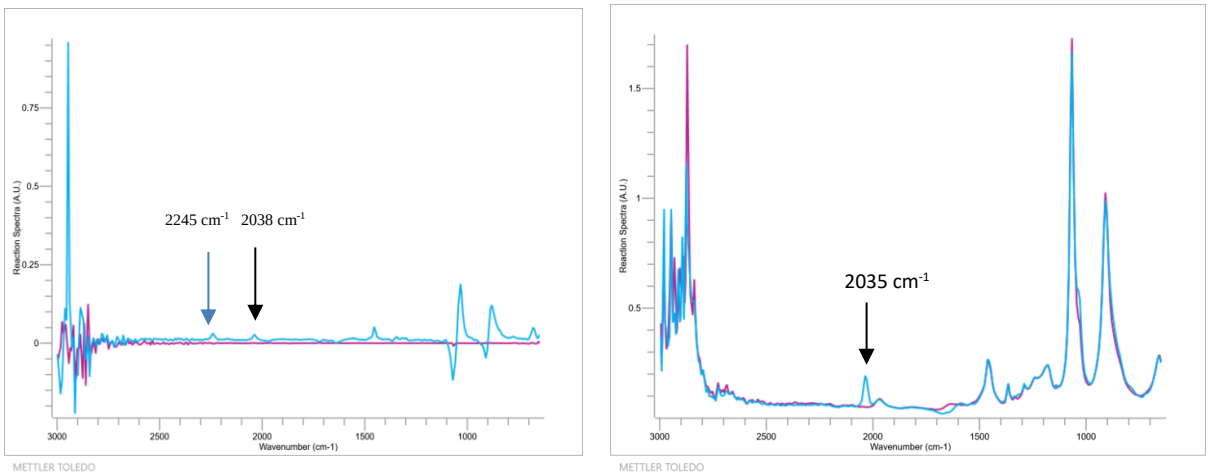


Figure 2.8: FTIR spectrum of reaction to produce **2a** without and with an amine mediator (blue) with overlayed starting material IR spectrum (pink).

The results obtained from our study on the FTIR show that the deprotonation of phenylacetonitrile **5** is a lot faster than the deprotonation of cyclohexanecarbonitrile **1** and in both cases the presence of the amine mediator results in a higher rate.

The results shown in Figure 2.9 are consistent with the pK_a of both nitriles and the presence of a conjugated system in phenylacetonitrile **5**. With phenylacetonitrile the negative charge generated can be delocalised around the ring making it more stable while with cyclohexanecarbonitrile the lack of aromaticity makes the anion less stable and the reaction to form it slower. The pK_a for phenylacetonitrile is 21.9[21] while the pK_a for propionitrile, an example of an aliphatic nitrile is 32.5.[21]

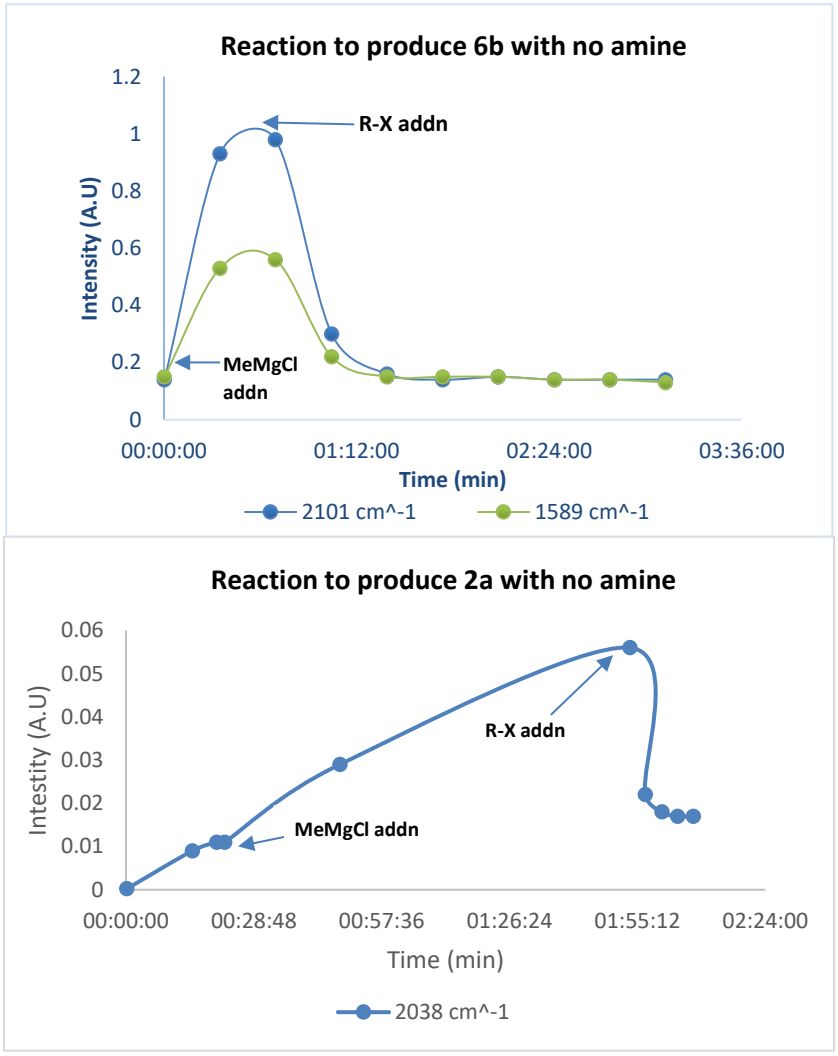


Figure 2.9: Deprotonation and alkylation of phenylacetonitrile **5** versus cyclohexanecarbonitrile **1**.

From searching the literature, we found that the use of ^{13}C NMR spectroscopy provides an excellent method for determining the metal coordination in metalated nitriles because the chemical shift of the nitrile carbon is sensitive to the local environment.[22] The ^{13}C NMR signal for the nitrile carbon of N-metalated nitriles, lies in the range δ = 140–157 ppm whereas, in the corresponding C-metalated nitriles it lies between δ = 115–138 ppm.[23]

During the project, we had the opportunity to use a spinsolve benchtop NMR spectrometer from Magritek. The use of this instrument would allow us to monitor the reaction and identify the metalated species present without the need for deuterated solvents. We were conscious that we only had the Grignard available to us as a 3 M solution in THF which could potentially interfere but felt we might gain some information.

In trying to identify the metalated species we observed during the FTIR studies, we started by carrying out a reaction to produce the anion derived from phenylacetonitrile **5**. This was done by omitting the amine and reacting phenylacetonitrile **5** with MeMgCl (1.2 eq) in THF at rt. After 30 mins, a sample was taken to be analysed on the bench top NMR, as the reaction was done in THF, some peaks were masked under the THF signal making it hard to interpret the results obtained from the ^{1}H NMR spectra. The results obtained from ^{13}C NMR spectra also gave little to no information. As this instrument was only available to us for a short time, we were limited to what we could do. We were however able to get a ^{1}H NMR spectrum for MeMgCl, which showed the signal for the methyl group at –1.79 ppm (Figure 2.10).

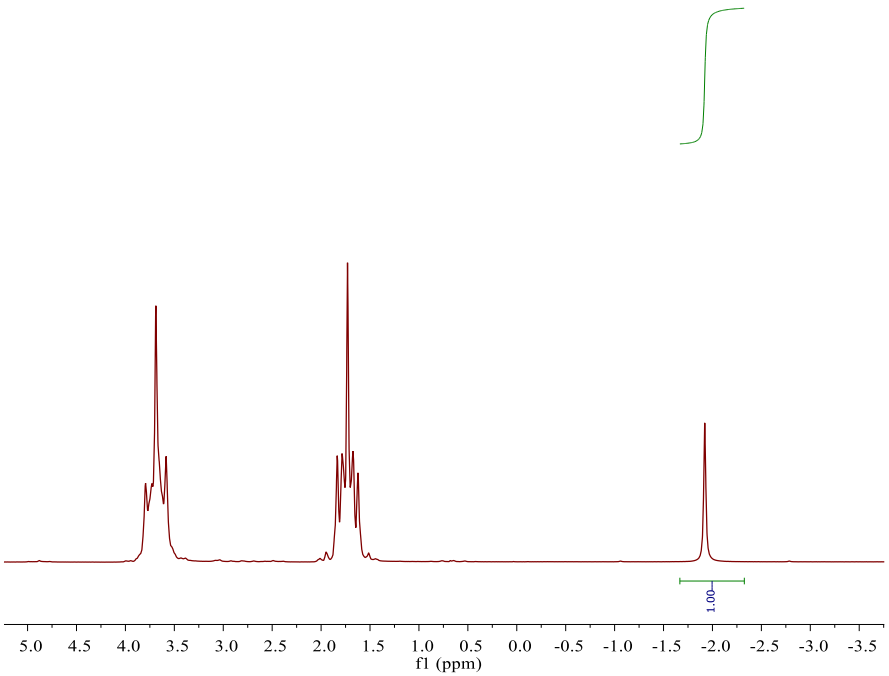


Figure 2.10: ^{1}H NMR spectrum of MeMgCl in THF.

With no success with the spinsolve benchtop NMR, we sought other ways to identify the metalated species. A review by Binev et al.,[24] reports IR absorption wavelengths due to phenylacetonitrile carbanion at 2095 and 2080 cm^{-1}. A strong IR band for the aromatic system was reported at 1579 cm^{-1}.

Although the IR bands reported by Binev are similar to the signals we observed on the FTIR of our reactions (2101 cm^{-1} and 1589 cm^{-1}), It was not enough to conclusively determine which species was present. Work discussed in chapter 1 suggest magnesiated nitriles tend towards N-magnesiation of arylnitriles.

Going by the many reports by Fleming,[24] we assumed the nitrile anion species derived from the phenylacetonitrile **5** was the N-metalated nitrile, where the MgCl coordinates to the nitrogen.

Figure 2.11 shows the IR spectrum of the reaction where the nitrile anion species. It's interesting to note, in the nitrile anion generated from nitrile **5** that the peak at 1589 cm^{-1} is not observed until the MeMgCl is added. This is thought to be due to the aromatic ring and differs from the aromatic signals in the starting material as the ring is now adjacent to the anion.

The pink line on the spectra shown in Figure 2.11 shows the observed spectrum before MeMgCl addition, while the blue line is the spectrum after the MeMgCl addition. This implies that the aromatic ring is in conjugation with the newly formed nitrile anion intermediate.

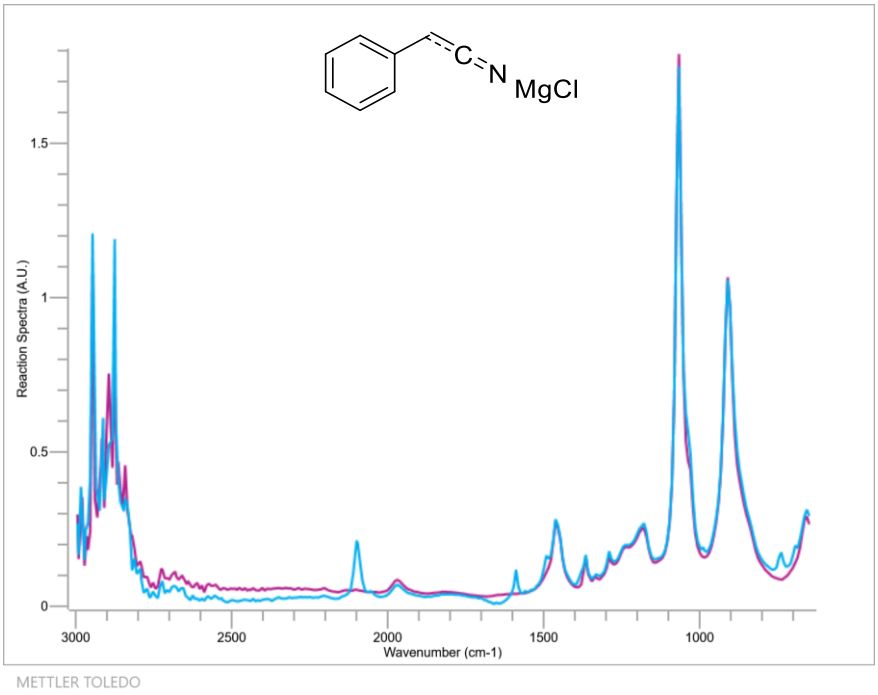
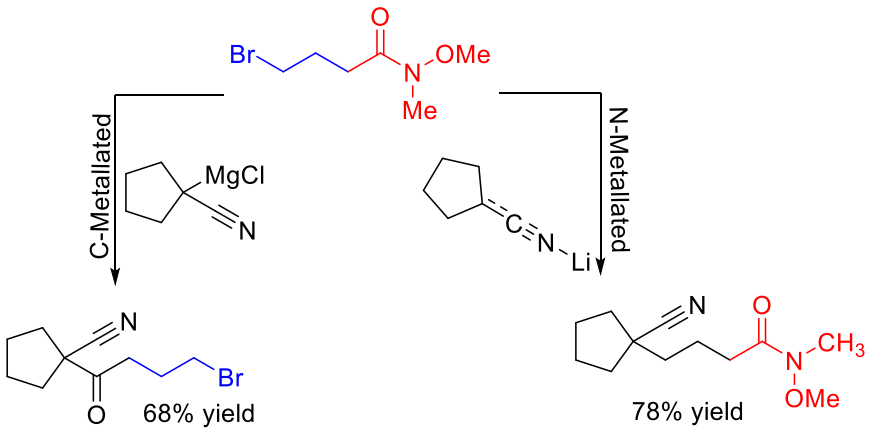


Figure 2.11: FTIR spectrum for nitrile anion of **5** (blue) with overlayed starting material IR spectrum (pink).

A series of reactions were also carried out to get a handle on whether the formation of the C-metalated nitrile or N-metalated nitriles was in some way temperature dependent. This may be important if we want to gain stereocontrol on the alkylation reaction. When the reaction to produce **6b** was repeated at reduced temperatures (-10 and -20 °C), the presence of the N-metalated nitrile species was still observed.

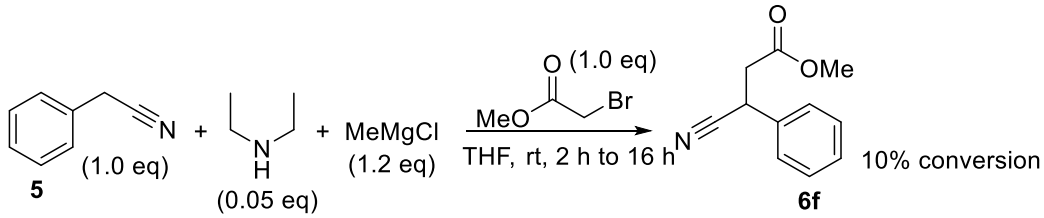
To further prove that the MeMgCl reacts *via* the C-metalated nitrile. We decided to carry out a chemoselective alkylation with a bifunctional electrophile. As discussed in Chapter 1, chemoselective reactions of metalated nitriles exploit the different reactivity of C- and N-metalated nitriles. A review by Fleming[25] in 2015 reports that C-magnesiated and N-lithiated nitriles derived from the same nitrile react with a bifunctional electrophile at different electrophilic sites. C-Magnesiated nitriles preferentially react with carbonyl electrophiles while N-lithiated nitriles favour S_N2 displacement of alkyl halides (Scheme 2.24).



Scheme 2.24: Chemoselective alkylation with a bifunctional bromoamide electrophile reported by Fleming.[25]

A similar reaction to that reported by Fleming was attempted albeit using phenylacetonitrile **5** and a different bifunctional electrophile. The reaction of phenylacetonitrile **5** with methyl bromoacetate under normal alkylating conditions was conducted. Surprisingly, upon analysis of the GC-MS we found that the product of bromide displacement predominated (Scheme 2.25). The reaction mixture contained a mixture of nitrile **5,** methyl bromoacetate and the nitrile ester product. However, due to the conversion of the product being low (10%), the product couldn't be isolated and both GC-MS and IR were used in its characterisation.

The results obtained from the reaction we conducted are in conflict with the review by Fleming,[26] where he states that C-magnesiated nitriles preferentially react with carbonyl electrophiles, whereas N-lithiated nitriles favour S_N2 displacement of alkyl halides.
We believe this could be because the methoxy group is a poor leaving group compared to the Weinreb amide group used by Fleming.



Scheme 2.25: Chemoselective alkylation of phenylacetonitrile **5**.

In the case of the anion derived from cyclohexanecarbonitrile **1**, a search in literature indicated that the nitrile anion species we observed is the ketenimine, where the MgCl coordinates to the nitrogen (N-metalated). A review by DeKimpe et al., reports IR absorption wavelengths due to alkyl ketenimines[27] at ~2000 to 2040 cm^{-1}, these values are consistent with the signal we observed at 2035 cm^{-1} in the FTIR of the reaction to give product **2a** (Figure 2.12).

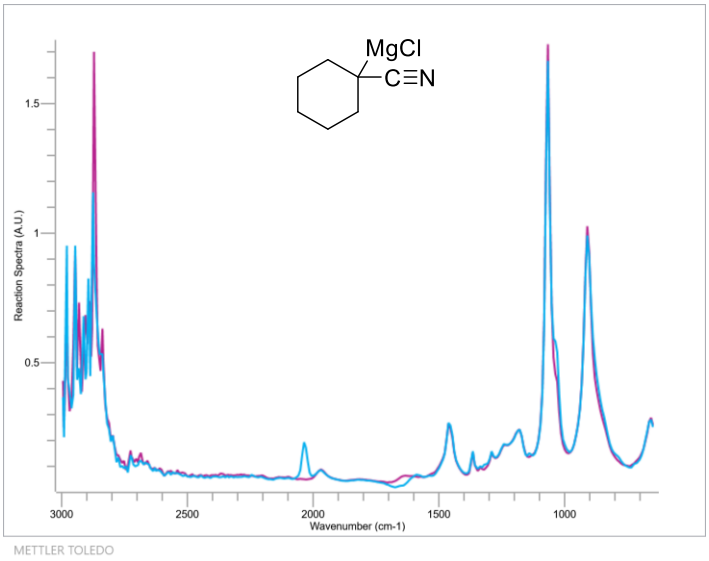
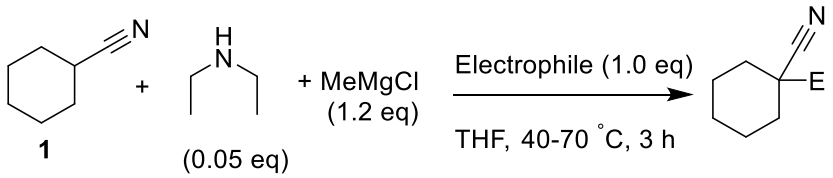


Figure 2.12: FTIR spectrum for nitrile anion of **1** (blue) overlayed with the IR spectrum of the starting material (pink).

The report by DeKimpe again conflicts with the work discussed in Chapter 1, where Fleming suggests magnesiated nitriles tend towards C-magnesiation of alkylnitriles. However, in our case, the FTIR data suggests the reverse of this. With the resources available to us we were not able to resolve this conflict absolutely.

2.1.6 Exploration of different electrophiles

From our initial study, the reaction of cyclohexanecarbonitrile **1** with butyl bromide and 1-bromo-2-ethylbutane worked well *via* late addition of MeMgCl to a solution of the other reagents. It was also found through our initial scoping that the reaction is not just limited to substitution reactions with alkyl halides and can be extended to the use of other reagents such as oxygen containing electrophiles. Reactions with oxygen electrophiles were explored further (Table 2.11). These reactions were carried out by preforming the anion and then adding the electrophile to the solution (Scheme 2.26). This was the preferred method as we knew many of the electrophiles would be susceptible to reaction with the Grignard should they be present simultaneously. This was supported by the result in Table 2.2 when we reacted the isobutyronitrile with cyclohexene oxide by both methods and achieved much better conversions using the preformed method.

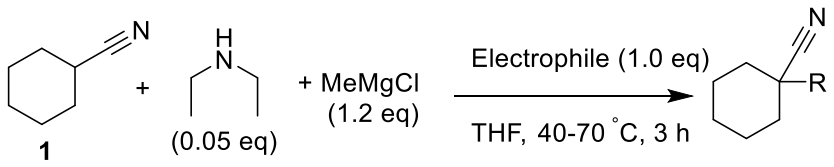


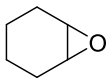
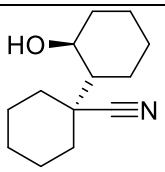
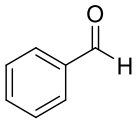
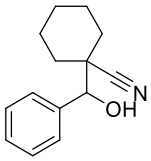
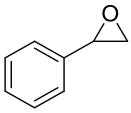
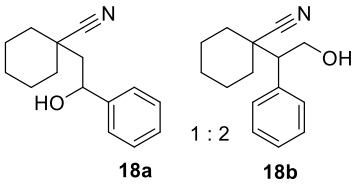
Scheme 2.26: Alkylation reaction via preformed anion method.

Reaction of the anion derived from nitrile **1** with cyclohexane oxide proceeded well with 100% conversion to the addition product **16** and a yield of 88%. The product **16** was isolated as needle like crystals from Et_2O and an X-ray structure of the product was obtained (Figure 2.13). The X-ray crystal structure of product **16** showed the anti-relationship between the nitrile and the alcohol group. In collaboration with a fellow postgraduate student, Francesco Civati, we were able to identify that the formation of the needle-like crystal of product **16** arises due to intermolecular hydrogen bonding interaction between the nitrile and the alcohol (Figure 2.14). The reaction of nitrile **1** with benzaldehyde *via* the preformed anion method was then carried out. As discussed in section 2.1.2, the addition of benzaldehyde to the substituted nitriles **6b** and **6c** *via* both the late addition and the preformed anion method was unsuccessful. When the reaction of nitrile **1** with benzaldehyde was carried out *via* the preformed anion method as shown in Scheme 2.26, the reaction gave a conversion of 85% to the cyanoalcohol **17** and a yield of 70%. The remainder of the crude mixture was benzaldehyde starting material. Following this, a reaction involving a non-symmetrical epoxide, styrene oxide was then attempted. In this reaction, attack of the nucleophile can occur at either the less hindered carbon or the more substituted carbon. This reaction gave combined yield of 69% with limited

selectivity for either of the two products **18a** and **18b**. A 2:1 (**18b:18a**) ratio favouring reaction at the more substituted carbon of the epoxide was obtained. The two products were successfully isolated by column chromatography with a 22% yield for product **18a** and a 47% for **18b**.

Table 2.11: Reaction of nitrile **1** with oxygen containing electrophiles.



Electrophile	Product	Product number	Ratio[a] (%) SM:Pdt %	Yield[b] %
		**16**	0:100	88
		**17**	15:85	70
	 18a 1 : 2 18b	**18a** and **18b**	NA	**18a** (22%) **18b** (47%)

Reaction conditions: 1 eq nitrile, 0.05 eq diethylamine 1.2 eq MeMgCl at rt. After 1h, 1 eq electrophile, reflux for 2 h **a)** Based on GC-MS **b)** Based on yield of isolated product.

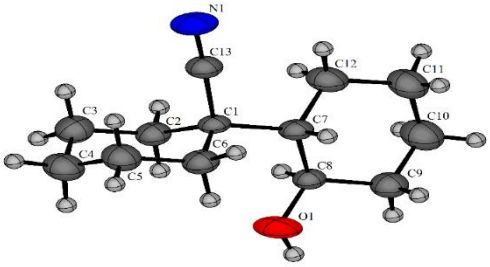


Figure 2.13: X-ray crystal structure of 2'-Hydroxy[1,1'-bi(cyclohexane)]1-carbonitrile **16**.

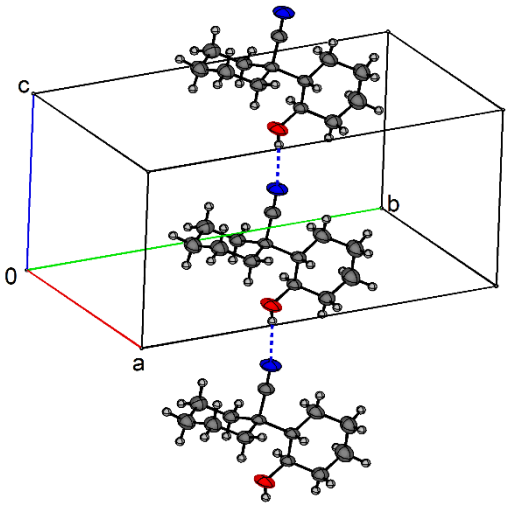
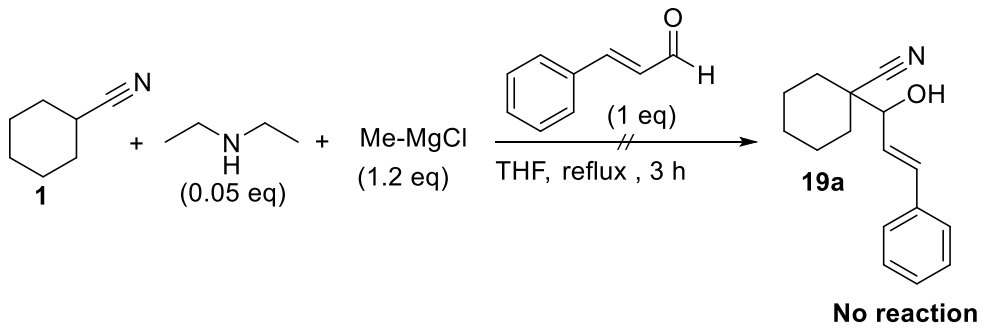


Figure 2.14: Intermolecular hydrogen bonding of **16** in solid state.

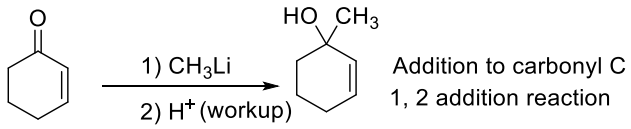
Having had success with epoxides and benzaldehyde, we wondered if we could get a reaction to occur with a different aldehyde. The reaction of nitrile **1** with cinnamaldehyde to form 1-(1-hydroxy-3-phenyl-allyl)-cyclohexanecarbonitrile **19a** was attempted (Scheme 2.27), however this reaction was unsuccessful. The reaction yielded unreacted starting material.



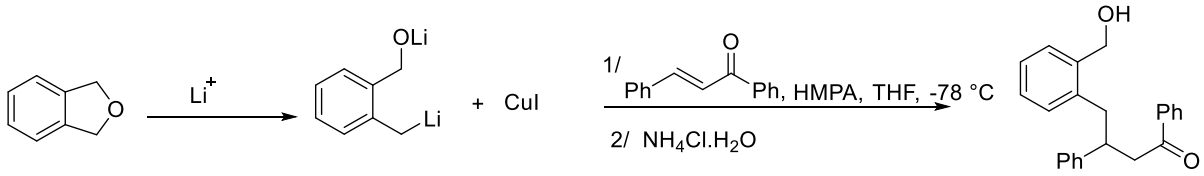
Scheme 2.27: Attempted reaction of nitrile **1** with cinnamaldehyde.

Although not all reactions were successful, it was clear from our investigation that the anion generated using the Grignard reagent will react with some oxygen-based electrophiles in high conversions and yields.

Searching the literature, anions derived from alkyllithiums were found to be used in S_N2 reactions, 1,2 additions (Scheme 2.28), and with the addition of a copper mediator can be used in 1,4 addition reactions (Scheme 2.29).[28]

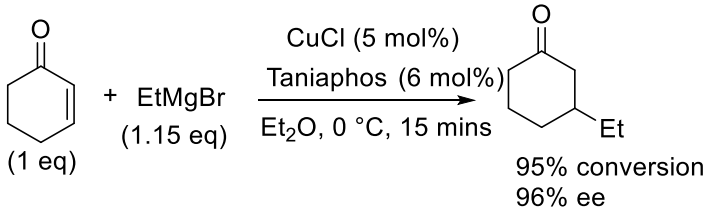


Scheme 2.28: 1,2 Addition reaction with an organolithium reagent.



Scheme 2.29: Copper-mediated 1,4 conjugate addition reaction.

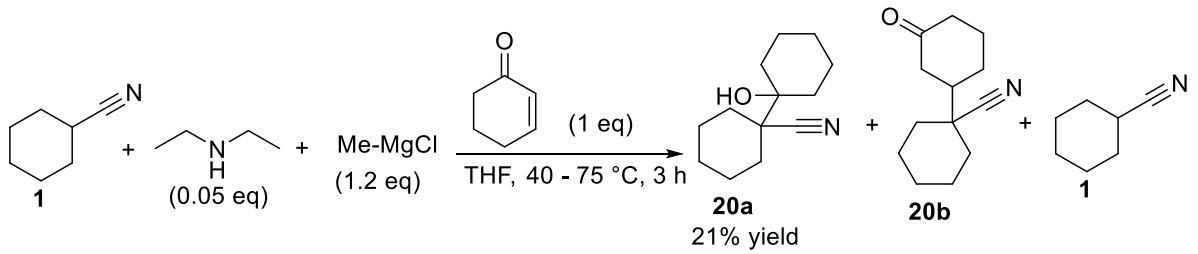
It is also known that Grignard reagents reactivity can be modified by the addition of copper salts (Scheme 2.30).[29,30] Addition to conjugated systems favours 1,2-addition in the absence of copper and 1,4 addition when copper salts are added even in les than stochiometric amounts.[30]



Scheme 2.30: Copper-catalyzed conjugate addition of EtMgBr to cyclohexenone.

We decided to check whether the magnesiated nitrile anions we were preparing could have their reactivity similarly modified if a copper salt were present (Table 2.11.1).

We started this aspect of the study by reacting cyclohexanecarbonitrile **1** with cyclohexenone *via* initial deprotonation with the Grignard using catalytic amine under the conditions set out previously (Scheme 2.31). The reaction gave a mixture of nitrile **1**, 1,2-addition product and 1,4-addition product in the ratio of 11:33:56 observed by GC-MS. The nitrile **1** starting material was initially removed *via* distillation, following this, the remainder of the crude mixture was purified by column chromatography. After chromatography, the 1,2-addition product **20a** was isolated in 21% yield. As our focus at the time was the 1,2addition product, the 1,4-addition product was not quantified.

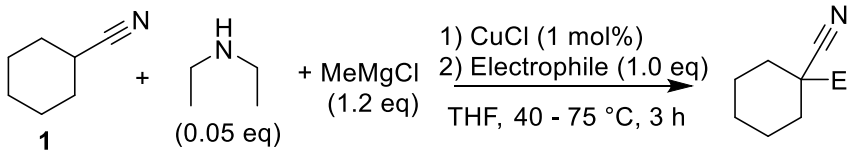


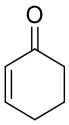
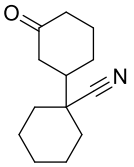
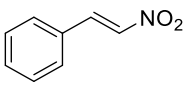
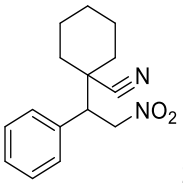
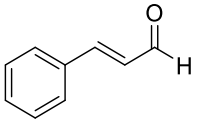
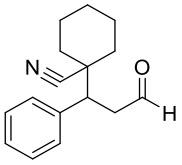
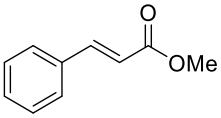
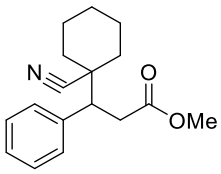
Scheme 2.31: 1,2-Addition reaction with nitrile **1**.

When the reaction of cyclohexanecarbonitrile **1** with cyclohexenone was repeated but with the addition of CuCl (0.1 eq), we found that the incorporation of the copper salt completely turned off the 1,2-addition reaction. The reaction produced a mixture of the nitrile **1** starting material and the 1, 4 addition product **20b** with small amounts of unknown impurities which were observed on GC-MS. Due to the presence of impurities, the conversion to the 1,4-addition product **20b** could not be accurately measured (ca 50%). The 1,4-addition product **20b** was isolated in 29% yield after column chromatography (Table 2.11.1).

The incorporation of the Cu salt into the reaction mixture appears to have resulted in the anion more selectively reacting with the softer end of the conjugated electrophile rather than the harder ketone centre, thus yielding 1, 4-addition product.

Table 2.11.1: 1,4 Additions with cyclohexanecarbonitrile **1**.



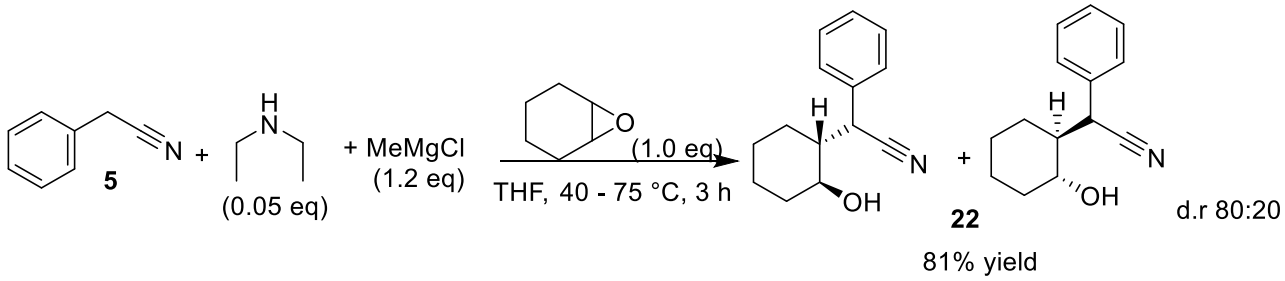
Entry	Electrophile	Product	Yield[a] (%)
1		 **20b**	29
2		 **21**	43
3[b]		 **19b**	0
4[b]		 **19c**	0

Reaction conditions: 1 eq nitrile, 0.05 eq diethylamine 1.2 eq MeMgCl at rt. After 1hr, 1 mol% CuCl and 30 mins after 1 eq electrophile, reflux for 2 h **a)** Based on yield of isolated product **b)** 1,2 and 1,4 addition attempted.

The 1,4-addition reaction to different α-β-unsaturated compounds was attempted. We conducted a reaction of cyclohexanecarbonitrile **1** with *trans*-β-nitrostyrene using 0.1 eq CuCl as an additive. This reaction produced a mixture of nitrile **1**, starting material, *trans*-β-nitrostyrene and product **21** present in the ratio 10:23:67 measured by GC-MS. The 1,4-addition product **21** was obtained in a yield of 43% after column chromatography (Table 2.11.1). When the reaction was repeated without the Cu salt, the reaction was unsuccessful, giving back the nitrile **1** SM and *trans*-β-nitrostyrene.

As the 1,4-addition could be achieved in the presence of a Cu salt, for some conjugated systems, a 1,4 variation of the reaction with cinnamaldehyde was attempted. The presence of the Cu salt had no positive effect on the reaction outcome. The reaction was unsuccessful giving back just unreacted starting material. The use of a different electrophile similar to cinnamaldehyde was attempted. The reaction of nitrile **1** with methyl *trans*-cinnamate was carried out. Just like with cinnamaldehyde, this reaction failed to produce the desired product with only unreacted starting material being isolated (Table 2.11.1).

The use of other nitriles was then explored (summarised in Table 2.12). The use of phenylacetonitrile **5** in reactions with the oxygen containing electrophiles was investigated. The reaction of phenylacetonitrile **5** with cyclohexene oxide was carried out and the reaction gave a mixture of the diastereomeric products **22** in a 97% conversion and 81% isolated yield. (Scheme 2.32). The diastereomeric product could not be separated but represented a ratio of 80:20 as observed on ^{1}H NMR spectroscopy.



Scheme 2.32: Reaction of nitrile **5** with cyclohexene oxide.

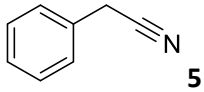
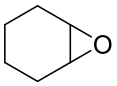
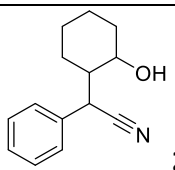
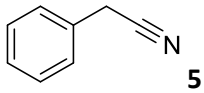
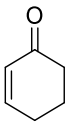
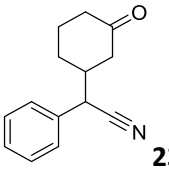
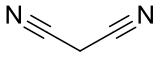
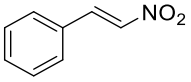
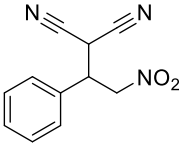
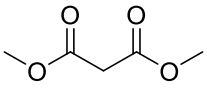
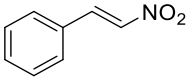
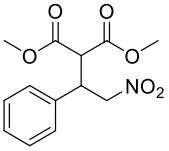
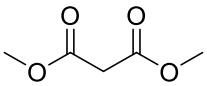
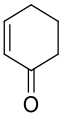
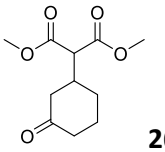
The reaction of nitrile **5** with cyclohexenone was also carried out. The reaction proceeded to give the 1,4-addition product **23** in 100% conversion. We were surprised to observe just the 1,4-addition product without the presence of Cu salt. It is believed that the 1,4-addition product is obtained because the anion is softer as the negative charge can be delocalised into the aromatic ring. This led us to explore the use of other nucleophiles which are softer due to the delocalisation of the anionic charge (Table 2.12).

The reaction of malononitrile **8** with *trans-β* nitrostyrene gave a mixture of *trans-β* nitrostyrene starting material and 1,4-addition product **24** present in the ratio of 20:80. The 1,4-addition product was isolated in 65% yield after bulb to bulb distillation. This methodology was also used to react dimethyl malonate with *trans-β* nitrostyrene. It is important to note in this reaction that although we have a diester compound along with catalytic amine present, there is no evidence of reaction of the Grignard with the ester. Furthermore, there is also no evidence of a reaction between the diethylamide species and the ester. This is interesting as in the sections to follow we describe the formation of amides from the reaction of diethylamide anion with ester compounds.

The reaction of dimethyl malonate **10a** with *trans-β* nitrostyrene proceeded well to give a mixture of the diester SM and the 1,4-addition product **25** in the ratio 18:82. The 1,4-addition product **25** was recrystalised from methanol and obtained in a 75% yield

Reaction of dimethyl malonate with cyclohexenone also gave the 1,4-addition product **26** in a 92% conversion and 61% yield.

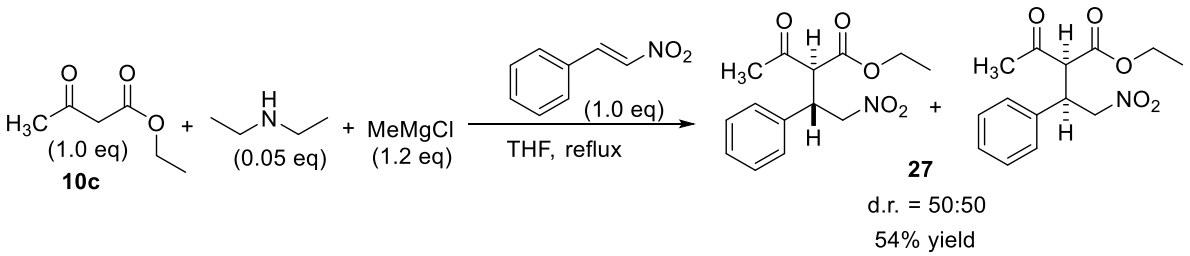
Table 2.12: 1,4 Addition reactions with methylene carbons.

Nucleophile	Electrophile	Product	Ratio[a] (%) SM:Pdt (%)	Yield[b] (%)	d.r[c]
 **5**		 **22**	3:97	81	80:20
 **5**		 **23**	0:100	85	60:40
 **8**		 **24**	20:80	65	N/A
 **10a**		 **25**	18:82	75	N/A
 **10a**		 **26**	6:2:92[d]	61	N/A

a) Based on GC-MS **b)** Based on yield of isolated product **c)** diastereomeric ratio as observed on ^{1}H NMR spectroscopy **d**) ratio of dimethyl malonate SM, cyclohexenone and product **26**; **Reaction conditions:** 1 eq nucleophile, 0.05 eq diethylamine 1.2 eq MeMgCl at rt. After 1hr 1 eq electrophile, reflux for 2 h.

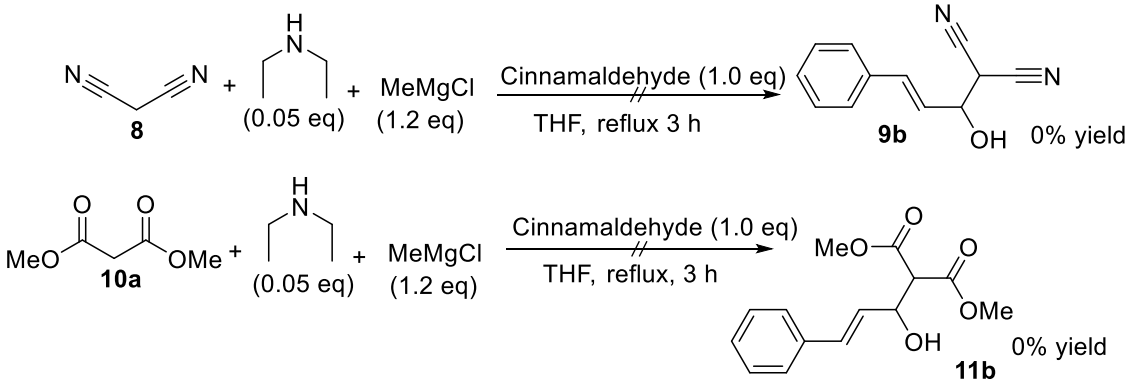
A similar reaction was carried out, reacting ethyl 3-ketobutanoate **10c** with *trans-β* nitrostyrene. Interestingly, although the Grignard could potentially react at either the ester or the ketone functionality, there is no evidence of the reaction of the Grignard with these two functionalities. The reaction produced the diastereomeric products **27** in a 77% conversion. The remainder of the crude mixture was 23% of the *trans-β* nitrostyrene.

The diastereomeric products **27** could not be separated and the diastereomeric ratio was virtually 1:1, measured by ^{1}H NMR spectroscopy, thus it was hard to be absolute in assigning spectral features to one diastereomer. A yield of 54% was obtained for a mixture of the diastereomeric products **27** after column chromatography (Scheme 2.33).



Scheme 2.33: 1,4-Addition reaction of ethyl 3-ketobutanoate.

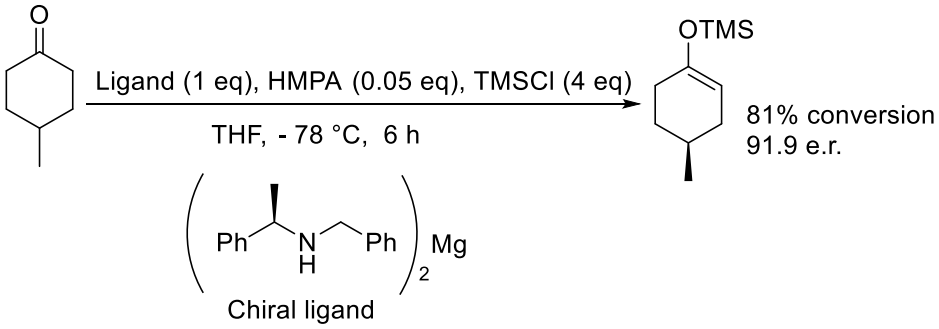
The presence of a Cu salt is not required for 1,4-addition to occur when the anions derived from the reaction of the magnesium diethylamide species with malononitrile or dimethyl malonate are used as the nucleophile. It also appears deprotonation and the cycling of the amine to deprotonated amide and back to amine again must be very rapid if no Grignard reaction with ester or ketone functionality is observed despite relatively rapid addition of the MeMgCl. We wondered if the use of a conjugated nucleophile would affect the outcome of the reaction with cinnamaldehyde. Both malononitrile and dimethyl malonate were reacted with cinnamaldehyde in the presence of diethylamine (0.05 eq) and MeMgCl (1.2 eq) (Scheme 2.34). The use of both malononitrile and dimethyl malonate showed no evidence of either 1,2- or 1,4-addition products. The reaction mixture contained just unreacted starting material when analysed by GC-MS in both cases.



Scheme 2.34: Attempted reaction between doubly-activated methylene carbon and cinnamaldehyde.

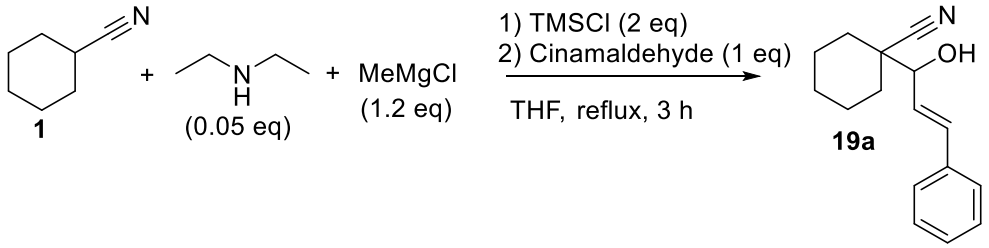
The alkylation reaction of nitrile **1**, involving a 1,2-addition reaction to cinnamaldehyde was revisited. This work was conducted by Ellen Muldoon, a final year student under my supervision.

Searching the literature, we found that TMSCl is often used in the trapping of enolates. When TMSCl is added along with a base in a reaction, the strong Si-O bond formed is responsible for the silyl enol ether being the major product. The formation of silyl enol ether is used as a tool in both asymmetric deprotonations and racemic deprotonation and the enol ether can be further reacted with a range of electrophiles[31] (Scheme 2.35).



Scheme 2.35: Formation of a silyl enol ether.

We started by looking at the reaction of the anion derived from nitrile **1** with cinnamaldehyde under the conditions set out for the alkylation *via* the preformed anion, but with the addition of TMSCl (2 eq) (Scheme 2.36).



Scheme 2.36: 1,2 alkylation of cinnamaldehyde.

The reaction seemed to have proceeded to give some of the desired product **19a**, however there were also a lot of side products present. From the ^{1}H NMR spectrum (Figure 2.15), the alkene groups of the product are present at 6.79 – 6.34 ppm and the peak at 4.31 – 4.28 ppm may represent the hydrogen next to alcohol of the 1, 2-alkylated product. GC-MS could not be used to obtain the conversion as there were too many peaks present, many of which were due to compounds we could not identify. Analysis of the crude mixture on ^{1}H NMR spectroscopy was consistent with the observations from the GC-MS but unfortunately, we still could not identify the impurities. The ^{1}HNMR spectrum did show the presence of unreacted starting material which was evident from the peak at 9.71 – 9.70 ppm, representing the hydrogen of the aldehyde. All attempts to optimise this reaction by increasing reaction time

and increasing the amount of TMSCl did not give the product any purer than before and isolation of the pure material still eluded us.

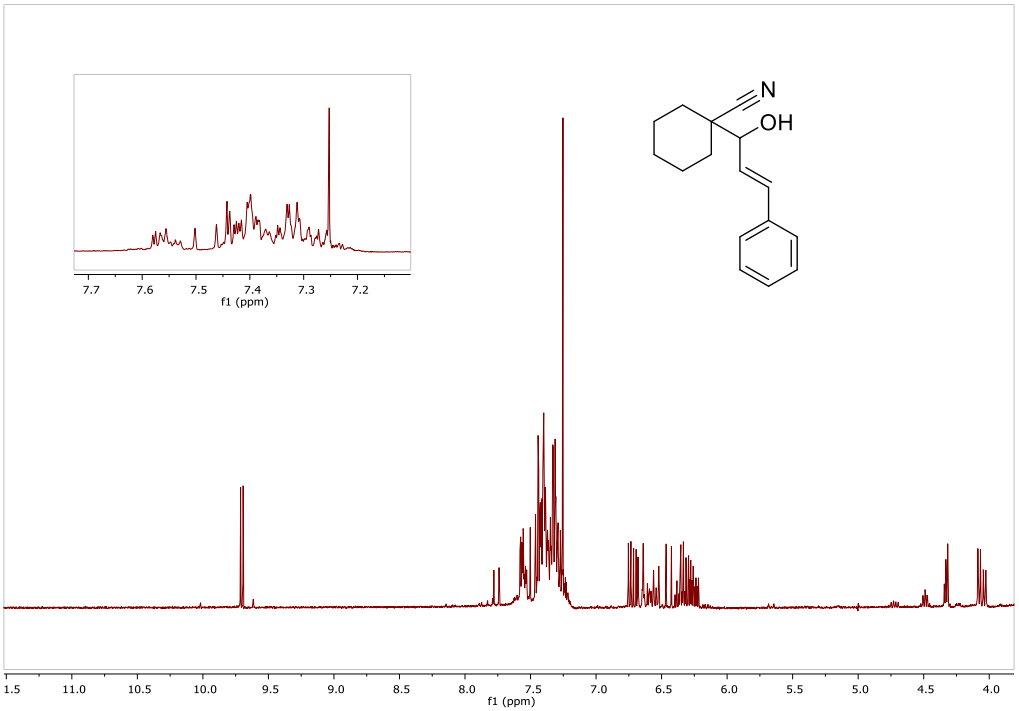
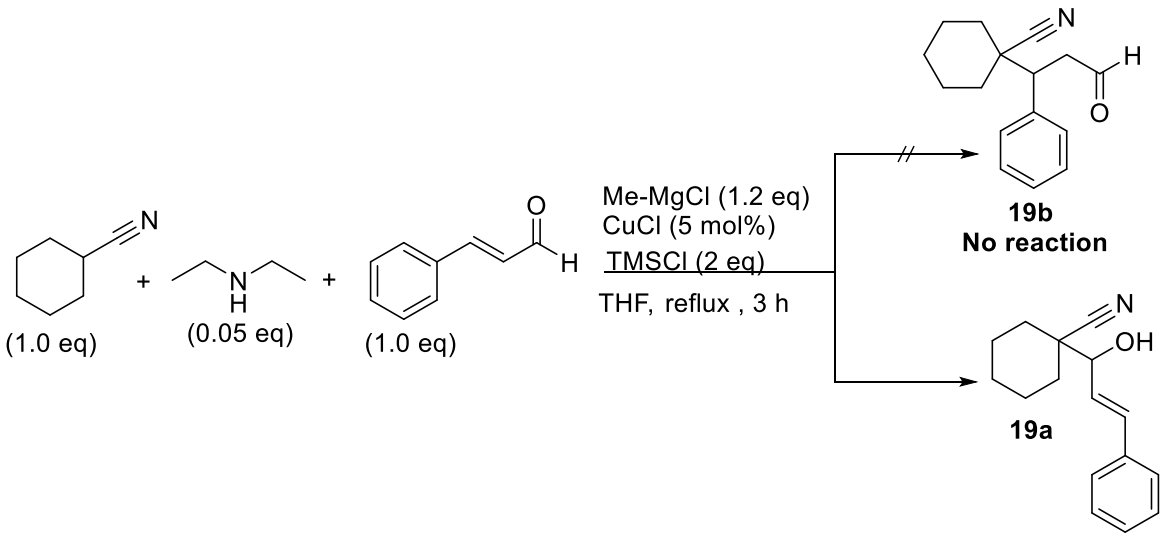


Figure 2.15: ^{1}H-NMR spectrum of 1, 2 alkylation on cinnamaldehyde.

As the presence of TMSCl did seem to help the reaction to form the 1,2-addition product, we wondered if it would be possible to implement similar reaction conditions to produce a 1,4-addition product. Knowing that the presence of copper promotes a 1,4-addition reaction, we carried out a similar reaction on the same compounds but combining the use of CuCl and TMSCl in the alkylation process (Scheme 2.37). On examining ^{1}H NMR spectra, there was no indication of the 1,4-addition product, a 1,2-reaction was observed instead. The ^{1}H NMR spectra of the crude was almost identical to ^{1}H NMR spectrum obtained for the 1,2-addition product. The amount of Cu salt was varied to try and change the outcome of the reaction, however there was no difference observed when the amount of Cu salt added was varied from 1 mol% to 5 mol%. As the reaction did not produce the desired product, the 1,2-addition product was not isolated. Although it was hard to obtain an accurate conversion for the 1,2-addition product from both GC-MS and ^{1}H NMR spectroscopy, we roughly estimate a 25% conversion to the 1,2-addition product.



Scheme 2.37: Attempted 1,4-alkylation reaction of nitrile **1** with cinnamaldehyde.

2.1.7 Conclusion

In this section we report on the use of methylmagnesium chloride with an amine modifier as a non-nucleophilic base in the alkylation of nitrile compounds. The role of the amine mediator was studied and although in some cases the reaction worked without the amine, yields were less reliable and side products were more prevalent. The reaction can be applied to form secondary, tertiary and quaternary nitrile compounds and can be used to add alkyl groups to methine (one addition) and methylene (one or two additions, homo or hetero) carbons. Where two groups are added they can be added sequentially, with purification in between, or in a one-pot fashion. Where two groups are added we have seen some differences in overall yield obtained depending on which group is added first. Although the nitrile, alkyl halide and Grignard reagent are present in the reaction mixture simultaneously, direct reaction of the Grignard with the nitrile or the alkyl halide is not seen, and the alkylation product is formed in high conversions and in moderate to high yields. We have also successfully alkylated acetonitrile with controlled addition of one alkyl group (currently limited to a benzyl group) and further elaboration to a quaternary nitrile.

This reaction can also be applied to the formation of quaternary centres using oxygen containing electrophiles. Regioselective 1,2- or 1,4-addition can be achieved with α, β unsaturated compounds. In a lot of cases efficient 1,4-additions are achieved without Cu salts.

The methodology was extended to the use of other nucleophiles such as the anions derived from the reaction of the magnesium base with malononitrile, dimethyl malonate and ethyl acetoacetate.

This methodology is applicable from small scale used by us to industrial scale used by Roche. It avoids the hazards associated with alkyllithiums and the consequent purchase, storage and handling costs. It avoids the use of alkane solvents and facilitates the use and recovery of “greener” ether solvents. Another green advantage is that extreme temperatures are not required, all reactions being run between 0 °C and 70 °C. The operational simplicity of the “late addition” methodology makes it ideally suited for continuous processing. We have successfully carried out the reactions in 2-Me-THF which is derived from renewable sources and is the greenest of the ether solvents and the reactions work equally well as our initial studies with THF.

Future work in this area would include extension of this methodology, with continuing focus on the ‘greeness’ of the process while also seeking to exploit the versatile nature of the nitrile functionality to synthesise molecules of biological interest.

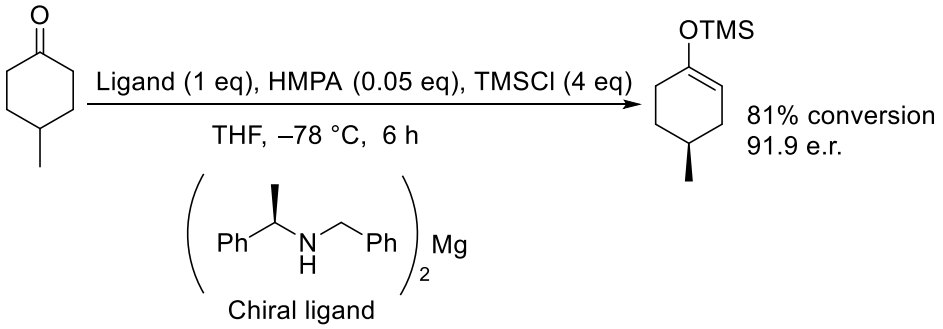
2.2 Enantioselective alkylation reactions

The enantioselective construction of quaternary carbon stereogenic centers remains one of the most significant challenges in synthetic chemistry.[32,33]

Given the past experience of the O'Leary research group in the design and use of chiral ligands in organic synthesis[34–36] we sought to study if the use of a chiral amine would give rise to stereocontrol in the alkylation reaction of nitriles.

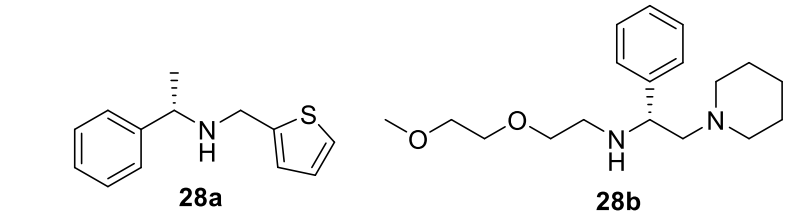
We were aware there was a potentially serious challenge in this aspect of the work. A search in the literature provides very little information on methods for the analytical separation of enantiomers of simple nitrile compounds. Known methods are not general in their applicability and involve the use of supercritical CO_2 HPLC systems[37] which are not widely available or the use of specialised columns which in many cases are specific to a narrow selection of nitriles.[38] It is possibly in this area that this study made most progress.

Chiral magnesium amide bases have proven to be effective reagents in asymmetric deprotonation of prochiral ketones due to their thermal stability (Scheme 2.38).[31] This is in contrast to the number of eq for lithium amide bases.



Scheme 2.38: Enantioselective deprotonation and silyl enol ether formation.

We chose to investigate the use of the thiazoline containing secondary amine (*S*)-1-phenyl-*N*-((thiophen-2-yl)methyl)ethanamine **28a**[39] and Koga's base **28b**[40] in the alkylation reactions (Figure 2.16). Chiral magnesium amide bases have proven to be effective reagents for the asymmetric deprotonation of prochiral ketones,[31,41] so we wanted to see if we could obtain selectivity with these chiral amine bases.



28a Thiophene containing amine base

28b Koga's base

Figure 2.16: Chiral amine bases.

One of our aims was to extend this method to the asymmetric alkylation of α-substituted phenylacetonitrile anions to construct challenging quaternary carbon stereogenic centers. In each alkylation reaction the catalytic chiral amine was used, and the reaction was conducted under the same conditions to that used for the alkylation reactions where diethylamine had previously been used.

This study began by investigating the reaction of phenylacetonitrile **5** and alkyl halides as shown in Table 2.13, the only difference being chiral amine **28a** was used instead of diethylamine.

Reaction of the anion derived from phenylacetonitrile **5** with iodomethane to produce **6a** proceeded to give the product in 89% conversion and 68% yield. The remainder of the reaction mixture was unreacted starting material and some dimethylated product **7a**. This result compares well to the reaction to produce **6a** using diethylamine which gave the monoalkylated product in 87% conversion and a yield of 66%.

The reaction to produce **6b** using chiral base **28a** proceeded well to give the product in 95% conversion and 73% isolated yield after column chromatography. Reaction to produce **6c** also proceeded well to give the product in 87% conversion and 69% yield. In all cases there was no evidence of residual chiral amine in the ^{1}H NMR and ^{13}C NMR spectra.

Chiral activity (limited) of the products were confirmed by measuring optical rotation. The specific rotation of the products was measured as $[\alpha]^{20}_{D}$ +6 deg cm^2 g^{-1} (c = 0.001, MeOH), $[\alpha]^{20}_{D}$ +4.5 deg cm^2 g^{-1} (c = 0.001, MeOH) and $[\alpha]^{20}_{D}$ +6.6 deg cm^2 g^{-1} (c = 0.001, MeOH) for the methyl, ethyl and 2-ethylbutyl substituted nitrile respectively. While these rotations are low they were consistent across replicate measurements.

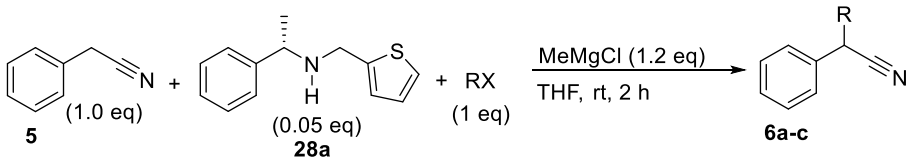
Although the specific rotations obtained gave an indication that there was an excess of one enantiomer, the analysis of the outcome of potentially enantioselective reactions *via* optical rotation was not ideal. The rotations measured were low and we had no available data on the rotations expected for the single enantiomers. The enantioselectivity could not be measured by this method.

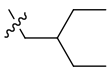
All of our initial attempts towards the resolution of the nitriles were unsuccessful. We attempted separation by HPLC using a variety of hexane:IPA ratios and by varying the flow rate and with the following chiral columns: Chiracel OD, Chiracel OD-H, Chiracel AD-H, Chiracel AD-RH, Chiracel OJ. We also varied detection wavelengths which of course would not affect separation, but the detection of the nitrile functionality was problematic.

We attempted resolution with these columns as they were what we had available to us and represented a reasonable spread of the commonly available stationary phases.

What follows in the next few pages show the attempts we made to either identify similar reactions we could conduct whose products we could separate or alternatively derivatisation methods that might allow us to analyse the stereochemical outcome of reactions by inference from the stereochemical ratio of the derivatives.

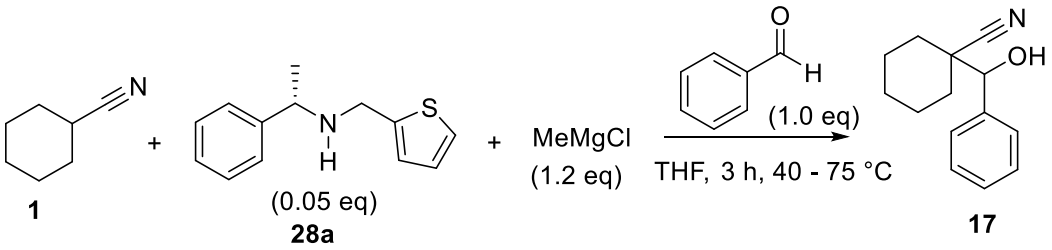
Table 2.13: Asymmetric alkylation of phenylacetonitrile **5**.



Entry (Product)	R[a]	Ratio[b](%) SM:Mono:Di	Yield[c] (%)	Specific[e] rotation (deg cm^2 g^{-1})
1 (**6a**)	Me	5:89:6	68[d]	+ 6
2 (**6b**)	Et	3:95:2	73	+ 4.5
3 (**6c**)		9:87:4	69	+ 6.6

a) X= I for entries 1 and 2 and X= Br for entry 3 **b)** Based on GC-MS. Starting material (SM):Monoalkylated:Dialkylated product **c)** Based on yield of isolated product for monoalkylation **d)** Yield of monoalkylated product based on crude weight isolated and composition by GC-MS. **e)** (c 0.001 in MeOH),

The reaction of the anion derived from nitrile **1** with benzaldehyde to produce the hydroxynitrile compound **17** was carried out (Scheme 2.39). We believed the resolution of the enantiomers of the product **17** of this reaction may be easier in comparison to the simple nitriles as the resolution of chiral alcohols is something that has been tackled more often. The asymmetric reaction was carried out with chiral amine base **28a** to form the alkylated product **17** in 83% conversion and a yield of 70% after distillation.



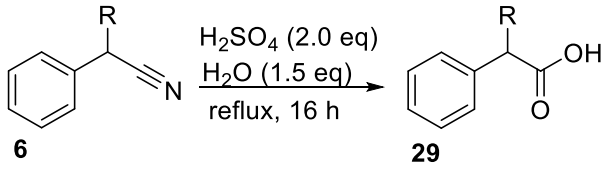
Scheme 2.39: Asymmetric alkylation to produce hydroxynitrile **17**.

Of the chiral columns we had available, the Chiracel OD-H column was the only column to resolve the hydroxynitrile product **17**. The hydroxynitrile compound **17** was analysed by chiral HPLC using Daicel Chiralpak OD-H column at 254 nm with a 90:10 (hexane:IPA) mobile phase. However reproducible separations of the enantiomers could not be achieved.

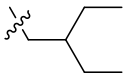
Having had no definitive answer in the resolution of the hydroxynitrile **17**, it was decided to transform the nitriles into a different functional group. This would serve two purposes. It may allow us to measure the enantiomeric excesses and it would demonstrate the synthetic utility of the nitrile functional group. A review by Wang[42] discusses the synthetic utility of the nitrile products and highlights how they can be converted to a range of functional groups such as carboxylic acids, esters and amines. The chiral nitriles **6b** and **6c** were successfully converted to carboxylic acids using 2 eq sulphuric acid and 1.5 eq water (Table 2.14). The work-up for this reaction involved extracting with DCM, followed by basifying the mixture with 1 M NaOH. The aqueous layer was then acidified with conc HCl and extracted with DCM. The reaction was conducted on a small scale and at high temperatures (110 °C).

Although the GC-MS conversions gave an indication that there was nothing else present, isolation of the acids proved difficult which resulted in very low yields. There was significant evidence of charring in the reaction which were generally black oils before workup which may indicate that though the required product was the only thing isolated significant decomposition was reducing the overall yield.

Table 2.14: Hydrolysis of nitriles.



6 **29**

Product	R	Yield[a] (%)	Conversion[b] (%)	%ee[c]
(29b)	Et	22	98	10
(29c)		25	100	8

Reaction conditions: 1 eq nitrile, 2.0 eq H_2SO_4, 1.5 eq H_2O at reflux, 16 h **a**) Based on yield of isolated product **b**) Based on GC-MS **c)** chiral HPLC.

The carboxylic acids synthesised are α-aryl carboxylic acids and similar compounds such as α-arylpropionic acids are widely used as non-steroidal anti-inflammatory drugs (e.g., iburopfen and naproxen). A search through the literature[43,44] on reported methods for the separation of the enantiomers of known compounds aided in the development of a method for the resolution of our acids. The synthesised acids were resolved under the following HPLC conditions: Chiralpak column AD-RH (mobile phase phosphate buffer (pH 2.0): acetonitrile (60:40). The enantiomeric excesses obtained were very low. In addition, the results obtained were not reproducible. Our measurements were done in triplicate and each time a different chromatogram was observed. No baseline resolution was achieved. As reproducibility was an issue, we began to suspect that it may be due to the age of the columns themselves.

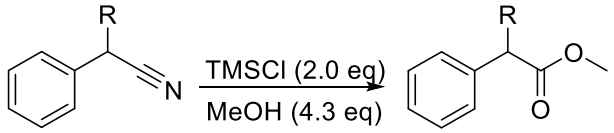
Having determined that our method for the resolution of the acids was unreliable we undertook to convert the nitriles to esters which we could potentially resolve. The nitriles were converted successfully to the methyl esters *via* reaction with TMSCl and MeOH at reflux for 16 h.[45] The methyl ester products were isolated after a workup which involved the addition of water to the reaction mixture followed by sodium carbonate and extraction with DCM (Table 2.14.1).

The reaction to produce ethyl substituted methyl ester **30b** proceeded to give a mixture of the recovered ethyl substituted nitrile **6b** and the product **30b** in a ratio of 23:77. This conversion was also confirmed by ^{1}H NMR spectroscopy. We wondered if we could push the reaction to completion by adding excess TMSCl and MeOH. The reaction to produce 2-ethylbutyl substituted methyl ester **30c** proceeded to give the product in 75% conversion. The remainder of the crude reaction mixture being the nitrile starting material **6c**.

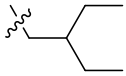
When the reaction to produce **30b** was repeated under the same conditions shown in Table 2.14.1 but with 4 eq of TMSCl and 8.6 eq of MeOH, the conversion of the product was unaffected, with 77% obtained. As the nitrile starting material **6b** and methyl ester products were similar in polarity it proved difficult to separate them *via* column chromatography. For this

reason, methyl ester products **30b** and **30c** could not be isolated. In addition to the GC-MS spectra, the methyl ester products were further identified by ^{1}H and ^{13}C NMR spectroscopy and IR spectroscopy.

Table 2.14.1: Ester formation from nitriles.



6 **30**

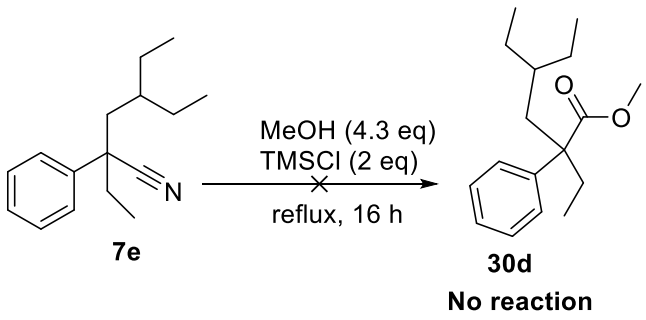
Product	R	Conversion[a] (%)	%ee[b]
(30b)	Et	77	10
(30c)		75	N/a

Reaction conditions: 1 eq nitrile, 2.0 eq MeOH, 4.3 eq TMSCl at reflux, 16 h; **a**) Based on GC-MS **b**) chiral HPLC.

The ethyl substituted methyl ester **30b** was resolved on chiral HPLC using Chiracel OD-H at 230 nm with hexane:IPA 99:1 mobile phase system.

Again, the enantiomeric excess (ee) was 10%. We suspect the low % ee could be because of racemization, which occurs during the reaction to form the ester. The proton α to nitrile is benzylic and, as the ester is formed, there are many possible mechanistic steps which could involve its loss, leading to a sp^2 hybridised carbon and scrambling of any chirality in the starting nitrile.

To get a better understanding of the mechanism of the reaction and to better understand the role the acidic proton plays, we attempted to convert a quaternary nitrile to the methyl ester under the same conditions outlined for the conversion of nitriles to esters above (Scheme 2.40). The reaction to convert the quaternary nitrile **7e** to the methyl ester **30d** was unsuccessful and gave back the nitrile SM **7e**. The result of this reaction supports the theory that removal of the α-proton is a key step in the reaction mechanism.



Scheme 2.40: Attempted reaction to form of di-substituted ester **30d**.

Luo[45] reports the use of TMSCl and EtOH in the conversion of p-nitrobenzylnitrile to the ethyl ester. In his paper he reports the role of the TMSCl as a source for generating HCl. A mechanism was devised based on Luo's report for the conversion of our substituted nitrile to the methyl ester, where the acidic proton protonates the nitrile.

The protonation of the nitrile by HCl, generated in situ from TMSCl and the first eq of MeOH, activates the nitrile for nucleophilic attack of another eq of MeOH to form the protonated imine which tautomerizes to the enamine. Hydrolysis of the iminium salt would give the ester product (Figure 2.17). In the mechanism shown intramolecular H^+ transfers are shown to simplify the scheme. In reality, intermolecular transfers are more likely.

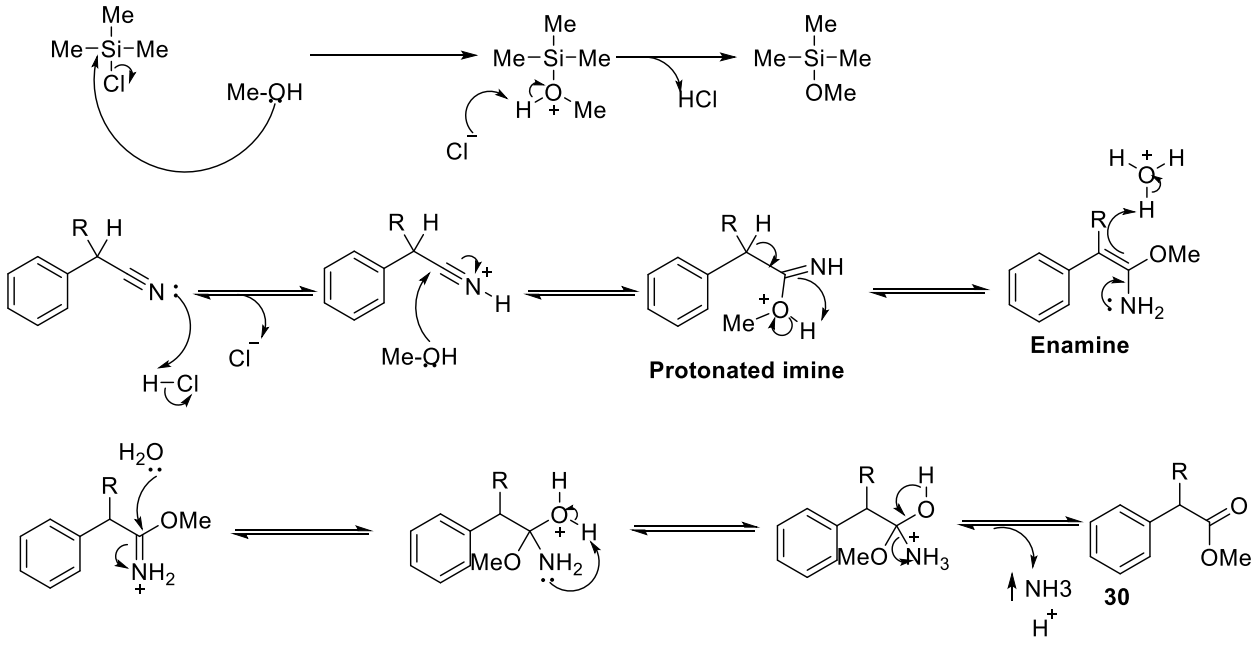


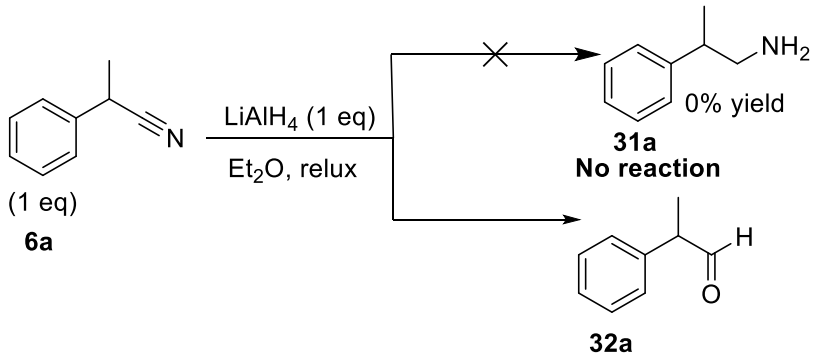
Figure 2.17: Proposed mechanism for ester formation from nitrile.

We also sought to reduce some of the nitriles to give amines showing the synthetic versatility of the nitriles as precursor chemicals.

The initial idea was to reduce the nitrile to the amine using $LiAlH_4$.[46] The reaction to produce the amine was carried out using 1 eq of $LiAlH_4$ in diethyl ether at reflux; this reaction was unsuccessful and did not lead to the formation of the amine. The reaction instead produced the aldehyde product after work-up (Figure 2.18).

The reaction conditions were varied in the hope of eliminating the formation of the aldehyde and forming the amine. Variations such as; doubling the number of eq of $LiAlH_4$, changing the reaction solvent from diethyl ether to THF were attempted, but all attempts led to the formation of the aldehyde (approximately 15% conversion) (Table 2.15).

Table 2.15: Attempted reduction of nitrile **6a** via $LiAlH_4$.



Eq of $LiAlH_4$	Solvent	Temp	Product (32)
1 eq	Et_2O	rt	aldehyde
1 eq	Et_2O	reflux	aldehyde
2 eq	THF	reflux	aldehyde

Reaction conditions: 1 eq nitrile, 1-2 eq $LiAlH_4$, solvent, 16 h.

The formation of the aldehyde product was confirmed *via* ^1H NMR analysis, where a peak at 9.7 ppm indicated the presence of the aldehyde proton. ^{13}C NMR spectroscopy also aided the identification of the compound as there was a peak at 200 ppm which is in the region where the carbonyl of the aldehyde is found. IR spectroscopy confirmed the presence of the aldehyde product, as a sharp peak at 1670 cm^{-1} was observed. The use of all these spectroscopic techniques satisfied us that the aldehyde product was being formed. The $LiAlH_4$ seems to have converted the nitrile to the imine which upon acidic work up gave the corresponding aldehyde even with the use of more than one eq of $LiAlH_4$ (Figure 2.18).

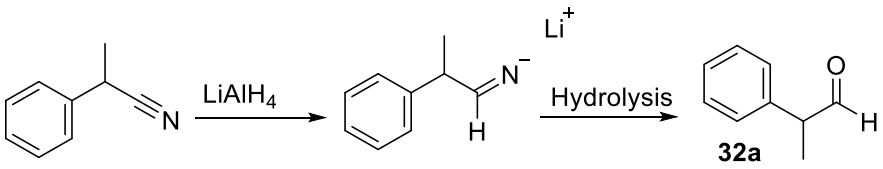
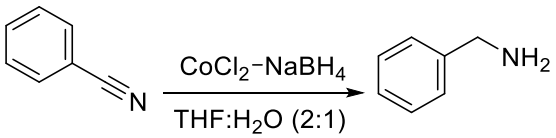


Figure 2.18: Aldehyde formation.

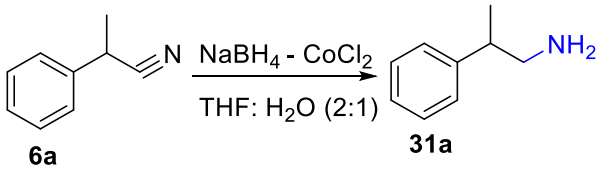
Other methods for reduction were sought, after the reduction to the amine using $LiAlH_4$ failed. The method documented by Osby et al[47] describes the use of a cobalt boride system ($NaBH_4$–$CoCl_2$) in the reduction of benzylnitrile to the benzylamine in one-pot in 91% yield (Scheme 2.41).



Scheme 2.41: Reduction of nitriles using cobalt boride system.

We wondered if we could implement the cobalt boride reduction system in the reduction of nitrile **6a**. Nitrile **6a** was successfully reduced to the primary amine employing the cobalt boride system and THF:H_2O (Table 2.15.1). As amines are basic compounds, the amine was isolated by acidic extraction. GC-MS and ^{1}H NMR spectroscopy were used in characterising the amine. As the conversions to the amine product were very low, resolution of the enantiomers on HPLC was not attempted.

Table 2.15.1: Reduction of nitrile **6a**.

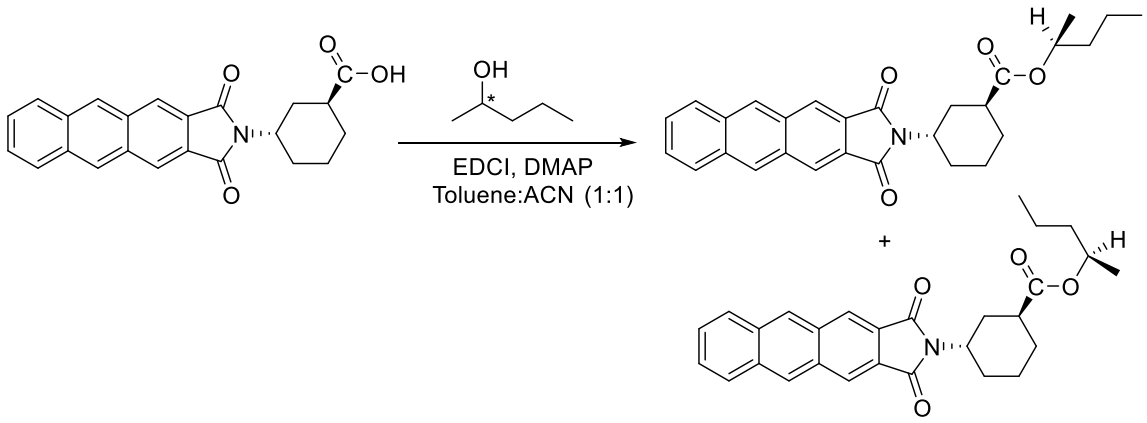


Entry	Time	Amine Conversion[a] (%)
1	2 h	20
2	16 h	33

a) Based on GC-MS; **Reaction conditions:** 1 eq nitrile, 0.1 eq $CoCl_2.6H_2O$, 2 eq $NaBH_4$ at rt

As we had no success in separating either the enantiomers of the simple nitriles, or those of the compounds we could prepare from them using chiral HPLC, we decided to explore other methods for separation.

The use of chiral derivatizing agents was then explored. Chiral agents are used to convert a mixture of enantiomers into diastereomers. As diastereomers have different physico-chemical properties, they are often separable, and even when not, analysis of mixtures can be conducted using NMR spectroscopy.[48] An example is shown in Scheme 2.42, where Ohuri reports derivatization of chiral secondary alcohols using (1S,2S)-(+)-(2,3-anthracenedicarboximide)cyclohexanecarboxylic acid.



Scheme 2.42: Chiral derivatization of an alcohol.[48]

We started by looking at the chiral derivatization of alcohols. The reaction of (S)-(+)-2-methylbutyric acid with the alcohol **16**, which we hoped had been prepared with some enantioselectivity, in the presence of DCC and DMAP was unsuccessful, with just unreacted starting material recovered. The presence of the unreacted starting material was confirmed by analysis by ^{1}H NMR spectroscopy.

As we had no success with derivatization of alcohol **16**, the use of the HPLC as a mode of separating the enantiomers was revisited. We had, in the interim, encountered Phenomenex, a company which provides analytical solutions to solve separation and purification problems. In collaboration with Phenomenex, we developed a method to separate the nitriles synthesised. We are very grateful to Prof. John O Reilly, an adjunct appointment in NUI Galway and formerly of Roche, who was very helpful in our interactions with Phenomenex.

From our initial scoping of the different columns they had available, we found that the use of Lux i-Cellulose-3 to be ideal for the separation of nitriles with non-polar functionalisation. While

the use of the Lux i-Cellulose-5 column was found to be better for the separation of the more polar nitrile compounds.

The stationary phase of the Lux i-Cellulose-3 column contains a cellulose tris(4-methylbenzoate) while the Lux i-Cellulose-5 column contains a cellulose tris(3,5-dichlorophenylcarbamate) chiral stationary phase.

We started this study by analysing the monoalkylated racemic nitrile samples **6a-c** on the chiral HPLC. We achieved the separation of the nitriles using the Lux i-Cellulose-3 column with a mobile phase of acetonitrile and water and detection at 205 nm.

Unless otherwise stated, detection of the products analysed was observed at 205nm.

Nitriles **6b** and **6c** were resolved using a mobile phase composition of acetonitrile and water (50:50).

Figure 2.19 shows the HPLC chromatography of the racemic nitrile sample **6c** with excellent baseline separation using the Lux i-Cellulose-3 column.

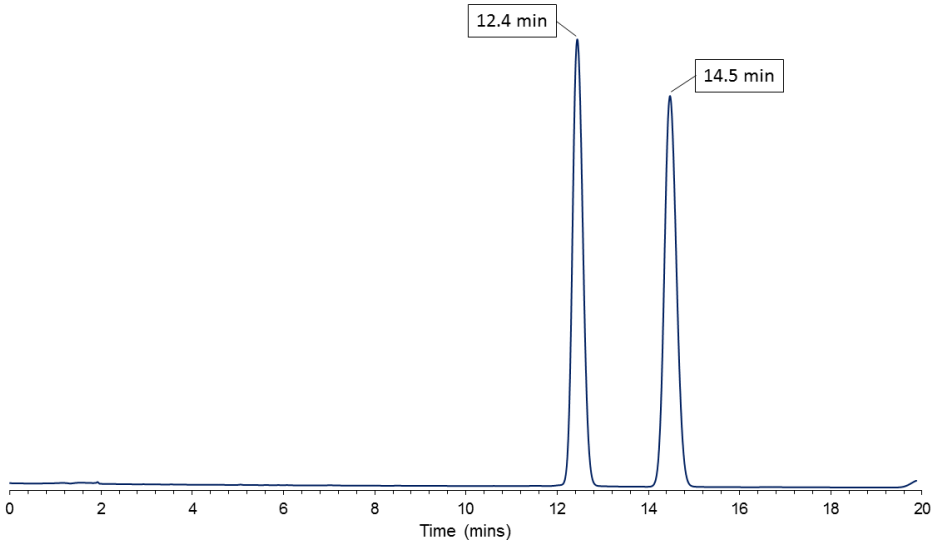


Figure 2.19: HPLC chromatogram of racemic sample **6c** using Lux i-Cellulose-3 column.

When the same mobile phase composition was used for the methyl substituted nitrile **6a**, we observed there was no baseline separation between the two peaks. Increasing the polarity of the mobile phase, to 30:70 (ACN:H_2O), we were able to successfully separate the enantiomers of the methyl substituted nitrile **6a**.

With the successful resolution of the racemic tertiary nitriles, we wondered if we could get resolution with quaternary nitrile **7e**. Using the same column and conditions described for the ethyl substituted nitrile **6b**, the quaternary nitrile **7e**, was successfully separated with a mobile phase of 50:50 (ACN:H_2O).

As both the tertiary and quaternary racemic nitriles were resolved successfully, we analysed the samples prepared using the chiral base **28a**.

The analysis of the nitriles produced using a chiral base gave a similar chromatogram to that observed for the racemic nitriles, with the retention times being consistent with that observed for the racemic samples (Table 2.16). Although the resolution of these compounds was successful, no enantiomeric excess was observed in any case. This separation method represents a highly useful development for any researchers seeking to develop chiral nitriles. Although we had finally been able to develop a method for the resolution of the nitrile compounds, our enantiomeric excess values were low. We wanted to see if we could influence the selectivity.

In trying to influence selectivity, the effect of an electron withdrawing group (EWG) on the aromatic ring in the alkylation reactions was investigated. The electron withdrawing group should make the anion more stable which may influence the reaction of the anion.

The use of 4-bromophenylacetonitrile **5b** in place of phenylacetonitrile **5** was used in the investigation. The reaction of 4-bromophenylacetonitrile using chiral base **28b** and different alkylating agents was carried out (Table 2.16).

The reaction of 4-bromophenylacetonitrile with iodomethane, gave the monoalkylated product **33a** in 82% conversion. The remainder of the crude mixture consisted of the starting material and the dialkylated product. Compound **33a** was analysed on the HPLC using the Lux i-Cellulose-3 column, with a 30:70 (ACN:H_2O) mobile phase. The result obtained from this reaction show that the presence of an EWG has almost no effect on the selectivity of the product as the enantiomeric excess value remained at 0%.

The reaction of 4-bromophenylacetonitrile with iodoethane gave the product **33b** in 92% conversion, with the remainder of the crude mixture being the dialkylated product.

Analysis of this compound again returned a 0% ee using a Lux i-Cellulose-3 column, with a 50:50 (ACN:H_2O) mobile phase. Although the presence of the EWG had no effect on the selectivity, the reaction outcome was affected (8% diethylated product). The amount of dialkylated product differs from the reaction of phenylacetonitrile **5** with iodoethane where just 2% of the diethylated product was produced.

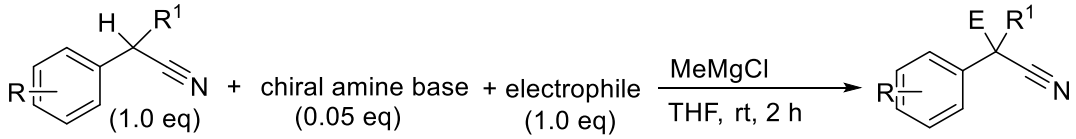
Reaction to produce **33c** gave 0% enantioselectivity when analysed under the same HPLC conditions as that used for the ethyl substituted product **33b**. Again, we observed a difference in the reaction product distribution. The product was formed in 78% conversion, remainder being the dialkylated product (22%). Just like in the reaction to produce **33b**, no starting material was observed and the amount of dialkylated product is significantly higher when compared to the non-brominated product **6c** which when formed also saw formation of the dialkylated product in 4% conversion.

Moving away from the straightforward alkyl halide, the reaction of 4-bromophenylacetonitrile with cyclohexene oxide gave the product **33d** in 100% conversion.

Compound **33d** was separated under the following HPLC conditions: Lux i-Cellulose-3 column with a mobile phase of 50:50 (ACN:H_2O). Although compound **33a** which contains an alcohol, is relatively polar, Lux i-Cellulose-3 was used in the separation of its enantiomers. The use of the Lux i-Cellulose-3 column however was unsuccessful in the separation of the enantiomers of the non-brominated compound **22** as will be discussed later.

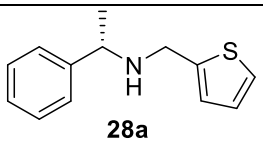
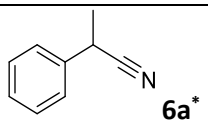
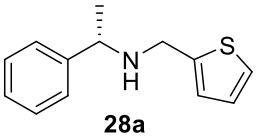
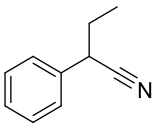
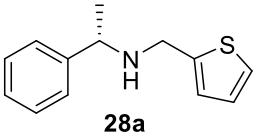
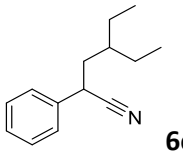
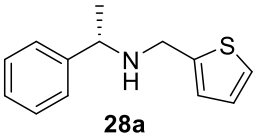
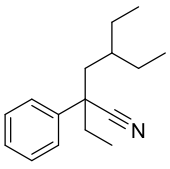
An enantiomeric excess of 4% was observed for this reaction. Although this is quite a low value, the value is believed to be real, our injections were done in triplicate and the same results was obtained in all cases.

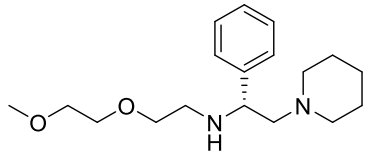
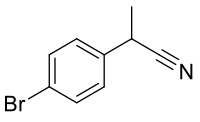
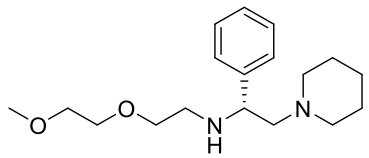
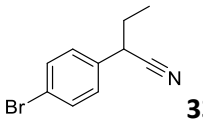
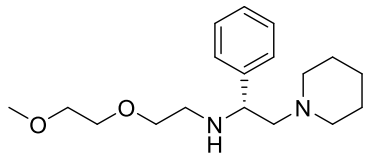
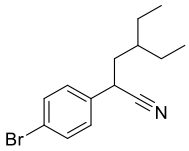
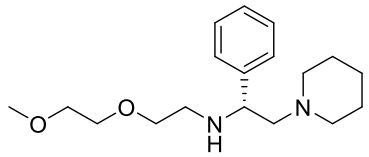
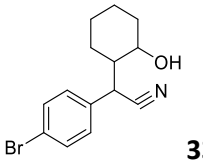
Table 2.16: Reverse phase HPLC results for asymmetric alkylation reactions using Lux i-Cellulose-3 column.



R= H or Br

R^1= H or 2-ethylbutyl

Chiral base	Products	% ee[b]	% Conversion[a] (SM: Mono:Di)
 **28a**	 **6a***	0	5:89:6
 **28a**	 **6b**	0	3:95:2
 **28a**	 **6c**	0	9:87:4
 **28a**	 **7e**	0	SM:Pdt 9:91

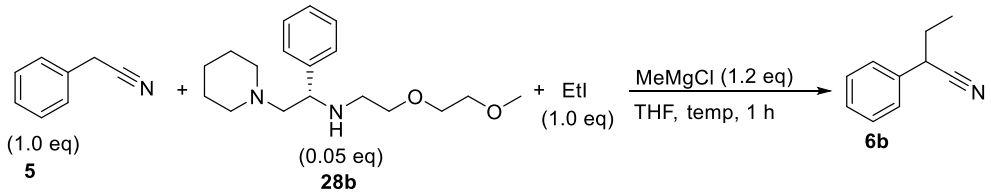
 **28b**	 **33a***	0	11:82:7
 **28b**	 **33b**	0	0:92:8
 **28b**	 **33c**	0	0:78:22
 **28b**	 **33d**	4 (d.r 90:10)	SM:Pdt 0:100

a) Based on GC-MS **b) HPLC Conditions**: 50:50 (H_2O:ACN), Lux i-Cellulose-3 column, 1 mL/min, (250 x 4.6 mm, 5 µm. * 70:30 (H_2O:ACN), 1 mL/min, (100 x 4.6 mm, 5 µm). **Reaction conditions**: nitrile 1 eq, chiral base 0.05 eq, electrophile 1 eq, MeMgCl 1.2 eq, THF, rt, 2 h.

After the initial scoping, it was decided to study the effect temperature may have on the reactions. We chose to start by studying the effect of temperature in the reaction to produce **6b**, using chiral base **28b** in the investigation (Table 2.17). The results obtained from these reactions show that the reaction at room temperate yields the best results, as an enantiomeric excess value of 8% was observed. The reaction at reflux gave an ee of 1%, and the reaction at 0°C gave a ee of 5%.

When the reaction to produce **6b** was carried out at –78 °C the reaction did not proceed. Although a 10% conversion to the monoalkylated product **6b** is reported, we suspect this is because of the reaction being quenched at rt.

Table 2.17: Effect of temperature in preparation of ethyl substituted nitrile **6b**.

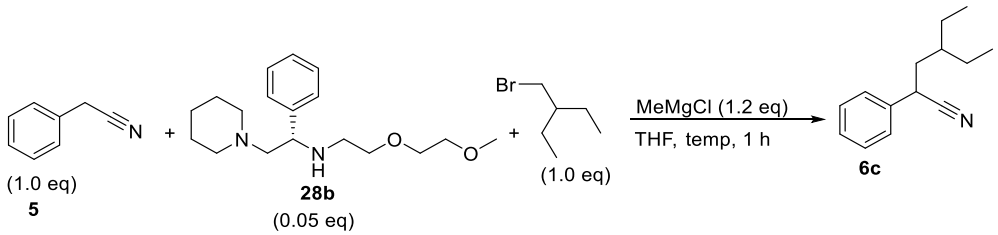


Temperature	% ee[b]	% Conversion[a] (SM: Mono: Di-alkylation)
Reflux	1	1:98:1
rt (25 °C)	8	3:96:1
0 °C	5	2:97:1
–-78 °C	0	90:10:0

a) Based on GC-MS **b) HPLC conditions**: 50:50 (H2O:ACN), 1 mL/min, Lux i-Cellulose-3 column (250 x 4.6 mm, 5 µm);

The effect of temperature in the reaction to produce **6c** was then studied, using chiral base **28b** (Table 2.17.1). We were curious to see if the size of the R group would influence selectivity. In this study, carrying out the reaction at 0 °C gave the best results, as an enantiomeric excess value of 8% was observed. The reaction at reflux and rt gave a ee of 0%. When the reaction was conducted at 0 °C we observed a significant change in the reactivity of the reaction. The monoalkylated product **6c** was only obtained in a 60% conversion and there was no dialkylated product observed. The remainder of the crude mixture was the nitrile **5** starting material.

Table 2.17.1: Effect of temperature in preparation of 2-ethylbutyl substituted nitrile **6c**.



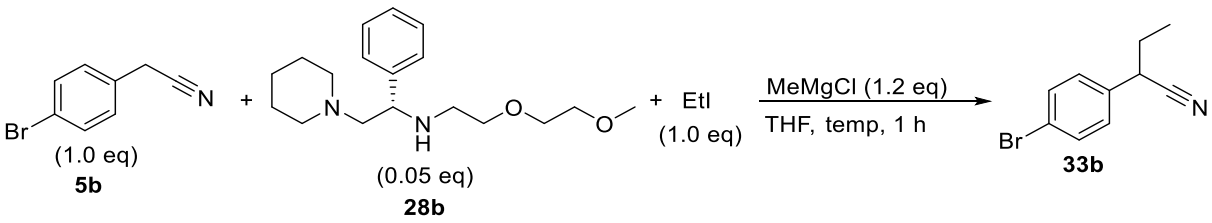
Temperature	% ee[b]	% Conversion[a] (SM: Mono: Di-alkylation)
Reflux	0	13:82:5
rt (25 °C)	0	6:90:4
0 °C	8	40:60:0

a) Based on GC-MS **b) HPLC conditions**: 50:50 (H_2O:ACN), 1 mL/min, Lux i-Cellulose-3 column (250 x 4.6 mm, 5 µm);

From our initial scoping, the presence of an electron withdrawing group did not influence selectivity. In this study however, we wanted to study the effect of an electron withdrawing group (EWG) at different reaction temperatures (Table 2.18).

4-Bromophenylacetonitrile **5b** was used in the investigation. The reaction of 4-bromophenylacetonitrile with iodoethane using chiral base **28b** was performed at different temperatures. The electron withdrawing group should make the anion more stable which may influence the reaction of the anion. It seemed from previous work that the stabilising of the anion favoured the dialkylation and we thus thought that maybe the reaction could be conducted at lower temperatures which may enhance the enantioselectivity. The results obtained from these reactions show that the presence of an EWG has no positive effect on the selectivity of the reactions. The reaction gave little or no enantioselectivity at any of the temperatures tried. By comparison the non-brominated nitrile gave 8% ee in reaction at rt. Not surprisingly the EWG affected the overall reactivity. No starting material was left in any of the reaction mixtures and increased amounts of dialkylated products (up to 26%) were observed when compared to the non-brominated compound's reaction which typically gave 1-3%. The result came as a surprise as only 1 eq of the ethyl iodide was used, and we expected to obtain the same amount of unreacted SM as dialkylated product. This could possibly be related to the small scale at which the reaction is being conducted, leading to potential errors in making up stoichiometric charges.

Table 2.18: Effect of EWG in alkylation reaction.

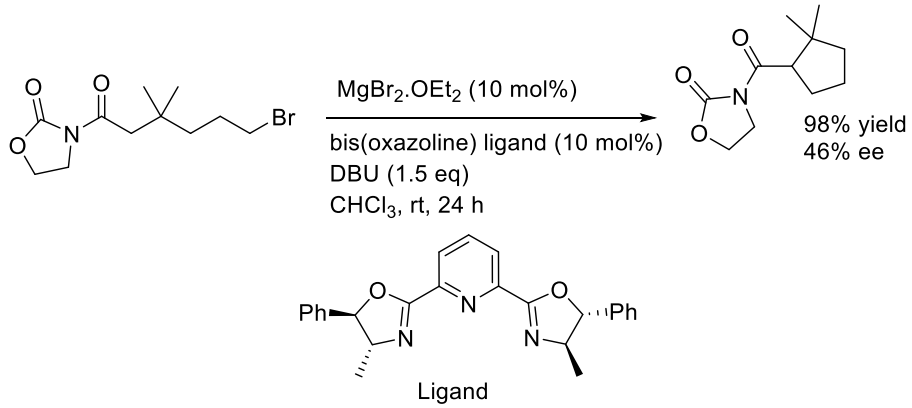


Temperature	% ee[b]	%Conversion[a] (Mono:Dialkylated)
Reflux	0	90:10
rt (25 °C)	0	92.8
0 °C	2	74:26

a) Based on GC-MS **b) HPLC conditions**: 50:50 (H_2O:ACN), 1 mL/min, Lux i-Cellulose-3 column (250 x 4.6 mm, 5 µm).

We had to this point used a chiral base on its own. Given our reactions involved the formation of magnesium species and we know magnesium can co-ordinate to nitrogen-based chiral

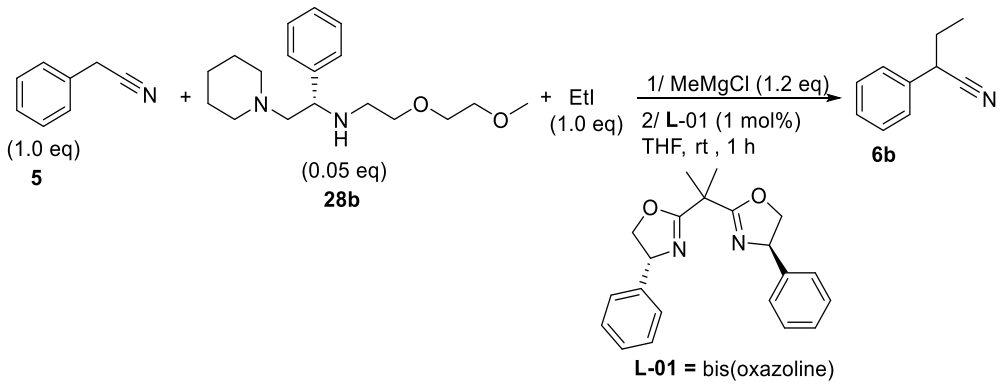
ligands (Scheme 2.43) leading to enantioselective reactions,[49,50] we wanted to study the effect the incorporation of bis(oxazoline) ligands into the reaction mixture may have on the reactions. C_2-Symmetric bis(oxazolines) are one of the most popular classes of chiral ligands employed in metal-catalysed asymmetric reaction. C_2-Symmetric bis(oxazoline) ligands have received a great deal of attention as ligands due to their topography and ease of synthesis from readily available chiral amino alcohols.[51–53]



Scheme 2.43: Magnesium-bis(oxazoline) complex in intramolecular alkylation.

One difficulty faced in the enantioselective work was the choice of solvents we were limited to. Any work involving chiral complex formation is generally more successful in a non-coordinating solvent. This prevents competition between the ligand and solvent for co-ordination to the magnesium. The use of a Grignard does limit our use of solvents such as dichloromethane. THF and other ether solvents can interrupt the co-ordination of the ligands to metals and any starting materials, intermediates or complexes that might be formed.
What follows in the next few pages show the attempts we made to influence the selectivity by the incorporation of a chiral ligand.

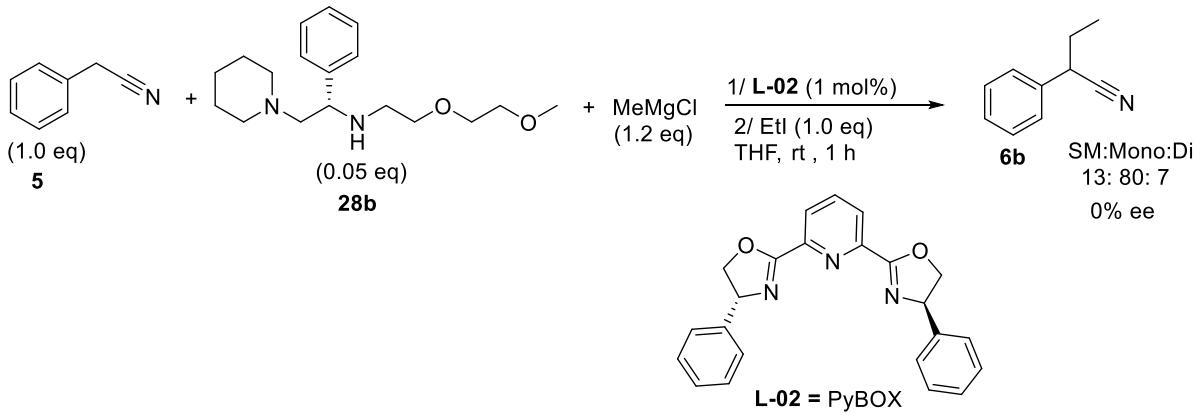
The reaction to produce **6b** in the presence of a bis(oxazoline) ligand, 2,2′-methylenebis[(4*S*)-4-phenyl-2-oxazoline **L-01** was carried out. The reaction was carried *via* the late addition and the preformed anion method. The reaction proceeded to produce the monoalkylated product **6b** in 98% and 97% conversion *via* the late addition of the MeMgCl and preformed anion method respectively. Although the reactions were successfully carried out with good conversions, the incorporation of the ligands had no positive effect on the enantioselectivity of the reaction. The reaction gave little or no enantioselectivity (Table 2.19).
Table 2.19: Effect of bis(oxazoline ligand in alkylation reaction to produce **6b**.



Method	Ligand	% ee[b]	% Conversion[a] (SM:Mono:Dialkylated)
"Late addition"	No ligand	0	3:96:1
"Late addition"	**L-01**	0	0:98:2
"Preformed anion"	**L-01**	4	0:97:3

a) Based on GC-MS **b) HPLC conditions**: 50:50 (H2O:ACN), 1 mL/min, Lux i-Cellulose-3 column (250 x 4.6 mm, 5 µm);

A similar reaction was carried out where we used a PyBOX ligand, (2,6-bis[(4R)-4-phenyl-2-oxazolinyl]pyridine) **L-02** in the reaction to produce **6b**. Again, the incorporation of this ligand to have no positive effect on the selectivity (Scheme 2.44).

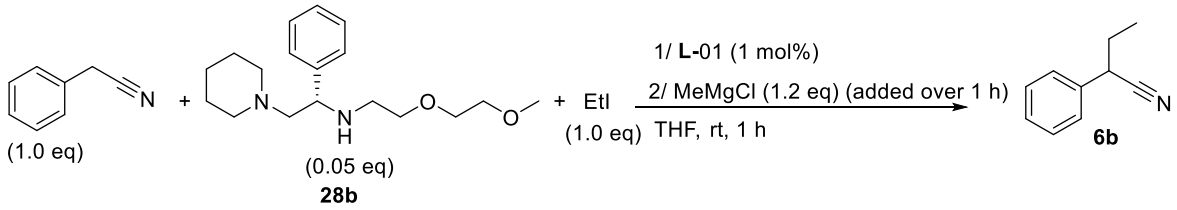


Scheme 2.44: Reaction to produce nitrile **6b** using both a chiral amine and PyBOX ligand.

It was previously noted that the reaction can proceed in the absence of the amine albeit slower and in less reliable yields. Given the chiral amines are significantly different in structure to

diethylamine we wondered whether the cycling of the amine may be slower and thus the non-enantioselective background reaction may be problematic. We decided to investigate the effect of slow addition of the Grignard reagent (Table 2.20) in these reactions which should limit the unmediated reaction. When the reaction to produce **6b** with the addition of the Grignard being conducted over an hour, the reaction gave no enantioselectivity with the chiral base **28b** but in the absence of the chiral ligand. When the reaction was repeated, incorporating the chiral ligand, the enantioselective outcome was unaffected. What we did find was the slow addition with the chiral ligand and chiral amine **28b** both in place gave a lower conversion than our standard addition method. The reaction produced a 50:50 ratio of starting material to monoalkylated product **6b**.

Table 2.20: Effect of slow addition of MeMgCl to produce **6b**.



Ligand	Conversion[a] SM:Mono:Di	%ee[b]
No ligand	1:95:4	0
L-01	50:50:0	0

a) Based on GC-MS **b) HPLC conditions**: 50:50 (H2O:ACN), 1 mL/min, Lux i-Cellulose-3 column (250 x 4.6 mm, 5 µm);

So far, an enantiomeric excess value no more than 8% for the simple alkylated nitriles has been observed. We wondered if the use of 1,3 dicarbonyls, dimethyl malonate and an α, β unsaturated compound would have an influence on the selectivity.

Th resolution of the racemic addition product **25** was attempted on the chiral HPLC using the same column as we had used for the straightforward alkylated products.

When a Lux i-Cellulose-3 column with a 50:50 (ACN:H_2O) mobile phase was used, there was separation between the two enantiomers on the HPLC chromatogram. Increasing the polarity of the mobile phase composition to 20:80 (ACN:H_2O) made no difference to the peak separation. A normal phase Lux i-Cellulose-5 column was used instead to try to resolve **25**. The racemic sample of **25** was successfully resolved with a mobile phase of 20:80

(EtOH:Hexane) and UV detection at 205 nm. The chromatogram observed for compound **25** showed good resolution of the peaks due to the two enantiomers (Figure 2.20).

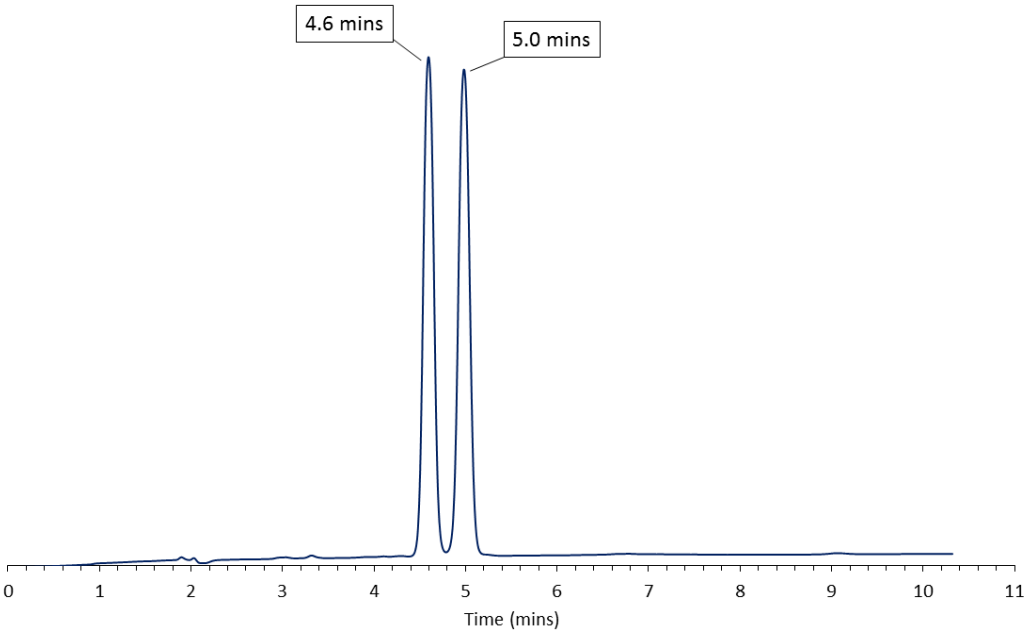


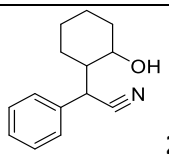
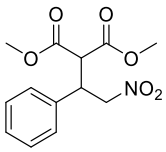
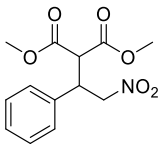
Figure 2.20: Normal phase HPLC chromatogram of racemic sample **25** using Lux i-Cellulose-5 column.

Having successfully separated the racemic product using chiral HPLC. The reaction of dimethyl malonate **10a** with *trans*-β-nitrostyrene using the chiral base **28a** was carried out in an effort to induce enantioselectivity. The reaction gave the product **25** in 98% conversion, with the remainder of the mixture being the *trans*-β-nitrostyrene starting material (2%). The addition product **25** prepared using the chiral base was analysed on the Lux i-Cellulose-5 gave a non-significant enantiomeric excess of 2% (Table 2.21).

When the reaction to produce **25** was repeated with chiral base **28b**, a 2% ee was also obtained.

We then decided to carry out a reaction of phenylacetonitrile **5** with cyclohexene oxide in the presence of MeMgCl and catalytic amine. The reaction to produce **22** was carried out using chiral base **28a**. The reaction produced the diastereomeric product **22** in 92% conversion. The addition products **22** was analysed on the Lux i-Cellulose-5 and gave an enantiomeric excess of 2%. The diastereomeric products were present in a ratio of 90:10 as observed on ^{1}H NMR spectroscopy (Table 2.21).

Table 2.21: Normal phase using Lux i-Cellulose-5 column.

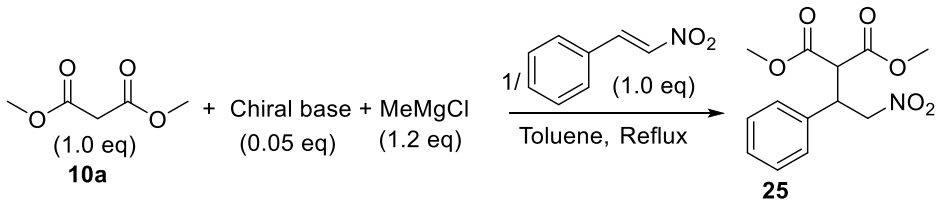
Chiral base	Products	% ee[b]	d.r	% Conversion[a] (SM:Pdt)
28a	 **22**	2	90:10	8:92
28a	 **25**	2	N/A	2:98
28b	 **25**	2	N/A	4:96

a) Based on GC-MS **b) HPLC Conditions**: 80:20 (Hexane:EtOH) 1.5 mL/min, (100 x 4.6 mm, 5 µm). **Reaction conditions:** 1 eq nitrile **5**/dimethyl malonate, 0.05 eq diethylamine, 1.2 eq MeMgCl at rt for 1 h, After 1 h, 1 eq electrophile added and reaction was reflux for 2 h.

We continued this study by investigating the reaction of dimethyl malonate with *trans*-β-nitrostyrene using catalytic chiral base in toluene. Up to this point, THF was used in all our reactions and very low levels of enantioselectivity was observed. We wanted to see if a change in solvent would influence selectivity.

Reaction to produce **25** was carried out by preforming the anion of dimethyl malonate using a chiral base and MeMgCl followed by the addition of *trans*-β-nitrostyrene. Using both chiral bases **28a** and **28b**, the reaction gave the addition product **25** in 100% conversion, however the ee was still low, with a 2% ee obtained in both cases (Table 2.22).

Table 2.22: Conjugate addition reaction to produce **25** in toluene.



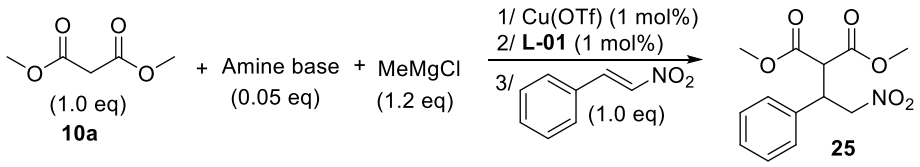
Base	% ee[b]	% Conversion[a] (SM:Product)
28a	2	0:100
28b	2	0:100

a) Based on GC-MS **b) HPLC conditions**: 80:20 (Hexane:EtOH) 1.5 mL/min, Lux i-Cellulose-5 column (250 x 4.6 mm, 5 µm)

Searching the literature, we found that C_2-symmetric bis(oxazoline)-derived Cu(I) and Cu(II) complexes have proven to be excellent catalysts for enantioselective processes such as cyclopropanation,[52] olefin aziridination,[54] and Diels-Alder reaction.[55] Copper species are also known to influence the addition to conjugated systems, favouring 1,4-addition as opposed to 1,2-addition. The idea of a chiral copper species (complex) being involved in influencing the direction of the reaction appealed to us as it opened the prospect of influencing chirality also. We wondered if we could use such copper complexes to influence the formation of the dimethyl malonate adduct.

Reaction of dimethyl malonate with chiral base **28b** and MeMgCl at rt was carried out. After 1.5 h $Cu^{ii}(OTf)_2$ and the bis(oxazoline) ligand **L-01** was added to the reaction mixture which was then stirred for 20 mins before the addition of *trans*-β-nitrostyrene. The reaction proceeded to give the addition product **25** in 100% conversion, however just 4% ee was obtained. When the reaction was repeated, but with the use of diethylamine instead of a chiral base, an ee of 6% was obtained. While the copper salt and BOX ligand's addition may have influenced the enantioselectivity slightly, it was not substantial enough to encourage us to investigate further (Table 2.22.1).

Table 2.22.1: Effect of bis-oxazoline ligand **L-01** in conjugate addition reaction to produce **25**.



Base	Ligand	% ee	% Conversion[a] (SM: Product)
28b	**L-01**	4	0:100
Diethylamine	**L-01**	6	0:100

a) Based on GC-MS **b) HPLC conditions**: 80:20 (Hexane:EtOH) 1.5 mL/min, Lux i-Cellulose-5 column (250 x 4.6 mm, 5 µm)

Reaction of cyclohexanecarbonitrile **1** with *trans*-*β*-nitrostyrene was also studied in the context of attempting to gain enantiocontrol. The reaction of nitrile **1** with *trans*-*β*-nitrostyrene in the presence of MeMgCl and $Cu^{II}(OTf)_2$ was conducted while varying the amine base used and the presence/absence of the bis(oxazoline) ligand **L-01**. (Table 2.23).

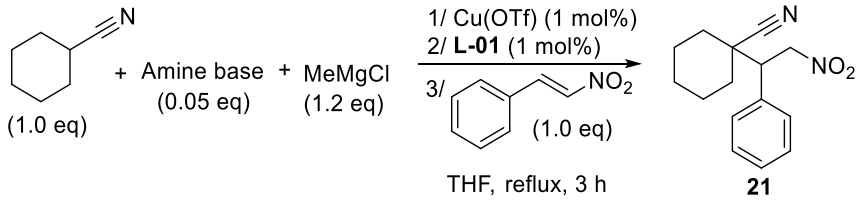
We began by carrying out the non-enantioselective reaction using our standard reaction conditions. Reaction to produce the addition product **21** was successful. The crude product was found to consist of 67% of the required product with no ketone product observed. The remainder of the crude mixture was the nitrile **1** (9%) and *trans*-β-nitrostyrene starting material (24%).

It was decided to incorporate bis(oxazoline) **L-01** into the reaction. Using diethylamine as amine base, the reaction to produce the addition product **21** was repeated. The reaction gave the crude product mixture consisting of the addition product **21** (22%) and the ketone side product (acetylcyclohexane), arising from the addition of MeMgCl to nitrile **1**. The remainder of the crude mixture being the nitrile **1** and *trans*-β-nitrostyrene starting material. Using previously isolated racemic addition product **21** as a reference, analyses of the chiral samples on HPLC indicated the reaction had no enantioselectivity.

When the reaction to produce **21** was carried out in the presence of chiral base **28b** and the chiral ligand **L-01**, we found the reaction occurred at a slower rate and the addition product **21** made up just 2% of the crude product. With such low conversions, resolution of the enantiomers on HPLC was not attempted.

In these reactions we found was that the use of the chiral ligand **L-01** reduced the rate of reaction and as a result the formation of the ketone, which arises from the direct attack of MeMgCl to nitrile **1**, became more prevalent.

Table 2.23: Effect of copper triflate and oxazoline ligand in reaction to produce **21**.

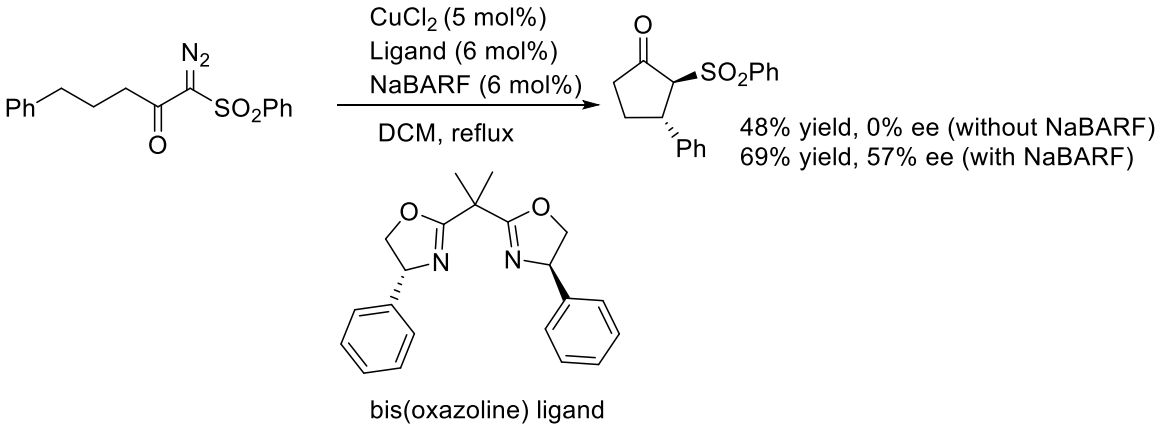


Base	Ligand	Product composition[a] (SM 1: ketone[c]:nitrosyrene:pdt)	%ee[b]
Diethylamine	No ligand	9:0:24:67	0
Diethylamine	**L-01**	9:28:41:22	0
28b	**L-01**	19:23:56:2	-

a) Based on GC-MS **b) HPLC conditions**: 80:20 (Hexane:EtOH) 1.5 mL/min, Lux i-Cellulose-5 column (250 x 4.6 mm, 5 µm)
c) Acetylcyclohexane

As we had no success so far in improving enantioselectivity, the use of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, (BARF) compounds were attempted. There have been a few reports which have demonstrated that addition of a weakly-coordinating borate anion $BARF^-$, from the salts NaBARF or KBARF, {BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} to a copper source and a bis(oxazoline) ligand results in complex formation that for some reactions gave enhanced enantioselectivities.[56,57]

In the report by Maguire et al.,[56] little to no enantioselectivity was observed in the absence of NaBARF. However, when they employed the weakly-coordinating counterion $BARF^-$ a large improvement in enantiocontrol was recorded (57% ee) (Scheme 2.45).

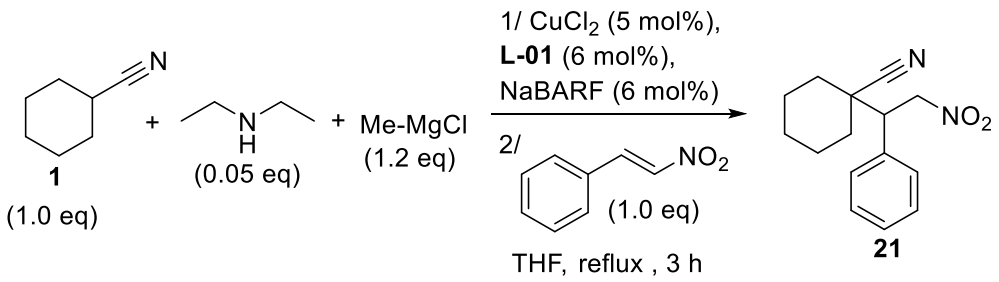


Scheme 2.45: Use of NaBARF in the asymmetric copper-catalysed intramolecular C-H insertion reactions by Maguire et al.

To investigate this, the same procedure reported by Maguire et al was followed, where the $CuCl_2$-L-NaBARF catalyst was generated *in situ* from a mixture of $CuCl_2$ (5 mol%), bis(oxazoline) ligand **L-01** (6 mol%) and NaBARF (6 mol%) in DCM (10 mL). This mixture was stirred under nitrogen at 40 °C for 1.5 h.

The $CuCl_2$-L-NaBARF mixture was then added to a solution of nitrile **1**, diethylamine and MeMgCl in anhydrous THF. The reaction mixture was stirred for an hour before the addition of *trans-β*-nitrostyrene and was left to stir at 40 °C for a further 2 hours. Upon analysis on GC-MS, the reaction to produce product **21** was unsuccessful, yielding just unreacted starting materials. We suspect that the presence of DCM in the reaction mixture was the cause for the reaction not taking place.

When the above reaction was repeated using just THF as a solvent in the generation of the $CuCl_2$-L-NaBARF (Scheme 2.46), the reaction proceeded to give a crude product consisting of product **21** (36%) with the remainder of the crude mixture being unreacted starting material. The mixture was analysed on HPLC under the following conditions: 80:20 (hexane:EtOH) 1.5 mL/min, Lux i-Cellulose-5 column (250 x 4.6 mm, 5 µm) and gave a 0% ee.



Scheme 2.46: Addition of NaBARF to the reaction to produce **21**.

Throughout our study we found all ee's were very low. We attempted several variations in conditions and methods in the hope of increasing stereoselectivity. Conditions such as temperature, solvent, chiral ligands and the nature of the chiral amine were varied but little control was achieved in any reaction.

Work on the in-process FTIR as seen in the racemic alkylation reactions show that the alkylation reactions occur very rapidly. Upon addition of the MeMgCl the anion is formed and reacts quickly. This inherent reactivity was always going to present an issue in terms of getting selectivity.

Although there is evidence from the FTIR studies that the intermediate derived from phenylacetonitrile **5** is the N-metalated nitrile, where the metal atom is located on the nitrogen atom, no selectivity was observed in all reactions conducted.

As we depend on the coordination of the chiral ligand and/or the chiral amine base to the Mg metal to influence selectivity, coordination is crucial as is the location of the magnesium on the nitrile anion.

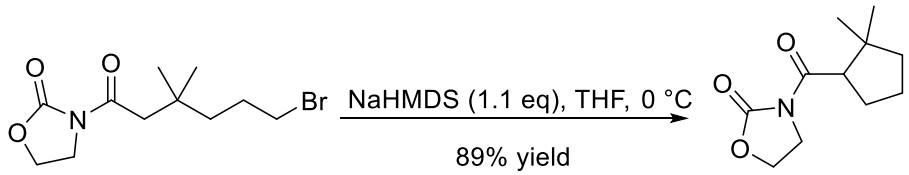
As MeMgCl is only commercially available in THF, we believe the coordination of THF to the magnesium species is favoured over the coordination of the chiral ligand and/or the chiral amine. This makes achieving stereoselectivity in these reactions more challenging.

2.3 Intramolecular alkylation reaction

We continued to explore the versatility of MeMgCl as a non-chiral base, to see if this method can be used in deprotonating adjacent to other functional groups besides nitriles.

We wondered if this methodology could deprotonate α to an amide, followed by an intramolecular alkylation.

We started by looking at a ring closing reaction, involving an intramolecular alkylation, as reported by De Rycke et al,[49] where they deprotonate 3-(6-bromo-3,3dimethylhexanoyl)oxazolidin-2-one in the presence of a sodium base (Scheme 2.47). The use of oxazolidinone imides was of interest because they undergo enolization with a range of metal salts.[58] This was significant as they intended to carry out the intramolecular alkylation of the oxazolidinone imides enantioselectively.



Scheme 2.47: Intramolecular alkylation of 3-(6-bromo-3,3-dimethylhexanoyl)oxazolidin-2-one.

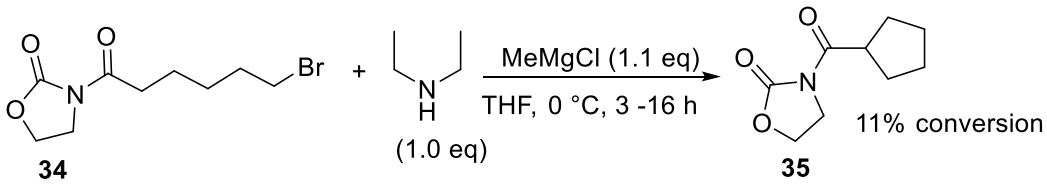
We wondered if we could extend our methodology to the intramolecular alkylation of 3-(6-bromohexanoyl)oxazolidin-2-one **34**.

We started by synthesising 3-(6-bromohexanoyl)oxazolidin-2-one. This was done by reacting 2-oxazolidine (1 eq) and 6-bromohexanoic acid (1.5 eq) in the presence of DCC (1.5 eq) using DCM as a solvent. The reaction gave the product in a yield of 72% after purification by column chromatography.

Under the standard conditions established for the monoalkylation reactions, we then reacted the 3-(6-bromohexanoyl)oxazolidin-2-one with catalytic diethylamine (0.05 eq) and MeMgCl (1.2 eq) at rt for 3 hours. Although the reaction proceeded to give the ring closed product, the starting material, 3-(6-bromohexanoyl)oxazolidin-2-one was present along with a lot of other side products we could not identify. The side products were evident on GC-MS from the presence of various additional peaks.

This reaction was repeated several times. The generation of the anion from the reaction of diethylamine (1.0 eq) and MeMgCl (1.2 eq) before the addition of 3-(6-bromohexanoyl)oxazolidin-2-one was attempted. However, the conversion to the product was not more than 10% in any attempt. The original reaction was then repeated as reported by De Rycke et al., albeit our compound was missing two methyl groups, where they used

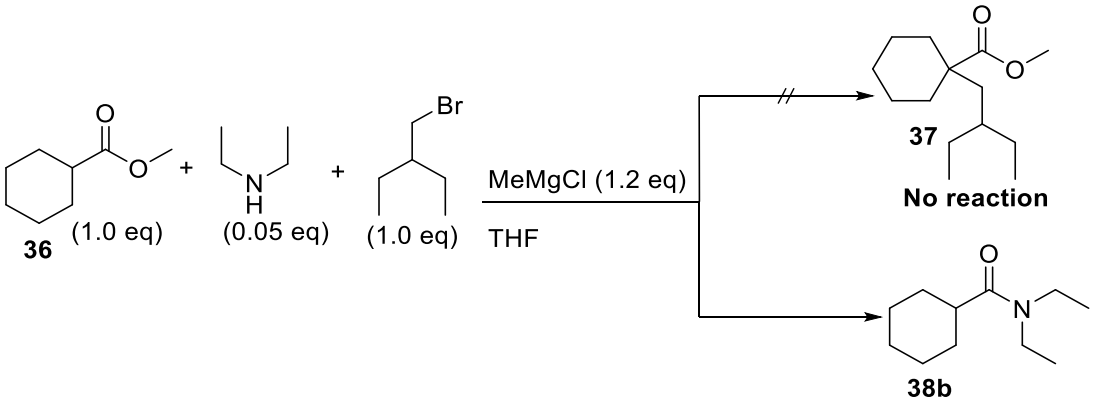
NaHMDS (1 M in THF, 1.1 eq) as the base and the reaction was carried out at 0 °C. When the reaction was repeated under the conditions reported, the reaction proceeded successfully with a 66% conversion to the ring closed product. The remainder of the crude mixture was starting material. We wondered if the use of a lower temperature (0°C) with MeMgCl would eliminate other side reactions from occurring (Scheme 2.48). When the reaction involving 3-(6-bromohexanoyl)oxazolidin-2-one, diethylamine (1 eq) and MeMgCl (1.2 eq) at 0°C was repeated, there was less side product formation. The reaction proceeded to give the ring closed product, however still at low conversion (11%) with the remainder of the crude mixture being starting material. We wondered if the conversion could be improved by leaving the reaction longer. We found the outcome to be unaffected after leaving the reaction stirring overnight. Due to the low conversions, attempts to purify the ring closed product *via* column chromatography and bulb to bulb distillation were unsuccessful. While not optimised it did demonstrate that the Grignard based system could be used beyond nitriles and in intramolecular reactions



Scheme 2.48: Intramolecular alkylation of 3-(6-bromohexanoyl)oxazolidin-2-one.

2.4 Amide formation reaction

The extension of the MeMgCl deprotonation methodology to further functional groups was explored. Knowing that it was possible to deprotonate alpha to an amide, albeit in poor yields for the alkylation step, we wondered if the MeMgCl chemistry would deprotonate adjacent to a methyl ester. The initial idea was to conduct an alkylation reaction; however, this approach did not lead to the formation of the desired coupled product. After studying the GC-MS traces obtained on analysing the reaction of methyl cyclohexanecarboxylate **36** with diethylamine and MeMgCl and an alkyl halide (Scheme 2.49), it was discovered the deprotonation of ester failed but amide formation was observed.



Scheme 2.49: Attempted alkylation of an ester.

As discussed in Chapter 1, the amide functionality is one of the most fundamental chemical building blocks found in nature. Amides and amide bonds are essential to life and play a significant role in the composition of biological systems. amide bonds being one of the most prolific moieties in pharmaceutical molecules.[59] Amide bonds are present in 25% of available drugs (Figure 2.21) and as a result there is a great interest in the development of new approaches for amide bond formation.[60,61]

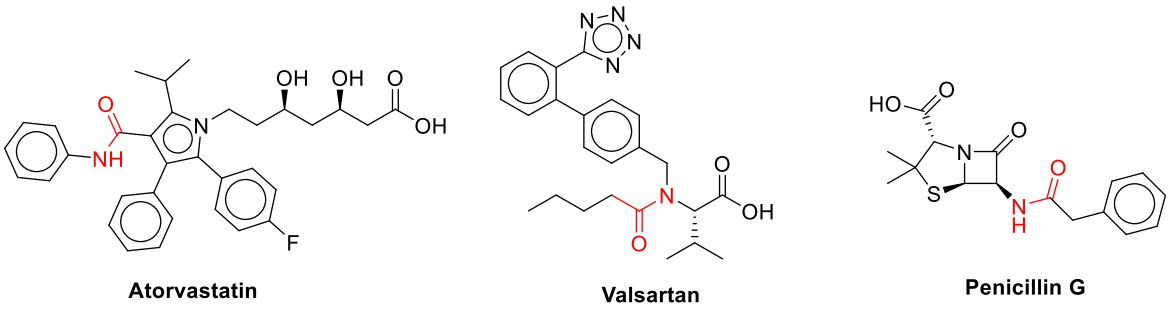
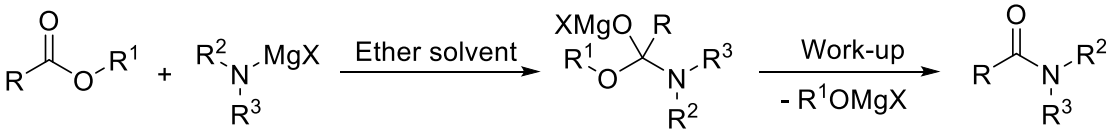


Figure 2.21: Drug compounds containing amide moiety.

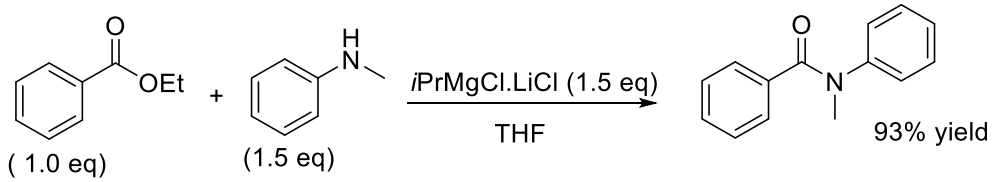
Although the reaction between an ester and an amine in the presence of an organomagnesium reagent (Bodroux reaction)[62] is already documented in the literature (Scheme 2.50), its use has been limited as the scope of this reaction has not been systematically studied. In the Bodroux reaction, the aminomagnesium halide moiety obtained by treatment of an amine with a Grignard reagent is generated before the addition of the ester.



Scheme 2.50: Bodroux reaction.

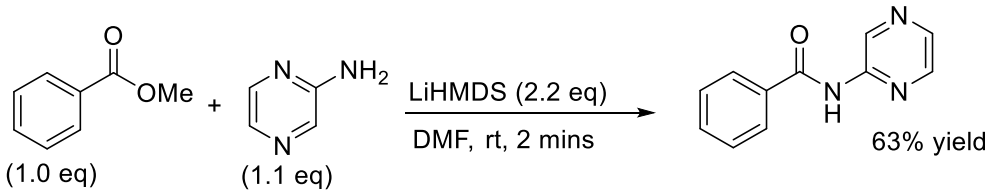
During the project, we became aware that there have been a few examples reported in the literature which have exploited the Bodroux reaction under flow reaction conditions.

In 2012, Alcázar[63] reported the use of an isopropylmagnesium chloride lithium chloride complex (turbo Grignard) in the formation of amides (Scheme 2.51). Although this method offers a broad scope and good functional group tolerance, an excess of the amine is required for the reaction to go to completion. This method also employs the use of a Grignard-lithium chloride complex.



Scheme 2.51: Amide formation mediated by isopropylmagnesium chloride under continuous flow conditions.

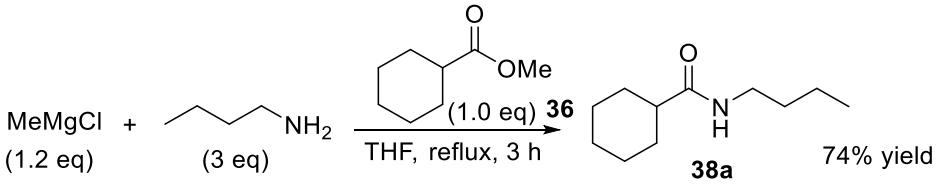
Another report by Alcázar[64] et al 2014, demonstrates the use of lithium bis(trimethylsilyl)amide (LHMDS) in the formation of amides (Scheme 2.52). Again, this method requires an excess of the amine and lithium amide base to afford the amide product in good yields. This reaction is also carried out in an unfavourable solvent, DMF.



Scheme 2.52: Amide formation mediated by LiHMDS under continuous flow conditions.

Knowing that this chemistry has been explored, our aim was to see if the addition of LiCl to the Grignard reagent was critical to the success of the reaction. We also wanted to expand the applicability to other amines and amino alcohols and further extend it to the formation of amide related compounds such as carbamates and ureas.

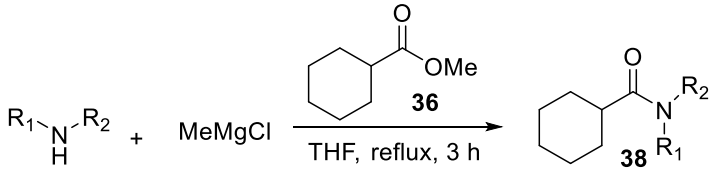
Research conducted by Fox[65] during a 4th year project in NUI Galway found that amide synthesis proceeded well in the presence of MeMgCl. When the reaction was carried out in the absence of the Grignard reagent, no amide product was observed. The reaction gave back unreacted starting material. Fox conducted a series of reactions similar to the Bodroux reaction and established that 3 eq of the amine were needed for the reaction to go to completion (Scheme 2.53).

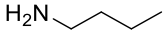
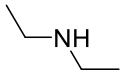
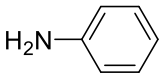
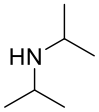
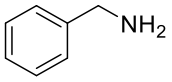
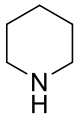


Scheme 2.53: Coupling of methyl cyclohexanecarboxylate with butylamine.

The conditions devised for the reaction with butylamine were subsequently extended to the coupling of ester **36** with an array of primary and secondary amines (Table 2.24).
The reactions carried out by Fox outlined in Table 2.24 were done by preforming the amide moiety, with the ester being added to the reaction mixture at reflux.

Table 2.24: Amide formation- cyclohexane carboxylate **36**.



Entry	Amine	Product	Conversion[b] (%)	Yield[a] (%)
1		**38a**	100	74
2		**38b**	100	94
3		**38c**	91	91
4		**38d**	71	67
5		**38e**	82	62
6		**38f**	100	89

a) Based on yield of isolated product **b)** Based on GC-MS; **Reaction conditions:** 3 eq amine, 1.2 eq MeMgCl at reflux temperature of 40 °C. After 2 h 1 eq methyl cyclohexanecarboxylate, reflux for 2 h.

To this point, all results reported were carried out by Fox albeit, we repeated many of them to ensure they were repeatable. Taking over the project, it was decided to expand the chemistry to aromatic esters. The conditions devised from the reaction of ester **36** with the amines listed above were then extended to methyl benzoate **39a**.

With methyl benzoate, we decided to vary the reaction conditions and conduct the reaction *via* the late addition method, where MeMgCl is added after all other regents avoiding the need for an intermediate formation.

We started by carrying out the reaction of methyl benzoate (1 eq) with diethylamine (1 eq) and the late addition of the Grignard reagent (1.2 eq) at reflux. Using just 1 eq of the amine the reaction produced the amide product **41a** in 100% conversion and a yield of 79% without further purification.

This result was encouraging, and we wondered if we needed elevated temperature for the reaction to occur. From our experience of the Grignard reagent in the alkylation reaction, we found that the deprotonation can occur at rt.

It was then decided to repeat the reaction of methyl benzoate **39a** with diethylamine but at rt. At rt the reaction also proceeded to give the amide product **41a** in 100% conversion and a yield of 76%

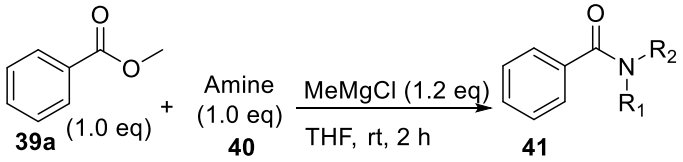
With the success of this, a standard condition for the synthesis of the amides was established, which involves the use of 1 eq of the ester **39a** and amine and addition to this of 1.2 eq of MeMgCl the reaction being conducted without heating or cooling.

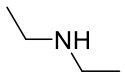
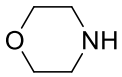
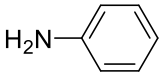
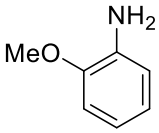
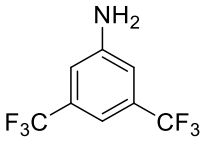
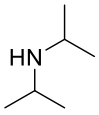
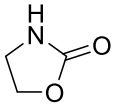
Using the reaction conditions devised, a series of reactions between methyl benzoate **39a** and amines were conducted.

Following the reaction of **39a** with diethylamine to produce **41a**, coupling of methyl benzoate **39a** with morpholine **40b** under the standard amide conditions proceeded to give the amide products **41b** in 100% conversion (Table 2.24.1).

The coupling of the ester with an amine is not just limited to aliphatic amines. The reaction of methyl benzoate with aniline **40c** gave the amide product **41c** in 94% conversion and a yield of 82% after recrystallisation, with the remainder of the crude product mixture being the ester SM **39a**. As the reactions were worked up with 1 M aqueous HCl, any unreacted amine SM would be washed into the aqueous layer. The effect of an EDG and EWG was then investigated. The reaction of methyl benzoate with 2-methoxyaniline also proceeded to give the amide product **41d** in 98% conversion and a yield of 65% after trituration. When the reaction was repeated with a CF_3 substituted amine **40e** to produce the amide **41e**, the conversion of the product was just 60%. This didn't come as a huge surprise as the presence of the electron withdrawing CF_3 groups stabilises the anion generated from the reaction of the electron poor amine with the Grignard reagent, making the anion less nucleophilic and thus influencing the reactivity. When we doubled the number of eq of MeMgCl to 2.4 and kept the amount of amine the same the reaction to produce amide **41e** proceeded to give 98% conversion (Table 2.24.1)

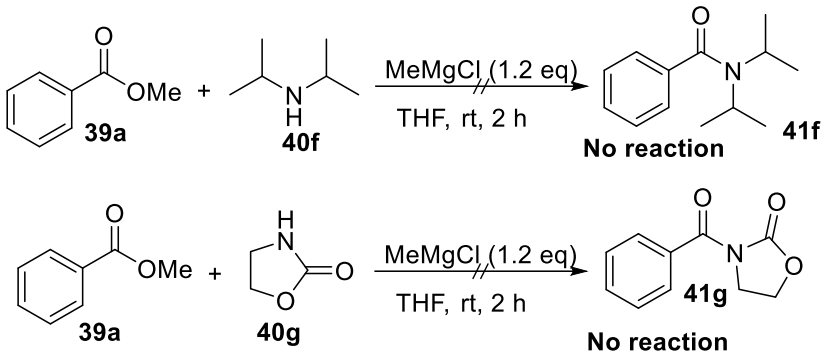
Table 2.24.1: Amide formation using methyl benzoate **39a**.



Entry	Amine	Product	Conversion[b] (%)	Yield[a] (%)
1	 **40a**	**41a**	100	76
2	 **40b**	**41b**	100	75
3	 **40c**	**41c**	94	82
4	 **40d**	**41d**	98	65
5	 **40e**	**41e[c]**	96	66
6	 **40f**	**41f**	0	0
7	 **40g**	**41g**	0	0

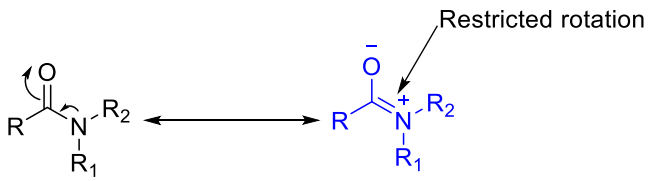
a) Based on yield of isolated product **b)** Based on GC-MS **c)** 2.4 eq of MeMgCl; **Reaction conditions:** 1 eq methyl benzoate, 1 eq amine, 1.2 eq MeMgCl at rt for 2 h.

The reaction of methyl benzoate **39a** with diisopropylamine **40f** was unsuccessful with no reaction observed. This is thought to be due to the bulkiness of diisopropylamine. Another unsuccessful reaction was the attempt to react methyl benzoate **39a** and 2-oxazolidone **40g** (Scheme 2.54). This reaction showed no formation of the amide product but left the starting material unchanged. This did not come as a huge surprise as the nitrogen is adjacent to a carbonyl meaning it is an amide and that on deprotonation if that occurs, resonance may have stabilised the anion making it less reactive. In both unsuccessful cases, no direct attack of the Grignard on the ester was observed.



Scheme 2.54: The attempted reaction of methyl benzoate with diisopropylamine and 2-oxazolidone.

^{1}H NMR spectra (see appendix) of some of the amide products were very difficult to interpret due to the presence of rotamers. Rotamers arise due to resonance delocalization of the nitrogen lone pair into the carbonyl of the amide. The carbon-nitrogen bond has partial double bond character (Scheme 2.55) and as a result, there is restricted rotation about that bond and rotation is thus slower than in a simple alkyl group. If the rotation was completely stopped, you would see isomers based on whether a group on the nitrogen was syn or anti to the carbonyl. If the rotation was rapid on the NMR timescale (order of seconds) then you would see a time-averaged signal for those N alkyl groups. Where the rate of rotation is of the order of NMR experiments, you see signal broadening particularly of those groups closest to the rotating bond. ^{13}C NMR spectra can also be affected but it is generally possible to see both rotamers as separate (if broadened) signals and this can be used as a help to elucidate the product structure.



Scheme 2.55: Rotamers in amides.

Searching the literature we found some disubstituted ureas exhibit biological activity for example against certain cancer cell lines.[66]

The disubstituted ureas shown in Figure 2.22 have been shown to potently inhibit cancer cell proliferation *in vitro* and repress the growth of mammary tumours in a mouse model of human melanoma CRL-2813 and human breast CRL-2351 cancer cell lines.

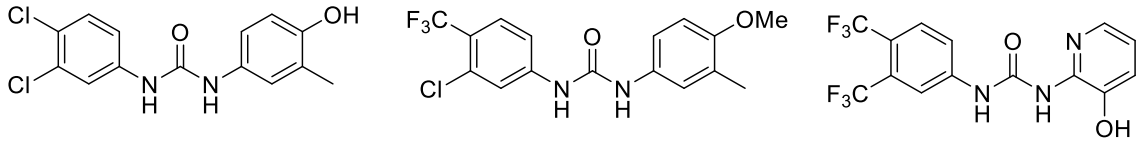


Figure 2.22: Bioactive non-symmetrical *N,N'*-diarylureas.

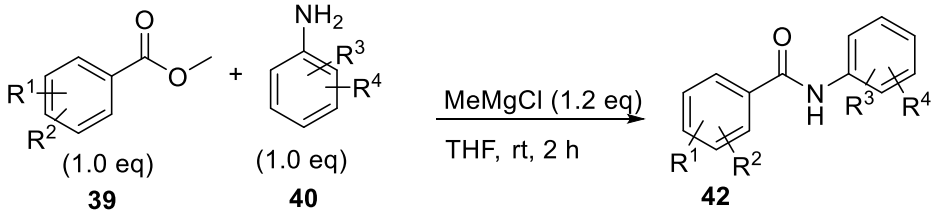
It was observed that the disubstituted ureas reported involved an electron deficient aromatic group on one side and an electron-rich aromatic group on the other. We thought we could make similar ureas or amides which may be of biological interest though the main aim was to challenge the chemistry to see if the amide formation reaction had general applicability.

We started this investigation by seeing if we could conduct a reaction between an aromatic ester-bearing an electron withdrawing group with an electron-rich aromatic amine. The reaction of methyl 3,5-dichlorobenzoate **39b** with 2-methoxyaniline **40d** was carried out (Table 2.24.2). Under the standard amide reaction conditions, the reaction gave the amide **42a** product in a 97% conversion and a yield of 75% after trituration with petroleum ether. The remainder of the crude mixture was the ester SM and aniline. The reaction also worked successfully when methyl 3,5-dichlorobenzoate **39b** was reacted with aniline **40c**. The amide product **42b** was obtained in 92% conversion and a yield of 73% yield. The use of other electron withdrawing esters was then explored; the reaction of methyl 3,5-bis-trifluoromethylbenzoate **39c** with 2-methoxyaniline **40d** with MeMgCl at rt, proceeded to give the amide product **42c** in 95% conversion and a yield of 77% yield after trituration.

Switching activating groups around, the reaction of the electron-rich ester with an electron poor amine was carried out.

The reaction of methyl 4-methoxybenzoate **39d** with 3,5-bis-(trifluoromethyl) aniline **40e** gave the amide product **42d** in 94% conversion, with a yield of 71% yield.

Table 2.24.2: Synthesis of substituted amides.



(1.0 eq) **39** (1.0 eq) **40** **42**

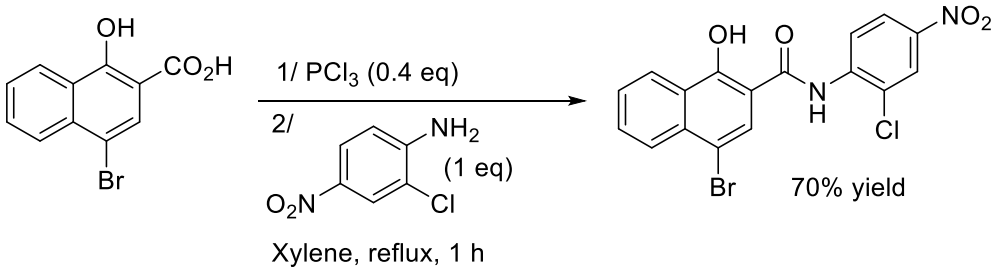
Entry/ Product no	R^1	R^2	R^3	R^4	Conversion[b] (%) Aniline:Ester:Pdt	Yield (%)
1 **(42a)**	3-Cl	5-Cl	2-OMe	H	1:2:97	75
2 **(42b)**	3-Cl	5-Cl	H	H	2:6:92	73
3[c] **(42c)**	3-CF_3	5-CF_3	2-OMe	H	0:5:95	67
4[c] **(42d)**	4-OMe	H	3-CF_3	5-CF_3	2:4:94	71

a) Based on yield of isolated product **b)** Based on GC-MS upon water workup **c**) for reaction 3 and 4, 2.4 eq of MeMgCl used.
Reaction conditions: 1 eq ester, 1 eq of amine, 1.2 eq MeMgCl at rt for 2 h.

A thorough search through the literature reports that similar amide compounds of the type **42** exhibit biological activity against certain diseases such as Hymenolepis nana (in rats),[67] and breast cancer.[68]

These compounds have been traditionally synthesised by generating the acid chloride *in situ*, followed by subsequent reaction with the amine (Scheme 2.56).

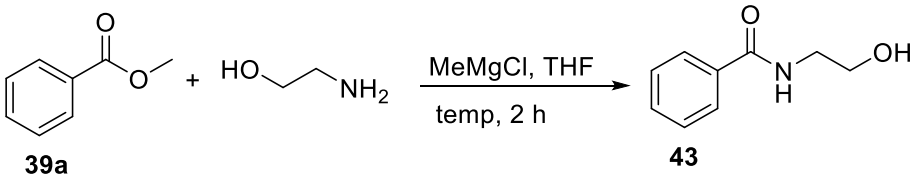
Although these methods can work in good yields, this method utilises PCl_3 which is an explosive and hazardous reagent according to Bretherick's Handbook of Reactive Chemical Hazards.[69] The production of PCl_3 also poses some issues on an industrial scale. The use of xylene in this reaction is considered problematic on an industrial scale.



Scheme 2.56: Synthesis of substituted 1-hydroxy-2-naphthanilide.

The results from these reactions indicate that there is no barrier to the use of the MeMgCl chemistry in the formation of more complex aromatic amides. Even with the late addition method, nucleophilic attack of MeMgCl on the ester group is not observed. This methodology offers a greener and more sustainable process for the synthesis of both simple and substituted amides.

Following the success of coupling with straightforward amines, we then decided to investigate the coupling reaction of methyl benzoate **39a** with amino alcohol substrates (Scheme 2.57). This work was conducted by a final year undergraduate student, Ellen Muldoon, under my supervision.



39a **43**

Scheme 2.57: Reaction of methyl benzoate **39a** with ethanolamine.

If successful, having an amide with an appended hydroxyl group would provide sites for possible further reactions. The investigation began by reacting ester **39a** with 1 eq of ethanolamine and 1.2 eq of MeMgCl at rt for 2 hours, the reaction resulted in 3% conversion to product, leaving 97% starting material unchanged based on GC-MS analysis.

The ethanolamine substrate is particularly interesting as there are two different reaction sites. The NH_2 group of most amino alcohol compounds has a pK_a value of ≈ 35 and the OH group with a pK_a value of ≈ 17. As the OH group is more acidic than that of the NH_2 group, it will be deprotonated first. Therefore, a higher number of eq of MeMgCl is required. The second eq of the MeMgCl should then abstract the proton from the NH_2, forming a dianionic species. As deprotonation of the NH_2 group occurred last, its anion is more reactive and reacts with the ester to form the amide (Figure 2.23).

Through varying the number of eq of MeMgCl a maximum conversion of 20% to the amide was found using 5 eq of MeMgCl (Table 2.24.3). Where a large excess of MeMgCl was used, the presence of acetophenone and 2-phenyl-2-propanol was observed by GC-MS in these reactions. An additional peak observed in the GC-MS analysis, with an m/z value of 223, was thought to be a daughter ion of 1,3-diphenyl-1,3-propanedione, however, this compound was not isolated and the formation of the 1,3-diphenyl-1,3-propanedione product, while suspected, was not confirmed. The acetophenone product is a result of the Grignard reagent attacking the methyl benzoate rather than the ethanolamine. Attack of MeMgCl at the carbonyl of the

newly formed acetophenone generates 2-phenyl-2-propanol while 1,3-diphenyl-1,3-propanedione is a result of the reaction between acetophenone and methyl benzoate.
The acetophenone is deprotonated by MeMgCl generating an enolate, which then reacts with methyl benzoate to form the dimer product observed. As the conversion to the desired product was very low it was very difficult to isolate the product. In addition to GC-MS, IR spectroscopy was used to confirm the formation of the product. A peak at 1633 cm^{-1} was observed which represents the amide carbonyl. No further attempts were made to optimise these reactions.

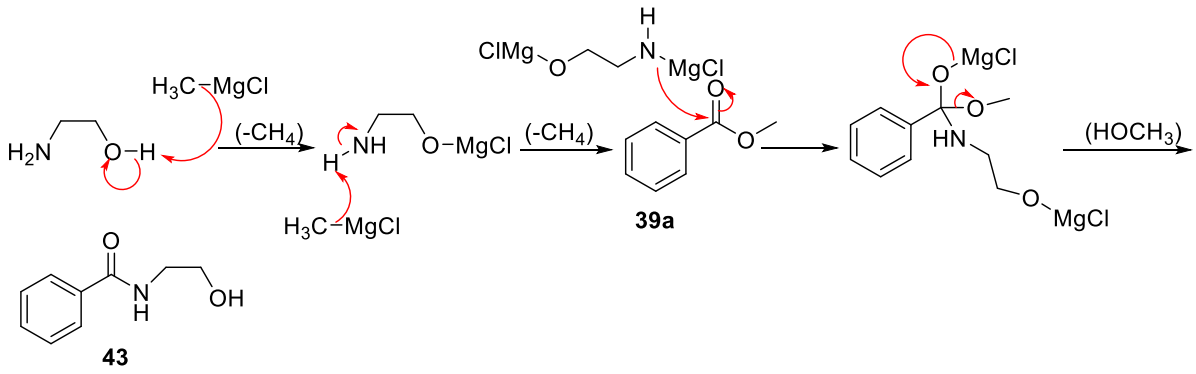
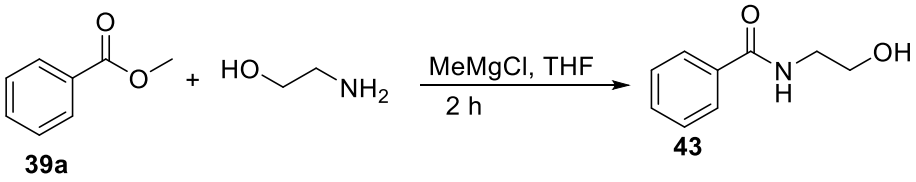


Figure 2.23: Reaction of methyl benzoate **39a** with ethanolamine.

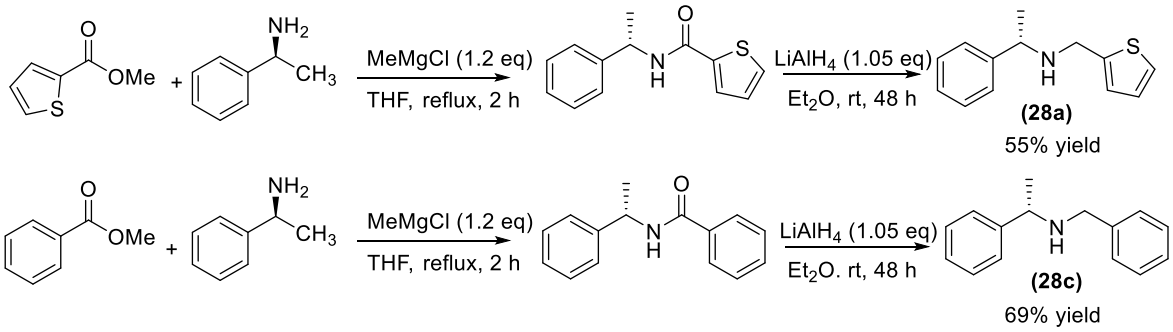
Table 2.24.3: Reaction of methyl benzoate and ethanolamine under varying conditions.



Method	Temp	Amount of ethanolamine	Amount of MeMgCl	Conversion[a] (%) to 43
Late addition	rt and reflux	1 eq	1.2 eq	3
Late addition	rt	2 eq	2 eq	5
Late addition	rt	1 eq	2.4 eq	10
Late addition	reflux	1 eq	2.4 eq	11
Late addition	rt	1 eq	5 eq	20
Preforming the amide moiety	reflux	1 eq	2.4 eq	15

a) Based on GC-MS.

The methodology used for the formation of the amides was then extended to the synthesis of chiral amine bases (Scheme 2.58). Under the similar reaction conditions as previously reported for the coupling of methyl benzoate with other amines, methyl thiophene-2-carboxylate (1 eq) was coupled with S-(-)-alpha-methylbenzylamine (1 eq) in the presence of MeMgCl (2 eq) at reflux to form the corresponding amide with 74% of the product mixture consisting of the required product. The remainder of the crude mixture was unreacted ester SM and amine. Reduction of the crude amide with $LiAlH_4$ afforded the chiral amine **28a** with 75% conversion and a yield of 55%. The results obtained for chiral amine **28a** using MeMgCl compares favourably with the method used by Kerr,[39] where chiral amine **28a** was achieved using 2-thiophenecarboxyaldehyde in 65% yield. The reaction of methyl benzoate **39a** with (S)-(-)-alpha-methylbenzylamine also proceeded to give the amide product in 80% conversion. The crude amide was reduced to form the chiral amine **28c** with a yield of 69%.



Scheme 2.58: Synthesis of chiral amine bases.

2.4.1 Carbamate formation

Having established the use of the MeMgCl chemistry in the synthesis of amides, the aim was to exploit this methodology to synthesise amide related functional groups such as ureas and carbamates.

It was decided to investigate the use of diethyl carbonate **44** in the place of an ester starting material, which would open synthetic routes to ureas and carbamates.

The carbamate functionality is structurally related to amides and carbamates are important constituents of many drug molecules and biomacromolecules [70] (Figure 2.24) and are one of the most widely used protecting group for amines.[71] Two of the most common nitrogen protecting groups are *tert*-butyloxycarbonyl (BOC) and carboxybenzyl (Cbz).

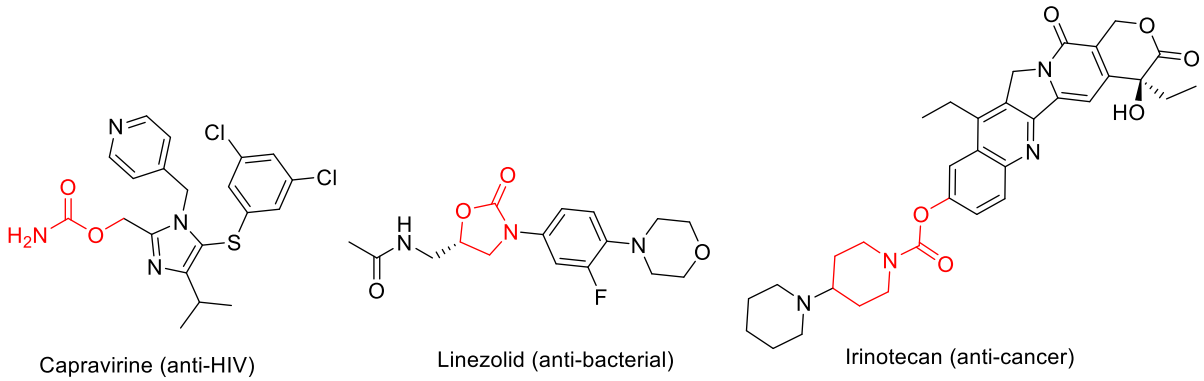
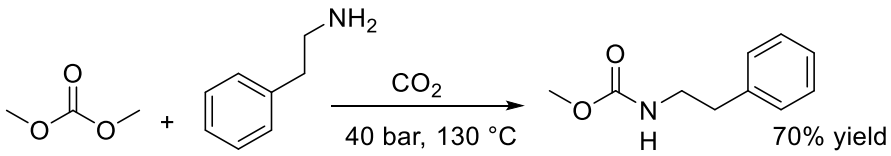


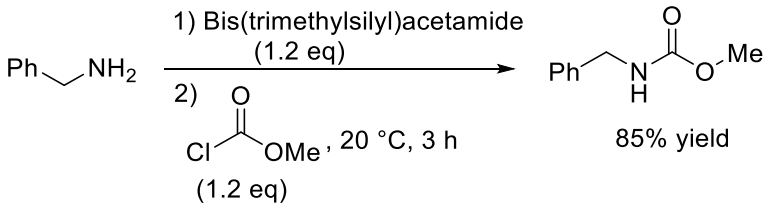
Figure 2.24: Drug molecules bearing the carbamate moiety.

There are a number of methods in the literature for the formation of carbamates, such as N-alkylation of primary carbamates by unactivated secondary alkyl halides,[72] carbonylation of amines using organic carbonates[73,74] and many others. The synthesis of carbamates *via* a carbonate and an amine has been reported in the literature, however, these methods report the use of various ionic liquids as catalysts[75] or using supercritical CO_2[76] (Scheme 2.59).



Scheme 2.59: Synthesis of methyl carbamates from amine and dimethyl carbonate in supercritical CO_2.

The one-step synthesis of carbamates from amines and dialkyl carbonates would be considered a good alternative in comparison to other conventional methods where phosgene or chloroformates are used (Scheme 2.60).



Scheme 2.60: Carbamate synthesis *via* chloroformates.[77]

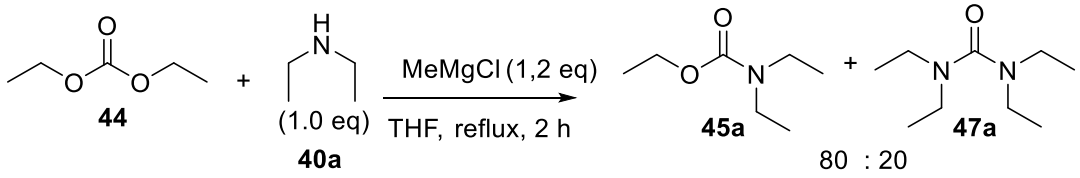
The use of a dialkyl carbonate and an amine in the synthesis of a carbamate is attractive for its green nature because the only by-product of this reaction is an alcohol, which can be easily removed from the reaction medium.

A test reaction was initially carried out to see if the reaction would occur without MeMgCl.

The reaction of diethyl carbonate **44** with morpholine in THF was carried out at rt and at reflux. After 4 hours, the reaction mixture was analysed by ^{1}H NMR spectroscopy. The results from the reaction showed that no reaction occurred and only starting material was recovered at both temperatures.

The amide formation reaction from esters was used as a template in the design of a synthetic method to synthesise carbamate groups from carbonates.

Replacing methyl benzoate **39a** with diethyl carbonate **44**, the first reaction attempted was the reaction of diethyl carbonate and diethylamine **40a**. We added diethyl carbonate (1 eq) **44** to diethylamine (1 eq) in THF followed by the addition of MeMgCl (1.2 eq). The reaction was held for 2 hours at reflux. Diethylamine reacted successfully at the carbonyl, resulting in the breaking of one of the C-O bonds (see mechanism Figure 2.25), however upon analysis of the reaction mixture by GC-MS it was found that in some cases a second eq of amine had attacked the carbonate, causing the second C-O bond to break and a urea product **47a** to form. The remainder of the product mixture was the monoaddition product **45a** (Scheme 2.61).



Scheme 2.61: Reaction of diethyl carbonate and diethylamine at elevated temperature.

When the reaction was repeated at rt it was found to be selective towards monoaddition product **45a**. The carbamate product **45a** was obtained in 100% conversion (Table 2.25). Using the rt conditions, the reaction of **44** with other secondary amines such as morpholine and *N*-methylaniline was successful, producing the carbamate products **45b** and **45f** in conversions >99% (Table 2.25).

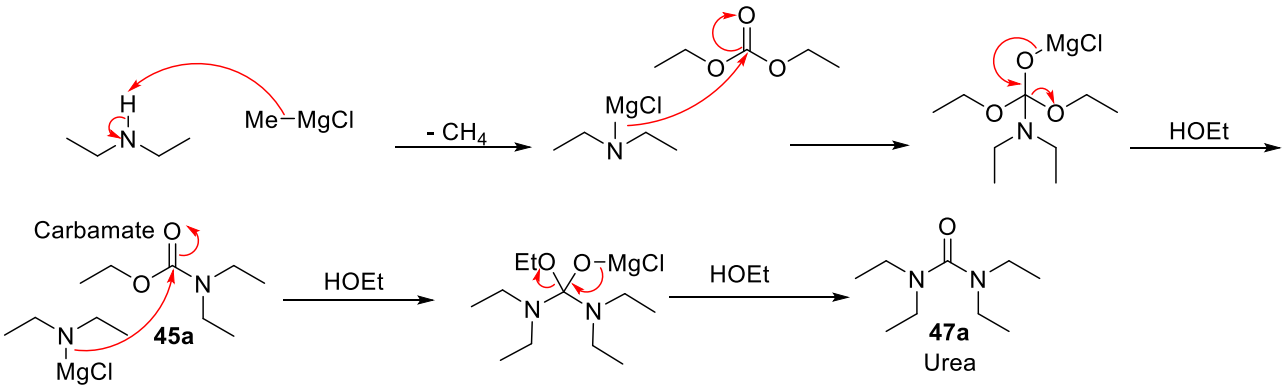
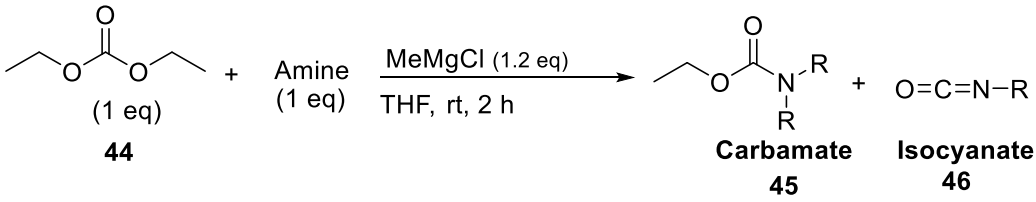
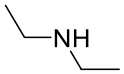
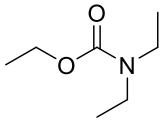
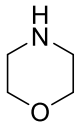
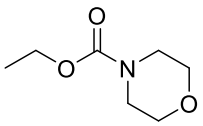
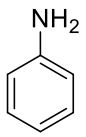
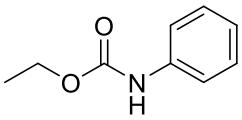
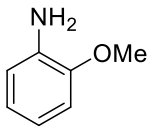
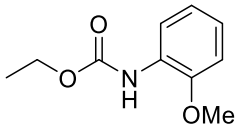
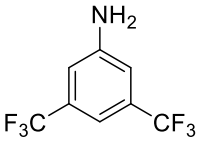
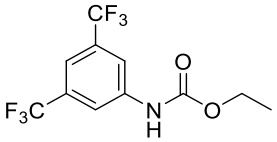
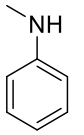
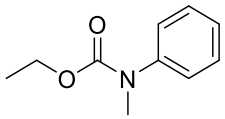


Figure 2.25: Formation of the urea derivative.

Table 2.25: Carbamate synthesis using diethyl carbonate **44**.



Entry/ Product	Amine	Product	Product composition[a] % Isocyanate:Pdt	Yield[b] (%)
1 (**45a**)[c]			0:100	-
2 (**45b**)			0:100	74
3* (**45c**)			4:96	77

4* (**45d)**			2:98	72
5* (**45e)**			2:98	73
6 (**45f)**			0:100	83

a) Based on GC-MS **b)** Based on yield of isolated product **c)** Impurity present as judged by NMR spectroscopy, no yield obtained; * For entries 3-5 2.4 eq of MeMgCl was used.

The same chemistry was attempted with primary aromatic amines, such as aniline. However, it was found that with just 1 eq of diethyl carbonate **44** and aniline **40c** and 1.2 eq of the MeMgCl the reaction did not go to completion, with the product **45c** being 67% of the product mixture and the other 33% being the aniline starting material (observed by GCMS). When the amount of MeMgCl was doubled to 2.4 eq, the reaction of diethyl carbonate **44** with aniline proceeded to give the product **45c** which made up 96% of the product mixture and a yield of 77%.

When the reaction was subjected to only a water workup analysis of the crude mixture by GC-MS showed the presence of small amounts of isocyanate **46c**, as well as the aniline 40c, starting material. When an acid workup (1 M HCl) was done as normal, the GC-MS showed the presence of only the product and the isocyanate as any unreacted aniline was taken up in the aqueous layer. Hence in these reactions, we report on reaction product composition rather than conversion as one of the relevant components is removed during the workup. Increasing the number of eq of MeMgCl in these reactions resulted in the formation of the iso cyanate side product. The isocyanate product was confirmed on the GC-MS as the mass obtained corresponded to the expected molecular weights.

The isocyanate side product is believed to form through elimination of ethanol arising from deprotonation of the carbamate by MeMgCl (Figure 2.26).

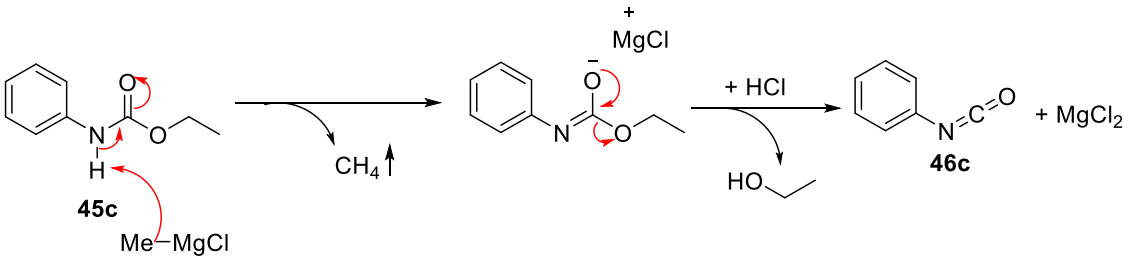


Figure 2.26: Proposed mechanism for isocyanate formation.

We wondered if we could extend the use of this carbamate formation reaction to both electron poor and electron rich aniline compounds.

The reaction of diethyl carbonate **44** with 3,5-bis-(trifluoromethyl)aniline **40e** was initially carried out. Using 1.2 eq of MeMgCl the carbamate product **45e** was 75% of the product mixture. This result is similar to that observed in the reaction to produce carbamate **45c** which gave a product mixture comprising of 67% **45c** when 1.2 eq of MeMgCl was used.

However, the number of eq of MeMgCl was doubled to 2.4, the reaction of diethyl carbonate **44** with 3,5-bis-(trifluoromethyl) aniline **40e** proceeded to give a mixture of the carbamate product **45e** (98%) and the isocyanate side product **46e** (2%). After trituration, the isolated carbamate product was obtained in 73% yield.

The reaction of diethyl carbonate **44** with an electron-rich aniline was then attempted.

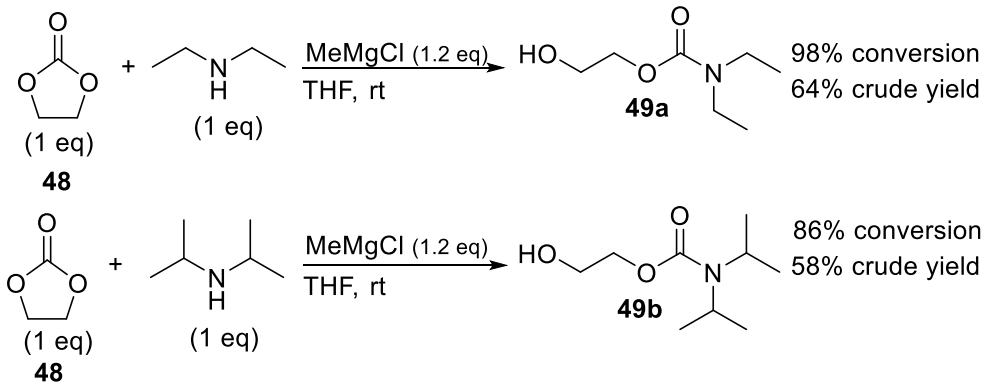
Using 1.2 eq of MeMgCl in the reaction to produce the ortho-methoxy carbamate **45d**, a product mixture comprising of 66% of the target amide was obtained. When the reaction to produce **45d** was repeated using 2.4 eq of MeMgCl the product mixture consisted of the carbamate **45d** (98%) and the isocyanate side product **46d** (2%).

The use of a secondary aromatic aniline was also attempted. The reaction of diethyl carbonate **44** (1 eq) with *N*-methylaniline (1 eq) and MeMgCl (1.2 eq) gave the carbamate **45f** in 100% conversion and a yield of 83% (Table 2.25).

As the MeMgCl chemistry was successfully exploited in the synthesis of amides from methyl esters and carbamates from carbonates, the plan was to expand the scope to the use of a cyclic ester.

Worked carried out by Jason Slattery, a fourth-year student under my supervision showed that this chemistry has general applicability. The reaction of ethylene carbonate **48** with diethylamine **41a** gave the product **49a** in 98% conversion and a crude yield of 64%. Ethylene carbonate was also reacted with diisopropylamine **41f** to give the product **49b** in 86% conversion and 58% crude yield (Scheme 2.62). Throughout our study, we haven't had success with diisopropylamine so this is an interesting reaction success. The reaction of

methyl benzoate **39a** with diisopropylamine **41f** failed to afford an amide. The reaction of diethyl carbonate **44** with diisopropylamine **41f** was also unsuccessful. Although these are preliminary studies, there is an indication that MeMgCl can mediate an alternative method for the synthesis of a hydroxylcarbamate.



Scheme 2.62: Amide formation using ethylene carbonate.

2.4.2 Synthesis of ureas

We continued our investigation by tackling the synthesis of the related urea functional group. The urea moiety has been exploited in the pharmaceutical sector and is present in many molecules which exhibit biological activities against certain cancers and many other diseases (Figure 2.27). [78,79]

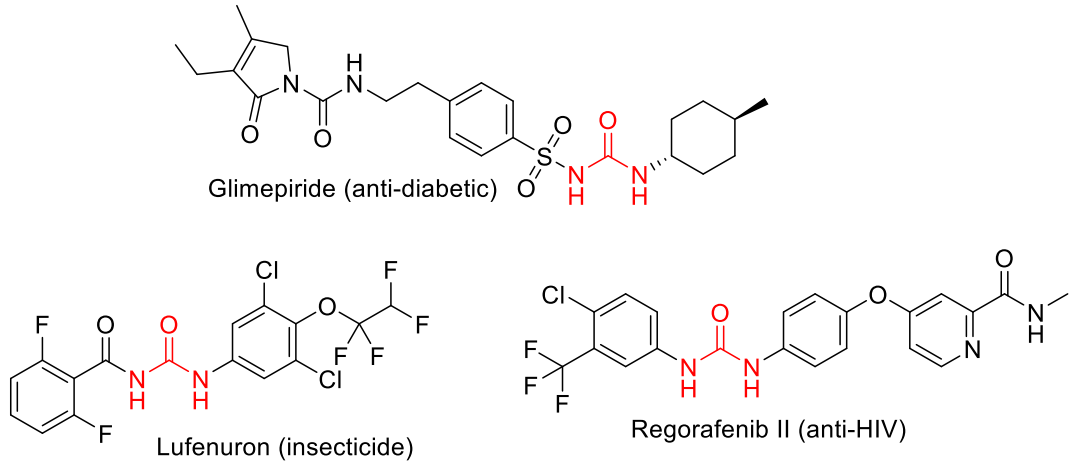
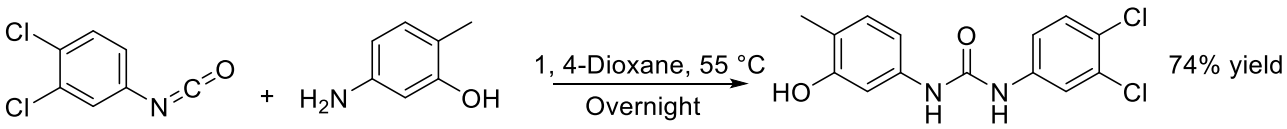


Figure 2.27: Bioactive urea compounds.

The formation of ureas has been extensively studied previously, and reports by Denoyelle et al[66] demonstrate the importance of the urea functionality within many biologically active compounds due to its hydrolytic stability. In the report by Denoyelle, the synthesis of ureas is achieved by reacting isocyanates with amines (Scheme 2.63). Isocyanates are generally made from phosgene.[80]



Scheme 2.63: Synthesis of di-substituted urea from isocyanate.[66]

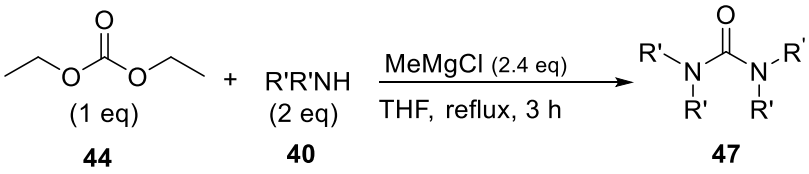
Having successfully synthesised the carbamates and given the fact we saw evidence of disubstituted urea product when the reaction of diethyl carbonate and amine was conducted at reflux, we decided to explore the use of the MeMgCl methodology to see if we could gain control of the di-substituted urea synthesis starting from diethyl carbonate **44**.

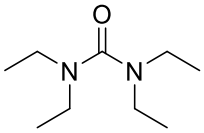
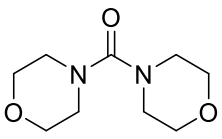
We started this study by seeing if a symmetrical urea could be formed in a one-step process. Previously the urea product was observed at elevated temperatures when we were trying to

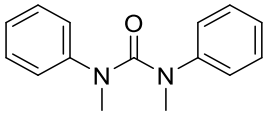
prepare the carbamate. It was decided to double the amount of amine and Grignard in the reaction to favour formation of the urea product.

The reaction of diethyl carbonate (1 eq) **44**, diethylamine **40a** (2 eq) and MeMgCl (2.4 eq) at reflux was initially studied. The results from this reaction show the major product being the mono-substituted carbamate **45a** and the minor product being the urea **47a** (observed by GC-MS). Work done by a final year undergraduate student, Jason Slattery established that 5 eq of the diethylamine species and 6 eq of MeMgCl was required to push the reaction to produce the urea product **47a**. When the reaction was repeated with diethyl carbonate **44** (1 eq), diethylamine (5 eq) and MeMgCl (6 eq), the urea product **47a** was formed in 100% purity (measured by GC-MS). It was questioned whether these conditions were required to form all symmetrical ureas. Interestingly, using morpholine **40b** as the amine species we could produce the urea product **47b** with a purity 100% using just 2 eq of morpholine and 2.4 eq of MeMgCl (Table 2.26). When *N*-methylaniline was used as the amine species, the crude urea product **47c** was 91% pure using 2 eq of *N*-methylaniline and 2.4 eq of MeMgCl. The remainder of the crude mixture was the amine starting material. The product was isolated in 60% yield.

Table 2.26: Synthesis of symmetrical ureas with secondary amines.



Entry/ Product number	Product	Crude product composition[a] % SM:Pdt	Yield[b] %
1 **(47a)**[c]		0:100	74
2 **(47b)**		0:100	75

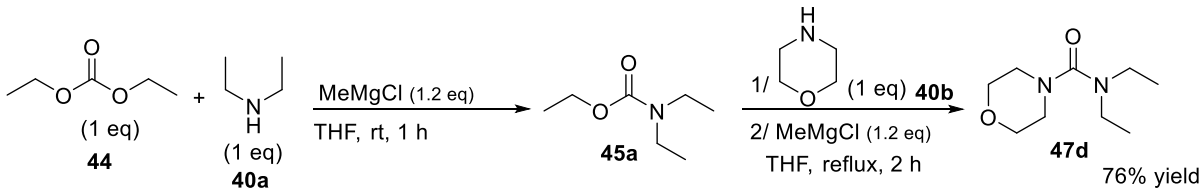
3 **(47c)**		9:91	60

a) Based on GC-MS **b)** Based on yield of isolated product **c)** 5 eq of amine and 6 eq of MeMgCl.

We thought that, given we could produce the carbamate and that we had also managed to react twice to give the urea, it may be possible to selectively form non-symmetrical ureas. We aimed to use very similar conditions to the one-pot heterodialkylation reaction described in 2.1.2, where the first addition of the amine was conducted at rt and the addition of the second and different amine occurred at reflux.

We successfully achieved the synthesis of the non-symmetrical urea product **47d** in a one-pot sequential process. The initial reaction of diethyl carbonate **44** with diethylamine **40a** (1 eq) at rt. This reaction was not worked up and morpholine **40b** (1 eq) was added along with a second portion of Grignard (1.2 eq) and the reaction was heated to reflux (Scheme 2.64).

This reaction sequence gave the di-substituted urea product in 100% purity by GC-MS when isolated in a yield of 76%. When the reaction to produce the di-substituted urea **47d** was carried out by adding the morpholine first **40b**, followed by the addition of diethylamine **40a**. The reaction also gave the urea product in 100% purity by GC-MS when isolated in a yield of 76%.



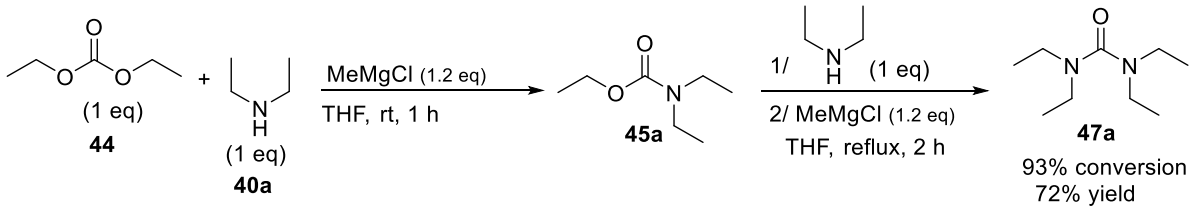
Scheme 2.64: Synthesis of non-symmetrical urea

Encouraged by the results obtained from the one-pot sequential addition. We decided to revisit the synthesis of the symmetrical ureas. The use of such excess of the diethylamine and MeMgCl for the reaction to go to completion raised a lot of questions. We wondered if the problem was a concentration issue. We suspected the presence of excess amounts of the amine and Grignard forms aggregates, which causes the reaction to favour the monosubstituted carbamate over the disubstituted urea.

This theory may be supported by the results when we implemented the sequential one-pot process to the reaction to produce the symmetrical urea **47a**. The reaction to synthesise the symmetrical urea with diethylamine was repeated. Under the same conditions used in the

synthesis of the non-symmetrical urea product **47d**, the reaction to produce **47a** was successful with a conversion of 93% and a 72% yield. The remainder being the mono-substituted carbamate **45a** (Scheme 2.65).

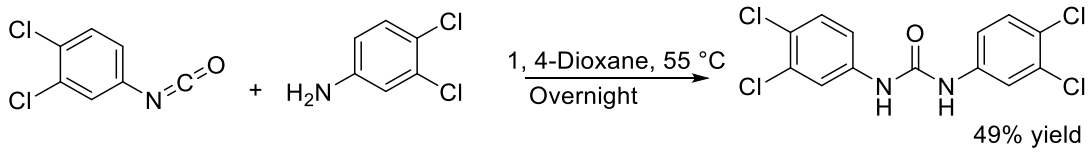
In this reaction at no point did we have >1 eq of the amide nucleophile present compared to the previous version where even at completion we had 3 eq. This would reduce concentration and discourage aggregates which may be why the reaction worked better in a stepwise manner.



Scheme 2.65: Sequential one-pot process in the reaction to produce **47a**.

Having had success with the one-pot and sequential addition reactions using secondary amines, this chemistry was then extended to primary aromatic amines such as aniline and substituted anilines.

Synthesis of substituted aromatic symmetrical ureas has been demonstrated by Denoyelle et al 2012.[66] As previously mentioned the ureas are made by the reaction of an isocyanate with a substituted aniline (Scheme 2.66).



Scheme 2.66: Synthesis of *N,N*,-diarylureas reported by Deneyelle.[66]

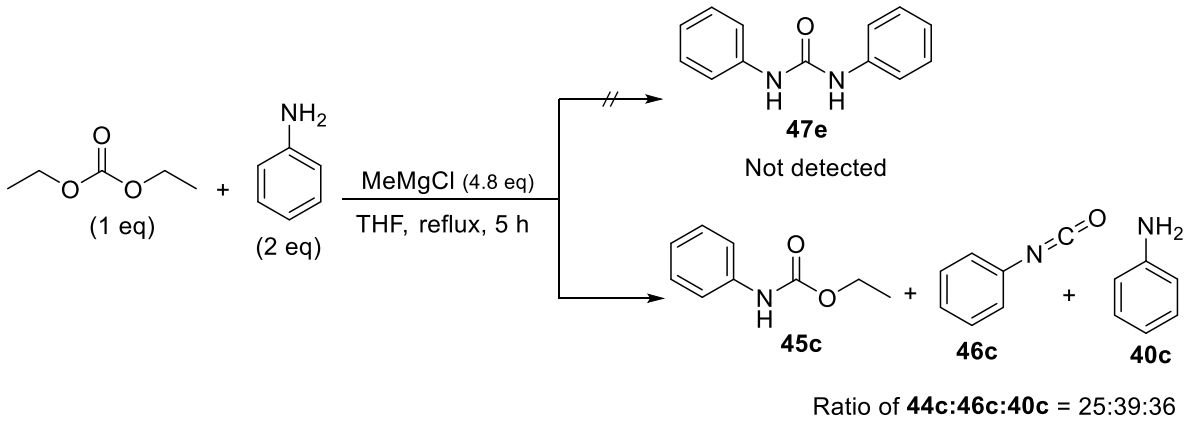
We wanted to investigate if it was possible to put two of the same aromatic groups on the diethyl carbonate group making symmetrical ureas.

In the synthesis of carbamates, when aromatic amine species were used, the reactions required 2.4 eq of MeMgCl for the reaction to go to completion.

With that knowledge, we started to investigate the synthesis of aromatic symmetrical ureas.

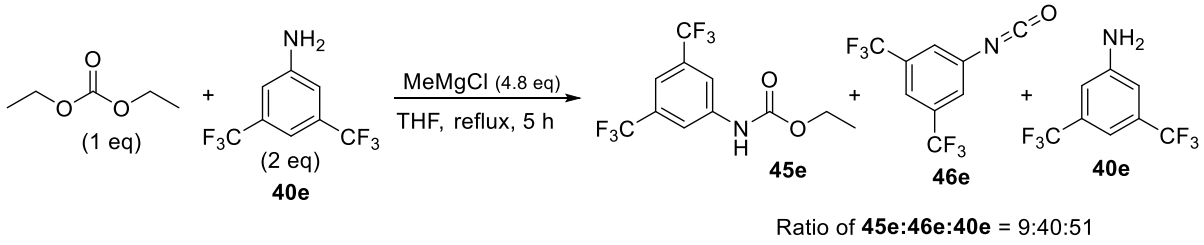
We started by reacting diethyl carbonate **44** (1 eq), aniline **40c** (2 eq) with MeMgCl (4.8 eq) at reflux. However, upon analysis by GC-MS, no urea product was observed. The GC-MS after

a water workup showed the presence of the corresponding carbamate **45c**, the corresponding isocyanate **46c** and the amine **40c** in the ratio 25:39:36 (Scheme 2.67).



Scheme 2.67: Attempted synthesis of diarylurea with aniline.

We wanted to investigate if an electron withdrawing substituent on the aniline would affect the reaction outcome. The reaction of diethyl carbonate **44** with 3,5-bis-(trifluoromethyl) aniline **40e** similarly did not lead to the urea product. The reaction upon a water work-up gave a mixture of the corresponding carbamate **45e**, the corresponding isocyanate **46e** and the amine **40e** in the ratio 9:40:51 (Scheme 2.68).

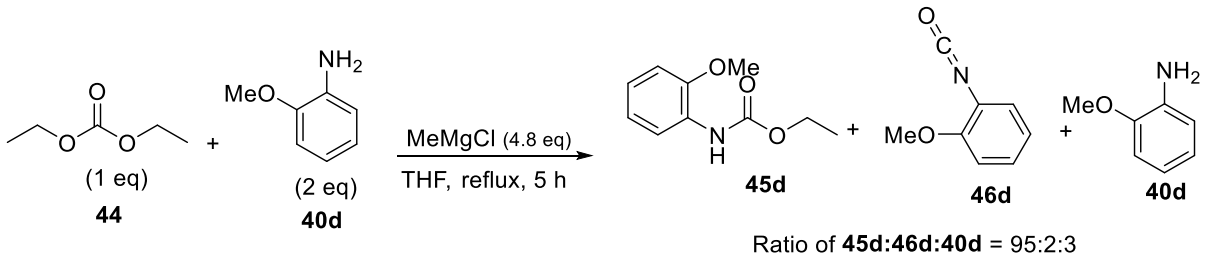


Scheme 2.68: Attempted reaction to produce a diarylurea using 3,5-bis-(trifluoromethyl)-aniline.

It was then decided to change the amine species from electron poor aniline **40e** to 2-methoxyaniline **40d** to try and eliminate the formation of the isocyanate. Attachment of an electron-rich aromatic substituent should inhibit the deprotonation of the carbamate proton, limiting the formation of the isocyanate.

The reaction of diethyl carbonate **44** with 2-methoxyaniline **40d** was carried out. However, the diarylurea product was again not observed. The reaction gave a mixture of the corresponding carbamate **45d,** the corresponding isocyanate **46d** and the amine **40d** in the ratio 95:2:3

measured by GC-MS (Scheme 2.69). Although the use of an electron-rich aniline did not produce the urea, the rationale behind the use of the electron donating group seemed to have been sound as only 2% isocyanate was observed.



Scheme 2.69: Attempted synthesis of symmetrical diarylurea with an electron donating aniline.

Having had no success with putting two of the same aromatic amine group on diethyl carbonate, we wondered if was still possible to synthesise a non-symmetrical urea with one aliphatic group on and one aromatic group.

These type of urea compounds are not new, as reports by Mistry et al[81] and Tomkinson[82] demonstrate the synthesis of these unsymmetrical ureas having an aromatic and an aliphatic group (Scheme 2.70). Ureas of this nature exhibit biological activity against diseases such as malaria[83] and bacterial infection (Figure 2.28).[84]

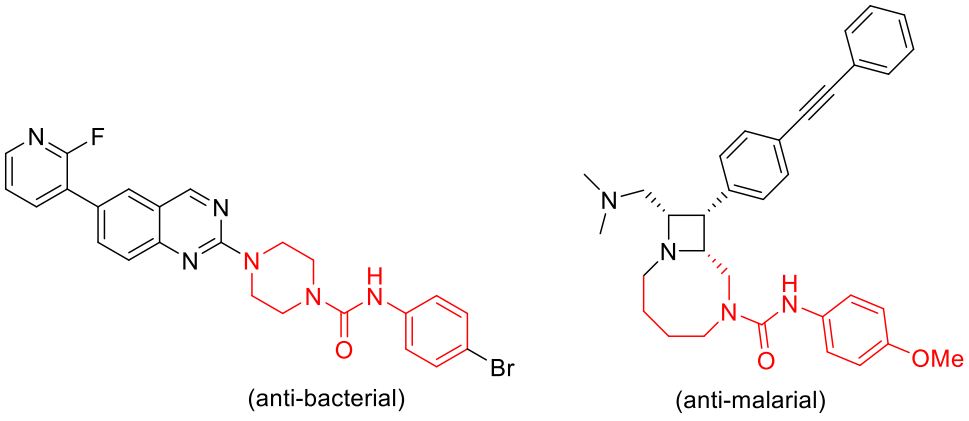
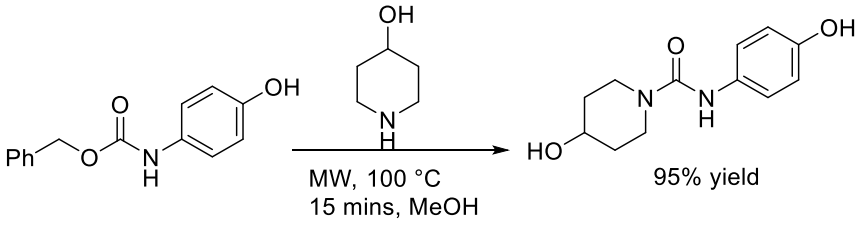


Figure 2.28: Biologically active ureas with an aliphatic and aromatic attachment.

In the method reported by Tomkinson[82], the carbamate starting material is synthesised by reacting a substituted aniline with benzyl chloroformate in dioxane. Although the carbamate is produced in high yields, the most used method for the synthesis of chloroformate requires the use of toxic and hazardous phosgene.

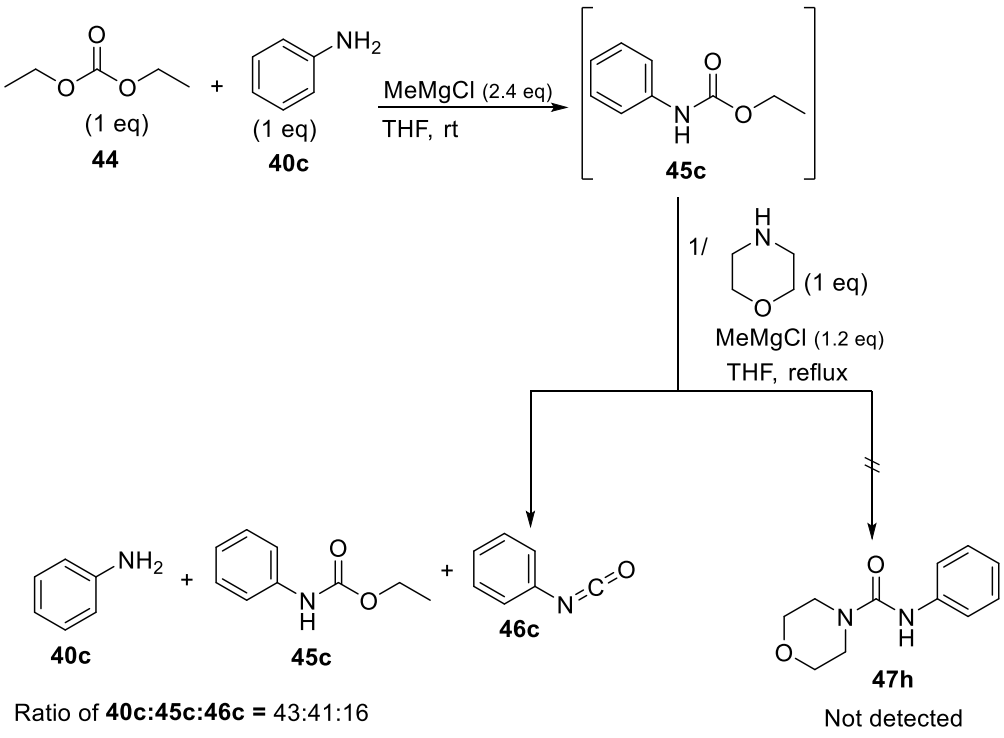


Scheme 2.70: Synthesis of non-symmetrical urea by Tomkinson.[82]

We started by looking at the reaction of diethyl carbonate **44**, aniline **40c** and an aliphatic amine, morpholine **40b**. We employed the same reaction condition as used in the synthesis of non-symmetrical aliphatic ureas.

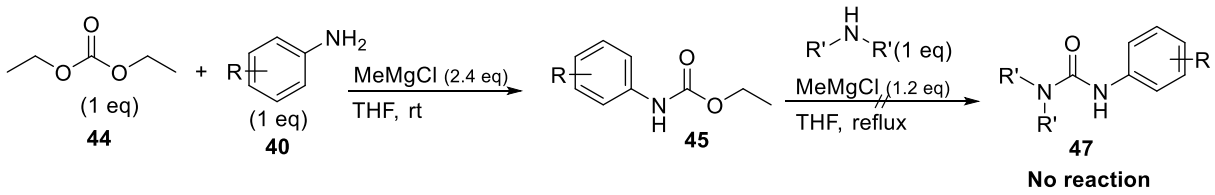
The reaction of diethyl carbonate **44** and aniline **40c** was carried out at rt, in the same pot, after an hour morpholine **40b** was added and the reaction was raised to reflux for 3 h. At each step 1.2 eq of MeMgCl was added (Scheme 2.71).

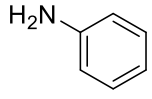
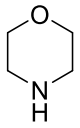
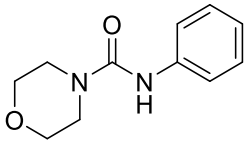
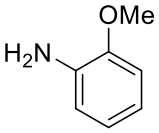
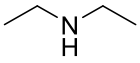
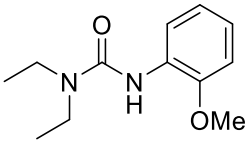
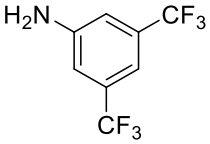
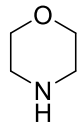
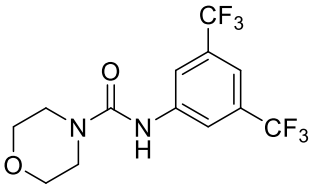
A short aqueous work-up followed by the addition of diethyl ether was performed. Upon analysis on GC-MS, we found the reaction produced similar results to that obtained in the reaction to produce symmetrical diarylureas. The reaction gave a mixture of the corresponding isocyanate **46c**, the aniline **40c**, and the corresponding carbamate **45c** in the ratio 16:43:41 but none of the desired urea (Table 2.26.1).



Scheme 2.71: Attempted synthesis of non-symmetrical ureas **47h**.

Table 2.26.1: Attempted synthesis of non-symmetrical ureas.



Entry/ Product number	Amine 1	Amine 2	Expected Pdt	Product mixture[a] % Isocyanate: amine:45:47
1 **(47h)**	 **40c**	 **40b**		16:43:41:0
2 **(47i)**	 **40d**	 **40a**		3:5:92:0
3 **(47j)**	 **40e**	 **40b**		50:41:9:0

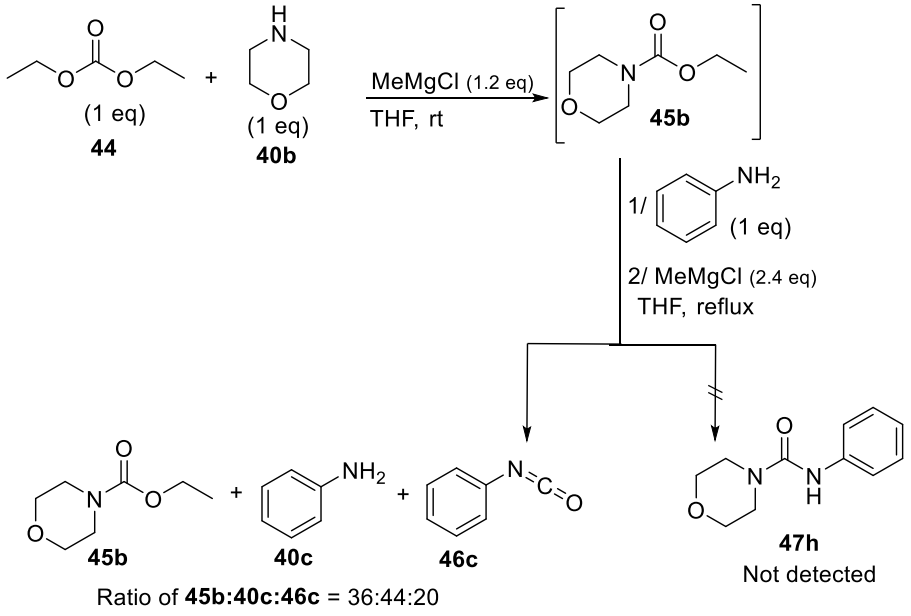
a) Based on GC-MS after water work up.

The use an electron poor aniline was also attempted (Table 2.26.1). The reaction of diethyl carbonate **44** with 3,5-bis-(trifluoromethyl) aniline **40e** at rt was carried out. This was followed by the addition of morpholine **40b** and the reaction was raised to reflux. The Grignard reagent was used as before. Just as observed with the diarylureas, the presence of the electron withdrawing group had no positive effect on the reaction. The use of an electron poor amine did, however, increase the amount of isocyanate observed. The desired urea product was not produced. The reaction gave a mixture of the corresponding isocyanate **46e**, the electron withdrawing aniline **40e**, and the corresponding carbamate **45e** in the ratio 50:41:9.

The use of an electron-rich aniline was also attempted. The reaction of diethyl carbonate **44** with 2-methoxyaniline **40d** at rt, followed by the addition of morpholine **40b** at reflux was carried out. With the use of 2-methoxyaniline as the amine species, a decrease in the

formation of the isocyanate side product was observed, however, the desired product was not observed.

The order of addition of the reagents was changed to see if the reaction would produce a different outcome. By putting the morpholine **40b** on first followed by the addition of the aniline **40c**, the reaction did not produce the disubstituted urea. The reaction gave a mixture of isocyanate **46c**, aniline **40c** and carbamate **45b** in the ratio 20:44:36 (Scheme 2.72).



Scheme 2.72: Attempted synthesis of di-substituted urea **47h**.

As the formation of the isocyanate side product was observed with aromatic primary anilines. It is likely that the presence of the proton attached to the nitrogen of the carbamate played a role in the formation of the isocyanate. When the pK_as of the compounds were calculated using a computer programme SPARC[85], the pK_as were 12.76, 12.66 and 10.76 respectively for ethyl phenylcarbamate **45c**, ethyl (2-methoxyphenyl)carbamate **45d** and ethyl (3,5-bis-trifluoromethylphenyl)carbamate **45e**. Although the values obtained suggest protons are relatively non-acidic, it indicates the strength of MeMgCl in deprotonation. As mentioned earlier, we believe the formation of the isocyanate product occurs *via* deprotonation of the carbamate proton by MeMgCl.

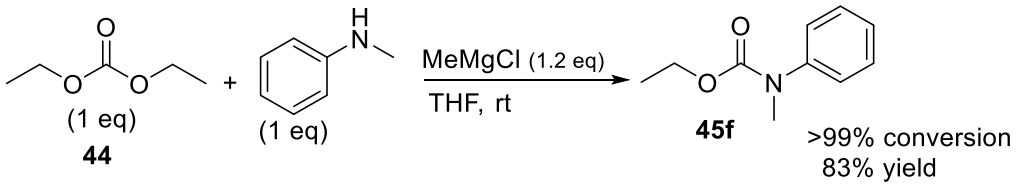
This was quite surprising as reports in literature for the synthesis of substituted non-symmetrical ureas *via* a self-tunable single-mode microwave synthesizer[82] propose that the reaction proceeding to the formation of the urea occurs *via* an intermediate isocyanate

formed *in situ* by deprotonation of the carbamate, followed by nucleophilic attack of the amine. However, this is not observed using MeMgCl.

Another report[86] shows the intermediate isocyanate is formed from the carbonate followed by fast addition of the second amine.

To confirm if the presence of the proton is involved in the formation of the isocyanate. It was decided to explore the use of *N*-methylaniline, a secondary aromatic amine. The use of *N*-methylaniline would produce a carbamate with no proton which should eliminate the possibility of isocyanate formation. Attack on the carbamate carbonyl is thus more likely which perhaps would promote the formation of the disubstituted urea.

A straightforward reaction to produce the carbamate **45f** was carried out (as prepared in Table 2.25). The reaction of diethyl carbonate **44** (1 eq) with *N*-methylaniline (1 eq) and MeMgCl (1.2 eq) at rt was conducted. This reaction proceeded to give the carbamate product **45f** in a conversion >99% (measured by GC-MS) and a yield of 83% (Scheme 2.73).



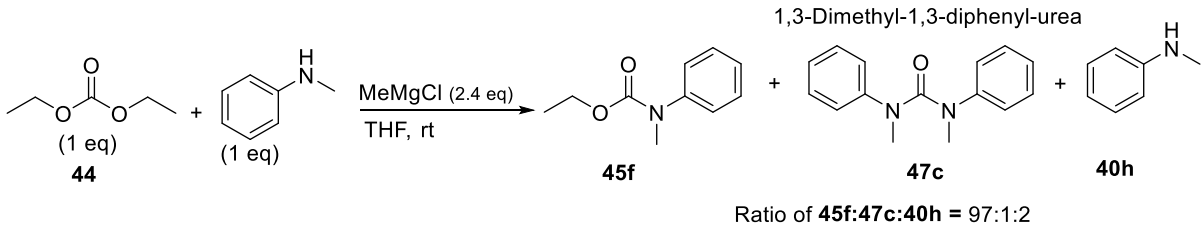
Scheme 2.73: Reaction to produce carbamate **45c** using *N*-methylaniline.

As the isocyanate side product was observed in the reactions of diethyl carbonate and primary aromatic amines using 2.4 eq of MeMgCl, it was decided to repeat the reaction to produce carbamate **45f**, however this time with 2.4 eq of MeMgCl.

This reaction proceeded to give a mixture of *N*-methylaniline, carbamate product **45f** and 1,3-dimethyl-1,3-diphenyl-urea **47c** in the ratio 2:97:1 (measured by GC-MS).

Although an excess of the Grignard was added in the reaction, the presence of the isocyanate was not observed.

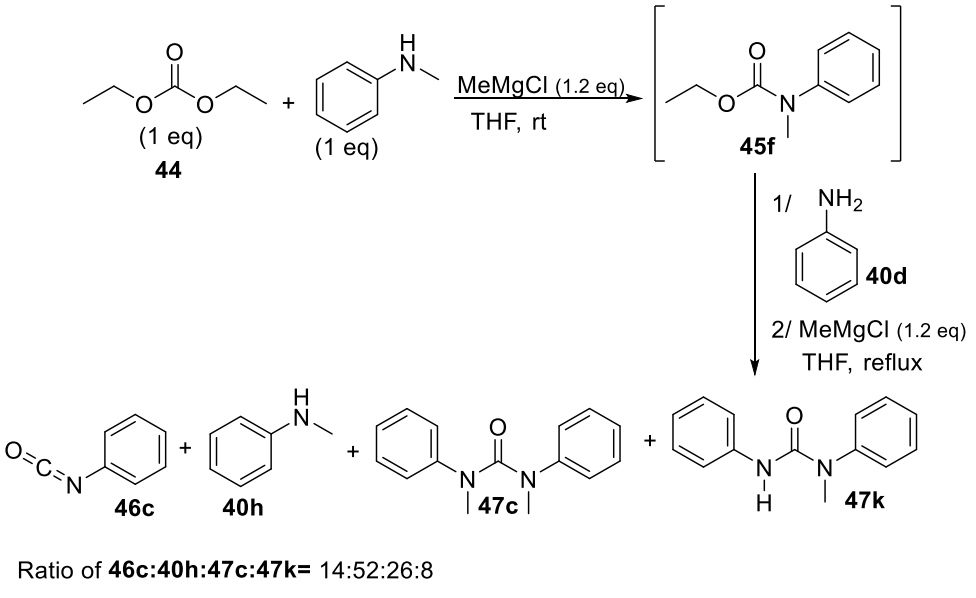
From this result, the role of the proton attached to the nitrogen of the carbamate was confirmed. Although the use of a secondary amine eliminated the formation of the isocyanate side product, increasing the number of eq of MeMgCl resulted in us observing an interesting 1,3-dimethyl-1,3-diphenyl-urea **47c** side product. Formation of 1,3-dimethyl-1,3-diphenyl-urea **47c** which is as a result of double addition of the *N*-methylaniline **40h** to the diethyl carbonate **44** was surprising as only 1 eq of *N*-methylaniline was used (Scheme 2.74).



Scheme 2.74: Reaction to produce carbamate **45c** using 2.4 eq MeMgCl.

Reasons as to why we observe the formation of 1,3-dimethyl-1,3-diphenyl-urea **47c** are explored later. The use of this *N*-methylaniline was extended to the synthesis of non-symmetrical ureas. A one-pot sequential process was conducted using similar conditions to the one-pot heterodialkylation reaction, where the addition of the first amine was conducted at rt and the addition of the second different amine occurred at reflux.

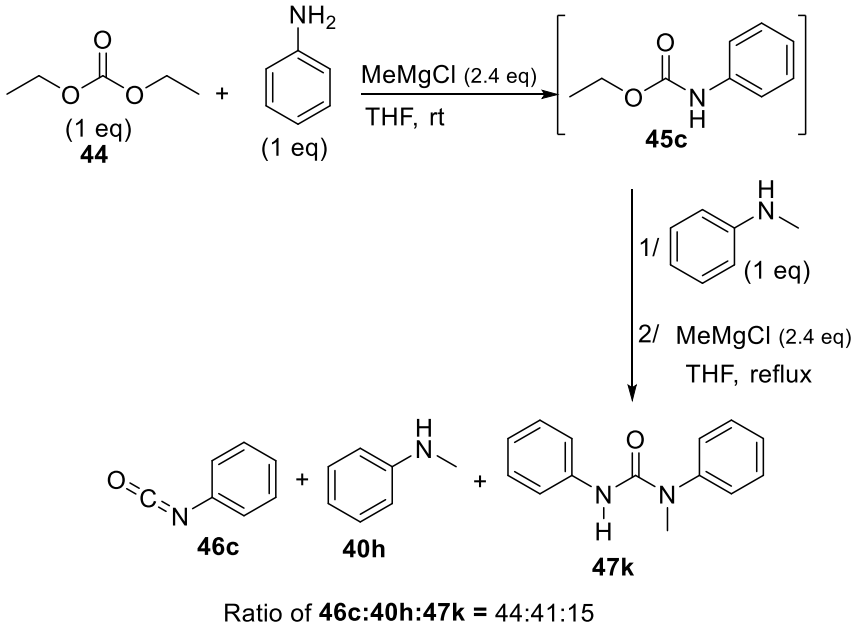
An initial reaction of diethyl carbonate **44**, *N*-methylaniline (1 eq) and MeMgCl (1.2 eq) at rt for 2 hours was carried out. The reaction produced the carbamate product **45f** in >99% conversion. In the same pot aniline **40c** (1 eq) and MeMgCl (2.4 eq) were added and the mixture was heated to reflux. The reaction gave a mixture of the isocyanate **46c**, *N*-methylaniline **40h**, 1,3-dimethyl-1,3-diphenyl-urea **47c** and the desired non-symmetrical urea product **47k** in the ratio 14:52:26:8 observed by GC-MS (Scheme 2.75). Although the desired urea was produced, the symmetrical 1,3-dimethyl-1,3-diphenyl-urea **47c** was the major product. It was a little surprising that the presence of the isocyanate side product was also observed.



Scheme 2.75: Use of *N*-methylaniline and aniline in the formation of diarylurea.

We wondered if we could eliminate the formation of 1,3-dimethyl-1,3-diphenyl-urea **47c** by changing the order in which the reagents were added.

The reaction to produce **47k** was repeated, however, this time aniline was added first at rt before the addition of *N*-methylaniline (Scheme 2.76). Although the formation of 1,3-dimethyl-1,3-diphenyl-urea **47c** was inhibited with this reaction sequence, the amount of isocyanate product increased significantly, while the desired urea product **47k** was obtained in low conversions. The reaction gave a mixture of isocyanate **46c**, *N*-methylaniline **40h** and non-symmetrical urea product **47k** in the ratio 44:41:15 measured by GC-MS. The desired urea product **47k** was not isolated due to the poor conversion. This route was also not viable due to isocyanate formation.



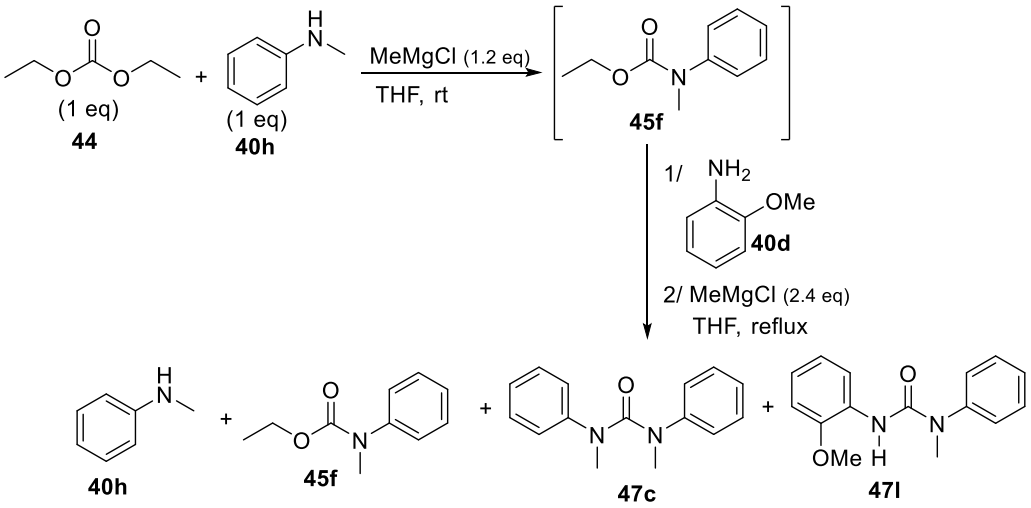
Scheme 2.76: Formation of diarylurea **47k**.

A similar reaction to that described above was conducted, where we replaced aniline with an electron-rich aniline. *N*-methylaniline was added first, followed by addition 2-methoxyaniline **40d**. 2-Methoxyaniline **40d** was the preferred amine for the second addition because, from previous studies with the synthesis of diarylureas, the electron donating amine **40d** was found to limit the formation of the isocyanate.

A one-pot sequential process was conducted. An initial reaction of diethyl carbonate **44**, *N*-methylaniline (1 eq) and MeMgCl (1.2 eq) at rt for 2 hours was carried out, followed by the addition of 2-methoxyaniline **40d** (1 eq) and MeMgCl (2.4 eq) in the same pot, the reaction mixture was then raised to reflux.

The use of the electron-rich aniline did indeed inhibit the formation of the isocyanate product, however, the 1,3-dimethyl-1,3-diphenyl-urea **47c** product resurfaced. The desired product **47l** was observed in just 17% conversion.

The remainder of the reaction mixture were *N*-methylaniline **40h**, carbamate **45f,** 1,3-dimethyl-1,3-diphenyl-urea **47c** obtained in 20%, 13% and 50% conversions respectively by GC-MS (Scheme 2.77).



Scheme 2.77: Use of *N*-methylaniline and 2-methoxylaniline in the formation of diarylurea.

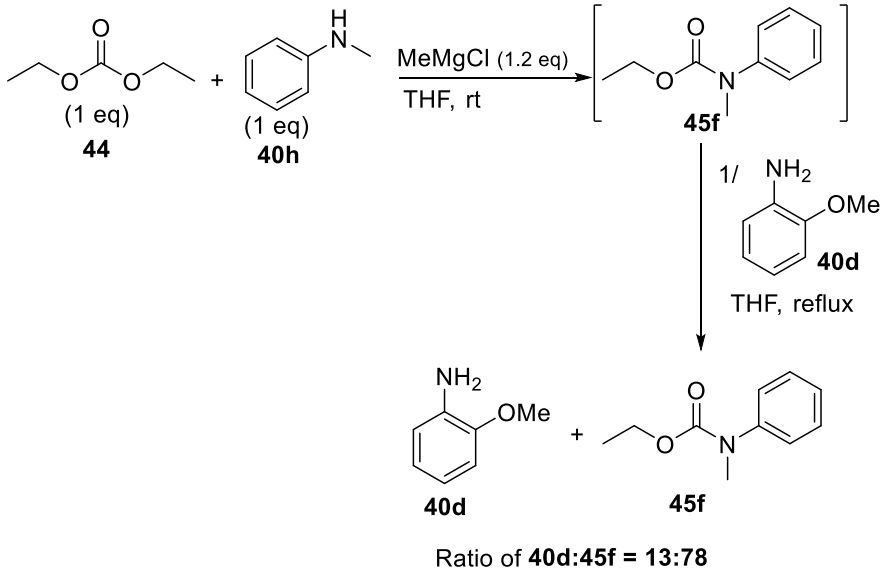
Due to the low conversion to the non-symmetrical urea product **47l,** the product could not be isolated. Attempts to isolate this product *via* column chromatography and *via* bulb to bulb distillation were to no avail.

As 1,3-dimethyl-1,3-diphenyl-urea **47c** was not observed in the synthesis of the carbamate **45f** using 1.2 eq of MeMgCl, we wondered if the presence of an excess amount of MeMgCl in the reaction mixture led to the formation of the **47c**.

To investigate this possibility, the reaction to produce **47l** omitting the second addition of MeMgCl was repeated (Scheme 2.78).

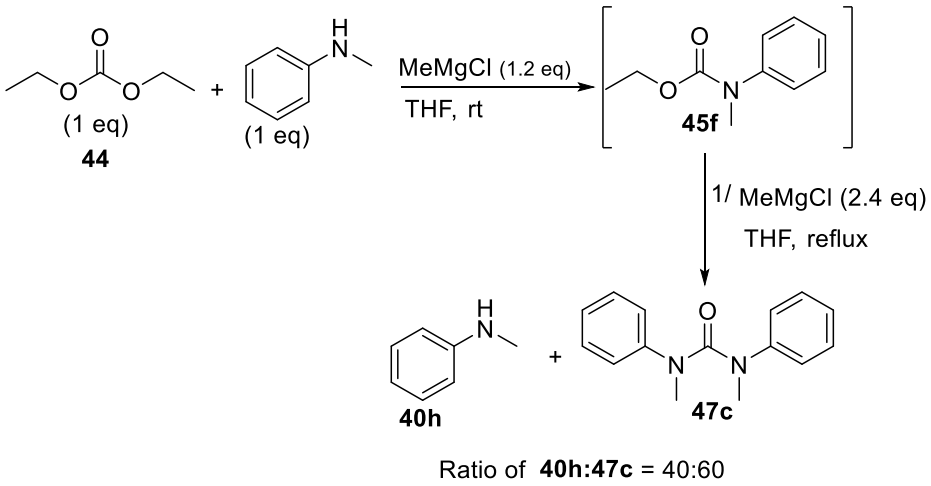
Just like before, an initial reaction of diethyl carbonate **44**, *N*-methylaniline (1 eq) and MeMgCl (1.2 eq) at rt for 2 hours was carried out, this was then followed by the addition of 2-methoxyaniline **40d** (1 eq) in the same pot at reflux.

With the omission of a second addition of MeMgCl, the reaction did not proceed to give the desired urea product. The reaction proceeded to give a mixture of 2-methoxylaniline **40d** and carbamate **45f** in the ratio 13:78 observed by GC-MS after an aqueous work-up.



Scheme 2.78: Attempted synthesis of diarylurea omitting the second addition of MeMgCl.

A similar one-pot sequential reaction was performed where the second amine was omitted (Scheme 2.79). A reaction of diethyl carbonate **44** (1 eq), *N*-methylamine (1 eq), and MeMgCl (1.2 eq) at rt followed by the addition of MeMgCl (2.4 eq) only, omitting the second addition of amine. With this sequence, the reaction proceeded to give a mixture of *N*-methylaniline **40h** and 1,3-dimethyl-1,3-diphenyl-urea **47c** in the ratio 40:60 as observed on GC-MS.



Scheme 2.79: Reaction of carbamate **45f** with MeMgCl with no second amine addition.

The results obtained from these experiments indicate that the presence of the excess MeMgCl plays an important role in the formation of **47c**.

It was suspected that the excess MeMgCl present in the reaction mixture is involved in a reaction with the carbamate intermediate **45f** *via* two nucleophilic addition reactions which causes the release of the *N*-methylaniline which reacts with another eq of the carbamate leading to the formation of 1,3-dimethyl-1,3-diphenyl-urea **47c**.

To investigate this possibility, we employed the use of PhMgCl in place of MeMgCl to observe any other side products on GC-MS. With MeMgCl, acetone was a potential side product which is very volatile and would not be seen on GC-MS.

We repeated the reaction of diethyl carbonate **44** (1 eq), *N*-methylaniline (1 eq), and PhMgCl (1.2 eq) at rt followed by the addition of PhMgCl (2.4 eq), omitting the addition of a second eq of the amine.

From the GC-MS analysis of the worked-up reaction mixture, we found the carbamate **45f** reacted to give a mixture of the triphenylmethanol **SP2**, amide **SP1** and **47c** in the ratio 68:5:28 (measured by GCMS) (Figure 2.29).

The presence of the triphenylmethanol formed was confirmed by ^{13}C NMR spectroscopy analysis as a peak at 83 ppm showed the presence a COH group. IR spectroscopy was also used in confirming the presence of the triphenylmethanol which caused a broad peak at 3310 cm^{-1}.

A mechanism was envisaged based on the components identified by GC-MS as shown in Figure 2.29. The mechanism begins with PhMgCl attacking the carbonyl of the carbamate **45f**, pushing electrons up onto the oxygen and back down again as the ethoxy group leaves forming an amide **SP1**. A second PhMgCl then attacks at the carbonyl of the newly formed amide **SP1** and forms the benzophenone which goes on to form alcohol product **SP2**. The second PhMgCl attack also releases an *N*-methylanilide anion. The formation of 1,3-dimethyl-1,3-diphenyl-urea occurs when the *N*-methylanilide anion attacks the carbamate **45f**. This explains how a reaction with no apparent amine present to react with a carbamate can react to produce a urea and is a real difficulty for us in reactions involving aromatic amines.

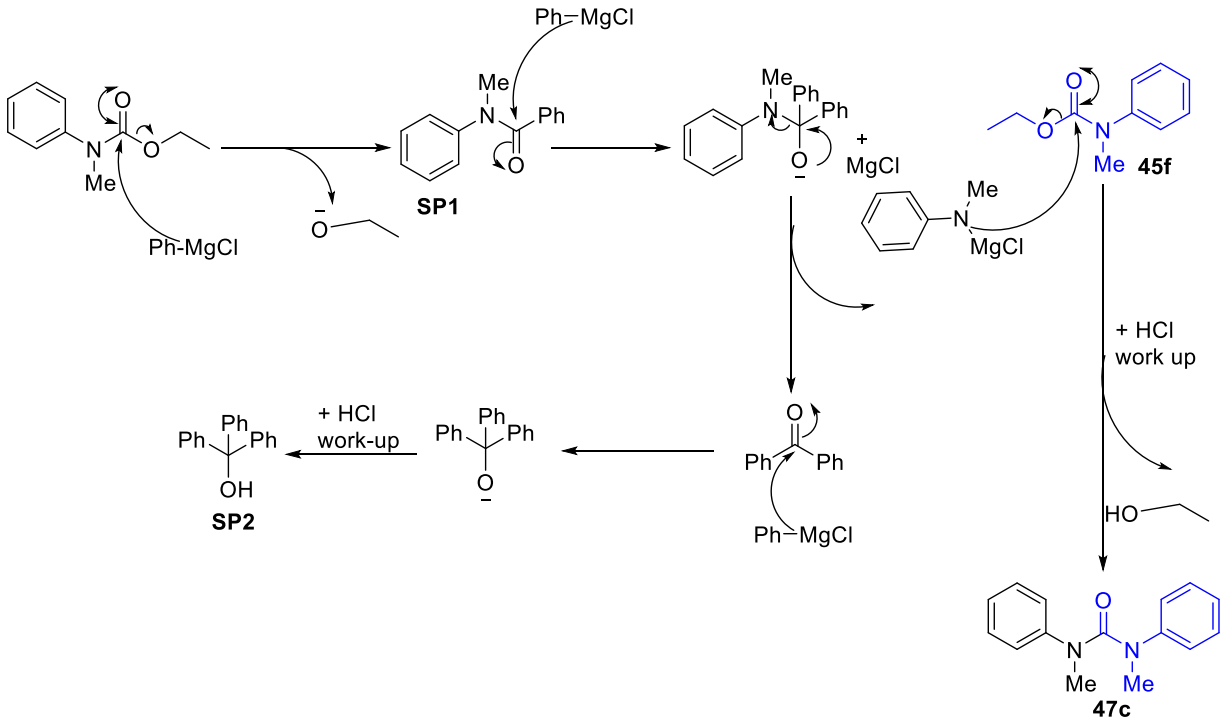
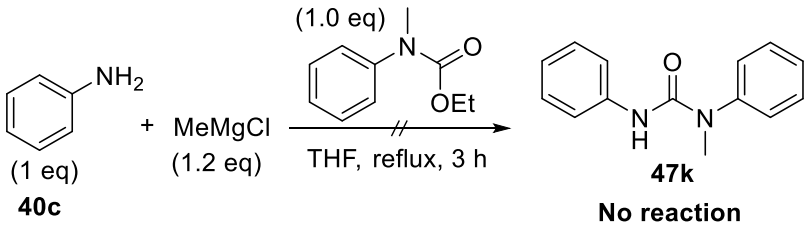


Figure 2.29: Proposed mechanism for urea **47c** formation.

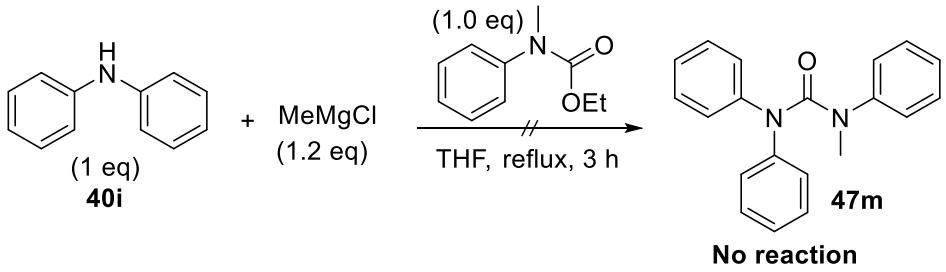
As it was identified that the carbamate **45f** reacts with MeMgCl leading to non-intended ureas we decided to take a different approach with the reaction. This involved targeting when the carbamate is in place and the second amine is added to form the urea. We intended generating the amine anion fully prior to the addition of the carbamates so the Grignard would have been consumed and could not cause a cross reaction. The anion was generated by the reaction of aniline **40c** (1 eq) and MeMgCl (1.2 eq) in THF at rt for 0.5 h. After this time, the carbamate **45f** was added and the temperature was raised to reflux. Upon analysis on the GC-MS, the reaction did not produce the desired product **47k** and the carbamate starting material was recovered (Scheme 2.80).



Scheme 2.80: Attempt to produce diarylurea **47k** with aniline carbanion.

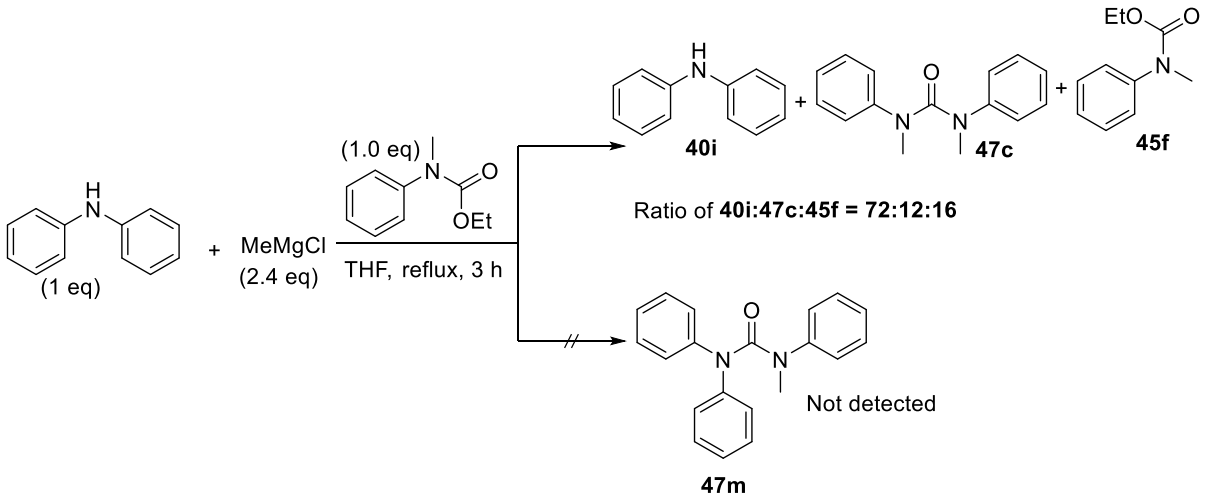
Using the same approach, a similar reaction was conducted, however with the use of diphenylamine **40i** in place of aniline **40c**. We wondered if the presence of just one proton

would allow the reaction to occur. The reaction of the anion derived from diphenylamine **40i** with carbamate **45f** did not yield the desired product but returned the carbamate starting material unchanged (Scheme 2.81).



Scheme 2.81: Attempt to produce diarylurea **47m** using diphenylamine.

When the reaction of the anion derived from diphenylamine **40i** with carbamate **45f** was repeated with 2.4 eq of MeMgCl. The reaction proceeded to give a mixture of 1,3-dimethyl-1,3-diphenyl-urea **47c**, diphenylamine **40i** and carbamate **45f** in the ratio 12:72:16 observed by GC-MS. The desired urea product was not observed.



Scheme 2.82: Attempted reaction to produce diarylurea **47m** with 2.4 eq MeMgCl.

The purpose of this study was to investigate the use of MeMgCl chemistry in the synthesis of di-substituted aromatic ureas. Unfortunately, the presence of either the isocyanate or the 1,3-dimethyl-1,3-diphenyl-urea **47c** side product prevented these reactions happening, an issue which still needs to be resolved, though we have certainly exposed many of the potential pitfalls involved in these reactions.

2.4.3 Synthesis of cyclic ureas

The reaction to form non-aromatic ureas was further explored to see if it was possible to extend this methodology to the formation of cyclic ureas. Cyclic ureas are common and important heterocyclic motifs in biologically active molecules[87–89] (Figure 2.30)[89,90]

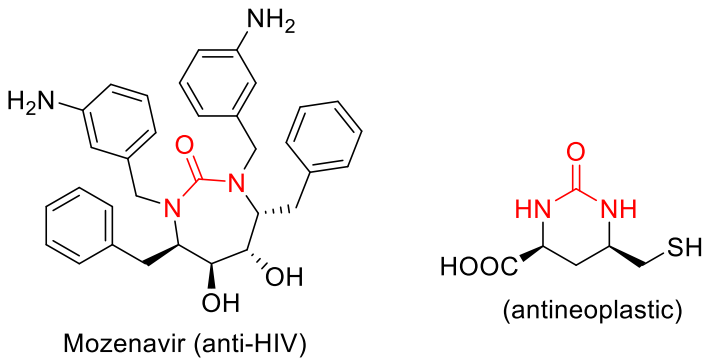
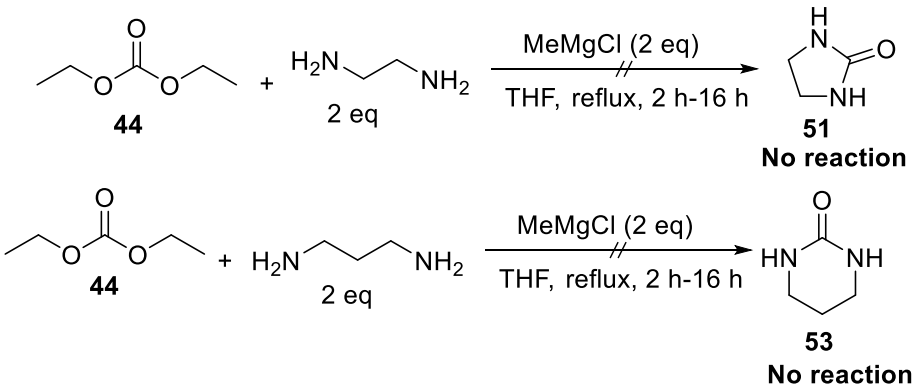


Figure 2.30: Examples of bioactive cyclic ureas.

The investigation began by attempting the reaction of diethyl carbonate with 1,2-diaminoethane which would yield a 5-membered cyclic urea.

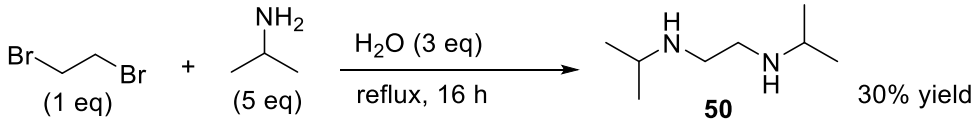
This reaction was conducted under the same conditions as that established for the synthesis of amides, where the reaction was done at rt. Under this condition, the reaction was unsuccessful, yielding back unreacted starting material.

When the reaction was attempted at reflux, no reaction occurred and starting material was recovered. The reaction of diethyl carbonate **44** with 1,3-diaminopropane was then attempted, the reaction was unsuccessful giving just unreacted starting material. Increasing the number of eq of 1,3-diaminopropane from 1 to 2 had no positive effect on the reaction (Scheme 2.83).



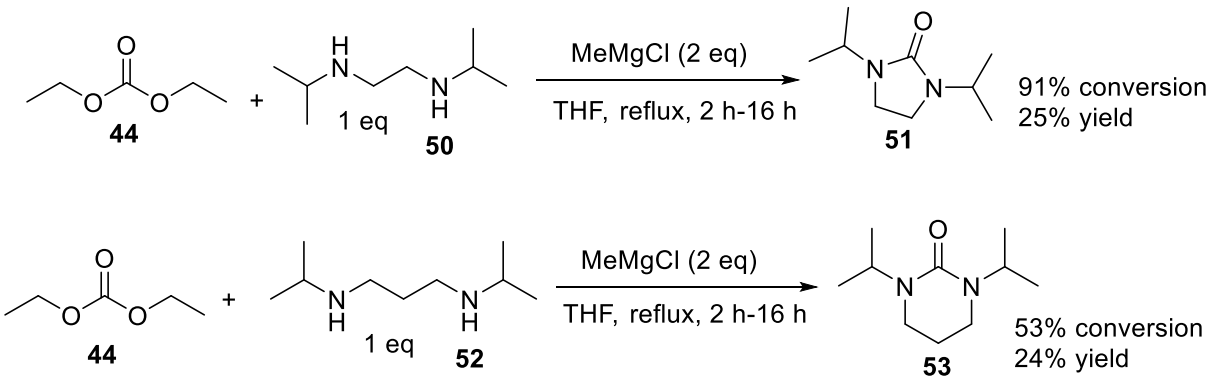
Scheme 2.83: Attempted formation of cyclic urea.

The presence of two protons on the NH_2 group was suspected to have made the reaction difficult. To eliminate this possibility, one proton was exchanged with an isopropyl group producing *N,N'*-diisopropyl-1,2-ethanediamine **50**. As isopropyl groups are inductively electron donating, the incorporation of the isopropyl groups would likely make the diamine compound more nucleophilic. **50** was prepared by reacting 1,2-dibromoethane (1.0 eq), water (3.0 eq) and isopropylamine (5.0 eq) at reflux overnight (Scheme 2.84). The reaction gave the product **50** in 30% yield after distillation. The remainder of the crude reaction mixture was the dimer, *N,N*-diisopropyl-*N*-(2-isopropylamino-ethyl)-ethane-1,2-diamine (from the reaction of two *N,N'*-diisopropyl-1,2-ethanediamine with 1,2- dibromoethane molecules).



Scheme 2.84: Synthesis of *N,N'*-diisopropyl-1,2-ethanediamine **50**

Revisiting the reaction to give the 5 membered pyrimidinone ring, another attempt to ring close was performed by reacting **50** (1 eq), diethyl carbonate (1 eq) **44** and MeMgCl (2 eq). The reaction gave the pyrrolidinone ring product **51** in a 91% conversion and 25% yield (Scheme 2.85). The remainder of the crude mixture was the carbonate **44** starting material.
The same procedure was repeated to produce the 6-membered pyrimidinone ring **53**. Reaction of 1,3-dibromopropane (1.0 eq), water (3.0 eq) and isopropylamine (5.0 eq) at reflux gave the *N,N'*-diisopropyl-1,3-propanediamine **52** product in 50% yield after distillation. The remainder of the crude mixture was the dimer, *N,N*-diisopropyl-*N*-(3-isopropylamino-propyl)-propane-1,3-diamine. Formation of the 6-membered pyrimidinone ring by reaction of *N,N'*-diisopropyl-1,3-propanediamine **52** (1 eq) diethyl carbonate (1 eq) **44** and MeMgCl (2 eq) was successfully achieved in 53% conversion and the product **53** was isolated in a 24% yield (Scheme 2.85).



Scheme 2.85: Synthesis of cyclic ureas.

2.4.4 Conclusion

In this chapter we discuss simple, high yielding methods for the preparation of amides, carbamates and ureas using methylmagnesium chloride as a base to form amide nucleophiles from amines.

Methylmagnesium chloride was utilized as a base in the one-pot synthesis of secondary and tertiary amides. This methodology can also be applied to reactions producing substituted amides. The synthesis of amides using MeMgCl works well *via* the late addition or *via* the generation of the anion before the addition of the ester and requires just 1 eq of the amine in most cases. These reactions also do not require elevated temperatures.

We have successfully produced carbamates in high yields from carbonates. Most of these reactions proceed with no need for further purification. When purification was needed the compounds were generally efficiently crystallised from petrol.

This reaction can be applied to the formation of symmetrical and un-symmetrical ureas with aliphatic amines. Efforts to produce non-symmetrical ureas from aromatic amines and carbamates were complicated by the elimination of the aromatic amine to produce an isocyanate. Non-symmetrical ureas are especially important as there is potential for such compounds to be used as anti-cancer agents and the use of MeMgCl is a viable method of synthesis. It is clear to see that there are more possibilities to be explored in the use of MeMgCl. Other simple and cyclic carbonates will be used in the preparation of carbamates and ureas.

This methodology continues to prove advantageous in terms of greenness. The synthesis of amides and similar functional groups from readily available and non-toxic starting material is desirable. It avoids the use of toxic and highly reactive phosgene and isocyanates and all reactions are done between rt and 70 °C.

2.5 References

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Chapter 3: Experimental

3.1 General experimental conditions

All materials were purchased from Aldrich chemical company, Acros Organics or Fischer Scientific and were used without further purification.

Reaction solvents were obtained from a Pure Soly^{TM} Solvent Purification System. Methylmagnesium chloride was purchased from Aldrich as a 22% solution in THF (equivalent to 3 M solution in THF). Phenylmagnesium chloride and pentylmagnesium chloride were purchased from Aldrich as a 2 M solution in THF.

Unless otherwise stated, all reactions were carried out under an inert atmosphere of nitrogen with dry glassware and apparatus, with the work up taking place in normal atmospheric conditions. Short workups were performed for reactions analysed mid-experiment, this was done taking a sample from the reaction mixture then quenching with the addition of H_2O followed by the addition of Et_2O.

Thin layer chromatography (TLC) procedures were carried out using preloaded aluminium silica gel sheets (Merck 60 F_{254}). Visualisation was achieved by UV (254 nm) light detection or vanillin stain. Column chromatography was carried out using a stationary phase of Aldrich silica (pore size 60 Å, 230 – 400 mesh particle size, 40 – 60 µm particle size) and the mobile phase indicated in the individual experimental procedures. Bulb to bulb vacuum distillation was carried out using a Kugelröhr Buchi Blass Oven B-580. Melting points were measured on a Stuart Scientific SMP1 apparatus. IR spectra were measured on a Perkin Elmer Spectrum One FT-IR with an ATR attachment. Gas chromatography/mass spectrometry (GC-MS) analysis was performed using a micromass GCT spectrometer with an Agilent 6890 series capillary gas chromatograph and a DB-1 fused silica column (length 30 m, film thickness 0.25 µm). The injector was held at 250 °C and the column oven followed the temperature program below.

Heating Rate (°C/min)	Temperature (°C)	Hold Time (min)	Run Time (min)
0.00	80	1.50	1.50
22.00	180	0.00	6.05
40.00	300	2.00	11.05

Helium was used as carrier gas at a flow rate of 2.3 mL/min. Percentage conversion/product composition was obtained from GC-MS unless otherwise stated and is based on total ion count. The mass spectrometry (accurate mass) system used was an Agilent 5975 series.

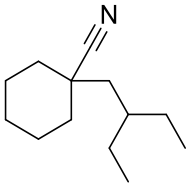
High resolution mass spectrometry (HRMS) was carried out using ESI time-of-flight mass spectrometer (TOFMS) in positive mode or negative mode. The precision of all accurate mass measurement was better than 5 ppm.

A JEOL ECX-400 NMR spectrometer was used to perform the ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopy analysis. All NMR analyses were carried out at probe temperatures of 20 °C in deuterated chloroform unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. ^{13}C spectra were assigned with the aid of DEPT experiments or by comparison to literature. HMQC aided in establishing links between protons and attached carbons and COSY established the links between proton and attached protons. Chiral HPLC analysis were carried out on a Varian Prostar instrument, with a diode array detector, with a Chiracel OD, Chiracel OD-H, Chiracel AD-H, Chiracel AD-RH, Chiracel OJ, Lux i-Cellulose-3 or Lux i-Cellulose-5 250 X 4.6 mm, 5µm column under conditions described for each experiment.

Optical rotation measurements were measured on a Schmidt and Haensch L1000 polarimeter at 589 nm (Na) in a 0.5 dm cell. Concentrations are expressed in g/mL. In line FTIR was used in some reactions for monitoring reaction progression. A ReactIR^{TM} 15 spectrometer with a SiComp silicon probe and an AgX x 6 mm x 1.5 m fibre (silver halide) probe interface was used. Data were collected in a sequence at a rate of 1 spectrum per 15 s in the range 3000-650 cm^{-1} and a resolution of 8 cm^{-1}.

3.2 Alkylation reactions

3.2.1 Late addition reactions



1-(2-Ethylbutyl)cyclohexane-1-carbonitrile **2a**.[1,2]

To a stirring solution of cyclohexanecarbonitrile **1** (1.8 mL, 15 mmol) in anhydrous THF (10 mL) was added diethylamine (80 µL, 0.75 mmol) and 1-bromo-2-ethylbutane (2.1 mL, 15 mmol). MeMgCl (6 mL, 3 M in THF, 18 mmol) was added dropwise at rt over a minute* and the mixture was left to stir for 2 h at rt at which stage all starting material (SM) had been consumed (GC-MS monitoring). The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The title compound **2a** (>99% pure GC-MS) (1.82 g, 63% yield) was recovered as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (d, J = 12.9 Hz, 2H, CNCCH_2CH), 1.76 – 1.56 (m, 5H, 5 x cyclohexyl-*H*), 1.50 – 1.34 (m, 7H, 2 x CHCH_2CH$_3$ and 3 x cyclohexyl-*H*), 1.25 – 1.08 (m, 3H, C*H*CH$_2$ and 2 x cyclohexyl-*H*), 0.87 (t, J = 7.3, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.3 (*C*N), 44.2 (C*C*H$_2$), 38.5 (C*CN*), 36.7, 36.4, 26.6, 25.4, 23.0, 10.9 (*C*H$_3$); IR υ_{max} /cm^{-1}: 2961, 2861, 2229 (CN) 1450; GC-MS m/z: 192 (5), 178 (9), 164 (64), 138 (100), 123 (45), 95 (20); HRMS (ESI) *m/z:* Calcd for $C_{13}H_{24}N$ [M+H$^+$]: 194.1909, found 194.1911.

* Upon addition of MeMgCl, the temperature rose to 70 °C. After 30 min, the reaction temperature had returned to rt and was left to stir for the remainder of the 2 h at which time full conversion was obtained (GC-MS monitoring).

Preparation of **2a** using FTIR probe.

To a stirring solution of anhydrous THF (10 mL) was inserted a silicon FTIR probe at 23.4°C, the THF spectrum was observed before the addition of cyclohexanecarbonitrile **1** (0.6 mL, 5 mmol), diethylamine (30 µL, 0.25 mmol) and MeMgCl (2 mL, 3 M in THF, 6 mmol). Upon addition of MeMgCl, the temperature rose to 28.2°C and a presence of a peak at 2035 cm^{-1} (ketenimine) was observed. After 15 min, the reaction temperature returned to 23.9 °C. 1-Bromo-2-ethylbutane (0.7 mL, 5 mmol) was added after 1 hour and the peak at 2035 cm^{-1} (ketenimine) disappeared almost instantaneously and the temperature decreased. The reaction was left to stir for 2 h at rt while the spectrum was being monitored on the iC IR software, at which stage all starting material (SM) had been consumed (GC-MS monitoring).

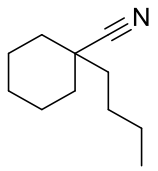
The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product.

The spectral data were consistent with that described for **2a** above.

Preparation of **2a** with no amine mediator

To a stirring solution of cyclohexanecarbonitrile **1** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise at rt over a minute and the reaction was left to stir for 2 h at rt at which stage there was the crude product mixture consisted of alkyl halide, nitrile **1**, 1-cyclohexylethanone and alkylated product **2a** in the ratio 66:26:2:6 (GC-MS monitoring). The reaction was left to stir further overnight at rt before being quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated. At this stage the ratio of the mixtures had changed to 28:10:2:60 for alkyl halide, nitrile **1**, 1-cyclohexylethanone and alkylated product **2a** respectively.

* The product was not isolated, and GC-MS was used to assess the product mixture.



1-Butylcyclohexanecarbonitrile **2b**.

This was prepared according to the procedure described for compound **2a** using cyclohexanecarbonitrile **1** (15 mmol) and 1-bromobutane (15 mmol). The title compound **2b** (>99% pure GC-MS) (1.99 g, 81% yield) was recovered as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (d, J = 12.8 Hz, 2H, 2 x cyclohexyl-*H*), 1.75 – 1.02 (m, 14H, 8 x cyclohexyl-*H,* $CH_2CH_2CH_2CH_3$ and CH_2CH_3), 0.91 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.0 (*C*N), 40.4, 39.1 (*C*CN), 35.8, 26.6, 25.6, 23.2, 22.9,14.0 (CH_3); IR: υ_{max} /cm^{-1}: 2937, 2232 (CN), 1451.

The spectral data were consistent with literature values.[3]

Preparation of **2b** using 2-Me-THF as solvent.

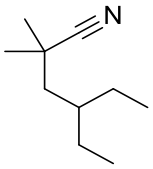
To a stirring solution of cyclohexanecarbonitrile **1** (1.8 mL, 15 mmol) in anhydrous 2-Me-THF (15 mL) was added diethylamine (80 µL, 0.75 mmol) and 1-bromobutane (1.6 mL, 15 mmol). MeMgCl (6 mL, 3 M in THF, 18 mmol) was added dropwise at rt over a minute and the reaction was left to stir for 2 h at rt at which stage all starting material (SM) had been consumed (GC-MS monitoring). The reaction was quenched with 1 M HCl (15 mL). The organic layer was separated and washed with H_2O (2 x 10 mL). The organic solution was concentrated to afford the title compound **2b** as a yellow oil (>99% pure GC-MS) (1.95 g, 79% yield).

The spectral data were consistent with that described for **2b** above.

Variations of the conditions used in the preparation of **2b** additional to those reported above.

Entry	**Solvent**	**Conditions**	**Comments**	**Conversion[a] %** Alkylhalide:1:acetylcyclohexanone:2b	**Yield[b] %**
1*	THF	**1** (5 mmol), THF (10 mL), bromobutane (5 mmol), MeMgCl (6 mmol), rt, 16 h.	MeMgCl with no amine	48:13:2:37	N/A
2	THF	**1** (5 mmol), THF (10 mL), diethylamine (0.25 mmol), bromobutane (5 mmol), PhMgCl (3 mL, 2M in THF, 6 mmol), rt, 2h.	PhMgCl	0:0:0:100	82
3*	THF	**1** (5 mmol), THF (10 mL), bromobutane (5 mmol), PhMgCl (3 mL, 2M in THF, 6 mmol), rt, 16 h.	PhMgCl with no amine	68:5:2:25	n/a
4	THF	**1** (5 mmol), THF (10 mL), DIPA (0.25 mmol) bromobutane (5 mmol), MeMgCl (6 mmol), rt, 2h.	DIPA	0:0:0:100	82

a) Based on GC-MS. *For entries 1 and 3 the product was not isolated and only GC-MS was used for product characterization. The mixture of products obtained were bromobutane:nitrile **1**:acetylcyclohexanone:alkylated product **2b** respectively**.** Spectral data for entry 2 are consistent with that described above.



4-Ethyl-2,2-dimethylhexanenitrile **4a**

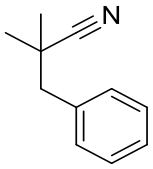
This was prepared according to the procedure described for compound **2a** with a change in scale using isobutyronitrile **3** (2.5 mmol) and 1-bromo-2-ethylbutane (2.5 mmol). Upon addition of MeMgCl (3 mmol) at this scale THF (10 mL), the temperature rose to 40 °C then returned to rt after 20 min. The title compound **4a** (>99% pure GC-MS) (0.28 g, 74% yield) was recovered as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 – 1.25 (m, 7H, 2 x CHC*H*$_2$CH$_3$, C*H*CH$_2$, C*H*$_2$CH and s, 6H, 2 x CNCC*H*$_3$), 0.82 (t, *J* = 6.8 Hz, 6H, 2 x CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.8 (*C*N), 44.3 (C*C*H$_2$), 37.6 (*C*H), 31.8 (*C*CN), 27.6 (2 x *C*H$_2$), 26.4 (2 x C*C*H$_3$), 10.7(2 x *C*H$_3$); IR: υ_{max} /cm^{-1}: 2965, 2878, 2235 (CN); HRMS (ESI) m/*z:* Calcd 154.1596 $C_{10}H_{20}N$ [*M*+H$^+$]: found 154.1595.

Preparation of **4a** without an amine mediator.

To a stirring solution of isobutyronitrile **3** (0.23 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise at rt over a minute and the reaction was left to stir for 2 h at rt at which stage there was a mixture of alkyl halide, nitrile **3** and alkylated product **4a** in the ratio 55:35:10 (GC-MS monitoring). The reaction was then left to stir further overnight at rt before being quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated. At this stage, the composition of the mixture had changed to 18:10:72 for alkyl halide, nitrile **3**, and alkylated product **4a** respectively.

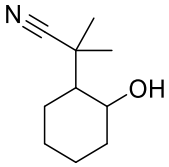
* The product was not isolated, and GC-MS was used to assess the product mixture.



2,2-Dimethyl-3-phenyl-propanenitrile **4b**.

This was prepared according to the procedure described for compound **2a** using isobutyronitrile **3** (5 mmol) and benzyl bromide (5 mmol). The title compound **4b** (>99% pure GC-MS) (0.31 g, 38% yield) was recovered as an oil which crystallised on standing. mp 52-55 °C, (lit[4]., 56 °C);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.23 (m, 5H, Ar-*H*), 2.81 (s, 2H, CH_2), 1.35 (s, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8 (Ar*C*), 130.3 (Ar*C*H), 128.5 (Ar*C*H), 127.4 (Ar*C*H), 124.9 (*C*N), 46.7 (*C*H_2), 33.6 (*C*CN), 26.6 (2 x *C*H_3); IR: υ_{max} /cm^{-1}: 3086, 2977, 2231(CN). The spectral data were consistent with literature values.[4]



2-(2-Hydroxycyclohexyl)-2-methylpropanenitrile **4c**.

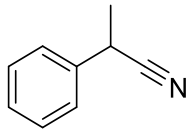
This was prepared according to the procedure described for compound **2a** using isobutyronitrile **3** (5 mmol) and cyclohexene oxide (5 mmol). The crude product mixture consisted of 2-chlorocyclohexanol and product in the ratio 39:61 (measured by GC-MS). The crude mixture was purified by column chromatography on silica petrol:EtOAc (70:30). The title compound **4c** (0.17 g, 40% yield) was recovered as an off white solid; mp 55-58 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (td, *J* = 10.1, 3.9 Hz, 1H, C*H*OH), 2.03 – 1.81 (m, 2H, CH_2CHOH), 1.78 – 0.98 (m, 14H, 6 x cyclohexyl-*H*, O*H*, C*H*CCH_3 and 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.4 (*C*N), 72.8 (*C*HOH), 51.1 (*C*HC), 37.3 (*C*H_2CHOH), 35.0 (*C*CH_3CH_3), 26.8 (*C*H_2), 25.9 (*C*H_3), 25.7 (*C*H_2), 25.0 (*C*H_3), 24.8 (*C*H_2); IR: υ_{max} /cm^{-1}: 3463 (br OH), 2938, 2237(CN); HRMS (ESI) *m/z:* Calcd for $C_{10}H_{17}NO$ [*M*+H$^+$]: 168.1388 found 168.1387

Preparation of **4c** by preforming the anion.

To a stirring solution of isobutyronitrile **3** (0.45 mL, 5 mmol) in anhydrous THF (15 mL) was added diethylamine (30 µL, 0.25 mmol). MeMgCl (2mL, 3 M in THF, 6 mmol) was added dropwise over a minute and the reaction was left to stir for 1 hour at rt. Cyclohexene oxide (0.5 mL, 5 mmol) was then added and the reaction temperature was raised to reflux and

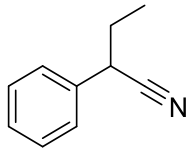
maintained at reflux for an additional 1.5 h. The reaction was quenched with 1 M HCl (10 mL) followed by the addition of Et_2O (10 mL). The organic layer was separated and washed with H_2O (2 x 10 mL) and then brine (10 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of 2-chlorocyclohexanol and product **4c** in the ratio 19:81 (measured by GC-MS). The crude mixture was purified by column chromatography on silica petrol:EtOAc (70:30). The title compound **4c** (0.55 g, 66% yield) was recovered as an off-white solid. The spectral data were consistent with that described for **4c** above.



2-Phenylpropionitrile **6a**.

This was prepared according to the procedure described for compound **2a** using phenylacetonitrile **5** (15 mmol) and iodomethane (15 mmol). The crude product mixture consisted of starting material (SM) **5**, mono and dialkylated product in the ratio 11:82:7 (measured by GC-MS) (1.58 g) and was isolated as a brown oil. This mixture proved difficult to separate but based on the recovery and crude product ratio it represents 66% crude yield of the product **6a**. The SM **5** and dialkylated product **7a** were evident in the ^{1}H NMR spectrum at 3.75 and 1.72 ppm, the integration of these signals was consistent with the ratio of products measured by GC-MS.

Diagnostic signals for **6a** in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.26 (m, 5H, Ar-*H*), 3.90 (q, *J* = 7.3 Hz, 1H, C*H*), 1.62 (d, *J* = 7.3 Hz, 3H, CH_3); diagnostic signals in ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (Ar*C*), 129.2 (Ar*C*H), 127.9 (Ar*C*H), 126.8 (Ar*C*H), 121.7 (*C*N), 31.4 (*C*H), 21.6 (*C*H_3); IR: υ_{max} /cm^{-1}: 3033, 2963, 2934, 2241 (CN), 1601. The spectral data were consistent with literature values.[5]



2-Phenylbutyronitrile **6b**

This was prepared according to the procedure described for compound **2a** using phenylacetonitrile **5** (10 mmol) and iodoethane (10 mmol). The crude product mixture consisted of SM, mono- and dialkylated product in the ratio 3:96:1 (measured by GC-MS). The

crude mixture was purified by column chromatography (petrol:Et_2O, 99:1) to afford the product **6b** (1.06 g, 73% yield) as a light-yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.25 (m, 5H, Ar-*H*), 3.74 (t, *J* = 7.2 Hz, 1H, C*H*CH_2), 2.08 - 1.72 (m, 2H, CHC*H*$_2$$CH_3$), 1.08 (t, *J* = 7.4 Hz, 3H, CH_2C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (Ar*C*), 129.1 (Ar*C*H), 128.1 (Ar*C*H), 127.4 (Ar*C*H), 120.9 (*C*N), 39.0 (*C*H), 29.3 (*C*H_2), 11.6 (*C*H_3); IR: υ_{max} /cm^{-1}: 3033, 2963, 2936, 2240 (CN), 1601. The spectral data were consistent with literature values.[6]

Preparation of **6b** using FTIR probe.

To a stirring solution of anhydrous THF (10mL) was inserted a silicon FTIR probe at 21.3°C, the THF spectrum was observed before the addition of phenylacetonitrile **5** (0.3 mL, 2.5 mmol), diethylamine (15 µL, 0.125 mmol) and MeMgCl (1 mL, 3 M in THF, 3 mmol). Upon addition of MeMgCl, the temperature rose to 27.0°C and new peaks at 2100 cm^{-1} (C-metalated nitrile) and 1589 cm^{-1} (aromatic C=C) were observed. After 15 min, the reaction temperature returned to 22.0 °C. Iodoethane (0.2 mL, 2.5 mmol) was added after 1 hour and the peaks at 2100 cm^{-1} (C-metalated nitrile) and 1589 cm^{-1} (aromatic C=C) disappeared instantaneously. The reaction was left to stir for a further 2 h at rt while the spectrum was being monitored on the iC IR software, at which stage the crude product mixture consisted of SM, mono- and dialkylated product in the ratio 4:94:2 (measured by GC-MS). The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product.

* The product was not isolated, and GC-MS was used to assess the product mixture.

Preparation of **6b** using 2-Me-THF as solvent.

To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous 2-MeTHF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and iodoethane (0.2 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute at rt and the reaction was left to stir for 2 h at rt. After 2 h, the crude product mixture consisted of SM, mono- and dialkylated product in the ratio 3:95:2 (measured by GC-MS).

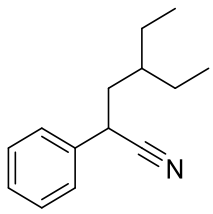
The reaction was quenched with 1 M HCl (15 mL). The organic layer was separated and washed with H_2O (2 x 10 mL). The organic solution was dried over Na_2SO_4 and, filtered. The Na_2SO_4 was washed with EtOAc the combined filtrate and washes were concentrated *in vacuo* to afford the alkylated product. The crude mixture was purified by column chromatography (petrol:Et_2O, 99:1) to afford the product **6b** as a yellow oil (0.25 g, 70% yield).

The spectral data were consistent with that described above.

Variation of conditions used for the preparation of **6b** additional to those reported above

Entry	Solvent	Conditions	Comments	Conversion[a] % SM:Mono:Di	Yield[b] %
1	THF	**5** (2.5 mmol), iodoethane (2.5 mmol), MeMgCl (3 mmol), rt, ON	MeMgCl with no amine	1:95:3	78
2	THF	**5** (2.5 mmol), diethylamine (0.125 mmol) iodoethane (2.5 mmol), PhMgCl (1.5 mL, 2M in THF, 3 mmol), rt, 2 h	PhMgCl	3:93:4	75
3	THF	**5** (2.5 mmol), diethylamine (0.125 mmol) iodoethane (2.5 mmol), PhMgCl (1.5 mL, 2M in THF, 3 mmol), 0 °C, 2 h	PhMgCl	4:95:1	-*
4	THF	**5** (2.5 mmol), DIPA (0.125 mmol) iodoethane (2.5 mmol), MeMgCl (3 mmol), rt, 2h	DIPA	2:96:2	73

a) Based on GC-MS **b)** Based on isolated yield for monoalkylation**.** * The product was not isolated, and GC-MS was used to identify product composition.



4-Ethyl-2-phenylhexanenitrile **6c**.

This was prepared according to the procedure described for compound **2a** using phenylacetonitrile **5** (30 mmol),1-bromo-2-ethylbutane (30 mmol) and THF (20 mL). The crude product consisted of SM **5**, mono- and dialkylated product in the ratio 9:91:1 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 99:1) giving the product **6c** (4.25 g, 70% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H, Ar-*H*), 3.80 (dd, *J* = 10.0, 6.2 Hz, 1H, PhC*H*CN), 1.92 (ddd, *J* = 13.8, 10.0, 5.0 Hz, 1H of CHCH_2CH), 1.69 (ddd, *J* = 13.8, 8.2, 6.2 Hz, 1H of CHCH_2CH), 1.54 – 1.21 (m, 5H, C*H*CH_2CH_3 and 2 x $CH_3CH_2CH_3$), 0.89 – 0.84 (m, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7 (Ar*C*), 129.2 (Ar*C*H), 128.1 (Ar*C*H),

127.3 (Ar*C*H), 121.2 (*C*N), 39.9 (Ph*C*H), 38.0 (CH_2CHCH_3) 35.5 (PhCHCH_2), 25.2(CH_2), 24.4 (CH_2), 10.7 (CH_3), 10.1 (CH_3); IR: υ_{max} /cm^{-1}: 3033, 2971, 2936, 2240 (CN), 1602; GC-MS m/z: 201 (38), 117 (100), 89 (85), 57 (35). HRMS (ESI) *m/z:* Calcd for $C_{14}H_{18}N$ [*M*-H^+]: 200.1439 found 200.1431.

Preparation of **6c** with no amine mediator.

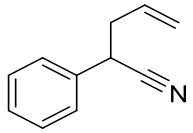
To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was added dropwise over a minute at rt and the reaction was left to stir for 2 h at rt. After 2 h the reaction was sampled and a mixture of alkyl halide SM and monoalkylated product in the ratio 32: 68 (measured by GC-MS). The reaction was then left to stir further for 16 h at rt before being quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo.* At this stage, the ratio of compounds in the crude mixture was 17:81:2 for alkyl halide, monoalkylated and dialkylated product respectively.

*The product was not isolated, and GC-MS was used to assess the product mixture.

Preparation of **6c** at low temperature (0 °C).

To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (80 µL, 0.125 mmol) and 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was added dropwise over a minute at 0° and the reaction was left to stir for 2 h at 0 °C. A crude mixture of SM **5**, mono- **6c** and dialkylated product **7c** in the ratio 24:75:1 (measured by GC-MS). The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product.

*The product was not isolated, and GC-MS was used to assess the product mixture.



2-Phenylpent-4-ene-1-nitrile **6d**.

This was prepared according to the procedure described for compound **2a** using phenylacetonitrile **5** (2.5 mmol) and allyl bromide (2.5 mmol).

The crude product mixture consisted of SM, mono- and dialkylated product in the ratio of 4:92:4 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 90:10) giving the product **6d** (0.27 g, 70% yield) as a clear oil;

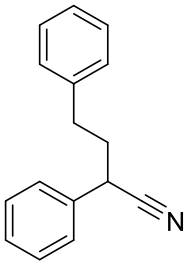
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.25 (m, 5H, Ar-*H*), 5.83 (td, J = 16.6, 7.7 Hz, 1H, C*H*=CH_2), 5.29 – 5.14 (m, 2H, CH=C*H*$_2$), 3.88 (t, J = 7.2 Hz, 1H, C*H*Ph), 2.68 – 2.60 (m, 2H, CH*CH*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3 (Ar*C*), 132.7 (CH=*C*H_2), 129.2 (Ar*C*H), 128.3 (Ar*C*H), 127.4 (Ar*C*H), 120.4 (*C*N), 119.5 (*C*H=CH_2), 40.0 (Ph*C*H), 37.6 (*C*H_2); IR: υ_{max} /cm^{-1}: 2924, 2851, 224(CN), 1601.

The spectral data were consistent with literature values.[7]

Preparation of **6d** at low temperature (0 °C).

To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (80 µL, 0.125 mmol) and allyl bromide (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute at 0 °C and the reaction was left to stir for 2 h at 0 °C. The crude product consisted of a mixture of SM **5**, mono- **6d** and dialkylated product **7d** in the ratio 19:80:1 (measured by GC-MS). The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The ratio of the crude mixture remained unchanged after isolation.

*The product was not isolated, and GC-MS was used to assess the product mixture.

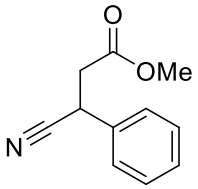


2,4-Diphenylbutanenitrile **6e**.

This was prepared according to the procedure described for compound **2a** using phenylacetonitrile **5** (2.5 mmol) and (2-bromoethyl)benzene (2.5 mmol).

The crude product consisted of SM **5**, (2-bromoethyl)benzene and product **6e** in the ratio of 4:6:90 (measured by GC-MS) in the crude product. The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 90:10) to afford **6e** (0.31 g, 56% yield) as a clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.01 (m, 10H, Ar-*H*), 3.80 – 3.67 (m, 1H, C*H*Ph), 2.89 – 2.70 (m, 2H, CH_2Ph), 2.35 – 2.02 (m, 2H, 1H of PhCHCH_2), and 1H of PhCHCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (Ar*C*), 135.7 (Ar*C*), 129.2 (Ar*C*H), 128.8 (Ar*C*H), 128.6 (Ar*C*H),128.3 (Ar*C*H), 127.4 (Ar*C*H), 126.6 (Ar*C*H), 120.8 (*C*N), 37.5 (Ph*C*H), 36.7 (Ph*C*H_2), 31.1 (*C*H_2); IR: υ_{max} /cm^{-1}: 3061, 2241(CN), 1601.

The spectral data were consistent with literature values.[8]



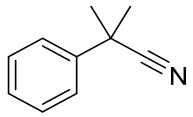
Methyl-3-cyano-3-phenylpropanoate **6f**.

This was prepared according to the procedure described for compound **2a** using phenylacetonitrile **5** (2.5 mmol) and methylbromoacetate (2.5 mmol). The crude product consisted of SM **5**, methylbromoacetate and product **6f** in the ratio of 50:43:7 (measured by GC-MS). As the conversion was low, the product was not isolated, and GC-MS was used to assess the product mixture.

Time variation (16 h)

The reaction was carried out according to the procedure for compound **2a**, using phenylacetonitrile **5** (2.5 mmol) and methylbromoacetate (2.5 mmol) on the scale described above, except the reaction time was extended 16 h. Analysis of the crude material by GC-MS showed no significant difference in the outcome with the extended reaction time. The crude

product consisted of SM **5**, methylbromoacetate and product **6f** in the ratio of 47:43:10 (measured by GC-MS).

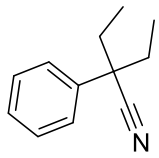


2-Methyl-2-phenylpropionitrile **7a**.

To a stirring solution of phenylacetonitrile **3** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and iodomethane (0.45 mL, 7.5 mmol). MeMgCl (2.5 mL, 7.5 mmol) was added dropwise over a minute at rt. Upon addition of MeMgCl the temperature rose to 45 ℃. The reaction temperature was raised to reflux then stirred for 3 h at reflux by which time the reaction was complete (GC-MS monitoring). The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The title compound **7a** (>99% pure GC-MS) (0.28 g, 77% yield) was recovered as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.45 (m, 2H, Ar-*H*). 7.41 – 7.33 (m, 2H, Ar-*H*), 7.32 – 7.26 (m, 1H, Ar-*H*), 1.73 (s, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 141.5, 129.0, 127. 9, 125.2, 124.6, 37.3, 29.3. **IR**: υ_{max} /cm^{-1}: 3032, 2234 (*C*N), 1601.

The spectral data were consistent with literature values.[11]

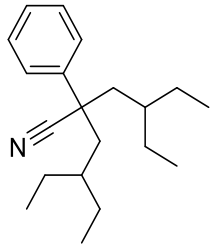


2-Ethyl-2-phenylbutyronitrile **7b**.

This was prepared according to the procedure described for compound **7a** using phenylacetonitrile **5** (2.5 mmol) and iodoethane (7.5 mmol). The title compound **7a** (>99% pure GC-MS) (0.33 g, 75% yield) was recovered as yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): 7.30 – 7.38 (m, 5H, Ar-*H*), 2.04 (dq, *J* = 14.7, 7.4 Hz, 2H, C*H*$_2$), 1.91 (dq, *J* = 14.7, 7.4 Hz, 2H, C*H*$_2$), 0.90 (t, 6H, *J* = 7.3 Hz, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1(Ar*C*), 128.9 (Ar*C*H), 127.7 (Ar*C*H), 126.2 (Ar*C*H), 122.4 (*C*N), 49.9 (*C*H), 33.9 (*C*H$_2$), 9.8 (*C*H$_3$); IR: υ_{max} /cm^{-1}: 3062, 2963, 2936, 2234 (CN), 1601.

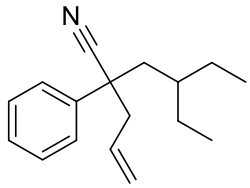
The spectral data were consistent with literature values.[11]



4-Ethyl-2-(2-ethylbutyl)-2-phenylhexanenitrile **7c**.

This was prepared according to the procedure described for compound **7a** using phenylacetonitrile **5** (2.5 mmol) and 1-bromo-2-ethylbutane (7.5 mmol). The title compound **7c** (>99% pure GC-MS) (0.56 g, 79% yield) was recovered as yellow oil;

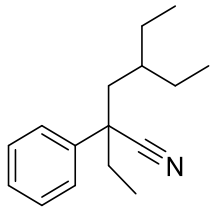
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.21 (m, 5H, Ar-*H*), 1.95 – 1.68 (m, 4H, 2 x C*H*$_2$CCN), 1.48 – 1.42 (m, 4H, 2 x C*H*$_2$CH$_3$), 1.32 – 1.17 (m, 2H, 2 x CH), 0.99 (p, *J* = 7.3 Hz, 4H, 2 x C*H*$_2$CH$_3$), 0.83 (t, *J* = 8.0 Hz, 6H, 2 x CH$_3$), 0.60 (t, *J* = 7.4 Hz, 6H, 2 x CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9 (Ar*C*), 128.7 (Ar*C*H), 127.5 (Ar*C*H), 126.4 (Ar*C*H), 123.2 (*C*N), 46.8 (*C*CN), 45.5 (2 x C*C*H$_2$), 37.2 (*C*HCH$_2$CH$_3$), 25.7 (*C*H$_2$), 10.4 (2 x *C*H$_3$), 10.2 (2 x *C*H$_3$); IR: υ_{max} /cm^{-1}: 2962, 2244 (CN), 1601; GC-MS m/z: 285 (8), 201 (100), 172 (85), 145 (16) 130 (80), 103 (58), 85 (16; HRMS (ESI) *m/z:* Calcd for $C_{20}H_{32}N$ [*M*+H$^+$]: 286.2535 found 286.2536.



2-Allyl-4-ethyl-2-phenylhexanitrile **7d**.

To a stirring solution of 2-phenylpent-4-enenitrile **6d** (0.135 g, 0.86 mmol) in anhydrous THF (10 mL) was added diethylamine (5 µL, 0.043 mmol) and 1-bromo-2-ethylbutane (0.12 mL, 0.86 mmol). MeMgCl (0.34 mL, 1.03 mmol) was added dropwise over a minute at rt. Upon addition of MeMgCl the temperature rose to 45 °C. The reaction temperature was raised to reflux then maintained at reflux for 2 hr. After 2 h, the crude product mixture consisted of SM **6d** and product **7d** in the ratio 4:96 (measured by GC-MS). The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. On workup, a ^{1}H NMR spectrum showed only the product **7d** which was isolated as a yellow oil (0.141g, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.33 (m, 4H, Ar-*H*), 7.32 – 7.19 (m, 1H, Ar-*H*), 5.76 – 5.55 (m, 1H, *CH*=CH$_2$), 5.15 – 4.93 (m, 2H, *CH*$_2$=CH), 2.67 (d, *J* = 6.8 Hz,

2H, $CH_2CH{=}CH_2$), 1.94 [dd, *J* = 14.4, 6.3 Hz, 1H of CH_2 (diastereotopic proton)], 1.82 [dd, *J* = 14.4, 4.9 Hz, 1H of CH_2 (diastereotopic proton)], 1.49 – 1.30 (m, 2H, 2 x CH_2CH_3), 1.29 – 1.22 (m, 1H, CH), 1.04 (p, *J* = 7.1 Hz, 2H, 2 x CH_2CH_3), 0.82 (t, *J* = 7.4 Hz, 3H, CH_3), 0.62 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 138.4, 132.0 (CH_2-Alkene), 128.8, 127.7, 126.3, 122.5 (CN), 120.0 (CH-alkene), 47.4, 46.5, 43.6, 37.3, 25.9, 25.6, 10.3. IR: υ_{max} /cm^{-1}: 2962, 2238 (conj.CN), 1643. GC-MS m/z: 241(20), 200 (13), 170 (16), 130 (100), 103 (20), 77 (10), 55 (9). HRMS (ESI) *m/z:* Calcd for $C_{17}H_{24}N$ *[M*+H^+]: 242.1909 found 242.190



2,4-Diethyl-2-phenylhexanenitrile **7e**.

Preparation of 7e by one pot heterodialkylation of phenylacetonitrile (addition of ethyl group first).

To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and iodoethane (0.2 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute and the reaction was left to stir for 2 h at rt. After 2 h, the crude product mixture consisted of SM, mono- and dialkyated product in the ratio 3:96:1 (measured by GC-MS). In the same pot, 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol), diethylamine (14 µL, 0.125 mmol) and MeMgCl (1 mL, 3 mmol) were then added. The reaction temperature was raised to reflux after addition of MeMgCl then maintained at reflux for 3 h. The reaction was quenched with 1 M HCl (15 mL) followed by Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of ethyl monoalkylated **7b** and dihetero product **7e** in the ratio 6:94 (measured by GC-MS). The crude mixture was purified by column chromatography (petrol:Et_2O, 99:1) to afford nitrile **7e** (0.435 g, 76% yield) as a colourless oil;

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.42 – 7.22 (m, 5H, Ar-*H*), 2.09 – 1.98 (m, 1H, 1 of CCH_2), 1.97 – 1.86 (m, 2H, 2 x $CHCH_2CH_3$), 1.80 (dd, *J* = 14.3, 4.9 Hz, 1H, 1 of CCH_2), 1.51 – 1.28 (m, 4H, 2 x $CHCH_2CH_3$), 1.27 – 1.13 (m, 1H, $CH_2CHCH_2CH_2$), 1.03 (p, *J* = 6.8 Hz, 2H, CCH_2CH_3), 0.87 (t, 7.4 Hz, 3H, CH_3), 0.83 (t, 7.4 Hz, 3H, CH_3), 0.62 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*138.5 (ArC), 128.8 (ArCH), 127.6 (ArCH), 126.3 (ArCH), 122.8

(*C*N), 48.3 (*C*CN), 44.4 (C*C*H_2), 37.4 (*C*HCH_2CH_3), 35.2 (*C*H_2), 25.9 (*C*H_2), 25.7 (*C*H_2), 10.3 (*C*H_3), 9.7 (*C*H_3). IR: υ_{max} /cm^{-1}: 3023, 2964, 2921, 2242 (CN); GC-MS m/z: 229 (7), 200 (6), 145 (100), 130 (82), 103 (53), 77 (22), 55 (13); HRMS (ESI) *m/z:* Calcd for $C_{16}H_{24}N$ [*M*+H^+]: 230.1909, found 230.1915.

One pot heterodialkylation of phenylacetonitrile (addition of 2-ethylbutyl group first).

To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute and the reaction was left to stir for 2 h at rt. After 2 h, the crude product mixture consisted of SM **5**, 2-ethylbutyl SM**,** monoalkylated product **6c** and dialkylated product **7c** in the ratio 10:5:84:1 (measured by GC-MS). In the same pot, iodoethane (0.2 mL, 2.5 mmol), diethylamine (14 µL, 0.125 mmol) and MeMgCl (1 mL, 3 mmol) were then added. The reaction temperature was raised to reflux after addition of MeMgCl then maintained at reflux for 3 h. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of 1-iodo-2-ethylbutane, monoethylated product **6b**, diethylated product **7b**, monoethylbutyl product **6c**, dihetero product **7e** and diethylbutyl product **7c** in the ratio (8:2:26:16:47:1) (measured by GC-MS) (0.443 g). The product **7e** was not isolated and only GC-MS was used to determine product composition.

Preparation of 7e by one pot heterodialkylation of phenylacetonitrile (addition of ethyl group first) with no amine addition before the second alkylation.

To a stirring solution of phenylacetonitrile **5** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and iodoethane (0.2 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute and the reaction was left to stir for 2 h at rt. After 2 h, the crude product mixture consisted of SM, mono- and dialkylated product in the ratio 4:95:1 (measured by GC-MS). To the same pot, 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol) and MeMgCl (1 mL, 3 mmol) were then added. Upon addition of MeMgCl, the temperature rose to 45 ℃. The reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL).

The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of 1-bromo-2-ethylbutane SM, ethyl monoalkylated **6b**, dihetero product **7e** and 2-ethylbutyl dialkylated product **7c** in the ratio

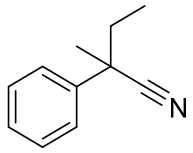
1:1:97:1 (measured by GC-MS). The crude mixture was purified by column chromatography (petrol:Et_2O, 99:1) to afford nitrile **7e** as a colourless oil (0.45 g, 79% yield).
The spectral data were consistent with that described for **7e** above.

Preparation of 7e, by sequential addition, from previously prepared 4-ethyl-2-phenylhexanenitrile 6c.

To a stirring solution of 4-ethyl-2-phenylhexanenitrile **6c** (1.01 g, 5 mmol) in anhydrous THF (10 mL) was added diethylamine (30 µL, 0.25 mmol), iodoethane (0.4 mL, 5 mmol). MeMgCl (1.7 mL, 3 M in THF, 5 mmol) was added dropwise over a minute. Upon addition of MeMgCl, the temperature rose to 47 °C. The reaction temperature was raised to reflux and maintained at reflux for 2 h. Upon cooling, the reaction was quenched with 1 M HCl (10 mL) followed by the addition of Et_2O (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of starting material **6c** and product **7e** in the ratio 6:94 (measured by GC-MS). The crude mixture was purified by column chromatography (petrol:Et_2O, 99:1) to afford the product **7e** as a colourless oil (0.82 g, 71% yield). The spectral data were consistent with that described for **7e** above.

Preparation of 7e, by sequential addition, from previously prepared 2-Phenylbutyronitrile 6b.

To a stirring solution of 2-Phenylbutyronitrile **6b** (0.36 g, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol), 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute. Upon addition of MeMgCl, the temperature rose to 47 °C. The reaction temperature was raised to reflux and maintained at reflux for 2 h. Upon cooling, the reaction was quenched with 1 M HCl (10 mL) followed by the addition of Et_2O (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of starting material **6b** and product **7e** in the ratio 4:96 (measured by GC-MS). The crude mixture was purified by column chromatography (petrol:Et_2O, 99:1) to afford the product **7e** as a colourless oil (0.44 g, 77% yield). The spectral data were consistent with that described for **7e** above.



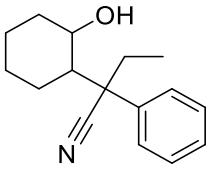
2-Methyl-2-phenylbutyronitrile **7f.**

Preparation of 7f by one pot heterodialkylation of phenylacetonitrile (addition of ethyl group first).

To a stirring solution of phenylacetonitrile **5** (0.6 mL, 5 mmol) in anhydrous THF (10 mL) was added diethylamine (30 µL, 0.25 mmol) and iodoethane (0.4 mL, 5 mmol). MeMgCl (2 mL, 3 M in THF, 6 mmol) was added dropwise over a minute. Upon addition of MeMgCl at this scale, the temperature rose to 40 °C. After 20 min, the reaction temperature returned to rt and the reaction was left to stir for 2 h at rt. After 2 h, the crude product mixture consisted of SM **5**, monoethylated product **6b** and diethylated product **7b** in the ratio 1:94:5 (measured by GC-MS). In the same pot, diethylamine (30 µL, 0.25 mmol), iodomethane (0.6 mL, 10 mmol), and MeMgCl (3.4 mL, 10 mmol) were added. The reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction was cooled and quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of dimethylated **7a**, di-ethylated **7b** and methylethyl product **7f** in the ratio 1:5:94 (measured by GC-MS). This mixture proved difficult to separate. The crude mixture was purified by column chromatography (petrol:Et_2O, 90:10) to afford nitrile **7f** as a pale-yellow oil (0.23g, 29% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 4H, Ar-*H*), 7.35 – 7.25 (m, 1H, Ar-*H*), 2.13 – 1.66 (m, 2H, CH_2), 1.70 (s, 3H, CH_3), 0.96 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 140.2 (Ar*C*), 128.9 (Ar*C*H), 127.8 (Ar*C*H), 125.6 (Ar*C*H), 123.5 (Ar*C*H), 43.3 (*C*CN), 35.4 (*C*H_2), 27.4 (*C*H_3), 10.0 (*C*H_3); IR: υ_{max}/cm^{-1}: 2974, 2238 (CN) 1602.

The spectral data were consistent with literature values.[12]

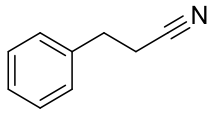


2-(2'-Hydroxycyclohexyl)-2-phenylbutyronitrile **7g**.

To a stirring solution of 2-phenylbutyronitrile **6b** (0.36 g, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and cyclohexene oxide (0.25 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute. The reaction temperature was raised to reflux and maintained at reflux for 2 h. Upon cooling, the reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford the alkylated product. The crude product mixture consisted of 2-chlorocyclohexanol, SM **6b** and product **7g** in the ratio 6:22:70 (measured by GC-MS). The crude mixture was purified by column chromatography (petrol: Et_2O, 80:20) to afford nitrile **7g** (0.25 g, 41% yield) as a clear oil. Only 2 diastereomers were observed on both ^1H and ^{13}C NMR spectra. Diastereomeric ratio A:B, 90:10);

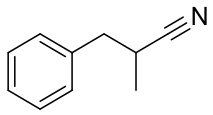
^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.24 (m, 5H, Ar-*H* both diastereomers), 3.74 – 3.41 (m, 1H, 2 x C*H*OH both diastereomers), 2.72 (dq, *J* = 14.5, 7.3 Hz, 0.1H, CH_2CH$_3$ for B), 2.33 – 1.50 (m, 5.9H, CH_2CH$_3$, CC*H*CHOH and 1H of CH_2CHOH, 2 x cyclohexyl-*H* (both diastereomers)] 1.47–0.98 [m, 5H, 1H of CH_2CHOH and 4 x cyclohexyl-*H* (both diastereomers)], 0.98 – 0.81 (m, 3H, CH_3 (both diastereomers));

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (Ar*C*), 128.9 (Ar*C*H) for A, 128.7 (Ar*C*H) for B, 127.9 (Ar*C*H) for A, 127.5 (Ar*C*H) for B, 127.2 (Ar*C*H) for A, 126.9 (Ar*C*H) for B, 122.6 (*C*N for B), 122.2 (*C*N) for A, 73.2 (*C*OH) for B, 72.8 (*C*OH) for A, 53.2 (*C*CN) for A, 53.1 (*C*CN) for B, 52.4 (*C*HCOH) for A, 52.4 (*CH**C**O*H) for B, 37.6 (*C*H_2COH) for B, 36.5(*C*H_2COH) for A, 32.3 (*C*H_2CH$_3$) for B, 31.2 (*C*H_2CH$_3$) for A, 27.7 (*C*H_2) for A, 27.6 (*C*H_2) for B, 25.6 (*C*H_2) for A, 25.6 (*C*H_2) for B, 24.5 (*C*H_2) for B, 24.3 (*C*H_2) for A, 10.1 (*C*H_3) for B, 9.9 (*C*H_3) for A; IR: υ_{max}/cm^{-1}: 3427 (OH), 2930, 2231 (CN); HRMS (ESI) *m/z:* Calcd for $C_1H_{22}NO$ [*M*+H$^+$]: 244.1701 found 244.1697



Hydrocinnamonitrile **13a**.

To a stirring solution of acetonitrile (0.78 mL, 15 mmol) in anhydrous THF (10 mL) was added diethylamine (80 µL, 0.75 mmol) and benzyl bromide (1.8 mL, 15 mmol) at 0 °C. MeMgCl (6 mL, 3 M in THF, 18 mmol) was added dropwise over a minute and the mixture was left to stir at 0℃ for 1 hour. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford the alkylated product. The crude product mixture consisted of benzyl bromide SM, product **13a** and *N*-benzyl-diethylamine (from the reaction of diethylamine and benzyl bromide) in the ratio 6:92:2 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 90:10) to afford the nitrile **13a** (1.6 g, 80% yield) as a light-yellow oil;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 - 7.20 (m, 5H, Ar- *H*), 2.94 (t, *J* = 7.8 Hz, 2H, *C*H_2Ph), 2.60 (t, *J* = 7.6 Hz, 2H, PhCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ138.2 (Ar*C*), 129.0 (Ar*C*H), 128.4 (Ar*C*H), 127.3 (Ar*C*H), 119.4 (*C*N), 31.6 (Ph*C*H_2), 19.4 (PhCH_2*C*H_2); IR: υ_{max} /cm^{-1}: 2976, 2240 (CN). The spectral data were consistent with literature values.[13]



3-Phenylbutyronitrle **14a**.

This was prepared according to the procedure described for compound **2a** using hydrocinnamonitrile **13a** (2.5 mmol) and iodomethane (2.5 mmol). The crude product mixture consisted of SM and monoalkylated product in the ratio 68:32 (measured by GC-MS). As the conversion of the product was low, the product was not isolated, and GC-MS was used to assess the product mixture.

Temperature variation

The reaction was carried out according to the procedure for compound **2a**, using hydrocinnamonitrile **13a** (2.5 mmol) and iodomethane (2.5 mmol) on the scale described above, except the reaction temperature was raised to reflux and maintained at reflux overnight. Analysis of the crude material by GC-MS showed no significant difference in the outcome at

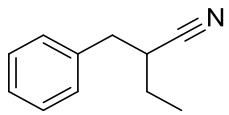
increased temperature. The crude product consisted of SM and monoalkylated product in the ratio 70:30 (measured by GC-MS).

Increased number of electrophile equivalents

This was prepared according to the procedure described for compound **2a** using hydrocinnamonitrile **13a** (2.5 mmol) and iodomethane (5 mmol). The crude product mixture consisted of SM **13a**, mono- **14a** and dialkylated **15a** product in the ratio 10:87:3 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 99:1) giving the product **14a** (0.25 g, 68% yield) as a clear oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.21 (m, 5H, Ar-*H*), 3.02 – 2.77 (m, 3H, C*H* and CH_2), 1.32 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (Ar*C*), 129.2 (Ar*C*H), 128.8 (Ar*C*H), 127.8 (Ar*C*H), 122.7 (*C*N), 40.1 (*C*H_2), 27.6 (*C*H), 17.7 (*C*H_3); IR: $_{max}$ /cm^{-1}: 2924, 2851, 2241 (CN), 1601.

The spectral data were consistent with literature values.[9]

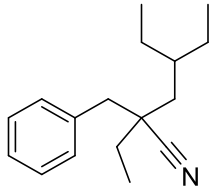


2-Benzylbutyronitrle **14b**.

This was prepared according to the procedure described for compound **2a** using hydrocinnamonitrile **13a** (7.5 mmol) and iodoethane (7.5 mmol). The crude product mixture consisted of SM **13a**, mono- **14b** and dialkylated **15b** product in the ratio of 1:90:8 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol: Et_2O, 90:10) to afford the product **14b** (0.85 g, 70% yield) as a clear oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.18 (m, 5H, Ar-*H*), 2.93 (dd, J = 13.6, 8.5 Hz, 1H of *CH*$_2$), 2.85 (dd, J = 13.6, 5.9 Hz, 1H of *CH*$_2$), 2.71 (tt, J= 8.5, 5.9 Hz, 1H, CH_2*CH*CH_2), 1.77 – 1.50 (m, 2H, Ph*CH*$_2$), 1.13 (t, J = 7.4 Hz, 3H, CH_2*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (Ar*C*), 129. 0 (Ar*C*H), 128.8 (Ar*C*H), 127.3 (Ar*C*H), 121.8 (*C*N) 38.2 (Ph*C*H_2), 35.5 (*C*H), 25.1 (*C*H_2CH_3), 11.6 (*C*H_3); IR: υ_{max} /cm^{-1}: 2924, 2851.

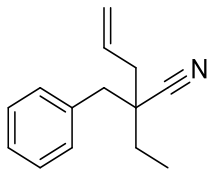
The spectral data were consistent with literature values. [10]



2-Benzyl-2,4-diethyl-hexanenitrile **15d.**

To a stirring solution of hydrocinnamonitrile **13a** (0.327 g, 0.33 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and iodoethane (0.2 mL, 2.5mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise at rt over a minute and the mixture was stirred for 2 h at rt. After 2 h, the crude product mixture consisted of SM, mono- and diethylated product in the ratio 1:96:3 (measured by GC-MS). In the same pot, diethylamine (14 µL, 0.125 mmol), 1-bromo-2-ethylbutane (0.35 mL, 2.5 mmol), and MeMgCl (1 mL, 3 mmol) were then added and the reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of dihetero product **15d** and the diethylated product in the ratio 98:2 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 90:10) to yield the product **15d** (0.53 g, 86% yield);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.22 (m, 5H, Ar-*H*), 2.84 (ABq, J_{AB} = 13.6, 20.4 Hz, 2H, *C*H_2Ph), 1.55 – 1.35 (m, 9H, 3 x CH_2 and CH), 1.06 (t, *J* = 7.4 Hz, 3H, CH_3), 0.87 (t, 3H, *J* = 7.4 Hz, CH_3), 0.83 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ135.6 (Ar*C*), 130.3 (Ar*C*H), 128.3 (Ar*C*H), 127.1 (Ar*C*H), 123.6 (*C*N), 43.0 (*C*CN), 41.7 (*C*CH_2), 39.7 (Ph*C*H_2), 36.8 (*C*HCH_2CH_3), 29.7 (*C*H_2), 26.3 (*C*H_2), 26.3 (*C*H_2), 10.6 (*C*H_3), 10.5 (*C*H_3), 8.9 (*C*H_3); IR: υ_{max} /cm^{-1}: 3031, 2963, 2231 (CN); GC-MS m/z: 243(50), 215(86), 186 (83), 171 (57), 115 (29), 91 (100), 65 (64); HRMS (ESI) *m/z:* Calcd for $C_{17}H_{24}N$ [*M*-H$^+$]: 242.1909 found 242.1902.



2-Benzyl-2-ethyl-pent-4-ene-nitrile **15e.**

One-pot heterodialkylation of hydrocinnamonitrile 13a (addition of allyl bromide first).

To a stirring solution of hydrocinnamonitrile **13a** (0.33 ml, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (0.125 mmol, 14 µL) and allyl bromide (0.21 ml, 2.5mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute and the reaction was stirred for 2 h at rt. After 2 h, the crude product mixture consisted of SM **13a**, monoalkylated and dialkylated product in the ratio 4:90:6 (measured by GC-MS). In the same pot, iodoethane (0.2 mL, 2.5 mmol), diethylamine (14 µL, 0.125 mmol) and MeMgCl (1 mL, 3 mmol) were then added. Upon addition of MeMgCl at this scale and temperature rose to 40 °C. The reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of monoalkylated SM, dihetero product **15e** and the di-allyl product in the ratio 5:90:5 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 90:10) to afford the product **15e** (0.40 g, 80% yield) as a light-yellow oil;

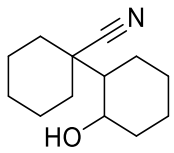
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.15 (m, 5H, Ar-*H*), 5.98 – 5.76 (m, 1H, *CH*=CH_2), 5.26 – 5.16 (m, 2H, CH=*CH*$_2$), 2.84 (s, 2H, C*H*$_2$Ph), 2.31 (d, J = 6.8 Hz, 2H, *CH*$_2$CH=), 1.73 – 1.51 (m, 2H, *CH*$_2$$CH_3$), 1.08 (t, J = 7.3 Hz, 3H, CH_2*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5 (Ar*C*), 132.0 (CH=*C*H_2), 130.5 (Ar*C*H), 128.5 (Ar*C*H), 127.4 (Ar*C*H), 123.1 (*C*N), 120.3 (*C*H=CH_2), 42.4 (*C*CN), 42.0 (*C*CH_2), 40.0 (Ph*C*H_2), 28.9 (*C*$H_2$$CH_3$), 9.0 (*C*$H_3$); IR: υ_{max} /cm^{-1}: 2240 (CN), 1640 (C=C). HRMS (ESI) *m/z:* Calcd for $C_{14}H_{18}N$ [*M*+H$^+$]: 200.1439 found 200.1445.

Preparation of 15e by one-pot hetero dialkylation of hydrocinnamonitrile 13a (addition of ethyl group first).

To a stirring solution of hydrocinnamonitrile **13a** (0.33 ml, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (0.125 mmol, 14 µL) and iodoethane (0.20 ml, 2.5mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute and the reaction was stirred for 2 h at rt. After 2 h, the crude product mixture consisted of SM **13a**, mono- **13b** and dialkylated product **15b** in the ratio 1:92:7 (measured by GC-MS). In the same pot, allyl

bromide (0.21 mL, 2.5 mmol), diethylamine (14 µL, 0.125 mmol) and MeMgCl (1 mL, 3 mmol) were added and the reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford the alkylated product. The crude product mixture consisted of monoalkylated SM **14b**, dihetero product **15e** and the dialkylated SM **15b** in the ratio 3:92:5 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 90:10) to afford the product **15e** (0.40 g, 80% yield) as a light-yellow oil. The spectral data were consistent with that described above.

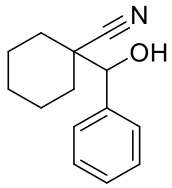
3.2.2 Preformed anion reactions



2'-Hydroxy[1,1'-bi(cyclohexane)]1-carbonitrile **16.**

To a stirring solution of cyclohexanecarbonitrile **1** (0.9 mL, 7.5 mmol) in anhydrous THF (10 mL) was added diethylamine (45 µL, 0.375 mmol). MeMgCl (3 mL, 3 M in THF, 9 mmol) was added dropwise over a minute. Upon addition of MeMgCl (9 mmol), the temperature rose to 55 °C then returned to rt after 20 min. The reaction mixture was then stirred at rt for 1 hour. Cyclohexene oxide (0.75 mL, 7.5 mmol) was then added and the reaction temperature was raised to reflux and was maintained at reflux for 2 h. The reaction was cooled and quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The title compound **16** (>99% pure GC-MS) (1.37 g, 88% yield) was recovered as an off-white crystalline solid; mp 73-75 °C;

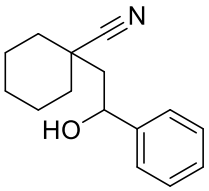
^{1}H NMR (400 MHz, $CDCl_3$), δ 3.75 – 3.51 (m, 1H, *CH*OH), 2.19 (d, J = 12.9 Hz, 1H, CHOHC*H*CCN), 2.05 – 1.89 (m, 3H, 3 x cyclohexyl-*H*), 1.85 – 1.01 (m, 15H, 7 x cyclohexyl-*H*, 3 x cyclohexyl-*H*, 5 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 124.1(*C*N), 72.8 (*C*HOH), 51.2, 42.3 37.5, 34.4, 32.9, 26.6, 25.8, 25.5, 24.6, 23.6, 23.3; IR: υ_{max} /cm^{-1}: 3370 (br, OH), 2936, 2856, 2230 (CN); HRMS (ESI) *m/z:* Calcd for $C_{13}H_{22}NO$ [*M*+H$^+$]: 208.1701, found 208.1710.



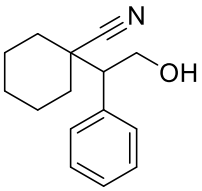
1-(Hydroxy-phenyl-methyl)-cyclohexanenitrile **17.**

This was prepared according to the procedure described for compound **16** using cyclohexanecarbonitrile **1** (2.5 mmol) and benzaldehyde (2.5 mmol). The crude product mixture consisted of benzaldehyde SM and product **17** in the ratio 15:85 (measured by GC-MS). The residual SM was removed by bulb to bulb distillation at 60 °C at 2.0 mm Hg and the title compound **17** (0.38g, 70% yield) was isolated as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.25 (m, 5H, Ar-*H*), 4.50 (s, 1H, C*H*OH), 2.31 (d, *J* = 13.4 Hz, 1H, 1 x cyclohexyl-*H*), 1.90 – 1.46 (m, 6H, 6 x cyclohexyl-*H*), 1.41 – 1.03 (m, 3H, 3 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): 139.1 (Ar*C*), 128.9 (Ar*C*H), 128.5 (Ar*C*H), 127.5 (Ar*C*H), 121.9 (*C*N), 79.3 (*C*OH), 46.0, 33.1, 31.8, 25.3, 22.9; IR: υ_{max} /cm^{-1}: 3449 (br, s, OH), 3021, 2934, 2238 (CN); GCMS m/z: 215 (2.5), 107(88), 77 (100), 51 (20); HRMS (ESI) *m/z:* Calcd for $C_{14}H_{18}NO$ [*M*+H^{+}]: 216.1388, found 216.1394. The spectral data were consistent with literature values.[14]



18a



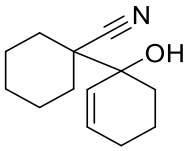
18b

1-(2-Hydroxy-2-phenylethyl)-cyclohexanecarbonitrile **18a** and 1-(2-Hydroxy-1-phenylethyl)-cyclohexanecarbonitrile **18b.**

This was prepared according to the procedure described for compound **16** using cyclohexanecarbonitrile **1** (7.5 mmol) and styrene oxide (7.5 mmol). The crude product mixture consisted of nitrile SM **1** and the regioisomeric products **18a** and **18b** in a ratio of 1:2 respectively (by ^{1}H NMR spectroscopy). The crude mixture was purified by column chromatography on silica (petrol:Et_2O, 70:30) affording the isolated compounds **18a** (0.38 g, 22% yield) and **18b** (0.81 g, 47% yield) as clear oils;

18a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.18 (m, 5H, Ar-*H*), 5.04 – 4.98 (m, 1H, C*H*OH), 2.35 – 1.85 (m, 4H, 2 x cyclohexyl-*H*, br OH, 1H of CHCH_2,), 1.82 – 1.55 (m, 6H, 5 x cyclohexyl-*H* and 1H of CHCH_2), 1.41 – 1.10 (m, 3H, 3 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (Ar*C*), 128.8 (Ar*C*H), 128.0 (Ar*C*H), 125.7 (Ar*C*H), 123.9 (*C*N), 71.9 (*C*HOH), 49.3 (CH*C*H_2), 38.1, 36.7, 36.1, 25.3, 23.1, 22.0. IR: υ_{max} /cm^{-1}: 3404 (br, OH), 2230 (CN); HRMS (ESI) *m/z:* Calcd for $C_{15}H_{20}NO$ [*M*+H$^+$]: 230.1545 Found 230.1543.

18b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.02 (m, 5H, Ar-*H*), 4.23 – 3.98 (m, 2H, CH_2OH), 2.79 (dd, *J* = 9.2, 5.5 Hz, 1H, CH_2C*H*Ph), 2.21 (d, *J* = 13.1 Hz, 1H, 1 x cyclohexyl-*H*), 1.87 (br s, 1H, O*H*), 1.79 – 1.25 (m, 7H, 4 x cyclohexyl-*H*, 2 x cyclohexyl-*H*, 1 x cyclohexyl-*H)*, 1.20-1.02 (m, 2H, 2 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (Ar*C*), 129.4 (Ar*C*H), 128.9 (Ar*C*H), 128.0 (Ar*C*H),122.6 (*C*N), 63.0 (*C*H_2OH), 56.3 (*C*HCH_2OH), 41.3, 35.7, 34.6, 25.2, 22.9; IR: υ_{max} /cm^{-1}: 3434 (br, OH), 2933, 2858, 2232 (CN); HRMS (ESI) *m/z:* Calcd for $C_{15}H_{20}NO$ [*M*+H$^+$]: 230.1545 Found 230.1544.

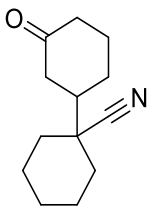


1'-Hydroxy-bicyclohexyl-2'-ene-1-carbonitrile **20a.**

This was prepared according to the procedure described for compound **16** using cyclohexanecarbonitrile **1** (15 mmol) and 2-cyclohexen-1-one (15 mmol).

The crude product mixture consisted of SM **1**, 1,2-addition product **20a** and 1,4-addition products **20b** in the ratio 11:33:56 (observed on GC-MS). The residual SM was removed by bulb to bulb distillation at 80 °C and 1.0 mm Hg. The crude mixture was then purified *via* column chromatography on silica (petrol:EtOAc, 70:30) affording the titled compound **20a** as yellow oil (0.11g, 21% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 – 5.98 (m, 1H, CH=*CH*CH_2), 5.90 – 5.75 (m, 1H, C*CH*=CH), 2.2 – 1.52 (m, 13H, CH=CH*CH*$_2$, 13 x cyclohexyl-*H*), 1.38 (dtd, *J* = 19.5, 13.1, 3.6 Hz, 2H, C*H*$_2$CH$_2$COH), 1.22 – 0.99 (m, 1H, 1 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 127.8 (2 x *C*H=CH), 122.8 (*C*N), 71.8 (*C*OH), 49.6, 30.8, 29.8, 29.0, 25.5, 25.2, 23.4, 23.3, 18.5; IR: υ_{max} /cm^{-1}: 3462 (br, OH), 2933, 2860, 2231 (CN). The spectral data were consistent with literature values.[15]

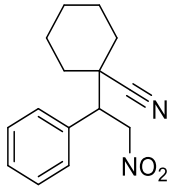


3'-Oxo-bicycloheyxl-1-carbonitrile **20b.**

To a stirring solution of cyclohexanecarbonitrile **1 (**1.8 mL, 15 mmol) in anhydrous THF (10 mL) was added diethylamine (80 µL, 0.75 mmol). MeMgCl (6 mL, 3 M in THF, 18 mmol) was added dropwise over a minute and the reaction mixture was stirred at rt for 2 h. CuCl (1 mol%) was added and the reaction was stirred for 3 min before the addition of 2-cyclohexen-1-one (1.45 mL, 15 mmol), The reaction temperature was raised to reflux and maintained at reflux for 2 h. The reaction was cooled and quenched with Et_2O (15 mL) and 1 M HCl (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of the nitrile SM **1** and product **20b** in the ratio 60:40 (measured by GC-MS). The crude mixture was then purified

via column chromatography on silica (petrol:EtOAc 70:30) affording the compound **20b** (0.89 g, 29%) as a white solid; mp 108-110 °C;

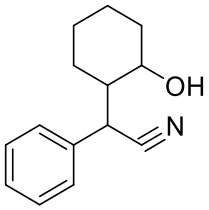
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 – 2.49 (m, 1H, 1 x cyclohexyl-*H*), 2.48 – 1.85 (m, 7H, 7 x cyclohexyl-*H*), 1.82 – 1.46 (m, 8H, 8 x cyclohexyl-*H*), 1.27 – 0.99 (m, 3H, 3 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (*C*O), 122.1 (*C*N), 46.6 (*C*CN), 43.2, 41.2, 33.8, 33.1, 26.3, 25.3, 24.7, 23.3, 23.1; IR: υ_{max}/cm^{-1}: 2969, 2228 (CN), 1706 (C=O); GC-MS m/z: 205 (8), 108 (15), 97 (100), 69 (77), 55 (45); HRMS (ESI) *m/z:* Calcd for $C_{13}H_{20}NO$ [*M*+H$^+$]: 206.1545, found 206.1541.



1-(2-Nitro-1-phenyl-ethyl)-cyclohexanecarbonitrile **21.**

This was prepared according to the procedure described for compound **20b** cyclohexanecarbonitrile **1** (2.5 mmol) and *trans-β*-nitrostyrene (2.5 mmol). The crude product mixture consisted of SM **1**, *trans*-β-nitrosytrene SM and product **21** in the ratio 9:24:67 (measured by GC-MS). The crude mixture was purified by column chromatography on silica petrol:Et_2O, 70:30) to afford a solid which was recrystalised from methanol. The title compound **21** was isolated as white crystals (0.28 g, 43% yield); mp 103-105 °C;

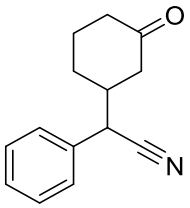
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.23 (m, 5H, Ar-*H*), 4.96 (d, *J* = 7.6 Hz, 2H, C*H*$_2$NO$_2$), 3.49 (t, *J* = 7.6 Hz, 1H, C*H*CH$_2$), 2.14 (dd, *J* = 12.8, 3.4 Hz, 1H, 1 x cyclohexyl-*H*), 1.82 – 1.28 (m, 7H, 7 x cyclohexyl-*H*), 1.25 – 0.99 (m, 2H, 2 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8 (Ar*C*), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 121.5 (*C*N), 76.9 (*C*H$_2$NO$_2$), 51.9 (*C*H), 41.9 (*C*CN), 35.4, 34.2, 24.9, 23.0, 22.8; IR: υ_{max} /cm^{-1}: 2934, 2235 (CN), 1551, 1382; GC-MS m/z: 258 (30), 150 (85), 104 (100), 91 (28), 78 (30); HRMS (ESI) *m/z:* Calcd for $C_{15}H_{19}N_2O_2$ [*M*+H$^+$]: 259.1447, found 259.1439.



2-(2-Hydroxycyclohexyl)-2-phenyl-acetonitrile **22.**

This was prepared according to the procedure described for compound **16** using phenylacetonitrile **5** (7.5 mmol) and cyclohexene oxide (7.5 mmol). The crude product mixture consisted of SM **5** and product in the ratio 3:97 (measured by GC-MS). The residual SM was removed by bulb to bulb distillation at 80 °C and 1.0 mm Hg giving the title compound **22** as a yellow oil (1.30 g, 81% yield). The compound contained a mixture of diastereomers in the ratio A:B (81:19) which were observed in both ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.25 (m, 5H, Ar-*H* both diastereomers), 4.72 (d, *J* = 3.4 Hz, 0.8H, *CH*CN for A), 4.59 (d, *J* = 3.7 Hz, 0.2H, *CH*CN for B), 3.75 – 3.60 (m, 0.8H, *CH*OH for A), 3.08 (dt, *J* = 10.6, 5.9 Hz, 0.2H, *CH*OH for B), 2.18 – 1.81 (m, 1H, 0.8H x cyclohexyl-*H* for A and 0.2H x cyclohexyl-*H* for B), 1.76 – 1.17 (m, 7H, 7 x cyclohexyl-*H* both diastereomers), 1.15 – 0.46 (m, 1H, 0.8H x cyclohexyl-*H* for A and 0.2H x cyclohexyl-*H* for B); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7 (Ar*C*) for A, 132.2 (Ar*C*) for B, 129.3 (Ar*C*H) for B, 128.9 (Ar*C*H) for A, 128.6 (Ar*C*H) for B, 128.1 (Ar*C*H) for B, 127.9 (Ar*C*H) for A, 127.8 (Ar*C*H) for A, 121.6 (*C*N) for B, 119.3 (*C*N) for A, 72.0 (*C*OH) for A, 70.1 (*C*OH) for B, 50.2 (*C*COH) for A, 48.7 (*C*COH), 38.5 (*C*HCN) for A, 37.5 (*C*HCN) for B, 36.1, 26.2, 25.4, 25.2, 25.1, 24.6, 24.5; IR: υ_{max} /cm^{-1}: 3370 (br, OH), 2936, 2856, 2230 (CN); GC-MS m/z: 215 (3), 197 (85), 130 (65), 117 (100), 81 (73), 68 (16), 55 (16); HRMS (ESI) *m/z:* Calcd for $C_{14}H_{18}NO$ [*M*+H^{+}]: 216.1388, found 216.1390.



(3-Oxo-cyclohexyl)-phenyl-acetonitrile **23.**

This was prepared according to the procedure described for compound **20b** using phenylacetonitrile **5** (2.5 mmol) and 2-cylohexen-1-one (2.5 mmol).

The title compound **23** (>99% pure GC-MS) (0.44 g, 81% yield) was recovered as a yellow oil; The compound contained a mixture of diastereomers in the ratio A:B (60:40) which were observed by GC-MS and by both ^{1}H and ^{13}C NMR spectroscopy;

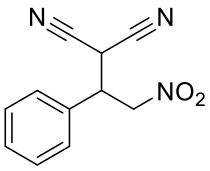
^{1}H NMR (400 MHz, $CDCl_3$) 7.60 – 7.02 (m, 5H, Ar-*H*, both diastereomers), 3.92 (d, *J* = 4.5 Hz, 0.6H, PhC*H* for A), 3.76 – 3.57 (m, 0.4H, PhC*H* for B), 2.57-1.87 (m, 7H, 6 x cyclohexenone-*H*, and 1H of CH_2CHCH_2 both diastereomers), 1.74 – 1.50 (m, 2H, 2 x cyclohexenone-*H,* both diastereomers). ^{13}C NMR (100 MHz, $CDCl_3$) 209.3 (*C*O), 133.3 (Ar*C*) for A, 133.0 (Ar*C*) for B, 129.3 (Ar*C*H), 129.2 (Ar*C*H), 128.6 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 119.1 (*C*N) for A, 118.9 (*C*N) for B, 46.0, 43.9, 43.5 (Ph*C*H) for B, 43.5 (Ph*C*H) for A, 43.3 (*C*HCH$_2$), 41.0, 41.0, 29.6, 27.7, 24.5, 24.4. IR: υ_{max} /cm^{-1}: 2947, 2241 (CN), 1701 (CO).

The spectral data were consistent with literature values.[21]

Preparation of **23** without Cu salt on the same scale.

To a stirring solution of using phenylacetonitrile **5 (**0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute and the reaction mixture was stirred at rt for 1 hour. After 1 hour, 2-cylohexen-1-one (1.45 mL, 15 mmol) was added and the reaction temperature was raised to reflux and maintained at reflux for a further 2 h. The reaction was cooled and quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The title compound **23** (>99% pure GC-MS) (0.46 g, 85% yield) was recovered as a yellow oil; (Diastereomeric ratio: A:B, 62:38 by GC-MS).

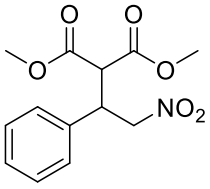
The spectral data were consistent with that described for **23** above.



2-(2-Nitro-1-phenylethyl)-malononitrile **24.**

This was prepared according to the procedure described for compound **16** using malononitrile (7.5 mmol) and *trans-β*-nitrostyrene (7.5 mmol). The crude product mixture consisted of SM (*trans*-β-nitrosytrene) and product **24** in the ratio 20:80 (measured by GC-MS). The residual SM was removed by bulb to bulb distillation at 80℃ and 1.00 mm Hg to afford the compound **24** (1.05 g, 65%) as a dark brown oil;

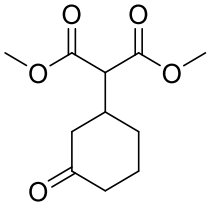
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.70 – 7.26 (m, 5H, Ar-*H*), 5.06 – 4.80 (m, 2H, *C*$H_2$$NO_2$), 4.44 (d, *J* = 6.0 Hz, 1H, CN*C*H*C*N), 4.08 (dt, *J* = 8.1, 6.0 Hz, 1H, Ph*C*H*C*H_2); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 131.9 (Ar*C*), 130.5 (Ar*C*H), 130.0 (Ar*C*H), 127.8 (Ar*C*H), 110.6 (*C*N), 110.5 (*C*N), 75.0 (*C*$H_2$$NO_2$), 43.7 (*C*HPh), 27.7 (*C*H); IR: υ_{max} /cm^{-1}: 2986, 2242 (CN), 1551 (NO). The spectral data were consistent with literature values.[16]



Dimethyl 2-(2-nitro-1-phenylethyl)-malonate **25.**

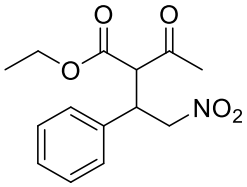
This was prepared according to the procedure described for compound **16** using dimethyl malonate (15 mmol) and *trans-β*-nitrostyrene (15 mmol). The crude product mixture consisted of dimethyl malonate SM and product **25** in the ratio 18:82 (measured by ^{1}H NMR spectroscopy). The crude mixture was purified *via* recrystallisation from methanol to afford the title compound **25** (3.16 g, 75%) as an off-white crystalline solid; mp 62-65 °C, (lit[17], 64 °C); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.33 – 7.15 (m, 5H, Ar-*H*), 4.95 – 4.84 (m, 2H, *C*$H_2$$NO_2$), 4.23 (td, *J* =9.1, 5.3 Hz, 1H, *C*H*C*H_2), 3.85 (d, *J* = 9.1 Hz, 1H, *C*H*C*OO*C*H_3), 3.75 (s, 3H, O*C*H_3), 3.55 (s, 3H, O*C*H_3); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.9 (*C*OOMe), 167.3 (*C*OOMe), 136.2 (Ar*C*), 129.1 (Ar*C*H), 128.5 (Ar*C*H), 128.0 (Ar*C*H), 77.5 (*C*$H_2$$NO_2$), 54.8 (*C*H), 53.1(O*C*H_3), 52.9 (O*C*H_3), 43.0 (*C*HPh); IR: υ_{max} /cm^{-1}: 1730 (C=O), 1551 (NO).

The spectral data were consistent with literature values.[18]



2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester **26.**

This was prepared according to the procedure described for compound **16** using dimethyl malonate (5 mmol) and 2-cylohexen-1-one (5 mmol). The crude product mixture consisted of dimethyl malonate SM, cyclohexenone and product in the ratio 6:2:92 (measured by GC-MS). The residual SM was removed by bulb to bulb distillation at 1.0 mm Hg and 50-80°C to afford a yellow oil. ^{1}H and ^{13}C NMR spectroscopy of the yellow oil showed the presence of an impurity. This mixture was then purified by column chromatography silica gel, using (petrol:Et_2O, 30:70) as an eluent affording the compound **26** (0.70 g, 61% yield) as a pale-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 – 3.67 (m, 6H, 2 x O*CH*$_3$), 3.33 – 3.24 (m, 1H, $(COOMe)_2$*CH*), 2.48 (ddt, *J* = 11.6, 7.8, 3.9 Hz, 1H, *CH*CH_2CO), 2.42 – 2.28 (m, 2H, 2 x cyclohexyl-*H*), 2.28 – 2.15 (m, 2H, 2 x cyclohexyl-*H*), 2.03 (ddd, *J* = 12.7, 6.4, 3.0 Hz, 1H, 1 x cyclohexyl-*H*), 1.95 – 1.81 (m, 1H, 1 x cyclohexyl-*H*), 1.77 – 1.54 (m, 1H, 1 x cyclohexyl-*H*), 1.53 – 1.34 (m, 1H, 1 x cyclohexyl-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6 (*C*O), 168.2(*C*OOMe), 56.7 (*C*H), 52.7 (*C*H), 45.1, 41.0, 38.2, 28.8, 24.6; IR: υ_{max} /cm^{-1}:1730. The spectral data were consistent with literature values.[19]



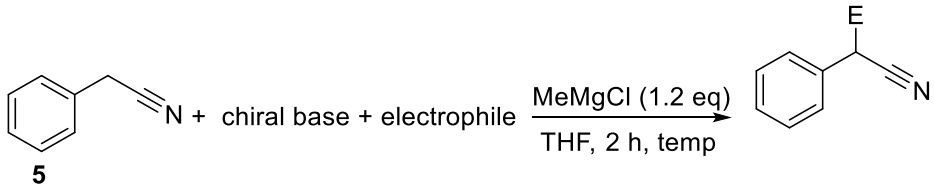
Ethyl 2-acetyl-4-nitro-3-phenylbutyrate **27.**

This was prepared according to the procedure described for compound **16** using ethyl acetoacetate (1 mmol) as the nucleophilic species and *trans*-*β*-nitrostyrene (1 mmol) as the electrophilic species. The crude product mixture consisted of nitrostyrene SM and product **27** in the ratio 23:77 [33:44 mixture of diastereomers] (measured by GC-MS). The crude mixture was purified by column chromatography on silica gel, using petrol:Et_2O (70:30) as an eluent affording the title compound **27** as a brown oil (0.15 g, 54% yield). The compound consisted of a mixture of diastereomers in the ratio A:B (48:52) established by ^{1}H NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$): 7.48 – 7.12 (m, 5H, Ar-*H*, both diastereomers), 4.87 – 4.78 (m, 2H, C*H*$_2$NO$_2$ for B), 4.74 (d, *J* = 6.1 Hz, 2H, C*H*$_2$NO$_2$ for A), 4.30 – 4.08 (m, 5H, OC*H*$_2$CH$_3$, *CH*CO for B and 2 x C*H*Ph both diastereomers), 4.04 – 3.91 (m, 3H, OC*H*$_2$CH$_3$ and *CH*CO for A), 2.29 (s, 1.5H, C*H*$_3$ for B), 2.04 (s, 1.5H, C*H*$_3$ for A), 1.27 (t, *J* = 7.1 Hz, 1.5H, OCH$_2$*CH*$_3$ for A), 0.99 (t, *J* = 7.1 Hz, 1.5H, OCH$_2$*CH*$_3$ for B); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 201.3 (*C*O) for A, 200.5 (*C*O) for B, 167.6 (*C*OOEt) for A, 167.0 (*C*OOEt) for B, 136.5 (Ar*C*) for A, 136.4 (Ar*C*) for B, 129.3 (Ar*C*H) for A, 129.0 (Ar*C*H) for B, 128.5 (Ar*C*H) for A, 128.4 (Ar*C*H) for B, 128.1 (Ar*C*H) for A, 128.0 (Ar*C*H) for B, 78.0 (*C*H$_2$NO$_2$) for B, 77.9 (*C*H$_2$NO$_2$) for A, 62.3 (O*C*H$_2$) for B, 62.1 (O*C*H$_2$) for A, 61.8 (CO*C*H) for A and B, 42.6 (*C*HPh) for A, 42.4 (*C*HPh) for B, 30.4 (*C*H) for B, 30.2 (*C*H) for A, 14.1 (*C*H$_3$) for B, 13.8 (*C*H$_3$) for A; IR: υ_{max} /cm^{-1}: 1738 (C=O), 1716 (C=O), 1552 (NO). The spectral data were consistent with literature values.[20]

3.2.3 Attempted asymmetric alkylation reactions

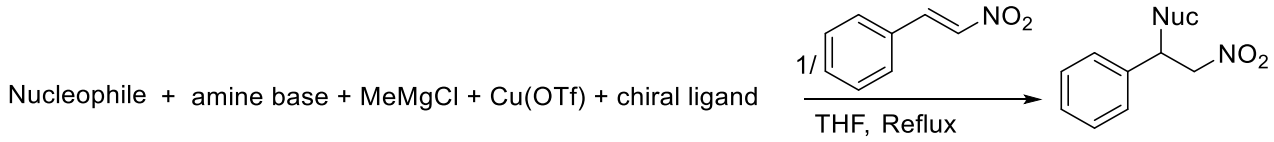
General Procedure 1



5

To a stirring solution of nitrile **5** (2.5 mmol) in anhydrous THF (10 mL) was added chiral base **28a** or **28b** (0.125 mmol) and electrophile (2.5 mmol). MeMgCl (3 M in THF, 3 mmol) was added dropwise at rt over a minute and the reaction was left to stir for 2 h at a given temperature. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The enantiomeric excess was determined without purification using HPLC with a Lux i-Cellulose-3 or Lux i-Cellulose-5 (250 x 4.6 mm) column. In all cases, the chromatograms of the products were compared against the known purified racemic mixture.

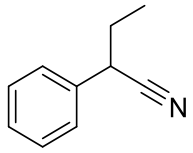
General Procedure 2



To a stirring solution of nucleophile (2.5 mmol) in anhydrous THF (10 mL) was added diethylamine or chiral base **28b** (0.125 mmol).

$Cu^{II}(OTf)_2$ (1 mol%) and 2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline **L0-1** (1 mol %) were added and the reaction mixture was stirred for 20 minutes before the addition of MeMgCl (3 M in THF, 3 mmol) dropwise at rt over a minute. The mixture was then stirred for 1.5 h at rt. After 1.5 h *trans-β*-nitrosytrene (2.5 mmol) was added and the reaction temperature was raised to reflux and maintained at reflux for a further 2 h.

The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The enantiomeric excess was determined without purification using HPLC with a Lux i-cellulose-5 (250 x 4.6 mm) column. In all cases, the chromatograms of the products were compared against the known purified racemic mixture.



2-Phenylbutyronitrile **6b**

This was prepared according to General Procedure 1 using phenylacetonitrile **5** (2.5 mmol), *(S)*-1-phenyl-*N*-((thiophen-2-yl)methyl)ethanamine **28a** (0.125 mmol) and iodoethane (2.5 mmol) at rt. The crude product mixture consisted of SM, mono- and dialkylated product in the ratio 3:95:2 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **6b** was consistent with that obtained for the racemic product.

The enantiomeric excess of **6b** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 7.2 min and 8.9 min, 0% ee.

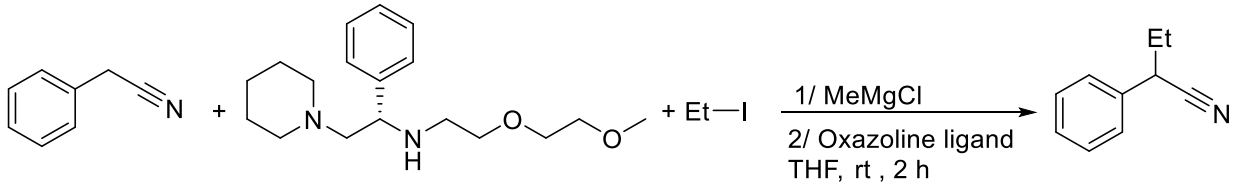
Variation of conditions used for the preparation of **6b**.

This was prepared according to General Procedure 1 using 1R-*N*-[2-(2-methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b**.

The enantiomeric excess of **6b** was determined on a chiral HPLC, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm.

Entry	Temperature	% Conversion SM: Mono:Dialkylation	% ee
1	Reflux	1:98:1	1
2	25 °C	3:96:1	8
3	0 °C	2:97:1	5
4	-78 °C	90:10:0	0

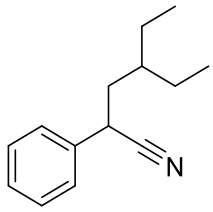
Preparation of **6b** using chiral base **28b** and bis-oxazoline ligand **L-01**



To a stirring solution of phenylacetonitrile (2.5 mmol) in anhydrous THF (10 mL) was added chiral base **28b** (0.125 mmol) and iodoethane (2.5 mmol). MeMgCl (3 M in THF, 3 mmol) was added dropwise at rt over a minute followed by the addition of 2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline (1 mol %) **L-01**. The reaction was then left to stir for 2 h at rt.

The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of mono- and dialkylated product in the ratio 98:2 (measured by GC-MS).

The enantiomeric excess of **6b** was determined without further purification on a chiral HPLC, using Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 7.1 min and 8.7 min, 0% ee.



4-Ethyl-2-phenylhexanenitrile **6c**.

This was prepared according to General Procedure 1 using phenylacetonitrile **5** (7.5 mmol), *(S)*-1-phenyl-N-((thiophen-2-yl)methyl)ethanamine **28a** (0.375 mmol) and 1-bromo-2-ethylbutane (7.5 mmol). A crude mixture of SM, mono- and dialkylated product was present in the ratio 9:87:4 (measured by GC-MS) in the crude product mixture. The ^{1}H NMR spectrum of the crude product **6c** was consistent with that obtained for the racemic product.

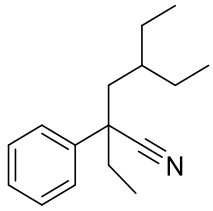
The enantiomeric excess of **6c** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 12.4 min and 14.5 min, 0% ee.

Variation of conditions used for the preparation of **6c**

This was prepared according to General Procedure 1 using 1R-*N*-[2-(2methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b**.

The enantiomeric excess of **6c** was determined on a chiral HPLC, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm.

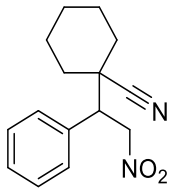
Entry	**Temperature**	**% Conversion (SM: Mono: Dialkylation)**	**% ee**
1	Reflux	13:82:5	0
2	25 °C	6:90:4	0
3	0 °C	40:60:0	8



2,4-Diethyl-2-phenylhexanenitrile **7e**.

This was prepared according to General Procedure 1 using 4-ethyl-2-phenylhexanenitrile **6c** (5.05 mmol), *(S)*-1-phenyl-*N*-((thiophen-2-yl)methyl)ethanamine **28a** (0.25 mmol) and iodoethane (0.4 mL, 5 mmol). The crude product mixture consisted of SM **6c** and product **7e** in the ratio 9:91 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **7e** was consistent with that obtained for the racemic product.

The enantiomeric excess of **7e** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column (100 x 4.6 mm) with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 5.4 min and 6.4 min, 0% ee.



1-(2-Nitro-1-phenylethyl)-cyclohexanecarbonitrile **21.**

To a stirring solution of cyclohexanecarbonitrile (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol).

$Cu^{II}(OTf)_2$ (1 mol%) and 2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline **L0-1** (1 mol %) were added and the reaction mixture was stirred for 20 minutes before the addition of MeMgCl (3 M in THF, 3 mmol) dropwise at rt over a minute. The mixture was then stirred for 1.5 h at rt. After 1.5 h *trans-β*-nitrosytrene (0.37 g, 2.5 mmol) was added and the reaction temperature was raised to reflux and maintained at reflux for a further 2 h.

The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of nitrile **1**, acetylcyclohexane, *trans-β*-nitrosytrene, and product **21** in the ratio 9:28:41:22 (measured by GC-MS).

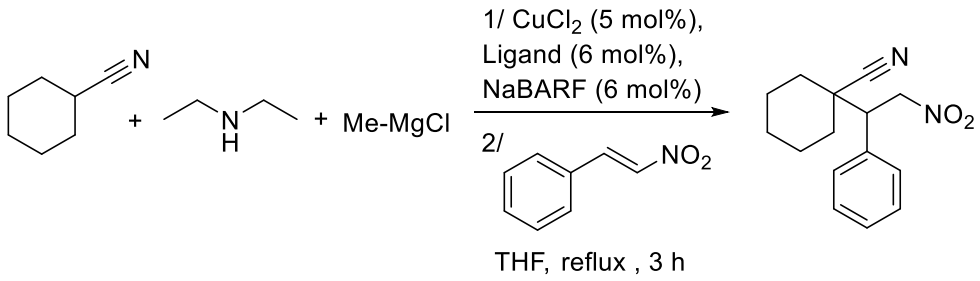
The ^{1}H NMR spectrum of the crude product **21** was consistent with that obtained for the racemic product. The enantiomeric excess of **21** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-5 column with hexane/EtOH = 80/20,

flow = 1.5 mL/min and detected at UV wavelength 205 nm. Retention times 5.1 min and 5.6 min, 0% ee.

Preparation of **21** using chiral base **28b**, $Cu^{ii}(OTf)_2$ and bis-oxazoline ligand **L-01**.

This was prepared according to General Procedure 2 using cyclohexanecarbonitrile (2.5 mmol), chiral base **28b** (0.125mmol) and *trans*-β-nitrostyrene (2.5 mmol). The crude product mixture consisted of nitrile **1**, acetylcyclohexane, *trans*-β-nitrostyrene, and product **21** in the ratio 19:23:56:2 (measured by GC-MS). As the conversion of the product was very low, the enantiomeric excess of **21** was not determined.

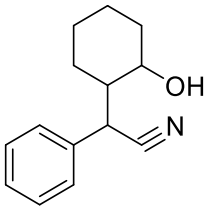
Preparation of **21** using NaBARF and bis-oxazoline ligand **L-01**.



To a stirring solution of cyclohexanecarbonitrile **1** (2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (0.125 mmol).

$Cu(Cl)_2$ (5 mol%), 2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline **L-01** (6 mol %) and NaBARF (6 mol%) were added and the reaction was stirred for 20 min before the addition of MeMgCl (3 M in THF, 3 mmol) dropwise at rt over a minute. The reaction mixture was stirred for 1.5 h at rt. *trans*-β-nitrostyrene (2.5 mmol) was then added after 1.5 h and the reaction temperature was raised to reflux and maintained at reflux for a further 2 h. The reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated and washed with H_2O (2 x 15 mL) and then brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product. The crude product mixture consisted of nitrile **1**, acetylcyclohexane, *trans*-β-nitrostyrene, unknown and product in the ratio 15:2:47:10:36 (measured by GC-MS).

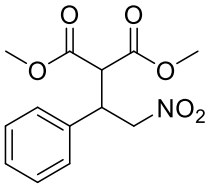
The enantiomeric excess of **21** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-5 column with hexane/EtOH = 80/20, flow = 1.5 mL/min and detected at UV wavelength 205 nm. Retention times 5.1 min and 5.6 min, 0% ee.



2-(2-Hydroxycyclohexyl)-phenyl-acetonitrile **22.**

This was prepared according to General Procedure 1 using phenylacetonitrile **5** (2.5 mmol), *(S)*-1-phenyl-N-((thiophen-2-yl)methyl)ethanamine **28a** (0.125 mmol) and cyclohexene oxide (2.5 mmol). The crude product mixture consisted of SM **5** and product **22** in the ratio 8:92 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **22** was consistent with that obtained for the racemic product.

The enantiomeric excess of **22** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-5 column with Hexane/EtOH = 80/20, flow = 1.5 mL/min and detected at UV wavelength 205 nm. Retention times 3.2 min and 3.4 min, d.r 90:10, 2% ee.



Dimethyl 2-(2-nitro-1-phenylethyl)-malonate **25.**

This was prepared according to General Procedure 1 using dimethyl malonate (2.5 mmol), 1R-*(S)*-1-phenyl-*N*-((thiophen-2-yl)methyl)ethanamine **28a** (0.125mmol) and *trans*-β-nitrostyrene (2.5 mmol). The crude product mixture consisted of dimethyl malonate SM and product **25** in the ratio 4:96 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **25** was consistent with that obtained for the racemic product.

The enantiomeric excess of **25** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-5 column with Hexane/EtOH = 80/20, flow = 1.5 mL/min and detected at UV wavelength 205 nm. Retention times 4.6 min and 5.1 min, 2% ee.

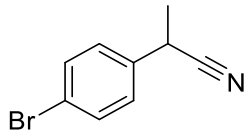
The variation of solvent to toluene and the use chiral base **28b** had no effect on the ee% achieved in the reactions with 2% ee obtained in both cases.

Variation of conditions used for the preparation of **25**

This was prepared according to General Procedure 2.

The enantiomeric excess of **25** was determined on a chiral HPLC, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 4.6 min and 5.1 min.

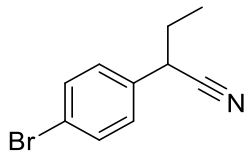
Entry	Base	% Conversion (SM:Pdt)	% ee
1	Diethylamine	0:100	6
2	Chiral base **28b**	0:100	4



2-(4-Bromophenyl)-propionitrile **33a**.

This was prepared according to the General Procedure 1 using 4-bromophenylacetonitrile (2.5 mmol), 1R-*N*-[2-(2-methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b** and iodomethane (2.5 mmol). The crude product mixture consisted of SM, mono- and dialkylated product in the ratio of 11:82:7 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **33a** was consistent with that obtained for the racemic product.

The enantiomeric excess of **33a** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 9.3 min and 10.2 min, 0% ee.



2-(4-Bromophenyl)-butyronitrile **33b**.

This was prepared according to the General Procedure 1 using 4-bromophenylacetonitrile (2.5 mmol), 1R-*N*-[2-(2-methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b** (0.125 mmol) and iodoethane (2.5 mmol) at rt. The crude product mixture consisted of mono- and dialkylated product in the ratio of 92:8 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **33b** was consistent with that of the racemic product.

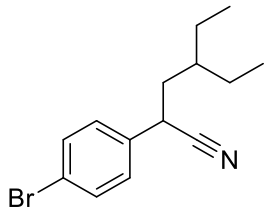
The enantiomeric excess of **33b** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 7.6 min and 7.9 min, 0% ee.

Variation of conditions used for the preparation of **33b**

This was prepared according to General Procedure 1 using 1R-*N*-[2-(2 -methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b**.

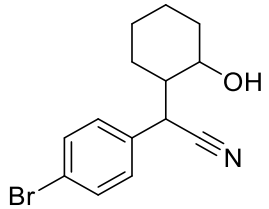
The enantiomeric excess of **33b** was determined on a chiral HPLC, using a Lux i-Cellulose-3 column with H_2O/ACN =50/50, flow= 1 mL/min and detected at UV wavelength 205 nm.

Entry	Temperature	% Conversion (Mono: Dialkylation)	% ee
1	Reflux	90:10	0
2	25 °C	92:8	0
3	0 °C	74:26	2



2-(4'-Bromophenyl)-4-ethylhexanenitrile **33c**.

This was prepared according to General Procedure 1 using 4-bromophenylacetonitrile (2.5 mmol), 1R-*N*-[2-(2-methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b** (0.125 mmol) and 1-bromo-2-ethylbutane (2.5 mmol). The crude product mixture consisted of mono- and dialkylated product in the ratio of 78:22 (measured by GC-MS). The ^{1}H NMR spectrum of the crude product **33c** was consistent with that obtained for the racemic product. The enantiomeric excess of **33c** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 20.0 min and 21.5 min, 0% ee.



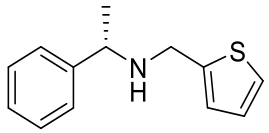
2-(4'-Bromophenyl)-2-(2'-hydroxycyclohexyl)-acetonitrile **33d.**

This was prepared according to the General Procedure 1 using 4-bromophenylacetonitrile (2.5 mmol), 1R-*N*-[2-(2-methoxyethoxy)ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b** (0.125 mmol) and cyclohexene oxide (2.5 mmol). The reaction gave title compound **33d**

(>99% pure GC-MS). The ^{1}H NMR spectrum of the crude product **33d** was consistent with that obtained for the racemic product.

The enantiomeric excess of **33d** was determined on a chiral HPLC without further purification, using a Lux i-Cellulose-3 column with H_2O/ACN = 50/50, flow = 1 mL/min and detected at UV wavelength 205 nm. Retention times 6.7 min and 7.0 min, d.r 90:10, 4% ee.

3.3 Synthesis of chiral amine bases



(1*S*)-1-Phenyl-*N*-(thiophen-2-yl) methyl)ethanamine **28a.**

Preparation of **28a** by amidation of ester using MeMgCl followed by reduction.

To a stirring solution of methyl thiophene-2-carboxylate (5.8 mL, 50 mmol) in anhydrous THF (30 mL) was added *(S)*-(-)-alpha-methylbenzylamine (7.7 mL, 60 mmol), the reaction mixture was heated to 40°C before the addition of MeMgCl (33.3 mL, 100 mmol) dropwise and the mixture temperature was raised to reflux. The mixture was then stirred for a further 2 h at reflux at which time there was 74% conversion (measured by GC-MS). The reaction mixture was left to cool to room temperature then quenched with 1 M HCl (20 mL) followed by the addition of Et_2O (20 mL). The resulting solution was washed with H_2O (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the amide. The unpurified amide was dissolved in anhydrous Et_2O (50 mL) and cooled to 0 °C under N_2. $LiAlH_4$ (1.05 eq., 52.5 mmol, 2.1 g) was then added portion-wise over 15 min. The resulting mixture was left to warm to room temperature over 2 h and then stirred for 48 h before quenching in the following manner: (i) H_2O (2.1 mL) and stirring for 15 min; (ii) 15% NaOH solution (2.1 mL) and stirring for 15 min and; (iii) H_2O (6.3 mL) and stirring for 30 min. The mixture was then filtered, and the filtrate concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of ester SM, amine SM and product in the ratio 10:15:75 (measured by GC-MS). The starting materials were removed *via* bulb to bulb distillation at 70 °C and 2 mm Hg affording the title compound **28a** (6.1 g, 55% yield) as a pale yellow oil; $[\alpha]_D^{20}$ – 49° (c 0.001 in MeOH), [lit[31],– 61.4° (c 1.5, $CHCl_3$)];

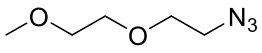
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.39 – 7.31 (m, 4H, Ar-*H*), 7.31 – 7.22 (m, 1H, Ar-*H*), 7.21 – 7.18 (m, 1H, Ar*H* on thiophene ring), 6.96 – 6.91 (m, 1H, ArC*H* on thiophene ring), 6.88 – 6.84 (m, 1H, CH on thiophene ring), 3.85 – 3.67 (m, 3H, C*H*CH_3 and NHC*H*$_2$), 1.67 (br s, 1H, N*H*), 1.37 (d, 3H, *J* = 6.6 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 145.3 (Ar*C*), 144.5 (ArC), 128.6 (Ar*C*H), 127.1 (Ar*C*H), 126.8 (Ar*C*H), 126.7 (Ar*C*H), 124.8 (Ar*C*H), 124.3 (Ar*C*H), 57.1 (*C*H), 46.1 (*C*H_2), 24.5 (*C*H_3); IR: υ_{max} (neat)/cm^{-1}: 3062 (NH), 1602.

The spectral data were consistent with literature values.[31]

Preparation of **28a** by reductive amidation of 2-thiophenecarboxyaldehyde.

To a stirring solution of 2-thiophenecarboxyaldehyde (4.7 mL, 50 mmol) in anhydrous Et_2O (30 mL) was added $MgSO_4$ (5 g). The reaction temperature was reduced to 0°C before the addition of *(S)*-(-)-alpha-methylbenzylamine (6.4 mL, 50 mmol) and $MgSO_4$ (5 g). The reaction mixture was then allowed warm to room temperature then stirred for 16 h at rt.

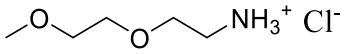
The reaction did not reach completion (88 % conversion by GC-MS) but the solid was removed by filtration and the filtrate was concentrated *in vacuo* to afford the imine which was used without further purification. The imine was dissolved in anhydrous Et_2O (80 ml) and cooled to 0 °C under N_2. $LiAlH_4$ (1.05 eq., 52.5 mmol, 2.1 g) was then added portion-wise over 15 min. The resulting mixture was allowed to warm to room temperature over 2 h and then stirred for 48 h at rt before quenching in the following manner: (i) H_2O (2.1 mL) and stirring for 15 min; (ii) 15% NaOH solution (2.1 mL) and stirring for 15 min and; (iii) H_2O (6.3 mL) and stirring for 30 min. The mixture was then filtered, and the filtrate concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of aldehyde SM, amine SM and product in the ratio 5:4:91 (measured by GC-MS). The starting materials were removed *via* bulb to bulb distillation at 60 °C and 1 mm Hg affording the purified product **28a** as a pale-yellow oil (7.05 g, 65% yield). The spectral data were consistent with that described for **28a** above.



1-(2-Azido-ethoxy)-2-methoxyethane **28aa.**

To a stirring solution of 2-(2-methoxyethoxyl)ethanol (7.2 mL, 60 mmol) in anhydrous DCM (70 mL) at 0 °C was added trimethylamine (16.7 mL, 120 mmol). Methanesulfonyl chloride (5.6 mL, 72 mmol) was then added dropwise and the mixture was stirred for 4 h at rt.

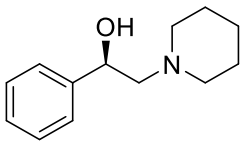
H_2O (50 mL) was added and the two layers were separated. The aqueous layer was extracted with DCM (2 x 50 mL) and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The impure mesylate was dissolved in DMF (200 mL) then sodium azide (4.68 g, 72 mmol) was added and the reaction temperature was raised to reflux and maintained for 16 h at reflux. Upon cooling, Et_2O (200 mL) was added along with saturated brine (150 mL) and the heterogeneous mixture was stirred vigorously for 1 h. The phases were separated. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the azide **28aa** (7.63 g, 88% yield) which was used immediately with purification. IR: υ_{max} (neat)/cm^{-1}: 2100 (N_3)



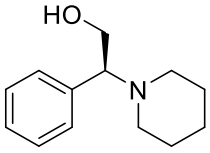
2-(2-Methoxyethoxy)ethylammonium chloride **28ab.**

To a stirring solution of the azide **28ab** (7.22 g, 49.7 mmol) in anhydrous THF at rt was added triphenylphosphine (15.54 g, 59.2 mmol). The reaction was stirred for 2 h before the addition of H_2O (150 mL). The reaction mixture was raised to reflux and maintained at reflux for 16 h. Upon cooling, 2 M HCl (240 mL) along with DCM (100 ml) was added and the mixture was stirred for 5 min before separating. The aqueous layer was extracted with DCM (3 x 100 mL). The aqueous layer was concentrated *in vacuo* and the crude product was dissolved in methanol (3 x 15 mL) which was removed under vacuum to remove any remaining water. The title compound **28ab** (7.02 g, 93% yield) was afforded as a yellow oil. ^{1}H NMR spectroscopy showed broad peaks due to the protonated amine.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 3H, NH_3^+), 3.80 (t, J = 4.4 Hz, 2H, $OCH_2CH_2NH_3^+Cl^-$), 3.65 (dd, J = 5.2, 2.9 Hz, 2H, 1H of OCH_2CH_2O and 1H of OCH_2CH_2O), 3.55 (dd, J = 5.2, 2.8 Hz, 2H, 1H of OCH_2CH_2O and 1H of OCH_2CH_2O), 3.35 (s, 3H, OCH_3), 3.27 (t, J = 4.4 Hz, 2H, $CH_2NH_3^+$ Cl^-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.7 (OCH_2CH_2O), 70.1 (OCH_2CH_2O), 66.8 ($OCH_2CH_2NH_3^+Cl^-$), 58.9 (OCH_3), 39.8 ($CH_2NH_3^+Cl^-$); IR: υ_{max} (neat)/cm^{-1}: 2876 (br s, NH_3^+). The spectral data were consistent with literature values.[33]



R-28ac



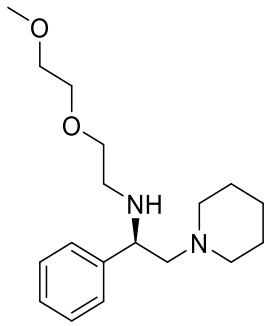
S-28ad

(1*R*)-1-Phenyl-2-piperidinylethanol **28ac** and (2*S*)-2-Phenyl-2-piperidinylethanol **28ad**

To a stirring solution of *R*-styrene oxide (2.4 mL, 21 mmol) in methanol at rt was added piperidine (3.4 mL, 34 mmol). The reaction mixture was raised to reflux and maintained at reflux for 12 h. Upon cooling, the solvent was removed *in vacuo*. Unreacted starting material was removed *via* bulb to bulb distillation at 100 °C and 1 mmHg leaving the regioisomeric mixture ***R*-28ac** and ***S*-28ad** in the ratio 66:33 respectively by ^{1}H NMR spectroscopy (4.04 g, 94% combined isolated yield) as a light-yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.02 (m, 10H, Ar-*H*), 4.72 (dd, J = 10.6, 3.5 Hz, 1H, PhC*H*CH_2 of *(R)*-28ac), 3.98 (t, J = 10.1 Hz, 1H, PhC*H*CH_2 of *(S)*-28ad), 3.69 (dd, J = 10.3, 5.2 Hz 1H, PhCHC*H*$_2$ of *(S)*-28ad), 3.60 (dd, J = 10.3, 5.2 Hz, 1H, PhCHC*H*$_2$ of *(S)*-28ad), 2.85 (br s, 1H, 1 x piperidinyl-*H*), 2.69 (br s, 2H, 2 x piperidinyl-*H*), 2.56 (br s, 1H,

1 x piperidinyl-H), 2.48 (dd, *J* = 12.5, 3.6 Hz, 1H, PhCHC*H*$_2$ of *(R)*-28ac), 2.44 – 2.32 (m, 4H, 1H of PhCHC*H*$_2$ and 3 x piperidinyl-*H*), 2.25 (br s, 1H, 1 x piperidinyl-*H*), 1.76- 1.23 (m, 12H, 8 x piperidinyl-*H*, 3 x piperidinyl-*H*, 1 x piperidinyl-H for both *(R)*-28ac and *(S)*-28ad); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 142.5 (Ar*C*), 129.1 (Ar*C*H), 128.4 (Ar*C*H),128.2 (Ar*C*H), 127.9 (Ar*C*H), 127.5 (Ar*C*H), 125.9 (Ar*C*H), 70.4 (Ph*C*H) of *(S)*-28ad, 68.7(Ph*C*H) of *(R)*-28ac, 67.0 (PhCH*C*H$_2$N) of *(R)*-28ac, 59.9 (PhCH*C*H$_2$OH) of *(S)*-28ad, 54.6 (4 x N*C*H$_2$CH$_2$) of *(R)*-28ac and *(S)*-28ad, 26.6 (NCH$_2$*C*H$_2$) of *(S)*-28ad, 26.2 (NCH$_2$*C*H$_2$) of *(R)*-28ac, 24.5 (NCH$_2$CH$_2$)$_2$*C*H$_2$) *(S)*-28ad, 24.4 (NCH$_2$CH$_2$)$_2$*C*H$_2$) of *(R)*-28ac; IR: υ_{max} (neat)/cm^{-1}: 3250, 1448. The spectral data were consistent with literature values.[33]



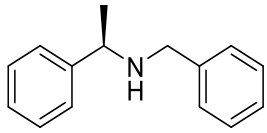
1*R*-*N*-[2-(2-Methoxyethoxy) ethyl]-1-phenyl-2-(1-piperidinyl)ethanamine **28b.**

To a stirring solution of the regioisomeric mixture of *R*-28ac and *S*-28ad (3.7 g, 18 mmol) in anhydrous THF (150 mL) at rt was added triethylamine (4 mL, 29 mmol). The reaction was cooled to 0°C before methanesulfonyl chloride (1.7 mL, 22 mmol) was added dropwise. The reaction was then stirred at 0°C for 40 min (formation of a sticky white precipitate). The solvent was removed *in vacuo* and triethylamine (5 mL, 36 mmol) was added and the reaction was stirred vigorously. A 1:1 mixture of 2-(2-methoxyethoxy)ethylamine hydrochloride (2.8 g, 18 mmol) and triethylamine (2.5 mL, 18 mmol) along with H_2O (100 mL) was added and the mixture was stirred for 30 min. THF (100 mL) was added and the heterogeneous mixture was stirred vigorously for 16 h at rt. The two layers were separated, and the aqueous layer was extracted with DCM (2 x 100 mL). The combined organic layer was dried, filtered and concentrated *in vacuo* to afford the crude product. The crude product was purified *via* bulb to bulb distillation at 190°C and 1.0 mm Hg affording a yellow oil (3.91g, 70% yield). $[\alpha]_D^{23}$ – 22° (c 0.001 in MeOH), [lit[34]., - 70° (c 2.01, benzene)];

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.47 – 7.12 (m, 5H, Ar-*H*), 3.76 (dd, *J* = 11.0, 3.5 Hz, 1H, PhC*H*NH), 3.64 – 3.41 (m, 6H, OC*H*$_2$C*H*$_2$O and OC*H*$_2$CH$_2$NH), 3.37 (s, 3H, OCH_3), 2.89 (br s, 1H, NH), 2.75 – 2.35 (m, 4H, OCH$_2$C*H*$_2$NH, NCH$_2$ and 1H of PhCHC*H*$_2$), 2.32 – 2.20 (br dd, *J* = 12.3, 3.7 Hz, 2H, 1H of PhCHC*H*$_2$ and NC*H*$_2$), 1.64 – 1.29 (m, 6H, *C*H$_2$CH$_2$NCH$_2$C*H*$_2$ and N(CH$_2$CH$_2$)$_2$C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 143.0 (Ar*C*), 128.4 (Ar*C*H), 127.5 (Ar*C*H),

127.1 (Ar*C*H), 72.1 (OCH_2CH_2O), 70.7 (OCH_2CH_2O), 70.3 (OCH_2CH_2NH), 66.5 ($PhCHCH_2N$), 59.9 ($PhCHCH_2N$), 59.2 (OCH_3), 54.6 (4 x NCH_2), 47.1 (OCH_2CH_2NH), 26.2 (NCH_2CH_2), 24.6 $(NCH_2CH_2)_2CH_2$; IR: υ_{max} (neat)/cm^{-1}: 3416 (br NH), 2934.

The spectral data were consistent with literature values. [33,34]



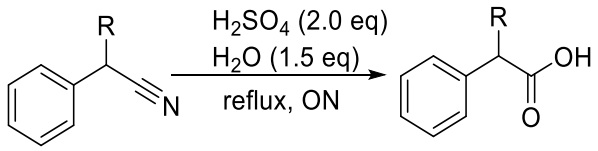
(R)-N-Benzyl-1-phenylethanamine **28c.**

To a stirring solution of methyl benzoate **39a** (3.8 mL, 50 mmol) in anhydrous THF (20 mL) was added *(R)*-(-)-alpha-methylbenzylamine (7.7 mL, 60 mmol), the reaction mixture was heated to 40°C before the addition of MeMgCl (33.3 mL, 100 mmol) dropwise and the mixture was raised to reflux. The mixture was then stirred for a further 2 h at reflux at which time there was 80% conversion (measured by GC-MS). The reaction mixture was allowed to cool to rt then quenched with 1 M HCl (20 mL) followed by the addition of Et_2O (20 mL). The resulting solution was washed with H_2O (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the amide. The unpurified amide was dissolved in anhydrous Et_2O and cooled to 0 °C under N_2. $LiAlH_4$ (1.05 eq., 52.5 mmol, 2.1 g) was then added portion-wise over 15 min. The resulting mixture was allowed to warm to room temperature over 2 h and then stirred for 48 h before quenching in the following manner: (i) H_2O (2.1 mL) and stirring for 15 min; (ii) 15% NaOH solution (2.1 mL) and stirring for 15 min and; (iii) H_2O (6.3 mL) and stirring for 30 min. The mixture was then filtered, and the filtrate concentrated to afford the crude product. The crude product mixture consisted of ester SM **39a**, amine SM and product **28c** in the ratio 10:9:81 (measured by GC-MS). Unreacted starting material was removed by bulb to bulb distillation at 70 °C and 1.0 mm Hg affording the title compound **28c** (7.28 g, 69% yield) as a brown oil; $[\alpha]_D^{23}$ + 54.5° (c 0.001, MeOH), [lit[32]., + 59.1° (c 1.2, EtOH)];

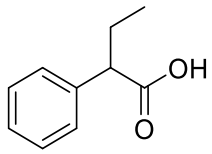
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.18 (m, 10H, Ar-*H*), 3.83 (q, *J* = 6.6 Hz, 1H, C*H*CH_3), 3.73 – 3.52 (m, 2H, NHC*H*$_2$), 1.63 (br s, 1H, N*H*), 1.39 (d, *J* = 6.6 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7 (Ar*C*), 140.8 (Ar*C*), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.2 (Ar*C*H), 127.0 (Ar*C*H), 127.0 (Ar*C*H), 126.8 (Ar*C*H), 57.6 (*C*H), 51.8 (CH_2), 24.6 (CH_3). The spectral data were consistent with literature values.[32]

3.4 Hydrolysis of nitriles

General procedure for hydrolysis of nitriles.



To a solution of H_2O (1.5 eq) was added H_2SO_4 (2 eq). The mixture was heated to 50 °C with stirring before the addition of nitrile (1 eq). The reaction mixture was raised to 110 °C and maintained at 110 °C overnight. Upon cooling, the mixture was dissolved in Et_2O (10 mL). The ether was extracted with 1 M NaOH (5 mL) and the aqueous extract was acidified with concentrated HCl. The acidified aqueous was extracted with Et_2O and the ether layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the acid.

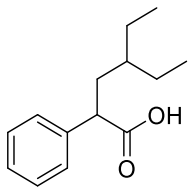


2-Phenylbutyric acid **29b.**

This was prepared from nitrile **6b** (5.3 mmol), according to the general procedure for the hydrolysis for nitriles. The reaction afforded the acid **29b** (0.19g, 22% yield, 98% purity by GC-MS) as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (br s, 1H, O*H*), 7.49 – 7.03 (m, 5H, Ar-*H*), 3.44 (t, *J* = 7.6 Hz, 1H, C*H*), 2.20 – 2.01 (m, 1H, 1H of CHCH_2CH$_3$), 1.91 – 1.73 (m, 1H, 1H of CHCH_2CH$_3$), 0.91 (td, *J* = 7.4, 2.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2 (*C*OOH), 138.9 (Ar*C*), 128.7 (Ar*C*H), 128.2 (Ar*C*H), 127.4 (Ar*C*H), 53.8 (*C*H), 26.4 (*C*H_2), 12.2 (*C*H_3); IR: υ_{max}/cm^{-1}: 2965, 1705 (C=O).

The spectral data were consistent with literature values.[46]



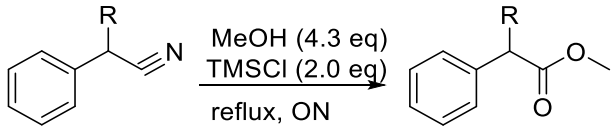
4-Ethyl-2-phenylhexanoic acid **29c**

This was prepared from nitrile **6c** (3.4 mmol), according to the general procedure for the hydrolysis of nitriles. The reaction afforded the acid **29c** (0.19 g, 25% yield, >99% pure GC-MS) as a colourless oil;

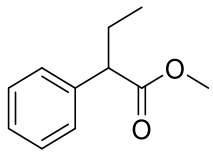
^{1}H NMR (400MHz, $CDCl_3$) δ 7.51 – 7.00 (m, 5H, Ar-*H*), 3.66 (t, *J* = 7.8 Hz, 1H, PhC*H*), 2.01 (p, *J* = 7.4 Hz, 1H of CHCH_2CH), 1.75 (p, *J* = 7.2 Hz, 1H of CHCH_2CH), 1.41-1.24 (m, 4H, 2 x CHCH_2CH$_3$), 1.15 (p, *J* = 6.2 Hz, 1H, C*H*), 0.82 (tt, *J* = 13.2, 7.4 Hz, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9 (*C*OOH), 138.8 (Ar*C*), 128.7 (Ar*C*H), 128.2 (Ar*C*H), 127.5 (Ar*C*H), 49.4 (Ph*C*H), 37.7 (CH_2*C*HCH$_3$), 36.6 (CH*C*H$_2$), 24.9 (*C*H$_2$), 10.5 (*C*H$_3$), 10.4 (*C*H$_3$). IR: υ_{max}/cm^{-1}: 2961, 2924, 1702; HRMS (ESI) *m/z:* Calcd for $C_{15}H_{21}O_2$ [*M*-H$^+$] 233.1542 found 233.1539

3.5 Esterification of nitriles

General procedure for esterification of nitriles.[47]



To a dry reaction vessel (100 mL) under a nitrogen atmosphere at room temperature was added MeOH (4.3 eq), TMSCl (2 eq), and nitrile (1 eq). The reaction mixture was raised to reflux and maintained at reflux overnight. Upon cooling, H_2O (10 mL) was added to the mixture, followed by the addition of Na_2CO_3 and DCM. The organic layer was washed with H_2O (2 x 15 mL) then with brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the ester product.

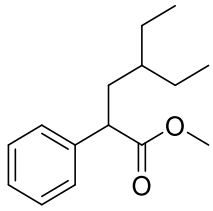


Methyl 2-phenylbutanoate **30b.**

This was prepared from nitrile **6b** (2 mmol) according to the general procedure for the esterification of nitriles. The crude product contained a mixture of nitrile SM **6b** and product **30b** in the ratio 23:77 (by ^{1}H NMR spectroscopy). This mixture proved difficult to separate on column chromatography and therefore the pure product could not be isolated. The nitrile SM **6b** was evident in the ^{1}H NMR spectrum at 1.07 ppm for CH_3 peak, integration of this signal was consistent with the ratio of products measured by GC-MS.

Diagnostic signals for **30b** in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.22 (m, 5H, Ar-*H*), δ 3.65 (s, 3H, OC*H*$_3$), 3.45 (t, *J* = 7.7 Hz, 1H, C*H*), 2.23-1.98 (m, 1H, 1H of CHC*H*$_2$CH$_3$), 1.79 – 1.67 (m, 1H, 1H of CHC*H*$_2$CH$_3$), 0.88 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); diagnostic signals in ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9 (*C*OOMe), 138.9 (Ar*C*), 128.7 (Ar*C*H), 128.0 (Ar*C*H), 127.3 (Ar*C*H), 53.5 (*C*H), 52.0 (O*C*H$_3$), 26.8 (*C*H$_2$), 12.3 (*C*H$_3$); IR: υ_{max}/cm^{-1}: 2994, 2960, 1731 (C=O)

The spectral data were consistent with literature values.[48]



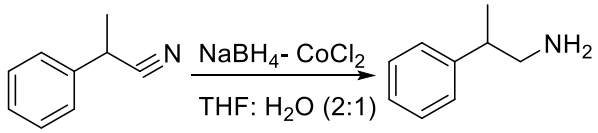
Methyl-4-ethyl-2-phenylhexanoate **30c**

This was prepared from nitrile **6c** (5.4 mmol) according to the general procedure for the esterification of nitriles. The crude product contained a mixture of nitrile SM **6c** and product **30c** in the ratio 25:75 (by ^{1}H NMR spectroscopy). This mixture proved difficult to separate on column chromatography and therefore pure product could not be isolated. The nitrile SM **6c** was evident in the ^{13}C NMR spectrum at 10.1 ppm for the CH_3, this signal was consistent with the ratio of products measured by GC-MS.

Diagnostic signals for **30c** in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.23 (m, 5H, Ar-*H*), 3.73 – 3.54 (m, 4H, OC*H*$_3$ and C*H*Ph), 2.10 – 1.80 (m, 1H, 1H of CHC*H*$_2$CH), 1.77 – 1.60 (m, 1H, 1H of C*H*$_2$, diastereotopic proton), 1.50 – 1.22 (m, 4H, 2 x C*H*$_2$), 1.16 – 0.99 (m, 1H, C*H*CH$_2$CH$_3$), 0.91-0.72 (m, 6H, 2 x C*H*$_3$); diagnostic signals in ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9 (*C*OOMe), 139.6 (Ar*C*), 128.7 (Ar*C*H), 128.1 (Ar*C*H), 127.2 (Ar*C*H), 52.0 (O*C*H$_3$), 49.4 (Ph*C*H), 37.9 (CH$_2$*C*HCH$_3$), 37.0(CH$_2$*C*H), 25.2 (*C*H$_2$), 25.0 (*C*H$_2$), 10.6, (*C*H$_3$), 10.5 (*C*H$_3$); IR: υ_{max}/cm^{-1}: 2976, 2946, 1730 (C=O)

3.6 Nitrile reduction

General Procedure for reduction of nitriles[49]



2-Phenyl-propylamine **31a**

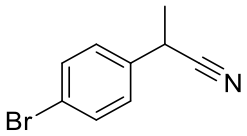
To a solution of THF (20 mL) and H_2O (10 mL) was added $CoCl_2.6H_2O$ (0.1 mol %) and nitrile (0.5046 g, 3.85 mmol, 1 eq). The reaction mixture was stirred vigorously and cooled intermittently with an ice-water bath while $NaBH_4$, (0.30 g, 7.7 mmol, 2 eq) was added in portions over 8 min. The reaction was exothermic, producing a black precipitate and copious quantities of hydrogen. TLC analysis after 50 min indicated traces of starting material, so additional $NaBH_4$, (0.41 g) was added. After a total time of 2 h, 28% NH_4OH solution (2 mL) was added and the mixture transferred to centrifuge tubes. After centrifugation, the supernatant (two liquid phases) was decanted and the sediment washed with more of the same solvent mixture. The combined supernatants were concentrated *in vacuo* to remove the THF, then the aqueous residue was extracted with DCM (4 x 40mL). The combined DCM, layers were dried over $MgSO_4$ and concentrated to afford the amine (20% conversion).

Diagnostic signals for **31a** in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 -7.03 (m, 5H, Ar-*H*), 2.82 (br s, 1H, N*H*$_2$) 2.65 (br s, 1H, 1H of C*H*$_2$), 2.7 (m, 2H, 1H of C*H*$_2$ and C*H*), 1.24 (d, *J* = 6.88 Hz, 3H, C*H*$_3$).

Time variation

The reaction was carried out as in general procedure for the reduction of nitrile except the reaction was left to stir overnight. Analysis of the crude material by GC-MS showed a 33% conversion to the amine.

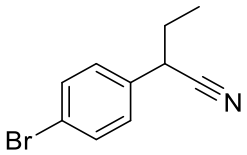
3.7 Alkylation of 4-bromophenylacetonitrile.



2-(4-Bromophenyl)-propionitrile **33a**.

To a stirring solution of 4-bromophenylacetonitrile (0.49 g, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol) and iodomethane (0.15 mL, 2.5 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise at rt over a minute and the mixture was left to stir for 2 h. The crude product mixture consisted of SM, mono- and dialkylated product in the ratio of 10:81:9 (measured by GC-MS). The mixture proved difficult to separate but based on the recovery and crude product ratio it represents 58% crude yield of the product. The SM and dialkylated product were evident in the ^{1}H NMR spectrum at 3.70 and 1.70 ppm and integration of these signals were consistent with the ratio of products measured by GC-MS. Diagnostic signals for **33a** in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.24 (d, J = 8.7 Hz, 2H, Ar-*H*), 3.86 (q, J = 7.3 Hz, 1H, C*H*), 1.62 (d, J = 7.3 Hz, 3H, CH_3); diagnostic signals in ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (Ar*C*), 132.4 (Ar*C*H), 128.5 (Ar*C*H), 122.2 (Ar*C*Br), 121.1 (*C*N), 30.9 (*C*H), 21.4 (*C*H_3); IR: υ_{max} /cm^{-1}: 2984, 2244 (CN), 1593.

The spectral data were consistent with literature values.[5]

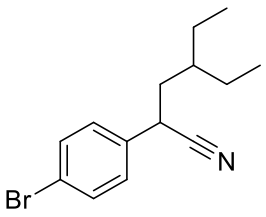


2-(4-Bromophenyl)-butyronitrile **33b**.

This was prepared according to the procedure described for compound **33a** using 4-bromophenylacetonitrile (2.5 mmol) and iodoethane (2.5 mmol).

A mixture of mono- and di-alkylated product was present in the ratio of 90:10 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (PE: Et_2O, 90:10) to afford the product **33b** as a yellow oil (0.39 g, 70% yield);

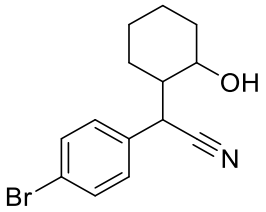
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.19 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 3.70 (t, *J* = 7.3 Hz, 1H, C*H*), 1.91 (p, *J* = 7.3 Hz, 2H, CH_2), 1.06 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8 (Ar*C*), 132.3 (Ar*C*H), 129.1 (Ar*C*H), 122.2 (Ar*C*Br), 120.3 (*C*N), 38.5 (*C*H), 29.2 (*C*H_2), 11.5 (*C*H_3); IR: υ_{max}/cm^{-1}: 2972, 2935, 2241 (CN), 1593; HRMS (ESI) *m/z:* Calcd for $C_{10}H_9NBr$ [M-H^{+}]: 221. 9918 found 221. 9922.



2-(4-Bromophenyl)-4-ethylhexanenitrile **33c**.

This was prepared according to the procedure described for compound **33a** using 4-bromophenylacetonitrile (2.5 mmol) and 1-bromo-2-ethylbutane (2.5 mmol). The crude product mixture consisted of mono- and dialkylated product in the ratio of 79:21 (measured by GC-MS). The crude mixture was purified by column chromatography on silica (petrol: Et_2O, 99:1) to afford the product **33c** (0.35 g, 50% yield) as a clear oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.7 Hz, 2H, Ar-*H*), 7.19 (d, J = 8.7 Hz, 2H, Ar-*H*), 3.75 (dd, J = 9.8, 6.2 Hz, 1H, CCNC*H*), 1.98 – 1.78 (m, 1H of CHC*H*$_2$CH), 1.74 – 1.49 (m, 1H of CHC*H*$_2$CH), 1.45 – 1.24 (m, 5H, C*H*CH$_2$CH$_3$ and 2 x *CH*$_2$CH$_3$), 0.88 – 0.82 (m, 6H, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7 (Ar*C*), 132.3 (Ar*C*H), 129.0 (Ar*C*H), 122.1 (Ar*C*Br), 120.7 (*C*N), 39.8 (Ph*C*H), 38.0 (*C*HCH$_2$CH$_3$), 35.0 (PhCH*C*H$_2$), 25.2 (*C*H$_2$), 24.4 (*C*H$_2$), 10.7 (*C*H$_3$), 10.2 (*C*H$_3$); IR: υ_{max} /cm^{-1}: 2962, 2932, 2242 (CN), 1593; HRMS (ESI) m/*z:* Calcd for $C_{14}H_{17}NBr$ [*M*-H$^+$]: 278.0544 found 278.0546.



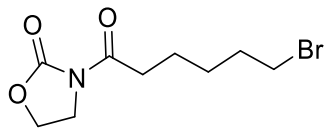
2-(4'-Bromophenyl)-2-(2'-hydroxycyclohexyl)-acetonitrile **33d.**

To a stirring solution of 4-bromophenylacetonitrile (0.49 g, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (14 µL, 0.125 mmol). MeMgCl (1 mL, 3 M in THF, 3 mmol) was added dropwise over a minute. Upon addition of MeMgCl (3 mmol), the temperature rose to 45 °C then returned to rt after 20 min. The reaction mixture was then stirred at rt for 1 hour. Cyclohexene oxide (0.25 mL, 2.5 mmol) was then added and the reaction temperature was raised to reflux and was maintained at reflux for 2 h. The reaction was cooled and quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the alkylated product.

The title compound **33d** (>99% pure GC-MS) (0.63g, 86% yield) was recovered as a yellow oil which solidified. The compound contained a mixture of diastereomers in the ratio A:B

(89:11) measured by ^{1}H NMR spectroscopy and evident in the ^{13}C NMR spectra. mp 105-109 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.49 – 7.41 (m, 2H, Ar-*H* for both diastereomers), 7.25 – 7.02 (m, 2H, Ar-*H* for both diastereomers), 4.63 (d, *J* = 3.3 Hz, 0.9H, *CH*CN for A), 4.52 (d, *J* = 3.5 Hz, 0.1H, *CH*CN for B), 3.59 (td, *J* = 10.0, 4.6 Hz, 0.9H, C*H*OH for A), 2.97 (dt, *J* = 10.4, 5.2 Hz, 0.1H, C*H*OH for B), 2.20 – 1.89 (m, 2H, O*H* and cyclohexyl-*H* for both diastereomers), 1.77 – 0.87 (m, 6.9H, cyclohexyl-*H* (both diastereomers), 0.87 – 0.67 (m, 0.1H, CH_2CHOH for B); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.8 (Ar*C*), 132.1 (Ar*C*H) for A, 131.7 (Ar*C*H) for B, 130.9 (Ar*C*H) for B, 129.5 (Ar*C*H) for A, 121.9 (*C*N), 118.8 (*C*Br), 72.0 (*C*OH) for A, 70.0 (*C*OH) for B, 50.2 (*C*COH) for A, 48.6 (*C*COH) for B, 38.1 (*C*HCN) for A, 37.0 (*C*HCN) for B, 36.1, 26.0, 25.3, 25.0, 24.5; IR: ν_{max}/cm^{-1}: 3299 (br, OH), 2938, 2860, 2239 (CN); HRMS (ESI) *m/z:* Calcd for $C_{14}H_{17}BrNO$ [*M*+H^+]: 294.0494, found 294.0488.

3.8 Intramolecular alkylation

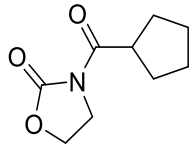


3-(6-Bromohexanoyl)-oxazolidin-2-one **34**.

To a flask containing 2-oxazolidine (0.871 g, 10 mmol, 1 eq), DMAP (0.186 g, 1.5 mmol, 0.15 eq), 6-bromohexanoic acid (2.93 g, 15 mmol, 1.5 eq) and DCM (40 ml) was added DCC (3.1 g, 15 mmol, 1.5 eq). The mixture was stirred overnight at room temperature at which point distilled H_2O (10 mL) was added. The solution was filtered through a silica plug and eluted with Et_2O (50 mL). The filtrate was concentrated *in vacuo*. To the residue was added distilled H_2O which was then extracted with Et_2O (4 x 20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The reaction gave a mixture of product and an unknown compound in the ratio 95:5 (measured by GC-MS). The crude mixture was purified *via* column chromatography on silica (petrol:EtOAc, 70:30) to afford the title compound **34** (1.9 g, 72% yield) as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (t, J = 8.1 Hz, 2H, OCH_2), 3.99 (t, J = 8.3 Hz, 2H, NCH_2), 3.38 (t, J = 6.8 Hz, 2H, CH_2Br), 2.90 (t, J = 7.4 Hz, 2H, CH_2CO), 1.93 – 1.77 (m, 2H, CH_2), 1.70 – 1.62 (m, 2H, CH_2), 1.56 – 1.33 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2 (O*C*ON), 153.7 (*C*ON), 62.2 (O*C*H_2), 42.6 (N*C*H_2), 34.9 (*C*H_2Br), 33.7, 32.5, 27.7, 23.4.

The spectral data were consistent with literature values.[22]

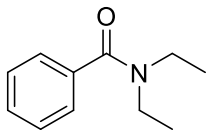


3-(Cyclopentanecarbonyl)-1,3-oxazolidin-one **35.**

To a stirring solution of 3-(6-bromohexanoyl)-oxazolidin-2-one **34** (0.156 g, 0.6 mmol) in anhydrous THF (10 mL) was added diethylamine (0.07 mL, 0.72 mmol) and MeMgCl (0.24 mL, 0.72 mmol) at 0 °C. The mixture was left to stir for 3 h at 0 °C. The reaction was brought to rt before being quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated to afford the ring closed alkylated product. The reaction gave a mixture of SM **34** product **35** and in the ratio 89:11 (measured by GC-MS). This mixture proved difficult to separate on column chromatography and *via* bulb to bulb distillation.

The product was not isolated, and GC-MS was used to assess the product mixture. Diagnostic signals in ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (t, J = 8.1 Hz, 2H, N*C*H$_2$), 1.99 – 1.71 (m, 4H, 2 x *C*H$_2$), 1.70 – 1.54 (m, 4H, 2 x *C*H$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.9 (*C*ON), 153.4 (*C*OON), 62.0 (O*C*H$_2$), 43.0 (N*C*H$_2$). 42.6 (*C*HCO).

3.9 Amide synthesis

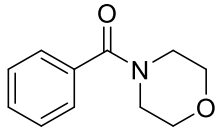


N,N-Diethylbenzamide **41a.**

To a stirred solution of methyl benzoate **39a** (1.9 mL, 15 mmol) in anhydrous THF (15 mL) was added diethylamine (1.6 mL, 15 mmol). MeMgCl (6 mL, 18 mmol) was added dropwise at rt and the mixture left to stir for 2 h at rt at which stage all starting material was consumed (GC-MS monitoring). The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The resulting solution was washed with H_2O (2 x 15 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford amide **41a**. The title compound **41a (**99% pure GC-MS) (2.02 g, 76% yield) was recovered as a brown oil; ^{1}H NMR spectroscopy showed the presence of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (br s, 5H, Ar-*H*), 3.48 (br s, 2H, NCH_2), 3.18 (br s, 2H, NCH_2), 1.18 (br s, 3H, CH_2CH_3), 1.04 (br s, 3H, CH_2CH_3), ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (*C*O), 137.3 (Ar*C*), 129.1 (Ar*C*H), 128.4 (Ar*C*H), 126.2 (Ar*C*H), 43.3 (CH_2), 39.3 (CH_2), 14.2 (CH_3), 12.9 (CH_3); IR: υ_{max} /cm^{-1}: 2973, 2935, 1625 (C=O).

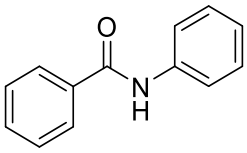
The spectral data were consistent with literature values.[23]



N-Benzoylmorpholine **41b.**

This was prepared according to the procedure described for compound **41a** using methyl benzoate **39a** (15 mmol), morpholine (15 mmol) and MeMgCl (18 mmol). The title compound **41b** (>99% pure GC-MS) (2.15g, 75%) was recovered as a as yellow oil which solidified. ^{1}H NMR spectroscopy showed presence of rotamers. mp 68-70 °C, (lit[24]., 72-74 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.30 (m, 5H, Ar-*H*), 3.98 – 3.36 (m, 8H, 2 x CH_2O, 2 x CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5(*C*O), 135.4 (Ar*C*), 130.0 (Ar*C*H), 128.7 (Ar*C*H) ,127.2 (Ar*C*H), 67.0 (CH_2O), 48.2 (CH_2N), 42.5 (CH_2N); IR: υ_{max} /cm^{-1}: 3240, 2980, 2860, 1623 (C=O). The spectral data were consistent with literature values.[25]

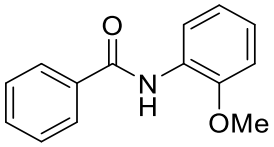


N-Phenylbenzamide **41c.**

This was prepared according to the procedure described for compound **41a** using methyl benzoate **39a** (15 mmol), aniline (15 mmol) and MeMgCl (18 mmol). The crude product mixture consisted of SM **39a** and product **41c** in the ratio 6:94 (observed by GC-MS). The crude mixture was recrystallized in methanol and the title compound **41c** (2.44g, 82% yield) was recovered as off-white crystals; mp 156-160 °C, (lit[26]., 165 -166 °C);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.78 (m, 2H, Ar-*H*), 7.84 (s, 1H, N*H*), 7.64 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.58 – 7.43 (m, 3H, 1 x Ar-*H* and 2 x Ar-*H*), 7.37 (t, *J* = 8.0 Hz, 2H, Ar-*H*), 7.15 (t, *J* = 7.4 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (*C*O), 138.0 (Ar*C*), 135.1 (Ar*C*H), 132.0 (Ar*C*H), 129.2 (Ar*C*H), 128.9 (Ar*C*H), 127.1 (Ar*C*), 124.7 (Ar*C*H), 120.3 (Ar*C*H); IR: υ_{max} /cm^{-1}: 3240 (NH), 2780, 2856, 1601 (C=O).

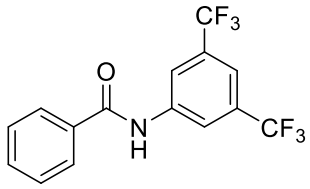
The spectral data were consistent with literature values.[27]



N-(2-Methoxyphenyl)benzamide **41d.**

To a stirred solution of methyl benzoate **39a** (0.3 mL, 2.5 mmol) in anhydrous THF (15 mL) was added 2-methoxyaniline (0.28 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was then added dropwise at rt and the mixture left to stir for 2 h at rt. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The resulting mixture was washed with H_2O (2 x 15 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the amide. The crude product mixture consisted of SM **39a** and product **41d** in a ratio of 2:98 (measured by GC-MS). The crude mixture was purified *via* column chromatography (petrol:Et_2O, 90:10) to afford the product **41d** (0.37 g, 65% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 – 8.50 (m, 2H, N*H* and 1 x Ar-*H*, CHC*H*COMe), 7.89 (d, *J* = 9.5 Hz, 2H, Ar-*H*), 7.60 – 7.42 (m, 3H, Ar-*H*), 7.12 – 6.96 (m, 2H, Ar-*H*), 6.91 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar-*H* C*H*CHCOMe), 3.90 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (*C*O), 148.3 (Ar*C*OMe), 135.4(Ar*C*), 131.8 (Ar*C*H), 128.9 (Ar*C*H), 127.9 (Ar*C*), 127.2 (Ar*C*H), 124.0 (Ar*C*H), 121.3 (Ar*C*H), 119.9 (Ar*C*H), 110.0 (Ar*C*H), 55.9 (O*C*H$_3$); IR: υ_{max} /cm^{1}: 3427 (NH), 1667(C=O).

The spectral data were consistent with literature values.[28]



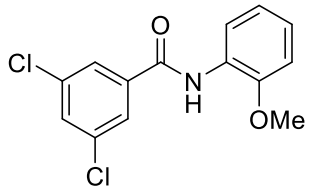
N-(3,5-Bis-trifluoromethyl-phenyl)benzamide **41e.**

To a stirred solution of methyl benzoate **39a** (0.31 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 3,5-bis-trifluoromethylaniline (0.39 mL, 2.5 mmol). MeMgCl (2 mL, 6 mmol, 2.4 eq) was added dropwise at rt and the mixture was left to stir for 2 h at rt. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The resulting mixture was washed with H_2O (2 x 15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the amide

The crude product mixture consisted of SM **39a** and product **41e** in a ratio of 4:96 (measured by GC-MS). The residue was triturated with petroleum ether. The title compound **41e** (0.55 g, 66% yield) was recovered as yellow crystals; mp 115-118 °C, (lit[29].,112-114 °C);

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.39 (s, 2H, Ar-*H*, 2 x C*H*CCF$_3$), 7.98 – 7.92 (m, 2H, Ar-*H*), 7.66 (s, 1H, Ar-*H*, C*H*CCF$_3$), 7.62 – 7.55 (m, 1H, Ar-*H*), 7.54 – 7.47 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, Methanol-D_3) δ 167.7 (*C*O), 140.9 (Ar*C*), 134.1 (Ar*C*), 132.1 (Ar*C*H), 132.0 (*C*CF$_3$, q, *J* = 40 Hz), 128.4 (Ar*C*H), 127.1 (Ar*C*H), 124.8 (*C*F$_3$, q, *J* = 270 Hz), 120.0 (Ar*C*H, m, 2 x *C*HCCF$_3$), 116.5 (Ar*C*H, m, *C*HCCF$_3$); IR: υ_{max} /cm^{-1}: 3267 (NH), 1655 (C=O).

The spectral data were consistent with literature values.[29]

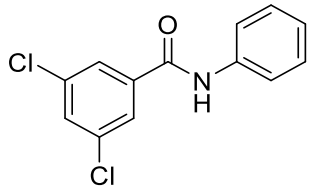


3,5-Dichloro-*N*-(2-methoxyphenyl)benzamide **42a.**

This was prepared according to the procedure described for compound **41d** using methyl 3,5-dichlorobenzoate **39b** (2.4 mmol), 2-methoxyaniline (2.4 mmol) and MeMgCl (2.88 mmol). The crude product mixture consisted of ester SM and product **42a** in the ratio 2:98 (observed by GC-MS). The residue was triturated with petroleum ether. The title compound **42a** (0.53 g, 75% yield) was recovered as an off-white crystalline solid; mp 107-110 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.35 (m, 2H, 1 of C*H*CCl and br N*H*), 7.77 – 7.70 (m, 2H, 2 of C*H*CCl), 7.53 (td, *J* = 7.8, 1.5 Hz, 1H, Ar-*H*), 7.11 (td, *J* = 7.9, 1.6 Hz, 1H, Ar-*H*), 7.06 – 6.95 (m, 1H, Ar-*H*), 6.93 (dd, *J* = 8.1, 1.0 Hz, 1H, Ar-*H*), 3.94 (s, 3H, OC*H*$_3$);

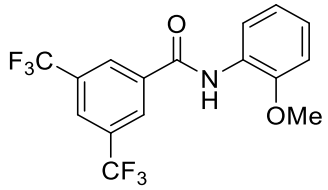
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (CO), 148.3 (Ar*C*OMe), 138.3 (Ar*C*), 135.7 (Ar*C*Cl), 131.7 (Ar*C*H), 127.2 (Ar*C*H), 125.8 (Ar*C*), 124.7 (Ar*C*H), 121.3 (Ar*C*H), 120.1 (Ar*C*H), 110.1 (Ar*C*H), 56.0 (O*C*H_3); IR: υ_{max} /cm^{-1}: 3315 (NH), 1647 (C=O). HRMS (ESI**)** *m/z:* Calcd for $C_{14}H_{12}Cl_2NO_2$ [*M*-H$^+$]: 296.0245 found 296.0246



3,5-Dichloro-*N*-phenylbenzamide **42b.**

This was prepared according to the procedure described for compound **41d** using methyl 3,5-dichlorobenzoate **39b** (1.7 mmol), aniline (1.7 mmol) and MeMgCl (2.04 mmol). The crude product mixture consisted of ester SM and product in the ratio 6:94 respectively by GC-MS. The residue was triturated with petroleum ether. The title compound **42b** (0.33 g, 73% yield) was recovered by as an off-white crystalline solid; mp 159-161 °C, (lit[30]., 150 °C);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H, N*H*), 7.71 (d, J = 1.8 Hz, 2H, Ar-*H*), 7.61 (d, J = 7.9 Hz, 2H, Ar-*H*), 7.51 (t, J = 1.8 Hz, 1H, Ar-*H*), 7.39 (m, 2H, Ar-*H*), 7.18 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (*C*O), 137.9 (Ar*C*), 137.3 (Ar*C*Cl), 135.8 (Ar*C*), 131.8 (Ar*C*H), 129.3 (Ar*C*H), 125.8 (Ar*C*H), 125.3 (Ar*C*H), 120.5 (Ar*C*H); IR: υ_{max} /cm^{-1}: 3316 (NH),1648 (C=O). The spectral data were consistent with literature values.[30]

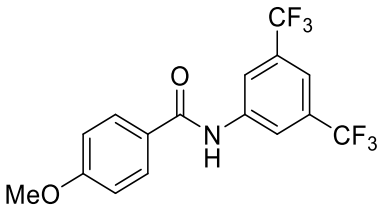


N-(2-Methoxyphenyl)-3,5-bis-trifluoromethylbenzamide **42c.**

To a stirred solution of methyl 3,5-bis-trifluormethylbenzoate **39c** (0.35 g, 1.3 mmol) in anhydrous THF (10 mL) was added and 2-methoxyaniline (0.15 mL, 1.3 mmol). MeMgCl (1.04 mL, 3.12 mmol, 2.4 eq) was added dropwise at rt and the mixture was left to stir for 2 h at rt. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The resulting mixture was washed with H_2O (2 x 15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the amide.

The crude product mixture consisted of ester SM and product **42c** in the ratio 5: 95 respectively by GC-MS. The residue was triturated with petroleum ether. The title compound **42c** (0.32 g, 67% yield) was recovered as off-white crystals; mp 116-120°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br s, 1H, N*H*), 8.45 (d, *J* = 8.0 Hz, 1H, Ar-*H*, C*H*COMe), 8.31 (s, 2H, Ar-*H*, 2 x C*H*CCF$_3$), 8.05 (s, 1H, Ar-*H*, C*H*CCF$_3$), 7.18 – 7.11 (m, 1H, Ar-*H*), 7.08 – 7.02 (m, 1H, Ar-*H*), 6.98 – 6.93 (m, 1H, Ar-*H*), 3.95 (s, 3H, OC*H$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (*C*O), 148.3 (Ar*C*OMe), 137.4 (Ar*C*), 132.7 (*C*CF$_3$, q, *J* = 34.3 Hz), 127.5 (Ar*C*), 126.9 (Ar*C*H), 125.3 (Ar*C*H), 125.0 (Ar*C*H), 121.6 (*C*F$_3$, q, *J* = 260 Hz), 121.4 (Ar*C*H, m, 2 x *C*HCCF$_3$), 120.3 (Ar*C*H, m, *C*HCCF$_3$), 110.1 (Ar*C*H), 56.0 (OMe); IR: υ_{max} /cm^{-1}: 3403 (NH), 1675 (C=O); GC-MS m/z: 363 (93), 344 (40), 332 (59), 241 (100), 213 (98), 194 (25), 163 (45); HRMS (ESI) *m/z:* Calcd for $C_{15}H_{10}F_6NO_2$ [*M*-H$^+$]: 364.0772 found 364.0771.

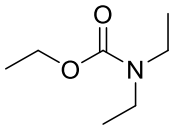


N-(3,5-Bis-trifluoromethyl-phenyl)-4-methoxy-benzamide **42d.**

To a stirred solution of methyl 4-methoxybenzoate **39d** (0.27 mL, 2 mmol) in anhydrous THF (10mL) was added 3,5-bis-(trifluoromethyl)aniline (0.30 mL, 2 mmol). MeMgCl (1.6 mL, 4.8 mmol, 2.4 eq) was added dropwise at rt and the mixture was left to stir for 2 h at rt. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The resulting mixture was washed with H_2O (2 x 15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the amide. The crude product mixture consisted of the ester SM and product **42d** in the ratio 4:96 respectively by GC-MS. The residue was triturated with petroleum ether. The title compound **42d** (0.51 g, 71% yield) was recovered as yellow crystals; mp 127-129 ℃;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 2H, Ar-*H,* 2 x C*H*CCF$_3$), 8.07 (br s, 1H, N*H*), 7.85 (d, *J* = 8.8 Hz, 2H, Ar-*H*, 2 x C*H*OMe), 7.61 (s, 1H, Ar-*H,* C*H*CCF$_3$), 6.97 (d, *J* = 8.8 Hz, 2*H*, Ar-*H*, 2 x C*H*CCO), 3.87 (s, 3H, OC*H$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (CO), 163.2 (COMe), 139.7 (ArC), 132.6 (*C*CF$_3$ q, *J* = 33.4 Hz), 129.2 (Ar*C*H), 125.8 (Ar*C*NH), 121.8 (*C*F$_3$ q, *J* = 270 Hz), 119.9 (Ar-CH, m, 2 x *C*HCCF$_3$), 117.6 (Ar*C*H*,* m*, C*HCCF$_3$), 114.3 (Ar*C*H), 55.6 (OMe); IR: υ_{max} /cm^{-1}: 3298 (NH), 3106, 1648 (C=O). GC-MS m/z: 363 (10), 344 (15), 135 (100), 92 (15). HRMS (ESI) *m/z:* Calcd for $C_{15}H_{10}F_6NO_2$ [*M*-H$^+$]: 364.0772 found 364.0771.

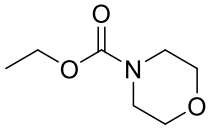
3.9.1 Carbamate synthesis



Ethyl *N,N*-diethylcarbamate **45a.**

To a stirred solution of diethyl carbonate **44** (0.6 mL, 5 mmol) in anhydrous THF (10 mL) was added diethylamine (0.26 mL, 5 mmol). MeMgCl (2 mL, 6 mmol) was then added dropwise at rt and the mixture left to stir at rt for 2 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the carbamate. The title compound **45a** was recovered as a light-yellow oil. Although a 100% was observed on GC-MS, ^1H and ^{13}C NMR spectroscopy showed the presence of a contaminant. The mixture proved difficult to separate on column chromatography and bulb to bulb distillation, therefore, the product was not isolated pure. ^1H NMR spectroscopy showed presence of rotamers.

Diagnostic signals in ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, J = 7.32 Hz, 2H, CH_3CH_2O), 3.28 (br s, 4H, 2 × CH_3CH_2N), 1.27 (t, J = 7.1 Hz, 3H, CH_3CH_2O), 1.12 (t, J = 7.1 Hz, 6H, 2 × CH_3CH_2N); diagnostic signals ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1(CO), 60.9 (CH_2O), 41.8 (broad 2 × CH_2N), 14.8(CH_3CH_2O),13.8 (broad, 2 × CH_3CH_2N); IR: υ_{max} /cm^{-1}: 2946, 1654 (C=O). The spectral data were consistent with literature values.[35]

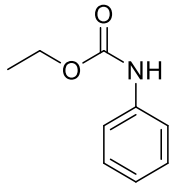


Ethyl *N*-morpholinecarbamate **45b.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added morpholine (0.22 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was then added dropwise at rt and the mixture left to stir at rt for 2 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the carbamate.

The title compound **45b** (> 99% pure GC-MS) (0.29 g, 74% yield) was recovered as a yellow oil; ^1H NMR spectroscopy showed presence of rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23-3.98 (m, 2H, OC*H*$_2$CH$_3$), 3.73 – 3.26 (m, 8H, 2 x C*H*$_2$*N* and 2 x C*H*$_2$*O*), 1.29 – 1.18 (m, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (*C*O), 66.7 (CH$_3$*C*H$_2$O), 61.6 (2 x *C*H$_2$O), 44.3 (2 x *C*H$_2$N), 14.7 (*C*H$_3$); IR: υ_{max} /cm^{-1}: 2976, 2163, 1734 (C=O). The spectral data were consistent with literature values.[36]



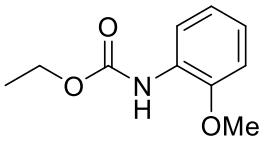
Ethyl *N*-phenylcarbamate **45c.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added aniline (0.23 mL, 2.5 mmol). MeMgCl (2 mL, 6 mmol) was added dropwise at rt and the mixture left to stir at rt for 2 h.

The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the carbamate. The crude product mixture consisted of phenyl isocyanate **46c** and product **45c** in the ratio 4:96 (observed by GC-MS). The ^{1}H NMR spectrum showed only the product which was isolated as a white solid (0.32 g, 77% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.23 (m, 4H, 2 x Ar-*H* and 2 x Ar-*H*), 7.14 – 6.93 (m, 1H, Ar-*H*), 6.73 (br s, 1H, N*H*), 4.22 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (*C*O), 138.1 (Ar*C*), 129.1 (Ar*C*H), 123.4 (Ar*C*H), 118.7 (Ar*C*H), 61.3 (O*C*H$_2$), 14.7 (*C*H$_3$). IR: υ_{max} /cm^{-1}: 2978, 1708/

The spectral data were consistent with literature values.[37]

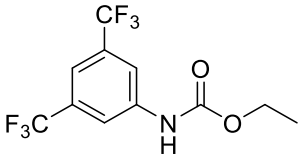


Ethyl *N*-(2-methoxyphenyl)carbamate **45d.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 2-methoxyaniline (0.28 mL, 2.5 mmol). MeMgCl (2 mL, 6 mmol) was added dropwise at rt and the mixture left to stir at rt for 2 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of 2-methoxyphenyl isocyanate **46d** and product **45d** in the ratio 2:98 (observed by GC-MS). The ^{1}H NMR spectrum showed only the product **45d** (0.35g, 72% yield) which was isolated as a peach oil;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (br s, 1H, N*H*), 7.23 (s, 1H, Ar-*H*), 7.15 – 6.93 (m, 2H, Ar-*H*), 6.86 – 6.78 (m, 1H, Ar-*H*), 4.23 (q, *J* = 6.8 Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100Hz, $CDCl_3$): δ 153.6 (*C*O), 147.6 (Ar*C*OMe), 127.8 (Ar*C*), 122.7 (Ar*C*H), 121.2 (Ar*C*H), 118.2 (Ar*C*H), 110.0 (Ar*C*H), 61.2 (O*C*H_2), 55.7 (O*C*H_3), 14.7 (CH_3). IR: υ_{max} /cm^{-1}: 3319 (NH), 1708.

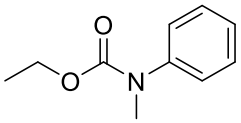
The spectral data were consistent with literature value.[38]



Ethyl *N*-[3,5-bis-(trifluoromethyl)phenyl]carbamate **45e.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 3,5-bis-(trifluoromethyl)aniline (0.38 mL, 2.5 mmol). MeMgCl (2 mL, 6 mmol) was added dropwise at rt and the mixture left to stir at rt for 2 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of 3**,**5-bis(trifluoromethyl)-phenyl isocyanate **46e** and product **45e** in the ratio 2:98 observed by GC-MS. The residue was triturated with warm petroleum ether. The title compound **45e** (>99% pure GC-MS) (0.54 g, 73% yield) was recovered as white crystals; mp 84-90 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 2H, Ar-*H,* 2 x C*H*CCF_3), 7.54 (s, 1H, Ar-*H,* C*H*CCF_3), 7.00 (br s, 1H, N*H*), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2), 1.29 (t, 2H, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (*C*O), 139.6 (Ar*C*), 132.7 (Ar*C*H), 132.4 (*C*CF_3, q, *J* = 30 Hz), 124.5 (CF_3 q, *J* = 210 Hz), 118.2 (Ar*C*H), 116.6 (Ar*C*H), 62.1(OCH_2), 14.5 (OCH_3). IR: υ_{max} /cm^{-1}: 3317 (NH), 1705; GC-MS m/z: 301 (51), 282 (35), 242 (90), 229 (100), 182 (25); HRMS (ESI) *m/z:* Calcd for $C_{11}H_{10}F_6NO_2$ [*M*-H$^+$]: 302.0616 found 302.0625



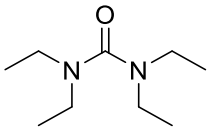
Ethyl *N*-methyl-*N*-phenylcarbamate **45f.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added 3 N-methylaniline (0.7 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was added dropwise at rt and the mixture left to stir at rt for 2 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The title compound **45f** (>99% GC-MS) (0. 37g, 83% yield) was recovered as a yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 2H, Ar-*H*), 7.27 – 7.14 (m, 3H, Ar-*H*), 4.15 (q, *J*= 7.3 Hz, 2H, OCH_2CH_3), 3.29 (s, 3H, NCH_3), 1.22 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (*C*O), 143.5 (Ar*C*), 128.9 (Ar*C*H), 126.0 (Ar*C*H), 125.8 (Ar*C*H), 61.8 (OCH_2), 37.7 (NCH_3), 14.7(CH_3); IR: υ_{max} /cm^{-1}: 2981, 1698 (C=O); GC-MS m/z: 179 (98), 151 (13), 134 (15), 120 (50), 106 (100), 77 (65), 66 (8); HRMS (ESI) *m/z:* Calcd for $C_{10}H_{14}NO_2$ [*M*+H$^+$]: 180.1025, found 180.1024.

The spectral data were consistent with literature values.[39]

3.9.2 Urea formation



N,N,N,N-Tetraethylurea **47a**

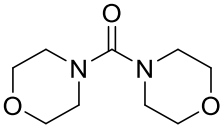
Preparation of **47a** by one pot synthesis from diethyl carbonate **44**

To a stirred solution of diethyl carbonate **44** (0.18 mL, 1.5 mmol) in anhydrous THF (10 mL) was added diethylamine (0.77 mL, 7.5 mmol). MeMgCl (3 mL, 9 mmol) was added dropwise over a minute. Upon addition of MeMgCl, the temperature was raised to reflux then maintained at reflux for 3 h at which stage all starting material (SM) had been consumed (GC-MS monitoring). The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the urea. The title compound **47a** (>99% pure GC-MS) (0.19 g, 74% yield) was recovered as pale-yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (q, J = 7.1 Hz, 8H, NCH_2), 1.06 (t, J = 7.1 Hz, 12H, NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (*C*O), 42.3 (CH_2), 13.3 (CH_3), IR: υ_{max} /cm ^{1}: 2968, 1641. The spectral data were consistent with literature values.[40]

Preparation of **47a** by sequential addition**.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added diethylamine (0.26 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was added dropwise over a minute and reaction was left to stir for 2 h at rt at which stage all SM had been consumed (GC-MS monitoring). After 2 h, diethylamine (0.26 mL, 2.5mmol) and MeMgCl (1 mL, 3 mmol) were added and the reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of carbamate **45a** and disubstituted product **47a** in the ratio 7:93 (measured by GCMS). The unreacted carbamate was removed *via* bulb to bulb distillation at 40°C and 1mm Hg affording the title compound **47a** (0.31 g, 72% yield) as a pale-yellow oil. The spectral data were consistent with that described for **47a** above.

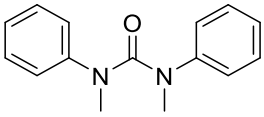


N,N-Carbonyldimorphiline **47b.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added morpholine (0.44 mL, 5 mmol). MeMgCl (2 mL, 6 mmol) was added dropwise over a minute at rt. Upon addition of MeMgCl, the temperature was raised to reflux then maintained at reflux for 3 h at which stage all starting material (SM) had been consumed (GC-MS monitoring). The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the urea. The title compound **47b** (>99% pure GC-MS) (0.21 g, 70% yield) was recovered as a white crystal solid; mp 123 °C, (lit[41].,142°C);

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (t, J = 4.88 Hz, 8H, 4 x NCH_2), 3.26 (t, J = 4.88 Hz, 8H, 4 x OCH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (*C*O), 66.7 (O*C*H$_2$), 47.3 (N*C*H$_2$); IR: υ_{max} /cm^{1}: 3297, 1649(C=O).

The spectral data were consistent with literature values.[41]

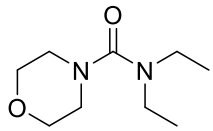


1,3-Dimethyl-1,3-diphenyl-urea **47c.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added N-methylaniline (0.54 mL, 5 mmol). MeMgCl (2 mL, 6 mmol) was then added dropwise over a minute at rt and then the temperature of the mixture was raised to reflux and maintained at reflux for 3 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the urea. The crude product mixture consisted of *N*-methylaniline SM and product **47c** in the ratio 9:91 (measured by GC-MS). The crude mixture was purified *via* column chromatography on silica (petrol:Et_2O, 30:70) to afford the title compound **47c** as a white solid (0.38 g, 60% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 6.98 (m, 4H, Ar-*H*), 6.95 – 6.88 (m, 2H, Ar-*H*), 6.76 – 6.70 (m, 4H, Ar-*H*), 3.18 (s, 6H, 2 x NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (*C*O), 145.7 (Ar*C*), 128.7 (Ar*C*H), 125.8 (Ar*C*H), 124.9 (Ar*C*H), 39.4 (*C*H$_3$); IR: υ_{max} /cm^{-1}: 2967, 1646.

The spectral data were consistent with literature values.[42]

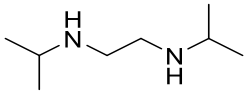


N,N -Diethylmorpholine-4-carboxamide **47d.**

To a stirred solution of diethyl carbonate **44** (0.3 mL, 2.5 mmol) in anhydrous THF (10 mL) was added morpholine (0.22 mL, 2.5 mmol). MeMgCl (1 mL, 3 mmol) was added dropwise over a minute and reaction was left to stir for 2 h at rt at which stage all starting material (SM) had been consumed (GC-MS monitoring). After 2 h, diethylamine (0.26 mL, 2.5mmol) and MeMgCl (1 mL, 3 mmol) were added and the reaction temperature was raised to reflux and maintained at reflux for 3 h. The reaction mixture was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the urea. The title compound **47d** (>99% pure GC-MS) (0.35 g, 76 % yield) was recovered as a colourless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, J = 4.6 Hz, 4H, 2 x OCH_2), 3.25 – 3.08 (m, 8H, 2 x NCH_2CH$_3$, 2 x NCH_2CH$_2$O), 1.10 (t, J = 6.9 Hz, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ164.6 (*C*O), 66.8 (O*C*H$_2$), 47.7 (N*C*H$_2$CH$_2$), 41.8 (N*C*H$_2$CH$_3$), 13.3 (*C*H$_3$). IR: υ_{max} /cm^{-1}: 2969, 1637 (C=O). The spectral data were consistent with literature values.[43]

3.9.3 Intermolecular urea formation (ring closing)

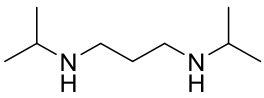


N,N'-Diisopropyl-1,2-ethanediamine **50.**[44]

To a cold (0 °C) mixture of 1,2-dibromoethane (1.25 mL, 14 mmol, 1.0 eq) and H_2O (0.76 mL, 42 mmol, 3.0 eq) was added isopropylamine (6mL, 72 mmol, 5.0 eq). The reaction mixture was slowly allowed to warm to rt and the reaction temperature was raised to reflux and maintained at reflux overnight. The resulting solution was cooled, diluted with H_2O (2 x 3 mL), and then saturated with solid potassium hydroxide (1 g). The mixture was then extracted with EtOAc (3 x 10 mL) and the combined extract was dried over Na_2SO_4 and concentrated *in vacuo* to afford a yellow oil. The crude product mixture consisted of product **50** and dimeric product in the ratio 54:46 (measured by GC-MS). The crude mixture was purified by bulb to bulb distillation at 60 °C and 4.0 mm Hg giving the title compound **50** as a white solid (0.60 g, 30% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 – 2.67 (m, 2H, 2 x C*H*), 2.66 (s, 4H, 2 x CH_2), 1.18 (br s, 2H, 2 x N*H*), 1.01 (d, *J* = 6.9 Hz, 12H, 4 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.9 (*C*H), 47.6 (*C*H_2), 23.2 (*C*H_3); IR: υ_{max} /cm^{-1}: 3249 (NH), 2963.

The spectral data were consistent with literature values.

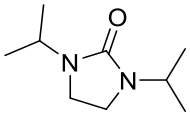


N,N'-Diisopropyl-1,3-propanediamine **52**.

To a cold (0 °C) mixture of 1,3-dibromopropane (2.0 mL, 21 mmol, 1.0 eq) and H_2O (1.1 mL, 63 mmol, 3.0 eq) was added isopropylamine (9mL, 100 mmol, 5.0 eq). The reaction mixture was slowly allowed to warm to rt and then heated to reflux and maintained at reflux overnight. The resulting solution was cooled, diluted with a small portion of H_2O (2 x 3 mL), and then saturated with solid potassium hydroxide (1 g). The mixture was then extracted with EtOAc (3 x 10 ml), dried over Na_2SO_4, and concentrated *in vacuo* to afford a yellow oil. The crude product mixture consisted of product **52** and dimeric product present in the ratio 77:23 (measured by GC-MS). The crude mixture was purified by bulb to bulb distillation at 80 °C and 4.0 mm Hg giving the title compound in a 93% purity by GC-MS. The ^{1}H NMR spectrum showed only the product which was isolated as a light-yellow oil (1.66 g, 50% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 – 2.60 (m, 2H, 2 x C*H*), 2.55 (tt, *J* = 7.1, 2.2 Hz, 4H, 2 x NHCH_2), 1.63 – 1.48 (m, 2H, CH_2), 0.94 (dt, *J* = 6.2, 2.3 Hz, 12H, 4 x CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 48.8 (NH*C*H), 46.2 (2 x NH*C*H_2), 31.2 (*C*H_2), 23.0 (*C*H_3); IR: υ_{max} /cm^{-1}: 3286 (NH), 1962. The spectral data were consistent with literature values.[44]

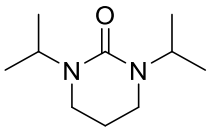


1,3-Diisopropylimidazolidin-2-one **51**.

To a stirring solution of *N,N'*-diisopropyl-1,2-ethanediamine **50** (0.45 g, 3.0 mmol, 1.0 eq) in anhydrous THF (10 mL) at rt was added MeMgCl (2 mL, 3 M in THF, 6 mmol). The reaction was left to stir for 30 min before the addition of diethyl carbonate **44** (0.36 ml, 3 mmol). The reaction was then raised to reflux and maintained at reflux for 3 h. Upon cooling, the reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of diethyl carbonate **44** and product **51** in the ratio 9:91 (measured by GC-MS). The crude mixture was purified by bulb to bulb distillation at 60 °C and 4.0 mm Hg giving the title compound **51** as a clear oil (0.13 g, 25% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 – 3.99 (m, 2H, 2 x C*H*), 3.18 (s, 4H, 2 x CH_2), 1.07 (d, *J* = 6.8 Hz, 12H, 4 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (*C*O), 43.5 (N*C*H), 37.3 (N*C*H_2), 19.6 (*C*H_3); IR: υ_{max} /cm^{-1}: 2970, 1683 (C=O), 1486, 1423.

The spectral data were consistent with literature values.[41]



1,3-Diisopropyl-tetrahydropyrimidin-2(1H)-one **53**

To a stirring solution of *N,N'*-diisopropyl-1,3-propanediamine **52** (0.73 g, 4.6 mmol, 1.0 eq) in anhydrous THF (10 mL) at rt was added MeMgCl (3.6 mL, 3 M in THF, 5.5 mmol). The mixture was left to stir for 30 min before the addition of diethyl carbonate **44** (0.55 ml, 4.6 mmol). The reaction temperature was then raised to reflux and maintained at reflux for 3 h. Upon cooling, the reaction was quenched with 1 M HCl (15 mL) followed by the addition of Et_2O (15 mL). The organic layer was separated, washed with H_2O (2 x 15 mL) and then with brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product. The crude product mixture consisted of the product **51** and the ring closed dimerised product in the ratio 53:47 (measured by GC-MS). The crude mixture was purified

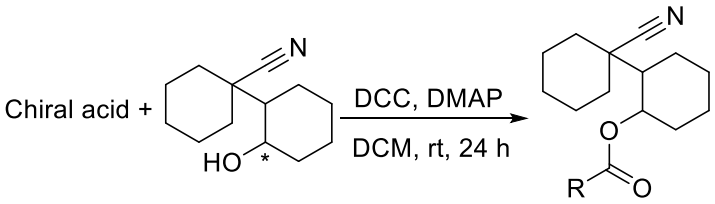
by bulb to bulb distillation at 130 °C and 5.0 mm Hg giving the title compound **53** as a clear oil (0.21 g, 24% yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 – 4.64 (m, 2H, 2 x C*H*), 3.04 (td, *J* = 5.9, 2.3 Hz, 4H, 2 x NCH_2), 1.80 – 1.70 (m, 2H, $CH_2CH_2CH_2$), 1.02 (dd, *J* = 6.8, 2.5 Hz, 12H, 4 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2 (*C*O), 44.7 (*C*H), 38.2 (NCH_2), 22.7 (CH_2), 19.7 (CH_3); IR: υ_{max} /cm^{-1}: 2971, 1607(C=O), 1492, 1437.

The spectral data were consistent with literature values.[45]

3.10 Chiral derivatization of alcohols

General Procedure for the esterification of alcohols 16.



To a stirring solution of the alcohol **16** (1 eq) and *(S)*-(+)-methylbutyric acid (3.1 eq) in anhydrous DCM was added DCC (3.1 eq) and DMAP (3.1 eq).

The reaction was stirred overnight at rt. The reaction was quenched with H_2O, Na_2CO_3 and DCM. The aqueous layer was washed with DCM (x 2) and the combined organic layer was dried, filtered and concentrated to afford a yellow oil which solidified.

GC-MS and NMR analysis of the yellow solid showed no indication of the ester product. Starting material was recovered.

Chiral acid variation.

(S)-(+)-Methylbutyric acid was converted to (*S)*-(+)-methylbutyryl chloride using oxalyl chloride in DCM with catalytic amounts of DMF. Derivatization was attempted with the acid chloride. (*S)*-(+)-methylbutyryl chloride was reacted with alcohol **16** in the presence of pyridine. The reaction was again unsuccessful yielding back unreacted starting material.

The use of *(S)*-(+)-phenylbutyric acid and its corresponding acid chloride was also attempted. Over several attempts, there was no indication of the desired product.

3.8 References

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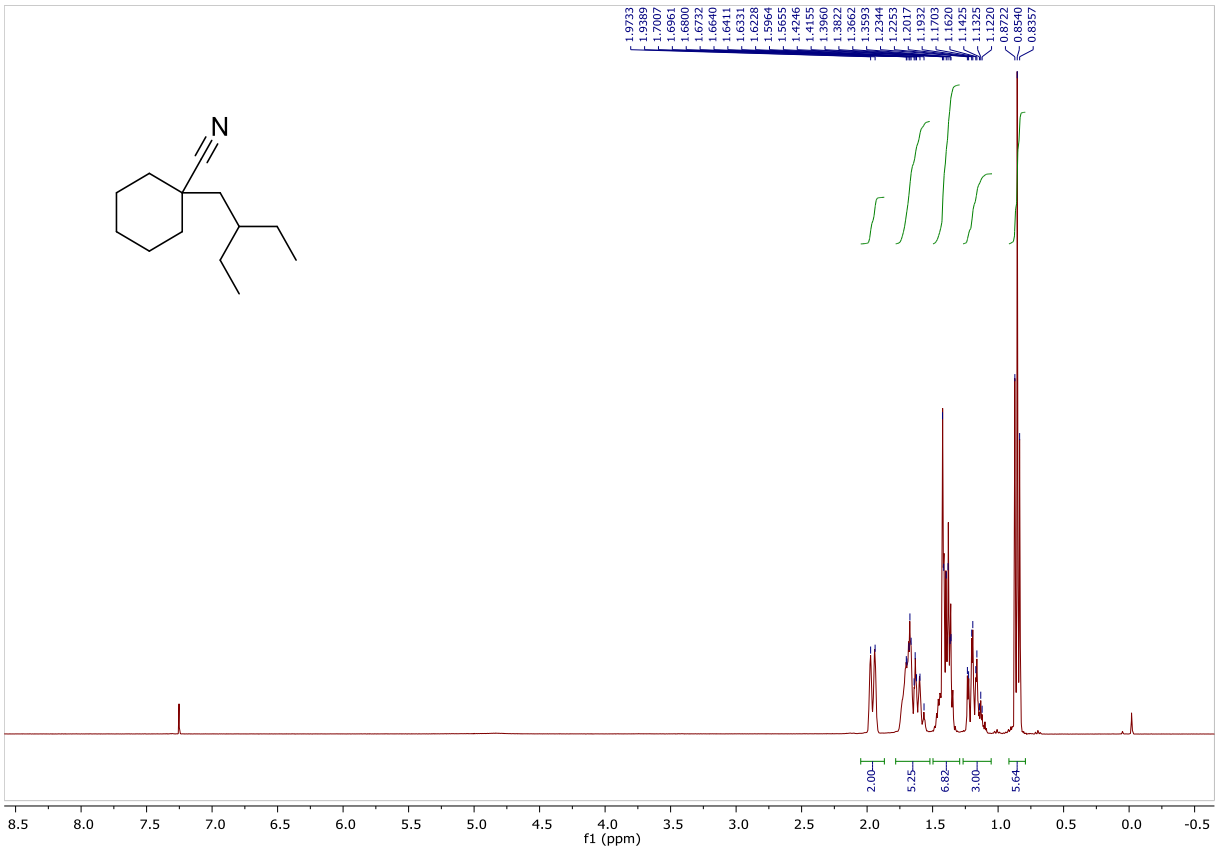
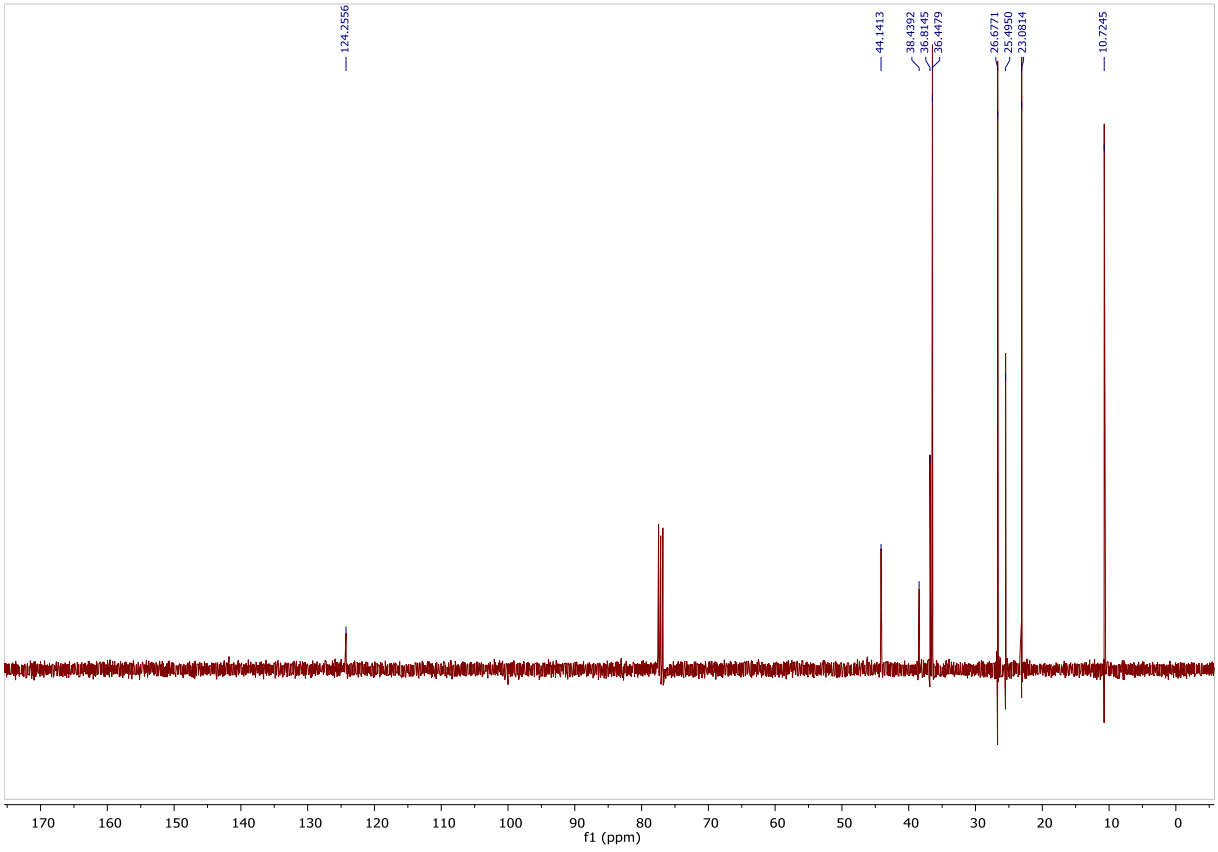
Appendix

^{1}H and ^{13}C NMR compound for **2a**





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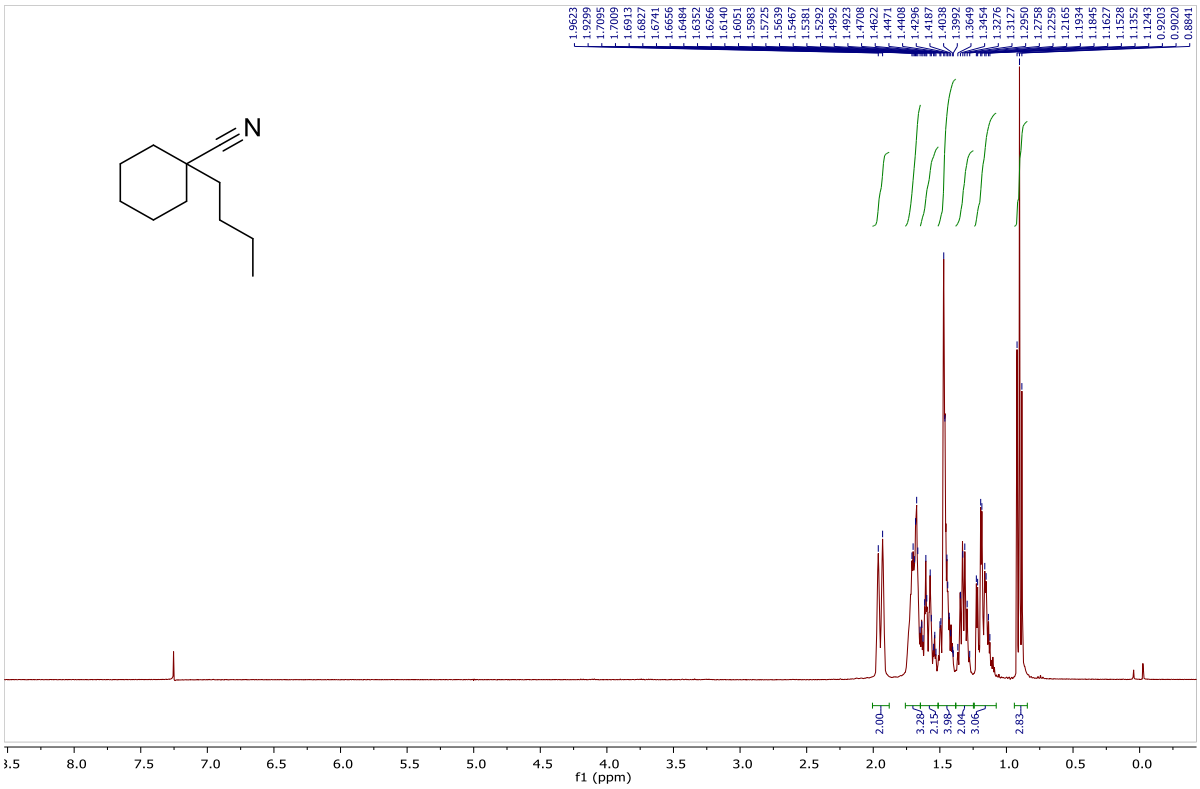
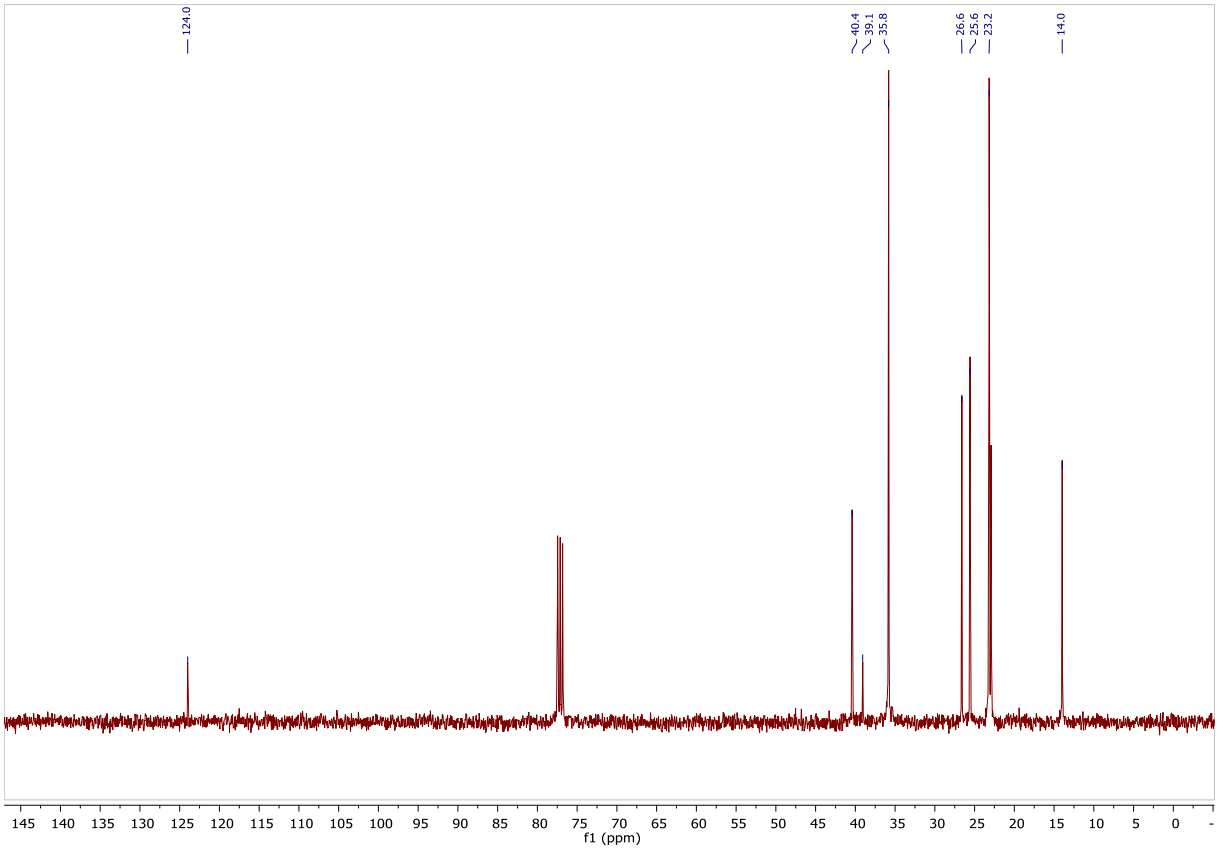
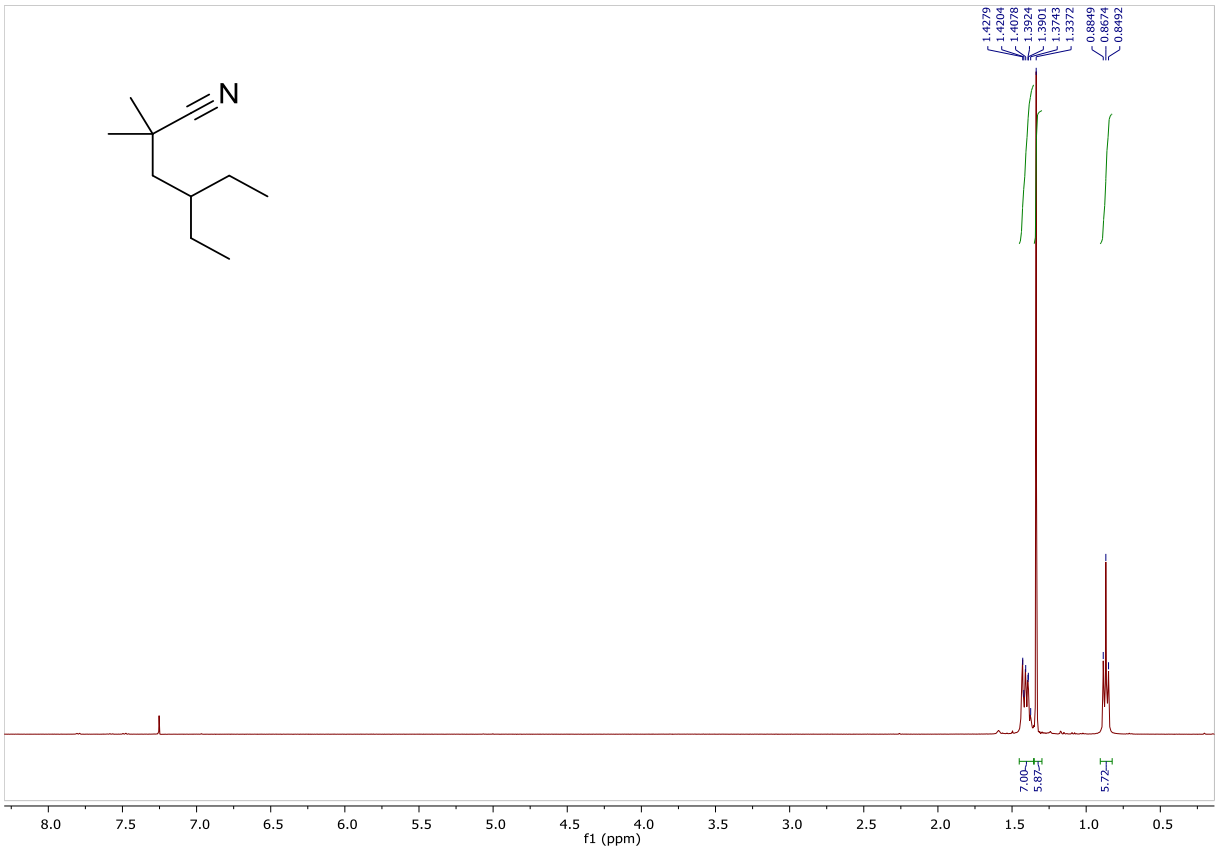
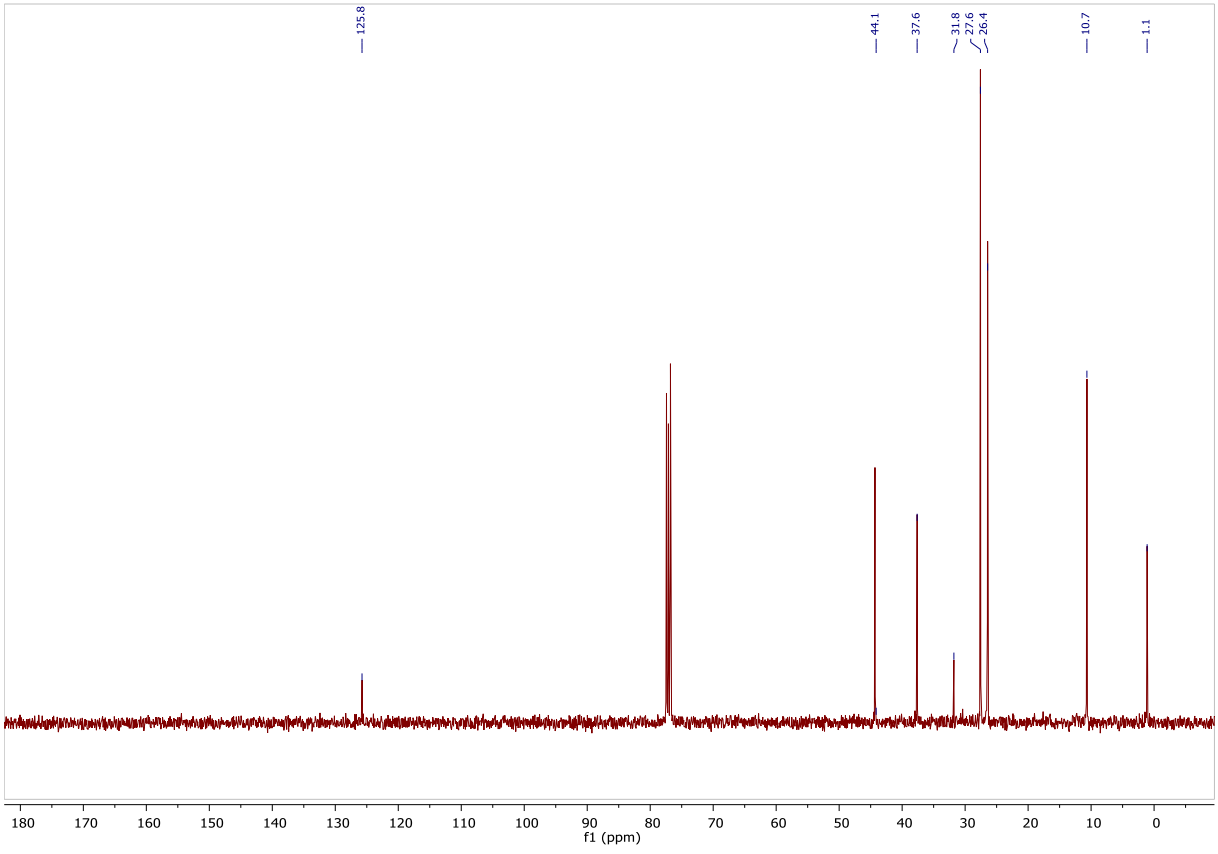




^{1}H and ^{13}C NMR compound for **4a**





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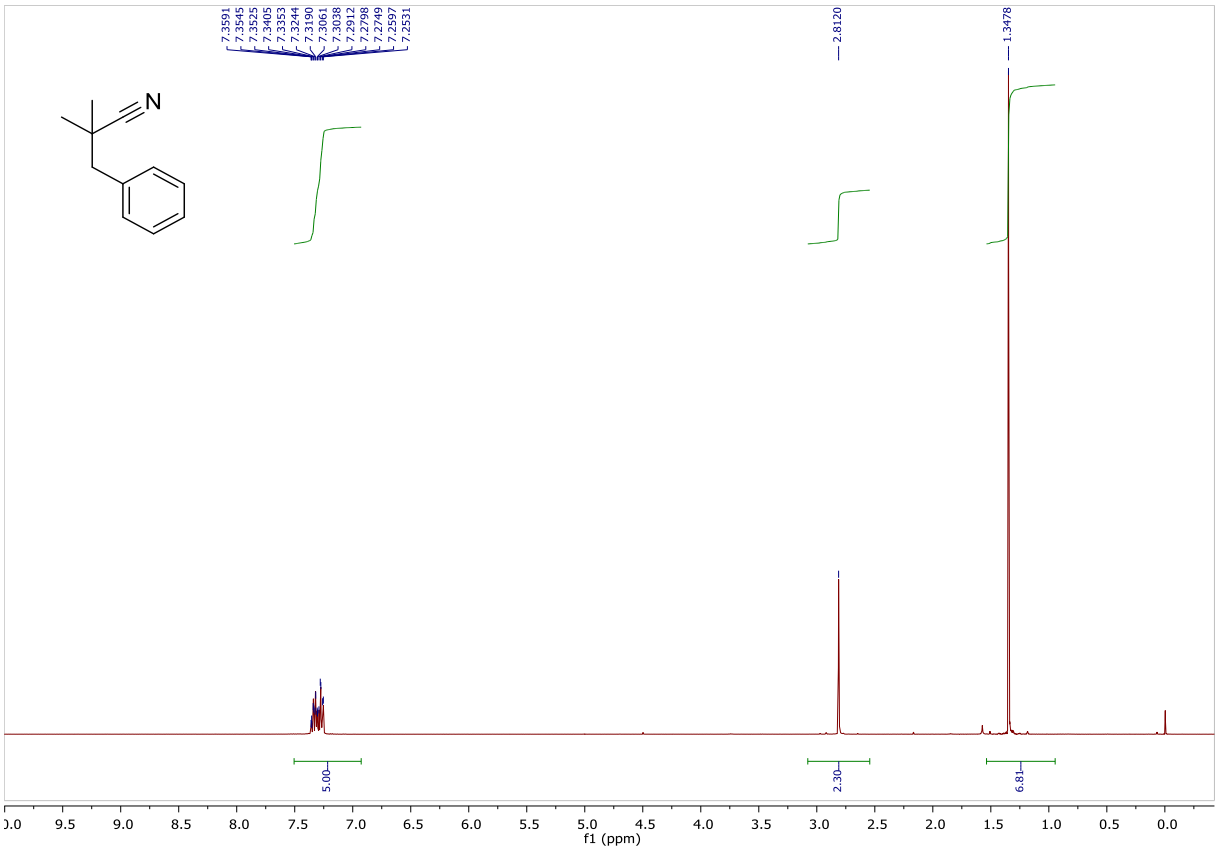

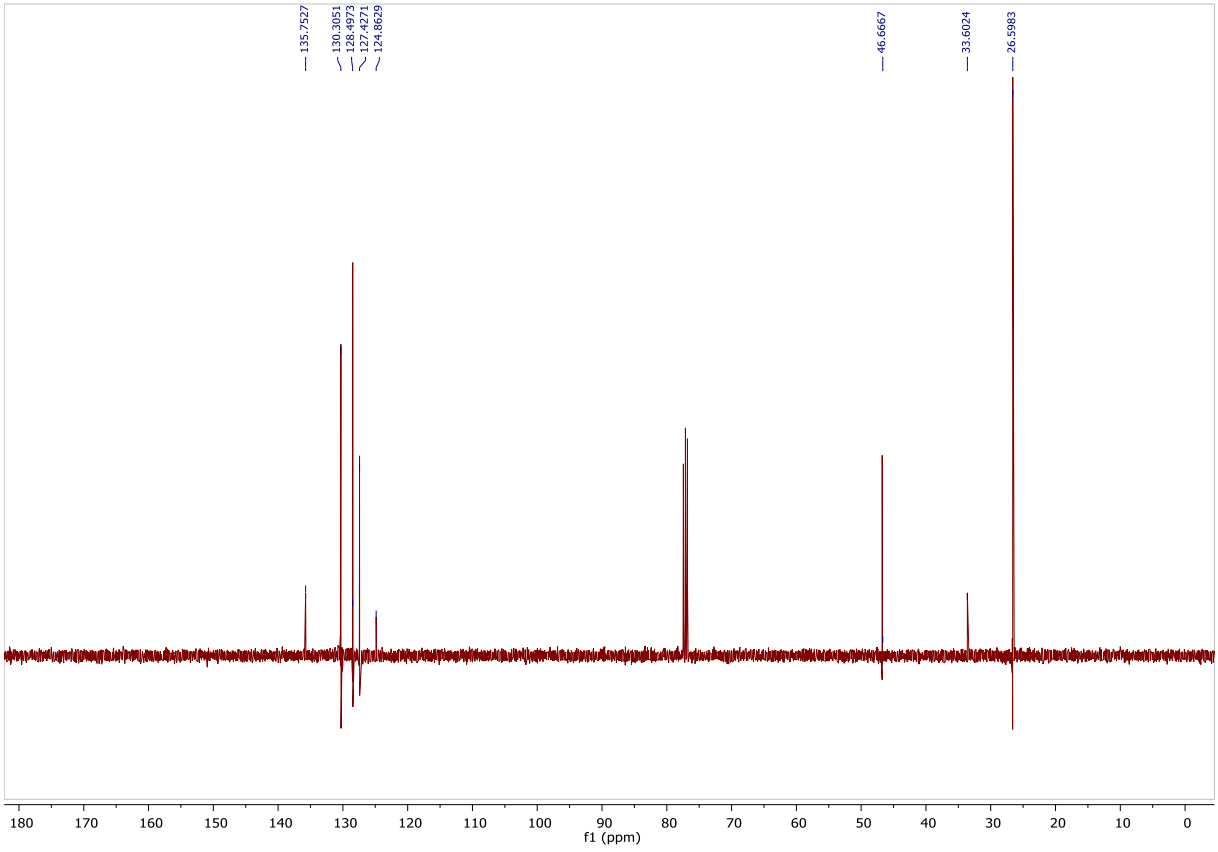

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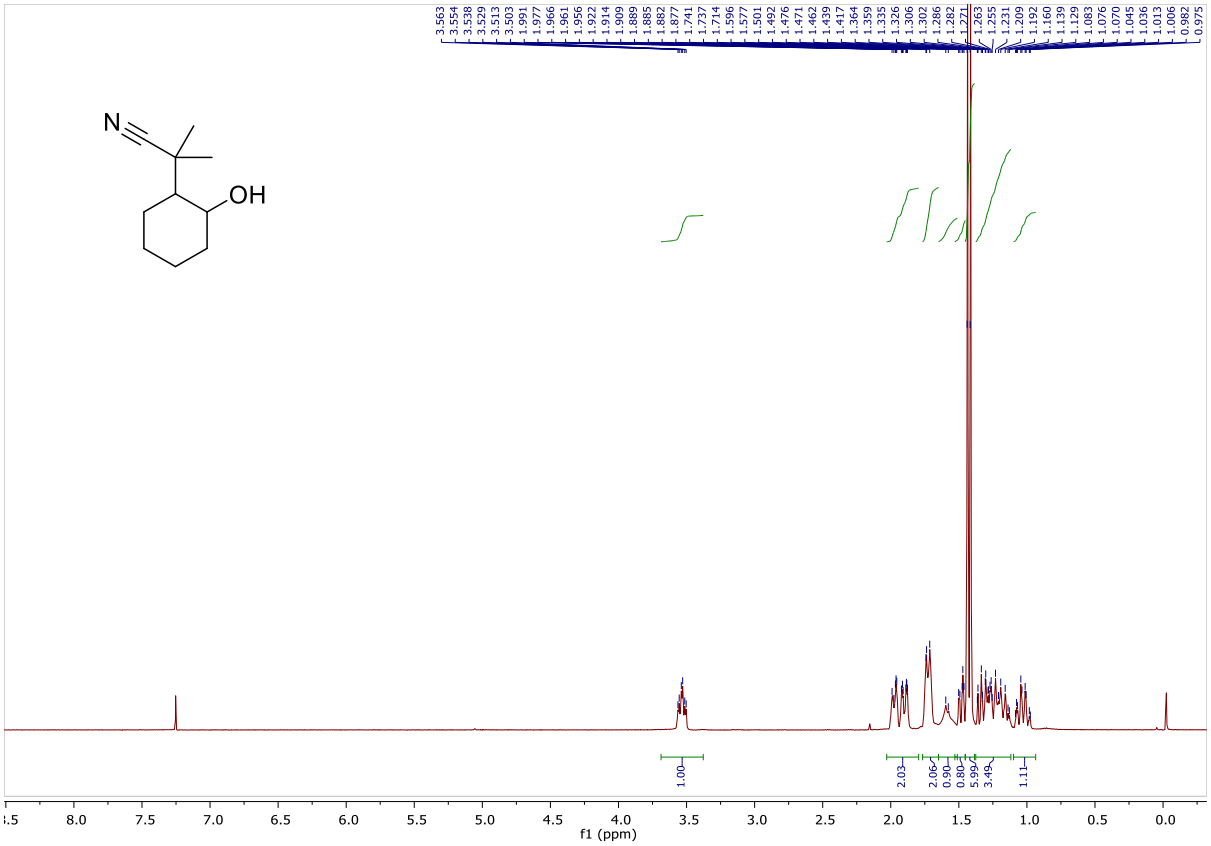
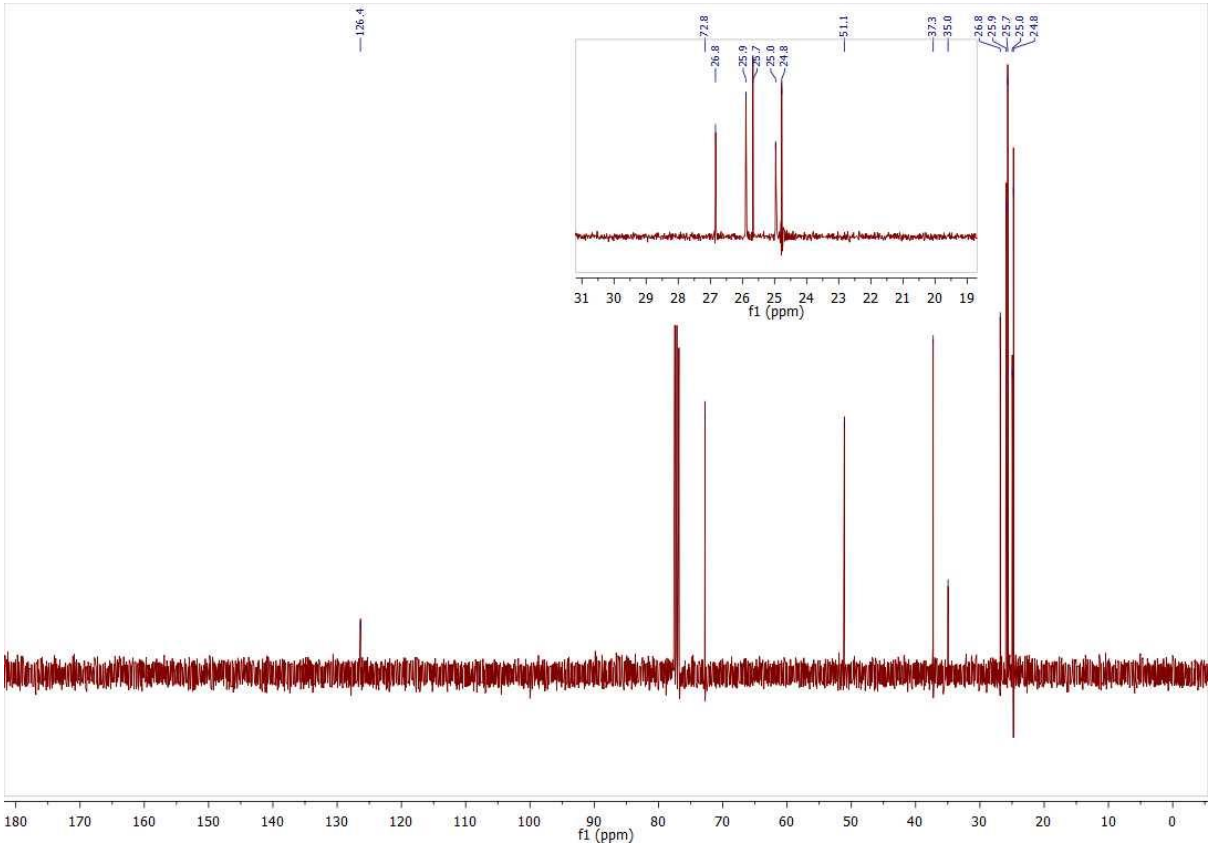
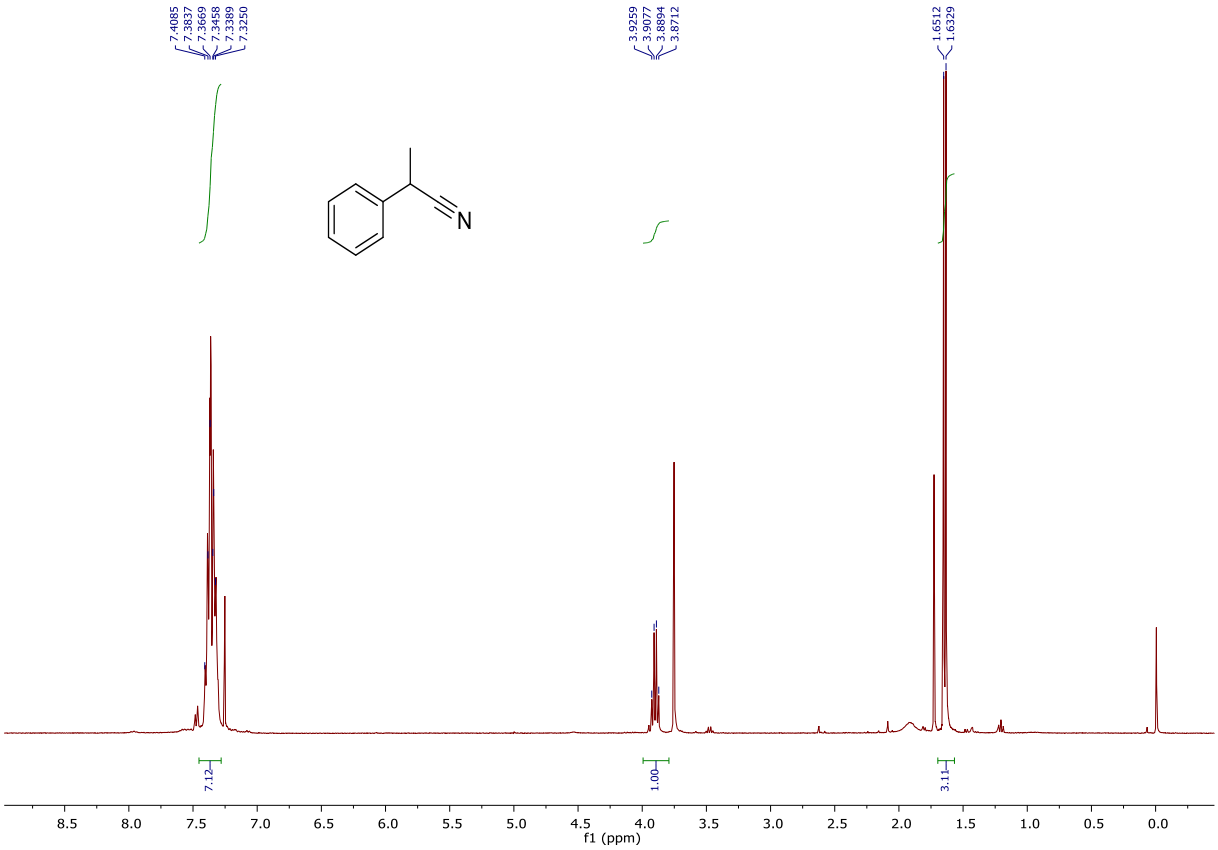
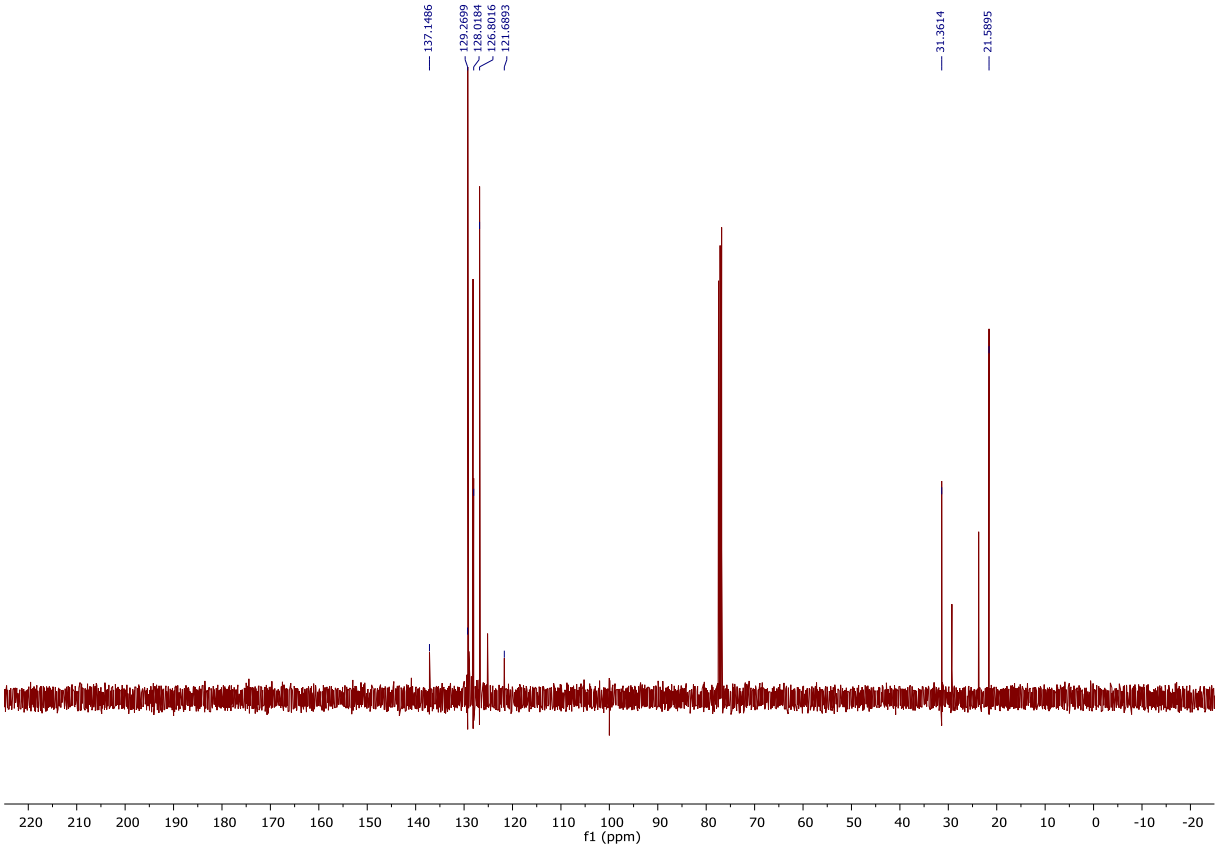




^{1}H and ^{13}C NMR for compound for **6a** (crude as described in experimental)





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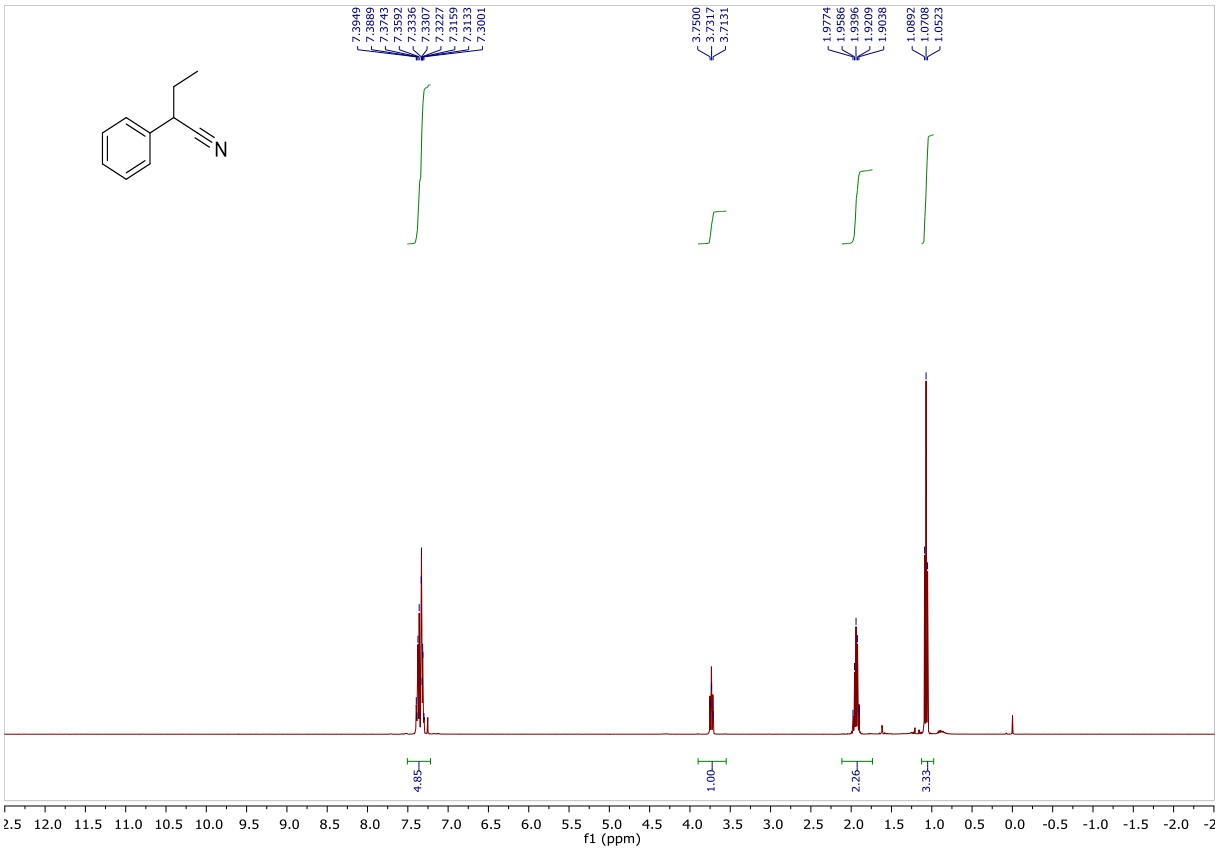

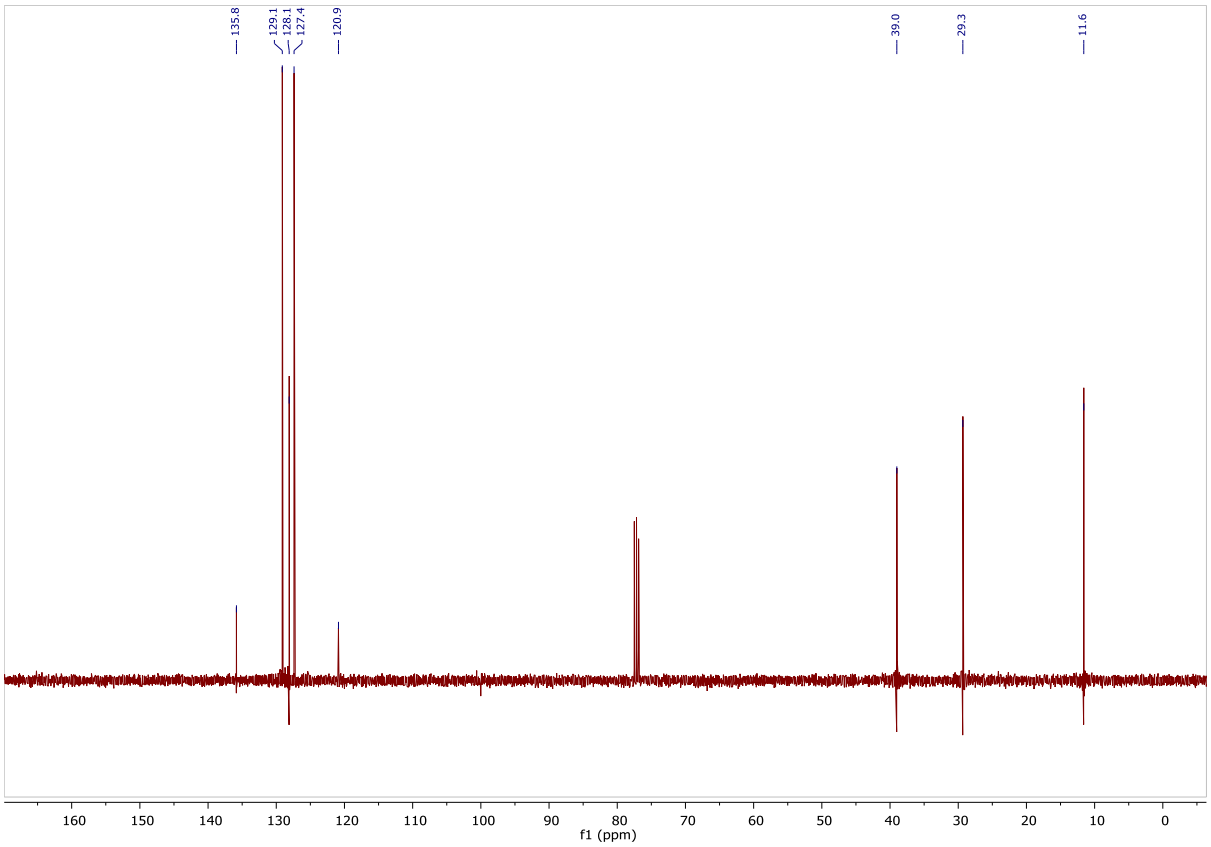

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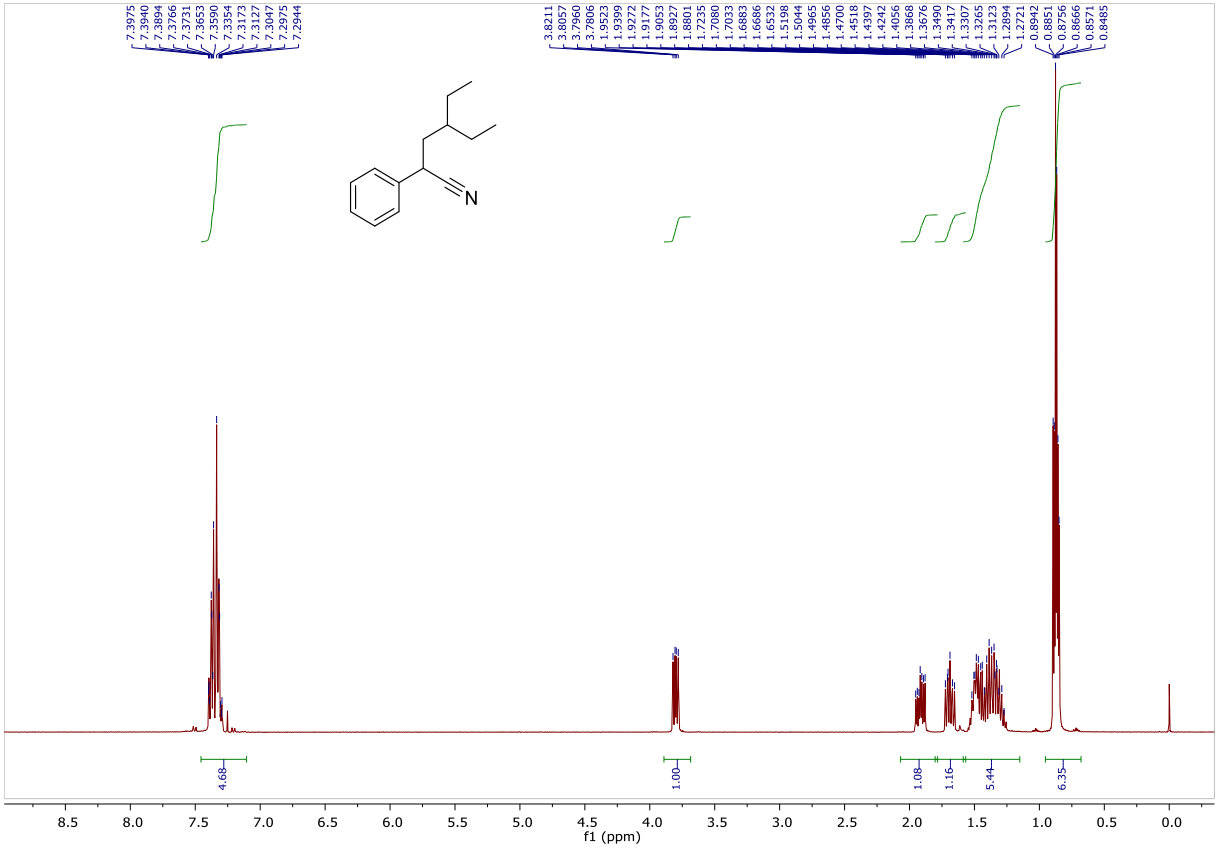
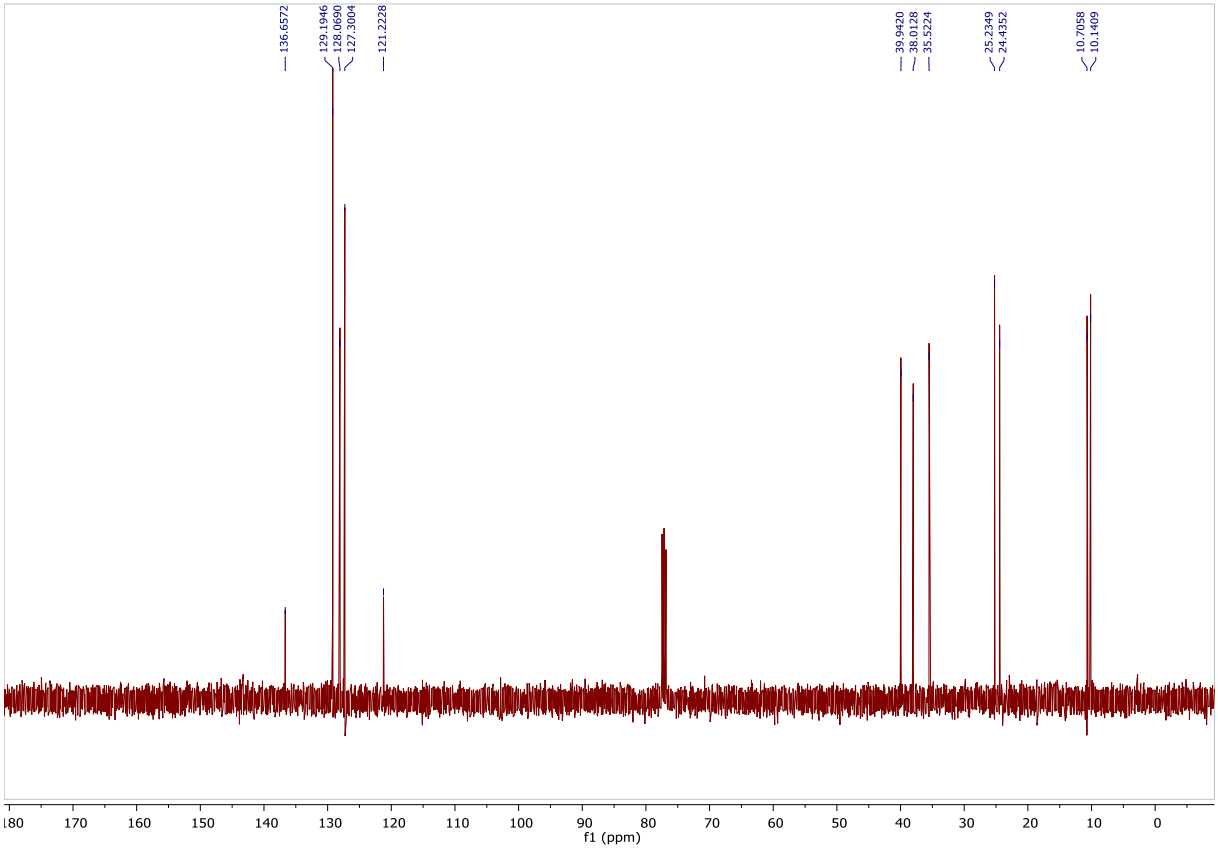
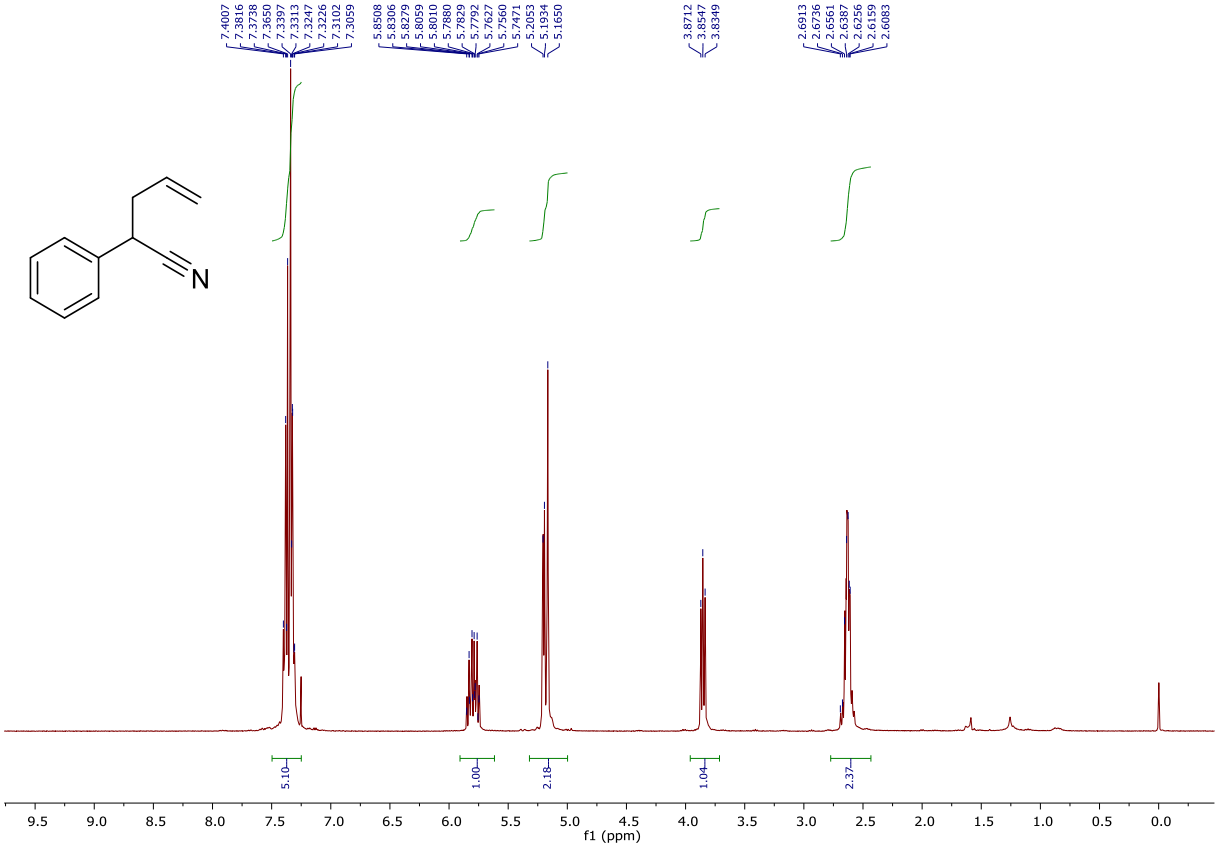
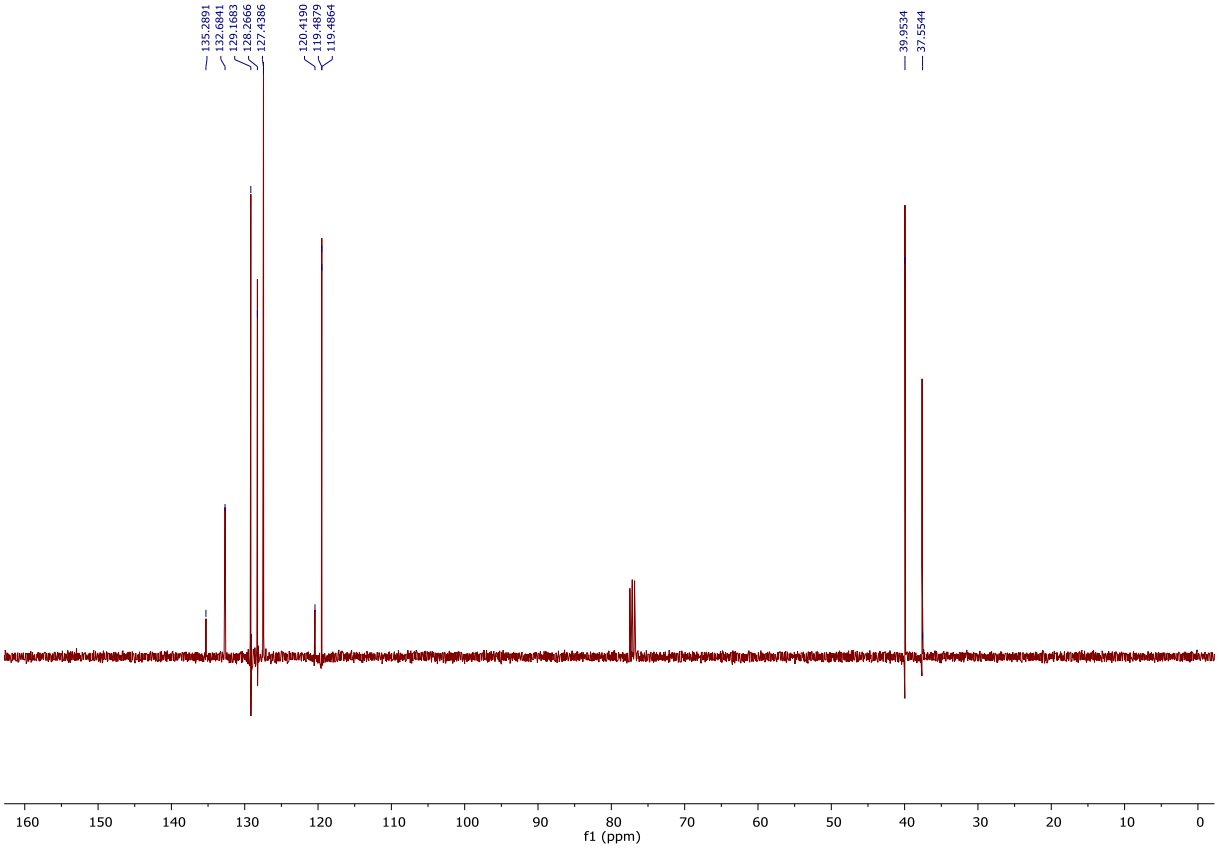




^{1}H and ^{13}C NMR compound for **6d**





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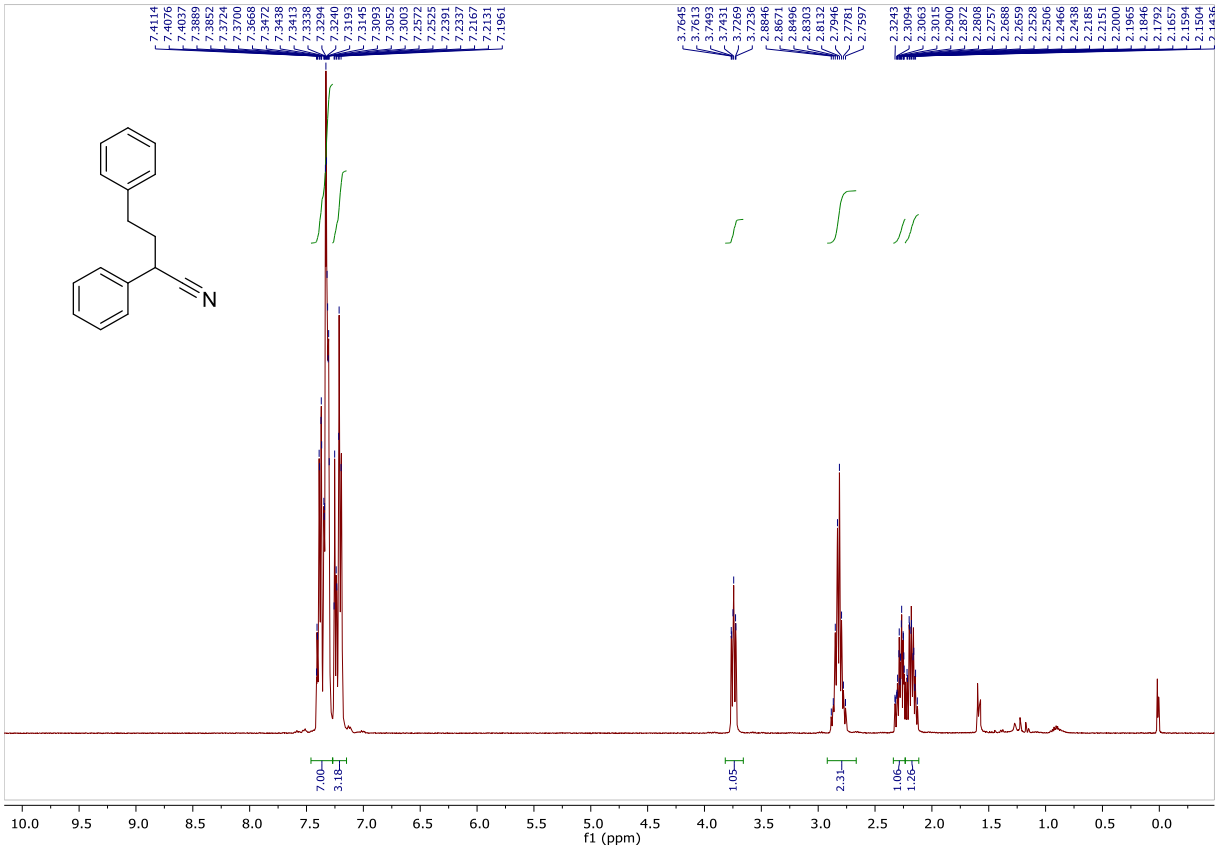

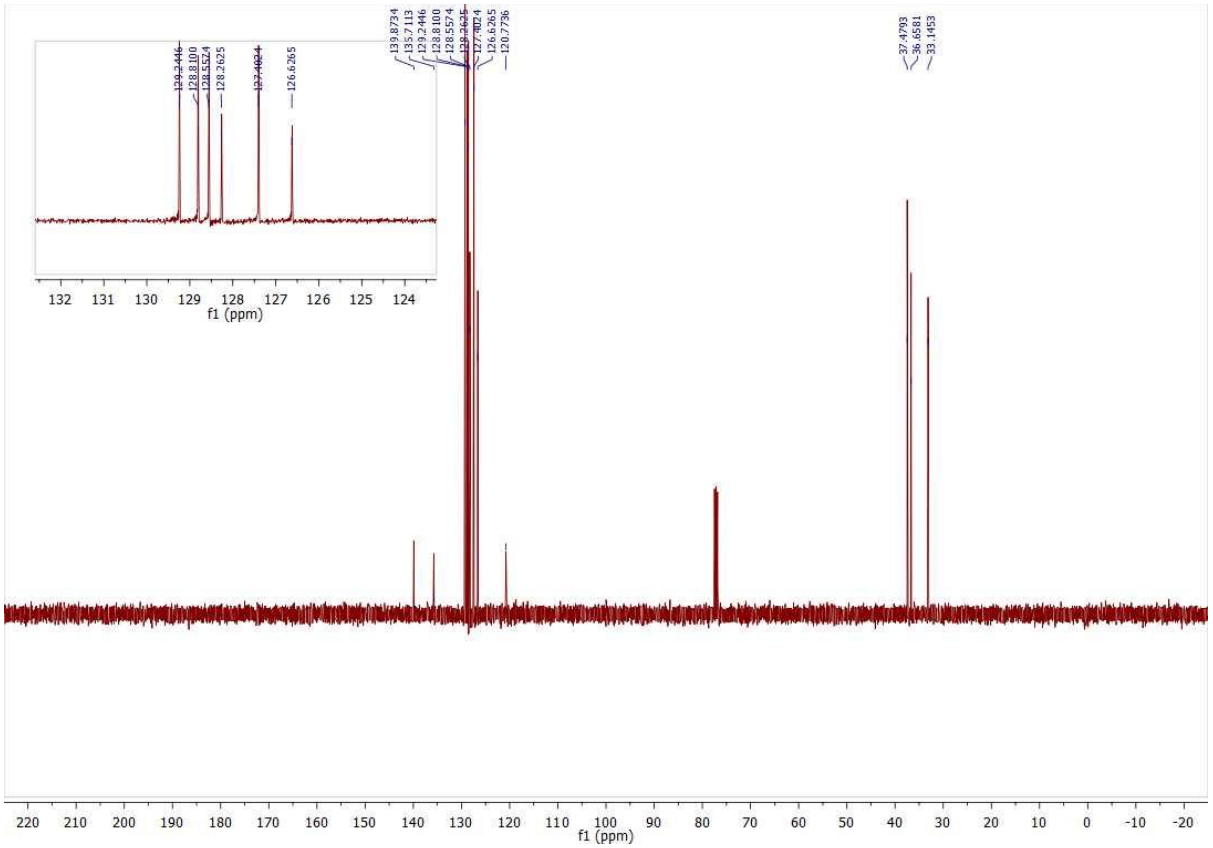

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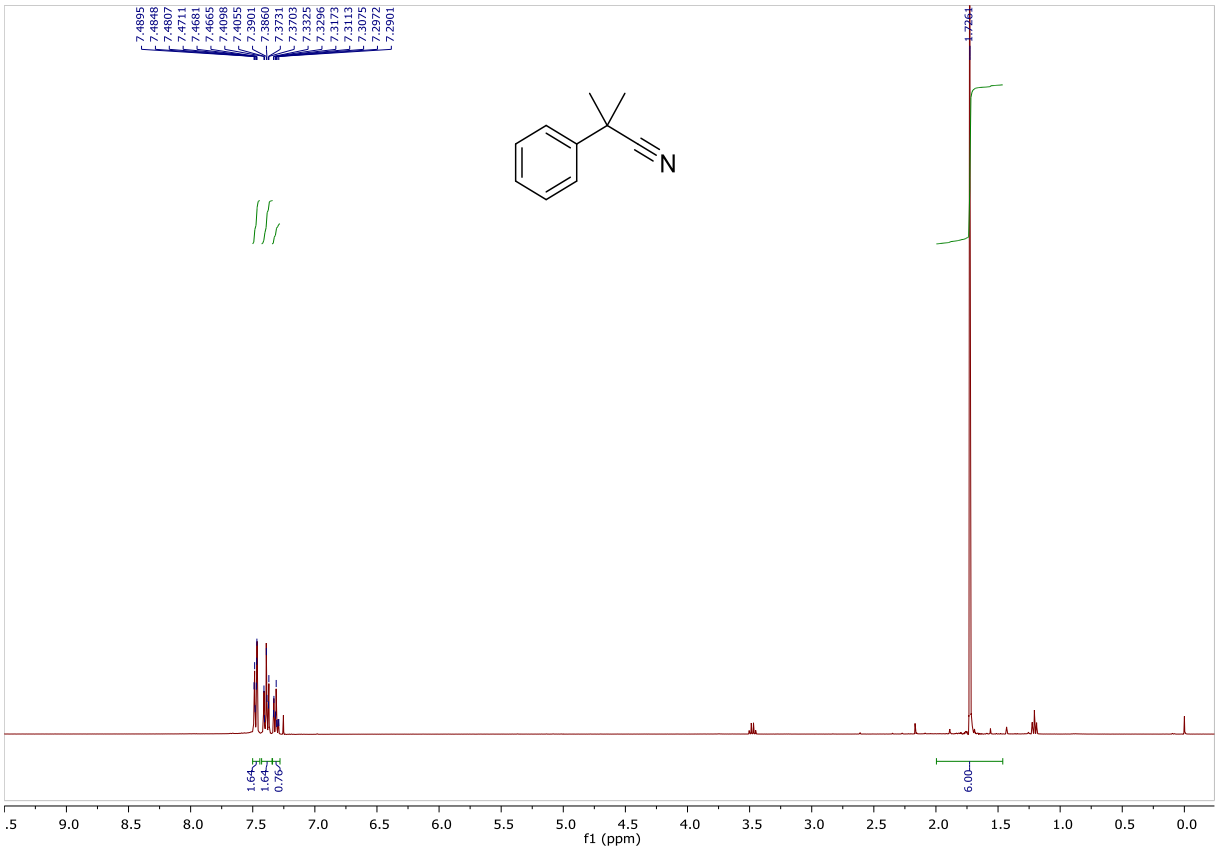
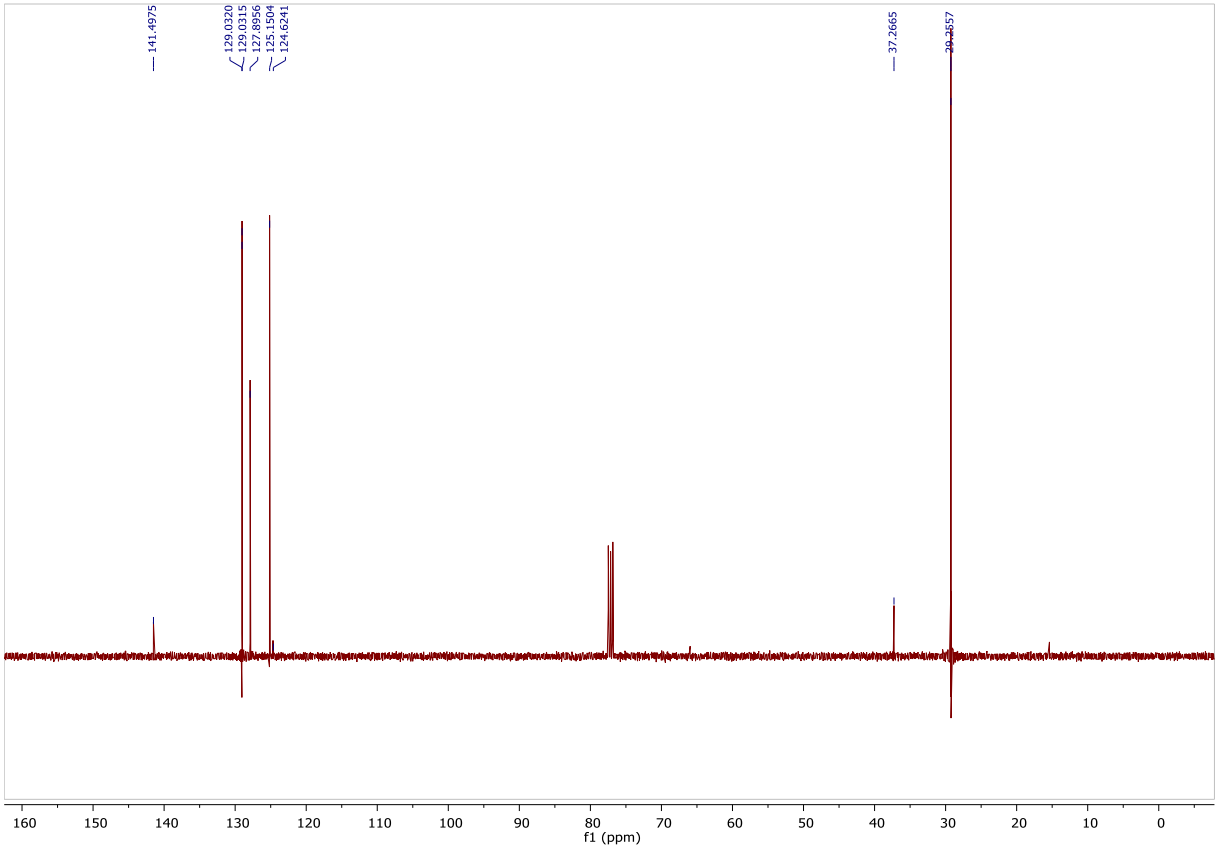
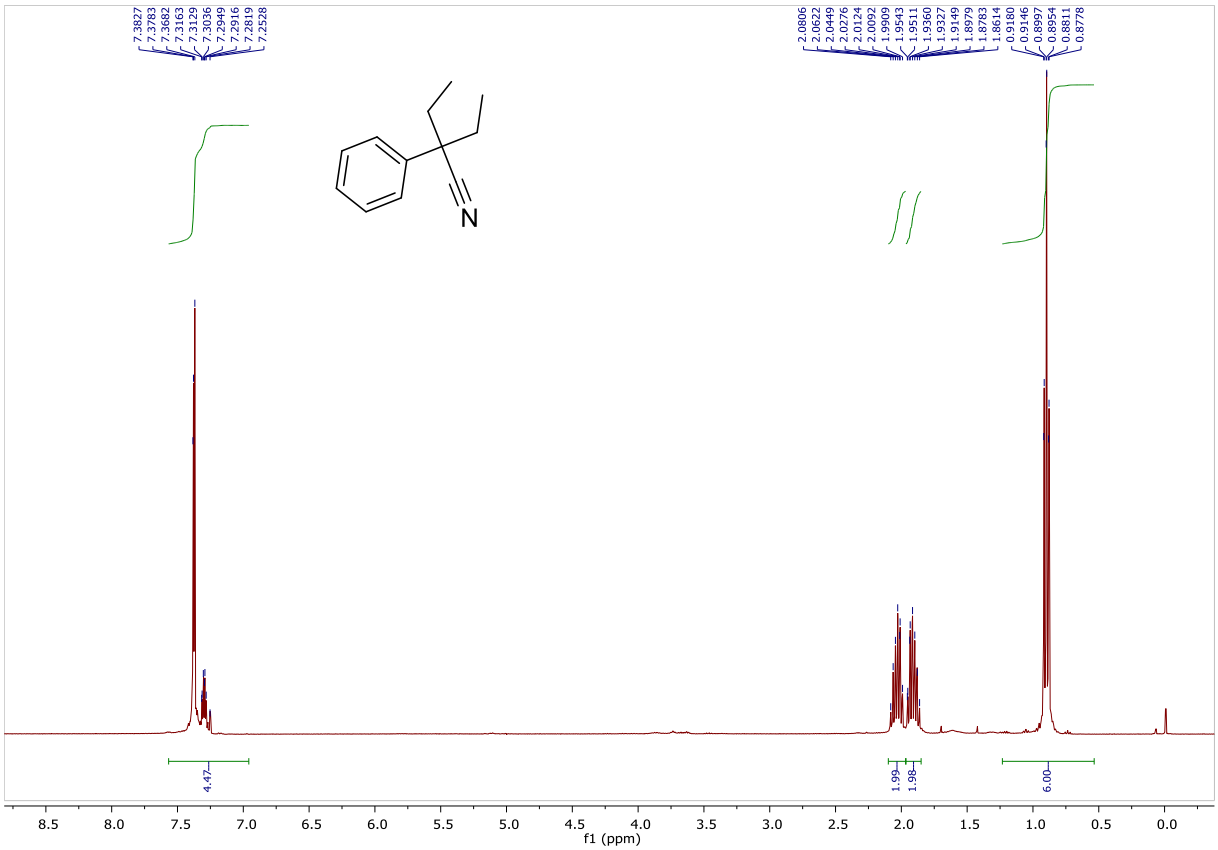
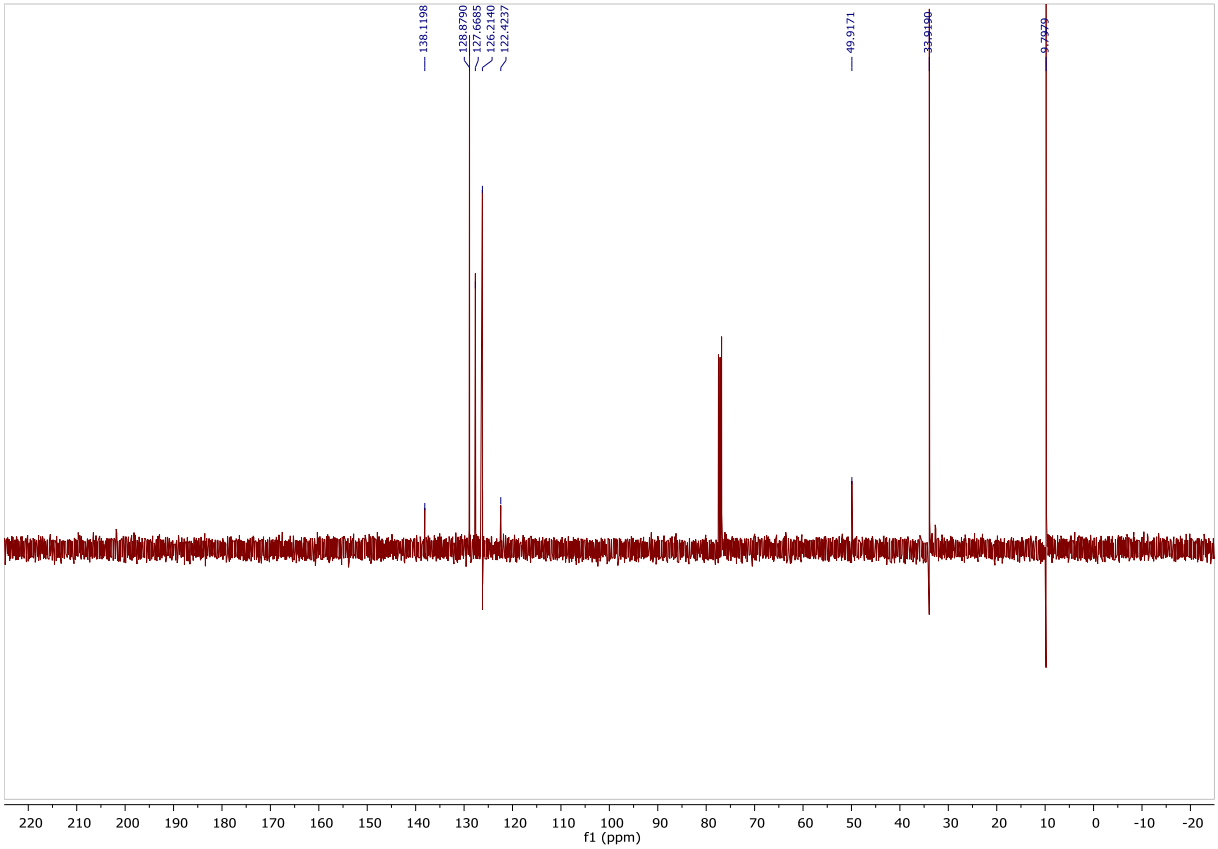




^{1}H and ^{13}C NMR compound for **7b**





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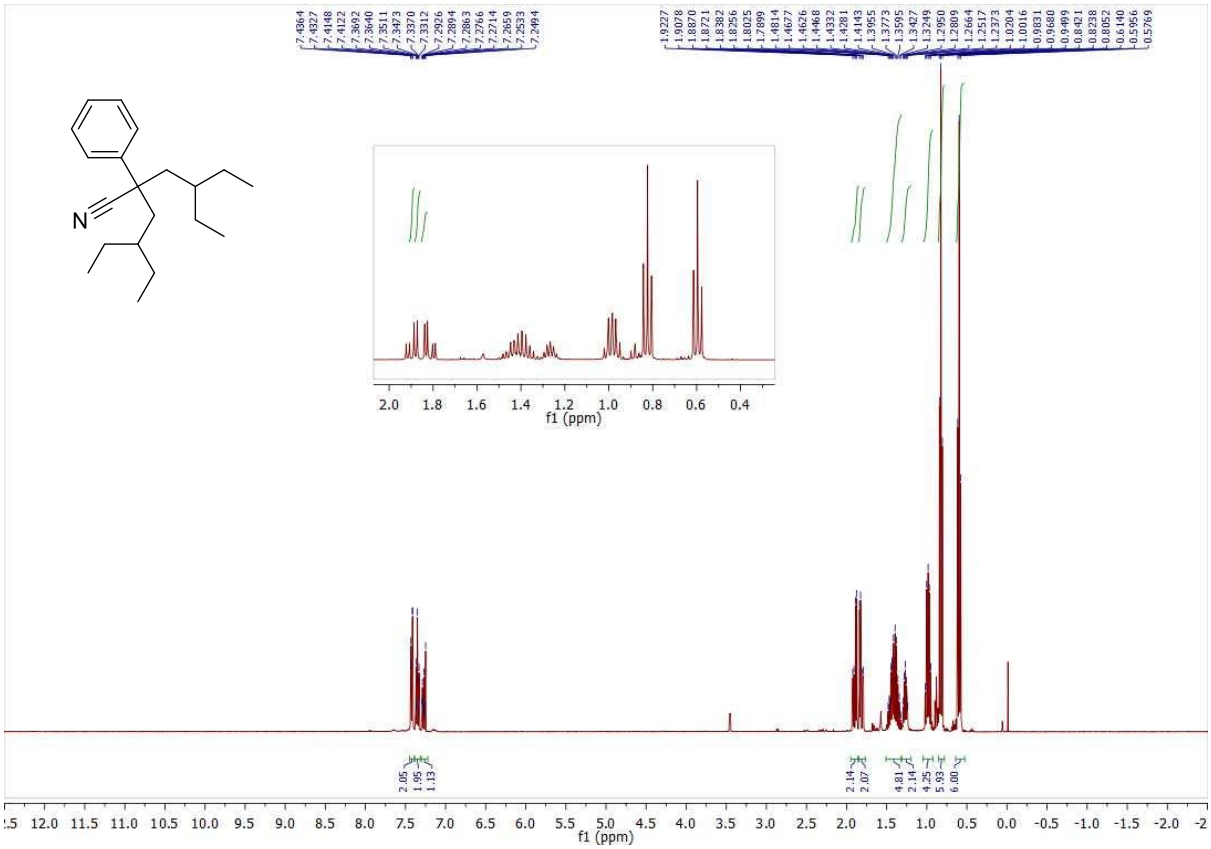
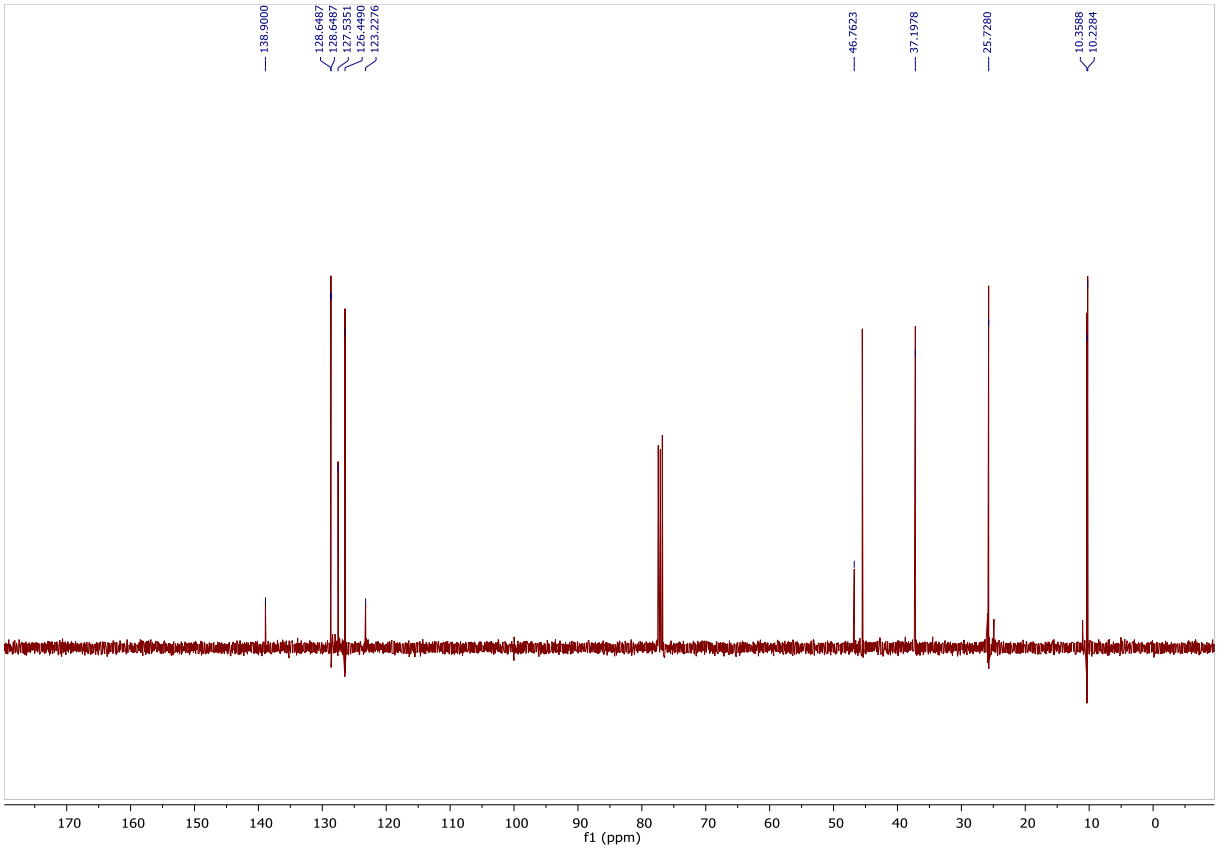
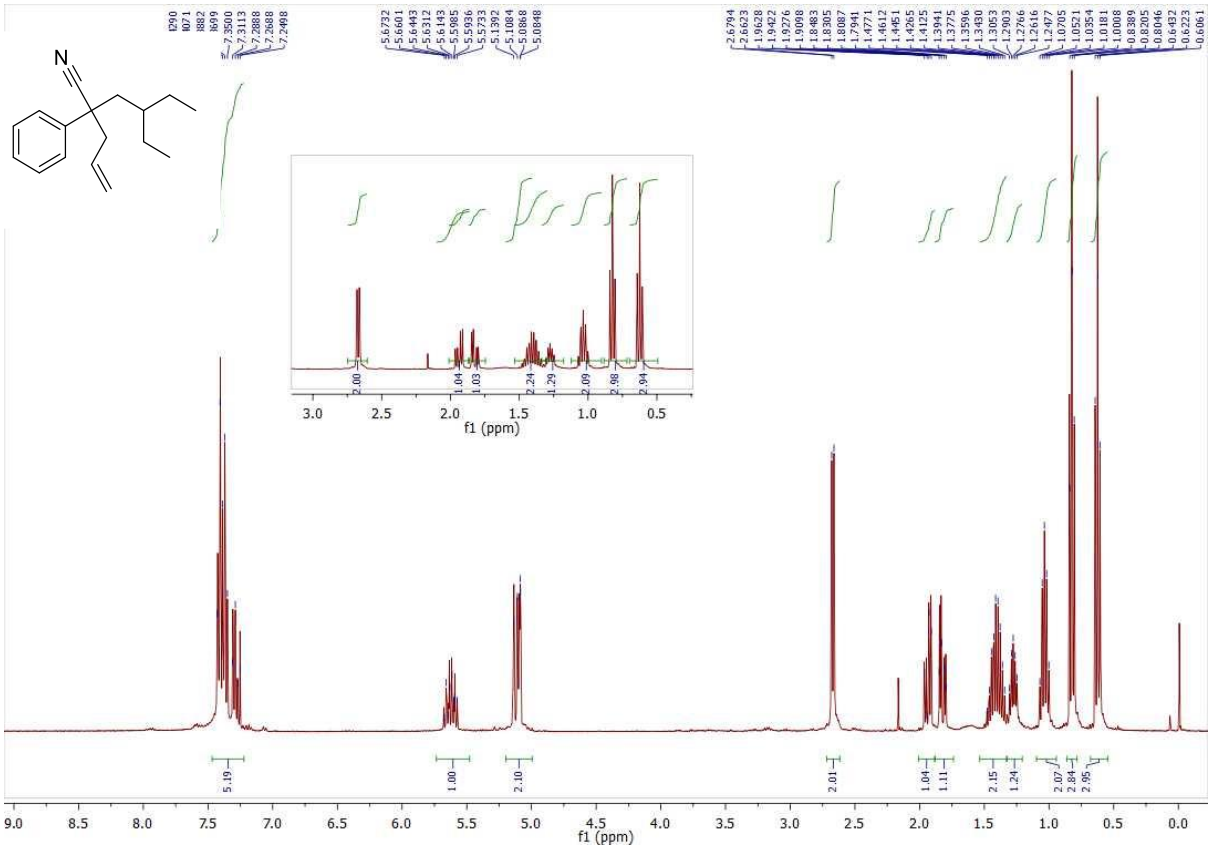
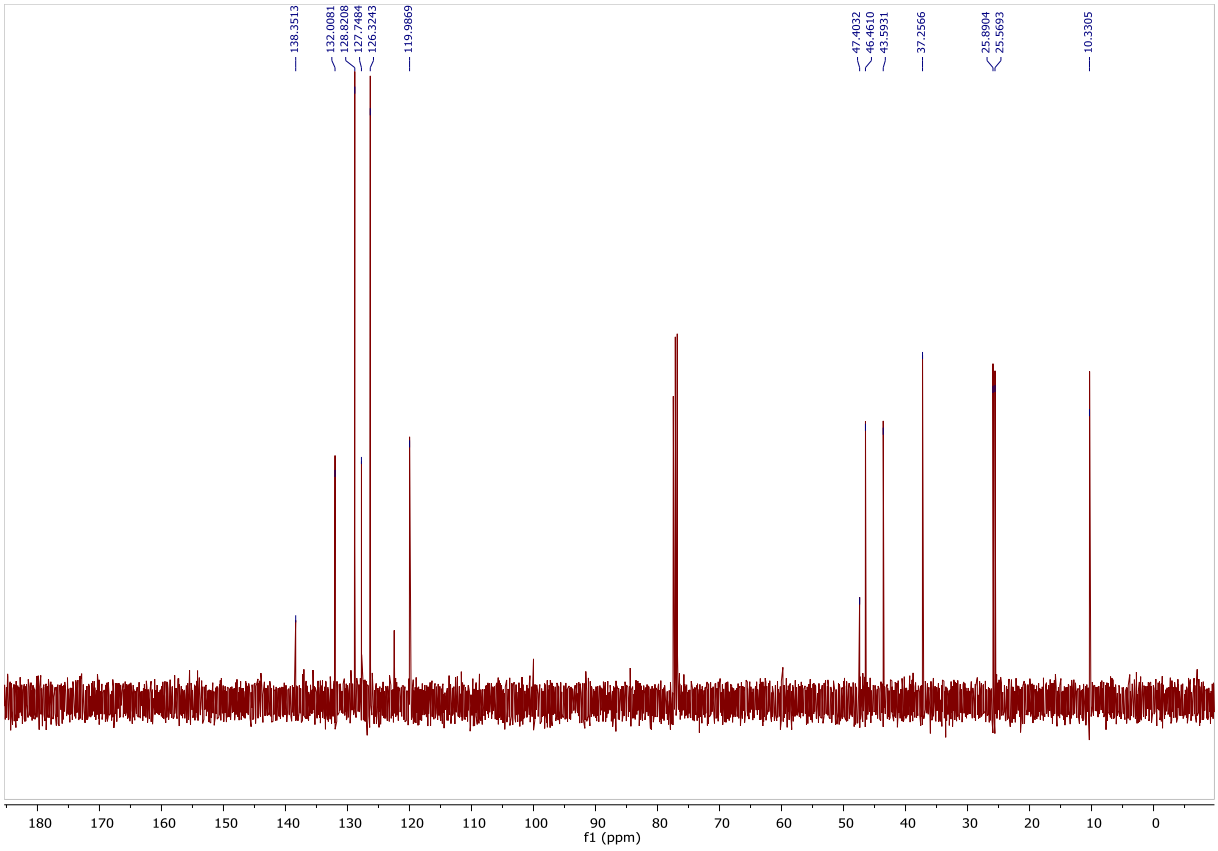


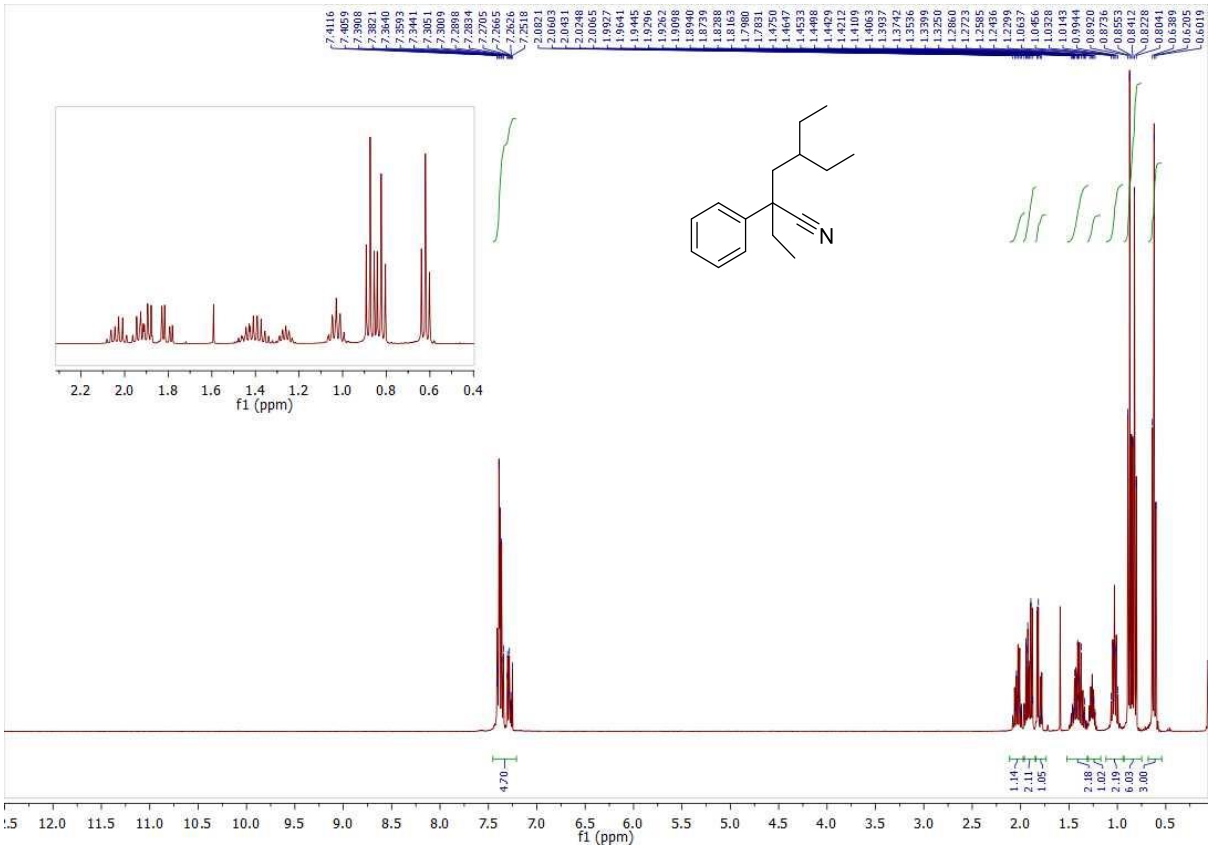


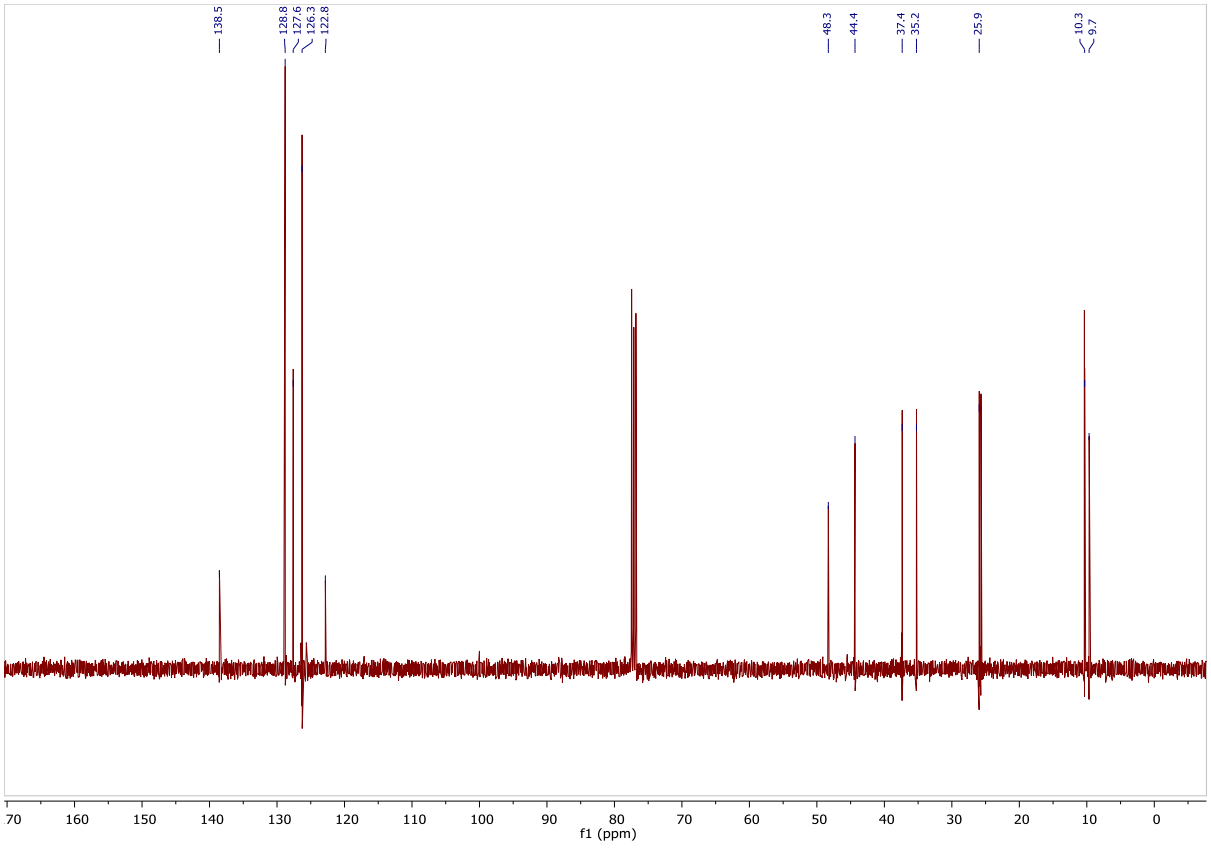
^{1}H and ^{13}C NMR compound for **7d**



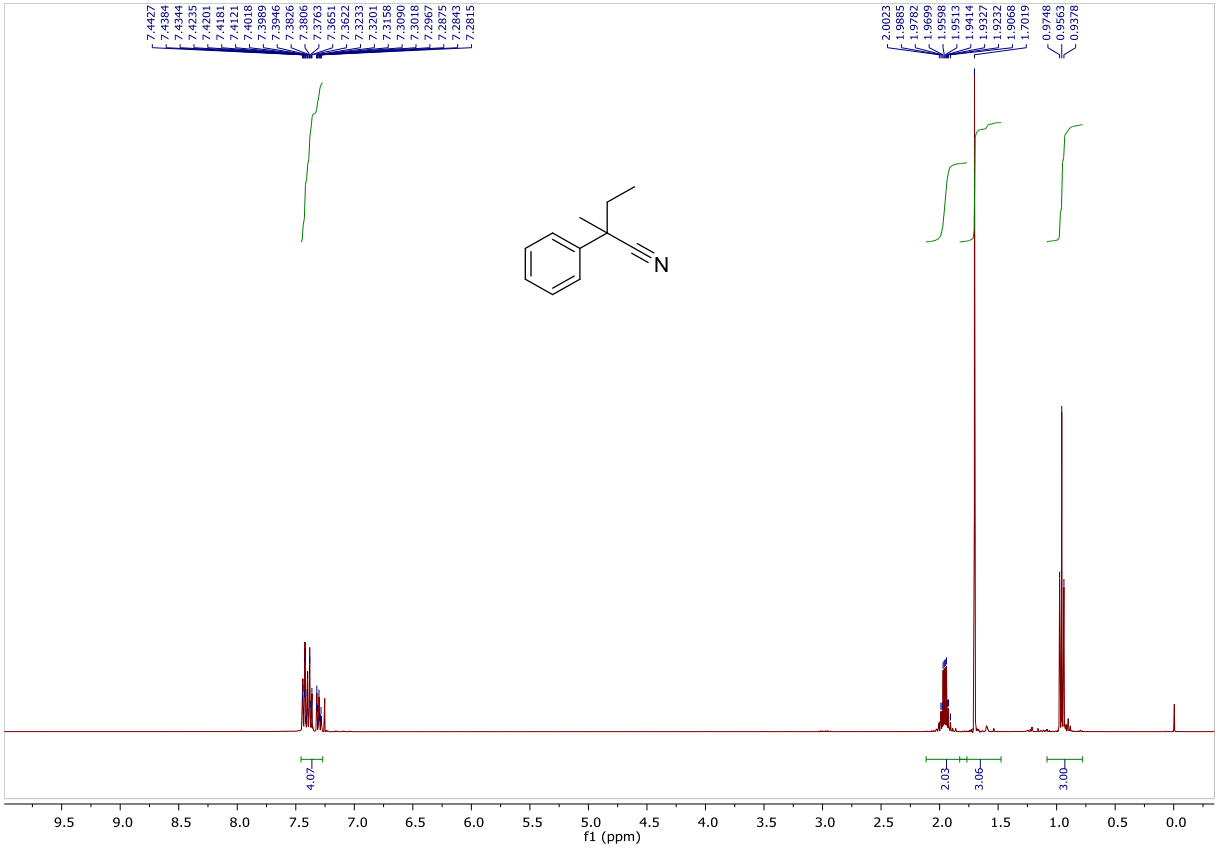


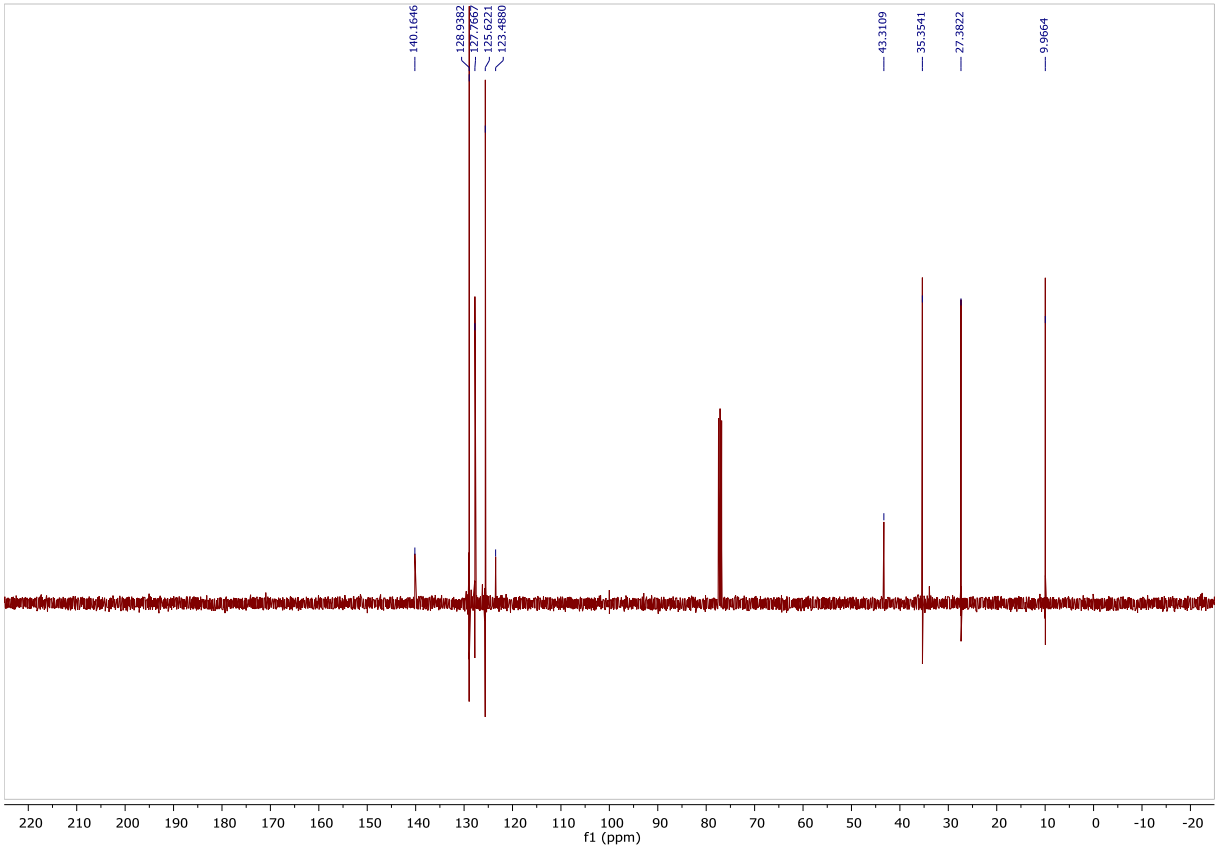
^{1}H and ^{13}C NMR compound for **7e**



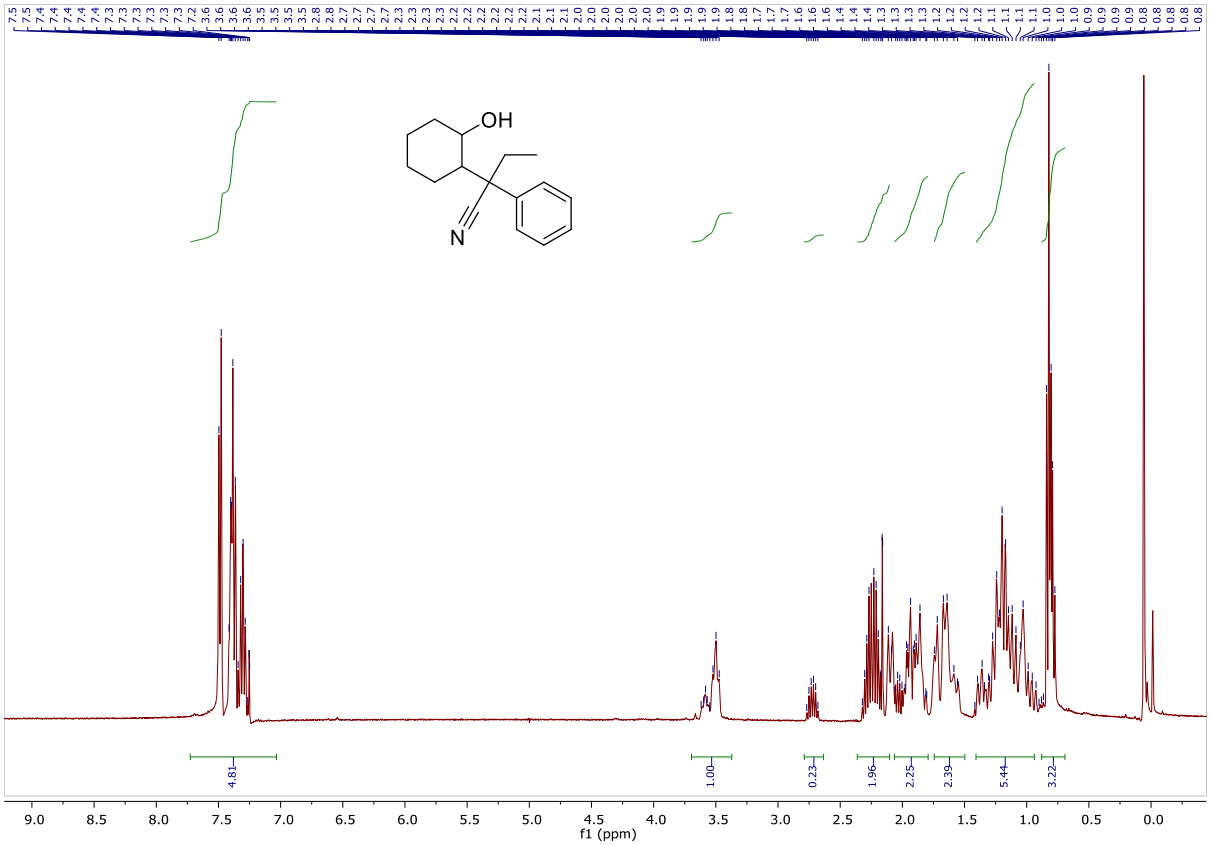


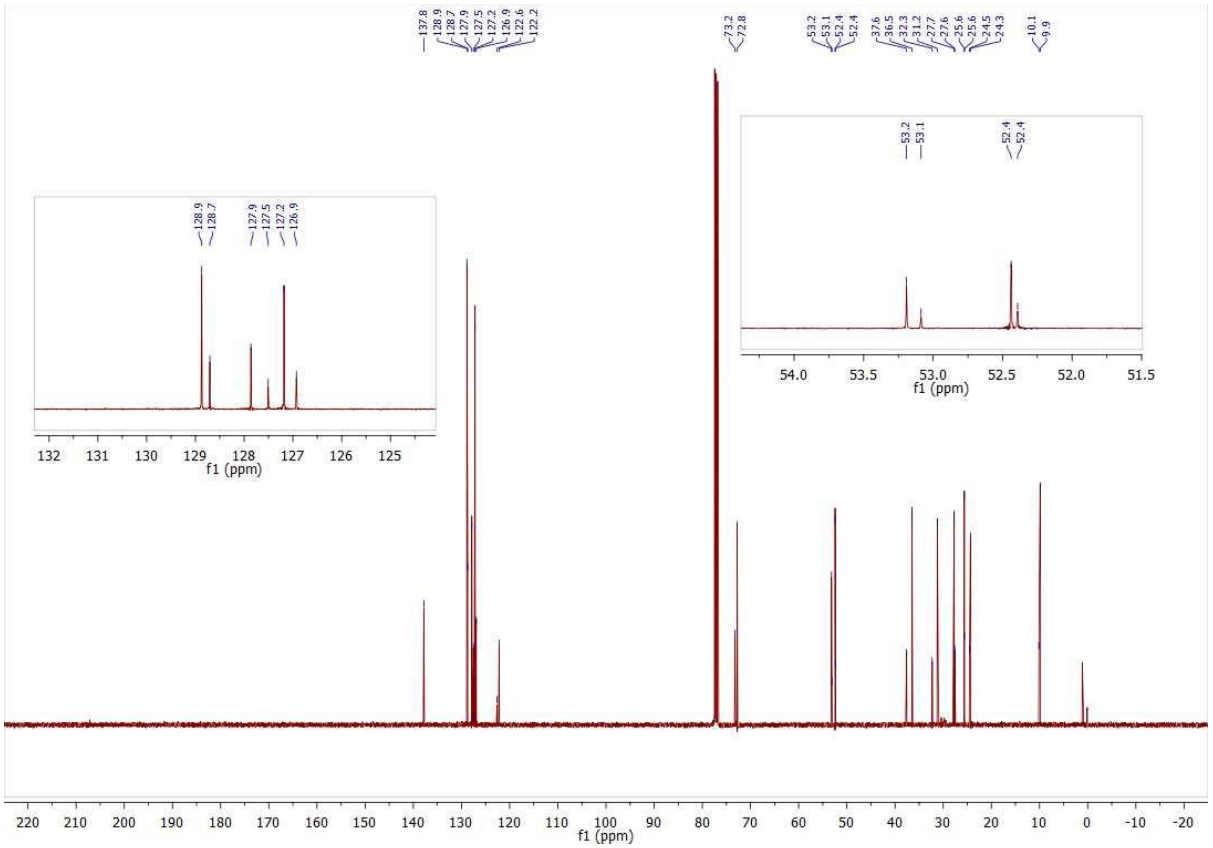
^{1}H and ^{13}C NMR compound for **7f**



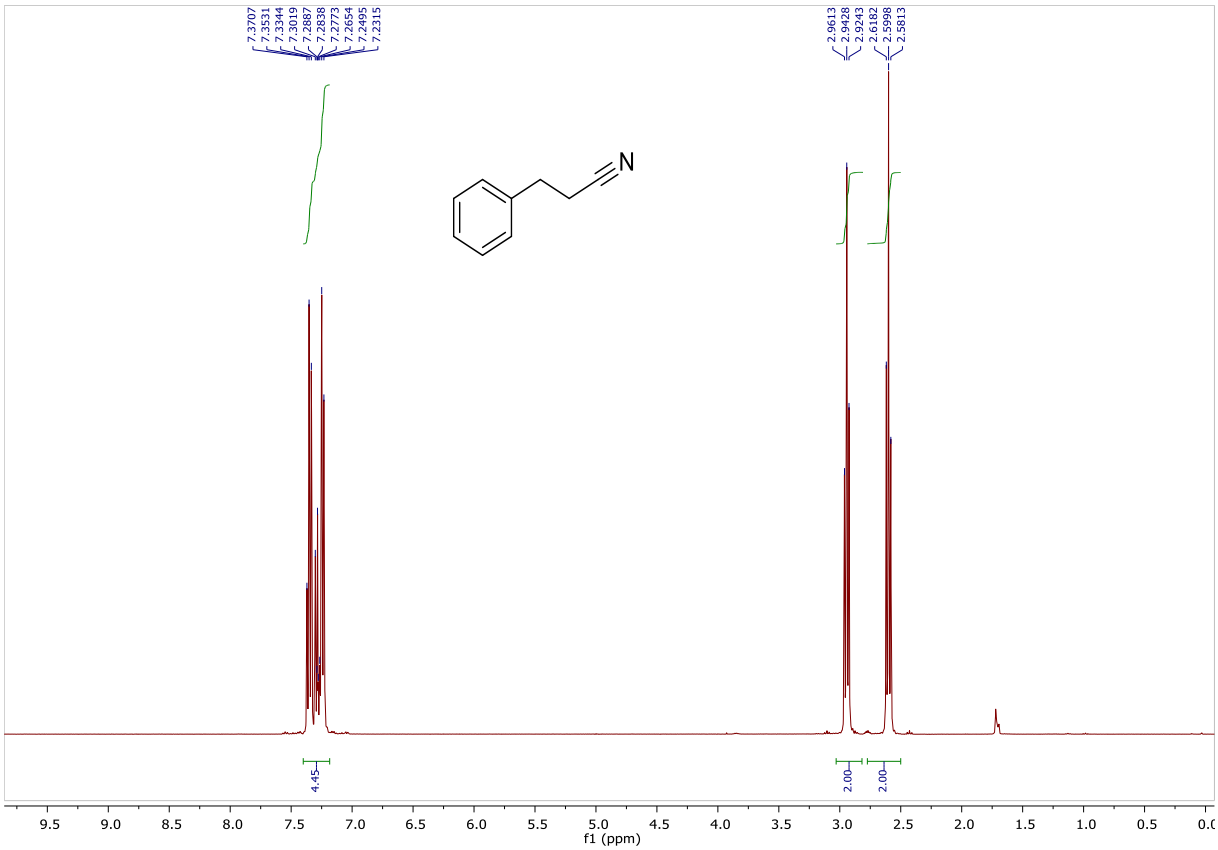


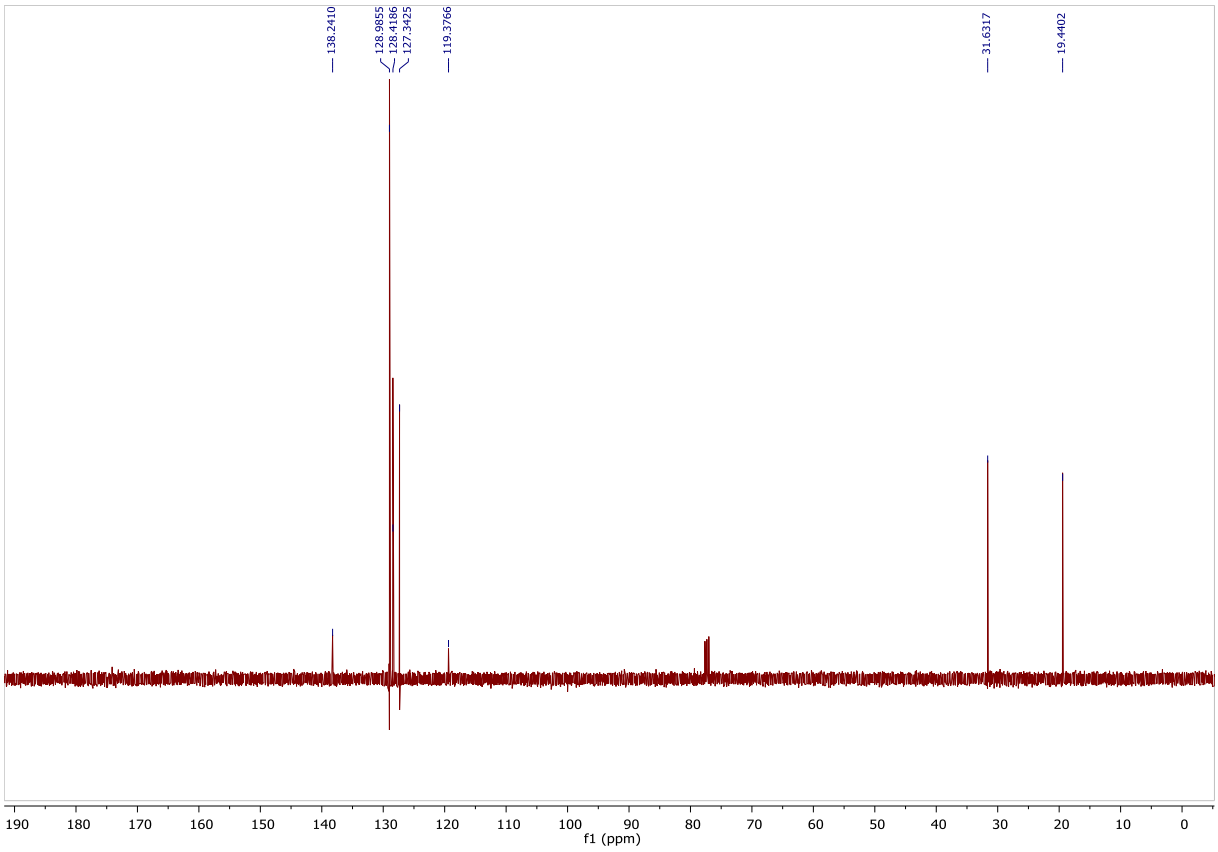
^{1}H and ^{13}C NMR compound for **7g**



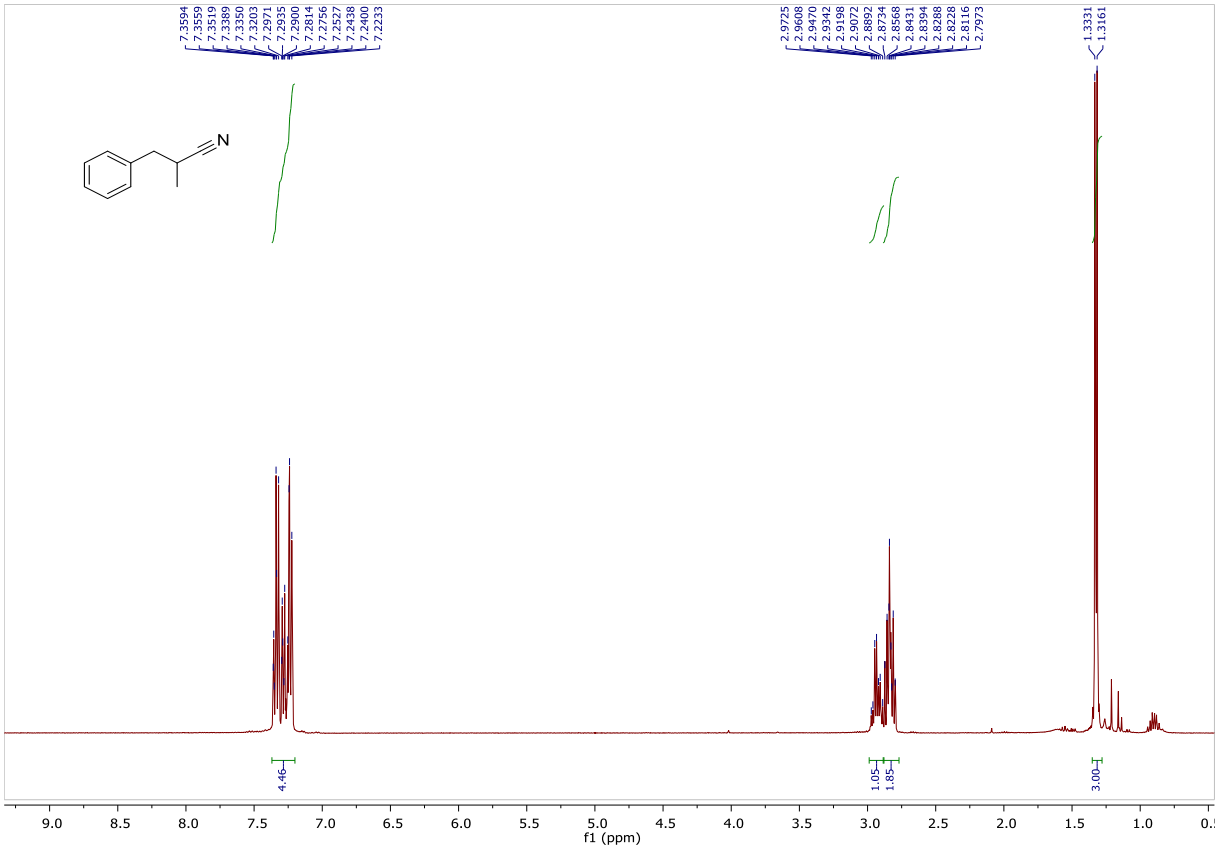


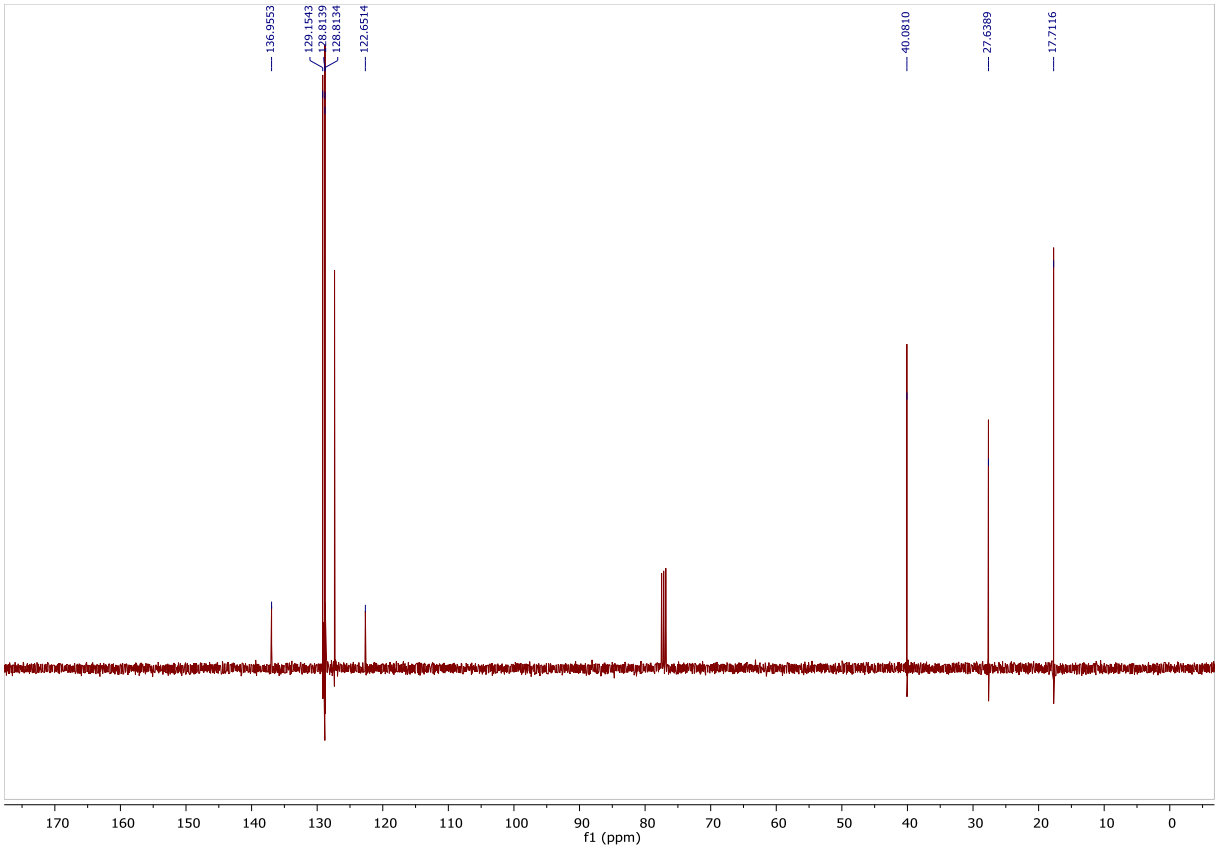
^{1}H and ^{13}C NMR compound for **13a**



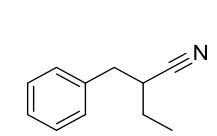


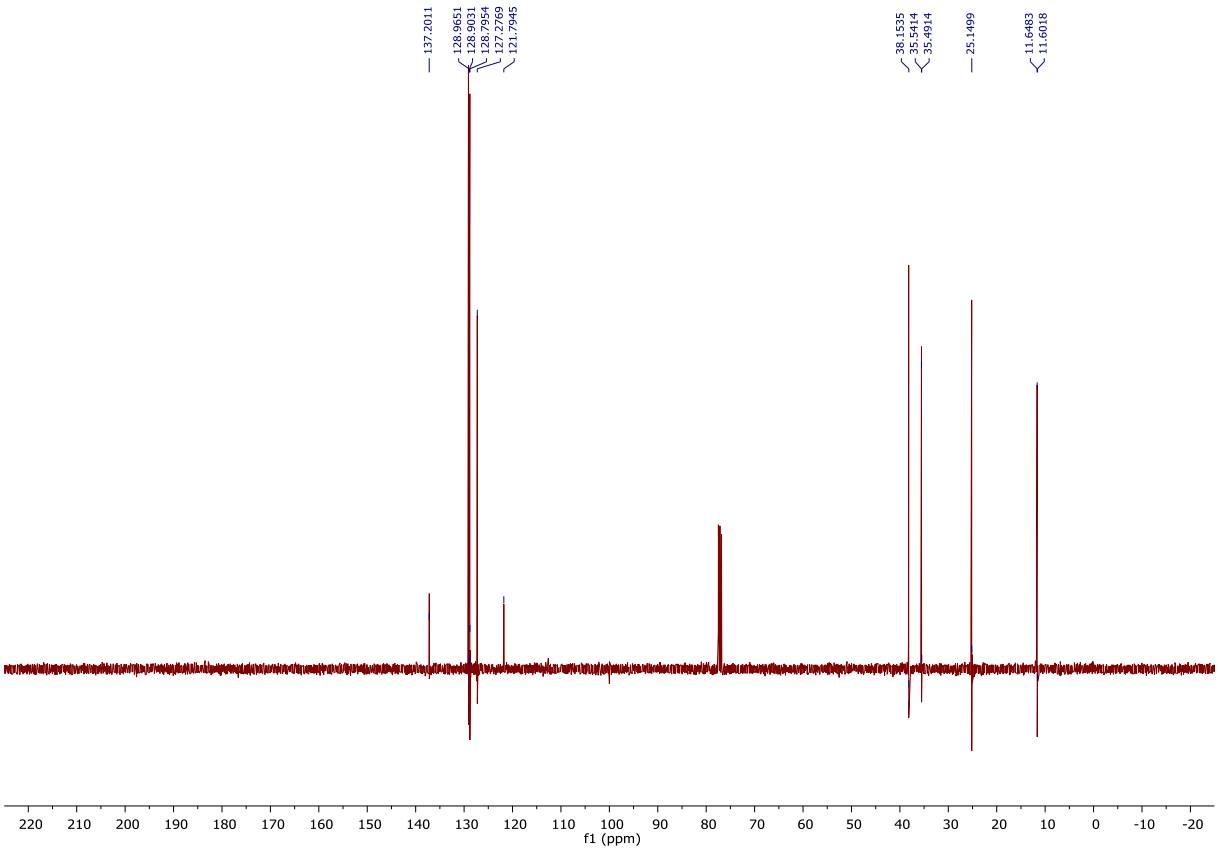
^{1}H and ^{13}C NMR compound for **14a**



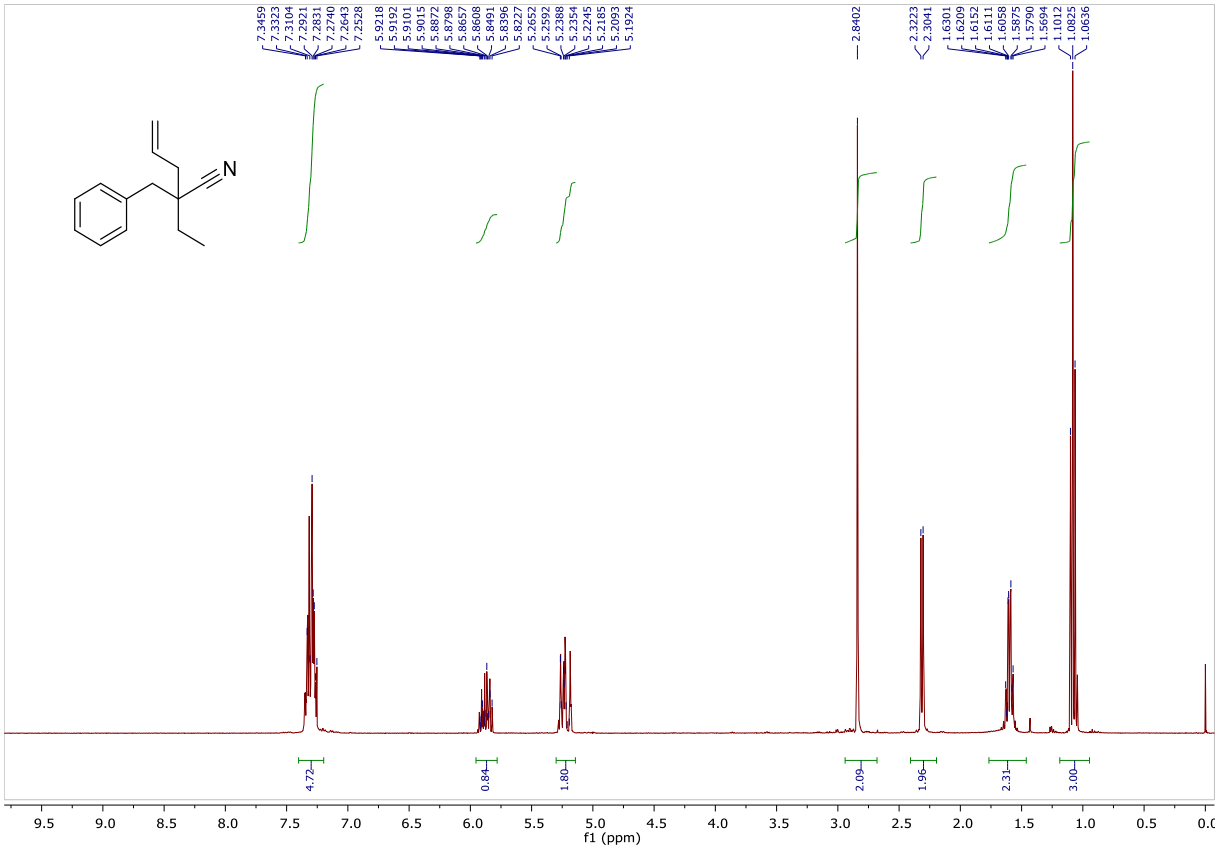


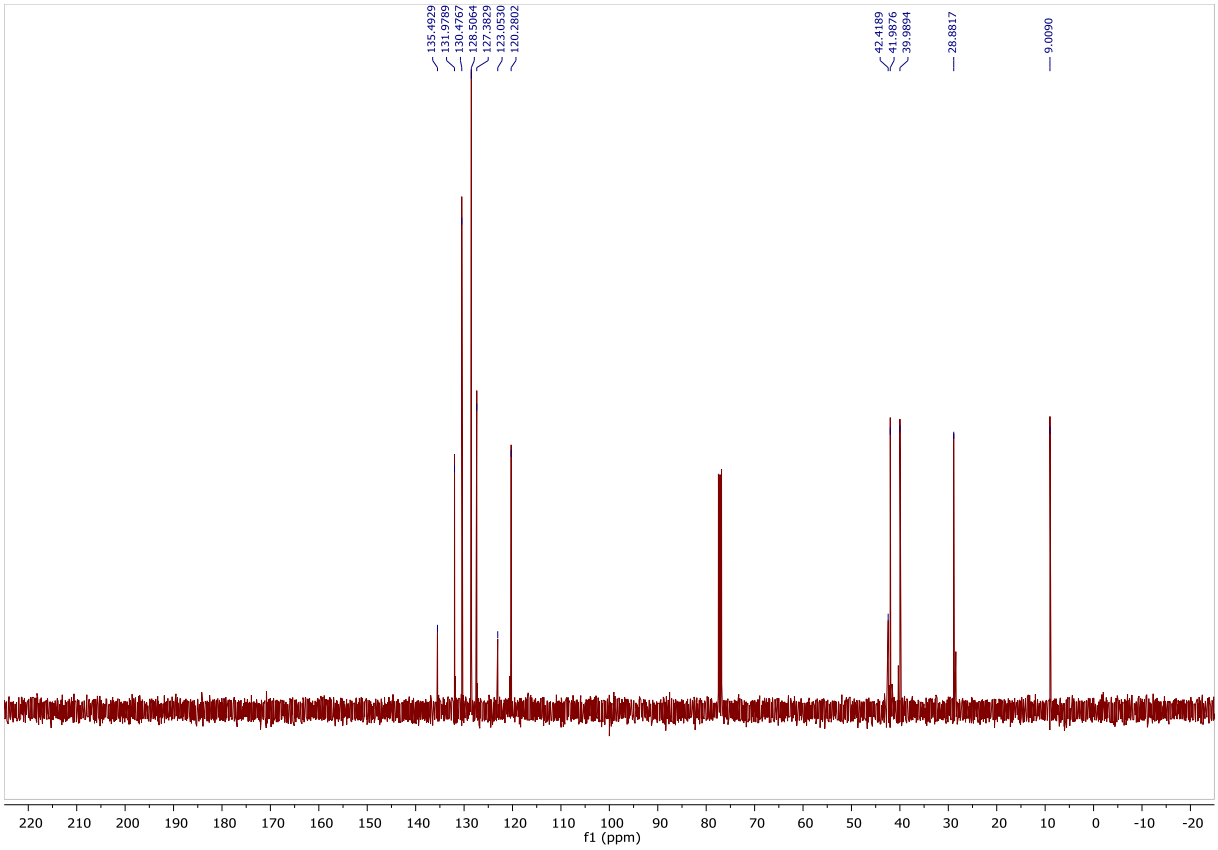
^{1}H and ^{13}C NMR compound for **14b**



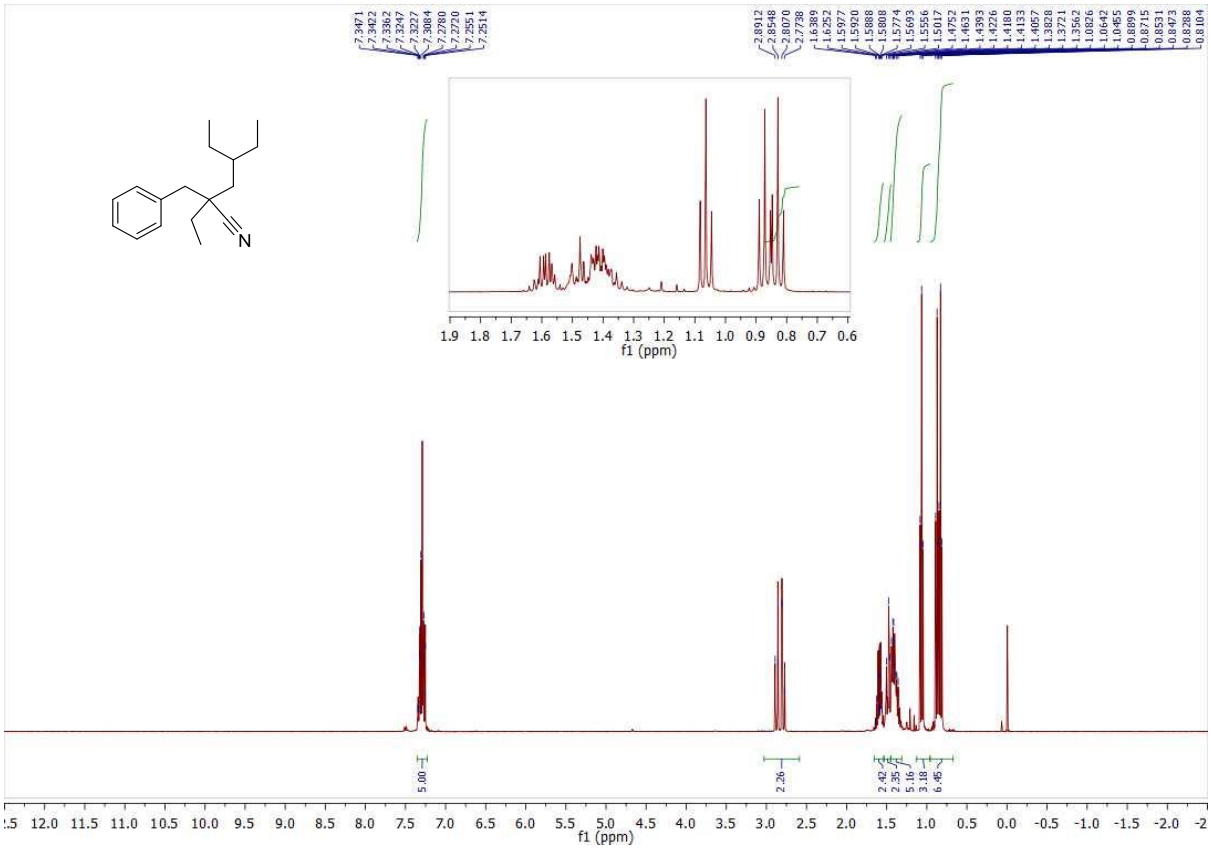


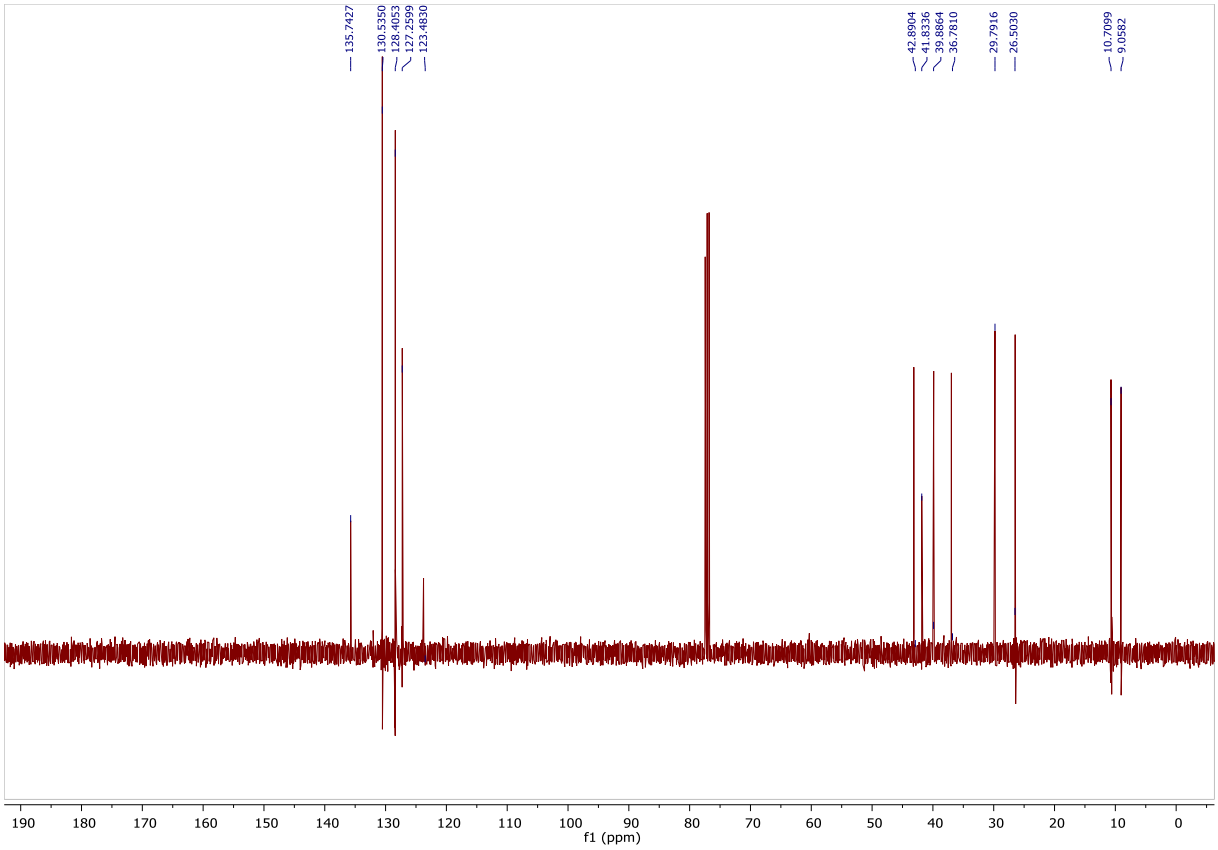
^{1}H and ^{13}C NMR compound for **15e**



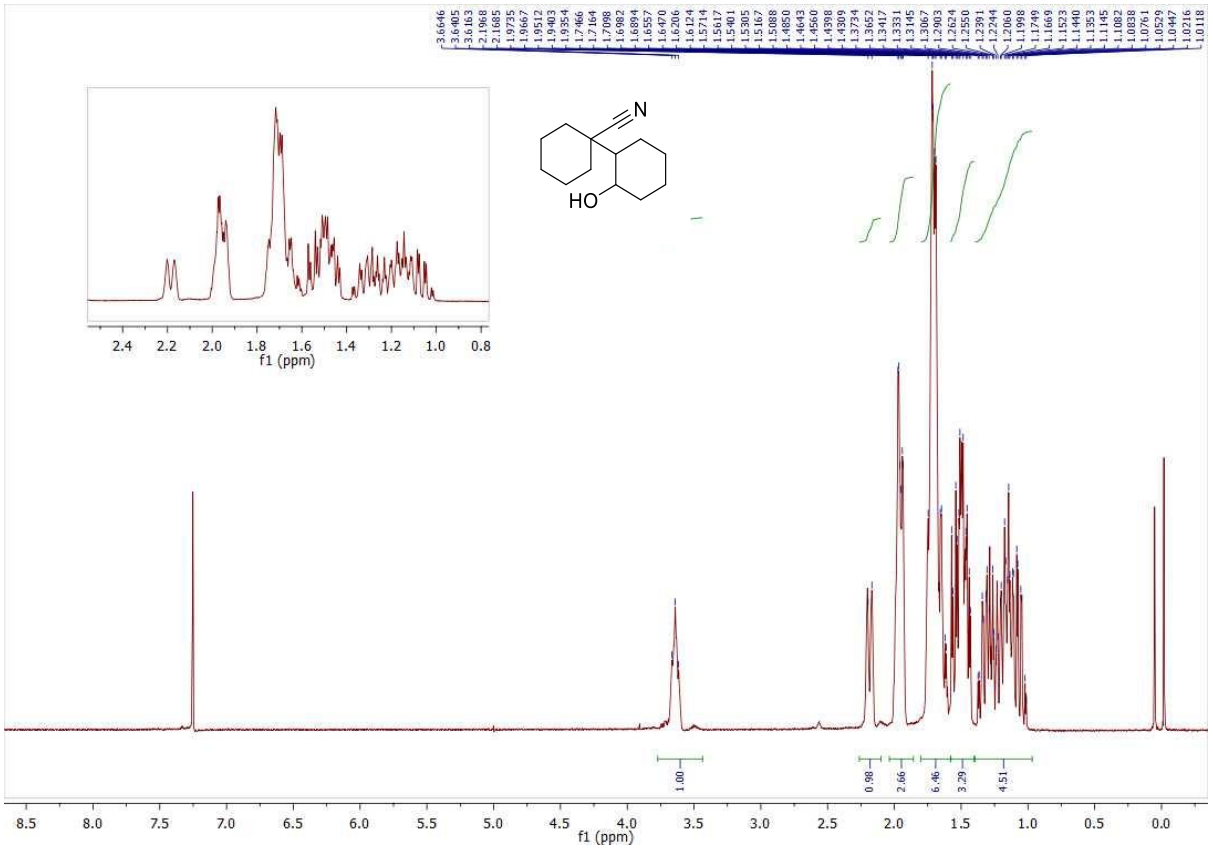


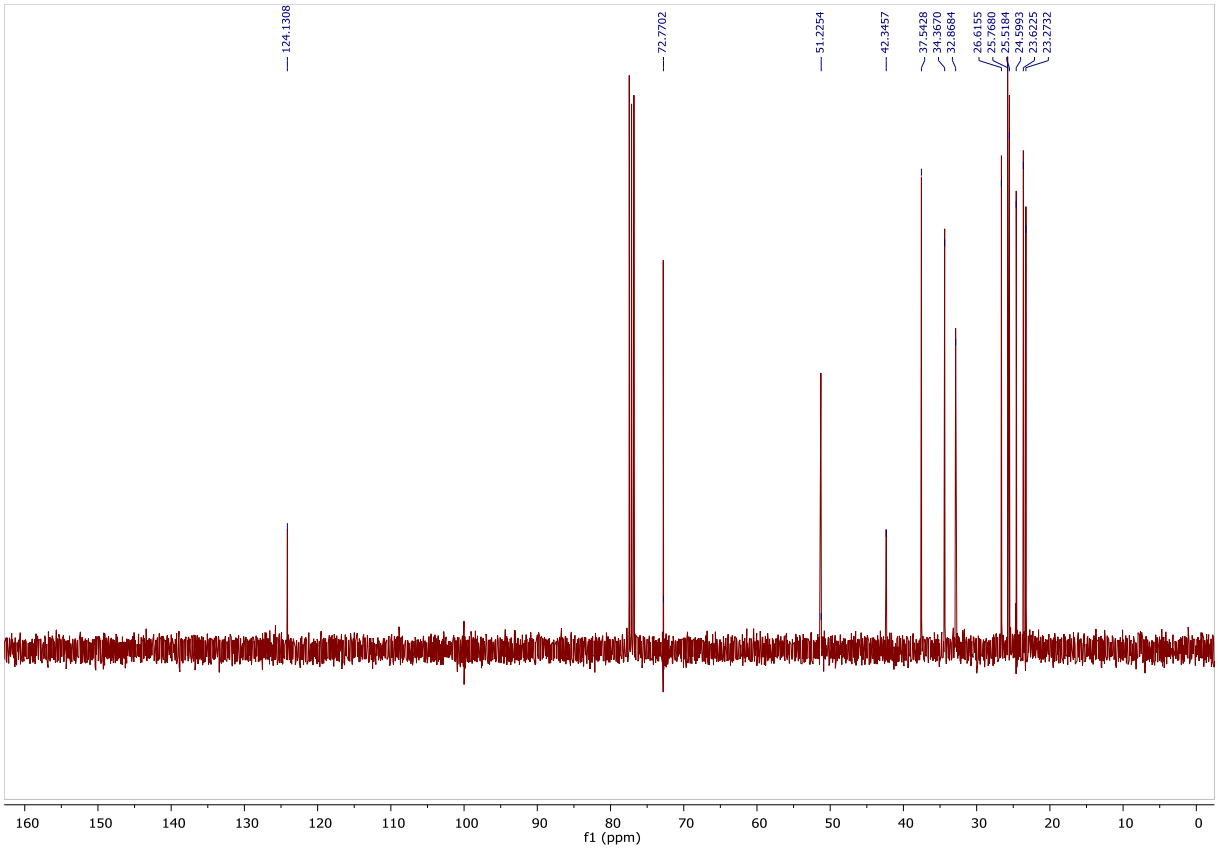
^{1}H and ^{13}C NMR compound for **15d**



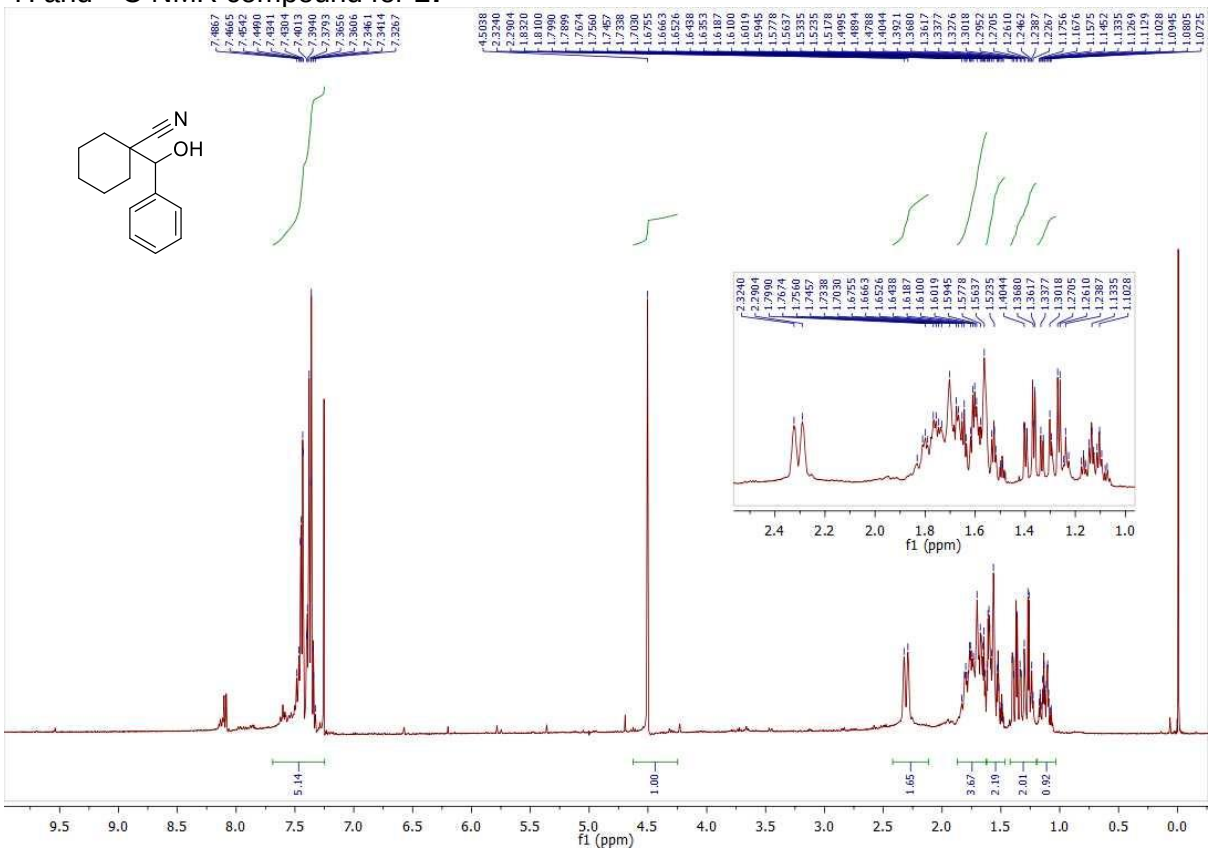


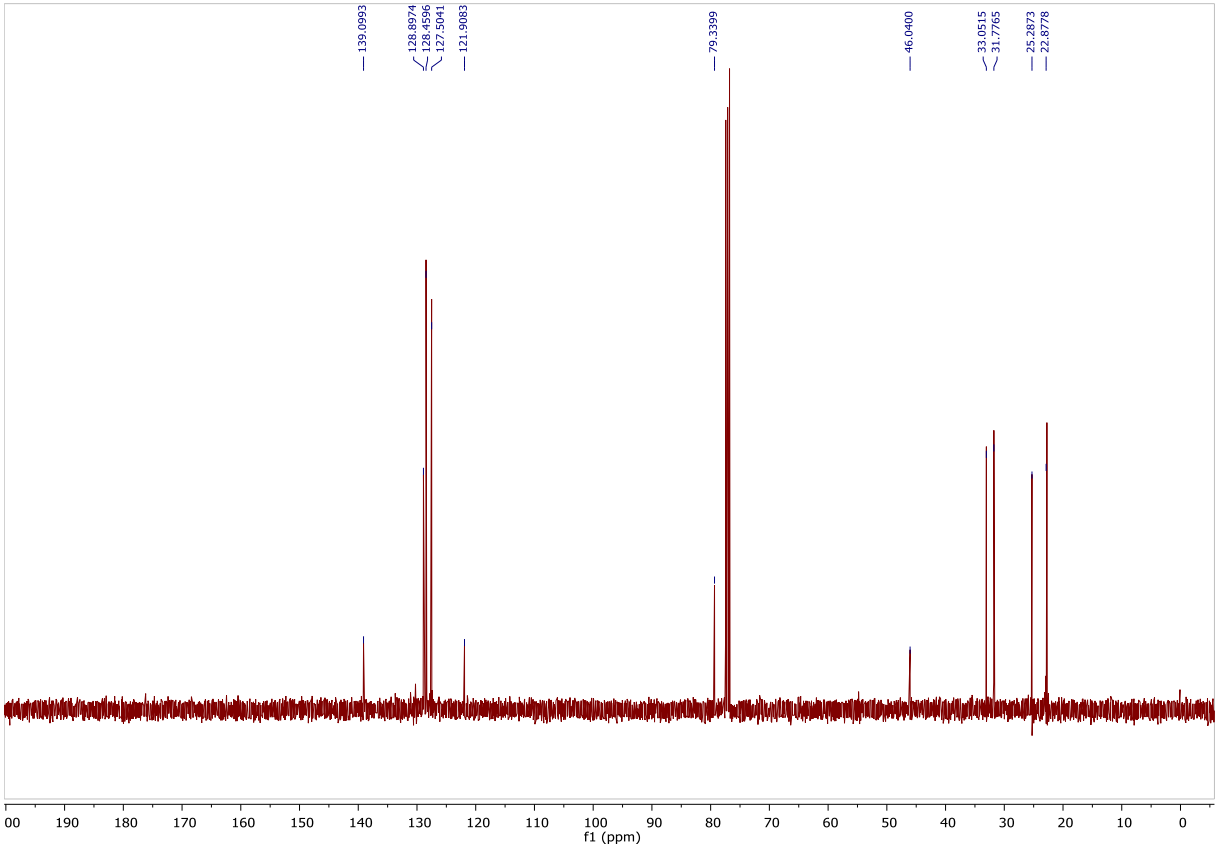
^{1}H and ^{13}C NMR compound for **16**



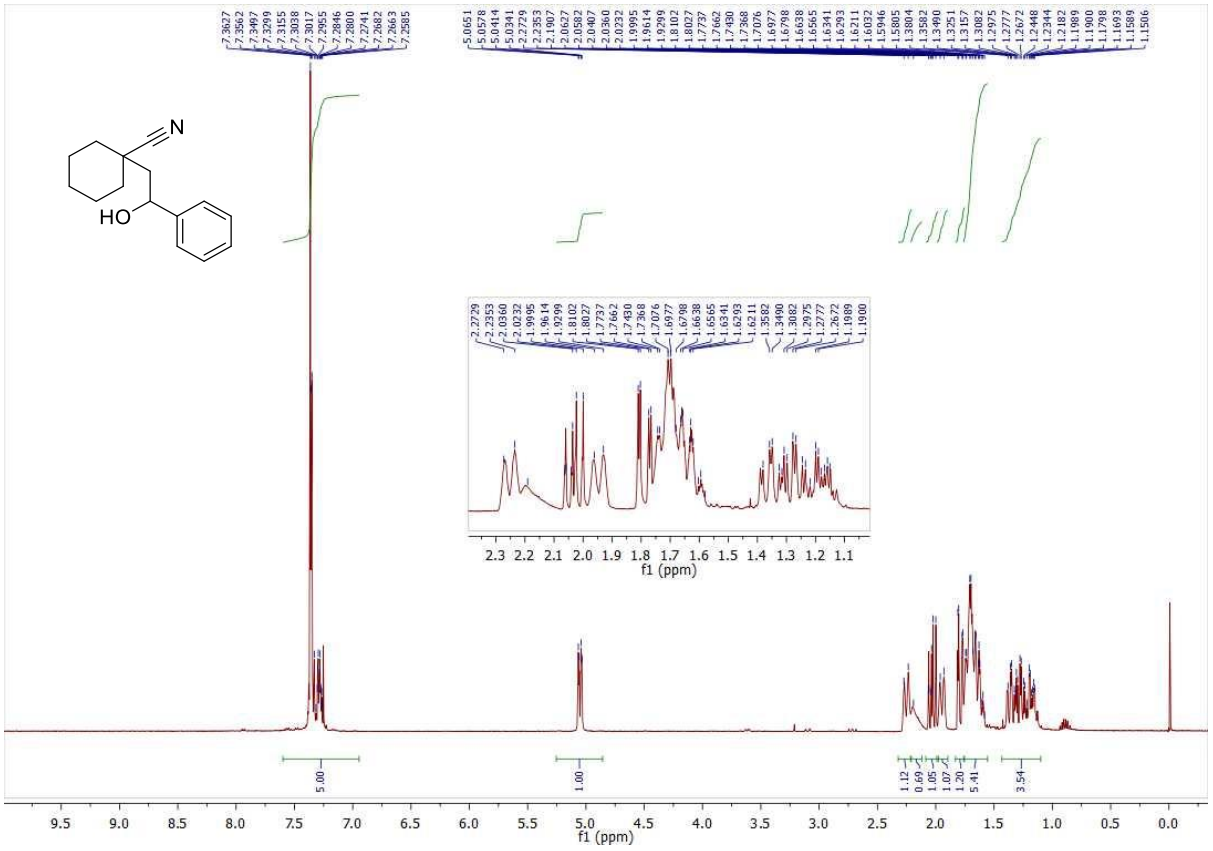


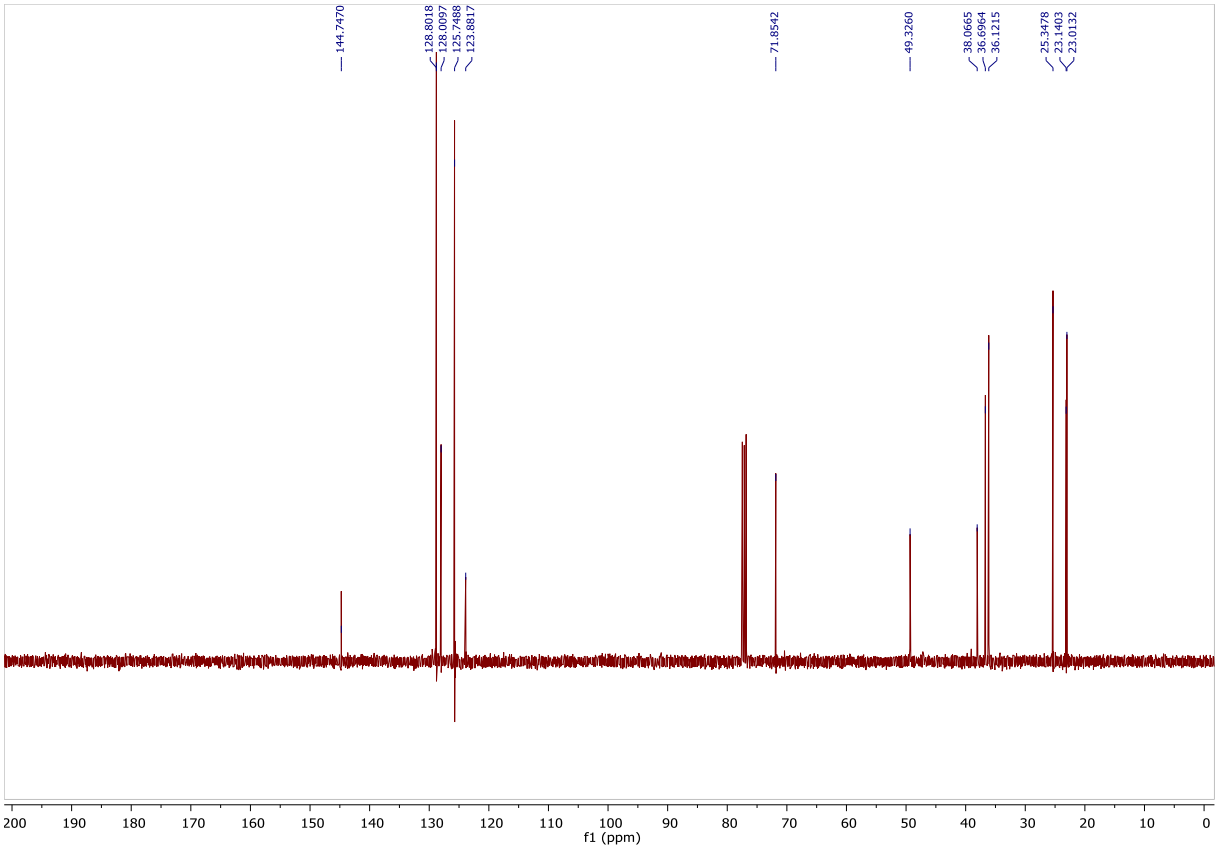
^{1}H and ^{13}C NMR compound for **17**



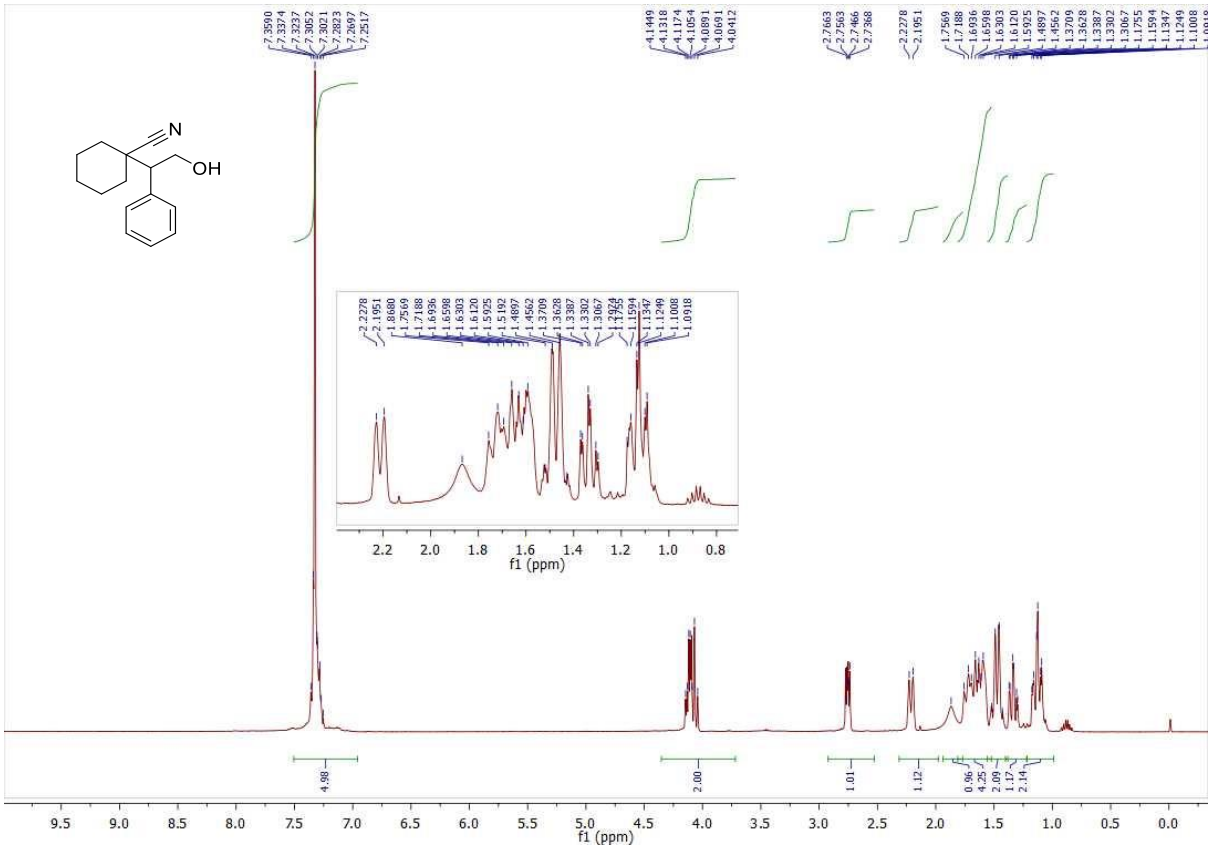


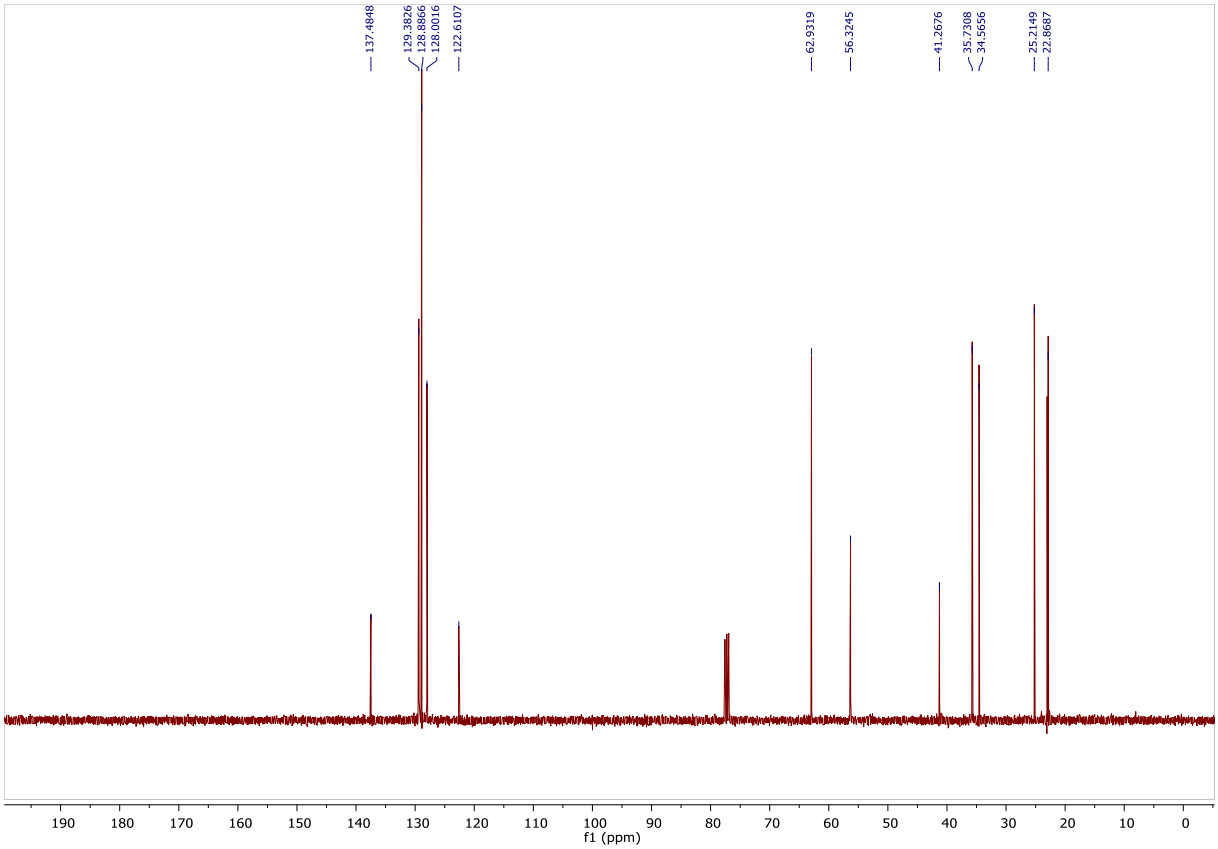
^{1}H and ^{13}C NMR compound for **18a**



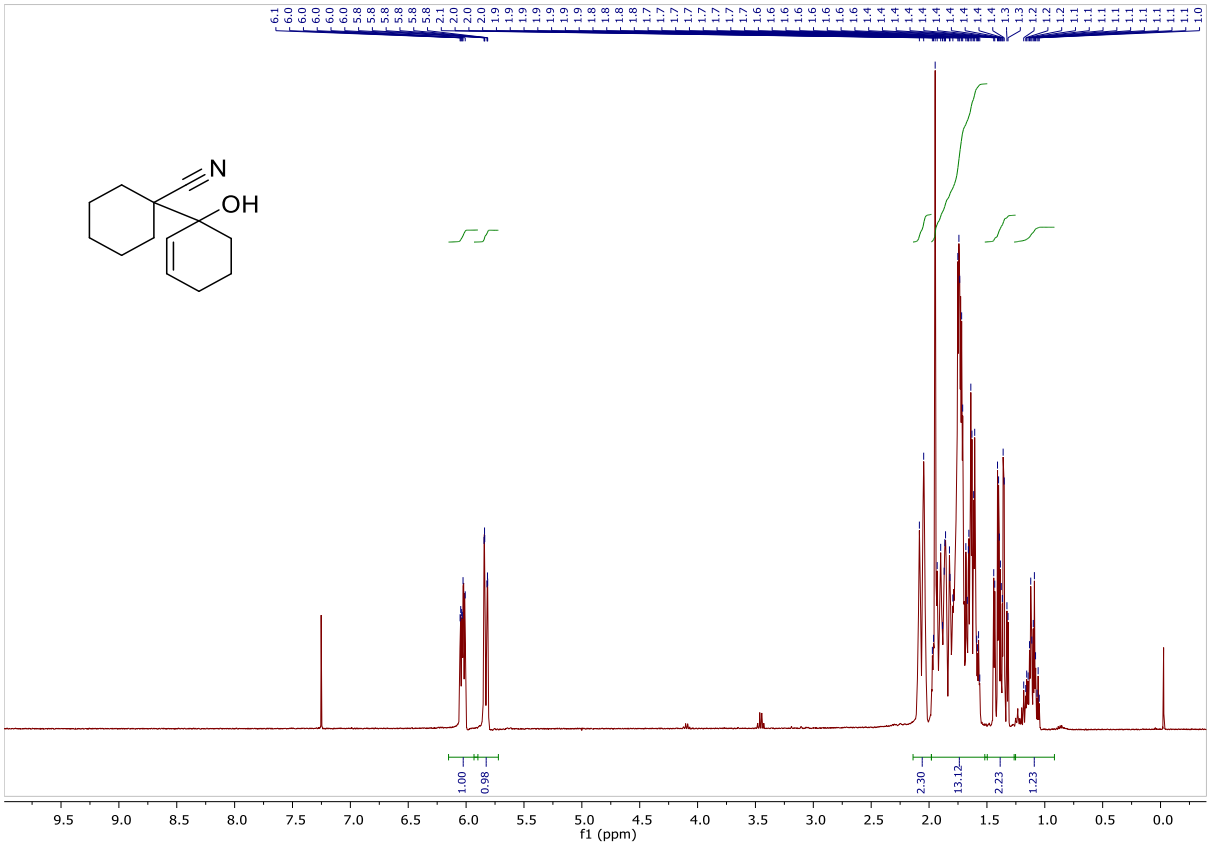


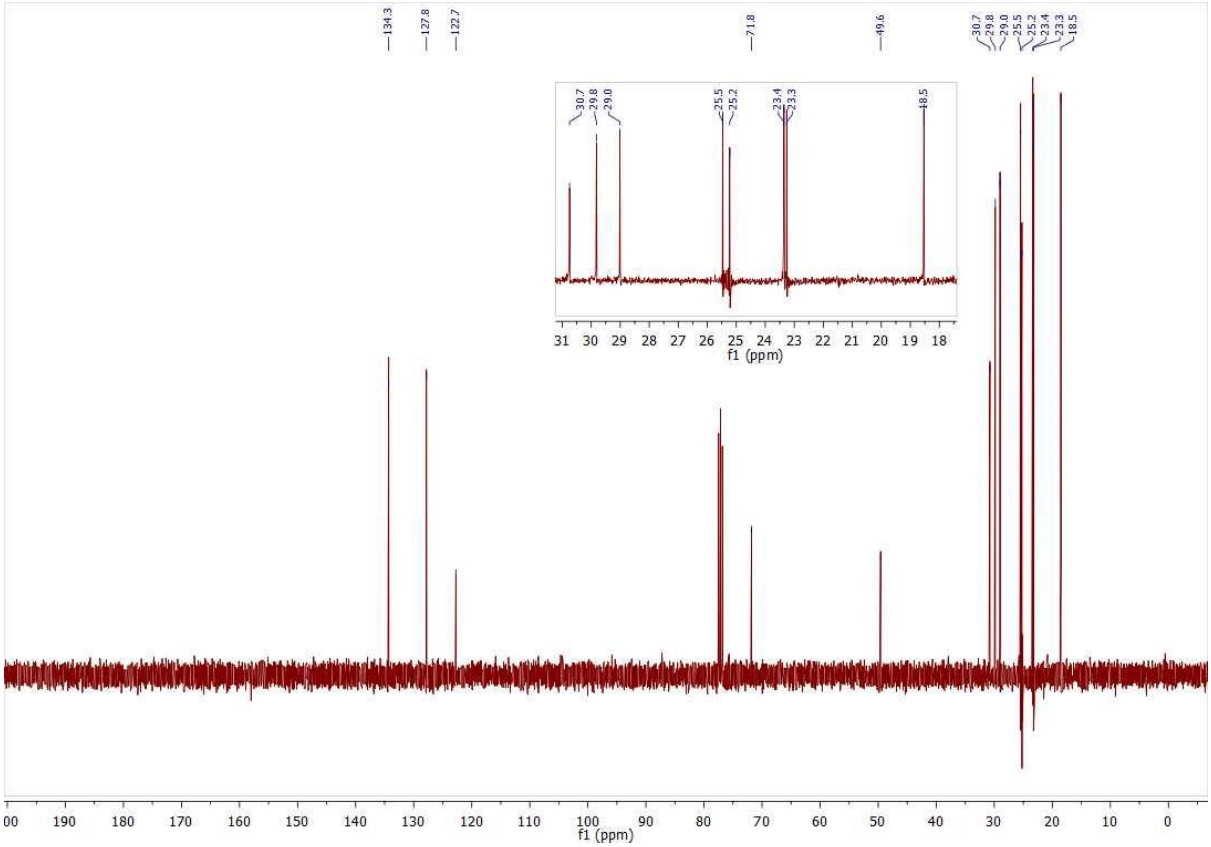
^{1}H and ^{13}C NMR compound for **18b**



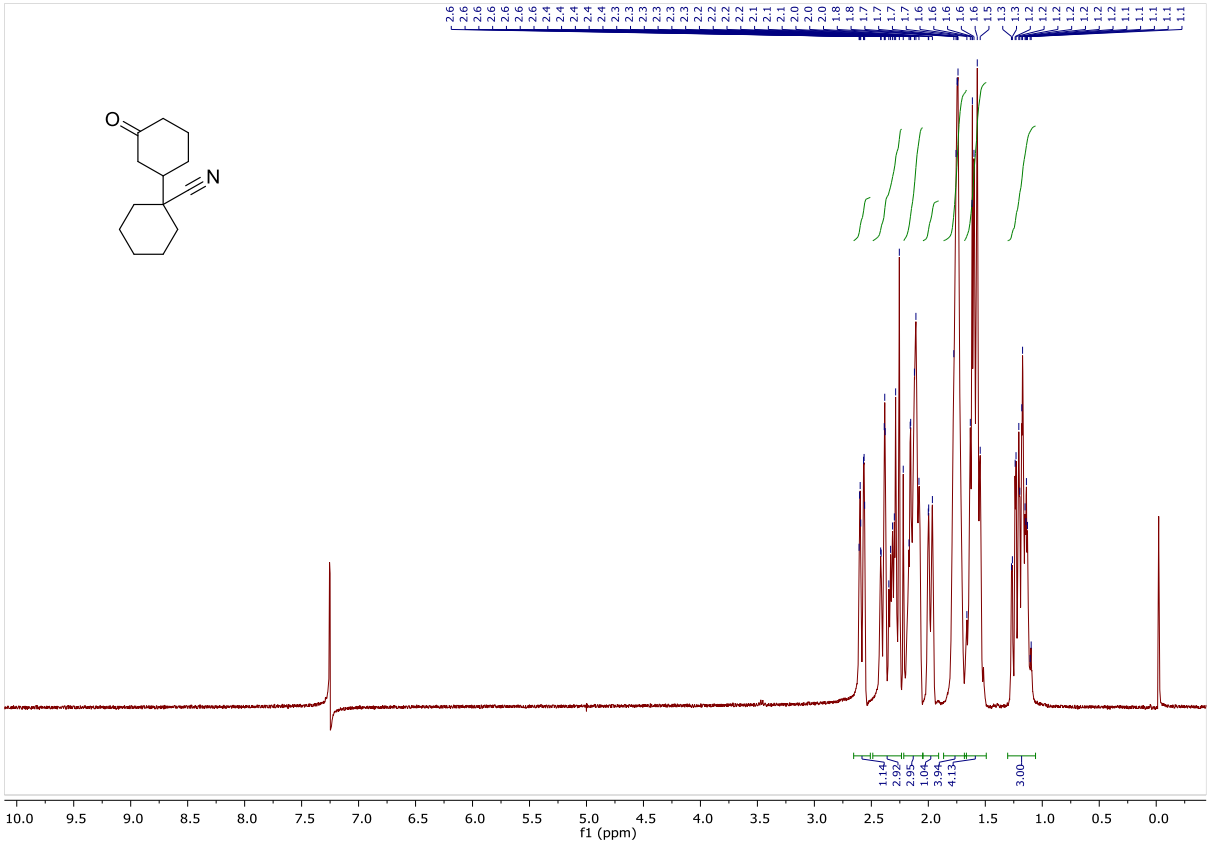


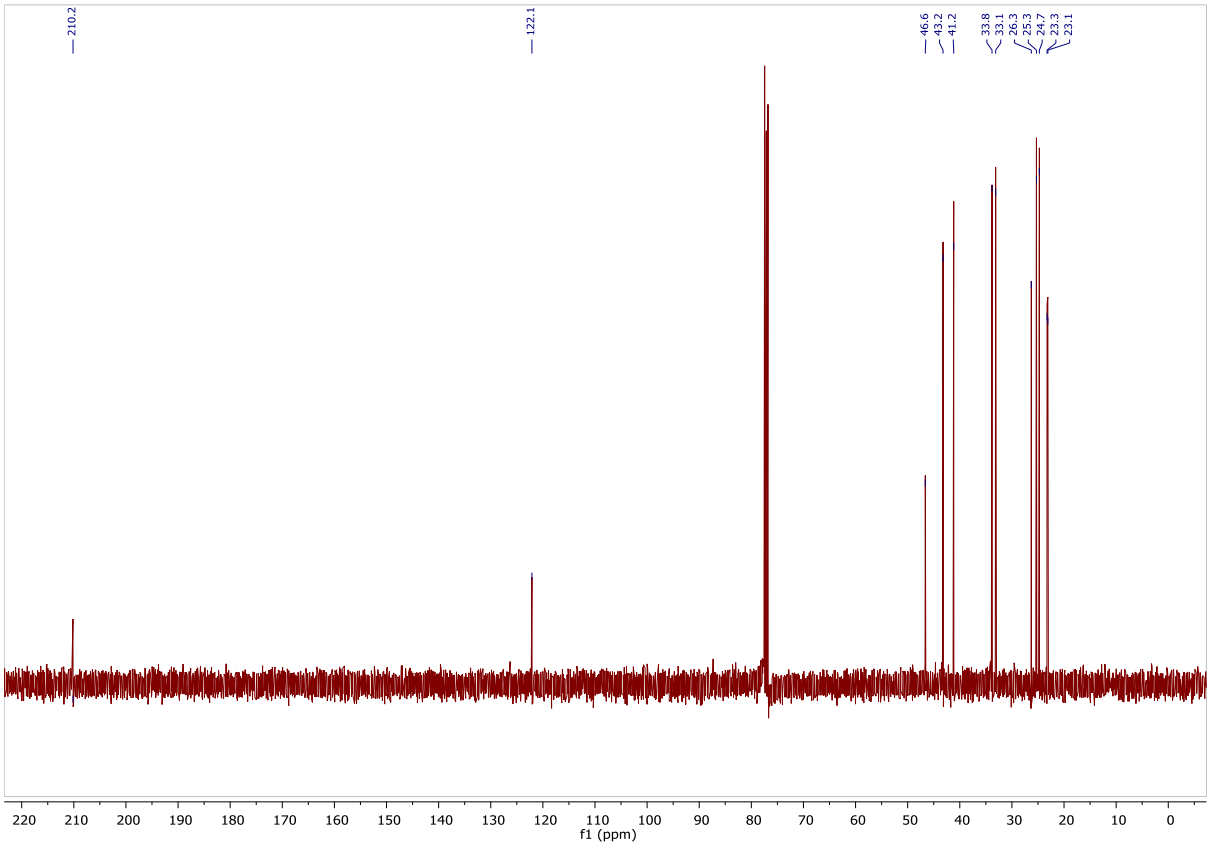
^{1}H and ^{13}C NMR compound for **20a**



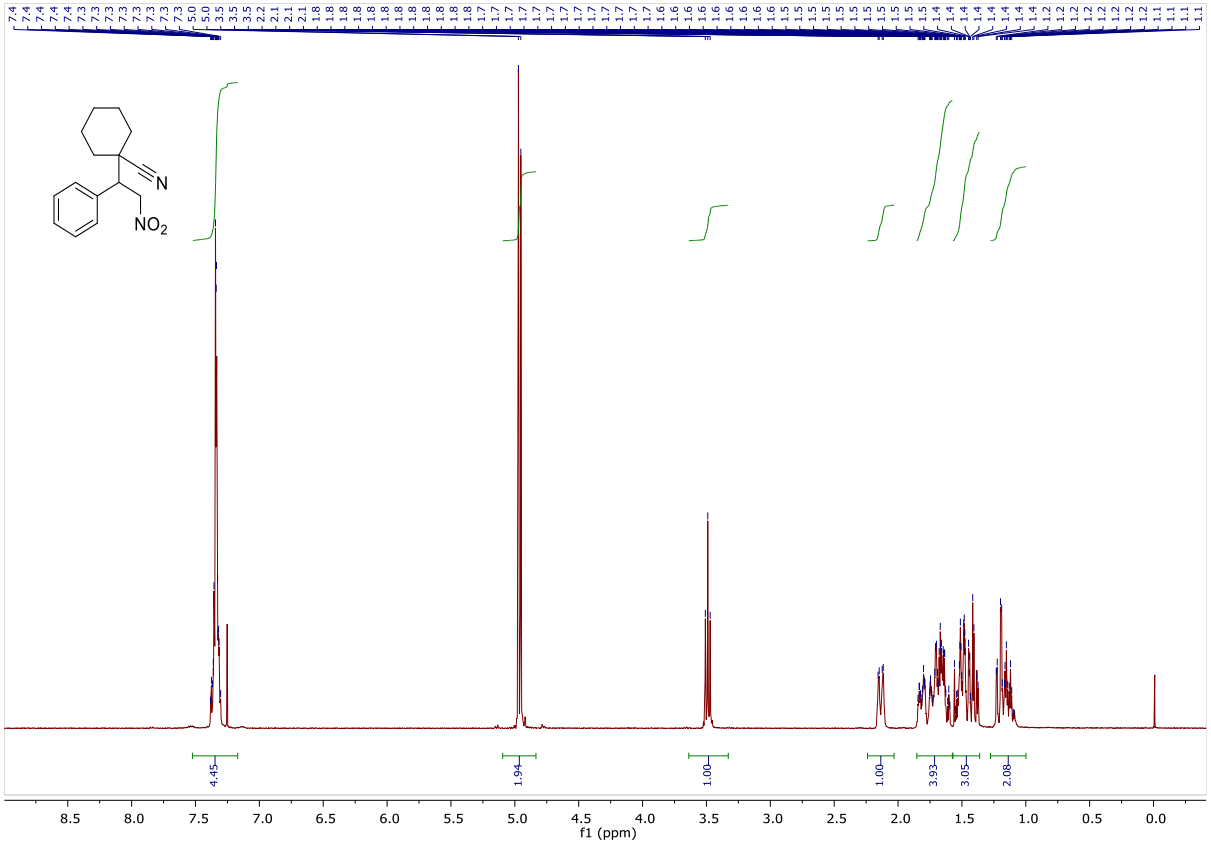


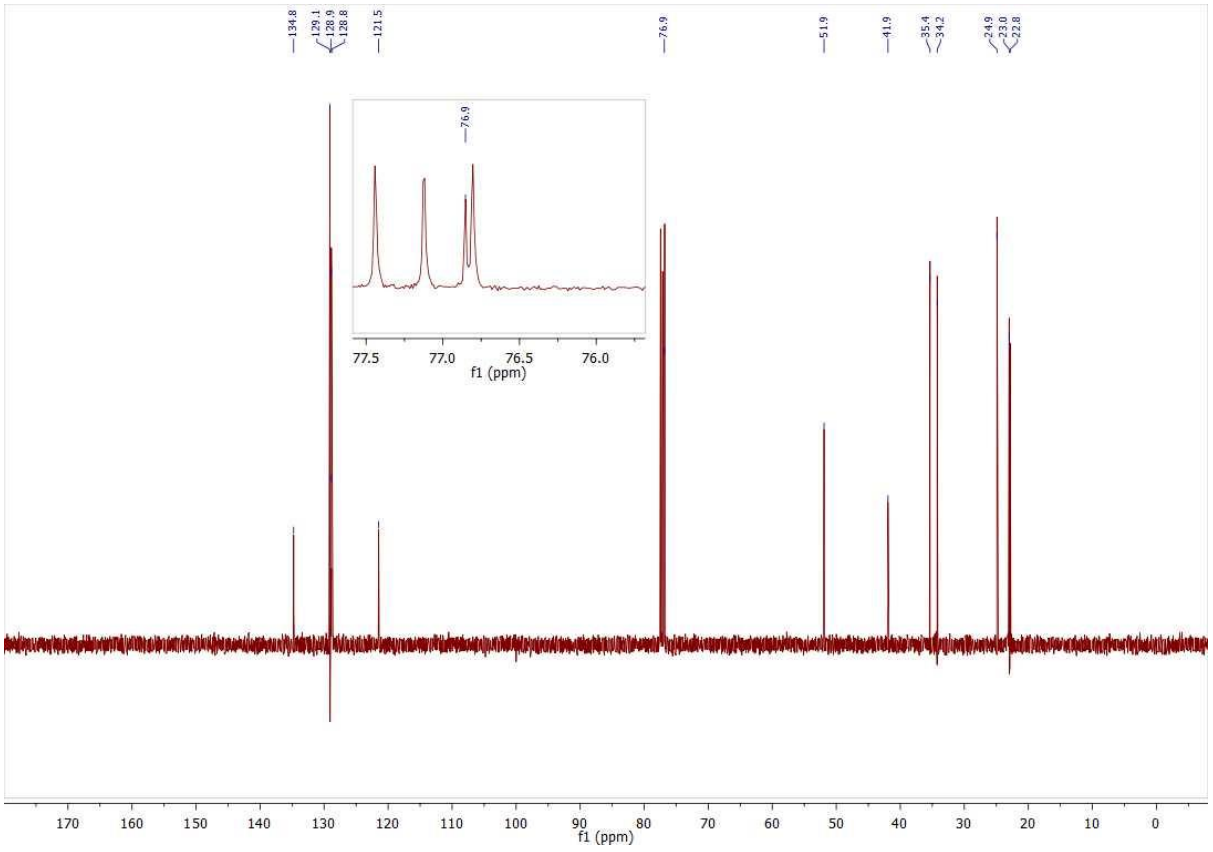
^{1}H and ^{13}C NMR compound for **20b**



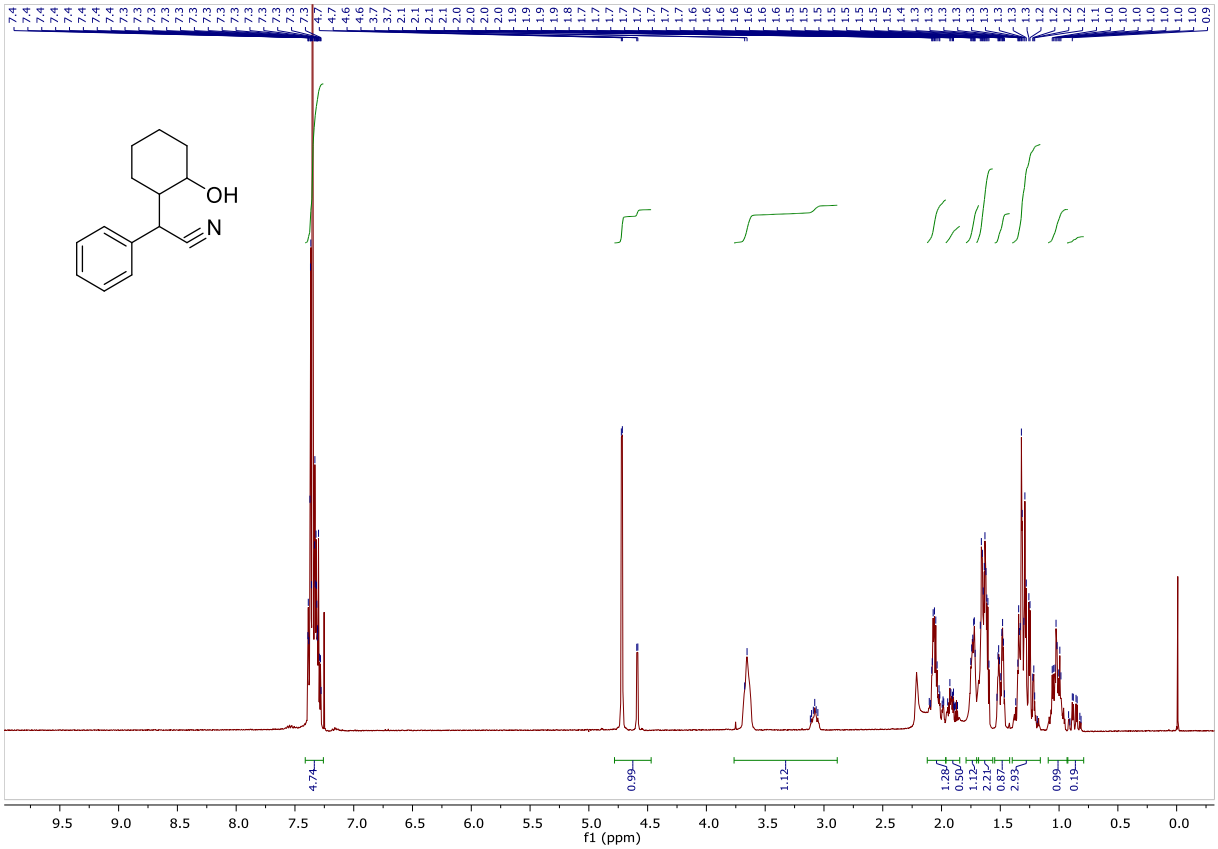


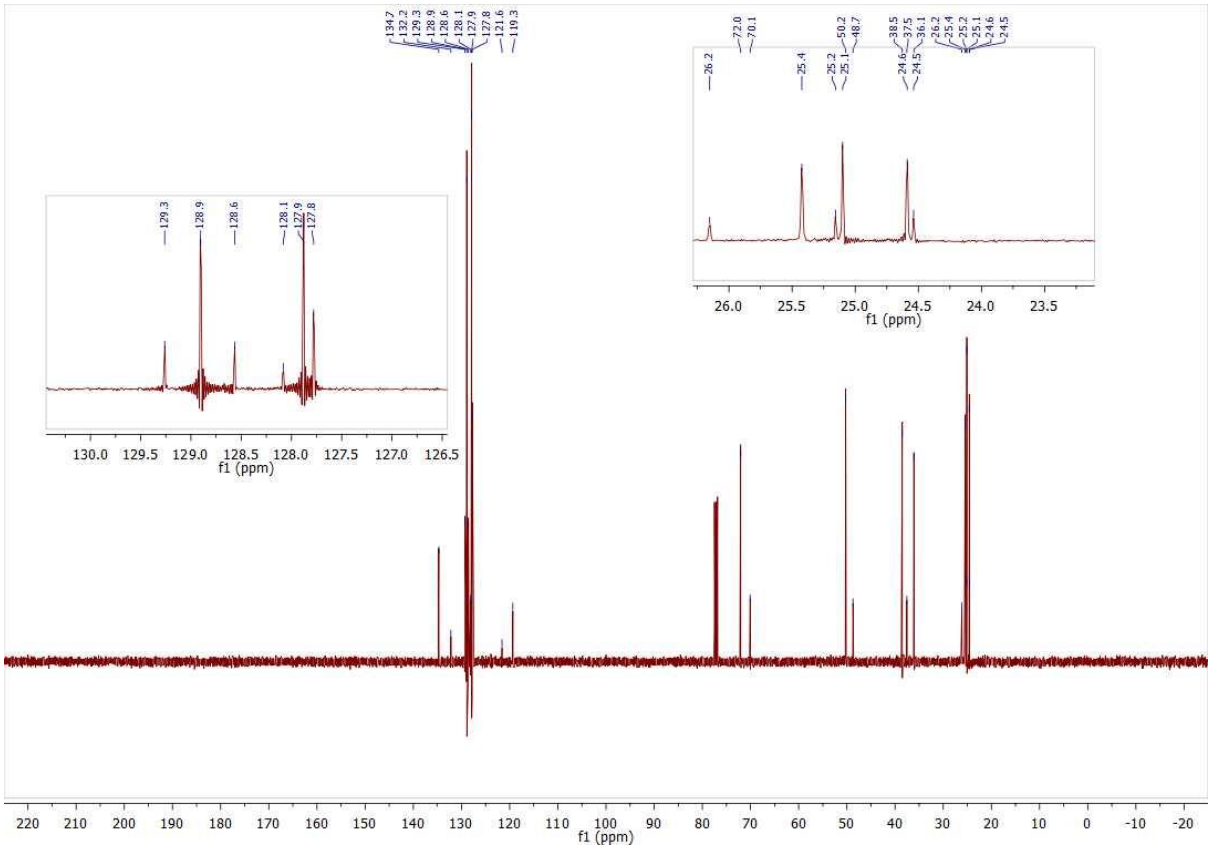
^{1}H and ^{13}C NMR compound for **21**



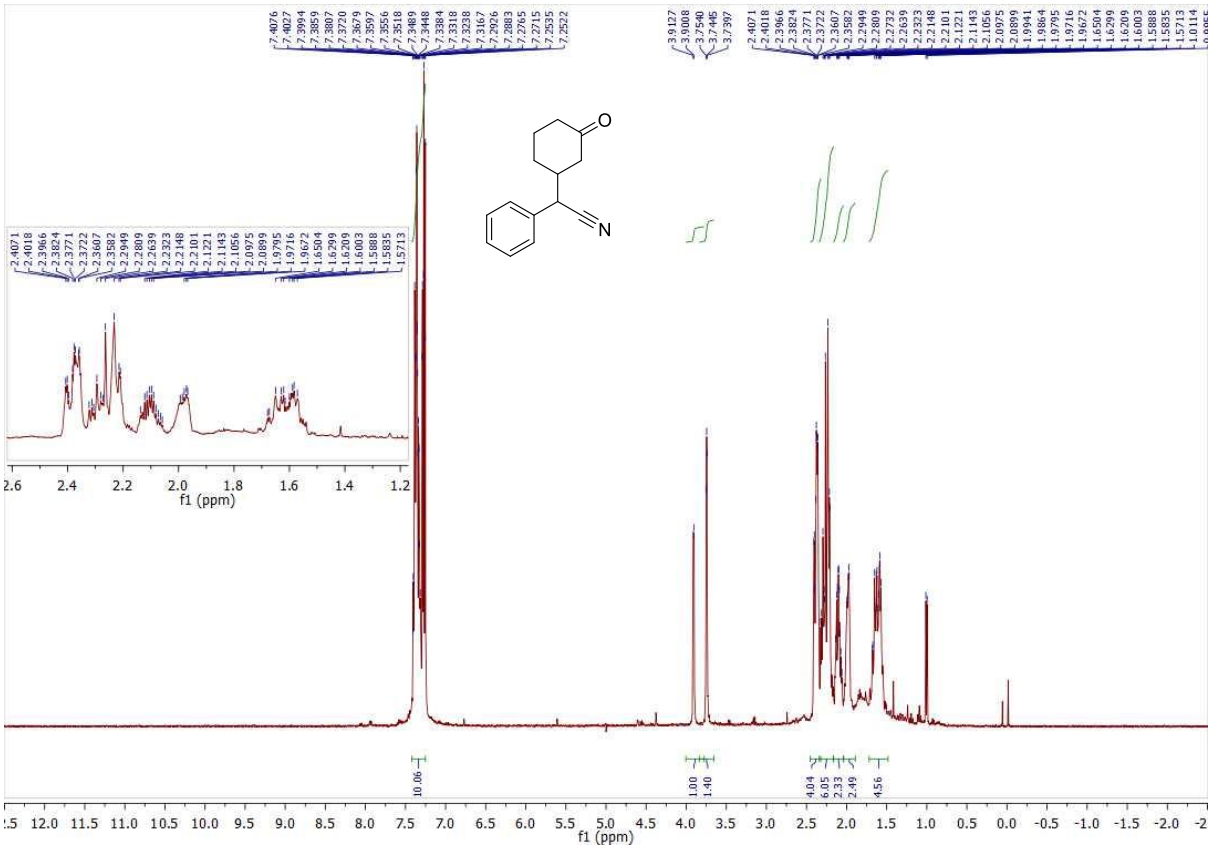


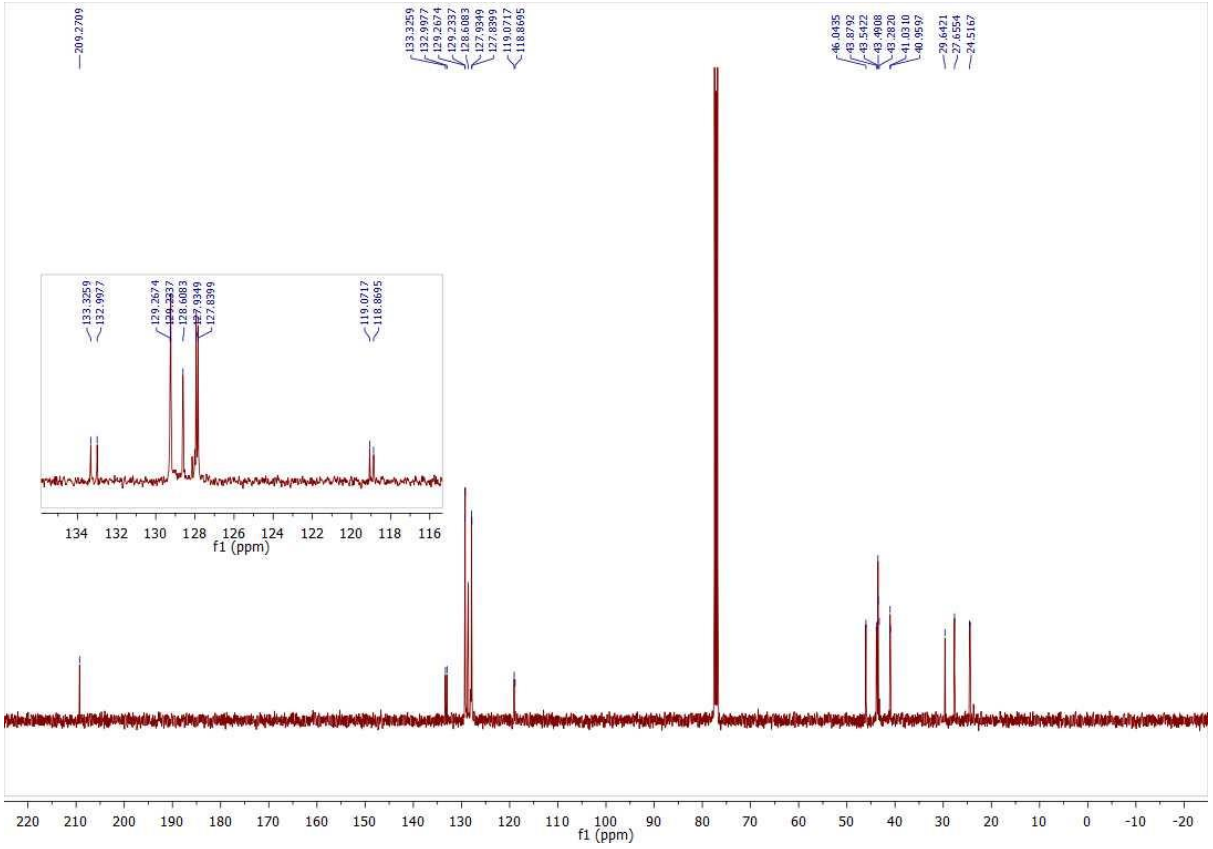
^{1}H and ^{13}C NMR compound for **22**



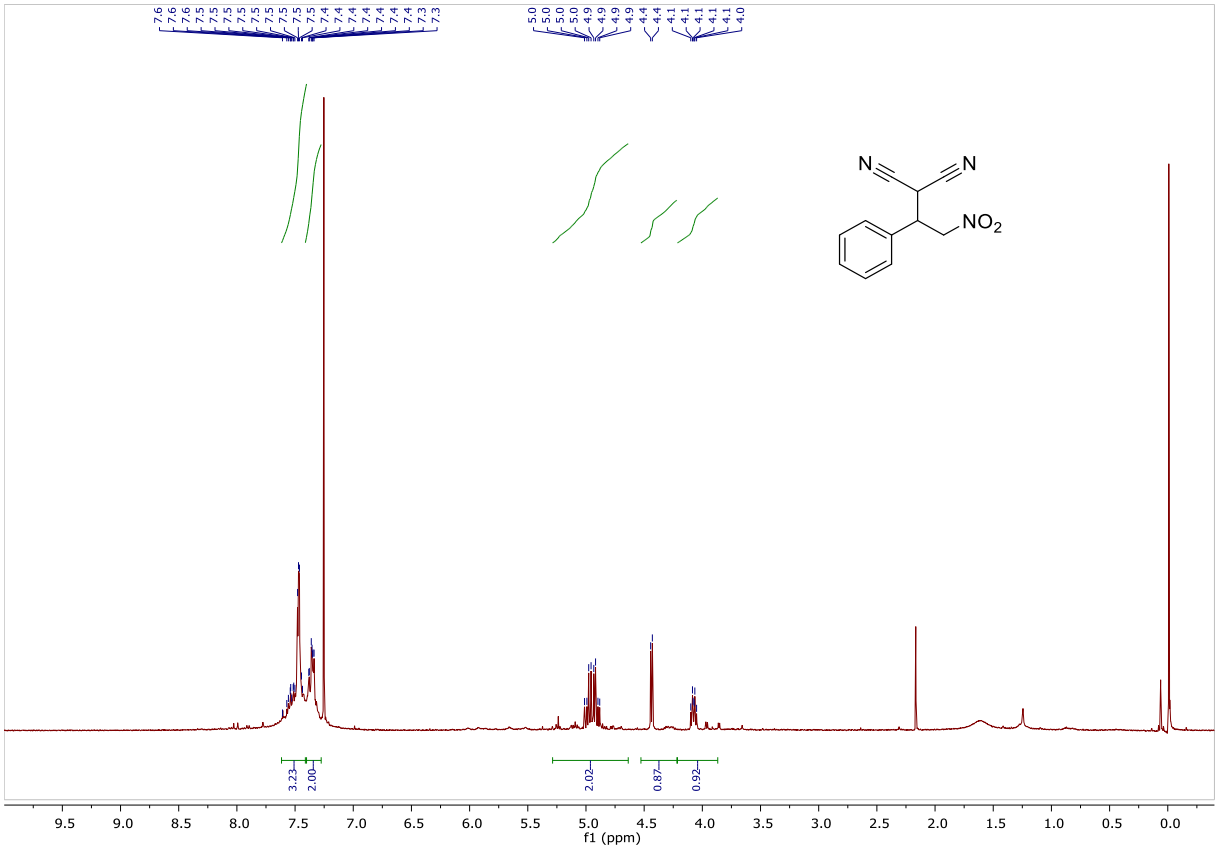


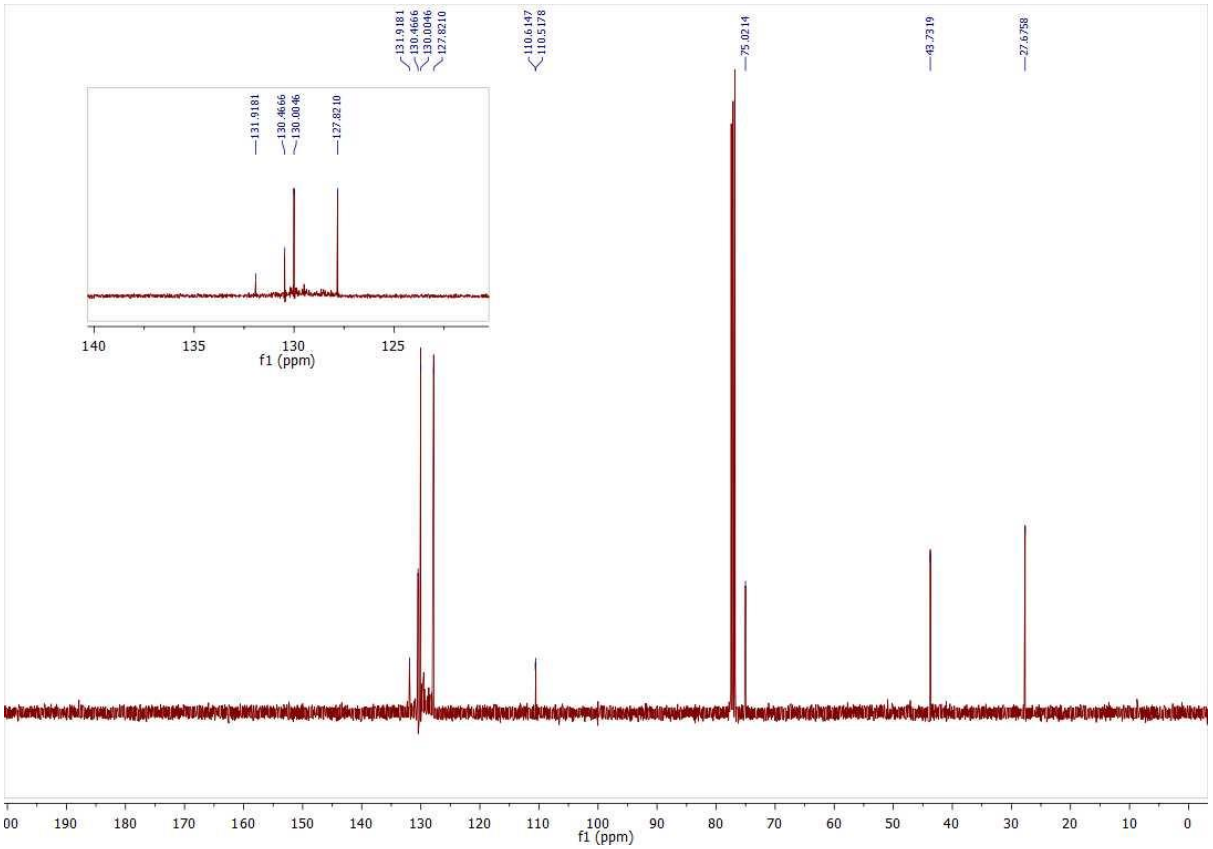
^{1}H and ^{13}C NMR compound for **23**



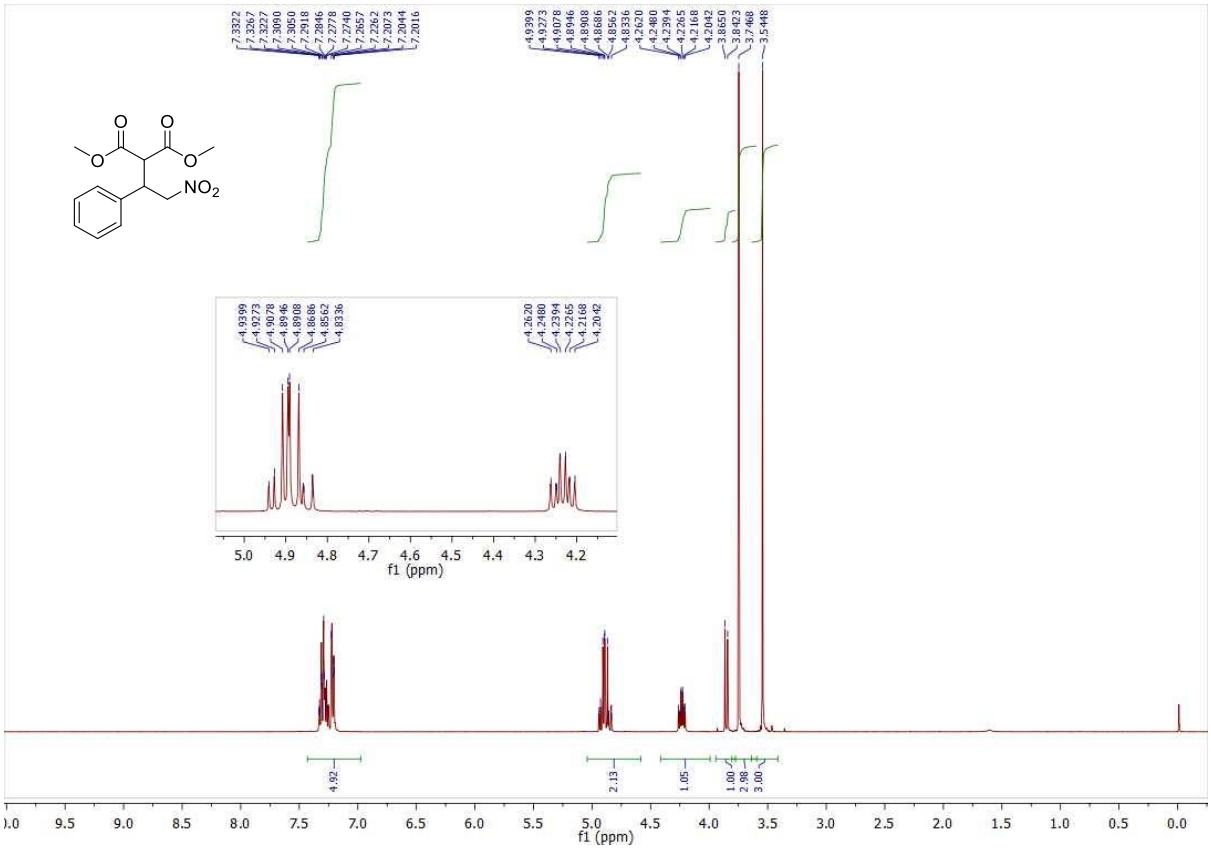


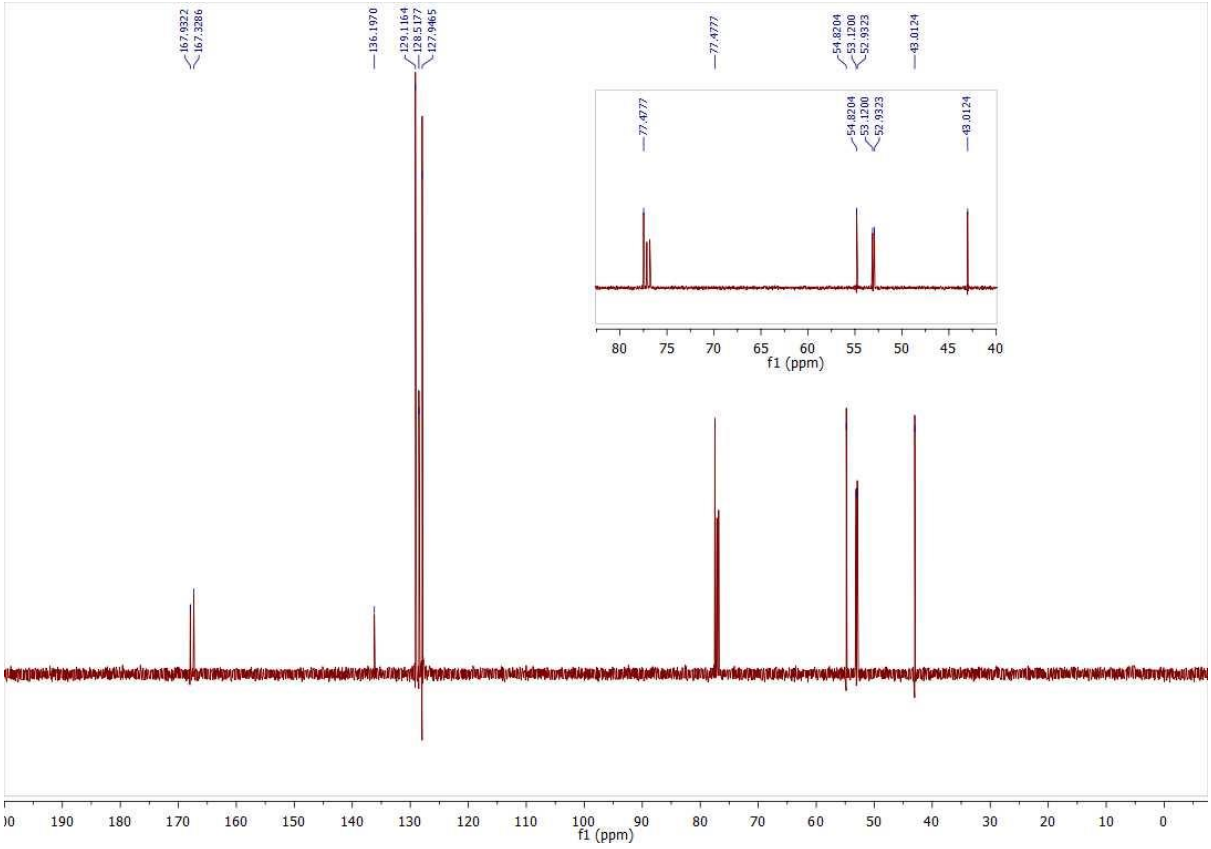
^{1}H and ^{13}C NMR compound for **24**



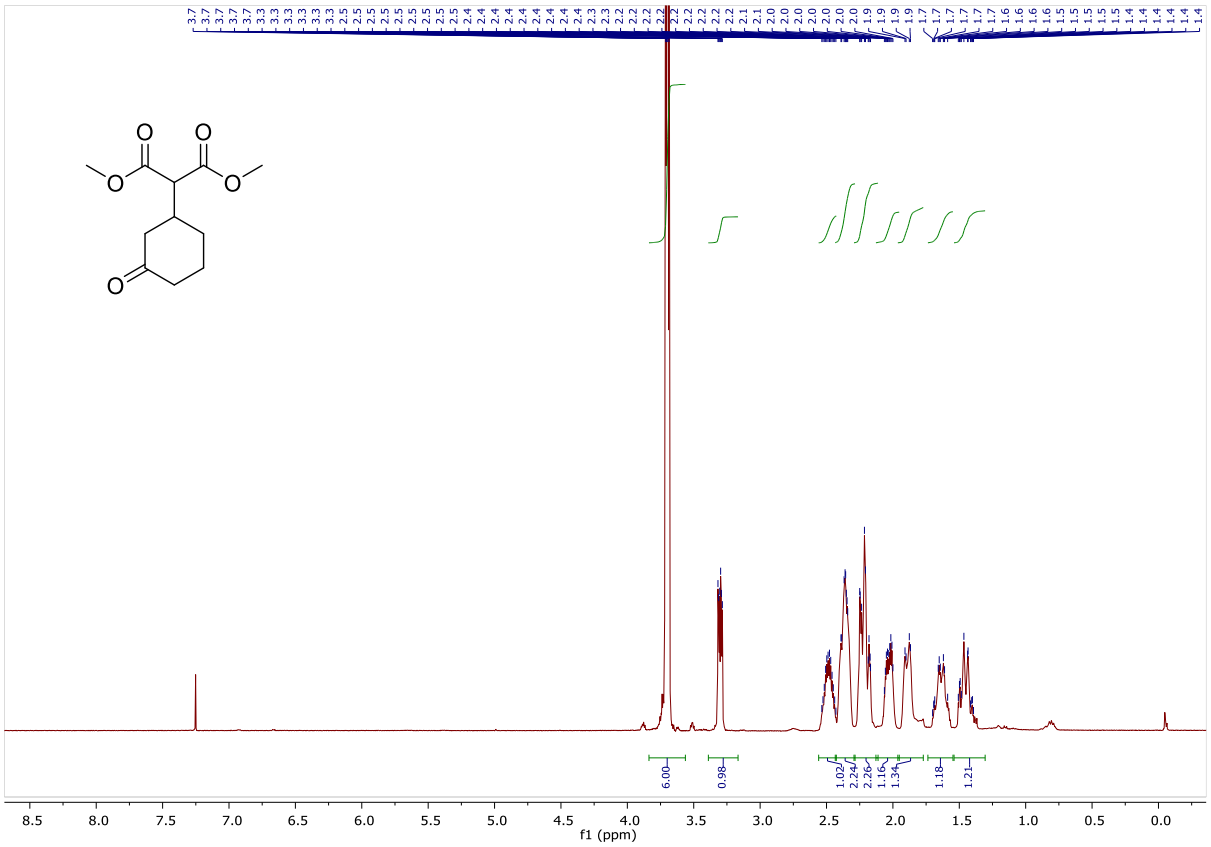


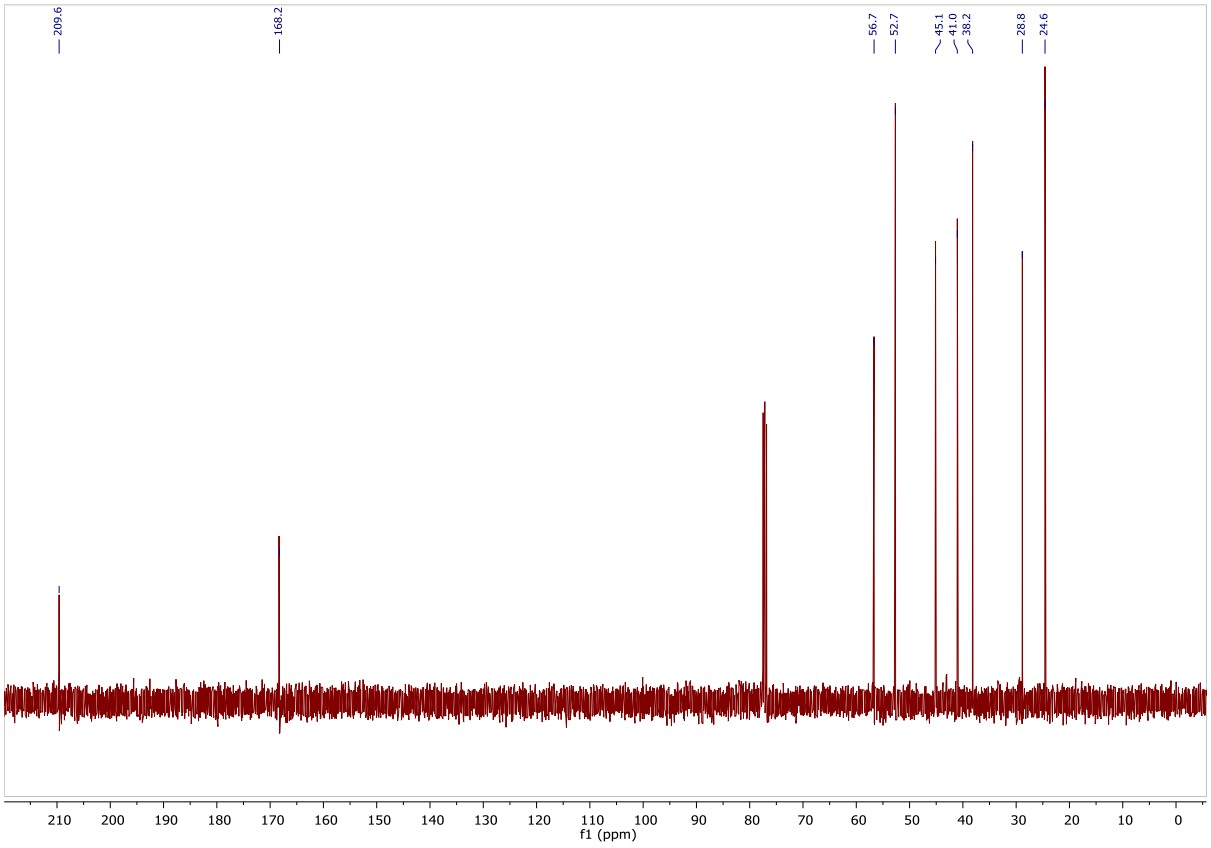
^{1}H and ^{13}C NMR compound for **25**



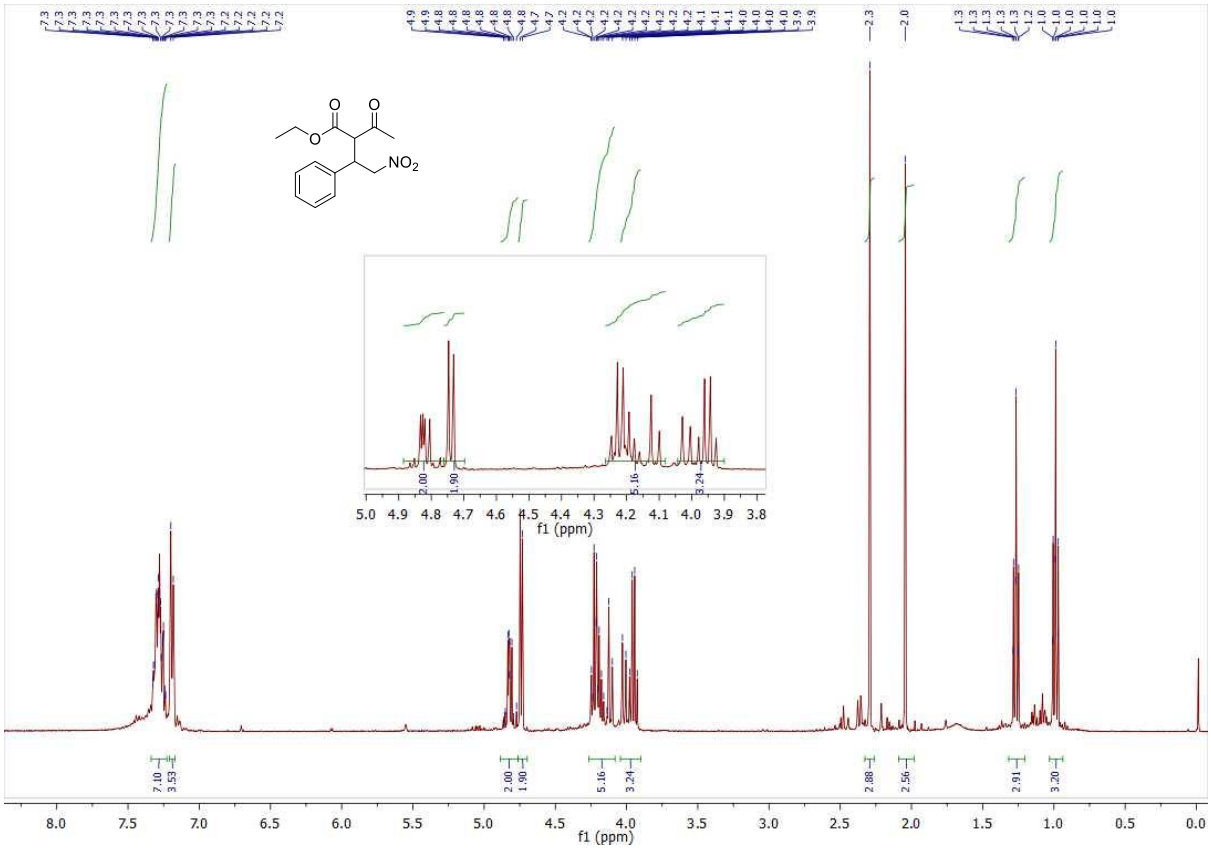


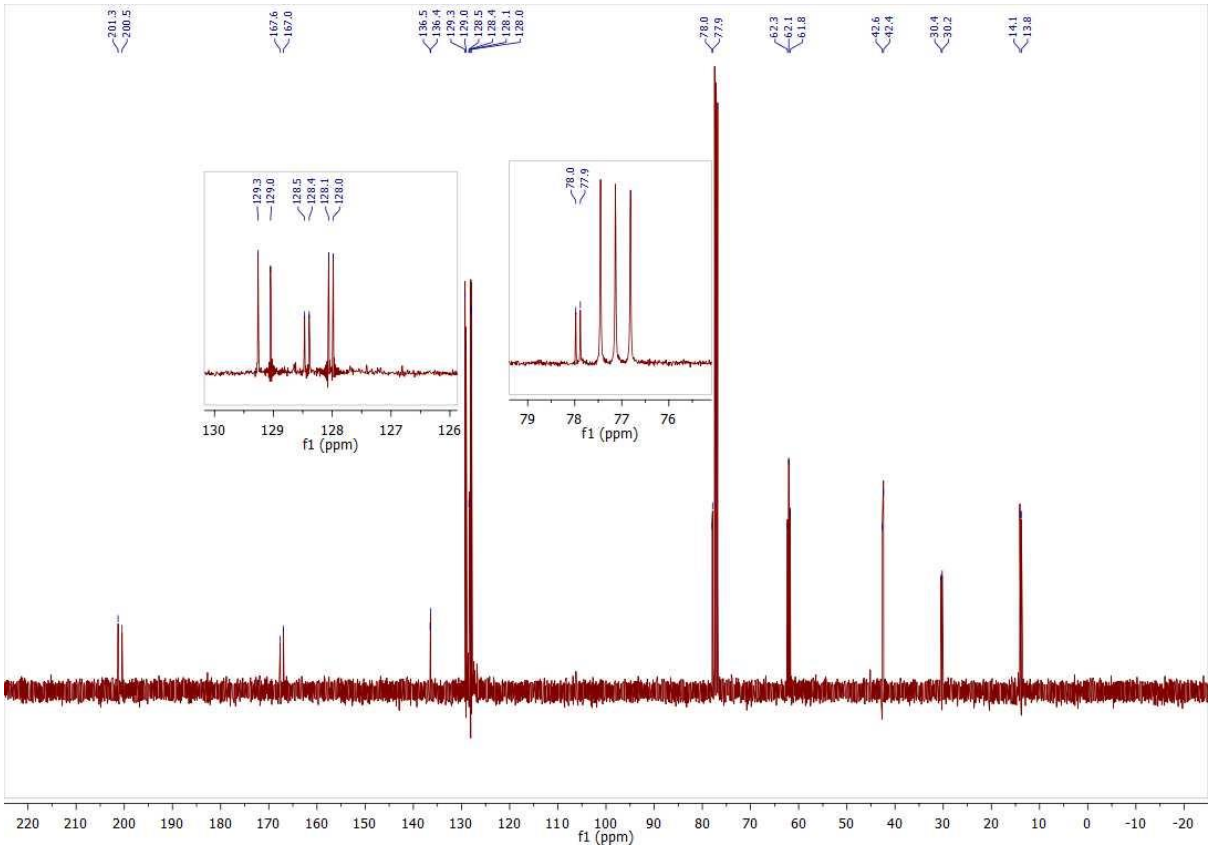
^{1}H and ^{13}C NMR compound for **26**



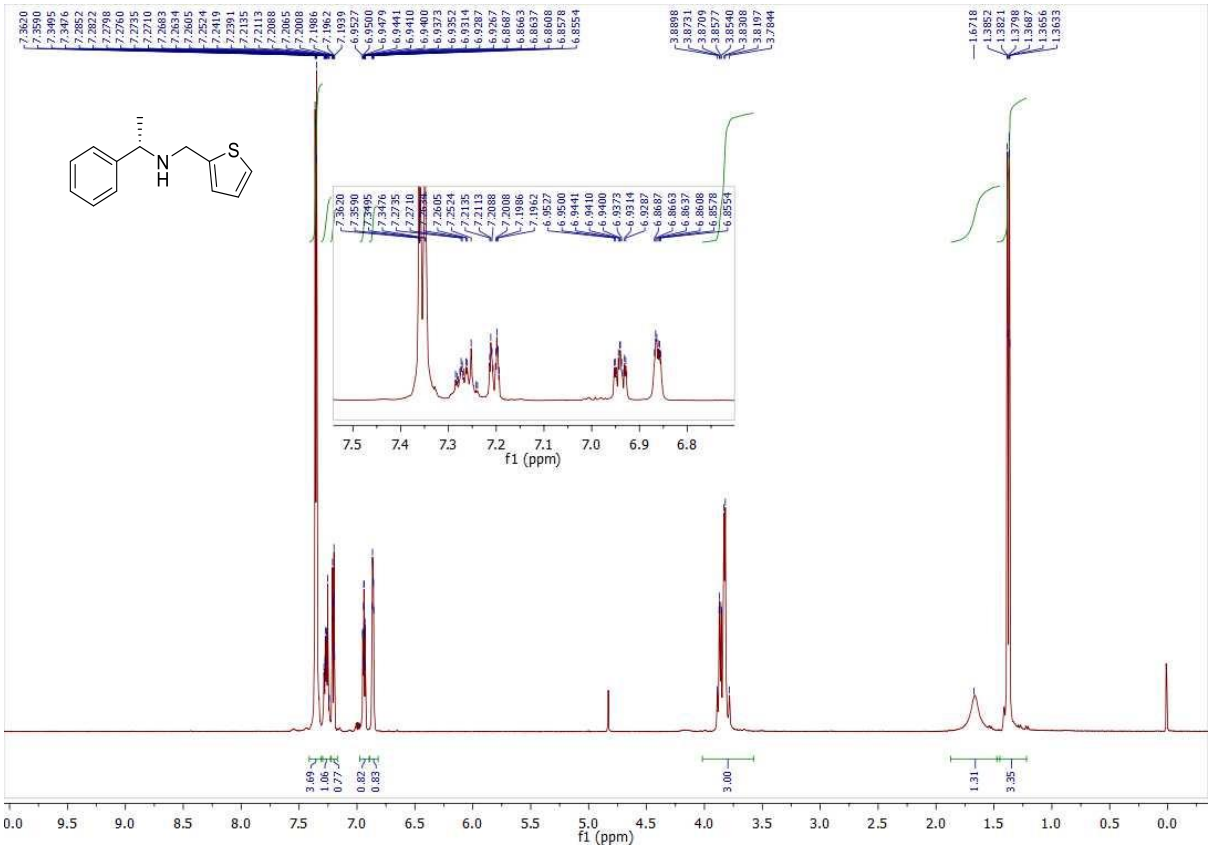


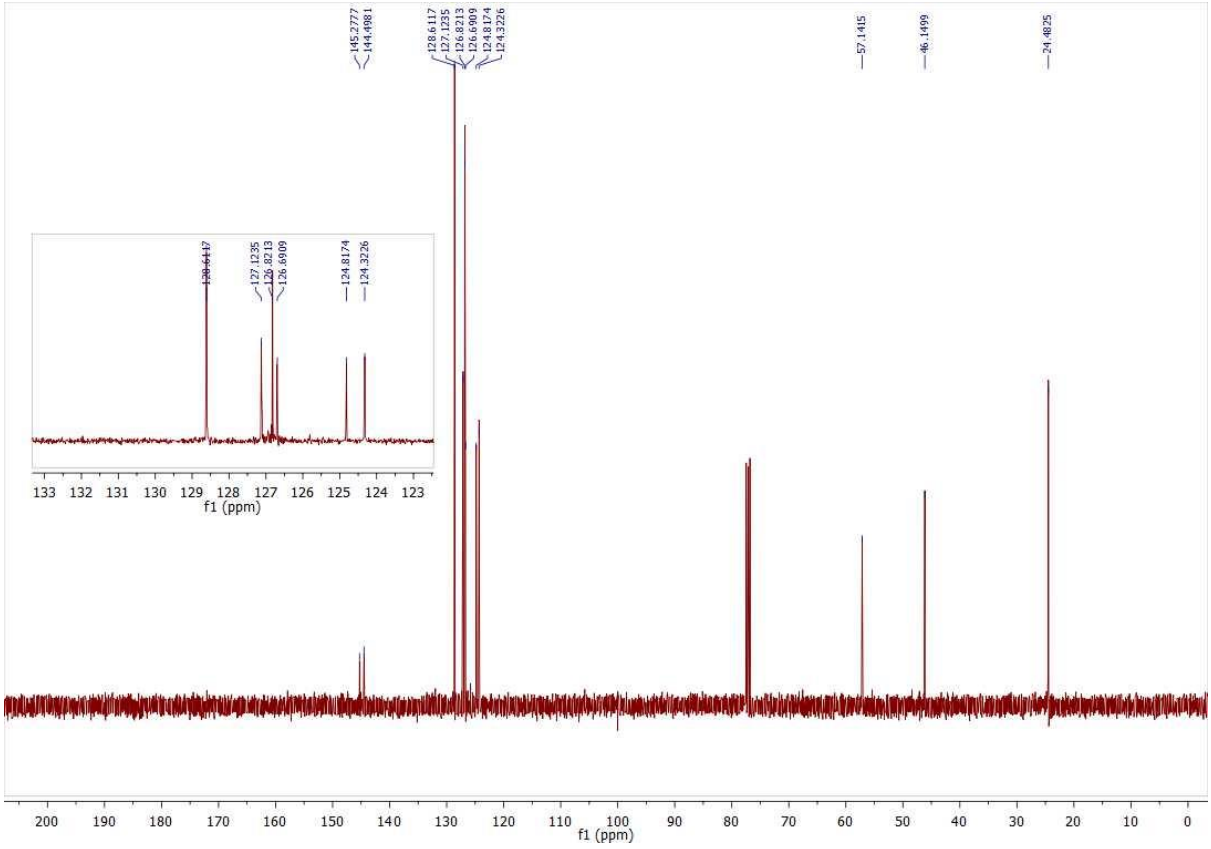
^{1}H and ^{13}C NMR compound for **27**



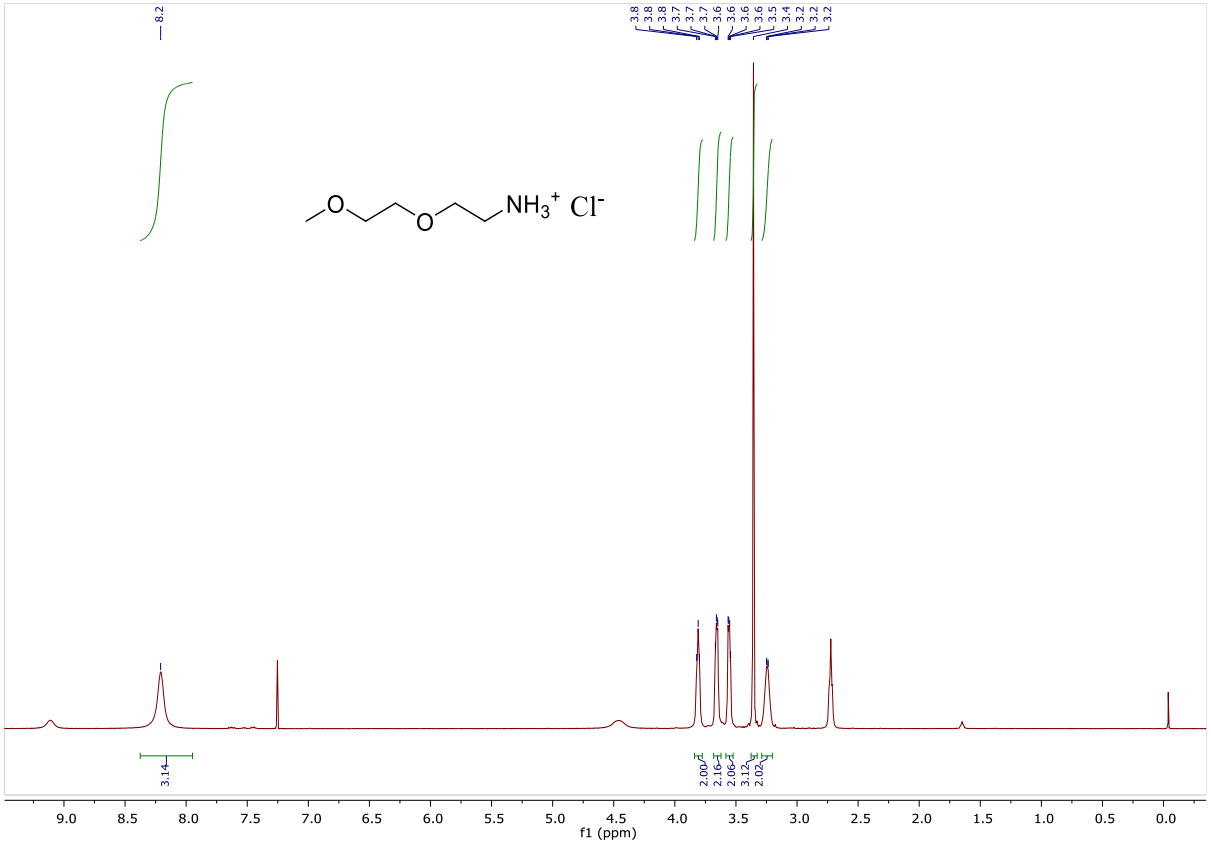


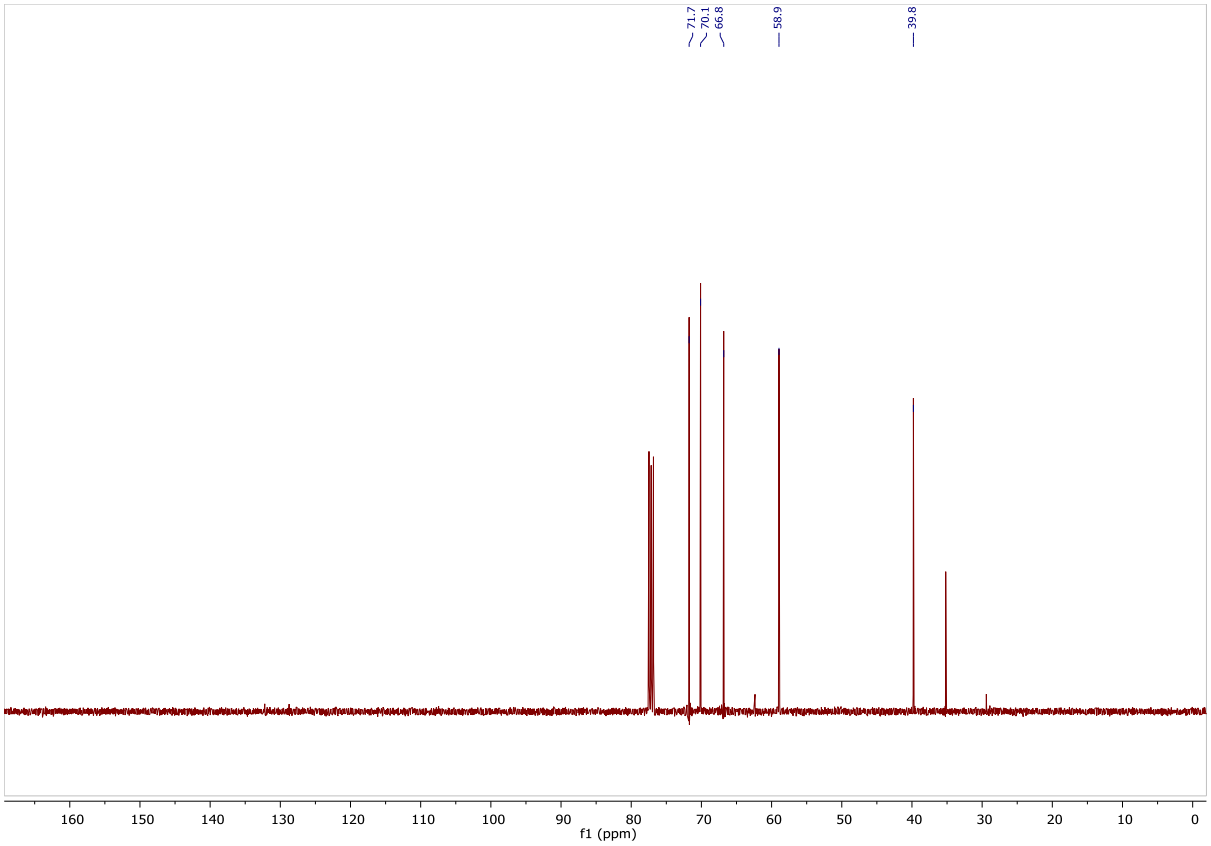
^{1}H and ^{13}C NMR compound for **28a**



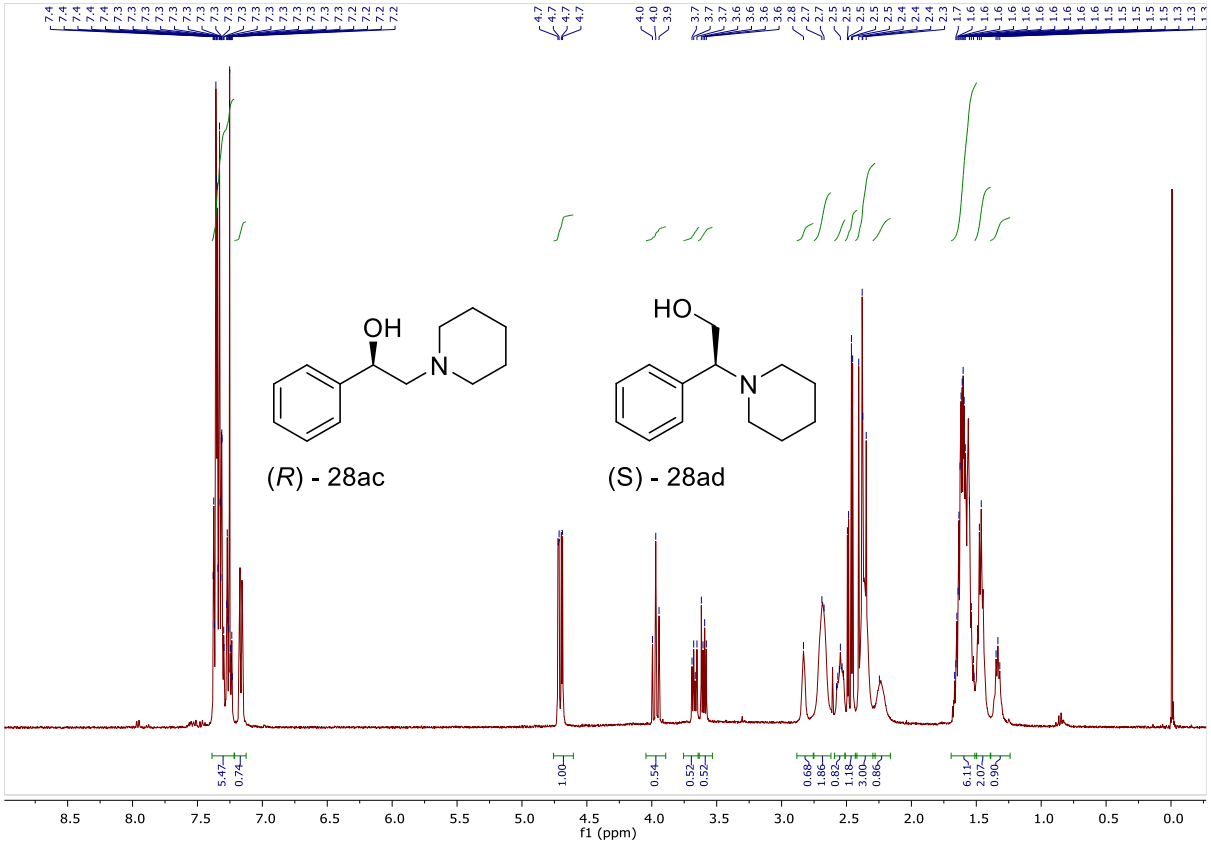


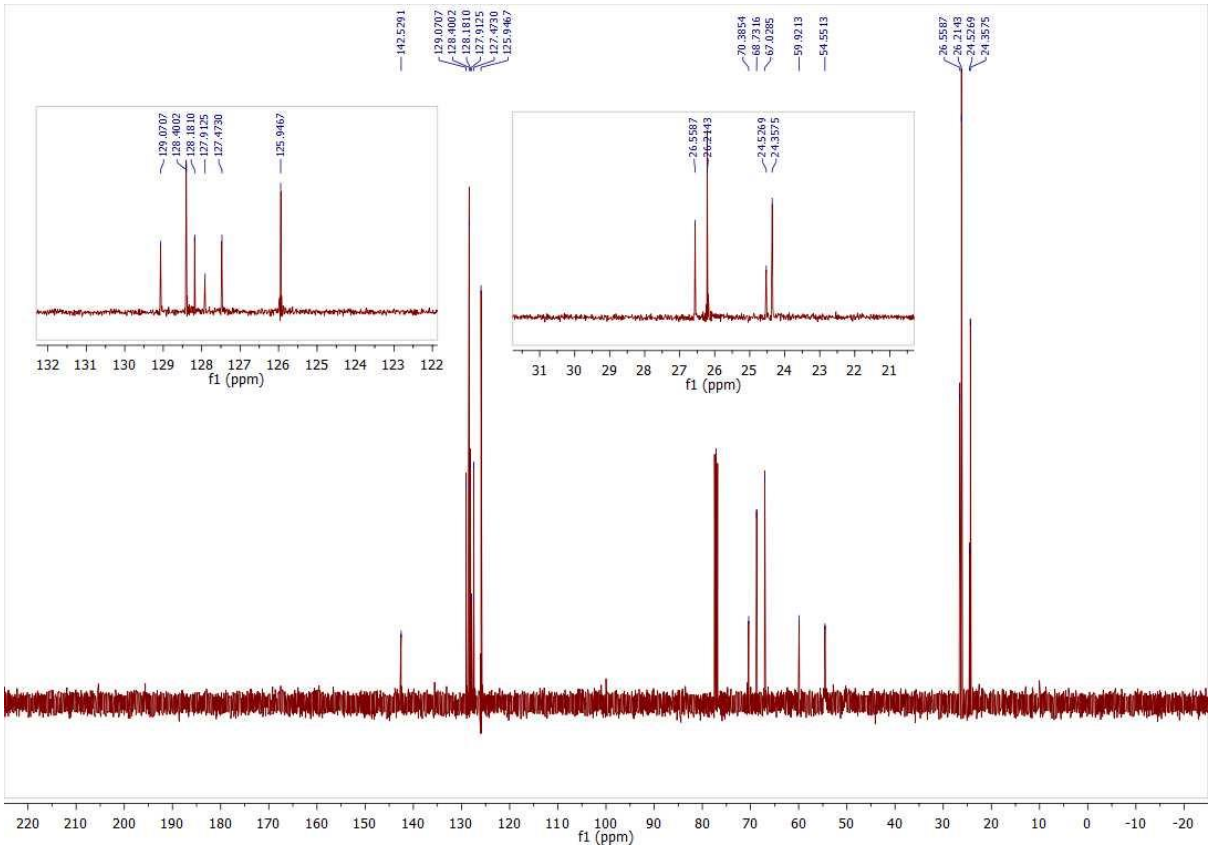
^{1}H and ^{13}C NMR compound for **28ab**



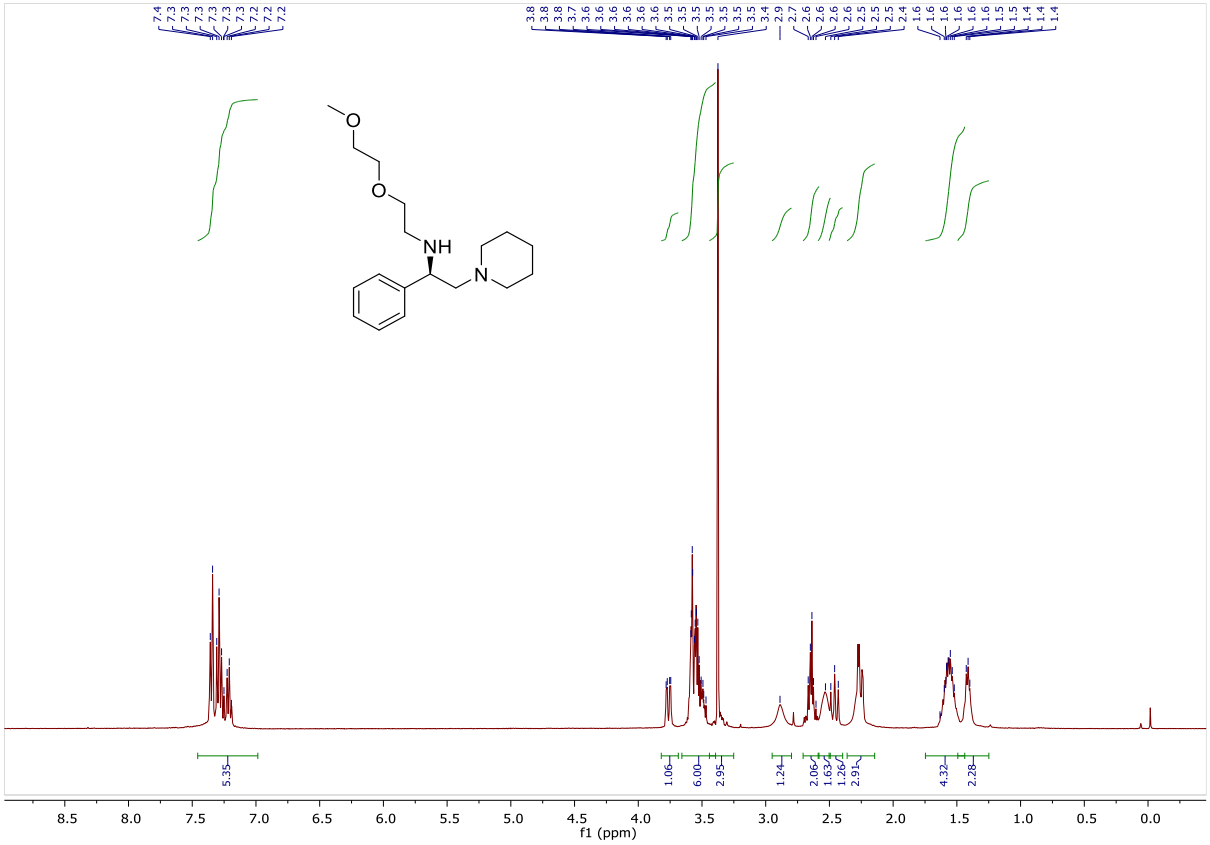


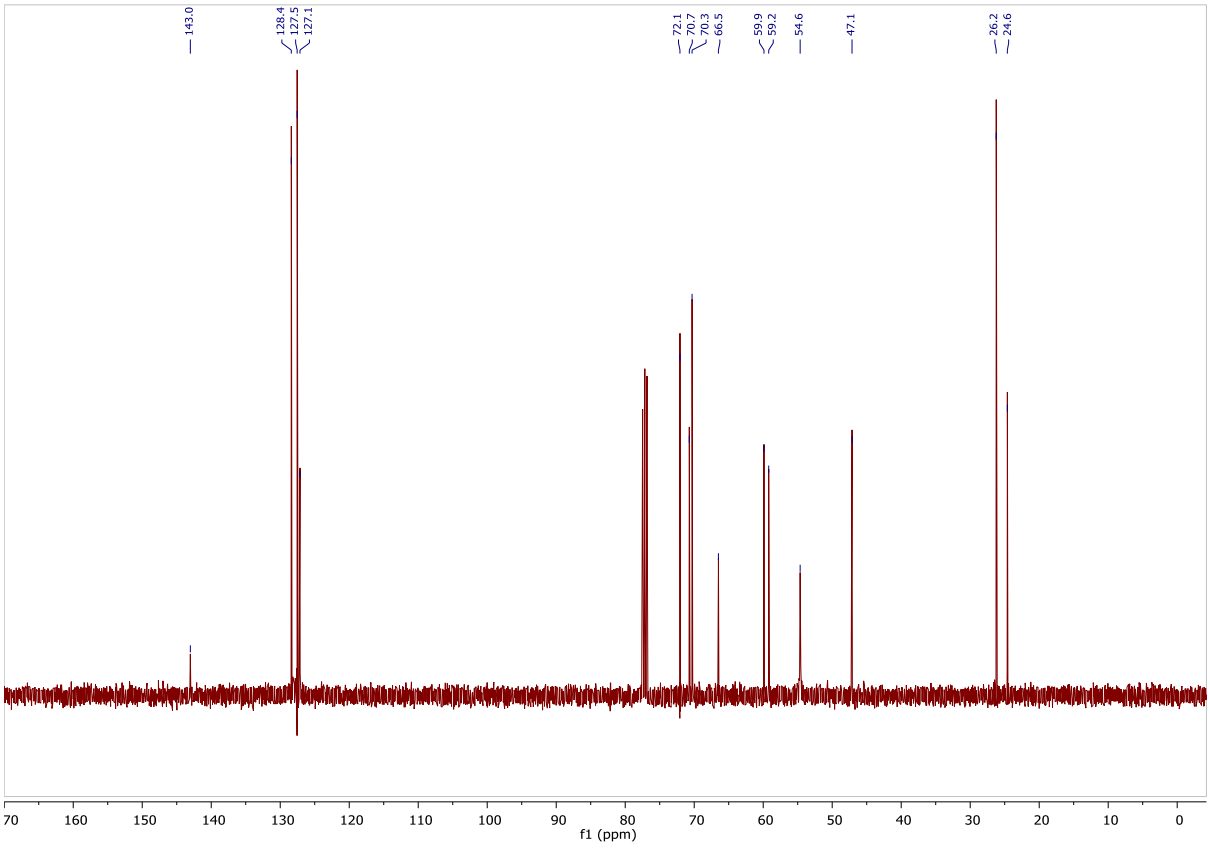
^{1}H and ^{13}C NMR compound for ***R*-28ac and *S*-28ad**



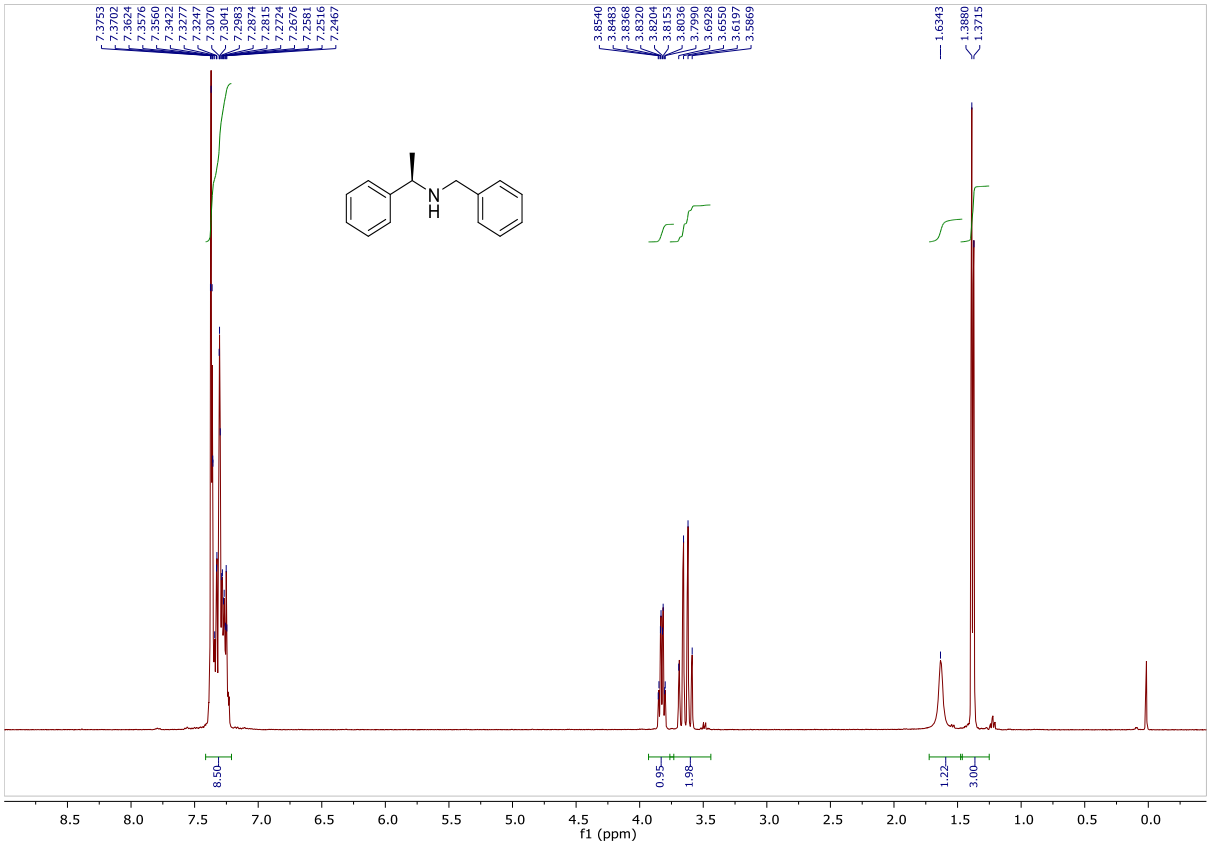


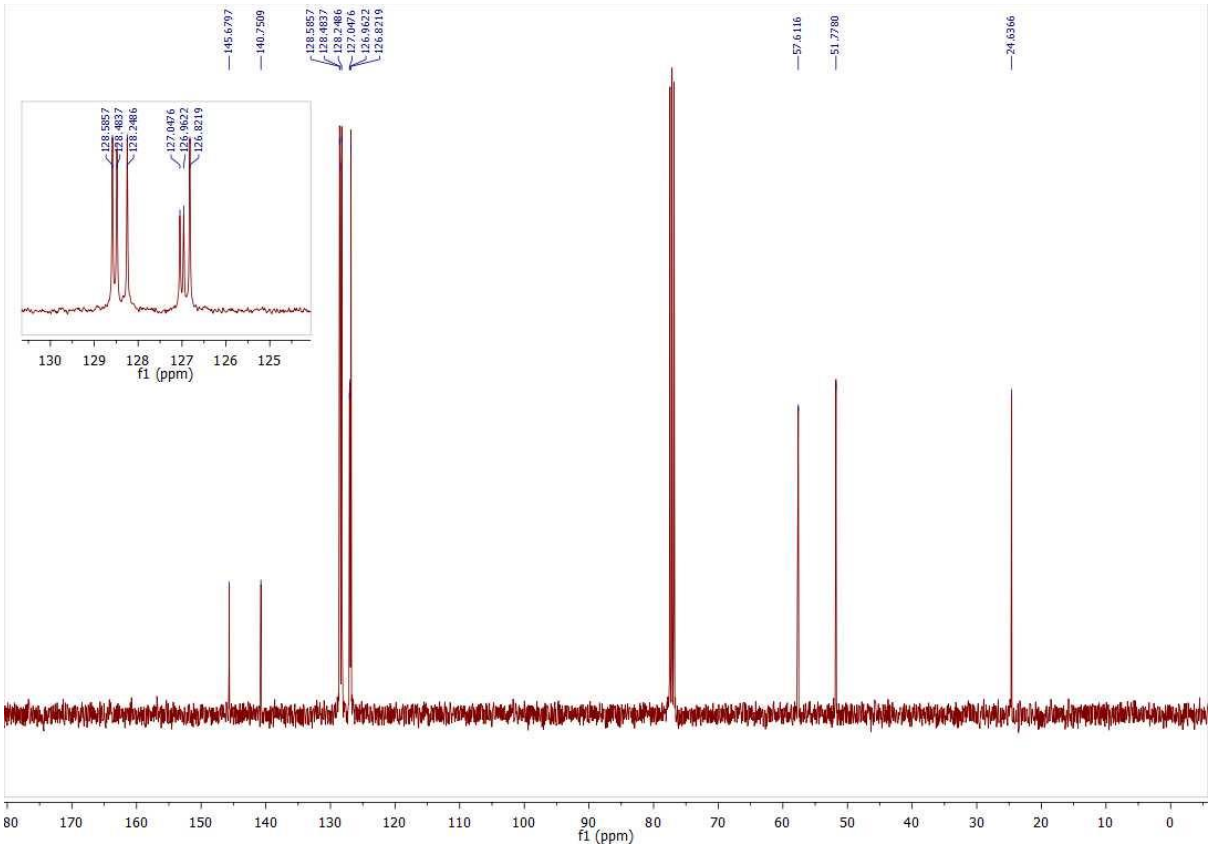
^{1}H and ^{13}C NMR compound for **28b**



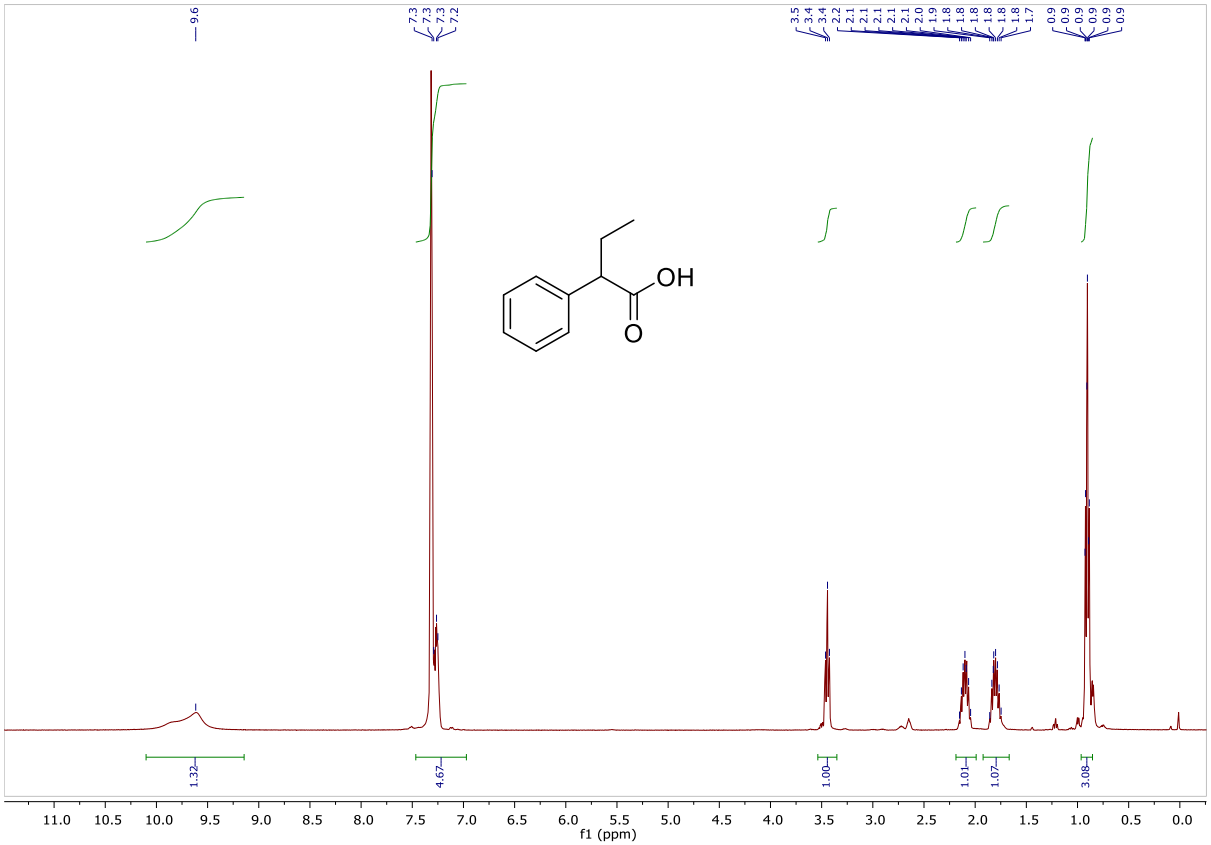


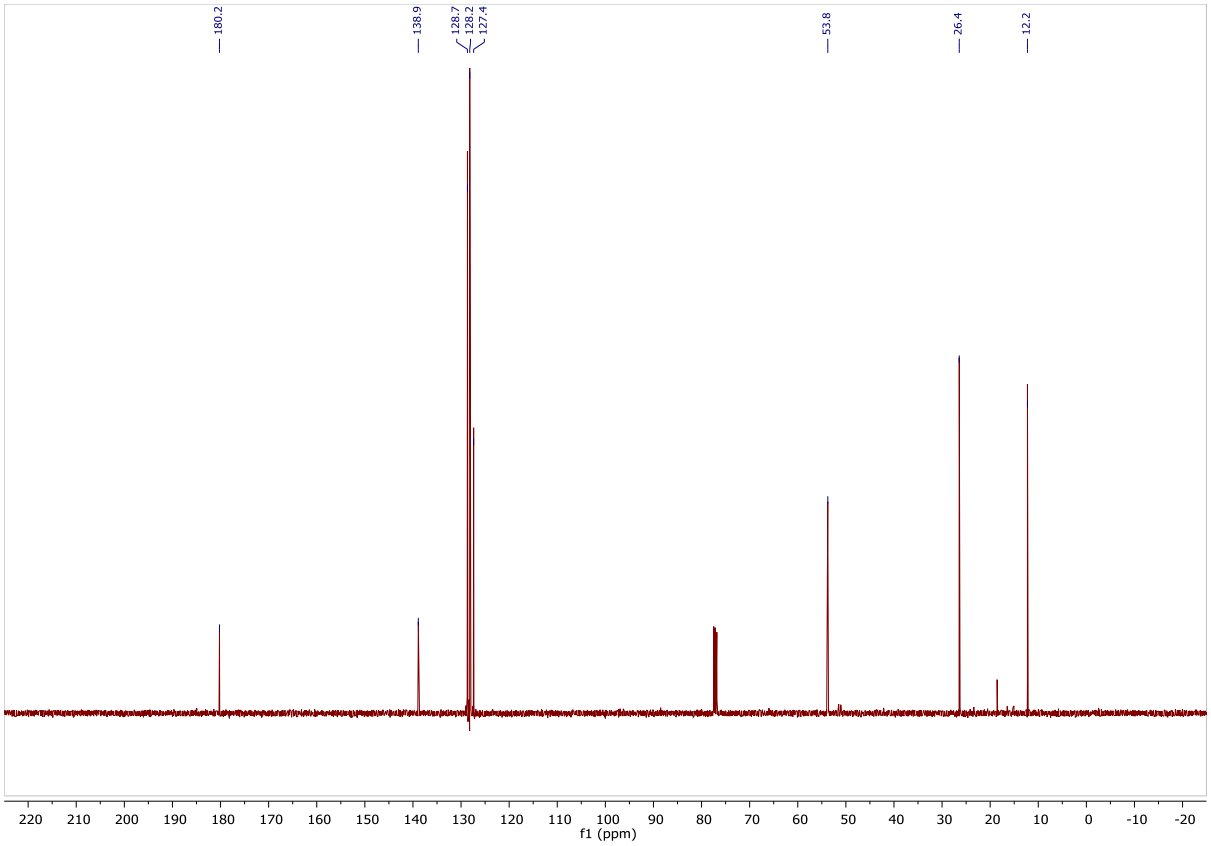
^{1}H and ^{13}C NMR compound for **28c**



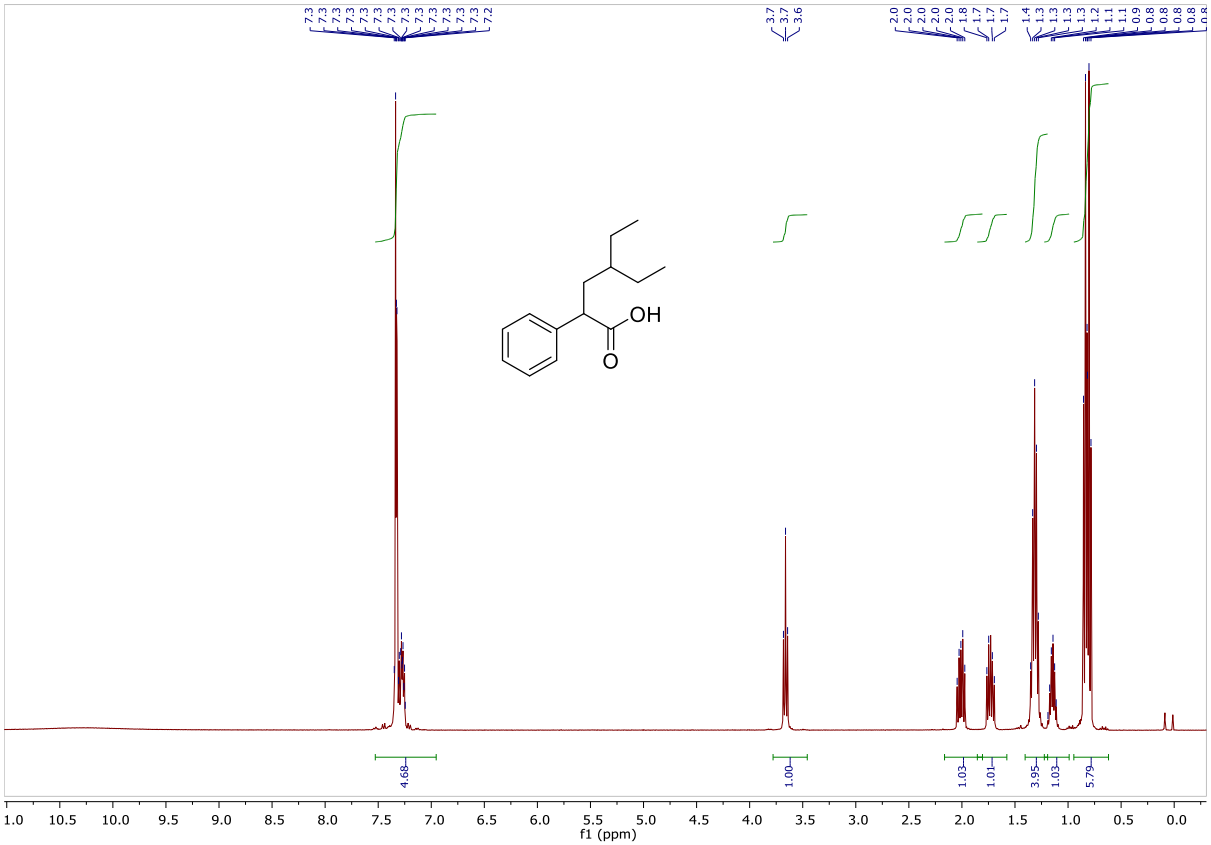


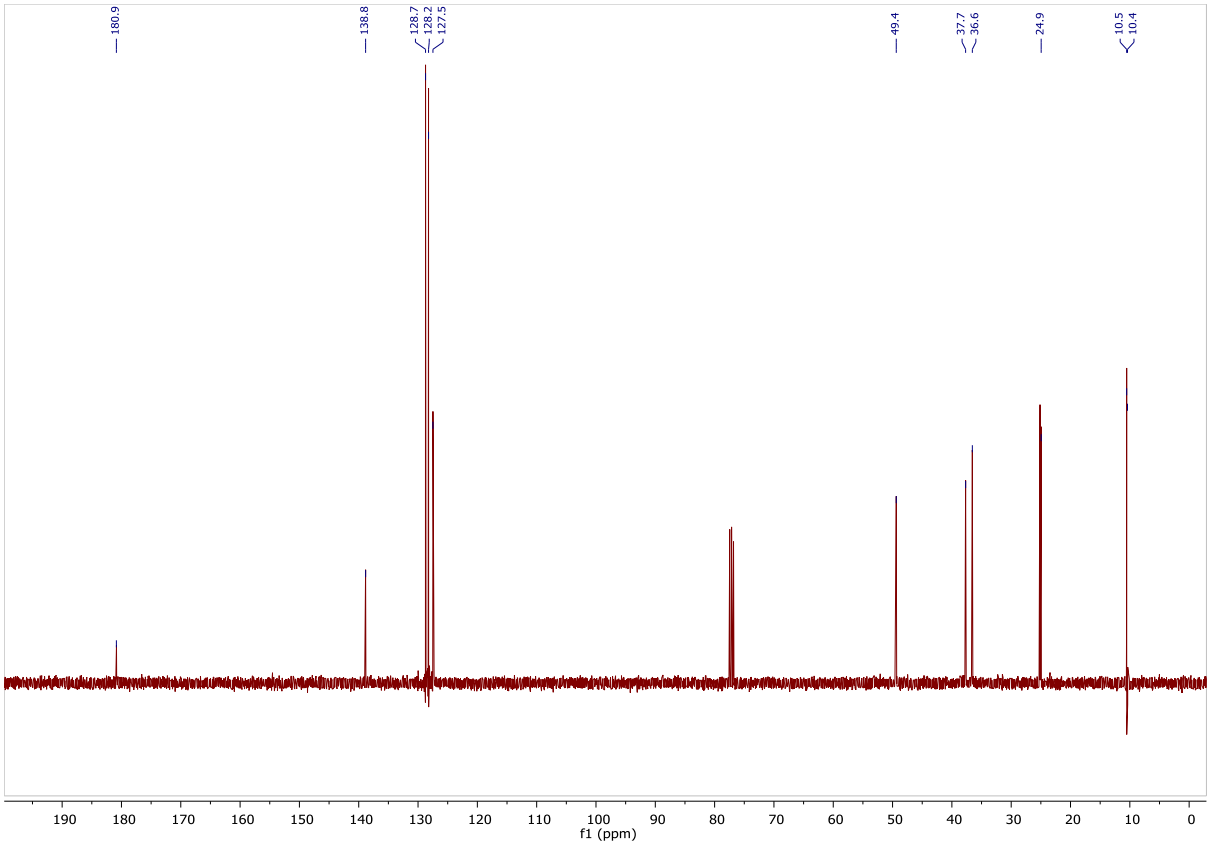
^{1}H and ^{13}C NMR compound for **29b**



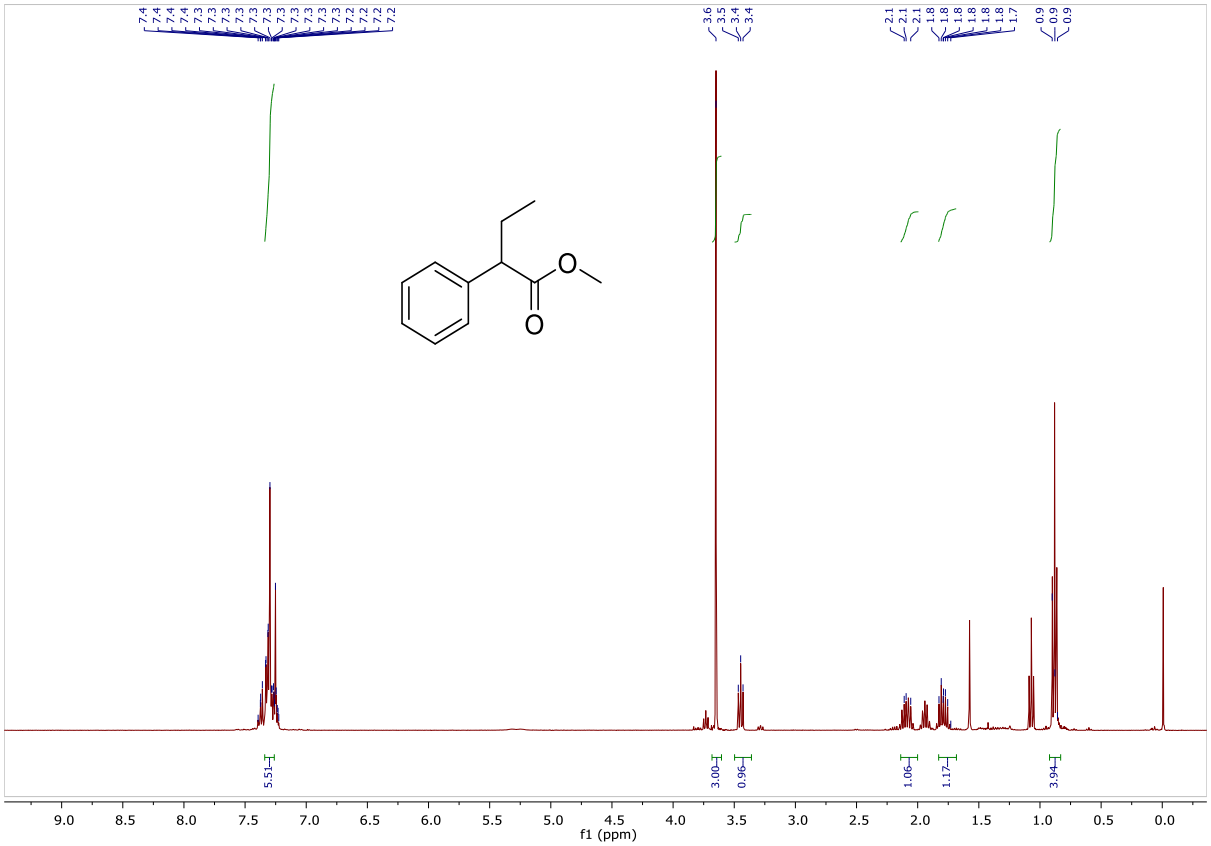


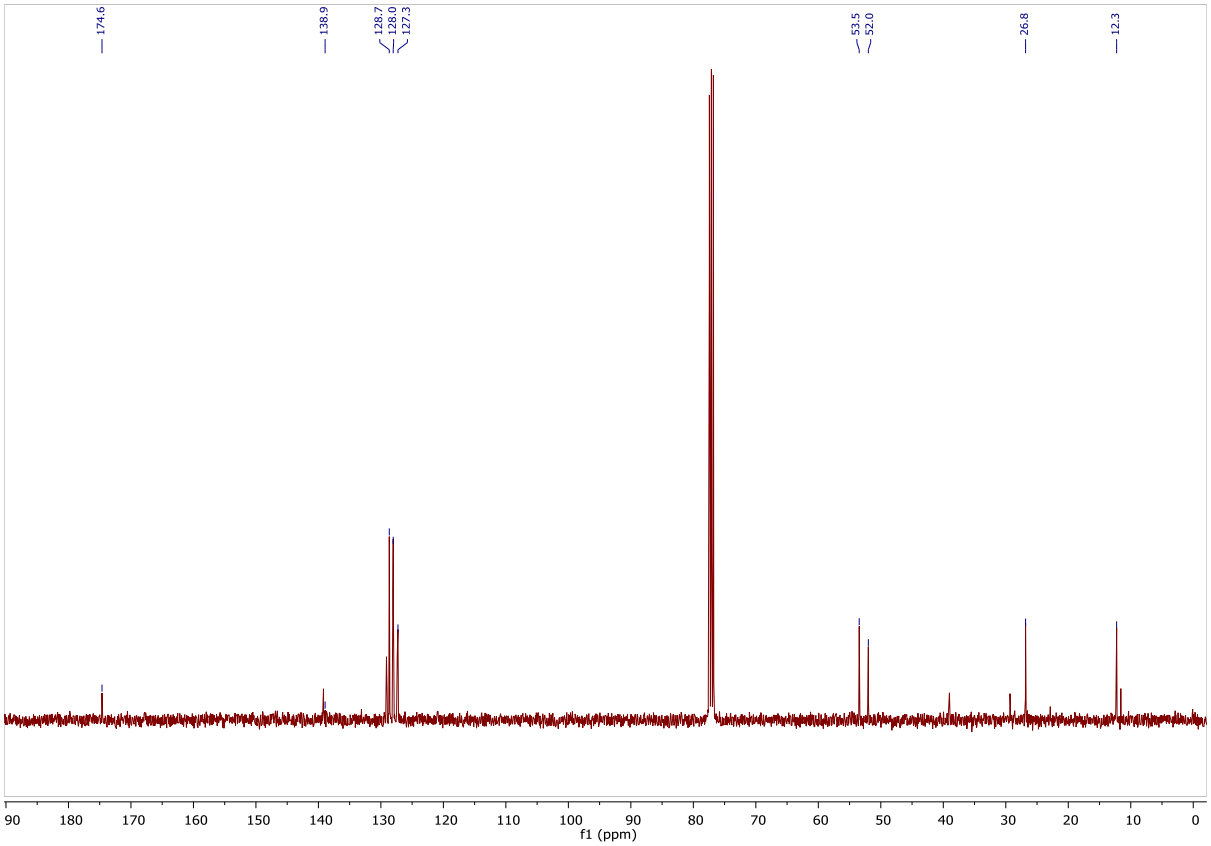
^{1}H and ^{13}C NMR compound for **29c**



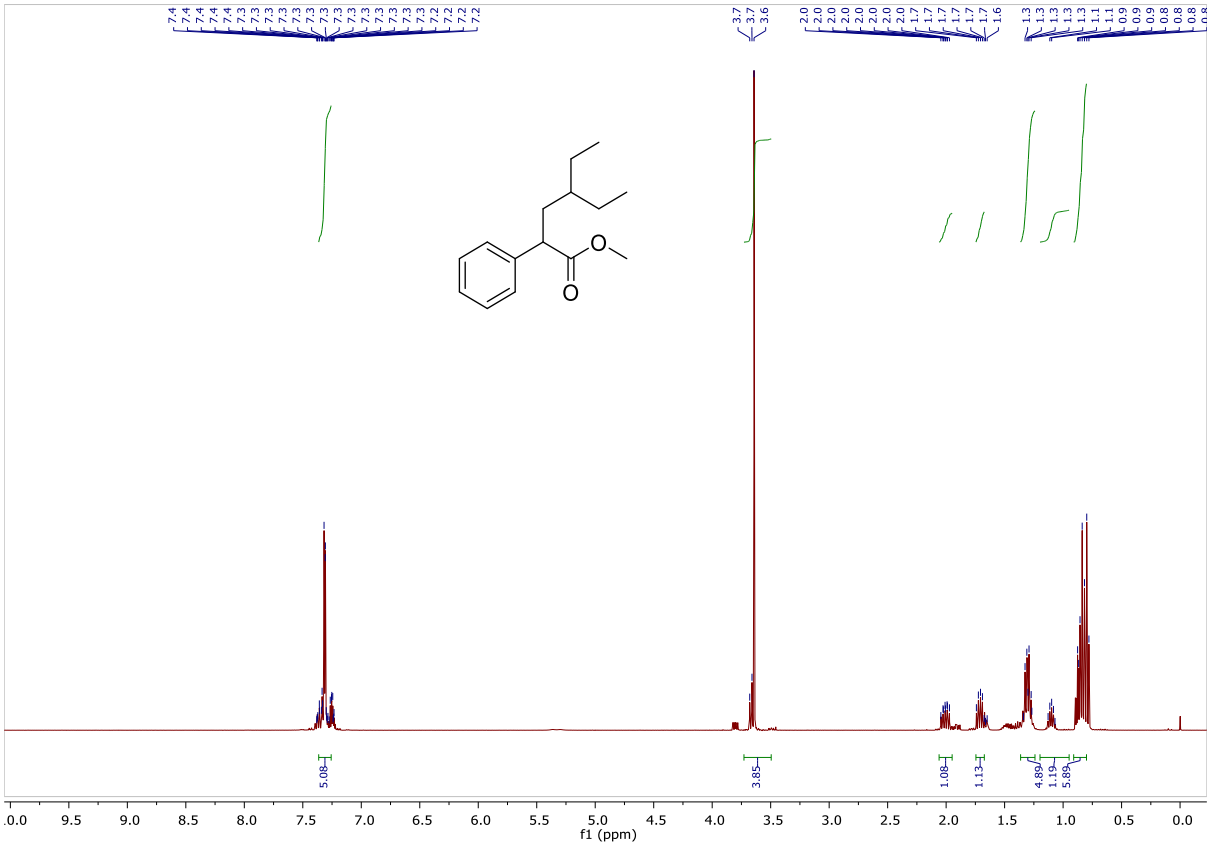


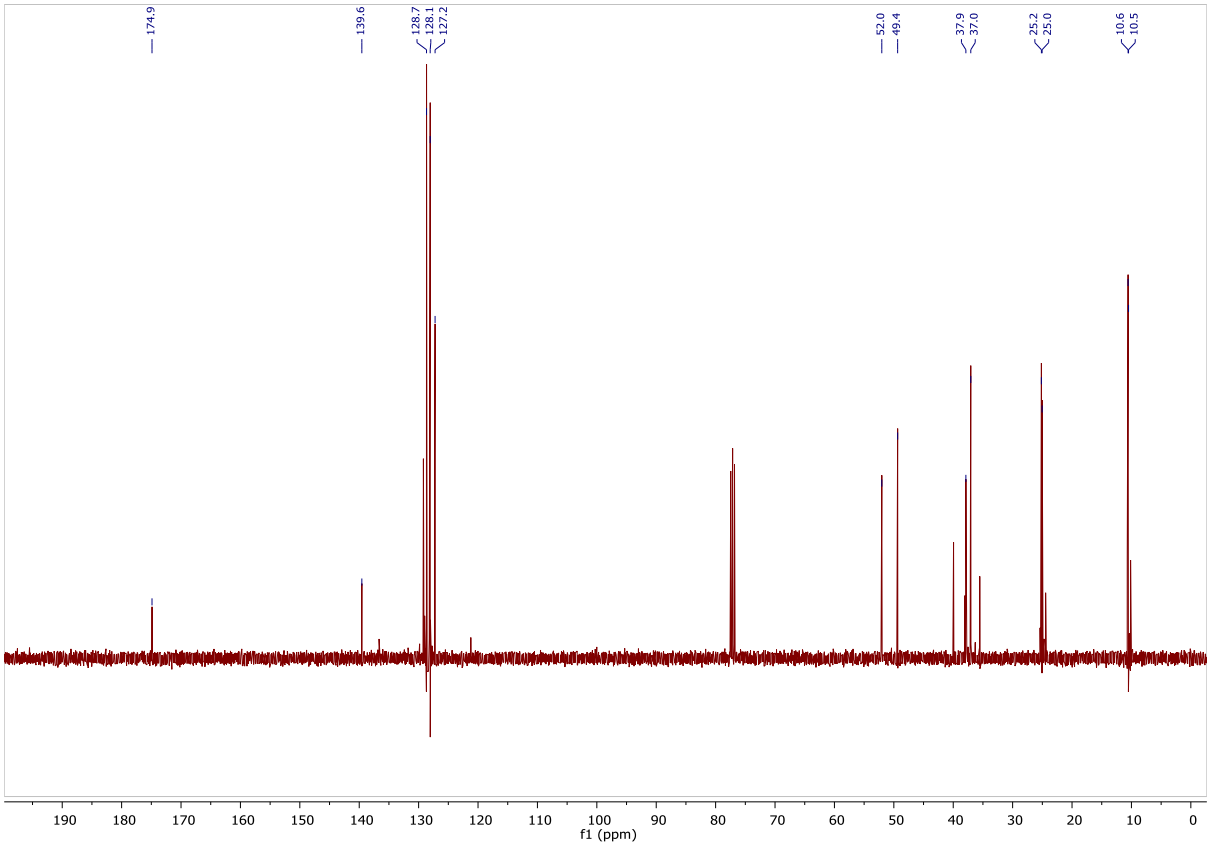
^{1}H and ^{13}C NMR compound for **30b** (crude as described in experiment)



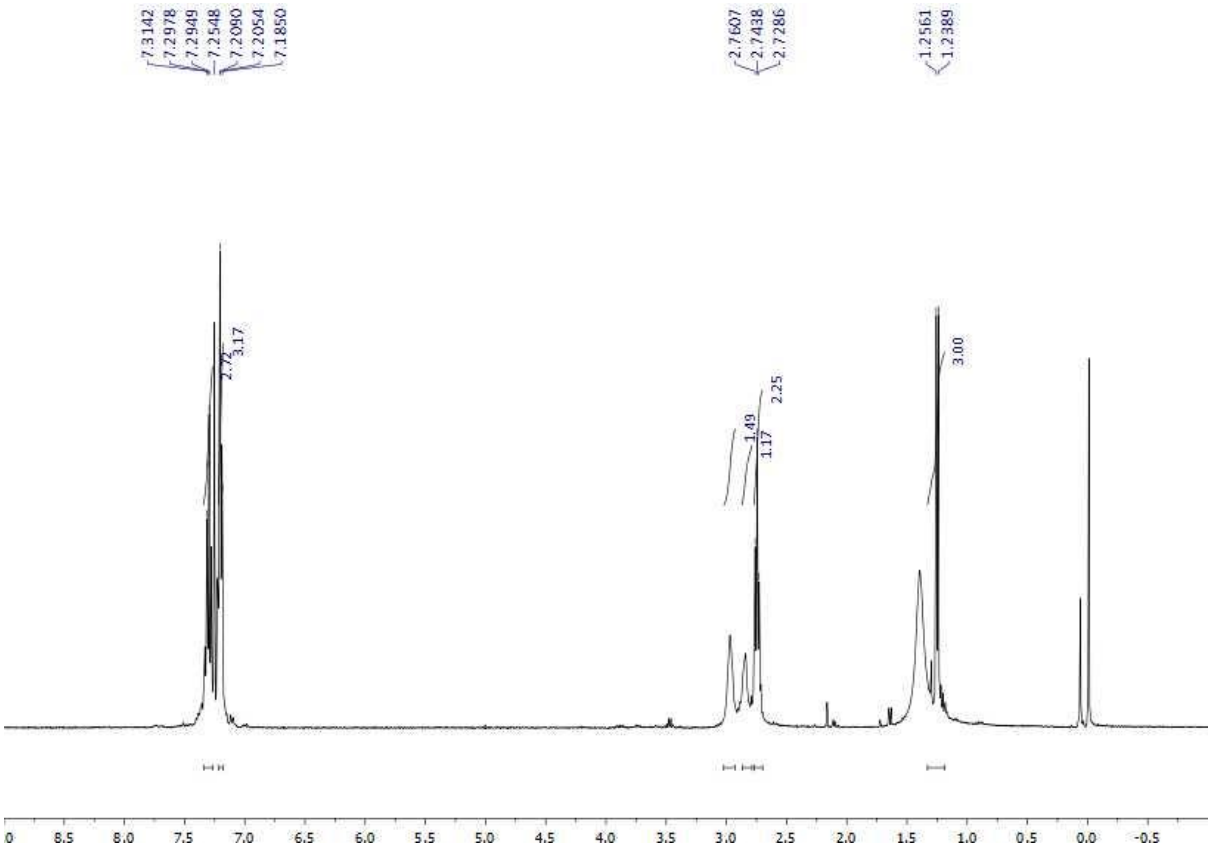


^{1}H and ^{13}C NMR compound for **30c** (crude as described in experiment)

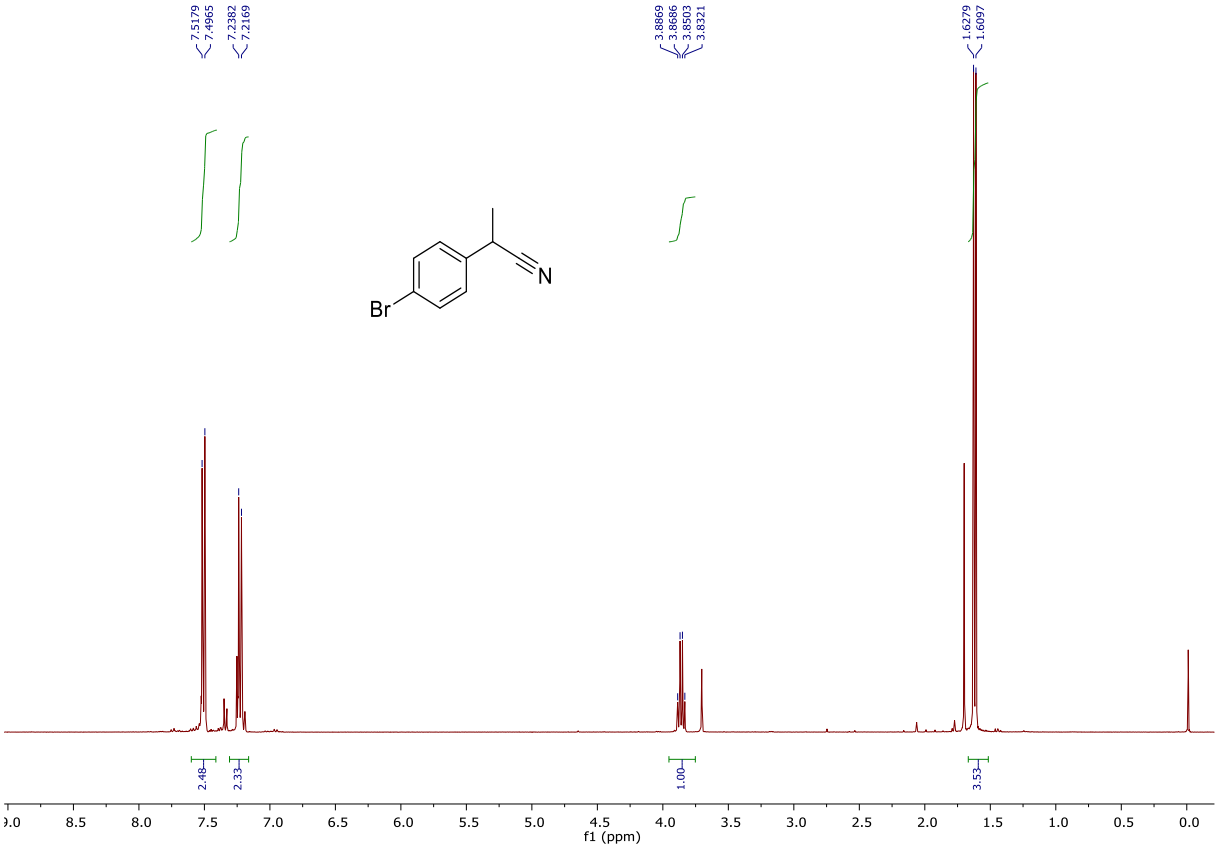


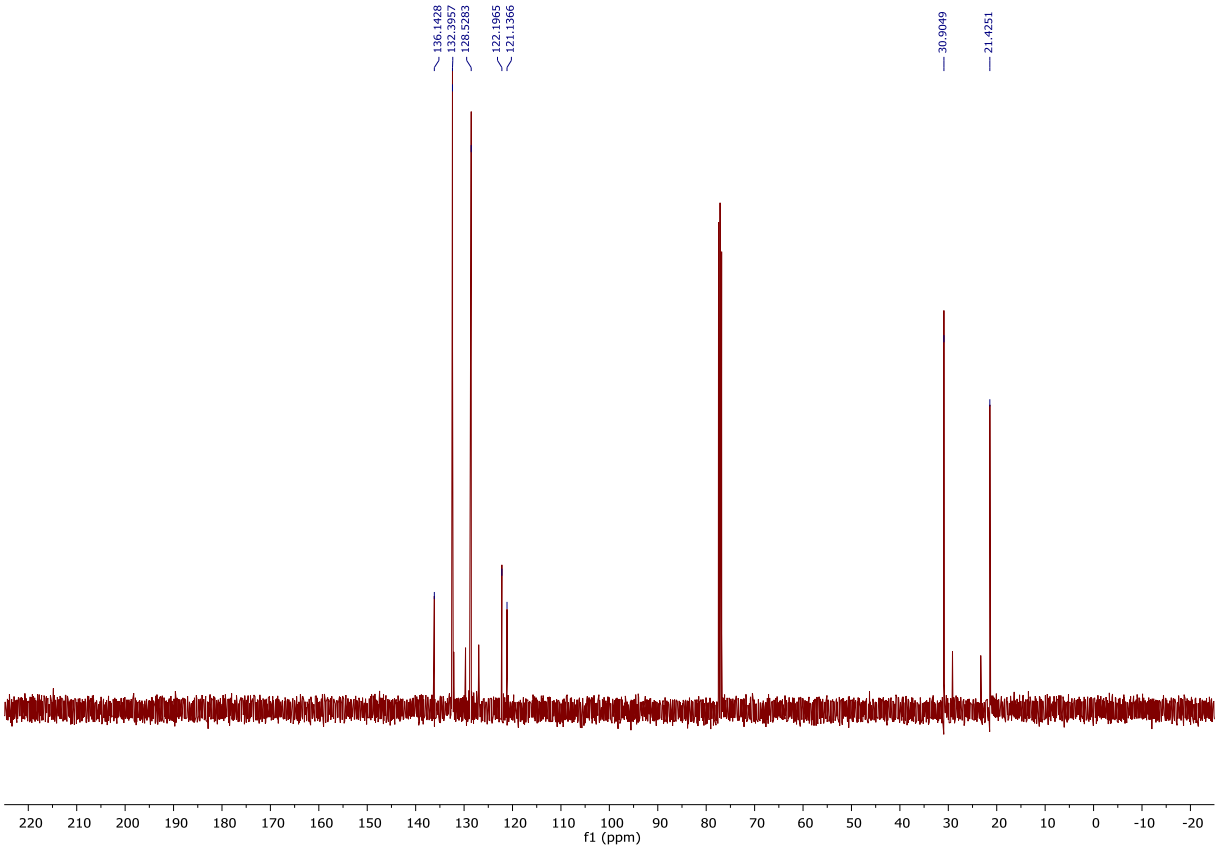


^{1}H NMR compound for **31a**

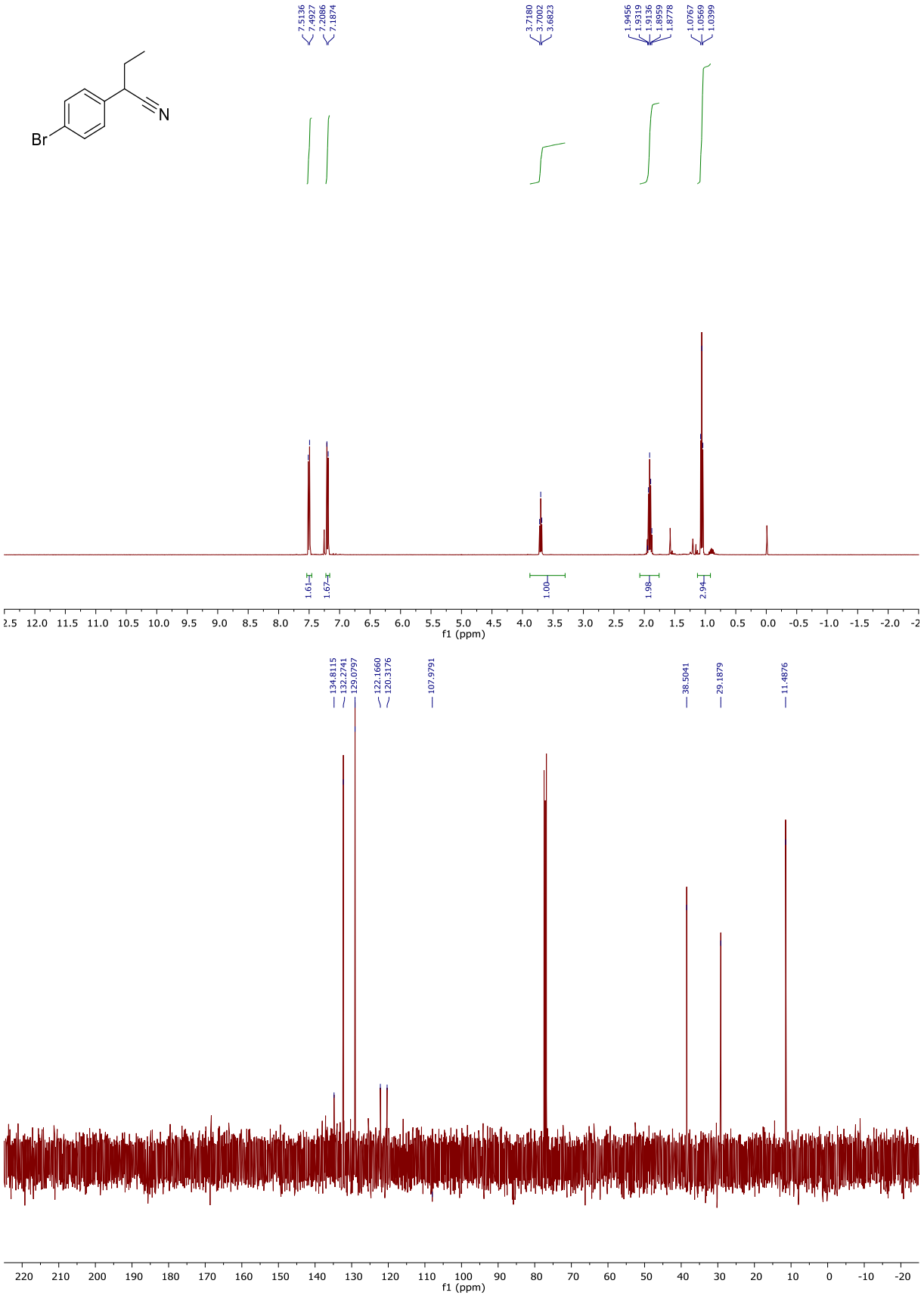


^{1}H and ^{13}C NMR compound for **33a** (crude as described in experimental)

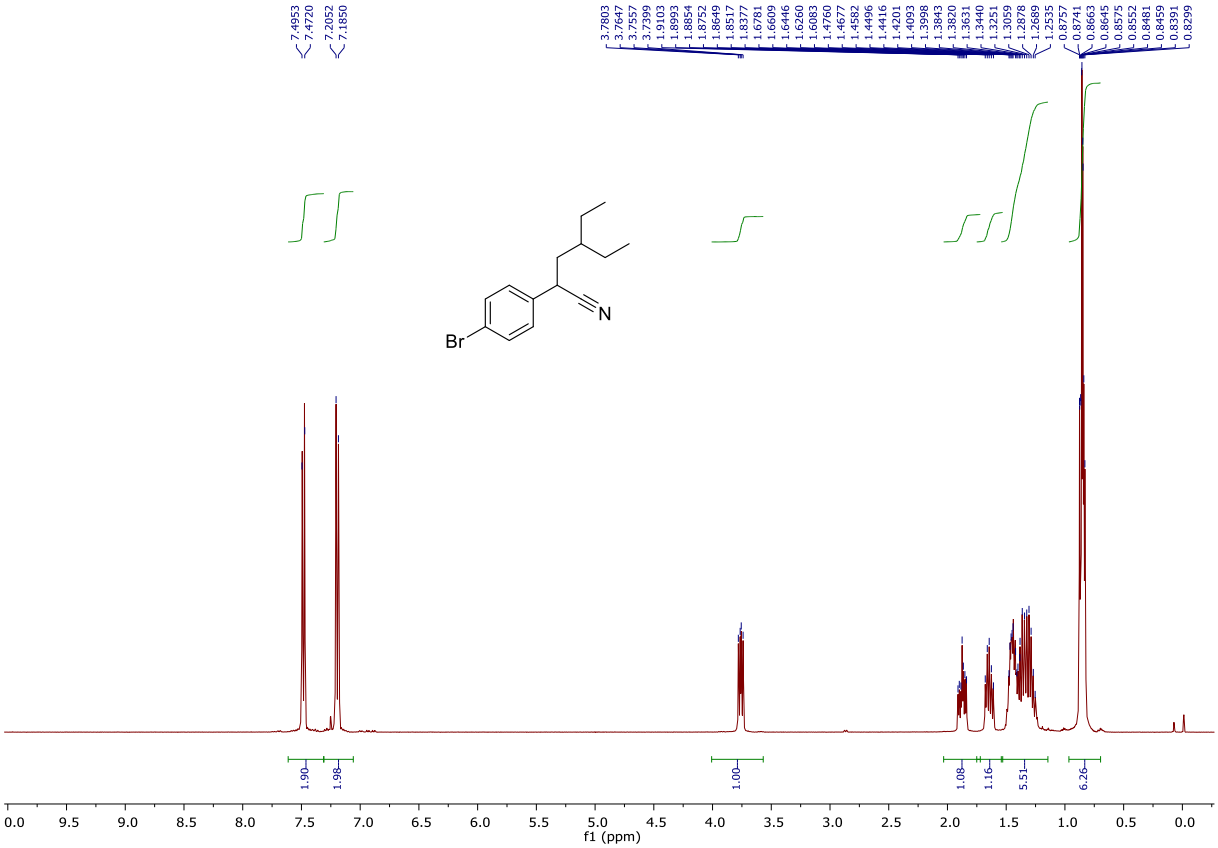


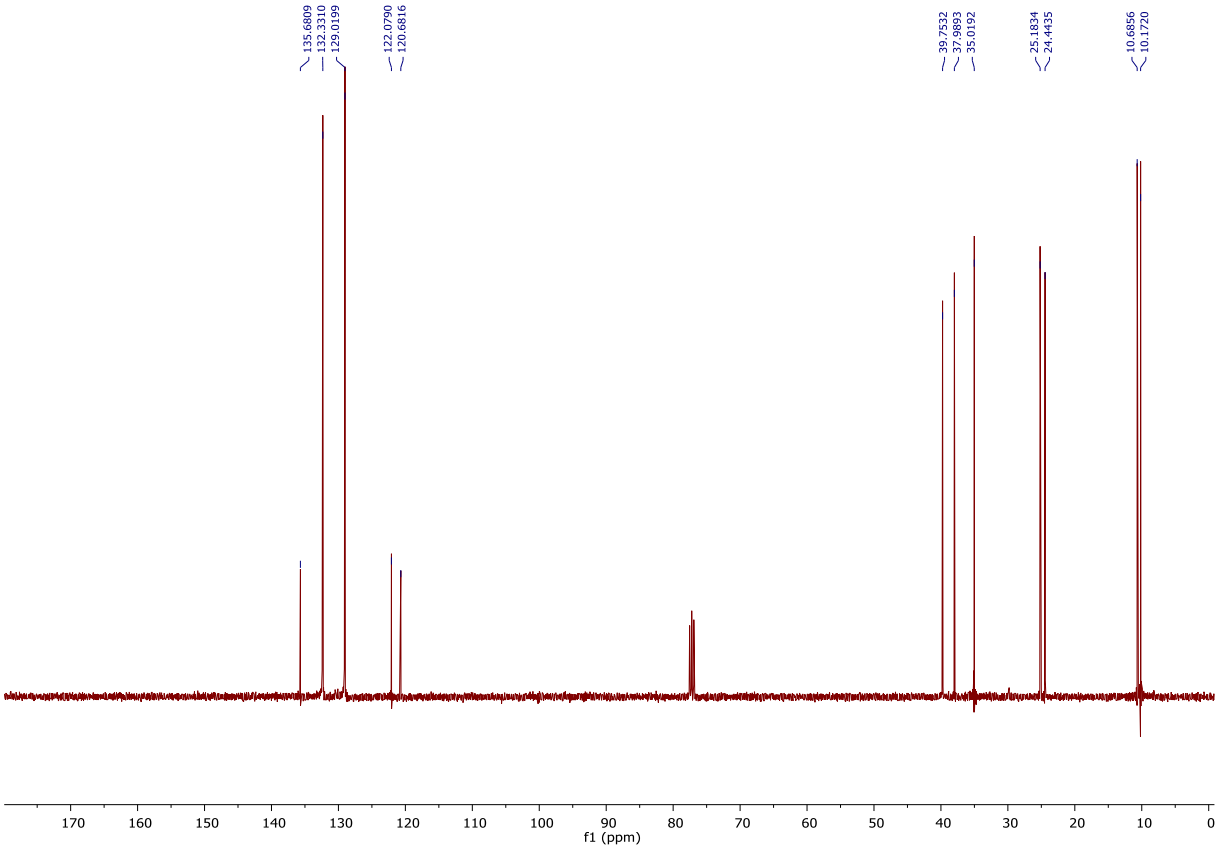


^{1}H and ^{13}C NMR compound for **33b**

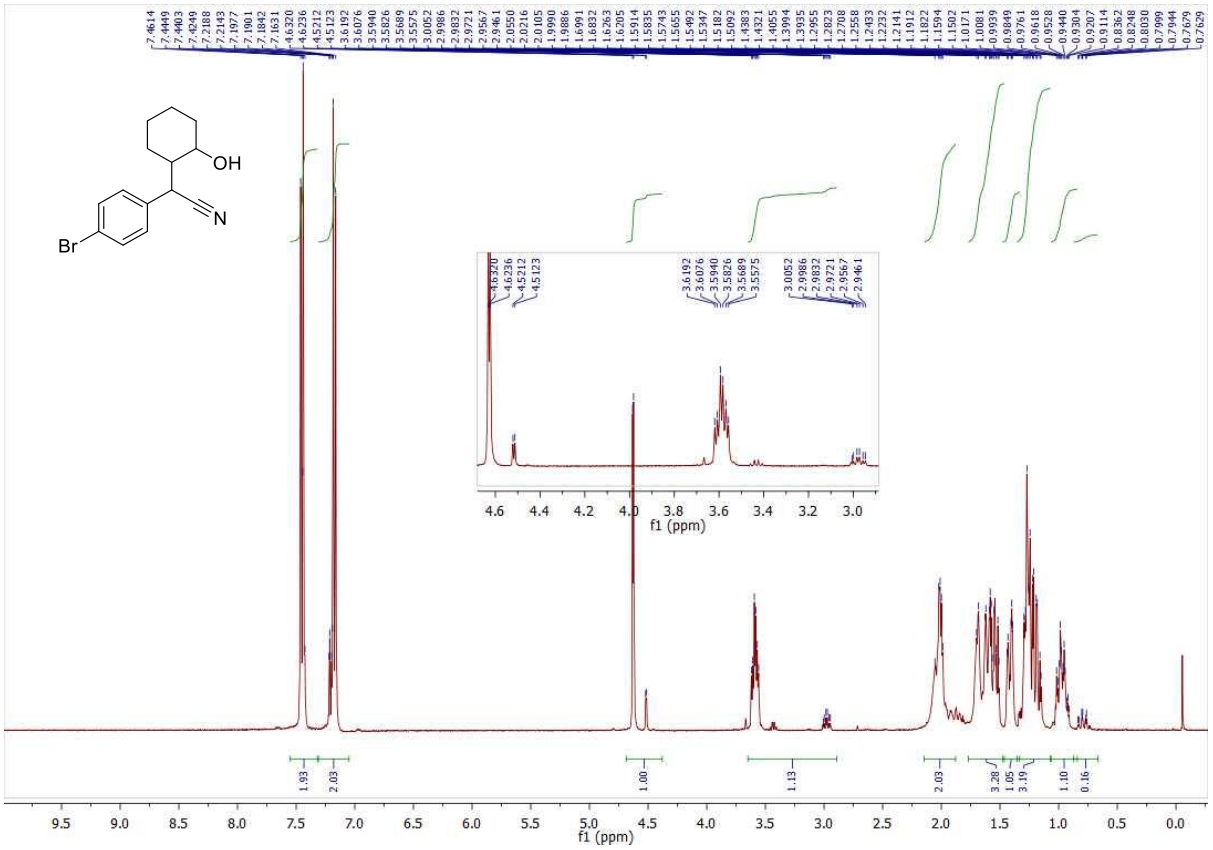


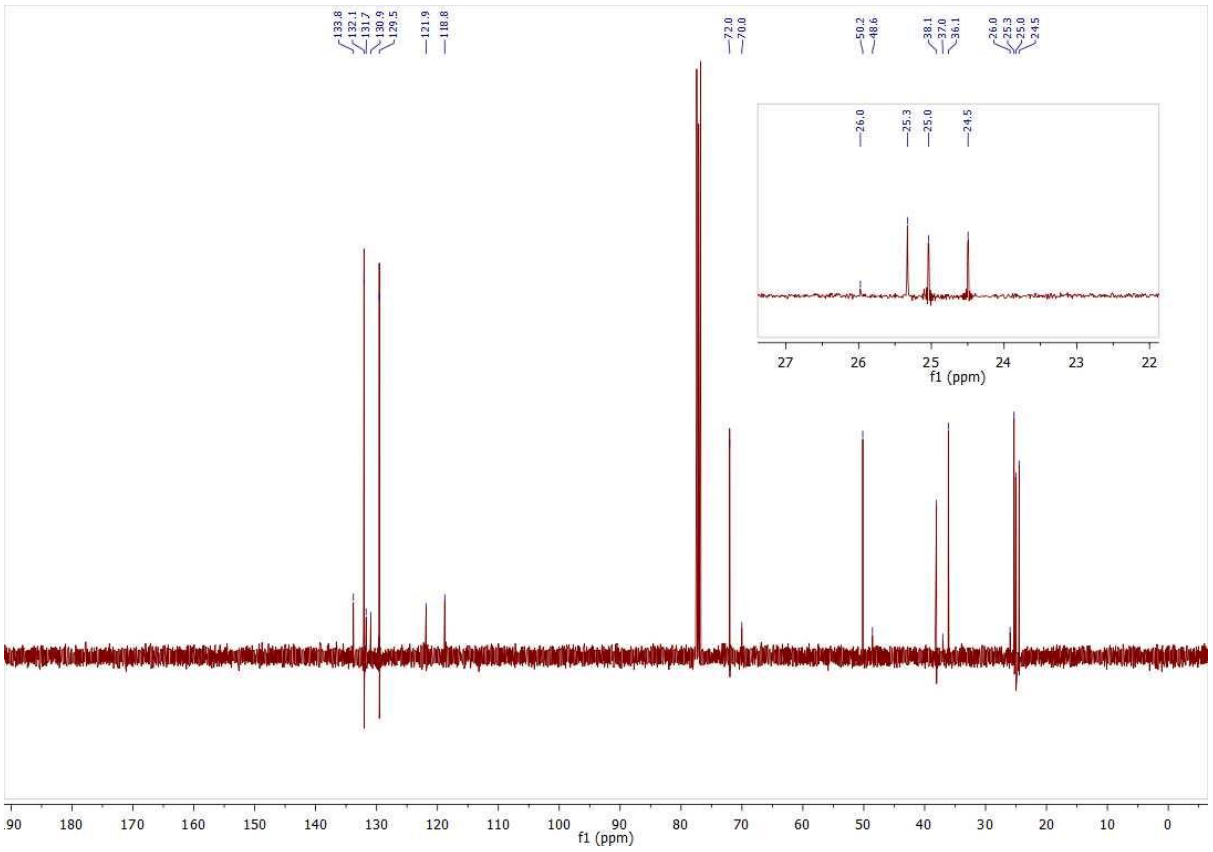
^{1}H and ^{13}C NMR compound for **33c**



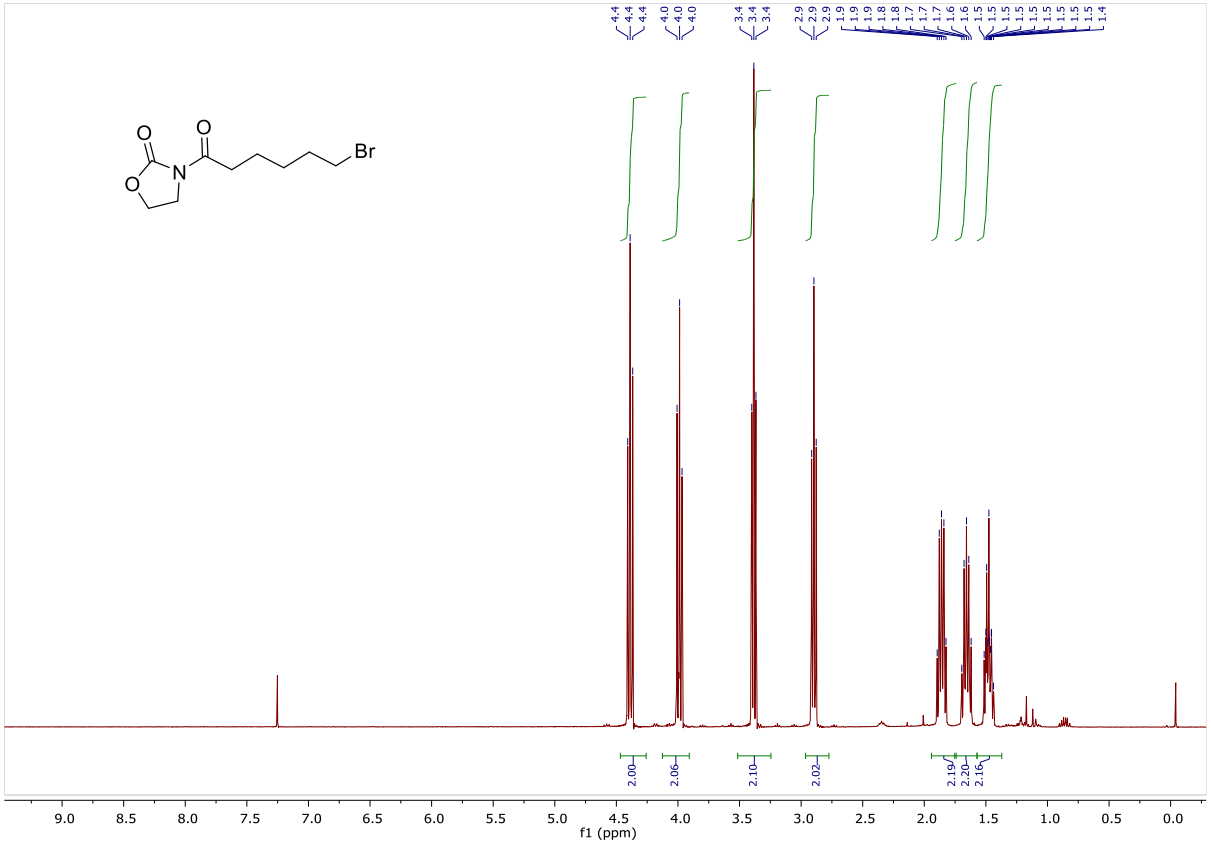


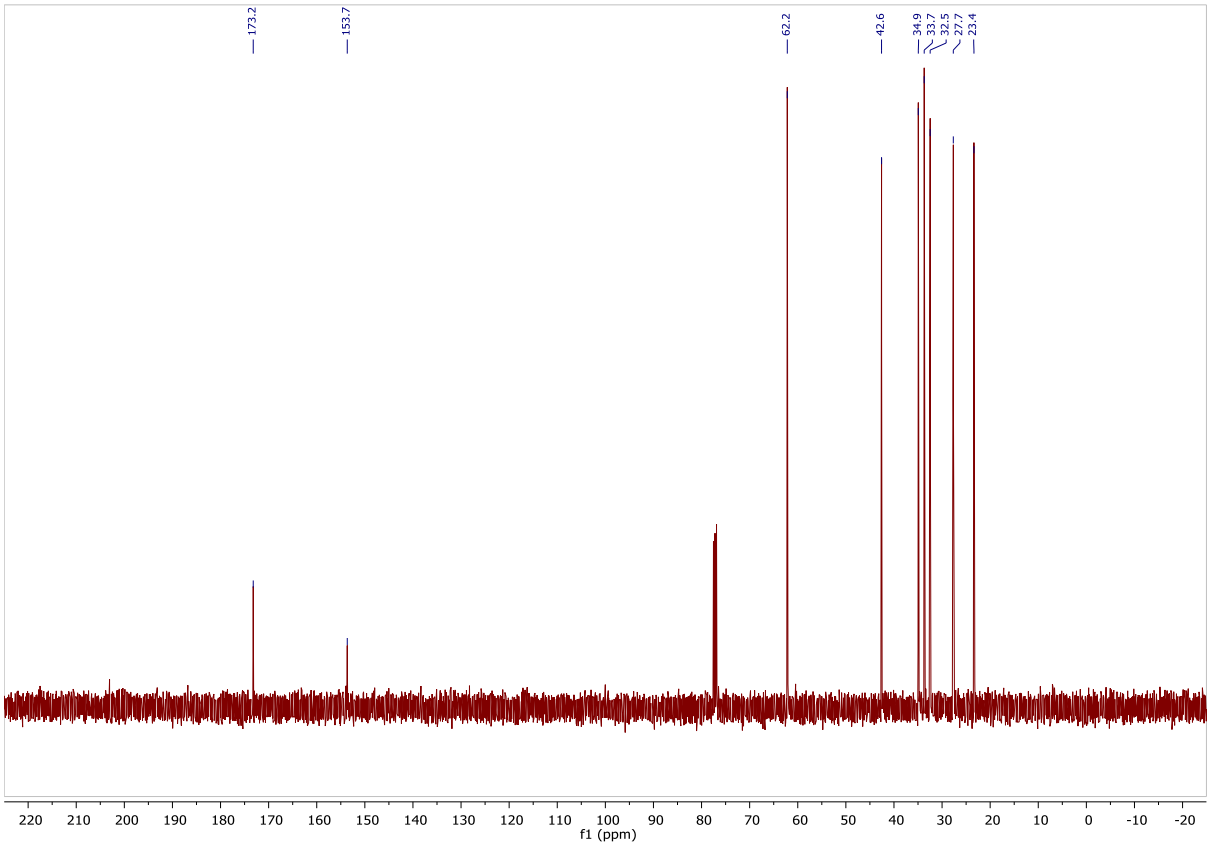
^{1}H and ^{13}C NMR compound for **33d**



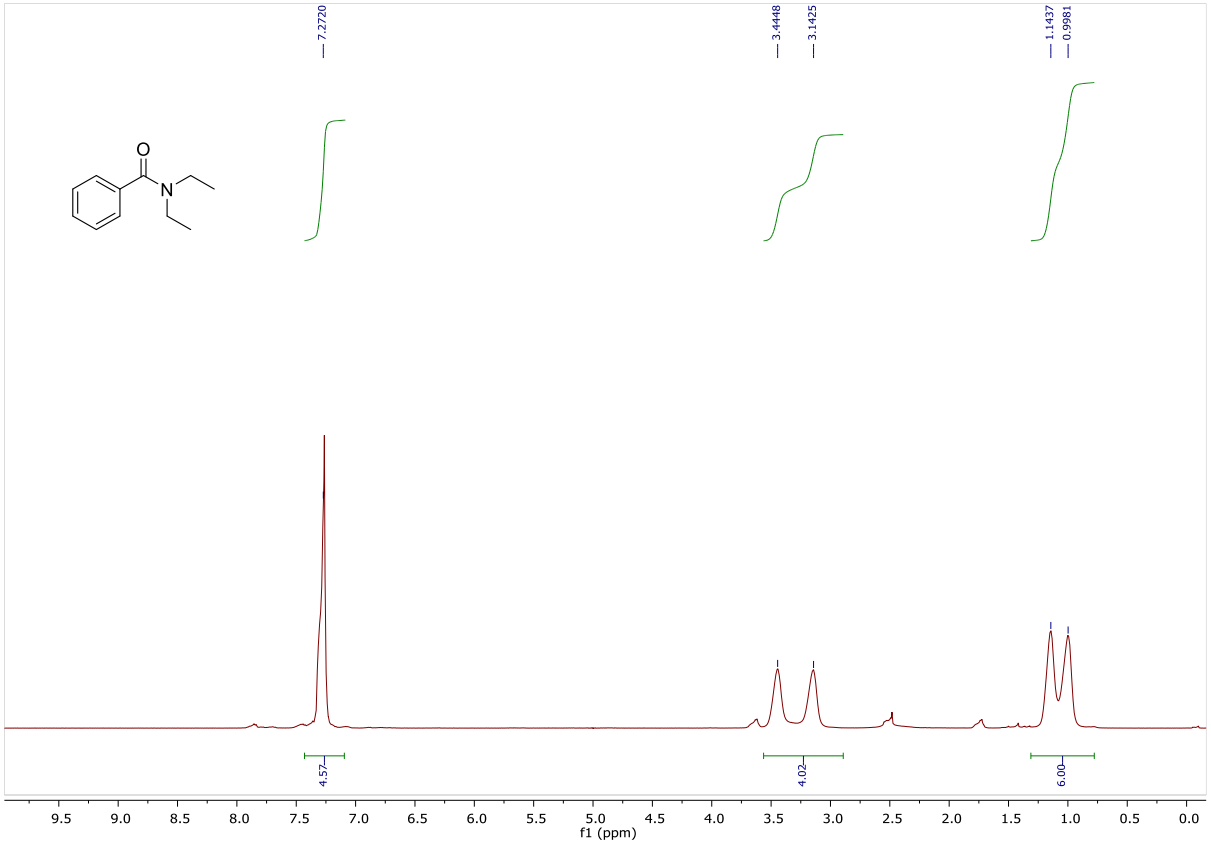


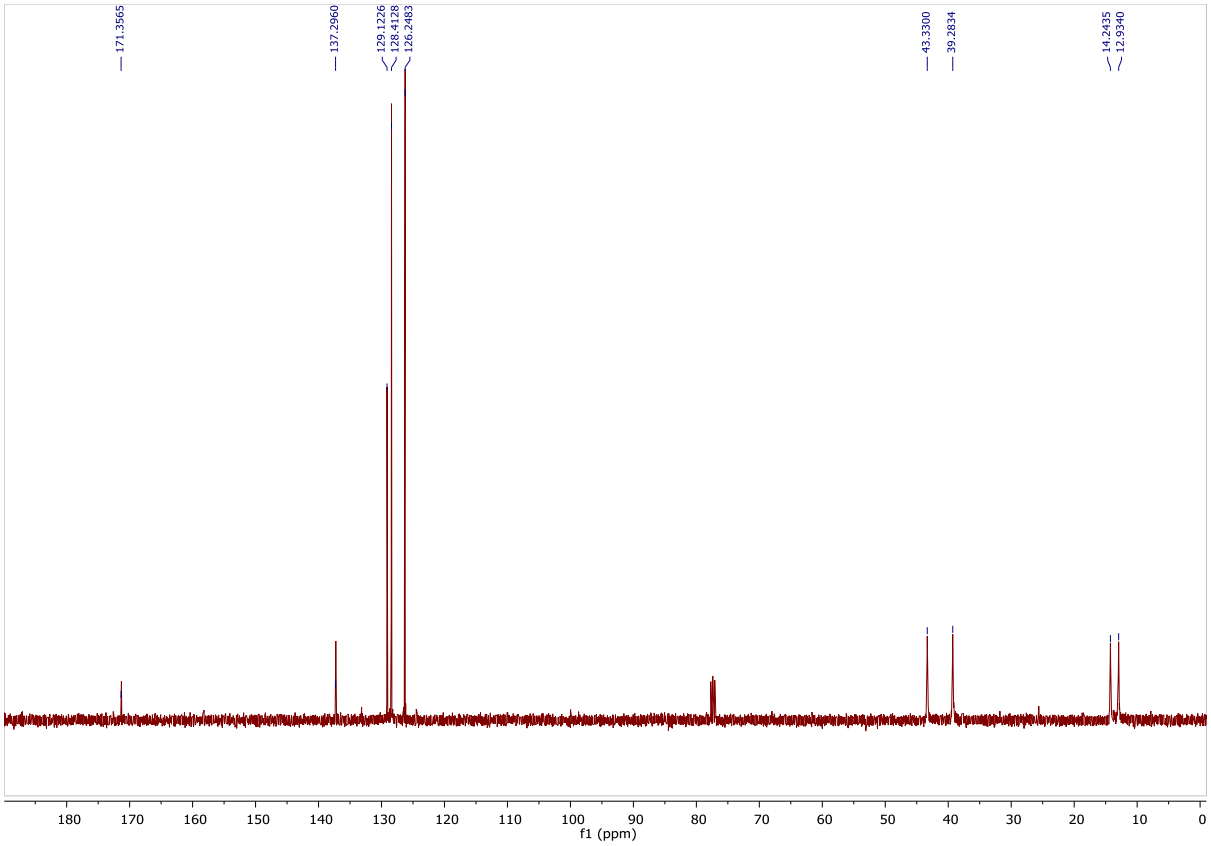
^{1}H and ^{13}C NMR compound for **34**



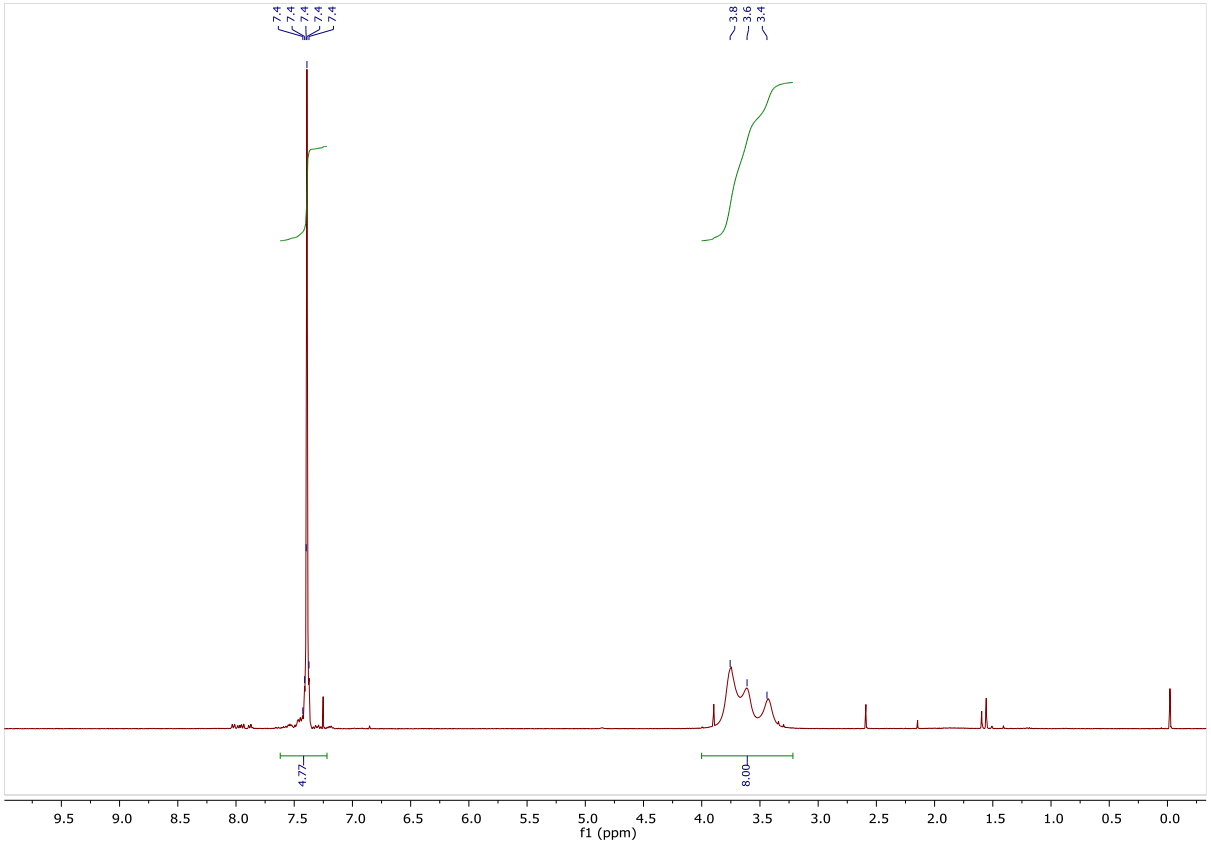


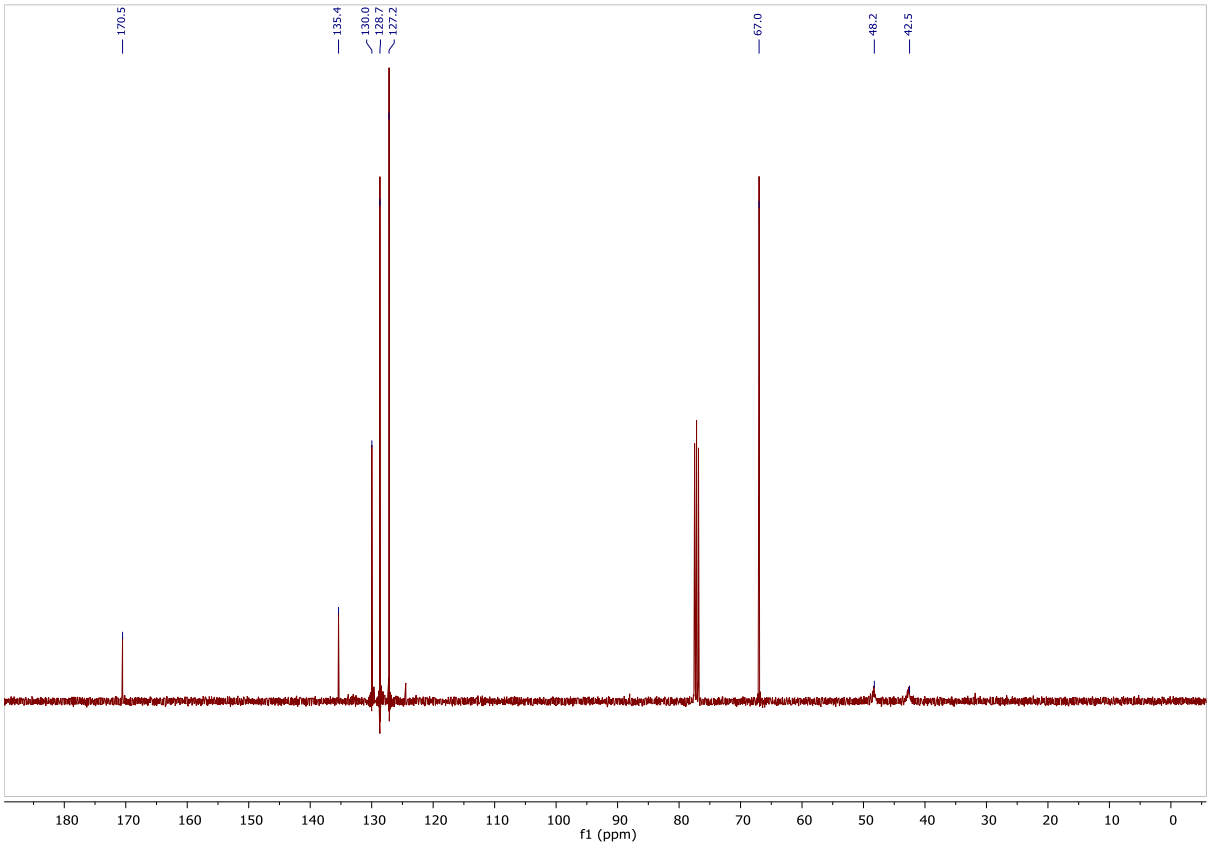
^{1}H and ^{13}C NMR compound for **41a**



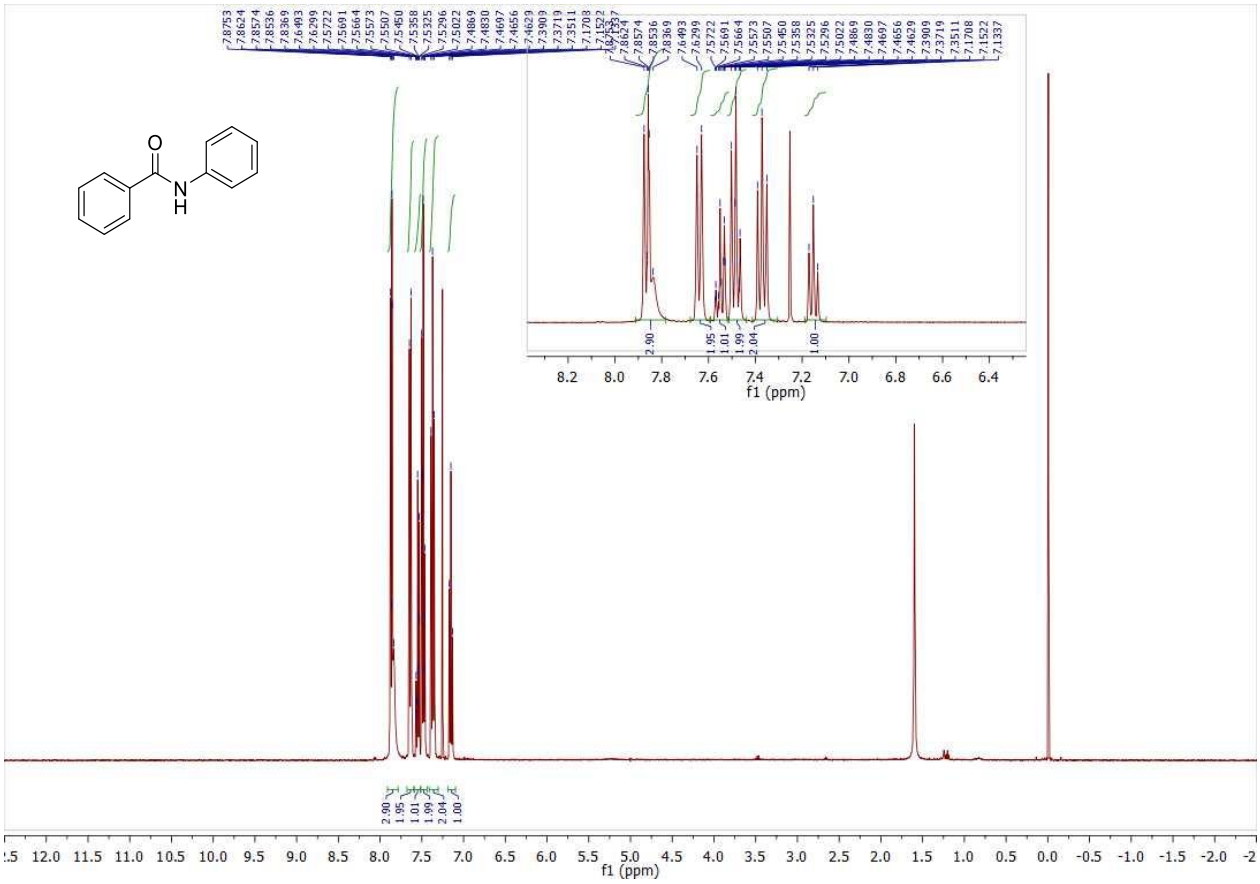


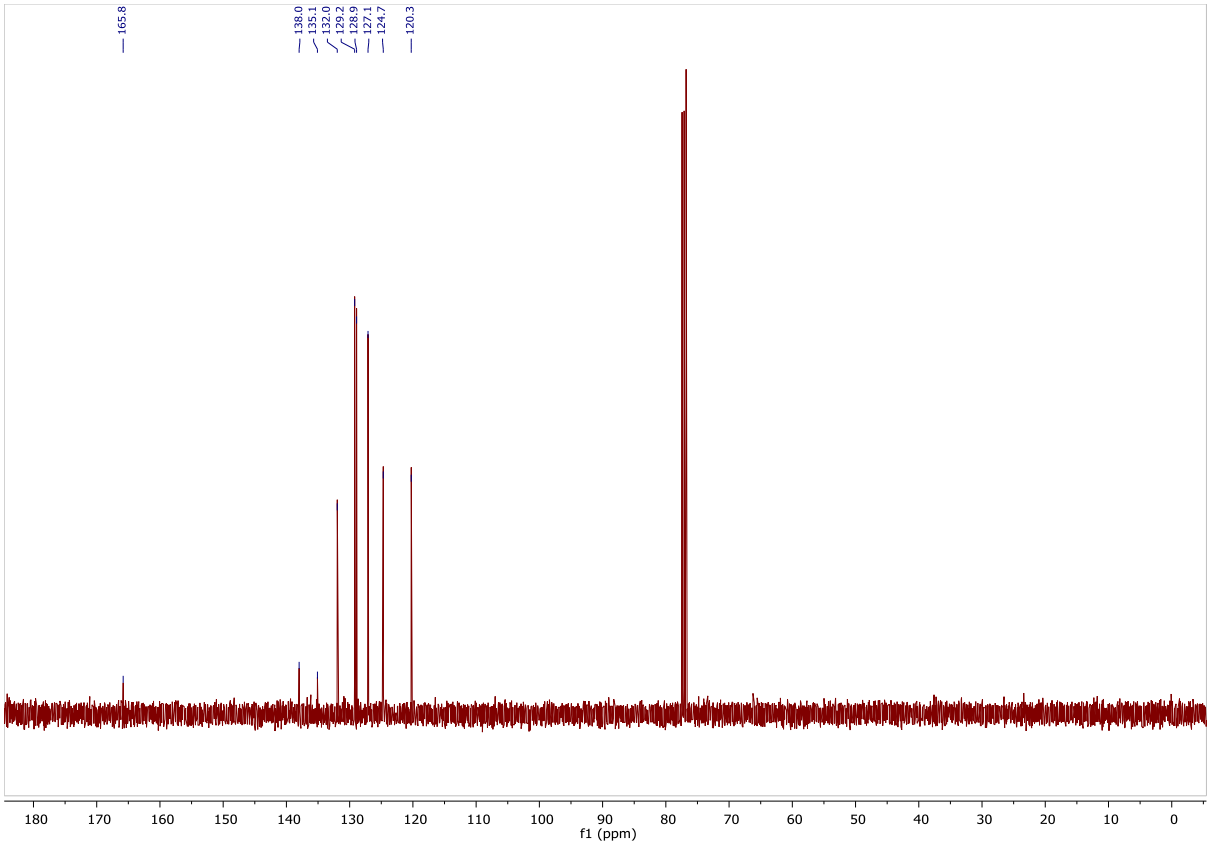
^{1}H and ^{13}C NMR compound for **41b**



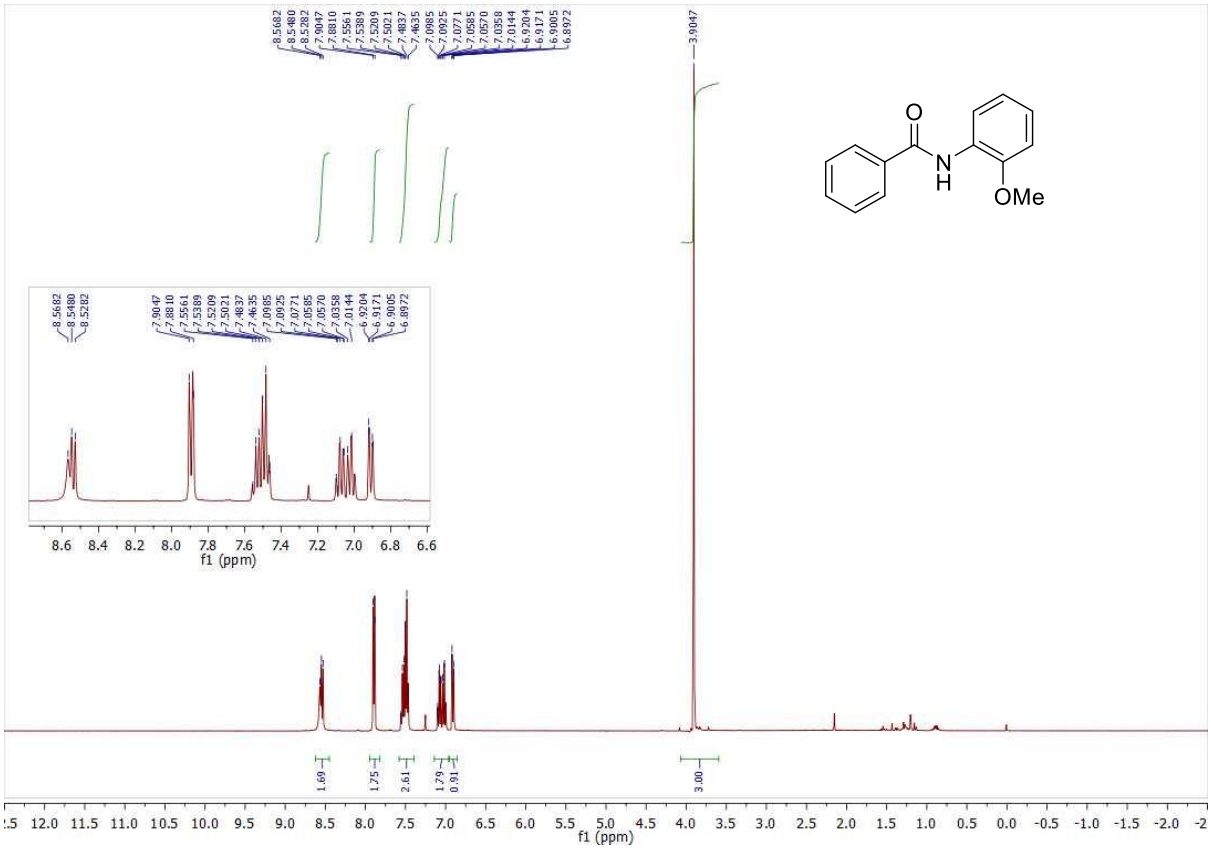


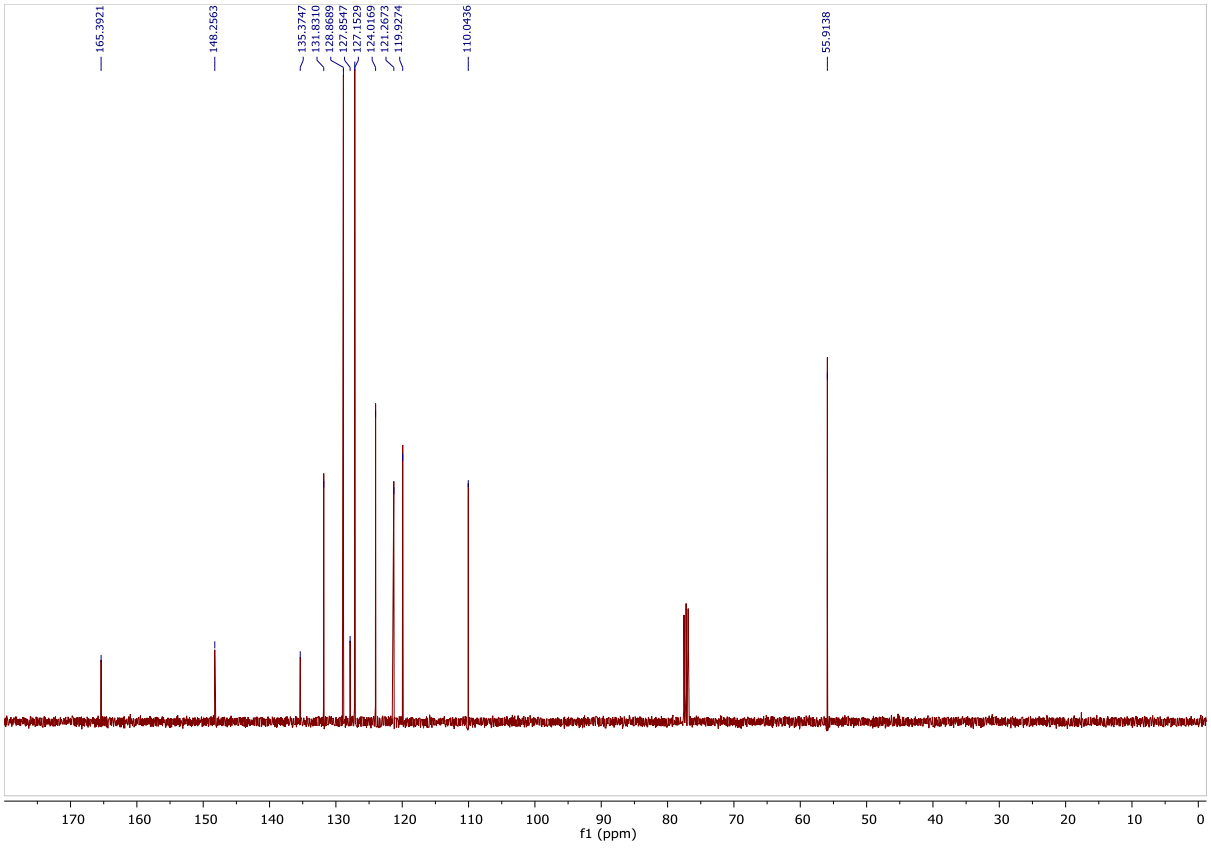
^{1}H and ^{13}C NMR compound for **41c**



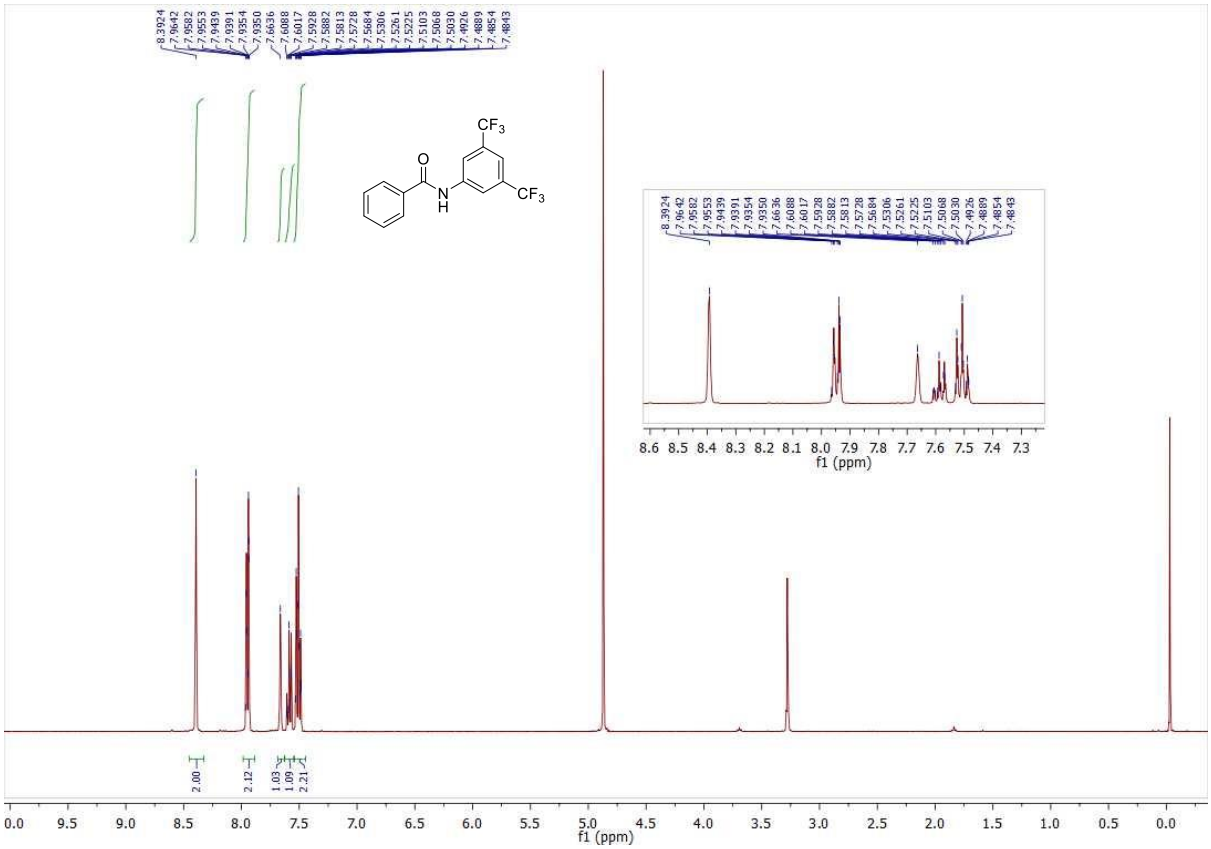


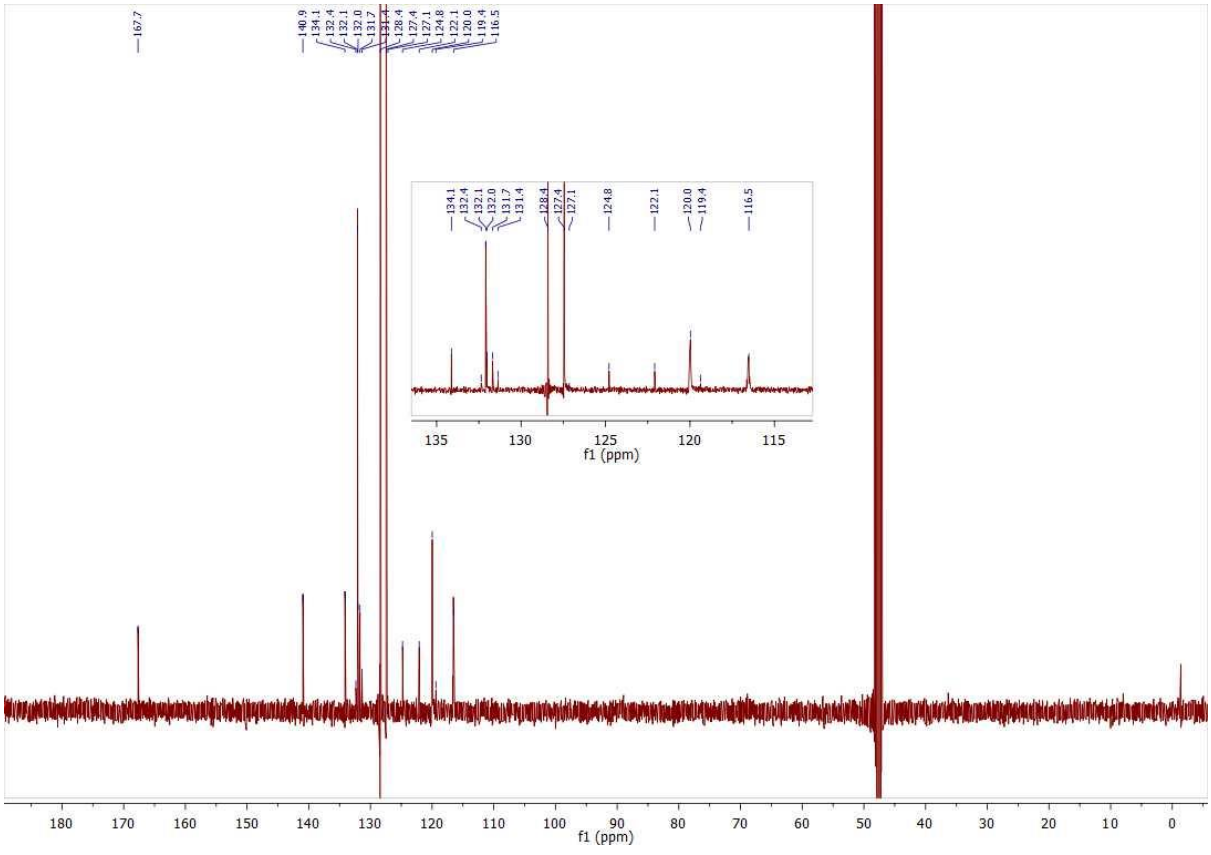
^{1}H and ^{13}C NMR compound for **41d**



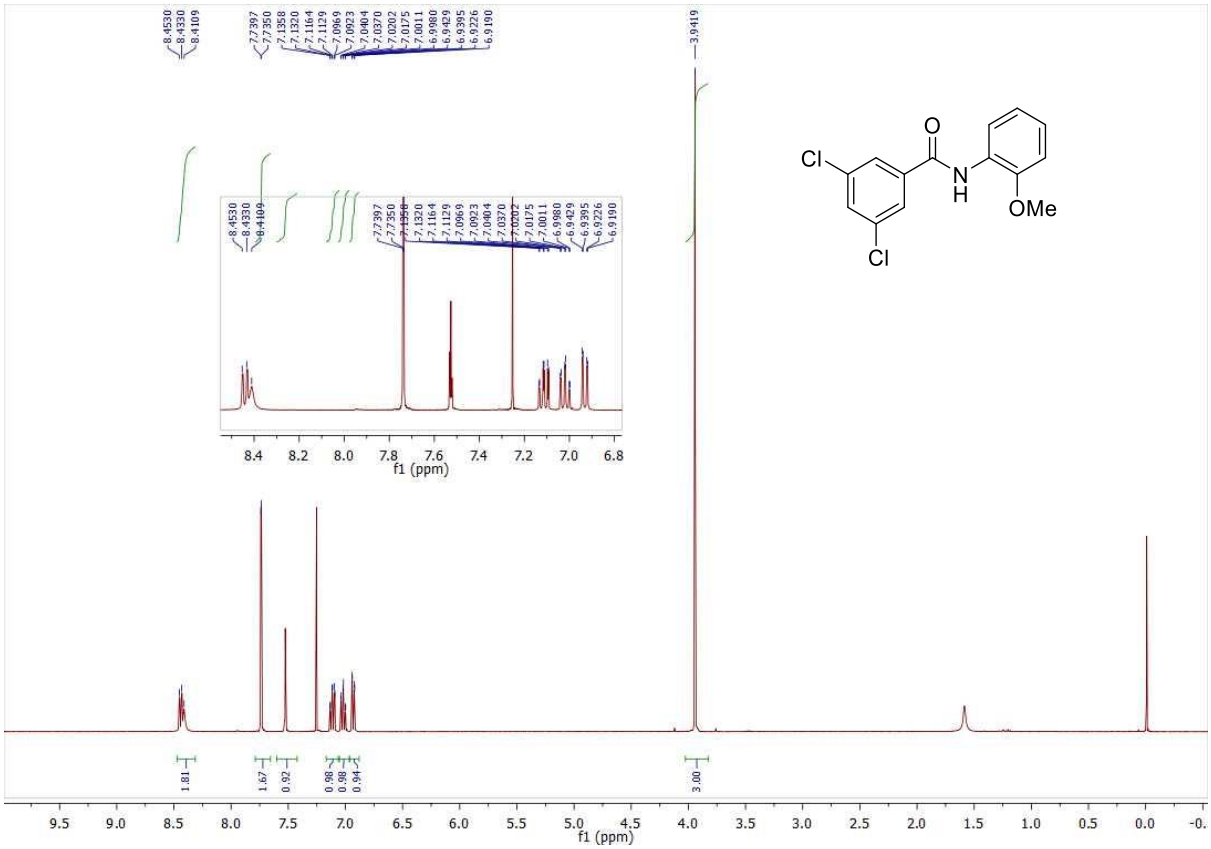


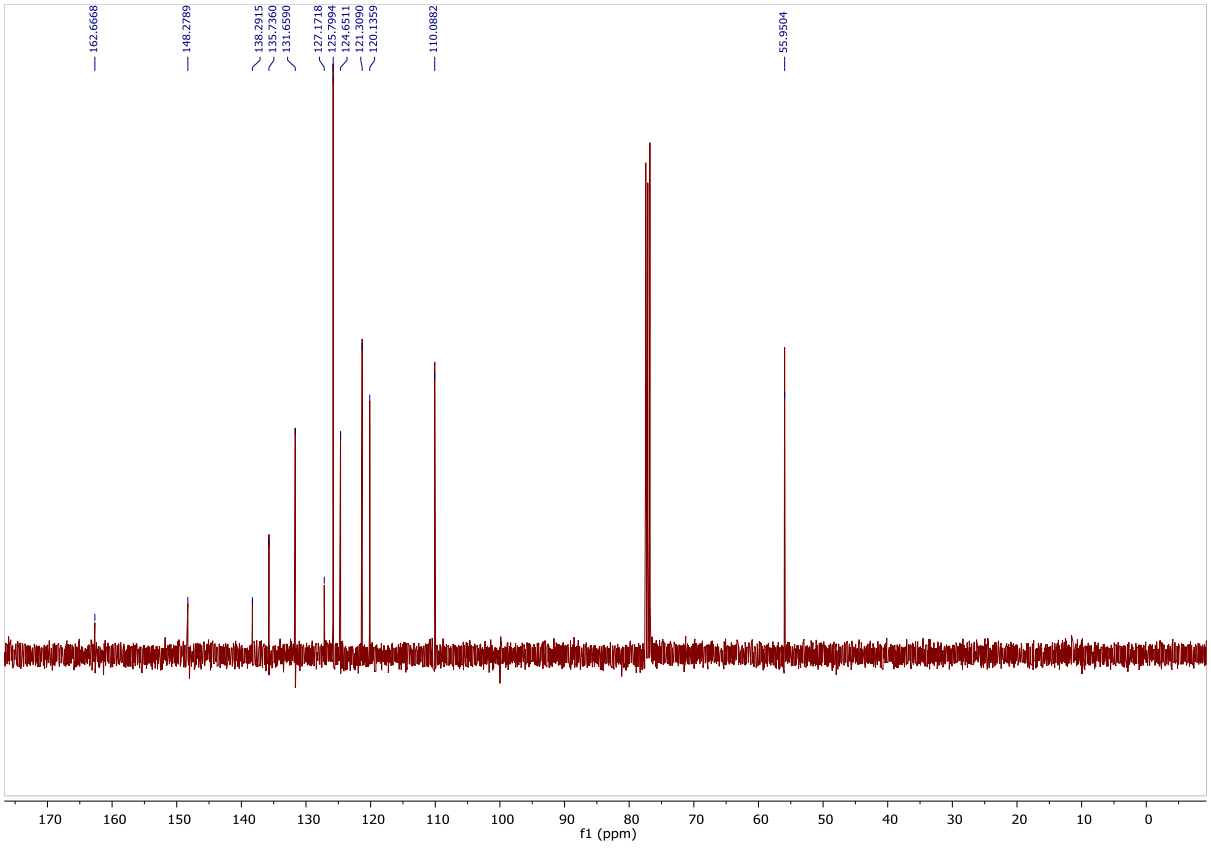
^{1}H and ^{13}C NMR compound for **41e**



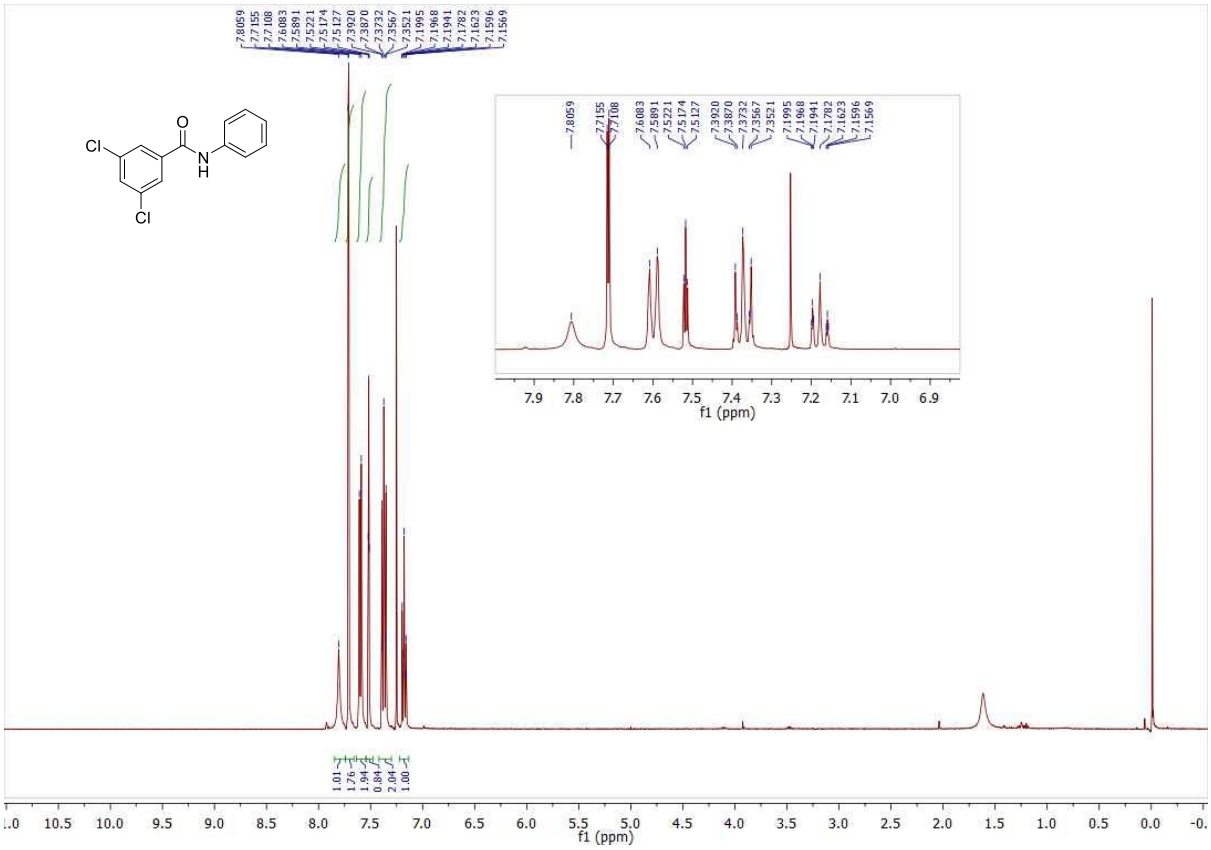


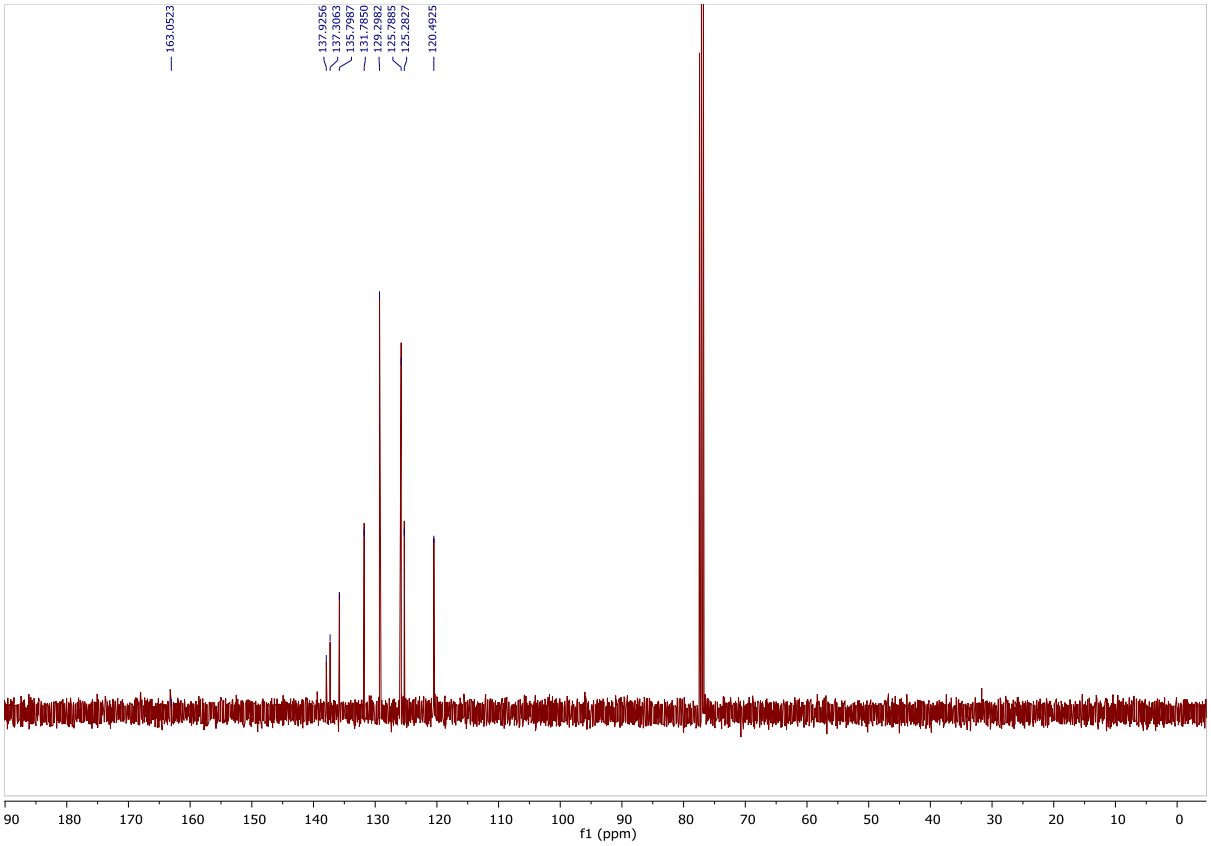
^{1}H and ^{13}C NMR compound for **42a**



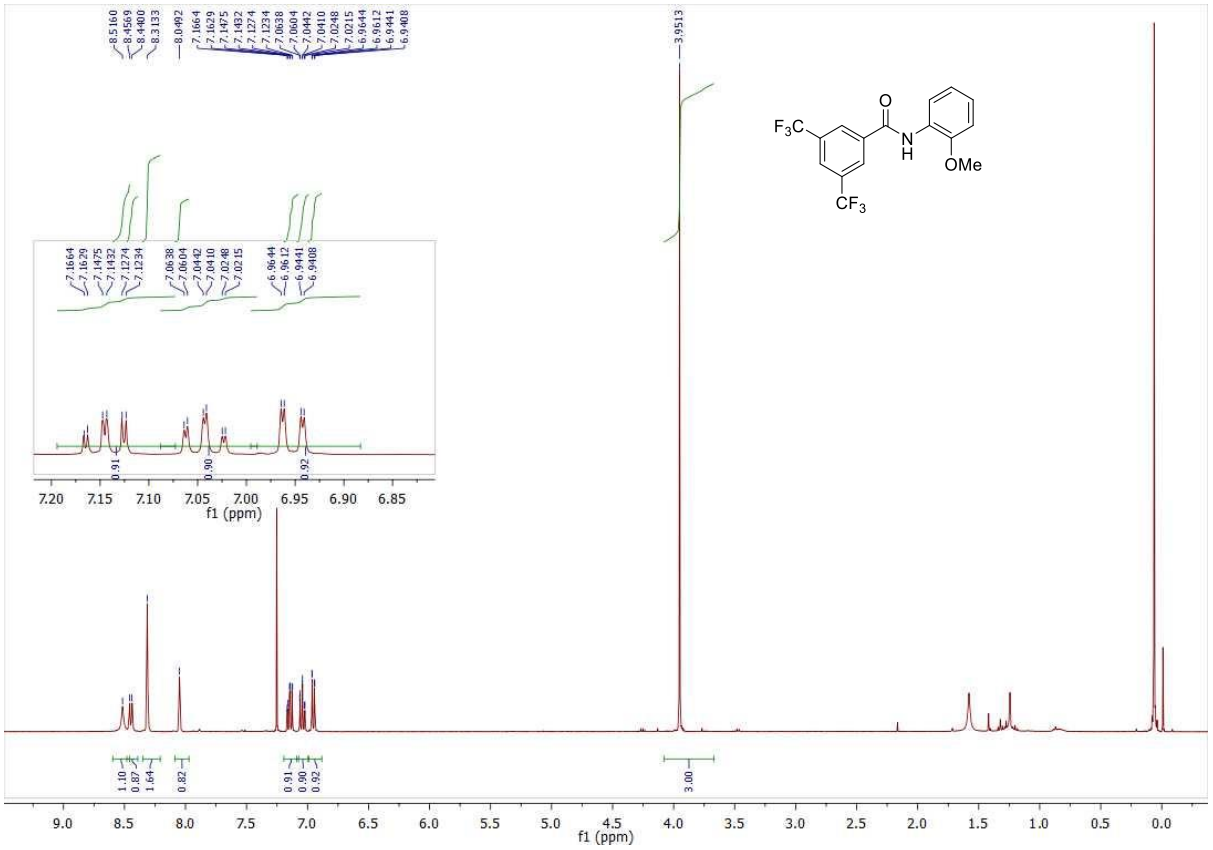


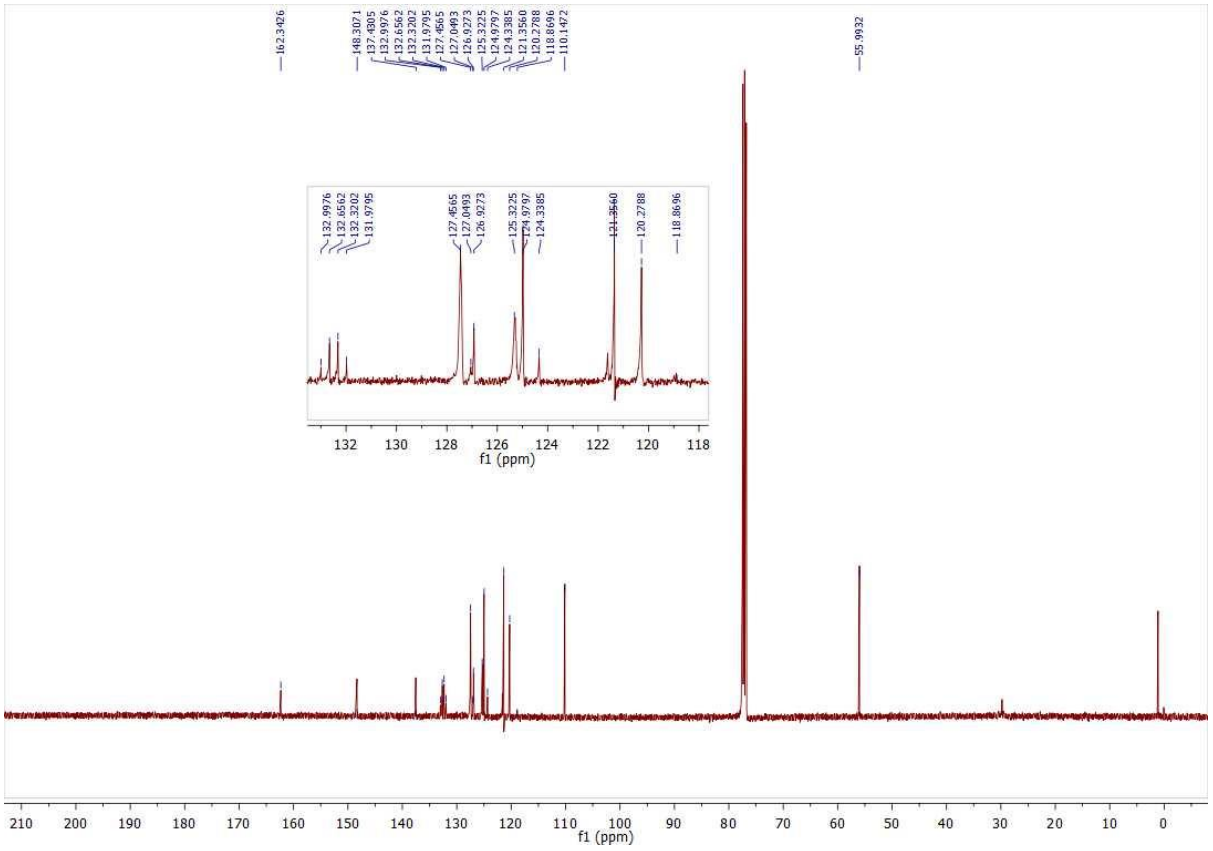
^{1}H and ^{13}C NMR compound for **42b**



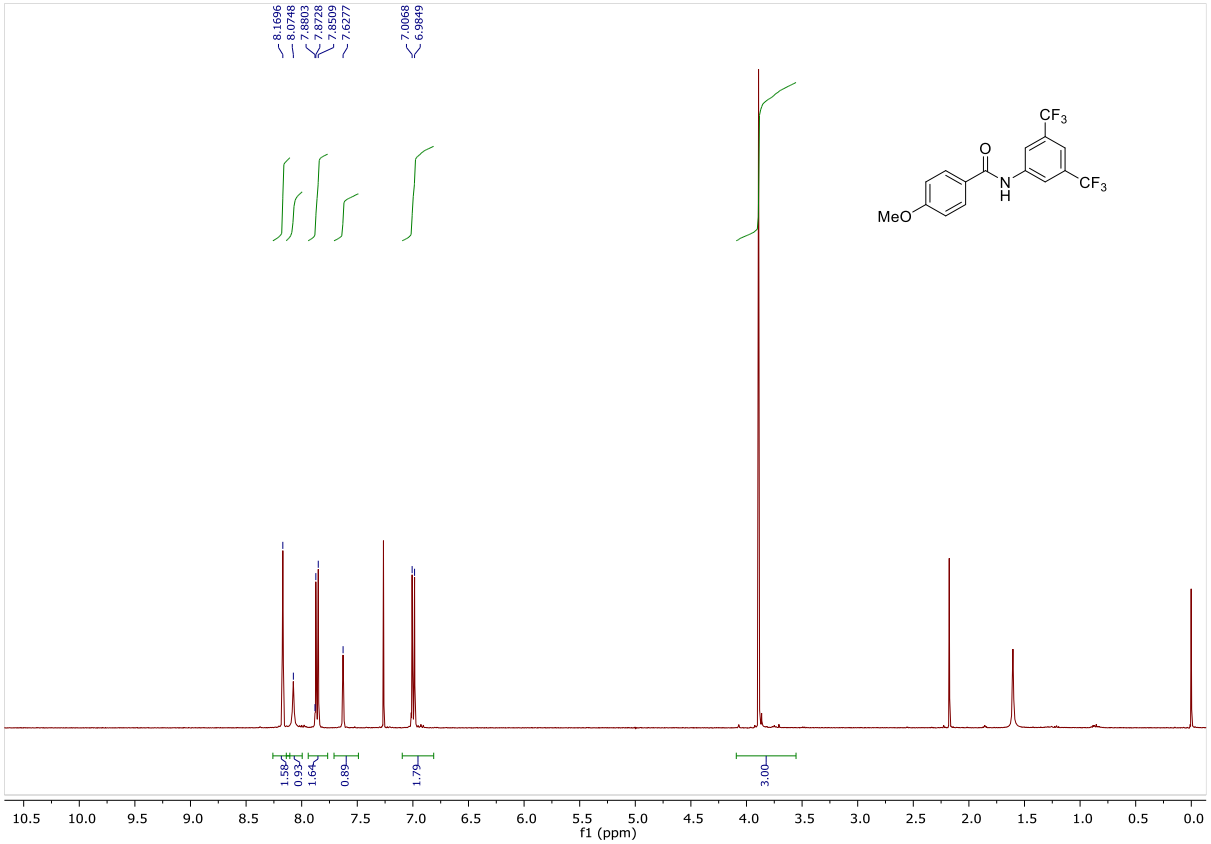


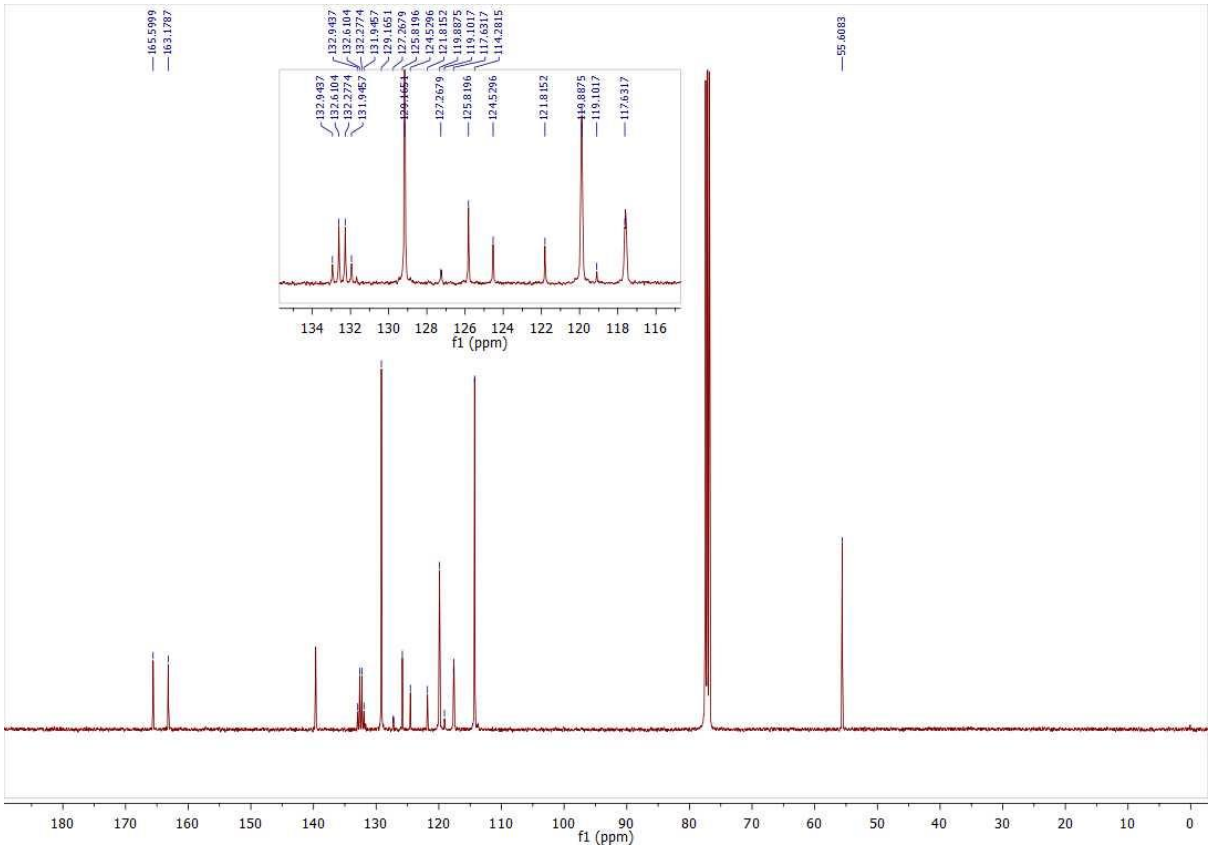
^{1}H and ^{13}C NMR compound for **42c**



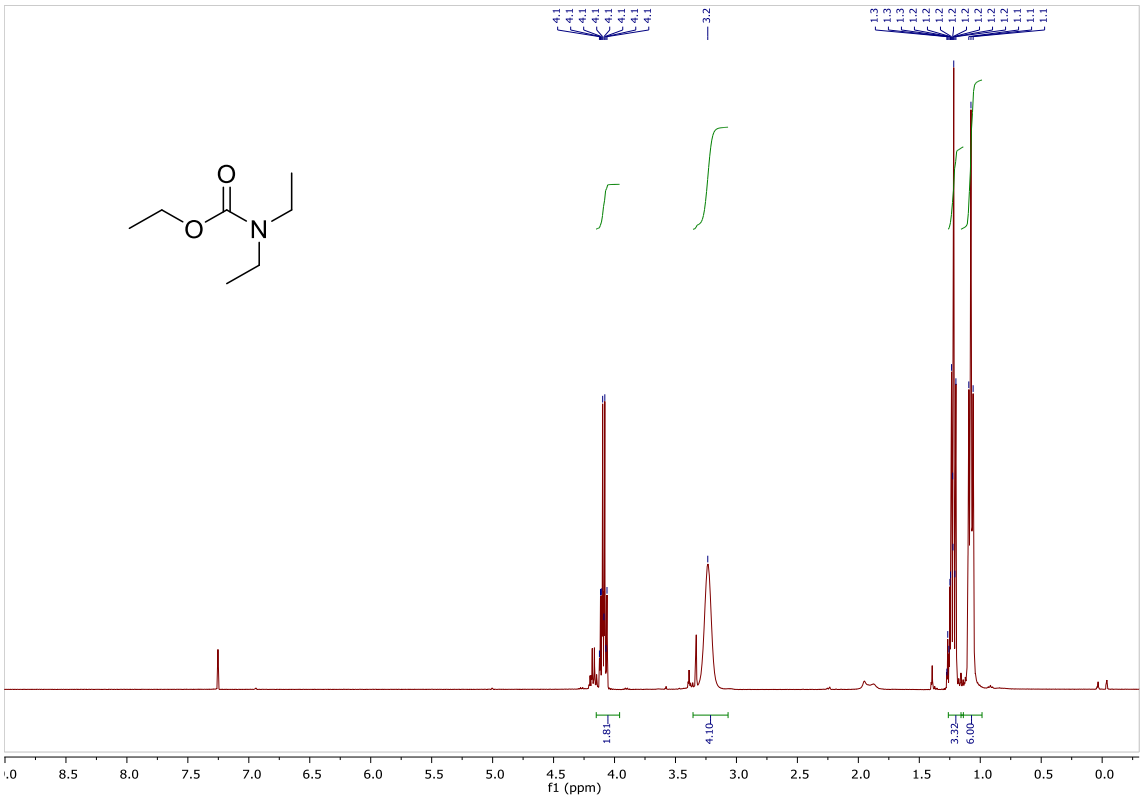


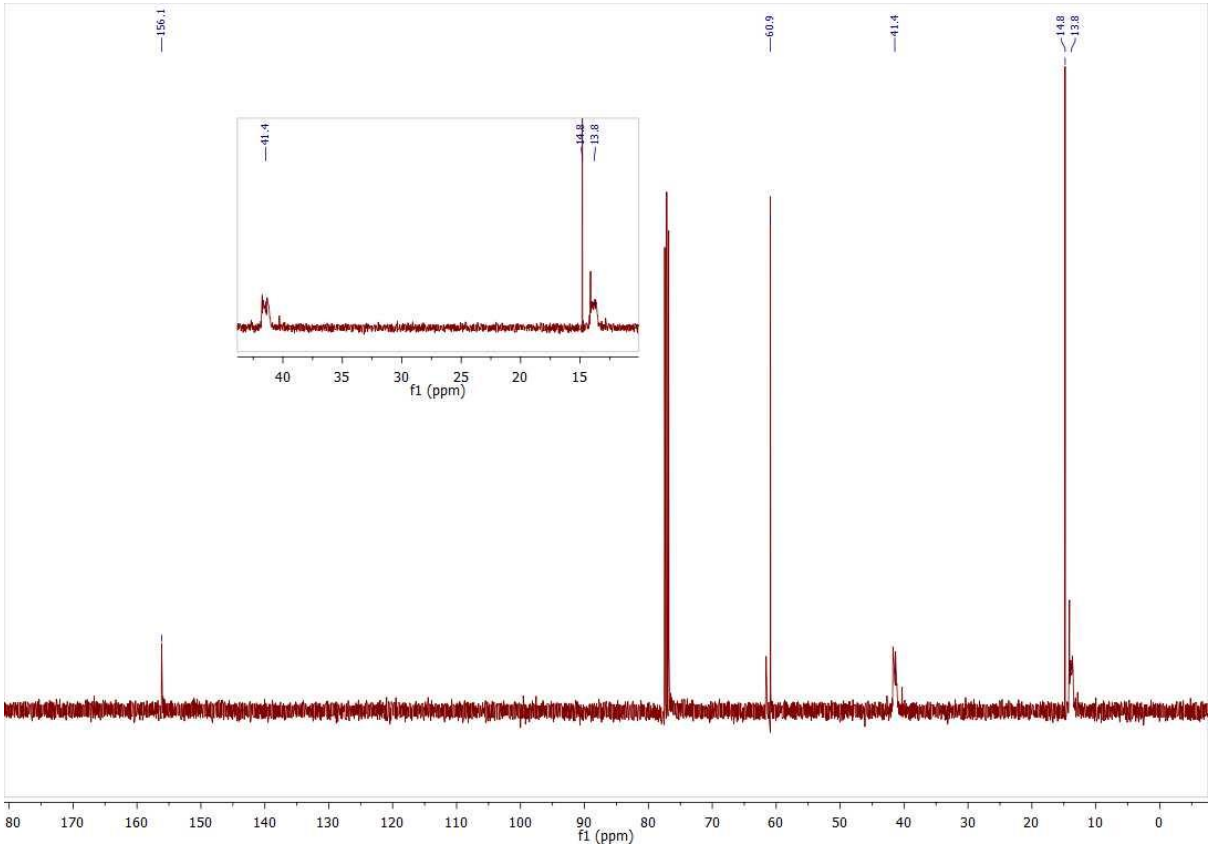
^{1}H and ^{13}C NMR compound for **42d**



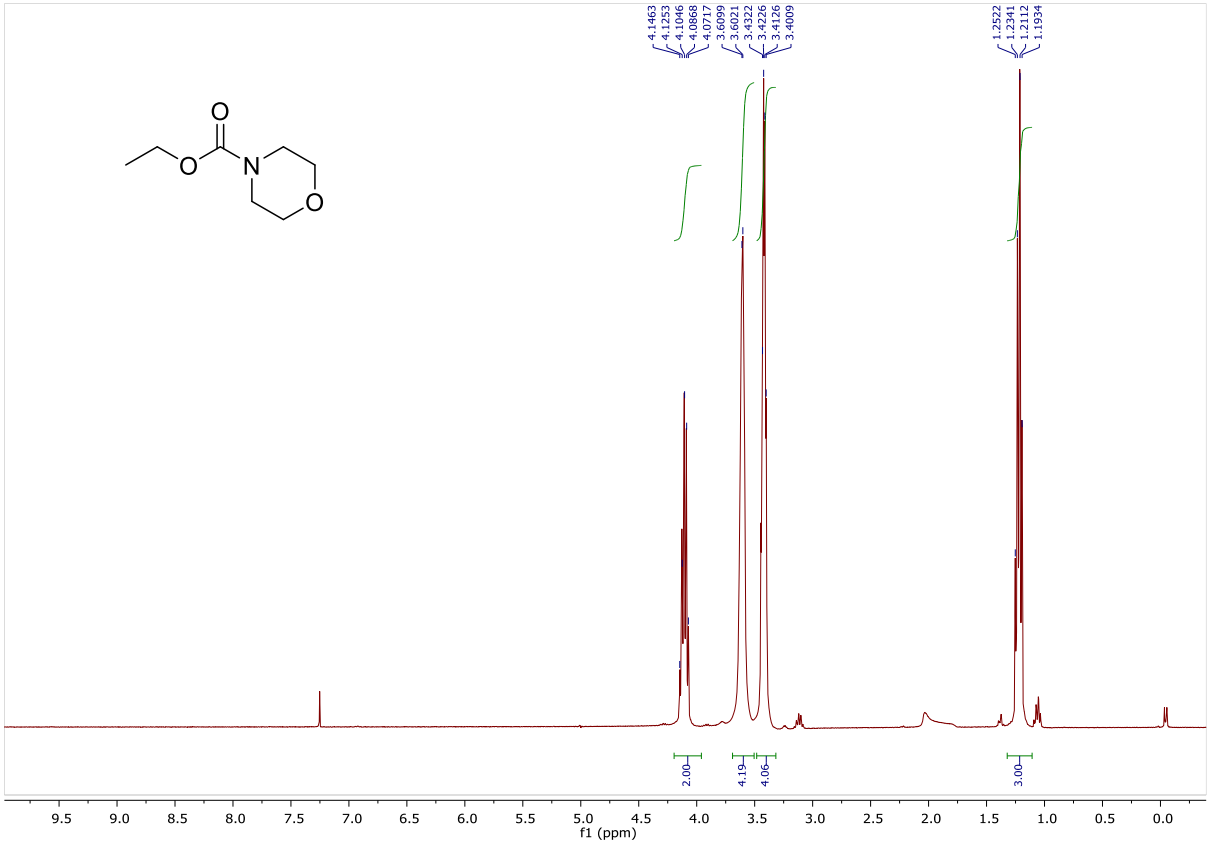


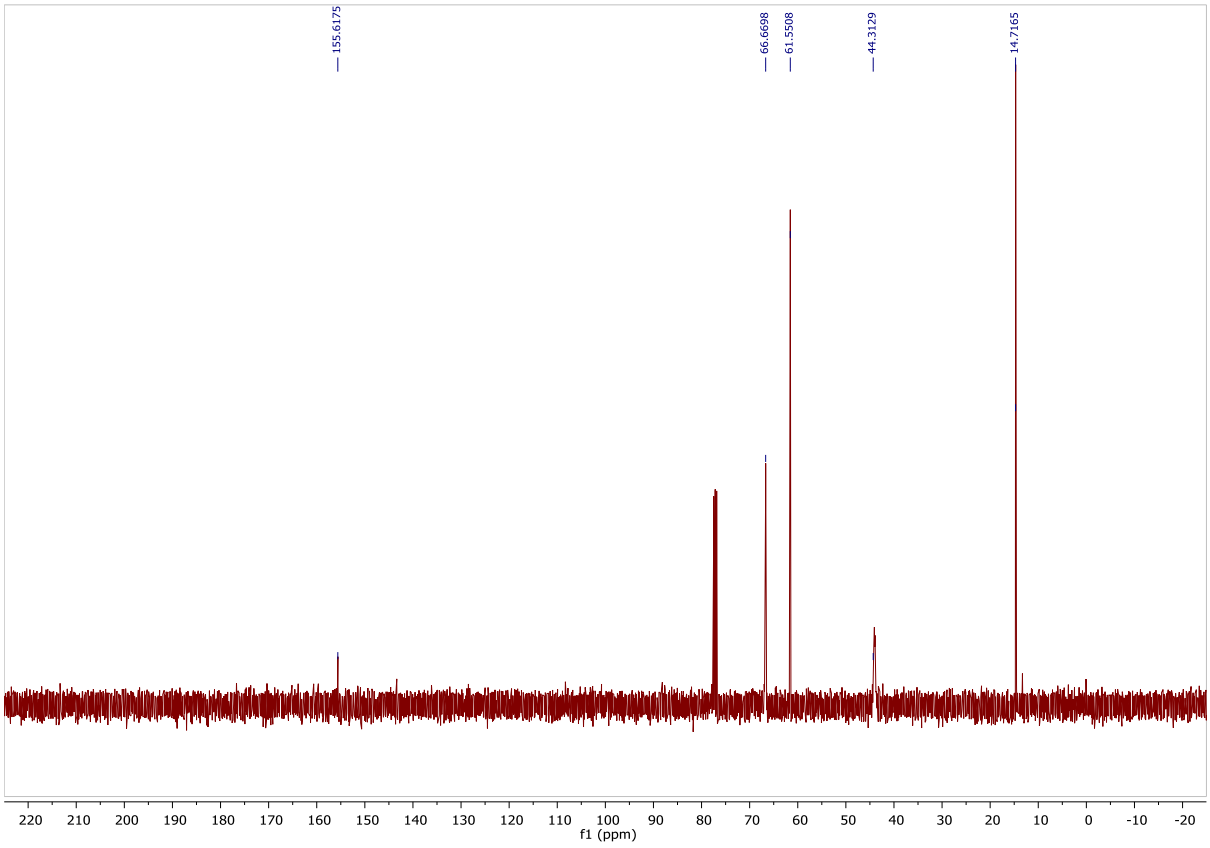
^{1}H and ^{13}C NMR compound for **45a**



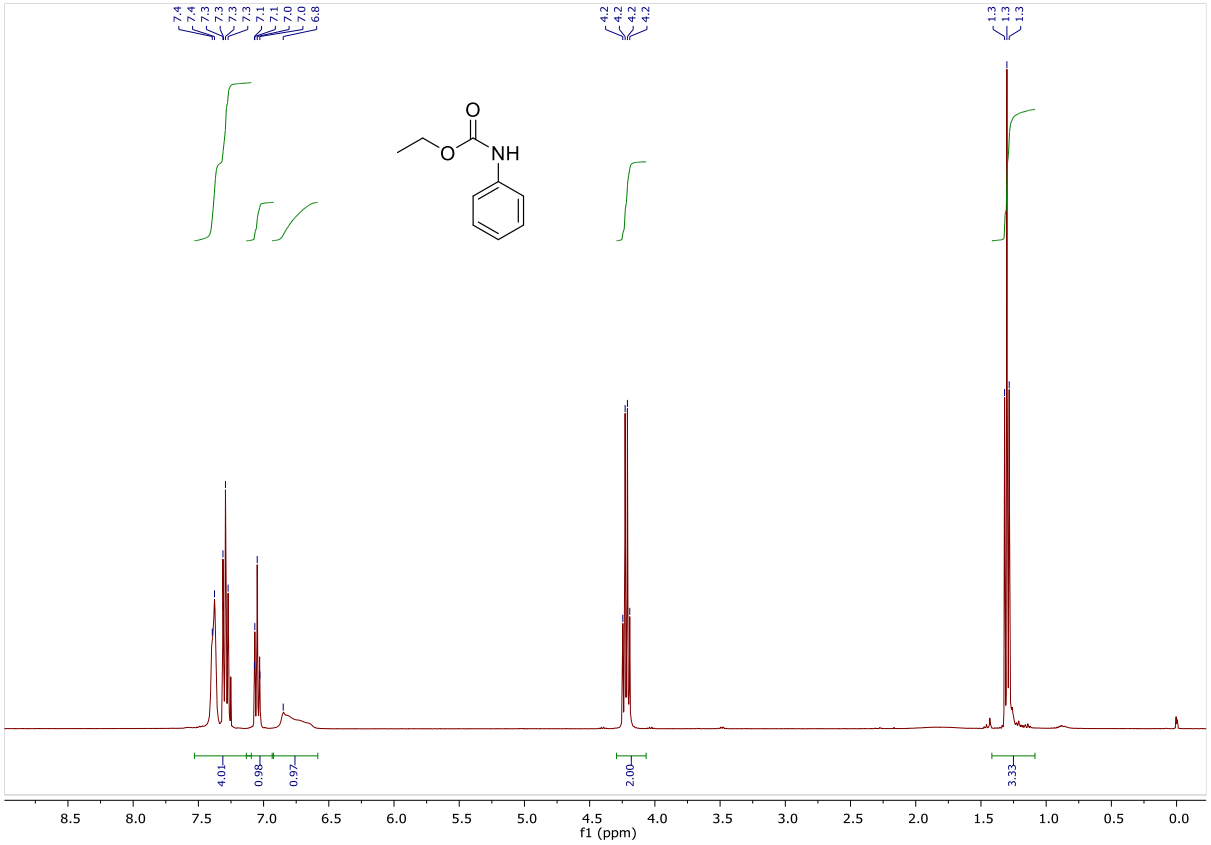


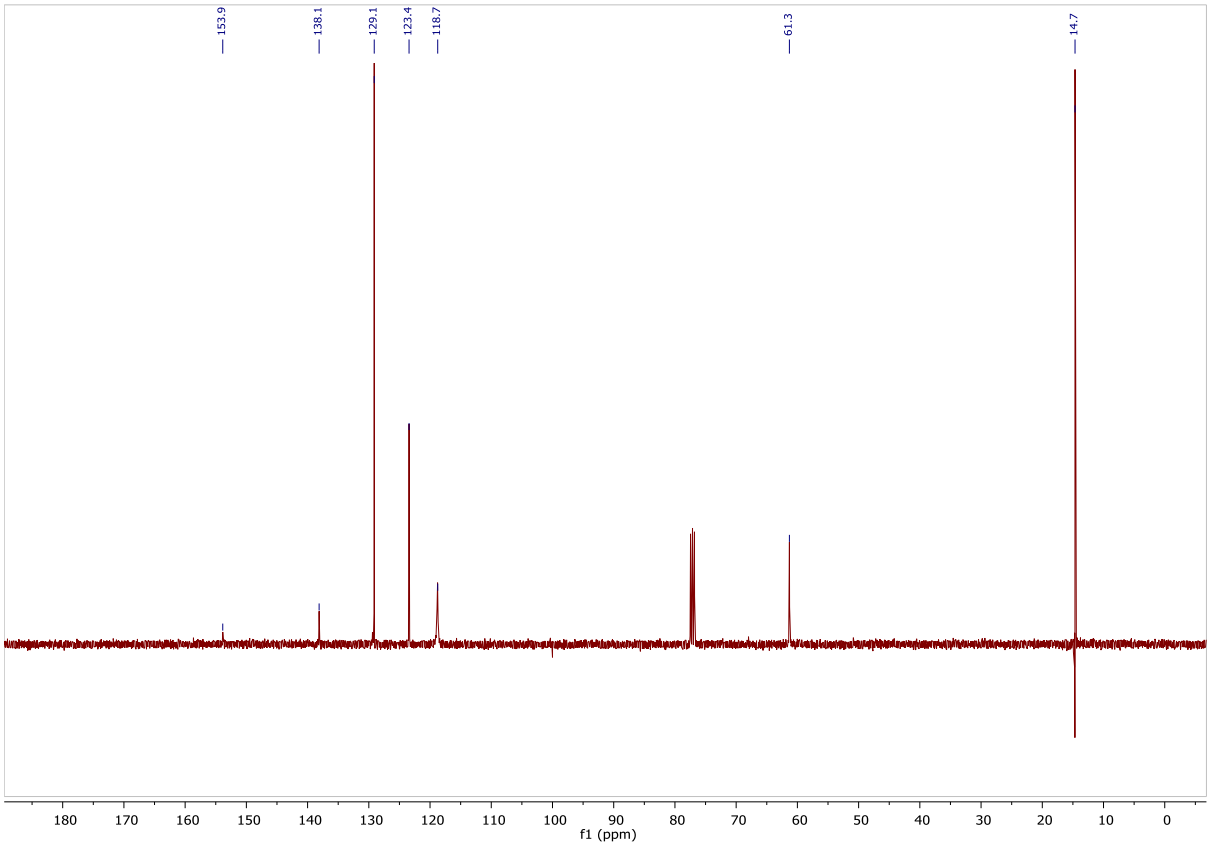
^{1}H and ^{13}C NMR compound for **45b**



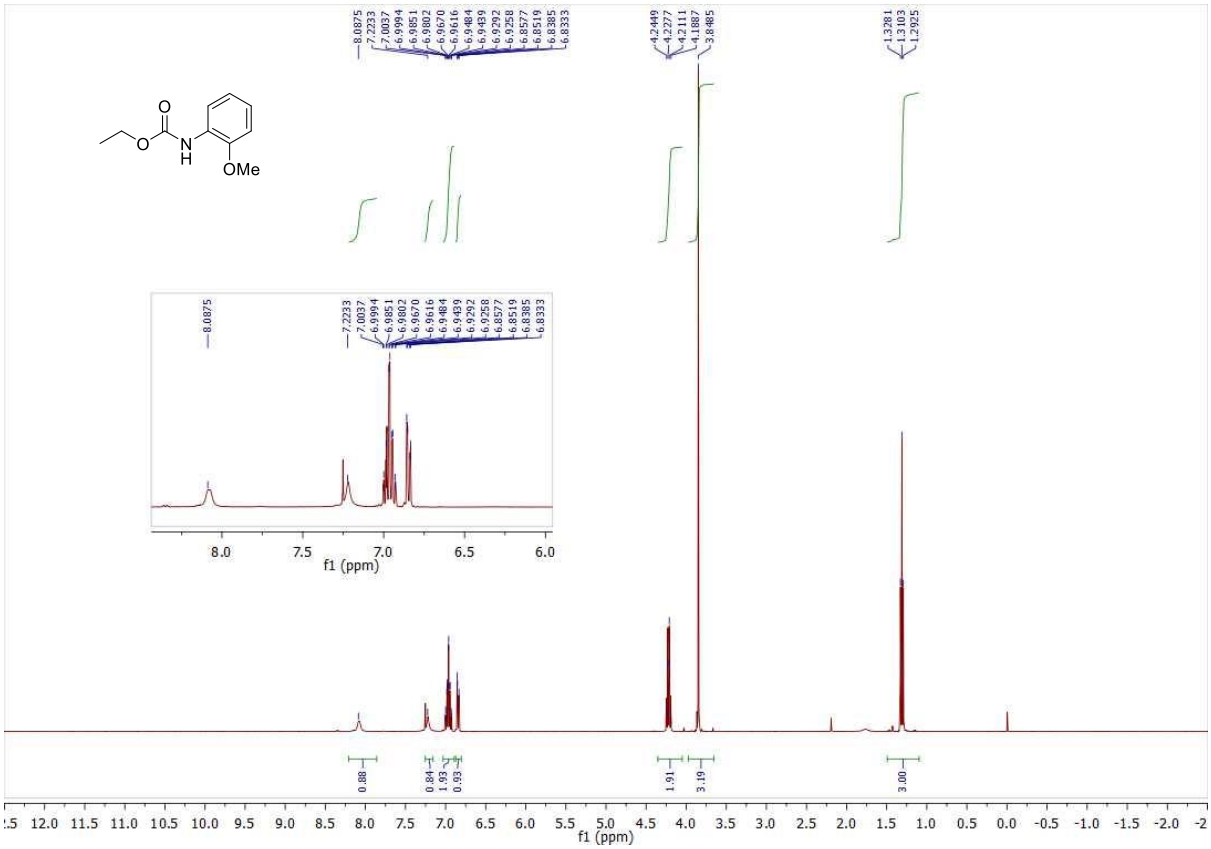


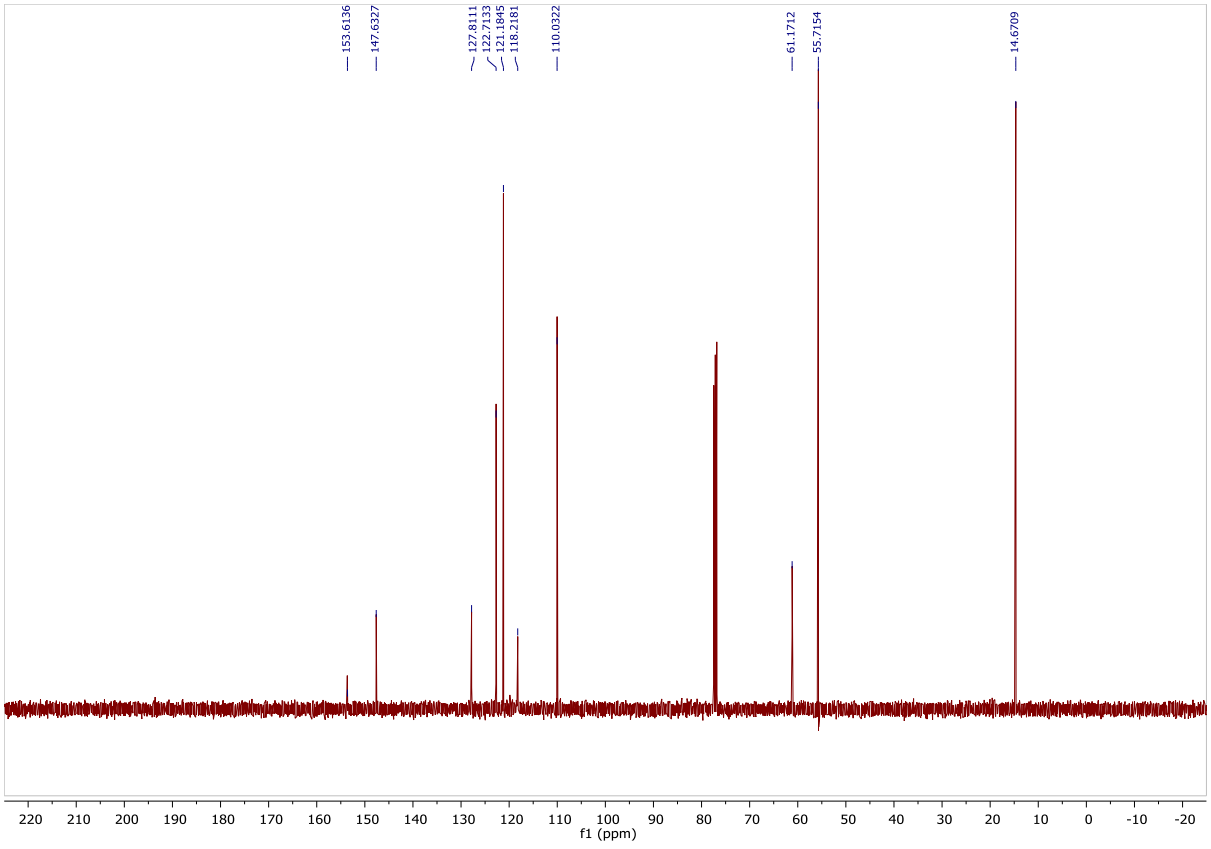
^{1}H and ^{13}C NMR compound for **45c**



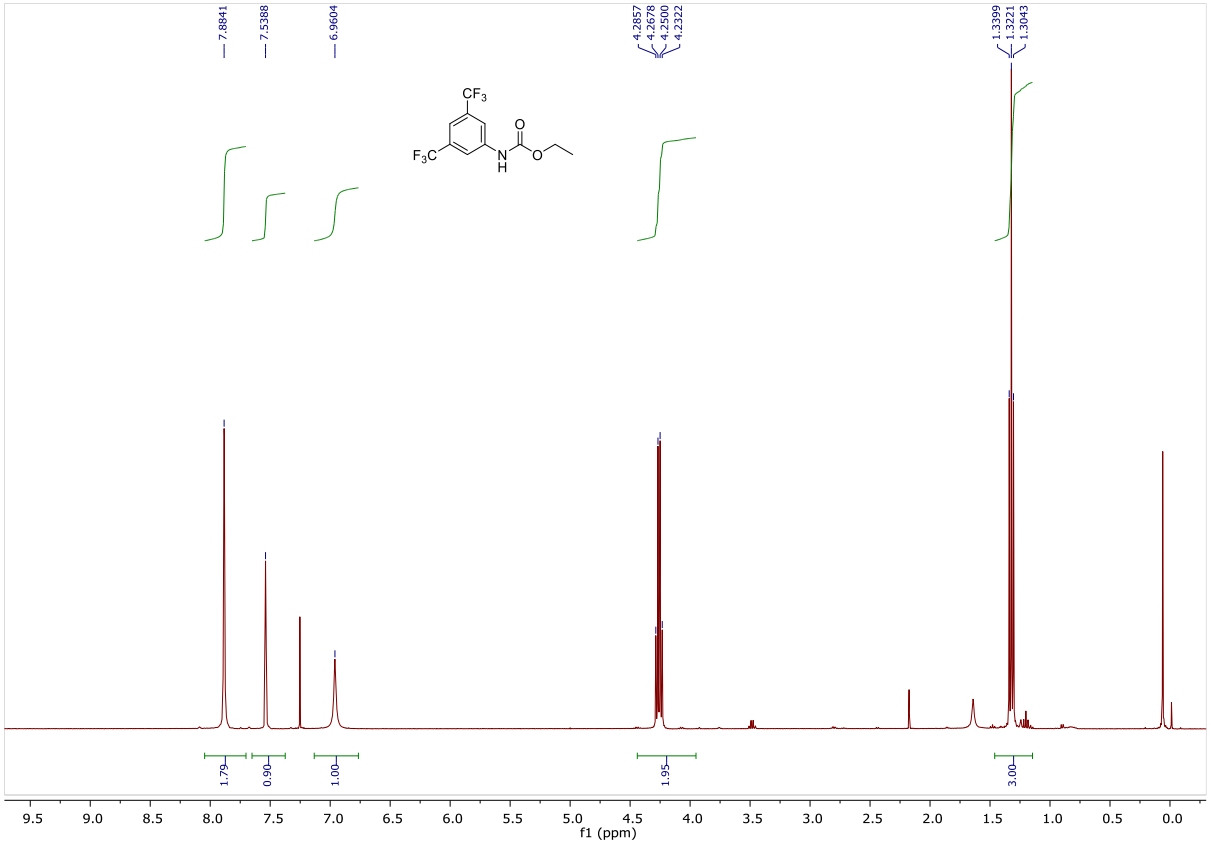


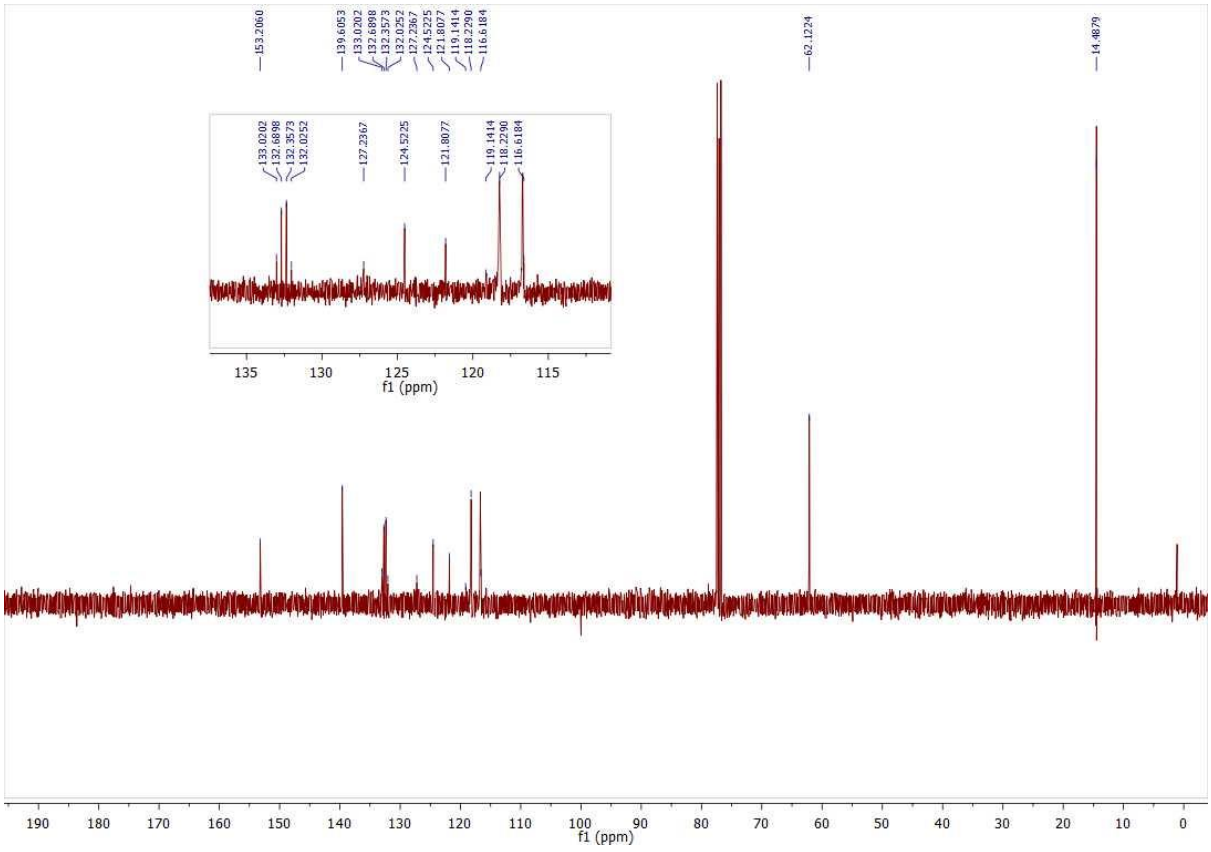
^{1}H and ^{13}C NMR compound for **45d**



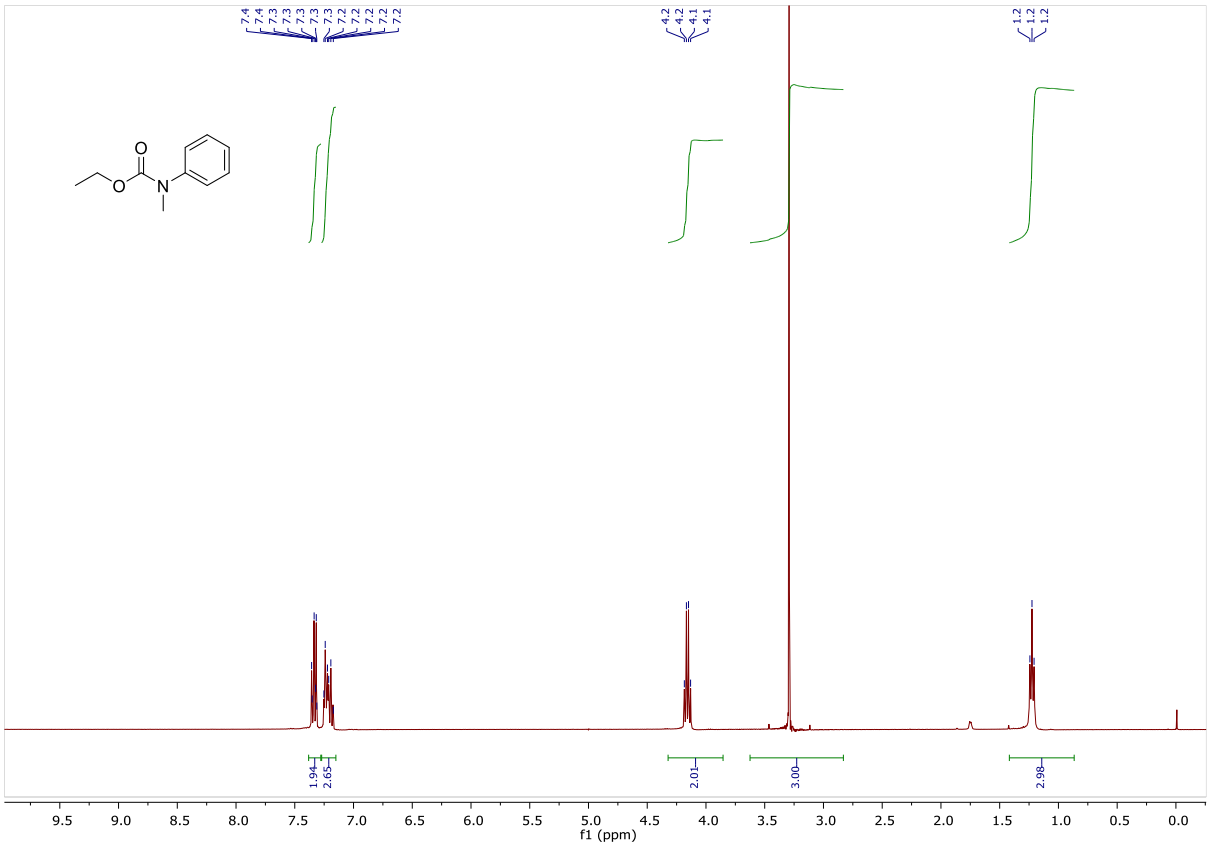


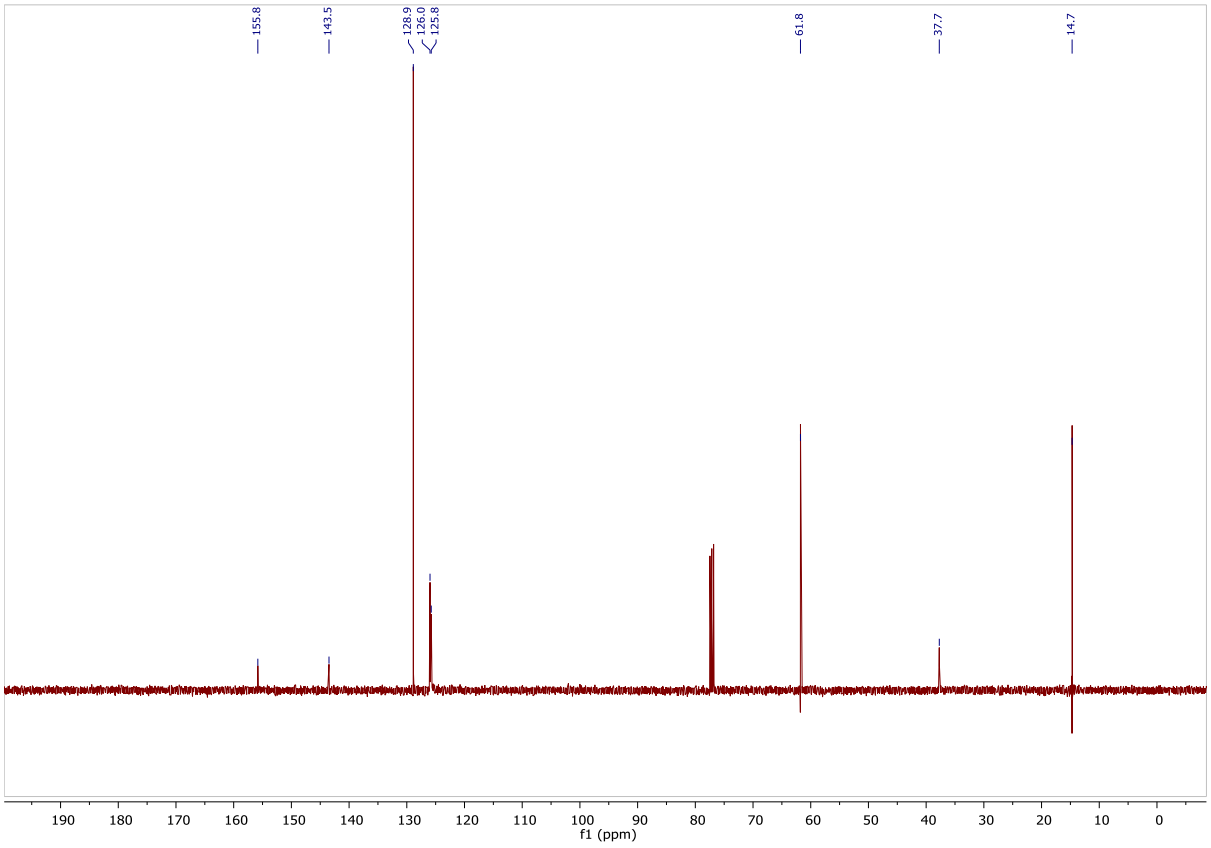
^{1}H and ^{13}C NMR compound for **45e**



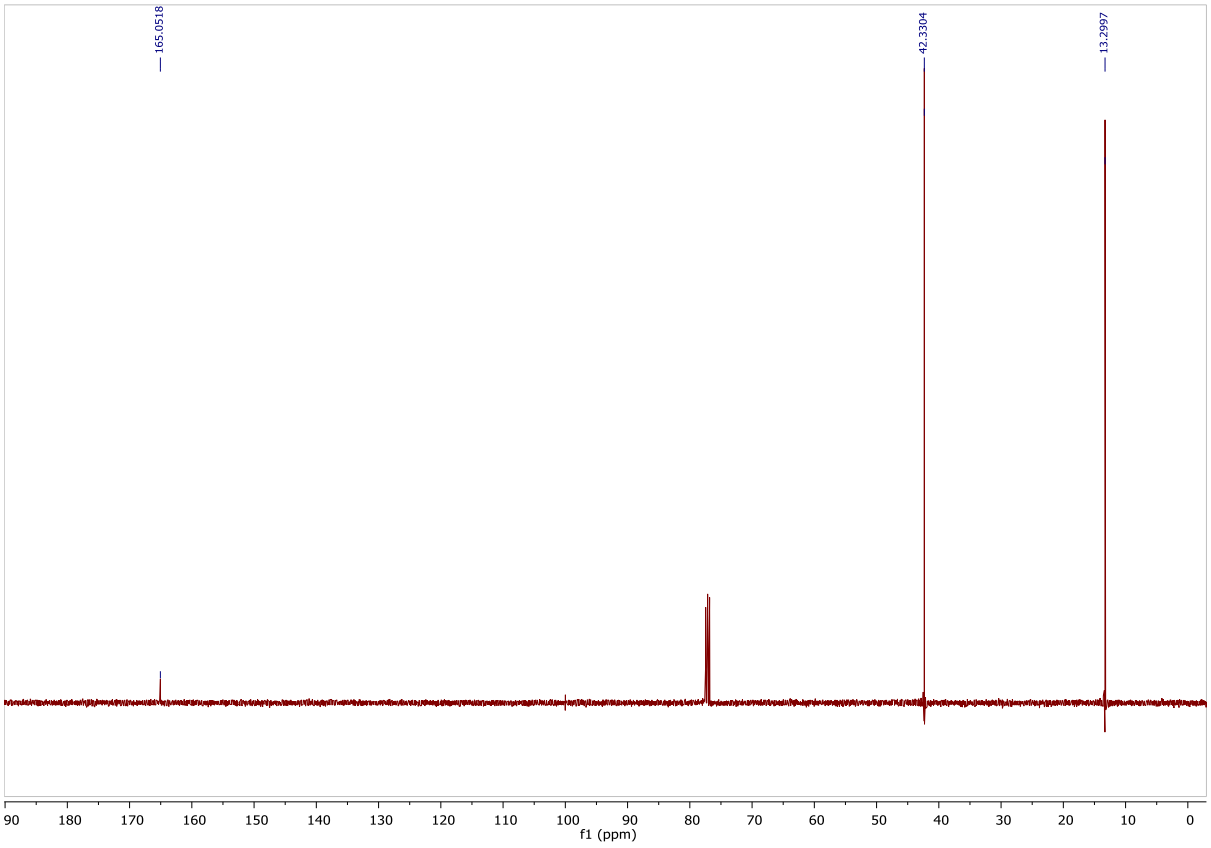


^{1}H and ^{13}C NMR compound for **45f**

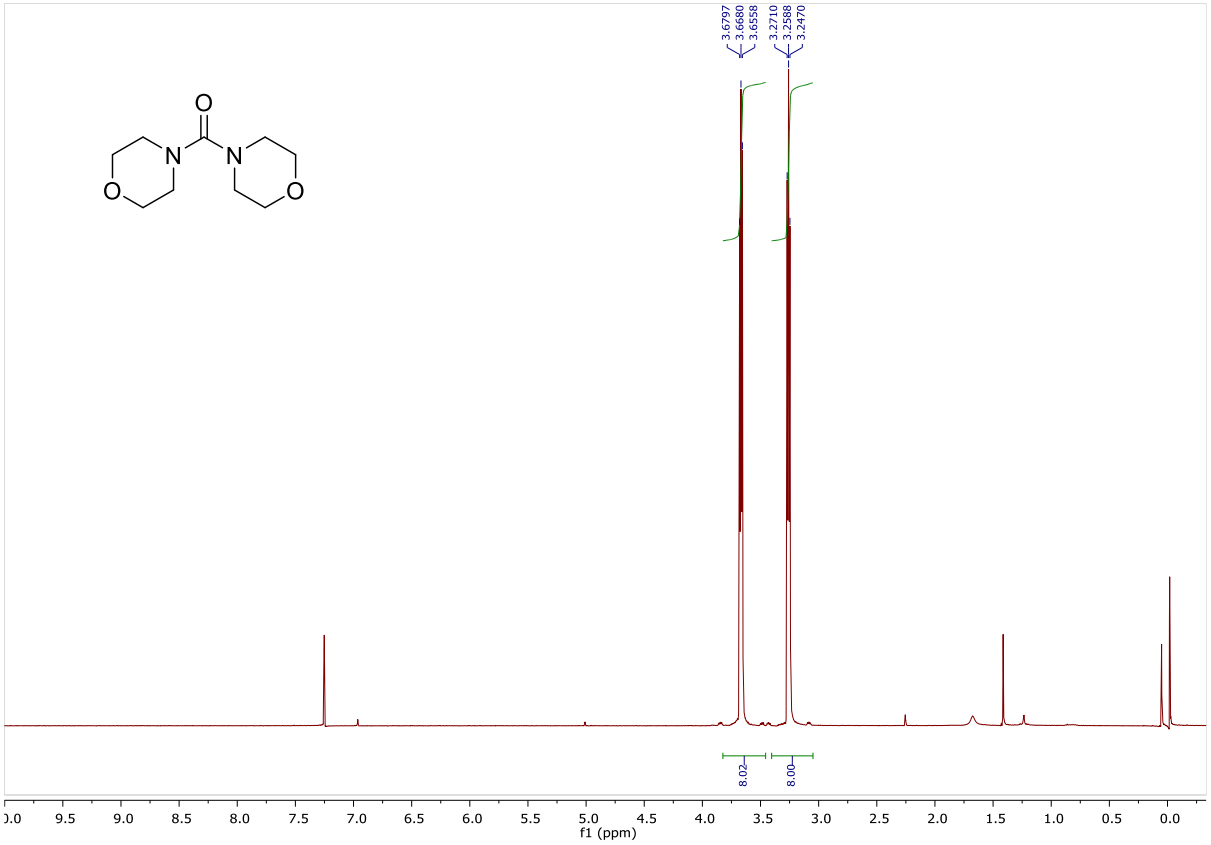


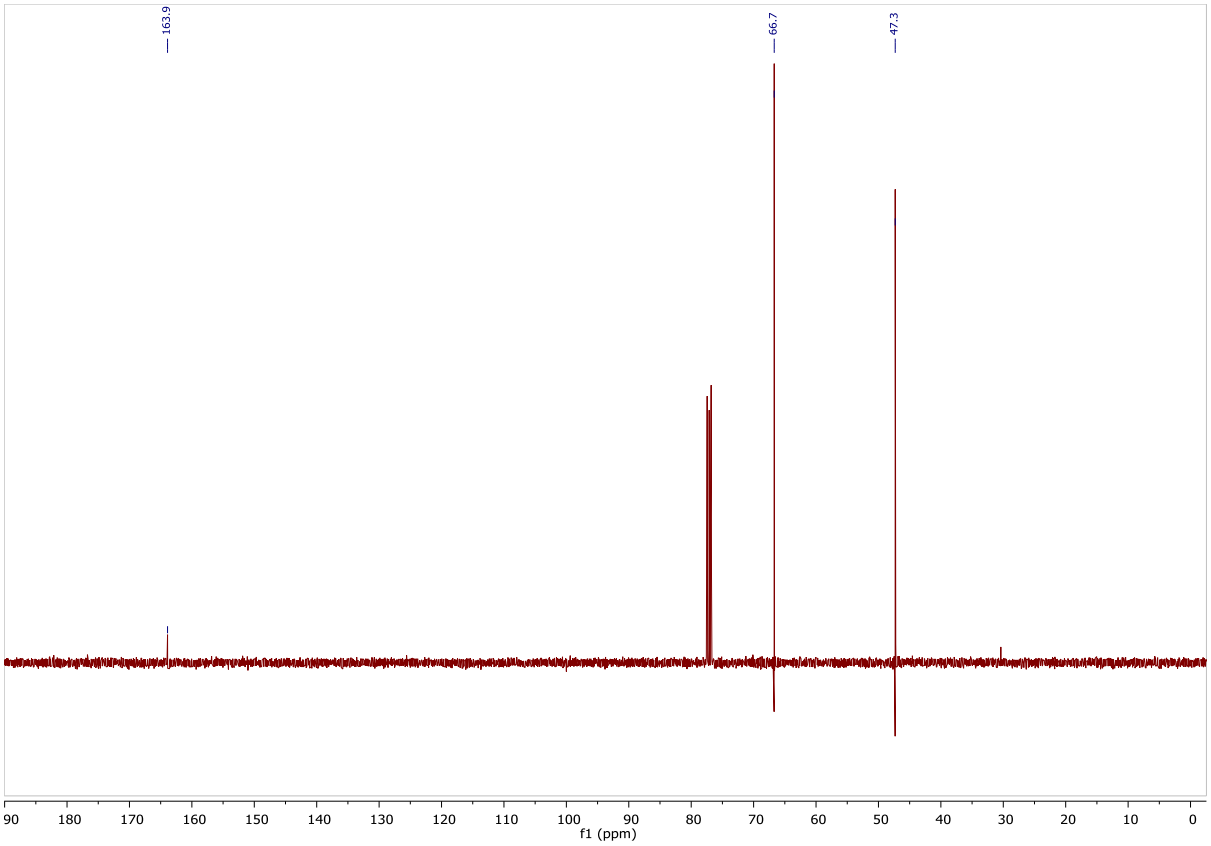


^{1}H and ^{13}C NMR compound for **47a**

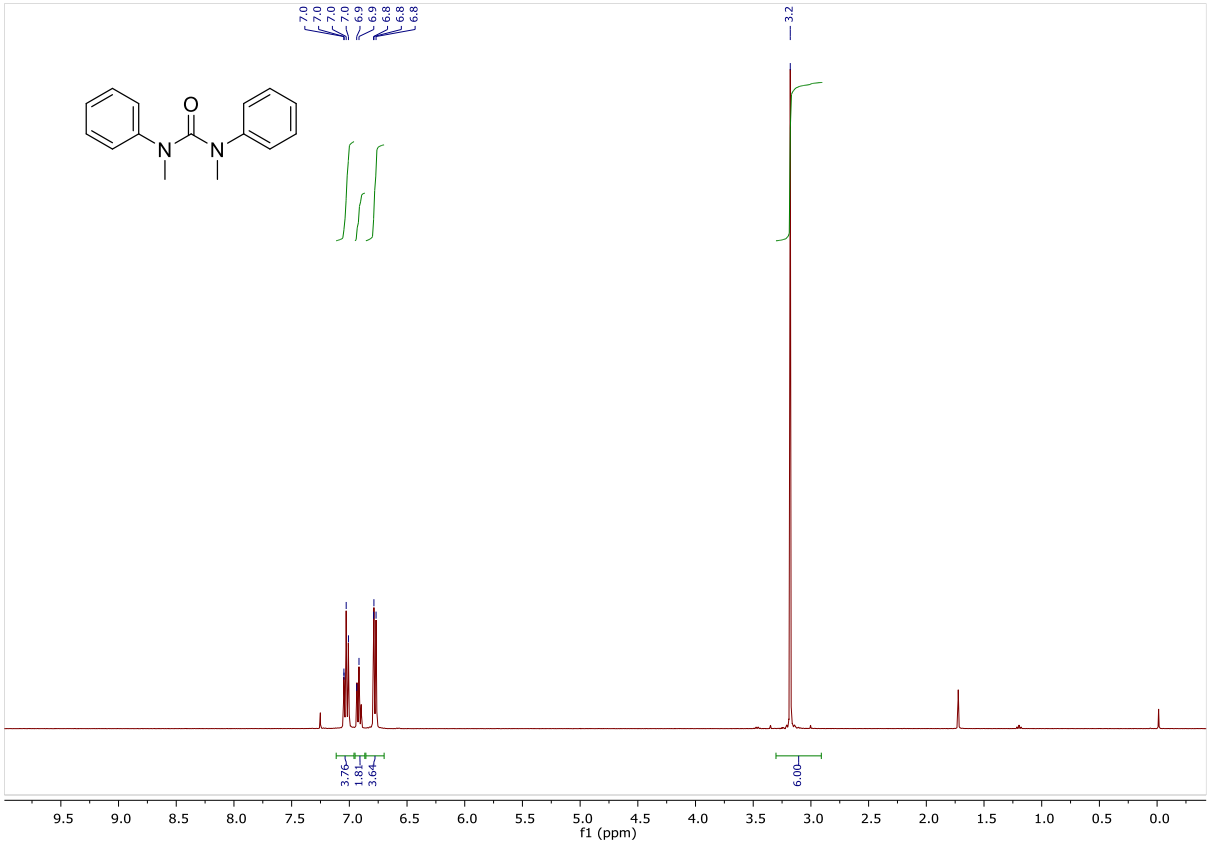


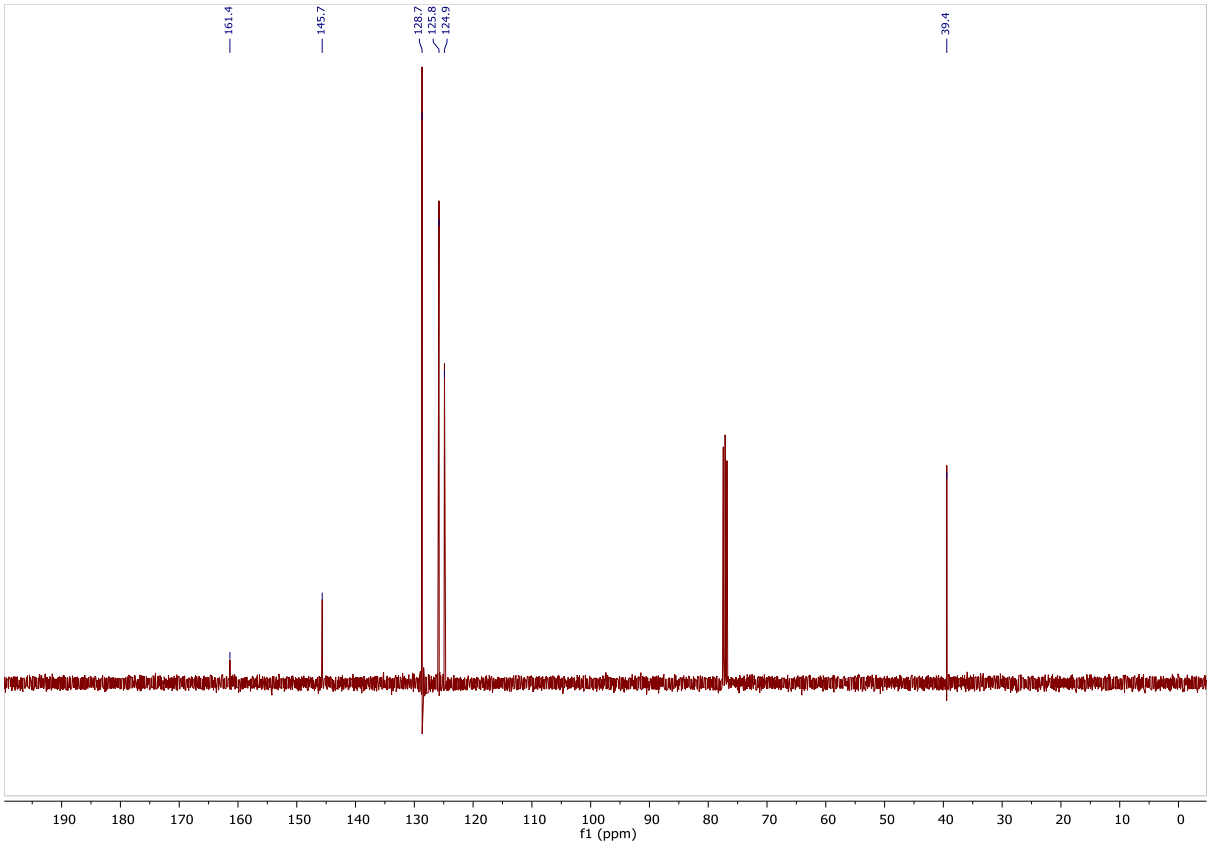
^{1}H and ^{13}C NMR compound for **47b**



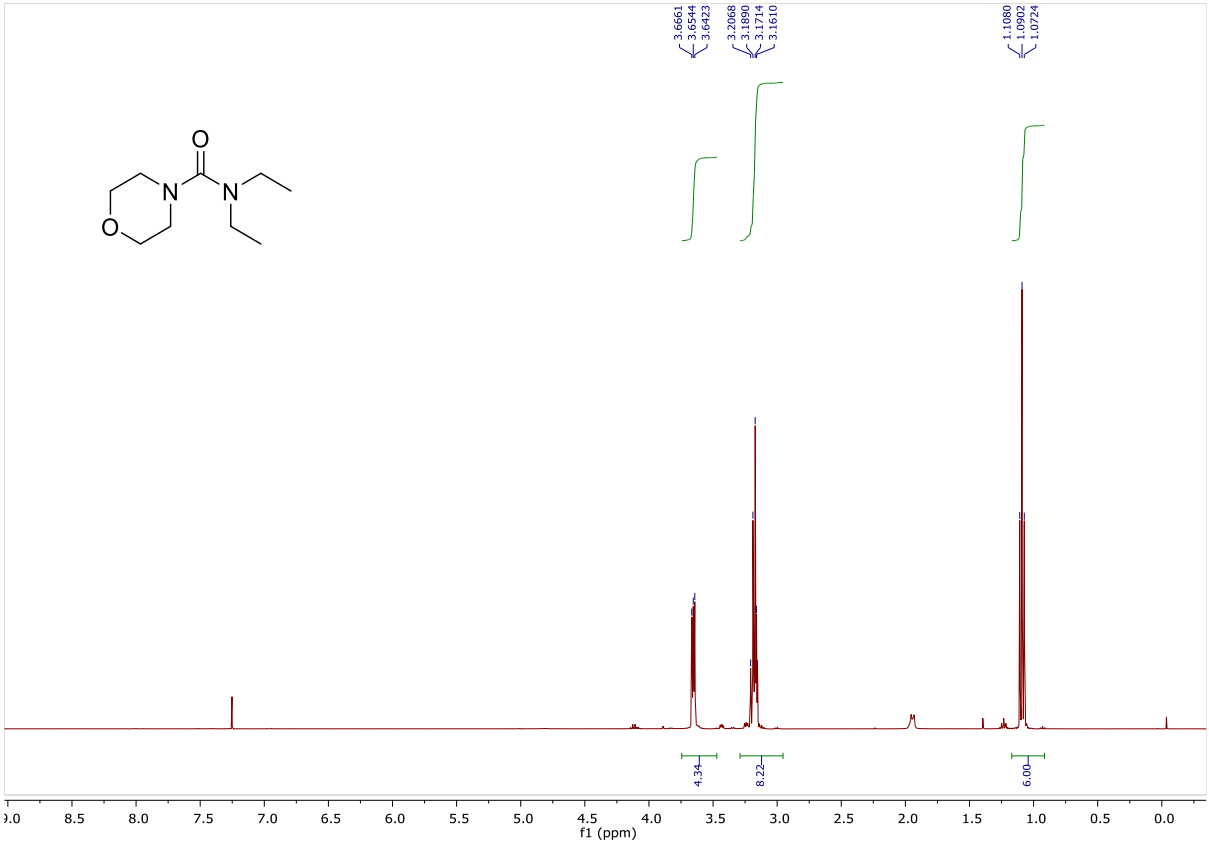


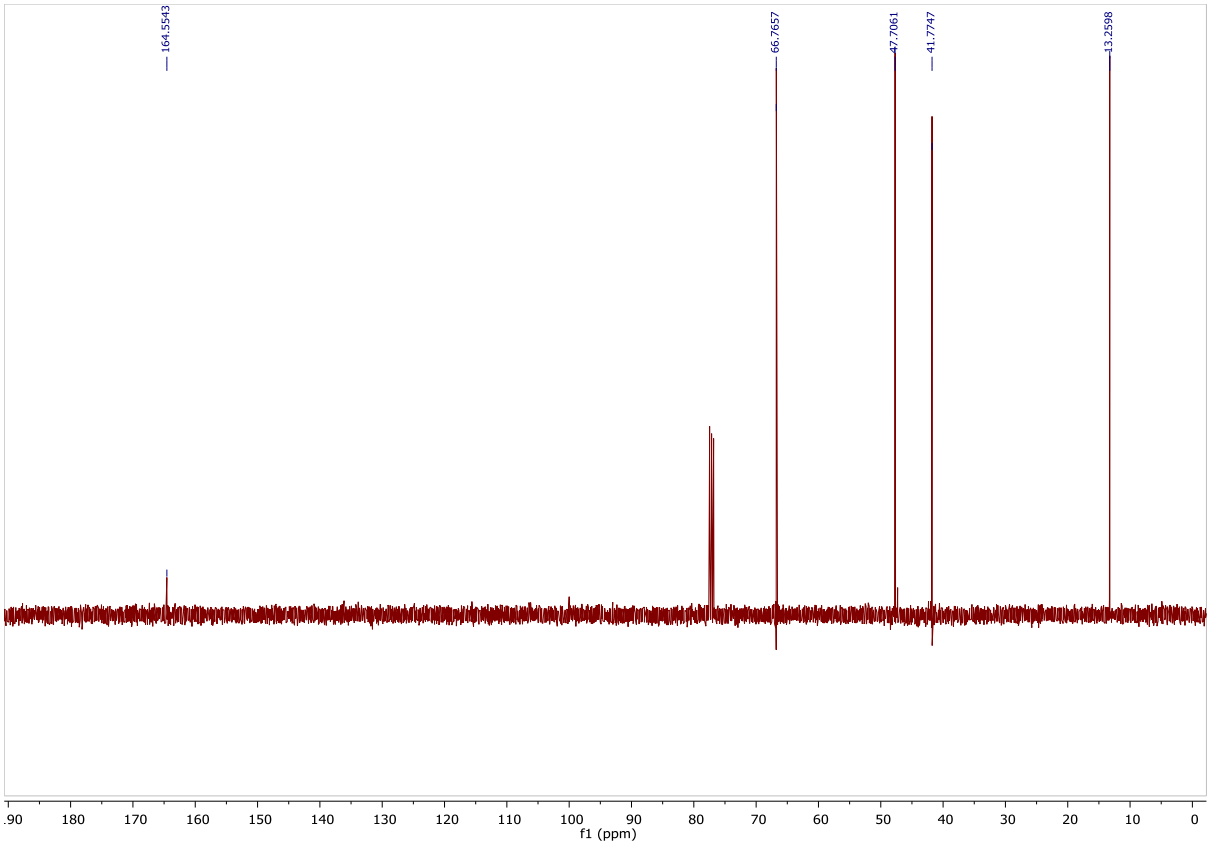
^{1}H and ^{13}C NMR compound for **47c**



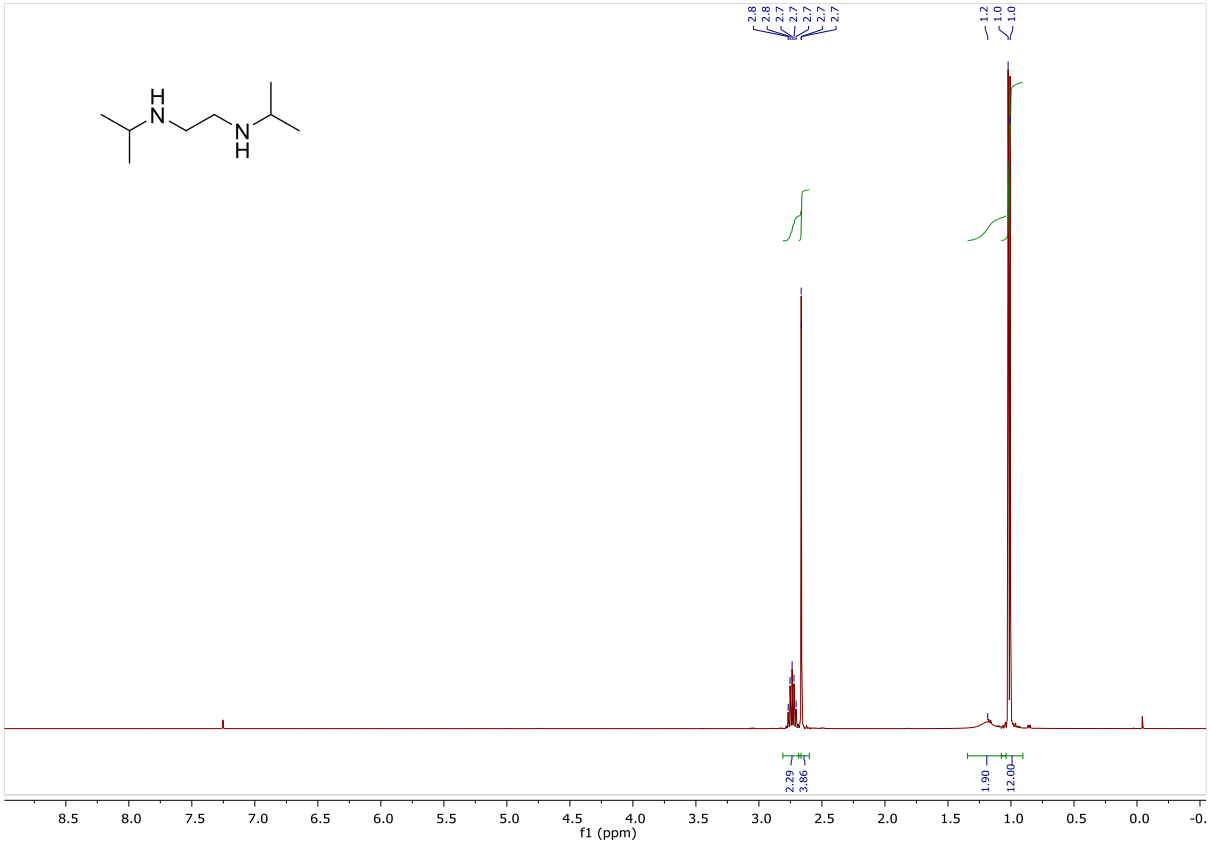


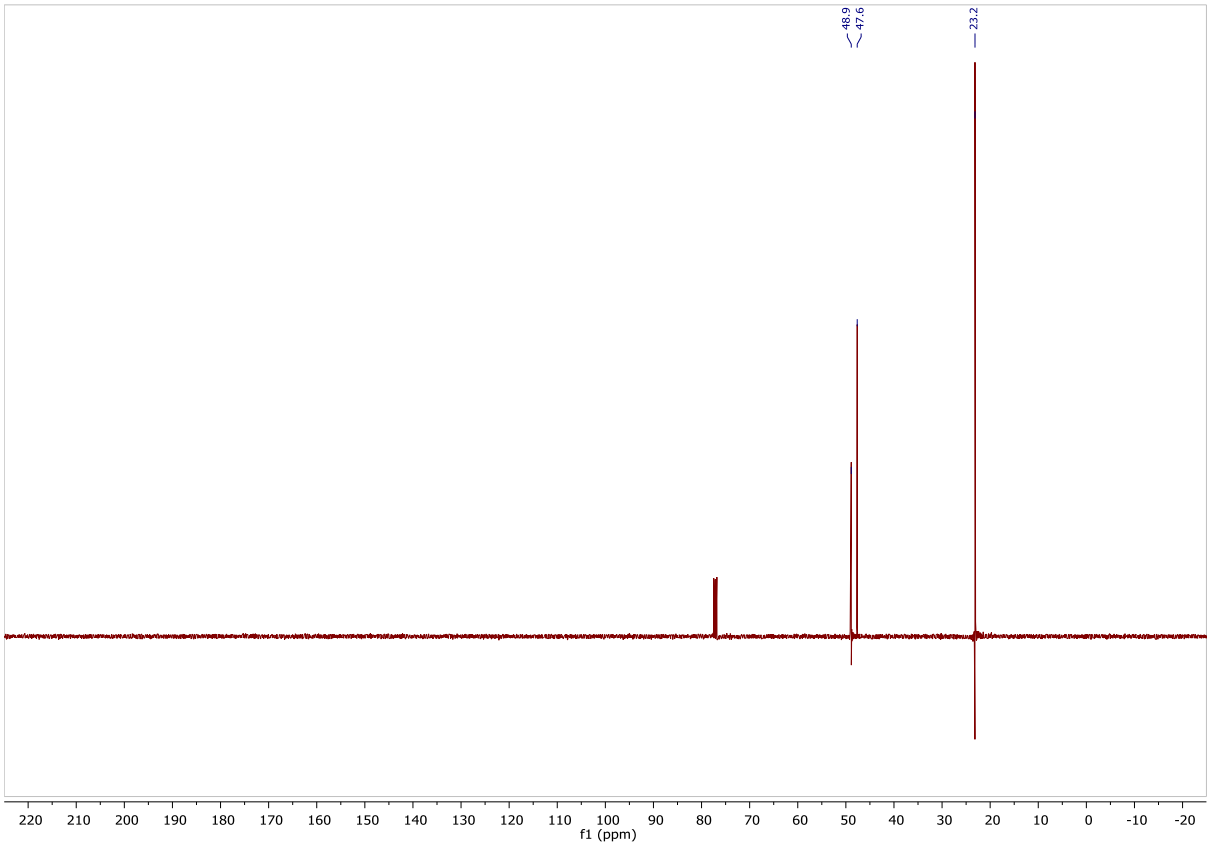
^{1}H and ^{13}C NMR compound for **47d**



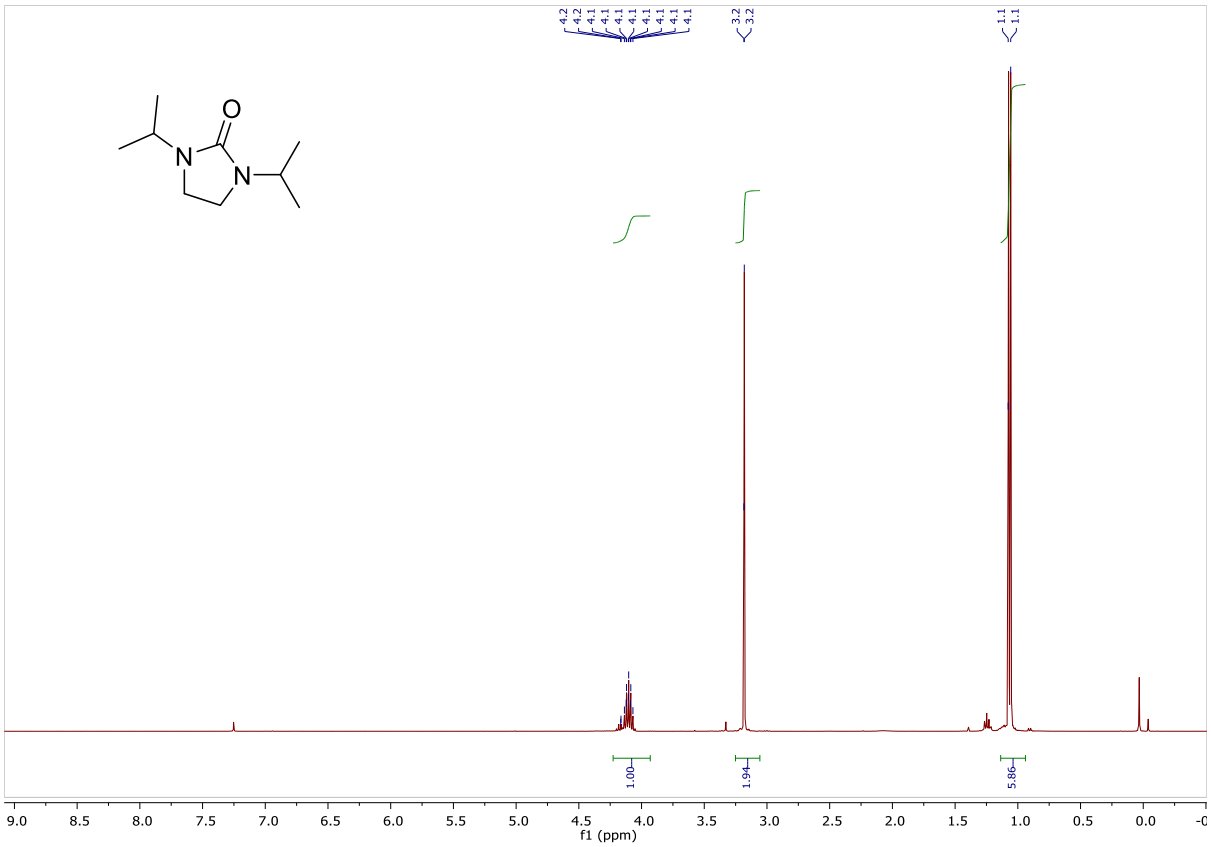


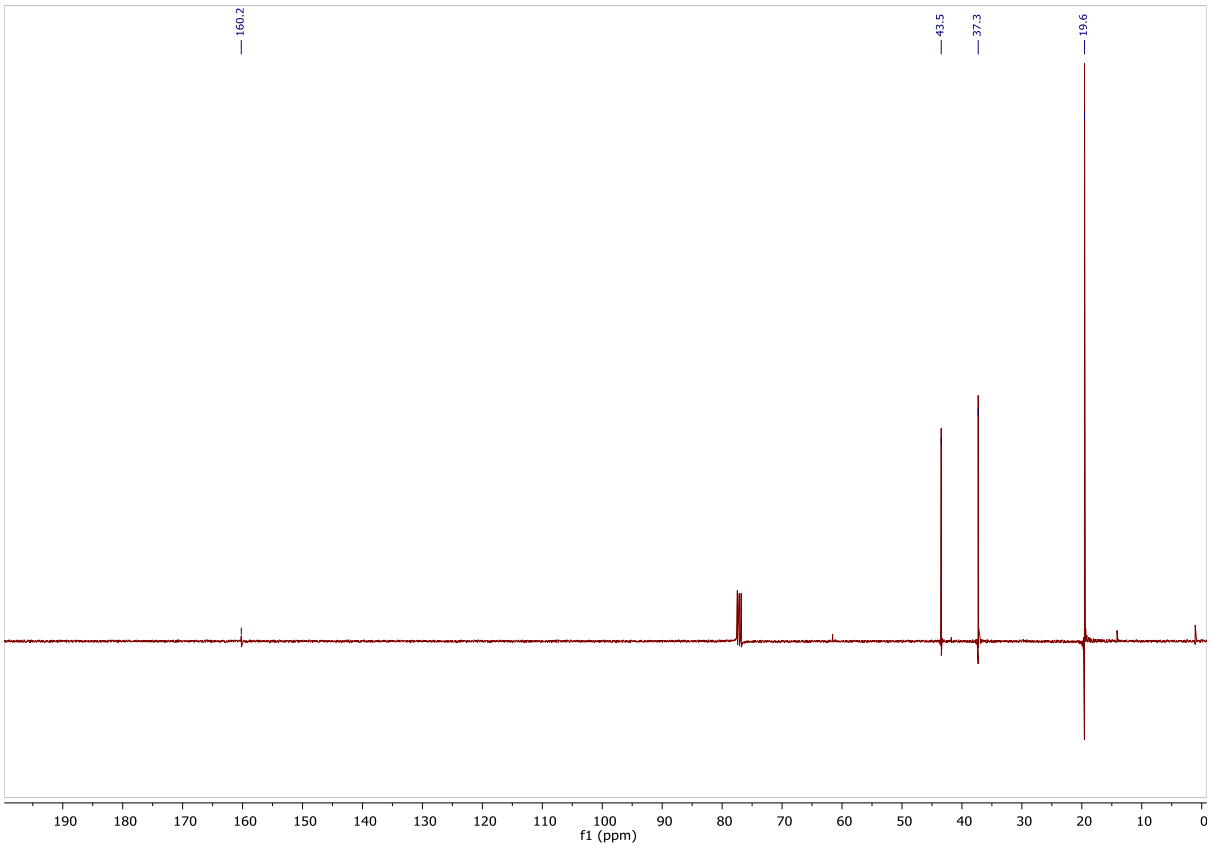
^{1}H and ^{13}C NMR compound for **50**



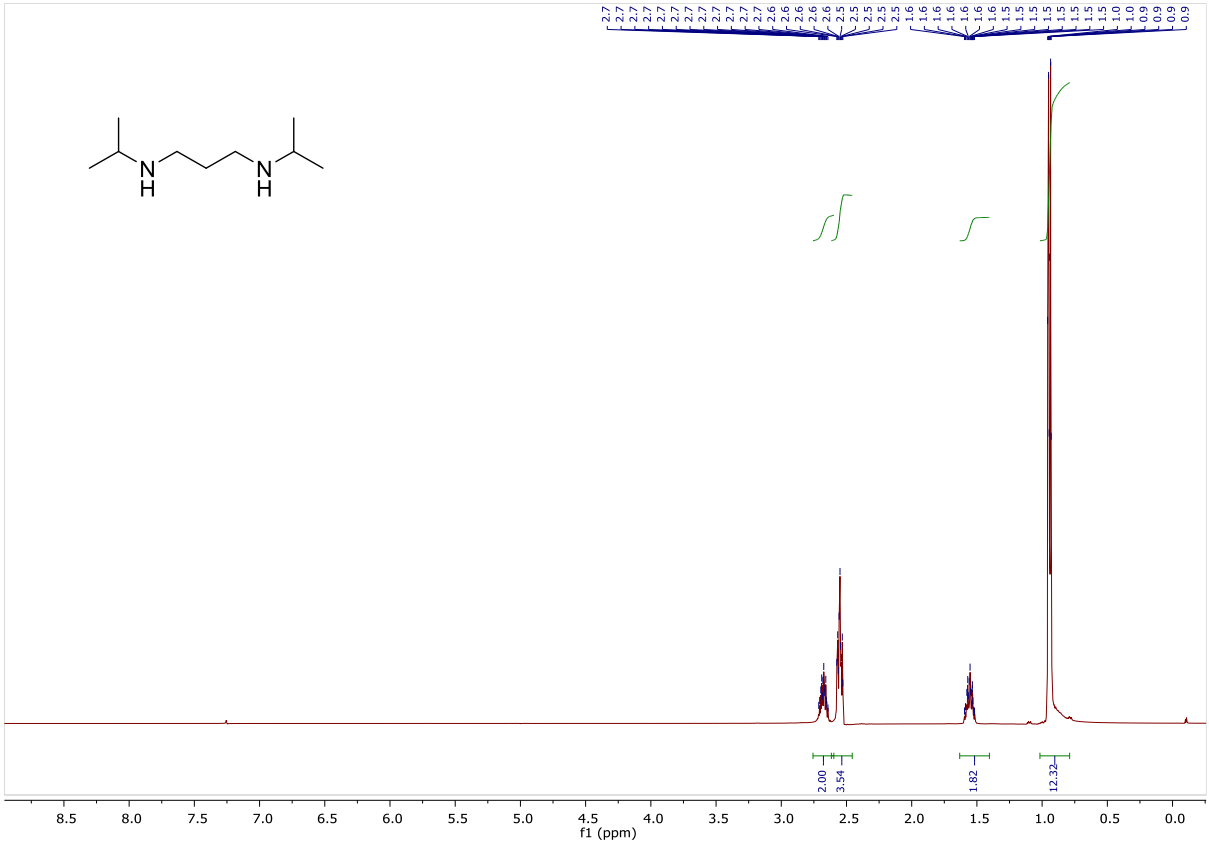


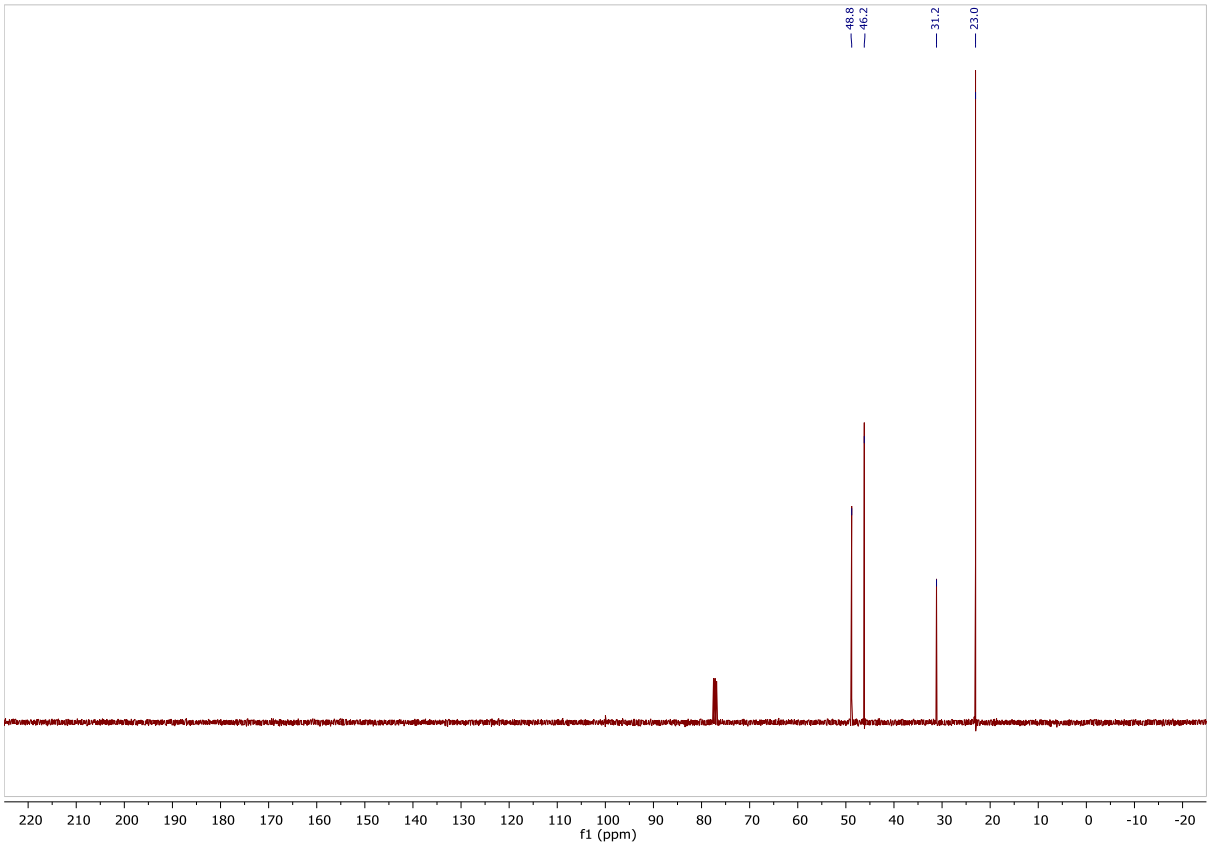
^{1}H and ^{13}C NMR compound for **51**



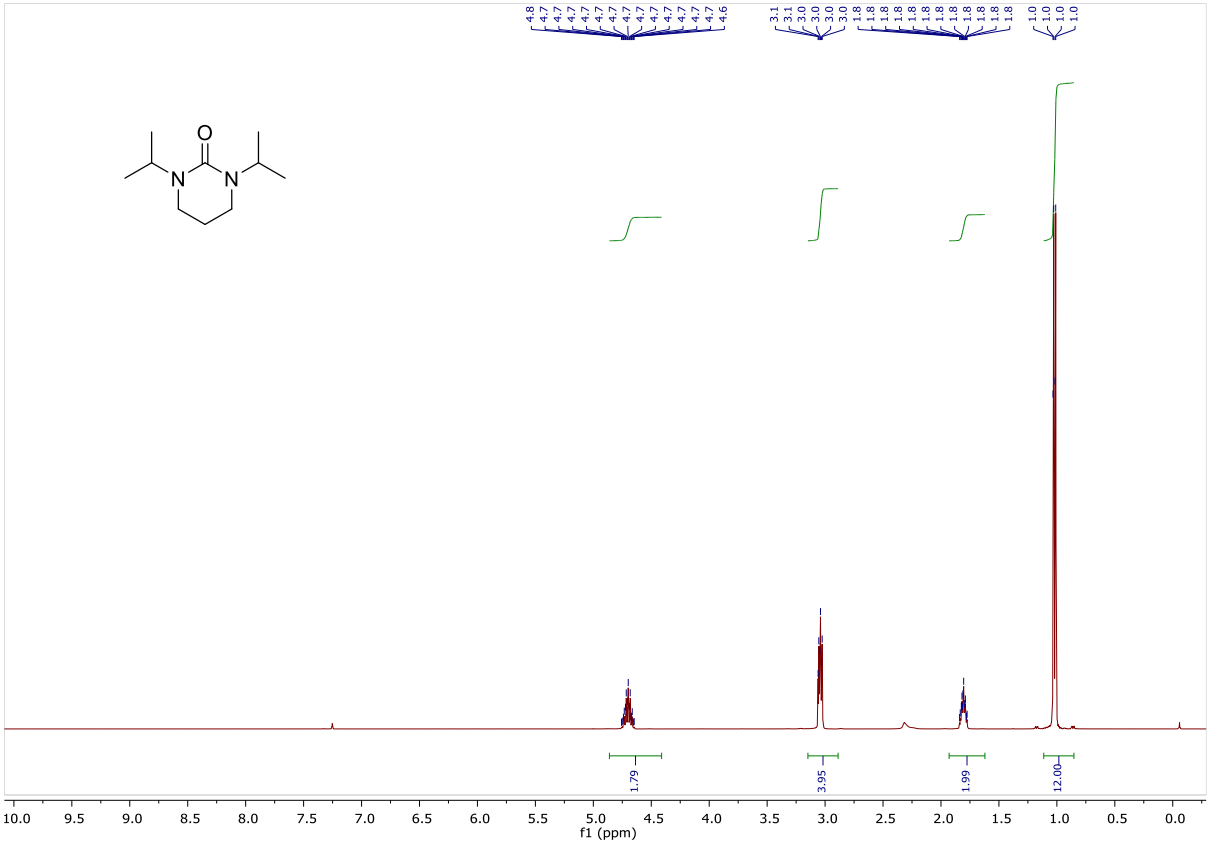


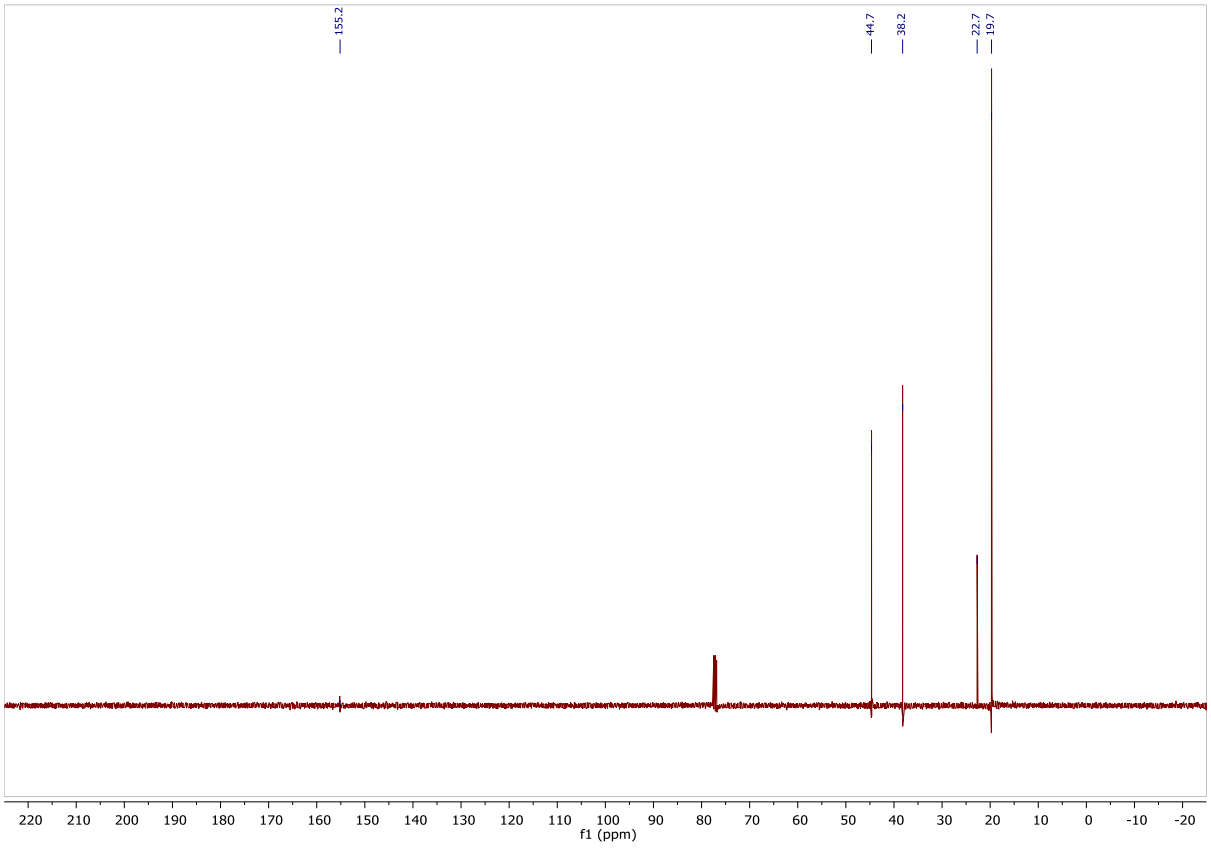
^{1}H and ^{13}C NMR compound for **52**



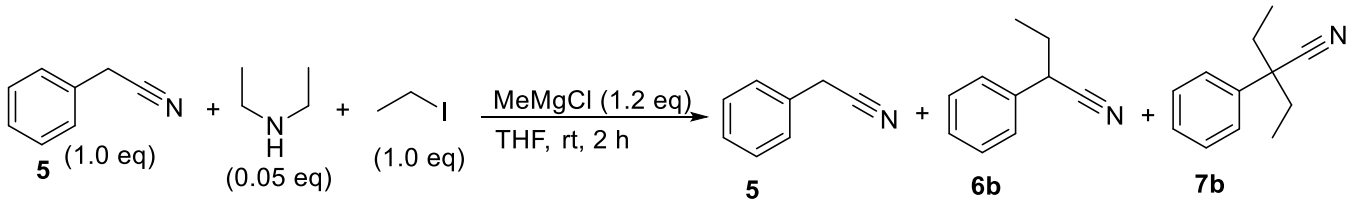


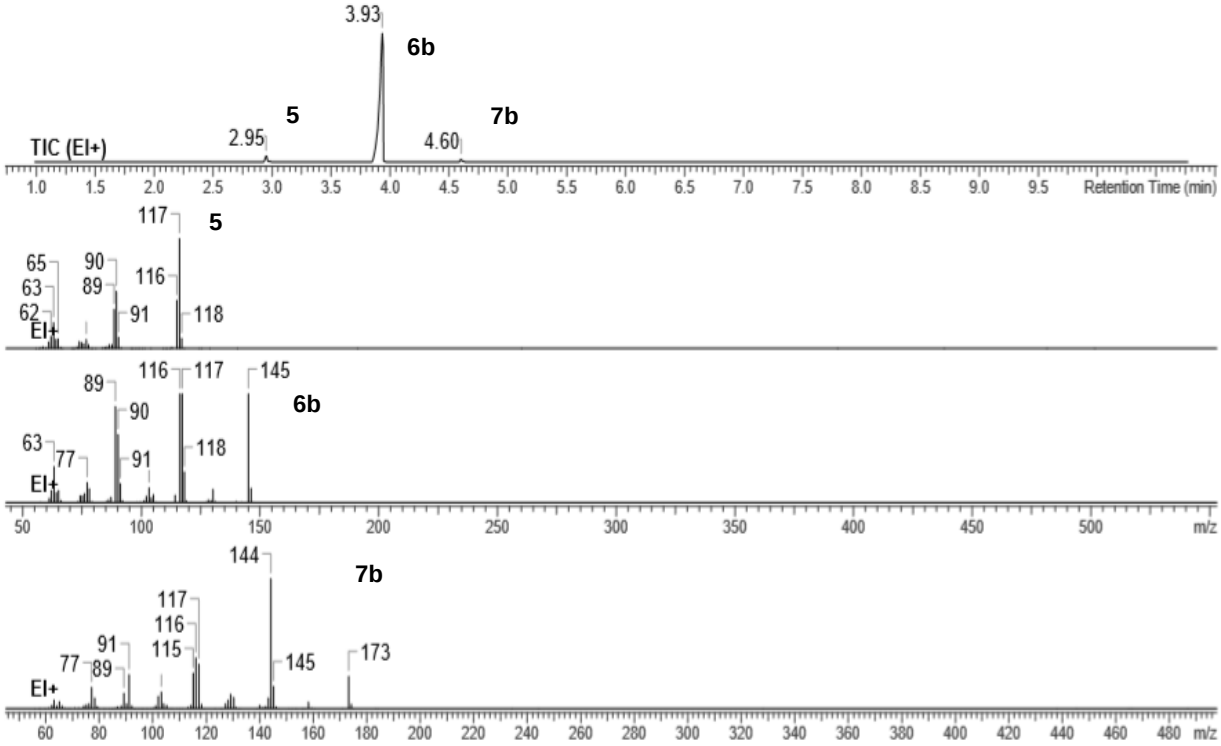
^{1}H and ^{13}C NMR compound for **53**



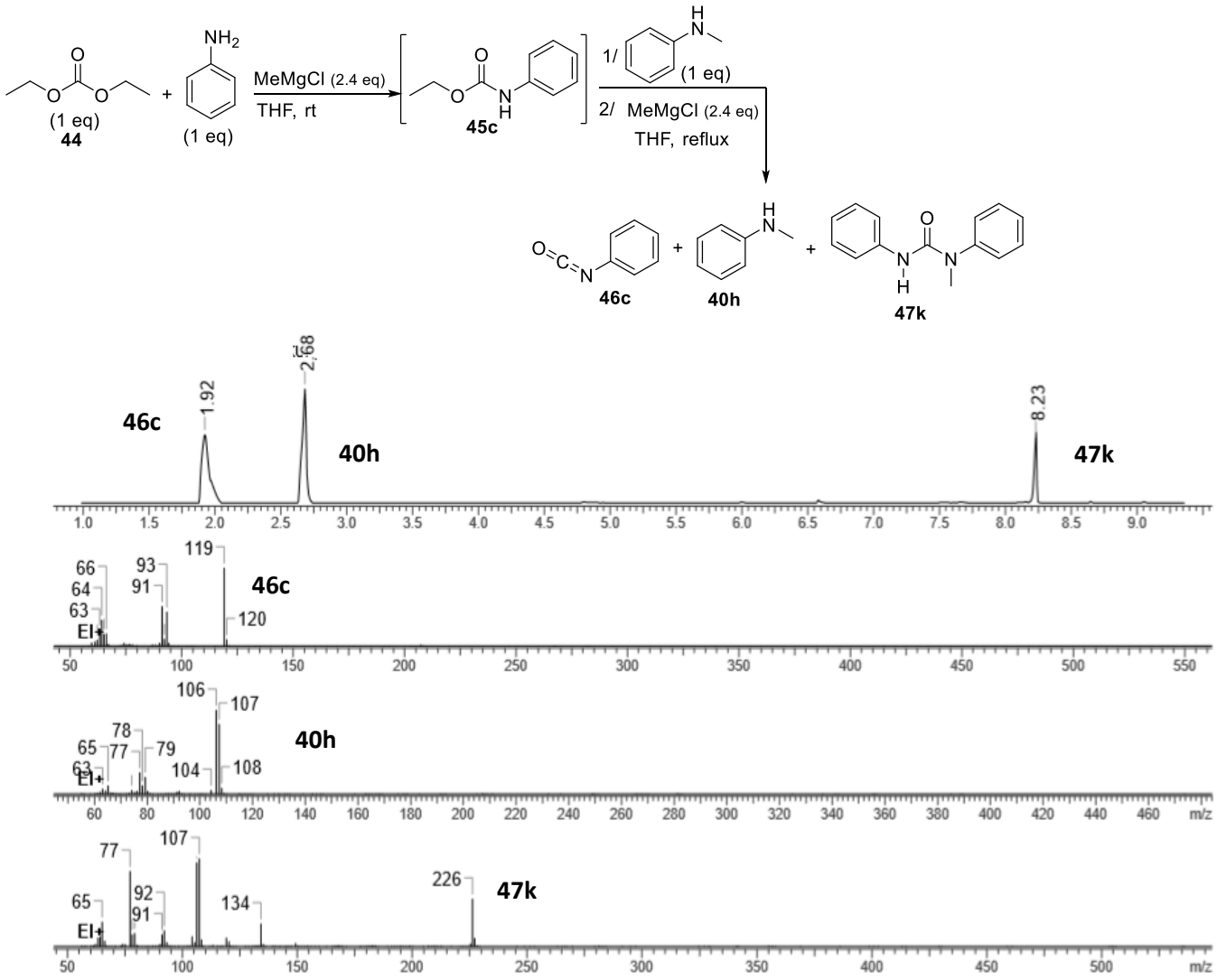


GC-MS traces for alkylation reaction to produce compound **6b**





GC-MS traces for the attempted reaction to produce compound **47k**



GC-MS traces for the reaction to produce compound **47c**